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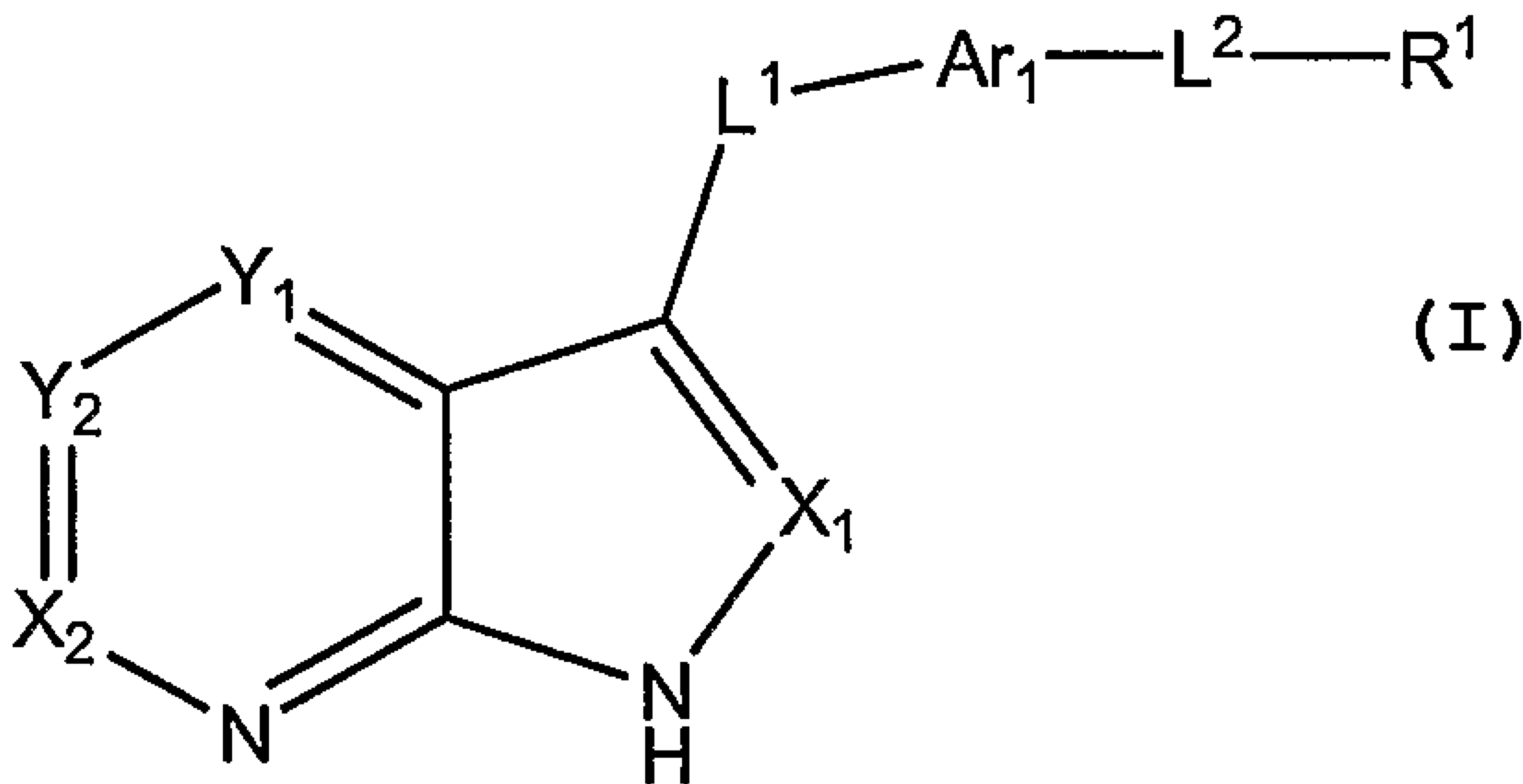
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Compounds active on the receptor protein tyrosine kinases c-kit and c-fms are provided herewith. Also provided herewith are compositions useful for treatment of c-kit mediated diseases or condition and c-fms-mediated diseases or condition, and methods for the use thereof.

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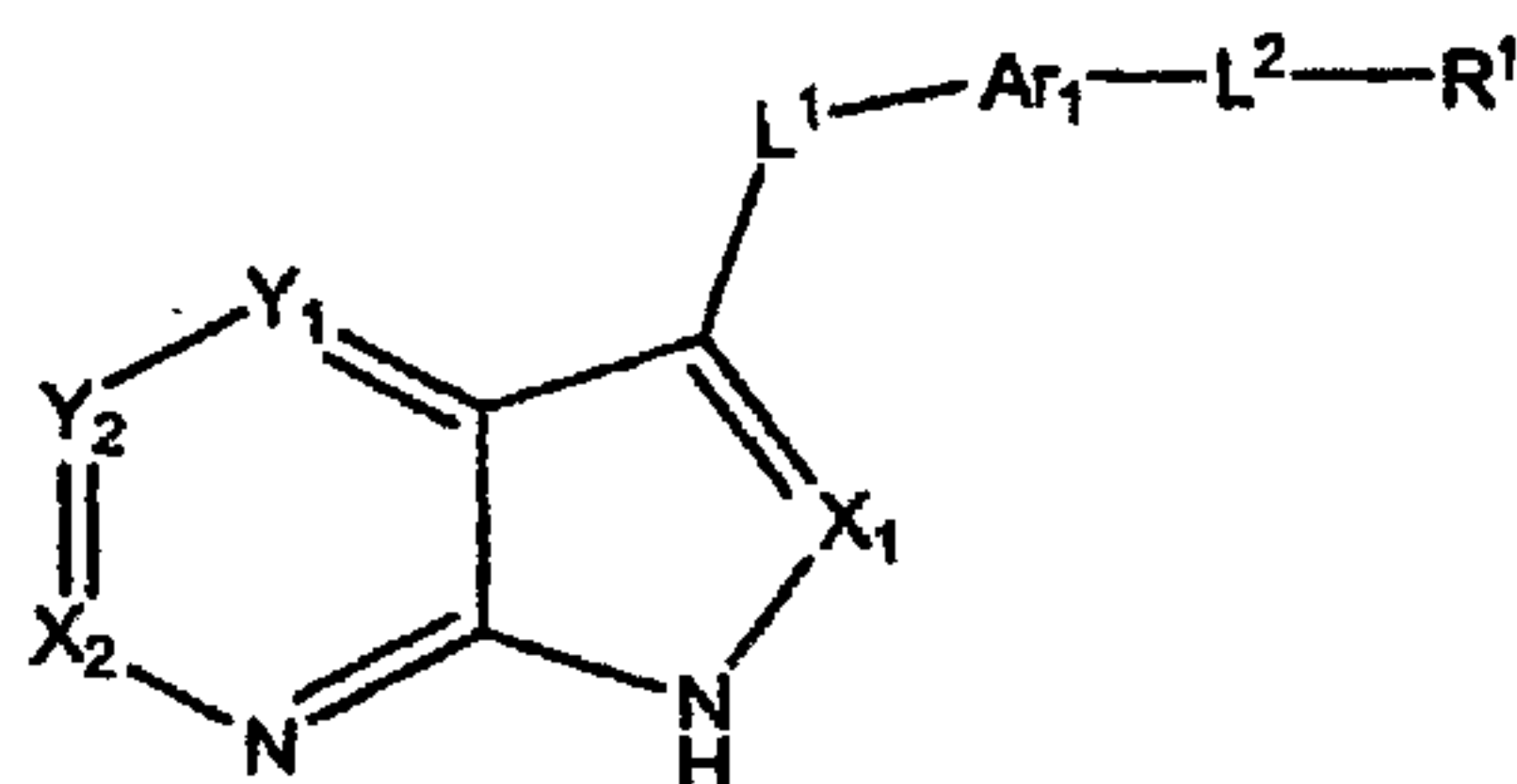
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(I)

(57) Abstract: Compounds active on the receptor protein tyrosine kinases c-kit and c-fms are provided herewith. Also provided herewith are compositions useful for treatment of c-kit mediated diseases or condition and c-fms-mediated diseases or condition, and methods for the use thereof.



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# **COMPOUNDS MODULATING C-KIT AND C-FMS ACTIVITY AND USES THEREFOR**

## **FIELD OF THE INVENTION**

[0001] This invention relates to ligands for c-kit and c-fms, and to methods for use thereof. The information provided is intended solely to assist the understanding of the reader. None of the information provided nor references cited is admitted to be prior art to the present invention. Each of the references cited is incorporated herein in its entirety and for any purpose.

## **BACKGROUND OF THE INVENTION**

[0002] C-kit and c-fms are both type III transmembrane receptor protein tyrosine kinases (RPTKs) that regulate key signal transduction cascades that control cellular growth and proliferation. Both receptors have similar structural features comprising five extracellular immunoglobulin (IG) domains, a single transmembrane domain, and a split cytoplasmic kinase domain separated by a kinase insert segment.

### **c-KIT**

[0003] The Stem Cell Factor (SCF) receptor c-kit plays an important role in the development of melanocytes and mast, germ and hematopoietic cells. Stem Cell Factor (SCF) is a protein encoded by the S1 locus, and has also been called "kit ligand" (KL) and mast cell growth factor (MGF), based on the biological properties used to identify it (reviewed in Tsujimura, *Pathol Int* 1996, 46:933-938; Loveland, et al., *J. Endocrinol* 1997, 153:337-344; Vliagoftis, et al., *Clin Immunol* 1997, 100:435-440; Broudy, *Blood* 1997, 90:1345-1364; Pignon, *Hematol Cell Ther* 1997, 39:114-116; and Lyman, et al., *Blood* 1998, 91:1101-1134.). Herein the abbreviation SCF refers to the physiological ligand for c-kit.

[0004] SCF is synthesized as a transmembrane protein with a molecular weight of 220 or 248 Dalton, depending on alternative splicing of the mRNA to encode exon 6. The larger protein can be proteolytically cleaved to form a soluble, glycosylated protein which noncovalently dimerizes. Both the soluble and membrane-bound forms of SCF can bind to and activate c-kit. For example, in the skin, SCF is predominantly expressed by fibroblasts, keratinocytes, and endothelial cells, which modulate the activity of melanocytes and mast cells expressing c-kit. In bone, marrow stromal cells express SCF and regulate hematopoiesis of c-kit expressing stem cells. In the gastrointestinal tract, intestinal epithelial cells express SCF and affect the interstitial cells of Cajal and intraepithelial lymphocytes. In the testis, sertoli cells and granulosa cells express SCF which regulates spermatogenesis by interaction with c-kit on germ cells.

### **c-Fms**

[0005] C-fms is a member of the family of genes originally isolated from the Susan McDonough strain of feline sarcoma viruses. The cellular proto-oncogene FMS (c-fms, cellular feline McDonough sarcoma) codes for the receptor for the macrophage colony-stimulating factor (M-CSF). C-fms is crucial for the growth and differentiation of the monocyte-macrophage lineage, and upon binding of M-CSF to the extracellular domain of c-fms, the receptor dimerizes and trans-autophosphorylates cytoplasmic tyrosine residues.

[0006] M-CSF, first described by Robinson and co-workers (*Blood*. 1969, 33:396-9), is a cytokine that controls the production, differentiation, and function of macrophages. M-CSF stimulates differentiation of progenitor cells to mature monocytes, and prolongs the



survival of monocytes. Furthermore, M-CSF enhances cytotoxicity, superoxide production, phagocytosis, chemotaxis, and secondary cytokine production of additional factors in monocytes and macrophages. Examples of such additional factors include granulocyte colony stimulating factor (G-CSF), interleukin-6 (IL-6), and interleukin-8 (IL-8). M-CSF stimulates hematopoiesis, promotes differentiation and proliferation of osteoclast progenitor cells, and has profound effects on lipid metabolism. Furthermore, M-CSF is important in pregnancy. Physiologically, large amounts of M-CSF are produced in the placenta, and M-CSF is believed to play an essential role in trophoblast differentiation (Motoyoshi, *Int J Hematol.* 1998, 67:109-22). The elevated serum levels of M-CSF in early pregnancy may participate in the immunologic mechanisms responsible for the maintenance of the pregnancy (Flanagan & Lader, *Curr Opin Hematol.* 1998, 5:181-5).

[0007] Related to c-fms and c-kit are two platelet-derived growth factor receptors, alpha (i.e., pdgfra) and beta (pdgfrb) (PDGF). The gene coding for pdgfra is located on chromosome 4q11-q12 in the same region of chromosome 4 as the oncogene coding for c-kit. The genes coding for pdgfra and c-fms appear to have evolved from a common ancestral gene by gene duplication, inasmuch as these two genes are tandemly linked on chromosome 5. They are oriented head-to-tail with the 5-prime exon of the c-fms gene located only 500 bp from the last 3-prime exon of the gene coding for pdgfra. Most gastrointestinal stromal tumors (GIST) have activating mutations in c-kit, and most patients with GISTs respond well to Gleevec, which inhibits c-kit. Heinrich et al. (*Science* 2003, 299:708-10) have shown that approximately 35% of GISTs lacking c-kit mutations have intragenic activation mutations in the gene encoding pdgfra, and that tumors expressing c-kit or pdgfra are indistinguishable with respect to activation of downstream signaling intermediates and cytogenetic changes associated with tumor progression. Thus, c-kit and pdgfra mutations appear to be alternative and mutually exclusive oncogenic mechanisms in GISTs.

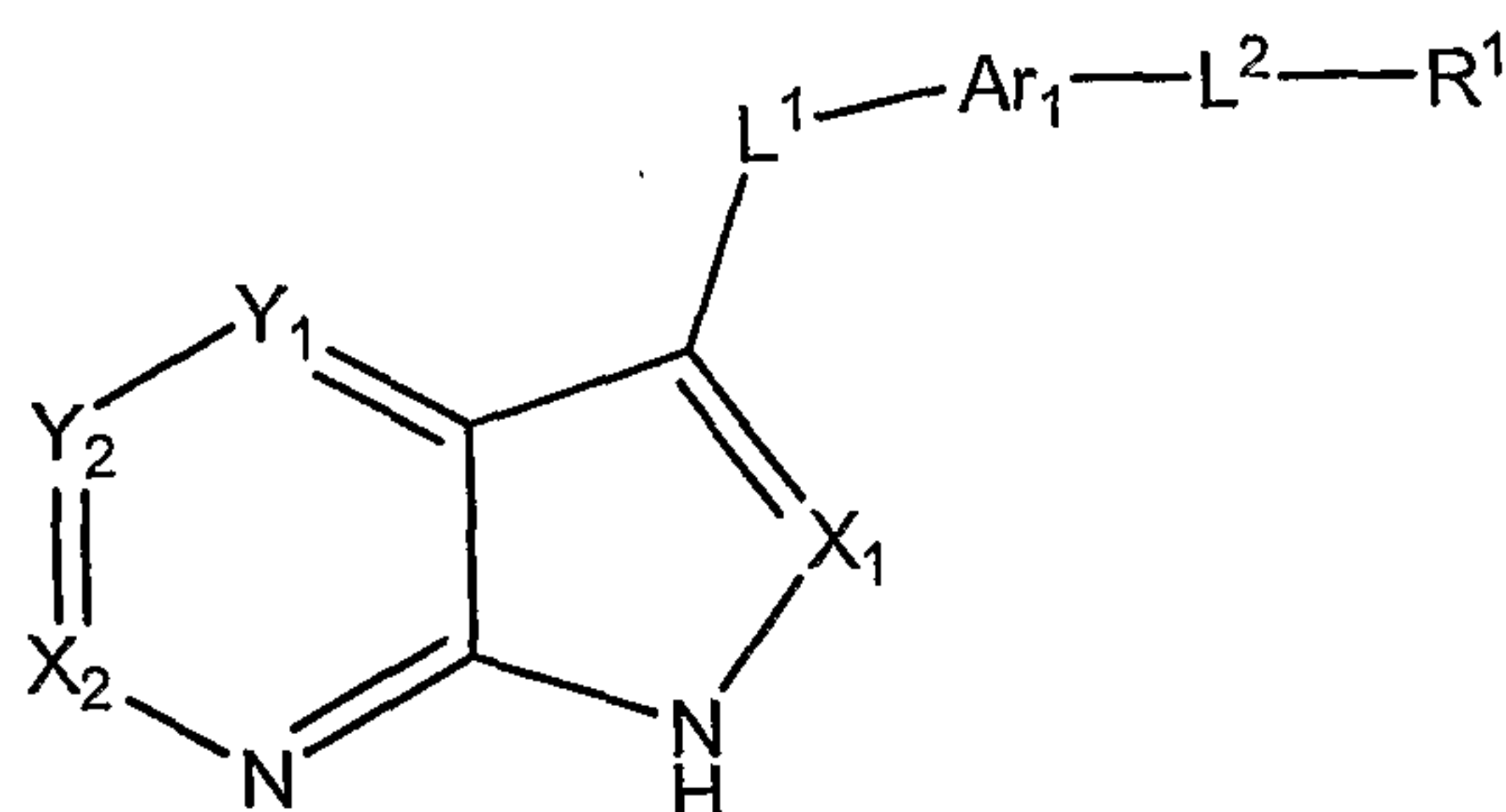
[0008] Similarly, the observation that production of M-CSF, the major macrophage growth factor, is increased in tissues during inflammation points out a role for c-fms in diseases, such as for example inflammatory diseases. More particularly, because elevated levels of M-CSF are found in the disease state, modulation of the activity of c-fms can ameliorate disease associated with increased levels of M-CSF.

[0009] Accordingly, there is need in the art for potent and specific inhibitors and modulators of c-kit and/or c-fms and methods for designing them.

### SUMMARY OF THE INVENTION

[0010] The present invention relates to compounds active on c-kit, c-fms, or both c-kit and c-fms. In accordance with one aspect of the present invention, it has been discovered that in the treatment of diseases amenable to treatment by an effective amount of a modulator of either c-kit alone or c-fms alone, the efficacy of treatment can be enhanced if said compounds are dual inhibitors of both c-kit and c-fms. In particular, the invention provides methods of using compounds of Formula I as described below. Thus, the invention provides methods of using compounds that can be used therapeutically and/or prophylactically involving modulation of c-kit, c-fms, or both c-kit and c-fms.

[0011] The compounds of Formula I have the following structure:



Formula I,

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

$X_1$  is N or  $CR^2$ ,  $X_2$  is N or  $CR^6$ ,  $Y_1$  is N or  $CR^4$ , and  $Y_2$  is N or  $CR^5$ , provided,

however, that not more than one of  $X_2$ ,  $Y_1$  and  $Y_2$  is N;

$L^1$  is selected from the group consisting of optionally substituted lower alkylene, -S-, -O-, -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, and -NR<sup>7</sup>-;

$L^2$  is selected from the group consisting of a bond, optionally substituted lower alkylene, -(alk)<sub>a</sub>-S-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-O-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-OC(O)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(O)O-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-OC(S)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(S)O-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(O)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(S)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(O)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-OC(O)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-OC(S)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(S)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-S(O)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-S(O)<sub>2</sub>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-S(O)<sub>2</sub>NR<sup>9</sup>-(alk)<sub>b</sub>-,

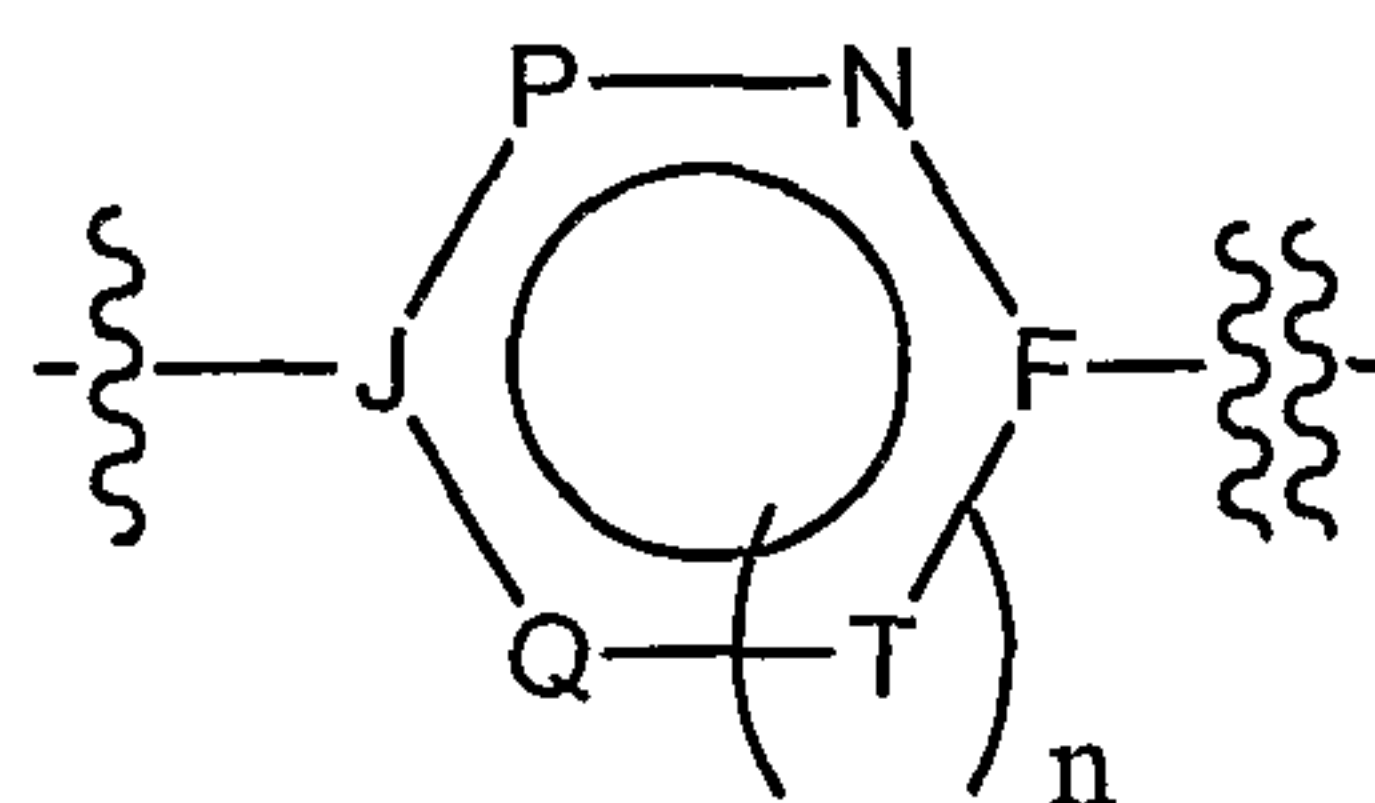


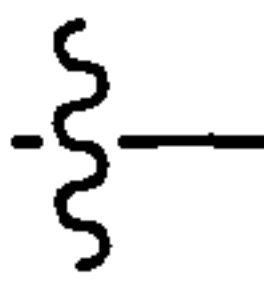
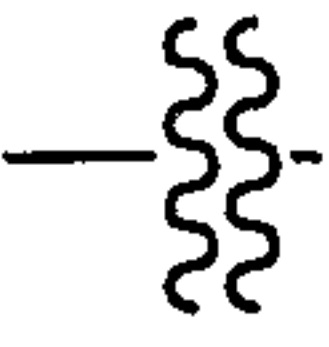
$-(\text{alk})_a-\text{NR}^9-(\text{alk})_b-$ ,  $-(\text{alk})_a-\text{NR}^9\text{C}(\text{O})-(\text{alk})_b-$ ,  $-(\text{alk})_a-\text{NR}^9\text{C}(\text{S})-(\text{alk})_b-$ ,  
 $-(\text{alk})_a-\text{NR}^9\text{C}(\text{O})\text{NR}^9-(\text{alk})_b-$ ,  $-(\text{alk})_a-\text{NR}^9\text{C}(\text{S})\text{NR}^9-(\text{alk})_b-$ ,  
 $-(\text{alk})_a-\text{NR}^9\text{C}(\text{O})\text{O}-(\text{alk})_b-$ ,  $-(\text{alk})_a-\text{NR}^9\text{C}(\text{S})\text{O}-(\text{alk})_b-$ ,  $-(\text{alk})_a-\text{NR}^9\text{S}(\text{O})_2-(\text{alk})_b-$ , and  
 $-(\text{alk})_a-\text{NR}^9\text{S}(\text{O})_2\text{NR}^9-(\text{alk})_b-$ , wherein alk is optionally substituted  $\text{C}_{1-3}$  alkylene  
 and a and b are independently 0 or 1;

$\text{R}^1$  is selected from the group consisting of optionally substituted lower alkyl,  
 optionally substituted cycloalkyl, optionally substituted heterocycloalkyl,  
 optionally substituted aryl, and optionally substituted heteroaryl;

$\text{R}^2$ ,  $\text{R}^4$ ,  $\text{R}^5$  and  $\text{R}^6$  are independently selected from the group consisting of hydrogen,  
 halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl,  
 optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally  
 substituted heterocycloalkyl, optionally substituted aryl, optionally substituted  
 heteroaryl,  $-\text{OH}$ ,  $-\text{NH}_2$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $-\text{C}(\text{O})\text{OH}$ ,  $-\text{C}(\text{S})\text{OH}$ ,  $-\text{C}(\text{O})\text{NH}_2$ ,  $-\text{C}(\text{S})\text{NH}_2$ ,  
 $-\text{S}(\text{O})_2\text{NH}_2$ ,  $-\text{NHC}(\text{O})\text{NH}_2$ ,  $-\text{NHC}(\text{S})\text{NH}_2$ ,  $-\text{NHS}(\text{O})_2\text{NH}_2$ ,  $-\text{NR}^{10}\text{R}^{11}$ ,  $-\text{NHR}^3$ ,  $-\text{OR}^3$ ,  
 $-\text{SR}^3$ ,  $-\text{C}(\text{O})\text{R}^3$ ,  $-\text{C}(\text{S})\text{R}^3$ ,  $-\text{S}(\text{O})\text{R}^3$ ,  $-\text{S}(\text{O})_2\text{R}^3$ ,  $-\text{C}(\text{O})\text{OR}^3$ ,  $-\text{C}(\text{S})\text{OR}^3$ ,  $-\text{C}(\text{O})\text{NHR}^3$ ,  
 $-\text{C}(\text{O})\text{NR}^3\text{R}^3$ ,  $-\text{C}(\text{S})\text{NHR}^3$ ,  $-\text{C}(\text{S})\text{NR}^3\text{R}^3$ ,  $-\text{S}(\text{O})_2\text{NHR}^3$ ,  $-\text{S}(\text{O})_2\text{NR}^3\text{R}^3$ ,  $-\text{NHC}(\text{O})\text{R}^3$ ,  
 $-\text{NR}^3\text{C}(\text{O})\text{R}^3$ ,  $-\text{NHC}(\text{S})\text{R}^3$ ,  $-\text{NR}^3\text{C}(\text{S})\text{R}^3$ ,  $-\text{NHS}(\text{O})_2\text{R}^3$ ,  $-\text{NR}^3\text{S}(\text{O})_2\text{R}^3$ ,  $-\text{NHC}(\text{O})\text{OR}^3$ ,  
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 $-\text{NR}^3\text{C}(\text{O})\text{NR}^3\text{R}^3$ ,  $-\text{NHC}(\text{S})\text{NHR}^3$ ,  $-\text{NHC}(\text{S})\text{NR}^3\text{R}^3$ ,  $-\text{NR}^3\text{C}(\text{S})\text{NH}_2$ ,  
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 $-\text{NR}^3\text{S}(\text{O})_2\text{NH}_2$ ,  $-\text{NR}^3\text{S}(\text{O})_2\text{NHR}^3$ , and  $-\text{NR}^3\text{S}(\text{O})_2\text{NR}^3\text{R}^3$ ;

$\text{Ar}_1$  is a 5 or 6 membered optionally substituted heteroarylene having the structure



wherein  indicates the point of attachment of  $\text{L}^1$  and  indicates the point of attachment of  $\text{L}^2$ , and wherein the indicated N is either  $=\text{N}-$  or  $-\text{N}=\text{}$ ;

n is 0 or 1;

F and J are both C or one of F and J is C and the other of F and J is N;

P and Q are independently selected from CR, N, NR, O or S;



T is selected from CR or N;

wherein

when n is 1, F and J are C, and P, T and Q are CR, or any one of P, T and Q is N and the other two of P, T and Q are CR,

when n is 0 and F and J are both C, then one of P and Q are CR, N or NR and the other of P and Q is C, N, NR, O or S, provided both P and Q are not CR,

when n is 0, one of F and J is N and the other of F and J is C, then one of P and Q is N and the other of P and Q is CR or both P and Q are CR, and R is hydrogen or an optional substituent as defined herein for optionally substituted heteroarylene that provides a stable compound;

R<sup>3</sup> at each occurrence is independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that no alkene carbon thereof is bound to any -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- of any of -OR<sup>3</sup>, -SR<sup>3</sup>, -C(O)R<sup>3</sup>, -C(S)R<sup>3</sup>, -S(O)R<sup>3</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -C(O)OR<sup>3</sup>, -C(S)OR<sup>3</sup>, -C(O)NHR<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>3</sup>, -C(S)NHR<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NHR<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NHR<sup>3</sup>, -NHC(O)R<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>, -NHC(S)R<sup>3</sup>, -NR<sup>3</sup>C(S)R<sup>3</sup>, -NHS(O)<sub>2</sub>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>R<sup>3</sup>, -NHC(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)OH, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NHC(S)OR<sup>3</sup>, -NR<sup>3</sup>C(S)OH, -NR<sup>3</sup>C(S)OR<sup>3</sup>, -NHC(O)NHR<sup>3</sup>, -NHC(O)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)NH<sub>2</sub>, -NR<sup>3</sup>C(O)NHR<sup>3</sup>, -NR<sup>3</sup>C(O)NR<sup>3</sup>R<sup>3</sup>, -NHC(S)NHR<sup>3</sup>, -NHC(S)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(S)NH<sub>2</sub>, -NR<sup>3</sup>C(S)NHR<sup>3</sup>, -NR<sup>3</sup>C(S)NR<sup>3</sup>R<sup>3</sup>, -NHS(O)<sub>2</sub>NHR<sup>3</sup>, -NHS(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>3</sup>S(O)<sub>2</sub>NHR<sup>3</sup>, or -NR<sup>3</sup>S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, optionally substituted lower alkynyl, provided, however, that no alkyne carbon thereof is bound to any -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- of any of -OR<sup>3</sup>, -SR<sup>3</sup>, -C(O)R<sup>3</sup>, -C(S)R<sup>3</sup>, -S(O)R<sup>3</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -C(O)OR<sup>3</sup>, -C(S)OR<sup>3</sup>, -C(O)NHR<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>3</sup>, -C(S)NHR<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NHR<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NHR<sup>3</sup>, -NHC(O)R<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>, -NHC(S)R<sup>3</sup>, -NR<sup>3</sup>C(S)R<sup>3</sup>, -NHS(O)<sub>2</sub>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>R<sup>3</sup>, -NHC(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)OH, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NHC(S)OR<sup>3</sup>, -NR<sup>3</sup>C(S)OH, -NR<sup>3</sup>C(S)OR<sup>3</sup>, -NHC(O)NHR<sup>3</sup>, -NHC(O)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)NH<sub>2</sub>, -NR<sup>3</sup>C(O)NHR<sup>3</sup>, -NR<sup>3</sup>C(O)NR<sup>3</sup>R<sup>3</sup>, -NHC(S)NHR<sup>3</sup>, -NHC(S)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(S)NH<sub>2</sub>, -NR<sup>3</sup>C(S)NHR<sup>3</sup>, -NR<sup>3</sup>C(S)NR<sup>3</sup>R<sup>3</sup>, -NHS(O)<sub>2</sub>NHR<sup>3</sup>, -NHS(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>3</sup>S(O)<sub>2</sub>NHR<sup>3</sup>, or -NR<sup>3</sup>S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, optionally substituted

cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^7$  is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^8$ , and  $-S(O)_2R^8$ ;

$R^8$  is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl;

$R^9$  at each occurrence is independently selected from the group consisting of hydrogen, lower alkyl, and lower alkyl substituted with one or more substituents selected from the group consisting of fluoro,  $-OH$ ,  $-NH_2$ , lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, fluoro substituted mono-alkylamino, di-alkylamino, fluoro substituted di-alkylamino, and  $-NR^{12}R^{13}$ , provided, however, that when  $R^9$  is substituted lower alkyl, any substitution on the alkyl carbon bound to the  $-N-$  of  $-NR^9-$  is fluoro;

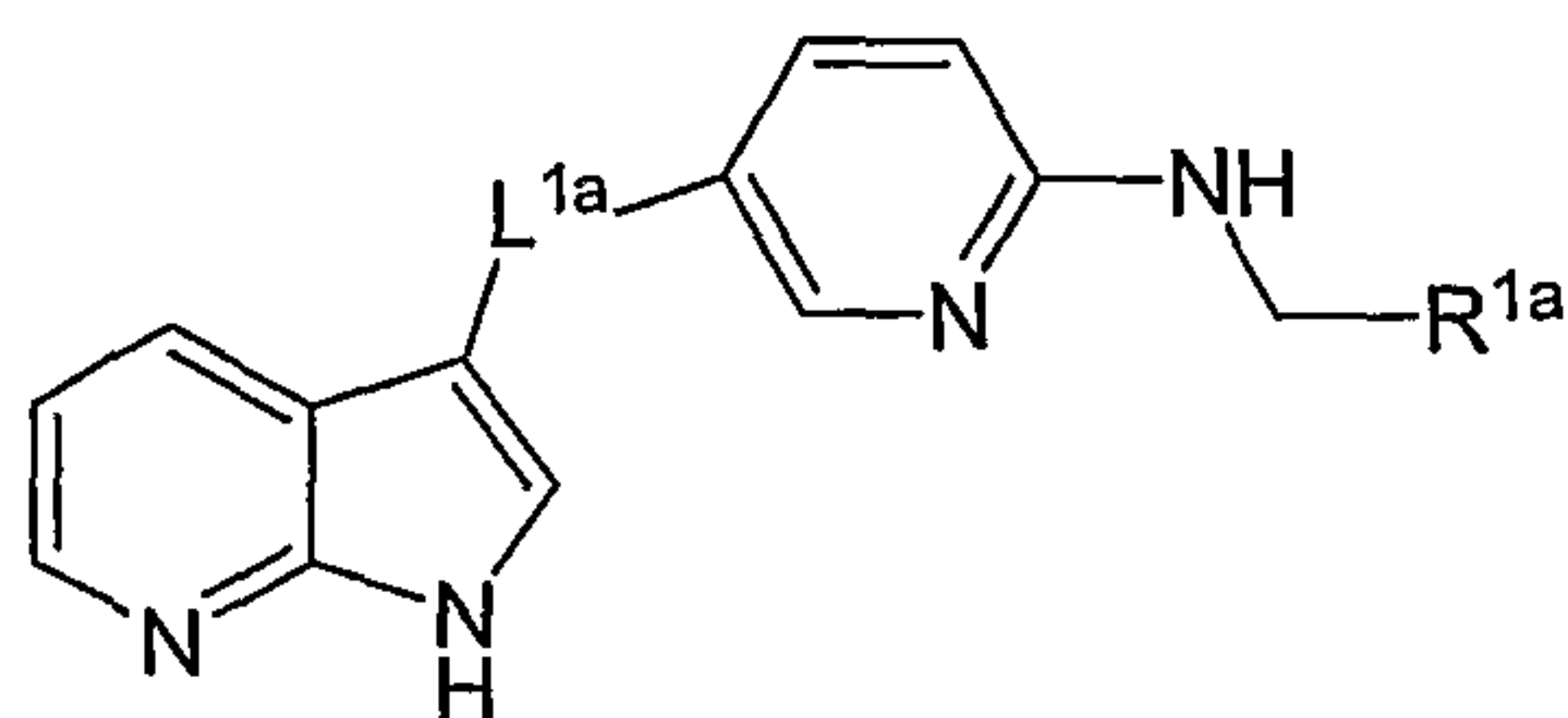
$R^{10}$  and  $R^{11}$  at each occurrence are independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that no alkene carbon thereof is bound to the nitrogen of  $-NR^{10}R^{11}$ , optionally substituted lower alkynyl, provided, however, that no alkyne carbon thereof is bound to the nitrogen of  $-NR^{10}R^{11}$ , optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; or

$R^{10}$  and  $R^{11}$  together with the nitrogen to which they are attached form a monocyclic 5-7 membered optionally substituted heterocycloalkyl or a monocyclic 5 or 7 membered optionally substituted nitrogen containing heteroaryl; and

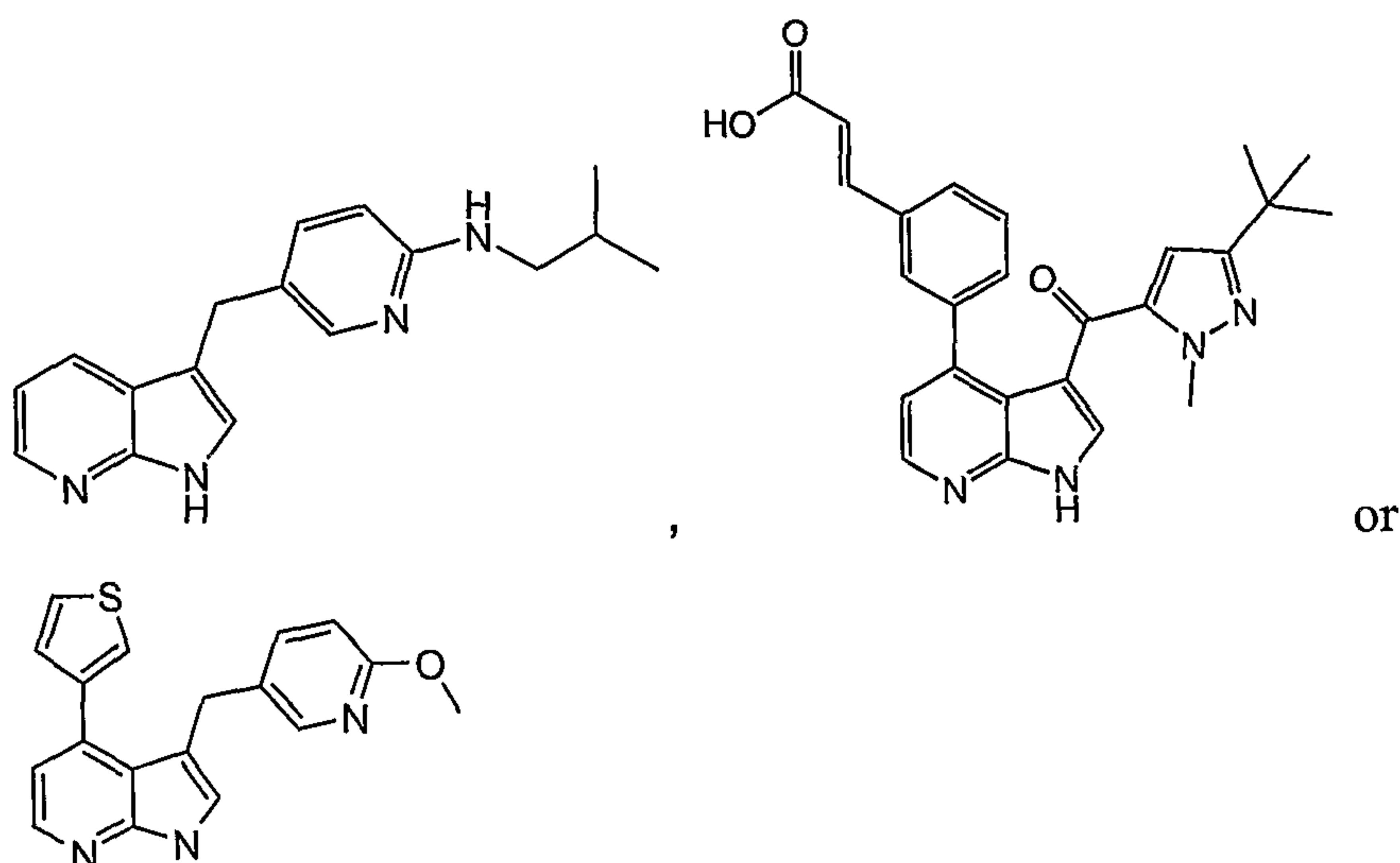
$R^{12}$  and  $R^{13}$  combine with the nitrogen to which they are attached to form a 5-7 membered heterocycloalkyl or 5-7 membered heterocycloalkyl substituted with one or more substituents selected from the group consisting of fluoro,  $-OH$ ,  $-NH_2$ , lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio;

provided, however that when compounds have the structure

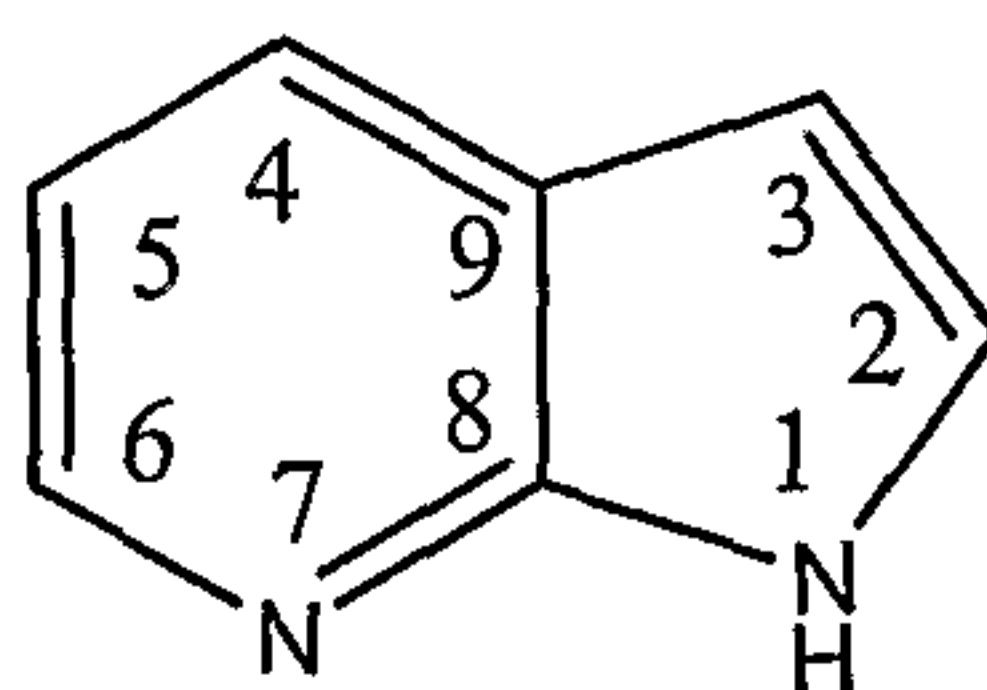




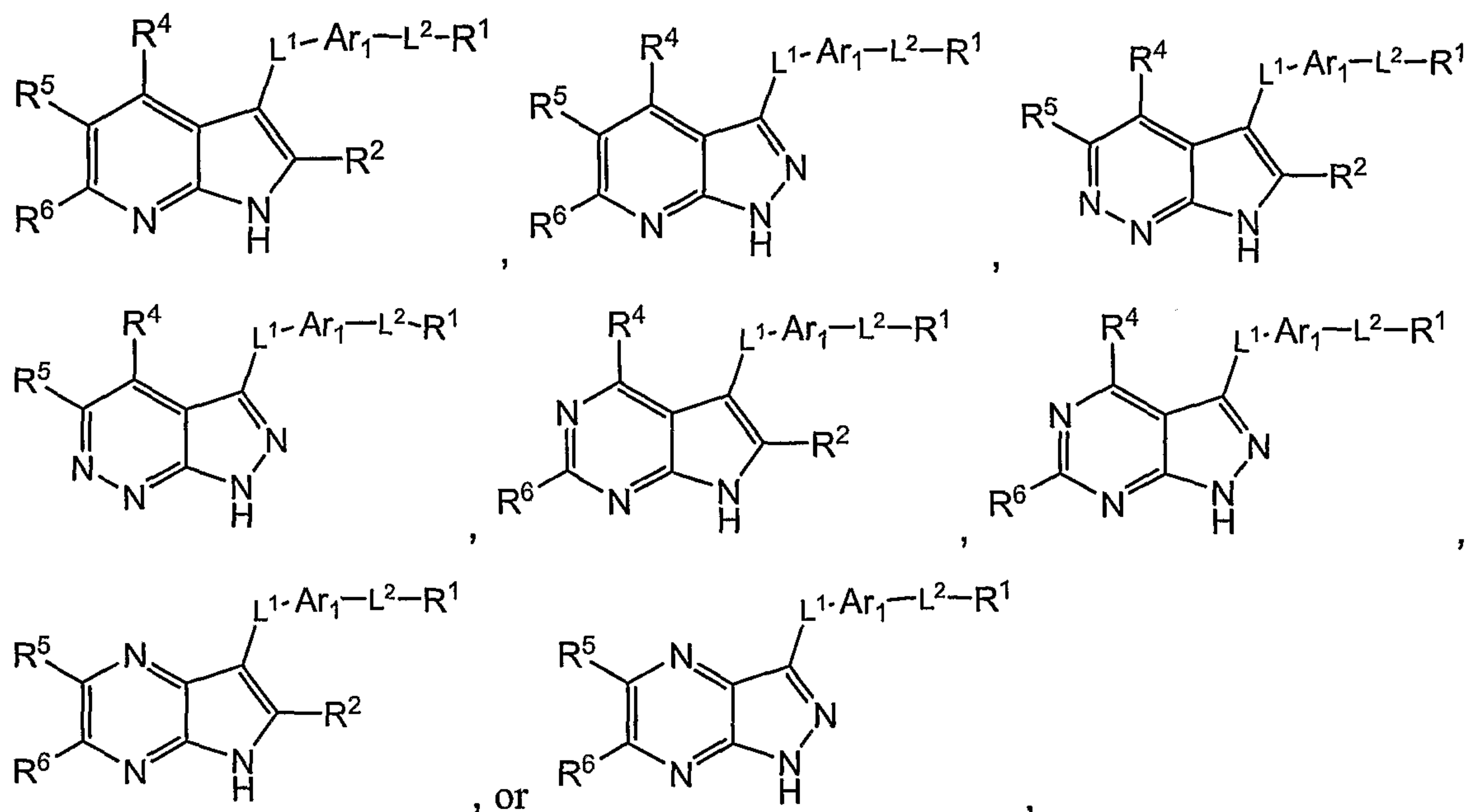
and  $L^{1a}$  is  $-\text{CH}_2-$ ,  $-\text{CH}(\text{OH})-$ , or  $-\text{C}(\text{O})-$ , then  $R^{1a}$  is not phenyl, 4-trifluoromethyl-phenyl, 4-methoxy-phenyl, 4-chloro-phenyl, 4-fluoro-phenyl, 4-methyl-phenyl, 3-fluoro-phenyl or thiophen-2-yl and compounds do not have the structure



**[0012]** In reference to Formula I, the core structure shown above with  $X_1$ ,  $X_2$ ,  $Y_1$  and  $Y_2$  as CH and with  $L^1\text{-Ar}_1\text{-L}^2\text{-R}^1$  replaced with H is referred to as the “azaindole core.” For that azaindole core, reference to ring atoms or ring positions is as shown in the following structure:



**[0013]** In one embodiment of compounds of Formula I, compounds have a structure selected from the following:



wherein  $L^1$ ,  $Ar_1$ ,  $L^2$ ,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$  and  $R^6$  are as defined for Formula I.

**[0014]** In one embodiment of compounds of Formula I,  $X_1$  and  $X_2$  are N or CH. In another embodiment,  $X_1$ ,  $X_2$  and  $Y_1$  are N or CH, where in a further embodiment,  $Y_2$  is  $CR^5$  and  $R^5$  is other than hydrogen. In another embodiment,  $X_1$ ,  $X_2$  and  $Y_2$  are N or CH, where in a further embodiment  $Y_1$  is  $CR^4$  and  $R^4$  is other than hydrogen. In another embodiment,  $X_1$ ,  $X_2$  and  $Y_1$  are CH, where in a further embodiment,  $Y_2$  is  $CR^5$  and  $R^5$  is other than hydrogen. In another embodiment,  $X_1$ ,  $X_2$  and  $Y_2$  are CH, where in a further embodiment  $Y_1$  is  $CR^4$  and  $R^4$  is other than hydrogen.

**[0015]** In one embodiment of compounds of Formula I, wherein  $X_1$ ,  $X_2$ ,  $Y_1$  and  $Y_2$  are independently  $CR^2$ ,  $CR^6$ ,  $CR^4$  and  $CR^5$  respectively, one of  $R^4$  or  $R^5$  is other than hydrogen, preferably where  $R^2$  and  $R^6$  are hydrogen. In one embodiment, wherein  $X_1$ ,  $X_2$ ,  $Y_1$  and  $Y_2$  are independently  $CR^2$ ,  $CR^6$ ,  $CR^4$  and  $CR^5$  respectively,  $R^2$ ,  $R^5$  and  $R^6$  are hydrogen and  $R^4$  is other than hydrogen. In one embodiment, wherein  $X_1$ ,  $X_2$ ,  $Y_1$  and  $Y_2$  are independently  $CR^2$ ,  $CR^6$ ,  $CR^4$  and  $CR^5$  respectively,  $R^2$ ,  $R^4$  and  $R^6$  are hydrogen and  $R^5$  is other than hydrogen.

**[0016]** In one embodiment of compounds of Formula I,  $X_1$  and  $X_2$  are N or CH, preferably wherein both  $X_1$  and  $X_2$  are CH.

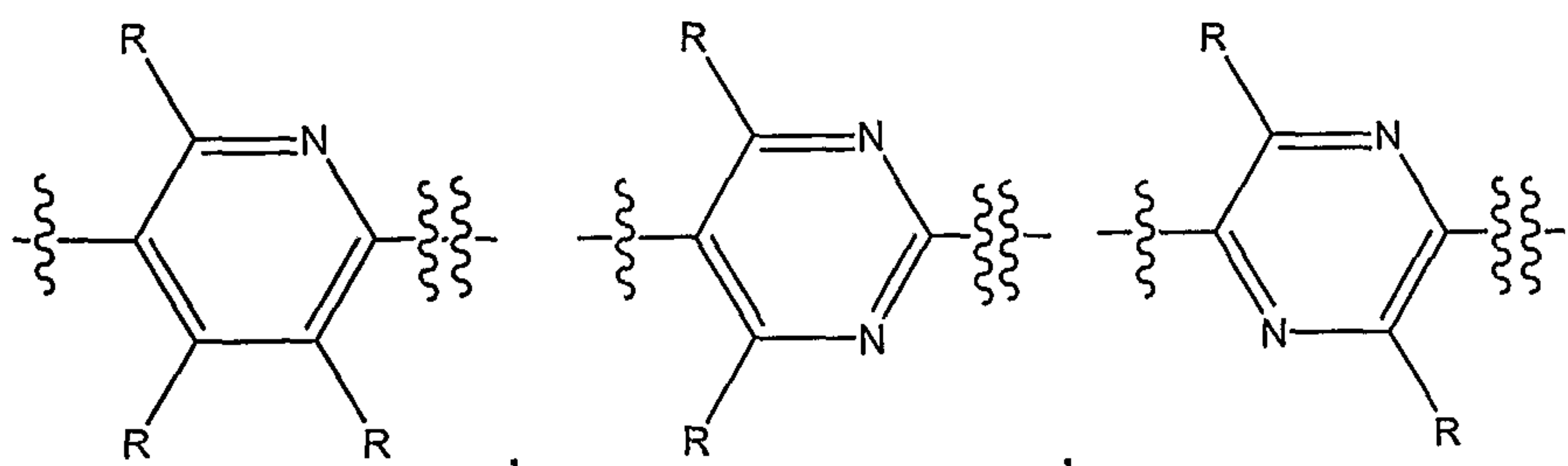
**[0017]** In one embodiment of compounds of Formula I,  $L^1$  is selected from the group consisting of  $-S-$ ,  $-O-$ , lower alkylene,  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)-$ ,  $-S(O)_2-$ , and  $-NR^7-$ ,

wherein lower alkylene is optionally substituted with fluoro, and wherein when  $L^2$  is optionally substituted lower alkylene or comprises optionally substituted  $C_{1-3}$  alkylene, the alkylene is optionally substituted with fluoro or lower alkyl. In one embodiment,  $L^1$  is selected from the group consisting of  $-S-$ ,  $-O-$ ,  $-CH_2-$ ,  $-CF_2-$ ,  $-C(O)-$ ,  $-C(S)-$ ,  $-S(O)-$ ,  $-S(O)_2-$ , and  $-NH-$ .

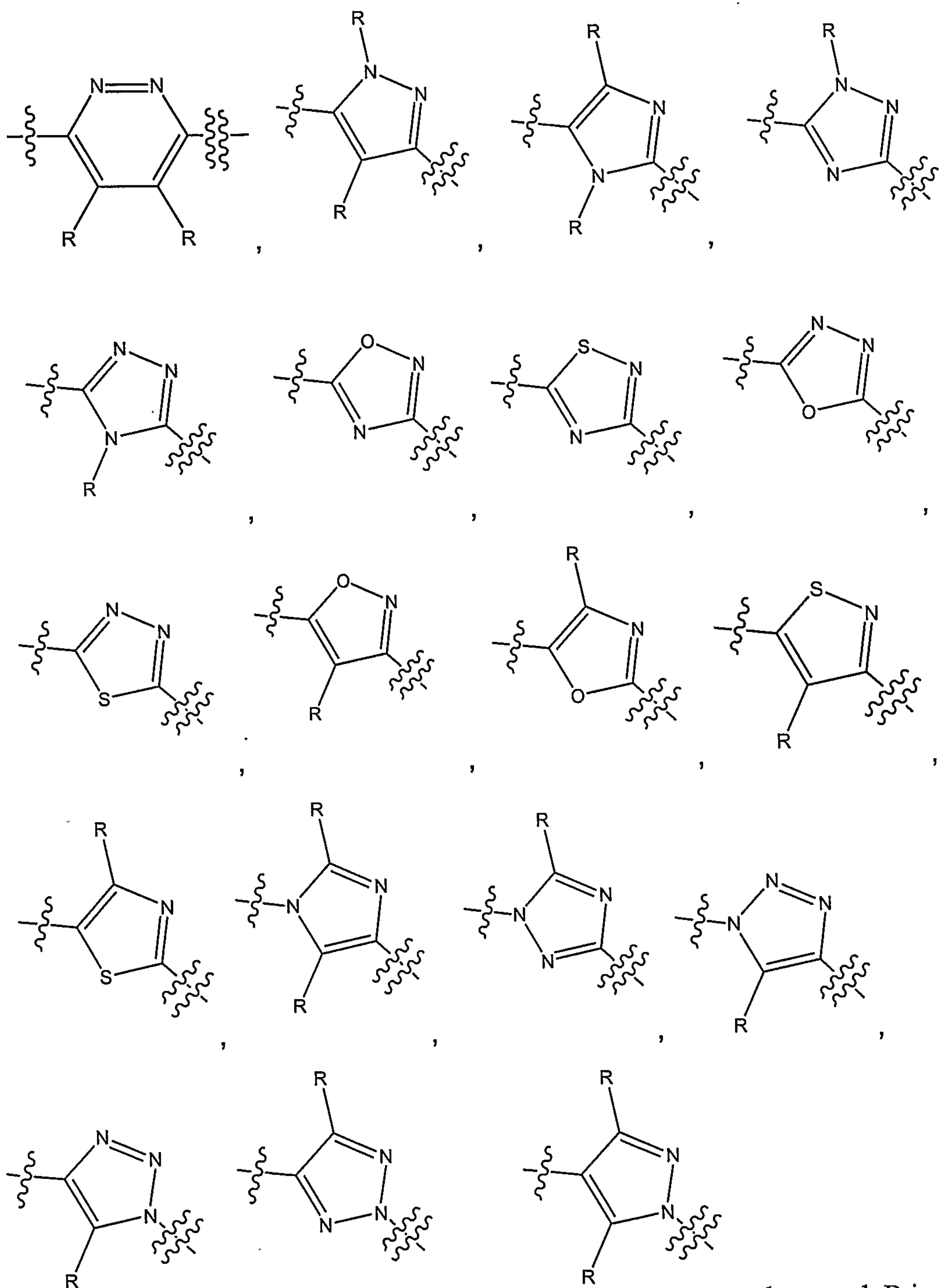
[0018] In one embodiment of compounds of Formula I,  $L^2$  is selected from the group consisting of a bond, optionally substituted lower alkylene,  $-O-(alk)_b-$ ,  $-OC(O)-(alk)_b-$ ,  $-C(O)O-(alk)_b-$ ,  $-OC(S)-(alk)_b-$ ,  $-C(S)O-(alk)_b-$ ,  $-C(O)-(alk)_b-$ ,  $-C(S)-(alk)_b-$ ,  $-C(O)NR^9-(alk)_b-$ ,  $-OC(O)NR^9-(alk)_b-$ ,  $-OC(S)NR^9-(alk)_b-$ ,  $-C(S)NR^9-(alk)_b-$ ,  $-S(O)-(alk)_b-$ ,  $-S(O)_2-(alk)_b-$ ,  $S(O)_2NR^9-(alk)_b-$ ,  $-NR^9-(alk)_b-$ ,  $-NR^9C(O)-(alk)_b-$ ,  $-NR^9C(O)O-(alk)_b-$ ,  $-NR^9C(S)-(alk)_b-$ ,  $-NR^9C(S)O-(alk)_b-$ ,  $-NR^9C(O)NR^9-(alk)_b-$ ,  $-NR^9C(S)NR^9-(alk)_b-$ ,  $-NR^9S(O)_2-(alk)_b-$ , and  $-NR^9S(O)_2NR^9-(alk)_b-$ .

[0019] Further to any of the above embodiments of Formula I, when  $L^1$  is substituted lower alkylene or when  $L^2$  is substituted lower alkylene or comprises substituted  $C_{1-3}$  alkylene, the alkylene is substituted with one or more, preferably 1, 2, or 3 substituents selected from the group consisting of fluoro,  $-OH$ ,  $-NH_2$ , lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and  $-NR^{12}R^{13}$ , wherein the alkyl chain(s) of lower alkoxy, lower alkylthio, mono-alkylamino or di-alkylamino are optionally substituted with one or more, preferably 1, 2, or 3 substituents selected from the group consisting of fluoro,  $-OH$ ,  $-NH_2$ , lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, or cycloalkylamino.

[0020] In one embodiment of the compounds of Formula I, the variables P, J, Q, T, F, and n are selected to provide structures of  $Ar_1$  selected from the group consisting of



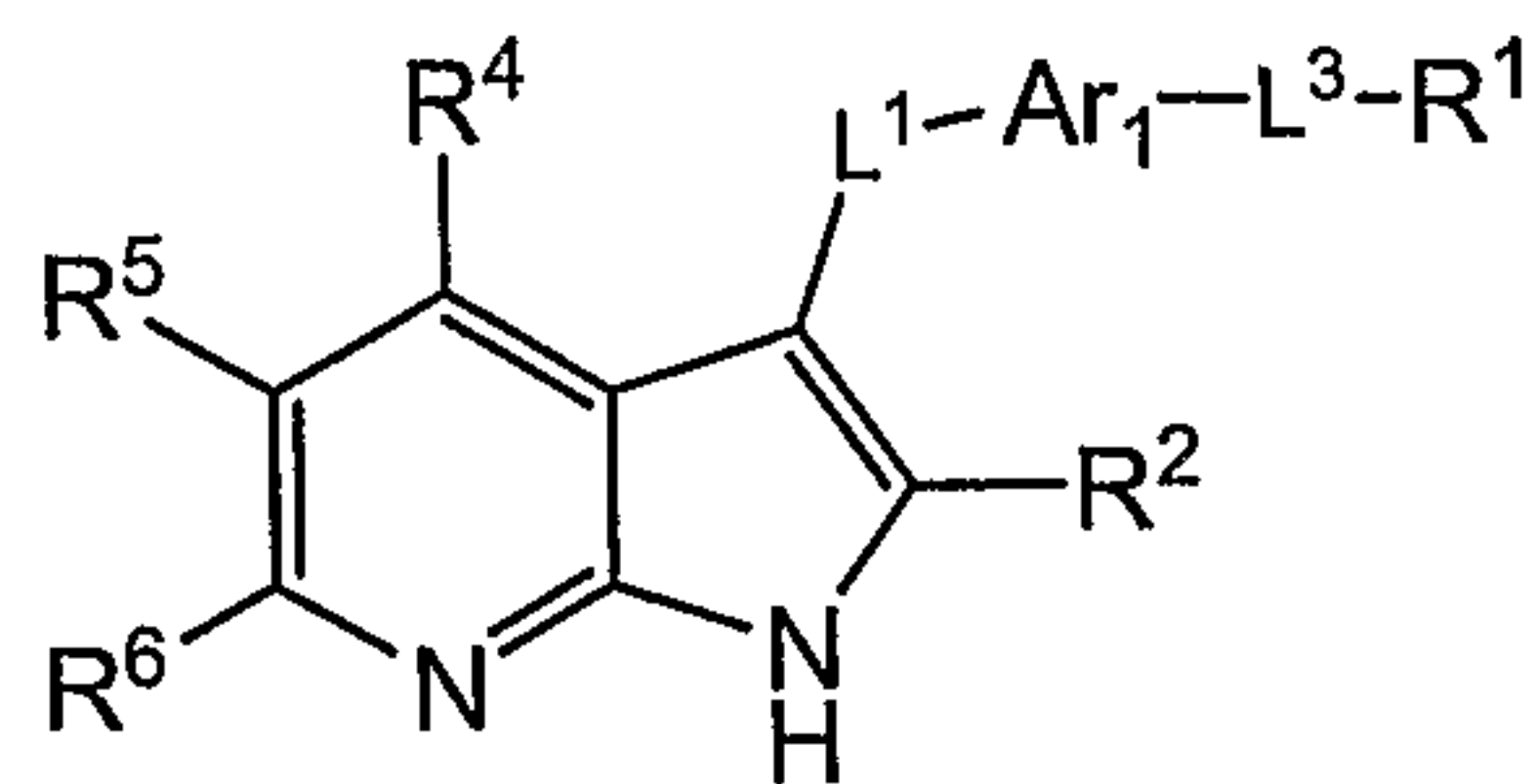




, and , where each R is independently hydrogen or an optional substituent as defined herein for optionally substituted heteroaryl.

[0021] The compounds of Formula I, and all sub-embodiments detailed herein, may be used to treat a subject suffering from or at risk of a Kit and/or Fms protein kinase mediated disease or condition, such as those disclosed in this application.

[0022] In one embodiment, a compound of Formula I has a structure according to the following sub-generic structure, Formula Ia,



Formula Ia

all salts, prodrugs, tautomers, and isomers thereof,

wherein  $L^1$ ,  $Ar_1$ ,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$  and  $R^6$  are as defined for Formula I;

$L^3$  is selected from the group consisting of a bond, optionally substituted lower alkylene,  $-O-(alk)_b-$ ,  $-S-(alk)_b-$ ,  $-NR^{14}-(alk)_b-$ ,  $-C(O)-(alk)_b-$ ,  $-C(S)-(alk)_b-$ ,  $-S(O)-(alk)_b-$ ,  $-S(O)_2-(alk)_b-$ ,  $-NR^{14}C(O)-(alk)_b-$ ,  $-C(O)NR^{14}-(alk)_b-$ ,  $-S(O)_2NR^{14}-(alk)_b-$ ,  $-NR^{14}S(O)_2-(alk)_b-$ ,  $-NR^{14}C(O)NR^{14}-(alk)_b-$ ,  $-NR^{14}C(S)NR^{14}-(alk)_b-$ , and  $-NR^{14}S(O)_2NR^{14}-(alk)_b-$ ;

alk is optionally substituted lower alkylene;

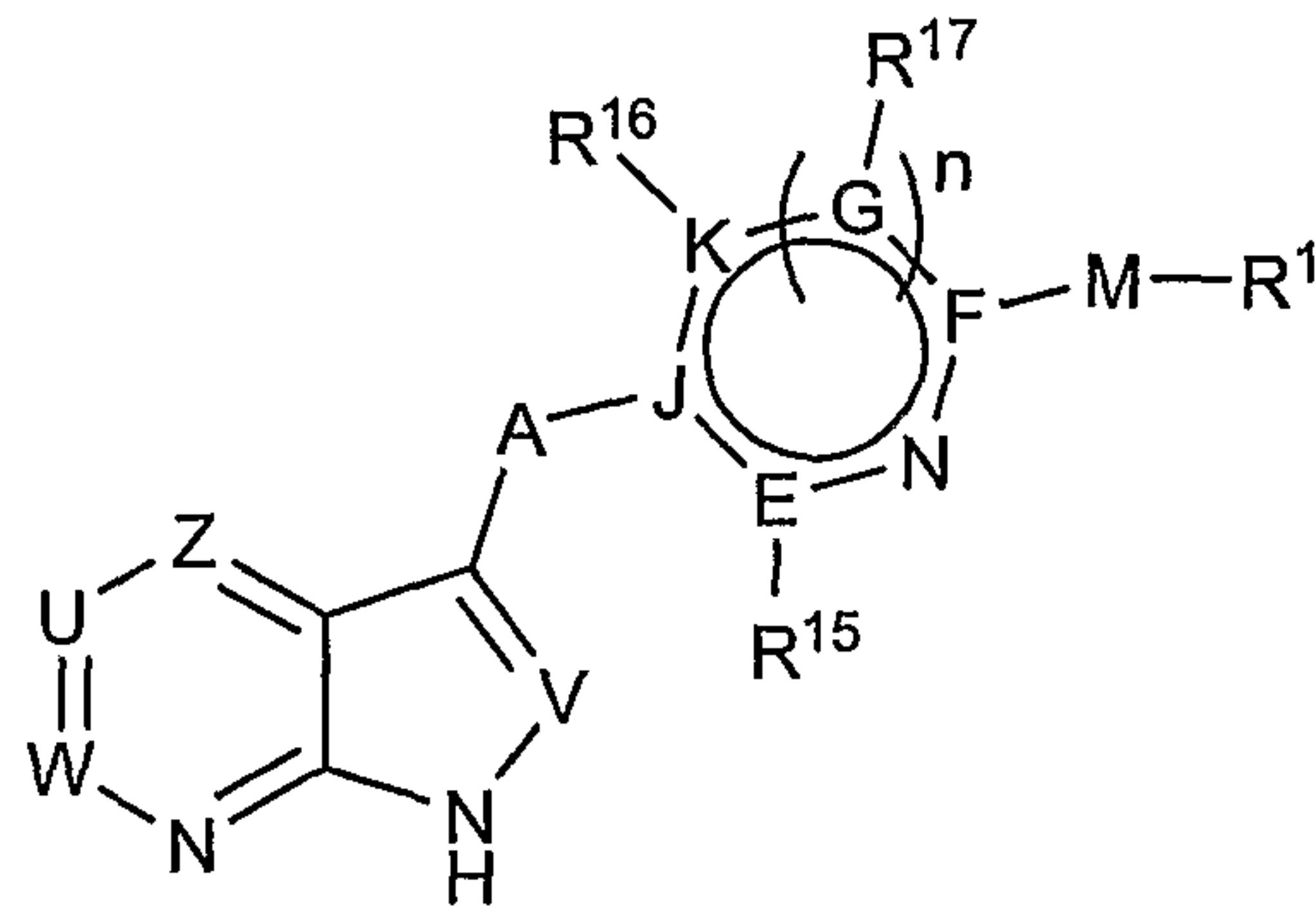
b is 0 or 1; and

$R^{14}$  is hydrogen or lower alkyl.

[0023] In another embodiment of compounds of Formula Ia,  $R^2$ ,  $R^5$  and  $R^6$  are hydrogen, further wherein  $R^4$  is other than hydrogen. In another embodiment,  $R^2$ ,  $R^4$  and  $R^6$  are hydrogen, further wherein  $R^5$  is other than hydrogen.

[0024] The compounds of Formula Ia, and all sub-embodiments detailed herein, may be used to treat a subject suffering from or at risk of a Kit and/or Fms protein kinase mediated disease or condition, such as those disclosed in this application.

[0025] In particular embodiments the compound of Formula I has a structure according to the following sub-generic structure, Formula Ib,



Formula Ib

all salts, prodrugs, tautomers, and isomers thereof,  
wherein:

V and W are independently selected from the group consisting of N and CH;  
U and Z are independently selected from the group consisting of N and CR<sup>18</sup>,  
provided, however, that not more than one of W, U and Z is N;  
A is selected from the group consisting of -CR<sup>19</sup>R<sup>20</sup>-, -C(O)-, -C(S)-, -S-, -S(O)-,  
-S(O)<sub>2</sub>-, -NR<sup>21</sup>-, and -O-;

n is 0 or 1;

F and J are both C or one of F and J is C and the other of F and J is N;

E and K are selected from C, N, O or S;

G is selected from C or N;

wherein

when n is 1, F and J are C, and E, G and K are C, or any one of E, G and K is N  
and the other two of E, G and K are C, provided that when E, G or K is N,  
R<sup>15</sup>, R<sup>17</sup> and R<sup>16</sup>, respectively, are absent,

when n is 0 and F and J are both C, then one of E and K is C or N and the other  
of E and K is C, N, O or S, provided both E and K are not C, and provided  
that when both E and K are N, one of R<sup>15</sup> and R<sup>16</sup> is absent, and provided  
that when one of E and K are N and the other is O or S, R<sup>15</sup> and R<sup>16</sup> are  
absent,

when n is 0, one of F and J is N and the other of F and J is C, then one of E and  
K is N and the other of E and K is C, or both E and K are C, provided that  
when E is N, R<sup>15</sup> is absent and when K is N, R<sup>16</sup> is absent;



- $R^1$  is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl;
- $R^{15}$  is selected from the group consisting of hydrogen, optionally substituted lower alkyl,  $-OR^{22}$ ,  $-SR^{22}$  and halogen when E is C, is absent when E is O or S or when  $n=1$  and E is N, and is absent or selected from the group consisting of hydrogen and optionally substituted lower alkyl when  $n=0$  and E is N;
- $R^{16}$  is selected from the group consisting of hydrogen, optionally substituted lower alkyl,  $-OR^{22}$ ,  $-SR^{22}$  and halogen when K is C, is absent when K is O or S or when  $n=1$  and K is N, and is absent or selected from the group consisting of hydrogen and optionally substituted lower alkyl when  $n=0$  and K is N;
- $R^{17}$  is selected from the group consisting of hydrogen, optionally substituted lower alkyl,  $-OR^{22}$ ,  $-SR^{22}$  and halogen when G is C, or is absent when G is N;
- $R^{18}$  is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OH$ ,  $-NH_2$ ,  $-NO_2$ ,  $-CN$ ,  $-NHC(O)NH_2$ ,  $-NHC(S)NH_2$ ,  $-NHS(O)_2NH_2$ ,  $-NR^{24}R^{25}$ ,  $-NHR^{23}$ ,  $-OR^{23}$ ,  $-SR^{23}$ ,  $-NHC(O)R^{23}$ ,  $-NR^{23}C(O)R^{23}$ ,  $-NHC(S)R^{23}$ ,  $-NR^{23}C(S)R^{23}$ ,  $-NHS(O)_2R^{23}$ ,  $-NR^{23}S(O)_2R^{23}$ ,  $-NHC(O)NHR^{23}$ ,  $-NR^{23}C(O)NH_2$ ,  $-NR^{23}C(O)NHR^{23}$ ,  $-NHC(O)NR^{23}R^{23}$ ,  $-NR^{23}C(O)NR^{23}R^{23}$ ,  $-NHC(S)NHR^{23}$ ,  $-NR^{23}C(S)NH_2$ ,  $-NR^{23}C(S)NHR^{23}$ ,  $-NHC(S)NR^{23}R^{23}$ ,  $-NR^{23}C(S)NR^{23}R^{23}$ ,  $-NHS(O)_2NHR^{23}$ ,  $-NR^{23}S(O)_2NH_2$ ,  $-NR^{23}S(O)_2NHR^{23}$ ,  $-NHS(O)_2NR^{23}R^{23}$ , and  $-NR^{23}S(O)_2NR^{23}R^{23}$ ;
- M is selected from the group consisting of a bond,  $-(CR^{19}R^{20})_u-$ ,  $-(CR^{19}R^{20})_t-C(O)-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-C(S)-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-C(O)O-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-C(S)O-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-C(O)NR^{26}-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-C(S)NR^{26}-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-S(O)-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-S(O)_2-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-S(O)_2NR^{26}-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-O-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-OC(O)-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-OC(S)-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-OC(O)NR^{26}-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-OC(S)NR^{26}-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-S-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-NR^{26}-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-NR^{26}C(O)-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-NR^{26}C(S)-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-NR^{26}C(O)O-(CR^{19}R^{20})_s-$ ,  $-(CR^{19}R^{20})_t-NR^{26}C(S)O-(CR^{19}R^{20})_s-$ ,

$-(\text{CR}^{19}\text{R}^{20})_t\text{-NR}^{26}\text{C(O)NR}^{26}\text{-(CR}^{19}\text{R}^{20})_s\text{-}$ ,  $-(\text{CR}^{19}\text{R}^{20})_t\text{-NR}^{26}\text{C(S)NR}^{26}\text{-(CR}^{19}\text{R}^{20})_s\text{-}$ ,  
 $-(\text{CR}^{19}\text{R}^{20})_t\text{-NR}^{26}\text{S(O)}_2\text{-(CR}^{19}\text{R}^{20})_s\text{-}$ , and  $-(\text{CR}^{19}\text{R}^{20})_t\text{-NR}^{26}\text{S(O)}_2\text{NR}^{26}\text{-(CR}^{19}\text{R}^{20})_s\text{-}$ ;

wherein  $\text{R}^{19}$  and  $\text{R}^{20}$  at each occurrence are independently selected from the group consisting of hydrogen, fluoro,  $-\text{OH}$ ,  $-\text{NH}_2$ , lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and  $-\text{NR}^{27}\text{R}^{28}$ , wherein the alkyl chain(s) of lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro,  $-\text{OH}$ ,  $-\text{NH}_2$ , lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or

any two of  $\text{R}^{19}$  and  $\text{R}^{20}$  on the same or different carbons combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl and any others of  $\text{R}^{19}$  and  $\text{R}^{20}$  are independently selected from the group consisting of hydrogen, fluoro,  $-\text{OH}$ ,  $-\text{NH}_2$ , lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and  $-\text{NR}^{27}\text{R}^{28}$ , wherein the alkyl chain(s) of lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro,  $-\text{OH}$ ,  $-\text{NH}_2$ , lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen,  $-\text{OH}$ ,  $-\text{NH}_2$ , lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

$\text{R}^{21}$  and  $\text{R}^{22}$  at each occurrence are independently hydrogen or optionally substituted lower alkyl;

$\text{R}^{23}$  at each occurrence is independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that no alkene carbon thereof is bound to any  $-\text{C(O)-}$ ,  $-\text{C(S)-}$ ,  $-\text{S(O)}_2\text{-}$ ,  $-\text{O-}$ ,  $-\text{S-}$ , or  $-\text{N-}$  of any of  $-\text{NHR}^{23}$ ,  $-\text{OR}^{23}$ ,  $-\text{SR}^{23}$ ,  $-\text{NHC(O)R}^{23}$ ,  $-\text{NR}^{23}\text{C(O)R}^{23}$ ,  $-\text{NHC(S)R}^{23}$ ,  $-\text{NR}^{23}\text{C(S)R}^{23}$ ,  $-\text{NHS(O)}_2\text{R}^{23}$ ,  $-\text{NR}^{23}\text{S(O)}_2\text{R}^{23}$ ,  $-\text{NHC(O)NHR}^{23}$ ,  $-\text{NR}^{23}\text{C(O)NH}_2$ ,  $-\text{NR}^{23}\text{C(O)NHR}^{23}$ ,  $-\text{NHC(O)NR}^{23}\text{R}^{23}$ ,  $-\text{NR}^{23}\text{C(O)NR}^{23}\text{R}^{23}$ ,



-NHC(S)NHR<sup>23</sup>, -NR<sup>23</sup>C(S)NH<sub>2</sub>, -NR<sup>23</sup>C(S)NHR<sup>23</sup>, -NHC(S)NR<sup>23</sup>R<sup>23</sup>,  
 -NR<sup>23</sup>C(S)NR<sup>23</sup>R<sup>23</sup>, -NHS(O)<sub>2</sub>NHR<sup>23</sup>, -NR<sup>23</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>23</sup>S(O)<sub>2</sub>NHR<sup>23</sup>,  
 -NHS(O)<sub>2</sub>NR<sup>23</sup>R<sup>23</sup>, or -NR<sup>23</sup>S(O)<sub>2</sub>NR<sup>23</sup>R<sup>23</sup>, optionally substituted lower alkynyl,  
 provided, however, that no alkyne carbon thereof is bound to any -C(O)-, -C(S)-, -  
 S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- of any of -NHR<sup>23</sup>, -OR<sup>23</sup>, -SR<sup>23</sup>, -NHC(O)R<sup>23</sup>,  
 -NR<sup>23</sup>C(O)R<sup>23</sup>, -NHC(S)R<sup>23</sup>, -NR<sup>23</sup>C(S)R<sup>23</sup>, -NHS(O)<sub>2</sub>R<sup>23</sup>, -NR<sup>23</sup>S(O)<sub>2</sub>R<sup>23</sup>,  
 -NHC(O)NHR<sup>23</sup>, -NR<sup>23</sup>C(O)NH<sub>2</sub>, -NR<sup>23</sup>C(O)NHR<sup>23</sup>, -NHC(O)NR<sup>23</sup>R<sup>23</sup>,  
 -NR<sup>23</sup>C(O)NR<sup>23</sup>R<sup>23</sup>, -NHC(S)NHR<sup>23</sup>, -NR<sup>23</sup>C(S)NH<sub>2</sub>, -NR<sup>23</sup>C(S)NHR<sup>23</sup>,  
 -NHC(S)NR<sup>23</sup>R<sup>23</sup>, -NR<sup>23</sup>C(S)NR<sup>23</sup>R<sup>23</sup>, -NHS(O)<sub>2</sub>NHR<sup>23</sup>, -NR<sup>23</sup>S(O)<sub>2</sub>NH<sub>2</sub>,  
 -NR<sup>23</sup>S(O)<sub>2</sub>NHR<sup>23</sup>, -NHS(O)<sub>2</sub>NR<sup>23</sup>R<sup>23</sup>, or -NR<sup>23</sup>S(O)<sub>2</sub>NR<sup>23</sup>R<sup>23</sup>, optionally  
 substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally  
 substituted aryl, and optionally substituted heteroaryl;

R<sup>24</sup> and R<sup>25</sup> at each occurrence are independently selected from the group consisting of  
 optionally substituted lower alkyl, optionally substituted lower alkenyl, provided,  
 however, that no alkene carbon thereof is bound to the nitrogen of -NR<sup>24</sup>R<sup>25</sup>,  
 optionally substituted lower alkynyl, provided, however, that no alkyne carbon  
 thereof is bound to the nitrogen of -NR<sup>24</sup>R<sup>25</sup>, optionally substituted cycloalkyl,  
 optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally  
 substituted heteroaryl; or

R<sup>24</sup> and R<sup>25</sup> together with the nitrogen to which they are attached form a monocyclic  
 5-7 membered optionally substituted heterocycloalkyl or a monocyclic 5 or 7  
 membered optionally substituted nitrogen containing heteroaryl;

R<sup>26</sup> at each occurrence is independently selected from the group consisting of  
 hydrogen, lower alkyl, and lower alkyl substituted with one or more substituents  
 selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, lower alkoxy, fluoro  
 substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-  
 alkylamino, fluoro substituted mono-alkylamino, di-alkylamino, fluoro substituted  
 di-alkylamino, and -NR<sup>27</sup>R<sup>28</sup>, provided, however, that when R<sup>26</sup> is substituted  
 lower alkyl, any substitution on the lower alkyl carbon bound to the -N- of -NR<sup>26</sup>-  
 is fluoro;

R<sup>27</sup> and R<sup>28</sup> combine with the nitrogen to which they are attached to form a 5-7  
 membered heterocycloalkyl or 5-7 membered heterocycloalkyl substituted with  
 one or more substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>,

lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio;

u is 1-6;

t is 0-3; and

s is 0-3;

provided that

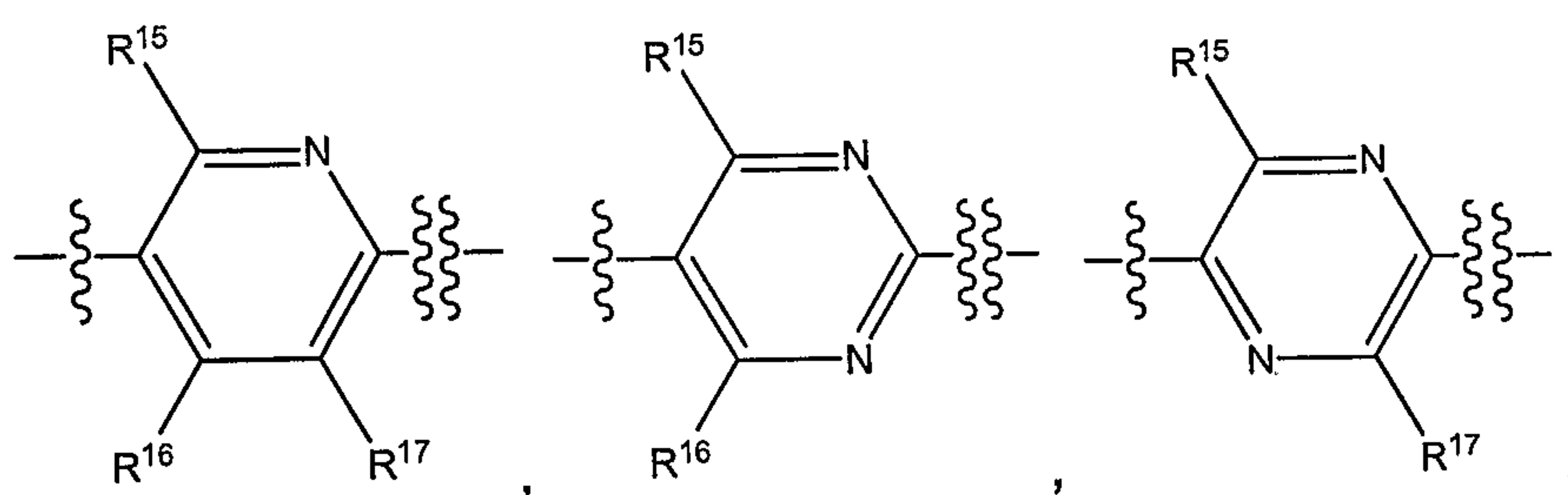
when V, W, U and Z are CH, n=1, E, F, G, J, and K are C, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, A is -CH<sub>2</sub>-, -CH(OH)-, or -C(O)-, and M is -NHCH<sub>2</sub>-, then R<sup>1</sup> is not phenyl, 4-trifluoromethyl-phenyl, 4-methoxy-phenyl, 4-chloro-phenyl, 4-fluoro-phenyl, 4-methyl-phenyl, 3-fluoro-phenyl or thiophen-2-yl,

when V, W, U and Z are CH, n=1, E, F, G, J, and K are C, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, and A is -CH<sub>2</sub>-, then M-R<sup>1</sup> is not -NHCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,

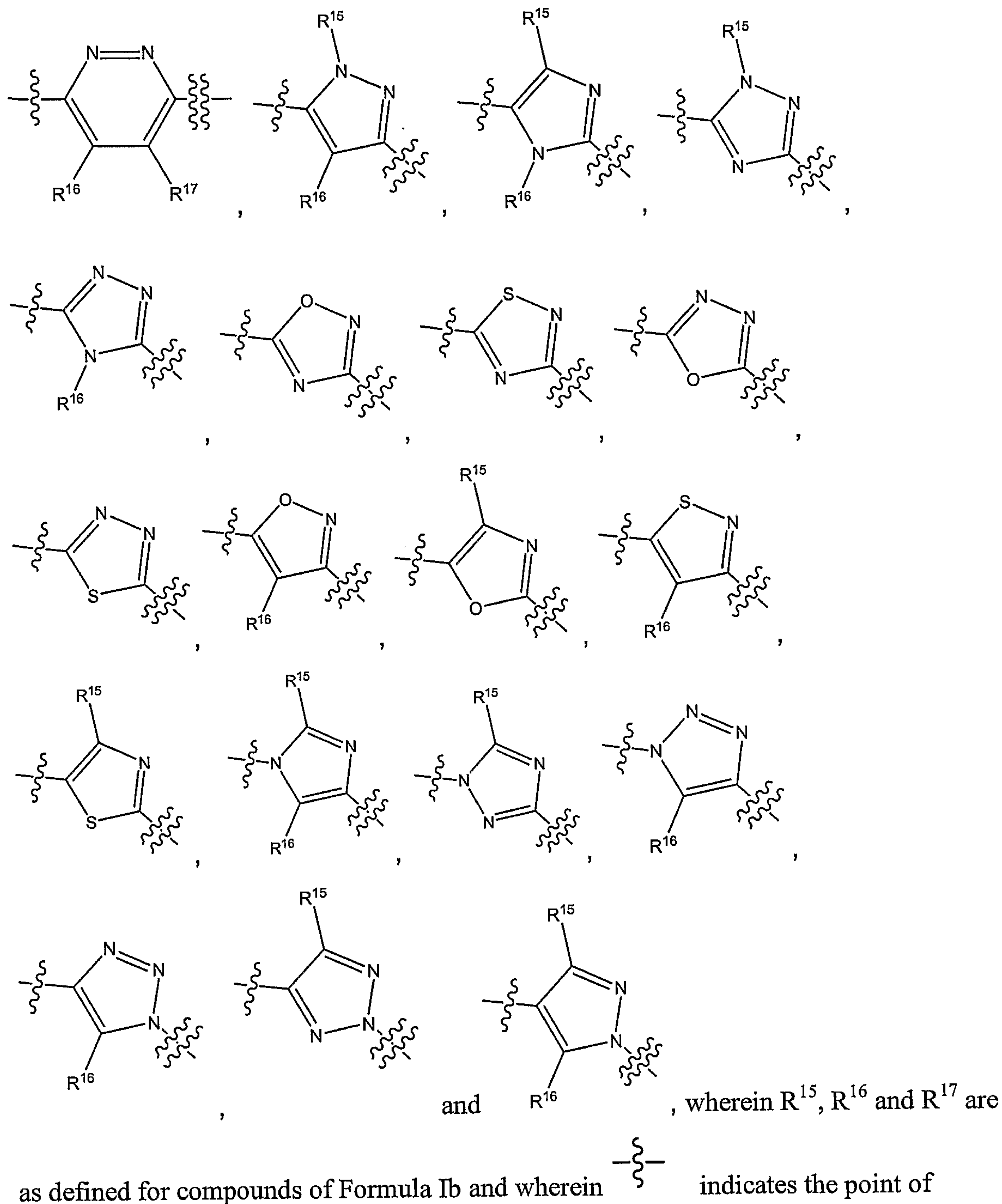
when V, W, and U are CH, n=1, E, F, G, J, and K are C, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, A is -CH<sub>2</sub>-, M-R<sup>1</sup> is -OCH<sub>3</sub>, and Z is CR<sup>18</sup>, then R<sup>18</sup> is not thiophen-3-yl, and

when V, W, and U are CH, n=0, F, J, and K are C, E is N, R<sup>15</sup> is CH<sub>3</sub>, R<sup>16</sup> is H, A is -C(O)-, M-R<sup>1</sup> is -CH(CH<sub>3</sub>)<sub>3</sub>, and Z is CR<sup>18</sup>, then R<sup>18</sup> is not 3-((E)-2-carboxy-vinyl)phenyl.

**[0026]** In one embodiment of the compounds of Formula Ib, E, J, K, G, F, n, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are selected to provide structures selected from the group consisting of







[0027] In one embodiment of compounds of Formula Ib, M is selected from the group consisting of  $-O-(CR^{19}R^{20})_{s^-}$ ,  $-S-(CR^{19}R^{20})_{s^-}$ ,  $-OC(O)-(CR^{19}R^{20})_{s^-}$ ,  $-OC(S)-(CR^{19}R^{20})_{s^-}$ ,  $-OC(O)NR^{26}-(CR^{19}R^{20})_{s^-}$ ,  $-OC(S)NR^{26}-(CR^{19}R^{20})_{s^-}$ ,  $-C(O)NR^{26}-(CR^{19}R^{20})_{s^-}$ ,  $-C(S)NR^{26}-(CR^{19}R^{20})_{s^-}$ ,  $-S(O)_2NR^{26}-(CR^{19}R^{20})_{s^-}$ ,  $-NR^{26}-(CR^{19}R^{20})_{s^-}$ ,

-NR<sup>26</sup>C(O)-(CR<sup>19</sup>R<sup>20</sup>)<sub>s</sub><sup>-</sup>, -NR<sup>26</sup>C(S)-(CR<sup>19</sup>R<sup>20</sup>)<sub>s</sub><sup>-</sup>, -NR<sup>26</sup>C(O)O-(CR<sup>19</sup>R<sup>20</sup>)<sub>s</sub><sup>-</sup>,  
 -NR<sup>26</sup>C(S)O-(CR<sup>19</sup>R<sup>20</sup>)<sub>s</sub><sup>-</sup>, -NR<sup>26</sup>C(O)NR<sup>26</sup>-(CR<sup>19</sup>R<sup>20</sup>)<sub>s</sub><sup>-</sup>, -NR<sup>26</sup>C(S)NR<sup>26</sup>-(CR<sup>19</sup>R<sup>20</sup>)<sub>s</sub><sup>-</sup>,  
 -NR<sup>26</sup>S(O)<sub>2</sub>-(CR<sup>19</sup>R<sup>20</sup>)<sub>s</sub><sup>-</sup>, and -NR<sup>26</sup>S(O)<sub>2</sub>NR<sup>26</sup>-(CR<sup>19</sup>R<sup>20</sup>)<sub>s</sub><sup>-</sup>.

**[0028]** In one embodiment of compounds of Formula Ib, R<sup>26</sup> at each occurrence is independently selected from the group consisting of hydrogen, lower alkyl, or lower alkyl substituted with 1, 2, or 3 substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino and cycloalkylamino, provided that any substitution on the carbon that is bound to the nitrogen of -NR<sup>26</sup> is fluoro.

**[0029]** In one embodiment of compounds of Formula Ib, R<sup>1</sup> is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl.

**[0030]** In one embodiment of the compounds of Formula Ib, Z is N or CH, n is 1, E-R<sup>15</sup> is N or CH, K-R<sup>16</sup> is N or CH, and G-R<sup>17</sup> is N or CH, provided no more than one of E-R<sup>15</sup>, K-R<sup>16</sup> and G-R<sup>17</sup> is N. In one embodiment, Z is N or CH, n is 1, and E-R<sup>15</sup>, K-R<sup>16</sup> and G-R<sup>17</sup> are CH.

**[0031]** In one embodiment of the compounds of Formula Ib, V, W and Z are CH, U is CR<sup>18</sup>, n is 1, E-R<sup>15</sup> is N or CH, K-R<sup>16</sup> is N or CH, and G-R<sup>17</sup> is N or CH, provided no more than one of E-R<sup>15</sup>, K-R<sup>16</sup> and G-R<sup>17</sup> is N. In another embodiment, V, W and Z are CH, U is CR<sup>18</sup>, n is 1, and E-R<sup>15</sup>, K-R<sup>16</sup> and G-R<sup>17</sup> are CH.

**[0032]** In one embodiment of the compounds of Formula Ib, Z is N or CH, n is 1, E-R<sup>15</sup>, K-R<sup>16</sup> and G-R<sup>17</sup> are CH, A is -CH<sub>2</sub>-, M is -NHCH<sub>2</sub>-, further wherein R<sup>1</sup> is optionally substituted phenyl. In another embodiment, V, Z, U and W are CH, n is 1, E-R<sup>15</sup> is N or CH, K-R<sup>16</sup> is N or CH, and G-R<sup>17</sup> is N or CH, provided no more than one of E-R<sup>15</sup>, K-R<sup>16</sup> and G-R<sup>17</sup> is N.

**[0033]** In one embodiment of the compounds of Formula Ib, Z is N or CH, n is 1, E-R<sup>15</sup> is N or CH, K-R<sup>16</sup> is N or CH, and G-R<sup>17</sup> is N or CH, provided no more than one of E-R<sup>15</sup>, K-R<sup>16</sup> and G-R<sup>17</sup> is N, and R<sup>1</sup> is phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, optionally substituted lower alkyl and -OR<sup>29</sup>, where R<sup>29</sup> is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl,



optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl.

**[0034]** In one embodiment of the compounds of Formula Ib, V, Z, U and W are CH, n is 1, E-R<sup>15</sup>, K-R<sup>16</sup> and G-R<sup>17</sup> are CH, A is -CH<sub>2</sub>-, M is -NHCH<sub>2</sub>, and R<sup>1</sup> is optionally substituted phenyl, further wherein R<sup>1</sup> is phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, optionally substituted lower alkyl and -OR<sup>29</sup>, where R<sup>29</sup> is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl.

**[0035]** In one embodiment of the compounds of Formula Ib, V, W and Z are CH, U is CR<sup>18</sup>, n is 1, E-R<sup>15</sup>, K-R<sup>16</sup> and G-R<sup>17</sup> are CH, A is -CH<sub>2</sub>-, M is -NHCH<sub>2</sub>, and R<sup>1</sup> is optionally substituted phenyl, further wherein R<sup>1</sup> is phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, optionally substituted lower alkyl and -OR<sup>29</sup>, where R<sup>29</sup> is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl.

**[0036]** In one embodiment of the compounds of Formula Ib, when n is 1, and E, K and G are C, at least one of R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> is other than hydrogen. In another embodiment, n is 1, one of E, K, and G are N and the other two of E, K, and G are C and at least one of R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> is other than hydrogen. In another embodiment, n is 1, E, K and G are C, and at least one of R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> is other than hydrogen.

**[0037]** In one embodiment of the compounds of Formula Ib, n is 1, V and W are CH, U and Z are independently CR<sup>18</sup>, one of E, K, and G are N and the other two of E, K, and G are C and at least one of R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> is other than hydrogen. In another embodiment, n is 1, V and W are CH, U and Z are independently CR<sup>18</sup>, E, K and G are C, and at least one of R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> is other than hydrogen.

**[0038]** In one embodiment of the compounds of Formula Ib, n is 1, one of E, K, and G are N and the other two of E, K, and G are C, at least one of R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> is other than



hydrogen, A is  $-\text{CH}_2-$ , M is  $-\text{NHCH}_2-$ , further wherein  $\text{R}^1$  is optionally substituted phenyl. In another embodiment, n is 1, E, K, and G are C, at least one of  $\text{R}^{15}$ ,  $\text{R}^{16}$  and  $\text{R}^{17}$  is other than hydrogen, A is  $-\text{CH}_2-$ , M is  $-\text{NHCH}_2-$ , further wherein  $\text{R}^1$  is optionally substituted phenyl.

[0039] In one embodiment of the compounds of Formula Ib, n is 1, V, Z, U and W are CH, one of E, K, and G are N and the other two of E, K, and G are C and at least one of  $\text{R}^{15}$ ,  $\text{R}^{16}$  and  $\text{R}^{17}$  is other than hydrogen. In another embodiment, V, Z, U and W are CH, E, K and G are C, and at least one of  $\text{R}^{15}$ ,  $\text{R}^{16}$  and  $\text{R}^{17}$  is other than hydrogen.

[0040] In one embodiment of the compounds of Formula Ib, Z is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, n is 1,  $\text{E-R}^{15}$  is N or CH,  $\text{K-R}^{16}$  is N or CH and  $\text{G-R}^{17}$  is N or CH. In another embodiment, Z is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, n is 1, and  $\text{E-R}^{15}$ ,  $\text{K-R}^{16}$  and  $\text{G-R}^{17}$  are CH. In another embodiment, Z is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, U is  $\text{CR}^{18}$ , V and W are CH, n is 1, and  $\text{E-R}^{15}$ ,  $\text{K-R}^{16}$  and  $\text{G-R}^{17}$  are CH, further wherein U is CH.

[0041] In one embodiment of the compounds of Formula Ib, Z is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, n is 1,  $\text{E-R}^{15}$ ,  $\text{K-R}^{16}$  and  $\text{G-R}^{17}$  are CH, A is  $-\text{CH}_2-$ , M is  $-\text{NHCH}_2-$ , further wherein  $\text{R}^1$  is optionally substituted phenyl. In a further embodiment, Z is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, U is  $\text{CR}^{18}$ , V and W are CH, n is 1,  $\text{E-R}^{15}$ ,  $\text{K-R}^{16}$  and  $\text{G-R}^{17}$  are CH, A is  $-\text{CH}_2-$ , M is  $-\text{NHCH}_2-$ , further wherein  $\text{R}^1$  is optionally substituted phenyl. In a further embodiment, Z is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, V, U and W are CH, n is 1,  $\text{E-R}^{15}$ ,  $\text{K-R}^{16}$  and  $\text{G-R}^{17}$  are CH, A is  $-\text{CH}_2-$ , M is  $-\text{NHCH}_2-$ , further wherein  $\text{R}^1$  is optionally substituted phenyl.

[0042] In one embodiment of the compounds of Formula Ib, U is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, n is 1,  $\text{E-R}^{15}$  is N or CH,  $\text{K-R}^{16}$  is N or CH and  $\text{G-R}^{17}$  is N or CH. In another embodiment, U is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, n is 1, and  $\text{E-R}^{15}$ ,  $\text{K-R}^{16}$  and  $\text{G-R}^{17}$  are CH. In another embodiment, U is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, Z is  $\text{CR}^{18}$ , V and W are CH, n is 1, and  $\text{E-R}^{15}$ ,  $\text{K-R}^{16}$  and  $\text{G-R}^{17}$  are CH, further wherein Z is CH.

[0043] In one embodiment of the compounds of Formula Ib, U is  $\text{CR}^{18}$ , wherein  $\text{R}^{18}$  is other than hydrogen, n is 1,  $\text{E-R}^{15}$ ,  $\text{K-R}^{16}$  and  $\text{G-R}^{17}$  are CH, A is  $-\text{CH}_2-$ , M is  $-\text{NHCH}_2-$ ,

further wherein  $R^1$  is optionally substituted phenyl. In a further embodiment, U is  $CR^{18}$ , wherein  $R^{18}$  is other than hydrogen, Z is  $CR^{18}$ , V and W are CH, n is 1, E- $R^{15}$ , K- $R^{16}$  and G- $R^{17}$  are CH, A is  $-CH_2-$ , M is  $-NHCH_2-$ , further wherein  $R^1$  is optionally substituted phenyl. In a further embodiment, U is  $CR^{18}$ , wherein  $R^{18}$  is other than hydrogen, V, Z and W are CH, n is 1, E- $R^{15}$ , K- $R^{16}$  and G- $R^{17}$  are CH, A is  $-CH_2-$ , M is  $-NHCH_2-$ , further wherein  $R^1$  is optionally substituted phenyl.

**[0044]** In one embodiment of the compounds of Formula Ib, further to any of the above embodiments,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are independently selected from the group consisting of halogen, -OH, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy. Further to any of these embodiments  $R^1$  is phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH,  $-NH_2$ ,  $-NO_2$ ,  $-CN$ , optionally substituted lower alkyl and  $-OR^{29}$ , where  $R^{29}$  is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl.

**[0045]** In one embodiment of the compounds of Formula Ib, further to any of the above embodiments,  $R^{18}$  is selected from the group consisting of halogen, -OH, optionally substituted lower alkyl and  $-OR^{29}$ , where  $R^{29}$  is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl. Further to any of these embodiments,  $R^1$  is phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, -OH,  $-NH_2$ ,  $-NO_2$ ,  $-CN$ , optionally substituted lower alkyl and  $-OR^{29}$ , where  $R^{29}$  is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl.

**[0046]** In another embodiment of compounds of Formula Ib, M is a bond and  $R^1$  is other than thiophenyl.

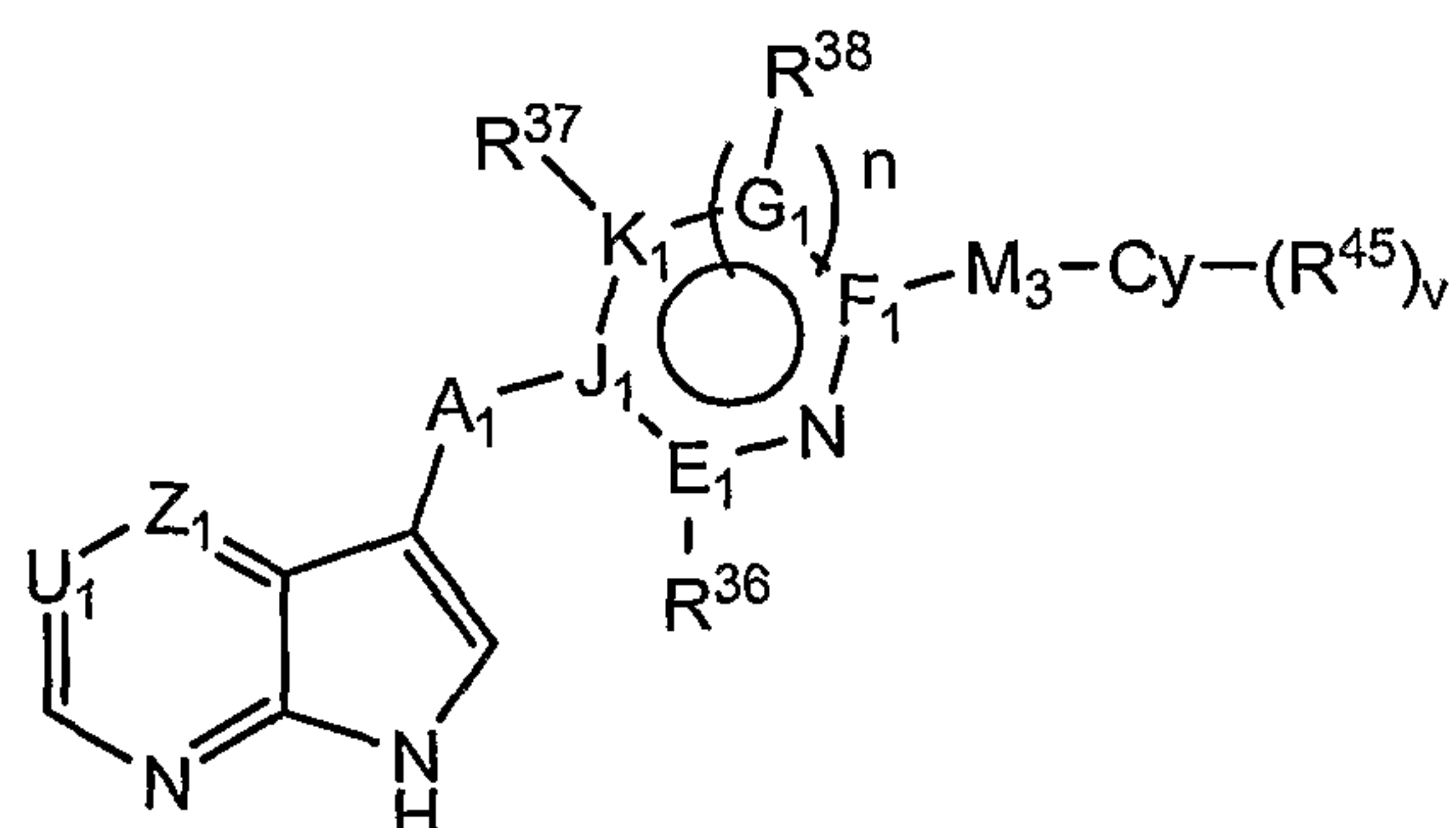
**[0047]** In another embodiment of the compounds of Formula Ib, Z is N or  $CR^{18}$  wherein  $R^{18}$  is not hydrogen. Further to this embodiment, as allowed in the description of Formula



Ib, E is  $\text{NR}^{15}$  or  $\text{CR}^{15}$ , K is  $\text{NR}^{16}$  or  $\text{CR}^{16}$  and G is  $\text{CR}^{17}$ , or combinations thereof, wherein at least one of  $\text{R}^{15}$ ,  $\text{R}^{16}$  and  $\text{R}^{17}$  is not hydrogen.

[0048] The compounds of Formula Ib, and all sub-embodiments detailed herein, may be used to treat a subject suffering from or at risk of a Kit and/or Fms protein kinase mediated disease or condition, such as those disclosed in this application.

[0049] In one embodiment, a compound of Formula I has a structure according to the following sub-generic structure, Formula Ig,



Formula Ig,

all salts, prodrugs, tautomers, and isomers thereof,

wherein:

$Z_1$  is selected from the group consisting of N and  $\text{CR}^{34}$ ;

$U_1$  is selected from the group consisting of N and  $\text{CR}^{35}$ ;

$A_1$  is selected from the group consisting of  $-\text{CH}_2-$  and  $-\text{C}(\text{O})-$ ;

$M_3$  is selected from the group consisting of a bond,  $-\text{NR}^{39}-$ ,  $-\text{S}-$ ,  $-\text{O}-$ ,  $-\text{NR}^{39}\text{CH}_2-$ ,  $-\text{NR}^{39}\text{CH}(\text{R}^{40})-$ ,  $-\text{SCH}_2-$ ,  $-\text{OCH}_2-$ ,  $-\text{C}(\text{O})\text{NR}^{39}-$ ,  $-\text{S}(\text{O})_2\text{NR}^{39}-$ ,  $-\text{CH}_2\text{NR}^{39}-$ ,  $-\text{CH}(\text{R}^{40})\text{NR}^{39}-$ ,  $-\text{NR}^{39}\text{C}(\text{O})-$ , and  $-\text{NR}^{39}\text{S}(\text{O})_2-$ ;

$n$  is 0 or 1;

$v$  is 0, 1, 2 or 3;

$F_1$  and  $J_1$  are both C or one of  $F_1$  and  $J_1$  is C and the other of  $F_1$  and  $J_1$  is N;

$E_1$  and  $K_1$  are selected from C, N, O or S;

$G_1$  is selected from C or N;

wherein

when  $n$  is 1,  $F_1$  and  $J_1$  are C, and  $E_1$ ,  $G_1$  and  $K_1$  are C, or any one of  $E_1$ ,  $G_1$  and  $K_1$  is N and the other two of  $E_1$ ,  $G_1$  and  $K_1$  are C, provided that when  $E_1$ ,  $G_1$  or  $K_1$  is N,  $\text{R}^{36}$ ,  $\text{R}^{37}$  and  $\text{R}^{38}$ , respectively, are absent.



when  $n$  is 0 and  $F_1$  and  $J_1$  are both C, then one of  $E_1$  and  $K_1$  is C or N and the other of  $E_1$  and  $K_1$  is C, N, O or S, provided both  $E_1$  and  $K_1$  are not C, and provided that when both  $E_1$  and  $K_1$  are N, one of  $R^{36}$  and  $R^{37}$  is absent, and provided that when one of  $E_1$  and  $K_1$  are N and the other is O or S,  $R^{36}$  and  $R^{37}$  are absent,

when  $n$  is 0, one of  $F_1$  and  $J_1$  is N and the other of  $F_1$  and  $J_1$  is C, then one of  $E_1$  and  $K_1$  is N and the other of  $E_1$  and  $K_1$  is C, or both  $E_1$  and  $K_1$  are C, provided that when  $E_1$  is N,  $R^{36}$  is absent and when  $K_1$  is N,  $R^{37}$  is absent;

Cy is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

$R^{34}$  and  $R^{35}$  are independently selected from the group consisting of hydrogen,  $-OR^{41}$ ,  $-SR^{41}$ ,  $-NHR^{41}$ ,  $-NR^{41}R^{41}$ ,  $-NR^{39}C(O)R^{41}$ ,  $-NR^{39}S(O)_2R^{41}$ , halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as  $R^{34}$  or  $R^{35}$ , or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CN$ ,  $-NO_2$ ,  $-S(O)_2NH_2$ ,  $-C(O)NH_2$ ,  $-OR^{42}$ ,  $-SR^{42}$ ,  $-NHR^{42}$ ,  $-NR^{42}R^{42}$ ,  $-NR^{39}C(O)R^{42}$ ,  $-NR^{39}S(O)_2R^{42}$ ,  $-S(O)_2R^{42}$ , halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

$R^{45}$  at each occurrence is independently selected from the group consisting of  $-OR^{41}$ ,  $-SR^{41}$ ,  $-NHR^{41}$ ,  $-NR^{41}R^{41}$ ,  $-NR^{39}C(O)R^{41}$ ,  $-NR^{39}S(O)_2R^{41}$ , halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as  $R^{45}$ , or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CN$ ,  $-NO_2$ ,  $-S(O)_2NH_2$ ,  $-C(O)NH_2$ ,  $-OR^{42}$ ,  $-SR^{42}$ ,  $-NHR^{42}$ ,  $-NR^{42}R^{42}$ ,

$-\text{NR}^{39}\text{C}(\text{O})\text{R}^{42}$ ,  $-\text{NR}^{39}\text{S}(\text{O})_2\text{R}^{42}$ ,  $-\text{S}(\text{O})_2\text{R}^{42}$ , halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

$\text{R}^{36}$  is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy when  $\text{E}_1$  is C, is absent when  $\text{E}_1$  is O or S or when  $n=1$  and  $\text{E}_1$  is N, and is absent or selected from the group consisting of hydrogen, lower alkyl, and fluoro substituted lower alkyl when  $n=0$  and  $\text{E}_1$  is N;

$\text{R}^{37}$  is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy when  $\text{K}_1$  is C, is absent when  $\text{K}_1$  is O or S or when  $n=1$  and  $\text{K}_1$  is N, and is absent or selected from the group consisting of hydrogen, lower alkyl, and fluoro substituted lower alkyl when  $n=0$  and  $\text{K}_1$  is N;

$\text{R}^{38}$  is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy when  $\text{G}_1$  is C, or is absent when  $\text{G}_1$  is N;

$\text{R}^{39}$  at each occurrence is independently selected from the group consisting of hydrogen and lower alkyl;

$\text{R}^{40}$  is selected from the group consisting of lower alkyl, and fluoro substituted lower alkyl;

$\text{R}^{41}$  is selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as  $\text{R}^{41}$  or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of  $-\text{OH}$ ,  $-\text{NH}_2$ ,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{S}(\text{O})_2\text{NH}_2$ ,  $-\text{C}(\text{O})\text{NH}_2$ ,  $-\text{OR}^{42}$ ,  $-\text{SR}^{42}$ ,  $-\text{NHR}^{42}$ ,  $-\text{NR}^{42}\text{R}^{42}$ ,  $-\text{NR}^{39}\text{C}(\text{O})\text{R}^{42}$ ,  $-\text{NR}^{39}\text{S}(\text{O})_2\text{R}^{42}$ ,  $-\text{S}(\text{O})_2\text{R}^{42}$ , halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and

$\text{R}^{42}$  at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro



substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

**[0050]** In one embodiment of compounds of Formula Ig,  $n$  is 1,  $G_1$  and  $K_1$  are C, and E is N or C, preferably wherein E is C.

**[0051]** In one embodiment of compounds of Formula Ig,  $M_3$  is selected from the group consisting of  $-NR^{39}-$ ,  $-O-$ ,  $-NR^{39}CH_2-$ ,  $-NR^{39}CH(R^{40})-$ ,  $-SCH_2-$ ,  $-OCH_2-$ ,  $-CH_2NR^{39}-$ ,  $-NR^{39}C(O)-$ , and  $-NR^{39}S(O)_2-$ , preferably wherein  $M_3$  is  $-NR^{39}CH_2-$ ,  $-NR^{39}CH(R^{40})-$ ,  $-SCH_2-$ ,  $-OCH_2-$ , or  $-CH_2NR^{39}-$ .

**[0052]** In one embodiment of compounds of Formula Ig,  $n$  is 1,  $G_1$  and  $K_1$  are C, and E is N or C, preferably wherein E is C, and  $M_3$  is selected from the group consisting of  $-NR^{39}-$ ,  $-O-$ ,  $-NR^{39}CH_2-$ ,  $-NR^{39}CH(R^{40})-$ ,  $-SCH_2-$ ,  $-OCH_2-$ ,  $-CH_2NR^{39}-$ ,  $-NR^{39}C(O)-$ , and  $-NR^{39}S(O)_2-$ , preferably wherein  $M_3$  is  $-NR^{39}CH_2-$ ,  $-NR^{39}CH(R^{40})-$ ,  $-SCH_2-$ ,  $-OCH_2-$ , or  $-CH_2NR^{39}-$ .

**[0053]** In one embodiment of compounds of Formula Ig, each  $R^{45}$  is selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CN$ ,  $-NO_2$ , halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower thioalkyl, fluoro substituted lower thioalkyl, mono-alkylamino, di-alkylamino and cycloalkylamino, preferably wherein  $v$  is 0, 1, or 2, also 0 or 1.

**[0054]** In one embodiment of compounds of Formula Ig,  $n$  is 1,  $G_1$  and  $K_1$  are C, and E is N or C, preferably wherein E is C,  $M_3$  is selected from the group consisting of  $-NR^{39}-$ ,  $-O-$ ,  $-NR^{39}CH_2-$ ,  $-NR^{39}CH(R^{40})-$ ,  $-SCH_2-$ ,  $-OCH_2-$ ,  $-CH_2NR^{39}-$ ,  $-NR^{39}C(O)-$ , and  $-NR^{39}S(O)_2-$ , preferably wherein  $M_3$  is  $-NR^{39}CH_2-$ ,  $-NR^{39}CH(R^{40})-$ ,  $-SCH_2-$ ,  $-OCH_2-$ , or  $-CH_2NR^{39}-$ , and each  $R^{45}$  is selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CN$ ,  $-NO_2$ , halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower thioalkyl, fluoro substituted lower thioalkyl, mono-alkylamino, di-alkylamino and cycloalkylamino, preferably wherein  $v$  is 0, 1, or 2, also 0 or 1.

**[0055]** In one embodiment of compounds of Formula Ig,  $Z_1$  is  $CR^{34}$ ,  $U_1$  is  $CR^{35}$ , and  $R^{34}$  and  $R^{35}$  are both hydrogen. In one embodiment,  $Z_1$  is  $CR^{34}$ ,  $U_1$  is  $CR^{35}$ , and  $R^{34}$  and  $R^{35}$  are independently selected from the group consisting of hydrogen,  $-OR^{41}$ , halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl,

heterocycloalkyl, aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -C(O)NH<sub>2</sub>, -OR<sup>42</sup>, -SR<sup>42</sup>, -NHR<sup>42</sup>, -NR<sup>42</sup>R<sup>42</sup>, -NR<sup>39</sup>C(O)R<sup>42</sup>, -NR<sup>39</sup>S(O)<sub>2</sub>R<sup>42</sup>, -S(O)<sub>2</sub>R<sup>42</sup>, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino, and wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino. In a further embodiment, one of R<sup>34</sup> and R<sup>35</sup> is hydrogen, and the other of R<sup>34</sup> and R<sup>35</sup> is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -C(O)NH<sub>2</sub>, -OR<sup>42</sup>, -SR<sup>42</sup>, -NHR<sup>42</sup>, -NR<sup>42</sup>R<sup>42</sup>, -NR<sup>39</sup>C(O)R<sup>42</sup>, -NR<sup>39</sup>S(O)<sub>2</sub>R<sup>42</sup>, -S(O)<sub>2</sub>R<sup>42</sup>, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino, and wherein lower alkyl and lower alkoxy are optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, further wherein the other of R<sup>34</sup> and R<sup>35</sup> is selected from the group consisting of halogen, lower alkyl, and lower alkoxy, wherein lower alkyl and lower alkoxy are optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

[0056] In one embodiment of compounds of Formula Ig, each R<sup>45</sup> is independently selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower thioalkyl, fluoro substituted lower thioalkyl, mono-alkylamino, di-alkylamino and cycloalkylamino, preferably wherein v is 0, 1, or 2, also 0 or 1, Z<sub>1</sub> is CR<sup>34</sup>, U<sub>1</sub> is CR<sup>35</sup>, and R<sup>34</sup> and R<sup>35</sup> are independently selected from the group consisting of hydrogen, -OR<sup>41</sup>, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -C(O)NH<sub>2</sub>, -OR<sup>42</sup>, -SR<sup>42</sup>, -NHR<sup>42</sup>, -NR<sup>42</sup>R<sup>42</sup>, -NR<sup>39</sup>C(O)R<sup>42</sup>, -NR<sup>39</sup>S(O)<sub>2</sub>R<sup>42</sup>, -S(O)<sub>2</sub>R<sup>42</sup>, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino, and wherein



lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino. In a further embodiment, both of  $R^{34}$  and  $R^{35}$  are hydrogen.

[0057] In one embodiment of compounds of Formula Ig, each  $R^{45}$  is selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower thioalkyl, fluoro substituted lower thioalkyl, mono-alkylamino, di-alkylamino and cycloalkylamino, preferably wherein  $v$  is 0, 1, or 2, also 0 or 1,  $Z_1$  is  $CR^{34}$ ,  $U_1$  is  $CR^{35}$ , one of  $R^{34}$  and  $R^{35}$  is hydrogen, and the other of  $R^{34}$  and  $R^{35}$  is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -C(O)NH<sub>2</sub>, -OR<sup>42</sup>, -SR<sup>42</sup>, -NHR<sup>42</sup>, -NR<sup>42</sup>R<sup>42</sup>, -NR<sup>39</sup>C(O)R<sup>42</sup>, -NR<sup>39</sup>S(O)<sub>2</sub>R<sup>42</sup>, -S(O)<sub>2</sub>R<sup>42</sup>, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino, and wherein lower alkyl and lower alkoxy are optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, further wherein the other of  $R^{34}$  and  $R^{35}$  is selected from the group consisting of halogen, lower alkyl, and lower alkoxy, wherein lower alkyl and lower alkoxy are optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

[0058] In one embodiment of compounds of Formula Ig,  $n$  is 1,  $G_1$  and  $K_1$  are C, and  $E$  is N or C, preferably wherein  $E$  is C,  $M_3$  is selected from the group consisting of -NR<sup>39</sup>-, -O-, -NR<sup>39</sup>CH<sub>2</sub>-, -NR<sup>39</sup>CH(R<sup>40</sup>)-, -SCH<sub>2</sub>-, -OCH<sub>2</sub>-, -CH<sub>2</sub>NR<sup>39</sup>-, -NR<sup>39</sup>C(O)-, and -NR<sup>39</sup>S(O)<sub>2</sub>-, preferably wherein  $M_3$  is -NR<sup>39</sup>CH<sub>2</sub>-, -NR<sup>39</sup>CH(R<sup>40</sup>)-, -SCH<sub>2</sub>-, -OCH<sub>2</sub>-, or -CH<sub>2</sub>NR<sup>39</sup>-, each  $R^{45}$  is selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower thioalkyl, fluoro substituted lower thioalkyl, mono-alkylamino, di-alkylamino and cycloalkylamino, preferably wherein  $v$  is 0, 1, or 2, also 0 or 1,  $Z_1$  is  $CR^{34}$ ,  $U_1$  is  $CR^{35}$ , and  $R^{34}$  and  $R^{35}$  are both hydrogen.



[0059] In one embodiment of compounds of Formula Ig,  $n$  is 1,  $G_1$  and  $K_1$  are C, and E is N or C, preferably wherein E is C,  $M_3$  is selected from the group consisting of  $-NR^{39}$ -,  $-O$ -,  $-NR^{39}CH_2$ -,  $-NR^{39}CH(R^{40})$ -,  $-SCH_2$ -,  $-OCH_2$ -,  $-CH_2NR^{39}$ -,  $-NR^{39}C(O)$ -, and  $-NR^{39}S(O)_2$ -, preferably wherein  $M_3$  is  $-NR^{39}CH_2$ -,  $-NR^{39}CH(R^{40})$ -,  $-SCH_2$ -,  $-OCH_2$ -, or  $-CH_2NR^{39}$ -, each  $R^{45}$  is selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CN$ ,  $-NO_2$ , halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower thioalkyl, fluoro substituted lower thioalkyl, mono-alkylamino, di-alkylamino and cycloalkylamino, preferably wherein  $v$  is 0, 1, or 2, also 0 or 1,  $Z_1$  is  $CR^{34}$  and  $U_1$  is  $CR^{35}$ , and  $R^{34}$  and  $R^{35}$  are independently selected from the group consisting of hydrogen,  $-OR^{41}$ , halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CN$ ,  $-NO_2$ ,  $-S(O)_2NH_2$ ,  $-C(O)NH_2$ ,  $-OR^{42}$ ,  $-SR^{42}$ ,  $-NHR^{42}$ ,  $-NR^{42}R^{42}$ ,  $-NR^{39}C(O)R^{42}$ ,  $-NR^{39}S(O)_2R^{42}$ ,  $-S(O)_2R^{42}$ , halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino, and wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino. In a further embodiment, one of  $R^{34}$  and  $R^{35}$  is hydrogen, and the other of  $R^{34}$  and  $R^{35}$  is selected from the group consisting of halogen, lower alkyl, lower alkoxy, aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CN$ ,  $-NO_2$ ,  $-S(O)_2NH_2$ ,  $-C(O)NH_2$ ,  $-OR^{42}$ ,  $-SR^{42}$ ,  $-NHR^{42}$ ,  $-NR^{42}R^{42}$ ,  $-NR^{39}C(O)R^{42}$ ,  $-NR^{39}S(O)_2R^{42}$ ,  $-S(O)_2R^{42}$ , halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino, and wherein lower alkyl and lower alkoxy are optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, further wherein the other of  $R^{34}$  and  $R^{35}$  is selected from the group consisting of halogen, lower alkyl, and lower alkoxy, wherein lower alkyl and lower alkoxy are optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, further wherein  $R^{34}$  is hydrogen.



[0060] The compounds of Formula Ig, and all sub-embodiments detailed herein, may be used to treat a subject suffering from or at risk of a Kit and/or Fms protein kinase mediated disease or condition, such as those disclosed in this application.

[0061] In certain embodiments of the above compounds, compounds are excluded where N (except where N is a heteroaryl ring atom), O, or S is bound to a carbon that is also bound to N (except where N is a heteroaryl ring atom), O, or S; or where N (except where N is a heteroaryl ring atom), O, C(S), C(O), or S(O)<sub>n</sub> (n is 0-2) is bound to an alkene carbon of an alkenyl group or bound to an alkyne carbon of an alkynyl group; accordingly, in certain embodiments compounds which include linkages such as the following are excluded from the present invention: -NR-CH<sub>2</sub>-NR-, -O-CH<sub>2</sub>-NR-, -S-CH<sub>2</sub>-NR-, -NR-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-O-, -S-CH<sub>2</sub>-O-, -NR-CH<sub>2</sub>-S-, -O-CH<sub>2</sub>-S-, -S-CH<sub>2</sub>-S-, -NR-CH=CH-, -CH=CH-NR-, -NR-C≡C-, -C≡C-NR-, -O-CH=CH-, -CH=CH-O-, -O-C≡C-, -C≡C-O-, -S(O)<sub>0-2</sub>-CH=CH-, -CH=CH-S(O)<sub>0-2</sub>-, -S(O)<sub>0-2</sub>-C≡C-, -C≡C-S(O)<sub>0-2</sub>-, -C(O)-CH=CH-, -CH=CH-C(O)-, -C≡C-C(O)-, or -C(O)-C≡C-, -C(S)-CH=CH-, -CH=CH-C(S)-, -C≡C-C(S)-, or -C(S)-C≡C-.

[0062] In another aspect, the invention provides methods for treating a c-kit-mediated disease or condition in an animal subject (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal c-kit activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of a c-kit-mediated disease or condition an effective amount of a compound of Formula I, Formula Ia, Formula Ib, or Formula Ig, and all sub-embodiments thereof. In one embodiment, the c-kit mediated disease is selected from the group consisting of malignancies, including mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.



**[0063]** In a related aspect, compounds of Formula I, Formula Ia, Formula Ib, or Formula Ig, and all sub-embodiments thereof, can be used in the preparation of a medicament for the treatment of a c-kit-mediated disease or condition selected from the group consisting of malignancies, including mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.

**[0064]** In a further aspect, the invention provides methods for treating a c-fms-mediated disease or condition in an animal subject (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal c-fms activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of a c-fms-mediated disease or condition an effective amount of compound of Formula I, Formula Ia, Formula Ib, or Formula Ig, and all sub-embodiments thereof. In one embodiment, the c-fms mediated disease is selected from the group consisting of immune disorders, including rheumatoid arthritis, systemic lupus erythematosus (SLE), Wegener's granulomatosis, and transplant rejection, inflammatory diseases including Chronic Obstructive Pulmonary Disease (COPD), emphysema, and atherosclerosis, metabolic disorders, including insulin resistance, hyperglycemia, and lipolysis, disorders of bone structure or mineralization, including osteoporosis, increased risk of fracture, hypercalcemia, and bone metastases, kidney diseases, including nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications, and hypertrophy and cancers, including multiple myeloma, acute myeloid leukemia, chronic myeloid leukemia (CML), breast cancer, and ovarian cancer.

**[0065]** In a related aspect, compounds of Formula I, Formula Ia, Formula Ib, or Formula Ig, and all sub-embodiments thereof, can be used in the preparation of a medicament for the treatment of a c-fms-mediated disease or condition selected from the group consisting



of immune disorders, including rheumatoid arthritis, systemic lupus erythematosus (SLE), Wegener's granulomatosis, and transplant rejection, inflammatory diseases including Chronic Obstructive Pulmonary Disease (COPD), emphysema, and atherosclerosis, metabolic disorders, including insulin resistance, hyperglycemia, and lipolysis, disorders of bone structure or mineralization, including osteoporosis, increased risk of fracture, hypercalcemia, and bone metastases, kidney diseases, including nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications, and hypertrophy and cancers, including multiple myeloma, acute myeloid leukemia, chronic myeloid leukemia (CML), breast cancer, and ovarian cancer.

[0066] In a further aspect, the invention provides methods for treating a c-fms-mediated and/or c-kit-mediated disease or condition in an animal subject (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal c-fms activity and/or c-kit activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of a c-fms-mediated and/or c-kit mediated disease or condition an effective amount of compound of Formula I, Formula Ia, Formula Ib, or Formula Ig, and all sub-embodiments thereof. In one embodiment, the c-fms and/or c-kit mediated disease is selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, canine mast cell tumors, hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosus, Wegener's granulomatosis, Chronic Obstructive Pulmonary Disease, emphysema, atherosclerosis, insulin resistance, hyperglycemia, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, hypercalcemia, bone metastases, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, and diabetes-associated renal complications.



[0067] In a related aspect, compounds of Formula I, Formula Ia, Formula Ib, or Formula Ig, and all sub-embodiments thereof, can be used in the preparation of a medicament for the treatment of a c-fms-mediated and/or c-kit mediated disease or condition selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, canine mast cell tumors, hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosus, Wegener's granulomatosis, Chronic Obstructive Pulmonary Disease, emphysema, atherosclerosis, insulin resistance, hyperglycemia, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, hypercalcemia, bone metastases, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, and diabetes-associated renal complications.

[0068] In another aspect, the invention provides methods of using compounds of Formula I, Formula Ia, Formula Ib, or Formula Ig, and all sub-embodiments thereof, as described herein (e.g. compounds that have advantageous levels of activity and/or selectivity on c-kit, c-fms or both c-kit and c-fms). In certain embodiments, the compounds are substituted at the 3-position of the core bicyclic ring structure (azaindole core) with a substituent group that in order includes a first linker bound to a first aryl or heteroaryl group, which is bound to a linker of 1 to 3 atoms bound to a second aryl or heteroaryl group. In certain embodiments including the just-described 3-position substituent group, the first linker is methylene, ethylene, -C(O)-, -C(S)-, -O-, -S-, or -S(O)<sub>2</sub>-; the first aryl or heteroaryl group is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, or oxazolyl; the second linker is methyl amino (NHCH<sub>2</sub>), ethyl amino (NHCH<sub>2</sub>CH<sub>2</sub>), amide (NHC(O)), or sulfonamide (NHSO<sub>2</sub>); the second aryl or heteroaryl group is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, furanyl, or oxazolyl; the second aryl or heteroaryl group is optionally substituted with a lower alkyl group (e.g. a methyl group, an ethyl group, a propyl group, or a butyl group), an alkoxy group (e.g. a methoxy group, an



ethoxy group, a propoxy group, or a butoxy group), a halo substituted lower alkyl (e.g. -CH<sub>2</sub>F, -CHF<sub>2</sub>, or -CF<sub>3</sub>), or halo (e.g. F or Cl). In particular embodiments, the second aryl or heteroaryl group is a 6-membered ring; the 6-membered ring is substituted at the para position; the 6-membered ring is substituted at the meta position; the 6-membered ring is substituted at the ortho position; or the 6-membered ring is substituted at the meta and para positions. In particular embodiments, the second aryl or heteroaryl group is a 5-membered ring; the 5-membered ring is substituted at a position adjacent to the atom bound to the second linker; or the 5-membered ring is substituted at a position not adjacent to the atom bound to the second linker. In particular embodiments, the 3-position substituent group is the only non-hydrogen substituent on the azaindole core.

[0069] In particular embodiments, the compound has an IC<sub>50</sub> of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-kit than on Ret, PDGF, or both Ret and PDGF. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-kit than on c-fms. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-fms than on c-kit. In certain embodiments, the compound has in combination each pairing of activity (e.g. IC<sub>50</sub>) and/or selectivity as specified in this paragraph.

[0070] In particular embodiments, the compound has an IC<sub>50</sub> of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, or less than 5 nM as determined in a generally accepted kinase activity assay for c-kit, c-fms, or both c-kit and c-fms kinase activity. In certain embodiments, the selectivity of the compound is such that the compound is at least 2-fold, 5-fold, 10-fold, or 100-fold more active on c-kit, c-fms, or both c-kit and c-fms than on Ret, PDGF, or both Ret and PDGF.

[0071] An additional aspect of this invention relates to compositions that include a therapeutically effective amount of a compound of Formula I (including Formula Ia, Ib, Ig and all sub-embodiments thereof) and at least one pharmaceutically acceptable carrier, excipient, and/or diluent. The composition can include a plurality of different

pharmacologically active compounds, which can include a plurality of compounds of Formula I (including Formula Ia, Ib, Ig and all sub-embodiments thereof).

[0072] In a related aspect, the invention provides kits that include a composition as described herein. In particular embodiments, the composition is packaged, e.g., in a vial, bottle, flask, which may be further packaged, e.g., within a box, envelope, or bag; the composition is approved by the U.S. Food and Drug Administration or similar regulatory agency for administration to a mammal, e.g., a human; the composition is approved for administration to a mammal, e.g., a human, for a c-kit- and/or c-fms-mediated disease or condition; the kit of the invention includes written instructions on use and/or other indication that the composition is suitable or approved for administration to a mammal, e.g., a human, for a c-kit- and/or c-fms-mediated disease or condition; the composition is packaged in unit dose or single dose form, e.g., single dose pills, capsules, or the like.

[0073] The invention also provides a method for identifying or developing additional compounds active on c-kit and c-fms, e.g., improved modulators, by determining whether any of a plurality of test compounds of Formula I, Formula Ia, Formula Ib, or Formula Ig, and all sub-embodiments thereof, active on c-kit and c-fms provides an improvement in one or more desired pharmacologic properties relative to a reference compound active on c-kit and c-fms, and selecting a compound if any, that has an improvement in the desired pharmacologic property, thereby providing an improved modulator.

[0074] In particular aspects of modulator development, the desired pharmacologic property is serum half-life longer than 2 hr or longer than 4 hr or longer than 8 hr, aqueous solubility, oral bioavailability more than 10%, or oral bioavailability more than 20%.

[0075] Furthermore, in particular aspects of modulator development, the process can be repeated multiple times, i.e., multiple rounds of preparation of derivatives and/or selection of additional related compounds and evaluation of such further derivatives of related compounds can be carried out, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more additional rounds.

[0076] In another aspect, the present invention also provides a method for modulating c-kit or c-fms activity by contacting c-kit or c-fms with an effective amount of a compound of Formula I (including Formula Ia, Ib, Ig and all sub-embodiments thereof) active on c-kit and/or c-fms (such as compounds developed using methods described



herein). The compound is preferably provided at a level sufficient to modulate the activity of the c-kit or c-fms by at least 10%, more preferably at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater than 90%. In many embodiments, the compound will be at a concentration of about 1  $\mu$ M, 100  $\mu$ M, or 1 mM, or in a range of 1-100 nM, 100-500 nM, 500-1000 nM, 1-100  $\mu$ M, 100-500  $\mu$ M, or 500-1000  $\mu$ M. In particular embodiments, the contacting is carried out *in vitro*.

[0077] Additional aspects and embodiments will be apparent from the following Detailed Description and from the claims.

### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0078] As used herein the following definitions apply:

[0079] "Halo" and "halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0080] "Hydroxyl" and "hydroxy" refer to the group -OH.

[0081] "Thiol" refers to the group -SH.

[0082] "Lower alkyl" alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless specifically defined) that includes a straight chain alkyl or branched alkyl. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. In many embodiments, a lower alkyl is a straight or branched alkyl group containing from 1-6, 1-4, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. "Optionally substituted lower alkyl" denotes lower alkyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of -F, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>a</sup>, -SR<sup>a</sup>, -OC(O)R<sup>a</sup>, -OC(S)R<sup>a</sup>, -C(O)R<sup>a</sup>, -C(S)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(S)OR<sup>a</sup>, -S(O)R<sup>a</sup>, -S(O)<sub>2</sub>R<sup>a</sup>, -C(O)NHR<sup>a</sup>, -C(S)NHR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>a</sup>, -C(S)NR<sup>a</sup>R<sup>a</sup>, -S(O)<sub>2</sub>NHR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -C(NH)NHR<sup>a</sup>, -C(NH)NR<sup>b</sup>R<sup>c</sup>, -NHC(O)R<sup>a</sup>, -NHC(S)R<sup>a</sup>, -NR<sup>a</sup>C(O)R<sup>a</sup>, -NR<sup>a</sup>C(S)R<sup>a</sup>,

-NHS(O)<sub>2</sub>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -NHC(O)NHR<sup>a</sup>, -NHC(S)NHR<sup>a</sup>, -NR<sup>a</sup>C(O)NH<sub>2</sub>,  
 -NR<sup>a</sup>C(S)NH<sub>2</sub>, -NR<sup>a</sup>C(O)NHR<sup>a</sup>, -NR<sup>a</sup>C(S)NHR<sup>a</sup>, -NHC(O)NR<sup>a</sup>R<sup>a</sup>, -NHC(S)NR<sup>a</sup>R<sup>a</sup>,  
 -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(S)NR<sup>a</sup>R<sup>a</sup>, -NHS(O)<sub>2</sub>NHR<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>a</sup>S(O)<sub>2</sub>NHR<sup>a</sup>,  
 -NHS(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NHR<sup>a</sup>, -NR<sup>a</sup>R<sup>a</sup>, -R<sup>e</sup>, -R<sup>f</sup>, and -R<sup>g</sup>. Further, possible  
 substitutions include subsets of these substitutions, such as are indicated herein, for  
 example, in the description of compounds of Formula I (including Formulae Ia, Ib, Ig and  
 all sub-embodiments thereof), attached at any available atom to produce a stable  
 compound. For example "fluoro substituted lower alkyl" denotes a lower alkyl group  
 substituted with one or more fluoro atoms, such as perfluoroalkyl, where preferably the  
 lower alkyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms.  
 While it is understood that substitutions are attached at any available atom to produce a  
 stable compound, when optionally substituted alkyl is an R group of a moiety such as -OR,  
 -NHR, -C(O)NHR, and the like, substitution of the alkyl R group is such that substitution  
 of the alkyl carbon bound to any -O-, -S-, or -N- of the moiety (except where -N- is a  
 heteroaryl ring atom) excludes substituents that would result in any -O-, -S-, or -N- of the  
 substituent (except where -N- is a heteroaryl ring atom) being bound to the alkyl carbon  
 bound to any -O-, -S-, or -N- of the moiety.

[0083] "Lower alkylene" refers to a divalent alkane-derived radical containing 1-6  
 carbon atoms, straight chain or branched, from which two hydrogen atoms are taken from  
 the same carbon atom or from different carbon atoms. Examples of lower alkylene  
 include, but are not limited to, methylene -CH<sub>2</sub>-, ethylene -CH<sub>2</sub>CH<sub>2</sub>-, propylene  
 -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, isopropylene -CH(CH<sub>3</sub>)CH-, and the like. "Optionally substituted lower  
 alkylene" denotes lower alkylene that is independently substituted, unless indicated  
 otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached  
 at any available atom to produce a stable compound, wherein the substituents are selected  
 from the group consisting of -F, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>,  
 -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>a</sup>,  
 -SR<sup>a</sup>, -OC(O)R<sup>a</sup>, -OC(S)R<sup>a</sup>, -C(O)R<sup>a</sup>, -C(S)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(S)OR<sup>a</sup>, -S(O)R<sup>a</sup>, -S(O)<sub>2</sub>R<sup>a</sup>,  
 -C(O)NHR<sup>a</sup>, -C(S)NHR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>a</sup>, -C(S)NR<sup>a</sup>R<sup>a</sup>, -S(O)<sub>2</sub>NHR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>,  
 -C(NH)NHR<sup>a</sup>, -C(NH)NR<sup>b</sup>R<sup>c</sup>, -NHC(O)R<sup>a</sup>, -NHC(S)R<sup>a</sup>, -NR<sup>a</sup>C(O)R<sup>a</sup>, -NR<sup>a</sup>C(S)R<sup>a</sup>,  
 -NHS(O)<sub>2</sub>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -NHC(O)NHR<sup>a</sup>, -NHC(S)NHR<sup>a</sup>, -NR<sup>a</sup>C(O)NHR<sup>a</sup>,  
 -NR<sup>a</sup>C(S)NH<sub>2</sub>, -NR<sup>a</sup>C(S)NHR<sup>a</sup>, -NHC(O)NR<sup>a</sup>R<sup>a</sup>, -NHC(S)NR<sup>a</sup>R<sup>a</sup>,



-NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(S)NR<sup>a</sup>R<sup>a</sup>, -NHS(O)<sub>2</sub>NHR<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>a</sup>S(O)<sub>2</sub>NHR<sup>a</sup>, -NHS(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NHR<sup>a</sup>, -NR<sup>a</sup>R<sup>a</sup>, -R<sup>e</sup>, -R<sup>f</sup>, and -R<sup>g</sup>, or two substituents on any one carbon or a substituent on each of any two carbons in the alkylene chain may join to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

**[0084]** "Lower alkenyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. Carbon to carbon double bonds may be either contained within a straight chain or branched portion. Examples of lower alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and the like. "Substituted lower alkenyl" denotes lower alkenyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of -F, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>a</sup>, -SR<sup>a</sup>, -OC(O)R<sup>a</sup>, -OC(S)R<sup>a</sup>, -C(O)R<sup>a</sup>, -C(S)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(S)OR<sup>a</sup>, -S(O)R<sup>a</sup>, -S(O)<sub>2</sub>R<sup>a</sup>, -C(O)NHR<sup>a</sup>, -C(S)NHR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>a</sup>, -C(S)NR<sup>a</sup>R<sup>a</sup>, -S(O)<sub>2</sub>NHR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -C(NH)NHR<sup>a</sup>, -C(NH)NR<sup>b</sup>R<sup>c</sup>, -NHC(O)R<sup>a</sup>, -NHC(S)R<sup>a</sup>, -NR<sup>a</sup>C(O)R<sup>a</sup>, -NR<sup>a</sup>C(S)R<sup>a</sup>, -NHS(O)<sub>2</sub>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -NHC(O)NHR<sup>a</sup>, -NHC(S)NHR<sup>a</sup>, -NR<sup>a</sup>C(O)NH<sub>2</sub>, -NR<sup>a</sup>C(S)NH<sub>2</sub>, -NR<sup>a</sup>C(O)NHR<sup>a</sup>, -NR<sup>a</sup>C(S)NHR<sup>a</sup>, -NHC(O)NR<sup>a</sup>R<sup>a</sup>, -NHC(S)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(S)NR<sup>a</sup>R<sup>a</sup>, -NHS(O)<sub>2</sub>NHR<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>a</sup>S(O)<sub>2</sub>NHR<sup>a</sup>, -NHS(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NHR<sup>a</sup>, -NR<sup>a</sup>R<sup>a</sup>, -R<sup>d</sup>, -R<sup>f</sup>, and -R<sup>g</sup>. Further, possible substitutions include subsets of these substitutions, such as are indicated herein, for example, in the description of compounds of Formula I (including Formulae Ia, Ib, Ig and all sub-embodiments thereof), attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkenyl" denotes a lower alkenyl group substituted with one or more fluoro atoms, where preferably the lower alkenyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro



atoms. While it is understood that substitutions are attached at any available atom to produce a stable compound, substitution of alkenyl groups are such that -F, -C(O)-, -C(S)-, -C(NH)-, -S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- (except where -N- is a heteroaryl ring atom), are not bound to an alkene carbon thereof. Further, where alkenyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)R, and the like, substitution of the moiety is such that any -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- thereof (except where -N- is a heteroaryl ring atom) are not bound to an alkene carbon of the alkenyl substituent or R group. Further, where alkenyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the alkenyl R group is such that substitution of the alkenyl carbon bound to any -O-, -S-, or -N- of the moiety (except where -N- is a heteroaryl ring atom) excludes substituents that would result in any -O-, -S-, or -N- of the substituent (except where -N- is a heteroaryl ring atom) being bound to the alkenyl carbon bound to any -O-, -S-, or -N- of the moiety. An "alkenyl carbon" refers to any carbon within an alkenyl group, whether saturated or part of the carbon to carbon double bond. An "alkene carbon" refers to a carbon within an alkenyl group that is part of a carbon to carbon double bond.

[0085] "Lower alkynyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl, and the like. "Substituted lower alkynyl" denotes lower alkynyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of -F, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>a</sup>, -SR<sup>a</sup>, -OC(O)R<sup>a</sup>, -OC(S)R<sup>a</sup>, -C(O)R<sup>a</sup>, -C(S)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(S)OR<sup>a</sup>, -S(O)R<sup>a</sup>, -S(O)<sub>2</sub>R<sup>a</sup>, -C(O)NHR<sup>a</sup>, -C(S)NHR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>a</sup>, -C(S)NR<sup>a</sup>R<sup>a</sup>, -S(O)<sub>2</sub>NHR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -C(NH)NHR<sup>a</sup>, -C(NH)NR<sup>b</sup>R<sup>c</sup>, -NHC(O)R<sup>a</sup>, -NHC(S)R<sup>a</sup>, -NR<sup>a</sup>C(O)R<sup>a</sup>, -NR<sup>a</sup>C(S)R<sup>a</sup>, -NHS(O)<sub>2</sub>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -NHC(O)NHR<sup>a</sup>, -NHC(S)NHR<sup>a</sup>, -NR<sup>a</sup>C(O)NH<sub>2</sub>, -NR<sup>a</sup>C(S)NH<sub>2</sub>, -NR<sup>a</sup>C(O)NHR<sup>a</sup>, -NR<sup>a</sup>C(S)NHR<sup>a</sup>, -NHC(O)NR<sup>a</sup>R<sup>a</sup>, -NHC(S)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(S)NR<sup>a</sup>R<sup>a</sup>, -NHS(O)<sub>2</sub>NHR<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>a</sup>S(O)<sub>2</sub>NHR<sup>a</sup>, -NHS(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NHR<sup>a</sup>, -NR<sup>a</sup>R<sup>a</sup>, -R<sup>d</sup>, -R<sup>e</sup>, and -R<sup>g</sup>. Further, possible



substitutions include subsets of these substitutions, such as are indicated herein, for example, in the description of compounds of Formula I (including Formulae Ia, Ib, Ig and all sub-embodiments thereof), attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkynyl" denotes a lower alkynyl group substituted with one or more fluoro atoms, where preferably the lower alkynyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions are attached at any available atom to produce a stable compound, substitution of alkynyl groups are such that -F, -C(O)-, -C(S)-, -C(NH)-, -S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- (except where -N- is a heteroaryl ring atom), are not bound to an alkyne carbon thereof. Further, where alkynyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)R, and the like, substitution of the moiety is such that any -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- thereof (except where -N- is a heteroaryl ring atom) are not bound to an alkyne carbon of the alkynyl substituent or R group. Further, where alkynyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the alkynyl R group is such that substitution of the alkynyl carbon bound to any -O-, -S-, or -N- of the moiety (except where -N- is a heteroaryl ring atom) excludes substituents that would result in any -O-, -S-, or -N- of the substituent (except where -N- is a heteroaryl ring atom) being bound to the alkynyl carbon bound to any -O-, -S-, or -N- of the moiety. An "alkynyl carbon" refers to any carbon within an alkynyl group, whether saturated or part of the carbon to carbon triple bond. An "alkyne carbon" refers to a carbon within an alkynyl group that is part of a carbon to carbon triple bond.

[0086] "Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-10, also 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like. "Cycloalkylene" is a divalent cycloalkyl. A "substituted cycloalkyl" is a cycloalkyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>a</sup>, -SR<sup>a</sup>, -OC(O)R<sup>a</sup>, -OC(S)R<sup>a</sup>, -C(O)R<sup>a</sup>, -C(S)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(S)OR<sup>a</sup>, -S(O)R<sup>a</sup>, -S(O)<sub>2</sub>R<sup>a</sup>, -C(O)NHR<sup>a</sup>,



-C(S)NHR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>a</sup>, -C(S)NR<sup>a</sup>R<sup>a</sup>, -S(O)<sub>2</sub>NHR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -C(NH)NHR<sup>a</sup>,  
 -C(NH)NR<sup>b</sup>R<sup>c</sup>, -NHC(O)R<sup>a</sup>, -NHC(S)R<sup>a</sup>, -NR<sup>a</sup>C(O)R<sup>a</sup>, -NR<sup>a</sup>C(S)R<sup>a</sup>, -NHS(O)<sub>2</sub>R<sup>a</sup>,  
 -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -NHC(O)NHR<sup>a</sup>, -NHC(S)NHR<sup>a</sup>, -NR<sup>a</sup>C(O)NH<sub>2</sub>, -NR<sup>a</sup>C(S)NH<sub>2</sub>,  
 -NR<sup>a</sup>C(O)NHR<sup>a</sup>, -NR<sup>a</sup>C(S)NHR<sup>a</sup>, -NHC(O)NR<sup>a</sup>R<sup>a</sup>, -NHC(S)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>a</sup>,  
 -NR<sup>a</sup>C(S)NR<sup>a</sup>R<sup>a</sup>, -NHS(O)<sub>2</sub>NHR<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>a</sup>S(O)<sub>2</sub>NHR<sup>a</sup>, -NHS(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>,  
 -NR<sup>a</sup>S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NHR<sup>a</sup>, -NR<sup>a</sup>R<sup>a</sup>, -R<sup>d</sup>, -R<sup>e</sup>, -R<sup>f</sup>, and -R<sup>g</sup>. "Substituted cycloalkylene" is a  
 divalent substituted cycloalkyl.

[0087] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally fused with benzo or heteroaryl of 5-6 ring members. Heterocycloalkyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. Heterocycloalkyl is also intended to include compounds in which one of the ring carbons is oxo substituted, i.e. the ring carbon is a carbonyl group, such as lactones and lactams. The point of attachment of the heterocycloalkyl ring is at a carbon or nitrogen atom such that a stable ring is retained. Examples of heterocycloalkyl groups include, but are not limited to, morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, pyrrolidonyl, piperazinyl, dihydrobenzofuryl, and dihydroindolyl. "Heterocycloalkylene" is a divalent heterocycloalkyl. A "substituted heterocycloalkyl" is a heterocycloalkyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>a</sup>, -SR<sup>a</sup>, -OC(O)R<sup>a</sup>, -OC(S)R<sup>a</sup>, -C(O)R<sup>a</sup>, -C(S)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(S)OR<sup>a</sup>, -S(O)R<sup>a</sup>, -S(O)<sub>2</sub>R<sup>a</sup>, -C(O)NHR<sup>a</sup>, -C(S)NHR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>a</sup>, -C(S)NR<sup>a</sup>R<sup>a</sup>, -S(O)<sub>2</sub>NHR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -C(NH)NHR<sup>a</sup>, -C(NH)NR<sup>b</sup>R<sup>c</sup>, -NHC(O)R<sup>a</sup>, -NHC(S)R<sup>a</sup>, -NR<sup>a</sup>C(O)R<sup>a</sup>, -NR<sup>a</sup>C(S)R<sup>a</sup>, -NHS(O)<sub>2</sub>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -NHC(O)NHR<sup>a</sup>, -NHC(S)NHR<sup>a</sup>, -NR<sup>a</sup>C(O)NH<sub>2</sub>, -NR<sup>a</sup>C(S)NH<sub>2</sub>, -NR<sup>a</sup>C(O)NHR<sup>a</sup>, -NR<sup>a</sup>C(S)NHR<sup>a</sup>, -NHC(O)NR<sup>a</sup>R<sup>a</sup>, -NHC(S)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(S)NR<sup>a</sup>R<sup>a</sup>, -NHS(O)<sub>2</sub>NHR<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>a</sup>S(O)<sub>2</sub>NHR<sup>a</sup>, -NHS(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NHR<sup>a</sup>, -NR<sup>a</sup>R<sup>a</sup>, -R<sup>d</sup>, -R<sup>e</sup>, -R<sup>f</sup>, and -R<sup>g</sup>. "Substituted heterocycloalkylene" is a divalent substituted heterocycloalkyl.



[0088] "Aryl" alone or in combination refers to a monocyclic or bicyclic ring system containing aromatic hydrocarbons such as phenyl or naphthyl, which may be optionally fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members. "Arylene" is a divalent aryl. A "substituted aryl" is an aryl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>a</sup>, -SR<sup>a</sup>, -OC(O)R<sup>a</sup>, -OC(S)R<sup>a</sup>, -C(O)R<sup>a</sup>, -C(S)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(S)OR<sup>a</sup>, -S(O)R<sup>a</sup>, -S(O)<sub>2</sub>R<sup>a</sup>, -C(O)NHR<sup>a</sup>, -C(S)NHR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>a</sup>, -C(S)NR<sup>a</sup>R<sup>a</sup>, -S(O)<sub>2</sub>NHR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -C(NH)NHR<sup>a</sup>, -C(NH)NR<sup>b</sup>R<sup>c</sup>, -NHC(O)R<sup>a</sup>, -NHC(S)R<sup>a</sup>, -NR<sup>a</sup>C(O)R<sup>a</sup>, -NR<sup>a</sup>C(S)R<sup>a</sup>, -NHS(O)<sub>2</sub>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -NHC(O)NHR<sup>a</sup>, -NHC(S)NHR<sup>a</sup>, -NR<sup>a</sup>C(O)NH<sub>2</sub>, -NR<sup>a</sup>C(S)NH<sub>2</sub>, -NR<sup>a</sup>C(O)NHR<sup>a</sup>, -NR<sup>a</sup>C(S)NHR<sup>a</sup>, -NHC(O)NR<sup>a</sup>R<sup>a</sup>, -NHC(S)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(S)NR<sup>a</sup>R<sup>a</sup>, -NHS(O)<sub>2</sub>NHR<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>a</sup>S(O)<sub>2</sub>NHR<sup>a</sup>, -NHS(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NHR<sup>a</sup>, -NR<sup>a</sup>R<sup>a</sup>, -R<sup>d</sup>, -R<sup>e</sup>, -R<sup>f</sup>, and -R<sup>g</sup>. A "substituted arylene" is a divalent substituted aryl.

[0089] "Heteroaryl" alone or in combination refers to a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, and indolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any heteroatoms are N. "Heteroarylene" is a divalent heteroaryl. A "substituted heteroaryl" is a heteroaryl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN,



-C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>a</sup>, -SR<sup>a</sup>, -OC(O)R<sup>a</sup>, -OC(S)R<sup>a</sup>, -C(O)R<sup>a</sup>, -C(S)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(S)OR<sup>a</sup>, -S(O)R<sup>a</sup>, -S(O)<sub>2</sub>R<sup>a</sup>, -C(O)NHR<sup>a</sup>, -C(S)NHR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>a</sup>, -C(S)NR<sup>a</sup>R<sup>a</sup>, -S(O)<sub>2</sub>NHR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -C(NH)NHR<sup>a</sup>, -C(NH)NR<sup>b</sup>R<sup>c</sup>, -NHC(O)R<sup>a</sup>, -NHC(S)R<sup>a</sup>, -NR<sup>a</sup>C(O)R<sup>a</sup>, -NR<sup>a</sup>C(S)R<sup>a</sup>, -NHS(O)<sub>2</sub>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -NHC(O)NHR<sup>a</sup>, -NHC(S)NHR<sup>a</sup>, -NR<sup>a</sup>C(O)NH<sub>2</sub>, -NR<sup>a</sup>C(S)NH<sub>2</sub>, -NR<sup>a</sup>C(O)NHR<sup>a</sup>, -NR<sup>a</sup>C(S)NHR<sup>a</sup>, -NHC(O)NR<sup>a</sup>R<sup>a</sup>, -NHC(S)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>C(S)NR<sup>a</sup>R<sup>a</sup>, -NHS(O)<sub>2</sub>NHR<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>a</sup>S(O)<sub>2</sub>NHR<sup>a</sup>, -NHS(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a</sup>, -NHR<sup>a</sup>, -NR<sup>a</sup>R<sup>a</sup>, -R<sup>d</sup>, -R<sup>e</sup>, -R<sup>f</sup>, and -R<sup>g</sup>. "Substituted heteroarylene" is a divalent substituted heteroaryl.

[0090] The variables R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, -R<sup>d</sup>, -R<sup>e</sup>, -R<sup>f</sup> and -R<sup>g</sup> as used in the description of optional substituents for alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are defined as follows:

each R<sup>a</sup>, R<sup>b</sup>, and R<sup>c</sup> are independently selected from the group consisting of -R<sup>d</sup>, -R<sup>e</sup>, -R<sup>f</sup>, and -R<sup>g</sup>, or R<sup>b</sup> and R<sup>c</sup> combine with the nitrogen to which they are attached to form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -NO<sub>2</sub>, -CN, -OH, -NH<sub>2</sub>, -OR<sup>u</sup>, -SR<sup>u</sup>, -NHR<sup>u</sup>, -NR<sup>u</sup>R<sup>u</sup>, -R<sup>x</sup>, and -R<sup>y</sup>;

each -R<sup>d</sup> is independently lower alkyl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>k</sup>, -SR<sup>k</sup>, -OC(O)R<sup>k</sup>, -OC(S)R<sup>k</sup>, -C(O)R<sup>k</sup>, -C(S)R<sup>k</sup>, -C(O)OR<sup>k</sup>, -C(S)OR<sup>k</sup>, -S(O)R<sup>k</sup>, -S(O)<sub>2</sub>R<sup>k</sup>, -C(O)NHR<sup>k</sup>, -C(S)NHR<sup>k</sup>, -C(O)NR<sup>k</sup>R<sup>k</sup>, -C(S)NR<sup>k</sup>R<sup>k</sup>, -S(O)<sub>2</sub>NHR<sup>k</sup>, -S(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -C(NH)NHR<sup>k</sup>, -C(NH)NR<sup>m</sup>R<sup>n</sup>, -NHC(O)R<sup>k</sup>, -NHC(S)R<sup>k</sup>, -NR<sup>k</sup>C(O)R<sup>k</sup>, -NR<sup>k</sup>C(S)R<sup>k</sup>, -NHS(O)<sub>2</sub>R<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>R<sup>k</sup>, -NHC(O)NHR<sup>k</sup>, -NHC(S)NHR<sup>k</sup>, -NR<sup>k</sup>C(O)NH<sub>2</sub>, -NR<sup>k</sup>C(S)NH<sub>2</sub>, -NR<sup>k</sup>C(O)NHR<sup>k</sup>, -NR<sup>k</sup>C(S)NHR<sup>k</sup>, -NHC(O)NR<sup>k</sup>R<sup>k</sup>, -NHC(S)NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>C(O)NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>C(S)NR<sup>k</sup>R<sup>k</sup>, -NHS(O)<sub>2</sub>NHR<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>k</sup>S(O)<sub>2</sub>NHR<sup>k</sup>, -NHS(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -NHR<sup>k</sup>, -NR<sup>k</sup>R<sup>k</sup>, -R<sup>i</sup>, and -R<sup>j</sup>;



each  $-R^e$  is independently lower alkenyl, wherein lower alkenyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>k</sup>, -SR<sup>k</sup>, -OC(O)R<sup>k</sup>, -OC(S)R<sup>k</sup>, -C(O)R<sup>k</sup>, -C(S)R<sup>k</sup>, -C(O)OR<sup>k</sup>, -C(S)OR<sup>k</sup>, -S(O)R<sup>k</sup>, -S(O)<sub>2</sub>R<sup>k</sup>, -C(O)NHR<sup>k</sup>, -C(S)NHR<sup>k</sup>, -C(O)NR<sup>k</sup>R<sup>k</sup>, -C(S)NR<sup>k</sup>R<sup>k</sup>, -S(O)<sub>2</sub>NHR<sup>k</sup>, -S(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -C(NH)NHR<sup>k</sup>, -C(NH)NR<sup>m</sup>R<sup>n</sup>, -NHC(O)R<sup>k</sup>, -NHC(S)R<sup>k</sup>, -NR<sup>k</sup>C(O)R<sup>k</sup>, -NR<sup>k</sup>C(S)R<sup>k</sup>, -NHS(O)<sub>2</sub>R<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>R<sup>k</sup>, -NHC(O)NHR<sup>k</sup>, -NHC(S)NHR<sup>k</sup>, -NR<sup>k</sup>C(O)NH<sub>2</sub>, -NR<sup>k</sup>C(S)NH<sub>2</sub>, -NR<sup>k</sup>C(O)NHR<sup>k</sup>, -NR<sup>k</sup>C(S)NHR<sup>k</sup>, -NHC(O)NR<sup>k</sup>R<sup>k</sup>, -NHC(S)NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>C(O)NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>C(S)NR<sup>k</sup>R<sup>k</sup>, -NHS(O)<sub>2</sub>NHR<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>k</sup>S(O)<sub>2</sub>NHR<sup>k</sup>, -NHS(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -NHR<sup>k</sup>, -NR<sup>k</sup>R<sup>k</sup>, -R<sup>h</sup>, and -R<sup>j</sup>;

each  $-R^f$  is independently lower alkynyl, wherein lower alkynyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>k</sup>, -SR<sup>k</sup>, -OC(O)R<sup>k</sup>, -OC(S)R<sup>k</sup>, -C(O)R<sup>k</sup>, -C(S)R<sup>k</sup>, -C(O)OR<sup>k</sup>, -C(S)OR<sup>k</sup>, -S(O)R<sup>k</sup>, -S(O)<sub>2</sub>R<sup>k</sup>, -C(O)NHR<sup>k</sup>, -C(S)NHR<sup>k</sup>, -C(O)NR<sup>k</sup>R<sup>k</sup>, -C(S)NR<sup>k</sup>R<sup>k</sup>, -S(O)<sub>2</sub>NHR<sup>k</sup>, -S(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -C(NH)NHR<sup>k</sup>, -C(NH)NR<sup>m</sup>R<sup>n</sup>, -NHC(O)R<sup>k</sup>, -NHC(S)R<sup>k</sup>, -NR<sup>k</sup>C(O)R<sup>k</sup>, -NR<sup>k</sup>C(S)R<sup>k</sup>, -NHS(O)<sub>2</sub>R<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>R<sup>k</sup>, -NHC(O)NHR<sup>k</sup>, -NHC(S)NHR<sup>k</sup>, -NR<sup>k</sup>C(O)NH<sub>2</sub>, -NR<sup>k</sup>C(S)NH<sub>2</sub>, -NR<sup>k</sup>C(O)NHR<sup>k</sup>, -NR<sup>k</sup>C(S)NHR<sup>k</sup>, -NHC(O)NR<sup>k</sup>R<sup>k</sup>, -NHC(S)NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>C(O)NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>C(S)NR<sup>k</sup>R<sup>k</sup>, -NHS(O)<sub>2</sub>NHR<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>k</sup>S(O)<sub>2</sub>NHR<sup>k</sup>, -NHS(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -NHR<sup>k</sup>, -NR<sup>k</sup>R<sup>k</sup>, -R<sup>h</sup>, and -R<sup>j</sup>;

each  $-R^g$  is independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>k</sup>, -SR<sup>k</sup>, -OC(O)R<sup>k</sup>, -OC(S)R<sup>k</sup>, -C(O)R<sup>k</sup>, -C(S)R<sup>k</sup>, -C(O)OR<sup>k</sup>, -C(S)OR<sup>k</sup>, -S(O)R<sup>k</sup>, -S(O)<sub>2</sub>R<sup>k</sup>, -C(O)NHR<sup>k</sup>, -C(S)NHR<sup>k</sup>, -C(O)NR<sup>k</sup>R<sup>k</sup>, -C(S)NR<sup>k</sup>R<sup>k</sup>, -S(O)<sub>2</sub>NHR<sup>k</sup>, -S(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -C(NH)NHR<sup>k</sup>, -C(NH)NR<sup>m</sup>R<sup>n</sup>, -NHC(O)R<sup>k</sup>, -NHC(S)R<sup>k</sup>, -NR<sup>k</sup>C(O)R<sup>k</sup>, -NR<sup>k</sup>C(S)R<sup>k</sup>, -NHS(O)<sub>2</sub>R<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>R<sup>k</sup>, -NHC(O)NHR<sup>k</sup>, -NHC(S)NHR<sup>k</sup>, -NR<sup>k</sup>C(O)NH<sub>2</sub>, -NR<sup>k</sup>C(S)NH<sub>2</sub>, -NR<sup>k</sup>C(O)NHR<sup>k</sup>, -NR<sup>k</sup>C(S)NHR<sup>k</sup>,



-NHC(O)NR<sup>k</sup>R<sup>k</sup>, -NHC(S)NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>C(O)NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>C(S)NR<sup>k</sup>R<sup>k</sup>, -NHS(O)<sub>2</sub>NHR<sup>k</sup>,  
 -NR<sup>k</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>k</sup>S(O)<sub>2</sub>NHR<sup>k</sup>, -NHS(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -NR<sup>k</sup>S(O)<sub>2</sub>NR<sup>k</sup>R<sup>k</sup>, -NHR<sup>k</sup>, -NR<sup>k</sup>R<sup>k</sup>,  
 -R<sup>h</sup>, -R<sup>i</sup>, and -R<sup>j</sup>;

wherein R<sup>k</sup>, R<sup>m</sup>, and R<sup>n</sup> at each occurrence are independently selected from the group consisting of -R<sup>h</sup>, -R<sup>i</sup>, and -R<sup>j</sup>, or R<sup>m</sup> and R<sup>n</sup> combine with the nitrogen to which they are attached form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -NO<sub>2</sub>, -CN, -OH, -NH<sub>2</sub>, OR<sup>u</sup>, -SR<sup>u</sup>, -NHR<sup>u</sup>, -NR<sup>u</sup>R<sup>u</sup>, -R<sup>x</sup>, and -R<sup>y</sup>;

wherein each -R<sup>h</sup> is independently lower alkyl optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>f</sup>, -SR<sup>f</sup>, -OC(O)R<sup>f</sup>, -OC(S)R<sup>f</sup>, -C(O)R<sup>f</sup>, -C(S)R<sup>f</sup>, -C(O)OR<sup>f</sup>, -C(S)OR<sup>f</sup>, -S(O)R<sup>f</sup>, -S(O)<sub>2</sub>R<sup>f</sup>, -C(O)NHR<sup>f</sup>, -C(S)NHR<sup>f</sup>, -C(O)NR<sup>f</sup>R<sup>f</sup>, -C(S)NR<sup>f</sup>R<sup>f</sup>, -S(O)<sub>2</sub>NHR<sup>f</sup>, -S(O)<sub>2</sub>NR<sup>f</sup>R<sup>f</sup>, -C(NH)NHR<sup>f</sup>, -C(NH)NR<sup>s</sup>R<sup>f</sup>, -NHC(O)R<sup>f</sup>, -NHC(S)R<sup>f</sup>, -NR<sup>f</sup>C(O)R<sup>f</sup>, -NR<sup>f</sup>C(S)R<sup>f</sup>, -NHS(O)<sub>2</sub>R<sup>f</sup>, -NR<sup>f</sup>S(O)<sub>2</sub>R<sup>f</sup>, -NHC(O)NHR<sup>f</sup>, -NHC(S)NHR<sup>f</sup>, -NR<sup>f</sup>C(O)NH<sub>2</sub>, -NR<sup>f</sup>C(S)NH<sub>2</sub>, -NR<sup>f</sup>C(O)NHR<sup>f</sup>, -NR<sup>f</sup>C(S)NHR<sup>f</sup>, -NHC(O)NR<sup>f</sup>R<sup>f</sup>, -NHC(S)NR<sup>f</sup>R<sup>f</sup>, -NR<sup>f</sup>C(O)NR<sup>f</sup>R<sup>f</sup>, -NR<sup>f</sup>C(S)NR<sup>f</sup>R<sup>f</sup>, -NHS(O)<sub>2</sub>NHR<sup>f</sup>, -NR<sup>f</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>f</sup>S(O)<sub>2</sub>NHR<sup>f</sup>, -NHS(O)<sub>2</sub>NR<sup>f</sup>R<sup>f</sup>, -NR<sup>f</sup>S(O)<sub>2</sub>NR<sup>f</sup>R<sup>f</sup>, -NHR<sup>f</sup>, -NR<sup>f</sup>R<sup>f</sup>, -R<sup>i</sup>, and -R<sup>j</sup>;

wherein each -R<sup>i</sup> is independently selected from the group consisting of lower alkenyl and lower alkynyl, wherein lower alkenyl or lower alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>f</sup>, -SR<sup>f</sup>, -OC(O)R<sup>f</sup>, -OC(S)R<sup>f</sup>, -C(O)R<sup>f</sup>, -C(S)R<sup>f</sup>, -C(O)OR<sup>f</sup>, -C(S)OR<sup>f</sup>, -S(O)R<sup>f</sup>, -S(O)<sub>2</sub>R<sup>f</sup>, -C(O)NHR<sup>f</sup>, -C(S)NHR<sup>f</sup>, -C(O)NR<sup>f</sup>R<sup>f</sup>, -C(S)NR<sup>f</sup>R<sup>f</sup>, -S(O)<sub>2</sub>NHR<sup>f</sup>, -S(O)<sub>2</sub>NR<sup>f</sup>R<sup>f</sup>, -C(NH)NHR<sup>f</sup>, -C(NH)NR<sup>s</sup>R<sup>f</sup>, -NHC(O)R<sup>f</sup>, -NHC(S)R<sup>f</sup>, -NR<sup>f</sup>C(O)R<sup>f</sup>, -NR<sup>f</sup>C(S)R<sup>f</sup>, -NHS(O)<sub>2</sub>R<sup>f</sup>, -NR<sup>f</sup>S(O)<sub>2</sub>R<sup>f</sup>, -NHC(O)NHR<sup>f</sup>, -NHC(S)NHR<sup>f</sup>, -NR<sup>f</sup>C(O)NH<sub>2</sub>, -NR<sup>f</sup>C(S)NH<sub>2</sub>, -NR<sup>f</sup>C(O)NHR<sup>f</sup>, -NR<sup>f</sup>C(S)NHR<sup>f</sup>, -NHC(O)NR<sup>f</sup>R<sup>f</sup>,



-NHC(S)NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>C(O)NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>C(S)NR<sup>r</sup>R<sup>r</sup>, -NHS(O)<sub>2</sub>NHR<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>NH<sub>2</sub>,  
-NR<sup>r</sup>S(O)<sub>2</sub>NHR<sup>r</sup>, -NHS(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -NHR<sup>r</sup>, -NR<sup>r</sup>R<sup>r</sup>, and -R<sup>j</sup>;

wherein each -R<sup>j</sup> is independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, -OR<sup>r</sup>, -SR<sup>r</sup>, -OC(O)R<sup>r</sup>, -OC(S)R<sup>r</sup>, -C(O)R<sup>r</sup>, -C(S)R<sup>r</sup>, -C(O)OR<sup>r</sup>, -C(S)OR<sup>r</sup>, -S(O)R<sup>r</sup>, -S(O)<sub>2</sub>R<sup>r</sup>, -C(O)NHR<sup>r</sup>, -C(S)NHR<sup>r</sup>, -C(O)NR<sup>r</sup>R<sup>r</sup>, -C(S)NR<sup>r</sup>R<sup>r</sup>, -S(O)<sub>2</sub>NHR<sup>r</sup>, -S(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -C(NH)NHR<sup>r</sup>, -C(NH)NR<sup>s</sup>R<sup>t</sup>, -NHC(O)R<sup>r</sup>, -NHC(S)R<sup>r</sup>, -NR<sup>r</sup>C(O)R<sup>r</sup>, -NR<sup>r</sup>C(S)R<sup>r</sup>, -NHS(O)<sub>2</sub>R<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>R<sup>r</sup>, -NHC(O)NHR<sup>r</sup>, -NHC(S)NHR<sup>r</sup>, -NR<sup>r</sup>C(O)NH<sub>2</sub>, -NR<sup>r</sup>C(S)NH<sub>2</sub>, -NR<sup>r</sup>C(O)NHR<sup>r</sup>, -NR<sup>r</sup>C(S)NHR<sup>r</sup>, -NHC(O)NR<sup>r</sup>R<sup>r</sup>, -NHC(S)NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>C(O)NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>C(S)NR<sup>r</sup>R<sup>r</sup>, -NHS(O)<sub>2</sub>NHR<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>r</sup>S(O)<sub>2</sub>NHR<sup>r</sup>, -NHS(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -NHR<sup>r</sup>, -NR<sup>r</sup>R<sup>r</sup>, cycloalkylamino, and -R<sup>x</sup>;

wherein each R<sup>r</sup>, R<sup>s</sup>, and R<sup>t</sup> at each occurrence are independently selected from the group consisting of lower alkyl, C<sub>3-6</sub> alkenyl, C<sub>3-6</sub> alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of -R<sup>y</sup>, fluoro, -OH, -NH<sub>2</sub>, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided that any substitution of the lower alkyl carbon bound to any -O-, -S-, or -N-, of -OR<sup>r</sup>, -SR<sup>r</sup>, -C(O)OR<sup>r</sup>, -C(S)OR<sup>r</sup>, -C(O)NHR<sup>r</sup>, -C(S)NHR<sup>r</sup>, -C(O)NR<sup>r</sup>R<sup>r</sup>, -C(S)NR<sup>r</sup>R<sup>r</sup>, -S(O)<sub>2</sub>NHR<sup>r</sup>, -S(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -C(NH)NHR<sup>r</sup>, -NR<sup>r</sup>C(O)R<sup>r</sup>, -NR<sup>r</sup>C(S)R<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>R<sup>r</sup>, -NHC(O)NHR<sup>r</sup>, -NHC(S)NHR<sup>r</sup>, -NR<sup>r</sup>C(O)NH<sub>2</sub>, -NR<sup>r</sup>C(S)NH<sub>2</sub>, -NR<sup>r</sup>C(O)NHR<sup>r</sup>, -NR<sup>r</sup>C(S)NHR<sup>r</sup>, -NHC(O)NR<sup>r</sup>R<sup>r</sup>, -NHC(S)NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>C(O)NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>C(S)NR<sup>r</sup>R<sup>r</sup>, -NHS(O)<sub>2</sub>NHR<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>r</sup>S(O)<sub>2</sub>NHR<sup>r</sup>, -NHS(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -NHR<sup>r</sup>, or -NR<sup>r</sup>R<sup>r</sup> is selected from the group consisting of fluoro and -R<sup>y</sup>, and wherein C<sub>3-6</sub> alkenyl or C<sub>3-6</sub> alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of -R<sup>y</sup>, fluoro, lower alkyl, fluoro

substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided that any substitution of the C<sub>3-6</sub> alkenyl or C<sub>3-6</sub> alkynyl carbon bound to any -O-, -S-, or -N-, of -OR<sup>r</sup>, -SR<sup>r</sup>, -C(O)OR<sup>r</sup>, -C(S)OR<sup>r</sup>, -C(O)NHR<sup>r</sup>, -C(S)NHR<sup>r</sup>, -C(O)NR<sup>r</sup>R<sup>r</sup>, -C(S)NR<sup>r</sup>R<sup>r</sup>, -S(O)<sub>2</sub>NHR<sup>r</sup>, -S(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -C(NH)NHR<sup>r</sup>, -NR<sup>r</sup>C(O)R<sup>r</sup>, -NR<sup>r</sup>C(S)R<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>R<sup>r</sup>, -NHC(O)NHR<sup>r</sup>, -NHC(S)NHR<sup>r</sup>, -NR<sup>r</sup>C(O)NH<sub>2</sub>, -NR<sup>r</sup>C(S)NH<sub>2</sub>, -NR<sup>r</sup>C(O)NHR<sup>r</sup>, -NR<sup>r</sup>C(S)NHR<sup>r</sup>, -NHC(O)NR<sup>r</sup>R<sup>r</sup>, -NHC(S)NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>C(O)NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>C(S)NR<sup>r</sup>R<sup>r</sup>, -NHS(O)<sub>2</sub>NHR<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>r</sup>S(O)<sub>2</sub>NHR<sup>r</sup>, -NHS(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -NR<sup>r</sup>S(O)<sub>2</sub>NR<sup>r</sup>R<sup>r</sup>, -NHR<sup>r</sup>, or -NR<sup>r</sup>R<sup>r</sup> is selected from the group consisting of fluoro, lower alkyl, fluoro substituted lower alkyl, or -R<sup>y</sup>, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkyl amino, di-alkyl amino, and cycloalkylamino, or R<sup>s</sup> and R<sup>t</sup> combine with the nitrogen to which they are attached form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -NO<sub>2</sub>, -CN, -OH, -NH<sub>2</sub>, OR<sup>u</sup>, -SR<sup>u</sup>, -NHR<sup>u</sup>, -NR<sup>u</sup>R<sup>u</sup>, -R<sup>x</sup>, and -R<sup>y</sup>;

wherein each R<sup>u</sup> is independently selected from the group consisting of lower alkyl, C<sub>3-6</sub> alkenyl, C<sub>3-6</sub> alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of -R<sup>y</sup>, fluoro, -OH, -NH<sub>2</sub>, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided that any substitution of the lower alkyl carbon bound to the -O- of -OR<sup>u</sup>, -S- of -SR<sup>u</sup>, or -N- of -NHR<sup>u</sup> is fluoro or -R<sup>y</sup>, and wherein C<sub>3-6</sub> alkenyl or C<sub>3-6</sub> alkynyl are optionally substituted with one or more, preferably 1, 2,



3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of  $-R^y$ , fluoro,  $-OH$ ,  $-NH_2$ , lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided that any substitution of the  $C_{3-6}$  alkenyl or  $C_{3-6}$  alkynyl carbon bound to the the  $-O-$  of  $-OR^u$ ,  $-S-$  of  $-SR^u$ , or  $-N-$  of  $-NHR^u$  is fluoro, lower alkyl, fluoro substituted lower alkyl, or  $-R^y$ , and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen,  $-OH$ ,  $-NH_2$ ,  $-NO_2$ ,  $-CN$ , lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkyl amino, di-alkyl amino, and cycloalkylamino;

wherein each  $-R^x$  is selected from the group consisting of lower alkyl, lower alkenyl and lower alkynyl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of  $-R^y$ , fluoro,  $-OH$ ,  $-NH_2$ , lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkyl amino, di-alkyl amino, and cycloalkylamino, and wherein lower alkenyl or lower alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of  $-R^y$ , fluoro,  $-OH$ ,  $-NH_2$ , lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkyl amino, di-alkyl amino, and cycloalkylamino;

wherein each  $-R^y$  is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen,  $-OH$ ,  $-NH_2$ ,  $-NO_2$ ,  $-CN$ , lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkyl amino, di-alkyl amino, and cycloalkylamino.

[0091] "Lower alkoxy" denotes the group  $-OR^z$ , where  $R^z$  is lower alkyl. "Substituted lower alkoxy" denotes lower alkoxy in which  $R^z$  is lower alkyl substituted with one or more substituents as indicated herein, for example, in the description of compounds of Formula I (including Formulae Ia, Ib, Ig and all sub-embodiments thereof), including descriptions of substituted cycloalkyl, cycloheteroalkyl, aryl and heteroaryl, attached at any available atom to produce a stable compound. Preferably, substitution of lower alkoxy is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkoxy" denotes lower alkoxy in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkoxy is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions on alkoxy are attached at any available atom to produce a stable compound, substitution of alkoxy is such that  $-O-$ ,  $-S-$ , or  $-N-$  (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkoxy  $-O-$ . Further, where alkoxy is described as a substituent of another moiety, the alkoxy oxygen is not bound to a carbon atom that is bound to an  $-O-$ ,  $-S-$ , or  $-N-$  of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0092] "Lower alkylthio" denotes the group  $-SR^{aa}$ , where  $R^{aa}$  is lower alkyl. "Substituted lower alkylthio" denotes lower alkylthio in which  $R^{aa}$  is lower alkyl substituted with one or more substituents as indicated herein, for example, in the description of compounds of Formula I (including Formulae Ia, Ib, Ig and all sub-embodiments thereof), including descriptions of substituted cycloalkyl, cycloheteroalkyl, aryl and heteroaryl, attached at any available atom to produce a stable compound. Preferably, substitution of lower alkylthio is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkylthio" denotes lower alkylthio in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkylthio is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions on alkylthio are attached at any available atom to produce a stable compound, substitution of alkylthio is such that  $-O-$ ,  $-S-$ , or  $-N-$  (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkylthio  $-S-$ . Further, where alkylthio is described as a substituent of another moiety, the alkylthio sulfur is not bound to a carbon atom that is bound to an  $-O-$ ,  $-S-$ , or  $-N-$  of the



other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0093] “Amino” or “amine” denotes the group  $\text{-NH}_2$ . “Mono-alkylamino” denotes the group  $\text{-NHR}^{\text{bb}}$  where  $\text{R}^{\text{bb}}$  is lower alkyl. “Di-alkylamino” denotes the group  $\text{-NR}^{\text{bb}}\text{R}^{\text{cc}}$ , where  $\text{R}^{\text{bb}}$  and  $\text{R}^{\text{cc}}$  are independently lower alkyl. “Cycloalkylamino” denotes the group  $\text{-NR}^{\text{dd}}\text{R}^{\text{ee}}$ , where  $\text{R}^{\text{dd}}$  and  $\text{R}^{\text{ee}}$  combine with the nitrogen to form a 5-7 membered heterocycloalkyl, where the heterocycloalkyl may contain an additional heteroatom within the ring, such as  $\text{-O-}$ ,  $\text{-N-}$ , or  $\text{-S-}$ , and may also be further substituted with lower alkyl. Examples of 5-7 membered heterocycloalkyl include, but are not limited to, piperidine, piperazine, 4-methylpiperazine, morpholine, and thiomorpholine. While it is understood that when mono-alkylamino, di-alkylamino, or cycloalkylamino are substituents on other moieties that are attached at any available atom to produce a stable compound, the nitrogen of mono-alkylamino, di-alkylamino, or cycloalkylamino as substituents is not bound to a carbon atom that is bound to an  $\text{-O-}$ ,  $\text{-S-}$ , or  $\text{-N-}$  of the other moiety.

[0094] As used herein, the term c-kit-mediated disease or condition refers to a disease or condition in which the biological function of c-kit affects the development and/or course of the disease or condition, and/or in which modulation of c-kit alters the development, course, and/or symptoms. For example, mutations in the c-kit gene such as the W42, Wv, and W41 mutations reported by Herbst et al al (J. Biol. Chem., 1992, 267: 13210-13216) confer severe, intermediate, and mild phenotypic characteristics, respectively. These mutations attenuate the intrinsic tyrosine kinase activity of the receptor to different degrees and are models for the effect of modulation of c-kit activity. A c-kit mediated disease or condition includes a disease or condition for which c-kit inhibition provides a therapeutic benefit, e.g. wherein treatment with c-kit inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0095] As used herein, the term c-fms-mediated disease or condition refers to a disease or condition in which the biological function of c-fms affects the development and/or course of the disease or condition, and/or in which modulation of c-fms alters the development, course, and/or symptoms. For example, the *Csflr*<sup>-</sup>/*Csflr*<sup>-</sup> mutant mouse of Dai et al (Blood, 2002, 99: 111-120) which lacks c-fms is an animal model for diseases or

conditions wherein c-fms activity has been abolished. A c-fms mediated disease or condition includes a disease or condition for which c-fms inhibition provides a therapeutic benefit, e.g. wherein treatment with c-fms inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition.

[0096] As used herein, the term "composition" refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes that contains at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient.

[0097] The term "pharmaceutically acceptable" indicates that the indicated material does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. For example, it is commonly required that such a material be essentially sterile, e.g., for injectibles.

[0098] In the present context, the terms "therapeutically effective" and "effective amount" indicate that the materials or amount of material is effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or medical condition, and/or to prolong the survival of the subject being treated.

[0099] Reference to particular amino acid residues in human c-kit polypeptide is defined by the numbering corresponding to the Kit sequence in GenBank NP\_000213 (SEQ ID NO:1). Reference to particular nucleotide positions in a nucleotide sequence encoding all or a portion of c-kit is defined by the numbering corresponding to the sequence provided in GenBank NM\_000222 (SEQ ID NO:2). Reference to particular amino acid residues in human c-fms polypeptide is defined by the numbering corresponding to the FMS precursor sequence in GenBank NP 005202 (SEQ ID NO:3). Reference to particular nucleotide positions in a nucleotide sequence encoding all or a portion of c-fms is defined by the numbering corresponding to the sequence provided in GenBank NM 005211 (SEQ ID NO:4).

[0100] The terms "kit", "c-kit", and "c-Kit" mean an enzymatically active kinase that contains a portion with greater than 90% amino acid sequence identity to amino acid



residues including the ATP binding site of full-length c-kit (e.g., human c-kit, e.g., the sequence NP\_000213, SEQ ID NO:1), for a maximal alignment over an equal length segment; or that contains a portion with greater than 90% amino acid sequence identity to at least 200 contiguous amino acids of native c-kit and retains kinase activity. Preferably the sequence identity is at least 95, 97, 98, 99, or even 100%. Preferably the specified level of sequence identity is over a sequence at least 100-500, at least 200-400, or at least 300 contiguous amino acid residues in length. Unless indicated to the contrary, the term includes reference to wild-type c-kit, allelic variants, and mutated forms (e.g., having activating mutations).

**[0101]** The terms "fms", "c-fms", "FMS", and "c-Fms" mean an enzymatically active kinase that contains a portion with greater than 90% amino acid sequence identity to amino acid residues including the ATP binding site of full-length c-fms (e.g. human c-fms, e.g. residues 20-972 of GenBank sequence NP 005202, SEQ ID NO:3), for a maximal alignment over an equal length segment; or that contains a portion with greater than 90% amino acid sequence identity to at least 200 contiguous amino acids of native c-fms and retains kinase activity. Preferably the sequence identity is at least 95, 97, 98, 99, or 100%. Preferably the specified level of sequence identity is over a sequence at least 100-150, at least 200-400, or at least 300 contiguous amino acid residues in length. Unless indicated to the contrary, the term includes wild-type c-fms, allelic variants, and mutated forms (e.g. having activating mutations). The term "pFMS" refers to phosphorylated c-fms. The term "c-fms activity" refers to a biological activity of c-fms, particularly including kinase activity. The abbreviation "M-CSF" refers to the ligand for the c-fms RPTK, and the abbreviation "SCF" refers to the ligand for the c-Kit RPTK.

**[0102]** The term "c-kit kinase domain" refers to a reduced length c-kit (*i.e.*, shorter than a full-length c-kit by at least 100 amino acids) that includes the kinase catalytic region in c-kit. The term "c-fms kinase domain" refers to a c-fms of reduced length (*i.e.*, shorter than a full-length c-fms by at least 100 amino acids) that includes the kinase catalytic region of c-fms. Highly preferably for use in this invention, the kinase domain retains kinase activity, preferably at least 60, 70, 80, 90, or 100% of the native c-fms kinase activity. The term "the kinase" or terms of similar import relate to either c-kit or c-fms.

[0103] As used herein, the terms “ligand” and “modulator” are used equivalently to refer to a compound that changes (*i.e.*, increases or decreases) the activity of a target biomolecule, *e.g.*, an enzyme such as a kinase or kinase. Generally a ligand or modulator will be a small molecule, where “small molecule” refers to a compound with a molecular weight of 1500 daltons or less, or preferably 1000 daltons or less, 800 daltons or less, or 600 daltons or less.

[0104] The term “binds” in connection with the interaction between a target and a potential binding compound indicates that the potential binding compound associates with the target to a statistically significant degree as compared to association with proteins generally (*i.e.*, non-specific binding). Thus, the term “binding compound” refers to a compound that has a statistically significant association with a target molecule. Preferably a binding compound interacts with a specified target with a dissociation constant ( $K_D$ ) of 1 mM or less. A binding compound can bind with “low affinity”, “very low affinity”, “extremely low affinity”, “moderate affinity”, “moderately high affinity”, or “high affinity” as described herein.

[0105] In the context of compounds binding to a target, the term “greater affinity” indicates that the compound binds more tightly than a reference compound, or than the same compound in a reference condition, *i.e.*, with a lower dissociation constant. In particular embodiments, the greater affinity is at least 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, 1000, or 10,000-fold greater affinity.

[0106] Also in the context of compounds binding to a biomolecular target, the term “greater specificity” indicates that a compound binds to a specified target to a greater extent than to another biomolecule or biomolecules that may be present under relevant binding conditions, where binding to such other biomolecules produces a different biological activity than binding to the specified target. Typically, the specificity is with reference to a limited set of other biomolecules, *e.g.*, in the case of c-kit or c-fms, other tyrosine kinases or even other type of enzymes. In particular embodiments, the greater specificity is at least 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, or 1000-fold greater specificity.

[0107] As used herein in connection with binding compounds or ligands, the term “specific for c-kit kinase”, “specific for c-kit”, and terms of like import mean that a



particular compound binds to c-kit to a statistically greater extent than to other kinases that may be present in a particular sample. Also, where biological activity other than binding is indicated, the term “specific for c-kit” indicates that a particular compound has greater biological effect associated with binding c-kit than to other tyrosine kinases, e.g., kinase activity inhibition. Preferably, the specificity is also with respect to other biomolecules (not limited to tyrosine kinases) that may be present in a particular sample. The term “specific for c-fms kinase”, “specific for c-fms”, and terms of like import mean that a particular compound binds to c-fms to a statistically greater extent than to other kinases that may be present in a particular sample. Also, where biological activity other than binding is indicated, the term “specific for c-fms” indicates that a particular compound has greater biological effect associated with binding c-fms than to other tyrosine kinases, e.g., kinase activity inhibition. Preferably, the specificity is also with respect to other biomolecules (not limited to tyrosine kinases) that may be present in a particular sample.

**[0108]** As used herein in connection with test compounds, binding compounds, and modulators (ligands), the term “synthesizing” and like terms means chemical synthesis from one or more precursor materials.

**[0109]** By “assaying” is meant the creation of experimental conditions and the gathering of data regarding a particular result of the experimental conditions. For example, enzymes can be assayed based on their ability to act upon a detectable substrate. A compound or ligand can be assayed based on its ability to bind to a particular target molecule or molecules.

**[0110]** As used herein, the term “modulating” or “modulate” refers to an effect of altering a biological activity, especially a biological activity associated with a particular biomolecule such as c-kit or c-fms. For example, an agonist or antagonist of a particular biomolecule modulates the activity of that biomolecule, e.g., an enzyme.

**[0111]** The term “c-kit activity” refers to a biological activity of c-kit, particularly including kinase activity. The term “c-fms activity” refers to a biological activity of c-fms, particularly including kinase activity.

**[0112]** In the context of the use, testing, or screening of compounds that are or may be modulators, the term “contacting” means that the compound(s) are caused to be in

sufficient proximity to a particular molecule, complex, cell, tissue, organism, or other specified material that potential binding interactions and/or chemical reaction between the compound and other specified material can occur.

[0113] As used herein in connection with amino acid or nucleic acid sequence, the term "isolate" indicates that the sequence is separated from at least a portion of the amino acid and/or nucleic acid sequences with which it would normally be associated.

[0114] In connection with amino acid or nucleic sequences, the term "purified" indicates that the particular molecule constitutes a significantly greater proportion of the biomolecules in a composition than in a prior composition, e.g., in a cell culture. The greater proportion can be 2-fold, 5-fold, 10-fold or more greater.

## I. General

[0115] In one aspect, the present invention concerns compounds of Formula I, Formula Ia, Formula Ib, or Formula Ig and all sub-embodiments thereof, that are inhibitors of c-kit, c-fms, or both c-kit and c-fms, and the use of the compounds in treating diseases that are mediated by c-kit, c-fms, or both c-kit and c-fms.

[0116] Exemplary compounds of Formula I, Formula Ia, Formula Ib or Formula Ig prepared following methods described in the Examples herein are as follows:

Benzyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0001),  
(6-Benzylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0002),  
[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4trifluoromethyl-benzyl)-amine (P-0003),  
(4-Methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0004),  
(4-Chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0005),  
(4-Fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0006),  
(4-Methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0007),



[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-thiophen-2-ylmethyl-amine (P-0008),  
[4-Chloro-benzyl]-[5-(4-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0009),  
[4-Chloro-benzyl]-[5-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0010),  
[5-(4-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0011),  
[6-Methoxy-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0012),  
[6-Methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0013),  
[4-Chloro-benzyl]-[6-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0014),  
[6-(4-Fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0015),  
[6-(3-Fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0016),  
[1H-Pyrrolo[2,3-b]pyridin-3-yl]-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-methanone (P-0017),  
[1H-Pyrrolo[2,3-b]pyridin-3-yl]-{6-[(thiophen-2-ylmethyl)-amino]-pyridin-3-yl}-methanone (P-0018),  
3-(6-Isopropyl-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0019),  
3-(6-tert-Butoxy-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0020),  
Dimethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0021),  
3-(6-Methoxy-pyridin-3-ylmethyl)-4-thiophen-3-yl-1H-pyrrolo[2,3-b]pyridine (P-0022),  
[6-Phenylamino-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0023),  
[6-Isopropylamino-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0024),  
[6-Isobutylamino-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0025),  
[6-(3-Benzoyloxy-phenylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0026),  
[6-(3-Hydroxy-phenylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0027),

Isobutyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0028),  
(6-Isobutylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (P-0029),  
[6-(Cyclopropylmethyl-amino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone  
(P-0030),  
[6-(Cyclohexylmethyl-amino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone  
(P-0031),  
Cyclopropylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine  
(P-0032),  
Cyclohexylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine  
(P-0033),  
[6-(Cyclopropylmethyl-amino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol  
(P-0034),  
[6-(Cyclohexylmethyl-amino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol  
(P-0035),  
(1H-Pyrrolo[2,3-b]pyridin-3-yl)-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-  
methanol (P-0036),  
[6-(4-Chloro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol  
(P-0037),  
[5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine  
(P-0038),  
(4-Chloro-benzyl)-{5-[methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-  
amine (P-0039),  
(4-Chloro-3-trifluoromethyl-benzyl)-{5-[methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-  
methyl]-pyridin-2-yl}-amine (P-0040),  
(4-Chloro-benzyl)-{5-[methoxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-  
pyridin-2-yl}-amine (P-0041),  
(4-Chloro-benzyl)-(5-{[5-(3-methanesulfonyl-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-  
methoxy-methyl}-pyridin-2-yl)-amine (P-0042),  
{5-[Methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-(4-trifluoromethyl-  
benzyl)-amine (P-0043),  
[6-(4-Chloro-benzylamino)-2-methyl-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-  
methanol (P-0046),



[2-Chloro-6-(4-chloro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0048),  
[2,6-Bis-(4-chloro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0049),  
[2-Chloro-6-(4-chloro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (P-0050),  
6-(4-Chloro-benzylamino)-3-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ol (P-0051),  
3-(2-Ethylsulfanyl-4,6-dimethyl-pyrimidin-5-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0052),  
[5-(5-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0053),  
[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0054),  
3-[6-(3-Chloro-benzyloxy)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (P-0055),  
3-[6-(4-Chloro-benzyloxy)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (P-0056),  
3-[6-(3-Trifluoromethyl-benzyloxy)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (P-0057),  
(4-Chloro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0058),  
(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0059),  
{5-[5-(2-Diethylamino-ethoxy)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine (P-0060),  
3-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridin-5-ol (P-0061),  
3-[6-(4-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridin-5-ol (P-0062),  
(4-Chloro-benzyl)-{5-[5-(2-morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (P-0063),  
{5-[5-(2-Pyrrolidin-1-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine (P-0064),

{5-[5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine (P-0065),  
{5-[5-(3-Diethylamino-propoxy)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine (P-0066),  
N-[5-(1H-Pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-4-trifluoromethyl-benzamide (P-0067),  
N-[5-(1H-Pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-4-trifluoromethyl-benzenesulfonamide (P-0068),  
(4-Chloro-benzyl)-{5-[5-(3-diethylamino-propoxy)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (P-0069),  
[6-(4-Chloro-benzylamino)-2-trifluoromethyl-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0070),  
N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-4-trifluoromethyl-benzenesulfonamide (P-0071),  
N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-4-trifluoromethyl-benzamide (P-0072),  
4-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (P-0073),  
4-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide (P-0074),  
[(S)-1-(4-Chloro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0075),  
5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridine-2-carboxylic acid (4-chloro-phenyl)-amide (P-0076),  
[2-(4-Chloro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0077),  
(4-Chloro-phenyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylmethyl]-amine (P-0078),  
3-[(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-methoxy-methyl]-1H-pyrrolo[2,3-b]pyridine (P-0079),  
3-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0080),  
(4-Chloro-benzyl)-[6-methoxy-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0081),



(4-Chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0082), and

(4-Chloro-benzyl)-[4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (P-0083),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide (P-0084),

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid phenylamide (P-0085),

[3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazol-1-yl]-phenyl-methanone (P-0086),

1-[3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazol-1-yl]-3-phenyl-propan-1-one (P-0087),

3-(3,5-Dimethyl-1-phenylmethanesulfonyl-1H-pyrazol-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0088),

3-[1-(Butane-1-sulfonyl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (P-0089), and

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid butylamide (P-0090).

#### **Exemplary Diseases Associated with c-Kit.**

[0117] The compounds described herein are useful for treating disorders related to c-kit e.g., diseases related to unregulated kinase signal transduction, including cell proliferative disorders, fibrotic disorders and metabolic disorders, among others. As described in more detail below and in Lipson et al., U.S. 20040002534 (U.S. application 10/600, 868, filed June 23, 2003) which is incorporated herein by reference in its entirety, cell proliferative disorders which can be treated by the present invention include cancers, and mast cell proliferative disorders.

[0118] The presence of c-kit has also been associated with a number of different types of cancers, as described below. In addition, the association between abnormalities in c-kit and disease are not restricted to cancer. As such, c-kit has been associated with malignancies, including mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors (GISTs), glioblastoma, astrocytoma, neuroblastoma,

carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, mastocytosis, melanoma, and canine mast cell tumors, and inflammatory diseases, including asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, and hypereosinophilia.

#### **Exemplary malignant diseases associated with c-kit**

[0119] Aberrant expression and/or activation of c-kit has been implicated in a variety of cancers. Evidence for a contribution of c-kit to neoplastic pathology includes its association with leukemias and mast cell tumors, small cell lung cancer, testicular cancer, and some cancers of the gastrointestinal tract and central nervous system. In addition, c-kit has been implicated in playing a role in carcinogenesis of the female genital tract (Inoue, et al., 1994, *Cancer Res.* 54(11):3049-3053), sarcomas of neuroectodermal origin (Ricotti, et al., 1998, *Blood* 91:2397-2405), and Schwann cell neoplasia associated with neurofibromatosis (Ryan, et al., 1994, *J. Neuro. Res.* 37:415-432). It was found that mast cells are involved in modifying the tumor microenvironment and enhancing tumor growth (Yang et al., 2003, *J Clin Invest.* 112:1851-1861; Viskochil, 2003, *J Clin Invest.* 112:1791-1793). Thus, c-kit is a useful target in treating neurofibromatosis as well as malignant tumors.

[0120] Small cell lung carcinoma: c-kit kinase receptor has been found to be aberrantly expressed in many cases of small cell lung carcinoma (SCLC) cells (Hibi, et al., 1991, *Oncogene* 6:2291-2296). Thus, as an example, inhibition of c-kit kinase can be beneficial in treatment of SCLC, e.g., to improve the long term survival of patients with SCLC.

[0121] Leukemias: SCF binding to the c-kit protects hematopoietic stem and progenitor cells from apoptosis (Lee, et al., 1997, *J. Immunol.* 159:3211-3219), thereby contributing to colony formation and hematopoiesis. Expression of c-kit is frequently observed in acute myelocytic leukemia (AML), and in some cases of acute lymphocytic leukemia (ALL) (for reviews, see Sperling, et al., 1997, *Haemat* 82:617-621; Escribano, et al., 1998, *Leuk. Lymph.* 30:459-466). Although c-kit is expressed in the majority of AML cells, its expression does not appear to be prognostic of disease progression (Sperling, et al, 1997, *Haemat* 82:617-621). However, SCF protected AML cells from apoptosis induced by



chemotherapeutic agents (Hassan, et al., 1996, *Acta. Hem.* 95:257-262). Inhibition of c-kit by the present invention will enhance the efficacy of these agents and can induce apoptosis of AML cells.

[0122] The clonal growth of cells from patients with myelodysplastic syndrome (Sawada, et al., 1996, *Blood* 88:319-327) or chronic myelogenous leukemia (CML) (Sawai, et al., 1996, *Exp. Hem.* 2:116-122) was found to be significantly enhanced by SCF in combination with other cytokines. CML is characterized by expansion of Philadelphia chromosome positive cells of the marrow (Verfaillie, et al., *Leuk.* 1998, 12:136-138), which appears to primarily result from inhibition of apoptotic death (Jones, *Curr. Opin. Onc.* 1997, 9:3-7). The product of the Philadelphia chromosome, p210<sup>BCR-ABL</sup>, has been reported to mediate inhibition of apoptosis (Bedi, et al., *Blood* 1995, 86:1148-1158). Since p210<sup>BCR-ABL</sup> and c-kit both inhibit apoptosis and p62<sup>dok</sup> has been suggested as a substrate (Carpino, et al., *Cell* 1997, 88:197-204), clonal expansion mediated by these kinases may occur through a common signaling pathway. However, c-kit has also been reported to interact directly with p210<sup>BCR-ABL</sup> (Hallek, et al., *Brit. J Haem.* 1996, 94:5-16), which suggests that c-kit has a more causative role in CML pathology. Therefore, inhibition of c-kit will be useful in the treatment of the above disorders.

[0123] Gastrointestinal cancers: Normal colorectal mucosa does not express c-kit (Bellone, et al., 1997, *J. Cell Physiol.* 172:1-11). However, c-kit is frequently expressed in colorectal carcinoma (Bellone, et al., 1997, *J. Cell Physiol.* 172: 1-11), and autocrine loops of SCF and c-kit have been observed in several colon carcinoma cell lines (Toyota, et al., 1993, *Turn Biol* 14:295-302; Lahm, et al., 1995, *Cell Growth & Differ* 6:1111-1118; Bellone, et al., 1997, *J. Cell Physiol.* 172:1-11). Furthermore, disruption of the autocrine loop by the use of neutralizing antibodies (Lahm, et al., 1995, *Cell Growth & Differ.* 6:1111-1118) and downregulation of c-kit and/or SCF significantly inhibits cell proliferation (Lahm, et al., 1995, *Cell Growth & Differ* 6:1111-1118; Bellone, et al., 1997, *J. Cell Physiol.* 172:1-11).

[0124] SCF/c-kit autocrine loops have been observed in gastric carcinoma cell lines (Turner, et al., 1992, *Blood* 80:374-381; Hassan, et al., 1998, *Digest. Dis. Science* 43:8-14), and constitutive c-kit activation also appears to be important for gastrointestinal stromal tumors (GISTs). GISTs are the most common mesenchymal tumor of the digestive



system. More than 90% of GISTs express c-kit, which is consistent with the putative origin of these tumor cells from interstitial cells of Cajal (ICCs) (Hirota, et al., 1998, *Science* 279:577-580). ICCs are thought to regulate contraction of the gastrointestinal tract, and patients lacking c-kit in their ICCs exhibited a myopathic form of chronic idiopathic intestinal pseudo-obstruction (Isozaki, et al., 1997, *Amer. J. of Gast.* 9 332-334). The c-kit expressed in GISTs from several different patients was observed to have mutations in the intracellular juxtamembrane domain leading to constitutive activation of c-kit (Hirota, et al., 1998, *Science* 279:577-580). Hence, inhibition of c-kit kinase will be an efficacious means for the treatment of these cancers.

[0125] Testicular cancers: Male germ cell tumors have been histologically categorized into seminomas, which retain germ cell characteristics, and nonseminomas which can display characteristics of embryonal differentiation. Both seminomas and nonseminomas are thought to initiate from a preinvasive stage designated carcinoma in situ (CIS) (Murty, et al., 1998, *Sem. Oncol.* 25:133-144). Both c-kit and SCF have been reported to be essential for normal gonadal development during embryogenesis (Loveland, et al., 1997, *J. Endocrinol* 153:337-344). Loss of either the receptor or the ligand resulted in animals devoid of germ cells. In postnatal testes, c-kit has been found to be expressed in Leydig cells and spermatogonia, while SCF was expressed in Sertoli cells (Loveland, et al., 1997, *J. Endocrinol* 153:337-344). Testicular tumors develop from Leydig cells with high frequency in transgenic mice expressing human papilloma virus 16 (HPV16) E6 and E7 oncogenes (Kondoh, et al., 1991, *J. Virol.* 65:3335-3339; Kondoh, et al., 1994, *J. Urol.* 152:2151-2154). These tumors express both c-kit and SCF, and an autocrine loop may contribute to the tumorigenesis (Kondoh, et al., 1995, *Oncogene* 10:341-347) associated with cellular loss of functional p53 and the retinoblastoma gene product by association with E6 and E7 (Dyson, et al., 1989, *Science* 243:934-937; Werness, et al., 1990, *Science* 248:76-79; Scheffner, et al., 1990, *Cell* 63:1129-1136). Defective signaling mutants of SCF (Kondoh, et al., 1995, *Oncogene* 10:341-347) or c-kit (Li, et al., 1996, *Canc. Res.* 56:4343-4346) inhibited formation of testicular tumors in mice expressing HPV16 E6 and E7. The c-kit kinase activation is pivotal to tumorigenesis in these animals and thus modulation of the c-kit kinase pathway by the present invention will prevent or treat such disorders.



[0126] Expression of c-kit in germ cell tumors shows that the receptor is expressed by the majority of carcinomas in situ and seminomas, but c-kit is expressed in only a minority of nonseminomas (Strohmeyer, et al., 1991, *Canc. Res.* 51:1811-1816; Rajpert-de Meyts, et al., 1994, *Int. J. Androl.* 17:85-92; Izquierdo, et al., 1995, *J. Pathol.* 177:253-258; Strohmeyer, et al., 1995, *J. Urol.* 153:511-515; Bokenmeyer, et al., 1996, *J. Cancer Res. Clin. Oncol.* 122:301-306; Sandlow, et al., 1996, *J. Androl.* 17:403-408). Therefore, inhibition of c-kit kinase provides a means for treating these disorders.

[0127] CNS cancers: SCF and c-kit are expressed throughout the CNS of developing rodents, and the pattern of expression indicates a role in growth, migration and differentiation of neuroectodermal cells. Expression of both receptor and ligand have also been reported in the adult brain (Hamel, et al., 1997, *J. Neuro-Onc.* 35:327-333). Expression of c-kit has also been observed in normal human brain tissue (Tada, et al. 1994, *J. Neuro* 80:1063-1073). Glioblastoma and astrocytoma, which define the majority of intracranial tumors, arise from neoplastic transformation of astrocytes (Levin, et al., 1997, *Principles & Practice of Oncology*:2022-2082). Expression of c-kit has been observed in glioblastoma cell lines and tissues (Berdel, et al., 1992, *Canc. Res.* 52:3498-3502; Tada, et al. 1994, *J. Neuro* 80:1063-1073; Stanulla, et al., 1995, *Act Neuropath* 89:158-165).

[0128] Cohen, et al., 1994, *Blood* 84:3465-3472 reported that all 14 neuroblastoma cell lines examined contained c-kit/SCF autocrine loops, and expression of both the receptor and ligand were observed in 45% of tumor samples examined. In two cell lines, anti-c-kit antibodies inhibited cell proliferation, suggesting that the SCF/c-kit autocrine loop contributed to growth (will Cohen, et al., 1994, *Blood* 84:3465-3472). Hence, c-kit kinase inhibitors can be used to treat these cancers.

#### **Exemplary Mast Cell Diseases Involving c-kit**

[0129] Excessive activation of c-kit is also associated with diseases resulting from an over-abundance of mast cells. Mastocytosis is the term used to describe a heterogeneous group of disorders characterized by excessive mast cell proliferation (Metcalfe, 1991, *J. Invest. Derm* 93:2S-4S; Golkar, et al., 1997, *Lancet* 349:1379-1385). Elevated c-kit expression was reported on mast cells from patients with aggressive mastocytosis (Nagata, et al., 1998, *Leukemia* 12:175-181).

[0130] Additionally, mast cells and eosinophils represent key cells involved in allergy, inflammation and asthma (Thomas, et al., 1996, *Gen. Pharmacol* 27:593-597; Metcalfe, et al., 1997, *Physiol Rev* 77:1033-1079; Naclerio, et al., 1997, *JAMA* 278:1842-1848; Costa, et al., 1997, *JAMA* 278:1815-1822). SCF, and hence c-kit, directly and indirectly regulates activation of both mast cells and eosinophils, thereby influencing the primary cells involved in allergy and asthma through multiple mechanisms. Because of this mutual regulation of mast cell and eosinophil function, and the role that SCF can play in this regulation, inhibition of c-kit can be used to treat allergy-associated chronic rhinitis, inflammation and asthma.

[0131] Mastocytosis: SCF (also known as mast cell growth factor) stimulation of c-kit has been reported to be essential for the growth and development of mast cells (Hamel, et al., 1997, *J. Neuro-Onc.* 35:327-333; Kitamura, et al., 1995, *Int. Arch. Aller. Immunol.* 107:54-56). Mice with mutations of c-kit that attenuate its signaling activity have exhibited significantly fewer mast cells in their skin (Tsujimura, 1996, *Pathol Int* 46:933-938). Excessive activation of c-kit can be associated with diseases resulting from an over abundance of mast cells.

[0132] Mastocytosis is limited to the skin in the majority of patients, but can involve other organs in 15-20% of patients (Valent, 1996, *Wein/Klin Wochenschr* 108:385-397; Golkar, et al., 1997, *Lancet* 349:1379-1385). Even among patients with systemic mastocytosis, the disease can range from having a relatively benign prognosis to aggressive mastocytosis and mast cell leukemia. (Valent, 1996, *Wein/Klin Wochenschr* 108:385-397; Golkar, et al., 1997, *Lancet* 349:1379-1385). c-kit has been observed on malignant mast cells from canine mast cell tumors (London, et al., 1996, *J. Compar. Pathol.* 115:399-414), as well as on mast cells from patients with aggressive systemic mastocytosis (Baghestanian, et al., 1996, *Leuk.:*116-122; Castells, et al., 1996, *J. Aller. Clin. Immunol.* 98:831-840).

[0133] SCF has been shown to be expressed on stromal cells as a membrane-bound protein, and its expression can be induced by fibrogenic growth factors such as PDGF. It has also been shown to be expressed on keratinocytes as a membrane-bound protein in normal skin. However, in the skin of patients with mastocytosis, an increased amount of soluble SCF has been observed (Longley, et al., 1993, *New Engl. J. Med.* 328:1302-1307).



[0134] Mast cell chymase has been reported to cleave membrane-associated SCF to a soluble and biologically active form. This mast cell-mediated process can generate a feedback loop to enhance mast cell proliferation and function (Longley, et al., 1997, Proc. Natl. Acad. Sci. 94:9017-9021), and may be important for the etiology of mastocytosis. Transgenic mice overexpressing a form of SCF that could not be proteolytically released from keratinocytes did not develop mastocytosis, while similar animals expressing normal SCF in keratinocytes exhibited a phenotype resembling human cutaneous mastocytosis (Kunisada, et al., 1998, J. Exp. Med. 187:1565-1573). Formation of large amounts of soluble SCF can contribute to the pathology associated with mastocytosis in some patients and the present invention can treat or prevent such disorders by modulating the interaction between SCF and c-kit kinase. Several different mutations of c-kit that resulted in constitutive kinase activity have been found in human and rodent mast cell tumor cell lines (Furitsu, et al., 1993, J. Clin. Invest. 92:1736-1744; Tsujimura, et al., 1994, Blood 9:2619-2626; Tsujimura, et al., 1995, Int. Arch. Allergy Immunol 106:377-385; Tsujimura, 1996, Pathol Int 46:933-938). In addition, activating mutations of the c-kit gene have been observed in peripheral mononuclear cells isolated from patients with mastocytosis and associated hematologic disorders (Nagata, et al., 1998, Mastocytosis Leuk 12:175-181), and in mast cells from a patient with urticaria pigmentosa and aggressive mastocytosis (Longley, et al., 1996, Nat. Gen. 12:312-314). Inhibition of c-kit kinase will therefore prove to have an excellent therapeutic role in the treatment of these disorders.

[0135] In some patients, activating mutations of c-kit may be responsible for the pathogenesis of the disease and these patients can be treated, or their diseases prevented, by modulation of the SCF interaction with c-kit kinase. SCF activation of c-kit as been shown to prevent mast cell apoptosis which may be critical for maintaining cutaneous mast cell homeostasis (Iemura, et al., 1994, Amer. J. Pathol 144:321-328; Yee, et al., 1994, J. Exp. Med. 179:1777-1787; Mekori, et al., 1994, J. Immunol 153:2194-2203; Mekori, et al., 1995, Int. Arch. Allergy Immunol. 107:137-138). Inhibition of mast cell apoptosis can lead to the mast cell accumulation associated with mastocytosis. Thus, observation of c-kit activation resulting from overexpression of the receptor, excessive formation of soluble SCF, or mutations of the c-kit gene that constitutively activate its kinase, provides a rationale that inhibition of the kinase activity of c-kit will decrease the number of mast cells and provide benefit for patients with mastocytosis.



[0136] For cells with activating c-kit mutations, it was found that inhibitors of c-kit inhibit or even kill the cells (Ma et al., 2000, *J Invest Dermatol.* 114:392-394), particularly for mutations in the regulatory region (Ma et al., 2002, *Blood* 99:1741-1744). Ma et al., 2002, also showed that for mutations in the catalytic region, inhibitors STI571 (Gleevec) and SU9529 did not inhibit the cells, such that additional types of c-kit inhibitors are useful. Thus, c-kit inhibitors can be used against both wild-type c-kit as well as c-kit having mutations, e.g., activating mutations in the regulatory region and/or catalytic region.

[0137] Asthma & Allergy: Mast cells and eosinophils represent key cells in parasitic infection, allergy, inflammation, and asthma (Thomas, et al., 1996, *Gen. Pharmacol* 27:593-597; Metcalfe, et al., 1997, *Physiol Rev* 77:1033-1079; Holgate, 1997, *CIBA Found. Symp.*; Naclerio, et al, 1997, *JAMA* 278:1842-1848; Costa, et al., 1997, *JAMA* 778:1815-1822). SCF has been shown to be essential for mast cell development, survival and growth (Kitamura, et al., 1995, *Int. Arch. Aller. Immunol.* 107:54-56; Metcalfe, et al., 1997, *Physiol Rev* 77:1033-1079). In addition, SCF cooperates with the eosinophil-specific regulator, IL-5, to increase the development of eosinophil progenitors (Metcalf, et al., 1998, *Proc. Natl. Acad. Sci., USA* 95:6408-6412). SCF has also been reported to induce mast cells to secrete factors (Okayama, et al., 1997, *Int. Arch. Aller. Immunol.* 114:75-77; Okayama, et al., 1998, *Eur. J. Immunol.* 28:708-715) that promote the survival of eosinophils (Kay, et al., 1997, *Int. Arch. Aller. Immunol.* 113:196-199), which may contribute to chronic, eosinophil-mediated inflammation (Okayama, et al., 1997, *Int. Arch. Aller. Immunol.* 114:75-77; Okayama, et al., 1998, *Eur. J. Immunol.* 28:708-715). In this regard, SCF directly and indirectly regulates activation of both mast cells and eosinophils.

[0138] SCF induces mediator release from mast cells, as well as priming these cells for IgE-induced degranulation (Columbo, et al., 1992, *J. Immunol* 149:599-602) and sensitizing their responsiveness to eosinophil-derived granule major basic protein (Furuta, et al., 1998, *Blood* 92:1055-1061). Among the factors released by activated mast cells are IL-5, GM-CSF and TNF- $\alpha$ , which influence eosinophil protein secretion (Okayama, et al., 1997, *Int. Arch. Aller. Immunol.* 114:75-77; Okayama, et al., 1998, *Eur. J. Immunol.* 28:708-715). In addition to inducing histamine release from mast cells (Luckacs, et al., 1996, *J. Immunol.* 156:3945-3951; Hogaboam, et al., 1998, *J. Immunol.* 160:6166-6171), SCF promotes the mast cell production of the eosinophil chemotactic factor, eotaxin



(Hogaboam, et al., 1998, *J. Immunol.* 160:6166-6171), and eosinophil infiltration (Luckacs, et al., 1996, *J. Immunol.* 156:3945-3951).

[0139] SCF also directly influences the adhesion of both mast cells (Dastych, et al., 1994, *J. Immunol.* 152:213-219; Kinashi, et al., 1994, *Blood* 83:1033-1038) and eosinophils (Yuan, et al., 1997, *J. Exp. Med.* 186:313-323), which in turn, regulates tissue infiltration. Thus, SCF can influence the primary cells involved in allergy and asthma through multiple mechanisms. Currently, corticosteroids are the most effective treatment for chronic rhinitis and inflammation associated with allergy (Naclerio, et al., 1997, *JAMA* 278:1842-1848; Meltzer, 1997, *Aller.* 52:33-40). These agents work through multiple mechanisms including reduction of circulating and infiltrating mast cells and eosinophils, and diminished survival of eosinophils associated with inhibition of cytokine production (Meltzer, 1997, *Aller.* 52:33-40). Steroids have also been reported to inhibit the expression of SCF by fibroblasts and resident connective tissue cells, which leads to diminished mast cell survival (Finotto, et al., 1997, *J. Clin. Invest.* 99 1721-1728). Because of the mutual regulation of mast cell and eosinophil function, and the role that SCF can play in this regulation, inhibition of c-kit kinase will provide a means to treat allergy-associated chronic rhinitis, inflammation and asthma.

[0140] Inflammatory arthritis (e.g. rheumatoid arthritis): Due to the association of mast cells with the arthritic process (Lee et al., 2002, *Science* 297:1689-1692), c-kit provides a useful target for prevention, delay, and/or treatment of inflammatory arthritis, such as rheumatoid arthritis.

[0141] Multiple sclerosis: Mast cells have been shown to play an extensive role in autoimmune diseases, as demonstrated in the mouse model of multiple sclerosis (MS), experimental allergic encephalomyelitis (EAE). Mast cells were indicated to be required for full manifestation of the disease. Secor et al., 2000, *J Exp Med* 191:813-821. Thus, c-kit also provides a useful target for the prevention, delay, and/or treatment of multiple sclerosis.

#### **Exemplary diseases associated with c-fms**

[0142] The presence of c-fms has been associated with a number of different types of diseases. As such, c-fms has been associated with immune disorders, including

rheumatoid arthritis, systemic lupus erythematosus (SLE), Wegener's granulomatosis, and transplant rejection, inflammatory diseases including Chronic Obstructive Pulmonary Disease (COPD), emphysema, and atherosclerosis, metabolic disorders, including insulin resistance, hyperglycemia, and lipolysis, disorders of bone structure or mineralization, including osteoporosis, increased risk of fracture, hypercalcemia, and bone metastases, kidney diseases, including nephritis (e.g. glomerulonephritis, interstitial nephritis, Lupus nephritis), tubular necrosis, diabetes-associated renal complications, and hypertrophy and cancers, including multiple myeloma, acute myeloid leukemia, chronic myeloid leukemia (CML), breast cancer, and ovarian cancer.

**[0143]** Aberrant expression and/or activation of c-fms has been implicated in acute myeloid leukemia, AML (Ridge et al, Proc. Nat. Acad. Sci., 1990, 87:1377-1380). Mutations at codon 301 are believed to lead to neoplastic transformation by ligand independence and constitutive tyrosine kinase activity of the receptor. The tyrosine residue at codon 969 has been shown to be involved in a negative regulatory activity, which is disrupted by amino acid substitutions. Accordingly, c-fms mutations are most prevalent (20%) in chronic myelomonocytic leukemia and AML type M4 (23%), both of which are characterized by monocytic differentiation.

**[0144]** A condition related to AML is chronic myeloid leukemia (CML). During the myeloid blast crisis (BC) of CML, non-random additional chromosome abnormalities occur in over 80% of patients. However, these cytogenetic changes have been reported to precede the clinical signs of CML-BC by several months to years suggesting that other biological events may participate in the multistep process of acute transformation of CML. The autocrine production of growth factors has been shown to occur in several hematological malignancies and particularly in AML. Specchia et al [Br J Haematol. 1992 Mar; 80(3):310-6] have demonstrated that IL-1 beta gene is expressed in almost all cases of CML in myeloid blast crisis, and that a high proportion of cases showed constitutive expression of the M-CSF gene. Many of the same patients in the Specchia et al study demonstrated simultaneous co-expression of c-fms. After exposure of leukemic cells to phorbol myristate acetate (PMA), release of M-CSF protein was documented in three of five patients studied; however, no significant interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF), was detected in these patients. This demonstrates that



different patterns of growth factors secretion exist in AML and CML, and that distinct molecular events are likely involved in the control of leukemic proliferation.

[0145] The observation that production of M-CSF, the major macrophage growth factor, is increased in tissues during inflammation (Le Meur et al, J. Leukocyte Biology. 2002;72:530-537) provides a role for c-fms in certain diseases. For example, COPD is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The chronic inflammation of COPD is observed through the airways, parenchyma, and pulmonary vasculature. The inflammatory cell population consists of neutrophils, macrophages, and T lymphocytes, along with eosinophils in some patients. Macrophages are postulated to play an orchestrating role in COPD inflammation by releasing mediators such as TNF- $\alpha$ , IL-8 and LTB<sub>4</sub>, which are capable of damaging lung structures and/or sustaining neutrophilic inflammation.

[0146] Further, M-CSF/Fms signaling is critical to osteoclast formation and survival of osteoclast precursors. For example, estrogen loss in menopause results in increased M-CSF and thus increased osteoclast number and bone resorption which leads to increased risk of fracture and osteoporosis. Accordingly, blockage of this signal is a target for the inhibition of bone resorption (Teitelbaum, Science. 2000;289:1504; Rohan, Science. 2000;289:1508.)

[0147] Atherosclerosis, an inflammatory disease of the vessel walls, is associated with significant morbidity and mortality. A effect for c-fms inhibition in the treatment and prevention of atherosclerosis depends on several observations (Libby, Nature. 2002;420:868-874.) First, monocytes resident in the arterial intima increase expression of scavenger receptors and internalize modified lipoproteins. The resulting lipid-laden macrophages develop into foam cells characteristic of the atherosclerotic lesion. Macrophages in atheroma secrete cytokines and growth factors involved in lesion progression. Additionally, macrophages replicate within the intima. Through c-fms, M-CSF activates the transition from monocyte to lipid-laden macrophage and augments expression of scavenger receptor A. Indeed, atherosclerotic plaques over-express M-CSF which is critical for atherosclerotic progression. Mice deficient in M-CSF have been found to experience less severe atherosclerosis than mice with normal M-CSF



(Rajavashisth, et. al., J. Clin. Invest. 1998;101:2702-2710; Qiao, et. al., Am. J. Path. 1997;150:1687-1699). Accordingly, inhibitors of c-fms disrupt M-CSF signaling, compromising monocyte to macrophage foam cell progression, macrophage survival and replication, and cytokine signaling that participates in lesion progression.

**[0148]** Wegener's granulomatosis, also known as vasculitis, is characterized by granulomatous inflammation of the blood vessels with necrosis. This inflammation limits blood flow to organs with consequent damage. Although the disease can involve any organ system, Wegener's granulomatosis mainly affects the respiratory tract (i.e., sinuses, nose, trachea, and lungs) and the kidneys. The endothelium plays a central role in the immunopathology of several vascular disorders in many inflammatory conditions such as Wegener's granulomatosis in which use of intravenous immunoglobulin (IV Ig) has been shown to be beneficial (see e.g., Basta et al, J Clin Invest 1994, 94:1729-1735). It has been reported (Xu et al, Am. J. Path. 1998;153:1257-1266) that IV Ig inhibits endothelial cell proliferation in a dose- and time-dependent manner and down-regulates the expression of adhesion molecule mRNA (ICAM-1 and VCAM-1), chemokine mRNA (MCP-1, M-CSF, and GM-CSF), and proinflammatory cytokine mRNA (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) induced by TNF- $\alpha$  or IL-1 $\beta$ . These results may explain, at least in part, the therapeutic effect of IV Ig in vascular and inflammatory disorders. Additionally, these results suggest that inhibition of M-CSF activity at the level of interaction with c-fms is an efficacious treatment strategy.

**[0149]** The role of M-CSF and c-fms in emphysema appears to involve the regulation of elastin metabolism through control of matrix metalloproteins. M-CSF has a role in the modulation of the accumulation and function of alveolar macrophages (AMs) in vivo (Shibata et al, Blood 2001, 98: pp. 2845-2852). Osteopetrotic (Op/Op) mice have no detectable M-CSF and show variable tissue-specific reductions in macrophage numbers. Accordingly, it was hypothesized that AMs would be decreased in number and have altered function in Op/Op mice because of the absence of M-CSF. Shibata et al found that lung macrophages identified in lung sections were decreased in number in 20-day-old Op/Op mice but not Op/Op mice older than 4 months compared with findings in age-matched littermate controls. The numbers of AMs recovered by bronchoalveolar lavage (BAL) were also reduced in young but not adult Op/Op mice compared with controls. Importantly, AMs of Op/Op mice spontaneously release higher levels of matrix



metalloproteinases (MMPs) than AMs of controls. Consistent with an increased release of MMP, Op/Op mice have abnormal elastin deposition and spontaneously develop emphysema in the absence of molecular or cellular evidence of lung inflammation. Accordingly, the modulation of metalloelastase activity in macrophages by M-CSF may control the degradation of elastin fibers in lungs or blood vessels.

**[0150]** Metastatic cancer cells cause bone destruction, with associated fracture, pain, deformation, and hypercalcaemia, due to production of osteoclastogenic factors including M-CSF by tumor cells (Clohisy et al, Clin. Orthop. 2000, 373: 104-14). Binding of M-CSF to the c-fms product stimulates formation of osteoclasts and osteolytic activity (Kodama et al, J. Exp., Med. 1991, 173: 269-72; Feng et al, Endocrinology 2002, 143: 4868-74). Accordingly, inhibition of osteoclast activity at the level of c-fms offers a compelling target for amelioration of bone metastasis.

**[0151]** Macrophage accumulation is a prominent feature in many forms of glomerulonephritis. Local proliferation of macrophages within the kidney has been described in human and experimental glomerulonephritis and may have an important role in augmenting the inflammatory response. Isabel et al (Nephrol Dial Transplant 2001, 16: 1638-1647) examined the relationship between local macrophage proliferation and renal expression of M-CSF. Glomerular and tubulointerstitial M-CSF expression was found to be up-regulated in human glomerulonephritis, being most prominent in proliferative forms of disease. Because this correlates with local macrophage proliferation, it suggests that increased renal M-CSF production plays an important role in regulating local macrophage proliferation in human glomerulonephritis. In a model of renal inflammation (UUO-unilateral ureteric obstruction) anti-c-fms antibody treatment reduced macrophage accumulation (Le Meur et.al., J Leukocyte Biology, 2002, 72: 530-537). Accordingly, inhibition of c-fms offers a target for therapeutic intervention in glomerulonephritis.

**[0152]** Insulin resistance and obesity are hallmark of type II diabetes and there is a strong correlation between insulin resistance and abdominal visceral fat accumulation (Bjorntrop, Diabetes Metab. Res. Rev., 1999, 15: 427-441). Current evidence indicates that macrophages accumulating in adipose tissue release TNF-a and other factors that cause adipocyte changes (hypertrophy, lipolysis, reduced insulin sensitivity) and also promote insulin resistance in surrounding tissues. Therefore, macrophage accumulation in

type 2 diabetes is important for disease progression. Accordingly, inhibition of c-fms has potential in preventing the development of insulin resistance and hyperglycemia.

[0153] Dewar et al. have recently demonstrated that the kinase inhibitor imatinib also specifically targets the macrophage colony stimulating factor receptor, c-fms, at therapeutic concentrations. Although this finding has important implications with regard to potential side effects in patients currently receiving imatinib therapy, these results suggest that imatinib may also be useful in the treatment of diseases where c-fms is implicated. This includes breast and ovarian cancer and inflammatory conditions such as rheumatoid arthritis. Dewar et al. also speculate that imatinib may be used in diseases where bone destruction occurs due to excessive osteoclast activity, such as in the haematologic malignancy, multiple myeloma (Dewar et al., *Cell Cycle* 2005, 4(7):851-3).

[0154] To determine the importance of M-CSF in driving macrophage proliferation during acute rejection, Jose et al. blocked the M-CSF receptor, c-fms, in a mouse model of acute renal allograft rejection. They observed that the severity of tubulointerstitial rejection was reduced in the treatment group as shown by decreased tubulitis and tubular cell proliferation. Macrophage proliferation during acute allograft rejection is dependent on the interaction of M-CSF with its receptor c-fms. They indicate that this pathway plays a significant and specific role in the accumulation of macrophages within a rejecting renal allograft (Jose et al., *Am J Transplant* 2003, 3(3):294-300).

[0155] Further, modulators of both c-fms and c-kit function can be used against diseases such as those indicated above, where in some instances, the dual activity of the modulator for both c-fms and c-kit provides distinct advantages in treating such diseases. The complementary activities provided by a single compound would provide added benefits over compounds targeting one or the other activity, or separate compounds targeting these activities. For example, by attenuating release of macrophage chemo-attractants by mast cells or mast cell chemoattractants by macrophages, these anti-inflammatory effects would synergize with the concomitant inhibition of intrinsic cellular function. Limitations in co-administration are absent in a dual inhibitor. Further, the dual activity may result in much lower effective doses for treatment.



## II. Production of c-kit and c-fms related Polypeptides

[0156] The native and mutated kinase polypeptides described herein may be chemically synthesized in whole or part using techniques that are well-known in the art (see, e.g., Creighton (1983) *Biopolymers* 22(1):49-58).

[0157] Alternatively, methods which are well known to those skilled in the art can be used to construct expression vectors containing the native or mutated kinase polypeptide coding sequence and appropriate transcriptional/translational control signals. These methods include *in vitro* recombinant DNA techniques, synthetic techniques and *in vivo* recombination/genetic recombination. See, for example, the techniques described in Maniatis, T (1989). Molecular cloning: A laboratory Manual. Cold Spring Harbor Laboratory, New York. Cold Spring Harbor Laboratory Press; and Ausubel, F.M. et al. (1994) Current Protocols in Molecular Biology. John Wiley & Sons, Secaucus, N.J.

[0158] A variety of host-expression vector systems may be utilized to express the kinase coding sequence. These include but are not limited to microorganisms such as bacteria transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing the kinase domain coding sequence; yeast transformed with recombinant yeast expression vectors containing the kinase domain coding sequence; insect cell systems infected with recombinant virus expression vectors (*e.g.* baculovirus) containing the kinase domain coding sequence; plant cell systems infected with recombinant virus expression vectors (*e.g.* cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.* Ti plasmid) containing the kinase domain coding sequence; or animal cell systems. The expression elements of these systems vary in their strength and specificities.

[0159] Depending on the host/vector system utilized, any of a number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used in the expression vector. For example, when cloning in bacterial systems, inducible promoters such as pL of bacteriophage  $\lambda$ , plac, ptrp, ptac (ptrp-lac hybrid promoter) and the like may be used; when cloning in insect cell systems, promoters such as the baculovirus polyhedrin promoter may be used; when cloning in plant cell systems, promoters derived from the genome of plant cells (*e.g.* heat shock promoters; the promoter for the small subunit of RUBISCO; the promoter for the chlorophyll a/b binding protein)



or from plant viruses (*e.g.* the 35S RNA promoter of CaMV; the coat protein promoter of TMV) may be used; when cloning in mammalian cell systems, promoters derived from the genome of mammalian cells (*e.g.* metallothionein promoter) or from mammalian viruses (*e.g.* the adenovirus late promoter; the vaccinia virus 7.5K promoter) may be used; when generating cell lines that contain multiple copies of the kinase domain DNA, SV40-, BPV- and EBV-based vectors may be used with an appropriate selectable marker.

[0160] Exemplary methods describing methods of DNA manipulation, vectors, various types of cells used, methods of incorporating the vectors into the cells, expression techniques, protein purification and isolation methods, and protein concentration methods are disclosed in detail in PCT publication WO 96/18738. This publication is incorporated herein by reference in its entirety, including any drawings. Those skilled in the art will appreciate that such descriptions are applicable to the present invention and can be easily adapted to it.

### III. Binding Assays

[0161] The methods of the present invention can involve assays that are able to detect the binding of compounds to a target molecule. Such binding is at a statistically significant level, preferably with a confidence level of at least 90%, more preferably at least 95, 97, 98, 99% or greater confidence level that the assay signal represents binding to the target molecule, *i.e.*, is distinguished from background. Preferably controls are used to distinguish target binding from non-specific binding. A large variety of assays indicative of binding are known for different target types and can be used for this invention.

[0162] Binding compounds can be characterized by their effect on the activity of the target molecule. Thus, a "low activity" compound has an inhibitory concentration ( $IC_{50}$ ) or effective concentration ( $EC_{50}$ ) of greater than 1  $\mu M$  under standard conditions. By "very low activity" is meant an  $IC_{50}$  or  $EC_{50}$  of above 100  $\mu M$  under standard conditions. By "extremely low activity" is meant an  $IC_{50}$  or  $EC_{50}$  of above 1 mM under standard conditions. By "moderate activity" is meant an  $IC_{50}$  or  $EC_{50}$  of 200 nM to 1  $\mu M$  under standard conditions. By "moderately high activity" is meant an  $IC_{50}$  or  $EC_{50}$  of 1 nM to 200 nM. By "high activity" is meant an  $IC_{50}$  or  $EC_{50}$  of below 1 nM under standard conditions. The  $IC_{50}$  or  $EC_{50}$  is defined as the concentration of compound at which 50% of the activity of the target molecule (*e.g.* enzyme or other protein) activity being measured is



lost or gained relative to the range of activity observed when no compound is present. Activity can be measured using methods known to those of ordinary skill in the art, *e.g.*, by measuring any detectable product or signal produced by occurrence of an enzymatic reaction, or other activity by a protein being measured.

[0163] By “background signal” in reference to a binding assay is meant the signal that is recorded under standard conditions for the particular assay in the absence of a test compound, molecular scaffold, or ligand that binds to the target molecule. Persons of ordinary skill in the art will realize that accepted methods exist and are widely available for determining background signal.

[0164] By “standard deviation” is meant the square root of the variance. The variance is a measure of how spread out a distribution is. It is computed as the average squared deviation of each number from its mean. For example, for the numbers 1, 2, and 3, the mean is 2 and the variance is:

$$\sigma^2 = \frac{(1-2)^2 + (2-2)^2 + (3-2)^2}{3} = 0.667 .$$

### Surface Plasmon Resonance

[0165] Binding parameters can be measured using surface plasmon resonance, for example, with a BIAcore<sup>®</sup> chip (Biacore, Japan) coated with immobilized binding components. Surface plasmon resonance is used to characterize the microscopic association and dissociation constants of reaction between an sFv or other ligand directed against target molecules. Such methods are generally described in the following references which are incorporated herein by reference. Vely F. et al., (2000) BIAcore<sup>®</sup> analysis to test phosphopeptide-SH2 domain interactions, *Methods in Molecular Biology*. 121:313-21; Liparoto et al., (1999) Biosensor analysis of the interleukin-2 receptor complex, *Journal of Molecular Recognition*. 12:316-21; Lipschultz et al., (2000) Experimental design for analysis of complex kinetics using surface plasmon resonance, *Methods*. 20(3):310-8; Malmqvist., (1999) BIACORE: an affinity biosensor system for characterization of biomolecular interactions, *Biochemical Society Transactions* 27:335-40; Alfthan, (1998) Surface plasmon resonance biosensors as a tool in antibody engineering, *Biosensors & Bioelectronics*. 13:653-63; Fivash et al., (1998) BIAcore for macromolecular interaction, *Current Opinion in Biotechnology*. 9:97-101; Price et al.; (1998) Summary report on the ISOBM TD-4 Workshop: analysis of 56 monoclonal

antibodies against the MUC1 mucin. *Tumour Biology* 19 Suppl 1:1-20; Malmqvist et al, (1997) Biomolecular interaction analysis: affinity biosensor technologies for functional analysis of proteins, *Current Opinion in Chemical Biology*. 1:378-83; O'Shannessy et al., (1996) Interpretation of deviations from pseudo-first-order kinetic behavior in the characterization of ligand binding by biosensor technology, *Analytical Biochemistry*. 236:275-83; Malmborg et al., (1995) BIAcore as a tool in antibody engineering, *Journal of Immunological Methods*. 183:7-13; Van Regenmortel, (1994) Use of biosensors to characterize recombinant proteins, *Developments in Biological Standardization*. 83:143-51; and O'Shannessy, (1994) Determination of kinetic rate and equilibrium binding constants for macromolecular interactions: a critique of the surface plasmon resonance literature, *Current Opinions in Biotechnology*. 5:65-71.

[0166] BIAcore<sup>®</sup> uses the optical properties of surface plasmon resonance (SPR) to detect alterations in protein concentration bound to a dextran matrix lying on the surface of a gold/glass sensor chip interface, a dextran biosensor matrix. In brief, proteins are covalently bound to the dextran matrix at a known concentration and a ligand for the protein is injected through the dextran matrix. Near infrared light, directed onto the opposite side of the sensor chip surface is reflected and also induces an evanescent wave in the gold film, which in turn, causes an intensity dip in the reflected light at a particular angle known as the resonance angle. If the refractive index of the sensor chip surface is altered (e.g. by ligand binding to the bound protein) a shift occurs in the resonance angle. This angle shift can be measured and is expressed as resonance units (RUs) such that 1000 RUs is equivalent to a change in surface protein concentration of 1 ng/mm<sup>2</sup>. These changes are displayed with respect to time along the y-axis of a sensorgram, which depicts the association and dissociation of any biological reaction.

### **High Throughput Screening (HTS) Assays**

[0167] HTS typically uses automated assays to search through large numbers of compounds for a desired activity. Typically HTS assays are used to find new drugs by screening for chemicals that act on a particular enzyme or molecule. For example, if a chemical inactivates an enzyme it might prove to be effective in preventing a process in a cell which causes a disease. High throughput methods enable researchers to assay thousands of different chemicals against each target molecule very quickly using robotic handling systems and automated analysis of results.



[0168] As used herein, "high throughput screening" or "HTS" refers to the rapid in vitro screening of large numbers of compounds (libraries); generally tens to hundreds of thousands of compounds, using robotic screening assays. Ultra high-throughput Screening (uHTS) generally refers to the high-throughput screening accelerated to greater than 100,000 tests per day.

[0169] To achieve high-throughput screening, it is advantageous to house samples on a multicontainer carrier or platform. A multicontainer carrier facilitates measuring reactions of a plurality of candidate compounds simultaneously. Multi-well microplates may be used as the carrier. Such multi-well microplates, and methods for their use in numerous assays, are both known in the art and commercially available.

[0170] Screening assays may include controls for purposes of calibration and confirmation of proper manipulation of the components of the assay. Blank wells that contain all of the reactants but no member of the chemical library are usually included. As another example, a known inhibitor (or activator) of an enzyme for which modulators are sought, can be incubated with one sample of the assay, and the resulting decrease (or increase) in the enzyme activity used as a comparator or control. It will be appreciated that modulators can also be combined with the enzyme activators or inhibitors to find modulators which inhibit the enzyme activation or repression that is otherwise caused by the presence of the known the enzyme modulator.

#### **Measuring Enzymatic and Binding Reactions During Screening Assays**

[0171] Techniques for measuring the progression of enzymatic and binding reactions, e.g., in multicontainer carriers, are known in the art and include, but are not limited to, the following.

[0172] Spectrophotometric and spectrofluorometric assays are well known in the art. Examples of such assays include the use of colorimetric assays for the detection of peroxides, as described in Gordon, A. J. and Ford, R. A., (1972) The Chemist's Companion: A Handbook Of Practical Data, Techniques, And References, John Wiley and Sons, N.Y., Page 437.

[0173] Fluorescence spectrometry may be used to monitor the generation of reaction products. Fluorescence methodology is generally more sensitive than the absorption

methodology. The use of fluorescent probes is well known to those skilled in the art. For reviews, see Bashford et al., (1987) Spectrophotometry and Spectrofluorometry: A Practical Approach, pp. 91-114, IRL Press Ltd.; and Bell, (1981) Spectroscopy In Biochemistry, Vol. I, pp. 155-194, CRC Press.

[0174] In spectrofluorometric methods, enzymes are exposed to substrates that change their intrinsic fluorescence when processed by the target enzyme. Typically, the substrate is nonfluorescent and is converted to a fluorophore through one or more reactions. As a non-limiting example, SMase activity can be detected using the Amplex<sup>®</sup> Red reagent (Molecular Probes, Eugene, OR). In order to measure sphingomyelinase activity using Amplex<sup>®</sup> Red, the following reactions occur. First, SMase hydrolyzes sphingomyelin to yield ceramide and phosphorylcholine. Second, alkaline phosphatase hydrolyzes phosphorylcholine to yield choline. Third, choline is oxidized by choline oxidase to betaine. Finally, H<sub>2</sub>O<sub>2</sub>, in the presence of horseradish peroxidase, reacts with Amplex<sup>®</sup> Red to produce the fluorescent product, Resorufin, and the signal therefrom is detected using spectrofluorometry.

[0175] Fluorescence polarization (FP) is based on a decrease in the speed of molecular rotation of a fluorophore that occurs upon binding to a larger molecule, such as a receptor protein, allowing for polarized fluorescent emission by the bound ligand. FP is empirically determined by measuring the vertical and horizontal components of fluorophore emission following excitation with plane polarized light. Polarized emission is increased when the molecular rotation of a fluorophore is reduced. A fluorophore produces a larger polarized signal when it is bound to a larger molecule (i.e. a receptor), slowing molecular rotation of the fluorophore. The magnitude of the polarized signal relates quantitatively to the extent of fluorescent ligand binding. Accordingly, polarization of the "bound" signal depends on maintenance of high affinity binding.

[0176] FP is a homogeneous technology and reactions are very rapid, taking seconds to minutes to reach equilibrium. The reagents are stable, and large batches may be prepared, resulting in high reproducibility. Because of these properties, FP has proven to be highly automatable, often performed with a single incubation with a single, premixed, tracer-receptor reagent. For a review, see Owickiet al., (1997), Application of Fluorescence Polarization Assays in High-Throughput Screening, Genetic Engineering News, 17:27.



[0177] FP is particularly desirable since its readout is independent of the emission intensity (Checovich, W. J., et al., (1995) *Nature* 375:254-256; Dandliker, W. B., et al., (1981) *Methods in Enzymology* 74:3-28) and is thus insensitive to the presence of colored compounds that quench fluorescence emission. FP and FRET (see below) are well-suited for identifying compounds that block interactions between sphingolipid receptors and their ligands. See, for example, Parker et al., (2000) *Development of high throughput screening assays using fluorescence polarization: nuclear receptor-ligand-binding and kinase/phosphatase assays*, *J Biomol Screen* 5:77-88.

[0178] Fluorophores derived from sphingolipids that may be used in FP assays are commercially available. For example, Molecular Probes (Eugene, OR) currently sells sphingomyelin and one ceramide fluorophores. These are, respectively, N-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-pentanoyl)sphingosyl phosphocholine (BODIPY® FL C5-sphingomyelin); N-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-dodecanoyl)sphingosyl phosphocholine (BODIPY® FL C12-sphingomyelin); and N-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-pentanoyl)sphingosine (BODIPY® FL C5-ceramide). U.S. Patent No. 4,150,949, (Immunoassay for gentamicin), discloses fluorescein-labelled gentamicins, including fluoresceinthiocarbonyl gentamicin. Additional fluorophores may be prepared using methods well known to the skilled artisan.

[0179] Exemplary normal-and-polarized fluorescence readers include the POLARION® fluorescence polarization system (Tecan AG, Hombrechtikon, Switzerland). General multiwell plate readers for other assays are available, such as the VERSAMAX® reader and the SPECTRAMAX® multiwell plate spectrophotometer (both from Molecular Devices).

[0180] Fluorescence resonance energy transfer (FRET) is another useful assay for detecting interaction and has been described. See, e.g., Heim et al., (1996) *Curr. Biol.* 6:178-182; Mitra et al., (1996) *Gene* 173:13-17; and Selvin et al., (1995) *Meth. Enzymol.* 246:300-345. FRET detects the transfer of energy between two fluorescent substances in close proximity, having known excitation and emission wavelengths. As an example, a protein can be expressed as a fusion protein with green fluorescent protein (GFP). When two fluorescent proteins are in proximity, such as when a protein specifically interacts with a target molecule, the resonance energy can be transferred from one excited molecule

to the other. As a result, the emission spectrum of the sample shifts, which can be measured by a fluorometer, such as a fMAX multiwell fluorometer (Molecular Devices, Sunnyvale Calif.).

**[0181]** Scintillation proximity assay (SPA) is a particularly useful assay for detecting an interaction with the target molecule. SPA is widely used in the pharmaceutical industry and has been described (Hanselman et al., (1997) *J. Lipid Res.* 38:2365-2373; Kahl et al., (1996) *Anal. Biochem.* 243:282-283; Udenfriend et al., (1987) *Anal. Biochem.* 161:494-500). See also U.S. Patent Nos. 4,626,513 and 4,568,649, and European Patent No. 0,154,734. One commercially available system uses FLASHPLATE<sup>®</sup> scintillant-coated plates (NEN Life Science Products, Boston, MA).

**[0182]** The target molecule can be bound to the scintillator plates by a variety of well known means. Scintillant plates are available that are derivatized to bind to fusion proteins such as GST, His6 or Flag fusion proteins. Where the target molecule is a protein complex or a multimer, one protein or subunit can be attached to the plate first, then the other components of the complex added later under binding conditions, resulting in a bound complex.

**[0183]** In a typical SPA assay, the gene products in the expression pool will have been radiolabeled and added to the wells, and allowed to interact with the solid phase, which is the immobilized target molecule and scintillant coating in the wells. The assay can be measured immediately or allowed to reach equilibrium. Either way, when a radiolabel becomes sufficiently close to the scintillant coating, it produces a signal detectable by a device such as a TOPCOUNT NXT<sup>®</sup> microplate scintillation counter (Packard BioScience Co., Meriden Conn.). If a radiolabeled expression product binds to the target molecule, the radiolabel remains in proximity to the scintillant long enough to produce a detectable signal.

**[0184]** In contrast, the labeled proteins that do not bind to the target molecule, or bind only briefly, will not remain near the scintillant long enough to produce a signal above background. Any time spent near the scintillant caused by random Brownian motion will also not result in a significant amount of signal. Likewise, residual unincorporated radiolabel used during the expression step may be present, but will not generate significant signal because it will be in solution rather than interacting with the target molecule. These



non-binding interactions will therefore cause a certain level of background signal that can be mathematically removed. If too many signals are obtained, salt or other modifiers can be added directly to the assay plates until the desired specificity is obtained (Nichols et al., (1998) *Anal. Biochem.* 257:112-119).

#### IV. Kinase Activity Assays

[0185] A number of different assays for kinase activity can be utilized for assaying for active modulators and/or determining specificity of a modulator for a particular kinase or group of kinases. In addition to the assay mentioned in the Examples below, one of ordinary skill in the art will know of other assays that can be utilized and can modify an assay for a particular application. For example, numerous papers concerning kinases described assays that can be used.

[0186] Additional alternative assays can employ binding determinations. For example, this sort of assay can be formatted either in a fluorescence resonance energy transfer (FRET) format, or using an AlphaScreen (*amplified luminescent proximity homogeneous assay*) format by varying the donor and acceptor reagents that are attached to streptavidin or the phospho-specific antibody.

#### V. Organic Synthetic Techniques

[0187] A wide array of organic synthetic techniques exist in the art to meet the challenge of constructing potential modulators. Many of these organic synthetic methods are described in detail in standard reference sources utilized by those skilled in the art. One example of such a reference is March, 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, New York, McGraw Hill. Thus, the techniques useful to synthesize a potential modulator of kinase function are readily available to those skilled in the art of organic chemical synthesis.

[0188] Regarding the synthetic examples described herein, solvents include polar and non-polar solvents known to those of skill in the art, including polar aprotic and polar protic solvents. Polar solvents include, without limitation, protic solvents such as methanol, ethanol, isopropyl alcohol, t-butanol, n-butanol, acetic acid, formic acid or water, or aprotic solvents such as tetrahydrofuran (THF), acetonitrile, dioxane, methylene chloride, dimethylsulfoxide (DMSO), acetone, N,N-dimethylformamide (DMF), N,N-

dimethylacetamide (DMA), ethyl acetate, 1,2-dimethoxyethane, 1,2-dichloroethane, chloroform, 1,2-dichloroethane, or pyridine. Polar solvents include a mixture of water with any of the above, or a mixture of any two or more of the above. Apolar solvents include, without limitation, toluene, benzene, chlorobenzene, xylenes and hexanes.

**[0189]** Regarding the synthetic examples described herein, reducing agent includes, without limitation, a reducing agent such as catalytic reducing agents using hydrogen and transition metal catalysts such as palladium, platinum, rhodium, etc.(e.g. Pt/acetic acid/H<sub>2</sub>); a mixture of trifluoroacetic acid and triethylsilane, borane tetrahydrofuran complex, diborane, borane dimethylsulfide complex, and a combination of sodium borohydride and boron trifluoride; metals such as reduced iron, zinc powder, magnesium etc.; metal hydrogen complex compounds such as alkali metal borohydrides (for example, potassium borohydride, sodium borohydride, lithium borohydride, zinc borohydride, sodium triacetoxyborohydride, etc.), aluminum lithium hydride, etc.; metal hydrides such as sodium hydride, etc.; organic tin compounds (triphenyltin hydride, etc.); and metal salts such as nickel compounds, zinc compounds, tin compounds (for example tin(II) chloride), and samarium iodide/pivalic acid/hexamethylphosphoric triamide.

**[0190]** Regarding the synthetic examples described herein, oxidizing agent includes, without limitation, an oxidizing agent such as Dess-Martin reagent, TEMPO (2,2,6,6-tetramethylpiperidine-N-oxide), DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone), PDC (pyridinium dichromate), PCC (pyridinium chlorochromate), Pyridine.SO<sub>3</sub>, Chromium trioxide, p-nitroperbenzoic acid, magnesium monoperoxyphthalate, sodium periodate, potassium periodate, hydrogen peroxide, urea peroxide, alkali metal bromates, cumene hydroperoxide, tert-butyl peroxide, peracids such as performic acid, peracetic acid, pertrifluoroacetic acid, perbenzoic acid, m-chloroperbenzoic acid, o-carboxyperbenzoic acid and the like; sodium metaperiodate, bichromic acid; bichromates such as sodium bichromate, potassium bichromate; permanganic acid; permanganates such as potassium permanganate, sodium permanganate; and lead salts such as lead tetraacetate.



## VI. Alternative Compound Forms or Derivatives

### (a) Isomers, Prodrugs, and Active Metabolites

[0191] Compounds contemplated herein are described with reference to both generic formulae and specific compounds. In addition, the invention compounds may exist in a number of different forms or derivatives, all within the scope of the present invention. These include, for example, tautomers, stereoisomers, racemic mixtures, regioisomers, salts, prodrugs (e.g. carboxylic acid esters), solvated forms, different crystal forms or polymorphs, and active metabolites.

### (b) Tautomers, Stereoisomers, Regioisomers, and Solvated Forms

[0192] It is understood that certain compounds may exhibit tautomerism. In such cases, the formulae provided herein expressly depict only one of the possible tautomeric forms. It is therefore to be understood that the formulae provided herein are intended to represent any tautomeric form of the depicted compounds and are not to be limited merely to the specific tautomeric form depicted by the drawings of the formulae.

[0193] Likewise, some of the compounds according to the present invention may exist as stereoisomers, i.e. they have the same sequence of covalently bonded atoms and differ in the spatial orientation of the atoms. For example, compounds may be optical stereoisomers, which contain one or more chiral centers, and therefore, may exist in two or more stereoisomeric forms (e.g. enantiomers or diastereomers). Thus, such compounds may be present as single stereoisomers (i.e., essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. As another example, stereoisomers include geometric isomers, such as *cis*- or *trans*- orientation of substituents on adjacent carbons of a double bond. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Unless specified to the contrary, all such stereoisomeric forms are included within the formulae provided herein.

[0194] In certain embodiments, a chiral compound of the present invention is in a form that contains at least 80% of a single isomer (60% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), or at least 85% (70% e.e. or d.e.), 90% (80% e.e. or d.e.), 95% (90% e.e. or d.e.), 97.5% (95% e.e. or d.e.), or 99% (98% e.e. or d.e.). As generally

understood by those skilled in the art, an optically pure compound having one chiral center is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. In certain embodiments, the compound is present in optically pure form.

[0195] For compounds in which synthesis involves addition of a single group at a double bond, particularly a carbon-carbon double bond, the addition may occur at either of the double bond-linked atoms. For such compounds, the present invention includes both such regioisomers.

[0196] Additionally, the formulae are intended to cover solvated as well as unsolvated forms of the identified structures. For example, the indicated structures include both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

### (c) Prodrugs and Metabolites

[0197] In addition to the present formulae and compounds described herein, the invention also includes prodrugs (generally pharmaceutically acceptable prodrugs), active metabolic derivatives (active metabolites), and their pharmaceutically acceptable salts.

[0198] Prodrugs are compounds or pharmaceutically acceptable salts thereof which, when metabolized under physiological conditions or when converted by solvolysis, yield the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolism, the ester group is cleaved to yield the active drug. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound.

[0199] As described in The Practice of Medicinal Chemistry, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, CA, 2001), prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. Generally, bioprecursor prodrugs are compounds that are inactive or have low activity compared to



the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity. Typically, the formation of active drug compound involves a metabolic process or reaction that is one of the follow types:

**[0200]** Oxidative reactions: Oxidative reactions are exemplified without limitation to reactions such as oxidation of alcohol, carbonyl, and acid functions, hydroxylation of aliphatic carbons, hydroxylation of alicyclic carbon atoms, oxidation of aromatic carbon atoms, oxidation of carbon-carbon double bonds, oxidation of nitrogen-containing functional groups, oxidation of silicon, phosphorus, arsenic, and sulfur, oxidative N-dealkylation, oxidative O- and S-dealkylation, oxidative deamination, as well as other oxidative reactions.

**[0201]** Reductive reactions: Reductive reactions are exemplified without limitation to reactions such as reduction of carbonyl groups, reduction of hydroxyl groups and carbon-carbon double bonds, reduction of nitrogen-containing functions groups, and other reduction reactions.

**[0202]** Reactions without change in the oxidation state: Reactions without change in the state of oxidation are exemplified without limitation to reactions such as hydrolysis of esters and ethers, hydrolytic cleavage of carbon-nitrogen single bonds, hydrolytic cleavage of non-aromatic heterocycles, hydration and dehydration at multiple bonds, new atomic linkages resulting from dehydration reactions, hydrolytic dehalogenation, removal of hydrogen halide molecule, and other such reactions.

**[0203]** Carrier prodrugs are drug compounds that contain a transport moiety, e.g., that improves uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, the prodrug and any release transport moiety are acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, e.g., certain polymers or other moieties, such as cyclodextrins. (See, e.g., Cheng et al., U.S. Patent Publ. No. 2004/0077595, Ser. No. 10/656,838, incorporated herein by reference.)

Such carrier prodrugs are often advantageous for orally administered drugs. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (e.g. stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of hydroxyl groups with lipophilic carboxylic acids, or of carboxylic acid groups with alcohols, e.g., aliphatic alcohols. Wermuth, The Practice of Medicinal Chemistry, Ch. 31-32, Ed. Wermuth, Academic Press, San Diego, CA, 2001.

[0204] Prodrugs may proceed from prodrug form to active form in a single step or may have one or more intermediate forms which may themselves have activity or may be inactive.

[0205] Metabolites, e.g., active metabolites, overlap with prodrugs as described above, e.g., bioprecursor prodrugs. Thus, such metabolites are pharmacologically active compounds or compounds that further metabolize to pharmacologically active compounds that are derivatives resulting from metabolic process in the body of a subject or patient. Of these, active metabolites are such pharmacologically active derivative compounds. For prodrugs, the prodrug compounds is generally inactive or of lower activity than the metabolic product. For active metabolites, the parent compound may be either an active compound or may be an inactive prodrug.

[0206] Prodrugs and active metabolites may be identified using routine techniques known in the art. See, e.g., Bertolini et al., 1997, *J. Med. Chem.*, 40:2011-2016; Shan et al., 1997, *J Pharm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev. Res.*, 34:220-230; Wermuth, The Practice of Medicinal Chemistry, Ch. 31-32, Academic Press, San Diego, CA, 2001.

#### **(d) Pharmaceutically acceptable salts**

[0207] Compounds can be formulated as or be in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without



preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

[0208] Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, chloride, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

[0209] Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see Remington's Pharmaceutical Sciences, 19<sup>th</sup> ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. Such salts can be prepared using the appropriate corresponding bases.

[0210] Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free-base form of a compound can be dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol solution containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt can be prepared by reacting the free base and acid in an organic solvent.

[0211] Thus, for example, if the particular compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such

as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0212] Similarly, if the particular compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[0213] The pharmaceutically acceptable salt of the different compounds may be present as a complex. Examples of complexes include 8-chlorotheophylline complex (analogous to, *e.g.*, dimenhydrinate: diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

[0214] Unless specified to the contrary, specification of a compound herein includes pharmaceutically acceptable salts of such compound.

#### **(e) Polymorphic forms**

[0215] In the case of agents that are solids, it is understood by those skilled in the art that the compounds and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

### **VII. Administration**

[0216] The methods and compounds will typically be used in therapy for human patients. However, they may also be used to treat similar or identical diseases in other vertebrates, *e.g.*, mammals such as other primates, animals of commercial significance, *e.g.*, sports animals, farm animals, *e.g.*, bovines, equines, porcines, and ovines, and pets such as dogs and cats.

[0217] Suitable dosage forms, in part, depend upon the use or the route of administration, for example, oral, transdermal, transmucosal, inhalant, or by injection



(parenteral). Such dosage forms should allow the compound to reach target cells. Other factors are well known in the art, and include considerations such as toxicity and dosage forms that retard the compound or composition from exerting its effects. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy, 21<sup>st</sup> edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (hereby incorporated by reference herein).

[0218] Compounds of the present invention (i.e. Formula I, including Formulae Ia, Ib, Ig and all sub-embodiments disclosed herein) can be formulated as pharmaceutically acceptable salts.

[0219] Carriers or excipients can be used to produce compositions. The carriers or excipients can be chosen to facilitate administration of the compound. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Examples of physiologically compatible solvents include sterile solutions of water for injection (WFI), saline solution, and dextrose.

[0220] The compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, transmucosal, rectal, transdermal, or inhalant. In some embodiments, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

[0221] Pharmaceutical preparations for oral use can be obtained, for example, by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate.

[0222] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain, for example, gum arabic, talc, poly-vinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0223] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin ("gelcaps"), 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, binders such as starches, and/or lubricants 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 (PEGs). In addition, stabilizers may be added.

[0224] Alternatively, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and/or subcutaneous. For injection, the compounds of the invention are formulated in sterile liquid solutions, preferably in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

[0225] Administration can also be by transmucosal, topical, transdermal, or inhalant means. For transmucosal, topical or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays or suppositories (rectal or vaginal).

[0226] The topical compositions of this invention are formulated preferably as oils, creams, lotions, ointments, and the like by choice of appropriate carriers known in the art. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin),



branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C<sub>12</sub>). The preferred carriers are those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Creams for topical application are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount solvent (e.g. an oil), is admixed. Additionally, administration by transdermal means may comprise a transdermal patch or dressing such as a bandage impregnated with an active ingredient and optionally one or more carriers or diluents known in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[0227] For inhalants, compounds of the invention may be formulated as dry powder or a suitable solution, suspension, or aerosol. Powders and solutions may be formulated with suitable additives known in the art. For example, powders may include a suitable powder base such as lactose or starch, and solutions may comprise propylene glycol, sterile water, ethanol, sodium chloride and other additives, such as acid, alkali and buffer salts. Such solutions or suspensions may be administered by inhaling via spray, pump, atomizer, or nebulizer, and the like. The compounds of the invention may also be used in combination with other inhaled therapies, for example corticosteroids such as fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and mometasone furoate; beta agonists such as albuterol, salmeterol, and formoterol; anticholinergic agents such as ipratropium bromide or tiotropium; vasodilators such as treprostinil and iloprost; enzymes such as DNAase; therapeutic proteins; immunoglobulin antibodies; an oligonucleotide, such as single or double stranded DNA or RNA, siRNA; antibiotics such as tobramycin; muscarinic receptor antagonists; leukotriene antagonists; cytokine antagonists; protease inhibitors; cromolyn sodium; nedocril sodium; and sodium cromoglycate.

[0228] The compounds of the invention may also be used in combination with other therapies for treating the same disease. Such combination use includes administration of the compounds and one or more other therapeutics at different times, or co-administration of the compound and one or more other therapies. In certain embodiments, dosage may be modified for one or more of the compounds of the invention or other therapeutics used in



combination, e.g., reduction in the amount dosed relative to a compound or therapy used alone, by methods well known to those of ordinary skill in the art.

[0229] It is understood that use in combination includes use with other therapies, drugs, medical procedures etc., where the other therapy or procedure may be administered at different times (e.g. within a short time, such as within hours (e.g. 1, 2, 3, 4-24 hours), or within a longer time (e.g. 1-2 days, 2-4 days, 4-7 days, 1-4 weeks)) than a compound of the present invention, or at the same time as a compound of the invention. Use in combination also includes use with a therapy or medical procedure that is administered once or infrequently, such as surgery, along with a compound of the invention administered within a short time or longer time before or after the other therapy or procedure. In certain embodiments, the present invention provides for delivery of compounds of the invention and one or more other drug therapeutics delivered by a different route of administration or by the same route of administration. The use in combination for any route of administration includes delivery of compounds of the invention and one or more other drug therapeutics delivered by the same route of administration together in any formulation, including formulations where the two compounds are chemically linked in such a way that they maintain their therapeutic activity when administered. In one aspect, the other drug therapy may be co-administered with one or more compounds of the invention. Use in combination by co-administration includes administration of co-formulations or formulations of chemically joined compounds, or administration of two or more compounds in separate formulations within a short time of each other (e.g. within an hour, 2 hours, 3 hours, up to 24 hours), administered by the same or different routes. Co-administration of separate formulations includes co-administration by delivery via one device, for example the same inhalant device, the same syringe, etc., or administration from separate devices within a short time of each other. Co-formulations of compounds of the invention and one or more additional drug therapies delivered by the same route includes preparation of the materials together such that they can be administered by one device, including the separate compounds combined in one formulation, or compounds that are modified such that they are chemically joined, yet still maintain their biological activity. Such chemically joined compounds may have a linkage that is substantially maintained *in vivo*, or the linkage may break down *in vivo*, separating the two active components.



[0230] The amounts of various compound to be administered as an effective amount can be determined by standard procedures taking into account factors such as the compound  $IC_{50}$ , the biological half-life of the compound, the age, size, and weight of the subject, and the disorder associated with the subject. The importance of these and other factors are well known to those of ordinary skill in the art. Generally, a dose will be between about 0.01 and 50 mg/kg, preferably 0.1 and 20 mg/kg of the subject being treated. Multiple doses may be used.

### VIII. Manipulation of c-kit and c-fms

[0231] As the full-length coding sequence and amino acid sequence of c-kit and c-fms from various mammals including human is known, cloning, construction of recombinant c-kit and c-fms, production and purification of recombinant protein, introduction of c-kit or c-fms into other organisms, and other molecular biological manipulations of c-kit and c-fms are readily performed.

[0232] Techniques for the manipulation of nucleic acids, such as, e.g., subcloning, labeling probes (e.g. random-primer labeling using Klenow polymerase, nick translation, amplification), sequencing, hybridization and the like are well disclosed in the scientific and patent literature, see, e.g., Sambrook, ed., *Molecular Cloning: a Laboratory Manual* (2nd ed.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989); *Current Protocols in Molecular Biology*, Ausubel, ed. John Wiley & Sons, Inc., New York (1997); *Laboratory Techniques in Biochemistry and Molecular Biology: Hybridization With Nucleic Acid Probes, Part I. Theory and Nucleic Acid Preparation*, Tijssen, ed. Elsevier, N.Y. (1993).

[0233] Nucleic acid sequences can be amplified as necessary for further use using amplification methods, such as PCR, isothermal methods, rolling circle methods, etc., are well known to the skilled artisan. See, e.g., Saiki, "Amplification of Genomic DNA" in *PCR Protocols*, Innis et al., Eds., Academic Press, San Diego, CA 1990, pp 13-20; Wharam et al., *Nucleic Acids Res.* 2001 Jun 1;29(11):E54-E54; Hafner et al., *Biotechniques* 2001 Apr;30(4):852-6, 858, 860 passim; Zhong et al., *Biotechniques* 2001 Apr;30(4):852-6, 858, 860 passim.

[0234] Nucleic acids, vectors, capsids, polypeptides, and the like can be analyzed and quantified by any of a number of general means well known to those of skill in the art.

These include, e.g., analytical biochemical methods such as NMR, spectrophotometry, radiography, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), and hyperdiffusion chromatography, various immunological methods, e.g. fluid or gel precipitin reactions, immunodiffusion, immuno-electrophoresis, radioimmunoassays (RIAs), enzyme-linked immunosorbent assays (ELISAs), immuno-fluorescent assays, Southern analysis, Northern analysis, dot-blot analysis, gel electrophoresis (e.g. SDS-PAGE), nucleic acid or target or signal amplification methods, radiolabeling, scintillation counting, and affinity chromatography.

[0235] Obtaining and manipulating nucleic acids used to practice the methods of the invention can be performed by cloning from genomic samples, and, if desired, screening and re-cloning inserts isolated or amplified from, e.g., genomic clones or cDNA clones. Sources of nucleic acid used in the methods of the invention include genomic or cDNA libraries contained in, e.g., mammalian artificial chromosomes (MACs), see, e.g., U.S. Patent Nos. 5,721,118; 6,025,155; human artificial chromosomes, see, e.g., Rosenfeld (1997) *Nat. Genet.* 15:333-335; yeast artificial chromosomes (YAC); bacterial artificial chromosomes (BAC); P1 artificial chromosomes, see, e.g., Woon (1998) *Genomics* 50:306-316; P1-derived vectors (PACs), see, e.g., Kern (1997) *Biotechniques* 23:120-124; cosmids, recombinant viruses, phages or plasmids.

[0236] The nucleic acids of the invention can be operatively linked to a promoter. A promoter can be one motif or an array of nucleic acid control sequences which direct transcription of a nucleic acid. A promoter can include necessary nucleic acid sequences near the start site of transcription, such as, in the case of a polymerase II type promoter, a TATA element. A promoter also optionally includes distal enhancer or repressor elements which can be located as much as several thousand base pairs from the start site of transcription. A "constitutive" promoter is a promoter which is active under most environmental and developmental conditions. An "inducible" promoter is a promoter which is under environmental or developmental regulation. A "tissue specific" promoter is active in certain tissue types of an organism, but not in other tissue types from the same organism. The term "operably linked" refers to a functional linkage between a nucleic acid expression control sequence (such as a promoter, or array of transcription factor



binding sites) and a second nucleic acid sequence, wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence.

[0237] The nucleic acids of the invention can also be provided in expression vectors and cloning vehicles, e.g., sequences encoding the polypeptides of the invention. Expression vectors and cloning vehicles of the invention can comprise viral particles, baculovirus, phage, plasmids, phagemids, cosmids, fosmids, bacterial artificial chromosomes, viral DNA (e.g. vaccinia, adenovirus, fowl pox virus, pseudorabies and derivatives of SV40), P1-based artificial chromosomes, yeast plasmids, yeast artificial chromosomes, and any other vectors specific for specific hosts of interest (such as bacillus, *Aspergillus* and yeast). Vectors of the invention can include chromosomal, non-chromosomal and synthetic DNA sequences. Large numbers of suitable vectors are known to those of skill in the art, and are commercially available.

[0238] The nucleic acids of the invention can be cloned, if desired, into any of a variety of vectors using routine molecular biological methods; methods for cloning *in vitro* amplified nucleic acids are disclosed, e.g., U.S. Pat. No. 5,426,039. To facilitate cloning of amplified sequences, restriction enzyme sites can be “built into” a PCR primer pair. Vectors may be introduced into a genome or into the cytoplasm or a nucleus of a cell and expressed by a variety of conventional techniques, well described in the scientific and patent literature. See, e.g., Roberts (1987) *Nature* 328:731; Schneider (1995) *Protein Expr. Purif.* 6435:10; Sambrook, Tijssen or Ausubel. The vectors can be isolated from natural sources, obtained from such sources as ATCC or GenBank libraries, or prepared by synthetic or recombinant methods. For example, the nucleic acids of the invention can be expressed in expression cassettes, vectors or viruses which are stably or transiently expressed in cells (e.g. episomal expression systems). Selection markers can be incorporated into expression cassettes and vectors to confer a selectable phenotype on transformed cells and sequences. For example, selection markers can code for episomal maintenance and replication such that integration into the host genome is not required.

[0239] In one aspect, the nucleic acids of the invention are administered *in vivo* for *in situ* expression of the peptides or polypeptides of the invention. The nucleic acids can be administered as “naked DNA” (see, e.g., U.S. Patent No. 5,580,859) or in the form of an expression vector, e.g., a recombinant virus. The nucleic acids can be administered by any



route, including peri- or intra-tumorally, as described below. Vectors administered *in vivo* can be derived from viral genomes, including recombinantly modified enveloped or non-enveloped DNA and RNA viruses, preferably selected from baculoviridae, parvoviridae, picornoviridae, herpesviridae, poxviridae, adenoviridae, or picornaviridae. Chimeric vectors may also be employed which exploit advantageous merits of each of the parent vector properties (See e.g., Feng (1997) *Nature Biotechnology* 15:866-870). Such viral genomes may be modified by recombinant DNA techniques to include the nucleic acids of the invention; and may be further engineered to be replication deficient, conditionally replicating or replication competent. In alternative aspects, vectors are derived from the adenoviral (e.g. replication incompetent vectors derived from the human adenovirus genome, see, e.g., U.S. Patent Nos. 6,096,718; 6,110,458; 6,113,913; 5,631,236); adeno-associated viral and retroviral genomes. Retroviral vectors can include those based upon murine leukemia virus (MuLV), gibbon ape leukemia virus (GaLV), Simian Immuno deficiency virus (SIV), human immuno deficiency virus (HIV), and combinations thereof; see, e.g., U.S. Patent Nos. 6,117,681; 6,107,478; 5,658,775; 5,449,614; Buchscher (1992) *J. Virol.* 66:2731-2739; Johann (1992) *J. Virol.* 66:1635-1640). Adeno-associated virus (AAV)-based vectors can be used to transduce cells with target nucleic acids, e.g., in the *in vitro* production of nucleic acids and peptides, and in *in vivo* and *ex vivo* gene therapy procedures; see, e.g., U.S. Patent Nos. 6,110,456; 5,474,935; Okada (1996) *Gene Ther.* 3:957-964.

[0240] The present invention also relates to fusion proteins, and nucleic acids encoding them. A polypeptide of the invention can be fused to a heterologous peptide or polypeptide, such as N-terminal identification peptides which impart desired characteristics, such as increased stability or simplified purification. Peptides and polypeptides of the invention can also be synthesized and expressed as fusion proteins with one or more additional domains linked thereto for, e.g., producing a more immunogenic peptide, to more readily isolate a recombinantly synthesized peptide, to identify and isolate antibodies and antibody-expressing B cells, and the like. Detection and purification facilitating domains include, e.g., metal chelating peptides such as polyhistidine tracts and histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification



system (Immunex Corp, Seattle WA). The inclusion of a cleavable linker sequences such as Factor Xa or enterokinase (Invitrogen, San Diego CA) between a purification domain and the motif-comprising peptide or polypeptide to facilitate purification. For example, an expression vector can include an epitope-encoding nucleic acid sequence linked to six histidine residues followed by a thioredoxin and an enterokinase cleavage site (see e.g., Williams (1995) *Biochemistry* 34:1787-1797; Dobeli (1998) *Protein Expr. Purif.* 12:404-414). The histidine residues facilitate detection and purification while the enterokinase cleavage site provides a means for purifying the epitope from the remainder of the fusion protein. In one aspect, a nucleic acid encoding a polypeptide of the invention is assembled in appropriate phase with a leader sequence capable of directing secretion of the translated polypeptide or fragment thereof. Technology pertaining to vectors encoding fusion proteins and application of fusion proteins are well disclosed in the scientific and patent literature, see e.g., Kroll (1993) *DNA Cell. Biol.* 12:441-53.

**[0241]** The nucleic acids and polypeptides of the invention can be bound to a solid support, e.g., for use in screening and diagnostic methods. Solid supports can include, e.g., membranes (e.g. nitrocellulose or nylon), a microtiter dish (e.g. PVC, polypropylene, or polystyrene), a test tube (glass or plastic), a dip stick (e.g. glass, PVC, polypropylene, polystyrene, latex and the like), a microfuge tube, or a glass, silica, plastic, metallic or polymer bead or other substrate such as paper. One solid support uses a metal (e.g. cobalt or nickel)-comprising column which binds with specificity to a histidine tag engineered onto a peptide.

**[0242]** Adhesion of molecules to a solid support can be direct (i.e., the molecule contacts the solid support) or indirect (a "linker" is bound to the support and the molecule of interest binds to this linker). Molecules can be immobilized either covalently (e.g. utilizing single reactive thiol groups of cysteine residues (see, e.g., Colliuod (1993) *Bioconjugate Chem.* 4:528-536) or non-covalently but specifically (e.g. via immobilized antibodies (see, e.g., Schuhmann (1991) *Adv. Mater.* 3:388-391; Lu (1995) *Anal. Chem.* 67:83-87; the biotin/streptavidin system (see, e.g., Iwane (1997) *Biophys. Biochem. Res. Comm.* 230:76-80); metal chelating, e.g., Langmuir-Blodgett films (see, e.g., Ng (1995) *Langmuir* 11:4048-55); metal-chelating self-assembled monolayers (see, e.g., Sigal (1996) *Anal. Chem.* 68:490-497) for binding of polyhistidine fusions.



[0243] Indirect binding can be achieved using a variety of linkers which are commercially available. The reactive ends can be any of a variety of functionalities including, but not limited to: amino reacting ends such as N-hydroxysuccinimide (NHS) active esters, imidoesters, aldehydes, epoxides, sulfonyl halides, isocyanate, isothiocyanate, and nitroaryl halides; and thiol reacting ends such as pyridyl disulfides, maleimides, thiophthalimides, and active halogens. The heterobifunctional crosslinking reagents have two different reactive ends, e.g., an amino-reactive end and a thiol-reactive end, while homobifunctional reagents have two similar reactive ends, e.g., bismaleimidohexane (BMH) which permits the cross-linking of sulfhydryl-containing compounds. The spacer can be of varying length and be aliphatic or aromatic. Examples of commercially available homobifunctional cross-linking reagents include, but are not limited to, the imidoesters such as dimethyl adipimidate dihydrochloride (DMA); dimethyl pimelimidate dihydrochloride (DMP); and dimethyl suberimidate dihydrochloride (DMS). Heterobifunctional reagents include commercially available active halogen-NHS active esters coupling agents such as N-succinimidyl bromoacetate and N-succinimidyl (4-iodoacetyl)aminobenzoate (SIAB) and the sulfosuccinimidyl derivatives such as sulfosuccinimidyl(4-iodoacetyl)aminobenzoate (sulfo-SIAB) (Pierce). Another group of coupling agents is the heterobifunctional and thiol cleavable agents such as N-succinimidyl 3-(2-pyridyldithio)propionate (SPDP) (Pierce Chemicals, Rockford, IL).

[0244] Antibodies can also be used for binding polypeptides and peptides of the invention to a solid support. This can be done directly by binding peptide-specific antibodies to the column or it can be done by creating fusion protein chimeras comprising motif-containing peptides linked to, e.g., a known epitope (e.g. a tag (e.g. FLAG, myc) or an appropriate immunoglobulin constant domain sequence (an "immunoadhesin," see, e.g., Capon (1989) *Nature* 377:525-531 (1989)).

[0245] Nucleic acids or polypeptides of the invention can be immobilized to or applied to an array. Arrays can be used to screen for or monitor libraries of compositions (e.g. small molecules, antibodies, nucleic acids, etc.) for their ability to bind to or modulate the activity of a nucleic acid or a polypeptide of the invention. For example, in one aspect of the invention, a monitored parameter is transcript expression of a gene comprising a nucleic acid of the invention. One or more, or, all the transcripts of a cell can be measured



by hybridization of a sample comprising transcripts of the cell, or, nucleic acids representative of or complementary to transcripts of a cell, by hybridization to immobilized nucleic acids on an array, or "biochip." By using an "array" of nucleic acids on a microchip, some or all of the transcripts of a cell can be simultaneously quantified. Alternatively, arrays comprising genomic nucleic acid can also be used to determine the genotype of a newly engineered strain made by the methods of the invention. Polypeptide arrays" can also be used to simultaneously quantify a plurality of proteins.

[0246] The terms "array" or "microarray" or "biochip" or "chip" as used herein is a plurality of target elements, each target element comprising a defined amount of one or more polypeptides (including antibodies) or nucleic acids immobilized onto a defined area of a substrate surface. In practicing the methods of the invention, any known array and/or method of making and using arrays can be incorporated in whole or in part, or variations thereof, as disclosed, for example, in U.S. Patent Nos. 6,277,628; 6,277,489; 6,261,776; 6,258,606; 6,054,270; 6,048,695; 6,045,996; 6,022,963; 6,013,440; 5,965,452; 5,959,098; 5,856,174; 5,830,645; 5,770,456; 5,632,957; 5,556,752; 5,143,854; 5,807,522; 5,800,992; 5,744,305; 5,700,637; 5,556,752; 5,434,049; see also, e.g., WO 99/51773; WO 99/09217; WO 97/46313; WO 96/17958; see also, e.g., Johnston (1998) *Curr. Biol.* 8:R171-R174; Schummer (1997) *Biotechniques* 23:1087-1092; Kern (1997) *Biotechniques* 23:120-124; Solinas-Toldo (1997) *Genes, Chromosomes & Cancer* 20:399-407; Bowtell (1999) *Nature Genetics Supp.* 21:25-32. See also published U.S. patent applications Nos. 20010018642; 20010019827; 20010016322; 20010014449; 20010014448; 20010012537; 20010008765.

### **Host Cells and Transformed Cells**

[0247] The invention also provides a transformed cell comprising a nucleic acid sequence of the invention, e.g., a sequence encoding a polypeptide of the invention, or a vector of the invention. The host cell may be any of the host cells familiar to those skilled in the art, including prokaryotic cells, eukaryotic cells, such as bacterial cells, fungal cells, yeast cells, mammalian cells, insect cells, or plant cells. Exemplary bacterial cells include *E. coli*, *Streptomyces*, *Bacillus subtilis*, *Salmonella typhimurium* and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*. Exemplary insect cells include *Drosophila* S2 and *Spodoptera* Sf9. Exemplary animal cells include CHO,



COS or Bowes melanoma or any mouse or human cell line. The selection of an appropriate host is within the abilities of those skilled in the art.

[0248] Vectors may be introduced into the host cells using any of a variety of techniques, including transformation, transfection, transduction, viral infection, gene guns, or Ti-mediated gene transfer. Particular methods include calcium phosphate transfection, DEAE-Dextran mediated transfection, lipofection, or electroporation.

[0249] Engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes of the invention. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter may be induced by appropriate means (e.g. temperature shift or chemical induction) and the cells may be cultured for an additional period to allow them to produce the desired polypeptide or fragment thereof.

[0250] Cells can be harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract is retained for further purification. Microbial cells employed for expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents. Such methods are well known to those skilled in the art. The expressed polypeptide or fragment can be recovered and purified from recombinant cell cultures by methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Protein refolding steps can be used, as necessary, in completing configuration of the polypeptide. If desired, high performance liquid chromatography (HPLC) can be employed for final purification steps.

[0251] Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts and other cell lines capable of expressing proteins from a compatible vector, such as the C127, 3T3, CHO, HeLa and BHK cell lines.

[0252] The constructs in host cells can be used in a conventional manner to produce the gene product encoded by the recombinant sequence. Depending upon the host employed



in a recombinant production procedure, the polypeptides produced by host cells containing the vector may be glycosylated or may be non-glycosylated. Polypeptides of the invention may or may not also include an initial methionine amino acid residue.

[0253] Cell-free translation systems can also be employed to produce a polypeptide of the invention. Cell-free translation systems can use mRNAs transcribed from a DNA construct comprising a promoter operably linked to a nucleic acid encoding the polypeptide or fragment thereof. In some aspects, the DNA construct may be linearized prior to conducting an *in vitro* transcription reaction. The transcribed mRNA is then incubated with an appropriate cell-free translation extract, such as a rabbit reticulocyte extract, to produce the desired polypeptide or fragment thereof.

[0254] The expression vectors can contain one or more selectable marker genes to provide a phenotypic trait for selection of transformed host cells such as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or ampicillin resistance in *E. coli*.

[0255] For transient expression in mammalian cells, cDNA encoding a polypeptide of interest may be incorporated into a mammalian expression vector, e.g. pcDNA1, which is available commercially from Invitrogen Corporation (San Diego, Calif., U.S.A.; catalogue number V490-20). This is a multifunctional 4.2 kb plasmid vector designed for cDNA expression in eukaryotic systems, and cDNA analysis in prokaryotes, incorporated on the vector are the CMV promoter and enhancer, splice segment and polyadenylation signal, an SV40 and Polyoma virus origin of replication, and M13 origin to rescue single strand DNA for sequencing and mutagenesis, Sp6 and T7 RNA promoters for the production of sense and anti-sense RNA transcripts and a Col E1-like high copy plasmid origin. A polylinker is located appropriately downstream of the CMV promoter (and 3' of the T7 promoter).

[0256] The cDNA insert may be first released from the above phagemid incorporated at appropriate restriction sites in the pcDNA1 polylinker. Sequencing across the junctions may be performed to confirm proper insert orientation in pcDNA1. The resulting plasmid may then be introduced for transient expression into a selected mammalian cell host, for example, the monkey-derived, fibroblast like cells of the COS-1 lineage (available from the American Type Culture Collection, Rockville, Md. as ATCC CRL 1650).



[0257] For transient expression of the protein-encoding DNA, for example, COS-1 cells may be transfected with approximately 8  $\mu\text{g}$  DNA per  $10^6$  COS cells, by DEAE-mediated DNA transfection and treated with chloroquine according to the procedures described by Sambrook et al, *Molecular Cloning: A Laboratory Manual*, 1989, Cold Spring Harbor Laboratory Press, Cold Spring Harbor N.Y, pp. 16.30-16.37. An exemplary method is as follows. Briefly, COS-1 cells are plated at a density of  $5 \times 10^6$  cells/dish and then grown for 24 hours in FBS-supplemented DMEM/F12 medium. Medium is then removed and cells are washed in PBS and then in medium. A transfection solution containing DEAE dextran (0.4 mg/ml), 100  $\mu\text{M}$  chloroquine, 10% NuSerum, DNA (0.4 mg/ml) in DMEM/F12 medium is then applied on the cells 10 ml volume. After incubation for 3 hours at 37 °C, cells are washed in PBS and medium as just described and then shocked for 1 minute with 10% DMSO in DMEM/F12 medium. Cells are allowed to grow for 2-3 days in 10% FBS-supplemented medium, and at the end of incubation dishes are placed on ice, washed with ice cold PBS and then removed by scraping. Cells are then harvested by centrifugation at 1000 rpm for 10 minutes and the cellular pellet is frozen in liquid nitrogen, for subsequent use in protein expression. Northern blot analysis of a thawed aliquot of frozen cells may be used to confirm expression of receptor-encoding cDNA in cells under storage.

[0258] In a like manner, stably transfected cell lines can also prepared, for example, using two different cell types as host: CHO K1 and CHO Pro5. To construct these cell lines, cDNA coding for the relevant protein may be incorporated into the mammalian expression vector pRC/CMV (Invitrogen), which enables stable expression. Insertion at this site places the cDNA under the expression control of the cytomegalovirus promoter and upstream of the polyadenylation site and terminator of the bovine growth hormone gene, and into a vector background comprising the neomycin resistance gene (driven by the SV40 early promoter) as selectable marker.

[0259] An exemplary protocol to introduce plasmids constructed as described above is as follows. The host CHO cells are first seeded at a density of  $5 \times 10^5$  in 10% FBS-supplemented MEM medium. After growth for 24 hours, fresh medium is added to the plates and three hours later, the cells are transfected using the calcium phosphate-DNA coprecipitation procedure (Sambrook et al, supra). Briefly, 3  $\mu\text{g}$  of DNA is mixed and incubated with buffered calcium solution for 10 minutes at room temperature. An equal



volume of buffered phosphate solution is added and the suspension is incubated for 15 minutes at room temperature. Next, the incubated suspension is applied to the cells for 4 hours, removed and cells were shocked with medium containing 15% glycerol. Three minutes later, cells are washed with medium and incubated for 24 hours at normal growth conditions. Cells resistant to neomycin are selected in 10% FBS-supplemented alpha-MEM medium containing G418 (1 mg/ml). Individual colonies of G418-resistant cells are isolated about 2-3 weeks later, clonally selected and then propagated for assay purposes.

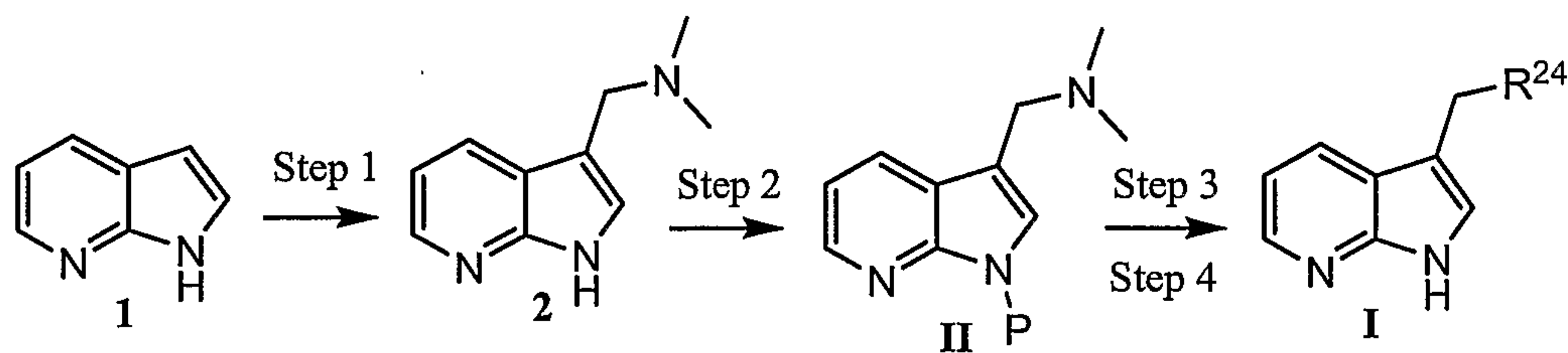
## EXAMPLES

[0260] A number of examples illustrative of the present invention are described below. In most cases, alternative techniques could also be used. The examples are intended to be illustrative and are not limiting or restrictive to the scope of the invention. Unless specifically noted to the contrary, in cases where a compound number is not preceded by a "P-" (e.g., "P-0001") in the Examples section, compound naming and/or enumeration is not related to naming and/or enumeration employed in other sections of this application. Similarly, structure and substituent naming and enumeration within the Examples are independent of structure and substituent naming and enumeration in above sections of this application unless clearly indicated otherwise.

**Example 1: Synthesis of compound of Formula I, where  $X_1$ ,  $X_2$ ,  $Y_1$  and  $Y_2$  are CH and  $L^1$  is  $-CH_2-$ :**

[0261] Compounds of Formula I where  $X_1$ ,  $X_2$ ,  $Y_1$  and  $Y_2$  are CH and  $L^1$  is  $-CH_2-$  or  $-CO-$  may be synthesized from 7-azaindole according to one of the following Schemes 1-3, where  $R^{24}$  is consistent with  $Ar_1$ , which can be further substituted to provide compounds where  $R^{24}$  is  $Ar_1-L^2-R^1$  as described for Formula I.

### Scheme – 1



*Step - 1- Synthesis of compound 2.*

[0262] Compound 2 is synthesized from commercially available 7-azaindole following the literature procedure (Robinson, *J. Am. Chem. Soc.*, **1955**, 77, p. 457).

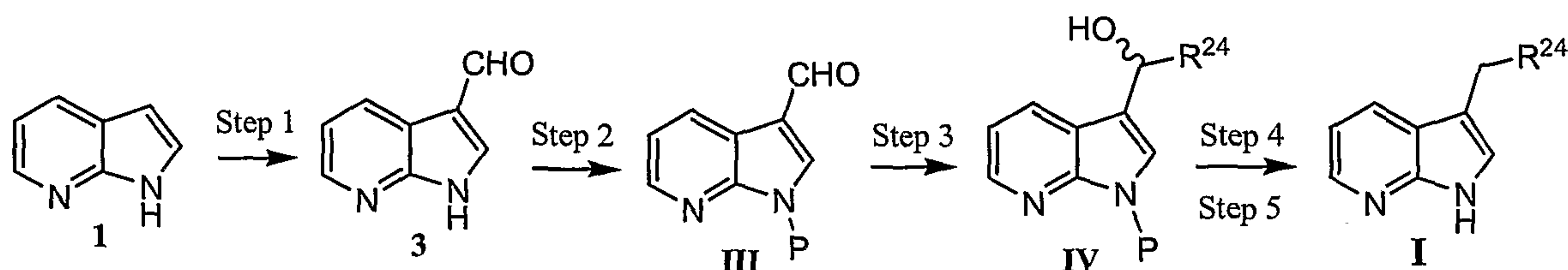
*Step -2- Synthesis of compound of Formula II*

[0263] Compound of Formula II is synthesized by deprotonation using base (e.g. BuLi, NaH) in aprotic solvent like tetrahydrofuran or ether and reacting the anion with a silyl chloride (e.g. TIPS) or an anhydride (e.g. Boc anhydride). The compound is isolated by following standard procedure (quenching with ice-cold brine, work up, and purification by flash silica gel chromatography).

*Steps -3 and 4 - Synthesis of compound of Formula I*

[0264] Compounds of Formula I, wherein R<sup>24</sup> is Ar<sub>1</sub> as defined in Formula I, is synthesized through the reaction of compounds of Formula II with isopropyl chloroformate (or ethyl chloroformate) at room temperature in toluene to give a 3-chloromethyl intermediate. This intermediate is cooled to -78 °C and immediately reacted with an organocopper reagent, which is generated from the reaction between a Grignard reagent (or organolithium reagent) and a solution of copper cyanide and LiCl. The mixture is stirred at -78 °C for one hour and allowed to warm to room temperature. The reaction is quenched with a solution of 4:1 ammonium chloride:ammonium hydroxide. The reaction is worked up in the usual manner and purified by flash silica gel chromatography to give the nitrogen-protected compound. The final compound can be realized through the deprotection of the protecting group (Boc, TIPS) using standard conditions (TFA or NH<sub>4</sub>F) at room temperature.

**Scheme – 2**



*Step - 1 – Synthesis of compound 3*

[0265] Compound 3 is synthesized by reacting commercially available 7-azaindole, compound 1, with hexamethyltetramine and acetic acid in water with heating to reflux for two hours. After cooling, the desired compound is precipitated and collected by filtration.



*Step - 2 – Synthesis of compound of Formula III*

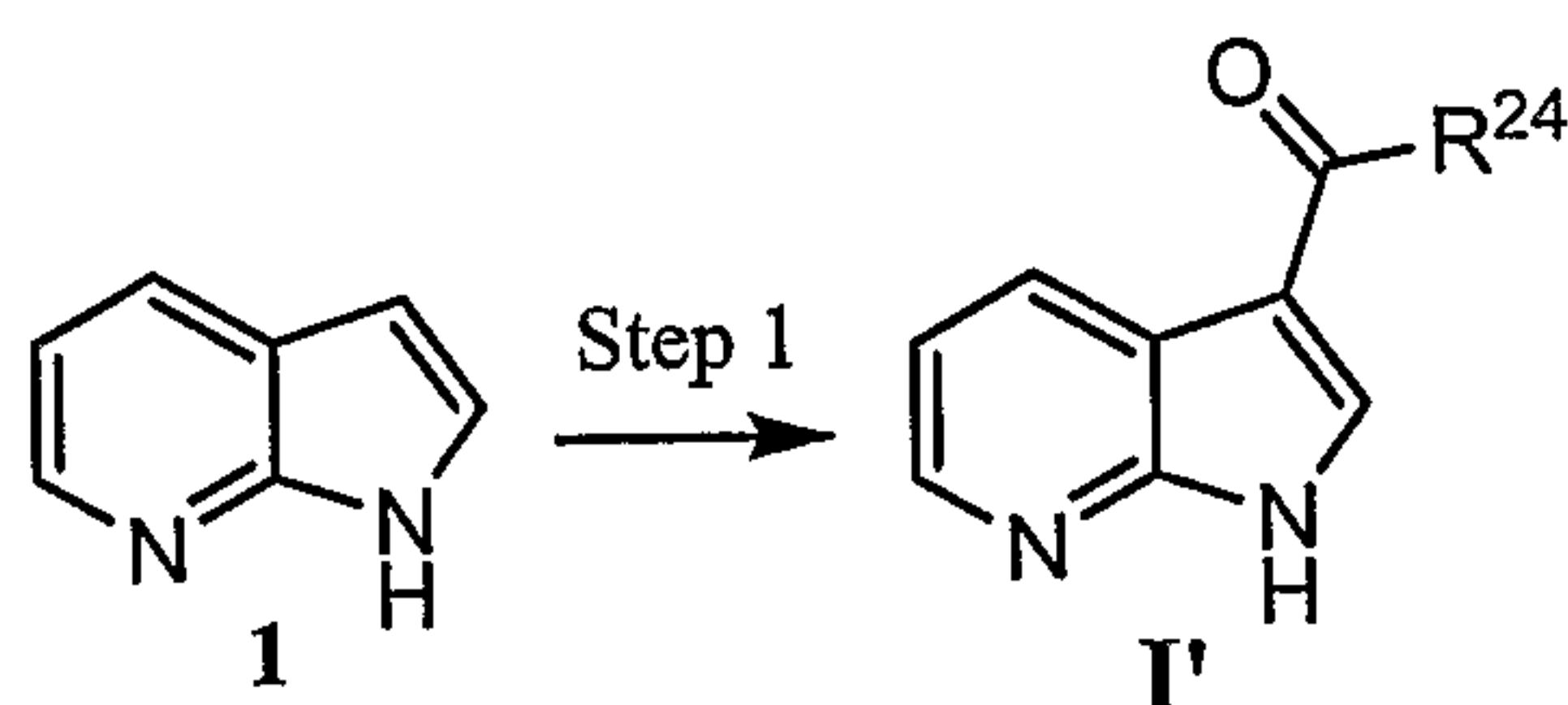
[0266] Compound of Formula III, where P is a protecting group, is synthesized by reacting compound 3 with an appropriate reagent to introduce a protecting group (e.g. *tert*-butyloxycarbonyl di anhydride) and a base (e.g. sodium hydride) in an appropriate solvent (e.g. tetrahydrofuran) typically at room temperature for 12-18 hours. The compound can be isolated by conventional means (e.g. extraction).

*Step - 3 – Synthesis of compound of Formula IV*

[0267] Compound of Formula IV, wherein R<sup>24</sup> is Ar<sub>1</sub>, is synthesized by reacting compound of Formula III in an appropriate solvent (e.g. 1,2-dimethoxyethane) with a Grignard reagent of the formula R<sup>24</sup>MgCl or R<sup>24</sup>MgBr (e.g. pyridinyl magnesium bromide) or an equivalent nucleophile in an appropriate solvent (e.g. tetrahydrofuran) under inert atmosphere cooled typically to -10 °C. The reaction is typically allowed to warm to room temperature and stirred for 12-18 hours. The desired compound is purified by reverse phase high pressure liquid chromatography.

*Steps – 4 and 5 – Synthesis of an intermediate of compound of Formula I*

[0268] An intermediate of compound of Formula I is synthesized by reacting compound of Formula IV with a reducing agent (e.g. sodium borohydride) in a polar solvent (e.g. ethanol) typically with heating to 80 °C for 1-4 hours. The reaction is quenched with the addition of methanol and concentrated and purified by reverse phase high performance liquid chromatography. Compound of Formula I where R<sup>24</sup> is Ar<sub>1</sub> is synthesized by reacting this intermediate with an appropriate reagent to remove the protecting group, P, (e.g. hydrochloric acid) in an apolar solvent (e.g. dioxane). The final compound is isolated by standard procedures (e.g. reverse phase preparative high pressure liquid chromatography).

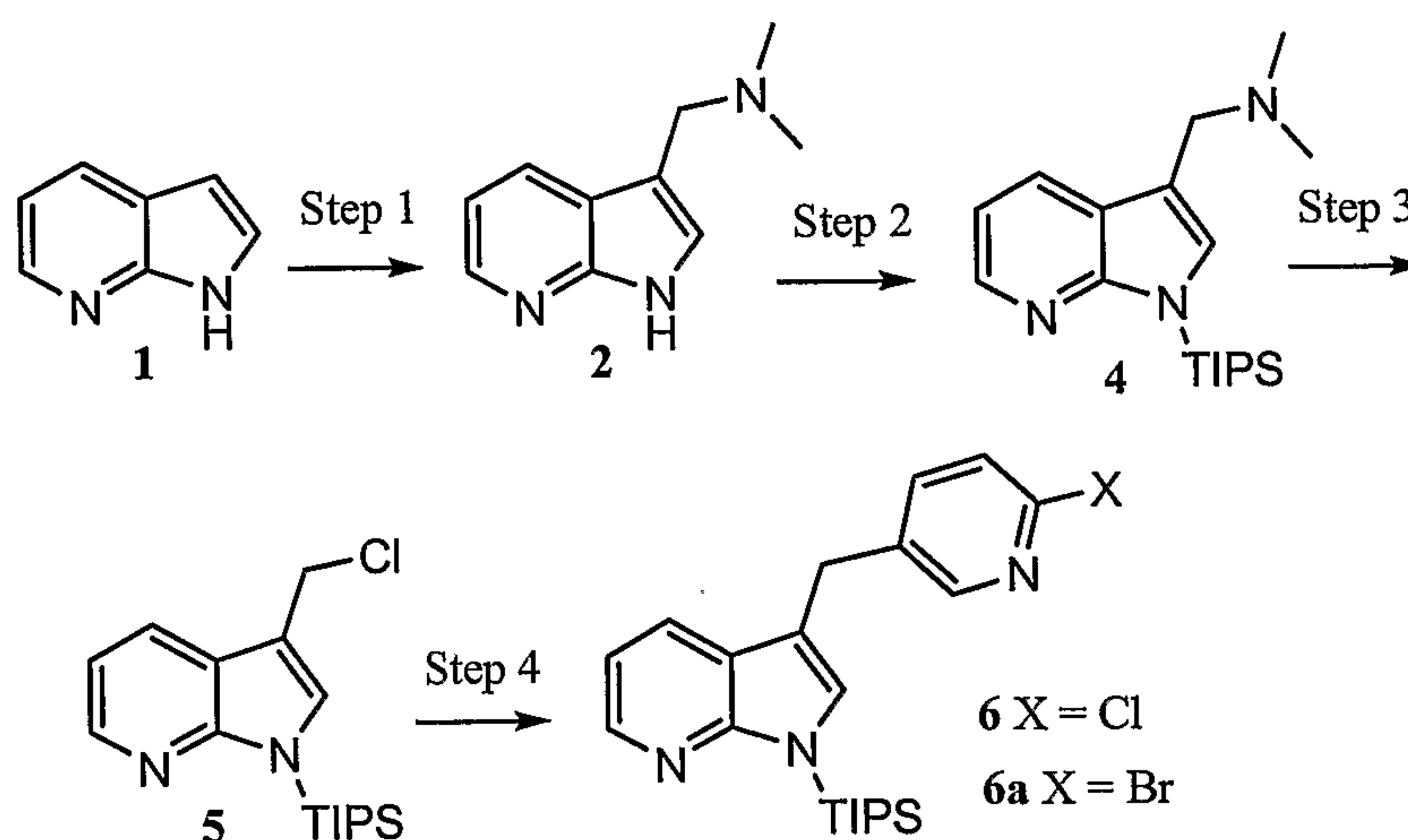
**Scheme – 3**

*Step - 1 – Synthesis of compound of Formula I'*

[0269] Compound of Formula I' where  $R^{24}$  is  $Ar_1$ , is synthesized by reacting compound 1 with an activating agent (e.g. methyl magnesium bromide and zinc dichloride or anhydrous aluminum chloride) and a heteroaryl acid chloride (e.g. nicotinic acid chloride) in a non-reactive solvent (e.g. dichloromethane), under inert atmosphere (e.g. argon), at room temperature or with heating up to reflux for 18-24 hours. The compound is isolated by standard procedures (e.g. extraction and silica-gel chromatography).

**Example 2: Synthesis of intermediate 3-(6-Chloro-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (6) and (3-(6-Bromo-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine) (6a)**

[0270] Compound 6, an intermediate to compounds of Formula I where  $X_1$ ,  $X_2$ ,  $Y_1$  and  $Y_2$  are CH, n is 1, P, Q and T are CH and  $L^1$  is  $-CH_2-$ , may be synthesized in four steps from 7-azaindole according to the following Scheme 4.

**Scheme - 4***Step -1- Synthesis of dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine (2)*

[0271] Into a 3-neck round bottom flask was added Isopropyl alcohol (320.0 mL) followed by the addition of 1H-pyrrolo[2,3-b]pyridine 1 (7.10 g, 60.1 mmol), dimethylamine hydrochloride (5.4 g, 0.066 mol), and formaldehyde (2.0 g, 0.066 mol). The reaction mixture was stirred at room temperature for 12 hours, and then refluxed for 30 minutes. The suspension solution was evaporated to dryness in *vacuo*. To the residue was added water (60.0 mL, 3.33 mol) and concentrated hydrochloric acid (6.0 mL, 0.20 mol). The water layer was extracted with ether and the aqueous layer was neutralized with



potassium carbonate. The aqueous layer was extracted with dichloromethane, dried over sodium sulfate and concentrated to give the compound, which was then further washed with ether and dried to afford compound **2** (7.1 g, yield = 67.4%), as a white solid.

*Step -2- Synthesis of dimethyl-(1-triisopropylsilylanyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine (4)*

**[0272]** Into a round bottom flask 7-Azagramine **2** (5.38 g, 30.7 mmol), N,N-dimethylformamide (25.0 mL), and sodium hydride (1.35 g, 33.8 mol) were combined. Into the reaction was added triisopropylsilyl chloride (6.8 mL, 0.032 mol). The reaction was stirred at 20 °C for 12 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified with biotage to give compound **4** (6.0 g, yield = 58.8%) as a colorless oil.

*Step - 3- Synthesis of 3-chloromethyl-1-triisopropylsilylanyl-1H-pyrrolo[2,3-b]pyridine (5)*

**[0273]** Into a round bottom flask was added compound **4** (500.0 mg, 1.51 mmol) and toluene (5.0 mL, 0.047 mol) under an atmosphere of nitrogen. Into the reaction mixture 1.0 M isopropyl chloroformate in toluene (1.6 mL) was added slowly at room temperature. The reaction mixture was stirred for another 2 hours to give desired compound **5** used for next step without purification.

*Step -4- Synthesis of 3-(6-Chloro-pyridin-3-ylmethyl)-1-triisopropylsilylanyl-1H-pyrrolo[2,3-b]pyridine (6)*

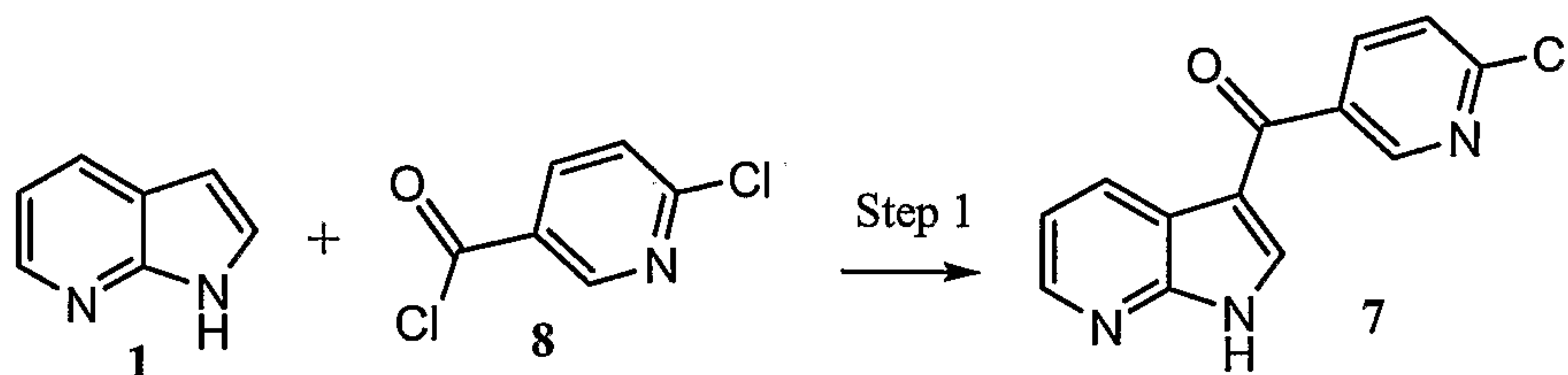
**[0274]** Into a round bottom flask was added 5-iodo-2-chloro-pyridine (315.0 mg, 1.32 mmol) and tetrahydrofuran (12.0 mL, 0.15 mol) at -40 °C under an atmosphere of nitrogen. Into the reaction 2.0 M of isopropylmagnesium chloride in tetrahydrofuran (0.72 mL, 1.44 mmol) was added. The reaction mixture was stirred for 40 minutes at -40 °C. TLC (hexane/ethyl acetate 2:1) indicated no starting material. Into the reaction mixture 0.6 M of CuCN.2LiCl in tetrahydrofuran (2.4 mL, 1.44 mmol) was added. The reaction mixture was allowed to come to room temperature for 5 minutes and trimethyl phosphite (0.29 mL, 2.4 mmol) was added. After 10 minutes, this solution was added into a round bottom flask containing compound **5** (315.0 mg) and toluene (8.0 mL). The reaction was stirred at 20 °C for 40 hours. The reaction mixture was poured into water and the compound extracted with ethyl acetate. The organic layer was washed with brine, dried

over sodium sulfate, concentrated and purified with biotage (dichloromethane/methanol 1:10) to give compound **6** (230 mg, yield = 59.0%) as a white solid. Compound **6a** (3-(6-Bromo-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine) (MS (ESI)  $[M+H]^+ = 288.1, 290.1$ ) was prepared substituting 5-iodo-2-chloro-pyridine with 5-iodo-2-bromo-pyridine in Step 4, with reaction conditions and work up procedure the same as that for the synthesis of compound **6**.

**Example 3: Synthesis of intermediate (6-Chloro-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (7)**

[0275] Compound **7**, an intermediate to compounds of Formula I where  $X_1, X_2, Y_1$  and  $Y_2$  are CH,  $n$  is 1, P, Q and T are CH and  $L^1$  is -CO-, may be synthesized in one step from 7-azaindole according to the following Scheme 5.

**Scheme - 5**



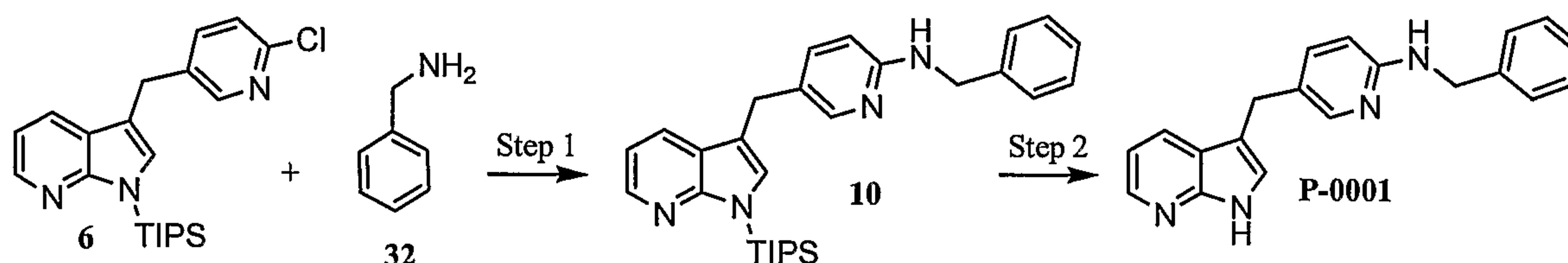
[0276] Into a round bottom flask was added aluminum trichloride (16.0 g, 0.12 mol) and dichloromethane (100.0 mL) under an atmosphere of nitrogen. Into the reaction mixture 1H-Pyrrolo[2,3-b]pyridine **1** (3.2 g, 0.027 mol) in dichloromethane (20.0 mL) was added. The reaction was stirred at room temperature for 70.0 minutes and 6-Chloropyridine-3-carbonyl chloride **8** (5.4 g, 0.031 mol) in dichloromethane (10.0 mL) was added. The reaction mixture was stirred at room temperature for 3 hours. Methanol (10 mL) was added to the reaction mixture and the solvent was evaporated in *vacuo*. The residue was poured into water and the precipitated compound was removed by filtration. The aqueous layer was extracted with ethyl acetate and the organic layer was dried and concentrated and combined with the solid isolated by filtration to give **7** (6.2 g, yield = 88.6%) as a white solid. MS (ESI)  $[M+H]^+ = 258$ .



**Example 4: Synthesis of benzyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0001)**

[0277] Benzyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0001) was prepared in two steps from 3-(6-Chloro-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (**6**) according to Scheme 6.

**Scheme – 6**



*Step -1- Synthesis of benzyl-[5-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (10):*

[0278] Into a round bottom flask was added 3-(6-Chloro-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine **6** (160.0 mg, 0.40 mmol, prepared as described in Example 2), benzylamine (**32**, 0.1 mL, 0.90 mmol), palladium acetate (17.0 mg, 0.076 mmol), toluene (10.0 mL), potassium tert-butoxide (80.0 mg, 0.71 mmol) and 2-(di-*t*-butylphosphino)biphenyl (31.4 mg, 0.11 mmol) under an atmosphere of nitrogen. The reaction was stirred under reflux for 3 hours. TLC and MS indicated no starting material. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified with biotage (dichloromethane/methanol 1:20) to give compound **10** (110 mg, yield = 58.5%) as a white solid. MS (ESI)  $[M+H]^+ = 471$ .

*Step -2- Synthesis of benzyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0001):*

[0279] Into a round bottom flask was added benzyl-[5-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **10** (400.0 mg, 0.85 mmol), tetrahydrofuran (20.0 mL) and tetra-*n*-butylammonium fluoride (240 mg, 0.93 mmol). The reaction mixture was stirred at 20 °C for 30 minutes. TLC indicated no starting material. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and

purified with biotage (dichloromethane/methanol 1:10) to give compound **P-0001** (220 mg, Yield = 82.4%) as a white solid. MS (ESI)  $[M+H]^+ = 315$ .

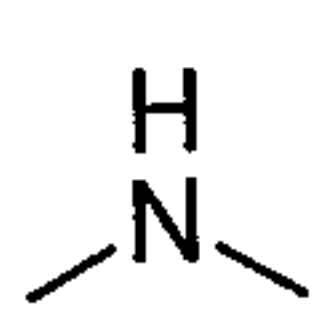
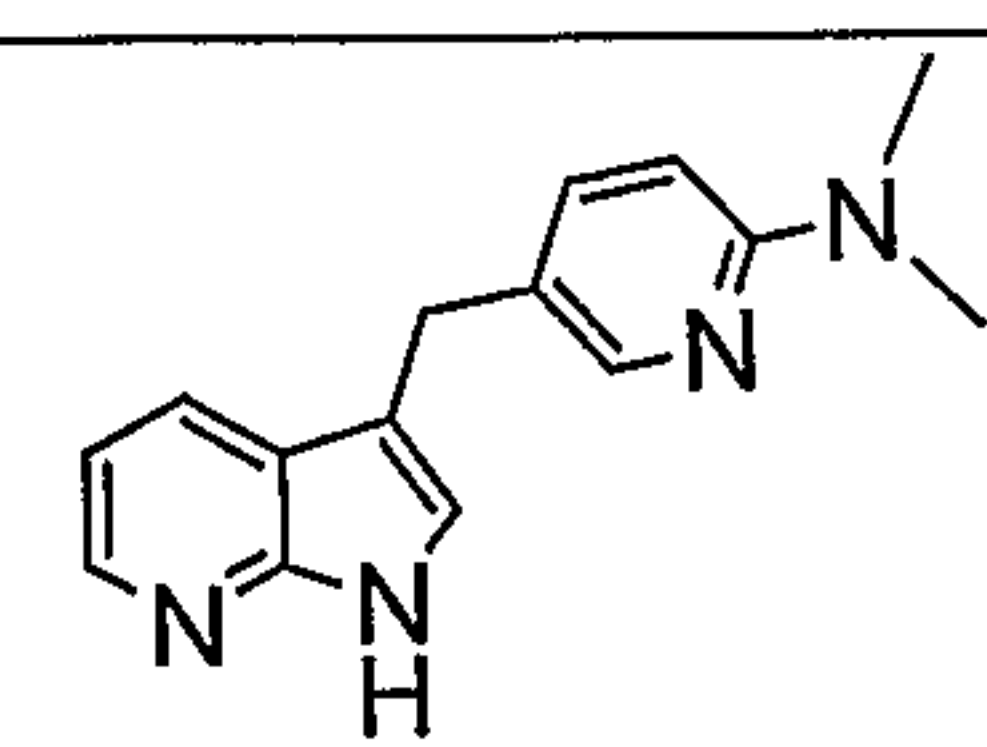
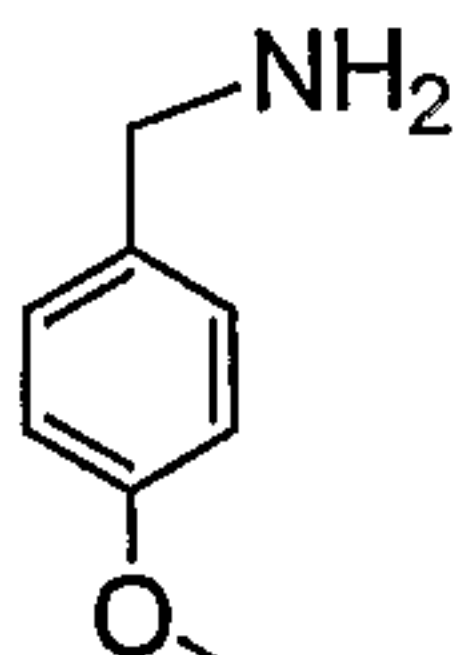
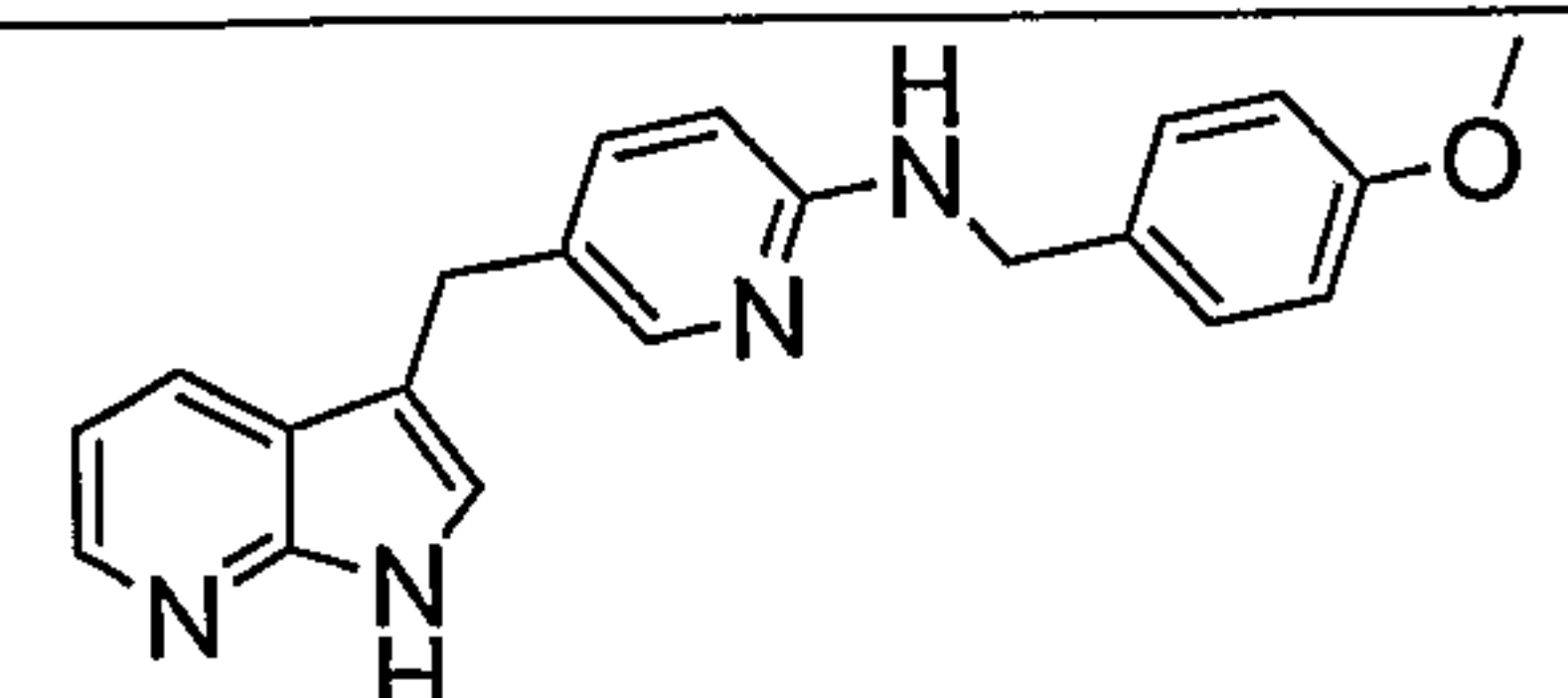
**[0280]** Additional compounds were prepared following the protocol of Scheme 6, substituting benzyl amine with a suitable amine in Step 1, and using either 3-(6-Chloro-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine **6** or 3-(6-Bromo-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine **6a**, in Step 1. The following compounds were made following this procedure:

Dimethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0021),  
(4-methoxy-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0004),

(4-chloro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0005),  
(4-fluoro-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0006),  
(4-methyl-benzyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0007), and

[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-thiophen-2-ylmethyl-amine (P-0008).

The following table indicates the amine used in Step 1 in place of benzyl amine in Column 2, and whether 3-(6-Chloro-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine or 3-(6-Bromo-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine was used in Step 1 in Column 3 (Cl or Br, respectively), with the compound structure in Column 4, experimental mass spectrometry result in Column 5, and compound number in Column 1.

	Starting azaindole	Amine	Compound	MS(ESI) $[M+H]^+$ observed
P-0021	Cl			253
P-0004	Br			344.4

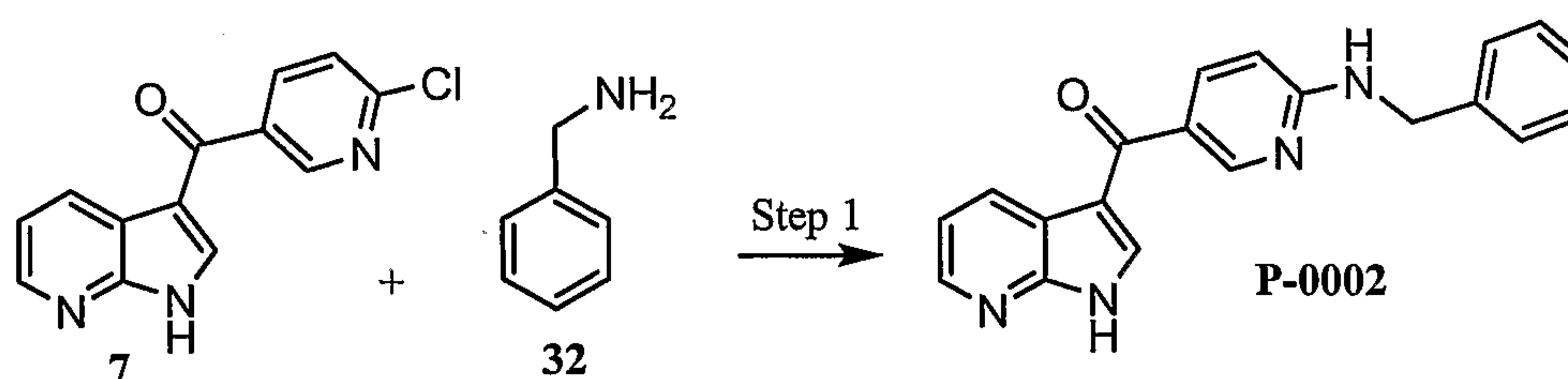


P-0005	Br			348.8
P-0006	Br			332.4
P-0007	Br			328.4
P-0008	Br			330.4

**Example 5: Synthesis of (6-Benzylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0002)**

[0281] (6-Benzylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0002) was prepared in one step from (6-Chloro-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (7) according to Scheme 7.

**Scheme – 7**



[0282] Into a pressure tube was added (6-Chloro-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone 7 (270.0 mg, 1.05 mmol, prepared as described in Example 3), and benzylamine (32, 0.7 mL, 0.006 mol) and tetrahydrofuran (25.0 mL) under an atmosphere of nitrogen. The reaction mixture was heated to 185 °C for 60 hours. The reaction mixture was concentrated to remove most of the solvent and the residue was poured into water and extracted with ethyl acetate. The organic layer was dried over

sodium sulfate, concentrated and purified with biotage (dichloromethane/methanol 1:20) to give compound **P-0002** (30 mg, yield = 8.7%) as a white solid. MS (ESI)  $[M+H]^+$  = 329.

**[0283]** Additional compounds were prepared following the protocol of Scheme 7, replacing benzylamine with a suitable amine. The following compounds were made following this procedure:

[6-(4-Fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0015),

[6-(3-Fluoro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0016),

(1H-Pyrrolo[2,3-b]pyridin-3-yl)-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-methanone (P-0017),

(1H-Pyrrolo[2,3-b]pyridin-3-yl)-{6-[(thiophen-2-ylmethyl)-amino]-pyridin-3-yl}-methanone (P-0018),

(6-Phenylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0023),

(6-Isopropylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0024),

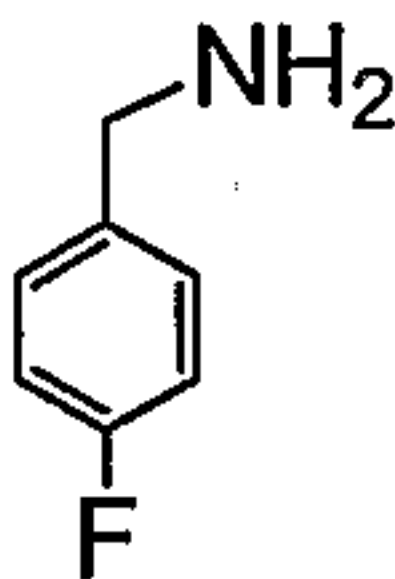
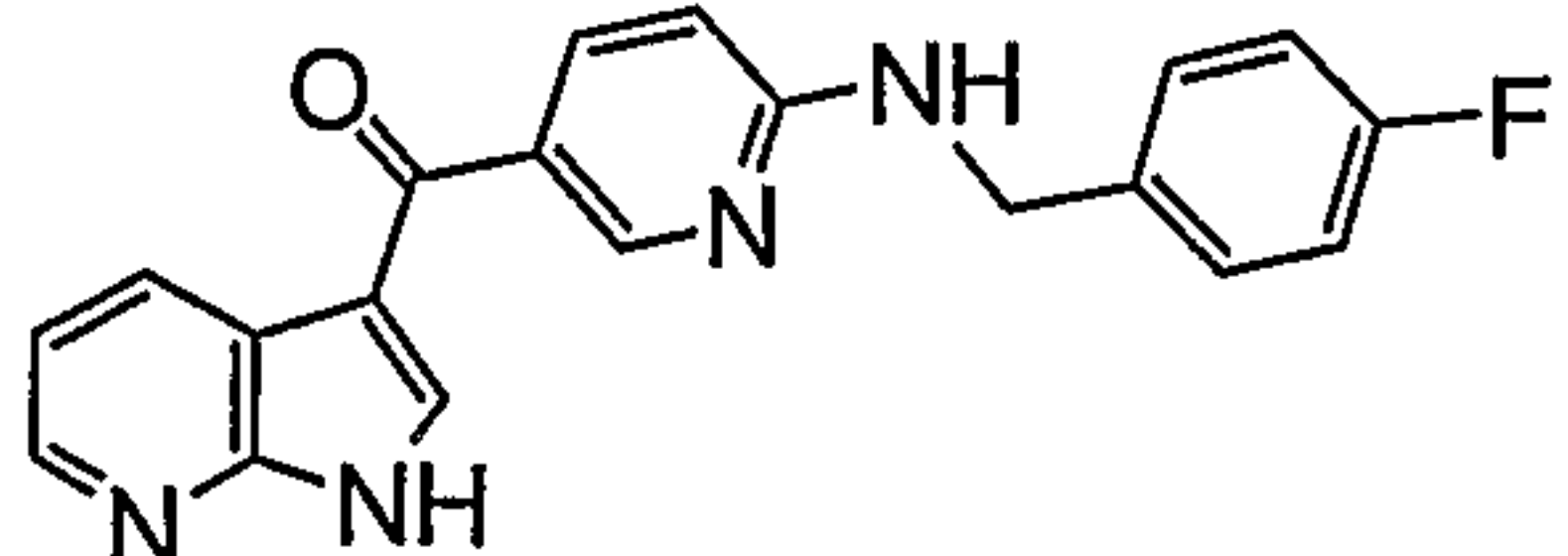
(6-Isobutylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0025),

[6-(3-Benzyloxy-phenylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0026),

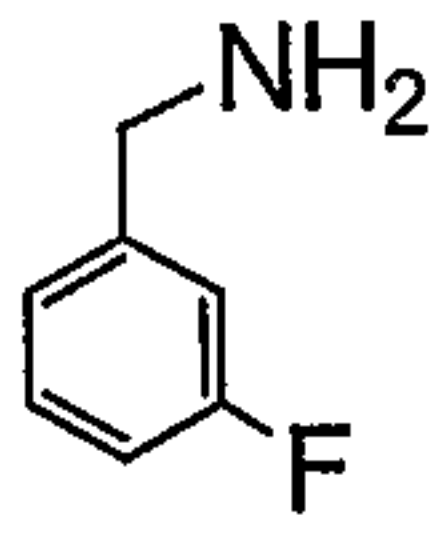
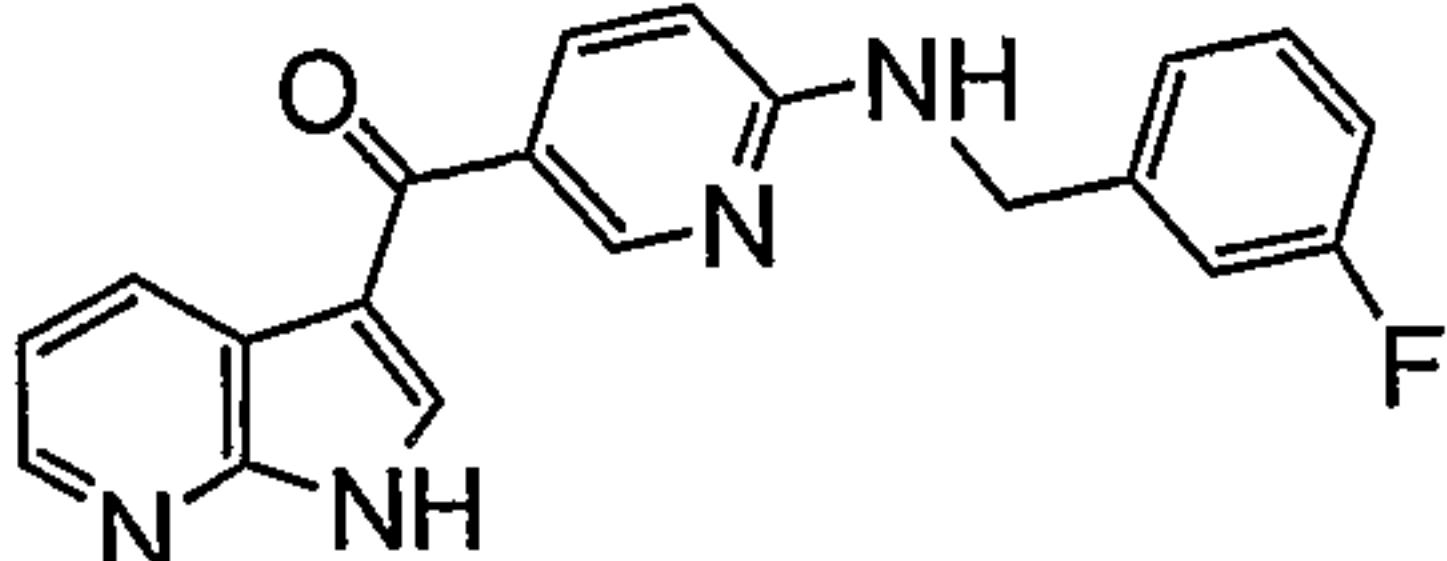
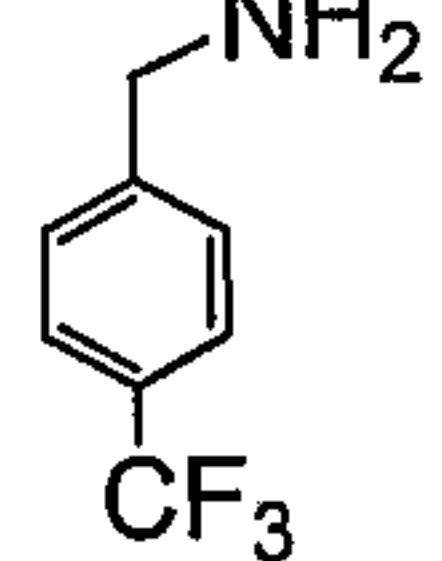
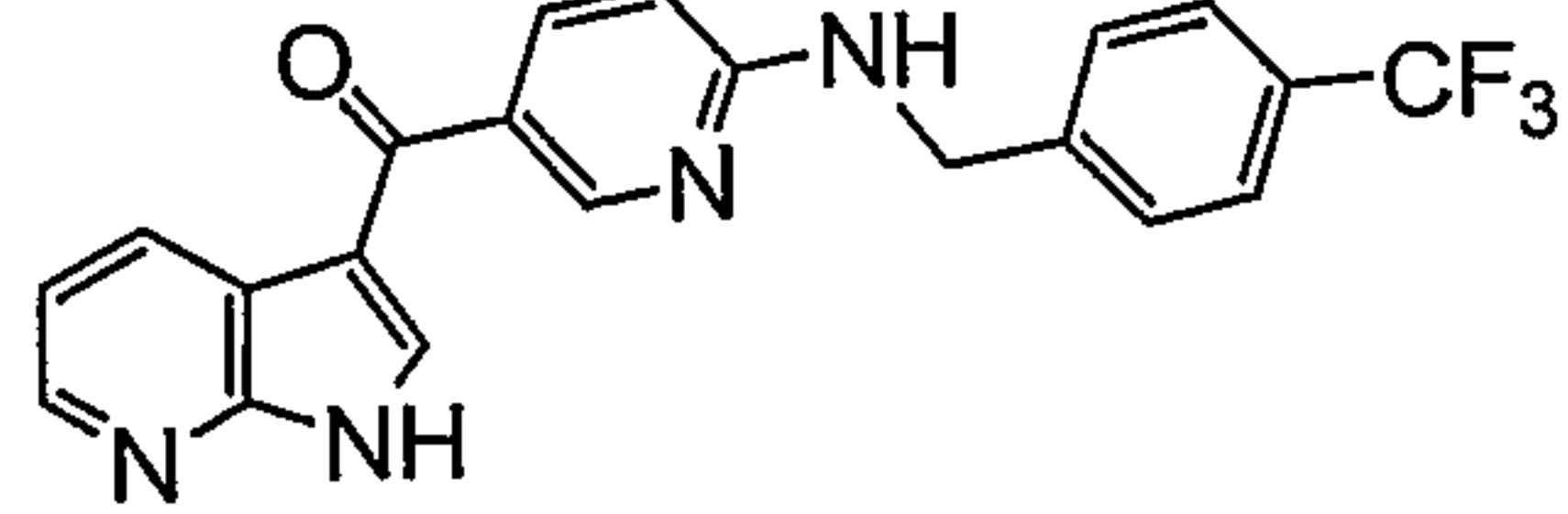
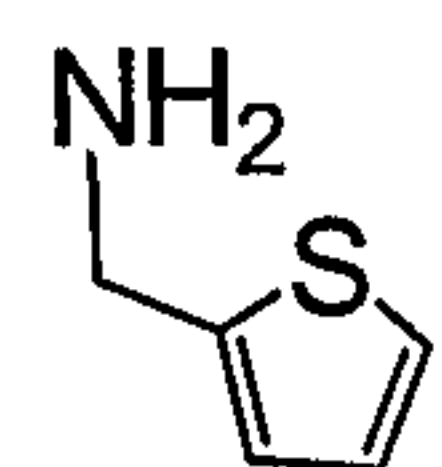
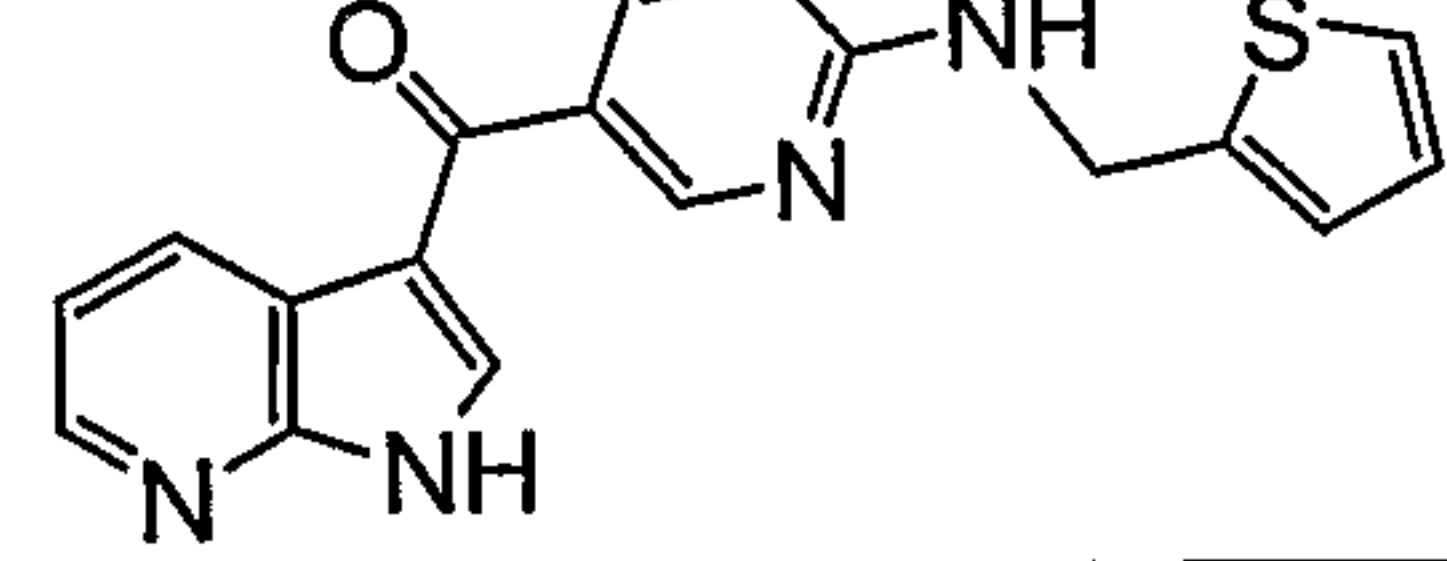
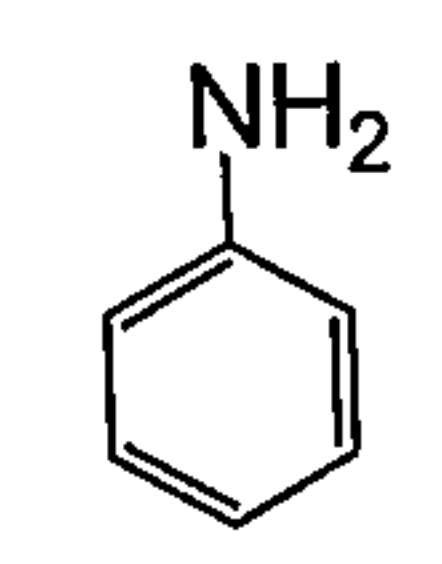
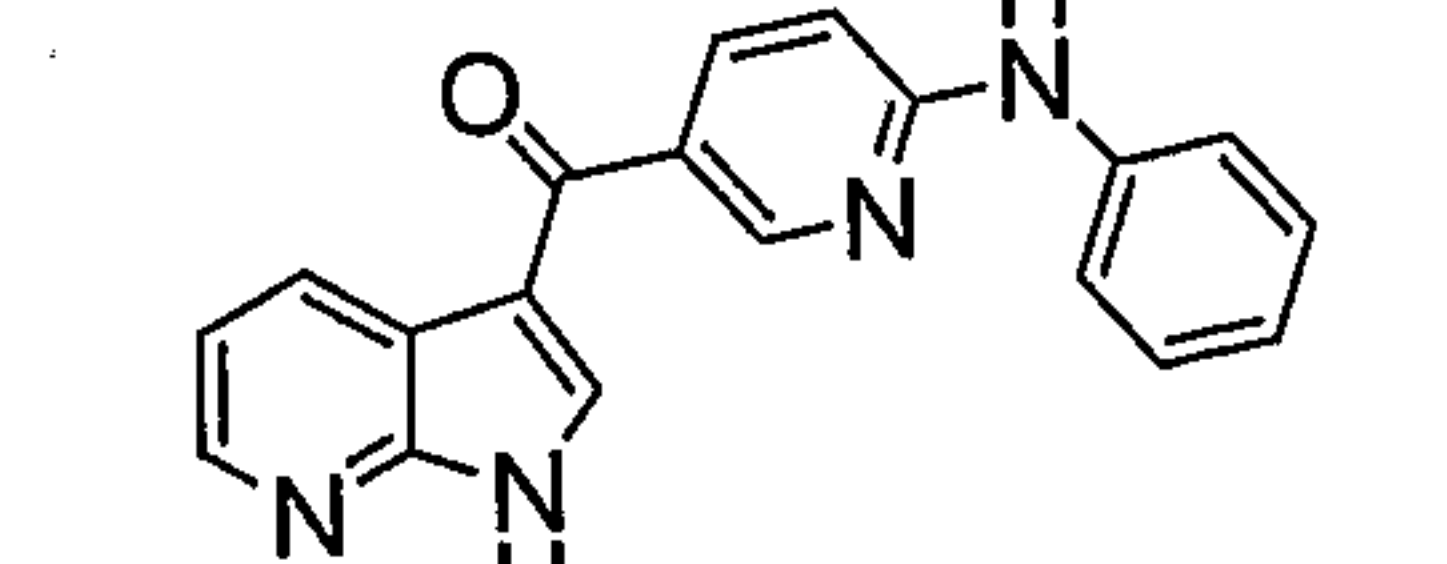
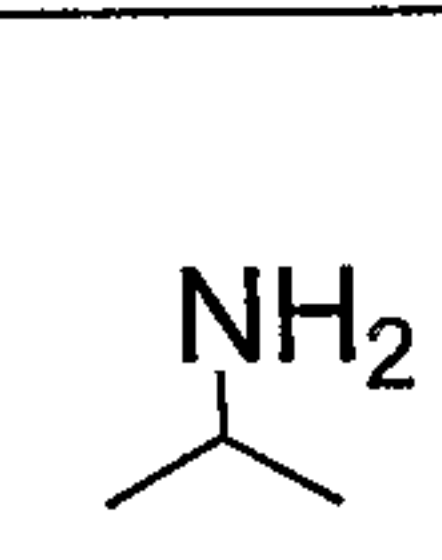
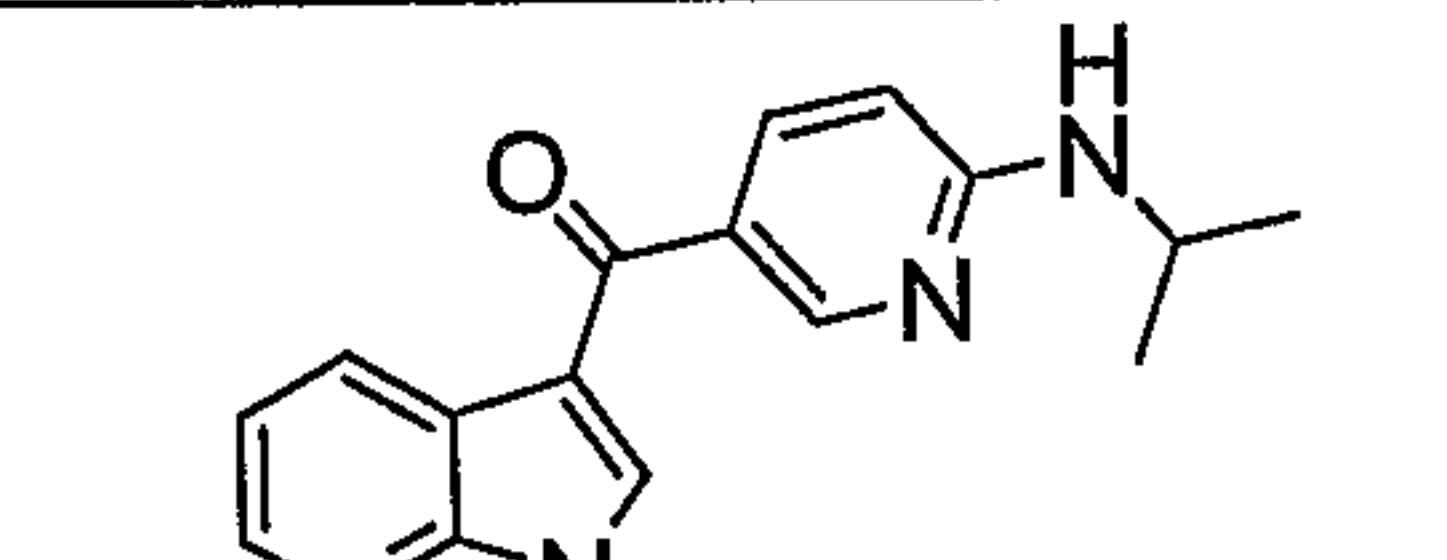
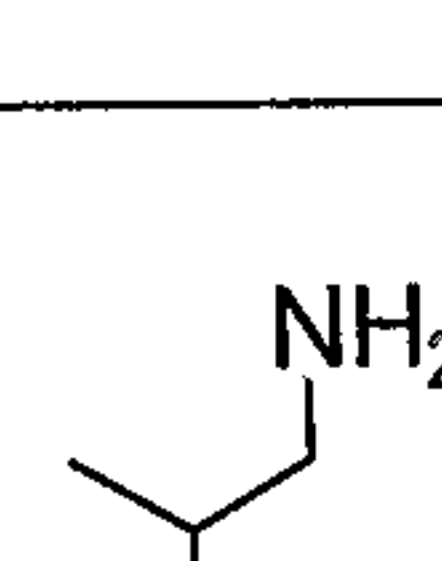
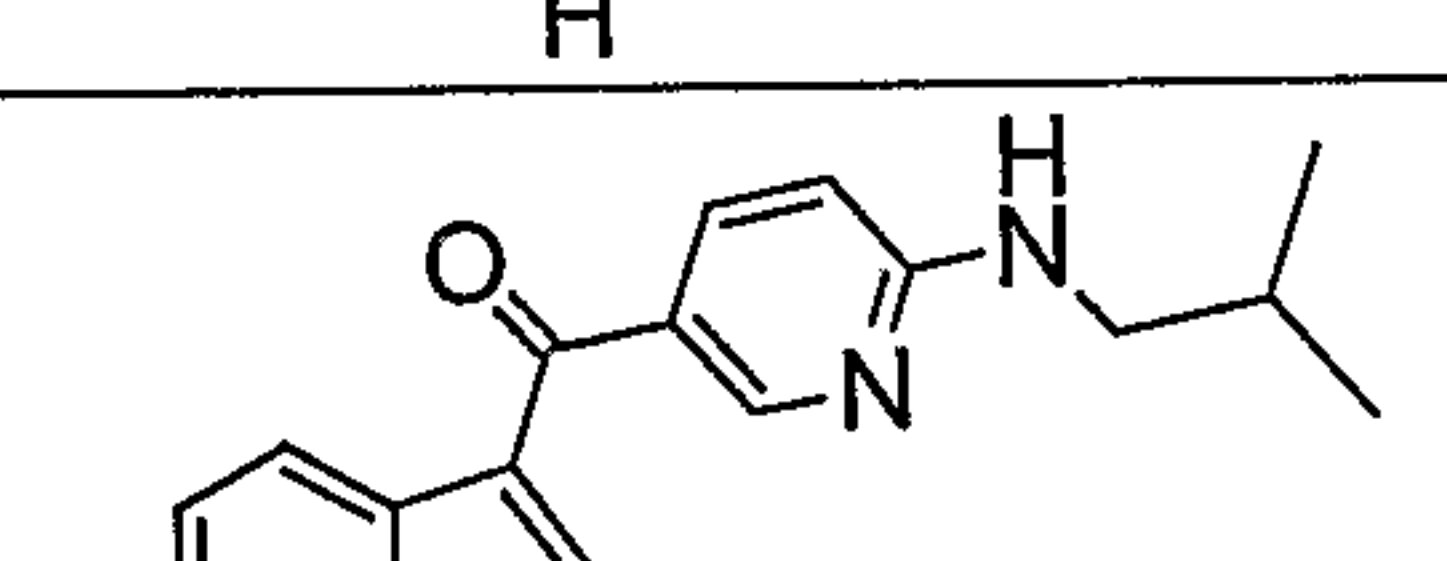
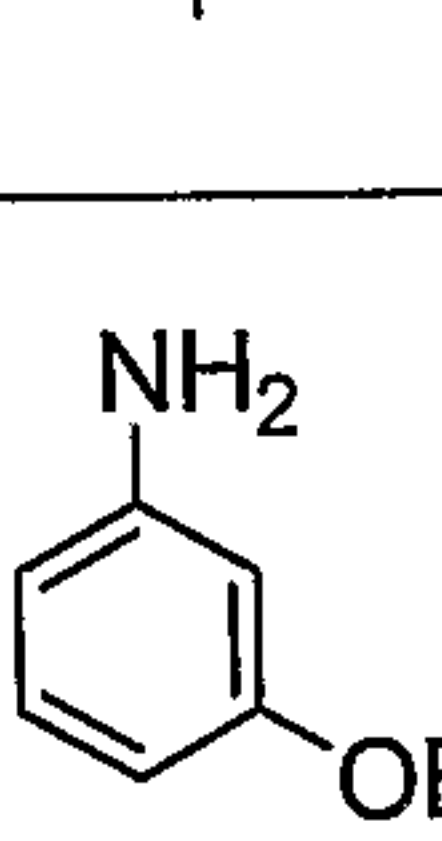
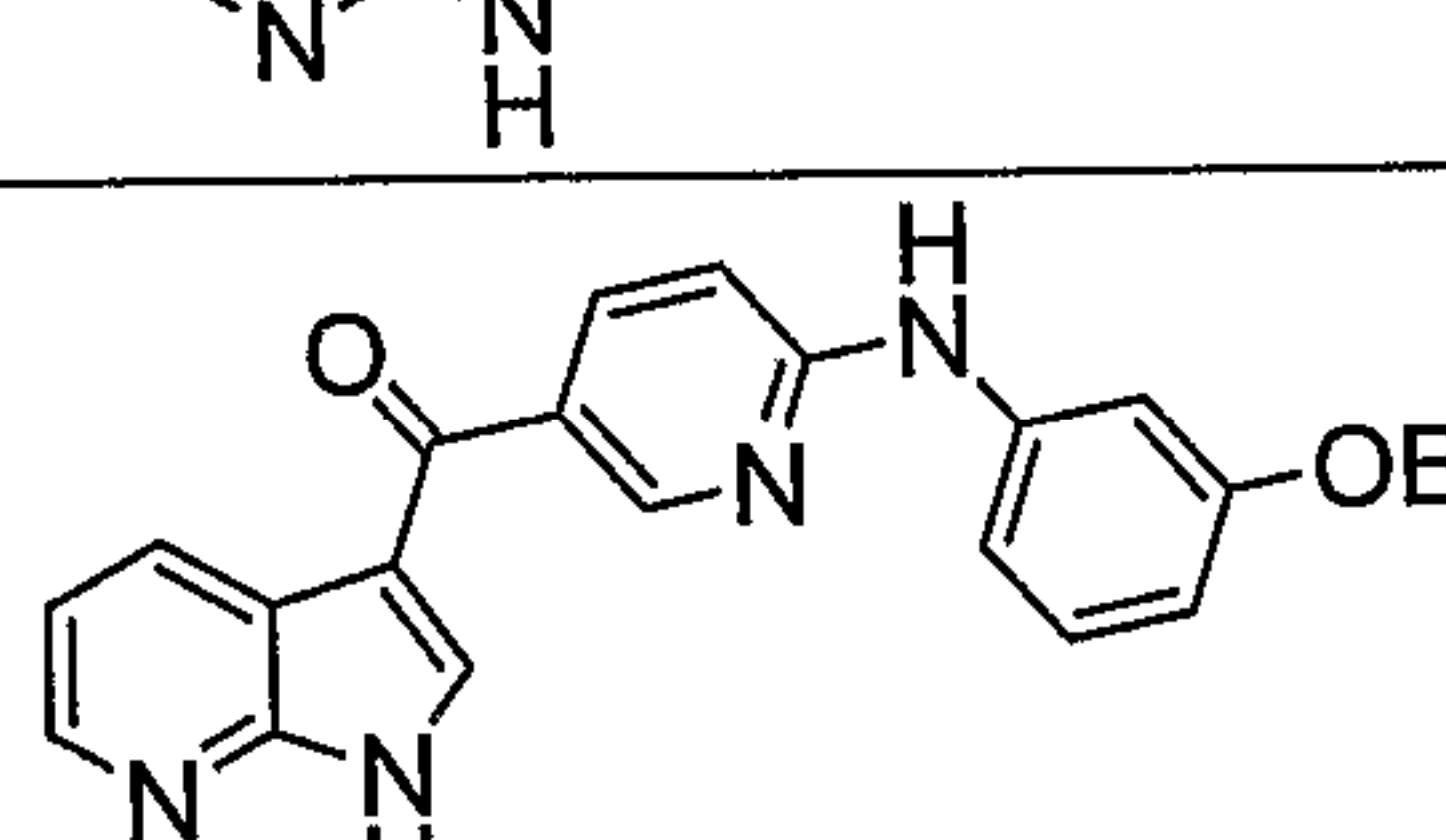
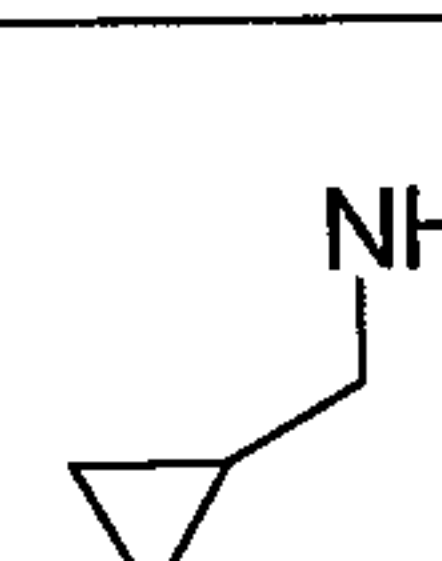
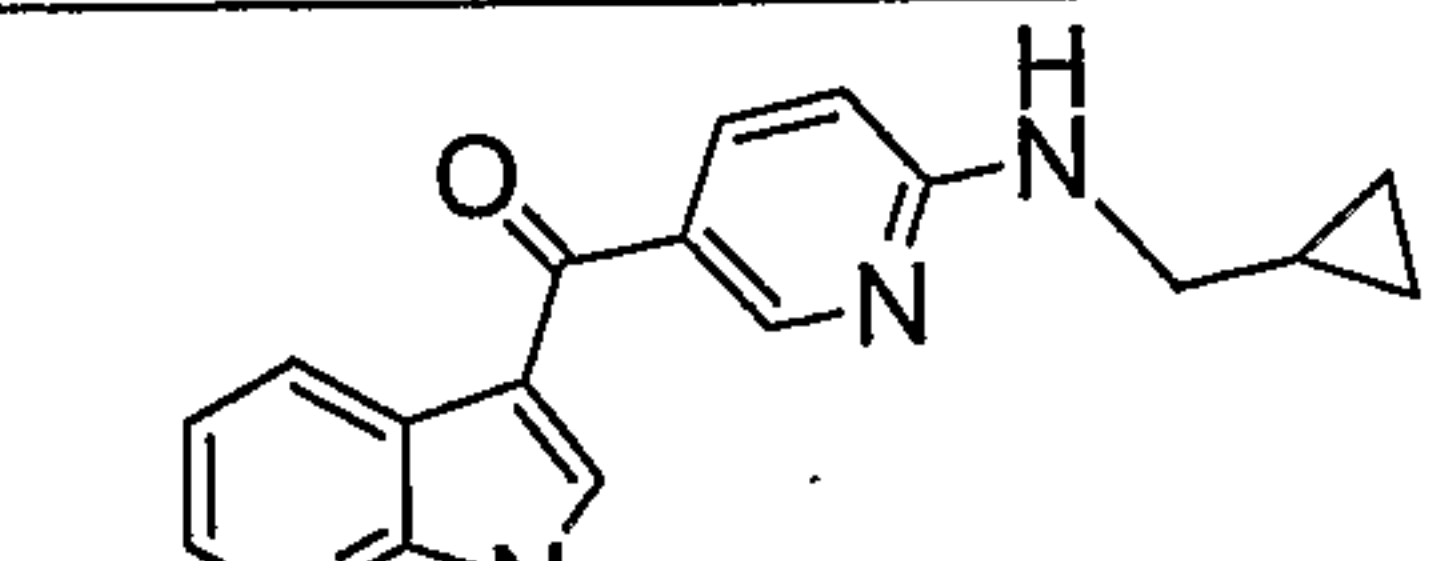
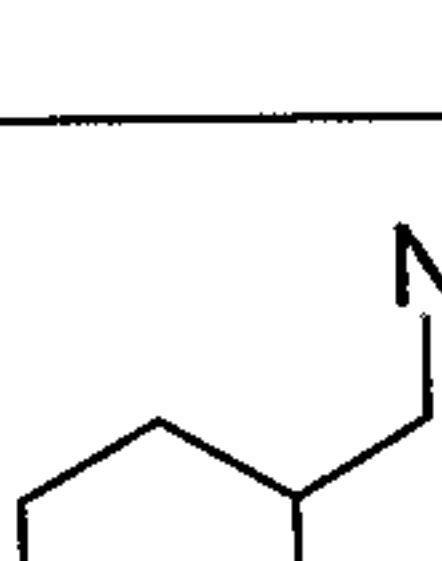
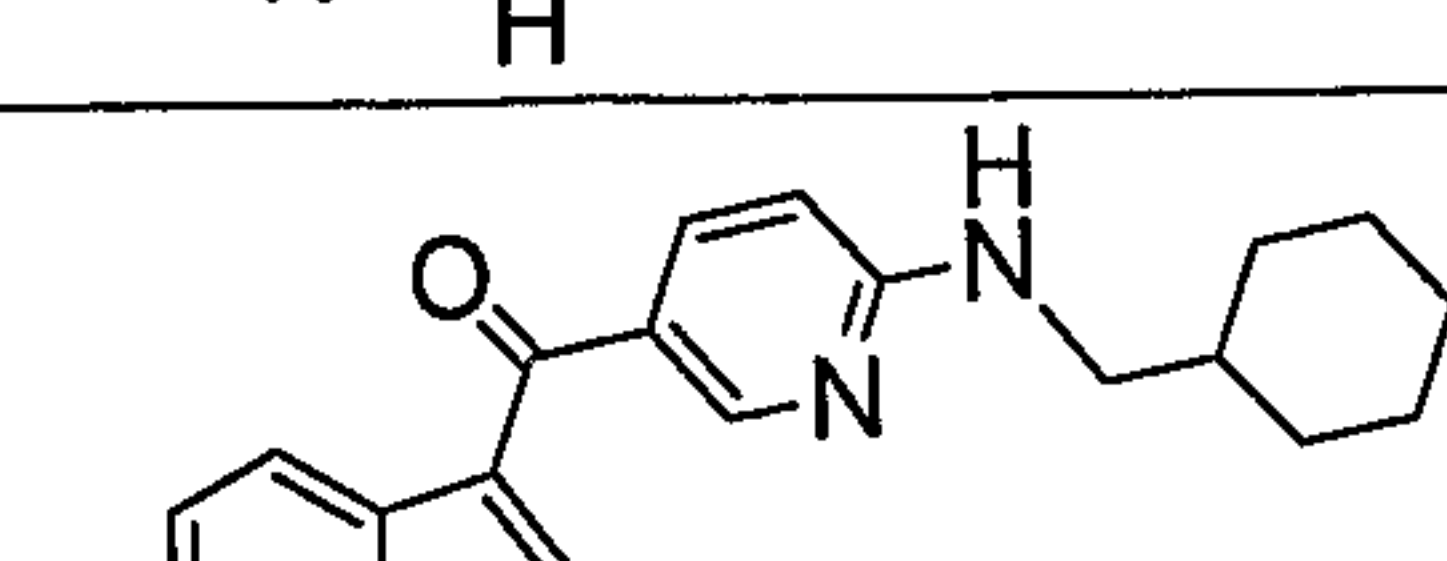
[6-(Cyclopropylmethyl-amino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0030),

[6-(Cyclohexylmethyl-amino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0031),

The following table indicates the amine substituted in place of benzylamine in column 2, to provide these compounds, shown by structure in column 3. Column 1 provides the compound number and column 4 gives the experimental mass spectrometry result.

	Amine	Compound	MS(ESI) $[M+H]^+$ observed
P-0015			347.0

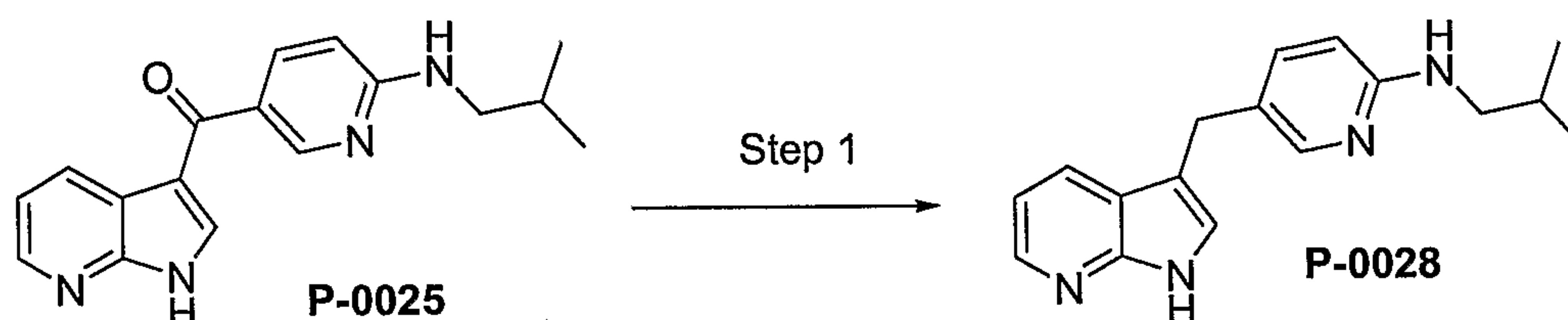


P-0016			347.1
P-0017			396.9
P-0018			335.0
P-0023			315.1
P-0024			279 [M-H <sup>+</sup> ]
P-0025			293 [M-H <sup>+</sup> ]
P-0026			419 [M-H <sup>+</sup> ]
P-0030			293.1
P-0031			335.2

**Example 6: Synthesis of Isobutyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0028**

[0284] Compound **P-0028** was synthesized in 1 step from 6-Isobutylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0025** as shown in Scheme 8.

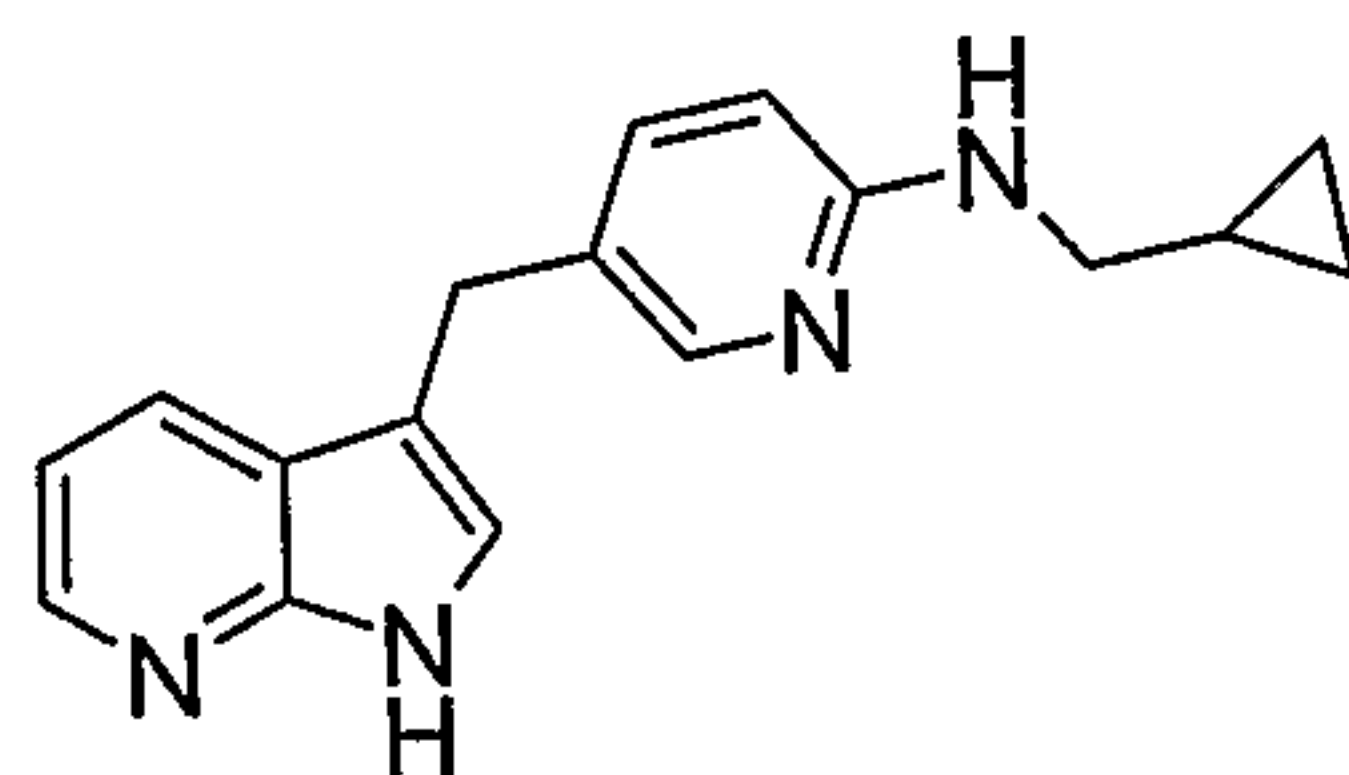
**Scheme 8**



*Step -1-Synthesis of Isobutyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0028).*

[0285] To (6-Isobutylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-0025**, 60.0 mg, 0.20 mmol, prepared as described in Example 5) in 1,2-ethanediol (5.0 mL) was added hydrazine (1.0 mL, 0.032 mol) and potassium hydroxide (200.0 mg, 3.56 mmol). The reaction mixture was heated to 180 °C overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 10% methanol in dichloromethane to give compound (**P-0028**, 10 mg, 16.7%). MS (ESI)  $[M+H]^+ = 281$ .

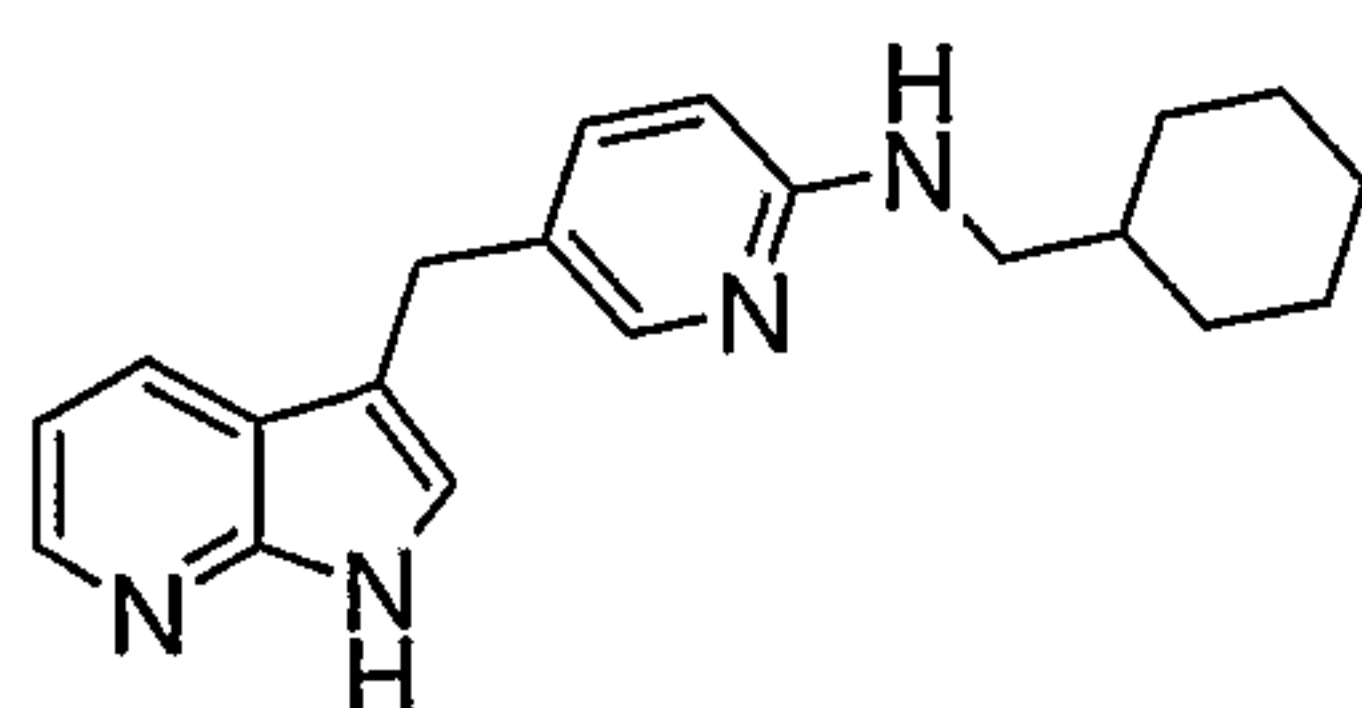
[0286] Cyclopropylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0032**)



was prepared following the protocol of Scheme 8, substituting (6-Isobutylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0025** with [6-(Cyclopropylmethyl-amino)-pyridin-3-yl]- (1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0030** (prepared as described in Example 5). MS (ESI)  $[M+H]^+ = 279$ .



[0287] Cyclohexylmethyl-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0033)

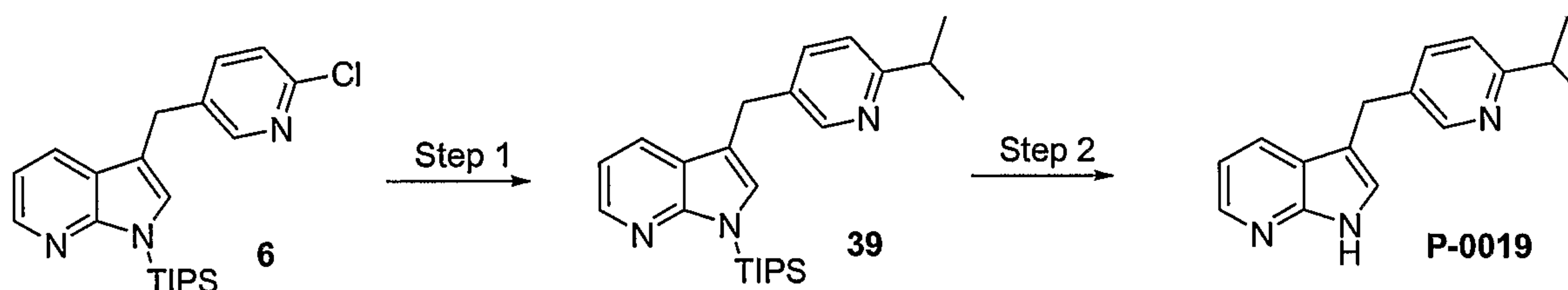


was prepared following the protocol of Scheme 8, substituting (6-Isobutylamino-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0025 with [6-(Cyclohexylmethyl-amino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0031, (prepared as described in Example 5). MS (ESI)  $[M+H]^+ = 321$ .

**Example 7: 3-(6-Isopropyl-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine P-0019**

[0288] 3-(6-Isopropyl-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine P-0019 was synthesized in 2 steps from 3-(6-Chloro-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine 6 as shown in Scheme 9.

**Scheme 9**



*Step -1-Synthesis of 3-(6-Isopropyl-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (39)*

[0289] To 3-(6-Chloro-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (6, 54.0 mg, 0.000135 mol, prepared as described in Example 2) in Tetrahydrofuran (4.0 mL) were added [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (23.0 mg) and Isopropylmagnesium Chloride (0.15 mL, 2.0 M in Tetrahydrofuran). The reaction was stirred at 20 °C under an atmosphere of Nitrogen for 3 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 10% methanol in dichloromethane to give compound 39 (38 mg, 70.4%).

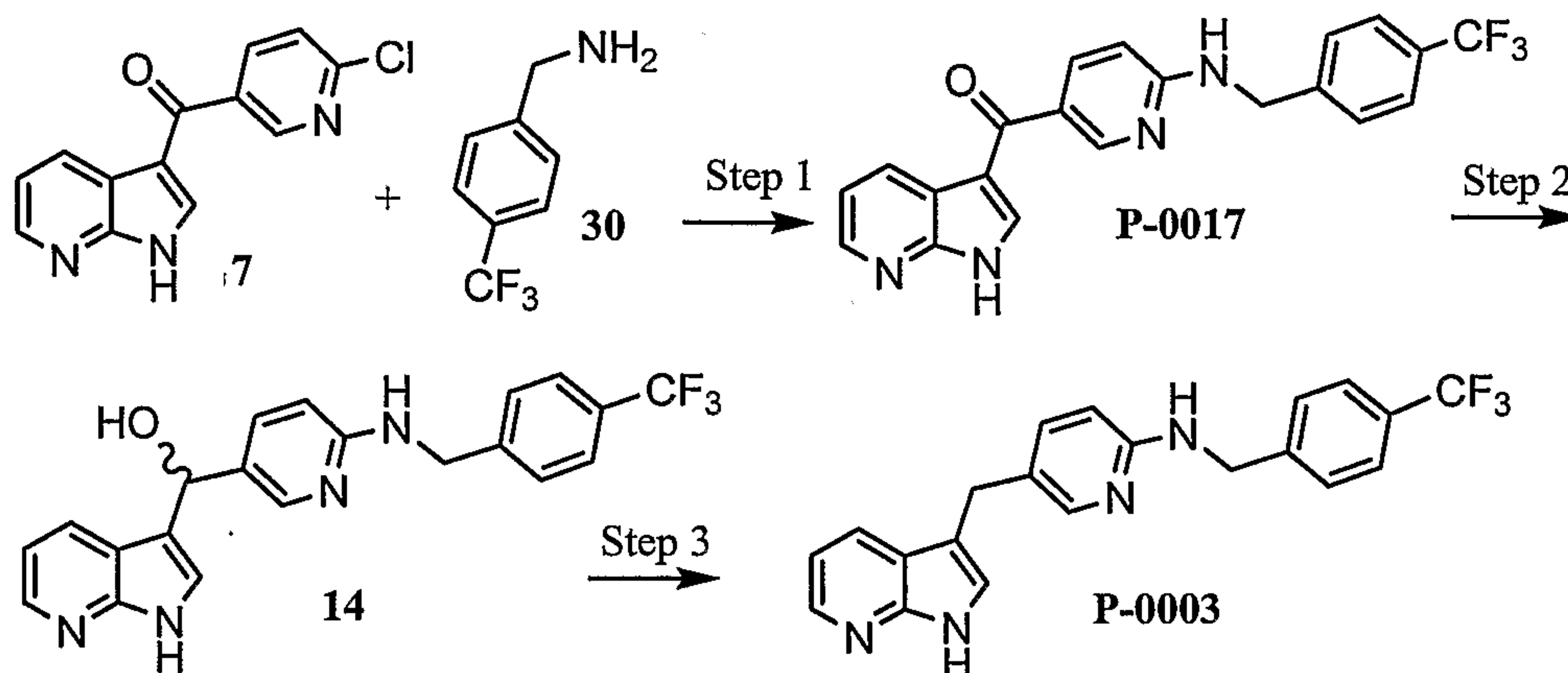
*Step-2-Synthesis of 3-(6-Isopropyl-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (P-0019)*

[0290] To 3-(6-Isopropyl-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (**39**, 35.0 mg, 0.086 mmol) in tetrahydrofuran (3.0 mL) was added tetra-n-butylammonium fluoride (29 mg, 0.11 mmol). The reaction was stirred at 20 °C for 30 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 10% methanol in dichloromethane to give compound (**P-0019**, 18.0 mg, 81.9%). MS (ESI)  $[M+H]^+ = 252$ .

**Example 8: Synthesis of [5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0003)**

[0291] [5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (**P-0003**) was prepared in three steps from (6-Chloro-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**7**) according to Scheme 10.

**Scheme 10**



*Step -1- Synthesis of (1H-Pyrrolo[2,3-b]pyridin-3-yl)-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-methanone (P-0017)*

[0292] Into a pressure flask was added (6-Chloro-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **7** (3.5 g, 0.014 mol, prepared as described in Example 3), 4-(trifluoromethyl)benzylamine (**30**, 9.0 g, 0.051 mol), tetrahydrofuran (30.0 mL, 0.37 mol), palladium acetate (200.0 mg, 0.890 mmol) and 2-(di-t-butylphosphino)biphenyl (200.0 mg, 0.67 mmol). The reaction mixture was stirred at 180 °C overnight, poured into water



and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. To the residue was added acetic acid (15.0 mL) and H<sub>2</sub>O (5.0 mL). The reaction mixture was stirred at 100 °C for 5 hours and concentrated to remove the acetic acid. The residue was then treated with aqueous Na<sub>2</sub>HCO<sub>3</sub> and extracted with ethyl acetate. The organic layer was washed, dried, concentrated and purified to give compound **P-0017** (1.0 g, yield = 18.5%) as a light yellow solid. MS (ESI) [M+H<sup>+</sup>]<sup>+</sup> = 397.

*Step -2- Synthesis of (1H-Pyrrolo[2,3-b]pyridin-3-yl)-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-methanol (14)*

**[0293]** Into a round bottom flask was added (1H-Pyrrolo[2,3-b]pyridin-3-yl)-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-methanone **P-0017** (210.0 mg, 0.53 mmol) and sodium tetrahydroborate (80.0 mg, 2.11 mmol), dissolved in N,N-dimethylformamide (5.0 mL) and ethanol (20.0 mL). The reaction was stirred at room temperature overnight, poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified with biotage (dichloromethane/methanol 1:20) to give compound **14** (63 mg, yield = 30%) as a white solid. MS (ESI) [M+H<sup>+</sup>]<sup>+</sup> = 399.

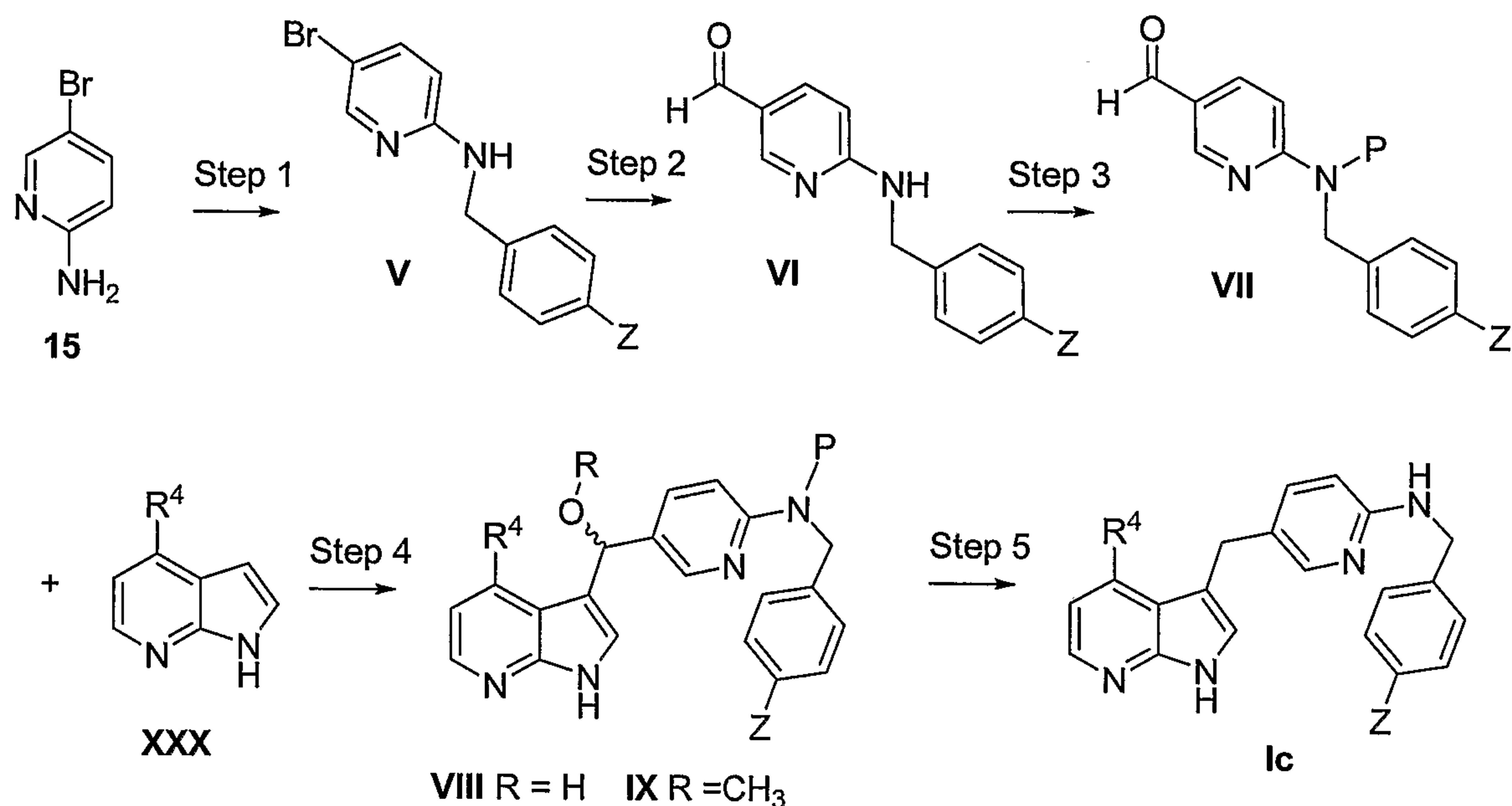
*Step -3- Synthesis of [5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0003)*

**[0294]** Into a round bottom flask was added (1H-Pyrrolo[2,3-b]pyridin-3-yl)-[6-(4-trifluoromethyl-benzylamino)-pyridin-3-yl]-methanol **14** (200.0 mg, 0.50 mmol), trifluoroacetic acid (5.0 mL, 0.065 mol) and triethylsilane (3.0 mL, 0.019 mol). The reaction was stirred at room temperature for 30 min, poured into aqueous sodium bicarbonate, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified to give pure compound **P-0003** (120.0 mg, yield = 62.8%) as a white solid. MS (ESI) [M+H<sup>+</sup>]<sup>+</sup> = 383.

**Example 9. Synthesis of compounds of Formula I where n is 1, P, Q and T are CH**  
**X<sub>1</sub>, X<sub>2</sub> and Y<sub>2</sub> are CH, Y<sub>1</sub> is CR<sup>4</sup>, L<sup>1</sup> is -CH<sub>2</sub>-, L<sup>2</sup> is -NHCH<sub>2</sub>-, and R<sup>1</sup> is 4 substituted phenyl (Formula Ic).**

[0295] Compounds of Formula Ic, where R<sup>4</sup> is as defined for Formula I and Z is a substituent as defined for optionally substituted aryl, can be synthesized in five Steps from 2-amino-5-bromopyridines as shown in the following general Scheme 11.

**Scheme 11**



*Step - 1 – Preparation of compounds of Formula V*

[0296] To a solution of an appropriately substituted benzaldehyde (e.g. *p*-trifluoromethyl benzaldehyde) in a non-reactive solvent (e.g. tetrahydrofuran) is added an appropriate 2-amino-5-bromo-pyridine **15**, followed by appropriate reagents to effect the reduction (e.g. dibutyltin dichloride and phenylsilane). Typically the reaction is heated (e.g. 50 °C) overnight. The solvent is removed at reduced pressure after heating to 50 °C overnight. Isolation by conventional means (e.g. extraction) affords compounds of Formula V.

*Step -2- Preparation of compounds of Formula VI*

[0297] Compound of Formula V is dissolved in a non-reactive solvent (e.g. tetrahydrofuran) and typically cooled at -78 °C under an inert atmosphere. To this mixture is added an organo lithium reagent (e.g. methyl lithium). The reaction mixture is typically stirred at -78 °C for several hours. To this mixture is added an organo lithium reagent (e.g. *tert*-butyl lithium), and the mixture is stirred for several hours. The reaction mixture is maintained at -78 °C, and an appropriate formylating reagent (e.g. 1-piperidine carboxaldehyde) is added. Typically, the reaction is allowed to stir at -78 °C for an



additional several hours and slowly warmed to room temperature. Isolation by conventional means (e.g. extraction) affords compounds of Formula **VI**.

*Step -3- Preparation of compounds of Formula VII*

[0298] Compound of Formula **VI** is dissolved in a non-reactive solvent (e.g. tetrahydrofuran) and stirred under an inert atmosphere. To this solution is added a base (e.g. triethylamine) and typically a catalyst (e.g. 4-dimethylaminopyridine). Typically, the mixture is stirred for a few minutes and then a reagent appropriate for the introduction of a protecting group (e.g. di-*tert*-butyldicarbonate) is added. Typically, the reaction is stirred overnight. Isolation by conventional means (e.g. extraction) affords compounds of Formula **VII**.

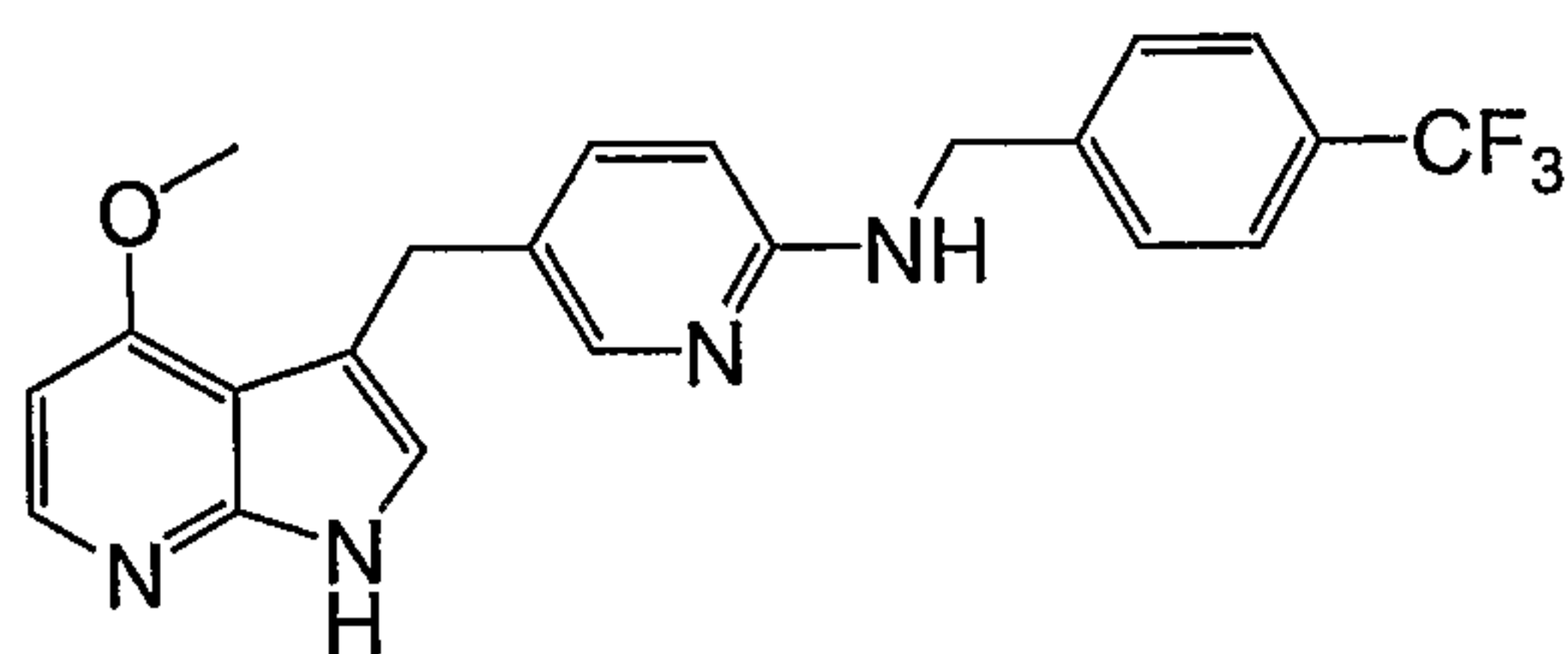
*Step - 4 – Preparation of compounds of Formula VIII and IX*

[0299] 4-Substituted 1H-pyrrolo[2,3-b]pyridine **XXX** is added to a stirring solution of base (e.g. potassium hydroxide) in an appropriate polar protic solvent (e.g. methanol). Compound of Formula **VII** is added, and the mixture is typically stirred at room temperature for several days. The solvent is evaporated, and 1 M HCl is added to the residue. Isolation by conventional means (e.g. extraction, silica gel chromatography) affords compounds of Formula **VIII** and **IX**.

*Step – 5 – Preparation of compounds of Formula Ic*

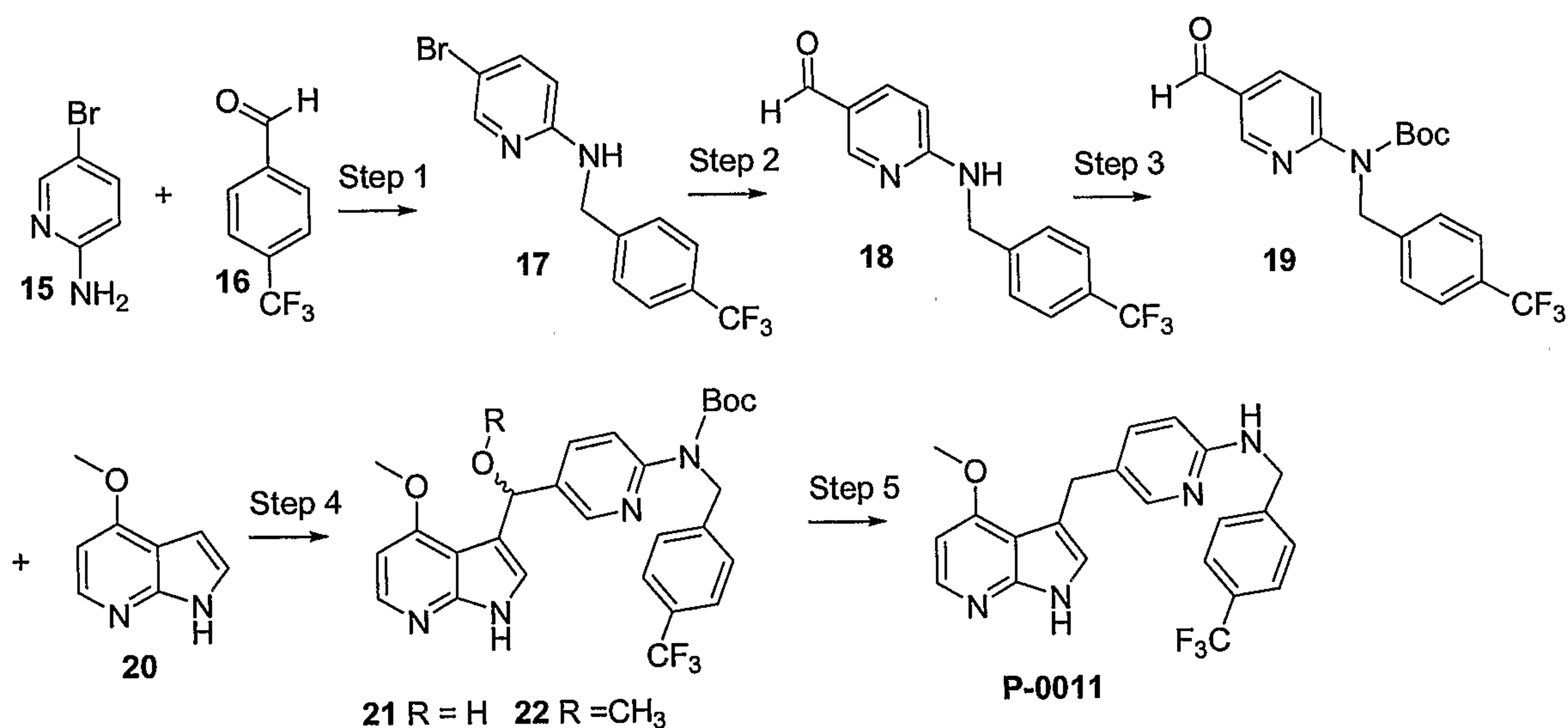
[0300] Typically, compounds of Formula **VIII** and **IX** is combined and dissolved in an appropriate polar aprotic solvent (e.g. acetonitrile). Reagents appropriate to effect the reduction (e.g. triethylsilane and trifluoroacetic acid) are added. Typically, the reactions are stirred at room temperature for several days. Isolation by conventional means (e.g. extraction, silica gel chromatography) affords compounds of Formula **Ic**.

**Example 10. Synthesis of [5-(4-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0011)**



[0301] [5-(4-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine **P-0011** was synthesized as shown in Scheme 12:

**Scheme 12**



*Step 1: Preparation of (5-Bromo-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-amine (17)*

[0302] Into a round bottom flask fitted with stirrer and reflux condenser was added 2-amino-5-bromopyridine (**15**, 1.73 mol, 300 g) and *p*-trifluoromethylbenzaldehyde (**16**, 1.723 mol, 300 g) to a solution of trifluoroacetic acid (400 mL), triethylsilane (825 mL) and acetonitrile (7500 mL). The reaction was heated to reflux overnight (24 hours). Solvents were removed and the residue was poured into aqueous  $K_2CO_3$  and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. The crude compound was crystallized with diethyl ether/hexane to afford compound **17**, 420 g (73.6%) as off white solid. MS (ESI)  $[M+H]^+ = 331.1$  and 333.1 (1:1 ratio).



*Step 2: Preparation of 6-(4-Trifluoromethyl-benzylamino)-pyridine-3-carbaldehyde (18)*

[0303] Into a 5 L round bottom flask was added compound **17** (0.6 mol, 198.6 g,) and tetrahydrofuran (2.5 L) under an atmosphere of argon at -78 °C. Into the reaction mixture was added 1.7 M tert-butyllithium in pentane (800 mL) over 60 mins. Two hours after the addition of tert-butyllithium, N,N-dimethylformamide (100 mL) was added. The reaction mixture was stirred at -78 °C for 2 hours, then allowed to stand at room temperature for another 1 hour. The reaction mixture was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and triturated with hexane/isopropyl ether (1:1) to give aldehyde compound **18**.

*Step 3: Preparation of (5-Formyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (19)*

[0304] Into a 2 L round bottom flask was added di-tert-butyl dicarbonate (90 g), aldehyde **18** (75 g), diisopropyl ethyl amine (60 g), 4-dimethylaminopyridine (2.0 g,) and dichloromethane (1000.0 mL). The reaction was stirred at room temperature overnight (18 hours) and the solvent was evaporated to give compound **19** (94 g).

*Steps 4 and 5: Preparation of [5-(4-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0011)*

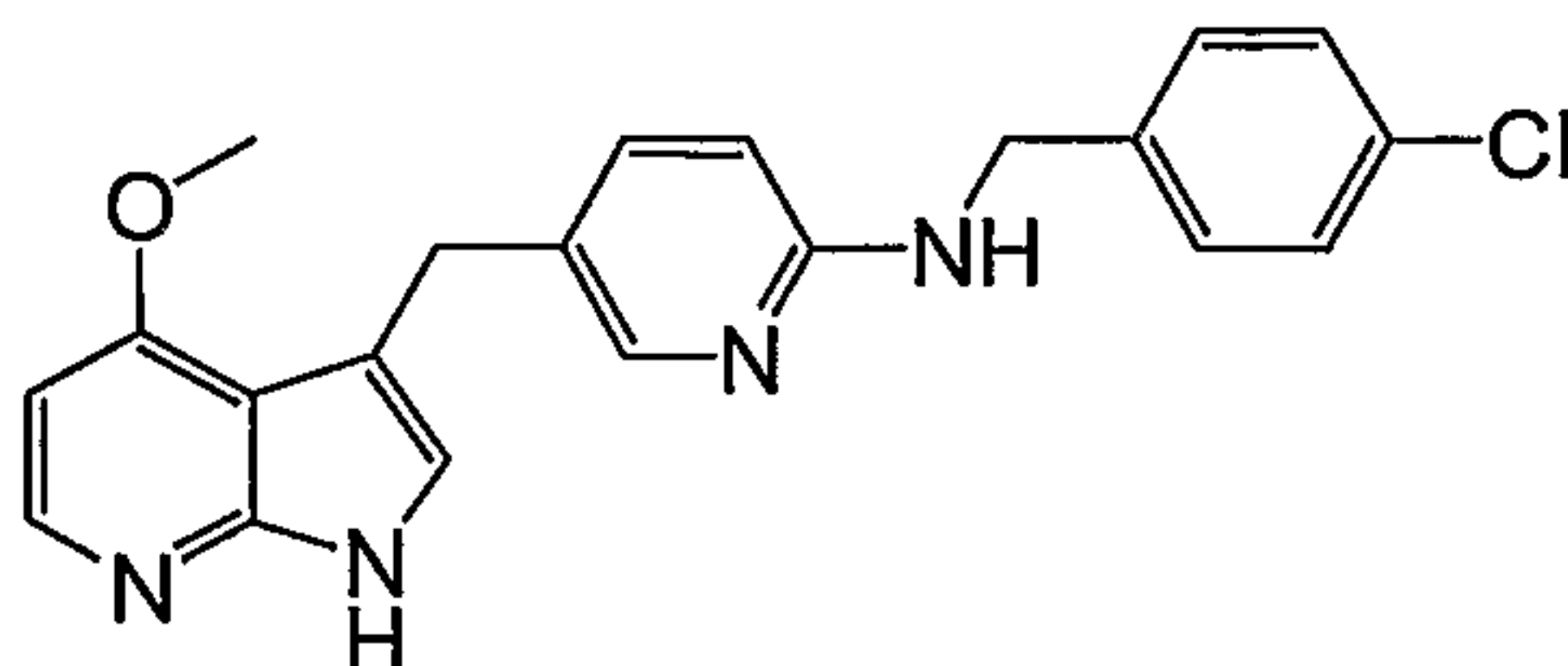
[0305] Step 4: Into a solution of methanol (20 mL, 0.5 mol) was added sodium hydroxide (0.62 g, 0.016 mol), followed by 4-methoxy-7-azaindole (**20**, 600 mg, 4 mmol, prepared as described in Example 12). Once the mixture was homogeneous, compound **19** (1.7 g, 4.46 mmol) was added and the mixture was stirred at room temperature for 48 hours. The solvent was evaporated and dilute HCl was added to the residue. The residue was extracted with ethyl acetate and washed with 10% sodium bicarbonate, followed by brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to give a mixture of crude compounds **21** and **22**, which was used in the next step.

[0306] Step 5: The mixture of **21** and **22** from Step 4 (2.36 g, 4.46 mmol) was dissolved in dichloromethane (60 mL, 0.9 mol) to which triethylsilane (3.6 mL, 0.022 mol) and trifluoroacetic Acid (2.1 mL, 0.027 mol) were added. The resulting mixture was stirred for 48 hours at room temperature. The solvent was evaporated and the mixture was extracted with dichloromethane:methanol (3:1). The organic layer was washed with

saturated bicarbonate followed by brine. The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated to give crude compound as a residue. The residue was purified by flash silica gel chromatography to give 1.15 g of solid **P-0011** for a 60% yield.

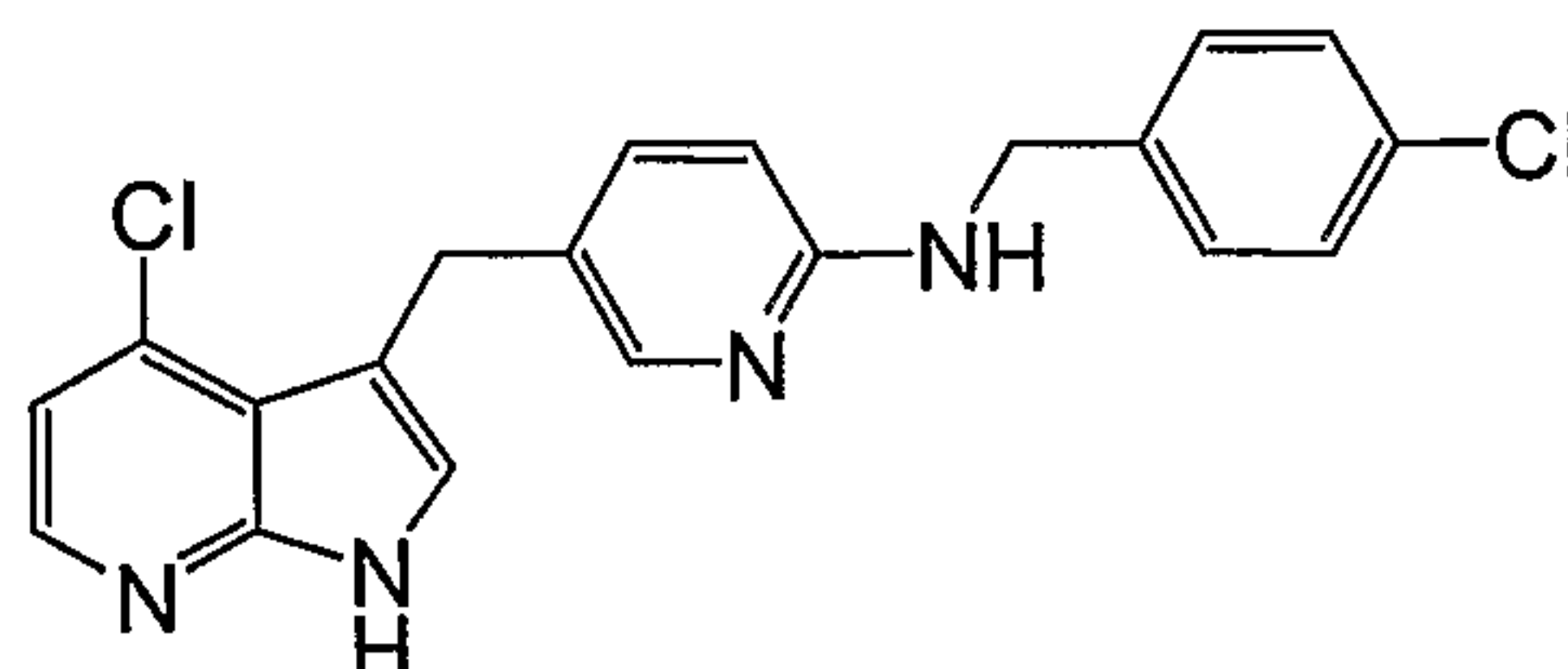
MS (ESI)  $[\text{M}+\text{H}^+]^+ = 413.24$ .

[0307] [5-(4-Methoxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine **P-0010**



was prepared following the protocol of Scheme 12, substituting 4-trifluoro-benzylamine with 4-chloro-benzylamine in Step 1. MS (ESI)  $[\text{M}+\text{H}^+]^+ = 379.2$  and  $381.2$  (3:1 ratio).

[0308] [5-(4-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine **P-0009**

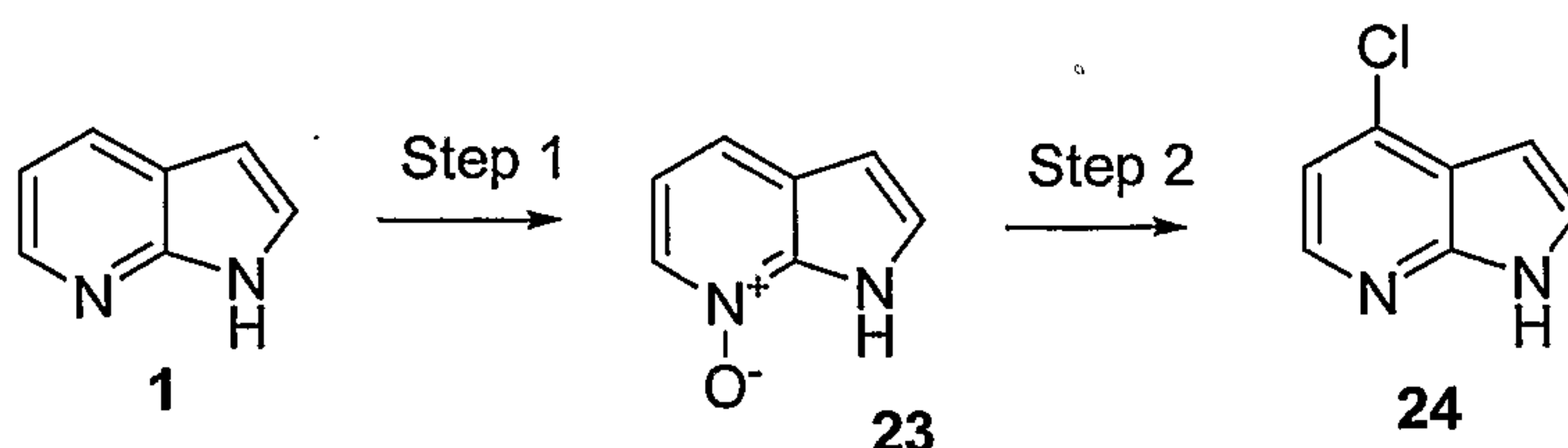


was prepared following the protocol of Scheme 12, substituting 4-trifluoro-benzylamine with 4-chloro-benzylamine in Step 1 and 4-methoxy-7-azaindole with 4-chloro-7-azaindole (**24**, prepared as described in Example 11) in Step 4. MS (ESI)  $[\text{M}+\text{H}^+]^+ = 381.1$  and  $383.0$ .

#### Example 11: Synthesis of 4-chloro-7-azaindole (**24**)

[0309] 4-chloro-7-azaindole **24** was synthesized in two Steps from 7-azaindole according to the protocol of Scheme 13.

#### Scheme 13





*Step -1 – Synthesis of 1H-Pyrrolo[2,3-b]pyridine 7-oxide (23)*

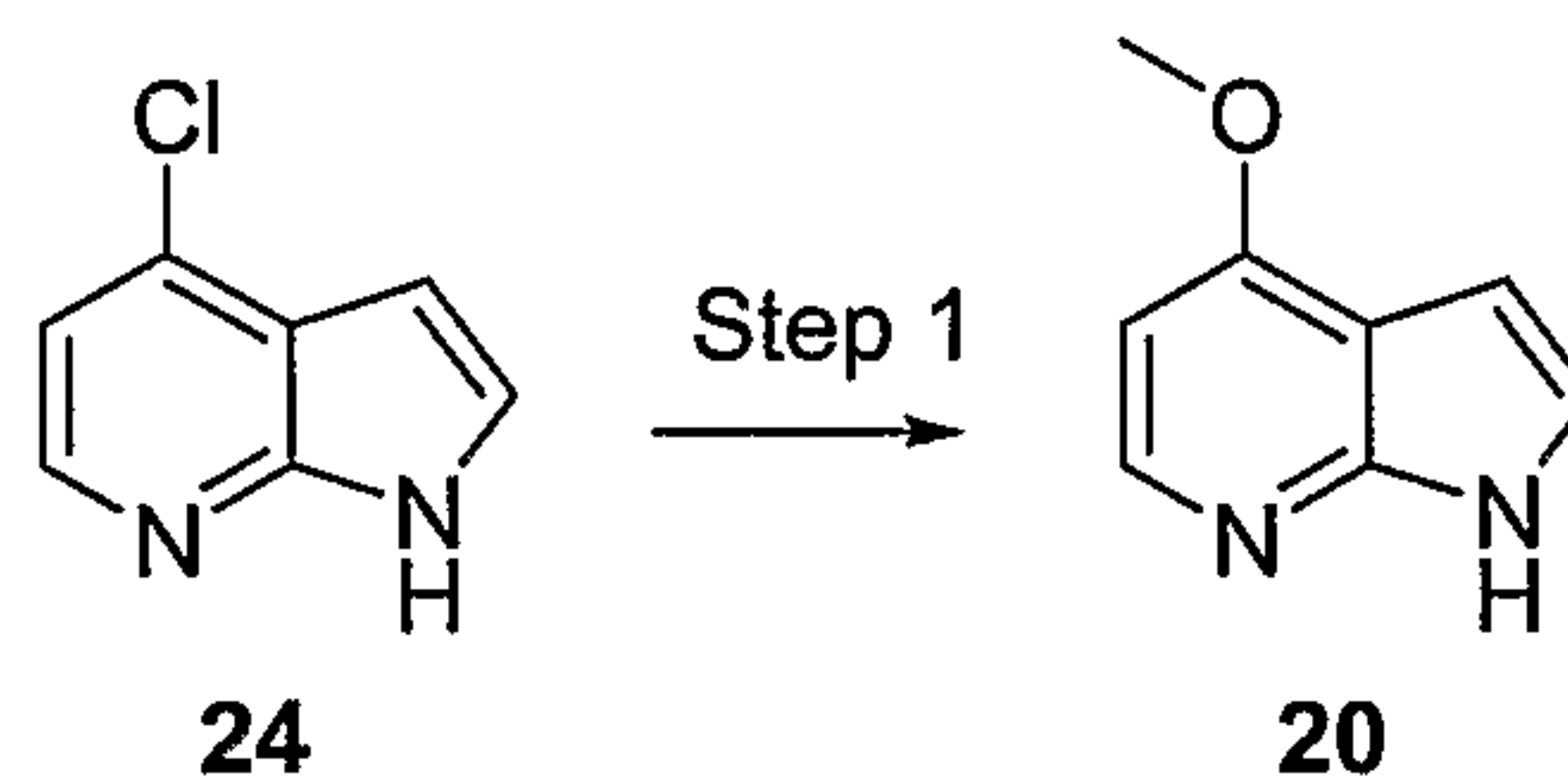
[0310] 1H-Pyrrolo[2,3-b]pyridine 7-oxide **23** was synthesized by reacting commercially available 7-azaindole **1** with an oxidizing agent (e.g. *m*-CPBA) in a non-reactive solvent (e.g. dimethoxyethane) as described by Schneller, S. W.; Luo, Jiann-Kuan. *J. Org. Chem.* 1980, 45:4045-4048. The compound was isolated by filtration of the resulting solid that forms upon standing at 5 °C for typically 1-3 h.

*Step - 2 – Synthesis of 4-chloro-7-azaindole (24)*

[0311] 4-chloro-7-azaindole **24** was synthesized by reacting 1H-Pyrrolo[2,3-b]pyridine 7-oxide **23** with a chlorinating agent (e.g. POCl<sub>3</sub>) neat as described by Schneller, S. W.; Luo, Jiann-Kuan. *J. Org. Chem.* 1980, 45:4045-4048. The resulting solution after heating for 3-5 h at elevated temperatures (100-150 °C) was neutralized with a base (e.g. NH<sub>4</sub>OH) until a solid precipitated. The solid was isolated by filtration.

**Example 12: Synthesis of 4-methoxy-7-azaindole (20)**

[0312] 4-methoxy-7-azaindole **20** was synthesized in one Step from 4-chloro-7-azaindole according to the protocol of Scheme 14.

**Scheme 14**

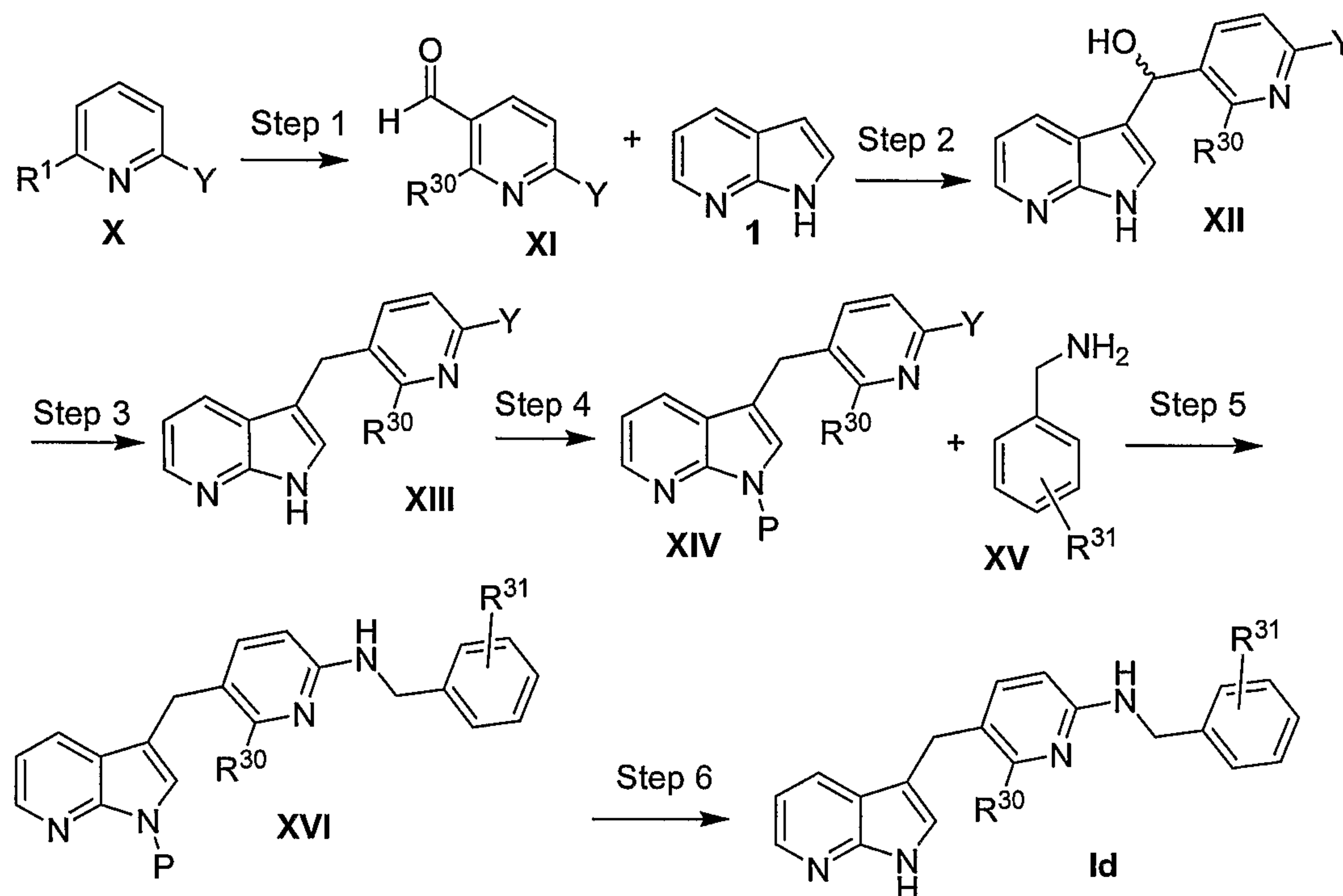
[0313] 4-methoxy-7-azaindole **20** was prepared by reacting 4-chloro-7-azaindole **24** (prepared as described in Example 9) with sodium hydroxide in methanol as described by Girgis, N. et.al., *J. Heterocyclic. Chem.* 1989, 26:317-325.

**Example 13: Synthesis of compounds of Formula I where n is 1, P is CR<sup>30</sup>, Q, T, X<sub>1</sub>, X<sub>2</sub>, Y<sub>1</sub> and Y<sub>2</sub> are CH, L<sup>1</sup> is -CH<sub>2</sub>-, L<sup>2</sup> is -NHCH<sub>2</sub>-, and R<sup>1</sup> is substituted phenyl (Formula Id).**

[0314] Compounds of Formula Id, where R<sup>30</sup> is a substituent as defined for optionally substituted heteroarylene (further defined in Scheme 13 below) and R<sup>31</sup> is a substituent as

defined for optionally substituted aryl, can be synthesized in six Steps from appropriately substituted 2-halopyridines as shown in the following general Scheme 15.

### Scheme 15



#### Step 1 - Preparation of compounds of Formula XI

[0315] To an appropriately substituted 2-halopyridine **X** (e.g. 2-chloro-6-methoxypyridine), where Y is a halogen, preferably chlorine or bromine, and R<sup>30</sup> is a group appropriate to direct the following lithiation to the 5-position (e.g. R<sup>30</sup> = methoxy), in a non-reactive solvent (e.g. tetrahydrofuran) typically cooled in a -78 °C acetone/dry ice bath is added a solution of organolithium reagent (e.g. tert-butyllithium). The reaction is allowed to stir for a period, typically 1 hour. An appropriate formylating agent (e.g. dimethylformamide) is added and the reaction is allowed to stir cooled for a period and then warmed to room temperature for a period, typically 30 minutes. The reaction can be placed back in the dry-ice bath and quenched with 6 N HCl (1.5 mL) followed by water and allowed to warm to room temperature. Isolation by conventional means (e.g. extraction) provides compounds of Formula **XI**.

#### Step 2 - Preparation of compounds of Formula XII

[0316] To 1H-pyrrolo[2,3-b]pyridine **1** and a compound of Formula **XI** is added an appropriate polar solvent (e.g. methanol) followed by an appropriate base (e.g. potassium



hydroxide). The reaction is typically allowed to stir at room temperature overnight. Isolation by conventional means (e.g. extraction, washing and filtering) affords compounds of Formula **XII**.

*Step 3 - Preparation of compounds of Formula XIII*

[0317] To a compound of Formula **XII** in an appropriate polar solvent (e.g. acetonitrile) is added a reducing agent (e.g. trifluoroacetic acid and triethylsilane). Typically, the reaction is allowed to stir at room temperature overnight. Isolation by conventional means (e.g. extraction and silica gel chromatography) affords compounds of Formula **XIII**.

*Step 4 - Preparation of compounds of Formula XIV*

[0318] To a solution of compound of Formula **XIII** in an appropriate polar solvent (e.g. dimethylformamide) is added a base (e.g. sodium hydride). Typically, the reaction is stirred at room temperature for 30 minutes, and then an appropriate reagent to introduce a protecting group ("P") is added (e.g. triisopropylsilyl chloride). The reaction typically is stirred at room temperature for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) affords compounds of Formula **XIV**.

*Step 5- Preparation of compounds of Formula XVI*

[0319] To a compound of Formula **XIV**, an appropriately substituted benzylamine **XV** (e.g. 4-(trifluoromethyl)benzylamine), a base (e.g. sodium tert-butoxide), a catalyst (e.g. tris(dibenzylideneacetone)dipalladium(0)), and ligand (e.g. 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl) are added a non-reactive solvent (e.g. toluene) under an inert atmosphere. Typically, the reaction is heated (e.g. 80 °C) for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) affords compounds of Formula **XVI**.

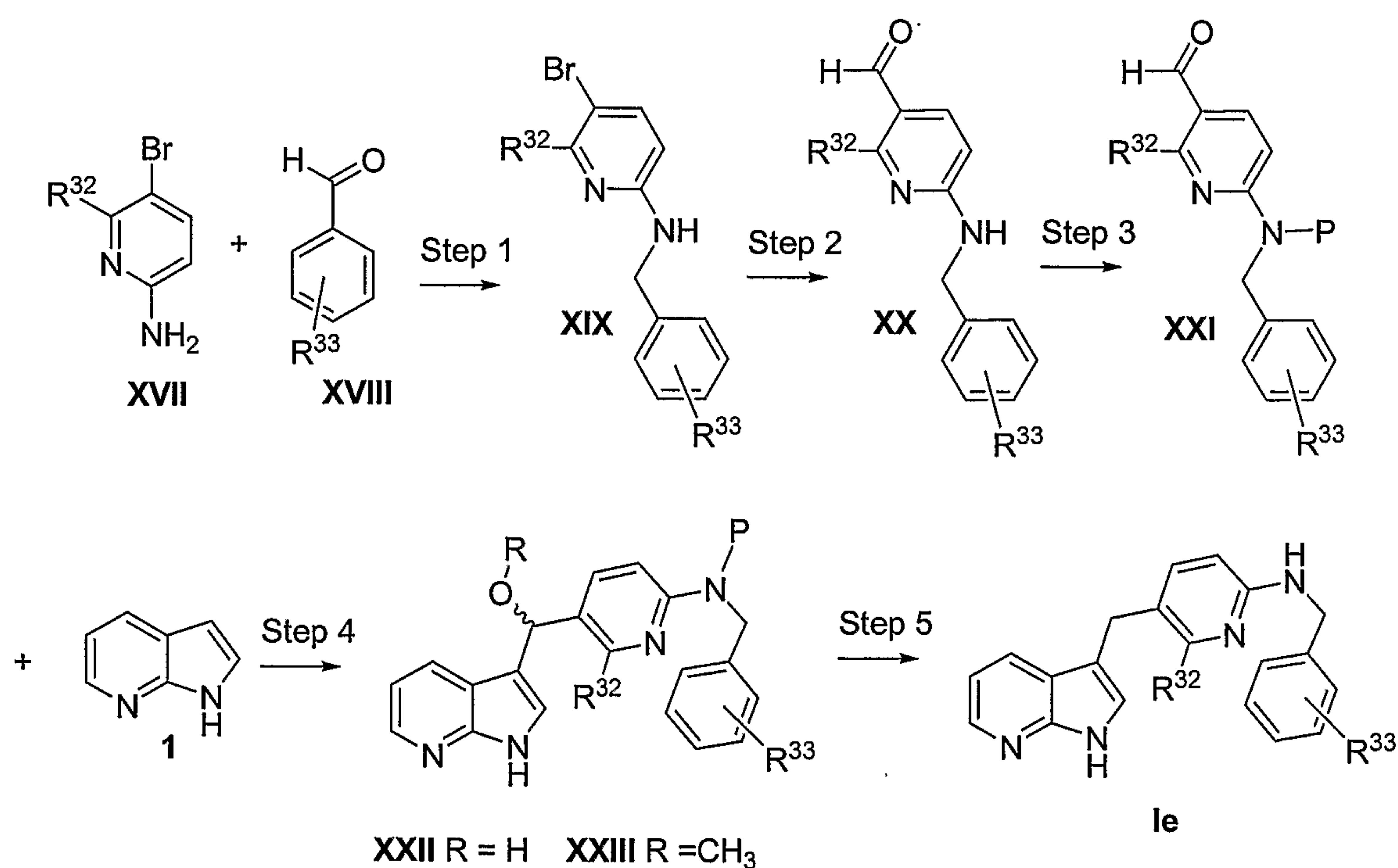
*Step 6 – Preparation of compounds of Formula Id*

[0320] To compound of Formula **XVI** is added an appropriate polar solvent (e.g. tetrahydrofuran) followed by an appropriate reagent to remove the protecting group (e.g. tetra-n-butylammonium fluoride). Typically, the reaction is allowed to stir at room temperature for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) affords compounds of Formula **Id**.

**Example 14: Synthesis of compounds of Formula I where n is 1, P is CR<sup>32</sup>, Q, T, X<sub>1</sub>, X<sub>2</sub>, Y<sub>1</sub> and Y<sub>2</sub> are CH, L<sup>1</sup> is -CH<sub>2</sub>-, L<sup>2</sup> is -NHCH<sub>2</sub>-, and R<sup>1</sup> is substituted phenyl (Formula Ie).**

[0321] Compounds of Formula Id, where R<sup>32</sup> is a substituent as defined for optionally substituted heteroarylene and R<sup>33</sup> is a substituent as defined for optionally substituted aryl, can be synthesized in five Steps from appropriately substituted 2-amino-5-bromopyridines as shown in the following general Scheme 16.

**Scheme 16**



*Step - 1 – Preparation of compounds of Formula XIX*

[0322] To a solution of an appropriately substituted benzaldehyde XVIII (e.g. *p*-trifluoromethyl benzaldehyde) in a non-reactive solvent (e.g. tetrahydrofuran) can be added an appropriate 2-amino-5-bromo-pyridine XVII (e.g. 2-amino-5-bromo-6-methylpyridine), followed by appropriate reagents to effect the reduction (e.g. dibutyltin dichloride and phenylsilane). Typically the reaction is heated (e.g. 50 °C) overnight. Isolation by conventional means (e.g. extraction) affords compounds of Formula XIX.



*Step -2- Preparation of compounds of Formula XX*

[0323] Compound of Formula XIX is dissolved in a non-reactive solvent (e.g. tetrahydrofuran) and typically cooled at -78 °C under an inert atmosphere. To this mixture is added an organolithium reagent (e.g. methyllithium). The reaction mixture is typically stirred at -78 °C for several hours. To this mixture is added an organolithium reagent (e.g. tert-butyllithium) and the mixture is stirred for several hours. The reaction mixture is maintained at -78 °C, and an appropriate formylating reagent (e.g. 1-piperidine carboxaldehyde) is added. Typically, the reaction is allowed to stir at -78 °C for an additional several hours and slowly warmed to room temperature. Isolation by conventional means (e.g. extraction) affords compounds of Formula XX.

*Step -3- Preparation of compounds of Formula XXI*

[0324] Compound of Formula XX is dissolved in a non-reactive solvent (e.g. tetrahydrofuran) and stirred under an inert atmosphere. To this solution is added a base (e.g. triethylamine) and typically a catalyst (e.g. 4-dimethylaminopyridine). Typically, the mixture is stirred for a few minutes, and then a reagent appropriate for the introduction of a protecting group (e.g. di-tert-butylidicarbonate) is added. Typically, the reaction is stirred overnight. Isolation by conventional means (e.g. extraction) affords compounds of Formula XXI.

*Step - 4 – Preparation of compounds of Formula XXII and XXIII*

[0325] 1H-Pyrrolo[2,3-b]pyridine 1 is added to a stirred solution of base (e.g. potassium hydroxide) in an appropriate polar solvent (e.g. methanol). Compound of Formula XXI is added, and the mixture is typically stirred at room temperature for several days. The solvent is evaporated and 1 M HCl is added to the residue. Isolation by conventional means (e.g. extraction, silica gel chromatography) affords compounds of Formula XXII and XXIII.

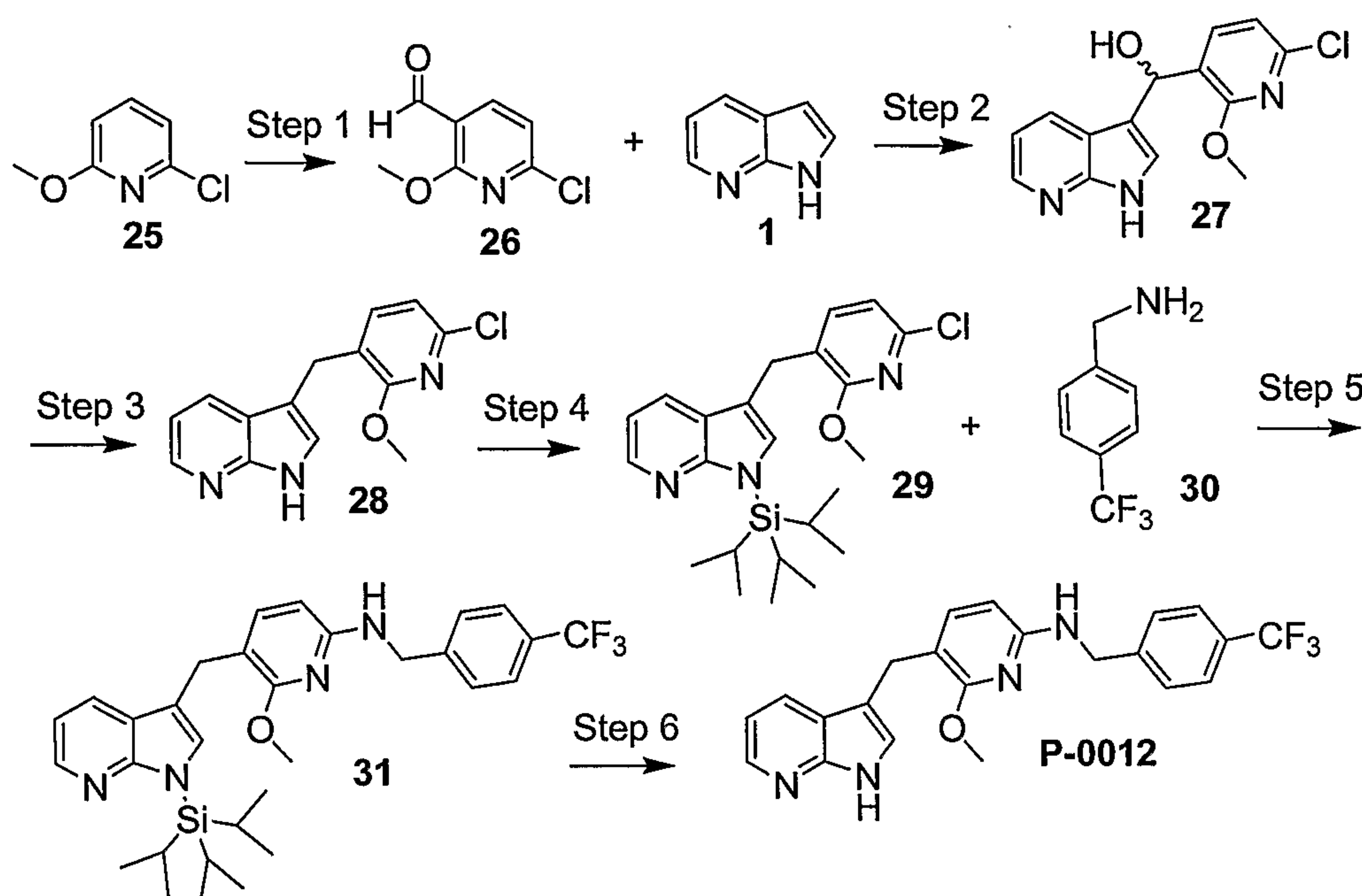
*Step – 5 – Preparation of compounds of Formula XIV of Scheme 14*

[0326] Typically, compounds of Formula XII and XIII are combined and dissolved in an appropriate polar aprotic solvent (e.g. acetonitrile). Reagents appropriate to effect the reduction (e.g. triethylsilane and trifluoroacetic acid) are added. Typically, the reaction is stirred at room temperature for several days. Isolation by conventional means (e.g. extraction, silica gel chromatography) affords compounds of Formula Ie.

**Example 15: Synthesis of [6-Methoxy-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0012)**

[0327] [6-Methoxy-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine **P-0012** was synthesized in five steps from commercially available 2-chloro-6-methoxypyridine and 7-azaindole as shown in Scheme 17.

**Scheme 17**



*Step 1 - Preparation of 6-chloro-2-methoxypyridine-3-carbaldehyde (26)*

[0328] To 2-Chloro-6-methoxypyridine (**25**, 0.511 g, 3.56 mmol) in tetrahydrofuran (10 mL) cooled in a  $-78^{\circ}\text{C}$  acetone/dry ice bath was added tert-butyllithium (1.7 M in pentane, 5.0 mL, 7.66 mmol). The reaction was allowed to stir for 1 hour. Dimethylformamide (0.673 mL, 17.4 mmol) was added and the reaction was allowed to continue for an additional 30 minutes at  $-78^{\circ}\text{C}$ , then stirred for 30 minutes outside of the dry-ice bath. The reaction was placed back in the dry-ice bath and quenched with 6 N HCl (1.5 mL) followed by water and allowed to warm to room temperature. The reaction was extracted with diethyl ether and aqueous (1M) sodium bicarbonate. The organic layer was separated, dried with anhydrous magnesium sulfate, filtered and volatiles removed by rotary evaporation, and the resulting yellow solid was dried under vacuum to provide 561 mg of compound **26** (3.27 mmol, 92% yield). MS(ESI)  $[\text{M}+\text{H}^+]^+ = 172.0$ .



*Step 2 - Preparation of (6-chloro-2-methoxypyridin-3-yl)(1H-pyrrolo[2,3-b]pyridin-3-yl)methanol (27)*

[0329] To 1H-Pyrrolo[2,3-b]pyridine (**1**, 0.455 g, 3.85 mmol) and 6-chloro-2-methoxypyridine-3-carbaldehyde (**26**, 0.661 g, 3.85 mmol) was added methanol (10 mL) followed by potassium hydroxide (0.310 g, 5.52 mmol). The reaction was allowed to stir at room temperature overnight. The reaction was extracted with diethyl ether/ethyl acetate and water. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and volatiles were removed by rotary evaporation to provide a solid that was treated with dichloromethane and stored in a freezer overnight. The white solid was collected by vacuum filtration and dried in vacuo to give 613 mg of compound **27** (2.12 mmol, 55%). MS(ESI)  $[M+H]^+ = 290.1$ .

*Step 3 - Preparation 3-(6-chloro-2-methoxypyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (28)*

[0330] To (6-chloro-2-methoxypyridin-3-yl)(1H-pyrrolo[2,3-b]pyridin-3-yl)methanol (**27**, 0.613 g, 2.12 mmol) in acetonitrile (10 mL) was added trifluoroacetic acid (0.82 mL, 10.0 mmol) followed by triethylsilane (1.69 mL, 10.6 mmol). The reaction was allowed to stir at room temperature for 2 days, then 60 °C for 4 hours. The reaction was extracted with diethyl ether and aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate and filtered. The desired material was isolated from the filtrate by silica gel column chromatography eluting with 1% methanol in dichloromethane to give 516 mg of a white solid compound **28** (1.88 mmol, 89%). MS(ESI)  $[M+H]^+ = 274.1$ .

*Step 4 - Preparation 3-(6-chloro-2-methoxypyridin-3-ylmethyl)-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine (29)*

[0331] To a clear solution of 3-(6-chloro-2-methoxypyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**28**, 0.516 g, 1.88 mmol) in dimethylformamide (10 mL) was added sodium hydride (60% dispersion, 0.113 g, 2.82 mmol). After stirring at room temperature for 30 minutes, triisopropylsilyl chloride (600  $\mu$ L, 2.83 mmol) was added. The reaction was stirred at room temperature for 2 hours, then poured into aqueous (1M) sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated, dried (magnesium sulfate), filtered and volatiles were removed by rotary evaporation to give a crude solid. The compound was purified by silica gel column chromatography eluting

with 2% ethyl acetate in hexanes. This provided 732 mg of the desired compound as a white, crystalline solid (**29**, 1.70 mmol, 90%). MS(ESI)  $[M+H]^+ = 430.2$ .

*Step 5- Preparation of [6-Methoxy-5-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (31)*

**[0332]** 3-(6-chloro-2-methoxypyridin-3-ylmethyl)-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine (**29**, 0.104 g, 0.242 mmol), 4-(Trifluoromethyl)benzylamine (**30**, 0.047 g, 0.266 mmol), sodium tert-butoxide (0.0325 g, 0.338 mmol), Tris(dibenzylideneacetone)-dipalladium (0) (0.00062 g, 0.0006 mmol), and 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (0.0011 g, 0.0018 mmol) were added to toluene (2 mL) under nitrogen. The reaction vial was placed in an oil bath at 80 °C for 3 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried (magnesium sulfate), filtered, and volatiles were removed by rotary evaporation. The residue was purified by silica gel column chromatography eluting with 2% ethyl acetate in hexanes. This provided 34 mg of the desired compound **31** (0.060 mmol, 25%). MS(ESI)  $[M+H]^+ = 569.3$ .

*Step 6 – Preparation of [6-Methoxy-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0012)*

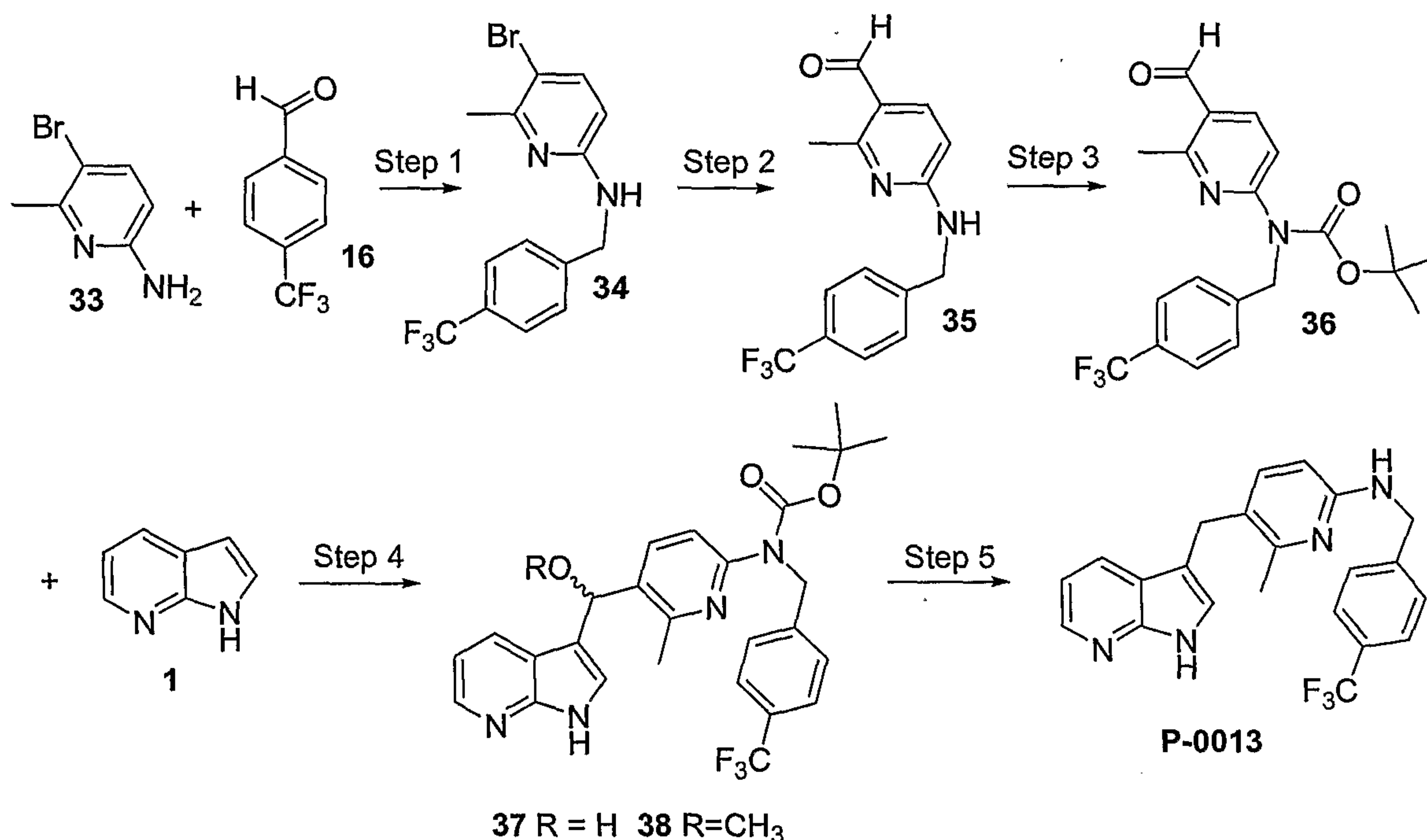
**[0333]** To [6-Methoxy-5-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (**31**, 0.0340 g, 0.0598 mmol) was added tetrahydrofuran (5 mL) followed by tetra-n-butylammonium fluoride (1M solution in tetrahydrofuran, 66 µL, 0.0658 mmol). The reaction was allowed to stir at room temperature for 2 hours, then poured into 1:1 water:saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered and the volatiles were removed by rotary evaporation. The resulting residue was purified by silica gel column chromatography, eluting with dichloromethane followed by 1% methanol in dichloromethane and finally 3% methanol in dichloromethane. This provided 20 mg of the desired compound as a white solid (**P-0012**, 0.048 mmol, 81%). MS(ESI)  $[M+H]^+ = 413.2$ .



**Example 16: Synthesis of [6-Methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0013)**

[0334] [6-Methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (**P-0013**) was synthesized in five steps from commercially available 2-amino-5-bromo-6-methylpyridine and 7-azaindole as shown in Scheme 18.

**Scheme 18**



*Step - 1 – Preparation of (5-Bromo-6-methyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-amine (34)*

[0335] To a solution of *p*-trifluoromethylbenzaldehyde (**16**, 1.00 g, 5.74 mmol) in tetrahydrofuran (9 mL) was added 2-amino-5-bromo-6-methylpyridine (**33**, 1.08 g, 5.77 mmol), followed by dibutyltin dichloride (40 mg, 0.13 mmol). The mixture was stirred for 5 minutes at 25 °C and phenylsilane (0.69 g, 6.4 mmol) was added. The reaction was heated at 50 °C overnight, then the solvent was removed at reduced pressure. Ethyl acetate was added to the resulting solid which was washed with saturated sodium carbonate, dried over magnesium sulfate and filtered. Concentration under reduced pressure afforded a light yellow solid (**34**, 1.7 g, 4.93 mmol). MS(ESI) [M + H]<sup>+</sup> = 345.1.

*Step -2- Preparation of 2-Methyl-6-(4-trifluoromethyl-benzylamino)-pyridine-3-carbaldehyde (35)*

[0336] (5-Bromo-6-methyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-amine (**34**, 1.7 g, 4.93 mmol) was dissolved in tetrahydrofuran (40 mL) and cooled at  $-78\text{ }^{\circ}\text{C}$  under a nitrogen atmosphere. To this mixture was added methyllithium (1.6 M in diethyl ether, 5.91 mmol) dropwise over 20 minutes. After the addition of methyllithium was completed, the reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 2 hours. To this mixture was added tert-butyllithium (1.7 M in pentane, 10.85 mmol) and the mixture was stirred for 4 hours. The reaction mixture was maintained at  $-78\text{ }^{\circ}\text{C}$ , and 1-piperidinecarboxaldehyde (0.60 mL, 5.42 mmol) was added dropwise. The reaction was allowed to stir at  $-78\text{ }^{\circ}\text{C}$  for an additional 2 hours and warming to  $25\text{ }^{\circ}\text{C}$  was achieved from the slow evaporation of the dry ice/acetone cooling bath. The reaction was quenched with ice cold saturated sodium chloride and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and filtered. Concentration under reduced pressure afforded an orange oil (**35**, 1.4 g, 4.93 mmol). MS(ESI)  $[\text{M} + \text{H}^+]^+ = 295.1$ .

*Step -3- Preparation of (5-Formyl-6-methyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (36)*

[0337] 2-Methyl-6-(4-trifluoromethyl-benzylamino)-pyridine-3-carbaldehyde (**35**, 1.4 g, 4.9 mmol) was dissolved in tetrahydrofuran (22 mL) and was stirred under an atmosphere of nitrogen. To this solution was added 4-dimethylaminopyridine (150 mg, 1.23 mmol) and triethylamine (0.66 mL, 4.9 mmol). The mixture was stirred for 5 minutes before solid di-tert-butyl dicarbonate (1.0 g, 4.9 mmol) was added directly to the reaction mixture. The mixture was stirred overnight at  $25\text{ }^{\circ}\text{C}$  and was diluted with ethyl acetate and washed with sodium bicarbonate, followed by washing with saturated sodium chloride. The resulting organic layer was dried over magnesium sulfate, filtered and evaporated to give a beige solid (**36**, 1.8 g, 4.6 mmol). MS(ESI)  $[\text{M} + \text{H}^+]^+ = 395.2$ .

*Step - 4 – Preparation of {5-[Hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-6-methyl-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (37) and {5-[Methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-6-methyl-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (38)*

[0338] 1H-Pyrrolo[2,3-b]pyridine (**1**, 540 mg, 4.57 mmol) was added to a stirring solution of potassium hydroxide (868 mg, 10.08 mmol) in methanol (33 mL). Once the

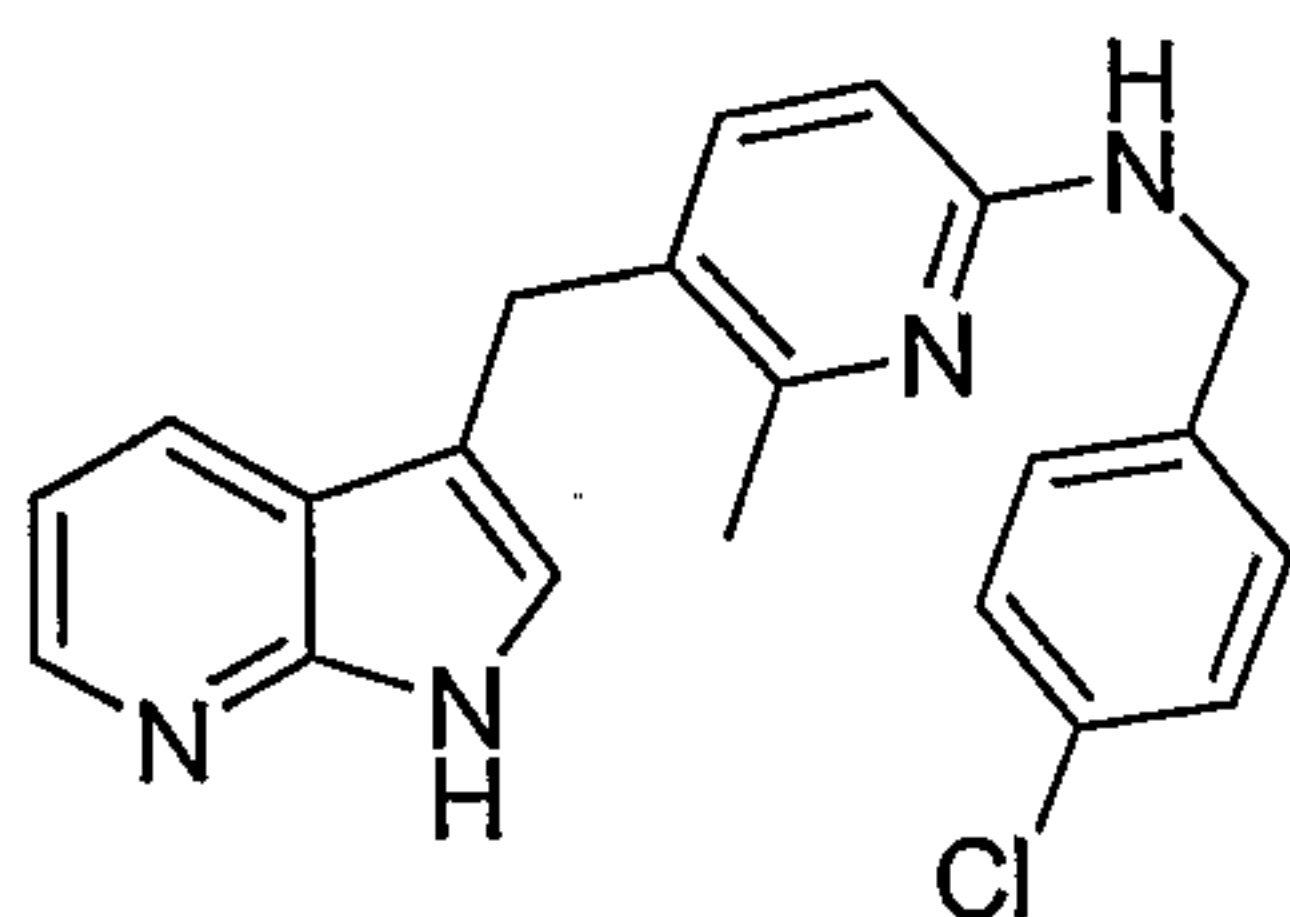


mixture was homogeneous, (5-formyl-6-methyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (**36**, 1.8 g, 4.6 mmol) was added and the mixture was stirred at 25 °C for 72 hours. The solvent was evaporated and 1 M HCl was added to the residue. The organic material was extracted with ethyl acetate and washed with 10% sodium bicarbonate, followed by washing with saturated sodium chloride. The organic layer was dried over magnesium sulfate. Concentration under reduced pressure afforded the crude material, which was purified by silica gel column chromatography (0 – 5% methanol in dichloromethane) to yield the desired compounds as a light yellow solid (**37** and **38** as a mixture, 294 mg; 13% yield). MS(ESI)  $[M + H]^+ = 511.2$  for **37** and MS(ESI)  $[M + H]^+ = 525.2$  for **38**.

*Step - 5 Preparation of [6-Methyl-5-(1H-pyrrolo[2,3-b]bipyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0013)*

[0339] The combined materials of {5-[Hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-6-methyl-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (**37**) and {5-[Methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-6-methyl-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (**38**) (194 mg, 0.378 mmol) were dissolved in acetonitrile (3 mL) and triethylsilane (0.30 mL, 1.9 mmol) and trifluoroacetic acid (0.17 mL, 2.3 mmol) were added. After stirring at 25 °C for overnight, TLC analysis indicated that the reaction was about 50% complete. To the reaction mixture was added triethylsilane (0.30 mL, 1.9 mmol), and trifluoroacetic acid (0.17 mL, 2.3 mmol). The mixture was allowed to stir for another 48 hours at 25 °C and the solvent, excess triethylsilane and trifluoroacetic acid were removed by evaporation. Ethyl acetate was added and washed with saturated sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated at reduced pressure to afford a brown oil. Purification of 80 mg of the crude material was carried out using preparatory chromatography (50% ethyl acetate in hexanes) to afford the compound as an off-white solid (**P-0013**, 10 mg, 0.025 mmol). MS(ESI)  $[M + H]^+ = 397.2$ .

[0340] (4-Chloro-benzyl)-[6-methyl-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0014**

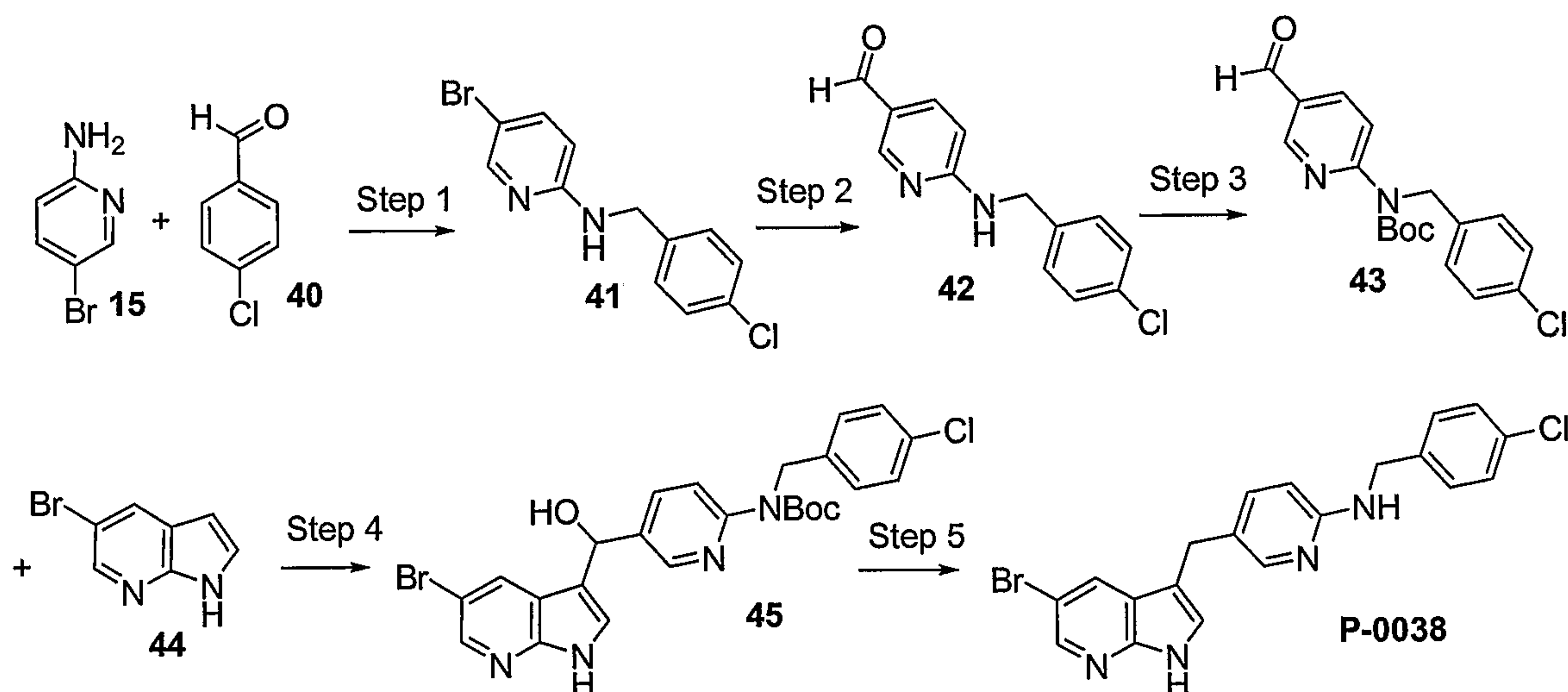


was prepared following the protocol of Scheme 18, substituting 4-trifluoromethyl benzaldehyde with 4-chlorobenzaldehyde (**40**) in Step 1. MS(ESI)  $[M + H]^+ = 363.1$ .

**Example 17: Synthesis of [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine (P-0038)**

[0341] [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine **P-0038** was synthesized in 5 steps from commercially available 2-Amino-5-bromopyridine **15** as shown in Scheme 19.

#### Scheme 19



#### Step 1- Synthesis of (5-Bromo-pyridin-2-yl)-(4-chloro-benzyl)-amine (**41**)

[0342] To 2-Amino-5-bromopyridine (**15**, 6.10 g, 0.0352 mol) in toluene (90.0 mL) were added 4-chlorobenzaldehyde (**40**, 5.00 g, 0.0356 mol), trifluoroacetic acid (8.0 mL, 0.10 mol) and triethylsilane (16.5 mL, 0.103 mol). The reaction was heated to reflux for 48 hours. The reaction was concentrated, poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium



sulfate and concentrated. The crude residue was crystallized with ethyl acetate to give compound (**41**, 6.8 g, 65.4%).

*Step 2 – Synthesis of 6-(4-Chloro-benzylamino)-pyridine-3-carbaldehyde (42)*

[0343] To (5-Bromo-pyridin-2-yl)-(4-chloro-benzyl)-amine (**41**, 10.00 g, 0.03360 mol) in tetrahydrofuran (400.0 mL) under an atmosphere of nitrogen at -78 °C was added n-butyllithium (17.5 mL, 2.00 M in cyclohexane). After 90 minutes, tert-butyllithium (42.00 mL, 1.70 M in hexane) was added to the reaction. After 80 minutes, N,N-dimethylformamide (6.9 mL, 0.089 mol) was added to the reaction. The reaction mixture was stirred at -78 °C for 2 hours, then allowed to warm to room temperature for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to give the crude compound, which was crystallized from *tert*-butoxyl methyl ether to provide compound (**42**, 7.66 g, 92.2%).

*Step 3 – Synthesis of (4-Chloro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (43)*

[0344] To 6-(4-Chloro-benzylamino)-pyridine-3-carbaldehyde (**42**, 2.00 g, 8.11 mmol) in dichloromethane (20.0 mL) were added triethylamine (1.70 mL, 12.2 mmol), di-*tert*-butyldicarbonate (2.00 g, 9.16 mmol) and 4-dimethylaminopyridine (52.3 mg, 0.43 mmol). The reaction was stirred at room temperature for 48 hours. The reaction was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give compound (**43**, 2.50 g, 89.3%).

*Step 4 – Synthesis of {5-[(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl}-(4-chloro-benzyl)-carbamic acid tert-butyl ester (45)*

[0345] To 5-bromo-7-azaindole (**44**, 198.0 mg, 1.01 mmol) in methanol (30.0 mL, 0.741 mol) were added (4-Chloro-benzyl)-(5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**43**, 355.0 mg, 1.02 mmol) and potassium hydroxide (80.0 mg, 1.42 mmol). The reaction was stirred at room temperature 48 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 8% methanol in dichloromethane to give compound (**45**, 200.0 mg, 36.8%).

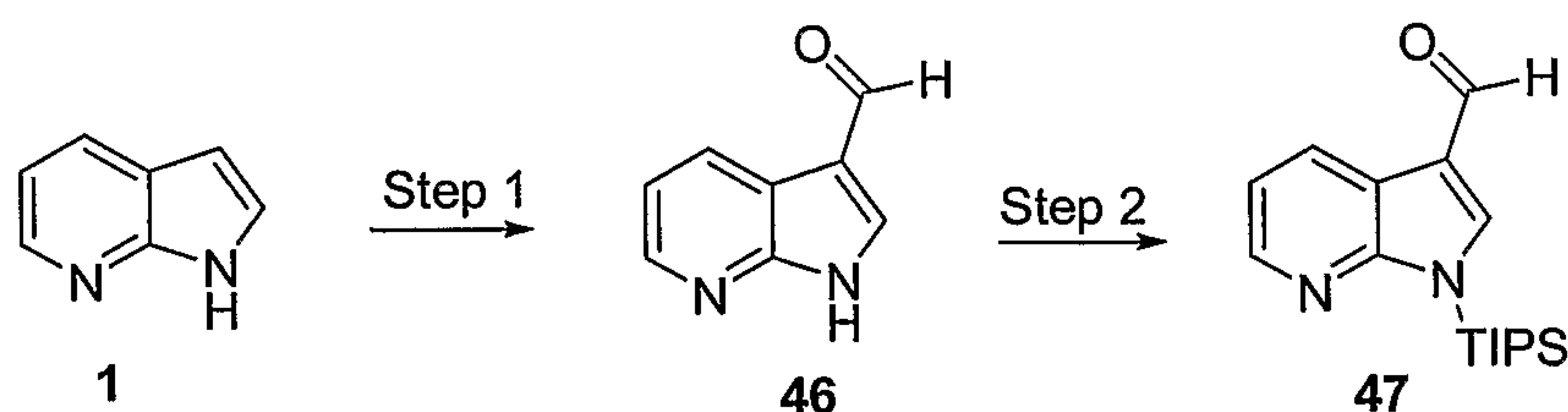
*Step 5 – Synthesis of [5-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-chloro-benzyl)-amine (P-0038)*

[0346] To {5-[(5-Bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-hydroxy-methyl]-pyridin-2-yl}-(4-chloro-benzyl)-carbamic acid tert-butyl ester (**45**, 180.0 mg, 0.33 mmol) in acetonitrile (30.0 mL) were added trifluoroacetic acid (2.0 mL, 0.026 mol) and triethylsilane (4.0 mL, 0.025 mol). The reaction was heated to reflux for 4 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 10% methanol in dichloromethane to give compound (**P-0038**, 120 mg, 85.2%). MS(ESI)[M+H]<sup>+</sup> = 427.2, 429.2.

**Example 18: Synthesis of 1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde 47.**

[0347] Compound **47** was synthesized in 2 steps from 7-azaindole **1** as described in Scheme 20.

**Scheme 20**



*Step 1 – Preparation of 1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (46):*

[0348] To 1H-Pyrrolo[2,3-b]pyridine (**1**, 16.0 g, 135 mmol) in water (110 mL), were added hexamethylenetetramine (26.0 g, 185 mmol), and acetic acid (55.0 mL, 967 mmol). The reaction was refluxed for 12 hours. Water (329 mL) was added and the reaction was cooled to room temperature. The reaction was filtrated and washed with water to give compound (**46**, 15.0 g, 76%). MS(ESI)[M+H]<sup>+</sup> = 147.

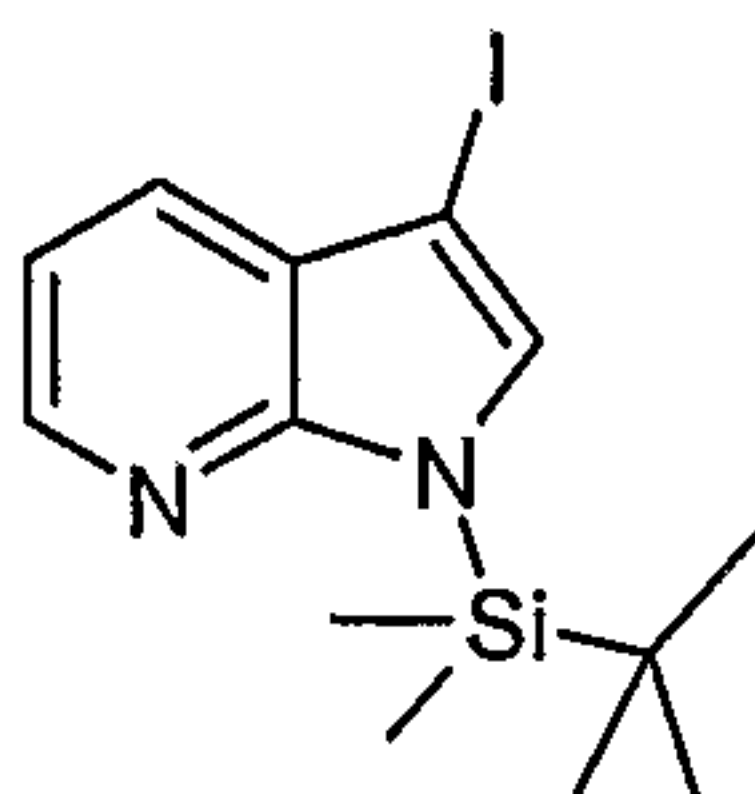
*Step 2 – Preparation of 1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (47):*

[0349] To 1H-Pyrrolo[2,3-b]pyridine-3-carbaldehyde (**46**, 4.05 g, 27.71 mmol) in tetrahydrofuran (30.0 mL) were added sodium hydride (60% in mineral oil, 1.5 g, 38 mmol) and triisopropylsilyl chloride (8.0 mL, 38 mmol) under an atmosphere of nitrogen.



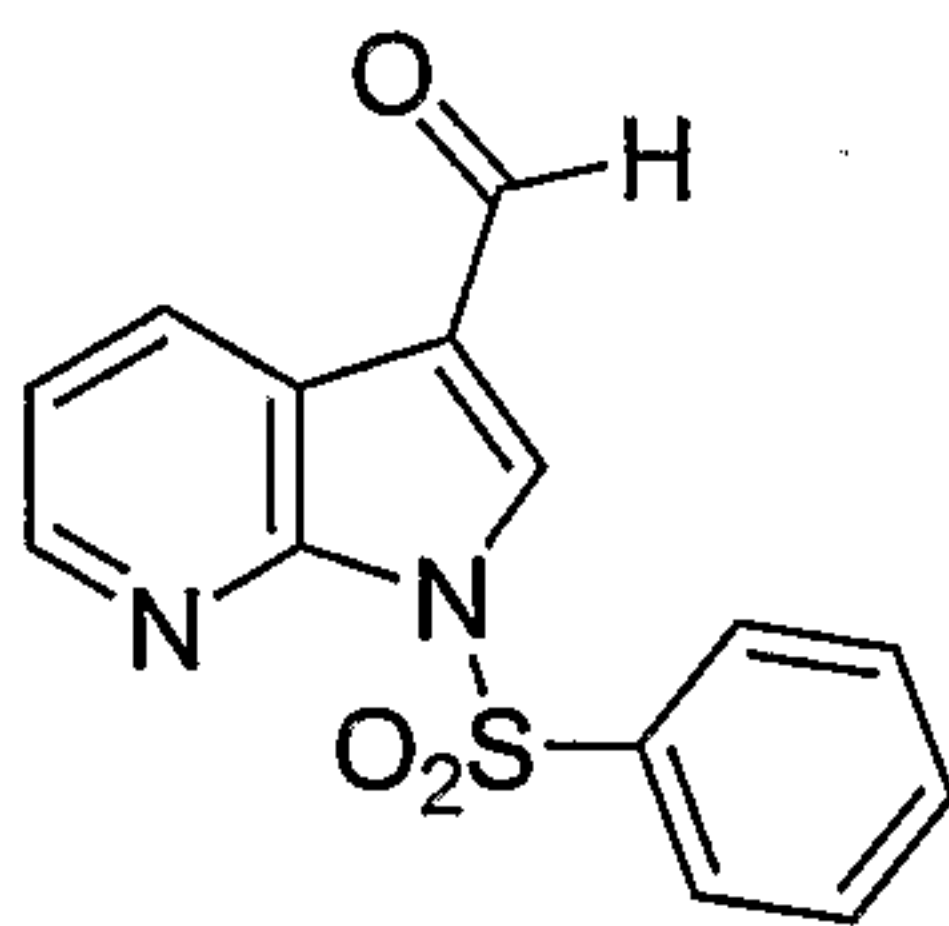
The reaction was stirred for 2 hours at room temperature. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 10 % ethyl acetate in hexane to give compound (**47**, 3.0 g, 36%). MS(ESI)[M+H<sup>+</sup>]<sup>+</sup> = 303.

[0350] 1-(tert-Butyl-dimethyl-silanyl)-3-iodo-1H-pyrrolo[2,3-b]pyridine **66**



was prepared following the protocol of Scheme 20 Step 2, substituting 1H-Pyrrolo[2,3-b]pyridine-3-carbaldehyde **46** with 3-iodo-1H-pyrrolo[2,3-b]pyridine and triisopropylsilyl chloride with tert-Butyl-dimethyl-silyl chloride.

[0351] 1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde **55**

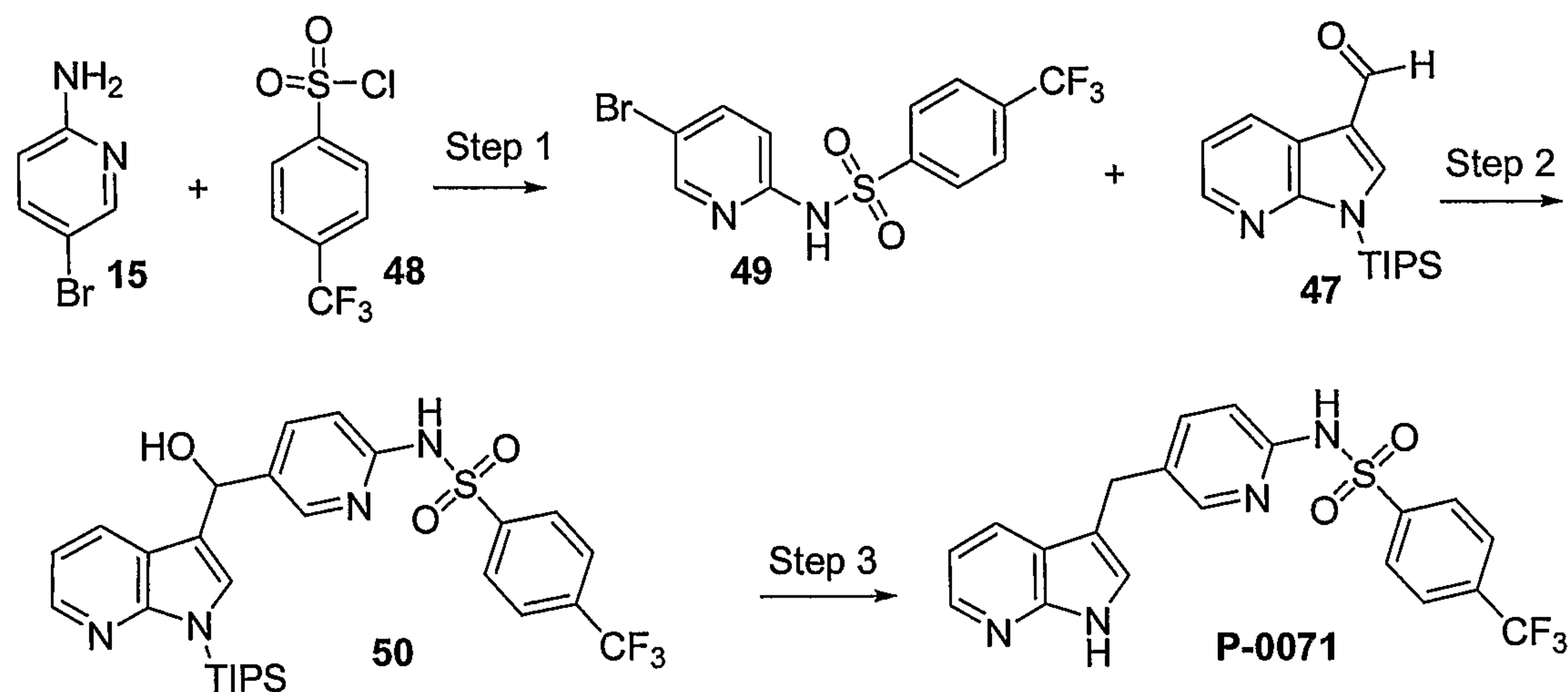


was prepared following the protocol of Scheme 20, substituting triisopropylsilyl chloride with benzenesulfonyl chloride in Step 2.

**Example 19: Synthesis of N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-4-trifluoromethyl-benzenesulfonamide (P-0071)**

[0352] N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-4-trifluoromethyl-benzenesulfonamide **P-0071** was synthesized in 3 steps from 2-Amino-5-bromopyridine **15** as shown in Scheme 21.

## Scheme 21



*Step 1 – Synthesis of N-(5-Bromo-pyridin-2-yl)-4-trifluoromethyl-benzenesulfonamide (49):*

[0353] To 2-Amino-5-bromopyridine (**15**, 1.50 g, 8.67 mmol) in acetonitrile (20.0 mL) were added pyridine (6.0 mL, 0.074 mol), 4-dimethylaminopyridine (0.10 g, 0.82 mmol) and 4-trifluoromethyl-benzenesulfonyl chloride (**48**, 2.14 g, 8.75 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was concentrated, poured into water, acidified with 1N HCl to pH = 2, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was washed with ethyl acetate to give a white solid as desired compound (**49**, 2.80 g, 84.8%). MS (ESI)  $[M+H]^+ = 381.0, 383.0$ .

*Step 2 – Synthesis of N-5-[Hydroxy-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl-4-trifluoromethyl-benzenesulfonamide (50):*

[0354] To N-(5-Bromo-pyridin-2-yl)-4-trifluoromethyl-benzenesulfonamide (**49**, 0.96 g, 2.5 mmol) in tetrahydrofuran (50.0 mL) under an atmosphere of nitrogen at -78 °C, tert-butyllithium (4.62 mL, 1.70 M in hexane) was added slowly. After 15 minutes, 1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**47**, 0.30 g, 0.99 mmol, prepared as described in Example 18) in tetrahydrofuran (15.0 mL) was added to the reaction. After 30 minutes, the reaction was allowed to come to room temperature for 10 minutes. The reaction was poured into water, acidified with 1N HCl to pH around 2, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column

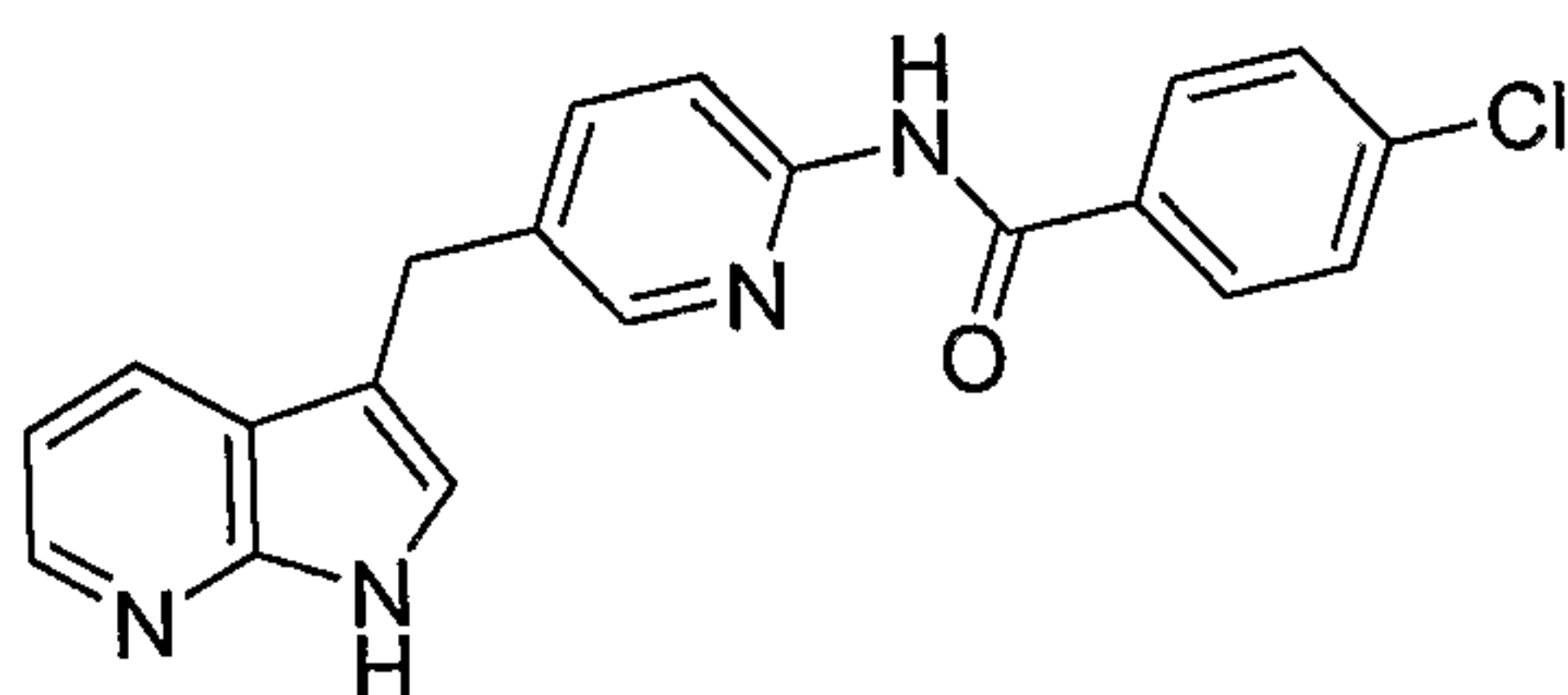


chromatography eluting with 20% ethyl acetate in hexane to give a white solid compound (**50**, 0.55 g, 90.1%). MS (ESI)  $[M+H]^+ = 605.3$ .

*Step 3 – Synthesis of N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-4-trifluoromethyl-benzenesulfonamide (P-0071):*

[0355] To N-5-[Hydroxy-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl-4-trifluoromethyl-benzenesulfonamide (**50**, 0.27 g, 0.45 mmol) in acetonitrile (15.0 mL) were added trifluoroacetic acid (1.0 mL, 0.013 mol) and triethylsilane (2.0 mL, 0.012 mol). The reaction was heated to 85 °C for 1 hour. The reaction was concentrated, poured into water and extracted with ethyl acetate. The organic layer was purified with silica gel column chromatography eluting with 50% ethyl acetate in hexane to give a white solid compound (**P-0071**, 28.5 mg, 14.7%). MS (ESI)  $[M+H]^+ = 433.2$ .

[0356] 4-Chloro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide **P-0074**



was prepared following the protocol of Scheme 21, substituting 4-trifluoromethyl-benzenesulfonyl chloride **48** with 4-chloro-benzoyl chloride in step 1. MS (ESI)  $[M+H]^+ = 363.2$ .

**Example 20: Synthesis of N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-4-trifluoromethyl-benzamide (P-0072)**

[0357] N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-4-trifluoromethyl-benzamide **P-0072** was synthesized in one step from (3-(6-Bromo-pyridin-3-ylmethyl)-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine **6a** as shown in Scheme 22.

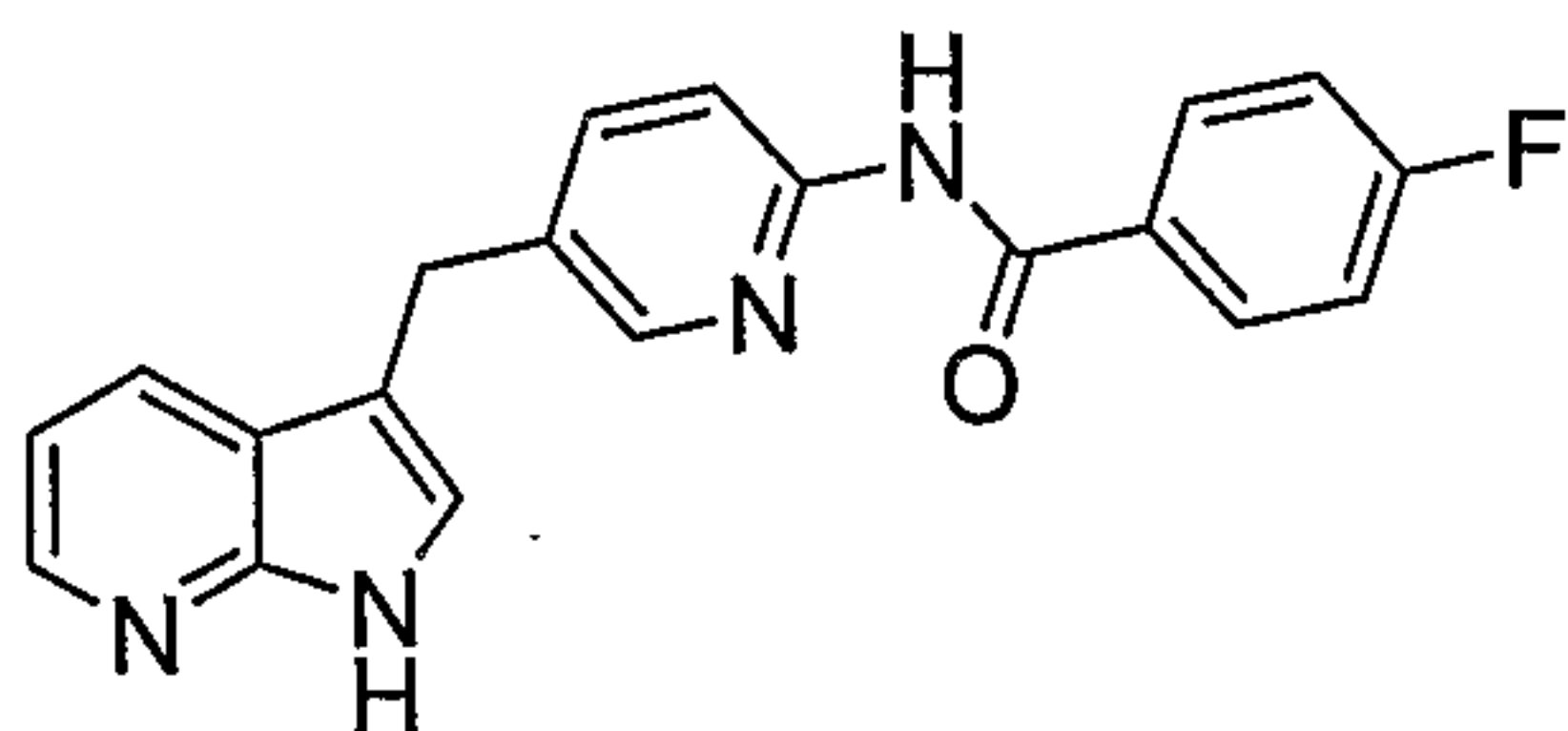
**Scheme 22**



*Step 1 – Synthesis of N-[5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-4-trifluoromethyl-benzamide (P-0072):*

[0358] To 3-(6-Bromo-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**6a**, 50.0 mg, 0.000174 mol, prepared as described in Example 2) in 1,4-dioxane (4.0 mL) were added 4-trifluoromethyl-benzamide (**51**, 70.0 mg, 0.37 mmol), Xanthphos (15.0 mg, 0.026 mmol), cesium carbonate (130.0 mg, 0.40 mmol) and Tris(dibenzylideneacetone)-dipalladium(0) (25.0 mg, 0.024 mmol) under an atmosphere of nitrogen. The reaction was heated to 120 °C for 10 minutes in a CEM Discover microwave instrument. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 50% ethyl acetate in hexane to give a white solid (**P-0072**, 4.7 mg, 6.8%). MS (ESI)  $[M+H]^+ = 397.2$ .

[0359] 4-Fluoro-N-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-benzamide **P-0073**



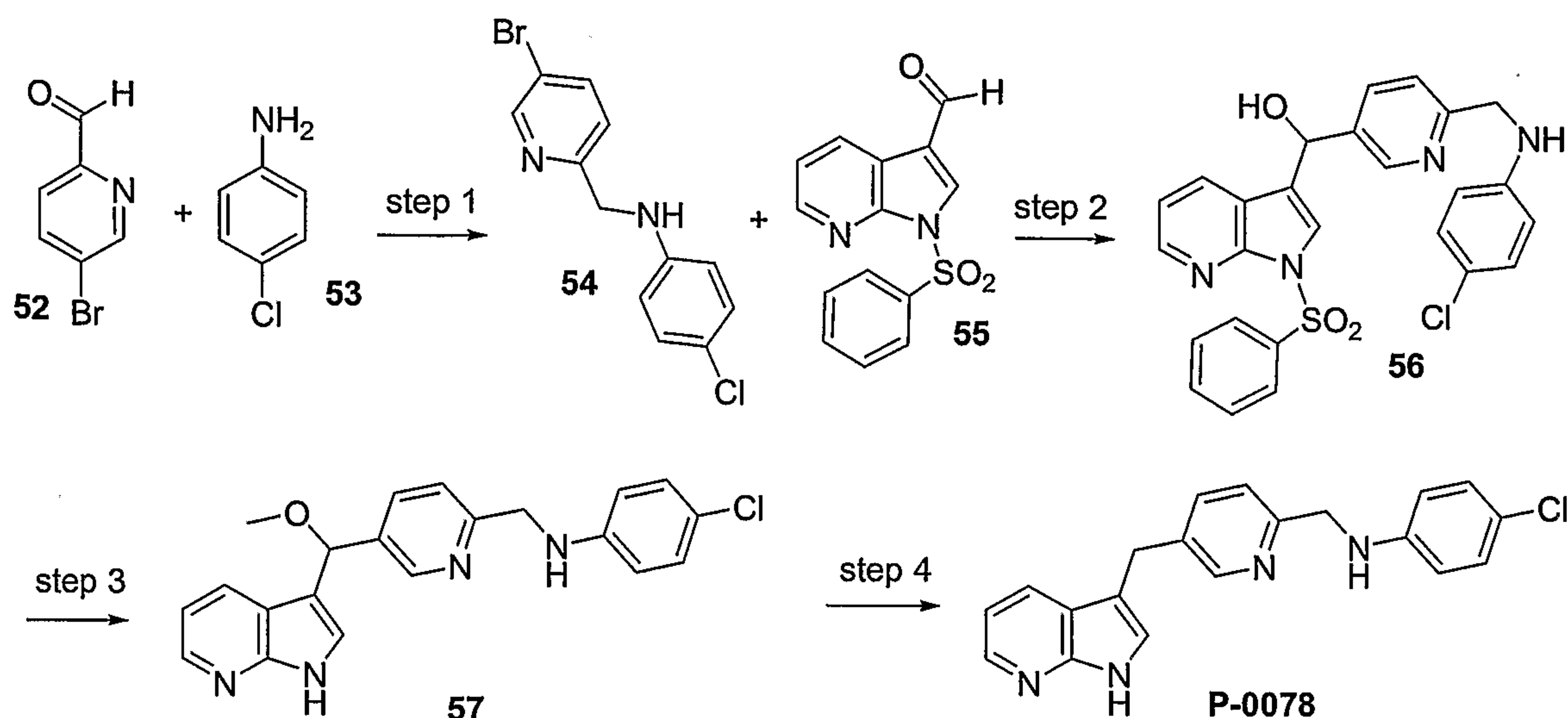
was prepared following the protocol of Scheme 22, substituting 4-trifluoromethyl-benzamide with 4-fluoromethyl-benzamide. MS (ESI)  $[M+H]^+ = 347.2$ .

**Example 21: Synthesis of (4-Chloro-phenyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylmethyl]-amine (P-0078)**

[0360] (4-Chloro-phenyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylmethyl]-amine **P-0078** was synthesized in 3 steps from 5-Bromo-pyridine-2-carbaldehyde **52** as shown in Scheme 23.



## Scheme 23



*Step 1 – Synthesis of (5-Bromo-pyridin-2-ylmethyl)-(4-chloro-phenyl)-amine (54):*

[0361] To 5-Bromo-pyridine-2-carbaldehyde (**52**, 1.00 g, 5.38 mmol) in acetonitrile (50.0 mL) were added p-chloroaniline (**53**, 0.686 g, 5.38 mmol), triethylsilane (6.00 mL, 0.0376 mol) and trifluoroacetic acid (3.00 mL, 0.0389 mol). The reaction was heated to reflux for 3 hours. The reaction was concentrated, poured into water and then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a white solid (**54**, 0.75 g, 47.0%).

*Step 2- Synthesis of (1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-[(4-chloro-phenylamino)-methyl]-pyridin-3-yl-methanol (56):*

[0362] To (5-Bromo-pyridin-2-ylmethyl)-(4-chloro-phenyl)-amine (**54**, 0.380 g, 1.28 mmol) in tetrahydrofuran (15.0 mL) under an atmosphere of nitrogen at -78 °C was added n-butyllithium (0.850 mL, 1.60 M in hexane). After 10 minutes, 1,2-bis-(chloro-dimethyl-silanyl)-ethane (0.135 g, 0.627 mmol) in tetrahydrofuran (5.0 mL) was added to the reaction. The reaction was allowed to warm to room temperature for 40 minutes. The reaction was cooled to -78 °C, followed by addition of 1.70 M tert-butyllithium in hexane (1.58 mL). After 30 minutes, 1-benzenesulfonyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**55**, 0.380 g, 1.33 mmol, prepared as described in Example 18) in tetrahydrofuran (10.0 mL) was added to the reaction. After 20 minutes, the reaction was allowed to warm to room temperature. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and

filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 50% ethyl acetate in hexane to give compound (**56**, 0.30 g, 46.0%). MS (ESI)  $[M+H]^+ = 505.3$ .

*Step 3- (4-Chloro-phenyl)-5-[methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-ylmethyl-amine (57):*

[0363] To (1-Benzenesulfonyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-[(4-chloro-phenylamino)-methyl]-pyridin-3-yl-methanol (**56**, 120.0 mg, 0.24 mmol) in methanol (20.0 mL) were added potassium hydroxide (0.400 g, 7.13 mmol) and water (5.0 mL, 0.28 mol). The reaction was heated to 50 °C for 10 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give compound (**57**, 30 mg, 33.0%). MS (ESI)  $[M+H]^+ = 379.4$ .

*Step 4- Synthesis of (4-Chloro-phenyl)-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-ylmethyl]-amine (P-0078):*

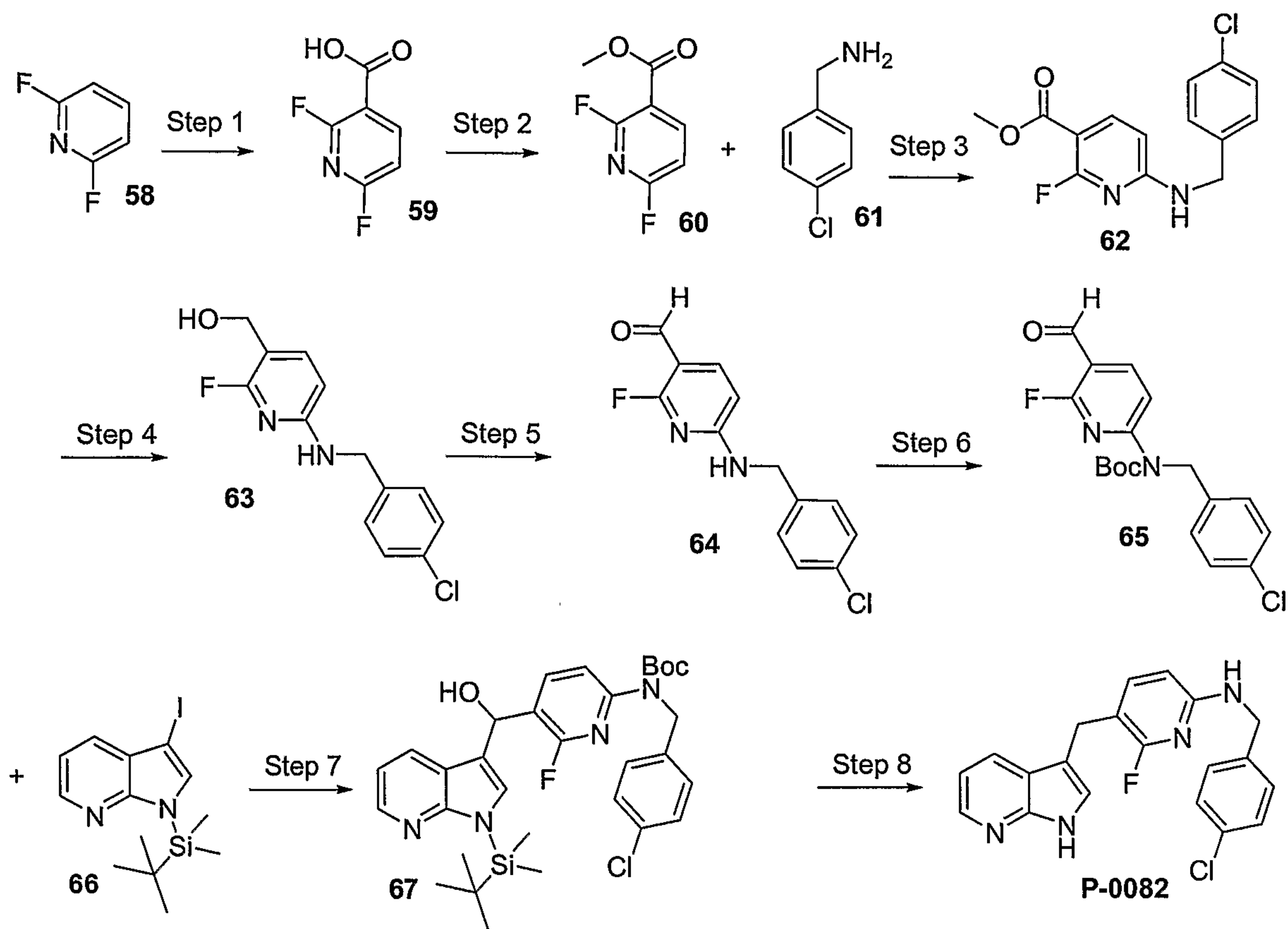
[0364] To (4-Chloro-phenyl)-5-[methoxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-ylmethyl-amine (**57**, 20.8 mg, 0.055 mmol) in acetonitrile (10.0 mL) were added trifluoroacetic acid (0.50 mL, 6.5 mmol) and triethylsilane (1.00 mL, 6.26 mmol). The reaction was heated to reflux for 3 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 10% methanol in dichloromethane to give compound (**P-0078**, 6.1 mg, 32.0%). MS (ESI)  $[M+H]^+ = 349.4$ .

**Example 22: Synthesis of (4-Chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0082)**

[0365] (4-Chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0082** was synthesized in 8 steps from 2,6-Difluoropyridine **58** as shown in Scheme 24.



## Scheme 24

*Step 1 – Synthesis of 2,6-Difluoro-nicotinic acid (59):*

[0366] To 2,6-difluoropyridine (**58**, 7.10 g, 0.0617 mol) in tetrahydrofuran (150.0 mL) under an atmosphere of nitrogen at -78 °C, n-butyllithium (26.0 mL, 2.50 M in hexane) was added slowly. After 30 minutes, dry ice (3.0 g) was added to the reaction. After 1 hour, the reaction was allowed to warm to room temperature, then poured into water and extracted with ethyl acetate. The aqueous layer was acidified with 1 N HCl to pH = 4-5 and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give the crude compound as a light yellow solid (**59**, 5.6 g, 57.0%).

*Step 2 – Synthesis of 2,6-Difluoro-nicotinic acid methyl ester (60):*

[0367] To 2,6-difluoro-nicotinic acid (**59**, 5.60 g, 0.0352 mol) in methanol (60.0 mL) was added concentrated sulfuric acid (1.0 mL, 0.019 mol). The reaction was heated to reflux overnight, then poured into water, basified with 1M potassium carbonate to pH around 9, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated to give a yellow oil (**60**, 3.5 g, 57.0%).

*Step 3 – Synthesis of 6-(4-Chloro-benzylamino)-2-fluoro-nicotinic acid methyl ester (62):*

[0368] To 2,6-difluoro-nicotinic acid methyl ester (**60**, 2.00 g, 0.0116 mol) in N,N-dimethylformamide (20.0 mL), under an atmosphere of nitrogen at -40 °C, was added p-chlorobenzylamine (**61**, 2.60 mL, 0.0214 mol). The reaction was stirred at -40 °C to -20 °C for 2 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 25% ethyl acetate in hexane to give compound (**62**, 2.0 g, 58.7%).

*Step 4 – Synthesis of [6-(4-Chloro-benzylamino)-2-fluoro-pyridin-3-yl]-methanol (63):*

[0369] To 6-(4-Chloro-benzylamino)-2-fluoro-nicotinic acid methyl ester (**62**, 2.00 g, 6.79 mmol) in tetrahydrofuran (100.0 mL) was added lithium tetrahydroaluminate (13.6 mL, 1.00 M in Tetrahydrofuran) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight. To the reaction was added an excessive amount of NaSO<sub>4</sub>·10H<sub>2</sub>O, and then stirred for 1 hour. Filtration, concentration and purification with silica gel column chromatography eluting with 30% ethyl acetate in hexane provided compound **63** (1.0 g, 55.0%).

*Step 5 – Synthesis of 6-(4-Chloro-benzylamino)-2-fluoro-pyridine-3-carbaldehyde (64):*

[0370] To [6-(4-Chloro-benzylamino)-2-fluoro-pyridin-3-yl]-methanol (**63**, 1.0 g, 3.7 mmol) in tetrahydrofuran (50.0 mL) was added Dess-Martin periodinane (1.75 g, 4.12 mmol). The reaction was stirred at room temperature for 10 minutes, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a white solid (**64**, 0.67 g, 68.0%).

*Step 6 – Synthesis of (4-Chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (65):*

[0371] To 6-(4-Chloro-benzylamino)-2-fluoro-pyridine-3-carbaldehyde (**64**, 670.0 mg, 2.53 mmol) in dichloromethane (16.2 mL) were added di-tert-butyl dicarbonate (1.23 g, 5.65 mmol) and 4-dimethylaminopyridine (16.2 mg, 0.133 mmol). The reaction was stirred at room temperature overnight. The reaction was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give a white solid (**65**, 0.63 g, 68.0%).



*Step 7 – Synthesis of (5-[1-(tert-Butyl-dimethyl-silanyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-hydroxy-methyl-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-carbamic acid tert-butyl ester (67):*

[0372] To 1-(tert-butyl-dimethyl-silanyl)-3-iodo-1H-pyrrolo[2,3-b]pyridine (**66**, 0.53 g, 0.0015 mol) and tetrahydrofuran (15.0 mL), under an atmosphere of nitrogen at -20 °C, was added isopropylmagnesium chloride (0.78 mL, 2.0 M in tetrahydrofuran). The reaction was allowed to warm to 0 °C (around 80 minutes), then cooled to -20 °C, followed by addition of (4-Chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**65**, 0.200 g, 0.55 mmol) in tetrahydrofuran (6.0 mL). The reaction was allowed to warm to room temperature in 1 hour, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a yellow solid (**67**, 0.20 g, 61.1%).

MS (ESI)  $[M+H]^+ = 597.4$ .

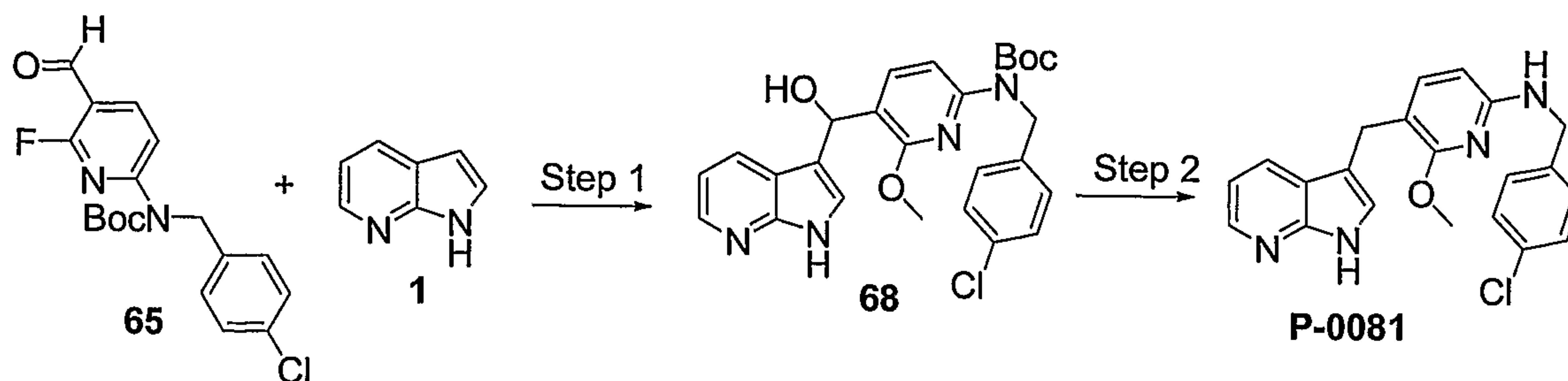
*Step 8 – Synthesis of (4-Chloro-benzyl)-[6-fluoro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0082):*

[0373] To (5-[1-(tert-Butyl-dimethyl-silanyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-hydroxy-methyl-6-fluoro-pyridin-2-yl)-(4-chloro-benzyl)-carbamic acid tert-butyl ester (**67**, 0.10 g, 0.17 mmol) in acetonitrile (10.0 mL) were added triethylsilane (1.00 mL, 6.26 mmol) and trifluoroacetic acid (0.50 mL, 6.5 mmol). The reaction was heated to reflux for 2 hours, then poured into aqueous potassium carbonate, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give a white solid (**P-0082**, 43.2 mg, 70.0%).

MS (ESI)  $[M+H]^+ = 367.4$ .

**Example 23:** Synthesis of (4-Chloro-benzyl)-[6-methoxy-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**P-0081**).

[0374] (4-Chloro-benzyl)-[6-methoxy-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0081** was synthesized in 2 steps from (4-Chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester **65** as shown in Scheme 25.

**Scheme 25**

*Step 1 – Synthesis of (4-Chloro-benzyl)-5-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-6-methoxy-pyridin-2-yl-carbamic acid tert-butyl ester (68):*

[0375] To 1H-Pyrrolo[2,3-b]pyridine (**1**, 90.0 mg, 0.76 mmol) in methanol (30.0 mL) were added (4-chloro-benzyl)-(6-fluoro-5-formyl-pyridin-2-yl)-carbamic acid tert-butyl ester (**65**, 300.0 mg, 0.82 mmol) and potassium hydroxide (720.0 mg, 12.83 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 2 hours, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give the compound (**68**, 60 mg, 15.9%). MS (ESI)  $[M+H^+]^+ = 495.3$ .

*Step 2 – Synthesis of (4-Chloro-benzyl)-[6-methoxy-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0081).*

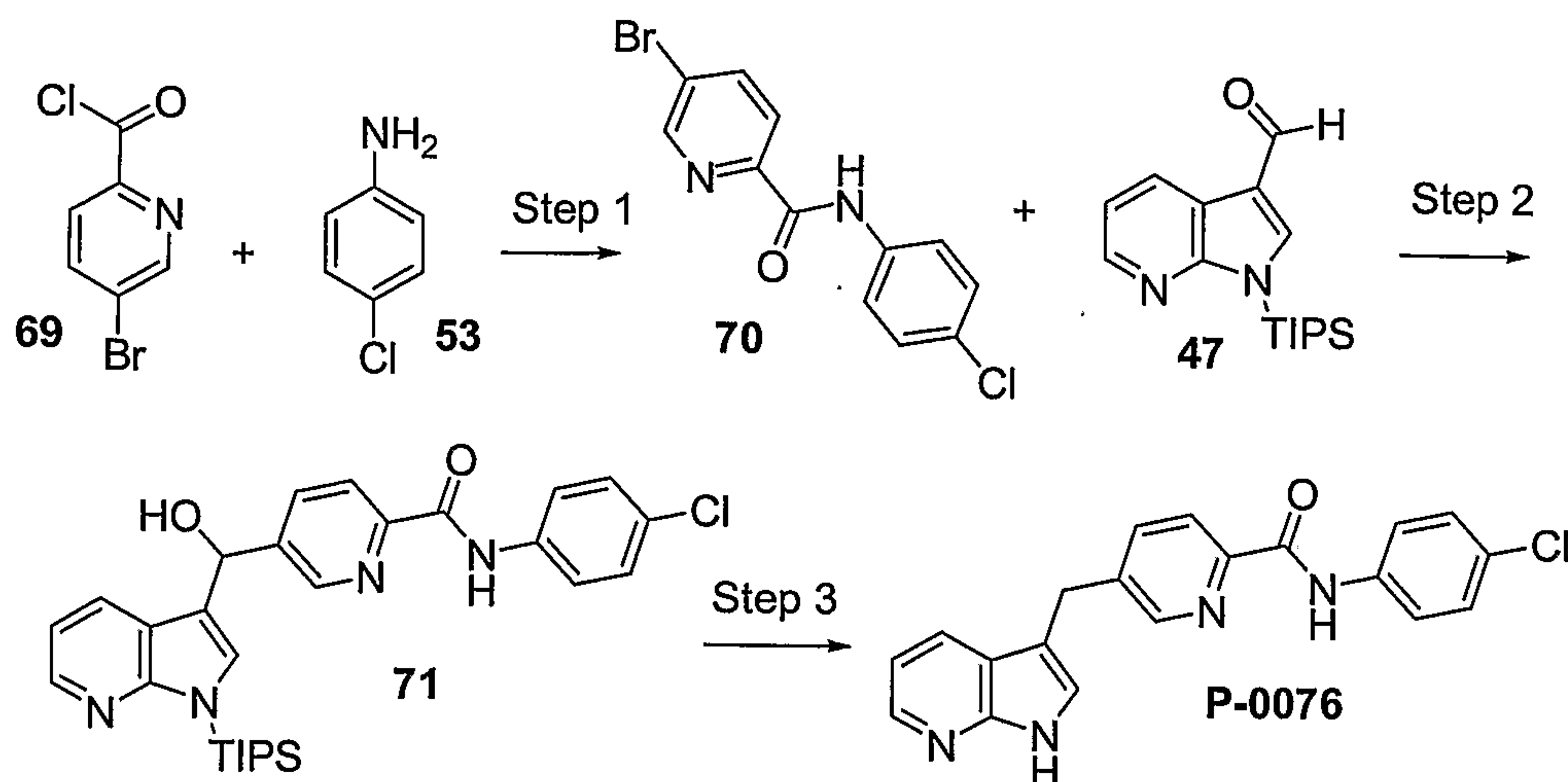
[0376] To (4-Chloro-benzyl)-5-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-6-methoxy-pyridin-2-yl-carbamic acid tert-butyl ester (**68**, 40.0 mg, 0.081 mmol) in acetonitrile (10.0 mL) were added trifluoroacetic acid (0.30 mL, 0.0039 mol) and triethylsilane (0.60 mL, 0.0038 mol). The reaction was heated to reflux for 3 hours. The reaction was concentrated to remove the solvents, then purified with silica gel column chromatography eluting with 40% ethyl acetate in hexane to give compound (P-0081, 10 mg, 32.7%). MS (ESI)  $[M+H^+]^+ = 379.4$ .

**Example 24: Synthesis of 5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridine-2-carboxylic acid (4-chloro-phenyl)-amide (P-0076)**

[0377] 5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridine-2-carboxylic acid (4-chloro-phenyl)-amide P-0076 was synthesized in 3 Steps from 5-Bromo-pyridine-2-carbonyl chloride **69** as shown in Scheme 26.



## Scheme 26



*Step 1 – Synthesis of 5-Bromo-pyridine-2-carboxylic acid (4-chloro-phenyl)-amide (70):*

[0378] To 5-Bromo-pyridine-2-carbonyl chloride (**69**, 0.76 g, 3.4 mmol) in acetonitrile (29.0 mL) were added p-chloroaniline (**53**, 0.702 g, 5.50 mmol), 4-dimethylamino-pyridine (0.12 g, 0.96 mmol) and pyridine (2.9 mL, 0.036 mol). The reaction was stirred at 68 °C overnight, then poured into water, acidified with 1 N HCl to pH around 1 and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with dichloromethane to give a white solid (**70**, 0.75 g, 70.0%).

*Step 2 – Synthesis of 5-[Hydroxy-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridine-2-carboxylic acid (4-chloro-phenyl)-amide (71):*

[0379] To 5-Bromo-pyridine-2-carboxylic acid (4-chloro-phenyl)-amide (**70**, 0.50 g, 1.60 mmol) in tetrahydrofuran (20.0 mL), under an atmosphere of nitrogen at -78 °C, tert-butyl lithium (3.02 mL, 1.70 M in Hexane) was added. After 20 minutes, 1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (**47**, 0.39 g, 1.3 mmol, prepared as described in Example 18) in tetrahydrofuran (10.0 mL) was added to the reaction. The reaction was stirred at -78 °C for 1 hour, then allowed to warm to room temperature for 10 minutes. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give the compound as colorless oil (**71**, 100 mg, 14%). MS (ESI)  $[M+H]^+ = 535.3$ .

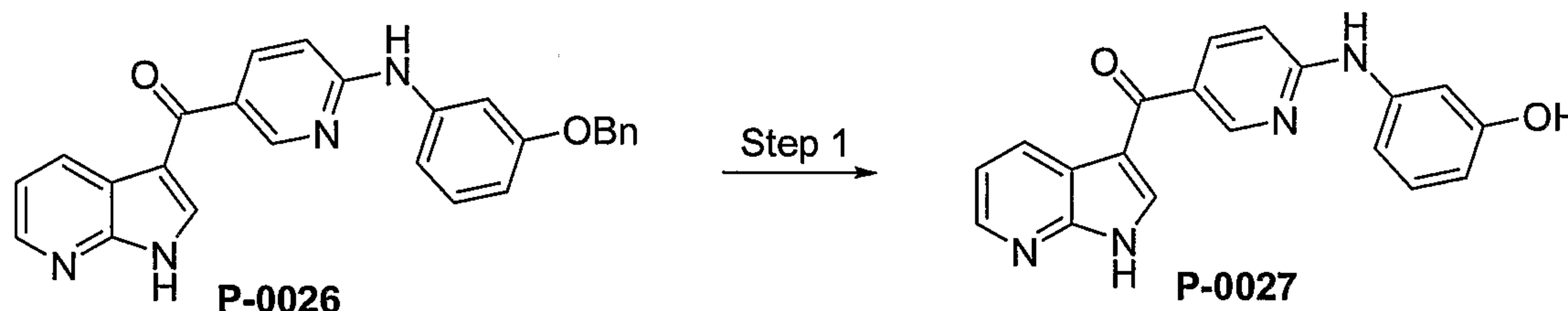
*Step 3 – Synthesis of 5-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridine-2-carboxylic acid (4-chloro-phenyl)-amide (P-0076):*

**[0380]** To 5-[Hydroxy-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridine-2-carboxylic acid (4-chloro-phenyl)-amide (**71**, 100.0 mg, 0.19 mmol) in acetonitrile (10.0 mL) were added trifluoroacetic acid (0.20 mL, 2.6 mmol) and triethylsilane (0.40 mL, 2.5 mmol). The reaction was stirred at 80 °C for 2 hours. The reaction was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a yellow solid compound (**P-0076**, 5.5 mg, 8.1%). MS (ESI)  $[M-H^+]^- = 361.1$ .

**Example 25: Synthesis of [6-(3-Hydroxy-phenylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0027)**

**[0381]** [6-(3-Hydroxy-phenylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0027** was synthesized in 1 Step from [6-(3-Benzyloxy-phenylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0026** as shown in Scheme 27.

**Scheme 27**



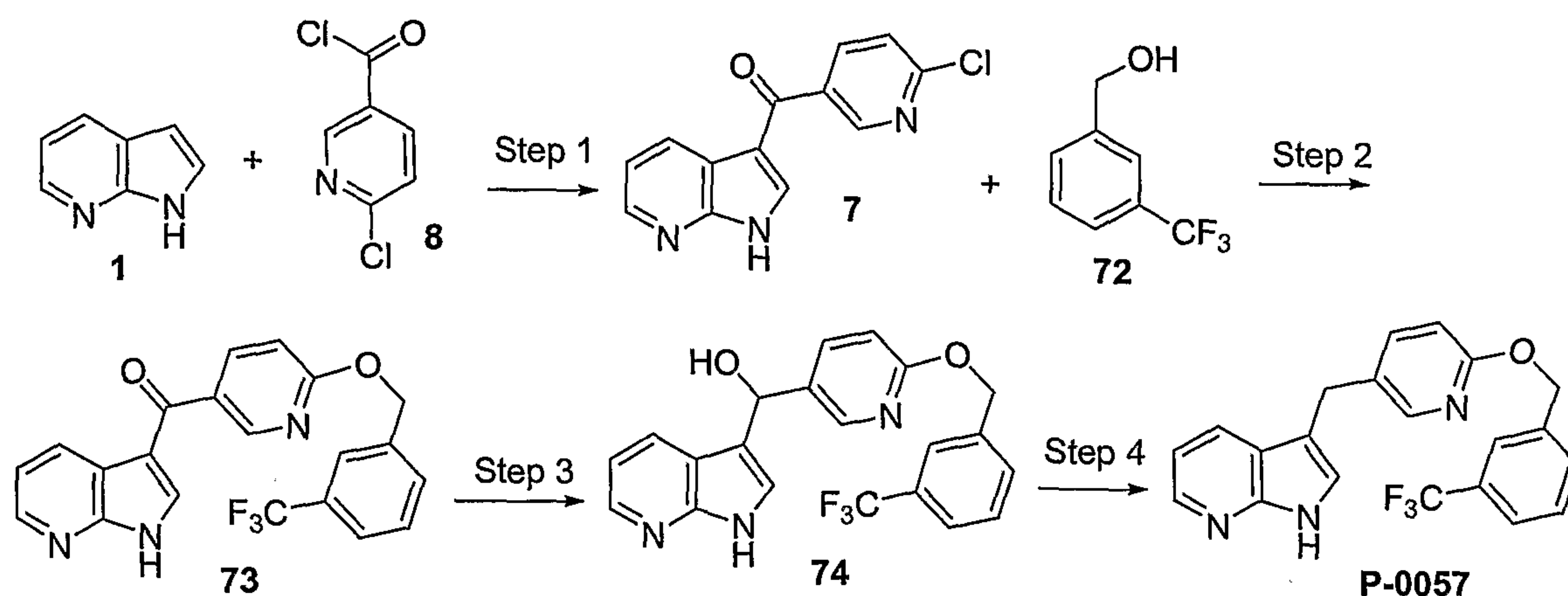
**[0382]** To [6-(3-Benzyloxy-phenylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-0026**, 12.0 mg, 0.0285 mmol) in methanol (5.0 mL) was added 20% palladium hydroxide on carbon (10.0 mg) under an atmosphere of hydrogen. The reaction was stirred at room temperature for 5 hours. Filtration and concentration gave compound (**P-0027**, 3.5 mg, 37%). MS (ESI)  $[M+H^+]^+ = 331$ .

**Example 26: Synthesis of 3-[6-(3-Trifluoromethyl-benzyloxy)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine P-0057**

**[0383]** 3-[6-(3-Trifluoromethyl-benzyloxy)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine **P-0057** was synthesized in 4 steps from commercially available 7-azaindole as shown in Scheme 28.



## Scheme 28



*Step 1 – Preparation of (6-Chloro-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (7):*

[0384] To 7-azaindole **1** in dichloromethane was added 6-chloronicotinoyl chloride **8**, followed by aluminum chloride, under an atmosphere of nitrogen at -10 °C. The reaction was stirred and allowed to warm to room temperature overnight. The reaction was quenched with 3 N hydrochloric acid and concentrated hydrochloric acid was added until all solids dissolved. The mixture was extracted with dichloromethane and the combined organic portions were dried with magnesium sulfate, filtered, and the filtrate was concentrated. The resulting solid material was recrystallized from chloroform/hexane to provide (6-Chloro-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **7** and used in the next step without further purification.

*Step 2 – Preparation of (1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-methanone (73):*

[0385] To (6-Chloro-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **7** in DMSO was added (3-trifluoromethyl-phenyl)-methanol **72**. Sodium hydride was added and the reaction was heated to 60 °C for two hours. The reaction was quenched with water and extracted with ethyl acetate. The organic portion was dried with magnesium sulfate and concentrated to provide (1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-methanone **73**, which was used in the next step without additional purification.

*Step 3 – Preparation (1H-Pyrrolo[2,3-b]pyridin-3-yl)-[6-(3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-methanol (74):*

[0386] To (1H-pyrrolo[2,3-b]pyridin-3-yl)-[6-(3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-methanone **73** in ethanol was added sodium borohydride. After one hour, the reaction was quenched with water and extracted with ethyl acetate. The organic portion was dried with magnesium sulfate and concentrated to provide (1H-Pyrrolo[2,3-b]pyridin-3-yl)-[6-(3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-methanol **74**, which was used in the next step without additional purification.

*Step 4 – Preparation of 3-[6-(3-Trifluoromethyl-benzyloxy)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine, P-0057*

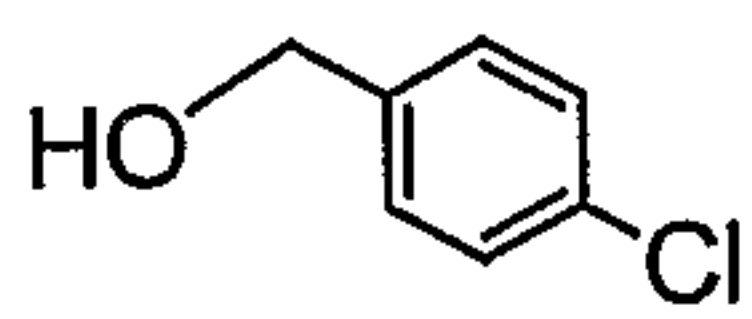
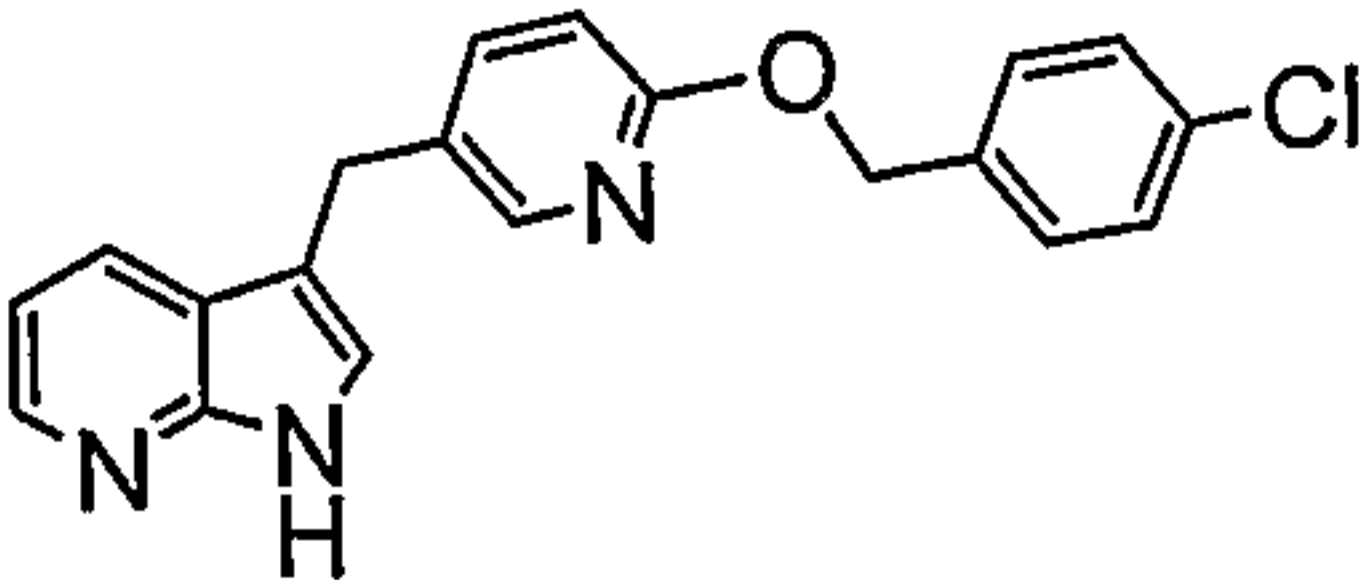
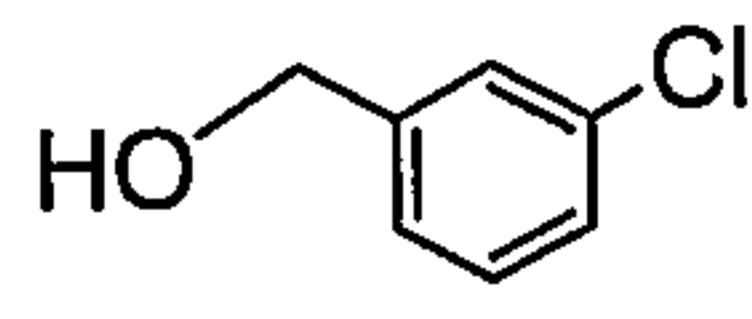
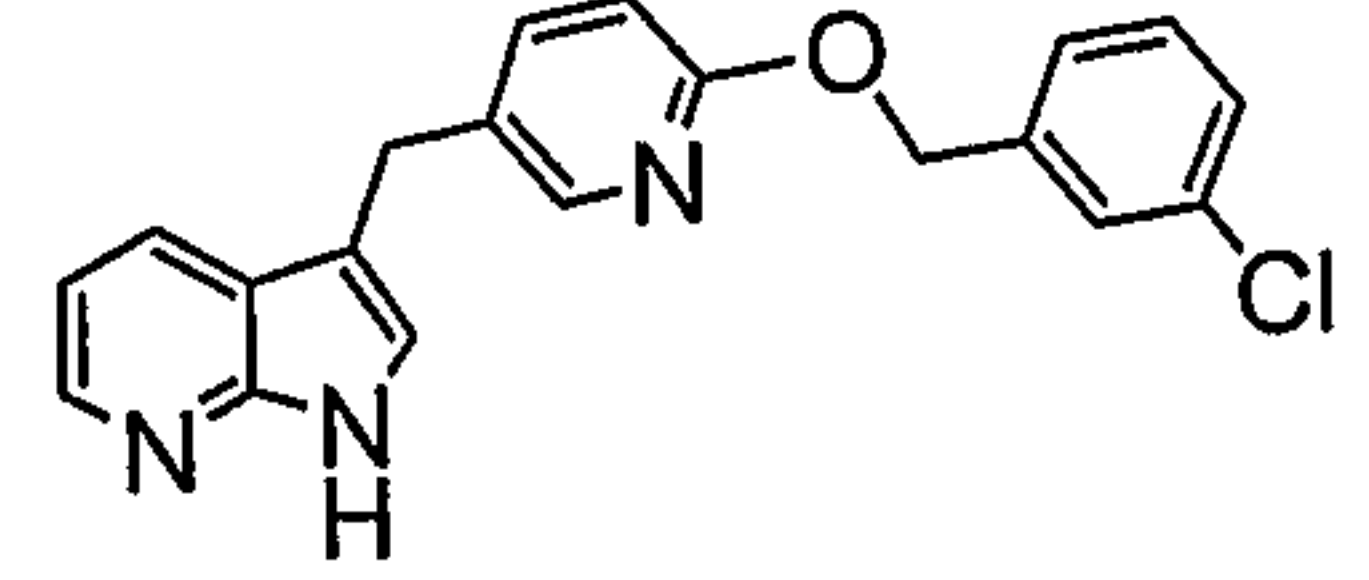
[0387] (1H-Pyrrolo[2,3-b]pyridin-3-yl)-[6-(3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-methanol **74** was dissolved in 9:1 trifluoroacetic acid: triethylsilane. The reaction was stirred at room temperature for 15 hours. The reaction was diluted with water and extracted with ethyl acetate and concentrated. The crude material was purified by reverse phase HPLC to provide 3-[6-(3-Trifluoromethyl-benzyloxy)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine **P-0057**. MS (ESI)  $[M+H]^+ = 384.3$ .

[0388] Additional compounds may be prepared using steps 2-4 of Scheme 28, replacing (3-trifluoromethyl-phenyl)-methanol with an appropriate benzyl alcohol. The following compounds were made following this procedure:

3-[6-(4-Chloro-benzyloxy)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (P-0056)

3-[6-(3-Chloro-benzyloxy)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (P-0055)

The benzyl alcohols used in step 2 of this procedure are indicated in column 2 of the following table, with the compound structure indicated in column 3. Column 1 provides the compound number and Column for the measured mass spectrometry result.

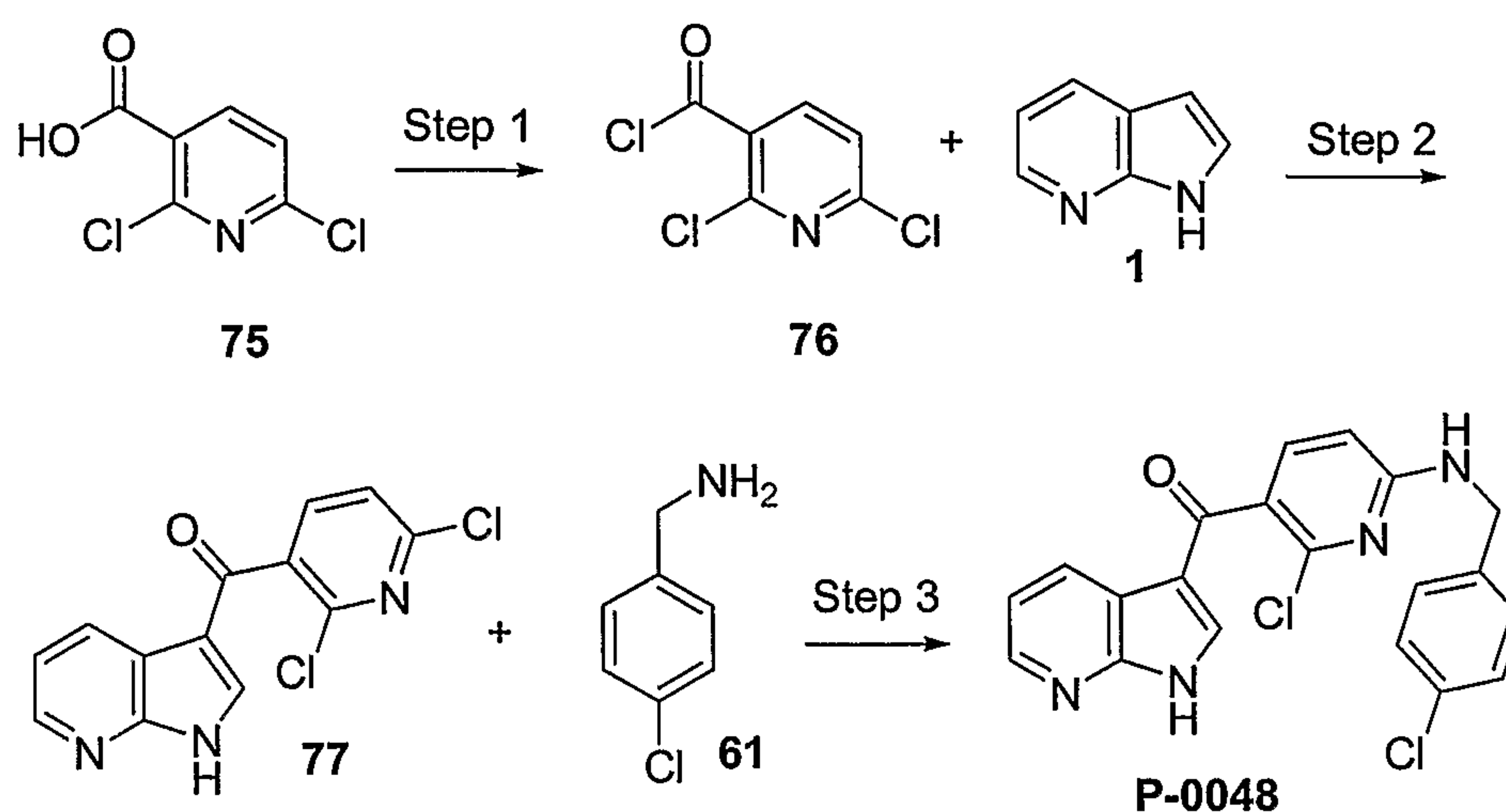
	Benzyl alcohol	Compound	MS(ESI) $[M+H]^+$ observed
P-0056			350.3
P-0055			350.3



**Example 27: Synthesis of [2-Chloro-6-(4-chloro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0048**

[0389] [2-Chloro-6-(4-chloro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0048** was synthesized in 3 steps from commercially available 2,6-dichloropyridine-3-carboxylic acid **75** as shown in Scheme 29.

**Scheme 29**



*Step 1— Preparation of 2,6-dichloropyridine-3-carbonyl chloride (76):*

[0390] To 2,6-dichloropyridine-3-carboxylic acid (**75**, 1.00 g, 0.00521 mol) in dichloromethane (75 mL) was added 2 M Oxalyl chloride (2.61 mL, 0.727 g, 0.00573 mol). The solution began to show vigorous gas evolution, which slowed but continued for about 2 hours. The reaction was allowed to continue at room temperature for an additional 3 hours. The reaction was concentrated to give the compound as a brown oil that crystallized on standing (**76**, 1.09 g, 99%).

*Step 2— Preparation of (2,6-dichloropyridin-3-yl)(1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (77):*

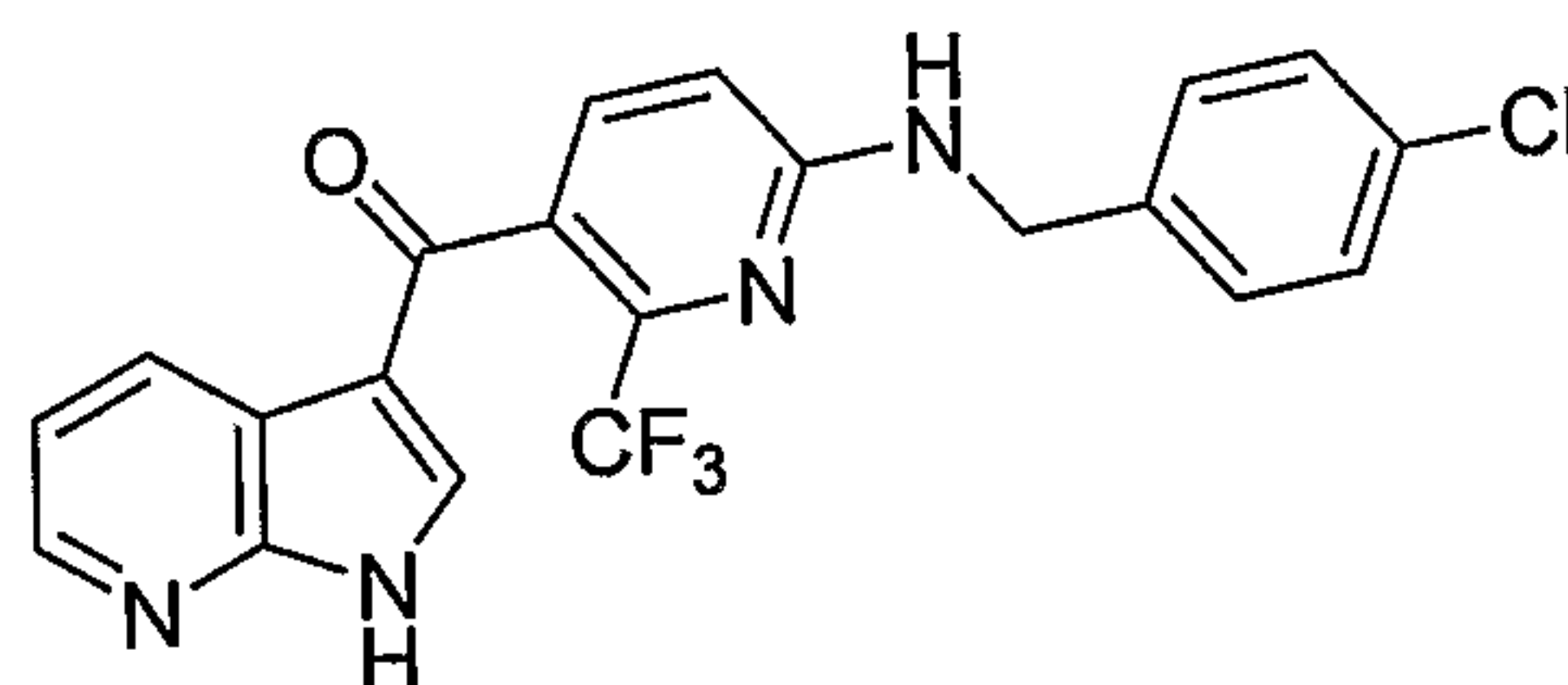
[0391] To Aluminum trichloride (4.18 g, 0.0314 mol) and dichloromethane (97.5 mL, 1.52 mol) under an atmosphere of nitrogen was added 1H-Pyrrolo[2,3-b]pyridine (**1**, 828.5 mg, 0.0070 mol) in dichloromethane (5.0 mL). The reaction was stirred at room temperature for 60 minutes, then added 2,6-dichloropyridine-3-carbonyl chloride (**76**, 1.09 g, 0.00523 mol) in dichloromethane (6.0 mL). The reaction was stirred at room temperature for 2 hours. A precipitate formed, and nitromethane was added in ~1 mL portions until almost all solid dissolved (8 mL). After an additional 60 minutes at room

temperature, the reaction was slowly poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to give 1.54 g of solid, which turned dark purple on sitting overnight. The solid was treated with dichloromethane, and the insoluble material was collected by vacuum filtration to give compound (77, 863 mg, 57%). MS (ESI)  $[M+H]^+ = 292.2$ .

*Step 3— Preparation of [2-Chloro-6-(4-chloro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0048):*

[0392] To (2,6-dichloropyridin-3-yl)(1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (77, 0.0570 g, 0.195 mmol) was added 2-propanol (1.5 mL) followed by p-chlorobenzylamine (61, 49.8  $\mu$ L, 0.410 mmol). The reaction was microwaved at 300 watts, 100 °C for 10 minutes, at 120 °C for 10 minutes, and finally at 150 °C for 10 minutes. Additional p-chlorobenzylamine (50  $\mu$ L, 0.410 mmol) was added and the reaction continued at 150 °C for 20 minutes. The reaction was extracted with ethyl acetate and 1 M sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with dichloromethane followed by 1% methanol to give compound (P-0048, 47 mg, 61%). MS (ESI)  $[M+H]^+ = 397.3$ .

[0393] Additional compounds may be prepared according to Scheme 29, replacing 2,6-dichloropyridine-3-carboxylic acid with an appropriate carboxylic acid. (6-(4-chlorobenzylamino)-2-(trifluoromethyl)pyridin-3-yl)(1H-pyrrolo[2,3-b]pyridin-3-yl)methanone P-0070



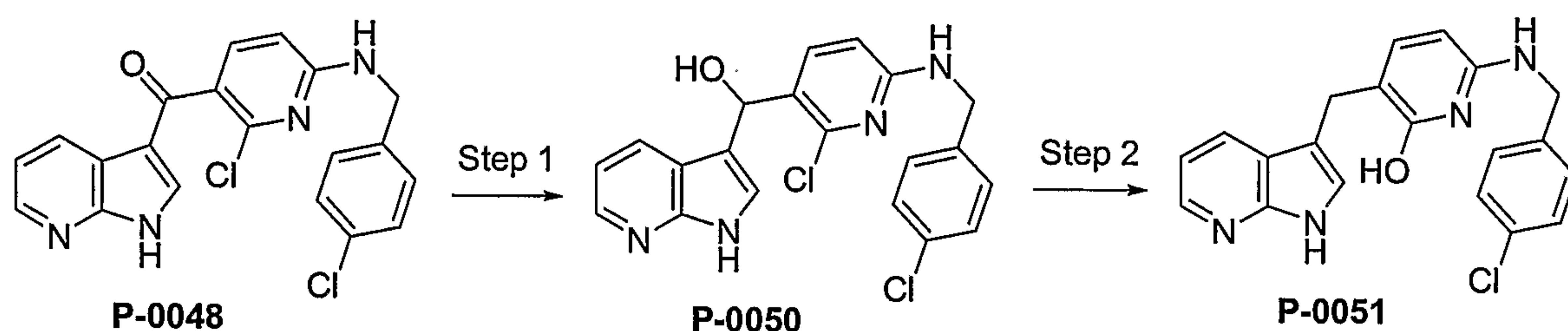
was made following this protocol, using 6-Chloro-2-trifluoromethyl-nicotinic acid as the carboxylic acid (prepared in two steps from commercially available 2-chloro-6-(trifluoromethyl)pyridine according to Cottet, F. and Schlosser, M. Eur. J. Org. Chem. 2004, 3793-3798). MS (ESI)  $[M+H]^+ = 431.2$ .



**Example 28: Synthesis of 3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-6-(4-chlorobenzylamino)pyridin-2-ol P-0051**

[0394] 3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-6-(4-chlorobenzylamino)pyridin-2-ol **P-0051** was synthesized in 2 steps from [2-Chloro-6-(4-chloro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0048** as shown in Scheme 30.

**Scheme 30**



*Step 1— Preparation of (6-(4-chlorobenzylamino)-2-chloropyridin-3-yl)(1H-pyrrolo[2,3-b]pyridin-3-yl)methanol (P-0050):*

[0395] To [2-Chloro-6-(4-chloro-benzylamino)-pyridin-3-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**P-0048**, 0.045 g, 0.00011 mol, prepared as described in Example 27) was added methanol (10 mL) and sodium borohydride (0.00428 g, 0.000113 mol). The reaction was allowed to stir at 50 °C overnight. The volatiles were removed from the reaction, and the resulting material was extracted with ethyl acetate and 1M aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with dichloromethane followed by 1% methanol in dichloromethane to give the compound (**P-0050**, 31 mg, 68%). MS (ESI)  $[M+H^+]^+ = 399.2$ .

*Step 2— Preparation of 3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-6-(4-chlorobenzylamino)pyridin-2-ol (P-0051):*

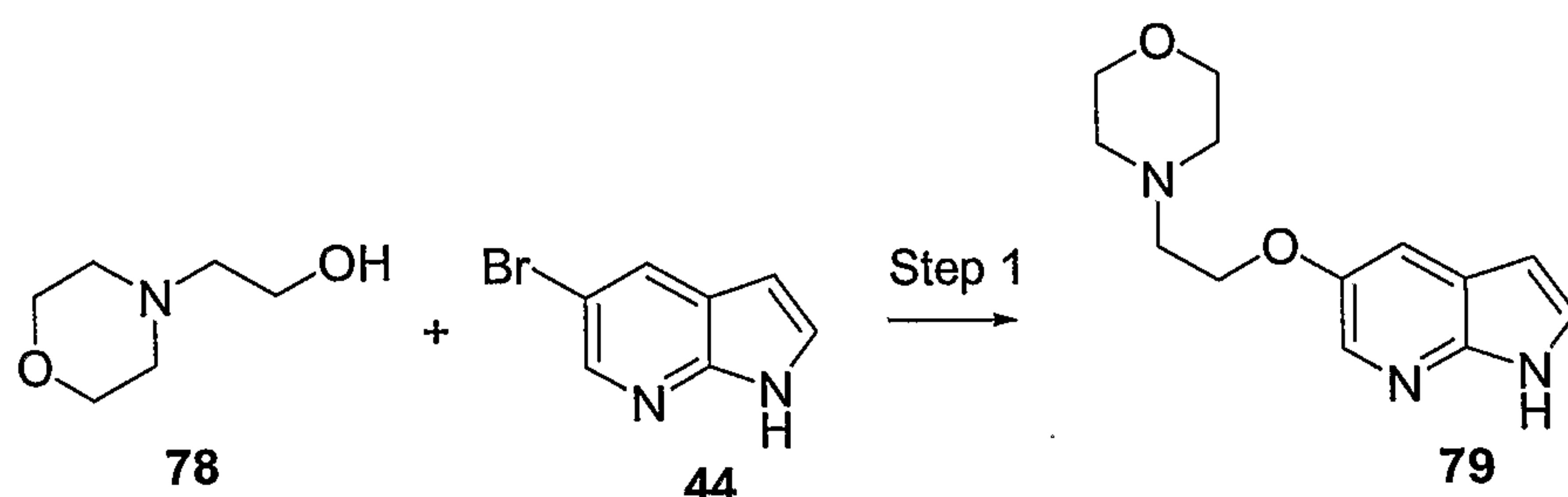
[0396] To (6-(4-chlorobenzylamino)-2-chloropyridin-3-yl)(1H-pyrrolo[2,3-b]pyridin-3-yl)methanol (**P-0050**, 0.028 g, 0.000070 mol) dissolved in acetonitrile (1 mL) was added triethylsilane (42.6 uL, 0.000266 mol) and trifluoroacetic acid (28.4 uL, 0.000368 mol). The reaction was heated at 85 °C overnight. The reaction was extracted with ethyl acetate and saturated sodium bicarbonate. The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with dichloromethane, 3%, 5% and finally 10% methanol

in dichloromethane to give the compound as a white solid (**P-0051**, 20 mg, 78%). MS (ESI)  $[M+H]^+ = 365.3$ .

**Example 29: Synthesis of 5 substituted 7-azaindole intermediates**

[0397] 5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine **79** was synthesized in 1 Step from commercially available 5-bromo-7-azaindole as shown in Scheme 31.

**Scheme 31**



*Step 1 – 5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine (79):*

[0398] To 4-morpholineethanol (30 mL, 0.2 mol) in N, N-dimethylformamide (30 mL) was slowly added sodium hydride (7 g, 60% dispersion in mineral oil, 0.2 mol). After the solution turned clear, a solution of 5-bromo-7-azaindole (**44**, 1.0 g, 0.0051 mol) in N,N-dimethylformamide (5 mL) and copper(I) bromide (1.4 g, 0.0098 mol) were added. The reaction mixture was stirred at 120 °C under nitrogen for 2 hours. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate and water. The organic layer was collected, washed with a solution of ammonium chloride and ammonium hydroxide (4:1), brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as an off-white solid (**79**, 0.62 g, 50%). MS (ESI)  $[M+H]^+ = 248.25$ .

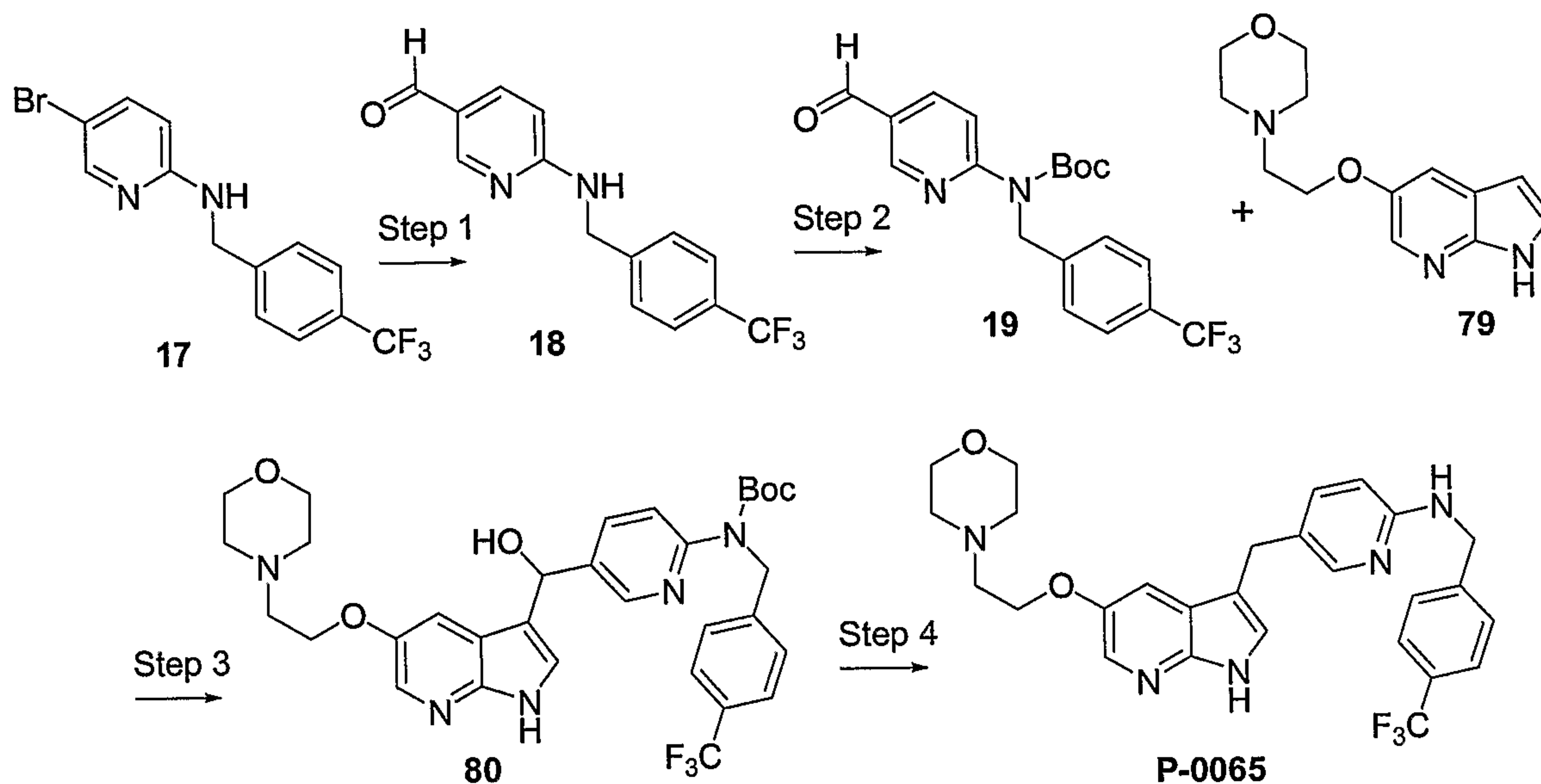
[0399] Additional 5-substituted 7-azaindoles were prepared following the protocol of Scheme 31, replacing 4-morpholineethanol with either 2-diethylamino-ethanol, 3-diethylamino-propan-1-ol, 2-piperidin-1-yl-ethanol, or 2-pyrrolidin-1-yl-ethanol to provide diethyl-[2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-ethyl]-amine, Diethyl-[3-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-propyl]-amine, 5-(2-piperidin-1-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine, and 5-(2-pyrrolidin-1-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine, respectively.



**Example 30: Synthesis of {5-[5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine P-0065:**

[0400] {5-[5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine P-0065 was synthesized in 4 Steps from (5-bromo-pyridin-2-yl)-(4-trifluoromethylbenzyl)-amine 17 as shown in Scheme 32.

**Scheme 32**



**Step 1 – Preparation of 6-(4-Trifluoromethyl-benzylamino)-pyridine-3-carbaldehyde (18):**

[0401] To a solution of (5-bromo-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-amine (17, 3.55 g, 0.0107 mol, commercially available, or prepared as described in Example 10) in tetrahydrofuran (150 mL) was added *tert*-butyllithium (13.2 mL, 1.70 M in pentane, 0.0224 mol) slowly under an atmosphere of nitrogen at -78 °C over 10 minutes. The reaction mixture was stirred at -78 °C for 90 minutes. N, N-Dimethylformamide (2.2 mL, 0.028 mol) was added slowly into the reaction mixture. The reaction mixture was stirred at -78 °C for 2 hours, then allowed to warm to room temperature. After stirring at room temperature for 2 hours, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic phase was washed with saturated sodium bicarbonate, brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a light yellow solid (18, 1.67 g, 56%).

*Step 2 – Preparation of (5-Formyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (19):*

[0402] To a solution of 6-(4-trifluoromethyl-benzylamino)-pyridine-3-carbaldehyde (**18**, 3.7 g, 0.013 mol) and di-*tert*-butyldicarbonate (3.4 g, 0.016 mol) in dichloromethane (100 mL) was added N,N-diisopropylethylamine (4.6 mL, 0.026 mol) and 4-diethylaminopyridine (0.2 g, 0.002 mol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated and then dissolved in ethyl acetate. The solution was washed with hydrochloric acid (10%), saturated sodium bicarbonate, brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a white solid (**19**, 4.38 g, 87%).

*Step 4 – Preparation of (5-{Hydroxy-[5-(2-morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methyl}-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (80):*

[0403] A mixture of (5-Formyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid *tert*-butyl ester (**19**, 315 mg, 0.828 mmol), 5-(2-morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridine (**79**, 205 mg, 0.829 mmol, prepared as described in Example 29), and potassium hydroxide (70 mg, 1 mmol) in methanol (25 mL) was stirred at room temperature overnight. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the compound as a yellow solid (**80**, 0.2 g, 40%). MS (ESI)  $[M+H]^+ = 628.42$ .

*Step 5 – Preparation of {5-[5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine (P-0065):*

[0404] A mixture of (5-{Hydroxy-[5-(2-morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-b]pyridin-3-yl]-methyl}-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid *tert*-butyl ester (**80**, 0.2 g, 0.3 mmol), triethylsilane (4 mL, 0.02 mol), and trifluoroacetic acid (2 mL, 0.02 mol) in acetonitrile (30 mL) was refluxed for 2 hours. After removal of solvent, the residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate, brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide



the compound as a light yellow solid (**P-0065**, 17 mg, 10%). MS (ESI)  $[M+H]^+ = 512.42$ .

**[0405]** Additional compounds may be prepared using steps 3 and 4 of Scheme 32, using (5-Formyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid *tert*-butyl ester **19** or replacing it with (5-Formyl-pyridin-2-yl)-(4-chloro-benzyl)-carbamic acid *tert*-butyl ester (**43**, prepared as described in Example 17) and replacing 5-(2-Morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-*b*]pyridine **79** with an appropriate azaindole, prepared as in Example 29 or 5-methoxy-7-azaindole (prepared as described in Example 31) or with commercially available 5-chloro-7-azaindole. The following compounds were made following this procedure:

[5-(5-Methoxy-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0053),

[5-(5-Chloro-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-pyridin-2-yl]-(4-trifluoromethyl-benzyl)-amine (P-0054),

(4-Chloro-benzyl)-[5-(5-methoxy-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0058),

(4-Chloro-benzyl)-[5-(5-chloro-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (P-0059),

{5-[5-(2-Diethylamino-ethoxy)-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine (P-0060),

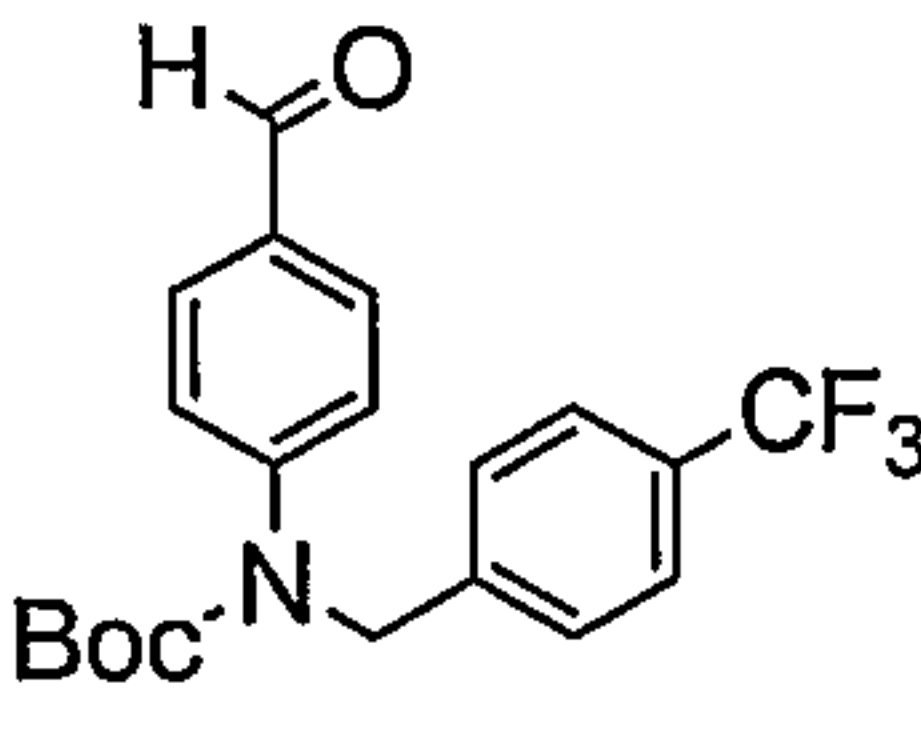
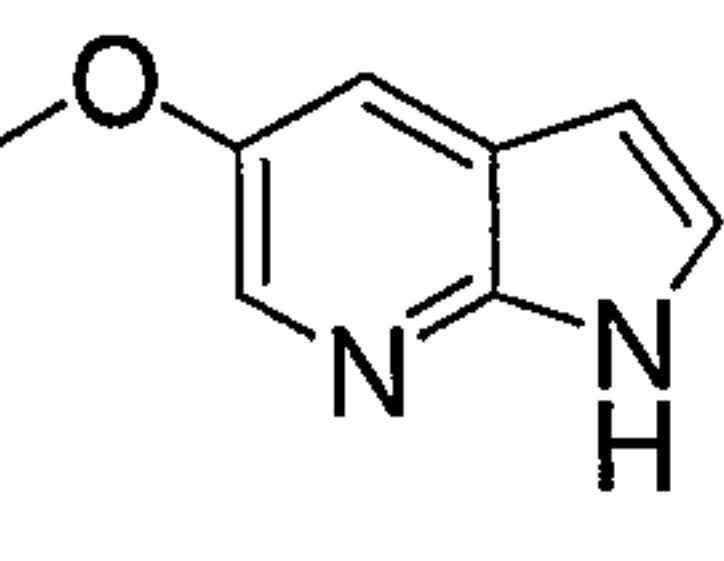
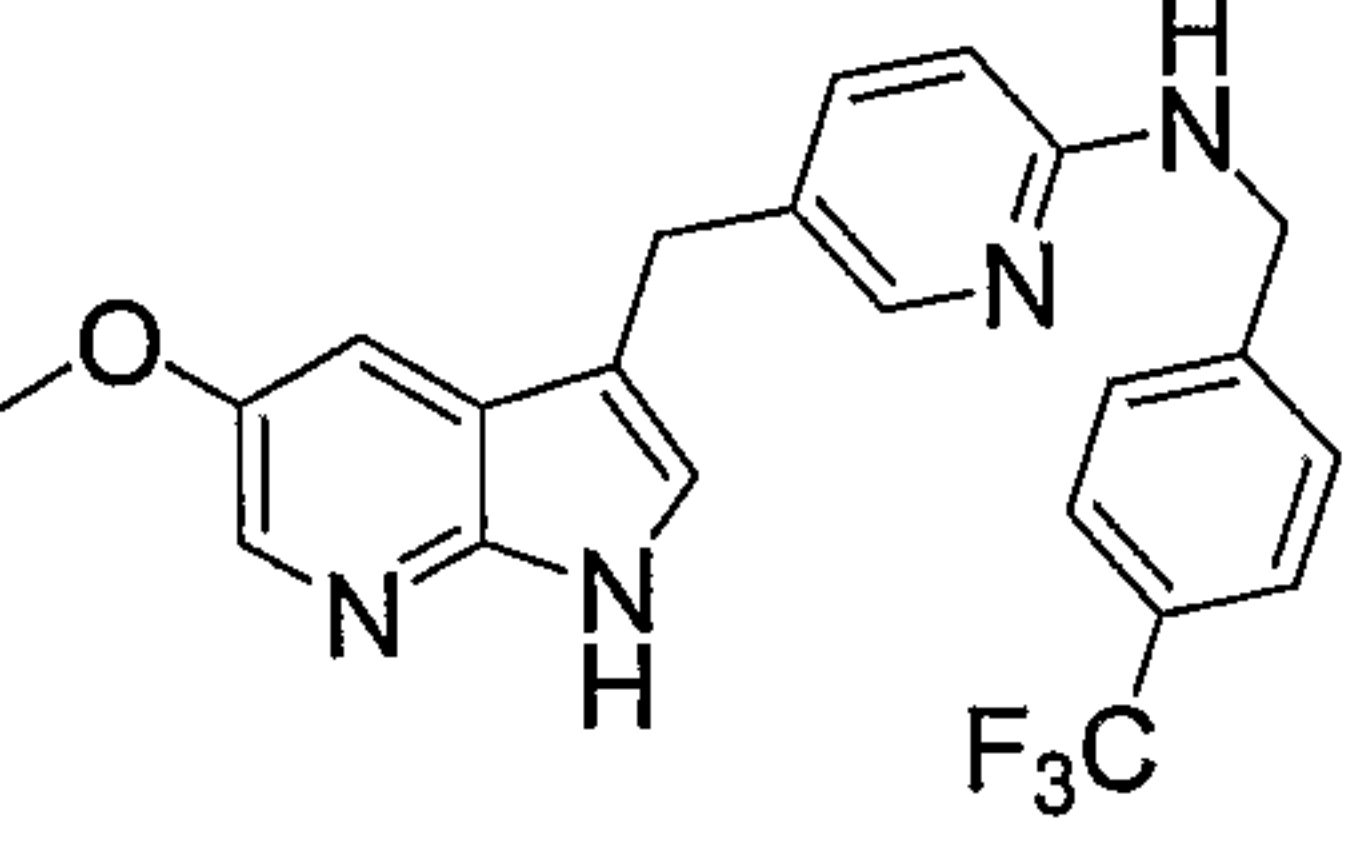
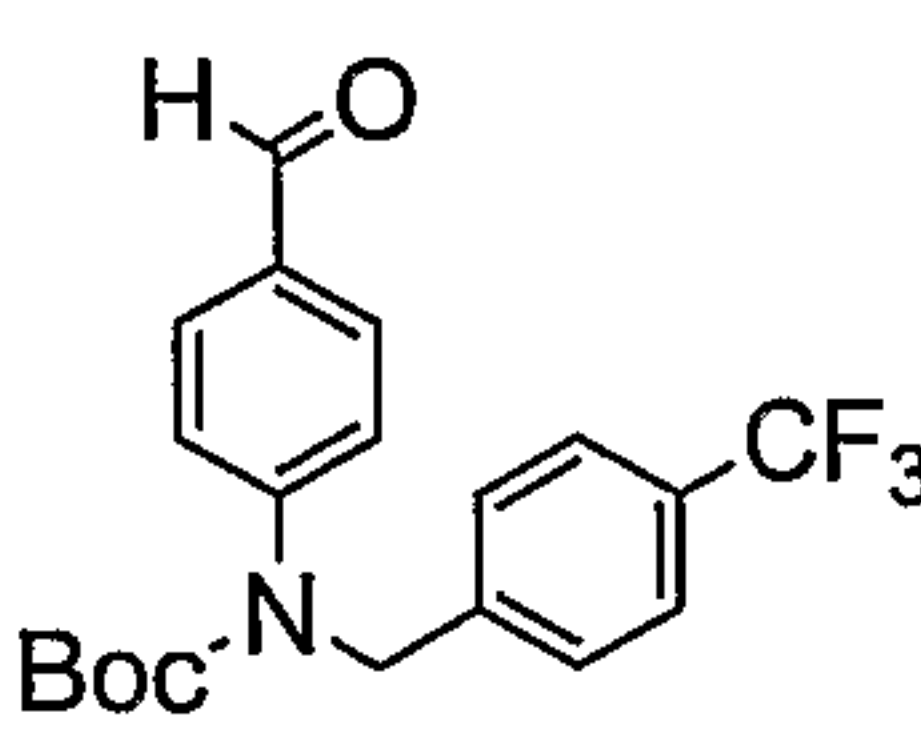
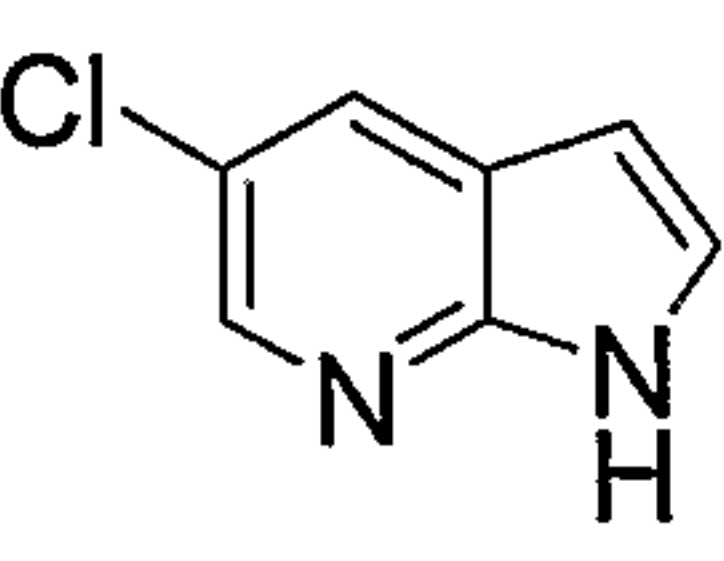
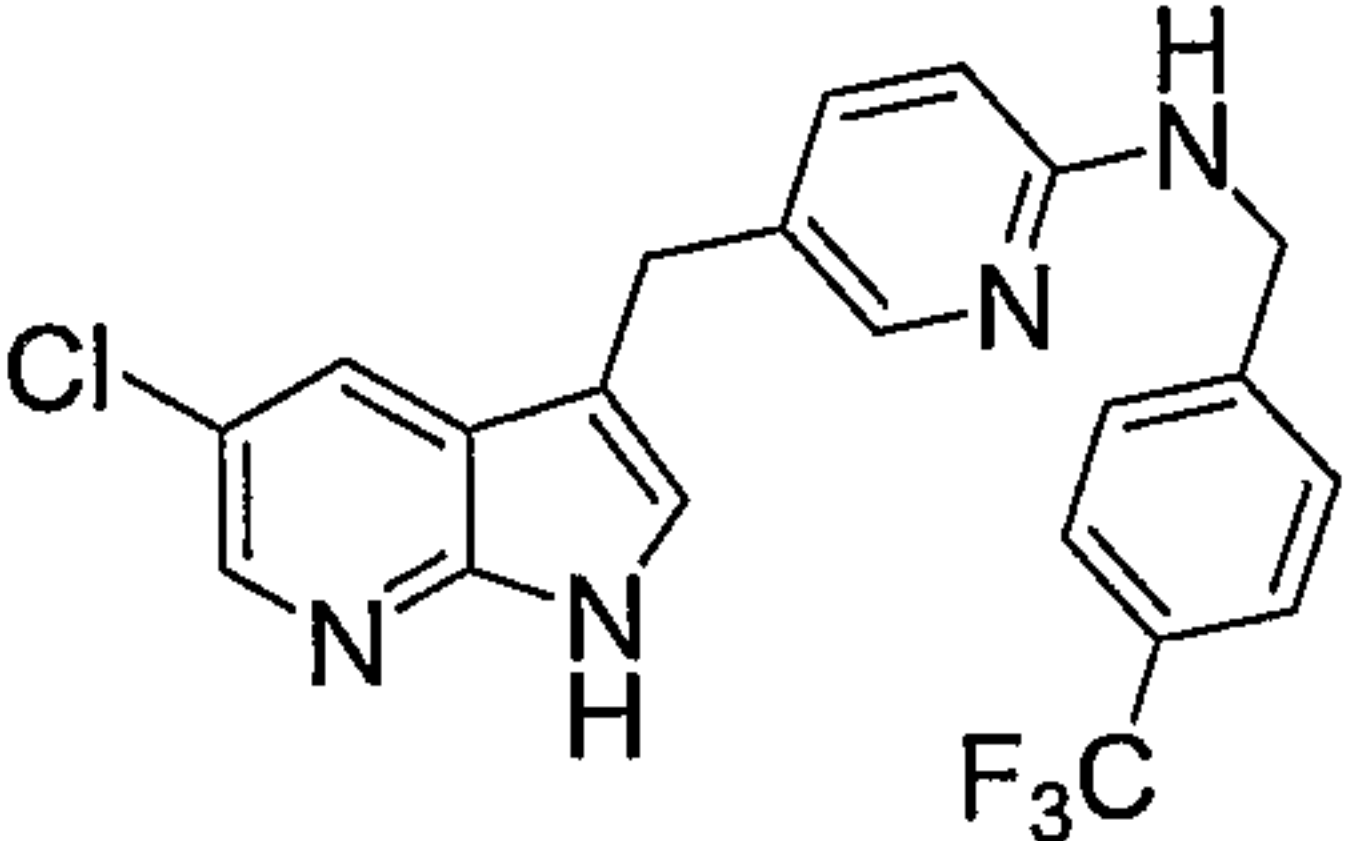
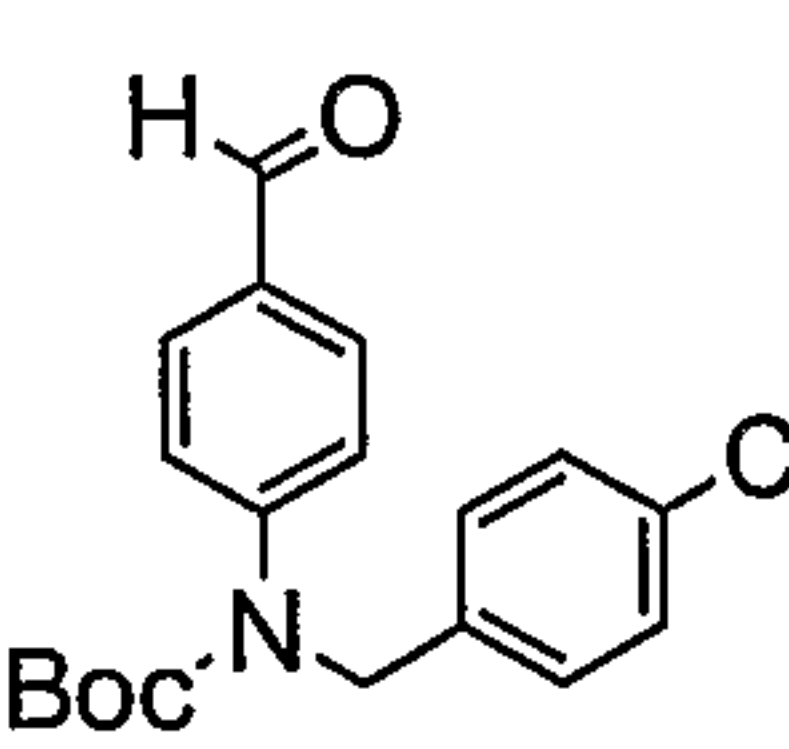
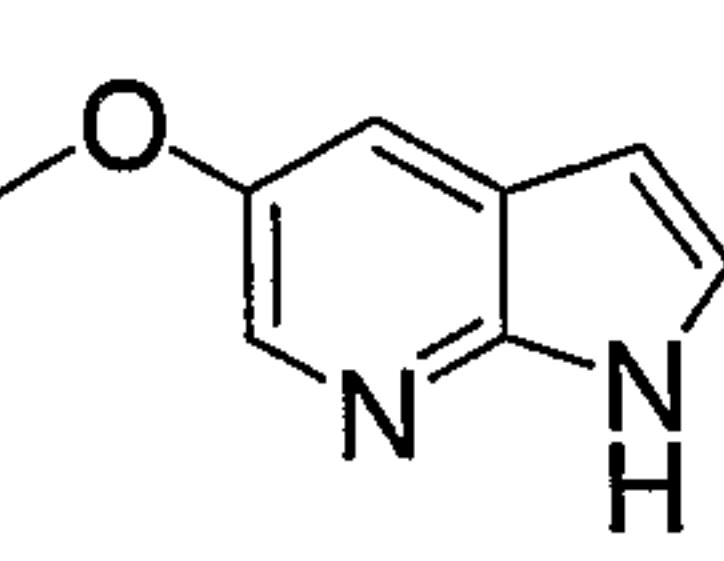
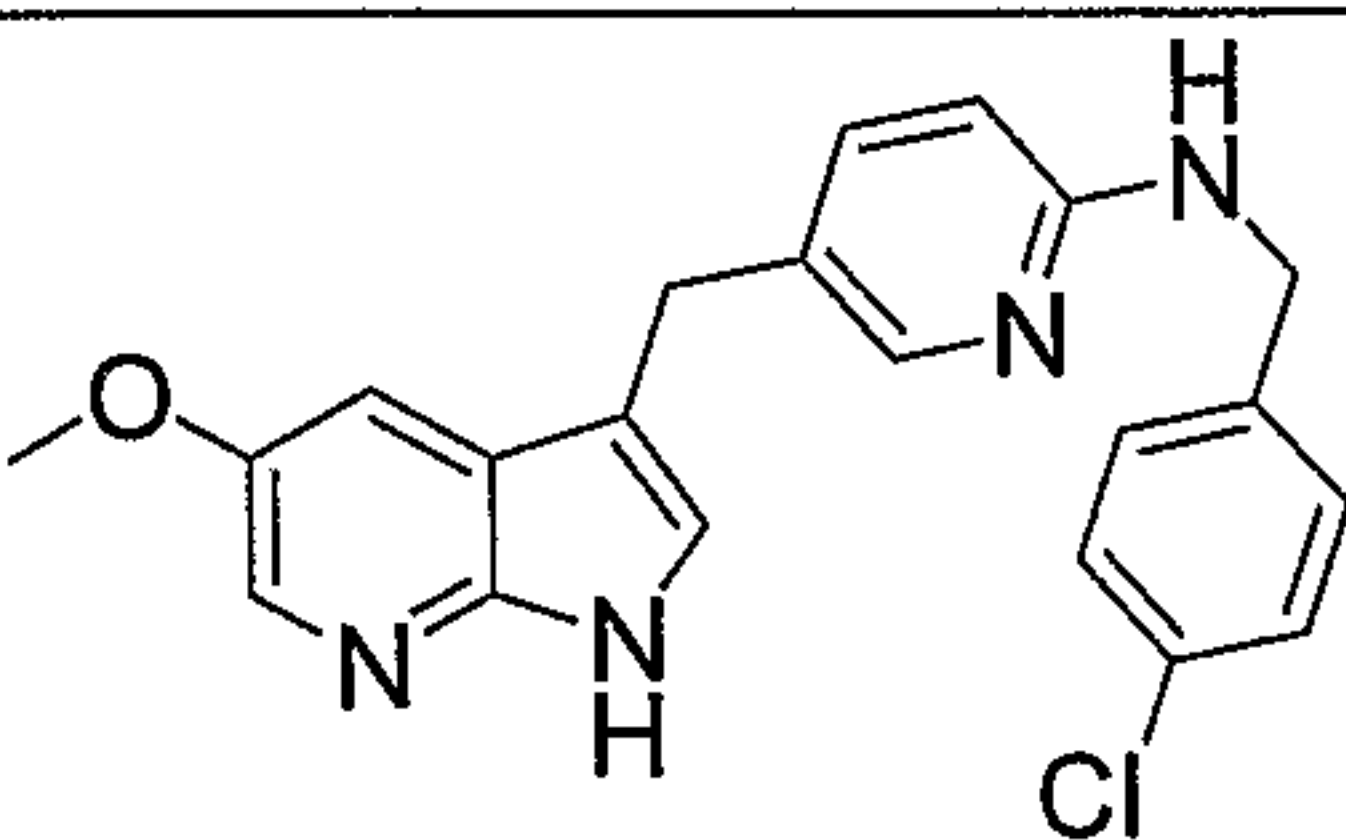
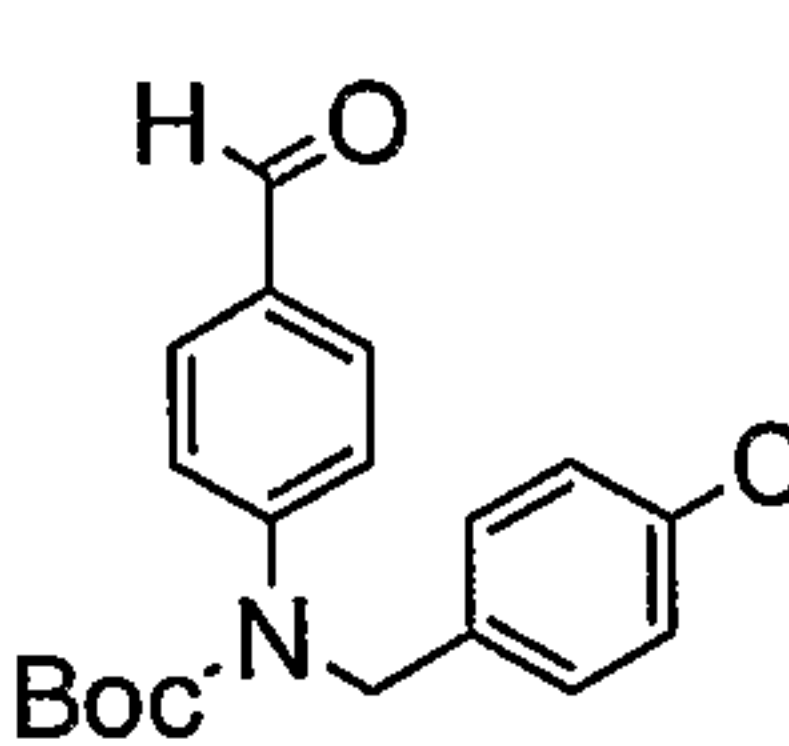
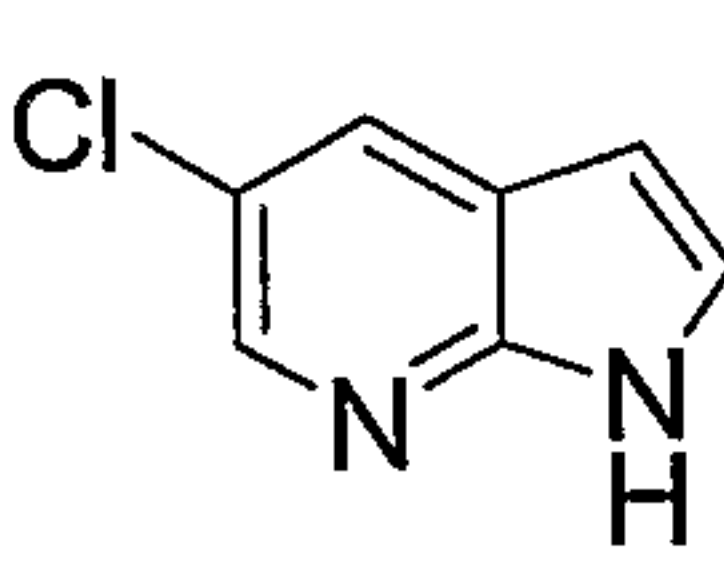
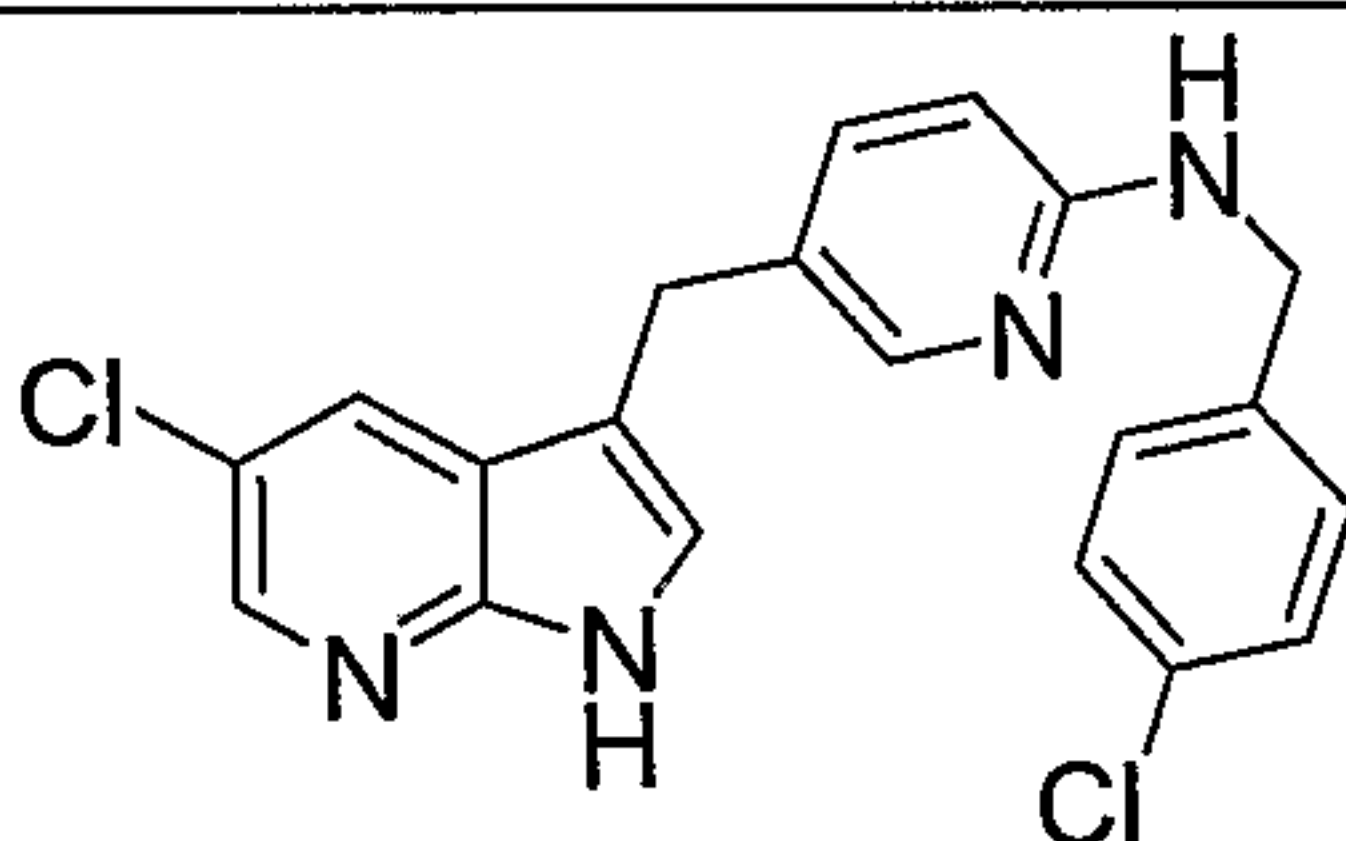
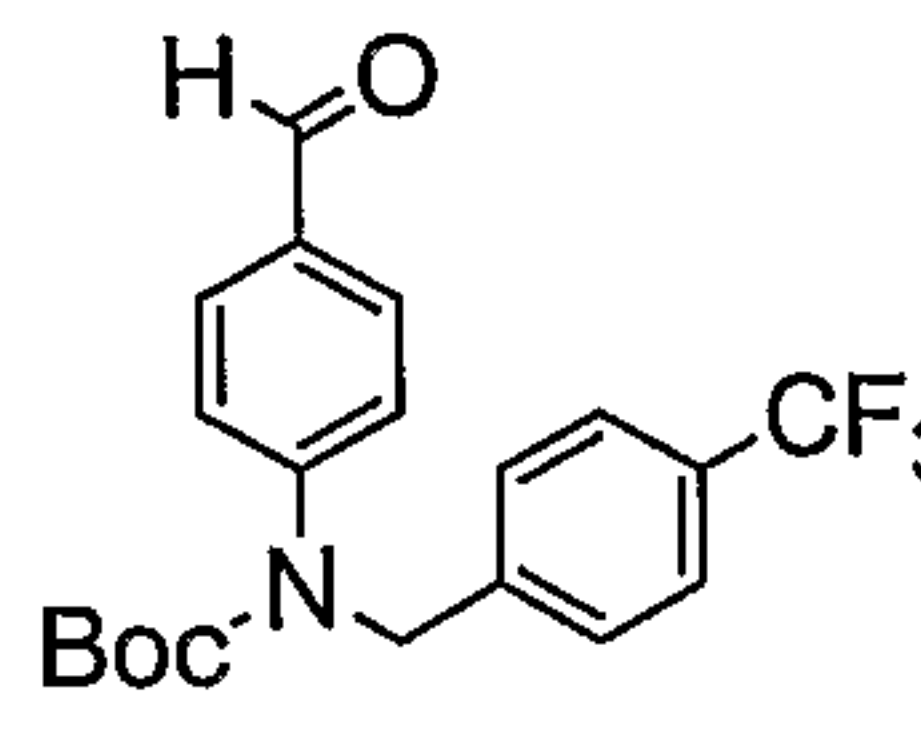
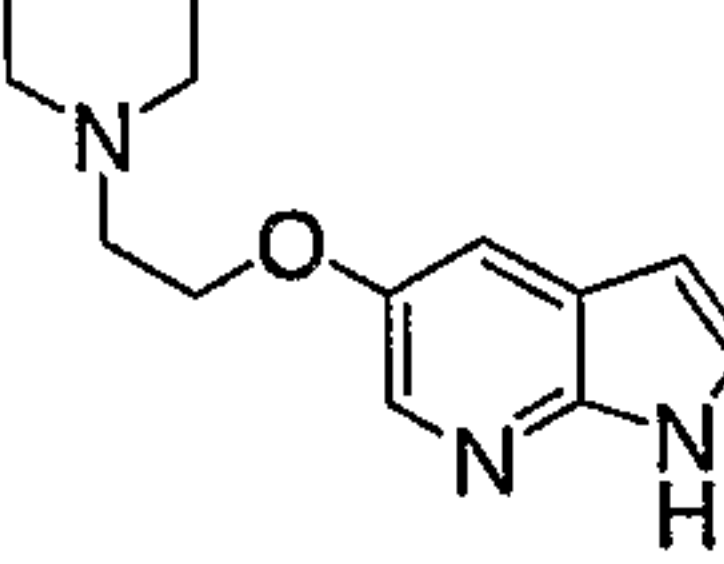
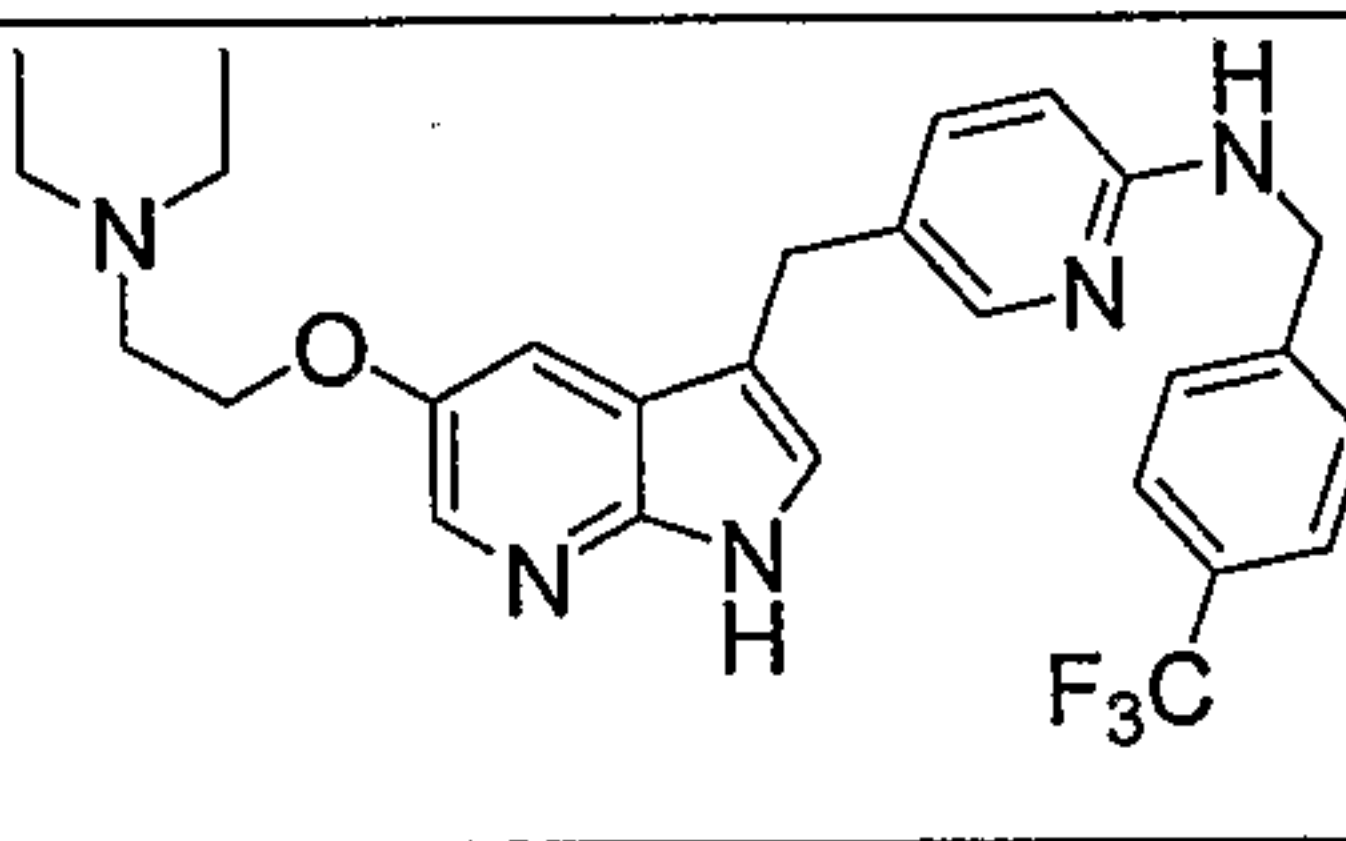
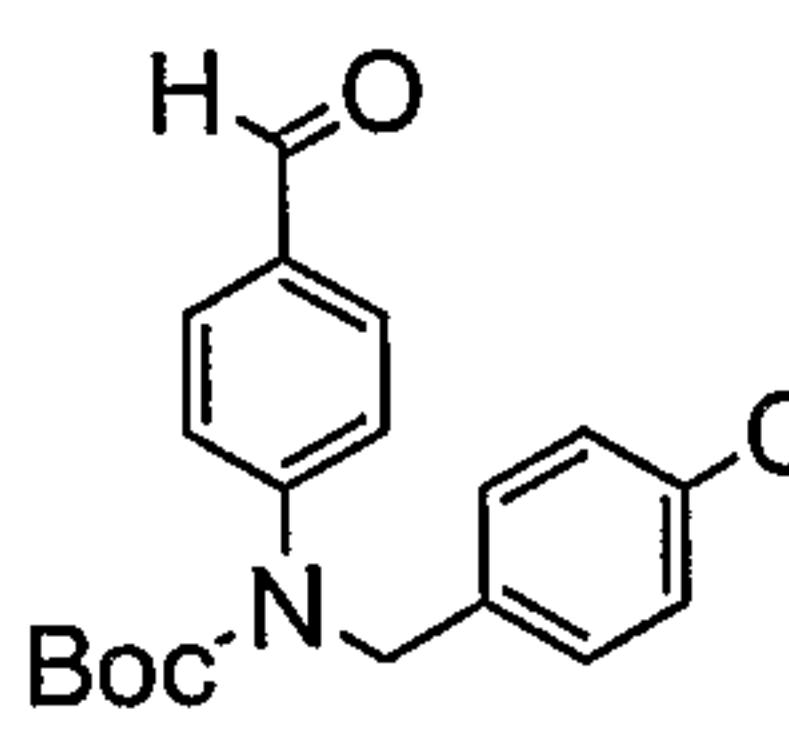
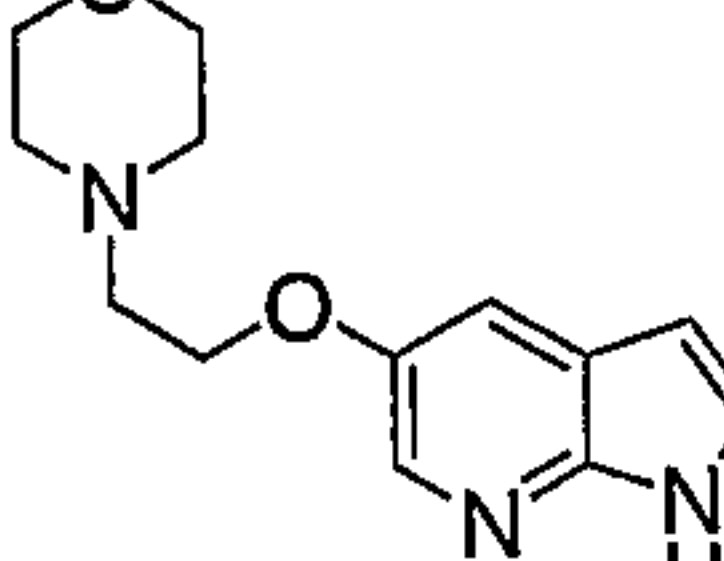
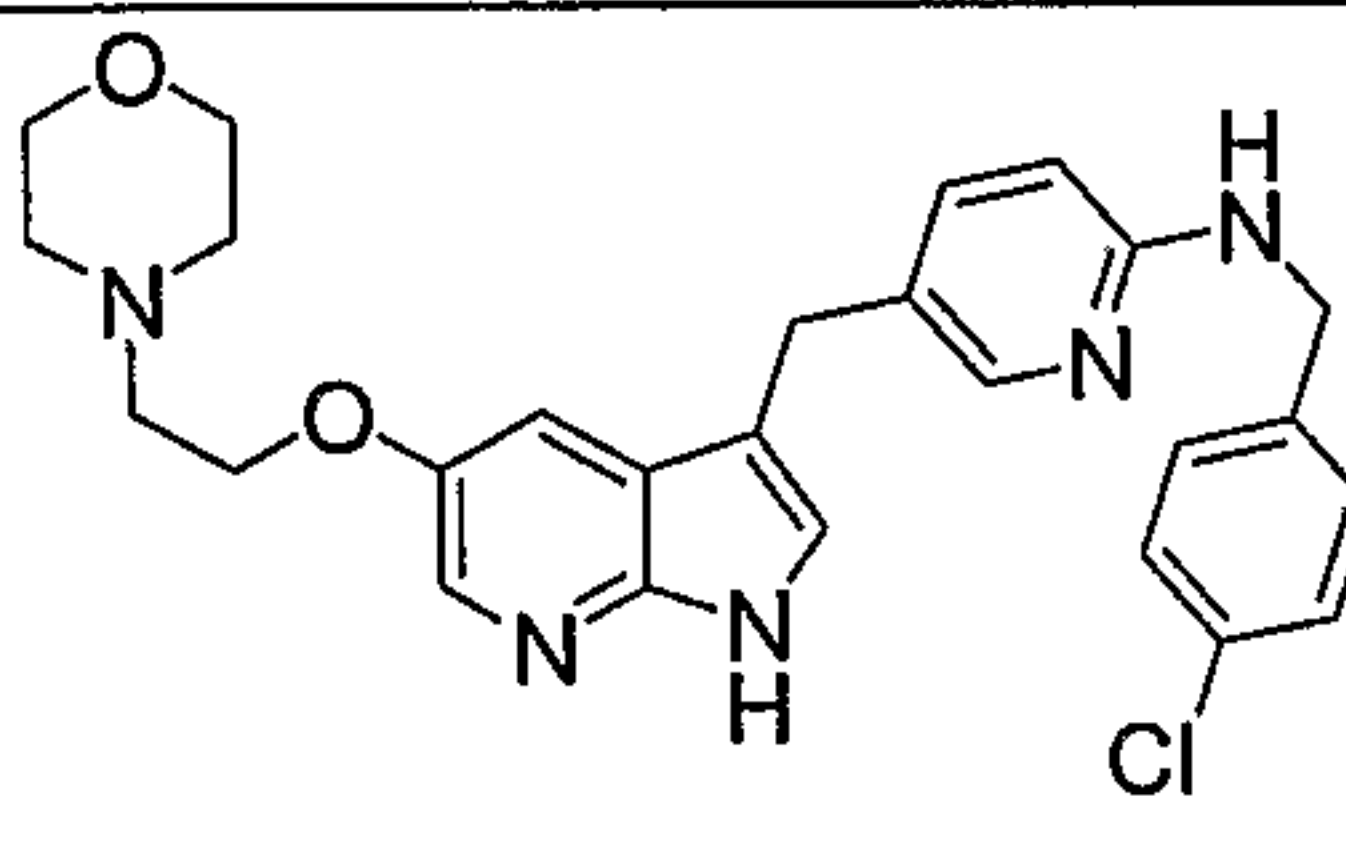
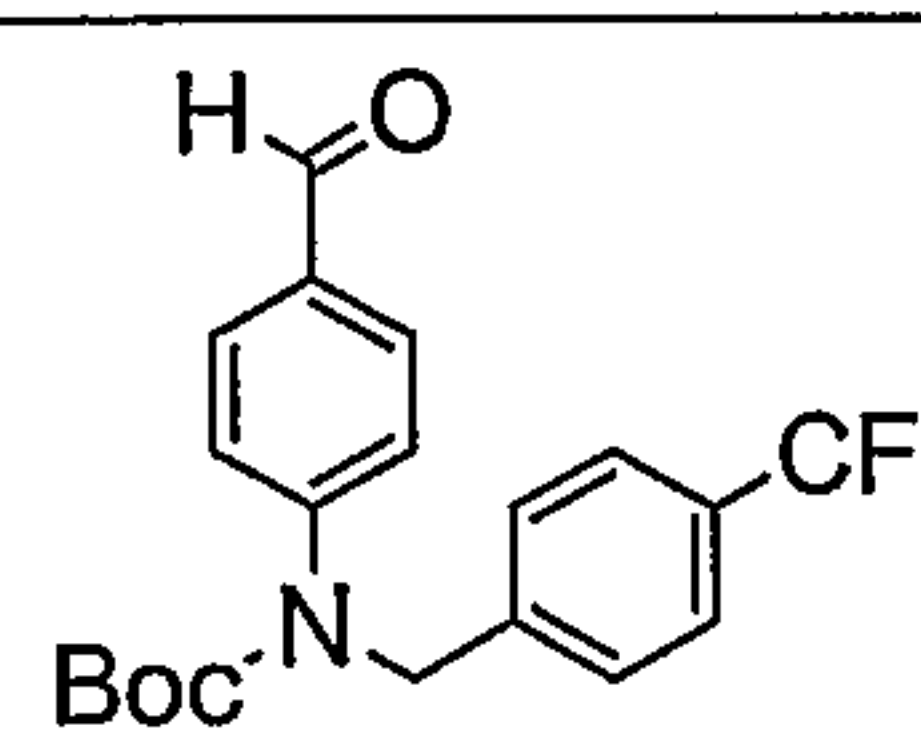
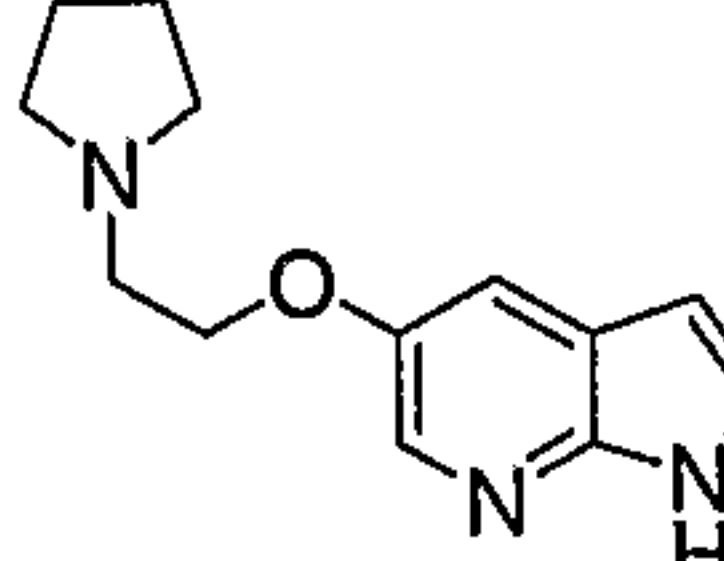
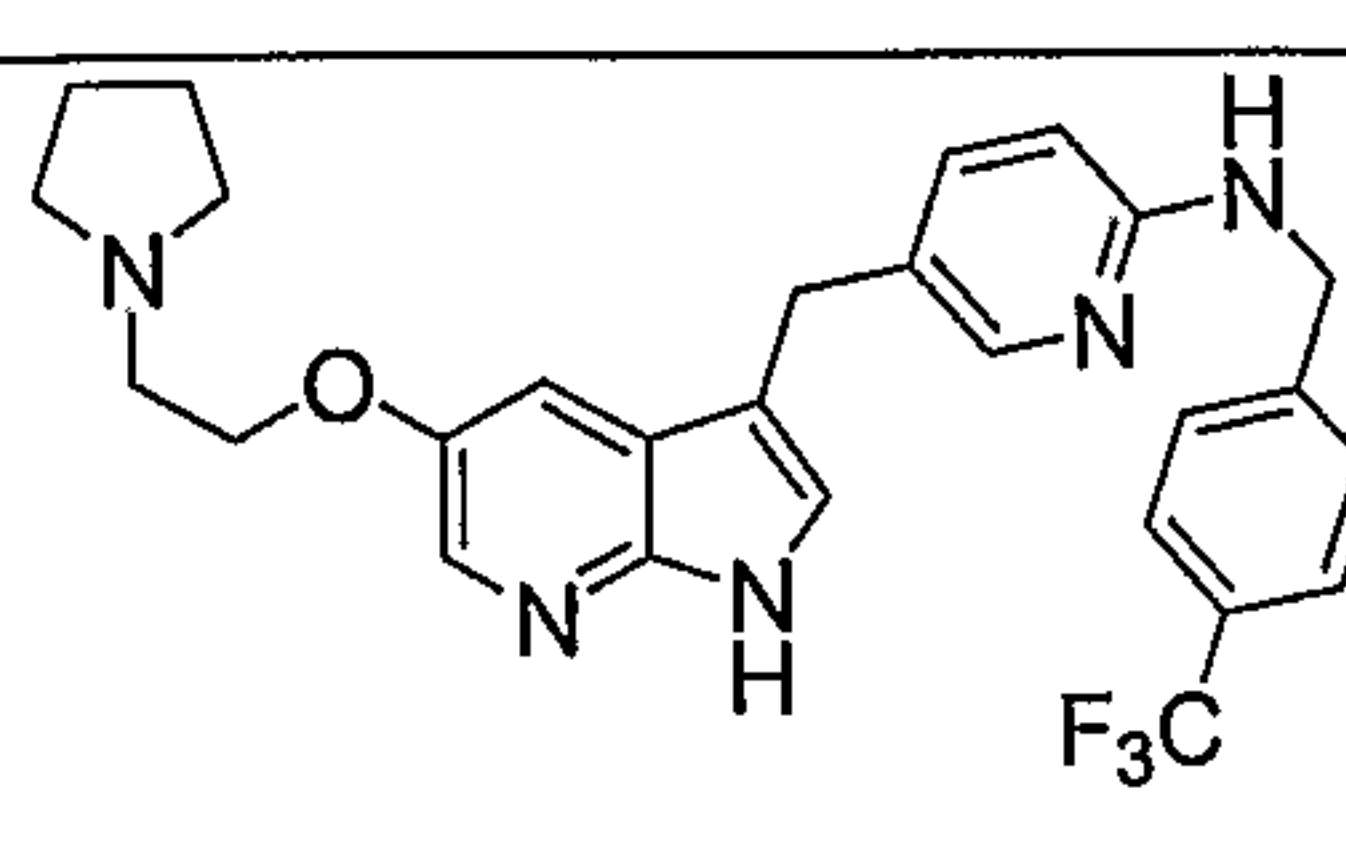
(4-Chloro-benzyl)-{5-[5-(2-morpholin-4-yl-ethoxy)-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (P-0063),

{5-[5-(2-Pyrrolidin-1-yl-ethoxy)-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine (P-0064),

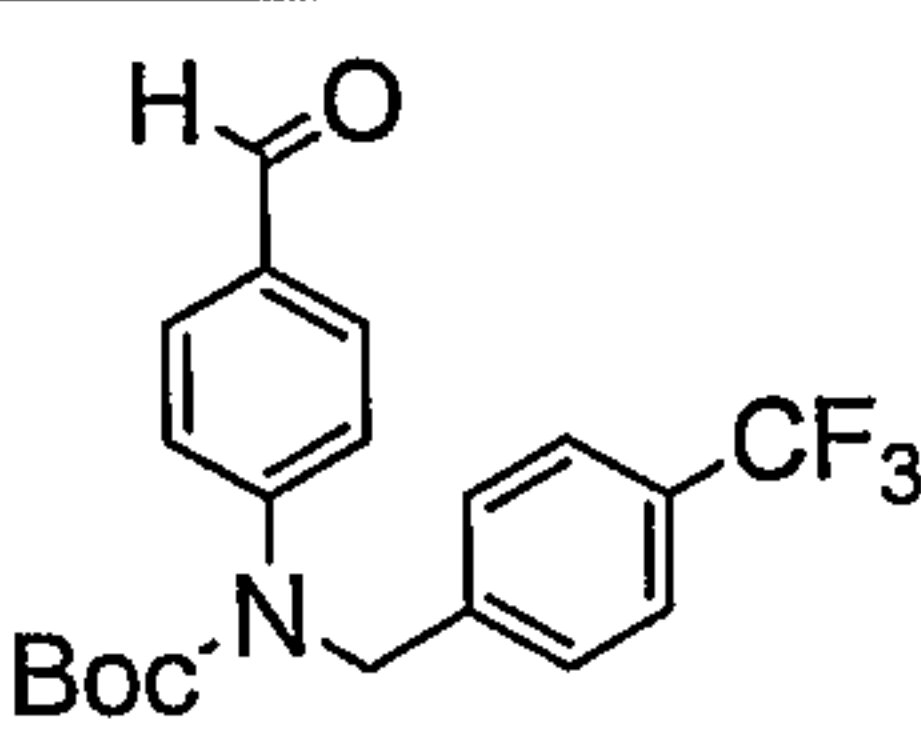
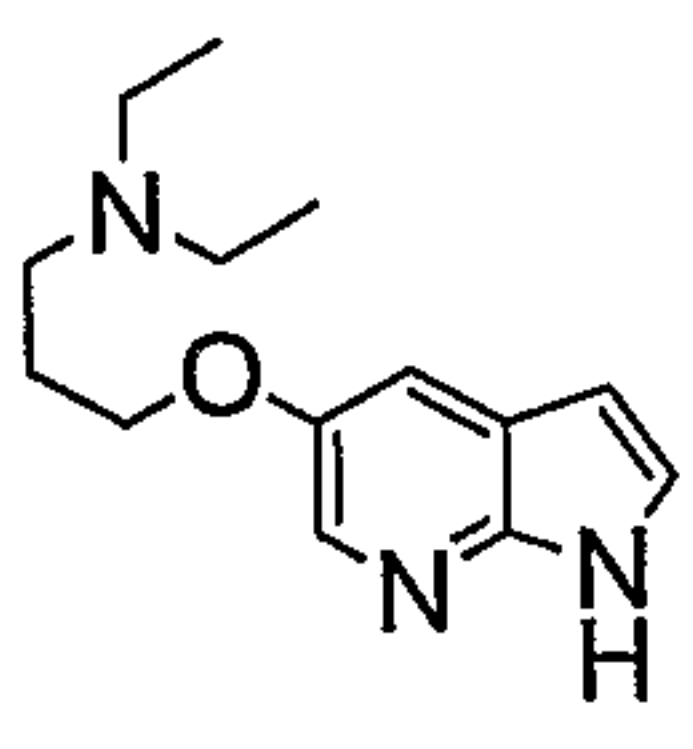
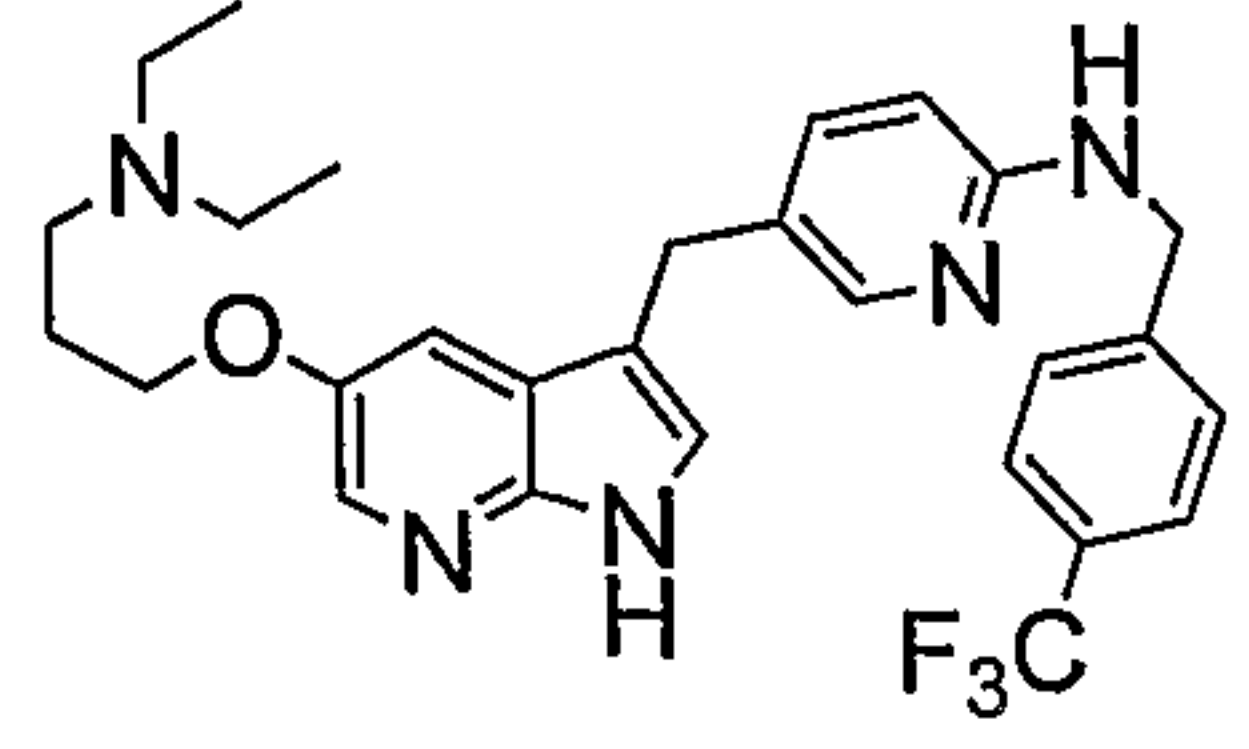
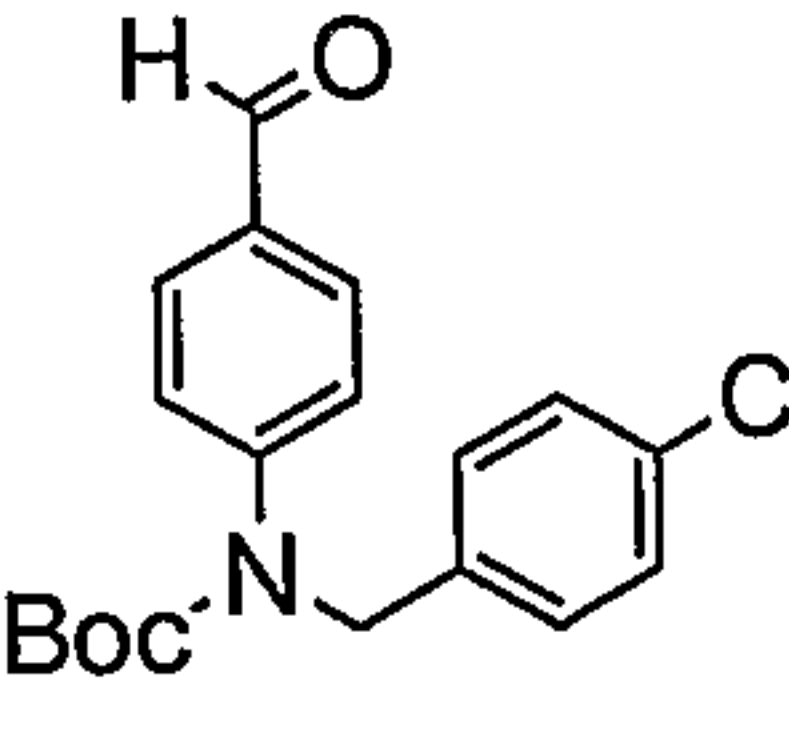
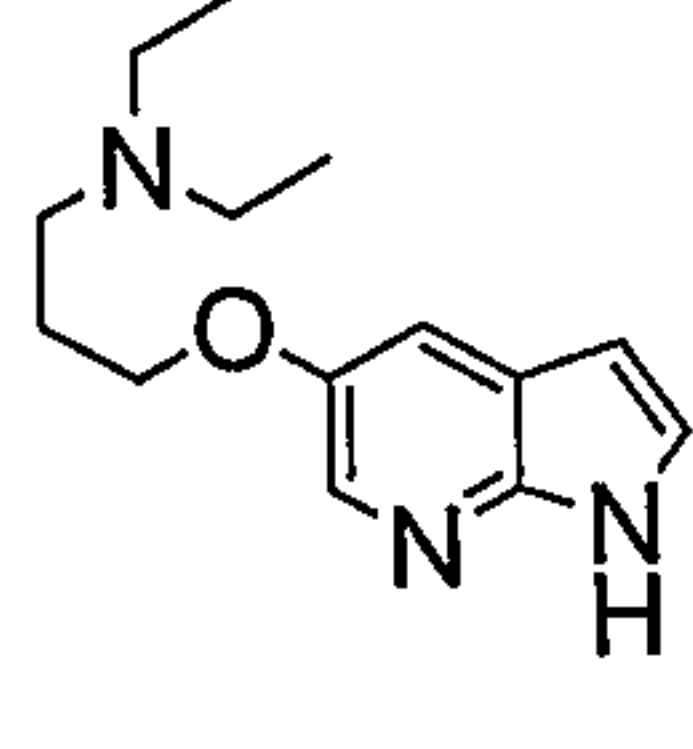
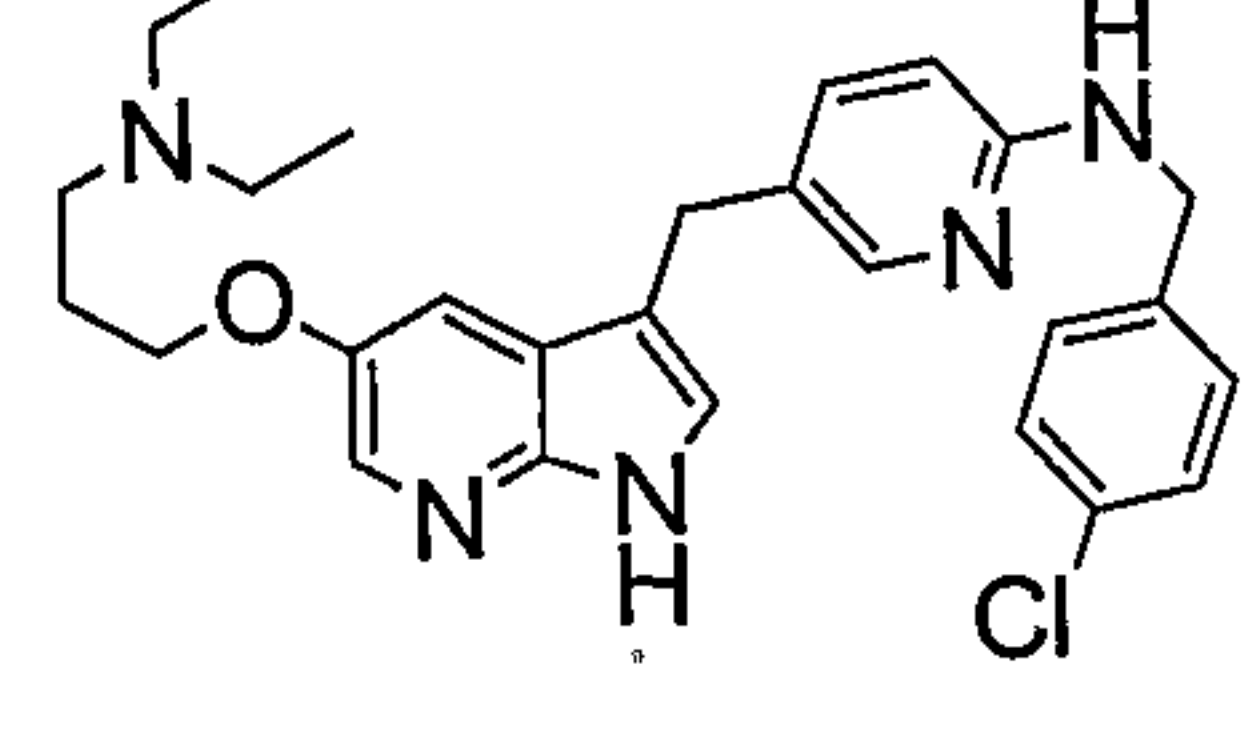
{5-[5-(3-Diethylamino-propoxy)-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-amine (P-0066),

(4-Chloro-benzyl)-{5-[5-(3-diethylamino-propoxy)-1H-pyrrolo[2,3-*b*]pyridin-3-ylmethyl]-pyridin-2-yl}-amine (P-0069),

The aldehyde and azaindole used in step 4 of this procedure are indicated in columns 2 and 3 of the following table, respectively, with the compound structure indicated in column 4. Column 1 provides the compound reference number and Column 5 the experimental mass spectrometry result.

	Aldehyde	Azaindole	Compound	MS(ESI) [M+H] <sup>+</sup> observed
P-0053				413.2
P-0054				417.2
P-0058				379.2
P-0059				383.2
P-0060				498.4
P-0063				478.3
P-0064				496.3

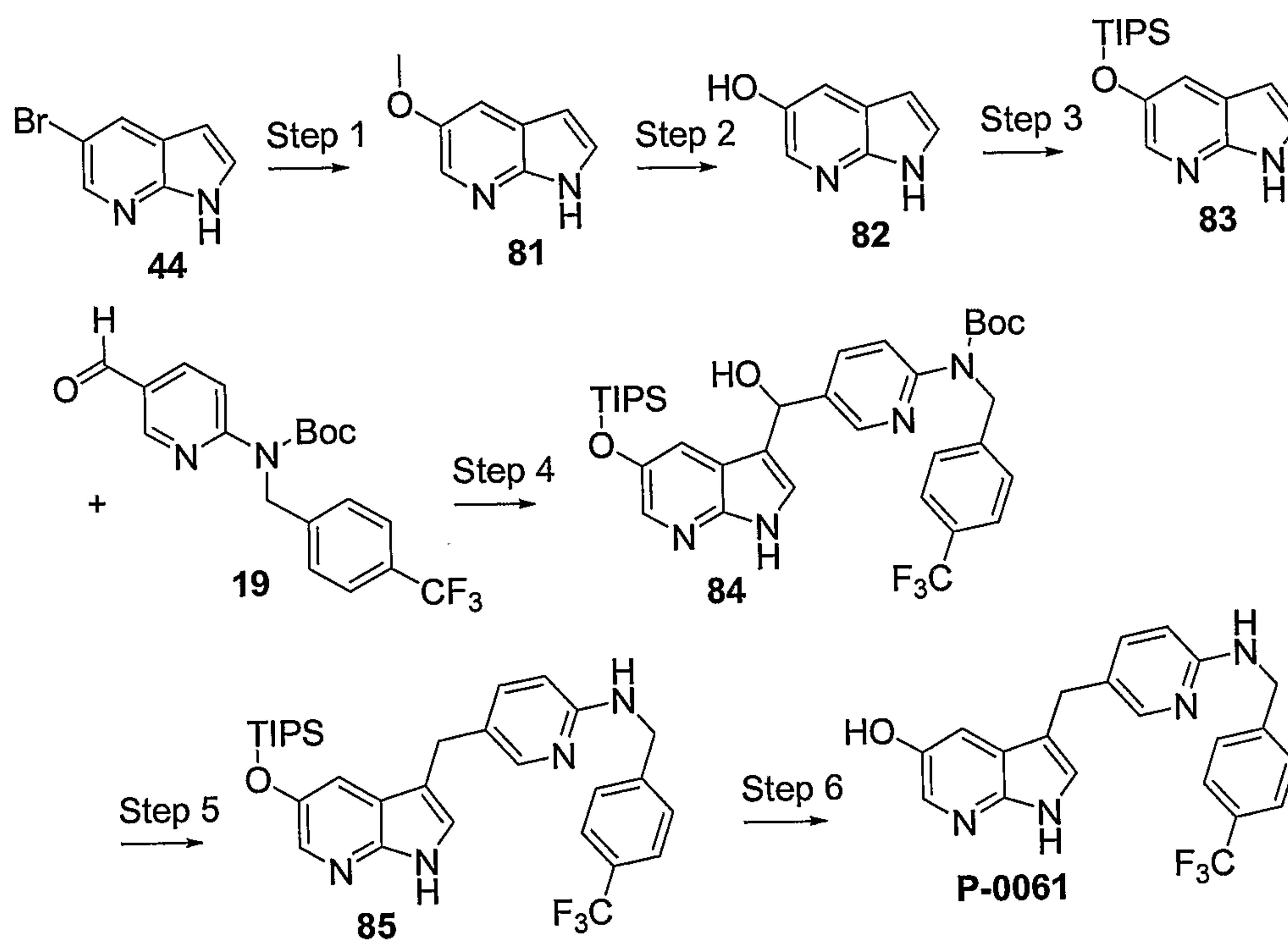


P-0066				512.3
P-0069				478.3

**Example 31: Synthesis of 3-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridin-5-ol P-0061:**

[0406] 3-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridin-5-ol P-0061 was synthesized in 6 Steps from 5-bromo-7-azaindole **44** as described in Scheme 33.

**Scheme 33**



*Step 1 – Preparation of 5-Methoxy-1H-pyrrolo[2,3-b]pyridine (81):*

[0407] To a mixture of 5-bromo-7-azaindole (1 g, 0.005 mol) in N, N-Dimethylformamide (20 mL) and methanol (20 mL) were added sodium methoxide (13 g, 0.24 mol) and Copper (I) bromide (0.7 g, 0.0048 mol) at room temperature. The reaction

mixture was stirred at 120 °C under nitrogen for 3 hours. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate and water. The organic layer was collected, washed with a solution of ammonium chloride and ammonium hydroxide (4:1), brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a white solid (**81**, 0.4 g, 50%). MS (ESI)  $[M+H]^+ = 149.09$ .

*Step 2 – Preparation of 1H-Pyrrolo[2,3-b]pyridin-5-ol (82):*

[0408] To a solution of 5-methoxy-1H-pyrrolo[2,3-b]pyridine (**81**, 0.5 g, 3 mmol) in tetrahydrofuran (20 mL) was added boron tribromide (1.5 g, 6.0 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, then stirred at room temperature for 3 hours. The reaction mixture was quenched by methanol. After repeated addition of methanol and removal of solvent, the concentrated reaction mixture was dissolved in ethyl acetate and water. The organic layer was collected, washed with brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as an off-white solid (**82**, 0.18 g, 40%).

*Step 3 – Preparation of 5-Triisopropylsilanyloxy-1H-pyrrolo[2,3-b]pyridine (83):*

[0409] To a solution of 1H-Pyrrolo[2,3-b]pyridin-5-ol (0.5 g, 0.004 mol) and 1H-imidazole (0.98 g, 0.014 mol) in N,N-dimethylformamide (5 mL) was added triisopropylsilyl chloride (1 mL, 0.005 mol). The reaction mixture was stirred at room temperature overnight. Dichloromethane (10 mL) was added and the solution was washed with brine and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a viscous liquid (**83**, 0.4 g, 40%).

*Step 4 – Preparation of {5-[Hydroxy-(5-triisopropylsilanyloxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (84):*

[0410] A mixture of (5-Formyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid tert-butyl ester (**19**, 41 mg, 0.11 mmol, prepared as described in Example 30), 5-triisopropylsilanyloxy-1H-pyrrolo[2,3-b]pyridine (**83**, 34 mg, 0.12 mmol) and potassium hydroxide (9.8 mg, 0.17 mmol) in methanol (10 mL) was stirred at room temperature overnight. The reaction mixture was poured into water, extracted with ethyl acetate,



washed with brine and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a viscous liquid (**84**, 0.05 g, 70%). MS (ESI)  $[M+H]^+ = 671.38$ .

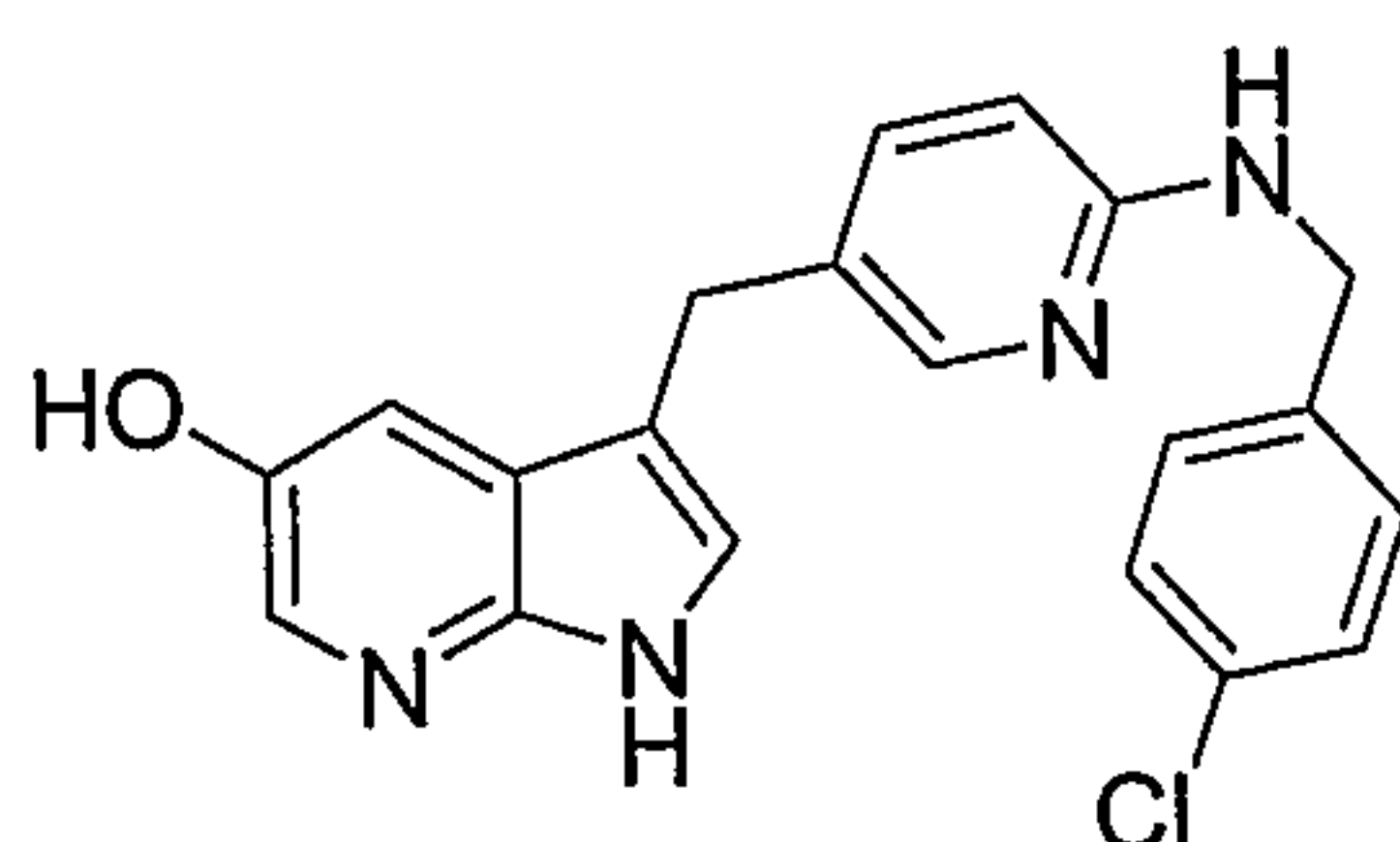
*Step 5 – Preparation of (4-Trifluoromethyl-benzyl)-[5-(5-triisopropylsilanyloxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (85):*

[0411] A mixture of {5-[hydroxy-(5-triisopropylsilanyloxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-pyridin-2-yl}-(4-trifluoromethyl-benzyl)-carbamic acid *tert*-butyl ester (**84**, 0.05 g, 0.07 mmol), trifluoroacetic acid (0.5 mL, 0.006 mol), and triethylsilane (1 mL, 0.006 mol) in acetonitrile (10 mL) was refluxed for 2 hours. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with saturated sodium bicarbonate, brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a viscous liquid (**85**, 0.04 g, 97%). MS (ESI)  $[M+H]^+ = 555.38$ .

*Step 6 – Preparation of 3-[6-(4-Trifluoromethyl-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridin-5-ol (P-0061):*

[0412] To (4-Trifluoromethyl-benzyl)-[5-(5-triisopropylsilanyloxy-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine (**85**, 0.13 g, 0.23 mmol) in tetrahydrofuran (10 mL) was added tetrabutylammonium fluoride (3 mL, 1.0 M in tetrahydrofuran, 3 mmol). The reaction mixture was stirred at room temperature overnight, and then was stirred at 65 °C for 48 hours. The reaction mixture was concentrated and purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a viscous liquid (**P-0061**, 0.062 g, 66%). MS (ESI)  $[M+H]^+ = 399.19$ .

[0413] 3-[6-(4-Chloro-benzylamino)-pyridin-3-ylmethyl]-1H-pyrrolo[2,3-b]pyridin-5-ol **P-0062**



was prepared following the protocol of Scheme 33, replacing (5-Formyl-pyridin-2-yl)-(4-trifluoromethyl-benzyl)-carbamic acid *tert*-butyl ester **19** with (5-Formyl-pyridin-2-yl)-(4-

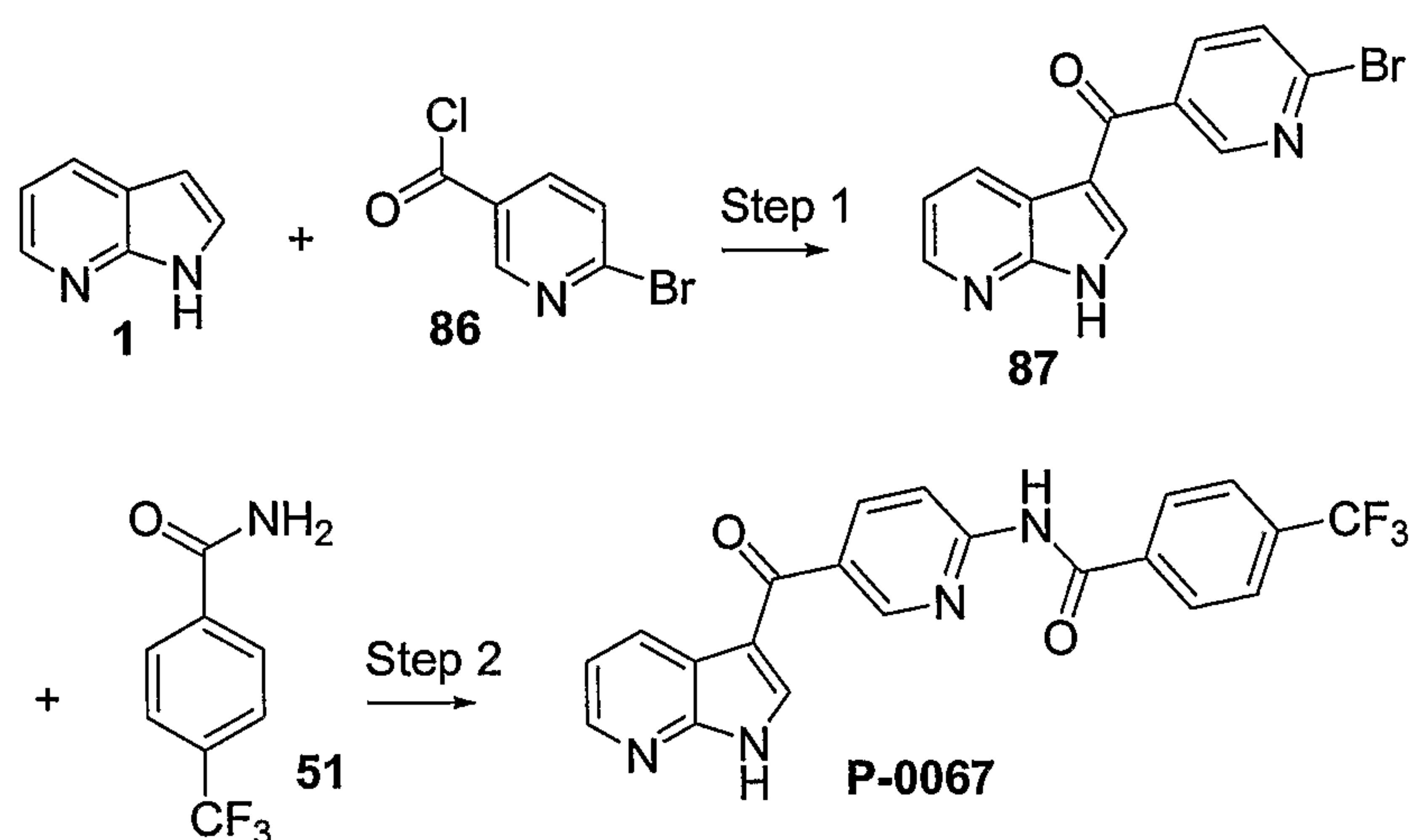
chloro-benzyl)-carbamic acid *tert*-butyl ester (**43**, prepared as described in Example 17).

MS (ESI)  $[M+H]^+ = 365.2$ .

**Example 32: Synthesis of N-[5-(1H-Pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-4-trifluoromethyl-benzamide P-0067**

[0414] N-[5-(1H-Pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-4-trifluoromethyl-benzamide **P-0067** was synthesized in 2 Steps from 7-azaindole **1** as described in Scheme 34.

**Scheme 34**



*Step 1 – Preparation of (6-Bromo-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (87):*

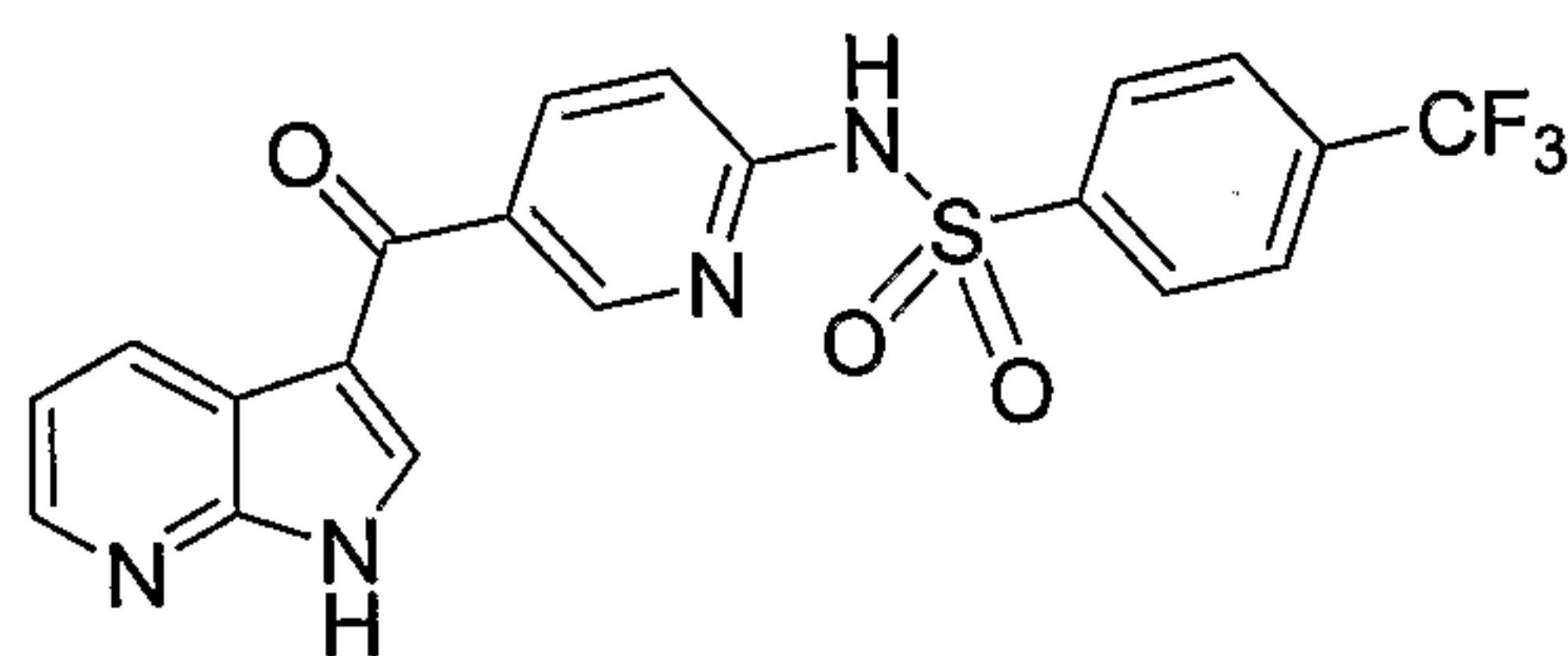
[0415] To a solution of 1H-Pyrrolo[2,3-*b*]pyridine (**1**, 1.2 g, 0.010 mol) in dichloromethane (50 mL) was added 6-bromo-nicotinoyl chloride (**86**, 2.6 g, 0.012 mol) at -10 °C. After the solution turned clear, aluminum trichloride (10.2 g, 0.0765 mol) was added in one portion with vigorous stirring. The reaction mixture was stirred at -10 °C for 30 minutes, then was allowed to warm to room temperature and stirred at room temperature overnight. The reaction was quenched with ice water and neutralized with sodium bicarbonate. The solution was extracted with dichloromethane, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the compound as a white solid (**87**, 0.35 g, 11%).



*Step 2 – Preparation of N-[5-(1H-Pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-4-trifluoromethyl-benzamide (P-0067):*

[0416] A mixture of (6-bromo-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**87**, 160 mg, 0.53 mmol), 4-trifluoromethyl benzamide (**51**, 130 mg, 0.69 mmol), xanthphos (9 mg, 0.02 mmol), cesium carbonate (245 mg, 0.752 mmol), and tris(dibenzylideneacetone)dipalladium (0) (5 mg, 0.005 mmol) in toluene (2 mL) in a sealed tube was stirred at 110 °C for 1 hour. The reaction was quenched with water and extracted with dichloromethane. The organic layer was collected, washed with brine and dried over sodium sulfate. After removal of the solvent, the residue was purified with silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as an off-white solid (**P-0067**, 0.42 mg, 19%). MS (ESI)  $[M+H]^+ = 411.17$ .

[0417] N-[5-(1H-Pyrrolo[2,3-b]pyridine-3-carbonyl)-pyridin-2-yl]-4-trifluoromethyl-benzenesulfonamide **P-0068**

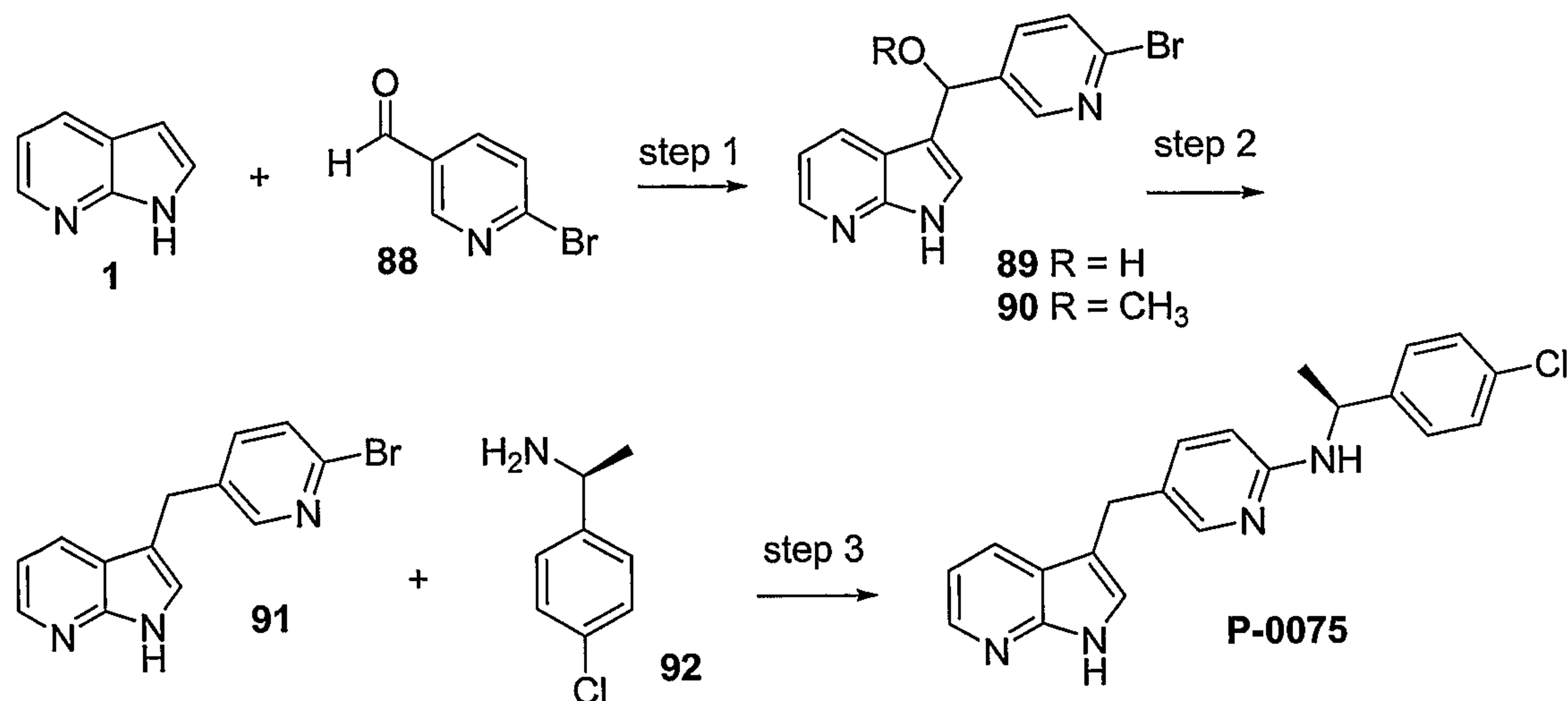


was prepared following the protocol of Scheme 34, replacing 4-trifluoromethyl benzamide **51** with 4-trifluoromethyl-benzenesulfonamide in Step 2. MS (ESI)  $[M+H]^+ = 445.1$ .

**Example 33: Synthesis of [(S)-1-(4-Chloro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0075**

[0418] [(S)-1-(4-Chloro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine **P-0075** was synthesized in 3 Steps from 7-azaindole **1** as described in Scheme 35.

## Scheme 35



*Step 1 – Preparation of (6-Bromo-pyridin-3-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanol (89):*

[0419] A mixture of 1H-Pyrrolo[2,3-*b*]pyridine (**1**, 1.2 g, 0.010 mol), 6-bromo-pyridine-3-carbaldehyde (**88**, 1.8 g, 0.0097 mol), and potassium hydroxide (1.8 g, 0.032 mol) in methanol (25 mL) was stirred at room temperature overnight. The reaction mixture was poured into ice water, extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with methanol in dichloromethane to provide the compound as a white solid (**89**, 1.4 g, 45%), or may be used as mixture of **89** and **90** in Step 2.

*Step 2 – Preparation of 3-(6-Bromo-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-*b*]pyridine (91):*

[0420] A mixture of (6-bromo-pyridin-3-yl)-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)-methanol (**89**, 1 g, 0.003 mol) and 3-[(6-bromo-pyridin-3-yl)-methoxy-methyl]-1H-pyrrolo[2,3-*b*]pyridine (**90**, 2 g, 0.006 mol), triethylsilane (1 mL, 0.006 mol), and trifluoroacetic acid (0.5 mL, 0.006 mol) in acetonitrile (25 mL) was refluxed for 2 hours. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate and water. The organic layer was collected, washed with saturated sodium bicarbonate, brine, and dried over sodium sulfate. After removal of the solvent, the residue was purified with silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as an off-white solid (**91**, 0.75 g, 60%). MS (ESI)  $[M+H]^+$  = 288.06, 290.00.



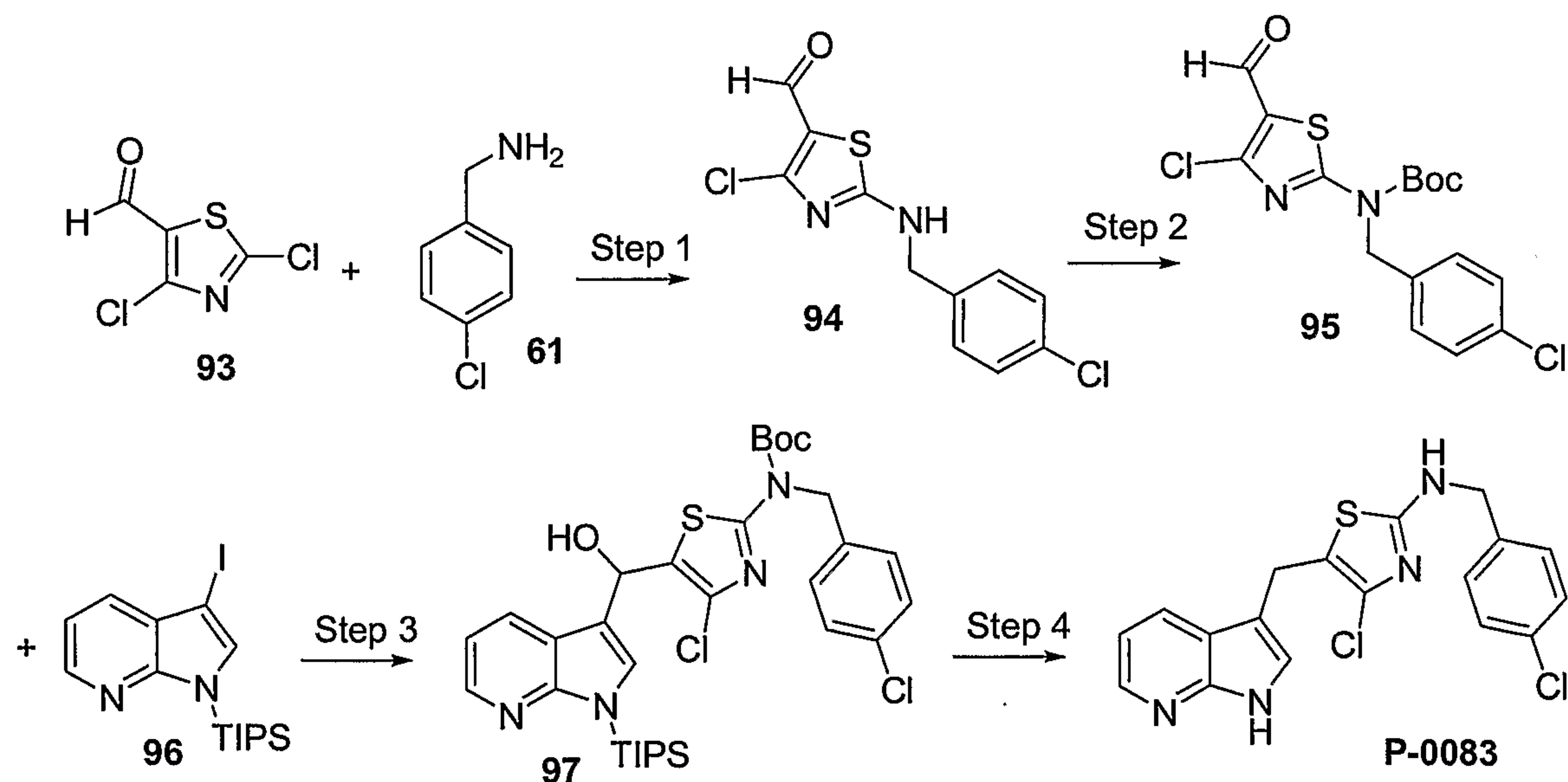
*Step 3 – Preparation of [(S)-1-(4-Chloro-phenyl)-ethyl]-[5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-amine P-0075:*

[0421] A mixture of 3-(6-bromo-pyridin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**91**, 100 mg, 0.0003 mol) and (S)-1-(4-chloro-phenyl)-ethylamine (**92**, 0.5 g, 0.003 mol) in N-methylpyrrolidine (3 mL) was stirred at 150 °C in microwave for 100 minutes. The reaction mixture was concentrated under vacuum and the residue was purified with silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a white solid (**P-0075**, 0.03 g, 20%). MS (ESI)  $[M+H]^+ = 363.18$ .

**Example 34: Synthesis of (4-Chloro-benzyl)-[4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine P-0083**

[0422] (4-Chloro-benzyl)-[4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine P-0083 was synthesized in 4 steps from 2,4-Dichloro-thiazole-5-carbaldehyde **93** as described in Scheme 36.

**Scheme 36**



*Step 1 – Preparation of 4-Chloro-2-(4-chloro-benzylamino)-thiazole-5-carbaldehyde (94):*

[0423] To a solution of p-chlorobenzylamine (**61**, 283 mg, 2.00 mmol) and N,N-Diisopropylethylamine (0.697 mL) in tetrahydrofuran (20mL) was slowly added 2,4-Dichloro-thiazole-5-carbaldehyde (**93**, 364 mg, 2.00 mmol) in tetrahydrofuran (10mL) at room temperature. The reaction was stirred at room temperature overnight. The reaction mixture was poured into iced water, extracted with ethyl acetate, washed with brine, and

dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a yellow solid (**94**, 0.3 g, 50%). MS (ESI)  $[M-H^+] = 286.97$ .

*Step 2 – Preparation of (4-Chloro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (95):*

**[0424]** To a solution of 4-Chloro-2-(4-chloro-benzylamino)-thiazole-5-carbaldehyde (**94**, 0.32 g, 0.0011 mol) in dichloromethane (20 mL) was slowly added N,N-diisopropylethylamine (0.4 mL, 0.002 mol), 4-dimethylaminopyridine (27 mg, 0.22 mmol), and a solution of di-tert-Butyldicarbonate (290 mg, 0.0013 mol) in dichloromethane (5 mL) at room temperature. The reaction mixture was stirred at room temperature overnight, then poured into iced water, extracted with dichloromethane, washed with brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a light brown solid (**95**, 0.32 g, 74%). MS (ESI)  $[M+H^+] = 387.26$ .

*Step 3 – Preparation of (4-Chloro-benzyl)-{4-chloro-5-[hydroxy-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-thiazol-2-yl}-carbamic acid tert-butyl ester (97):*

**[0425]** To a solution of 3-Iodo-1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridine (**96**, 99 mg, 0.25 mmol) in tetrahydrofuran (5 mL) at -20 °C under nitrogen was added 2.0 M solution isopropylmagnesium chloride in tetrahydrofuran (0.2 mL, 0.31 mmol). The reaction mixture was stirred for 1.5 hours, then allowed to warm to 5 °C. After the reaction mixture was cooled down to -20 °C, a solution of (4-Chloro-benzyl)-(4-chloro-5-formyl-thiazol-2-yl)-carbamic acid tert-butyl ester (**95**, 80 mg, 0.2 mmol) in tetrahydrofuran (5 mL) was slowly added. The reaction mixture was stirred for 2.5 hrs, then allowed to warm to 5 °C. The reaction mixture was poured into iced water, extracted with ethyl acetate, washed with brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as an off-white solid (**97**, 76 mg, 50%). MS (ESI)  $[M+H^+] = 661.32, 663.32$ .



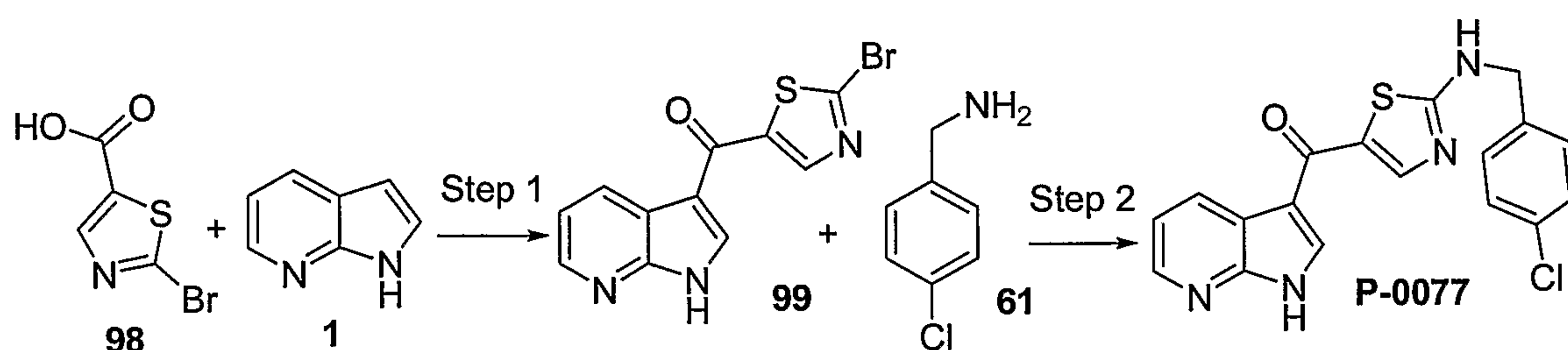
*Step 4 – Preparation of (4-Chloro-benzyl)-[4-chloro-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-thiazol-2-yl]-amine (P-0083):*

[0426] A mixture of (4-Chloro-benzyl)-{4-chloro-5-[hydroxy-(1-triisopropylsilyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-thiazol-2-yl}-carbamic acid tert-butyl ester (**97**, 76 mg, 0.11 mmol), triethylsilane (0.5 mL, 3 mmol), and trifluoroacetic acid (0.25 mL, 3.2 mmol) in acetonitrile (5 mL) was refluxed for 3 hours. The reaction mixture was poured into iced water, extracted with ethyl acetate, washed with sodium bicarbonate, brine, and dried over sodium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a yellow solid (**P-0083**, 5.6 mg, 14%). MS (ESI) [M+H+] = 389.35, 390.36.

**Example 35: Synthesis of [2-(4-Chloro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone P-0077:**

[0427] [2-(4-Chloro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone **P-0077** was synthesized in 2 steps from 2-Bromo-thiazole-5-carboxylic acid **98** and 1H-pyrrolo[2,3-b]pyridine **1** as shown in Scheme 37.

**Scheme 37**



*Step 1 – Preparation of (2-Bromo-thiazol-5-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (99):*

[0428] A suspension of 2-Bromo-thiazole-5-carboxylic acid (**98**, 0.5 g, 0.002 mol) in oxalyl chloride (3 mL) was stirred at room temperature until it turned into a clear solution. Solvent was removed and the residue was dried over vacuum. A light yellow solid was obtained and was dissolved in dichloromethane (10 mL) and slowly added to a solution of 1H-Pyrrolo[2,3-b]pyridine (**1**, 0.34 g, 0.0029 mol) in dichloromethane (30 mL) at -10 °C. To the mixture was then added aluminum trichloride (2.6 g, 0.019 mol) in one portion with vigorous stirring. The reaction was held at -10 °C for 30 minutes, then allowed to warm to room temperature. The reaction mixture was stirred at ambient temperature

overnight. The reaction was quenched with ice-water and acidified with hydrochloric acid (10%) to pH 4. The solution was then extracted with dichloromethane. The organic layer was collected, washed with brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a white solid (**99**, 12 mg, 2%). MS (ESI)  $[M-H^+] = 369.09$ .

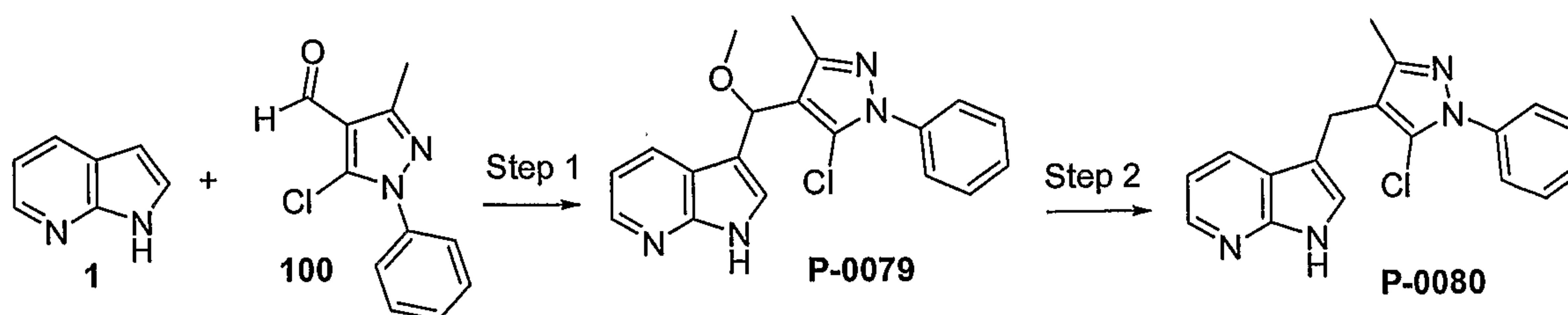
*Step 2 – Preparation of [2-(4-Chloro-benzylamino)-thiazol-5-yl]-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (P-0077):*

**[0429]** A mixture of (2-Bromo-thiazol-5-yl)-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methanone (**99**, 5 mg, 0.02 mmol), p-chlorobenzylamine (**61**, 10 mg, 0.08 mmol), and N,N-Diisopropylethylamine (10  $\mu$ L, 0.08 mmol) in tetrahydrofuran (10 mL), in a sealed reaction vessel, was stirred room temperature overnight. The reaction mixture was poured into iced water, extracted with ethyl acetate, washed with brine, and dried over magnesium sulfate. After removal of solvent, the residue was purified by silica gel column chromatography eluting with ethyl acetate in hexane to provide the compound as a light yellow solid (**P-0077**, 2 mg, 30%). MS (ESI)  $[M+H^+] = 305.90, 307.88$ .

**Example 36: Synthesis of 3-((5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)-1H-pyrrolo[2,3-b]pyridine P-0080**

**[0430]** 3-((5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)-1H-pyrrolo[2,3-b]pyridine **P-0080** was synthesized in 2 steps from 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde **100** and 7-azaindole **1** as shown in Scheme 38.

**Scheme 38**



*Step 1 – Preparation of 3-((5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)(methoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (P-0079):*

**[0431]** To 1H-Pyrrolo[2,3-b]pyridine (**1**, 0.100 g, 0.846 mmol) and 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (**100**, 0.205 g, 0.931 mmol) was added 2 mL of



methanol to give a solution. Potassium hydroxide (0.0475 g, 0.846 mmol) was added and the reaction was allowed to stir at room temperature for 48 hours. The reaction was extracted with ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with a gradient of 0-5% methanol in dichloromethane to give the compound (**P-0079**, 32 mg, 11%). MS (ESI)  $[M+H]^+ = 353.2$ .

*Step 2 – Preparation of 3-((5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)-1H-pyrrolo[2,3-b]pyridine (P-0080):*

[0432] To 3-((5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)(methoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (**P-0079**, 0.030 g, 0.085 mmol) was added acetonitrile (10 mL, 0.2 mol). Trifluoroacetic acid (500 uL, 0.006 mol) and triethylsilane (500 uL, 0.003 mol) were added and the reaction allowed to stir at room temperature for 16 hours. The reaction was extracted with ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with dichloromethane followed 5% methanol in dichloromethane to give the compound as a yellowish foam (**P-0080**, 29 mg, 98%). MS (ESI)  $[M+H]^+ = 323.2$ .

### **Example 37: cKit Kinase Domain and Construction of c-Kit sequences**

[0433] c-Kit cDNA sequence is available from NCBI, e.g., as GenBank accession number NM\_000222. Using this sequence, c-kit DNA sequences can be cloned from commercially available libraries (e.g. cDNA libraries) or can be synthesized by conventional cloning methods.

[0434] Using conventional cloning methods, constructs encoding three c-kit polypeptides were prepared, and used to express c-kit kinase domain polypeptides. One such active c-kit kinase domain sequence included residues P551-S948, with the deletion of residues Q694-T753.

### **Example 38: Expression and Purification of c-Kit kinase domain**

[0435] Purified c-kit kinase domain can be obtained using conventional expression and purification methods. Exemplary methods are described, for example, in Lipson et al.,

U.S. 20040002534 (U.S. application 10/600, 868, filed June 23, 2003), which is incorporated herein by reference in its entirety.

### **Example 39: Binding Assays**

[0436] Binding assays can be performed in a variety of ways, including a variety of ways known in the art. For example, as indicated above, binding assays can be performed using fluorescence resonance energy transfer (FRET) format, or using an AlphaScreen

[0437] Alternatively, any method which can measure binding of a ligand to the ATP-binding site can be used. For example, a fluorescent ligand can be used. When bound to c-kit, the emitted fluorescence is polarized. Once displaced by inhibitor binding, the polarization decreases.

[0438] Determination of IC<sub>50</sub> for compounds by competitive binding assays. (Note that K<sub>I</sub> is the dissociation constant for inhibitor binding; K<sub>D</sub> is the dissociation constant for substrate binding.) For this system, the IC<sub>50</sub>, inhibitor binding constant and substrate binding constant can be interrelated according to the following Formula:

[0439] When using radiolabeled substrate

$$K_I = \frac{IC_{50}}{1 + [L^*]/K_D},$$

[0440] the IC<sub>50</sub> ~ K<sub>I</sub> when there is a small amount of labeled substrate.

### **Example 40: Cell-based assays of c-fms kinase activity or c-kit kinase activity.**

[0441] M-CSF dependent RAW264.7 cells were seeded on a 12 well plate, 2.5x10<sup>5</sup> cells/well and the cells were allowed to attach overnight at 37 °C, 5% CO<sub>2</sub>. The cells were then starved in serum-free medium overnight at 37 °C, 5% CO<sub>2</sub>. The cells were treated with compound for 1 hour in serum-free media (1% DMSO final concentration); and then stimulated with 20 ng/ml M-CSF for 5 minutes. After stimulation, the cells were lysed on ice, and the lysates were centrifuged at 13,000 rpm for 1 minute. The amount of protein in the sample was quantitated, sample buffer was added, and the samples were boiled at 95 °C for 10 minutes. The samples were then centrifuged at 13,000 rpm for 1 minute. The



samples (15-20  $\mu\text{g}/\text{lane}$ ) were loaded and run on 4-12% tris-glycine gel at 75V, and then transferred onto a PVDF membrane. The membrane was blocked for 1 hour with 5% BSA in PBS/1% Tween-20 (PBST); or 5% milk, depending on the primary antibody used. Then the blots were incubated with primary antibody overnight at 4 degrees with gentle shaking. After incubation with the capture antibody, the membranes were washed 3 x 10 minutes with PBST; then incubated with detection antibody Goat Anti-Rabbit-HRP for 1 hour, with gentle shaking. The membranes were washed again 3 x 10 minutes with PBST. ECL Plus substrate was then added to the blots, the image captured with chemiluminescence camera, and the bands quantitated for pFMS and FMS levels.

[0442] The Fms inhibitors may also be assessed using M-NFS-60 mouse myelogenous leukemia cell line (ATCC catalog #CRL-1838). This cell line proliferation is stimulated by M-CSF, which binds and activates the fms tyrosine kinase receptor. Inhibitors of fms kinase activity reduce or eliminate the M-CSF stimulated kinase activity, resulting in reduced cell proliferation. This inhibition is measured as a function of compound concentration to assess  $\text{IC}_{50}$  values. M-NFS-60 cells were seeded at  $5 \times 10^4$  cells per well of a 96 well cell culture plate in 50  $\mu\text{l}$  of cell culture medium of RPMI 1640 (CellGro Mediatech catalog #10-040-CV) supplemented with 10 % FBS (HyClone catalog #SH30071.03). Compounds were dissolved in DMSO at a concentration of 1 mM and were serially diluted 1:3 for a total of eight points and added to the cells to final concentrations of 10, 3.3, 1.1, 0.37, 0.12, 0.041, 0.014 and 0.0046  $\mu\text{M}$  in 100  $\mu\text{l}$  cell culture medium (final concentration 0.2% DMSO). Cells were also treated with staurosporine as a positive control. The cells were stimulated by adding 20  $\mu\text{l}$  of 372 ng/ml M-CSF to a final concentration of 62 ng/ml (R&D Systems catalog #216-MC). The cells were incubated at 37  $^{\circ}\text{C}$ , 5%  $\text{CO}_2$  for three days. CellTiter-Glo Buffer (Promega Cell Viability Assay catalog #G7573) and substrate were equilibrated to room temperature, and enzyme/substrate Recombinant Firefly Luciferase/Beetle Luciferin was reconstituted. The cell plates were equilibrated to room temperature for 30 minutes, then lysed by addition of an equivalent volume of the Celltiter-Glo Reagent. The plate was mixed for 2 minutes on a plate shaker to lyse the cells, then incubated for 10 minutes at room temperature. The plates were read on a Victor Wallac II using Luminescence protocol modified to read 0.1s per well. The luminescence reading assesses the ATP



content, which correlates directly with cell number such that the reading as a function of compound concentration was used to determine the IC<sub>50</sub> value.

[0443] The c-Kit inhibitors were assessed using M-07e cell line (DSMZ catalog #ACC 104). The M-07e proliferation is stimulated by SCF (Stem Cell Factor), which binds and activates c-Kit tyrosine kinase receptor. Inhibitors of c-Kit kinase reduce or eliminate the SCF mediated kinase activation, resulting in reduced cell proliferation of SCF stimulated cells. This inhibition is measured by the effect of compound concentration on cell growth to assess IC<sub>50</sub> values. M-07e cells were seeded at  $5 \times 10^4$  cells per well of a 96 well cell culture plate in 50  $\mu$ l of cell culture medium of Iscove's Medium 1X (MOD, CellGro Mediatech catalog #15-016-CV) supplemented with 10% FBS (HyClone catalog #SH30071.03). Compounds were dissolved in DMSO at a concentration of 0.1 mM and were serially diluted 1:3 for a total of eight points and added to the cells to final concentrations of 1, 0.33, 0.11, 0.037, 0.012, 0.0041, 0.0014 and 0.00046  $\mu$ M in 100  $\mu$ l cell culture medium (final concentration 0.2% DMSO). Cells were also treated with staurosporine as a positive control. Cells were stimulated by adding 20  $\mu$ l of 600 ng/ml SCF to a final concentration of 100 ng/ml (Biosource International SCF kit ligand catalog #PHC2115) in cell culture medium. The cells were incubated at 37 °C, 5% CO<sub>2</sub> for three days. CellTiter-Glo Buffer (Promega Cell Viability Assay catalog #G7573) and substrate were equilibrated to room temperature, and enzyme/substrate Recombinant Firefly Luciferase/Beetle Luciferin was reconstituted. The cell plates were equilibrated to room temperature for 30 minutes, then lysed by addition of an equivalent volume of the Celltiter-Glo Reagent. The plate was mixed for 2 minutes on a plate shaker to lyse the cells, then incubated for 10 minutes at room temperature. The plates were read on a Victor Wallac II using Luminescence protocol modified to read 0.1s per well. The luminescence reading assesses the ATP content, which correlates directly with cell number such that the reading as a function of compound concentration is used to determine the IC<sub>50</sub> value.

[0444] This cell based assay was also used to assess phosphorylation. Samples were prepared with compounds as described for the growth inhibition assay only M-07e cells were seeded at  $2 \times 10^5$  cells per well in a 96 well filter plate. Cells were incubated for 1 hour at 37 °C with the compounds as described above, and then stimulated by adding SCF to a final concentration of 50 ng/ml and incubated for 10 minutes at 37 °C. The culture



medium was removed by centrifugation and the cells were lysed by addition of 30  $\mu$ l lysis buffer (25 mM Tris HCl pH 7.5, 150 mM NaCl, 5 mM EDTA, 1% Triton X100, 5 mM NaF, 1 mM NaVanadate, 10 mM Beta-glycerophosphate, no EDTA (Boehringer-Roche catalog #1873580) and placed on ice for 30 minutes. A 15  $\mu$ l aliquot of the lysate was taken and assayed according to Biosource Immunoassay Kit: Human c-Kit [pY823] (Catalog # KHO0401) by diluting the aliquot with 85  $\mu$ l dilution buffer in the assay plate, incubating for 2 hours at room temperature and washing the plate 4 times with wash buffer. Detection antibody (100  $\mu$ l) was added to the plate and samples incubated for 1 hour at room temperature, then washed 4 times with wash buffer. HRP anti-rabbit antibody (100  $\mu$ l) was added and samples incubated for 30 minutes at room temperature, then washed 4 times with wash buffer. Stabilized chromogen (100  $\mu$ l) was added and samples incubated for 15-25 minutes at room temperature, then washed 4 times with wash buffer. Stop solution (100  $\mu$ l) was added and the samples read on a Wallac Victor reader at 450 nm. The absorbance was plotted against the compound concentration and the IC<sub>50</sub> concentration was determined.

#### **Example 41: c-Kit and c-Fms Activity Assays**

[0445] The effect of potential modulators of kinase activity of c-kit and other kinases can be measured in a variety of different assays known in the art, e.g., biochemical assays, cell-based assays, and *in vivo* testing (e.g. model system testing). Such *in vitro* and/or *in vivo* assays and tests can be used in the present invention. As an exemplary kinase assay, the kinase activity of c-kit or Fms is measured in AlphaScreening (Packard BioScience).

#### **Exemplary c-kit biochemical assay**

[0446] The c-kit (or kinase domain thereof) is an active kinase in AlphaScreen. IC<sub>50</sub> values are determined with respect to inhibition of c-Kit kinase activity, where inhibition of phosphorylation of a peptide substrate is measured as a function of compound concentration. Compounds to be tested were dissolved in DMSO to a concentration of 20 mM. These were diluted 30  $\mu$ l into 120  $\mu$ l of DMSO (4 mM) and 1  $\mu$ l was added to an assay plate. These were then serially diluted 1:3 (50  $\mu$ l to 100  $\mu$ l DMSO) for a total of 8 points. Plates were prepared such that each kinase reaction is 20  $\mu$ l in 1x kinase buffer (50 mM HEPES, pH 7.2, 5 mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.01% NP-40, 0.2% BSA), 5% DMSO

and 10  $\mu$ M ATP. Substrate was 100 nM biotin-(E4Y)3 (Open Source Biotech, Inc.). C-kit kinase was at 0.1 ng per sample. After incubation of the kinase reaction for 1 hour at room temperature, 5  $\mu$ l of donor beads (Streptavidin coated beads (Perkin Elmer Life Science) final concentration 1  $\mu$ g/ml) in stop buffer (50mM EDTA in 1x kinase buffer) was added, the sample was mixed and incubated for 20 minutes at room temperature before adding 5  $\mu$ l of acceptor beads (PY20 coated beads (Perkin Elmer Life Science) final concentration 1  $\mu$ g/ml) in stop buffer. The samples were incubated for 60 minutes at room temperature and the signal per well was read on AlphaQuest reader. Phosphorylated substrate results in binding of the PY20 antibody and association of the donor and acceptor beads such that signal correlates with kinase activity. The signal vs. compound concentration was used to determine the IC<sub>50</sub>.

[0447] Compounds were also tested using a similar assay with a 10-fold higher ATP concentration. For these samples, compounds to be tested were dissolved in DMSO to a concentration of 20 mM. These were diluted 30  $\mu$ l into 120  $\mu$ l of DMSO (4 mM) and 1  $\mu$ l was added to an assay plate. These were then serially diluted 1:3 (50  $\mu$ l to 100  $\mu$ l DMSO) for a total of 8 points. Plates were prepared such that each kinase reaction is 20  $\mu$ l in 1x kinase buffer (8 mM MOPS pH 7.0, 1 mM MgCl<sub>2</sub>, 2 mM MnCl<sub>2</sub>, 0.01% Tween-20, 1 mM DTT, and 0.001% BSA), 5% DMSO and 100  $\mu$ M ATP. Substrate was 30 nM biotin-(E4Y)10 (Upstate Biotech, Cat# 12-440). C-kit kinase was at 1 ng per sample. After incubation of the kinase reaction for 1 hour at room temperature, 5  $\mu$ l of donor beads (Streptavidin coated beads (Perkin Elmer Life Science) final concentration 10  $\mu$ g/ml) in stop buffer (8 mM MOPS pH 7.0, 100 mM EDTA, 0.3% BSA) was added, the sample was mixed and incubated for 20 minutes at room temperature before adding 5  $\mu$ l of acceptor beads (PY20 coated beads (Perkin Elmer Life Science) final concentration 10  $\mu$ g/ml) in stop buffer. The samples were incubated for 60 minutes at room temperature and the signal per well was read on AlphaQuest reader. Phosphorylated substrate results in binding of the PY20 antibody and association of the donor and acceptor beads such that signal correlates with kinase activity. The signal vs. compound concentration was used to determine the IC<sub>50</sub>.

[0448] The c-kit enzyme used in the above assay was either obtained from Cell Signaling Technology (Cat. #7754) or was prepared as follows: A plasmid encoding kit



(DNA and encoded protein sequences shown below) was engineered using common polymerase chain reaction (PCR) methods. Complementary DNA cloned from various human tissues were purchased from Invitrogen, and these were used as substrates in the PCR reactions. Specific custom synthetic oligonucleotide primers were designed to initiate the PCR product, and also to provide the appropriate restriction enzyme cleavage sites for ligation with the plasmids. The entire sequence encoding the enzyme was made through a gene synthesis procedure, using custom synthetic oligonucleotides covering the entire coding sequence (Invitrogen, see below).

**[0449]** The plasmid used for ligation with the kinase-encoding inserts was derivative of pET (Novagen) for expression using *E. coli*. The Kit kinase was engineered to include a Histidine tag for purification using metal affinity chromatography. The kinase-encoding plasmid was engineered as bicistronic mRNA to co-express a second protein that modifies the kinase protein during its expression in the host cell. Protein tyrosine phosphatase 1B (PTP), was co-expressed for dephosphorylation of the phospho-Tyrosines.

**[0450]** For protein expression, the plasmid containing the Kit gene was transformed into *E. coli* strains BL21(DE3)RIL and transformants selected for growth on LB agar plates containing appropriate antibiotics. Single colonies were grown overnight at 37°C in 200ml TB (Terrific broth) media. 16x1L of fresh TB media in 2.8L flasks were inoculated with 10ml of overnight culture and grown with constant shaking at 37°C. Once cultures reached an absorbance of 1.0 at 600nm, IPTG was added and cultures were allowed to grow for a further 12 to 18hrs at temperatures ranging from 12-30°C. Cells were harvested by centrifugation and pellets frozen at -80°C until ready for lysis.

**[0451]** For protein Purification; frozen *E. coli* cell pellets were resuspended in lysis buffer and lysed using standard mechanical methods. Protein was purified via poly-Histidine tags using immobilized metal affinity purification IMAC. The Kit kinase was purified using a 3 step purification process utilizing; IMAC, size exclusion chromatography and ion exchange chromatography. The poly-Histidine tag was removed using Thrombin (Calbiochem).

**[0452]** Compounds were assayed using a similar assay to that described above, using in a final reaction volume of 25 µl: c-Kit (h) (5-10 mU) in 8mM MOPS pH 7.0, 0.2 mM

EDTA, 10 mM MnCl<sub>2</sub>, 0.1 mg/ml poly (Glu, Tyr) 4:1, 10 mM MgAcetate and  $\gamma$ -<sup>33</sup>P-ATP (approximately 500 cpm/pmol), with appropriate concentrations of compound. Incubated for 40 minutes at room temperature and stopped by addition of 5  $\mu$ l of 3% phosphoric acid. Spotted 10  $\mu$ l of each sample onto Filtermat A and washed 3x with 75 mM phosphoric acid, once with methanol, dried and measured on scintillation counter (performed at Upstate USA, Charlottesville, VA).

[0453] Compounds P-0001, P-0002, P-0003, P-0004, P-0005, P-0006, P-0007, P-0008, P-0009, P-0010, P-0011, P-0012, P-0013, P-0014, P-0015, P-0016, P-0017, P-0018, P-0020, P-0022, P-0024, P-0025, P-0026, P-0027, P-0028, P-0030, P-0031, P-0032, P-0033, P-0038, P-0053, P-0054, P-0055, P-0056, P-0057, P-0058, P-0059, P-0060, P-0061, P-0062, P-0063, P-0064, P-0065, P-0066, P-0069, P-0071, P-0072, P-0073, P-0074, P-0075, P-0078, and P-0082 had IC<sub>50</sub> of less than 1  $\mu$ M in at least one of the c-kit assays described above in Examples 40 and 41.

### Kit

#### PCR primers

KIT	8K1A	ATGTACGAAGTTCAGTGGAAAGTTGTTGAAGAAATCAACGG (SEQ ID NO:___)	1776
	8K1B	GGTCGATGTAAACGTAGTTGTTACCGTTGATTTCTTCAACAACTTT (SEQ ID NO:___)	1777
	8K2A	AACAACACTACGTTTACATCGACCCGACCCAGCTGCCGTACGAC (SEQ ID NO:___)	1779
	8K2B	GTTACGCGGGAACCTCCCATTTGTGGTTCGTACGGCAGCTGGGTC (SEQ ID NO:___)	1781
	8K3A	AAATGGGAGTTCCTCCGCGTAACCGTCTGTCTTTCGGTAAAACCC (SEQ ID NO:___)	1782
	8K3B	ACCGAACGCACCCGCACCCAGGGTTTTACCGAAAGACAGAC (SEQ ID NO:___)	1783
	8K4A	GGTGCGGGTGCGTTCGGTAAAGTTGTTGAAGCGACCGCGTACG (SEQ ID NO:___)	1784
	8K4B	GCCGCGTCAGATTTGATCAGACCGTACGCGGTCGCTTCAAC (SEQ ID NO:___)	1785
	8K5A	CTGATCAAATCTGACGCGGCGATGACCGTTGCGGTTAAAATGC (SEQ ID NO:___)	1786



8K5B	GTCAGGTGCGCAGACGGTTTCAGCATTTTAACCGCAACGGTCA (SEQ ID NO:___)	1787
8K6A	AAACCGTCTGCGCACCTGACCGAACGTGAAGCGCTGATGTCTG (SEQ ID NO:___)	1788
8K6B	CCAGGTAAGACAGAACTTTTCAGTTCAGACATCAGCGCTTCACGT (SEQ ID NO:___)	1789
8K7A	CTGAAAGTTCTGTCTTACCTGGGTAACCACATGAACATCGTTAA (SEQ ID NO:___)	1791
8K7B	GGTGCACGCACCCAGCAGGTTAACGATGTTTCATGTGGTTAC (SEQ ID NO:___)	1792
8K8A	CTGCTGGGTGCGTGACCATCGGTGGTCCGACCTGGTTATCA (SEQ ID NO:___)	1793
8K8B	GTCACCGTAGCAGCAGTATTCGGTGATAACCAGGGTCCGACCA (SEQ ID NO:___)	1794
8K9A	GAATACTGCTGCTACGGTGACCTGCTGAACTTCCTGCGTCGTA (SEQ ID NO:___)	1795
8K9B	AGAGCAGATGAAAGAGTCACGTTTACGACGCAGGAAGTTCAGC (SEQ ID NO:___)	1796
8K10A	CGTGACTCTTTCATCTGCTCTAAACAGGAAGACCACCGGGAAG (SEQ ID NO:___)	1797
8K10B	CAGCAGGTTTTTGTACAGCGCCGCTTCCGCGTGGTCTTCTGT (SEQ ID NO:___)	1798
8K11A	GCGCTGTACAAAACCTGCTGCACTCTAAAGAATCTTCTTGCTC (SEQ ID NO:___)	1799
8K11B	CCATGTATTTCGTTGGTAGAGTCAGAGCAAGAAGATTCTTTAGAGT (SEQ ID NO:___)	1811
8K11A	GACTCTACCAACGAATACATGGACATGAAACCGGGTGTCTTCTTA (SEQ ID NO:___)	1812
8K11B	TCCGCTTTGGTCGGAACAACGTAAGAAACACCCGGTTTCATGT (SEQ ID NO:___)	1813
8K12A	GTTGTTCCGACCAAAGCGGACAAACGTCGTTCTGTTTCGTATCG (SEQ ID NO:___)	1814
8K12B	TAACGTCACGTTTCGATGTAAGAACCGATACGAACAGAACGACGTTT (SEQ ID NO:___)	1815
8K13A	TCTTACATCGAACGTGACGTTACCCCGCGATCATGGAAGACG (SEQ ID NO:___)	1816

8K13B	CCAGGTCCAGCGCCAGTTCGTCGTCTTCCATGATCGCCGG (SEQ ID NO:___)	1817
8K14A	GAACTGGCGCTGGACCTGGAAGACCTGCTGTCTTCTCTTACC (SEQ ID NO:___)	1818
8K14B	GAACGCCATACCTTTCGCAACCTGGTAAGAGAAAGACAGCAGGT (SEQ ID NO:___)	1819
8K15A	GTTGCGAAAGGTATGGCGTTCCTGGCGTCTAAAACTGCATCCA (SEQ ID NO:___)	1821
8K15B	CGCGCCGCCAGGTACCGGTGGATGCAGTTTTTAGACGCC (SEQ ID NO:___)	1822
8K16A	CGTGACCTGGCGGCGGTAACATCCTGCTGACCCACGGTTCG (SEQ ID NO:___)	1823
8K16B	ACCGAAGTCGCAGATTTTGGTGATACGACCGTGGGTCAGCAGG (SEQ ID NO:___)	1824
8K17A	ACCAAAATCTGCGACTTCGGTCTGGCGCGTGACATCAAAAACG (SEQ ID NO:___)	1825
8K17B	GTTACCTTTAACAACGTAGTTAGAGTCGTTTTTGATGTCACGCGCC (SEQ ID NO:___)	1826
8K18A	TCTAACTACGTTGTTAAAGGTAACGCGCGTCTGCCGGTTAAATG (SEQ ID NO:___)	1827
8K18B	GAAGATAGATTCCGGCGCCATCCATTTAACCGGCAGACGCGC (SEQ ID NO:___)	1829
8K19A	ATGGCGCCGGAATCTATCTTCAACTGCGTTTACACCTTCGAATC (SEQ ID NO:___)	1831
8K19B	GATACCGTAAGACCAAACGTCAGATTCGAAGGTGTAAACGCAG (SEQ ID NO:___)	1832
8K20A	GACGTTTGGTCTTACGGTATCTTCTGTTGGGAACTGTTCTCTC (SEQ ID NO:___)	1833
8K20B	CCTGTGGGAACTGTTCTCTCTGGGTTCTTCTCCGTACCCGG (SEQ ID NO:___)	1834
8K21A	GGTTCTTCTCCGTACCCGGGTATGCCGTTGACTCTAAATTCTAT (SEQ ID NO:___)	1835
8K21B	CGGAAACCTTCTTTGATCATTGTTGTAAGATTTAGAGTCAACCGGC (SEQ ID NO:___)	1836
8K22A	AAAATGATCAAAGAAGGTTTCCGTATGCTGTCTCCGGAACACG (SEQ ID NO:___)	1837



8K22B	ATGTCGTACATTTCCGCCGGCGCGTGTTCGGAGACAGCATA (SEQ ID NO:___)	1838
8K23A	CCGGCGGAAATGTACGACATCATGAAAACCTGCTGGGACGCG (SEQ ID NO:___)	1839
8K23B	AAGGTCGGACGTTTCAGCGGGTCCGCGTCCCAGCAGGTTTTC (SEQ ID NO:___)	1841
8K24A	CCGCTGAAACGTCCGACCTTCAAACAGATCGTTCAGCTGATCG (SEQ ID NO:___)	1842
8K24B	TTGGTAGATTTCAGAGATCTGTTTTTCGATCAGCTGAACGATCTGTT (SEQ ID NO:___)	1843
8K25A	AAACAGATCTCTGAATCTACCAACCACATCTACTCTAACCTGGC (SEQ ID NO:___)	1844
8K25B	TGACGGTTCCGGAGAGCAGTTCGCCAGGTTAGAGTAGATGTGG (SEQ ID NO:___)	1845
8K26A	AACTGCTCTCCGAACCGTCAGAAACCGGTTGTTGACCACTCTG (SEQ ID NO:___)	1846
8K26B	GTAGAACCAACAGAGTTGATACGAACAGAGTGGTCAACAACCGGT (SEQ ID NO:___)	1847
8K27A	CGTATCAACTCTGTTGGTTCTACCGCGTCTTCTTCTCAGCCG (SEQ ID NO:___)	1848
8K27B	AACGTCGTCGTGAACCAGCAGCGGCTGAGAAGAAGACGCG (SEQ ID NO:___)	1849
8K-F	GTTGTTTCATATGTACGAAGTTCAGTGGAAAG (SEQ ID NO:___)	1851
8K-R	GTTGTTTGTCGACTAAACGTCGTCGTGAACCAGCAG (SEQ ID NO:___)	1852
KIT COD-K948X	GTTCTTGTCGACTAtttctgacggttcggagagc (SEQ ID NO:___)	3411





[0454] In general, any protein kinase assay can be adapted for use with c-kit. For example, assays (e.g. biochemical and cell-based assays) as described in Lipson et al., U.S. Patent Publ. 20040002534 (incorporated herein by reference in its entirety) can be used in the present invention.

#### ***In vivo* model system testing**

[0455] For *in vivo* testing, a suitable animal model system can be selected for use. For example, for multiple sclerosis, the rodent experimental allergic encephalomyelitis (EAE) is commonly used. This system is well-known, and is described, for example, in Steinman, 1996, Cell 85:299-302 and Secor et al., 2000, J Exp. Med 5:813-821, which are incorporated herein by reference in their entireties.

[0456] Similarly, other model systems can be selected and used in the present invention.

#### **Exemplary Fms biochemical assay**

[0457] IC<sub>50</sub> values were determined with respect to inhibition of Fms kinase activity, where inhibition of phosphorylation of a peptide substrate is measured as a function of compound concentration. Compounds to be tested, dissolved in DMSO (1  $\mu$ L), were added to a white 384-well plate (Costar #3705). Working stocks of Fms kinase (Upstate Biotech, #14-551), biotin-(E4Y)<sub>10</sub> substrate (Upstate Biotech, Cat# 12-440), and ATP (Sigma, Cat#A-3377) were prepared in 8 mM MOPS pH 7.4, 2 mM MgCl<sub>2</sub>, 8 mM MnCl<sub>2</sub>, 2 mM DTT, and 0.01% Tween-20. All components were added to the 384-well plate for a final concentration of 0.5 ng/well Fms, 30 nM biotin-(E4Y)<sub>10</sub> (Upstate Biotechnology) and 10  $\mu$ M ATP in a volume of 20  $\mu$ L. Each sample was at 5% DMSO. The plate was then incubated for 60 minutes at room temperature. Just before use, working stocks of donor and acceptor beads from the AlphaScreen PY20 Detection Kit (PerkinElmer, Cat#676601M) were prepared in 8 mM MOPS, pH 7.4, 100 mM EDTA, 0.3% BSA. To stop the reaction, the plate was uncovered in the dark and 5  $\mu$ l of Donor Beads solution (Streptavidin beads) was added to each well. The plate was incubated at room temperature for 20 minutes. Five microliters of Acceptor Beads solution (PY20 coated beads) were then added to each well. The final concentration of each bead was 20  $\mu$ g/mL. The plates were incubated at room temperature for 60 minutes. Fluorescence signal was recorded on the Fusion Alpha reader or AlphaQuest reader. Phosphorylated substrate results in binding of the PY20 antibody and association of the donor and acceptor beads such that

signal correlates with kinase activity. The signal vs. compound concentration was used to determine the IC<sub>50</sub>.

[0458] Compounds were also tested using a similar assay with a 10-fold higher ATP concentration. Compounds to be tested, dissolved in DMSO (1  $\mu$ L), were added to a white 384-well plate (Costar #3705). Working stocks of Fms kinase (Upstate Biotech, #14-551), biotin-(E4Y)<sub>10</sub> substrate (Upstate Biotech, Cat# 12-440), and ATP (Sigma, Cat#A-3377) were prepared in 8 mM MOPS pH 7.0, 2 mM MgCl<sub>2</sub>, 8 mM MnCl<sub>2</sub>, 2 mM DTT, 50 mM NaCl, 0.01% BSA, and 0.01% Tween-20. All components were added to the 384-well plate for a final concentration of 0.5 ng/well Fms, 30 nM biotin-(E4Y)<sub>10</sub> (Upstate Biotechnology) and 100  $\mu$ M ATP in a volume of 20  $\mu$ L. Each sample was at 5% DMSO. The plate was then incubated for 20 minutes at 30°C. Just before use, working stocks of donor and acceptor beads from the AlphaScreen PY20 Detection Kit (PerkinElmer, Cat#676601M) were prepared in 8 mM MOPS, pH 7.0, 100 mM EDTA, 0.01% BSA. To stop the reaction, the plate was uncovered in the dark and 5  $\mu$ l of Donor Beads solution (Streptavidin beads) was added to each well. The plate was incubated at room temperature for 20 minutes. Five microliters of Acceptor Beads solution (PY20 coated beads) were then added to each well. The final concentration of each bead was 10  $\mu$ g/mL. The plates were incubated at room temperature for 60 minutes. Fluorescence signal was recorded on the Fusion Alpha reader or AlphaQuest reader. Phosphorylated substrate results in binding of the PY20 antibody and association of the donor and acceptor beads such that signal correlates with kinase activity. The signal vs. compound concentration was used to determine the IC<sub>50</sub>.

[0459] Compounds were assayed using a similar assay to that described above, using in a final reaction volume of 25  $\mu$ l: Fms (h) (5-10 mU) in 8mM MOPS pH 7.0, 0.2 mM EDTA, 250 mM KKKSPGEYVNIEFG (SEQ ID NO:\_\_\_), 10 mM MgAcetate and  $\gamma$ -<sup>33</sup>P-ATP (approximately 500 cpm/pmol), with appropriate concentrations of compound. Samples were incubated for 40 minutes at room temperature and stopped by addition of 5  $\mu$ l of 3% phosphoric acid. 10  $\mu$ l of each sample is spotted onto a P30 filtermat and washed 3x with 75 mM phosphoric acid, once with methanol, dried and measured on scintillation counter (Upstate USA, Charlottesville, VA).



[0460] Compounds P-0001, P-0002, P-0003, P-0004, P-0005, P-0006, P-0007, P-0008, P-0009, P-0010, P-0011, P-0013, P-0014, P-0015, P-0016, P-0028, P-0032, P-0033, P-0038, P-0053, P-0054, P-0055, P-0056, P-0057, P-0058, P-0059, P-0060, P-0061, P-0062, P-0063, P-0064, P-0065, P-0066, P-0069, P-0072, P-0073, P-0074, P-0075, P-0076, P-0078, P-0081, and P-0082 had IC<sub>50</sub> of less than 1  $\mu$ M in at least one of the Fms assays described above in Examples 40 or 41.

**Example 42: Site-directed Mutagenesis of c-Kit, c-Fms and other Kinases**

[0461] Mutagenesis of c-kit and other kinases (as well as other sequences of interest) can be carried out according to the following procedure as described in Molecular Biology: Current Innovations and Future Trends. Eds. A.M. Griffin and H.G.Griffin. (1995) ISBN 1-898486-01-8, Horizon Scientific Press, PO Box 1, Wymondham, Norfolk, U.K., among others.

[0462] *In vitro* site-directed mutagenesis is an invaluable technique for studying protein structure-function relationships, gene expression and vector modification. Several methods have appeared in the literature, but many of these methods require single-stranded DNA as the template. The reason for this, historically, has been the need for separating the complementary strands to prevent reannealing. Use of PCR in site-directed mutagenesis accomplishes strand separation by using a denaturing step to separate the complementing strands and allowing efficient polymerization of the PCR primers. PCR site-directed methods thus allow site-specific mutations to be incorporated in virtually any double-stranded plasmid; eliminating the need for M13-based vectors or single-stranded rescue.

[0463] It is often desirable to reduce the number of cycles during PCR when performing PCR-based site-directed mutagenesis to prevent clonal expansion of any (undesired) second-site mutations. Limited cycling which would result in reduced product yield, is offset by increasing the starting template concentration. A selection is used to reduce the number of parental molecules coming through the reaction. Also, in order to use a single PCR primer set, it is desirable to optimize the long PCR method. Further, because of the extendase activity of some thermostable polymerases it is often necessary to incorporate an end-polishing step into the procedure prior to end-to-end ligation of the PCR-generated product containing the incorporated mutations in one or both PCR primers.

[0464] The following protocol provides a facile method for site-directed mutagenesis and accomplishes the above desired features by the incorporation of the following steps: (i) increasing template concentration approximately 1000-fold over conventional PCR conditions; (ii) reducing the number of cycles from 25-30 to 5-10; (iii) adding the restriction endonuclease DpnI (recognition target sequence: 5-Gm6ATC-3, where the A residue is methylated) to select against parental DNA (note: DNA isolated from almost all common strains of E. coli is Dam-methylated at the sequence 5-GATC-3); (iv) using Taq Extender in the PCR mix for increased reliability for PCR to 10 kb; (v) using Pfu DNA polymerase to polish the ends of the PCR product, and (vi) efficient intramolecular ligation in the presence of T4 DNA ligase.

[0465] Plasmid template DNA (approximately 0.5 pmole) is added to a PCR cocktail containing, in 25 ul of 1x mutagenesis buffer: (20 mM Tris HCl, pH 7.5; 8 mM MgCl<sub>2</sub>; 40 ug/ml BSA); 12-20 pmole of each primer (one of which must contain a 5-prime phosphate), 250 uM each dNTP, 2.5 U Taq DNA polymerase, 2.5 U of Taq Extender (Stratagene).

[0466] The PCR cycling parameters are 1 cycle of: 4 min at 94 C, 2 min at 50 C and 2 min at 72°C; followed by 5-10 cycles of 1 min at 94°C, 2 min at 54 C and 1 min at 72°C (step 1).

[0467] The parental template DNA and the linear, mutagenesis-primer incorporating newly synthesized DNA are treated with DpnI (10 U) and Pfu DNA polymerase (2.5U). This results in the DpnI digestion of the in vivo methylated parental template and hybrid DNA and the removal, by Pfu DNA polymerase, of the Taq DNA polymerase-extended base(s) on the linear PCR product.

[0468] The reaction is incubated at 37°C for 30 min and then transferred to 72°C for an additional 30 min (step 2).

[0469] Mutagenesis buffer (1x, 115 ul, containing 0.5 mM ATP) is added to the DpnI-digested, Pfu DNA polymerase-polished PCR products.

[0470] The solution is mixed and 10 ul is removed to a new microfuge tube and T4 DNA ligase (2-4 U) added.



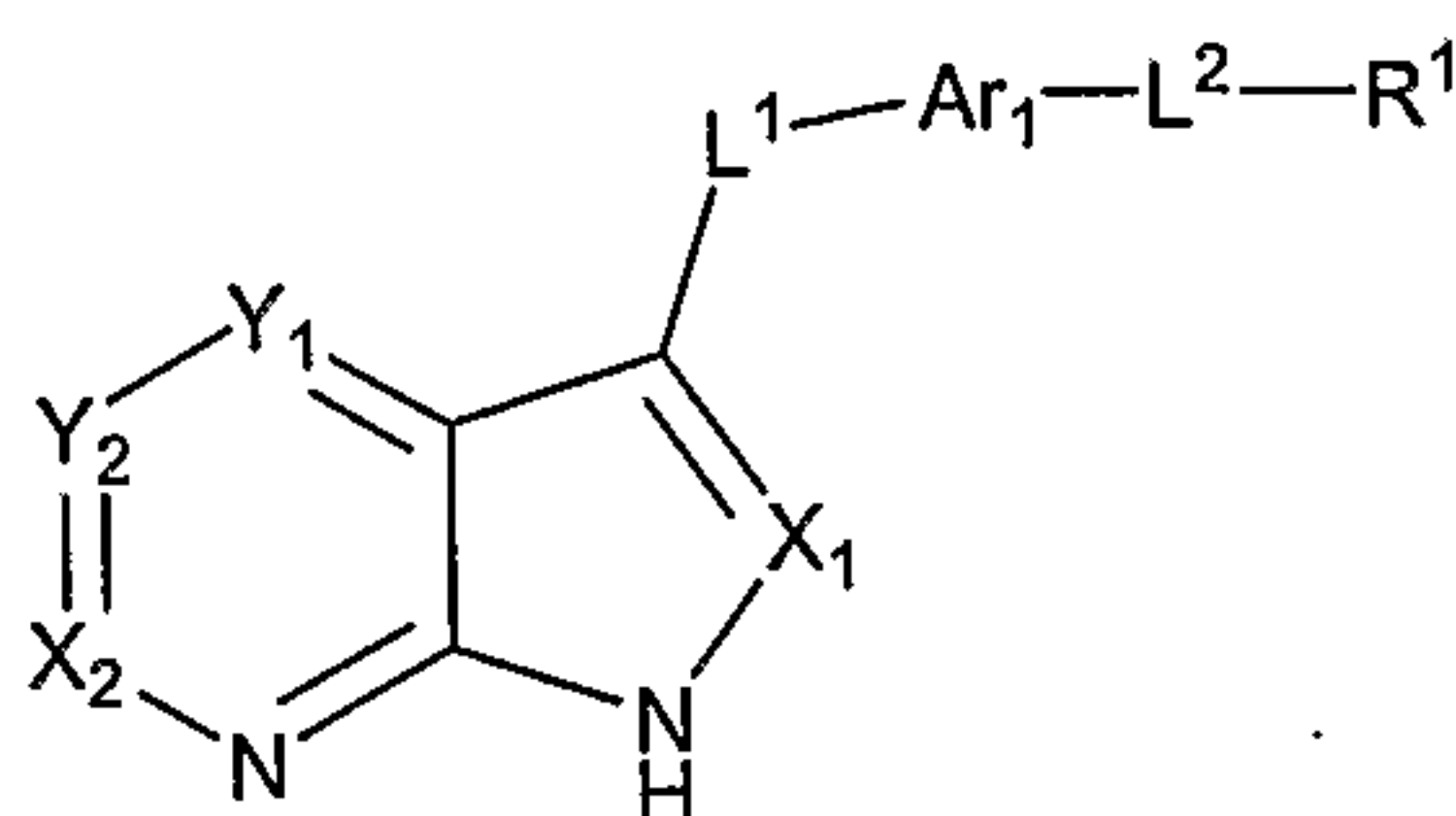
[0471] The ligation is incubated for greater than 60 min at 37°C (step 3).

[0472] The treated solution is transformed into competent E. coli (step 4).

[0473] In addition to the PCR-based site-directed mutagenesis described above, other methods are available. Examples include those described in Kunkel (1985) Proc. Natl. Acad. Sci. 82:488-492; Eckstein et al. (1985) Nucl. Acids Res. 13:8764-8785; and using the GeneEditor™ Site-Directed Mutagenesis System from Promega.

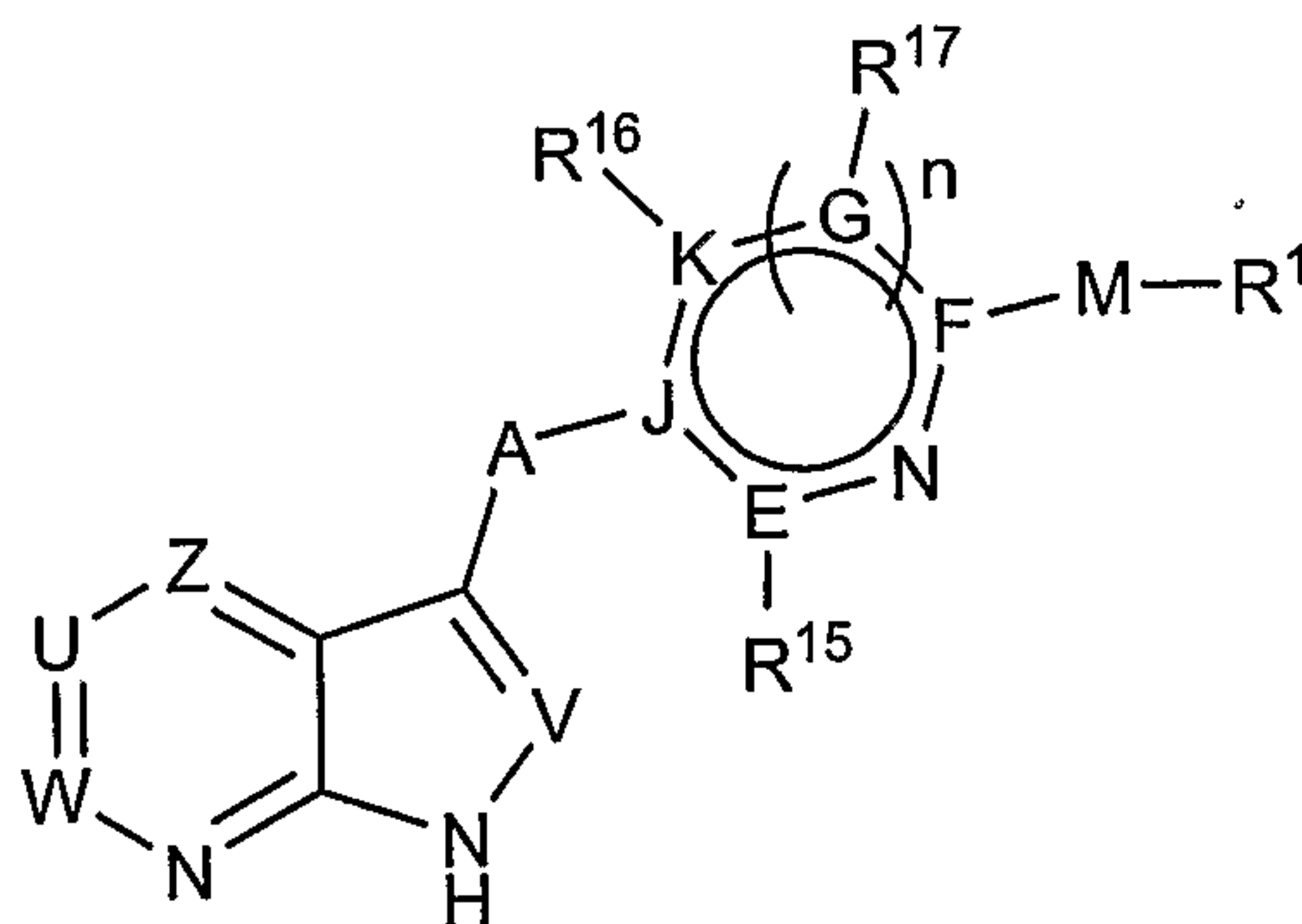
[0474] In the following Examples, as well as in Examples 1-36 above, it is understood that the solvents and reagents used or suggested are not limiting, and can be substituted appropriately with solvents and reagents known to those of skill in the art. Reaction products may be isolated by means known in the art, such as extraction with a suitable solvent, precipitation from a suitable solvent, chromatography using a suitable solvent system, including silica gel column chromatography, HPLC, preparative TLC, and the like.

[0475] Synthetic routes available to Formula I



Formula I

wherein X<sub>1</sub>, X<sub>2</sub>, Y<sub>1</sub>, Y<sub>2</sub>, L<sub>1</sub>, Ar<sub>1</sub>, L<sub>2</sub> and R<sup>1</sup> are as defined in Formula I of [0012] or Formula Ib

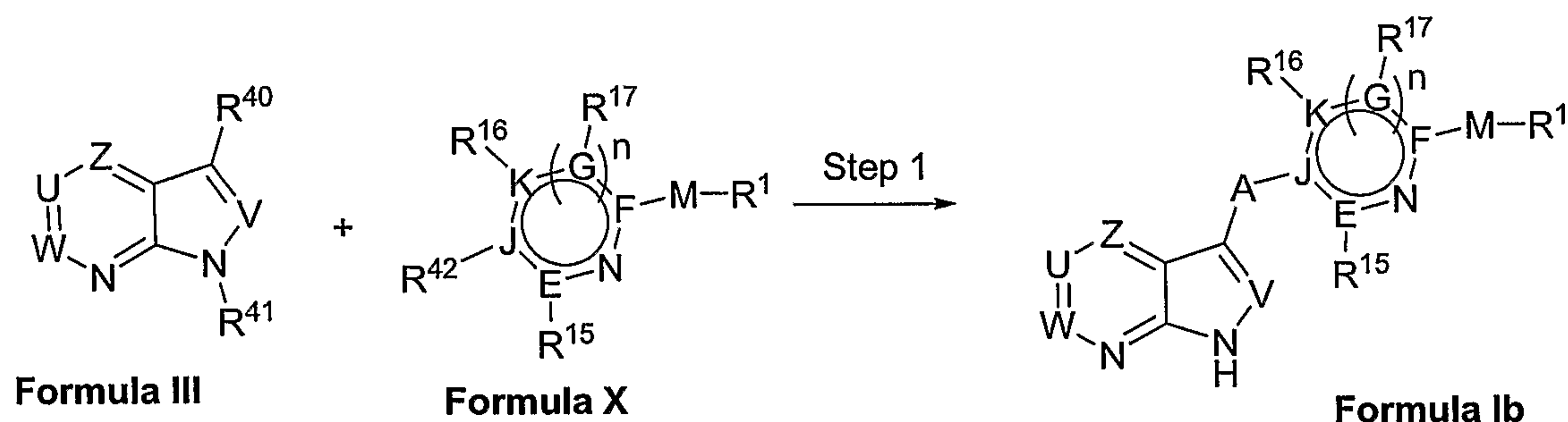


Formula Ib

wherein U, V, W, Z, R<sup>1</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, A, M, E, G, J, K, F and n are as defined in Formula Ib of [0025] are described in the schemes and examples below. While the methods described below are shown in terms of Formula Ib, it would be clear to one skilled in the art that the methods may be used to prepare compounds of either Formula I or Formula Ib. With reference to the schemes and examples below, unless clearly specified to the contrary, Formula and compound enumeration are defined for each scheme or example independently of such enumeration in the specification above, although general reference to Formula I and Ib indicate the Formulae above described in [0012] and [0026], respectively.

[0476] Compounds of Formula Ib can be prepared from compounds of Formula III and Formula X as described in Scheme 39.

**Scheme 39:**

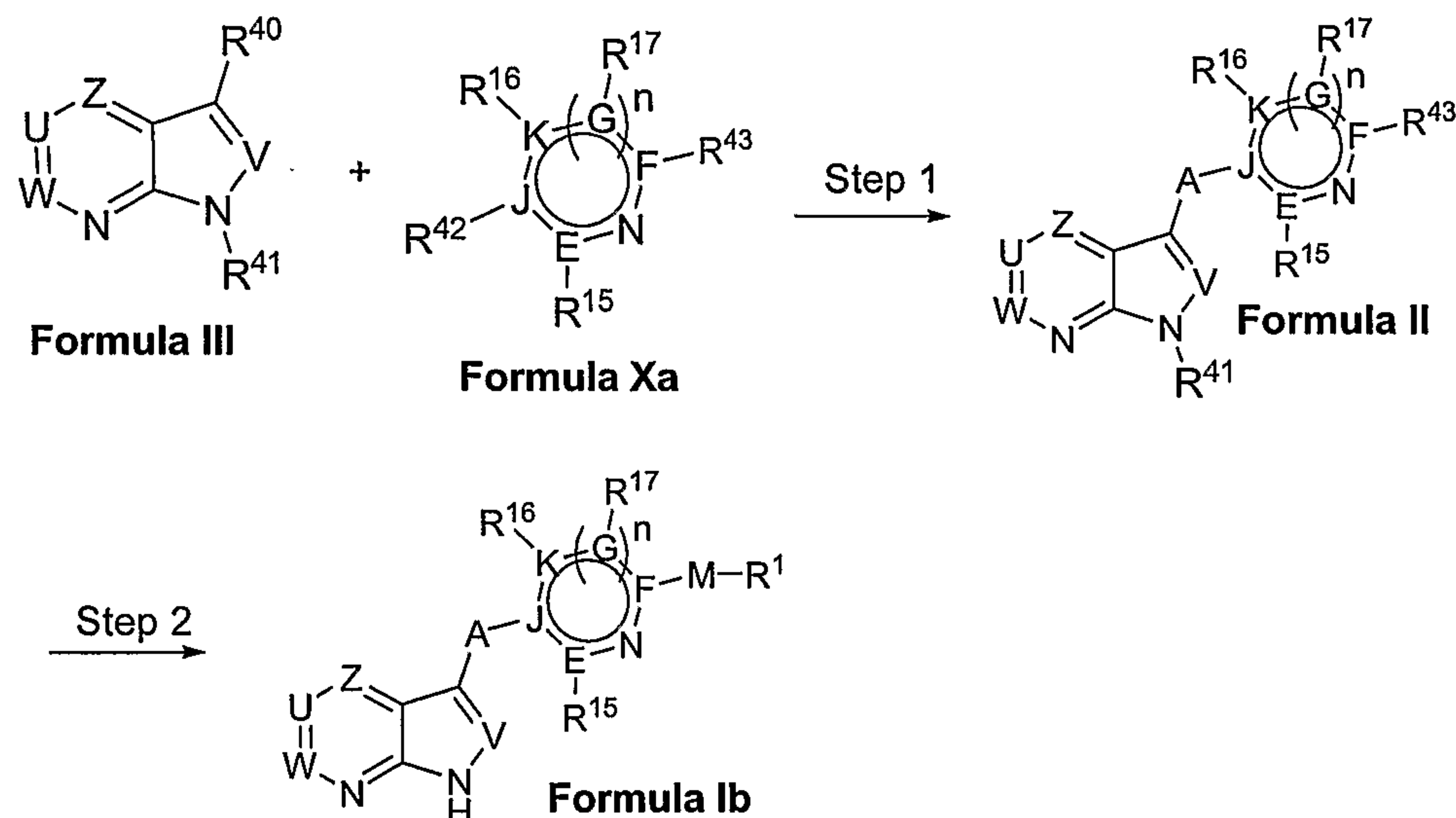


[0477] Compound of Formula III, where R<sup>41</sup> is either hydrogen or a protecting group P (e.g. phenylsulfone, *t*-butyloxycarbonyl, triisopropylsilyl) and R<sup>40</sup> is either hydrogen or a functional group appropriate for the coupling (e.g. Br, SH, OH, CHO etc.) is reacted with compound of Formula X where R<sup>42</sup> is a functional group appropriately chosen, based on R<sup>40</sup>, to form the linkage A using standard coupling conditions known to one skilled in the art to provide a compound of Formula Ib.

[0478] Compounds of Formula Ib can be prepared from compounds of Formula III and Formula Xa, where R<sup>43</sup> is a functional group appropriate for introduction of M-R<sup>1</sup>, is described in Scheme 40.



## Scheme 40:



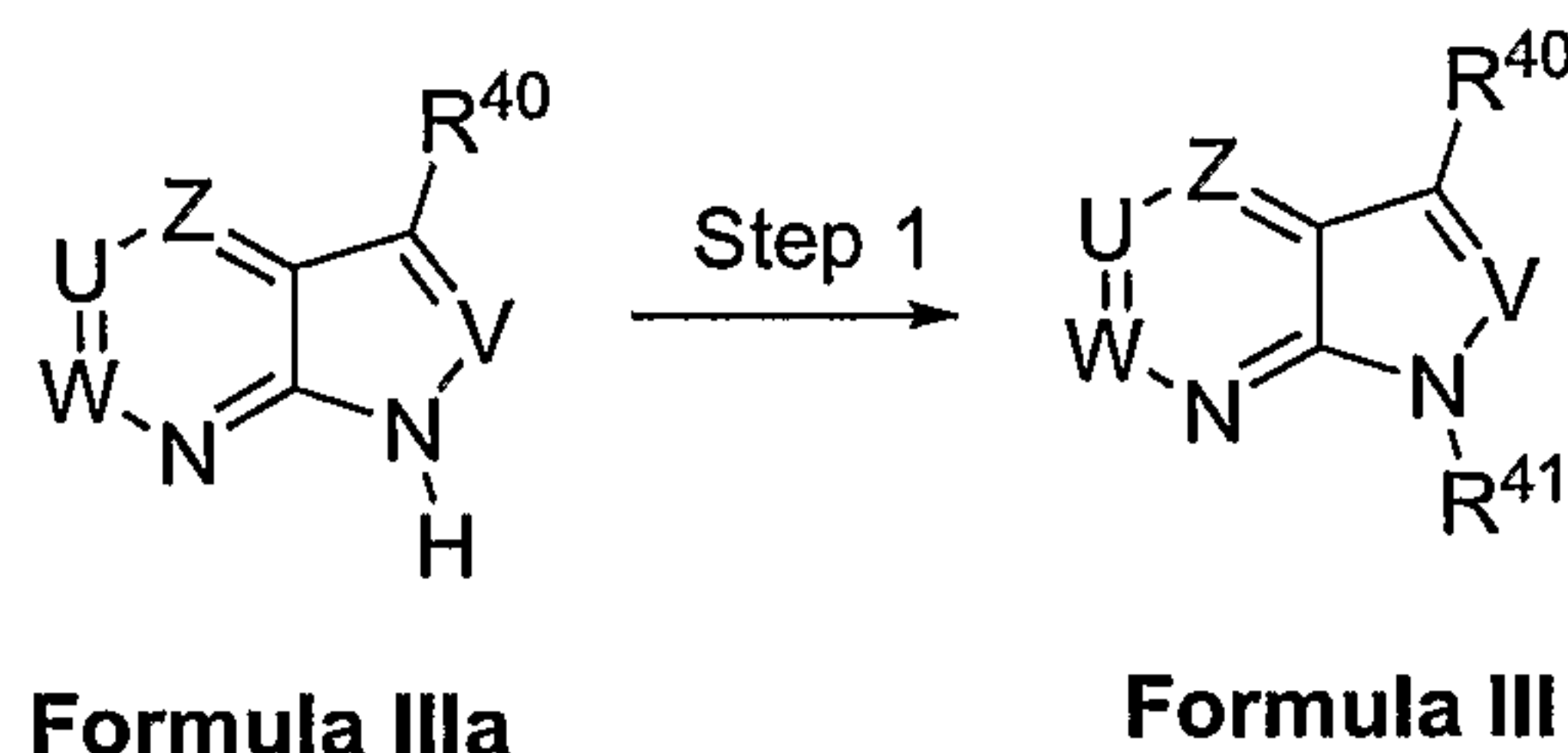
[0479] Compound of Formula III, where R<sup>41</sup> is either hydrogen or a protecting group P (e.g. phenylsulfone, *t*-butyloxycarbonyl, triisopropylsilyl) and R<sup>40</sup> is either hydrogen or a functional group appropriate for the coupling (e.g. Br, SH, OH, CHO etc.,) is reacted with compound of Formula Xa where R<sup>42</sup> is a functional group appropriately chosen, based on R<sup>40</sup>, and R<sup>43</sup> is a functional group appropriate to introduce M-R<sup>1</sup>, to form the linkage A using standard coupling conditions known to one skilled in the art to provide compound of Formula II. Compound of Formula II is further functionalized to introduce M-R<sup>1</sup> using conditions known to one skilled in the art to provide compound of Formula Ib.

[0480] Steps 1 and 2 of Scheme 40 may be reversed such that compounds of Formula X are prepared from compounds of Formula Xa by methods of Step 2, followed by coupling of the resulting compounds of Formula X with compounds of Formula III following the methods of Step 1.

[0481] Many compounds of Formula X or Xa of Scheme 39 or 40 are commercially available or may be prepared in many different routes known in the literature, depending upon the specific ring system and substitution pattern that is desired, including substitution of nitrogen containing heterocycles, as well as *de novo* synthesis of the aromatic heterocycle.

[0482] General synthesis of compound of Formula III of Scheme 39 or 40 where R<sup>40</sup> is H or a functional group appropriate for coupling to compounds of Formula X or Xa (e.g. aldehyde, carboxylic acid, amine) is described in Scheme 41.

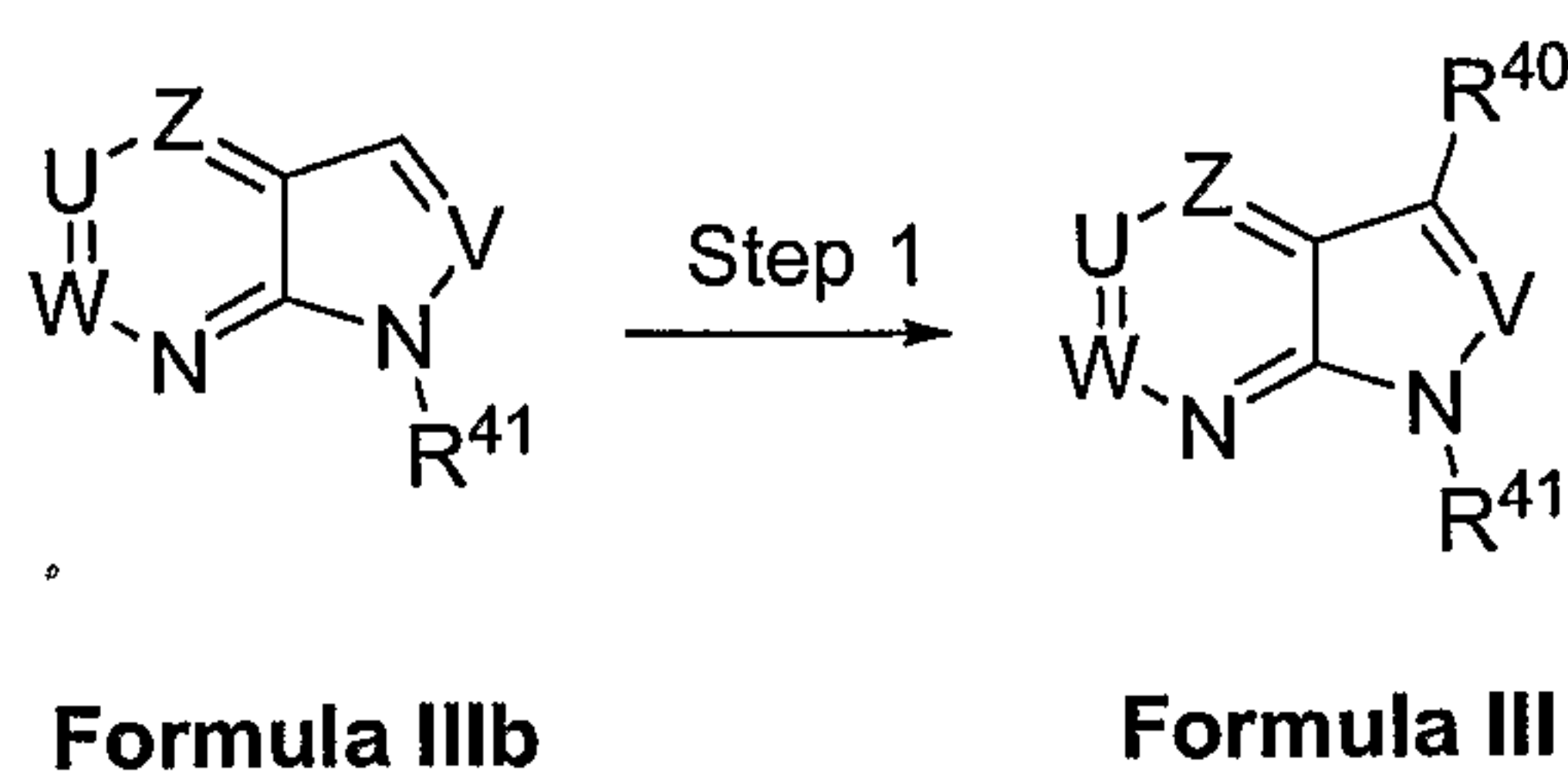
**Scheme 41:**



[0483] Compounds of Formula IIIa, where U or Z is C-Br, C-Cl, C-NO<sub>2</sub> or C-NH<sub>2</sub>, can be generally prepared from commercially available appropriate single heterocyclic ring or fused two ring heterocyclic compounds using methods known to one skilled in the art. Compound of Formula IIIa is further subjected to modification to provide appropriately substituted compounds of Formula III, where U or Z is C-Br, C-Cl, C-NO<sub>2</sub> or C-NH<sub>2</sub>, and R<sup>41</sup> is H or protecting group P, using methods known to one skilled in the art.

[0484] General synthesis of compound of Formula III of Scheme 39 or 40 from compound of Formula IIIb, where R<sup>40</sup> is H, is described in Scheme 42.

**Scheme 42:**



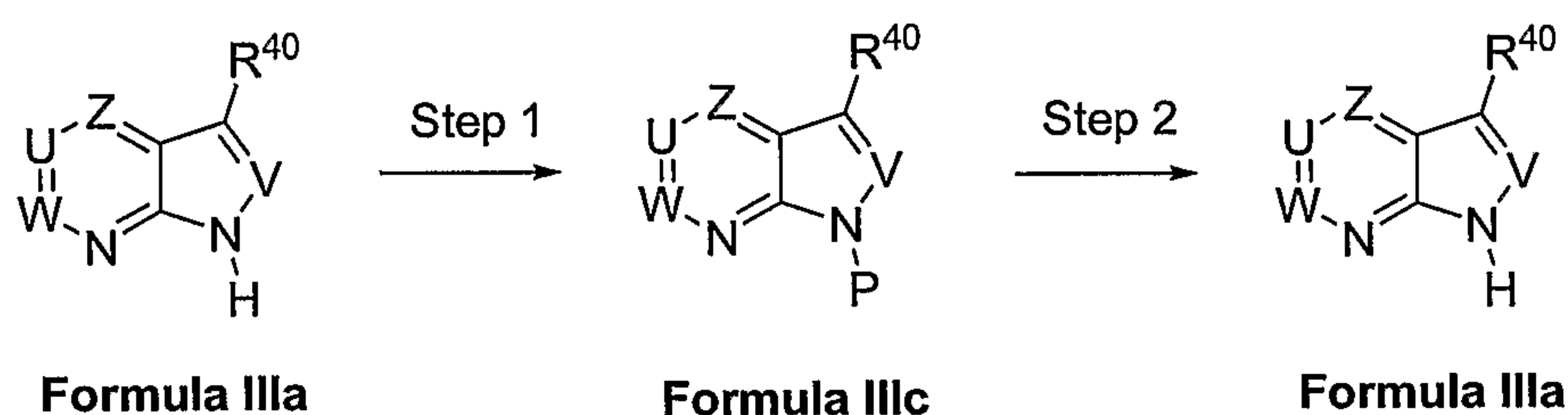
[0485] Compounds of Formula III, where R<sup>41</sup> is either hydrogen or a protecting group P and R<sup>40</sup> is appropriate for coupling to compounds of Formula X or Xa of Scheme 39 or 40 (e.g. aldehyde, carboxylic acid, amine) or appropriate for modification to such substituents (e.g. ester, nitro) may also be prepared from compounds of Formula IIIb (here R<sup>40</sup> is H) using synthetic methods known to one skilled in the art, for example as described by Merour and Joseph in *Curr. Org. Chem.* 2001, 5:471-506.



[0486] In addition to these schemes, the reactions shown in the following Examples may be combined in different sequences to provide compounds of Formula Ib. The transformations shown in Schemes 39-42 and the following Schemes and Examples as a single step should be considered to represent the general overall transformation, as some specific cases may require more than one reaction step to realize the desired compound.

[0487] In the preparation of compounds of Formula Ib, Formula II and Formula III it may frequently be advantageous to substitute the hydrogen of the N-H in the 7-azaindole or its analog with a protecting group as exemplified in Scheme 43, Step 1. The protecting group can then be removed when appropriate to reveal the N-H according to Step 2.

**Scheme 43:**



*Step 1 – Preparation of Formula IIIc where  $R^{41}$  is a protecting group P*

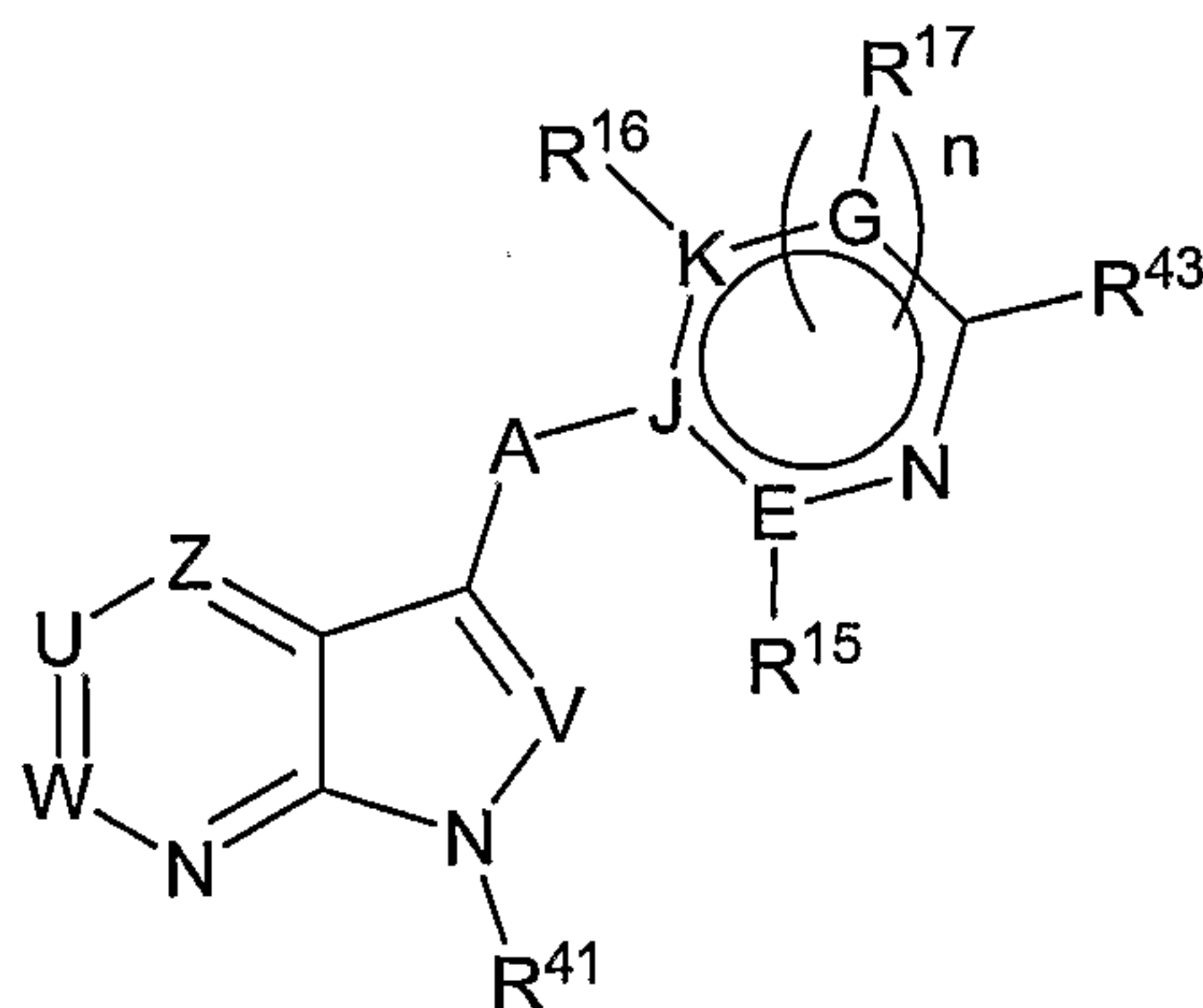
[0488] Compound of Formula IIIc where  $R^{41}$  is a protecting group P may be prepared by dissolving compound of Formula IIIa where  $R^{41}$  is hydrogen in a non-reactive solvent (e.g. dimethylformamide, tetrahydrofuran) and adding a base (e.g. aqueous sodium hydroxide, sodium hydride) and possibly a catalyst (e.g. tetrabutylammonium hydrogen sulfate). A reagent appropriate for the introduction of the protecting group (e.g. phenylsulfonyl chloride, triisopropylsilyl chloride, Boc anhydride) is then added and the reaction is allowed to stir for one to several hours. Isolation and purification by conventional means (e.g. extraction, silica gel chromatography) provides compounds of Formula IIIc where  $R^{43}$  is a protecting group.

*Step 2 – Preparation of Formula IIIa where  $R^{41}$  is hydrogen*

[0489] Compound of Formula IIIa where  $R^{41}$  is hydrogen may be prepared by dissolving compound of Formula IIIc where  $R^{41}$  is a protecting group P in a suitable solvent (e.g. ethanol, tetrahydrofuran, dichloromethane) and adding a reagent appropriate for the removal of the protecting group (e.g. potassium hydroxide, tetrabutylammonium fluoride, trifluoroacetic acid). The reaction is allowed to stir for 30 minutes to several hours with

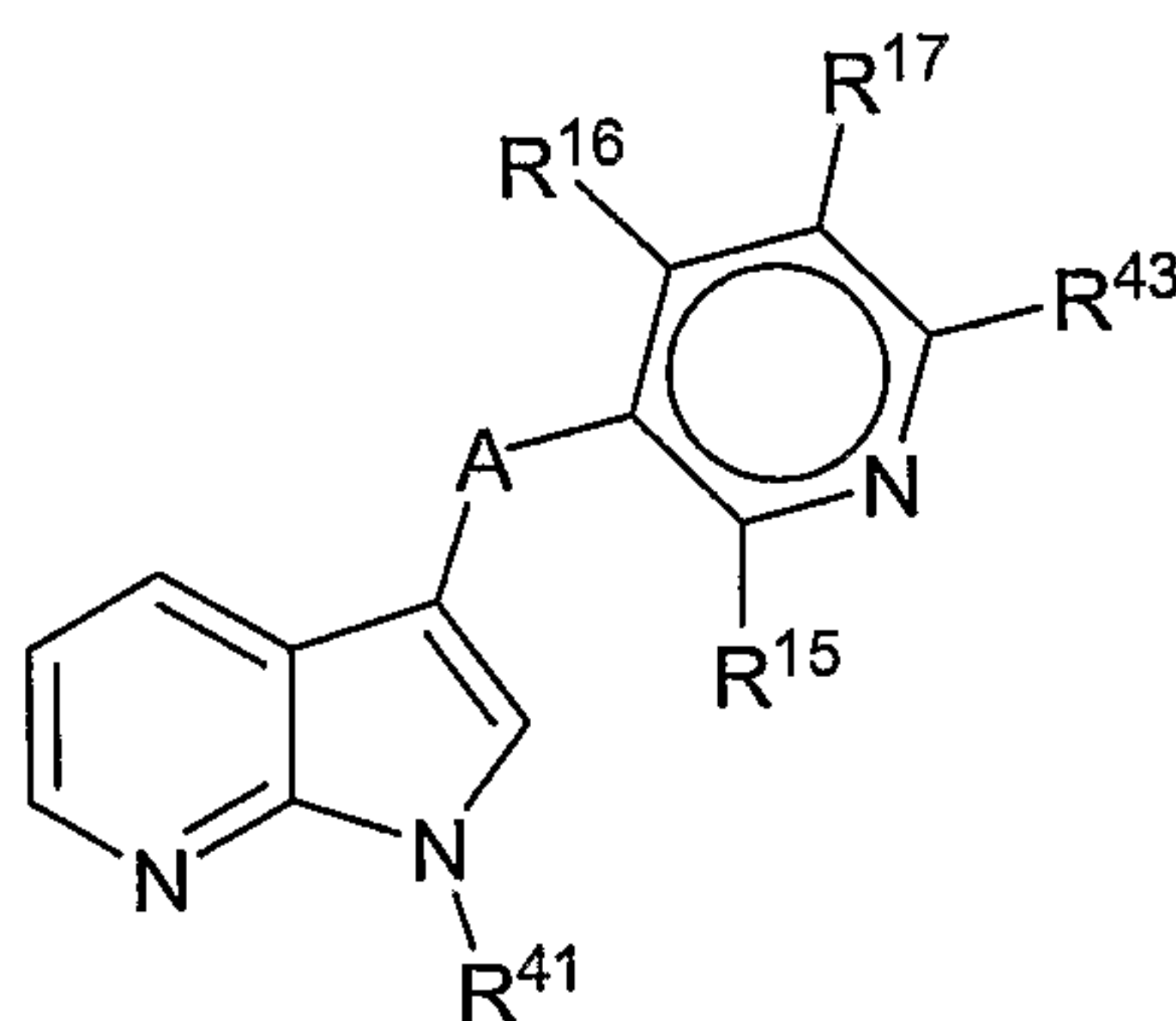
heating. Isolation and purification by conventional means (e.g. extraction, silica gel chromatography) provides compounds of Formula IIIa where  $R^{43}$  is hydrogen.

[0490] Compounds of Formula II above are similar to compounds of Formula Ib as shown, where  $R^{43}$  is defined as  $M-R^1$  or a substituent appropriate for further substitution to provide  $M-R^1$ , and  $R^{41}$  is hydrogen or a protecting group P.



Formula II

[0491] Compounds of Formula II where U, V, W, Z, J, E, F, G, K are C and n is 1 form compounds of Formula IIa below.



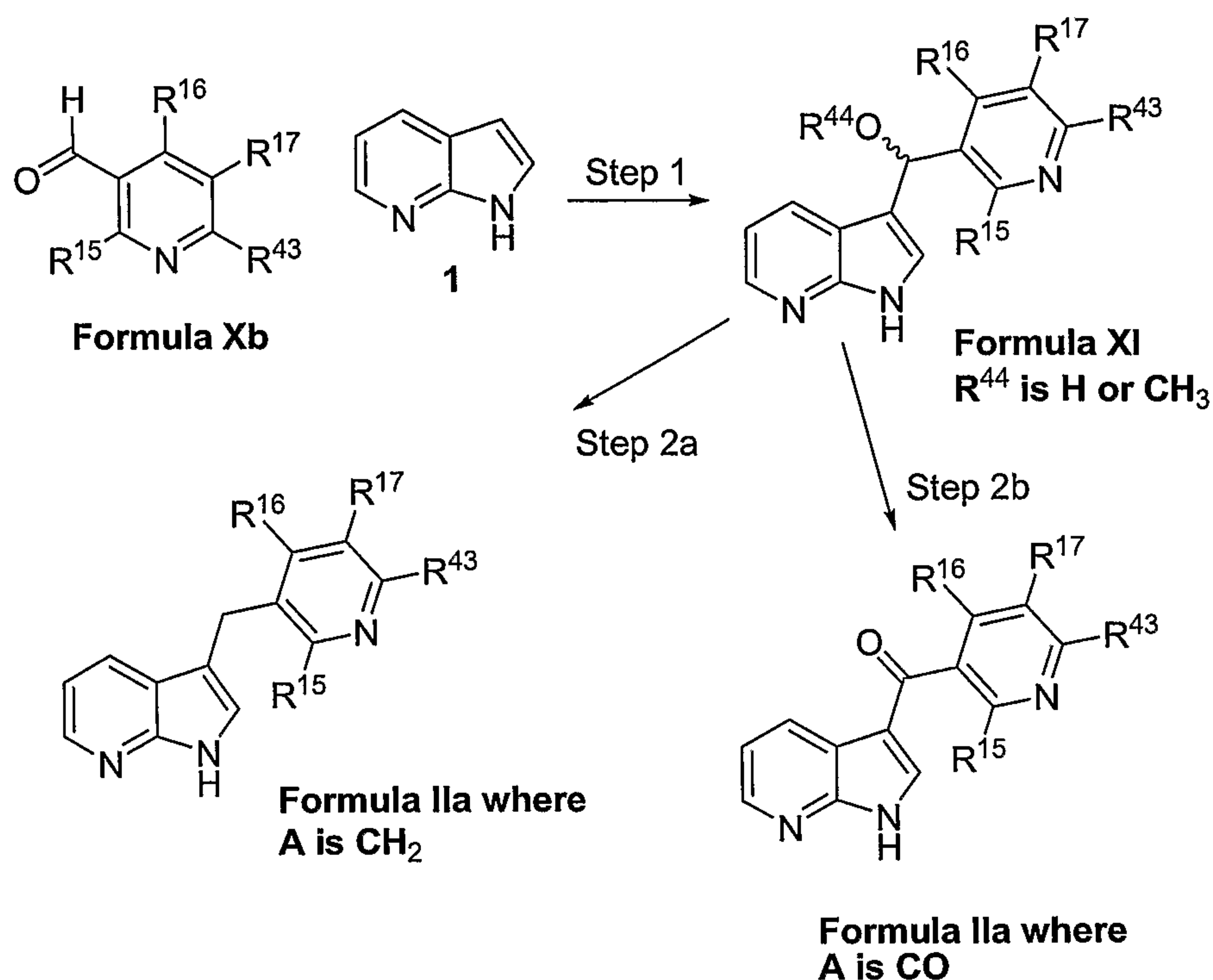
Formula IIa

[0492] The examples provided for the synthesis of compounds of Formula IIa are also applicable to many compounds meeting other definitions of Formula Ib and Formula II. For example, 7-azaindole, Compound 1, may be replaced in these syntheses by compounds where U, V, W, and Z are other than C-H.



**Example 43: Synthesis of compounds of Formula IIa, where A is CH<sub>2</sub> or C(O)**

[0493] Compounds of Formula IIa, where A is CH<sub>2</sub> or C(O) may be synthesized from compounds of Formula Xb (Formula Xa wherein R<sup>42</sup> is C(O)H, J, E, F, G and K are C and n is 1) and compound 1 in two Steps according to Scheme 100.

**Scheme 100**

*Step 1 – Preparation of Formula XI where R<sup>44</sup> is hydrogen or methyl*

[0494] To 7-azaindole 1 and a compound of Formula Xb is added an appropriate solvent (e.g. polar solvents such as methanol, tetrahydrofuran, and acetonitrile, or apolar solvents such as toluene) followed by an appropriate hydroxide or alkoxide base (e.g. potassium hydroxide, sodium methoxide). The reaction is typically allowed to stir at room temperature overnight. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula XI where R<sup>44</sup> is hydrogen or compounds of Formula XI where R<sup>44</sup> is methyl when methanol is used as a solvent, or a mixture of compounds of Formula XI where R<sup>44</sup> is hydrogen or methyl when methanol is used as a solvent. A resulting mixture may be separated by chromatography or used as a mixture in Step 2.

*Step 2a – Preparation of Formula IIa where A is CH<sub>2</sub>*

[0495] To a compound of Formula XI where R<sup>44</sup> is hydrogen or methyl, in an appropriate polar solvent, (e.g. acetonitrile) is added a reducing agent (e.g. trifluoroacetic acid and triethylsilane). Typically, the reaction is allowed to stir at room temperature overnight. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIa where A is CH<sub>2</sub> and R<sup>41</sup> is H.

*Step 2b – Preparation of Formula IIa where A is C(O)*

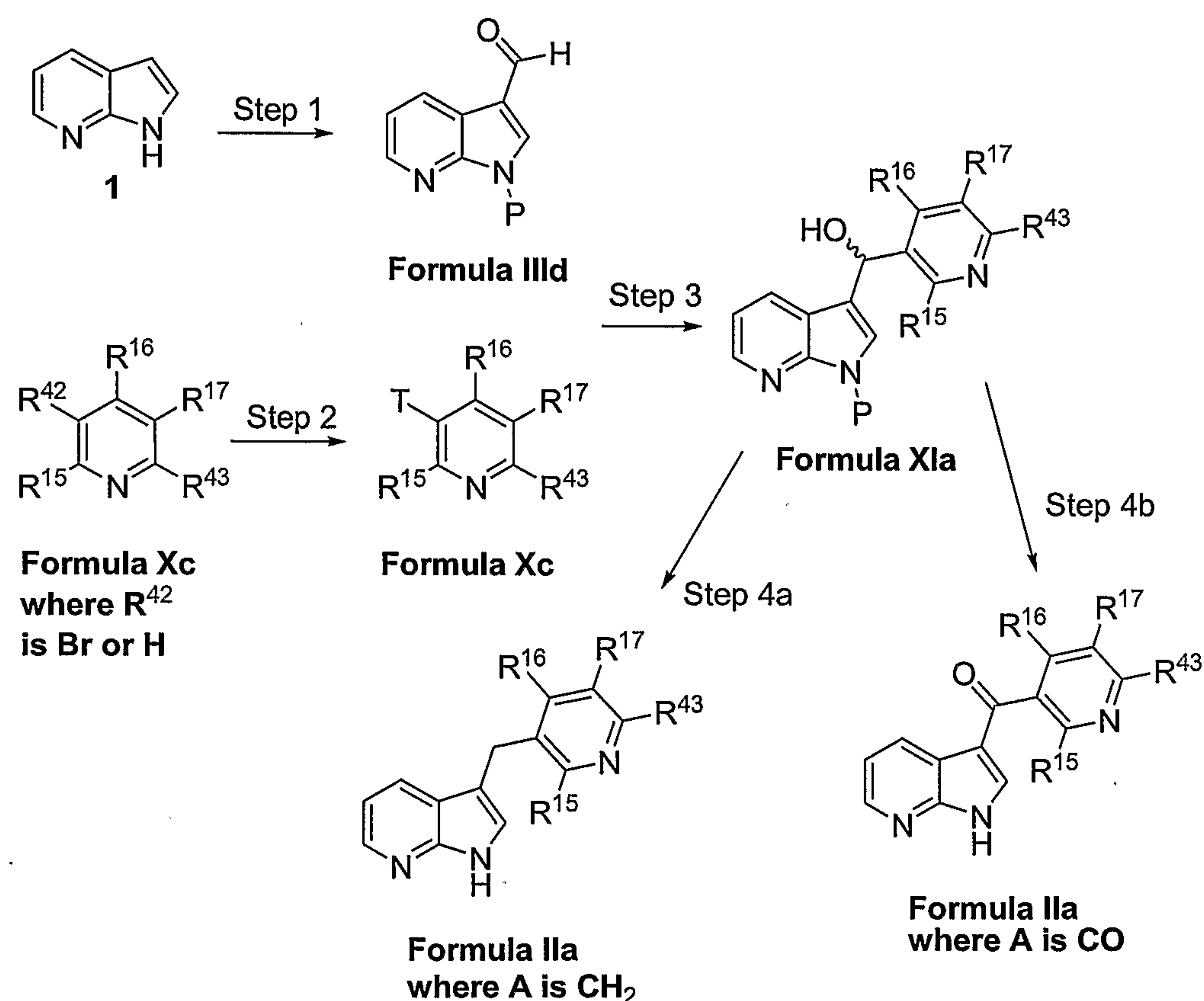
[0496] Compound of Formula IIa where A is C(O) is prepared by oxidizing a compound of Formula XI where R<sup>44</sup> is hydrogen with an appropriate oxidizing agent (e.g. Dess-Martin reagent, TEMPO) in a non-reactive solvent (e.g. tetrahydrofuran). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is C(O) and R<sup>41</sup> is H.

[0497] The reaction of Scheme 100 may be applied generally to compounds of Formula Xa, and also by replacing 7-azaindole 1, with 7-azaindoles substituted at the 4, 5, or 6 positions, preferable the 4 or 5 positions, to provide compounds of Formula I wherein X<sub>1</sub> is CH and X<sub>2</sub>, Y<sub>1</sub> and Y<sub>2</sub> are CR<sup>6</sup>, CR<sup>4</sup> and CR<sup>5</sup>, respectively, or Formula Ib wherein V and W are CH and U and Z are independently CR<sup>18</sup>. The compound of Formula Xa may be commercially available, or may be synthesized following the protocols of Examples herein. As such, a compound of Formula IIa where A is CH<sub>2</sub> (or analogous Formula I, Formula Ib) is prepared by reacting a 7-azaindole compound, optionally substituted at the 4, 5 or 6 position, with a suitable heteroaryl aldehyde (Formula Xa wherein R<sup>42</sup> is C(O)H) in an appropriate solvent (e.g. methanol, tetrahydrofuran, acetonitrile, toluene) with a hydroxide or alkoxide base (e.g. potassium hydroxide, sodium methoxide). The resulting compound is reacted in a polar solvent (e.g. acetonitrile) under reducing conditions to provide the desired compound. A compound of Formula IIa where A is C(O) (or analogous Formula I, Formula Ib) is prepared by reacting a 7-azaindole compound, optionally substituted at the 4, 5 or 6 position, with a suitable heteroaryl aldehyde (Formula Xa wherein R<sup>42</sup> is C(O)H) in an appropriate solvent (e.g. methanol, tetrahydrofuran, acetonitrile, toluene) with a hydroxide or alkoxide base (e.g. potassium hydroxide, sodium methoxide). From the resulting compound, the alcohol intermediate (e.g. Formula XI where R<sup>44</sup> is OH) is isolated and reacted in a non-reactive solvent (e.g. tetrahydrofuran) under oxidizing conditions to provide the desired compound.



**Example 44: Synthesis of compounds of Formula IIa, where A is CH<sub>2</sub> or C(O)**

[0498] Compounds of Formula IIa, where A is CH<sub>2</sub> or C(O) may also be synthesized from compounds of Formula Xc (Formula Xa wherein J, E, F, G and K are C, n is 1, and R<sup>42</sup> is an organometallic substituent T) and compound IIIId (Formula III wherein U, V, W and Z are CH, R<sup>40</sup> is C(O)H and R<sup>41</sup> is P) in four Steps according to Scheme 101.

**Scheme 101***Step 1 – Preparation of Formula IIIId*

[0499] 7-azaindole **1** is treated with hexamethyltetramine and acetic acid in water with heating to reflux for a few hours to introduce an aldehyde at the 3-position. This intermediate is isolated by concentration and extraction. A protecting group P is added to the N-1 position of the intermediate as described in Scheme 43, Step 1 to provide compound of Formula IIIId.

*Step 2 – Preparation of Formula Xc where R<sup>42</sup> is T*

[0500] Compound of Formula Xc where R<sup>42</sup> is an organometallic substituent T (e.g. lithium, MgBr) is obtained by treating compound of Formula Xc, where R<sup>42</sup> is bromine,

with an organolithium reagent (e.g. butyllithium) or magnesium, or via ortholithiation with an organolithium reagent (e.g. butyllithium) when  $R^{42}$  is hydrogen, in a non-reactive solvent (e.g. tetrahydrofuran), typically at reduced temperature (e.g.  $-78\text{ }^{\circ}\text{C}$ ) and used in Step 3 without isolation.

*Step 3 – Preparation of Formula XIa*

[0501] Compound of Formula Xc where  $R^{42}$  is T is added to compound of Formula IIIc in a non-reactive solvent (e.g. tetrahydrofuran) at reduced temperature (e.g.  $-78\text{ }^{\circ}\text{C}$ ) and stirred for several hours. After warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula XIa.

*Step 4a – Preparation of Formula IIa where A is  $\text{CH}_2$*

[0502] To a compound of Formula XIa, in an appropriate polar solvent, (e.g. acetonitrile) is added a reducing agent (e.g. trifluoroacetic acid and triethylsilane). Typically, the reaction is allowed to stir at room temperature overnight. Isolation by conventional means (e.g. extraction and silica gel chromatography), followed by deprotection of the N-P according to Scheme 43, Step 2 provides compounds of Formula IIa where A is  $\text{CH}_2$  and  $R^{41}$  is H.

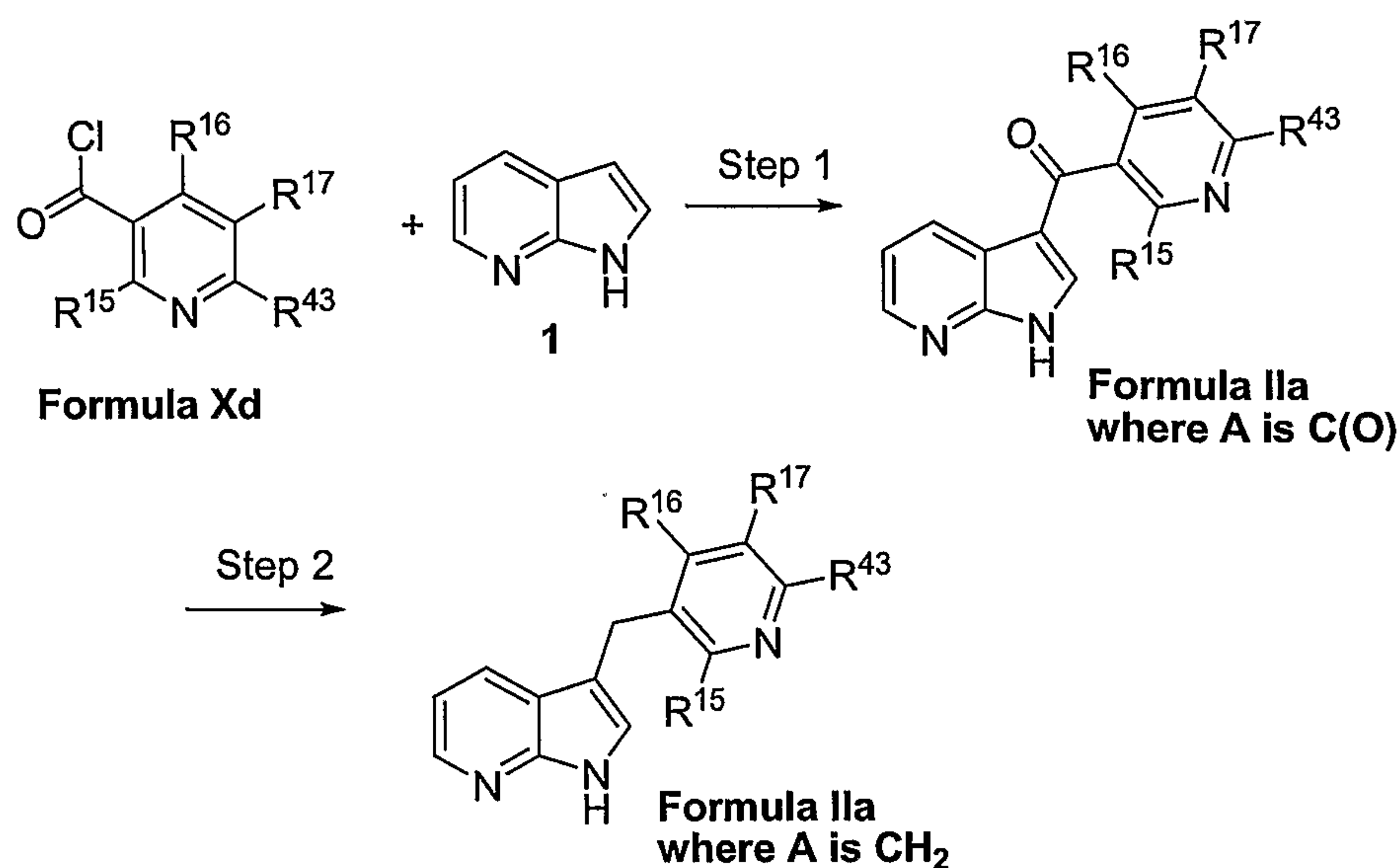
*Step 4b – Preparation of Formula IIa where A is  $\text{C}(\text{O})$*

[0503] Compound of Formula IIa where A is  $\text{C}(\text{O})$  is prepared from compound of Formula XIa following the protocol of Example 43, Step 2b, followed by deprotection according to Scheme 43, Step 2 to provide compound where  $R^{41}$  is H.

**Example 45: Synthesis of compounds of Formula IIa, where A is  $\text{C}(\text{O})$  or  $\text{CH}_2$**

[0504] Compounds of Formula IIa, where A is  $\text{C}(\text{O})$  or  $\text{CH}_2$ , may be synthesized from compounds of Formula Xd (Formula Xa wherein J, E, F, G and K are C, n is 1, and  $R^{42}$  is  $\text{C}(\text{O})\text{Cl}$ ) and compound 1 in one and two Steps, respectively, according to Scheme 102.



**Scheme 102***Step 1 – Preparation of Formula IIa where A is C=O*

**[0505]** Compound of Formula IIa where A is a carbonyl is prepared by reacting compound **1** with an acid chloride of Formula Xd in the presence of a Lewis acid (e.g. aluminum trichloride) in a non-reactive solvent (e.g. dichloromethane) with stirring at room temperature for several hours. The reaction may be quenched with methanol and isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is C=O and R<sup>41</sup> is H.

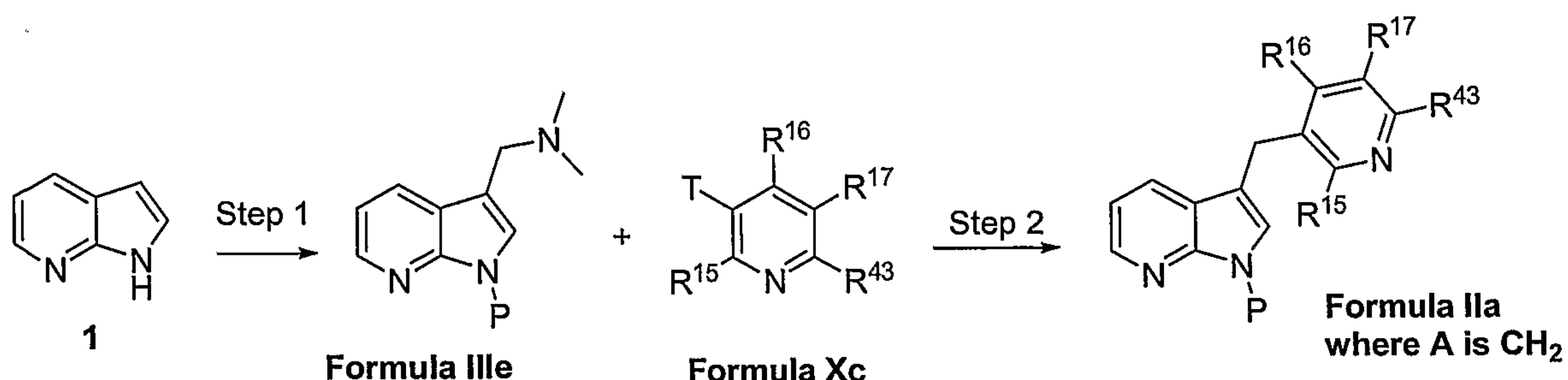
*Step 2 – Preparation of Formula IIa where A is CH<sub>2</sub>*

**[0506]** Compound of Formula IIa where A is CH<sub>2</sub> may be prepared by reacting compound IIa where A is C(O) with a reducing agent (e.g. lithium aluminum hydride) in a non-reactive solvent (e.g. tetrahydrofuran) for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is CH<sub>2</sub> and R<sup>41</sup> is H.

**Example 46: Synthesis of compounds of Formula IIa, where A is CH<sub>2</sub>**

**[0507]** Compounds of Formula IIa, where A is CH<sub>2</sub> may be synthesized from compound **1** in two Steps according to Scheme 103.

## Scheme 103

*Step 1 – Preparation of Formula IIIe*

[0508] Compound of Formula IIIe (Formula III where U, V, W and Z are CH,  $R^{41}$  is P and  $R^{40}$  is  $\text{CH}_2\text{N}(\text{CH}_3)_2$ ) is synthesized from compound **1** following the literature procedure (Robinson, J. Am. Chem. Soc., **1955**, 77, p. 457), followed by protection of the N-H according to Scheme 43, Step 1.

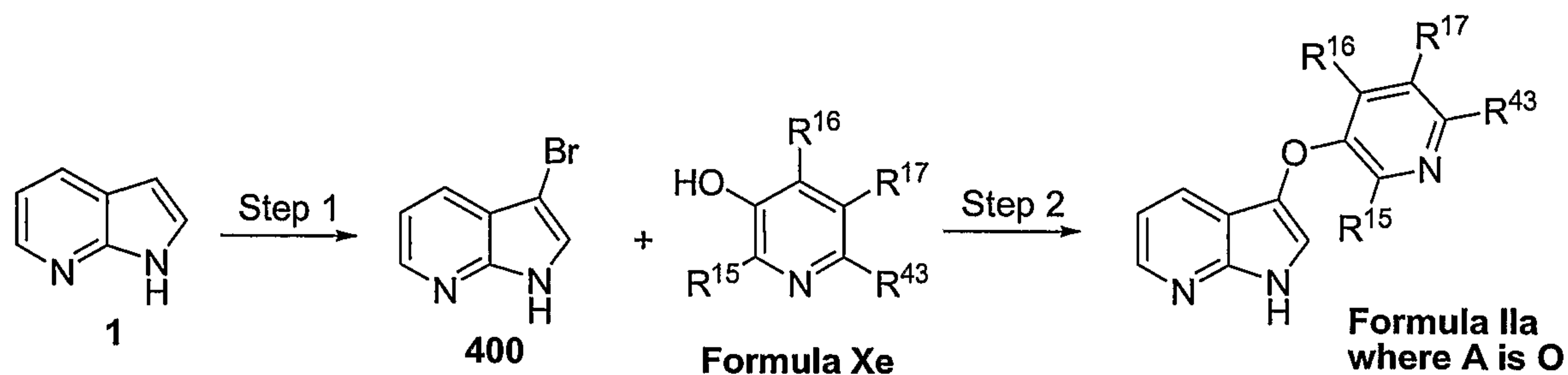
*Step 2 – Preparation of Formula IIa where A is CH<sub>2</sub>*

[0509] Compounds of Formula IIa where A is  $\text{CH}_2$  is synthesized through the reaction of compounds of Formula IIIe with isopropyl chloroformate (or ethyl chloroformate) at room temperature in toluene to give a 3-chloromethyl intermediate. This intermediate, cooled to  $-78\text{ }^\circ\text{C}$ , is reacted with an organocopper reagent of Formula Xc where  $R^{42}$  is the metal (prepared as described in Example 44, step 2) and a solution of copper cyanide and lithium chloride. The reaction may be stirred at  $-78\text{ }^\circ\text{C}$  for one hour then allowed to warm to room temperature and quenched with a solution of 4:1 ammonium chloride: ammonium hydroxide. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is  $\text{CH}_2$  and  $R^{41}$  is P, which can be removed according to Scheme 43 Step 2 to provide the compound where  $R^{41}$  is H.

**Example 47: Synthesis of compounds of Formula IIa, where A is O**

[0510] Compounds of Formula IIa, where A is O may be synthesized from compound **1** in two Steps according to Scheme 104.



**Scheme 104***Step 1 - Preparation of Compound 400*

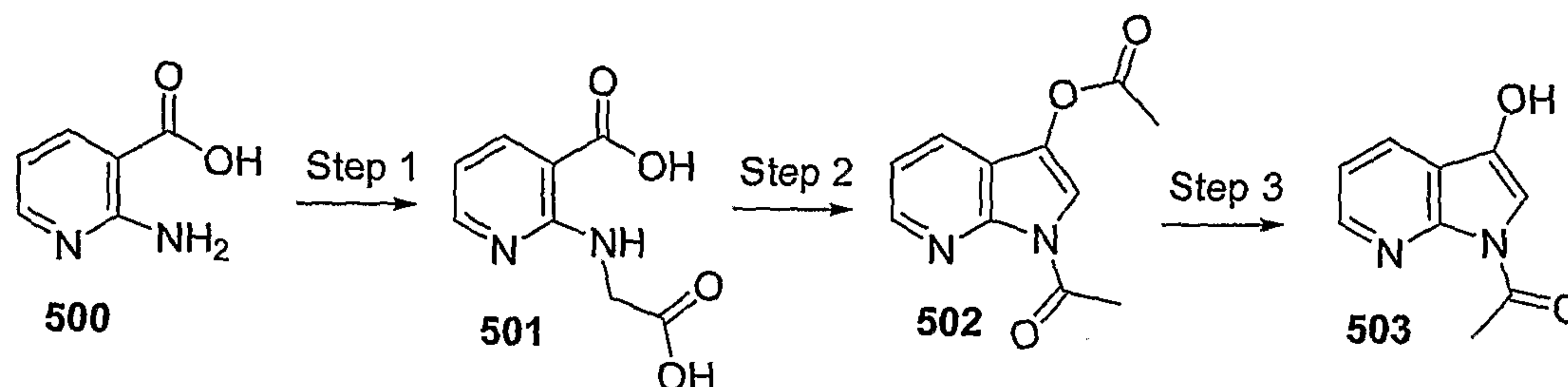
[0511] 3-bromo-7-azaindole **400** may be prepared by dissolving 7-azaindole **1** in chloroform and slowly adding Br<sub>2</sub> in carbon tetrachloride at 0 °C. After stirring for 1-2 hours, the reaction may be quenched in aqueous hydrochloric acid. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound **400**.

*Step 2 - Preparation of Formula IIa where A is O*

[0512] Compound of Formula IIa where A is O is prepared by reacting 3-bromo-7-azaindole **400**, protected at N-H according to Scheme 43, Step 1, with compound of Formula Xe (Formula Xa wherein J, E, F, G and K are C, n is 1, and R<sup>42</sup> is OH) in the presence of a base (e.g. sodium hydride) and a copper catalyst (e.g. copper bromide) in a non-reactive solvent (e.g. dimethylformamide) with heating (e.g. 120 °C) for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography), followed by removal of the protecting group according to Scheme 43, Step 2 provides compounds of Formula IIa where A is O and R<sup>41</sup> is H.

**Example 48: Synthesis of intermediate 1-(3-Hydroxy-pyrrolo[2,3-b]pyridin-1-yl)-ethanone (503)**

[0513] 1-(3-Hydroxy-pyrrolo[2,3-b]pyridin-1-yl)-ethanone **503** may be synthesized in three Steps from 2-Amino-nicotinic acid **500** as described in Scheme 105. The compound is an exemplary compound of Formula III wherein U, V, W and Z are CH, R<sup>40</sup> is OH and R<sup>41</sup> is P (e.g. acetyl).

**Scheme 105***Step 1 - Preparation of 2-(Carboxymethyl-amino)-nicotinic acid (501)*

[0514] 2-(Carboxymethyl-amino)-nicotinic acid **501** is prepared by reacting commercially available 2-Amino-nicotinic acid **500** with 2-chloroacetic acid in the presence of base (e.g. sodium carbonate) typically at room temperature for 1-4 hours followed by purification and isolation by conventional means (e.g. acid base extraction and recrystallization).

*Step 2 - Preparation of Acetic acid 1-acetyl-1H-pyrrolo[2,3-b]pyridin-3-yl ester (502)*

[0515] Acetic acid 1-acetyl-1H-pyrrolo[2,3-b]pyridin-3-yl ester **502** is prepared by reacting 2-(Carboxymethyl-amino)-nicotinic acid **501** with sodium acetate in refluxing acetic anhydride for several hours, followed by purification and isolation by conventional means (e.g. recrystallization) (Su & Tsou; *J. Am. Chem. Soc.*, 82, 1960, 1187).

*Step 3 - Preparation of 1-(3-Hydroxy-pyrrolo[2,3-b]pyridin-1-yl)-ethanone (503)*

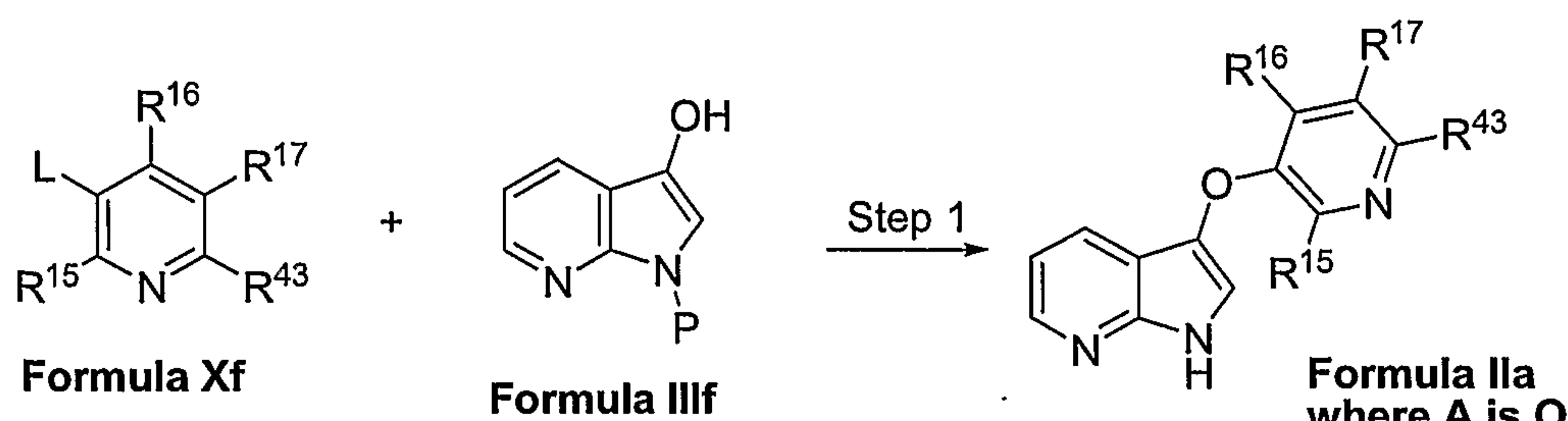
[0516] 1-(3-Hydroxy-pyrrolo[2,3-b]pyridin-1-yl)-ethanone **503** is prepared from acetic acid 1-acetyl-1H-pyrrolo[2,3-b]pyridin-3-yl ester **502** by selective removal of the acetate at the 3-position by reaction with sodium in methanol at room temperature typically for 30 minutes to one hour, followed by purification and isolation by conventional means (e.g. extraction and recrystallization).

**Example 49: Synthesis of compounds of Formula IIa, where A is O**

[0517] Compounds of Formula IIa, where A is O may be synthesized from compound of Formula IIIf (Formula III where U, V, W and Z are CH, R<sup>41</sup> is P and R<sup>40</sup> is OH) and compound of Formula Xf (Formula Xa wherein J, E, F, G and K are C, n is 1, and R<sup>42</sup> is leaving group L) in one Step according to Scheme 106.



## Scheme 106

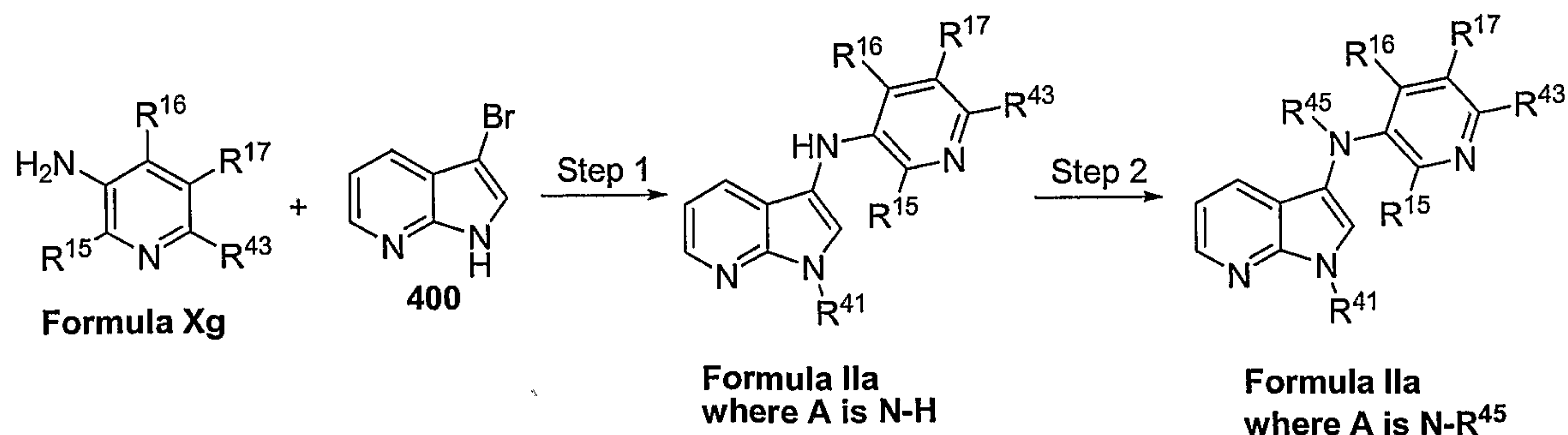
*Step 1 - Preparation of Formula IIa where A is O*

[0518] Formula IIa where A is O is prepared by dissolving compound of Formula Xf, where L is a leaving group (e.g. halogen or triflate), in a non-reactive solvent (e.g. dimethylformamide) in the presence of a base (e.g. sodium hydride). Compound of Formula IIIf is added in the presence of a copper catalyst (e.g. copper bromide) with heating for several hours. Removal of the protecting group according to Scheme 43, Step 2 followed by isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIa where A is O and R<sup>41</sup> is H.

**Example 50: Synthesis of compounds of Formula IIa, when A is NH or N-R<sup>45</sup>**

[0519] Compounds of Formula IIa, where A is NH or NR<sup>45</sup> (R<sup>45</sup> consistent with definition of A for compounds of Formula Ib or L<sup>1</sup> for compounds of Formula I) may be synthesized from 3-bromo-7-azaindole **400** and a compound of Formula Xg (Formula Xa wherein J, E, F, G and K are C, n is 1, and R<sup>42</sup> is NH<sub>2</sub>) in two Steps according to Scheme 107.

## Scheme 107



**Step 1 - Preparation of Formula IIa where A is NH**

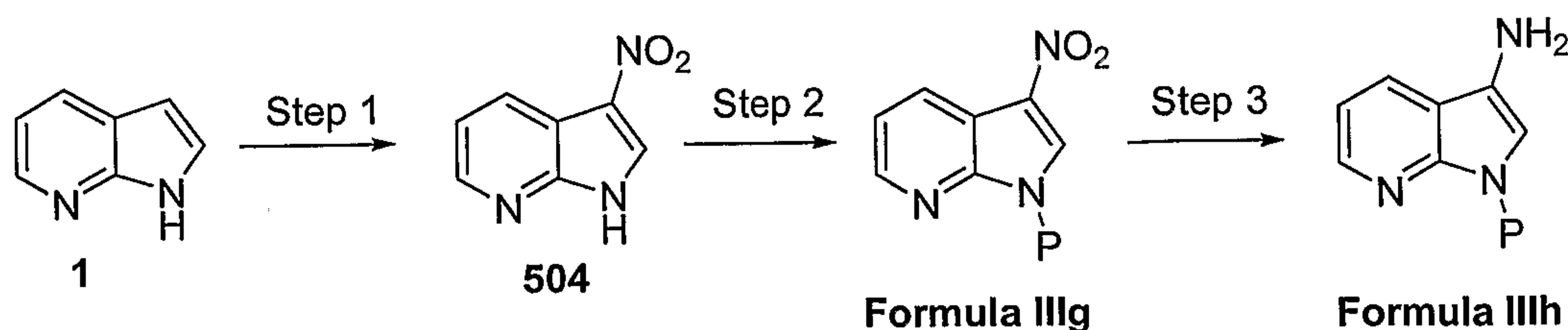
[0520] Compound of Formula IIa where A is NH is prepared by reacting 3-bromo-7-azaindole **400** with neat compound of Formula Xg with heating for several hours (e.g. 150 °C). Alternatively, **400** may be reacted with compound of Formula Xg using palladium catalyzed Buchwald-Hartwig conditions (i.e. a palladium catalyst (e.g. Tris(dibenzylideneacetone)dipalladium(0)), a ligand (e.g. tri-*t*-butylphosphine), and a base (e.g. sodium *t*-butoxide) in a non-reactive solvent (e.g. toluene) with heating (e.g. 80 °C) for several hours). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is NH and R<sup>41</sup> is P. Removal of the protecting group according to Scheme 43, Step 2 provides compounds of Formula IIa where A is NH and R<sup>41</sup> is H.

**Step 2 - Preparation of Formula IIa where A is N-R<sup>45</sup>**

[0521] Compound of Formula IIa where A is N-R<sup>45</sup> is prepared by reacting compound of Formula IIa, where R<sup>41</sup> is P and A is NH, with an appropriate reagent with a leaving group (e.g. methyl iodide, acetyl chloride) in the presence of a base (e.g. potassium carbonate, diisopropylethylamine) in a non-reactive solvent (e.g. dimethylformamide) for several hours at room temperature. Removal of the protecting group according to Scheme 43, Step 2 and isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is N-R<sup>45</sup> and R<sup>41</sup> is H.

**Example 51: Synthesis of intermediate of Formula IIIh where R<sup>40</sup> is NH<sub>2</sub>**

[0522] Compounds of Formula IIIh (Formula III where U, V, W and Z are CH, R<sup>41</sup> is H and R<sup>40</sup> is NH<sub>2</sub>) may be synthesized from 7-azaindole **1** in three Steps according to Scheme 108.

**Scheme 108**



**Step 1 - Preparation of 3-nitro-7-azaindole (504)**

[0523] 3-nitro-7-azaindole **504** is prepared by adding 7-azaindole **1** to fuming nitric acid while cooling (e.g. 0 °C). After stirring for one to several hours, water is carefully added and the mixture neutralized with saturated sodium bicarbonate. The solids are collected by filtration and dried to provide 3-nitro-7-azaindole **504**.

**Step 2 - Preparation of Formula IIIg**

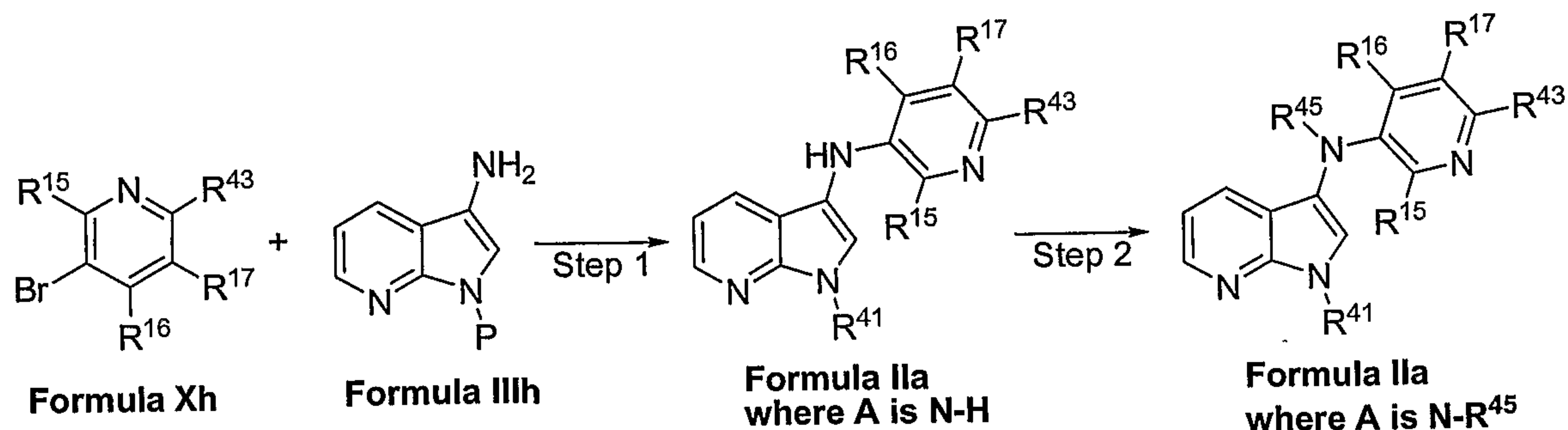
[0524] Compound of IIIg (Formula III where U, V, W and Z are CH, R<sup>41</sup> is H and R<sup>40</sup> is NH<sub>2</sub>) is prepared from 3-nitro-7-azaindole **504** according to Scheme 43, Step 1.

**Step 3 - Preparation of Formula IIIh**

[0525] Compound of Formula IIIh is prepared from compound of Formula IIIg by reduction of the nitro group (e.g. hydrogen gas and palladium on carbon in methanol). The mixture is filtered and concentrated to provide compound of Formula IIIh.

**Example 52: Synthesis of compounds of Formula IIa where A is NH or NR<sup>45</sup>**

[0526] Compounds of Formula IIa where A is NH or NR<sup>45</sup> (R<sup>45</sup> consistent with definition of A for compounds of Formula Ib or L<sup>1</sup> for compounds of Formula I) may be synthesized from a compound of Formula IIIh and a compound of Formula Xh (Formula Xa wherein J, E, F, G and K are C, n is 1, and R<sup>42</sup> is Br) in two Steps as described in Scheme 109.

**Scheme 109****Step 1 - Preparation of Formula IIa where A is NH**

[0527] Compound of Formula IIa where A is NH is prepared by reacting compound of Formula Xh with compound of Formula IIIh (prepared as described in Example 51) with heating for several hours (e.g. 100 °C). Alternatively, compound of Formula IIIh is

reacted with compound of Formula Xh using palladium catalyzed Buchwald-Hartwig conditions (i.e. a palladium catalyst (e.g. Tris(dibenzylideneacetone)dipalladium(0)), a ligand (e.g. tri-*t*-butylphosphine), and a base (e.g. sodium *t*-butoxide) in a non-reactive solvent (e.g. toluene) with heating (e.g. 80 °C) for several hours). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is NH and R<sup>41</sup> is P. Removal of the protecting group according to Scheme 43, Step 2 provides compounds of Formula IIa where A is NH and R<sup>41</sup> is H.

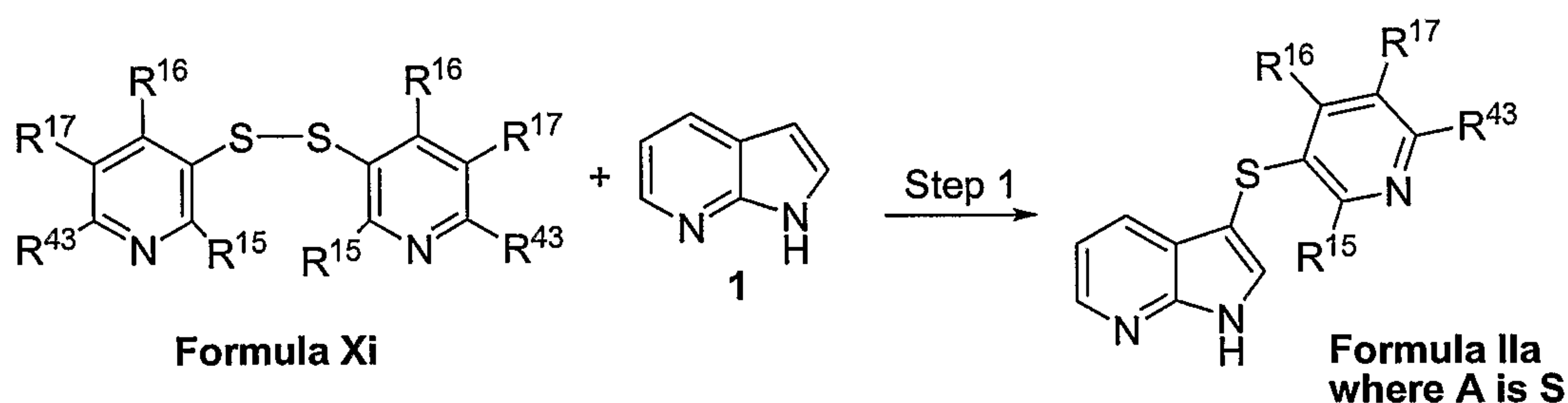
*Step 2 - Preparation of Formula IIa where A is N-R<sup>45</sup>*

[0528] Compound of Formula IIa where A is N-R<sup>45</sup> is prepared as described in Example 50, Step 2.

**Example 53: Synthesis of compounds of Formula IIa where A is S**

[0529] Compounds of Formula IIa where A is S may be synthesized from 7-azaindole **1** and a compound of Formula Xi (Formula Xa wherein J, E, F, G and K are C, n is 1, and R<sup>42</sup> is an aryl disulfide) in one Step as described in Scheme 110.

**Scheme 110**



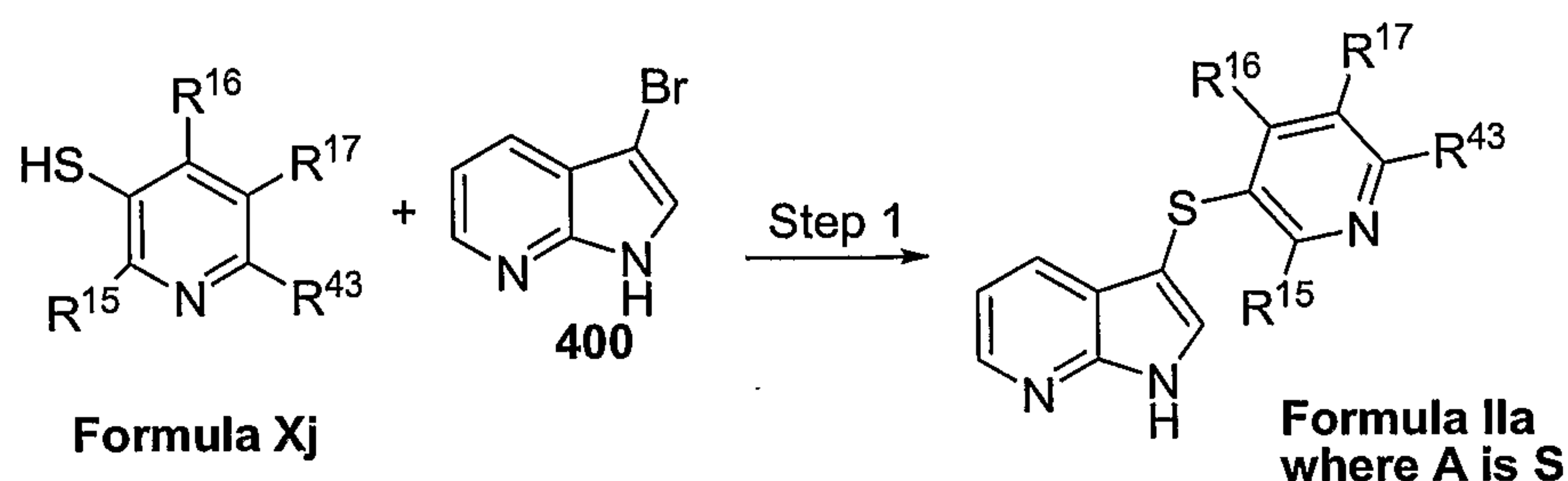
*Step 1 - Preparation of Formula IIa where A is S*

[0530] Compound of Formula IIa where A is S is prepared by dissolving 7-azaindole **1** in an appropriate solvent (e.g. dimethylformamide) with a base (e.g. sodium hydride), followed by the addition of a symmetrical aryl disulfide of Formula Xi. After sitting at room temperature for several hours, the reaction is quenched with water, followed by isolation by conventional means (e.g. extraction and silica gel chromatography) to provide compounds of Formula IIa where A is S and R<sup>41</sup> is H.



**Example 54: Synthesis of compounds of Formula IIa where A is S**

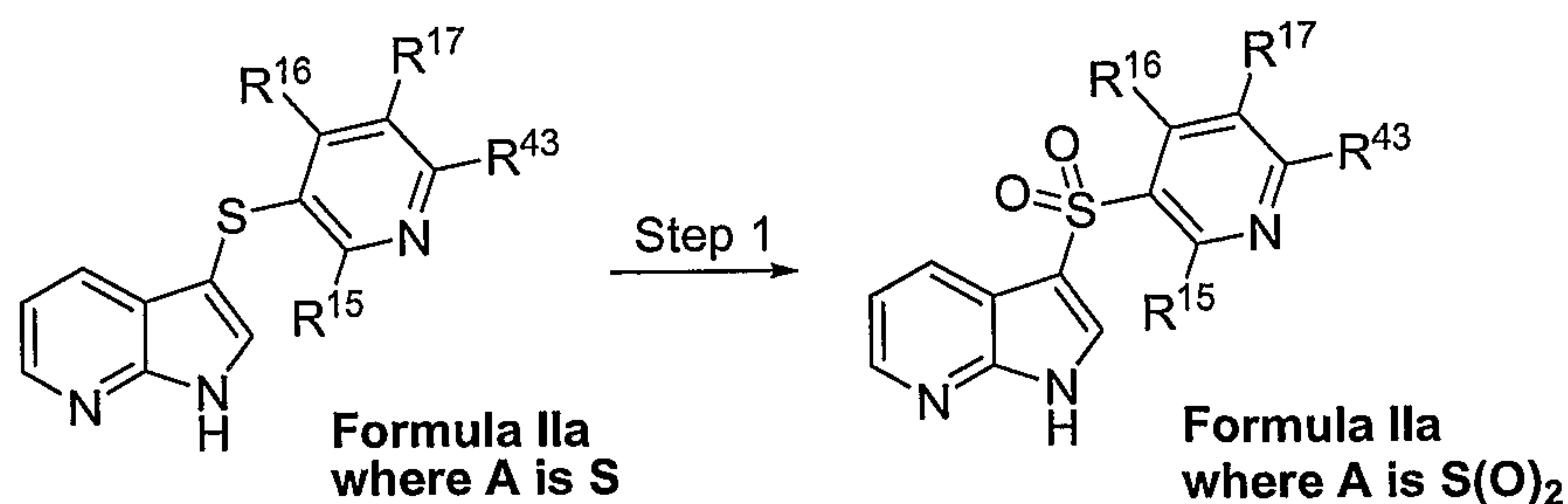
[0531] Compounds of Formula IIa where A is S may be synthesized from 3-bromo-7-azaindole **400** and a compound of Formula Xj (Formula Xa wherein J, E, F, G and K are C, n is 1, and R<sup>42</sup> is an SH) in one Step as described in Scheme 111.

**Scheme 111***Step 1 - Preparation of Formula IIa where A is S*

[0532] Compound of Formula IIa where A is S is prepared by reacting 3-bromo-7-azaindole **400** with compound of Formula Xj in the presence of a base (e.g. sodium hydride) in an appropriate solvent (e.g. dimethylformamide) with heating for several hours (e.g. 100 °C). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is S and R<sup>41</sup> is H.

**Example 55: Synthesis of compounds of Formula IIa, where A is S(O)<sub>2</sub>**

[0533] Compounds of Formula IIa where A is S(O)<sub>2</sub> may be synthesized from a compound of Formula IIa where A is S and R<sup>41</sup> is H in one Step as described in Scheme 112.

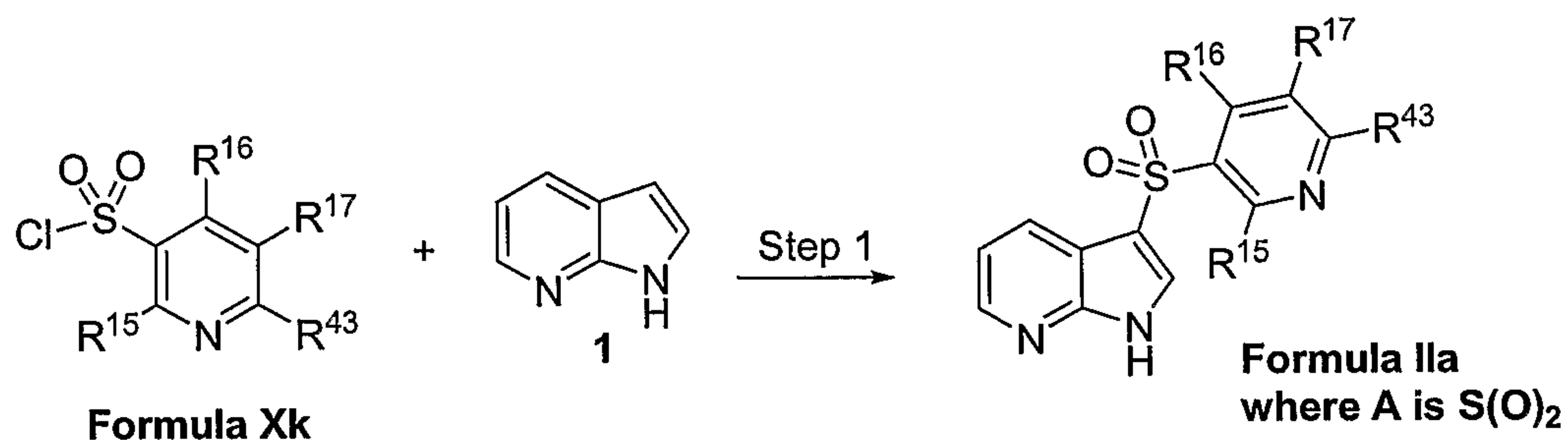
**Scheme 112**

*Step 1 - Preparation of Formula IIa where A is S(O)<sub>2</sub>*

[0534] Compound of Formula IIa where A is S(O)<sub>2</sub> is prepared by reacting a compound of Formula IIa where A is S (prepared as described in Example 53 or 54) with an oxidizing agent (e.g. meta-chloro-peroxybenzoic acid, hydrogen peroxide) in an appropriate aprotic solvent (e.g. dichloromethane). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is S(O)<sub>2</sub> and R<sup>41</sup> is H.

**Example 56: Synthesis of compounds of Formula IIa where A is S(O)<sub>2</sub>**

[0535] Compounds of Formula IIa where A is S(O)<sub>2</sub> may be synthesized from 7-azaindole **1** and a compound of Formula Xk (Formula Xa wherein J, E, F, G and K are C, n is 1, and R<sup>42</sup> is an S(O)<sub>2</sub>Cl) in one Step as described in Scheme 113.

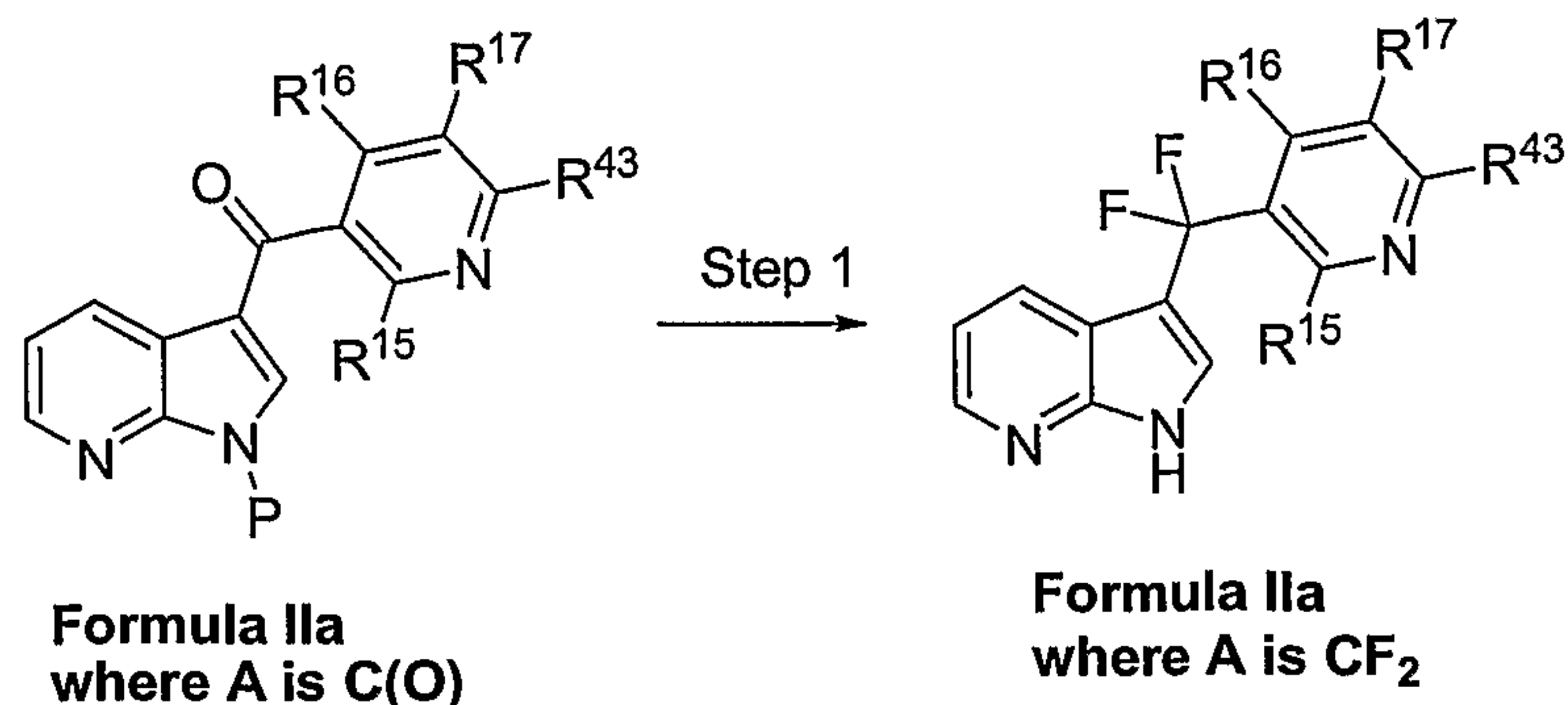
**Scheme 113***Step 1 - Preparation of Formula IIa where A is S(O)<sub>2</sub>*

[0536] Compound of Formula IIa where A is S(O)<sub>2</sub> is prepared by reacting 7-azaindole **1** with a sulfonyl chloride of Formula Xk dissolved in trifluoroacetic acid, in the presence of a catalyst (e.g. indium trichloride) and trifluorosulfonic acid with heating (e.g. 70 °C) for a few hours. Neutralization with sodium hydroxide and isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is S(O)<sub>2</sub> and R<sup>41</sup> is H (Garzya et al., Tetrahedron Lett. 2004, 45:1499-1501).

**Example 57: Synthesis of compounds of Formula IIa where A is CF<sub>2</sub>**

[0537] Compounds of Formula IIa where A is CF<sub>2</sub> may be synthesized from a compound of Formula IIa where A is C(O) and R<sup>41</sup> is P in one Step as described in Scheme 114.

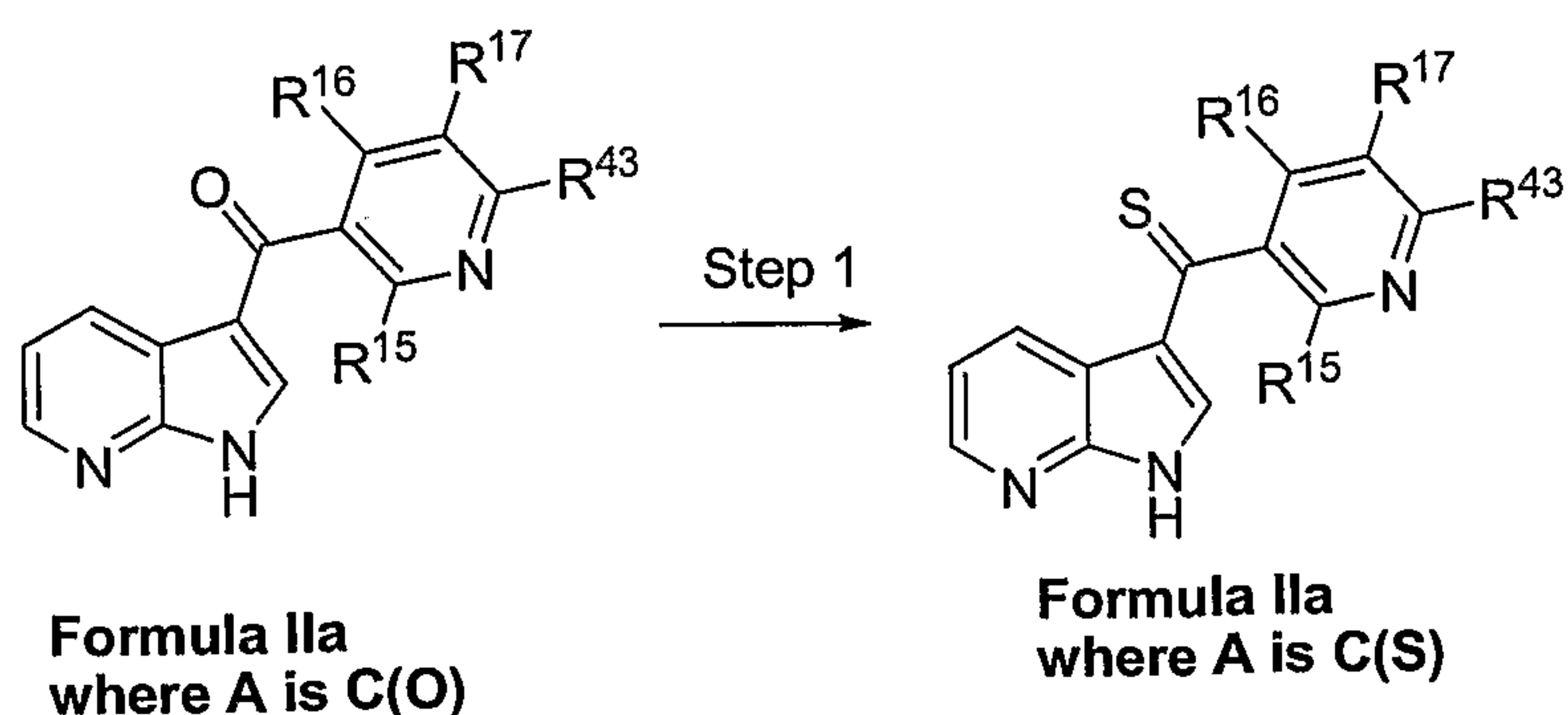


**Scheme 114***Step 1 - Preparation of Formula IIa where A is CF<sub>2</sub>*

[0538] Compound of Formula IIa where A is CF<sub>2</sub> is prepared by reacting a compound of Formula IIa where A is C(O) and R<sup>41</sup> is P (prepared as described in Example 44) with a fluorinating agent (e.g. (diethylamino)sulfur trifluoride) with heating for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is CF<sub>2</sub> and R<sup>41</sup> is H.

**Example 58: Synthesis of compounds of Formula IIa where A is C(S)**

[0539] Compounds of Formula IIa where A is C(S) may be synthesized from a compound of Formula IIa where A is C(O) and R<sup>41</sup> is H in one Step as described in Scheme 115.

**Scheme 115***Step 1 - Preparation of Formula IIa where A is C(S)*

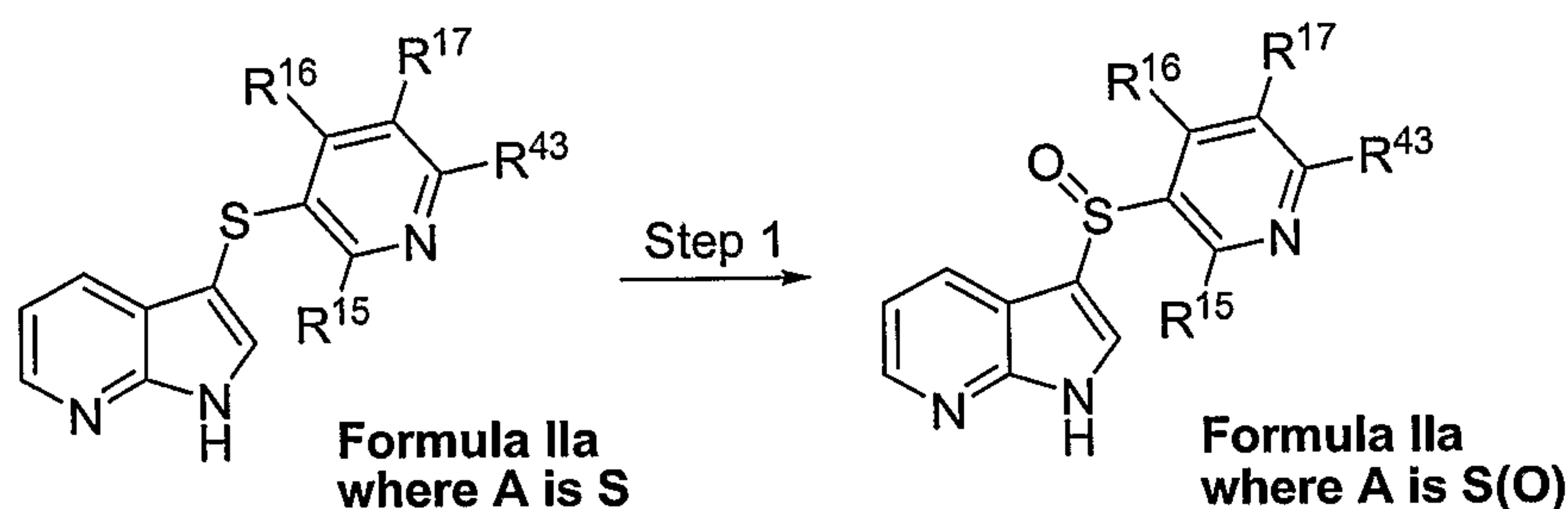
[0540] Compound of Formula IIa where A is C(S) is prepared by reacting a compound of Formula IIa where A is C(O) and R<sup>41</sup> is H (prepared as described in Example 43, 44 or 45) with Lawesson's reagent, (1,3,2,4-dithiadiphosphetane-2,3-disulfide), in an

appropriate solvent (e.g. tetrahydrofuran) with heating for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is C(S) and R<sup>41</sup> is H.

**Example 59:** Synthesis of compounds of Formula IIa where A is S(O)

[0541] Compounds of Formula IIa where A is S(O) may be synthesized from a compound of Formula IIa where A is S and R<sup>41</sup> is H in one Step as described in Scheme 116.

**Scheme 116**

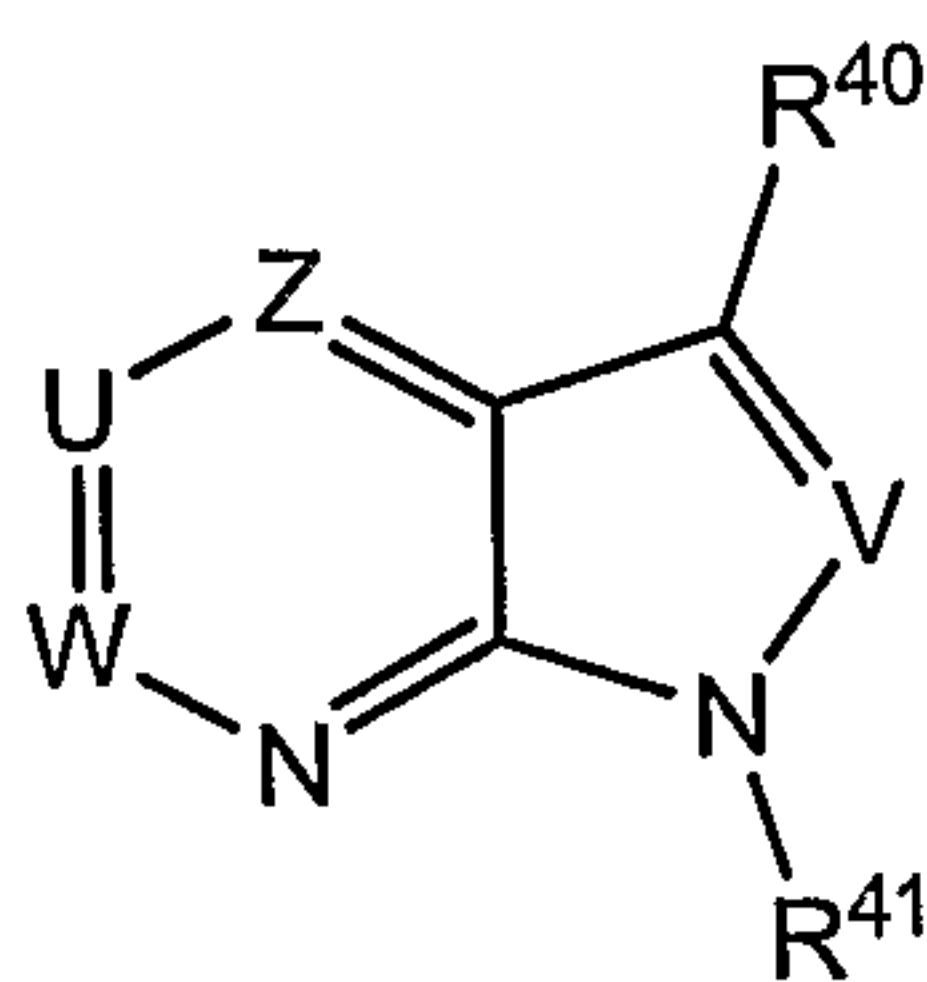


*Step 1 - Preparation of Formula IIa where A is S(O)*

[0542] Compound of Formula IIa where A is S(O) is prepared by reacting compound of Formula IIa where A is S and R<sup>41</sup> is H (prepared as described in Example 53 or 54) with one equivalent of an oxidizing agent (e.g. meta-chloro-peroxybenzoic acid, hydrogen peroxide, oxone) in an appropriate aprotic solvent (e.g. dichloromethane). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIa where A is S(O) and R<sup>41</sup> is H.

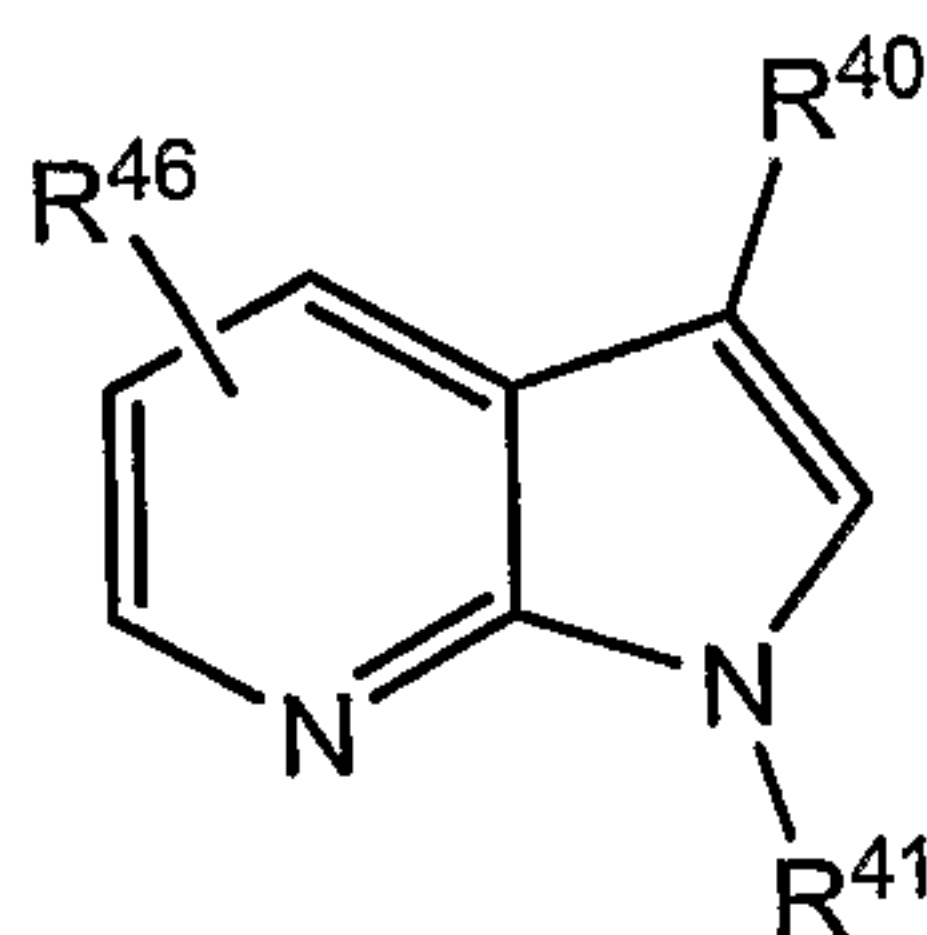
[0543] Compounds of Formula III may be used in the preparation of compounds of Formula Ib or IIa as described in Examples 43-59 by substituting the 7-azaindole or analog shown in the example with a compound of Formula III. R<sup>40</sup> is the substituent at the 3-position used in the example appropriate for coupling to compounds of Formula X (e.g. hydrogen, C(O)H, CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, C(O)Cl, bromo, amino, hydroxy, thio) and R<sup>41</sup> is hydrogen or protecting group P.





Formula III

[0544] Compounds of Formula IIIi, i.e. Formula III where V and W are CH, at least one of U and Z are CR<sup>46</sup>, preferably one of U and Z is CR<sup>46</sup> and the other of U and Z is CH, where R<sup>46</sup> is as defined for R<sup>18</sup>, excluding hydrogen, in Formula Ib of [0025], may be used in the synthesis of compounds of Formula Ib and IIa as described for compounds for Formula III.



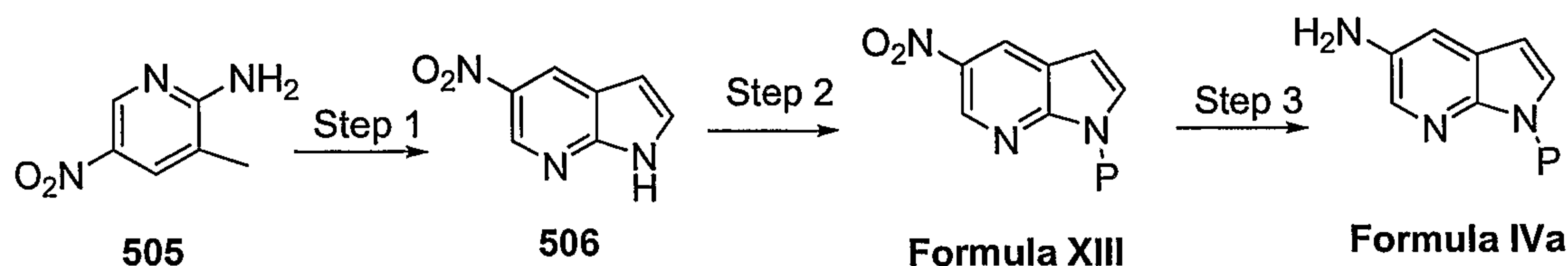
Formula IIIi

[0545] The examples provided for the synthesis of compounds of Formula IIIi are also applicable to many compounds meeting other definitions of Formula III or compounds of Formula IIIi can be further substituted, particularly at the 3-position, to provide compounds of Formula III, or related compounds that may be used to synthesize compounds of Formula I.

[0546] Additionally, the techniques used for preparation of compounds of Formula III and IIIi may be applied to compounds of Formula Ib where R<sup>5</sup> is bromo, chloro, or amino, to provide other compounds of Formula Ib.

#### Example 60: Synthesis of Intermediate of Formula IVa

[0547] Compounds of Formula IVa may be synthesized from 3-methyl-5-nitro-pyridin-2-ylamine **505** in three Steps as described in Scheme 117.

**Scheme 117***Step 1 - Preparation of 5-Nitro-1H-pyrrolo[2,3-b]pyridine (506)*

[0548] 5-Nitro-1H-pyrrolo[2,3-b]pyridine **506** is prepared by reacting 3-methyl-5-nitro-pyridin-2-ylamine **505** with t-butyloxycarbonyl anhydride in an appropriate solvent (e.g. ethyl acetate and hexanes). Concentration and extraction provides a Boc-protected intermediate that is then reacted with 2 equivalents of butyllithium in an appropriate polar solvent (e.g. tetrahydrofuran) with cooling (e.g. 0 °C), followed by the addition of dimethylformamide and stirring for 30 minutes to one hour, followed by addition of 5.5 M HCl. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides **506**. (Hands et. al., Synthesis 1996, 877-882.)

*Step 2 - Preparation of Formula XIII*

[0549] Compound of Formula XIII is prepared by reacting 5-Nitro-1H-pyrrolo[2,3-b]pyridine **506** as described in Scheme 43, Step 1.

*Step 3 - Preparation of Formula IVa*

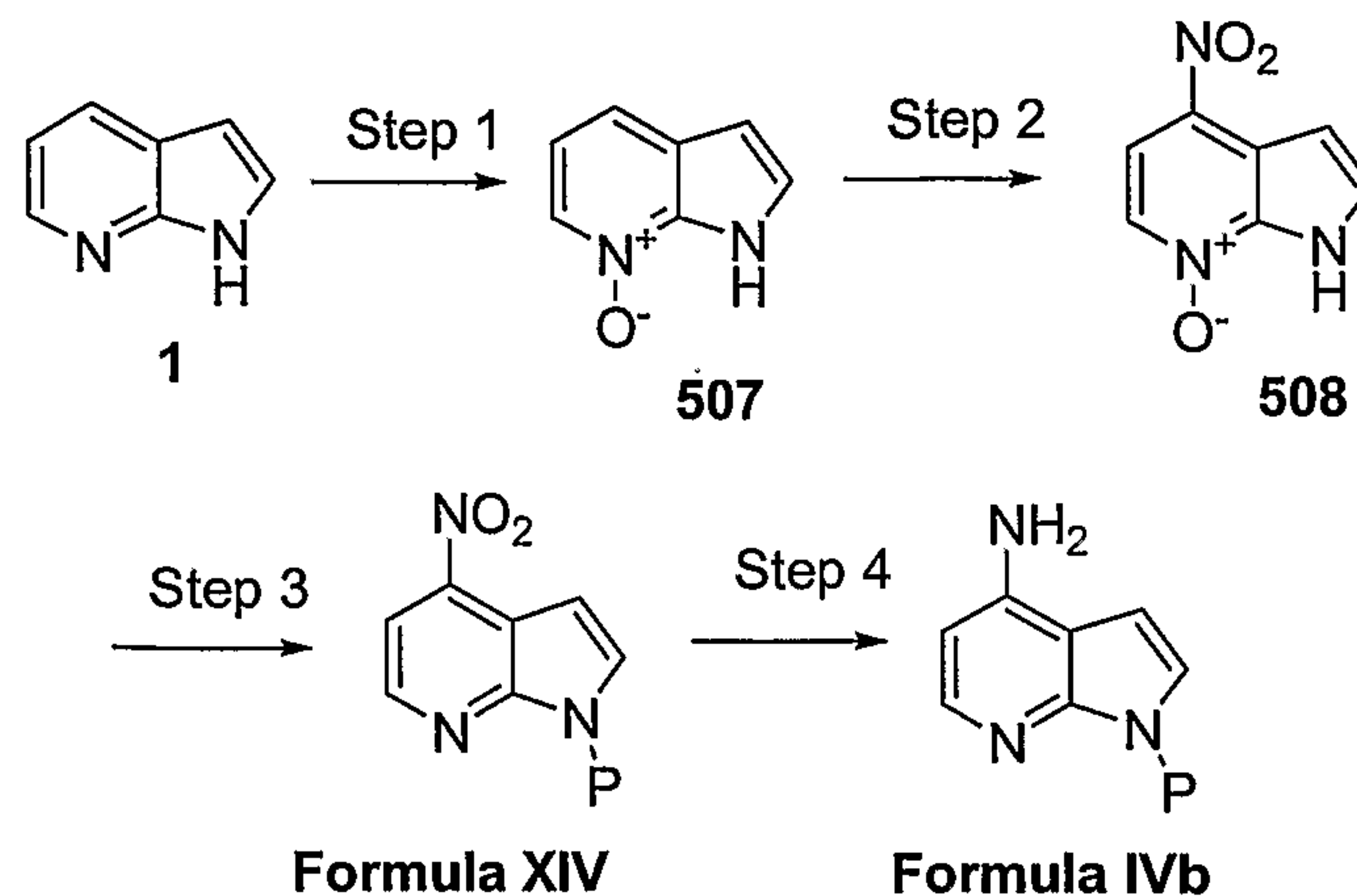
[0550] Compound of Formula IVa is prepared from compound of Formula XIII by reduction of the nitro group (e.g. hydrogen gas and palladium on carbon in methanol). The mixture is filtered and concentrated to provide compound of Formula IVa.

**Example 61: Synthesis of Intermediate of Formula IVb**

[0551] Compounds of Formula IVa may be synthesized from 7-azaindole **1** in four Steps as described in Scheme 118.



## Scheme 118

*Step 1 - Preparation of 1H-Pyrrolo[2,3-b]pyridine 7-oxide (507)*

[0552] 1H-Pyrrolo[2,3-b]pyridine 7-oxide **507** is prepared by reacting 7-azaindole **1** with an oxidizing agent (e.g. *m*-chloro-peroxybenzoic acid) in an appropriate solvent (e.g. dichloromethane). After stirring at room temperature for 30 minutes to one hour, compound **507** is collected by filtration.

*Step 2 - Preparation of 4-Nitro-1H-pyrrolo[2,3-b]pyridine 7-oxide (508)*

[0553] 4-Nitro-1H-pyrrolo[2,3-b]pyridine 7-oxide **508** is prepared by dissolving 1H-Pyrrolo[2,3-b]pyridine 7-oxide **507** in nitric acid, followed by the addition of sulfuric acid. Heating (e.g. 70 °C) for one hour, followed by pouring into water provides compound **508**, which is isolated by filtration. (Schneller et. al., J. Org. Chem. 1980, 45:4045)

*Step 3 - Preparation of compound of Formula XIV*

[0554] Compound of Formula XIV is prepared from 4-Nitro-1H-pyrrolo[2,3-b]pyridine 7-oxide **508** by addition of phosphorous trichloride in an appropriate solvent (e.g. ethyl acetate) and heating (e.g. 80 °C) for several minutes. Neutralization with base (e.g. potassium carbonate) followed by extraction affords the intermediate that can then be protected at the N-1 hydrogen according to Scheme 43, Step 1, to provide compound of Formula XIV.

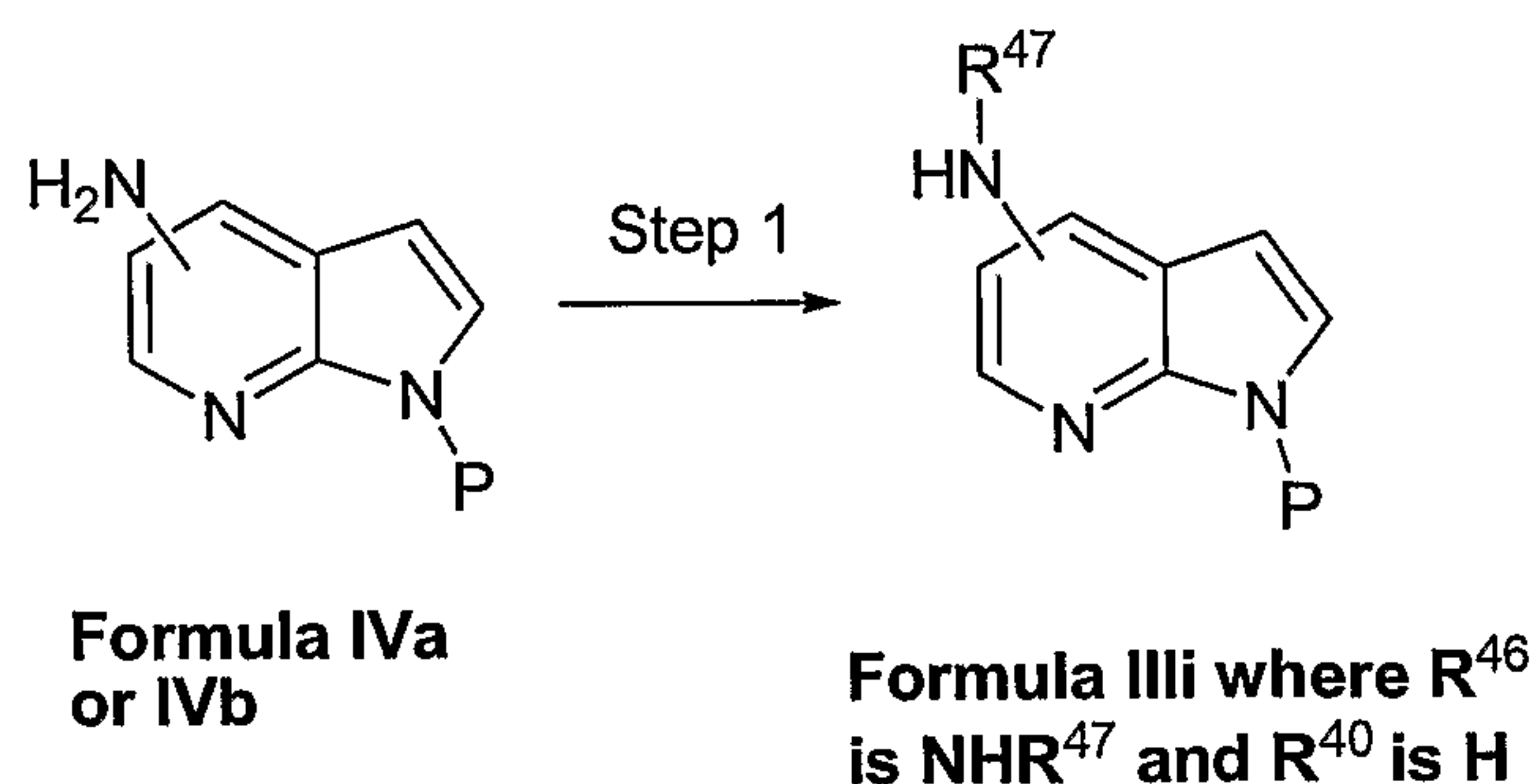
*Step 4 - Preparation of Formula IVb*

[0555] Compound of IVb is prepared from compound of Formula XIV by reduction of the nitro group (e.g. hydrogen gas and palladium on carbon in methanol). The mixture can be filtered and concentrated to provide compound of Formula IVb.

**Example 62: Synthesis of compounds of Formula IIIi where  $R^{46}$  is  $NHR^{47}$  and  $R^{40}$  is H**

[0556] Compounds of Formula IIIi where  $R^{46}$  is  $NHR^{47}$  and  $R^{40}$  is H may be synthesized from a compound of Formula IVa or IVb in one Step as described in Scheme 119.

**Scheme 119**



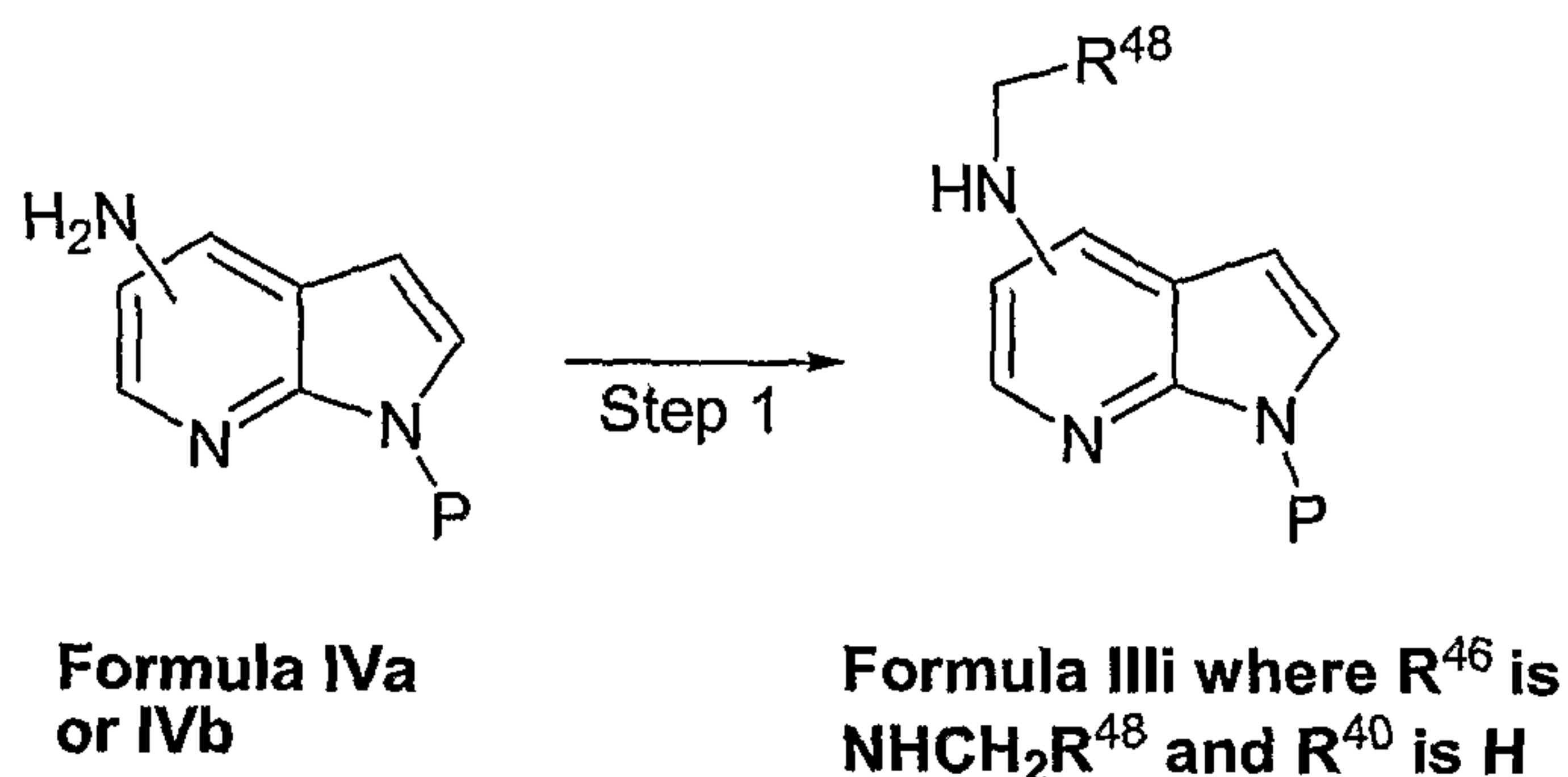
*Step 1 - Preparation of compound of Formula IIIi where  $R^{46}$  is  $NHR^{47}$  and  $R^{40}$  is H*

[0557] Compound of Formula IIIi where  $R^{46}$  is  $NHR^{47}$  and  $R^{40}$  is H ( $R^{47}$  is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl) is prepared from intermediate Formula IVa (Example 60) or IVb (Example 61) by reaction with  $R^{47}\text{-X}$ , where X is a leaving group, (e.g. alkylating agent such as methyl iodide) in the presence of a base (e.g. potassium carbonate) in an appropriate solvent (e.g. dimethylformamide) for several hours at room temperature. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIIi where  $R^{46}$  is  $NHR^{47}$ ,  $R^{40}$  is H and  $R^{41}$  is P.

**Example 63: Synthesis of compounds of Formula IIIi where  $R^{46}$  is  $NHCH_2R^{48}$  and  $R^{40}$  is H**

[0558] Compounds of Formula IIIi where  $R^{46}$  is  $NHCH_2R^{48}$  and  $R^{40}$  is H may be synthesized from a compound of Formula IVa or IVb in one Step as described in Scheme 120.



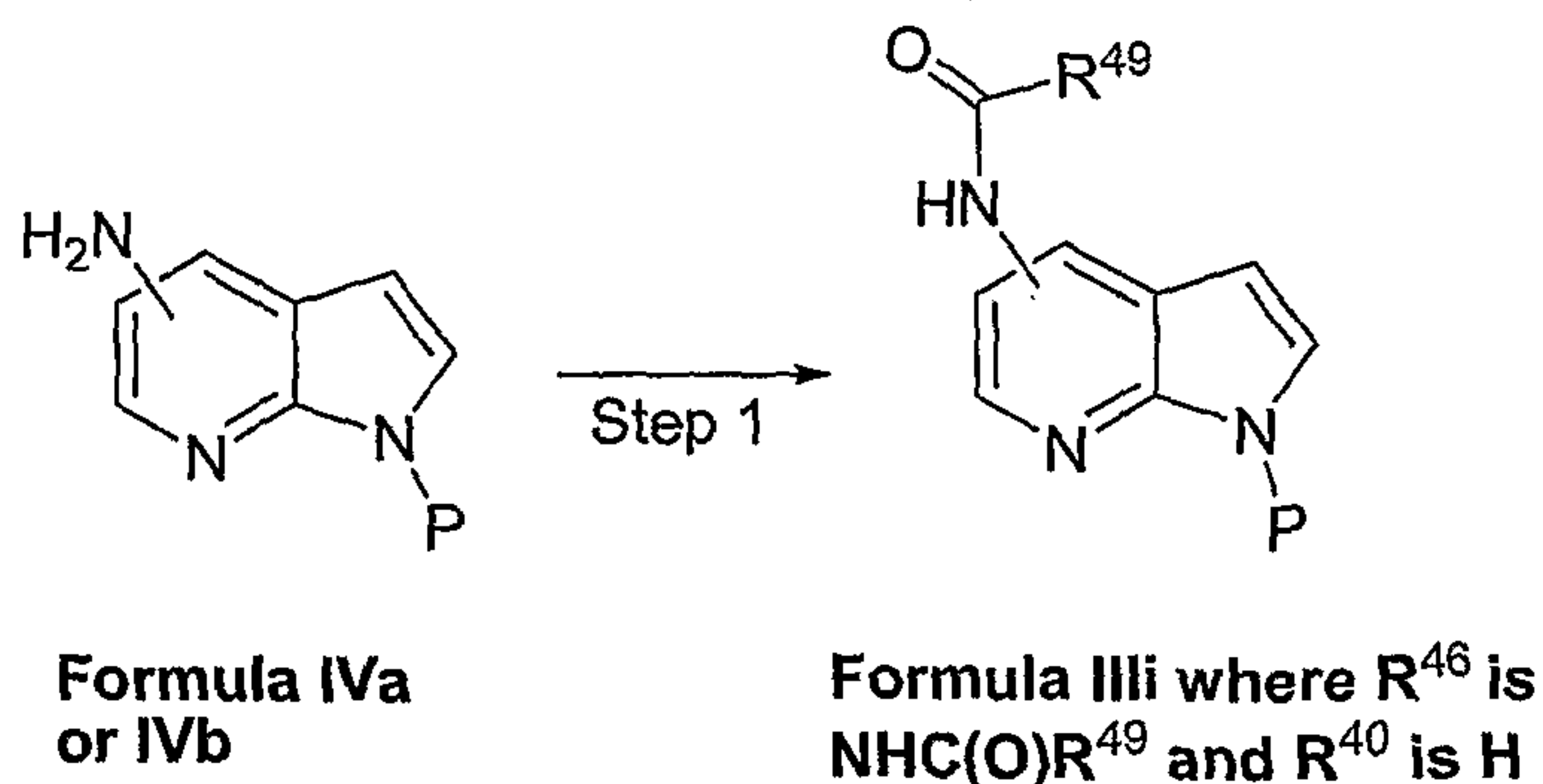
**Scheme 120**

*Step 1 - Preparation of compound of Formula IIIc where R<sup>46</sup> is NHCH<sub>2</sub>R<sup>48</sup> and R<sup>40</sup> is H*

**[0559]** Compound of Formula IIIi where R<sup>46</sup> is NHCH<sub>2</sub>R<sup>48</sup> and R<sup>40</sup> is H (R<sup>48</sup> is consistent with optionally substituted lower alkyl) is prepared from intermediate Formula IVa (Example 60) or IVb (Example 61) by reductive amination using an aldehyde of the formula R<sup>48</sup>-C(O)H in the presence of a catalytic amount of acid (e.g. acetic acid) and a reducing agent (e.g. sodium triacetoxyborohydride) in a non-reactive solvent (e.g. dichloroethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIIi where R<sup>46</sup> is NHCH<sub>2</sub>R<sup>48</sup>, R<sup>40</sup> is H and R<sup>41</sup> is P.

**Example 64: Synthesis of compounds of Formula IIIi where R<sup>46</sup> is NHC(O)R<sup>49</sup> and R<sup>40</sup> is H**

**[0560]** Compounds of Formula IIIi where R<sup>46</sup> is NHC(O)R<sup>49</sup> and R<sup>40</sup> is H may be synthesized from a compound of Formula IVa or IVb in one Step as described in Scheme 121.

**Scheme 121**

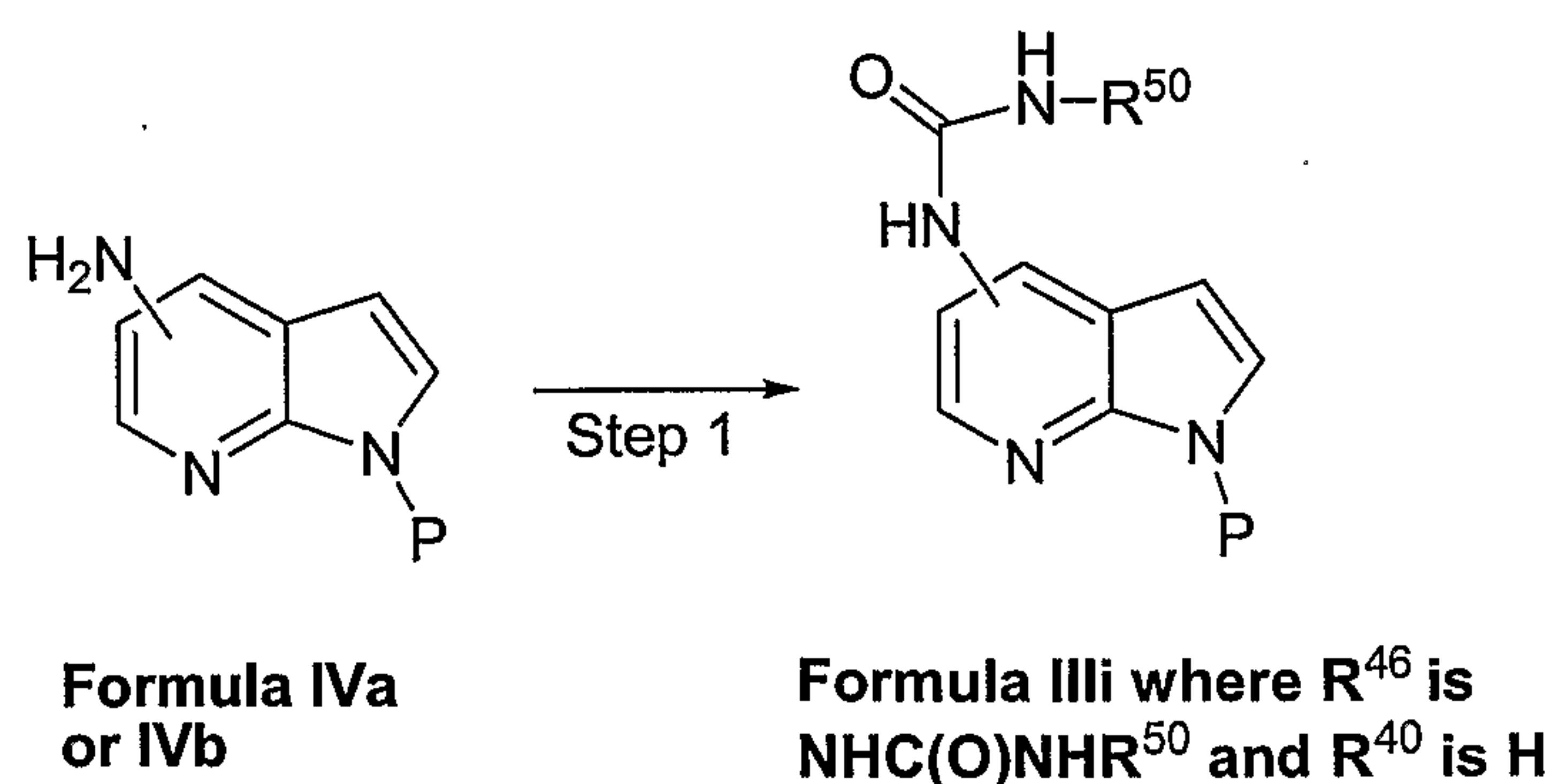
*Step 1 - Preparation of compound of Formula IIIi where  $R^{46}$  is  $NHC(O)R^{49}$  and  $R^{40}$  is H*

[0561] Compound of Formula IIIi where  $R^{46}$  is  $NHC(O)R^{49}$  and  $R^{40}$  is H ( $R^{49}$  is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl) is prepared from intermediate Formula IVa (Example 60) or IVb (Example 61) by reaction with an activated carboxylic acid of the formula  $R^{49}-C(O)X$  where X is a leaving group such as chloro (e.g. benzoyl chloride) in the presence of a base (e.g. N,N-diisopropylethylamine (DIEA)) in a non-reactive solvent (e.g. dichloromethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIIi where  $R^{46}$  is  $NHC(O)R^{49}$ ,  $R^{40}$  is H and  $R^{41}$  is P.

**Example 65: Synthesis of compounds of Formula IIIi where  $R^{46}$  is  $NHC(O)NHR^{50}$  and  $R^{40}$  is H**

[0562] Compounds of Formula IIIi where  $R^{46}$  is  $NHC(O)NHR^{50}$  and  $R^{40}$  is H may be synthesized from a compound of Formula IVa or IVb in one Step as described in Scheme 122.

**Scheme 122**



*Step 1 - Preparation of compound of Formula IIIi where  $R^{46}$  is  $NHC(O)NHR^{50}$  and  $R^{40}$  is H*

[0563] Compound of Formula IIIi where  $R^{46}$  is  $NHC(O)NHR^{50}$  and  $R^{40}$  is H ( $R^{50}$  is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl) is

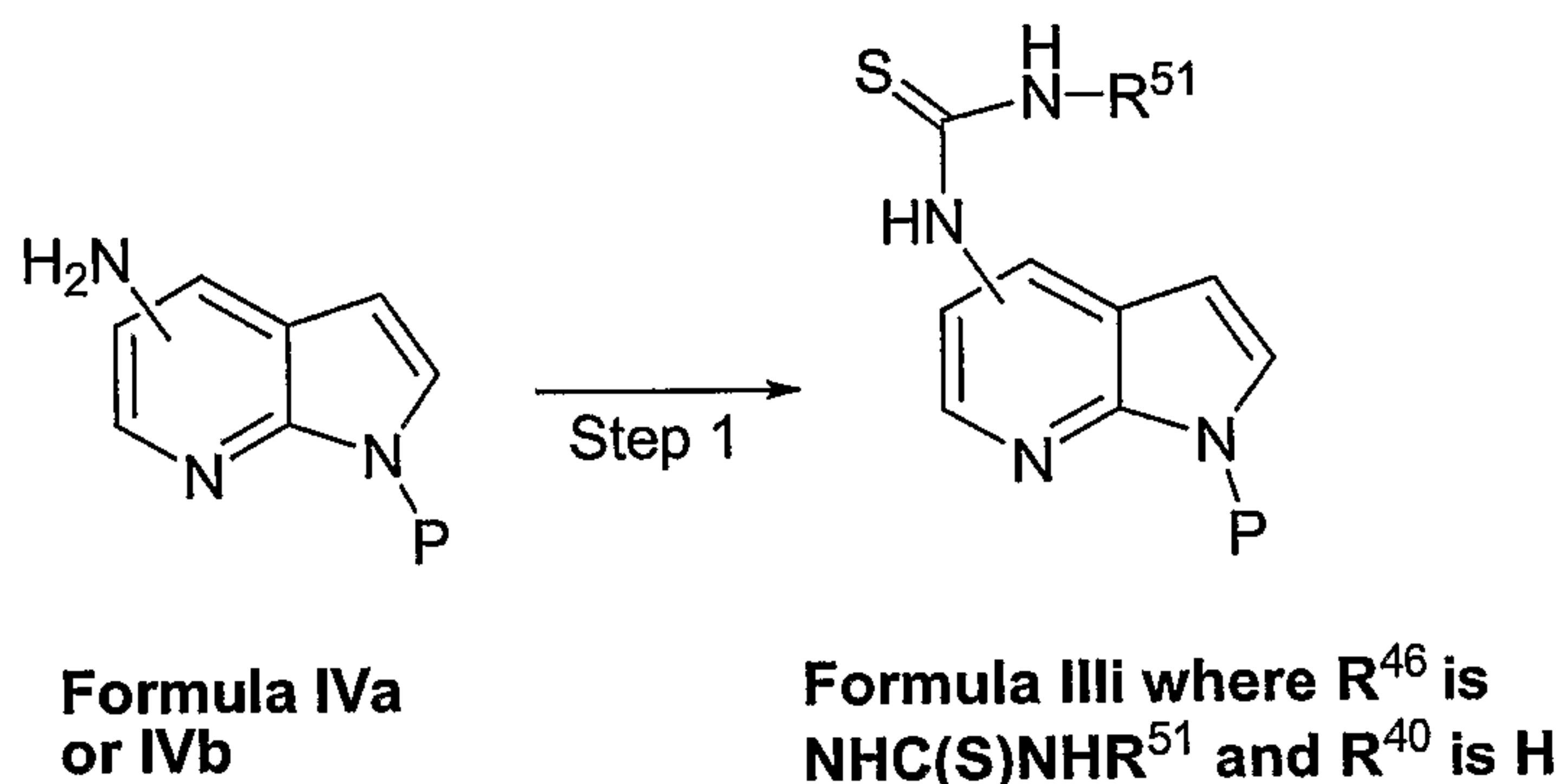


prepared from intermediate Formula IVa (Example 60) or IVb (Example 61) by reaction with an isocyanate of the formula  $R^{50}$ -NCO (e.g. propylisocyanate) in the presence of a base (e.g. DIEA) in a non-reactive solvent (e.g. dichloromethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIIi where  $R^{46}$  is  $NHC(O)NHR^{50}$ ,  $R^{40}$  is H and  $R^{41}$  is P.

**Example 66: Synthesis of compounds of Formula IIIi where  $R^{46}$  is  $NHC(S)NHR^{51}$  and  $R^{40}$  is H**

[0564] Compounds of Formula IIIi where  $R^{46}$  is  $NHC(S)NHR^{51}$  and  $R^{40}$  is H may be synthesized from a compound of Formula IVa or IVb in one Step as described in Scheme 123.

**Scheme 123**



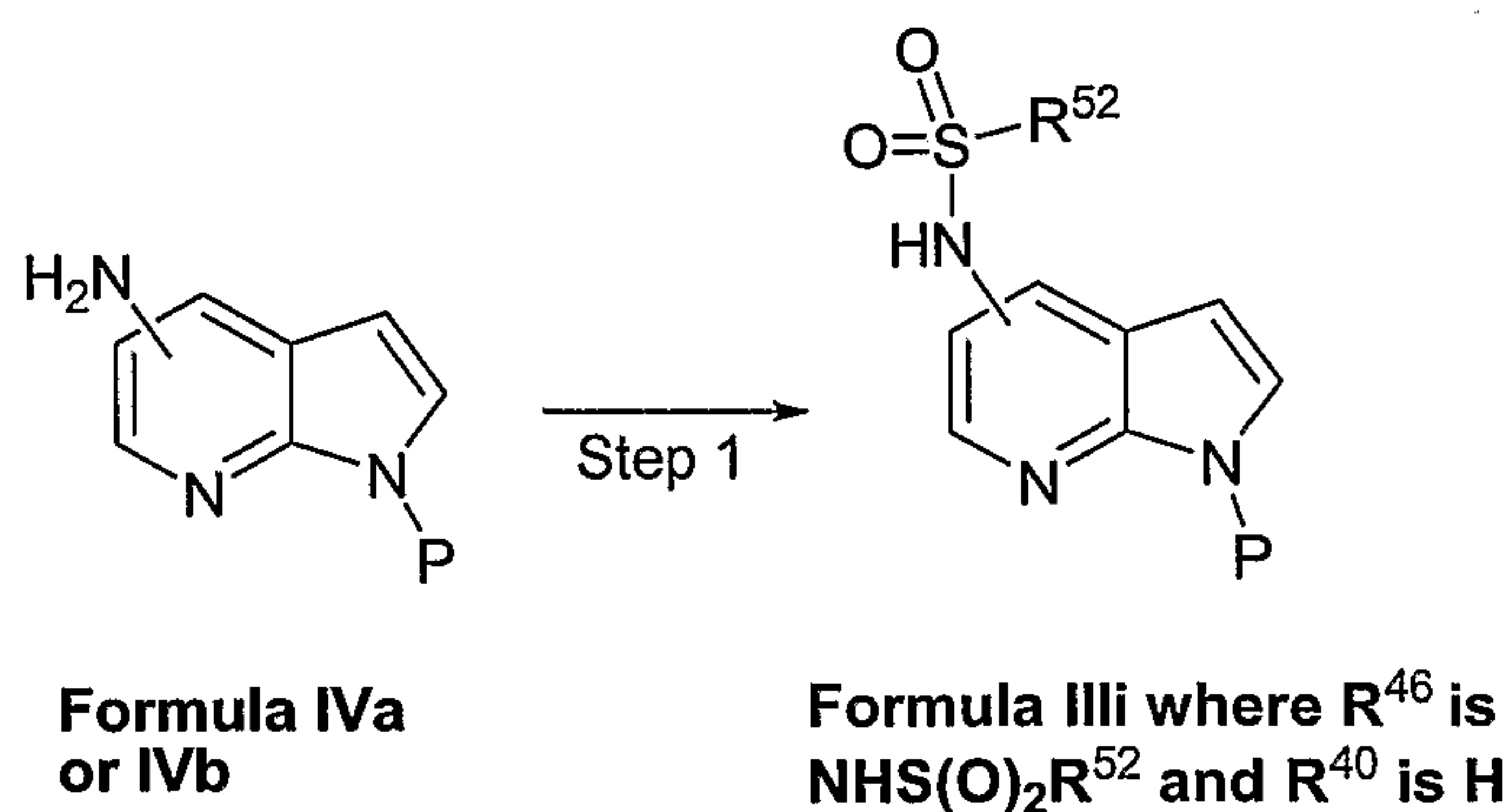
*Step 1 - Preparation of compound of Formula IIIi where  $R^{46}$  is  $NHC(S)NHR^{51}$  and  $R^{40}$  is H*

[0565] Compound of IIIi where  $R^{46}$  is  $NHC(S)NHR^{51}$  and  $R^{40}$  is H ( $R^{51}$  is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl) is prepared from intermediate Formula IVa (Example 60) or IVb (Example 61) by reaction with an isothiocyanate of the formula  $R^{51}$ -NCS (e.g. propylisothiocyanate) in the presence of a base (e.g. DIEA) in a non-reactive solvent (e.g. dichloromethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIIi where  $R^{46}$  is  $NHC(S)NHR^{51}$ ,  $R^{40}$  is H and  $R^{41}$  is P.

**Example 67: Synthesis of compounds of Formula IIIi where  $R^{46}$  is  $NHS(O)_2R^{52}$  and  $R^{40}$  is H**

[0566] Compounds of Formula IIIi where  $R^{46}$  is  $NHS(O)_2R^{52}$  and  $R^{40}$  is H may be synthesized from a compound of Formula IVa or IVb in one Step as described in Scheme 124.

**Scheme 124**



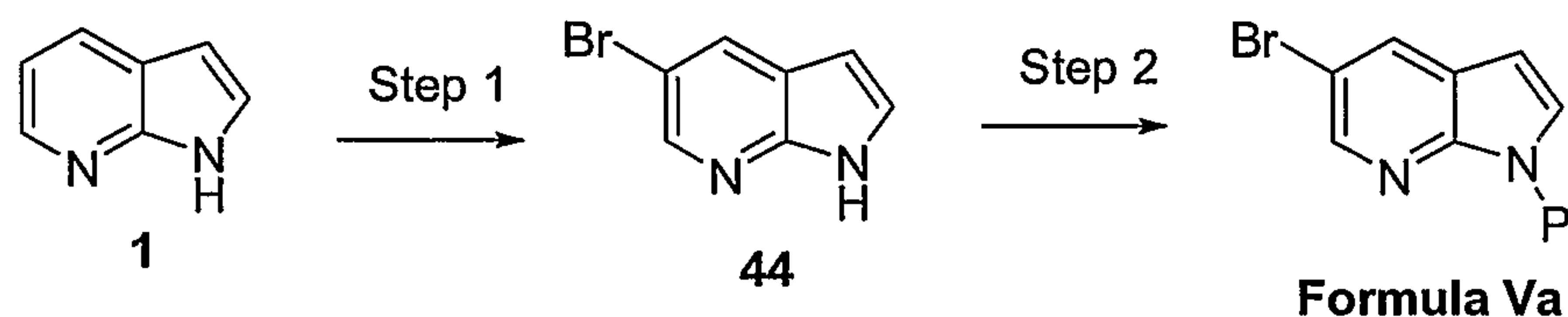
*Step 1 - Preparation of compound of Formula IIIi where  $R^{46}$  is  $NHS(O)_2R^{52}$  and  $R^{40}$  is H*

[0567] Compound Formula IIIi where  $R^{46}$  is  $NHS(O)_2R^{52}$  and  $R^{40}$  is H ( $R^{52}$  is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl) is prepared from intermediate Formula IVa (Example 60) or IVb (Example 61) by reaction with a sulfonyl chloride of the formula  $R^{52}-S(O)_2Cl$  (e.g. propylsulfonyl chloride) in the presence of a base (e.g. DIEA, pyridine) in a non-reactive solvent (e.g. dichloromethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIIi where  $R^{46}$  is  $NHS(O)_2R^{52}$ ,  $R^{40}$  is H and  $R^{41}$  is P.

**Example 68: Synthesis of Intermediate of Formula Va**

[0568] Compounds of Formula Va may be synthesized from 7-azaindole 1 in two Steps as described in Scheme 125.



**Scheme 125***Step 1 - Preparation of 5-bromo-7-azaindole (44)*

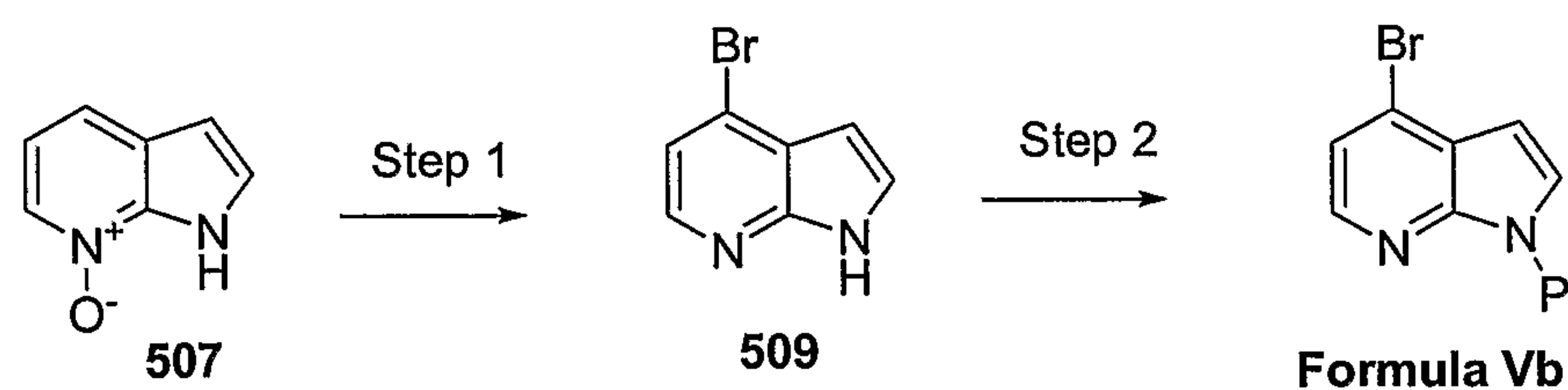
[0569] 5-bromo-7-azaindole **44** is prepared from 7-azaindole **1** as described in Mazeas et. al., Heterocycles 1999, 50:1065-1080.

*Step 2 - Preparation of intermediate of Formula Va*

[0570] Intermediate of Formula Va is prepared by protecting 5-bromo-7-azaindole **44** as described in Scheme 43, Step 1.

**Example 69: Synthesis of Intermediate of Formula Vb**

[0571] Compounds of Formula Vb may be synthesized from 1H-Pyrrolo[2,3-b]pyridine 7-oxide **507** in two Steps as described in Scheme 126.

**Scheme 126***Step 1 - Preparation of 4-bromo-7-azaindole (509)*

[0572] 4-bromo-7-azaindole **509** is prepared from 1H-Pyrrolo[2,3-b]pyridine 7-oxide **507** (prepared as described in Example 61) as described in Thibault et. al., Org. Lett. 2003, 5:5023-5025.

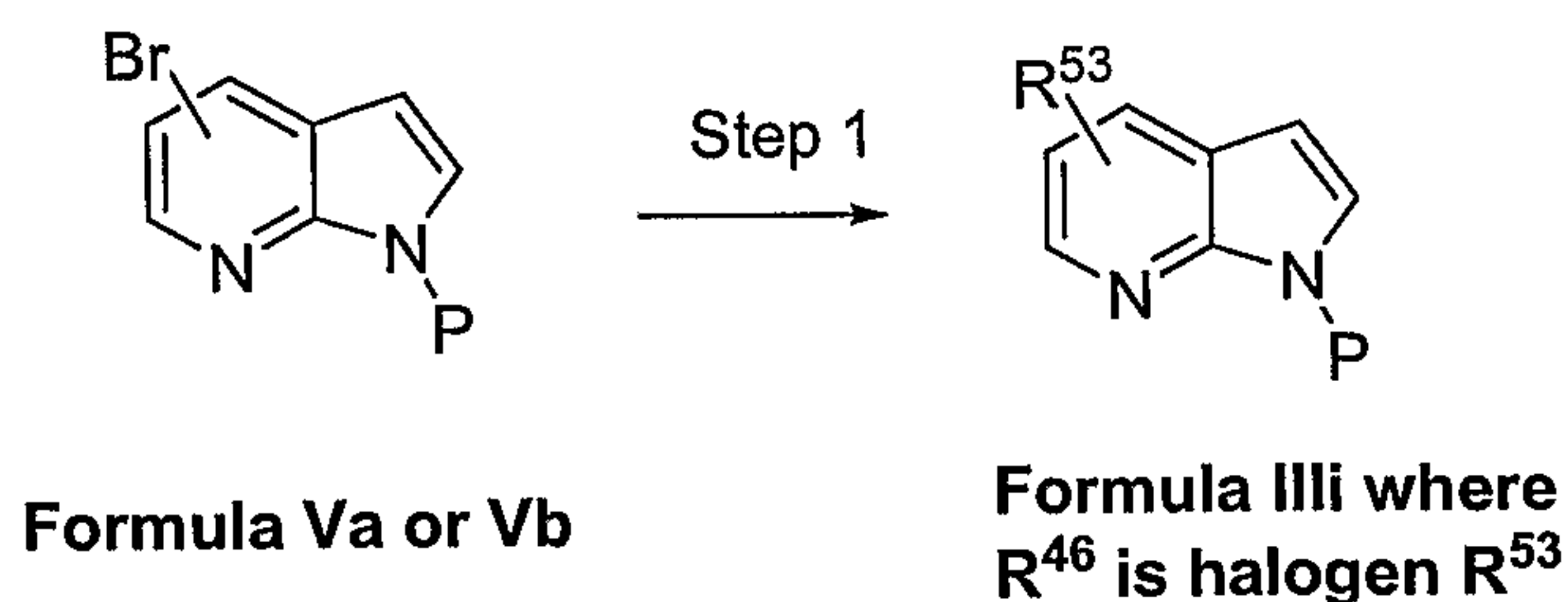
*Step 2 - Preparation of intermediate of Formula Vb*

[0573] Intermediate of Formula Vb is prepared by protecting 4-bromo-7-azaindole **509** as described in Scheme 43, Step 1.

**Example 70: Synthesis of Compounds of Formula IIIi where  $R^{46}$  is a halogen and  $R^{40}$  is H**

[0574] Compounds of Formula IIIi where  $R^{46}$  is a halogen and  $R^{40}$  is H may be synthesized from a compound of Formula Va or Vb in one Step as described in Scheme 127.

**Scheme 127**



*Step 1 - Preparation of compound of Formula IIIi where  $R^{46}$  is F or Cl and  $R^{40}$  is H*

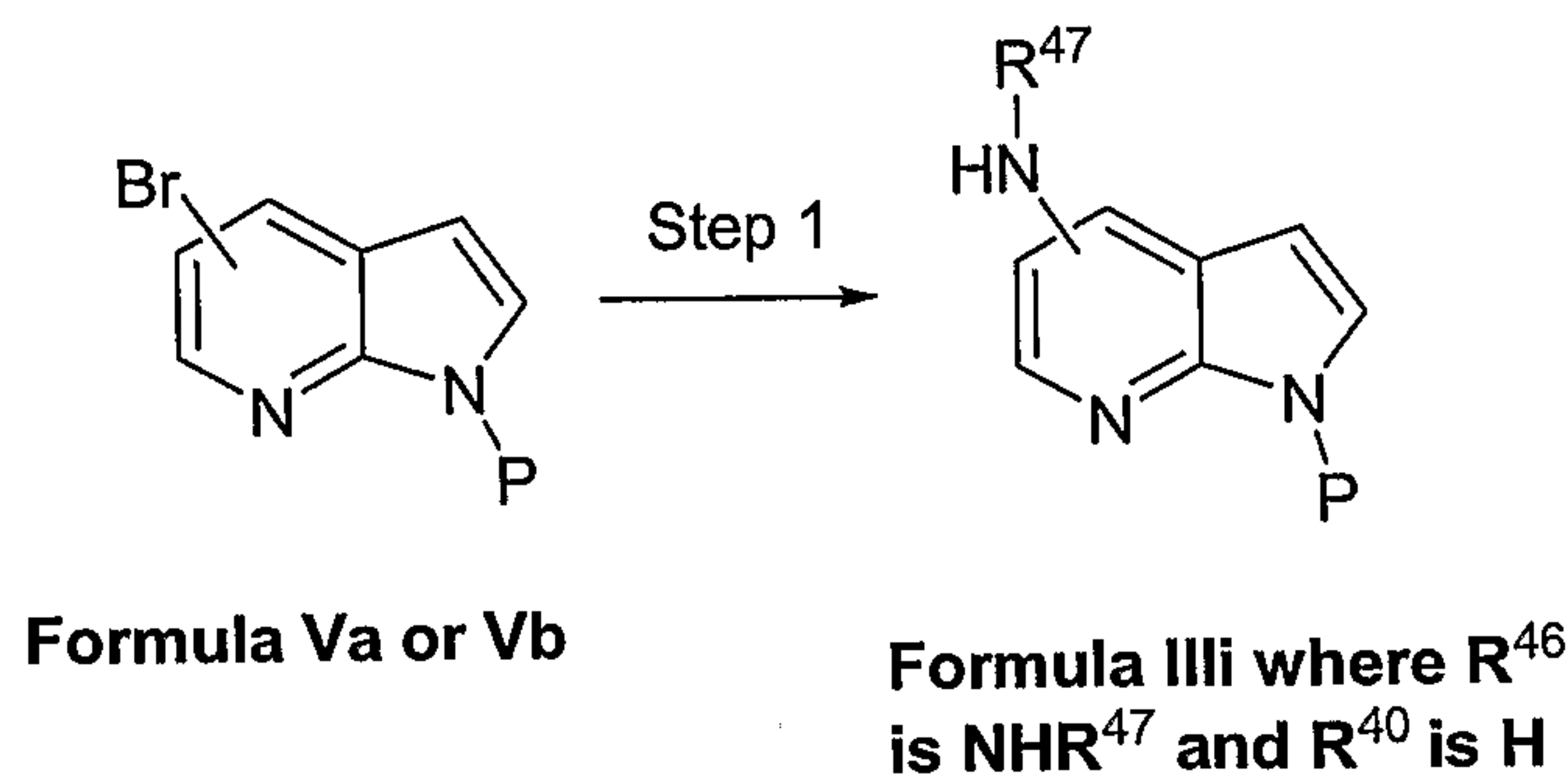
[0575] Compound of Formula IIIi where  $R^{46}$  is halogen  $R^{53}$  (preferably fluoro or chloro) and  $R^{40}$  is hydrogen is prepared by dissolving the corresponding bromo intermediates of Formula Va (Example 68) or Vb (Example 69) in an appropriate solvent (e.g. tetrahydrofuran) with cooling (e.g.  $-78\text{ }^{\circ}\text{C}$ ) and reacting with an organolithium reagent to effect the lithium-halogen exchange of the bromo (e.g. *t*-butyllithium), followed by addition of a source of fluorine (e.g. *N*-fluorobenzenesulfimide) or chlorine (e.g. hexachloroethane), similar to that described by Thibault et. al., Org. Lett. 2003, 5:5023-5025. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIIi where  $R^{46}$  is F or Cl,  $R^{40}$  is H and  $R^{41}$  is P.

**Example 71: Synthesis of compounds of Formula IIIi where  $R^{46}$  is  $\text{NHR}^{47}$  and  $R^{40}$  is H**

[0576] Compounds of Formula IIIi where  $R^{46}$  is  $\text{NHR}^{47}$  and  $R^{40}$  is H may be synthesized from a compound of Formula Va or Vb in one Step as described in Scheme 128.



## Scheme 128



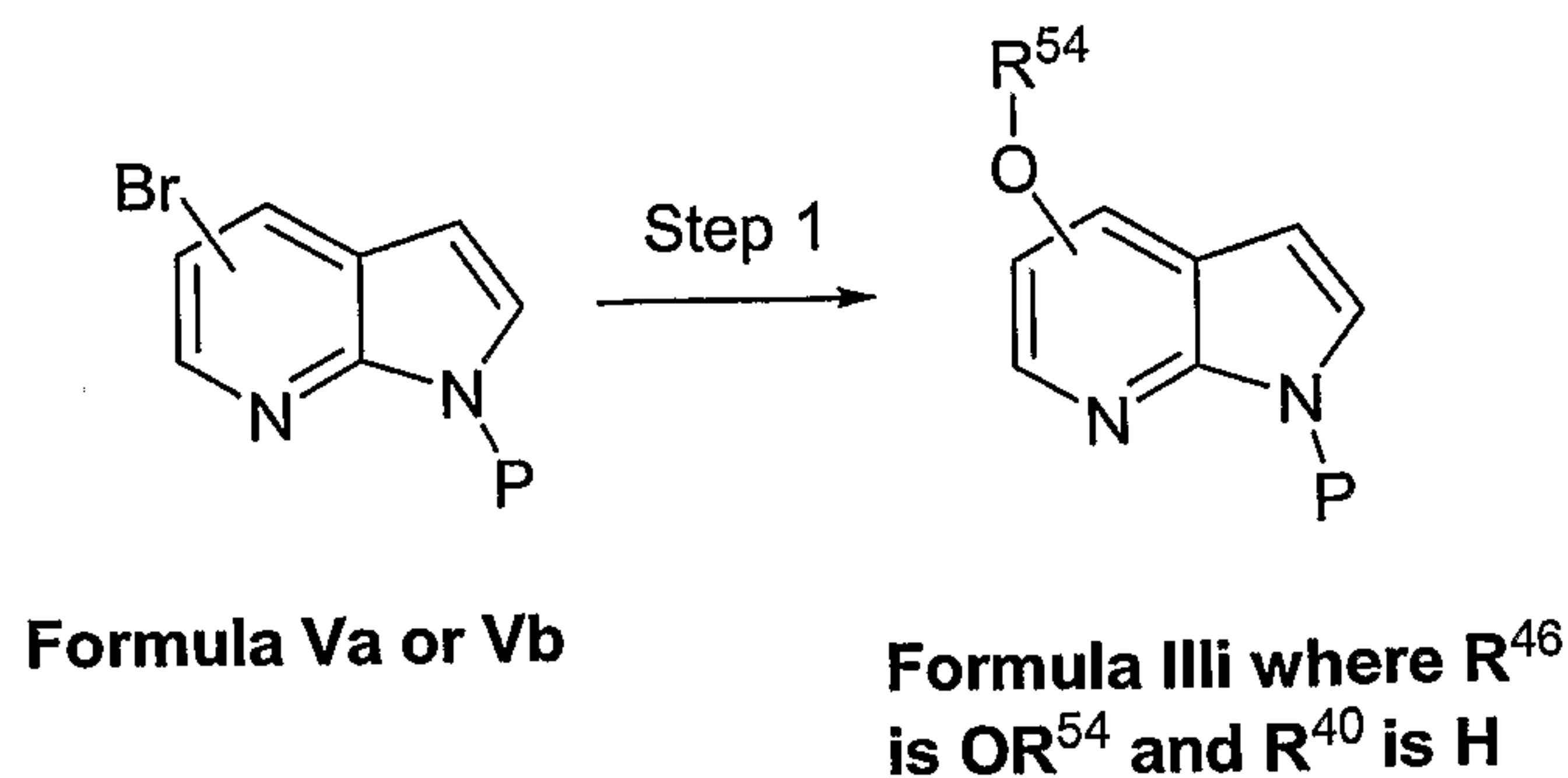
*Step 1 - Preparation of compound of Formula IIIi where R<sup>46</sup> is NHR<sup>47</sup> and R<sup>40</sup> is H*

[0577] Compound of Formula IIIi where R<sup>46</sup> is NHR<sup>47</sup> and R<sup>40</sup> is H (R<sup>47</sup> as defined in Example 62) is prepared by reacting intermediate Formula Va (Example 68) or Vb (Example 69) with an amine of Formula R<sup>47</sup>-NH<sub>2</sub> using palladium catalyzed Buchwald-Hartwig conditions (i.e. a palladium catalyst (e.g. palladium(II) acetate), a ligand (e.g. dicyclohexyl(*o*-biphenyl)phosphine), and a base (e.g. sodium *t*-butoxide) in a non-reactive solvent (e.g. 1,4-dioxane) with heating (e.g. 100 °C) for several hours). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIIi where R<sup>46</sup> is NHR<sup>47</sup>, R<sup>40</sup> is H and R<sup>41</sup> is P.

**Example 72: Synthesis of Compounds of Formula IIIi where R<sup>46</sup> is OR<sup>54</sup> and R<sup>40</sup> is H**

[0578] Compounds of Formula IIIi where R<sup>46</sup> is OR<sup>54</sup> and R<sup>40</sup> is H may be synthesized from a compound of Formula Va or Vb in one Step as described in Scheme 129.

## Scheme 129



*Step 1 - Preparation of compound of Formula IIIi where R<sup>46</sup> is OR<sup>54</sup> and R<sup>40</sup> is H*

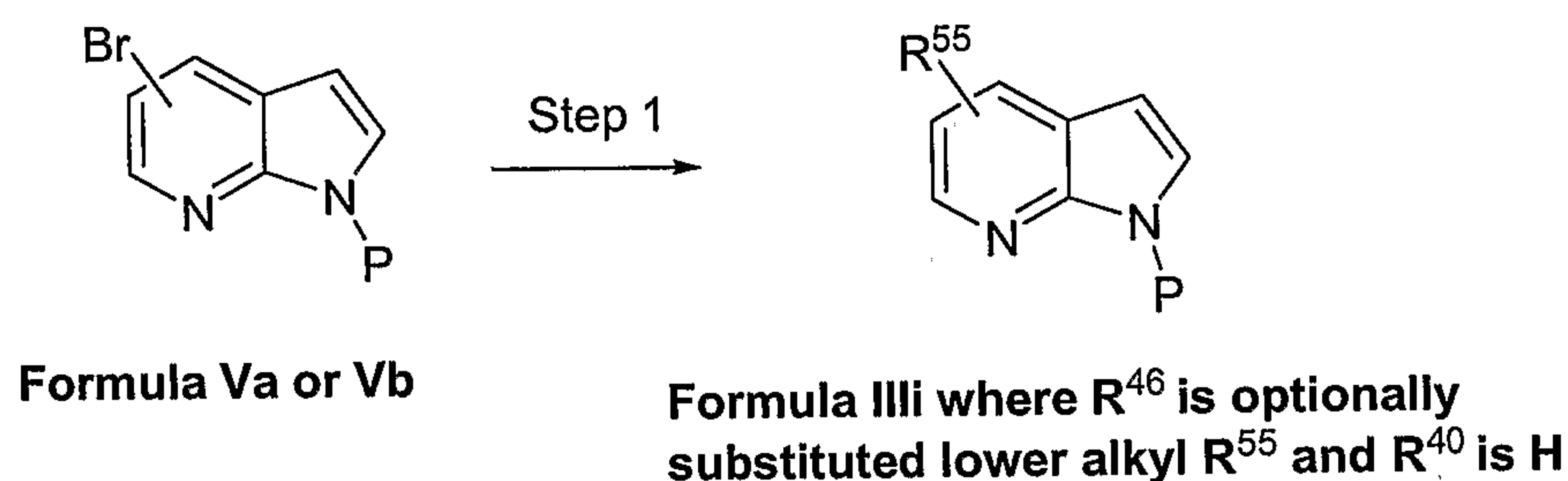
[0579] Compound of Formula IIIi where R<sup>46</sup> is OR<sup>54</sup> and R<sup>40</sup> is H (R<sup>54</sup> is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl,

optionally substituted aryl or optionally substituted heteroaryl) is prepared by reacting intermediate Formula Va (Example 68) or Vb (Example 69) with an alcohol of Formula  $R^{54}$ -OH in the presence of a base (e.g. sodium hydride) and a copper catalyst (e.g. copper bromide) in a non-reactive solvent (e.g. dimethylformamide) with heating (e.g. 120 °C) for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography), provides compounds of Formula IIIi where  $R^{46}$  is  $OR^{54}$ ,  $R^{40}$  is H and  $R^{41}$  is P.

**Example 73: Synthesis of Compounds of Formula IIIi where  $R^{46}$  is optionally substituted lower alkyl and  $R^{40}$  is H**

[0580] Compounds of Formula IIIi where  $R^{46}$  is optionally substituted lower alkyl and  $R^{40}$  is H may be synthesized from a compound of Formula Va or Vb in one Step as described in Scheme 130.

**Scheme 130**



*Step 1 - Preparation of compound of Formula IIIi where  $R^{46}$  is optionally substituted lower alkyl and  $R^{40}$  is H*

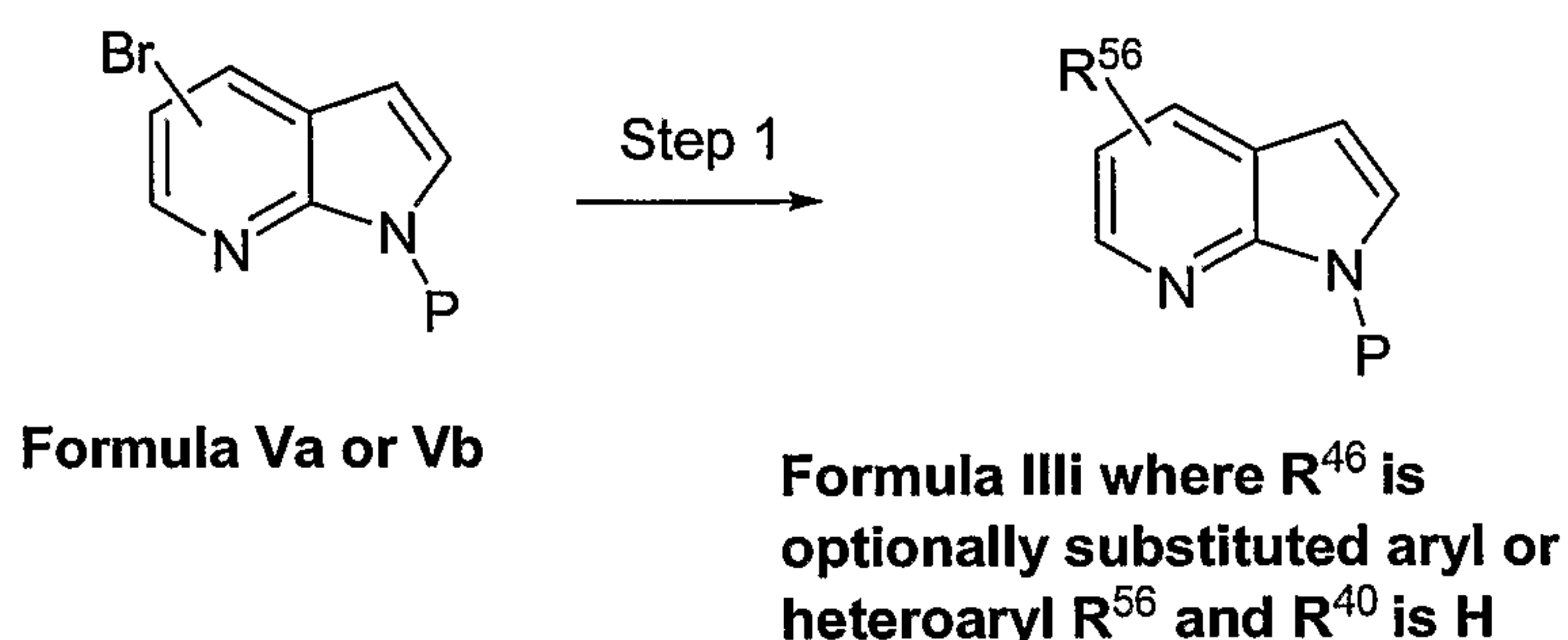
[0581] Compound of Formula IIIi where  $R^{46}$  is optionally substituted lower alkyl  $R^{55}$  and  $R^{40}$  is H is prepared by dissolving intermediate Formula Va (Example 68) or Vb (Example 69) in an appropriate solvent (e.g. toluene) followed by the addition of a palladium catalyst (e.g. [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (1:1)). After several minutes, a Grignard reagent of the Formula  $R^{55}$ -MgBr may be added and the reaction heated (e.g. 90 °C) for one to several hours. After filtration through Celite, isolation by conventional means (e.g. extraction and silica gel chromatography), provides compounds of Formula IIIc where  $R^{46}$  is optionally substituted lower alkyl,  $R^{40}$  is H and  $R^{41}$  is P.



**Example 74: Synthesis of Compounds of Formula IIIi where  $R^{46}$  is optionally substituted aryl or optionally substituted heteroaryl and  $R^{40}$  is H**

[0582] Compound of Formula IIIi where  $R^{46}$  is optionally substituted aryl or optionally substituted heteroaryl and  $R^{40}$  is H may be synthesized from a compound of Formula Va or Vb in one Step as described in Scheme 131.

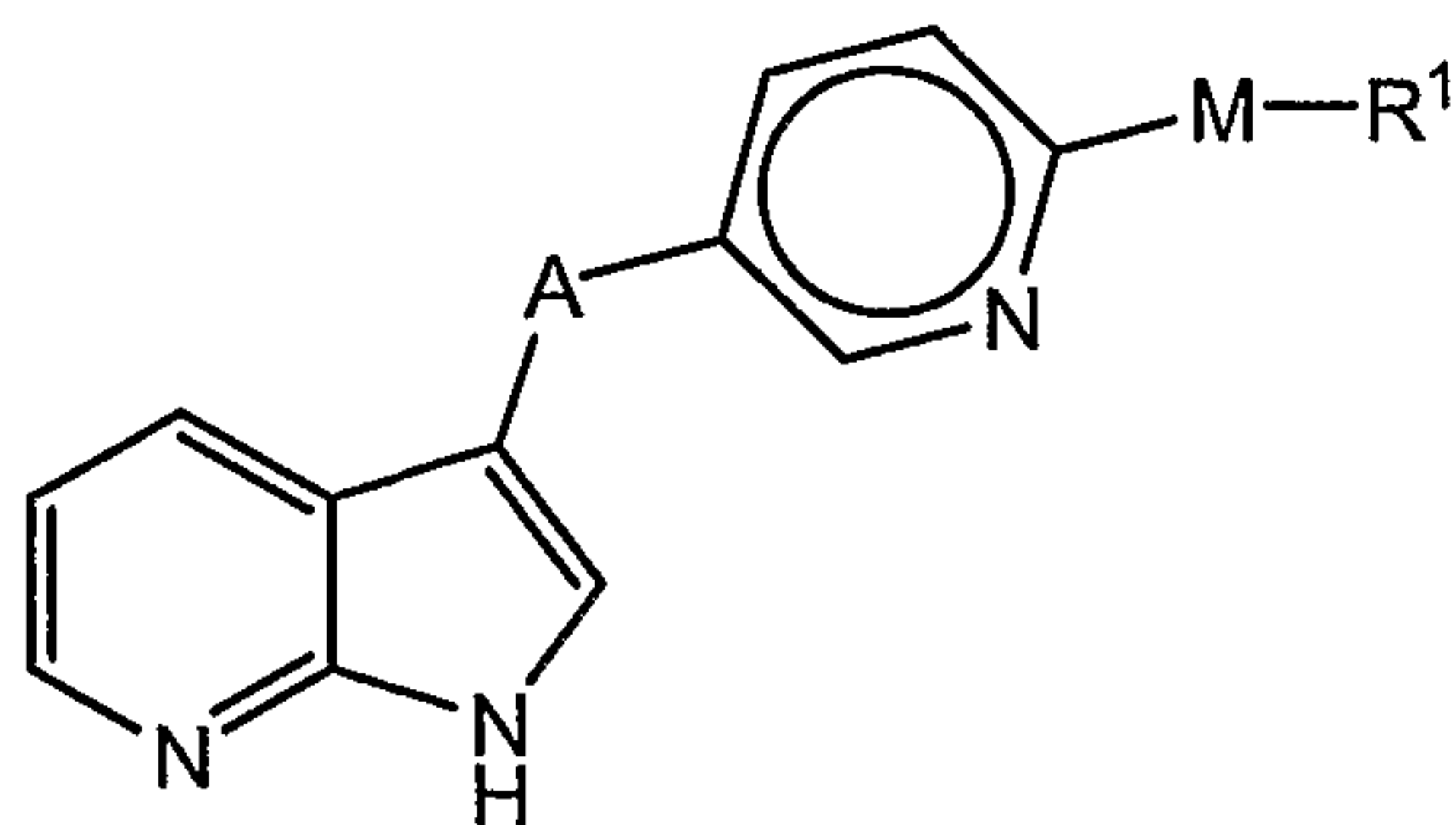
**Scheme 131**



*Step 1 - Preparation of compound of Formula IIIi where  $R^{46}$  is optionally substituted aryl or optionally substituted heteroaryl and  $R^{40}$  is H*

[0583] Compound of Formula IIIi where  $R^{46}$  is optionally substituted aryl or optionally substituted heteroaryl  $R^{56}$  and  $R^{40}$  is H is prepared by reacting intermediate Formula Va (Example 68) or Vb (Example 69) with a boronic acid of the Formula  $R^{56}$ -B(OH)<sub>2</sub> or boronic ester of the Formula  $R^{56}$ -B(OR)<sub>2</sub> under Suzuki coupling conditions (Muyaura and Suzuki, Chem. Rev. 1995, 95:2457), such as in the presence of a palladium catalyst (e.g. Tetrakis(triphenylphosphine)palladium(0)) and a base (e.g. aqueous potassium carbonate) in an appropriate solvent (e.g. tetrahydrofuran, acetonitrile) with heating thermally (e.g. 80 °C) for one to several hours or heating with a microwave instrument (e.g. 120 °C for 10 minutes). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIIi where  $R^{46}$  is optionally substituted aryl or optionally substituted heteroaryl,  $R^{40}$  is H and  $R^{41}$  is P.

[0584] Compounds of Formula Ib where V, W, U, and Z are CH, J, E, F, G, and K are C, n is 1, and  $R^{15}$ ,  $R^{16}$ , and  $R^{17}$  are hydrogen form compounds of Formula VI.



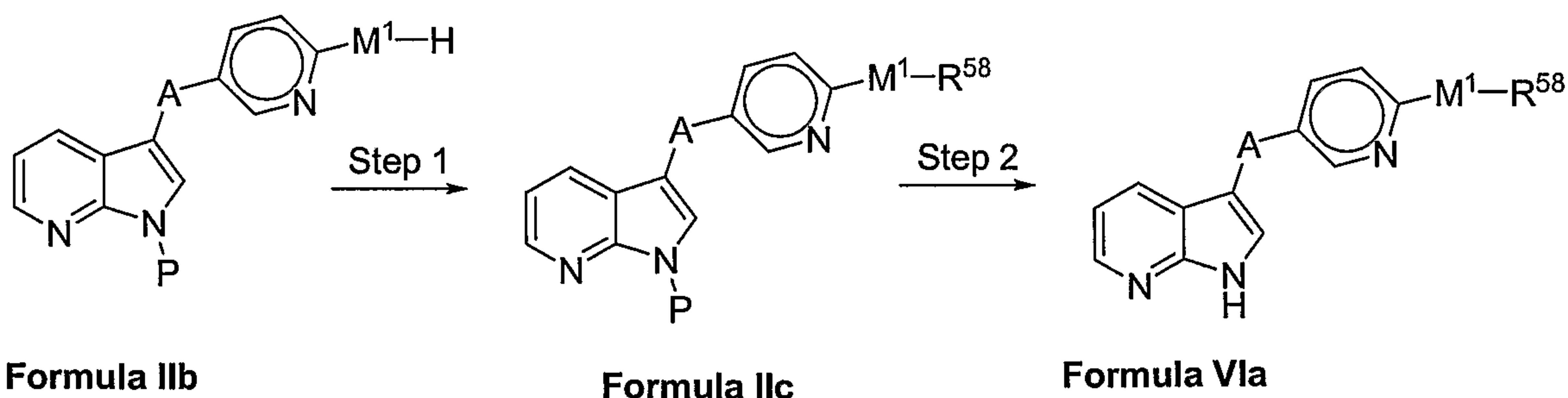
Formula VI

[0585] The examples provided for the synthesis of compounds of Formula VI are also applicable to many compounds meeting other definitions of Formula I or Formula Ib.

**Example 75: Synthesis of Compounds of Formula VI where M is NR<sup>57</sup> or O and R<sup>1</sup> is optionally substituted aryl or optionally substituted heteroaryl**

[0586] Compound of Formula VIa (Formula VI where M is NR<sup>57</sup> or O (R<sup>57</sup> consistent with definition of M for compounds of Formula Ib or L<sup>2</sup> for compounds of Formula I) and R<sup>1</sup> is optionally substituted aryl or optionally substituted heteroaryl) may be synthesized from a compound of Formula IIb in two Steps as described in Scheme 132.

**Scheme 132**



*Step 1 - Preparation of compound of Formula IIc*

[0587] Compound of Formula IIc (Formula IIa where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, R<sup>43</sup> is M<sup>1</sup>R<sup>58</sup>, where M<sup>1</sup> is O or NR<sup>57</sup> and R<sup>58</sup> is optionally substituted aryl or optionally substituted heteroaryl) is prepared by reacting compound of Formula IIb (Formula IIa where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, R<sup>43</sup> is M<sup>1</sup>H, where M<sup>1</sup> is O or NR<sup>57</sup>) with a compound of Formula R<sup>58</sup>-X, where X is an appropriate leaving group such as a halogen or triflate, in the presence of a base (e.g. sodium hydride) in an appropriate solvent (e.g. dimethylformamide) with heating (e.g. 80 °C) for several hours. Alternatively, the reaction may be catalyzed by a metal (e.g. palladium acetate and tri-*t*-butylphosphine



when  $M^1$  is  $NR^{57}$ , copper bromide when  $M^1$  is O). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIc.

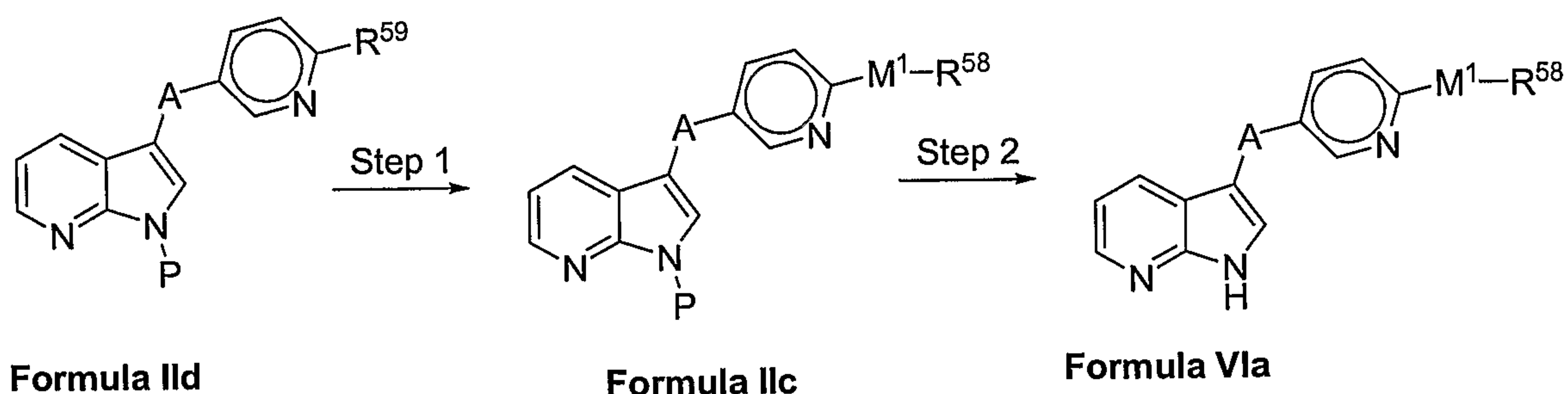
*Step 2 - Preparation of compound of Formula VI where M is  $NR^{57}$  or O and  $R^1$  is optionally substituted aryl or optionally substituted heteroaryl*

[0588] Compound of Formula VIa (Formula VI where M is  $NR^{57}$  or O ( $M^1$ ),  $R^1$  is optionally substituted aryl or optionally substituted heteroaryl ( $R^{58}$ )) is prepared from compound of Formula IIc by removal of the N-1 protecting group according to Scheme 43, Step 2.

**Example 76: Synthesis of Compounds of Formula VI where M is  $NR^{57}$  or O and  $R^1$  is optionally substituted aryl or optionally substituted heteroaryl**

[0589] Compound of Formula VIa (Formula VI where M is  $NR^{57}$  or O ( $R^{57}$  consistent with definition of M for compounds of Formula Ib or  $L^2$  for compounds of Formula I) and  $R^1$  is optionally substituted aryl or optionally substituted heteroaryl) may be synthesized from a compound of Formula IId in two Steps as described in Scheme 133.

### Scheme 133



*Step 1 - Preparation of compound of Formula IIc*

[0590] Compound of Formula IIc (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $M^1R^{58}$ , where  $M^1$  is O or  $NR^{57}$  and  $R^{58}$  is optionally substituted aryl or optionally substituted heteroaryl) is prepared by reacting compound of Formula IId (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is a halogen,  $R^{59}$ , e.g. chloro) with a compound of Formula  $R^{58}$ -OH or of Formula  $R^{58}$ - $NR^{57}$  in the presence of a base (e.g. sodium hydride) in an appropriate solvent (e.g. dimethylformamide) with heating (e.g. 80 °C) for several hours. Alternatively, the reaction may be catalyzed by a metal (e.g. palladium acetate and tri-*t*-butylphosphine when  $M^1$  is  $NR^{57}$ , copper bromide when  $M^1$  is

O). Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIc.

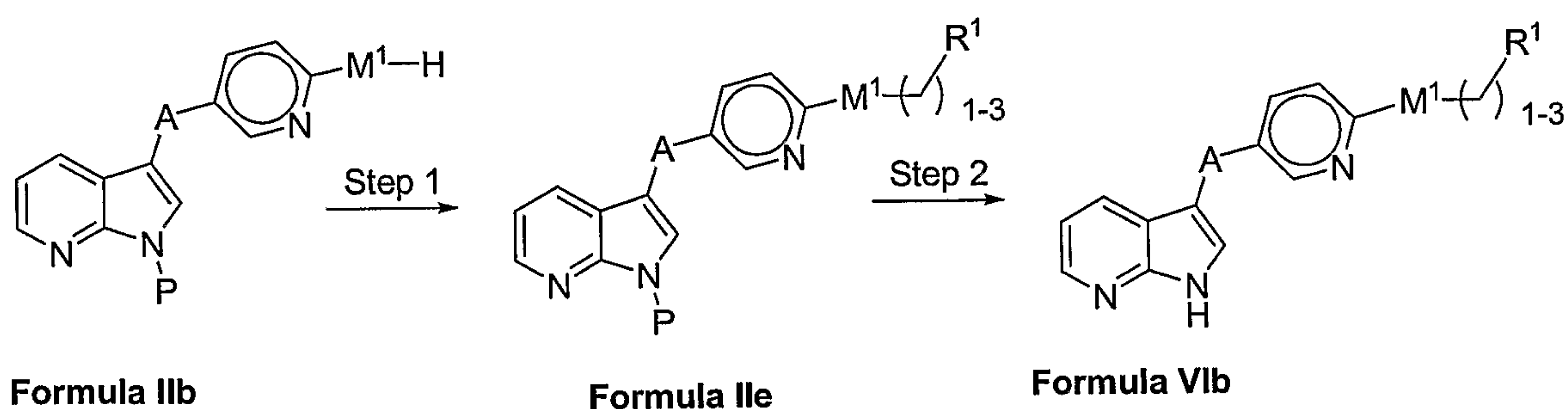
*Step 2 - Preparation of compound of Formula VI where M is NR<sup>57</sup> or O and R<sup>1</sup> is optionally substituted aryl or optionally substituted heteroaryl*

[0591] Compound of Formula VIa (Formula VI where M is NR<sup>57</sup> or O (M<sup>1</sup>), R<sup>1</sup> is optionally substituted aryl or optionally substituted heteroaryl (R<sup>58</sup>)) is prepared from compound of Formula IIc by removal of the N-1 protecting group according to Scheme 43, Step 2.

**Example 77: Synthesis of Compounds of Formula VI where M is -O-alk- or -NR<sup>57</sup>-alk-**

[0592] Compound of Formula VIb (Formula VI where M is -O-alk- or -NR<sup>57</sup>-alk- (R<sup>57</sup> consistent with definition of M for compounds of Formula Ib or L<sup>2</sup> for compounds of Formula I)) may be synthesized from a compound of Formula IIb in two Steps as described in Scheme 134.

**Scheme 134**



*Step 1 - Preparation of compound of Formula IIe*

[0593] Compound of Formula IIe (Formula IIa where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, R<sup>43</sup> is M<sup>1</sup>(CH<sub>2</sub>)<sub>1-3</sub>R<sup>1</sup> where M<sup>1</sup> is O or NR<sup>57</sup>) is prepared by reacting compound of Formula IIb (Formula IIa where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, R<sup>43</sup> is M<sup>1</sup>H, where M<sup>1</sup> is O or NR<sup>57</sup>) with a compound of Formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>1-3</sub>-X where X is a leaving group (e.g. halogen, mesylate) in the presence of a base (e.g. sodium hydride, potassium carbonate) in an appropriate solvent (e.g. dimethylformamide, acetonitrile) with heating (e.g. 80 °C) for one to several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography), provides compounds of Formula IIe.



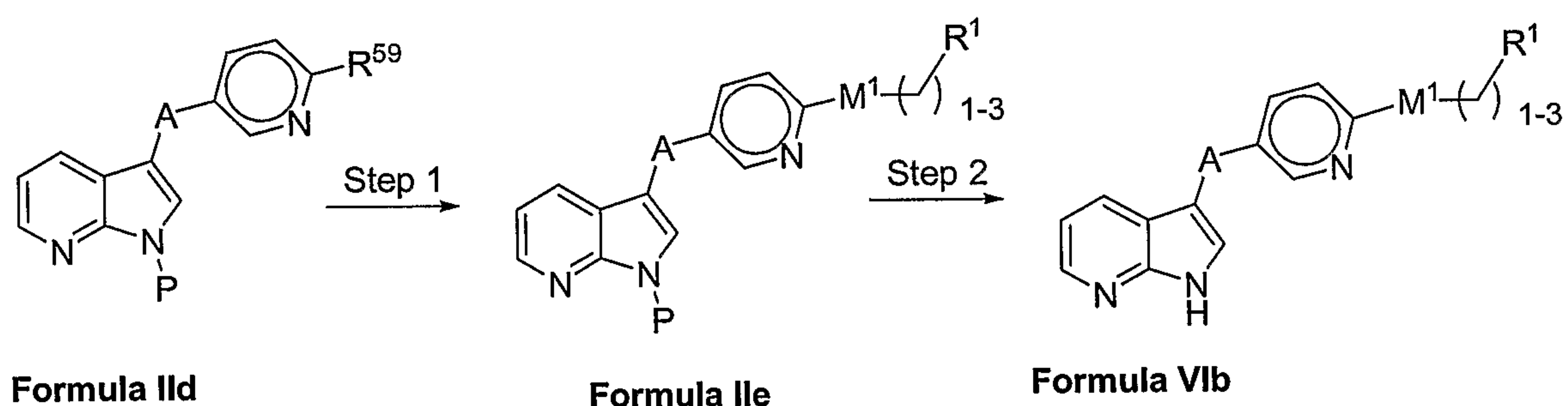
*Step 2 - Preparation of compound of Formula VI where M is  $M^1(CH_2)_{1-3}$  and  $M^1$  is O or  $NR^{57}$*

[0594] Compound of Formula VIb (Formula VI where M is  $O(CH_2)_{1-3}$  or  $NR^{57}(CH_2)_{1-3}$ ) is prepared from compound of Formula IIe by removal of the N-1 protecting group according to Scheme 43, Step 2.

**Example 78: Synthesis of Compounds of Formula VI where M is -O-alk- or - $NR^{57}$ -alk-**

[0595] Compound of Formula VIb (Formula VI where M is -O-alk- or - $NR^{57}$ -alk- ( $R^{57}$  consistent with definition of M for compounds of Formula Ib or  $L^2$  for compounds of Formula I)) may be synthesized from a compound of Formula IId in two Steps as described in Scheme 135.

#### Scheme 135



*Step 1 - Preparation of compound of Formula IIe*

[0596] Compound of Formula IIe (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $M^1(CH_2)_{1-3}R^1$  where  $M^1$  is O or  $NR^{57}$ ) is prepared by reacting compound of Formula IId (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is a halogen,  $R^{59}$ , e.g. chloro) with a compound of Formula  $R^1-(CH_2)_{1-3}-OH$  or  $R^1-(CH_2)_{1-3}-NR^{57}$  in the presence of a base (e.g. sodium hydride, potassium carbonate) in an appropriate solvent (e.g. dimethylformamide, acetonitrile) with heating (e.g. 80 °C) for one to several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography), provides compound of Formula IIe.

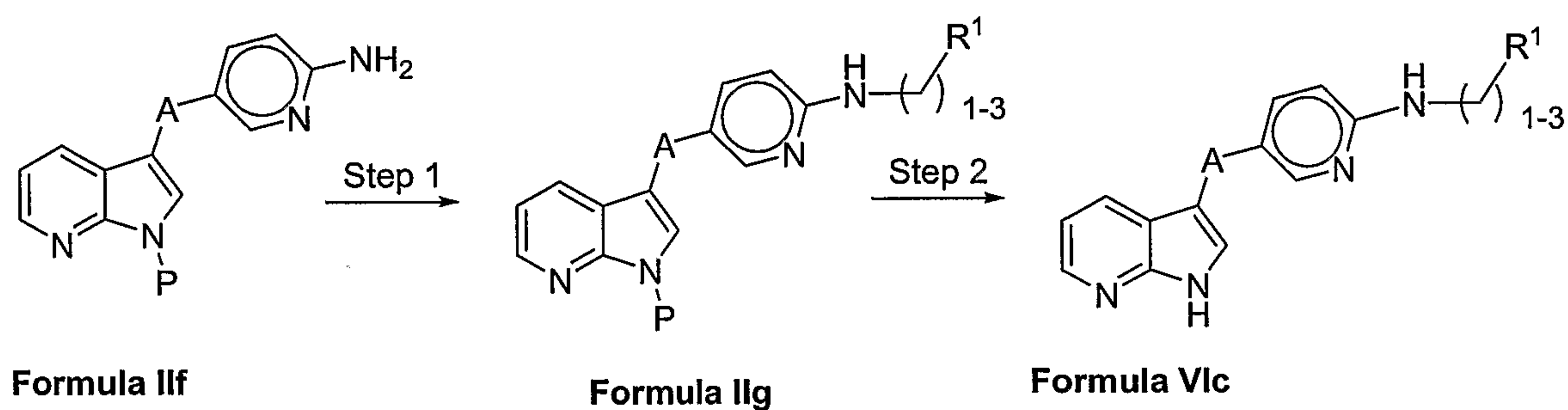
*Step 2 - Preparation of compound of Formula VI where M is  $M^1(CH_2)_{1-3}$  and  $M^1$  is O or  $NR^{57}$*

[0597] Compound of Formula VIb (Formula VI where M is  $O(CH_2)_{1-3}$  or  $NR^{57}(CH_2)_{1-3}$ ) is prepared from compound of Formula IIe by removal of the N-1 protecting group according to Scheme 43, Step 2.

**Example 79: Synthesis of Compounds of Formula VI where M is NH-alk-**

[0598] Compound of Formula VIc (Formula VI where M is -NH-alk-) may be synthesized from a compound of Formula IIf in two Steps as described in Scheme 136.

**Scheme 136**



*Step 1 - Preparation of compound of Formula IIg*

[0599] Compound of Formula IIg (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $NH(CH_2)_{1-3}R^1$ ) is prepared from compound of Formula IIf (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $NH_2$ ) by reductive amination using an aldehyde of the formula  $R^1-(CH_2)_{0-2}-CHO$  in the presence of a catalytic amount of acid (e.g. acetic acid) and a reducing agent (e.g. sodium triacetoxyborohydride) in a non-reactive solvent (e.g. dichloroethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIg.

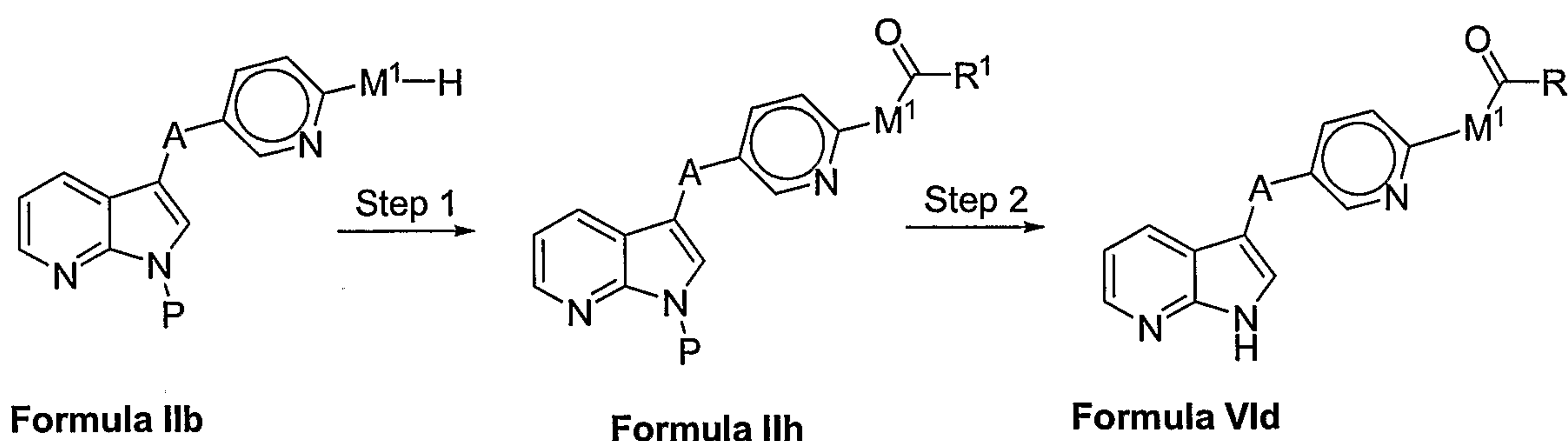
*Step 2 - Preparation of compound of Formula VI where M is  $NH(CH_2)_{1-3}$*

[0600] Compound of Formula VIc (Formula VI where M is  $NH(CH_2)_{1-3}$ ) is prepared from compound of Formula IIg by removal of the N-1 protecting group according to Scheme 43, Step 2.



**Example 80: Synthesis of Compounds of Formula VI where M is NR<sup>57</sup>C(O) or OC(O)**

[0601] Compound of Formula VI<sub>d</sub> (Formula VI where M is NR<sup>57</sup>C(O) or OC(O) where R<sup>57</sup> is consistent with definition of M for compounds of Formula Ib or L<sup>2</sup> for compounds of Formula I) may be synthesized from a compound of Formula II<sub>b</sub> in two Steps as described in Scheme 137.

**Scheme 137***Step 1 - Preparation of compound of Formula III<sub>h</sub>*

[0602] Compound of Formula III<sub>h</sub> (Formula II<sub>a</sub> where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, R<sup>43</sup> is M<sup>1</sup>C(O)R<sup>1</sup> where M<sup>1</sup> is O or NR<sup>57</sup>) is prepared by reacting compound of Formula II<sub>b</sub> (Formula II<sub>a</sub> where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, R<sup>43</sup> is M<sup>1</sup>H, where M<sup>1</sup> is O or NR<sup>57</sup>) with an activated carboxylic acid of Formula R<sup>1</sup>-COX where X is a leaving group such as chloro (e.g. benzoyl chloride) in the presence of a base (e.g. DIEA) in a non-reactive solvent (e.g. dichloromethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula III<sub>h</sub>.

*Step 2 - Preparation of compound of Formula VI where M is OC(O) or NR<sup>57</sup>C(O)*

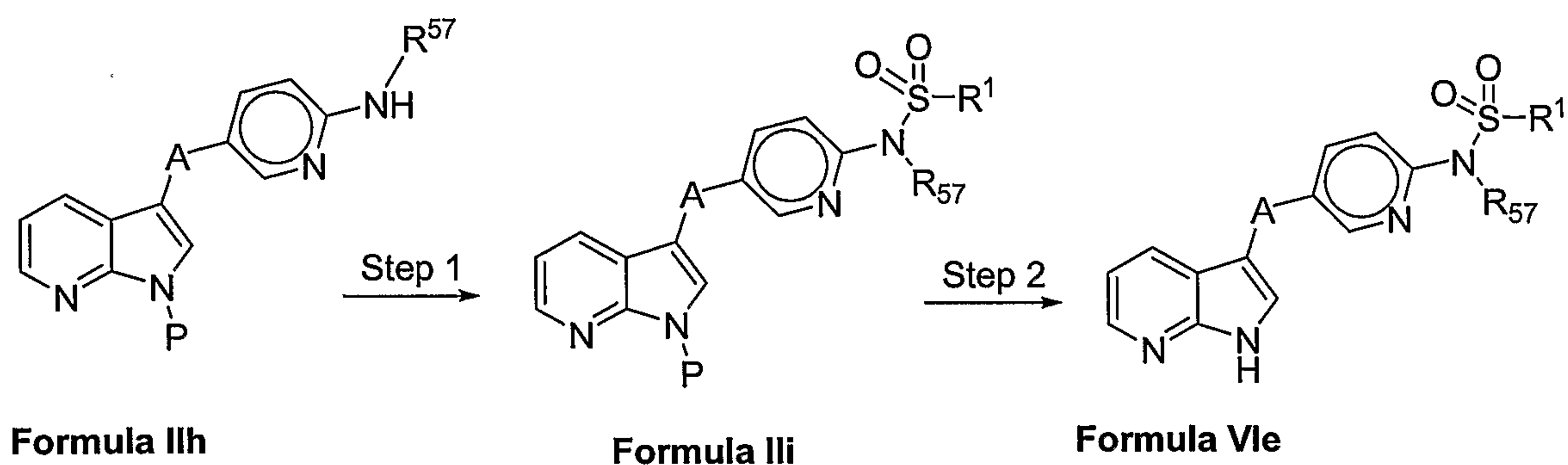
[0603] Compounds of Formula VI<sub>d</sub> (Formula VI where M is OC(O) or NR<sup>57</sup>C(O)) is prepared from compound of Formula III<sub>h</sub> by removal of the N-1 protecting group according to Scheme 43, Step 2.

**Example 81: Synthesis of Compounds of Formula VI where M is NR<sup>57</sup>S(O)<sub>2</sub>**

[0604] Compound of Formula VI<sub>e</sub> (Formula VI where M is NR<sup>57</sup>S(O)<sub>2</sub> where R<sup>57</sup> is consistent with definition of M for compounds of Formula Ib or L<sup>2</sup> for compounds of

Formula I) may be synthesized from a compound of Formula IIh in two Steps as described in Scheme 138.

### Scheme 138



#### Step 1 - Preparation of compound of Formula III

**[0605]** Compound of Formula III (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $NR^{57}S(O)_2R^1$ ) is prepared by reacting compound of Formula IIh (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is  $NR^{57}H$ ) by reaction with a sulfonyl chloride of the formula  $R^1-SO_2Cl$  (e.g. phenylsulfonyl chloride) in the presence of a base (e.g. DIEA, pyridine) in a non-reactive solvent (e.g. dichloromethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula III.

#### Step 2 - Preparation of compound of Formula VI where M is $NR^{57}S(O)_2$

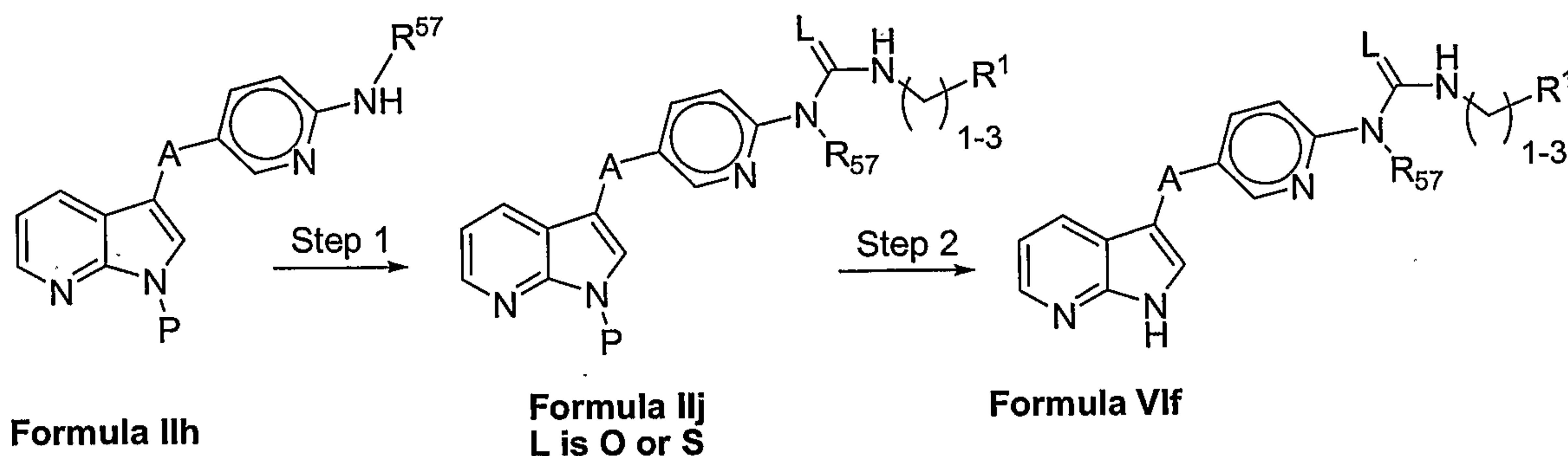
**[0606]** Compound of Formula VIe (Formula VI where M is  $NR^{57}S(O)_2$ ) is prepared from compound of Formula III by removal of the N-1 protecting group according to Scheme 43, Step 2.

#### Example 82: Synthesis of Compounds of Formula VI where M is $NR^{57}C(O)NH(CH_2)_{1-3}$ or $NR^{57}C(S)NH(CH_2)_{1-3}$

**[0607]** Compound of Formula VI (Formula VI where M is  $NR^{57}C(O)NH(CH_2)_{1-3}$  or  $NR^{57}C(S)NH(CH_2)_{1-3}$ , where  $R^{57}$  is consistent with definition of M for compounds of Formula Ib or L<sup>2</sup> for compounds of Formula I) may be synthesized from a compound of Formula IIh in two Steps as described in Scheme 139.



## Scheme 139

*Step 1 - Preparation of compound of Formula IIj*

[0608] Compound of Formula IIj (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $NR^{57}C(L)NH(CH_2)_{1-3}R^1$ , where L is O or S) is prepared by reacting compound of Formula IIIh (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is  $NR^{57}H$ ) with a compound of the formula  $R^1-(CH_2)_{1-3}NCL$  where L is either O to form an isocyanate (e.g. phenyl isocyanate) or L is S to form a thioisocyanate (e.g. phenyl isothiocyanate) in the presence of a base (e.g. DIEA) in a non-reactive solvent (e.g. dichloromethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIj.

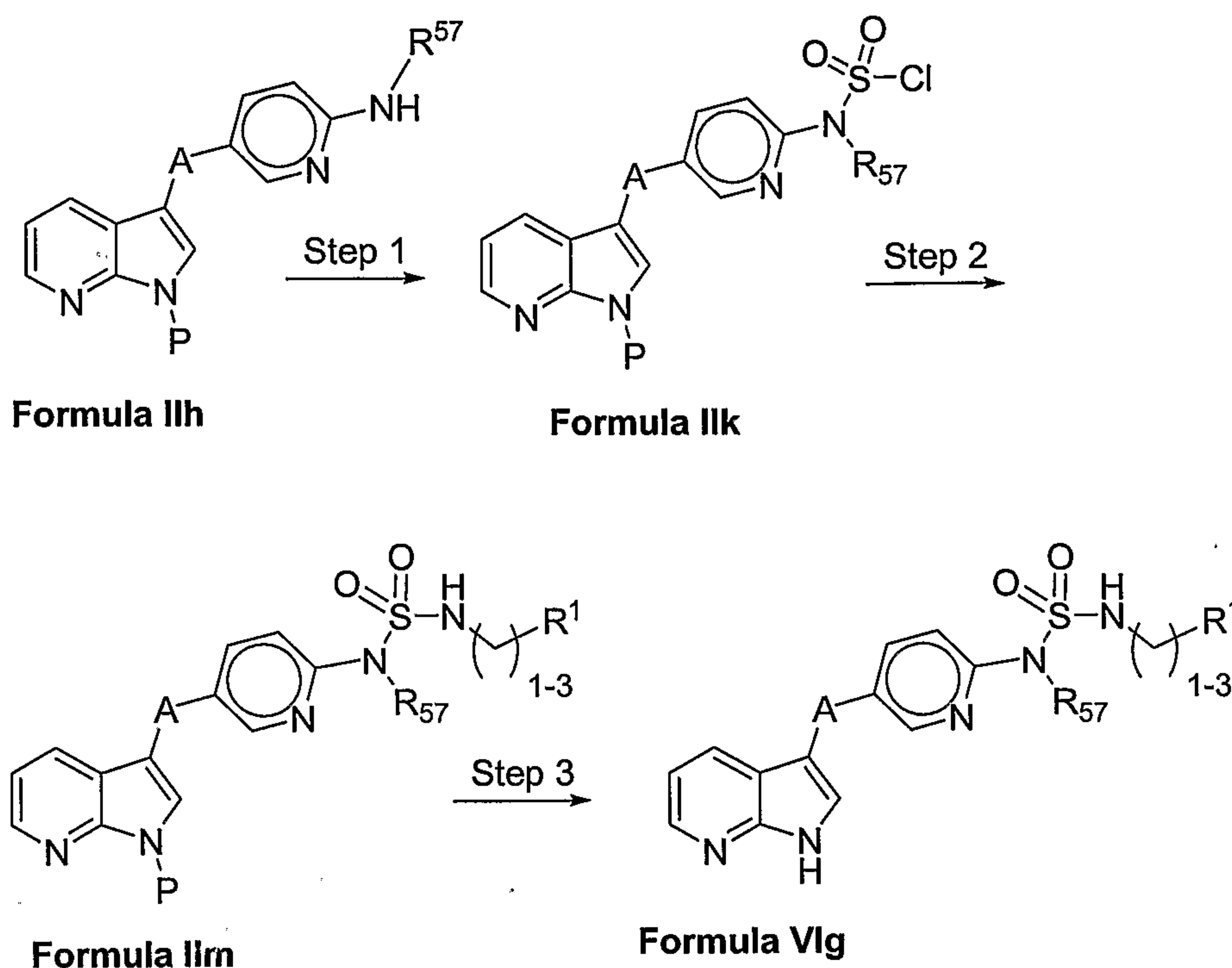
*Step 2 - Preparation of compound of Formula VI where B is NR and D is  $C(=L)NH(CH_2)_q$* 

[0609] Compound of Formula VI (Formula VI where M is  $NR^{57}C(O)NH(CH_2)_{1-3}$  or  $NR^{57}C(S)NH(CH_2)_{1-3}$ ) is prepared from compound of Formula IIj by removal of the N-1 protecting group according to Scheme 43, Step 2.

**Example 83: Synthesis of Compounds of Formula VI where M is  $NR^{57}S(O)_2NH(CH_2)_{1-3}$**

[0610] Compound of Formula VIg (Formula VI where M is  $NR^{57}S(O)_2NH(CH_2)_{1-3}$ , where  $R^{57}$  is consistent with definition of M for compounds of Formula Ib or  $L^2$  for compounds of Formula I) may be synthesized from a compound of Formula IIIh in three Steps as described in Scheme 140.

## Scheme 140

*Step 1 - Preparation of compound of Formula IIk*

[0611] Compound of Formula IIk (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $\text{NR}^{57}\text{S}(\text{O})_2\text{Cl}$ ) is prepared by reacting compound of Formula IIh (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is  $\text{NR}^{57}\text{H}$ ) with sulfonyl chloride in a non-reactive solvent (e.g. dichloromethane) possibly with heating (eg.  $60^\circ\text{C}$ ). After stirring for several hours, the reaction can be concentrated to provide compound of Formula IIk that is used without further purification.

*Step 2 - Preparation of compound of Formula IIm*

[0612] Compound of Formula IIm (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $\text{NR}^{57}\text{S}(\text{O})_2\text{NH}(\text{CH}_2)_{1-3}\text{R}^1$ ) is prepared from compound of Formula IIk by reaction with an amine of the formula  $\text{NH}_2(\text{CH}_2)_{1-3}\text{R}^1$  in the presence of a base (e.g. DIEA) in a non-reactive solvent (e.g. dichloromethane). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIm.



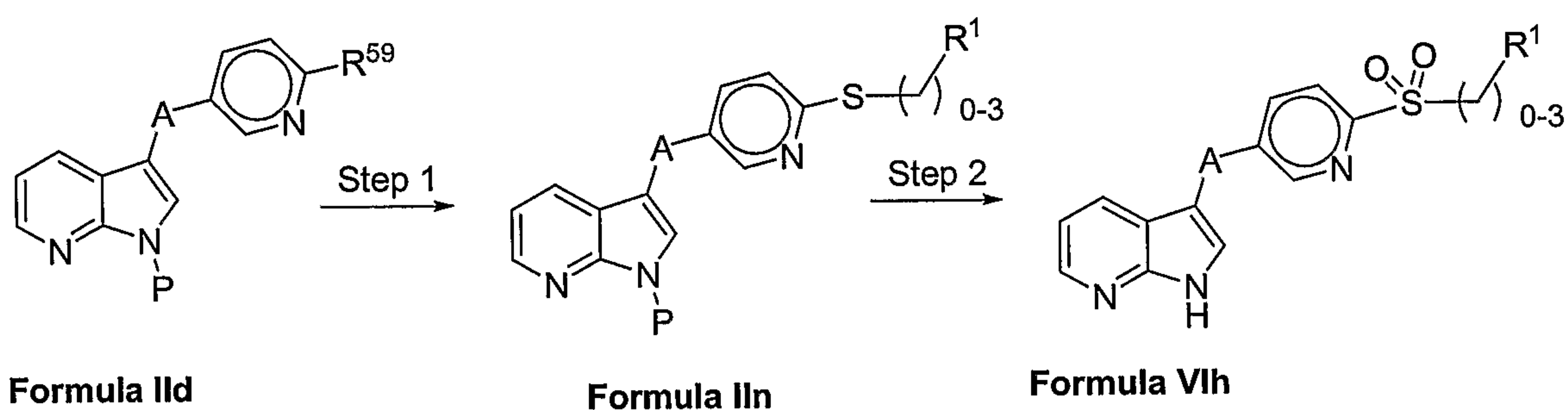
*Step 3 - Preparation of compound of Formula VI where M is  $NR^{57}S(O)_2NH(CH_2)_{1-3}$*

[0613] Compound of Formula VIg (Formula VI where M is  $NR^{57}S(O)_2NH(CH_2)_{1-3}$ ) is prepared from compound of Formula IIm by removal of the N-1 protecting group according to Scheme 43, Step 2.

**Example 84: Synthesis of Compounds of Formula VI where M is  $S(O)_2(CH_2)_{0-3}$  or  $S(CH_2)_{0-3}$**

[0614] Compound of Formula VIh (Formula VI where M is  $S(O)_2(CH_2)_{0-3}$  or  $S(CH_2)_{0-3}$ ) may be synthesized from a compound of Formula IId in two Steps as described in Scheme 141.

**Scheme 141**



*Step 1 - Preparation of compound of Formula IIn*

[0615] Compound of Formula IIn (Formula IId where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $S(CH_2)_{0-3}R^1$ ) is prepared by reacting compound of Formula IId (Formula IId where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is a halogen,  $R^{59}$ , e.g. chloro) with a compound of Formula  $R^1-(CH_2)_{0-3}-SH$  in the presence of a base (e.g. sodium hydride, potassium carbonate) in an appropriate solvent (e.g. dimethylformamide, acetonitrile) with heating (e.g. 80 °C) for one to several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIn. This can be taken to the next step, or the N-1 protecting group P can be removed according to Scheme 43, Step 2 to provide compound of Formula VI where M is  $S(CH_2)_{0-3}$ .

*Step 2 - Preparation of compound of Formula VI where M is  $SO_2(CH_2)_{0-3}$*

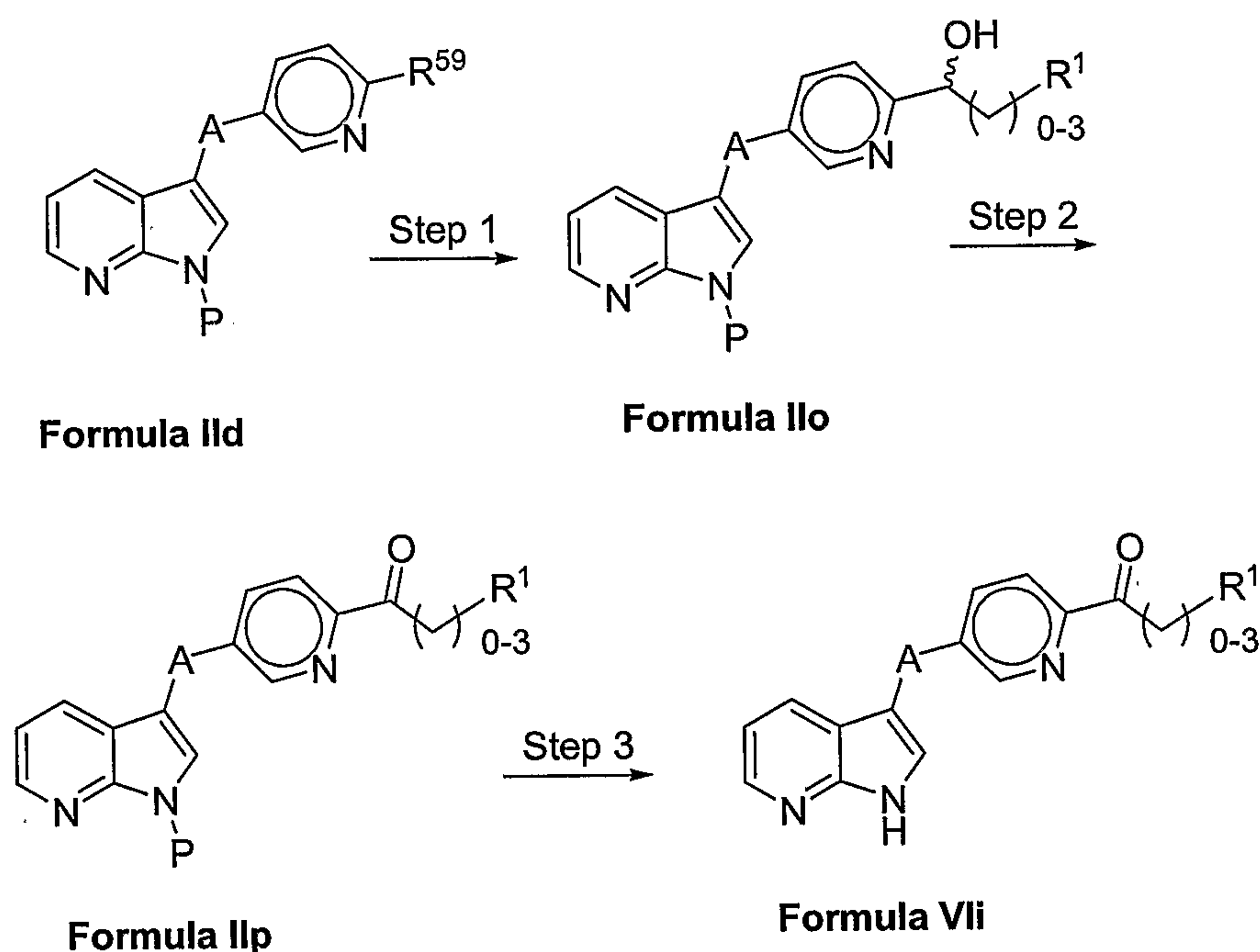
[0616] Compounds of Formula VIh (Formula VI where M is  $S(O)_2(CH_2)_{0-3}$ ) is prepared from compound of Formula IIn by reacting with an oxidizing agent (e.g. meta-chloro-peroxybenzoic acid, hydrogen peroxide) in an appropriate aprotic solvent (e.g.

dichloromethane). Isolation by conventional means (e.g. extraction and silica gel chromatography) followed by removal of the N-1 protecting group according to Scheme 43, Step 2 provides compound of Formula VIh.

**Example 85: Synthesis of Compounds of Formula VI where M is C(O)(CH<sub>2</sub>)<sub>0-3</sub>**

[0617] Compound of Formula VII (Formula VI where M is C(O)(CH<sub>2</sub>)<sub>0-3</sub>) may be synthesized from a compound of Formula IId in three Steps as described in Scheme 142.

**Scheme 142**



*Step 1 - Preparation of compound of Formula IIo*

[0618] Compound of Formula IIo (Formula IIa where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, R<sup>43</sup> is C(OH)(CH<sub>2</sub>)<sub>0-3</sub>R<sup>1</sup>) is prepared by reacting compound of Formula IId (Formula IIa where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, and R<sup>43</sup> is a halogen, R<sup>59</sup>, e.g. chloro) with an organolithium reagent (e.g. butyllithium) to effect the lithium-halogen exchange at reduced temperature (e.g. -78 °C) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of an aldehyde of Formula R<sup>1</sup>-(CH<sub>2</sub>)<sub>0-3</sub>-C(O)H. After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIo.



*Step 2 - Preparation of compound of Formula IIp*

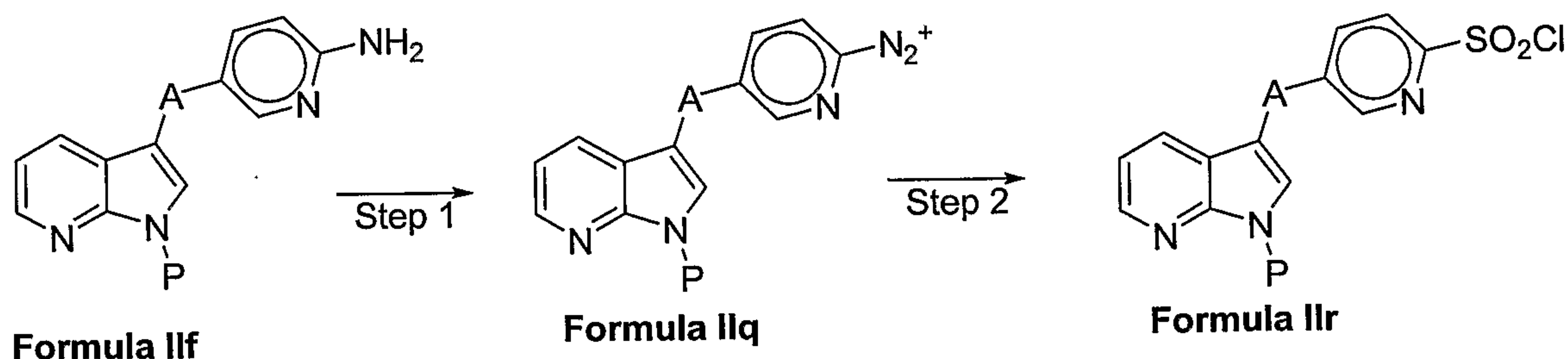
[0619] Compound of Formula IIp (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P,  $R^{43}$  is  $C(O)(CH_2)_{0-3}R^1$ ) is prepared by reacting compound of Formula IIo with an oxidizing agent (e.g. Dess-Martin periodinane), in an appropriate solvent (e.g. tetrahydrofuran). After stirring for one to several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula IIp.

*Step 3 - Preparation of compound of Formula VI where B is C=O and D is  $(CH_2)_w$* 

[0620] Compound of Formula VIi (Formula VI where M is  $C(O)(CH_2)_{0-3}$ ) is prepared from compound of Formula IIp by removal of the N-1 protecting group according to Scheme 43, Step 2.

**Example 86: Synthesis of Compounds of Formula IIr**

[0621] Compound of Formula IIr ((Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is  $S(O)_2Cl$ ) may be synthesized from a compound of Formula IIf in two Steps as described in Scheme 143.

**Scheme 143***Step 1 - Preparation of compound of Formula IIq*

[0622] Compound of Formula IIq ((Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is  $N_2^+$ ) is prepared by reacting compound of Formula IIf (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is  $NH_2$ ) with aqueous hydrochloric acid and aqueous sodium nitrite. Addition of water and salt results in precipitation of the compound and filtration affords the chloride salt of the diazonium of Formula IIq.

*Step 2 - Preparation of compound of Formula IIr*

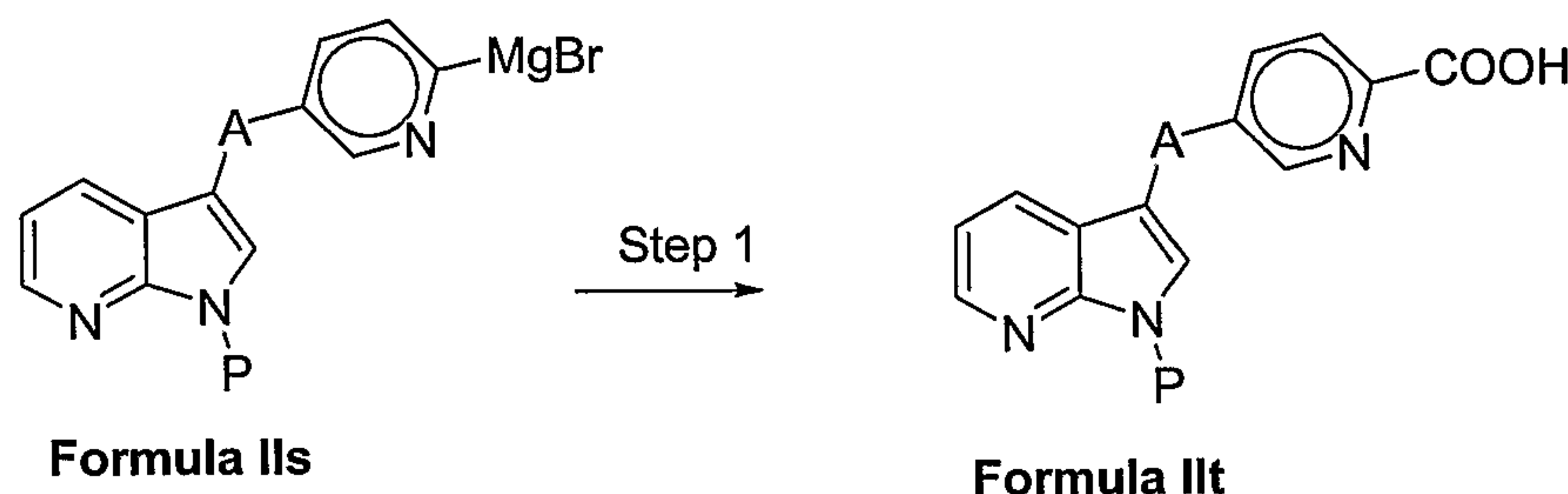
[0623] Compound of Formula IIr (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is  $S(O)_2Cl$ ) is prepared by reacting compound of Formula IIq (Formula IIa where

$R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is  $N_2^+$ ) with a mixture of cuprous chloride in acetic acid saturated with sulfur dioxide, while cooling (e.g. 10 °C). After stirring for 30 minutes to one hour, the mixture is poured into water and the compound is isolated by extraction and concentration of the dried organic portions to provide compound of Formula IIr. (Organic Syntheses, Coll. Vol. 7, p.508; Vol. 60, p.121).

### Example 87: Synthesis of Compounds of Formula IIr

[0624] Compound of Formula IIr ((Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is COOH) may be synthesized from a compound of Formula IIs in one Step as described in Scheme 144.

#### Scheme 144



#### Step 1 - Preparation of compound of Formula IIr

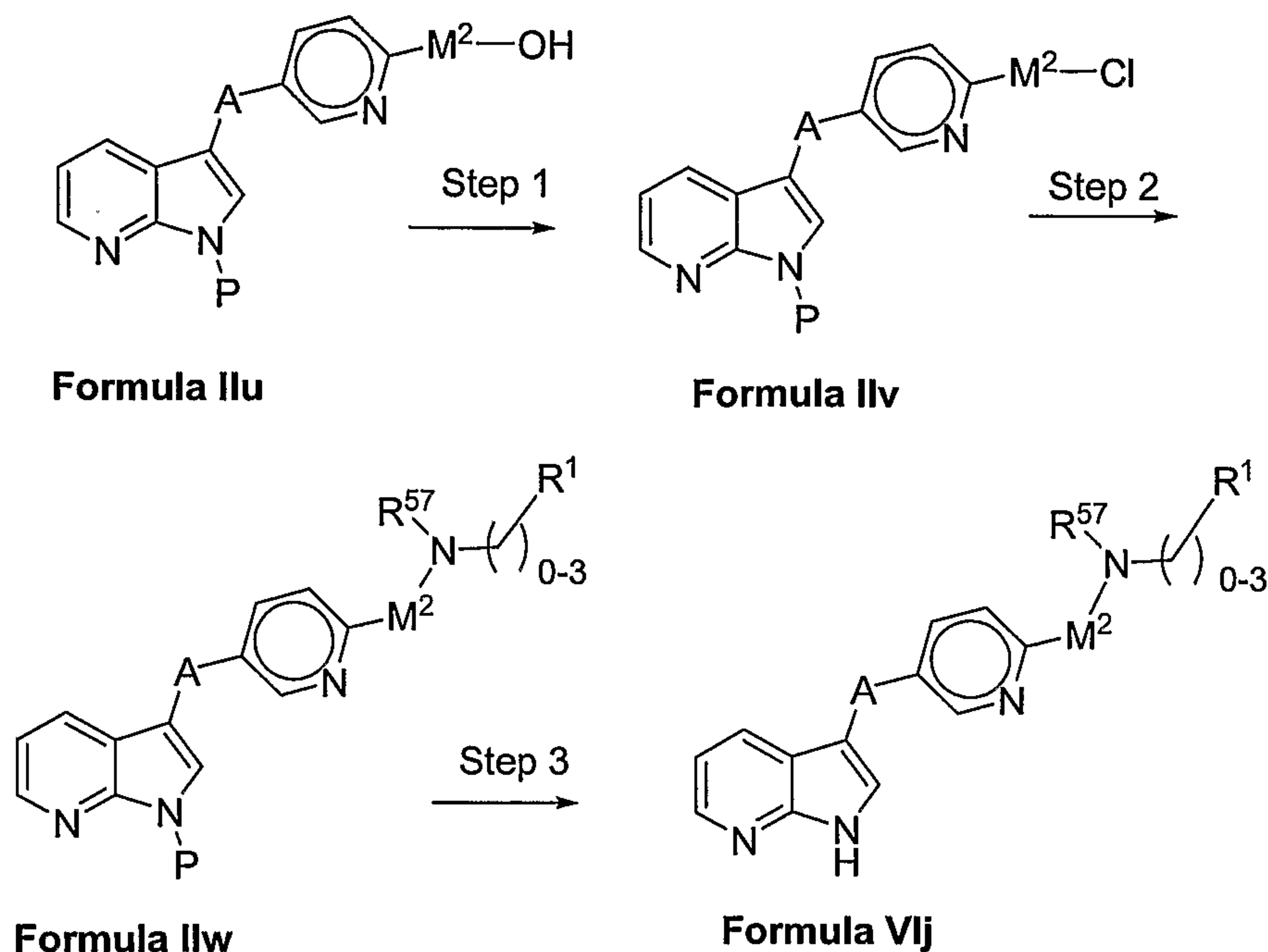
[0625] Compound of Formula IIr (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is COOH) is prepared by reacting compound of Formula IIs (Formula IIa where  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H,  $R^{41}$  is P, and  $R^{43}$  is MgBr) dissolved in an appropriate solvent (e.g. tetrahydrofuran) with dry ice. Addition of water and acid-base extraction of the compound provides compound of Formula IIr.

### Example 88: Synthesis of Compounds of Formula VI where M is $C(O)NR^{57}(CH_2)_{0-3}$ or $S(O)_2NR^{57}(CH_2)_{0-3}$

[0626] Compound of Formula VIj (Formula VI where M is  $C(O)NR^{57}(CH_2)_{0-3}$  or  $S(O)_2NR^{57}(CH_2)_{0-3}$ ), where  $R^{57}$  is consistent with definition of M for compounds of Formula Ib or  $L^2$  for compounds of Formula I) may be synthesized from a compound of Formula IIu in three Steps as described in Scheme 145.



## Scheme 145

*Step 1 - Preparation of compound of Formula IIv*

[0627] Compound of Formula IIv (Formula IIa where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, and R<sup>43</sup> is M<sup>2</sup>Cl, where M<sup>2</sup> is C(O) or S(O)<sub>2</sub>) is prepared by reacting compound of Formula IIu (Formula IIa where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, and R<sup>43</sup> is M<sup>2</sup>OH, where M<sup>2</sup> is C(O) or S(O)<sub>2</sub>) with an appropriate reagent to effect the formation of the acid chloride or sulfonyl chloride (e.g. thionyl chloride) with heating (e.g. 80 °C) for several hours, possibly in a solvent (e.g. toluene). Concentration of the reaction mixture provides compound of Formula IIv that is used without further purification.

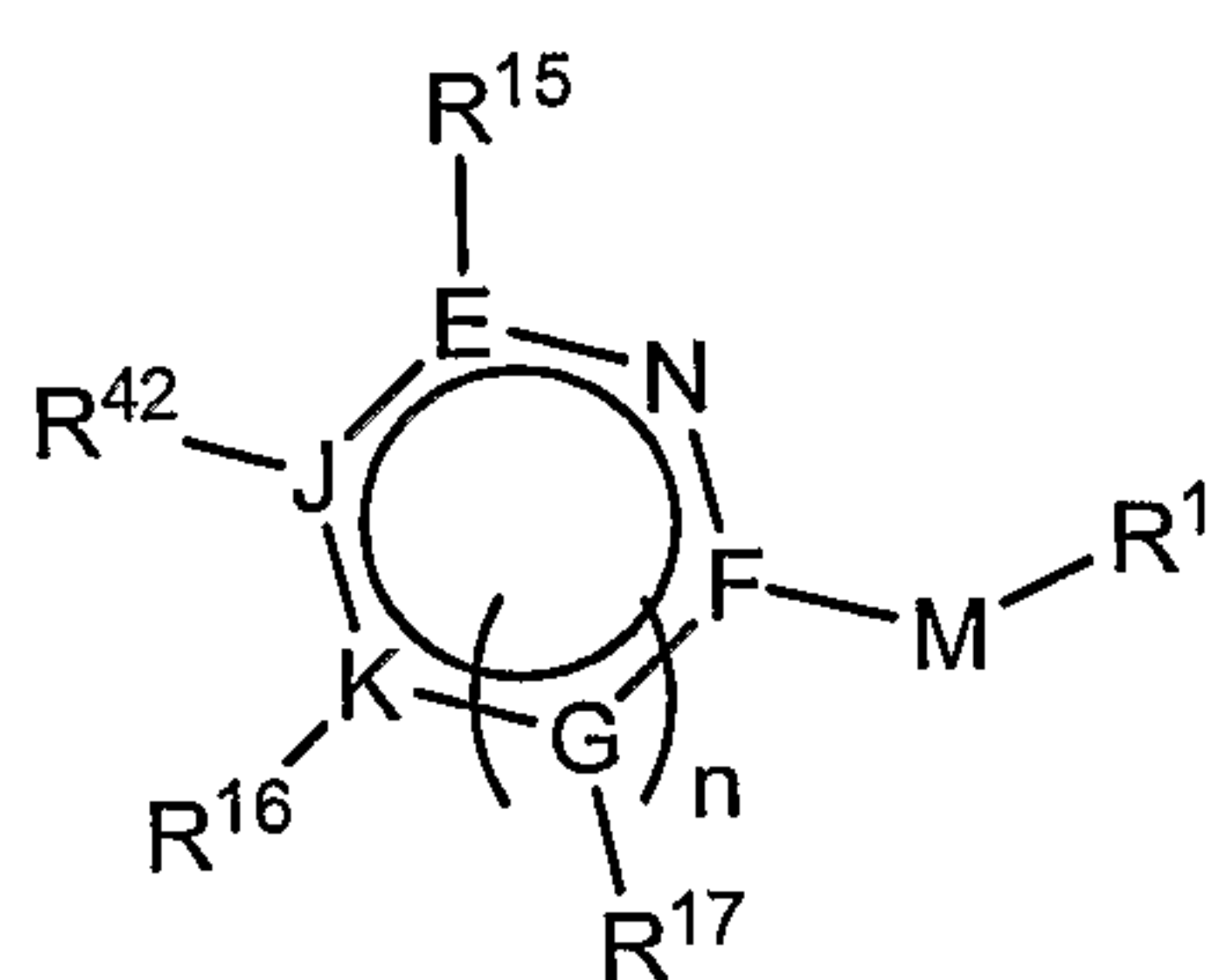
*Step 2 - Preparation of compound of Formula IIw*

[0628] Compound of Formula IIw (Formula IIa where R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are H, R<sup>41</sup> is P, and R<sup>43</sup> is M<sup>2</sup>NR<sup>57</sup>(CH<sub>2</sub>)<sub>0-3</sub>R<sup>1</sup>, where M<sup>2</sup> is C(O) or S(O)<sub>2</sub>) is prepared by reacting compound of Formula IIv with an amine of the formula NR<sup>57</sup>H(CH<sub>2</sub>)<sub>0-3</sub>R<sup>1</sup> in the presence of a base (e.g. DIEA) in an appropriate aprotic solvent (e.g. dimethylformamide, dichloromethane). After stirring for one to several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula IIw.

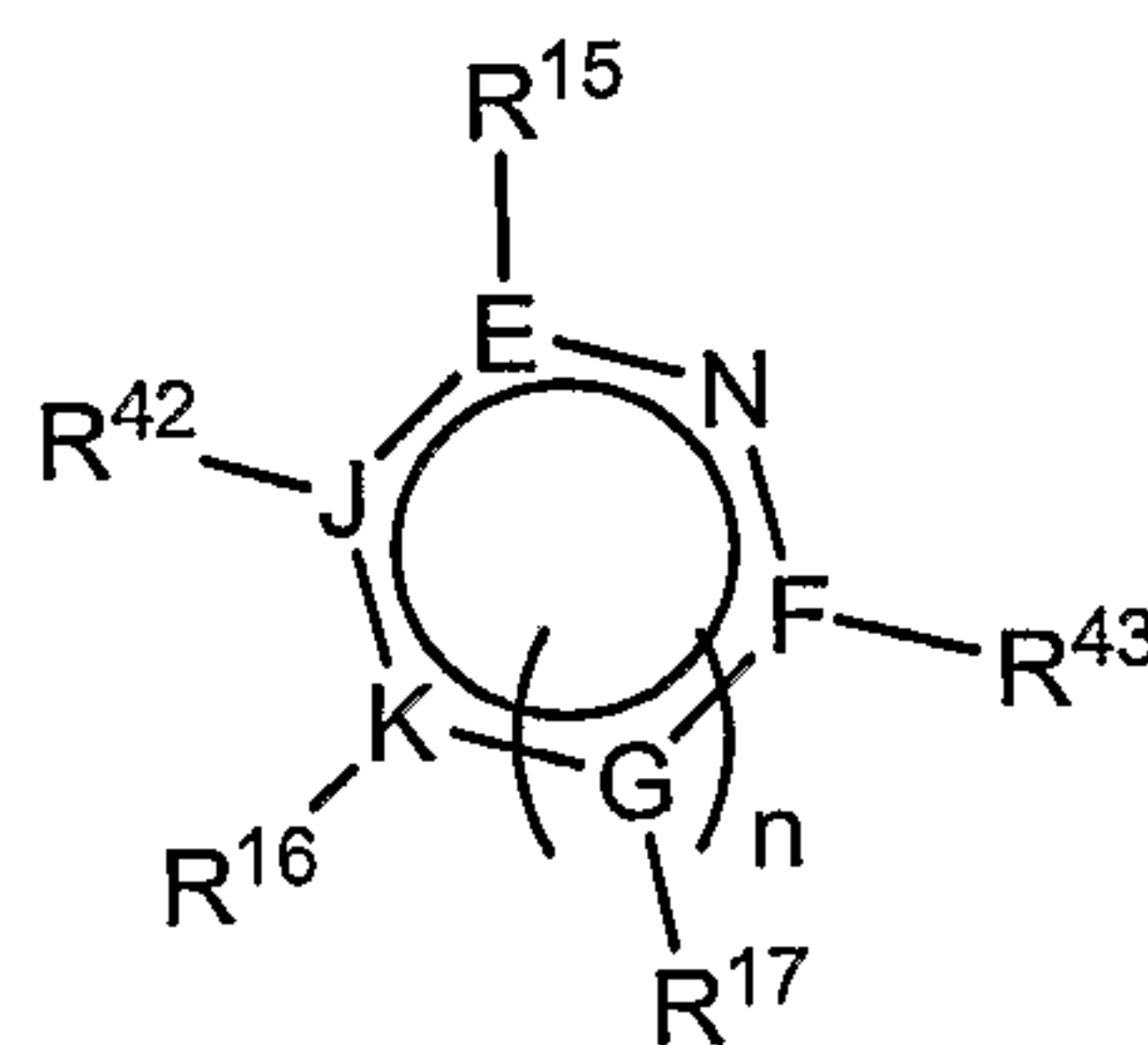
Step 3 - Preparation of **compound of Formula VI** where M is  $C(O)NR^{57}(CH_2)_{0-3}$  or  $S(O)_2NR^{57}(CH_2)_{0-3}$

[0629] Compounds of Formula VIj (Formula VI where M is  $C(O)NR^{57}(CH_2)_{0-3}$  or  $S(O)_2NR^{57}(CH_2)_{0-3}$ ) is prepared from compound of Formula IIw by removal of the N-1 protecting group according to Scheme 43, Step 2.

[0630] Compounds of Formula X or Xa, where  $R^{43}$  is a substituent appropriate for further substitution to provide M- $R^1$  (e.g. chloro,  $NHR^{57}$ , OH, MgBr,  $C(O)OH$ ,  $S(O)_2OH$ ; as described in Examples 78-88), and  $R^{42}$  is a functionality appropriate for coupling to the 7-azaindole ring or its analog to form A or  $L^1$ , are useful in the synthesis of compounds of Formula I or Ib or compounds of Formula II as described in Examples 43-59.



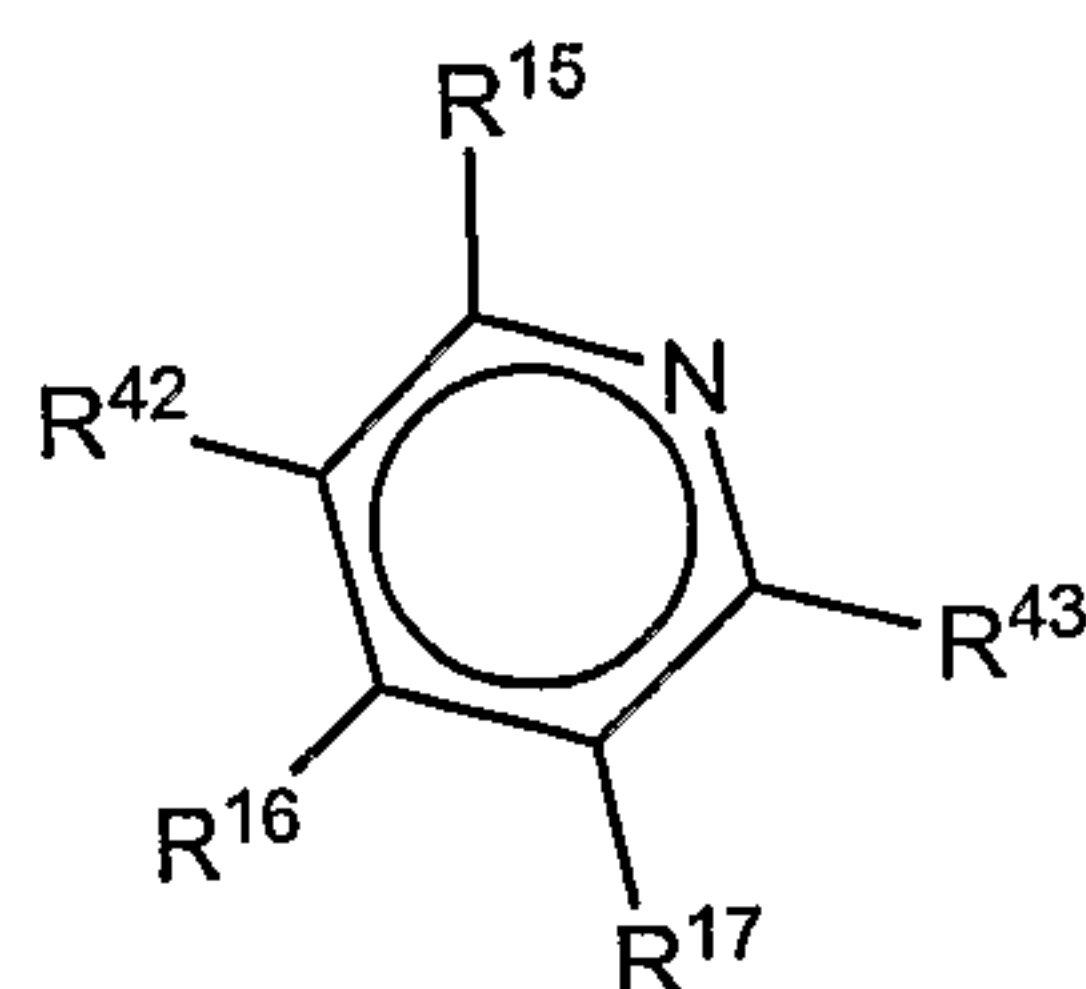
Formula X



Formula Xa

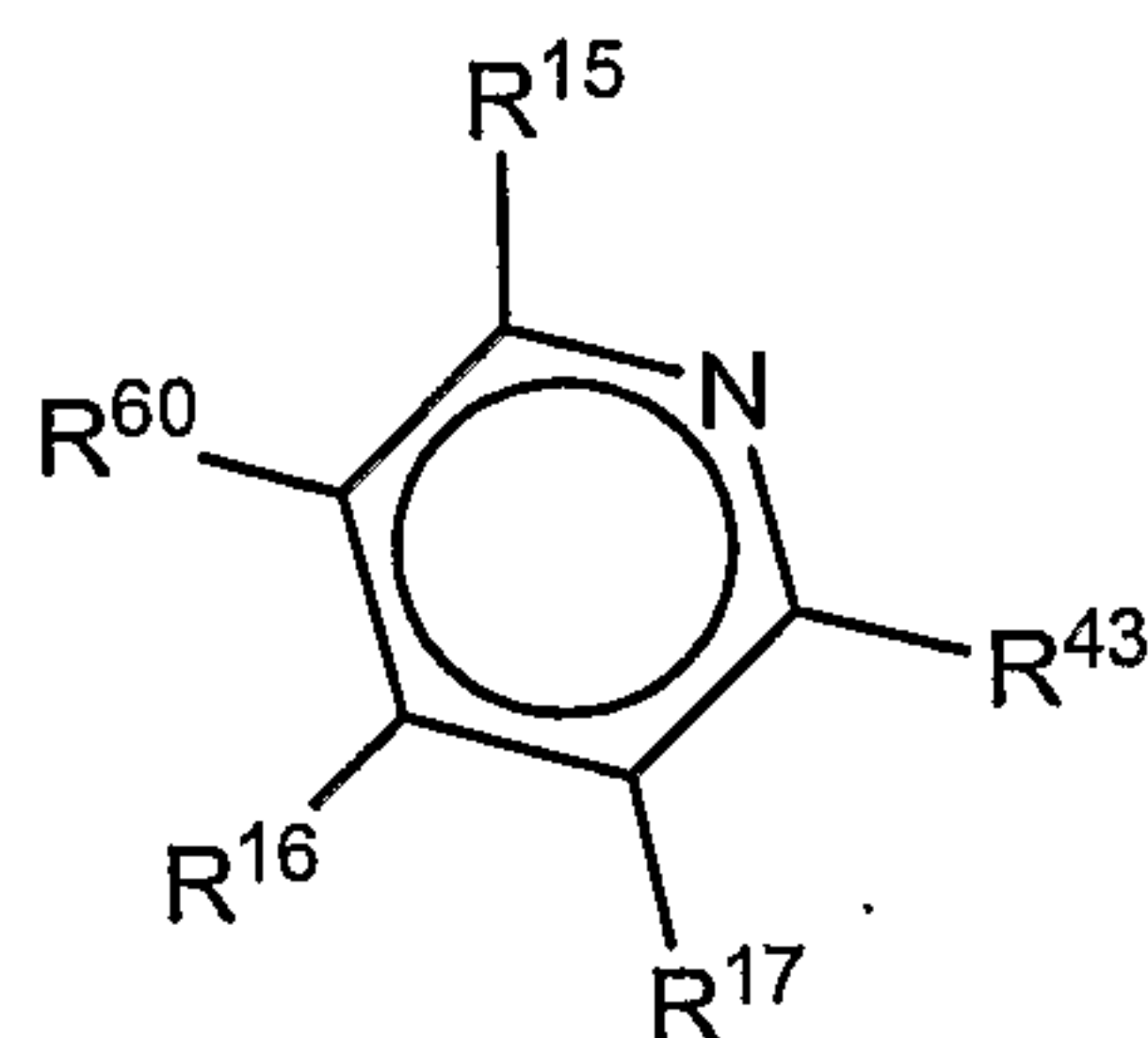
[0631] Many compounds of Formula X or Xa are commercially available; for example, many 5- and 6-membered nitrogen-containing heterocycles where  $R^{43}$  is chloro or amino and  $R^{42}$  is a carboxylic acid or aldehyde are commercially available or may be prepared using known methods.

[0632] Compounds of Formula Xa where E, F, G, K, L are C and n is 1 form compounds of Formula  $X_{10}$ . Examples for the synthesis of compounds of Formula  $X_{10}$  and their use in the synthesis of compounds of Formula I, Ib, and II may also be applied to other compounds fitting the definition of Formula X.

Formula  $X_{10}$



[0633] Compounds of Formula Xa, where  $R^{42}$  is a hydrogen or halogen ( $R^{60}$ ), and  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are either as defined for Formula Xa or are appropriate substituents for further modification to provide compounds of Formula X<sub>10</sub>, form compounds of Formula X<sub>20</sub>, which are useful in the synthesis of compounds of Formula Xa.

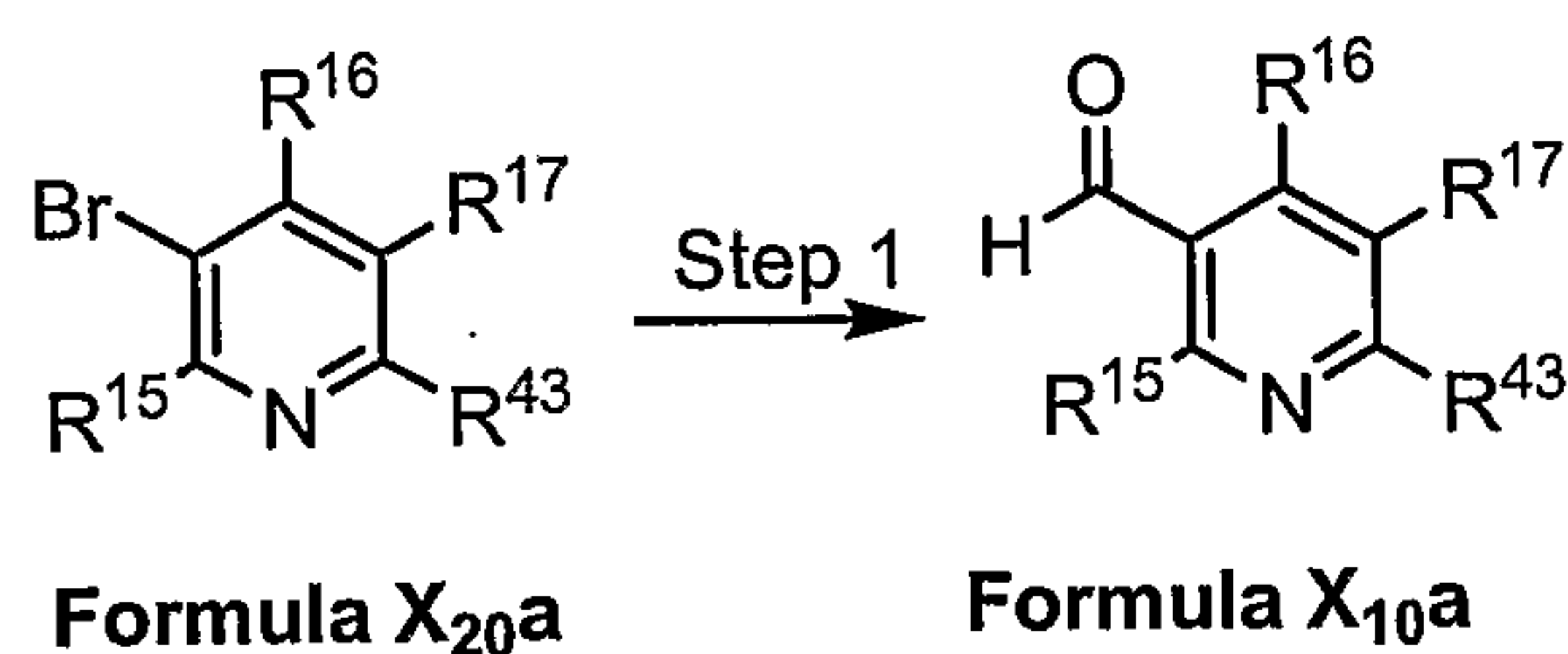
Formula X<sub>20</sub>

[0634] Use of compounds of Formula X<sub>10</sub> or X<sub>20</sub> are exemplified in the following examples as representative examples of reactions that may also be useful in the analogous reactions using compounds of Formula X or Xa.

**Example 89: Synthesis of Compounds of Formula X<sub>10</sub> where  $R^{42}$  is C(O)H**

[0635] Compound of Formula X<sub>10a</sub> (Formula X<sub>10</sub> where  $R^{42}$  is C(O)H) may be synthesized from a compound of Formula X<sub>20a</sub> in one Step as described in Scheme 146.

**Scheme 146**



*Step 1 - Preparation of compound of Formula X<sub>20b</sub>*

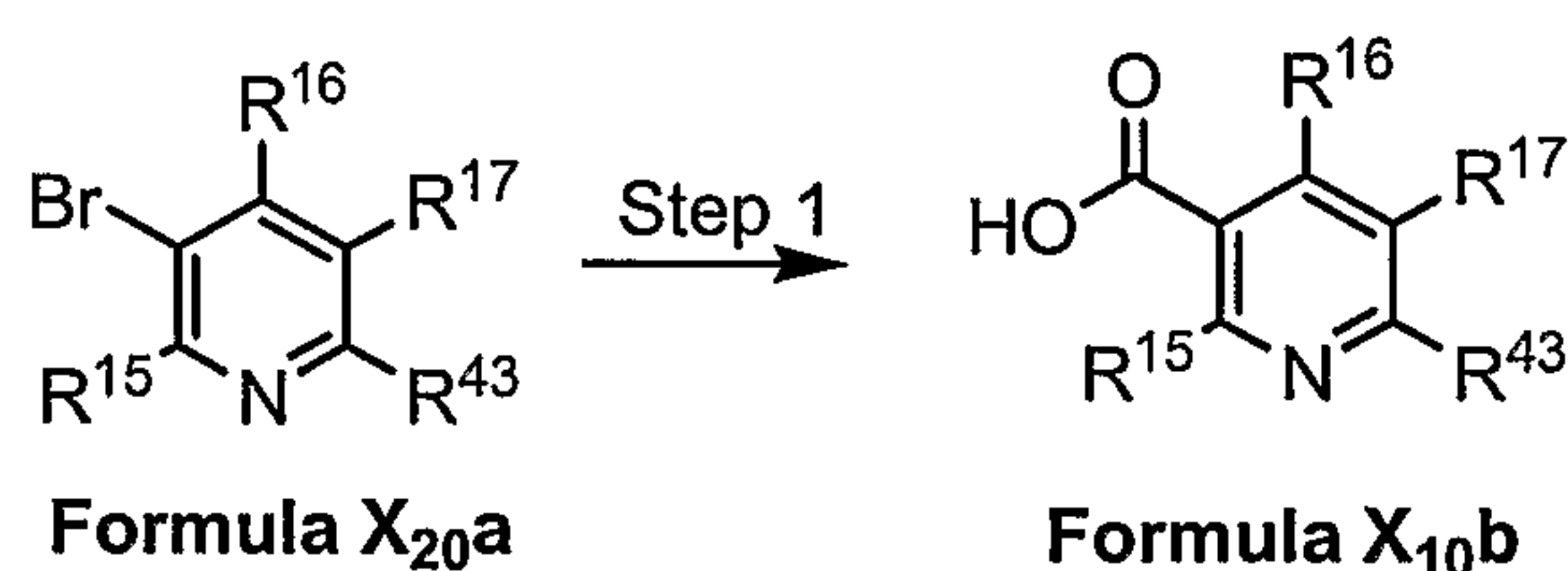
[0636] Compound of Formula X<sub>10a</sub> (Formula X<sub>10</sub> where  $R^{42}$  is C(O)H) is prepared by reacting compound of Formula X<sub>20a</sub> (Formula X<sub>20</sub> where  $R^{60}$  is Br) with an organolithium reagent (e.g. butyllithium) to effect the lithium-halogen exchange at reduced temperature (e.g.  $-78\text{ }^{\circ}\text{C}$ ) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica

gel chromatography), provides compounds of Formula X<sub>10a</sub>. Preferred compounds of X<sub>20a</sub> for this reaction have R<sup>15</sup> as optionally substituted lower alkyl, trifluoromethyl, CH<sub>2</sub>CF<sub>3</sub>, OR, or SR, wherein R is optionally substituted lower alkyl.

**Example 90: Synthesis of Compounds of Formula X<sub>10</sub> where R<sup>42</sup> is C(O)OH**

[0637] Compound of Formula X<sub>10b</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)OH) may be synthesized from a compound of Formula X<sub>20a</sub> in one Step as described in Scheme 147.

**Scheme 147**



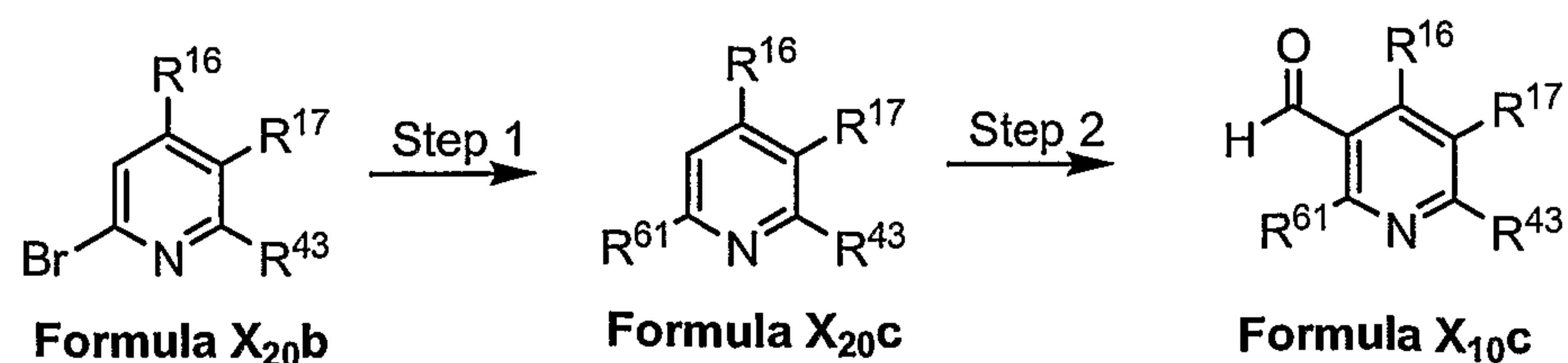
*Step 1 - Preparation of compound of Formula X<sub>10b</sub>*

[0638] Compound of Formula X<sub>10b</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)OH) is prepared by reacting compound of Formula X<sub>20a</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is Br) with solid magnesium in an appropriate solvent (e.g. tetrahydrofuran) possibly with a catalyst (e.g. iodine) and with heating (e.g. 80 °C) to afford the corresponding Grignard reagent. Dry ice is then added to the reaction to quench the Grignard and form the carboxylic acid at R<sup>42</sup>. Isolation by evaporation and acid-base extraction provides compound of Formula X<sub>10b</sub>.

**Example 91: Synthesis of Compounds of Formula X<sub>10</sub> where R<sup>15</sup> is optionally substituted lower alkyl and R<sup>42</sup> is C(O)H**

[0639] Compound of Formula X<sub>10c</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>15</sup> is optionally substituted lower alkyl) may be synthesized from a compound of Formula X<sub>20b</sub> in two Steps as described in Scheme 148.

**Scheme 148**





*Step 1 - Preparation of compound of Formula X<sub>20c</sub>*

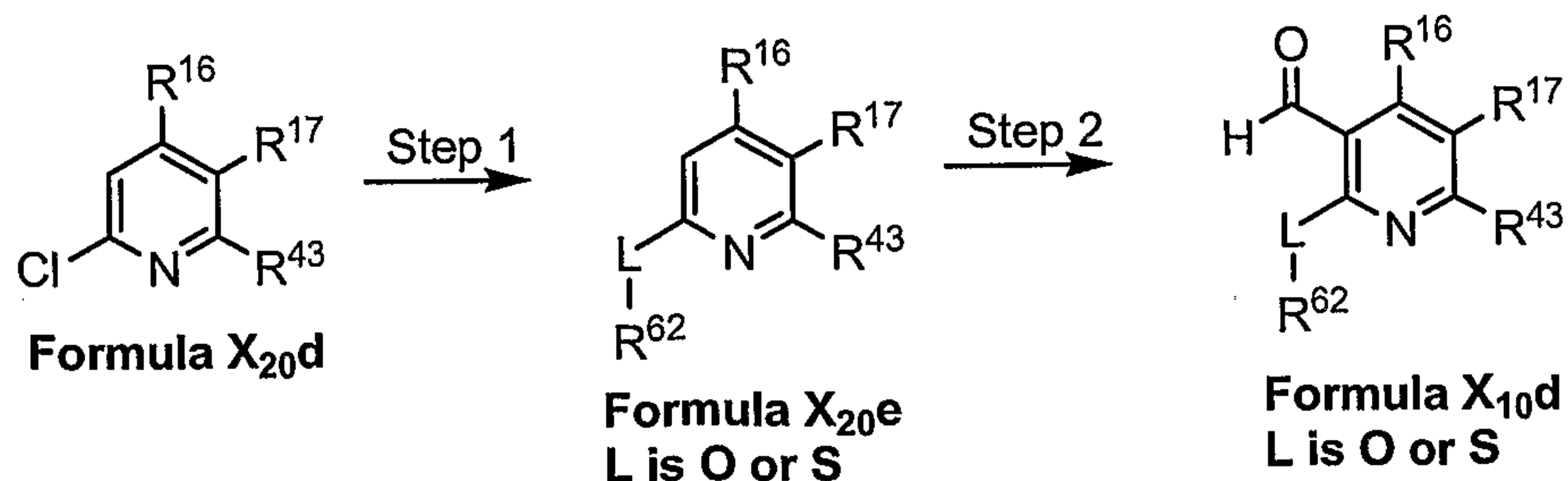
[0640] Compound of Formula X<sub>20c</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>15</sup> is optionally substituted lower alkyl R<sup>61</sup>) is prepared by dissolving compound of Formula X<sub>20b</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>15</sup> is Br) in an appropriate solvent (e.g. toluene), followed by the addition of a palladium catalyst (e.g. [1,1'-Bis(diphenylphosphino)-ferrocene] dichloropalladium(II), complex with dichloromethane (1:1)). After several minutes, a Grignard reagent of the formula R<sup>61</sup>-MgBr (where R<sup>61</sup> is optionally substituted lower alkyl) may be added and the reaction heated (e.g. 90 °C) for one to several hours. After filtration through Celite, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>20c</sub>.

*Step 2 - Preparation of compound of Formula X<sub>10c</sub>*

[0641] Compound of Formula X<sub>10c</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>15</sup> is optionally substituted lower alkyl) is prepared by reacting compound of Formula X<sub>20c</sub> with an organolithium reagent (e.g. lithium diisopropylamine) to effect the lithiation at the R<sup>42</sup> position at reduced temperature (e.g. -78 °C) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>10c</sub>.

**Example 92: Synthesis of Compounds of Formula X<sub>10</sub> where R<sup>15</sup> is OR<sup>62</sup> or SR<sup>62</sup> and R<sup>42</sup> is C(O)H**

[0642] Compound of Formula X<sub>10d</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>15</sup> is OR<sup>62</sup> or SR<sup>62</sup>, where R<sup>62</sup> is optionally substituted lower alkyl) may be synthesized from a compound of Formula X<sub>20d</sub> in two Steps as described in Scheme 149.

**Scheme 149**

*Step 1 - Preparation of compound of Formula X<sub>20e</sub>*

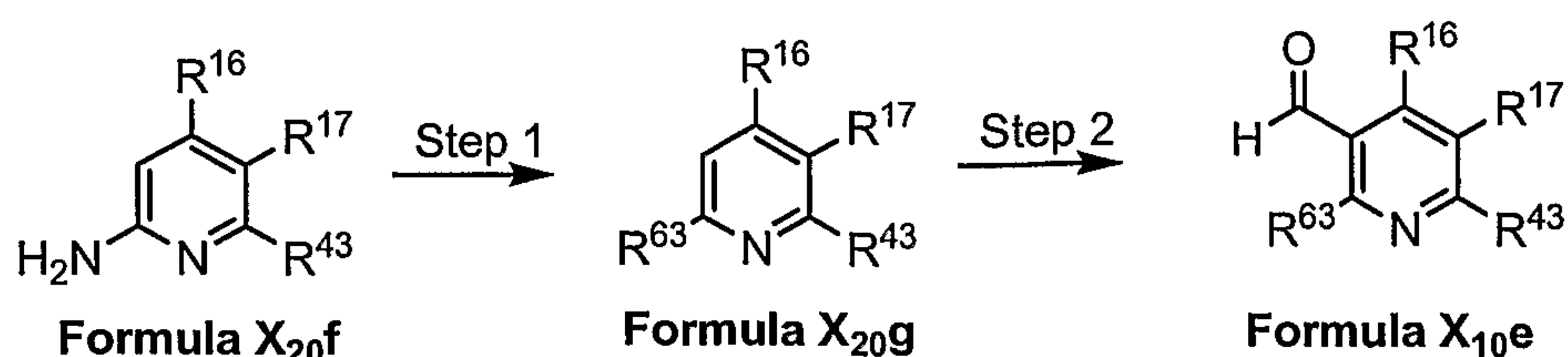
[0643] Compound of Formula X<sub>20e</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>15</sup> is LR<sup>62</sup>, where L is O or S and R<sup>62</sup> is optionally substituted lower alkyl) is prepared by reacting compound of Formula X<sub>20d</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>15</sup> is Cl) with a compound of Formula R<sup>62</sup>-OH or R<sup>62</sup>-SH in the presence of a base (e.g. sodium hydride) in an appropriate solvent (e.g. dimethylformamide, tetrahydrofuran) with heating (e.g. 80 °C). After stirring for several hours, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>20e</sub>.

*Step 2 - Preparation of compound of Formula X<sub>10d</sub>*

[0644] Compound of Formula X<sub>10d</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>15</sup> is LR<sup>62</sup>, where L is O or S and R<sup>62</sup> is optionally substituted lower alkyl) is prepared by reacting compound of Formula X<sub>20e</sub> with an organolithium reagent (e.g. lithium diisopropylamine) to effect the ortholithiation at the R<sup>42</sup> position at reduced temperature (e.g. -78 °C) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>10d</sub>.

**Example 93: Synthesis of Compounds of Formula X<sub>10</sub> where R<sup>15</sup> is halogen and R<sup>42</sup> is C(O)H**

[0645] Compound of Formula X<sub>10e</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>15</sup> is halogen) may be synthesized from a compound of Formula X<sub>20f</sub> in two Steps as described in Scheme 150.

**Scheme 150***Step 1 - Preparation of compound of Formula X<sub>20g</sub>*



[0646] Compound of Formula X<sub>20g</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>15</sup> is chloro or bromo (halogen R<sup>63</sup>)) is prepared by reacting compound of Formula X<sub>20f</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>15</sup> is NH<sub>2</sub>) in glacial acetic acid with sodium nitrite in acid (e.g. hydrochloric acid, sulfuric acid) to afford the diazonium intermediate. To form the compounds where R<sup>63</sup> is chloro or bromo, the diazonium salt is added to cuprous chloride or cuprous bromide, respectively, in hydrochloric acid with heating (e.g. 80 °C) for 30 minutes to one hour. Upon addition of the reaction to water, followed by isolation by conventional means (e.g. extraction and silica gel chromatography), compound of Formula X<sub>20g</sub> where R<sup>63</sup> is chloro or bromo are obtained.

[0647] Compound of Formula X<sub>20g</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>15</sup> is fluoro (halogen R<sup>63</sup>)) is prepared by reacting compound of Formula X<sub>20f</sub> in an appropriate aprotic solvent (e.g. tetrahydrofuran or dichloromethane) with boron trifluoride etherate. Subsequently, tert-butyl nitrite is added while the reaction is cooled (e.g. -15 °C) to afford the diazonium tetrafluoroborate intermediate as a precipitate that can be collected by filtration. To form the compound where R<sup>63</sup> is fluoro, the diazonium salt is heated dry with a burner to initiate the evolution borontrifluoride which subsequently proceeds spontaneously. After isolation by conventional means (e.g. extraction and silica gel chromatography) compound of Formula X<sub>20g</sub> where R<sup>63</sup> is fluoro are obtained. (Doyle and Bryker, J. Org. Chem. 1979, 44:1572; Schiemann and Winkelmueller, Org. Syn. Coll. Vol. 2:299).

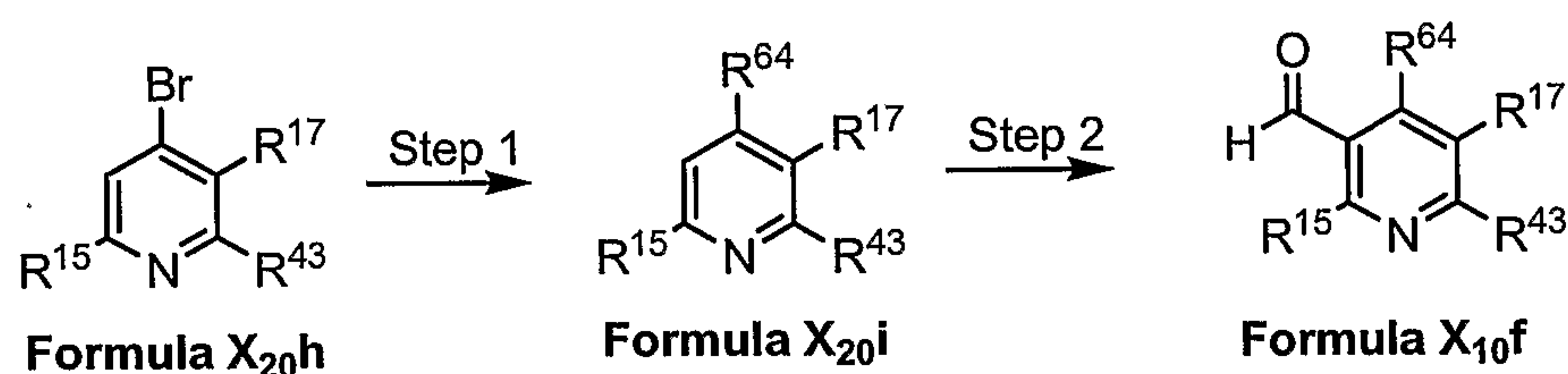
*Step 2 - Preparation of compound of Formula X<sub>10e</sub>*

[0648] Compound of Formula X<sub>10e</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>15</sup> is halogen R<sup>63</sup>) is prepared by reacting compound of Formula X<sub>20g</sub> with an organolithium reagent (e.g. lithium diisopropylamine) to effect the ortholithiation at the R<sup>42</sup> position at reduced temperature (e.g. -78 °C) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>10e</sub>.

**Example 94: Synthesis of Compounds of Formula X<sub>10</sub> where R<sup>16</sup> is optionally substituted lower alkyl and R<sup>42</sup> is C(O)H**

[0649] Compound of Formula X<sub>10f</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>16</sup> is optionally substituted lower alkyl) may be synthesized from a compound of Formula X<sub>20h</sub> in two Steps as described in Scheme 151.

**Scheme 151**



*Step 1 - Preparation of compound of Formula X<sub>20i</sub>*

[0650] Compound of Formula X<sub>20i</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>16</sup> is optionally substituted lower alkyl R<sup>64</sup>) is prepared by dissolving compound of Formula X<sub>20h</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>16</sup> is Br) in an appropriate solvent (e.g. toluene), followed by the addition of a palladium catalyst (e.g. [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (1:1)). After several minutes, a Grignard reagent of the Formula R<sup>64</sup>-MgBr (R<sup>64</sup> is optionally substituted lower alkyl) is added and the reaction heated (e.g. 90 °C) for one to several hours. After filtration through Celite, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>20i</sub>.

*Step 2 - Preparation of compound of Formula X<sub>10f</sub>*

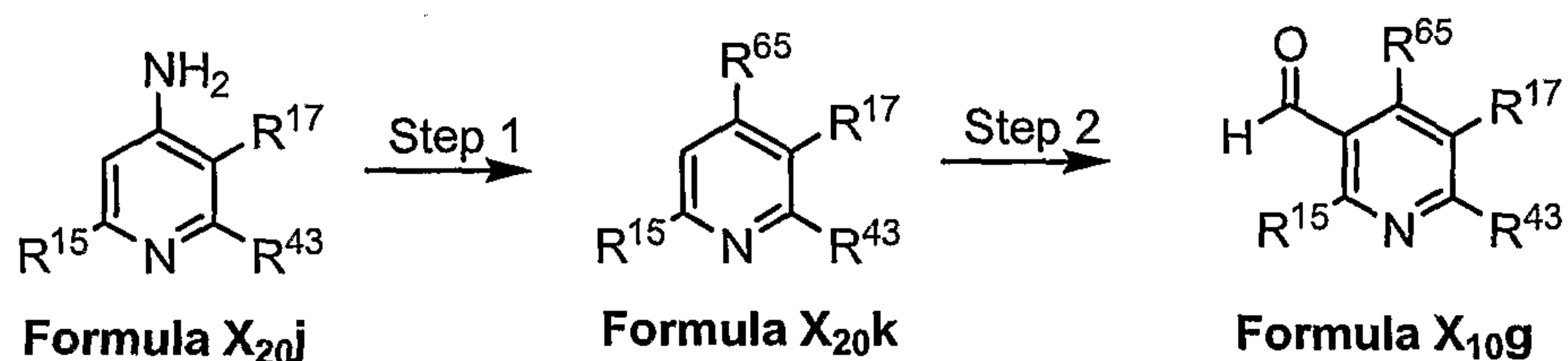
[0651] Compound of Formula X<sub>10f</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>16</sup> is optionally substituted lower alkyl R<sup>64</sup>) is prepared by reacting compound of Formula X<sub>20i</sub> with an organolithium reagent (e.g. lithium diisopropylamine) to effect the lithiation at the R<sup>42</sup> position at reduced temperature (e.g. -78 °C) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>10f</sub>.



**Example 95: Synthesis of Compounds of Formula X<sub>10</sub> where R<sup>16</sup> is halogen and R<sup>42</sup> is C(O)H**

[0652] Compound of Formula X<sub>10g</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>16</sup> is halogen) may be synthesized from a compound of Formula X<sub>20j</sub> in two Steps as described in Scheme 152.

**Scheme 152**



*Step 1 - Preparation of compound of Formula X<sub>20k</sub>*

[0653] Compound of Formula X<sub>20k</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>16</sup> is chloro or bromo (halogen R<sup>65</sup>)) is prepared by reacting compound of Formula X<sub>20j</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>16</sup> is NH<sub>2</sub>) in glacial acetic acid with sodium nitrite in acid (e.g. hydrochloric acid, sulfuric acid) to afford the diazonium intermediate. To form the compound where R<sup>65</sup> is chloro or bromo, the diazonium salt is added to cuprous chloride or cuprous bromide, respectively, in hydrochloric acid with heating (e.g. 80 °C) for 30 minutes to one hour. Upon addition of the reaction to water, followed by isolation by conventional means (e.g. extraction and silica gel chromatography) compound of Formula X<sub>20k</sub> where R<sup>65</sup> is bromo or chloro are obtained.

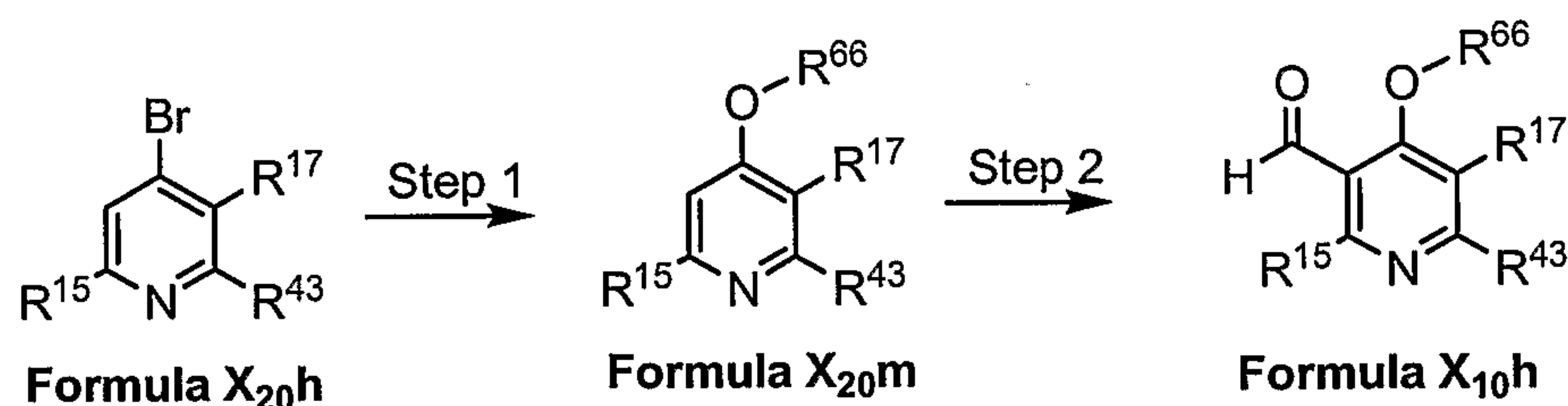
[0654] Compound of Formula X<sub>20k</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>16</sup> is fluoro (halogen R<sup>65</sup>)) is prepared by reacting compound of Formula X<sub>20j</sub> in an appropriate aprotic solvent (e.g. tetrahydrofuran or dichloromethane) with boron trifluoride etherate. Subsequently, tert-butyl nitrite may be added while the reaction is cooled (e.g. -15 °C) to afford the diazonium tetrafluoroborate intermediate as a precipitate that may be collected by filtration. To form the compounds where R<sup>65</sup> is fluoro, the diazonium salt is heated dry with a burner to initiate the evolution borontrifluoride which subsequently proceeds spontaneously. After isolation by conventional means (e.g. extraction and silica gel chromatography), compound of Formula X<sub>20k</sub> where R<sup>15</sup> is H and R<sup>65</sup> is fluoro are obtained. (Doyle and Bryker, J. Org. Chem. 1979, 44:157; Schiemann and Winkelmueller, Org. Syn. Coll. Vol. 2:299.)

*Step 2 - Preparation of compound of Formula X<sub>10g</sub>*

[0655] Compound of Formula X<sub>10g</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>16</sup> is halogen R<sup>65</sup>) is prepared by reacting compound of Formula X<sub>20k</sub> Formula Xa with an organolithium reagent (e.g. lithium diisopropylamine) to effect the lithiation at the R<sup>42</sup> position at reduced temperature (e.g. -78 °C) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula X<sub>10g</sub>.

**Example 96: Synthesis of Compounds of Formula X<sub>10</sub> where R<sup>16</sup> is OR<sup>66</sup> and R<sup>42</sup> is C(O)H**

[0656] Compound of Formula X<sub>10h</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>16</sup> is OR<sup>66</sup>, where R<sup>66</sup> is optionally substituted lower alkyl) may be synthesized from a compound of Formula X<sub>20h</sub> in two Steps as described in Scheme 153.

**Scheme 153***Step 1 - Preparation of compound of Formula X<sub>20m</sub>*

[0657] Compound of Formula X<sub>20m</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>16</sup> is OR<sup>66</sup>, where R<sup>66</sup> is optionally substituted lower alkyl) is prepared by reacting compound of Formula X<sub>20h</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>16</sup> is Br) with compound of the Formula R<sup>66</sup>-OH (R<sup>66</sup> is optionally substituted lower alkyl) in the presence of a base (e.g. sodium hydride) and a copper catalyst (e.g. copper bromide) in a non-reactive solvent (e.g. dimethylformamide) with heating (e.g. 120 °C) for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>20m</sub>.

*Step 2 - Preparation of compound of Formula X<sub>10h</sub>*

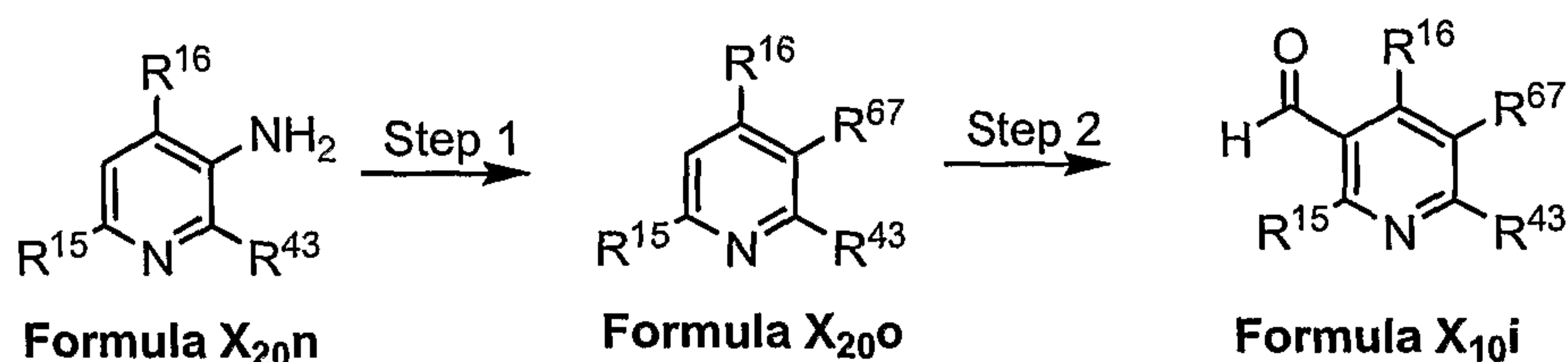


[0658] Compound of Formula X<sub>10h</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>16</sup> is OR<sup>66</sup>, where R<sup>66</sup> is optionally substituted lower alkyl) is prepared by reacting compound of Formula X<sub>20m</sub> with an organolithium reagent (e.g. lithium diisopropylamine) to effect the ortholithiation at the R<sup>42</sup> position at reduced temperature (e.g. -78 °C) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>10h</sub>.

**Example 97: Synthesis of Compounds of Formula X<sub>10</sub> where R<sup>17</sup> is halogen and R<sup>42</sup> is C(O)H**

[0659] Compound of Formula X<sub>10i</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>17</sup> is halogen) may be synthesized from a compound of Formula X<sub>20n</sub> in two Steps as described in Scheme 154.

**Scheme 154**



*Step 1 - Preparation of compound of Formula X<sub>20o</sub>*

[0660] Compound of Formula X<sub>20o</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>17</sup> is chloro or bromo (halogen R<sup>67</sup>)) is prepared by reacting compound of Formula X<sub>20n</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>17</sup> is NH<sub>2</sub>) in glacial acetic acid with sodium nitrite in acid (e.g. hydrochloric acid, sulfuric acid) to afford the diazonium intermediate. To form the compounds where R<sup>67</sup> is chloro or bromo, the diazonium salt is added to cuprous chloride or cuprous bromide, respectively, in hydrochloric acid with heating (e.g. 80 °C) for 30 minutes to one hour. Upon addition of the reaction to water, followed by isolation by conventional means (e.g. extraction and silica gel chromatography) compound of Formula X<sub>20o</sub> where R<sup>67</sup> is bromo or chloro are obtained.

[0661] Compound of Formula X<sub>20o</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>17</sup> is fluoro (halogen R<sup>67</sup>)) is prepared by reacting compound of Formula X<sub>20n</sub> in an appropriate

aprotic solvent (e.g. tetrahydrofuran or dichloromethane) with boron trifluoride etherate. Subsequently, tert-butyl nitrite may be added while the reaction is cooled (e.g.  $-15\text{ }^{\circ}\text{C}$ ) to afford the diazonium tetrafluoroborate intermediate as a precipitate that can be collected by filtration. To form the compounds where  $\text{R}^{67}$  is fluoro, the diazonium salt is heated dry with a burner to initiate the evolution borontrifluoride which subsequently proceeds spontaneously. After isolation by conventional means (e.g. extraction and silica gel chromatography) compounds of Formula  $\text{X}_{20\text{o}}$  where  $\text{R}^{67}$  is fluoro are obtained. (Doyle and Bryker, J. Org. Chem. 1979, 44:1572. Schiemann and Winkelmueller, Org. Syn. Coll. Vol. 2:299).

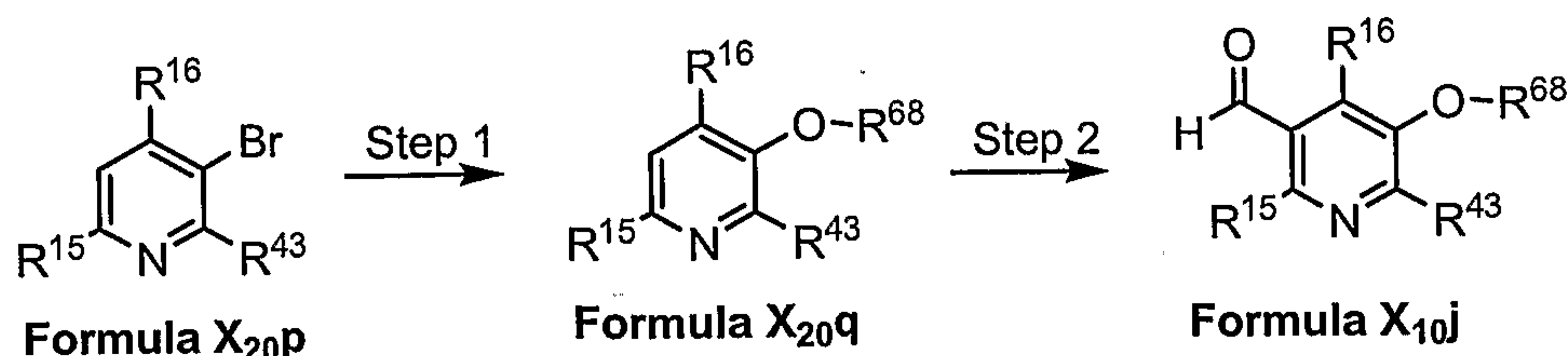
*Step 2 - Preparation of compound of Formula  $\text{X}_{10\text{i}}$*

[0662] ] Compound of Formula  $\text{X}_{10\text{i}}$  (Formula  $\text{X}_{10}$  where  $\text{R}^{42}$  is  $\text{C}(\text{O})\text{H}$  and  $\text{R}^{17}$  is halogen  $\text{R}^{67}$ ) is prepared by reacting compound of Formula  $\text{X}_{20\text{o}}$  with an organolithium reagent (e.g. lithium diisopropylamine) to effect the lithiation at the  $\text{R}^{42}$  position at reduced temperature (e.g.  $-78\text{ }^{\circ}\text{C}$ ) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula  $\text{X}_{10\text{i}}$ .

**Example 98: Synthesis of Compounds of Formula  $\text{X}_{10}$  where  $\text{R}^{17}$  is  $\text{OR}^{68}$  and  $\text{R}^{42}$  is  $\text{C}(\text{O})\text{H}$**

[0663] Compound of Formula  $\text{X}_{10\text{j}}$  (Formula  $\text{X}_{10}$  where  $\text{R}^{42}$  is  $\text{C}(\text{O})\text{H}$  and  $\text{R}^{17}$  is  $\text{OR}^{68}$ , where  $\text{R}^{68}$  is optionally substituted lower alkyl) may be synthesized from a compound of Formula  $\text{X}_{20\text{p}}$  in two Steps as described in Scheme 155.

**Scheme 155**





*Step 1 - Preparation of compound of Formula X<sub>20q</sub>*

[0664] Compound of Formula X<sub>20q</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>17</sup> is OR<sup>68</sup>, where R<sup>68</sup> is optionally substituted lower alkyl) is prepared by reacting compound of Formula X<sub>20p</sub> (Formula X<sub>20</sub> where R<sup>60</sup> is H and R<sup>17</sup> is Br) with compound of the Formula R<sup>68</sup>-OH (R<sup>68</sup> is optionally substituted lower alkyl) in the presence of a base (e.g. sodium hydride) and a copper catalyst (e.g. copper bromide) in a non-reactive solvent (e.g. dimethylformamide) with heating (e.g. 120 °C) for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>20q</sub>.

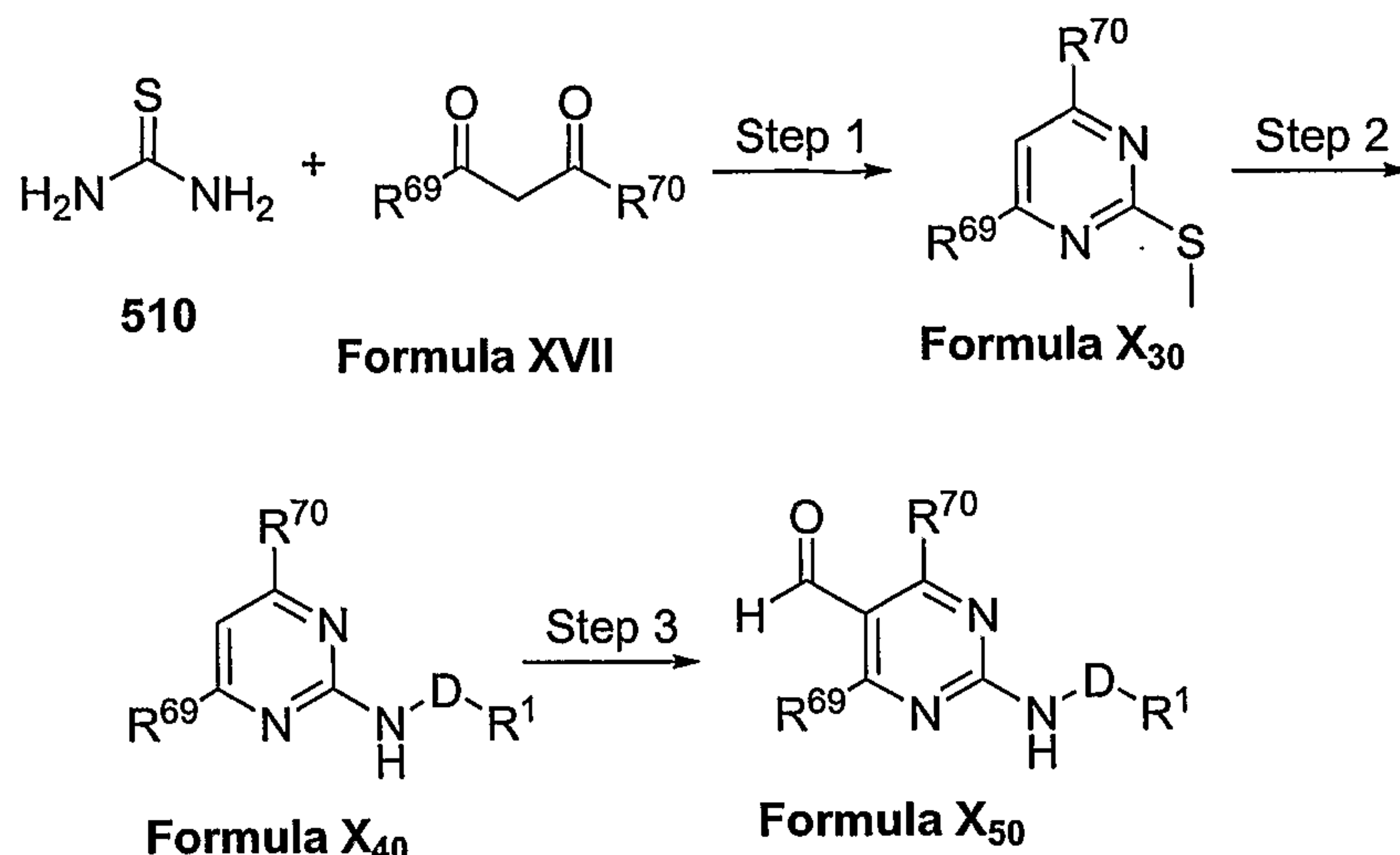
*Step 2 - Preparation of compound of Formula X<sub>10j</sub>*

[0665] Compound of Formula X<sub>10j</sub> (Formula X<sub>10</sub> where R<sup>42</sup> is C(O)H and R<sup>17</sup> is OR<sup>68</sup>, where R<sup>68</sup> is optionally substituted lower alkyl) is prepared by reacting compound of Formula X<sub>20q</sub> with an organolithium reagent (e.g. lithium diisopropylamine) to effect the lithiation at the R<sup>42</sup> position at reduced temperature (e.g. -78 °C) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula X<sub>10j</sub>.

**Example 99: Synthesis of Compounds of Formula X where n=1; G is N; K, J, F and E are C; R<sub>15</sub> and R<sub>16</sub> are optionally substituted lower alkyl; M is NH-D- and R<sup>42</sup> is C(O)H**

[0666] Compounds of Formula X where n=1 and G is N are pyrimidine derivatives that may be prepared through many routes known in the literature and used in reactions analogous to those described for compounds of Formula X<sub>a</sub>, such as in Examples 89-98. M is NH-D, where D is consistent with the definition of M. The synthesis of one such compound is exemplified in Scheme 156 as follows.

## Scheme 156

*Step 1 - Preparation of compound of Formula X<sub>30</sub>*

[0667] Compound of Formula X<sub>30</sub> (Formula Xa where n=1, G is N, K, J, F and E are C, R<sup>15</sup> and R<sup>16</sup> are optionally substituted lower alkyl (R<sup>69</sup> and R<sup>70</sup>, respectively), R<sup>43</sup> is S-Me and R<sup>42</sup> is H) is prepared by reacting thiourea **510** with compound of Formula XVII (R<sup>69</sup> and R<sup>70</sup> are independently optionally substituted lower alkyl) in the presence of a base (e.g. sodium hydroxide) in a non-reactive solvent (e.g. ethanol) for several hours. Subsequently, the addition of methyl iodide with heating (e.g. 60 °C) for several hours, followed by isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula X<sub>30</sub>.

*Step 2 - Preparation of compound of Formula X<sub>40</sub>*

[0668] Compounds of Formula X<sub>40</sub> (Formula X where n=1, G is N, K, J, F and E are C, R<sup>15</sup> and R<sup>16</sup> are optionally substituted lower alkyl (R<sup>69</sup> and R<sup>70</sup>, respectively), M is NH-D- (D is consistent with definition of M of Formula Ib or L<sup>2</sup> or Formula I) and R<sup>42</sup> is H) is prepared by reacting compound of Formula X<sub>30</sub> with compound of Formula NH<sub>2</sub>-D-R<sup>1</sup> (e.g. benzyl amine or other suitable nucleophile) in the presence of a base (e.g. sodium hydride) in a non-reactive solvent (e.g. dimethylformamide) for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula X<sub>40</sub>.

*Step 3 - Preparation of compound of Formula X<sub>50</sub>*

[0669] Compounds of Formula X<sub>50</sub> (Formula X where n=1, G is N, K, J, F and E are C, R<sup>15</sup> and R<sup>16</sup> are optionally substituted lower alkyl (R<sup>69</sup> and R<sup>70</sup>, respectively), M is NH-D-

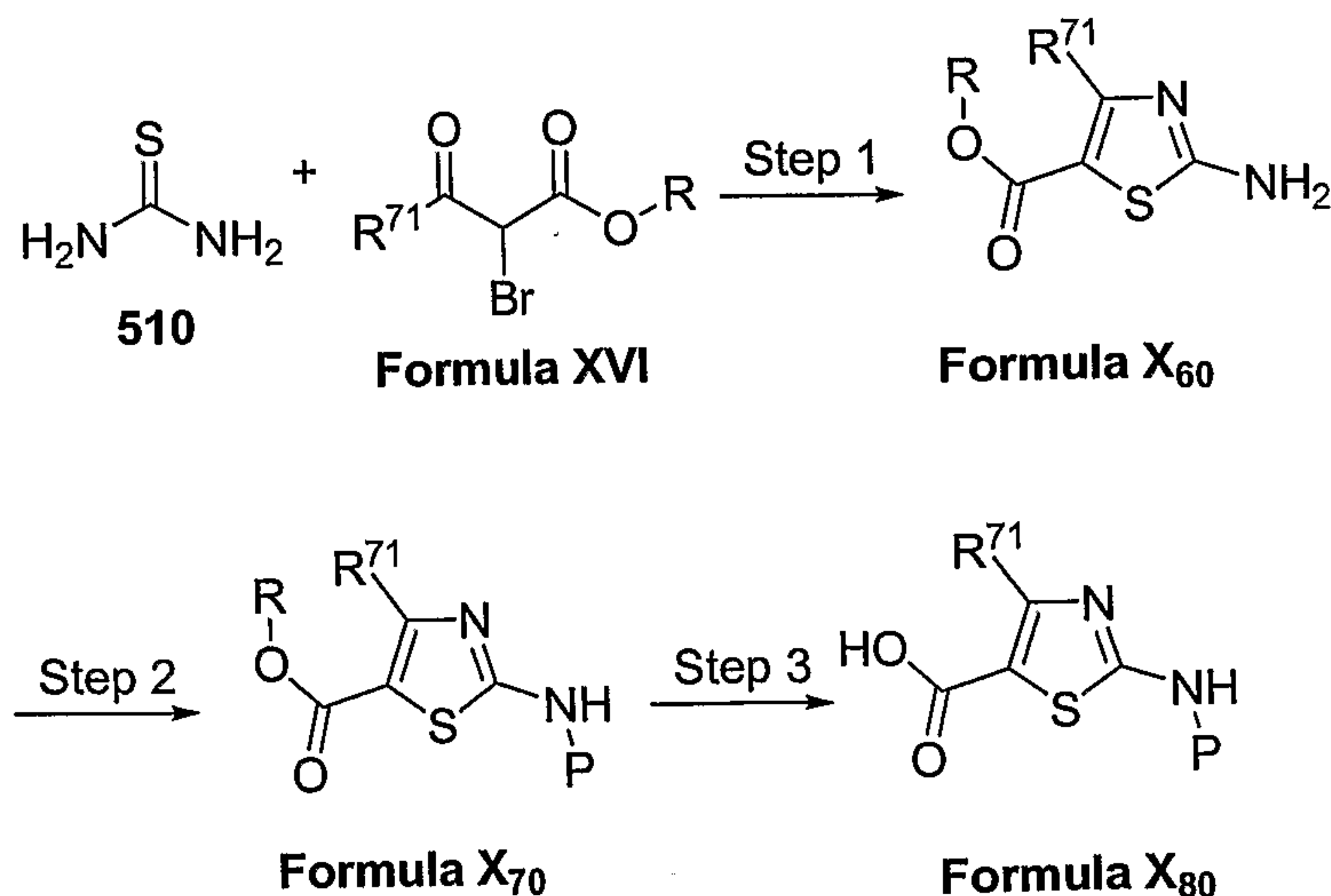


(D is consistent with definition of M of Formula Ib or L<sup>2</sup> or Formula I) and R<sup>42</sup> is C(O)H) is prepared by reacting compound of Formula X<sub>40</sub> with an organolithium reagent (e.g. lithium diisopropylamine) to effect the lithiation at the R<sup>42</sup> position at reduced temperature (e.g. -78 °C) in an appropriate solvent (e.g. tetrahydrofuran) followed by addition of a formylating reagent (e.g. dimethylformamide). After stirring for several hours and warming to room temperature, isolation by conventional means (e.g. extraction and silica gel chromatography) provides compounds of Formula X<sub>50</sub>, which may be used in the synthesis of compound of Formula II, which may be used in the synthesis of compound of Formula Ib.

**Example 100: Synthesis of Compounds of Formula Xa where n=0; K is S; J, E, and F are C; R<sup>43</sup> is NHP; R<sup>15</sup> is optionally substituted lower alkyl or optionally substituted lower alkoxy and R<sup>42</sup> is COOH**

[0670] Compounds of Formula X where n=0 are 5-membered heterocycles that may be prepared through many routes known in the literature and used in reactions analogous to those described for compounds of Formula Xa, such as in Examples 89-98. The synthesis of one such compound is exemplified in Scheme 157 as follows.

**Scheme 157**



*Step 1 - Preparation of compound of Formula X<sub>60</sub>*

[0671] Compound of Formula X<sub>60</sub> (Formula Xa where n=0, K is S, J, E, and F are C, R<sup>43</sup> is NH<sub>2</sub>, R<sup>15</sup> is R<sup>71</sup> (R<sup>71</sup> is optionally substituted lower alkyl or O-R<sup>72</sup>, where R<sup>72</sup> is optionally substituted lower alkyl) and R<sup>42</sup> is CO<sub>2</sub>R, where R is lower alkyl) is prepared by

reacting thiourea **510** with compound of Formula XVI where  $R^{71}$  is optionally substituted lower alkyl or  $O-R^{72}$  ( $R^{72}$  is optionally substituted lower alkyl) and R is lower alkyl in a non-reactive solvent (e.g. dimethylformamide, ethanol) with heating (e.g. 60 °C) for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula  $X_{60}$ .

*Step 2 - Preparation of compound of Formula  $X_{70}$*

[0672] Compound of Formula  $X_{70}$  (Formula Xa where  $n=0$ , K is S, J, E, and F are C,  $R^{43}$  is NHP, where P is a protecting group [e.g. triisopropylsilyl, t-butyloxycarbonyl]),  $R^{15}$  is  $R^{71}$  and  $R^{42}$  is  $CO_2R$ , where R is lower alkyl) is prepared by reacting compound of Formula  $X_{60}$  with a reagent appropriate to introduce the protecting group (e.g. triisopropylsilyl chloride, Boc anhydride) in the presence of a base (e.g. sodium hydride, diisopropylethylamine) in a non-reactive solvent (e.g. dimethylformamide) for several hours. Isolation by conventional means (e.g. extraction and silica gel chromatography) provides compound of Formula  $X_{70}$ .

*Step 3 - Preparation of compound of Formula  $X_{80}$*

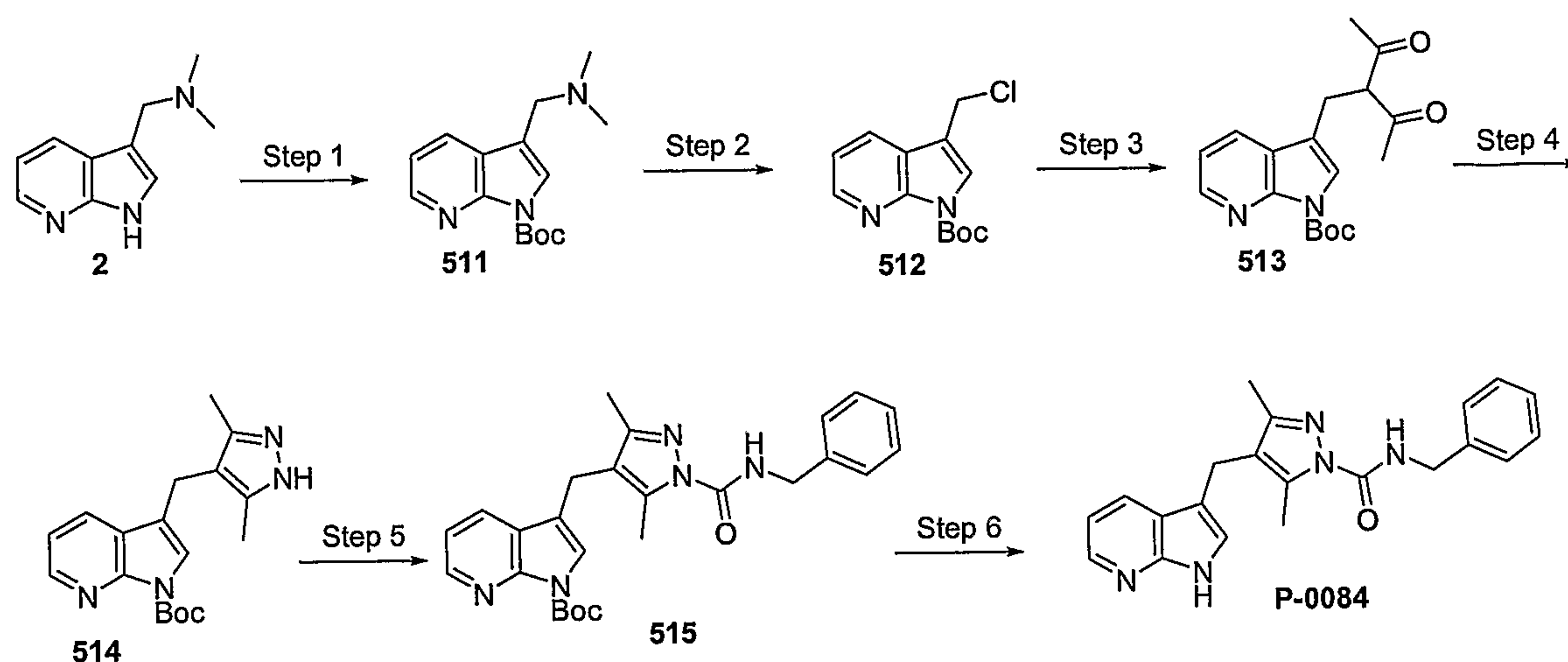
[0673] Compound of Formula  $X_{80}$  (Formula Xa where  $n=0$ , K is S, J, E, and F are C,  $R^{43}$  is NHP,  $R^{15}$  is  $R^{71}$  and  $R^{42}$  is  $CO_2H$ ) is prepared by reacting compound of Formula  $X_{70}$  with a base (e.g. lithium hydroxide) in an appropriate solvent (e.g. tetrahydrofuran and water) for several hours. Isolation by conventional means (e.g. acid-base extraction) provides compound of  $X_{80}$ , which may be used in the synthesis of compound of Formula II where  $R^{43}$  is NHP, which may be used to make compound of Formula Ib.

**Example 101 Synthesis of 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide P-0084**

[0674] 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide P-0084 was synthesized in 6 steps from dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine **2** as shown in scheme 158.



## Scheme – 158



*Step 1: Preparation of 3-Dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (511)*

[0675] To dimethyl-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amine (**2**, 2.50 g, 14.3 mmol, prepared as described in Example 2, Scheme 4, Step 1) in tetrahydrofuran (200.0 mL) was added sodium hydride (0.685 g, 60% in mineral oil, 17.1 mmol). After 10 minutes, di-*tert*-butyldicarbonate (3.74 g, 17.1 mmol) was added to the reaction. The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give as a white solid (**511**, 3.80 g, 96.7%).

*Step 2: Preparation of 3-Chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (512)*

[0676] To 3-dimethylaminomethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**511**, 2.60 g, 9.44 mmol) in toluene (50.00 mL) was added isopropyl chloroformate (11.3 mL, 1.0 M in toluene) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 3 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 20% ethyl acetate in hexane to give a white solid (**512**, 2.0 g, 79.4%).

*Step 3 – Preparation of 3-(2-Acetyl-3-oxo-butyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (513):*

[0677] To acetylacetone (0.563 g, 5.62 mmol) in dimethyl sulfoxide (29.0 mL) was added sodium hydride (0.225 g, 60% in mineral oil, 5.62 mmol). After 20 minutes, 3-chloromethyl-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**512**, 1.00 g, 3.75 mmol) was added to the reaction. The reaction was stirred at room temperature for 2 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 40% ethyl acetate in hexane to give a colorless oil (**513**, 0.59 g, 48.0%). MS (ESI)  $[M+H]^+ = 331.4$ .

*Step 4 – Preparation of 3-(3,5-Dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (514)*

[0678] To 3-(2-acetyl-3-oxo-butyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**513**, 1.20 g, 3.63 mmol) in methanol (15.0 mL), cooled to -20 °C under an atmosphere of nitrogen, was added hydrazine (0.128 g, 4.00 mmol) in dichloromethane (6.0 mL). The reaction was stirred for 2 hours. The reaction was concentrated to remove the solvents, and the residue was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 60% ethyl acetate in hexane to give a white solid (**514**, 1.0 g, 84.4%). MS (ESI)  $[M+H]^+ = 327.4$ .

*Step 5 – Preparation of 3-(1-Benzylcarbamoyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (515)*

[0679] To 3-(3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**514**, 60.0 mg, 0.18 mmol) in dichloromethane (6.0 mL) were added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.033 mL, 0.220 mmol) and benzyl isocyanate (29.4 mg, 0.220 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 2 hours. The reaction was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give crude compound (**515**, approx. 50 mg) that was used in the next step directly. MS (ESI)  $[M+H]^+ = 460.5$ .



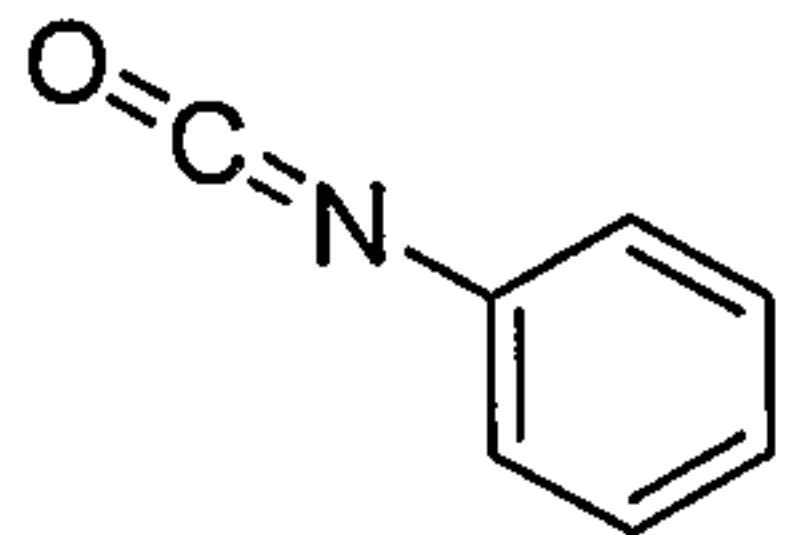
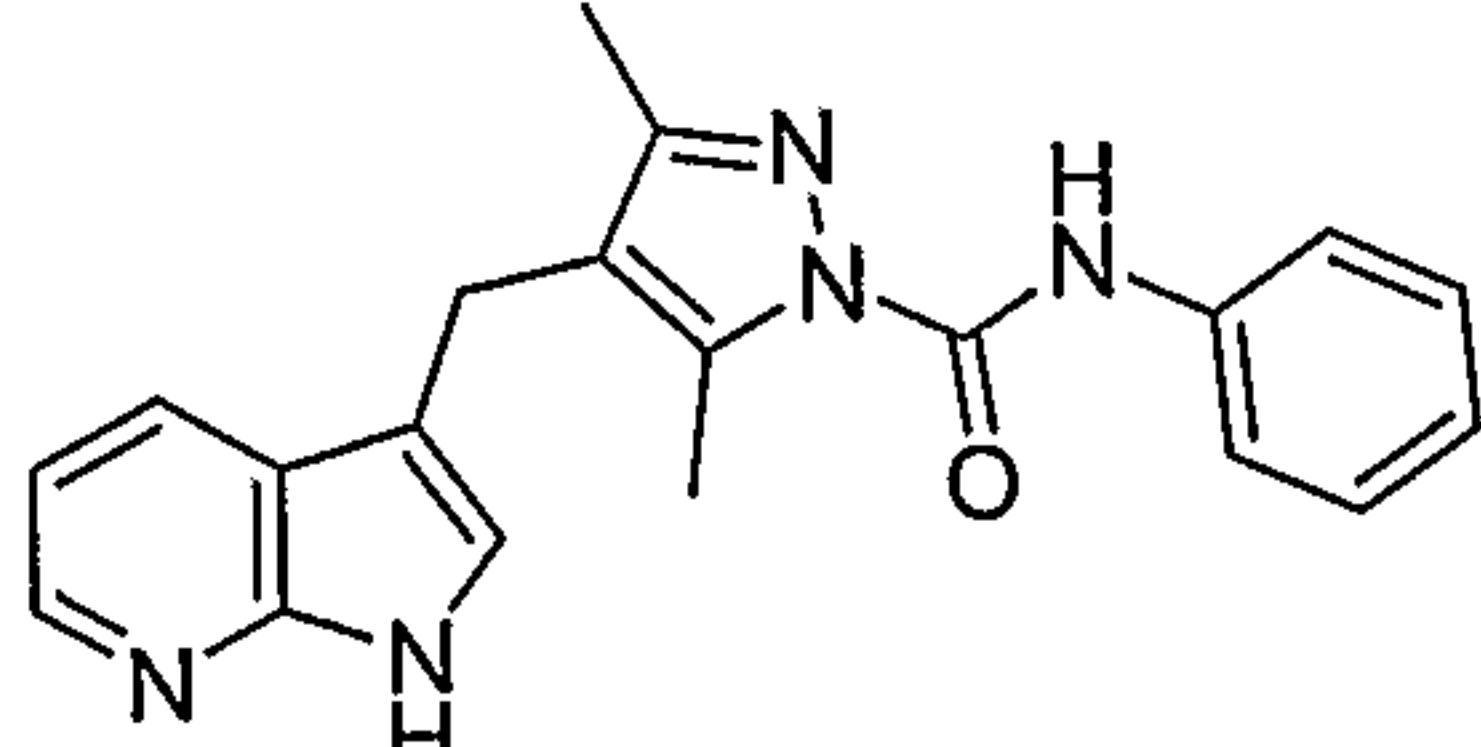
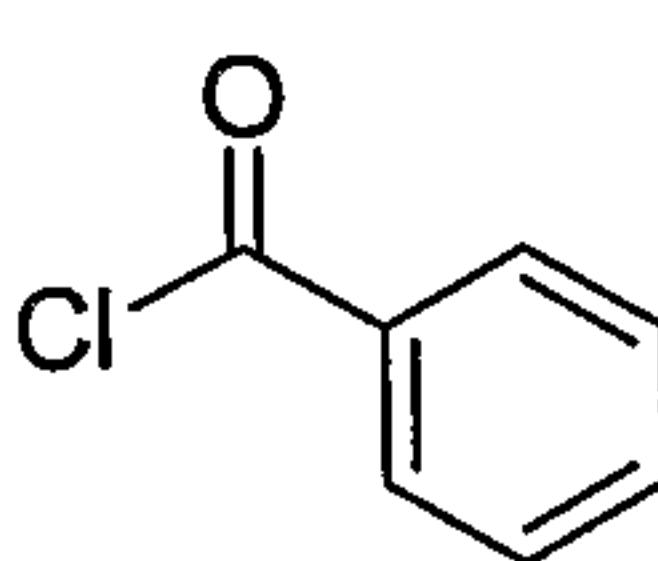
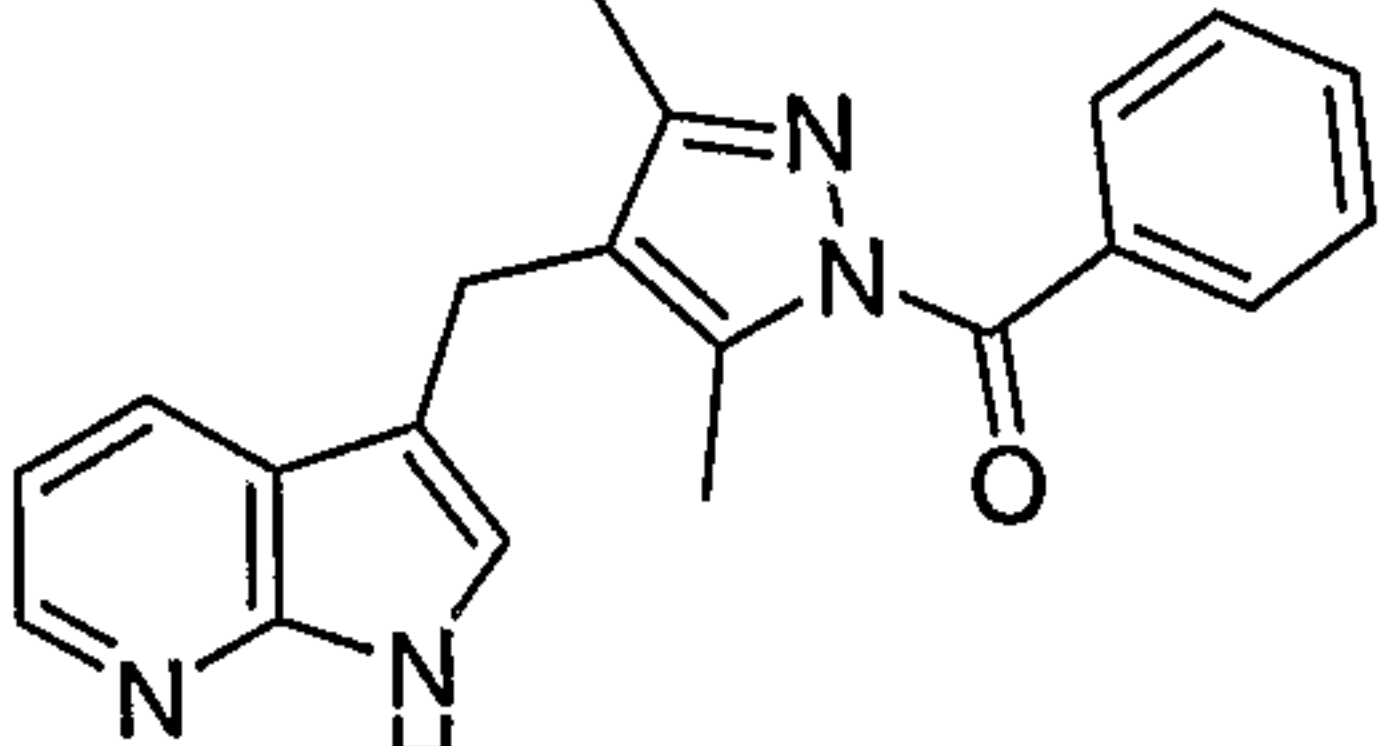
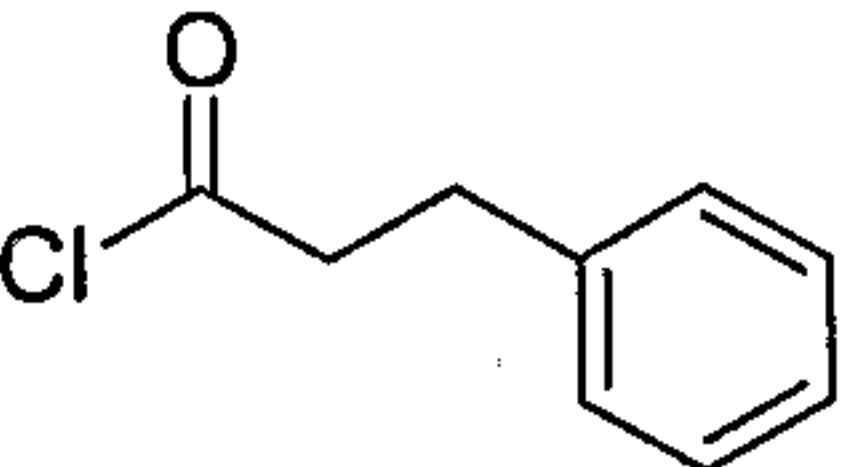
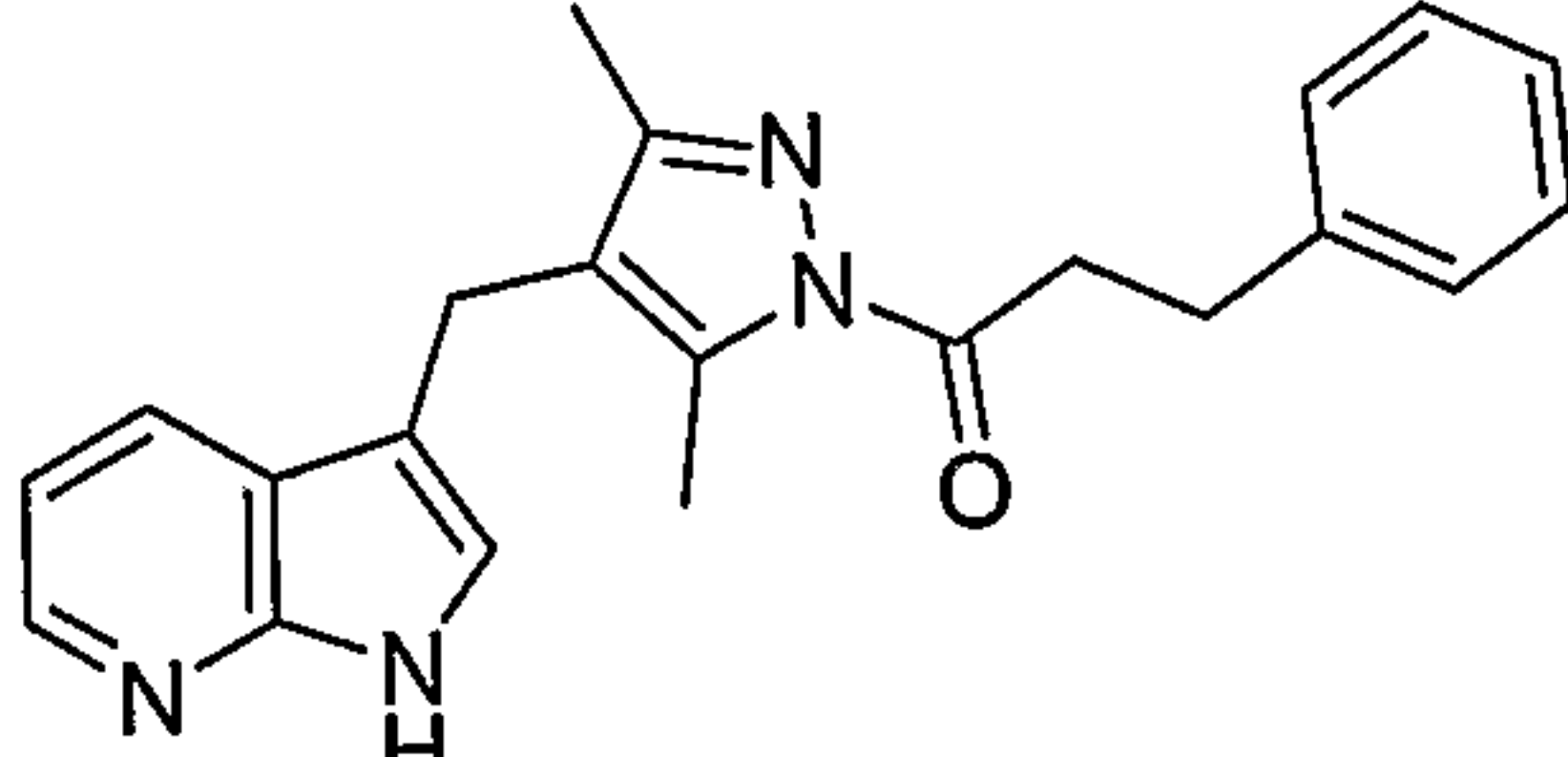
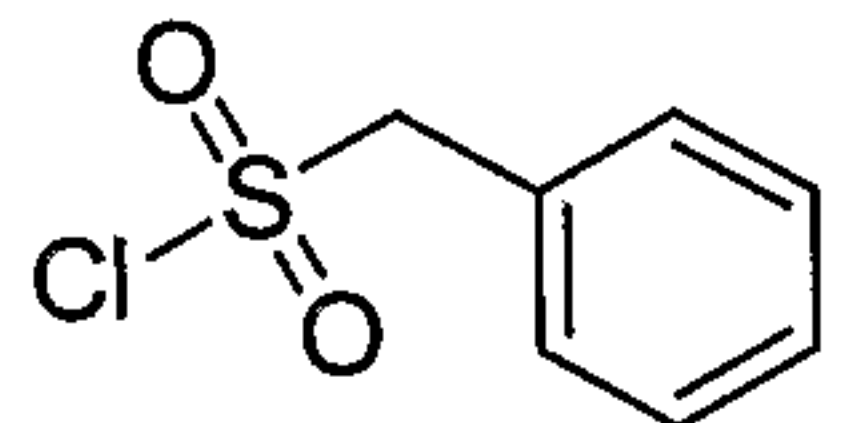
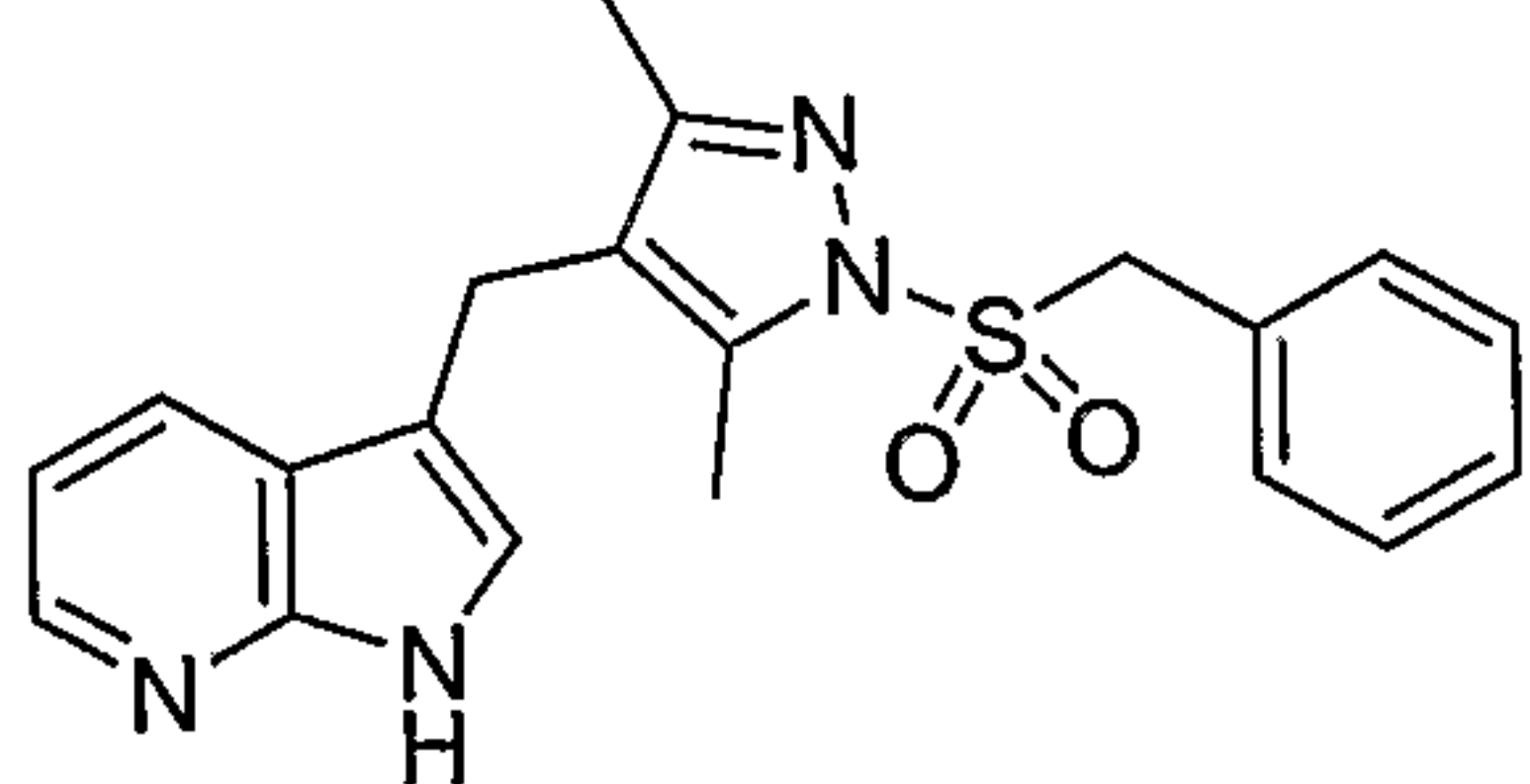
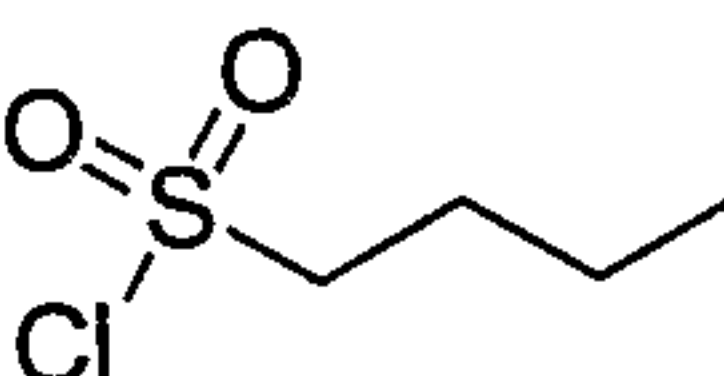
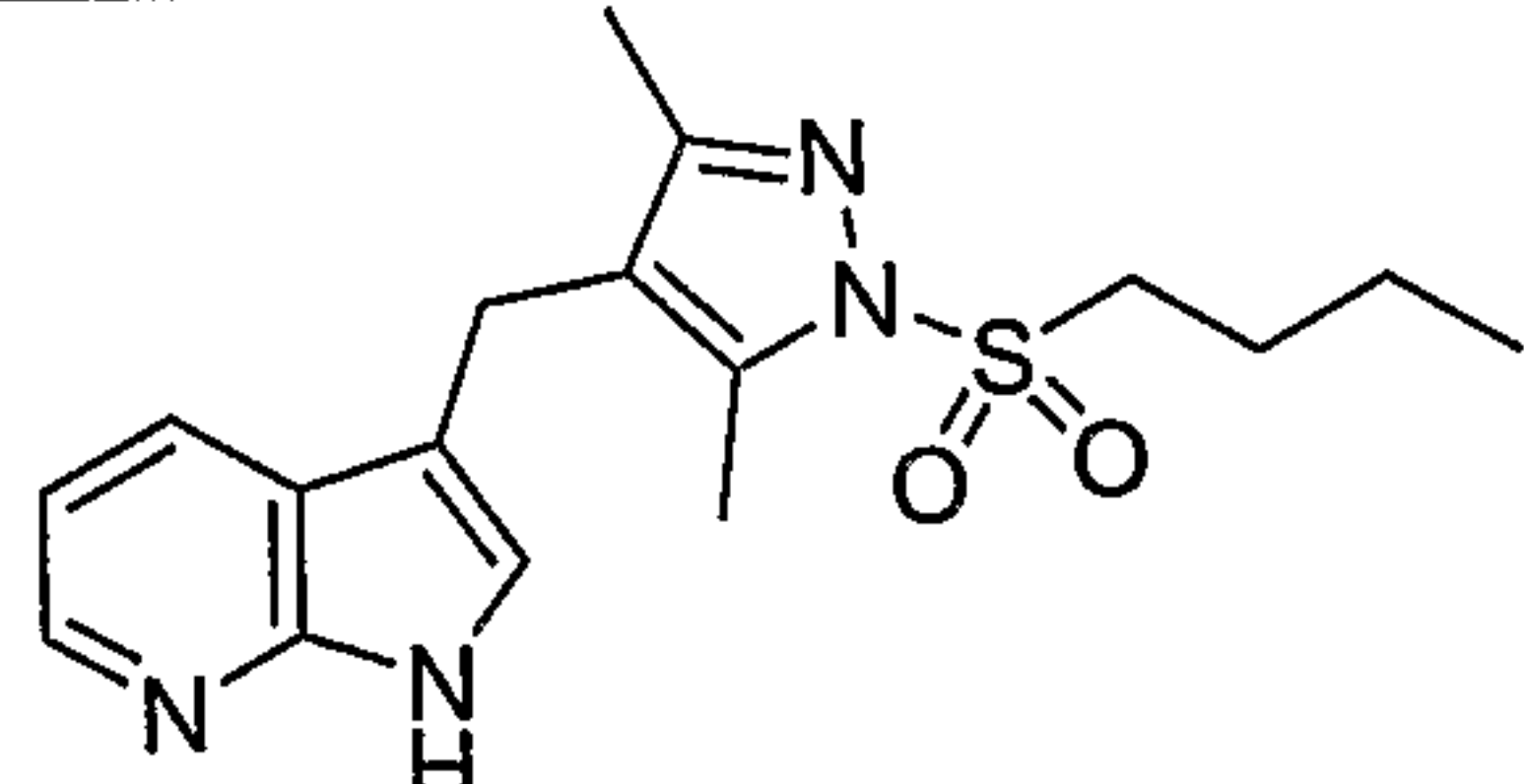
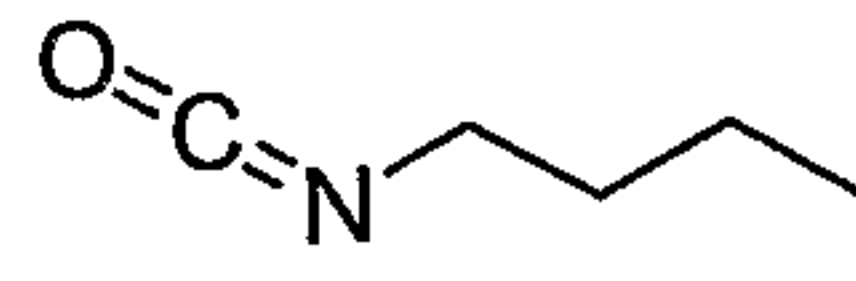
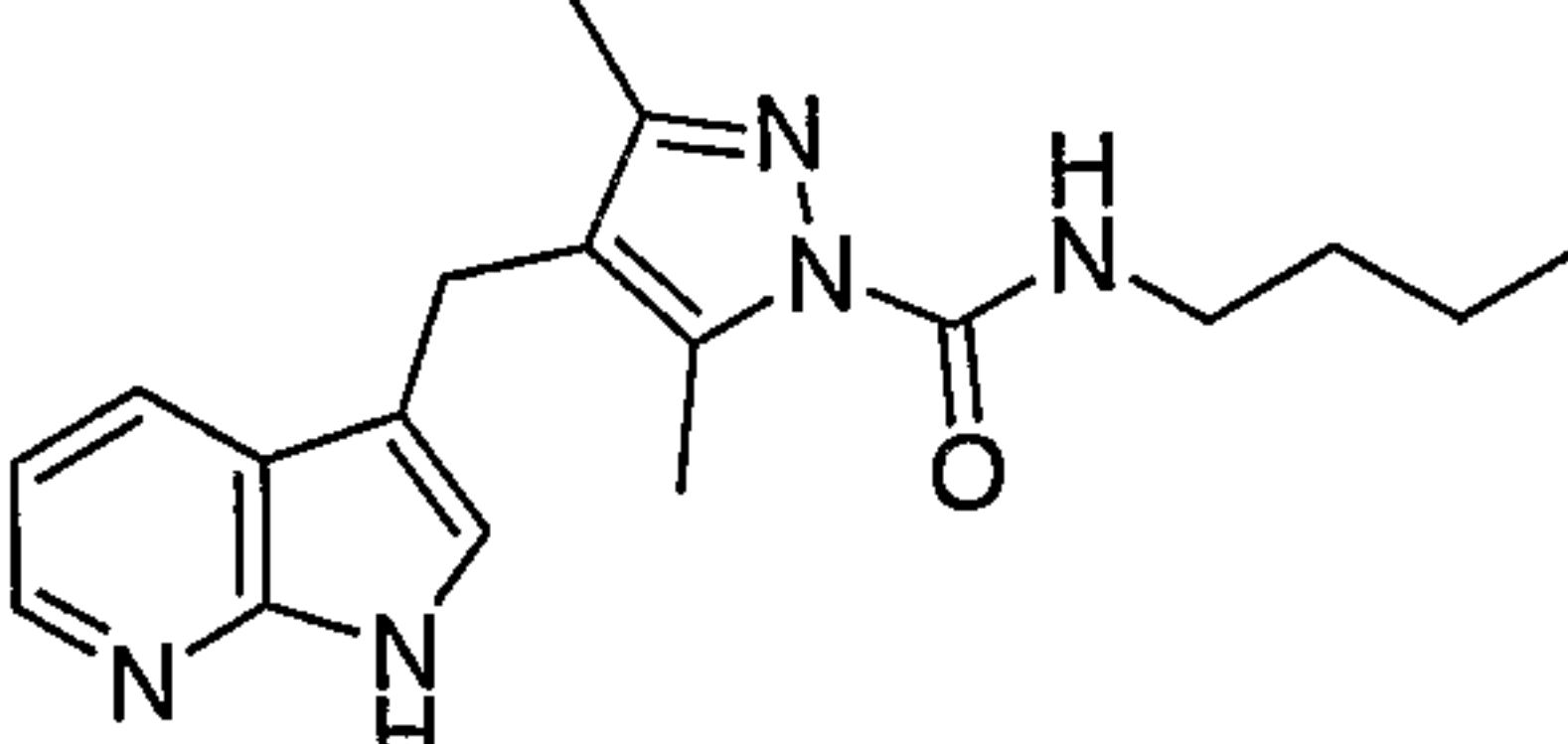
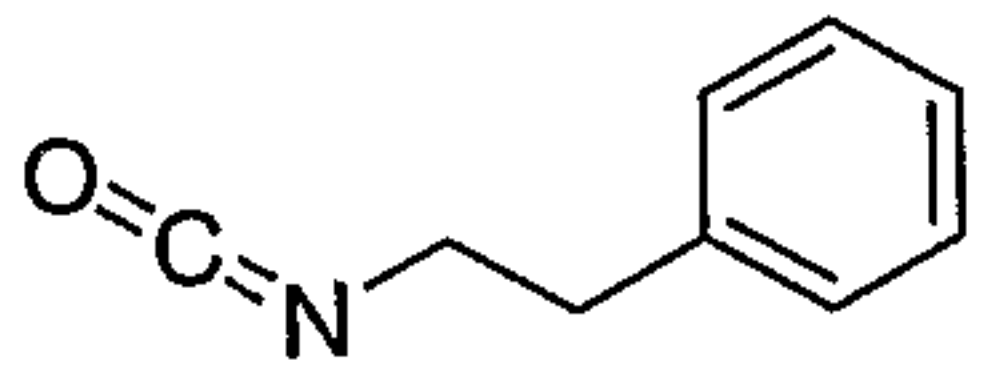
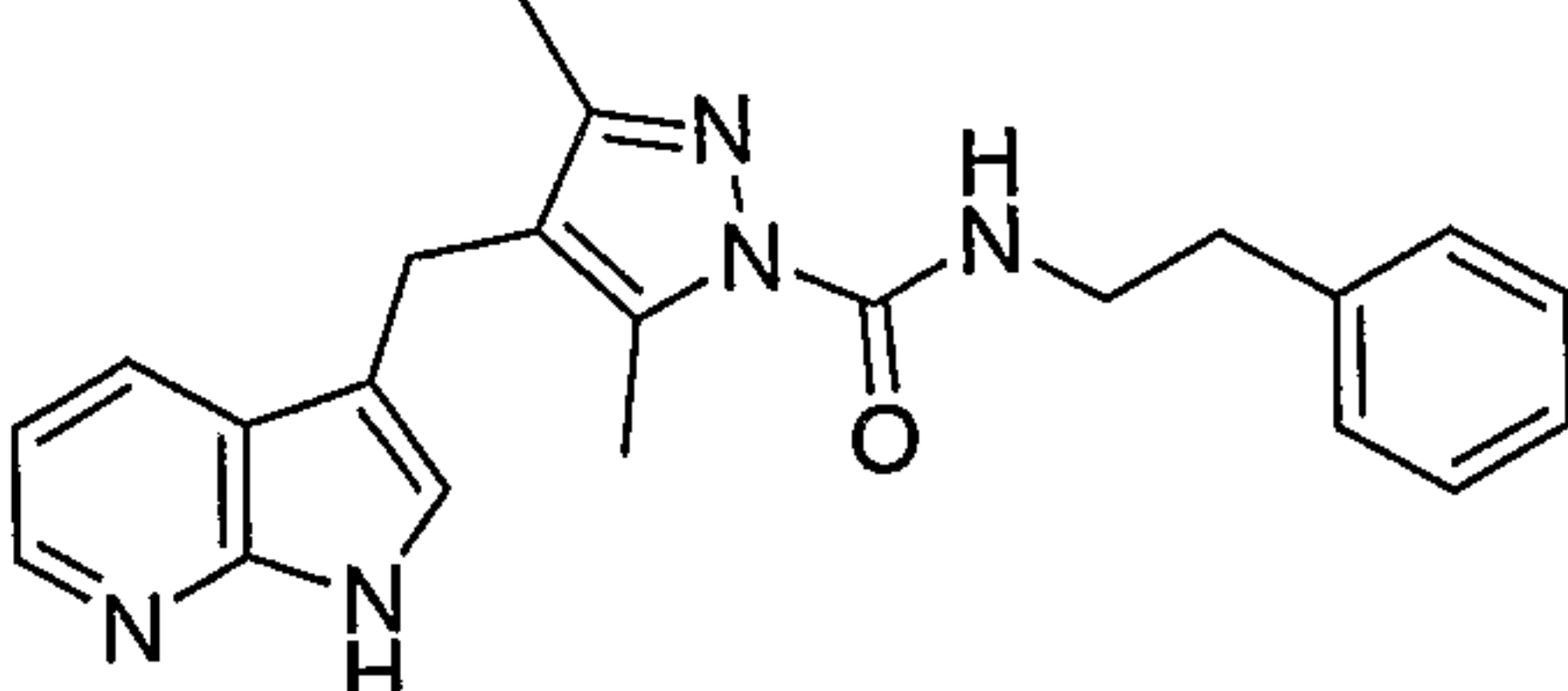
*Step 6 - 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid benzylamide (P-0084)*

[0680] To 3-(1-benzylcarbamoyl-3,5-dimethyl-1H-pyrazol-4-ylmethyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid tert-butyl ester (**515**, 50.0 mg, 0.11 mmol) in dichloromethane (6.0 mL) was added trifluoroacetic acid (0.20 mL, 2.6 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature for 20 minutes. The reaction was poured into aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to give a white solid (**P-0084**, 11.0 mg, 28.1%). MS (ESI)  $[M+H]^+$  = 360.5.

[0681] Additional compounds were prepared following the protocol of Scheme 158, replacing benzyl isocyanate with an appropriate electrophile in Step 5. The following compounds were made following this procedure:

3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid phenylamide (**P-0085**), [3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazol-1-yl]-phenyl-methanone (**P-0086**), 1-[3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazol-1-yl]-3-phenyl-propan-1-one (**P-0087**), 3-(3,5-Dimethyl-1-phenylmethanesulfonyl-1H-pyrazol-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine (**P-0088**), 3-[1-(Butane-1-sulfonyl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-1H-pyrrolo[2,3-b]pyridine (**P-0089**), 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid butylamide (**P-0090**), and 3,5-Dimethyl-4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyrazole-1-carboxylic acid phenethyl-amide (**P-0091**).

[0682] The electrophile used in place of benzyl isocyanate in Step 5 is indicated in Column 2 of the following table, with the compound structure given in Column 3. Column 1 provides the compound number and Column 4 the experimental mass spectrometry result.

	Electrophile	Compound	MS(ESI) [M+H] <sup>+</sup> observed
P-0085			346.4
P-0086			331.2
P-0087			359.2
P-0088			381.2
P-0089			347.2
P-0090			326.2
P-0091			

[0683] All patents and other references cited in the specification are indicative of the level of skill of those skilled in the art to which the invention pertains, and are



incorporated by reference in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

[0684] One skilled in the art would readily appreciate that the present invention is well adapted to obtain the ends and advantages mentioned, as well as those inherent therein. The methods, variances, and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

[0685] It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. For example, variations can be made to provide additional compounds of Formula I and/or various methods of administration can be used. Thus, such additional embodiments are within the scope of the present invention and the following claims.

[0686] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

[0687] In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

**[0688]** Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

**[0689]** Thus, additional embodiments are within the scope of the invention and within the following claims.



## DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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## JUMBO APPLICATIONS/PATENTS

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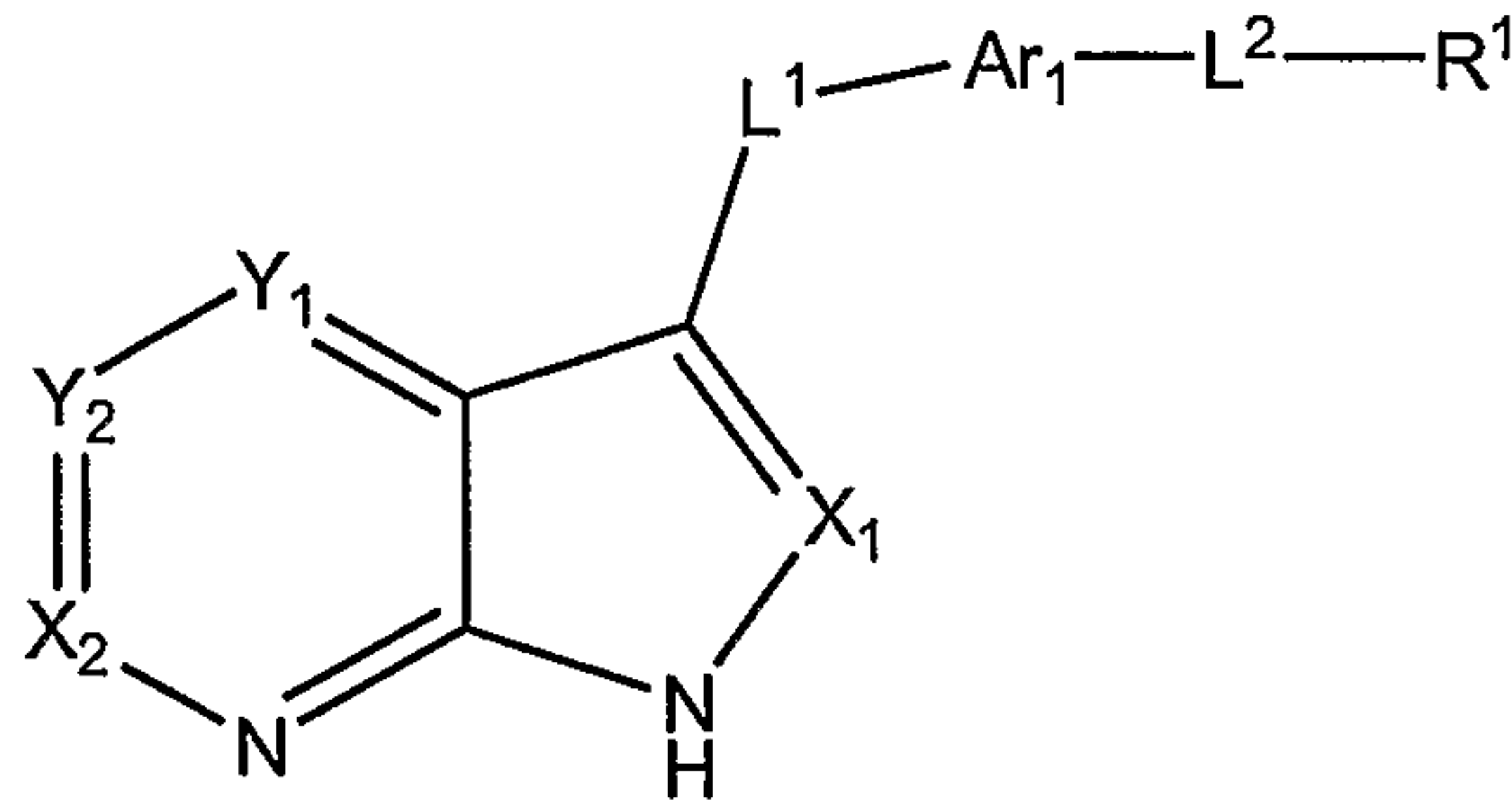
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## CLAIMS

What is claimed is:

1. A compound having the chemical structure



all salts, prodrugs, tautomers, and isomers thereof,

wherein:

$X_1$  is N or  $CR^2$ ,  $X_2$  is N or  $CR^6$ ,  $Y_1$  is N or  $CR^4$ , and  $Y_2$  is N or  $CR^5$ , provided, however, that not more than one of  $X_2$ ,  $Y_1$  and  $Y_2$  is N;

$L^1$  is selected from the group consisting of optionally substituted lower alkylene, -S-, -O-, -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, and -NR<sup>7</sup>-;

$L^2$  is selected from the group consisting of a bond, optionally substituted lower alkylene, -(alk)<sub>a</sub>-S-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-O-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-OC(O)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(O)O-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-OC(S)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(S)O-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(O)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(S)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(O)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-OC(O)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-OC(S)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-C(S)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-S(O)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-S(O)<sub>2</sub>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-S(O)<sub>2</sub>NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-NR<sup>9</sup>C(O)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-NR<sup>9</sup>C(S)-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-NR<sup>9</sup>C(O)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-NR<sup>9</sup>C(S)NR<sup>9</sup>-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-NR<sup>9</sup>C(O)O-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-NR<sup>9</sup>C(S)O-(alk)<sub>b</sub>-, -(alk)<sub>a</sub>-NR<sup>9</sup>S(O)<sub>2</sub>-(alk)<sub>b</sub>-, and -(alk)<sub>a</sub>-NR<sup>9</sup>S(O)<sub>2</sub>NR<sup>9</sup>-(alk)<sub>b</sub>-, wherein alk is optionally substituted C<sub>1-3</sub> alkylene and a and b are independently 0 or 1;

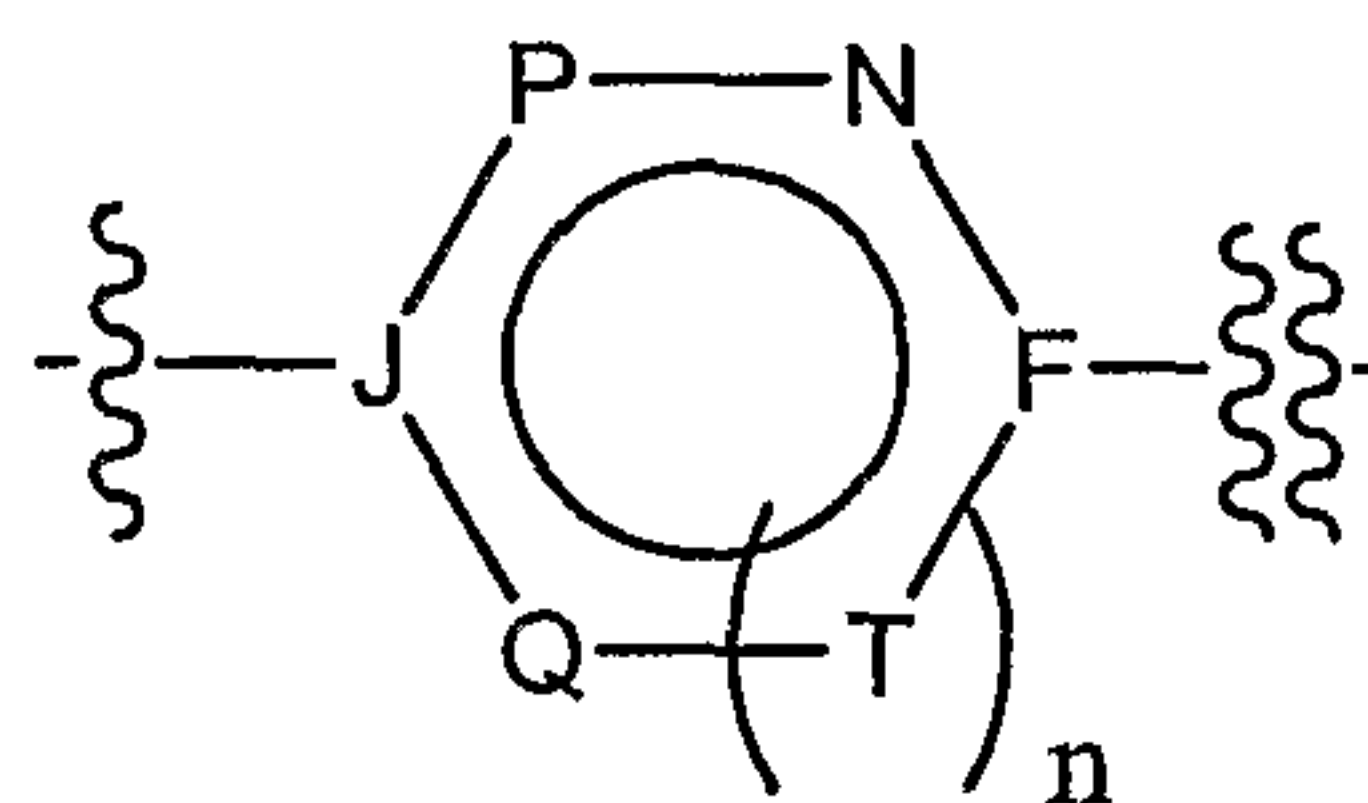
$R^1$  is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;


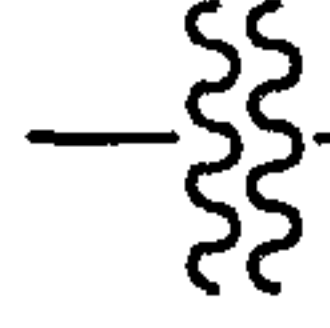
$R^2$ ,  $R^4$ ,  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally



substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CN, -C(O)OH, -C(S)OH, -C(O)NH<sub>2</sub>, -C(S)NH<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -NHC(O)NH<sub>2</sub>, -NHC(S)NH<sub>2</sub>, -NHS(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>10</sup>R<sup>11</sup>, -NHR<sup>3</sup>, -OR<sup>3</sup>, -SR<sup>3</sup>, -C(O)R<sup>3</sup>, -C(S)R<sup>3</sup>, -S(O)R<sup>3</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -C(O)OR<sup>3</sup>, -C(S)OR<sup>3</sup>, -C(O)NHR<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>3</sup>, -C(S)NHR<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NHR<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NHC(O)R<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>, -NHC(S)R<sup>3</sup>, -NR<sup>3</sup>C(S)R<sup>3</sup>, -NHS(O)<sub>2</sub>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>R<sup>3</sup>, -NHC(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)OH, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NHC(S)OR<sup>3</sup>, -NR<sup>3</sup>C(S)OH, -NR<sup>3</sup>C(S)OR<sup>3</sup>, -NHC(O)NHR<sup>3</sup>, -NHC(O)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)NH<sub>2</sub>, -NR<sup>3</sup>C(O)NHR<sup>3</sup>, -NR<sup>3</sup>C(O)NR<sup>3</sup>R<sup>3</sup>, -NHC(S)NHR<sup>3</sup>, -NHC(S)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(S)NH<sub>2</sub>, -NR<sup>3</sup>C(S)NHR<sup>3</sup>, -NR<sup>3</sup>C(S)NR<sup>3</sup>R<sup>3</sup>, -NHS(O)<sub>2</sub>NHR<sup>3</sup>, -NHS(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>3</sup>S(O)<sub>2</sub>NHR<sup>3</sup>, and -NR<sup>3</sup>S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>;

Ar<sub>1</sub> is a 5 or 6 membered optionally substituted heteroarylene having the structure



wherein  indicates the point of attachment of L<sup>1</sup> and  indicates the point of attachment of L<sup>2</sup>, and wherein the indicated N is either =N- or -N=;

n is 0 or 1;

F and J are both C or one of F and J is C and the other of F and J is N;

P and Q are independently selected from CR, N, NR, O or S;

T is selected from CR or N;

wherein,

when n is 1, F and J are C, and P, T and Q are CR, or any one of P, T and Q is N and the other two of P, T and Q are CR,

when n is 0 and F and J are both C, then one of P and Q are CR, N or NR and the other of P and Q is C, N, NR, O or S, provided both P and Q are not CR,

when n is 0, one of F and J is N and the other of F and J is C, then one of P and Q is N and the other of P and Q is CR or both P and Q are CR, and R is hydrogen or a substituent of substituted heteroarylene;

$R^3$  at each occurrence is independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that no alkene carbon thereof is bound to any -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- of any of -OR<sup>3</sup>, -SR<sup>3</sup>, -C(O)R<sup>3</sup>, -C(S)R<sup>3</sup>, -S(O)R<sup>3</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -C(O)OR<sup>3</sup>, -C(S)OR<sup>3</sup>, -C(O)NHR<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>3</sup>, -C(S)NHR<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NHR<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NHR<sup>3</sup>, -NHC(O)R<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>, -NHC(S)R<sup>3</sup>, -NR<sup>3</sup>C(S)R<sup>3</sup>, -NHS(O)<sub>2</sub>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>R<sup>3</sup>, -NHC(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)OH, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NHC(S)OR<sup>3</sup>, -NR<sup>3</sup>C(S)OH, -NR<sup>3</sup>C(S)OR<sup>3</sup>, -NHC(O)NHR<sup>3</sup>, -NHC(O)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)NH<sub>2</sub>, -NR<sup>3</sup>C(O)NHR<sup>3</sup>, -NR<sup>3</sup>C(O)NR<sup>3</sup>R<sup>3</sup>, -NHC(S)NHR<sup>3</sup>, -NHC(S)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(S)NH<sub>2</sub>, -NR<sup>3</sup>C(S)NHR<sup>3</sup>, -NR<sup>3</sup>C(S)NR<sup>3</sup>R<sup>3</sup>, -NHS(O)<sub>2</sub>NHR<sup>3</sup>, -NHS(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>3</sup>S(O)<sub>2</sub>NHR<sup>3</sup>, or -NR<sup>3</sup>S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, optionally substituted lower alkynyl, provided, however, that no alkyne carbon thereof is bound to any -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- of any of -OR<sup>3</sup>, -SR<sup>3</sup>, -C(O)R<sup>3</sup>, -C(S)R<sup>3</sup>, -S(O)R<sup>3</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -C(O)OR<sup>3</sup>, -C(S)OR<sup>3</sup>, -C(O)NHR<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>3</sup>, -C(S)NHR<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NHR<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NHR<sup>3</sup>, -NHC(O)R<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>, -NHC(S)R<sup>3</sup>, -NR<sup>3</sup>C(S)R<sup>3</sup>, -NHS(O)<sub>2</sub>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>R<sup>3</sup>, -NHC(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)OH, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NHC(S)OR<sup>3</sup>, -NR<sup>3</sup>C(S)OH, -NR<sup>3</sup>C(S)OR<sup>3</sup>, -NHC(O)NHR<sup>3</sup>, -NHC(O)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)NH<sub>2</sub>, -NR<sup>3</sup>C(O)NHR<sup>3</sup>, -NR<sup>3</sup>C(O)NR<sup>3</sup>R<sup>3</sup>, -NHC(S)NHR<sup>3</sup>, -NHC(S)NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(S)NH<sub>2</sub>, -NR<sup>3</sup>C(S)NHR<sup>3</sup>, -NR<sup>3</sup>C(S)NR<sup>3</sup>R<sup>3</sup>, -NHS(O)<sub>2</sub>NHR<sup>3</sup>, -NHS(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>3</sup>S(O)<sub>2</sub>NHR<sup>3</sup>, or -NR<sup>3</sup>S(O)<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^7$  is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>8</sup>, and -S(O)<sub>2</sub>R<sup>8</sup>;



$R^8$  is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl;

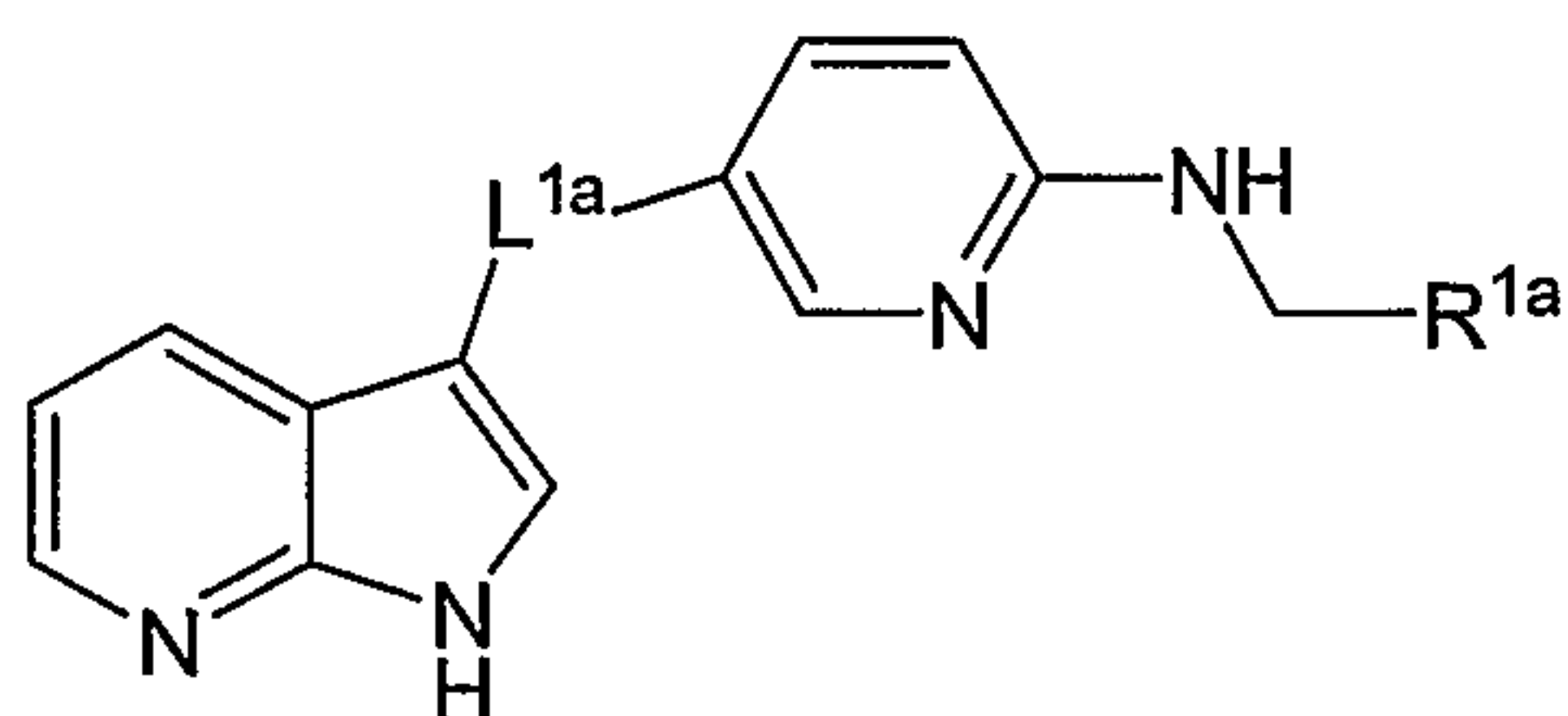
$R^9$  at each occurrence is independently selected from the group consisting of hydrogen, lower alkyl, and lower alkyl substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, fluoro substituted mono-alkylamino, di-alkylamino, fluoro substituted di-alkylamino, and -NR<sup>12</sup>R<sup>13</sup>, provided, however, that when  $R^9$  is substituted lower alkyl, any substitution on the alkyl carbon bound to the -N- of -NR<sup>9</sup>- is fluoro;

$R^{10}$  and  $R^{11}$  at each occurrence are independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that no alkene carbon thereof is bound to the nitrogen of -NR<sup>10</sup>R<sup>11</sup>, optionally substituted lower alkynyl, provided, however, that no alkyne carbon thereof is bound to the nitrogen of -NR<sup>10</sup>R<sup>11</sup>, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; or

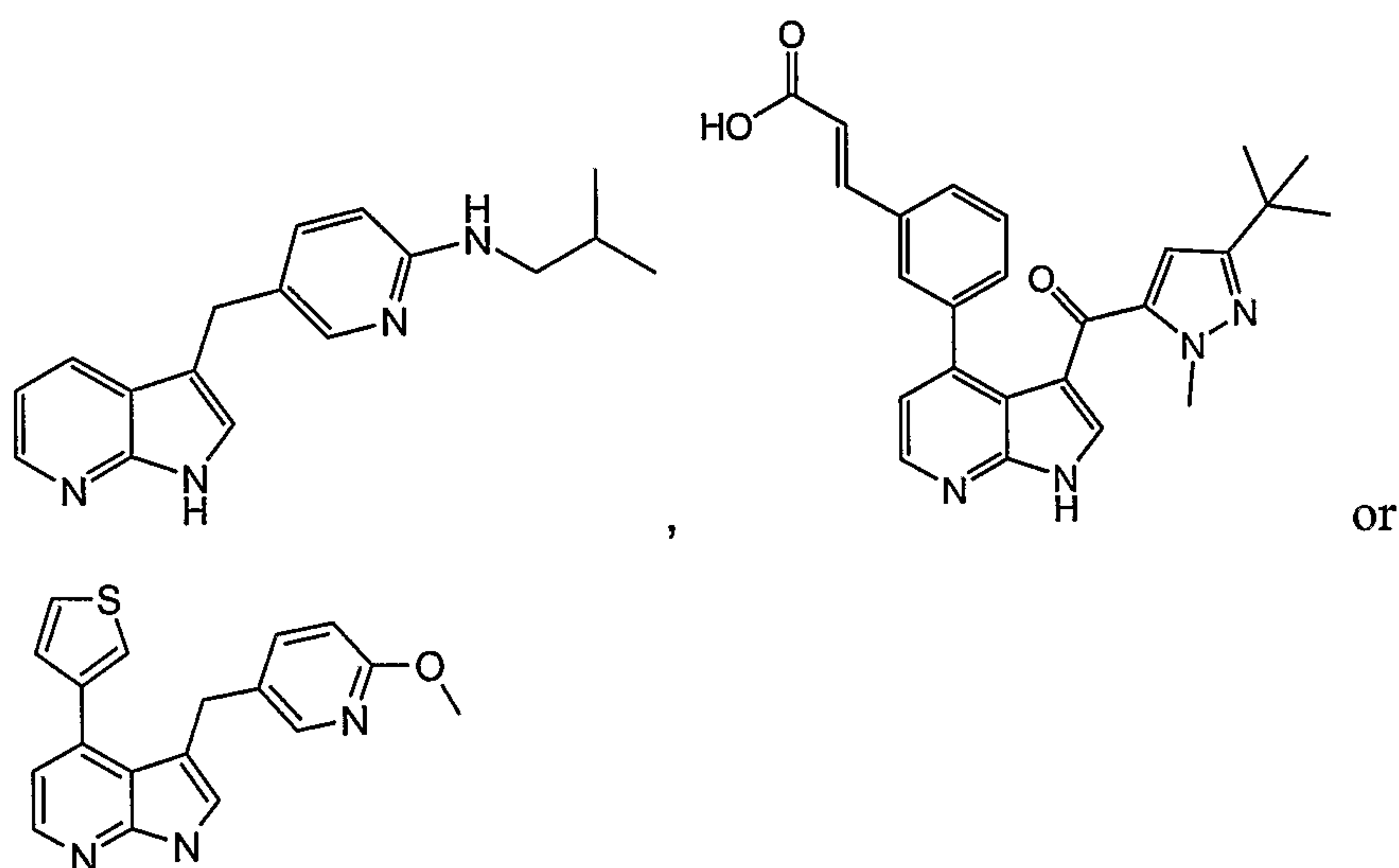
$R^{10}$  and  $R^{11}$  together with the nitrogen to which they are attached form a monocyclic 5-7 membered optionally substituted heterocycloalkyl or a monocyclic 5 or 7 membered optionally substituted nitrogen containing heteroaryl; and

$R^{12}$  and  $R^{13}$  combine with the nitrogen to which they are attached to form a 5-7 membered heterocycloalkyl or 5-7 membered heterocycloalkyl substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio;

provided, however that when compounds have the structure



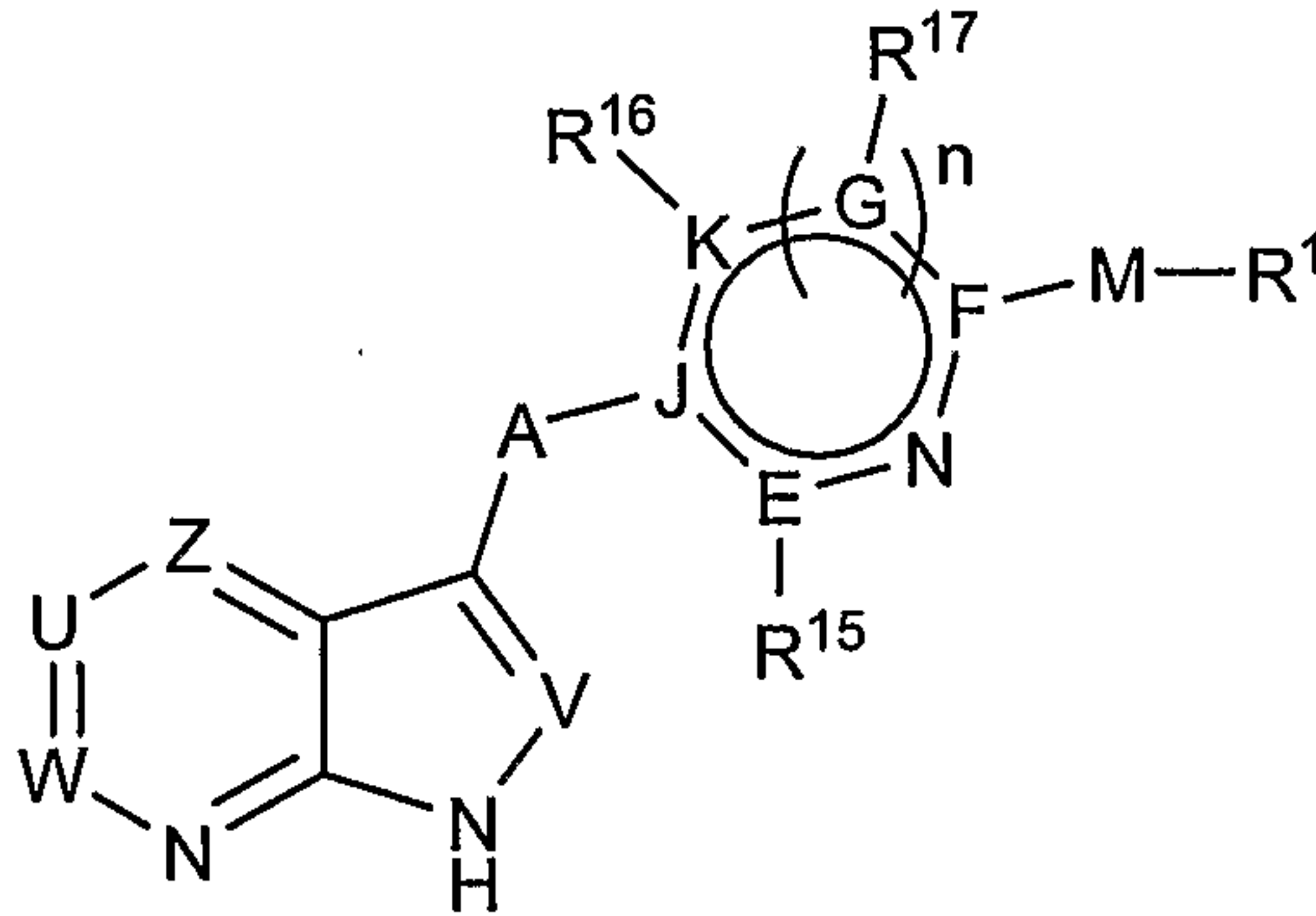
and  $L^{1a}$  is  $-\text{CH}_2-$ ,  $-\text{CH}(\text{OH})-$ , or  $-\text{C}(\text{O})-$ , then  $R^{1a}$  is not phenyl, 4-trifluoromethyl-phenyl, 4-methoxy-phenyl, 4-chloro-phenyl, 4-fluoro-phenyl, 4-methyl-phenyl, 3-fluoro-phenyl or thiophen-2-yl and compounds do not have the structure



2. The compound according to Claim 1, wherein  $X_1$  and  $X_2$  are CH.
3. The compound according to Claim 2, wherein  $Y_1$  is N or CH and  $Y_2$  is  $\text{CR}^5$ .
4. The compound according to Claim 3, wherein  $Y_1$  is CH and  $R^5$  is other than hydrogen.
5. The compound according to Claim 4, wherein  $L_1$  is  $-\text{CH}_2-$  or  $\text{C}(\text{O})-$ .
6. The compound according to Claim 3, wherein  $Y_1$  is CH and  $R^5$  is hydrogen.
7. The compound according to Claim 6, wherein  $L_1$  is  $-\text{CH}_2-$  or  $\text{C}(\text{O})-$ .
8. The compound according to Claim 2, wherein  $Y_2$  is N or CH and  $Y_1$  is  $\text{CR}^4$ .
9. The compound according to Claim 8, wherein  $Y_2$  is CH and  $R^4$  is other than hydrogen.
10. The compound according to Claim 9, wherein  $L_1$  is  $-\text{CH}_2-$  or  $\text{C}(\text{O})-$ .
11. The compound according to Claim 8, wherein  $Y_2$  is CH and  $R^4$  is hydrogen.
12. The compound according to Claim 11, wherein  $L_1$  is  $-\text{CH}_2-$  or  $\text{C}(\text{O})-$ .



13. The compound according to Claim 1 having the chemical structure



all salts, prodrugs, tautomers, and isomers thereof,

wherein:

V and W are independently selected from the group consisting of N and CH;

U and Z are independently selected from the group consisting of N and CR<sup>18</sup>,

provided, however, that not more than one of W, U and Z is N;

A is selected from the group consisting of -CR<sup>19</sup>R<sup>20</sup>-, -C(O)-, -C(S)-, -S-,

-S(O)-, -S(O)<sub>2</sub>-, -NR<sup>21</sup>-, and -O-;

n is 0 or 1;

F and J are both C or one of F and J is C and the other of F and J is N;

E and K are selected from C, N, O or S;

G is selected from C or N;

wherein,

when n is 1, F and J are C, and E, G and K are C, or any one of E, G and K is N and the other two of E, G and K are C, provided that when E, G or K is N, R<sup>15</sup>, R<sup>17</sup> and R<sup>16</sup>, respectively, are absent,

when n is 0 and F and J are both C, then one of E and K is C or N and the other of E and K is C, N, O or S, provided both E and K are not C, and provided that when both E and K are N, one of R<sup>15</sup> and R<sup>16</sup> is absent, and provided that when one of E and K are N and the other is O or S, R<sup>15</sup> and R<sup>16</sup> are absent,

when n is 0, one of F and J is N and the other of F and J is C, then one of E and K is N and the other of E and K is C, or both E and K are C, provided that when E is N, R<sup>15</sup> is absent and when K is N, R<sup>16</sup> is absent;

$R^1$  is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl;

$R^{15}$  is selected from the group consisting of hydrogen, optionally substituted lower alkyl,  $-OR^{22}$ ,  $-SR^{22}$  and halogen when E is C, is absent when E is O or S or when  $n=1$  and E is N, and is absent or selected from the group consisting of hydrogen and optionally substituted lower alkyl when  $n=0$  and E is N;

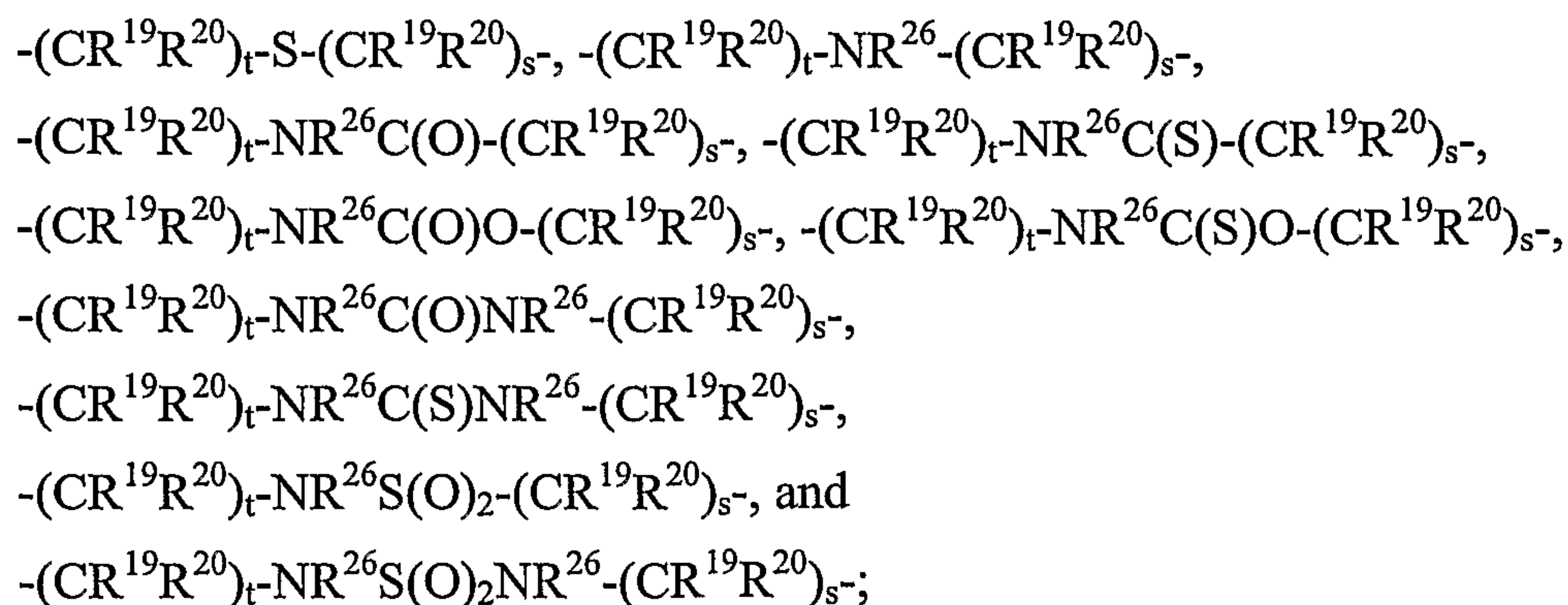
$R^{16}$  is selected from the group consisting of hydrogen, optionally substituted lower alkyl,  $-OR^{22}$ ,  $-SR^{22}$  and halogen when K is C, is absent when K is O or S or when  $n=1$  and K is N, and is absent or selected from the group consisting of hydrogen and optionally substituted lower alkyl when  $n=0$  and K is N;

$R^{17}$  is selected from the group consisting of hydrogen, optionally substituted lower alkyl,  $-OR^{22}$ ,  $-SR^{22}$  and halogen when G is C, or is absent when G is N;

$R^{18}$  is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OH$ ,  $-NH_2$ ,  $-NO_2$ ,  $-CN$ ,  $-NHC(O)NH_2$ ,  $-NHC(S)NH_2$ ,  $-NHS(O)_2NH_2$ ,  $-NR^{24}R^{25}$ ,  $-NHR^{23}$ ,  $-OR^{23}$ ,  $-SR^{23}$ ,  $-NHC(O)R^{23}$ ,  $-NR^{23}C(O)R^{23}$ ,  $-NHC(S)R^{23}$ ,  $-NR^{23}C(S)R^{23}$ ,  $-NHS(O)_2R^{23}$ ,  $-NR^{23}S(O)_2R^{23}$ ,  $-NHC(O)NHR^{23}$ ,  $-NR^{23}C(O)NH_2$ ,  $-NR^{23}C(O)NHR^{23}$ ,  $-NHC(O)NR^{23}R^{23}$ ,  $-NR^{23}C(O)NR^{23}R^{23}$ ,  $-NHC(S)NHR^{23}$ ,  $-NR^{23}C(S)NH_2$ ,  $-NR^{23}C(S)NHR^{23}$ ,  $-NHC(S)NR^{23}R^{23}$ ,  $-NR^{23}C(S)NR^{23}R^{23}$ ,  $-NHS(O)_2NHR^{23}$ ,  $-NR^{23}S(O)_2NH_2$ ,  $-NR^{23}S(O)_2NHR^{23}$ ,  $-NHS(O)_2NR^{23}R^{23}$ , and  $-NR^{23}S(O)_2NR^{23}R^{23}$ ;

M is selected from the group consisting of a bond,  $-(CR^{19}R^{20})_u-$ ,  $-(CR^{19}R^{20})_t-C(O)-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-C(S)-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-C(O)O-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-C(S)O-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-C(O)NR^{26}-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-C(S)NR^{26}-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-S(O)-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-S(O)_2-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-S(O)_2NR^{26}-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-O-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-OC(O)-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-OC(S)-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-OC(O)NR^{26}-(CR^{19}R^{20})_{s-}$ ,  $-(CR^{19}R^{20})_t-OC(S)NR^{26}-(CR^{19}R^{20})_{s-}$ ,





wherein  $\text{R}^{19}$  and  $\text{R}^{20}$  at each occurrence are independently selected from the group consisting of hydrogen, fluoro, -OH, -NH<sub>2</sub>, lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and  $-\text{NR}^{27}\text{R}^{28}$ , wherein the alkyl chain(s) of lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino; or

any two of  $\text{R}^{19}$  and  $\text{R}^{20}$  on the same or different carbons combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl and any others of  $\text{R}^{19}$  and  $\text{R}^{20}$  are independently selected from the group consisting of hydrogen, fluoro, -OH, -NH<sub>2</sub>, lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, di-alkylamino, and  $-\text{NR}^{27}\text{R}^{28}$ , wherein the alkyl chain(s) of lower alkyl, lower alkoxy, lower alkylthio, mono-alkylamino, or di-alkylamino are optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein the monocyclic cycloalkyl or monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, -NH<sub>2</sub>, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

$R^{21}$  and  $R^{22}$  at each occurrence are independently hydrogen or optionally substituted lower alkyl;

$R^{23}$  at each occurrence is independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that no alkene carbon thereof is bound to any -C(O)-, -C(S)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- of any of -NHR<sup>23</sup>, -OR<sup>23</sup>, -SR<sup>23</sup>, -NHC(O)R<sup>23</sup>, -NR<sup>23</sup>C(O)R<sup>23</sup>, -NHC(S)R<sup>23</sup>, -NR<sup>23</sup>C(S)R<sup>23</sup>, -NHS(O)<sub>2</sub>R<sup>23</sup>, -NR<sup>23</sup>S(O)<sub>2</sub>R<sup>23</sup>, -NHC(O)NHR<sup>23</sup>, -NR<sup>23</sup>C(O)NH<sub>2</sub>, -NR<sup>23</sup>C(O)NHR<sup>23</sup>, -NHC(O)NR<sup>23</sup>R<sup>23</sup>, -NR<sup>23</sup>C(O)NR<sup>23</sup>R<sup>23</sup>, -NHC(S)NHR<sup>23</sup>, -NR<sup>23</sup>C(S)NH<sub>2</sub>, -NR<sup>23</sup>C(S)NHR<sup>23</sup>, -NHC(S)NR<sup>23</sup>R<sup>23</sup>, -NR<sup>23</sup>C(S)NR<sup>23</sup>R<sup>23</sup>, -NHS(O)<sub>2</sub>NHR<sup>23</sup>, -NR<sup>23</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>23</sup>S(O)<sub>2</sub>NHR<sup>23</sup>, -NHS(O)<sub>2</sub>NR<sup>23</sup>R<sup>23</sup>, or -NR<sup>23</sup>S(O)<sub>2</sub>NR<sup>23</sup>R<sup>23</sup>, optionally substituted lower alkynyl, provided, however, that no alkyne carbon thereof is bound to any -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -O-, -S-, or -N- of any of -NHR<sup>23</sup>, -OR<sup>23</sup>, -SR<sup>23</sup>, -NHC(O)R<sup>23</sup>, -NR<sup>23</sup>C(O)R<sup>23</sup>, -NHC(S)R<sup>23</sup>, -NR<sup>23</sup>C(S)R<sup>23</sup>, -NHS(O)<sub>2</sub>R<sup>23</sup>, -NR<sup>23</sup>S(O)<sub>2</sub>R<sup>23</sup>, -NHC(O)NHR<sup>23</sup>, -NR<sup>23</sup>C(O)NH<sub>2</sub>, -NR<sup>23</sup>C(O)NHR<sup>23</sup>, -NHC(O)NR<sup>23</sup>R<sup>23</sup>, -NR<sup>23</sup>C(O)NR<sup>23</sup>R<sup>23</sup>, -NHC(S)NHR<sup>23</sup>, -NR<sup>23</sup>C(S)NH<sub>2</sub>, -NR<sup>23</sup>C(S)NHR<sup>23</sup>, -NHC(S)NR<sup>23</sup>R<sup>23</sup>, -NR<sup>23</sup>C(S)NR<sup>23</sup>R<sup>23</sup>, -NHS(O)<sub>2</sub>NHR<sup>23</sup>, -NR<sup>23</sup>S(O)<sub>2</sub>NH<sub>2</sub>, -NR<sup>23</sup>S(O)<sub>2</sub>NHR<sup>23</sup>, -NHS(O)<sub>2</sub>NR<sup>23</sup>R<sup>23</sup>, or -NR<sup>23</sup>S(O)<sub>2</sub>NR<sup>23</sup>R<sup>23</sup>, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

$R^{24}$  and  $R^{25}$  at each occurrence are independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted lower alkenyl, provided, however, that no alkene carbon thereof is bound to the nitrogen of -NR<sup>24</sup>R<sup>25</sup>, optionally substituted lower alkynyl, provided, however, that no alkyne carbon thereof is bound to the nitrogen of -NR<sup>24</sup>R<sup>25</sup>, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; or

$R^{24}$  and  $R^{25}$  together with the nitrogen to which they are attached form a monocyclic 5-7 membered optionally substituted heterocycloalkyl or a



monocyclic 5 or 7 membered optionally substituted nitrogen containing heteroaryl;

$R^{26}$  at each occurrence is independently selected from the group consisting of hydrogen, lower alkyl, and lower alkyl substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, fluoro substituted mono-alkylamino, di-alkylamino, fluoro substituted di-alkylamino, and -NR<sup>27</sup>R<sup>28</sup>, provided, however, that when R<sup>26</sup> is substituted lower alkyl, any substitution on the lower alkyl carbon bound to the -N- of -NR<sup>26</sup>- is fluoro;

$R^{27}$  and  $R^{28}$  combine with the nitrogen to which they are attached to form a 5-7 membered heterocycloalkyl or 5-7 membered heterocycloalkyl substituted with one or more substituents selected from the group consisting of fluoro, -OH, -NH<sub>2</sub>, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio;

u is 1-6;

t is 0-3; and

s is 0-3;

provided that

when V, W, U and Z are CH, n=1, E, F, G, J, and K are C,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H, A is -CH<sub>2</sub>-, -CH(OH)-, or -C(O)-, and M is -NHCH<sub>2</sub>-, then R<sup>1</sup> is not phenyl, 4-trifluoromethyl-phenyl, 4-methoxy-phenyl, 4-chloro-phenyl, 4-fluoro-phenyl, 4-methyl-phenyl, 3-fluoro-phenyl or thiophen-2-yl,

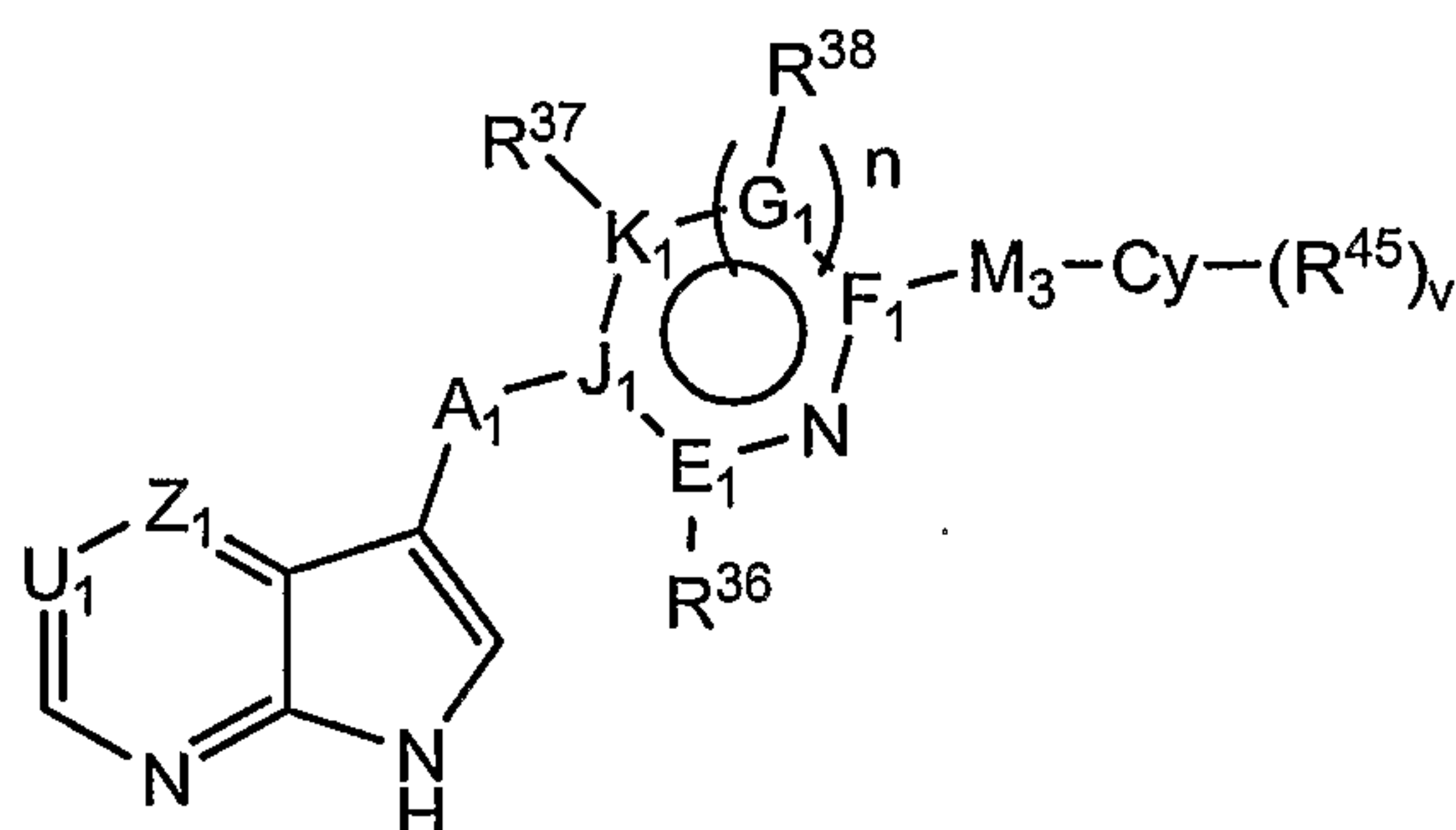
when V, W, U and Z are CH, n=1, E, F, G, J, and K are C,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H, and A is -CH<sub>2</sub>-, then M-R<sup>1</sup> is not -NHCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,

when V, W, and U are CH, n=1, E, F, G, J, and K are C,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are H, A is -CH<sub>2</sub>-, M-R<sup>1</sup> is -OCH<sub>3</sub>, and Z is CR<sup>18</sup>, then R<sup>18</sup> is not thiophen-3-yl, and

when V, W, and U are CH, n=0, F, J, and K are C, E is N,  $R^{15}$  is CH<sub>3</sub>,  $R^{16}$  is H, A is -C(O)-, M-R<sup>1</sup> is -CH(CH<sub>3</sub>)<sub>3</sub>, and Z is CR<sup>18</sup>, then R<sup>18</sup> is not 3-((E)-2-carboxy-vinyl)phenyl.

14. A compound of Claim 13, wherein V and W are CH.

15. A compound of Claim 14, wherein U and Z are independently CR<sup>18</sup>.
16. A compound of Claim 15, wherein n is 1.
17. A compound of Claim 16, wherein G and K are C.
18. A compound of Claim 17, wherein E is N.
19. A compound of Claim 17, wherein E is C.
20. A compound of Claim 1 having the structure



all salts, prodrugs, tautomers, and isomers thereof,

wherein:

Z<sub>1</sub> is selected from the group consisting of N and CR<sup>34</sup>;

U<sub>1</sub> is selected from the group consisting of N and CR<sup>35</sup>;

A<sub>1</sub> is selected from the group consisting of -CH<sub>2</sub>- and -C(O)-;

M<sub>3</sub> is selected from the group consisting of a bond, -NR<sup>39</sup>-, -S-, -O-,  
 -NR<sup>39</sup>CH<sub>2</sub>-, -NR<sup>39</sup>CH(R<sup>40</sup>)-, -SCH<sub>2</sub>-, -OCH<sub>2</sub>-, -C(O)NR<sup>39</sup>-, -S(O)<sub>2</sub>NR<sup>39</sup>-,  
 -CH<sub>2</sub>NR<sup>39</sup>-, -CH(R<sup>40</sup>)NR<sup>39</sup>-, -NR<sup>39</sup>C(O)-, and -NR<sup>39</sup>S(O)<sub>2</sub>-;

n is 0 or 1;

v is 0, 1, 2 or 3;

F<sub>1</sub> and J<sub>1</sub> are both C or one of F<sub>1</sub> and J<sub>1</sub> is C and the other of F<sub>1</sub> and J<sub>1</sub> is N;

E<sub>1</sub> and K<sub>1</sub> are selected from C, N, O or S;

G<sub>1</sub> is selected from C or N;

wherein,

when n is 1, F<sub>1</sub> and J<sub>1</sub> are C, and E<sub>1</sub>, G<sub>1</sub> and K<sub>1</sub> are C, or any one of E<sub>1</sub>, G<sub>1</sub> and K<sub>1</sub> is N and the other two of E<sub>1</sub>, G<sub>1</sub> and K<sub>1</sub> are C, provided that when E<sub>1</sub>, G<sub>1</sub> or K<sub>1</sub> is N, R<sup>36</sup>, R<sup>37</sup> and R<sup>38</sup>, respectively, are absent, when n is 0 and F<sub>1</sub> and J<sub>1</sub> are both C, then one of E<sub>1</sub> and K<sub>1</sub> is C or N and the other of E<sub>1</sub> and K<sub>1</sub> is C, N, O or S, provided both E<sub>1</sub> and K<sub>1</sub> are not C, and provided that when both E<sub>1</sub> and K<sub>1</sub> are N, one of R<sup>36</sup>



and  $R^{37}$  is absent, and provided that when one of  $E_1$  and  $K_1$  are N and the other is O or S,  $R^{36}$  and  $R^{37}$  are absent,

when  $n$  is 0, one of  $F_1$  and  $J_1$  is N and the other of  $F_1$  and  $J_1$  is C, then one of  $E_1$  and  $K_1$  is N and the other of  $E_1$  and  $K_1$  is C, or both  $E_1$  and  $K_1$  are C, provided that when  $E_1$  is N,  $R^{36}$  is absent and when  $K_1$  is N,  $R^{37}$  is absent;

Cy is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

$R^{34}$  and  $R^{35}$  are independently selected from the group consisting of hydrogen,  $-OR^{41}$ ,  $-SR^{41}$ ,  $-NHR^{41}$ ,  $-NR^{41}R^{41}$ ,  $-NR^{39}C(O)R^{41}$ ,  $-NR^{39}S(O)_2R^{41}$ , halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as  $R^{34}$  or  $R^{35}$ , or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CN$ ,  $-NO_2$ ,  $-S(O)_2NH_2$ ,  $-C(O)NH_2$ ,  $-OR^{42}$ ,  $-SR^{42}$ ,  $-NHR^{42}$ ,  $-NR^{42}R^{42}$ ,  $-NR^{39}C(O)R^{42}$ ,  $-NR^{39}S(O)_2R^{42}$ ,  $-S(O)_2R^{42}$ , halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

$R^{45}$  at each occurrence is independently selected from the group consisting of  $-OR^{41}$ ,  $-SR^{41}$ ,  $-NHR^{41}$ ,  $-NR^{41}R^{41}$ ,  $-NR^{39}C(O)R^{41}$ ,  $-NR^{39}S(O)_2R^{41}$ , halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as  $R^{45}$ , or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of  $-OH$ ,  $-NH_2$ ,  $-CN$ ,  $-NO_2$ ,  $-S(O)_2NH_2$ ,  $-C(O)NH_2$ ,  $-OR^{42}$ ,  $-SR^{42}$ ,  $-NHR^{42}$ ,  $-NR^{42}R^{42}$ ,

$-\text{NR}^{39}\text{C}(\text{O})\text{R}^{42}$ ,  $-\text{NR}^{39}\text{S}(\text{O})_2\text{R}^{42}$ ,  $-\text{S}(\text{O})_2\text{R}^{42}$ , halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

$\text{R}^{36}$  is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy when  $\text{E}_1$  is C, is absent when  $\text{E}_1$  is O or S or when  $n=1$  and  $\text{E}_1$  is N, and is absent or selected from the group consisting of hydrogen, lower alkyl, and fluoro substituted lower alkyl when  $n=0$  and  $\text{E}_1$  is N;

$\text{R}^{37}$  is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy when  $\text{K}_1$  is C, is absent when  $\text{K}_1$  is O or S or when  $n=1$  and  $\text{K}_1$  is N, and is absent or selected from the group consisting of hydrogen, lower alkyl, and fluoro substituted lower alkyl when  $n=0$  and  $\text{K}_1$  is N;

$\text{R}^{38}$  is selected from the group consisting of hydrogen, halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, and fluoro substituted lower alkoxy when  $\text{G}_1$  is C, or is absent when  $\text{G}_1$  is N;

$\text{R}^{39}$  at each occurrence is independently selected from the group consisting of hydrogen and lower alkyl;

$\text{R}^{40}$  is selected from the group consisting of lower alkyl, and fluoro substituted lower alkyl;

$\text{R}^{41}$  is selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as  $\text{R}^{41}$  or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of  $-\text{OH}$ ,  $-\text{NH}_2$ ,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{S}(\text{O})_2\text{NH}_2$ ,  $-\text{C}(\text{O})\text{NH}_2$ ,  $-\text{OR}^{42}$ ,  $-\text{SR}^{42}$ ,  $-\text{NHR}^{42}$ ,  $-\text{NR}^{42}\text{R}^{42}$ ,  $-\text{NR}^{39}\text{C}(\text{O})\text{R}^{42}$ ,  $-\text{NR}^{39}\text{S}(\text{O})_2\text{R}^{42}$ ,  $-\text{S}(\text{O})_2\text{R}^{42}$ , halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and

$\text{R}^{42}$  at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is



optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

**21.** The compound of Claim 20,

wherein

each  $R^{45}$  is selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>,

halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower thioalkyl, fluoro substituted lower thioalkyl, mono-alkylamino, di-alkylamino and cycloalkylamino,

$Z_1$  is  $CR^{34}$  and  $U_1$  is  $CR^{35}$ , and

$R^{34}$  and  $R^{35}$  are independently selected from the group consisting of hydrogen, -OR<sup>41</sup>, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl,

wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally

substituted with one or more substituents selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -C(O)NH<sub>2</sub>, -OR<sup>42</sup>, -SR<sup>42</sup>, -NHR<sup>42</sup>, -NR<sup>42</sup>R<sup>42</sup>, -NR<sup>39</sup>C(O)R<sup>42</sup>, -NR<sup>39</sup>S(O)<sub>2</sub>R<sup>42</sup>, -S(O)<sub>2</sub>R<sup>42</sup>, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino, and

wherein lower alkyl is optionally substituted with one or more substituents

selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

**22.** The compound of Claim 21 wherein  $v$  is 0, 1, or 2.

**23.** The compound of Claim 22, wherein  $n$  is 1, and  $G_1$  and  $K_1$  are C.

**24.** The compound of Claim 23, wherein  $E_1$  is N.

**25.** The compound of Claim 23, wherein  $E_1$  is C.

**26.** The compound of Claim 25, wherein  $M_3$  is selected from the group consisting of -NR<sup>39</sup>-, -O-, -NR<sup>39</sup>CH<sub>2</sub>-, -NR<sup>39</sup>CH(R<sup>40</sup>)-, -SCH<sub>2</sub>-, -OCH<sub>2</sub>-, -CH<sub>2</sub>NR<sup>39</sup>-, -NR<sup>39</sup>C(O)-, and -NR<sup>39</sup>S(O)<sub>2</sub>-.

**27.** The compound of Claim 26, wherein  $M_3$  is selected from the group consisting of -NR<sup>39</sup>CH<sub>2</sub>-, -NR<sup>39</sup>CH(R<sup>40</sup>)-, -SCH<sub>2</sub>-, -OCH<sub>2</sub>-, and -CH<sub>2</sub>NR<sup>39</sup>-.

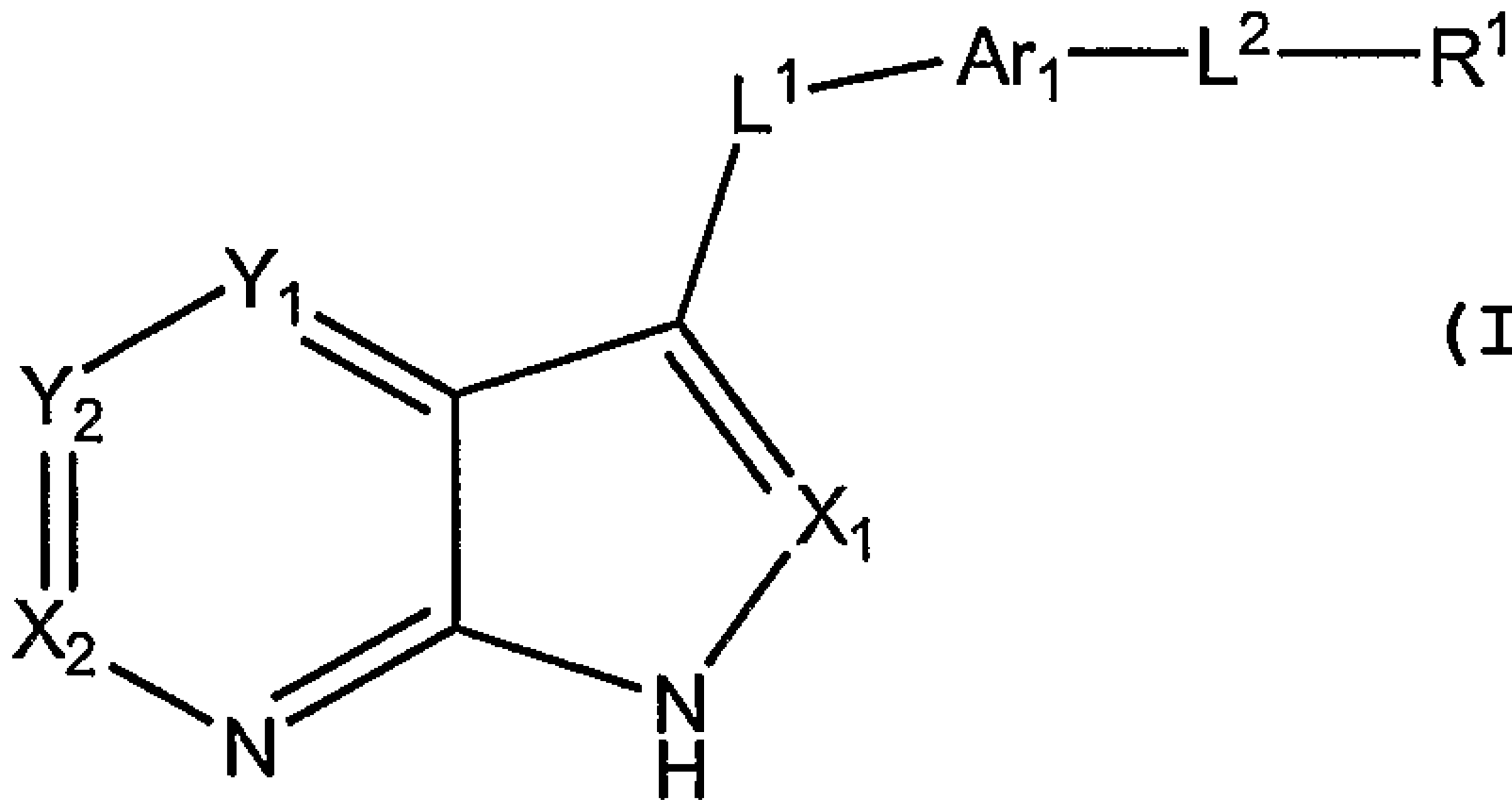
28. The compound of Claim 27, wherein both of  $R^{34}$  and  $R^{35}$  are hydrogen.
29. The compound of Claim 27,  
wherein  
one of  $R^{34}$  and  $R^{35}$  is hydrogen, and  
the other of  $R^{34}$  and  $R^{35}$  is selected from the group consisting of halogen, lower alkyl, lower alkoxy, aryl and heteroaryl,  
wherein aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH<sub>2</sub>, -CN, -NO<sub>2</sub>, -S(O)<sub>2</sub>NH<sub>2</sub>, -C(O)NH<sub>2</sub>, -OR<sup>42</sup>, -SR<sup>42</sup>, -NHR<sup>42</sup>, -NR<sup>42</sup>R<sup>42</sup>, -NR<sup>39</sup>C(O)R<sup>42</sup>, -NR<sup>39</sup>S(O)<sub>2</sub>R<sup>42</sup>, -S(O)<sub>2</sub>R<sup>42</sup>, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino, and  
wherein lower alkyl and lower alkoxy are optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.
30. The compound according to Claim 29, wherein  $R^{34}$  is hydrogen.
31. The compound according to Claim 29,  
wherein  
one of  $R^{34}$  and  $R^{35}$  is hydrogen, and  
the other of  $R^{34}$  and  $R^{35}$  is selected from the group consisting of halogen, lower alkyl, and lower alkoxy,  
wherein lower alkyl and lower alkoxy are optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.
32. The compound of Claim 31, wherein  $R^{34}$  is hydrogen.
33. A composition comprising:  
a pharmaceutically acceptable carrier; and  
a compound according to Claim 1.



- 34.** A composition comprising:  
a pharmaceutically acceptable carrier; and  
a compound of Claim 13.
- 35.** A composition comprising:  
a pharmaceutically acceptable carrier; and  
a compound of Claim 20.
- 36.** A method for treating a subject suffering from or at risk of a c-kit or c-fms mediated disease or condition, comprising administering to the subject an effective amount of a compound of Claim 1.
- 37.** A method for treating a subject suffering from or at risk of a c-kit or c-fms mediated disease or condition, comprising administering to the subject an effective amount of a compound of Claim 13.
- 38.** A method for treating a subject suffering from or at risk of a c-kit or c-fms mediated disease or condition, comprising administering to the subject an effective amount of a compound of Claim 20.
- 39.** The method of any of Claims 36-38, wherein the compound is approved for administration to a human.
- 40.** The method of Claim 39, wherein the disease or condition is selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, canine mast cell tumors, hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosus, Wegener's granulomatosis, Chronic Obstructive Pulmonary Disease, emphysema, atherosclerosis, insulin resistance, hyperglycemia, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, hypercalcemia, bone metastases, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, and diabetes-associated renal complications.
- 41.** A kit comprising a composition according to any of Claims 33-35.

42. The kit of Claim 41, wherein the composition is approved for a medical indication selected from the group consisting of mast cell tumors, small cell lung cancer, testicular cancer, gastrointestinal stromal tumors, glioblastoma, astrocytoma, neuroblastoma, carcinomas of the female genital tract, sarcomas of neuroectodermal origin, colorectal carcinoma, carcinoma in situ, Schwann cell neoplasia associated with neurofibromatosis, acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, multiple myeloma, mastocytosis, melanoma, breast cancer, ovarian cancer, canine mast cell tumors, hypertrophy, asthma, rheumatoid arthritis, allergic rhinitis, multiple sclerosis, inflammatory bowel syndrome, transplant rejection, systemic lupus erythematosus, Wegener's granulomatosis, Chronic Obstructive Pulmonary Disease, emphysema, atherosclerosis, insulin resistance, hyperglycemia, lipolysis, hypereosinophilia, osteoporosis, increased risk of fracture, hypercalcemia, bone metastases, glomerulonephritis, interstitial nephritis, Lupus nephritis, tubular necrosis, and diabetes-associated renal complications.





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