



(86) **Date de dépôt PCT/PCT Filing Date:** 2013/12/10  
(87) **Date publication PCT/PCT Publication Date:** 2014/06/19  
(85) **Entrée phase nationale/National Entry:** 2016/05/30  
(86) **N° demande PCT/PCT Application No.:** US 2013/074191  
(87) **N° publication PCT/PCT Publication No.:** 2014/093383  
(30) **Priorités/Priorities:** 2012/12/14 (US61/737,618);  
2013/12/09 (US14/101,109)

(51) **Cl.Int./Int.Cl.** **C07D 471/04** (2006.01),  
**A61K 31/437** (2006.01), **A61P 35/00** (2006.01),  
**A61P 9/00** (2006.01)  
(71) **Demandeur/Applicant:**  
ARRIEN PHARMACEUTICALS LLC, US  
(72) **Inventeurs/Inventors:**  
VANKAYALAPATI, HARIPRASAD, US;  
YERRAMREDDY, VENKATAKRISHNAREDDY, IN;  
GANIPISETTY, VENU BABU, IN;  
TALLURI, SURESHKUMAR, IN;  
APPALANENI, RAJENDRA P., US  
(74) **Agent:** MOFFAT & CO.

(54) **Titre : DERIVES SUBSTITUES DE 1H-PYRROLO[2,3-B]PYRIDINE ET 1H-PYRAZOLO[3,4-B]PYRIDINE EN TANT QU'INHIBITEURS DE KINASES 2 INDUCTIBLES PAR UN SEL (SIK2)**  
(54) **Title: SUBSTITUTED 1H-PYRROLO[2,3-B]PYRIDINE AND 1H-PYRAZOLO[3,4-B]PYRIDINE DERIVATIVES AS SALT INDUCIBLE KINASE 2 (SIK2) INHIBITORS**

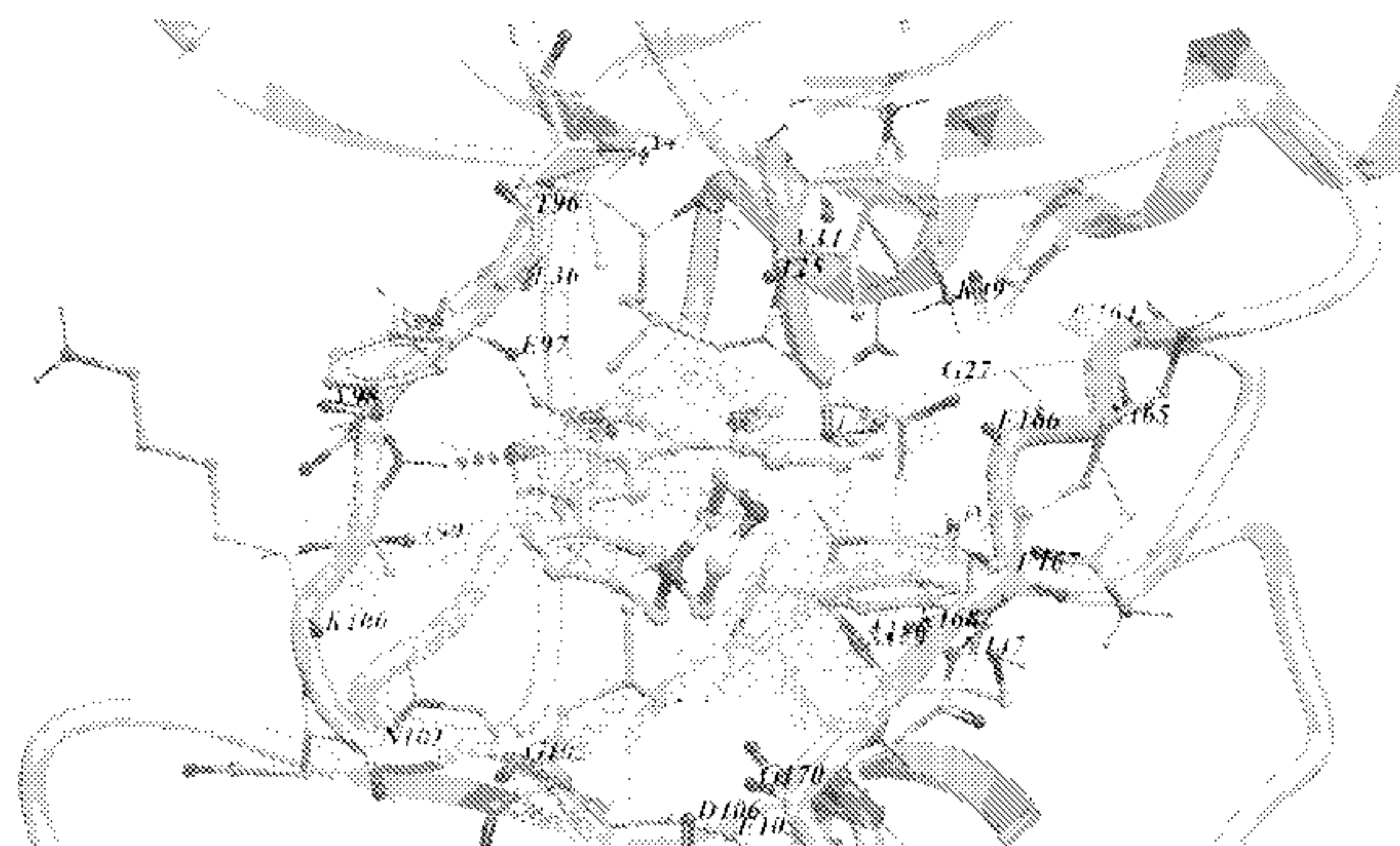
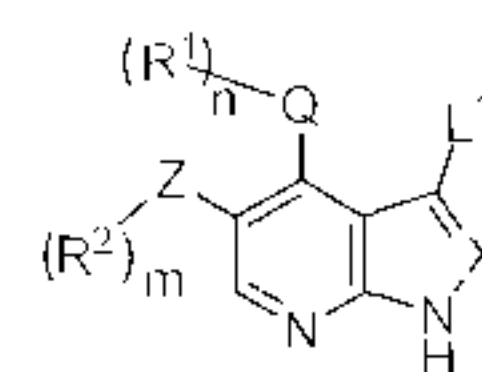
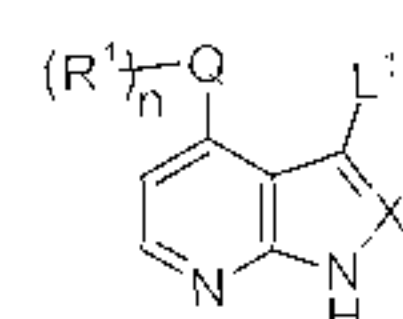


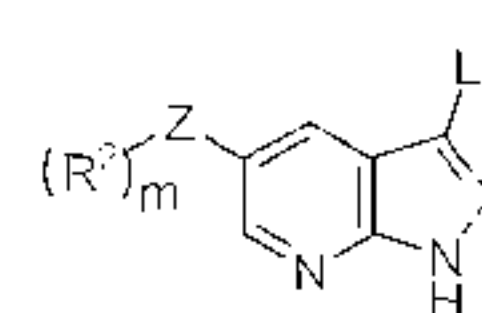
**FIG. 4:** Homology model of SIK2 in complex with an inhibitor. The critical active site residues shown in colour-by-atom in stick representations. The inhibitor binding site depicted in surface in complex with SIK2. Compound belongs to 1H-pyrrolo[2,3-b]pyridine structural class of the present invention.



(I)



(IA)



(IB)

(57) **Abrégé/Abstract:**

The present invention relates to compounds according to Formulas I, IA or IB: to pharmaceutically acceptable composition, salts thereof, their synthesis and their use as SIK2 inhibitors including such compounds and methods of using said compounds in the treatment of various diseases and or disorders such as cancer, stroke, cardiovascular, obesity and type II diabetes.



## Abstract

The present invention relates to compounds according to Formulas I, IA or IB: to pharmaceutically acceptable composition, salts thereof, their synthesis and their use as SIK2 inhibitors including such compounds and methods of using said compounds in the treatment of various diseases and or disorders such as cancer, stroke, cardiovascular, obesity and type II diabetes.

WO 2014/093383

PCT/US2013/074191

TITLE: Substituted 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine  
Derivatives as Salt Inducible Kinase 2 (SIK2) Inhibitors

## FIELD OF INVENTION

[001] The present invention is directed to compounds, their synthesis, and their use as modulators or inhibitors of the Salt Inducible Kinase 2 (“SIK2” kinase). The compounds of the present invention are useful for modulating (e.g. inhibiting) SIK2 activity and for treating diseases or conditions mediated by SIK2 such as for example, disease states associated with abnormal cell growth such as cancer, stroke, obesity and type 2 diabetes.

## BACKGROUND OF THE INVENTION

[002] Substituted 5-(pyrazin-2-yl)-1*H*-pyrazolo [3, 4-*b*] pyridine and pyrazolo [3, 4-*b*] pyridine derivatives as protein kinase inhibitors are described in US patent publication No. 2013/0102586 and International Publication No. WO2012/135631.

[003] Salt Inducible Kinase 2 (SIK2) is a centrosome kinase required for bipolar mitotic spindle formation and is a Ser/Thr kinase. Three isoforms of SIK family have been reported; SIK1 (SNF1LK), SIK2 (SNF1LK, QIK) and SIK3 (QSK). The SIK2 is amplified in large B-cell lymphoma, ovarian, melanoma and breast cancer patients. Recent findings suggest that SIK2 over expression enhanced cell death after ischemia and metabolic diseases as well. Inhibition of SIK2 was reported to cause SIK2-dependent centrosome splitting in interphase while SIK2 depletion blocked centrosome separation in mitosis, sensitizing ovarian cancers to paclitaxel in culture and in xenografts. Depletion of SIK2 also delayed G1/S transition and reduced AKT phosphorylation. Higher expression of SIK2 significantly correlated with poor survival in patients with high-grade serous ovarian cancers (Bast, Jr., et al., Cancer Cell., 18, 109–121, 2010) and is a plausible therapeutic target for therapy in ovarian cancers.

[004] The Salt Inducible Kinase 2 (SIK2) depletion in cancer cells had a significant decrease in cancer cell growth, delayed mitotic progression and G1/S transition and decreased AKT phosphorylation. Deficiency of SIK2 significantly sensitized cancer cells to taxane and paclitaxel in vivo xenograft models in interfering with mitotic progression. In this work we established the basis of utilizing SIK2 as a target for therapy in cancer by evaluating its effect on taxane, paclitaxel sensitization in a panel of cell lines, confirming activity in xenografts that the SIK2 is over-expressed in 30% of ovarian cancers and to further develop an assay to measure SIK2 activity. Ovarian Cancer (OC) accounts 3% of cancers in women and is the fifth leading cause of cancer related death among women. Nearly 22,240 women were diagnosed in 2013 with OC in US alone with about 14,030 women estimated to die from this deadly

gynecologic malignancy of American women. Ovarian cancer is one of the cancers difficult to detect prior to its advanced stage. The currently available treatments, other than surgery and radiation, are chemotherapeutics and the few approved targeted agents.

[005] Additionally, an advantage of SIK2 inhibitors that block SIK2 activity is to recruit melanogenesis. This leads to recovery of brown hair in 6 to 8 weeks.

[006] Recent reports suggests that the over expression of SIK2 controlled the TORC1 (Transducer of regulated CREB activity-1) from entering the nucleus and activating CREB, and this enhanced cell death after ischemia. The SIK2 inhibitor could enhance CREB (cAMP Responsive Element-Binding) protein activity and prevent neuron death in response to ischemia. The SIK2 deficient mice were protected from stroke suggests that SIK2 degradation after ischemia is required for neurons.

[007] There continues to be a need for new drugs to treat multiple cancer indications, melanogenesis, stroke, cardiovascular, obesity and type II diabetes diseases where SIK2 and its isoforms play a pivotal role in these multiple disease indications. Using the homology structure of the SIK2 and our FFDD (Fragment Field Drug Design) or FIELDS guided lead identification, screening and SAR efforts; we have discovered the first-in-class novel *H*-pyrrolo[2,3-*b*]pyridine and 1*H*-pyrazolo[3,4-*b*]pyridine inhibitors of SIK2 that would be useful for treating multiple disease indications, including cancer (ovarian, breast, prostate, diffuse large B-cell lymphoma and melanoma), stroke, obesity, type II diabetes. We disclose here the composition and method of use for inhibitors of SIK2.

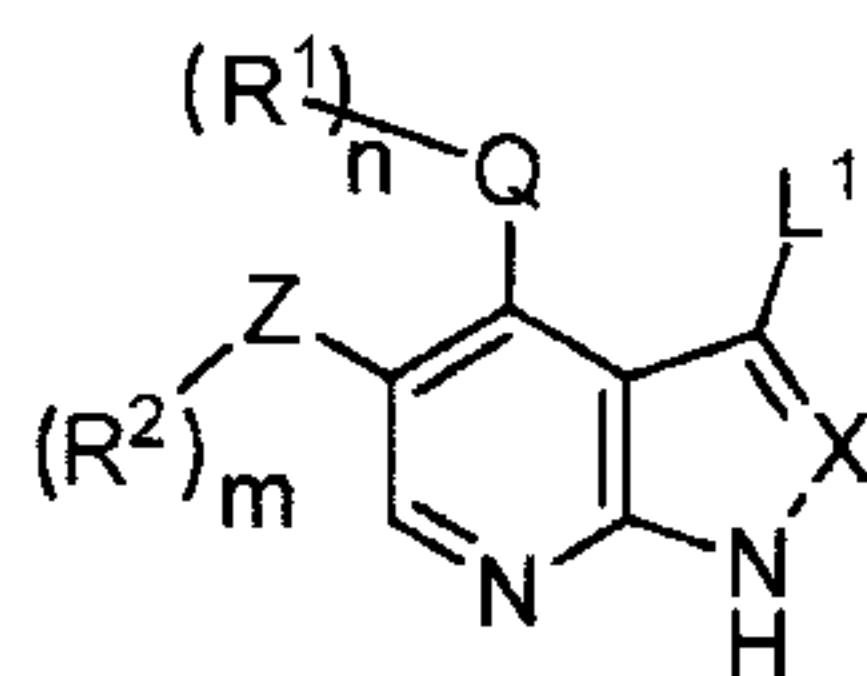
[008] Accordingly, the present invention is directed to composition and method of use for novel *H*-pyrrolo[2,3-*b*]pyridine and 1*H*-pyrazolo[3,4-*b*]pyridine inhibitors of SIK2 and SIK3 useful for treating multiple disease indications, including cancer (ovarian, breast, prostate, diffuse large B-cell lymphoma, lung, NSCL and melanoma), autophagy function, stroke, obesity, and type II diabetes.

#### SUMMARY OF THE INVENTION

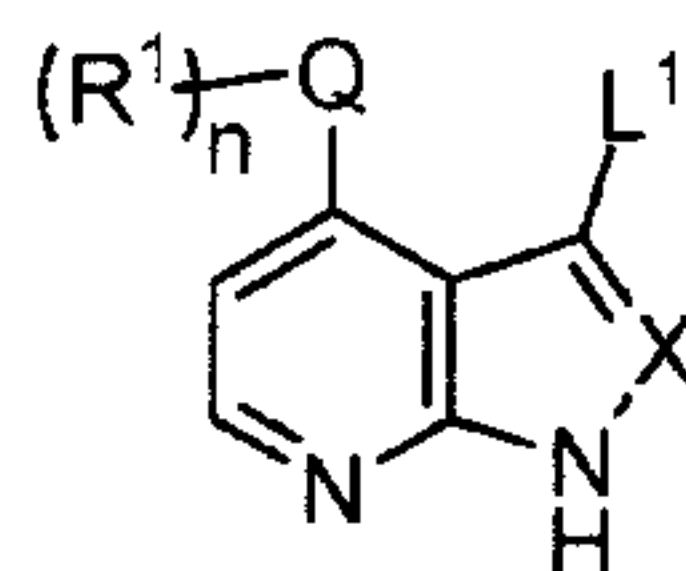
[009] The present invention concerns compounds active on protein kinases, specifically SIK1, SIK2 and SIK3, and in general, including but not limited to CLK1, CLK2, DYRK1, DYRK1A, ITK, Janus family of kinases (JAK1, JAK2, JAK3 and TYK2), LRRK2, LRRK2 G2019, MELK, MAP4K1, MAP4K5, NIK, PKCd, RSK4, STK2, STK3, STK4, STK10 and TNIK1, including any mutations of these kinases and the use thereof in treating disease and conditions associated with regulations of the activity of these kinases. More specifically the invention concerns compounds of Formula **I**, **IA**, and **IB** as described below. Thus the invention provides novel use of compounds for therapeutic methods involving inhibition and

or modulation of protein kinases specifically SIK family of kinases; SIK1 (SNF1LK), SIK2 (SNF1LK, QIK) and SIK3 (QSK), as well as novel compounds that can be used for the therapeutic methods involving modulation of these protein kinases.

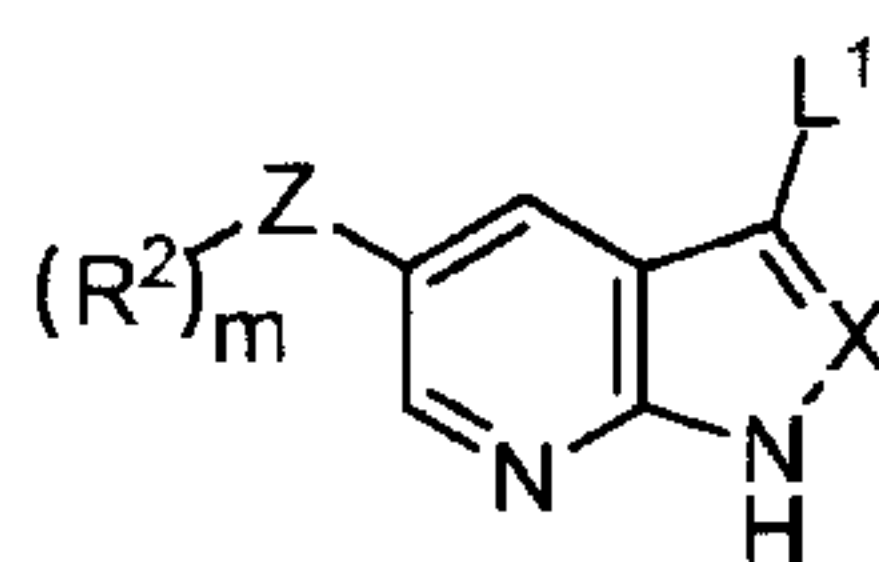
[0010] The present invention relates to compounds according to Formulas I, IA or IB:



(I)



(IA)



(IB)

to pharmaceutically acceptable composition, salts thereof, their synthesis and their use as SIK2 inhibitors including such compounds and methods of their use in the treatment of various diseases and disorders such as cancer, stroke, obesity and type II diabetes.

#### BRIEF DESCRIPTION OF THE FIGURES

[0011] **Fig. 1:** shows two panels of SIK2 inhibitor examples: Panel A on the left: 135 (▪), 142 (Δ) and Panel B on the right: 133 (▪) and 168 (Δ). The percent activity is plotted against log M.

[0012] **Fig. 2:** shows SIK2 inhibitor examples tested in SK-OV-3 cell lines on the left Panel A and OVCAR3 cell lines on the right Panel B with Cisplatin as control. The survival fraction is plotted against the concentration.

[0013] **Fig. 2b1:** Effects of four 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives on the SIK2-expressed SKOv3 cells.

[0014] **Fig. 2b2:** Effects of four 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives on the SIK2-expressed OVCAR3 cells.

[0015] **Fig. 2b3:** Effects of four 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives on the SIK2-expressed ES-2 cells.

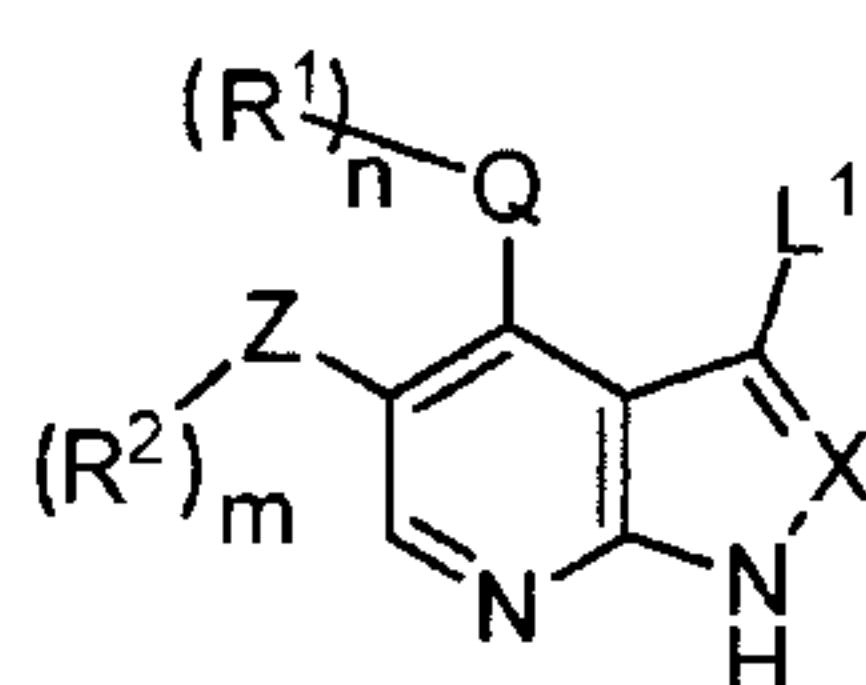
[0016] **Fig. 3:** depicts the structure based sequence alignment in Clustal W of the catalytic protein kinase domains of SIK1 (SNF1LK), SIK2 (SNF1LK, QIK), SIK3 (QSK), AMPK and MARK2. Amino acid residue annotation were identical residues (\*), highly conserved residues (:), and similar residues (.) The active site residues highlighted in yellow and the gatekeeper residues in turquoise and the DFG residues shown in yellow.

[0017] **Fig. 4:** Homology model of SIK2 in complex with one of the lead inhibitor. The critical active site residues shown in color-by-atom in stick representations. The inhibitor binding site depicted in surface in complex with SIK2. Compound belongs to 1*H*-pyrrolo [2, 3-*b*] pyridine structural class claimed.

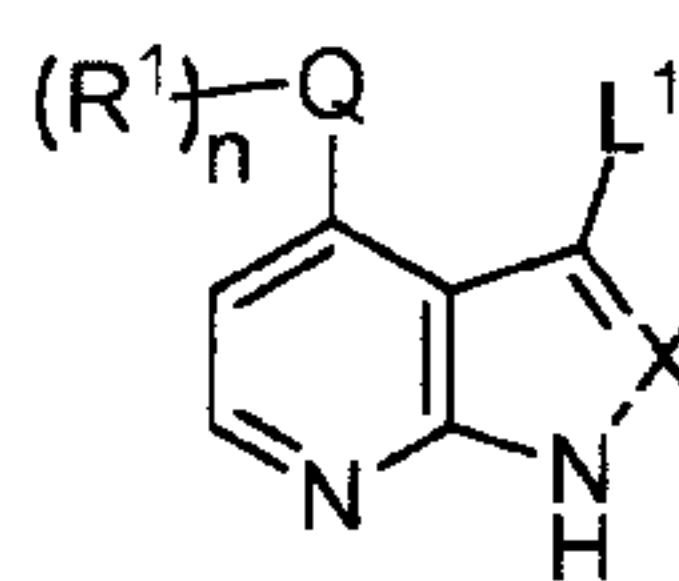
[0018] **Fig. 5a-c:** Plots of tumor volume, weight, and number against a control, two 1*H*-Pyrrolo [2, 3-*b*] pyridine compounds, taxol, and a combination. The data show that the compounds of the present invention and taxol have significant antitumor effects and as a single agent these series dissemination of tumor cell in vivo.

[0019] DETAILED DESCRIPTION OF THE INVENTION

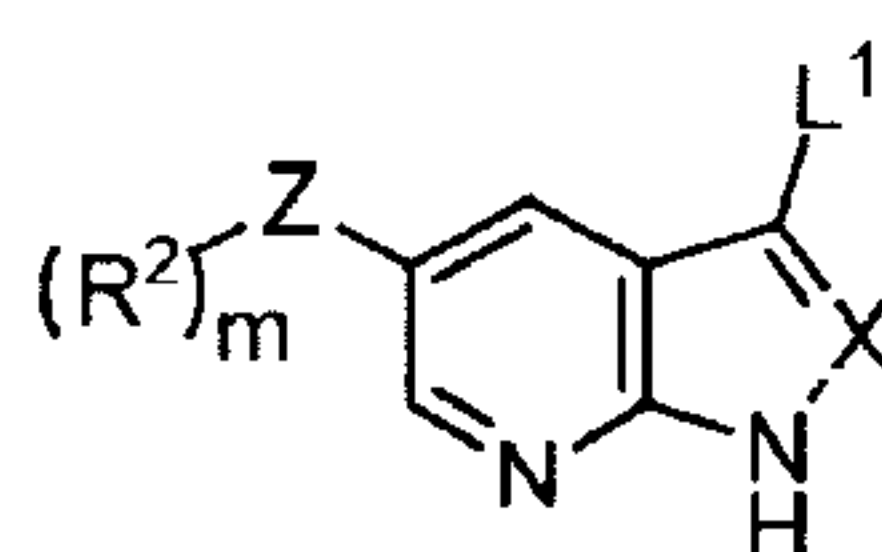
[0020] Compounds of the present invention are described by the Formulas I, IA or IB:



(I)



(IA)



(IB)

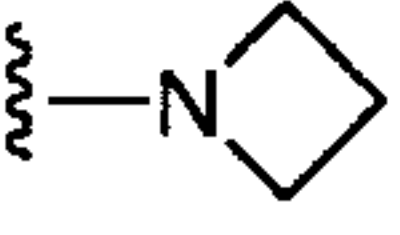
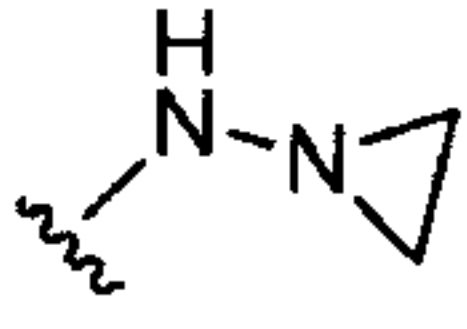
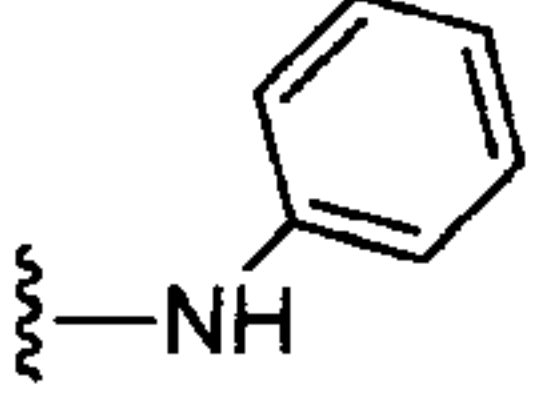
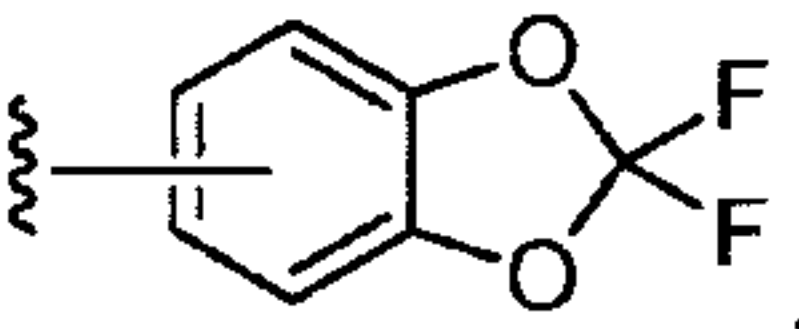
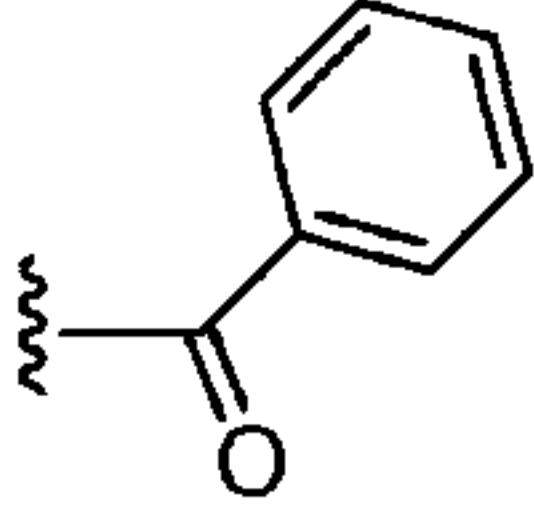
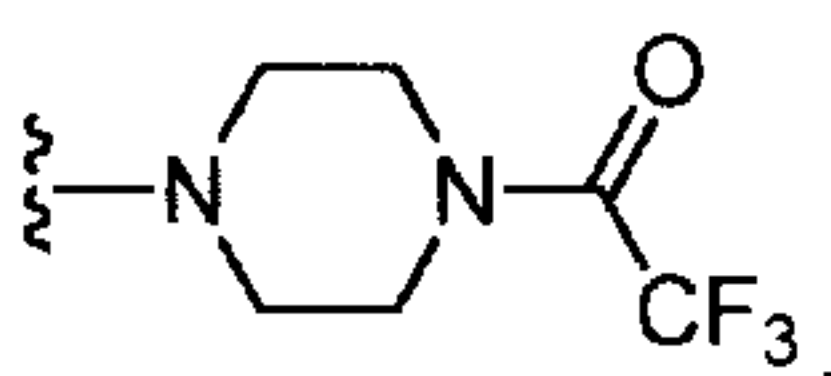
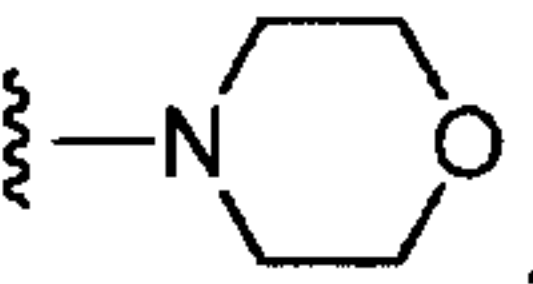
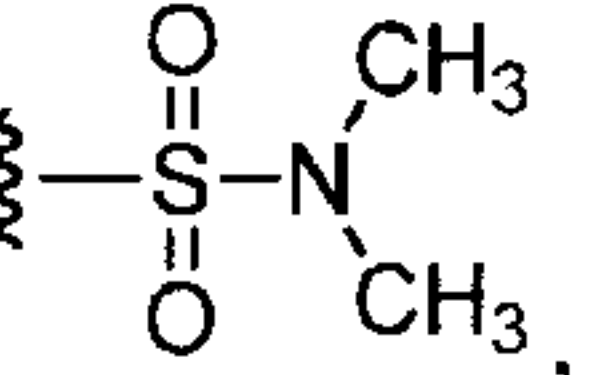
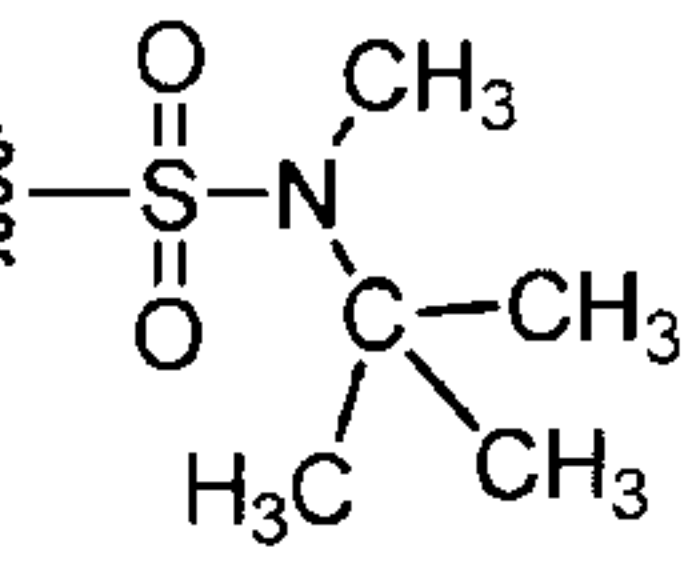
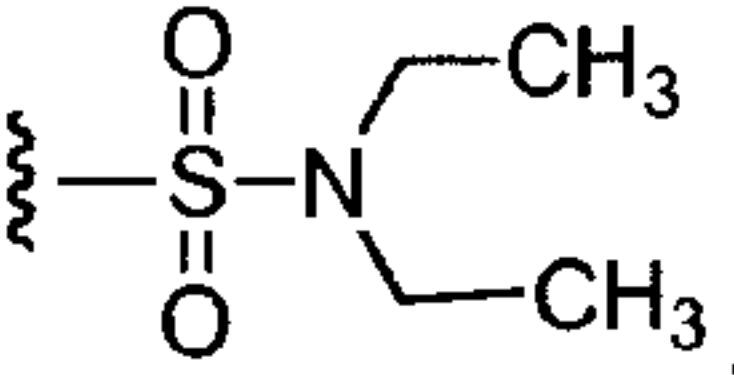
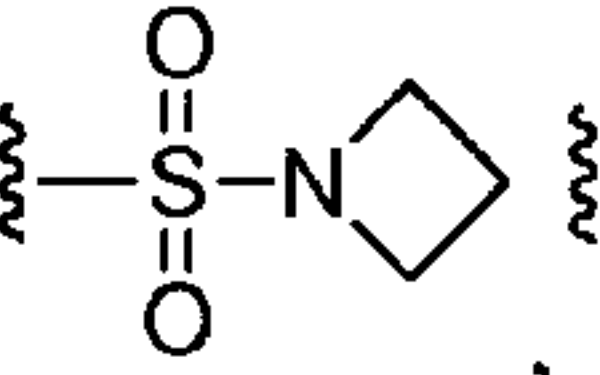
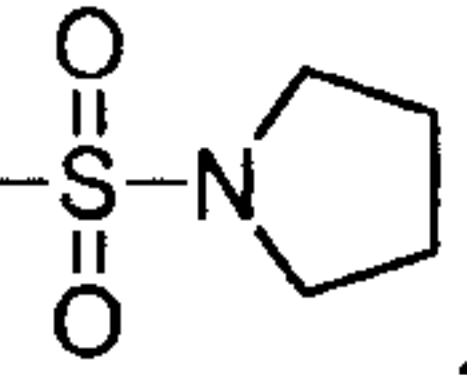
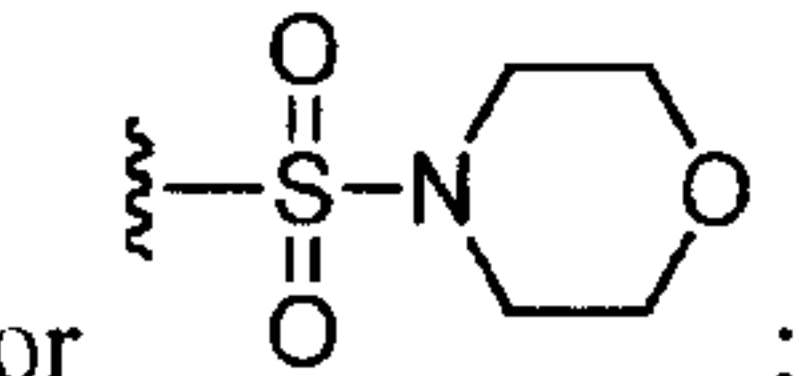
or a pharmaceutically acceptable salt thereof, wherein:

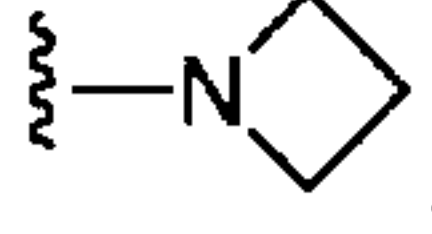
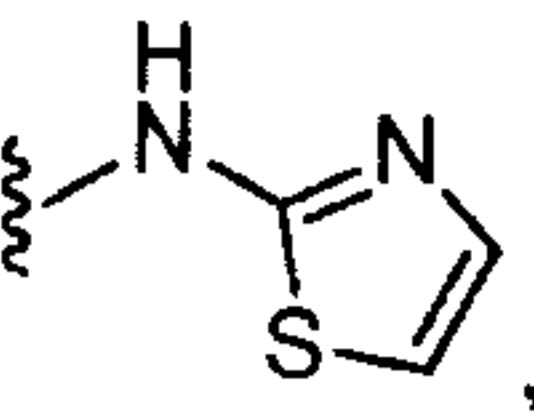
X is N or CH;

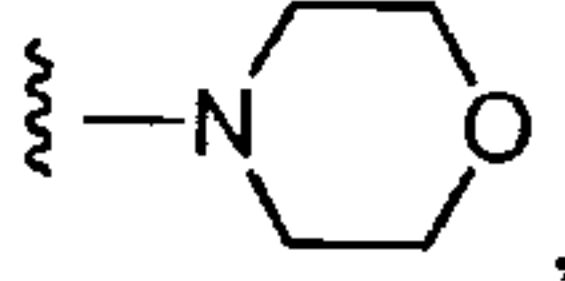
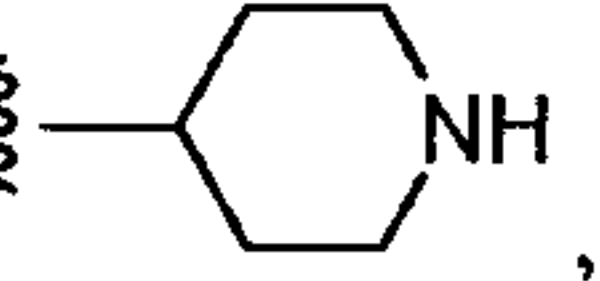
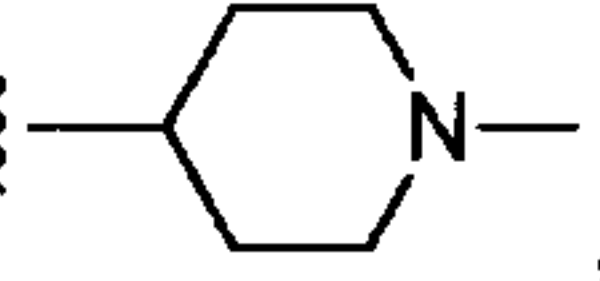
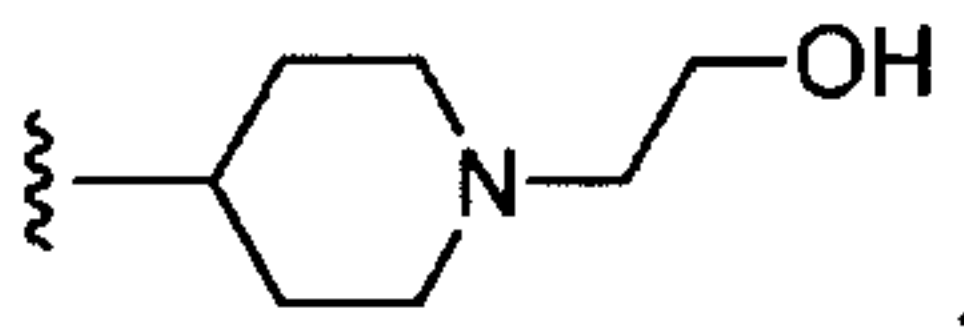
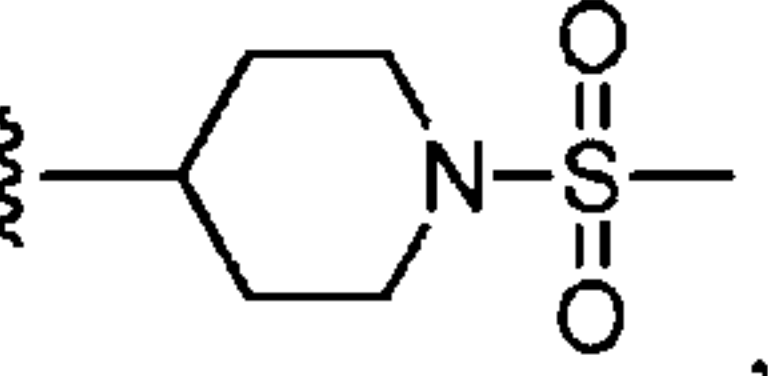
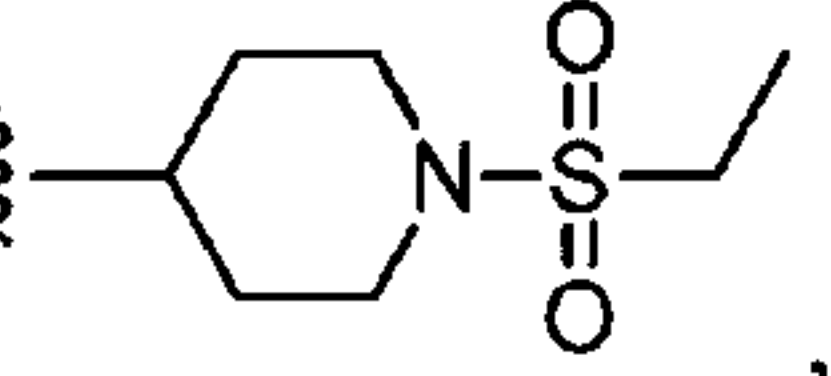
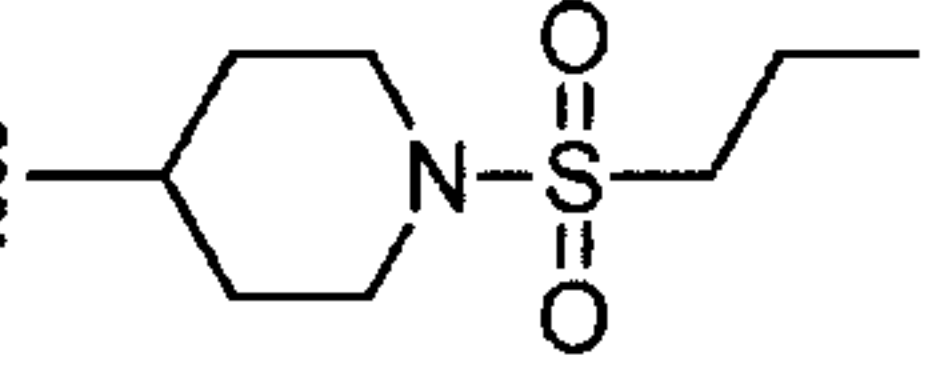
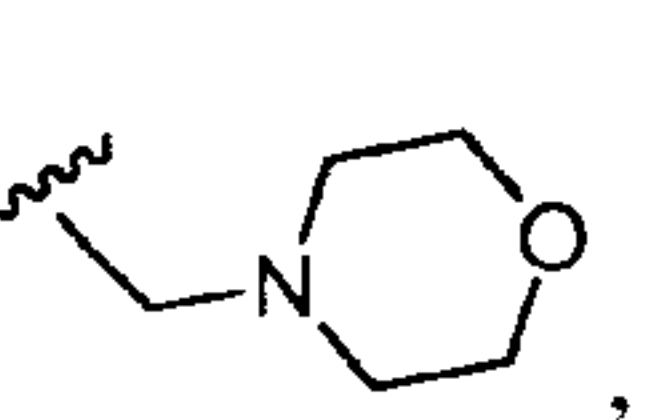
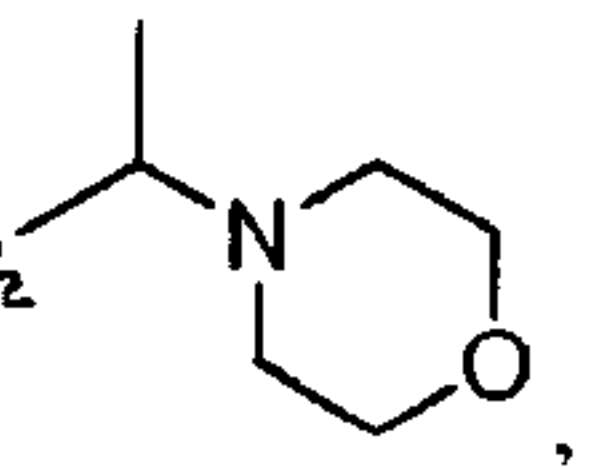
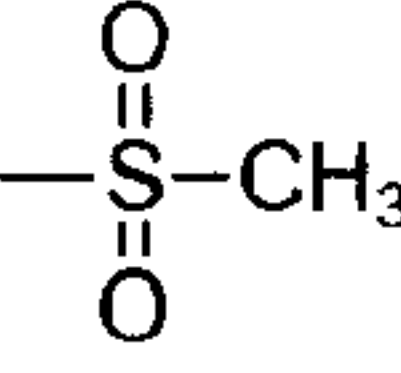
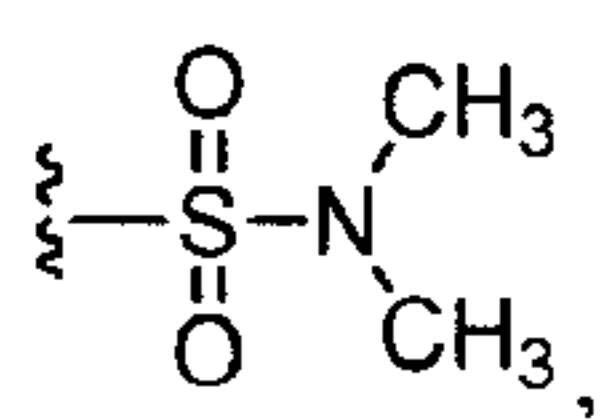
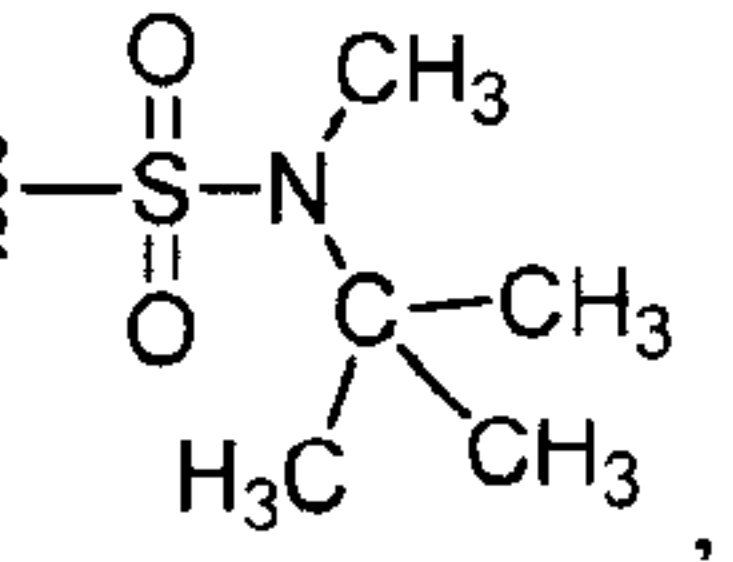
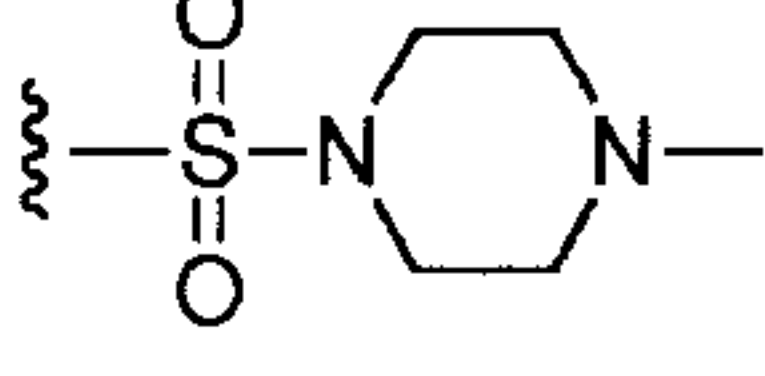
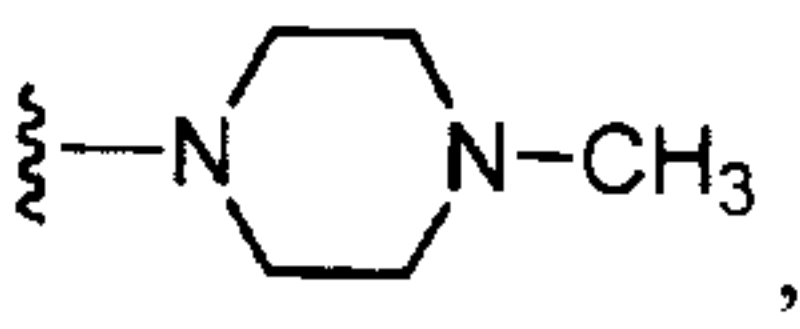
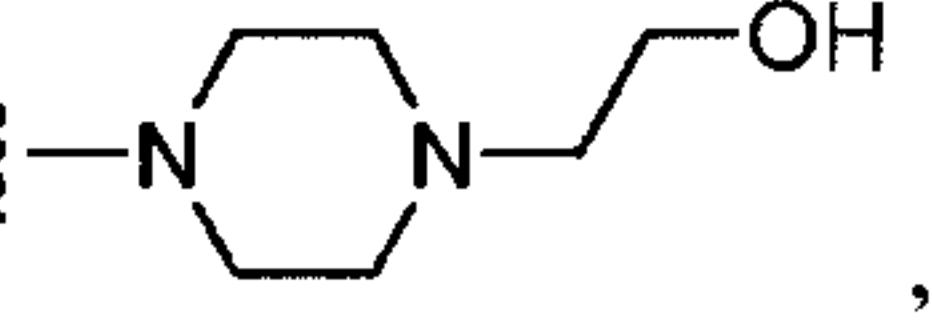
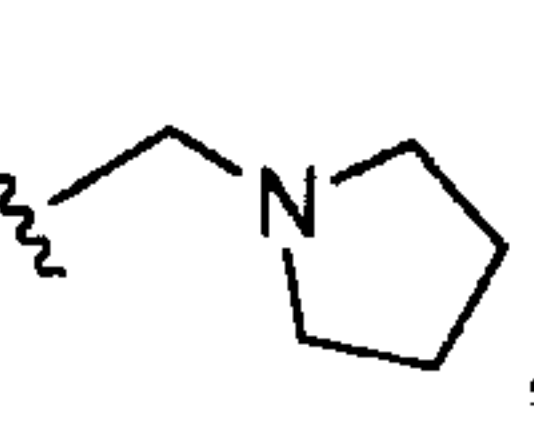
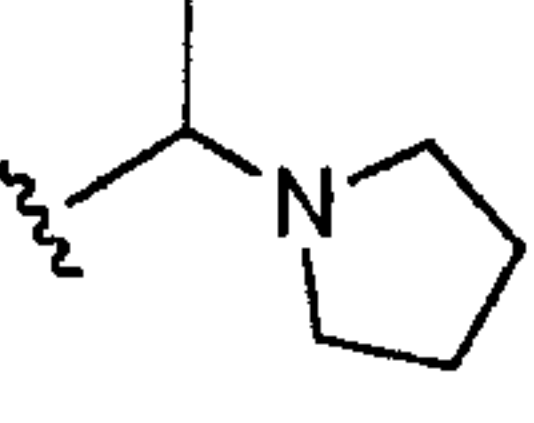
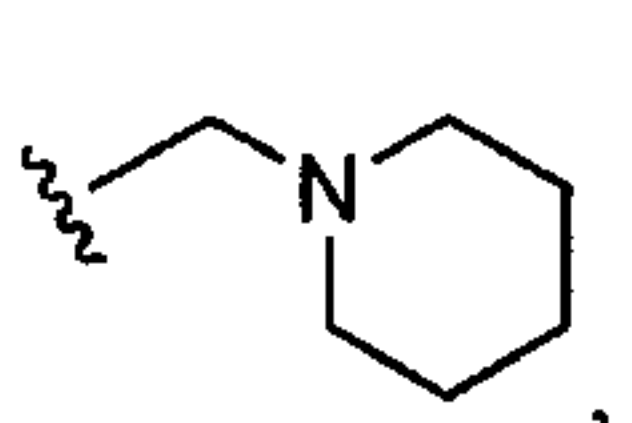
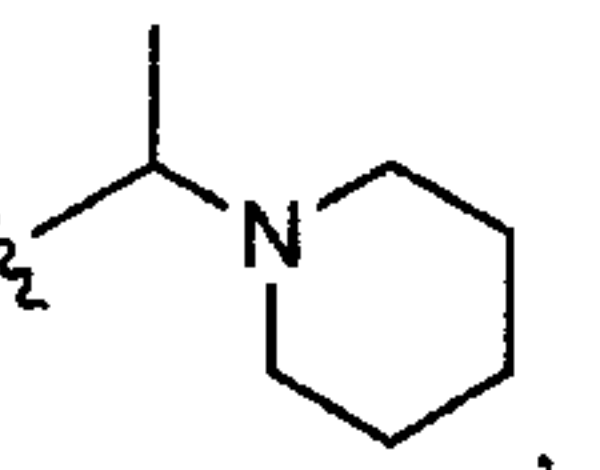
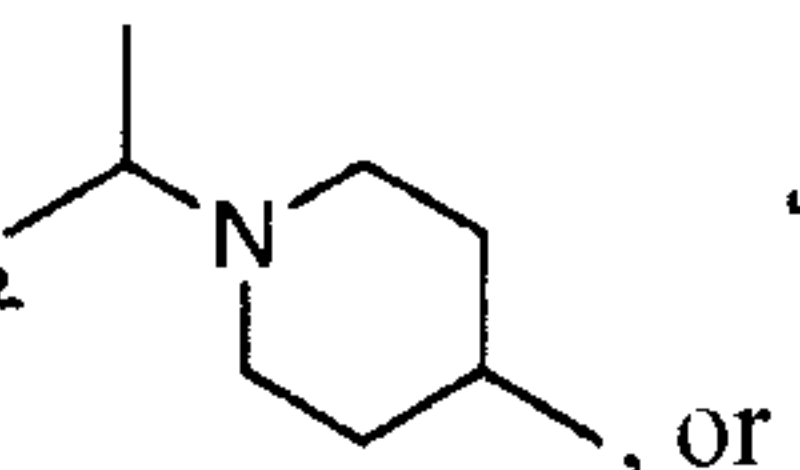
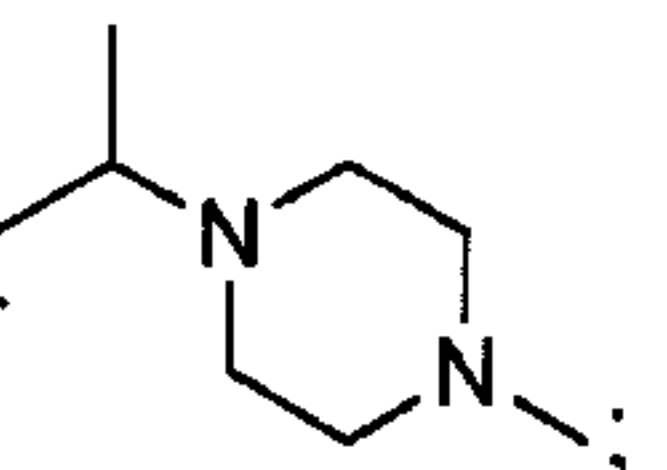
L<sup>1</sup> is H, F; or

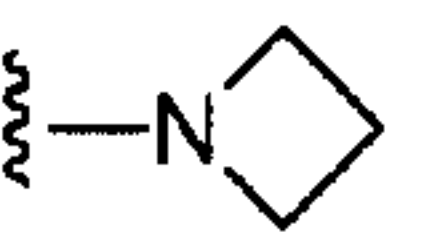
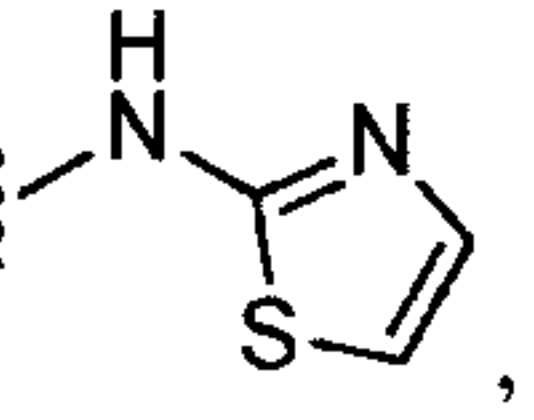
WO 2014/093383

PCT/US2013/074191

$L^1$  is thienyl, phenyl, pyrrolyl, pyridyl, , piperazinyl, , , , or , any of which is optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl, methylpiperazinyl, , , , , , , , or ;

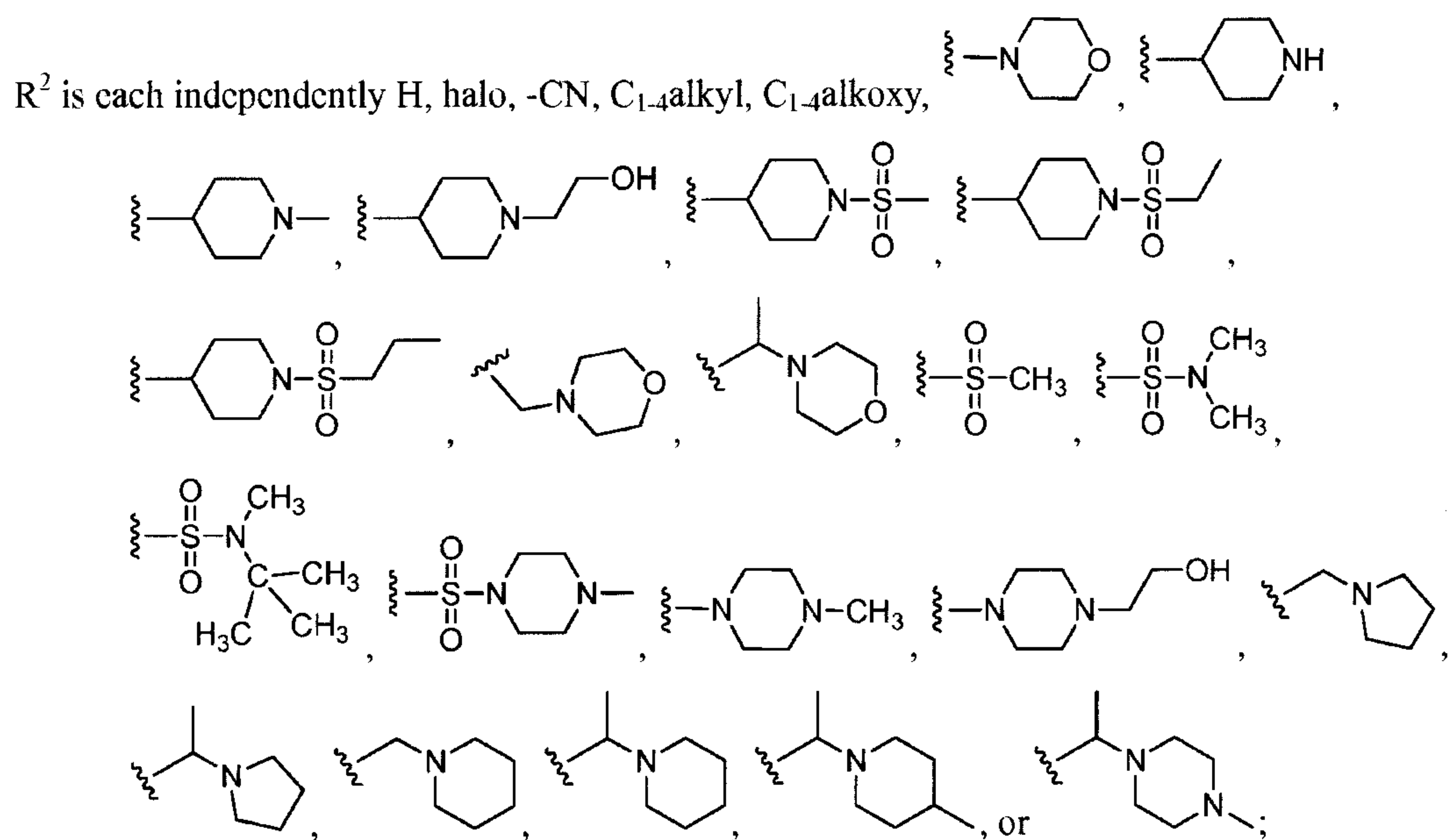
$Q$  is a direct bond, thienyl, thiazolyl, phenyl, , , furanyl, piperazinyl, or pyrazolyl;

$R^1$  is each H, halo, -CN,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, , , , , , , , , , , , , , , , , , , , , or ;

$Z$  is a direct bond, thienyl, thiazolyl, phenyl, , , furanyl, piperazinyl, or pyrazolyl;

WO 2014/093383

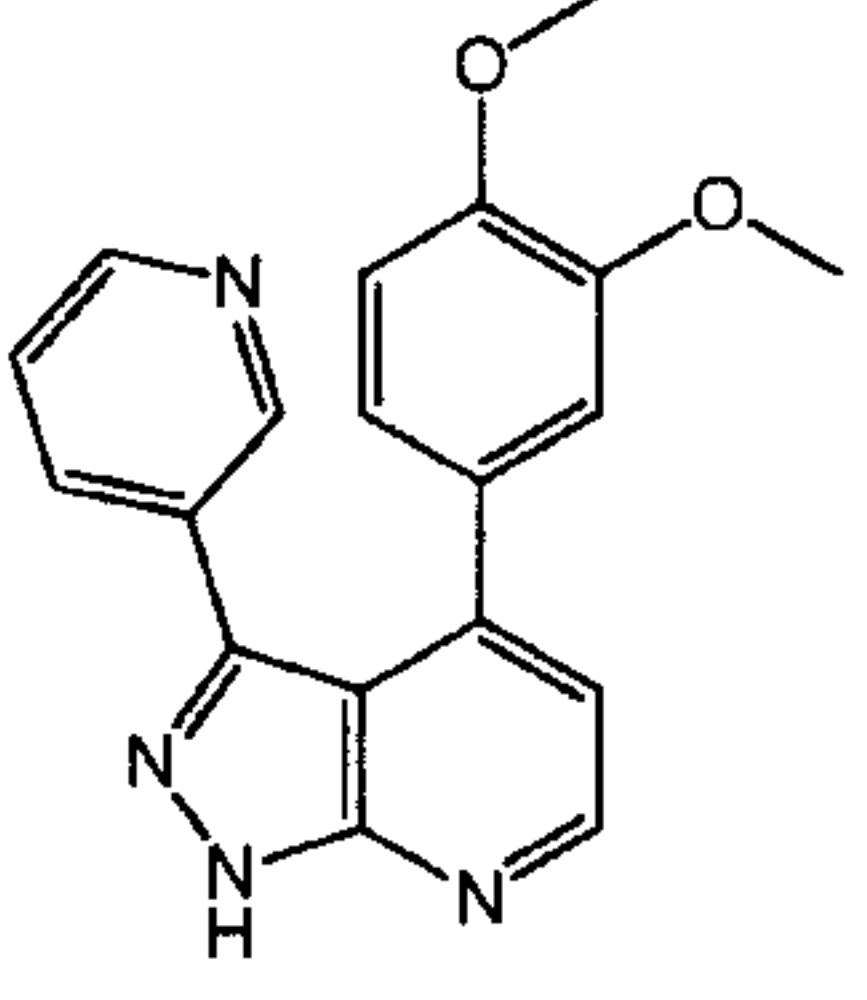
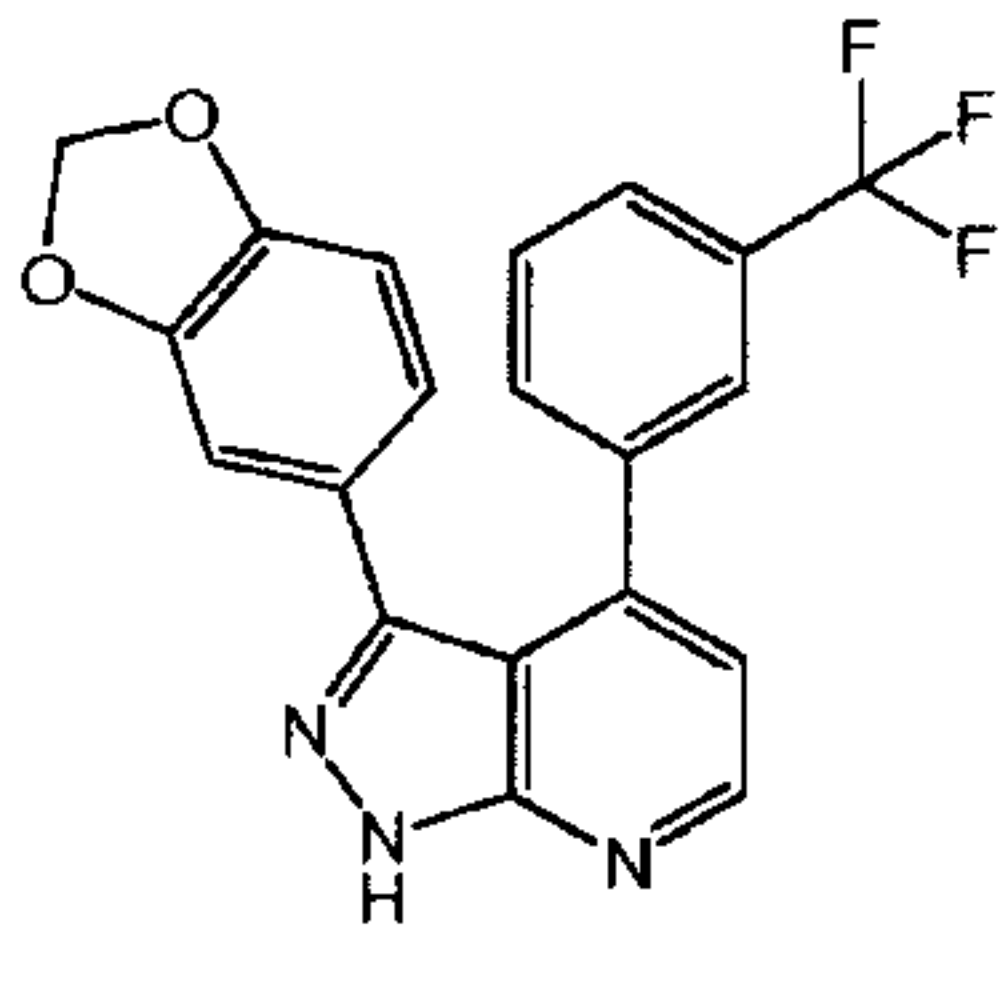
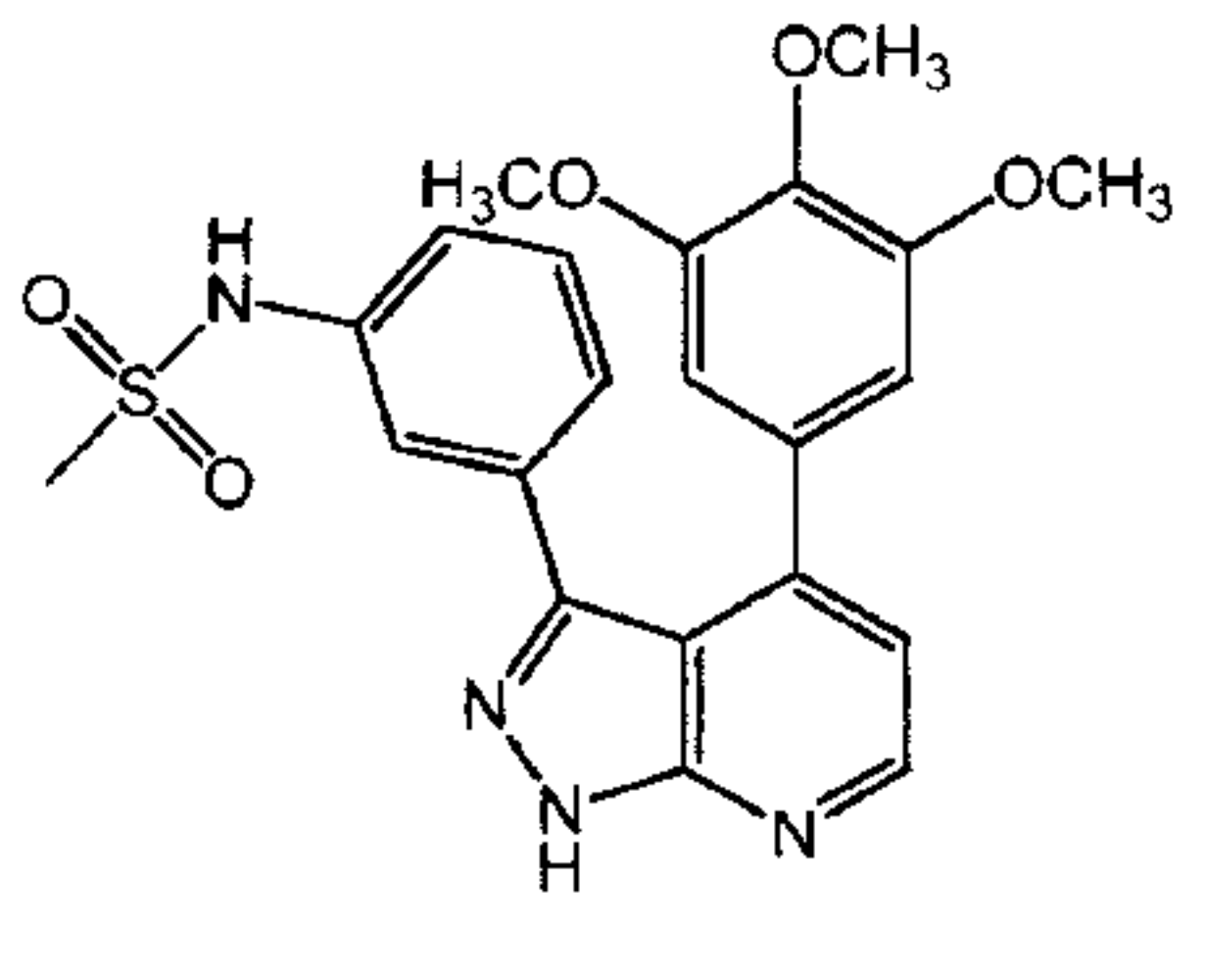
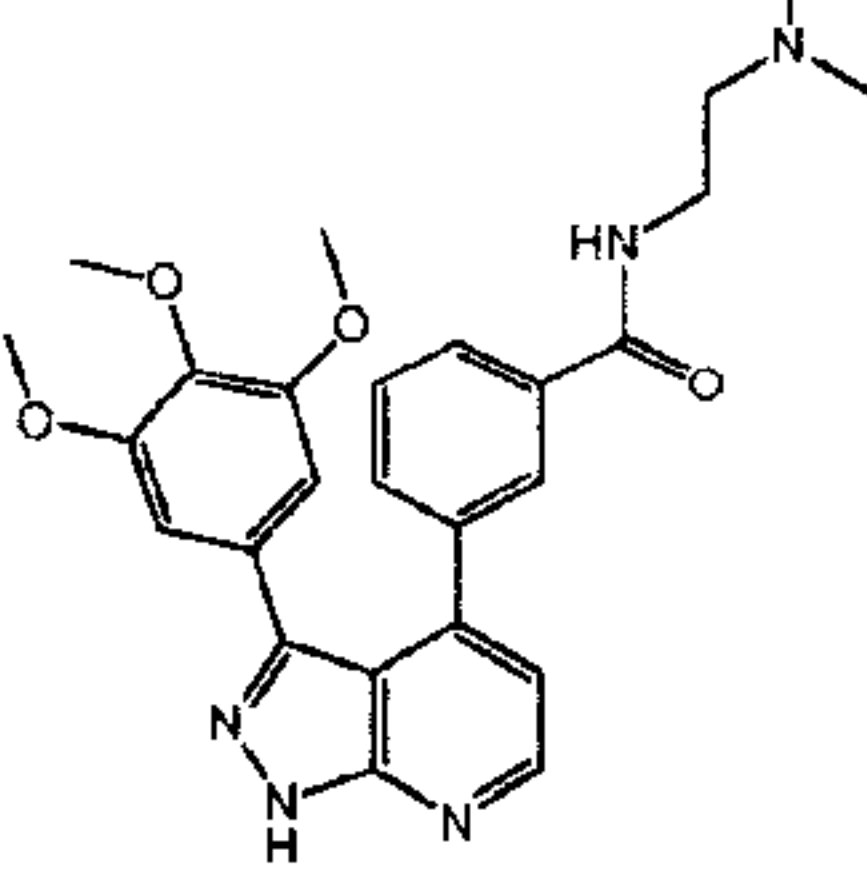
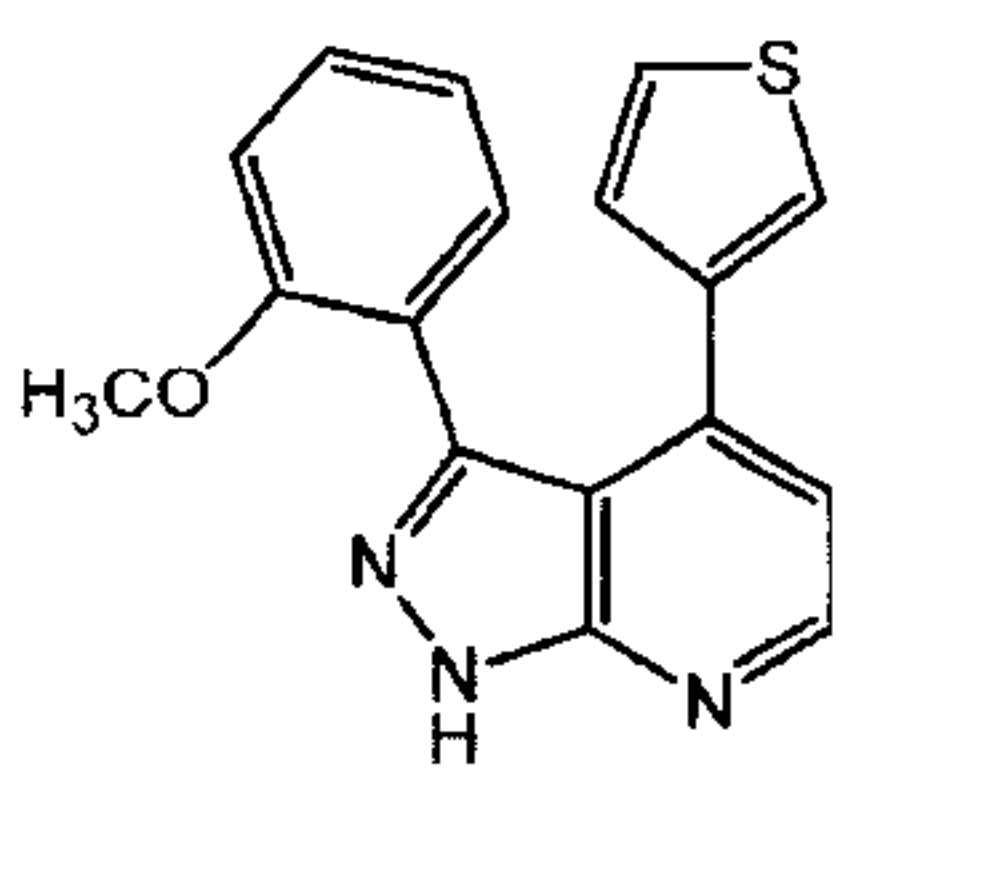
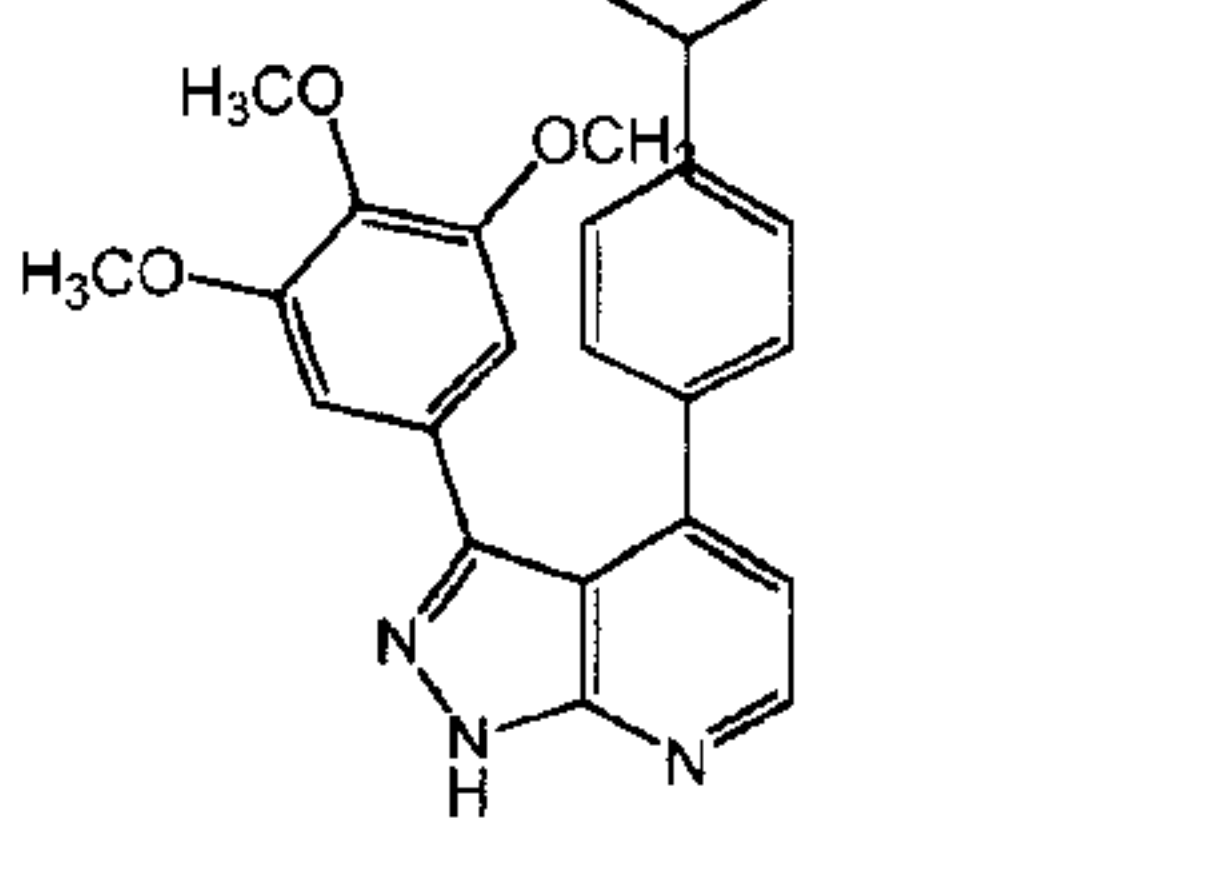
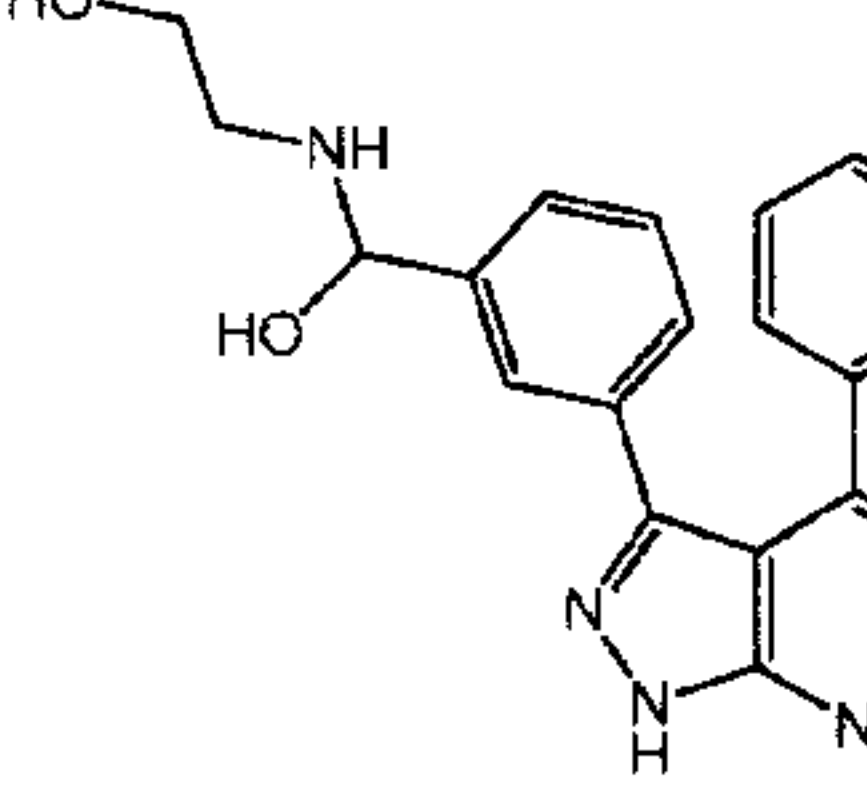
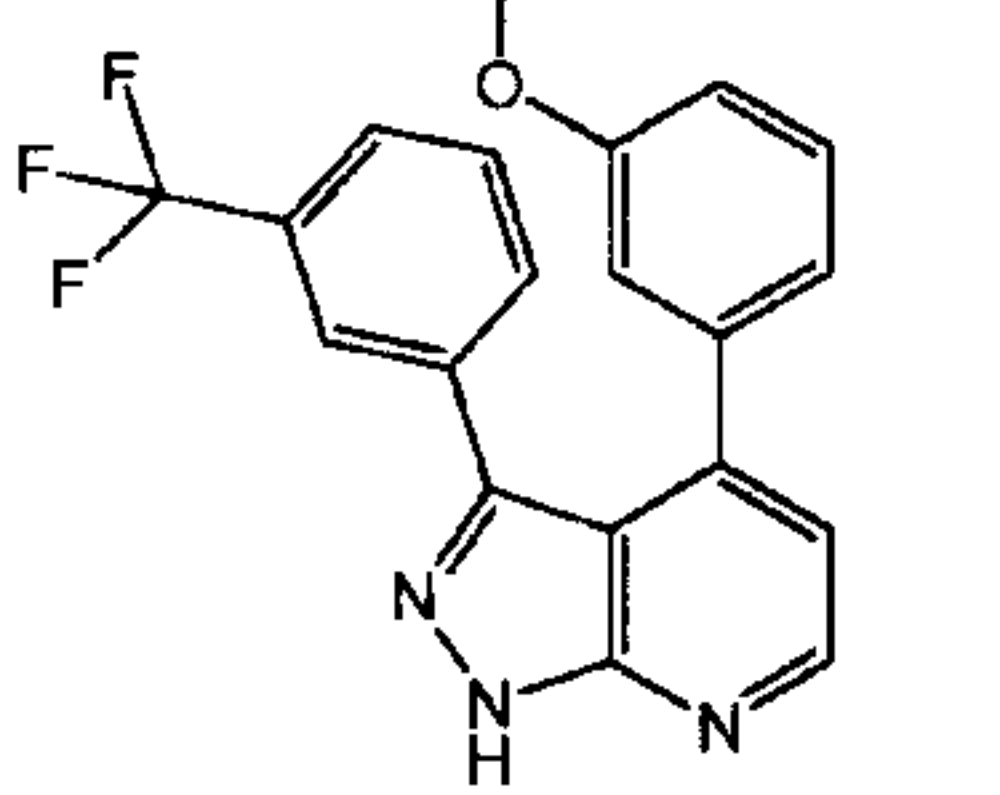
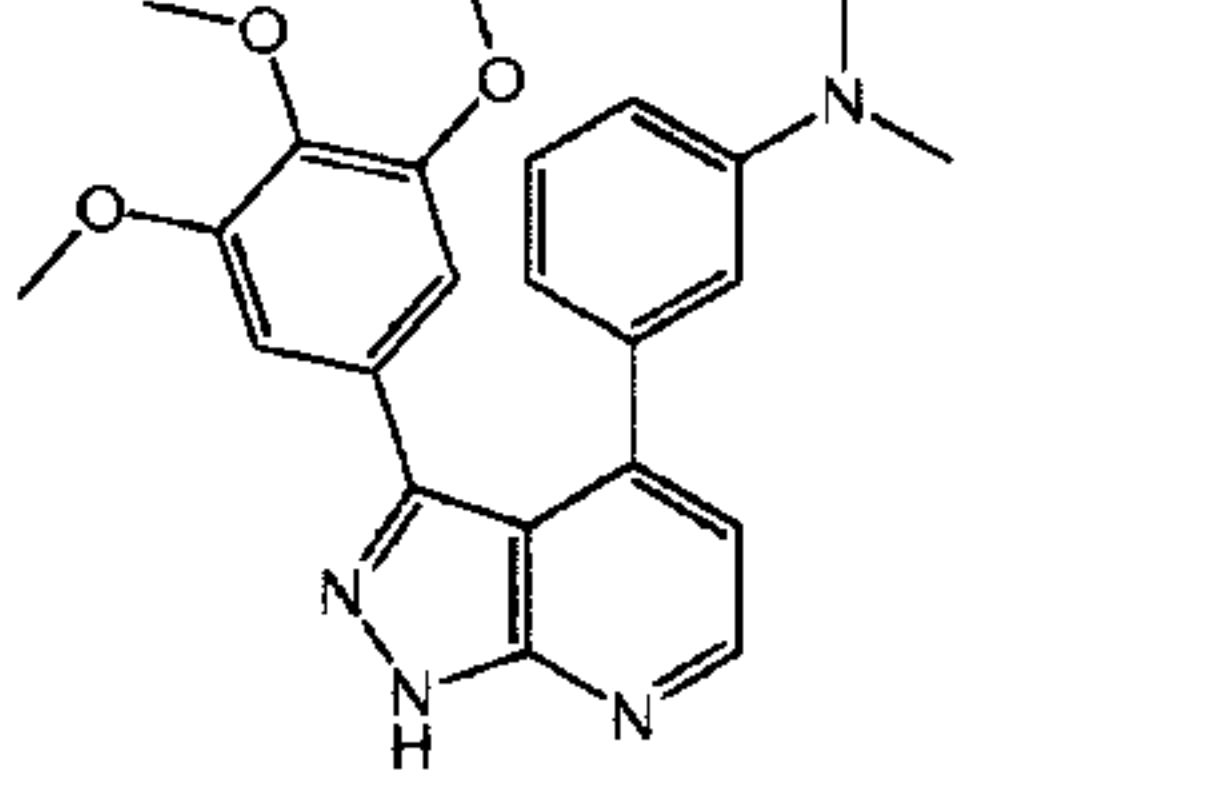
PCT/US2013/074191

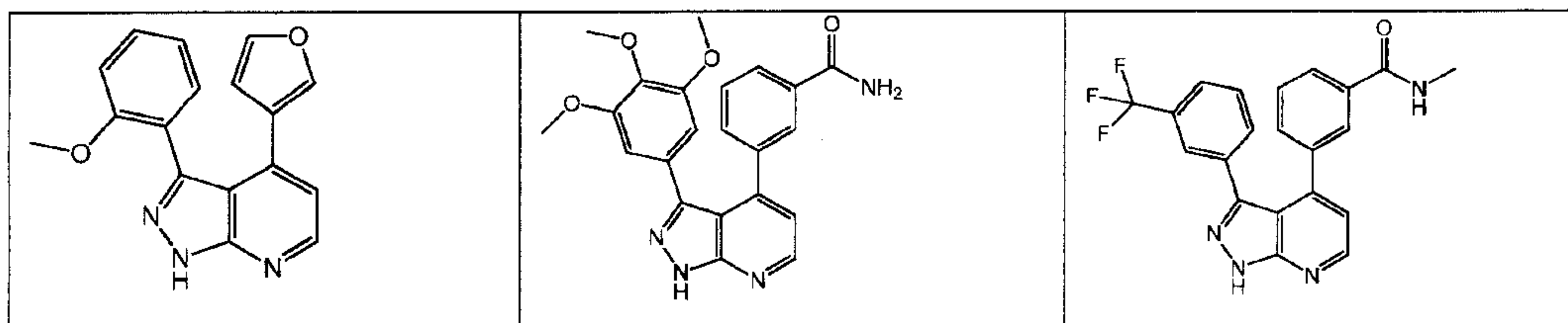


$n$  is 0, 1, or 2; and

$m$  is 0, 1, or 2;

provided that the compound is not a compound selected from the following list ("Exclusion List"):

|                                                                                     |                                                                                      |                                                                                       |
|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
|  |  |  |
|  |  |  |
|  |  |  |

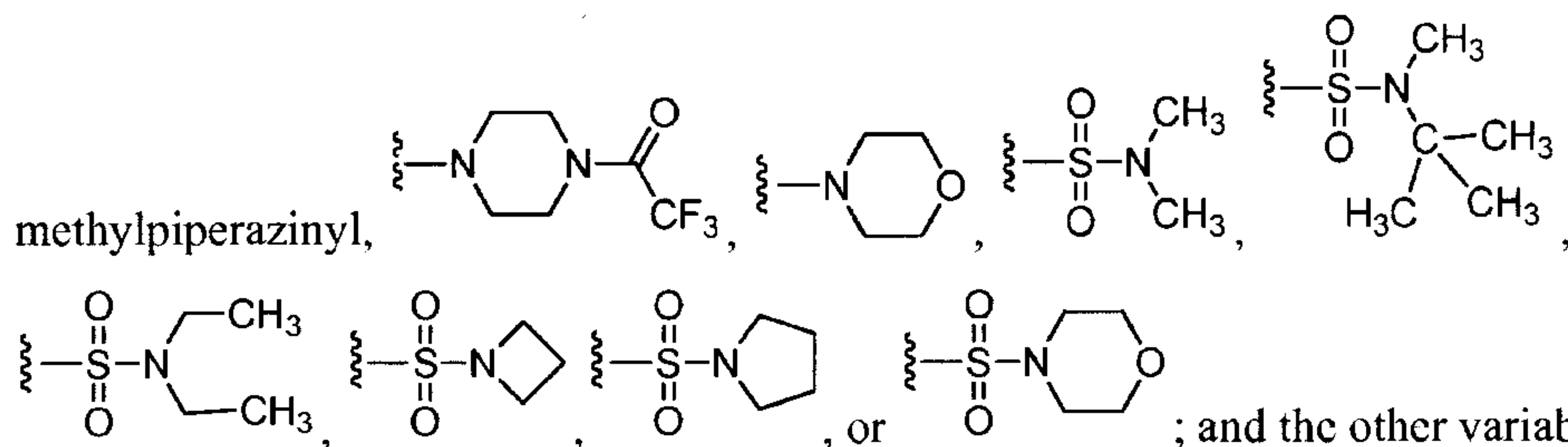


and further provided that at least one of  $L^1$ ,  $R^1$ , and  $R^2$  is not H.

[0021] In an aspect of the invention, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List and at least one of  $L^1$ ,  $R^1$ , and  $R^2$  is not H.

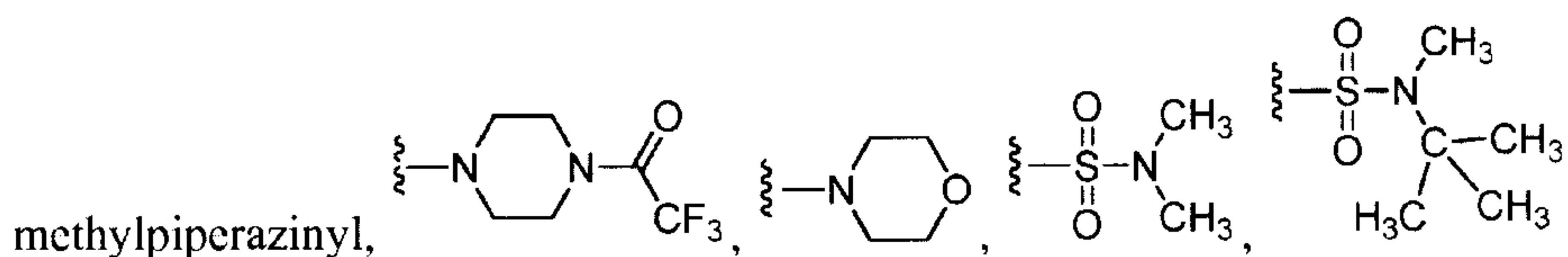
[0022] In one embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH;  $L^1$  is H or F; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List and at least one of  $R^1$  and  $R^2$  is not H.

[0023] In another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH;  $L^1$  is thienyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,



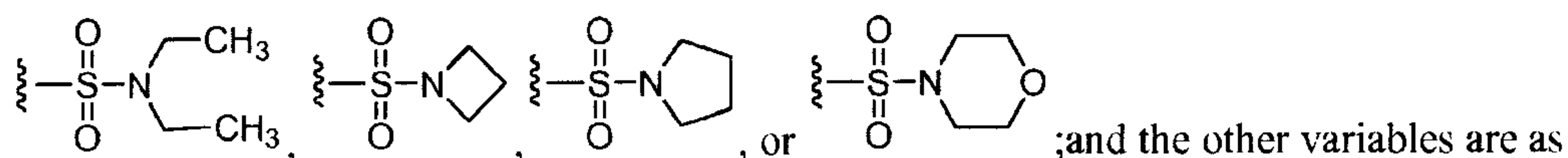
defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

[0024] In still another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH;  $L^1$  is phenyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,



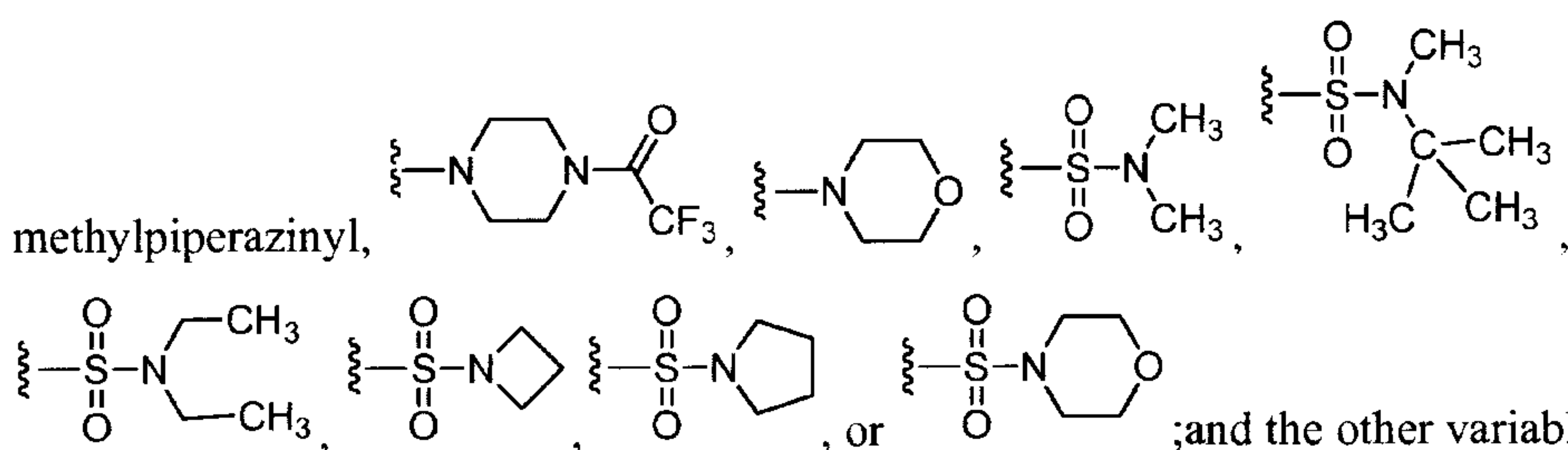
WO 2014/093383

PCT/US2013/074191



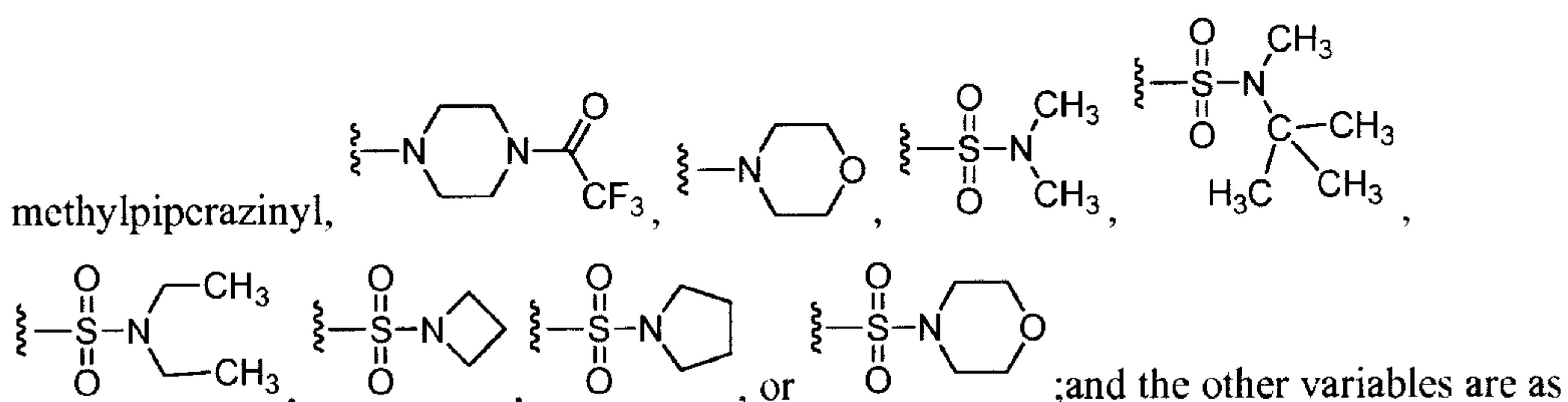
defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

[0025] In yet another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup> is pyrrolyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,



defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

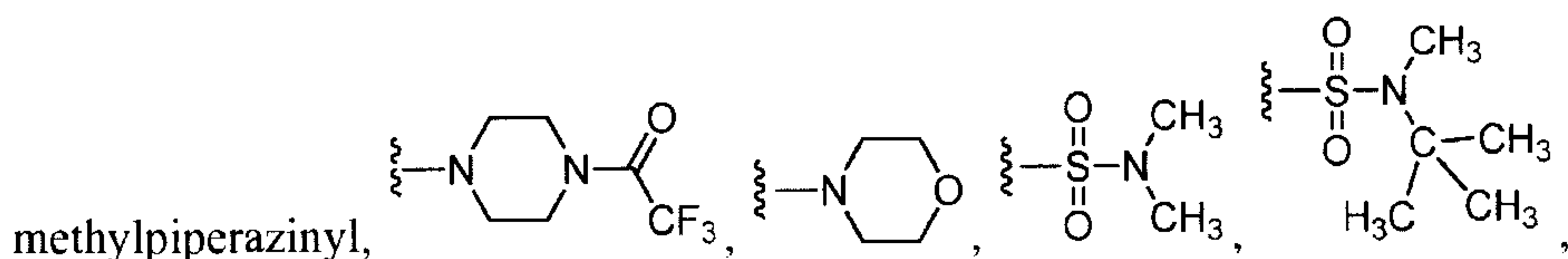
[0026] In still another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup> is pyridyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,



defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

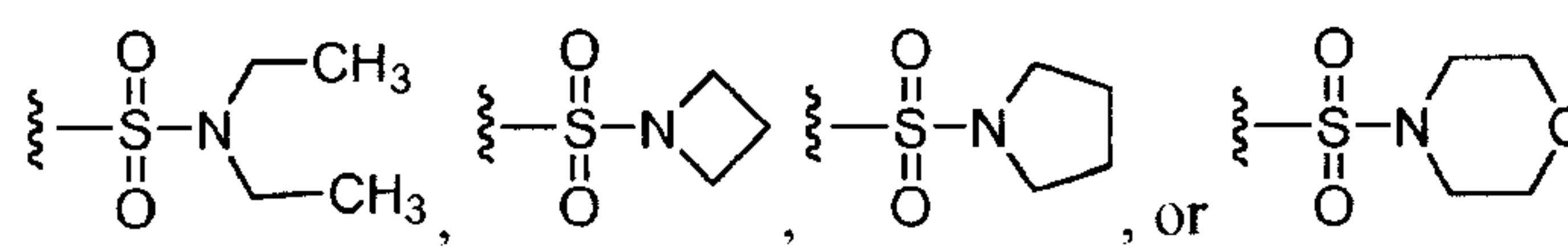
[0027] In another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup>

is optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

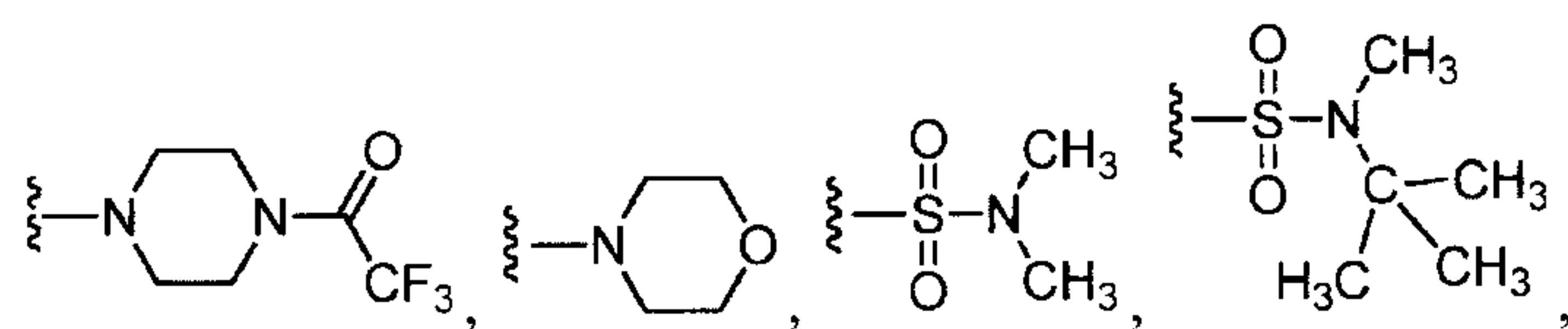
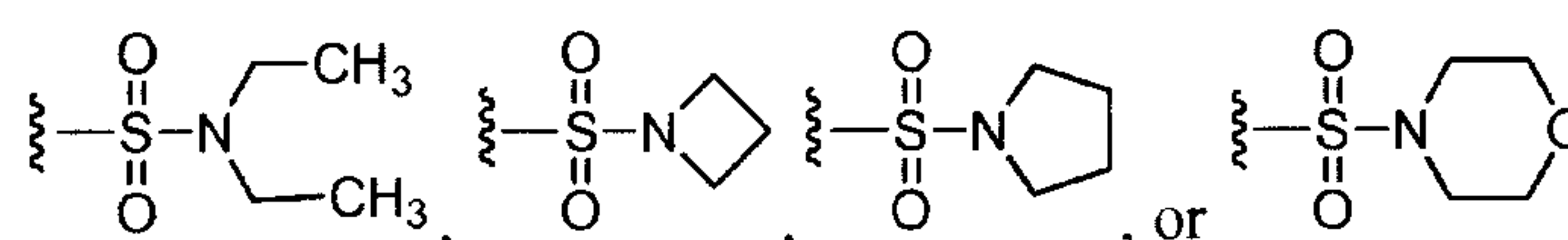


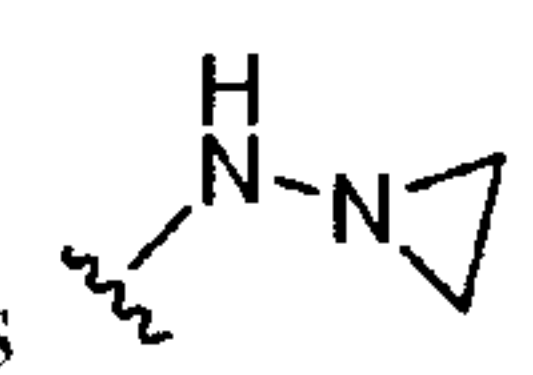
WO 2014/093383

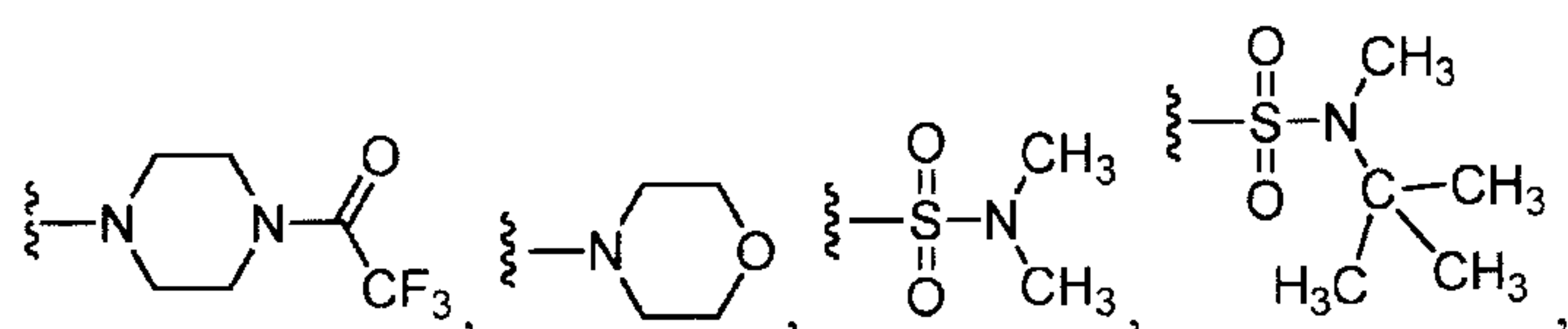
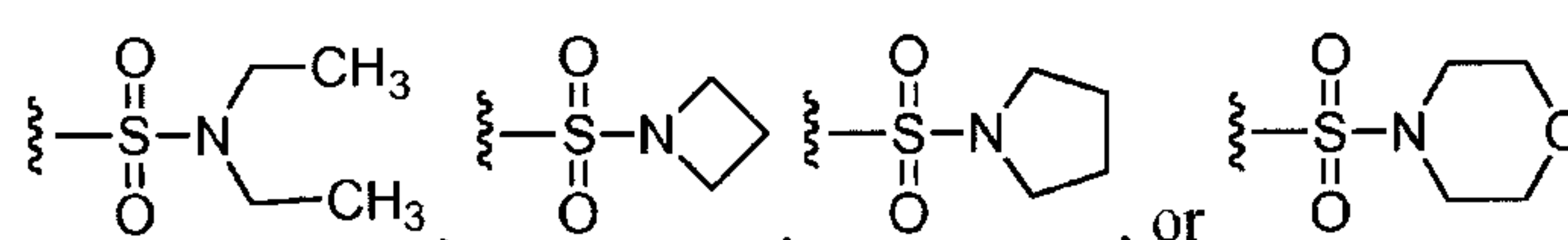
PCT/US2013/074191

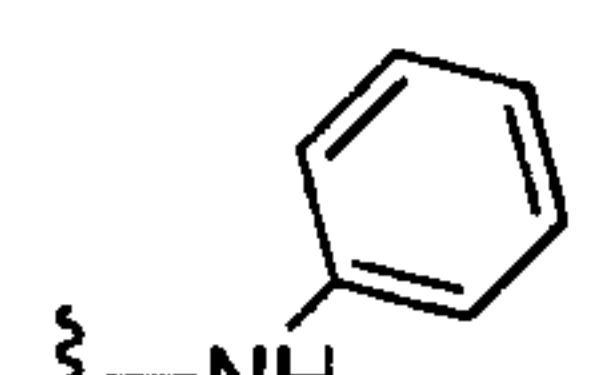

 ;and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

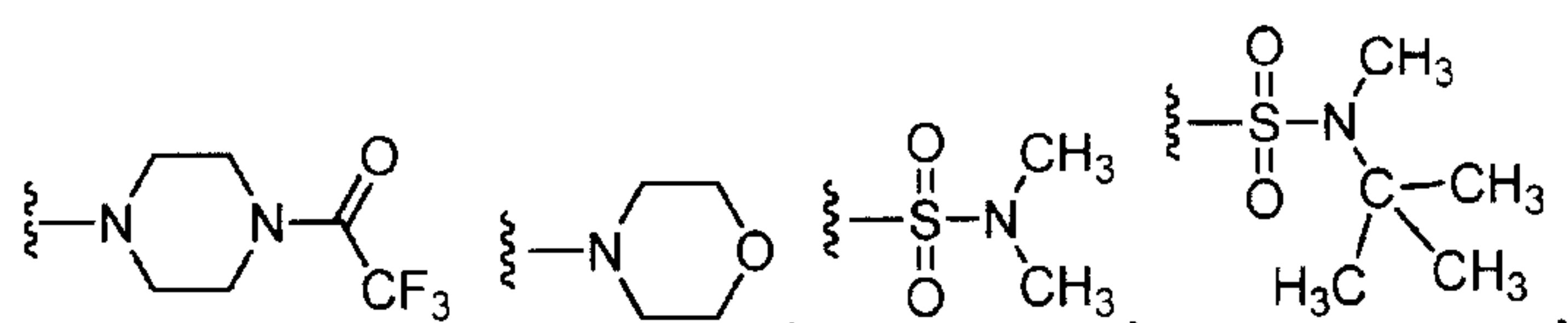
[0028] In yet another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup> is piperazinyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

methypiperazinyl,
 
  

 ;and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

[0029] In another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup> is  optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

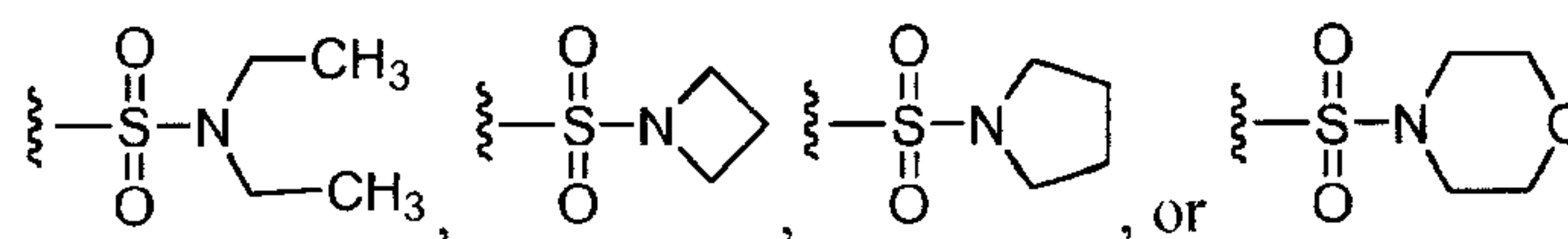
methypiperazinyl,
 
  

 ;and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

[0030] In another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup> is  optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

methypiperazinyl,
 

WO 2014/093383

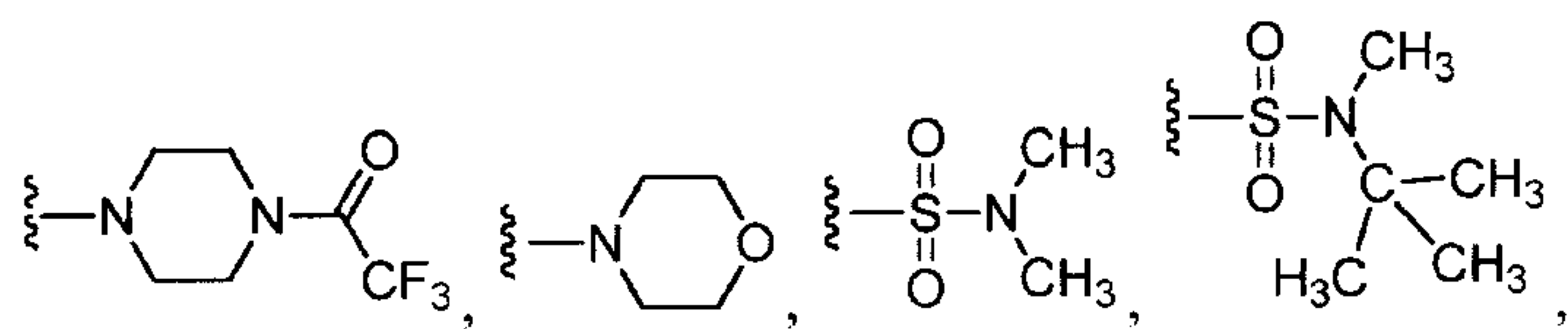
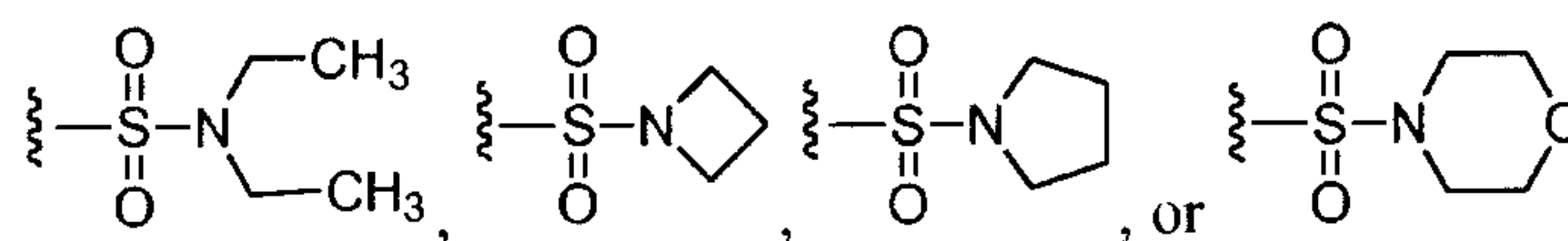
PCT/US2013/074191


 ; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

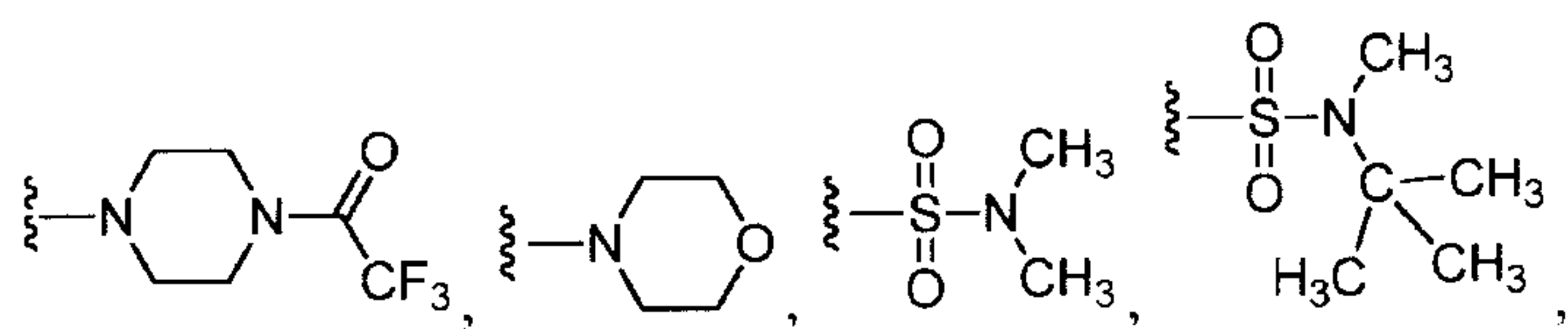
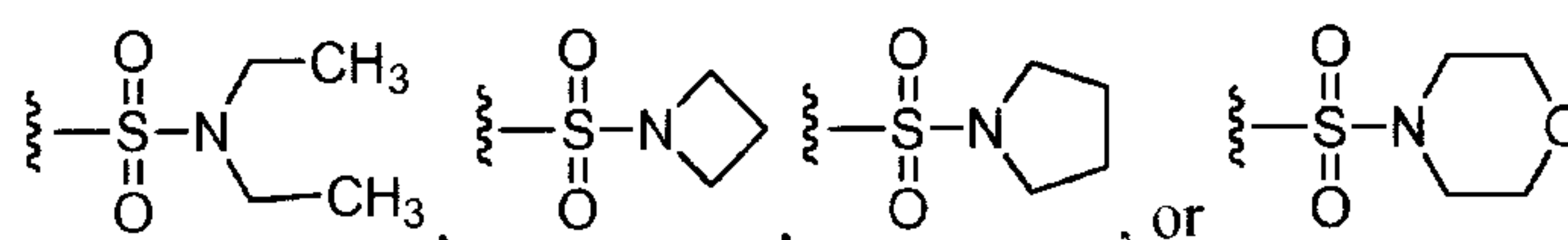
[0031] In an aspect of the invention, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List and at least one of  $L^1$ ,  $R^1$ , and  $R^2$  is not H.

[0032] In one embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N;  $L^1$  is H or F; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List and at least one of  $R^1$  and  $R^2$  is not H.

[0033] In another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N;  $L^1$  is thienyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

methylpiperazinyl, , 
 ; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

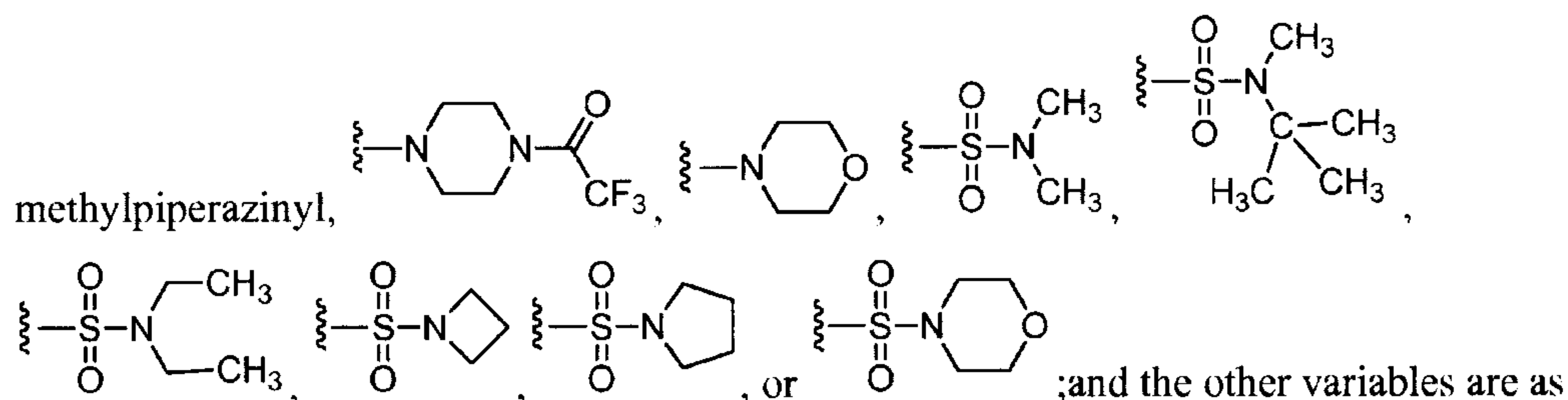
[0034] In still another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N;  $L^1$  is phenyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

methylpiperazinyl, , 
 ; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

WO 2014/093383

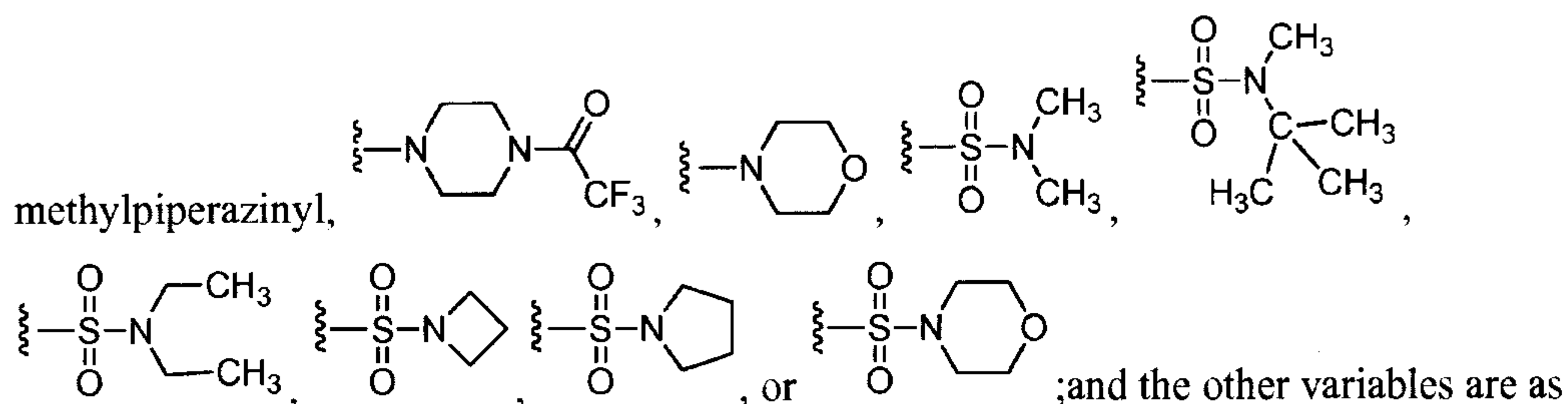
PCT/US2013/074191

[0035] In yet another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N; L<sup>1</sup> is pyrrolyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,



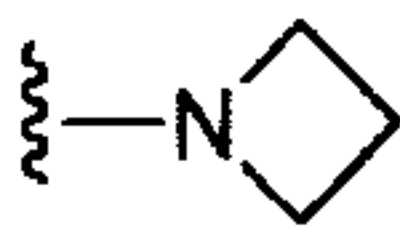
defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

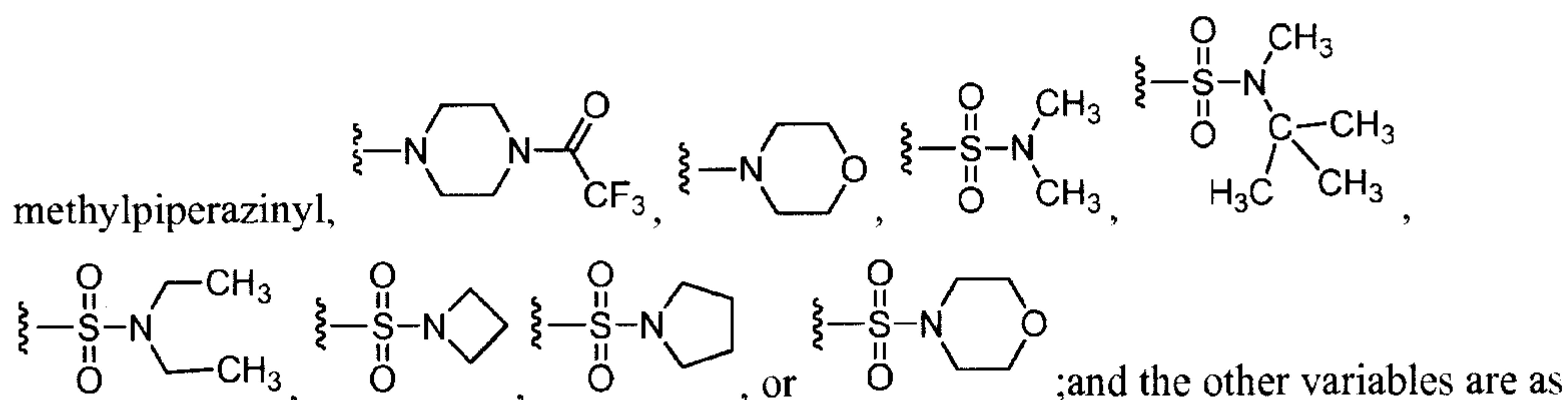
[0036] In still another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N; L<sup>1</sup> is pyridyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,



defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

[0037] In another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N; L<sup>1</sup> is

 optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,



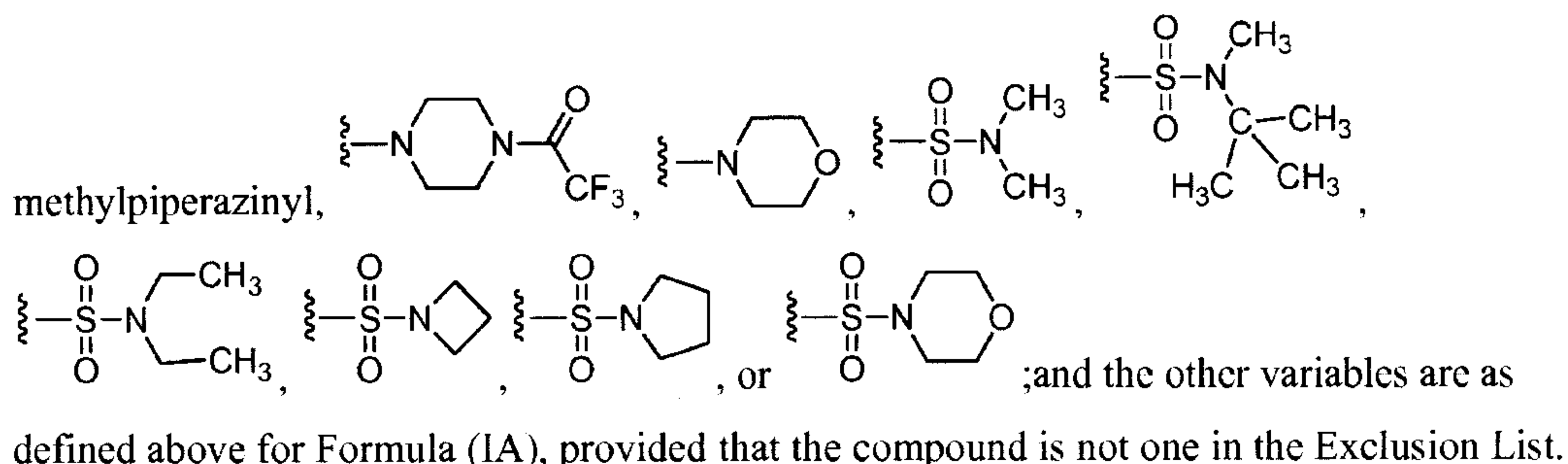
defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

[0038] In yet another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N; L<sup>1</sup> is

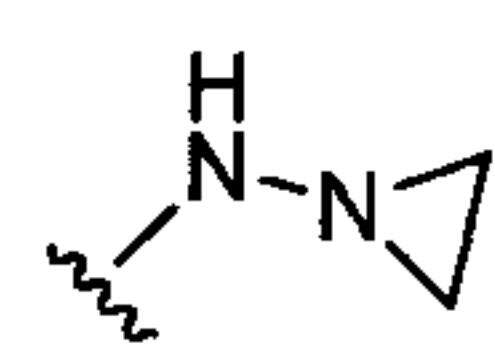
WO 2014/093383

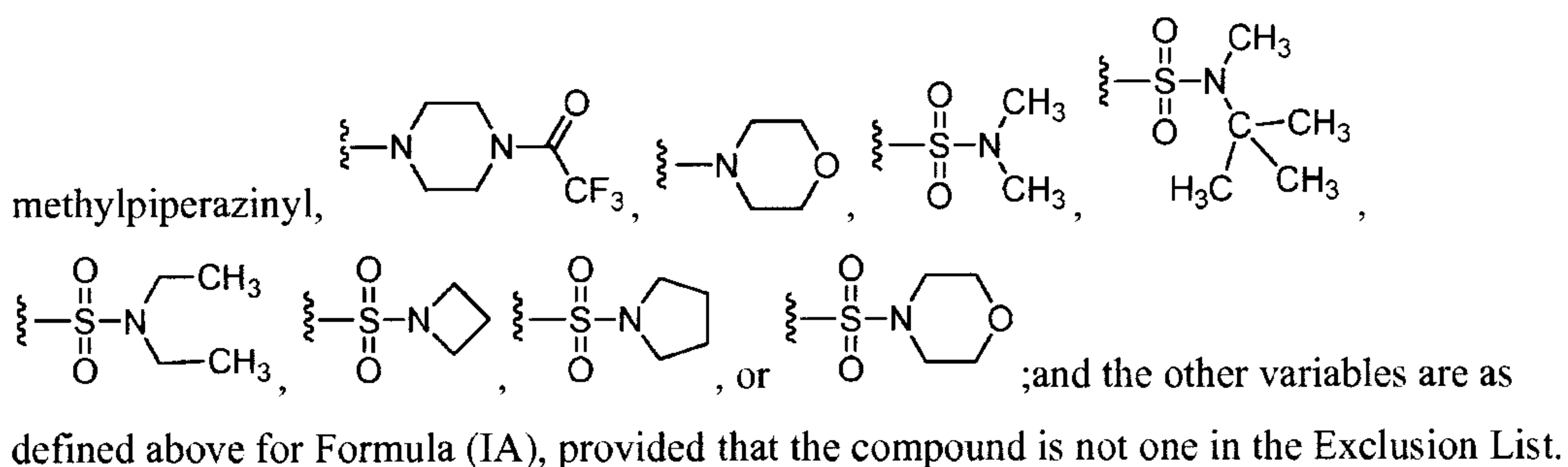
PCT/US2013/074191

piperazinyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

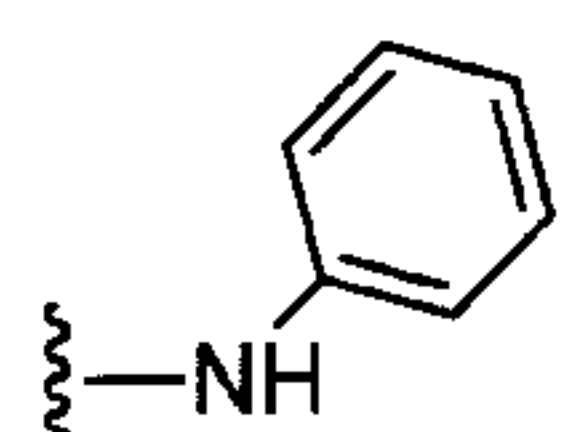
methylpiperazinyl, ; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

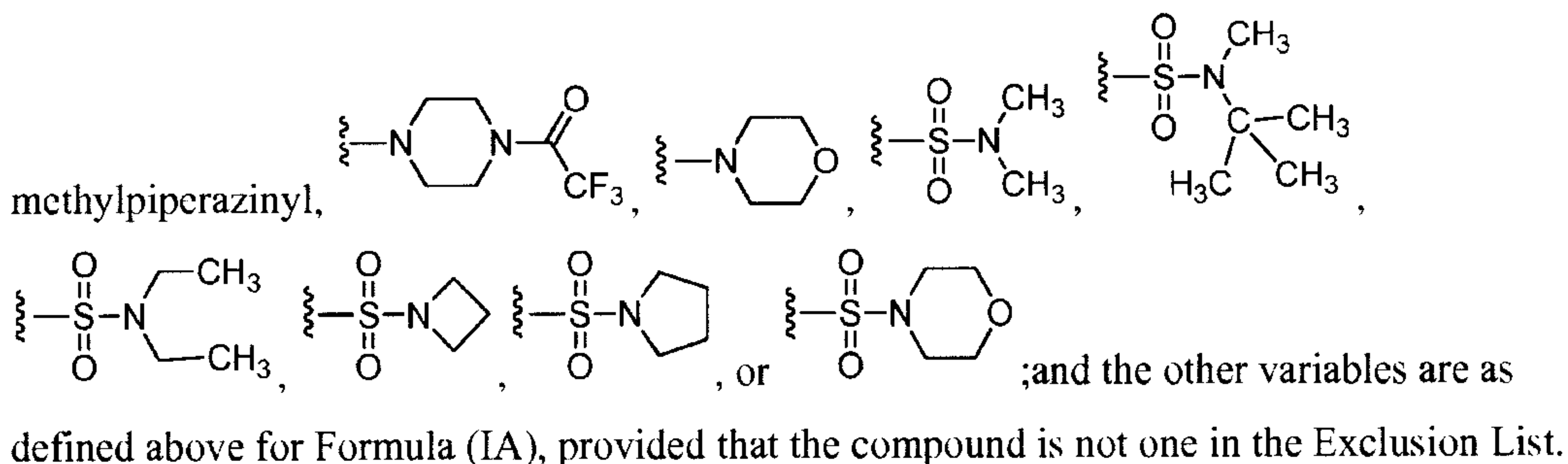
[0039] In another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N; L<sup>1</sup> is

 optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

methylpiperazinyl, ; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

[0040] In another embodiment of this aspect, compounds of the present invention are described by Formula (IA) and pharmaceutically acceptable salts thereof, wherein X is N; L<sup>1</sup> is

 optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

methylpiperazinyl, ; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

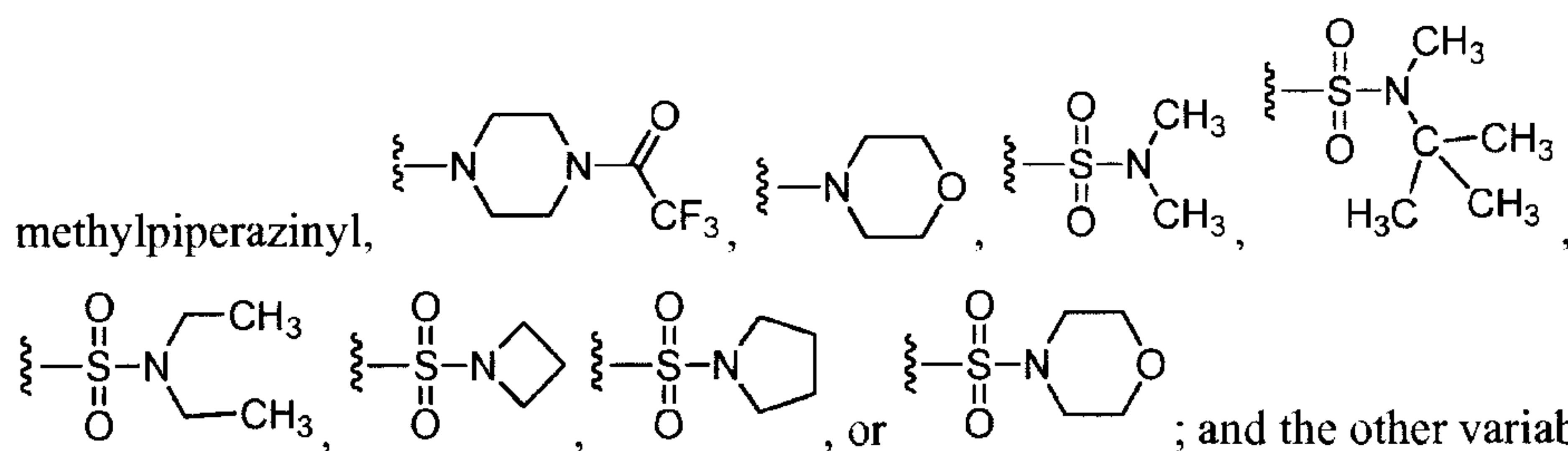
WO 2014/093383

PCT/US2013/074191

[0041] In an aspect of the invention, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH; and the other variables are as defined above for Formula (IB), provided that the compound is not one in the Exclusion List and at least one of  $L^1$ ,  $R^1$ , and  $R^2$  is not H.

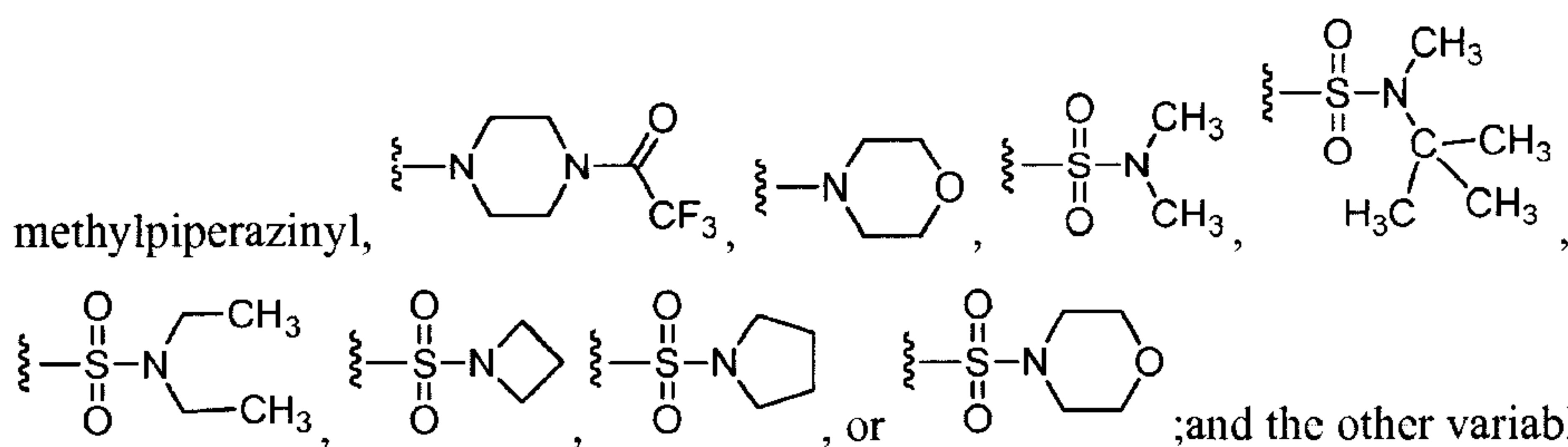
[0042] In one embodiment of this aspect, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH;  $L^1$  is H or F; and the other variables are as defined above for Formula (IB), provided that the compound is not one in the Exclusion List and at least one of  $R^1$  and  $R^2$  is not H.

[0043] In another embodiment of this aspect, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH;  $L^1$  is thienyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,



defined above for Formula (IB), provided that the compound is not one in the Exclusion List.

[0044] In still another embodiment of this aspect, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH;  $L^1$  is phenyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

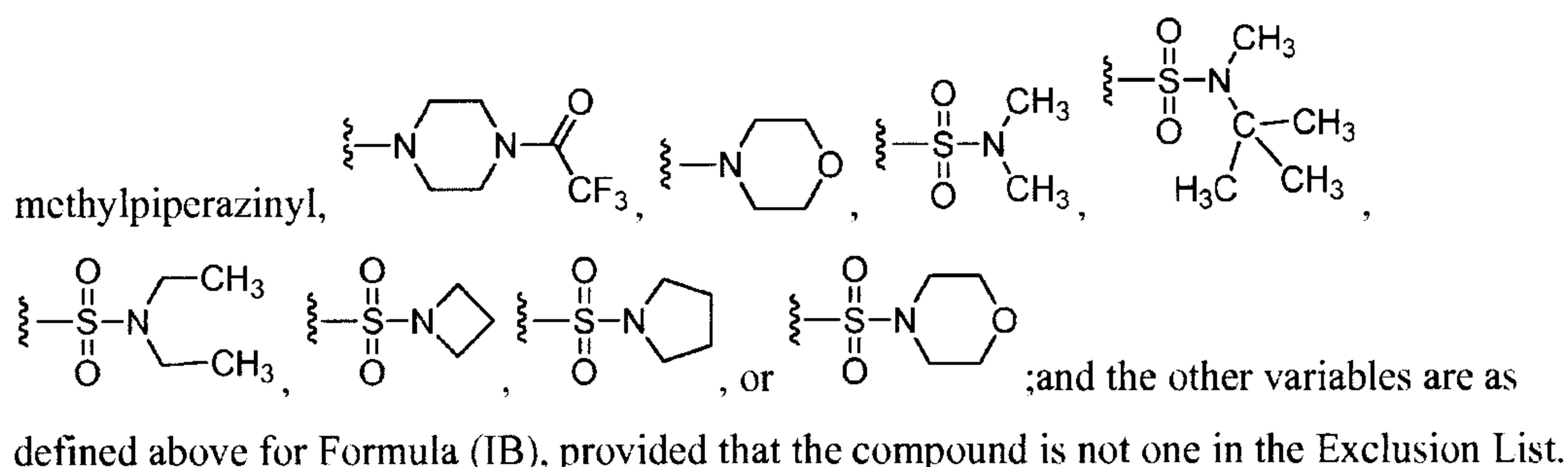


defined above for Formula (IB), provided that the compound is not one in the Exclusion List.

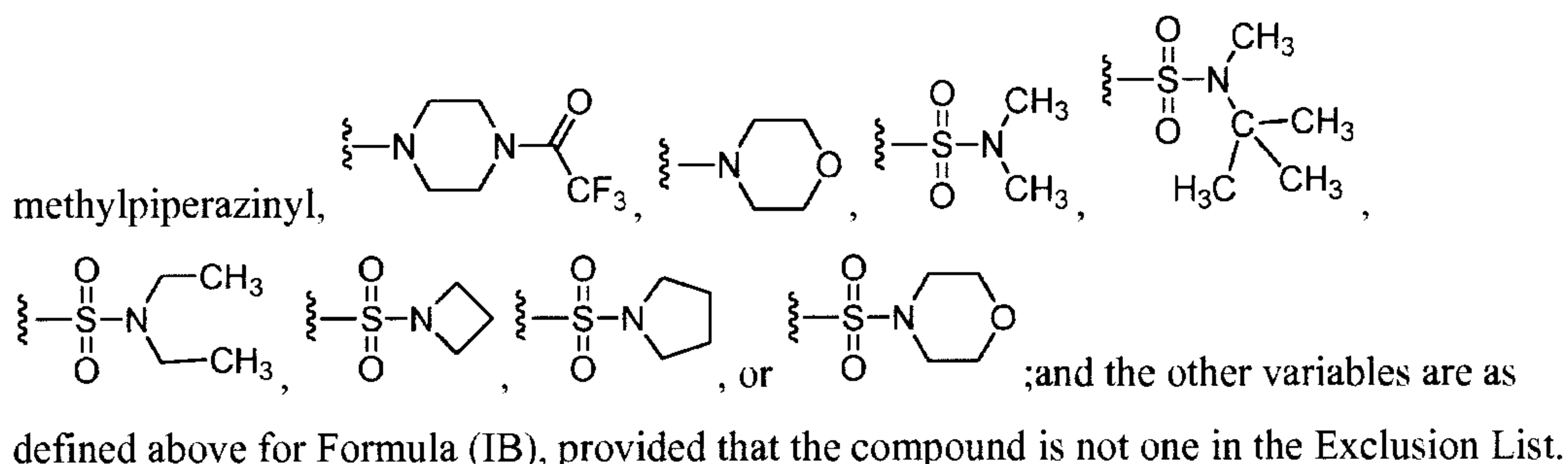
[0045] In yet another embodiment of this aspect, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH;  $L^1$  is pyrrolyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl,

WO 2014/093383

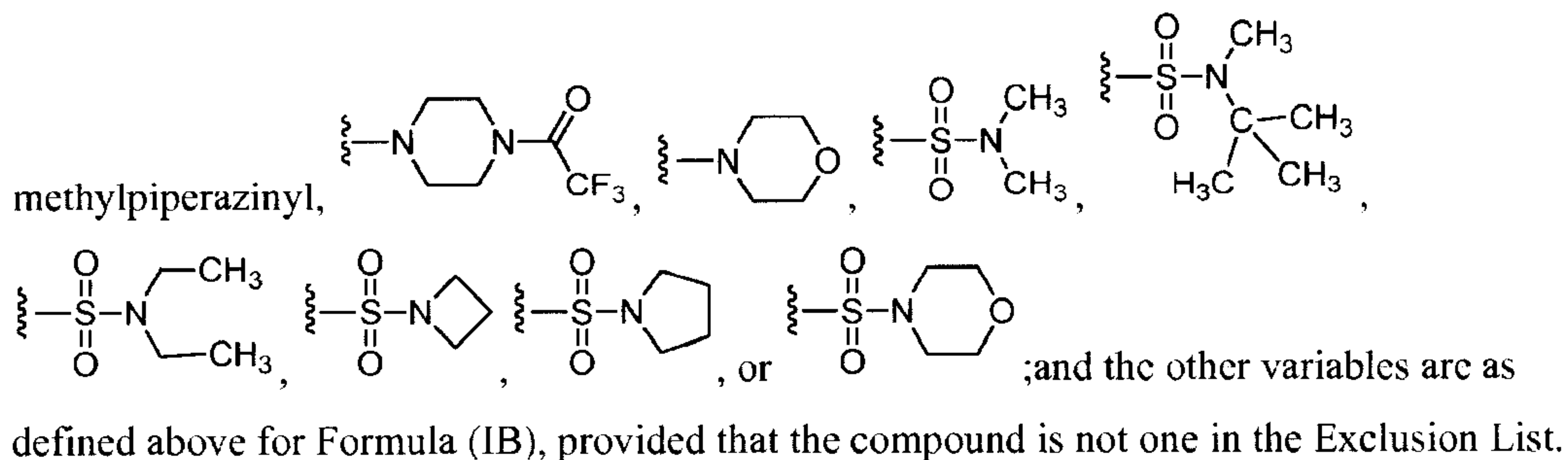
PCT/US2013/074191



[0046] In still another embodiment of this aspect, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup> is pyridyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyll,



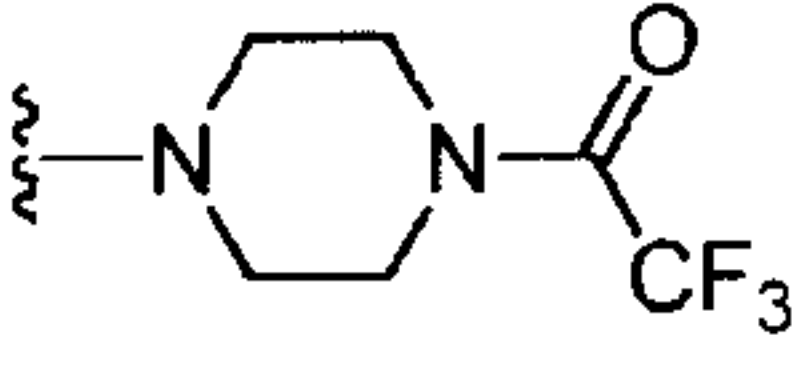
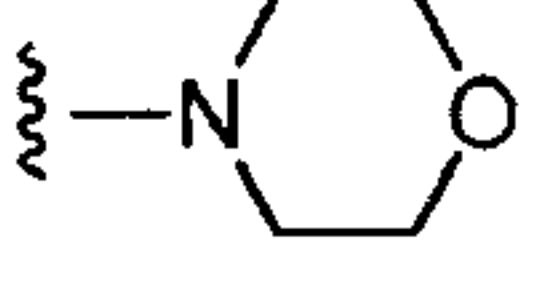
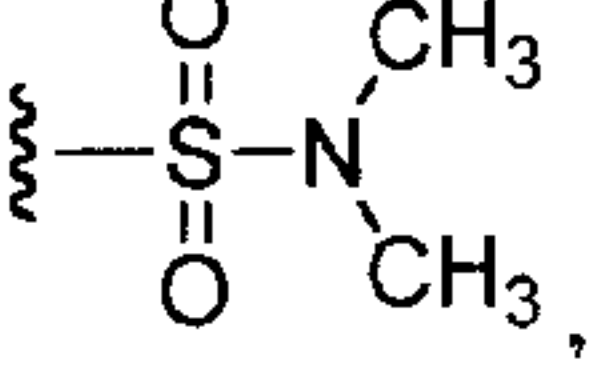
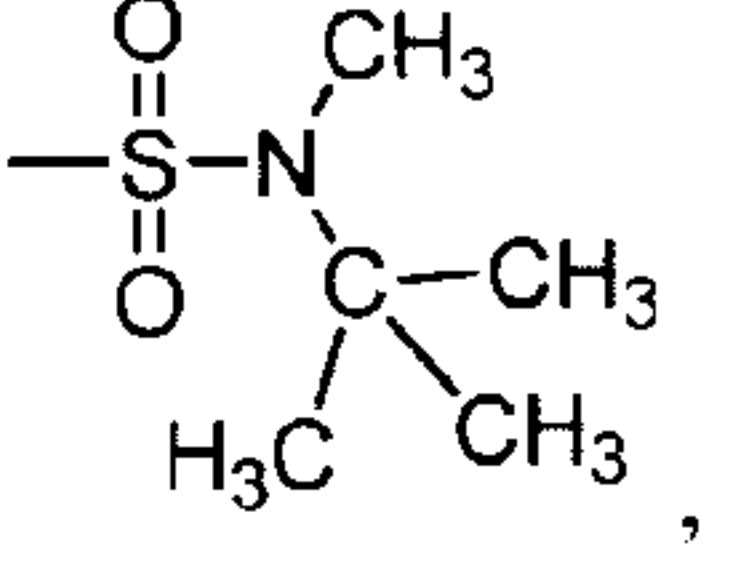
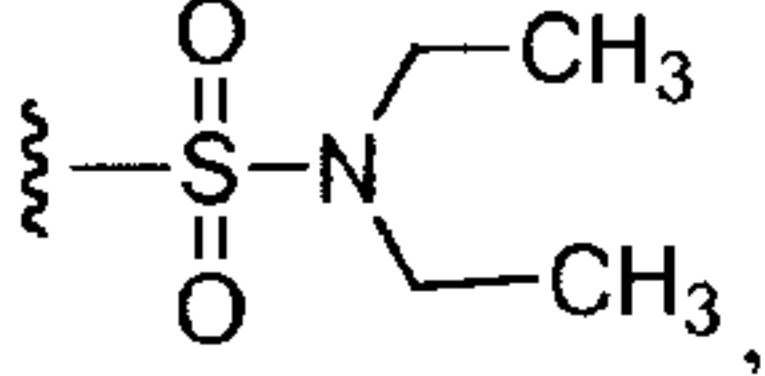
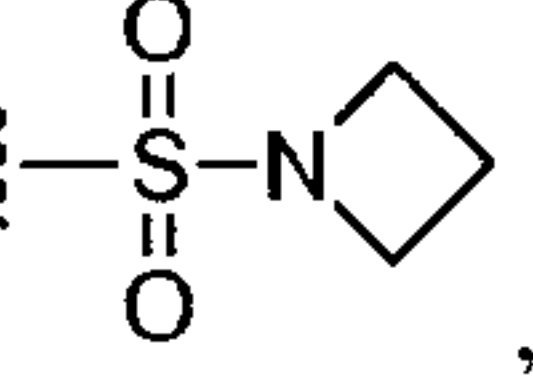
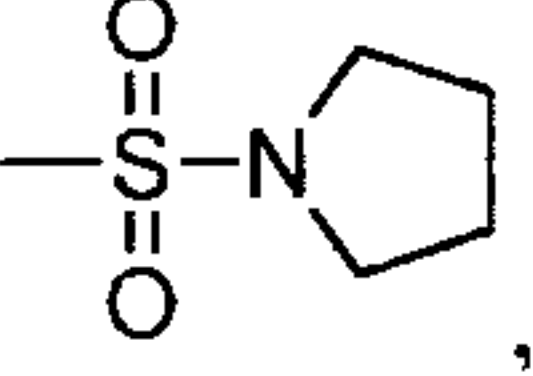
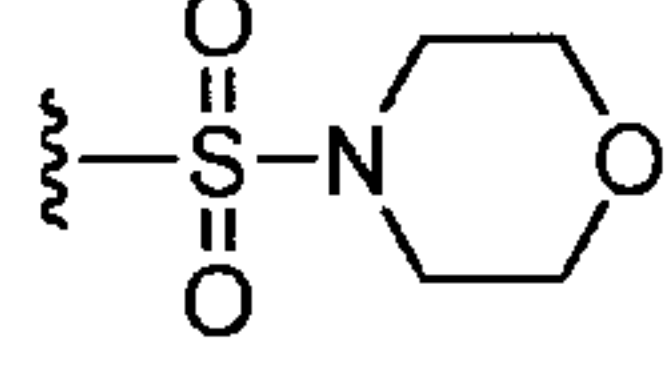
[0047] In another embodiment of this aspect, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup> is optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyll,



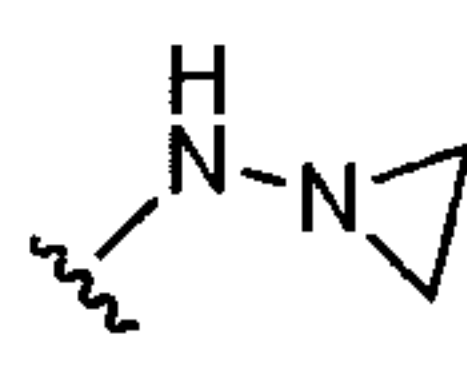
[0048] In yet another embodiment of this aspect, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup> is piperazinyll optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyll,

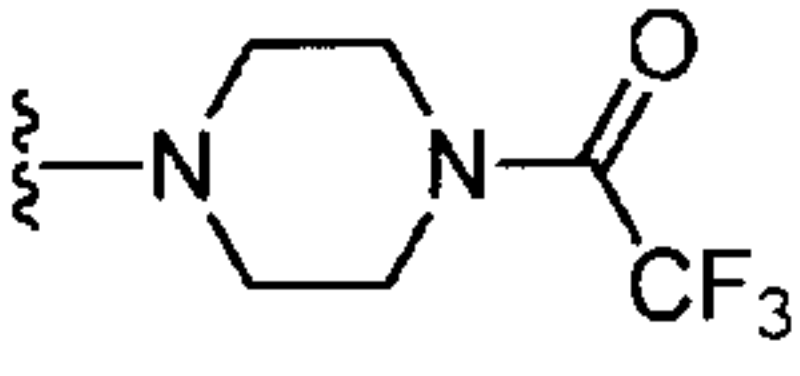
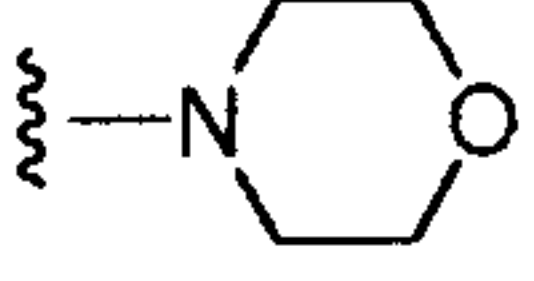
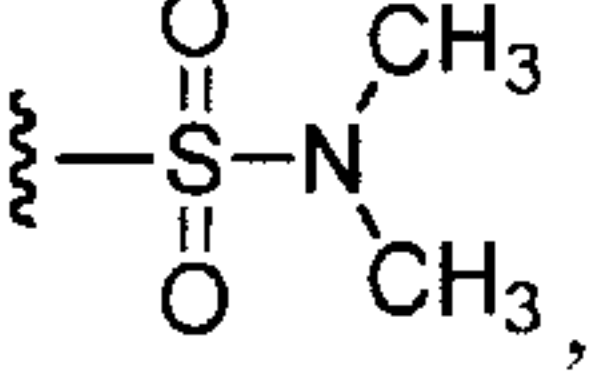
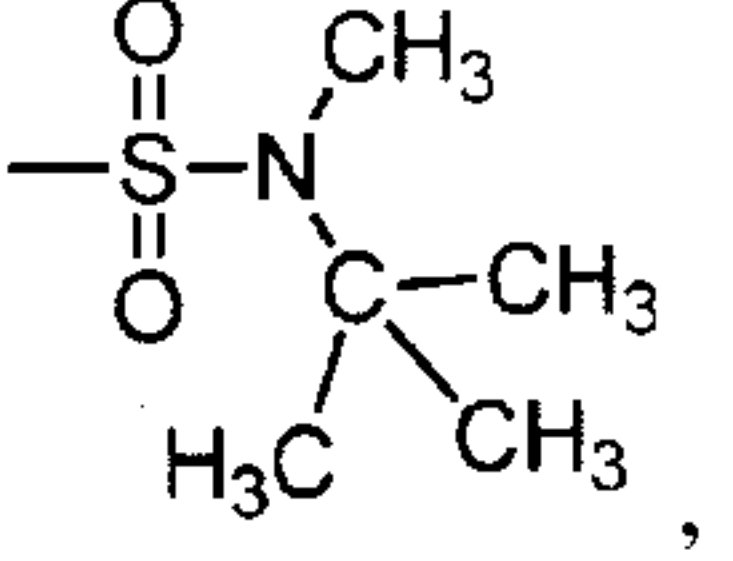
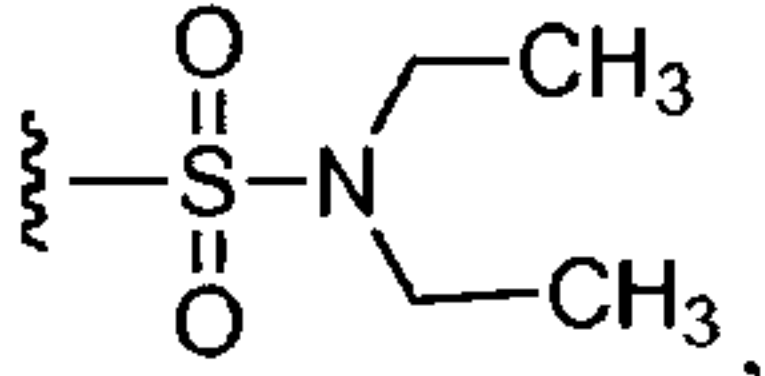
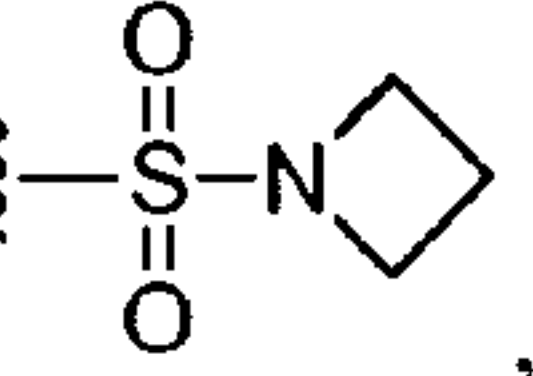
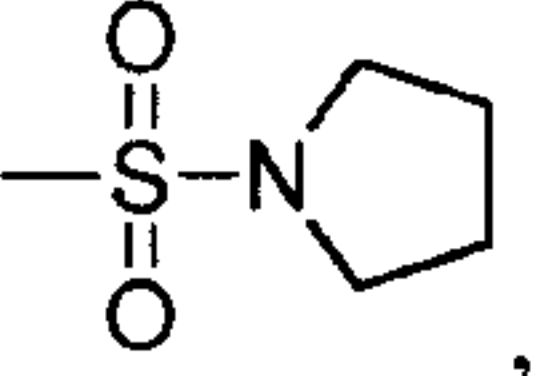
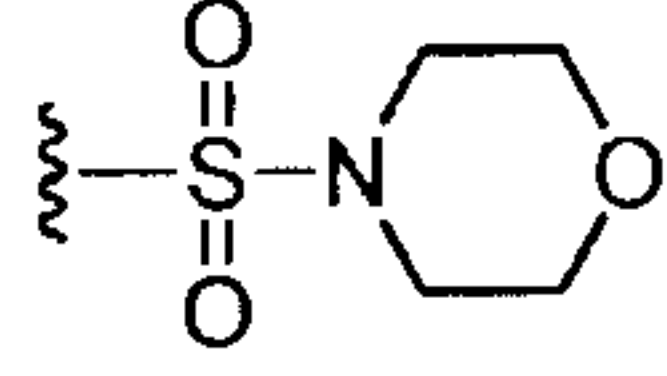
WO 2014/093383

PCT/US2013/074191

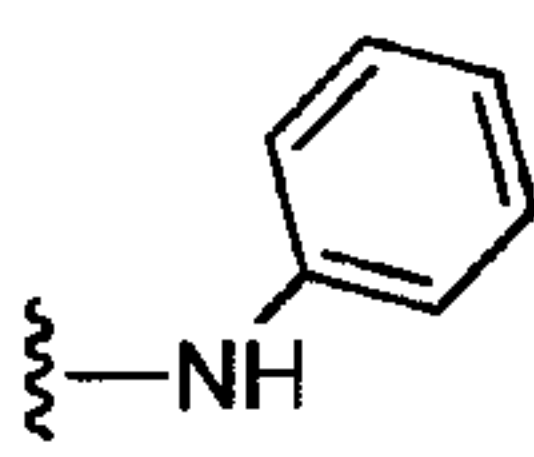
methylnpiperazinyll, , , , , , , , or ; and the other variables are as defined above for Formula (IB), provided that the compound is not one in the Exclusion List.

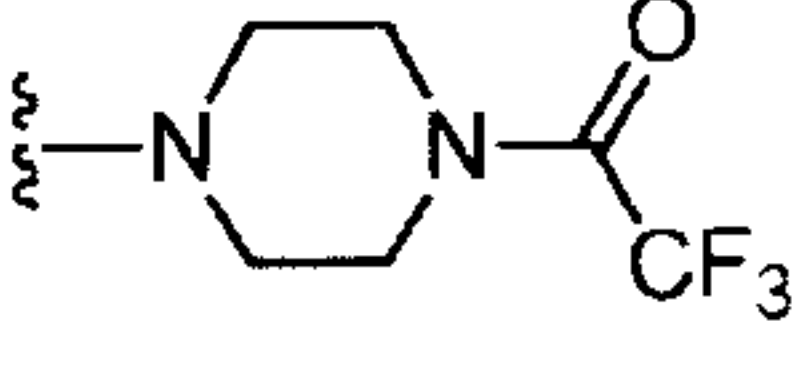
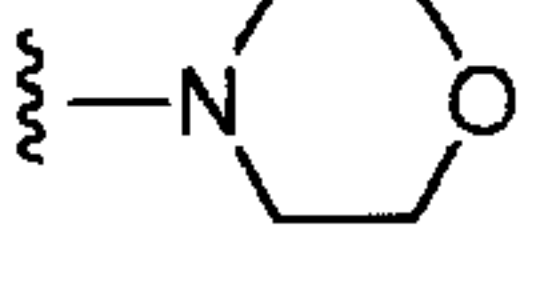
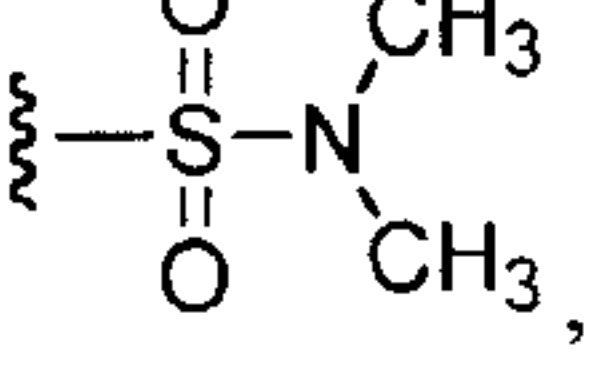
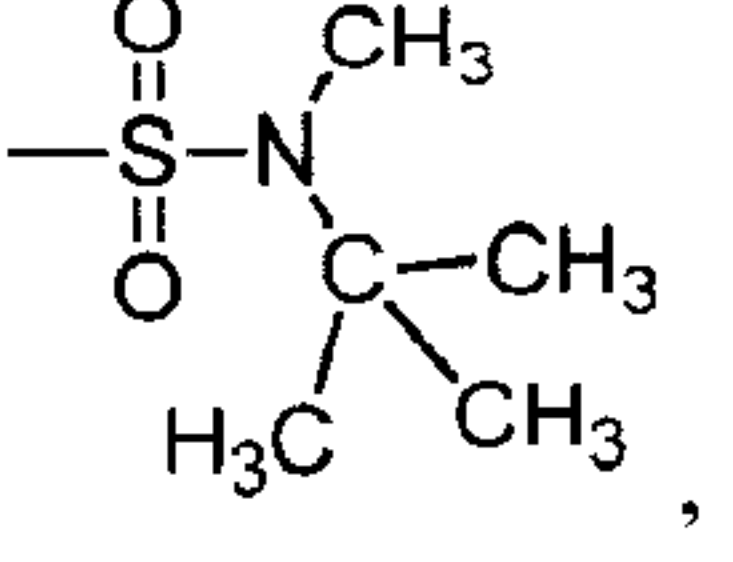
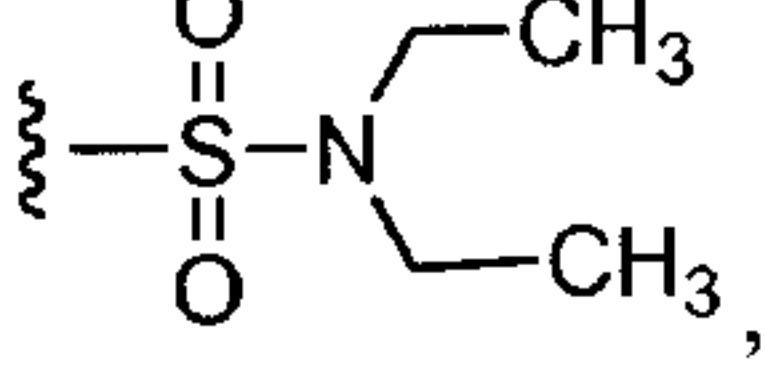
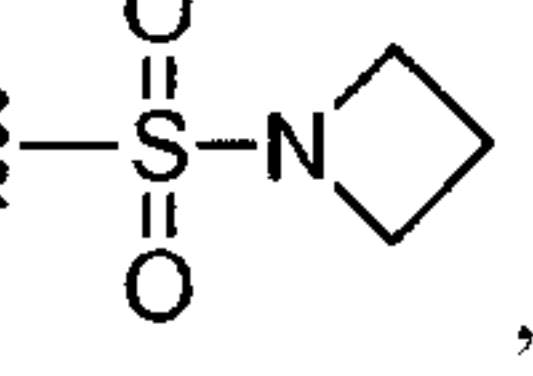
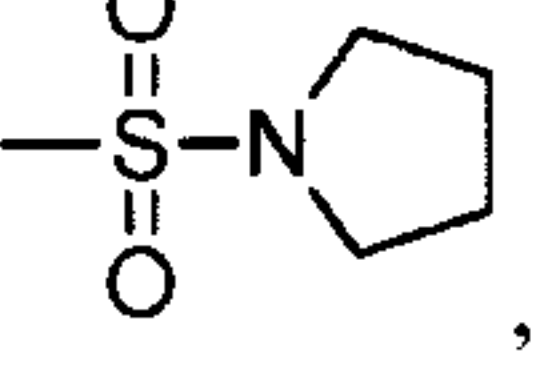
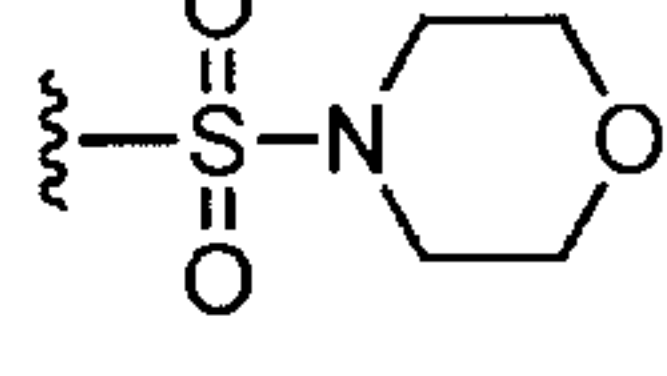
[0049] In another embodiment of this aspect, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup>

is  optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyll,

methylnpiperazinyll, , , , , , , , or ; and the other variables are as defined above for Formula (IA), provided that the compound is not one in the Exclusion List.

[0050] In another embodiment of this aspect, compounds of the present invention are described by Formula (IB) and pharmaceutically acceptable salts thereof, wherein X is CH; L<sup>1</sup>

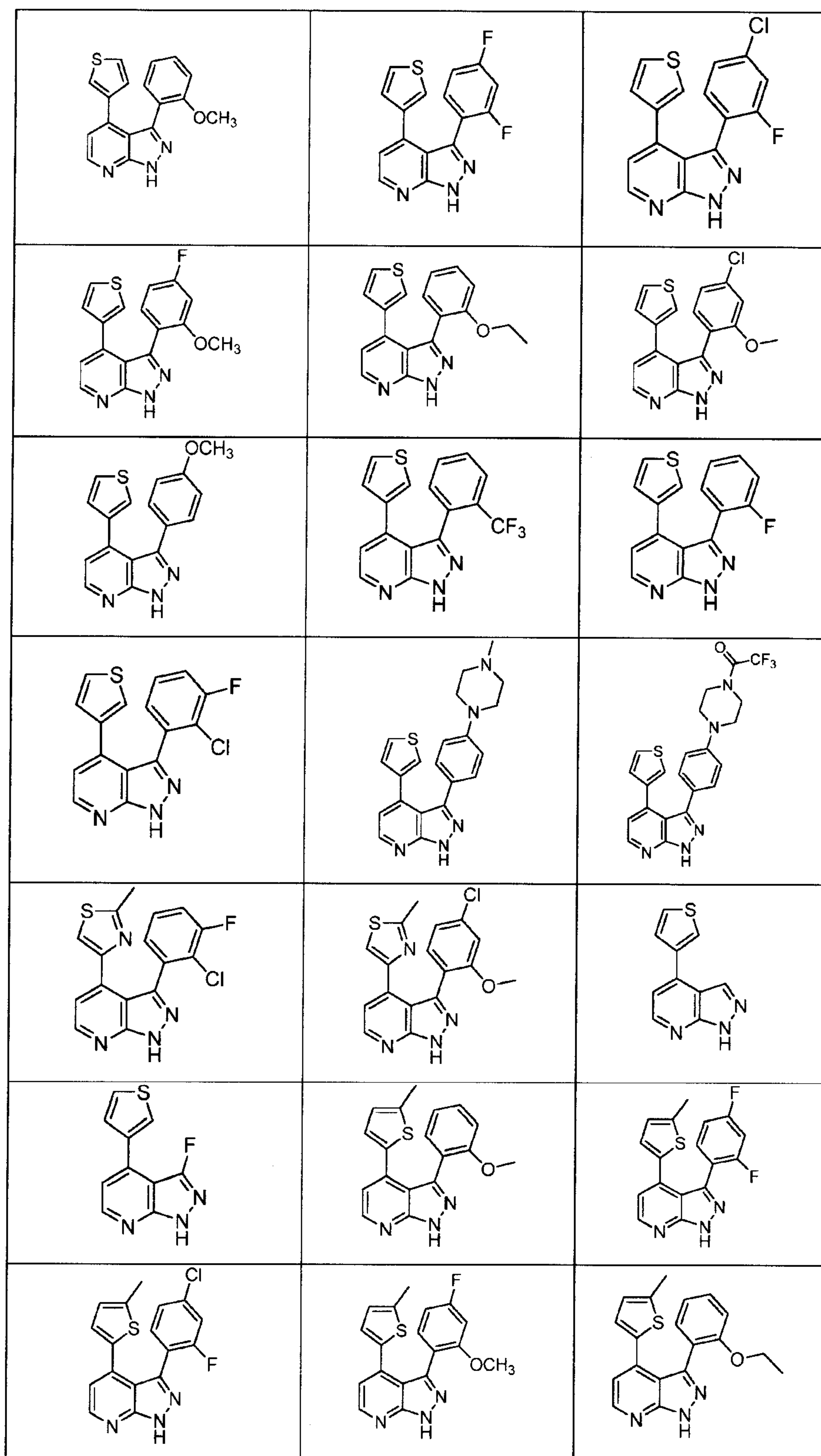
is  optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyll,

methylnpiperazinyll, , , , , , , , or ; and the other variables are as defined above for Formula (IB), provided that the compound is not one in the Exclusion List.

[0051] Compounds of the present invention include:

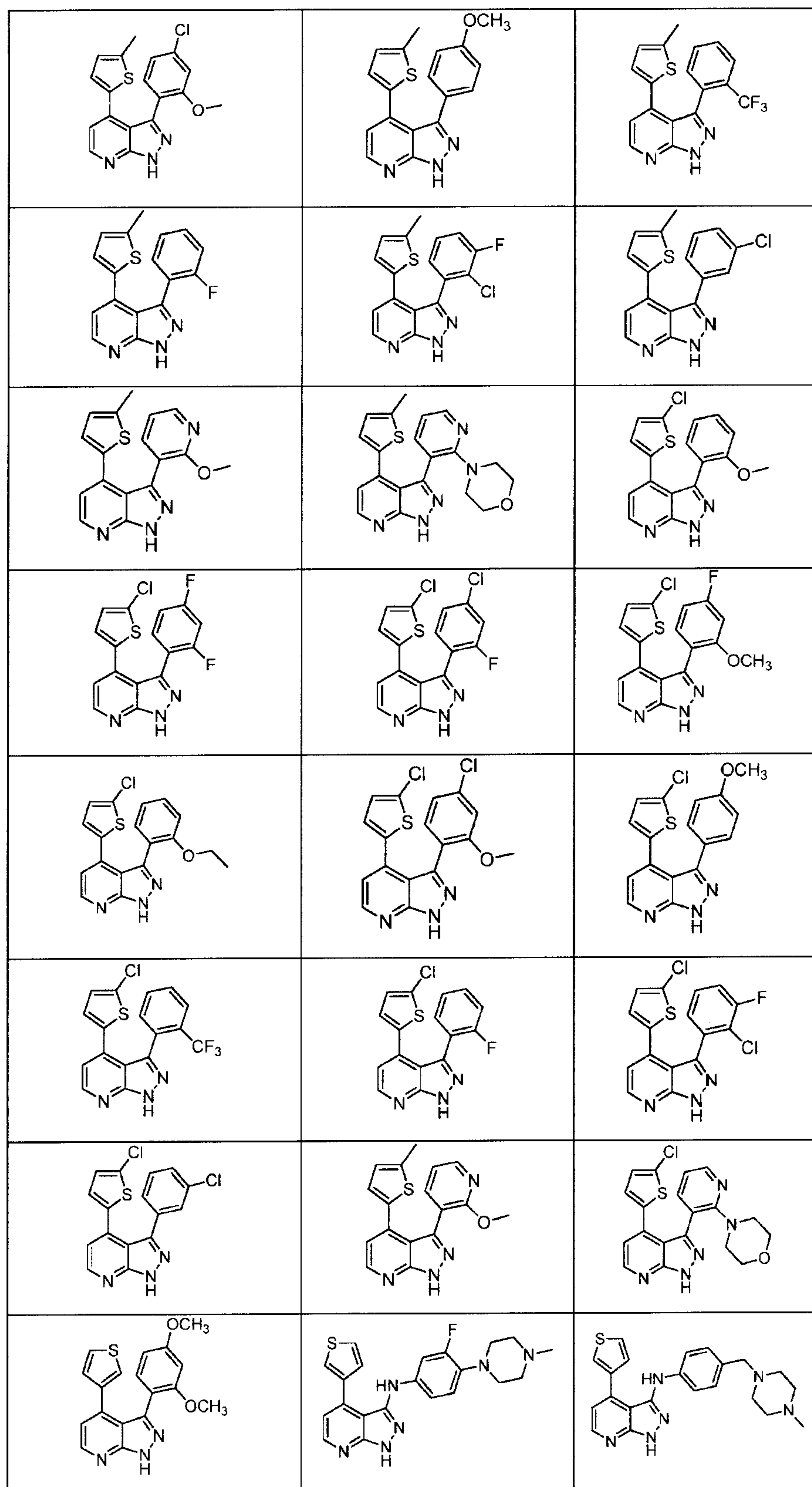
WO 2014/093383

PCT/US2013/074191



WO 2014/093383

PCT/US2013/074191



WO 2014/093383

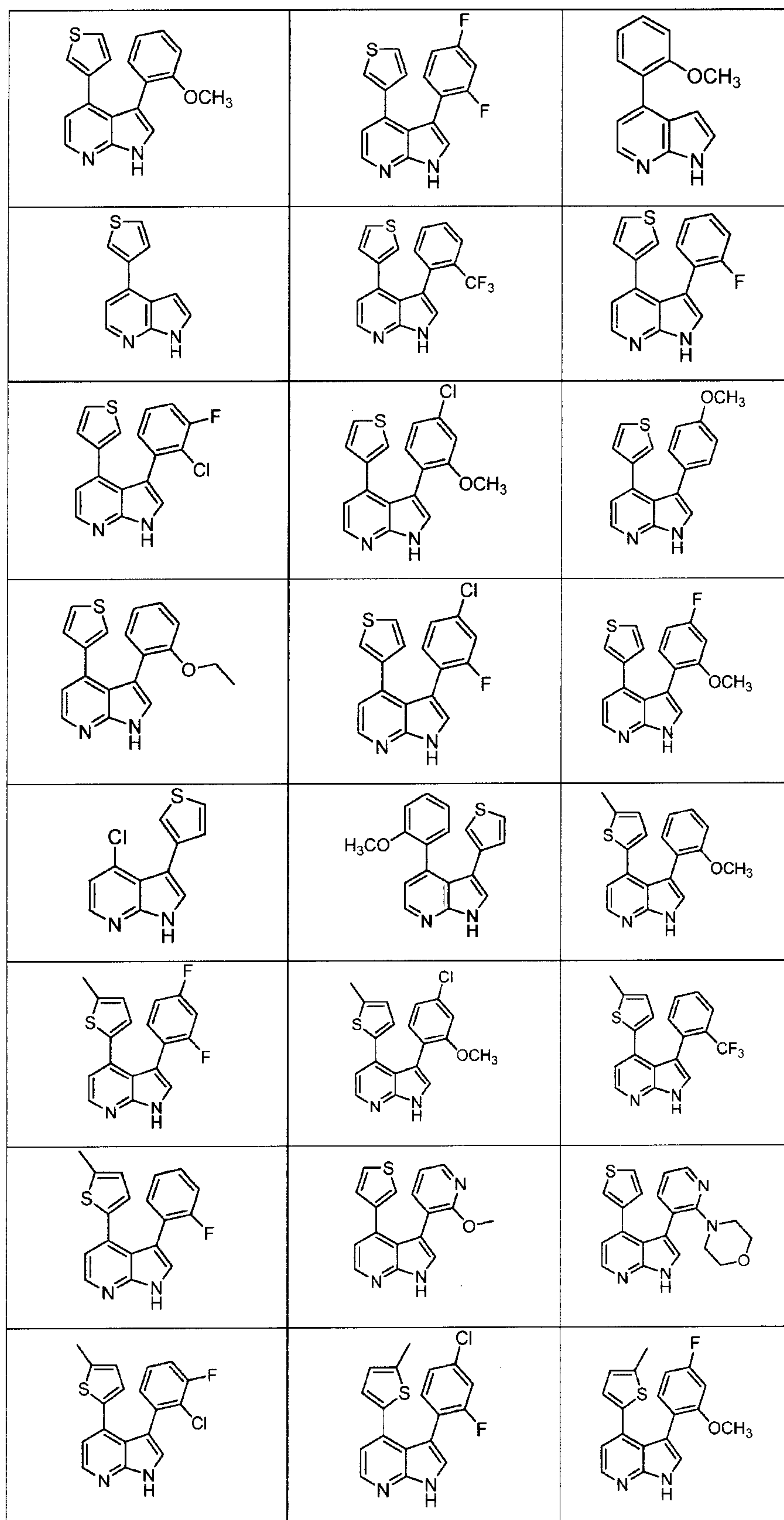
PCT/US2013/074191

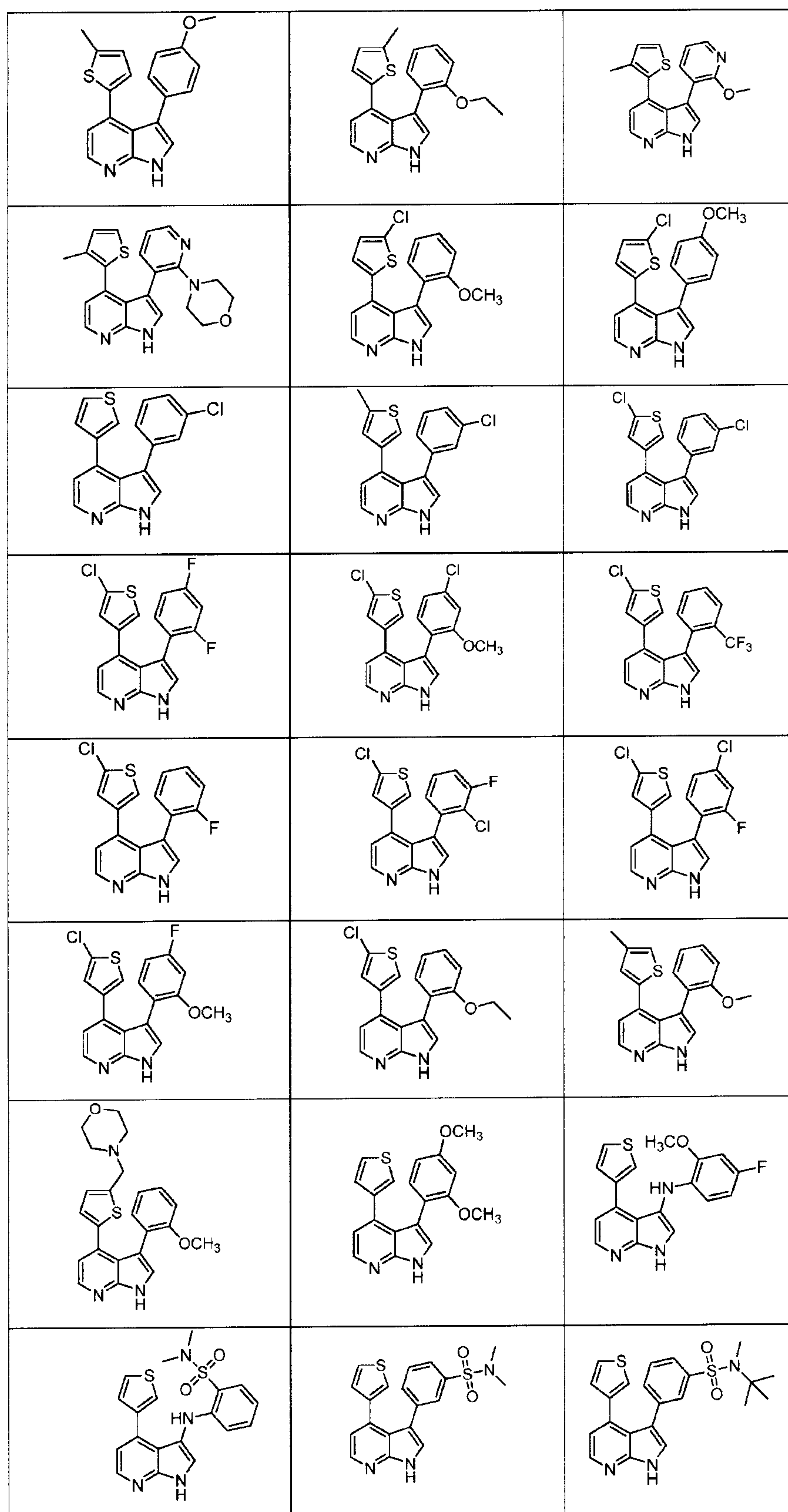
|  |  |  |
|--|--|--|
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

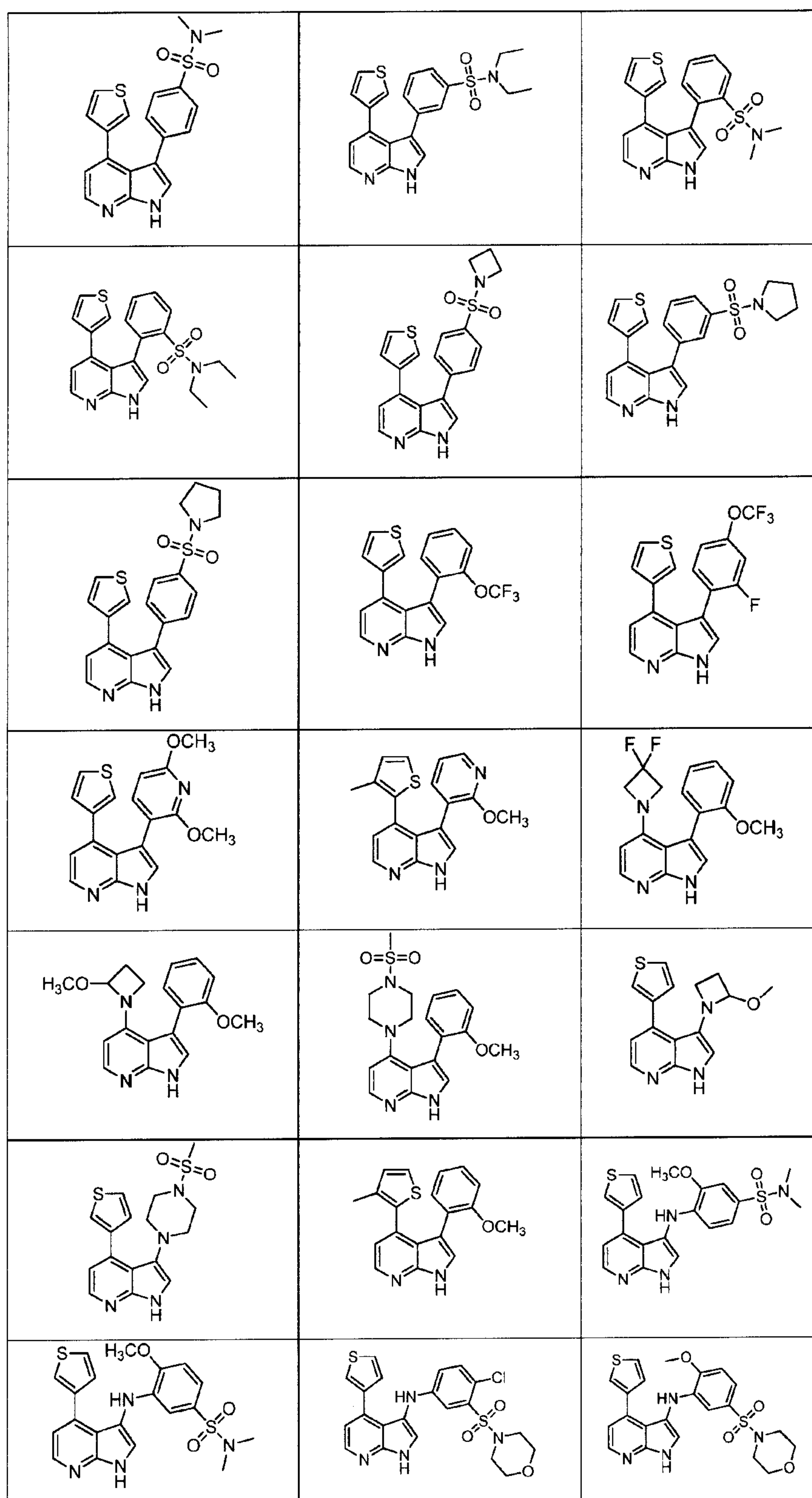
[0052] Other compounds of the present invention include:

WO 2014/093383

PCT/US2013/074191

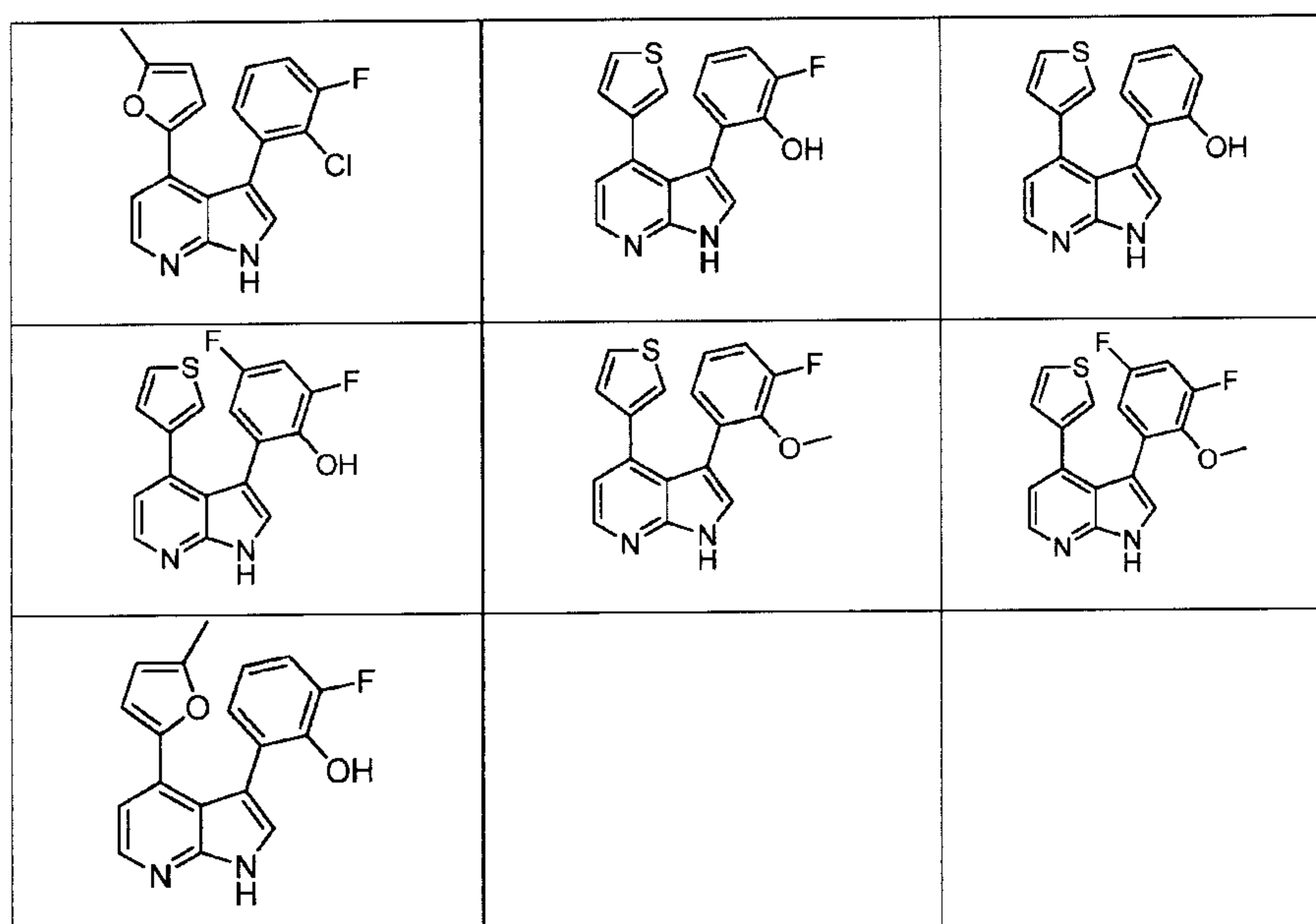




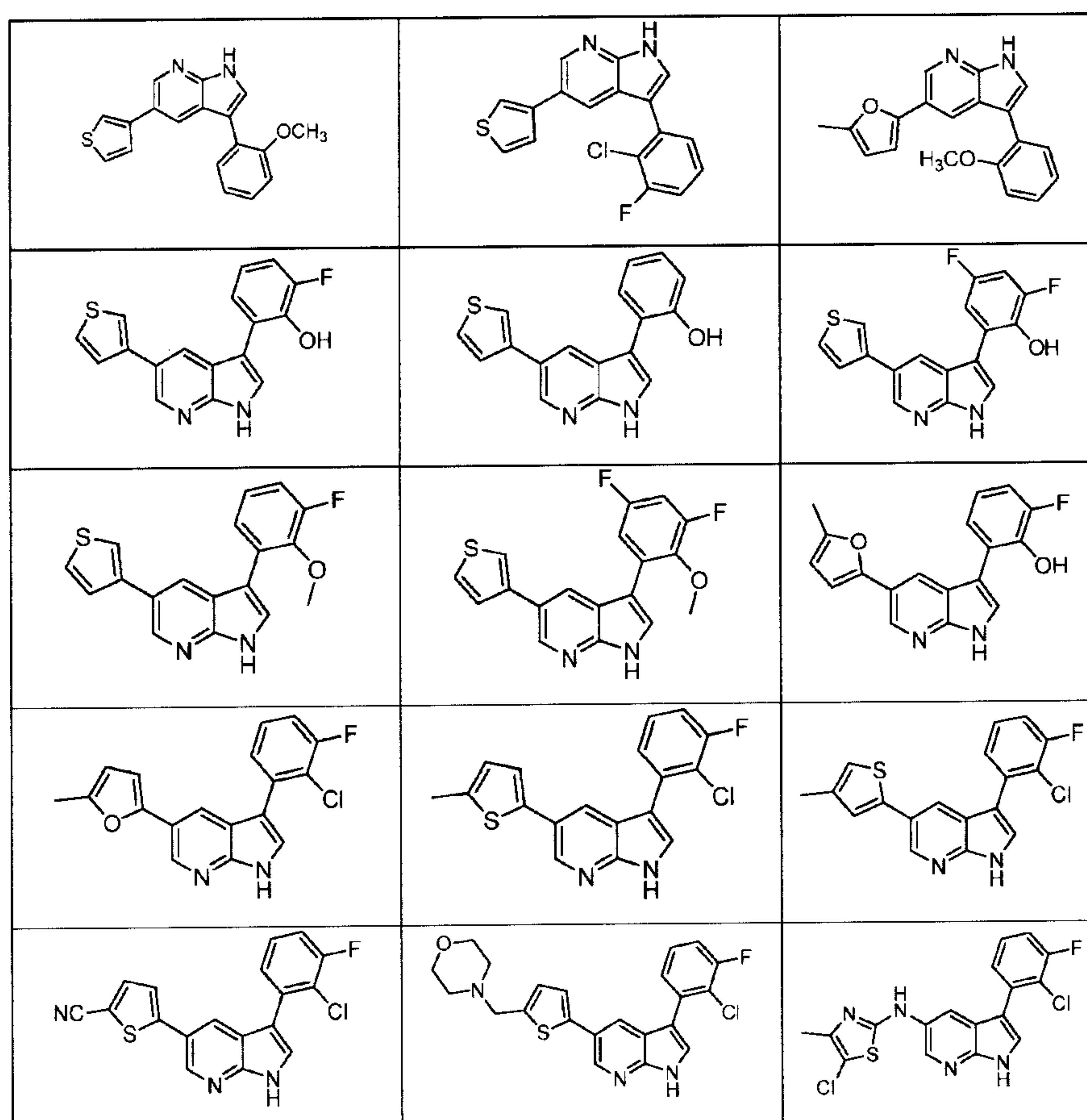


WO 2014/093383

PCT/US2013/074191

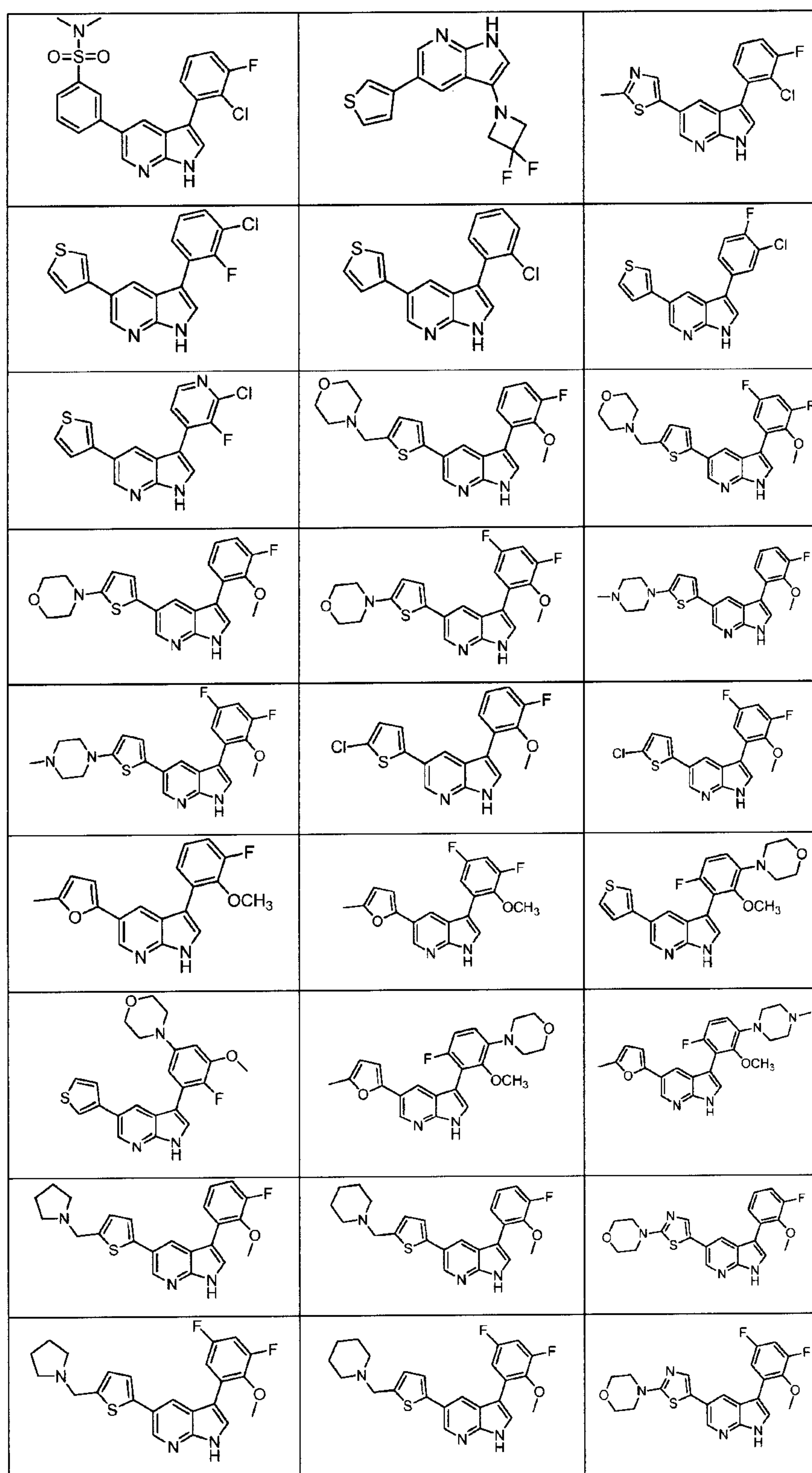


[0053] Other compounds of the present invention include:



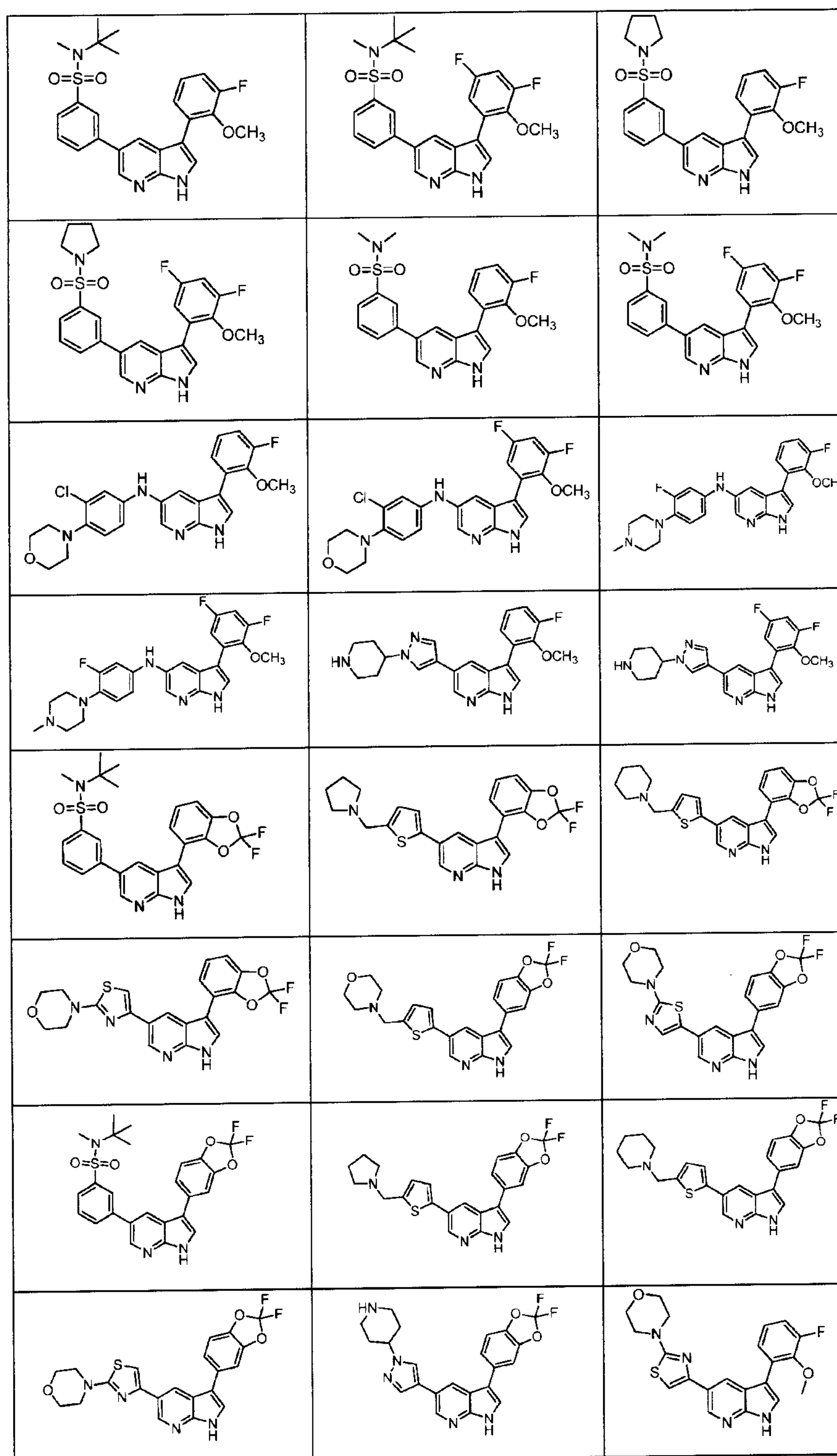
WO 2014/093383

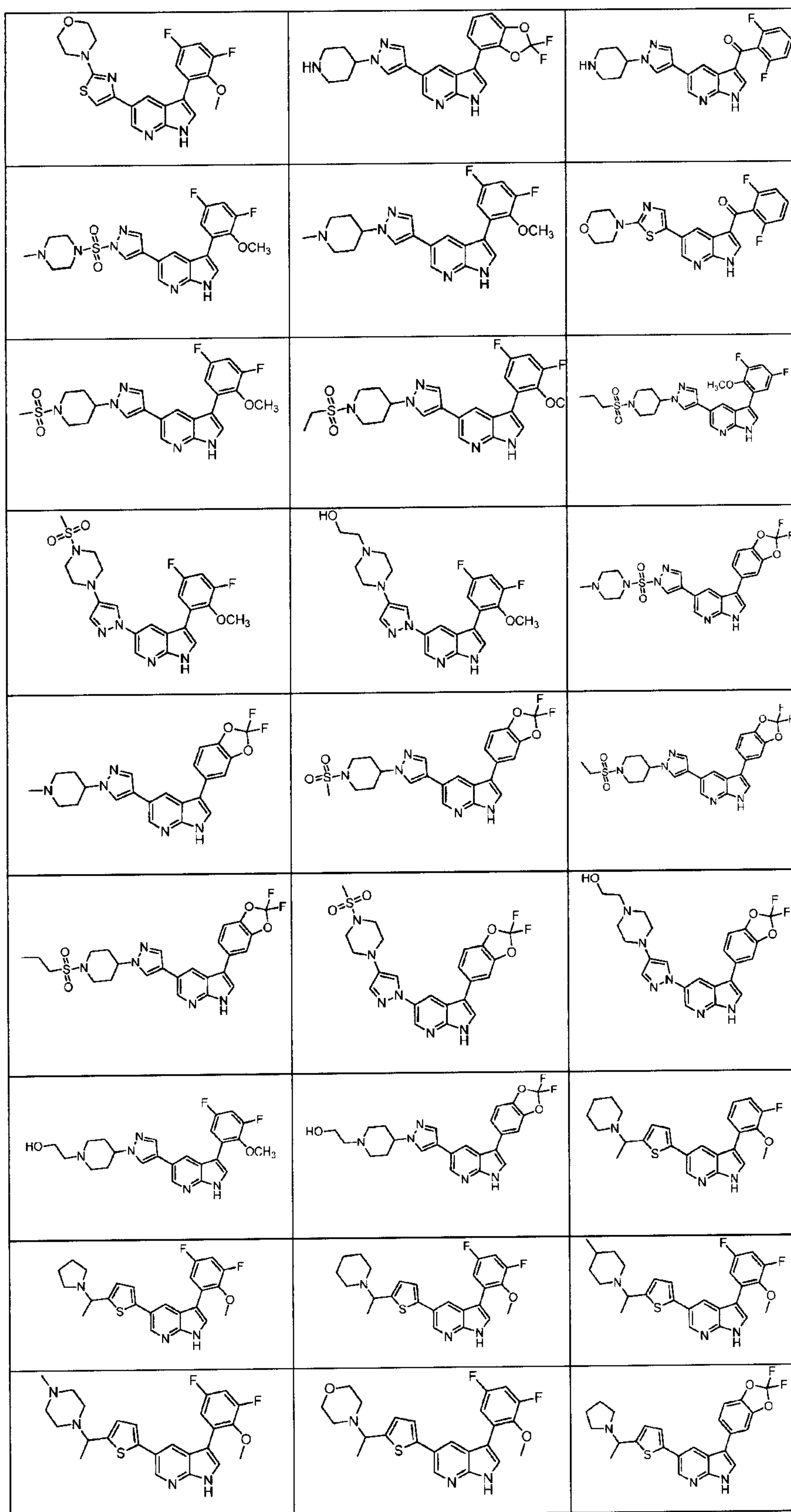
PCT/US2013/074191

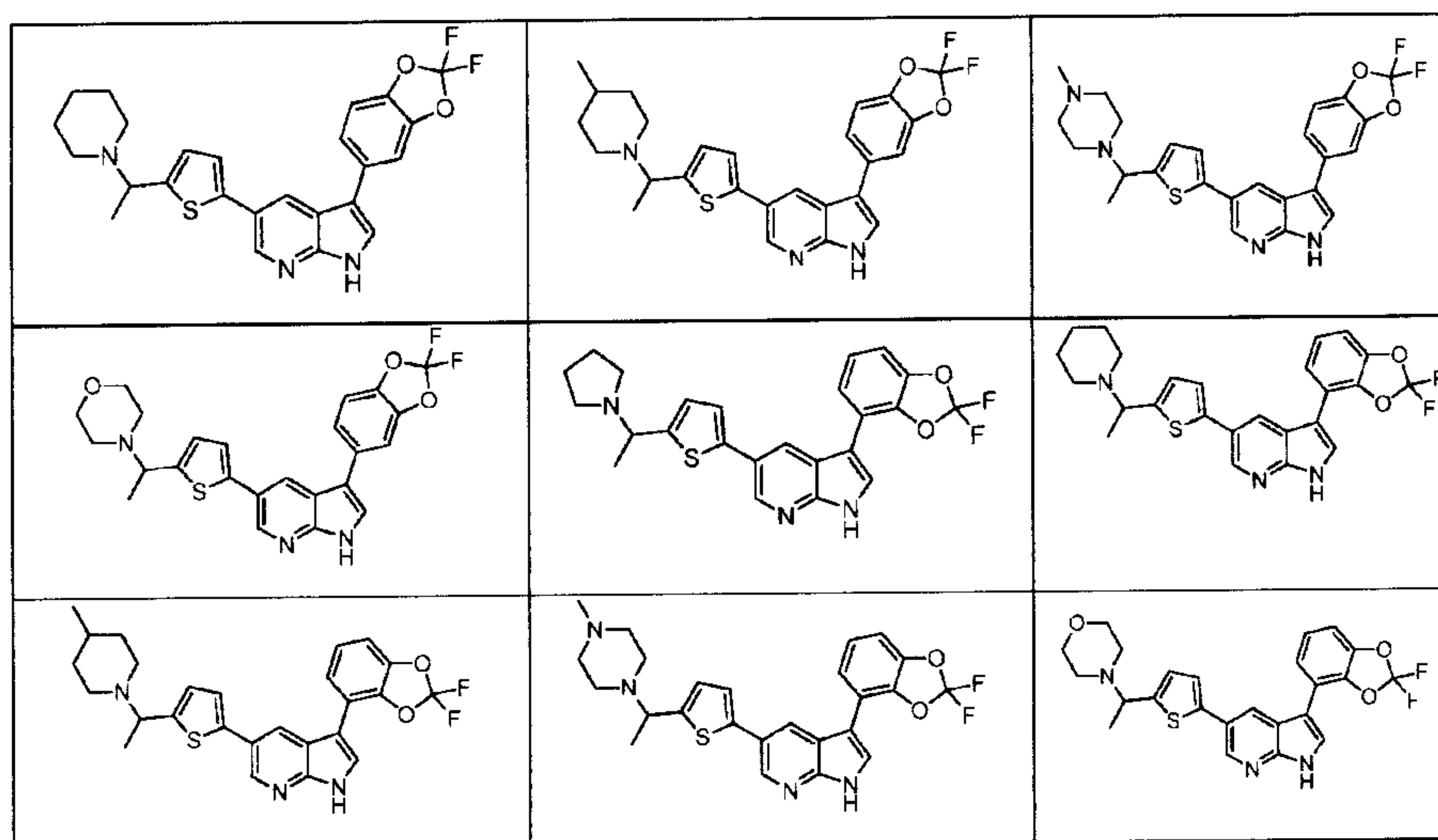


WO 2014/093383

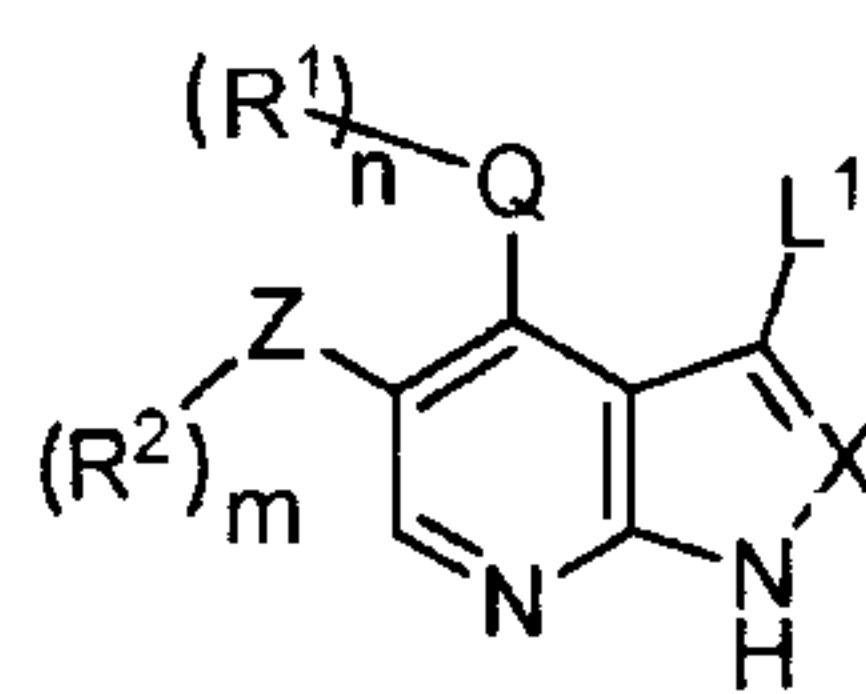
PCT/US2013/074191



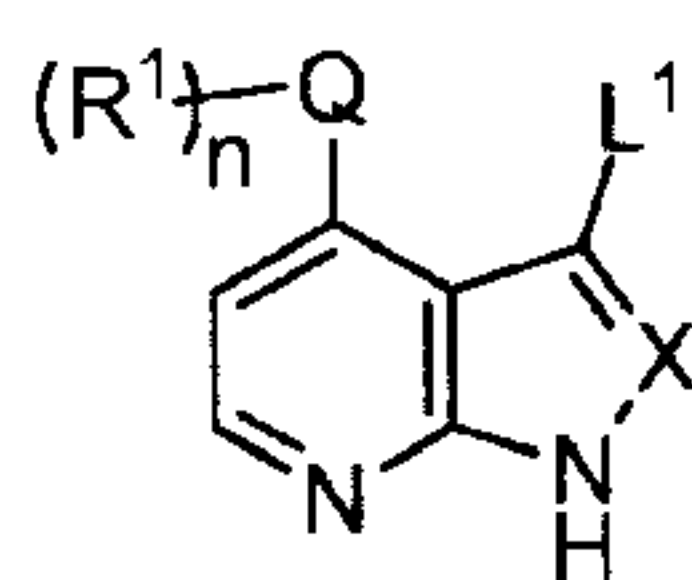




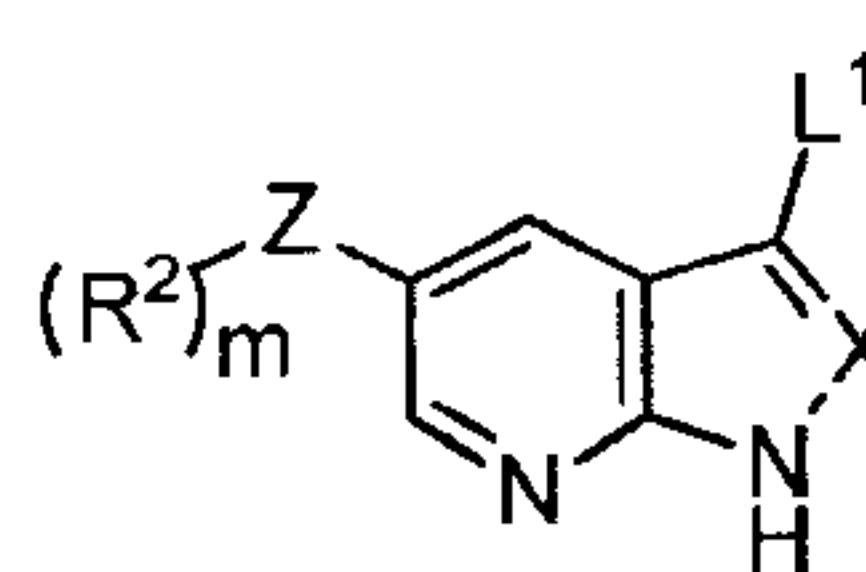
[0054] In an aspect, the present invention is a method of treating cancer or hyperproliferative disorders by administering an effective amount of a compound according to Formulas I, IA or IB:



(I)



(IA)

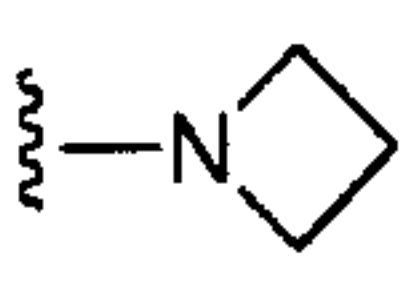
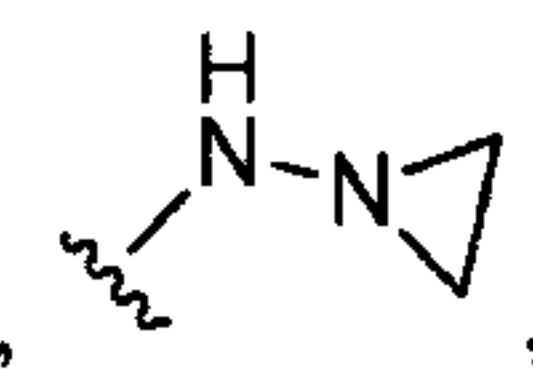
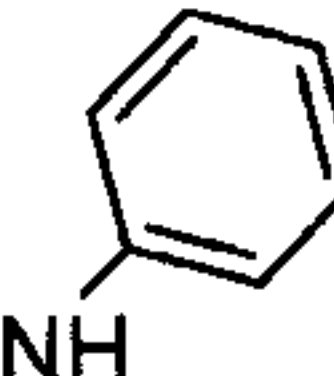


(IB)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

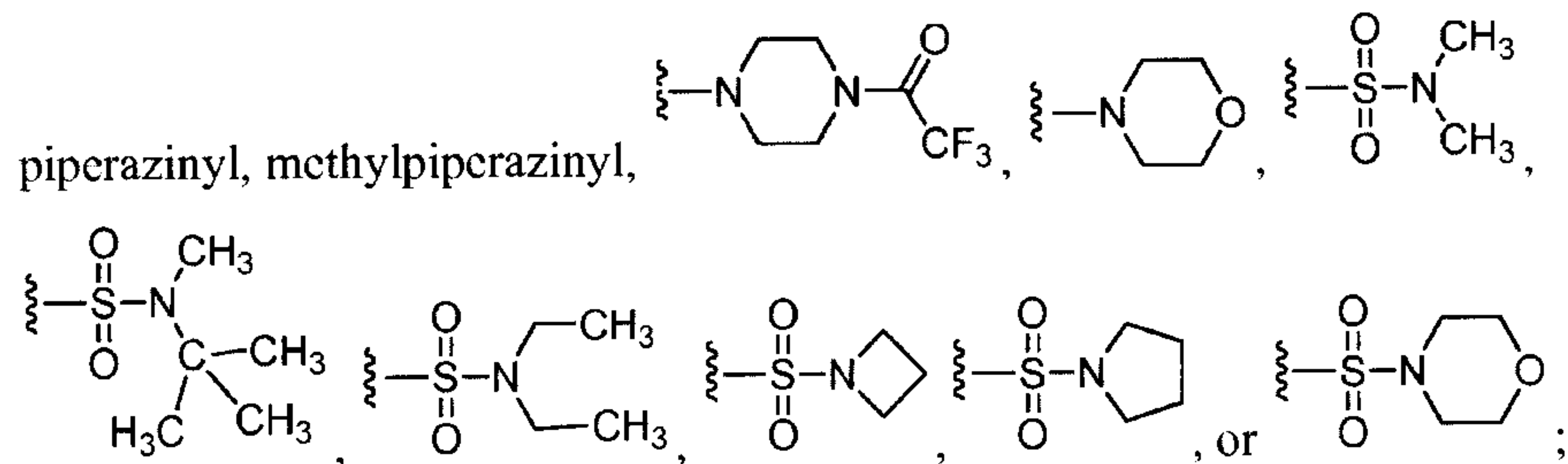
L<sup>1</sup> is H, F; or

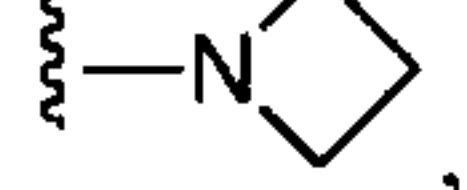
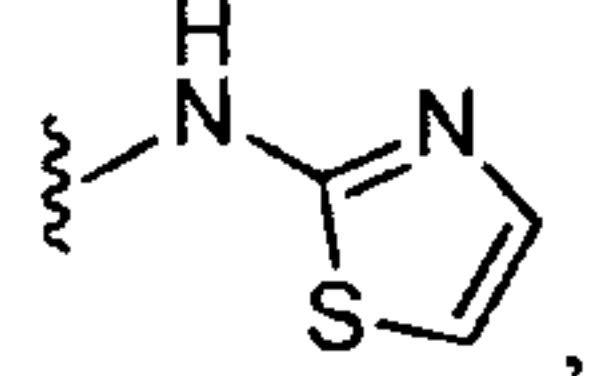
L<sup>1</sup> is thienyl, phenyl, pyrrolyl, pyridyl, , piperazinyl, , or  any of which is optionally substituted with 1-3 substituents, each substituent independently

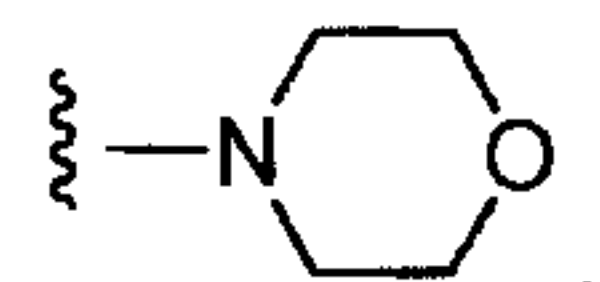
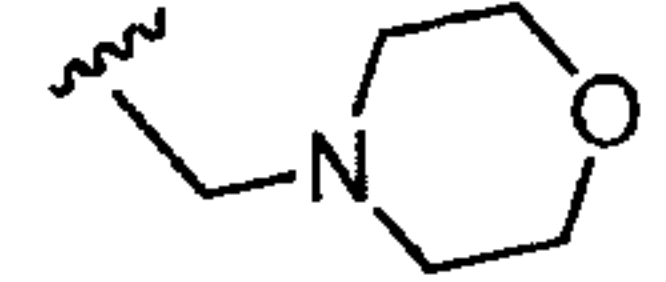
WO 2014/093383

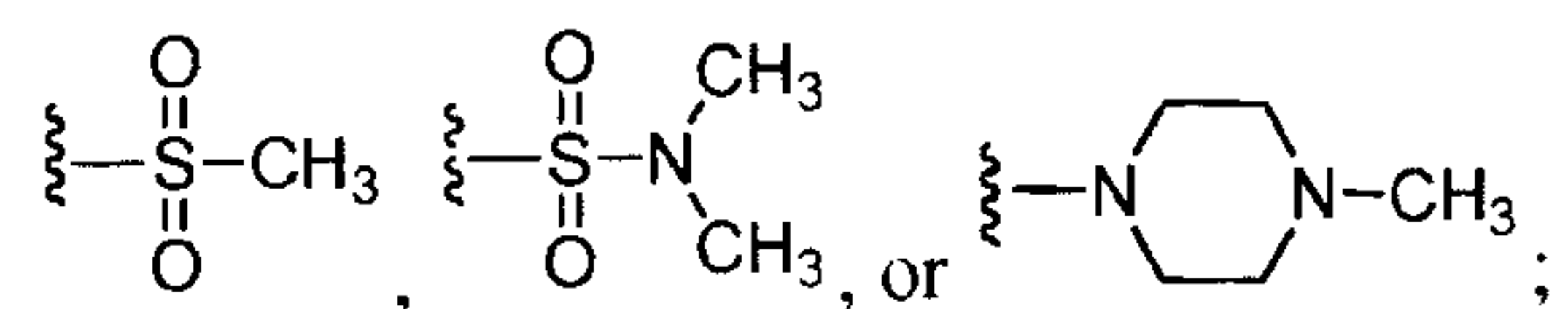
PCT/US2013/074191

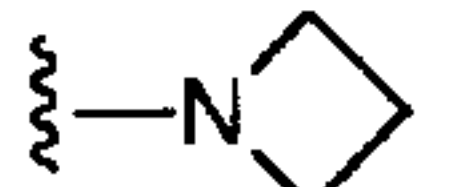
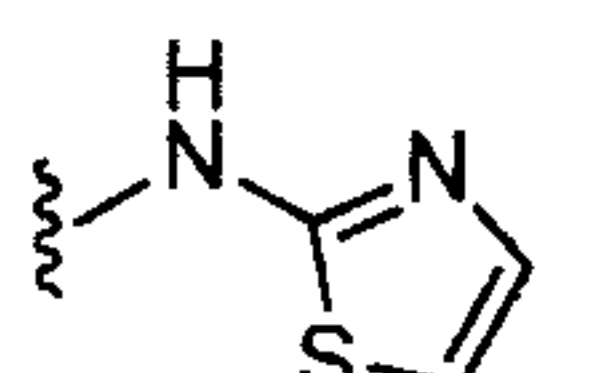
selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy,

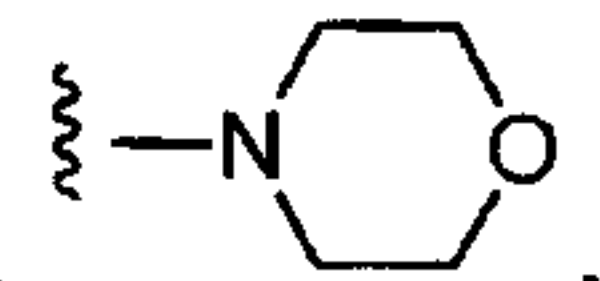
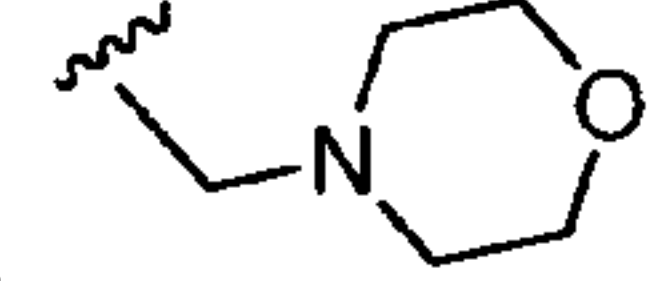


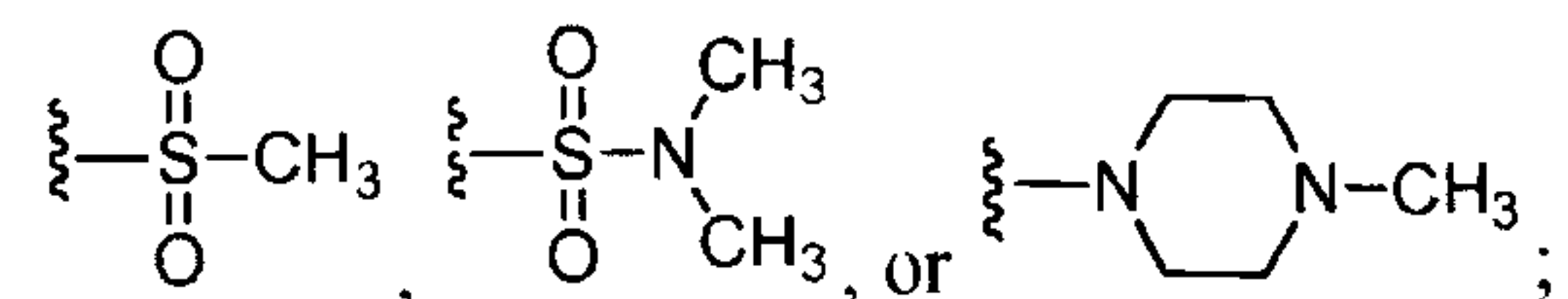
Q is a direct bond, thienyl, thiazolyl, phenyl, , , furanyl, or piperazinyl;

R<sup>1</sup> is each independently H, halo, -CN, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, , ,



Z is a direct bond, thienyl, thiazolyl, phenyl, , , furanyl, or piperazinyl;

R<sup>2</sup> is each independently H, halo, -CN, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, , ,



n is 0, 1, or 2; and

m is 0, 1, or 2;

provided that at least one of L<sup>1</sup>, R<sup>1</sup>, and R<sup>2</sup> is not H

[0055] In an embodiment of the aspect, the cancer is of colon, breast, stomach, prostate, pancreas, or ovarian tissue.

[0056] In another embodiment of the aspect, the cancer or hyperproliferative disorder is lung cancer, NSCLC (non small cell lung cancer), oat-cell cancer, bone cancer, pancreatic cancer, skin cancer, dermatofibrosarcoma protuberans, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colo-rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, hepatocellular cancer, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, pancreas, parathyroid or adrenal glands), sarcomas of soft tissues,

cancer of the urethra, cancer of the penis, prostate cancer (particularly hormone-refractory), chronic or acute leukemia, solid tumors of childhood, hypercosinophilia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, pediatric malignancy, neoplasms of the central nervous system, primary CNS lymphoma, spinal axis tumors, medulloblastoma, brain stem gliomas, pituitary adenomas, Barrett's esophagus, pre-malignant syndrome, neoplastic cutaneous disease, psoriasis, mycoses fungoides, benign prostatic hypertrophy, diabetic retinopathy, retinal ischemia, and retinal neovascularization, hepatic cirrhosis, angiogenesis, cardiovascular disease, atherosclerosis, immunological disease, autoimmune disease, or renal.

[0057] These and other aspects of the invention will be apparent upon reference to the following detailed description. To that end, certain patent and other documents are cited herein to more specifically set forth various aspects of this invention. Each of these documents is hereby incorporated by reference in its entirety.

[0058] Unless otherwise stated the following terms used in the specification and claims have the meanings discussed below:

[0059] "Alkyl" refers to a saturated straight or branched hydrocarbon radical of one to six carbon atoms, preferably one to four carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl, and the like, preferably methyl, ethyl, propyl, or 2-propyl. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Cyclic alkyls are referred to herein as a "cycloalkyl."

[0060] Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively.) Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 3-methyl-1-butyne, and the like.

[0061] "C<sub>0-4</sub>alkyl" refers to an alkyl with 0, 1, 2, 3, or 4 carbon atoms. C<sub>0-4</sub>alkyl with 0 carbon atoms is a hydrogen atom when terminal and is a direct bond when linking.

[0062] "Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g., methylene, ethylene, 2,2-dimethylethylene, propylene, 2-methylpropylene, butylene, pentylene, and the like, preferably methylene, ethylene, or propylene.

[0063] "Cycloalkyl" refers to a saturated cyclic hydrocarbon radical of three to eight carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0064] "Alkoxy" means a radical  $-OR_a$  where  $R_a$  is an alkyl as defined above, e.g., methoxy, ethoxy, propoxy, butoxy and the like.

[0065] "Halo" means fluoro, chloro, bromo, or iodo, preferably fluoro and chloro.

[0066] "Haloalkyl" means alkyl substituted with one or more, preferably one, two or three, same or different halo atoms, e.g.,  $-CH_2Cl$ ,  $-CF_3$ ,  $-CH_2CF_3$ ,  $-CH_2CCl_3$ , and the like.

[0067] "Haloalkoxy" means a radical  $-OR_b$  where  $R_b$  is an haloalkyl as defined above, e.g., trifluoromethoxy, trichloroethoxy, 2,2-dichloropropoxy, and the like.

[0068] "Acyl" means a radical  $-C(O)R_c$  where  $R_c$  is hydrogen, alkyl, or haloalkyl as defined herein, e.g., formyl, acetyl, trifluoroacetyl, butanoyl, and the like.

[0069] "Aryl" refers to an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups of 6 to 12 carbon atoms having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthyl and anthracenyl. The aryl group may be substituted or unsubstituted. Unless specifically stated otherwise, "substituted aryl" refers to the aryl group being substituted with one or more, more preferably one, two or three, even more preferably one or two substituents independently selected from the group consisting of alkyl (wherein the alkyl may be optionally substituted with one or two substituents), haloalkyl, halo, hydroxy, alkoxy, mercapto, alkylthio, cyano, acyl, nitro, phenoxy, heteroaryl, heteroaryloxy, haloalkyl, haloalkoxy, carboxy, alkoxycarbonyl, amino, alkylamino, dialkylamino, aryl, heteroaryl, carbocycle or heterocycle (wherein the aryl, heteroaryl, carbocycle or heterocycle may be optionally substituted).

[0070] "Heteroaryl" refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group of 5 to 12 ring atoms containing one, two, three or four ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, purine, triazole, tetrazole, triazine, and carbazole. The heteroaryl group may be unsubstituted or substituted, such as, for example, 5-methylthiazolyl. Unless specifically stated otherwise, "substituted heteroaryl" refers to the heteroaryl group being substituted with one or more, more preferably one, two or three, even more preferably one or two substituents independently selected from the group consisting of alkyl (wherein the alkyl may be optionally substituted with one or two substituents), haloalkyl, halo, hydroxy, alkoxy, mercapto, alkylthio, cyano, acyl, nitro, haloalkyl, haloalkoxy, carboxy,

alkoxycarbonyl, amino, alkylamino dialkylamino, aryl, heteroaryl, carbocycle or heterocycle (wherein the aryl, heteroaryl, carbocycle or heterocycle may be optionally substituted).

[0071] "Carbocycle" refers to a saturated, unsaturated or aromatic ring system having 3 to 14 ring carbon atoms. The term "carbocycle", whether saturated or partially unsaturated, also refers to rings that are optionally substituted. The term "carbocycle" includes aryl. The term "carbocycle" also includes aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as in a decahydronaphthyl or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring. The carbocycle group may be substituted or unsubstituted. Unless specifically stated otherwise, "substituted carbocycle" refers to the carbocycle group being substituted with one or more, more preferably one, two or three, even more preferably one or two substituents independently selected from the group consisting of alkyl (wherein the alkyl may be optionally substituted with one or two substituents), haloalkyl, halo, hydroxy, alkoxy, mercapto, alkylthio, cyano, acyl, nitro, haloalkyl, haloalkoxy, carboxy, alkoxycarbonyl, amino, alkylamino dialkylamino, aryl, heteroaryl, carbocycle or heterocycle (wherein the aryl, heteroaryl, carbocycle or heterocycle may be optionally substituted).

[0072] "Heterocycle" refers to a saturated, unsaturated or aromatic cyclic ring system having 3 to 14 ring atoms in which one, two or three ring atoms are heteroatoms selected from N, O, or S(O)<sub>m</sub> (where m is an integer from 0 to 2), the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl group. The term "heterocycle" includes heteroaryl. Unless specifically stated otherwise, "substituted heterocyclyl" refers to the heterocyclyl ring being substituted independently with one or more, preferably one, two, or three substituents selected from alkyl (wherein the alkyl may be optionally substituted with one or two substituents), haloalkyl, cycloalkylamino, cycloalkylalkyl, cycloalkylaminoalkyl, cycloalkylalkylaminoalkyl, cyanoalkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, hydroxyalkyl, carboxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, carbocycle, heterocycle (wherein the aryl, heteroaryl, carbocycle or heterocycle may be optionally substituted), aralkyl, heteroaralkyl, saturated or unsaturated heterocycloamino, saturated or unsaturated heterocycloaminoalkyl, and -COR<sub>d</sub> (where R<sub>d</sub> is alkyl). More specifically the term heterocyclyl includes, but is not limited to, tetrahydropyranyl, 2,2-dimethyl-1,3-dioxolane, piperidino, N-methylpiperidin-3-yl, piperazino, N-methylpyrrolidin-3-yl, pyrrolidino, morpholino, 4-cyclopropylmethylpiperazino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, 4-ethyloxycarbonylpiperazino, 3-oxopiperazino, 2-imidazolidone, 2-pyrrolidinone, 2-oxohomopiperazino, tetrahydropyrimidin-2-one, and the derivatives thereof,

including 2-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-c]pyridinyl. In certain embodiments, the heterocycle group is optionally substituted with one or two substituents independently selected from halo, alkyl, alkyl substituted with carboxy, ester, hydroxy, alkylamino, saturated or unsaturated heterocycloamino, saturated or unsaturated heterocycloaminoalkyl, or dialkylamino.

[0073] "Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocyclic group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocycle group is substituted with an alkyl group and situations where the heterocycle group is not substituted with the alkyl group.

[0074] Lastly, unless specifically stated otherwise, the term "substituted" as used herein means any of the above groups (e.g., alkyl, aryl, heteroaryl, carbocycle, heterocycle, etc.) wherein at least one hydrogen atom is replaced with a substituent. In the case of an oxo substituent ("=O") two hydrogen atoms are replaced. "Substituents" within the context of this invention, if not specified, include halogen, hydroxy, oxo, cyano, nitro, amino, alkylamino, dialkylamino, alkyl, alkoxy, thioalkyl, haloalkyl (e.g., -CF<sub>3</sub>), hydroxyalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, -NR<sub>e</sub>R<sub>f</sub>, -NR<sub>e</sub>C(=O)R<sub>f</sub>, -NR<sub>e</sub>C(=O)NR<sub>e</sub>R<sub>f</sub>, -NR<sub>e</sub>C(=O)OR<sub>f</sub>, -NR<sub>e</sub>SO<sub>2</sub>R<sub>f</sub>, -OR<sub>e</sub>, -C(=O)R<sub>e</sub>, -C(=O)OR<sub>e</sub>, -C(=O)NR<sub>e</sub>R<sub>f</sub>, -OC(=O)NR<sub>e</sub>R<sub>f</sub>, -SH, -SR<sub>e</sub>, -SOR<sub>e</sub>, -S(=O)<sub>2</sub>R<sub>e</sub>, -OS(=O)<sub>2</sub>R<sub>e</sub>, -S(=O)<sub>2</sub>OR<sub>e</sub>, wherein R<sub>e</sub> and R<sub>f</sub> are the same or different and independently hydrogen, alkyl, haloalkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl.

[0075] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups; a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing

rules of Cahn and Prelog (Cahn, R., Ingold, C., and Prelog, V. *Angew. Chem.* 78:413-47, 1966; *Angew. Chem. Internat. Ed. Eng.* 5:385-415, 511, 1966), or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0076] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Ch. 4 of *ADVANCED ORGANIC CHEMISTRY*, 4<sup>th</sup> edition, March, J., John Wiley and Sons, New York City, 1992).

[0077] The compounds of the present invention may exhibit the phenomena of tautomerism and structural isomerism. This invention encompasses any tautomeric or structural isomeric form and mixtures thereof which possess the ability to modulate SIK2 activity and is not limited to, any one tautomeric or structural isomeric form.

[0078] It is contemplated that a compound of the present invention would be metabolized by enzymes in the body of the organism such as human being to generate a metabolite that can modulate the activity of the protein kinases. Such metabolites are within the scope of the present invention.

[0079] A compound of the present invention or a pharmaceutically acceptable salt thereof can be administered as such to a human patient or can be administered in pharmaceutical compositions in which the foregoing materials are mixed with suitable carriers or excipient(s). Techniques for formulation and administration of drugs may be found, for example, in *REMMINGTON'S PHARMACOLOGICAL SCIENCES*, Mack Publishing Co., Easton, PA, latest edition.

[0080] A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof, with other chemical components, such as pharmaceutically acceptable excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

[0081] "Pharmaceutically acceptable excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

[0082] "Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the parent compound. Such salts may include: (1) acid addition salt which is obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D)- or (L)-malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like, preferably hydrochloric acid or (L)-malic acid; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0083] The compound of the present invention may also act, or be designed to act, as a prodrug. A "prodrug" refers to an agent, which is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention, which is, administered as an ester (the "prodrug"), phosphate, amide, carbamate, or urea.

[0084] "Therapeutically effective amount" refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of cancer, a therapeutically effective amount refers to that amount which has the effect of: (1) reducing the size of the tumor; (2) inhibiting tumor metastasis; (3) inhibiting tumor growth; and/or (4) relieving one or more symptoms associated with the cancer.

[0085] The term "disease", as used herein, means any disease or other deleterious condition in which a SIK2 is known to play a role. The term "disease" also means those diseases or conditions that are alleviated by treatment with SIK2 modulators. Such conditions include, without limitation, cancer and other hyperproliferative disorders as well as inflammation. In certain embodiments, the cancer is a cancer of colon, breast, stomach, prostate, pancreas, or ovarian tissue.

[0086] The term "SIK2 activity-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which SIK2 activity is known to play a role. The term

"SIK2 activity-mediated condition" also means those diseases or conditions that are alleviated by treatment with a SIK2 inhibitor.

[0087] As used herein, "administer" or "administration" refers to the delivery of an inventive compound or of a pharmaceutically acceptable salt thereof or of a pharmaceutical composition containing an inventive compound or a pharmaceutically acceptable salt thereof of this invention to an organism for the purpose of prevention or treatment of a protein kinase-related disorder.

[0088] Suitable routes of administration may include, without limitation, oral, rectal, transmucosal or intestinal administration or intramuscular, subcutaneous, intramedullary, intrathecal, direct intraventricular, intravenous, intravitreal, intraperitoneal, intranasal, or intraocular injections. In certain embodiments, the preferred routes of administration are oral and intravenous. Alternatively, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a solid tumor, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. In this way, the liposomes may be targeted to and taken up selectively by the tumor.

[0089] Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0090] Pharmaceutical compositions for use in accordance with the present invention may be formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0091] For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0092] For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient.

Pharmaceutical preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding other suitable auxiliaries if desired, to obtain tablets or dragee cores. Useful excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, cellulose preparations such as, for example, maize starch, wheat starch, rice starch and potato starch and other materials such as gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl-pyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid. A salt such as sodium alginate may also be used.

[0093] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0094] Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. Stabilizers may be added in these formulations, also. Pharmaceutical compositions which may also be used include hard gelatin capsules. The capsules or pills may be packaged into brown glass or plastic bottles to protect the active compound from light. The containers containing the active compound capsule formulation are preferably stored at controlled room temperature (15-30°C).

[0095] For administration by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray using a pressurized pack or a nebulizer and a suitable propellant, e.g., without limitation, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0096] The compounds may also be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

[0097] Pharmaceutical compositions for parenteral administration include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally, suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0098] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

[0099] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

[00100] In addition to the formulations described previously, the compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. A compound of this invention may be formulated for this route of administration with suitable polymeric or hydrophobic materials (for instance, in an emulsion with a pharmacologically acceptable oil), with ion exchange resins, or as a sparingly soluble derivative such as, without limitation, a sparingly soluble salt.

[00101] A non-limiting example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer and an aqueous phase such as the VPD cosolvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD cosolvent system (VPD: D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This cosolvent system dissolves hydrophobic compounds well, and itself produces low toxicity

upon systemic administration. Naturally, the proportions of such a cosolvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the cosolvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80, the fraction size of polyethylene glycol may be varied, other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone, and other sugars or polysaccharides may substitute for dextrose.

[00102] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In addition, certain organic solvents such as dimethylsulfoxide also may be employed, although often at the cost of greater toxicity.

[00103] Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[00104] The pharmaceutical compositions herein also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00105] Many of the SIK2-modulating compounds of the invention may be provided as physiologically acceptable salts wherein the claimed compound may form the negatively or the positively charged species. Examples of salts in which the compound forms the positively charged moiety include, without limitation, quaternary ammonium (defined elsewhere herein), salts such as the hydrochloride, sulfate, carbonate, lactate, tartrate, malate, maleate, succinate wherein the nitrogen atom of the quaternary ammonium group is a nitrogen of the selected compound of this invention which has reacted with the appropriate acid. Salts in which a compound of this invention forms the negatively charged species include, without limitation, the sodium, potassium, calcium and magnesium salts formed by the reaction of a carboxylic acid group in the compound with an appropriate base (e.g. sodium hydroxide (NaOH), potassium hydroxide (KOH), calcium hydroxide (Ca(OH)<sub>2</sub>), etc.).

[00106] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve

the intended purpose, e.g., the modulation of protein kinase activity and/or the treatment or prevention of a protein kinase-related disorder.

[00107] More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

[00108] Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[00109] For any compound used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the  $IC_{50}$  as determined in cell culture (i.e., the concentration of the test compound which achieves a half-maximal inhibition of the SIK2, or surrogate marker activity). Such information can then be used to more accurately determine useful doses in humans.

[00110] Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the  $IC_{50}$  and the  $LD_{50}$  (both of which are discussed elsewhere herein) for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See, e.g., GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Ch. 3, 9<sup>th</sup> ed., Ed. by Hardman, J., and Limbard, L., McGraw-Hill, New York City, 1996, p.46.)

[00111] Dosage amount and interval may be adjusted individually to provide plasma levels of the active species which are sufficient to maintain the kinase modulating effects. These plasma levels are referred to as minimal effective concentrations (MECs). The MEC will vary for each compound but can be estimated from *in vitro* data, e.g., the concentration necessary to achieve 50-90% inhibition of SIK2, or surrogate marker may be ascertained using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

[00112] Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[00113] At present, the therapeutically effective amounts of compounds of the present invention may range from approximately 2.5mg/m<sup>2</sup> to 1500mg/m<sup>2</sup> per day. Additional illustrative amounts range from 0.2-1000mg/qid, 2-500mg/qid, and 20-250mg/qid.

[00114] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration, and other procedures known in the art may be employed to determine the correct dosage amount and interval.

[00115] The amount of a composition administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

[00116] The compositions may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or of human or veterinary administration. Such notice, for example, may be of the labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Suitable conditions indicated on the label may include treatment of a tumor, inhibition of angiogenesis, treatment of fibrosis, diabetes, and the like.

[00117] As mentioned above, the compounds and compositions of the invention will find utility in a broad range of diseases and conditions mediated by protein kinases, including diseases and conditions mediated by SIK2 activity. Such diseases may include by way of example and not limitation, cancers such as lung cancer, NSCLC (non small cell lung cancer), oat-cell cancer, bone cancer, pancreatic cancer, skin cancer, dermatofibrosarcoma protuberans, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colo-rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, hepatocellular cancer, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, pancreas,

parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer (particularly hormone-refractory), chronic or acute leukemia, solid tumors of childhood, hypereosinophilia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, medulloblastoma, brain stem gliomas or pituitary adenomas), Barrett's esophagus (pre-malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides, and benign prostatic hypertrophy, diabetes related diseases such as diabetic retinopathy, retinal ischemia, and retinal neovascularization, hepatic cirrhosis, angiogenesis, cardiovascular disease such as atherosclerosis, immunological disease such as autoimmune disease and renal disease.

[00118] The inventive compound can be used in combination with one or more other chemotherapeutic agents. The dosage of the inventive compounds may be adjusted for any drug-drug reaction. In one embodiment, the chemotherapeutic agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, cell cycle inhibitors, enzymes, topoisomerase inhibitors such as CAMPTOSAR (irinotecan), biological response modifiers, anti-hormones, antiangiogenic agents such as MMP-2, MMP-9 and COX-2 inhibitors, anti-androgens, platinum coordination complexes (cisplatin, etc.), substituted ureas such as hydroxyurea; methylhydrazine derivatives, e.g., procarbazine; adrenocortical suppressants, e.g., mitotane, aminoglutethimide, hormone and hormone antagonists such as the adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate), estrogens (e.g., diethylstilbesterol), antiestrogens such as tamoxifen, androgens, e.g., testosterone propionate, and aromatase inhibitors, such as anastrozole, and AROMASIN (exemestane).

[00119] Examples of alkylating agents that the above method can be carried out in combination with include, without limitation, fluorouracil (5-FU) alone or in further combination with leukovorin; other pyrimidine analogs such as UFT, capecitabine, gemcitabine and cytarabine, the alkyl sulfonates, e.g., busulfan (used in the treatment of chronic granulocytic leukemia), improsulfan and piposulfan; aziridines, e.g., benzodepa, carboquone, meturedopa and uredepa; ethyleneimines and methylmelamines, e.g., altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolmelamine; and the nitrogen mustards, e.g., chlorambucil (used in the treatment of chronic lymphocytic leukemia, primary macroglobulinemia and non-Hodgkin's lymphoma), cyclophosphamide (used in the treatment of Hodgkin's disease, multiple myeloma,

neuroblastoma, breast cancer, ovarian cancer, lung cancer, Wilm's tumor and rhabdomyosarcoma), estramustine, ifosfamide, novembrichin, prednimustine and uracil mustard (used in the treatment of primary thrombocytosis, non-Hodgkin's lymphoma, Hodgkin's disease and ovarian cancer); and triazines, e.g., dacarbazine (used in the treatment of soft tissue sarcoma).

[00120] Examples of antimetabolite chemotherapeutic agents that the above method can be carried out in combination with include, without limitation, folic acid analogs, e.g., methotrexate (used in the treatment of acute lymphocytic leukemia, choriocarcinoma, mycosis fungoides, breast cancer, head and neck cancer and osteogenic sarcoma) and pteropterin; and the purine analogs such as mercaptopurine and thioguanine which find use in the treatment of acute granulocytic, acute lymphocytic and chronic granulocytic leukemias.

[00121] Examples of natural product-based chemotherapeutic agents that the above method can be carried out in combination with include, without limitation, the vinca alkaloids, e.g., vinblastine (used in the treatment of breast and testicular cancer), vincristine and vindesine; the epipodophyllotoxins, e.g., etoposide and teniposide, both of which are useful in the treatment of testicular cancer and Kaposi's sarcoma; the antibiotic chemotherapeutic agents, e.g., daunorubicin, doxorubicin, epirubicin, mitomycin (used to treat stomach, cervix, colon, breast, bladder and pancreatic cancer), dactinomycin, temozolomide, plicamycin, bleomycin (used in the treatment of skin, esophagus and genitourinary tract cancer); and the enzymatic chemotherapeutic agents such as L-asparaginase.

[00122] An inventive compound can also be used with other signal transduction inhibitors, such as agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, such as HERCEPTIN (Genentech, Inc., South San Francisco, CA). EGFR inhibitors are described in, for example in WO 95/19970, WO 98/14451, WO 98/02434, and U.S. Pat. No. 5,747,498 and such substances can be used in the present invention as described herein.

[00123] EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems, Inc., New York, NY), the compounds erlotinib (OSI Pharmaceuticals, Inc., Melville, NY), ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc., Annandale, NJ), and OLX-103 (Merck & Co., Whitehouse Station, NJ), and EGF fusion toxin (Seragen Inc., Hopkinton, MA).

[00124] These and other EGFR-inhibiting agents can be used in the present invention. VEGF inhibitors, for example SU-5416 and SU-6668 (Sugen Inc., South San Francisco, CA), can also be combined with an inventive compound. VEGF inhibitors are described in, for example, WO 01/60814 A3, WO 99/24440, PCT International Application PCT/IB99/00797, WO 95/21613, WO 99/61422, U.S. Pat. No. 5,834,504, WO 01/60814, WO 98/50356, U.S. Pat. No. 5,883,113, U.S. Pat. No. 5,886,020, U.S. Pat. No. 5,792,783, WO 99/10349, WO 97/32856, WO 97/22596, WO 98/54093, WO 98/02438, WO 99/16755, and WO 98/02437, all of which are incorporated herein in their entireties by reference. Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc., Kirkland, WA); anti-VEGF monoclonal antibody of Genentech, Inc.; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, CO) and Chiron (Emeryville, CA). These and other VEGF inhibitors can be used in the present invention as described herein. Further, pErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc., The Woodlands, TX) and 2B-1 (Chiron), can furthermore be combined with an inventive compound, for example, those indicated in WO 98/02434, WO 99/35146, WO 99/35132, WO 98/02437, WO 97/13760, WO 95/19970, U.S. Pat. No. 5,587,458 and U.S. Pat. No. 5,877,305, which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in U.S. Pat. No. 6,284,764, incorporated in its entirety herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with an inventive compound, in accordance with the present invention.

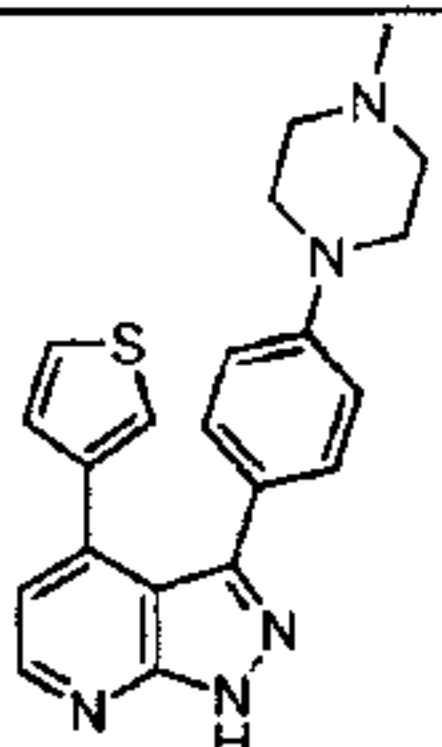
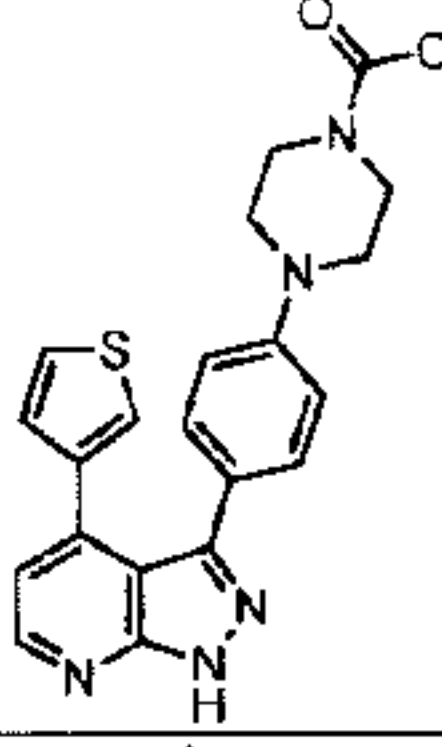
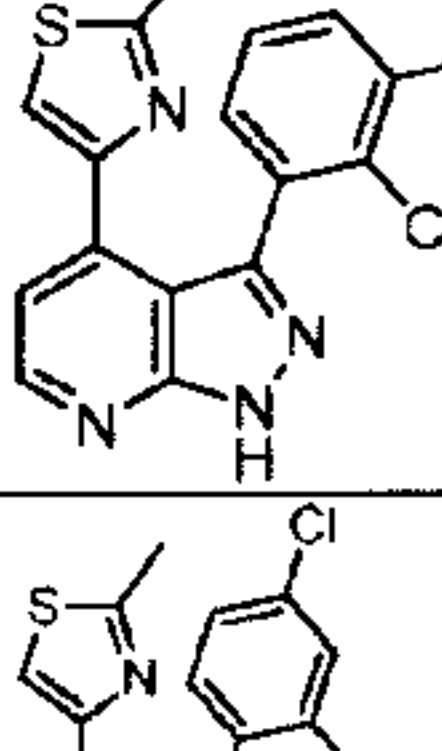
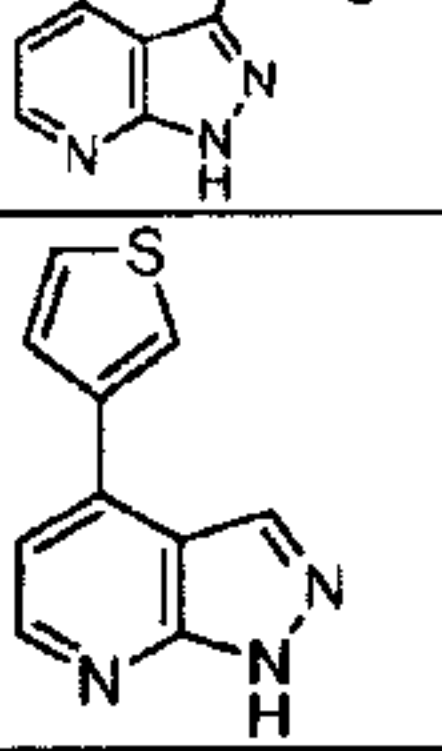
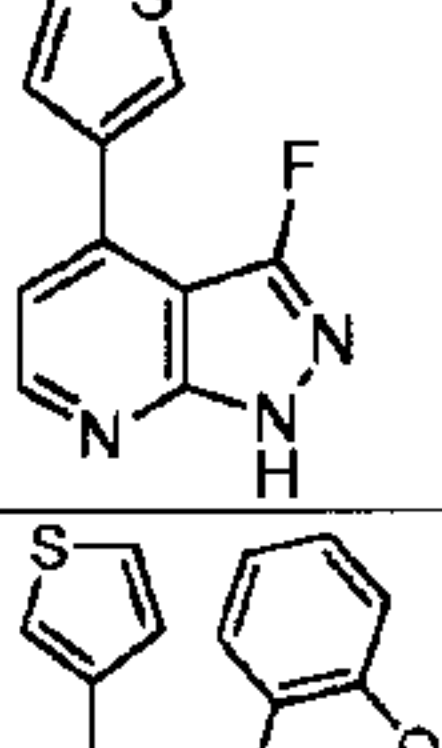
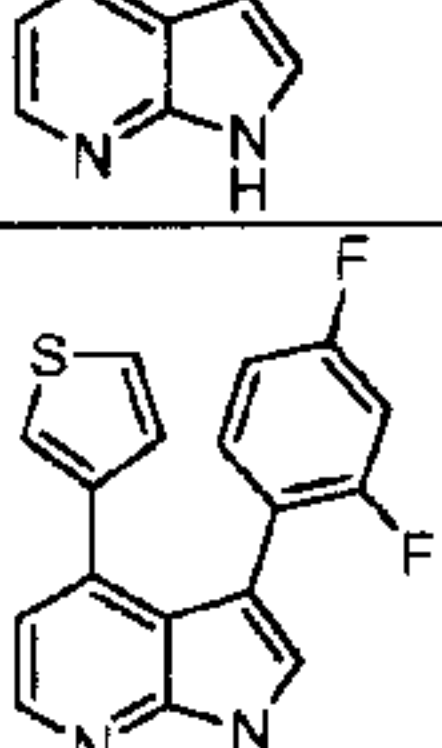
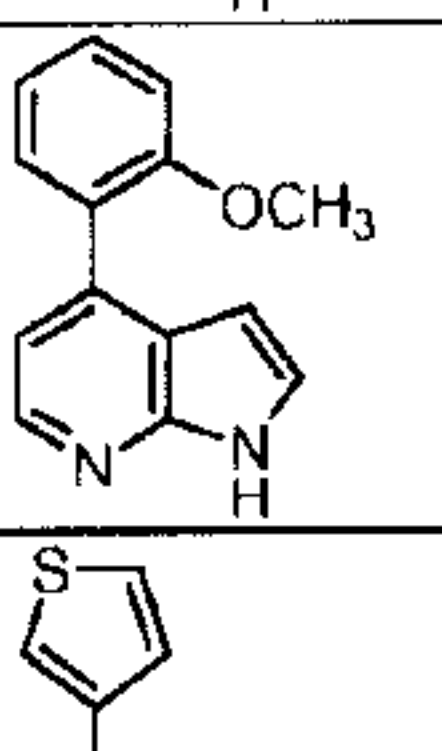
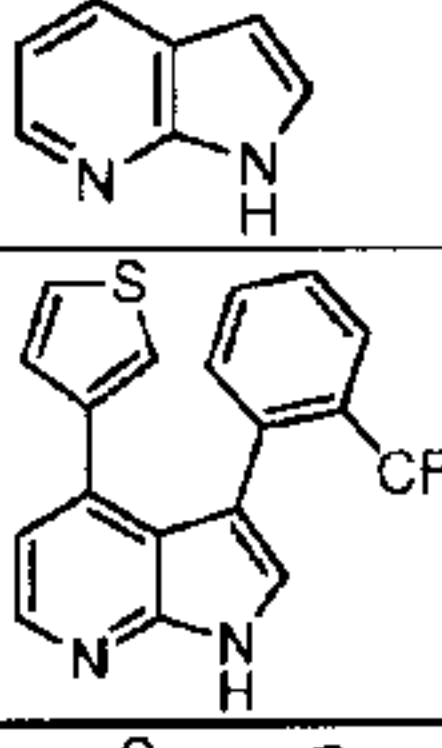
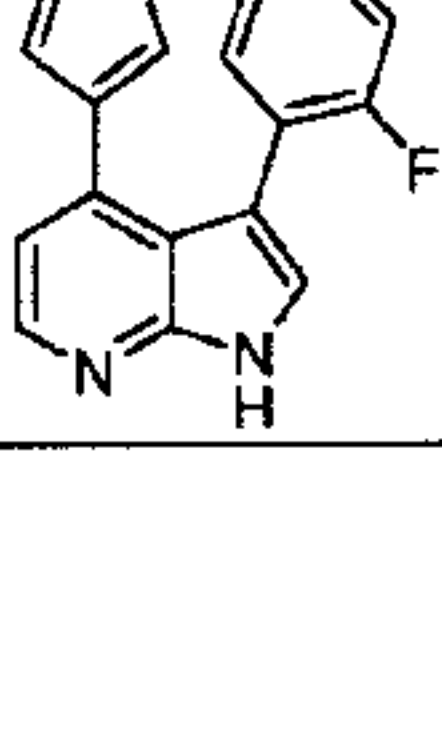
[00125] An inventive compound can also be used with other agents useful in treating cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocyte antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors described in the references cited in the "Background" section, of U.S. Pat. No., 6,258,824 B1.

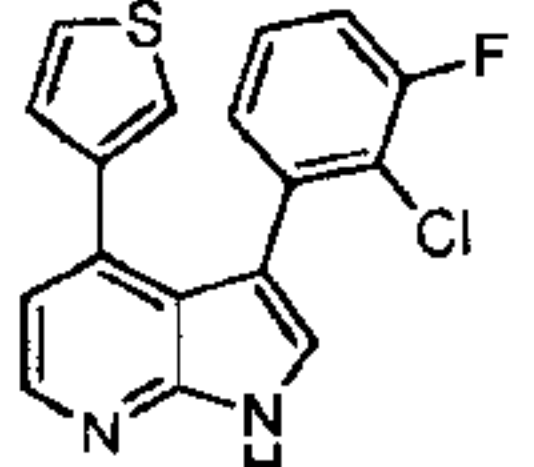
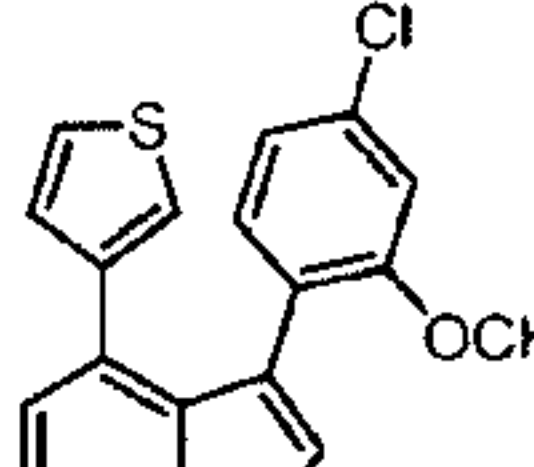
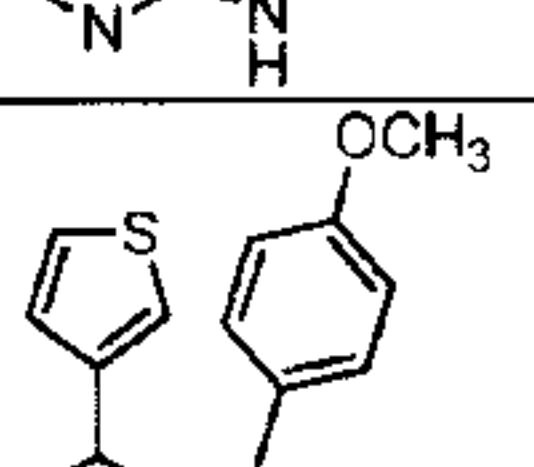
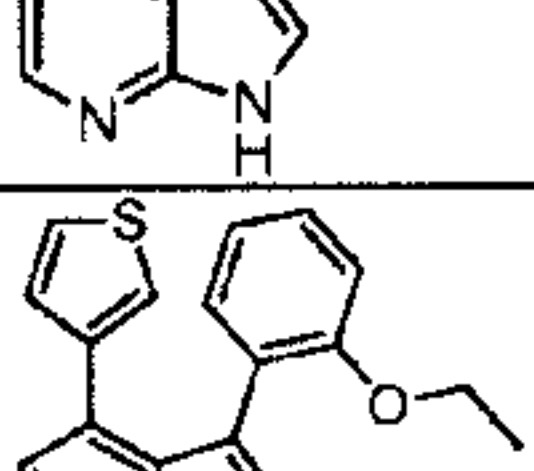
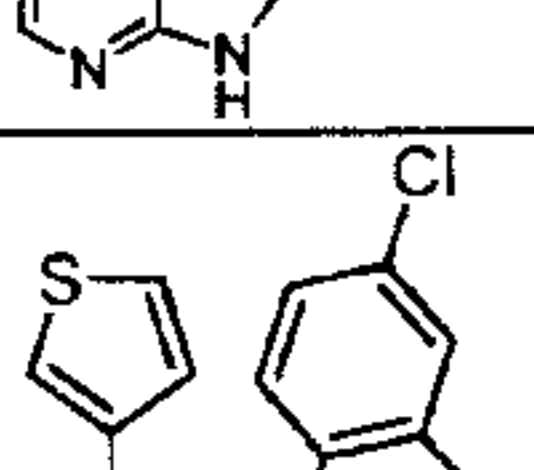
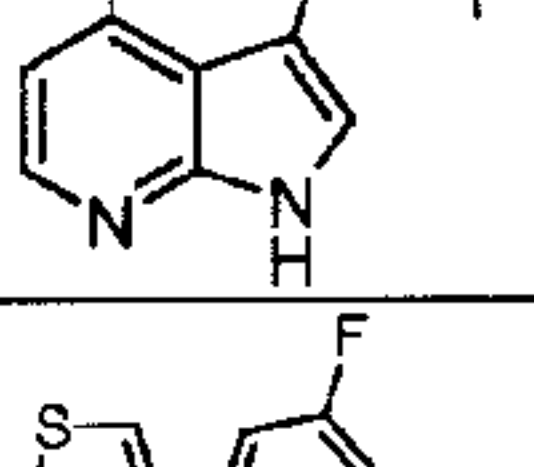
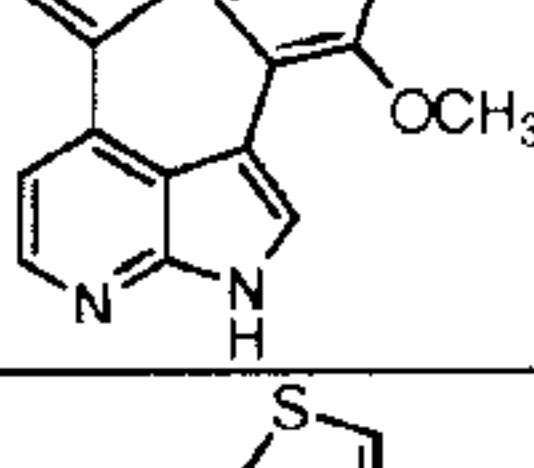
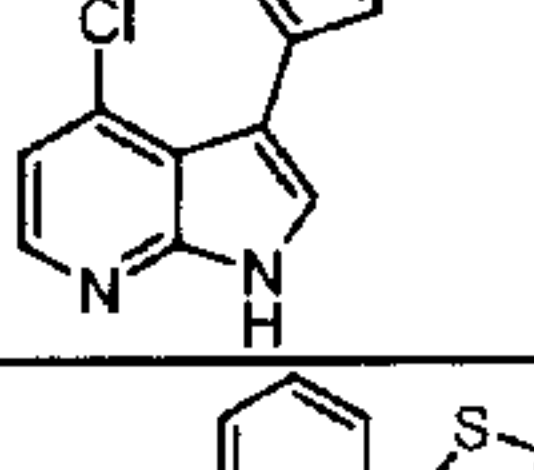
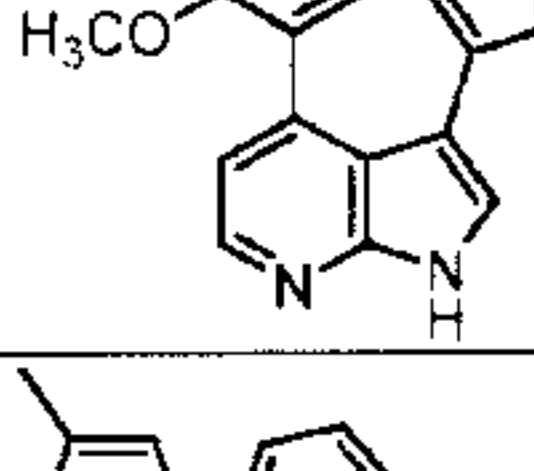
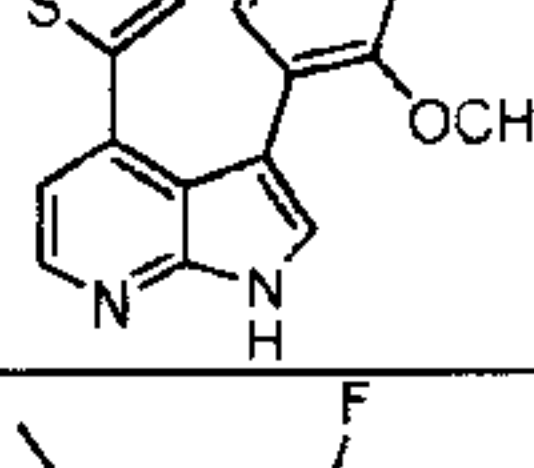
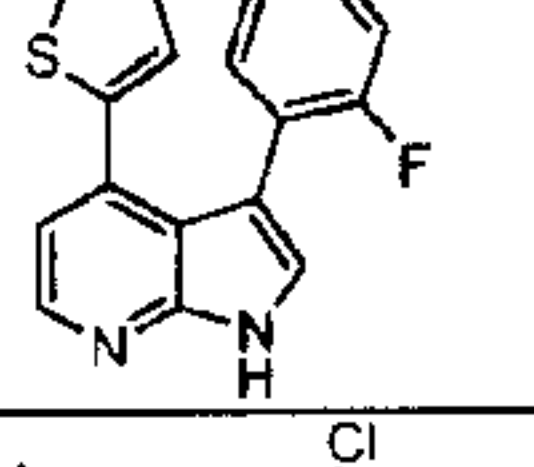
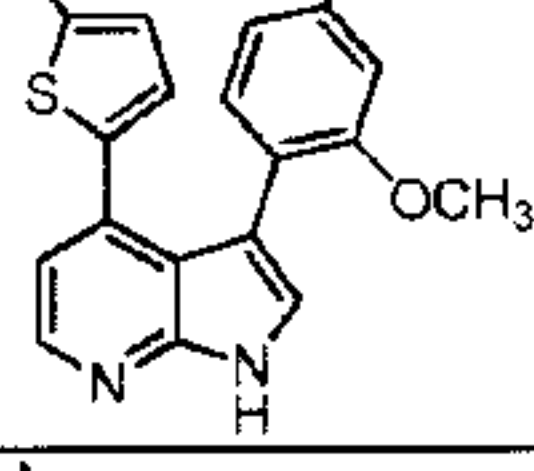
[00126] The above method can also be carried out in combination with radiation therapy, wherein the amount of an inventive compound in combination with the radiation therapy is effective in treating the above diseases. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the invention in this combination therapy can be determined as described herein.

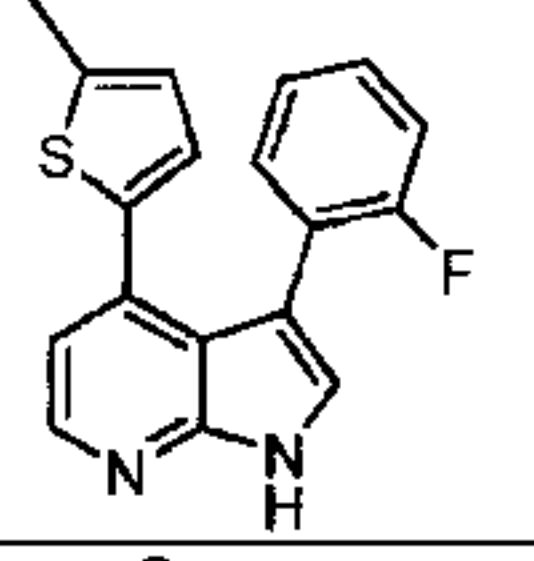
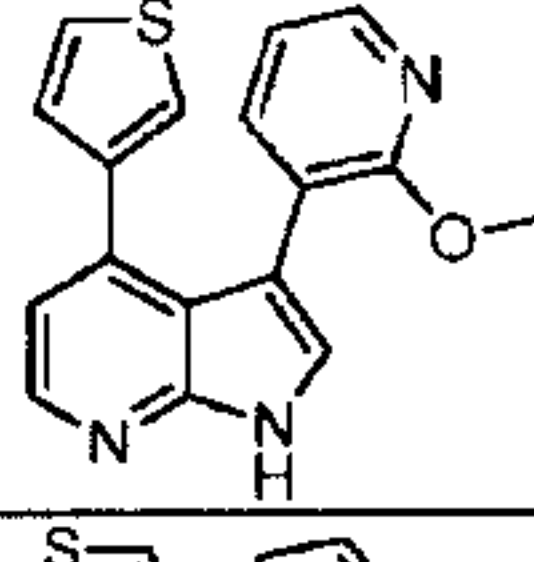
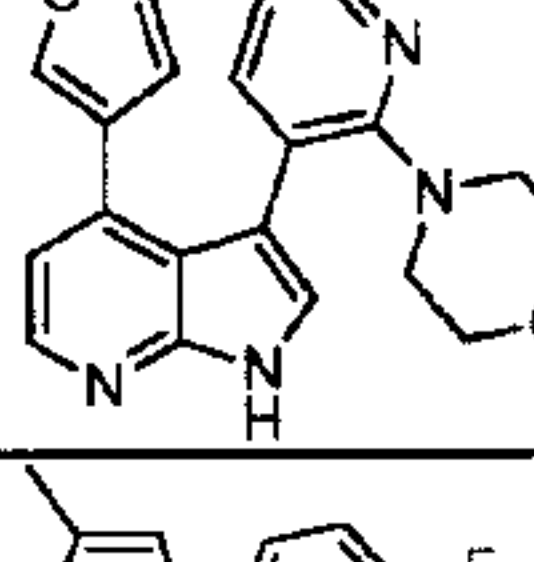
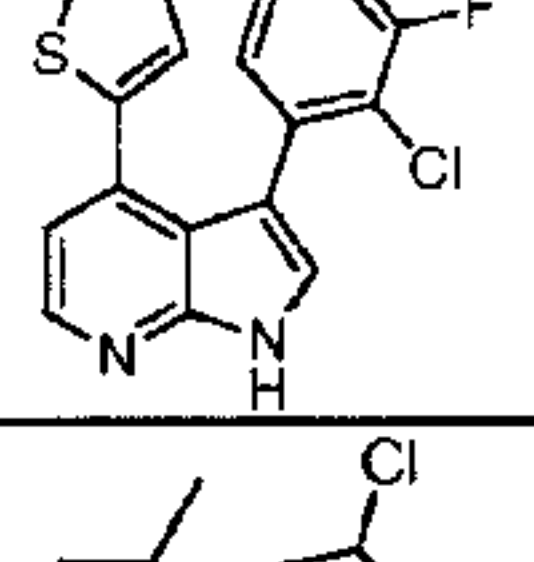
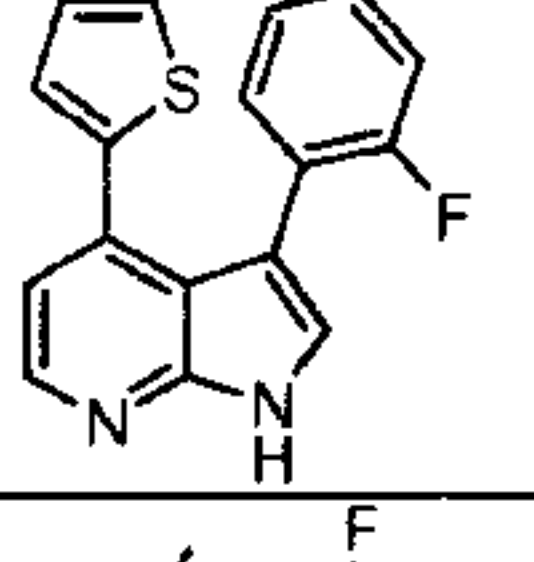
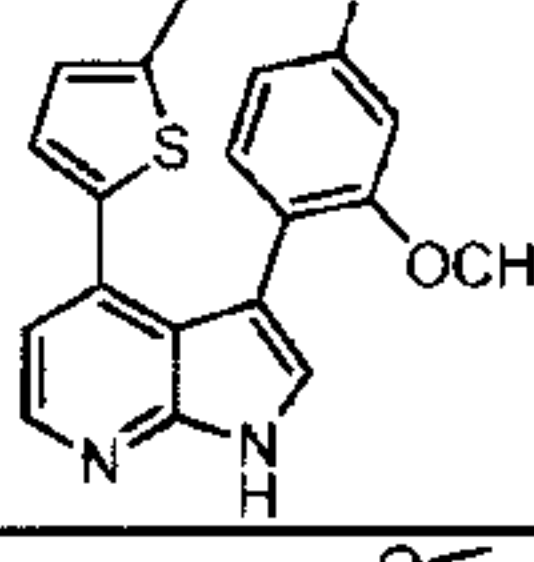
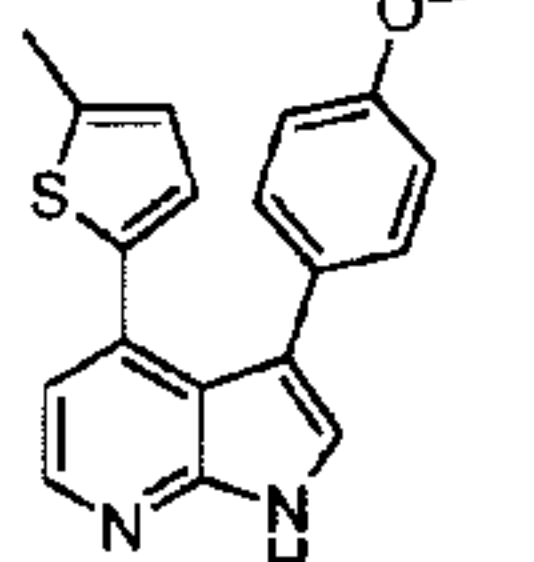
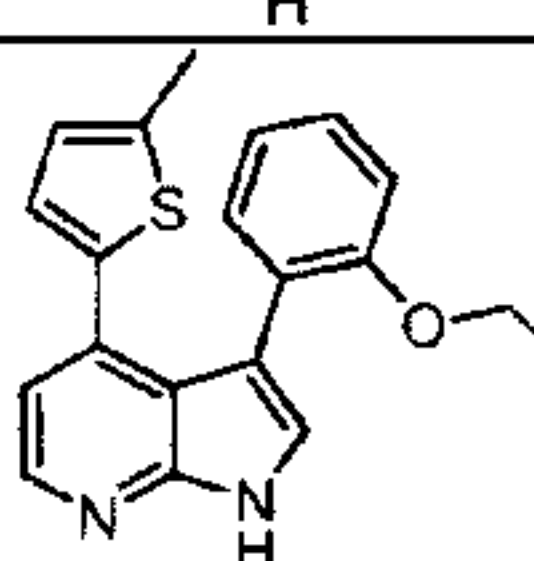
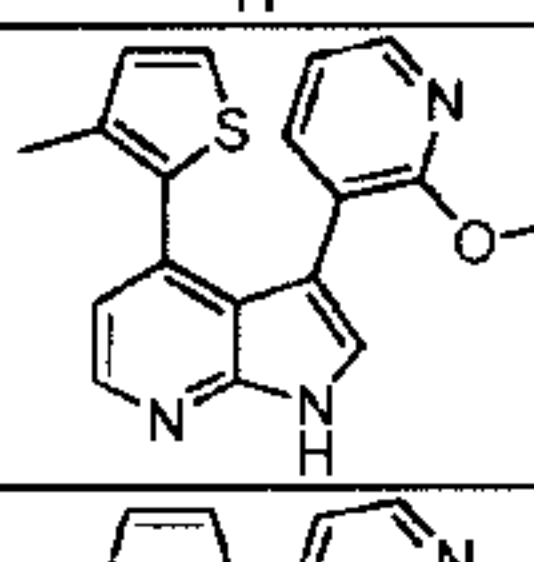
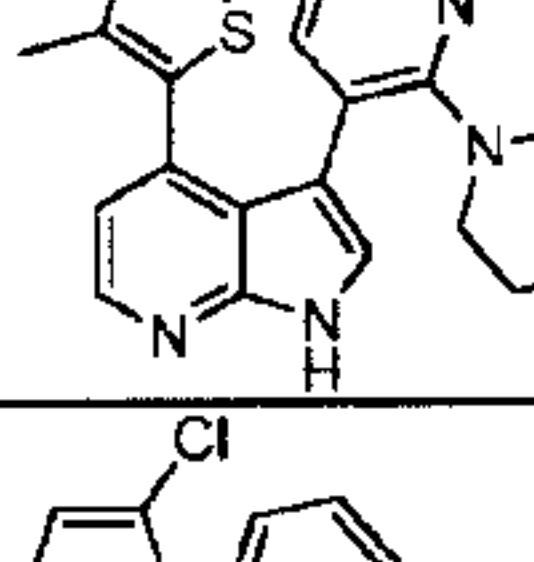
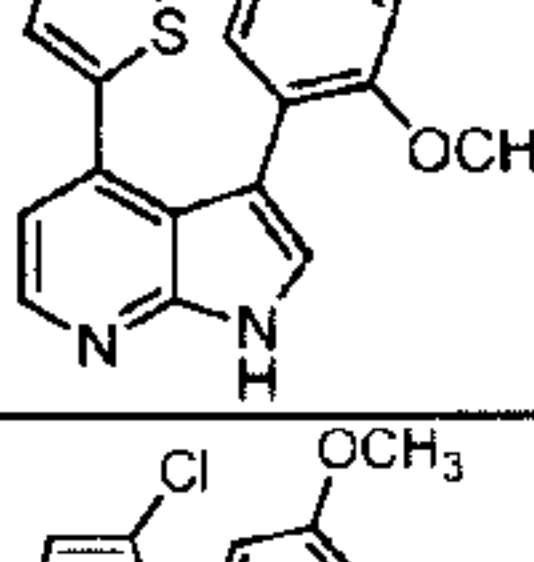
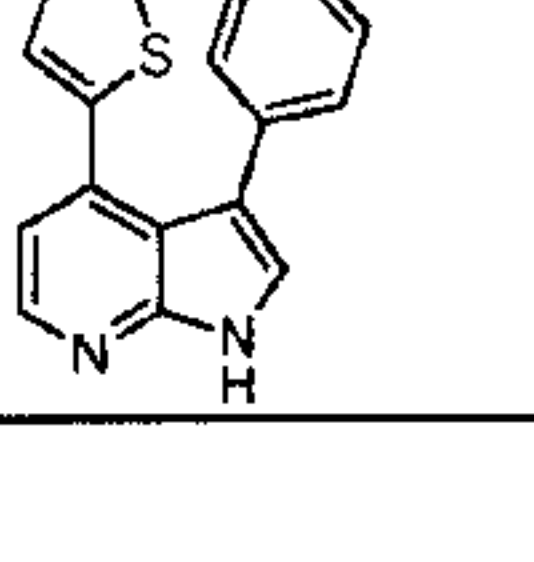
[00127] The invention will be further understood upon consideration of the following non-limiting Examples. In other aspects or embodiments are included any of the compounds in Table 1, Tables 2, 2A, 2B, and Table 3 that fall within the scope of any of the embodiments described above of the compounds of Formula I, IA and IB, or pharmaceuticals acceptable salts thereof.

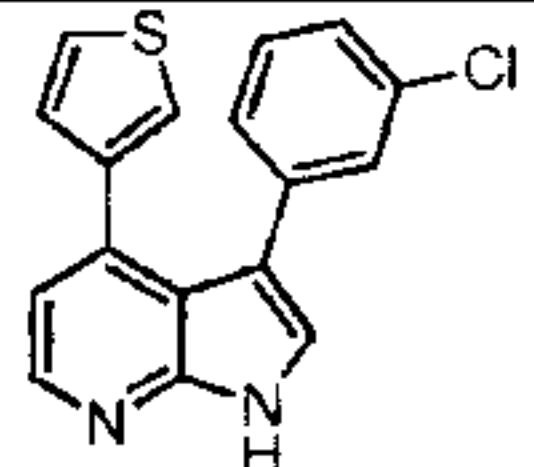
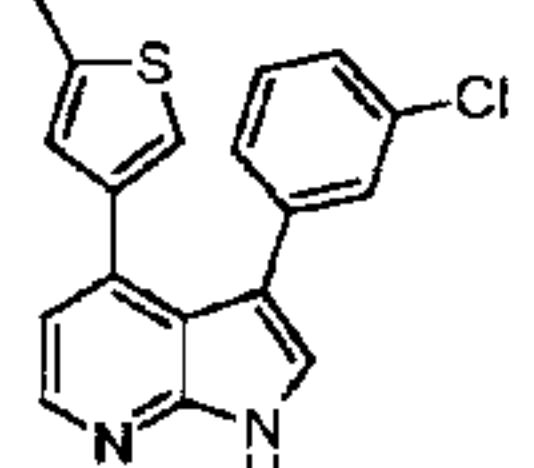
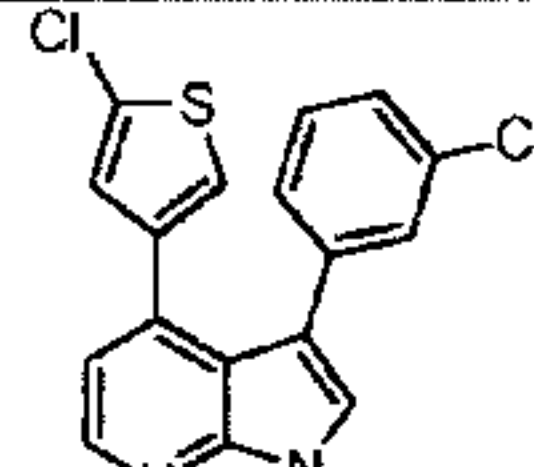
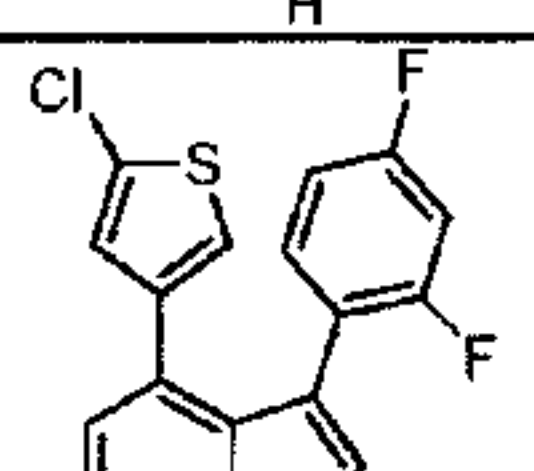
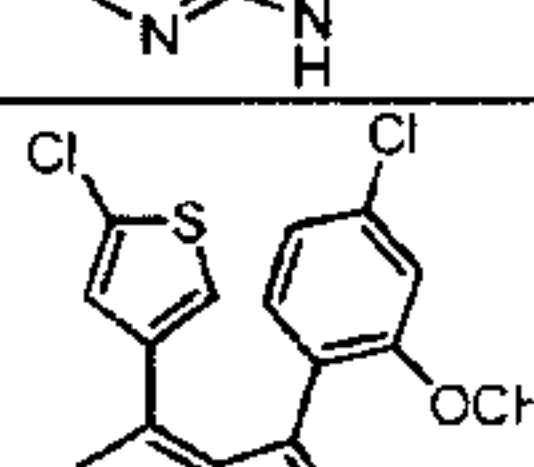
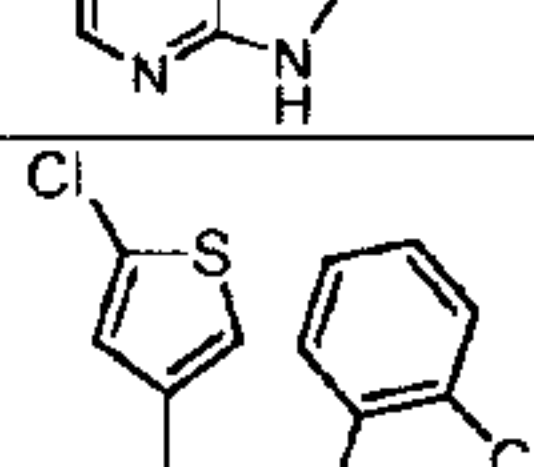
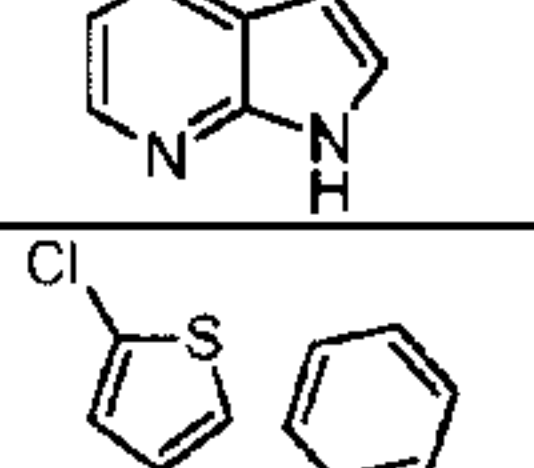
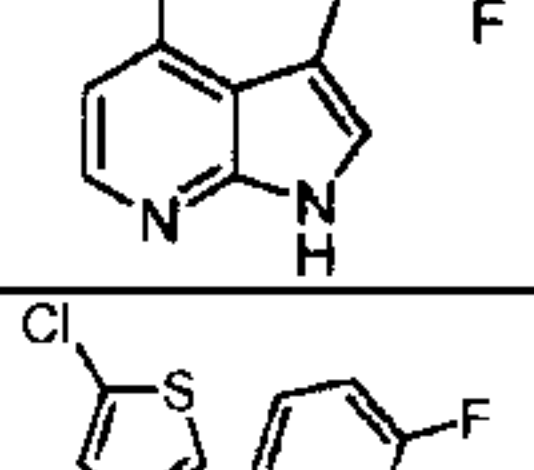
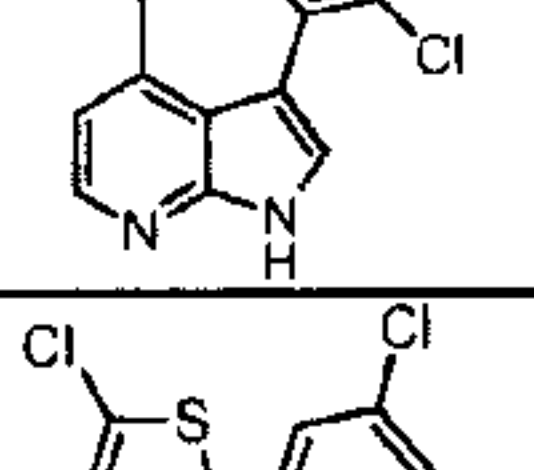
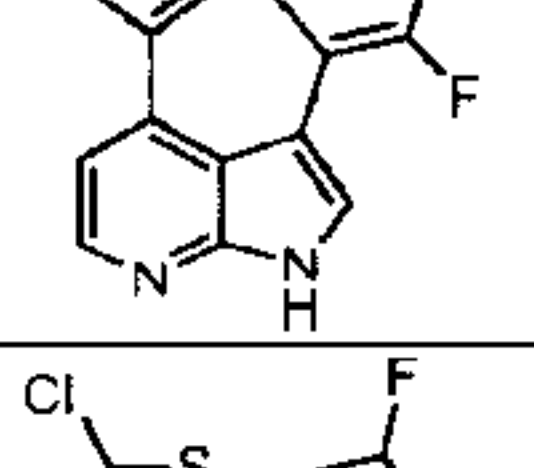
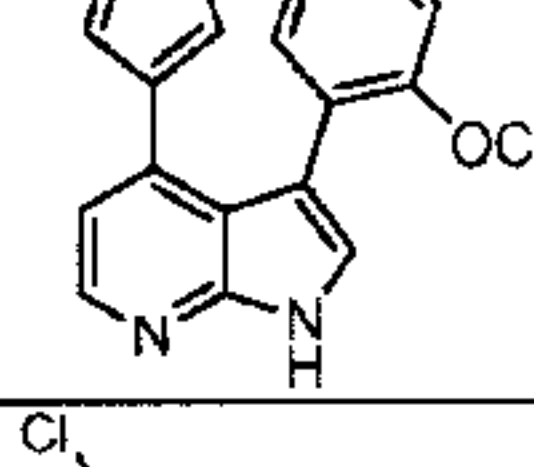
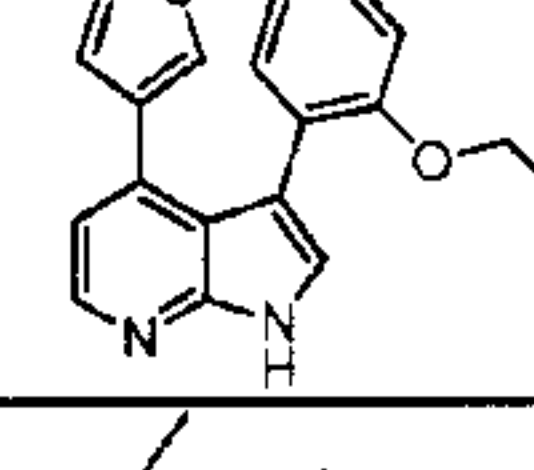
**Table 1: List of Examples**

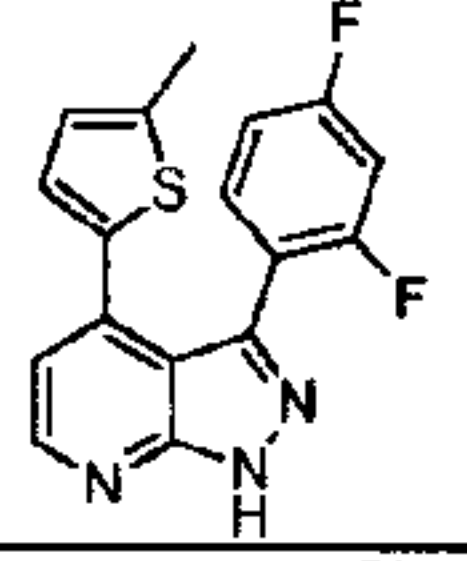
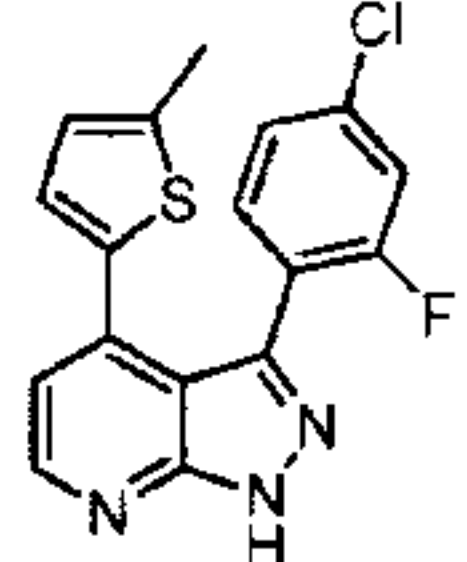
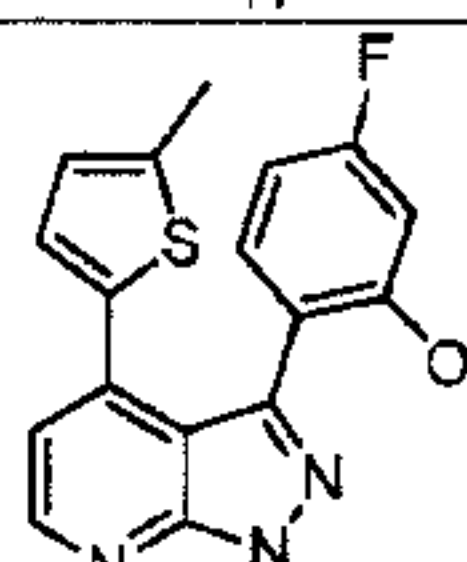
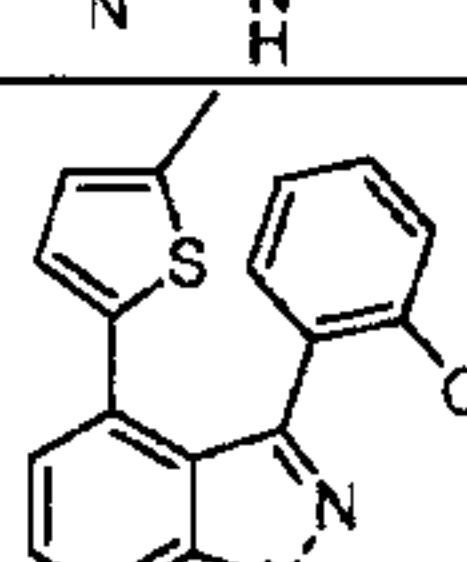
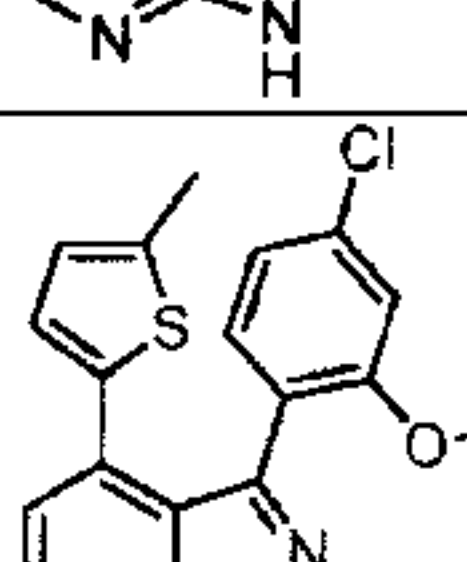
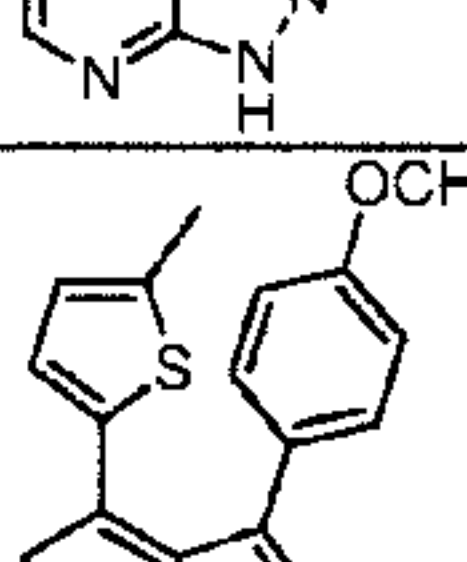
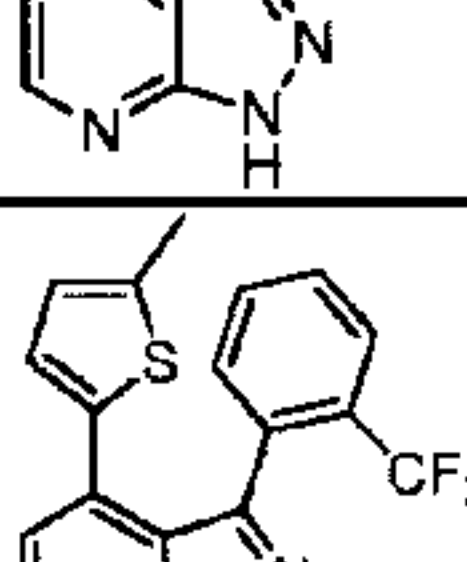
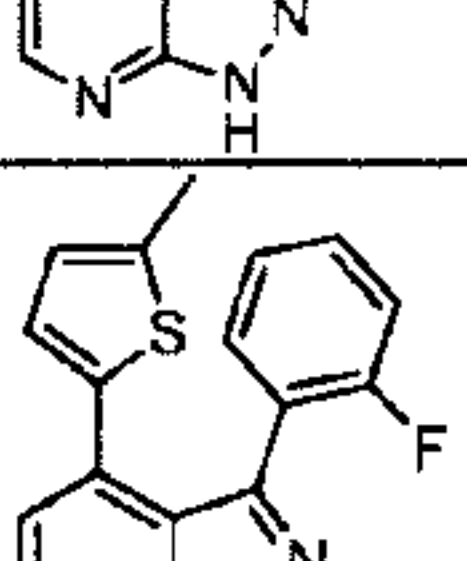
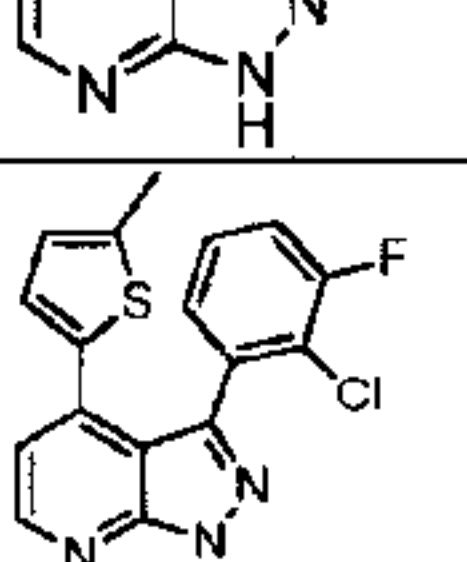
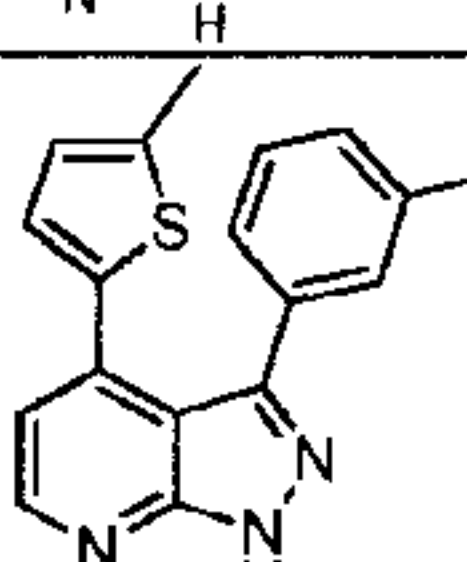
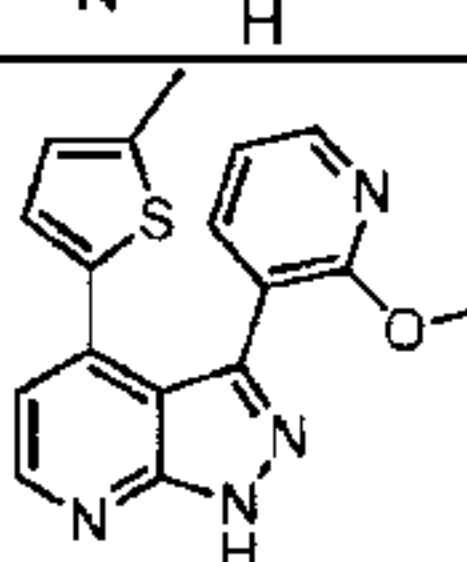
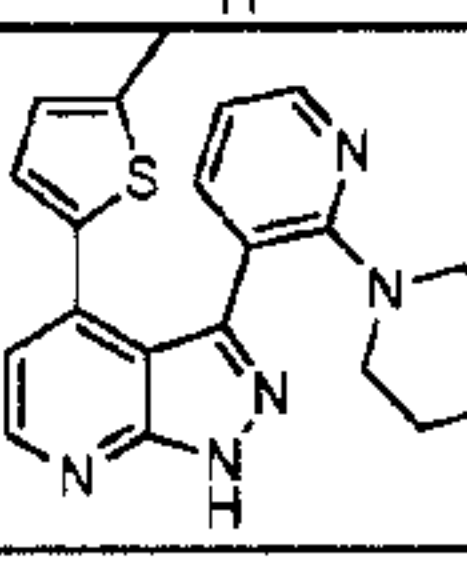
| EX. | Structure | Chemical Name                                                              | Mol. Wt |
|-----|-----------|----------------------------------------------------------------------------|---------|
| 1   |           | 3-(2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine            | 307.2   |
| 2   |           | 3-(2,4-difluorophenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine        | 312.8   |
| 3   |           | 3-(4-chloro-2-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine   | 329.78  |
| 4   |           | 3-(4-fluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine  | 325.36  |
| 5   |           | 3-(2-ethoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine            | 321.40  |
| 6   |           | 3-(4-chloro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine  | 341.81  |
| 7   |           | 3-(4-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine           | 307.37  |
| 8   |           | 4-(thiophen-3-yl)-3-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine | 345.34  |
| 9   |           | 3-(2-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine            | 295.33  |
| 10  |           | 3-(2-chloro-3-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine   | 329.78  |

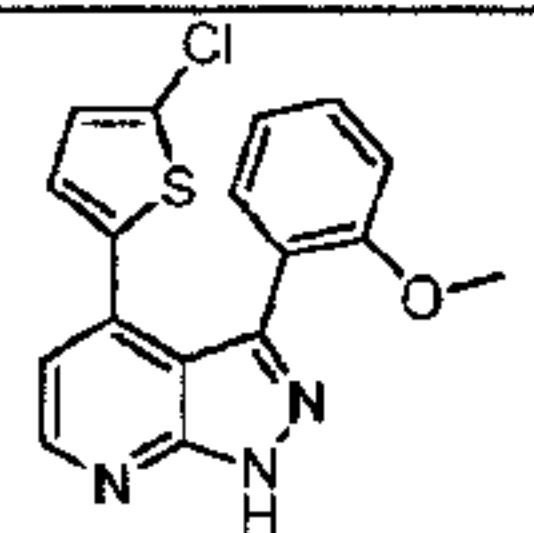
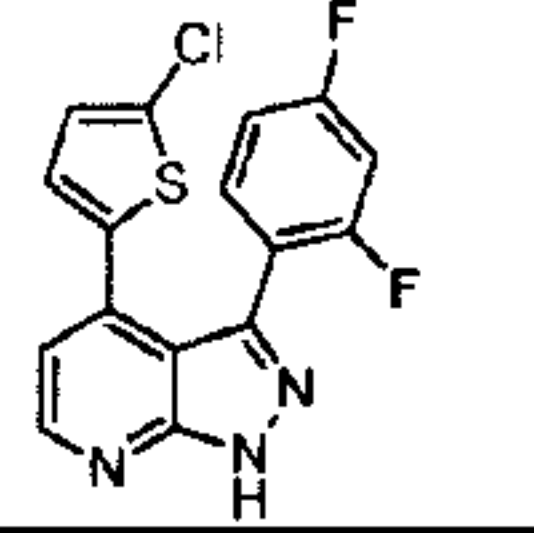
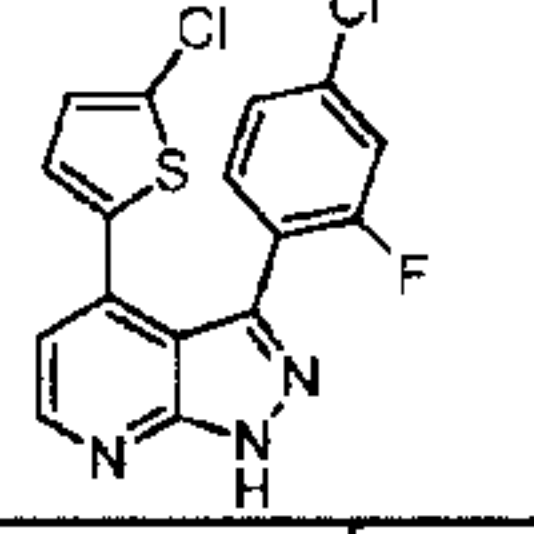
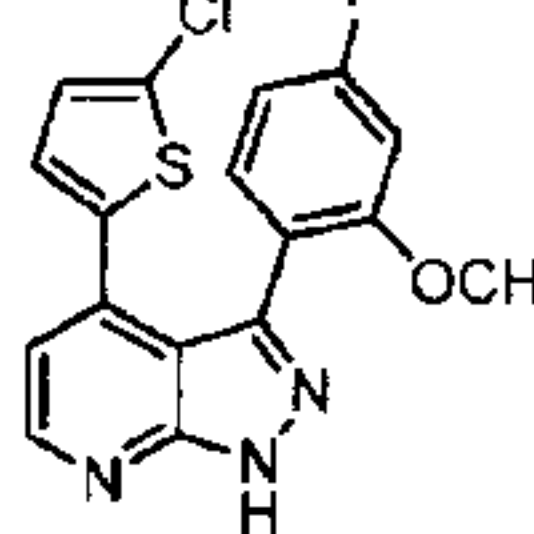
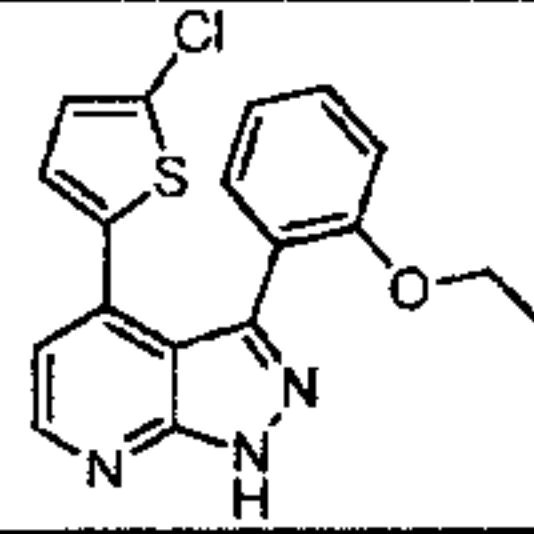
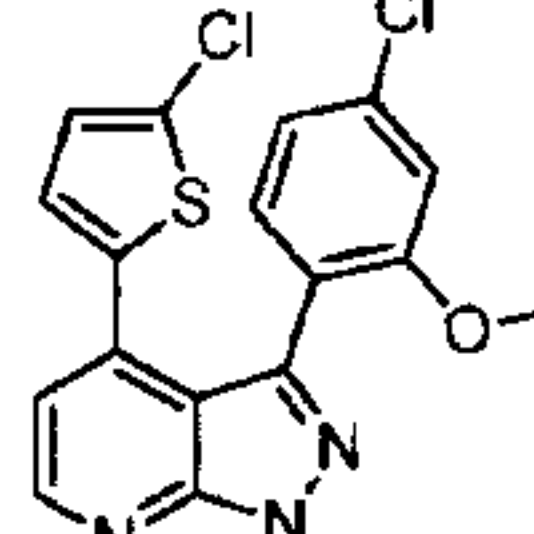
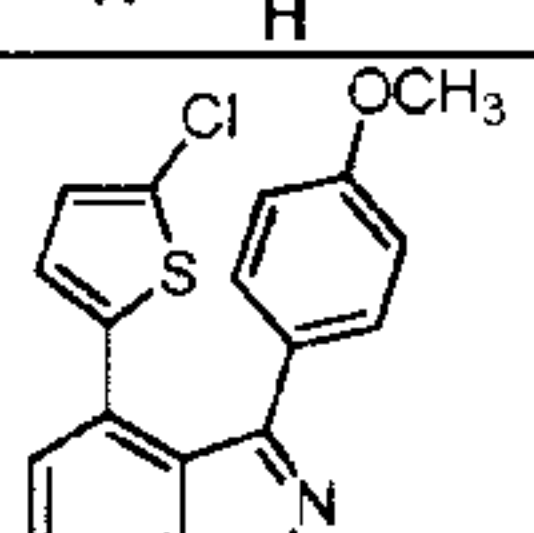
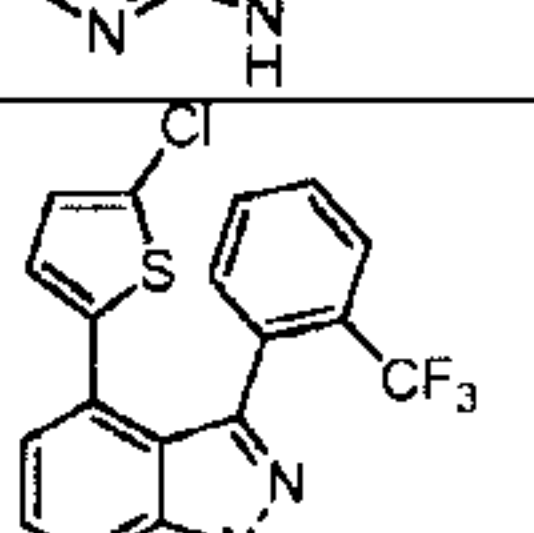
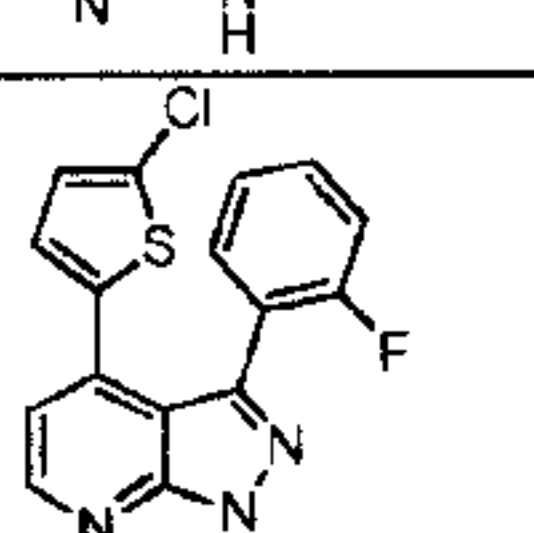
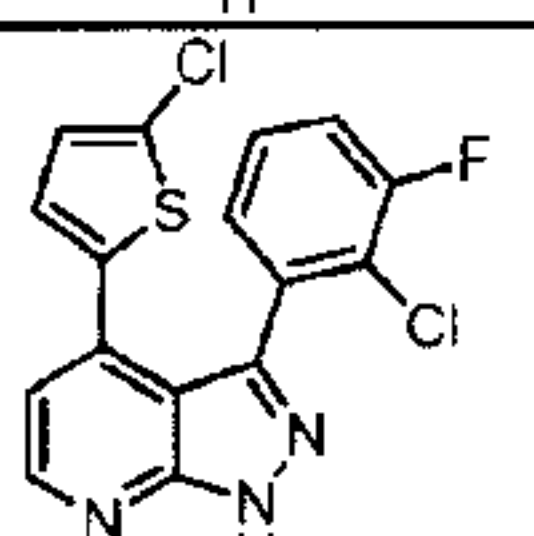
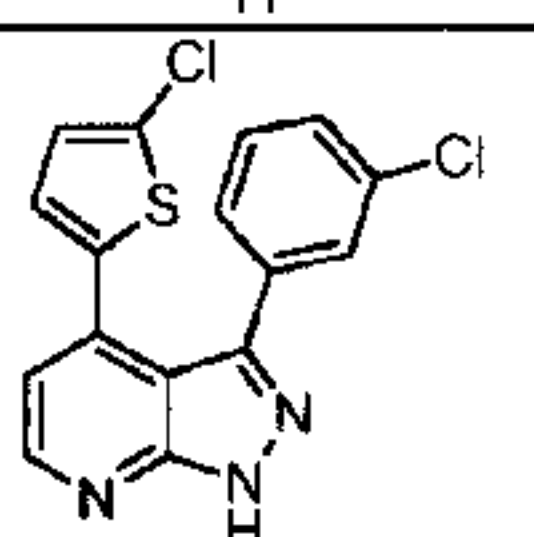
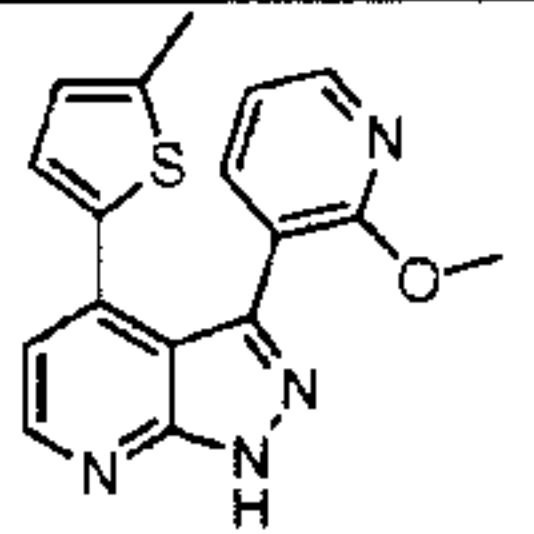
|    |                                                                                     |                                                                                                          |         |
|----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|---------|
| 11 |    | 3-(4-(4-methylpiperazin-1-yl)phenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine                        | 375.49  |
| 12 |    | 2,2,2-trifluoro-1-(4-(4-(4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)phenyl)piperazin-1-yl)ethanone | 457.47  |
| 13 |   | 4-(3-(2-chloro-3-fluorophenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)-2-methylthiazole                          | 344.79  |
| 14 |  | 4-(3-(4-chloro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)-2-methylthiazole                         | 356.83  |
| 15 |  | 4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine                                                             | 201.25  |
| 16 |  | 3-fluoro-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine                                                    | 219.24  |
| 17 |  | 3-(2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                                          | 306.382 |
| 18 |  | 3-(2,4-difluorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                                       | 312.337 |
| 19 |  | 4-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine                                                            | 224.258 |
| 20 |  | 4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                                                              | 200.260 |
| 21 |  | 4-(thiophen-3-yl)-3-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine                                | 344.354 |
| 22 |  | 3-(2-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                                           | 294.346 |

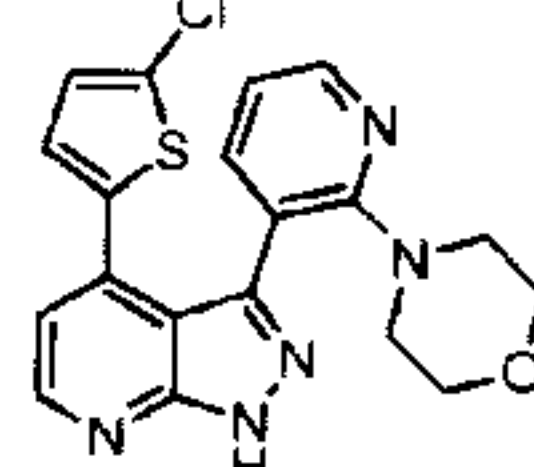
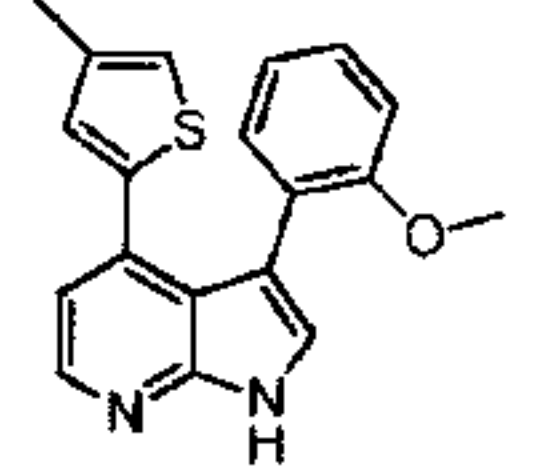
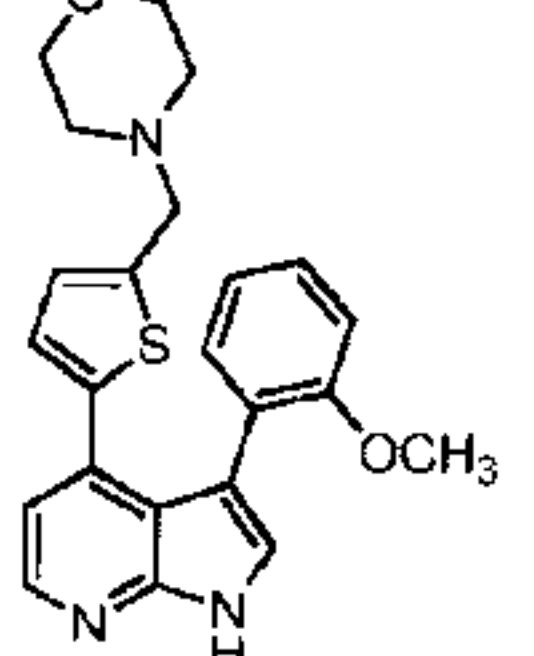
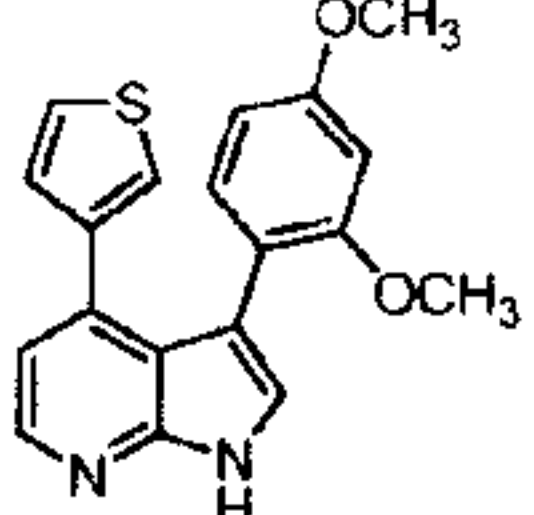
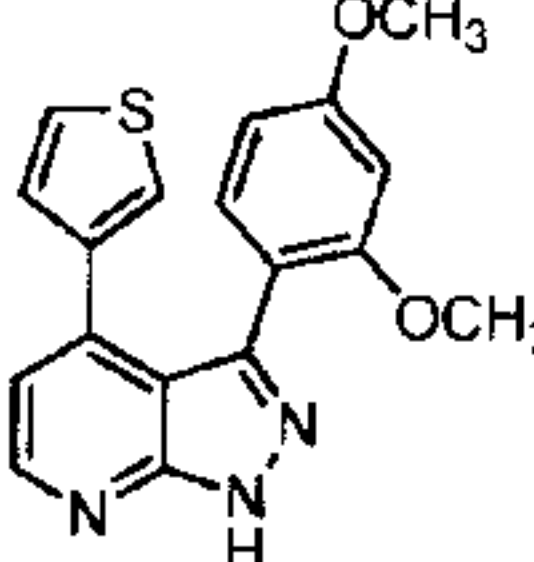
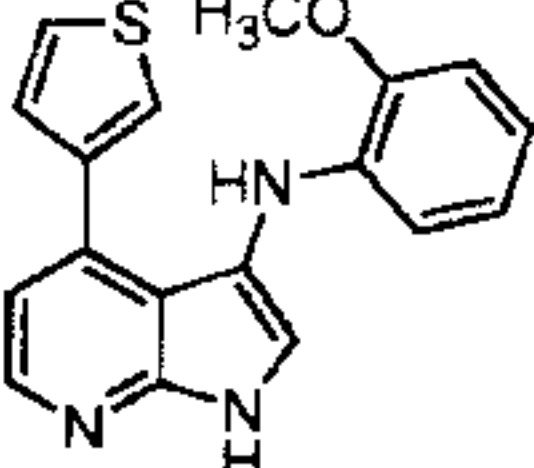
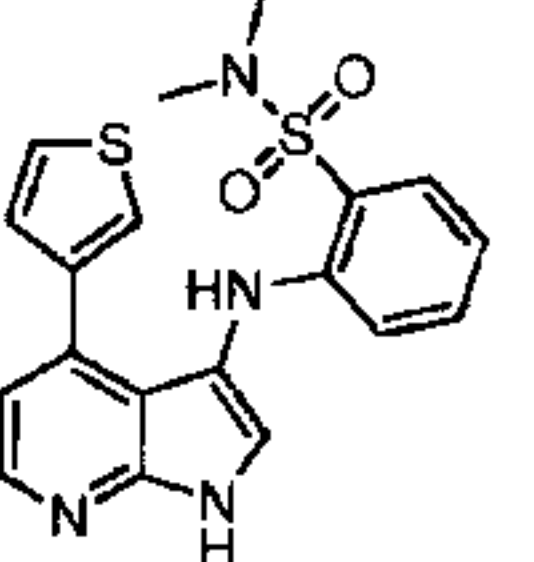
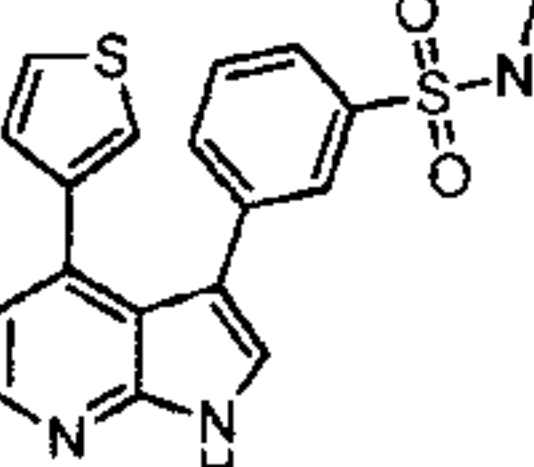
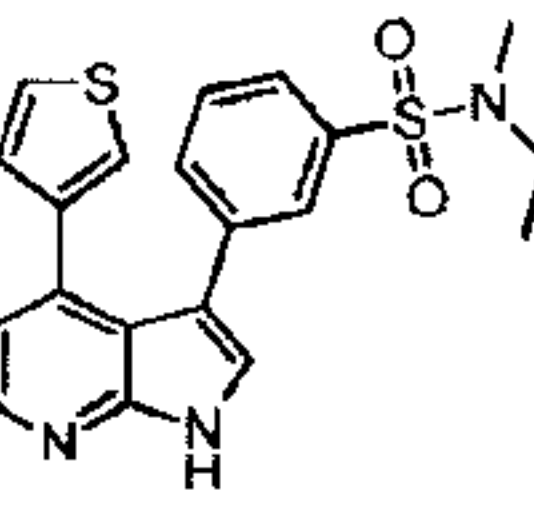
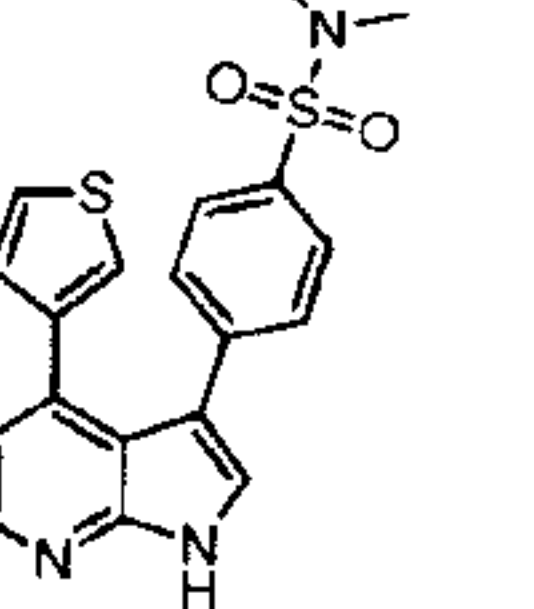
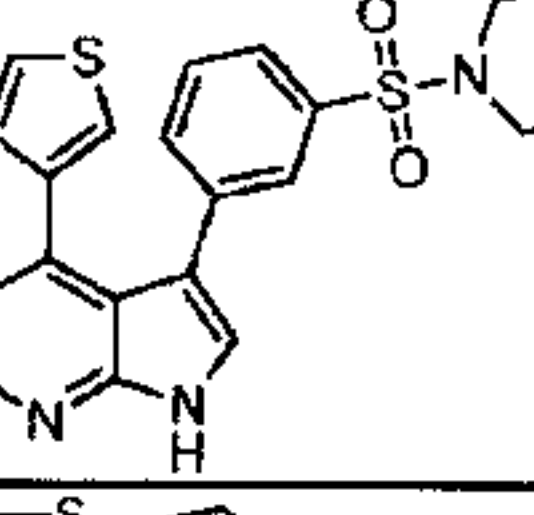
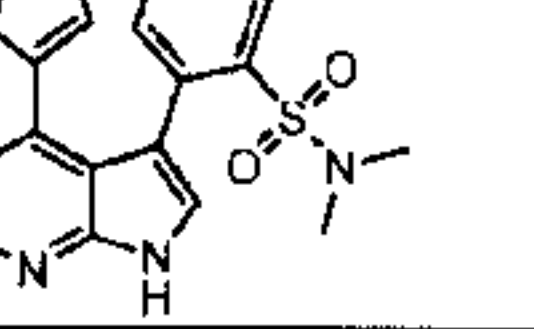
|    |                                                                                     |                                                                                   |         |
|----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------|
| 23 |    | 3-(2-chloro-3-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine           | 328.791 |
| 24 |    | 3-(4-chloro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine          | 340.827 |
| 25 |    | 3-(4-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                   | 306.382 |
| 26 |   | 3-(2-ethoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                    | 320.408 |
| 27 |  | 3-(4-chloro-2-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine           | 328.791 |
| 28 |  | 3-(4-fluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine          | 324.372 |
| 29 |  | 4-chloro-3-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                              | 234.705 |
| 30 |  | 4-(2-methoxyphenyl)-3-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                   | 306.382 |
| 31 |  | 3-(2-methoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine           | 320.408 |
| 32 |  | 3-(2,4-difluorophenyl)-4-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine        | 326.363 |
| 33 |  | 3-(4-chloro-2-methoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine  | 354.853 |
| 34 |  | 4-(5-methylthiophen-2-yl)-3-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine | 358.380 |

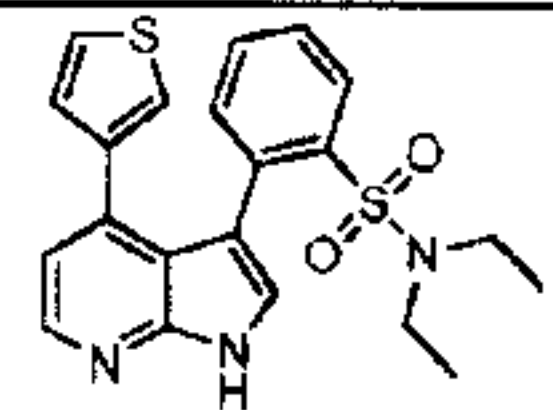
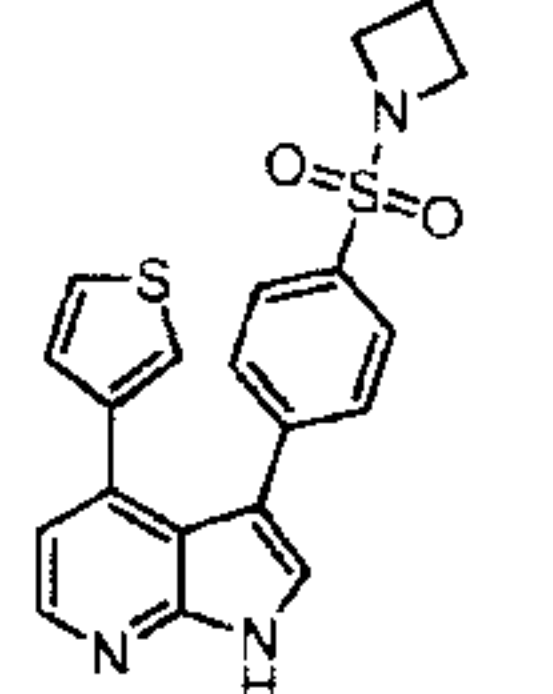
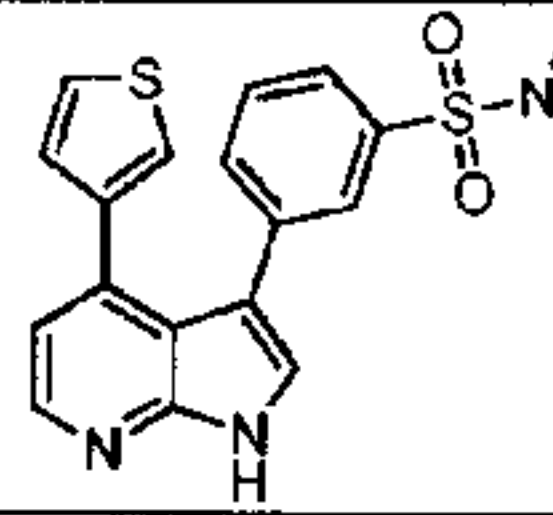
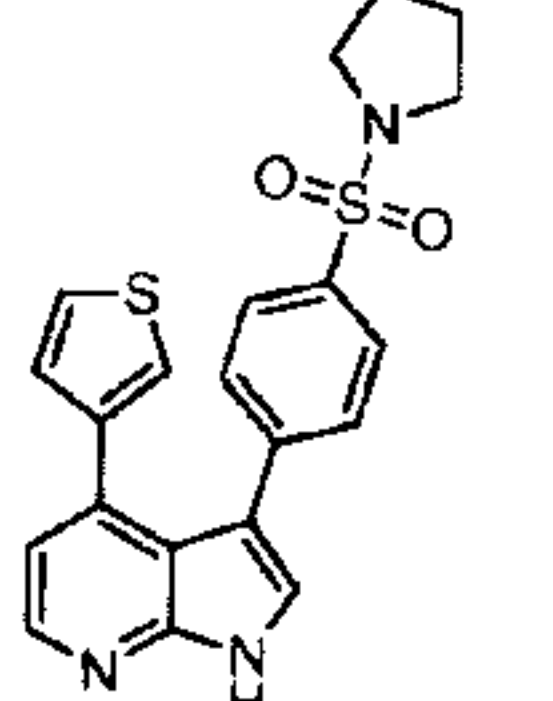
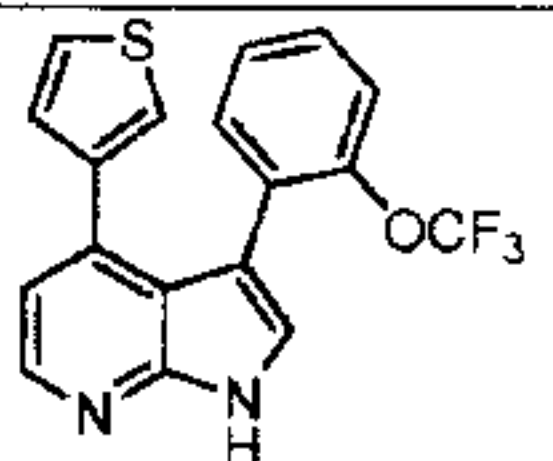
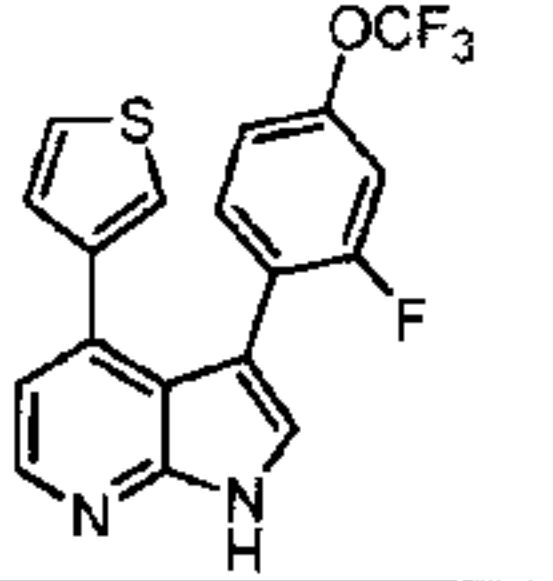
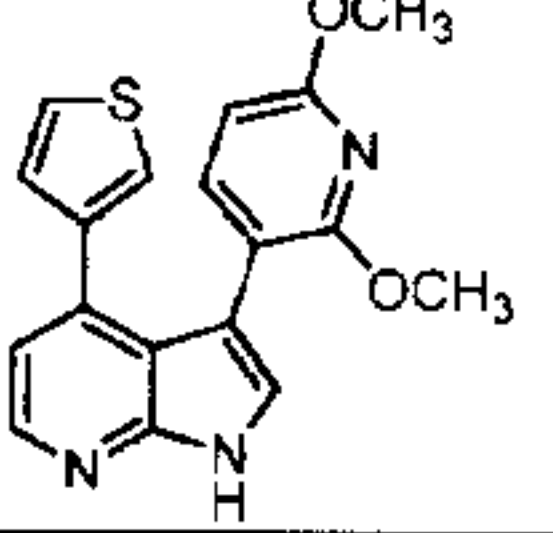
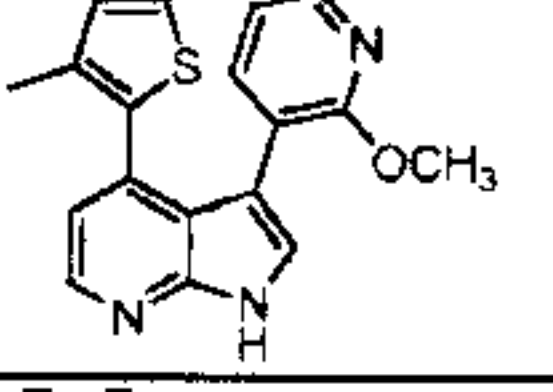
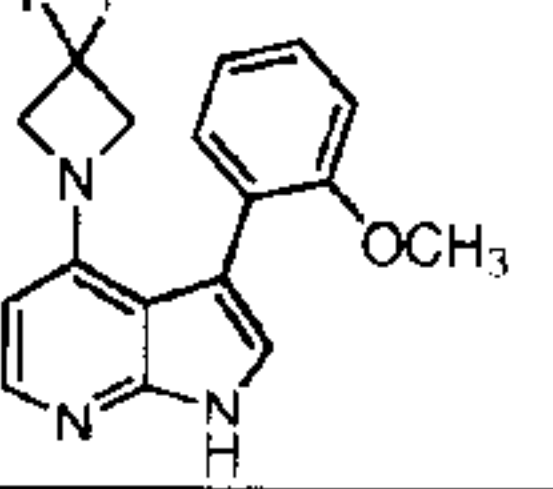
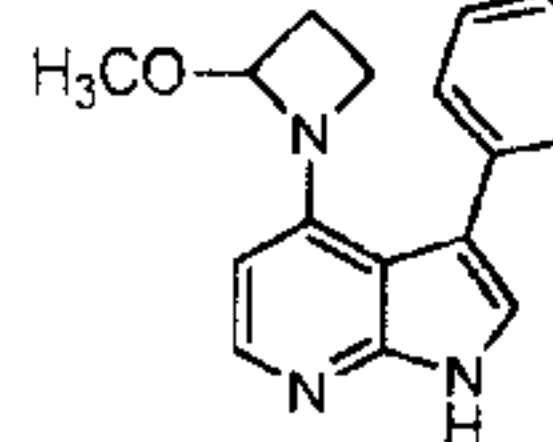
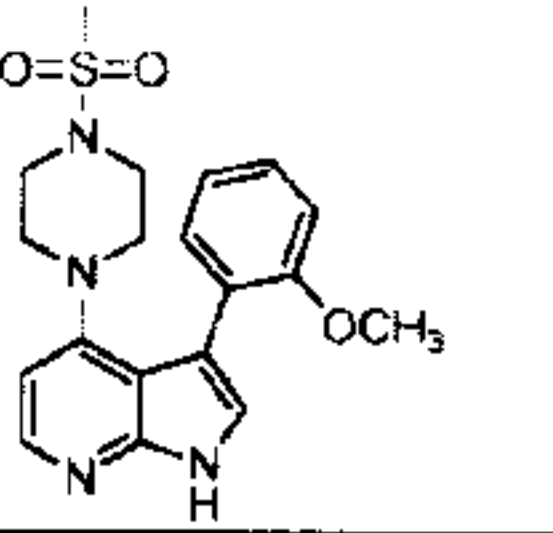
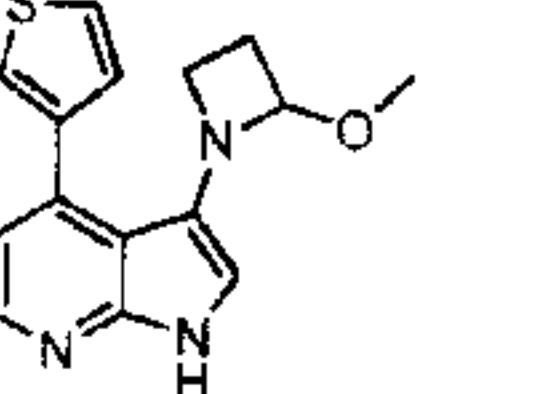
|    |                                                                                     |                                                                                       |         |
|----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------|
| 35 |    | 3-(2-fluorophenyl)-4-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine                | 308.373 |
| 36 |    | 3-(2-methoxypyridin-3-yl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                 | 307.370 |
| 37 |    | 4-(3-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)morpholine         | 362.448 |
| 38 |   | 3-(2-chloro-3-fluorophenyl)-4-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine       | 342.818 |
| 39 |  | 3-(4-chloro-2-fluorophenyl)-4-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine       | 342.818 |
| 40 |  | 3-(4-fluoro-2-methoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine      | 338.399 |
| 41 |  | 3-(4-methoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine               | 320.408 |
| 42 |  | 3-(2-ethoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine                | 334.435 |
| 43 |  | 3-(2-methoxypyridin-3-yl)-4-(3-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine         | 321.396 |
| 44 |  | 4-(3-(4-(3-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)morpholine | 376.475 |
| 45 |  | 4-(5-chlorothiophen-2-yl)-3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine               | 340.827 |
| 46 |  | 4-(5-chlorothiophen-2-yl)-3-(4-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine               | 340.827 |

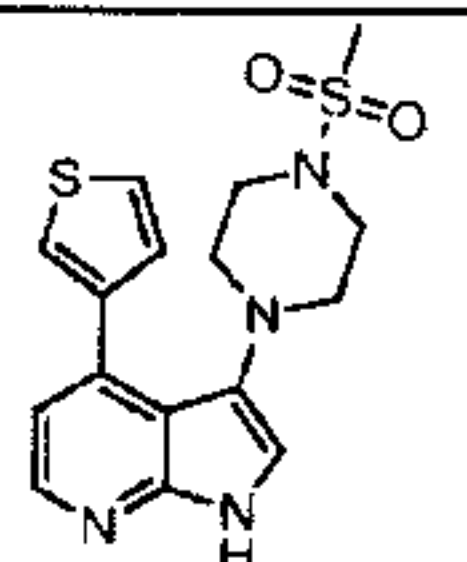
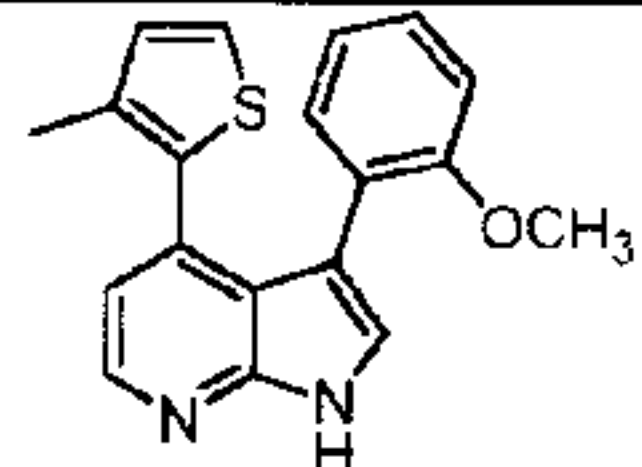
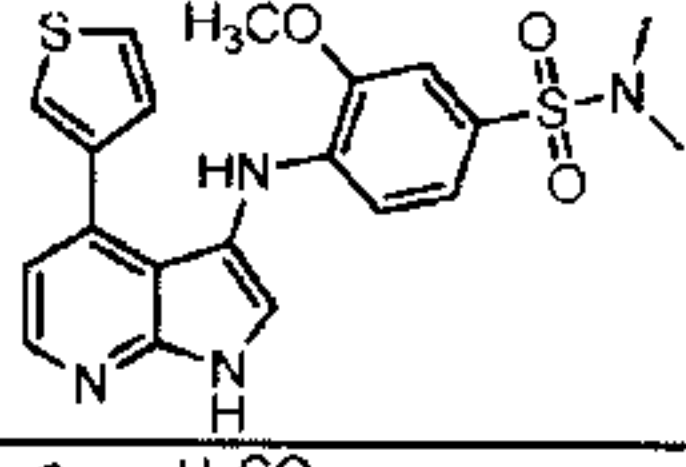
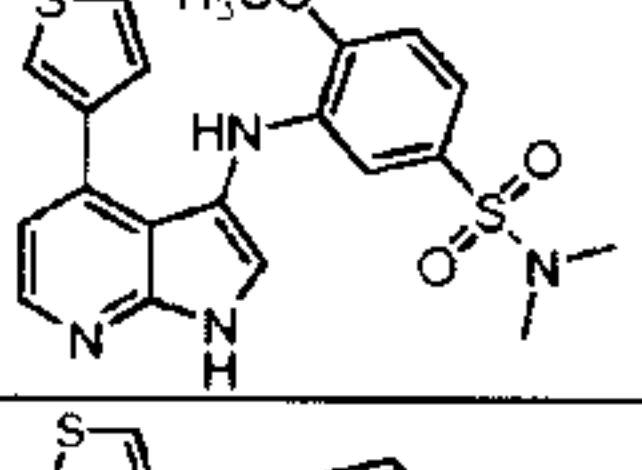
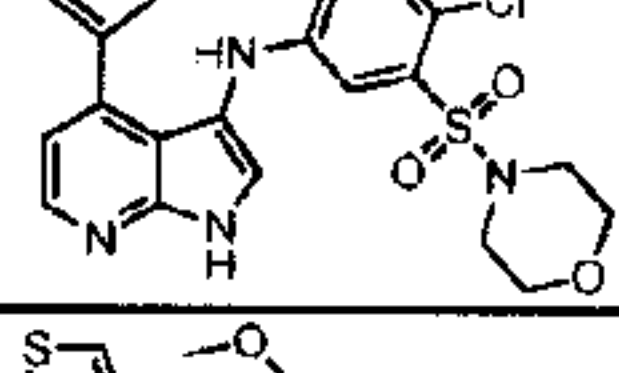
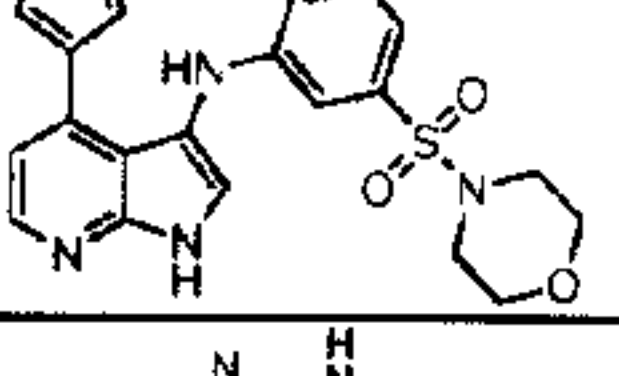
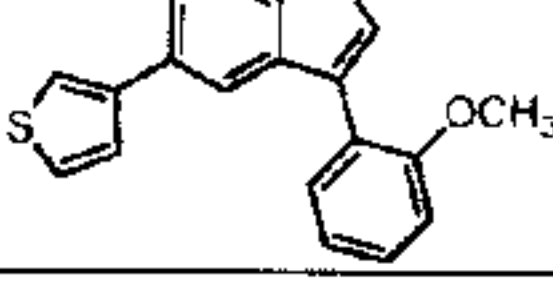
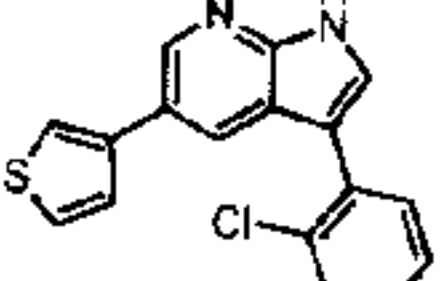
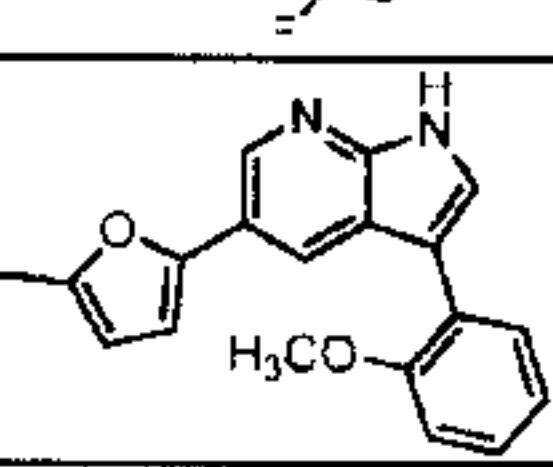
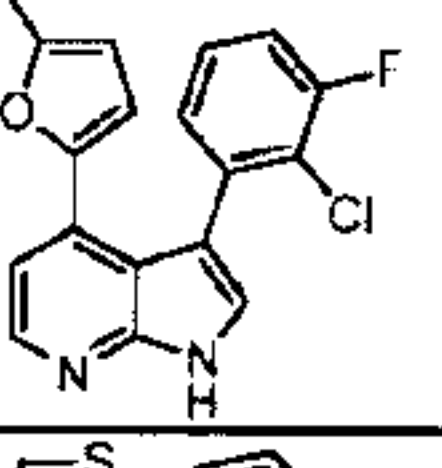
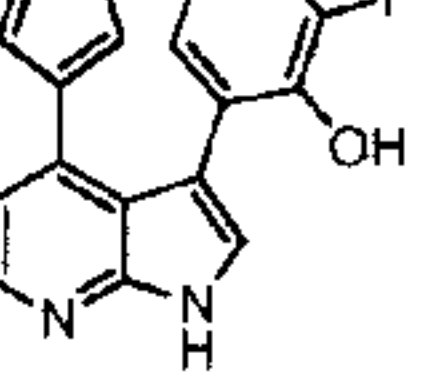
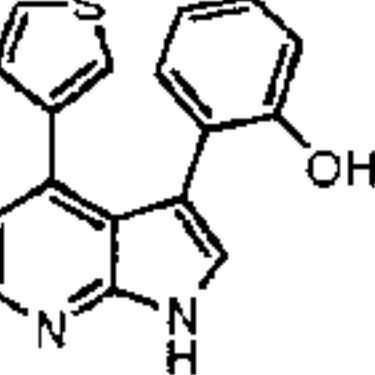
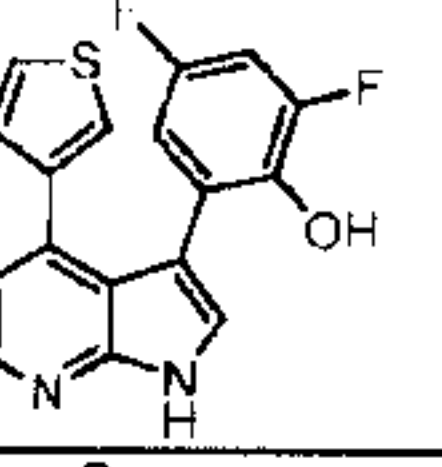
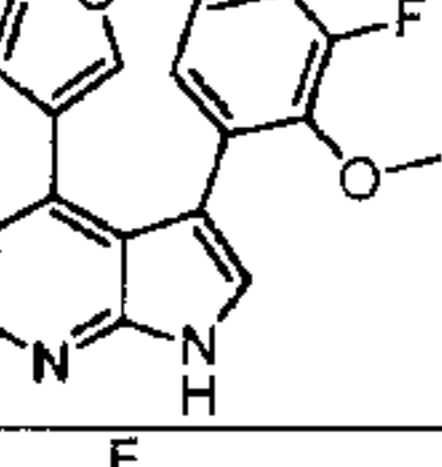
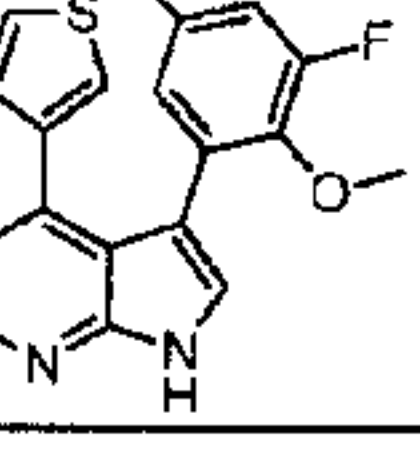
|    |                                                                                     |                                                                                   |         |
|----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------|
| 47 |    | 3-(3-chlorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                    | 310.801 |
| 48 |    | 3-(3-chlorophenyl)-4-(5-methylthiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine            | 324.827 |
| 49 |    | 3-(3-chlorophenyl)-4-(5-chlorothiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine            | 345.246 |
| 50 |   | 4-(5-chlorothiophen-3-yl)-3-(2,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridine        | 346.782 |
| 51 |  | 3-(4-chloro-2-methoxyphenyl)-4-(5-chlorothiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine  | 375.272 |
| 52 |  | 4-(5-chlorothiophen-3-yl)-3-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine | 378.799 |
| 53 |  | 4-(5-chlorothiophen-3-yl)-3-(2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine            | 328.791 |
| 54 |  | 3-(2-chloro-3-fluorophenyl)-4-(5-chlorothiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine   | 363.236 |
| 55 |  | 3-(4-chloro-2-fluorophenyl)-4-(5-chlorothiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine   | 363.236 |
| 56 |  | 4-(5-chlorothiophen-3-yl)-3-(4-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine  | 358.817 |
| 57 |  | 4-(5-chlorothiophen-3-yl)-3-(2-ethoxyphenyl)-1H-pyrrolo[2,3-b]pyridine            | 354.853 |
| 58 |  | 3-(2-methoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine          | 321.396 |

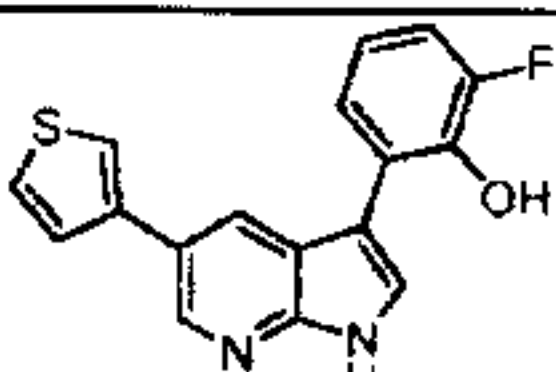
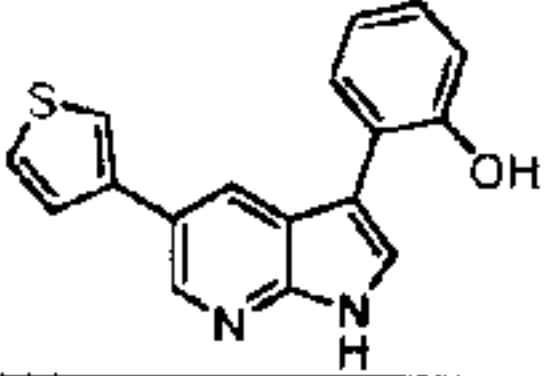
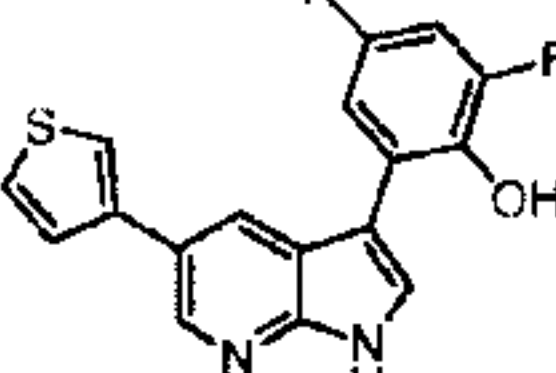
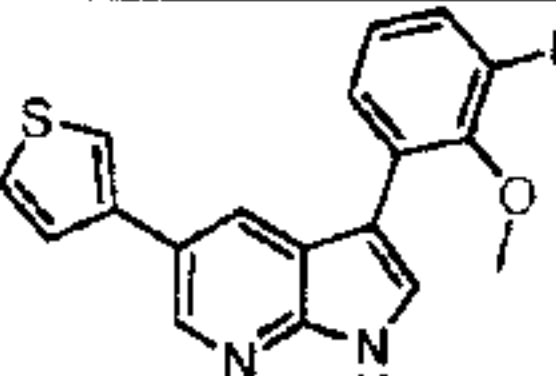
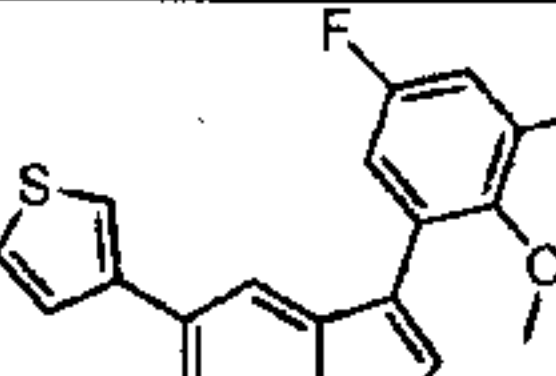
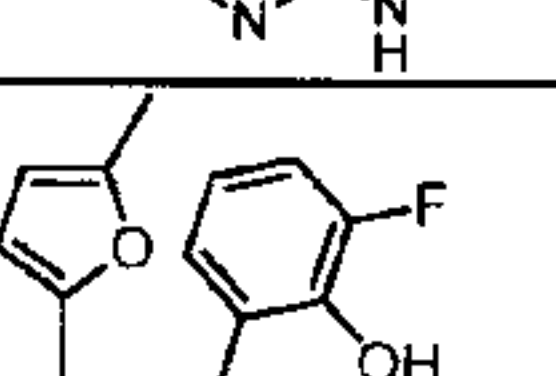
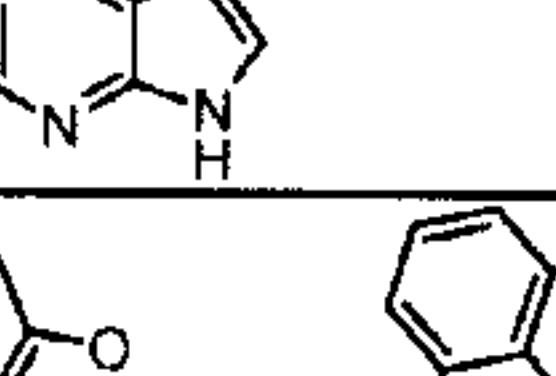
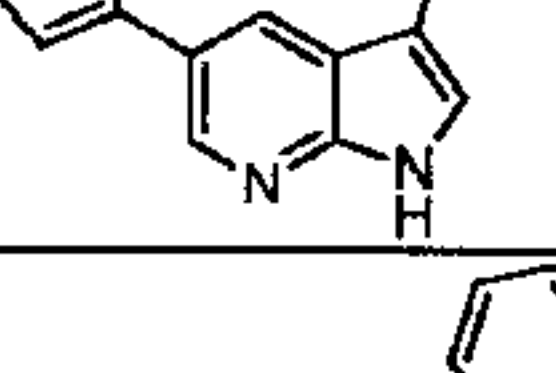
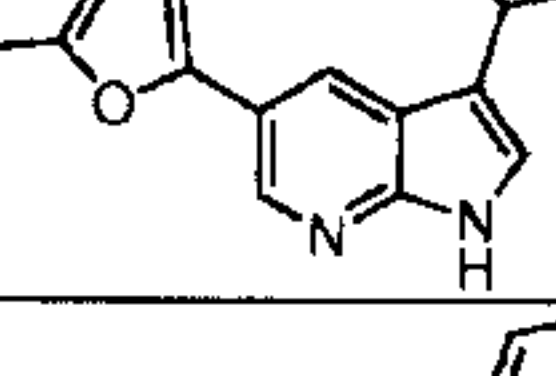
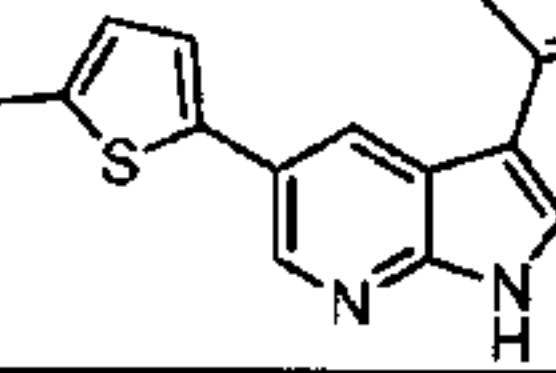
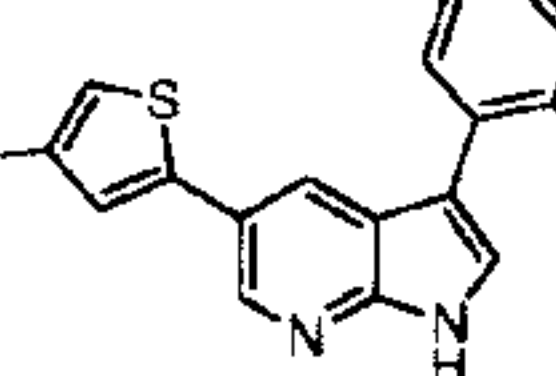
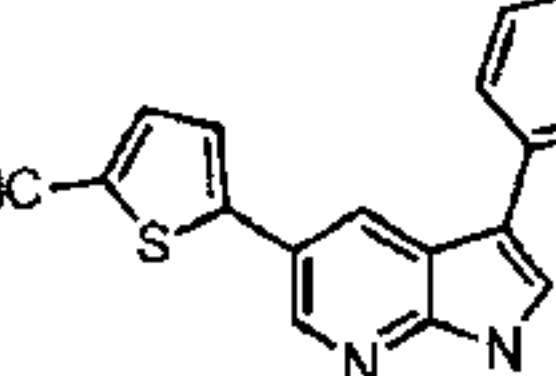
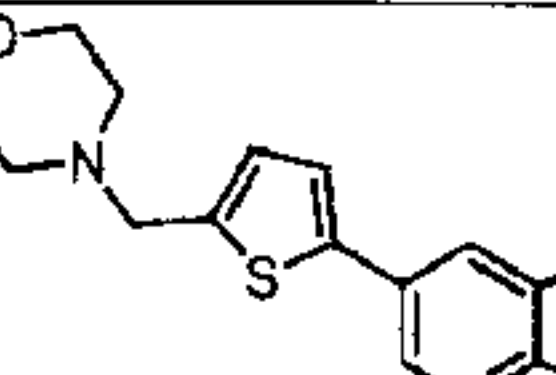
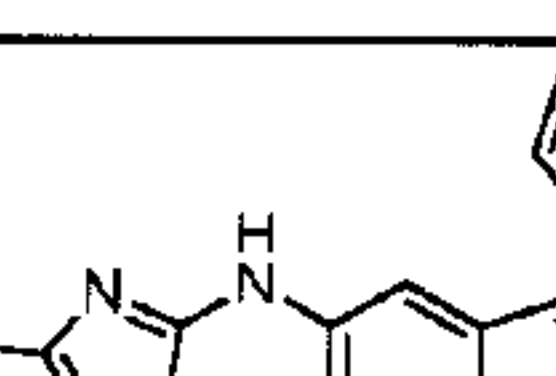
|    |                                                                                     |                                                                                        |         |
|----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------|
| 59 |    | 3-(2,4-difluorophenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine            | 327.351 |
| 60 |    | 3-(4-chloro-2-fluorophenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine       | 343.806 |
| 61 |    | 3-(4-fluoro-2-methoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine      | 339.387 |
| 62 |   | 3-(2-ethoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine                | 335.423 |
| 63 |  | 3-(4-chloro-2-methoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine      | 355.841 |
| 64 |  | 3-(4-methoxyphenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine               | 321.396 |
| 65 |  | 4-(5-methylthiophen-2-yl)-3-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine     | 359.368 |
| 66 |  | 3-(2-fluorophenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine                | 309.361 |
| 67 |  | 3-(2-chloro-3-fluorophenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine       | 343.806 |
| 68 |  | 3-(3-chlorophenyl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine                | 325.815 |
| 69 |  | 3-(2-methoxypyridin-3-yl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine         | 322.384 |
| 70 |  | 4-(3-(4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyridin-2-yl)morpholine | 377.463 |

|    |                                                                                     |                                                                                    |         |
|----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------|
| 71 |    | 4-(5-chlorothiophen-2-yl)-3-(2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridine           | 341.815 |
| 72 |    | 4-(5-chlorothiophen-2-yl)-3-(2,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridine        | 347.770 |
| 73 |    | 3-(4-chloro-2-fluorophenyl)-4-(5-chlorothiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine   | 364.224 |
| 74 |   | 4-(5-chlorothiophen-2-yl)-3-(4-fluoro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridine  | 359.805 |
| 75 |  | 4-(5-chlorothiophen-2-yl)-3-(2-ethoxyphenyl)-1H-pyrazolo[3,4-b]pyridine            | 355.841 |
| 76 |  | 3-(4-chloro-2-methoxyphenyl)-4-(5-chlorothiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine  | 376.260 |
| 77 |  | 4-(5-chlorothiophen-2-yl)-3-(4-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridine           | 341.815 |
| 78 |  | 4-(5-chlorothiophen-2-yl)-3-(2-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine | 379.787 |
| 79 |  | 4-(5-chlorothiophen-2-yl)-3-(2-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine            | 329.779 |
| 80 |  | 3-(2-chloro-3-fluorophenyl)-4-(5-chlorothiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine   | 364.224 |
| 81 |  | 3-(3-chlorophenyl)-4-(5-chlorothiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine            | 346.234 |
| 82 |  | 3-(2-methoxypyridin-3-yl)-4-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine     | 322.384 |

|    |                                                                                     |                                                                                               |         |
|----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------|
| 83 |    | 4-(3-(4-(5-chlorothiophen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyridin-2-yl)morpholine        | 397.881 |
| 84 |    | 3-(2-methoxyphenyl)-4-(4-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine                       | 320.408 |
| 85 |    | 4-(((5-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)thiophen-2-yl)methyl)morpholine     | 405.513 |
| 86 |   | 3-(2,4-dimethoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                           | 336.408 |
| 87 |  | 3-(2,4-dimethoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine                          | 337.396 |
| 88 |  | N-(4-fluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-amine               | 339.387 |
| 89 |  | N,N-dimethyl-2-((4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)amino)benzenesulfonamide     | 398.502 |
| 90 |  | N,N-dimethyl-3-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide            | 383.487 |
| 91 |  | N-(tert-butyl)-N-methyl-3-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide | 425.567 |
| 92 |  | N,N-dimethyl-4-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide            | 383.487 |
| 93 |  | N,N-diethyl-3-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide             | 411.540 |
| 94 |  | N,N-dimethyl-2-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide            | 383.487 |

|     |                                                                                     |                                                                                     |         |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------|
| 95  |    | N,N-diethyl-2-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide   | 411.540 |
| 96  |    | 3-(4-(azetidin-1-ylsulfonyl)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine     | 395.498 |
| 97  |    | 3-(3-(pyrrolidin-1-ylsulfonyl)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine   | 409.524 |
| 98  |   | 3-(4-(pyrrolidin-1-ylsulfonyl)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine   | 409.524 |
| 99  |  | 4-(thiophen-3-yl)-3-(2-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-b]pyridine          | 360.353 |
| 100 |  | 3-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine | 378.343 |
| 101 |  | 3-(2,6-dimethoxypyridin-3-yl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine           | 337.396 |
| 102 |  | 3-(2-methoxypyridin-3-yl)-4-(3-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine       | 321.396 |
| 103 |  | 4-(3,3-difluoroazetidin-1-yl)-3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine         | 315.317 |
| 104 |  | 4-(2-methoxyazetidin-1-yl)-3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine            | 309.362 |
| 105 |  | 3-(2-methoxyphenyl)-4-(4-(methylsulfonyl)piperazin-1-yl)-1H-pyrrolo[2,3-b]pyridine  | 386.468 |
| 106 |  | 3-(2-methoxyazetidin-1-yl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine              | 285.364 |

|     |                                                                                     |                                                                                                     |         |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------|
| 107 |    | 3-(4-(methylsulfonyl)piperazin-1-yl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                    | 362.470 |
| 108 |    | 3-(2-methoxyphenyl)-4-(3-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine                             | 320.408 |
| 109 |    | 3-methoxy-N,N-dimethyl-4-((4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)amino)benzenesulfonamide | 428.528 |
| 110 |   | 4-methoxy-N,N-dimethyl-3-((4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)amino)benzenesulfonamide | 428.528 |
| 111 |  | N-(4-chloro-3-(morpholinosulfonyl)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-amine        | 474.984 |
| 112 |  | N-(2-methoxy-5-(morpholinosulfonyl)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-amine       | 470.564 |
| 113 |  | 3-(2-methoxyphenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                                     | 306.382 |
| 114 |  | 3-(2-chloro-3-fluorophenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                             | 328.791 |
| 115 |  | 3-(2-methoxyphenyl)-5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridine                                | 304.343 |
| 116 |  | 3-(2-chloro-3-fluorophenyl)-4-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridine                        | 326.752 |
| 117 |  | 2-fluoro-6-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                                  | 310.345 |
| 118 |  | 2-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                                           | 292.355 |
| 119 |  | 2,4-difluoro-6-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                              | 328.336 |
| 120 |  | 3-(3-fluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                            | 324.372 |
| 121 |  | 3-(3,5-difluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                        | 342.362 |

|     |                                                                                     |                                                                                                  |         |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------|
| 122 |    | 2-fluoro-6-(5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                               | 310.345 |
| 123 |    | 2-(5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                                        | 292.355 |
| 124 |    | 2,4-difluoro-6-(5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                           | 328.336 |
| 125 |    | 3-(3-fluoro-2-methoxyphenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                         | 324.372 |
| 126 |   | 3-(3,5-difluoro-2-methoxyphenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                     | 342.362 |
| 127 |  | 2-fluoro-6-(4-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                          | 308.306 |
| 128 |  | 2-fluoro-6-(5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                          | 308.306 |
| 129 |  | 3-(2-chloro-3-fluorophenyl)-5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridine                     | 326.752 |
| 130 |  | 3-(2-chloro-3-fluorophenyl)-5-(5-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine                  | 342.818 |
| 131 |  | 3-(2-chloro-3-fluorophenyl)-5-(4-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine                  | 342.818 |
| 132 |  | 5-(3-(2-chloro-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophene-2-carbonitrile            | 353.801 |
| 133 |  | 4-((5-(3-(2-chloro-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine | 427.922 |
| 134 |  | 5-chloro-N-(3-(2-chloro-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-4-methylthiazol-2-amine   | 393.265 |
| 135 |  | 3-(3-(2-chloro-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N,N-dimethylbenzenesulfonamide     | 429.895 |

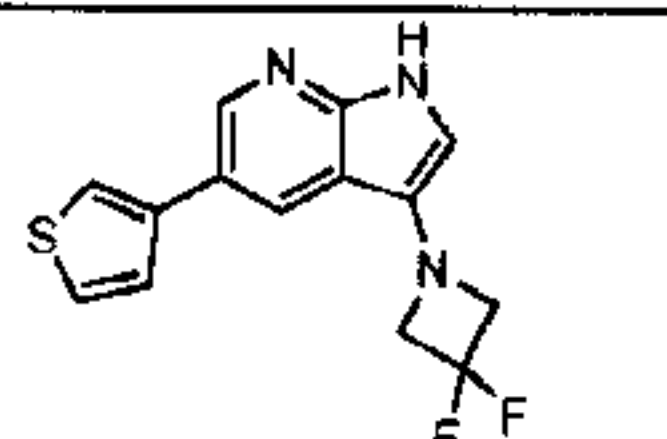
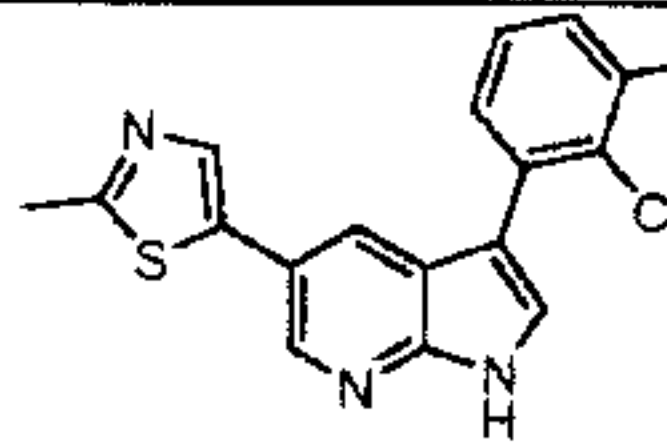
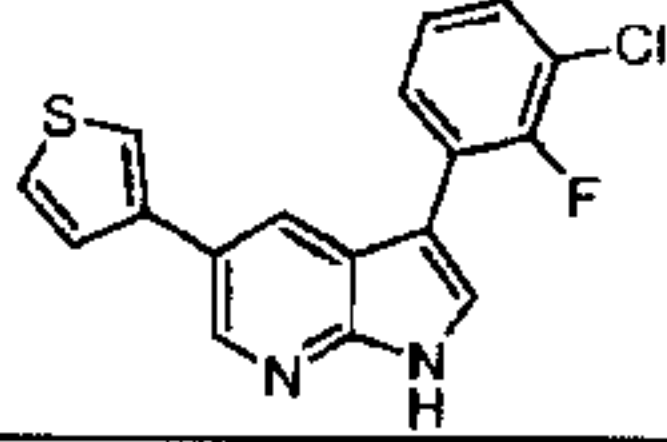
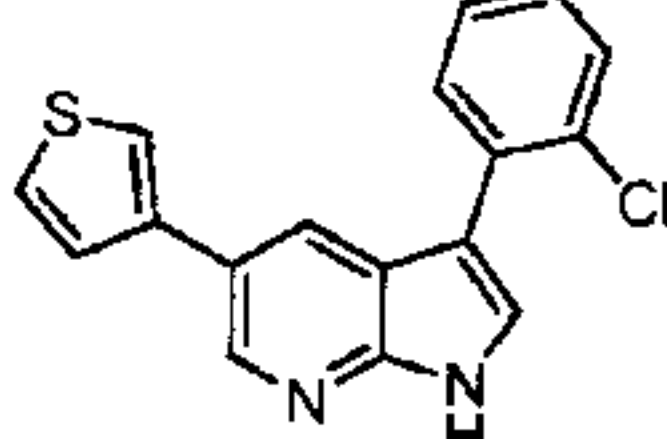
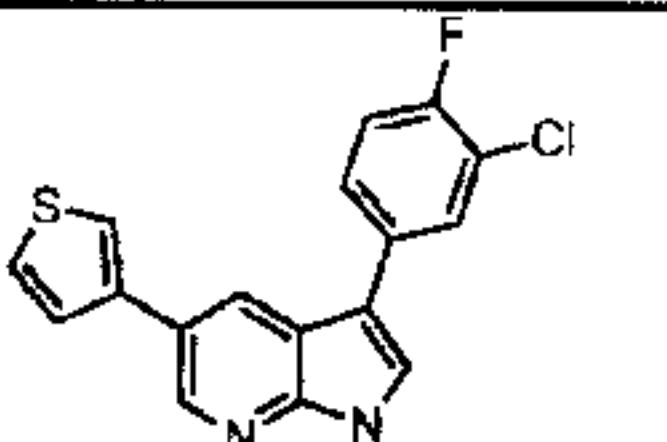
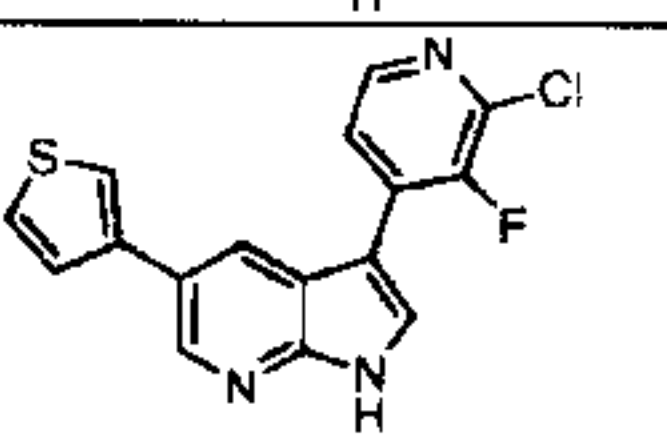
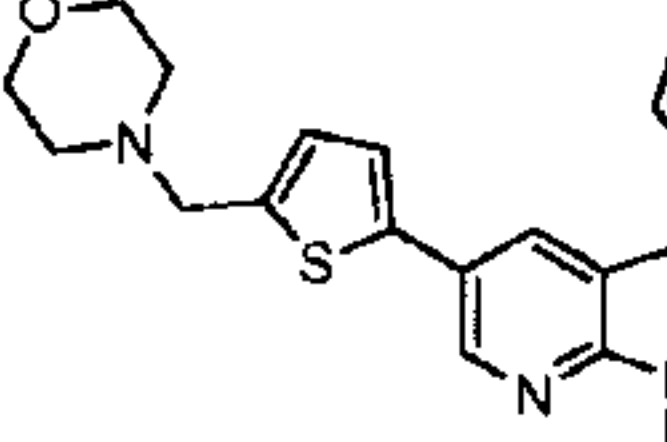
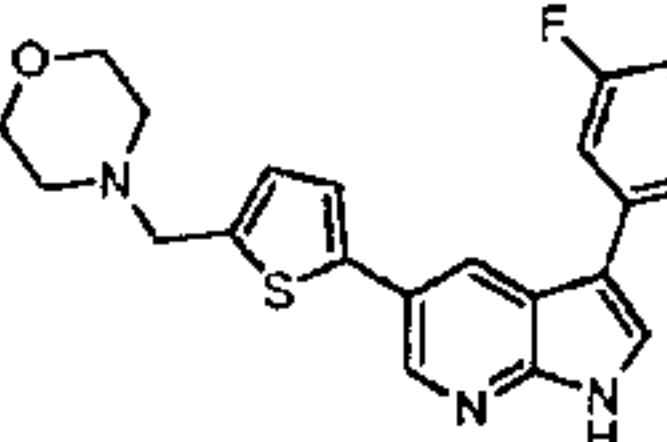
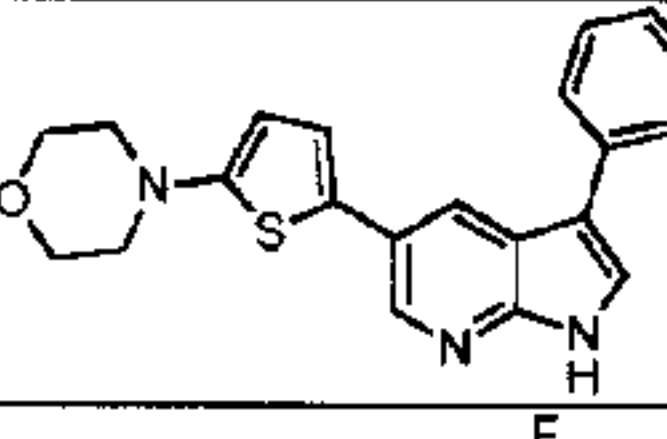
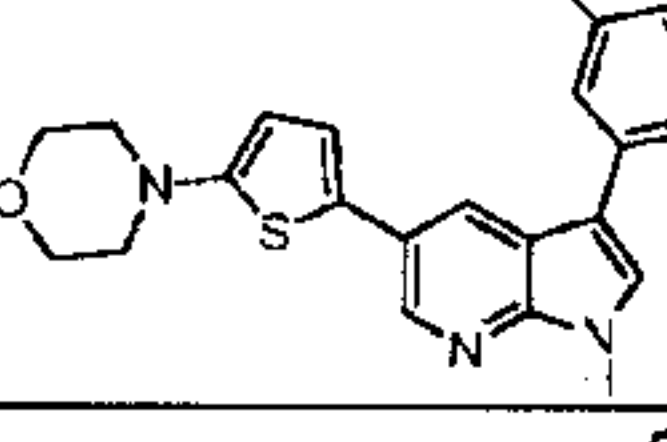
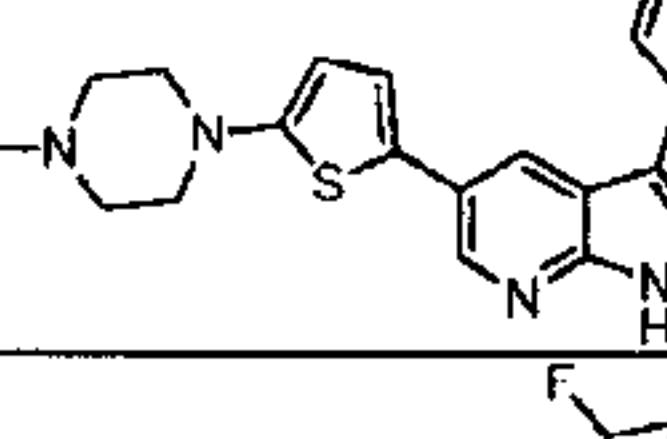
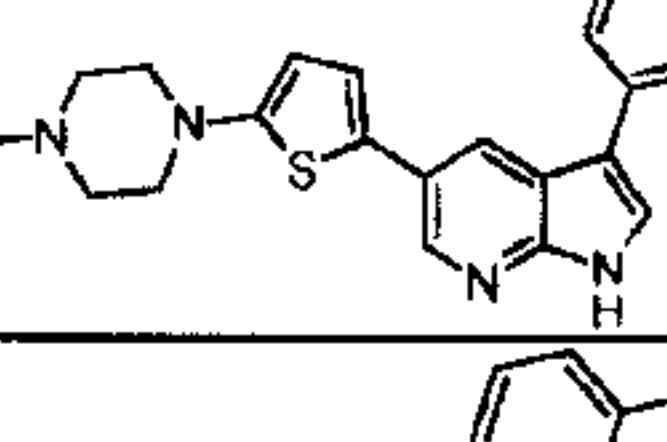
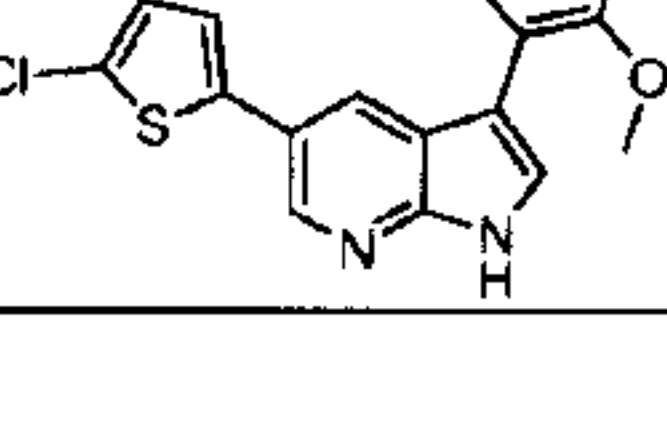
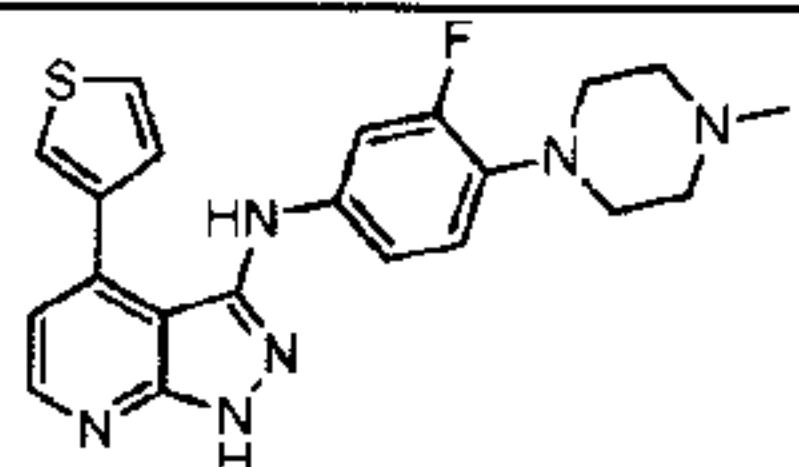
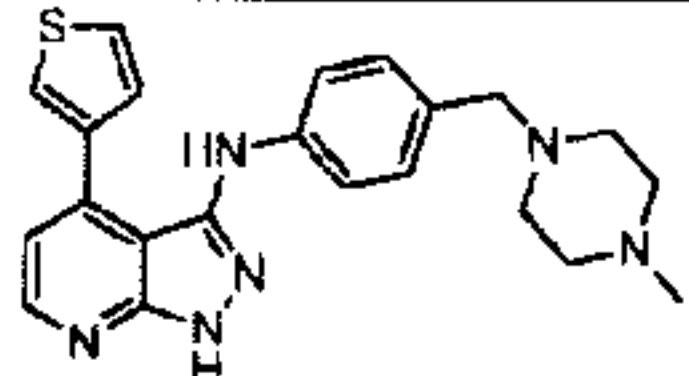
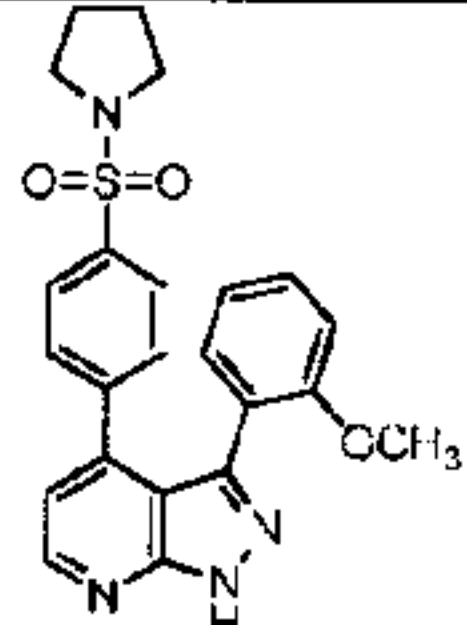
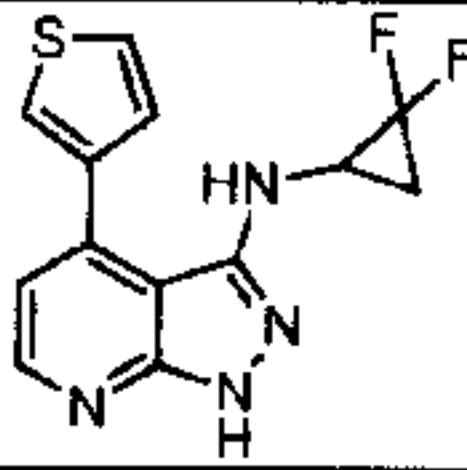
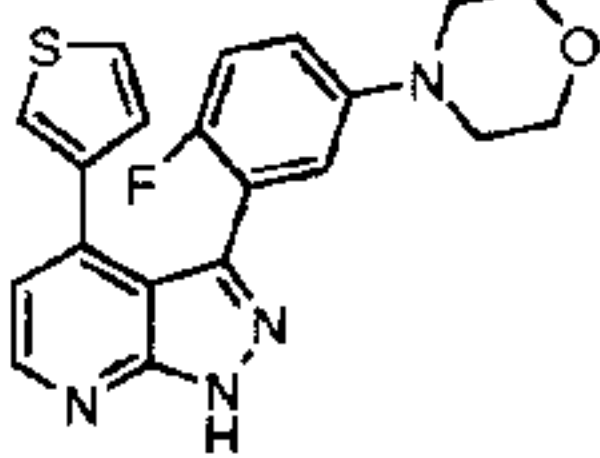
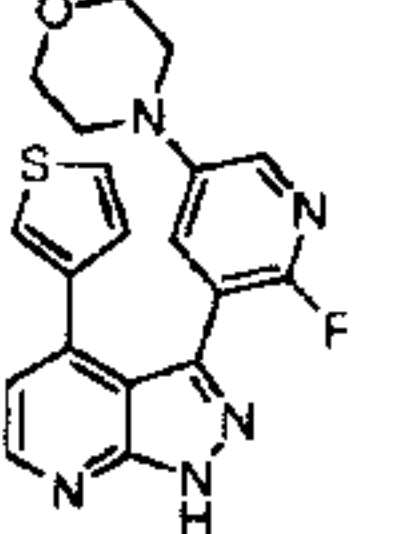
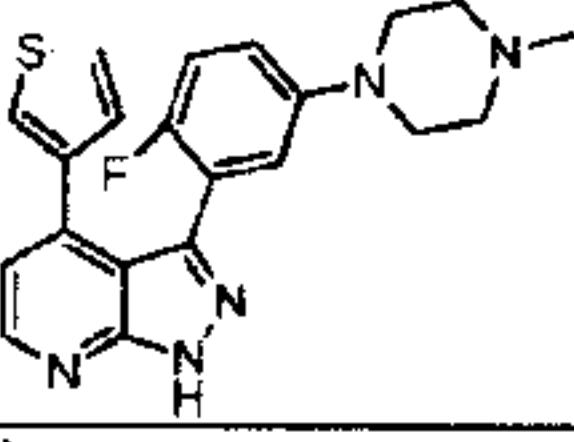
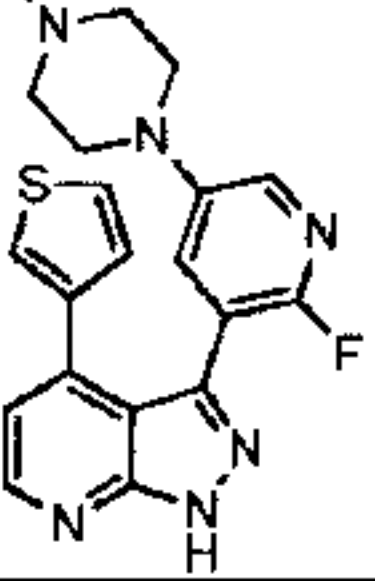
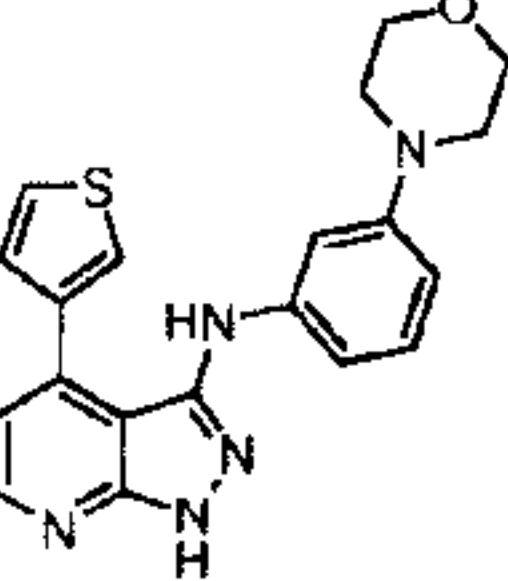
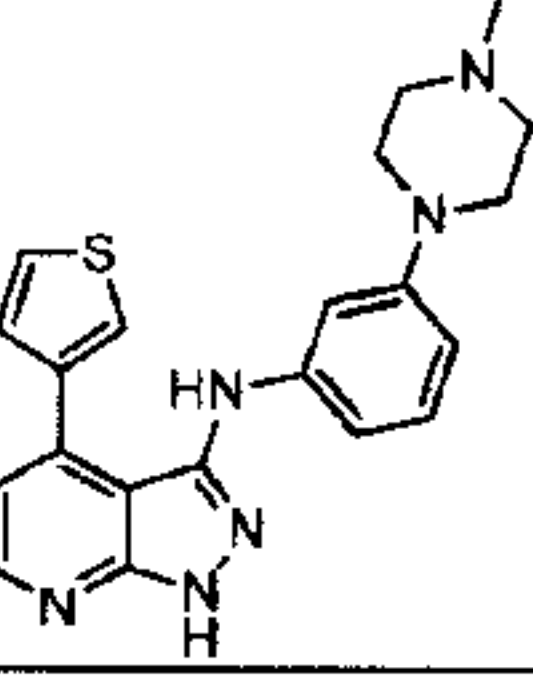
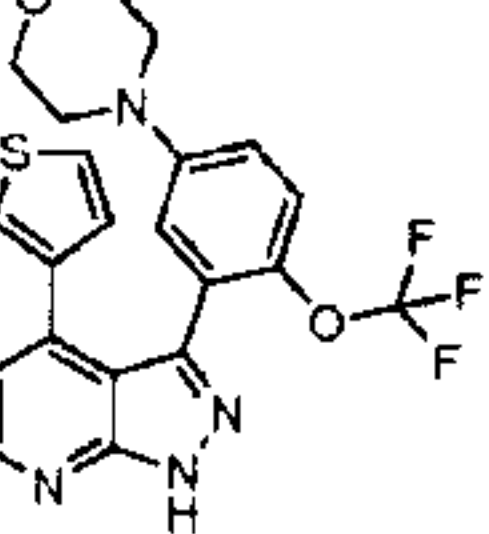
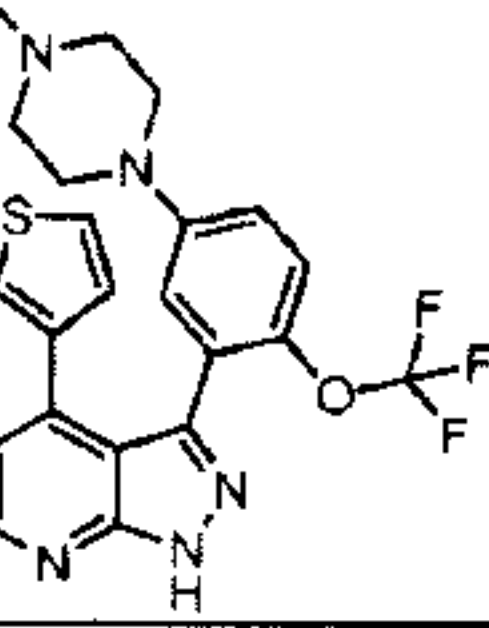
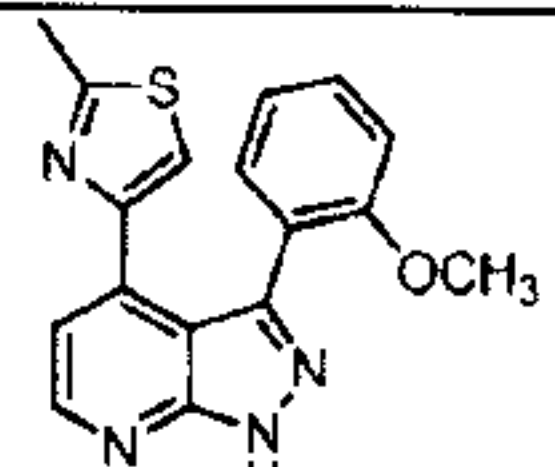
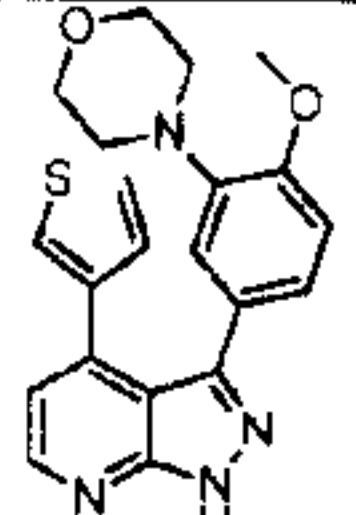
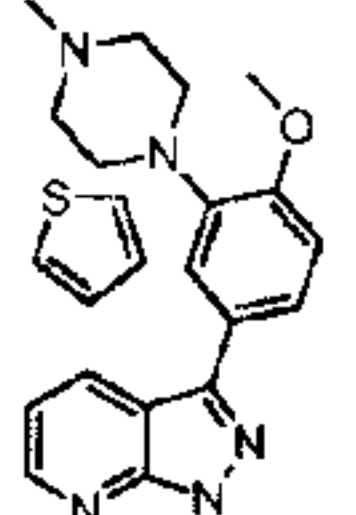
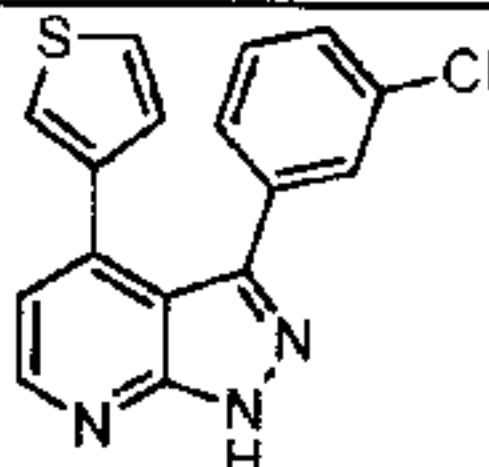
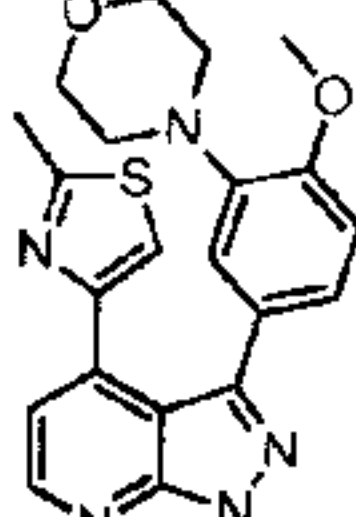
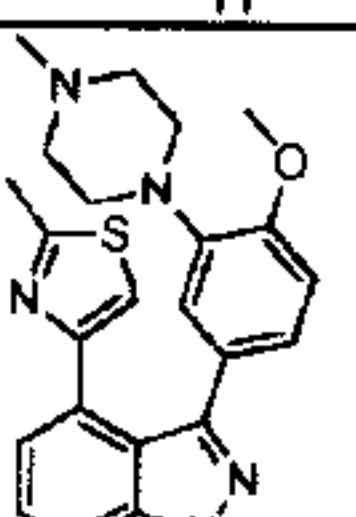
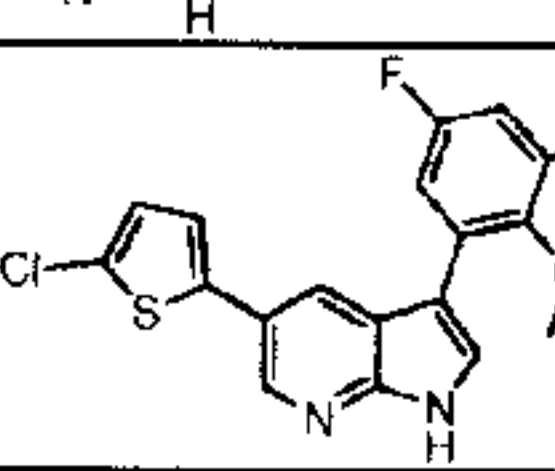
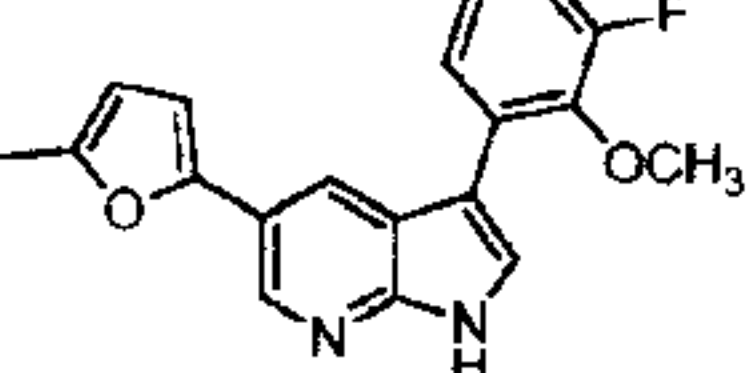
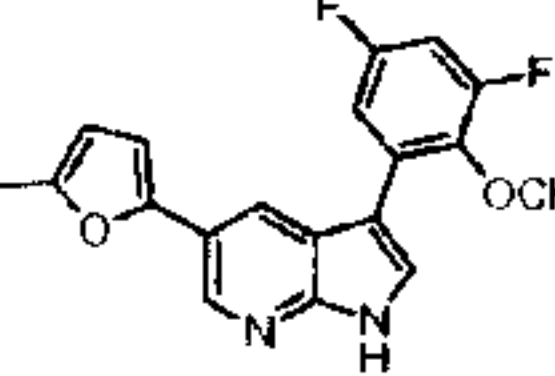
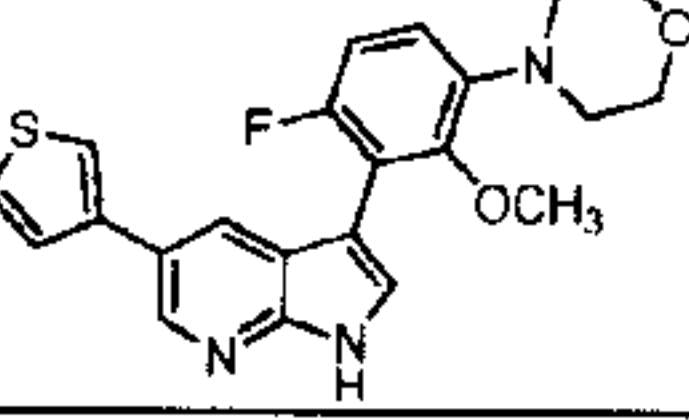
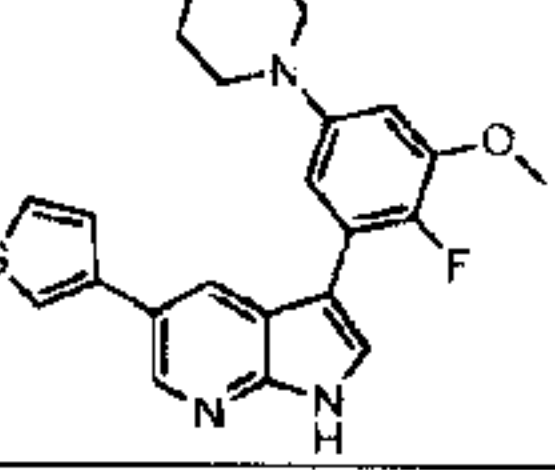
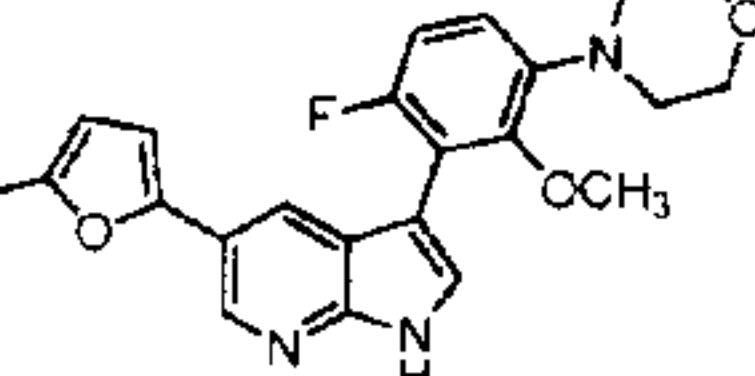
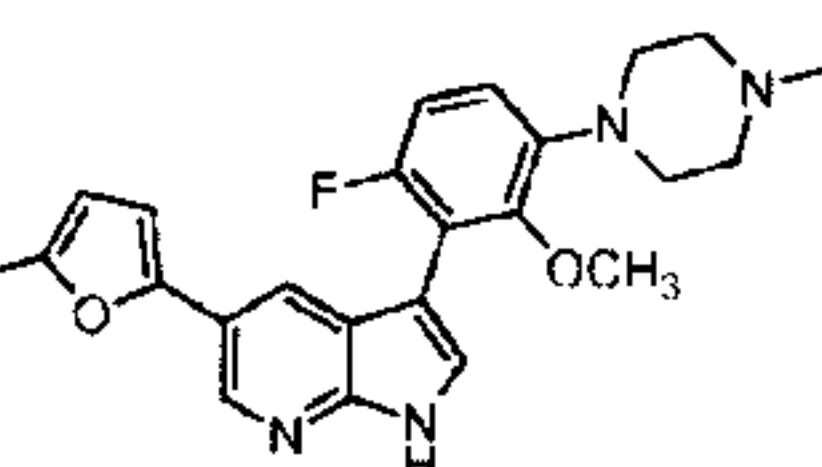
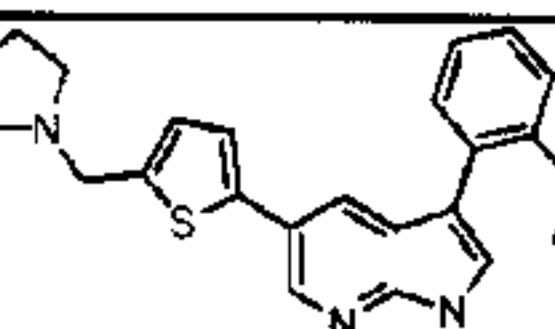
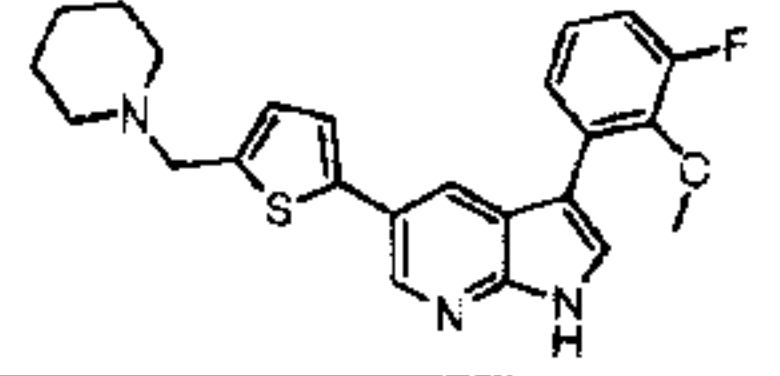
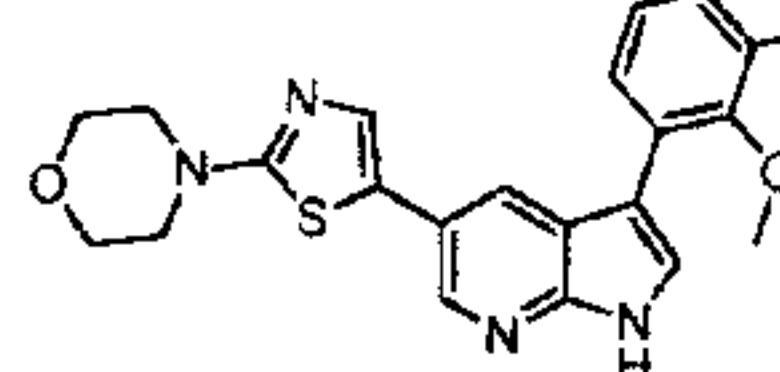
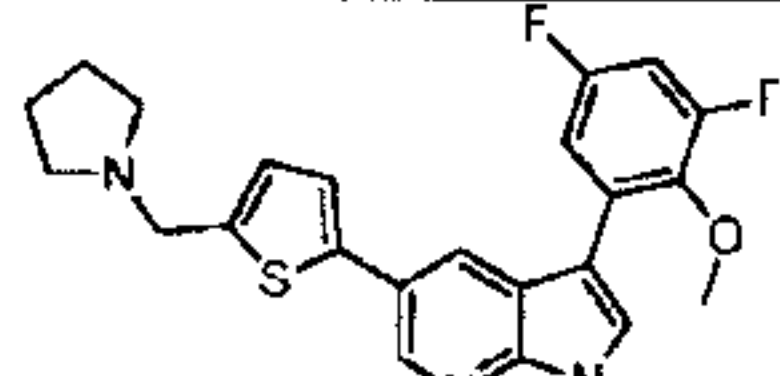
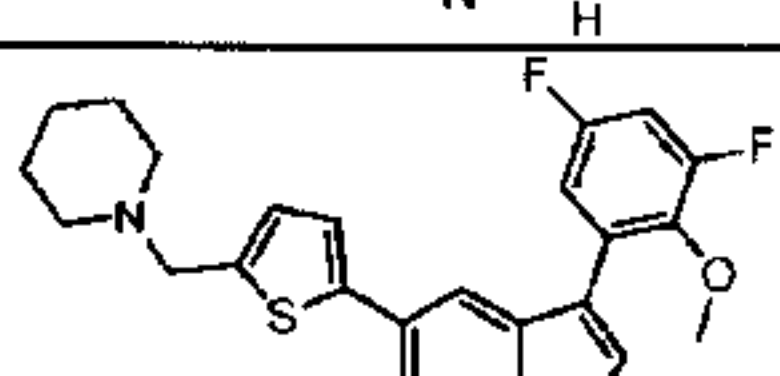
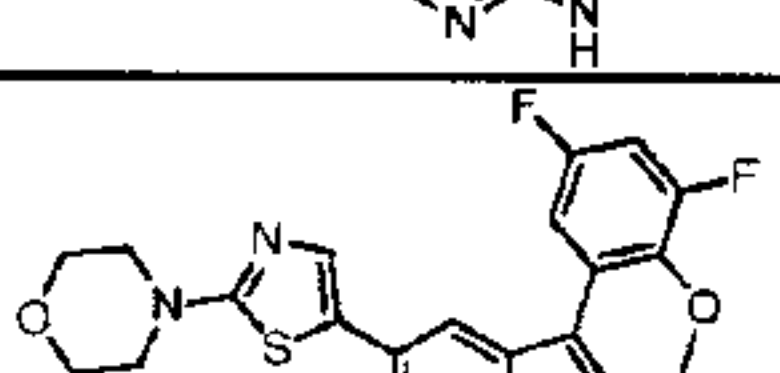
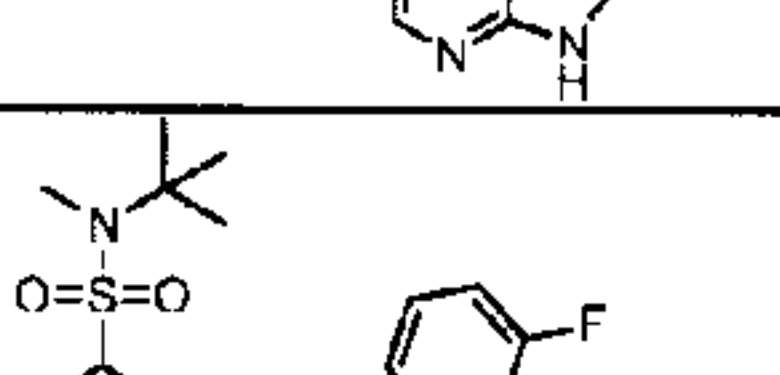
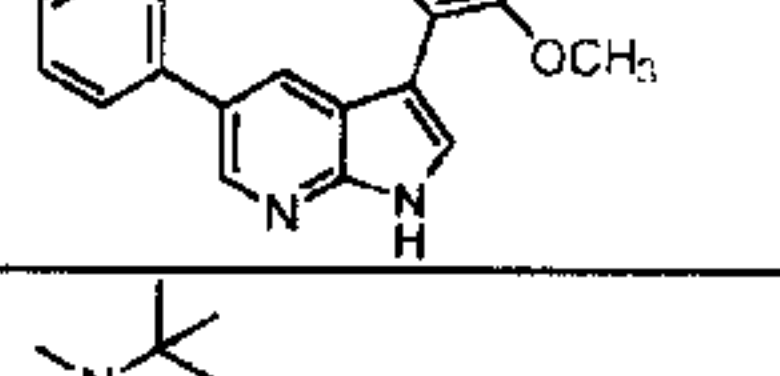
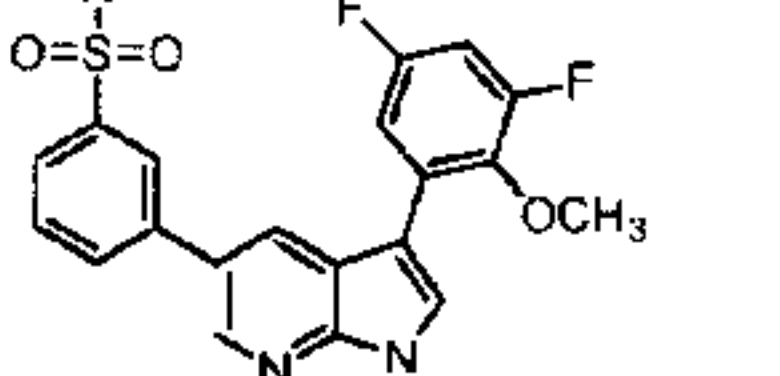
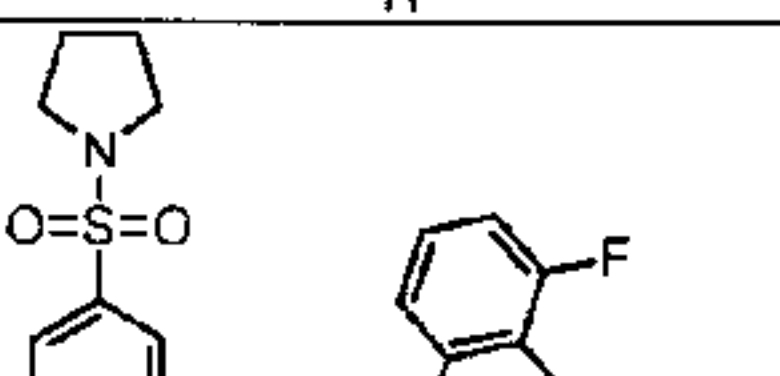
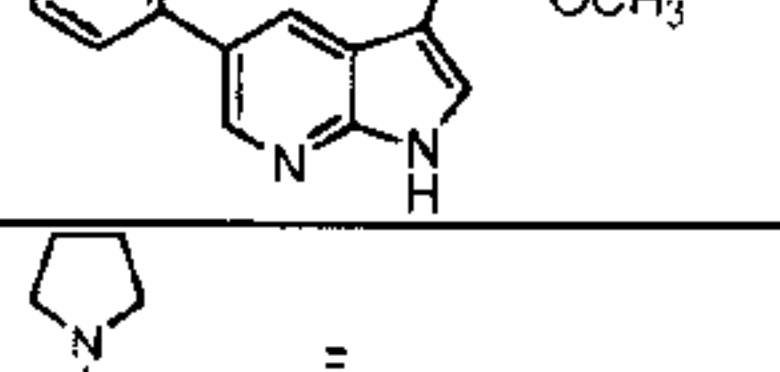
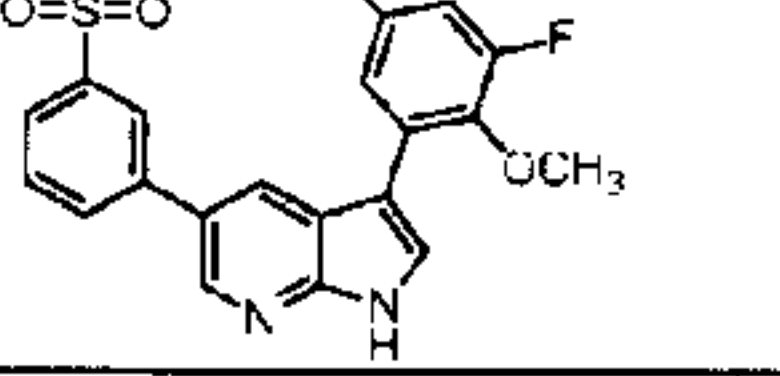
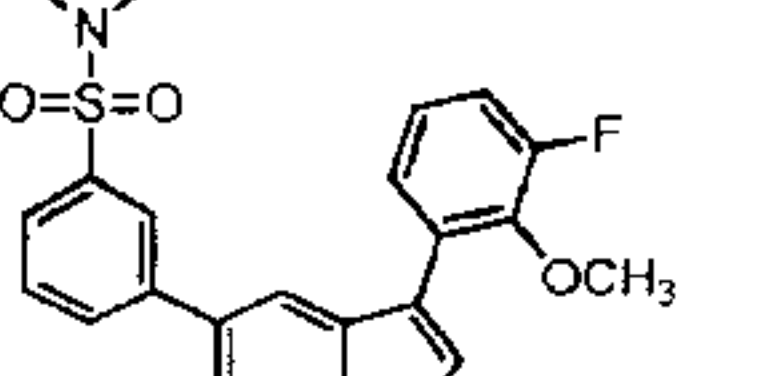
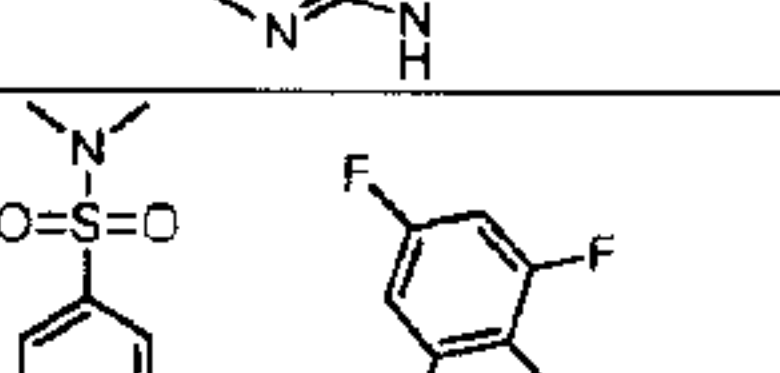
|     |                                                                                     |                                                                                                        |         |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------|
| 136 |    | 3-(3,3-difluoroazetidin-1-yl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                              | 291.319 |
| 137 |    | 5-(3-(2-chloro-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-methylthiazole                         | 343.806 |
| 138 |    | 3-(3-chloro-2-fluorophenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                                | 328.791 |
| 139 |    | 3-(2-chlorophenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                                         | 310.801 |
| 140 |   | 3-(3-chloro-4-fluorophenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                                | 328.791 |
| 141 |  | 3-(2-chloro-3-fluoropyridin-4-yl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine                          | 329.779 |
| 142 |  | 4-((5-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine      | 423.503 |
| 143 |  | 4-((5-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine  | 441.494 |
| 144 |  | 4-(5-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)morpholine              | 409.477 |
| 145 |  | 4-(5-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)morpholine          | 427.467 |
| 146 |  | 3-(3-fluoro-2-methoxyphenyl)-5-(5-(4-methylpiperazin-1-yl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine     | 422.518 |
| 147 |  | 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-(4-methylpiperazin-1-yl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine | 440.509 |
| 148 |  | 5-(5-chlorothiophen-2-yl)-3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine                       | 358.817 |

Table 2: List of further Examples:

| EX. | Structure | Chemical Name | Mol. Wt |
|-----|-----------|---------------|---------|
|-----|-----------|---------------|---------|

|     |                                                                                     |                                                                                                        |        |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------|
| 149 |    | N-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine      | 408.50 |
| 150 |    | N-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine       | 404.53 |
| 151 |    | 3-(2-methoxyphenyl)-4-(4-(pyrrolidin-1-yl)sulfonyl)phenyl)-1H-pyrazolo[3,4-b]pyridine                  | 434.52 |
| 152 |   | N-(2,2-difluorocyclopropyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine                        | 292.31 |
| 153 |  | 4-(4-fluoro-3-(4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)phenyl)morpholine                      | 380.44 |
| 154 |  | 4-(6-fluoro-5-(4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyridin-3-yl)morpholine                | 381.43 |
| 155 |  | 3-(2-fluoro-5-(4-methylpiperazin-1-yl)phenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine             | 393.48 |
| 156 |  | 3-(2-fluoro-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine       | 394.47 |
| 157 |  | N-(3-morpholinophenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine                             | 377.46 |
| 158 |  | N-(3-(4-methylpiperazin-1-yl)phenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine               | 390.50 |
| 159 |  | 4-(3-(4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(trifluoromethoxy)phenyl)morpholine          | 446.45 |
| 160 |  | 3-(5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine | 459.49 |

|     |                                                                                     |                                                                                                          |        |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------|
| 161 |    | 4-(3-(2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)-2-methylthiazole                                  | 322.38 |
| 162 |    | 4-(2-methoxy-5-(4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)phenyl)morpholine                       | 392.47 |
| 163 |    | 3-(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine              | 405.52 |
| 164 |   | 3-(3-chlorophenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine                                          | 311.79 |
| 165 |  | 4-(2-methoxy-5-(4-(2-methylthiazol-4-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)phenyl)morpholine                | 407.49 |
| 166 |  | 4-(3-(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)-2-methylthiazole       | 420.53 |
| 167 |  | 5-(5-chlorothiophen-2-yl)-3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine                     | 376.80 |
| 168 |  | 3-(3-fluoro-2-methoxyphenyl)-5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridine                            | 322.33 |
| 169 |  | 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridine                        | 340.32 |
| 170 |  | 4-(4-fluoro-2-methoxy-3-(5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenyl)morpholine               | 409.47 |
| 171 |  | 3-(6-fluoro-2-methoxy-3-(4-methylpiperazin-1-yl)phenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine      | 422.51 |
| 172 |  | 4-(4-fluoro-2-methoxy-3-(5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenyl)morpholine          | 407.43 |
| 173 |  | 3-(6-fluoro-2-methoxy-3-(4-methylpiperazin-1-yl)phenyl)-5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridine | 420.47 |
| 174 |  | 3-(3-fluoro-2-methoxyphenyl)-5-(5-(pyrrolidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine        | 407.50 |

|     |                                                                                     |                                                                                                              |        |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------|
|     |                                                                                     | pyrrolo[2,3-b]pyridine                                                                                       |        |
| 175 |    | 3-(3-fluoro-2-methoxyphenyl)-5-(5-(piperidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine             | 421.53 |
| 176 |    | 4-(5-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine                     | 410.46 |
| 177 |    | 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-(pyrrolidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine        | 425.49 |
| 178 |    | 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-(piperidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine         | 439.51 |
| 179 |   | 4-(5-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine                 | 428.45 |
| 180 |  | N-(tert-butyl)-3-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methylbenzenesulfonamide     | 467.55 |
| 181 |  | N-(tert-butyl)-3-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methylbenzenesulfonamide | 485.54 |
| 182 |  | 3-(3-fluoro-2-methoxyphenyl)-5-(3-(pyrrolidin-1-ylsulfonyl)phenyl)-1H-pyrrolo[2,3-b]pyridine                 | 451.51 |
| 183 |  | 3-(3,5-difluoro-2-methoxyphenyl)-5-(3-(pyrrolidin-1-ylsulfonyl)phenyl)-1H-pyrrolo[2,3-b]pyridine             | 469.50 |
| 184 |  | 3-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N,N-dimethylbenzenesulfonamide                | 425.76 |
| 185 |  | 3-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N,N-dimethylbenzenesulfonamide            | 443.46 |
| 186 |  | N-(3-chloro-4-morpholinophenyl)-3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-amine                | 452.90 |
| 187 |  | N-(3-chloro-4-morpholinophenyl)-3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-amine            | 470.89 |

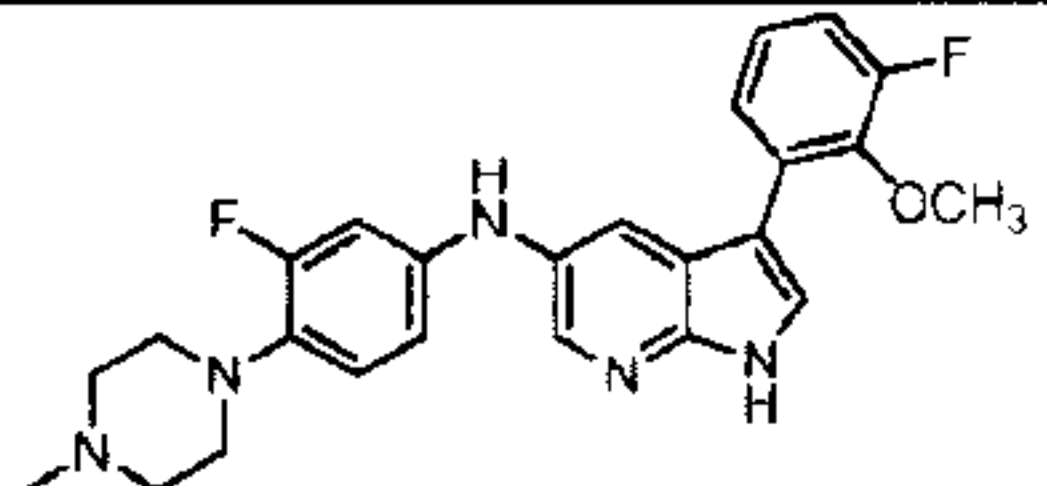
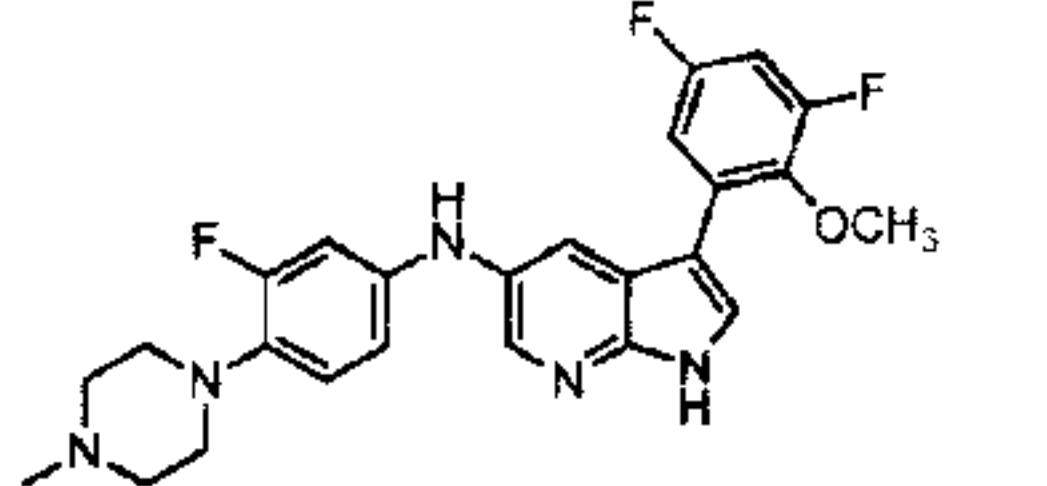
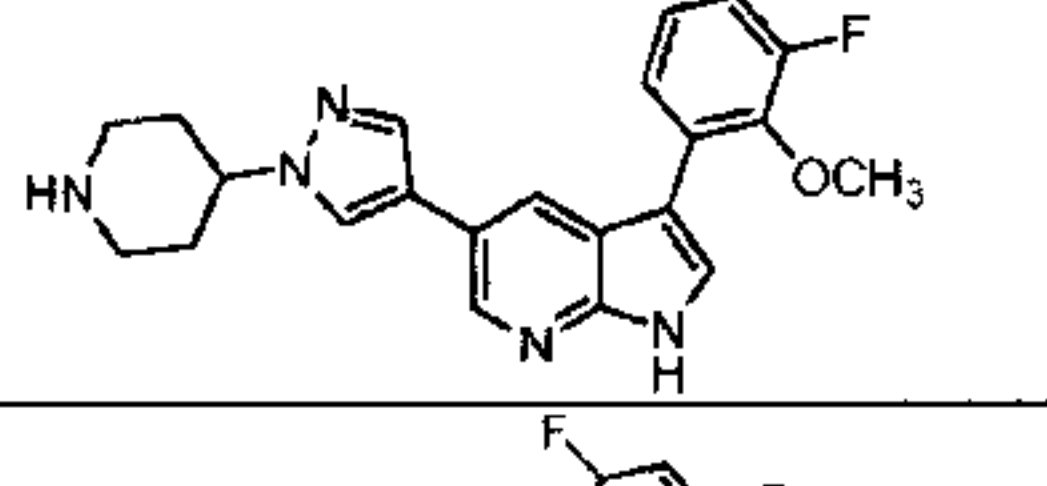
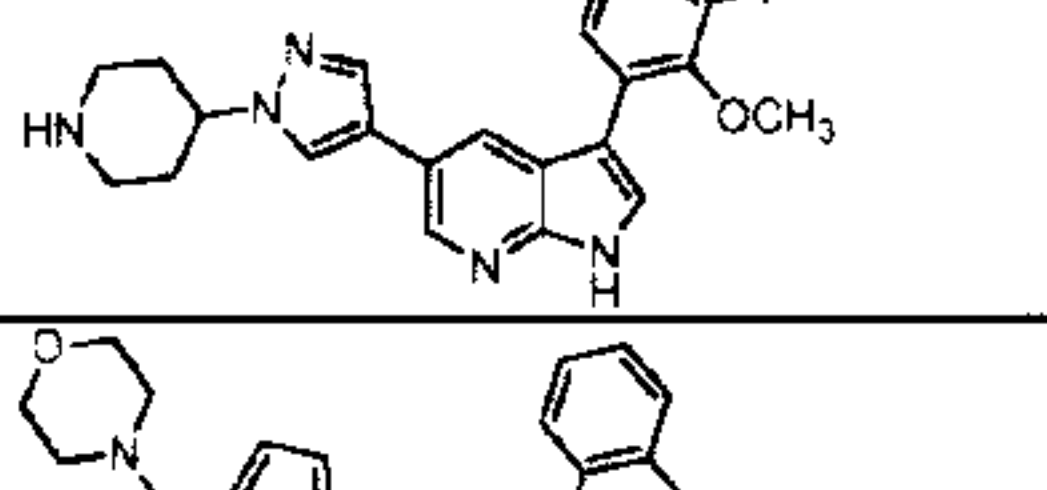
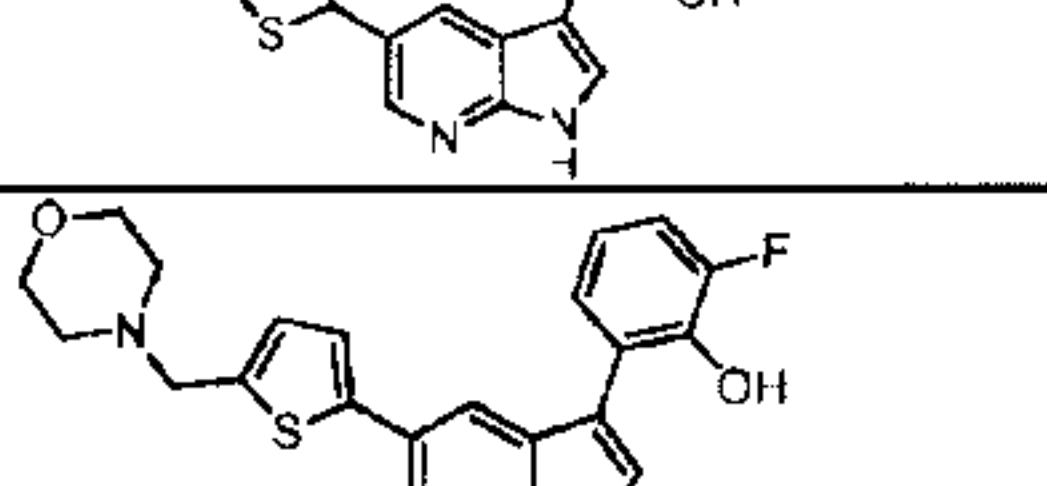
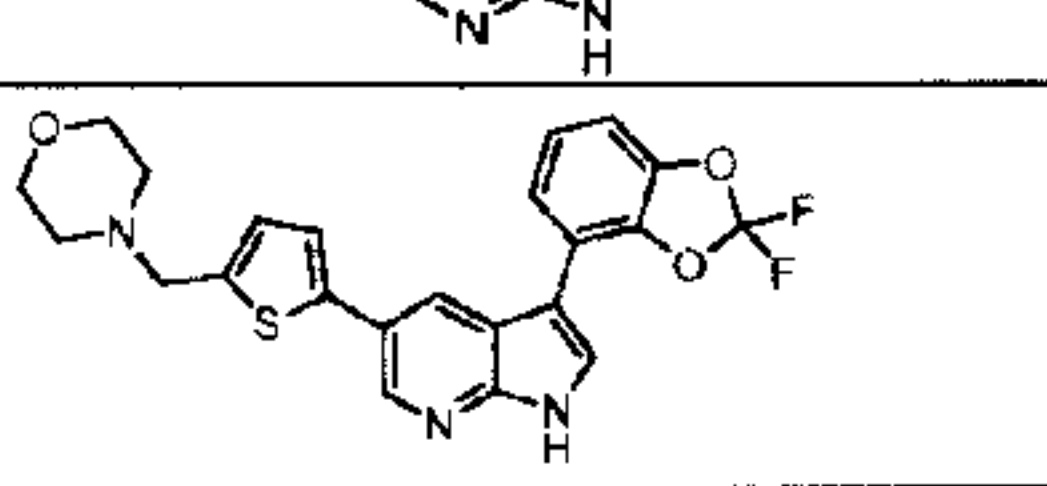
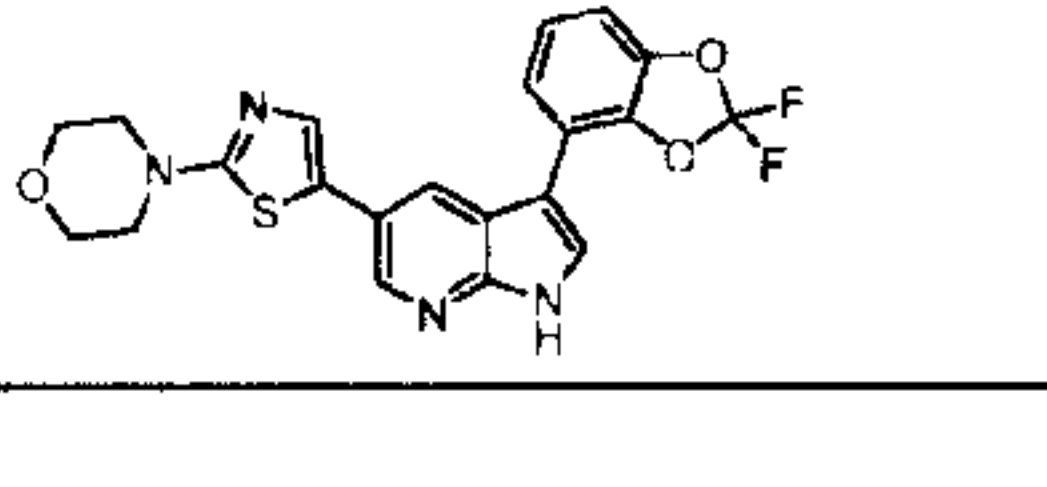
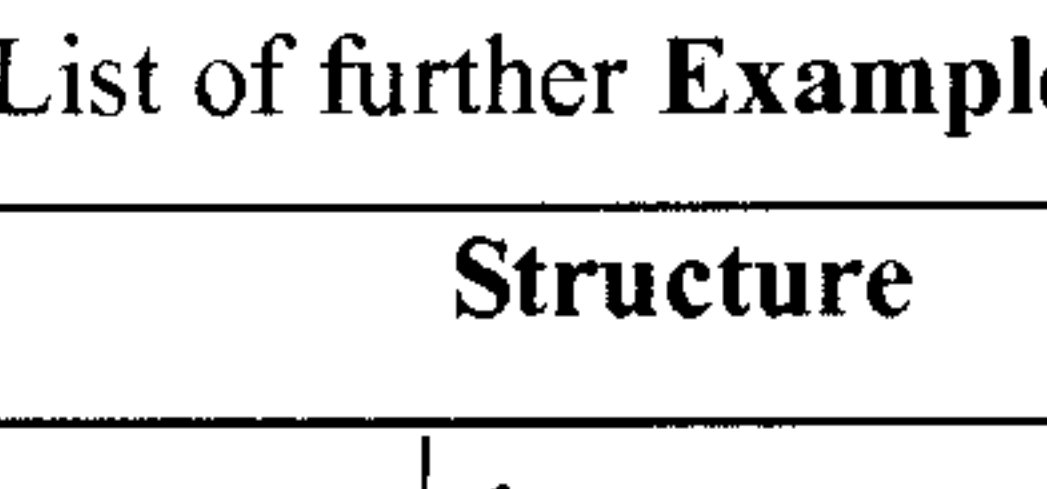
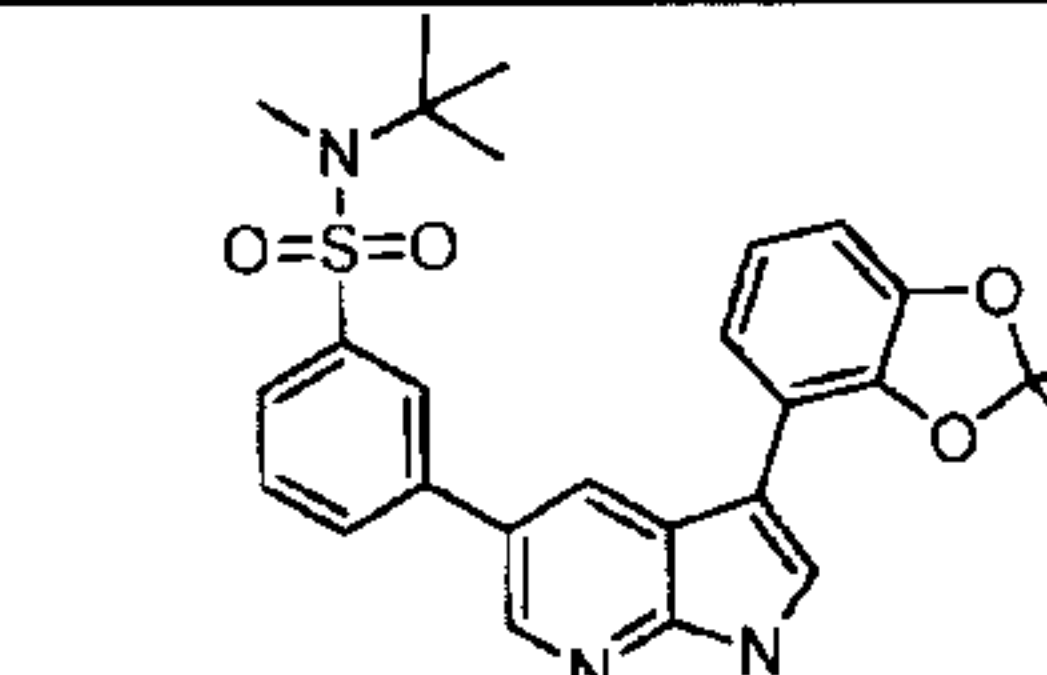
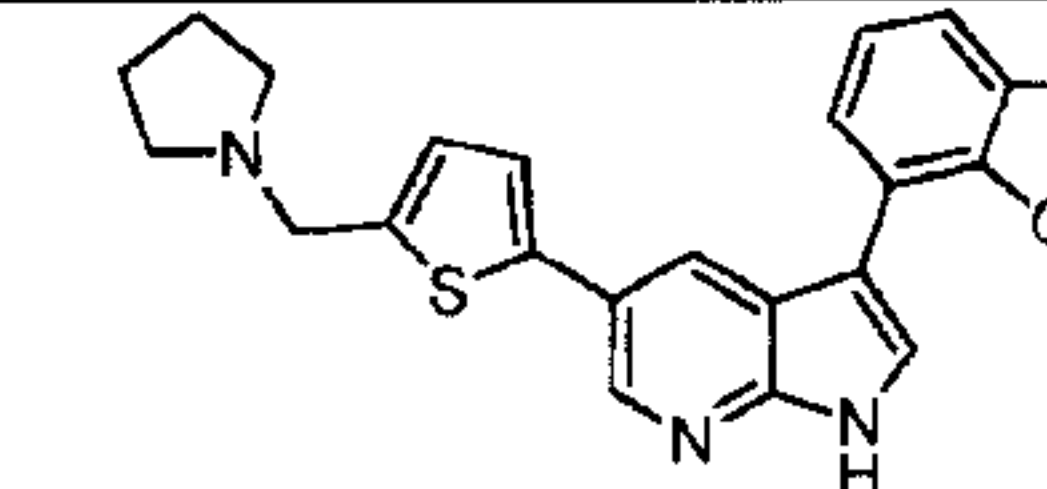
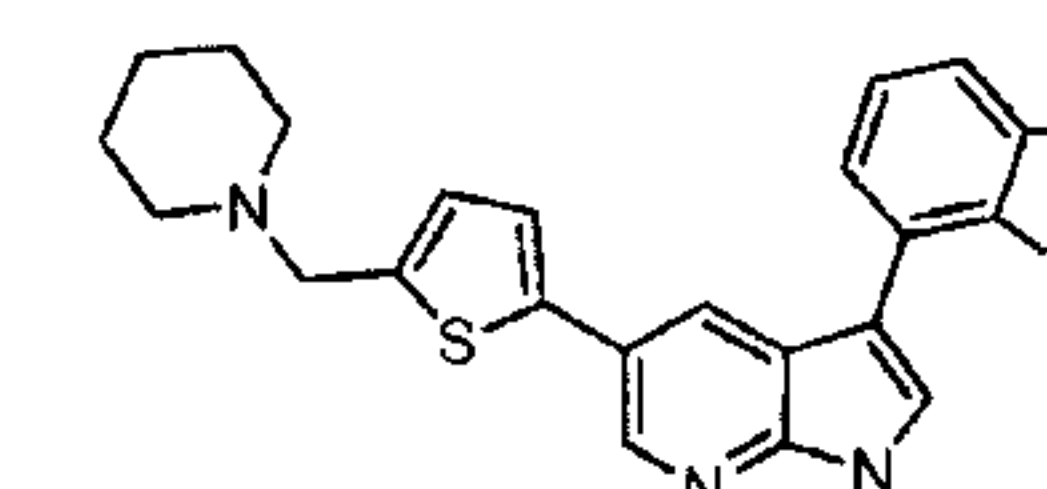
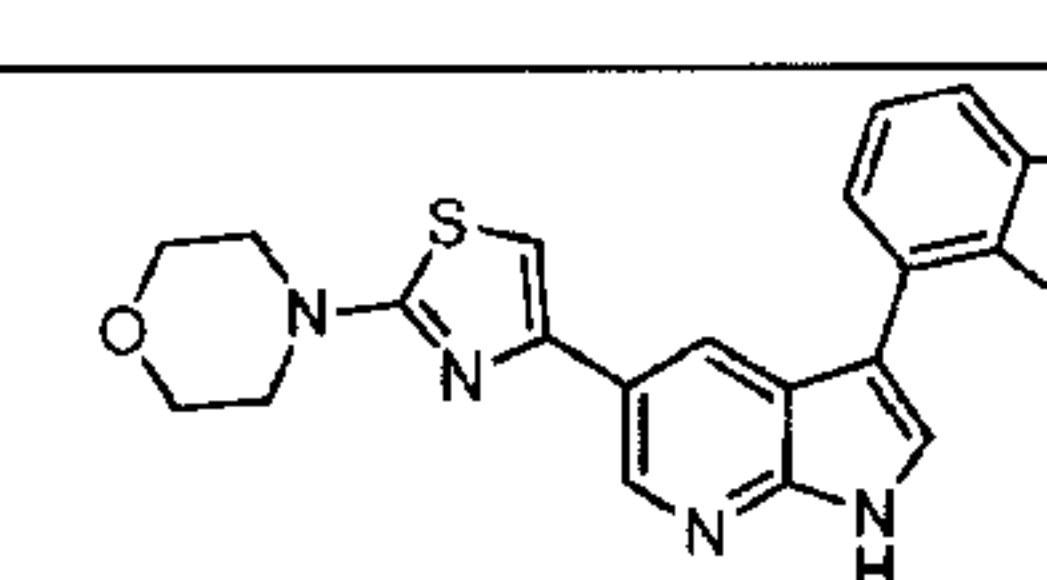
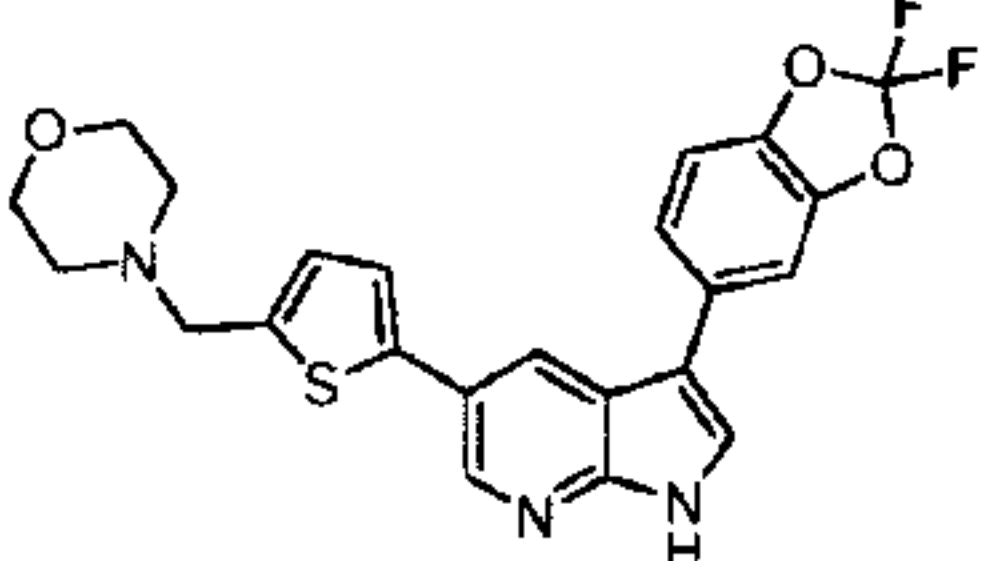
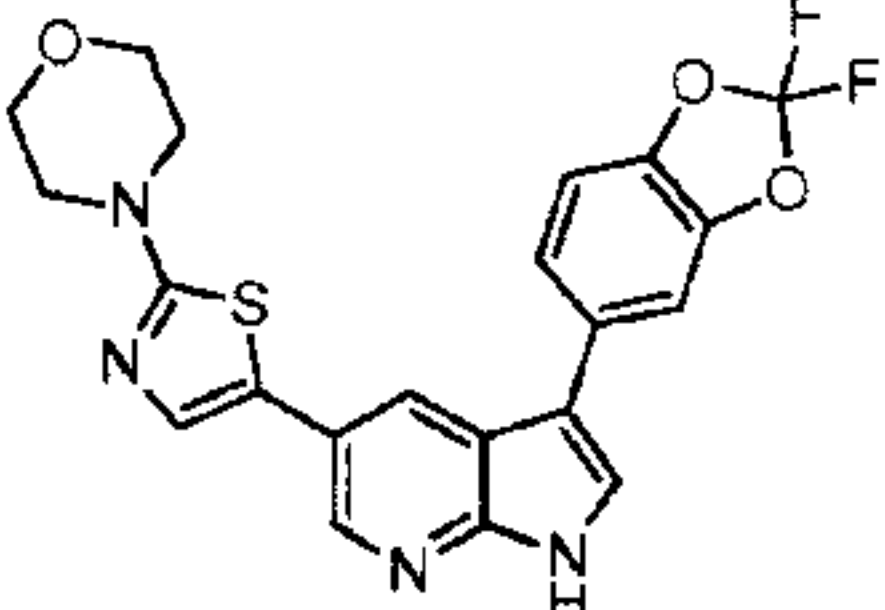
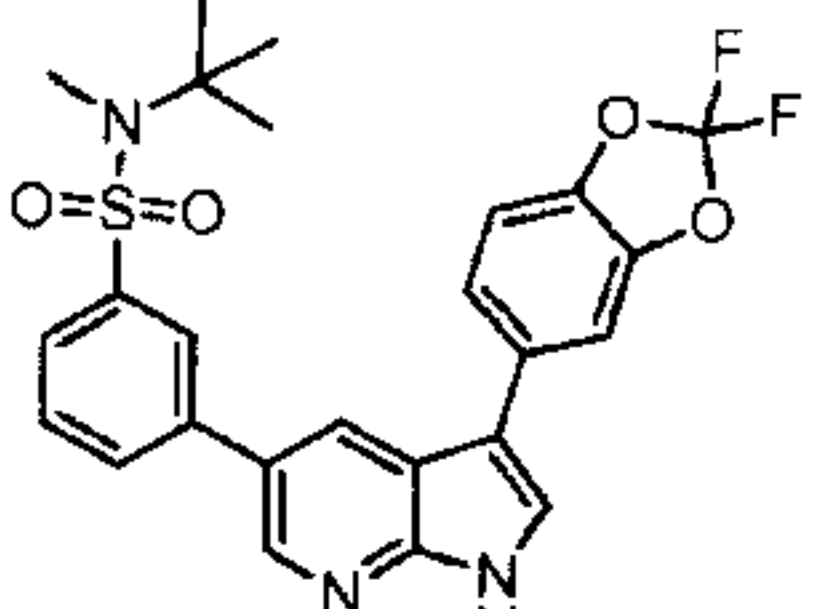
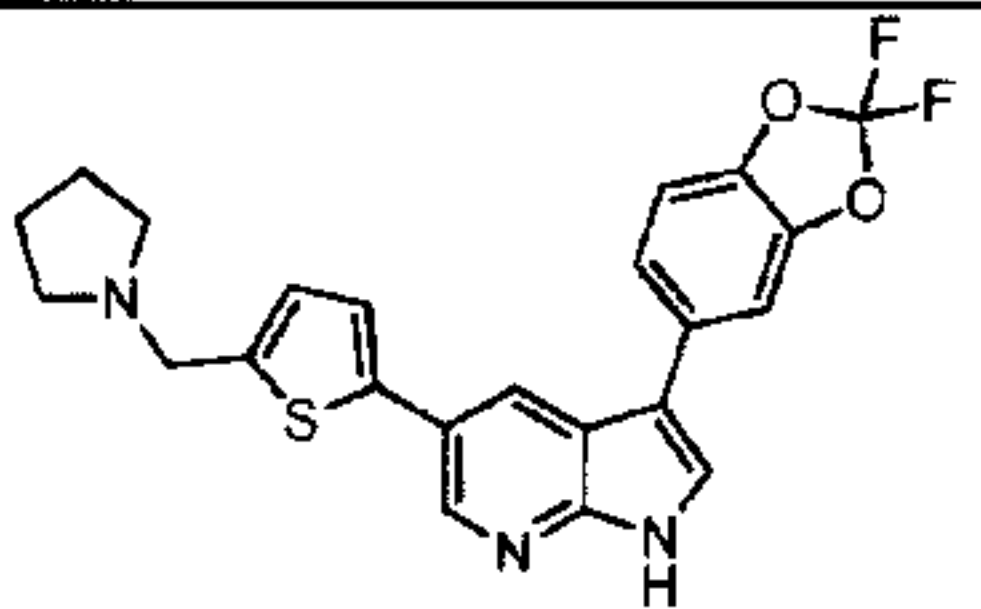
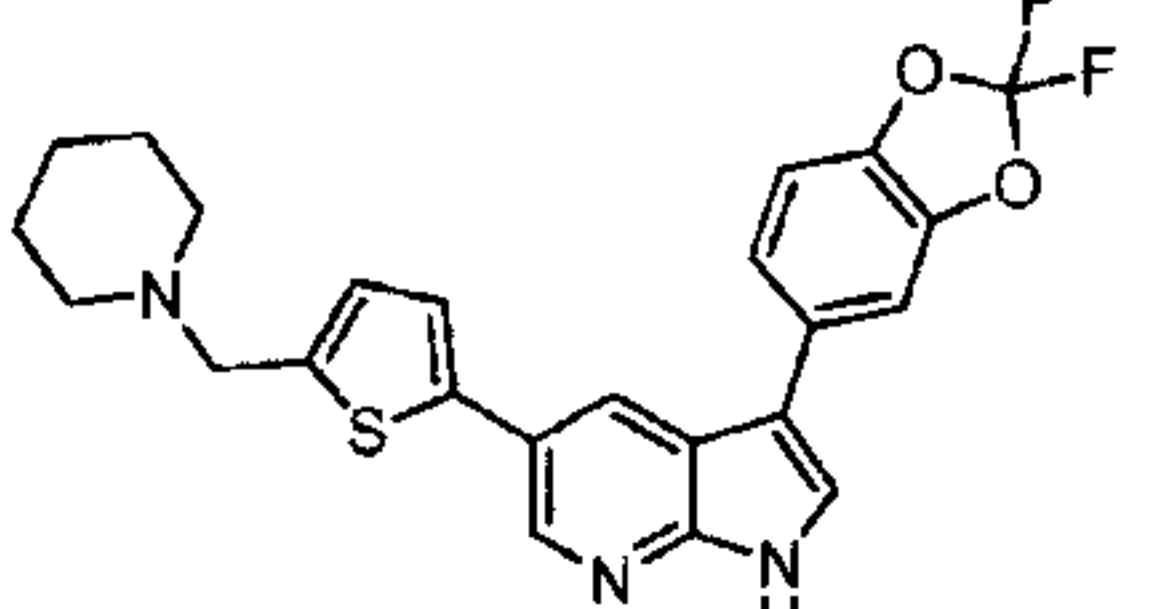
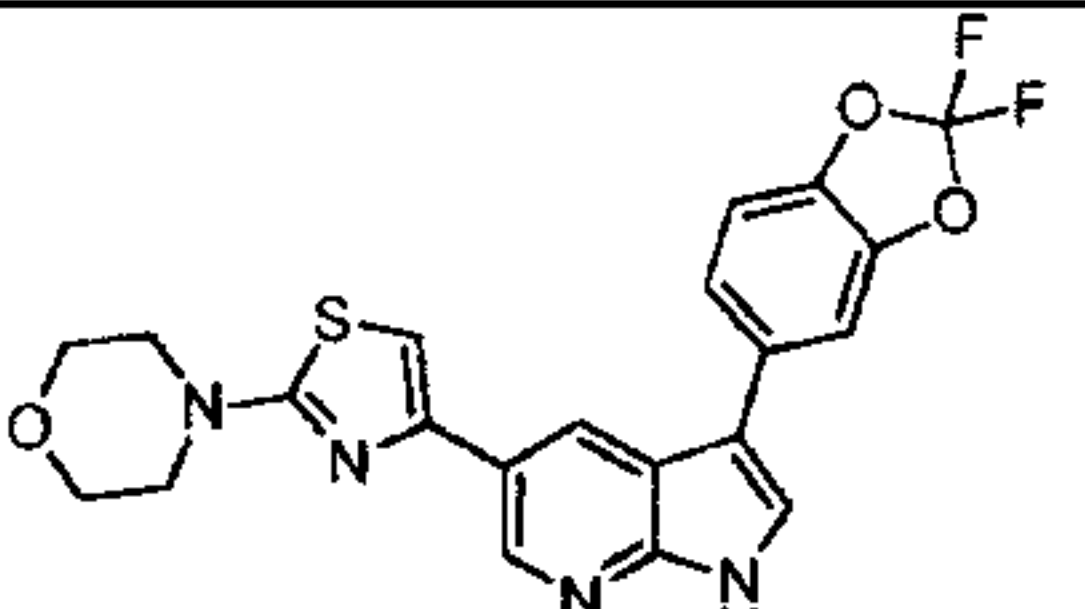
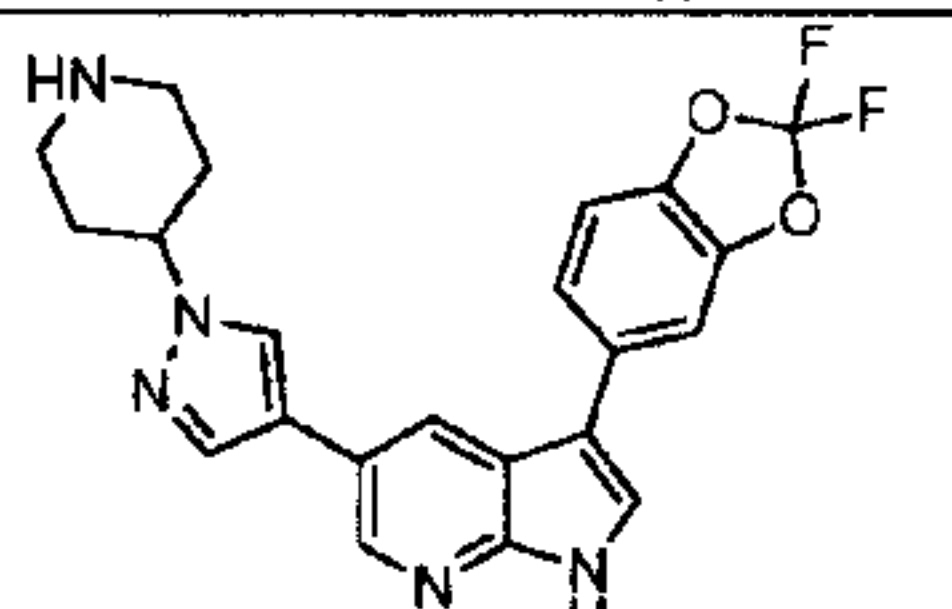
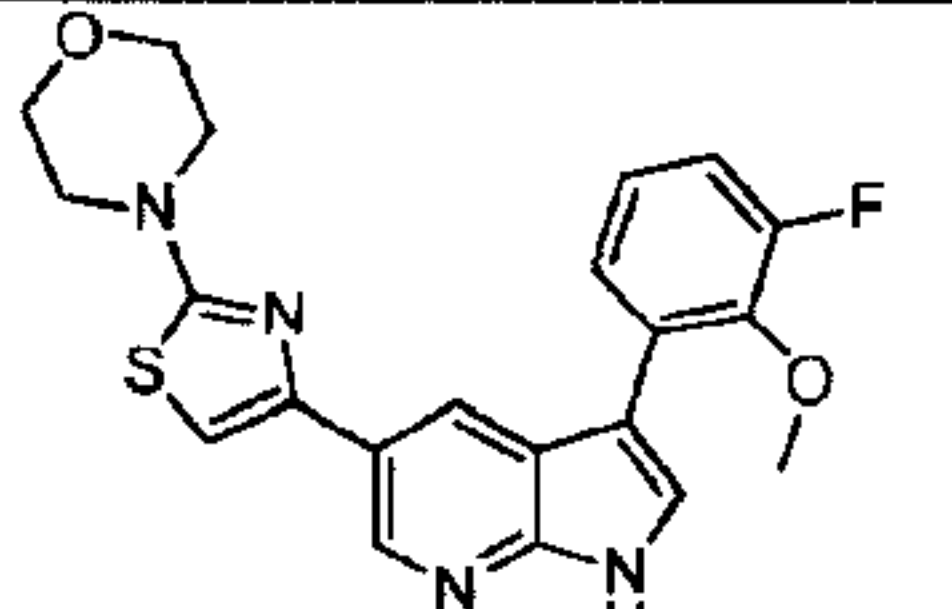
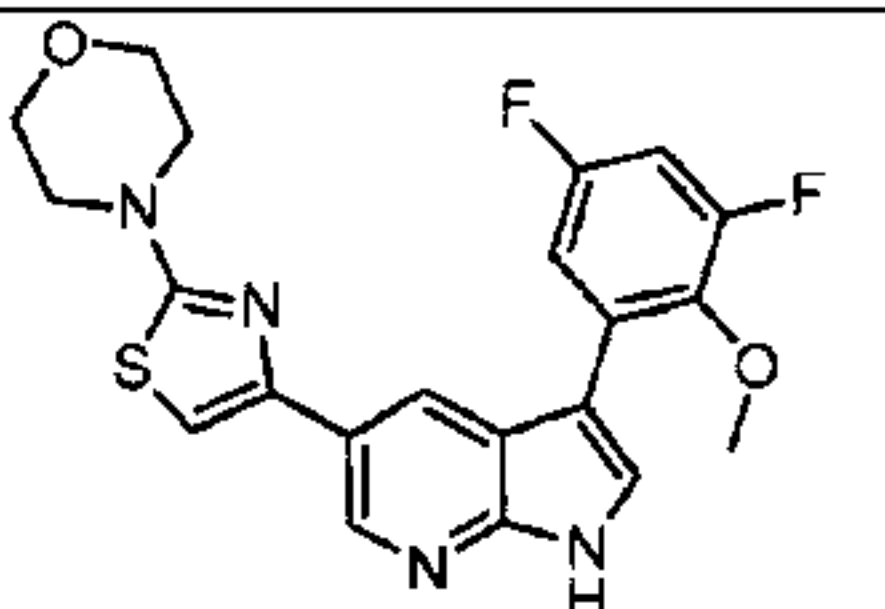
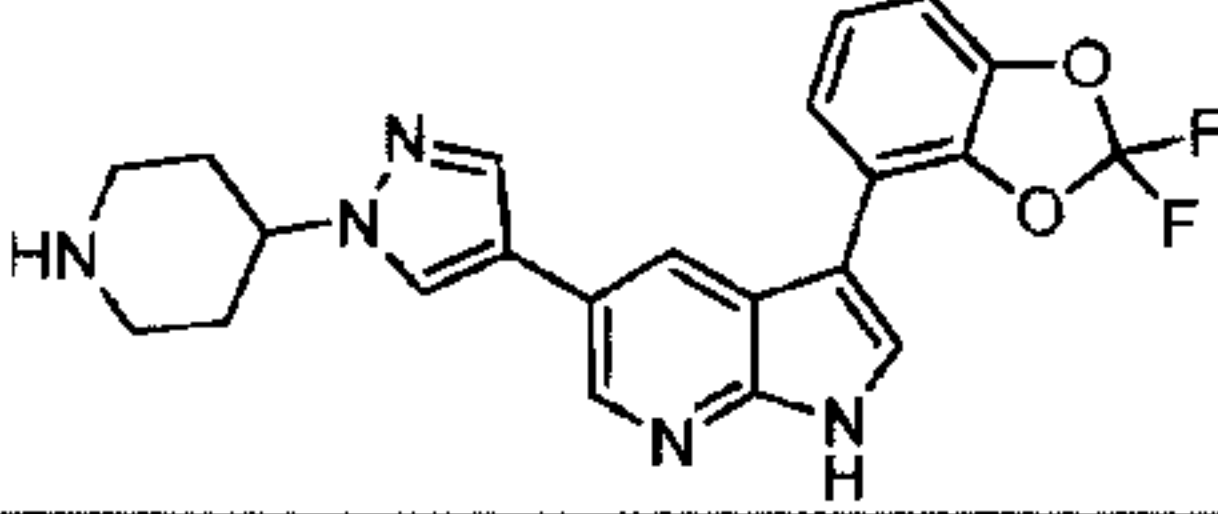
|     |                                                                                     |                                                                                                                 |         |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------|
| 188 |    | 3-(3-fluoro-2-methoxyphenyl)-N-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-amine     | 449.49  |
| 189 |    | 3-(3,5-difluoro-2-methoxyphenyl)-N-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrrolo[2,3-b]pyridin-5-amine | 467.48  |
| 190 |    | 3-(3-fluoro-2-methoxyphenyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine                   | 391.44  |
| 191 |   | 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine               | 409.43  |
| 192 |  | 2-(5-(5-(morpholinomethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                                   | 391.486 |
| 193 |  | 2-fluoro-6-(5-(5-(morpholinomethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol                          | 409.477 |
| 194 |  | 4-((5-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine   | 455.457 |
| 195 |  | 4-(5-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine            | 442.439 |

Table 2A: List of further Examples:

| EX. | Structure                                                                           | Chemical Name                                                                                                        | Mol. Wt |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---------|
| 196 |  | N-(tert-butyl)-3-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methylbenzenesulfonamide | 499.43  |
| 197 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(5-(pyrrolidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine        | 439.47  |
| 198 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(5-(piperidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine         | 453.50  |
| 199 |  | 4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine                 | 442.43  |

|     |                                                                                     |                                                                                                                      |        |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--------|
| 200 |    | 4-((5-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine        | 455.47 |
| 201 |    | 4-(5-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine                 | 442.43 |
| 202 |    | N-(tert-butyl)-3-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methylbenzenesulfonamide | 499.53 |
| 203 |   | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(pyrrolidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine        | 439.47 |
| 204 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(piperidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine         | 453.50 |
| 205 |  | 4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine                 | 442.43 |
| 206 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine            | 423.41 |
| 207 |  | 4-(4-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine                             | 410.46 |
| 208 |  | 4-(4-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine                         | 428.45 |
| 209 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine            | 423.41 |

|     |  |                                                                                                                             |        |
|-----|--|-----------------------------------------------------------------------------------------------------------------------------|--------|
| 210 |  | (2,6-difluorophenyl)(5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone                         | 407.41 |
| 211 |  | 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-((4-methylpiperazin-1-yl)sulfonyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine         | 488.51 |
| 212 |  | 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine                   | 423.45 |
| 213 |  | (2,6-difluorophenyl)(5-(2-morpholinothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone                                   | 426.43 |
| 214 |  | 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-(methylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine         | 487.52 |
| 215 |  | 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-(ethylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine          | 501.54 |
| 216 |  | 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-(propylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine         | 515.57 |
| 217 |  | 3-(3,5-difluoro-2-methoxyphenyl)-5-(4-(4-(methylsulfonyl)piperazin-1-yl)-1H-pyrazol-1-yl)-1H-pyrrolo[2,3-b]pyridine         | 488.51 |
| 218 |  | 2-(4-(1-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-4-yl)piperazin-1-yl)ethanol             | 454.47 |
| 219 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-((4-methylpiperazin-1-yl)sulfonyl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine | 502.49 |

|     |  |                                                                                                                             |        |
|-----|--|-----------------------------------------------------------------------------------------------------------------------------|--------|
| 220 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine           | 437.44 |
| 221 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-(methylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine | 501.50 |
| 222 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-(ethylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine  | 515.53 |
| 223 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-(propylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine | 529.55 |
| 224 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(4-(4-(methylsulfonyl)piperazin-1-yl)-1H-pyrazol-1-yl)-1H-pyrrolo[2,3-b]pyridine | 502.49 |
| 225 |  | 2-(4-(1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-4-yl)piperazin-1-yl)ethanol     | 468.45 |
| 226 |  | 2-(4-(4-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanol             | 453.48 |
| 227 |  | 2-(4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanol     | 467.46 |
| 228 |  | 3-(3-fluoro-2-methoxyphenyl)-5-(5-(1-(piperidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine                         | 435.55 |

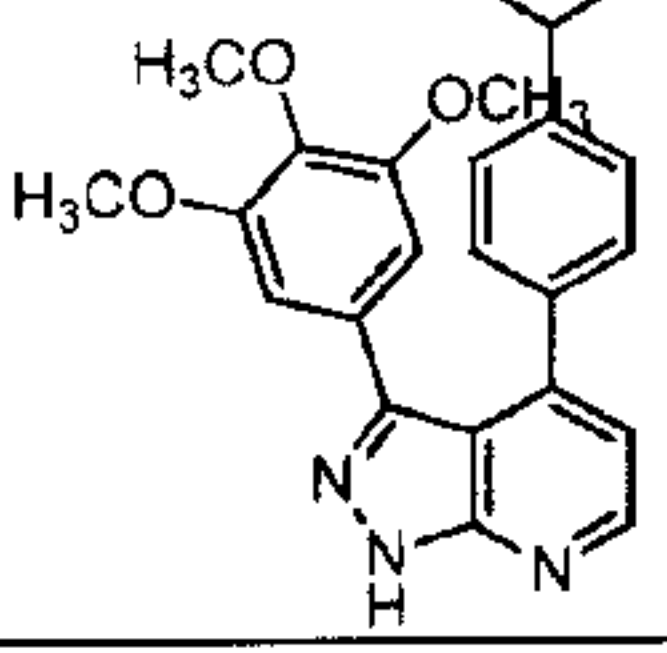
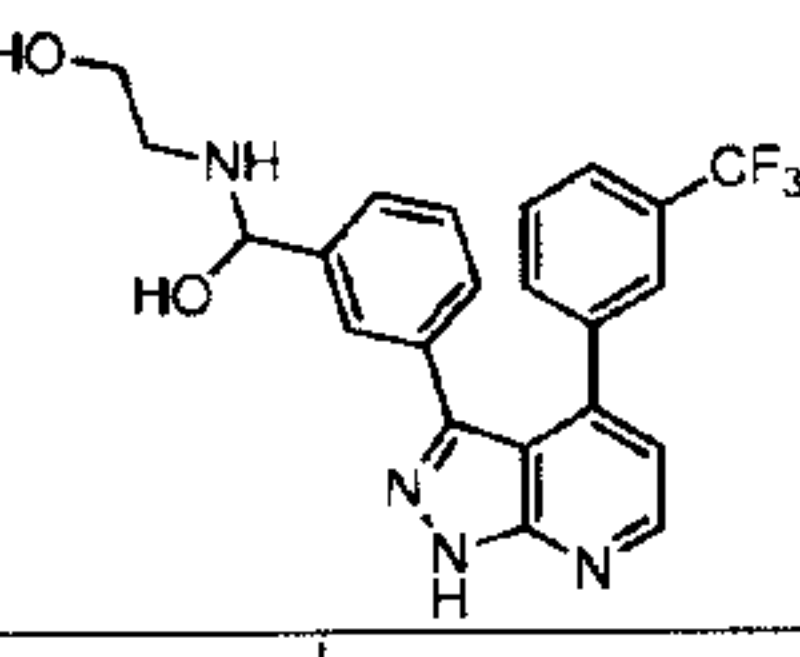
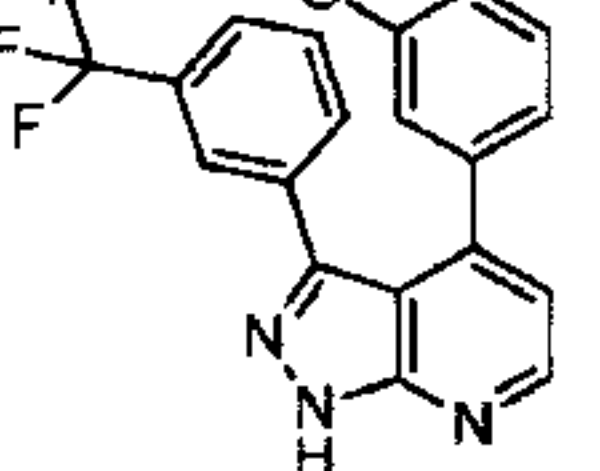
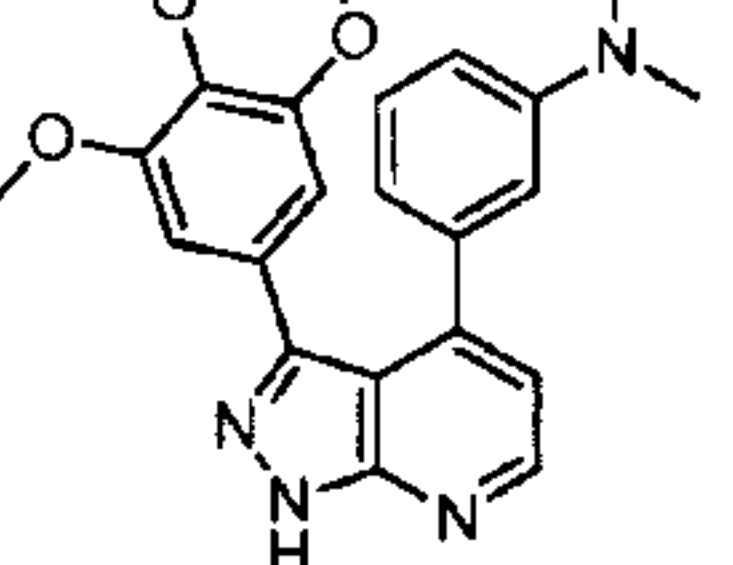
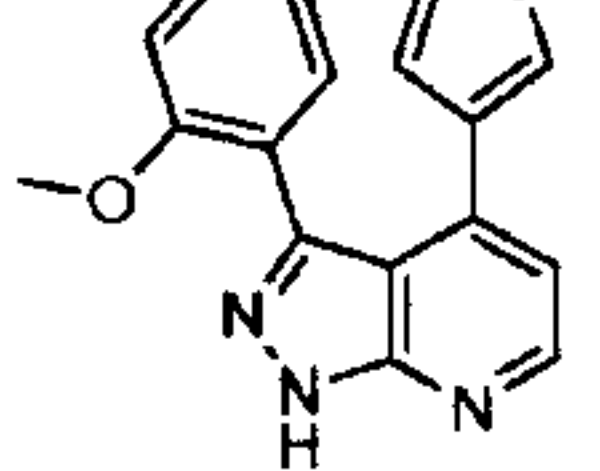
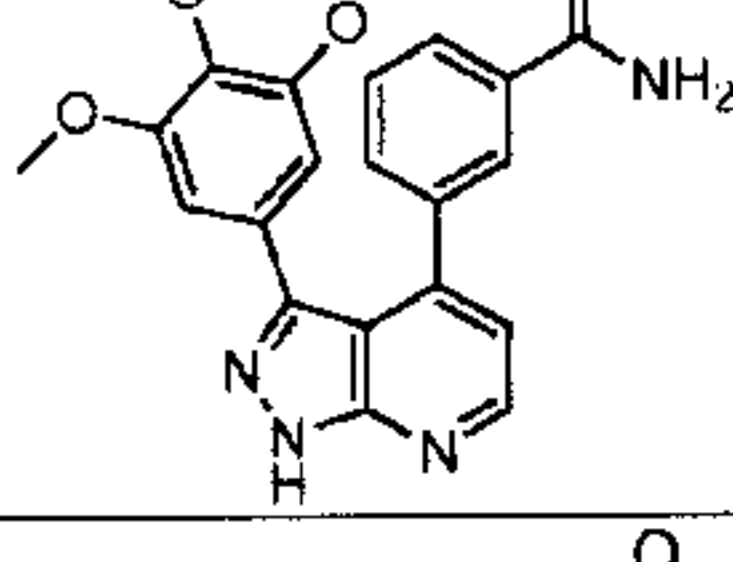
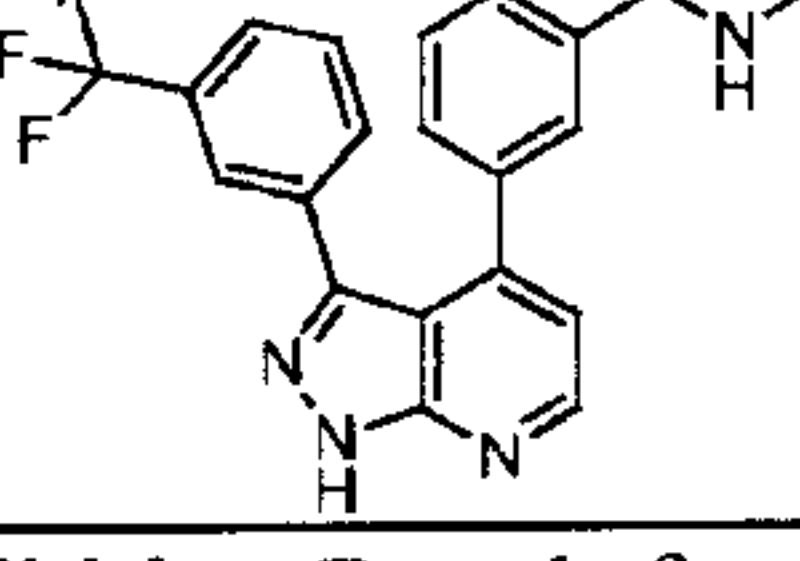
Table 2B: List of further Examples:

| EX. | Structure | Chemical Name                                                                                                           | Mol. Wt |
|-----|-----------|-------------------------------------------------------------------------------------------------------------------------|---------|
| 229 |           | 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-(1-(pyrrolidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine                | 439.52  |
| 230 |           | 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-(1-(piperidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine                 | 453.55  |
| 231 |           | 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-(1-(4-methylpiperidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine         | 467.57  |
| 232 |           | 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-(1-(4-methylpiperazin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine         | 468.56  |
| 233 |           | 4-(1-(5-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)ethyl)morpholine                  | 455.52  |
| 234 |           | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(1-(pyrrolidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine        | 453.50  |
| 235 |           | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(1-(piperidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine         | 467.53  |
| 236 |           | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(1-(4-methylpiperidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine | 481.56  |
| 237 |           | 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(1-(4-methylpiperazin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine | 482.55  |
| 238 |           | 4-(1-(5-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)ethyl)morpholine          | 469.50  |

|     |  |                                                                                                                         |        |
|-----|--|-------------------------------------------------------------------------------------------------------------------------|--------|
| 239 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(5-(1-(pyrrolidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine        | 453.13 |
| 240 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(5-(1-(piperidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine         | 467.53 |
| 241 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(5-(1-(4-methylpiperidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine | 481.56 |
| 242 |  | 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(5-(1-(4-methylpiperazin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine | 482.55 |
| 243 |  | 4-(1-(5-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)ethyl)morpholine          | 469.50 |

Table 3: List of Compounds purchased from vendor library

| Cmpd No | Structure | Chemical Name                                                                                     | Mol.Wt  | SIK2 IC <sub>50</sub> $\mu$ M |
|---------|-----------|---------------------------------------------------------------------------------------------------|---------|-------------------------------|
| 1       |           | 4-(3,4-dimethoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazolo[3,4-b]pyridine                               | 332.356 | **                            |
| 2       |           | 3-(benzo[d][1,3]dioxol-5-yl)-4-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine             | 383.323 | *                             |
| 3       |           | N-(3-(4-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)phenyl)methanesulfonamide         | 454.499 | *                             |
| 4       |           | N-(2-(dimethylamino)ethyl)-3-(3-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)benzamide | 475.54  | *                             |
| 5       |           | 3-(2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine                                  | 307.370 | ***                           |

|    |                                                                                     |                                                                                                         |         |     |
|----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|---------|-----|
| 6  |    | 4-(4-isopropylphenyl)-3-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-b]pyridine                             | 403.474 | **  |
| 7  |    | 2-((hydroxy(3-(4-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)phenyl)methyl)amino)ethanol | 426.391 | *   |
| 8  |    | 4-(3-methoxyphenyl)-3-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine                            | 369.34  | *   |
| 9  |  | N,N-dimethyl-3-(3-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)aniline                       | 404.462 | *   |
| 10 |  | 4-(furan-3-yl)-3-(2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridine                                           | 292.304 | *** |
| 11 |  | 3-(3-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)benzamide                                  | 404.419 | *   |
| 12 |  | N-methyl-3-(3-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl)benzamide                      | 396.365 | *   |

\*Kinase Inhibition Result for Selected Compounds

\*\*\* <0.1  $\mu$ M, \*\* >0.1  $\mu$ M, \* >1  $\mu$ M

ND = Not Determined

List of abbreviation and meaning used through out this application

| Abbreviation                       | Meaning                                           |
|------------------------------------|---------------------------------------------------|
| CHCl <sub>3</sub>                  | Chloroform – CHCl <sub>3</sub>                    |
| CDCl <sub>3</sub>                  | Chloroform deuterated solvent – CDCl <sub>3</sub> |
| DCM                                | Dichloromethane – CH <sub>2</sub> Cl <sub>2</sub> |
| DME                                | 1,2-Dimethoxyethane                               |
| DMF                                | N,N-Dimethylformamide                             |
| DMSO                               | Dimethylsulfoxide                                 |
| DMSO-d <sub>6</sub>                | Dimethylsulfoxide deuterated solvent              |
| Pd <sub>2</sub> (pda) <sub>3</sub> | Tris(dibenzylideneacetone)dipalladium(0)          |
| Pd(PH <sub>3</sub> ) <sub>4</sub>  | Tetrakis(trifluorophosphine)palladium(0)          |
| PTSA                               | p-Toluene Sulfonic Acid                           |
| THF                                | Tetrahydrofuran                                   |

|                                                          |                                                                     |
|----------------------------------------------------------|---------------------------------------------------------------------|
| ±BINAP                                                   | <i>rac</i> 2,2'-Bis(diphenylphosphino)-9,9-dimethylxanthene         |
| Xantphos                                                 | 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene                     |
| Pd(dppf)Cl <sub>2</sub> •CH <sub>2</sub> Cl <sub>2</sub> | [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium II DCM      |
| Et                                                       | Ethyl                                                               |
| Me                                                       | Methyl                                                              |
| MeOH                                                     | Methanol                                                            |
| EtOH                                                     | Ethanol                                                             |
| EtOAc                                                    | Ethylacetate                                                        |
| AcCN/MeCN                                                | Acetonitrile                                                        |
| DIPEA                                                    | Diisopropylethylamine                                               |
| IP                                                       | Isopropanol                                                         |
| Na <sub>2</sub> CO <sub>3</sub>                          | Sodium Carbonate                                                    |
| K <sub>2</sub> CO <sub>3</sub>                           | Potassium Carbonate                                                 |
| Cs <sub>2</sub> CO <sub>3</sub>                          | Cesium Carbonate                                                    |
| TFA                                                      | Trifluoroacetic acid                                                |
| EDC HCl                                                  | <i>N</i> -Ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide HCl |
| HOBt                                                     | 1-Hydroxybenzotriazole hydrate                                      |
| HOAc                                                     | Acetic Acid                                                         |
| Et                                                       | Ethyl                                                               |
| TMS                                                      | Trimethylsilyl                                                      |
| NBS                                                      | N-Bromosuccinamide                                                  |
| NCS                                                      | N-Chlorosuccinamide                                                 |
| PG                                                       | Protecting Group                                                    |
| g, gm                                                    | Gram(s)                                                             |
| mg                                                       | Milligram(s)                                                        |
| h, hr                                                    | Hour                                                                |
| min                                                      | Minute(s)                                                           |
| M                                                        | Molar, molarity                                                     |
| mM                                                       | Millimolar                                                          |
| μM                                                       | Micromolar                                                          |
| nM                                                       | Nanomolar                                                           |
| L, l                                                     | Liter(s)                                                            |
| mL, mL                                                   | Milliliter(s)                                                       |
| μL                                                       | Microliter(s)                                                       |
| RM                                                       | Reaction Mixture or Reaction Mass                                   |
| SM                                                       | Starting Material                                                   |
| RT, rt                                                   | Room Temperature                                                    |
| HPLC                                                     | High-Performance Liquid Chromatography                              |
| LCMS                                                     | Liquid Chromatography Mass Spectrometry                             |
| MS or ms                                                 | Mass Spectrometry                                                   |
| NMR                                                      | Nuclear Magnetic Resonance Spectroscopy                             |
| TLC                                                      | Thin Layer Chromatography                                           |
| UV                                                       | Ultra-Violet Spectrometry                                           |
| s                                                        | Singlet                                                             |
| d, Dt, dt                                                | Doublet, doublet of doublet                                         |
| t, tr                                                    | Triplet                                                             |
| m                                                        | Multiplet                                                           |

## METHODS OF PREPARATION OF COMPOUNDS

[00128] In certain embodiments, the Examples depicted below are compounds prepared according to general procedures given in the following sections. Although the synthetic methods and Schemes depict the syntheses of certain compounds of the present invention, the methods and other methods known to one of ordinary skill in the art can be applied to all the compounds of the genus, the genus sub-class and species of each of these compounds as described herein. All aspects of this invention can be understood from the following Schemes. The following are exemplary and are not intended to limit the scope of the invention.

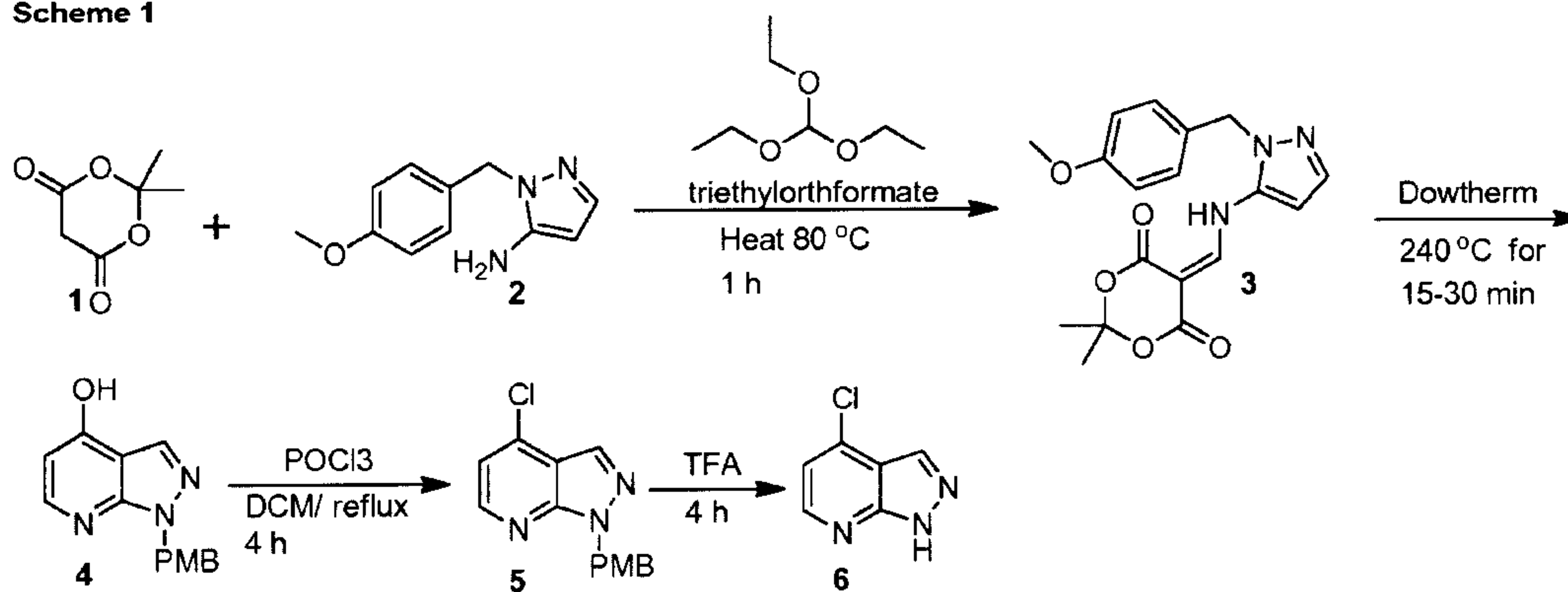
## EXAMPLES

### Experimental Details and Examples

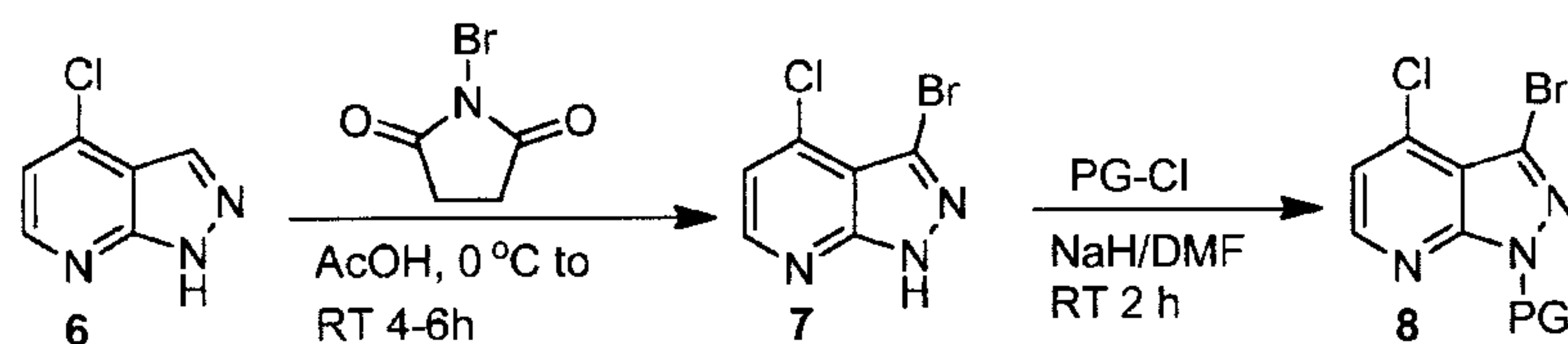
[00129] Melting points were determined in a MP-96 digital Polmon apparatus.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at rt in  $\text{CDCl}_3$  or  $\text{DMSO}-d_6$  at Jeol 400-MHz NMR spectrophotometer using solvent peaks for  $\text{CDCl}_3$ : 7.27 and  $\text{DMSO}-d_6$  2.50 (D) as internal references. The assignment of chemical shifts is based on standard NMR experiments ( $^1\text{H}$ ,  $^{13}\text{C}$ ). Mass spectra were recorded on a Shimadzu LCMS LC-210EV spectrometer with an API-ES ionization source. Jasco-FTIR-4100 was used to record the IR spectra. TLC analyses were performed on silica F254 and detection by UV light at 254nm, or by spraying with phosphomolybdic- $\text{H}_2\text{SO}_4$  dyeing reagent,  $\text{KMnO}_4$  or iodine. Column chromatography were performed on silica Gel 60 (230 mesh). Purifications and separations were performed on a standard silica flash chromatography system. The purity of the samples has been determined by HPLC for the % area peak corresponding to the retention of compound and elemental analysis for C, H, N and O was carried out using Perkin-Elmer 2400 elemental analyser and chloride analysis performed using calorimetric titration at the Intertek USA Inc., QTI.

### General Synthesis Schemes 1-3

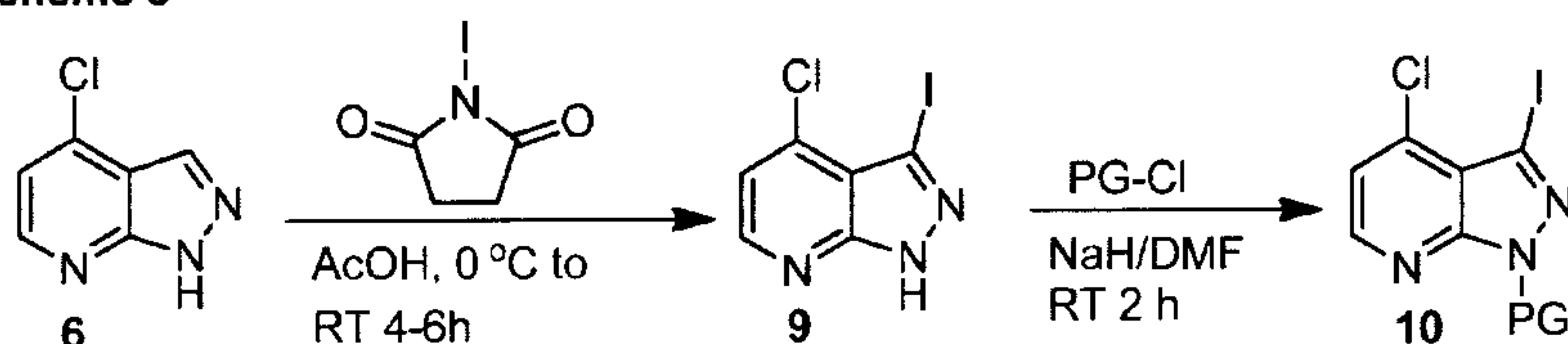
Scheme 1



Scheme 2

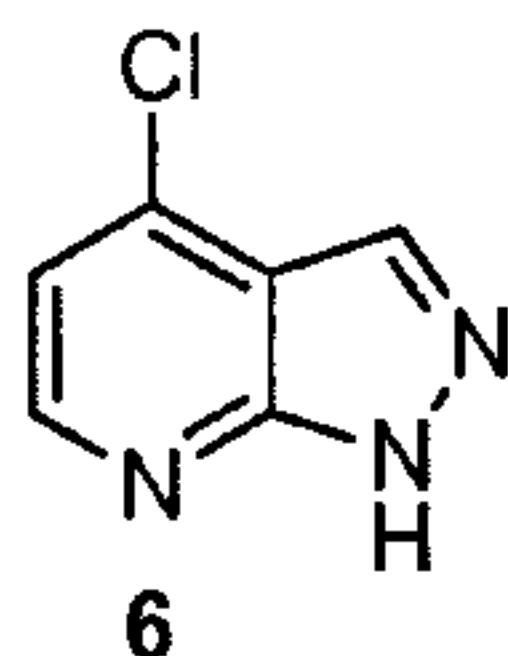


Scheme 3



[00130] “PG” represents a protecting group, or protecting groups (PGs), and refers to a group used to protect a certain functional moiety to prevent it from participation in chemical reactions until the PG is removed. Well known to the skilled artisan, these protective groups can be removed by acid, base, and hydrogenolysis conditions in the presence or absence of organic solvents. Such PGs employed in the above synthesis schemes 1-3 include, but are not limited to, *p*-methoxybenzyl (PMB), 2,4-dimethoxybenzyl, benzyl (Bn), 4-toluenesulfonyl chloride (tosyl chloride or TsCl), 2-(trimethylsilyl) ethoxymethyl chloride (SEM-Cl), trityl chloride (triphenylmethyl chloride), dimethoxytrityl, tetrahydropyranyl (THP), di-*tert*-butyl dicarbonate (*tert*-Boc), fluorenylmethyloxycarbonyl chloride (Fmoc-Cl), *tert*-butyldimethylsilyl chloride (TBDMS-Cl), and carboxybenzyl (Cbz) groups.

**INTERMEDIATE 6:** Preparation of 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine (**6**)

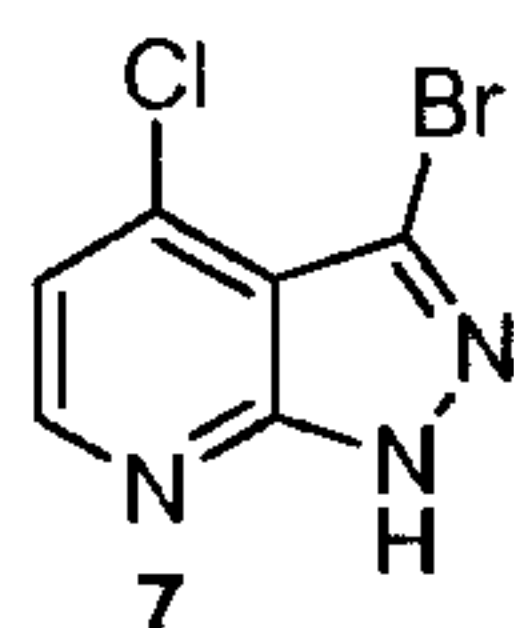


[00131] 2,2-dimethyl-1,3-dioxane-4,6-dione **1** (meldrum's acid) (20g, 139mmol), 1-(4-methoxybenzyl)-1*H*-pyrazol-5-amine (**2**) (28.2g, 139mmol, 1eq) (prepared according to the procedure described by Misra, R.N., et al. *Bioorg. Med. Chem. Lett.*(2003), **13**, 1133-1136) in presence of triethoxymethane (30.8g, 208mmol, 1eq) was heated to 85°C for 1hr, subsequently worked up and treated with diethyl ether, and provided the pure 5-(((1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3**) as yellow solid (39.3g). To a stirred solution of DOWTHERM™ (80mL) was added compound **3** (39.3g at 200°C under N<sub>2</sub> in portions over a 30min). After completion of additions, the RM was heated at 240°C for 1hr. After completion of the reaction from TLC, the mixture was diluted with hexanes (300mL) to separate the DOWTHERM™ from the crude RM. The resulting crude

mixture on treatment with DCM and diethyl ether provided the off-white solid of 1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridin-4-ol (**4**) (24.56g). Chlorination of compound **4** (24g, 94mmol) on treatment with phosphoryl trichloride (43g, 282mmol) in dichloroethane (10mL) at 40°C for 4hr yielded 19g of 4-chloro-1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine **5**.

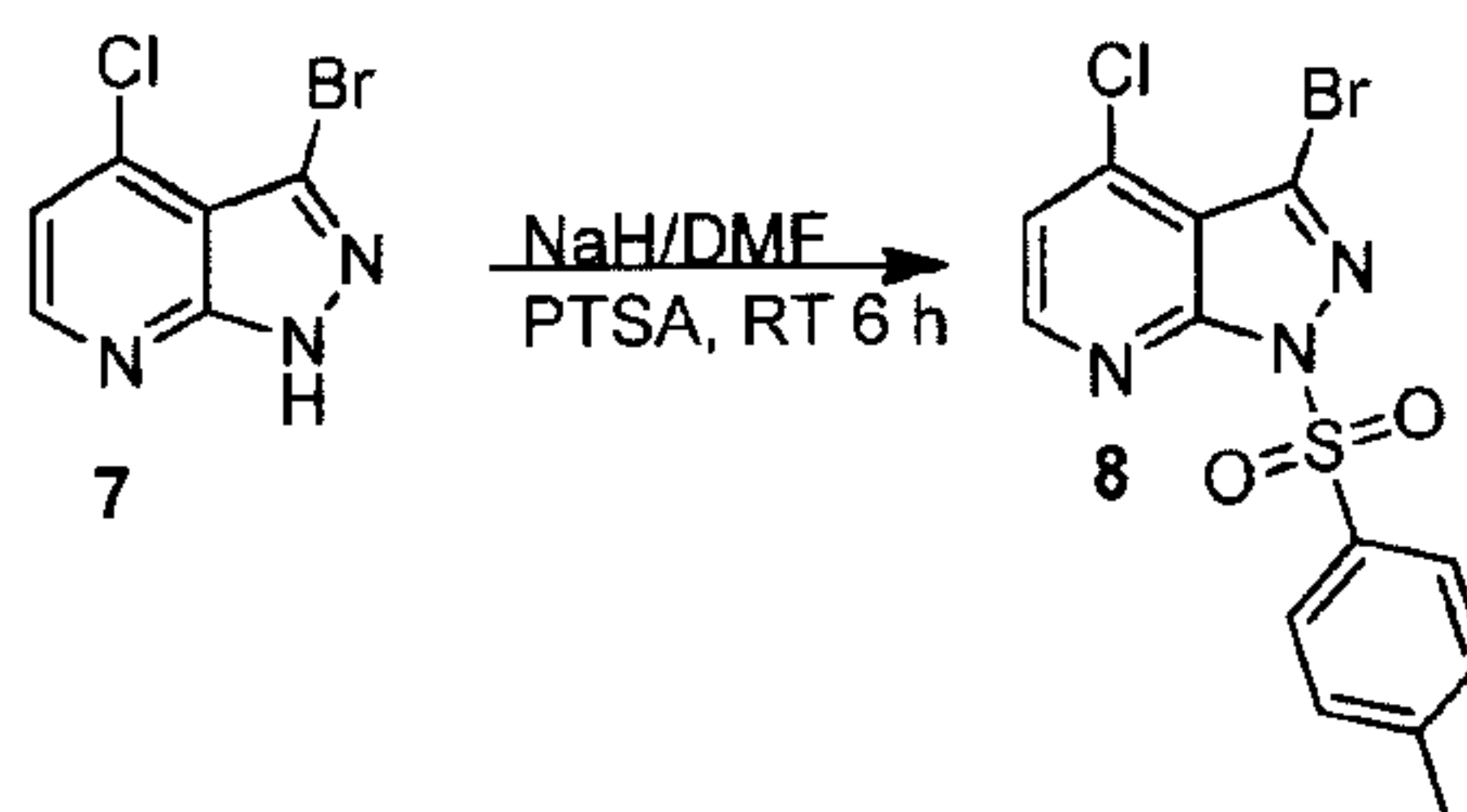
[00132] 4-Chloro-1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine (**5**) 19g (69.4mmol) in neat TFA (30mL, 389mmol) was stirred at 80°C for 4hr. The resulting RM was concentrated and MeOH was added and the obtained precipitate was filtered and washed with MeOH. The crude solid was treated with EtOAc, saturated NaHCO<sub>3</sub> and dried over Na<sub>2</sub>SO<sub>4</sub>, to yield the desired product as a half white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 13.23 (br s, 1H), 8.52 (d, *J*=5.1 Hz, 1H), 8.10 (s, 1H), 7.32 (m, 1H).

**INTERMEDIATE 7:** Preparation of 3-bromo-4-chloro-1H-pyrazolo[3,4-b]pyridine (**7**)



[00133] 4-chloro-1H-pyrazolo[3,4-b]pyridine (**6**) 1g (6.53mmoles) in acetic acid (10mL) cooled to 0°C was added *N*-bromosuccinimide 2.31g (13.06mmol) and the resulting RM was stirred for 4hr at rt. After completion of the SM, the RM was quenched with ice water and extracted with dichloromethane (2 x 10mL). The combined organic layer was dried over sodium sulphate, and the solvent evaporated to yield compound **7** (Yield: 0.9 g, 60%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 13.19 (br s, 1H), 8.21 (s, 1H), 7.39 (m, 1H).

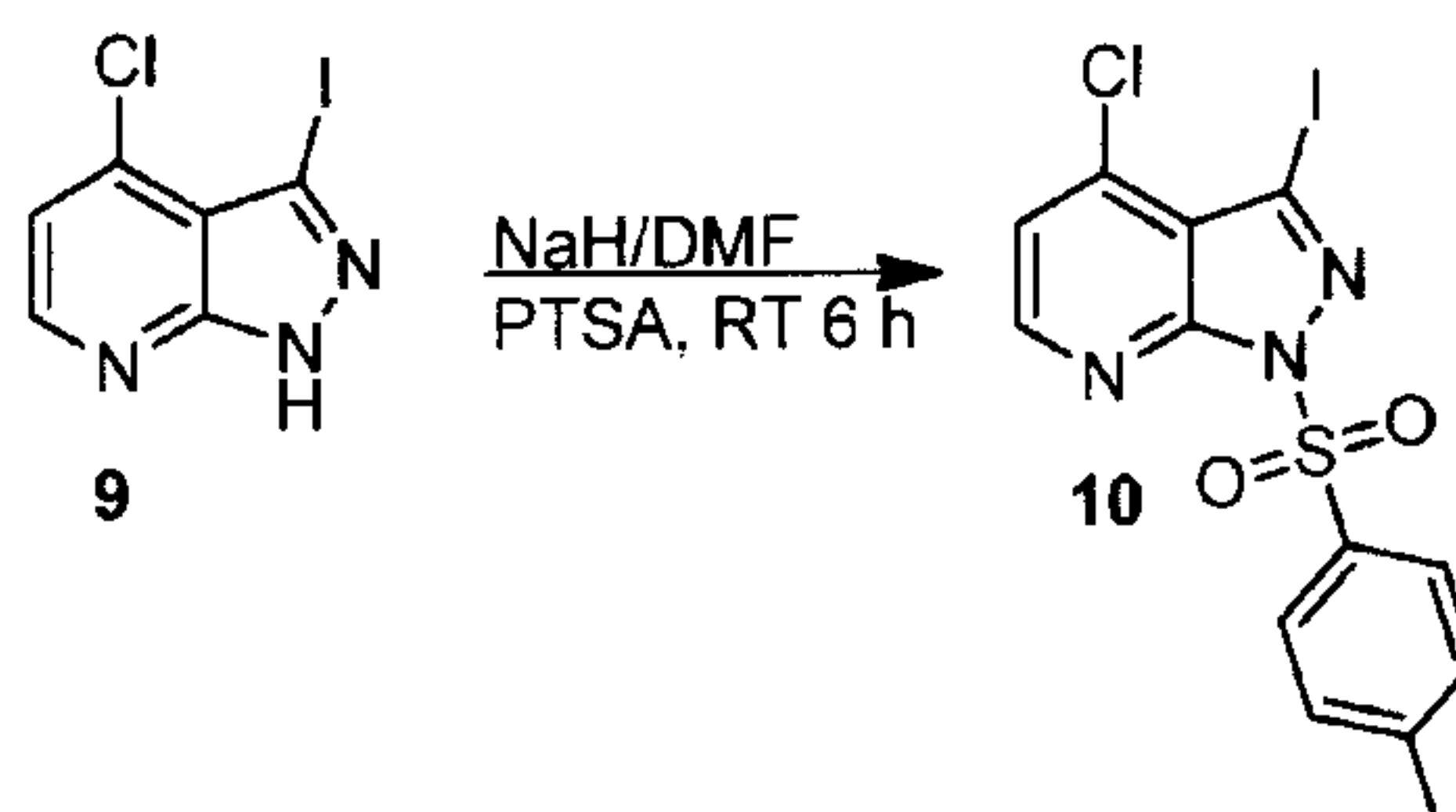
**INTERMEDIATE 8:** Preparation of 3-bromo-4-chloro-1-tosyl-1H-pyrazolo[3,4-b]pyridine (**8**)



[00134] To 3-bromo-4-chloro-1H-pyrazolo[3,4-b]pyridine (**7**) 1g (4.345mmol, 1eq) in DMF (5mL) cooled to 0°C was add sodium hydride 0.156g (6.51mmols, 1.5 eq) slowly under nitrogen atmosphere for 15min followed by the addition of *p*-toluene sulfonyl chloride 0.91g (4.77mmol, 1.1eq). The resulting RM was stirred for 2hr and after completion of the SMs from TLC; the RM was quenched with ice cold water and extracted with chloroform. The combined

organic layer was washed with brine solution and the organic layer was dried over sodium sulphate. The solvents were removed to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound **8** at 6-7% ethyl acetate in hexane (Yield: 1.2 g, 72%).

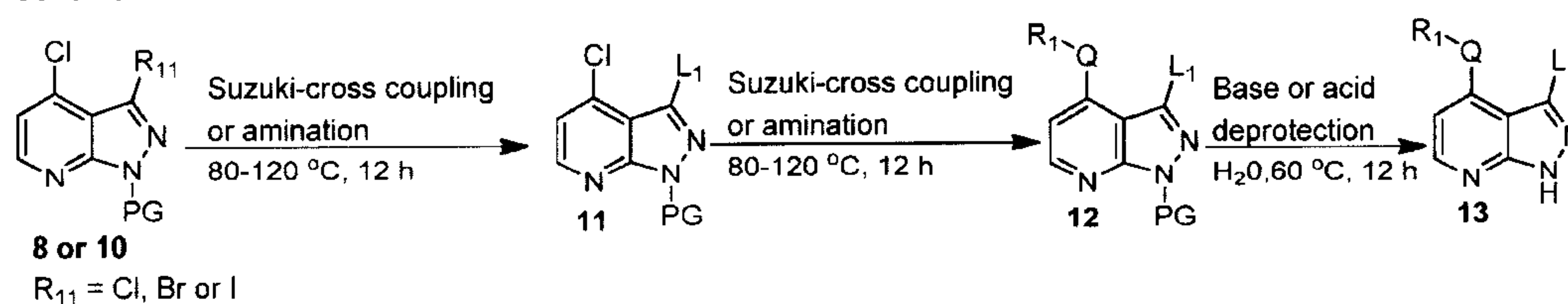
**INTERMEDIATE 10:** Preparation of 4-chloro-3-iodo-1-tosyl-1*H*-pyrazolo[3,4-*b*]pyridine (**10**).



[00135] A solution of compound **9** (230mg, 0.8273mmol) in DMF (7mL) was cooled to 0°C and sodium hydride (49mg, 1.2409mmol) was added slowly under nitrogen atmosphere and was stirred for 20min. The PTSA (p-toluene sulfonic acid) was added slowly to the RM and stirred for 2hrs at RT. After completion of the reaction, the reaction was quenched with ice water and extracted with ethyl acetate twice. The organic layer was completely distilled off to get the crude material which was passed over 100-200 mesh silica gel eluting the pure compound at 5-6% ethyl acetate in hexane as eluent to get the title compound as half white colored solid **10**.

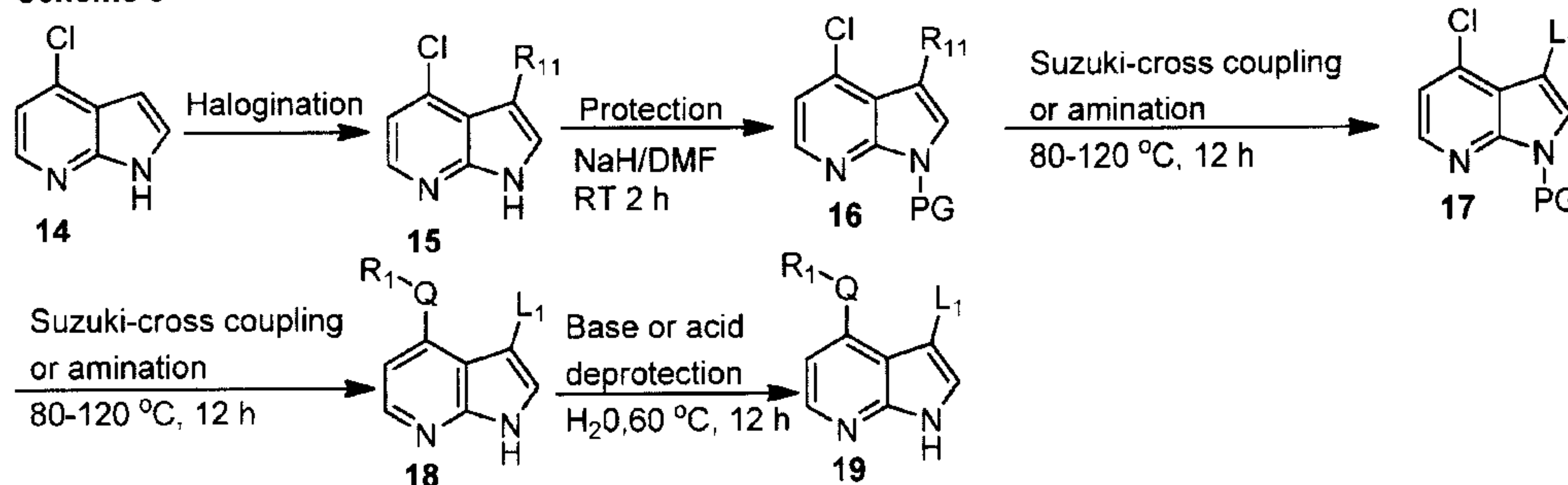
General **Scheme 4** synthesis Examples:

**Scheme 4**



General **Scheme 5** for the synthesis of Examples:

**Scheme 5**

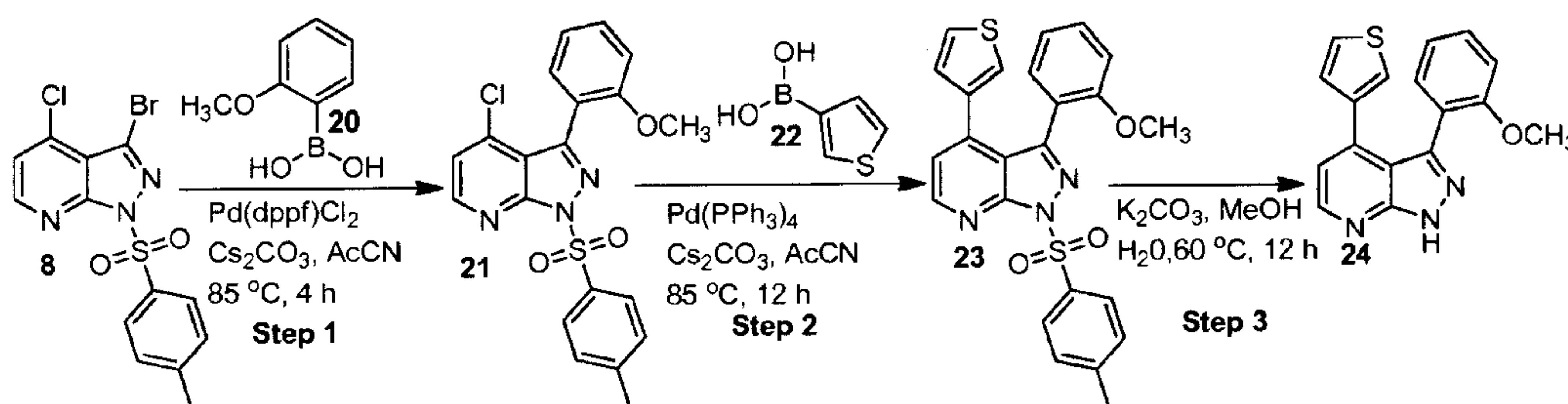


### General Procedures for the Preparation Examples

[00136] The key intermediates 3-bromo-4-chloro-1H-pyrazolo[3,4-b]pyridine (**7**) or 4-chloro-3-iodo-1H-pyrazolo[3,4-b]pyridineprotected (**9**) were prepared from *N*-chloro- or *N*-bromo- succinamide, 2eq in presence of acetic acid as solvent at rt for 4 to 6hr, which afforded ~50-60 yields. Both the compounds **7** and **9** protected with *p*-toluenesulfonyl chloride (*p*-TsCl) (1eq) on treatment with sodium hydride in DMF at rt for 2hr and after completion of the SMs from TLC; the RM was quenched with ice cold water and extracted with chloroform. The combined organic layer was washed with brine solution and the organic layer was dried over sodium sulphate and the solvents were removed to get the crude product, which was passed through through 100-200 mesh silica gel eluting the pure compounds **8** and **10** at 10% ethyl acetate in hexane and gave greater than 70% yields.

[00137] In subsequent step of the Suzuki-Cross coupling reactions, variously substituted aryl boronic acids and/or aryl boronic esters were reacted with either compound **8** or **10** with 1eq. each in presence of one of the solvents: 1,4-dioxane, THF, DMF, DMSO, toluene, or acetonitrile. The resulting RM was degassed, purged with argon or N<sub>2</sub> gas a few times and was charged with NaCO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, tBuOK, Na-tBuOK, potassium acetate or NaHCO<sub>3</sub> (1.5 to 2eq) followed by the addition of palladium catalysts (0.01 to 0.05eq). After the addition of catalysts the contents of the reaction were purged and degassed again and heated at 80 to 100°C for 8 to 16 or 24hr. After completion of the reaction monitored from TLC, the contents were cooled to rt and diluted with CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub> or EtOAc. The organic layers were passed through a Celite pad then the solvent was completely distilled off to get the crude product, which was subjected to flash to column chromatography purification to get the variously substituted title compounds **11** and **12**.

### PREPARATION OF EXAMPLE 1: 3-(2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine (**24**)



#### Step 1:

[00138] A stirred solution of (**8**) (0.150 g 0.387mmol) and (2-methoxyphenyl) boronic acid (**20**) (58mg 0.387mmol) in acetonitrile (10mL) was degassed and purged with nitrogen for 10min. Then cesium carbonate (250mg, 0.774mmol) and Pd(dppf)Cl<sub>2</sub> (15mg, 0.019mmol) was

added, then again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction, the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as an off white colored compound **21**.

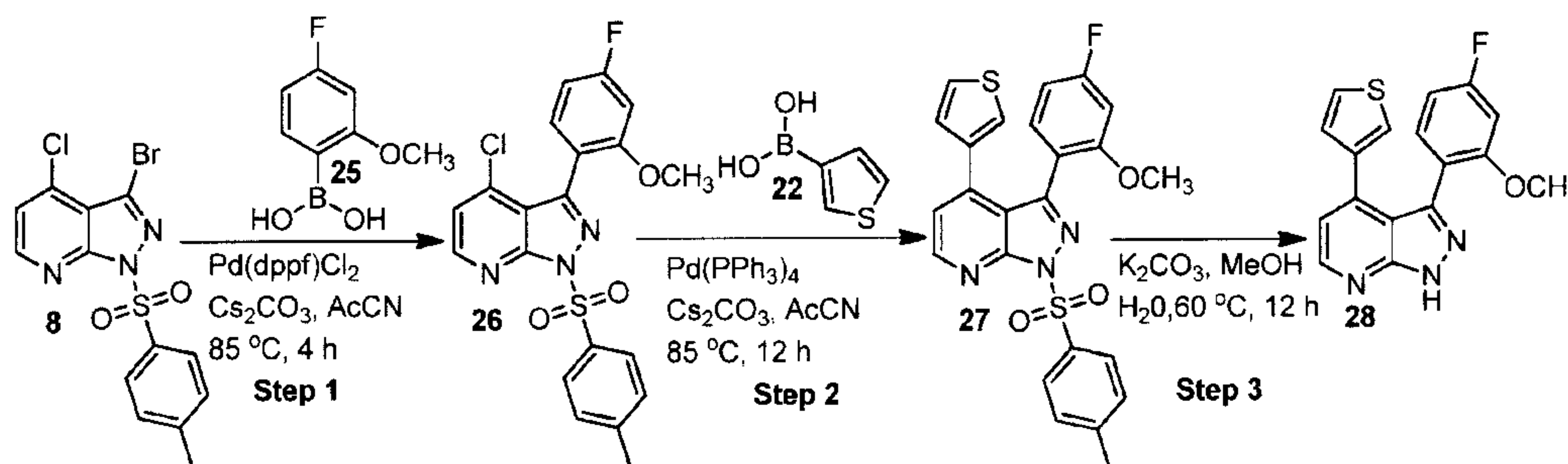
Step 2:

[00139] To a stirred solution of 4-chloro-3-(2-methoxyphenyl)-1-tosyl-1H-pyrazolo[3,4-b]pyridine (**21**) (100mg, 0.242mmol) and thiophen-3-ylboronic acid (**22**) (30mg, 0.242mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (158mg, 0.484mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (13.9mg, 0.0121mmol) and again degassed and purged with nitrogen for 15min. Then the RM was heated to 85°C overnight in a sealed tube. After completion of the SM the RM was cooled to rt and diluted with chloroform. The organic layer was passed through a celite bed. The organic layer was completely distilled off the solvent to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid 3-(2-methoxyphenyl)-4-(thiophen-3-yl)-1-tosyl-1H-pyrazolo[3,4-b]pyridine (**23**).

Step 3:

[00140] To a stirred solution of (**23**) (50mg, 0.108mmol) in methanol (5mL) and water (5mL) was added potassium carbonate (29mg, 0.216mmol). The RM was heated to 60°C overnight. After completion of the SM, the solvents were completely distilled off and diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid (**24**). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 11.05 (1H), 8.57 (d, J=4.75 1H), 7.50 (m, J=5.85 1H), 7.48 (m, J=5.73 1H), 7.16 (m, J=4.87 1H), 7.12 (m, J=3.17 1H), 6.98 (m, J=4.87 3H), 6.61(d, J=8.17 1H), 3.21(3H) and MS m/z = 308.1.

**PREPARATION OF EXAMPLE 4: 3-(4-fluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine (**28**)**



Step 1:

[00141] To a stirred solution of 3-bromo-4-chloro-1-tosyl-1H-pyrazolo[3,4-b]pyridine **8** (150mg 0.387mmol) and (4-fluoro-2-methoxyphenyl)boronic acid **25** (65mg, 0.387mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10 min, cesium carbonate (252mg 0.775mmol) and Pd(dppf)Cl<sub>2</sub> (15mg, 0.0193mmol) were added. The resulting RM degassed and purged again with nitrogen for 15min. The RM was heated to 85°C for 4hr in a sealed tube. After completion of the reaction, it was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude compound **26**. The crude material was passed through 100-200 mesh silica gel and eluting the pure compound at 7-8% ethyl acetate in hexane obtained off white colored solid **26**.

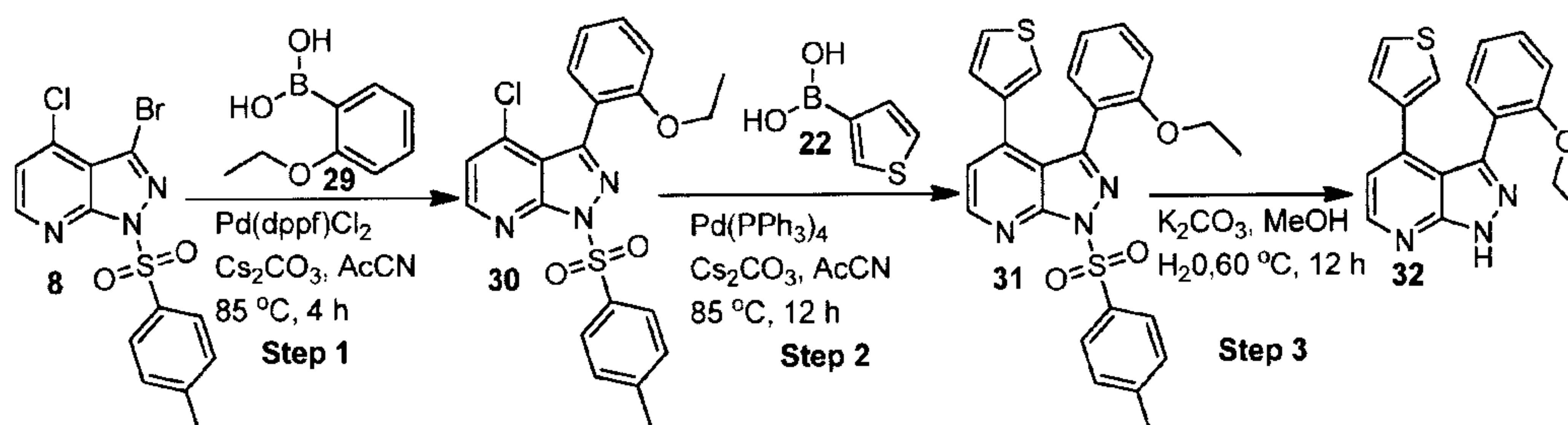
Step 2:

[00142] To a stirred solution of compound **26** (100mg, 0.231mmol) and compound **22** (33mg, 0.254mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (150mg, 0.463mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (13mg, 0.0115mmol) and degassed and purged again with nitrogen for 15min. Then the RM was heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound **27** at 10-11% ethyl acetate in hexane as off white solid.

Step 3:

[00143] To a stirred solution of 3-(4-fluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1-tosyl-1H-pyrazolo[3,4-b]pyridine **27** (50mg 0.102mmol) in methanol (10mL) and water (5mL) was added potassium carbonate (0.204mmol) and the RM was heated to 60°C overnight. After completion of the SM the the solvents was completely distilled off, diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate. The crude product was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid of cpmpound 3-(4-fluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine **28**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.56(d,1H), 7.44(m,1H), 7.23(m,1H), 7.16(m,1H), 7.02(m,1H), 6.95(m,1H), 6.73(m,1H), 6.34(m,1H) and MS m/z = 325.8.

**PREPARATION OF EXAMPLE 5: 3-(2-ethoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine (32)**



Step 1:

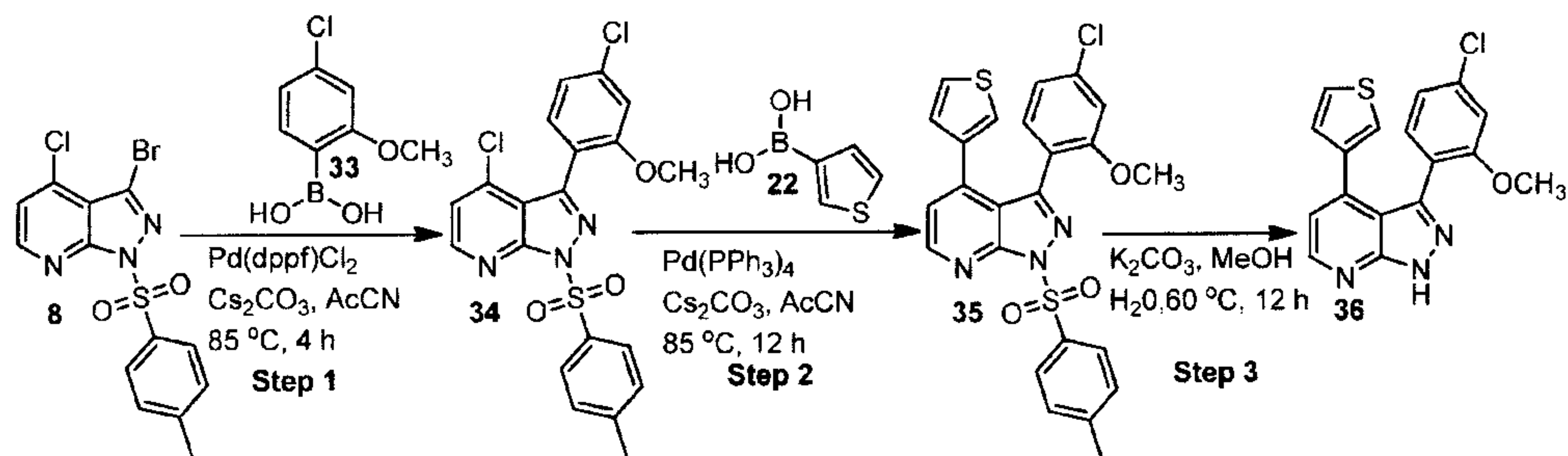
[00144] To a stirred solution of compound **8** (150mg, 0.387mmol) and **29** (65mg, 0.387mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (252mg, 0.775mmol) and Pd(dppf)Cl<sub>2</sub> (15mg, 0.0193mmol), again degassed and purged with nitrogen for 15min and the RM was heated to 85°C for 4hr in a sealed tube. After completion of the reaction, the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid **30**.

Step 2:

[00145] To a stirred solution of **30** (79mg, 0.163mmol) and **22** (23mg, 0.179mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (107mg, 0.497mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (9mg, 0.00817mmol) and again degassed and purged with nitrogen for 15min. The RM was heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **31**.

Step 3:

To a stirred solution of **31** (50mg, 0.105mmol) in methanol (40mL) and water (5mL) was added potassium carbonate (30mg, 0.210mmol) and the RM heated to 60°C overnight. After completion of the SM, the solvents were completely distilled off, diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate. The crude was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid of compound **32**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 11.28(s, 1H), 8.57(d, 1H), 7.52(m, 1H), 7.32(m, 1H), 7.17(d, 1H), 7.00(m, 2H) 6.95(m, 1H), 6.57(m, 1H); and MS m/z = 321.9

**PREPARATION OF EXAMPLE 6: (36)**Step 1:

[00146] To a stirred solution of compound **8** (150mg, 0.387mmol) and **33** (72mg, 0.387mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added  $\text{Cs}_2\text{CO}_3$  (253mg, 0.775mmol) and  $\text{Pd(dppf)Cl}_2$  (16mg, 0.0193mmol). The resulting RM was degassed, purged with nitrogen again for 15min and was heated to 85°C for 4hr in a sealed tube. After completion of the reaction was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude compound **34**. The crude was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid **34**.

Step 2:

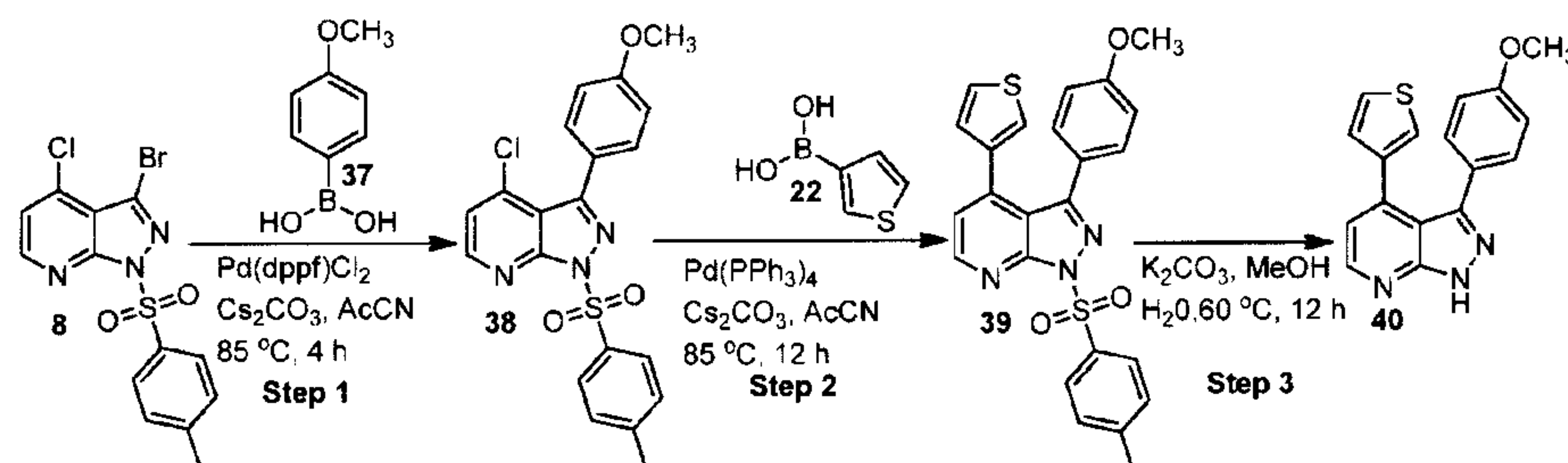
[00147] To a stirred solution of **34** (65mg, 0.149mmol) and compound **22** (21mg, 0.159mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added  $\text{Cs}_2\text{CO}_3$  (95mg, 0.289mmol) and  $\text{Pd(PPh}_3)_4$  (8mg, 0.00724mmol) and continued degassing and purging with nitrogen for another 15min. The resulting RM was heated to 85°C overnight for 12hrs in a sealed tube. After completion of the SM monitored from TLC, the RM was cooled to rt, diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off to get the crude product **35**. The crude product was passed through 100-200 mesh silica gel eluting the pure compound **35** at 10-11% ethyl acetate in hexane as off white solid compound.

Step 3:

[00148] To a stirred solution of compound **35** (60mg, 0.120mmol) in methanol (10mL) and water (5mL) was added  $\text{K}_2\text{CO}_3$  (33mg, 0.241mmol) and the RM heated to 60°C for 12hr. After completion of the SM, the solvents were removed, diluted with water and extracted with chloroform in two volumes. The organic layer was dried over sodium sulphate. The crude material was passed through 100-200 mesh silica gel, eluting the the compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid of compound **36**.  $^1\text{H}$  NMR

(CDCl<sub>3</sub>)  $\delta$ : 10.84(s,1H), 8.56(d,1H), 7.41(d,1H), 7.17(m,2H), 7.03(m,2H), 6.97(d,1H), 6.61(d,1H), 3.21(s,3H); and MS  $m/z$  = 341.8

**PREPARATION OF EXAMPLE 7: 3-(4-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine (40)**



Step 1:

[00149] A stirred solution of 3-bromo-4-chloro-1-tosyl-1H-pyrazolo[3,4-b]pyridine **8** (150mg, 0.387mmol) and (4-methoxyphenyl)boronic acid **37** (59mg, 0.387mmol) in acetonitrile (5mL) was degassed and purged with nitrogen for 10min. Cesium carbonate (252mg, 0.774mmol) and Pd(dppf)Cl<sub>2</sub> (15mg, 0.0193mmol) was added to the RM and degassed and purged with nitrogen again for 15min. The resulting RM was heated to 85°C for 4hr in a sealed tube. After completion of the reaction the crude RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off. The obtained crude was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane to provide off white colored solid of compound **38**.

Step 2:

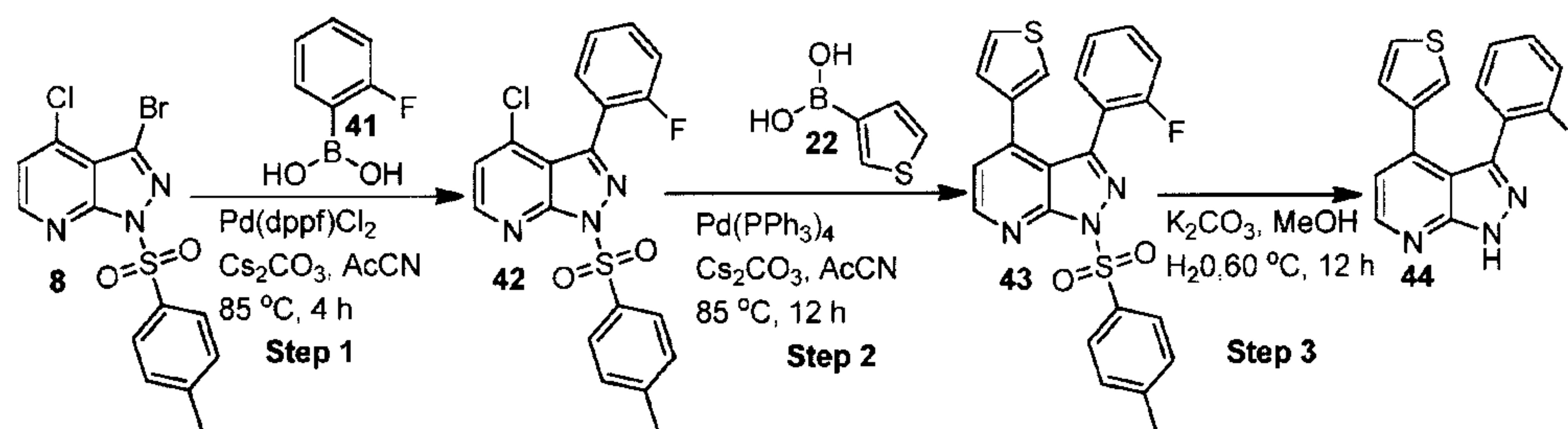
[00150] To a stirred solution of 3-(4-methoxyphenyl)-4-(thiophen-3-yl)-1-tosyl-1H-pyrazolo[3,4-b]pyridine **38** (75mg, 0.181mmol) and thiophen-3-ylboronic acid **22** (25mg, 0.199mmol) in acetonitrile(5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (0.118g 0.363mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (10mg, 0.0090mmol) and again degassed and purged with nitrogen for 15min. Then the RM was heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane giving an off white solid of 3-(4-methoxyphenyl)-4-(thiophen-3-yl)-1-tosyl-1H-pyrazolo[3,4-b]pyridine **39**.

Step 3:

[00151] To a stirred solution of compound **39** (35mg, 0.0758mmol) in methanol (10mL) and water (5mL) was added potassium carbonate (20mg, 0.151mmol) and the RM heated to 60°C overnight. After completion of the SM, the RM was completely distilled off, diluted with water

and extracted with chloroform twice. The organic layer was dried over sodium sulphate and the solvent was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid of compound **40**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 10.71(s, 1H), 8.57 (d, 1H), 7.18 (m, 4H), 7.09 (m, 1H), 6.92 (m, 1H), 6.74 (m, 1H), 3.81 (s, 3H) and MS  $m/z$  = 307.9.

**PREPARATION OF EXAMPLE 9: 3-(2-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine (**44**)**



Step 1:

[00152] To a stirred solution of compound **8** (150mg, 0.387mmol) and **41** (54mg, 0.387mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added  $\text{Cs}_2\text{CO}_3$  (253mg 0.775mmol) and  $\text{Pd(dppf)Cl}_2$  (15mg 0.0193mmol). The resulting RM was degassed, purged with nitrogen again for 15min again and heated to 85°C for 4hr in a sealed tube. After completion of the reaction, it was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude compound **38**. The crude was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid **42**.

Step 2:

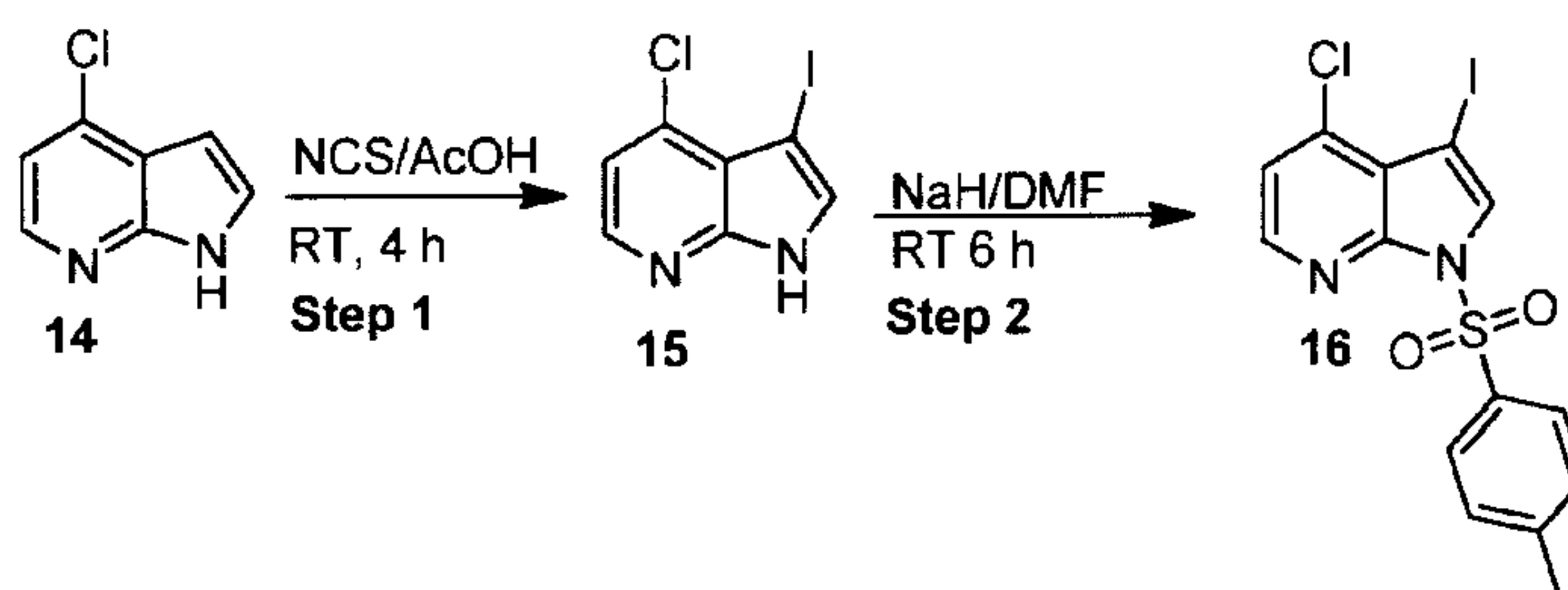
[00153] To a stirred solution of **42** (100mg, 0.248mmol) and compound **22** (35mg, 0.273mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added  $\text{Cs}_2\text{CO}_3$  (162mg 0.497mmol) and  $\text{Pd(PPh}_3)_4$  (14mg, 0.0124mmol) and continued degassing and purging with nitrogen for another 15min. The resulting RM was heated to 85°C overnight or 12hrs in a sealed tube. After completion of the SM monitored from TLC, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off to get the crude product **43**. The crude product was passed through 100-200 mesh silica gel, eluting the pure compound **43** at 10-11% ethyl acetate in hexane as off white solid compound.

Step 3:

[00154] To a stirred solution of compound **43** (60mg, 0.1334mmol) in methanol (40mL) and water (5mL) was added  $\text{K}_2\text{CO}_3$  (36.9mg, 0.266mmol) and the RM heated to 60°C for 12hr.

After completion of the SM, the solvents were removed, diluted with water and extracted with chloroform in two volumes. The organic layer was dried over sodium sulphate. The crude material was passed through 100-200 mesh silica gel eluting the compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid of compound **44**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.66 (d, 1H), 7.31 (m, 1H), 7.20 (m, 1H), 7.19 (m, 2H), 7.02 (m, 1H), 6.93 (m, 2H), 6.71 (m, 2H) and MS  $m/z$  = 295.8.

**PREPARATION OF INTERMEDIATE 16: 4-chloro-3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (16)**



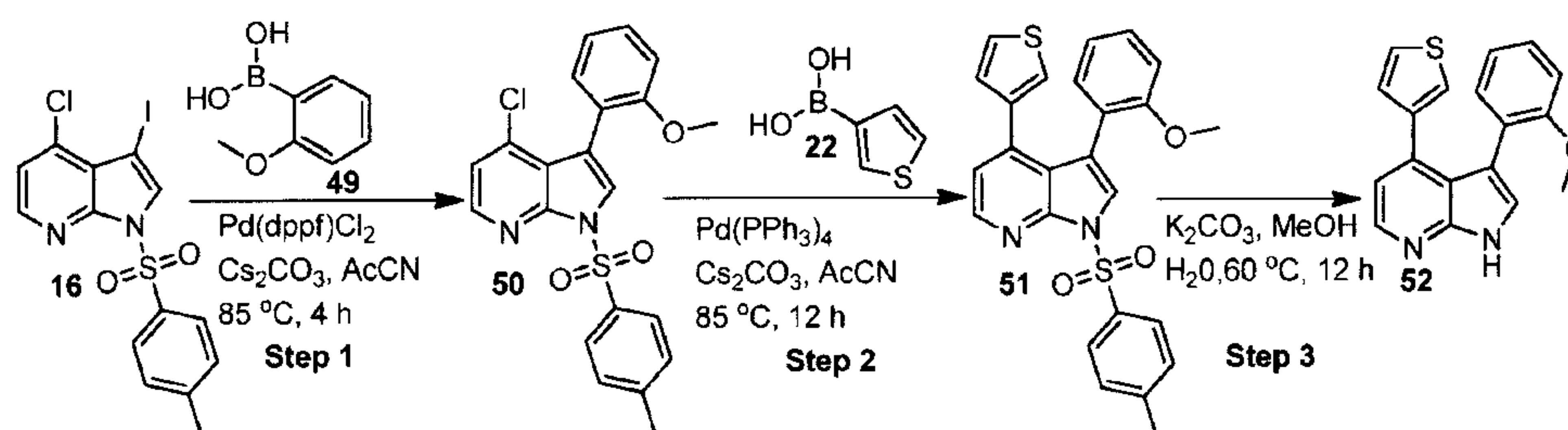
Step 1:

[00155] 4-chloro-1H-pyrrolo[2,3-b]pyridine (**14**) 1g (6.55mmol) in acetic acid (10mL) cooled to 0°C and was added *N*-chlorosuccinimide (0.875g, 6.55mmol). The resulting RM was stirred for 4hr at rt. After completion of the SM, the RM was quenched with ice water and extracted with dichloromethane (2 x 10mL). The combined organic layer was dried over sodium sulphate, and the solvent evaporated to yield compound 4-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine **15**.

Step 2:

[00156] To compound **15** (0.8 g, 2.87mmol) in DMF (5mL) cooled to 0°C was add sodium hydride (0.138 g, 5.75mmol, 2 eq) slowly under nitrogen atmosphere for 15min followed by the addition of *p*-toluene sulfonyl chloride (0.820 g, 4.31mmol, 1.5 eq). The resulting RM was stirred for 6hr and after completion of the SMs from TLC; the RM was quenched with ice cold water and extracted with chloroform. The combined organic layer was washed with brine solution and the organic layer was dried over sodium sulphate. The solvents were removed to get the crude product, which was passed through through 100-200 mesh silica gel eluting the pure compound **16** at 6-7% ethyl acetate in hexane.

**PREPARATION OF EXAMPLE 17: 3-(2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (52)**

Step 1:

[00157] A stirred solution of compound **16** (150mg, 0.347mmol) and **49** (52.7mg, 0.347mmol) in acetonitrile (5mL) was degassed, purged with nitrogen for 10min and to which was added  $\text{Cs}_2\text{CO}_3$  (151.1mg, 0.485mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (14.1mg, 0.017mmol). The resulting RM was degassed, purged with nitrogen again for 15min and was heated to 85°C for 4hr in a sealed tube. After completion, the reaction was cooled to rt, diluted with chloroform, and filtered through celite bed. The organic layer was completely distilled off to get the crude compound **50**. The crude was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid **50**.

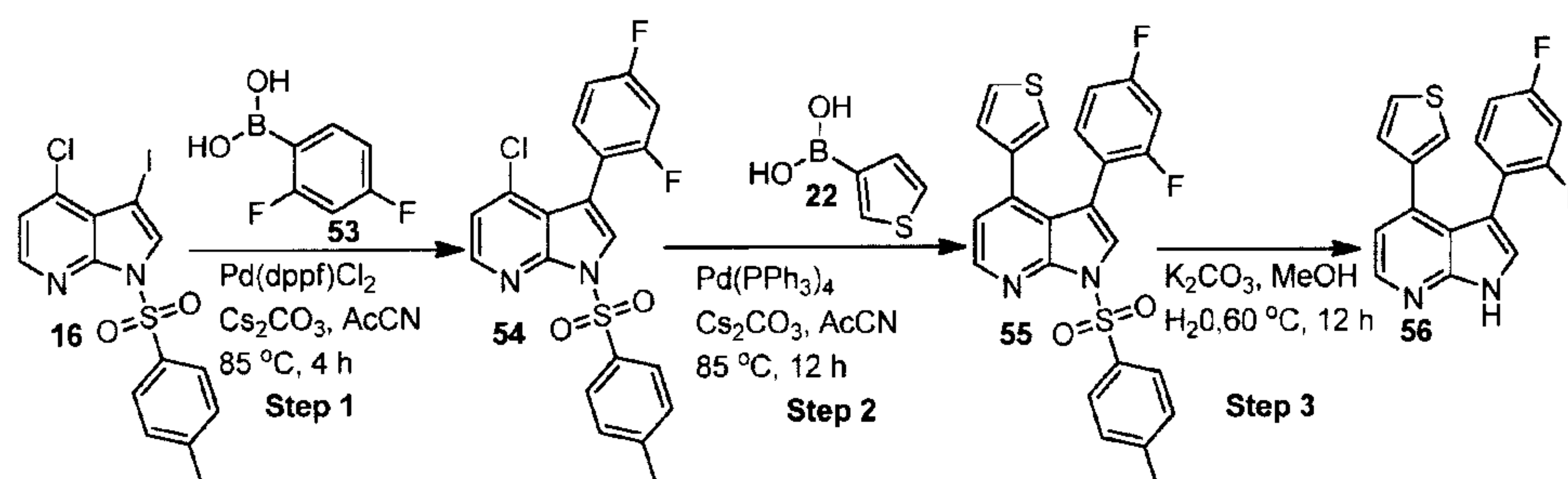
Step 2:

[00158] To a stirred solution of **50** (100mg, 0.242mmol) and compound **22** (34.1mg, 0.266mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added  $\text{Cs}_2\text{CO}_3$  (151.1mg, 0.485mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (14mg, 0.0121mmol) and continued degassing and purging with nitrogen for another 15min. The resulting RM was heated to 85°C overnight or 12hrs in a sealed tube. After completion of the SM monitored from TLC, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off to get the crude product **51**. The crude product was passed through 100-200 mesh silica gel eluting the pure compound **51** at 4-5% ethyl acetate in hexane as off white solid compound.

Step 3:

[00159] To a stirred solution of compound **51** (50mg, 0.108mmol) in methanol (10mL) and water (5mL) was added  $\text{K}_2\text{CO}_3$  (29.9mg, 0.217mmol) and the RM heated to 60°C for 12hr. After completion of the SM, the solvents were removed, diluted with water and extracted with chloroform in two volumes. The organic layer was dried over sodium sulphate. The crude material was passed through 100-200 mesh silica gel eluting the compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid of compound **48**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 9.00(1-H), 8.33(d,  $J=4.87$  1-H), 7.35(m,  $J=2.31$  1-H), 7.23(m,  $J=4.14$  3-H), 7.11(m,  $J=5.00$  1-H), 7.04(m,  $J=3.04$  1-H), 6.90(m,  $J=7.56$  1-H), 6.56(d,  $J=7.92$  1-H), 3.27(3-H); and MS  $m/z$  = 307.2.

**PREPARATION OF EXAMPLE 18: 3-(2,4-difluorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (56)**



Step 1:

[00160] To a stirred solution of compound **16** (150mg, 0.346mmol) and **53** (54mg, 0.346mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added  $\text{Cs}_2\text{CO}_3$  (282mg, 0.866mmol) and  $\text{Pd}(\text{dppf})\text{Cl}_2$  (11mg, 0.013mmol). The resulting RM was degassed, purged with nitrogen again for 15min and was heated to 85°C for 4hr in a sealed tube. After completion, the reaction was cooled to rt and diluted with chloroform 50mL and filtered through celite bed. The organic layer was completely distilled off to get the crude compound **54**. The crude was passed through 100-200 mesh silica gel eluting the pure compound at 6% ethyl acetate in hexane as off white colored solid **54**.

Step 2:

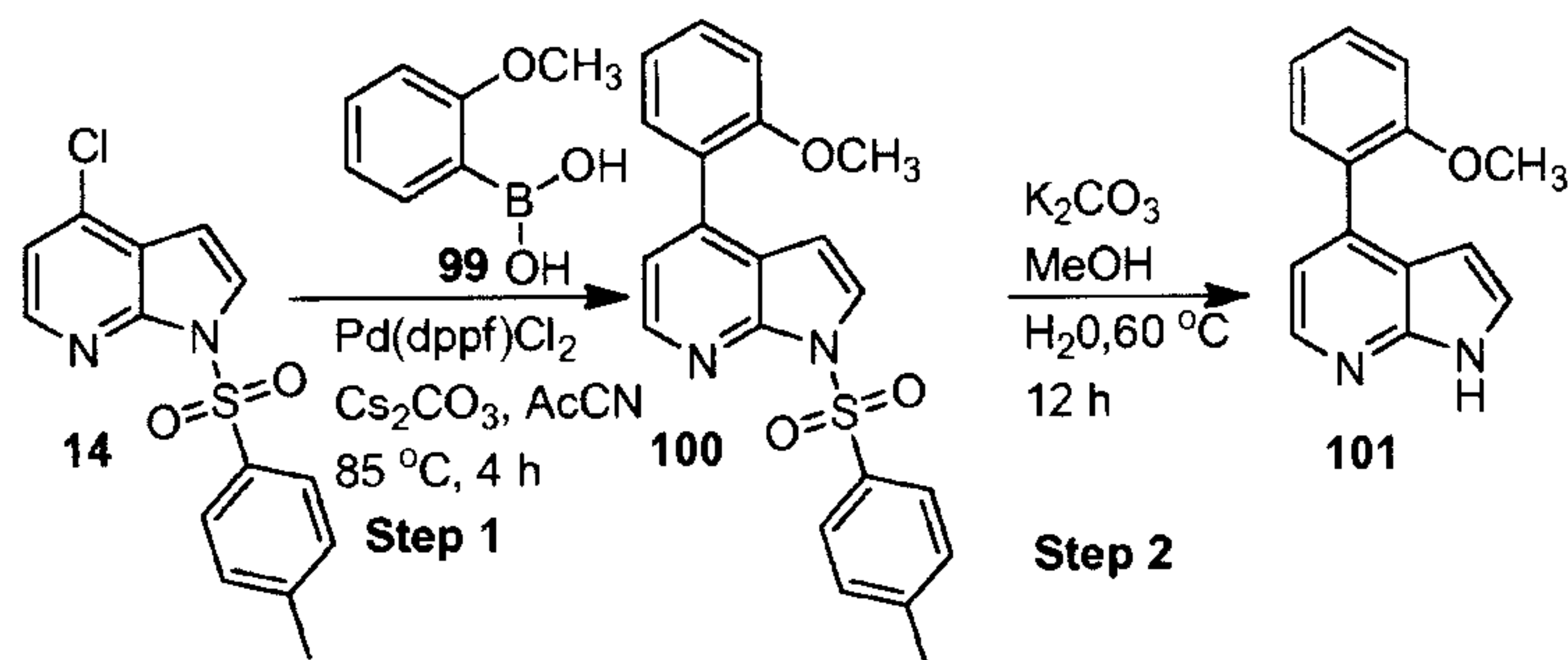
[00161] To a stirred solution of **54** (100mg, 0.239mmol) and compound **22** (30mg, 0.239mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added  $\text{Cs}_2\text{CO}_3$  (194mg, 0.597mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (11mg, 0.00956mmol) and continued degassing and purging with nitrogen for another 15min. The resulting RM was heated to 85°C overnight or 12hr in a sealed tube. After completion of the SM monitored from TLC, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off to get the crude product **55**. The crude product was passed through 100-200 mesh silica gel eluting the pure compound **55** at 10% ethyl acetate in hexane as off white solid compound.

Step 3:

[00162] To a stirred solution of compound **55** (50mg, 0.107mmol) in methanol (10mL) and water (5mL) was added  $\text{K}_2\text{CO}_3$  (37mg, 0.268mmol) and the RM heated to 60°C for 12hr. After completion of the SM, the solvents were removed, diluted with water and extracted with chloroform in two volumes. The organic layer was dried over sodium sulphate. The crude material was passed through 100-200 mesh silica gel eluting the the compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid of compound **56**. 1H

NMR (CDCl<sub>3</sub>)  $\delta$  : 9.43(1-H), 8.37(d, J=5.00 1-H), 7.40(s, 1-H), 7.13(m, J=4.87 1-H), 7.00(m, J=6.58 2-H) 6.96(m, J=5.12 2-H) 6.87(d, J=3.78 1-H) 6.60(m, J=6.95 2-H); and MS m/z = 312.8

**PREPARATION OF EXAMPLE 19: 4-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine\_(101)**



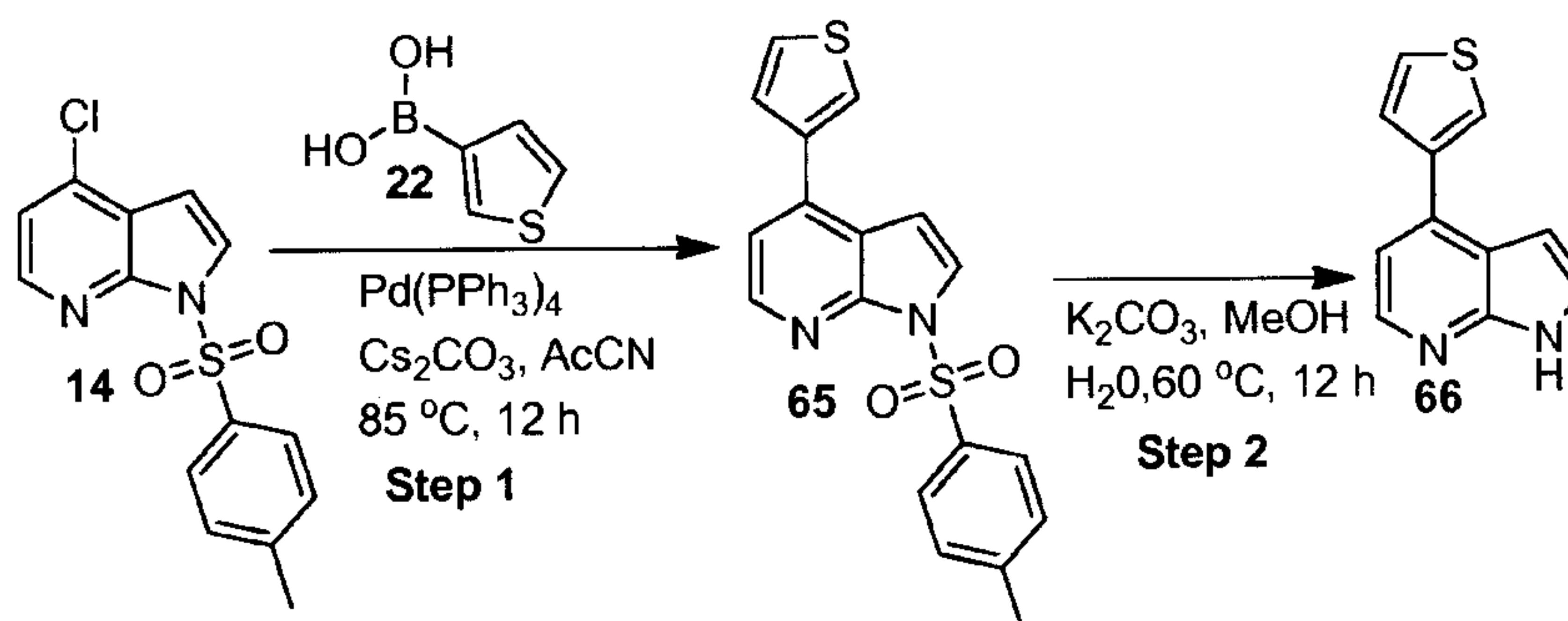
Step 1:

[00163] To a stirred solution of tosylated **14** (100mg, 0.326mmol) and **99** (49.6mg, 0.326mmol) in acetonitrile (6mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (214mg, 0.653mmol) and Pd(dppf)Cl<sub>2</sub> (18.8mg, 0.0163mmol), again degassed and purged with nitrogen for 15 min, and the RM heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **100**.

Step 2:

[00164] To a stirred solution of **100** (45mg, 0.119mmol) in methanol (10mL) and water (5mL) was added potassium carbonate (33mg, 0.238mmol) and the RM heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **101**. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  : 9.43 (1-H), 8.31(d, J=5.12 1-H), 7.46(m, J=5.85 2-H), 7.30(d, J=3.53 1-H), 7.19(d, J=5.00 1-H), 7.08 (m, J=7.43 2-H), 6.42 (d, J=3.53 1-H), 3.81( s, 3-H).

**PREPARATION OF EXAMPLE 20: 4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (66)**

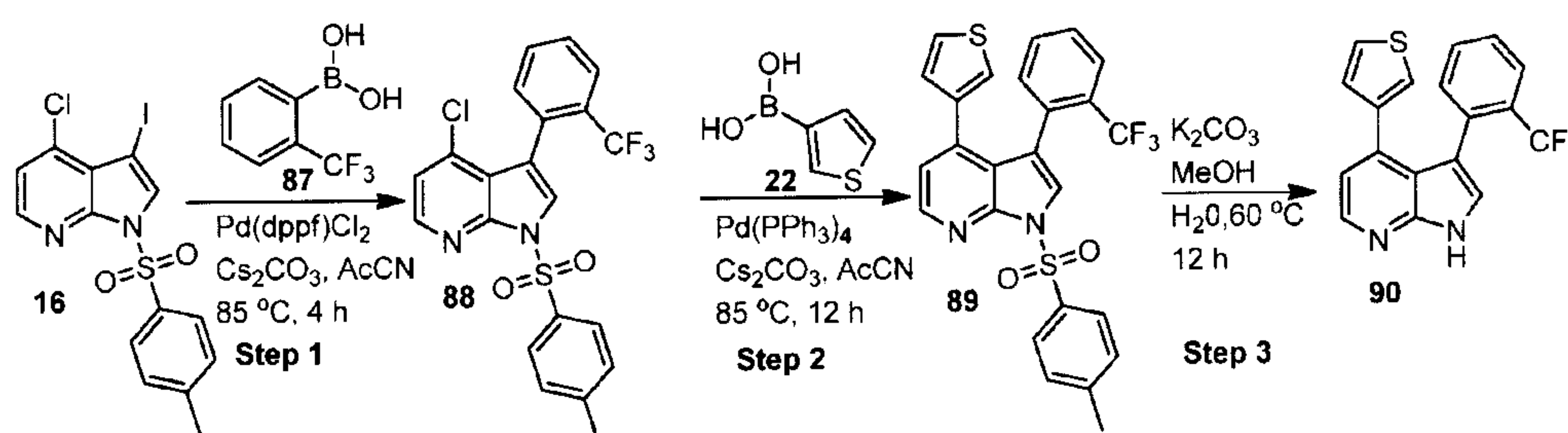
**Step 1:**

[00165] To a stirred solution of **14** (100mg, 0.326mmol) and **22** (50mg 0.392mmol) in DME (5mL) and water (1mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (214mg, 0.653mmol) and Pd(pph<sub>3</sub>)<sub>4</sub> (18.8mg, 0.0163mmol) and again degassed and purged with nitrogen for 15min. Then the RM was heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel, eluting the pure compound **65** at 5% ethyl acetate in hexane as off white solid.

**Step 2:**

[00166] To a stirred solution of **65** (30mg, 0.0847mmol) in methanol (5mL) and water (1mL) was added potassium carbonate (23.2mg, 0.169mmol) and heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water then extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid **66**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.14(1-H), 8.33(M, J=5.00 1-H), 7.75(m, J=1.58 1-H), 7.56(m, J=3.78 1-H) 7.49(m, J=2.92 1-H), 7.38(m, J=3.41 1-H), 7.22(m, J=2.56 1-H), 6.78(m, J=1.95 1-H) and MS m/z = 201.2.

**PREPARATION OF EXAMPLE 21: 4-(thiophen-3-yl)-3-(2-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine (**90**)**



Step 1:

[00167] To a stirred solution of **16** (150mg, 0.346mmol) and **87** (65.8mg, 0.346mmol) in acetonitrile (8mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (225.9mg, 0.693mmol) and Pd(dppf)Cl<sub>2</sub> (14.1mg, 0.0173mmol), again degassed and purged with nitrogen again for 15min, and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid compound **88**.

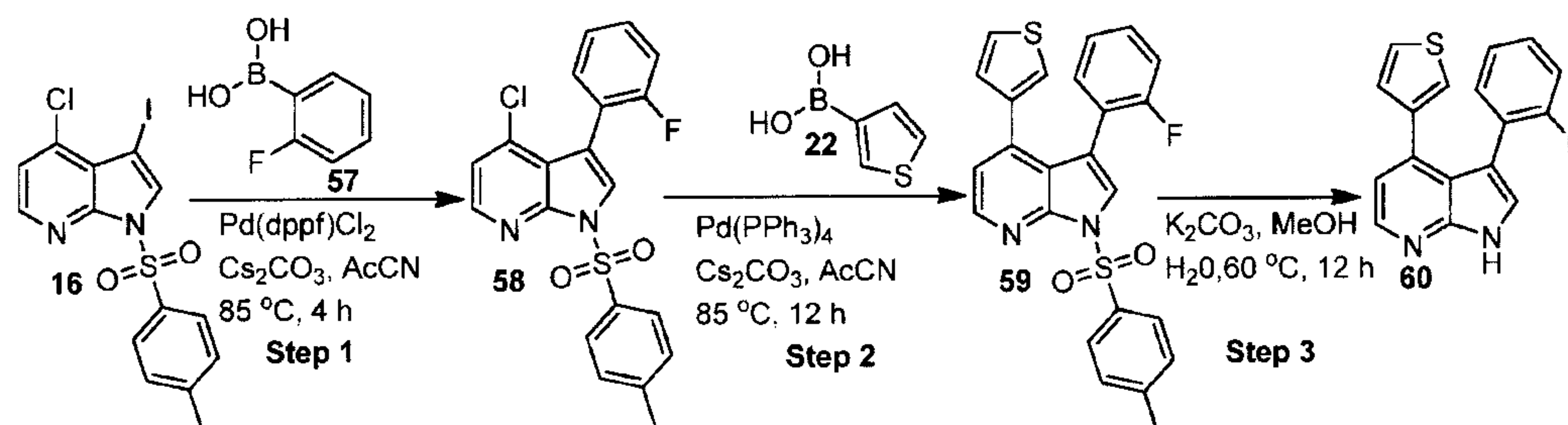
Step 2:

[00168] To a stirred solution of **88** (80mg, 0.177mmol) and **22** (22mg, 0.177mmol) in acetonitrile (6mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (115mg, 0.354 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (10mg, 0.0088mmol), again degassed and purged with nitrogen for 15min, and the RM heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **89**.

Step 3:

[00169] To a stirred solution of **89** (40mg, 0.0803mmol) in methanol (15mL) and water (5mL) was added potassium carbonate (22mg, 0.160mmol) and the RM heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **90**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.21 (1-H), 8.35 (d, J=4.51 1-H), 7.64(d, J=7.8 1-H), 7.52(s, J=9.39 1-H), 7.09 (m, J=4.26 2-H), 6.88(m, J=12.19 3-H), 6.73(d, J=4.63 1-H); and MS m/z = 344.8.

**PREPARATION OF EXAMPLE 22: 3-(2-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (60)**



**Step 1:**

[00170] To a stirred solution of **16** (150mg, 0.346mmol) and **57** (48mg, 0.346mmol) in acetonitrile (8mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (282mg, 0.866mmol) and Pd(dppf)Cl<sub>2</sub> (11mg, 0.0138mmol), then degassed and purged with nitrogen again for 15min and the RM was heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform (50mL) and filtered through celite bed. The organic layer was completely distilled off to get the crude. The crude was passed through 100-200 mesh silica gel eluting the pure compound **58** at 5% ethyl acetate in hexane as off white colored solid.

**Step 2:**

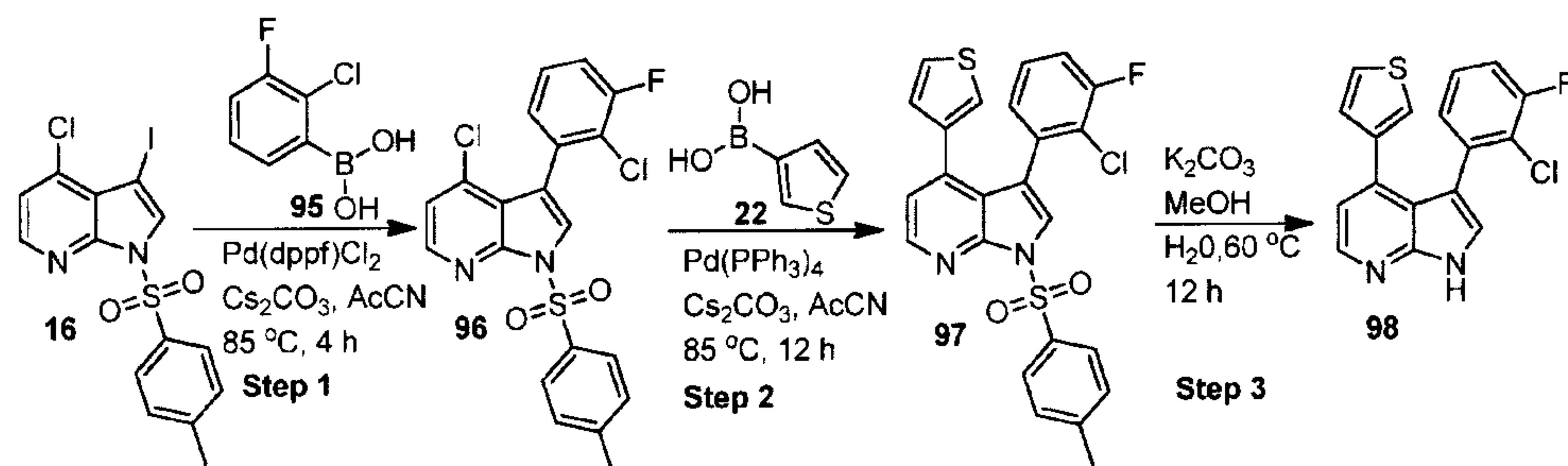
[00171] To a stirred solution of **58** (100mg, 0.249 m mol) and **22** (31mg, 0.249mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (203mg, 0.623 m mol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (11mg, 0.0997mmol), and again degassed and purged with nitrogen for 15min. Then the RM was heated to 85°C overnight in a sealed tube. After completion of the SM the RM was cooled to rt and diluted with chloroform (50mL) and the organic layer passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound **59** at 10-11% ethyl acetate in hexane as off white solid.

**Step 3:**

[00172] To a stirred solution of **59** (50mg, 0.111mmol) in methanol (7mL) and water (3mL) was added potassium carbonate (38mg, 0.278 m mol) and heated to 60°C overnight. After completion of the SM, the RM was completely distilled off, diluted with water and extracted with chloroform (50mL) twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound **60** at 17% ethyl acetate in hexane as eluent to get the pale yellow colored solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.08(1-H), 8.36(d, J=4.87 1-H), 7.42(d, J=2.31 1-

H), 7.28(m, J=52.6 2-H), 7.17(m, J=5.24 2-H) 7.13(m, J=4.84 2-H) 7.05(m, J=5.00 2-H) 6.94(m, J=7.19 1-H), MS m/z = 294.9.

**PREPARATION OF EXAMPLE 23: 3-(2-chloro-3-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (98)**



Step 1:

[00173] To a stirred solution of **16** (150mg, 0.346mmol) and **95** (60mg, 0.346mmol) in acetonitrile (8mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (282mg, 0.866mmol) and Pd(dppf)Cl<sub>2</sub> (11mg, 0.0138mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid **96**.

Step 2:

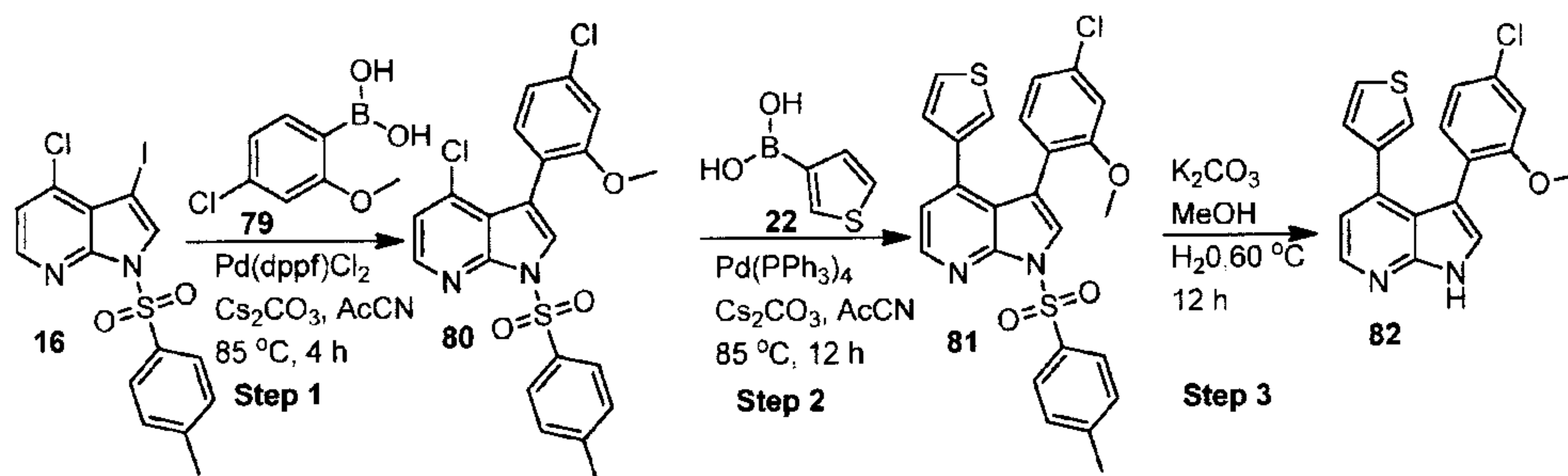
[00174] To a stirred solution of **96** (0.229mmol) and **22** (0.229mmol) in acetonitrile (6mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (0.574mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.00968mmol), again degassed and purged with nitrogen for 15min, and the RM heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid **97**.

Step 3:

[00175] To a stirred solution of **97** (30mg, 0.0621mmol) in methanol (10mL) and water (5mL) was added potassium carbonate (17mg, 0.124mmol) and the RM heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water then extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed

through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **98**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.19 (1-H), 8.38(d, J=4.75 1-H), 7.40 (d, J=2.56 1-H), 7.13(d, J=4.87 1-H), 7.01(m, J=4.26 3-H) 6.85 (m, J=8.53 3-H); and MS m/z = 328.8

**PREPARATION OF EXAMPLE 24: 3-(4-chloro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**82**)**



Step 1:

[00176] To a stirred solution of **16** (150mg, 0.347mmol) and **79** (64.3mg, 0.347mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (228mg, 0.694mmol) and Pd(dppf)Cl<sub>2</sub> (14.1mg, 0.0173mmol), again degassed and purged with nitrogen again for 15min and the RM was heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude, which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid compound **80**.

Step 2:

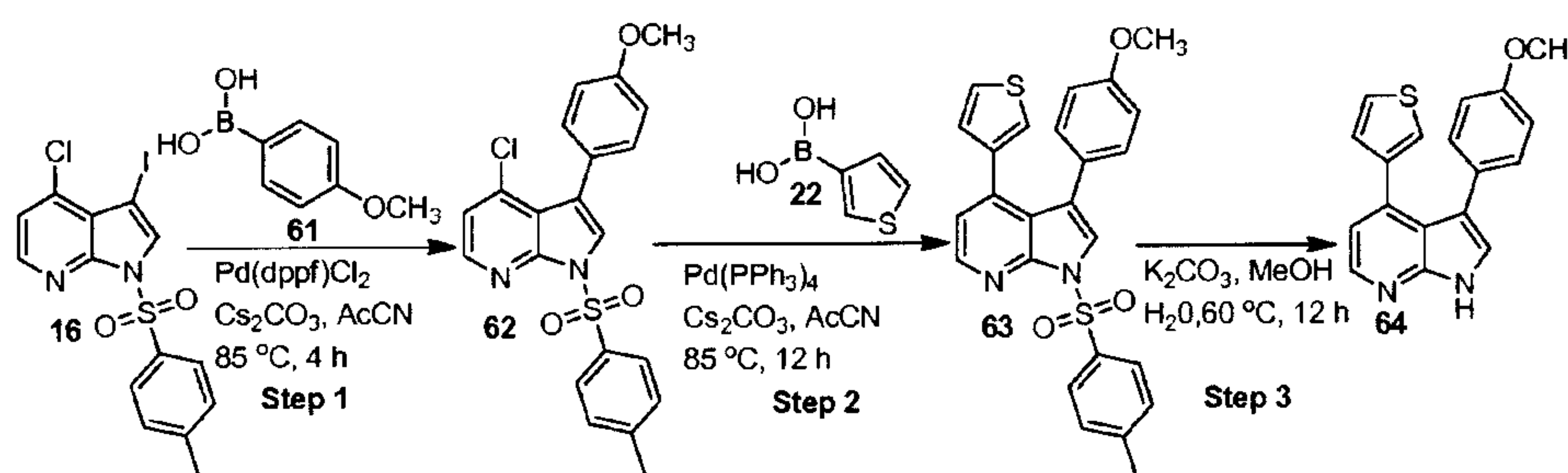
[00177] To a stirred solution of **80** (100mg, 0.224mmol) and **22** (31.5mg, 0.224mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (147mg, 0.448mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (12.9mg, 0.011mmol), again degassed and purged with nitrogen for 15min, and the RM heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **81**.

Step 3:

[00178] To a stirred solution of **81** (60mg, 0.121mmol) in methanol (10mL) and water (5mL) was added potassium carbonate (33mg, 0.2424mmol) and heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water

then extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **82**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 9.13 (1-H), 8.34 (d,  $J=4.87$  1-H), 7.33 (d,  $J=2.31$  1-H), 7.09 (m,  $J=5.00$  1-H), 6.88(m,  $J=5.97$  3-H), 6.55(d,  $J=1.95$  1-H) 3.28 (s, 3-H) and MS  $m/z$  = 341.3.

**PREPARATION OF EXAMPLE 25: 3-(4-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**64**)**



Step 1:

[00179] To a stirred solution of **16** (150mg, 0.346mmol) and **61**(52mg, 0.346mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (282mg 0.865mmol) and Pd(dppf)Cl<sub>2</sub> (11mg, 0.013mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform (50mL) and filtered through celite bed. The organic layer was completely distilled off to get the crude, which was passed through 100-200 mesh silica gel eluting the pure compound **62** at 7-8% ethyl acetate in hexane as off white colored solid.

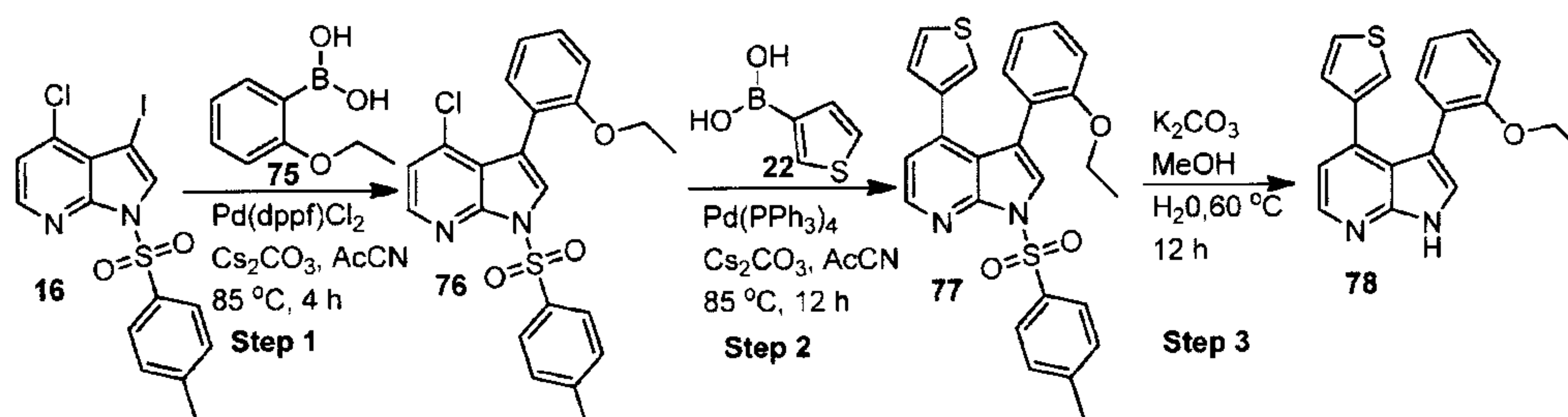
Step 2:

[00180] To a stirred solution of **62** (100mg, 0.242mmol) and **22** (31mg, 0.242mmol) in acetonitrile (6mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (197mg, 0.605mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (11mg 0.00908mmol), and again degassed and purged with nitrogen for 15min and heated to 85°C overnight in a sealed tube. After completion of the SM the RM was cooled to rt and diluted with chloroform (50mL) and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **63**.

Step 3:

[00181] To a stirred solution of **63** (40mg 0.086mmol) in methanol (7mL) and water (3mL) was added potassium carbonate 30mg (0.215mmol) and heated to 60°C overnight. After completion of the SM, the RM was completely distilled off, diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 20% ethyl acetate in hexane as eluent to get the pale yellow colored solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.26 (1H), 8.35(d, J=4.87 1H), 7.33 (d, J=2.43 1H), 7.12(d, J=4.87 1-H), 7.07 (m, J=3.04 1-H) 6.95(m, J=5.48 2-H) 6.93(m, J=4.63 2-H) 6.87 (m, J=3.65 1-H), 6.67(m, J=4.51 2-H), 3.79 (s 3-H); and MS m/z = 307.2.

**PREPARATION OF EXAMPLE 26: 3-(2-ethoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**78**)**



Step 1:

[00182] To a stirred solution of **16** (150mg, 0.347mmol) and **75** (57.6mg, 0.347mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (228.1mg, 0.694mmol) and Pd(dppf)Cl<sub>2</sub> (11mg, 0.0138mmol), again degassed and purged with nitrogen again for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform (50mL) and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid **76**.

Step 2:

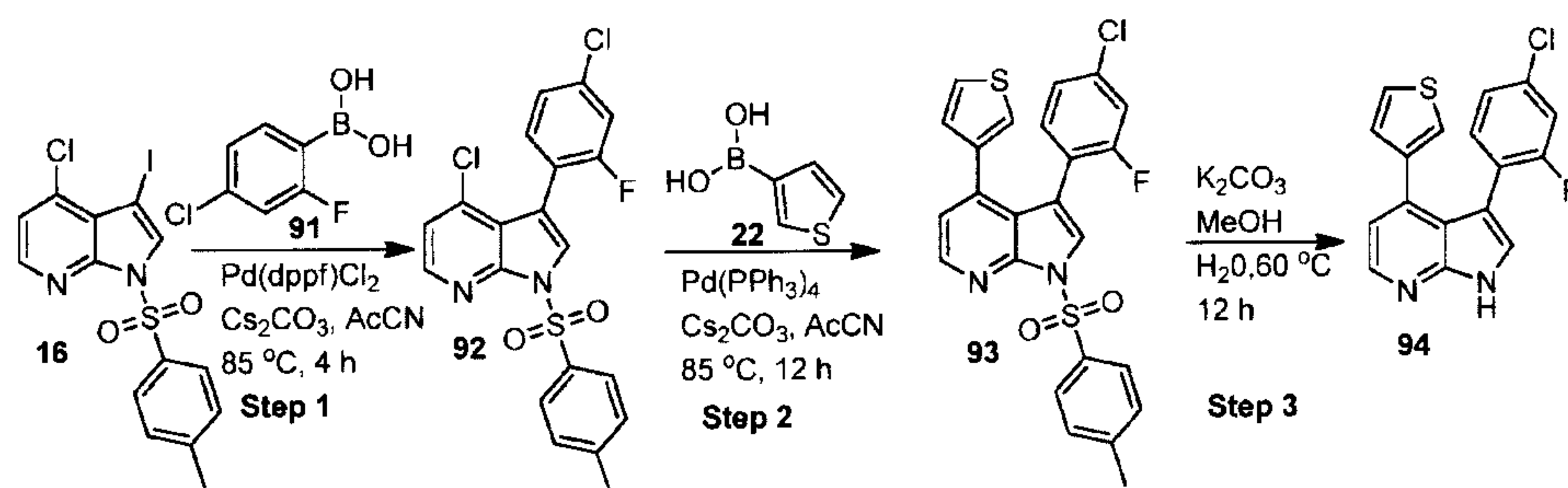
[00183] To a stirred solution of **76** (100mg, 0.234mmol) and **22** (30mg, 0.234mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (153mg, 0.469mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (11mg, 0.0093mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform (50mL) and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get

the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **77**.

#### Step 3:

[00184] To a stirred solution of **77** (30mg 0.063mmol) in methanol (5mL) and water (1mL) was added potassium carbonate (21.8mg, 0.158mmol) and the RM heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **78**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.10 (1-H), 8.33 (d, J=4.87 1-H), 7.36 (d, J=2.31 1-H), 7.20(m, J=5.61 2-H), 7.11 (d, J=5.00 1-H), 7.04(m, J=2.92 1-H), 6.98(m, J=6.70 1-H), 6.87(m, J=7.31 2-H), 6.55 (d, J=8.17 1-H), 3.47(q, J=6.95 2-H), 1.04(t, J=6.95 3-H); and MS m/z =321.2.

#### PREPARATION OF EXAMPLE 27: 3-(4-chloro-2-fluorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**94**)



#### Step 1:

[00185] To a stirred solution of **16** (150mg, 0.346mmol) and **91** (60mg, 0.346mmol) in acetonitrile (8mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (282mg, 0.865mmol) and Pd(dppf)Cl<sub>2</sub> (11mg, 0.0138mmol), again degassed and purged with nitrogen again for 15min, and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid compound **92**.

#### Step 2:

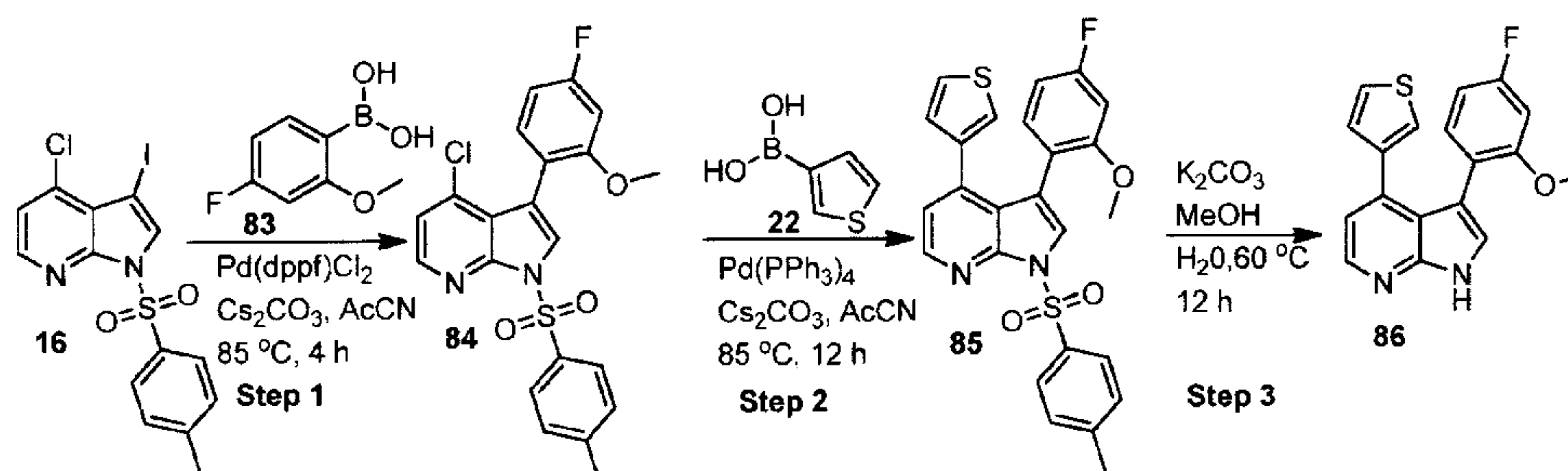
[00186] To a stirred solution of **92** (100mg, 0.229mmol) and **2** (29mg, 0.229mmol) in acetonitrile (6mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (186mg, 0.574mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (10mg, 0.0091mmol), again degassed and purged with

nitrogen for 15min, and the RM heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **93**.

#### Step 3:

[00187] To a stirred solution of **93** (30mg, 0.0621mmol) in methanol (10mL) and water (5mL) was added potassium carbonate (17mg, 0.124mmol) and the RM heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **94**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.51 (1-H), 8.37(d, J=4.75 1-H), 7.43(s, 1-H) 7.11(m, J=8.29 2-H), 6.91(m, J=8.29 5-H), and MS m/z = 327.6.

#### PREPARATION OF EXAMPLE 28: 3-(4-fluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**86**)



#### Step 1:

[00188] To a stirred solution of **16** (150mg, 0.347mmol) and **83** (59mg, 0.347mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (285mg, 0.868mmol) and Pd(dppf)Cl<sub>2</sub> (11mg, 0.0138mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid compound **84**.

#### Step 2:

WO 2014/093383

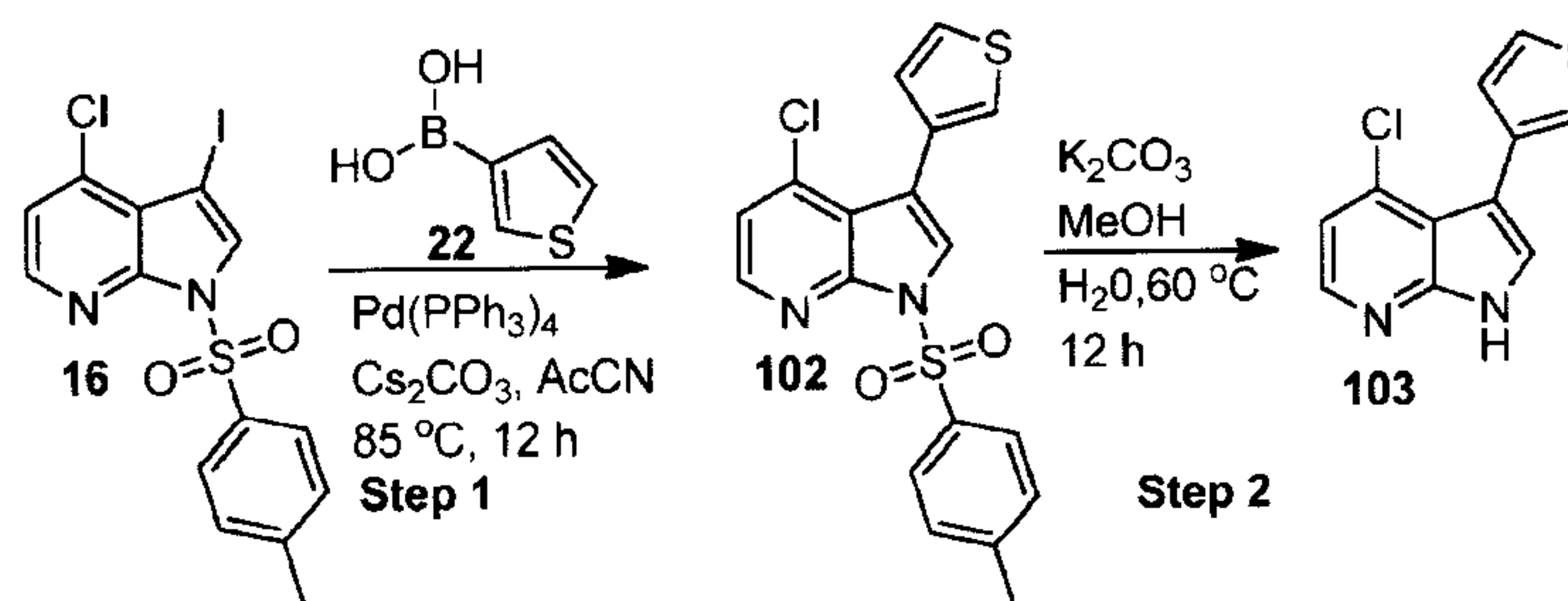
PCT/US2013/074191

[00189] To a stirred solution of **84** (110mg, 0.255mmol) and **22** (32mg, 0.255mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (209mg, 0.638mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (11mg, 0.0102mmol), again degassed and purged with nitrogen for 15min, and the RM heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **85**.

#### Step 3:

[00190] To a stirred solution of **85** (30mg, 0.062mmol) in methanol (10mL) and water (5mL) was added potassium carbonate (17mg, 0.125mmol) and the RM heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water then extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **86**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.11 (1-H), 8.33(d, J=311 1-H), 7.32 (s, 2-H), 7.11(m, J=13.17 3-H), 6.90(d, J=4.50 2-H), 6.61(t, J=6.09 1-H), 6.30 (d, J=9.14 1-H) 3.20(s, 3-H) and MS m/z = 324.8

#### PREPARATION OF EXAMPLE 29: 4-chloro-3-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (103)



#### Step 1:

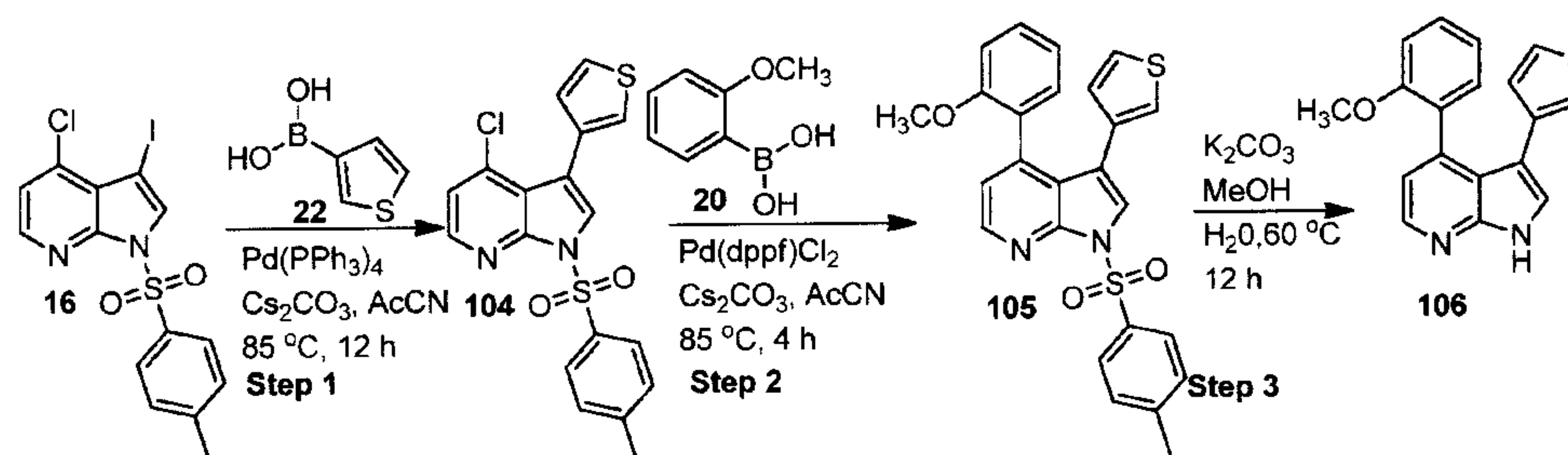
[00191] To a stirred solution of **16** (150mg, 0.347mmol) and **22** (44mg, 0.347mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg, 0.866mmol) and Pd(dppf)Cl<sub>2</sub> (14mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-

200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid compound **102**.

Step 2:

[00192] To a stirred solution of **102** (70mg, 0.180mmol) in methanol (15mL) and water (5mL) was added potassium carbonate (49mg, 0.360mmol) and the RM heated to 60°C overnight. After completion of the SM, methanol was completely distilled and the RM diluted with water then extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **103**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.78 (1-H), 8.21(d, J=5.12 1H), 7.39(d, J=2.31 1-H), 7.35 (m, J=3.04 2-H), 7.29 (m, J=2.92 1-H), 7.13(d, J=5.12 1-H); and MS m/z = 234.8.

**PREPARATION OF EXAMPLE 30: 4-(2-methoxyphenyl)-3-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (106)**



Step 1:

[00193] To a stirred solution of **16** (150mg, 0.347mmol) and **22** (44mg, 0.347mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg, 0.866mmol) and Pd(dppf)Cl<sub>2</sub> (14mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid compound **104**.

Step 2:

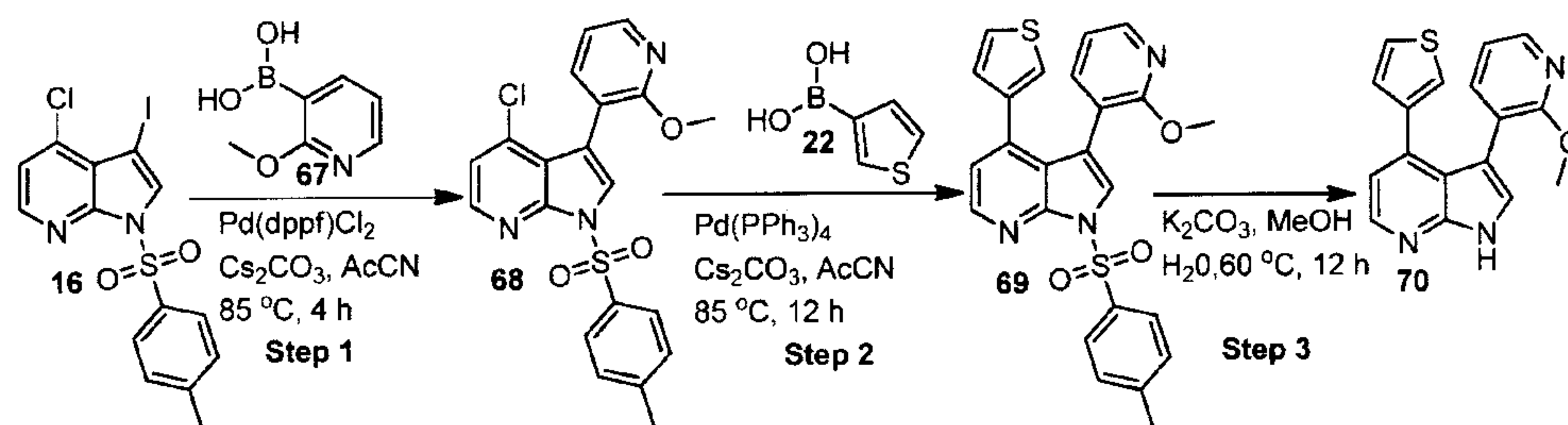
[00194] To a stirred solution of **104** (100mg, 0.257mmol) and **20** (39.1mg, 0.257mmol) in acetonitrile (6mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (167.4mg, 0.513mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (14.8mg, 0.0128mmol), again degassed and purged with nitrogen for 15min, and the RM heated to 85°C overnight in a sealed tube. After completion of

the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **105**.

### Step 3:

[00195] To a stirred solution of **105** (45mg, 0.0978mmol) in methanol (15mL) and water (5mL) was added potassium carbonate (26.9mg, 0.1949mmol) and the RM heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **106**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.95(s,1H), 8.38(d,1H), 7.34 (d,1H), 7.30 (m,1H), 7.23 (d,1H), 7.06 (d,1H), 6.96 (m,2H), 6.62 (m,2H), 6.51 (m,1H) 3.29 (s,3H); and MS m/z = 306.8.

### PREPARATION OF EXAMPLE 36: 3-(2-methoxypyridin-3-yl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**70**, ARN-3088)



### Step 1:

[00196] To a stirred solution of **16** (150mg, 0.346mmol) and **67** (53mg 0.346mmol) in acetonitrile (6mL), degassed and purged with nitrogen for 10min, was added cesium carbonate 225mg, (0.693mmol) and Pd(dppf)Cl<sub>2</sub> (14mg 0.0173mmol), again degassed and purged with nitrogen again for 15min and the RM was heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform (50mL) and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-200 mesh silica gel eluting the pure compound **68** at 7-8% ethyl acetate in hexane as off white colored solid.

### Step 2:

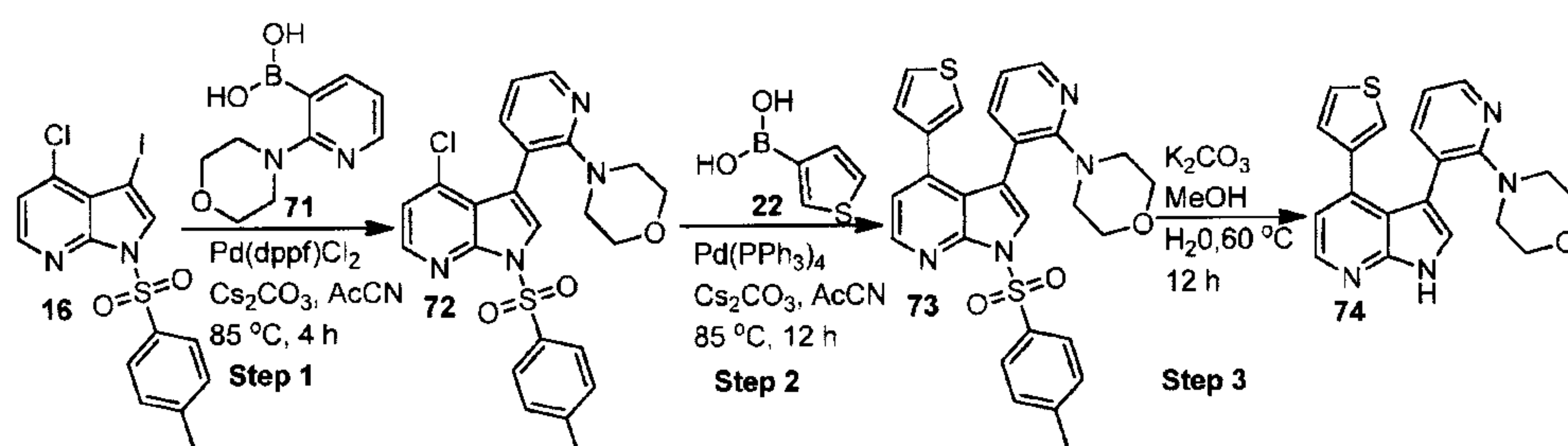
[00197] To a stirred solution of **68** (130mg, 0.314mmol) and **22** (45mg 0.345mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (205mg, 0.628mmol) and Pd(pph<sub>3</sub>)<sub>4</sub> (18mg, 0.0157mmol), again degassed and purged with

nitrogen for 15min, and heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform (50mL) and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound **69** at 10-11% ethyl acetate in hexane as off white solid.

### Step 3:

[00198] To a stirred solution of **69** (50mg, 0.108mmol) in methanol (10mL) and water(5mL) was added potassium carbonate (30mg, 0.216 m mol) and heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water and extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **70**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.05(1-H), 8.35(d, J=4.87 1-H), 8.04(m, j=3.04 1-H), 7.41(m, J=1.95 2-H), 7.12(d, J=4.87 1-H), 7.07(m, J=3.04 1-H), 6.90(m, J=5.36 2-H), 6.79(m, J=5.12 1-H), 3.49(s, 1-H), and MS m/z = 307.9 .

### PREPARATION OF EXAMPLE 37: 4-(3-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)morpholine (**74**)



### Step 1:

[00199] To a stirred solution of **16** (150mg, 0.346mmol) and **71** (72mg, 0.346mmol) in acetonitrile (6mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (225mg, 0.693mmol) and Pd(dppf)Cl<sub>2</sub> (14mg, 0.0173mmol), again degassed and purged with nitrogen again for 15min and heated to 85°C for 4hr in a sealed tube. After completion of the reaction, the RM was cooled to rt and diluted with chloroform (50mL) and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid compound **72**.

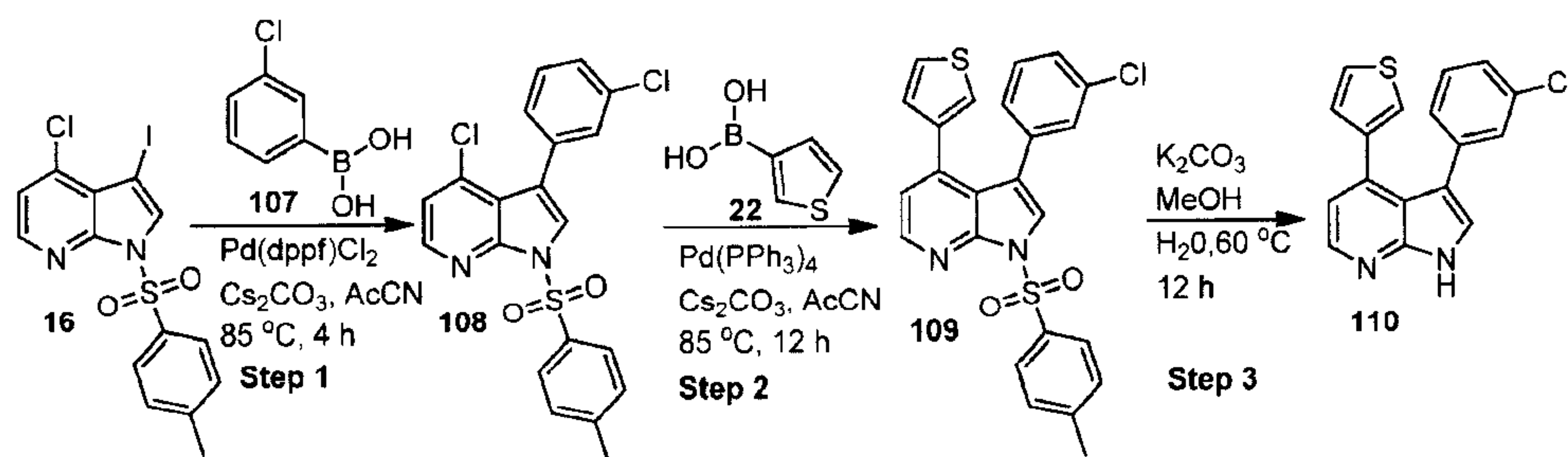
### Step 2:

[00200] To a stirred solution of **72** (100mg, 0.213mmol) and **22** (30mg 0.345mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (139mg, 0.426mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (12mg, 0.0106mmol), again degassed and purged with nitrogen for 15min, and heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform (50mL) and the organic layer was passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white solid compound **73**.

#### Step3:

[00201] To a stirred solution of **73** (40mg, 0.0774mmol) in methanol (10mL) and water (5mL) was added potassium carbonate (22mg, 0.154mmol), then heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water then extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **74**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 11.98 (1-H), 8.28(d, J=4.87 1-H), 8.08(M, J=2.92 1-H), 7.61(d, J=2.56 1-H), 7.55(m, J=5.48 1-H), 7.24(m, J=2.92 1-H) 7.14 (d, J=4.87 1-H), 6.94(m, J=4.87 3-H), 3.33(s, 4-H), 3.07 (s, 4-H) and MS m/z = 362.9.

#### PREPARATION OF EXAMPLE 47: 3-(3-chlorophenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**110**, ARN-3111)



#### Step 1:

[00202] To a stirred solution of **16** (150mg, 0.343mmol) and **107** (88mg, 0.343mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (223mg, 0.686mmol) and Pd(dppf)Cl<sub>2</sub> (14mg, 0.0171mmol), again degassed and purged with nitrogen for 15min, and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt, diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude which was passed through 100-

WO 2014/093383

PCT/US2013/074191

200 mesh silica gel eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid compound **108**.

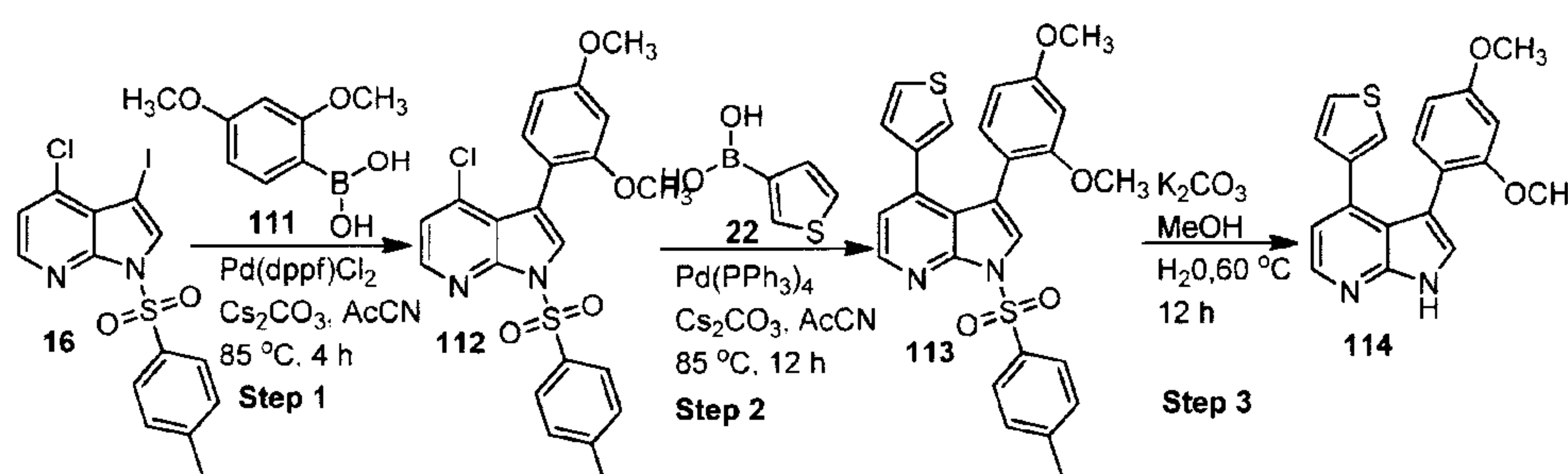
#### Step 2:

[00203] To a stirred solution of **108** (100mg, 0.239mmol) and **22** (31mg, 0.240mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (155mg, 0.475mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (10mg, 0.019mmol), again degassed and purged with nitrogen for 15min, and the RM heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt, diluted with chloroform and the organic layer passed through celite bed. The organic layer was completely distilled off the solvent to get the crude product which was passed through 100-200 mesh silica gel eluting the pure compound **109** at 10-11% ethyl acetate in hexane as off white solid.

#### Step 3:

[00204] To a stirred solution of **109** (45mg, 0.097mmol) in methanol (10mL) and water (10mL) was added potassium carbonate (40mg, 0.29mmol) and the RM heated to 60°C overnight. After completion of the SM, methanol was completely distilled off and the RM diluted with water, then extracted with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **110**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.18(s,1H), 8.41(m,1H), 7.39(m,1H), 7.13(m,6H), 6.89 (m,2H), and MS m/z = 310.8.

#### PREPARATION OF EXAMPLE 86: 3-(2,4-dimethoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**114**):



#### Step 1:

[00205] To a stirred solution of **16** (150mg, 0.347mmol) and **111** (59mg, 0.347mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (228mg, 0.694mmol) and Pd(dppf)Cl<sub>2</sub> (14mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed.

WO 2014/093383

PCT/US2013/074191

The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 10-11% ethyl acetate in hexane as off white colored solid compound **112**.

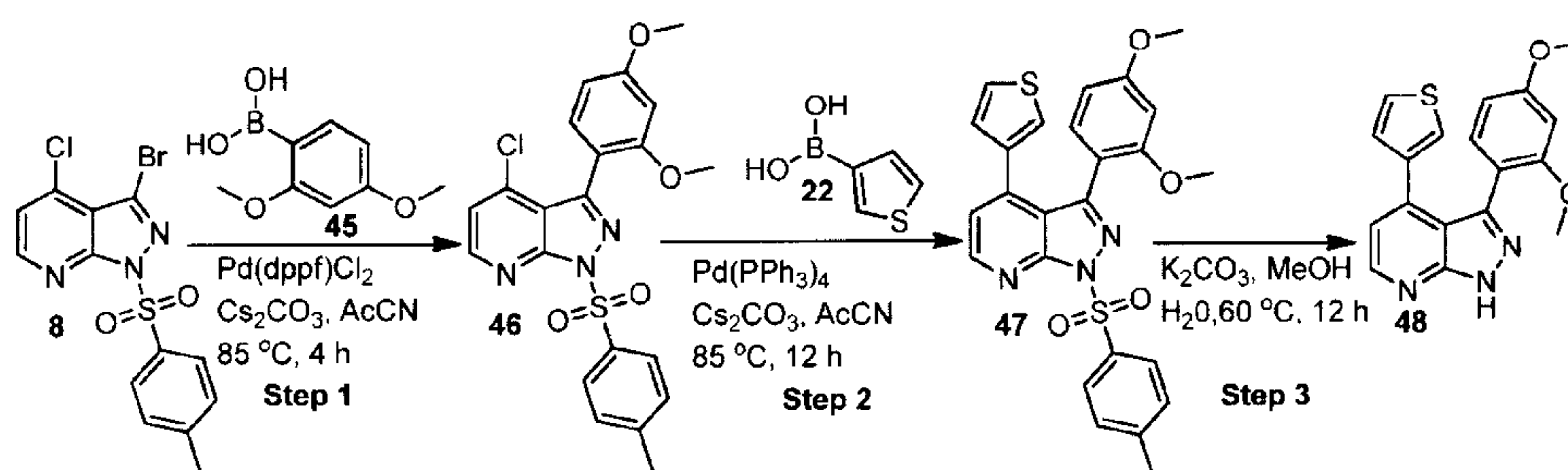
#### Step 2:

[00206] To a stirred solution of **112** (100mg, 0.339mmol) and **22** (44mg, 0.339mmol) in acetonitrile (7mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (229mg, 0.678mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (20mg, 0.017mmol), and again degassed and purged with nitrogen for 15min. Then the RM was heated to 85°C overnight in a sealed tube. After completion of the SM, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound in 11-13% ethyl acetate and hexane as off white solid compound **113**.

#### Step 3:

[00207] To a stirred solution of **113** (40mg, 0.0816mmol) in methanol (10mL) and water (10mL) was added potassium carbonate (28mg, 0.204mmol). The RM was heated to 60°C overnight. After completion of the SMs, the solvent methanol was completely distilled off and diluted with water extracted with chloroform twice. The organic layer was dried over sodium sulphate and the solvents removed to get the crude product, which was passed through 100-200 mesh silica gel eluting the compound at 25-20% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **114**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.06 (s, 1H), 8.32 (d, 1H), 7.30 (d, 1H), 7.12 (m, 2H), 7.07 (m, 1H), 6.94 (m, 1H), 6.90 (m, 1H), 6.44 (m, 1H), 6.16 (d, 1H), 3.82 (s, 3H), 3.24 (s, 3H). MS/Mz: 337.2.

#### PREPARATION OF EXAMPLE 87: 3-(2,4-difluorophenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridine (**48**)



#### Step 1:

[00208] To a stirred solution of compound **8** (150mg, 0.387mmol) and **45** (66mg, 0.387mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added Cs<sub>2</sub>CO<sub>3</sub> (253mg 0.775mmol) and Pd(dppf)Cl<sub>2</sub> (15mg 0.0193mmol). The resulting RM was

WO 2014/093383

PCT/US2013/074191

degassed, purged with nitrogen again for 15min and heated to 85°C for 4hr in a sealed tube. After completion of the reaction, it was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude compound **46**. The crude was passed through 100-200 mesh silica gel, eluting the pure compound at 7-8% ethyl acetate in hexane as off white colored solid **46**.

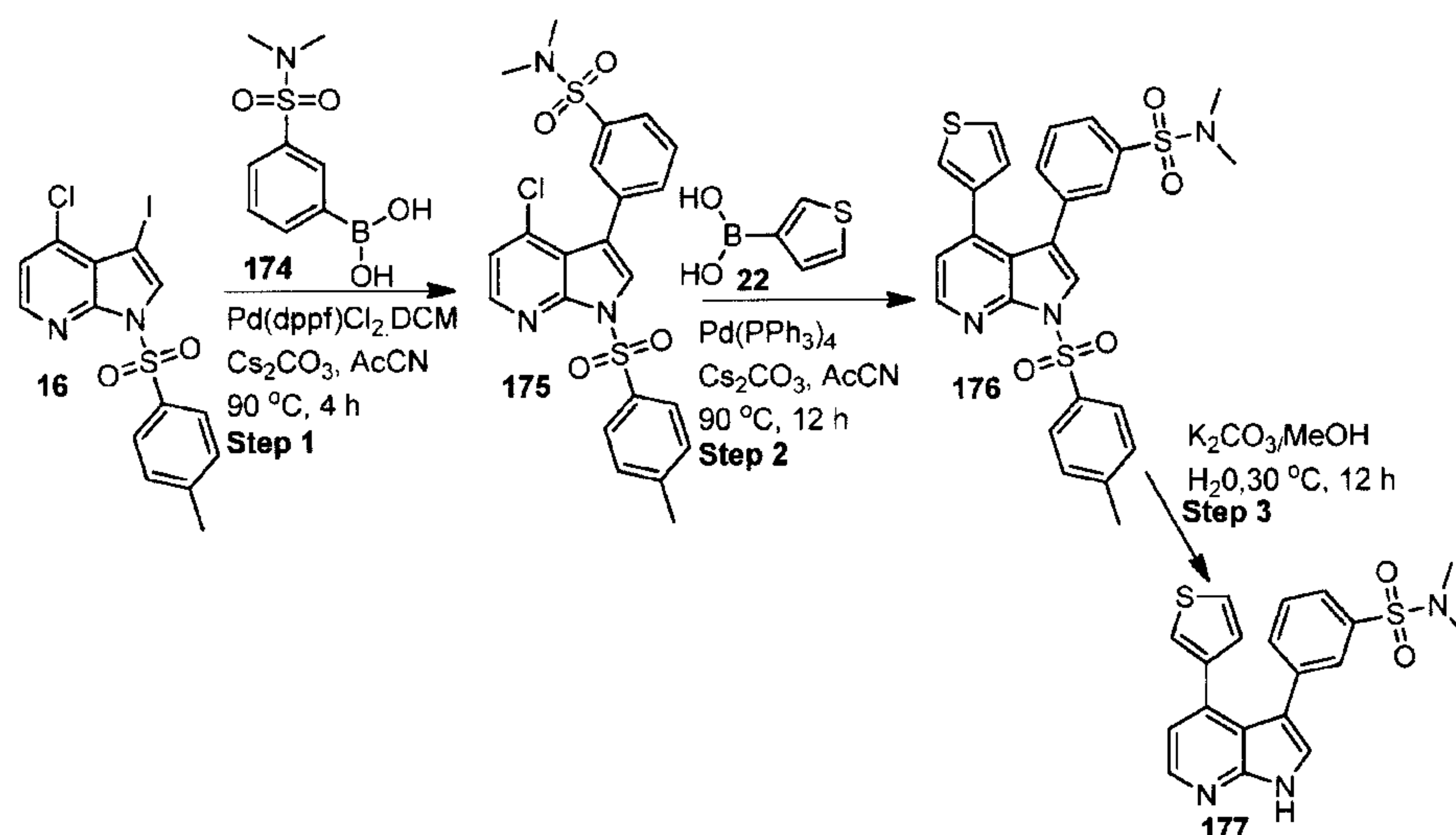
Step 2:

[00209] To a stirred solution of **46** (60mg, 0.2135mmol) and compound **22** (20mg, 0.148mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added Cs<sub>2</sub>CO<sub>3</sub> (88mg, 0.79mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (8mg, 0.00675mmol) and continued degassing and purging with nitrogen for another 15min. The resulting RM was heated to 85°C overnight or 12 hrs in a sealed tube. After completion of the SM monitored from TLC, the RM was cooled to rt and diluted with chloroform and the organic layer was passed through celite bed. The organic layer was completely distilled off to get the crude product **47**. The crude product was passed through 100-200 mesh silica gel eluting the pure compound **47** at 10-11% ethyl acetate in hexane as off white solid compound.

Step 3:

[00210] To a stirred solution of compound **47** (40mg, 0.0813mmol) in methanol (10mL) and water (5mL) was added K<sub>2</sub>CO<sub>3</sub> (22mg, 0.162mmol) and heated to 60°C for 12hr. After completion of the SM, the solvents were removed, diluted with water and extracted with chloroform in two volumes. The organic layer was dried over sodium sulphate. The crude material was passed through 100-200 mesh silica gel eluting the the compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid of compound **48**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 10.65(s,1H), 8.54(d,1H), 7.52(s,1H), 7.39(m,2H), 7.13(m,2H), 6.55(m,1H), 6.19(d,1H), 3.85(s,3H), 3.18(s,3H) and MS m/z = 338.3

**PREPARATION OF EXAMPLE 90:** N,N-dimethyl-3-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide (**177**):



### Step 1

[00211] To a stirred solution of **115** (150mg, 0.347mmol) and **174** (79mg, 0.347mmol) in acetonitrile (10mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg 0.694mmol) and Pd(dppf)Cl<sub>2</sub> (14mg, 0.017mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction, the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **175**.

### Step 2

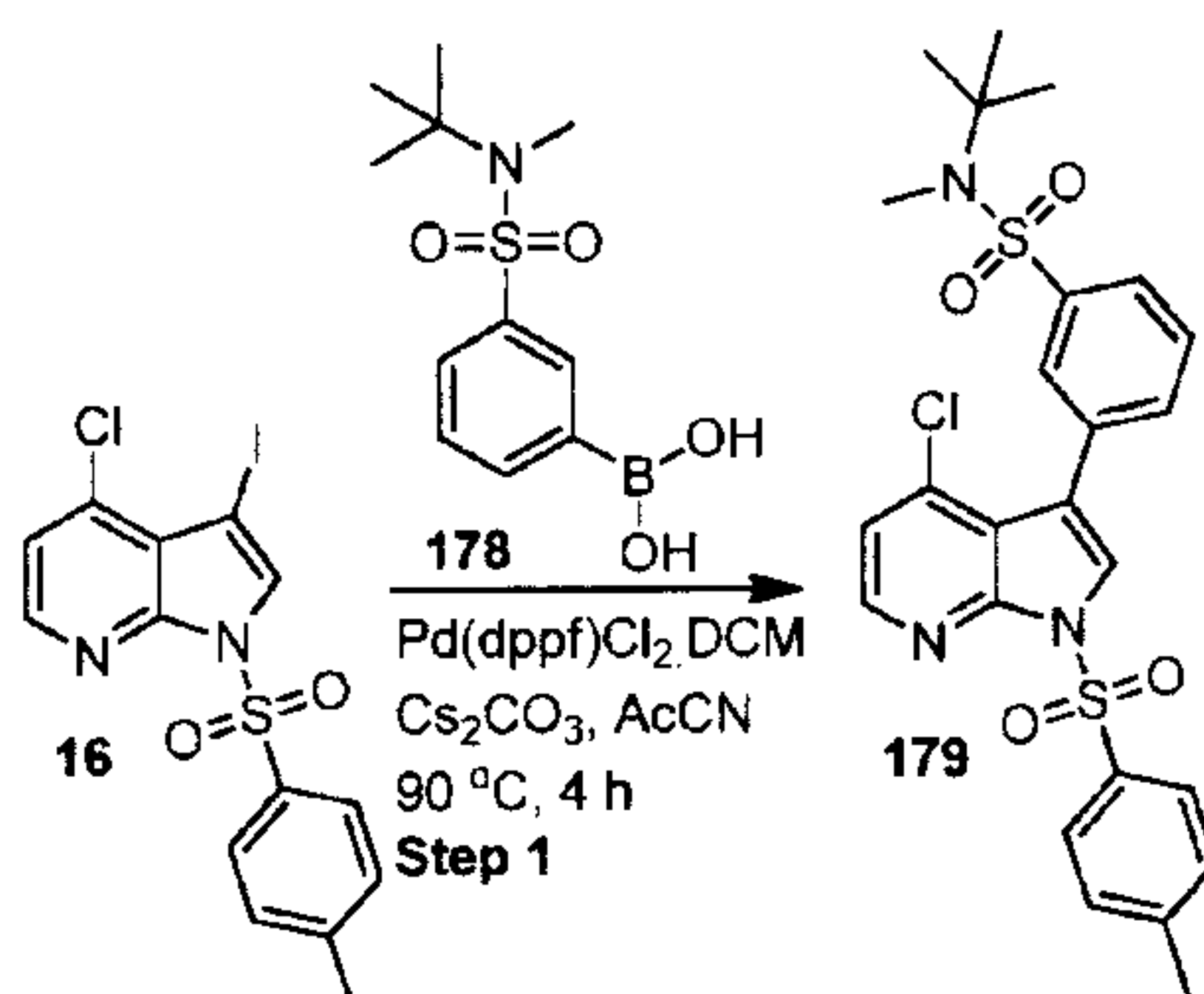
[00212] To a stirred solution of **175** (100mg, 0.204mmol) and **22** (26mg, 0.204mmol) in acetonitrile (10mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (133mg, 0.408mmol) and Pd(dppf)Cl<sub>2</sub> (8mg, 0.0102mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction, the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **176**.

### Step 3

[00213] To a stirred solution of **177** (45mg, 0.0773mmol) in methanol (15mL) was added water(10mL) and potassium carbonate (26mg 0.193mmol) and the RM heated to 60°C overnight .after completion of the SM, the RM was completely distilled off and diluted with water and extract with chloroform twice. The organic layer was dried over sodium sulphate and

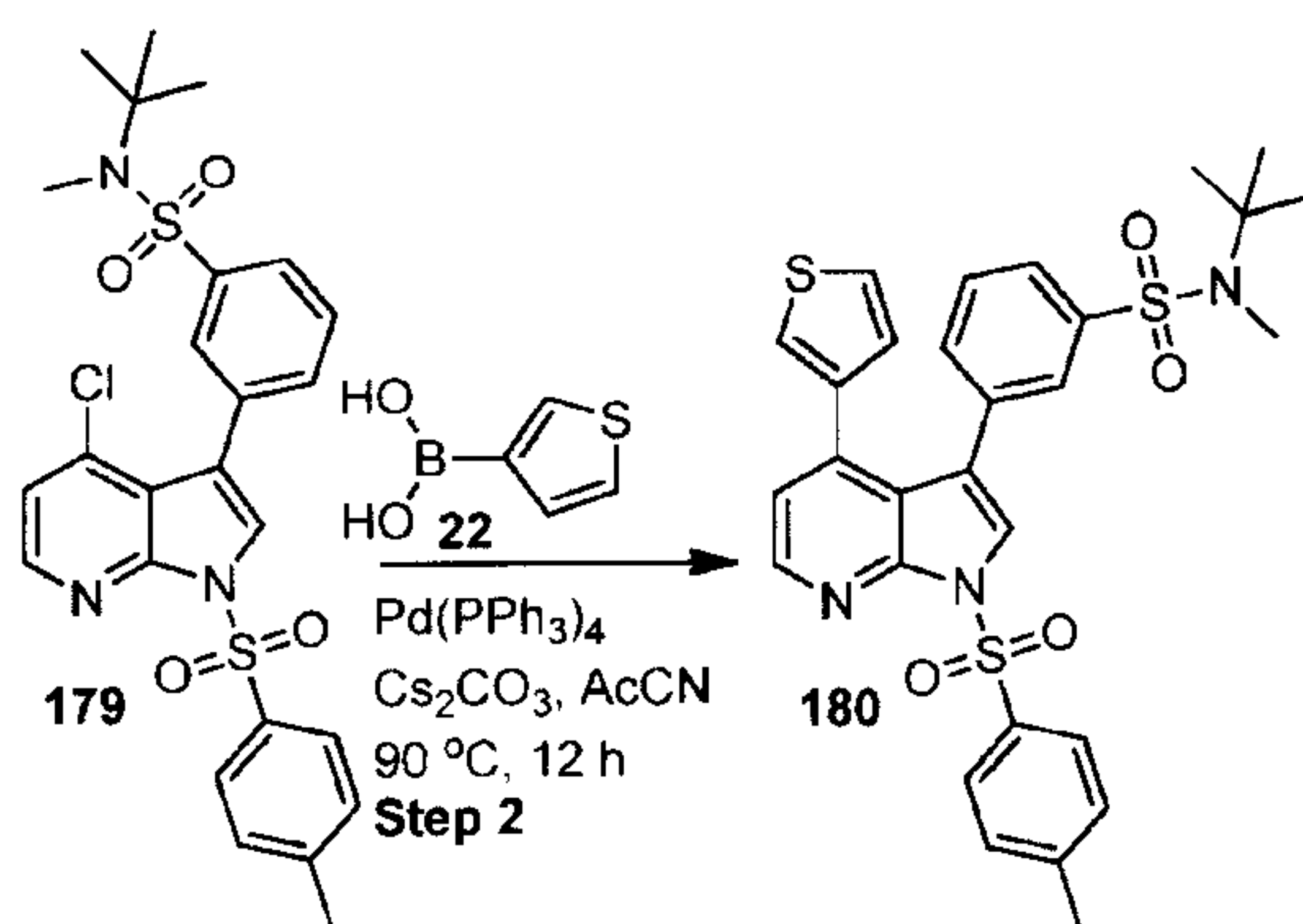
completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **177**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 9.09 (1-H), 8.39 (d,  $J=4.75$  1H), 7.55(m,  $J=6.9$  3-H), 7.52(m,  $J=14.39$  1-H), 7.20(d,  $J=7.80$  2-H), 7.16 (m,  $J=4.87$  2-H), 7.07(m,  $J=11.58$  1-H), 6.84(d,  $J=4.87$  1-H), 2.67 (6-H) and MS  $m/z$  = 383.2 ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 91: N-(tert-butyl)-N-methyl-3-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide (**181**):**



#### Step 1:

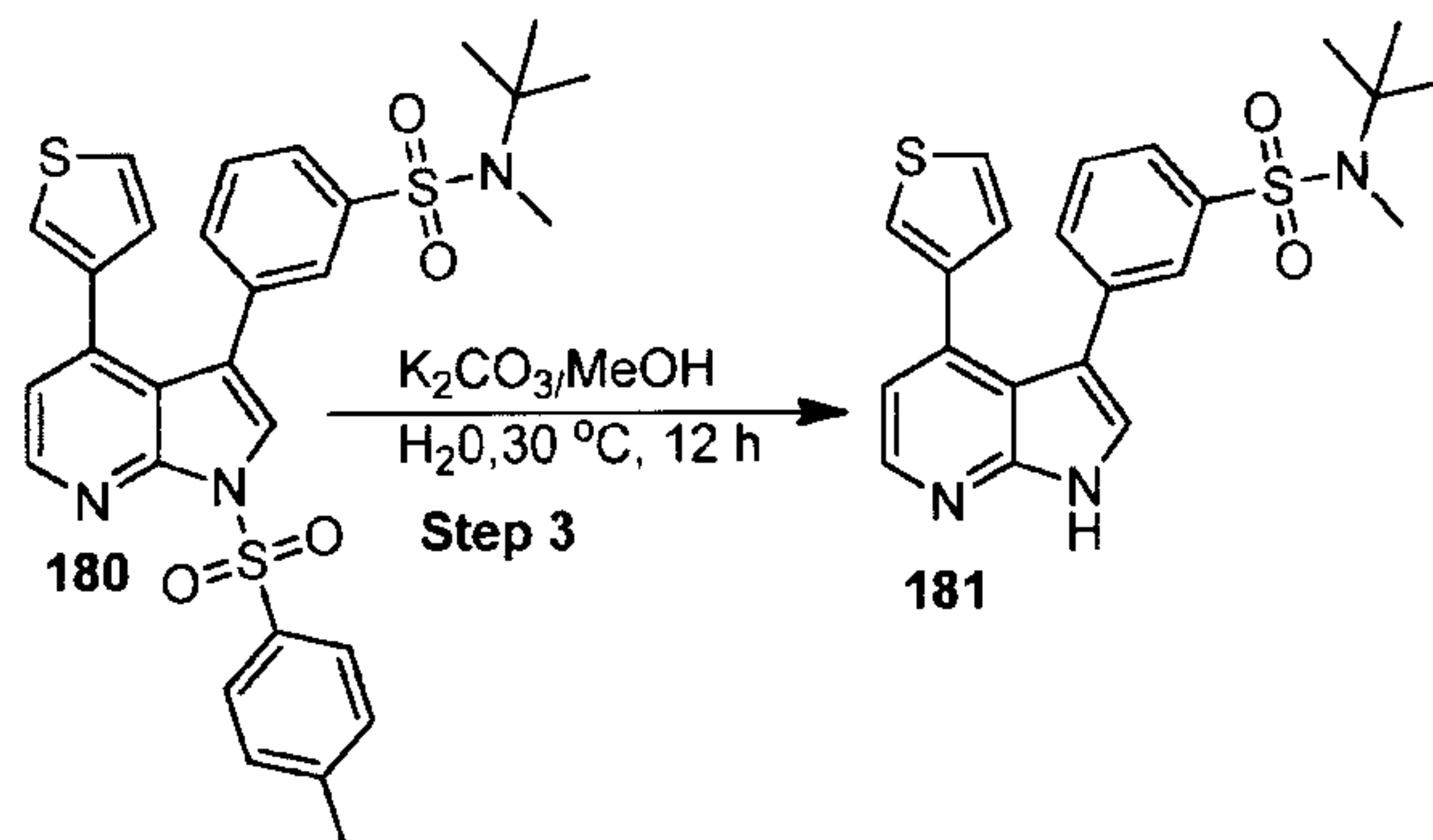
[00214] To a stirred solution of **16** (150mg, 0.347mmol) and **178** (94mg, 0.347mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (228mg, 0.694mmol) and  $\text{Pd(dppf)Cl}_2$  (14.1mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to  $85^\circ\text{C}$  for 4hr in a sealed tube. After completion of the reaction, the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **179**.



#### Step 2:

[00215] To a stirred solution of **179** (80mg, 0.150mmol) and **22** (21mg, 0.165mmol) in acetonitrile(5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate

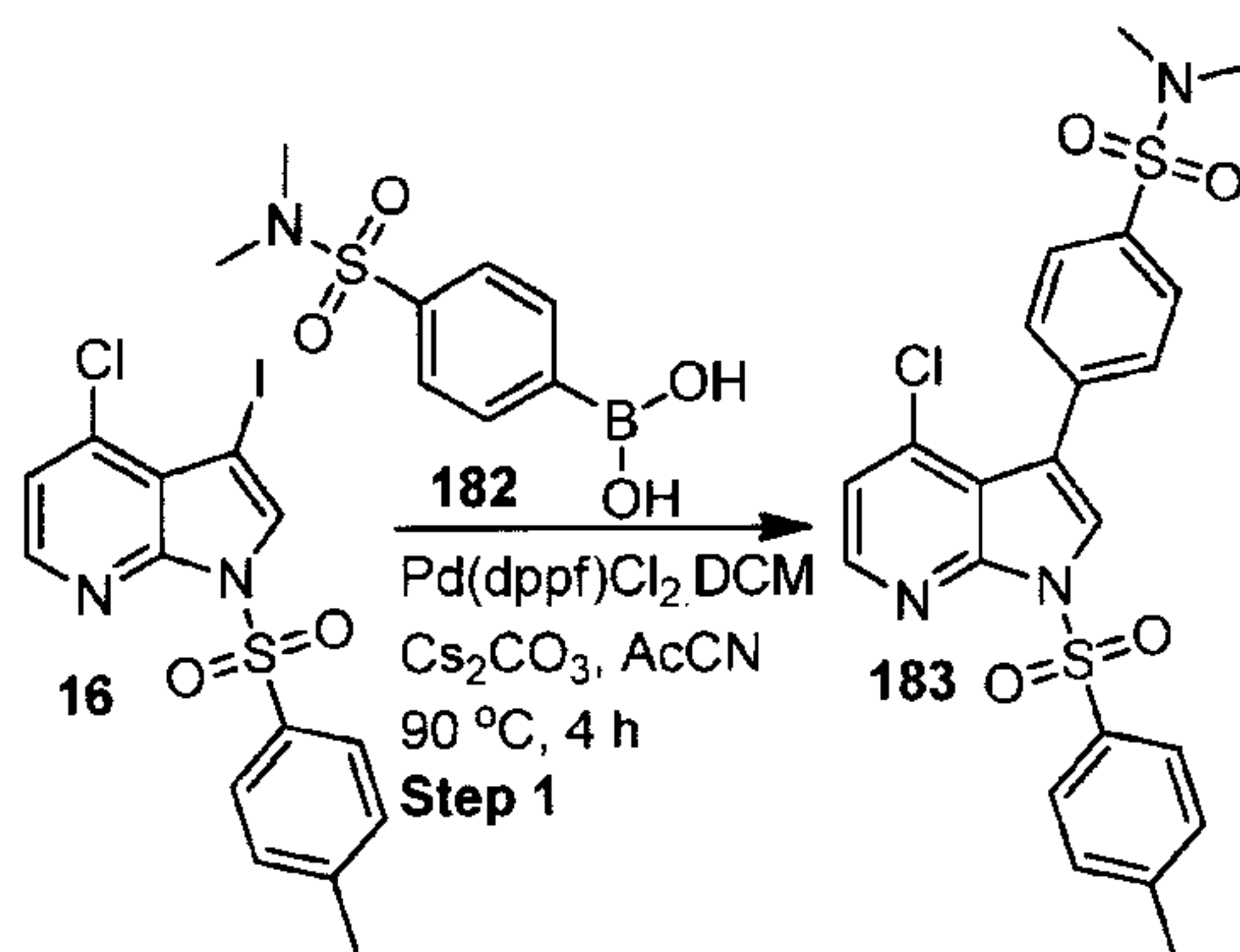
and Pd(dppf)Cl<sub>2</sub>, again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **180**.



#### Step 3:

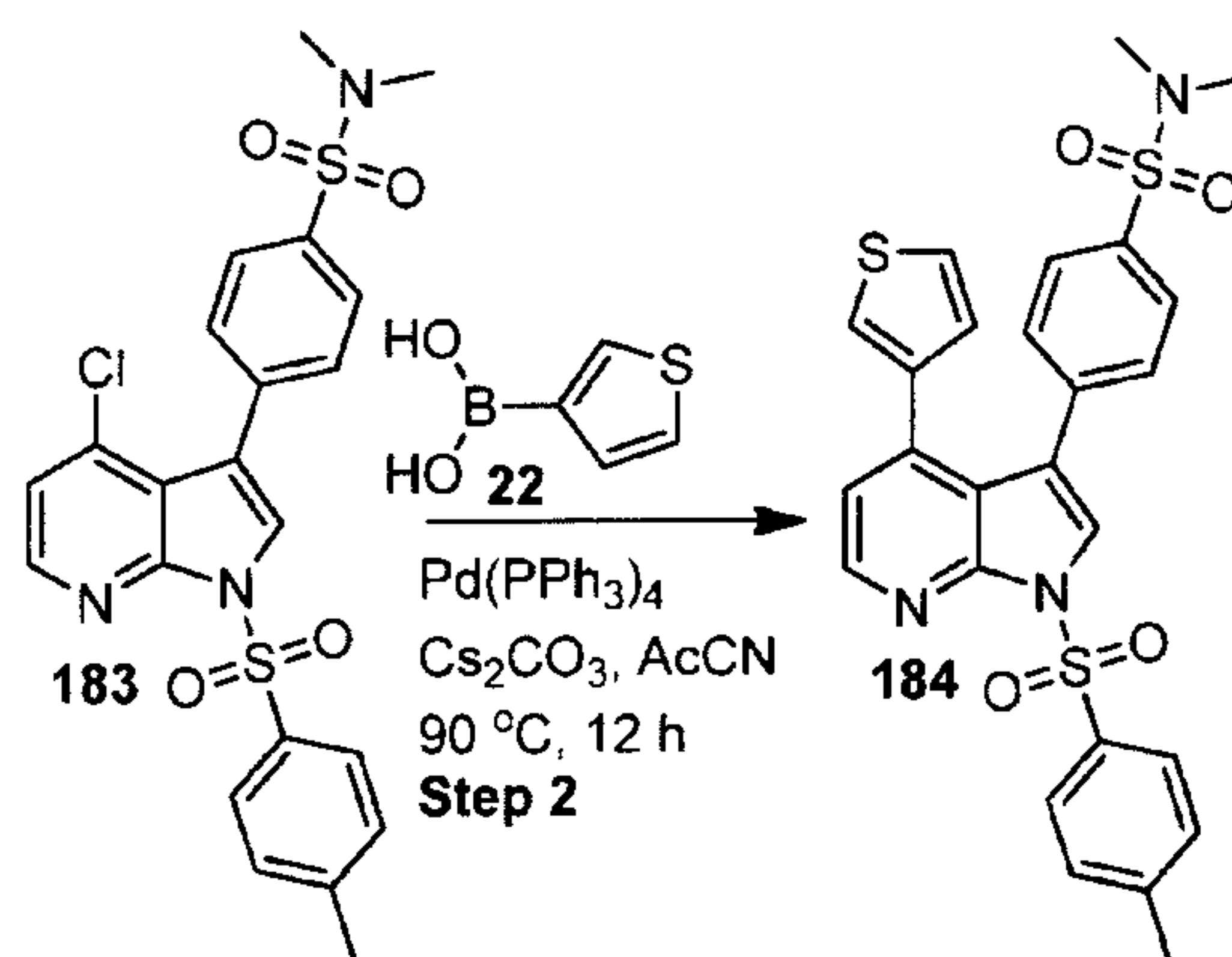
[00216] To a stirred solution of **180** (80mg, 0.138mmol) in methanol (15mL) was added water (10mL) and potassium carbonate (47mg 0.345mmol) and the RM heated to 60°C overnight. After completion of the SM, the RM was completely distilled off and diluted with water and extract with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **181**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 12.17 (1H), 8.31(d, J=4.26 1H), 7.72(s, 1-H), 7.52 (m, J=8.04 2-H), 6.95 (m, J=7.56, 6H), 2.85 (s, 3H), 1.25 (s, 9H), MS m/z = 426.3 (M+H)<sup>+</sup>.

**PREPARATION OF EXAMPLE 92:** N,N-dimethyl-4-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide (**185**):



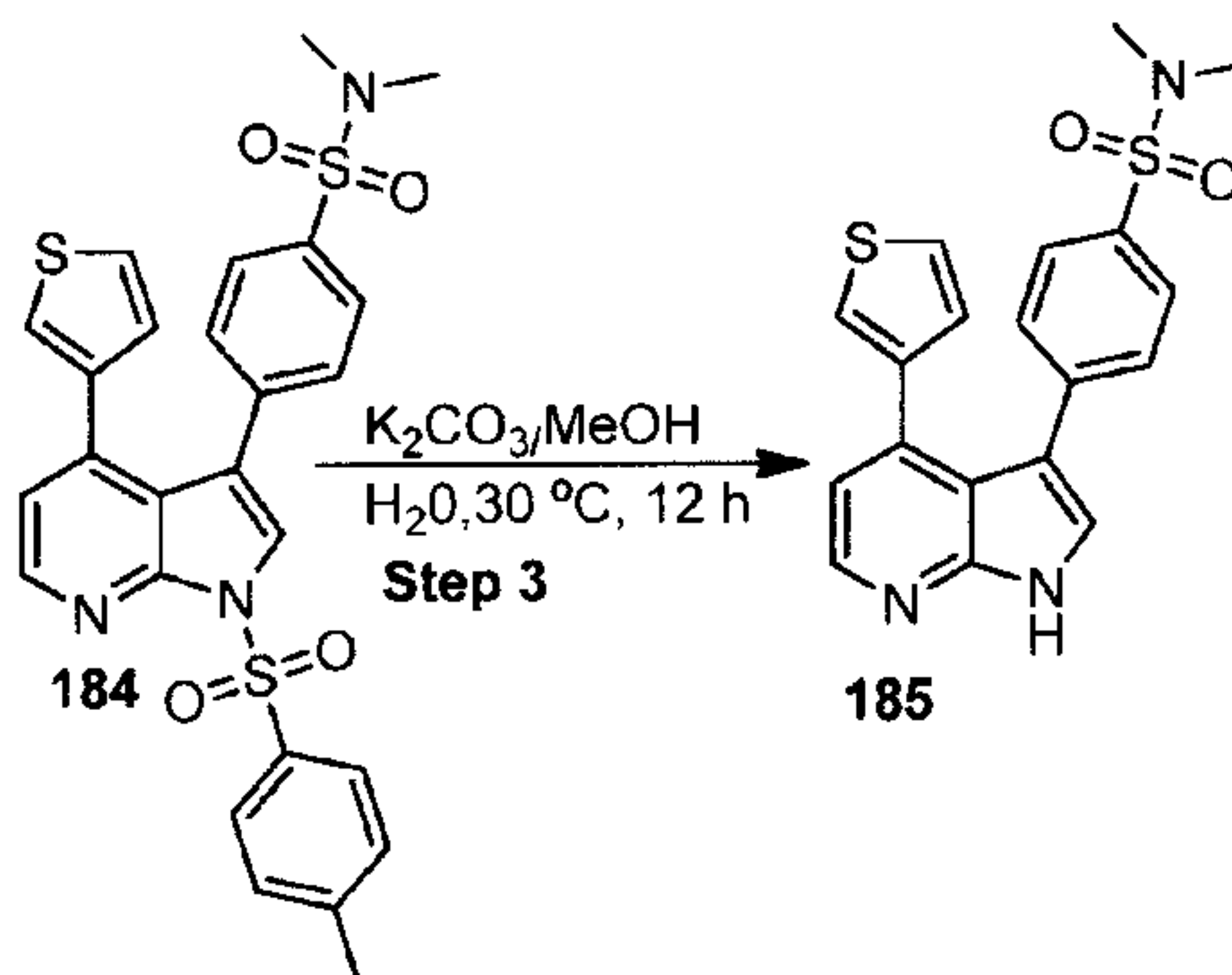
#### Step 1:

[00217] To a stirred solution of **16** (150mg, 0.347mmol) and **182** (79.5mg, 0.347mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg, 0.695mmol) and Pd(dppf)Cl<sub>2</sub> (14mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **183**.



#### Step 2:

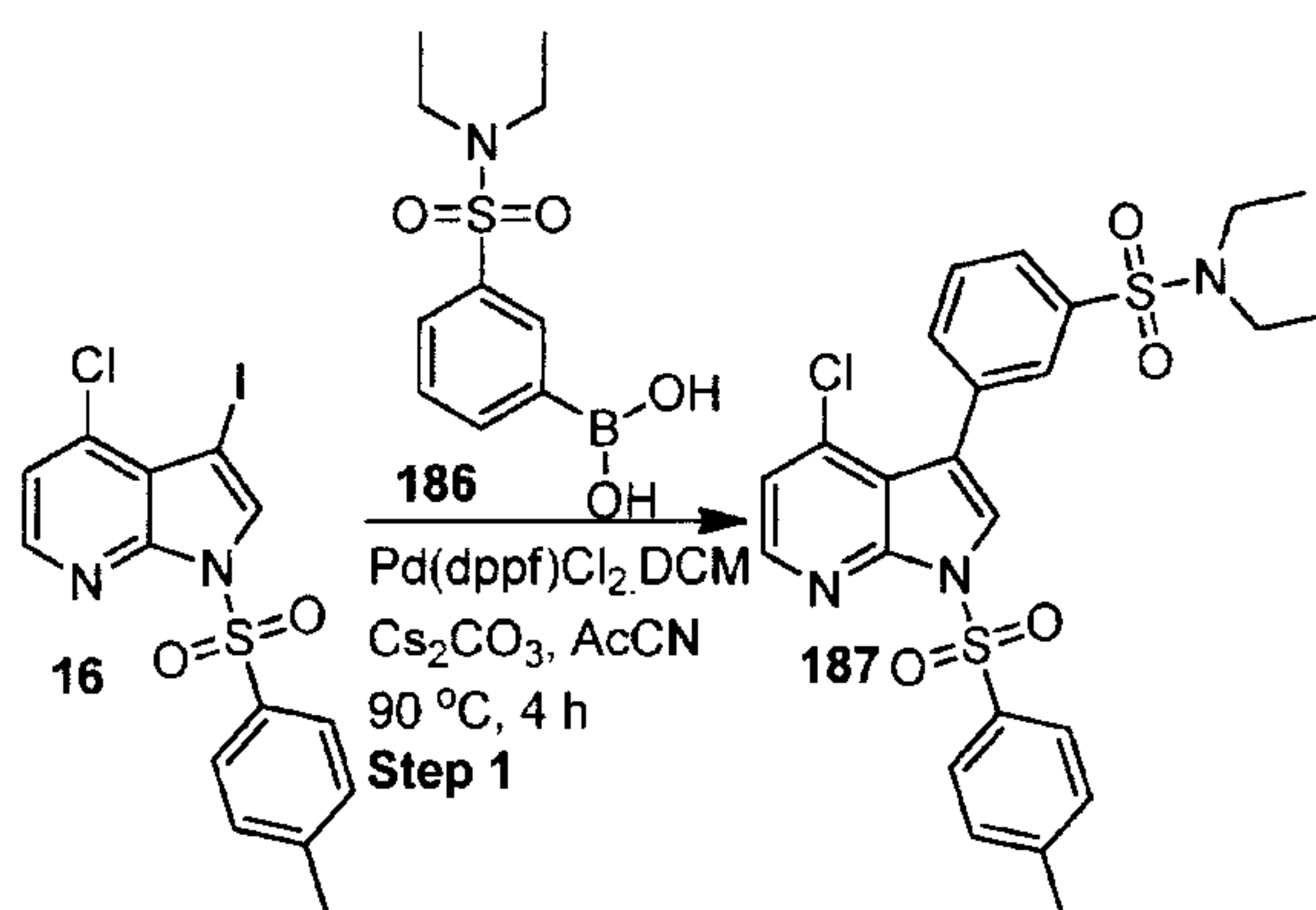
[00218] To a stirred solution of **183** (120mg, 0.255mmol) and **22** (49mg, 0.384mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (166mg, 0.512mmol) and Pd(dppf)Cl<sub>2</sub> (10mg, 0.0127mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **184**.



#### Step 3:

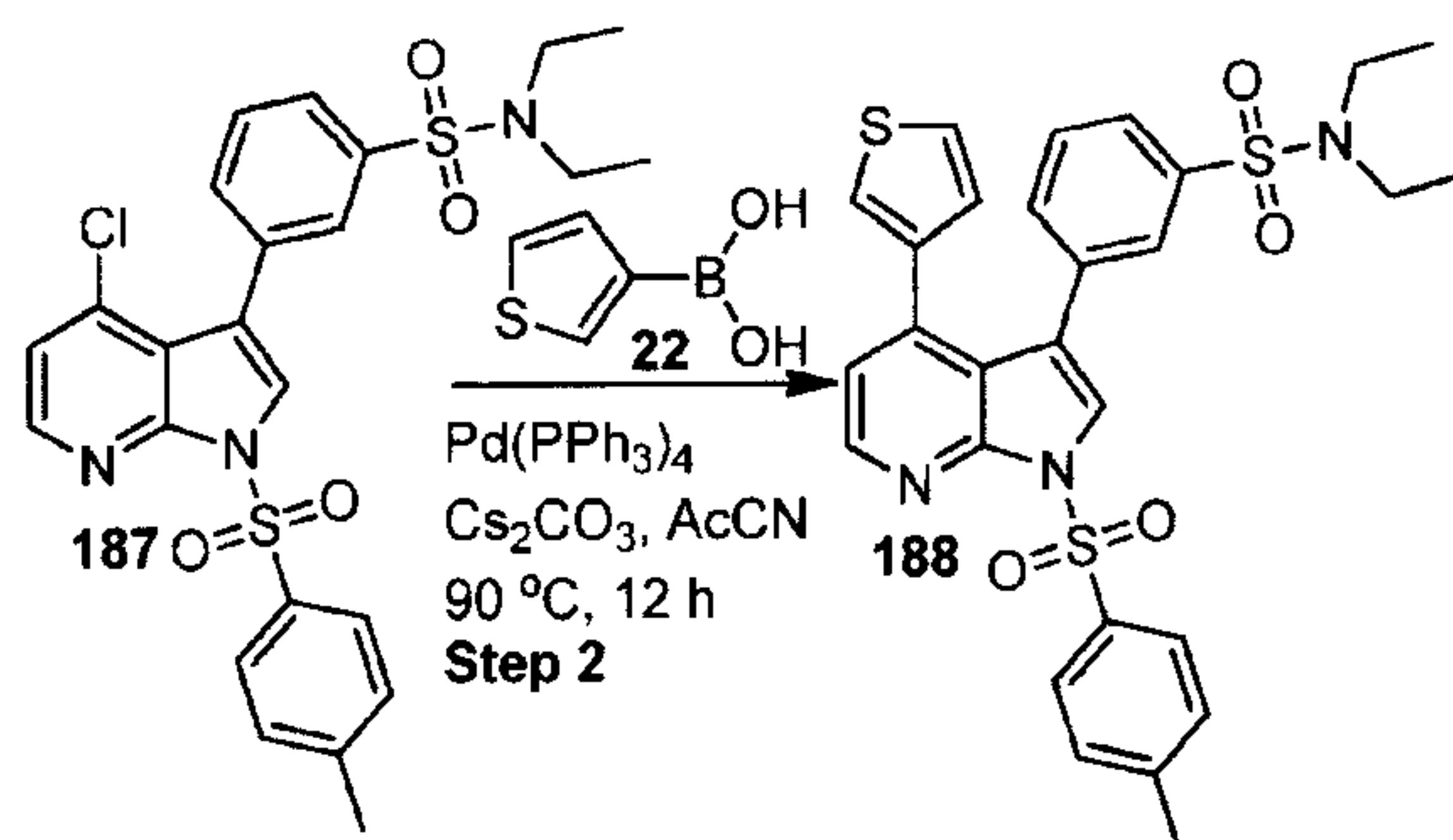
[00219] To a stirred solution of **184** (40mg, 0.0744mmol) in methanol (15mL) was added water (10mL) and potassium carbonate (25mg, 0.186mmol) and the RM heated to 60°C overnight. After completion of the SM, the RM was completely distilled off and diluted with water and extract with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **185**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  : 9.25(1-H), 8.41(d,  $J=4.87$  1-H), 7.51(m,  $J=8.4$  2-H), 7.45(d,  $J=2.56$  1-H), 7.17(m,  $J=5.00$  3-H), 7.10(m,  $J=3.04$  1-H), 6.98(m,  $J=4.14$  1-H), 6.88(m,  $J=4.87$  1-H), 2.72(s, 6-H) and MS  $m/z$  = 383.9 ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 93: N,N-diethyl-3-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide (189):**

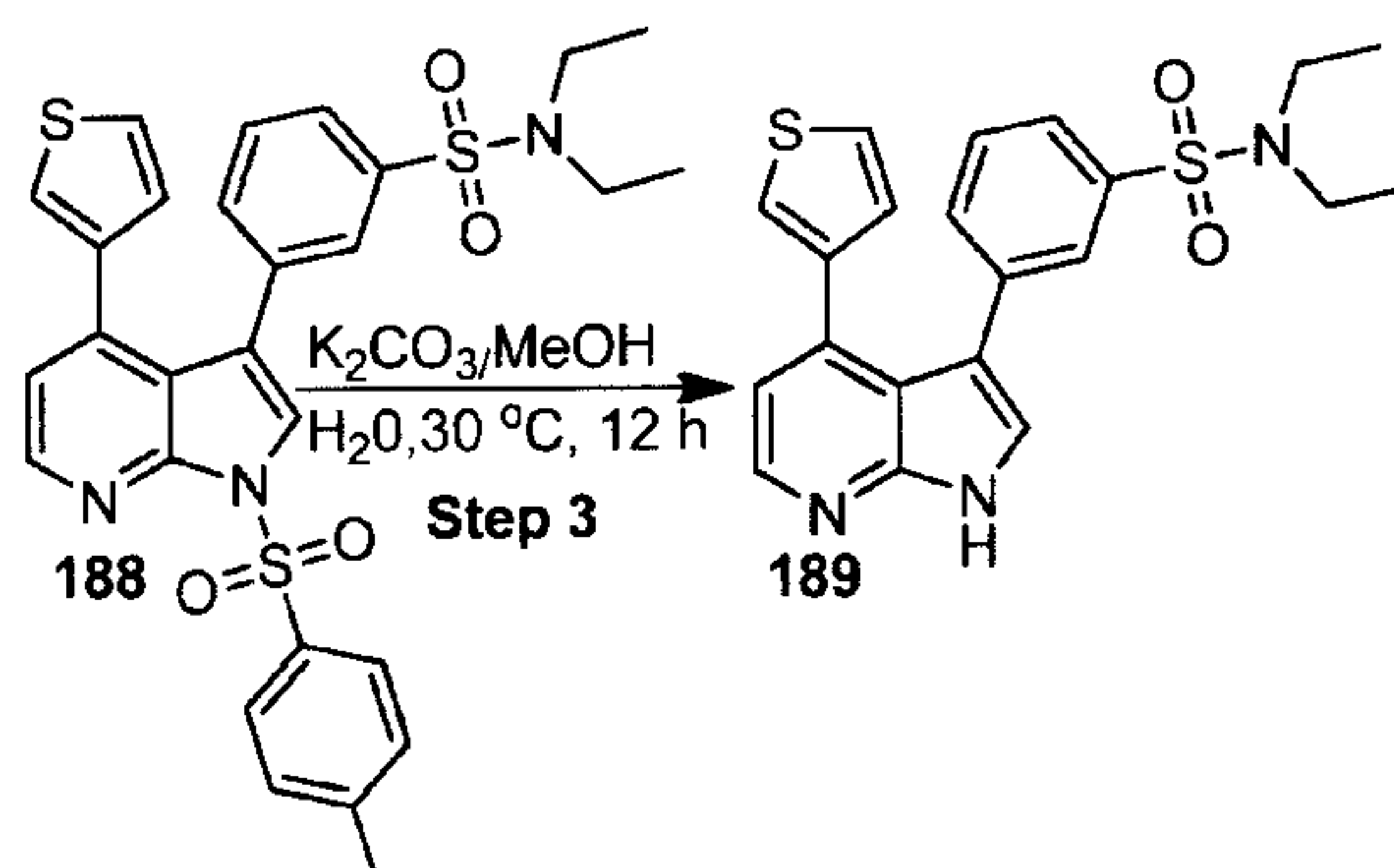


Step 1:

[00220] To a stirred solution of **16** (150mg, 0.347mmol) and **186** (89mg, 0.347mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg, 0.694mmol) and  $\text{Pd(dppf)Cl}_2$  (14mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to  $85^\circ\text{C}$  for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **187**.

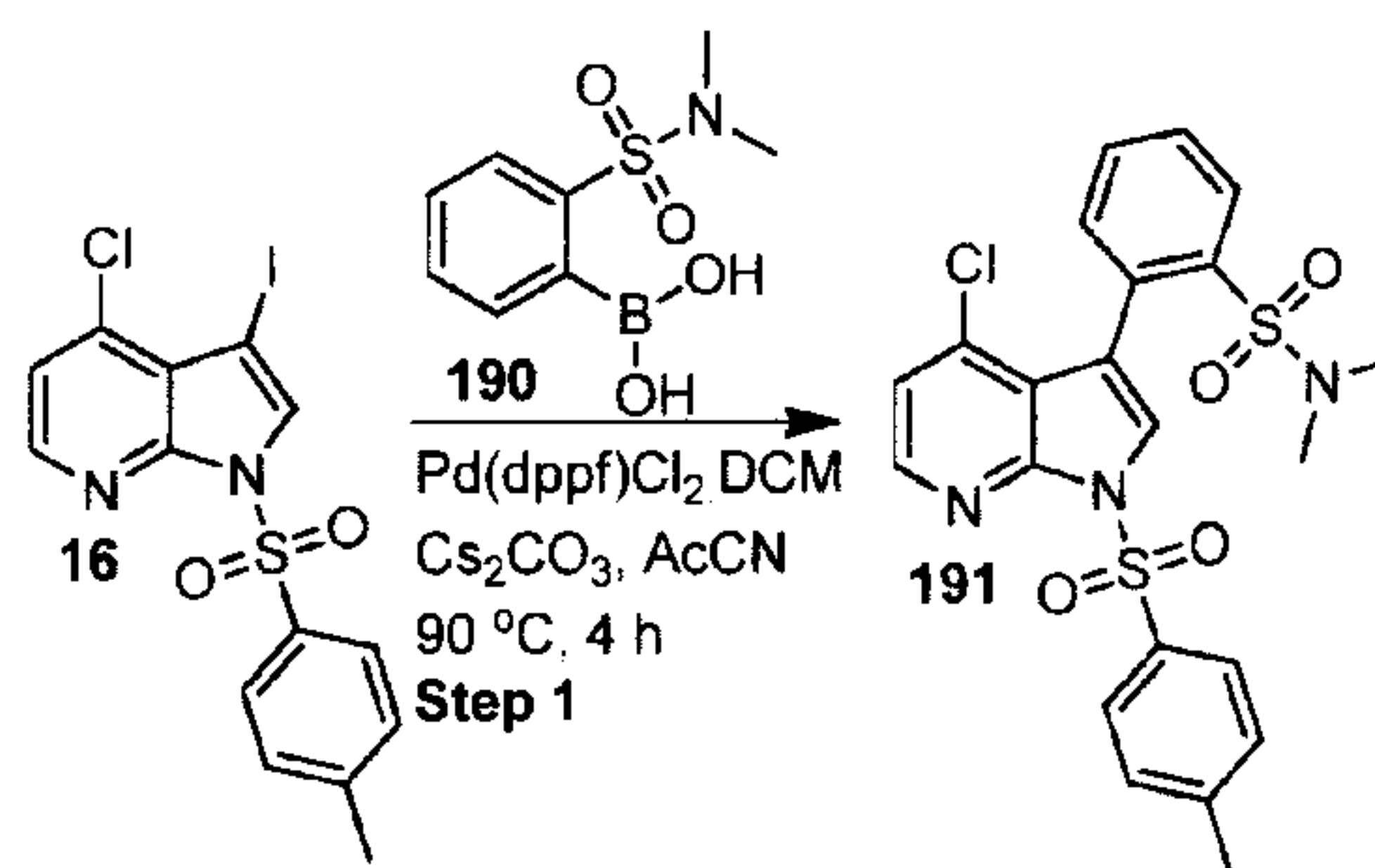
Step 2:

[00221] To a stirred solution of **187** (100mg, 0.198mmol) and **22** (64mg, 0.198mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (129mg, 0.396mmol) and  $\text{Pd(dppf)Cl}_2$  (6mg, 0.0079mmol), again degassed and purged with nitrogen for 15min and the RM heated to  $85^\circ\text{C}$  for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **188**.

Step 3:

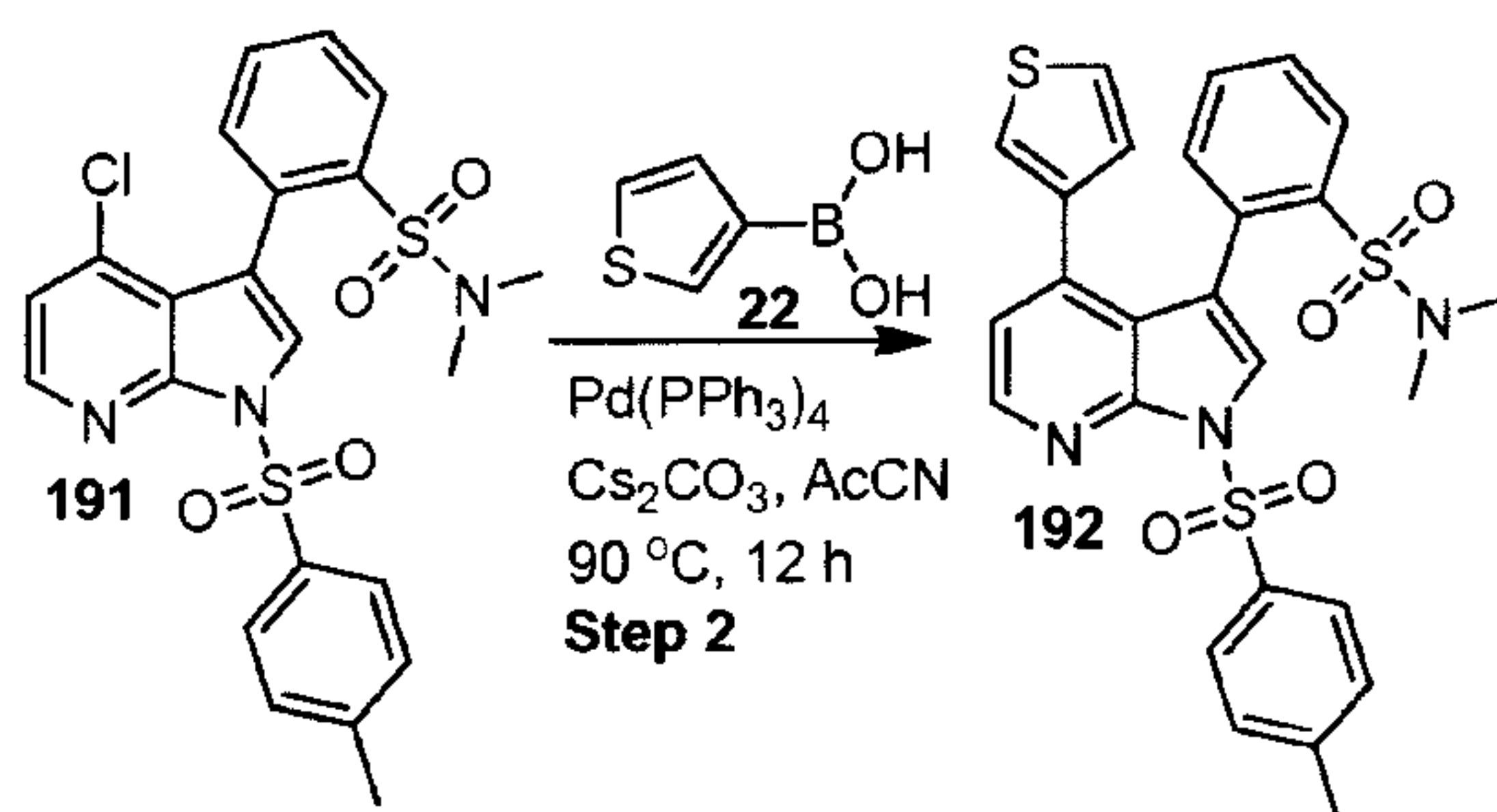
[00222] To a stirred solution of **188** (60mg, 0.1087mmol) in methanol (10mL) was added water (5mL) and potassium carbonate (45mg, 0.326mmol) and the RM heated to  $60^\circ\text{C}$  overnight. After completion of the SM, the RM was completely distilled off and diluted with water and extract with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **189**.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 9.45(1-H), 8.40(S, 1-H), 7.68 (S, 1-H), 7.57 (d,  $J=43.1$ , 1-H), 7.43 (S, 1-H), 7.17 (m,  $J=42.56$ , 2-H), 6.98 (m,  $J=18.41$ , 3-H), 6.85 (d,  $J=52.1$ , 1-H), 3.21 (m,  $J=6.95$ , 4-H), 1.13 (S, 6-H) and MS  $m/z = 412.3$  ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 94:** N,N-dimethyl-2-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)benzenesulfonamide (**193**):



Step 1:

[00223] To a stirred solution of **16** (150mg, 0.347mmol) and **190** (79mg, 0.347mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg, 0.694mmol) and  $\text{Pd(dppf)Cl}_2$  (14mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to  $85^\circ\text{C}$  for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **190**.

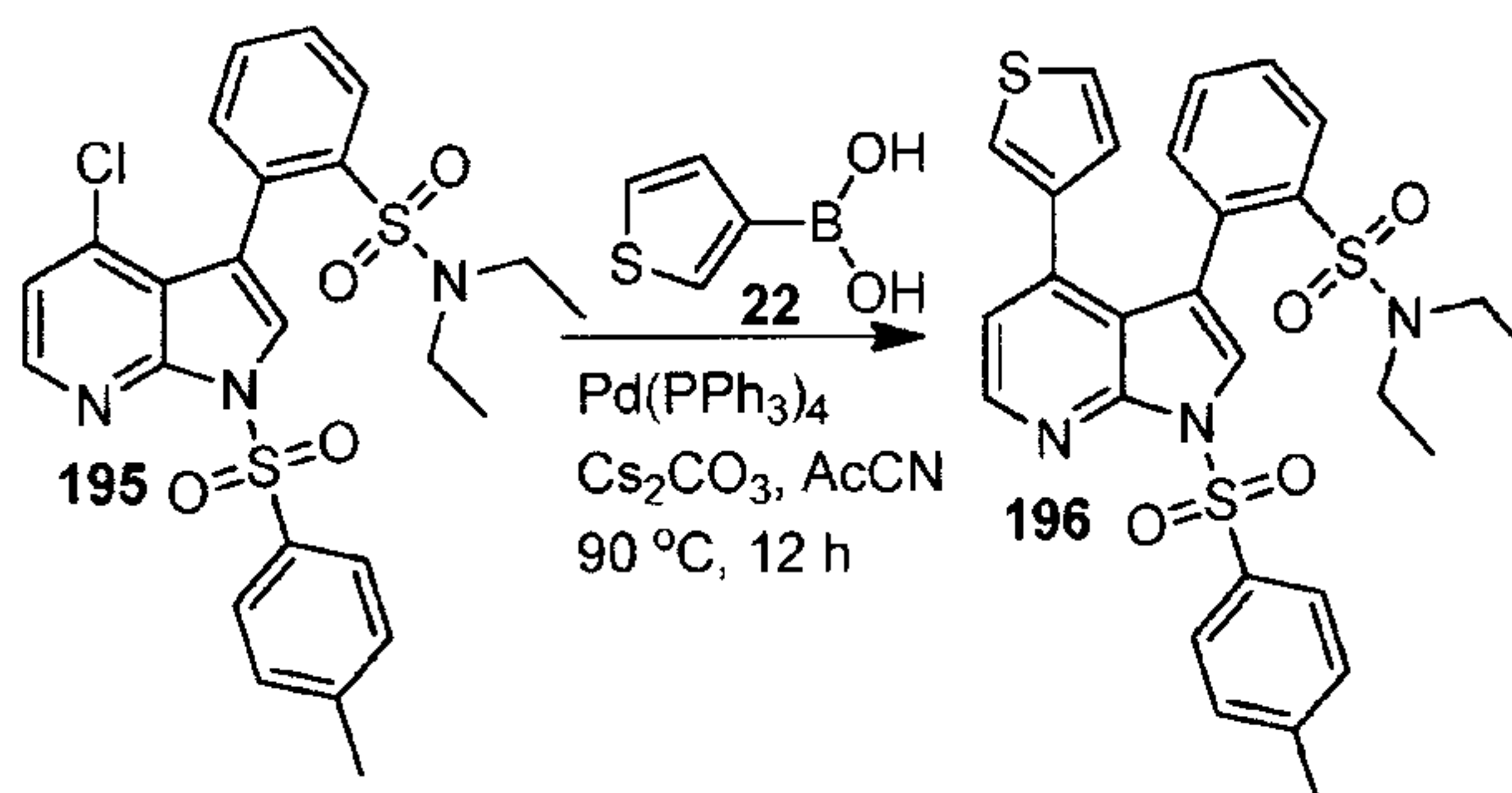


Step 2:

[00224] To a stirred solution of **191** (100mg, 0.204mmol) and **22** (26mg, 0.204mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (134mg, 0.408mmol) and  $\text{Pd(dppf)Cl}_2$  (8mg, 0.0101mmol), again degassed and purged with nitrogen for 15min and the RM heated to  $85^\circ\text{C}$  for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **192**.

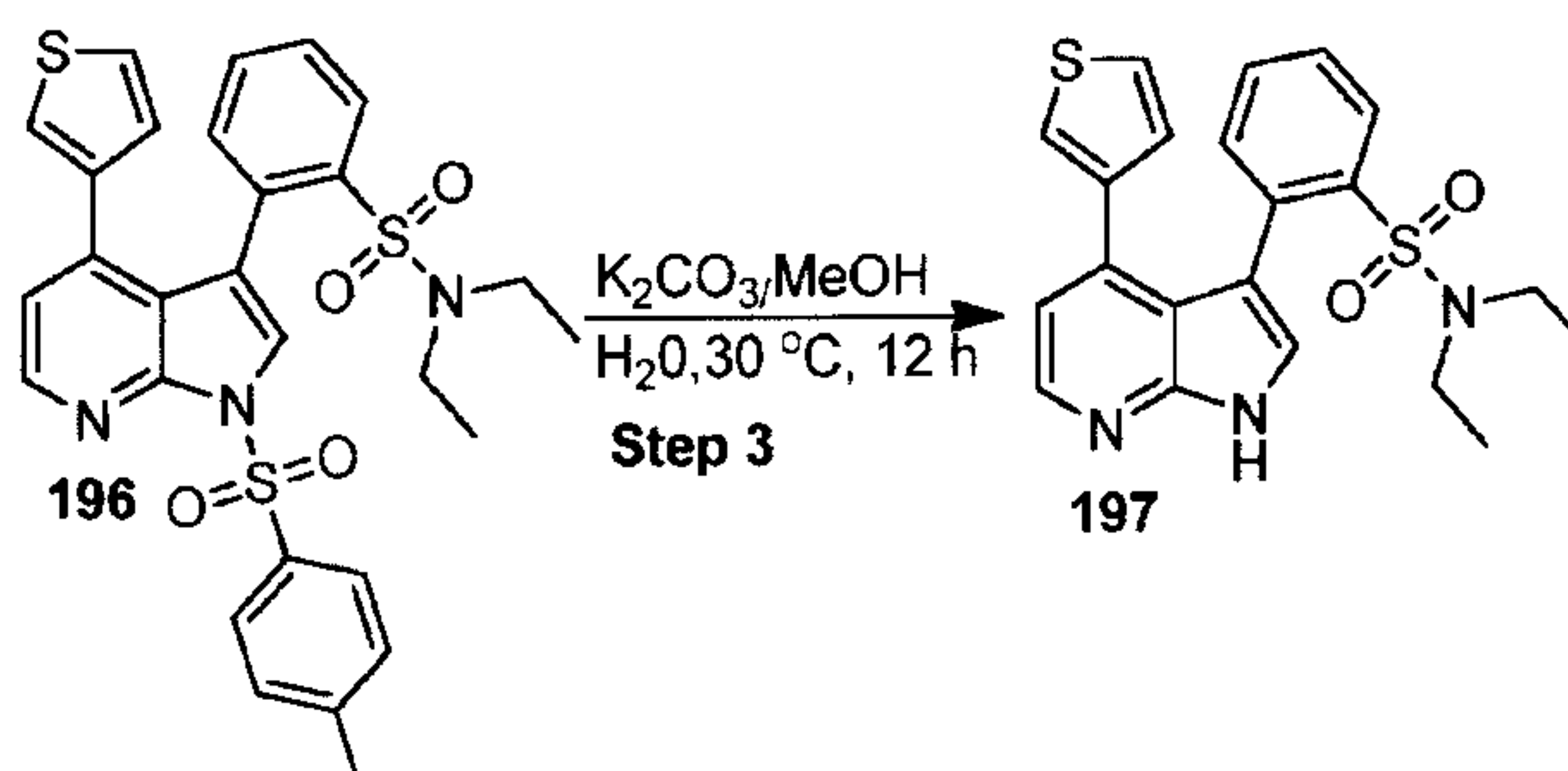


through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **195**.



#### Step 2:

[00227] To a stirred solution of **195** (100mg, 0.198mmol) and **22** (64mg, 0.198mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (129mg, 0.396mmol) and Pd(dppf)Cl<sub>2</sub> (6mg, 0.0079mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **196**.

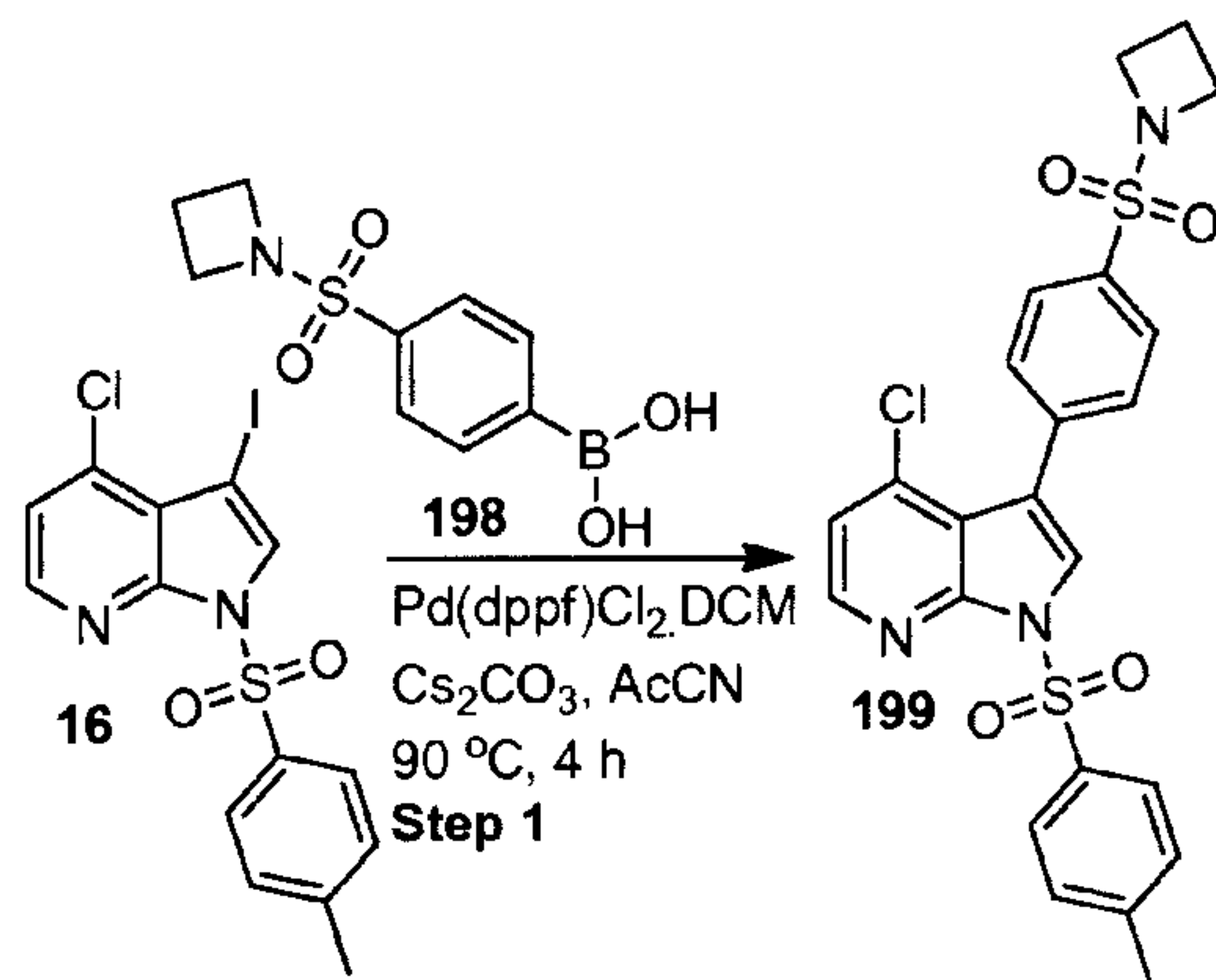


#### Step 3:

[00228] To a stirred solution of **196** (60mg, 0.108mmol) in methanol (10mL) was added water (5mL) and potassium carbonate (45mg, 0.326mmol) and the RM heated to 60°C overnight. After completion of the SM, the RM was completely distilled off and diluted with water and extract with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **197**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.00 (1H), 8.36 (d, J=5.0, 1-H), 7.78 (dd, J=7.92, 1H), 7.63 (d, J=63.04, 1H), 7.23 (m, J=7.92, 1-H), 7.07 (m, J=8.04 2H), 6.96 (m,

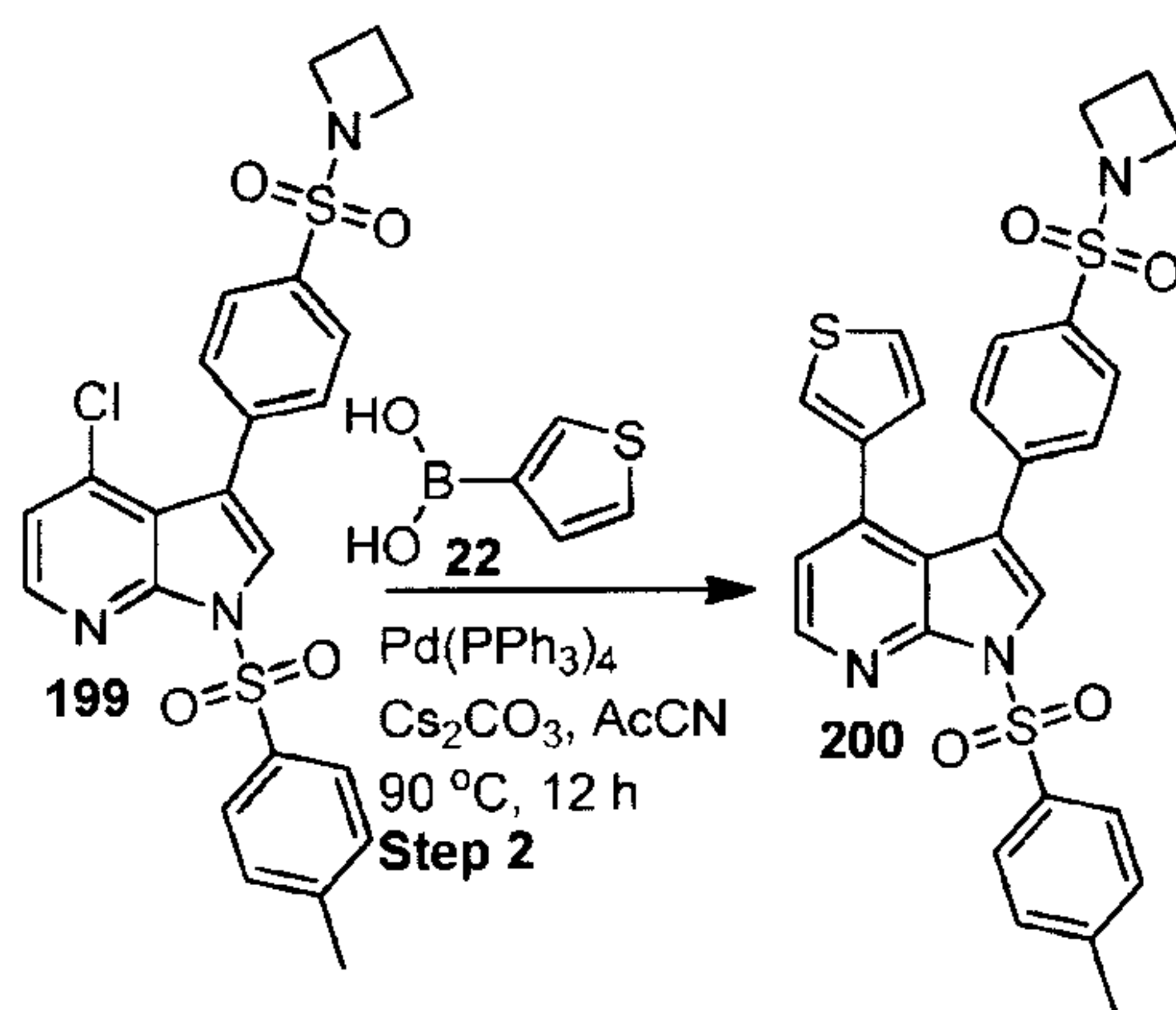
$J=1.7$ , 1H), 6.92 (m,  $J=2.92$  1H), 6.83 (m,  $J=6.46$ , 2H), 3.2 (m,  $J=7.07$ , 4H), 1.11 (m,  $J=7.07$ , 6-H) and MS  $m/z = 412.7$  ( $M+H$ )<sup>+</sup>.

**PREPARATION OF EXAMPLE 96:** 3-(4-(azetidin-1-ylsulfonyl)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**201**):



Step 1:

[00229] To a stirred solution of **16** (150mg, 0.347mmol) and **198** (83mg, 0.347mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg) and  $\text{Pd(dppf)Cl}_2$  (14mg, 0.0176mmol), again degassed and purged with nitrogen for 15min and the RM heated to  $85^\circ\text{C}$  for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. the organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **199**.



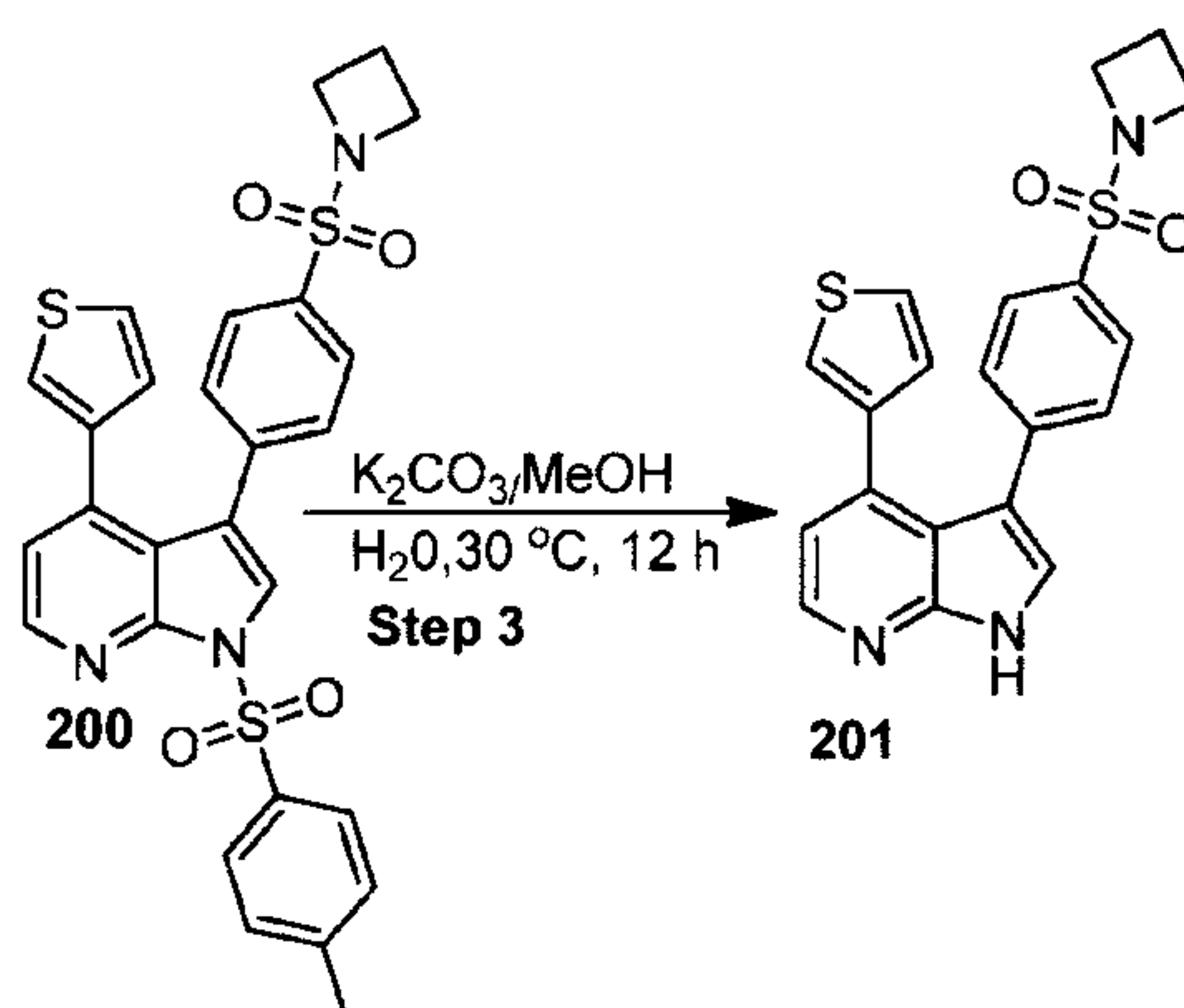
Step 2:

[00230] To a stirred solution of **199** (100mg, 0.204mmol) and **22** (26mg, 0.204mmol) in acetonitrile (5mL) degassed and purged with nitrogen for 10min, was added cesium carbonate (133mg, 0.409mmol) and  $\text{Pd(dppf)Cl}_2$  (6mg, 0.00819mmol), again degassed and purged with

WO 2014/093383

PCT/US2013/074191

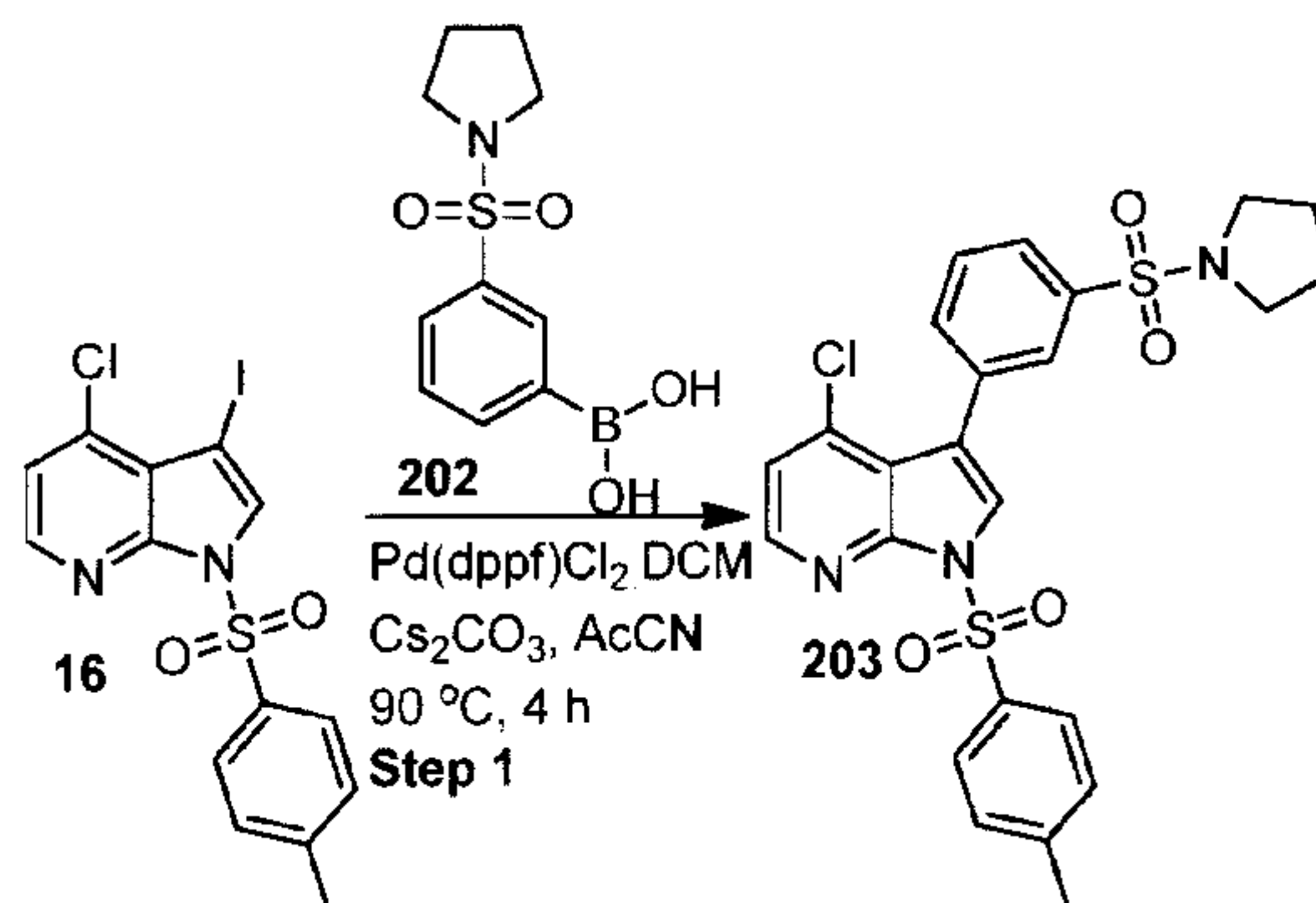
nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **200**.



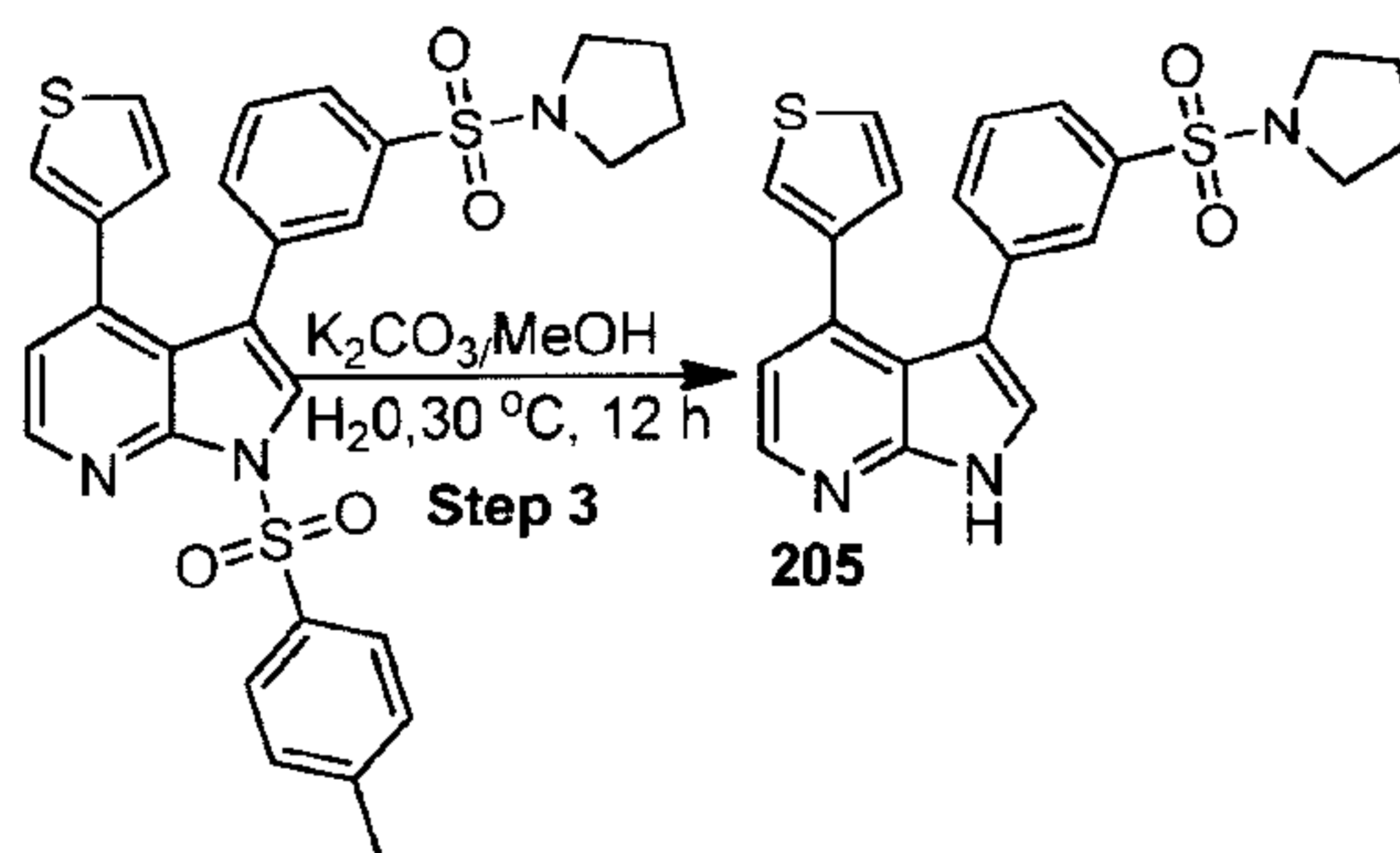
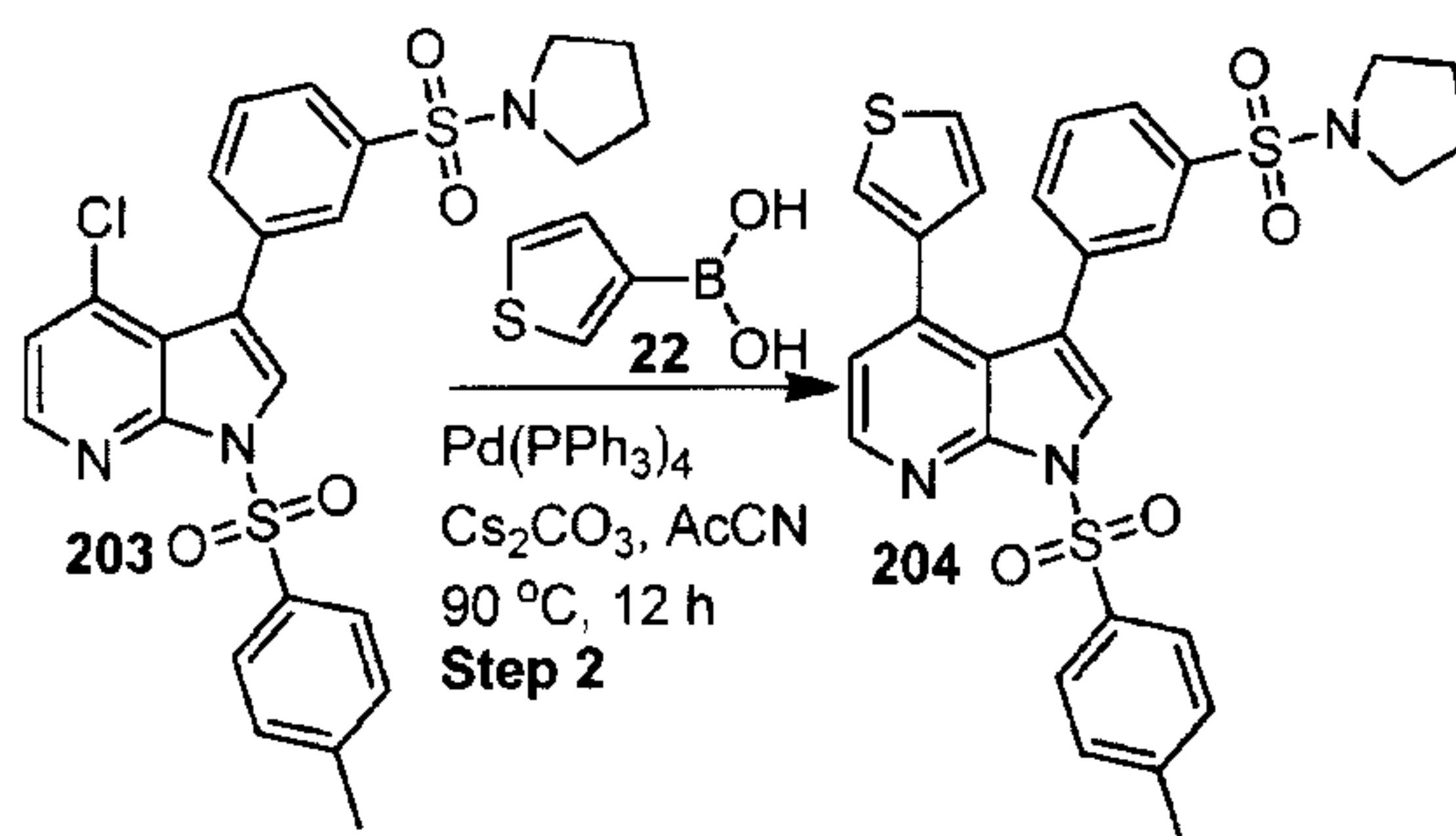
#### Step 3:

[00231] To a stirred solution of **200** (60mg, 0.112mmol) in methanol (10mL) was added water (5mL) and potassium carbonate (46mg, 0.336mmol) and the RM heated to 60°C overnight. After completion of the reaction, the RM was completely distilled off and diluted with water and extract with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **201**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.30(s, 1-H), 8.42(d, J=353.77, 1-H), 7.58(m, J=8.29 2-H), 7.2(d, J=8.29, 1-H), 7.13(m, J=21.21, 3-H), 7.11(m, J=3.04, 1-H), 6.93(m, J=4.74, 2-H) 3.79(t, J=7.43, 4-H), 2.13 (m, J=7.56, 2-H) and MS m/z = 396.3 (M+H)<sup>+</sup>.

**PREPARATION OF EXAMPLE 97: 3-(3-(pyrrolidin-1-ylsulfonyl)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (205):**

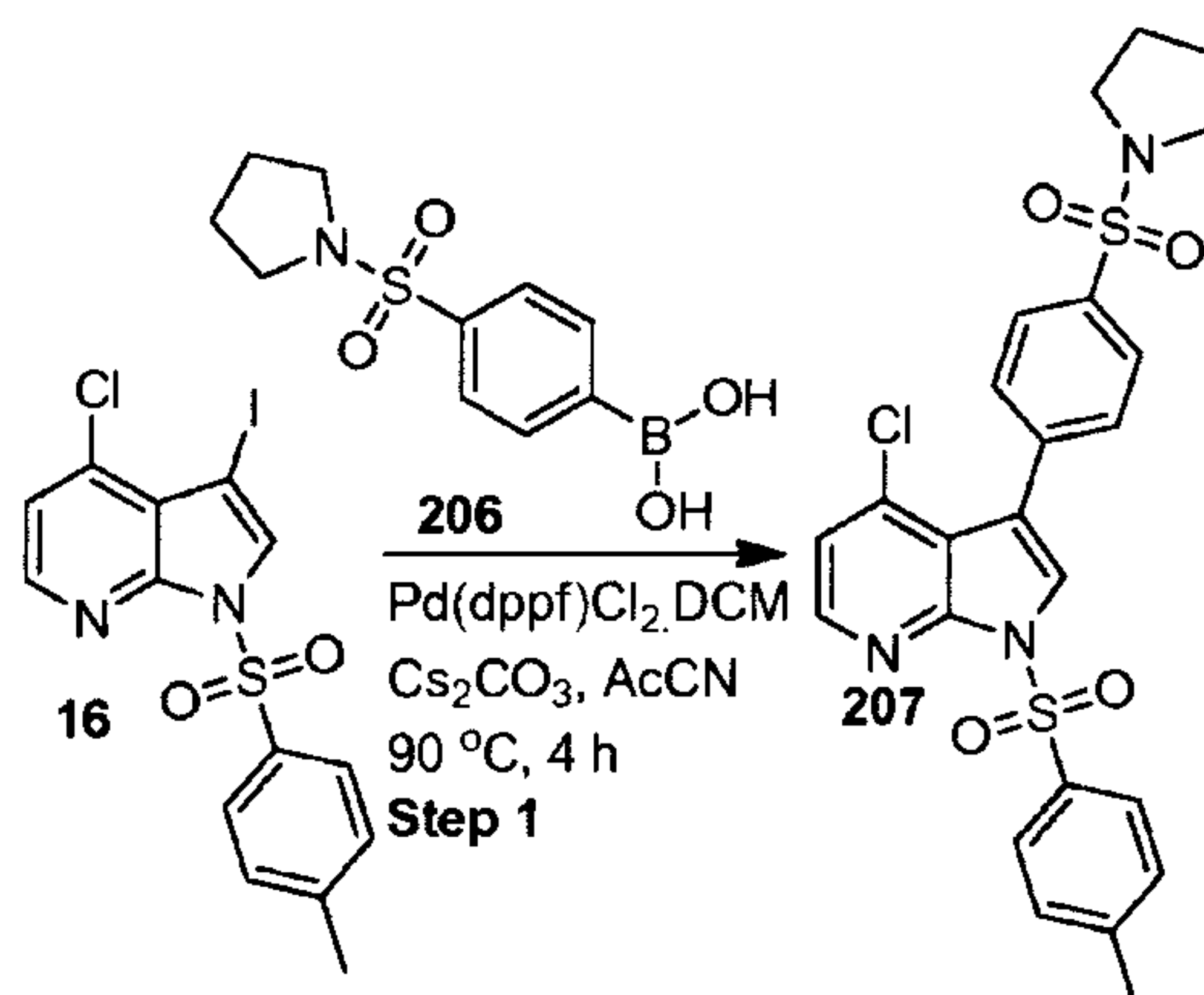


#### Step 1:



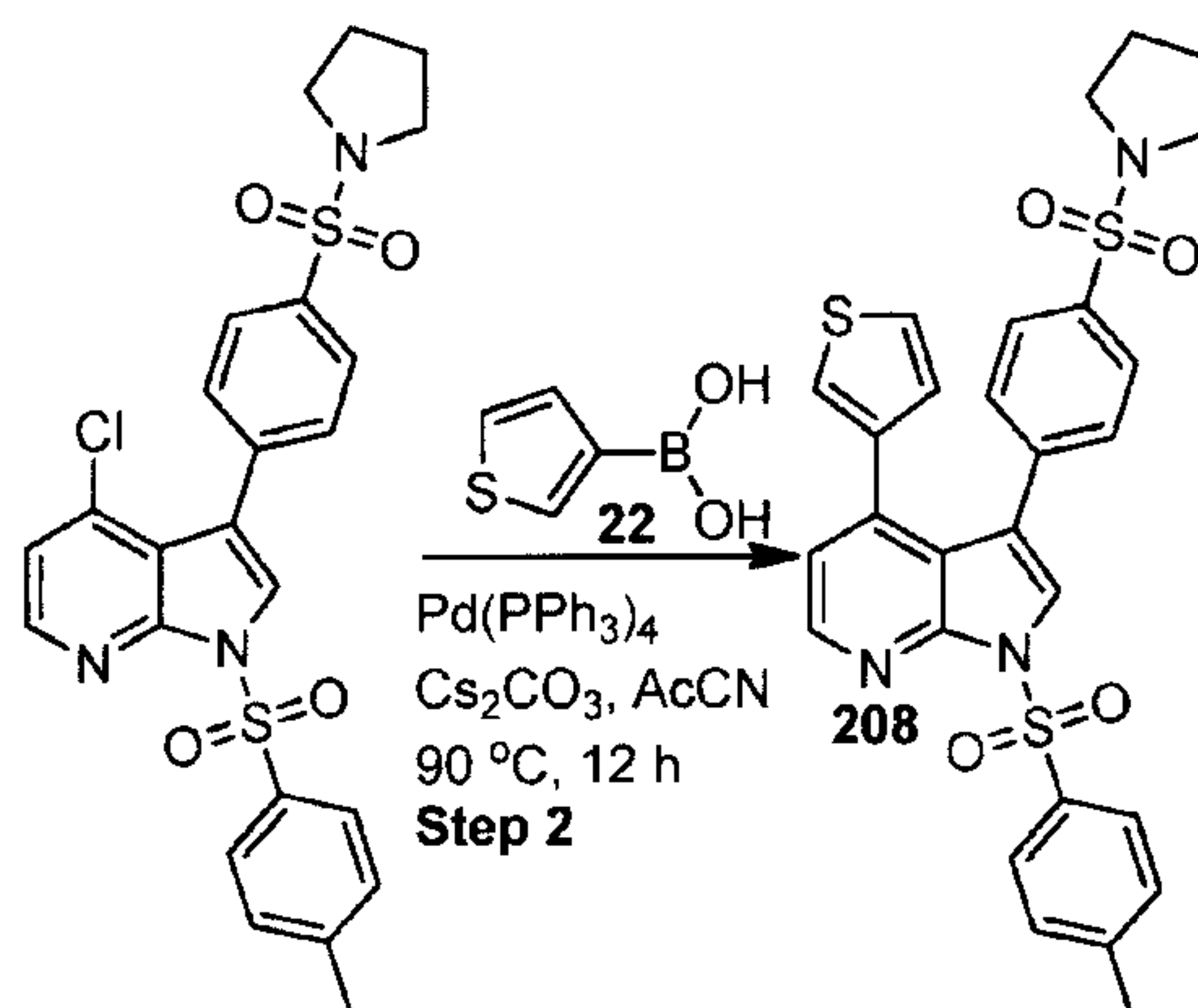
extract with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **205**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 9.31(1H), 8.40 (d,  $J=4.75$  1H), 7.69 (s, 1H), 7.60 (m,  $J=7.56$  1H), 7.43 (d,  $J=2.56$  1H), 7.17 (m,  $J=6.95$  2H), 7.07(m,  $J=3.17$  2H), 6.97 (m,  $J=2.19$  1H), 6.84 (m,  $J=4.87$  1H), 3.22 (m,  $J=6.70$  4H), 1.77 (m,  $J=2.92$  4H) and MS  $m/z = 410.3$  ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 98: 3-(4-(pyrrolidin-1-ylsulfonyl)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (209):**

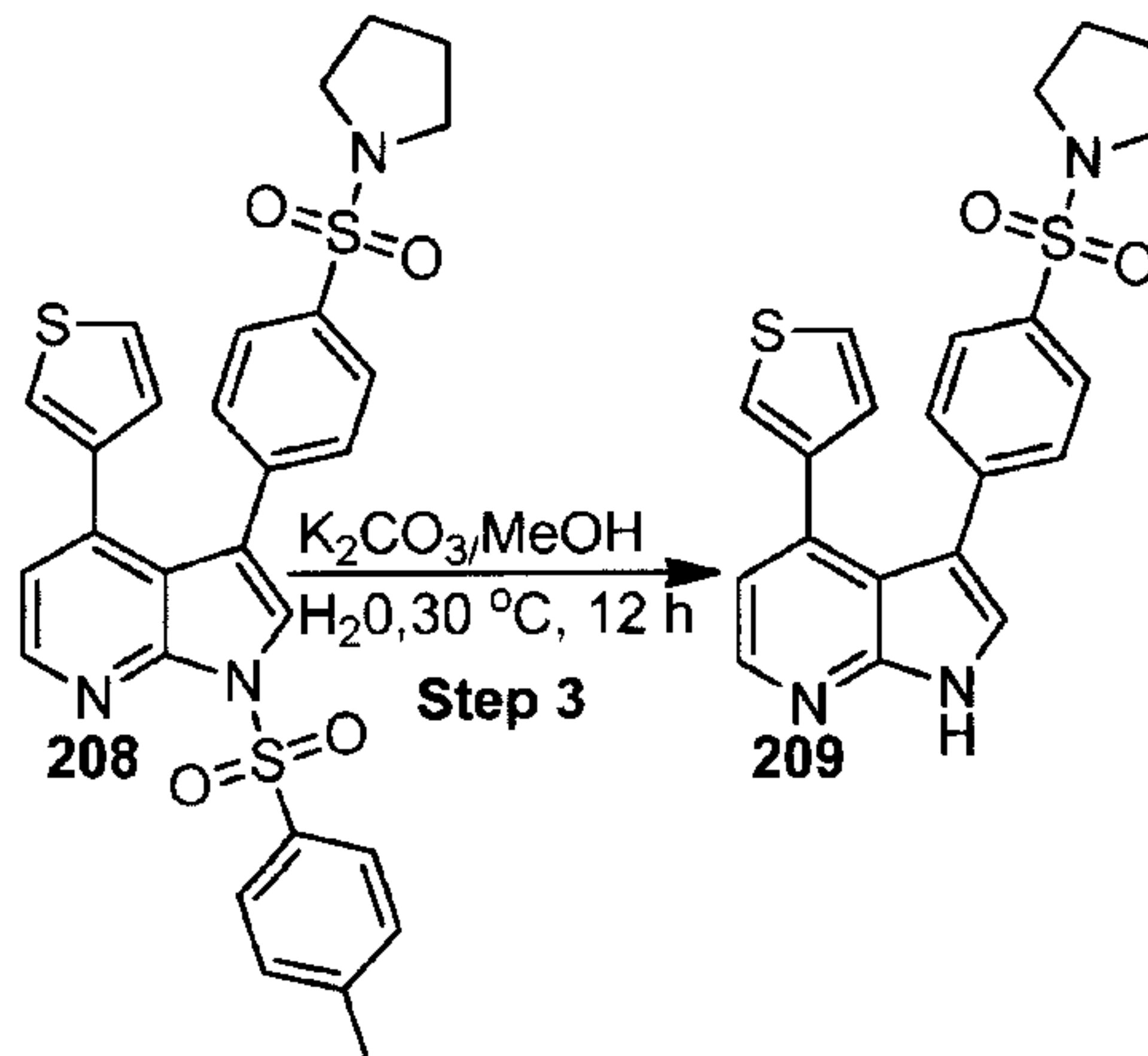


Step 1:

[00235] To a stirred solution of **16** (150mg, 0.347mmol) and **206** (88mg, 0.347mmol) in acetonitrile (5mL) was degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg, 0.694mmol) and  $\text{Pd(dppf)Cl}_2$  (14mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to  $85^\circ\text{C}$  for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **207**.

Step 2:

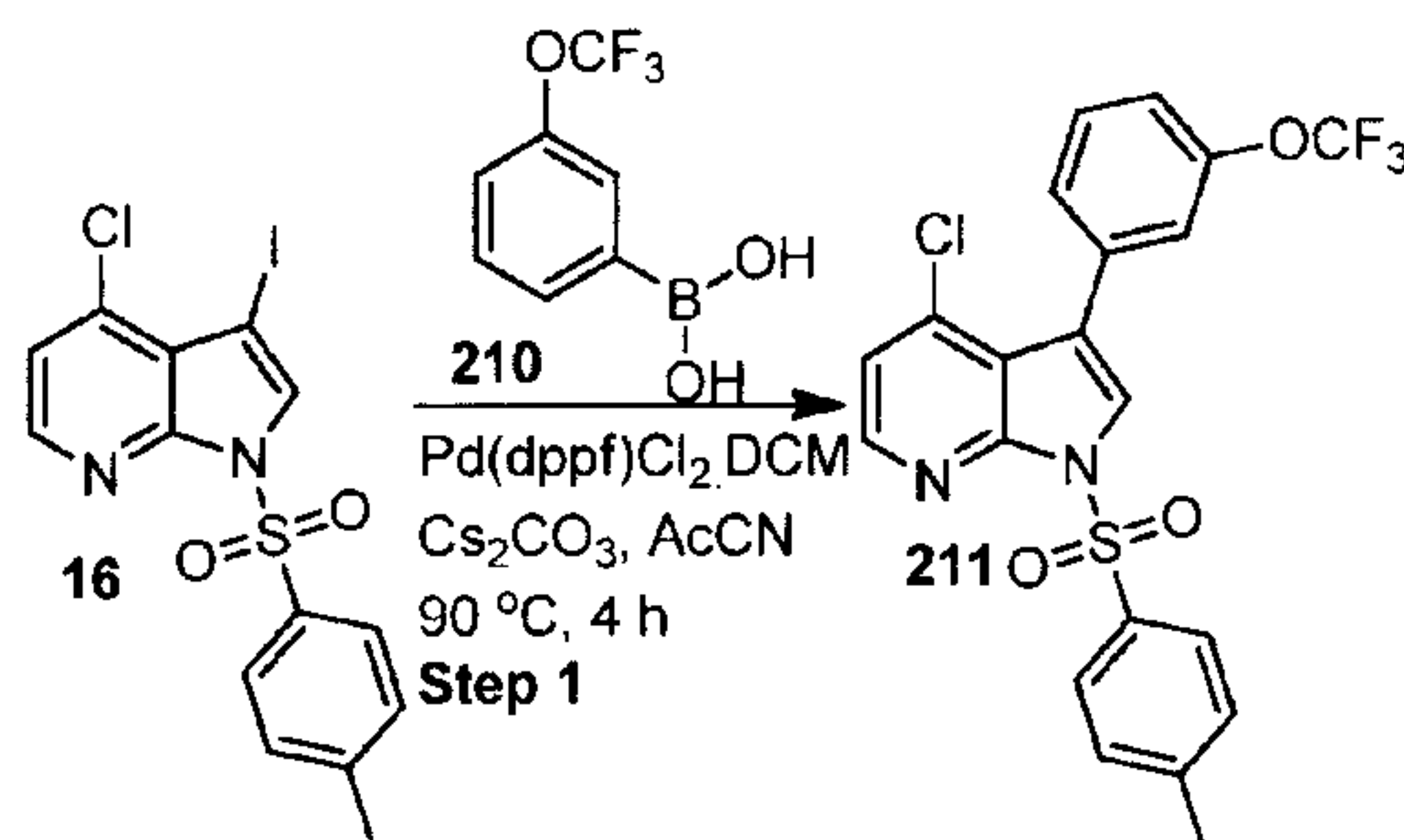
[00236] To a stirred solution of **207** (100mg, 0.193mmol) and **22** (24mg, 0.193mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (126mg, 0.387mmol) and Pd(dppf)Cl<sub>2</sub> (8mg, 0.00968mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **208**.

Step 3:

[00237] To a stirred solution of **208** (50mg, 0.0886mmol) in methanol (10mL) was added water (5mL) and potassium carbonate (36.8mg, 0.265mmol) and the RM heated to 60°C overnight. After completion of the SM, the RM was completely distilled off and diluted with water and extract with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale

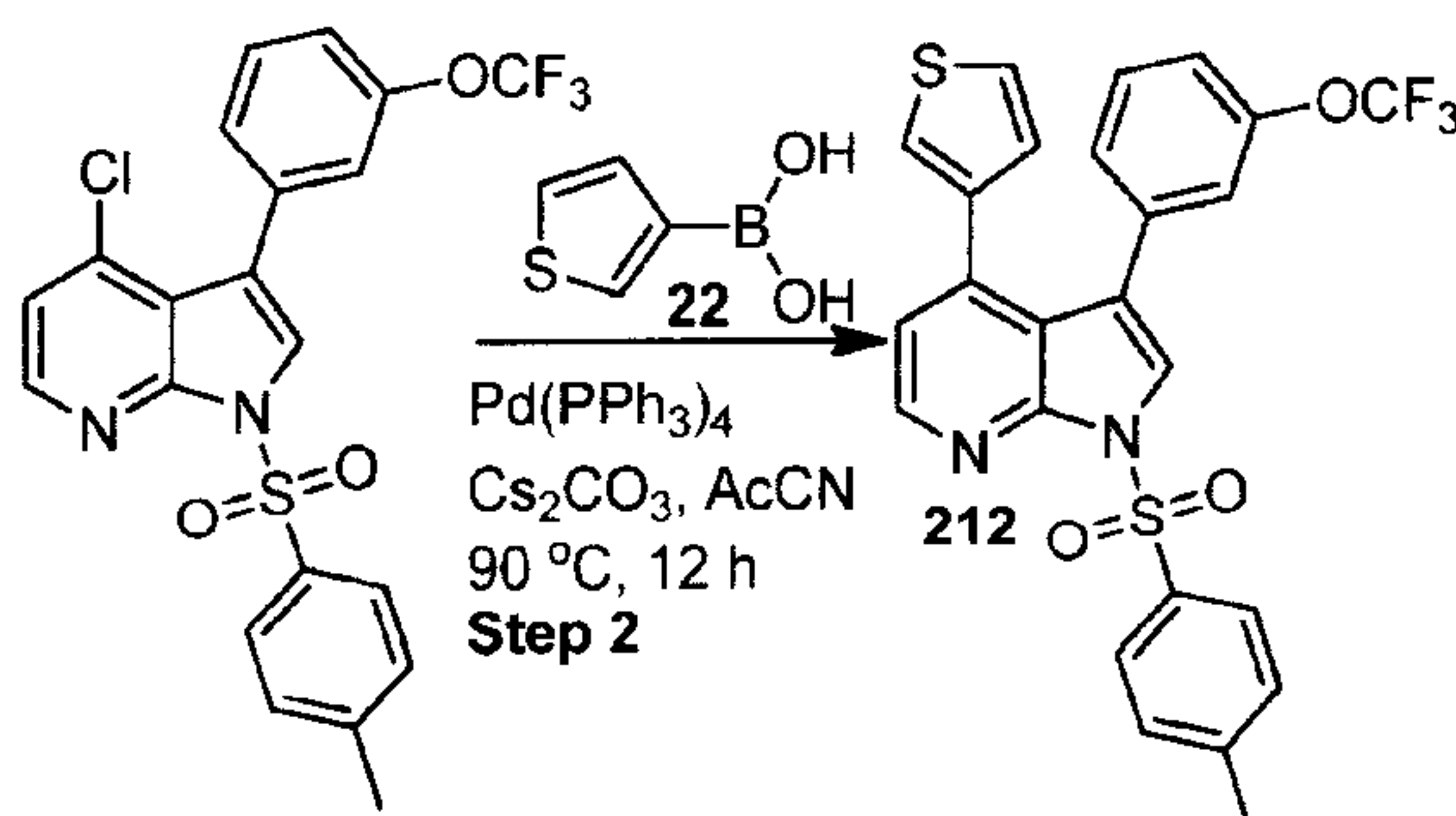
yellow colored solid compound **209**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 9.18 (s, 1H), 8.40 (d,  $J=5.00$  1H), 7.56 (m,  $J=8.29$  2-H), 7.45 (d,  $J=43.93$  1-H), 7.16 (m,  $J=6.46$  3H), 7.08 (m,  $J=3.04$  1-H), 6.91 (m,  $J=4.63$  2-H), 3.25 (m  $J=6.70$  4-H) 1.82 (m  $J=6.58$  4-H) and MS  $m/z = 409.9$  ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 99: 4-(thiophen-3-yl)-3-(2-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-b]pyridine (213):**



#### Step 1:

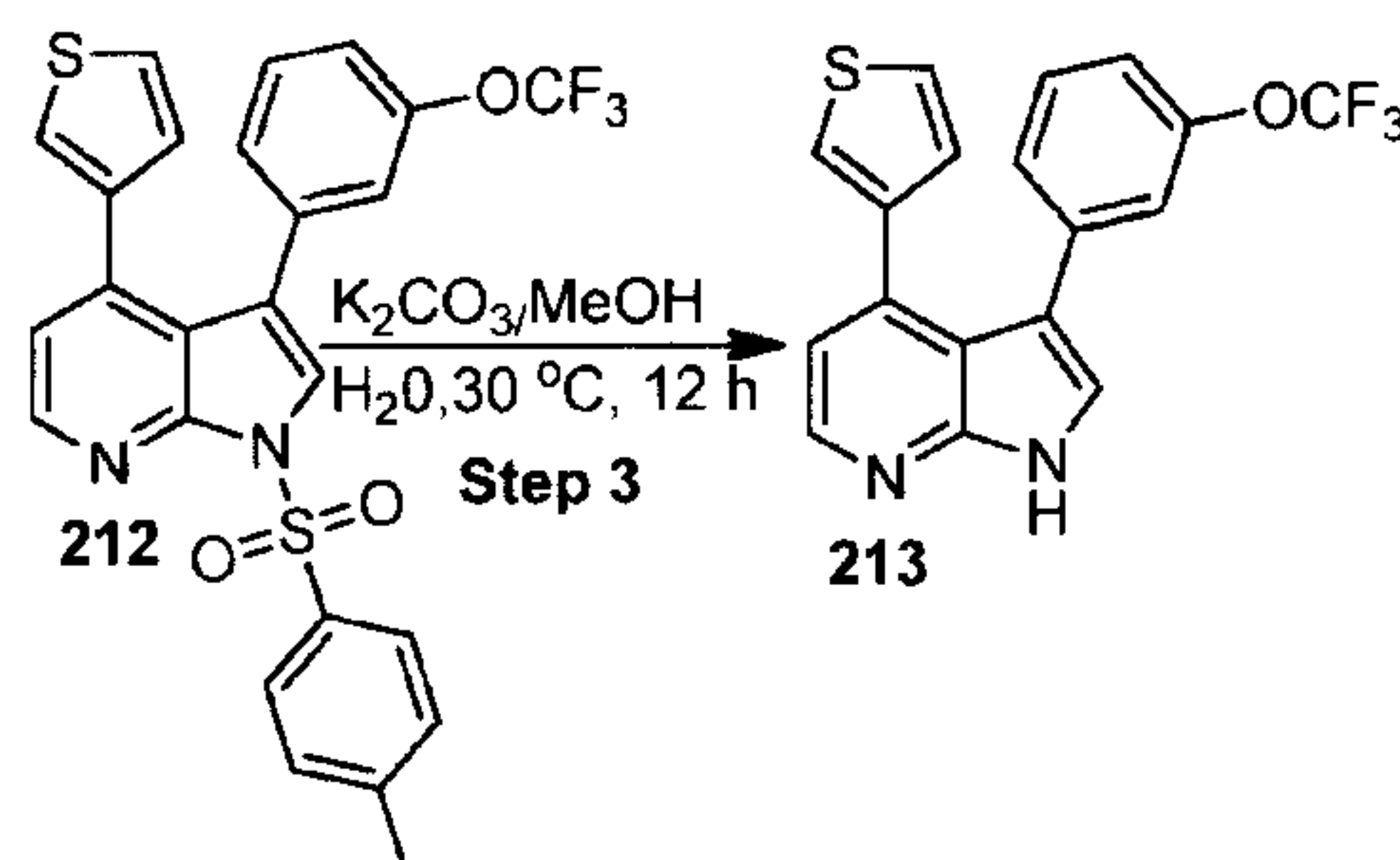
[00238] To a stirred solution of **16** (150mg, 0.347mmol) and **210** (48mg, 0.347mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg, 0.694mmol) and  $\text{Pd(dppf)Cl}_2$  (14mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to  $85^\circ\text{C}$  for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **211**.



#### Step 2:

[00239] To a stirred solution of **211** (100mg, 0.214mmol) and **22** (27.3mg, 0.214mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (174mg, 0.535mmol) and  $\text{Pd(dppf)Cl}_2$  (7mg, 0.0107mmol), again degassed and purged with nitrogen for 15min and the RM heated to  $85^\circ\text{C}$  for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed

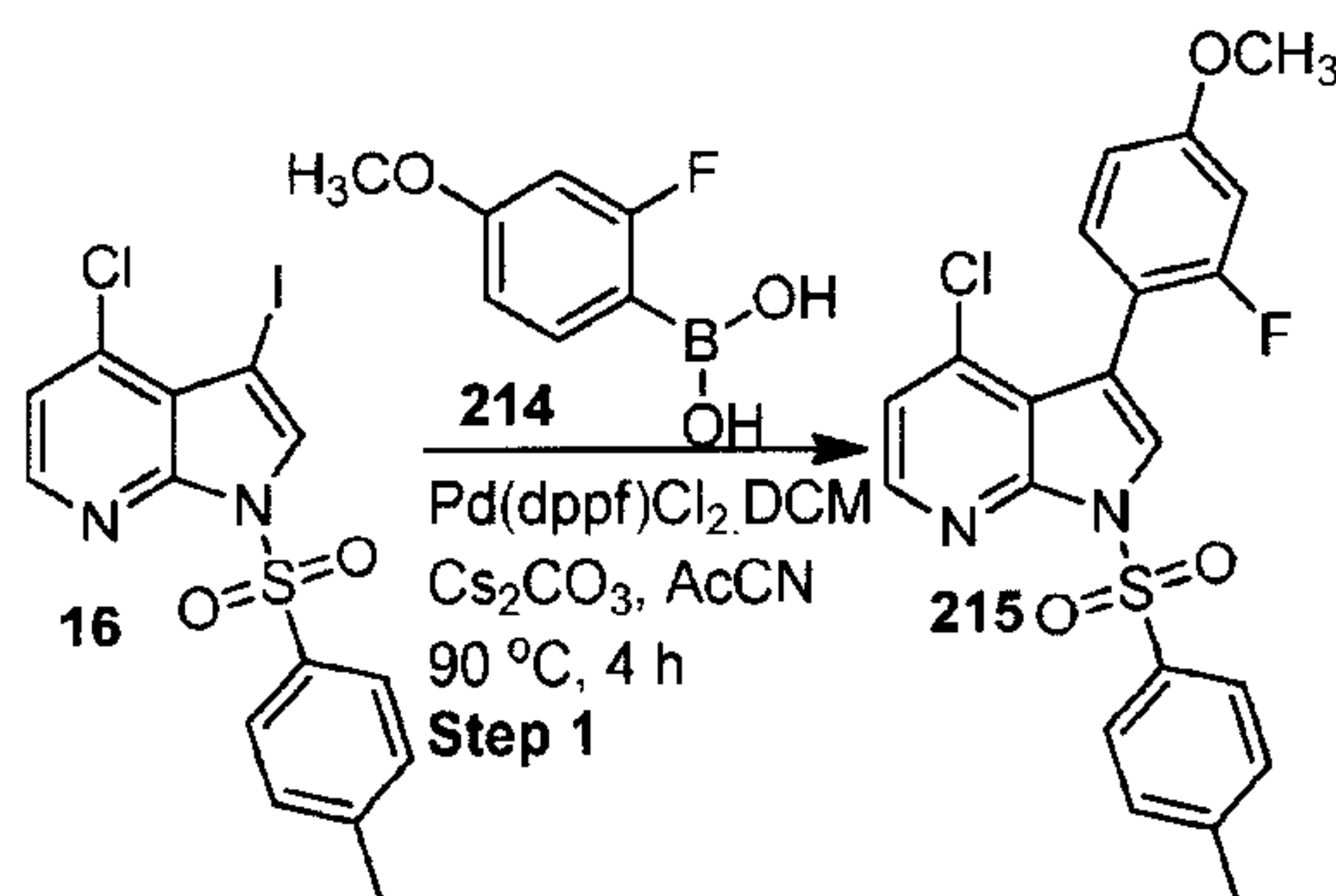
through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid **212**.



#### Step 3:

[00240] To a stirred solution of **212** (50mg, 0.097mmol) in methanol (10mL) was added water (5mL) and potassium carbonate (40mg, 0.291mmol) and the RM heated to 60°C overnight. After completion of the sm the RM was completely distilled off and diluted with water and extract with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **213**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.52 (s, 1-H), 8.37 (d, J=5.00 1-H), 7.44 (s, 1-H), 7.20 (m, J=8.29 1-H), 7.18 (m, J=3.78 2-H), 7.02 (m J=5.00 3-H), 6.89 (m, J=2.92 1-H), 6.85 (m, J=4.87 1-H) and MS m/z = 361.2 (M+H)<sup>+</sup>.

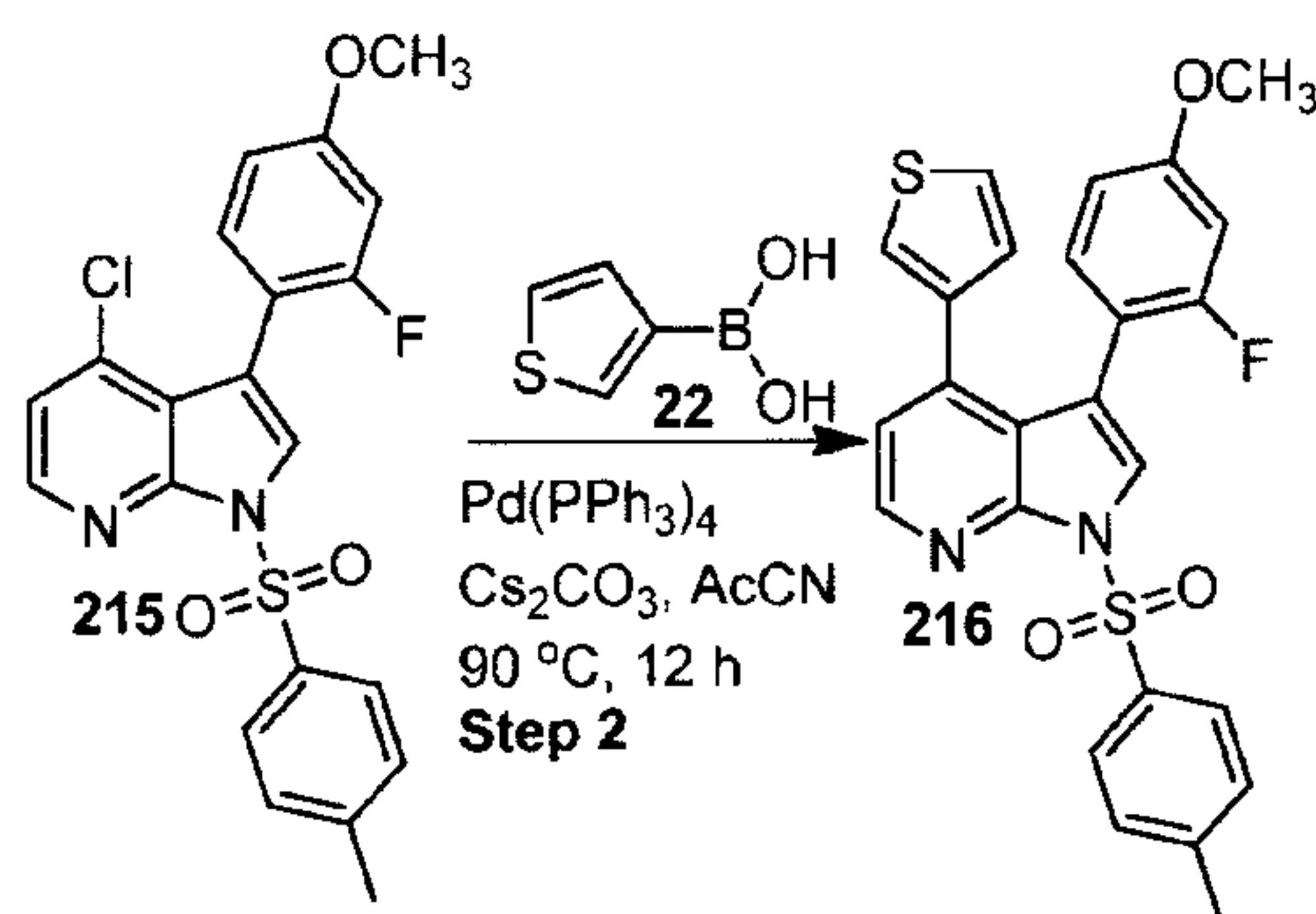
**PREPARATION OF EXAMPLE 100: 3-(2-fluoro-4-(trifluoromethoxy)phenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**217**):**



#### Step 1:

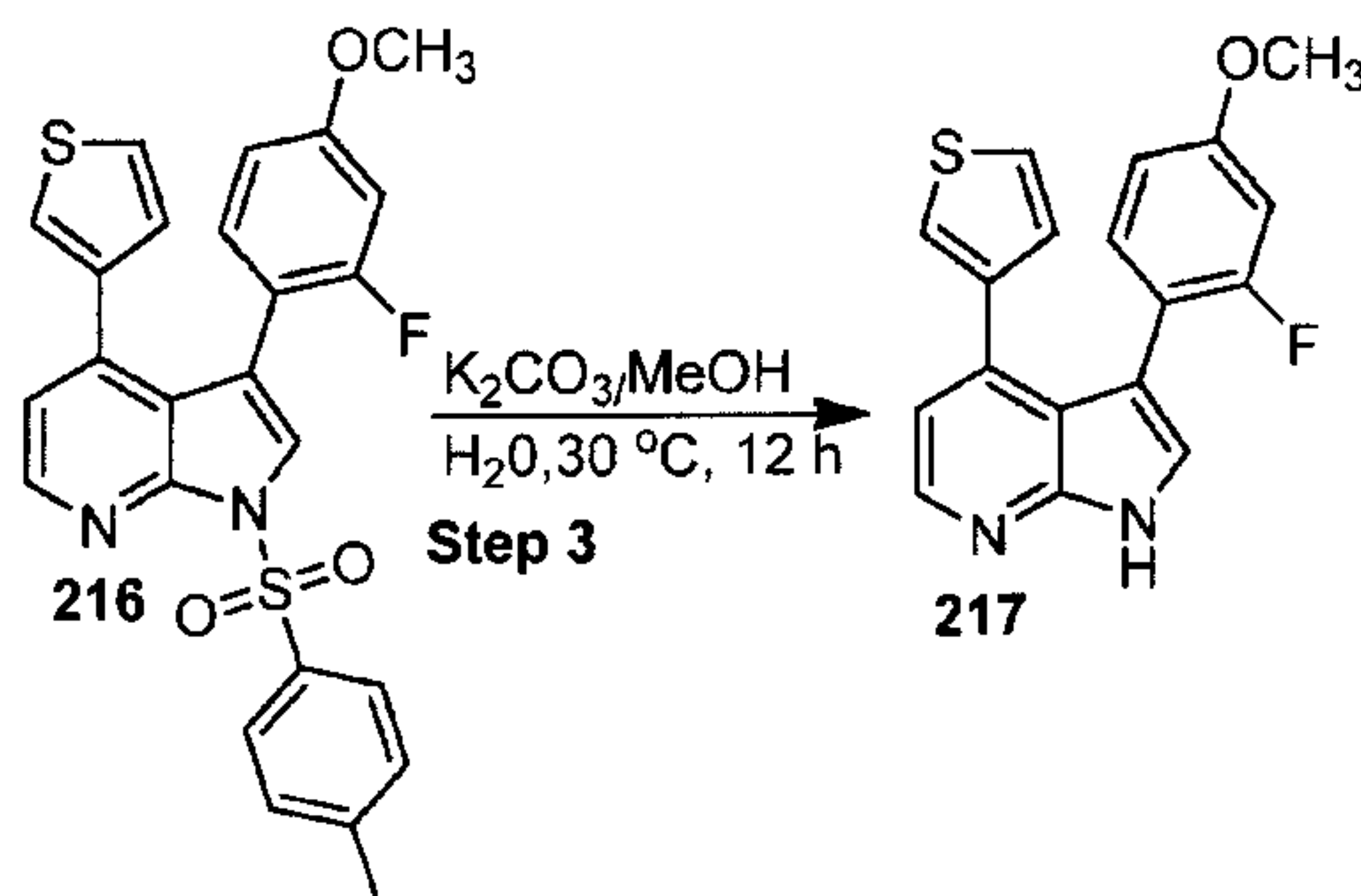
[00241] To a stirred solution of **16** (150mg, 0.347mmol) and **214** (77mg, 0.347mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg, 0.694mmol) and Pd(dppf)Cl<sub>2</sub> (14mg, 0.0176mmol), again degassed and purged with nitrogen for 15min and the RM was heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed

through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **215**.



#### Step 2:

[00242] To a stirred solution of **215** (100mg, 0.206mmol) and **22** (26.4mg, 0.206mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (134mg, 0.412mmol) and Pd(dppf)Cl<sub>2</sub> (6.7mg, 0.0082mmol), again degassed and purged with nitrogen for 15min and the RM was heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude. the crude was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **216**.



#### Step 3:

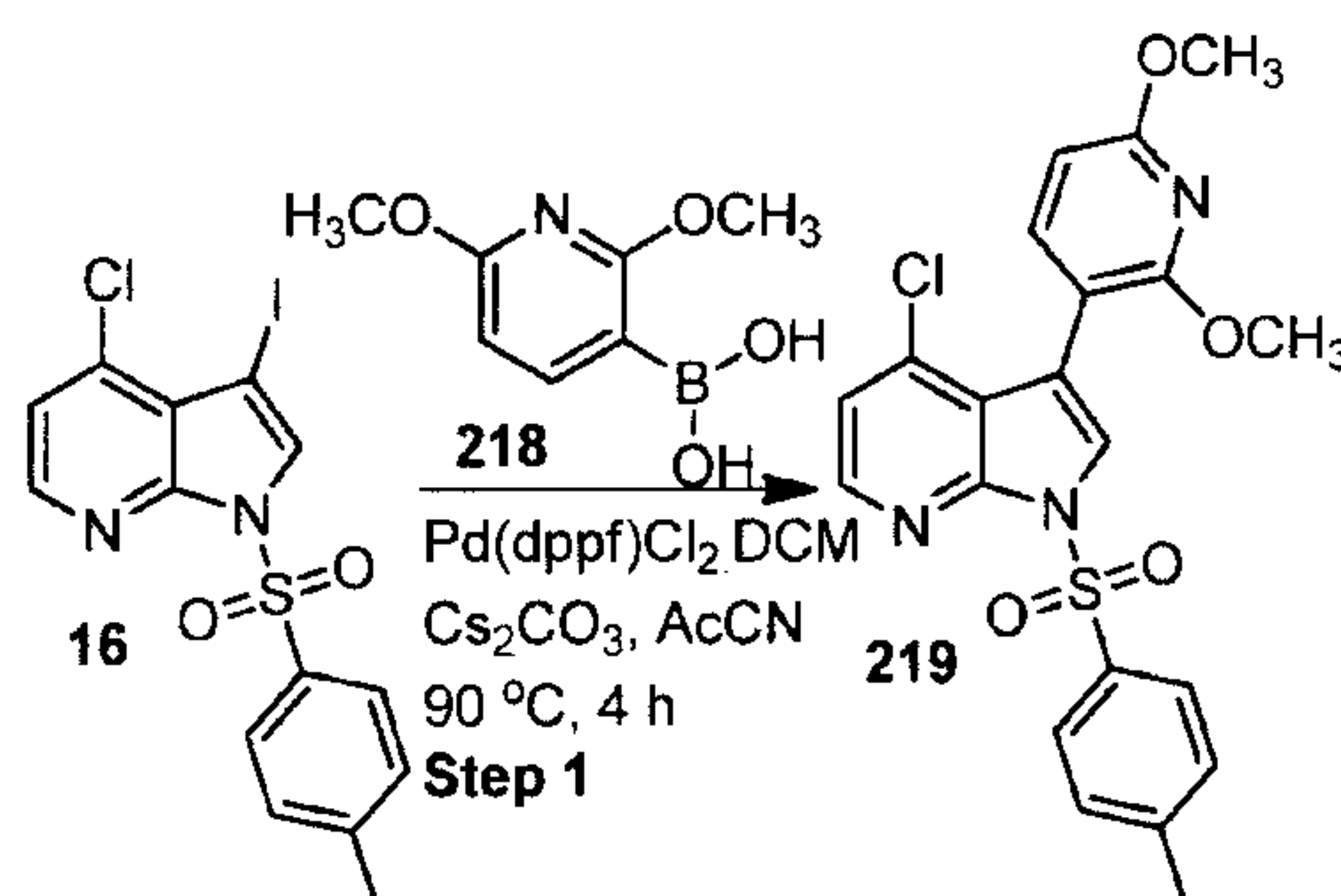
[00243] To a stirred solution of **216** (60mg, 0.112mmol) in methanol (10mL) was added water (5mL) and potassium carbonate (46mg, 0.336mmol) and the RM heated to 60°C overnight. After completion of the SM, the RM was completely distilled off and diluted with water and extract with chloroform twice. the organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **217**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 9.53(s, 1-H), 8.39(d, J=4.87 1-H),

WO 2014/093383

PCT/US2013/074191

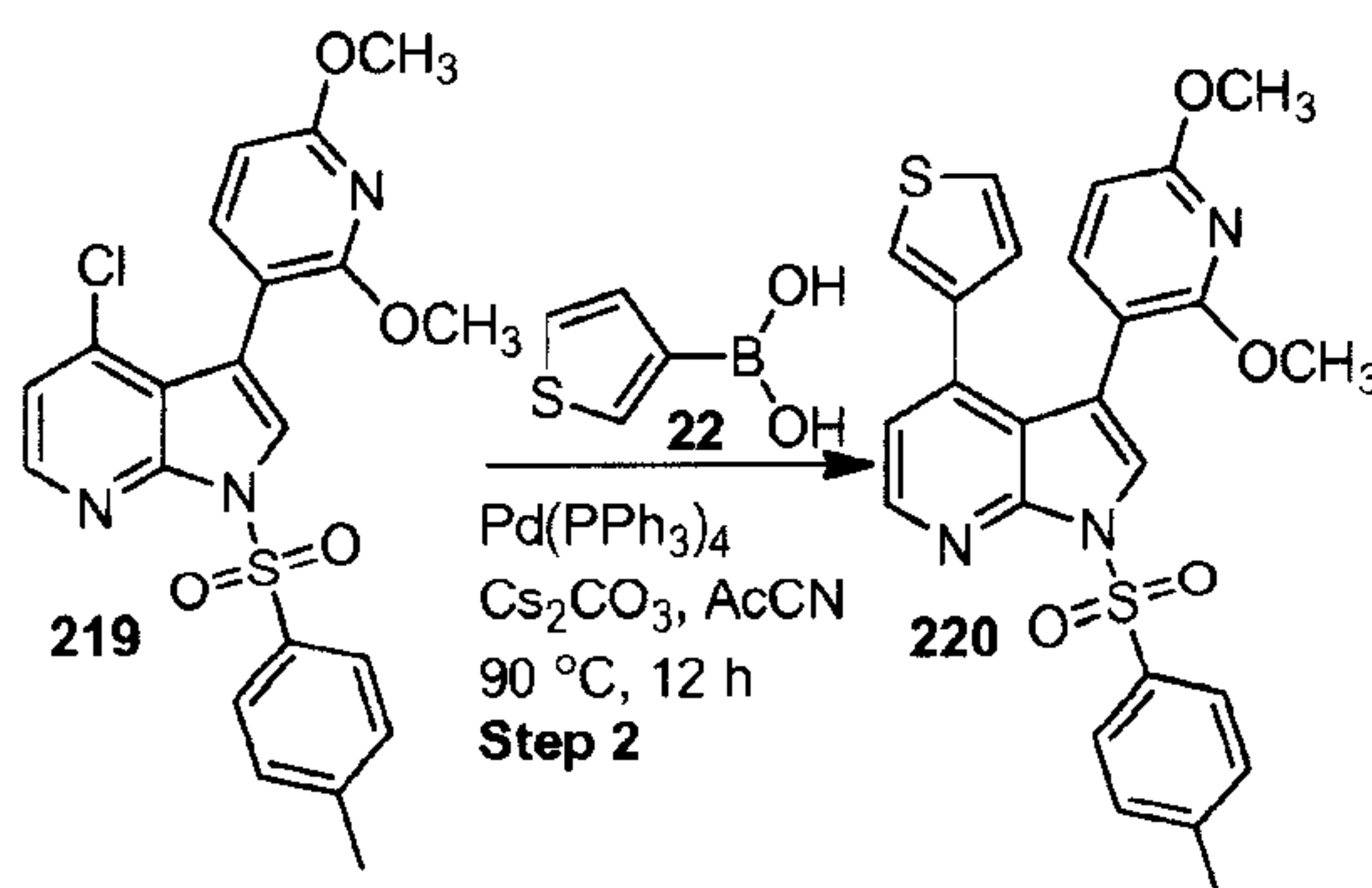
7.44(d, J=2.31 1-H), 7.40(d, J=4.87 1-H), 7.06(m, J=3.04 2-H), 6.97(m, J=7.19 1-H), 6.80(m, J=9.63 3-H) and MS m/z = 378.8 (M+H)<sup>+</sup>.

**PREPARATION OF EXAMPLE 101:** 3-(2,6-dimethoxypyridin-3-yl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**221**):



#### Step 1:

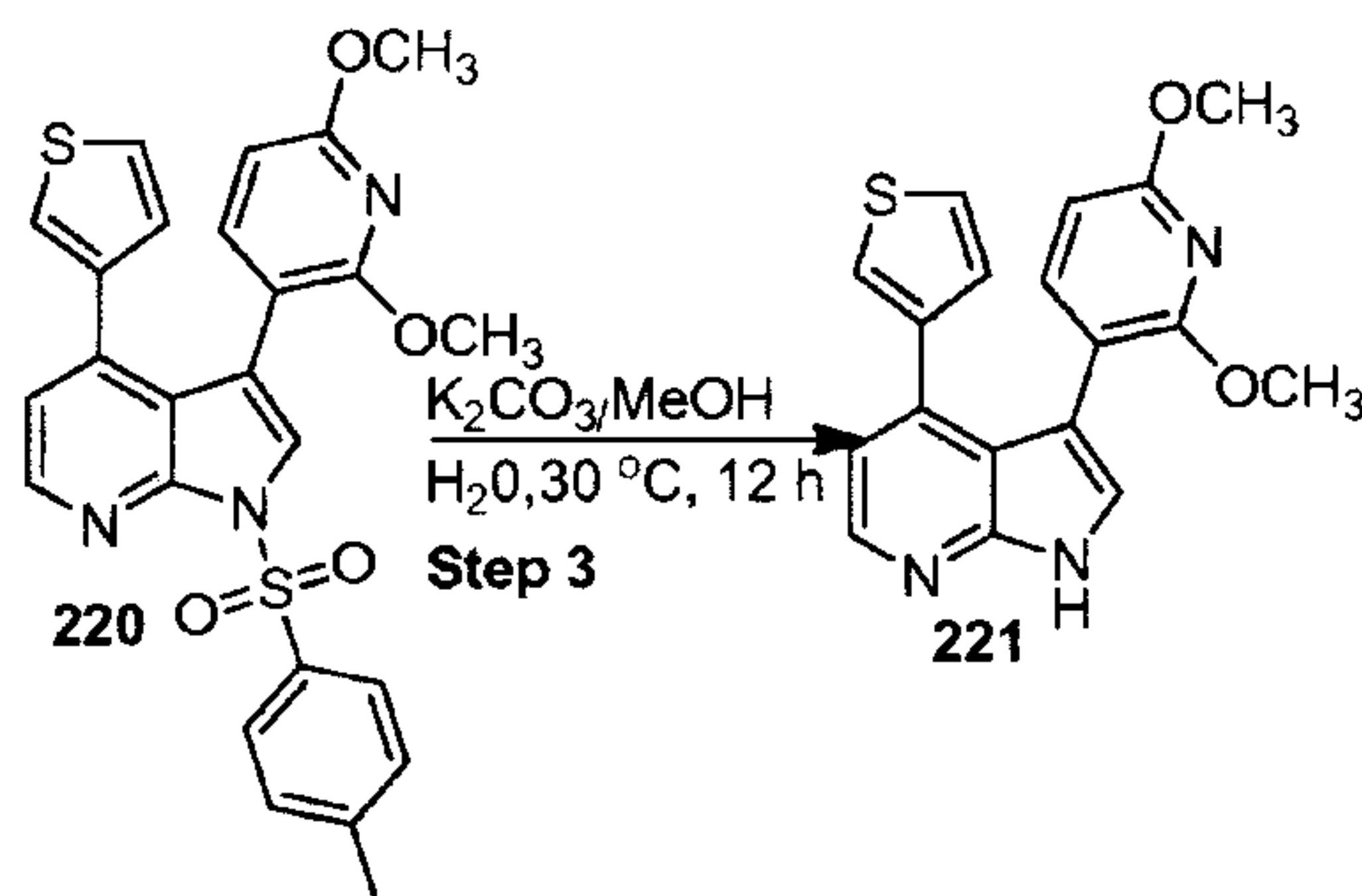
[00244] To a stirred solution of **16** (150mg, 0.347mmol) and **218** (63.5mg, 0.347mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (226mg, 0.694mmol) and Pd(dppf)Cl<sub>2</sub> (14mg, 0.0173mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed .the organic layer was completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pure compound at 5% ethyl aceate in hexane as off white colored solid compound **219**.



#### Step 2:

[00245] To a stirred solution of **219** (100mg, 0.225mmol) and **22** (29mg, 0.225mmol) in acetonitrile (5mL), degassed and purged with nitrogen for 10min, was added cesium carbonate (183mg, 0.563mmol) and Pd(dppf)Cl<sub>2</sub> (7.3mg, 0.00112mmol), again degassed and purged with nitrogen for 15min and the RM heated to 85°C for 4hr in a sealed tube. After completion of the reaction the RM was cooled to rt and diluted with chloroform and filtered through celite bed. The organic layer was completely distilled off to get the crude product, which was passed

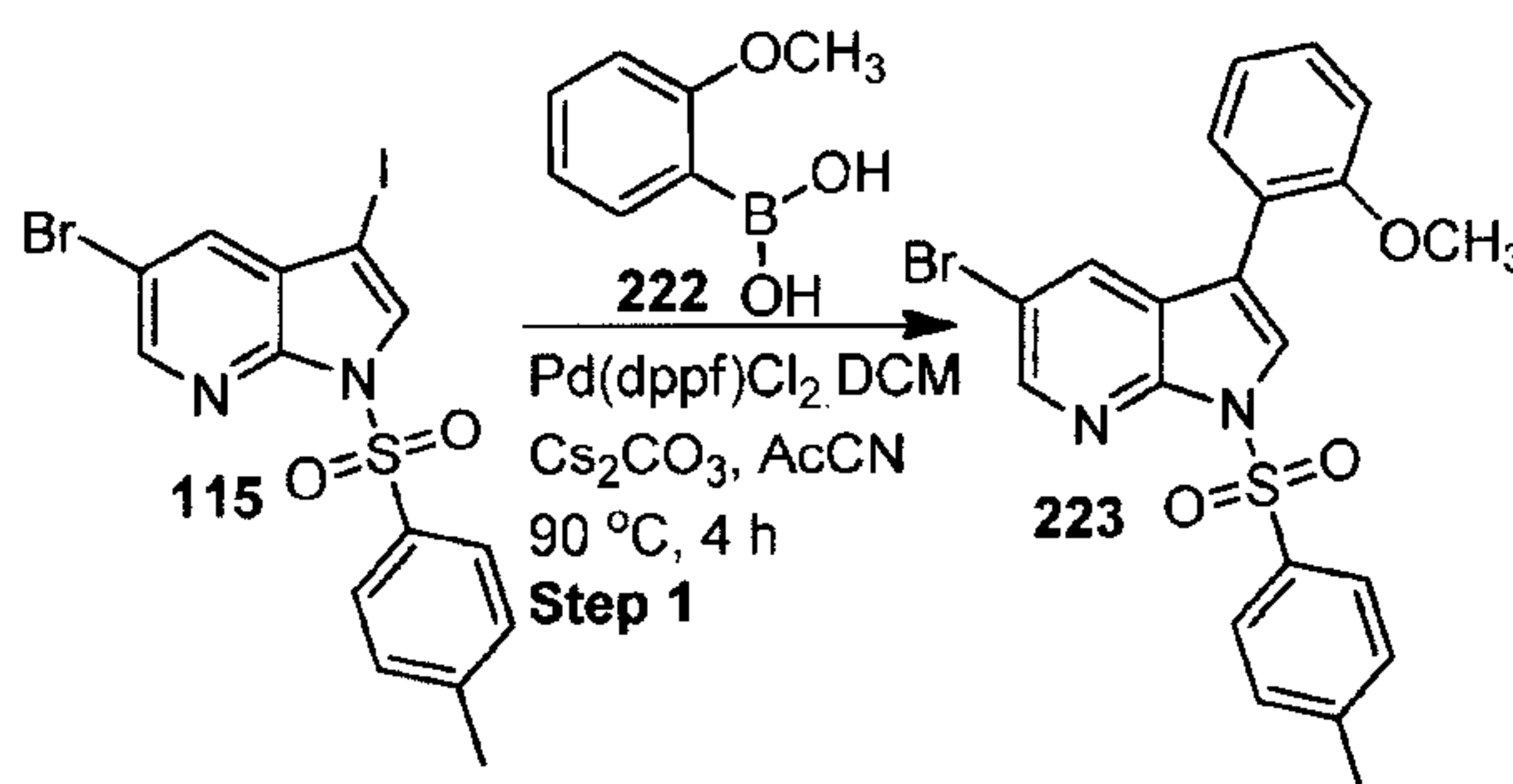
through 100-200 mesh silica gel eluting the pure compound at 5% ethyl acetate in hexane as off white colored solid compound **220**.



#### Step 3:

[00246] To a stirred solution of **220** (50mg, 0.101mmol) in methanol (10mL) was added water (5mL) and potassium carbonate (42mg, 0.305mmol) and the RM heated to 60°C overnight. After completion of the SM, the RM was completely distilled off and diluted with water and extract with chloroform twice. The organic layer was dried over sodium sulphate and completely distilled off to get the crude product, which was passed through 100-200 mesh silica gel eluting the pre compound at 28-30% ethyl acetate in hexane as eluent to get the pale yellow colored solid compound **221**. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ: 9.26 (s, 1-H), 8.34 (d, J=4.75 1-H), 7.33 (m, J=6.21 2-H), 7.10 (m, J=5.00 2-H), 6.91 (m, J=5.48 2-H), 6.22 (d, J=7.92 1-H), 3.88 (s, 3-H), 3.47 (s, 3-H) and MS m/z = 337.8 (M+H)<sup>+</sup>.

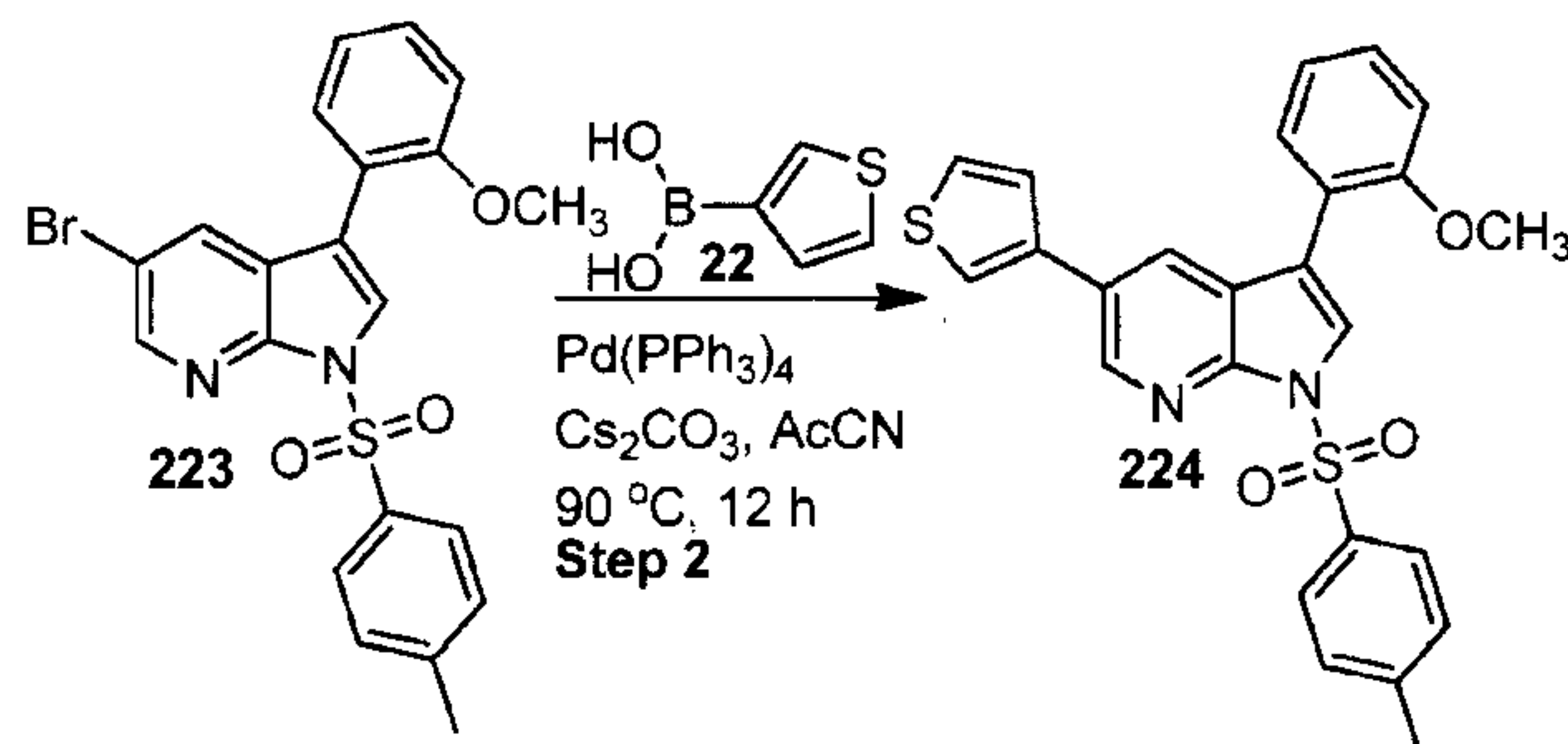
**PREPARATION OF EXAMPLE 113: 3-(2-methoxyphenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (224):**



#### Step 1:

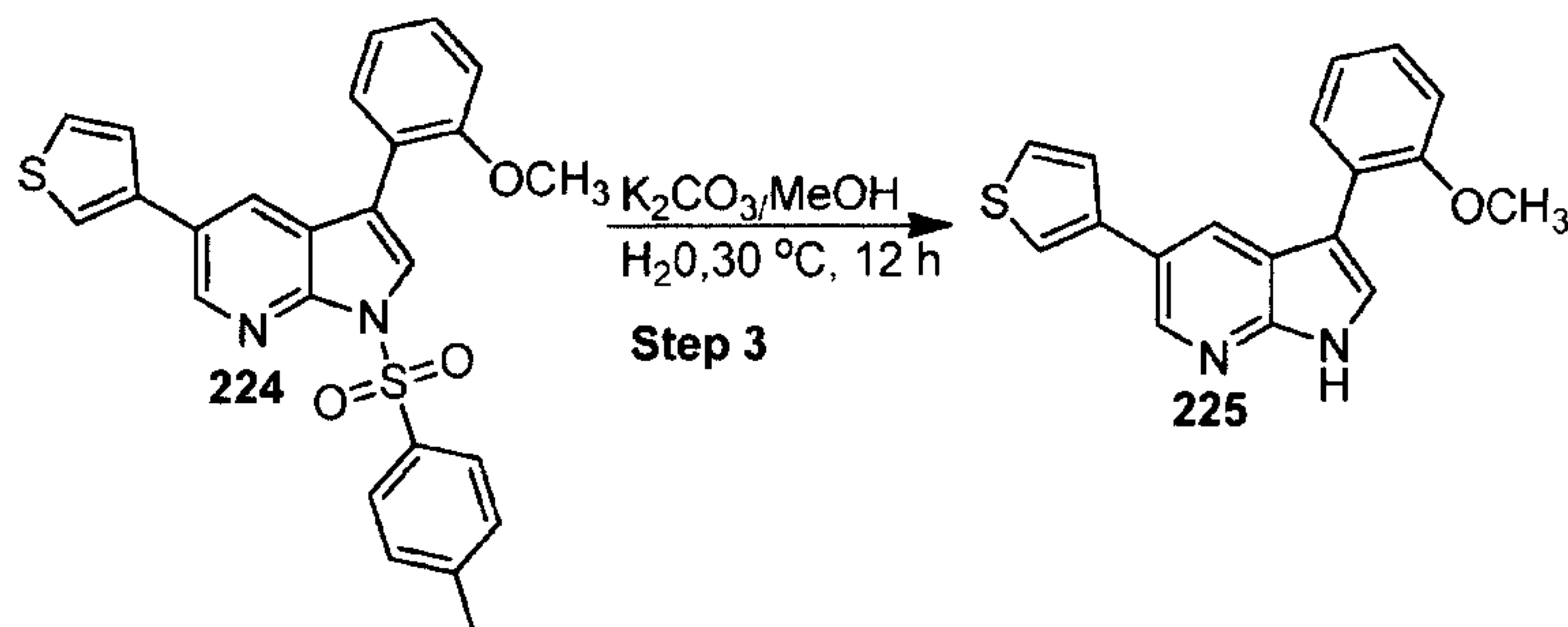
[00247] A solution of **115** (0.150g, 0.315mmol) and **222** (0.048g, 0.315mmol) in acetonitrile (7mL) in a sealed tube was added Cs<sub>2</sub>CO<sub>3</sub> (0.204gm, 0.628mmol) and degassed for 15min. To the resulting RM was added Pd(dppf)Cl<sub>2</sub> DCM (0.012 gm, 0.0157mmol) and degassed again for another 15min and the contents were stirred for 3hr at 90°C. After TLC monitoring, the RM allowed to cool to rt and diluted with DCM (50mL) and filtered through celite and evaporated.

The resulting crude material was purified thorough silica gel chromatography using a gradient of 6% ethyl acetate: hexane to afford the pure compound **223**.



#### Step 2:

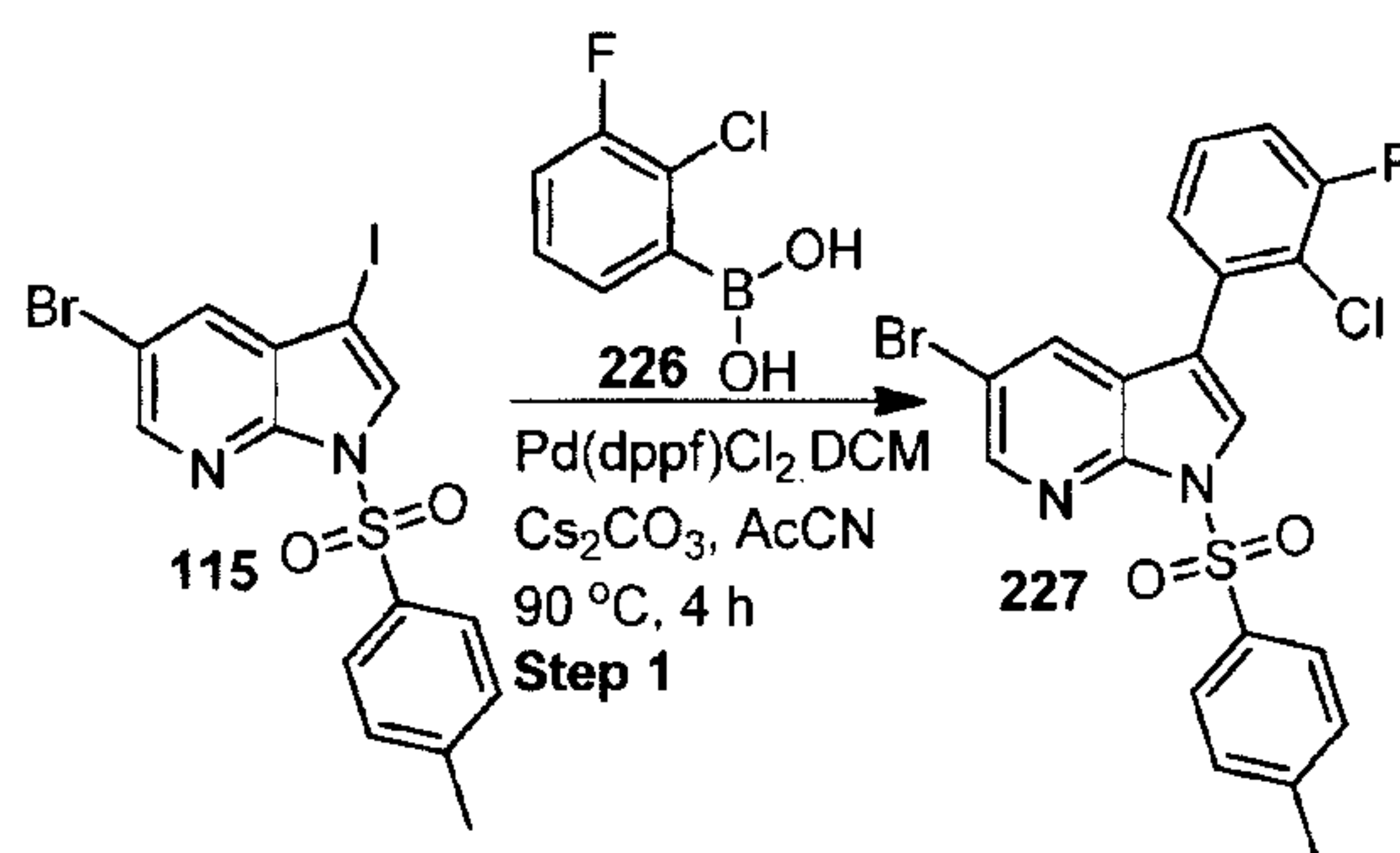
[00248] A solution of **223** (0.1g, 0.219mmol) and **22** (26mg, 0.219mmol) in acetonitrile (7mL) in a sealed tube was added  $\text{Cs}_2\text{CO}_3$  (143mg, 0.438mmol) and degassed for 15min. To the RM was  $\text{Pd(PPh}_3)_4$  (12.6mg, 0.0109mmol) and degassed again for 15min. RM stirred for 3hr at  $90^\circ\text{C}$ . After completion of the reaction, the RM was allowed to cool to rt and diluted with DCM (50mL) and filtered through celite. The resulting crude material was purified through silica gel chromatography using a gradient of 6% ethyl acetate: hexane to afford the compound **224**.



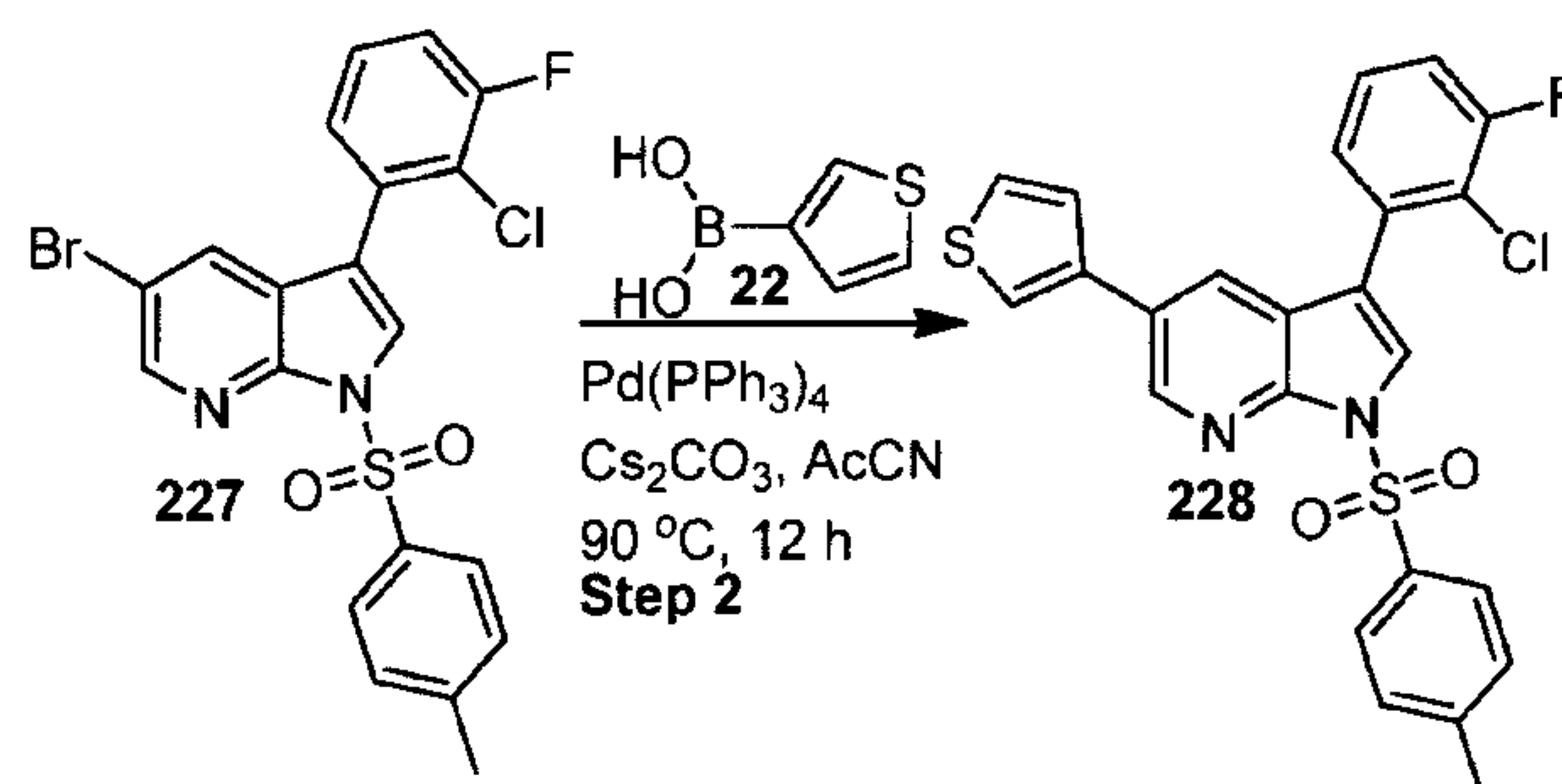
#### Step 3:

[00249] A solution of **224** (0.060g, 0.1247mmol) in  $\text{MeOH}$  (5mL), water (5mL) and  $\text{K}_2\text{CO}_3$  (0.051g, 0.3742mmol) was stirred overnight at  $70^\circ\text{C}$ . After the termination of reaction was allowed to cool and the solvents were removed and diluted with DCM (50mL), extracted and the organic layer washed with water and dried over  $\text{Na}_2\text{SO}_4$  and evaporated. The resulting crude material was purified through silica gel chromatography using a gradient of 25% ethyl acetate: hexane to afford title compound **225**.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.87 (s, 1H), 8.59 (d, 1H), 8.24 (d, 1H), 7.60 (m, 2H), 7.43 (m, 3H), 7.31 (m, 1H), 7.07 (m, 2H), 3.88 (s, 3H),  $\text{MS m/z} = 306.8$  ( $\text{M}+\text{H}$ ) $^+$ .

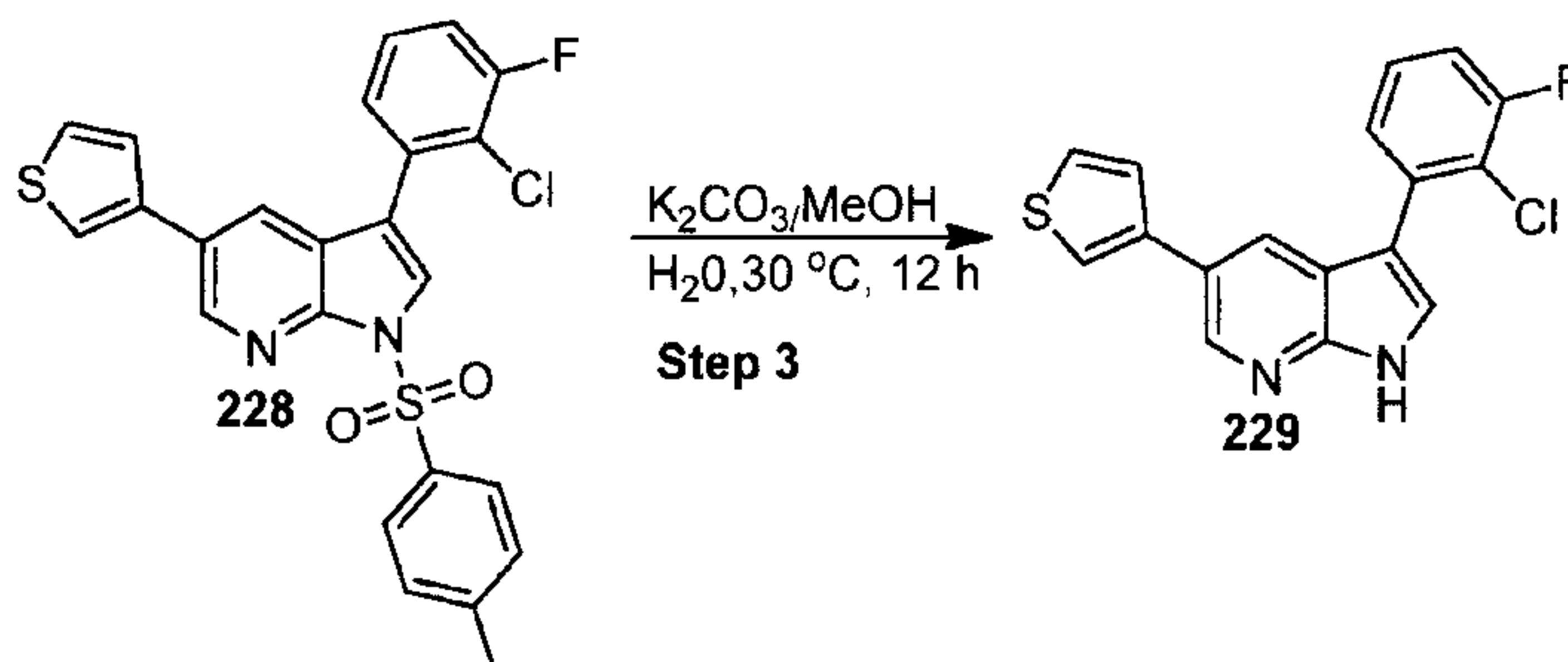
**PREPARATION OF EXAMPLE 114: 3-(2-chloro-3-fluorophenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (**229**):**

Step 1:

[00250] A solution of **115** (0.150g, 0.315mmol) and **226** (0.54.8mg, 0.315mmol) in acetonitrile (7mL) in a sealed tube was added  $\text{Cs}_2\text{CO}_3$  (0.206g, 0.628mmol) and degassed for 15min. To the resulting RM was added  $\text{Pd(dppf)Cl}_2$  DCM (0.012g, 0.0157mmol) and degassed again for another 15min and the contents were stirred for 3hr at  $90^\circ\text{C}$ . After TLC monitoring, the RM allowed to cool to rt and diluted with DCM (50mL) and filtered through celite and evaporated. The resulting crude material was purified thorough silica gel chromatography using a gradient of 6% ethyl acetate: hexane to afford the pure compound **227**.

Step 2:

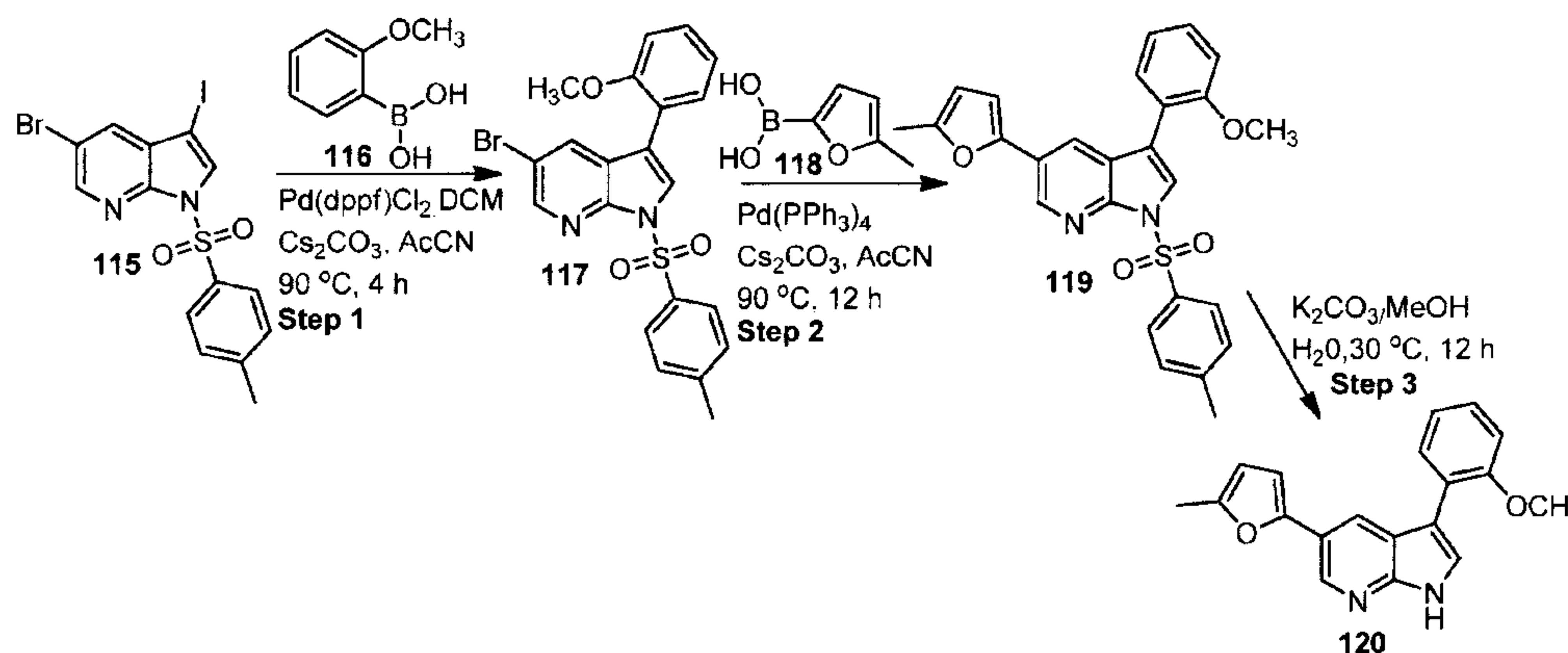
[00251] A solution of **227** (0.1g, 0.219mmol) and **22** (26.7mg, 0.209mmol) in acetonitrile (7mL) in a sealed tube was added  $\text{Cs}_2\text{CO}_3$  (137mg, 0.418mmol) and degassed for 15min. To the RM was  $\text{Pd(PPh}_3)_4$  (12mg, 0.0104mmol) and degassed again for 1 min. RM stirred for 3hr at  $90^\circ\text{C}$ . After completion of the reaction was allowed to cool to rt and diluted with DCM (50mL) and filtered through celite. The resulting crude material was purified through silica gel chromatography using a gradient of 6% ethyl acetate: hexane to afford the compound **228**.



Step 3:

[00252] A solution of **228** (0.060g, 0.1247mmol) in MeOH (5mL), water (5mL) and K<sub>2</sub>CO<sub>3</sub> (0.051g, 0.3742mmol) was stirred overnight at 70°C. After the termination of reaction was allowed to cool and the solvents were removed and diluted with DCM (50mL) extracted and the organic layer washed with water and dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The resulting crude material was purified through silica gel chromatography using a gradient of 25% ethyl acetate: hexane to afford title compound **229**. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ: <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): 9.41 (s, 1H), 8.65 (s, 1H), 8.11 (s, 1H), 7.60 (d, 1H), 7.44 (m, 3H), 7.34 (m, 2H), 7.18 (m, 1H), MS m/z = 328.8 (M+H)<sup>+</sup>.

**PREPARATION OF EXAMPLE 115: 3-(2-methoxyphenyl)-5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-*b*]pyridine (119)**

Step 1:

[00253] A solution of **115** (150mg, 0.314mmol) and **116** (47mg, 0.314mmol) in acetonitrile (7mL) was taken into a sealed tube, Cs<sub>2</sub>CO<sub>3</sub> (204mg, 0.628mmol) added, and degassed for 15min. To the RM was added Pd(dppf)Cl<sub>2</sub> DCM (0.012 g, 0.01572mmol) and degassed again for 15min, and stirred for 4hr at 90°C. After 2hr, the TLC confirmed the reaction and the RM allowed to cool to rt. The crude material was taken in to DCM (100mL) and filtered through celite. The resulting crude material was purified via silica gel chromatography using a gradient of 5% ethyl acetate: hexane to afford compound **117**.

Step 2:

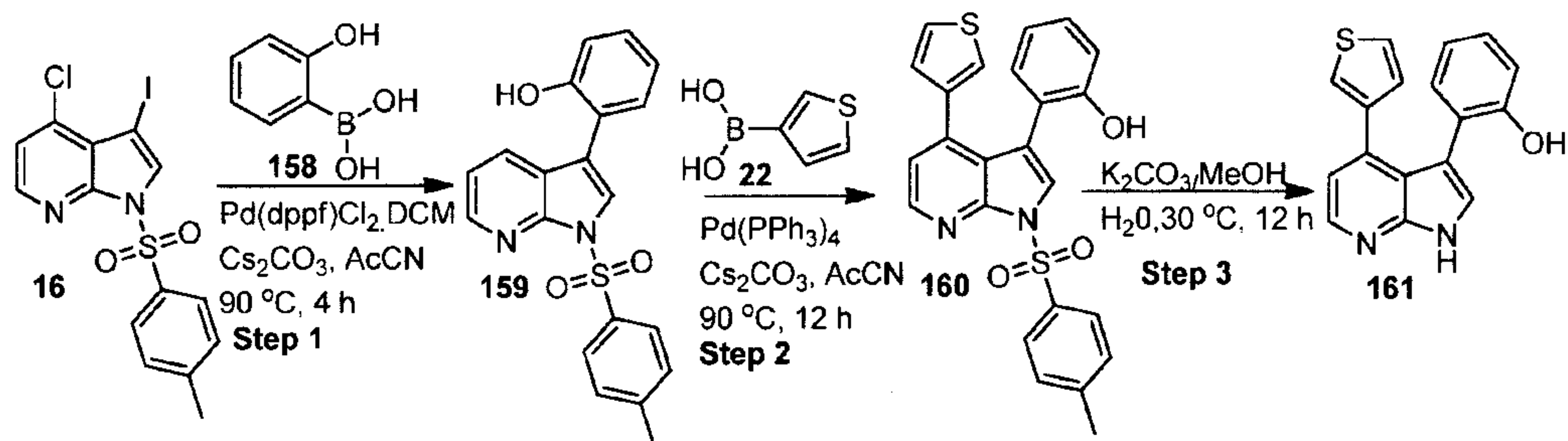
[00254] A solution of **117** (0.075g, 0.164mmol) and **118** (0.034g, 0.1641mmol) in 5mL acetonitrile in a sealed tube was added Cs<sub>2</sub>CO<sub>3</sub> (0.04 g, 0.628mmol), and degassed for 15min in presence of Pd(PPh<sub>3</sub>)<sub>4</sub>. The resulting RM was stirred overnight at 90°C, allowed to cool to rt and taken in to DCM (100mL) and filtered through celite. The resulting oil was purified via

silica gel chromatography using a gradient of 10% ethyl acetate: hexane to afford compound **119**.

**Step 3:**

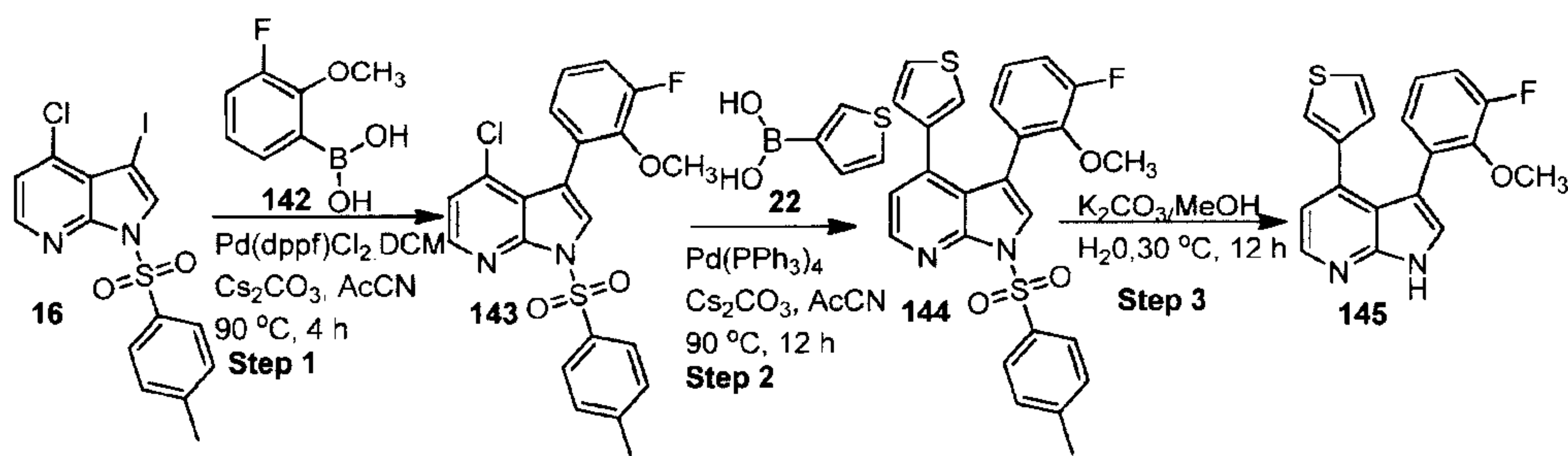
[00255] To a solution of **119** (0.070g, 0.1528mmol) in MeOH (5mL) and H<sub>2</sub>O (5mL) was added K<sub>2</sub>CO<sub>3</sub> and the RM stirred overnight at 70°C. The resulting RM was allowed to cool and evaporated completely and extracted in to DCM (50mL) followed by water wash for two times. Organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated. The crude product was purified by silica gel chromatography using a gradient of 25% ethyl acetate: hexane to afford compound **120**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ : 8.95 (s, 1H), 8.64 (s, 1H), 8.28 (d, 1H), 7.61 (m, 2H), 7.33 (m, 1H), 7.12 (m, 2H), 6.53 (d, 1H), 6.06 (d, 1H), 3.88 (s, 3H), 2.38 (s, 3H). MS m/z 304.91 [M+H]<sup>+</sup>.

**PREPARATION OF EXAMPLE 118: 2-(4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol (161) :**



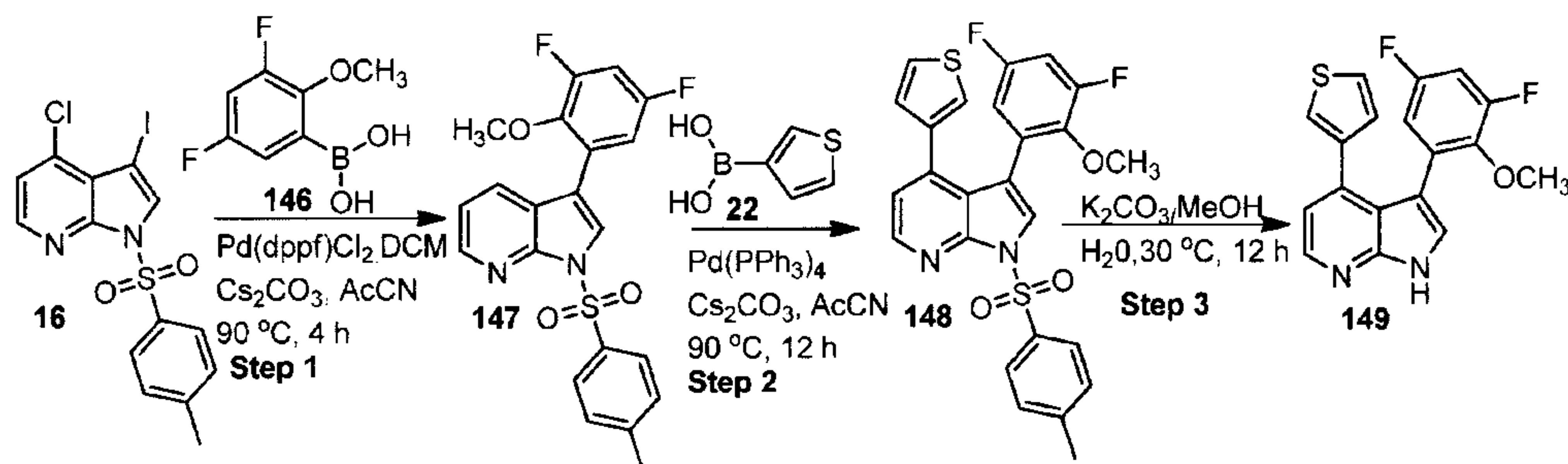
[00256] Compound 161: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 9.41 (bs, 1H), 8.26 (bs, 1H), 7.67 (m, 2H), 7.52 (m, 4H), 7.32 (m, 2H), 7.01 (m, 1H), 6.96 (m, 2H), MS m/z ESI: 278.8 (M+H)<sup>+</sup>.

**PREPARATION OF EXAMPLE 120: 3-(3-fluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (145)**



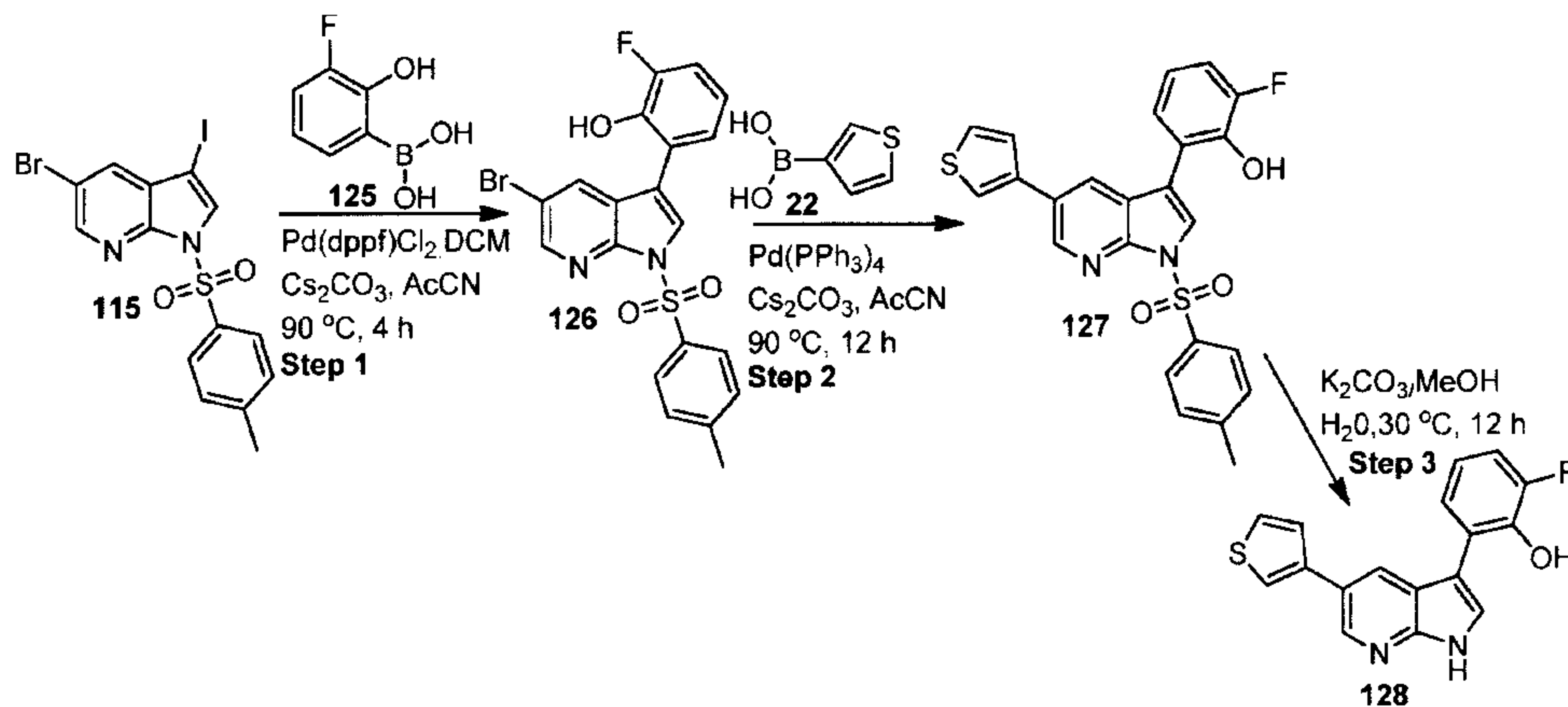
[00257] Compound 145: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 9.43 (1s, 1H), 8.37 (d, 1H), 8.36 (m, 1H), 7.15 (d, 1H), 7.14 (m, 1H), 6.94 (m, 3H), 6.93 (m, 2H), 3.53 (s, 3H), MS m/z: 324.0 (M+H)<sup>+</sup>.

**PREPARATION OF EXAMPLE 121: 3-(3,5-difluoro-2-methoxyphenyl)-4-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (149)**



[00258] Compound 149: <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ: 9.8 (b, 1H), 8.39 (d, 1H), 7.48 (s, 1H) 7.15 (m, 2H) 7.0 (m, 1H), 6.7 (m, 1H), 6.7 (m, 1H), 6.43 (m, 1H), 3.52 (m, 3H), MS m/z ESI: +342.9 (M+H)<sup>+</sup>.

**PREPARATION OF EXAMPLE 122: 2-fluoro-6-(5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol (128)**



Step 1:

[00259] A solution of **115** (150mg, 0.314mmol.) and **121** (49mg, 0.3144mmol) was dissolved in acetonitrile (10mL) in a sealed tube and was charged with Cs<sub>2</sub>CO<sub>3</sub> (204mg, 0.628mmol). The resulting RM was degassed for 15min. To this RM was added Pd(dppf)Cl<sub>2</sub>·DCM (12mg, 0.0157mmol) and degassed again for 15min. RM was stirred for 4hr at 90°C. After 4hr and TLC monitoring confirms the consumption of SM, the RM was cooled to rt and diluted with DCM (100mL) and filtered through celite. The resulting crude material was purified through silica gel chromatography using a gradient of 5% ethyl acetate in hexane afforded the compound **122**.

Step 2:

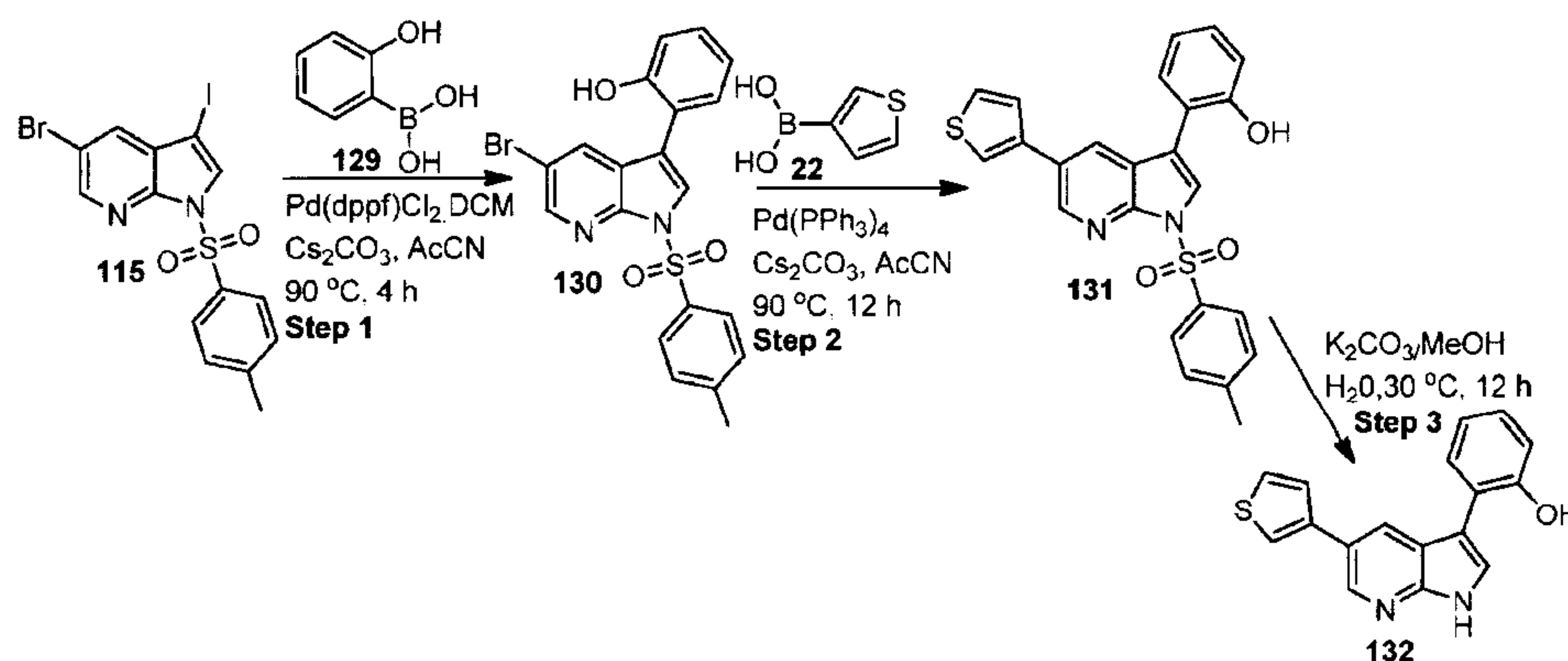
[00260] A solution of **122** (125mg, 0.271mmol) and **22** (34mg, 0.27mmol) was dissolved in acetonitrile (5mL) in a sealed tube. To this RM was added  $\text{Cs}_2\text{CO}_3$  (176mg, 0.542mmol) and subjected to degassing for 15min. The catalyst  $\text{Pd}(\text{PPh}_3)_4$  (15mg, 0.0135mmol) was added and degassed again for 15min. The resulting RM was stirred overnight at 90°C. After TLC with the  $R_f$  changes from the SM confirmed the completion of the reaction, the contents were cooled to rt and diluted with DCM (100mL) and filtered through celite. The resulting crude material was purified from silica gel chromatography using a gradient of 10% ethyl acetate: hexane to afford compound **123**.

#### Step 3:

[00261] Compound **123** (50mg, 0.105mmol) in MeOH (10mL) and  $\text{H}_2\text{O}$  (5mL) was added  $\text{K}_2\text{CO}_3$  (36mg, 0.262mmol) and the RM was stirred overnight at 70°C. After completion of the reaction from TLC, the solvent MeOH was evaporated completely and the crude material was diluted with DCM (50mL) followed by water wash for two times and the organic layer was dried with  $\text{Na}_2\text{SO}_4$  and evaporated. The resulting crude compound was purified from silica gel chromatography using a gradient of 25% ethyl acetate: hexane to afford the compound **128**.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ) : 10.24 (s, 1H), 8.55 (s, 1H), 8.33 (d, 1H), 7.67 (s, 1H), 7.43 (m, 3H), 7.1(d, 1H), 7.09 (m, 1H), 6.96 (m, 1H), 5.34 (s, 1H), MS  $m/z$ : 310.8 ( $\text{M}+\text{H}$ ) $^+$ .

#### PREPARATION OF EXAMPLE 123: 2-(5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol (**132**):



#### Step 1:

[00262] A solution of **115** (150mg, 0.314mmol.) and **129** (43mg, 0.314mmol) was dissolved in acetonitrile (10mL) in a sealed tube and charged with  $\text{Cs}_2\text{CO}_3$  (204mg, 0.628mmol). The resulting RM was degassed for 15min. To this RM was added  $\text{Pd}(\text{dppf})\text{Cl}_2$  DCM (12mg, 0.0157mmol) and degassed again for 15min. RM was stirred for 4hr at 90°C. After 4hr and TLC monitoring confirmed the consumption of SM, the contents of reaction was cooled to rt

and diluted with DCM (100mL) and filtered through celite. The resulting crude material was purified through silica gel chromatography using a gradient of 5% ethyl acetate in hexane to afford the compound **130**.

Step 2:

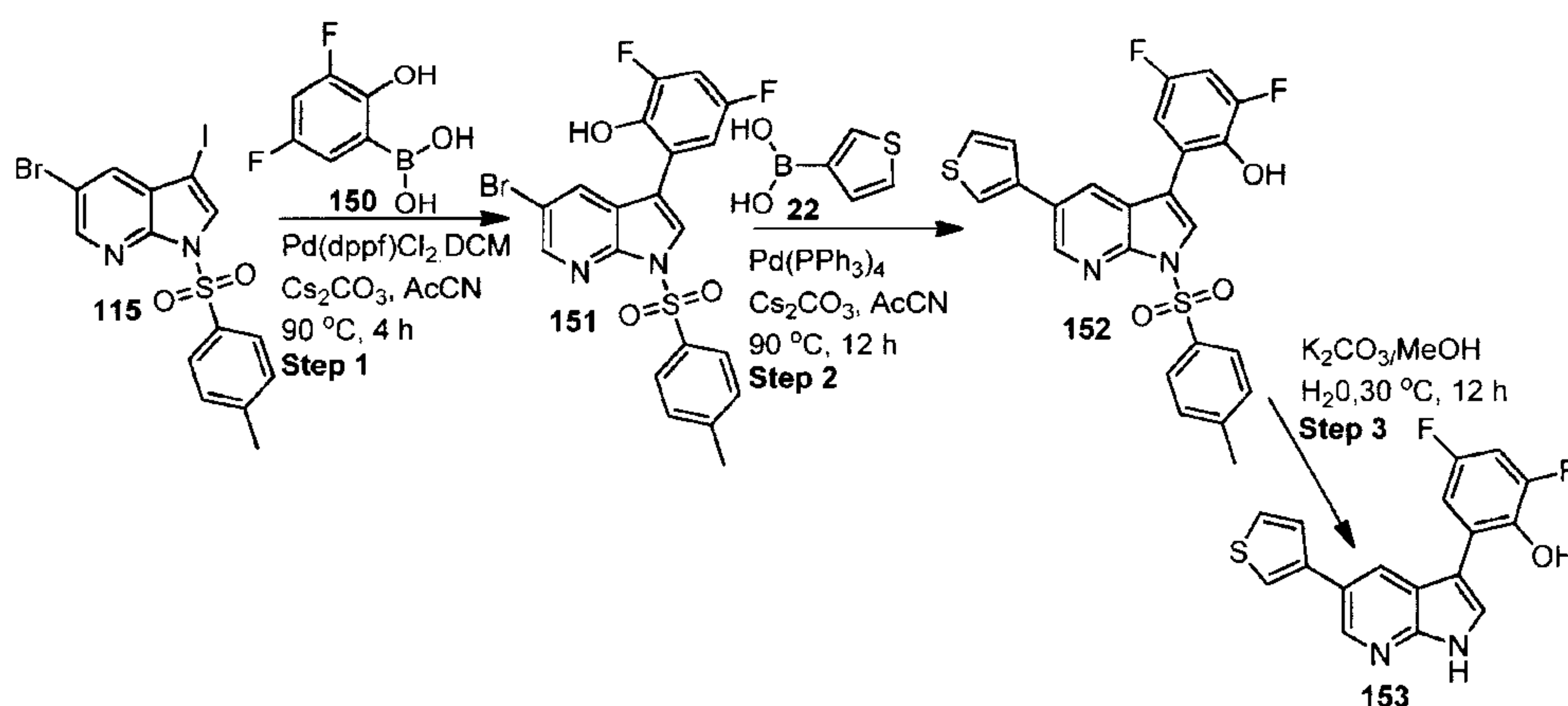
[00263] A solution of **130** (100mg, 0.25mmol) and **22** (34mg, 0.27mmol) was dissolved in acetonitrile (5mL) in a sealed tube. To this RM was added  $\text{Cs}_2\text{CO}_3$  (147mg, 0.542mmol) and degassed for 15min. The catalyst  $\text{Pd}(\text{PPh}_3)_4$  (13mg, 0.0122mmol) was added and degassed again for 15min. The resulting RM was stirred overnight at 90°C. After TLC with the Rf changes from the SM confirmed the completion of the reaction, the contents were cooled to rt and diluted with DCM (100mL) and filtered through celite. The resulting crude material was purified from silica gel chromatography using a gradient of 10% ethyl acetate: hexane to afford compound **131**.

Step 3:

[00264] Compound **131** (60mg, 0.131mmol) in MeOH (10mL) and  $\text{H}_2\text{O}$  (5mL) was added  $\text{K}_2\text{CO}_3$  (45mg, 0.38mmol) and the RM was stirred overnight at 70°C. After completion of the reaction from TLC, the solvent MeOH was evaporated completely and the crude material was diluted with DCM (50mL) followed by water wash for two times and the organic layer was dried with  $\text{Na}_2\text{SO}_4$  and evaporated. The resulting crude compound was purified from silica gel chromatography using a gradient of 25% ethyl acetate: hexane to afford the compound **132**.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 11.80 (s, 1H), 9.53 (s, 1H), 8.62(d, 1H), 8.30(d, 1H), 7.87(m, 1H), 7.74(d, 2H), 7.6(m, 3H), 7.13(m, 1H), 6.93(m, 2H). MS m/z: 292.7 ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 124: 2,4-difluoro-6-(5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol (**153**)**

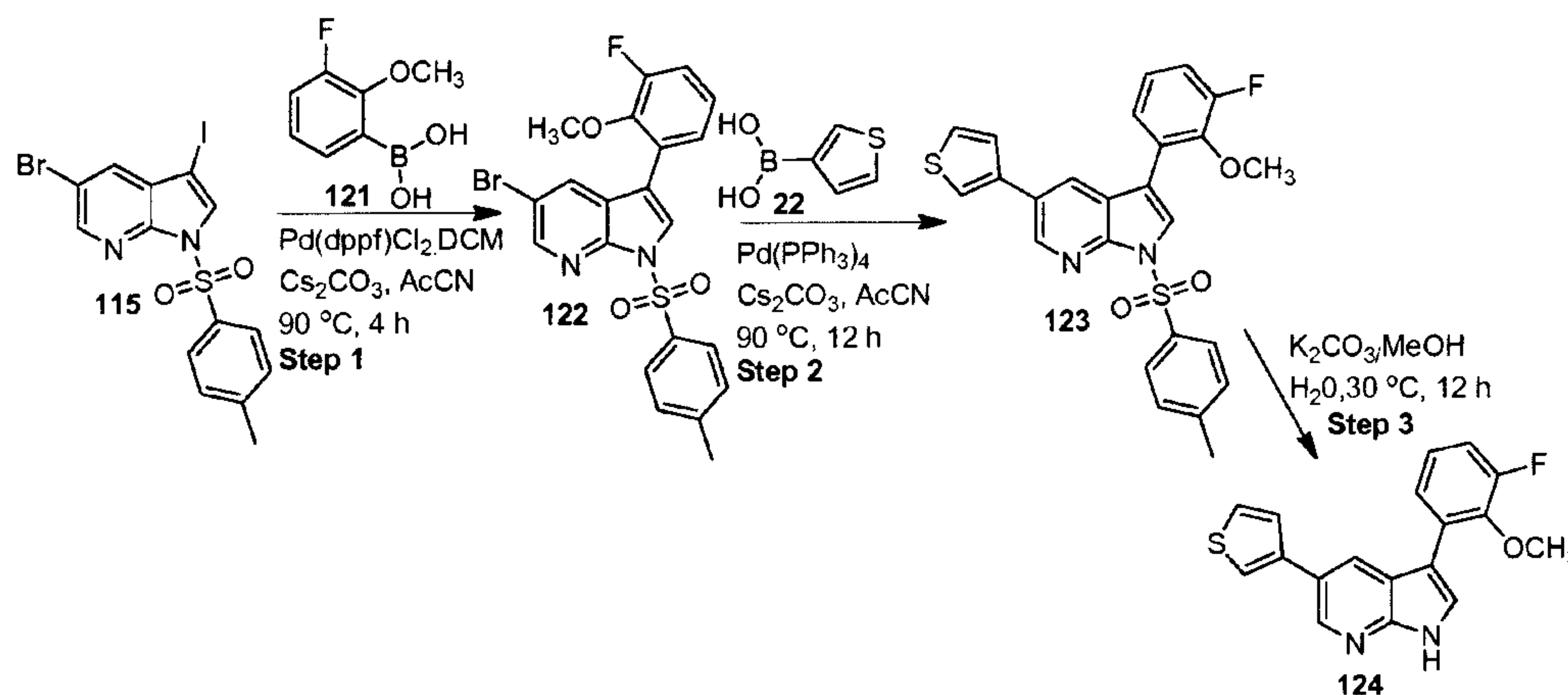


WO 2014/093383

PCT/US2013/074191

[00265] Compound 153:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 12.0 (s, 1H), 8.64 (d, 1H), 8.31 (d, 1H), 7.90 (m, 1H), 7.84 (s, 1H), 7.65 (m, 2H), 7.22 (m, 1H), 7.1 (m, 1H), MS  $m/z$  ESI: 328.8.  $(\text{M}+\text{H})^+$ .

**PREPARATION OF EXAMPLE 125: 3-(3-fluoro-2-methoxyphenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (124)**



Step 1:

[00266] To a solution of **115** (0.150g, 0.314mmol) and **121** (0.049g, 0.314mmol) in a sealed tube was dissolved acetonitrile (7mL) and then  $\text{Cs}_2\text{CO}_3$  (0.204g, 0.628mmol) was charged. The resulting RM was degassed for 15min. To this RM was added  $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$  (0.012g, 0.0157mmol) and degassed again for 15min. The resulting RM was stirred for 2hr at 90°C. After 4hr, TLC monitoring confirmed the consumption of SMs and the RM was cooled to rt and diluted with DCM (100mL) and filtered through celite. The resulting crude material was purified via silica gel chromatography using a gradient of 5% ethyl acetate in hexane to afford compound **122**.

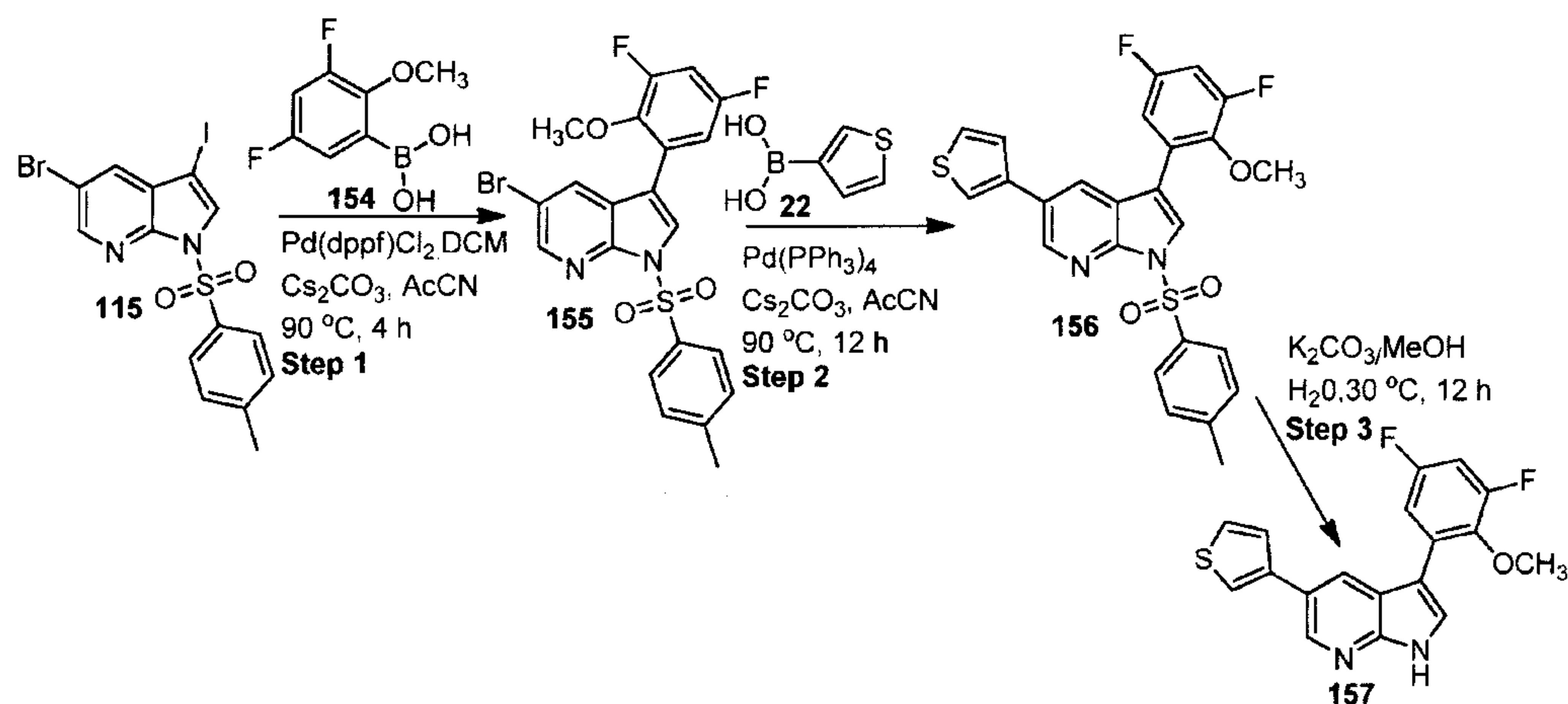
Step 2:

[00267] A solution of **122** (0.100g, 0.210mmol) and **22** (0.027g, 0.210mmol) was dissolved in acetonitrile (5mL) in a sealed tube. To this RM,  $\text{Cs}_2\text{CO}_3$  (0.137 g, 0.421mmol) was added and degassed for 15min. The catalyst  $\text{Pd}(\text{PPh}_3)_4$  (0.012g, 0.010mmol) was added and degassed again for 15min. The resulting RM was stirred overnight at 90°C. After TLC showed completion of changes from the SM, the RM was allowed to cool to rt. DCM (100mL) was added and filtered through celite. The resulting oil was purified via silica gel chromatography at a gradient of 10% ethyl acetate: hexane to afford compound **123**.

Step 3:

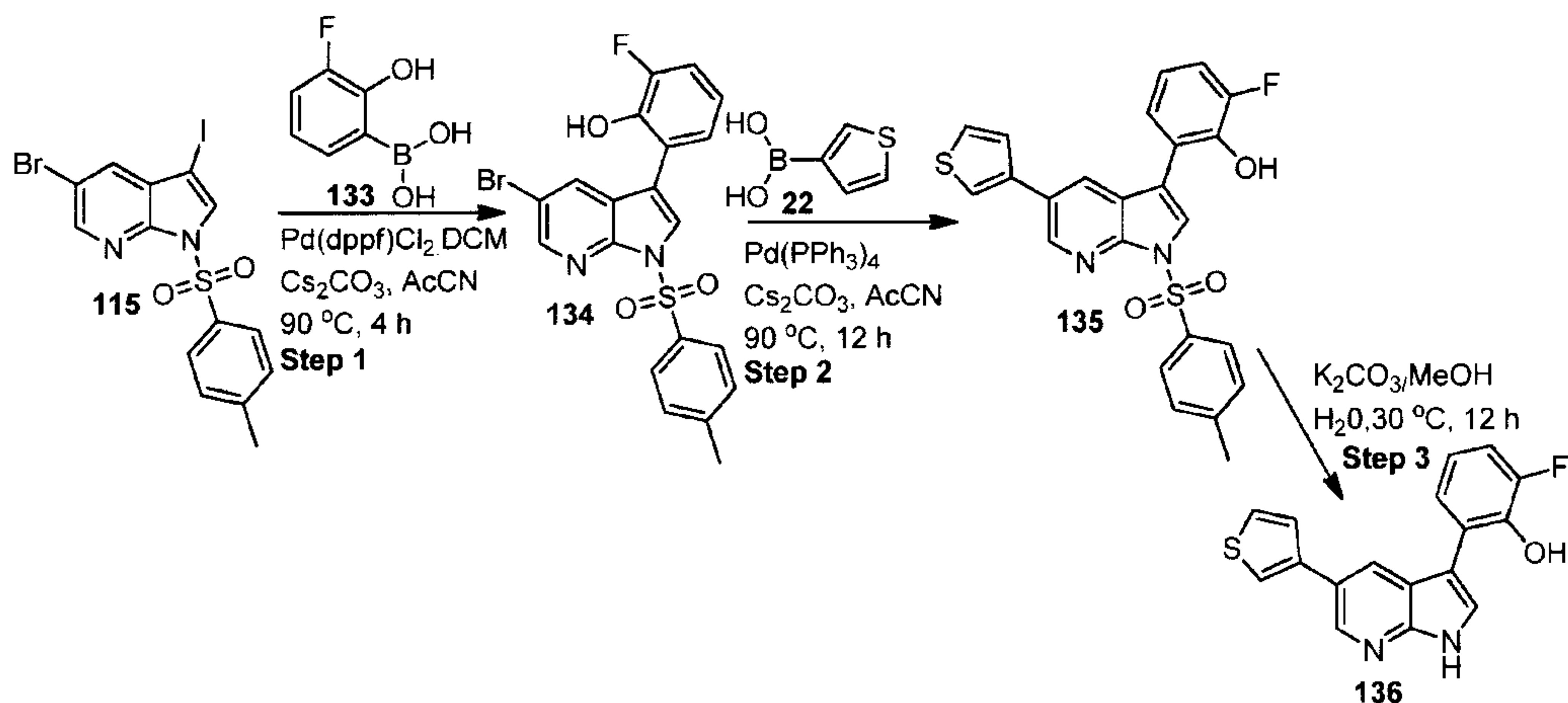
[00268] To Compound **123** (0.050g, 0.104mmol) in MeOH (10mL) and H<sub>2</sub>O (5mL) was added K<sub>2</sub>CO<sub>3</sub> (0.035g, 0.260mmol) and the RM stirred overnight at 70°C. After completion of the reaction from TLC, the resulting contents were evaporated of methanol completely and diluted with DCM (50mL) followed by water wash for two times and the organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated. The resulting crude was purified via silica gel chromatography using a gradient of 25% ethyl acetate: hexane to afford compound **124**.  
<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 9.26 (s, 1H), 8.63 (s, 1H), 8.31 (d, 1H), 7.69 (d, 1H), 7.48 (d, 1H), 7.44 d, 2H), 7.38 (m, 1H), 7.11 (m, 2H), 3.75 (s, 3H). MS m/z: 324.8 (M+H)<sup>+</sup>.

**PREPARATION OF EXAMPLE 126: 3-(3,5-difluoro-2-methoxyphenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (157):**



[00269] Compound 157: <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ: 12.14, (t, 1H), 6.8 (m, 1H), 8.32 (m, 1H), 7.87 (m, 2H), 7.65 (m, 2H), 7.31 (m, 2H), 3.61 (m, 3H), MS m/z ESI: 342.8 (M+H)<sup>+</sup>.

**PREPARATION OF EXAMPLE 128: 2-fluoro-6-(5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol (136):**

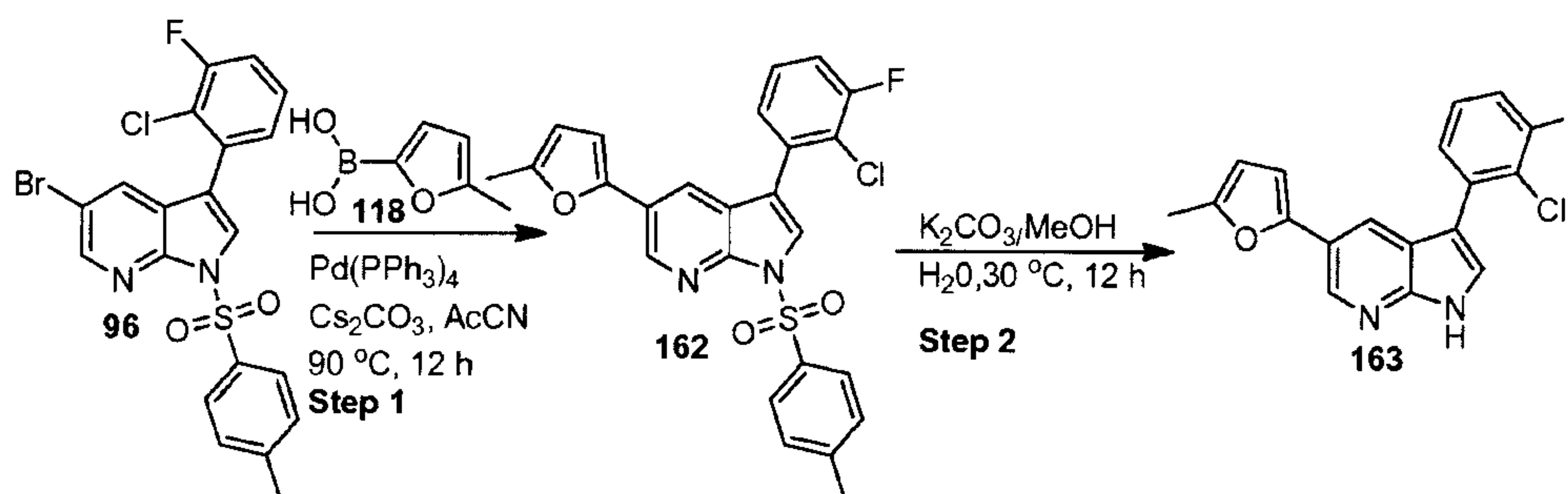


WO 2014/093383

PCT/US2013/074191

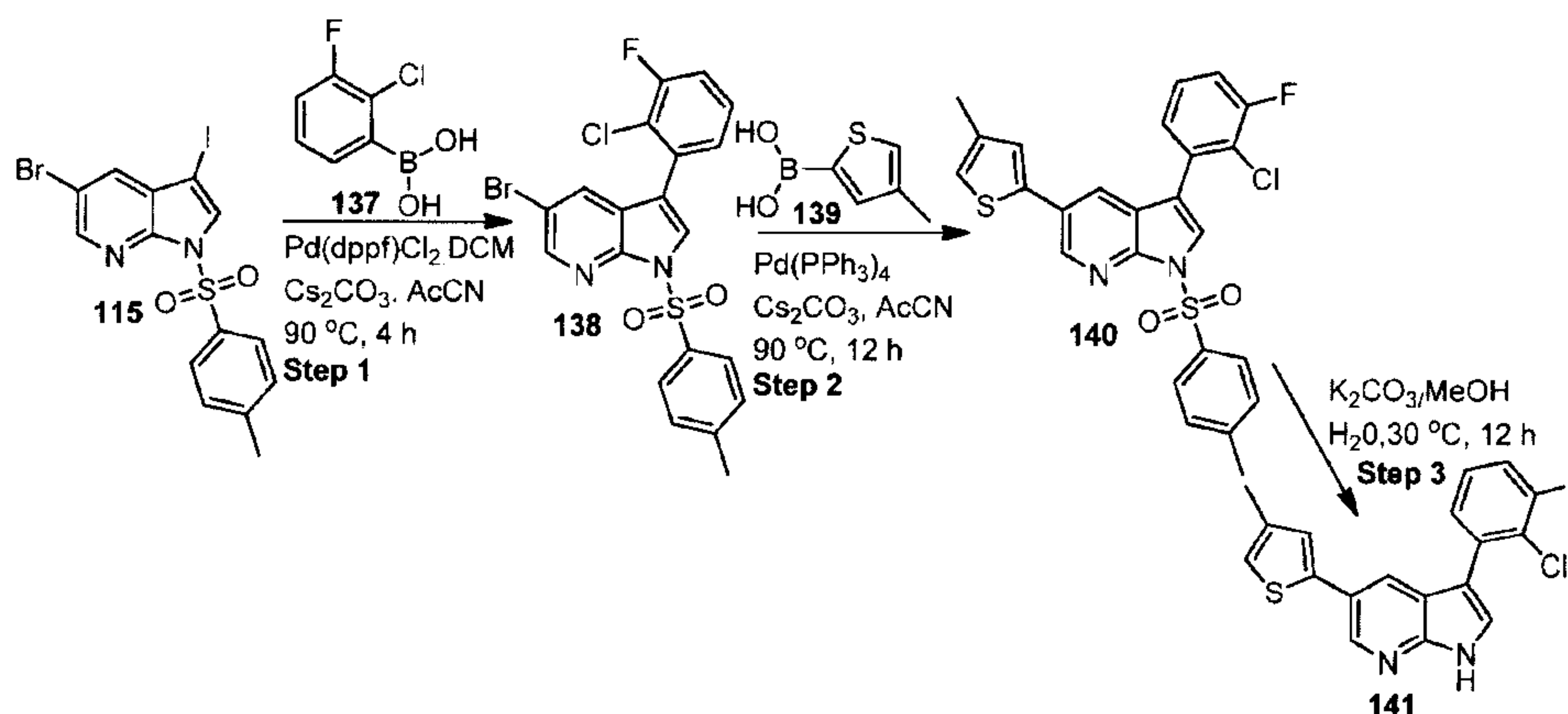
[00270] Compound 136:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 10.03 (s,1H), 8.61 (d,1H), 8.31 (d,1H), 7.65 (s,1H), 7.34 (m,1H), 7.12 (m,1H), 6.99 (m,1H), 6.54 (d,1H), 6.07 (d,1H), 2.13 (s,3H), MS  $m/z$ : 308.8 ( $\text{M}+\text{H}$ ) $^-$ .

**PREPARATION OF EXAMPLE 129: 3-(2-chloro-3-fluorophenyl)-5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridine (163):**



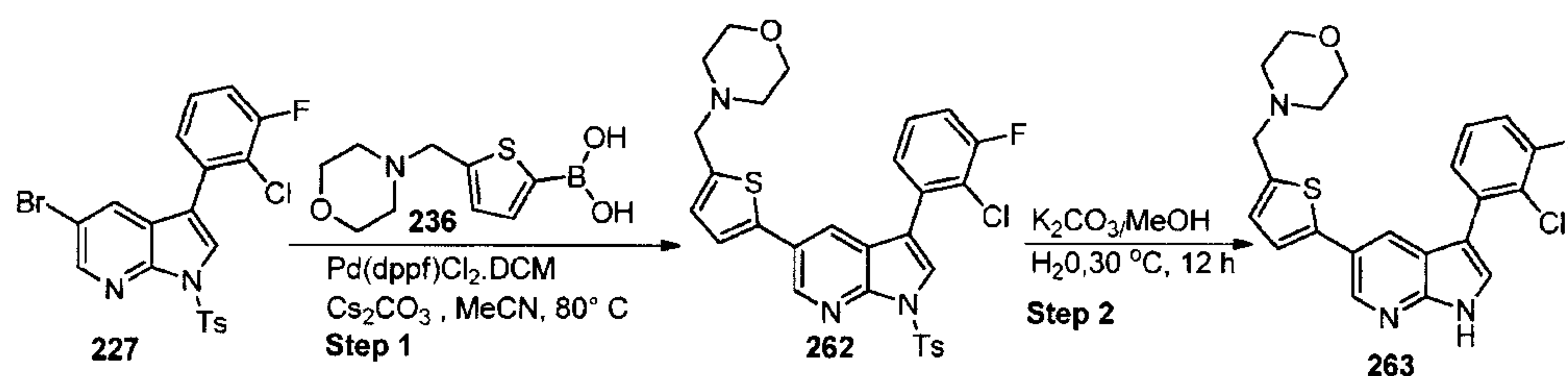
[00271] Compound 163:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.99 (s,1H), 8.16 (d,1H), 7.62 (d,1H), 7.36 (m,2H), 7.19 (m, 1H), 7.56 (d, 1H), 6.08 (m, 1H), MS  $m/z$  ESI: 326.9 ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 131: 3-(2-chloro-3-fluorophenyl)-5-(4-methylthiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (141)**



[00272] Compound 141:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.08 (s,1H), 8.62 (s,1H), 8.09 (s,1H), 7.59 (d,1H), 7.34 (m,2H), 7.32 (m,1H), 7.12 (s,1H), 6.88 (t,1H), 2.30 (s,3H), MS  $m/z$ : 342.7 ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 133: 4-((5-(3-(2-chloro-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine (263):**

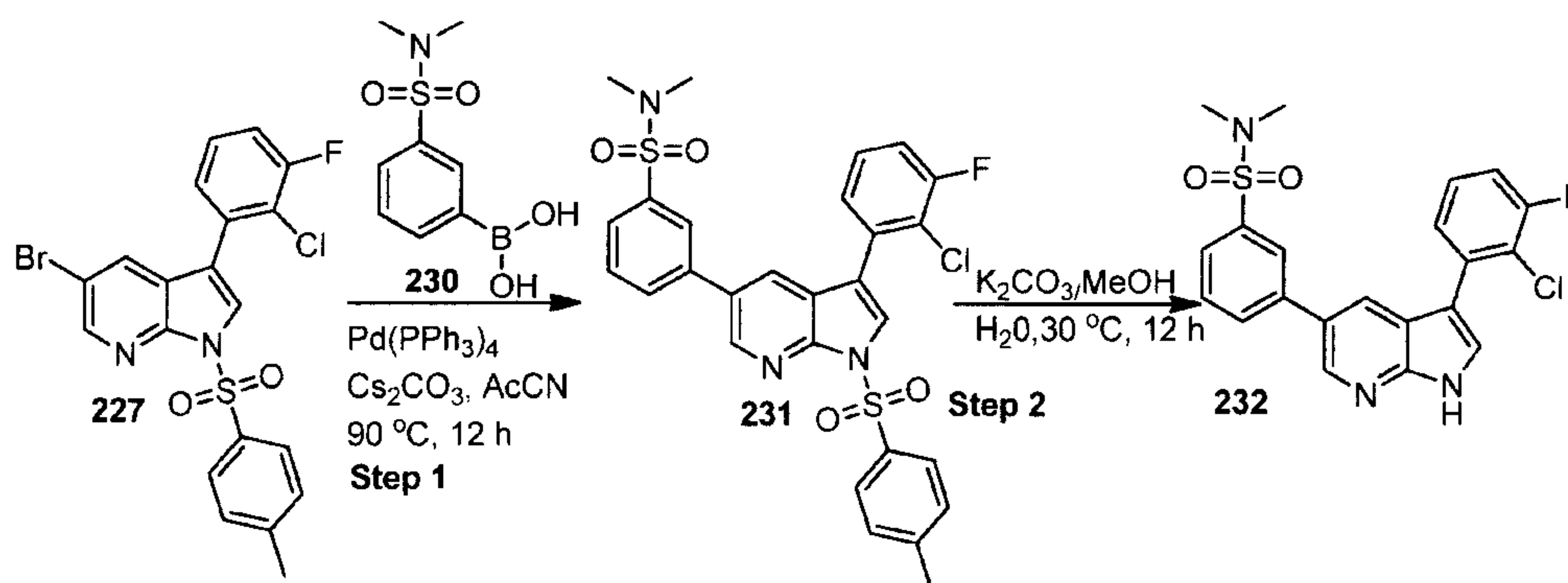
**Step 1:**

[00273] To a solution of **227** (100mg, 0.208mmol) and **236** (47mg, 0.208mmol), in acetonitrile (7mL) was added cesium carbonate (135mg, 0.416mmol). The RM was degassed and purged with nitrogen for 10min.  $\text{Pd(dppf)Cl}_2$  (8mg, 0.01042mmol) was added to the reaction. The RM was again degassed and purged with nitrogen for another 5min, and heated to  $80^\circ\text{C}$  in a sealed tube overnight. The reaction was allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude product, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white colored solid compound **262**.

**Step 2:**

[00274] A solution of **262** (60mg, 0.103mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (42mg, 0.3092mmol). The reaction was heated to  $60^\circ\text{C}$  overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice ( $2 \times 25\text{mL}$ ). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude material, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 60% ethyl acetate in hexane as pale yellow solid compound **263**.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ): 9.42 (bs, 1H), 8.62 (d, 1H), 8.07 (d, 1H), 7.60 (d, 1H), 7.32 (m, 2H), 7.17 (m, 2H), 6.90 (d, 1H), 4.05 (m, 4H), 3.74 (m, 6H), 3.44 (m, 4H), MS-ES+ 426.01.

**PREPARATION OF EXAMPLE 135:** 3-(3-(2-chloro-3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N,N-dimethylbenzenesulfonamide (**231**):

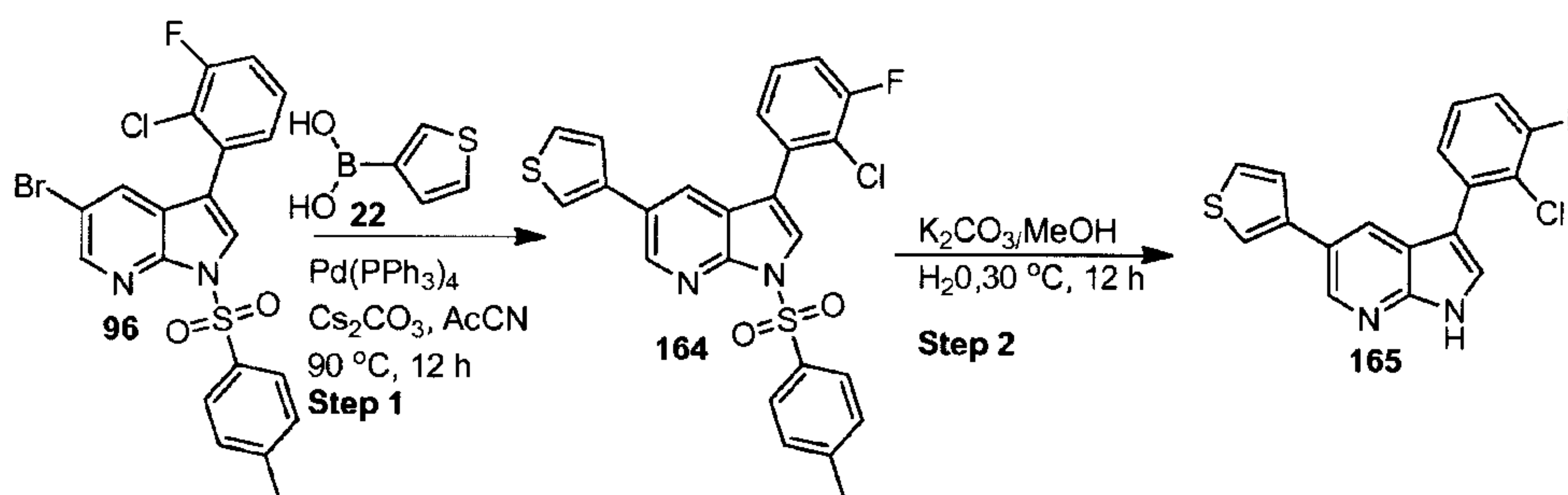


WO 2014/093383

PCT/US2013/074191

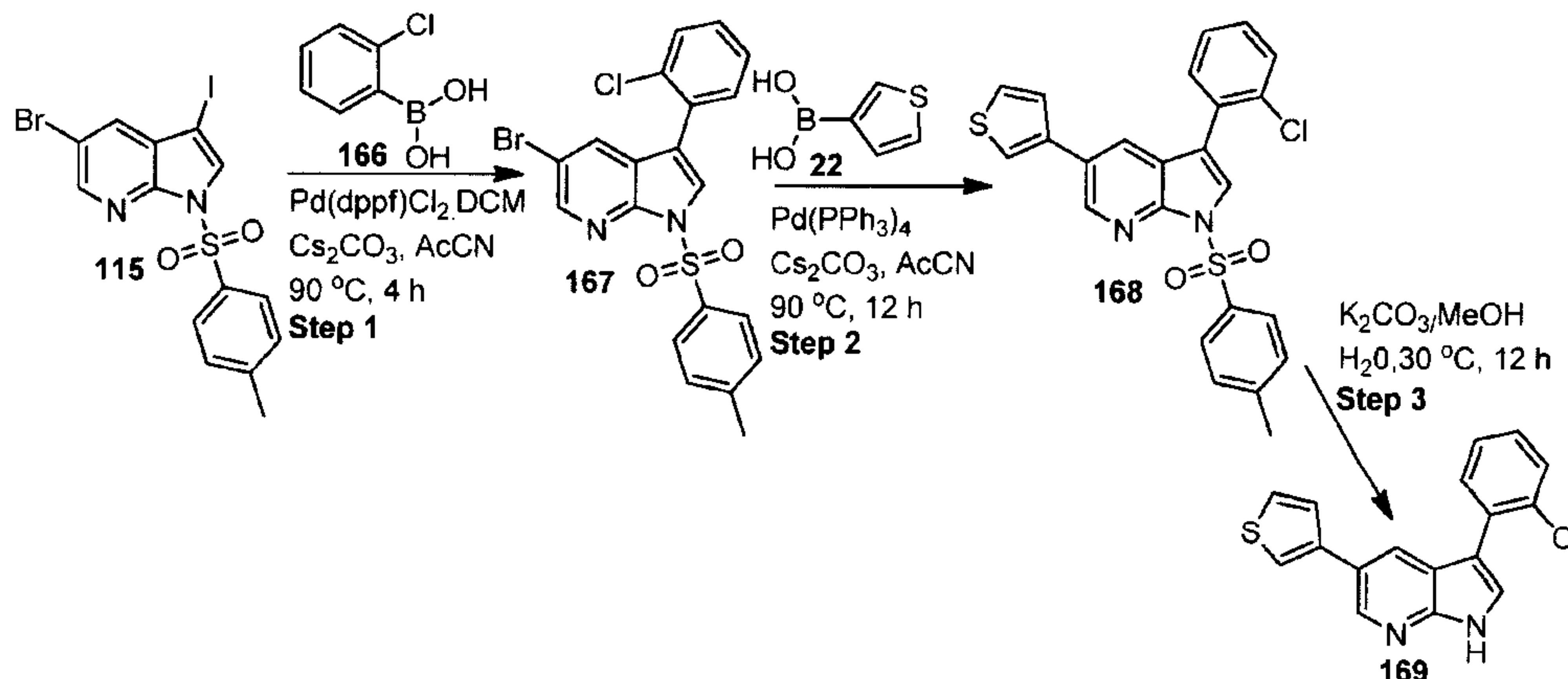
[00275] **Compound 232:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.86(s, 1H), 8.63(d, 1H), 8.13(d, 1H), 8.01(s, 1H), 7.85(d, 1H), 7.77(m, 1H), 7.65(m, 2H), 7.35(m, 2H), 7.19(m, 1H), 2.76(s, 6H), MS  $m/z = 329.9$  ( $\text{M}+\text{H}$ ) $^-$ .

**PREPARATION OF EXAMPLE 138: 3-(3-chloro-2-fluorophenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (165):**



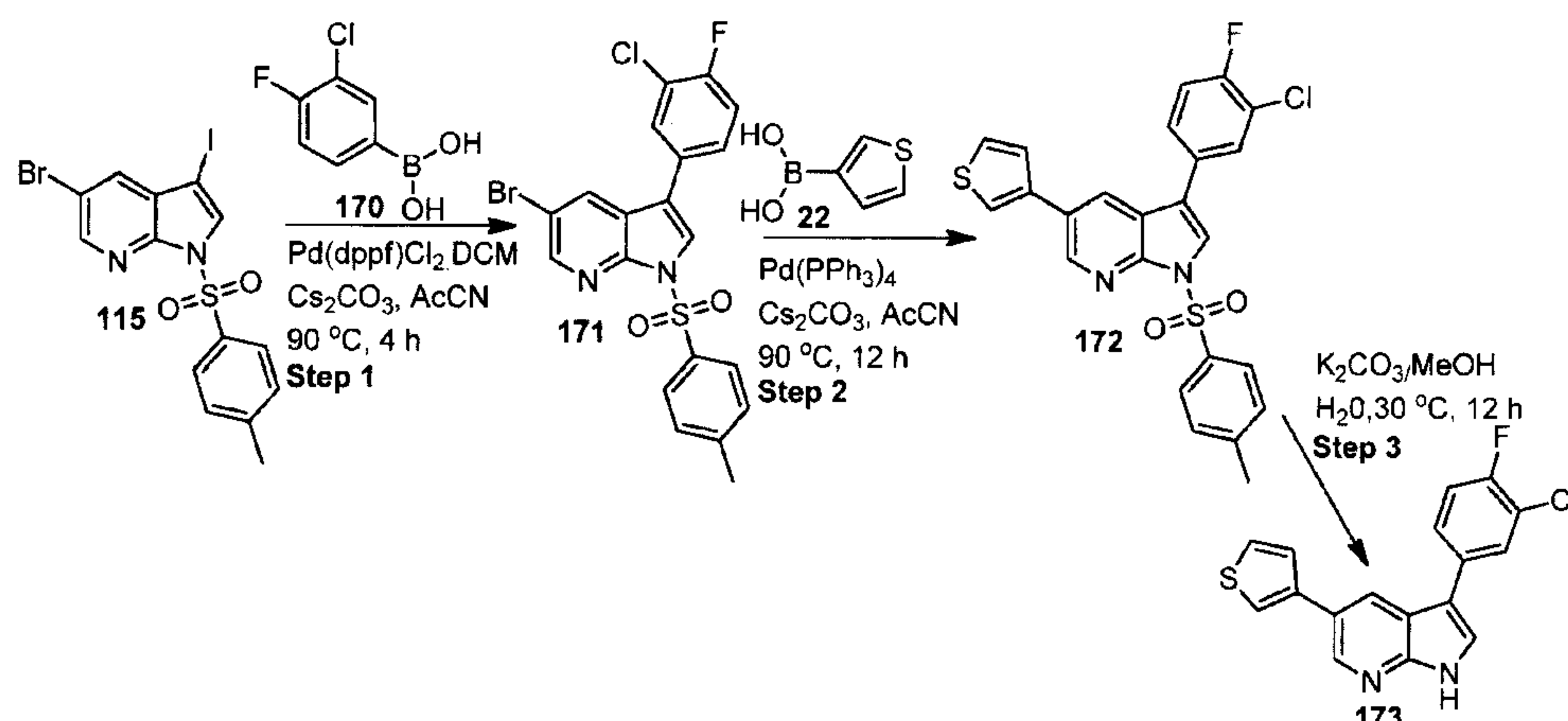
[00276] **Compound 165:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.71 (m, 1H), 8.66 (d, 1H), 8.27 (s, 1H), 7.67 (s, 1H), 7.58 (m, 1H), 7.5 (m, 1H), 7.49 (m, 2H), 7.45 (m, 1H), 7.19 (t, 1H), MS  $m/z$  ESI: 328.8 ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 139: 3-(2-chlorophenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (169):**



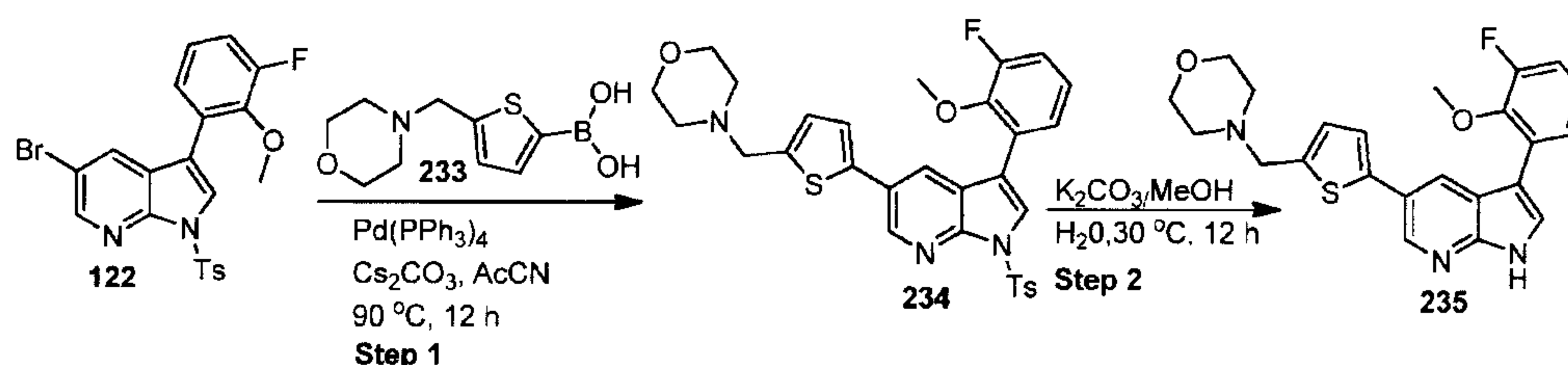
[00277] **Compound 169:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.7 (s, 1H), 8.65 (d, 1H), 8.13 (d, 1H), 7.6 (d, 1H), 7.54 (m, 2H), 7.46 (m, 1H), 7.43 (m, 2H), 7.42 (m, 2H), MS  $m/z$  ESI: 310.8 ( $\text{M}+\text{H}$ ) $^+$ .

**PREPARATION OF EXAMPLE 140: 3-(3-chloro-4-fluorophenyl)-5-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridine (173):**



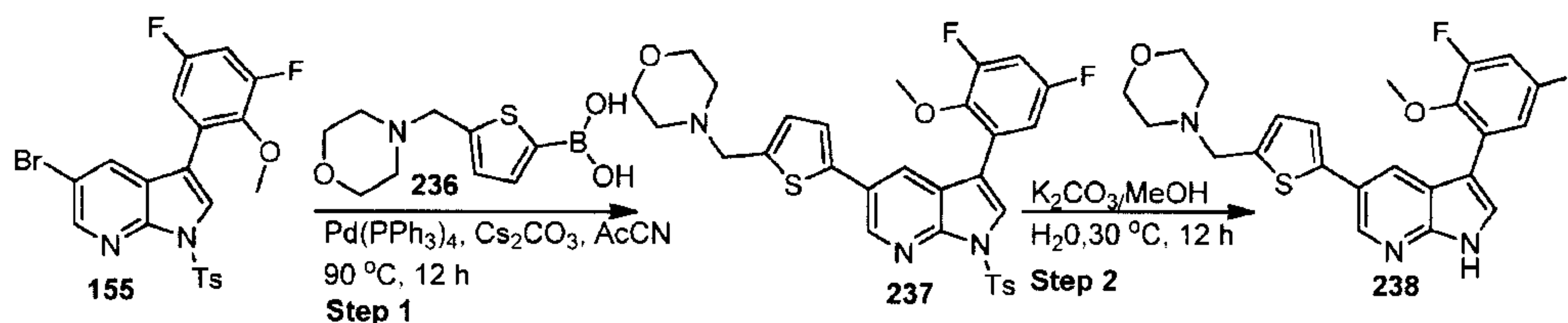
[00278] Compound 173:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.09 (b, 1H), 8.64 (m, 1H), 8.28 (s, 1H), 7.66 (d, 1H), 7.46-7.49 (m, 4H), MS  $m/z$  ESI: 326.8,  $(\text{M}+\text{H})^+$ .

**PREPARATION OF EXAMPLE 142:** 4-((5-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine (235):



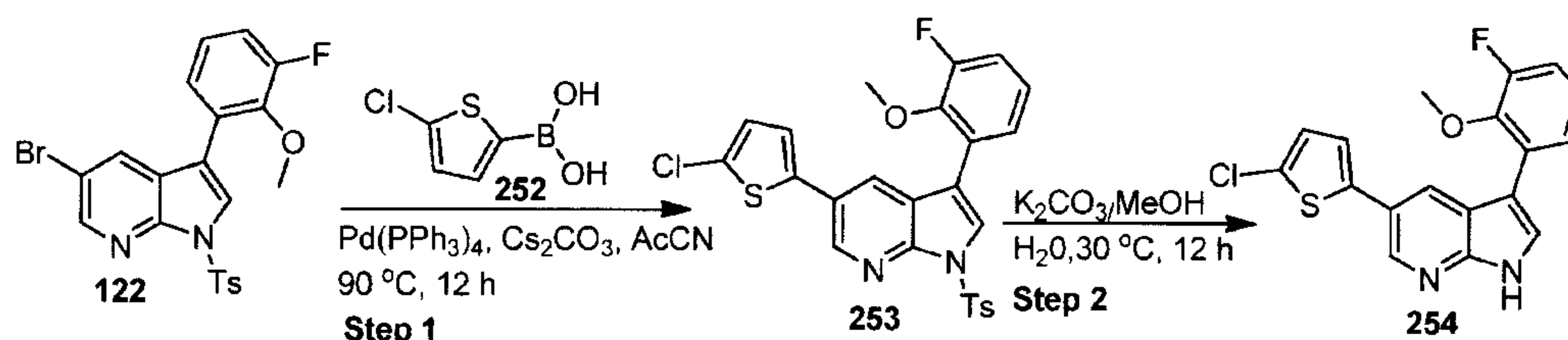
[00279] Compound 235:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.94 (s, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 7.66 (d, 1H), 7.35 (m, 1H), 7.15 (m, 1H), 7.06 (m, 3H), 6.90 (d, 1H), 3.76 (m, 3H), 3.72 (s, 2H), 2.54 (m, 4H), 1.94 (m, 4H), MS  $m/z$  = 422.1  $(\text{M}+\text{H})^+$ .

**PREPARATION OF EXAMPLE 143:** 4-((5-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine (238):



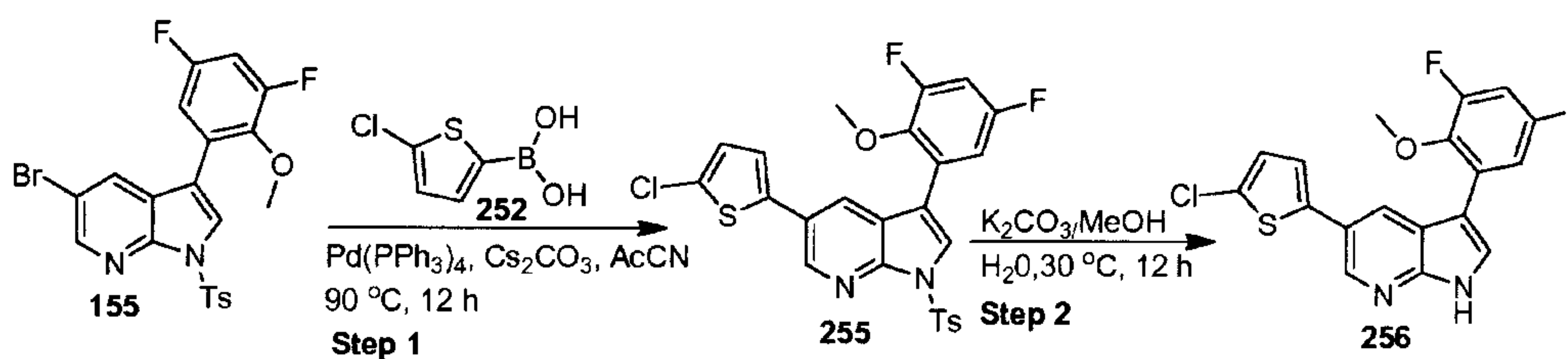
[00280] Compound 238:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.26 (bs, 1H), 8.63 (bs, 1H), 8.27 (s, 1H), 7.71 (d, 1H), 7.17 (d, 1H), 7.09 (m, 1H), 6.92 (d, 1H), 6.84 (m, ), 3.75 (m, 5H), 2.55 (bs, 4H), 1.95 (m, 2H), 1.68 (m, 2H), MS  $m/z$  = 440.1  $(\text{M}+\text{H})^+$ .

**PREPARATION OF EXAMPLE 148: 5-(5-chlorothiophen-2-yl)-3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine (254):**



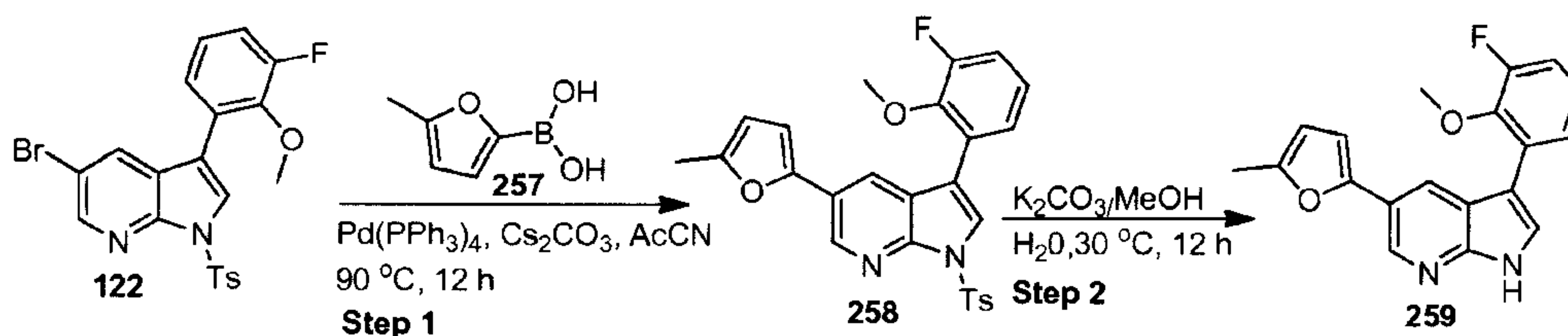
[00281] Compound 254:  $^1\text{H}$ NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.02 (s, 1H), 8.54(s, 1H), 8.20 (d, 1H), 7.67 (d, 1H), 7.33 (m, 1H), 7.09 (m, 3H), 6.92 (d, 1H), 3.76 (s, 3H); MS  $m/z$  = 358.9 (M+H).

**PREPARATION OF EXAMPLE 167: 5-(5-chlorothiophen-2-yl)-3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine (256):**



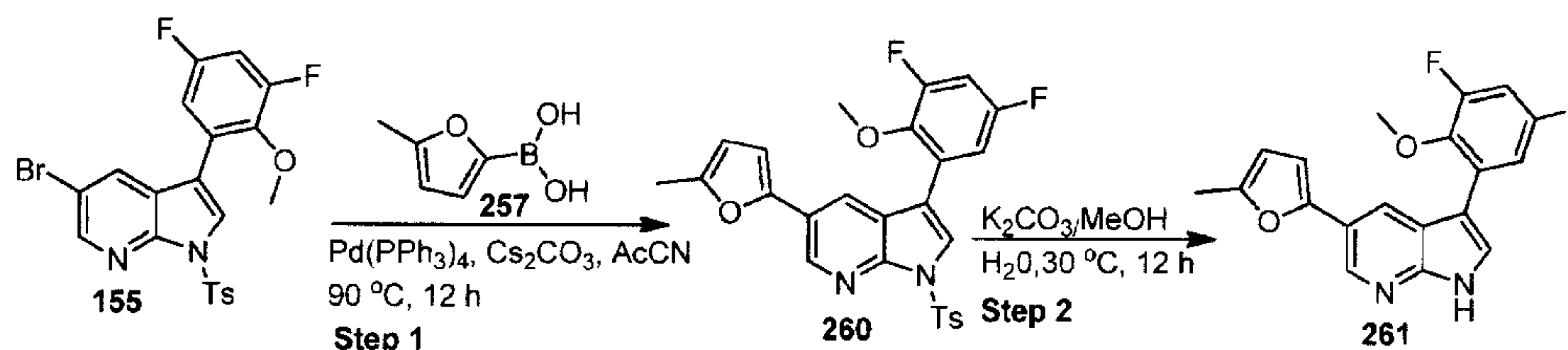
[00282] Compound 256:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.40 (s, H), 8.55 (d, 1H), 8.21(d, 1H), 7.73 (s, 1H), 7.09 (m, 2H), 6.93 (d, 1H), 6.85 (m, 1H), 3.69 (s, 3H), MS  $m/z$  = 376.9 (M+H).

**PREPARATION OF EXAMPLE 168: 3-(3-fluoro-2-methoxyphenyl)-5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridine (259):**



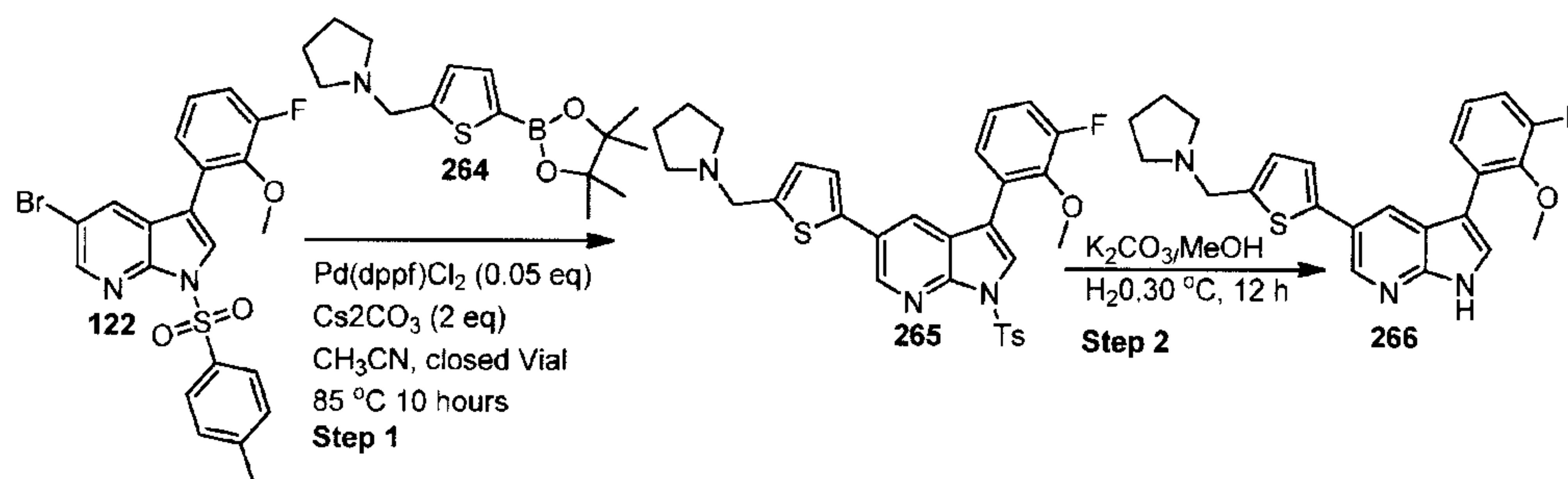
[00283] Compound 259:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.91 (s,1H), 8.68 (d,1H), 8.34 (d,1H), 7.69 (s,1H), 7.38 (d, 1H), 7.16 (m, 2H), 6.56 (d, 1H), 6.08 (d, 1H), 3.75 (s, 1H), 2.40 (s, 3H), MS  $m/z$  = 322.9 (M+H).

**PREPARATION OF EXAMPLE 169: 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-methylfuran-2-yl)-1H-pyrrolo[2,3-b]pyridine (261):**



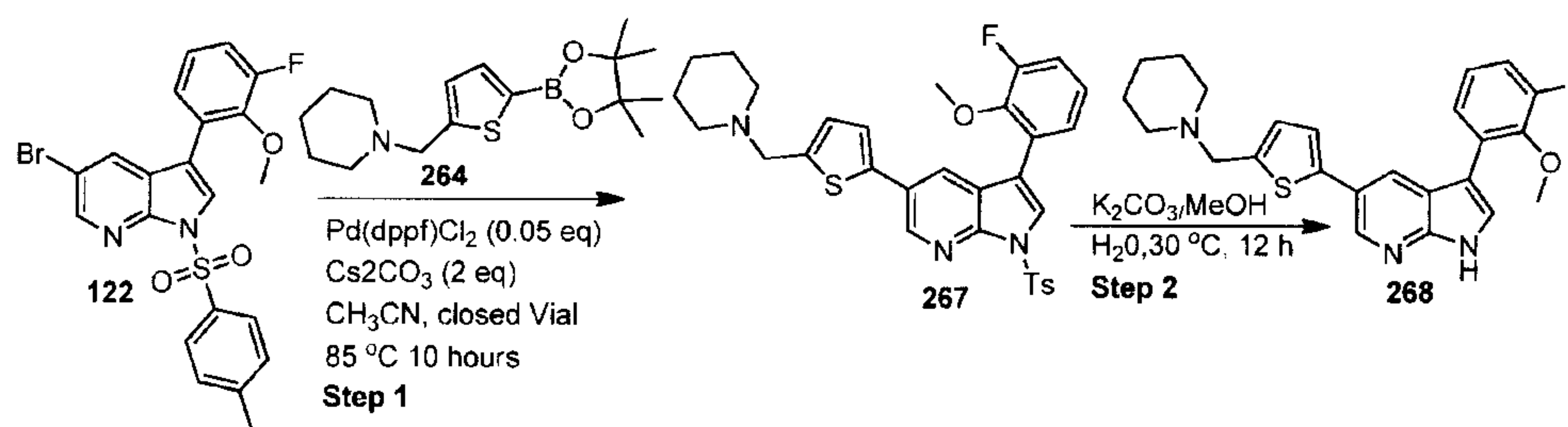
[00284] Compound 261:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.32 (s, 1H), 8.67 (d, 1H), 8.32 (d, 1H), 7.71 (s, 1H), 7.14 (m, 1H), 6.84 (m, 1H), 6.57 (m, 1H), 6.08 (m, 1H), 3.69 (s, 3H), 2.41 (s, 3H), MS  $m/z$  = 339.0 (M+H).

**PREPARATION OF EXAMPLE 174: 3-(3-fluoro-2-methoxyphenyl)-5-(5-(pyrrolidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (266):**



[00285] Compound 266:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.19(bs,1H), 8.62(s,1H), 8.28(bs,1H), 7.68(d,1H), 7.35(d,1H), 7.14(m,3H), 7.05(s,1H), 3.86(s,2H), 3.76(s,3H), 2.64(bs,4H), 1.84(bs,4H), MS-ES+ 406.1 (M+H).

**PREPARATION OF EXAMPLE 175: 3-(3-fluoro-2-methoxyphenyl)-5-(5-(piperidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (268):**

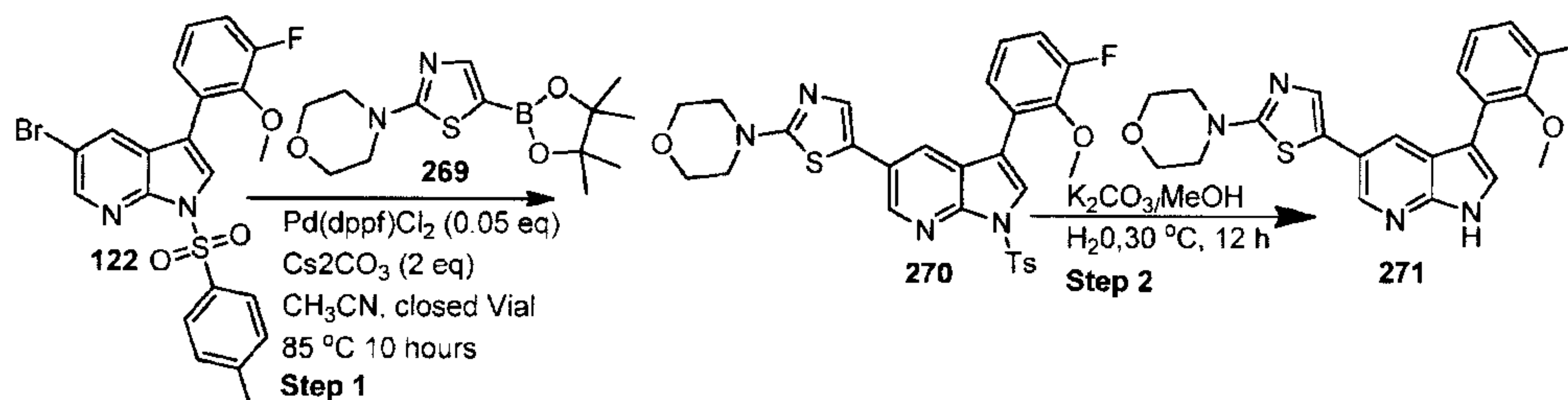


WO 2014/093383

PCT/US2013/074191

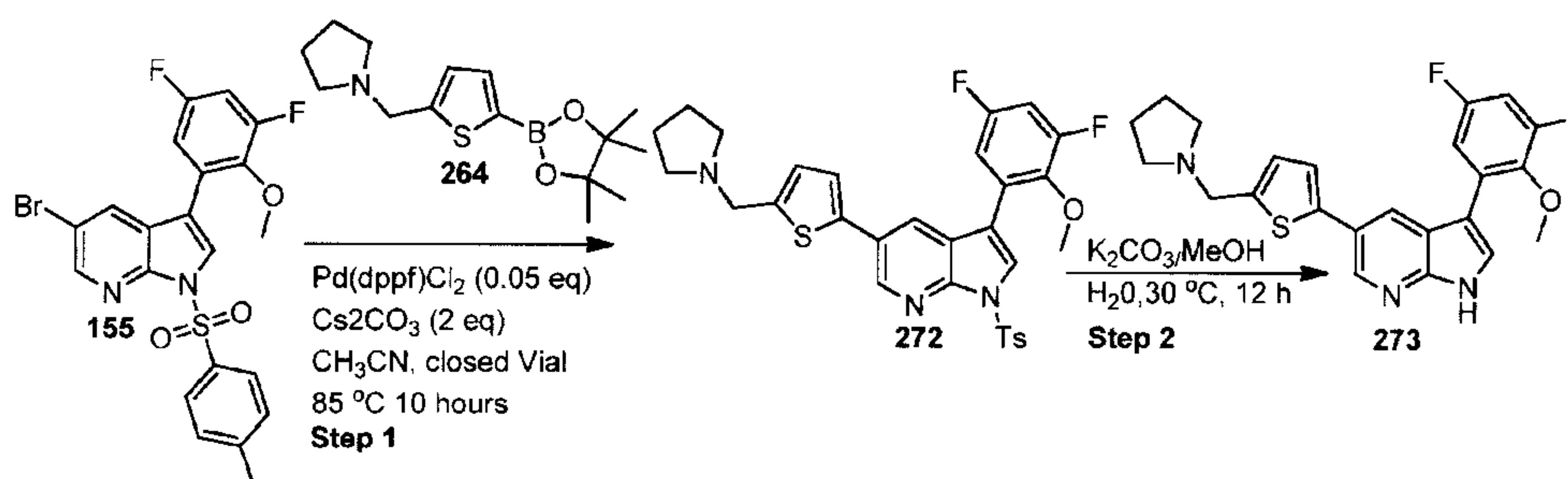
[00286] **Compound 268:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.10(bs, 1H), 8.62(d, 1H), 8.27(d, 1H), 7.67(d, 1H), 7.36(m, 1H), 7.12(m, 3H), 6.89(bs, 1H), 3.76(m, 3H), 3.71(m, 2H), 2.48(m, 4H), 1.62(m, 4H), 1.45(m, 2H), MS-ES+ 422.1 (M+H).

**PREPARATION OF EXAMPLE 176:** 4-(5-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine (**271**):



[00287] **Compound 271:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.64(s, 1H), 8.49(s, 1H), 8.12(d, 1H), 7.68(d, 1H), 7.33(d, 1H), 7.14(m, 1H), 7.08(m, 2H), 3.85(m, 4H), 3.75(s, 3H), 3.52(m, 4H), MS-ES+ 411.0 (M+H).

**PREPARATION OF EXAMPLE 177:** 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-(pyrrolidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (**273**):

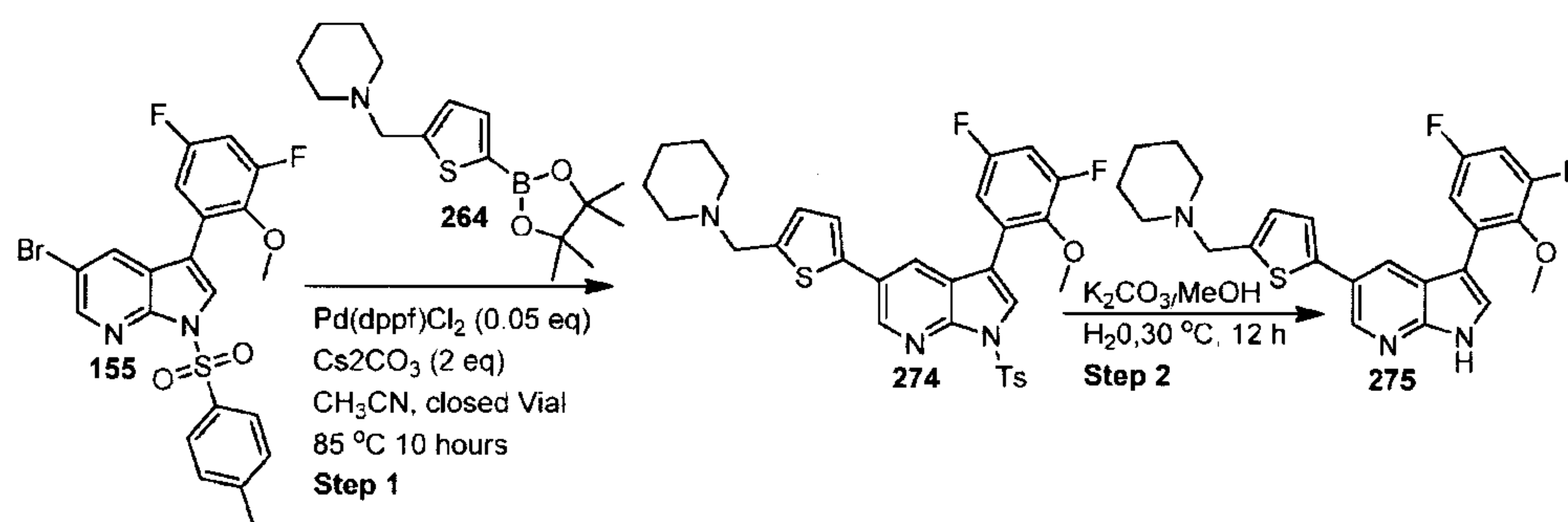


[00288] **Compound 273:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.62(s, 1H), 8.63(d, 1H), 8.28(d, 1H), 7.73(d, 1H), 7.17(d, 1H), 7.09(m, 1H), 6.92(d, 1H), 6.84(m, 1H), 3.86(s, 2H), 3.70(s, 3H), 2.63(bs, 4H), 1.83(bs, 4H), MS-ES+ 426.0 (M+H).

**PREPARATION OF EXAMPLE 178:** 3-(3,5-difluoro-2-methoxyphenyl)-5-(5-(piperidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (**275**):

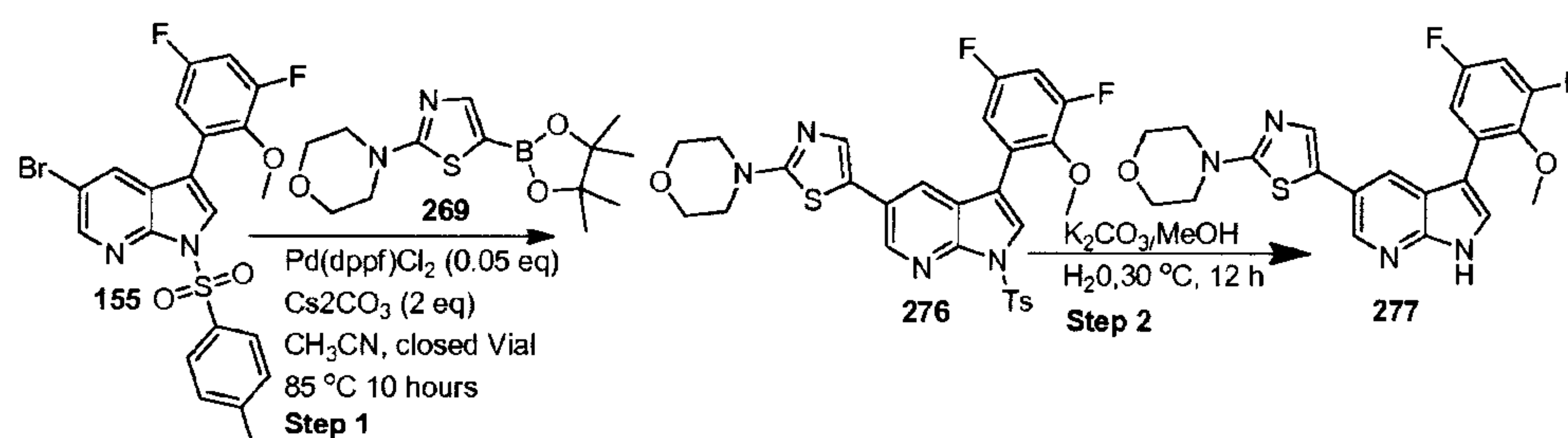
WO 2014/093383

PCT/US2013/074191



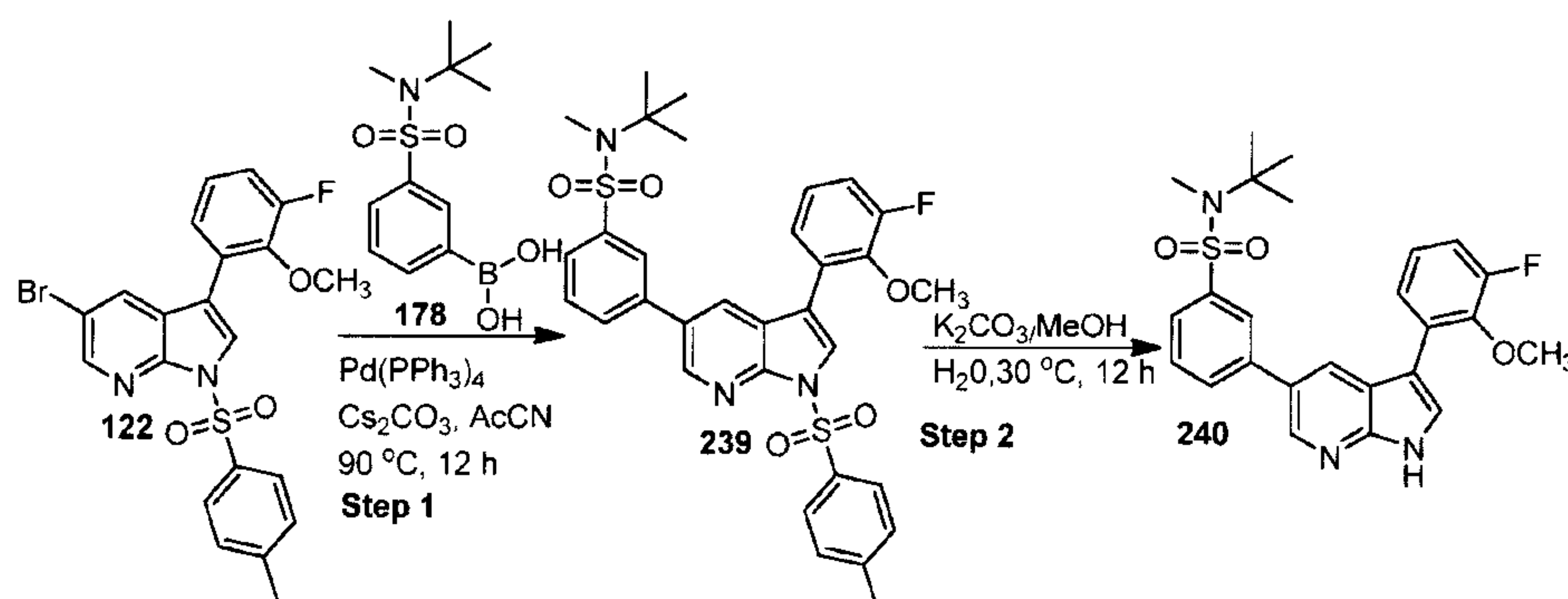
[00289] **Compound 275:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.49 (bs, 1H), 8.63 (s, 1H), 8.27 (d, 1H), 7.73 (bs, 1H), 7.17 (d, 1H), 7.10 (m, 1H), 6.84 (m, 1H), 6.81 (m, 1H), 4.05 (m, 2H), 3.70 (m, 5H), 3.48 (m, 2H), 2.48 (bs, 4H), 1.92 (m, 2H), MS-ES+ 440.0 (M+H).

**PREPARATION OF EXAMPLE 179:** 4-(5-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine (277):



[00290] **Compound 277:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.43(s, 1H), 8.51(d, 1H), 8.12(d, 1H), 7.72(d, 1H), 7.42(s, 1H), 7.08(m, 1H), 6.84(m, 1H), 3.84(m, 4H), 3.69(s, 3H), 3.53(m, 4H), MS-ES+ 429.0 (M+H).

**PREPARATION OF EXAMPLE 180:** N-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-4-(thiophen-3-yl)-1H-pyrazolo[3,4-b]pyridin-3-amine (240)

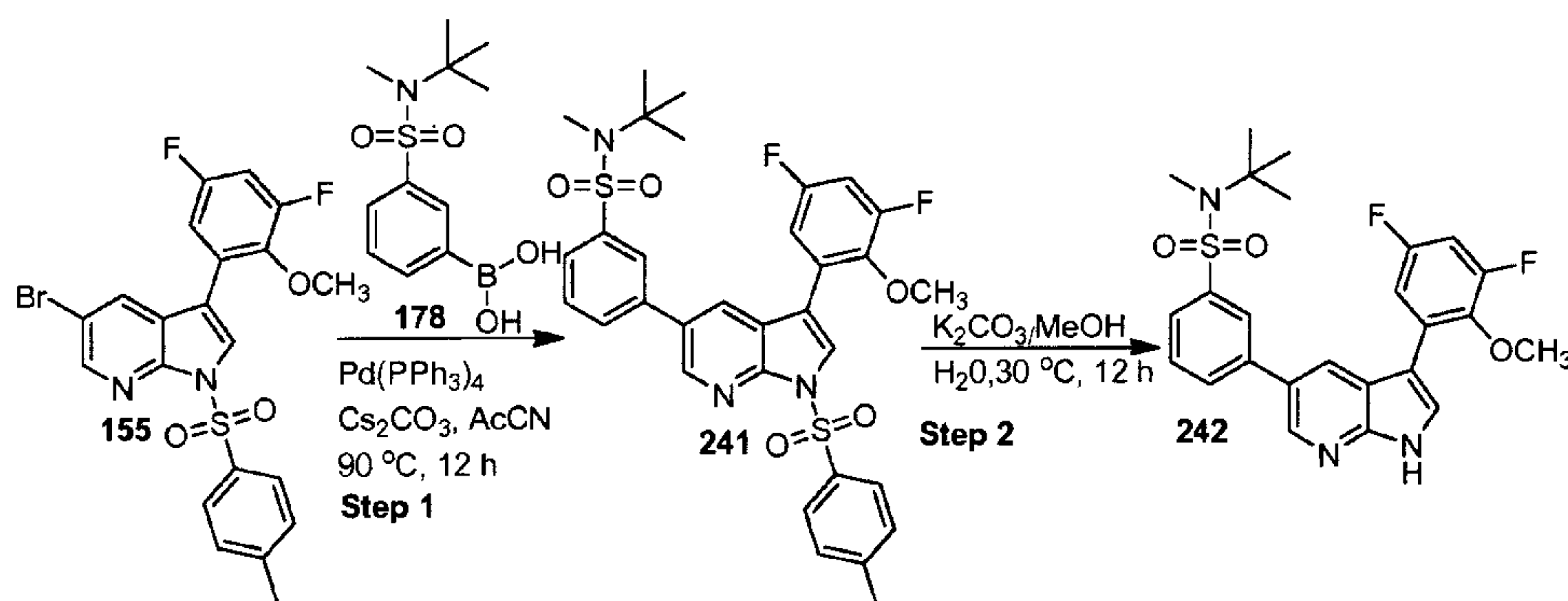


WO 2014/093383

PCT/US2013/074191

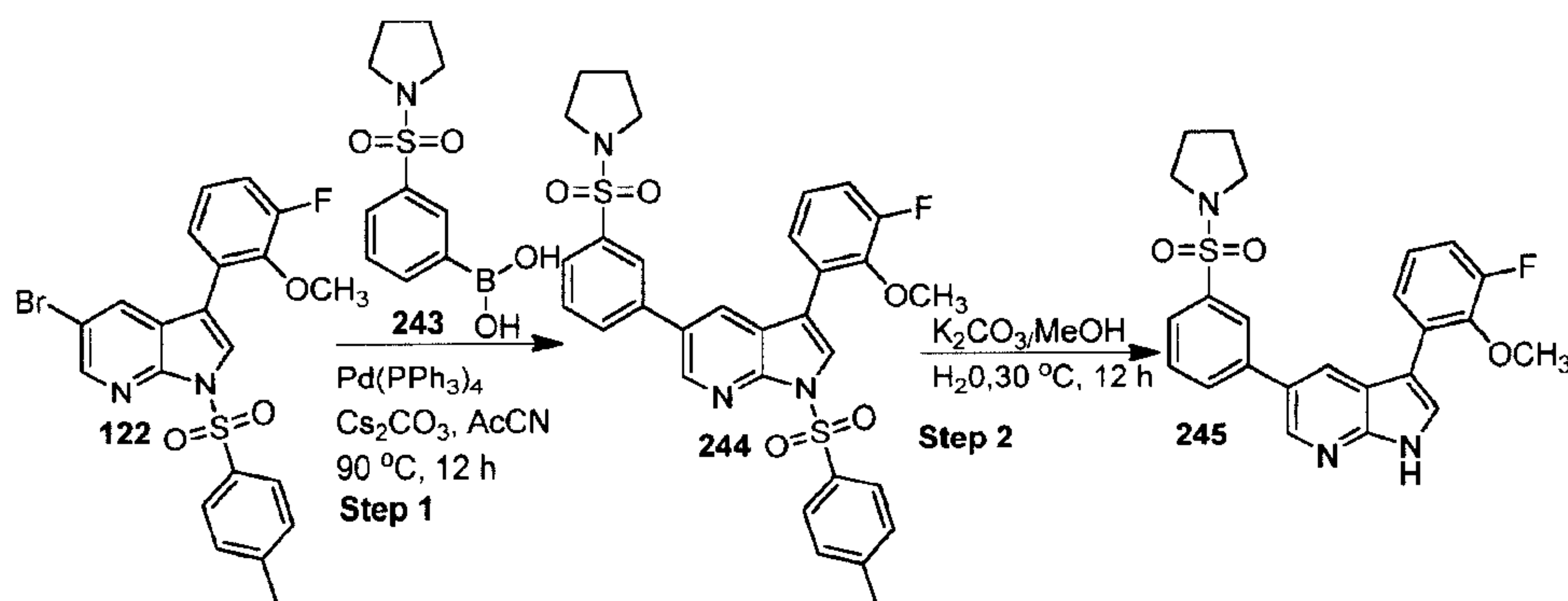
[00291] **Compound 240:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.61 (s, 1H), 8.32 (s, 1H), 8.09 (s, 1H), 7.80 (m, 3H), 7.60 (m, 1H), 7.36 (d, 1H), 7.15 (m, 2H), 3.77 (s, 3H), 3.01 (s, 3H), 1.39 (s, 9H); MS  $m/z$  = 468.1 (M+H).

**PREPARATION OF EXAMPLE 181:** N-(tert-butyl)-3-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methylbenzenesulfonamide (**242**)



[00292] **Compound 242:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.55 (s, 1H), 8.62 (s, 1H), 8.31 (s, 1H), 8.08 (s, 1H), 7.79 (m, 3H), 7.60 (t, 1H), 7.10 (m, 1H), 6.85 (m, 1H), 3.70 (s, 3H), 3.02 (s, 3H), 1.39 (s, 9H), MS  $m/z$  = 486.1 (M+H).

**PREPARATION OF EXAMPLE 182:** 3-(3-fluoro-2-methoxyphenyl)-5-(3-(pyrrolidin-1-ylsulfonyl)phenyl)-1H-pyrrolo[2,3-b]pyridine (**245**):

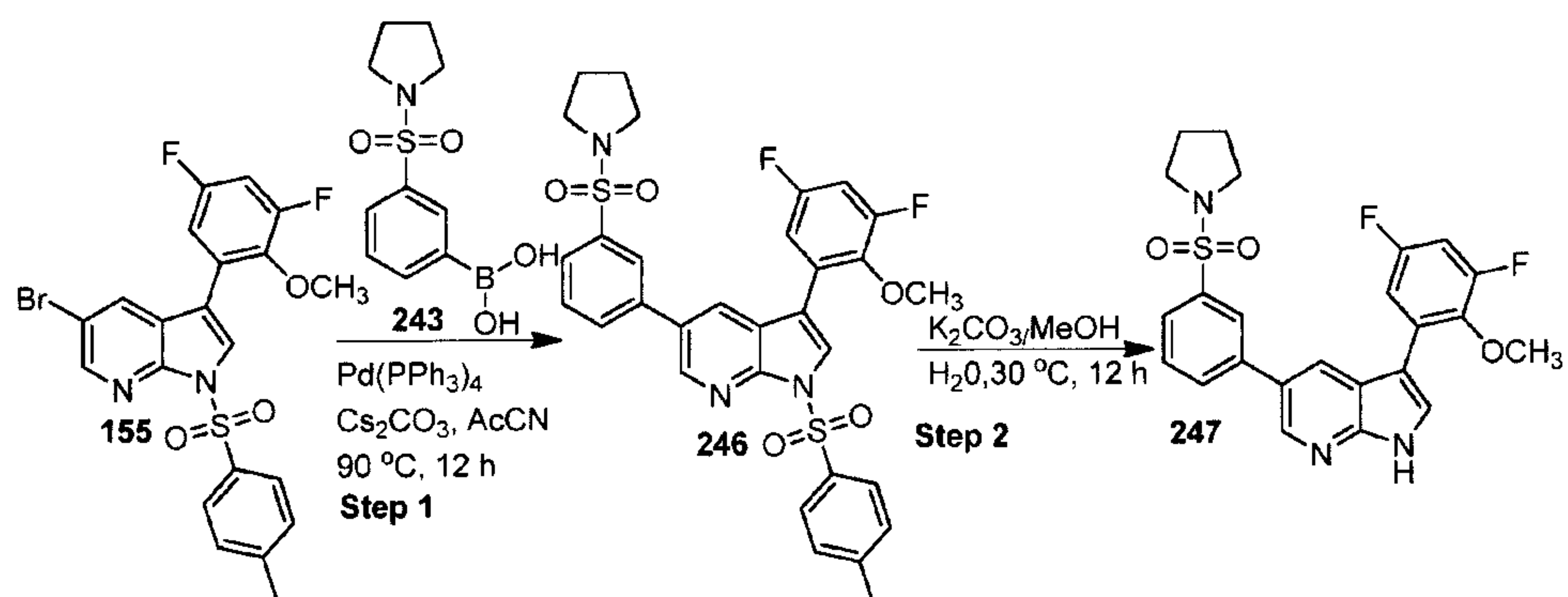


[00293] **Compound 245:**  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.25(s, 1H), 8.61(s, 1H), 8.31(d, 1H), 8.08(d, 1H), 7.82(m, 2H), 7.72(d, 1H), 7.63(t, 1H), 7.36(m, 1H), 7.11(m, 2H), 3.76(s, 3H), 3.30(m, 4H), 1.79(m, 4H), MS  $m/z$  = 452.0 (M+H).

**PREPARATION OF EXAMPLE 183:** 3-(3,5-difluoro-2-methoxyphenyl)-5-(3-(pyrrolidin-1-ylsulfonyl)phenyl)-1H-pyrrolo[2,3-b]pyridine (**247**):

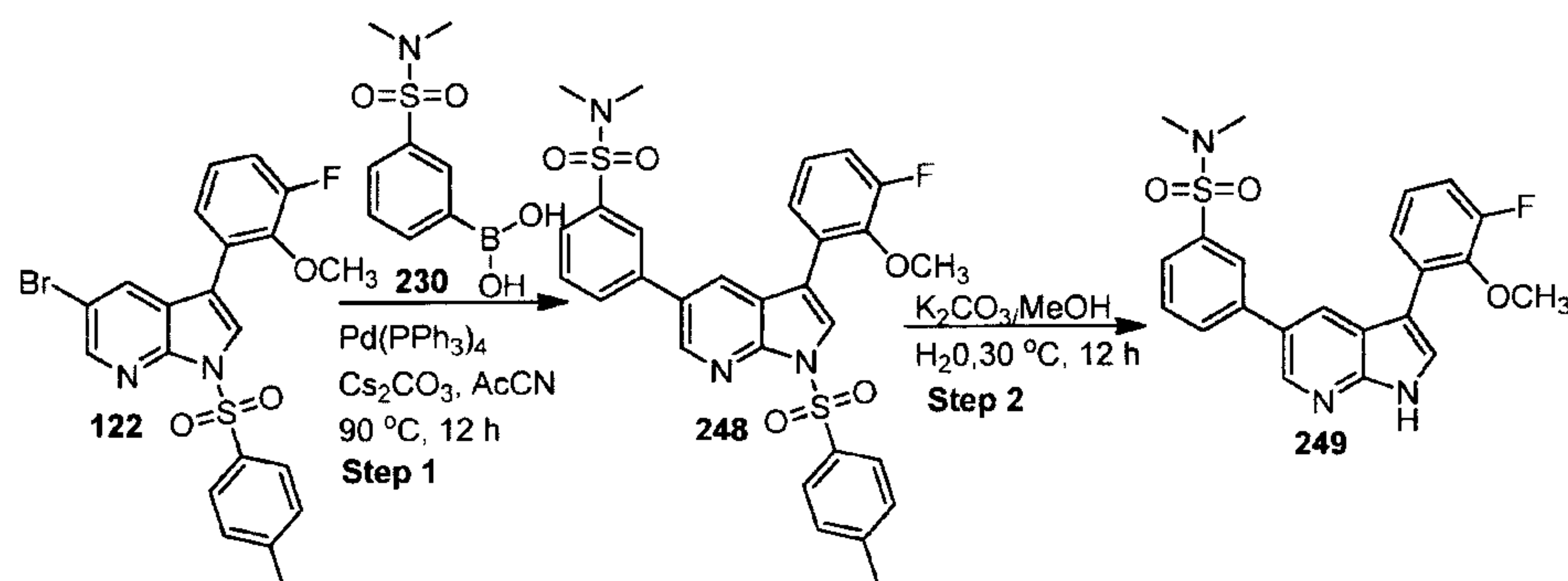
WO 2014/093383

PCT/US2013/074191



[00294] Compound 247:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.63(s,1H), 8.63(s,1H), 8.31(s,1H), 8.09(s,1H), 7.85(m,2H), 7.67(m,1H), 7.63(m,1H), 7.09(m,1H), 6.86(m,1H), 3.70(s,3H), 3.31(m,4H), 1.80(m,4H), MS  $m/z$  = 470.1(M+H).

**PREPARATION OF EXAMPLE 184:** 3-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N,N-dimethylbenzenesulfonamide (**249**):

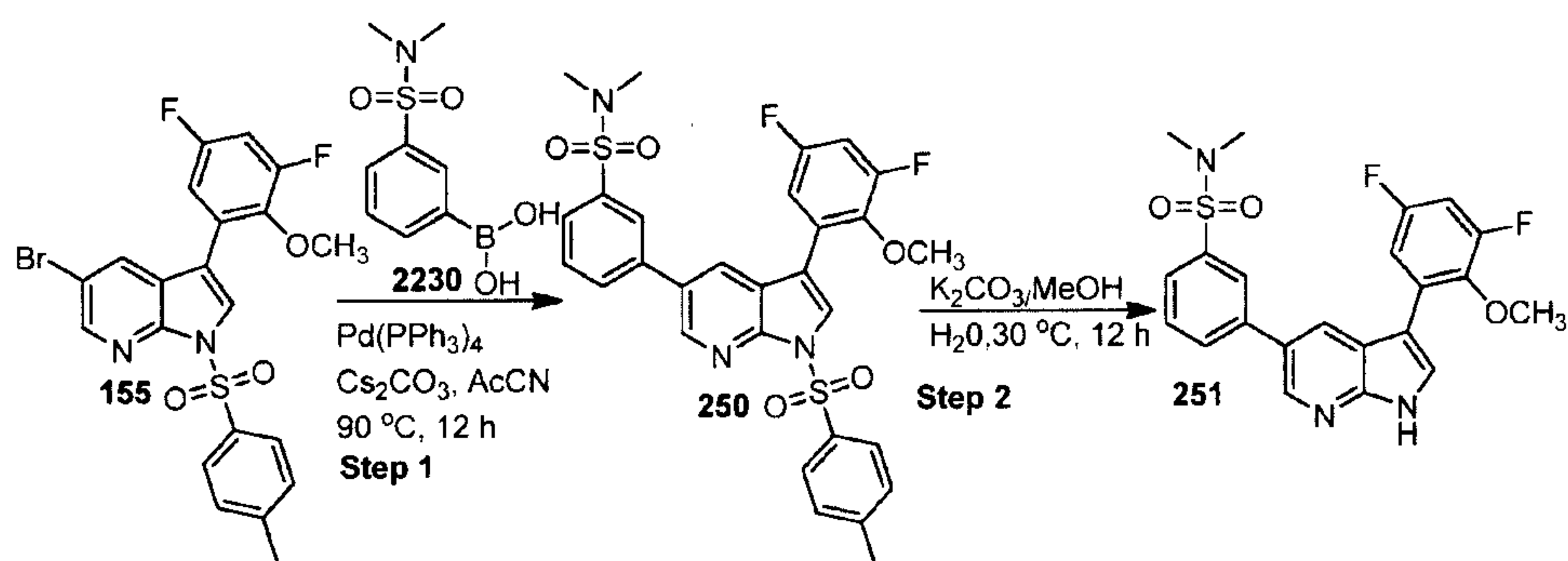


[00295] Compound 249:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.63(s,1H), 8.63(s,1H), 8.31(s,1H), 8.09(s,1H), 7.85(m,2H), 7.67(m,1H), 7.63(m,1H), 7.09(m,1H), 6.86(m,1H), 3.70(s,3H), 3.31(m,4H), 1.80(m,4H), MS  $m/z$  = 470.1(M+H).

**PREPARATION OF EXAMPLE 185:** 3-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N,N-dimethylbenzenesulfonamide (**251**):

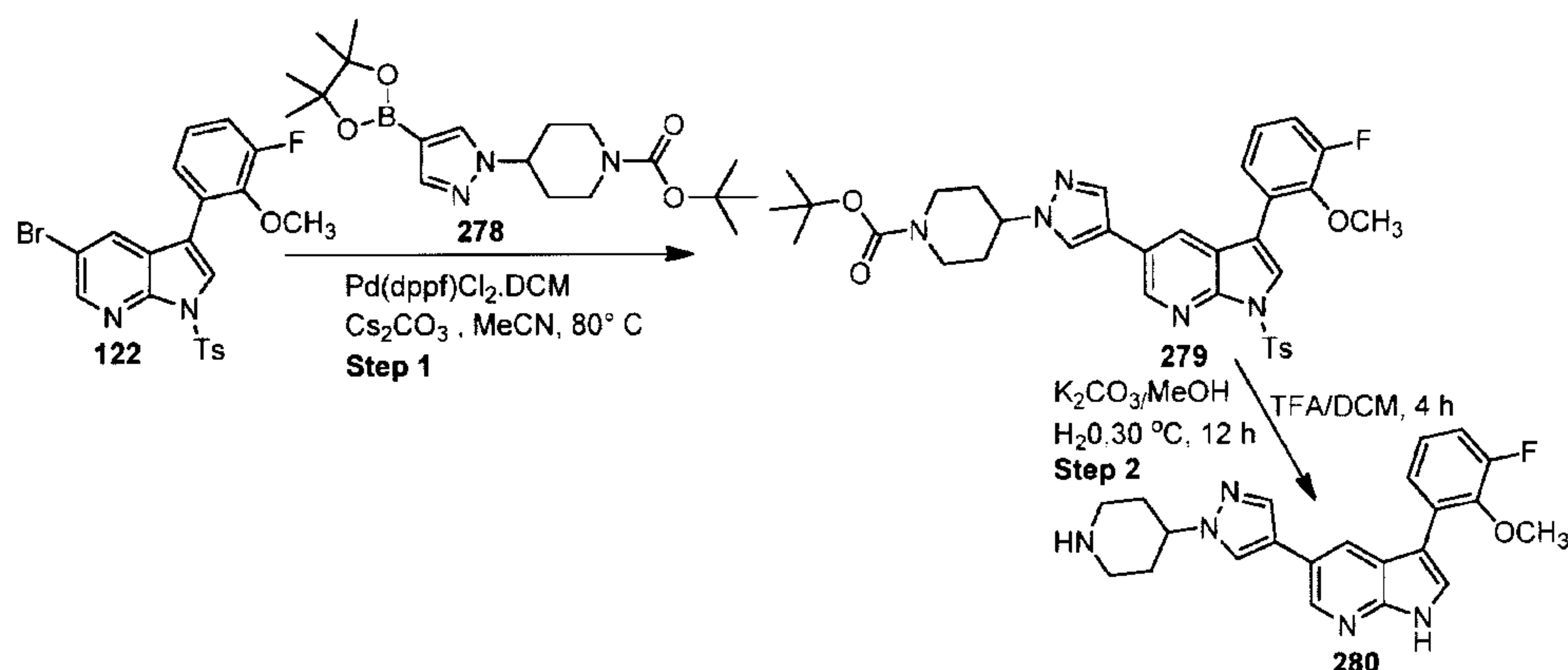
WO 2014/093383

PCT/US2013/074191



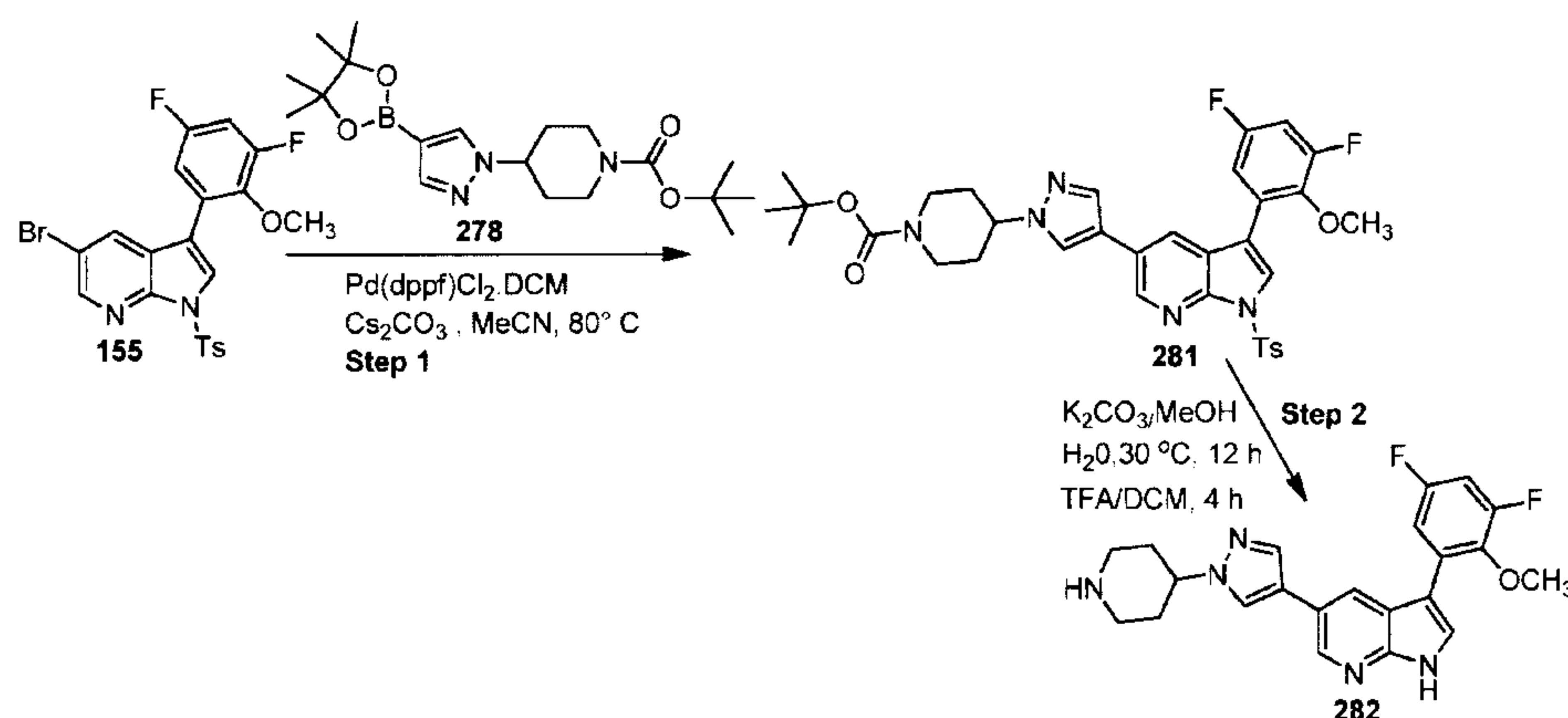
[00296] Compound 251:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.77 (s,1H), 8.61 (s,1H), 8.31 (s,1H), 8.03 (s,1H), 7.86 (d,1H), 7.78 (m,2H), 7.65 (m,1H), 7.09 (m,1H), 6.86 (m,1H), 3.70 (s,3H), 2.77 (s,6H), MS  $m/z$  = 446.13 (M+H).

**PREPARATION OF EXAMPLE 190:** 3-(3-fluoro-2-methoxyphenyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**280**):



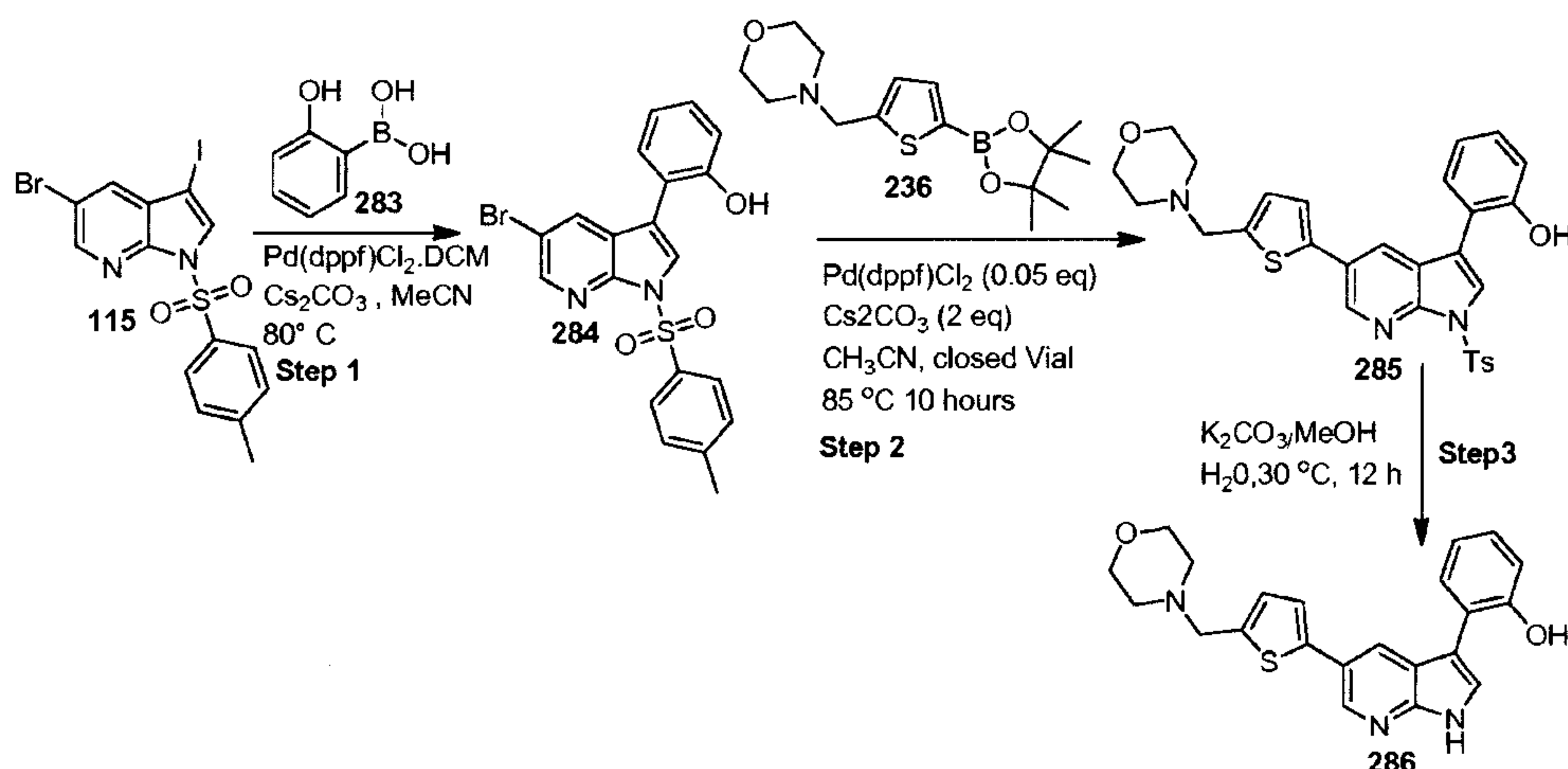
[00297] Compound 280:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.36(s,1H), 8.50(s,1H), 8.17(d,1H), 7.76(m,2H), 7.65(s,1H), 7.35(s,1H), 7.08(m,2H), 4.29(m,1H), 4.05(m,4H), 3.73(s,3H), 3.28(m,2H), 2.81(m,2H), MS-ES+ 392.1 (M+H).

**PREPARATION OF EXAMPLE 191:** 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**282**):



[00298] Compound 282:  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 12.06(s,1H), 8.65(s,1H), 8.57(s,1H), 8.40(d,1H), 8.30(d,1H), 8.20(s,1H), 7.82(d,1H), 7.25(m,2H), 4.50(m,1H), 3.60(s,3H), 3.09(m,2H), 2.23(m,4H), MS-ES+ 410.1 (M+H).

**PREPARATION OF EXAMPLE 192: 2-(5-(5-(morpholinomethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol (286):**



#### Step 1:

[00299] To a solution of **115** (150mg, 0.314mmol) and (2-hydroxyphenyl) boronic acid **283** (43mg, 0.314mmol) in acetonitrile (5mL) was added cesium carbonate (204mg, 0.628mmol). The resulting reaction was degassed and purged with nitrogen for 10min. Pd (dppf)  $\text{Cl}_2$  (12mg, 0.0157mmol) was added to the reaction and the reaction was again degassed and purged with nitrogen for another 5min. The reaction was heated to  $80^\circ\text{C}$  in a sealed tube overnight. After completion, the reaction was allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by

WO 2014/093383

PCT/US2013/074191

using 100-200 mesh silica gel. The compound was eluted at 30% ethyl acetate in hexane as half white coloured solid compound 2-(5-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol **284**.

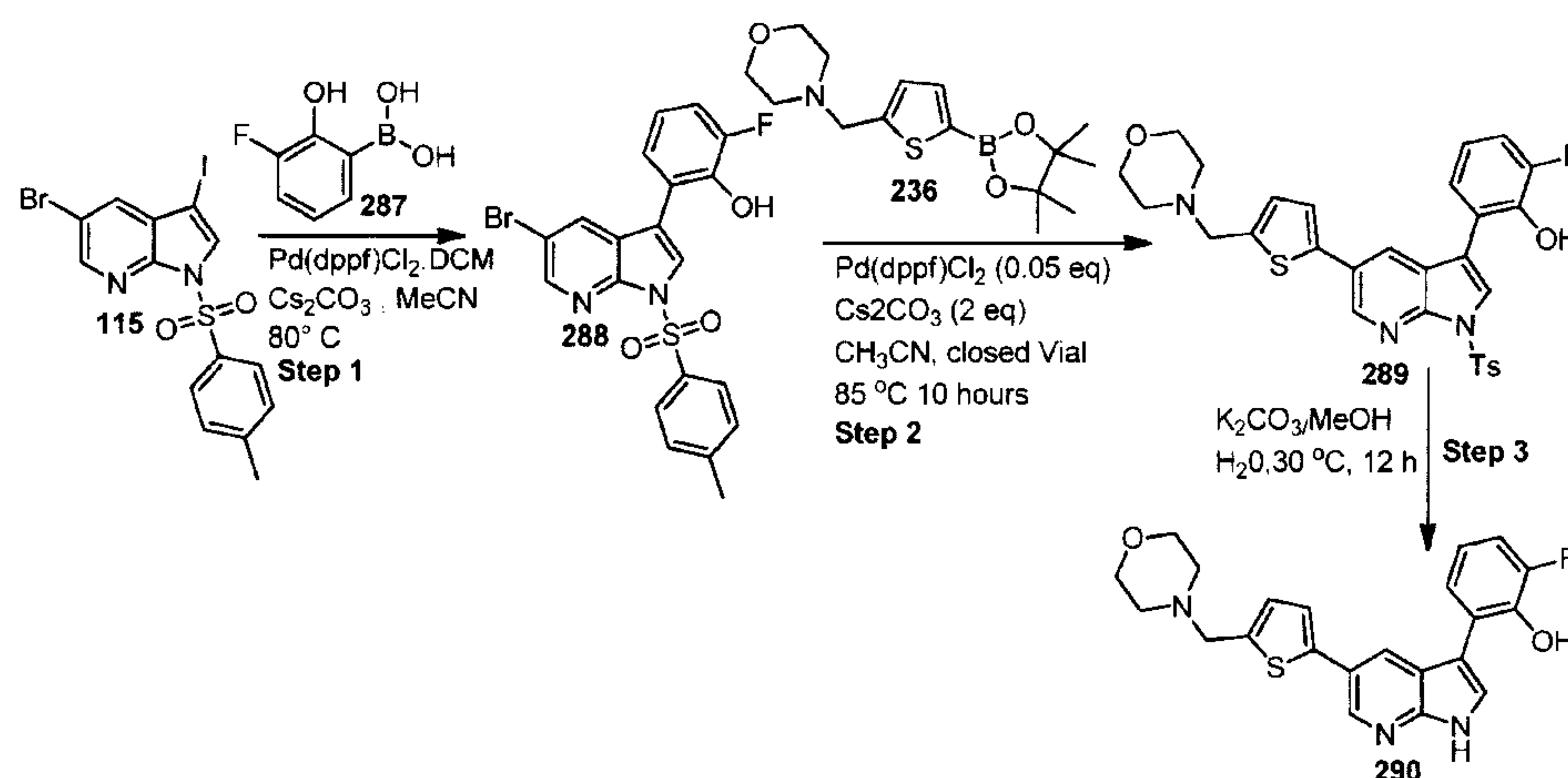
Step 2:

[00300] To a solution of compound **284** (100mg, 0.225mmol) and **236** (51mg, 0.225mmol) in acetonitrile (5mL) was added cesium carbonate (146mg, 0.4451mmol). The reaction was degassed and purged with nitrogen for 10min. Pd (dppf) Cl<sub>2</sub> (9mg, 0.01127mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight. The reaction was allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 60% ethyl acetate in hexane as half-white coloured solid compound **285**.

Step 3:

[00301] To a solution of **285** (50mg, 0.0916mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (37mg, 0.274mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2X25mL). The combined organic layer was dried over sodium sulphate, filtered, and concentrated to get the crude, which was purified through flash chromatography by using neutral alumina. The compound was eluted at 0.5 % methanol in dichloromethane as pale yellow solid compound 2-(5-(5-(morpholinomethyl) thiophen-2-yl)-1H-pyrrolo [2, 3-b] pyridin-3-yl) phenol **286**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.33 (bs, 1H), 8.63 (bs, 1H), 8.11 (d, 1H), 7.52 (d, 1H), 7.41 (m, 2H), 7.30 (m, 1H), 7.12 (m, 1H), 7.07(m, 2H), 6.90 (d, 1H), 3.76 (m, 6H), 2.53(m, 4H) and MS m/z = 392 (M+H).

**PREPARATION OF EXAMPLE 193:** 2-fluoro-6-(5-(5-(morpholinomethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl)phenol (**290**):

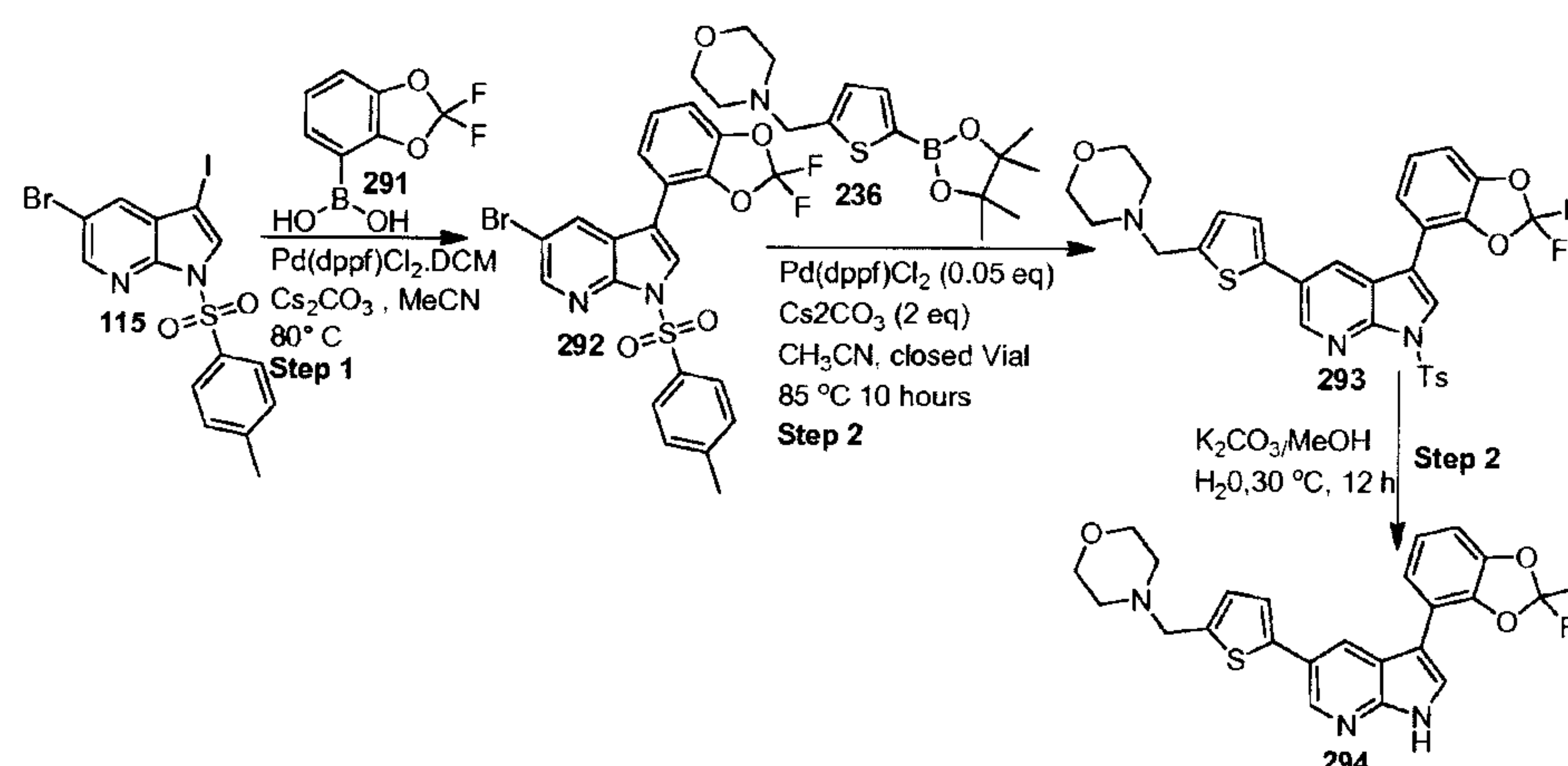
Step 1:

[00302] To a solution of **288** (100mg, 0.216mmol) and **236** (49mg, 0.216mmol) in acetonitrile (7mL) was added cesium carbonate (141mg, 0.433mmol). The reaction was degassed and purged with nitrogen for 10min. Pd(dppf)Cl<sub>2</sub> (8mg, 0.108mmol) was added to the RM, which was again degassed and purged with nitrogen for another 5min. The RM was heated to 80°C in a sealed tube overnight. The reaction was allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude product, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 42% ethyl acetate in hexane as half white colored solid compound **289**.

Step 2:

[00303] To a solution of **289** (50mg, 0.0887mmol) in methanol (15mL) and water (5mL) was added potassium carbonate (36mg, 0.266mmol). The RM was heated to 60°C overnight. The solvent was completely distilled and the RM diluted with water (25mL) and extracted with chloroform twice (2x25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude compound, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 65% ethyl acetate in hexane as pale yellow solid compound **290**. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): 12.00 (bs, 1H), 9.62 (bs, 1H), 8.55 (d, 1H), 8.17 (d, 1H), 7.77 (d, 1H), 7.35 (m, 2H), 7.12 (m, 1H), 6.97 (d, 1H), 6.89 (m, 1H), 3.67 (bs, 2H), 3.57 (m, 4H), 2.43 (m, 4H); MS-ES+ 408.8

**PREPARATION OF EXAMPLE 194:** 4-((5-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine (**294**):

Step 1:

[00304] To a solution of **115** (150mg, 0.314mmol) and **291** (63mg, 0.314mmol) in acetonitrile (5mL) was added cesium carbonate (204mg, 0.628mmol). The RM was degassed and purged with nitrogen for 10min.  $\text{Pd(dppf)Cl}_2$  (12mg, 0.0157mmol) was added and the RM was again degassed and purged with nitrogen for another 5min. The RM was heated to  $80^\circ\text{C}$  in a sealed tube overnight and then allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude product, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 6% ethyl acetate in hexane as half white colored solid compound **292**.

Step 2:

[00305] To a solution of **292** (100mg, 0.197mmol) and **236** (44mg, 0.197mmol) in acetonitrile (7mL) was added cesium carbonate (128mg, 0.394mmol). The RM was degassed and purged with nitrogen for 10min.  $\text{Pd(dppf)Cl}_2$  (8mg, 0.00985mmol) was added, and the RM was again degassed and purged with nitrogen for another 5min, then heated to  $80^\circ\text{C}$  in a sealed tube overnight. The RM was allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude product, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white colored solid compound **293**.

Step 3:

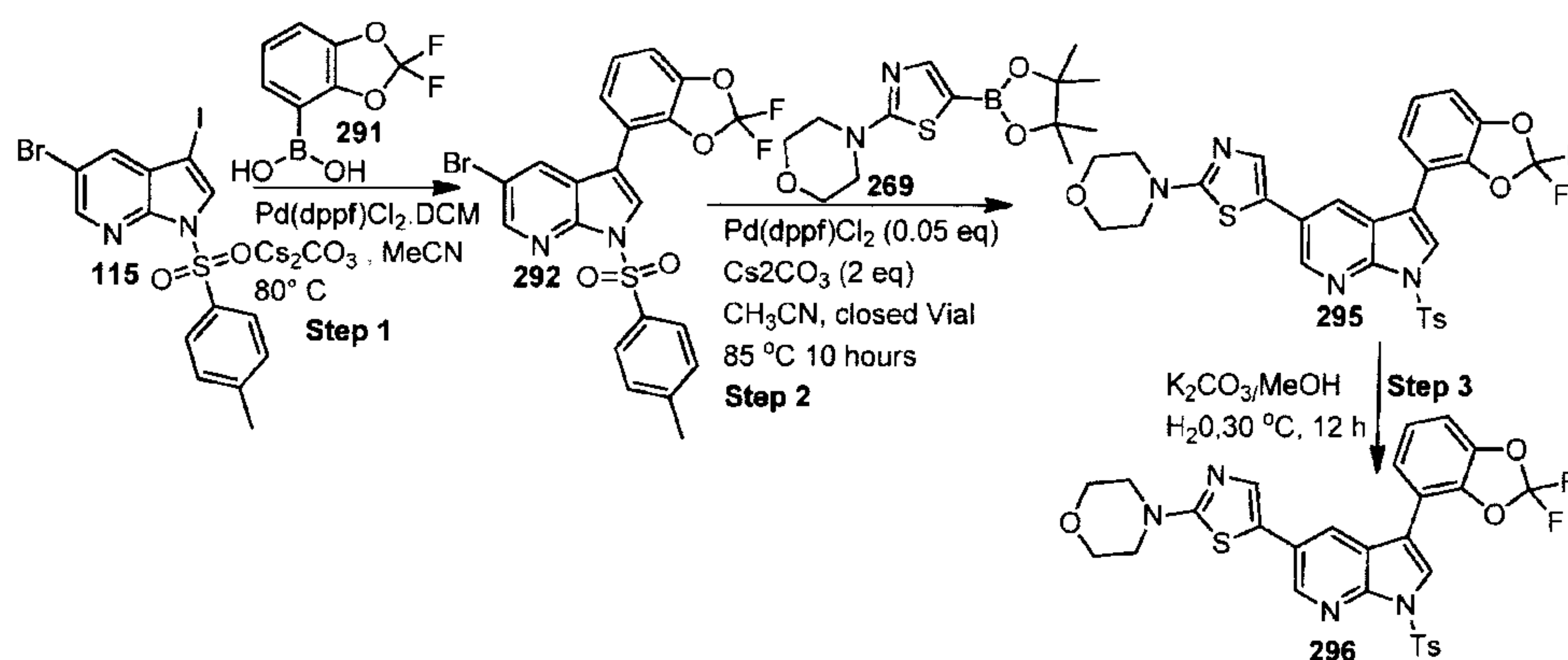
[00306] To a solution of **293** (60mg, 0.9836mmol) in methanol (20mL) and water (8mL) was added potassium carbonate (40mg, 0.295mmol). The RM was heated to  $60^\circ\text{C}$  overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2x25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude compound, which was purified through flash

WO 2014/093383

PCT/US2013/074191

chromatography by using 100-200 mesh silica gel. The compound was eluted at 60% ethyl acetate in hexane as pale yellow solid compound **294**. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): 9.75 (s, 1H), 8.66 (d, 1H), 8.39 (d, 1H), 7.81 (d, 1H), 7.49 (d, 1H), 7.20 (m, 2H), 7.00 (d, 1H), 6.93 (d, 1H), 3.74 (m, 6H), 2.55 (m, 4H) MS-ES+ 456.1

**PREPARATION OF EXAMPLE 195: 4-(5-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine (296):**



#### Step 1:

[00307] To a solution of **292** (100mg, 0.197mmol) and **269** (42mg, 0.197mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.394mmol). The RM was degassed and purged with nitrogen for 10min. Pd(dppf)Cl<sub>2</sub> (8mg, 0.00985mmol) was added and the RM was again degassed and purged with nitrogen for another 5min. The RM was heated to 80°C in a sealed tube overnight, then allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude product, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white colored solid compound **295**.

#### Step 2:

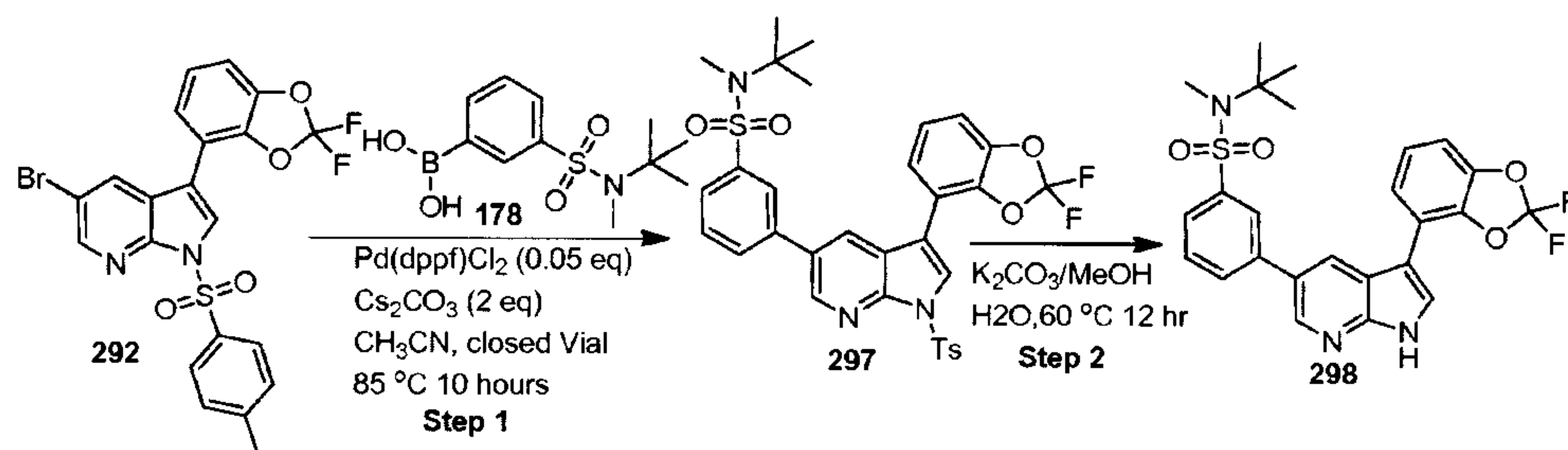
[00308] To a solution of **295** (60mg, 0.1005mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (41mg, 0.3016mmol). The RM was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2x25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude compound. The crude was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 70% ethyl acetate in hexane as pale yellow solid compound **296**. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): 9.51 (bs,

WO 2014/093383

PCT/US2013/074191

1H), 8.52 (d, 1H), 8.23 (d, 1H), 7.77 (d, 1H), 7.44 (m, 2H), 7.20 (t, 1H), 7.00 (d, 1H), 3.84 (m, 4H), 3.53 (m, 4H). MS-ES+ 443.09

**PREPARATION OF EXAMPLE 196:** N-(tertbutyl)-3-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methylbenzene-sulfonamide (**298**)



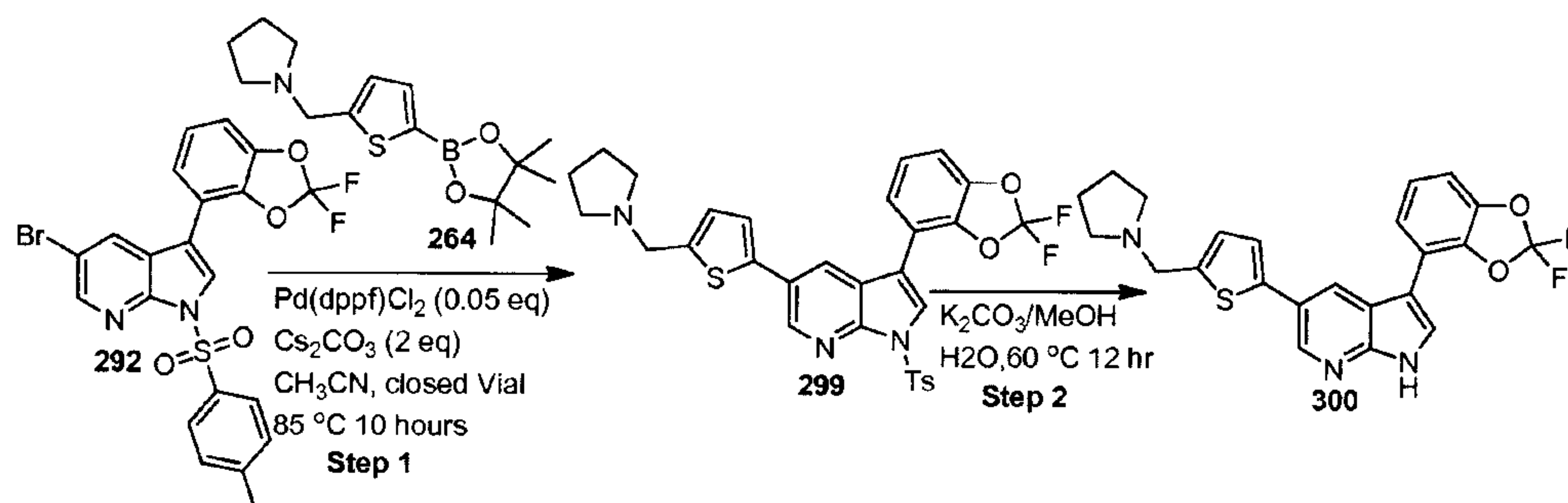
Step 1:

[00309] To a solution of compound **292** (100mg, 0.1971mmol) and **178** (0.53mg, 0.197mol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min and charged with Pd(dppf)Cl<sub>2</sub> (8mg, 0.009856mmol). The reaction was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt, and diluted with chloroform. The organic layer was concentrated to get the crude. The crude was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 35 % ethyl acetate in hexane as half white coloured solid compound **297**.

Step 2:

[00310] To a solution of **297** (70mg, 0.10707mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (44mg, 0.3212mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using neutral alumina. The compound was eluted at 2% methanol in chloroform as half white solid **298**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.66 (bs, 1H), 8.64 (bs, 1H), 8.41 (d, 1H), 8.10 (m, 1H), 7.83 (m, 3H), 7.59 (m, 1H), 7.49 (m, 1H), 7.21 (m, 1H), 7.01 (m, 1H), 3.02 (s, 3H), 1.39 (s, 9H) and MS m/z = 500.1 (M+H).

**PREPARATION OF EXAMPLE 197:** 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(5-(pyrrolidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (**300**)

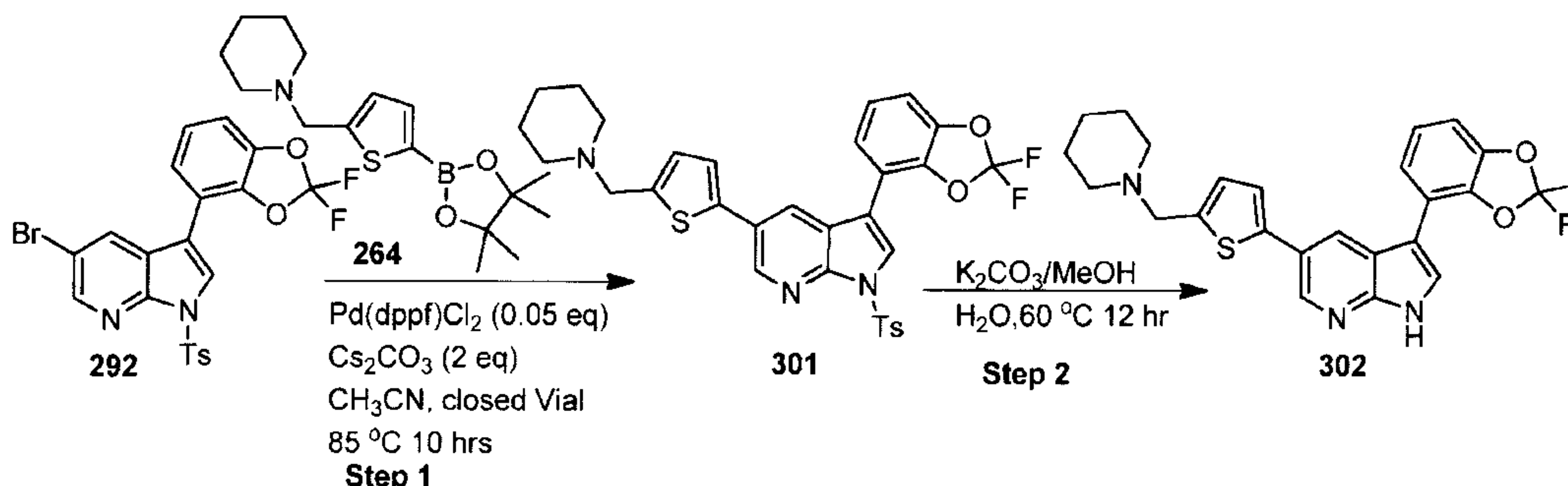
Step 1:

[00311] To a solution of compound **292** (100mg, 0.1971mmol) and **264** (57mg, 0.1971mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min. Pd (dppf) Cl<sub>2</sub> (8mg, 0.00985mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. Eluting at 40% ethyl acetate in hexane gave a half white coloured solid **299**.

Step 2:

[00312] To a solution of **299** (60mg, 0.101mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (41mg, 0.303mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL), and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered, and concentrated to get the crude, which was purified through flash chromatography by using neutral alumina. The compound was eluted at 0.5% methanol in chloroform as pale brown solid compound **300**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.50 (bs, 1H), 8.65 (d, 1H), 8.39 (d, 1H), 7.79 (d, 1H), 7.49 (dd, 1H), 7.20 (m, 2H), 6.99 (dd, 1H), 6.92 (d, 1H), 3.86 (s, 2H), 2.63 (m, 4H), 1.83 (m, 4H) and MS m/z = 440.0 (M+H).

**PREPARATION OF EXAMPLE 198:** 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(5-(piperidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (**302**)



WO 2014/093383

PCT/US2013/074191

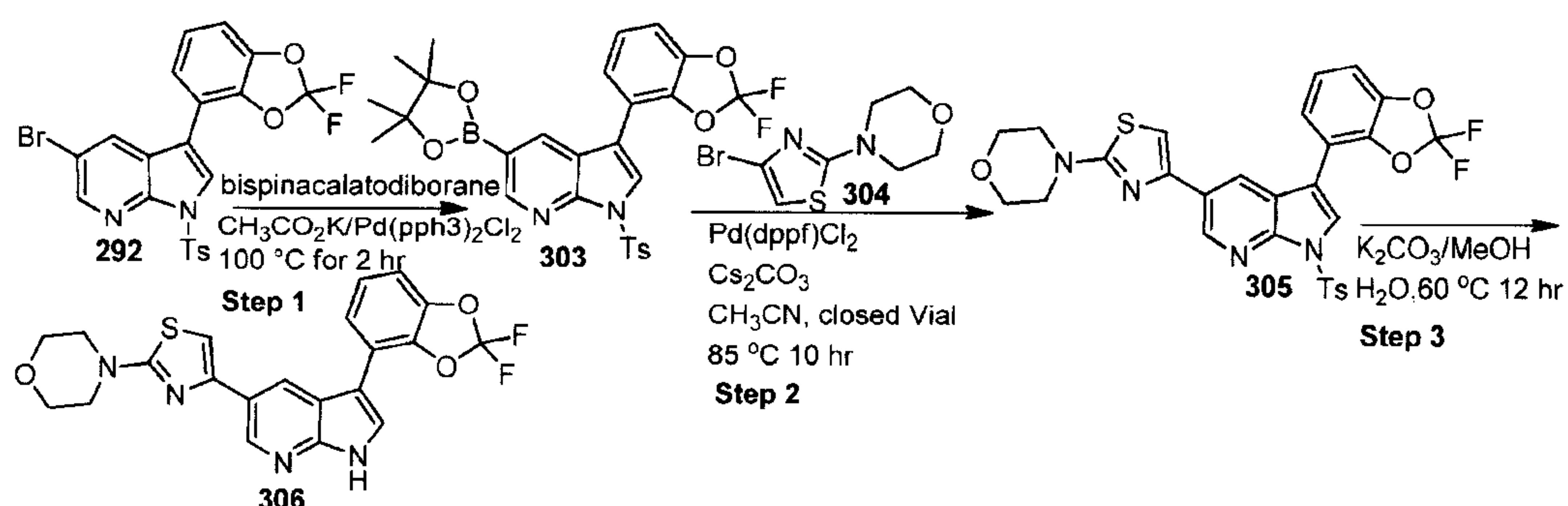
Step 1:

[00313] To a solution of compound **292** (100mg, 0.1971mmol) and **264** (0.53mg, 0.197mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min and Pd (dppf) Cl<sub>2</sub> (8mg, 0.009856mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight. The reaction was allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white coloured solid **301**.

Step 2:

[00314] To a solution of **301** (60mg, 0.0987mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (40mg, 0.2963mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off, the remainder diluted with water (25mL), and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate filtered and concentrated to get the crude, which was purified through flash chromatography by using neutral alumina. The compound was eluted at 1.5% methanol in chloroform as pale yellow solid **302**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.53 (bs, 1H), 8.66 (d, 1H), 8.39 (d, 1H), 7.79 (d, 1H), 7.49 (d, 1H), 7.20 (m, 2H), 7.00 (d, 1H), 6.90 (d, 1H), 3.71 (s, 2H), 2.48 (bs, 4H), 1.63 (m, 4H), 1.45 (m, 2H) and MS m/z = 454.1 (M+H).

**PREPARATION OF EXAMPLE 199:** 4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine (**306**).

Step 1:

[00315] To a solution of **292** (400mg, 0.788mmol) in DMF was added potassium acetate (154mg, 1.576mmol) and bispinacalatodiborane (400mg, 1.576mmol). The reaction mixture was degassed and purged with nitrogen for 10min. Pd (pph<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (27mg, 0.03942mmol) was added and again degassed and purged with nitrogen for 10min. The reaction was heated to

100°C for 2h. After completion of the reaction, the RM was diluted with chloroform and washed with cold water followed by Brine solution. The organic layer was dried over sodium sulphate and evaporated to get the crude, which was triturated with Hexane to afford a brown solid 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine **303** taken up for next step without further purification.

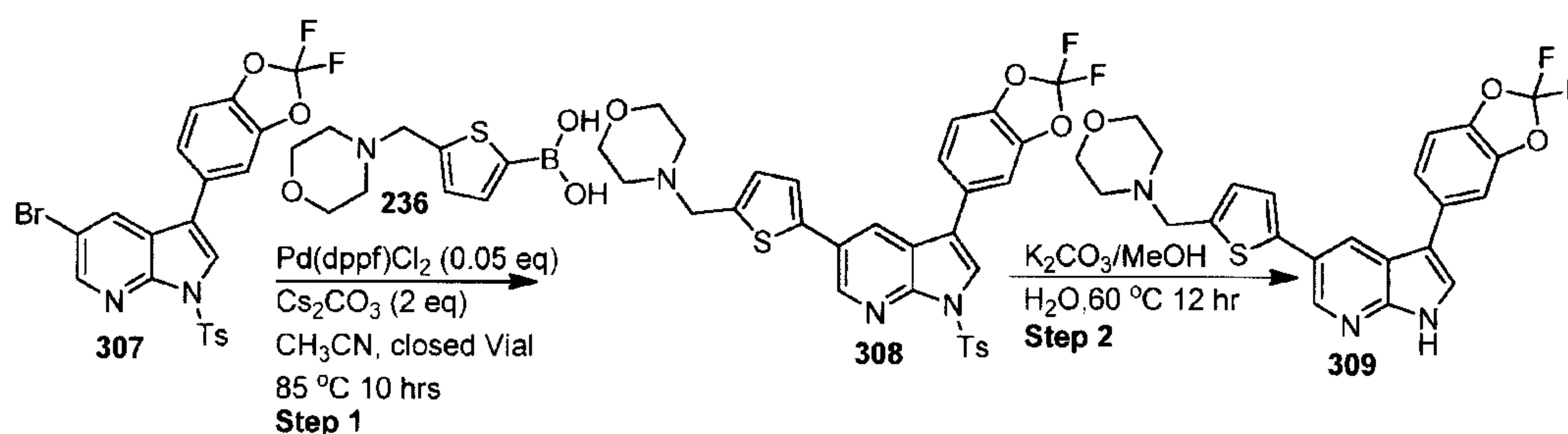
#### Step 2:

[00316] To a solution of **303** (438mg, 0.786mmol) and **304** (196mg, 0.786mmol) in acetonitrile (10mL) was added cesium carbonate (512mg, 0.157mmol). The reaction was degassed and purged with nitrogen for 10min. Pd (dppf) Cl<sub>2</sub> (32mg, 0.0393mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight. The reaction was allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white coloured solid **305**.

#### Step 3:

[00317] To a solution of **305** (200mg, 0.335mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (138mg, 1.01005mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 5 % methanol in chloroform as pale yellow solid 4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine **306**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 12.30 (s, 1H), 8.87 (d, 1H), 8.67 (d, 1H), 7.95 (d, 1H), 7.61 (m, 1H), 7.41 (s, 1H), 7.31 (m, 2H), 3.73 (m, 4H), 3.45 (m, 4H) and MS m/z = 443.0 (M+H).

**PREPARATION OF EXAMPLE 200:** 4-((5-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine (**309**).



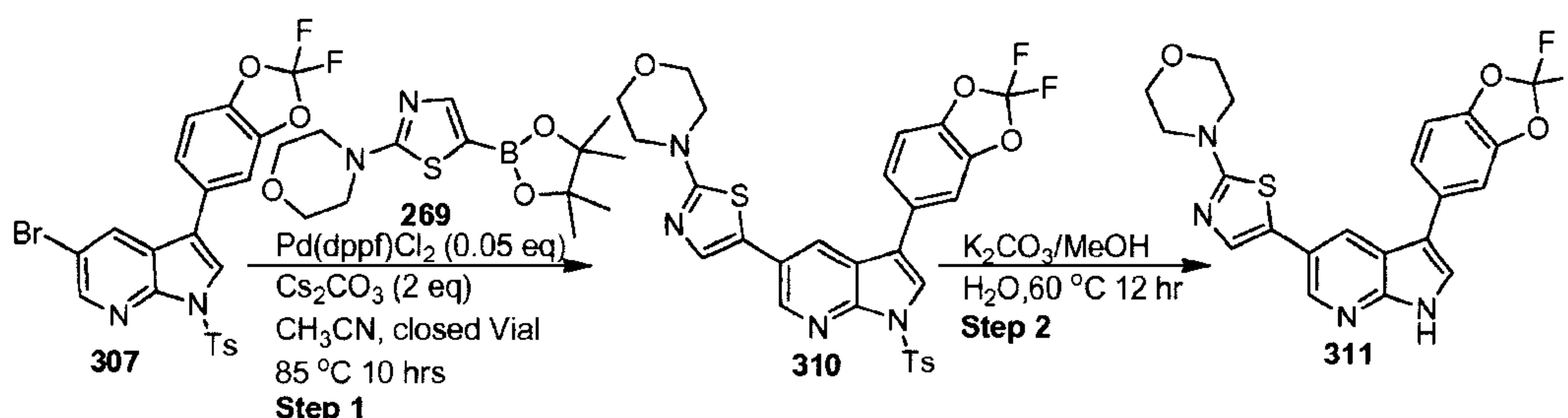
#### Step 1:

[00318] To a solution of **307** (100mg, and 0.197mmol) and **236** (60mg, 0.197mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min. Pd (dppf) Cl<sub>2</sub> (8mg, 0.00985mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt, and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 50% ethyl acetate in hexane as half white coloured solid **308**.

#### Step 2:

[00319] To a solution of **308** (70mg, 0.1148mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (47mg, 0.344mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using neutral alumina. The compound was eluted at 2% methanol in dichloromethane as pale yellow solid 4-((5-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiophen-2-yl)methyl)morpholine **309**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.13 (s, 1H), 8.63 (d, 1H), 8.25 (d, 1H), 7.45 (d, 1H), 7.32 (m, 2H), 7.15 (m, 2H), 6.92 (d, 1H), 3.75 (m, 4H), 3.73 (m, 2H), 2.55 (m, 4H) and MS m/z = 454.1 (M+H).

**PREPARATION OF EXAMPLE 201:** 4-(5-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine (**311**)



#### Step 1:

[00320] A solution of **307** (100mg, 0.1971mmol) and **269** (58mg, 0.01971mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min. Pd (dppf) Cl<sub>2</sub> (8mg, 0.009856mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through

WO 2014/093383

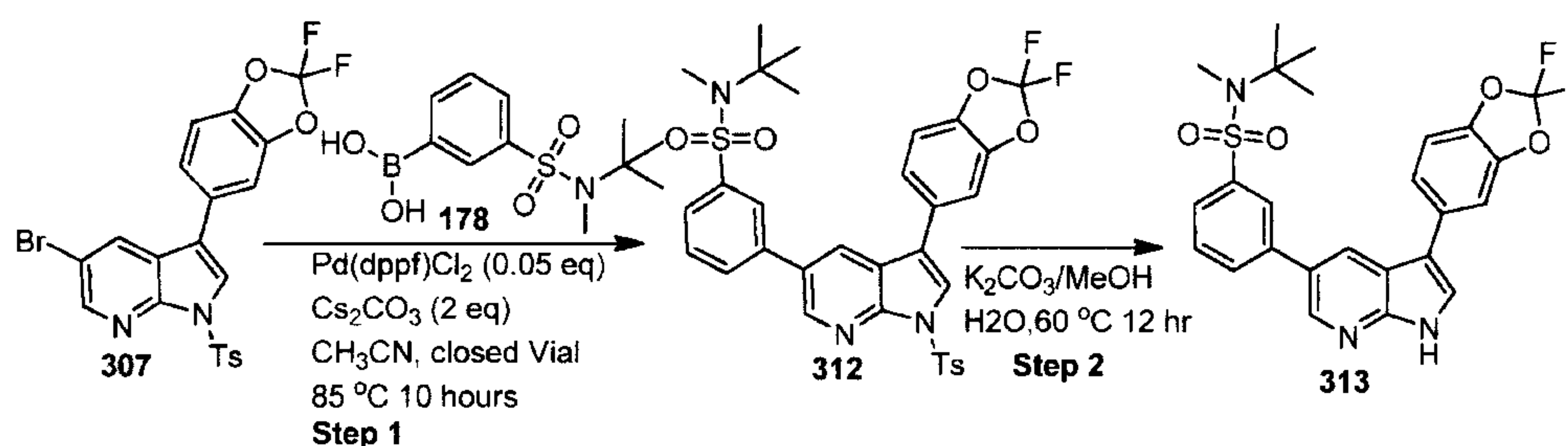
PCT/US2013/074191

flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 30% ethyl acetate in hexane as half white coloured solid **310**.

#### Step 2:

[00321] To a solution of **310** (60mg, 0.1005mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (41mg, 0.30169mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using neutral alumina. The compound was eluted at 70% ethyl acetate in hexane as a half white solid 4-(5-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine **311**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.19 (s, 1H), 8.51 (s, 1H), 8.09 (d, 1H), 7.45 (m, 2H), 7.30 (m, 2H), 7.15 (d, 1H), 3.84 (m, 4H), 3.53 (m, 4H) and MS m/z = 443.0 (M+H).

**PREPARATION OF EXAMPLE 202:** N-(tert-butyl)-3-(3-(2,2-difluorobenzo[d][1,3] dioxol-5-yl) 1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methylbenzenesulfonamide (**313**).



#### Step 1:

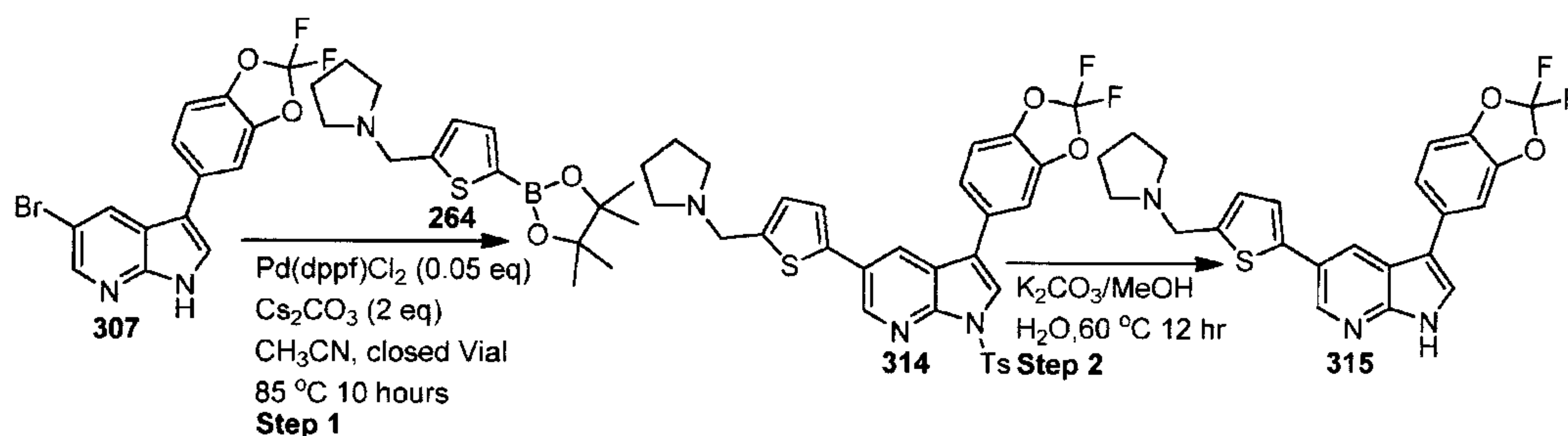
[00322] To a solution of **307** (100mg, 0.1971mmol) and **178** (53mg, 0.1971mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min. Pd (dppf) Cl<sub>2</sub> (8mg, 0.009856mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 46 % ethyl acetate in hexane as half white coloured solid **313**.

#### Step 2:

[00323] To a solution of **313** (70mg, 0.10708mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (44mg, 0.3212mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was

dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 1.5 % methanol in chloroform as pale yellow solid N-(tert-butyl)-3-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N methylbenzene-sulphonamide **313**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.44 (s, 1H), 8.61 (d, 1H), 8.29 (d, 1H), 8.08 (d, 1H), 7.81 (m, 2H), 7.60 (t, 1H), 7.52 (m, 1H), 7.34 (m, 2H), 7.16 (d, 1H), 3.01 (s, 3H), 1.39 (s, 9H) and MS ES + 500.1.

**PREPARATION OF EXAMPLE 203:** 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(pyrrolidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (**315**)



#### Step 1:

[00324] To a solution of **292** (100mg, 0.0001971mmol) and **264** (58mg, 0.1971mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min and Pd (dppf) Cl<sub>2</sub> DCM (8mg, 0.00985mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 36 % ethyl acetate in hexane as half white coloured solid compound **314**.

#### Step 2:

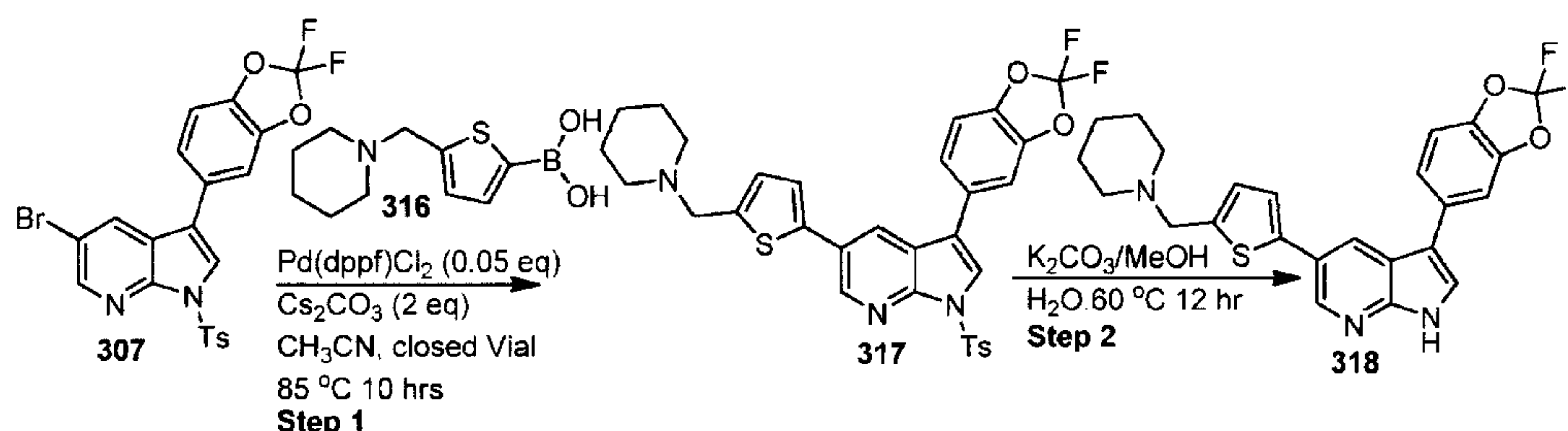
[00325] To a solution of **314** (60mg, 0.101mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (41mg, 0.303mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 3% Methanol in chloroform as half white solid 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(pyrrolidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine **315**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 9.27 (s, 1H),

WO 2014/093383

PCT/US2013/074191

8.63 (d, 1H), 8.26 (d, 1H) 7.45 (d, 1H), 7.34 (m, 2H), 7.16 (m, 2H), 6.91 (d, 1H), 3.85 (s, 2H), 2.62 (bs, 4H), 1.83 (bs, 4H) MS ES+ 440.0.

**PREPARATION OF EXAMPLE 204:** 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(piperidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (**318**).



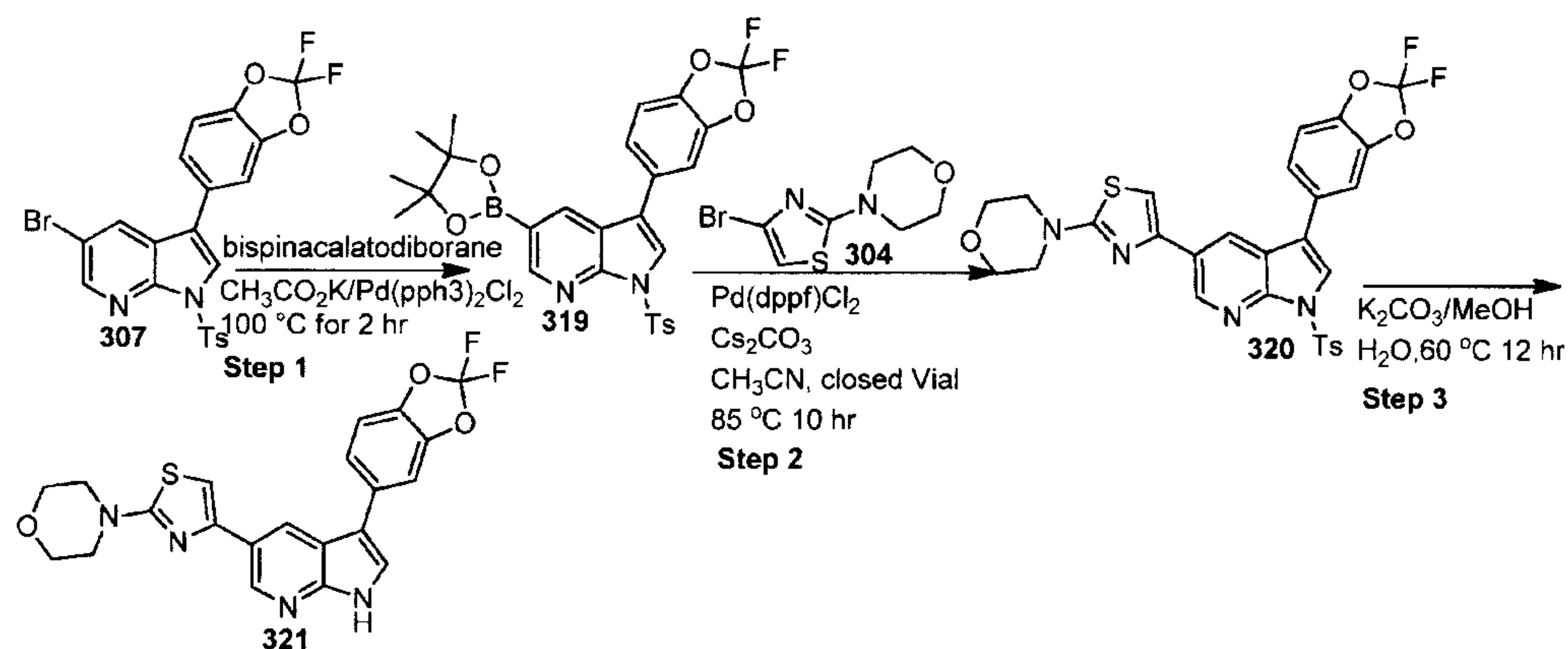
#### Step 1:

[00326] To a solution of **307** (100mg, 0.1971mmol) and **316** (60mg, 0.1971mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min.  $\text{Pd(dppf)Cl}_2$  (8mg, 0.00985mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to  $80^\circ\text{C}$  in a sealed tube overnight, allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 45 % ethyl acetate in hexane as half white coloured solid **317**.

#### Step 2:

[00327] To a solution of **317** (60mg, 0.0987mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (40mg, 0.2962mmol). The reaction was heated to  $60^\circ\text{C}$  overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude. The crude was purified through flash chromatography by using neutral alumina. The compound was eluted at 0.5 % methanol in dichloromethane as pale yellow solid 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(5-(piperidin-1-ylmethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine **318**.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 9.29 (s, 1H), 8.63 (d, 1H), 8.26 (d, 1H), 7.45 (d, 1H), 7.32 (m, 2H), 7.15 (m, 2H), 6.89 (d, 1H), 3.70 (s, 2H), 2.47 (s, 4H), 1.61 (m, 4H), 1.25 (m, 2H) and MS ES+ 454.1.

**PREPARATION OF EXAMPLE 205:** 4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine (**321**)

Step 1:

[00328] To a solution of **307** (400mg, 0.788mmol) in DMF was added potassium acetate (154mg, 1.576mmol) and bispinacalatodiborane (400mg, 1.576mmol). The reaction mixture was degassed and purged with nitrogen for 10min.  $\text{Pd}(\text{pph}_3)_2\text{Cl}_2$  (27mg, 0.03942mmol) was added and again degassed and purged with nitrogen for 10min. The reaction was heated to  $100^\circ\text{C}$  for 2h. After completion of the reaction the RM was diluted with chloroform and washed with cold water followed by Brine solution. The organic layer was dried over sodium sulphate and evaporated to get the crude, which was triturated with Hexane to afford brown solid **319**. The solid itself proceeded for next step without further purification.

Step 2:

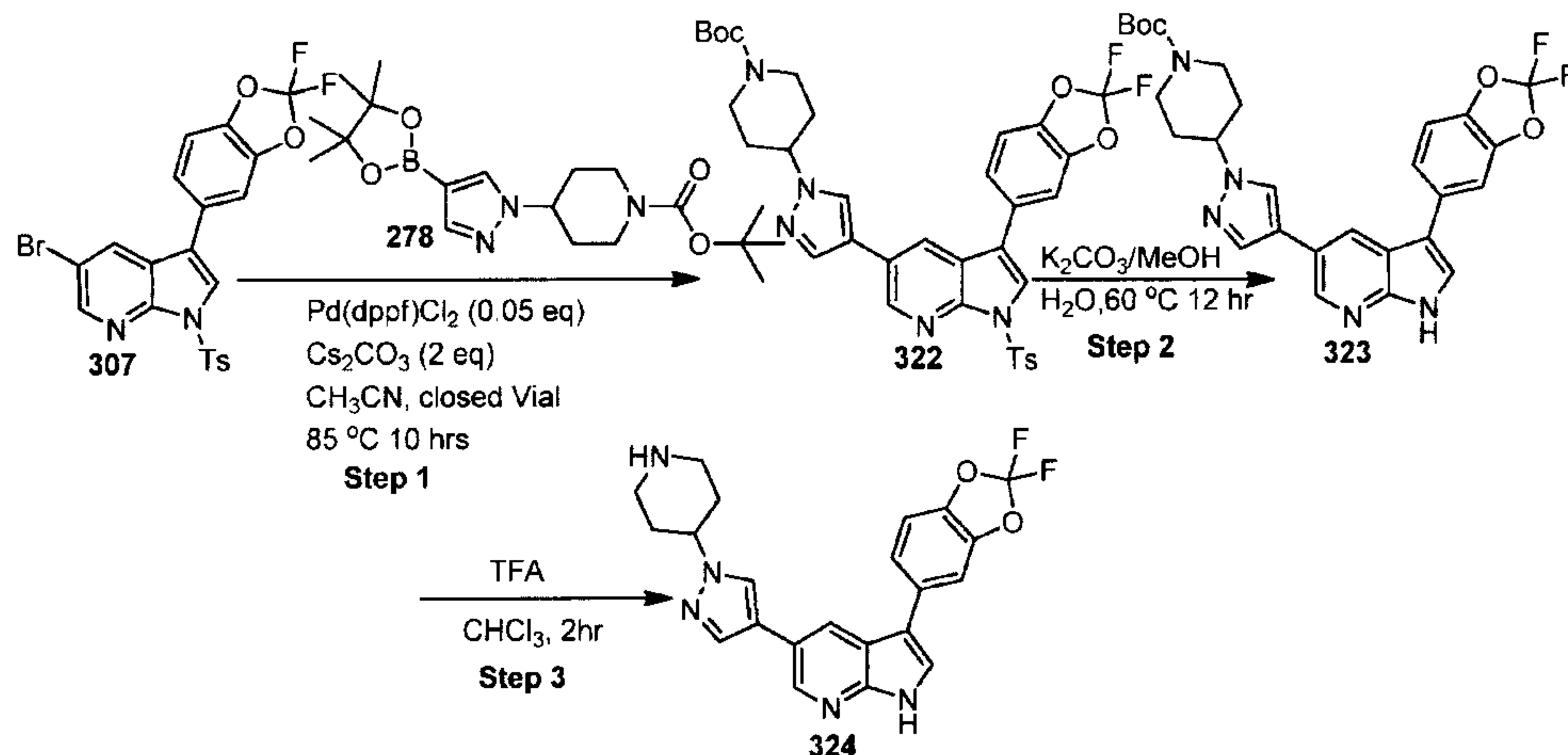
[00329] To a solution of **319** (438mg, 0.786mmol) and **304** (196mg, 0.786mmol) in acetonitrile (10mL) was added cesium carbonate (512mg, 0.157mmol). The reaction was degassed and purged with nitrogen for 10min.  $\text{Pd}(\text{dppf})\text{Cl}_2$  (32mg, 0.0393mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to  $80^\circ\text{C}$  in a sealed tube overnight, allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white coloured solid **320**.

Step 3:

[00330] To a solution of **320** (200mg, 0.335mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (138mg, 1.01005mmol). The reaction was heated to  $60^\circ\text{C}$  overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at

5 % methanol in chloroform as pale yellow solid 4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine **321**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 10.05 (s, 1H), 8.84 (s, 1H), 8.53 (s, 1H), 7.44 (d, 1H), 7.34 (d, 3H), 7.14 (d, 1H), 6.83 (s, 1H), 3.85 (t, 4H), 3.55 (t, 4H) and MS ES + 443.00.

**PREPARATION OF EXAMPLE 206:** 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**324**).



#### Step 1:

[00331] To a solution of **307** (100mg, 0.1971mmol) and **278** (74mg, 0.1971mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min and Pd (dppf) Cl<sub>2</sub> (8mg, 0.00985mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white coloured solid **322**.

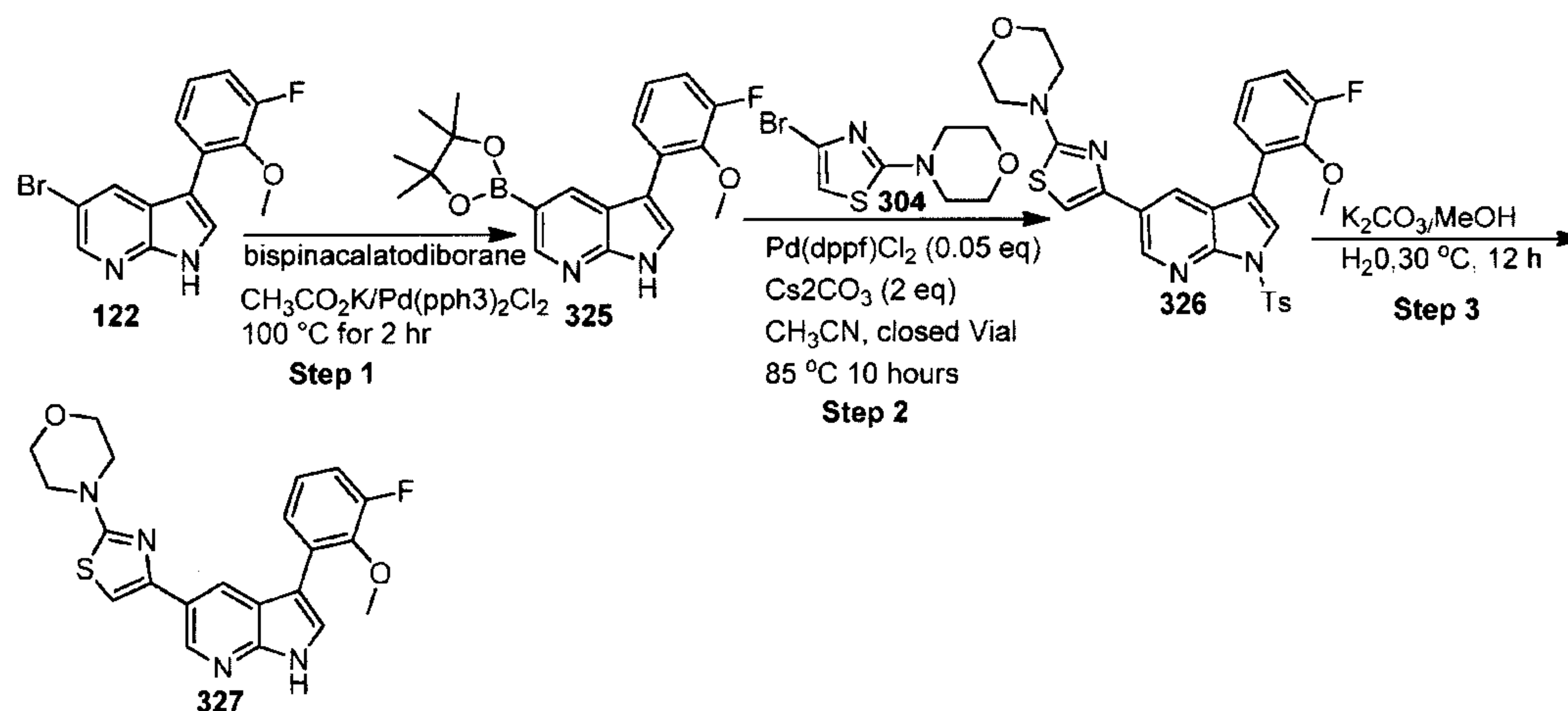
#### Step 2:

[00332] To a solution of **322** (70mg, 0.1033mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (42mg, 0.31009mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 70% ethyl acetate in Hexane as pale yellow solid **323**.

#### Step 3:

[00333] A solution of **323** (0.050mg, 0.0955mmol) in  $\text{CHCl}_3$  (20mL) was taken and added TFA (5mL) at rt. The reaction mixture was stirred for 2h at rt. After confirmation of TLC, the reaction mixture evaporated TFA completely then taken in  $\text{CHCl}_3$  and washed with  $\text{Na}_2\text{CO}_3$  solution followed by water wash. Organic layer was dried with  $\text{Na}_2\text{SO}_4$  and evaporated. The resulting crude was purified via silica gel chromatography using a gradient of 3% methanol in chloroform to afford pale brown solid 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **324**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 11.94 (s, 1H), 8.55 (d, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 7.99 (s, 1H), 7.89 (s, 1H), 7.79 (s, 1H), 7.59 (d, 1H), 7.44 (d, 1H), 4.17 (m, 1H), 3.04 (m, 2H), 2.57 (m, 2H), 1.98 (m, 2H), 1.81 (m, 2H) and MS ES+ 424.0.

**PREPARATION OF EXAMPLE 207:** 4-(4-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine (**327**).



#### Step 1:

[00334] To a solution of **122** (400mg, 0.8415mmol) in DMF was added potassium acetate (165mg, 1.683mmol) and bispinacalatodiborane (427mg, 1.683mmol). The reaction mixture was degassed and purged with nitrogen for 10min and  $\text{Pd}(\text{pph}_3)_2\text{Cl}_2$  (29mg, 0.0427mmol) was added, again degassed and purged with nitrogen for 10min. The reaction was heated to 100°C for 2h. After completion of the reaction, the RM was diluted with chloroform and washed with cold water followed by brine solution. The organic layer was dried over sodium sulphate and evaporated to get the crude, which was triturated with hexane to afford brown solid. The solid itself was used in the next step without further purification.

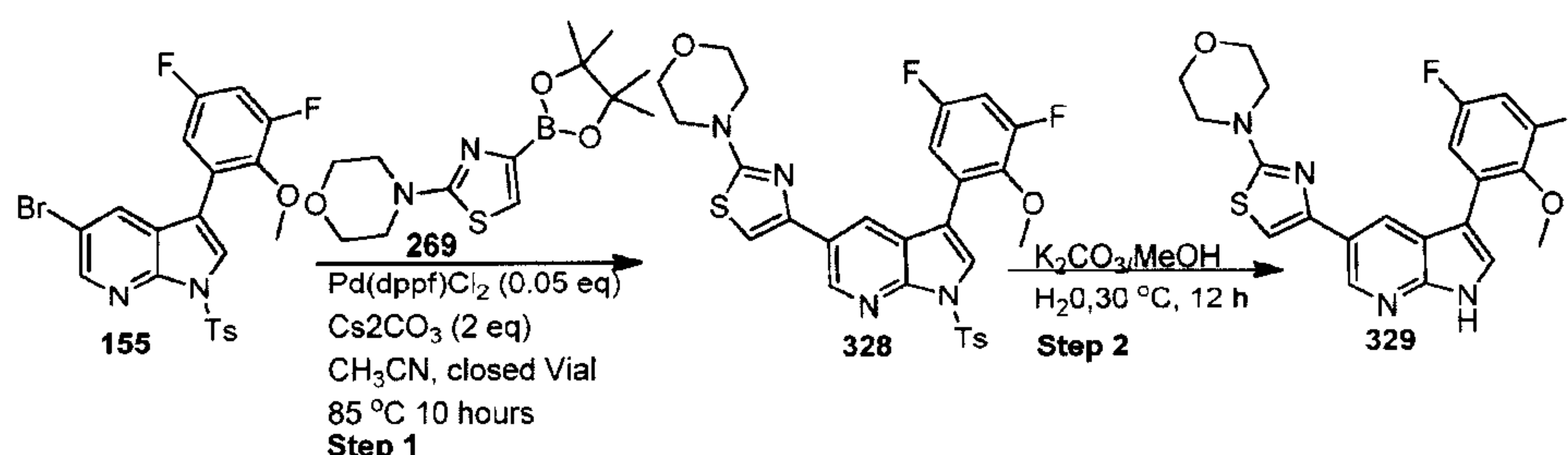
#### Step 2:

[00335] To a solution of **325** (441mg, 0.841mmol) and **304** (209mg, 0.841mmol) in acetonitrile (10mL) was added cesium carbonate (547mg, 1.681mmol). The reaction was degassed and purged with nitrogen for 10min. Pd(dppf)Cl<sub>2</sub> DCM (34mg, 0.04203mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt, and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white coloured solid **326**.

#### Step 3:

[00336] To a solution of **326** (200mg, 0.335mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (138mg, 1.0056 mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 5 % methanol in chloroform as pale yellow solid 4-(4-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine **327**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 9.52 (s, 1H), 8.86 (s, 1H), 8.54 (s, 1H), 7.68 (s, 1H), 7.38 (d, 1H), 7.07 (m, 2H), 6.82 (s, 1H), 3.85 (t, 4H), 3.75 (s, 3H), 3.55 (t, 4H) and MS ES+ 411.0.

#### PREPARATION OF EXAMPLE 208: 4-(4-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine (**329**)



#### Step 1:

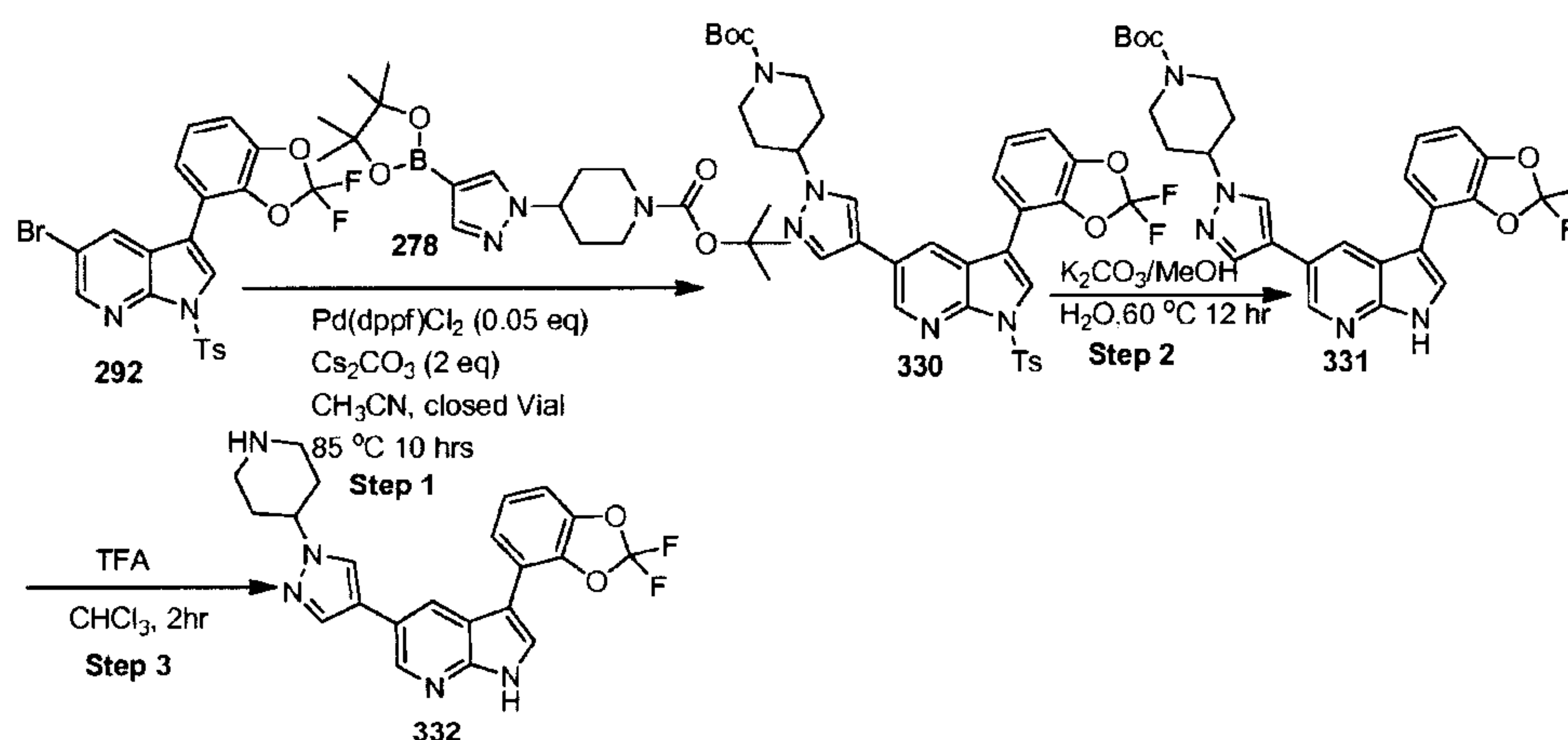
[00337] To a solution of **155** (40mg, 0.08108mmol) and **269** (24mg, 0.08108mmol) in acetonitrile (5mL) was added cesium carbonate (52mg, 0.161mmol). The reaction was degassed and purged with nitrogen for 10min. Pd(dppf)Cl<sub>2</sub> (3mg, 0.04054mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt, and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through

flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white coloured solid **328**.

#### Step 2:

[00338] To a solution of **328** (25mg, 0.0429mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (17mg, 0.107mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using neutral alumina. The compound was eluted at 1.5 % methanol in chloroform as pale yellow solid 4-(4-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thiazol-2-yl)morpholine **329**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 9.46 (s, 1H), 8.87 (s, 1H), 8.54 (s, 1H), 7.73 (s, 1H), 7.14 (s, 1H), 6.84 (m, 2H), 3.85 (m, 4H), 3.69 (s, 3H), 3.57 (m, 4H) and MS ES + 429.0.

**PREPARATION OF EXAMPLE 209: 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**332**)**



#### Step 1:

[00339] To a solution of **292** (100mg, 0.1971mmol) and **278** (74mg, 0.1971mmol) in acetonitrile (5mL) was added cesium carbonate (128mg, 0.3942mmol). The reaction was degassed and purged with nitrogen for 10min. Pd(dppf)Cl<sub>2</sub> (8mg, 0.00985mmol) was added to the reaction, which was again degassed and purged with nitrogen for another 5min. The reaction was heated to 80°C in a sealed tube overnight, allowed to cool to rt, and diluted with chloroform. The organic layer was concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 40% ethyl acetate in hexane as half white coloured solid **330**.

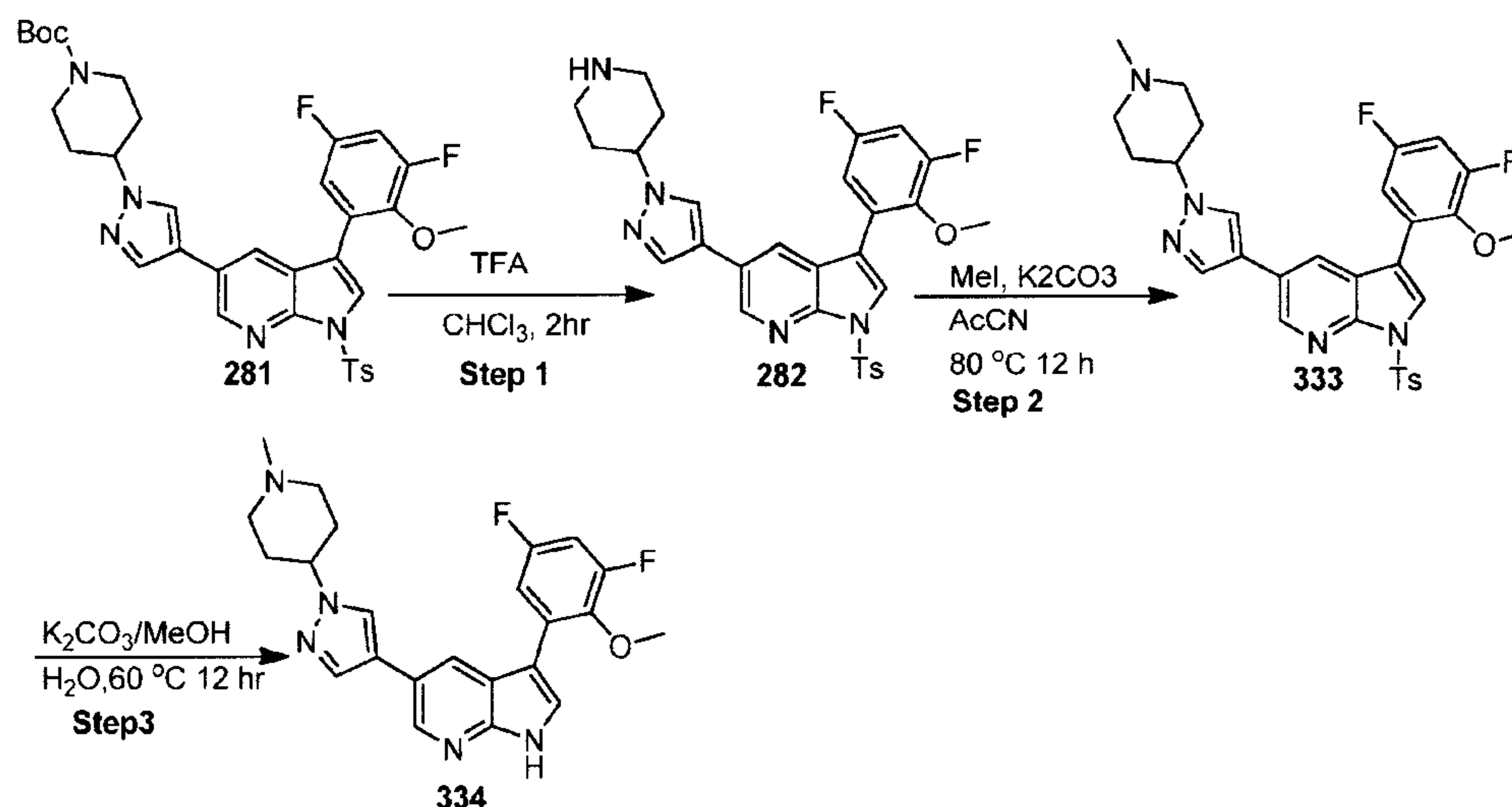
Step 2:

[00340] To a solution of **330** (70mg, 0.1033mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (42mg, 0.31009mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 70% ethyl acetate in hexane as pale yellow solid **331**.

Step 3:

[00341] A solution of **331** (0.050 gm, 0.0955mmol) in CHCl<sub>3</sub> (20mL) was taken and added TFA (5mL) at rt. The reaction mixture was stirred for 2 hr at rt. After TLC confirmation, the RM was evaporated TFA completely then taken in CHCl<sub>3</sub> and washed with Na<sub>2</sub>CO<sub>3</sub> solution followed by water wash. Organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated. The resulting crude was purified via silica gel chromatography using a gradient of 3% methanol in chloroform to afford pale brown solid 3-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **332**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.90 (s, 1H), 8.59 (d, 1H), 8.29 (d, 1H), 7.89 (s, 1H), 7.84 (d, 1H), 7.77 (d, 1H), 7.49 (dd, 1H), 7.18 (t, 1H), 7.00 (dd, 1H), 4.29 (m, 1H), 3.29 (d, 2H), 2.80 (m, 2H), 2.21 (m, 2H), 2.03 (m, 2H) and MS ES +424.0.

**PREPARATION OF EXAMPLE 212:** 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**334**).

Step 1:

WO 2014/093383

PCT/US2013/074191

[00342] A solution of **281** (300mg, 0.451mmol) in  $\text{CHCl}_3$  (20mL) was taken and added TFA (5mL) at rt. The reaction mixture was stirred for 2h at rt. After TLC confirmation, RM evaporated TFA completely, then taken in  $\text{CHCl}_3$  and washed with  $\text{Na}_2\text{CO}_3$  solution followed by water wash. Organic layer was dried with  $\text{Na}_2\text{SO}_4$  and evaporated. The resulting crude was purified via silica gel chromatography using a gradient of 3% methanol in chloroform to afford pale brown solid **282**.

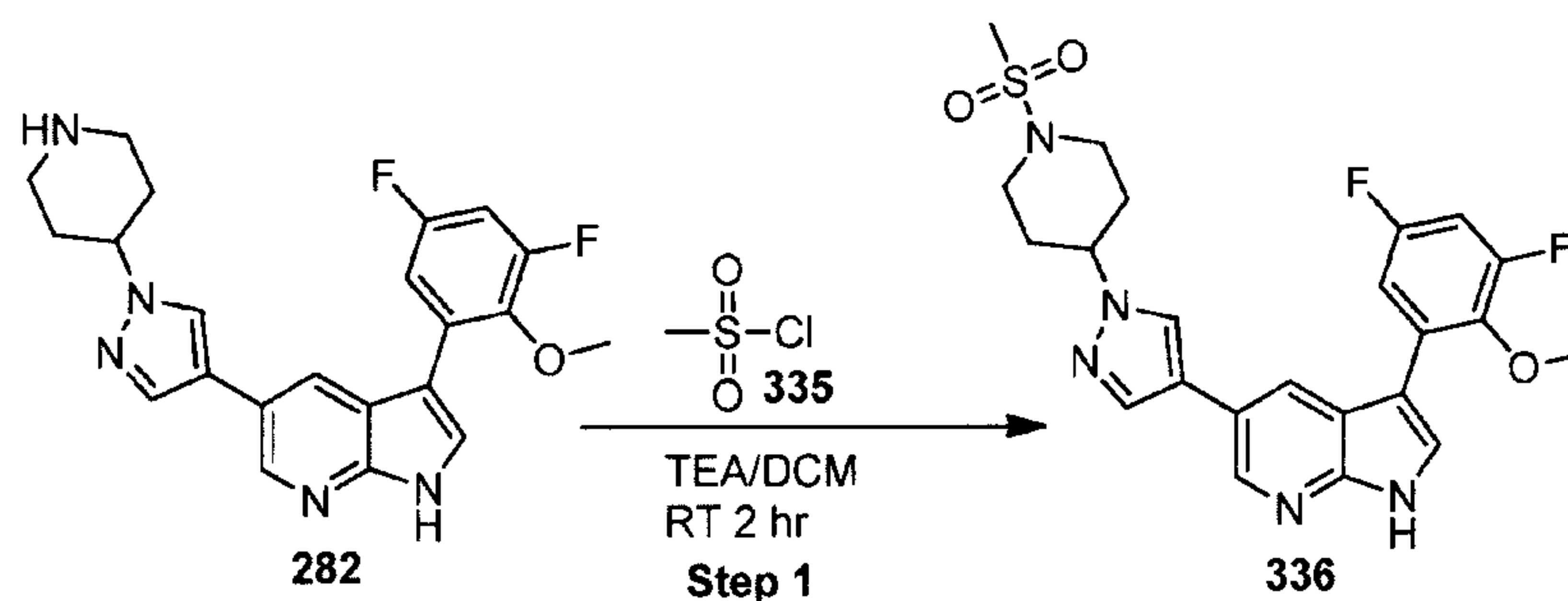
Step 2:

[00343] A solution of **282** (150mg, 0.266mmol) in acetonitrile was taken and add potassium carbonate (73mg, 0.5322mmol) and methyl iodide (56mg, 0.399mmol). The RM was stirred at  $80^\circ\text{C}$  overnight. After completion of the reaction the RM was diluted with chloroform and filtered off the solids. The organic layer was evaporated to dryness. The resulting crude was purified via silica gel chromatography using 4% methanol in chloroform to afford off white solid **333**.

Step 3:

[00344] To a solution of **333** (0.1731mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (71mg, 0.5193mmol). The reaction was heated to  $60^\circ\text{C}$  overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using 100-200 mesh silica gel. The compound was eluted at 5 % methanol in chloroform as pale yellow solid 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **334**.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$ : 12.08 (s, 1H), 8.57 (d, 1H), 8.43 (s, 1H), 8.18 (d, 1H), 8.02 (s, 1H), 7.82 (d, 1H), 7.23 (m, 2H), 4.46 (m, 1H), 3.55 (m, 7H), 3.17 (d, 6H), 2.32 (m, 4H) and MS ES+ 424.10.

**PREPARATION OF EXAMPLE 214:** 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-(methylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**336**)



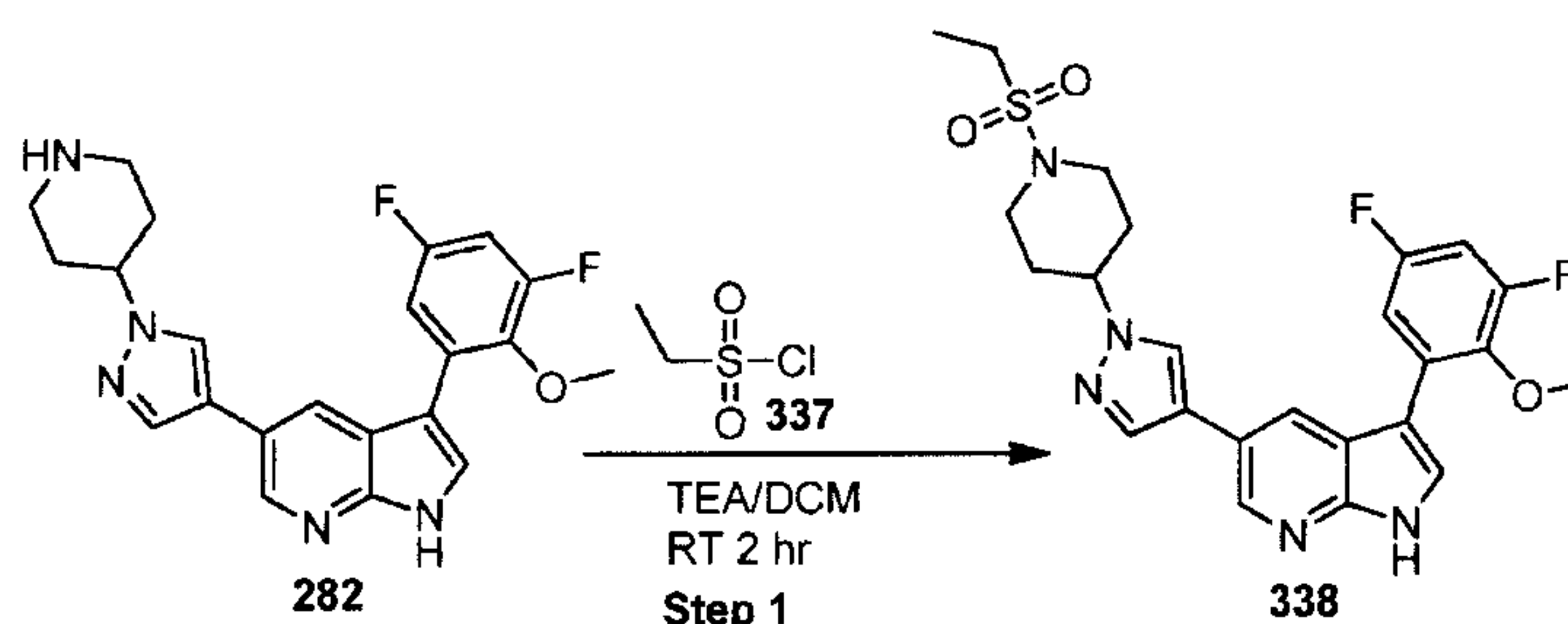
Step 1:

WO 2014/093383

PCT/US2013/074191

[00345] To a solution of **282** (100mg, 0.244mmol) in DCM was added triethylamine (49mg, 0.4887mmol). Methanesulfonyl chloride **335** (41mg, 0.3665mmol) was added to the reaction and stirred for 2h at rt. The reaction mixture was diluted with dichloromethane and washed with water twice. The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified by flash column using 100-200 mesh silica gel. The compound was eluted at 2% methanol in chloroform as off white coloured solid 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-(methanesulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **336**. <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 12.05 (s, 1H), 8.55 (d, 1H), 8.30 (s, 1H), 8.19 (d, 1H), 7.97 (s, 1H), 7.82 (d, 1H), 7.24 (m, 2H), 4.33 (m, 1H), 3.65 (d, 2H), 3.60 (s, 3H), 2.94, (m, 2H), 2.92 (s, 3H), 2.03 (m, 2H), 1.98 (m, 2H) and MS ES+ 488.0.

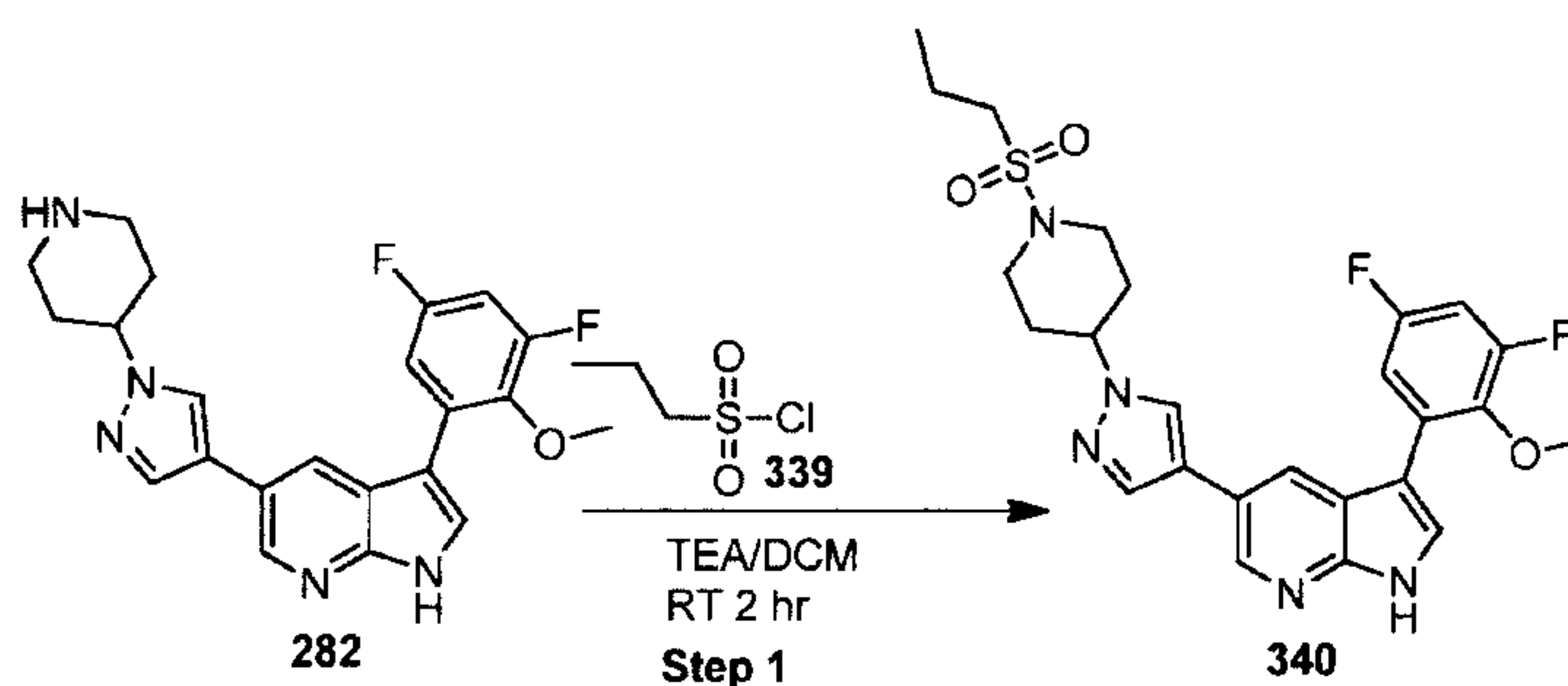
**PREPARATION OF EXAMPLE 215:** 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-(ethanesulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**338**).



#### Step 1:

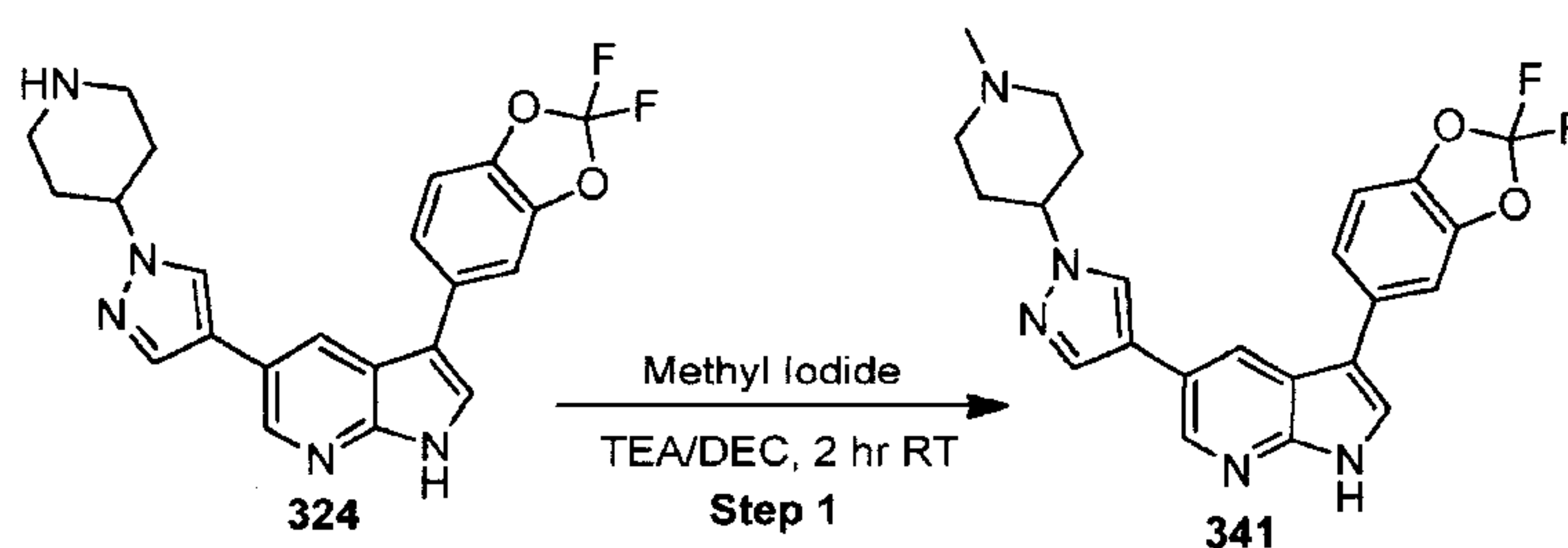
[00346] To a solution of **282** (100mg, 0.244mmol) in DCM was added triethylamine (49mg, 0.4887mmol). Ethane sulfonyl chloride **337** (47mg, 0.3665mmol) was added to the reaction and stirred it for 2h at rt. The reaction mixture was diluted with dichloromethane and washed with water twice. The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified by flash column using 100-200 mesh silica gel. The compound was eluted at 2% methanol in chloroform as off white coloured solid 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-(ethanesulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **338**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.58 (s, 1H), 8.52 (d, 1H), 8.17 (d, 1H), 7.84 (s, 1H), 7.72 (m, 2H), 7.09 (m, 1H), 6.82 (m, 1H), 4.31 (m, 1H), 3.96 (m, 2H), 3.68 (s, 3H), 3.06 (m, 2H), 3.00 (m, 3H), 2.29 (m, 2H), 2.14 (m, 2H), 1.40 (m, 5H), 1.25 (m, 5H) and MS ES+ 502.1.

**PREPARATION OF EXAMPLE 216:** 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-(propylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**340**)

**Step 1:**

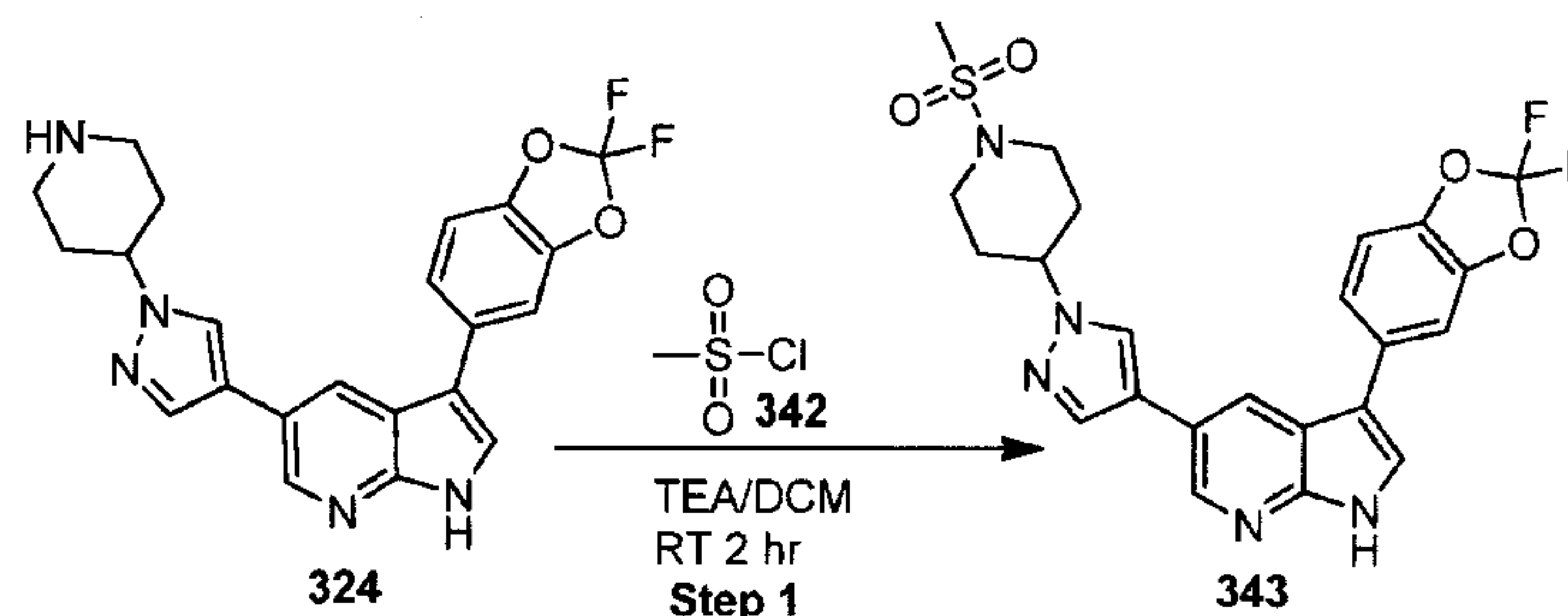
[00347] To a solution of **282** (100mg, 0.244mmol) in DCM was added triethylamine (49mg, 0.4887mmol). Propane sulfonyl chloride **339** (52mg, 0.366mmol) was added to the reaction and stirred for 2h at rt. The reaction mixture was diluted with dichloromethane and washed with water twice. The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified by flash column using 100-200 mesh silica gel. The compound was eluted at 2% methanol in chloroform as off white coloured solid 3-(3,5-difluoro-2-methoxyphenyl)-5-(1-(1-(propylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **340**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 9.68 (s, 1H), 8.53 (d, 1H), 8.17 (d, 1H), 7.84 (s, 1H), 7.73 (m, 2H), 7.09 (m, 1H), 6.82 (m, 1H), 4.31 (m, 1H), 3.95 (m, 2H), 3.68 (d, 3H), 3.01 (m, 2H), 2.94 (m, 2H), 2.36 (m, 2H), 2.14 (m, 2H), 1.86 (m, 2H), 1.06 (m, 3H) and MS ES+ 516.1.

**PREPARATION OF EXAMPLE 220:** 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**341**).



[00348] To a solution of **324** (50mg, 0.1182mmol) in DCM was added triethylamine (17.9mg, 0.236mmol). Methyl iodide (18.3mg, 0.130mmol) was added to the reaction and stirred for 2h at rt. The reaction mixture was diluted with dichloromethane and washed with water twice. The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified by flash column using 100-200 mesh silica gel. The compound was eluted at 2% methanol in chloroform as off white coloured solid 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **341**.

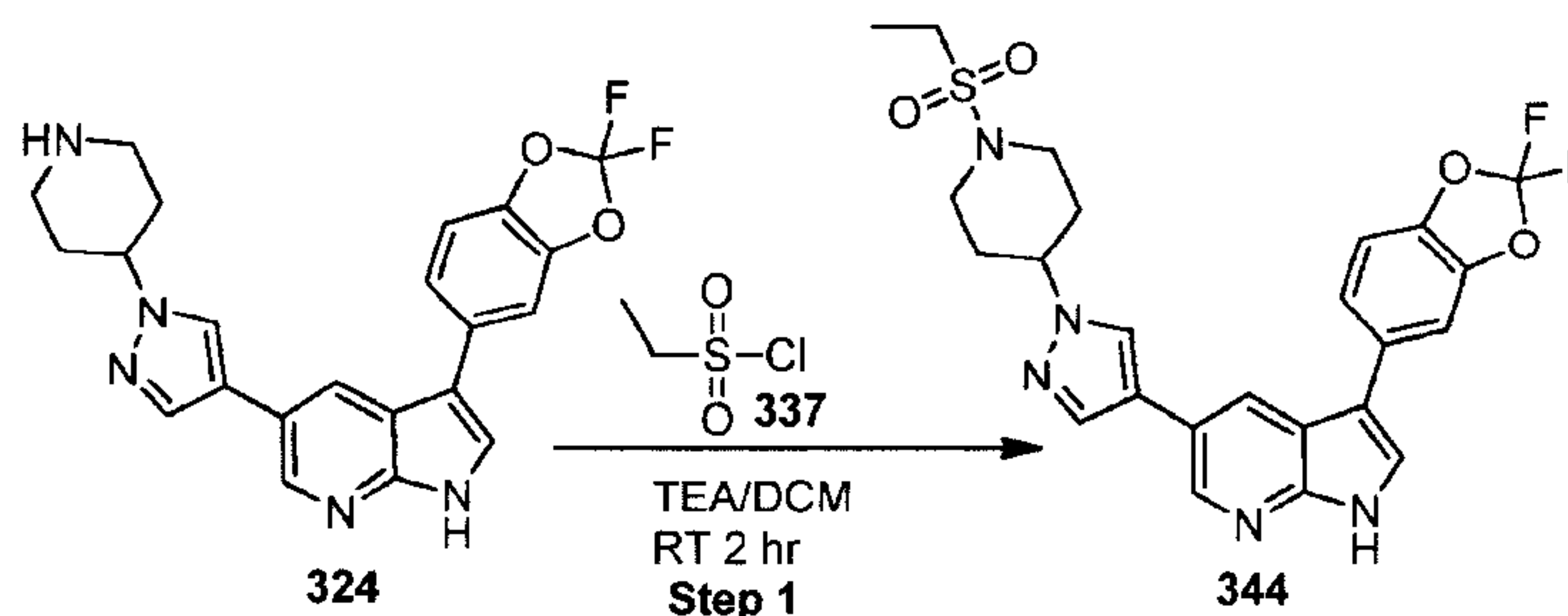
**PREPARATION OF EXAMPLE 221:** 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-(methylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**343**)



Step 1:

[00349] To a solution of **324** (50mg, 0.1182mmol) in DCM was added triethylamine (17.9mg, 0.1773mmol). Methane sulfonyl chloride **342** (13.5mg, 0.1182mmol) was added to the reaction and stirred for 2h at rt. The reaction mixture was diluted with dichloromethane and washed with water twice. The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified by flash column using 100-200 mesh silica gel. The compound was eluted at 2% methanol in chloroform as off white coloured solid 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-(methylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **343**. <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 11.94 (s, 1H), 8.55 (d, 1H), 8.39 (m, 2H), 8.03 (s, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.58 (m, 1H), 7.44 (d, 1H), 4.31 (m, 1H), 3.66 (m, 2H), 2.95 (s, 3H), 2.16 (m, 2H), 2.01 (m, 2H) and MS ES+ 502.1.

**PREPARATION OF EXAMPLE 222:** 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-(ethylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**344**)



Step 1:

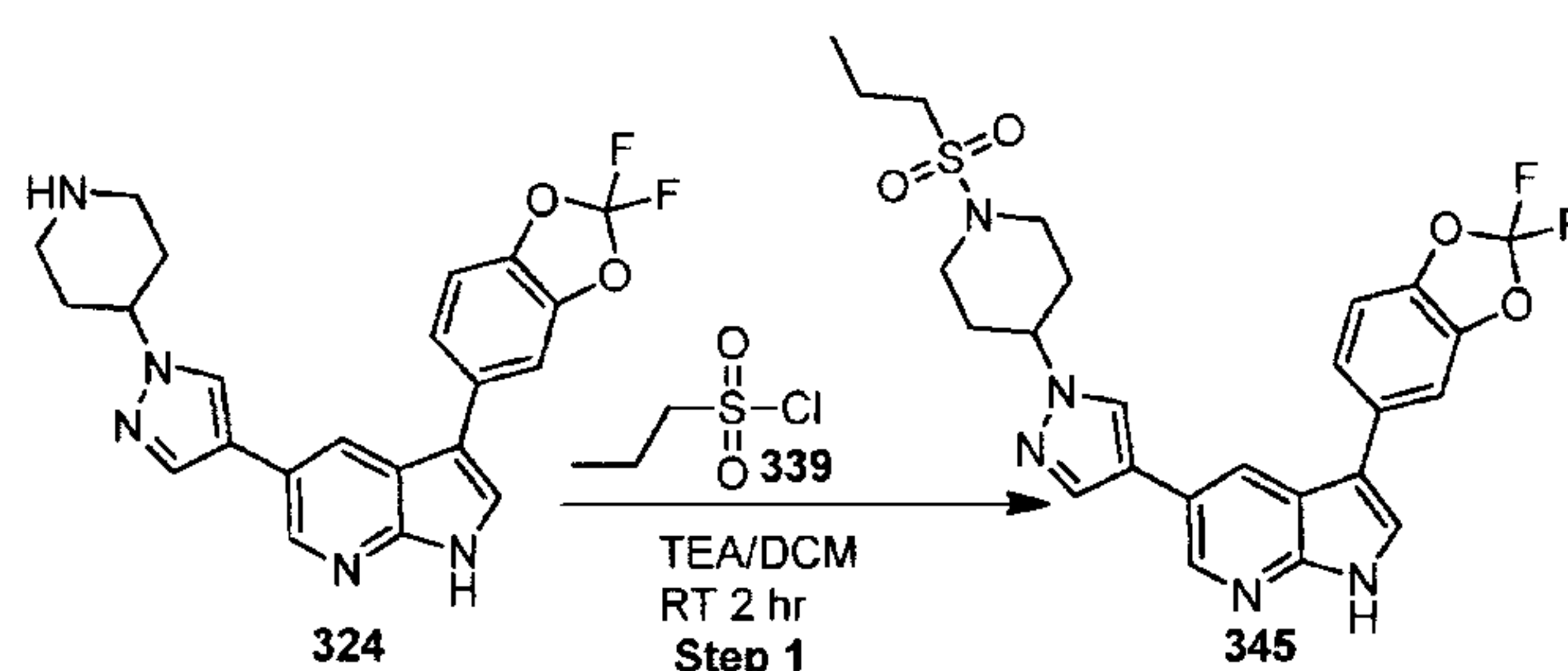
[00350] To a solution of **324** (50mg, 0.1182mmol) in DCM was added triethylamine (17.9mg, 0.1771mmol). Ethane sulfonyl chloride **337** (15mg, 0.1182mmol) was added to the reaction and stirred for 2h at rt. The reaction mixture was diluted with dichloromethane and washed with water twice. The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified by flash column using 100-200 mesh silica gel. The

WO 2014/093383

PCT/US2013/074191

compound was eluted at 2% methanol in chloroform to give off white coloured solid 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-(ethylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **344**. <sup>1</sup>HNMR (400 MHz, DMSO)  $\delta$ : 11.95 (s, 1H), 8.55 (d, 1H), 8.39 (m, 2H), 8.02 (s, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.58 (m, 1H), 7.44 (d, 1H), 4.33 (m, 1H), 3.71 (m, 2H), 3.04 (m, 4H), 2.14 (m, 2H), 1.97 (m, 2H), 1.21 (m, 4H) and Ms ES +516.1.

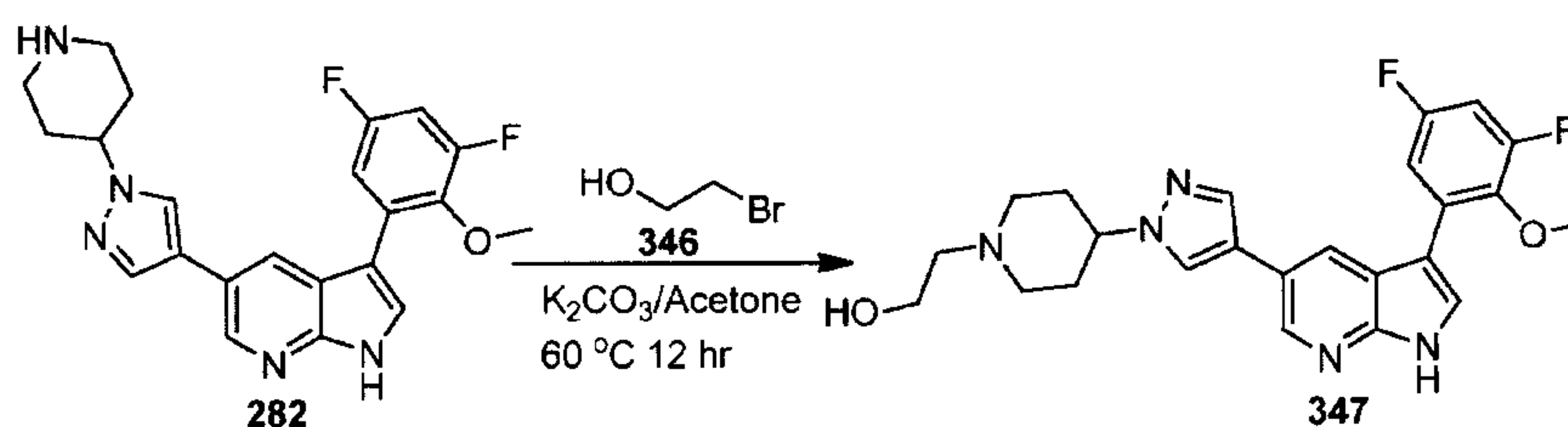
**PREPARATION OF EXAMPLE 223:** 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5-(1-(1-(propylsulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (**345**)



#### Step 1:

[00351] To a solution of **324** (50mg, 0.1182mmol) in DCM was added triethylamine (17.9mg, 0.1773mmol) and propane sulfonyl chloride **339** (16.7mg, 0.1182mmol) and stirred for 2h at rt. The RM was diluted with dichloromethane and washed with water twice. The organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified by flash column using 100-200 mesh silica gel. The compound was eluted at 2% Methanol in chloroform as off white coloured solid **345**. <sup>1</sup>HNMR(400 MHz, DMSO)  $\delta$ : 11.95 (s, 1H), 8.55 (d, 1H), 8.39 (m, 2H), 8.03 (s, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.58 (m, 1H), 7.44 (d, 1H), 4.35 (m, 1H), 3.69 (m, 2H), 3.03 (m, 4H), 2.14 (m, 2H), 1.97 (m, 2H), 1.70 (m, 2H), 1.00 (m, 3H) and MS ES+ 530.1.

**PREPARATION OF EXAMPLE 226:** 2-(4-(4-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanol (**347**)



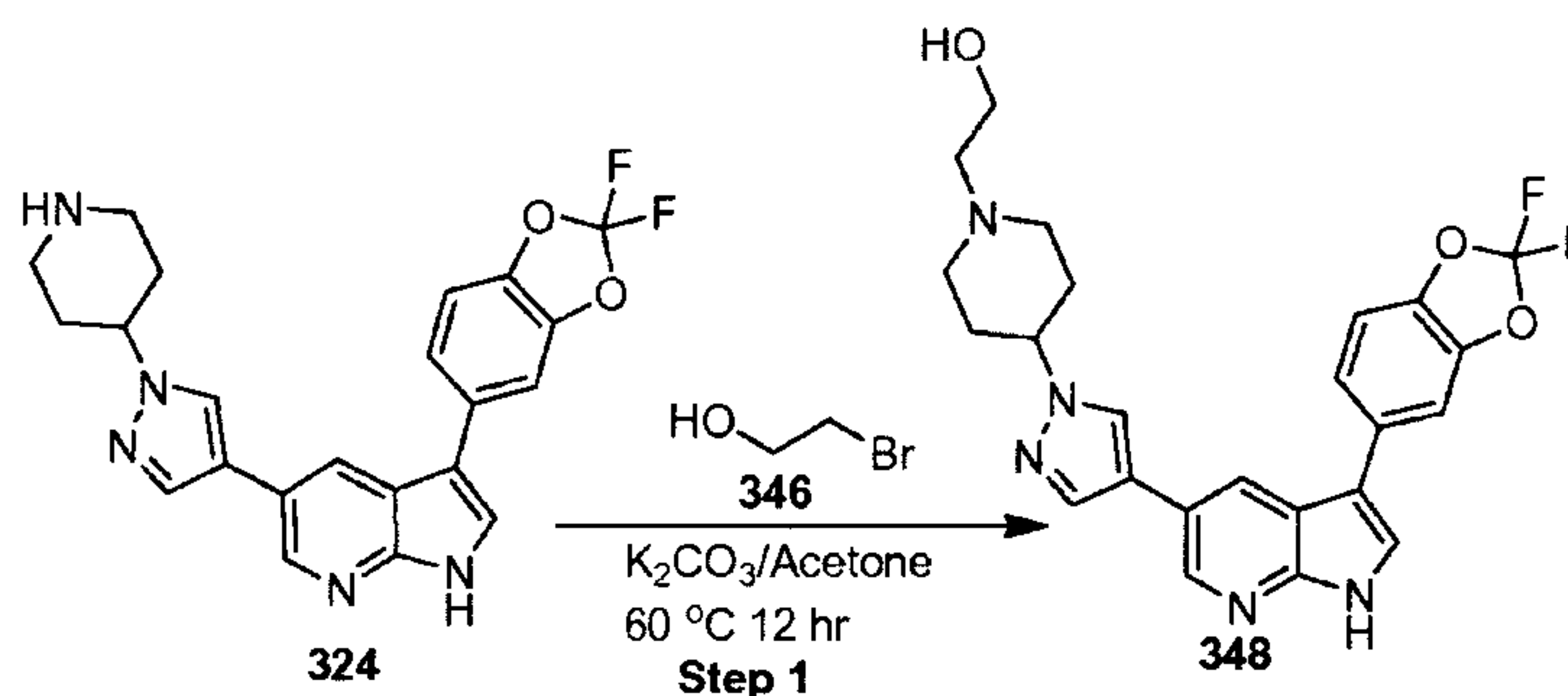
#### Step 1:

WO 2014/093383

PCT/US2013/074191

[00352] To a solution of **282** (50mg, 0.122mmol) in acetone was added potassium carbonate (25mg, 0.244mmol) and 2-bromo ethanol (18.3mg, 0.146mmol) and stirred for 12h at 60°C. The reaction was filtered through celite bed and washed with ethyl acetate. The organic layer was concentrated to get the crude, which was purified by neutral alumina and the compound was eluted at 2% methanol in chloroform as half white coloured solid 2-(4-(4-(3-(3,5-difluoro-2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanol **347**. <sup>1</sup>HNMR(400 MHz, DMSO) δ: 12.04 (s, 1H), 8.54 (d, 1H), 8.31 (s, 1H), 8.18 (d, 1H), 7.93 (s, 1H), 7.81 (d, 1H), 7.22 (m, 2H), 4.39 (m, 1H), 4.10 (m, 1H), 4.00 (m, 1H), 3.60 (s, 3H), 3.50 (m, 2H), 2.96 (d, 2H), 2.42 (m, 2H), 2.13 (m, 2H), 1.99 (m, 3H), 1.16 (t, 1H) and MS ES+ 454.0.

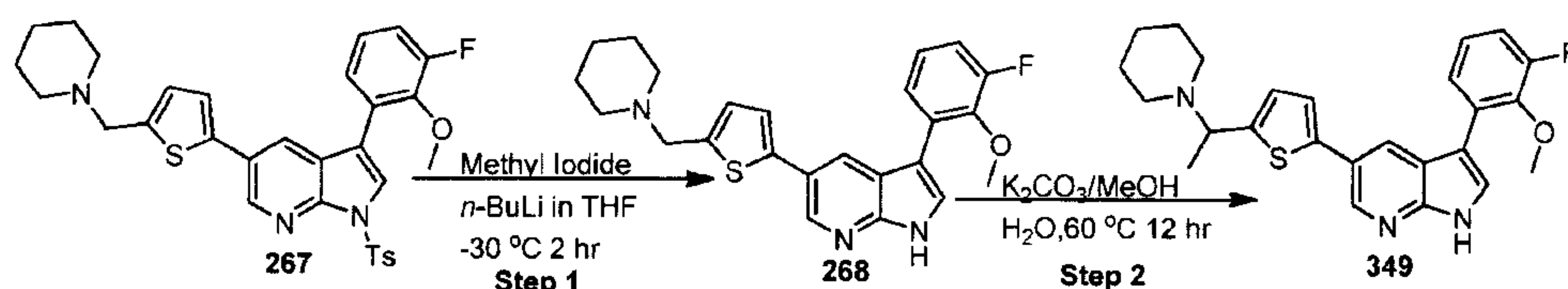
**PREPARATION OF EXAMPLE 227:** 2-(4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanol (**348**)



#### Step 1:

[00353] To a solution of **324** (50mg, 0.118mmol) in acetone was added potassium carbonate (32mg, 0.236mmol) and 2-bromo ethanol (17.7mg, 0.141 mmol), and stirred for 12h at 60°C. The reaction was filtered through celite bed and washed with ethyl acetate. The organic layer was concentrated to get the crude, which was purified by neutral alumina and the compound was eluted at 2% methanol in chloroform as half white coloured solid 2-(4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidin-1-yl)ethanol **348**. <sup>1</sup>HNMR (400 MHz, DMSO) δ: 11.93 (s, 1H), 8.54 (d, 1H), 8.38 (m, 2H), 7.99 (s, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.58 (m, 1H), 7.43 (d, 1H), 4.39 (m, 1H), 4.11 (m, 1H), 3.50 (m, 2H), 2.97 (d, 2H), 2.43 (m, 2H), 2.14 (m, 2H), 1.96 (m, 4H) and MS ES+ 468.0.

**PREPARATION OF EXAMPLE 228:** 3-(3-fluoro-2-methoxyphenyl)-5-(5-(1-(piperidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine (**349**)

Step 1:

[00354] To a solution of **267** (50mg, 0.386mmol) in THF was added n-butyl lithium (11mg, 0.173mmol). Methyl iodide (18.3mg, 0.129mmol) was added to the reaction and stirred for 2h at -30°C. The RM was quenched with ammonium chloride solution and stirred for 15min. The aqueous phase was extracted twice with ethyl acetate. The resulting organic layer was dried over sodium sulphate and concentrated to get the crude, which was purified by flash column using 100-200 mesh silica gel. The compound was eluted at 2% methanol in chloroform as off white coloured solid **268**.

Step 2:

[00355] To a solution of **268** (30mg, 0.0508mmol) in methanol (20mL) and water (5mL) was added potassium carbonate (21mg, 0.152mmol). The reaction was heated to 60°C overnight. The solvent was completely distilled off and the remainder diluted with water (25mL) and extracted with chloroform twice (2 x 25mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated to get the crude, which was purified through flash chromatography by using neutral alumina. The compound was eluted at 5% methanol in chloroform as pale yellow solid (10mg) compound 3-(3-fluoro-2-methoxyphenyl)-5-(5-(1-(piperidin-1-yl)ethyl)thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridine **349**.

**PHARMACEUTICAL SALTS**

[00356] Hydrochloric acid salts of the foregoing compounds were prepared by solubilizing the compound in a minimum of ethanol and a solution of ethanolic HCl 20% was added drop wise and the mixture stirred for 1 hour followed by addition of diethyl ether. A precipitated off-white solid hydrochloride was separated by filtration, washed with diethyl ether and dried. In certain embodiments, the invention contemplates the treatment of diseases or patients using a compound, or a prodrug, tautomeric, an isomeric, pharmaceutically acceptable salt, N-oxide, or stereoisomeric form thereof, having a structure of Formula I, IA and IB. Pharmaceutically acceptable salts are derivatives of the claimed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts

include the standard non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic and isethionic salts. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by established chemical methods. Such salts can be prepared by reacting free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, EtOAc, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18<sup>th</sup> ed., Mack Publishing Company, Easton, PA, 1990, p. 1445.

#### ADDITIONAL EXAMPLES

#### USAGE METHOD

[00357] The subject matter disclosed herein relates to the substituted 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives as inhibitors of SIK1 (SNF1LK), SIK2 (SNF1LK, QIK) and SIK3 (QSK). Pharmaceutical compositions containing the Formula I, IA and IB compounds and methods of using the compounds or compositions to treat various types of diseases or conditions mediated by SIK family isoform (SIK1, SIK2 and SIK3) such as for example, disease states associated with abnormal cell growth such as cancer, stroke, obesity and type II diabetes. Additionally these compounds and compositions containing the compounds are employed to treat ovarian and breast cancers. In addition, these compounds are important future therapeutic agents for the treatment of lung, prostate and testicular tumours cancers. Methods of making the compounds and pharmaceutical salts thereof are also described herein.

[00358] The in vivo efficacy of 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives in an established human ovarian xenograft growth inhibition experiments conducted is described and in combination with taxane and paclitaxel drugs. The potent and selective 2 SIK2 inhibitors were administered orally in dose escalation in vivo experiments

starting from 20, 40, 60 and 80mg/Kg after 2 weeks of sub-cutaneous SKOV3 ovarian cancer cells injection into 32 female nu/nu mice.

### ***IN VITRO* INHIBITION ASSAY**

#### **SIK2 Kinase assay**

[00359] Procedure: Enzyme was incubated with substrate peptide in reaction buffer in the presence and absence of test compounds or Staurosporine. All additions were done on ice, followed by the addition of ATP mix. Wells were uniformly mixed using an Eppendorff plate shaker and incubated at 30°C for 20min, and stopped by the addition of 5µL of 3% phosphoric acid. Volume was increased to 100µL by adding 0.8% phosphoric acid which was then transferred to PC filter mats (Millipore), pre-equilibrated with 70% ethanol and water. Plates were washed thrice with 100µL 0.8% phosphoric acid and dried for an hour at 60°C. 100µL scintillation fluid was added into each well and reading taken in Perkin Elmer TOPCOUNT beta counter. The data analysis was performed by averaging the duplicate top count readings for each standard, negative, positive control (enzyme control) and samples and subtracting the average negative control from each reading which results in corrected values. A validation EC<sub>50</sub> curve was generated by plotting CPM for each Staurosporine concentration on y-axis against the Log concentration of Staurosporine (nM) on the x-axis followed by a best fit curve through the points.

$$\% \text{ Inhibition} = ((\text{Enzyme Control} - \text{Compound Treated}) / \text{Enzyme Control}) \times 100$$

[00360] Coefficient of Variance (% CV) between replicates: The % CV values between the replicates were mostly within the acceptable limits of a radiometric experiment. Z' factor evaluation: The value of Z' factor was found to be 0.8 for SIK2 and 0.9 was derived for others.

[00361] All the compounds were tested in 10-dose IC<sub>50</sub> mode with 3 fold serial dilution starting at 100 µM. The control compound Staurosporine was tested in 10 dose IC<sub>50</sub> with 3 fold serial dilution starting at 20 µM. The reactions were carried out at 10 µM ATP for SIK2 and the results shown in **Figure. 1**. Referring to **Figure.1**, SIK2 inhibitor examples: Panel A: 135 (▪), 142 (Δ) and Palel B: 133 (▪) and 168 (Δ).

#### **General Protein Kinase Assay Methodology employed for Selected Kinases**

[00362] In vitro profiling of the 337 member kinase panel was performed at Reaction Biology Corporation using the "HotSpot" assay platform. Briefly, specific kinase/substrate pairs along with required cofactors were prepared in reaction buffer; 20 mM Hepes (pH 7.5), 10 mM MgCl<sub>2</sub>, 1 mM EGTA, 0.02% Brij35, 0.02mg/ml BSA, 0.1 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM DTT, 1% DMSO. Compounds were delivered into the reaction, followed ~20min later by addition of

a mixture of ATP (Sigma) and <sup>33</sup>P ATP (PerkinElmer) to a final concentration of 10  $\mu$ M. Reactions were carried out at 25 °C for 120 min, followed by spotting of the reactions onto P81 ion exchange filter paper (Whatman). Unbound phosphate was removed by extensive washing of filters in 0.75% phosphoric acid. After subtraction of background derived from control reactions containing inactive enzyme, kinase activity data were expressed as the percent remaining kinase activity in test samples compared to vehicle (dimethyl sulfoxide) reactions. IC<sub>50</sub> values and curve fits were obtained using Prism (GraphPad Software). Kinome tree representations were prepared using Kinome Mapper (<http://www.reactionbiology.com/apps/kinome/mapper/LaunchKinome.htm>).

**Table 4:** List of Compounds and Corresponding three isoforms of SIK family\*

| EX. | SIK2 (QIK) | SIK1 | SIK3 (QSK) |
|-----|------------|------|------------|
| 1   | **         | *    | *          |
| 2   | **         | *    | *          |
| 5   | **         | *    | ***        |
| 6   | **         | **   | *          |
| 7   | **         | ND   | ND         |
| 17  | **         | **   | **         |
| 20  | *          | ND   | ND         |
| 22  | *          | ND   | ND         |
| 23  | **         | ND   | ND         |
| 24  | **         | ND   | ND         |
| 25  | *          | ND   | ND         |
| 26  | **         | ND   | ND         |
| 28  | **         | ND   | ND         |
| 29  | **         | ND   | ND         |
| 30  | *          | ND   | ND         |
| 36  | **         | **   | ND         |
| 37  | **         | **   | ND         |
| 47  | **         | ND   | ND         |
| 87  | **         | *    | ND         |
| 94  | *          | ND   | ND         |
| 95  | *          | *    | *          |
| 96  | *          | *    | *          |
| 97  | *          | *    | *          |
| 98  | *          | *    | *          |
| 99  | *          | ND   | ND         |
| 100 | *          | ND   | ND         |
| 101 | **         | ND   | ND         |
| 113 | **         | ND   | ND         |
| 114 | ***        | **   | *          |
| 115 | ***        | **   | *          |
| 116 | **         | *    | *          |

WO 2014/093383

PCT/US2013/074191

|     |     |     |     |
|-----|-----|-----|-----|
| 120 | *** | **  | **  |
| 123 | **  | **  | **  |
| 124 | **  | **  | **  |
| 125 | *** | *   | ND  |
| 126 | *   | ND  | ND  |
| 128 | *** | **  | **  |
| 132 | **  | ND  | ND  |
| 133 | *** | *   | **  |
| 134 | **  | **  | *   |
| 135 | *** | **  | **  |
| 136 | *** | **  | **  |
| 137 | **  | ND  | ND  |
| 138 | *** | **  | **  |
| 139 | *   | ND  | ND  |
| 140 | *   | ND  | ND  |
| 141 | *** | *   | **  |
| 142 | *** | *   | *** |
| 168 | *** | *   | *   |
| 174 | *** | *   | **  |
| 175 | *** | *   | **  |
| 176 | *** | *   | **  |
| 177 | *** | *   | **  |
| 178 | *** | *   | **  |
| 179 | *** | *   | **  |
| 180 | *** | *   | **  |
| 181 | *** | *   | **  |
| 182 | *** | *   | **  |
| 183 | *** | *   | **  |
| 184 | *** | *   | **  |
| 185 | *** | *   | **  |
| 191 | *** | **  | **  |
| 192 | *** | **  | **  |
| 193 | *** | **  | **  |
| 196 | *** | **  | *** |
| 197 | *** | **  | *** |
| 198 | *** | **  | *** |
| 199 | *** | **  | **  |
| 200 | *** | **  | *** |
| 201 | *   | *   | *   |
| 202 | *** | **  | *** |
| 203 | *** | *   | *   |
| 204 | *** | **  | *** |
| 205 | *** | **  | *** |
| 206 | *** | **  | *** |
| 207 | *** | **  | *** |
| 208 | *** | **  | *** |
| 209 | *** | *** | *** |
| 210 | *** | **  | *** |
| 211 | *** | **  | *** |
| 212 | *** | **  | *** |

|     |     |    |     |
|-----|-----|----|-----|
| 213 | *** | ** | *** |
| 214 | **  | *  | **  |
| 215 | **  | *  | **  |
| 216 | **  | *  | **  |
| 217 | *** | ** | *** |
| 218 | *** | ** | *** |
| 219 | *** | ** | *** |
| 220 | **  | *  | *   |
| 221 | *   | *  | *   |
| 222 | *   | *  | *   |
| 223 | *   | *  | *   |
| 224 | *** | ** | *** |
| 225 | *** | ** | *** |
| 226 | *** | ** | *** |
| 227 | *** | ** | *** |
| 228 | ND  | ND | ND  |

\*Kinase Inhibition Result for Selected Compounds

\*\*\* <0.1  $\mu$ M, \*\* >0.1  $\mu$ M, \* >1  $\mu$ M

ND = Not Determined

### Protein Kinase Selectivity Profiler

[00363] Selected compounds were tested against 299 protein kinases + 17 additional preview kinases in single dose duplicate mode at a concentration of 1  $\mu$ M). A control compound was tested in 10-dose IC<sub>50</sub> mode with 3-fold serial dilution starting at 20  $\mu$ M. Reactions were carried out at 10  $\mu$ M ATP. Data pages include raw data, % Enzyme activity (relative to DMSO controls), and curve fits.

### CELL CULTURE MODELS OF CANCER

#### Determining 50% inhibition concentration (IC<sub>50</sub>) of 3 compounds on 2 human tumor cell lines

[00364] **CellTiter-Glo (CTG)** (Product No.: G7572, Promega. Store CellTiter-Glo buffer and CellTiter-Glo substrate at -20°C), the following protocol is recommended for the preparation of CTG reagent. Thaw the CellTiter-Glo Buffer, and equilibrate to rt prior to use. For convenience the CellTiter-Glo buffer may be thawed and stored at rt for up to 48hr prior to use. Equilibrate the lyophilized CellTiter-Glo substrate to rt prior to use. Transfer 100mL of CellTiter-Glo buffer into the amber bottle containing CellTiter-Glo substrate to reconstitute the lyophilized enzyme/substrate mixture. This forms the CellTiter-Glo reagent. Mix by gently vortexing, swirling or inverting the contents to obtain a homogeneous solution. The CellTiter-Glo substrate should go into solution easily in less than 1 minute. Aliquot and store the CTG reagent at -20°C freezer for long term storage.

WO 2014/093383

PCT/US2013/074191

**Cytotoxicity and IC<sub>50</sub> determination**

[00365] Day 1: The cells will be harvested during the logarithmic growth period and counted with hemocytometer. The cell viability should be over 98% by trypan blue exclusion. Adjust cell solution to the appropriate concentration with respective medium according the seeding density. Add 90  $\mu$ l cell suspensions to 96-well plates; the final cell seeding density is  $5 \times 10^3$  cells/90 $\mu$ l/well for OVCAR-3,  $5 \times 10^3$  cells/90 $\mu$ l/well for SK-OV-3. Incubate the assay plate for 24 hours at 37°C in a humidified, 5% CO<sub>2</sub> atmosphere. Day 2: Prepare serial solution of test articles with DMSO then dilute with PBS to prepare 10X injection solution. Prepare 10X positive drug injection solution with PBS (see appendix 1). Dispense 10 $\mu$ L drug injection solution in each well. The plates will be cultured for another 72h, and then measured by means of MTS assay or CTG assay. Day 5: Thaw the MTS Solution and the PMS Solution, just before addition to the culture plate containing cells, mix PMS Solution with MTS Solution at 1:20 ratio immediately, the final volume was based on the actual requirement. Gently swirl the tube to ensure complete mixing of the combined MTS/PMS solution. Pipet 20 $\mu$ L of the combined MTS/PMS solution into the assay wells in one 96 well plate. Incubate the plate for 1-4h at 37°C in a humidified, 5% CO<sub>2</sub> atmosphere, record the absorbance at 490nm using SpectraMax. Thaw CTG reagent and equilibrate to rt, pipet 25 $\mu$ L to the assay wells in another 96 well plate, shake for 2min with the plate shaker, and incubate for 10min at dark place, then record luminescence reading using Envision.

**Data analysis**

[00366] The data will be displayed graphically using GraphPad Prism 5.0 software. In order to calculate IC<sub>50</sub>, a dose-responsive curve will be fitted using nonlinear regression model with a sigmoidal dose response. The IC<sub>50</sub> will be automatically produced by GraphPad Prism 5.0.

**Fig. 2** displays two such plots of SIK2 inhibitor (**191**, **206**) examples tested in SK-OV-3 and OVCAR3 cell lines with Cisplatin as control. The SK-OV-3 is on the left and the OVCAR3 is on the right.

[00367] Survival rate is calculated with the formula of  $\text{Value}_{\text{sample}} / \text{Value}_{\text{vehicle control}} * 100\%$  for CTG assay, and calculated with the formula of  $(\text{Value}_{\text{sample}} - \text{Value}_{\text{blank control}}) / (\text{Value}_{\text{vehicle control}} - \text{Value}_{\text{blank control}}) * 100\%$

**[00368] Effects of the test compounds on the SIK2-expressed SKOV3, OVCAR3, ES-2 and HEY cells**

Test compound at various concentrations are added in duplicate and the cells were incubated for 72h. After incubation, CellTiter-Glo<sup>®</sup> Reagent are added to each test well and mixed for 2min on an orbital shaker. The plates are shortly centrifuged and incubated at rt for additional

10min to stabilize the luminescent signal and the luminescence signals are recorded on Pherastar Plus. The cell viability after 72h compound treatment was assayed. 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine series of compounds and its analogues were tested on panel of ovarian cancer cell lines where 1*H*-Pyrazolo [3, 4-*b*] pyridine series inhibited SKOv3 (1.2  $\mu$ M), OVCAR-3 (0.7  $\mu$ M), HEY 0.07  $\mu$ M), ES-2 (1.2  $\mu$ M) (**Figures 2b1-3**) and COV434, COV504, EFO-27, HO-8910, OV56, OV90, OVCAR-4, OVISe, OVSAHO, OVTOKO, SW626, TOV-112D and TOV-21G cells inhibited by 1*H*-Pyrazolo [3, 4-*b*] pyridine series with an IC<sub>50</sub> between 0.5 to 3.0  $\mu$ M.

[00369] **Functional kinase assay and the onset of SIK2 inhibition:** The functional assays was conducted in order to examine the phosphorylation of SIK2 at Thr175 that is required for kinase activity and downstream targets on treatment with 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives. In SKOv3, OVCAR-3, HEY cells the inhibition of phosphorylation of SIK2 at Thr175 and Ser186 monitored after the 1h treatment with 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives. The treatment with 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives results in inhibition of SIK2 kinase activity will examined from ovarian cancer cell lines by western blot. Levels of phospho-SIK2 relative to total-SIK2 upon exposure to 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives was determined. The experimental details involves 10 thousand SKOV3ip ovarian carcinoma cells plated in 6 cm plates and will be allowed to adhere overnight. All plates treated with demecolcine for 6h, cells were collected released in to new media containing 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives at 1h at rt. The cell lysates will be used in Western blot analysis.

[00370] **Effects of 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives on ovarian carcinoma proliferation and apoptosis:** As a part of cellular efficacy and possible mechanisms causing the tumor growth inhibition evidenced in the 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives experiments, we further examined the effects on tumor cell proliferation by calculating the proliferative index after immunohistochemistry on tumors collected at necropsy from all efficacy experiments. In the SKOv3 model, the proliferation index for animals treated with vehicle, 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives alone and in combination with paclitaxel and monitor the proliferative indices. Further to gain additional insight into downstream effects of 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives, we will conduct the expression profile studies on SKOv3, OVCAR-3, HEY tumors

harvested from either vehicle- or 1*H*-Pyrrolo [2, 3-*b*] pyridine and 1*H*-Pyrazolo [3, 4-*b*] pyridine derivatives treated animals.

#### IN VIVO MODELS OF SIK2

[00371] SKOV3 ovarian cancer cells injected sub-cutaneous into 32 female nu/nu mice of approximately and four groups of 8 mice observed with twice weekly measurements and weekly weights. Treatment with SIK2 inhibitors when progressive growth is observed at 7-14 days. In separate experiments, each of two SIK2 inhibitors 1*H*-Pyrrolo [2, 3-*b*] pyridine derivatives delivered daily by gavage in 3 different concentrations (20, 40 and 80mg/kg) in a volume of 2 mL. Vehicle will be administered for 4th group by gavage. When the control xenografts have grown to 1.5 cm in diameter, all mice will be sacrificed, tumors weighed and tumor tissue cryopreserved and fixed for routine and EM studies and the duration of time required ~ 4 to 6 weeks. The 1*H*-Pyrrolo [2, 3-*b*] pyridine compounds had significant antitumor effects as a single agent over combination with taxol.

[00372] **Efficacy of 1*H*-Pyrrolo [2, 3-*b*] pyridine derivatives in nu/nu SKOv3 xenograft mice:** We examined the growth-inhibitory effect of 1*H*-Pyrrolo [2, 3-*b*] pyridine derivatives in-vivo employing an i.p. xenograft model in which nu/nu mice were inoculated i.p. with sensitive cell line SKOv3 cells. One week after inoculation, mice were randomized into six treatment groups receiving vehicle, 1*H*-Pyrrolo [2, 3-*b*] pyridine derivatives 30, 60mg/kg, taxol 10 mg/kg and 1*H*-Pyrrolo [2, 3-*b*] pyridine plus taxol. Drug treatment was well tolerated except i.p. treatment second group, with no apparent toxicity throughout the study. At the end of an experiment, all mice were sacrificed for tumor volume, weight and each mice examined and recorded at autopsy. The two 1*H*-Pyrrolo [2, 3-*b*] pyridine compounds and taxol groups all inhibited the abdominal tumor growth and tumor cell dissemination (reduced tumor numbers) (**Figure 5a-c**). Taken together, these findings indicates that two 1*H*-Pyrrolo [2, 3-*b*] pyridine compounds, taxol had significant antitumor effects and compound as a single agent with the ability not only to inhibit ovarian tumor growth, but also inhibits dissemination of tumor cells in vivo.

[00373] **The effect of 1*H*-Pyrrolo [2, 3-*b*] pyridine compounds on SKOv3 induced orthotopic murine model:** Dose-finding experiments initiated by injecting SKOV3ip1 (SKOV3ip1 cells were collected from cultures using either 0.25% trypsin-EDTA (Life Technologies) on the cell line) tumor cells i.p. ( $2.5 \times 10^5$ ) into athymic female mice. 19 days after tumor cell orthotopic inoculation and when i.p. tumors were palpable, then the mice randomized into 6 dosage groups: 0 mg (vehicle alone, group 1), 20 and 40 mg/kg (groups 2,

WO 2014/093383

PCT/US2013/074191

3) received 1*H*-Pyrrolo [2, 3-*b*] pyridine compound i.p QD for 3 days (M/W/F), 60 and 80 mg/kg (groups 4, 5) received 1*H*-Pyrrolo [2, 3-*b*] pyridine compound p.o BID for 3 days (M/W/F) and 100 mg/kg group received 1*H*-Pyrrolo [2, 3-*b*] pyridine compound +Taxol p.o BID for 3 days (M/W/F). BID (twice daily doses) of inhibitor or vehicle were administered by p.o 12 h apart and the treatment continued until the vehicle-treated animals showed significant tumor burden (for a total of 4 to 6 weeks) and terminate the study at the end of 4 or 6<sup>th</sup> week and sacrifice animals (mice were sacrificed at 24, 48, and 72 h after the final i.p/p.o) and tumors were harvested for tumor growth inhibition percent and immunohistochemistry to see the effect of each animal in the group and all tumor nodules were collected, counted, and weighed at necropsy. In order to establish the optimal dose and frequency of dosing to effectively inhibit SIK2 in-vivo, these dose-finding experimental samples from orthotopic murine models and using functional assay we at first investigated the SIK2 expression profiling in control group mice and inhibition of phosphorylation of SIK2 by 1*H*-Pyrrolo [2, 3-*b*] pyridine compound and Taxol. Additionally, we performed quantitative RT-PCR, Western blot, and immunocytology experiments to identify overexpression of SIK2 in control groups against treatment groups along with SIK2 inhibition of transcription factor CREB via phosphorylation of its cofactor TORC2/CRTC2 as a biological indicator of SIK2 kinase activity. Further characterized the effects of SIK2 kinase inhibition on tumor growth inhibition, examined the tumor nodule formation. 1*H*-Pyrrolo [2, 3-*b*] pyridine compound, taxol had significant antitumor effects and compound as a single agent, with the ability not only to inhibit ovarian tumor growth, but also inhibits dissemination of tumor cells in vivo.

[00374] **The Effect of 1*H*-Pyrrolo [2, 3-*b*] pyridine compound on OVCAR-3 induced orthotopic murine model:** Dose-finding experiments initiated by injecting OVCAR-3 (OVCAR-3 cells were collected from cultures using either 0.1% EDTA (Life Technologies) on the cell line) tumor cells i.p. ( $2.5 \times 10^5$ ) into athymic female mice. Similar study design protocols and analysis performed as described under SKOv3 orthotopic murine experiments.

#### **PHARMACOKINETICS/ADME/Tox:**

[00375] The objective of this study was to investigate the bio-availability and pharmacokinetics of a 1*H*-Pyrrolo [2, 3-*b*] pyridine compound in male Sprague Dawley rats. A total of 6 male rats were used in the study. The study was performed using parallel design (n=3) with serial sampling, as summarized in the **Table 5**:

Table 5

| Route           | Group # | No. of rats | Dose (mg/kg) | Dose volume (mL/kg) | Strength (mg/mL) |
|-----------------|---------|-------------|--------------|---------------------|------------------|
| IV <sup>a</sup> | 1       | 3           | 5            | 2.5                 | 2                |
| PO <sup>b</sup> | 2       | 3           | 20           | 10                  | 2                |

<sup>a</sup> Ethyl alcohol (5% v/v), Polyethylene glycol-300 (50% v/v), Propylene glycol (20% v/v) and water for injection q.s.

<sup>b</sup> Ethyl alcohol (5% v/v), Polyethylene glycol-300 (50% v/v), Propylene glycol (20% v/v) and Milli-Q<sup>®</sup> water q.s.

1*H*-Pyrrolo [2, 3-*b*] pyridine compound is orally bioavailable with %F is >20, T<sub>max</sub> (h) is 6 and T<sub>1/2</sub> (h) is 5.

[00376] 1*H*-Pyrrolo [2, 3-*b*] pyridine compound had solubility at pH 3 is 380 µg/mL, in SGF/SIF its stability is over 120 min (half-life), P-gp substrate classification is negative. It has no hERG inhibition (IC<sub>50</sub> >10 µM) and the P450 IC<sub>50</sub> for 1A2, 2C19, 2C9, 2D6 >10 µM. 1*H*-Pyrrolo [2, 3-*b*] pyridine compound hepatocytes clearance is 9.12 (CL<sub>int</sub> mL/min/g liver) and in microsomes is 8 (CL<sub>int</sub> mL/min/g liver).

[00377] Dose formulations were prepared on the day of doing. Blood samples were collected at 0.083 (only IV), 0.25, 0.5, 1, 2, 4, 8 and 24 h post-dose. At each time point, approximately 0.2mL of blood was withdrawn from each cannulated rat through jugular vein and transferred to a pre-labeled microfuge tube containing 20 µL of 200 mM K<sub>2</sub>EDTA per mL of blood. Following collection of blood sample, equal volume of heparinized saline was flushed into jugular vein of rat. The blood samples were centrifuged at 5000 g for 5 minutes at 4 ± 2 °C. The plasma was separated within 30min of scheduled time and stored below -60 °C until bio-analysis. The plasma samples were analyzed for **114** using a fit-for purpose liquid chromatographic tandem mass spectrometric detection (LC-MS/MS) method with a lower limit of quantification of 2.21 ng/mL. The pharmacokinetic parameters for compound **114** were calculated using the non-compartmental analysis tool of validated WinNonlin<sup>®</sup> software (Version 5.2).

Table 6

| Route (Dose) | T <sub>max</sub> (h)         | C <sub>max</sub> (ng/mL)      | AUC <sub>last</sub> (ng.h/mL) | AUC <sub>inf</sub> (ng.h/mL) | CL (mL/min/kg) | V <sub>ss</sub> (L/kg) | T <sub>1/2</sub> (h) | F <sup>a</sup> (%) |
|--------------|------------------------------|-------------------------------|-------------------------------|------------------------------|----------------|------------------------|----------------------|--------------------|
| IV (5mg/kg)  | NA                           | 3849.91 <sup>b</sup> ± 710.44 | 2599.10 ± 636.93              | 2617.38 ± 647.47             | 33.42 ± 9.57   | 1.61 ± 0.28            | 0.54 ± 0.05          | -                  |
| PO (20mg/kg) | 0.25 <sup>c</sup> (0.25-0.5) | 852.56 ± 83.61                | 1583.84 ± 179.45              | 1599.77 ± 182.86             | NA             | NA                     | NA                   | 15                 |

<sup>a</sup> AUC<sub>inf</sub> and nominal doses were used for bioavailability (%F) calculation; <sup>b</sup> concentration at time zero; <sup>c</sup> T<sub>max</sub> is represented as median (range)

**Table 6:** Rat PK: The pharmacokinetic profiles of test compound **114** following intravenous bolus administration and oral gavage in male Sprague Dawley rats.

### STRUCTURAL HOMOMOLOGY MODELING – Salt Inducible Kinase 2 (SIK2)

[00378] The compounds of Formula I, **IA** and **IB** provided in **Tables 1-3** were designed using a structural homology model of SIK2 and its mutant form of SIK2. The homology model of structural model of the kinase domain of SIK2 was constructed using Salt Inducible Kinase 2 (SIK2) domain region sequence (11-336) from the full length protein sequence NP\_9056006 (**Fig. 3**).

[00379] Referring to **Fig. 3**, Structure based sequence alignment in Clustal W of the catalytic protein kinase domains of SIK1 (SNF1LK), SIK2 (SNF1LK, QIK), SIK3 (QSK), AMPK and MARK2. Amino acid residue annotation were identical residues (\*), highly conserved residues (:), and similar residues (.) The active site residues highlighted in yellow and the gatekeeper residues in turquoise and the DFG residues shown in yellow.

[00380] Sequence search with in the RCSB provided the 2 homologues X-ray crystal structure templates with ~52% sequence identity and ~65% sequence similarities was considered as starting point for multiple sequence alignment using Clustal W alignment (**FIG. 4**) and homology modeling. The Swiss-Model was applied in sequence alignment, model building, loop prediction and refinement. With the application of FFDDTM (Fragment-Field Drug Design) workflow design strategy, the final models of SIK2 shown in **Figure. 4** were utilized and served as template for designing claimed compounds. Based on the 3-D profile scoring the structural template chosen from PDB database and were both MARK2 and AMP-activated protein kinase (AMPK) crystal structures (PDB ID: 2ROI and 3AQV). Several models were built and refined to check the 3D profile and are shown in **Figure. 4**.

[00381] Referring to **Figure. 4**, the homology model of SIK2 in complex with one of the lead inhibitor is shown. The critical active site residues shown in color-by-atom in stick representations. The inhibitor binding site depicted in surface in complex with SIK2. Compound belongs to 1*H*-pyrrolo [2, 3-*b*] pyridine structural class claimed.

### REFERENCES

1. Ovarian Cancer National Alliance at <http://www.ovariancancer.org/about-ovarian-cancer/statistics/>.
2. Bast R. C Jr, Molecular approaches to personalizing management of ovarian cancer, *Ann Oncol.* **2011**, 22 Suppl 8:viii5-viii15.
3. Bast R. C Jr., Hennessy B, Mills G. B. The biology of ovarian cancer: new opportunities for translation. *Nature Rev Cancer*, **2009**, 9, 415-428.

4. Banerjee, S, Kaye, S.  
B. New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. *Clin Cancer Res.* **2013** 1, 19(5), 961-968.
5. Ahmed, A. A, Lu, Z, Jennings, N. B, Etemadmoghadam, D, Capalbo, L, Jacamo, R. O, Barbosa-Morais, N, Le, XF; Australian Ovarian Cancer Study Group, Vivas-Mejia, P, Lopez-Berestein, G, Grandjean, G, Bartholomeusz, G, Liao, W, Andreeff M, Bowtell, D, Glover, D. M, Sood, A. K, Bast, R. C Jr. SIK2 is a centrosome kinase required for bipolar mitotic spindle formation that provides a potential target for therapy in ovarian cancer. *Cancer Cell.* **2010**, 9, 18(2), 109-121.
6. Kumagai, A, Horike, N, Satoh, Y, Uebi, T, Sasaki, T, Itoh, Y, Hirata, Y, Uchio-Yamada, K, Kitagawa, K, Uesato, S, Kawahara, H, Takemori, H, Nagaoka, Y. A potent inhibitor of SIK2, 3, 3', 7-trihydroxy-4'-methoxyflavon (4'-O-methylfisetin), promotes melanogenesis in B16F10 melanoma cells. *PLoS One.* **2011**, 6(10), e26148.
7. Perez de Castro, I, de Carcer, G, Montoya, G, Malumbres, M. Emerging cancer therapeutic opportunities by inhibiting mitotic kinases. *Curr. Opin. Pharmacol.*, **2008**, 8, 375-383.
8. Nagel, S, Leich, E, Quentmeier, H, Meyer, C, Kaufmann, M, Zaborski, M, Rosenwald, A, Drexler, H. G, Macleod, R. A. Amplification at 11q23 targets protein kinase SIK2 in diffuse large B-cell lymphoma. *Leuk Lymphoma.* **2010**, 51(5), 881-891.
9. Vankayalapati, H. Identification of Novel Inhibitors of SIK2 Kinase: A Novel Ser/Thr Kinase for Multiple Disease Indications presented at Emerging Targeted Oncology Partnering Forum, February 19-20, **2012**, San Francisco, CA.
10. Jia, L, Zhang S, Ye, Y, Li, X, Mercado-Urbe, I, Bast, R. C Jr, Liu, J. Paclitaxel inhibits ovarian tumor growth by inducing epithelial cancer cells to benign fibroblast-like cells. *Cancer Lett.* **2012**, 30, 326(2), 176-182.
11. Horike, N, Kumagai, A, Shimono, Y, Onishi, T, Itoh, Y, Sasaki, T, Kitagawa, K, Hatano, O, Takagi, H, Susumu, T, Teraoka, H, Kusano, K, Nagaoka, Y, Kawahara, H, Takemori, H. Downregulation of SIK2 expression promotes the melanogenic program in mice. *Pigment Cell Melanoma Res.* **2010**, 23(6), 809-819.
12. Clark, K, Mackenzie, K.F, Petkevicius, K, Kristariyanto, Y, Zhang, J, Choi, H. G, Peggie, M, Plater, L, Pedrioli, P. G, McIver, E, Gray, N. S, Arthur, J. S, Cohen, P. Phosphorylation of CRTC3 by the salt-inducible kinases controls the interconversion of classically activated and regulatory macrophages. *Proc Natl Acad Sci U S A.* **2012** 16, 109(42)16986-16991.
13. Henriksson, E, Jones, H. A, Patel, K, Peggie, M, Morrice, N, Sakamoto, K, Göransson, O. The AMPK-related kinase SIK2 is regulated by cAMP via phosphorylation at Ser358 in adipocytes. *Biochem J.* **2012**, 15, 444(3), 503-514. Pmid: 22462548.
14. Sasaki, T, Takemori H, Yagita, Y, Terasaki, Y, Uebi, T, Horike, N, Takagi, H, Susumu, T, Teraoka, H, Kusano, K, Hatano, O, Oyama, N, Sugiyama, Y, Sakoda, S, Kitagawa, K. SIK2 is a key regulator for neuronal survival after ischemia via TORC1-CREB. *Neuron.* **2011**, 13, 69(1), 106-109.
15. Liu, Y, Poon, V, Sanchez-Watts, G, Watts, A.G, Takemori. H, Aguilera, G. Salt-inducible kinase is involved in the regulation of corticotropin-releasing hormone transcription in hypothalamic neurons in rats. *Endocrinology.* **2012**, 153(1), 223-233.
16. Gallo, E. F, Ladecola, C. Balancing life and death in the ischemic brain: SIK and TORC weigh in. *Neuron.* **2011**, 13, 69(1), 3-6.
17. Muraoka, M, Fukushima, A, Viengchareun, S, Lombès, M, Kishi, F, Miyauchi, A, Kanematsu, M, Doi, J, Kajimura, J, Nakai, R, Uebi, T, Okamoto, M, Takemori, H. Involvement of SIK2/TORC2 signaling cascade in the regulation of insulin-induced PGC-1 $\alpha$  and UCP-1 gene expression in brown adipocytes. *Am J Physiol Endocrinol Metab.* **2009**, 296(6), E1430-439.

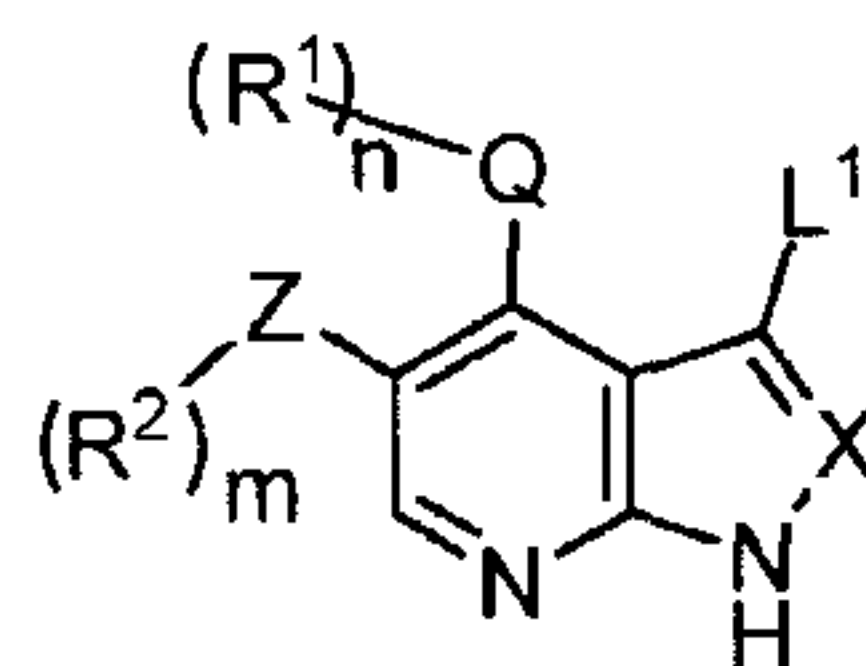
18. Du, J, Chen, Q, Takemori, H, Xu, H. SIK2 can be activated by deprivation of nutrition and it inhibits expression of lipogenic genes in adipocytes. *Obesity* (Silver Spring). **2008**, 6(3), 531-538.
19. Hashimoto, Y. K, Satoh, T, Okamoto, M, Takemori, H. Importance of autophosphorylation at Ser186 in the A-loop of salt inducible kinase 1 for its sustained kinase activity. *J Cell Biochem.* **2008**, 1, 104(5), 1724-3179.
20. Ryu, D, Oh, K. J, Jo, H. Y, Hedrick, S, Kim, Y. N, Hwang, Y. J, Park, T. S, Han, J. S, Choi, C. S, Montminy, M, Koo, S. H. TORC2 regulates hepatic insulin signaling via a mammalian phosphatidic acid phosphatase, LIPIN1. *Cell Metab.* **2009**, 9(3), 240-251.
21. Charoenfuprasert, S, Yang, Y. Y, Lee, Y. C, Chao, K. C, Chu, P. Y, Lai, C. R, Hsu, K. F, Chang, K. C, Chen, Y. C, Chen, L. T, Chang, J. Y, Leu, S. J, Shih, N. Y. Identification of salt-inducible kinase 3 as a novel tumor antigen associated with tumorigenesis of ovarian cancer. *Oncogene.* **2011**, 18, 30(33), 3570-3584.
22. Kitagawa, K, Sasaki, T, Terasaki, Y, Yagita, Y, Mochizuki, H. CREB activation is a key player for ischemic tolerance in the brain. *Rinsho Shinkeigaku.* **2012**, 52(11), 904-907.
23. Imielinski, M, Berger, A. H, Hammerman, P. S, Hernandez, B, Pugh, T. J, Hodis, E, Cho, J, Suh, J, Capelletti, M, Sivachenko, A, Sougnez, C, Auclair, D, Lawrence, M. S, Stojanov, P, Cibulskis, K, Choi, K, de Waal, L, Sharifnia, T, Brooks, A, Greulich, H, Banerji, S, Zander, T, Seidel, D, Leenders, F, Ansén, S, Ludwig, C, Engel-Riedel, W, Stoelben E, Wolf J, Goparju C, Thompson K, Winckler W, Kwiatkowski D, Johnson, B. E, Jänne, P. A, Miller, V. A, Pao, W, Travis, W. D, Pass, H. I, Gabriel, S. B, Lander, E. S, Thomas, R. K, Garraway, L.A, Getz, G, Meyerson, M. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell.* **2012**, 4, 150(6), 1107-1120.
24. Copps, K. D, White, M. F. Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. *Diabetologia.* **2012**, 55(10), 2565-2582.
25. Wang, Y, Li, G, Goode, J, Paz, J. C, Ouyang, K, Screatton, R, Fischer, W. H, Chen, J, Tabas, I, Montminy, M. Inositol-1,4,5-trisphosphate receptor regulates hepatic gluconeogenesis in fasting and diabetes. *Nature.* **2012**, 8; 485(7396), 128-132.
26. Bricambert, J, Miranda, J, Benhamed, F, Girard, J, Postic, C, Dentin, R. Salt-inducible kinase 2 links transcriptional coactivator p300 phosphorylation to the prevention of ChREBP-dependent hepatic steatosis in mice. *J Clin Invest.* **2010**, 120(12), 4316-4331.
27. Salisbury, J. L. A centrosome kinase modulates antitumor drug sensitivity. *Cancer Cell.* **2010**, 9, 18(2), 99-100.
28. Wang, B, Goode, J, Best, J, Meltzer, J, Schilman, P. E, Chen, J, Garza, D, Thomas, J. B, Montminy, M. The insulin-regulated CREB coactivator TORC promotes stress resistance in *Drosophila*. *Cell Metab.* **2008**, 7(5), 434-44.
29. Katoh, Y, Takemori, H, Horike, N, Doi, J, Muraoka, M, Min, L, Okamoto, M. Salt-inducible kinase (SIK) isoforms: their involvement in steroidogenesis and adipogenesis. *Mol Cell Endocrinol.* **2004**, 31; 217(1-2), 109-112.

WO 2014/093383

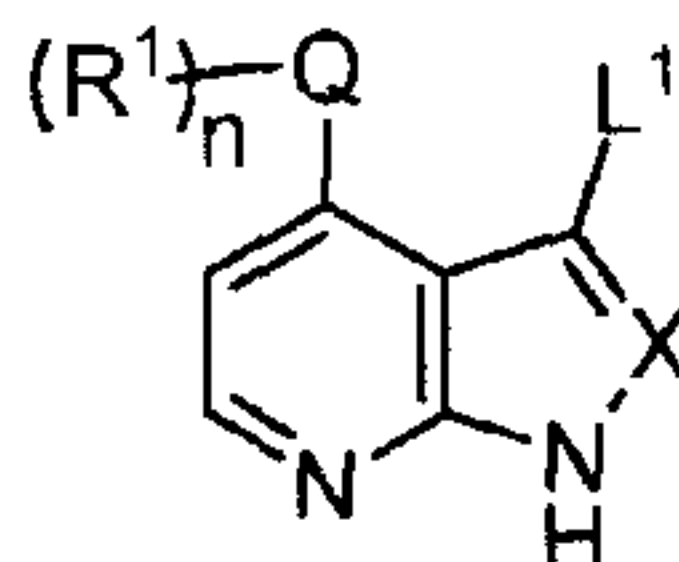
PCT/US2013/074191

What is claimed is:

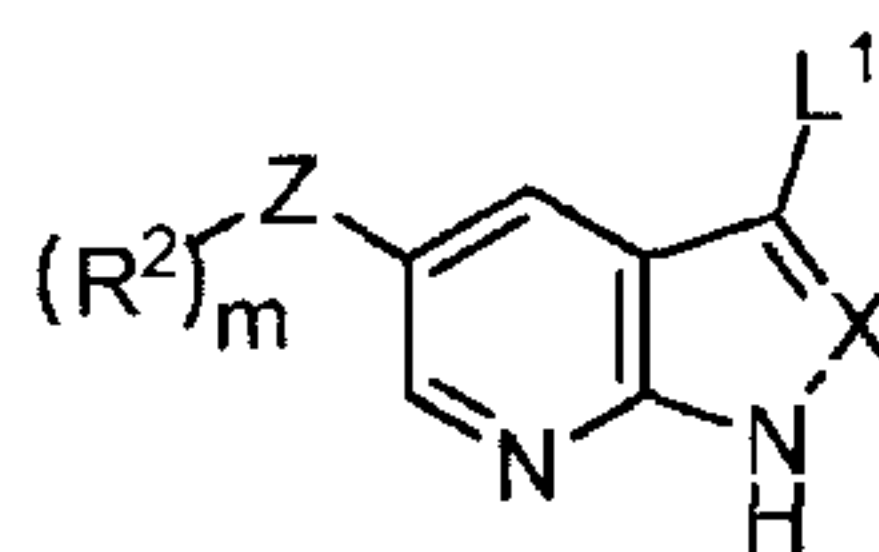
Claim 1. A compound having the structure according to Formulas I, IA or IB:



(I)



(IA)

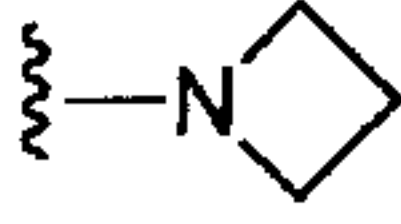
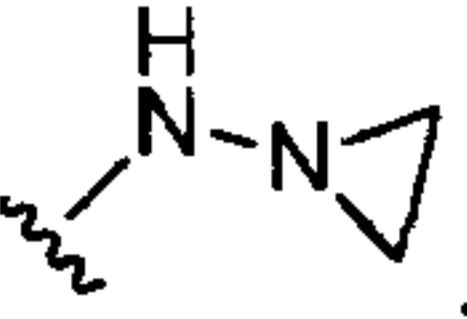


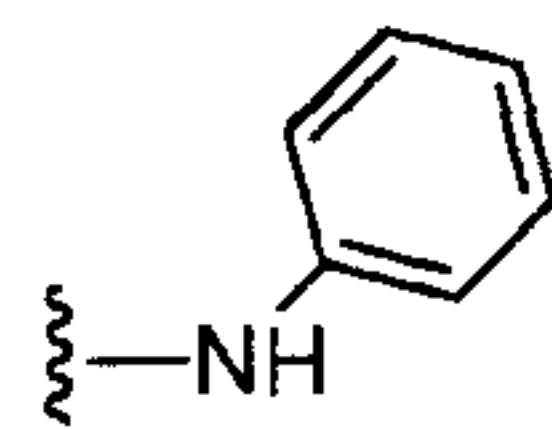
(IB)

or a pharmaceutically acceptable salt thereof, wherein:

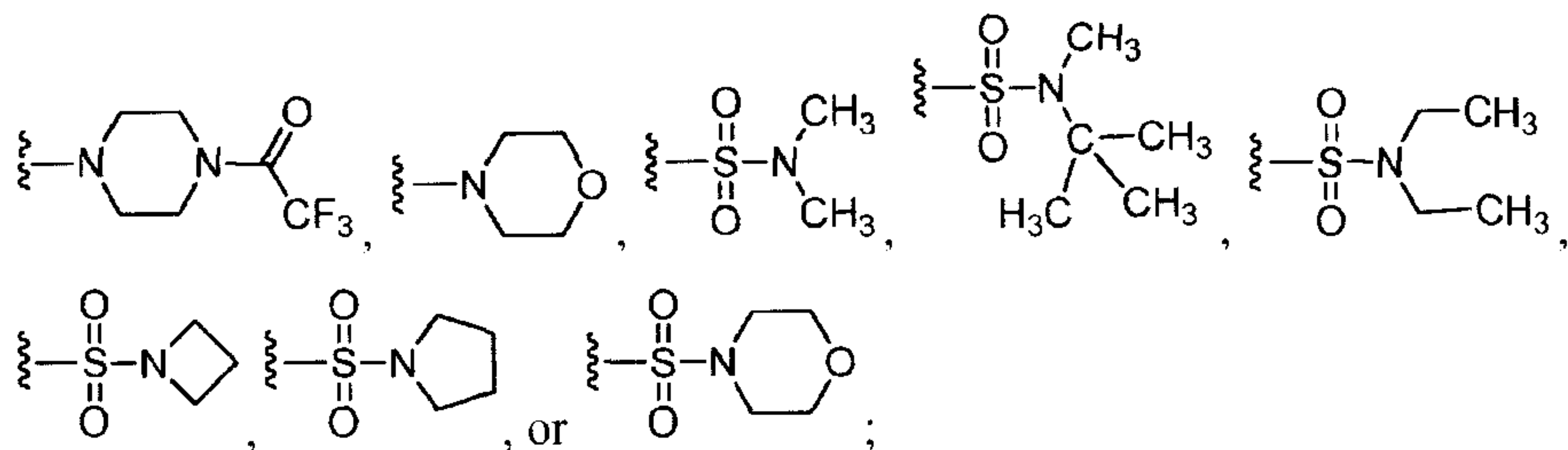
X is N or CH;

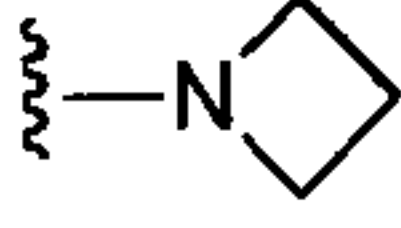
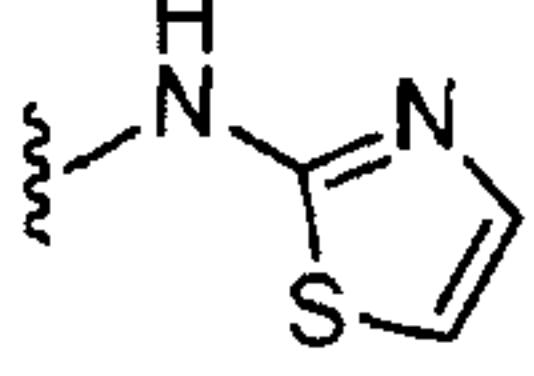
L<sup>1</sup> is H, F; or

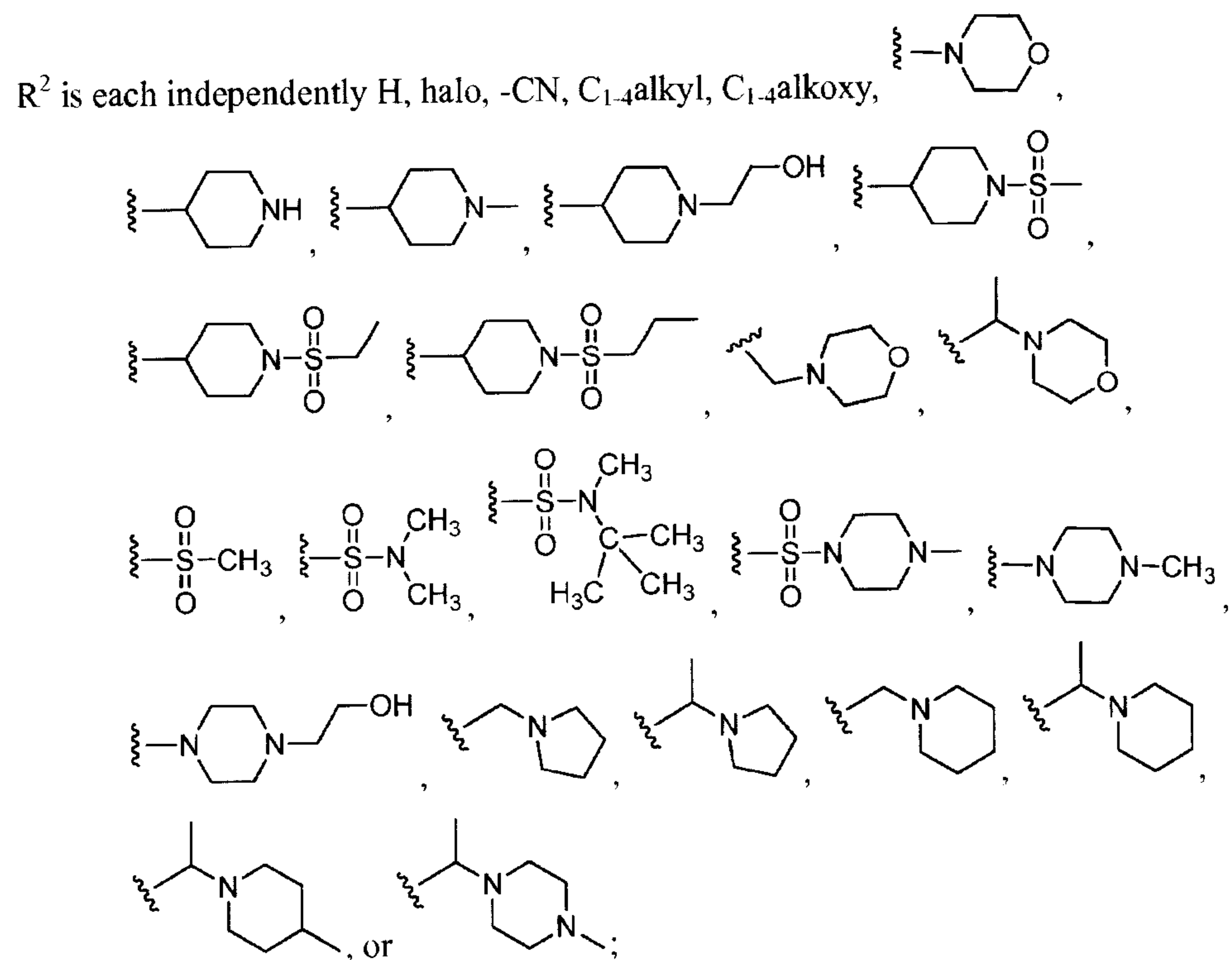
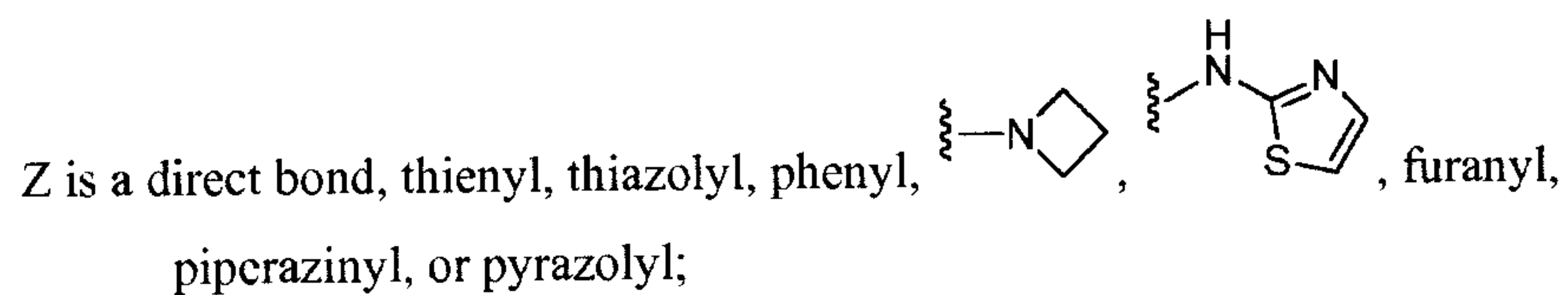
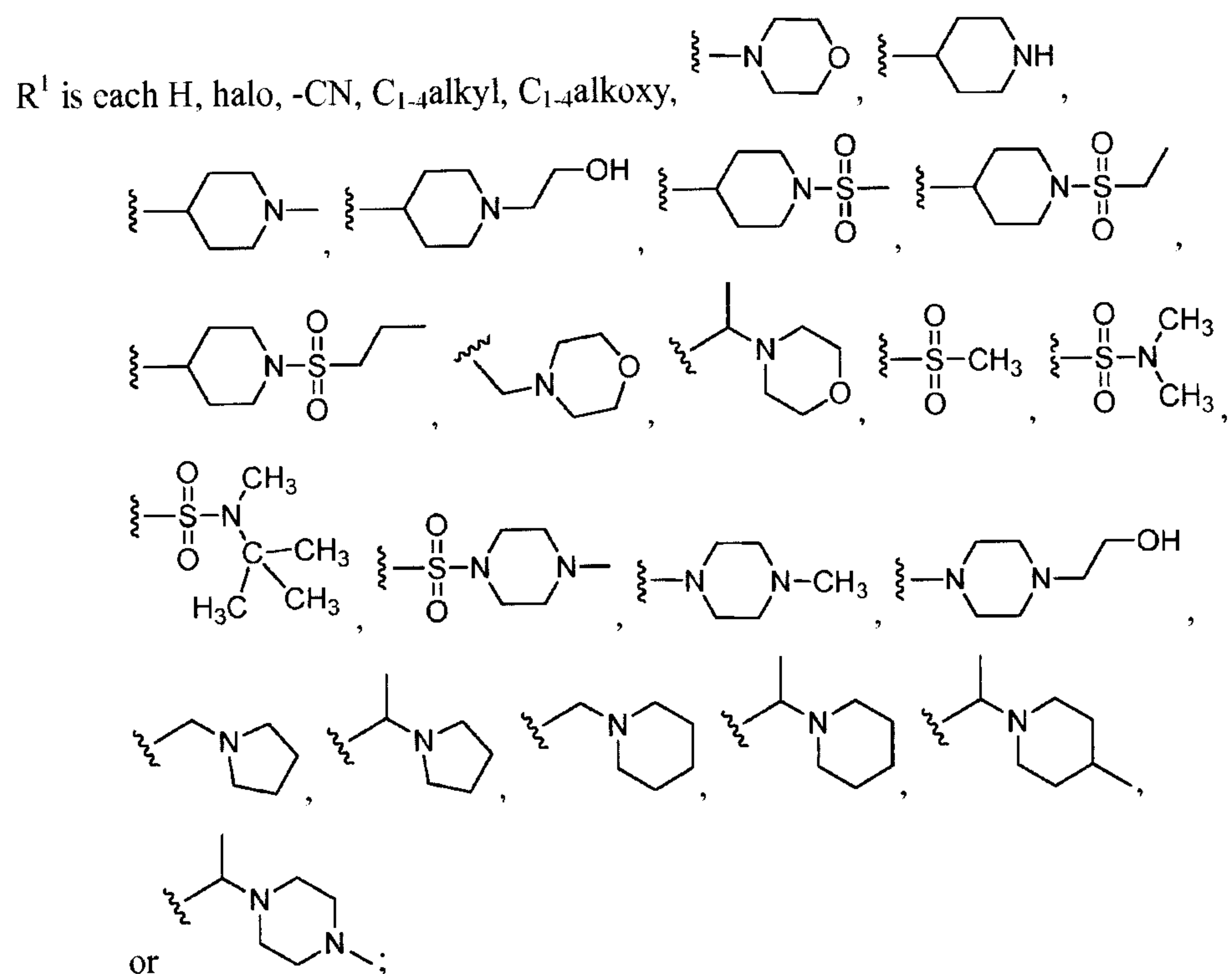
L<sup>1</sup> is thienyl, phenyl, pyrrolyl, pyridyl, , piperazinyl, , or



, any of which is optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl, methylpiperazinyl,



Q is a direct bond, thienyl, thiazolyl, phenyl, , , furanyl, piperazinyl, or pyrazolyl;



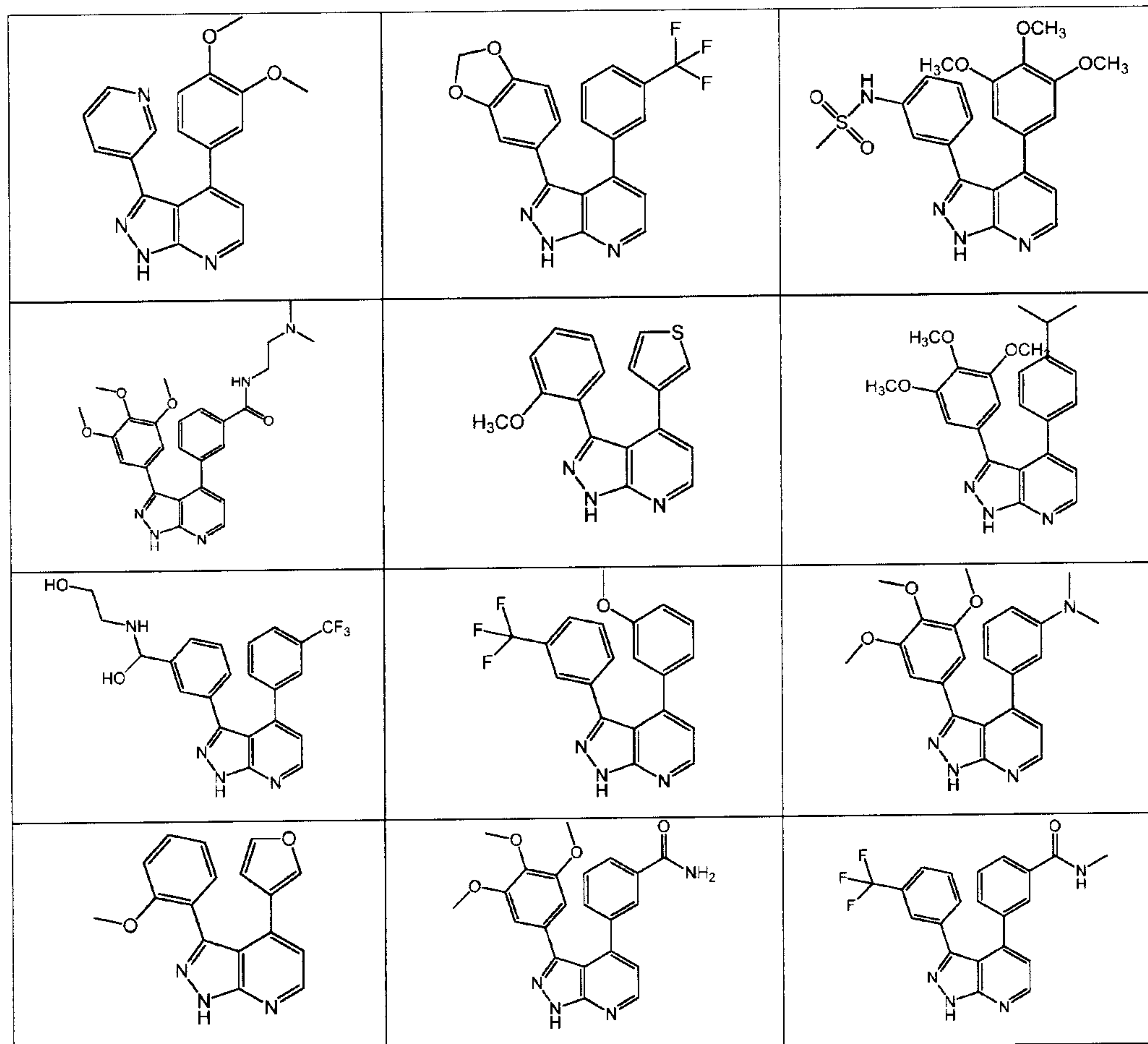
WO 2014/093383

PCT/US2013/074191

n is 0, 1, or 2; and

m is 0, 1, or 2;

provided that the compound is not a compound selected from

and further provided that at least one of  $L^1$ ,  $R^1$ , and  $R^2$  is not H.

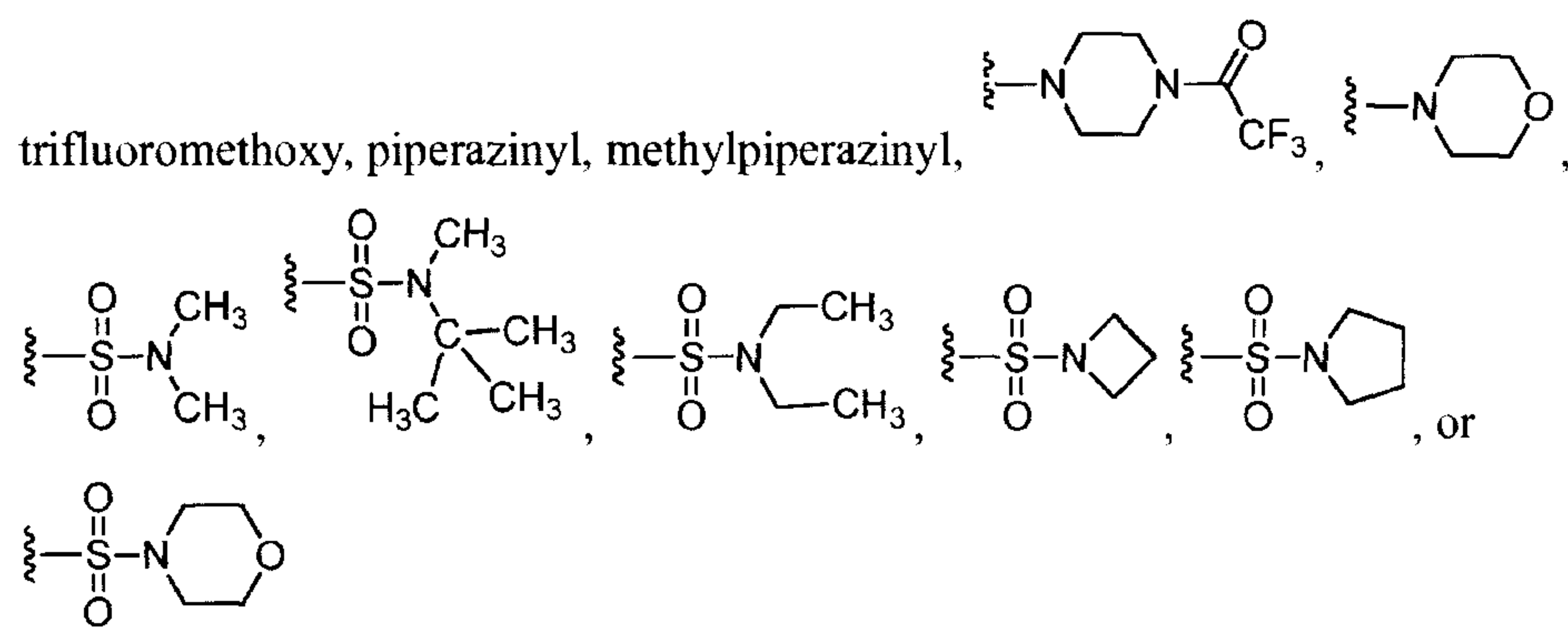
Claim 2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is described by Formula IA, and X is CH.

Claim 3. A compound according to claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  is H or F.

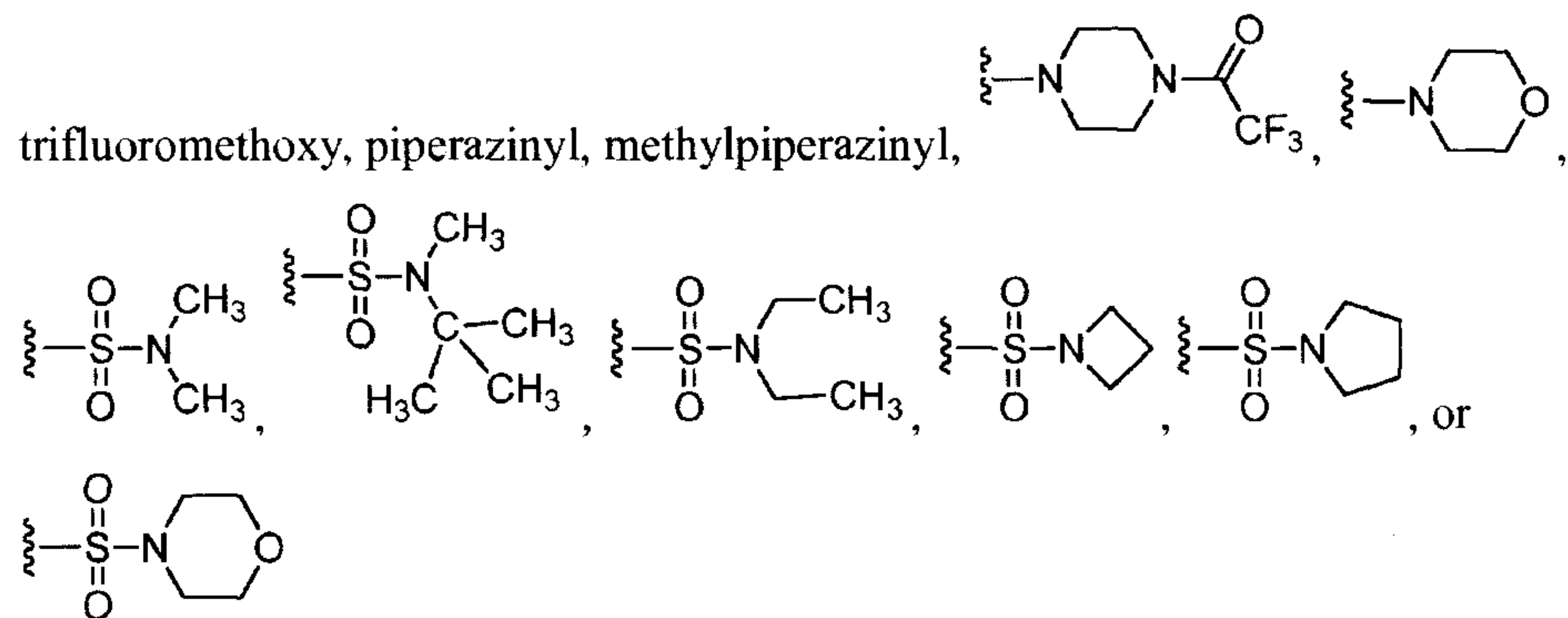
Claim 4. A compound according to claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  is phenyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl,

WO 2014/093383

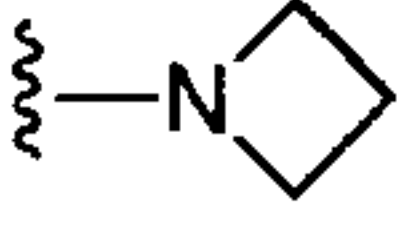
PCT/US2013/074191

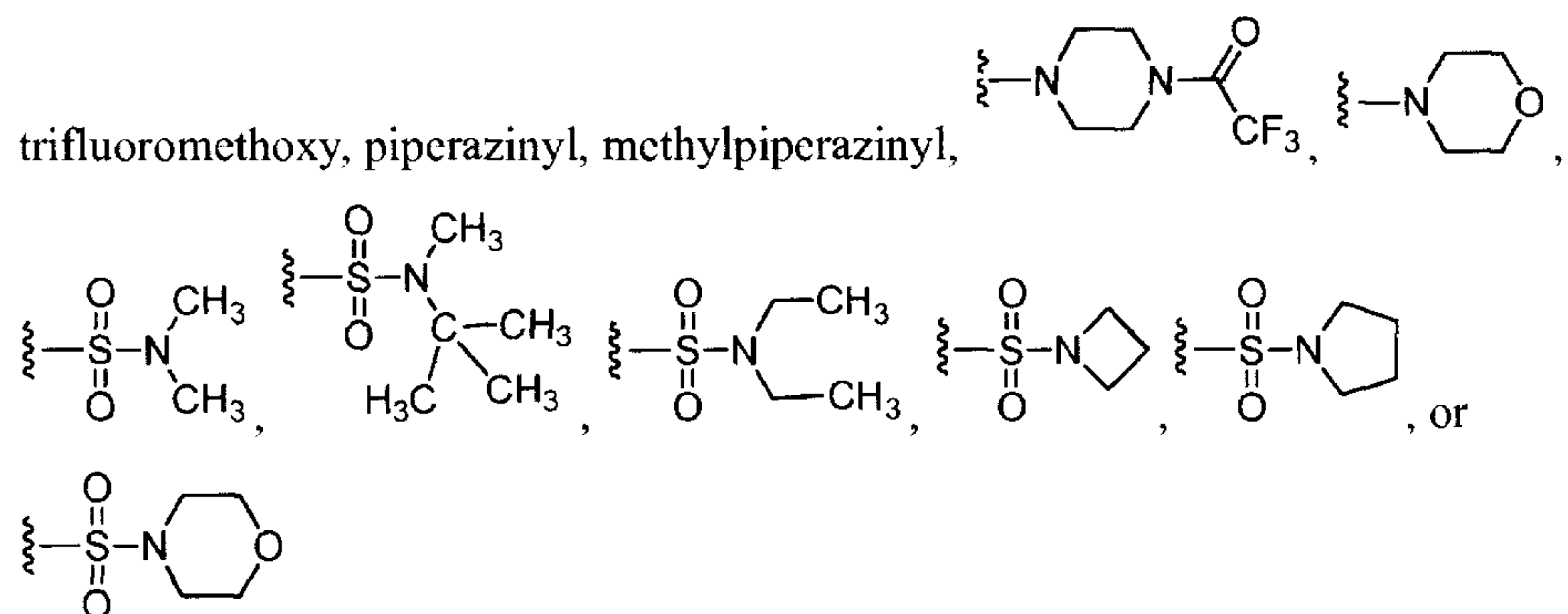


Claim 5. A compound according to claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  is pyridyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl,



Claim 6. A compound according to claim 2, or a pharmaceutically acceptable salt thereof,

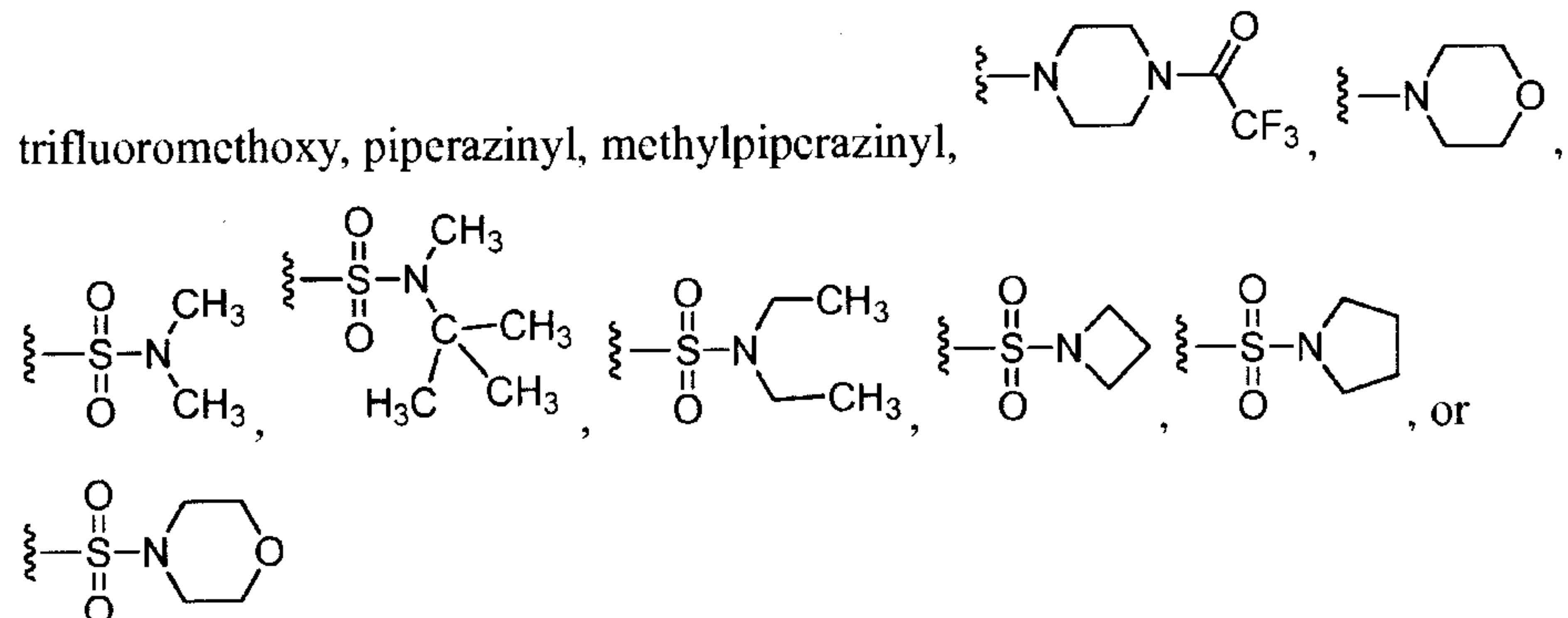
wherein  $L^1$  is  optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl,



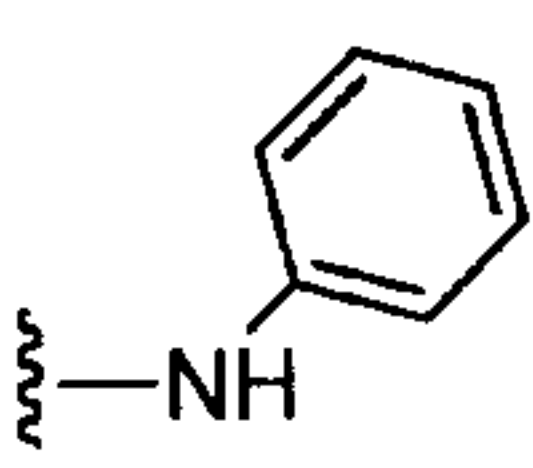
WO 2014/093383

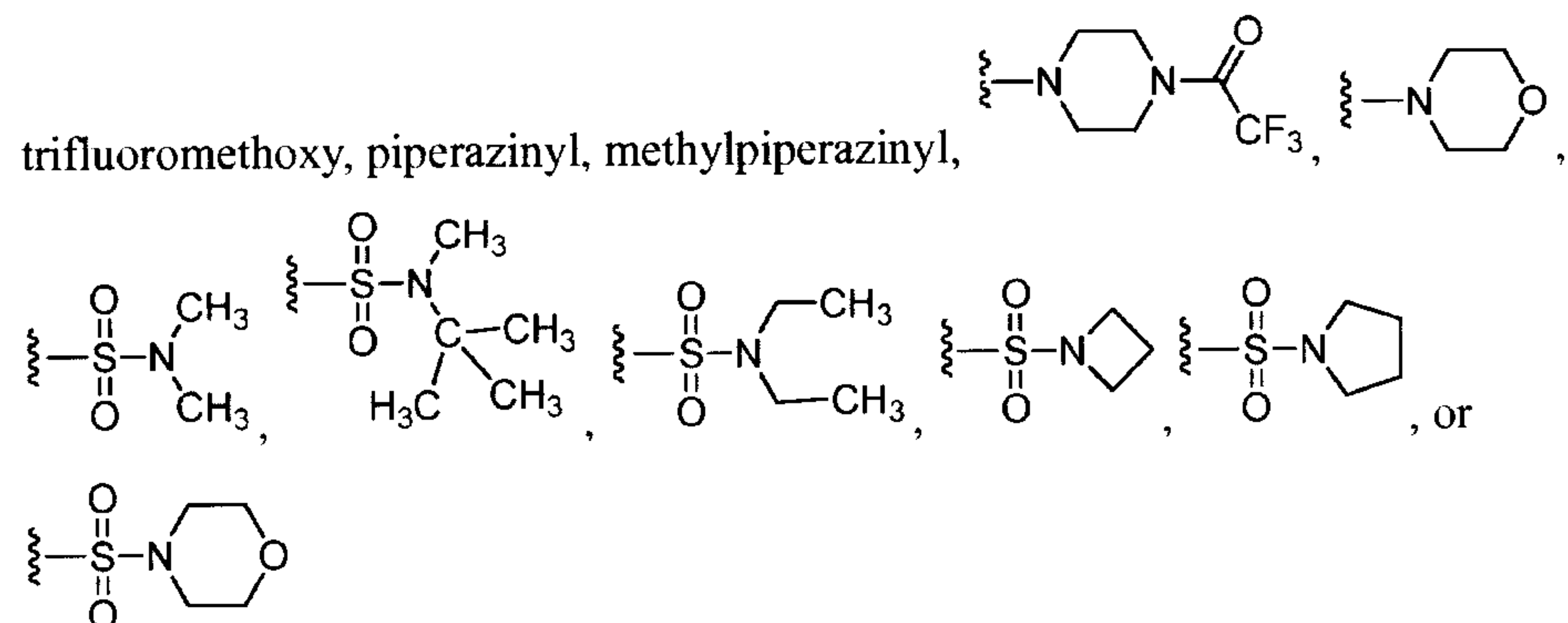
PCT/US2013/074191

Claim 7. A compound according to claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  is piperazinyl optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl,



Claim 8. A compound according to claims 1 or 2, or a pharmaceutically acceptable salt thereof,

wherein  $L^1$  is  optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl,



Claim 9. A compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Q is a direct bond.

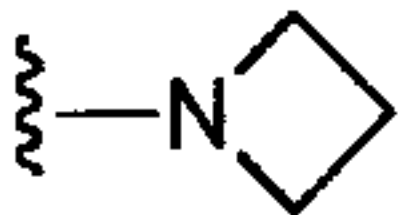
Claim 10. A compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Q is thienyl.

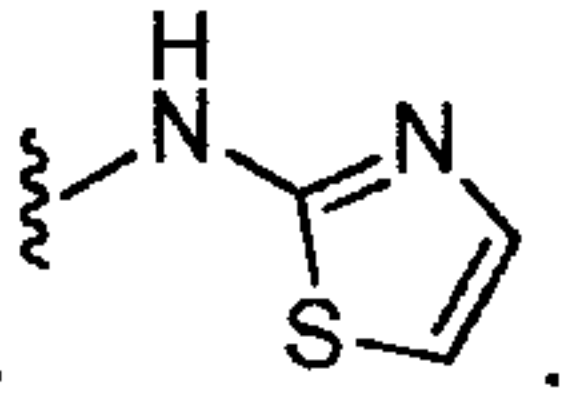
Claim 11. A compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Q is thiazolyl.

WO 2014/093383

PCT/US2013/074191

Claim 12. A compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Q is phenyl.

Claim 13. A compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Q is .

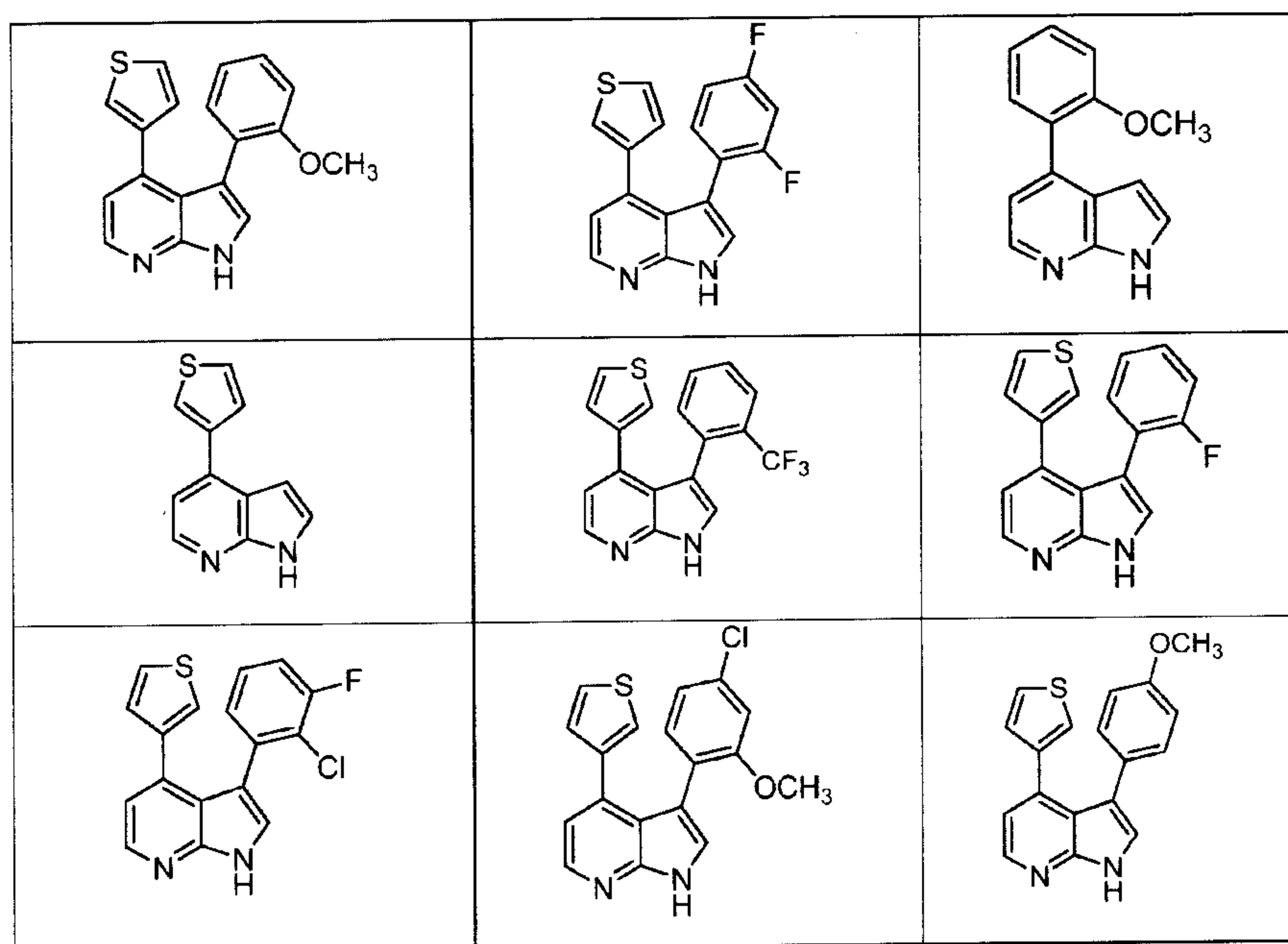
Claim 14. A compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Q is .

Claim 15. A compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Q is furanyl.

Claim 16. A compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Q is piperazinyl.

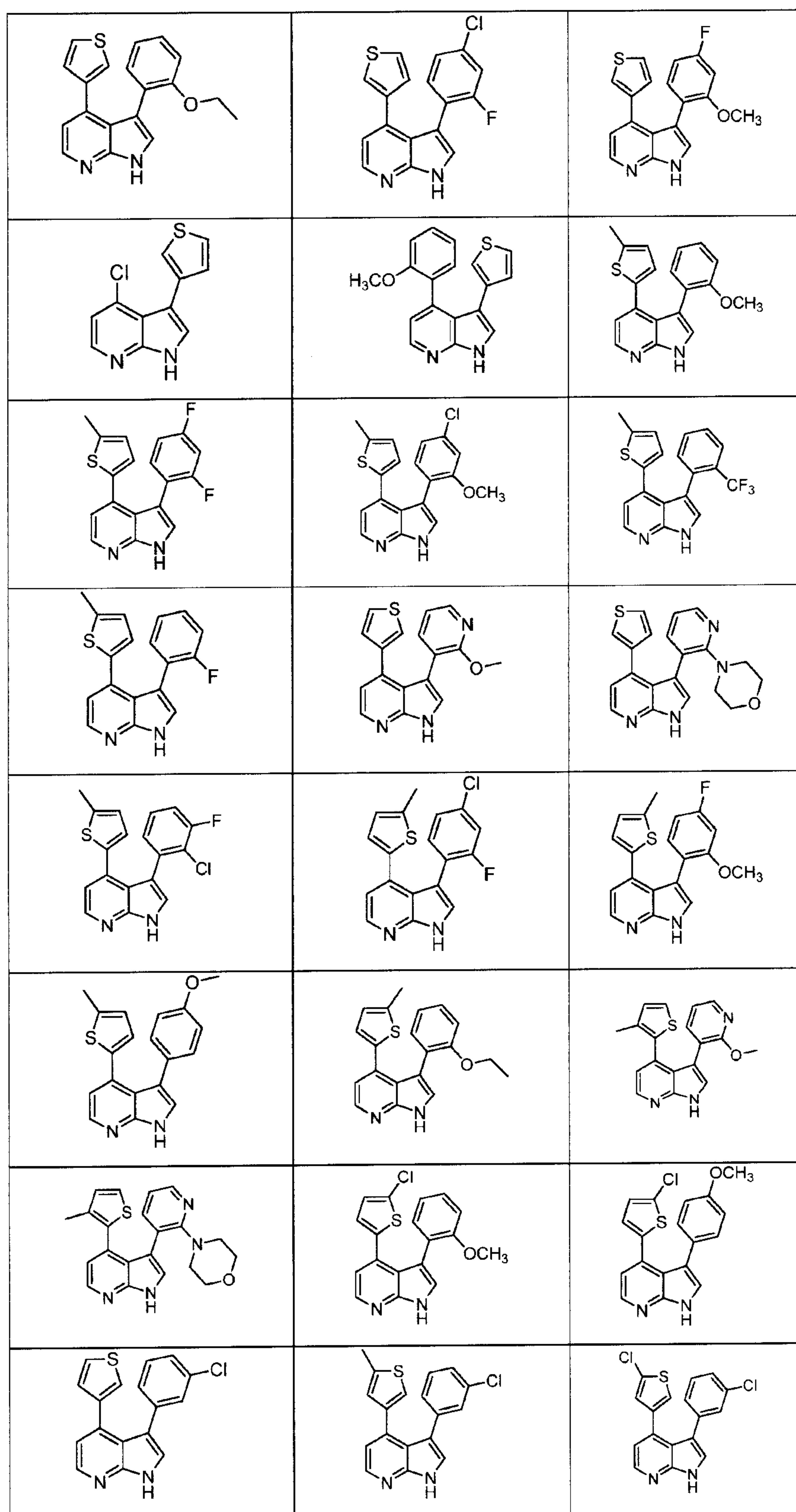
Claim 17. A compound according to any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Q is pyrazolyl.

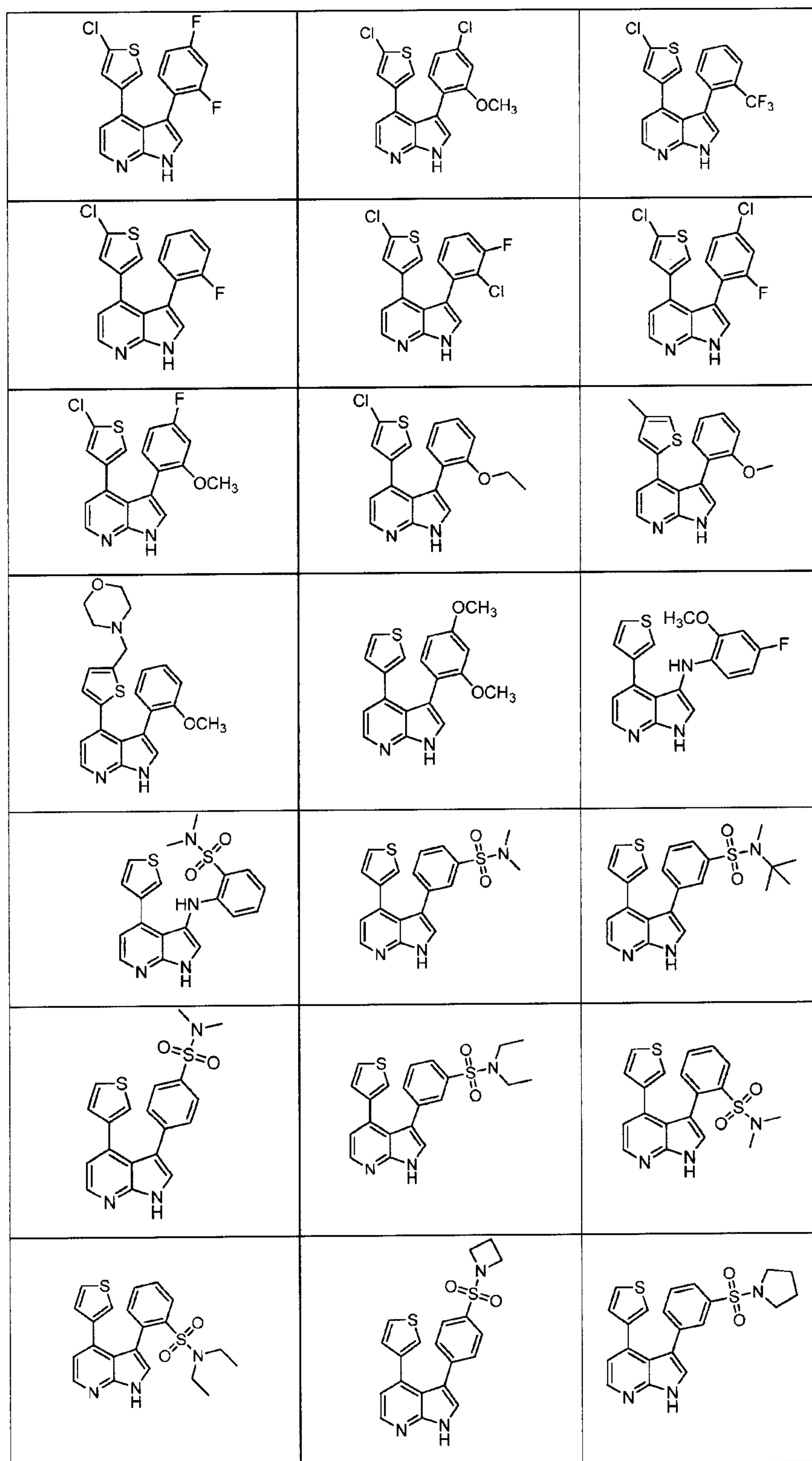
Claim 18. A compound according to claim 2 comprising a compound selected from



WO 2014/093383

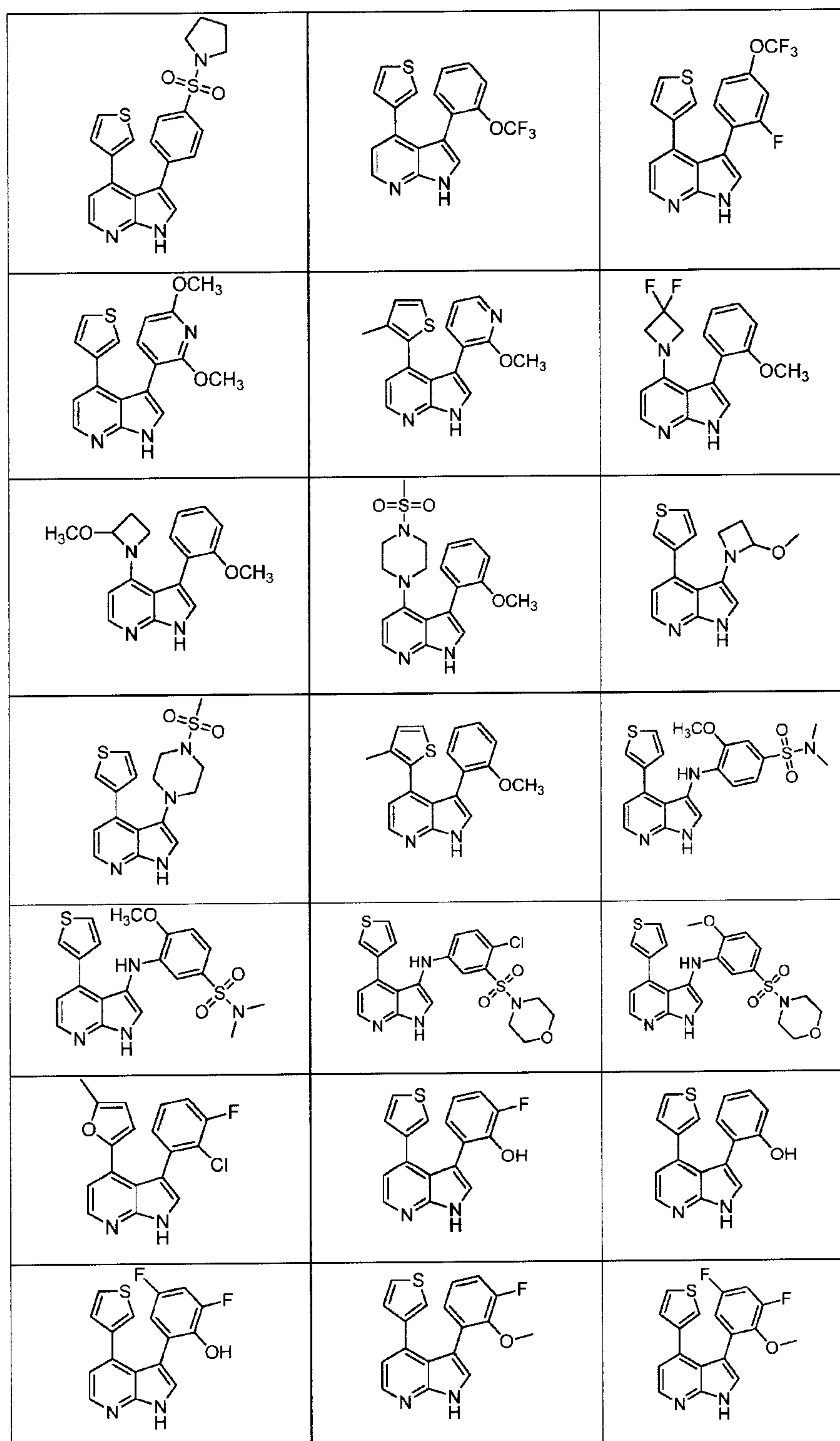
PCT/US2013/074191





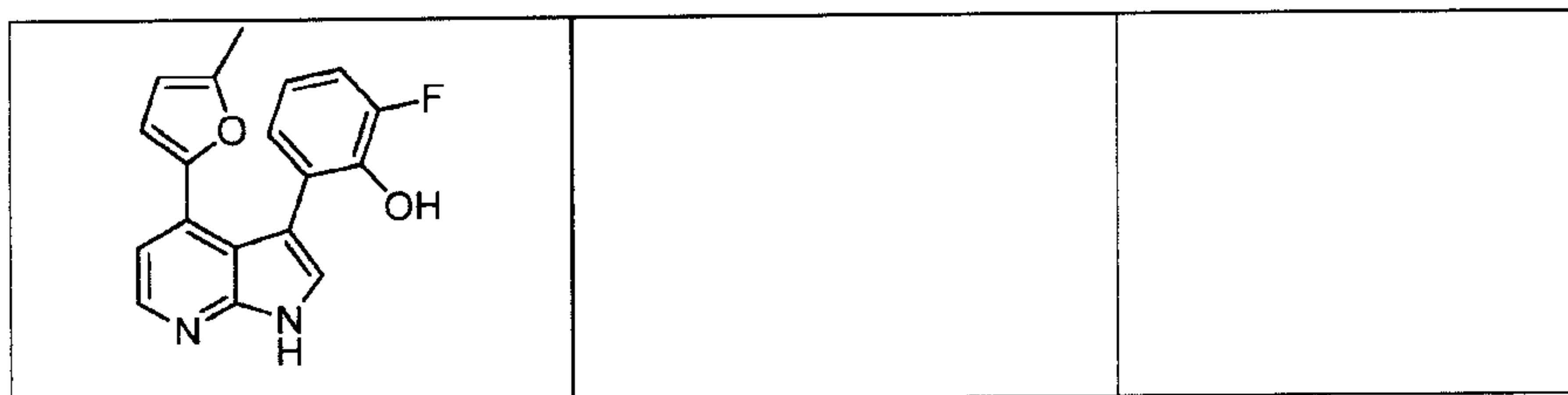
WO 2014/093383

PCT/US2013/074191



WO 2014/093383

PCT/US2013/074191

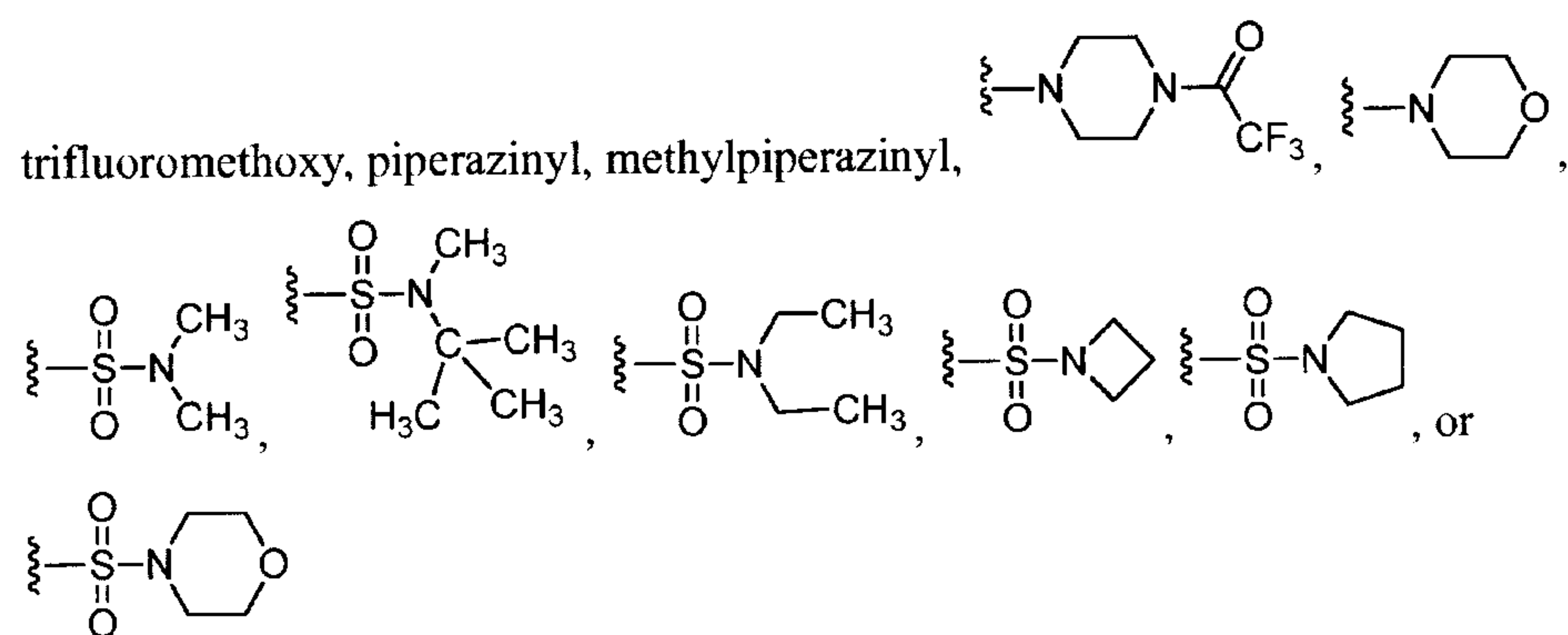


or a pharmaceutically acceptable salt thereof.

Claim 19. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is described by Formula IA, and X is N.

Claim 20. A compound according to claims 1 or 19, or a pharmaceutically acceptable salt thereof, wherein L<sup>1</sup> is H.

Claim 21. A compound according to claims 1 or 19, or a pharmaceutically acceptable salt thereof, wherein L<sup>1</sup> is phenyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl,

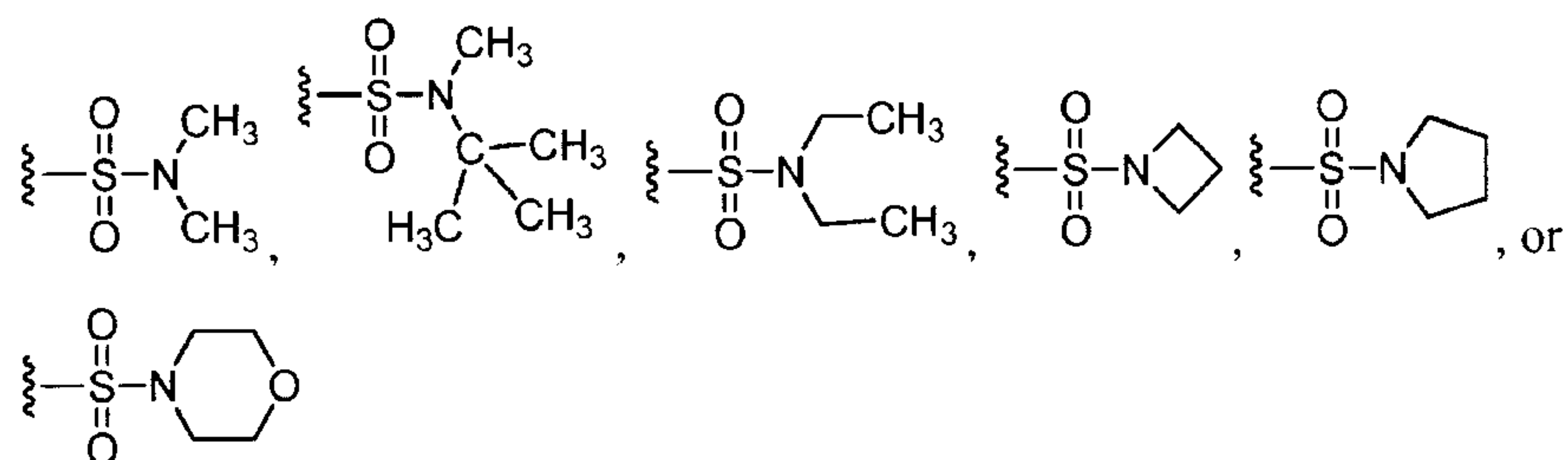


Claim 22. A compound according to claims 1 or 19, or a pharmaceutically acceptable salt thereof, wherein L<sup>1</sup> is pyridyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl,

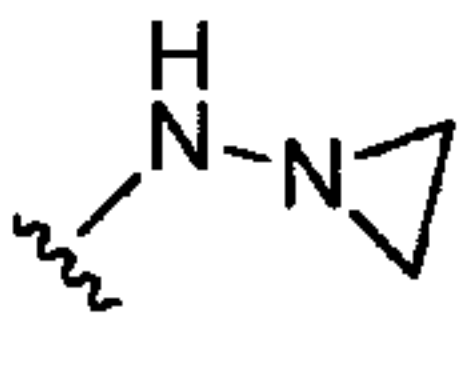


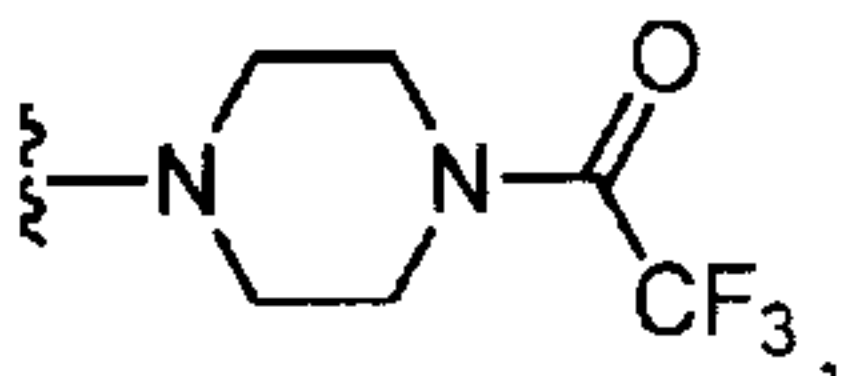
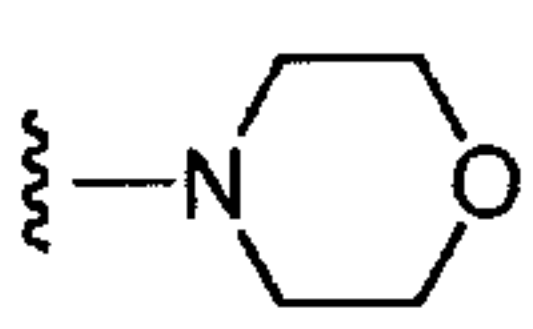
WO 2014/093383

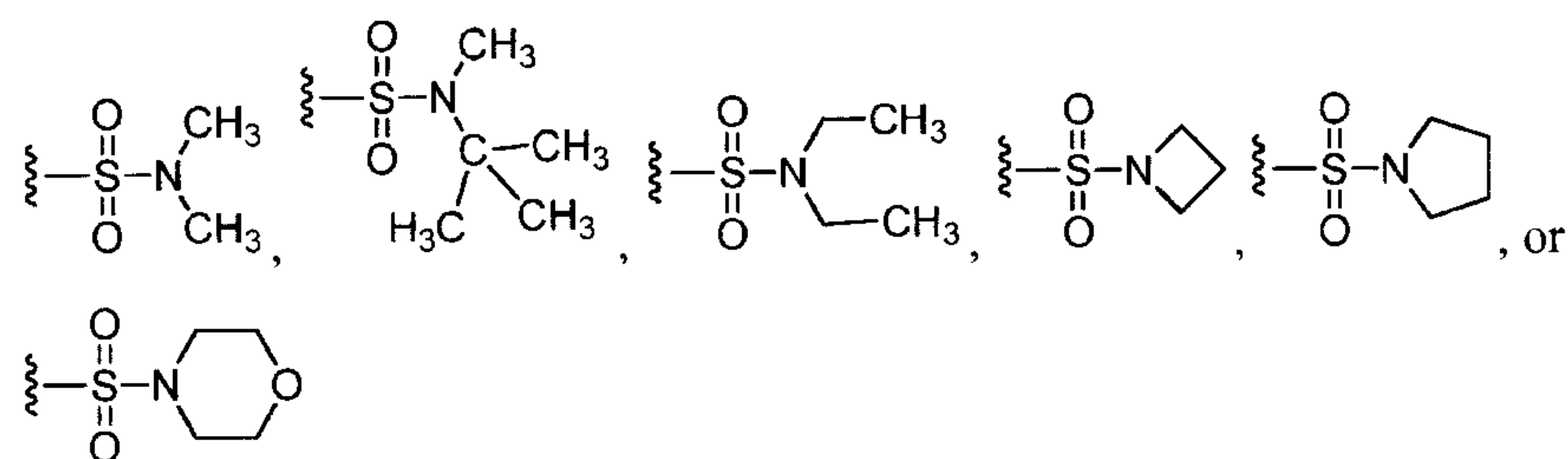
PCT/US2013/074191



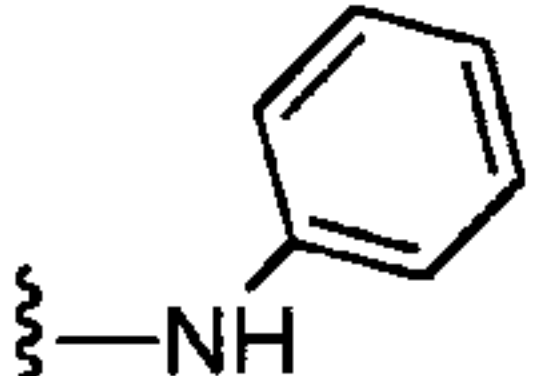
Claim 23. A compound according to claims 1 or 19, or a pharmaceutically acceptable salt

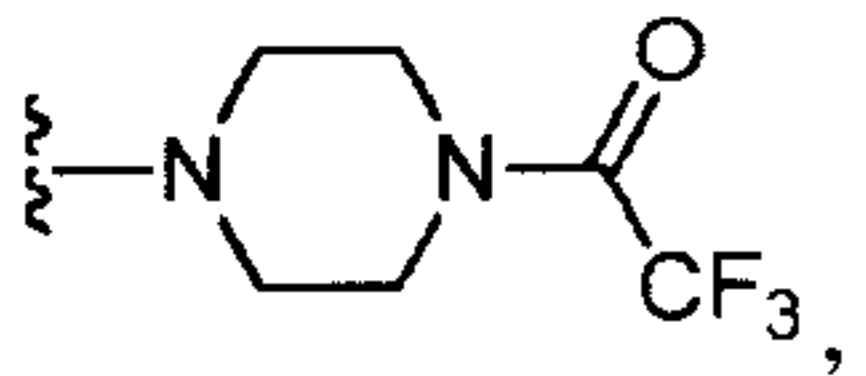
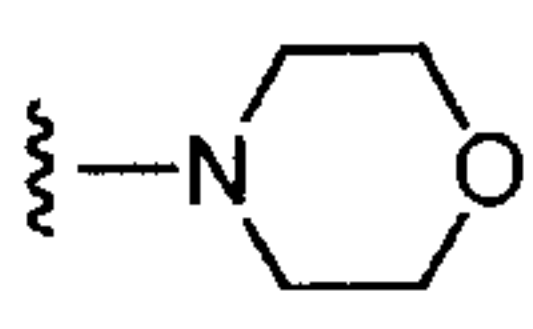
thereof, wherein  $L^1$  is  optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl,

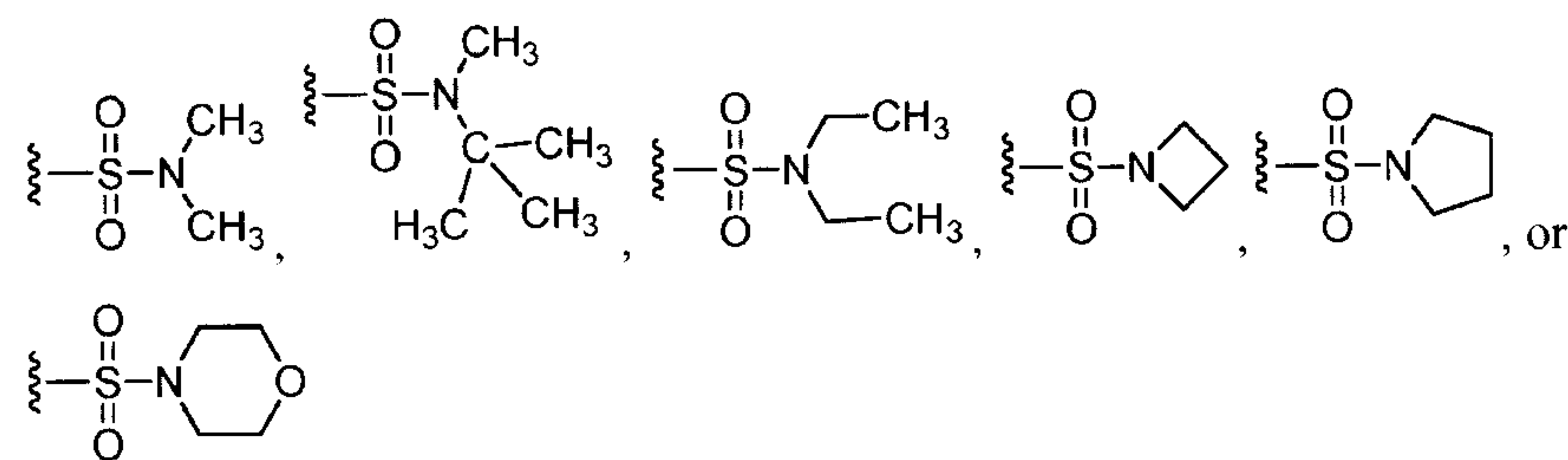
trifluoromethoxy, piperazinyl, methylpiperazinyl, , ,



Claim 24. A compound according to claims 1 or 19, or a pharmaceutically acceptable salt

thereof, wherein  $L^1$  is  optionally substituted with 1-3 substituents, each substituent independently selected from halo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, trifluoromethyl,

trifluoromethoxy, piperazinyl, methylpiperazinyl, , ,



WO 2014/093383

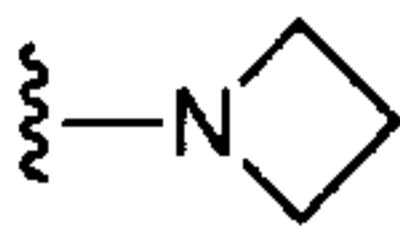
PCT/US2013/074191

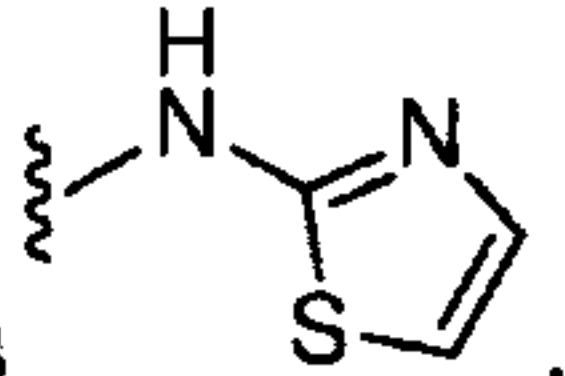
Claim 25. A compound according to any of claims 1, or 19 to 24, or a pharmaceutically acceptable salt thereof, wherein Q is a direct bond.

Claim 26. A compound according to any of claims 1, or 19 to 24, or a pharmaceutically acceptable salt thereof, wherein Q is thienyl.

Claim 27. A compound according to any of claims 1, or 19 to 24, or a pharmaceutically acceptable salt thereof, wherein Q is thiazolyl.

Claim 28. A compound according to any of claims 1, or 19 to 24, or a pharmaceutically acceptable salt thereof, wherein Q is phenyl.

Claim 29. A compound according to any of claims 1, or 19 to 24, or a pharmaceutically acceptable salt thereof, wherein Q is .

Claim 30. A compound according to any of claims 1, or 19 to 24, or a pharmaceutically acceptable salt thereof, wherein Q is .

Claim 31. A compound according to any of claims 1, or 19 to 24, or a pharmaceutically acceptable salt thereof, wherein Q is furanyl.

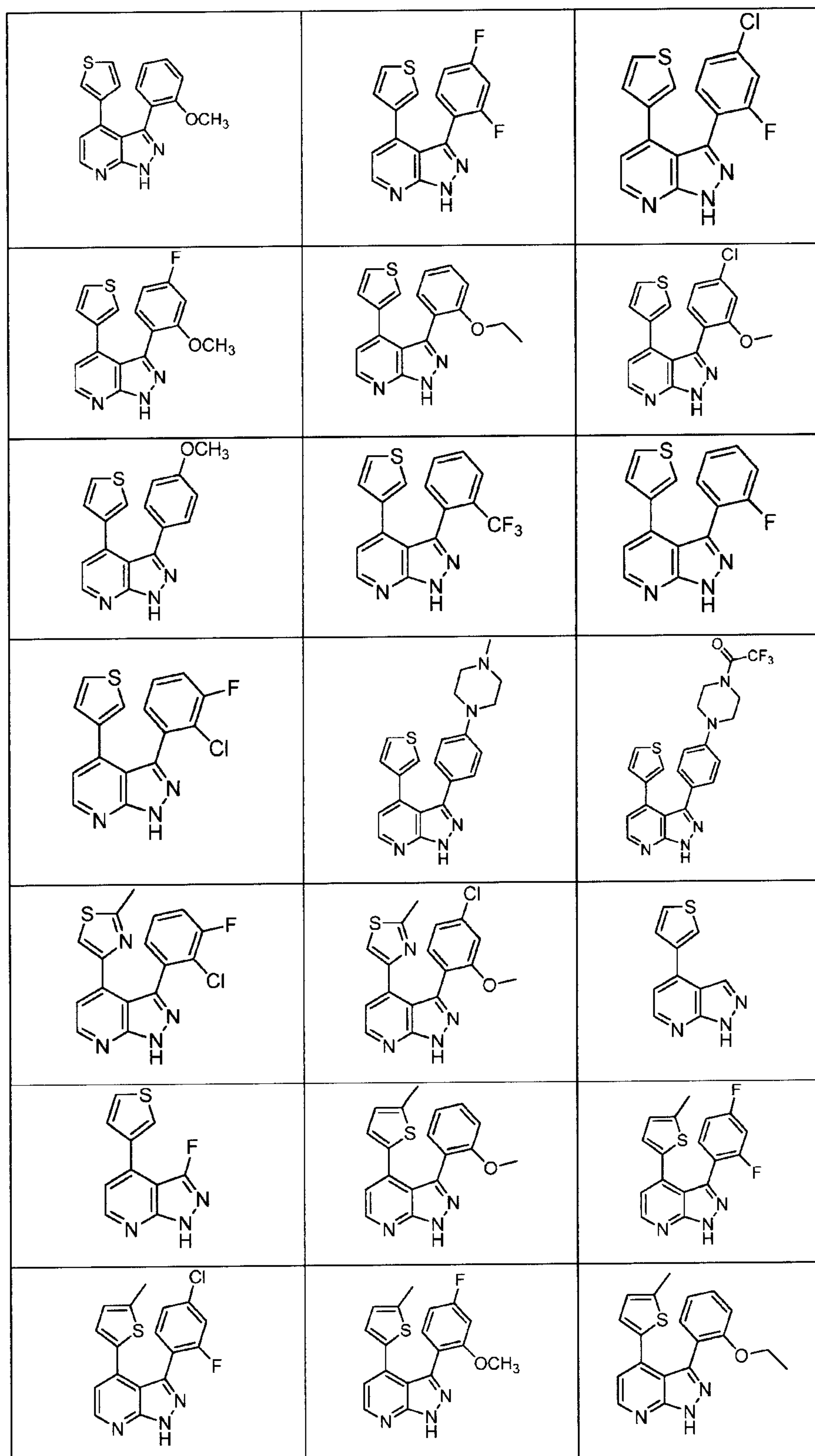
Claim 32. A compound according to any of claims 1, or 19 to 24, or a pharmaceutically acceptable salt thereof, wherein Q is piperazinyl.

Claim 33. A compound according to any of claims 1, or 19 to 24, or a pharmaceutically acceptable salt thereof, wherein Q is pyrazolyl.

Claim 34. A compound according to claims 1 or 19, comprising a compound selected from

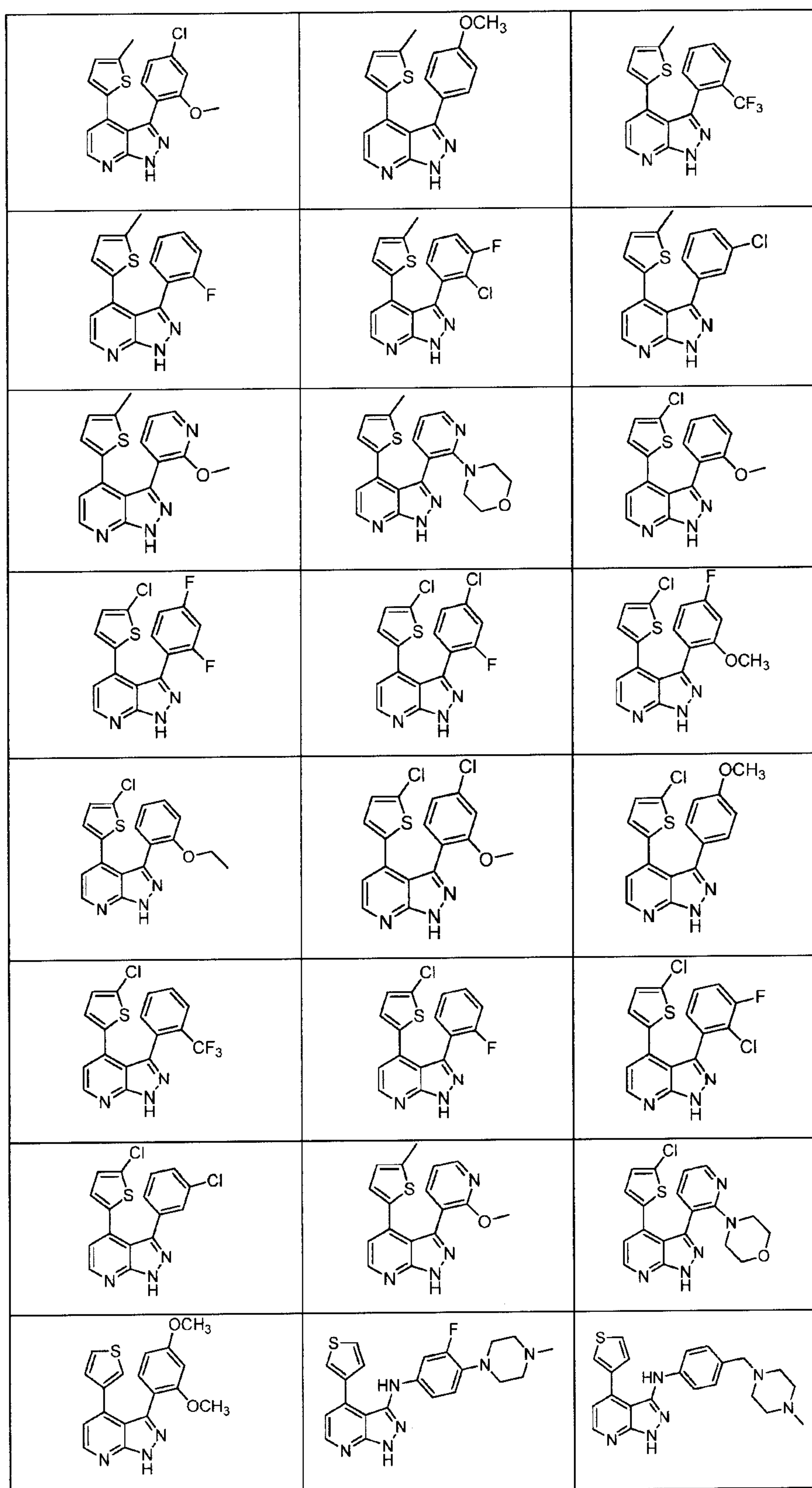
WO 2014/093383

PCT/US2013/074191



WO 2014/093383

PCT/US2013/074191



WO 2014/093383

PCT/US2013/074191

|  |  |  |
|--|--|--|
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

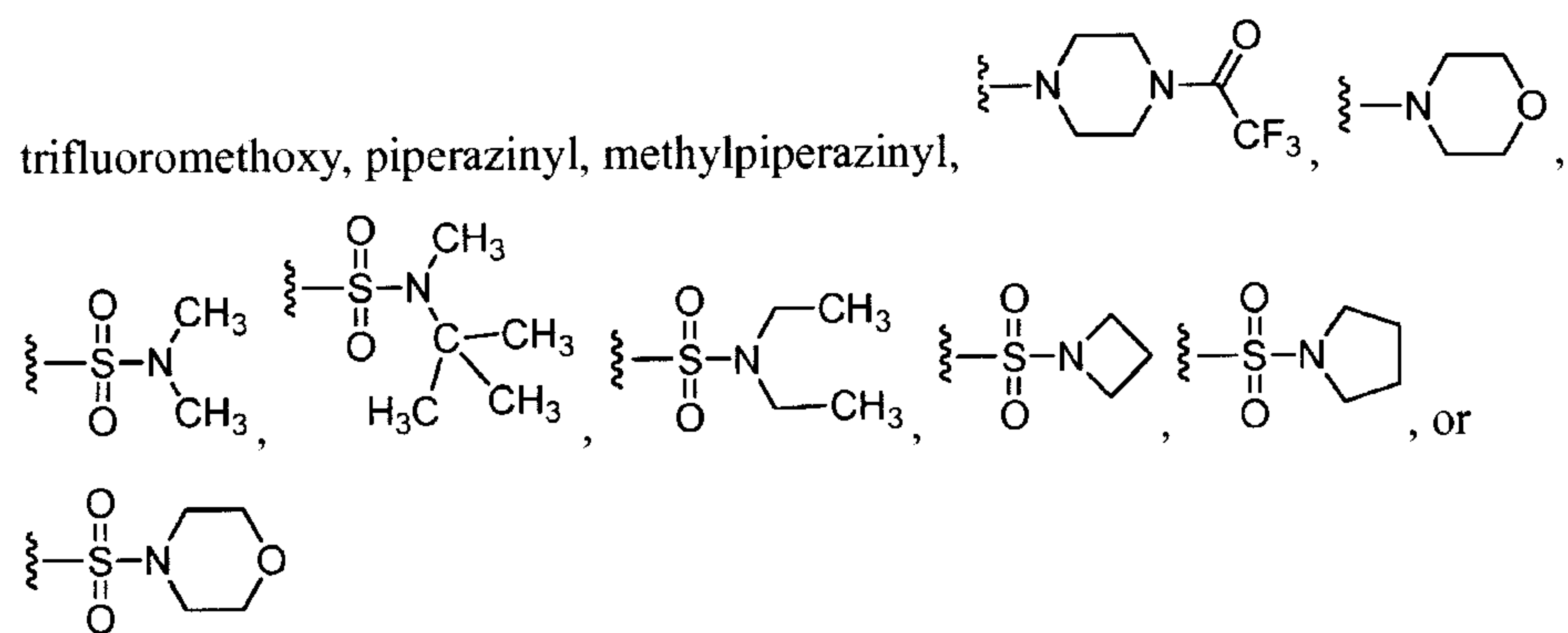
or a pharmaceutically acceptable salt thereof.

WO 2014/093383

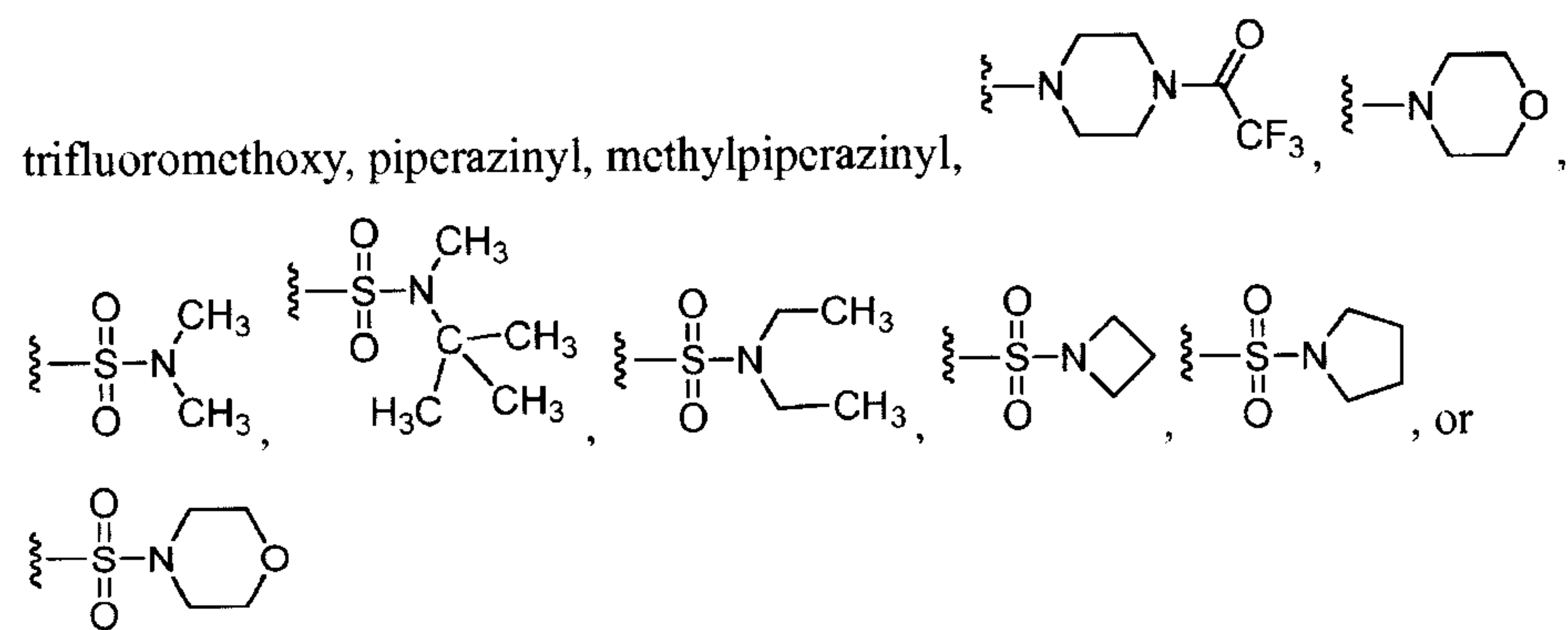
PCT/US2013/074191

Claim 35. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is described by Formula IB, and X is CH.

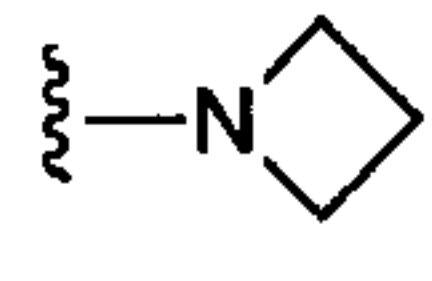
Claim 36. A compound according to claims 1 or 35, or a pharmaceutically acceptable salt thereof, wherein L<sup>1</sup> is phenyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl,

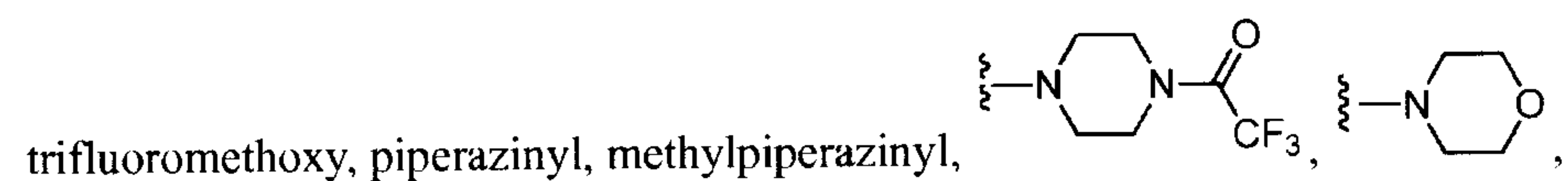


Claim 37. A compound according to claims 1 or 35, or a pharmaceutically acceptable salt thereof, wherein L<sup>1</sup> is pyridyl optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl,



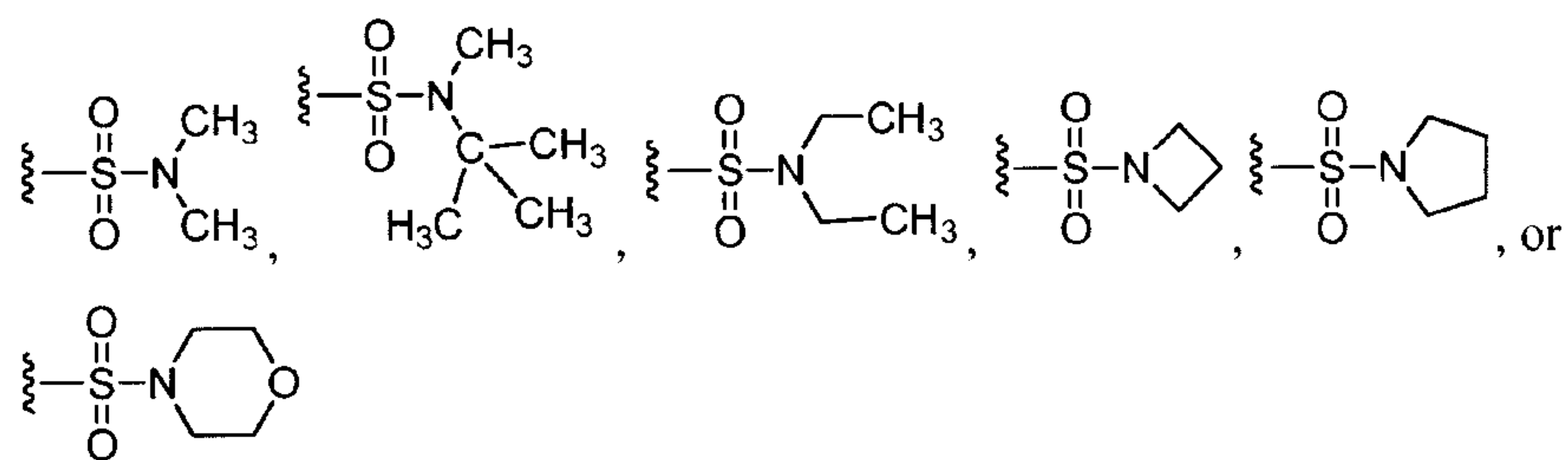
Claim 38. A compound according to claims 1 or 35, or a pharmaceutically acceptable salt

thereof, wherein L<sup>1</sup> is  optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl,



WO 2014/093383

PCT/US2013/074191

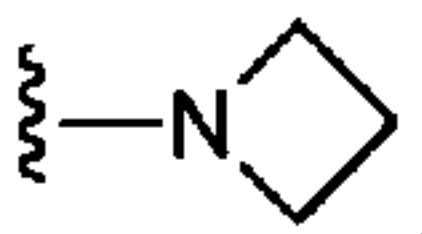


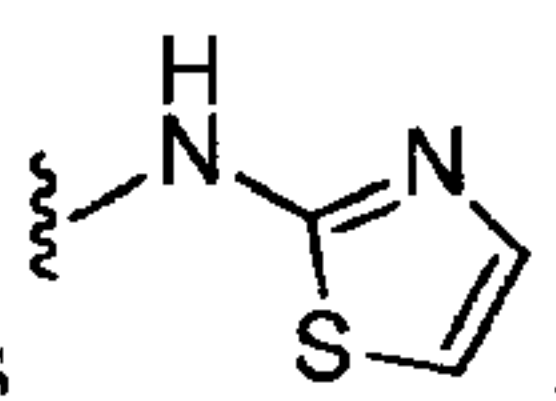
Claim 39. A compound according to any of claims 1, or 35 to 38, or a pharmaceutically acceptable salt thereof, wherein Z is a direct bond.

Claim 40. A compound according to any of claims 1, or 35 to 38, or a pharmaceutically acceptable salt thereof, wherein Z is thienyl.

Claim 41. A compound according to any of claims 1, or 35 to 38, or a pharmaceutically acceptable salt thereof, wherein Z is thiazolyl.

Claim 42. A compound according to any of claims 1, or 35 to 38, or a pharmaceutically acceptable salt thereof, wherein Z is phenyl.

Claim 43. A compound according to any of claims 1, or 35 to 38, or a pharmaceutically acceptable salt thereof, wherein Z is .

Claim 44. A compound according to any of claims 1, or 35 to 38, or a pharmaceutically acceptable salt thereof, wherein Z is .

Claim 45. A compound according to any of claims 1, or 35 to 38, or a pharmaceutically acceptable salt thereof, wherein Z is furanyl.

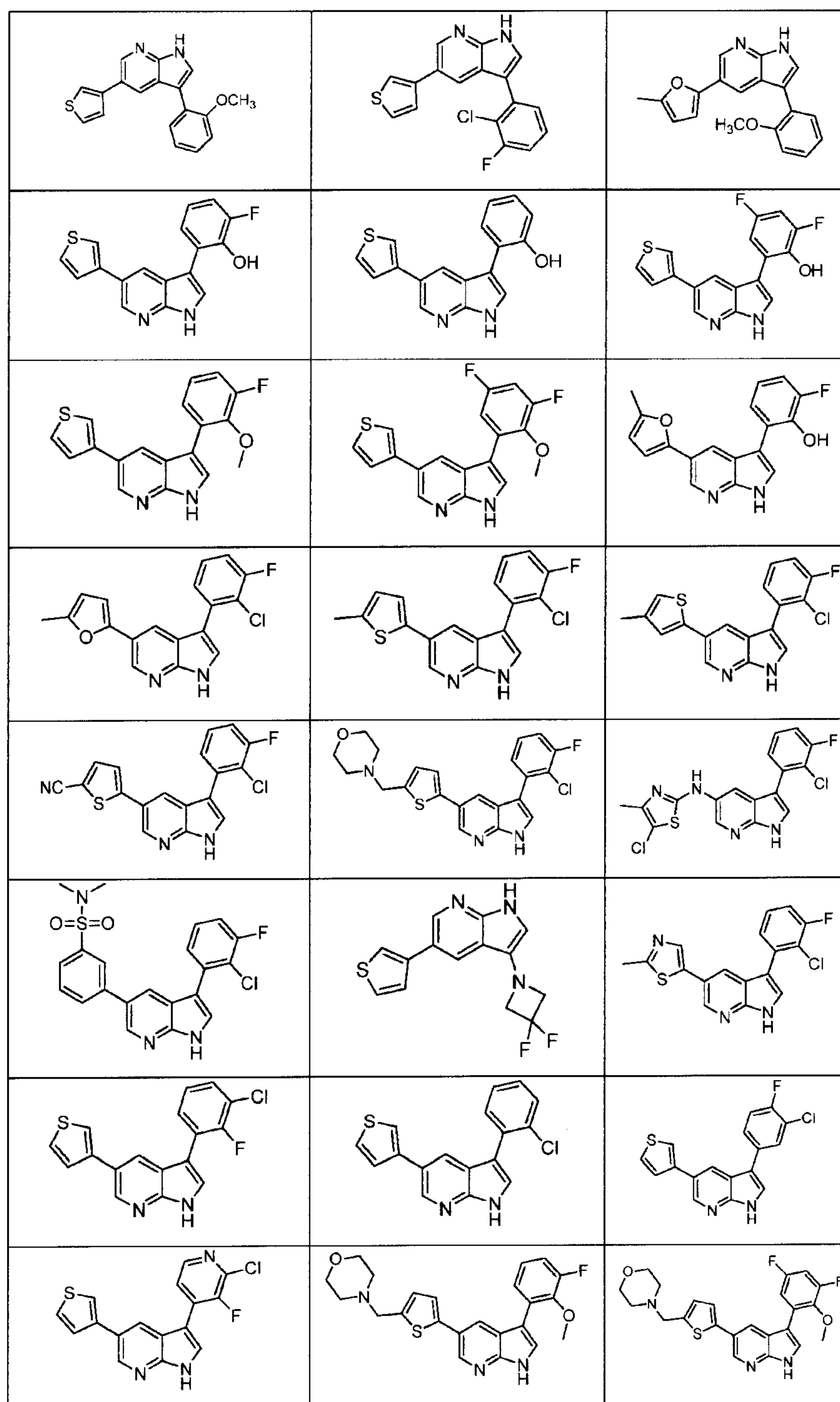
Claim 46. A compound according to any of claims 1, or 35 to 38, or a pharmaceutically acceptable salt thereof, wherein Z is piperazinyl.

Claim 47. A compound according to any of claims 1, or 35 to 38, or a pharmaceutically acceptable salt thereof, wherein Z is pyrazolyl

WO 2014/093383

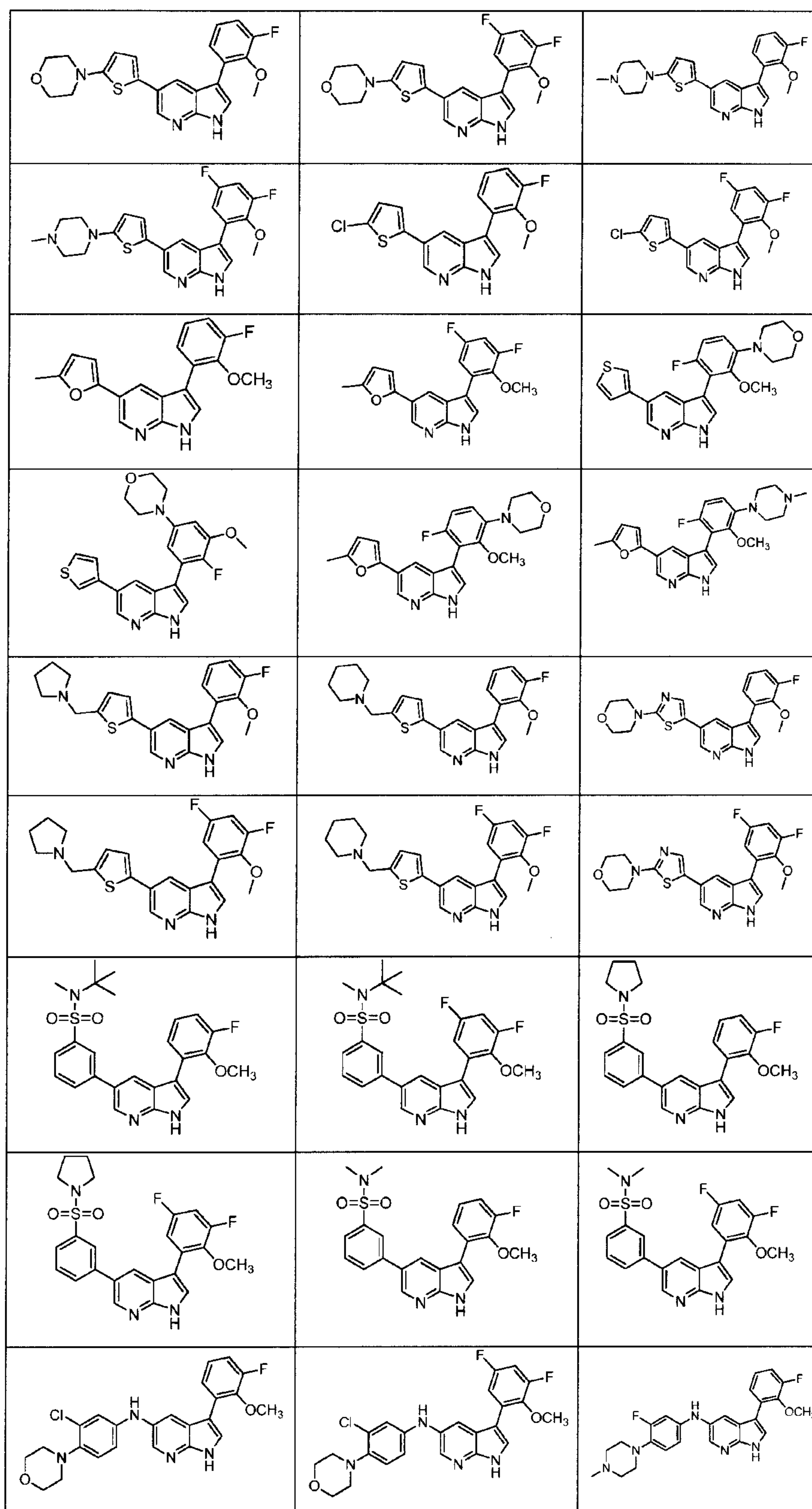
PCT/US2013/074191

Claim 48. A compound according to claims 1 or 35 comprising a compound selected from



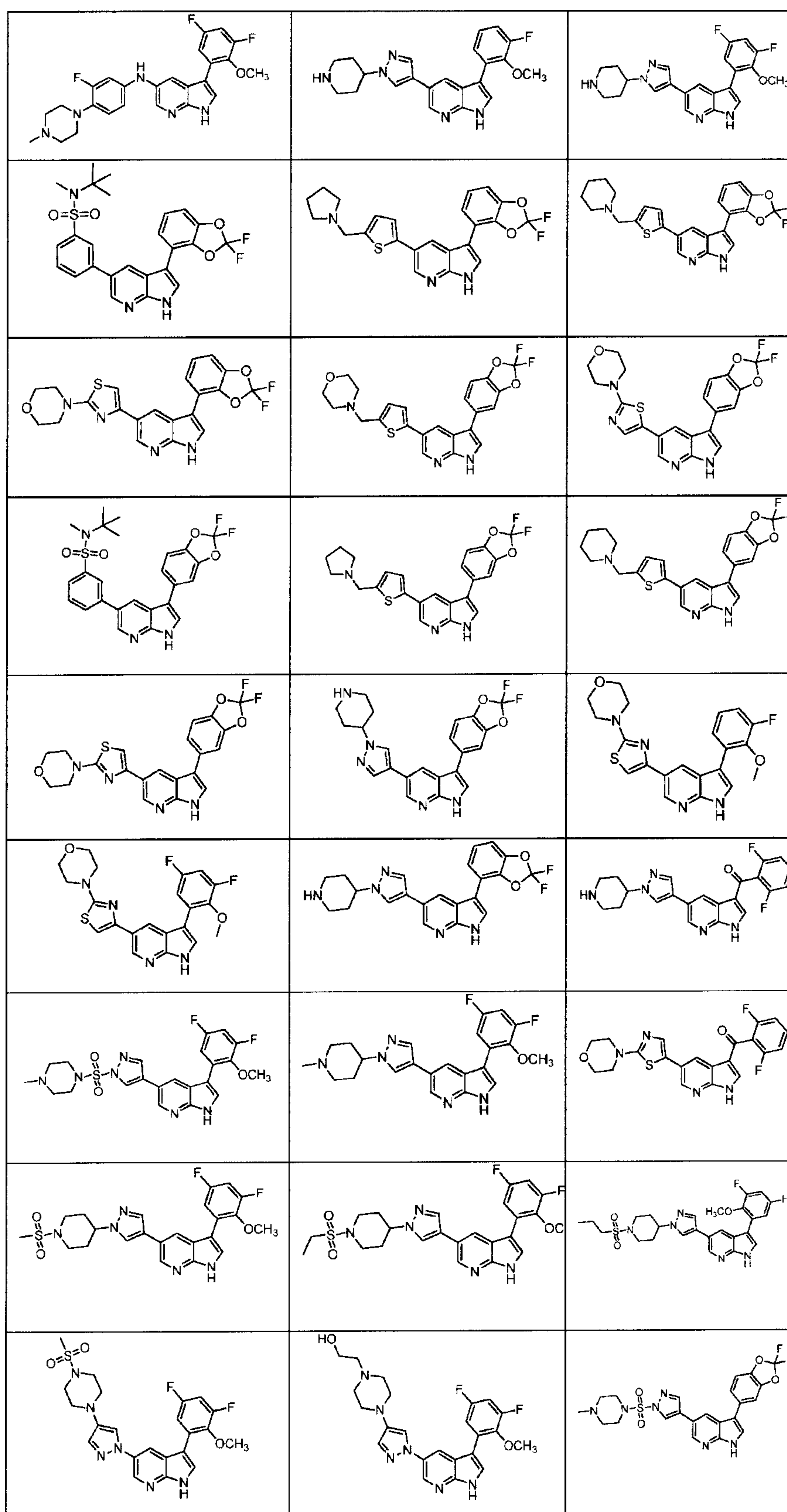
WO 2014/093383

PCT/US2013/074191



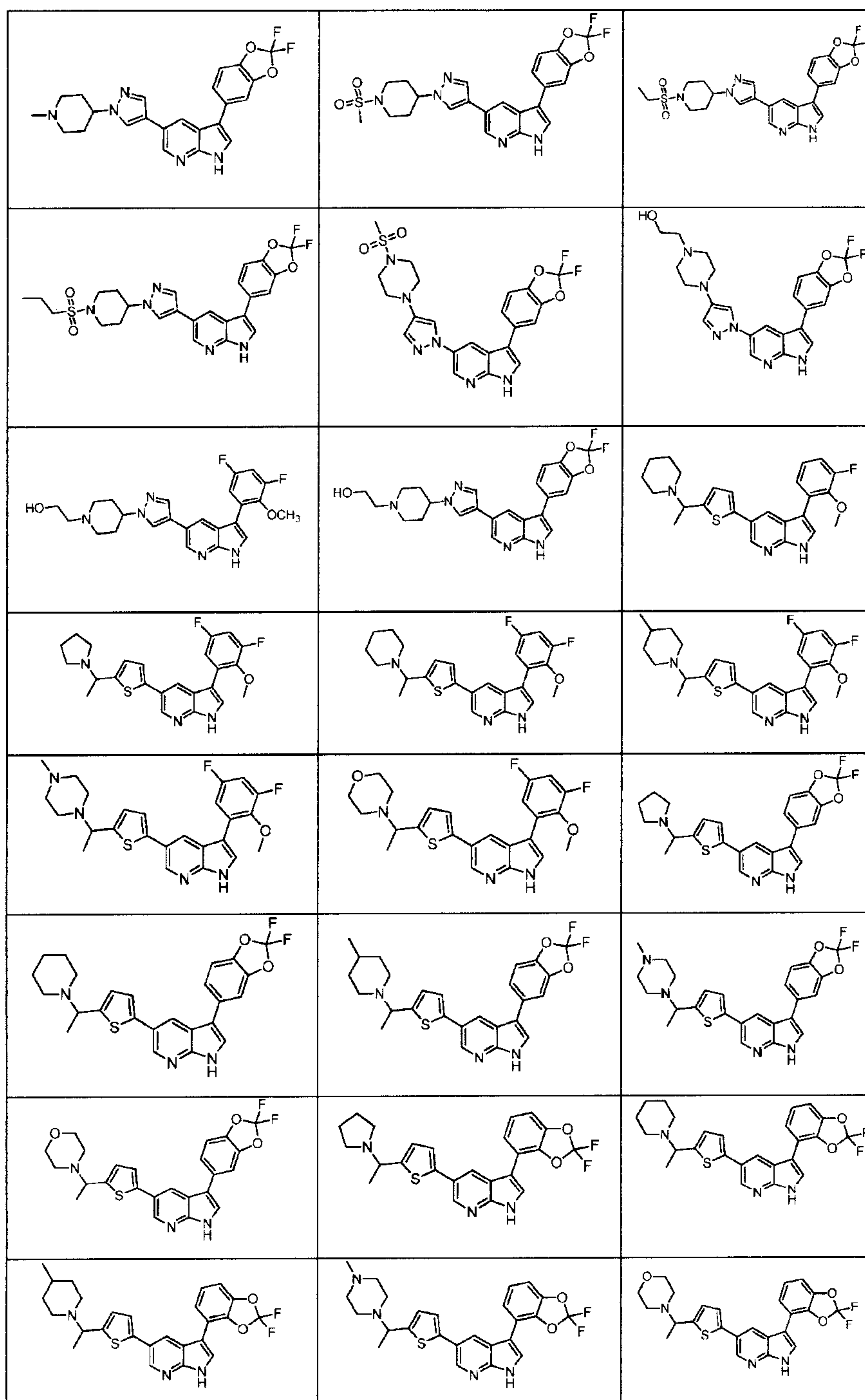
WO 2014/093383

PCT/US2013/074191



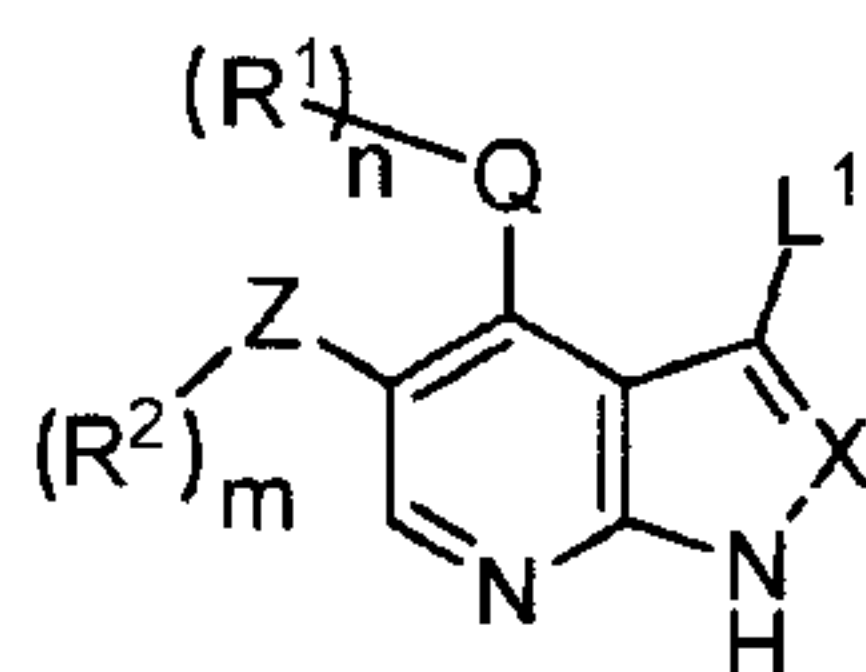
WO 2014/093383

PCT/US2013/074191

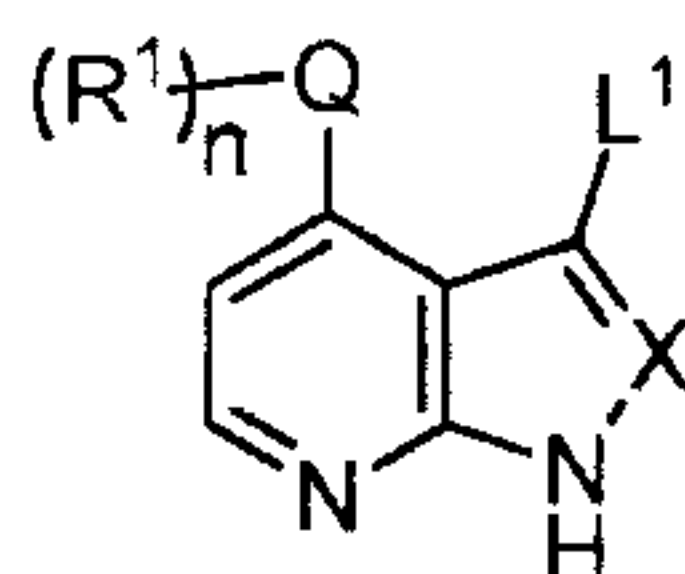


or a pharmaceutically acceptable salt thereof;

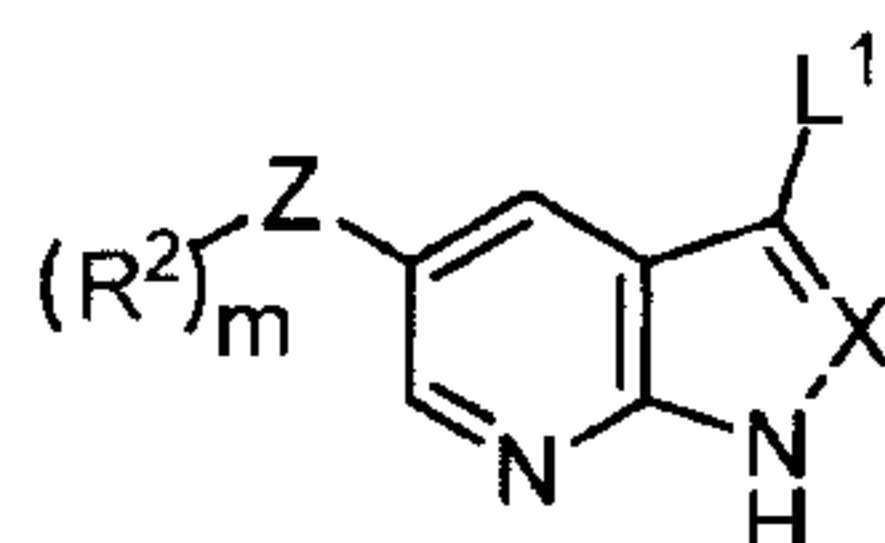
Claim 49. A method of treating cancer or hyperproliferative disorders, stroke, obesity, or type II diabetes by administering an effective amount of a compound according to Formulas I, IA or IB:



(I)



(IA)

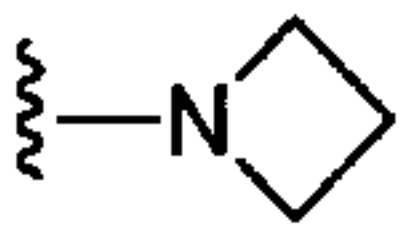
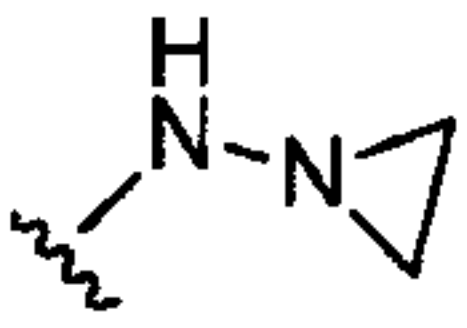


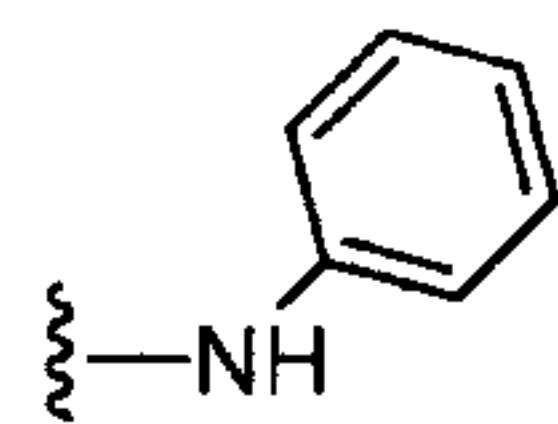
(IB)

or a pharmaceutically acceptable salt thereof, wherein:

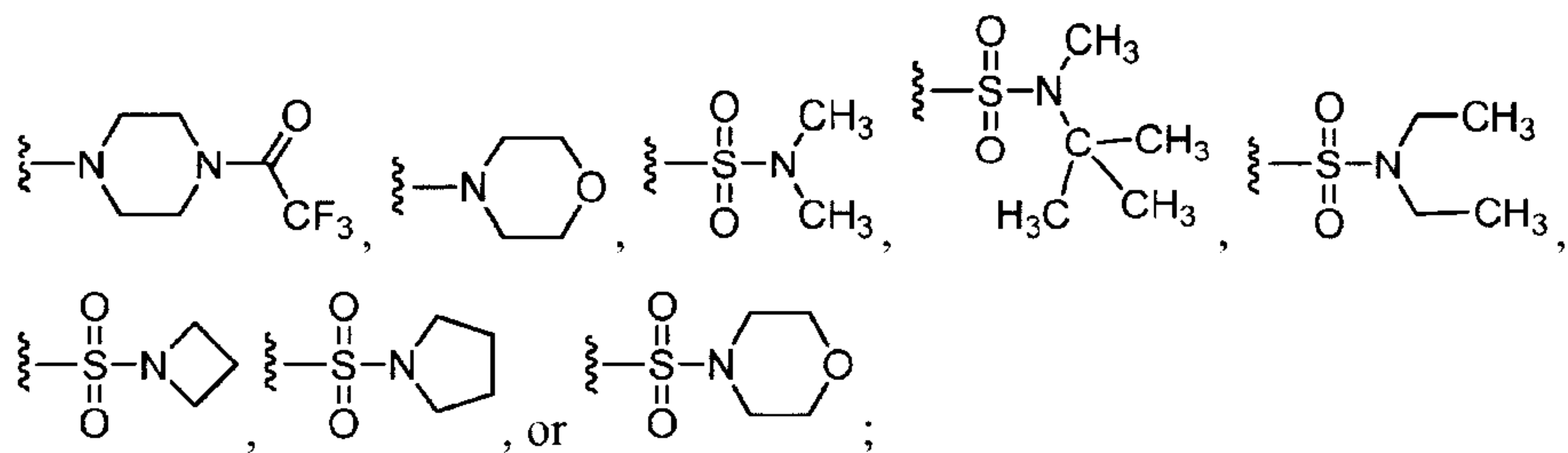
X is N or CH;

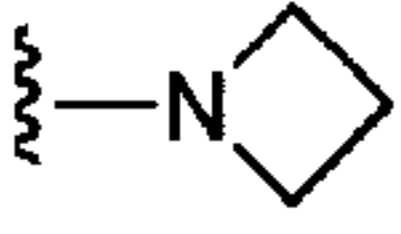
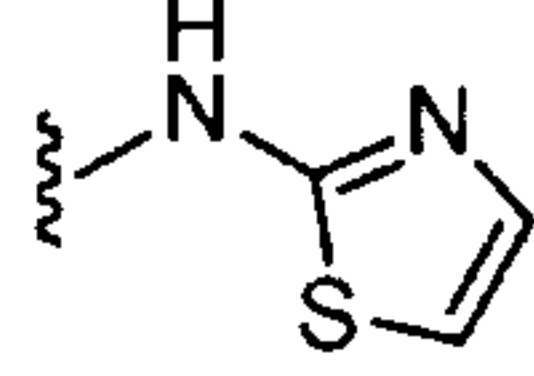
L<sup>1</sup> is H, F; or

L<sup>1</sup> is thienyl, phenyl, pyrrolyl, pyridyl, , piperazinyl, , or



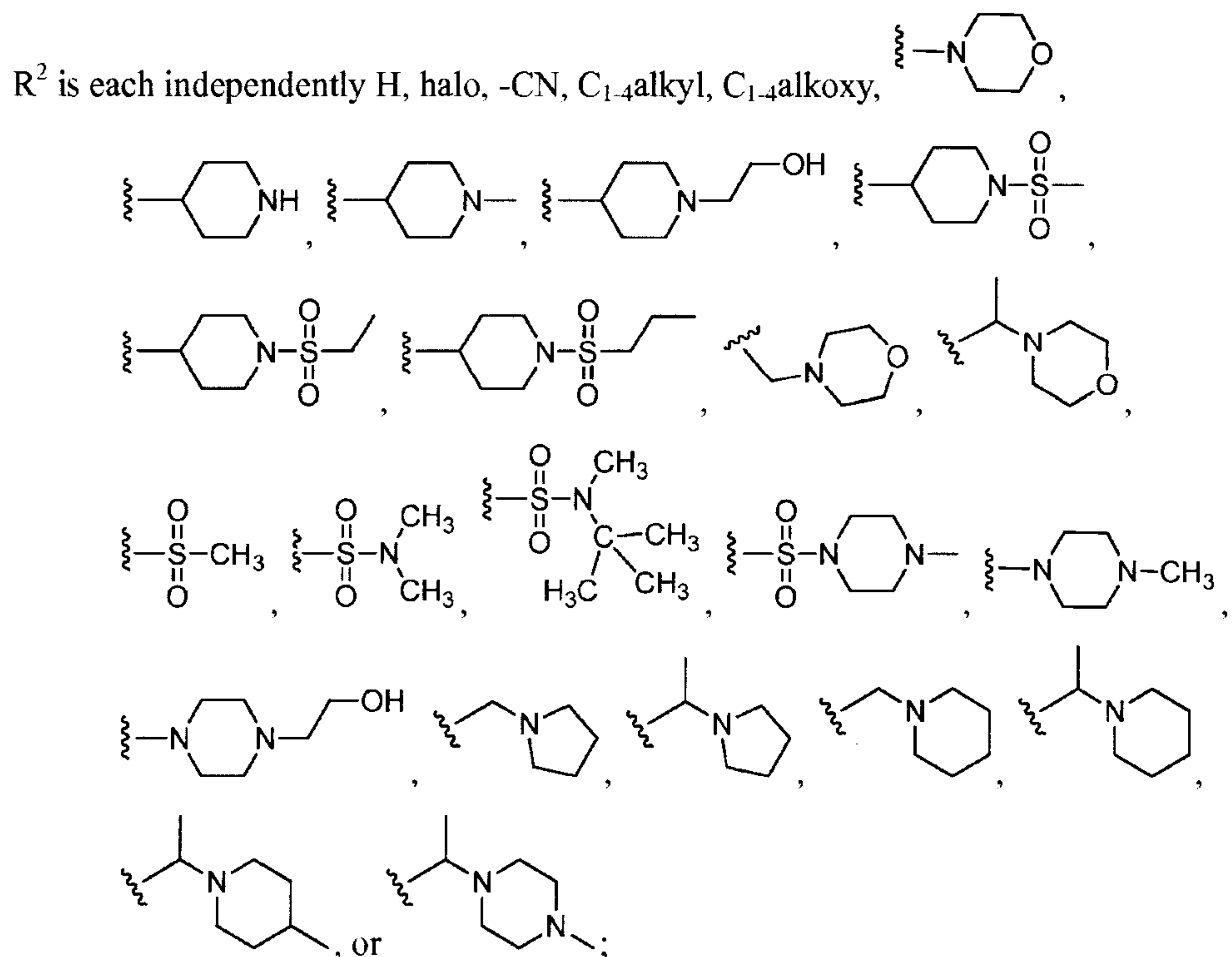
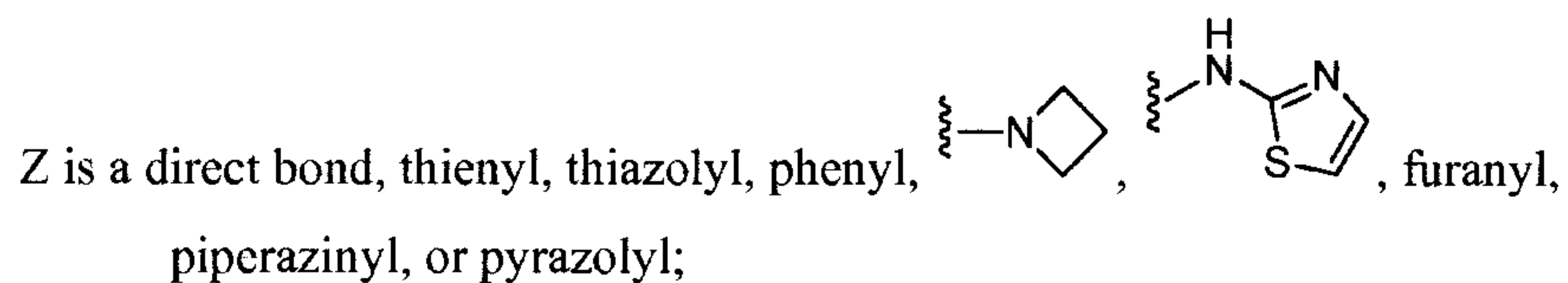
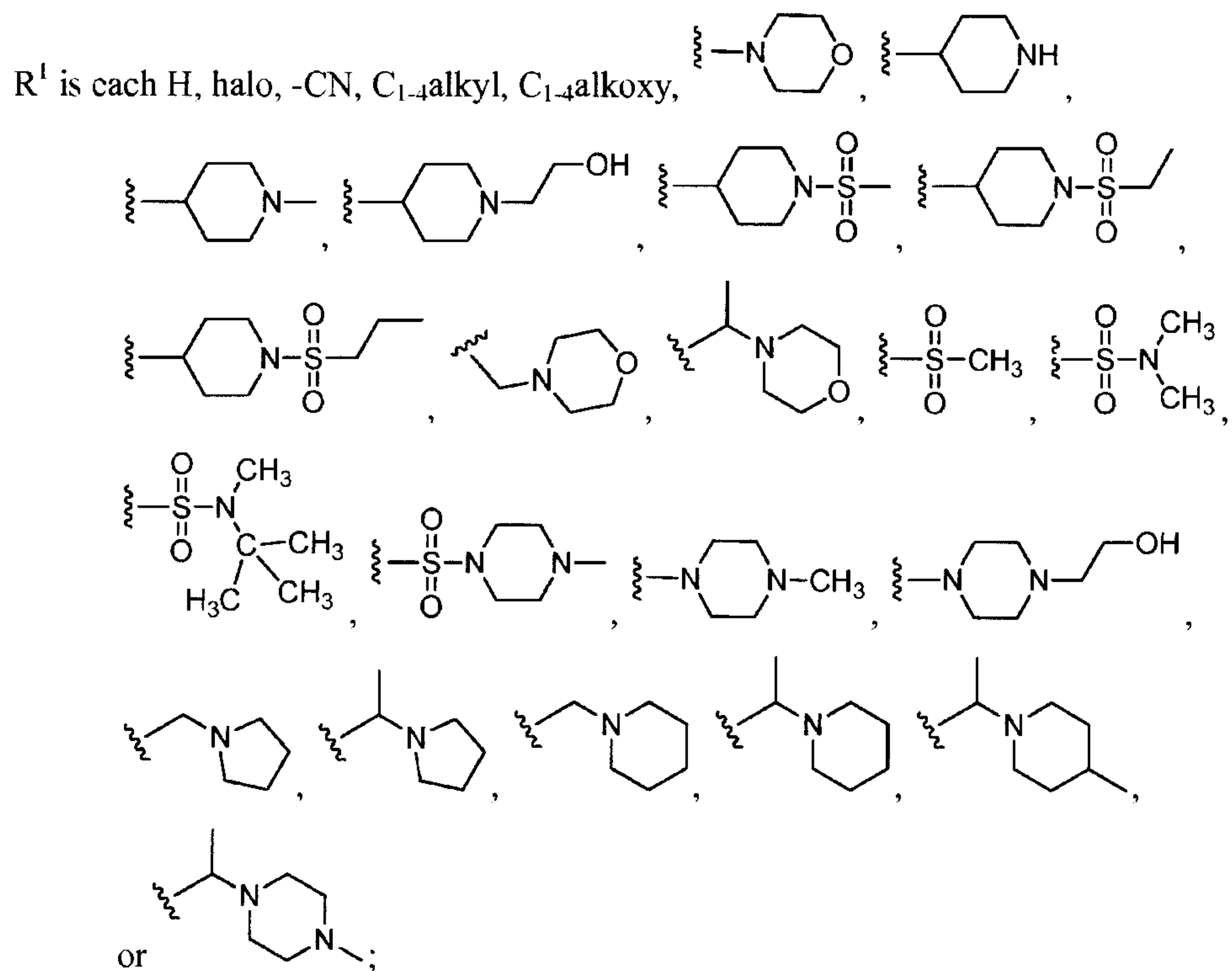
, any of which is optionally substituted with 1-3 substituents, each substituent independently selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, trifluoromethyl, trifluoromethoxy, piperazinyl, methylpiperazinyl,



Q is a direct bond, thienyl, thiazolyl, phenyl, , , furanyl, piperazinyl, or pyrazolyl;

WO 2014/093383

PCT/US2013/074191



WO 2014/093383

PCT/US2013/074191

n is 0, 1, or 2; and

m is 0, 1, or 2;

provided that at least one of  $L^1$ ,  $R^1$ , and  $R^2$  is not H

Claim 50. The method of claim 49, wherein the cancer is of colon, breast, stomach, prostate, pancreas, or ovarian tissue.

Claim 51. The method of claim 50, wherein the cancer or hyperproliferative disorder is lung cancer, NSCLC (non small cell lung cancer), oat-cell cancer, bone cancer, pancreatic cancer, skin cancer, dermatofibrosarcoma protuberans, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colo-rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, hepatocellular cancer, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, pancreas, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer (particularly hormone-refractory), chronic or acute leukemia, solid tumors of childhood, hypereosinophilia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, pediatric malignancy, neoplasms of the central nervous system, primary CNS lymphoma, spinal axis tumors, medulloblastoma, brain stem gliomas, pituitary adenomas, Barrett's esophagus, pre-malignant syndrome, neoplastic cutaneous disease, psoriasis, mycoses fungoides, benign prostatic hypertrophy, diabetic retinopathy, retinal ischemia, and retinal neovascularization, hepatic cirrhosis, angiogenesis, cardiovascular disease, atherosclerosis, immunological disease, autoimmune disease, or renal.

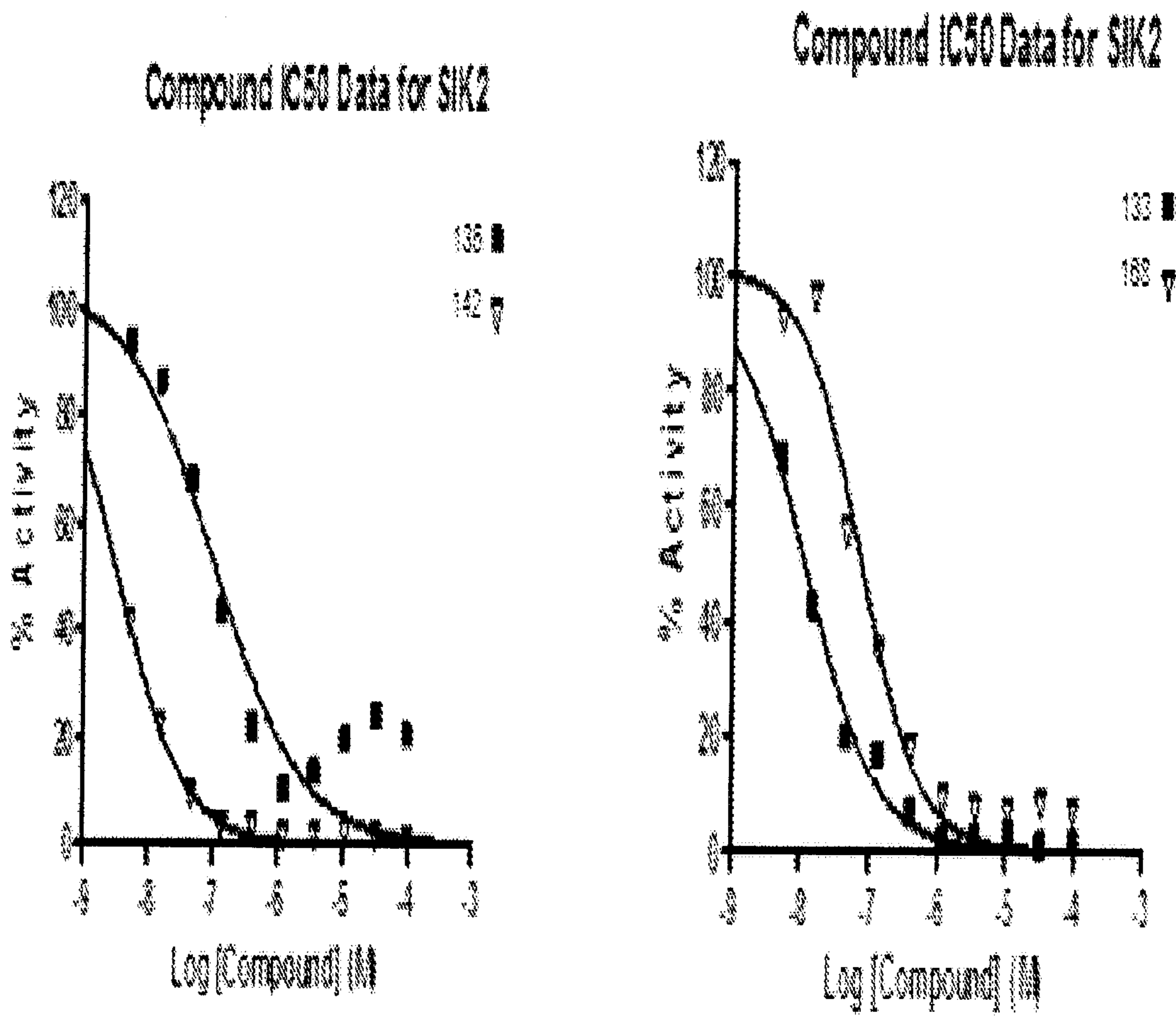


Fig. 1

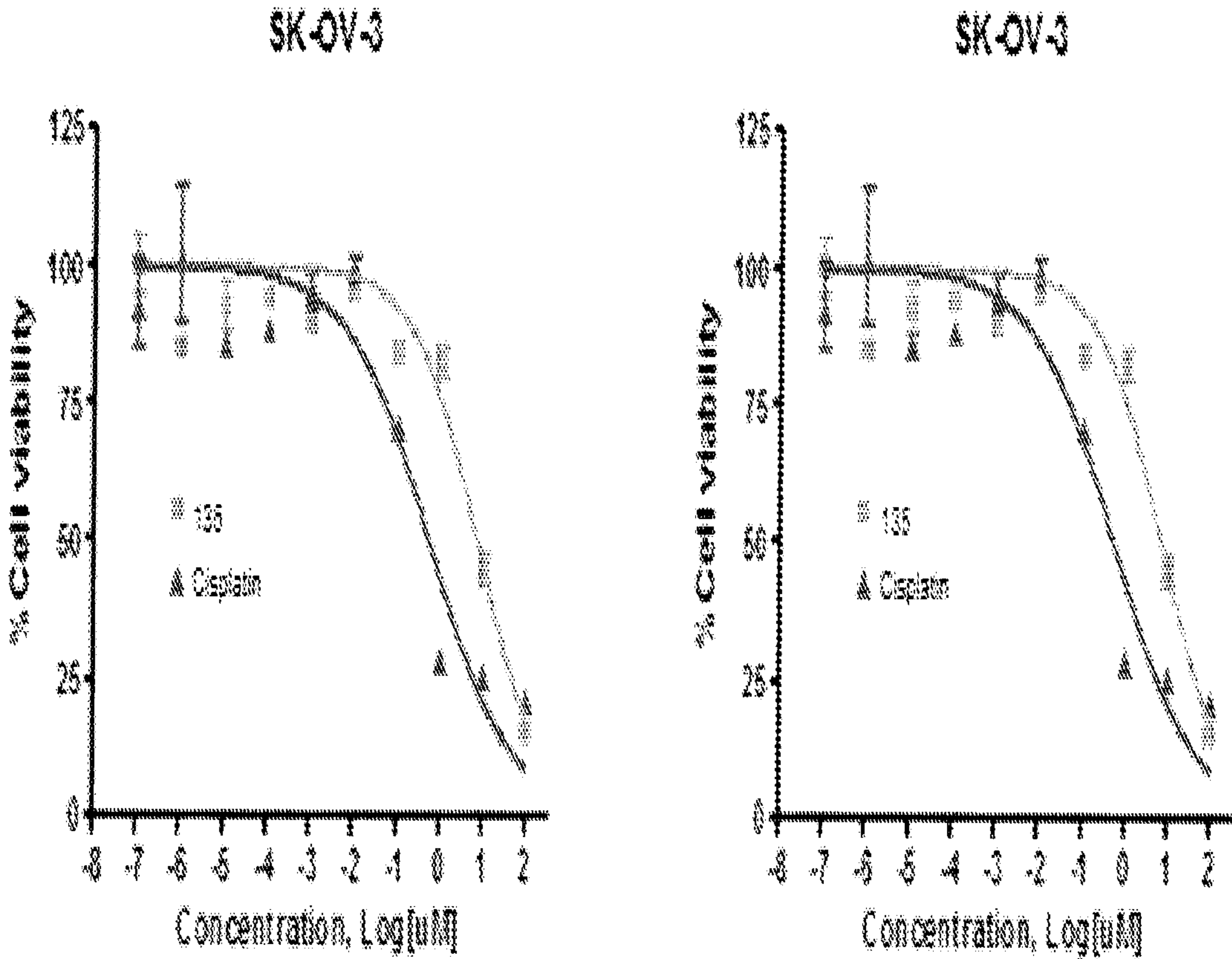


Fig. 2

3/10

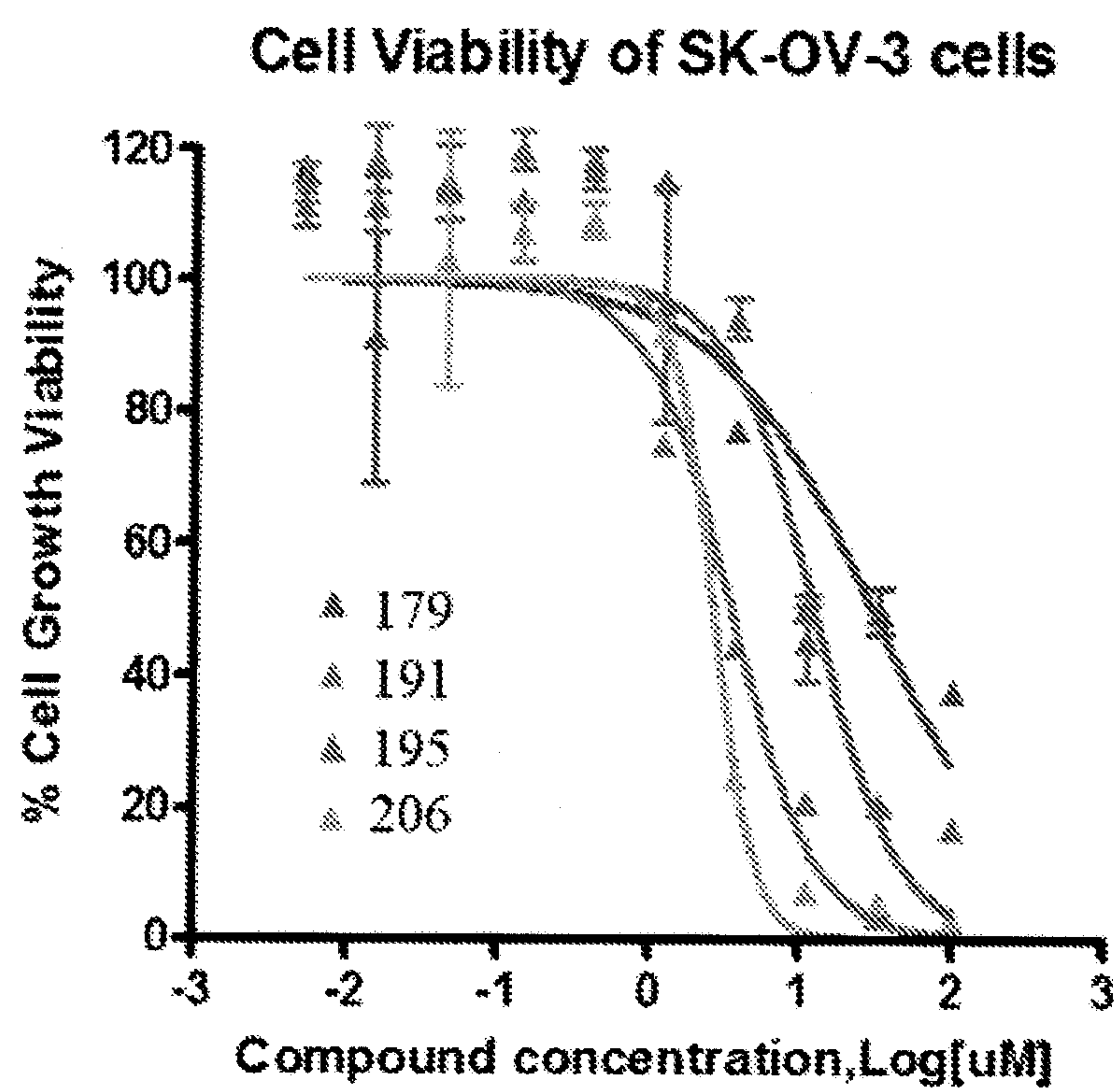


Fig. 2b1

4/10

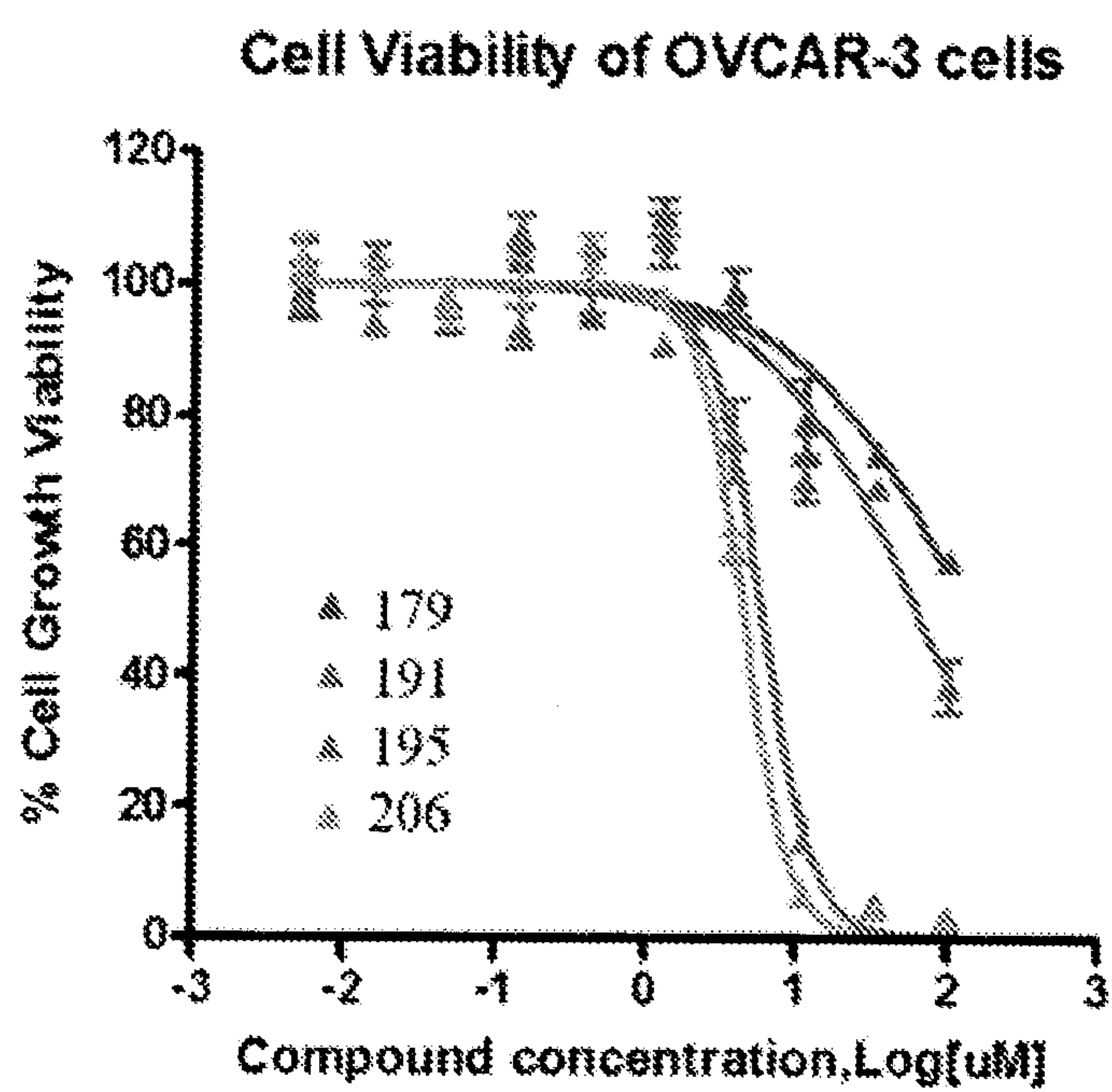


Fig. 2b2

5/10

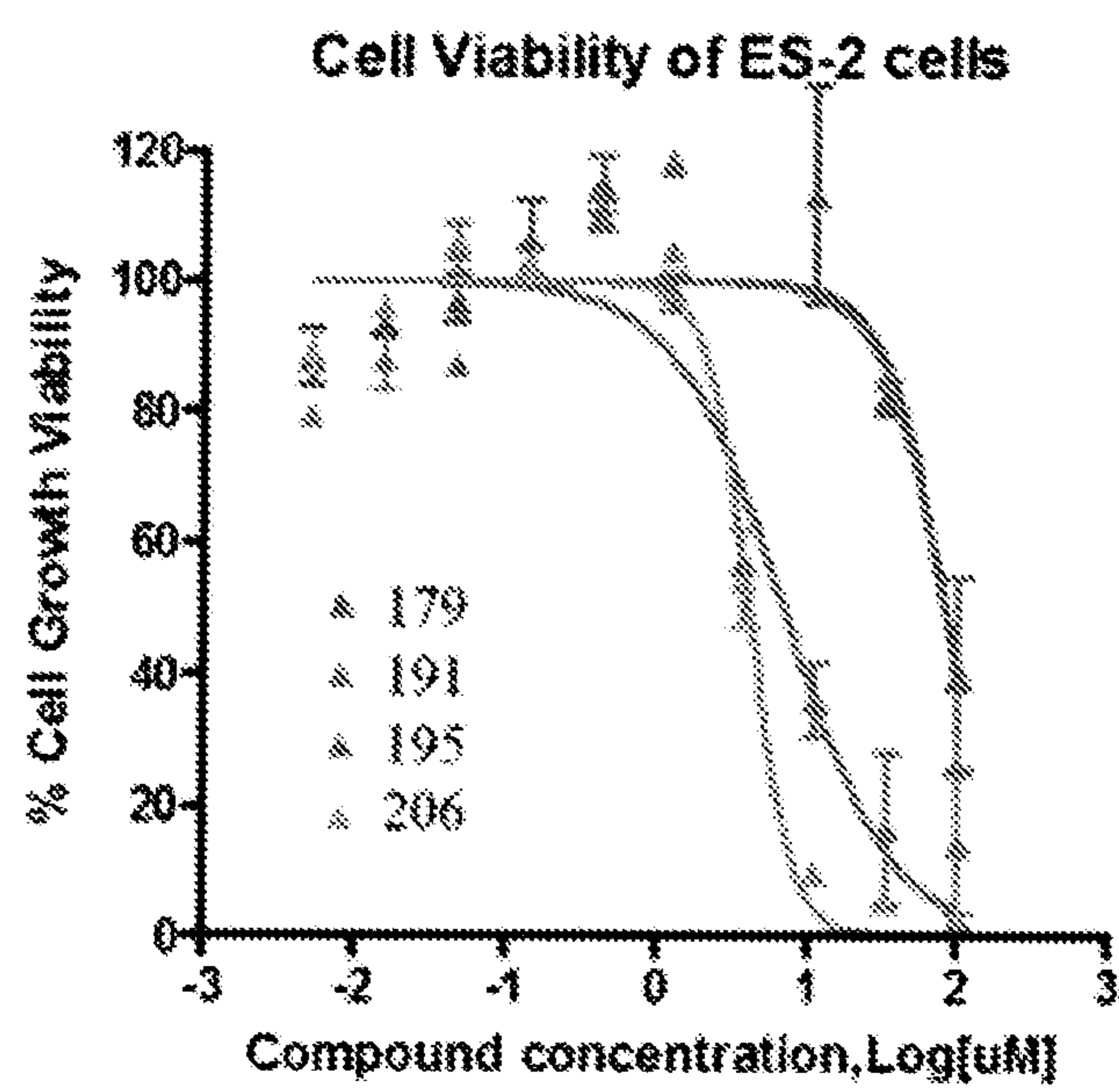


Fig. 2b3

|       |     |                                                              |     |
|-------|-----|--------------------------------------------------------------|-----|
| SIK1  | 1   | MVIMSEFSADPAGQGGQKPLRVGFYDIERTLKGKGNFAVVKLARHRVTKTQVAIKIIDK  | 60  |
| SIK2  | 1   | -----QRGPFVRVGFYDIEGTLKGKGNFAVVKLRHRITKTEVAIKIIDK            | 53  |
| SIK3  | 1   | -----MPARIGYYEIDRTIGKGNFAVVKRATHLVTKAKVAIKIIDK               | 41  |
| AMPK  | 7   | -----HDGRVKIGHYVLGDTLGVGTFFGKVKIGEHOITGCHKVAVKIILNR          | 49  |
| MARK2 |     | -----GNSATSADQPHIGNYRLLLKTIGKGNFAVVKLAPHILITGKEVAVKIILK      |     |
|       |     | : * * : * : * . * . * . * : * : * : * : * :                  |     |
| SIK1  | 61  | TRLB-SSNLEKIYREVQIMKLLNHPHIKLYQVMETKMDLYIVLQVQVDFDYLTSG      | 119 |
| SIK2  | 54  | SQLD-AVNLEKIYREVQIMKMLDHPHIKLYQVMETKSMLYLVVQVQVDFDYLANHG     | 112 |
| SIK3  | 42  | TQLD-EENLEKIYREVQIMKMLCHPHIIRLYQVMETERMIYLVVQVQVDFDHLVANG    | 100 |
| AMPK  | 50  | QKIRSLDVVGKIKREIQNLKLFRRHPHIKLYQVISTPTDFFMVQVQVDFDYICKHG     | 109 |
| MARK2 |     | TQLN-SSSLQKLFRVIRIMKVLNHPNIVKLFVETETKTLVQVQVDFDYLVANG        |     |
|       |     | : : : * : * : * : : * : * : * : * : * : * : * : * : * : *    |     |
| SIK1  | 120 | HLSENEARKKFWQILSAVEYCHDHHIVHRDLKTENLLLDGNMMDIKLAFHFGNFKSGEP  | 179 |
| SIK2  | 113 | PLNESEAPRKFWQILSAVDYCHGRKIVHRDLKAENLLLDNNMNIKIAHFGNFKSGEL    | 172 |
| SIK3  | 101 | RMAEKEARRKFKQIVTAVYFCHGRNIVHRDLKAENLLLDANLNKIAHFGSNLFTPGQL   | 169 |
| AMPK  | 110 | RVEEMEARRLFQQILSAVDYCHRRMIVHRDLKPENVLLDAHMNAKIAHFGSNMMSDGEF  | 169 |
| MARK2 |     | BMKEKEARAKFRQIVSAVQYCHQKPIVHRDLKAENLLLDAMNIAHFGSNEFTFGNK     |     |
|       |     | : : * * * * * * * : * : * : * : * : * : * : * : * : * : *    |     |
| SIK1  | 180 | LSTWCGSPFYAAPVFEFGKEYEGPQLDIWSLGVVLYVLVCGSLPFDGPNLPTLRQRVLEG | 239 |
| SIK2  | 173 | LATWCGSPFYAAPVFEFGQYEGPQLDIWSMGVVLYVLVCGALPFDGPTLPILRQRVLEG  | 232 |
| SIK3  | 161 | LKTWCGSPFYAAPVFEFGKEYDGPQVBIWSLGVVLYVLVCGALPFDGSTLQNLRARVLSG | 220 |
| AMPK  | 170 | LRDSCGSPNYAAPVETISGRLYAGPEVDIWSGCVILYALLCGTLPEDEHVPTLEKKIRGG | 229 |
| MARK2 |     | LDTECGSPFYAAPVLFQGGKYDGPVDVWSLGVILYTLVSGSLPFDGQNLKELRERVLRG  |     |
|       |     | * * * * * * * : * : * : * : * : * : * : * : * : * : *        |     |
| SIK1  | 240 | RFRIPFEMSQDCESLIRRMVLVDPPARRITIAQIRQHRWMAEPOLPGPACPAFSAHSYTS | 299 |
| SIK2  | 233 | RFRIPYFMSEDCEHLIRRMVLVDPSKRLTIAQIKHKKWMLIEVPVQRPVLYFQ        | 292 |
| SIK3  | 221 | KFRIPFEMSTECESLIRRMVLVDPNKRLSMEQICKHKKWMLGDAPNEDRLIADCCQLKE  | 280 |
| AMPK  | 230 | VFYIPEYLNRSVATLLMHMLQVDPKLRATIKDIREHEWFHQDLPSYLPPE-----      | 279 |
| MARK2 |     | KYRIPFYMSTDCENLLKKFLILNPSKRGTLQIMKRWNVGHEDDELKPYVAPLEPYKD    |     |
|       |     | : * * : : * : * : * : * : * : * : * : * : * : *              |     |

Fig. 3

7/10

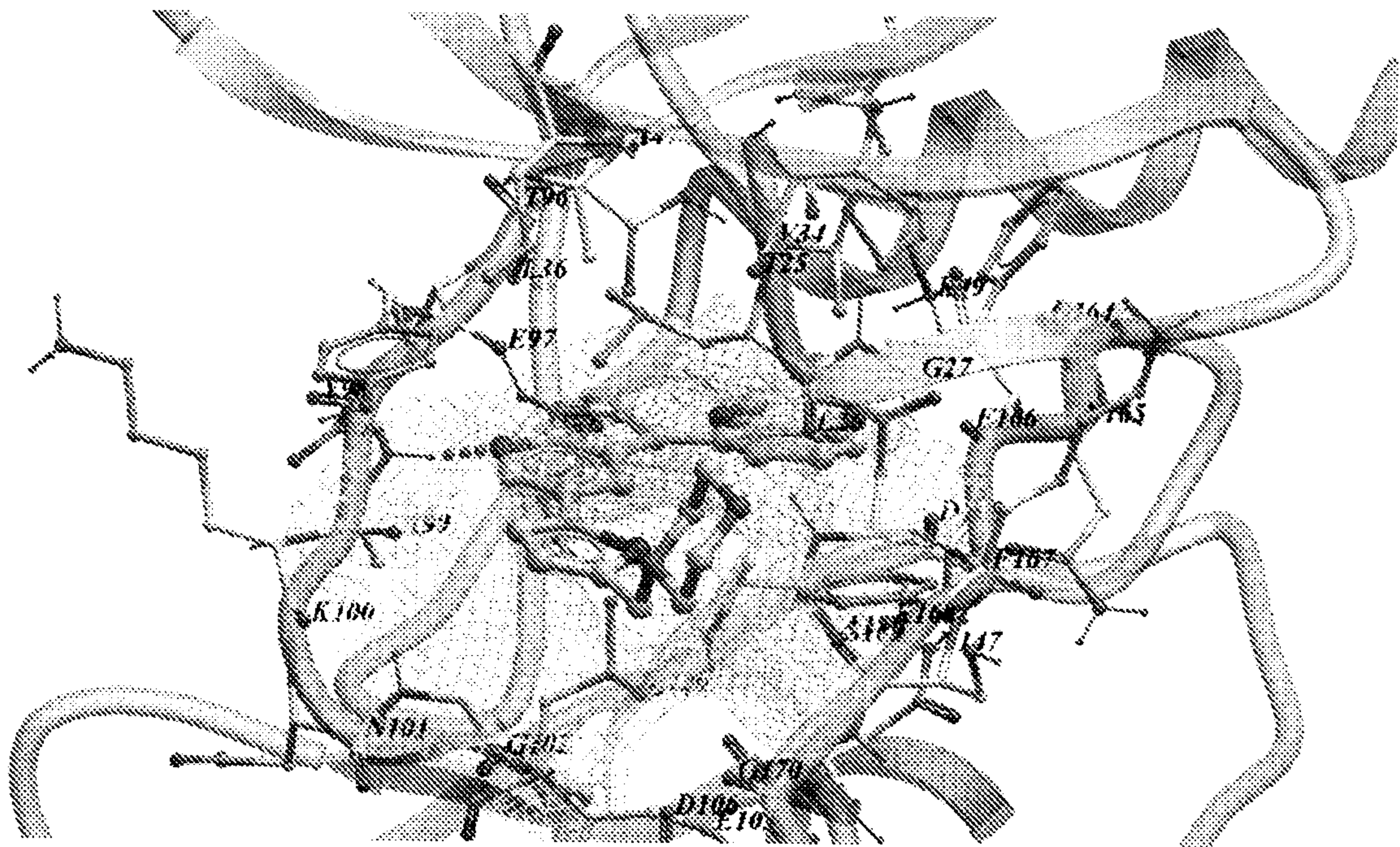


Fig. 4

8/10

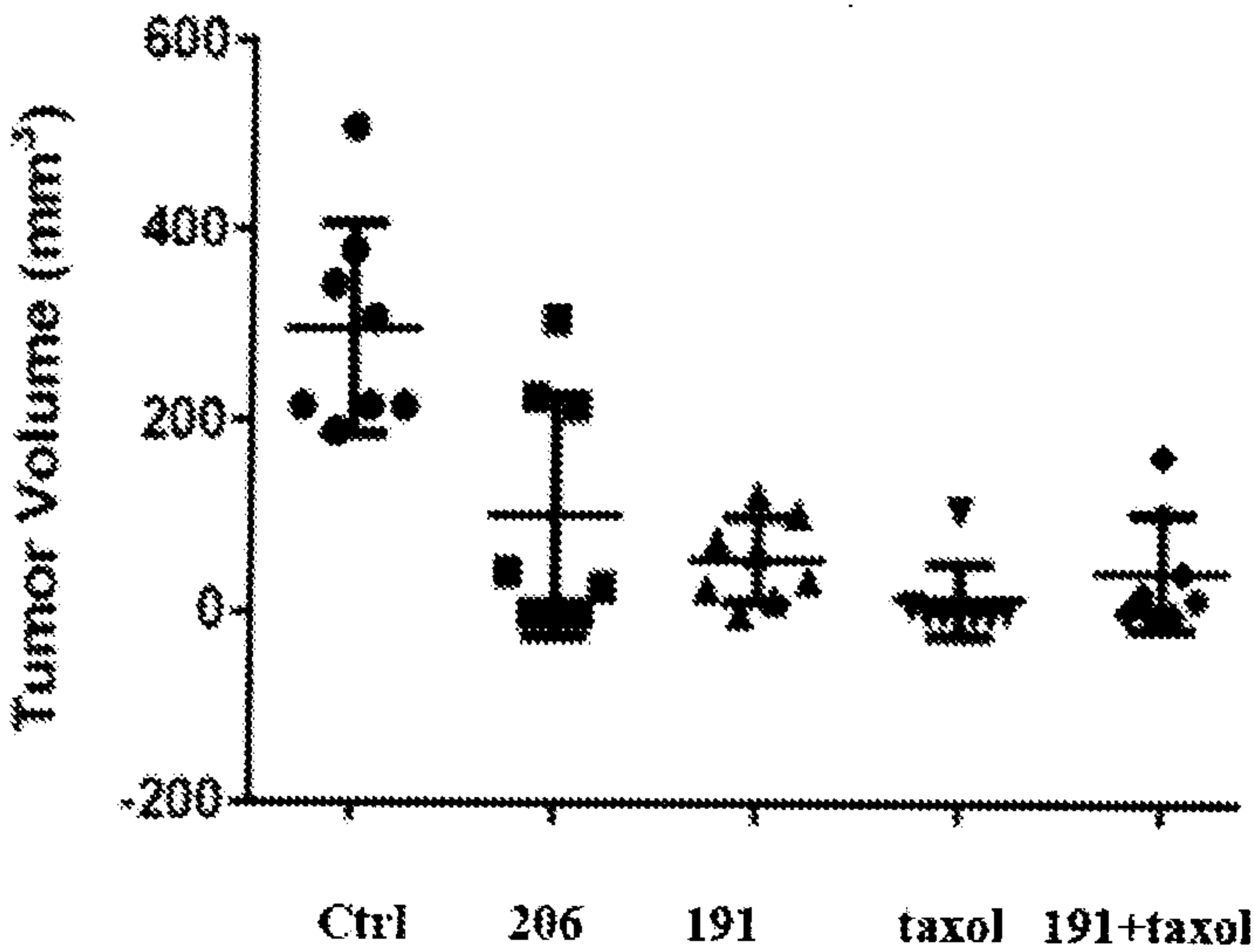


Fig. 5a

9/10

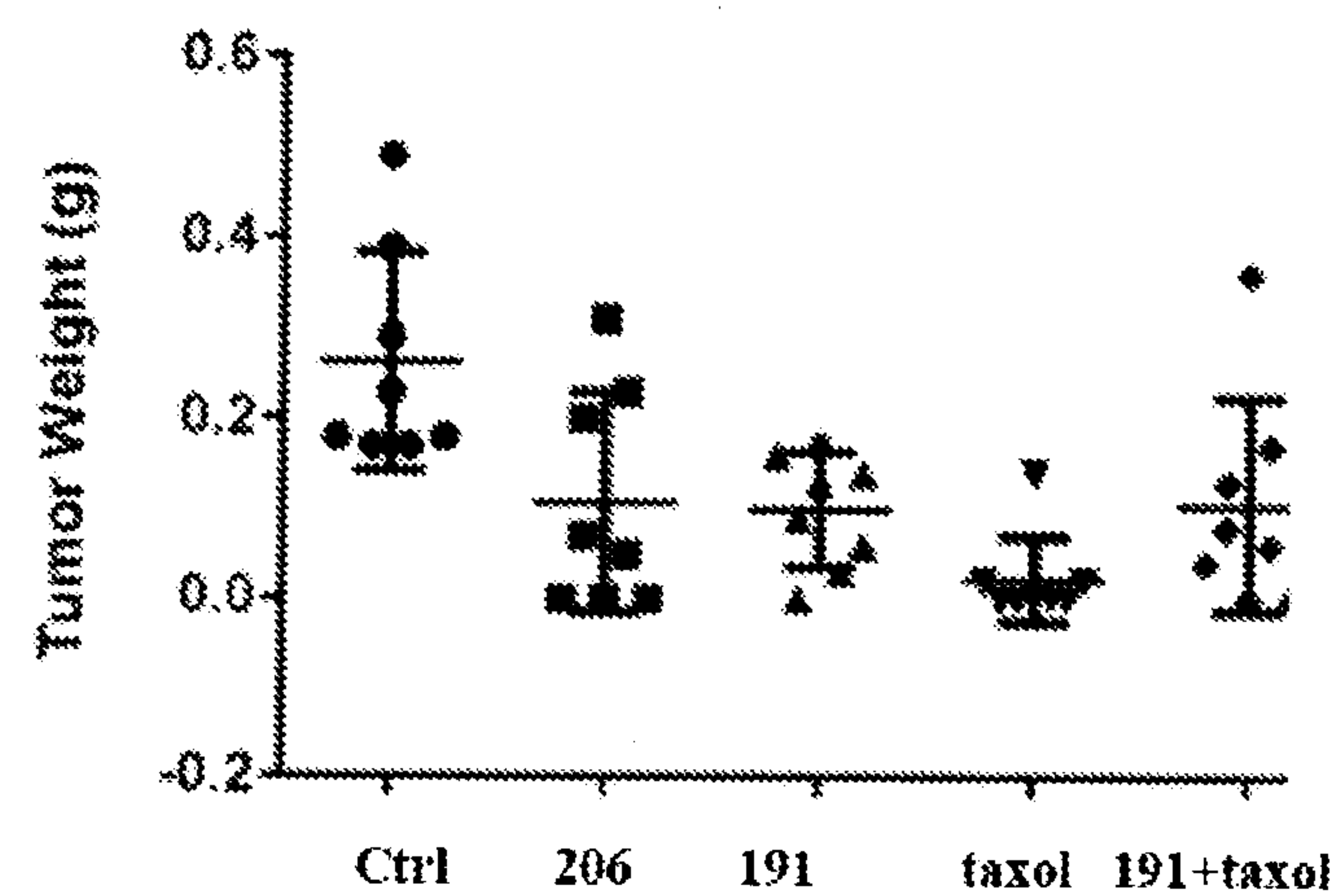


Fig. 5b

10/10

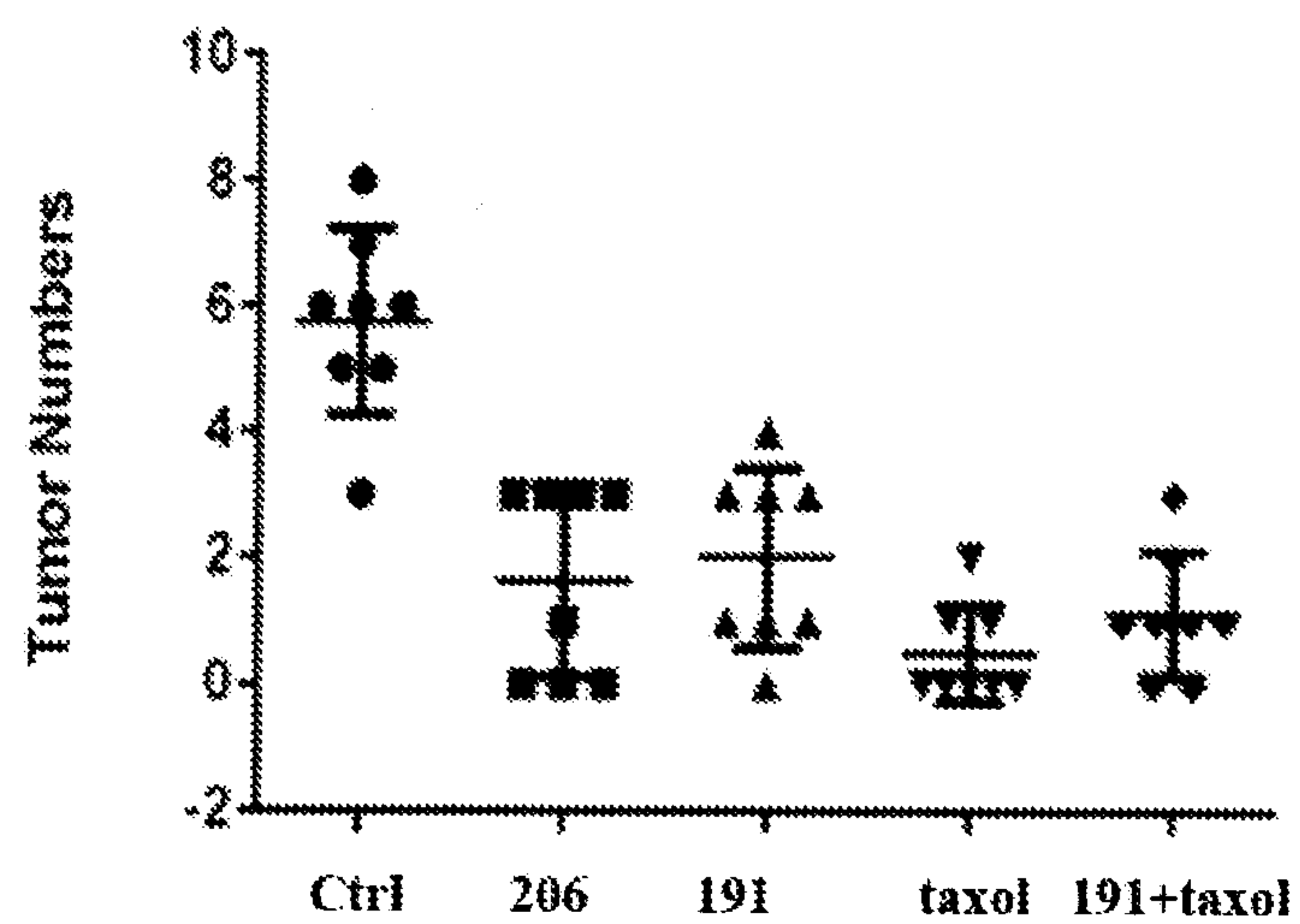


Fig. 5c

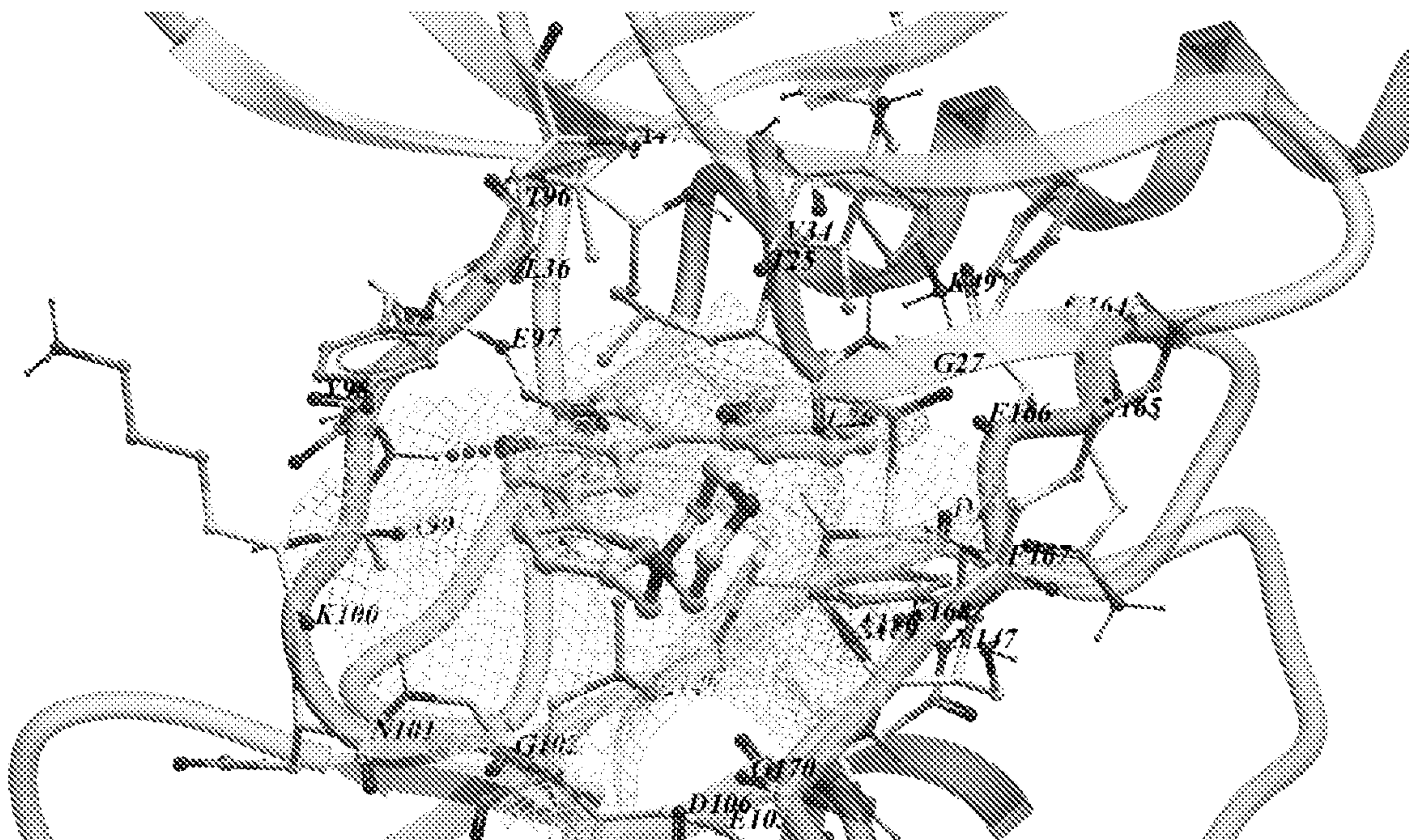
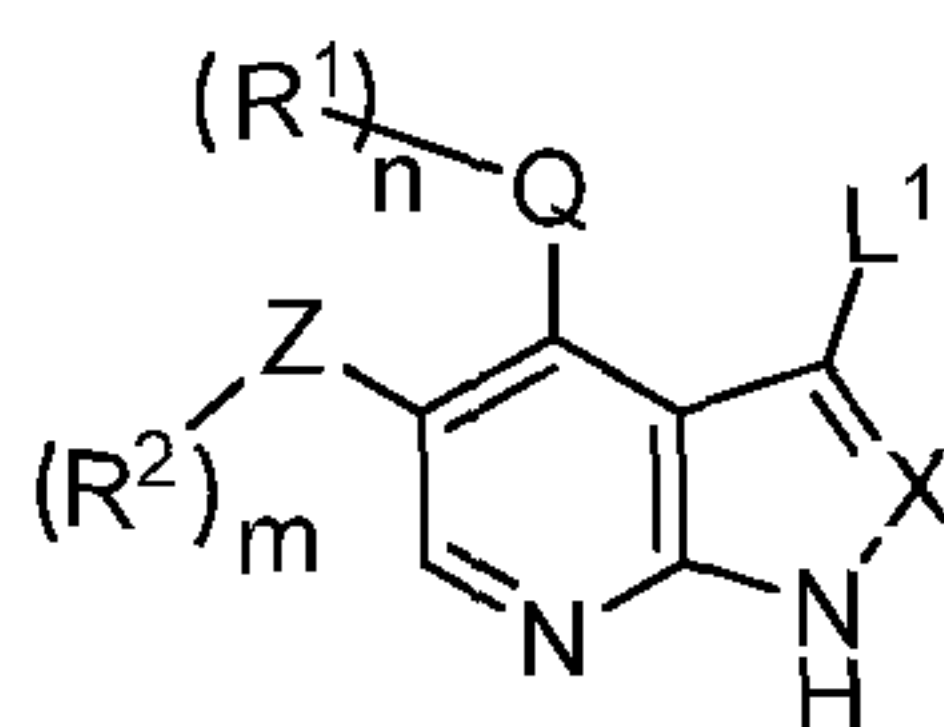
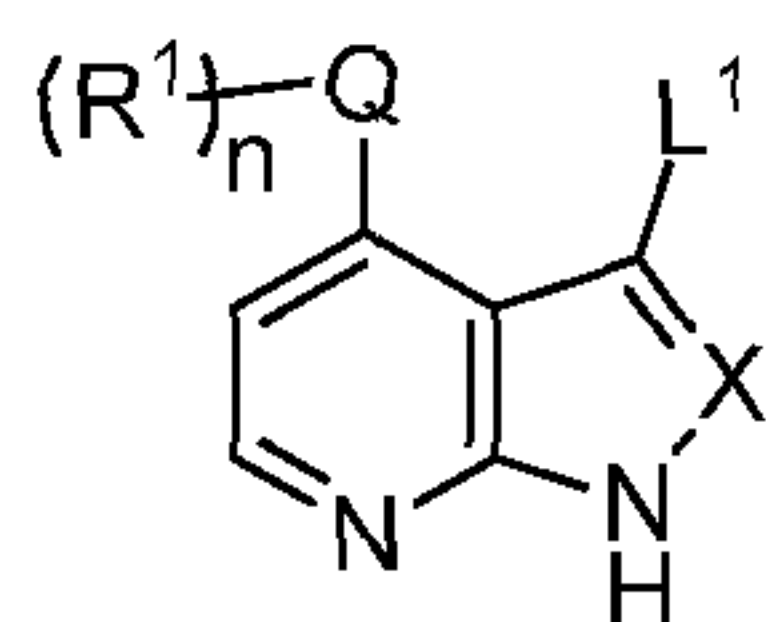


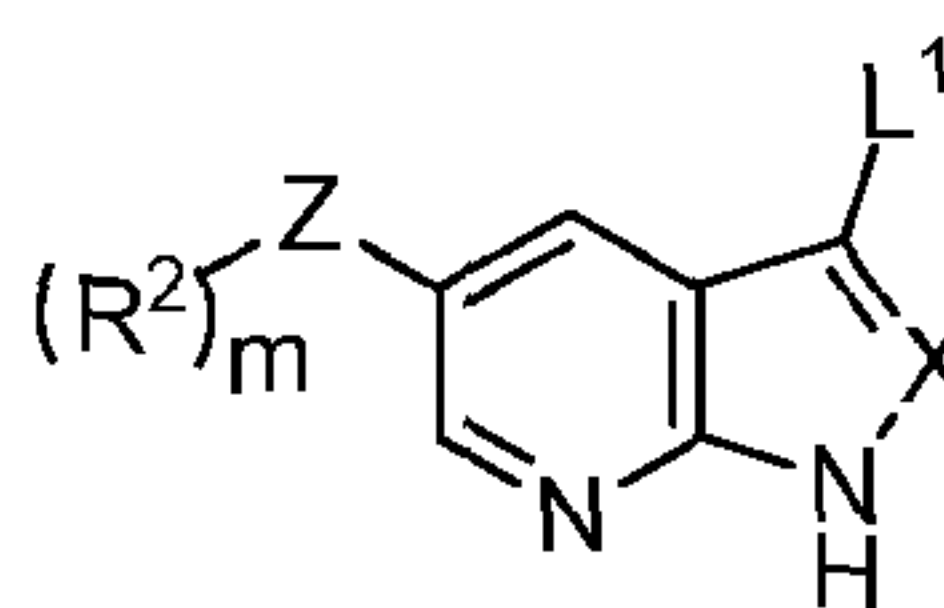
**FIG. 4:** Homology model of SIK2 in complex with an inhibitor. The critical active site residues shown in colour-by-atom in stick representations. The inhibitor binding site depicted in surface in complex with SIK2. Compound belongs to 1*H*-pyrrolo [2, 3-*b*] pyridine structural class of the present invention.



(I)



(IA)



(IB)