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(54) **Titre : INHIBITEURS DE KINASES DE LIGNEE MIXTE ET PROCEDES THERAPEUTIQUES**
(54) **Title: MIXED LINEAGE KINASE INHIBITORS AND METHOD OF TREATMENTS**

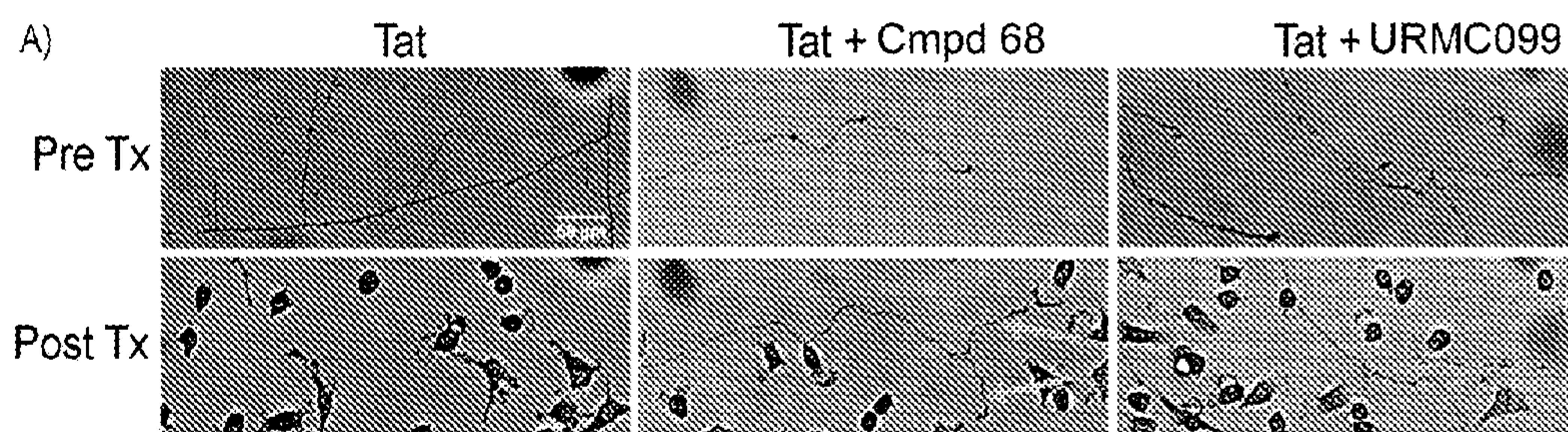


FIG. 1

(57) **Abrégé/Abstract:**

Provided herein are imidazopyridine compounds having an inhibitory effect on mixed lineage kinases (MLKs), methods of their synthesis, and methods of their therapeutic. Also provided are pharmaceutical compositions comprising the compounds and methods of using the compounds and pharmaceutical compositions.

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A) 

(57) Abstract: Provided herein are imidazopyridine compounds having an inhibitory effect on mixed lineage kinases (MLKs), methods of their synthesis, and methods of their therapeutic. Also provided are pharmaceutical compositions comprising the compounds and methods of using the compounds and pharmaceutical compositions.

MIXED LINEAGE KINASE INHIBITORS AND METHOD OF TREATMENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority Application Serial No. 61/774,211, filed on March 7, 2013, which is expressly incorporated herein by reference in its entirety.

GOVERNMENT SUPPORT

[0002] This work was supported in part by Small Business Innovation Research Grants 1R43MH093270-01 and 2R44MH093270-02 from the National Institutes of Mental Health of the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The present disclosure relates to imidazopyridine compounds having an inhibitory effect on mixed lineage kinases (MLKs), including family members in groups (*e.g.*, MLK-1, MLK-2, MLK-3), and their synthesis. The disclosure also relates to pharmaceutical compositions comprising the compounds disclosed herein, and methods for therapeutic and/or prophylactic use of these compounds. In a particular aspect, the disclosure relates to compounds that inhibit the MLK-3 family.

INTRODUCTION

[0004] Mixed lineage kinases (MLKs) are MAPK kinase kinases that target activated c-Jun N-terminal kinases (JNK) and p38 MAPK for activation in response to diverse stimuli associated with cell stress. As a result, MLKs regulate a broad range of cellular processes. MLK-3 is the most widely expressed MLK family and is present in neurons.

[0005] JNKs are major control nodes in mammalian apoptotic cell death pathways. For example, GTP-bound forms of the G proteins Rac1 and Cdc42 promote autophosphorylation and activation of MLKs which, in turn, phosphorylate and activate mitogen-activated protein kinase kinases 4 and 7 (MKK₄ or MKK₇), which ultimately phosphorylate and activate JNKs. MLK-3 is widely distributed and up-regulated in inflammatory states in various organs including the brain and heart. The first generation, pan-MLK inhibitor CEP-1347 has been shown to protect primary rat hippocampal neurons as well as dorsal root ganglion neurons from the otherwise lethal effects of exposure to HIV-1 gp120. (Bodner, A., Toth, P.T. & Miller, R.J. Activation of c-Jun N-terminal kinase mediates gp120IIIB- and nucleoside analogue-induced sensory neuron toxicity. *Exp Neurol* **188**, 246-253 (2004); Bodner, A. *et al.* Mixed lineage kinase 3 mediates gp120IIIB-induced neurotoxicity. *J Neurochem* **82**, 1424-1434 (2002)). Neurotoxic HIV gene

products Tat and gp120 induce autophosphorylation and activation of MLK-3 in primary rat neurons and this process can be abolished by the addition of CEP-1347. CEP-1347 enhances survival of both rat and human neurons and inhibited the activation of human monocytes after exposure to Tat and gp120. Furthermore, overexpression of wild-type MLK-3 leads to the induction of neuronal death, whereas expression of a dominant negative MLK-3 mutant protected neurons from the toxic effects of Tat. CEP-1347 is neuroprotective in an in vivo model of HIV-1 infection, reversing microglial activation and restoring normal synaptic architecture, as well as restoring macrophage secretory profiles to a trophic vs. toxic phenotype in response to HIV-1 infection. (Eggert, D. *et al.* Neuroprotective activities of CEP-1347 in models of neuroAIDS. *J Immunol* **184**, 746-756 (2010)). Collectively, these studies suggest that MLK-3 activity is increased by HIV-1 neurotoxins, resulting in downstream signaling events that trigger neuronal death and damage, along with monocyte activation (accompanied by release of inflammatory cytokines). Unfortunately CEP-1347, a close analog of staurosporine, is non-specific for MLK-3, and is a large molecule where no evidence has been published showing that it penetrates the CNS. Pharmacokinetic studies in mice have demonstrated poor CNS penetration for CEP-1347. (Goodfellow et al, Discovery, synthesis, and characterization of an orally bioavailable, brain penetrant inhibitor of mixed lineage kinase 3, *J Med Chem* **56** 8032-48 (2013). Further, development of CEP-1347 was halted for unknown reasons.

[0006] The central nervous system (CNS) can be infected and injured by HIV-1, leading to the development of HIV-Associated Neurocognitive Disorders (HAND). Recent estimates of the prevalence of HAND suggest that over 50% of the population living with AIDS is affected. Because combination antiretroviral therapy (cART), even in CNS penetrating forms, has not altered the prevalence of HAND (Heaton, R. *et al.* HIV-associated Neurocognitive Impairment Remains Prevalent in the Era of Combination ART: The CHARTER Study. *16th Conference on Retroviruses and Opportunistic Infections*; 2009), new therapeutic strategies for counteracting the effects of HIV infection in the CNS are needed. Preliminary studies have shown that inhibition of key signaling kinases is likely one of the best strategies for affecting HAND-related inflammatory and cellular injury cascades. Sui, Z. *et al.* Inhibition of mixed lineage kinase 3 prevents HIV-1 Tat-mediated neurotoxicity and monocyte activation. *J Immunol* **177**, 702-711 (2006); Dewhurst, S., Maggirwar, S.B., Schifitto, G., Gendelman, H.E. & Gelbard, H.A. Glycogen synthase kinase 3 beta (GSK-3 beta) as a therapeutic target in neuroAIDS. *J Neuroimmune Pharmacol* **2**, 93-96 (2007).

[0007] MLK-3 also modulates neuroinflammation through effects on cytokine production by microglia and brain macrophages. In particular, CEP-1347-mediated inhibition of MLK-3 results in a significant decrease in Tat-stimulated release of tumor necrosis factor alpha (TNF- α) and

interleukin (IL)-6 by macrophage and microglia. (Sui, Z., Kovacs, A.D. & Maggirwar, S.B. Recruitment of active glycogen synthase kinase-3 into neuronal lipid rafts. *Biochem Biophys Res Commun* **345**, 1643-1648 (2006)). Similar results have been demonstrated in macrophages with CNS penetrant MLK-3 inhibitor URM-099. (Goodfellow et al, 2013.) TNF- α mediates a significant part of Tat-mediated toxicity in models of HAND, and inhibition of this pathway by CEP-1347 may account for the reduction in neuroinflammation observed in an in vivo model for HAND. Recently a the potent and brain penetrant MLK3 inhibitor, URM-099 has demonstrated *in vivo* efficacy for preservation of normal synaptic architecture and reversal of neuroinflammation following CNS exposure to HIV-1 Tat. (Marker et al, The new small-molecule mixed-lineage kinase 3 inhibitor URM-099 is neuroprotective and anti-inflammatory in models of human immunodeficiency virus-associated neurocognitive disorders, *J Neurosci* **24** 9998-10010 (2013).) URM-099 however is not a selective inhibitor of MLK3. In order to limit off target activity there is a need to identify and develop compounds with greater specificity for MLK3.

[0008] Previously it has been shown that blockade of the MLK-3 pathway may interfere with the neurotoxic effect of beta amyloid oligomers. (Xu Y, Hou XY, Liu Y, Zong YY, Different protection of K252a and N-acetyl-L-cysteine against amyloid-beta peptide-induced cortical neuron apoptosis involving inhibition of MLK3-MKK7-JNK3 signal cascades. *J Neurosci Res.* 2009 Mar;87(4):918-27.) Inhibition of the C-jun/JNK pathway blocks hyperphosphorylation of tau in cultured hippocampal neurons. (*J. Neurosci.* 2009 Jul 15;29(28):9078-89). Consequently, MLK-3 inhibitors may be of value in the treatment of Alzheimer disease and other neurodegenerative diseases involving the C-jun/JNK pathway.

[0009] Recent evidence also suggests that acute and temporary blockade of the c-jun/JNK pathway at early stages of stroke may improve outcomes. (*J. Neurosci.* 2012 Jun 13;32(24):8112-5).

[0010] Attenuation of microglial activation via MLK-3 inhibition protects hippocampal synapses in experimental autoimmune encephalomyelitis models of multiple sclerosis. MLK-3 inhibitors may be useful for the treatment of multiple sclerosis and other inflammatory neurological diseases. (Bellizzi M and Gelbard, H. *Neurology* April 25, 2012; 78(Meeting Abstracts 1): P05.112.)

[0011] Small molecule inhibition of MLK-3 attenuates cardiac fibroblast activation and pathologic cardiac remodeling. (Martin, M. L., Dewhurst, S., Gelbard, H. A., Goodfellow, V., Blaxall, B. C.; *Circulation Research* 111 (4) A88 (2012)). Consequently, MLK-3 inhibitors may be useful for the treatment of heart failure.

[0012] MLK-3 blockade inhibits stellate cell proliferation in the liver and pancreas and may be useful for treatment of cirrhotic diseases of these organs. (Cancer Research 59 2195-2202(1999)). MLK3 blockade may serve as a useful treatment for steatohepatitis. (Ibrahim SH, Gores GJ, Hirsova P, Kirby M, Miles L, Jaeschke A, Kohli R. Mixed lineage kinase 3 deficient mice are protected against the high fat high carbohydrate diet-induced steatohepatitis. (*Liver Int.* 2013 Oct 06. PMID:24256559)

[0013] Inhibition of MLK-3 may also be useful for the treatment of various cancers such as cancers of the pancreas and breast. (*Cancer Growth and Metastasis* 2010;3 1–9). MLK-3 regulates the proliferation of some tumor cell types, including human schwannoma and meningioma cells and breast cancer cells also over-express MLK-3. (Chen J, Miller EM, Gallo KA. *Oncogene*. 2010;29(31):4399-411). RNA-mediated knockdown of MLK-3 inhibits growth and lymph node metastasis of human breast cancer cells in a mouse xenograft model. (*Oncogene*. 2011 PMC: 3297722)). MLK-3 inhibitors may be efficacious in treating metastasized breast tumors and compounds which are highly CNS penetrant may be especially useful in treating metastasized tumors in the brain associated with breast cancer.

[0014] Both HAND and Parkinson's Dementia have similar underlying pathology involving dopaminergic pathways and synaptodendritic damage. Destruction of striatal dopaminergic neurons results in a significant loss of dendritic spines on medium spiny projection neurons (MSNs) in Parkinson's disease. MSNs are the main output neurons of the striatum. MSNs are the primary synaptic target of both nigrostriatal dopaminergic and cortico-striatal glutamatergic afferent neurons. Dendritic spines are critical sites for synaptic integration . For a treatment for Parkinson's Disease to be effective, dopaminergic neurotransmission must be normalized and MSN spine loss and dendritic atrophy need to be reversed. The MLK3 inhibitor, CEP-1347, was developed as a clinical candidate for Parkinson's Disease. CEP-1347 exhibited striking positive activity in numerous *in vitro* and *in vivo* models for PD including neuroprotection using methamphetamine-exposed human mesencephalic-derived neurons. CEP-1347 prevented the induction of neuronal cell death, motor deficits and neuronal degeneration in the MPTP model of Parkinsonism in mice and monkeys. However, the compound failed to exhibit efficacy in human trials for preventing the development of disease progression in early stage Parkinson's Disease. (PRECEPT GROUP, Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson disease, *Neurology* 15 1480-90 (2007).) The only available pharmacokinetic data for CEP-1347 shows wide patient variability of plasma levels for the drug in patients, suggesting metabolic or induction issues. (Ma et al, *J Neurovirol* 19 254-60 (2013.) Pharmacokinetic studies in mice have shown very poor blood brain barrier penetration for CEP-1347 (Goodfellow

et al, 2013). A compound with substantially increased ability to maintain high brain concentration levels may offer better potential for treating Parkinson's Disease.

[0015] Accordingly, there still is a great need to develop potent inhibitors of MLKs, including groups MLK-3, that are useful in treating various conditions associated with MLK activation.

SUMMARY OF THE INVENTION

[0016] Disclosed herein are compounds having an inhibitory effect on MLKs, including the families MLK-1, MLK-2, and MLK-3. Also provided are pharmaceutical compositions thereof, methods of preparation thereof, and methods of use thereof, such as in treatment of a malcondition mediated by MLKs receptor activation, or when modulation or potentiation of MLK-3 receptor is medically indicated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1 shows images of E18 primary hippocampal neurons which were plated in microfluidic chambers before and after introduction of BV-2 microglial cells treated with HIV-1 Tat (1 μ g/mL) and test inhibitor compounds (100 nM). Arrows show examples of continued axonogenesis in the presence of Tat-activated microglia, facilitated by a compound of the present disclosure (Compound 68).

[0018] FIG. 2 is a graph illustrating the quantification of axon elimination in the presence of HIV tat and certain inhibitors including compounds of the present disclosure.

[0019] FIG. 3 is a graph illustrating the quantification of axon length in the presence of HIV tat and certain inhibitors including compounds of the present disclosure.

[0020] FIG. 4 is a graph illustrating dose-dependent neuroprotection from NMDA excitotoxic activation of matrix metalloproteinases with cleavage of intercellular adhesion molecule type 5 (ICAM-5).

[0021] FIG. 5 is a graph illustrating the inhibition of synaptodendritic beading induced by N-methyl-D-aspartate (NMDA) receptor.

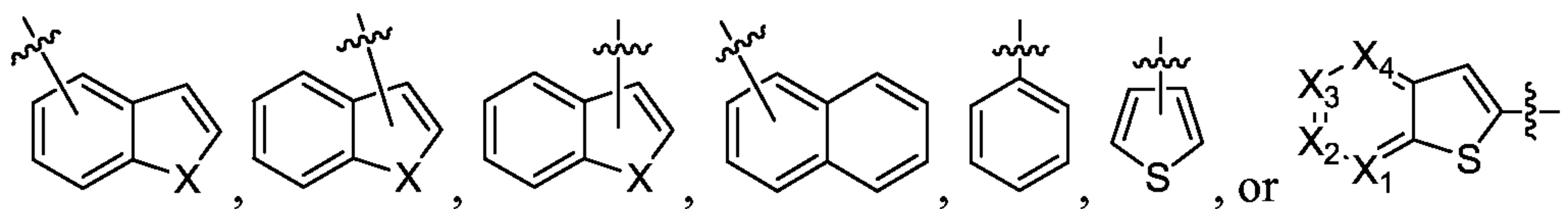
DETAILED DESCRIPTION OF THE INVENTION

[0022] Certain embodiments of the present disclosure provides a compound having the structure of Formula I

**I**

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

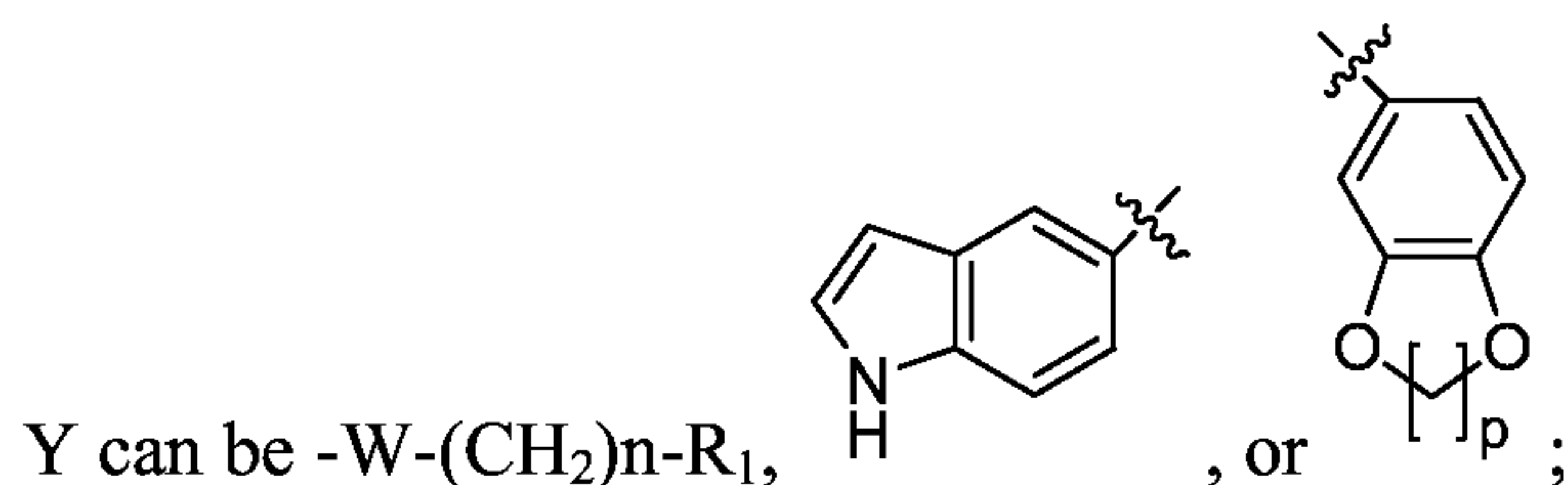
J has a structure of



where J (i.e., any carbon atom on J) can be optionally substituted with up to four R_{10} , each R_{10} can be independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy, haloalkoxy -OH, and -OCOR₆;

X can be NR₁₂ or S;

X₁, X₂, X₃, and X₄ can be H or N and wherein no more than one of X₁, X₂, X₃, and X₄ is N;



Y can be -W-(CH₂)_n-R₁,

W can be null, phenylene, or -NR₆-phenylene, where the NR₆ is attached to the imidazopyridazine core structure of Formula I;

R₁ can be -NR₂R₃, or piperazinyl, where the nitrogen atom of the piperazinyl can be optionally substituted with alkyl or alkoxy;

R₂ can be H or alkyl; R₃ can be selected from the group consisting of C₂-C₁₀ alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, where any atom of R₃ can be optionally substituted with one or more R₇; or R₂ and R₃ taken together with the N atom to which they are attached form a 3- to 7-membered heterocyclic ring optionally substituted with R₈;

R₄ can be H or alkyl;

R₅ can be H, alkyl, or NHR₉;

R₆ can be H or alkyl;

each R_7 can be independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, perhaloalkoxy, halo, oxo, -OH, hydroxyalkyl, $-\text{COOR}_{11}$, or $-\text{O}-(\text{CH}_2)_m-\text{OH}$;

R_8 can be alkoxy, hydroxyalkyl, or COOR_{11} ;

R_9 can be H, alkyl, or cycloalkyl;

R_{11} can be H, or alkyl;

R_{12} can be H, or alkyl;

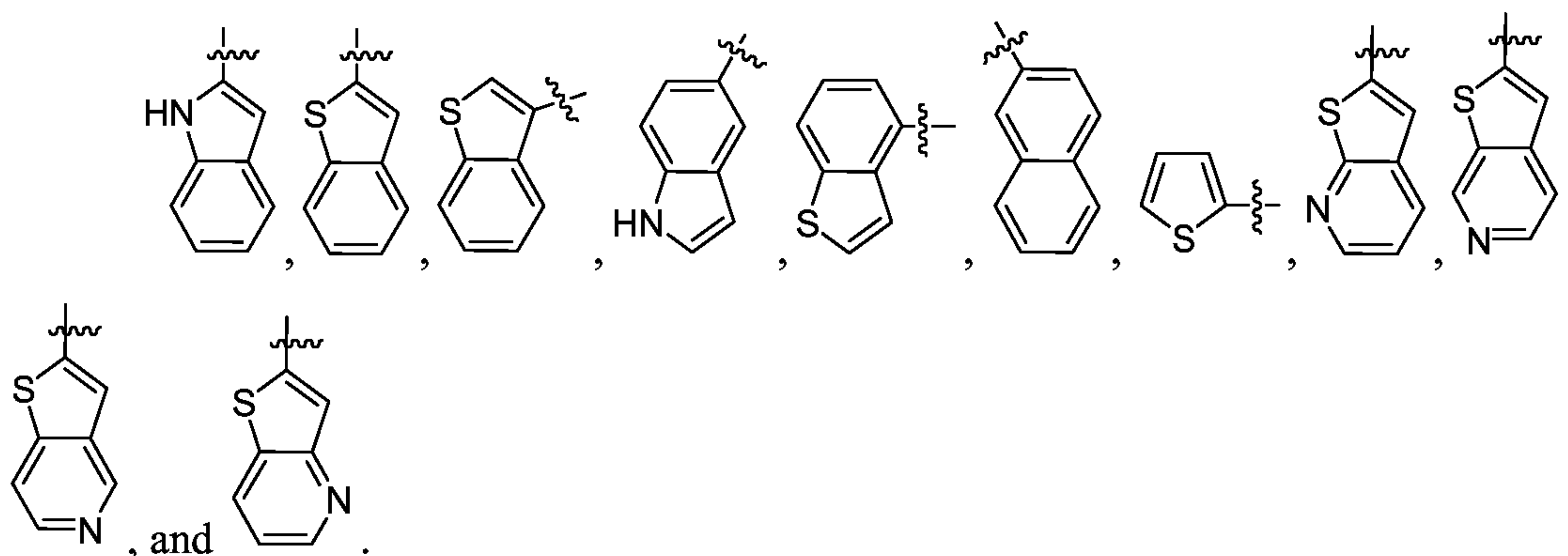
n can be 0 or 1;

m can be 1, 2, or 3; and

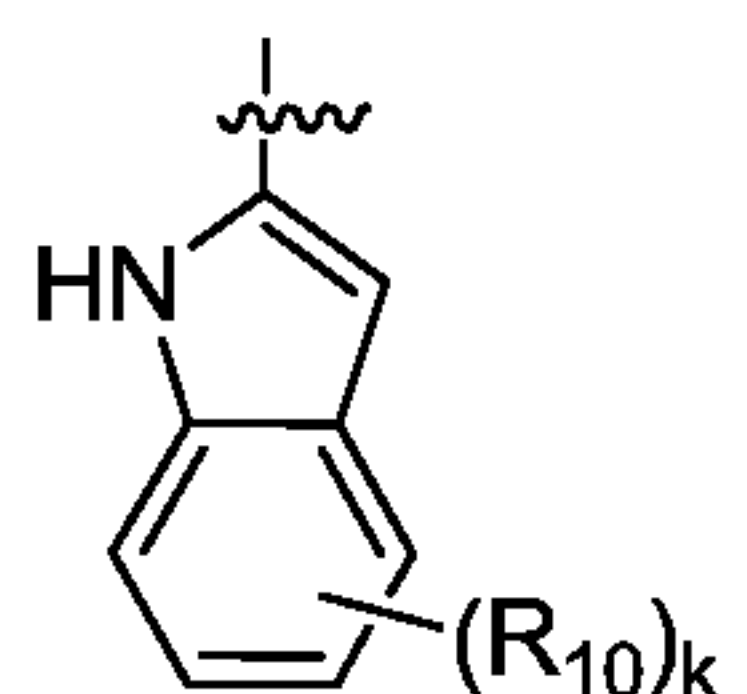
p can be 1, 2, or 3;

with the proviso that if J is an unsubstituted benzothiophene, then R_3 is either aryl or heteroaryl, where any atom of R_3 can be optionally substituted with one or more R_7 .

[0023] In certain of such embodiments, the disclosure provides compounds where J can be selected from the group consisting of

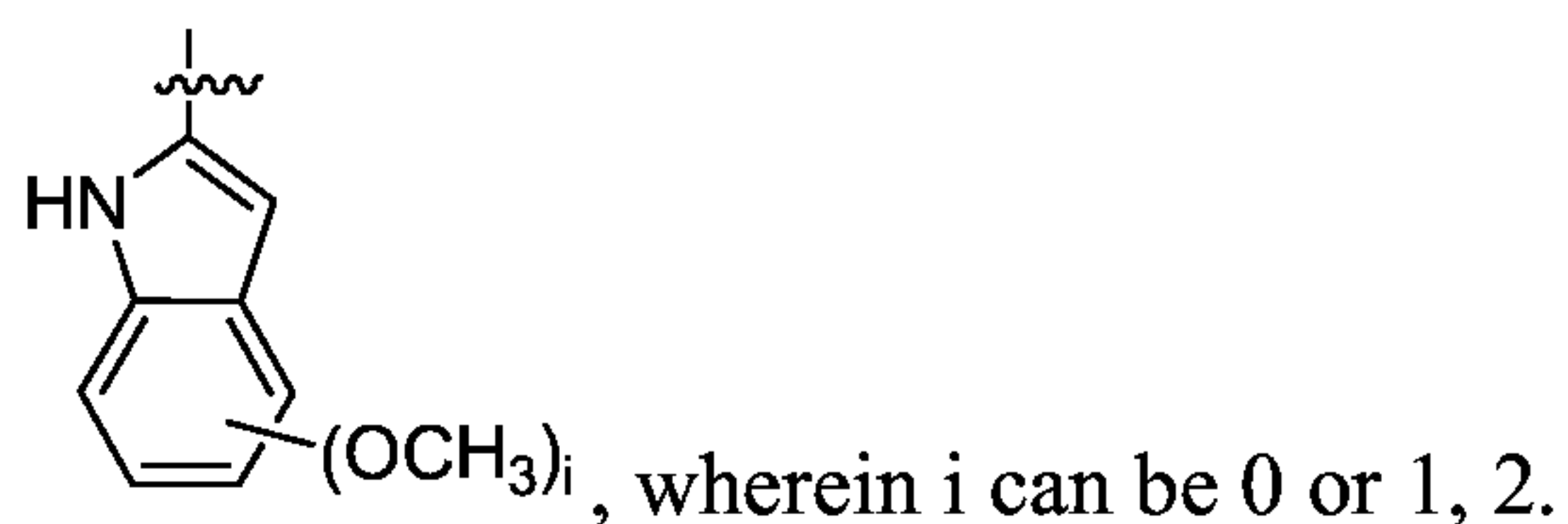


[0024] In certain embodiments, J can be

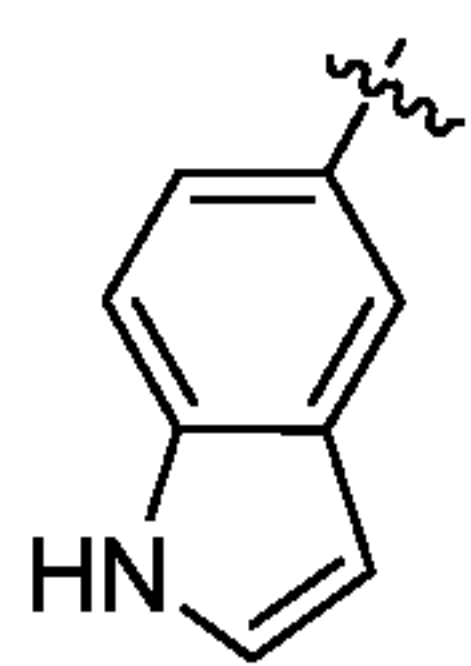


$(\text{R}_{10})_k$ wherein each R_{10} can be independently selected from the group consisting of F, Cl, -OH, methyl, methoxy, ethoxy, propoxy, isopropoxy, and $-\text{OCOCH}_3$; and k can be 0, 1, 2, or 3.

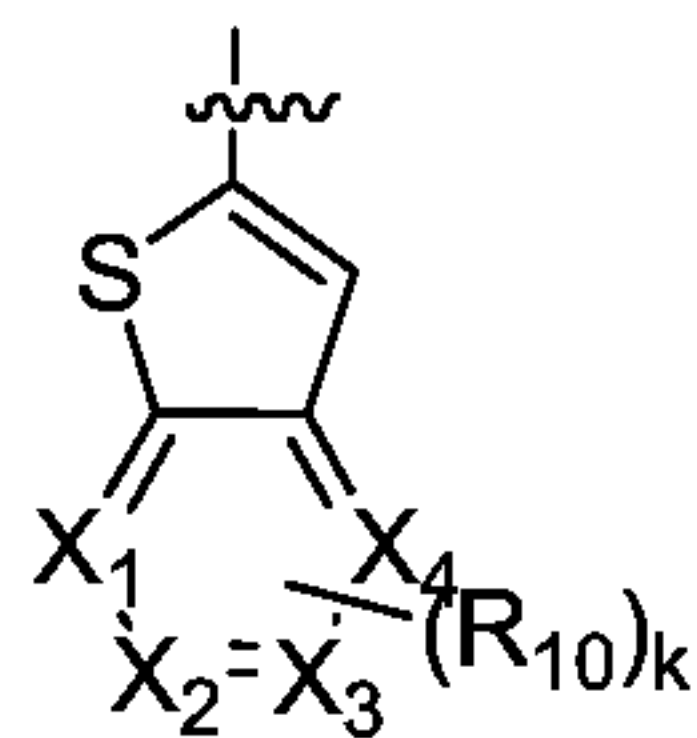
[0025] In certain embodiments, J can be



[0026] In certain embodiments, wherein J can be

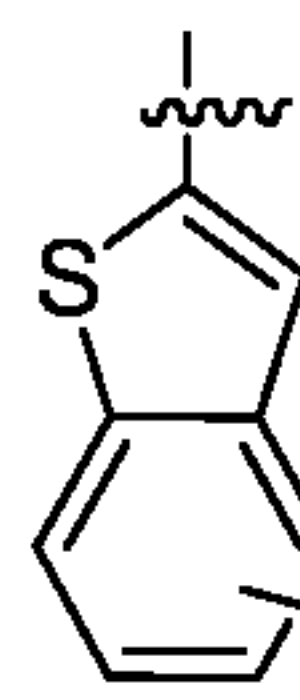


[0027] In certain embodiments, J can be



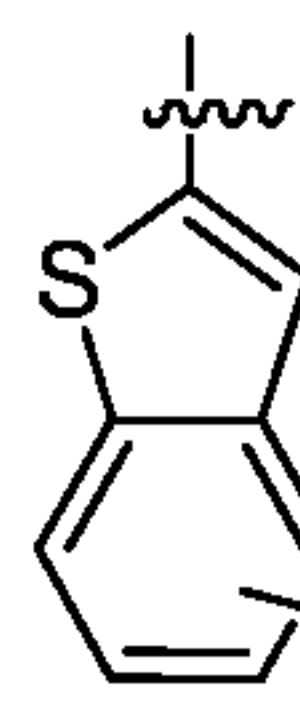
, wherein each R_{10} can be independently selected from the group consisting of F, Cl, -OH, methyl, methoxy, ethoxy, propoxy, isopropoxy, and $-\text{OCOCH}_3$; and k can be 0, 1, 2, or 3. In certain embodiments, R_{10} can be -OH or $-\text{OCOCH}_3$. In one embodiment, each of X_1 , X_2 , X_3 , and X_4 can be CH. In one embodiment, X_1 can be N, and each of X_2 , X_3 , and X_4 can be CH. In one embodiment, X_2 can be N, and each of X_1 , X_3 , and X_4 can be CH. In one embodiment, X_3 can be N, and each of X_1 , X_2 , and X_4 can be CH. In one embodiment, X_4 can be N, and each of X_1 , X_2 , and X_3 can be CH.

[0028] In certain embodiments, J can be



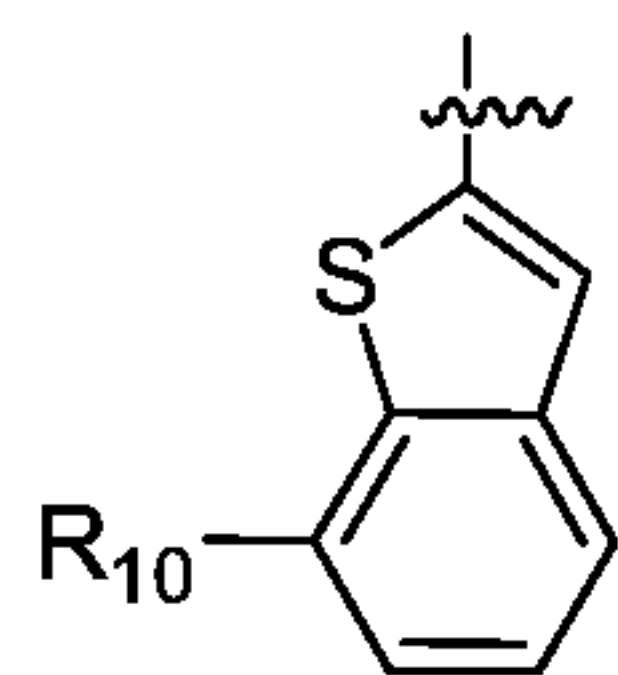
, wherein each R_{10} can be independently selected from the group consisting of F, Cl, -OH, methyl, methoxy, ethoxy, propoxy, isopropoxy, and $-\text{OCOCH}_3$; and k can be 0, 1, 2, or 3.

[0029] In certain embodiments, J is



, wherein k can be 0, 1, or 2.

[0030] In certain embodiments, J is



wherein R_{10} can be selected from the group consisting of F, Cl, -OH, methyl, methoxy, ethoxy, propoxy, isopropoxy, and $-\text{OCOCH}_3$.

[0031] In certain embodiments, the disclosure provides compounds where Y can be -W- $(\text{CH}_2)_n$ - R_1 . In certain embodiments, Y can be R_1 . In certain embodiments, R_1 can be $-\text{NR}_2\text{R}_3$.

[0032] In certain embodiments, R_2 can be H.

[0100] In certain embodiments, R_3 can be C_2 - C_{10} alkyl, aryl, and cycloalkyl, where any atom of R_3 can be optionally substituted with one or more R_7 , where any atom of R_3 can be optionally substituted with one or more R_7 . In certain embodiments, R_3 can be phenyl optionally substituted with one or more R_7 , wherein each R_7 can be independently selected from the group consisting of hydroxyl, methoxy, $-COOH$, $-O-(CH_2)_m-OH$, cyclopropylmethoxy, cyclopentylmethoxy, and isopropyl. In certain embodiments, each R_7 can be independently selected from the group consisting of methoxy, $-COOH$, and $-O-(CH_2)_3-OH$.

[0033] In certain embodiments, R_3 can be C_2 - C_{10} alkyl or cycloalkyl, where any atom of R_3 can be optionally substituted with one or more R_7 .

[0034] In certain embodiments, R_3 can be aryl. In further embodiments, R_3 can be phenyl. In certain embodiments, R_3 can be phenyl substituted with one or more R_7 , where each R_7 can be independently selected from the group consisting of hydroxyl, methoxy, $-COOH$, $-O-(CH_2)_m-OH$, cyclopropylmethoxy, cyclopentylmethoxy, and isopropyl. In further embodiments, each R_7 can be independently selected from the group consisting of methoxy, $-COOH$, and $-O-(CH_2)_3-OH$. In certain embodiments, R_3 can be phenyl substituted with at least one R_7 and wherein the at least one R_7 can be methoxy. In certain embodiments, the at least one methoxy substituent can be substituted at the ortho position of the phenyl. In certain embodiments, the at least one methoxy substituent can be substituted at the meta position of the phenyl.

[0035] In certain embodiments, R_3 can be 3,4-dimethoxyphenyl. In certain embodiments, R_3 can be further substituted with $-COOH$ or $-O-(CH_2)_m-OH$. In certain embodiments, R_3 can be further substituted with $-O-(CH_2)_3-OH$. In certain embodiments, R_3 can be phenyl substituted with at least one R_7 . In certain of such embodiments, R_7 can be $-COOH$. In further of such embodiment, one of the at least one $-COOH$ substituent of the phenyl can be at the meta position of the phenyl.

[0036] In certain embodiments, R_3 can be cycloalkyl. In certain of such embodiments, the cyclohexyl can be substituted with one or more R_7 , where each R_7 can be independently selected from the group consisting of alkyl, $-OH$, hydroxyalkyl, and alkoxy. In certain embodiments, the one or more R_7 can be each independently selected from the group consisting of methyl, $-OH$, hydroxymethyl, and methoxy. In certain embodiments, the cyclohexyl can be substituted with one R_7 at the 3-position of the cyclohexyl. In certain embodiments, the cyclohexyl can be substituted with one R_7 at the 4-position of the cyclohexyl. In certain embodiments, the cyclohexyl can be disubstituted with two R_7 at the 4-position of the cyclohexyl.

[0037] In certain embodiments, the substituted cyclohexyl can be in the form of a pure diastereomer and/or enantiomer, as a racemate or as a non-equimolar or equimolar blend of the diastereomers and/or enantiomers.

[0038] In certain embodiments, R_3 can be heteroaryl.

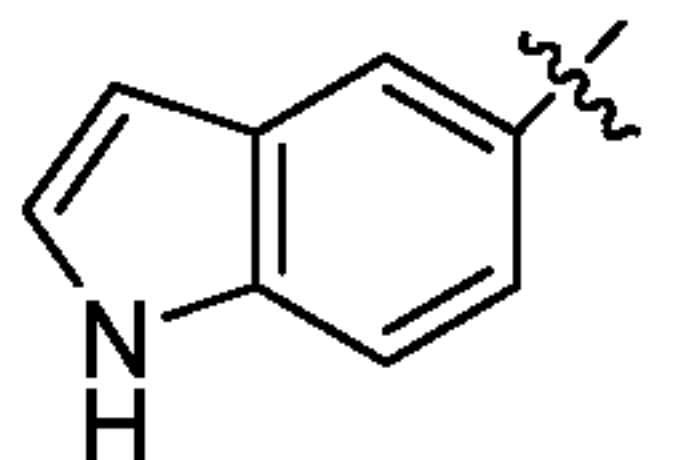
[0039] In certain embodiments, R_3 can be pyridinyl. In certain of such embodiments, R_3 can be pyridinyl substituted with oxo or methoxy.

[0040] In certain embodiments, R_2 and R_3 taken together with the N atom to which they are attached form a 3- to 7-membered heterocyclic ring optionally substituted with R_8 . In certain of such embodiments, the heterocyclic ring can be a 5- or 6-membered heterocyclic ring. In certain embodiments, R_8 is $-\text{COOCH}_3$, or hydroxymethyl.

[0041] In certain embodiments, W can be 1,3-phenylene or 1,4-phenylene. In certain of such embodiments, n can be 0 or 1. In certain embodiments, R_1 can be piperazinyl. In certain of such embodiments, the nitrogen atom of the piperazinyl can be substituted with methyl.

[0042] In certain embodiments, W can be $-\text{NR}_6$ -phenylene. In certain of such embodiments, the phenylene group can be 1,3-phenylene or 1,4-phenylene. In certain of such embodiments, n can be 0 or 1. In certain embodiments, R_1 can be piperazinyl. In certain of such embodiments, the nitrogen atom of the piperazinyl can be substituted with methyl.

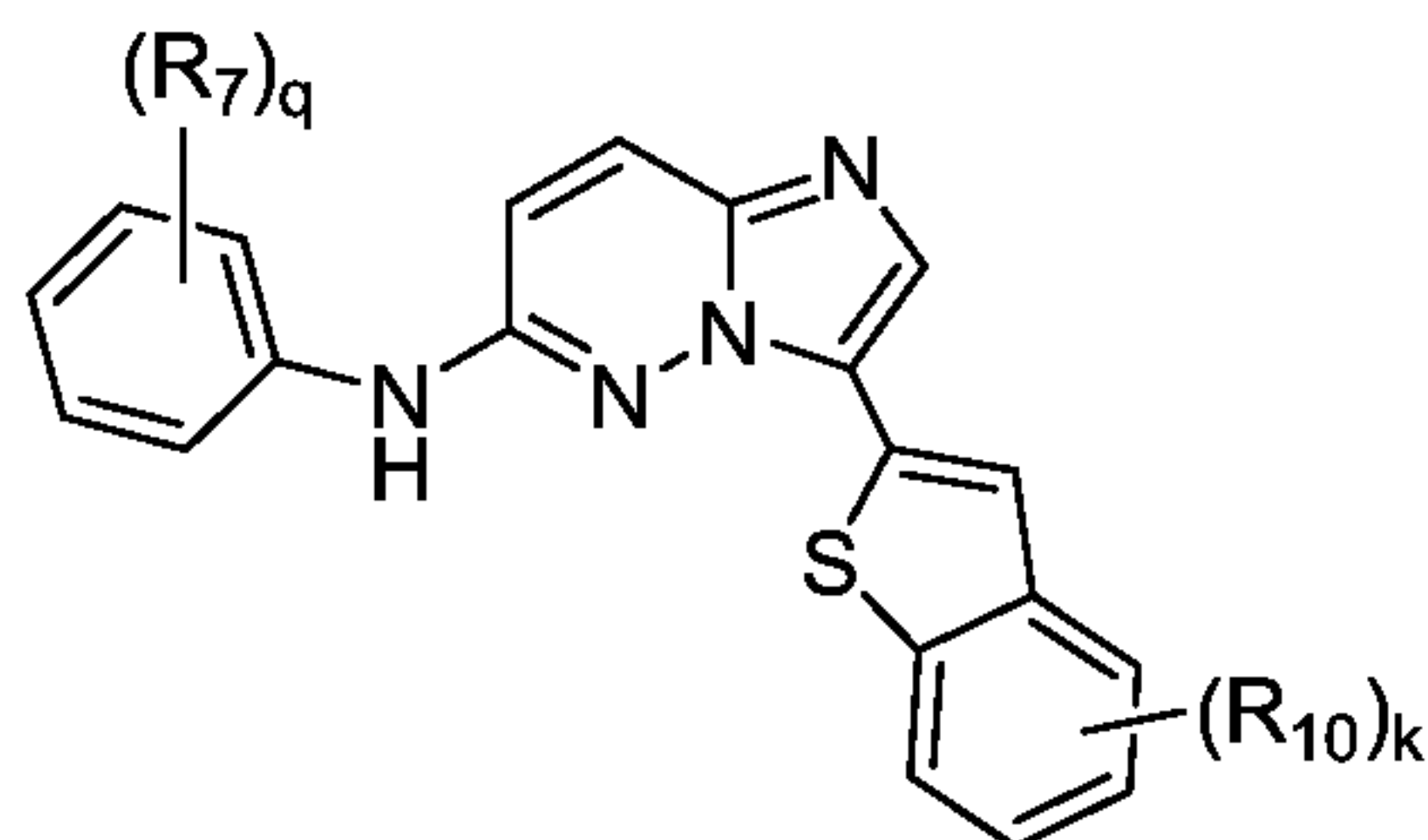
[0043] In certain embodiments, Y can be



[0044] In certain embodiments, R_4 can be H. In other embodiments, R_4 can be alkyl, such as, lower alkyl including methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, *etc.*

[0045] In certain embodiments, R_5 can be H.

[0046] Certain embodiments of the present disclosure provides a compound having the structure of Formula II



II

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

each R_{10} can be independently selected from the group consisting of halo, alkyl, alkoxy, -OH, and -OCOR₆;

each R_7 can be independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, perhaloalkoxy, halo, oxo, -OH, hydroxyalkyl, -COOR₁₁, or -O-(CH₂)_m-OH;

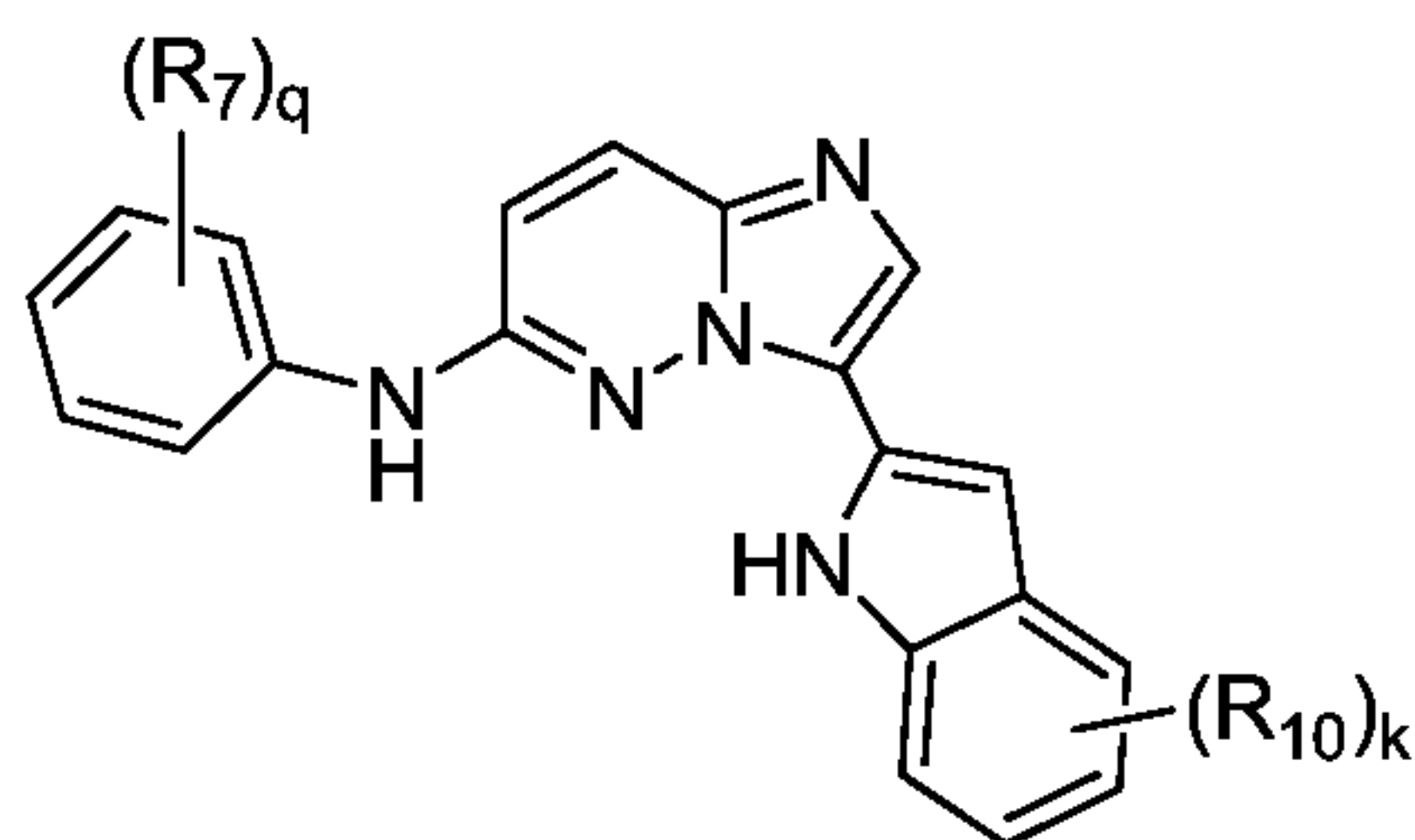
k can be 0, 1, 2, or 3; and

q can be 0, 1, 2, or 3.

[0047] In certain embodiments, each R_7 can be independently selected from the group consisting of methoxy, -COOH, and -O-(CH₂)₃-OH.

[0048] In certain embodiments, wherein q can be 1, 2, or 3 and at least one of R_7 can be methoxy.

[0049] Certain embodiments of the present disclosure provides a compound having the structure of Formula III



III

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

each R_{10} can be independently selected from the group consisting of halo, alkyl, alkoxy, -OH, and -OCOR₆;

each R_7 can be independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, perhaloalkoxy, halo, oxo, -OH, hydroxyalkyl, -COOR₁₁, or -O-(CH₂)_m-OH;

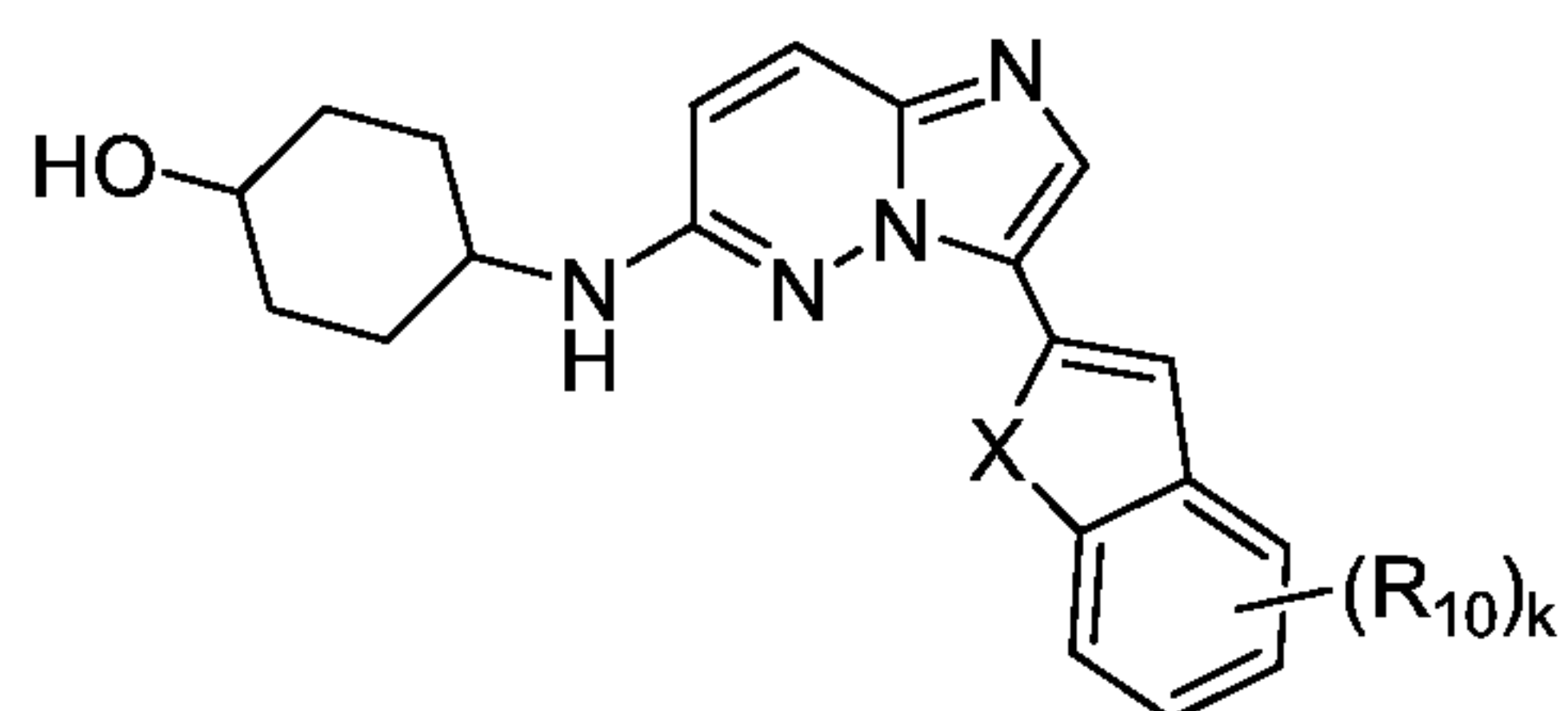
k can be 0, 1, 2, or 3; and

q can be 0, 1, 2, or 3.

[0050] In certain embodiments, each R_7 can be independently selected from the group consisting of methoxy, -COOH, and -O-(CH₂)₃-OH.

[0051] In certain embodiments, q can be 1, 2, or 3 and at least one of R_7 can be methoxy.

[0052] Certain embodiments of the present disclosure provides a compound having the structure of Formula IV

**IV**

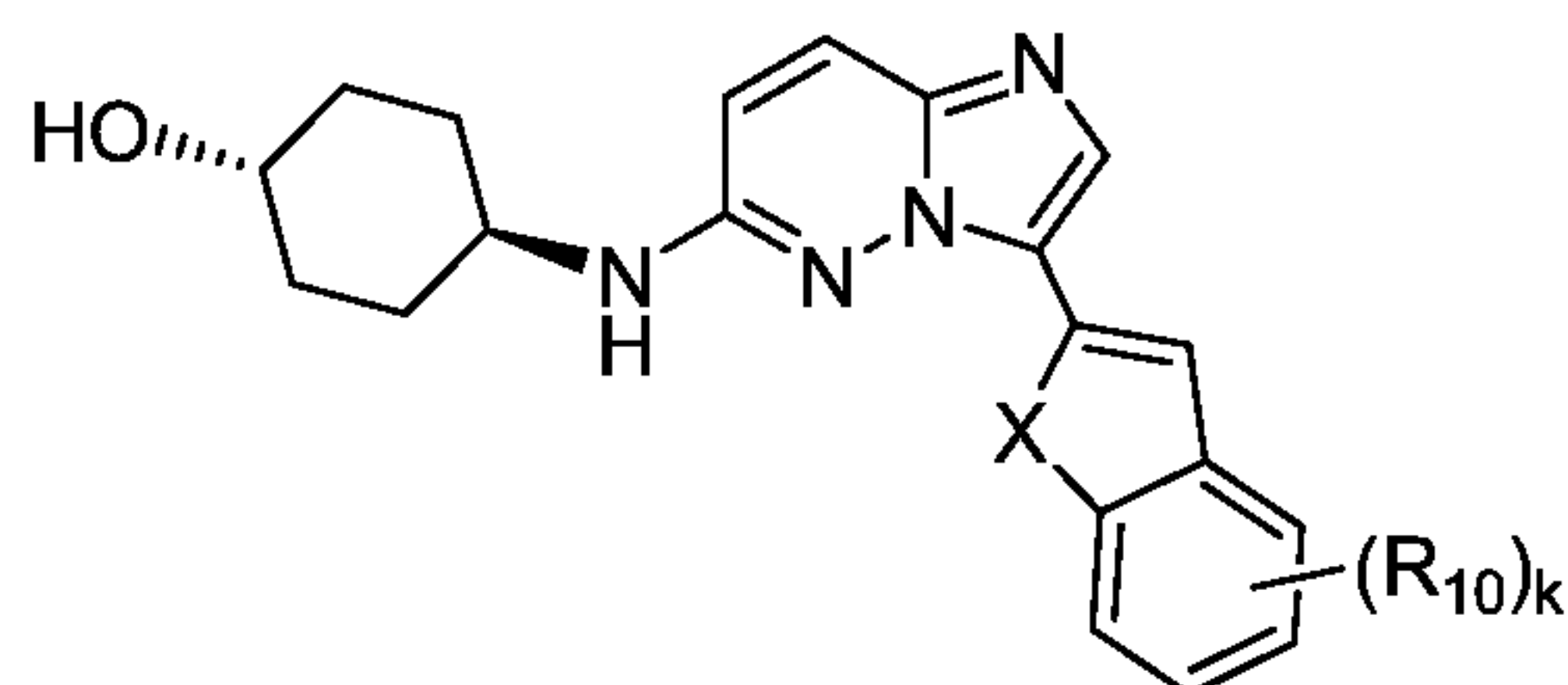
or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

X can be NH or S;

each R_{10} can be independently selected from the group consisting of halo, alkyl, alkoxy, -OH, and -OCOR₆; and

k can be 0, 1, 2, or 3.

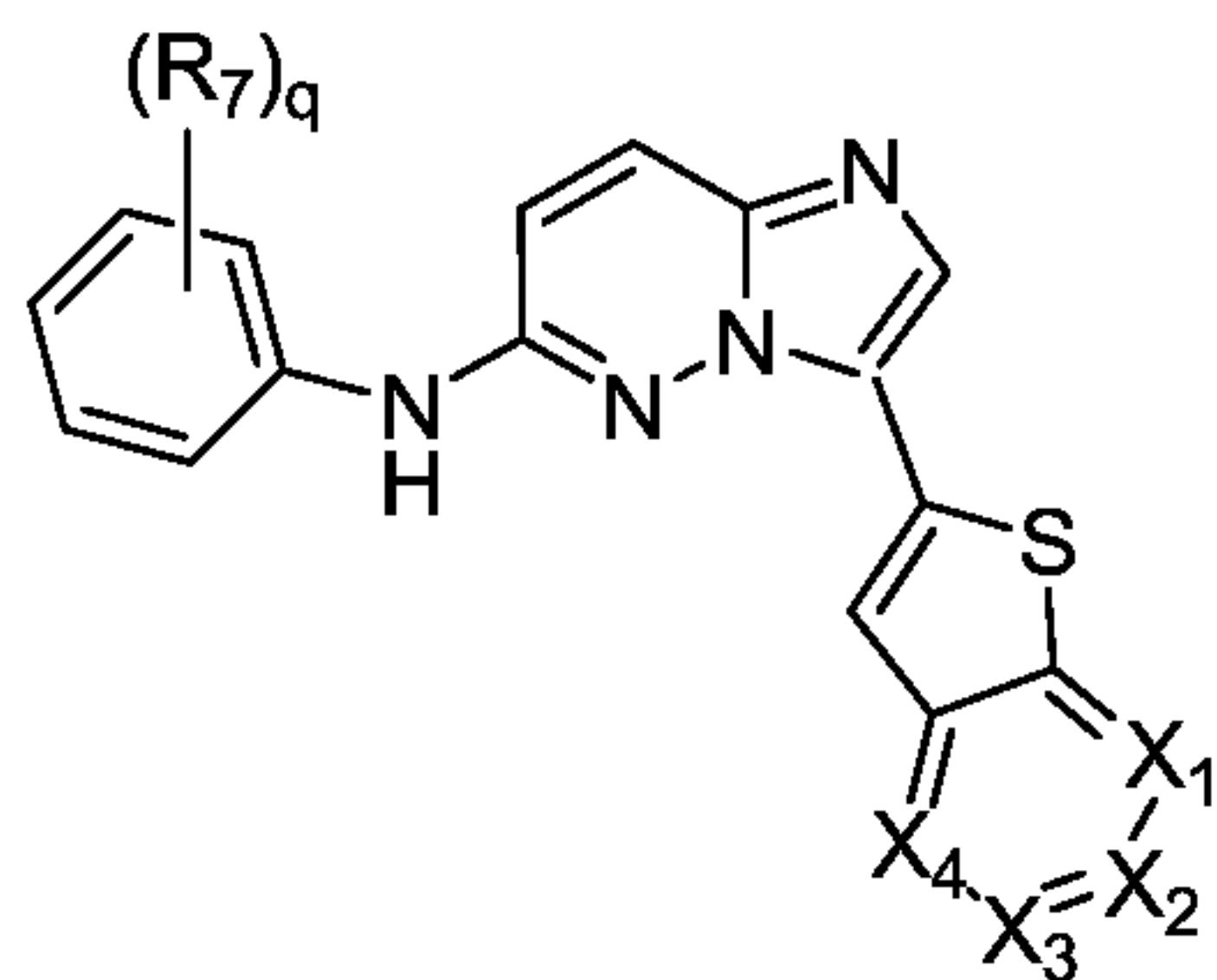
[0053] In further embodiments, the present disclosure provides a compound having the structure of Formula **IV-A**

**IV-A**

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof.

[0054] In certain embodiments, X can be NH. In certain embodiments, X can be S. In certain embodiments, k can be 1. In certain embodiments, R_{10} can be alkoxy. In further embodiments, R_{10} can be methoxy.

[0055] Certain embodiments of the present disclosure provides a compound having the structure of Formula **V**

**V**

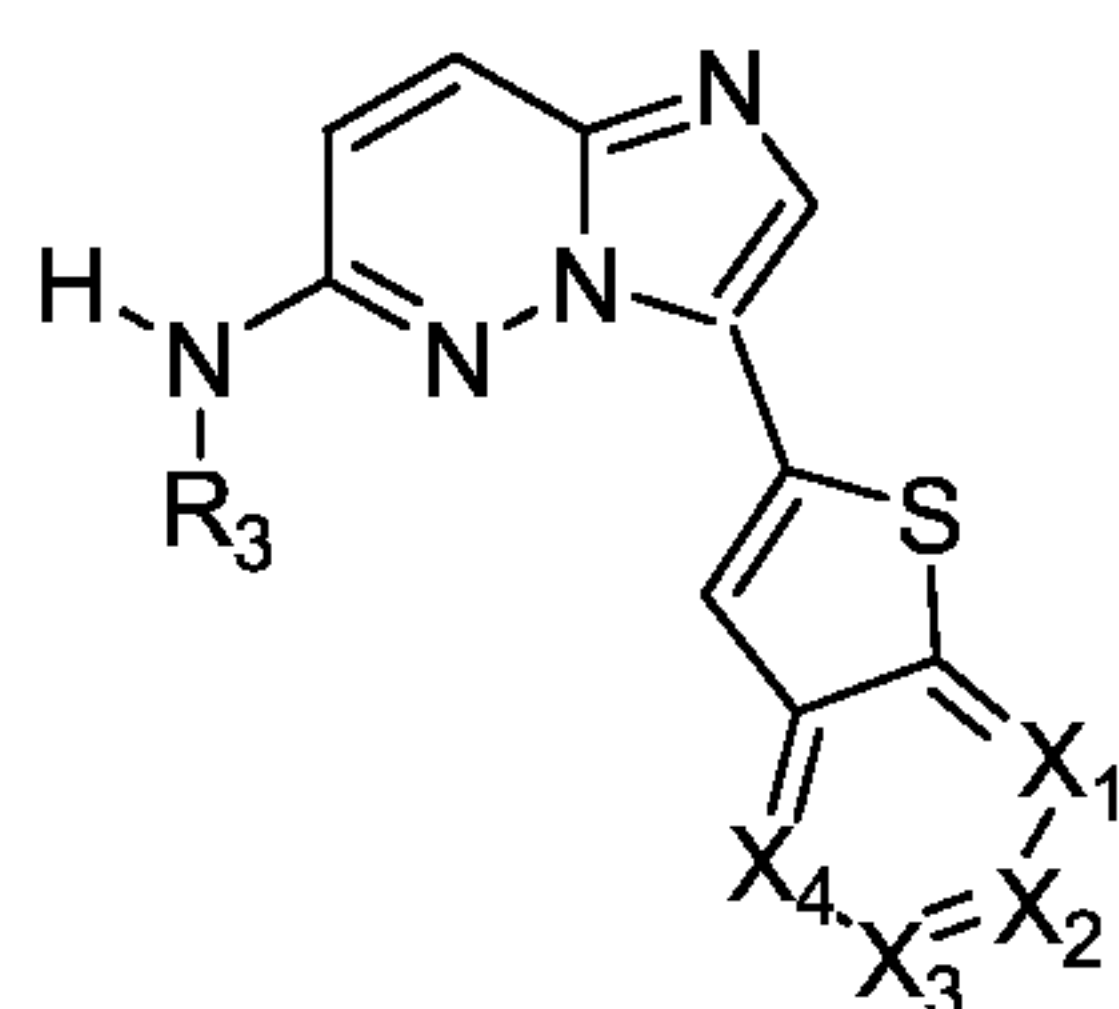
or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

each R_7 can be independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, perhaloalkoxy, halo, oxo, -OH, hydroxyalkyl, -COOR₁₁, or -O-(CH₂)_m-OH;

q can be 1, 2, or 3; and

each X_1 , X_2 , X_3 , and X_4 can be independently H or N and wherein no more than one of X_1 , X_2 , X_3 , and X_4 is N.

[0056] Certain embodiments of the present disclosure provides a compound having the structure of Formula **VI**



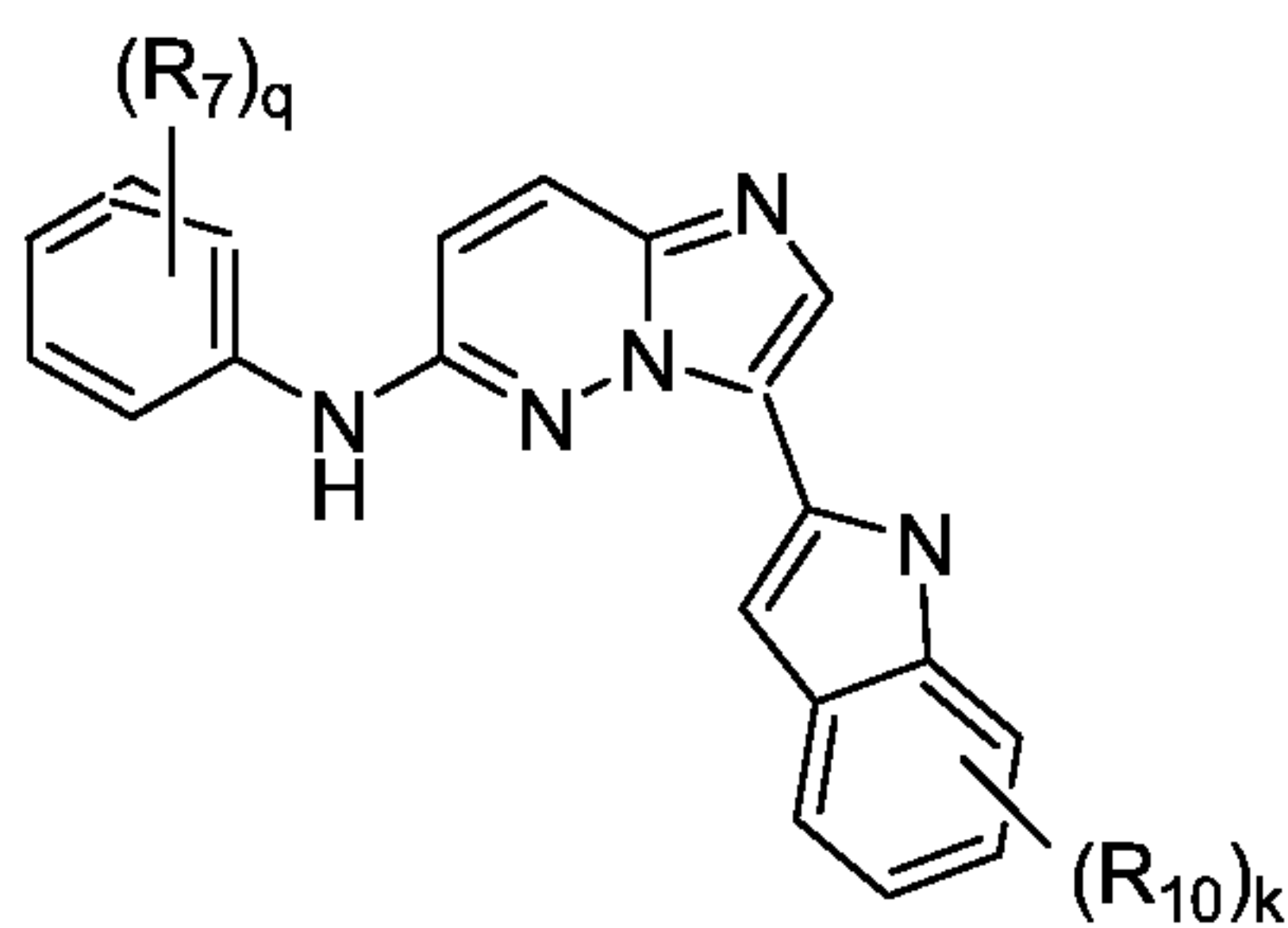
VI

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

R_3 can be selected from the group consisting of C₂-C₁₀ alkyl, aryl, and cycloalkyl; and

each X_1 , X_2 , X_3 , and X_4 can be independently H or N and wherein no more than one of X_1 , X_2 , X_3 , and X_4 is N.

[0057] Certain embodiments of the present disclosure provides a compound having the structure of Formula **VII**



VII

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

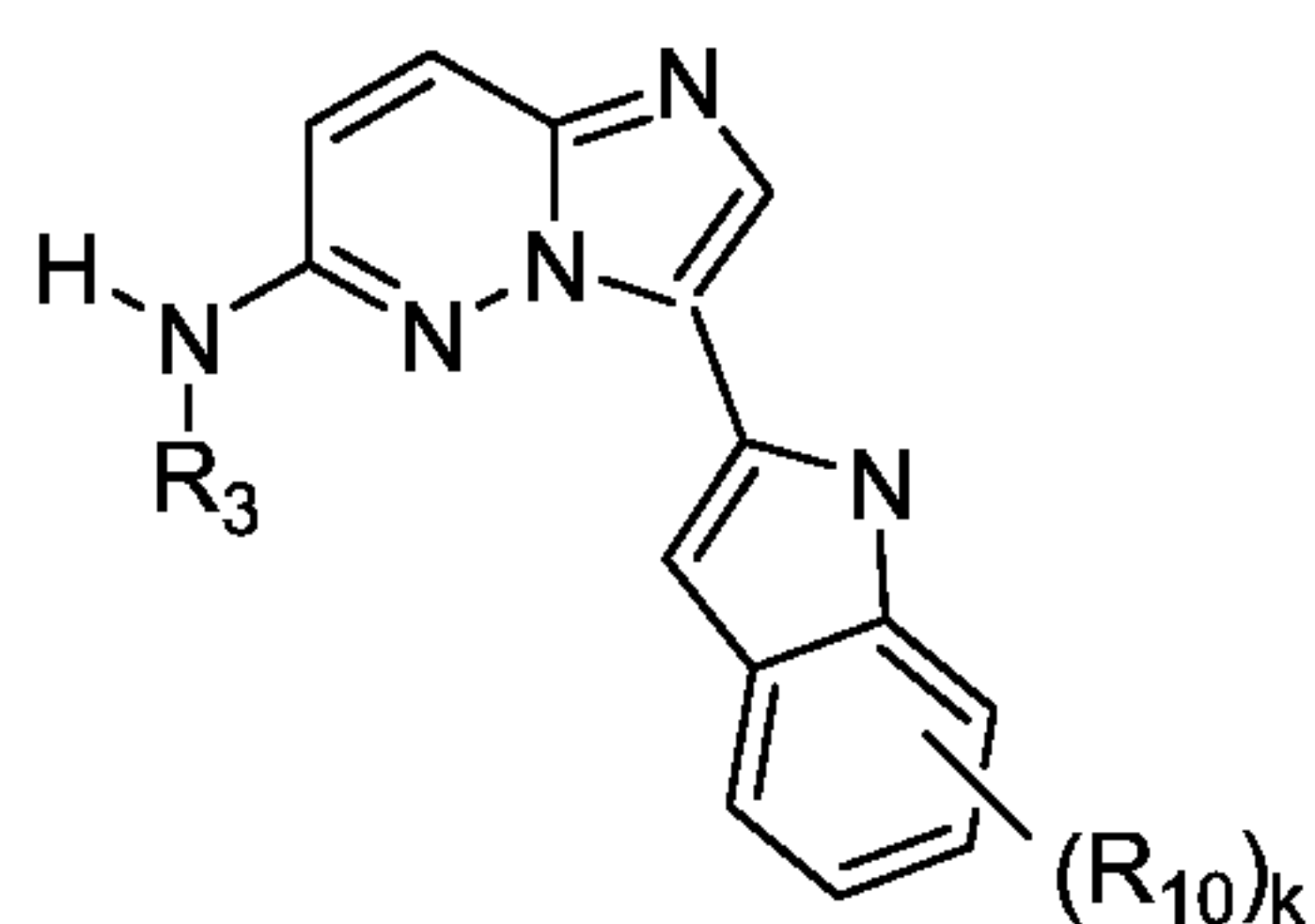
each R_7 can be independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, perhaloalkoxy, halo, oxo, -OH, hydroxyalkyl, -COOR₁₁, or -O-(CH₂)_m-OH;

q can be 1, 2, or 3;

each R_{10} can be independently selected from the group consisting of F, Cl, -OH, methoxy, ethoxy, propoxy, isopropoxy, and -OCOCH₃; and

k can be 0, 1, 2, or 3.

[0058] Certain embodiments of the present disclosure provides a compound having the structure of Formula **VIII**



VIII

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

R_3 can be selected from the group consisting of C₂-C₁₀ alkyl, aryl, and cycloalkyl;

each R_{10} can be independently selected from the group consisting of F, Cl, -OH, methoxy, ethoxy, propoxy, isopropoxy, and -OCOCH₃; and

k can be 0, 1, 2, or 3.

[0059] Certain embodiments of the present invention provide pharmaceutical compositions including a compound of the invention, and a pharmaceutical carrier, excipient or diluent. In this aspect of the invention, the pharmaceutical composition can comprise one or more of the compounds described herein.

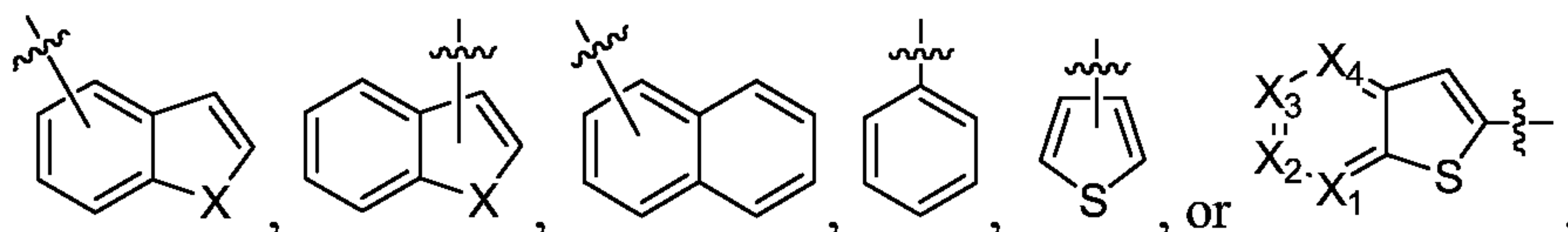
[0060] In certain embodiments, the disclosure provides one or more of the following compounds 3-9, 11-50, 52-102, 104, 107, 110-112, 114, 115, 118, 119-127, 129-132, 134-143, 148-150, 158-163, 166-221, or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, isotope, hydrate, or solvate thereof. In certain of such embodiments, the disclosure provides a compound selected from compounds 3-5, 67, 68, 87, 169, 170, 175, 177, 206, 213, 215-216, and 218 or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, isotope, or hydrate, or solvate thereof.

[0061] In certain embodiments, a pharmaceutical composition comprising a compound having the structure of Formula **I** can be provided:

**I**

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

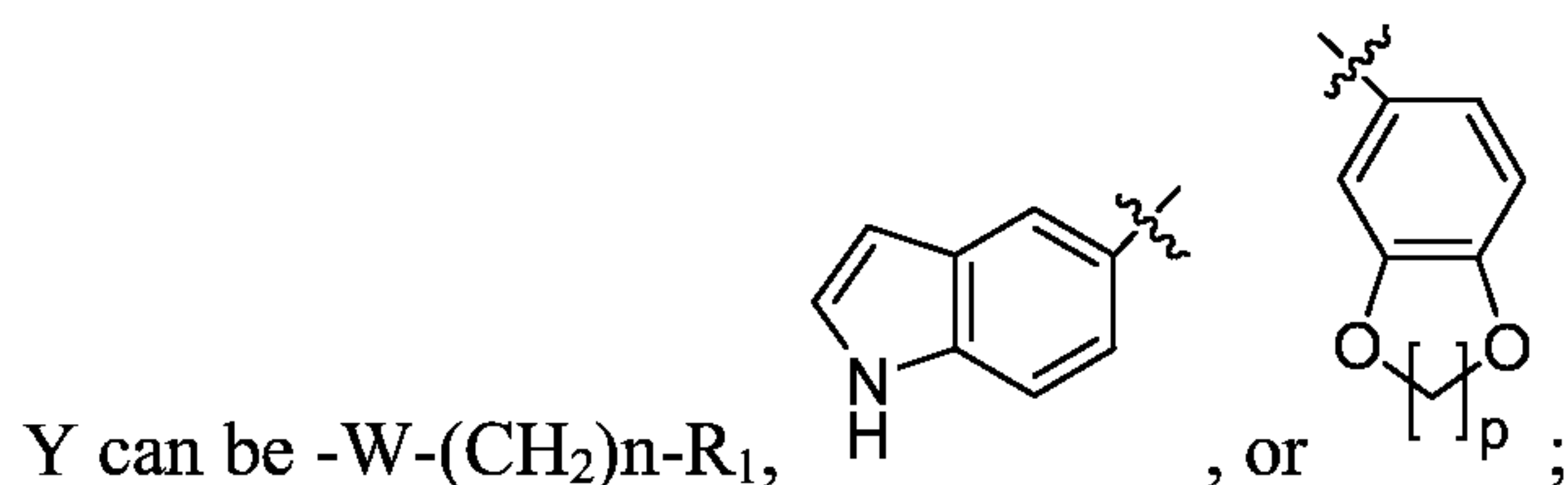
J has a structure of



where J can be optionally substituted with up to four R_{10} , each R_{10} can be independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy, haloalkoxy, -OH, and -OCOR₆;

X can be N R₁₂ or S;

each X₁, X₂, X₃, and X₄ can be independently CH or N and wherein no more than one of X₁, X₂, X₃, and X₄ is N;



Y can be -W-(CH₂)_n-R₁,

W can be null, phenylene, or -NR₆-phenylene, where the NR₆ is attached to the imidazopyridazine core structure of Formula I;

R₁ can be -NR₂R₃, or piperazinyl, where the nitrogen atom of the piperazinyl can be optionally substituted with alkyl or alkoxy;

R₂ can be H or alkyl; R₃ can be selected from the group consisting of C₂-C₁₀ alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, where any atom of R₃ can be optionally substituted with one or more R₇; or R₂ and R₃ taken together with the N atom to which they are attached form a 3- to 7-membered heterocyclic ring optionally substituted with R₈;

R₄ can be H or alkyl;

R₅ can be H, alkyl, or NHR₉;

R₆ can be H or alkyl;

each R₇ can be independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, perhaloalkoxy, halo, oxo, -OH, hydroxyalkyl, -COOR₁₁, or -O-(CH₂)_m-OH;

R₈ can be alkoxy, hydroxyalkyl, or COOR₁₁;

R₉ can be H, alkyl, or cycloalkyl;

R₁₁ can be H, or alkyl;

R₁₂ can be H, or alkyl;

n can be 0 or 1;

m can be 1, 2, or 3;

p can be 1, 2, or 3; and

together with at least one pharmaceutically acceptable carrier, diluent or excipient.

[0062] In certain embodiments, a pharmaceutical composition comprising a compound of Formula **II**, **III**, **IV** **IV-A**, **V**, **VI**, **VII** or **VIII**, or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, isotope, or hydrate, or solvate thereof, together with at least one pharmaceutically acceptable carrier, diluent or excipient is provided.

[0063] In other embodiments, a pharmaceutical composition comprising a compound of Formula **II**, **III**, **IV** **IV-A**, **V**, **VI**, **VII** or **VIII** or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, isotope, or hydrate, or solvate thereof, and a second medicament is provided.

[0064] In certain embodiments, a pharmaceutical composition comprising a compound of the invention disclosed herein, together with at least one pharmaceutically acceptable carrier, diluent or excipient is provided. The particular carrier employed in these pharmaceutical compositions may vary depending upon the type of administration desired (*e.g.*, intravenous, oral, topical, suppository, or parenteral).

[0065] Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric and galacturonic

acid. Examples of pharmaceutically unacceptable acid addition salts include, for example, perchlorates and tetrafluoroborates.

[0066] Suitable pharmaceutically acceptable base addition salts of compounds of the invention include, for example, metallic salts including alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, *N,N*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Examples of pharmaceutically unacceptable base addition salts include lithium salts and cyanate salts. Although pharmaceutically unacceptable salts are not generally useful as medicaments, such salts may be useful, for example, as intermediates in the synthesis of Formula **I, II, III, IV IV-A, V, VI, VII or VIII** compounds, for example in their purification by recrystallization. All of these salts may be prepared by conventional means from the corresponding compound according to Formula **I, II, III, IV IV-A, V, VI, VII or VIII** by reacting, for example, the appropriate acid or base with the compound according to Formula **I, II, III, IV IV-A, V, VI, VII or VIII**. The term "pharmaceutically acceptable salts" refers to nontoxic inorganic or organic acid and/or base addition salts, see, for example, Lit *et al.*, Salt Selection for Basic Drugs (1986), *Int J. Pharm.*, **33**, 201-217, incorporated by reference herein.

[0067] A "hydrate" is a compound that exists in a composition with water molecules. The composition can include water in stoichiometric quantities, such as a monohydrate or a dihydrate, or can include water in random amounts. As the term is used herein a "hydrate" refers to a solid form, *i.e.*, a compound in water solution, while it may be hydrated, is not a hydrate as the term is used herein.

[0068] A "salt" as is well known in the art includes an organic compound such as a carboxylic acid, a sulfonic acid, or an amine, in ionic form, in combination with a counterion. For example, acids in their anionic form can form salts with cations such as metal cations, for example sodium, potassium, and the like; with ammonium salts such as NH_4^+ or the cations of various amines, including tetraalkyl ammonium salts such as tetramethylammonium, or other cations such as trimethylsulfonium, and the like. A "pharmaceutically acceptable" or "pharmacologically acceptable" salt is a salt formed from an ion that has been approved for human consumption and is generally non-toxic, such as a chloride salt or a sodium salt. A "zwitterion" is an internal salt such as can be formed in a molecule that has at least two ionizable groups, one forming an anion and the other a cation, which serve to balance each other. For example, amino acids such as glycine can exist in a zwitterionic form. A "zwitterion" is a salt within the meaning herein. The compounds of the present invention may take the form of salts.

The term "salts" embraces addition salts of free acids or free bases which are compounds of the invention. Salts can be "pharmaceutically-acceptable salts." The term "pharmaceutically-acceptable salt" refers to salts which possess toxicity profiles within a range that affords utility in pharmaceutical applications. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present invention, such as utility in processes of synthesis, purification or formulation of compounds of the invention.

[0069] A "solvate" is a similar composition except that a solvent other than water replaces the water. For example, methanol or ethanol can form an "alcoholate", which can again be stoichiometric or non-stoichiometric. As the term is used herein a "solvate" refers to a solid form, *i.e.*, a compound in solution in a solvent, while it may be solvated, is not a solvate as the term is used herein.

[0070] A "prodrug" as is well known in the art is a substance that can be administered to a patient where the substance is converted *in vivo* by the action of biochemicals within the patient's body, such as enzymes, to the active pharmaceutical ingredient. Examples of prodrugs include esters of carboxylic acid groups, which can be hydrolyzed by endogenous esterases as are found in the bloodstream of humans and other mammals.

[0071] In preparing the compositions in oral liquid dosage forms (*e.g.*, suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (*e.g.*, powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like can be employed.

[0072] As set forth herein, compounds of the invention include stereoisomers, tautomers, solvates, hydrates, isotopes, esters, salts including pharmaceutically acceptable salts, and mixtures thereof. Compositions containing a compound of the invention can be prepared by conventional techniques, *e.g.*, as described in Remington: *The Science and Practice of Pharmacy*, 19th Ed., 1995, incorporated by reference herein. The compositions can appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

[0073] Typical compositions include a compound of the invention and a pharmaceutically acceptable excipient which can be a carrier or a diluent. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which can be in the form of an ampoule, capsule, sachet, paper, or other container. When the active compound is mixed with a carrier, or when the carrier serves as a diluent, it can be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active

compound can be adsorbed on a granular solid carrier, for example, contained in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent can include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

[0074] The formulations can be mixed with auxiliary agents which do not deleteriously react with the active compounds. Such additives can include wetting agents, emulsifying and suspending agents, salt for influencing osmotic pressure, buffers and/or coloring substances, preserving agents, sweetening agents or flavoring agents. The compositions can also be sterilized if desired.

[0075] The route of administration can be any route which effectively transports the active compound of the invention to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral, *e.g.*, rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment.

[0076] For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid solubility or serve as preservatives can also be included. Furthermore, injectable suspensions can also be prepared, in which case appropriate liquid carriers, suspending agents and the like can be employed.

[0077] If a solid carrier is used for oral administration, the preparation can be tableted, placed in a hard gelatin capsule, in powder or pellet form or it can be in the form of a troche or lozenge, for example. If a liquid carrier is used, the preparation can be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution or the like.

[0078] Injectable dosage forms generally include aqueous suspensions or oil suspensions which can be prepared using a suitable dispersant or wetting agent and a suspending agent. Injectable forms can be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils can be employed as solvents or suspending agents. Preferably, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

[0079] For injection, the formulation can also be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations can optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these. The compounds can be formulated for parenteral administration by injection such as by bolus injection or continuous infusion. A unit dosage form for injection can be in ampoules or in multi-dose containers.

[0080] The formulations of the invention can be designed to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. Thus, the formulations can also be formulated for controlled release or for slow release.

[0081] Compositions contemplated by the present invention can include, for example, micelles or liposomes, or some other encapsulated form, or can be administered in an extended release form to provide a prolonged storage and/or delivery effect. Therefore, the formulations can be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections. Such implants can employ known inert materials, such as silicones and biodegradable polymers, *e.g.*, polylactide-polyglycolide. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides).

[0082] For nasal administration, the preparation can contain a compound of the invention in powder form or dissolved or suspended in a liquid carrier, preferably an aqueous carrier, for aerosol application. The carrier can contain additives such as solubilizing agents, *e.g.*, propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives, such as parabens.

[0083] For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

[0084] Dosage forms can be administered daily, or more than once a day, such as twice or thrice daily. Alternatively dosage forms can be administered less frequently than daily, such as every other day, or weekly, if found to be advisable by a prescribing physician.

[0085] An embodiment of the invention also encompasses prodrugs of a compound of the invention which on administration undergo chemical conversion by metabolic or other physiological processes before becoming active pharmacological substances. Conversion by metabolic or other physiological processes includes without limitation enzymatic (*e.g.*, specific enzymatically catalyzed) and non-enzymatic (*e.g.*, general or specific acid or base induced) chemical transformation of the prodrug into the active pharmacological substance. In general, such prodrugs will be functional derivatives of a compound of the invention which are readily

convertible in vivo into a compound of the invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, Bundgaard, H., Ed., Elsevier, 1985.

[0086] In another embodiment, there are provided methods of making a composition of a compound described herein including formulating a compound of the invention with a pharmaceutically acceptable carrier or diluent. In some embodiments, the pharmaceutically acceptable carrier or diluent is suitable for oral administration. In some such embodiments, the methods can further include the step of formulating the composition into a tablet or capsule. In other embodiments, the pharmaceutically acceptable carrier or diluent is suitable for parenteral administration. In certain embodiments, the methods further include the step of lyophilizing the composition to form a lyophilized preparation.

[0087] The expression “effective amount,” when used to describe use of a compound of the invention in providing therapy to a patient suffering from a disorder or malcondition mediated by MLK (including MLK-1, MLK-2, and MLK-3), refers to the amount of a compound of the invention that is effective to inhibit the activity of MLK. Similarly, as used herein, an “effective amount” or a “therapeutically effective amount” of a compound of the invention refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with the disorder or condition, or halts or slows further progression or worsening of those symptoms, or prevents or provides prophylaxis for the disorder or condition. In particular, a “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result by acting as an inhibitor of MLK activity. A therapeutically effective amount is also one in which any toxic or detrimental effects of compounds of the invention are outweighed by the therapeutically beneficial effects. For example, in the context of treating a malcondition mediated by MLK, a therapeutically effective amount of an MLK inhibitor of the invention is an amount sufficient to control the malcondition, to mitigate the progress of the malcondition, or to relieve the symptoms of the malcondition. Examples of malconditions that can be so treated include, but are not limited to, diabetes mellitus, hyperglycemia, retinopathy, nephropathy, neuropathy, ulcers, micro- and macroangiopathies, gout and diabetic foot disease, insulin resistance, metabolic syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, peripheral inflammation, cancer, hepatitis, HIV associated neurocognitive disorders, HIV associated neuropathy, Alzheimer disease, Parkinson’s disease, Multiple Sclerosis, and other neurodegenerative diseases, cirrhotic diseases in liver or pancreas, and the like.

[0088] As used herein, the term “medicament” refers to any substance or combination of substances that has a beneficial and/or therapeutic effect.

[0089] As used herein, the term “subject” (as in the subject of the treatment) means both mammals and non-mammals. Mammals means any member of the mammalia class including, but not limited to, humans; non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. Examples of non-mammals include, but are not limited to, birds, and the like. The term “subject” does not denote a particular age or sex.

[0090] “Treating” or “treatment” refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder.

[0091] A “MLK-mediated disease” refers to a disease state which may be relieved by inhibiting MLK activity, where MLK signaling is involved in disease pathology. Examples of MLK-mediated disorders include, stroke, diabetes mellitus, hyperglycemia, retinopathy, nephropathy, neuropathy, ulcers, micro- and macroangiopathies, gout and diabetic foot disease, insulin resistance, metabolic syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, peripheral inflammation, cancer, hepatitis, HIV associated neurocognitive disorders, HIV associated neuropathy, Alzheimer disease, Parkinson’s disease, Multiple Sclerosis, and other neurodegenerative diseases, cirrhotic diseases in liver or pancreas, and the like.

[0092] The term “acyl,” as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety where the atom attached to the carbonyl is carbon. An “acetyl” group refers to a —C(O)CH_3 group. An “alkylcarbonyl” or “alkanoyl” group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[0093] The term “alkenyl,” as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term “alkenylene” refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [R—CH=CH—], (—C::C—). Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-propenyl, 2-methylpropenyl, butenyl, isobutenyl, 1,4-butadienyl, isoprenyl, vinyl, and the like. Unless otherwise specified, the term “alkenyl” may include “alkenylene” groups.

[0094] The term “alkoxy,” as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals

include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[0095] Cycloalkoxy groups are alkyoxy groups forming a ring structure, which can be substituted or unsubstituted, wherein the ring is either completely saturated, partially unsaturated, or fully unsaturated, wherein if there is unsaturation, the conjugation of the pi-electrons in the ring do not give rise to aromaticity. The term “cycloalkoxy” embraces saturated oxy-containing carbocyclic radicals and, unless otherwise specified, a cycloalkoxy radical typically has from 3 to 8 carbon atoms. When a cycloalkoxy radical carries two or more substituents, the substituents may be the same or different. Examples of such cycloalkoxy groups include cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, and the like.

[0096] The term “alkyl,” as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms, and typically from 1 to 12 carbons (C₁-C₁₂ alkyl), or, in some embodiments, from 1 to 8 carbon atoms (C₁-C₈ alkyl), or, in some embodiments, from 1 to 4 carbon atoms (C₁-C₄ alkyl). Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, nonyl and the like. The term “alkylene,” as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene (—CH₂—). Unless otherwise specified, the term “alkyl” may include “alkylene” groups.

[0097] Cycloalkyl groups are alkyl groups forming a ring structure, which can be substituted or unsubstituted, wherein the ring is either completely saturated, partially unsaturated, or fully unsaturated, wherein if there is unsaturation, the conjugation of the pi-electrons in the ring do not give rise to aromaticity. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 3 to 6, or 3 to 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalanyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups can be mono-substituted or substituted one or more times with any of the groups listed above, for example, but not limited to, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

[0098] Cycloalkylalkyloxy groups refer to alkyloxy groups as defined above in which a hydrogen or carbon bond of the alkyloxy group is replaced with a bond to a cycloalkyl group as

defined above. Examples of such cycloalkylalkyloxy groups include, but are not limited to, cyclopropylmethoxy, cyclopropylethoxy, cyclopropylpropoxy, cyclopropylbutoxy, cyclobutylmethoxy, cyclobutylethoxy, cyclobutylpropoxy, cyclobutylbutoxy, cyclopentylmethoxy, cyclopentylethoxy, cyclopentylpropoxy, cyclopentylbutoxy, cyclohexylmethoxy, cyclohexylethoxy, cyclohexylpropoxy, cyclohexylbutoxy, and the like.

[0099] The term “alkylamino,” as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[00100] The term “alkylthio,” as used herein, alone or in combination, refers to an alkyl thioether (R—S—) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[00101] The term “alkynyl,” as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkynyl comprises from 2 to 6 carbon atoms. In further embodiments, said alkynyl comprises from 2 to 4 carbon atoms. The term “alkynylene” refers to a carbon-carbon triple bond attached at two positions such as ethynylene (—C:::C—, —CC—). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, Butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term “alkynyl” may include “alkynylene” groups.

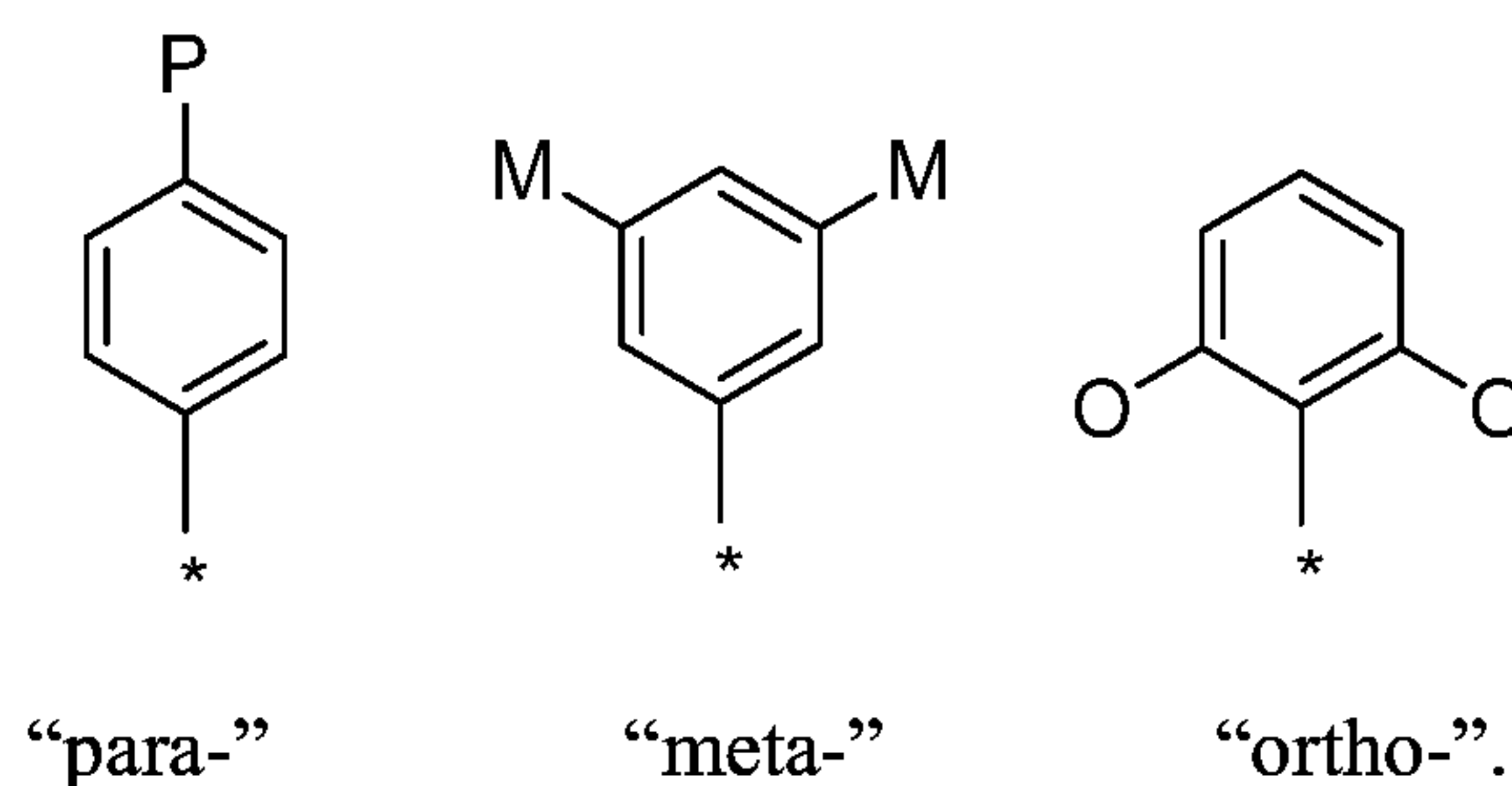
[00102] The terms “amido” and “carbamoyl,” as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or *vice versa*. The term “C-amido” as used herein, alone or in combination, refers to a —C(O)N(RR') group with R and R' as defined herein or as defined by the specifically enumerated “R” groups designated. The term “N-amido” as used herein, alone or in combination, refers to a RC(O)N(R')— group, with R and R' as defined herein or as defined by the specifically enumerated “R” groups designated. The term “acylamino” as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an “acylamino” group is acetylamino (CH₃C(O)NH—).

[00103] The term “amino,” as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently chosen from hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted.

Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted.

[00104] The term “aryl,” as used herein, alone or in combination, refers to a cyclic aromatic hydrocarbons that do not contain heteroatoms. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain 6-14 carbons in the ring portions of the groups. The phrase “aryl groups” includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (*e.g.*, indanyl, tetrahydronaphthyl, and the like), and also includes substituted aryl groups that have other groups, including but not limited to alkyl, halo, amino, hydroxy, cyano, carboxy, nitro, thio, or alkoxy groups, bonded to one of the ring atoms. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or naphthyl groups, which can be substituted with groups including but not limited to those listed above.

[00105] The compounds of the present invention may have a particular spatial arrangement of substituents on the aromatic rings, which is related to the structure activity relationship demonstrated by the compound class. Often such substitution arrangement is denoted by a numbering system; however, numbering systems are often not consistent between different ring systems. In six-membered aromatic systems, the spatial arrangements are specified by the common nomenclature “para” for 1,4-substitution, “meta” for 1,3-substitution and “ortho” for 1,2-substitution as shown below.



[00106] The term “arylalkenyl” or “aralkenyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[00107] The term “arylalkoxy” or “aralkoxy,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[00108] The term “arylalkyl” or “aralkyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[00109] The term “arylalkynyl” or “aralkynyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

[00110] The term “arylalkanoyl” or “aralkanoyl” or “aroyl,” as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, naphthoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, and the like.

[00111] The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[00112] The terms “benzo” and “benz,” as used herein, alone or in combination, refer to the divalent radical $C_6H_4=$ derived from benzene. Examples include benzothiophene and benzimidazole.

[00113] The term “carbamate,” as used herein, alone or in combination, refers to an ester of carbamic acid ($—NRC(O)O—$) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein. The term “O-carbamyl” as used herein, alone or in combination, refers to a $—OC(O)NRR'$ group; and the term “N-carbamyl” as used herein, alone or in combination, refers to a $ROC(O)NR'—$ group. R and R' are as defined herein, or as defined by the specifically enumerated “R” groups designated.

[00114] The term “carbonyl,” as used herein, when alone includes formyl [$—C(O)H$] and in combination is a $—C(O)—$ group.

[00115] The term “carboxyl” or “carboxy,” as used herein, refers to $—C(O)OH$ or the corresponding “carboxylate” anion, such as is in a carboxylic acid salt. An “O-carboxy” group refers to a $RC(O)O—$ group, where R is as defined herein. A “C-carboxy” group refers to a $—C(O)OR$ groups where R is as defined herein.

[00116] The term “cyano,” as used herein, alone or in combination, refers to $—CN$.

[00117] The term “ester,” as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[00118] The term “ether,” as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[00119] The term “halo,” or “halogen,” as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[00120] The term “haloalkoxy,” as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom. Haloalkoxy includes perhaloalkoxy. The term “perhaloalkoxy” refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms. An example of perhaloalkoxy is perfluoromethoxy.

[00121] The term “haloalkyl,” as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a

halogen. Specifically embraced are monohaloalkyl, dihaloalkyl, polyhaloalkyl, and perhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene (—CFH—), difluoromethylene ($\text{—CF}_2\text{—}$), chloromethylene (—CHCl—) and the like. The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms. Examples include perfluoromethyl.

[00122] The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms chosen from O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, $\text{—CH}_2\text{—NH—OCH}_3$.

[00123] The term "heteroaryl," as used herein, alone or in combination, refers to a 3 to 15 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom chosen from O, S, and N. Additionally, a heteroaryl may contain one or two C(O), S(O), or S(O)₂ groups as ring members. In certain embodiments, said heteroaryl will comprise from 5 to 10 atoms. In certain embodiments, said heteroaryl will comprise from 5 to 7 atoms. In certain embodiments, said heteroaryl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heteroaryl will comprise from 1 to 2 heteroatoms as ring members. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl,

pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, triazinyl, triazolyl, tetrazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, quinoxaliny, quinazoliny, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumariny, benzopyranyl, tetrahydroquinoliny, tetrazolopyridazinyl, tetrahydroisoquinoliny, thienopyridiny, furopyridiny, pyrrolopyridiny and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthroliny, dibenzofuranyl, acridiny, phenanthridiny, xanthenyl and the like.

[00124] The terms “heterocycloalkyl” and, interchangeably, “heterocycle,” as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each said heteroatom may be independently chosen from N, O, and S. Additionally, a heterocycloalkyl may contain one or two C(O), S(O), or S(O)₂ groups as ring members. In certain embodiments, said heterocycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heterocycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said heterocycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said heterocycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said heterocycloalkyl will comprise from 5 to 6 ring members in each ring. “Heterocycloalkyl” and “heterocycle” are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycloalkyls include furan-2-yl, furan-3-yl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholiny. The heterocycle groups may be optionally substituted unless specifically prohibited.

[00125] The term “hydroxy,” as used herein, alone or in combination, refers to —OH.

[00126] The term “lower,” as used herein, alone or in a combination, where not otherwise specifically defined, means containing from 1 to and including 6 carbon atoms.

[00127] The term “lower alkyl,” as used herein, alone or in a combination, means C₁-C₆ straight or branched chain alkyl. The term “lower alkenyl” means C₂-C₆ straight or branched chain alkenyl. The term “lower alkynyl” means C₂-C₆ straight or branched chain alkynyl.

[00128] The term “lower aryl,” as used herein, alone or in combination, means phenyl or naphthyl, either of which may be optionally substituted as provided.

[00129] The term “lower heteroaryl,” as used herein, alone or in combination, means either 1) monocyclic heteroaryl comprising five or six ring members, of which between one and four said

members may be heteroatoms chosen from O, S, and N, or 2) bicyclic heteroaryl, wherein each of the fused rings comprises five or six ring members, comprising between them one to four heteroatoms chosen from O, S, and N.

[00130] The term “lower cycloalkyl,” as used herein, alone or in combination, means a monocyclic cycloalkyl having between three and six ring members. Lower cycloalkyls may be unsaturated. Examples of lower cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00131] The term “lower heterocycloalkyl,” as used herein, alone or in combination, means a monocyclic heterocycloalkyl having between three and six ring members, of which between one and four may be heteroatoms chosen from O, S, and N. Lower heterocycloalkyls may be unsaturated.

[00132] The term “lower amino,” as used herein, alone or in combination, refers to —NRR' , wherein R and R' are independently chosen from hydrogen, lower alkyl, and lower heteroalkyl, any of which may be optionally substituted. Additionally, the R and R' of a lower amino group may combine to form a five- or six-membered heterocycloalkyl, either of which may be optionally substituted.

[00133] The term “nitro,” as used herein, alone or in combination, refers to —NO_2 .

[00134] The term “oxy,” as used herein, alone or in combination, refer to —O— .

[00135] The term “oxo,” as used herein, alone or in combination, refers to =O .

[00136] The term “perhaloalkyl” as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms. Perhaloalkyl groups include, but are not limited to, —CF_3 .

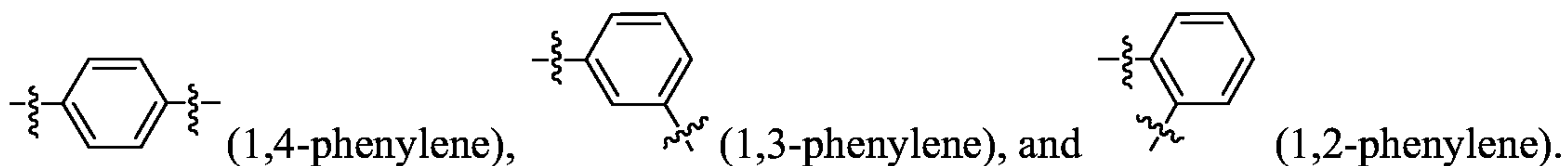
[00137] The term “perhaloalkoxy” refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms. Perhaloalkoxy groups include, but are not limited to, —OCF_3 .

[00138] The term “haloalkyl” as used herein, alone or in combination, refers to an alkyl group where at least one of the hydrogen atoms are replaced by halogen atoms. Haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, trifluoromethylethyl, and the like.

[00139] The term “haloalkoxy” refers to an alkoxy group where at least one of the hydrogen atoms are replaced by halogen atoms. Haloalkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, trifluoromethylethoxy, and the like.

[00140] The term “arylene” refers to a divalent radical formed by the removal of two hydrogen atoms from one or more rings of an aryl group. One specific example, the term

"phenylene" refers to a divalent radical formed by the removal of two hydrogen atoms from one or more rings of a phenyl group. Example of phenylene groups include



[00141] The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the $\text{—SO}_3\text{H}$ group and its anion as the sulfonic acid is used in salt formation.

[00142] The term "thio," as used herein, alone or in combination, refer to a —S— group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio. The term "sulfanyl," as used herein, alone or in combination, refers to —S— . The term "sulfinyl," as used herein, alone or in combination, refers to —S(O)— . The term "sulfonyl," as used herein, alone or in combination, refers to $\text{—S(O)}_2\text{—}$.

[00143] The term "thiol," as used herein, alone or in combination, refers to an —SH group.

[00144] The term "thiocarbonyl," as used herein, when alone includes thioformyl —C(S)H and in combination is a —C(S)— group.

[00145] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[00146] When a group is defined to be "null," what is meant is that said group is absent.

[00147] The term "optionally substituted" means the antecedent group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3 , SH , SCH_3 , C(O)CH_3 , CO_2CH_3 , CO_2H , pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered

carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (*e.g.*, —CH₂CH₃), fully substituted (*e.g.*, —CF₂CF₃), monosubstituted (*e.g.*, —CH₂CH₂F) or substituted at a level anywhere in-between fully substituted and monosubstituted (*e.g.*, —CH₂CF₃). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as “substituted,” the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, “optionally substituted with.”

[00148] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety chosen from hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R_n where $n = (1, 2, 3, \dots n)$, every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (*e.g.*, aryl, heterocycle, R, *etc.*) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as —C(O)N(R)— may be attached to the parent moiety at either the carbon or the nitrogen.

[00149] When two “R” groups are said to be joined together or taken together to form a ring, it means that together with the carbon atom or a non-carbon atom (*e.g.*, nitrogen atom), to which they are bonded, they may form a ring system. In general, they are bonded to one another to form a 3- to 7-membered ring, or a 5- to 7-membered ring. Non-limiting specific examples are the cyclopentyl, cyclohexyl, cycloheptyl, piperidiny, piperazinyl, pyrrolidiny, pyrrolyl, pyridiny.

[00150] Certain compounds disclosed herein contain one or more asymmetric centers. For compounds having asymmetric centers, it should be understood that all of the optical isomers and mixtures thereof are encompassed. Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers, but rather includes all tautomeric forms. Certain compounds are described herein using a general formula that includes variables. Unless otherwise specified, each variable within such a formula is defined independently of other variables.

Compositions and Combination Treatments

[00151] Another embodiment of the invention provides compositions of the compounds of the disclosure, alone or in combination with another MLK inhibitor or another type of therapeutic agent, or both.

[00152] In certain embodiments, the disclosure provides a pharmaceutical combination comprising a compound of the disclosure and a second medicament. In various embodiments, the second medicament (or second therapeutic agent) is medically indicated for the treatment of diseases and conditions which can be affected by SGLT inhibition, such as antidiabetic agents, lipid-lowering/lipid-modulating agents, agents for treating diabetic complications, anti-obesity agents, antihypertensive agents, antihyperuricemic agents, and agents for treating chronic heart failure, atherosclerosis or related disorders. Examples of second medicaments which can be used in combination with compounds disclosed herein include lithium, valproate and other agents used in neuroprotection, PAF receptor antagonists, antioxidants including mitochondrially-targeted antioxidants, activators of SIRT₁ and other sirtuins, inhibitors of indoleamine 2,3 dehydrogenase (IDO), agents which enhance trans-blood brain barrier (BBB) uptake of drugs, including compounds that inhibit drug pumps at the BBB, such as ritonavir; HAART drugs and other agents for use in HIV treatment; agents for the treatment of cardiovascular, heart, and metabolic disorders, such as HMG-CoA reductase inhibitors including statins, insulin and insulin mimetics, and glycogen synthase kinase-3 beta (GSK3 β) inhibitors; agents which “normalize” mitochondrial function; antiinflammatory agents including PAF receptor antagonists or PAF acetylhydrolase, cyclooxygenase inhibitors (including COX-2 selective and nonselective) such as aspirin, ibuprofen, naproxen, and celecoxib; and agents for blocking liver cell proliferation, such as JNK inhibitors.

[00153] In certain embodiments, the second medicament is used for the treatment of HIV infection or AIDS. In certain of such embodiments, the second medicament comprises atazanavir, ritonavir, zidovudine, lamivudine, or efavirenz.

[00154] In certain embodiments, MLK-3 antagonists may have a synergistic effect on HIV treatment.

[00155] In certain embodiments, the methods of treatment disclosed herein additionally comprise the administration of a second therapeutic agent, as part of a therapeutic regimen. The pharmaceutical combination (i.e., the compounds of the present disclosure and a second medicament) can be administered orally in the same dosage form, in a separate oral dosage form (e.g., sequentially or non-sequentially) or by injection together or separately (e.g., sequentially or non-sequentially).

[00156] The specific amount of the second therapeutic agent will depend on the specific agent used, and the severity and stage of diseases, and the amount(s) of a MLK inhibitor and any optional additional active agents concurrently administered to the patient.

Method of Treatments

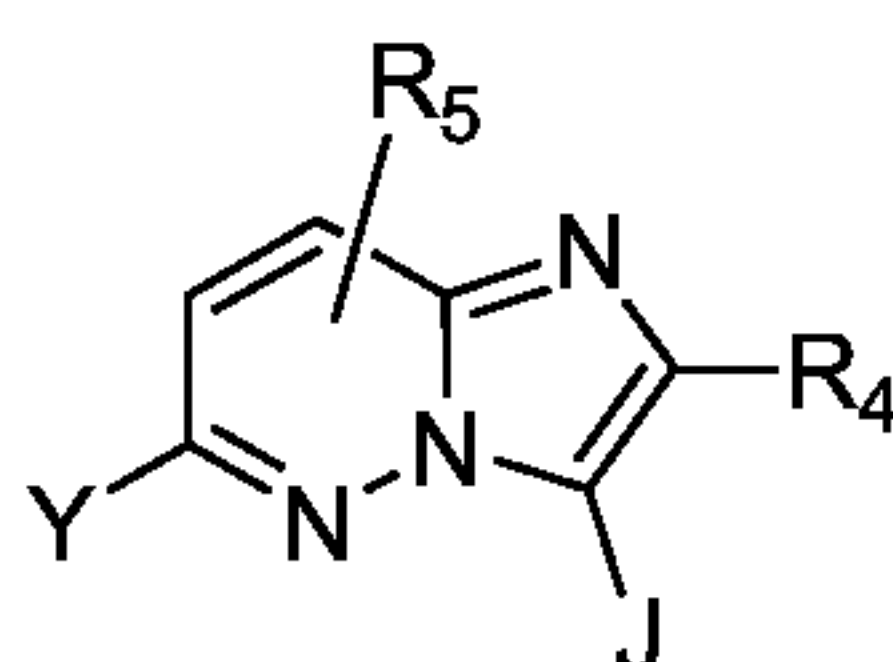
[00157] The disclosure is based, in part, on the belief that a MLK inhibitor can work alone or in combination with another active agent to effectively treat a MLK-mediated disease.

[00158] In certain embodiments, a method is provided for treatment of a MLK-mediated disease where such method comprises administering an effective amount to a subject a compound, pharmaceutical composition or pharmaceutical combination of the disclosure. In certain embodiments, such mammal is a human.

[00159] In certain embodiments, a method is provided for inhibiting the activity, expression, or function of MLKs. In certain embodiments, the present disclosure provides selective inhibition. In certain embodiments, the disclosure provides a selective inhibitor provides selective inhibition of MLKs, especially MLK-3, over one or more other kinases.

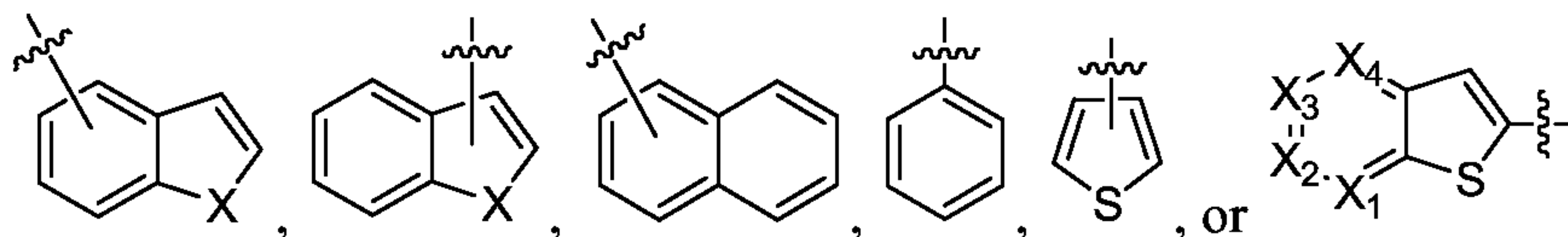
[00160] In certain embodiments, compounds according to the disclosure exhibit a surprising and unexpected selectivity in inhibiting a MLKs. In a specific embodiment, compounds according to the disclosure exhibit a surprising and unexpected selectivity in inhibiting a MLK-3. For examples, when compared to the compounds described in Table 51, the compounds according to the invention are surprisingly more selective for a MLK-3 over other kinases.

[00161] In certain embodiments, the present disclosure also provides a method for treatment of a MLK-mediated disease comprising administering to a subject a therapeutically effective amount of a pharmaceutical composition comprising a compound having the structure of Formula I



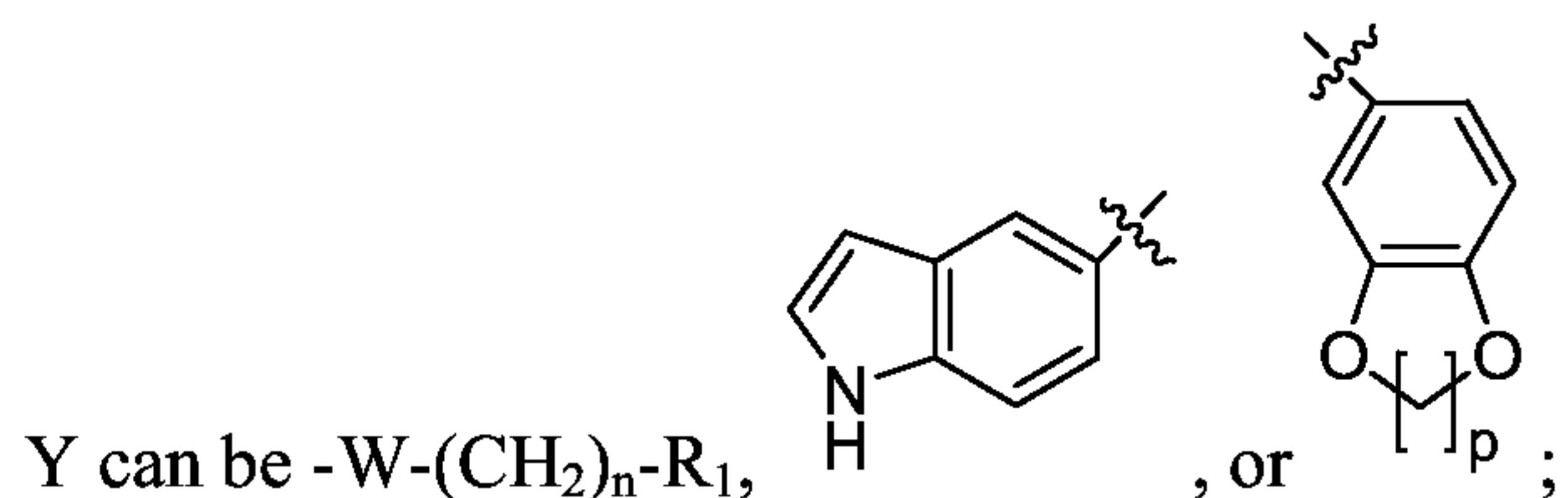
I

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein J has a structure of



optionally substituted with up to four R_{10} , each R_{10} can be independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy, haloalkoxy, -OH, and -OCOR₆; X can be N or S;

each X_1 , X_2 , X_3 , and X_4 can be independently CH or N and wherein no more than one of X_1 , X_2 , X_3 , and X_4 can be N;



W can be null, phenylene, or $-NR_6$ -phenylene, where the NR_6 can be attached to the imidazopyridazine core structure of Formula I; R_1 can be $-NR_2R_3$, or piperazinyl, where the nitrogen atom of the piperazinyl is optionally substituted with alkyl or alkoxy; R_2 can be H or alkyl; R_3 can be selected from the group consisting of C_2 - C_{10} alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, where any atom of R_3 can be optionally substituted with one or more R_7 ; or R_2 and R_3 taken together with the N atom to which they are attached form a 3- to 7-membered heterocyclic ring optionally substituted with R_8 ; R_4 can be H or alkyl; R_5 can be H, alkyl, or NHR_9 ; R_6 can be H or alkyl;

each R_7 can be independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, perhaloalkoxy, halo, oxo, $-OH$, hydroxyalkyl, $-COOR_{11}$, or $-O-(CH_2)_m-OH$; R_8 can be alkoxy, hydroxyalkyl, or $COOR_{11}$; R_9 can be H, alkyl, or cycloalkyl; R_{11} can be H, or alkyl; R_{12} can be H, or alkyl; n can be 0 or 1; m can be 1, 2, or 3; and p can be 1, 2, or 3.

[00162] In certain embodiments, a method is provided for the preparation of a medicament useful for treating a MLK-mediated disease, where the medicament comprising a pharmaceutical composition disclosed herein.

[00163] In certain embodiments, the present disclosure provides a use of the compound of the present disclosure (imidazopyridine compounds) in preparation of a medicament for treating a MLK-mediated disease, such as stroke, diabetes mellitus, hyperglycemia, retinopathy, nephropathy, neuropathy, ulcers, microangiopathies, macroangiopathies, gout, diabetic foot disease, insulin resistance, metabolic syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, peripheral inflammation, cancer, hepatitis, steatohepatitis, HIV associated neurocognitive disorder, HIV associated neuropathy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, neurodegenerative disease, cirrhotic liver disease, and cirrhotic pancreatic disease.

[00164] In certain embodiments, the present disclosure provides a use of the compound of the present disclosure in preparation of a medicament for treating a MLK-mediated disease, such as HIV associated neurocognitive disorders, HIV associated neuropathy, heart failure, cirrhotic liver disease, cirrhotic pancreatic disease, steatohepatitis, pancreatic cancer, breast cancer, Alzheimer's disease, Parkinson's disease, and neurodegenerative disease.

Method of Making

[00165] Another embodiment of the invention provides methods for synthesis of certain compounds including compounds of the invention. In certain other embodiments, the invention provides certain intermediate compounds associated with such methods of synthesis.

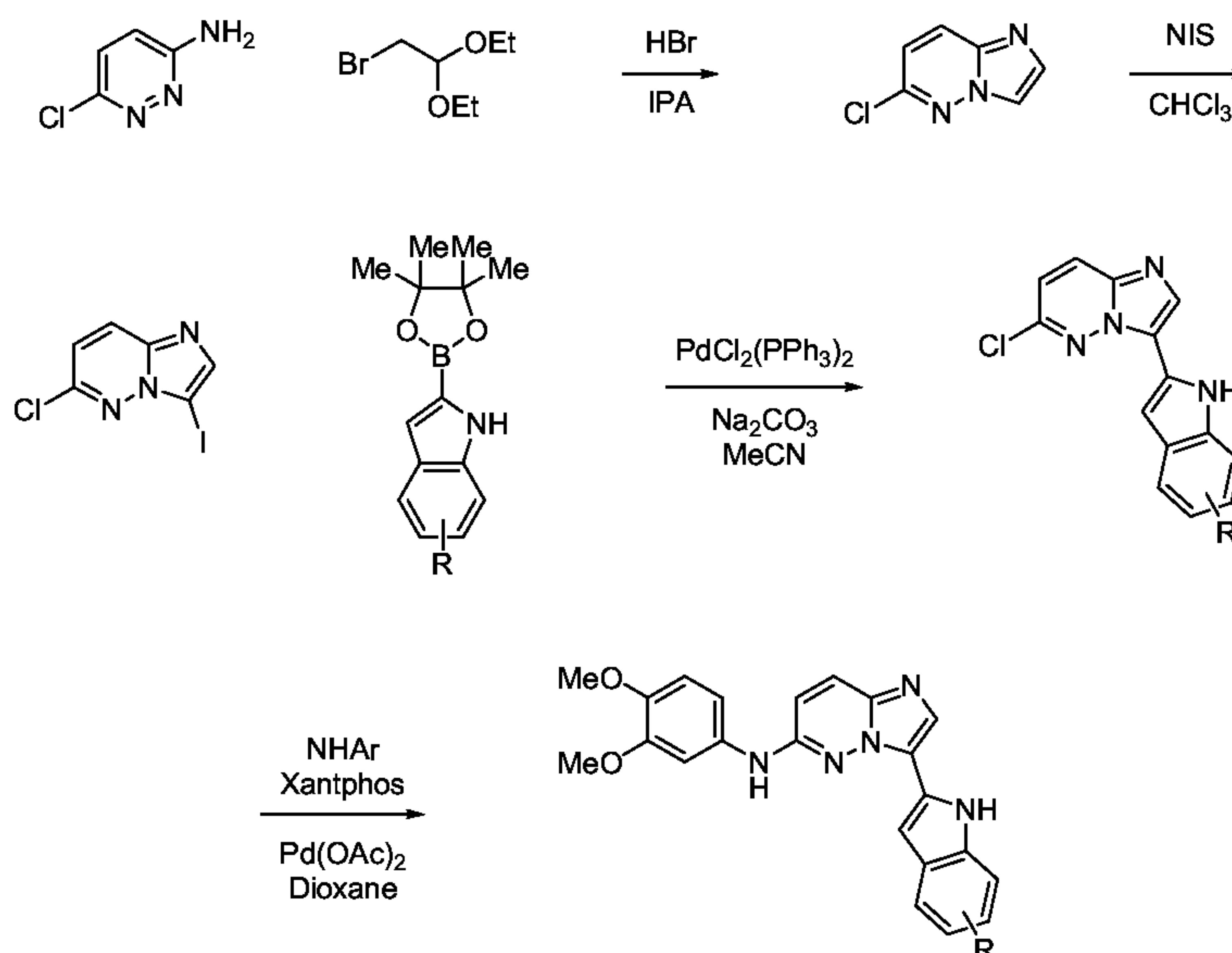
[00166] A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the following examples are intended to illustrate but not limit the scope of invention described in the claims.

General Synthetic Methods for Preparing Compounds

[00167] Molecular embodiments of the present invention can be synthesized using standard synthetic techniques known to those of skill in the art. Compounds of the present invention can be synthesized using the general synthetic procedures set forth in Schemes 1-64.

[00168] Example 1 – Synthesis of Compounds 3-5, 195

[00169] **Scheme 1**



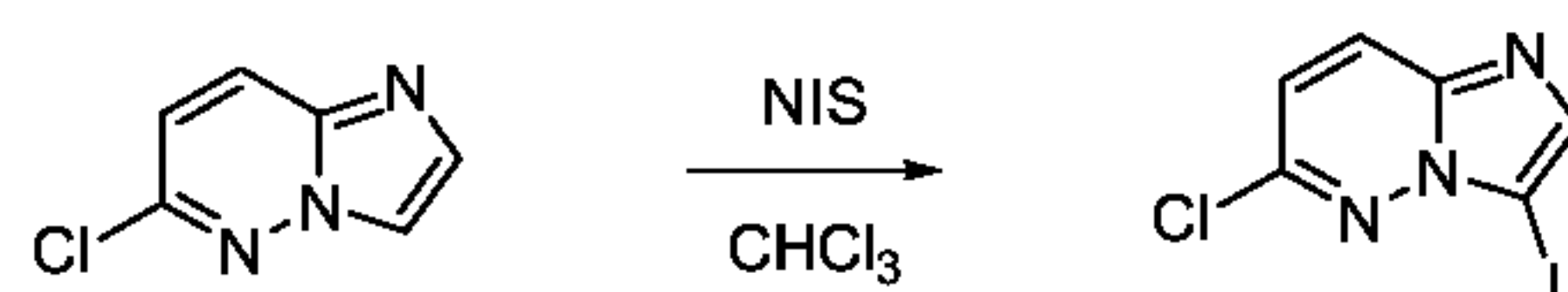
[00170] **Preparation of 6-chloroimidazo[1,2-b]pyridazine**



[00171] Bromoacetaldehyde diethylacetal (13.7 g, 69.5 mmol, 1.8 equiv) was added to hydrobromic acid (4.0 mL) and heated to reflux for 1.5 h. The reaction mixture was cooled to rt then poured into a reaction flask containing excess sodium bicarbonate in isopropanol. The solution was stirred for 3 min and then filtered. To the mother liquor was added 3-amino-6-

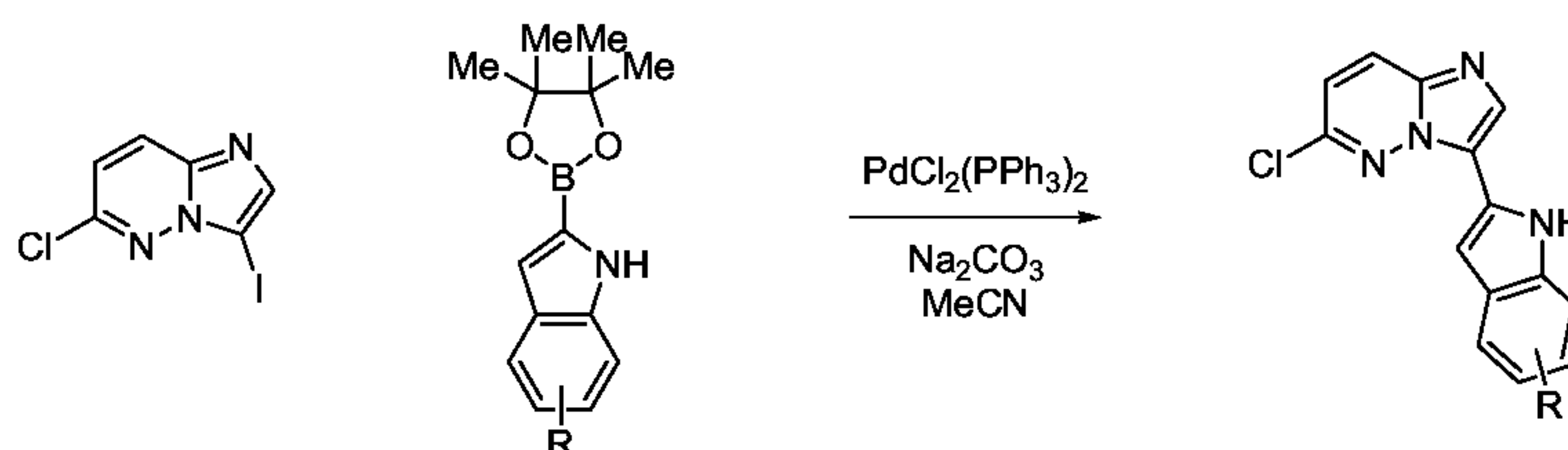
chlorpyridazine (5.0 g, 38.6 mmol, 1.0 equiv) and heated to reflux for 2 h. The reaction mixture was quenched with water and extracted with ethyl acetate. Purification using column chromatography gave 5.1 g of the brown solid, 86%: ^1H NMR (400 MHz, CDCl_3) δ 7.89 (s, 1H), 7.88 (d, $J = 9.3$ Hz, 1H), 7.74 (s, 1H), 7.01 (d, $J = 9.3$ Hz, 1H).

[00172] Preparation of 6-chloro-3-iodoimidazo[1,2-b]pyridazine



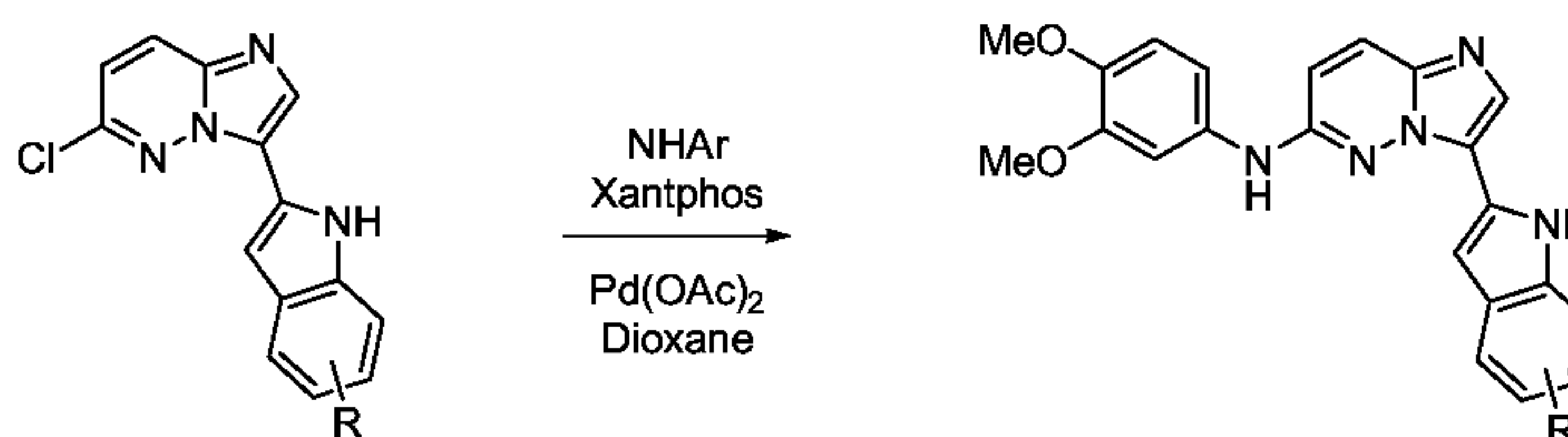
[00173] 6-chloroimidazo[1,2-b]pyridazine (2.0 g, 13.0 mmol, 1.0 equiv) in chloroform (20 mL) at room temperature was added N-iodosuccinimide (2.9 g, 13.0 mmol, 1.0 equiv) then stirred vigorously overnight. The reaction mixture was diluted in water and extracted with ethyl acetate. Purification using column chromatography gave 3.3 g of the yellow solid, 90%: ^1H NMR δ 8.21 (d, $J = 7.6$ Hz, 1H), 7.96 (s, 1H), 7.41 (d, $J = 7.6$ Hz, 1H).

[00174] Preparation of 6-chloro-3-(alkyl-1H-indol-2-yl)imidazo[1,2-b]pyridazine



[00175] 6-chloro-3-iodoimidazo[1,2-b]pyridazine (324 mg, 1.159 mmol, 1.0 equiv), in acetonitrile (10 mL), was added methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (1.51 mmol, 1.3 equiv), bis(triphenylphosphine)palladium(II) chloride (42 mg, 0.0579 mmol, 0.05 equiv), then sodium carbonate (11.6 mL, 1.0 M aqueous solution, 10 equiv). The reaction mixture was stirred overnight at room temperature. Purification by column chromatography gave of the product.

[00176] Preparation of 3-(alkyl-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine



[00177] To a solution of 6-chloro-3-(7-methoxy-1H-indol-2-yl)imidazo[1,2-b]pyridazine (59 mg, 0.198 mmol, 1.0 equiv), xantphos (23 mg, 0.0395 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0198 mmol, 0.1 equiv), and potassium carbonate (546 mg, 3.95 mmol, 20 equiv) in dioxane

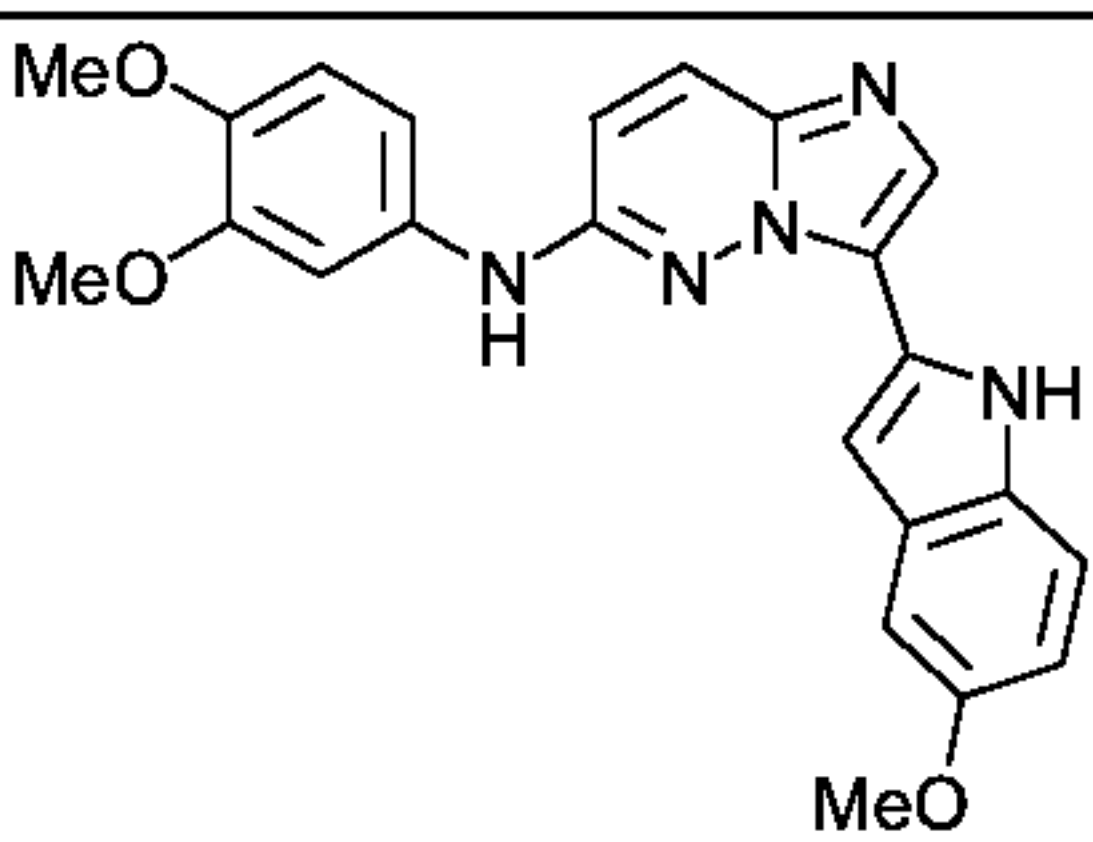
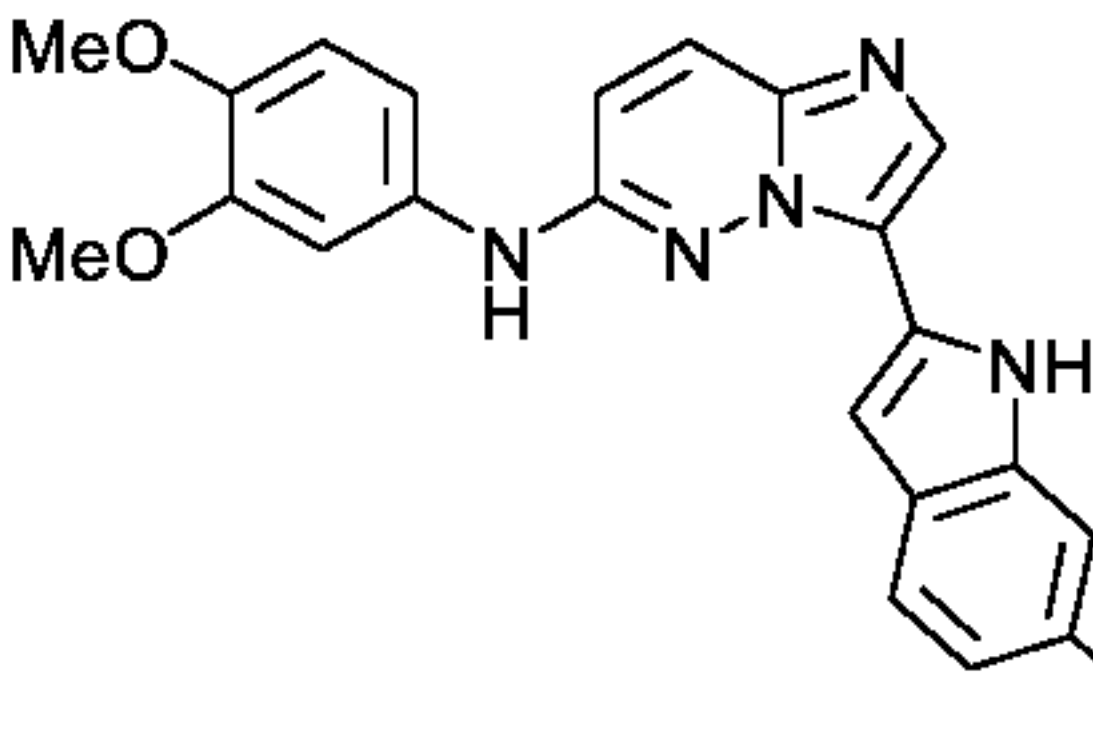
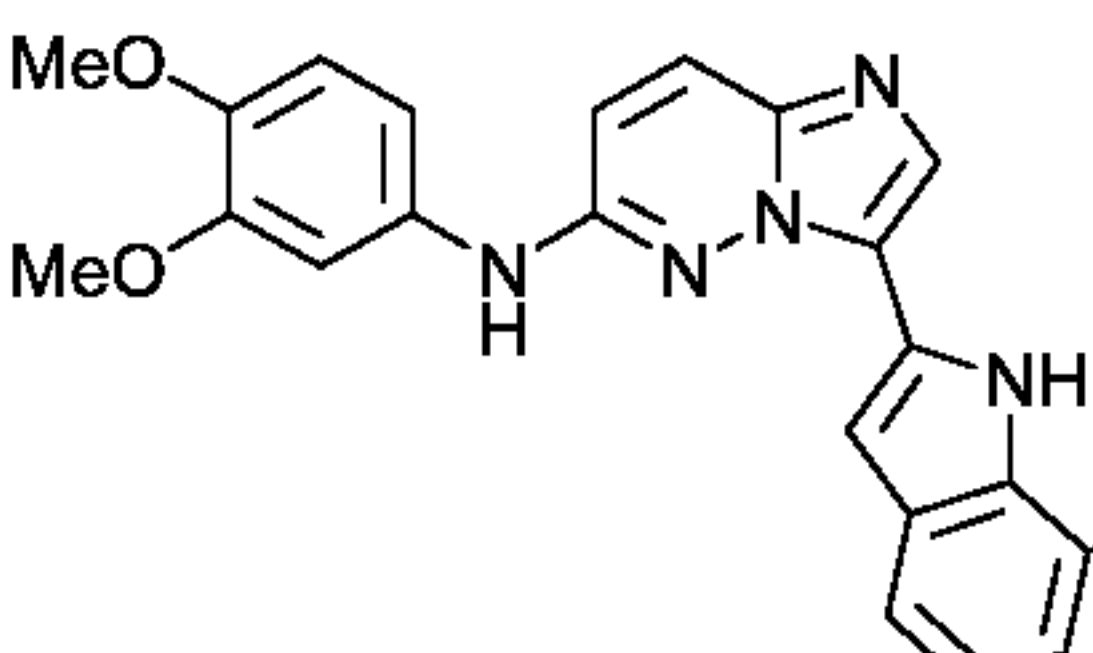
(5.0 mL) was added amine (0.395 mmol, 2.0 equiv) and heated to 100 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

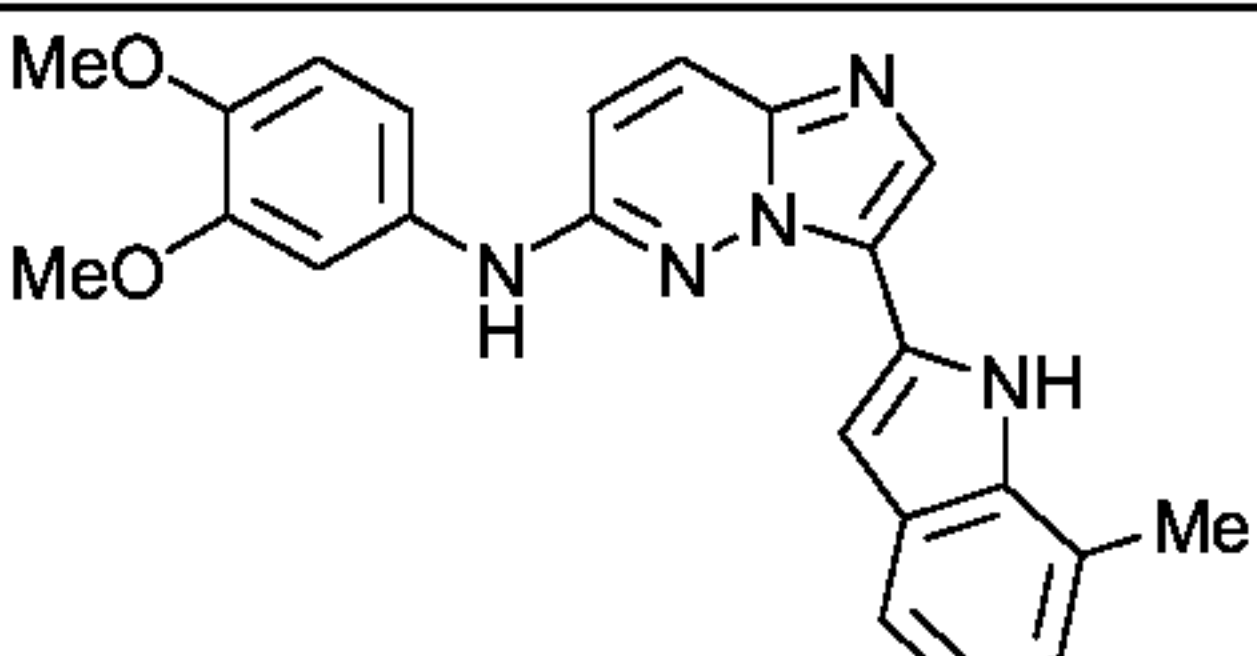
Table 1-a

Cd.	Boronic Acid	Amine	Purified Compound Isolated
3	5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole	3,4-dimethoxyaniline	3-(5-methoxy-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
4	6-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole	3,4-dimethoxyaniline	3-(6-methoxy-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
5	7-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole	3,4-dimethoxyaniline	3-(7-methoxy-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
195	7-methyl-1H-indol-2-yl-2-boronic acid	3,4-dimethoxyaniline	N-(3,4-dimethoxyphenyl)-3-(7-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-amine

[00178] Compounds 3-5, 195 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 1-b**.

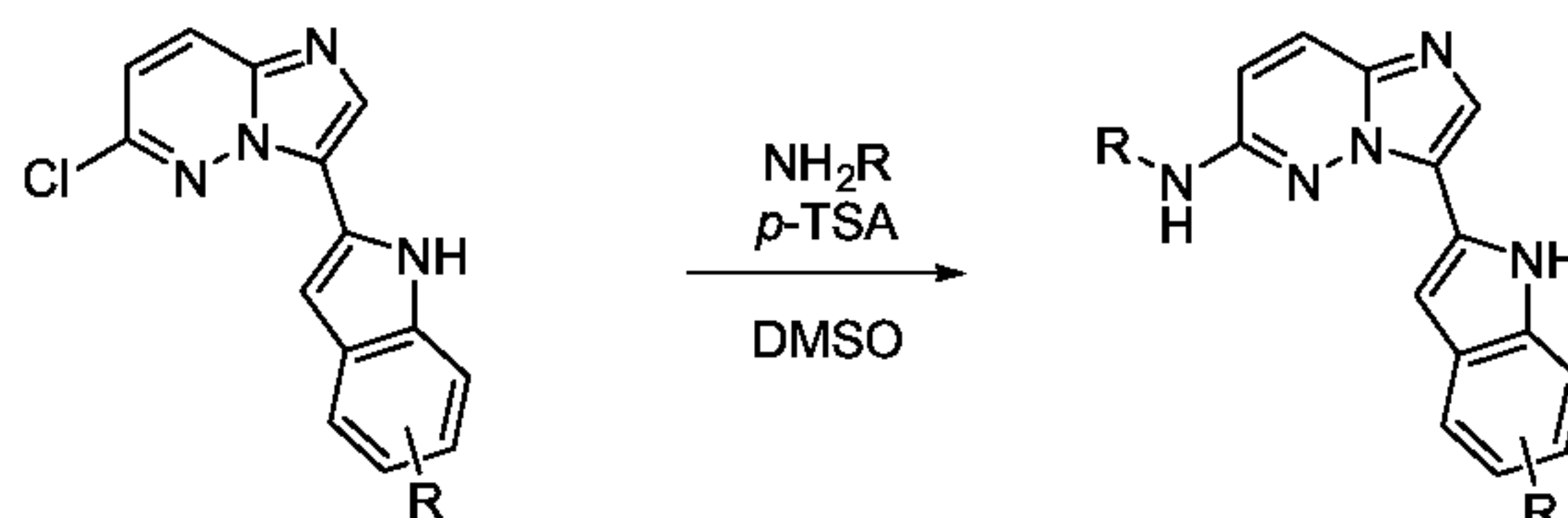
Table 1-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
3		3-(5-methoxy-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	416.2
4		3-(6-methoxy-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	416.0
5		3-(7-methoxy-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	416.0

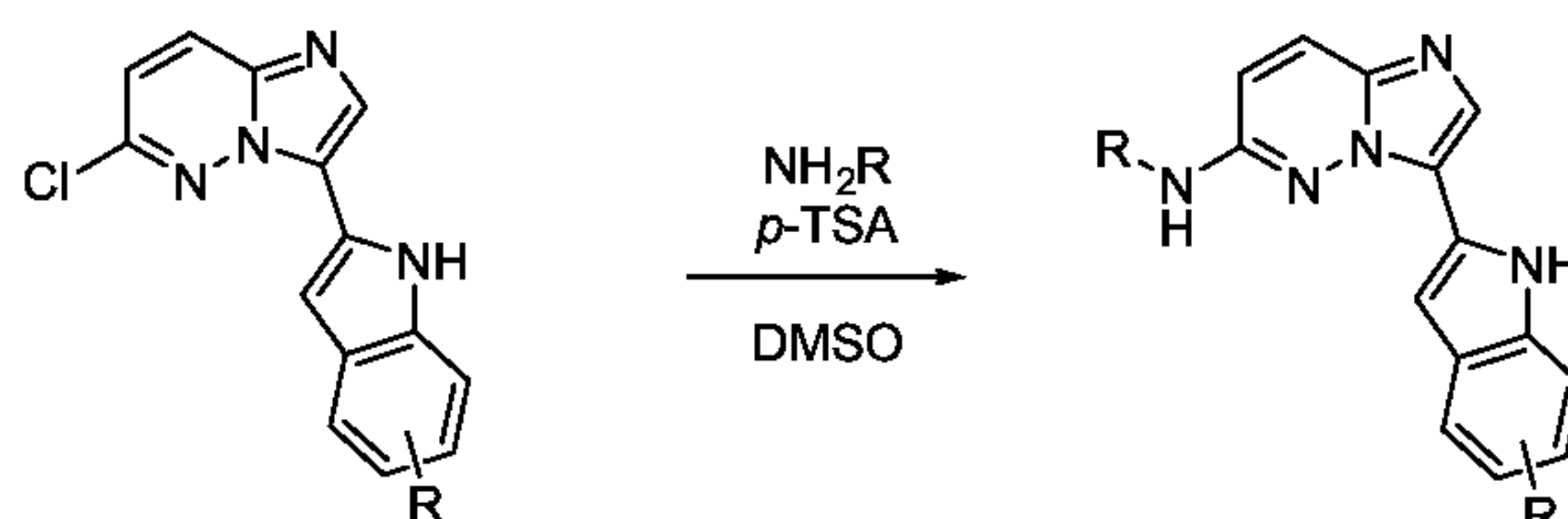
195		N-(3,4-dimethoxyphenyl)-3-(7-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-amine	400.2
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[00179] Example 2 – Synthesis of Compounds 85-88, 159, 196

[00180] **Scheme 2**



[00181] **Preparation of 3-(alkyl-1H-indol-2-yl)-N-alkylimidazo[1,2-b]pyridazin-6-amine**



[00182] To a solution of 6-chloro-3-(1H-indol-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.167 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (32 mg, 0.167 mmol, 1.0 equiv) and amine (1.67 mmol, 10.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave the product.

Table 2-a

Cd.	Boronic ester	Amine	Pure Isolated Compound
85	5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(5-methoxy-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
86	6-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(6-methoxy-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
87	7-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(7-methoxy-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
88	1H-indol-2-yl-2-	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(1H-indol-2-

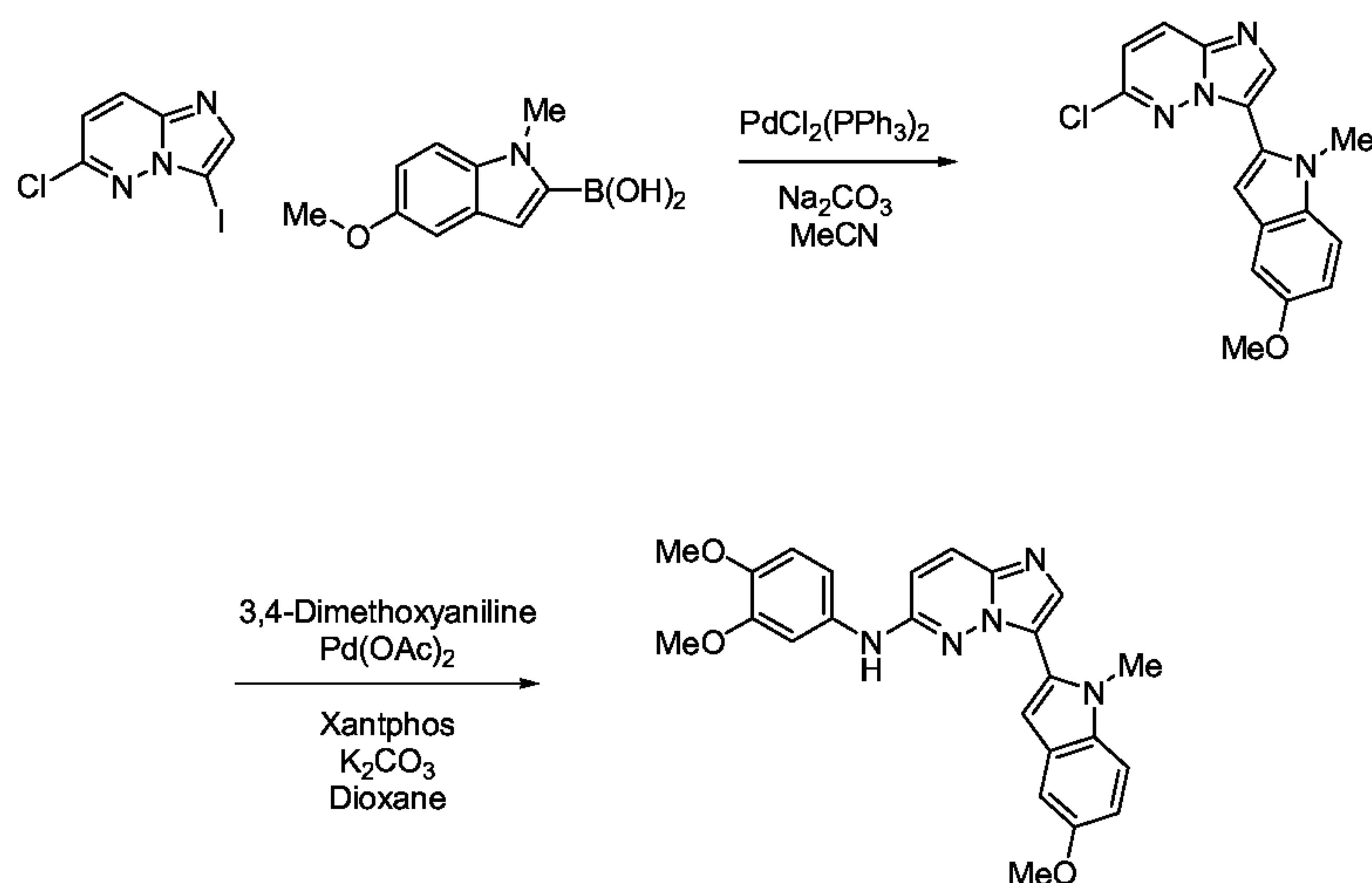
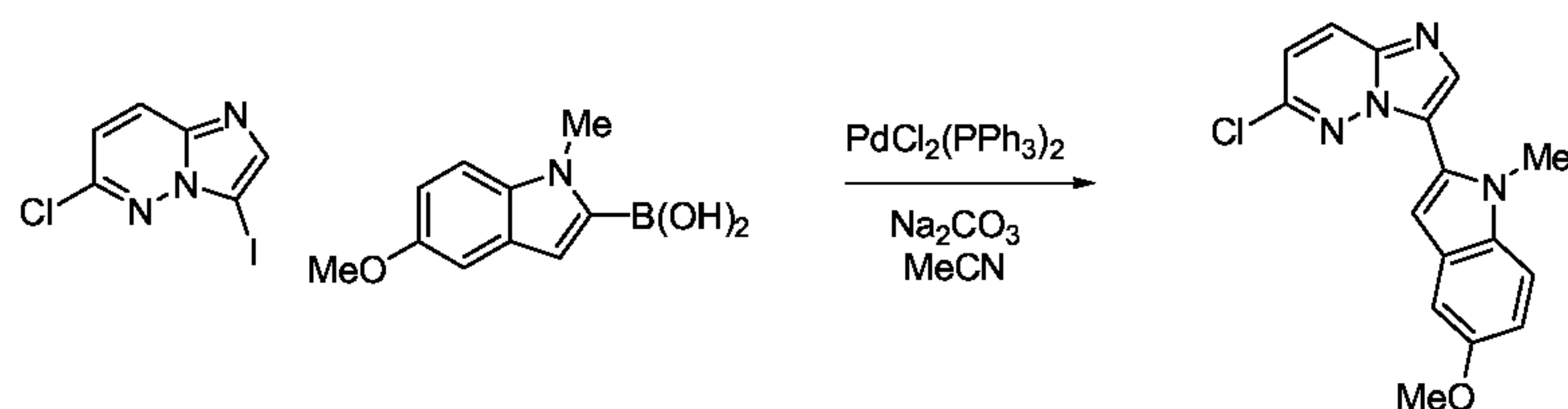
	boronic acid		yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
159	1H-indol-2-yl-2-boronic acid	1-propylamine	3-(1H-indol-2-yl)-N-propylimidazo[1,2-b]pyridazin-6-amine
196	7-methyl-1H-indol-2-yl-2-boronic acid	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(7-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
198	5-methoxy-1H-indol-2-yl-2-boronic acid	<i>trans</i> -4-methoxycyclohexanamine	<i>trans</i> -3-(5-methoxy-1H-indol-2-yl)-N-(4-methoxycyclohexyl)imidazo[1,2-b]pyridazin-6-amine
199	7-methoxy-1H-indol-2-yl-2-boronic acid	<i>trans</i> -4-methoxycyclohexanamine	<i>trans</i> -3-(7-methoxy-1H-indol-2-yl)-N-(4-methoxycyclohexyl)imidazo[1,2-b]pyridazin-6-amine

[00183] Compounds 85-88, 159, 196, 198-199 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 2-b**.

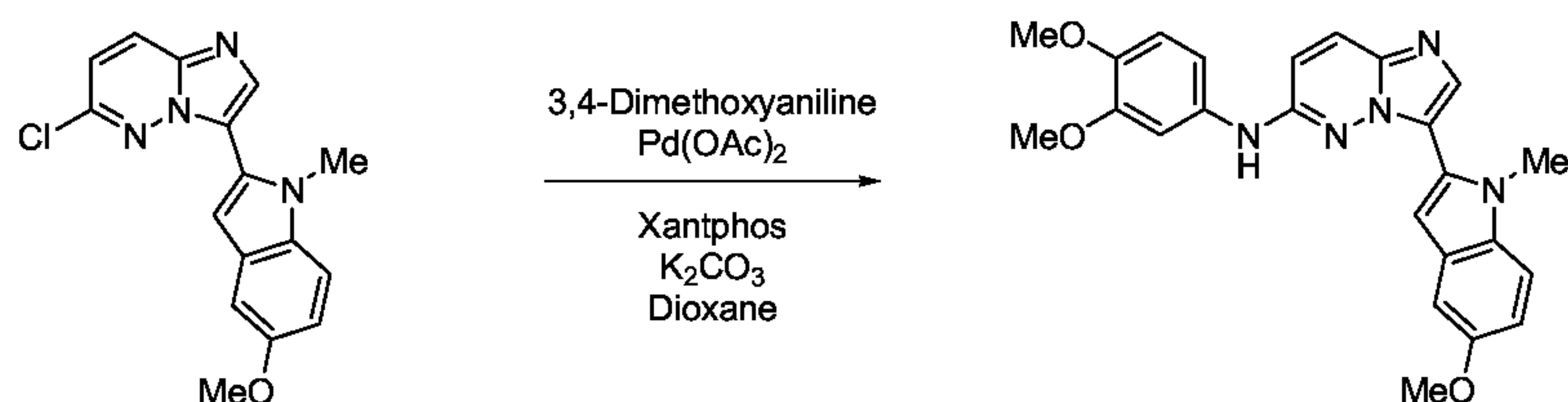
Table 2-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
85		<i>trans</i> -4-(3-(5-methoxy-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	378.2
86		<i>trans</i> -4-(3-(6-methoxy-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	378.4
87		<i>trans</i> -4-(3-(7-methoxy-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	378.2
88		<i>trans</i> -4-(3-(1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	348.5
159		3-(1H-indol-2-yl)-N-propylimidazo[1,2-b]pyridazin-6-amine	292.7
196		<i>trans</i> -4-(3-(7-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	362.2
198		<i>trans</i> -3-(5-methoxy-1H-indol-2-yl)-N-(4-methoxycyclohexyl)imidazo[1,2-b]pyridazin-6-amine	392.5
199		<i>trans</i> -3-(7-methoxy-1H-indol-2-yl)-N-(4-methoxycyclohexyl)imidazo[1,2-b]pyridazin-6-amine	392.3

[00184] Example 2C – Synthesis of Compounds 193

[00185] Scheme 2C**[00186] Preparation of 6-chloro-3-(5-methoxy-1-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazine**

[00187] To a solution of 5-methoxy-1-methyl-1H-indol-2-yl-2-boronic acid (243 mg, 1.19 mmol, 1.2 equiv) in acetonitrile (9.88 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (276 mg, 0.988 mmol, 1.0 equiv), palladium catalyst (72 mg, 0.100 mmol, 0.1 equiv) and sodium carbonate (9.88 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 200 mg of the yellow solid, 65%.

[00188] Preparation of 3-(5-methoxy-1-methyl-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine

[00189] To a solution of 6-chloro-3-(5-methoxy-1-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazine (49 mg, 0.157 mmol, 1.0 equiv), xantphos (18 mg, 0.0313 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0156 mmol, 0.1 equiv), and potassium carbonate (433 mg, 3.13 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (26 mg, 0.172 mmol, 1.1 equiv)

and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 40 mg, 0.152 mmol of the yellow solid, 59%.

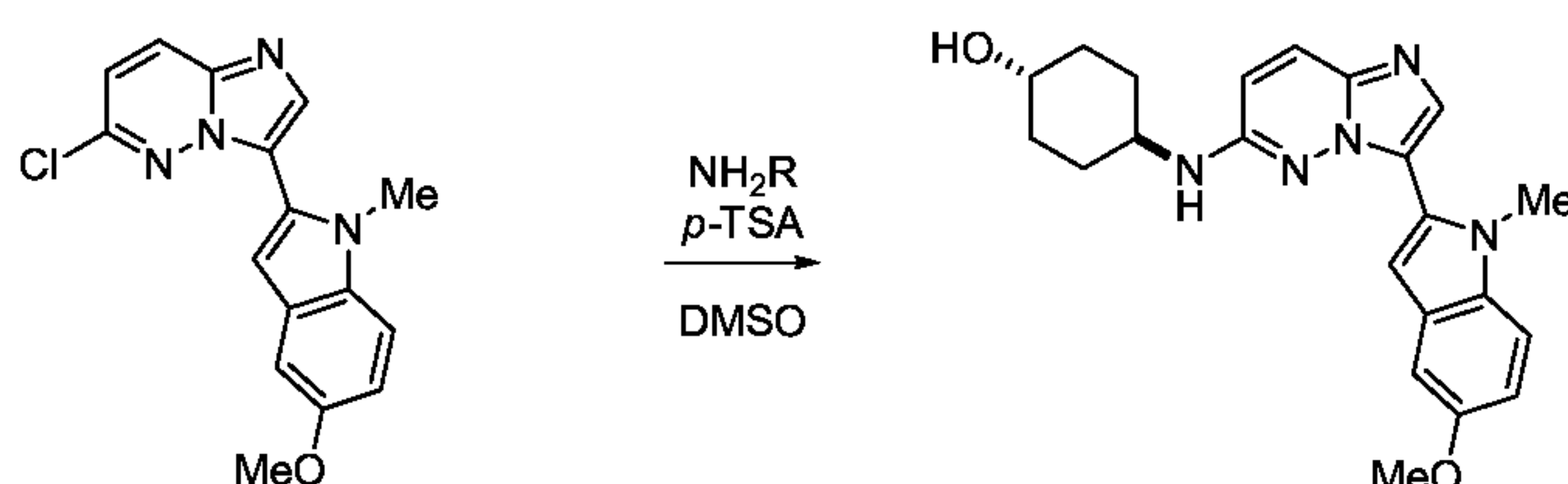
[00190] Compound 193 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table X.

[00191] Table 2C

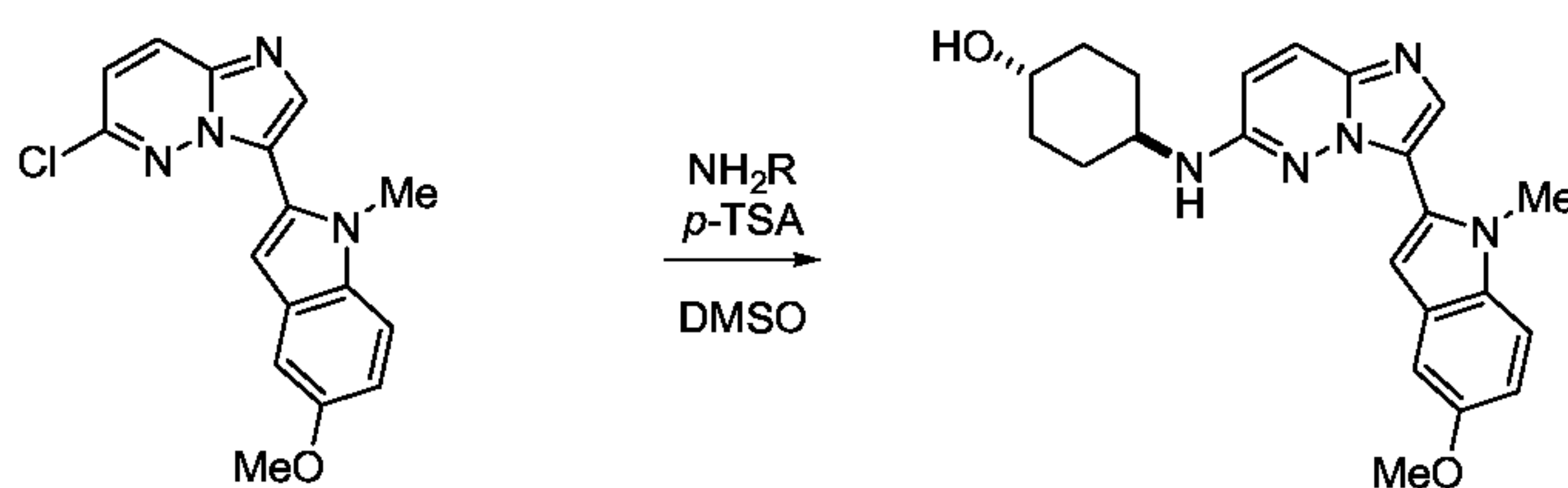
Cd.	Structure	IUPAC Name	[M+H] ⁺
193		3-(5-methoxy-1-methyl-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	430.5

[00192] Example 2D – Synthesis of Compound 194

[00193] Scheme 2D



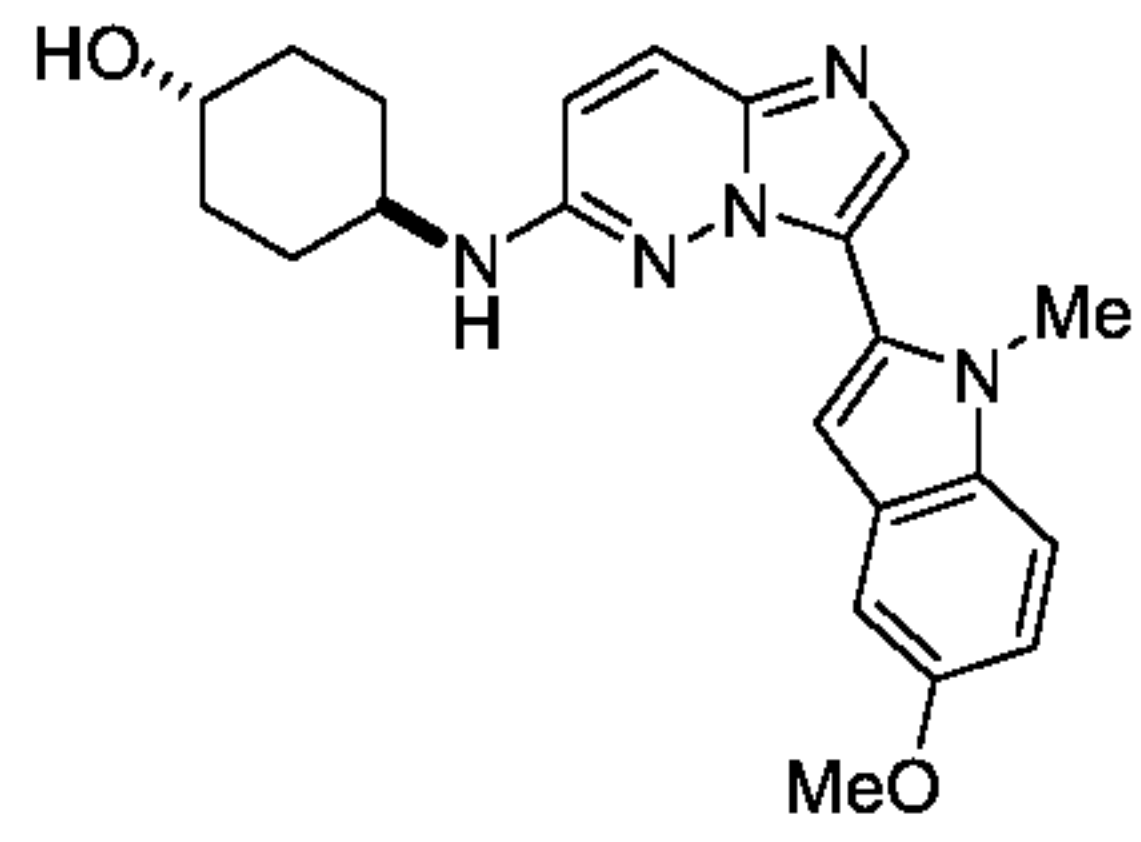
[00194] Preparation of *trans*-4-(3-(5-methoxy-1-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

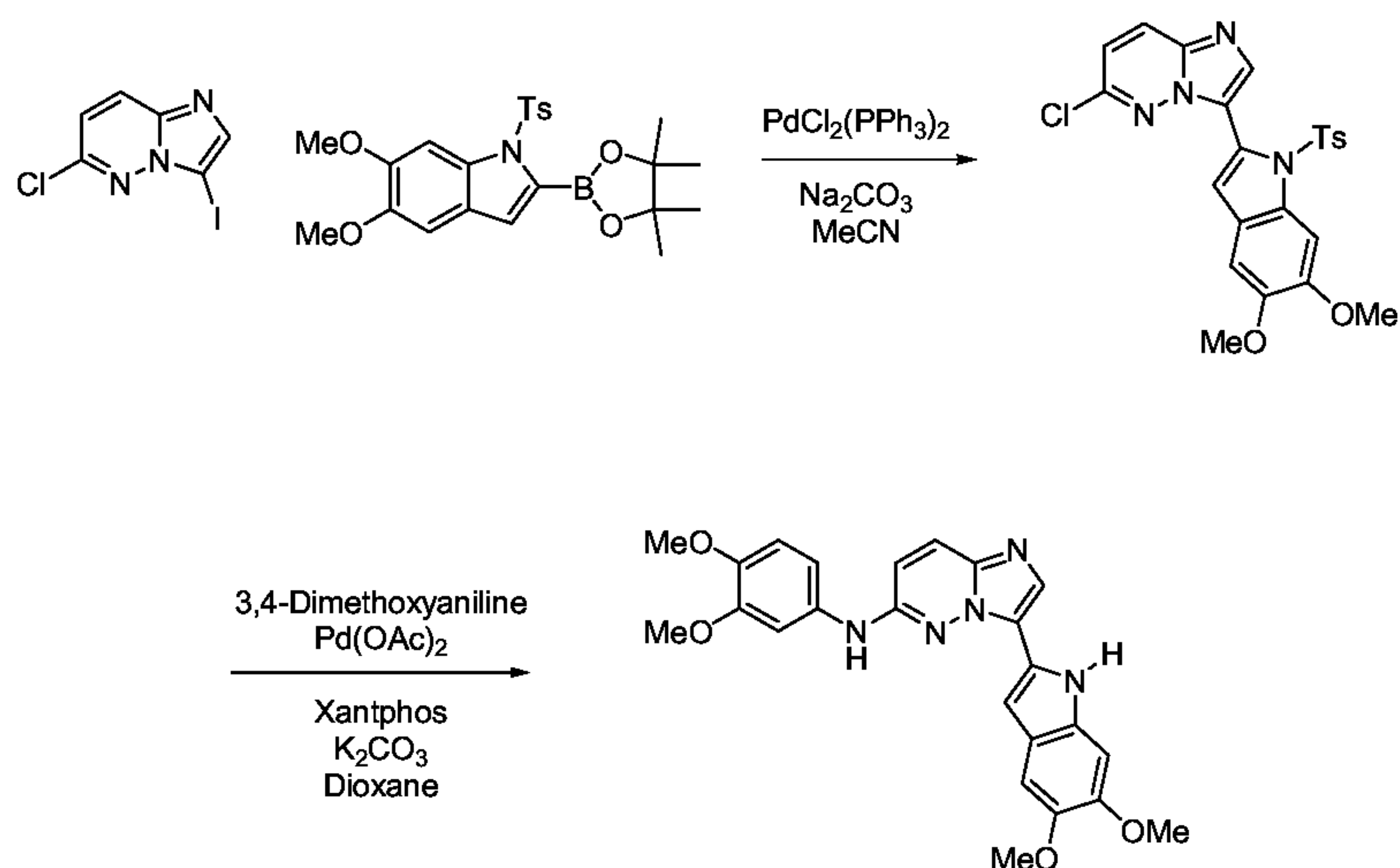
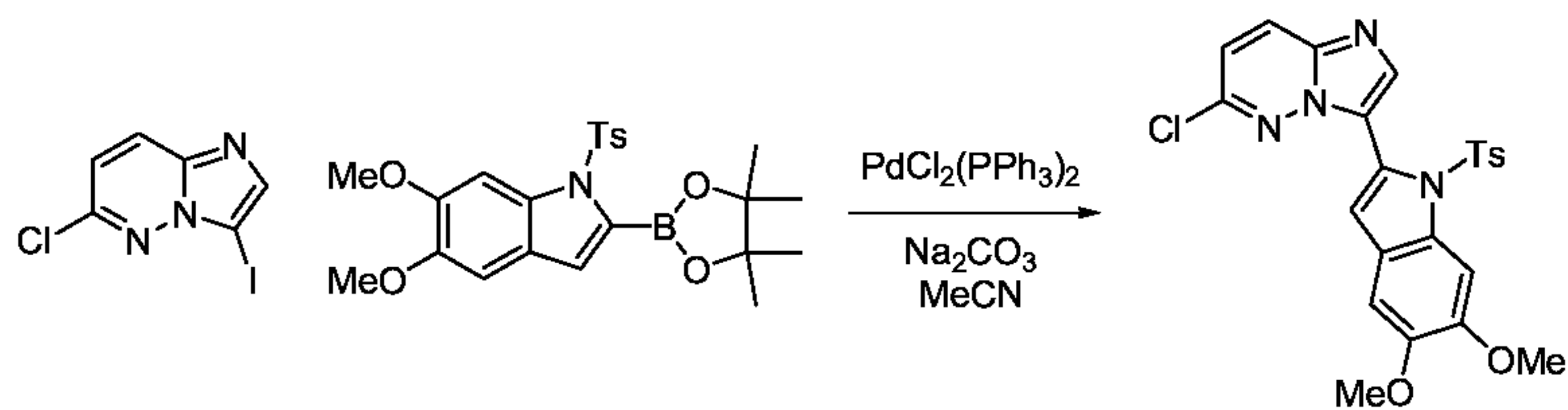


[00195] To a solution of 6-chloro-3-(5-methoxy-1-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.160 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (30 mg, 0.160 mmol, 1.0 equiv) and amine (0.800 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 35 mg of the yellow solid..

[00196] Compound 194 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 2D.

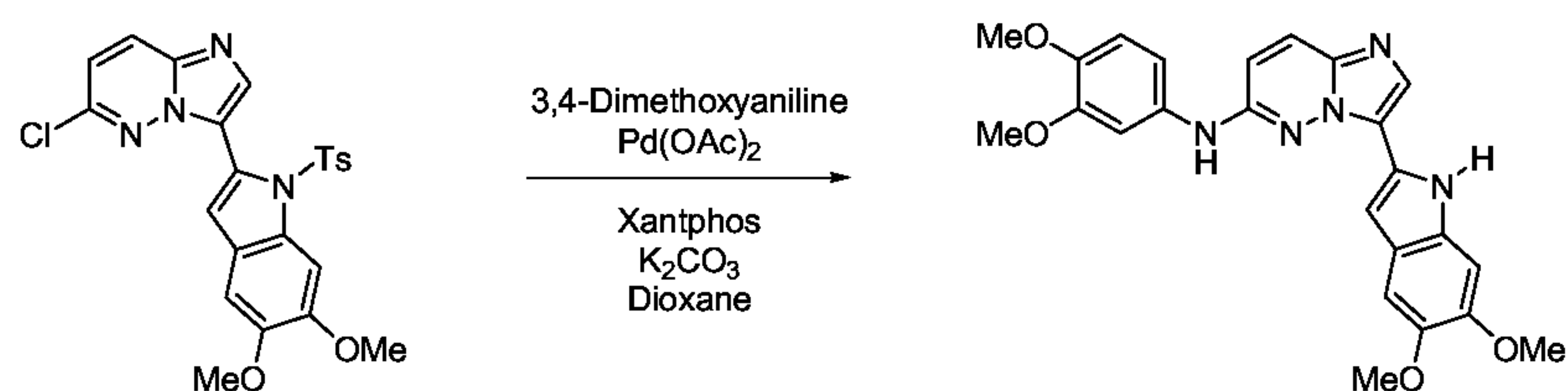
Table 2D.

Cd.	Structure	IUPAC Name	[M+H] ⁺
194		<i>trans</i> -4-(3-(5-methoxy-1-methyl-1H-indol-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	392.3

[00197] Example 2E – Synthesis of Compounds 197[00198] **Scheme 2E**[00199] **Preparation of 6-chloro-3-(5,6-dimethoxy-1-tosyl-1H-indol-2-yl)imidazo[1,2-b]pyridazine**

[00200] To a solution of 5,6-dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-indole (120 mg, 0.262 mmol, 1.0 equiv) in acetonitrile (3.41 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (95 mg, 0.341 mmol, 1.3 equiv), palladium catalyst (25 mg, 0.0341 mmol, 0.1 equiv) and sodium carbonate (3.41 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 80 mg of the yellow solid, 63%.

[00201] **Preparation of 3-(5,6-dimethoxy-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine**



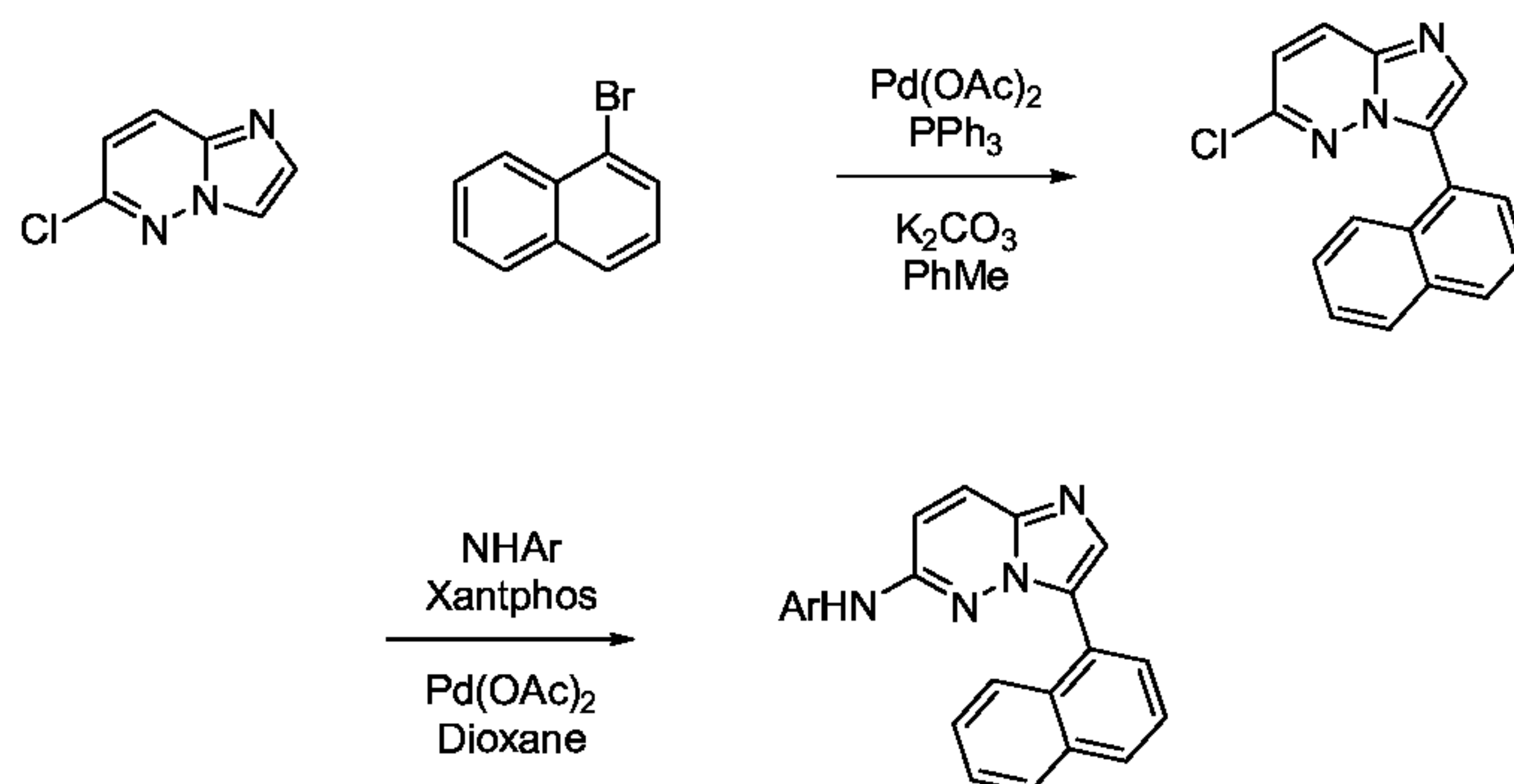
[00202] To a solution of 6-chloro-3-(5,6-dimethoxy-1-tosyl-1H-indol-2-yl)imidazo[1,2-b]pyridazine (68 mg, 0.141 mmol, 1.0 equiv), xantphos (16 mg, 0.0282 mmol, 0.2 equiv), palladium acetate (3 mg, 0.0141 mmol, 0.1 equiv), and potassium carbonate (389 mg, 2.82 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (24 mg, 0.155 mmol, 1.1 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 20 mg of the yellow solid. .

[00203] Table 2E

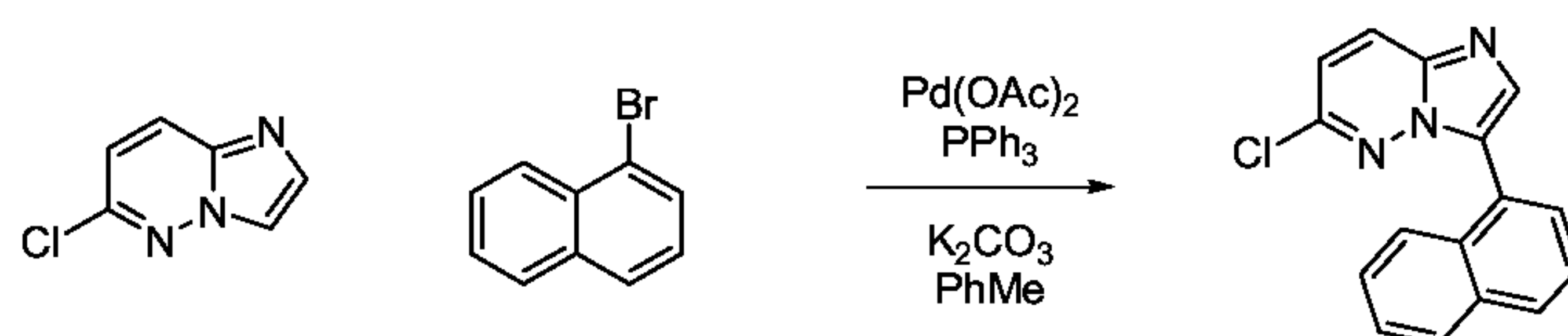
Cd.	Structure	IUPAC Name	[M+H] ⁺
197		3-(5,6-dimethoxy-1H-indol-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	446.5

[00204] Example 3 – Synthesis of Compounds 6-7

[00205] Scheme 3



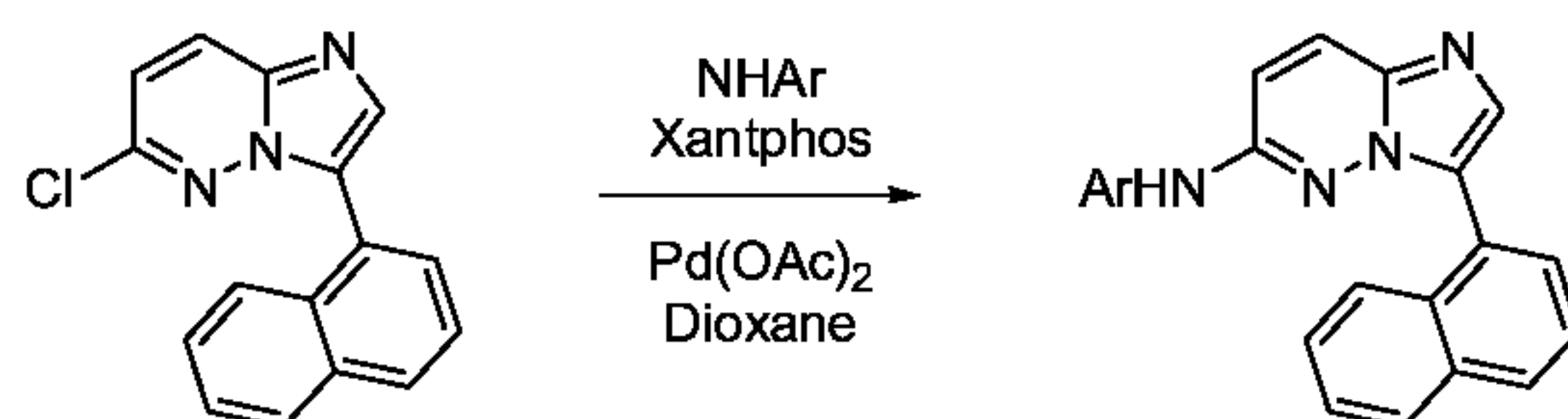
[00206] Preparation of 6-chloro-3-(naphthalen-1-yl)imidazo[1,2-b]pyridazine



[00207] To a stirred solution of 6-chloroimidazo[1,2-b]pyridazine (1.55 g, 10.1 mmol) in 10.0 mL of toluene was added aryl bromide (2.11 mL, 15.1 mmol, 1.5 equiv), potassium carbonate (2.79 g, 18.2 mmol, 2.0 equiv), triphenylphosphine (529 mg, 2.02 mmol, 0.2 equiv) and

palladium acetate (227 mg, 1.01 mmol, 0.1 equiv). The solution was stirred to reflux for 24 h. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 43% of the yellow solid.

[00208] Preparation of 3-(naphthalen-1-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine



[00209] To a solution of 6-chloro-3-(naphthalen-1-yl)imidazo[1,2-b]pyridazine (50 mg, 0.179 mmol, 1.0 equiv), xantphos (21 mg, 0.0358 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0179 mmol, 0.1 equiv), and potassium carbonate (495 mg, 3.58 mmol, 20 equiv) in dioxane (5.0 mL) was added amine (0.179 mmol, 1.0 equiv) and heated to 100 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

Table 3-a

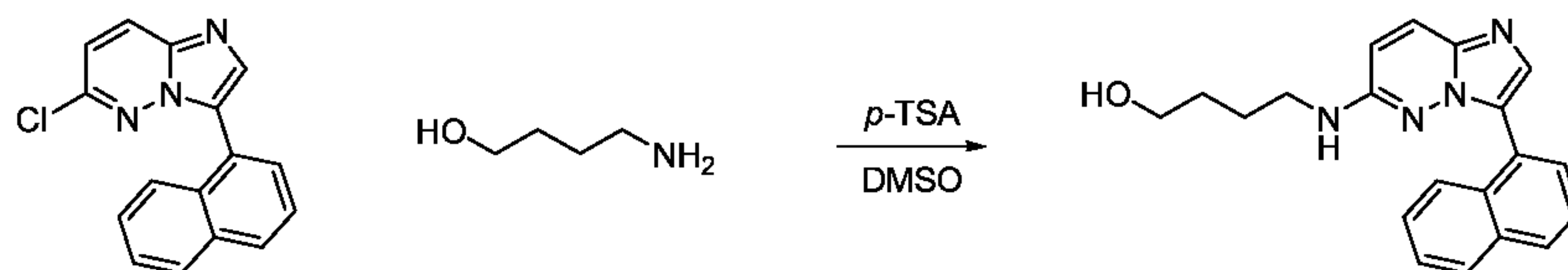
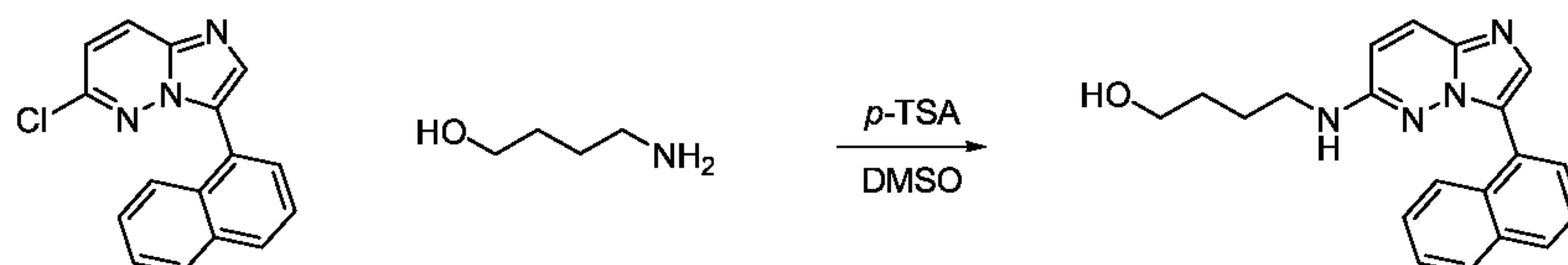
Cd.	Amine	Purified Compound Isolated
6	3,4-dimethoxyaniline	N-(3,4-dimethoxyphenyl)-3-(naphthalen-1-yl)imidazo[1,2-b]pyridazin-6-amine
7	3-aminobenzoic acid	3-(3-(naphthalen-1-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid

[00210] Compounds 6-7 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 3-b**.

Table 3-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
6		N-(3,4-dimethoxyphenyl)-3-(naphthalen-1-yl)imidazo[1,2-b]pyridazin-6-amine	397.7
7		3-(3-(naphthalen-1-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid	381.8

[00211] Example 4 – Synthesis of Compound 89

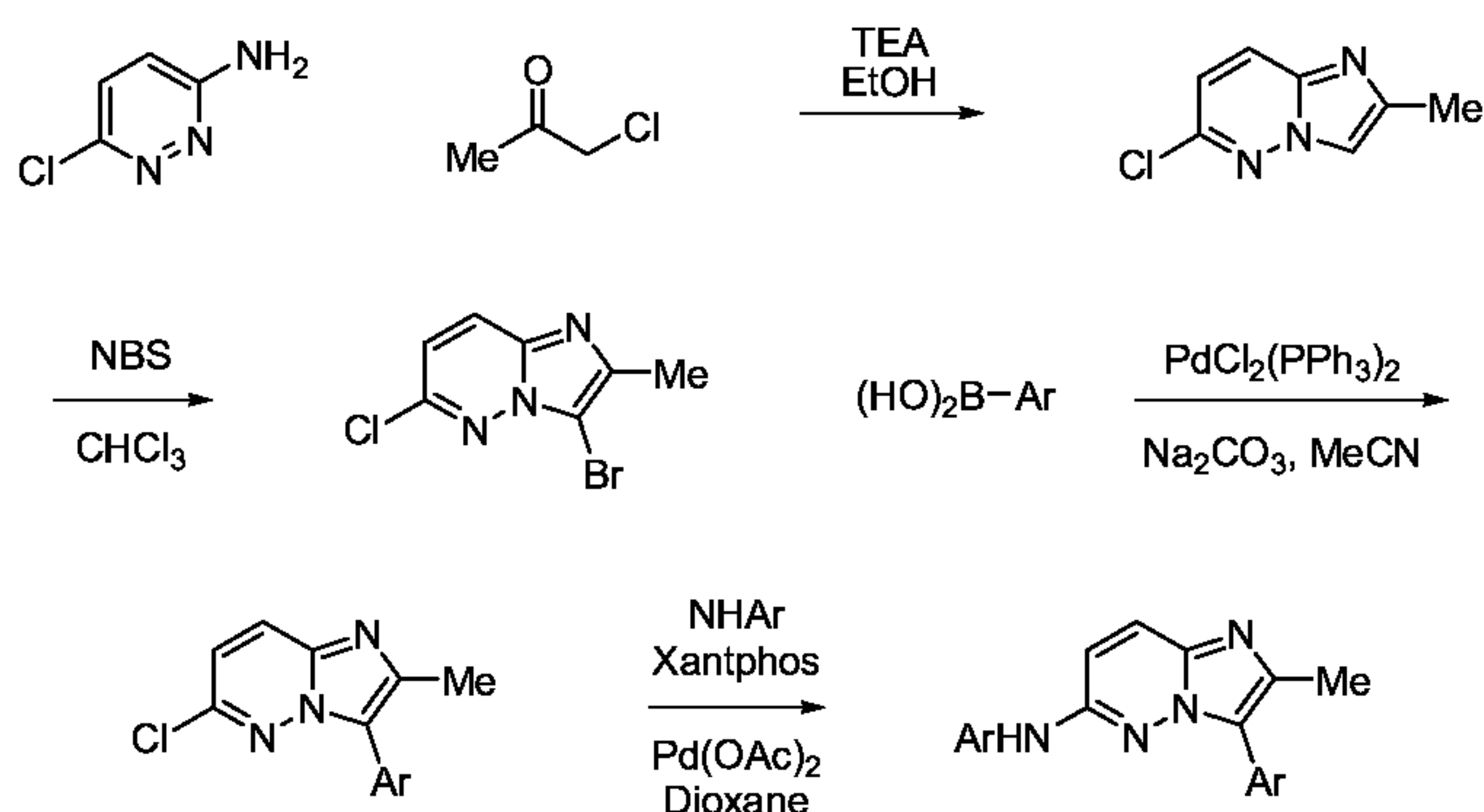
[00212] Scheme 4**[00213] Preparation of 4-(3-(naphthalen-1-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol**

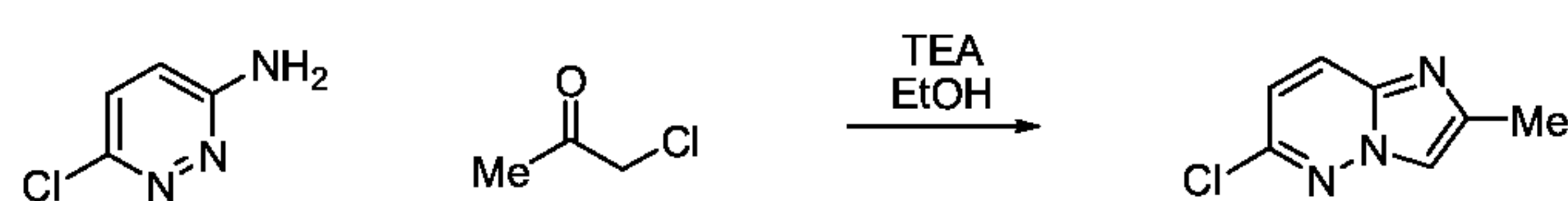
[00214] To a solution of 6-chloro-3-(naphthalen-1-yl)imidazo[1,2-b]pyridazine (50 mg, 0.179 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (35 mg, 0.184 mmol, 1.0 equiv) and 4-aminobutan-1-ol (200 mg, 2.24 mmol, 12.5 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 30 mg of a white solid, 50%.

[00215] Compound 89 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 4-b**.

Table 4-b

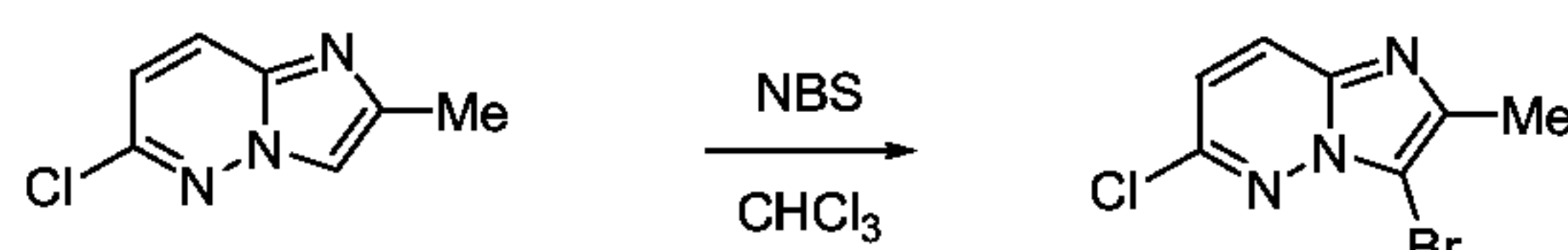
Cd.	Structure	IUPAC Name	[M+H] ⁺
89		4-(3-(naphthalen-1-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol	333.7

[00216] Example 5 – Synthesis of Compounds 8, 17-21**[00217] Scheme 5****[00218] Preparation of 6-chloro-2-methylimidazo[1,2-b]pyridazine**



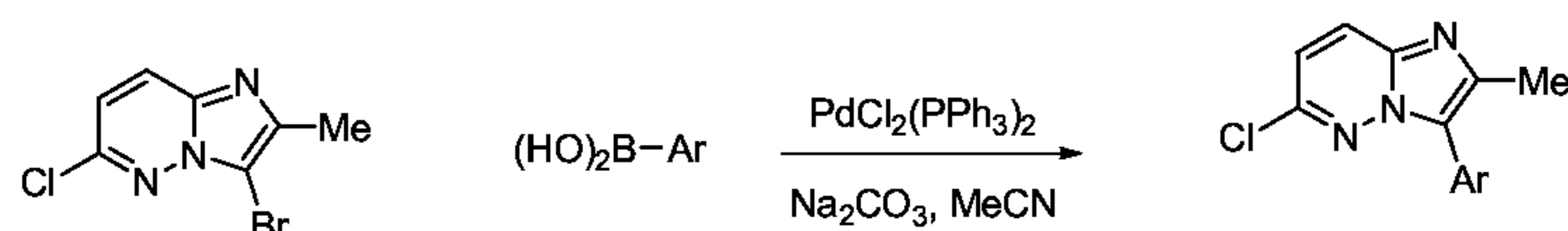
[00219] To a solution of 6-chloropyridazin-3-amine (2.35 g, 18.1 mmol, 1.0 equiv) in ethanol (15 mL) was added 1-chloropropan-2-one (2.92 mL, 36.3 mmol, 2.0 equiv) and triethylamine (2.53 mL, 18.1 mmol, 1.0 equiv). The solution was heated at 150 °C for 30 min then quenched with water. Purification by column chromatography using 30% ethyl acetate in hexanes elution gave 2.43 g of the brown solid, 80%.

[00220] Preparation of 3-bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine



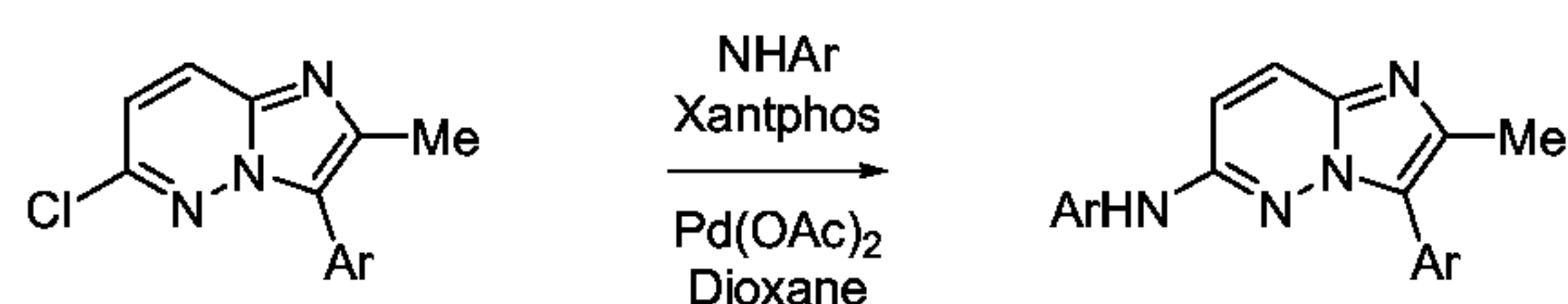
[00221] To a solution of 6-chloro-2-methylimidazo[1,2-b]pyridazine (2.00 g, 11.9 mmol, 1.0 equiv) in chloroform (50 mL) was added *N*-bromosuccinimide (2.55 g, 14.3 mmol, 1.2 equiv). The reaction was stirred at room temperature for 15 h. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 2.64 g of the yellow solid, 90%.

[00222] Preparation of 6-chloro-2-methyl-3-arylimidazo[1,2-b]pyridazine



[00223] To a solution of 3-bromo-6-chloro-2-methylimidazo[1,2-b]pyridazine (865 mg, 5.16 mmol, 1.0 equiv) in acetonitrile (15 mL) was added boronic acid (5.16 mmol, 1.0 equiv), bis(triphenylphosphine)palladium(II) dichloride (0.516 mmol, 0.1 equiv), then sodium carbonate (1.0 M aqueous solution, 10 equiv). The reaction mixture was irradiated in the microwave at 150 °C for 10 min. Purification by column chromatography gave of the product.

[00224] Preparation of 2-methyl-N,3-bisarylimidazo[1,2-b]pyridazin-6-amine



[00225] To a solution of 6-chloro-2-methyl-3-arylimidazo[1,2-b]pyridazine (100 mg, 0.33 mmol, 1.0 equiv), xantphos (39 mg, 0.07 mmol, 0.2 equiv), palladium acetate (7 mg, 0.03 mmol, 0.1 equiv), and potassium carbonate (922 mg, 6.67 mmol, 20 equiv) in dioxane (5.0 mL) was added amine (0.367 mmol, 1.1 equiv) and heated to 100 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

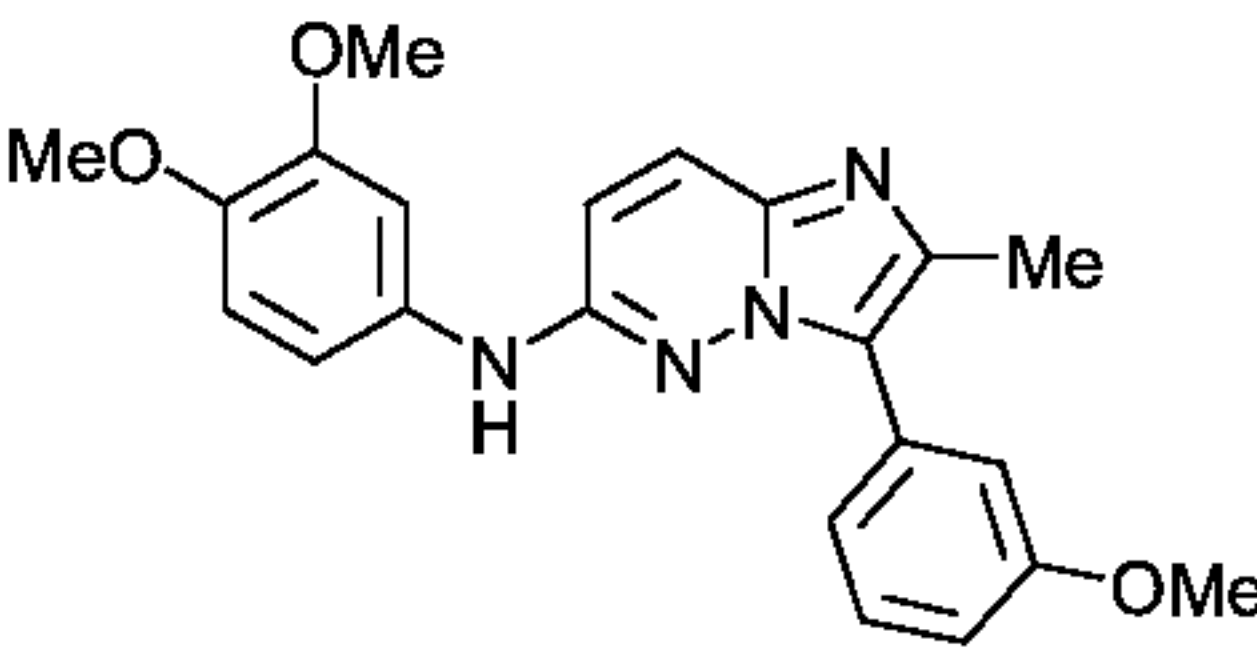
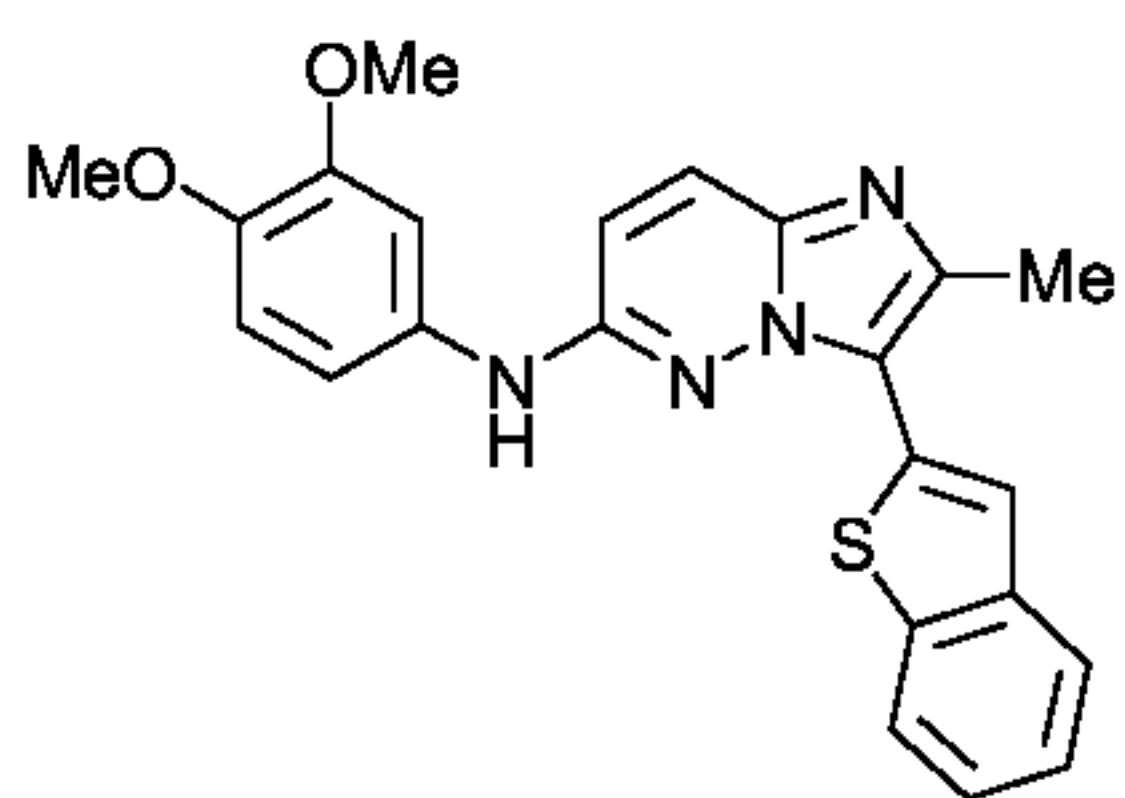
Table 5-a

Cd.	Boronic Acid	Amine	Purified Compound Isolated
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8	3-methoxyphenylboronic acid	3,4-dimethoxyaniline	N-(3,4-dimethoxyphenyl)-3-(3-methoxyphenyl)-2-methylimidazo[1,2-b]pyridazin-6-amine
17	benzo[b]thiophen-2-yl-2-boronic acid	3,4-dimethoxyaniline	3-(benzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)-2-methylimidazo[1,2-b]pyridazin-6-amine
18	benzo[b]thiophen-2-yl-2-boronic acid	3-(4-methylpiperazin-1-yl)benzenamine	3-(benzo[b]thiophen-2-yl)-2-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine
19	benzo[b]thiophen-2-yl-2-boronic acid	4-(4-methylpiperazin-1-yl)benzenamine	3-(benzo[b]thiophen-2-yl)-2-methyl-N-(4-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine
20	benzo[b]thiophen-2-yl-2-boronic acid	3-((4-methylpiperazin-1-yl)methyl)benzenamine	3-(benzo[b]thiophen-2-yl)-2-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine
21	benzo[b]thiophen-2-yl-2-boronic acid	4-((4-methylpiperazin-1-yl)methyl)benzenamine	3-(benzo[b]thiophen-2-yl)-2-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine

[00226] Compounds 8, 17-21 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 5-b**.

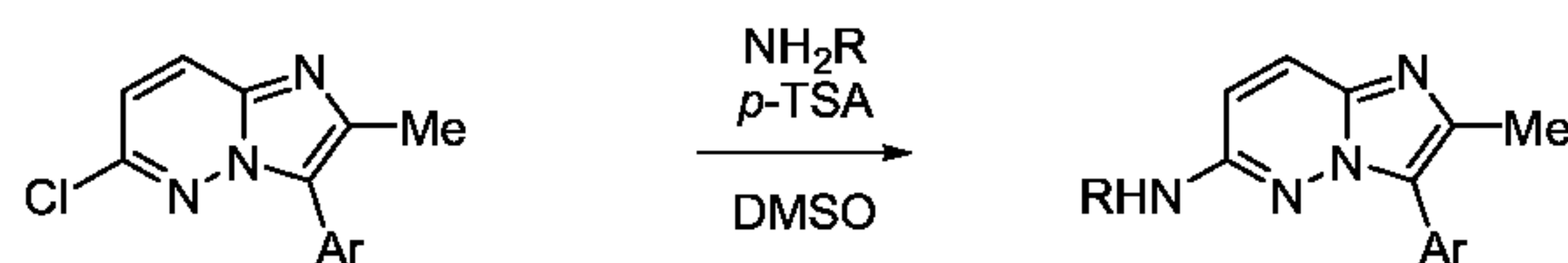
Table 5-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
8		N-(3,4-dimethoxyphenyl)-3-(3-methoxyphenyl)-2-methylimidazo[1,2-b]pyridazin-6-amine	391.7
17		3-(benzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)-2-methylimidazo[1,2-b]pyridazin-6-amine	417.7

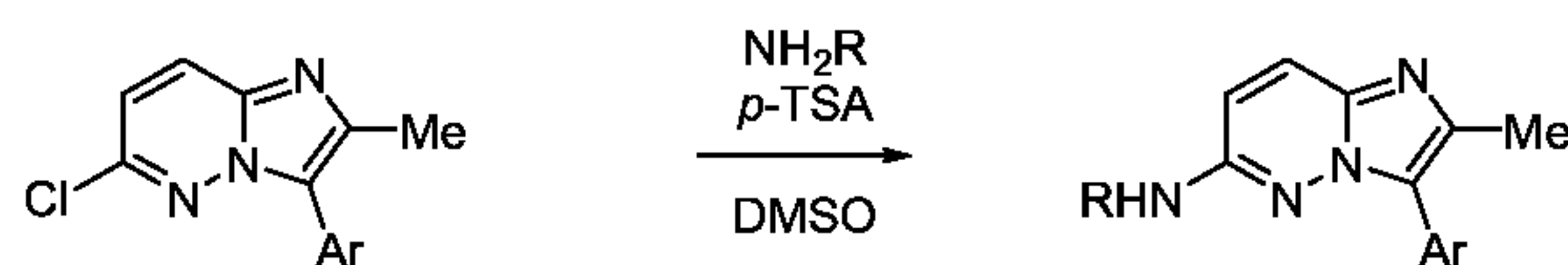
18		3-(benzo[b]thiophen-2-yl)-2-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	455.7
19		3-(benzo[b]thiophen-2-yl)-2-methyl-N-(4-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	455.7
20		3-(benzo[b]thiophen-2-yl)-2-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	469.8
21		3-(benzo[b]thiophen-2-yl)-2-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	469.7

[00227] Example 6 – Synthesis of Compounds 111-112, 114-115

[00228] **Scheme 6**



[00229] **Preparation of N-alkyl-2-methyl-3-arylimidazo[1,2-b]pyridazin-6-amine**



[00230] To a solution of 6-chloro-2-methyl-3-arylimidazo[1,2-b]pyridazine (150 mg, 0.500 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (95 mg, 0.500 mmol, 1.0 equiv) and amine (1.95 mmol, 4.0 equiv) and heated to 100 °C for 24 h. The

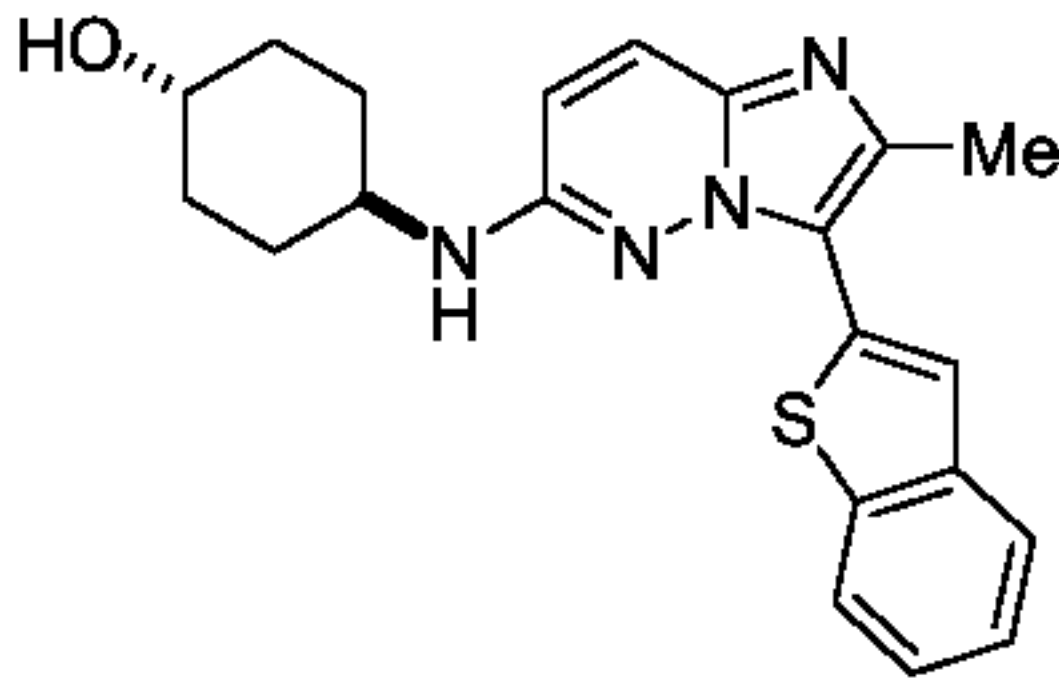
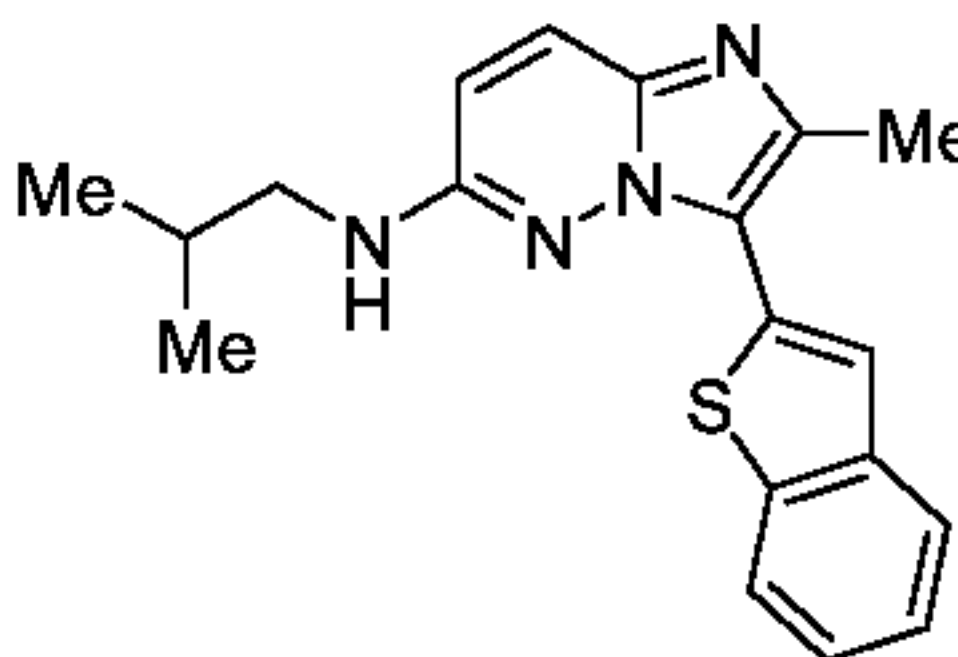
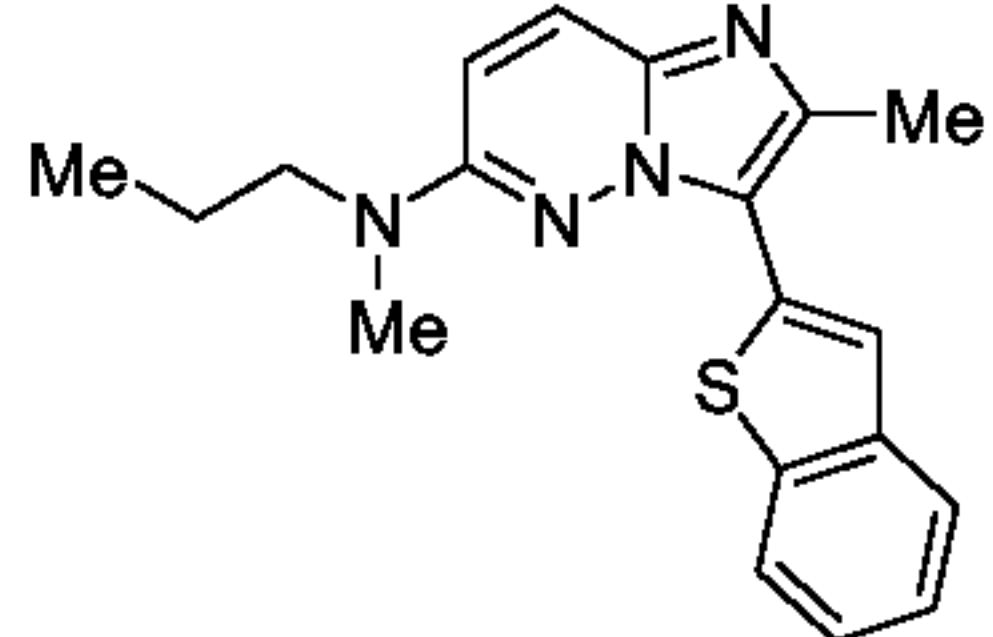
reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave the product.

Table 6-a

Cd.	Boronic Acid	Amine	Purified Compound Isolated
111	benzo[b]thiophen-2-yl-2-boronic acid	<i>trans</i> -4-aminocyclohexanol	4-(3-(benzo[b]thiophen-2-yl)-2-methylimidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
112	benzo[b]thiophen-2-yl-2-boronic acid	2-methylpropan-1-amine	3-(benzo[b]thiophen-2-yl)-N-isobutyl-2-methylimidazo[1,2-b]pyridazin-6-amine
114	benzo[b]thiophen-2-yl-2-boronic acid	N-methylpropyl-1-amine	3-(benzo[b]thiophen-2-yl)-N,2-dimethyl-N-propylimidazo[1,2-b]pyridazin-6-amine
115	benzo[b]thiophen-2-yl-2-boronic acid	pentan-1-amine	3-(benzo[b]thiophen-2-yl)-2-methyl-N-pentylimidazo[1,2-b]pyridazin-6-amine

[00231] Compounds 111-112, 114-115 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 6-b**.

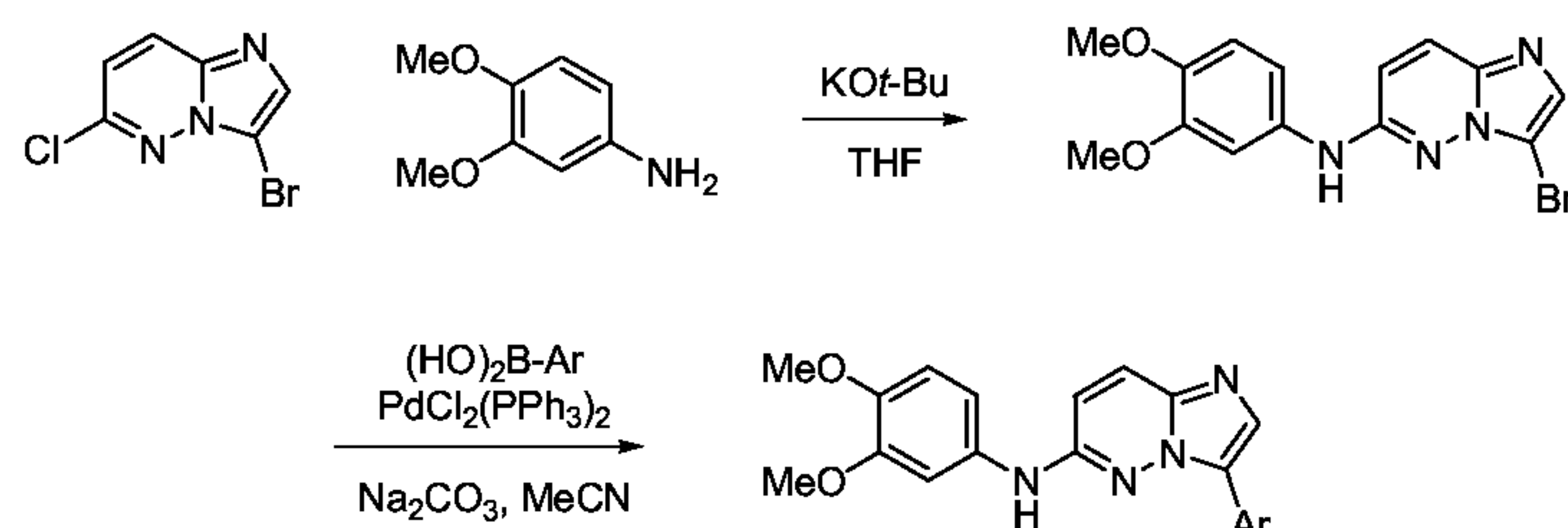
Table 6-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
111		4-(3-(benzo[b]thiophen-2-yl)-2-methylimidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	379.7
112		3-(benzo[b]thiophen-2-yl)-N-isobutyl-2-methylimidazo[1,2-b]pyridazin-6-amine	387.6
114		3-(benzo[b]thiophen-2-yl)-N,2-dimethyl-N-propylimidazo[1,2-b]pyridazin-6-amine	337.7

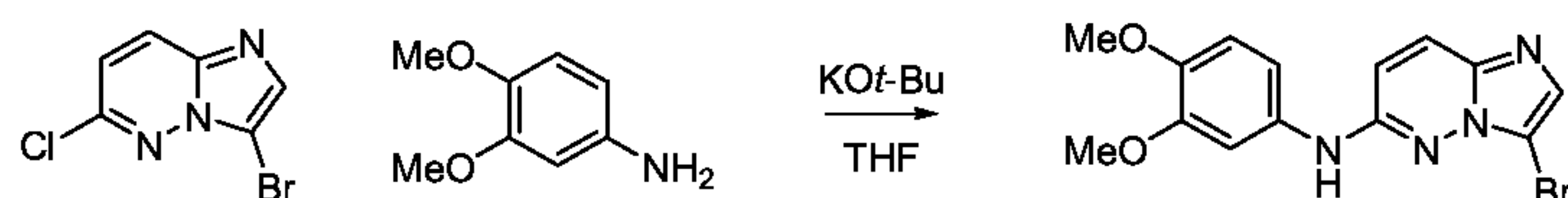
115		3-(benzo[b]thiophen-2-yl)-2-methyl-N-pentylimidazo[1,2-b]pyridazin-6-amine	353.8
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[00232] Example 7 – Synthesis of Compounds 9, 11

[00233] **Scheme 7**

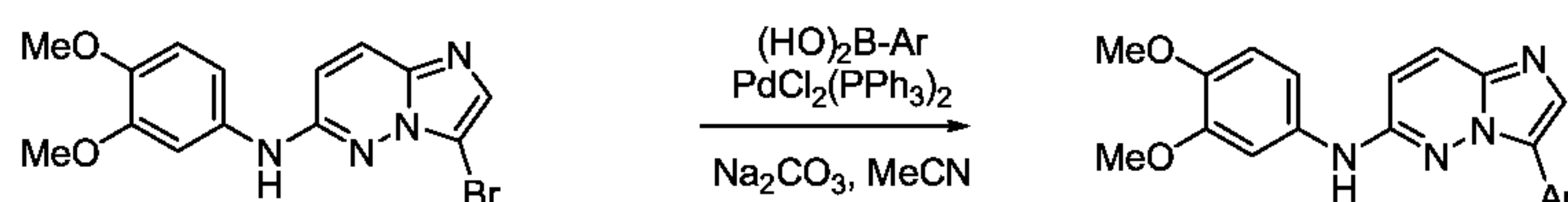


[00234] **Preparation of 3-bromo-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine**



[00235] To a solution of 3,4-dimethoxyaniline (178 mg, 1.16 mmol, 2.0 equiv) in THF (5 mL) was added potassium *tert*-butoxide (131 mg, 1.16 mmol, 2.0 equiv) and heated to 60 °C for 30 min. The reaction mixture was cooled to room temperature then 3-bromo-6-chloroimidazo[1,2-b]pyridazine (135 mg, 0.582 mmol, 1.0 equiv) was added and stirred at room temperature for 15 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 102 mg of the dark brown solid, 50%.

[00236] **Preparation of N-(3,4-dimethoxyphenyl)-3-arylimidazo[1,2-b]pyridazin-6-amine**



[00237] To a solution of 3-bromo-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine (45 mg, 0.129 mmol, 1.0 equiv) in acetonitrile (1.30 mL) was added boronic acid (0.193 mmol, 1.5 equiv), bis(triphenylphosphine)palladium(II) dichloride (0.013 mmol, 0.1 equiv), then sodium carbonate (1.0 M aqueous solution, 10 equiv). The reaction mixture was irradiated in the microwave at 150 °C for 10 min. Purification by column chromatography gave of the product.

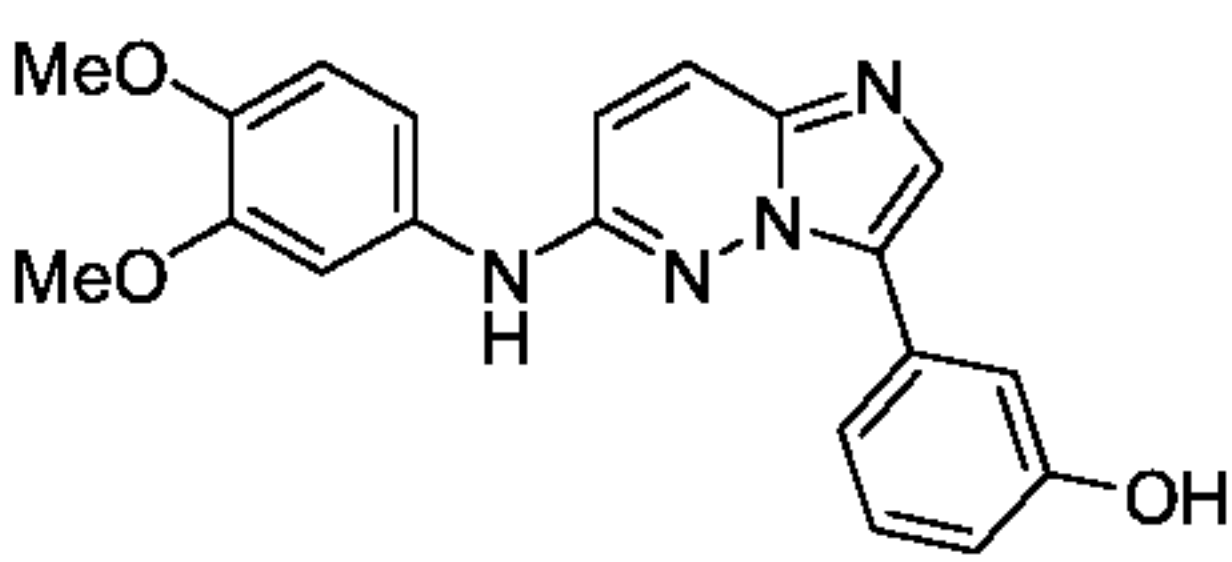
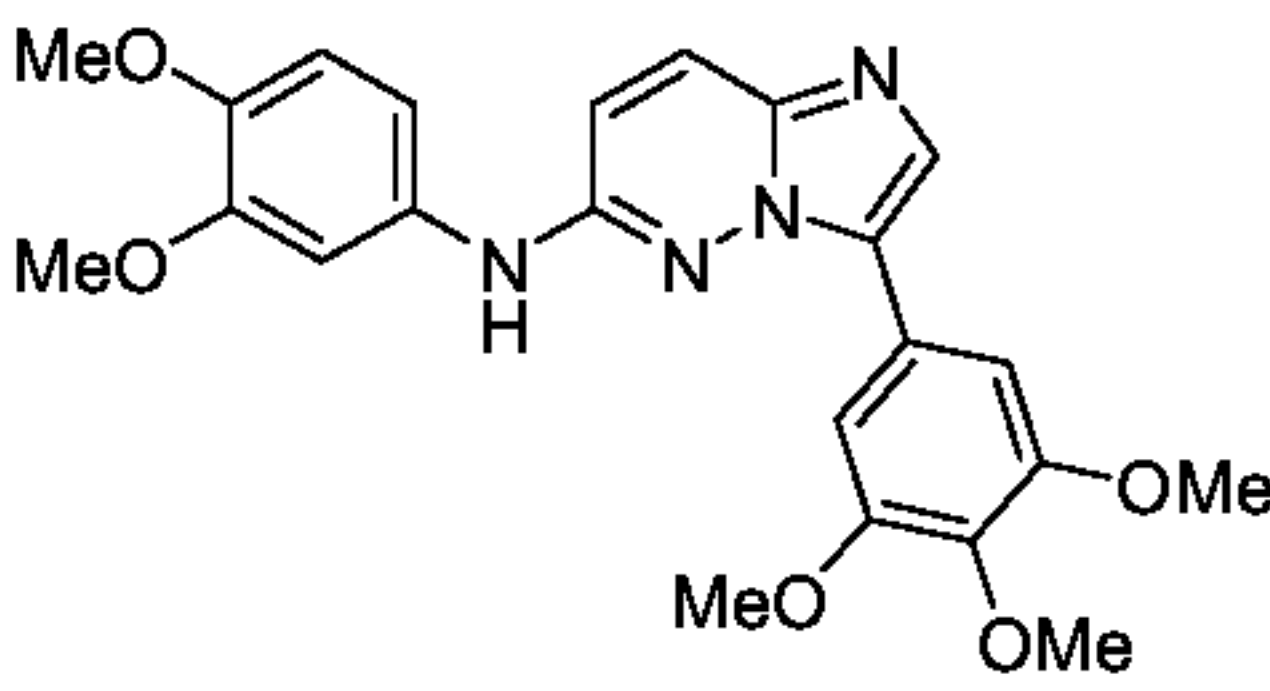
Table 7-a

Cd.	Boronic Acid	Purified Compound Isolated
9	3-hydroxyphenylboronic acid	3-(6-(3,4-

		dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)phenol
11	3,4,5-trimethoxyphenylboronic acid	3-(3,4,5-trimethoxyphenyl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine

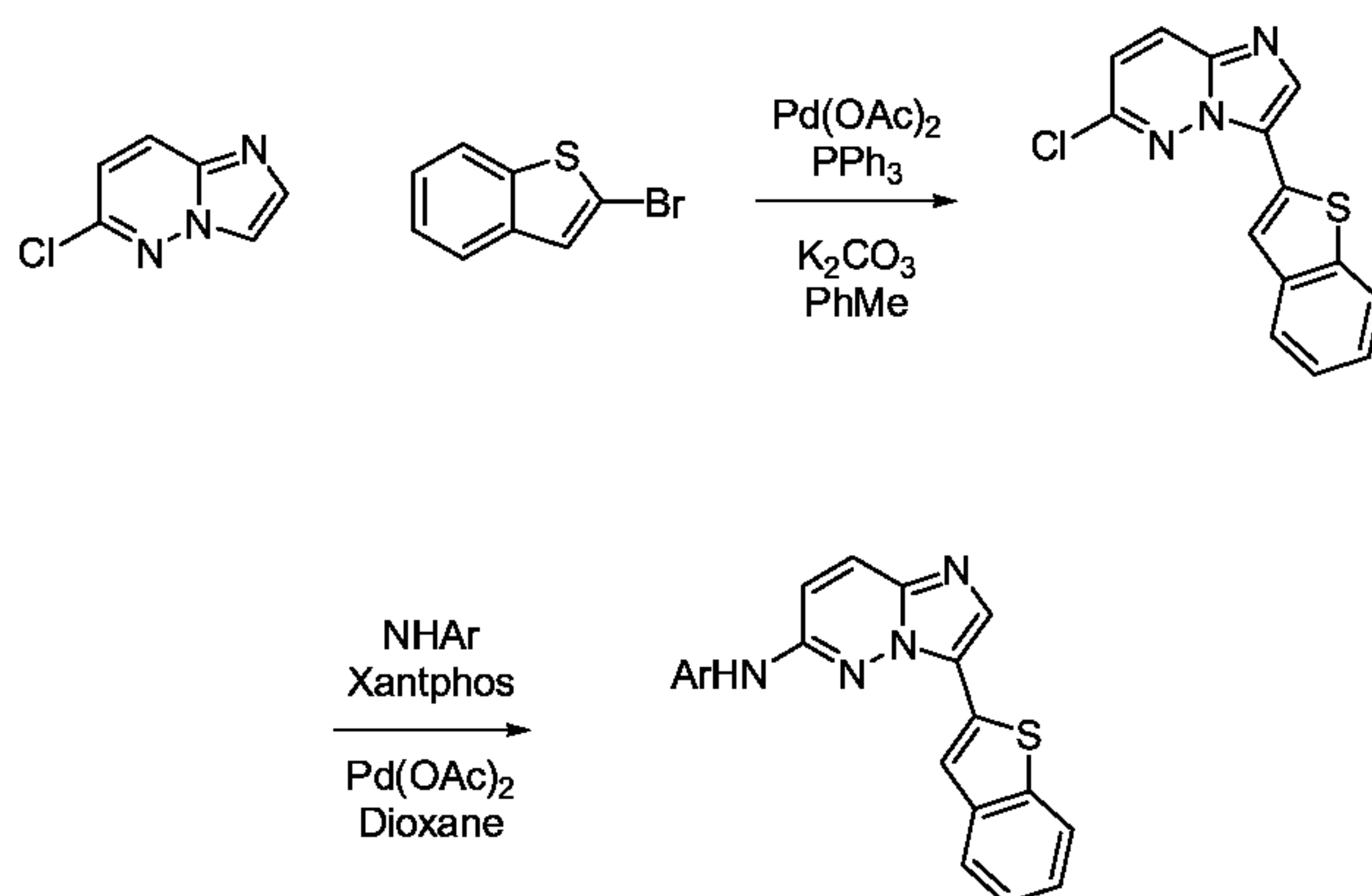
[00238] Compounds 9, 11 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 7-b**.

Table 7-b

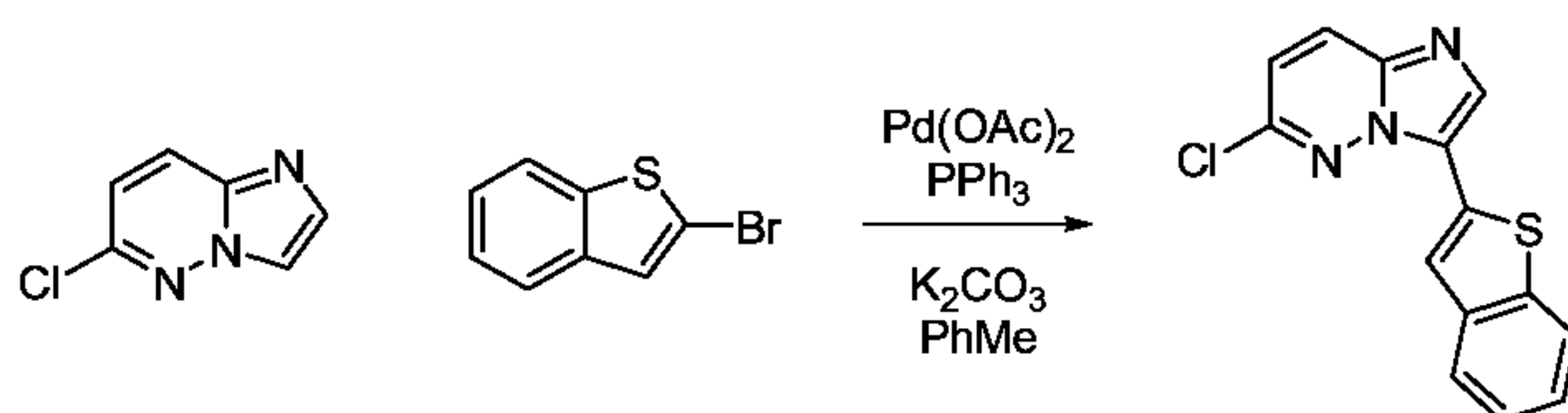
Cd.	Structure	IUPAC Name	[M+H] ⁺
9		3-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)phenol	363.9
11		3-(3,4,5-trimethoxyphenyl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	437.4

[00239] Example 8 – Synthesis of Compounds 12-16, 22-38, 41-45, 47-48

[00240] **Scheme 8**

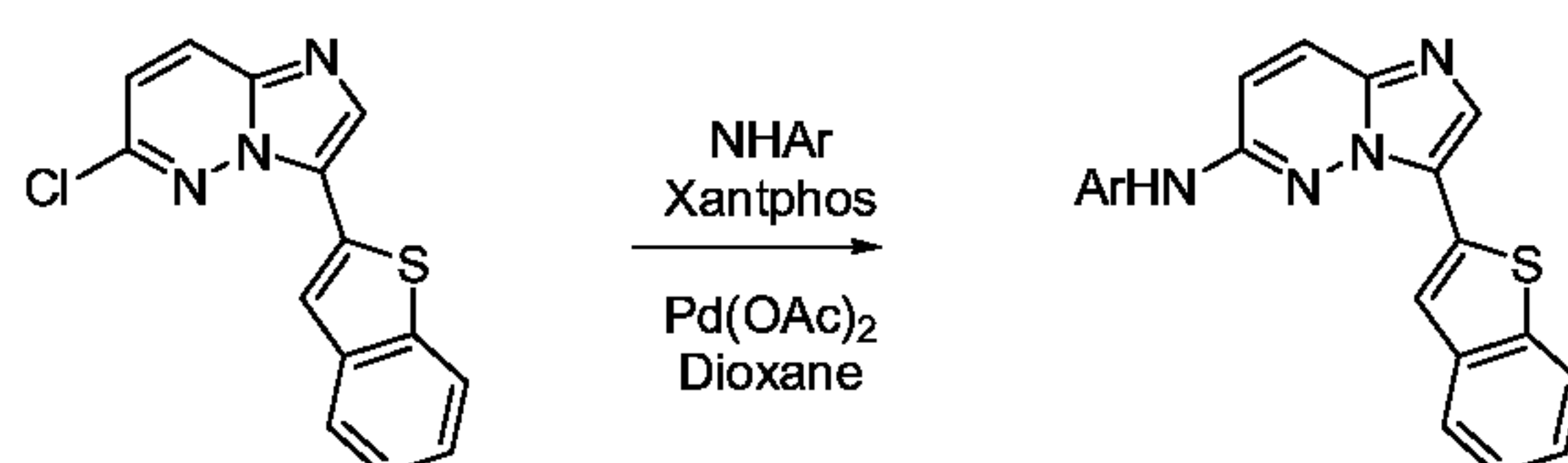


[00241] **Preparation of 3-(benzo[b]thiophen-2-yl)-6-chloroimidazo[1,2-b]pyridazine**



[00242] To a stirred solution of 6-chloroimidazo[1,2-b]pyridazine (1.59 g, 10.3 mmol, 1.1 equiv) in 28.0 mL of toluene was added 2-bromobenzo[b]thiophene (2.00 g, 9.38 mmol, 1.0 equiv), potassium carbonate (2.59 g, 18.8 mmol, 2.0 equiv), triphenylphosphine (592 mg, 1.88 mmol, 0.2 equiv) and palladium acetate (211 mg, 0.938 mmol, 0.1 equiv). The solution was stirred to reflux for 24 h. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 1.50 g of the yellow solid, 56%.

[00243] Preparation of 3-(benzo[b]thiophen-2-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine



[00244] To a solution of 6-chloro-2-methyl-3-arylimidazo[1,2-b]pyridazine (100 mg, 0.33 mmol, 1.0 equiv), xantphos (39 mg, 0.07 mmol, 0.2 equiv), palladium acetate (7 mg, 0.03 mmol, 0.1 equiv), and potassium carbonate (922 mg, 6.67 mmol, 20 equiv) in dioxane (5.0 mL) was added amine (0.367 mmol, 1.1 equiv) and heated to 100 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

Table 8-a

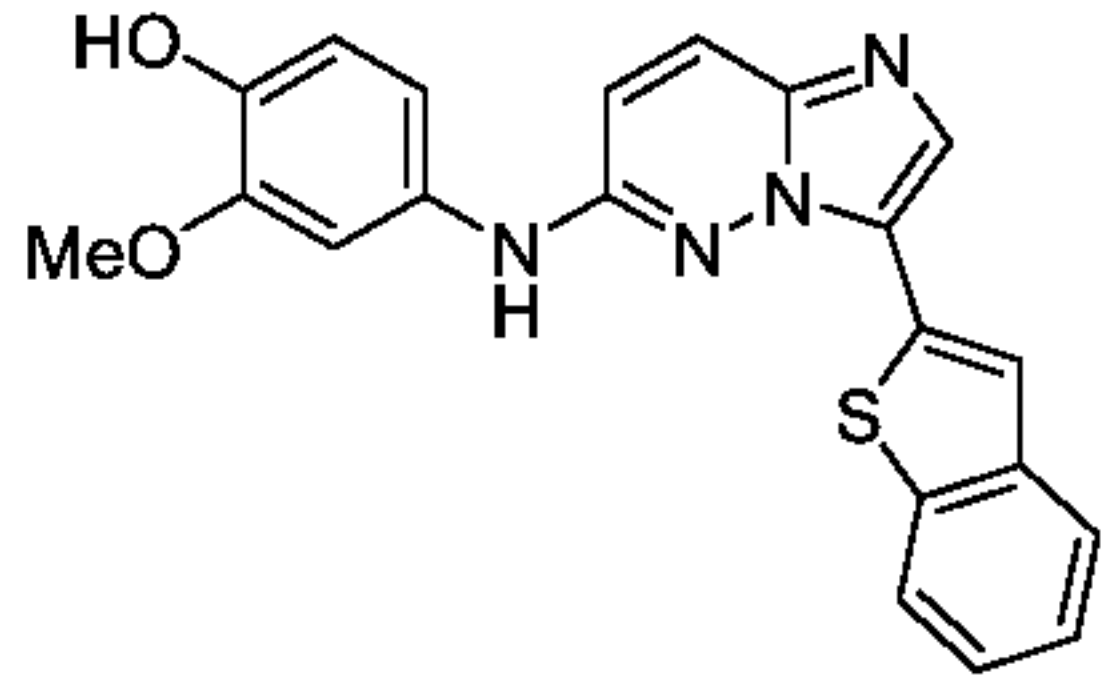
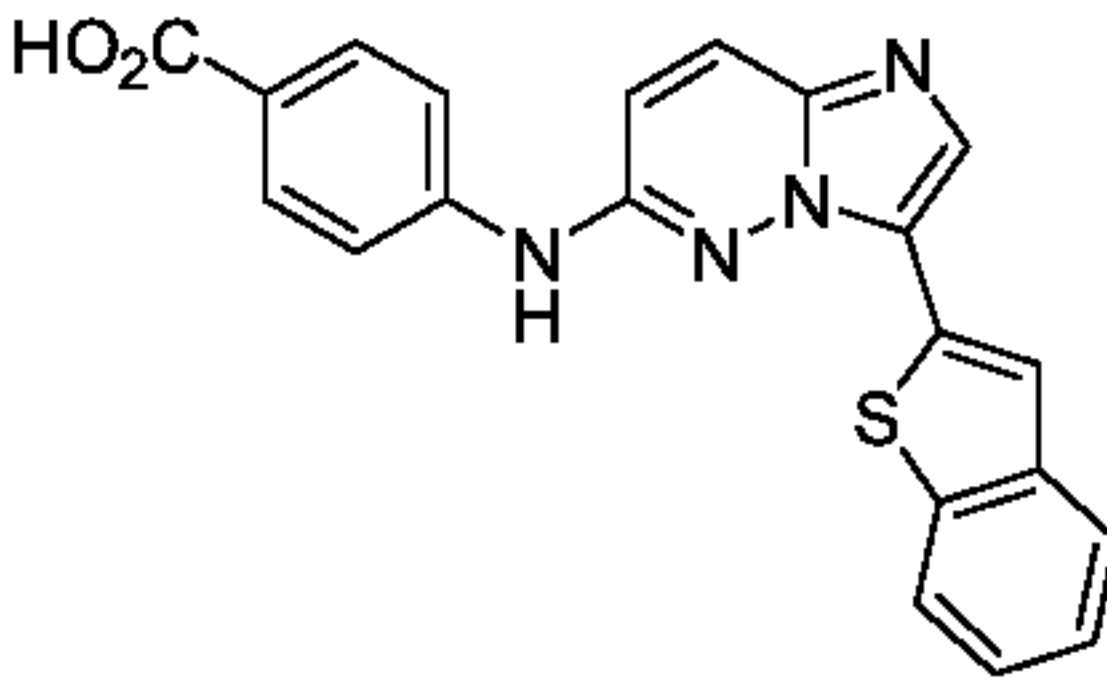
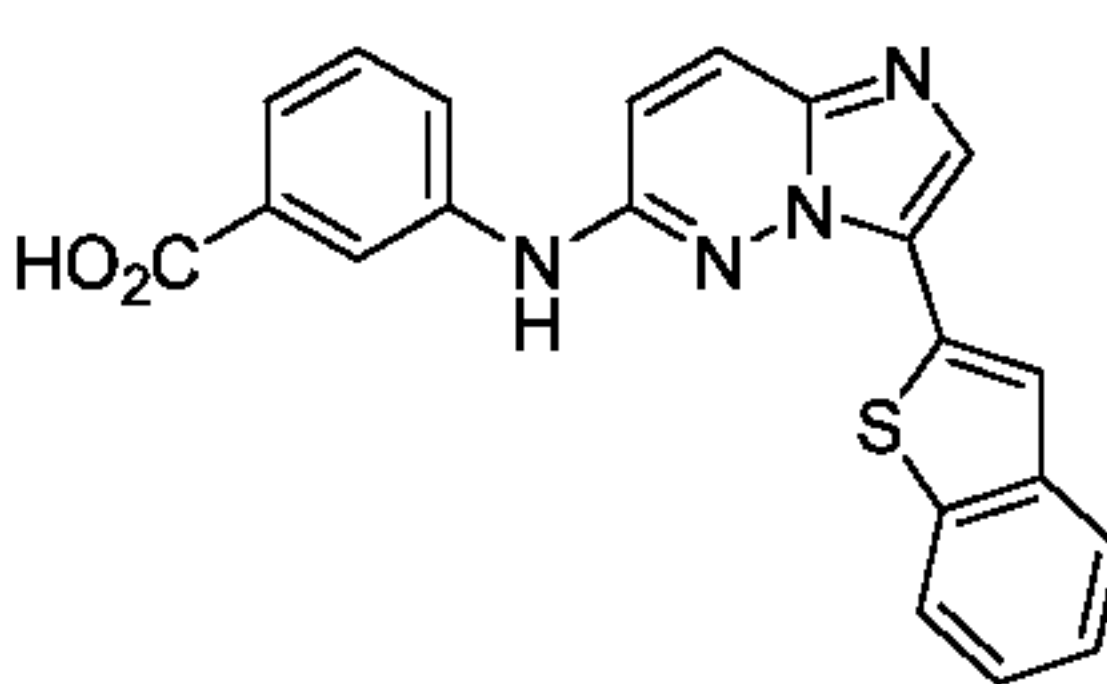
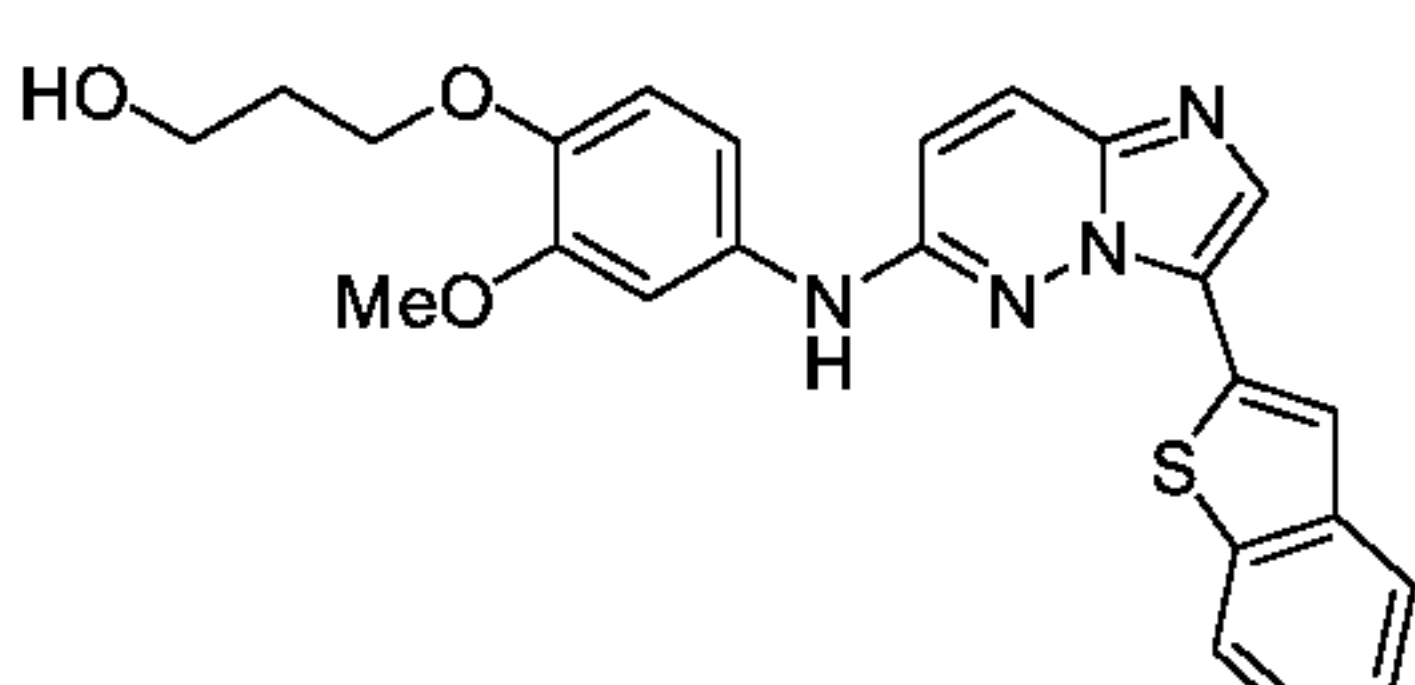
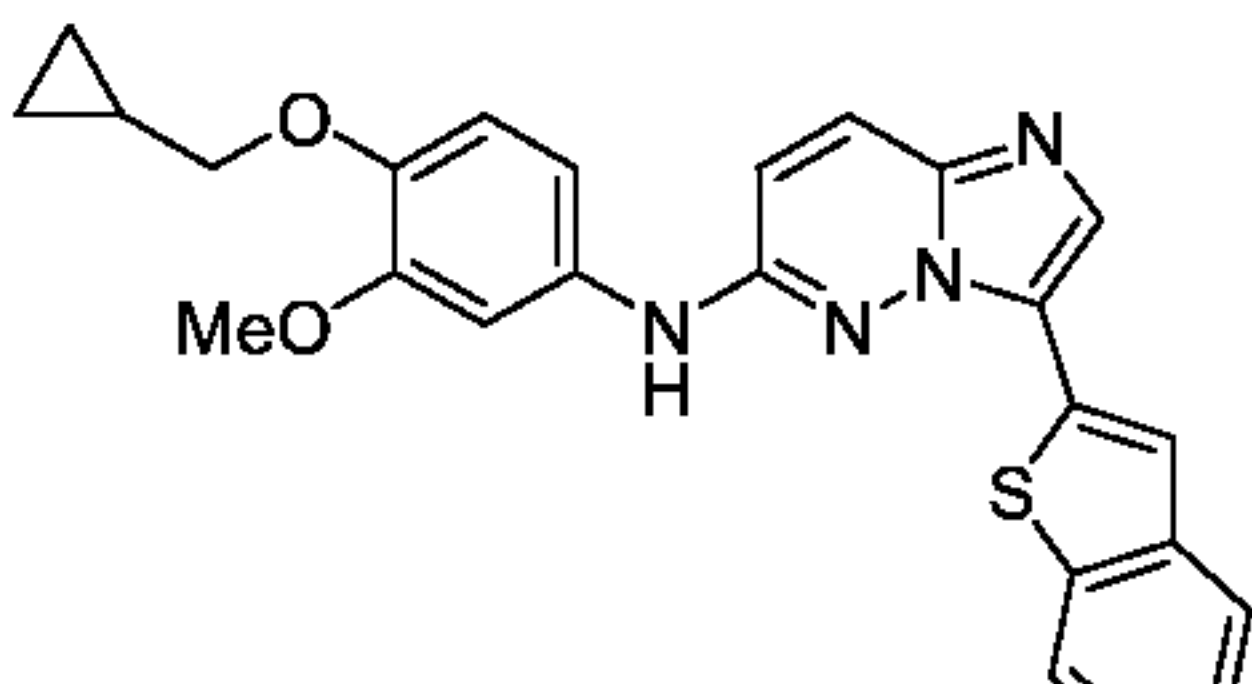
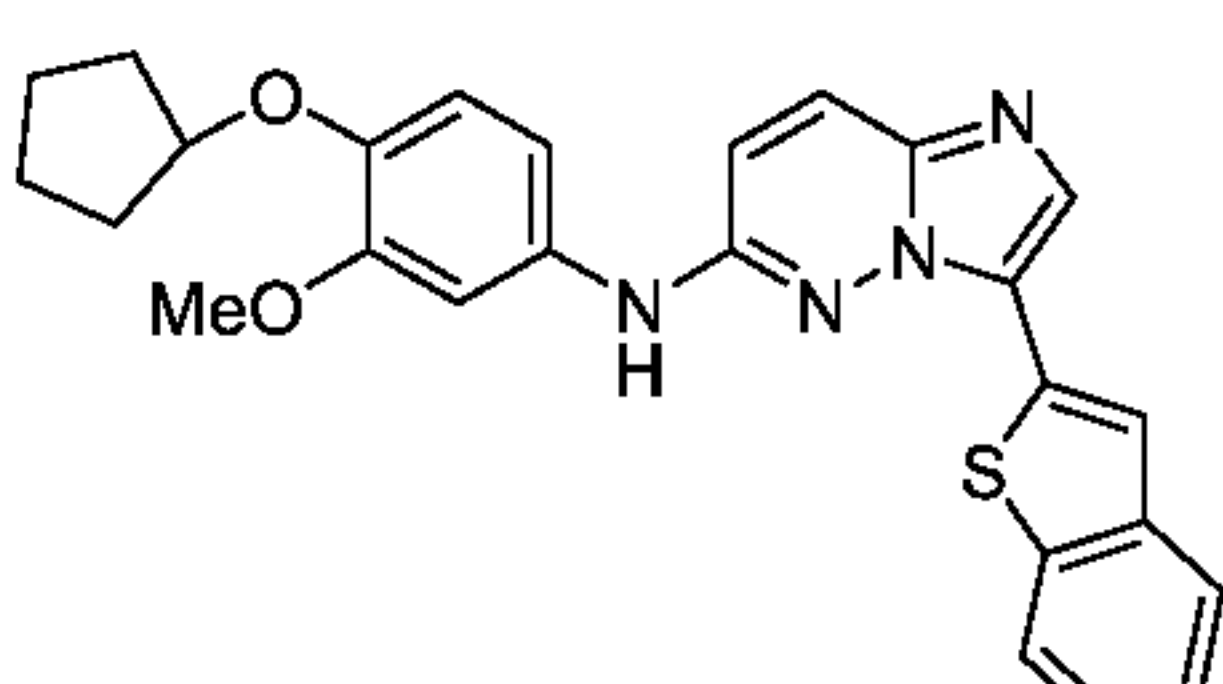
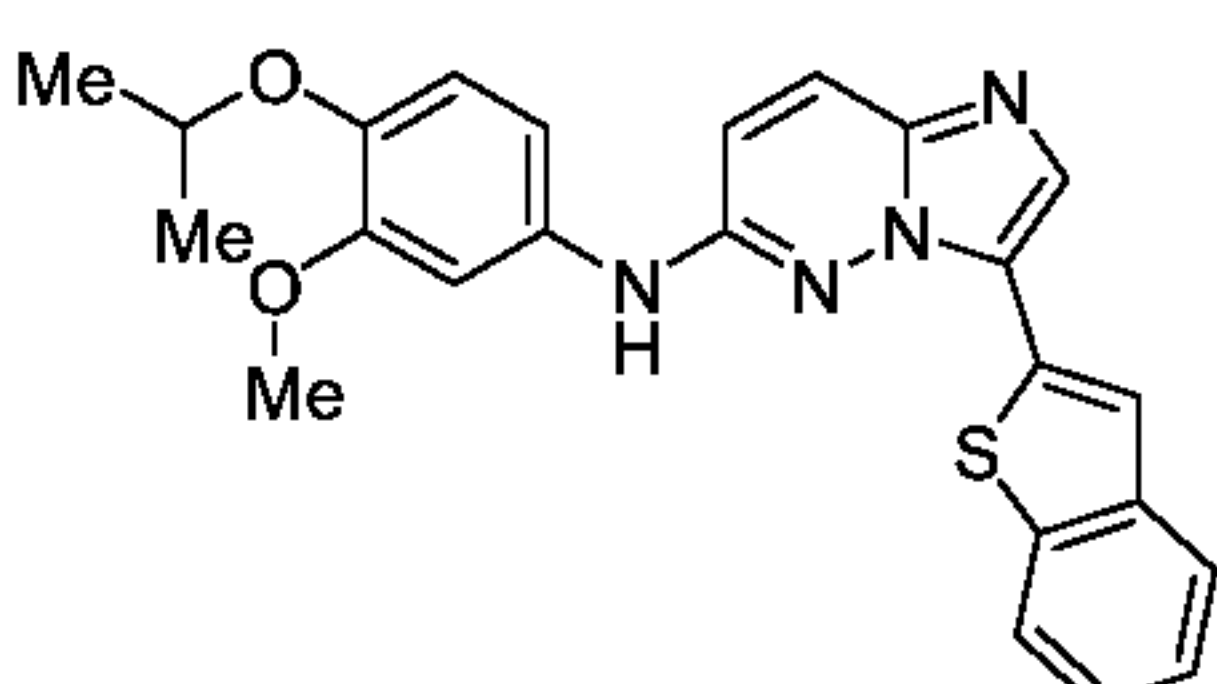
Cd.	Amine	Purified Compound Isolated
12	3,4-dimethoxyaniline	3-(benzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
13	3-(4-methylpiperazin-1-yl)benzenamine	3-(benzo[b]thiophen-2-yl)-N-(3-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine
14	3,4,5-trimethoxybenzenamine	3-(benzo[b]thiophen-2-yl)-N-(3,4,5-trimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
15	3-methoxybenzenamine	3-(benzo[b]thiophen-2-yl)-N-(3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
16	4-methoxybenzenamine	3-(benzo[b]thiophen-2-yl)-N-(4-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
22	methyl 4-aminobenzoate	methyl 4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoate
23	methyl 3-aminobenzoate	methyl 3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoate
24	4-amino-2-methoxyphenol	4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenol
25	methyl 4-aminobenzoate	4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid
26	methyl 3-aminobenzoate	3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid

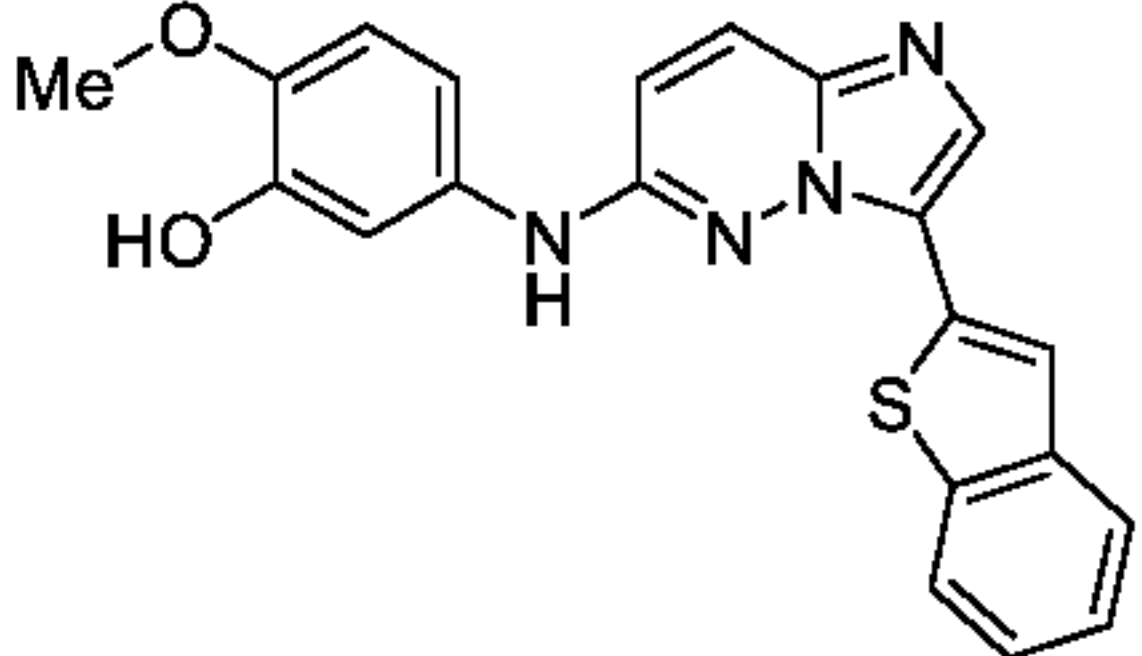
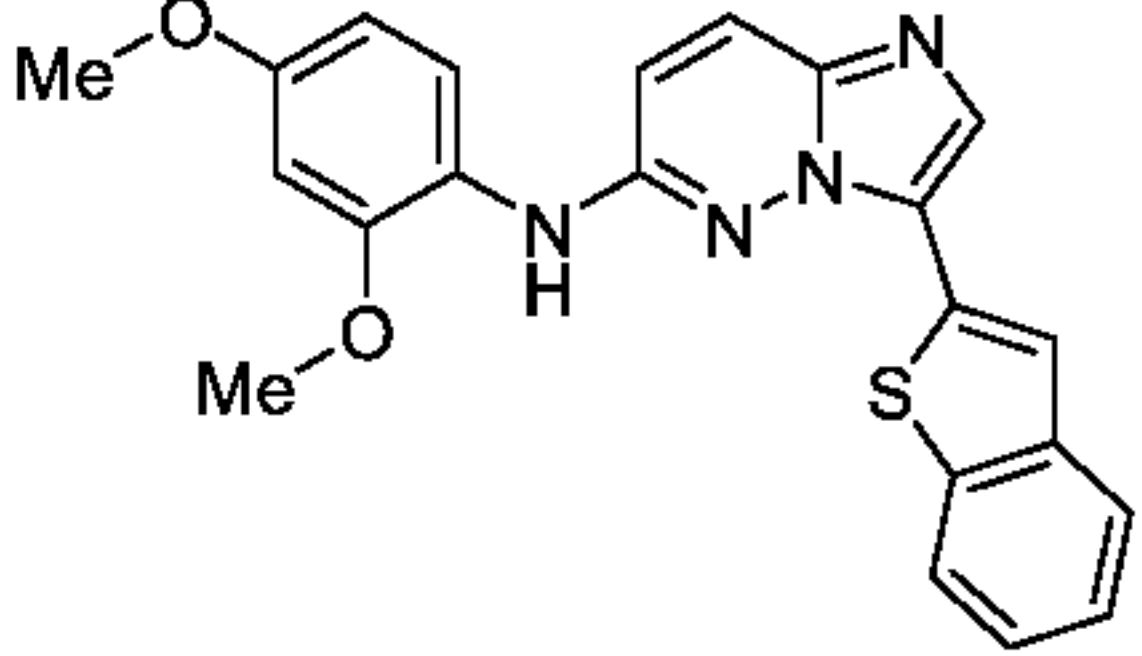
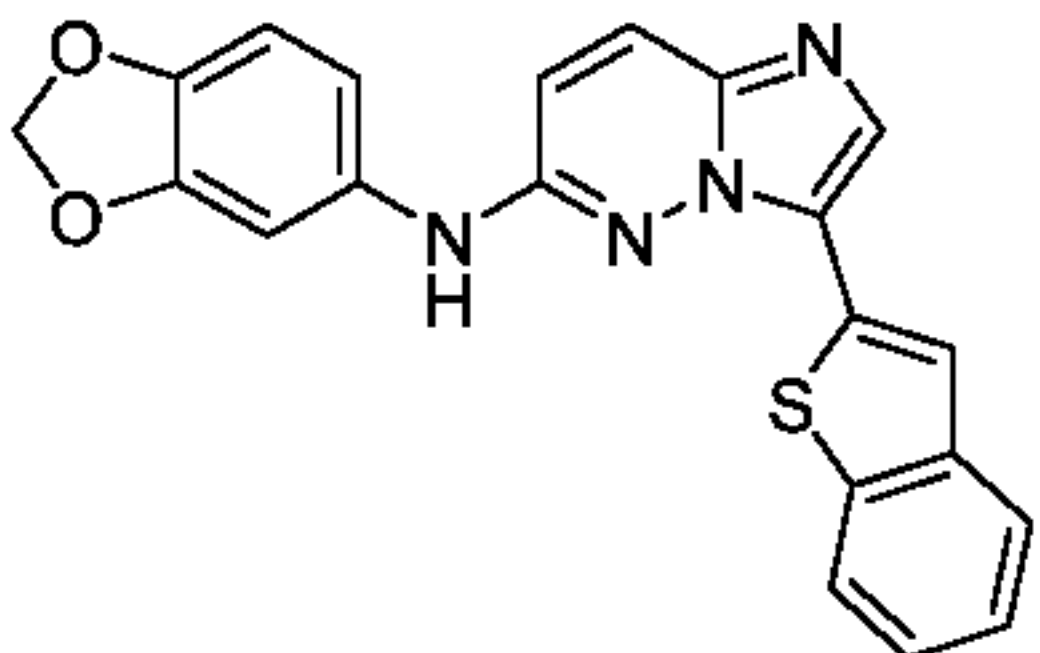
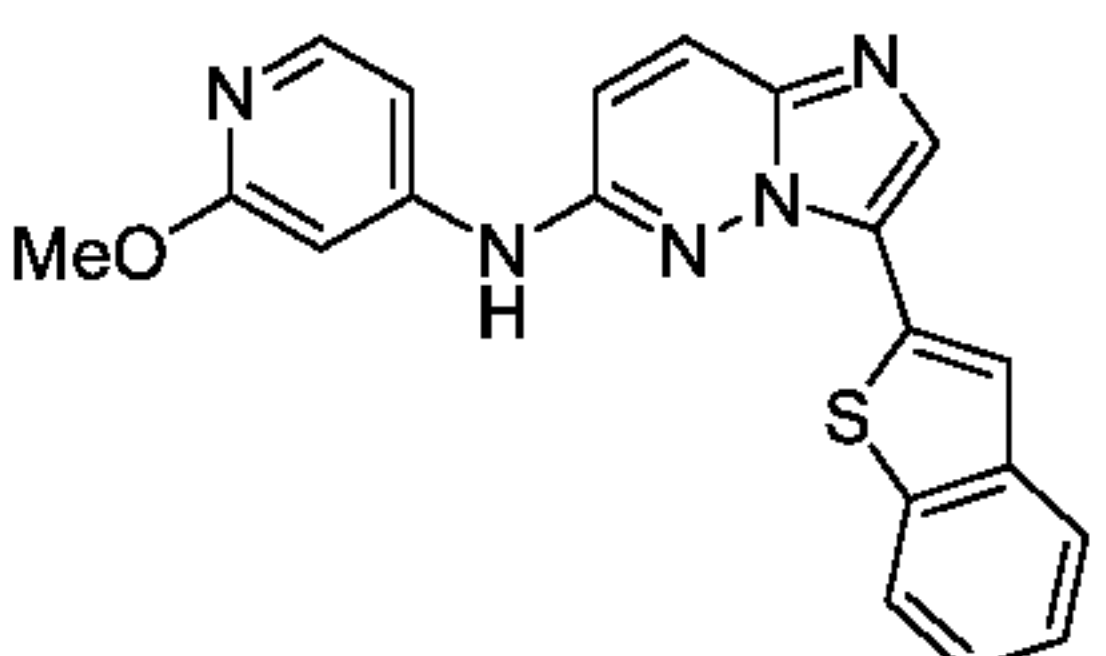
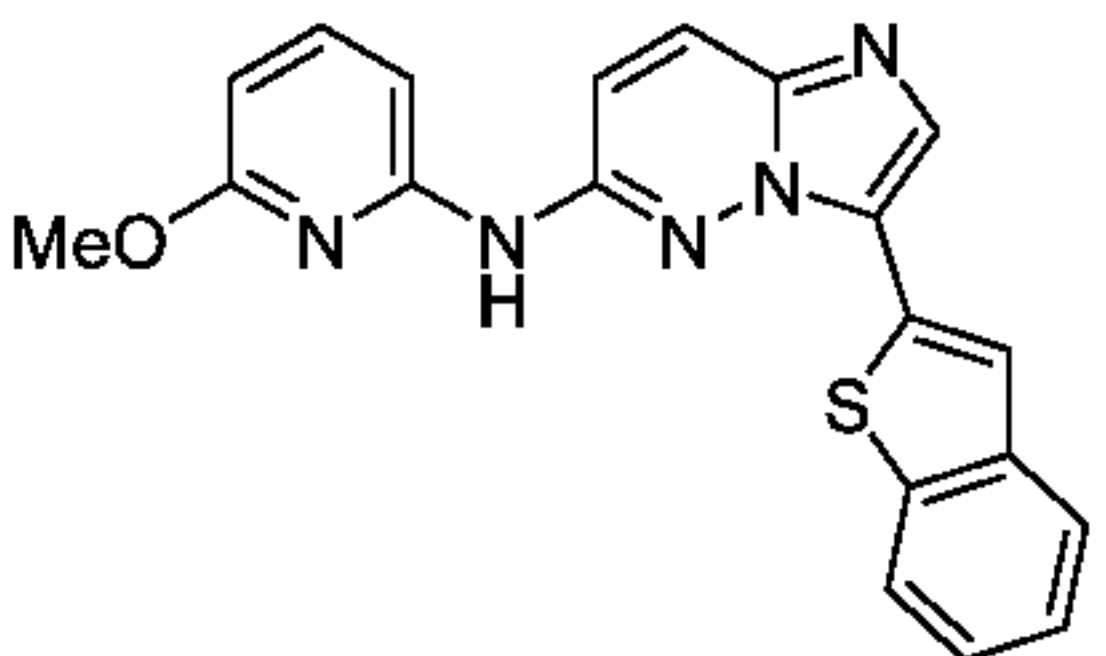
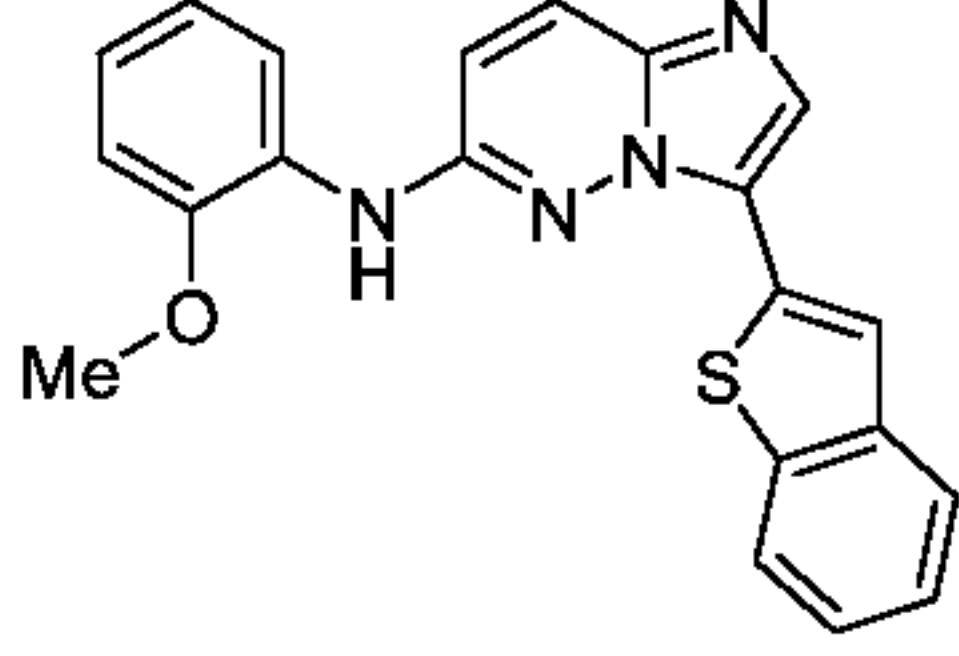
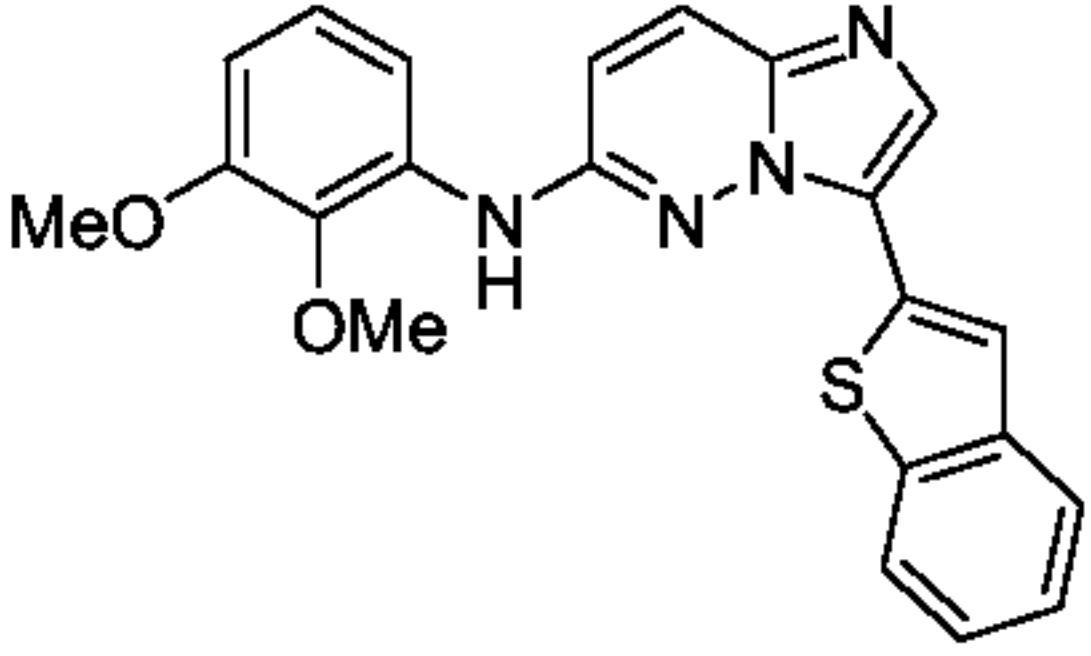
27	3-(4-amino-2-methoxyphenoxy)propan-1-ol	3-(4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenoxy)propan-1-ol
28	4-(cyclopropylmethoxy)-3-methoxybenzenamine	3-(benzo[b]thiophen-2-yl)-N-(4-(cyclopropylmethoxy)-3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
29	4-(cyclopentylmethoxy)-3-methoxybenzenamine	3-(benzo[b]thiophen-2-yl)-N-(4-(cyclopentylmethoxy)-3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
30	4-isopropoxy-3-methoxybenzenamine	3-(benzo[b]thiophen-2-yl)-N-(4-isopropoxy-3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
31	5-amino-2-methoxyphenol	5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenol
32	2,4-dimethoxybenzenamine	3-(benzo[b]thiophen-2-yl)-N-(2,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
33	benzo[d][1,3]dioxol-5-amine	3-(benzo[b]thiophen-2-yl)-N-(benzo[d][1,3]dioxol-6-yl)imidazo[1,2-b]pyridazin-6-amine
34	2-methoxypyridin-4-amine	3-(benzo[b]thiophen-2-yl)-N-(2-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine
35	6-methoxypyridin-2-amine	3-(benzo[b]thiophen-2-yl)-N-(6-methoxypyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine
36	2-methoxybenzenamine	3-(benzo[b]thiophen-2-yl)-N-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
37	2,3-dimethoxybenzenamine	3-(benzo[b]thiophen-2-yl)-N-(2,3-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
38	3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-amine	3-(benzo[b]thiophen-2-yl)-N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-8-yl)imidazo[1,2-b]pyridazin-6-amine
41	2-methoxypyridin-4-amine	4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)pyridin-2-ol
42	3-(5-amino-2-methoxyphenoxy)propan-1-ol	3-(5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenoxy)propan-1-ol
43	methyl 5-amino-2-methoxybenzoate	5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxybenzoic acid
44	methyl 2-(3-hydroxypropoxy)-5-aminobenzoate	5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-(3-hydroxypropoxy)benzoic acid
45	6-methoxypyridin-2-amine	6-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)pyridin-2-ol
47	3,4-dichlorobenzenamine	3-(benzo[b]thiophen-2-yl)-N-(3,4-dichlorophenyl)imidazo[1,2-b]pyridazin-6-amine
48	3-(trifluoromethoxy)benzenamine	3-(benzo[b]thiophen-2-yl)-N-(3-(trifluoromethoxy)phenyl)imidazo[1,2-b]pyridazin-6-amine

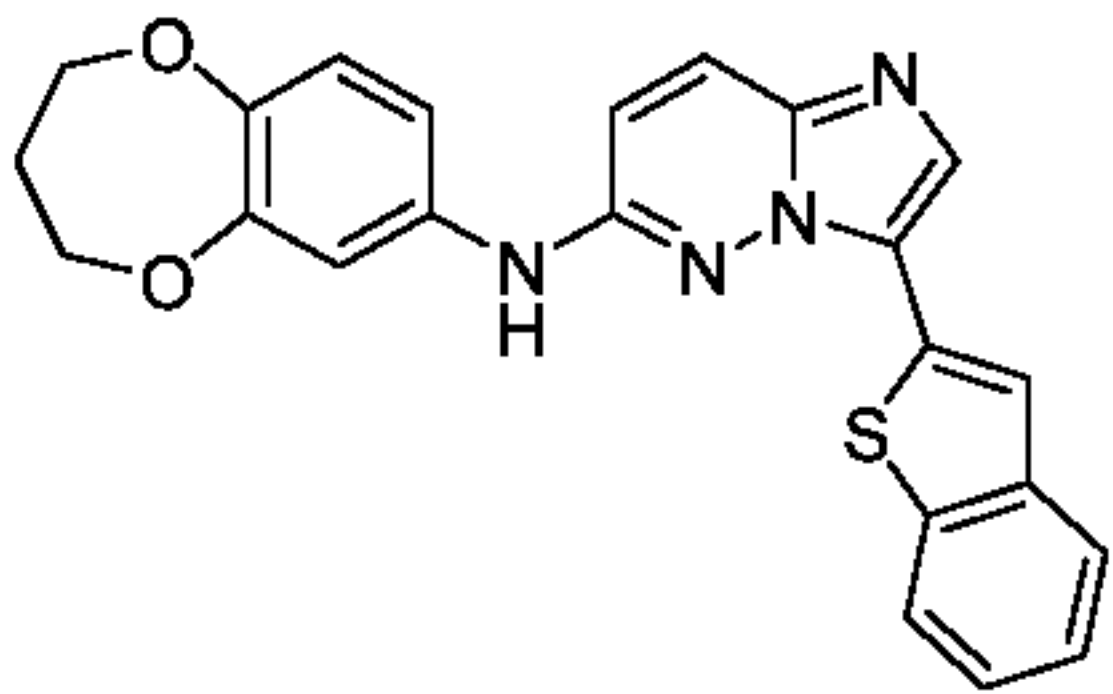
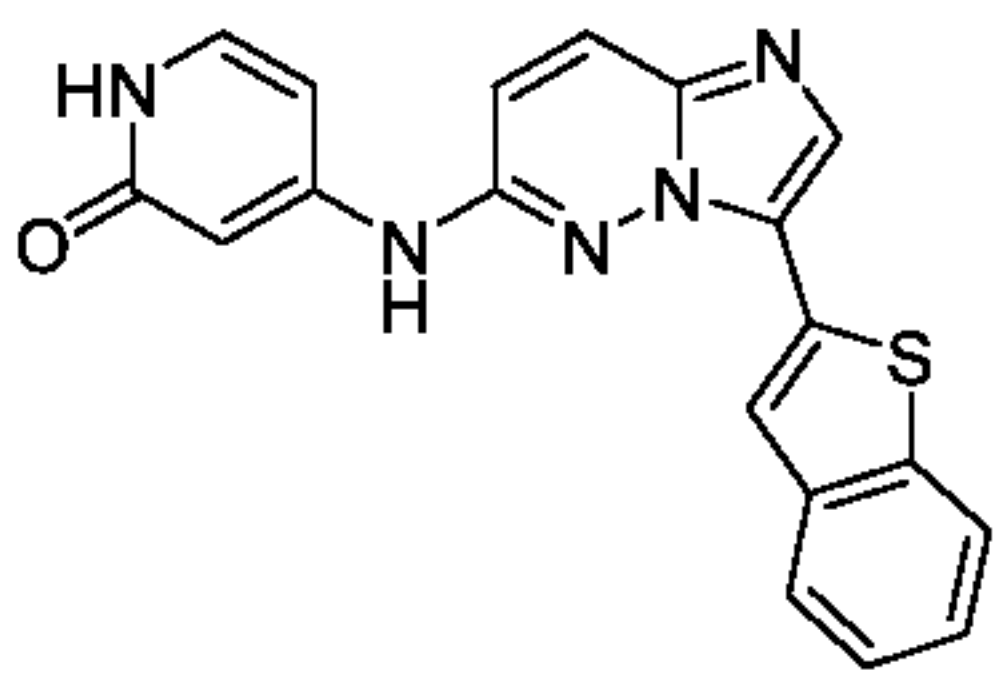
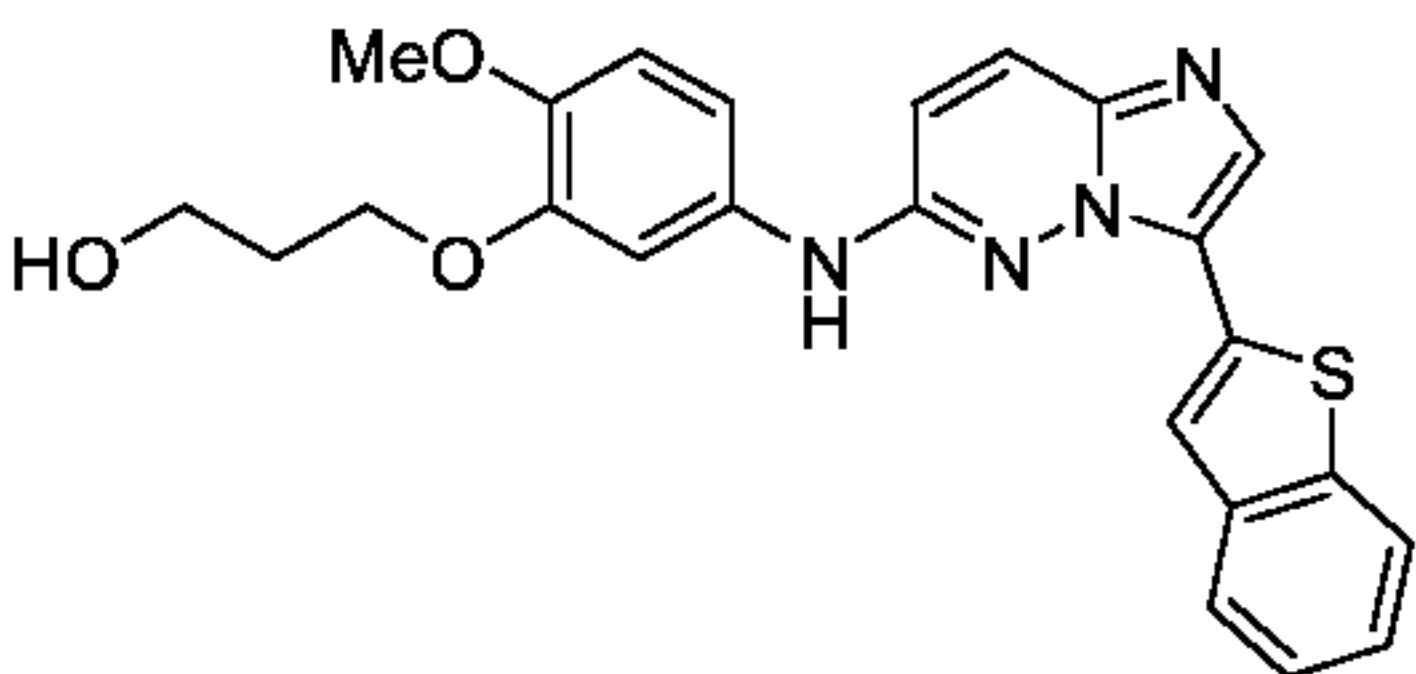
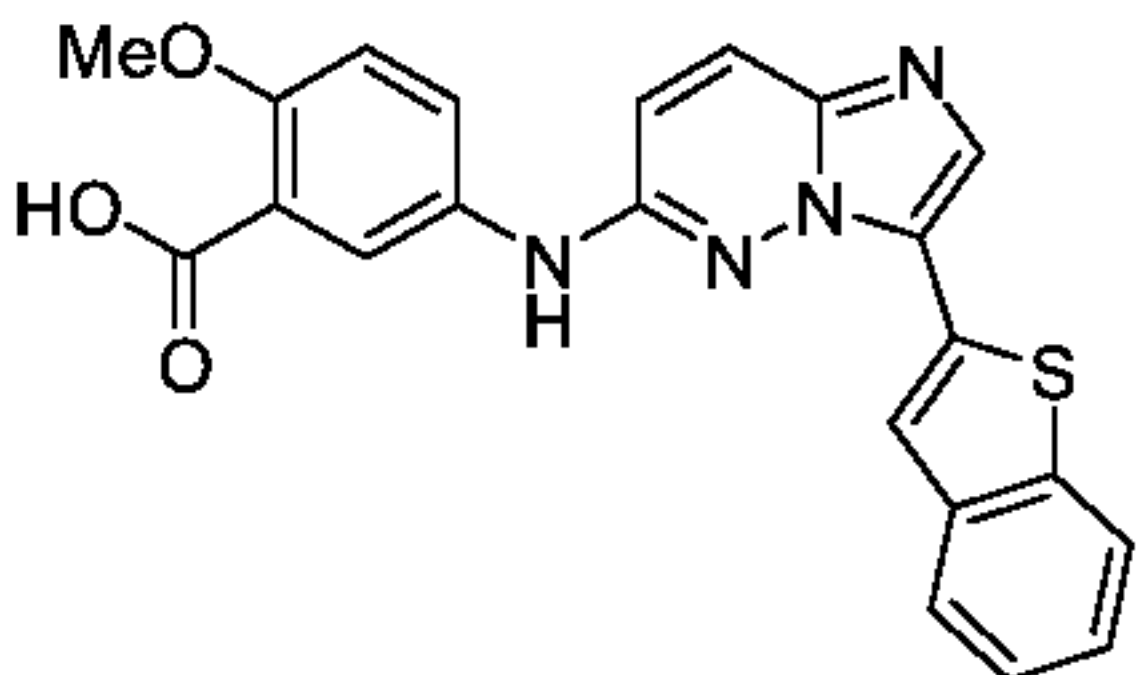
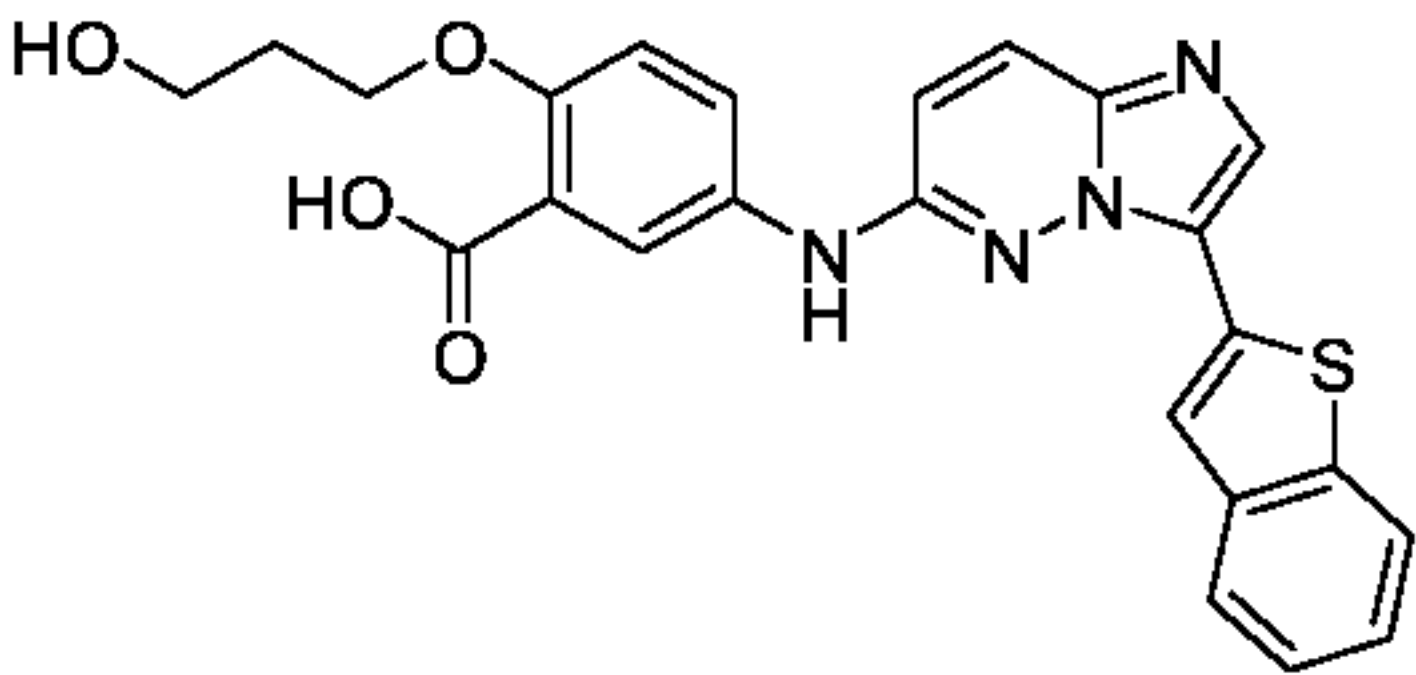
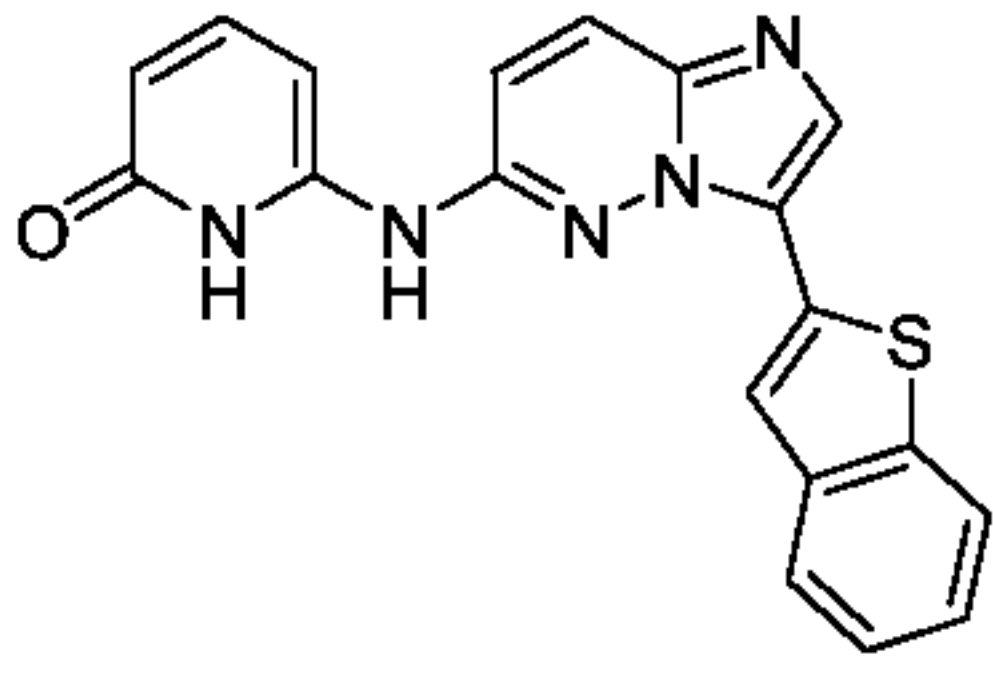
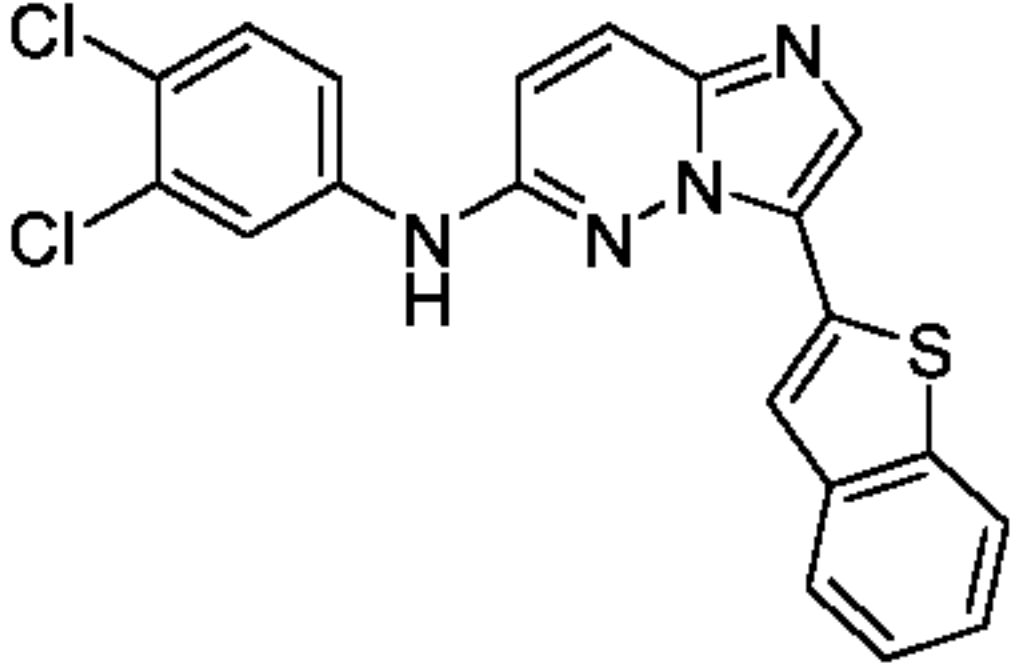
[00245] Compounds 12-16, 22-38, 41-45, 47-48 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 8-b**.

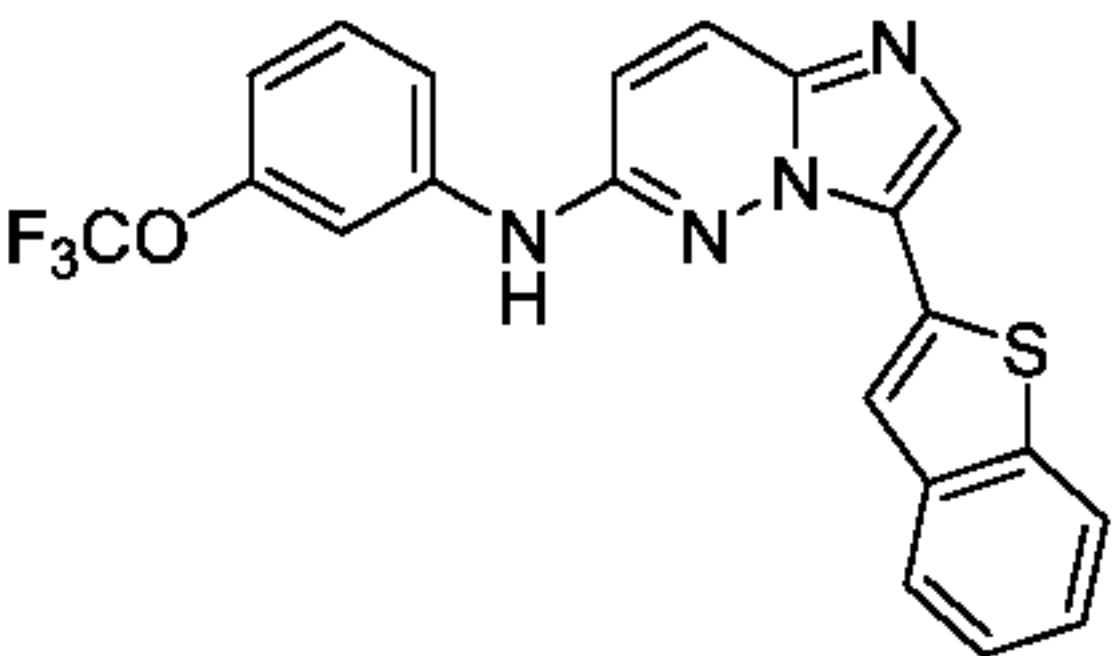
Table 8-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
12		3-(benzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	403.6
13		3-(benzo[b]thiophen-2-yl)-N-(3-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	441.6
14		3-(benzo[b]thiophen-2-yl)-N-(3,4,5-trimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	433.7
15		3-(benzo[b]thiophen-2-yl)-N-(3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	373.6
16		3-(benzo[b]thiophen-2-yl)-N-(4-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	373.6
22		methyl 4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoate	401.6
23		methyl 3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoate	401.7

24		4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenol	389.6
25		4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid	387.6
26		3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid	387.7
27		3-(4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenoxy)propan-1-ol	447.6
28		3-(benzo[b]thiophen-2-yl)-N-(4-(cyclopropylmethoxy)-3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	443.7
29		3-(benzo[b]thiophen-2-yl)-N-(4-(cyclopentylmethoxy)-3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	457.7
30		3-(benzo[b]thiophen-2-yl)-N-(4-isopropoxy-3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	431.8

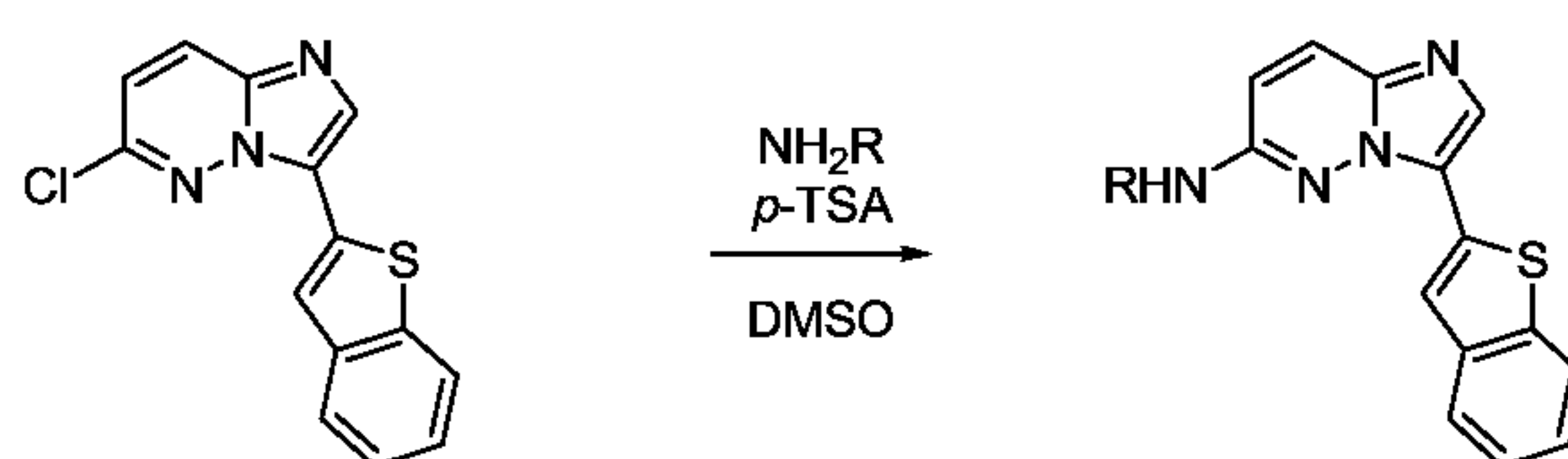
31		5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenol	389.8
32		3-(benzo[b]thiophen-2-yl)-N-(2,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	403.6
33		3-(benzo[b]thiophen-2-yl)-N-(benzo[d][1,3]dioxol-6-yl)imidazo[1,2-b]pyridazin-6-amine	387.6
34		3-(benzo[b]thiophen-2-yl)-N-(2-methoxypyridin-4-yl)imidazo[1,2-b]pyridazin-6-amine	374.8
35		3-(benzo[b]thiophen-2-yl)-N-(6-methoxypyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	376.8
36		3-(benzo[b]thiophen-2-yl)-N-(2-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	373.6
37		3-(benzo[b]thiophen-2-yl)-N-(2,3-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	403.7

38		3-(benzo[b]thiophen-2-yl)-N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-8-yl)imidazo[1,2-b]pyridazin-6-amine	415.8
41		4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)pyridin-2-ol	360.5
42		3-(5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenoxy)propan-1-ol	447.8
43		5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxybenzoic acid	417.9
44		5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-(3-hydroxypropoxy)benzoic acid	461.8
45		6-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)pyridin-2-ol	360.6
47		3-(benzo[b]thiophen-2-yl)-N-(3,4-dichlorophenyl)imidazo[1,2-b]pyridazin-6-amine	411.4, 415.4

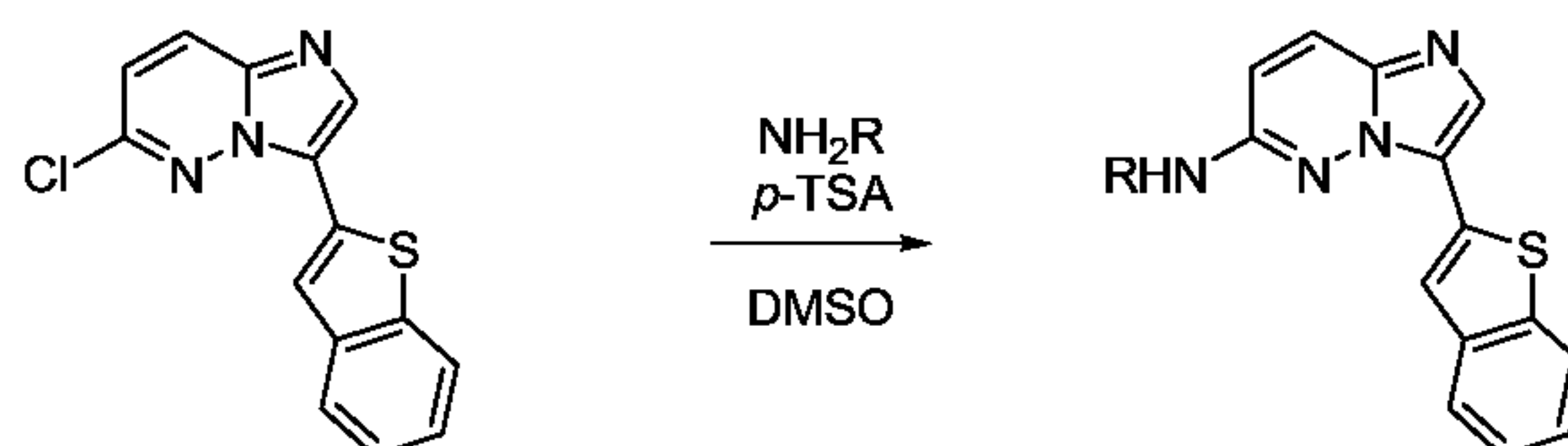
48		3-(benzo[b]thiophen-2-yl)-N-(3-(trifluoromethoxy)phenyl)imidazo[1,2-b]pyridazin-6-amine	427.6

[00246] Example 9 – Synthesis of Compounds 105, 107-110, 119, 122-127, 129-132, 134-139

[00247] **Scheme 9**



[00248] **Preparation of 3-(benzo[b]thiophen-2-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine**



[00249] To a solution of 3-(benzo[b]thiophen-2-yl)-6-chloroimidazo[1,2-b]pyridazine (100 mg, 0.350 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (67 mg, 0.350 mmol, 1.0 equiv) and amine (1.75 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave the product.

Table 9-a

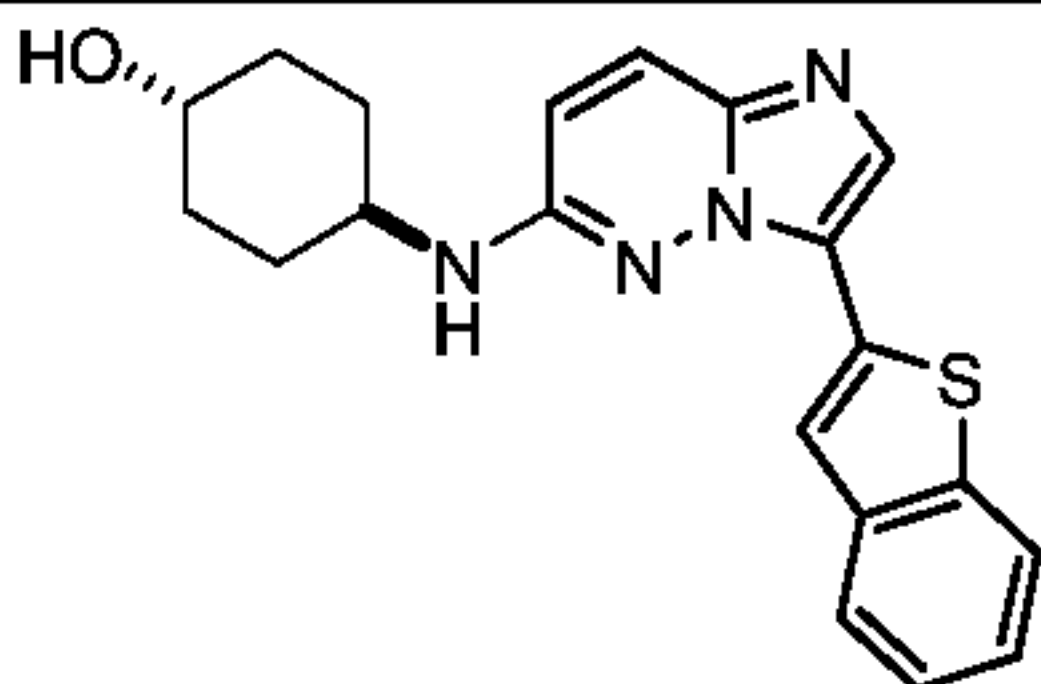
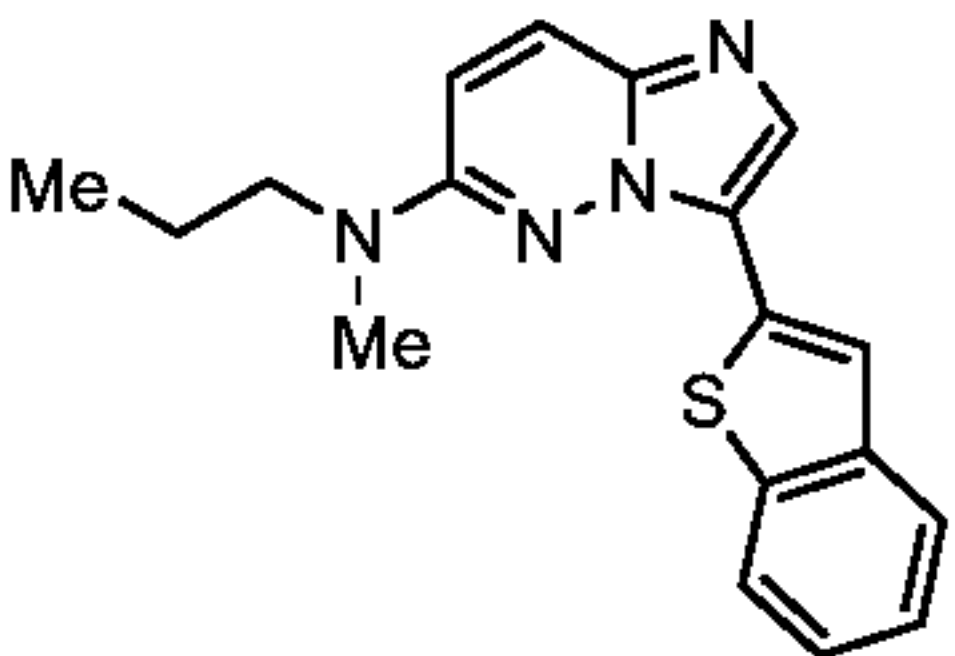
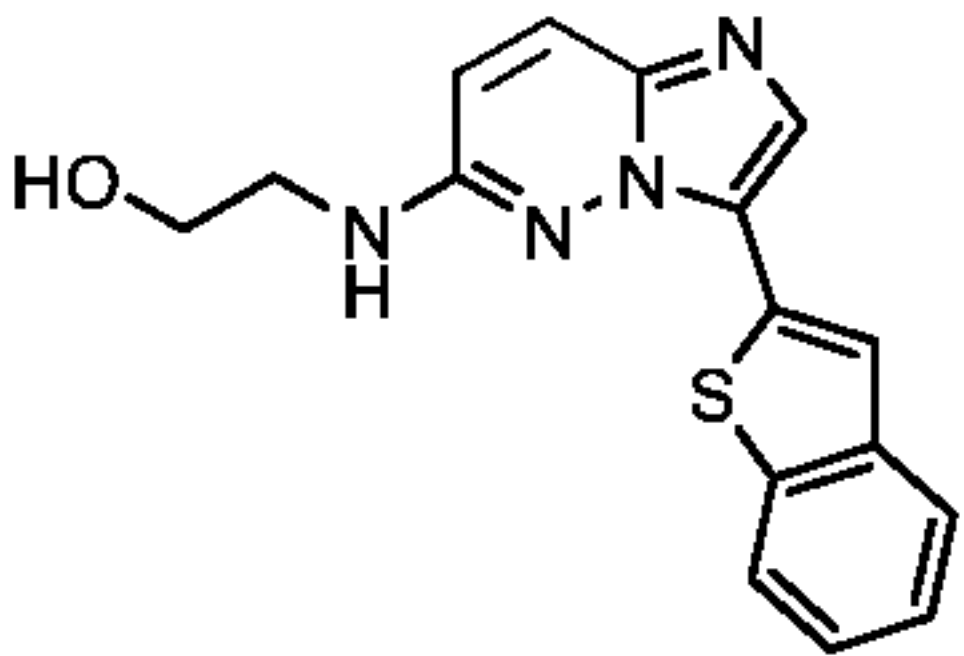
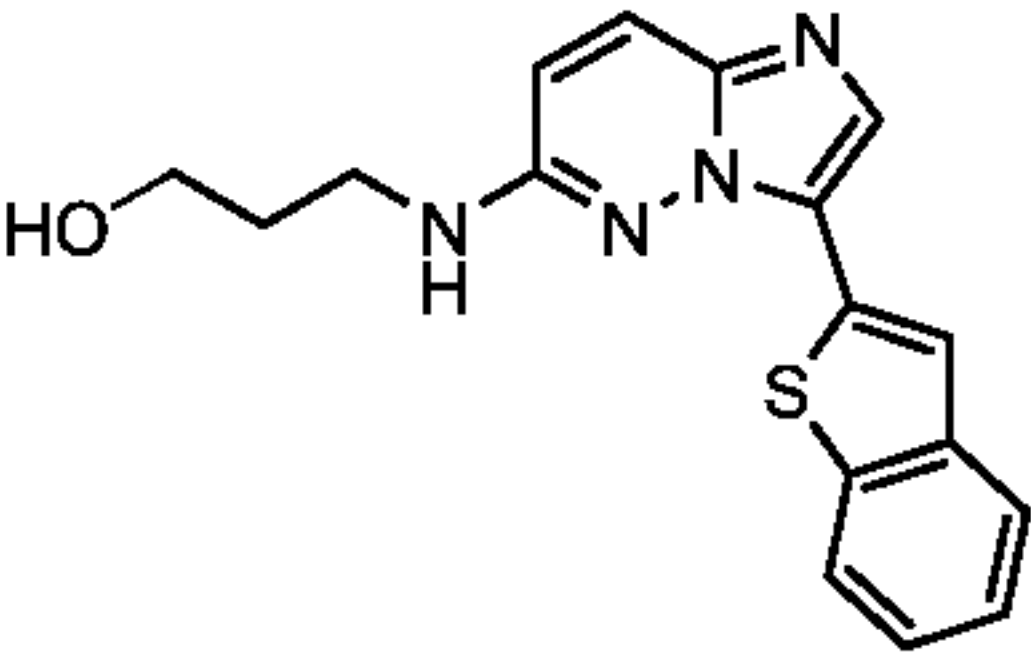
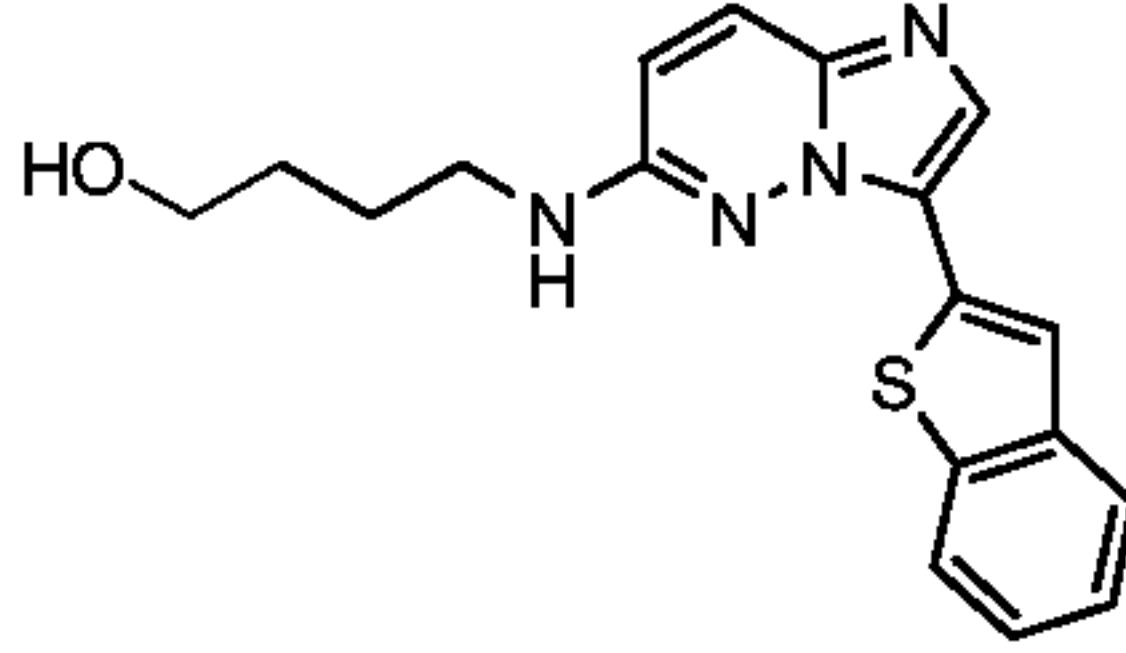
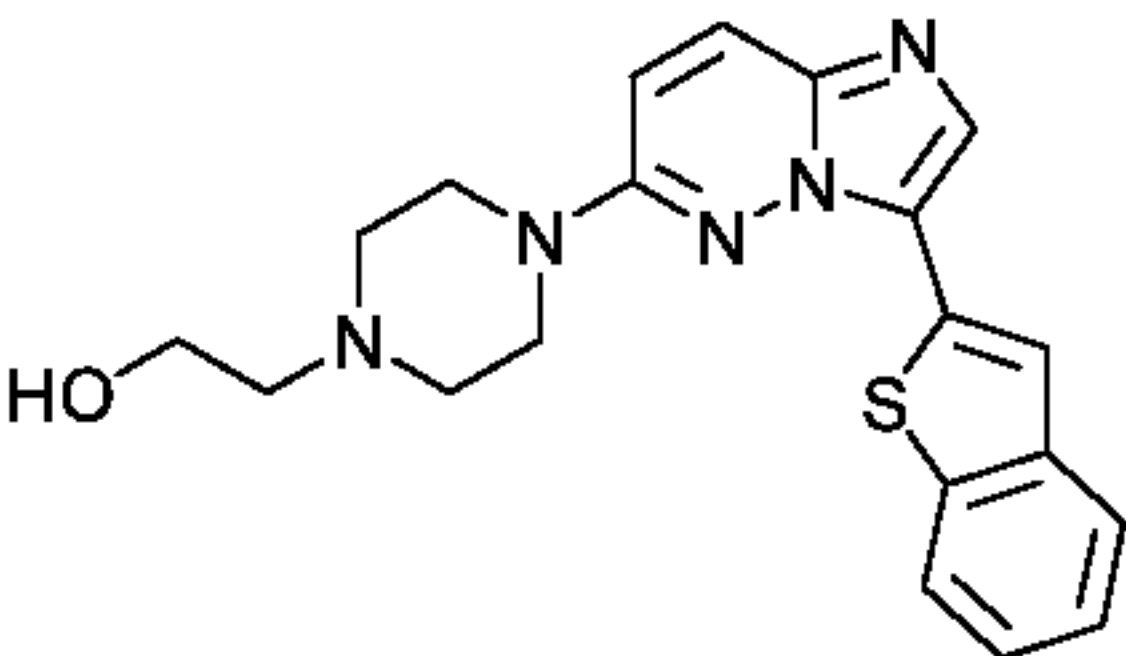
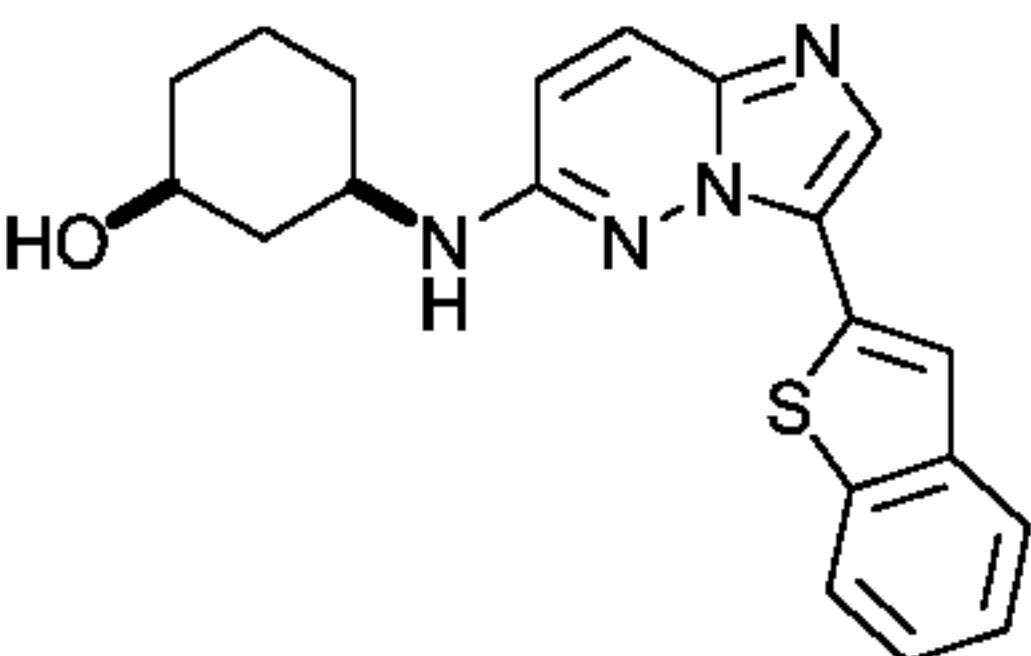
Cd.	Amine	Purified Compound Isolated
105	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
107	N-methylpropan-1-amine	3-(benzo[b]thiophen-2-yl)-N-methyl-N-propylimidazo[1,2-b]pyridazin-6-amine
108	2-aminoethanol	2-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)ethanol
109	3-aminopropan-1-ol	3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)propan-1-ol

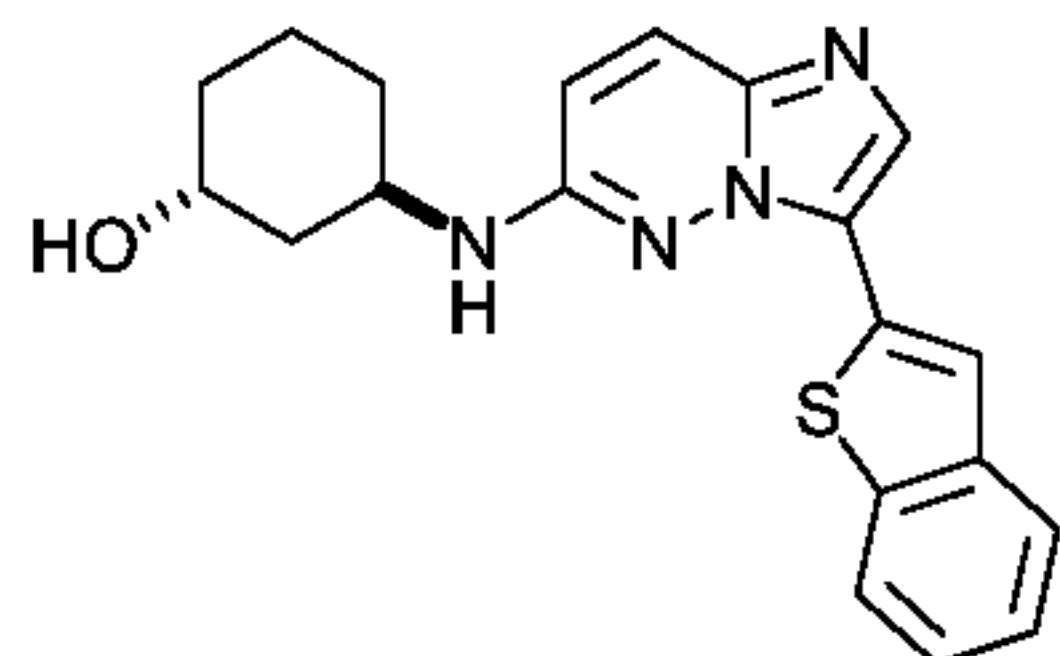
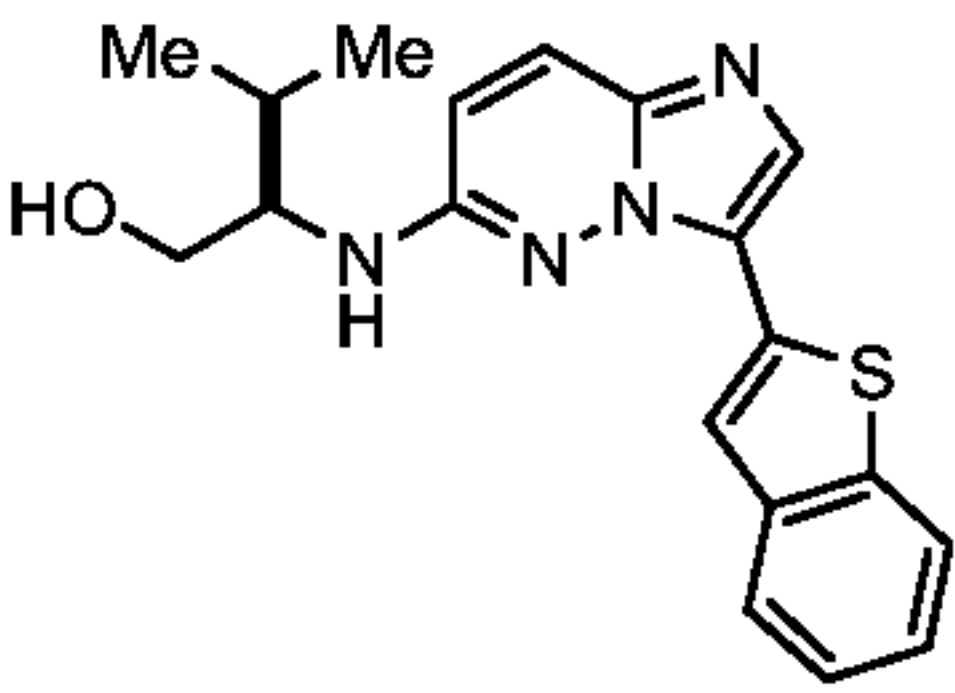
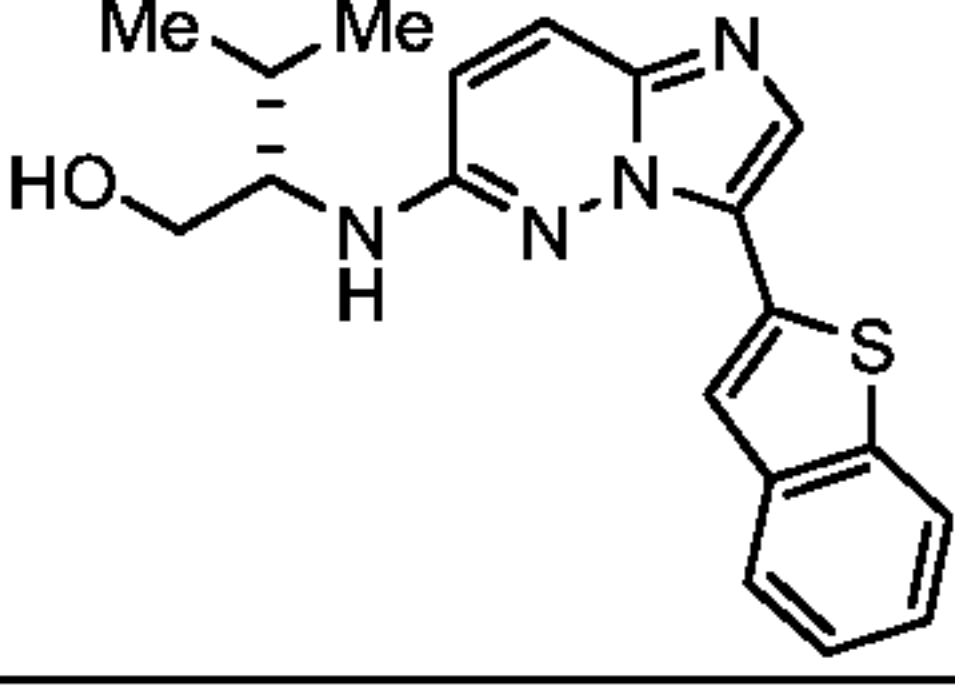
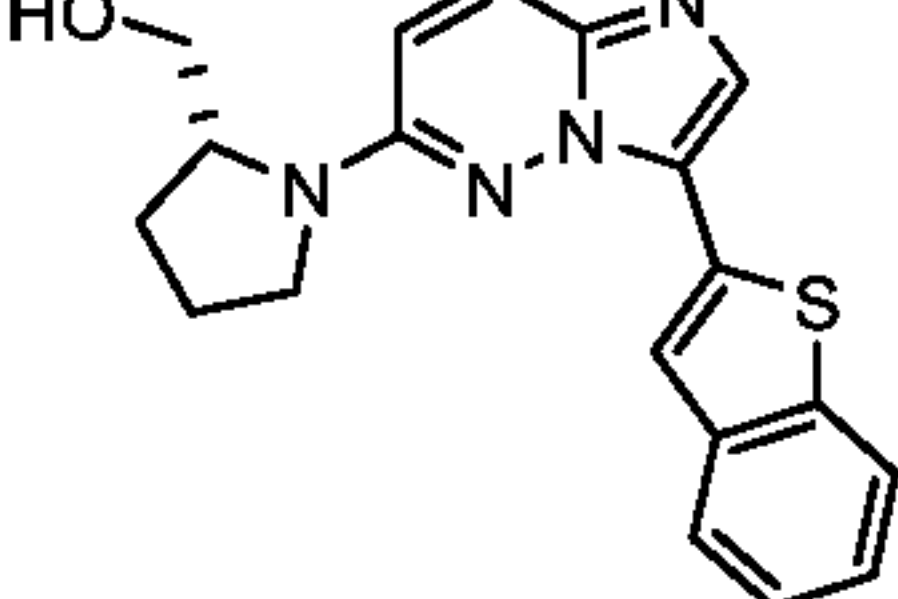
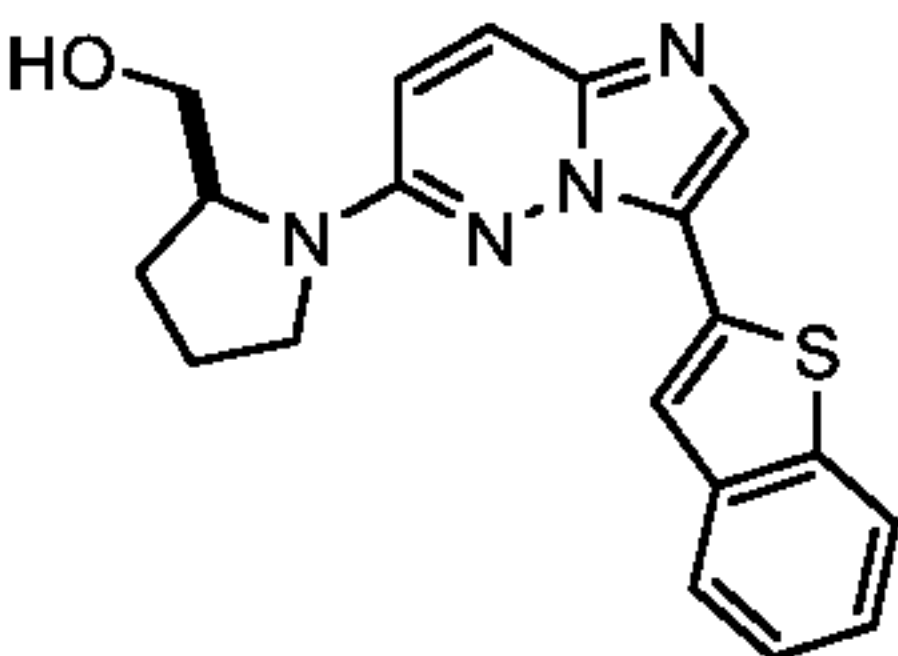
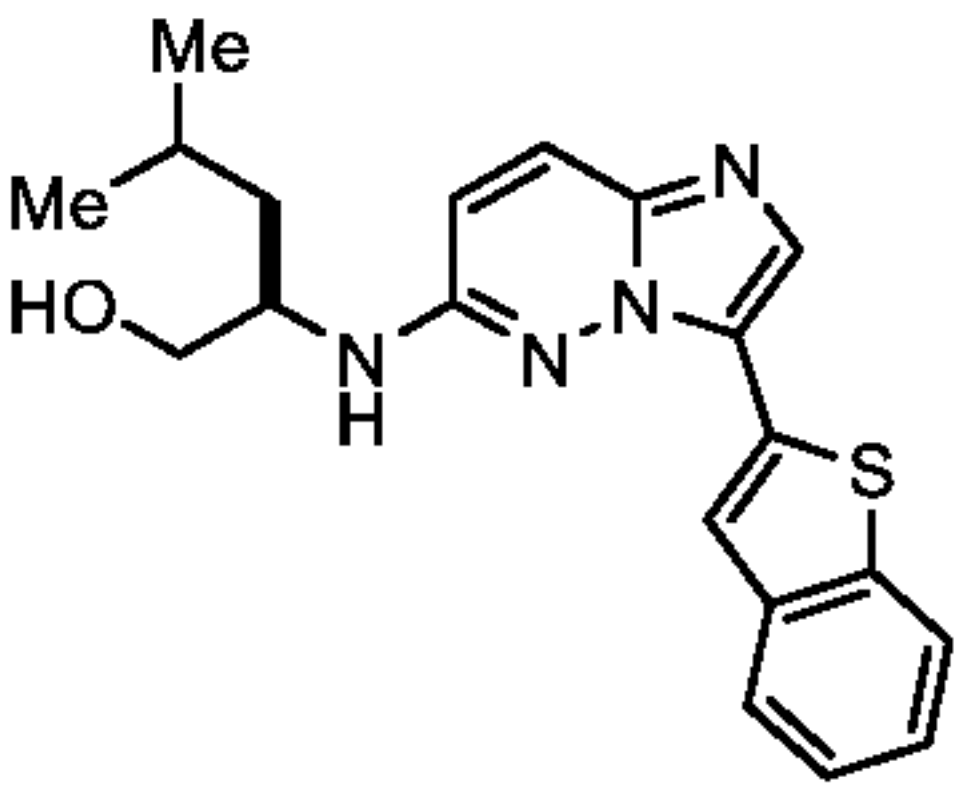
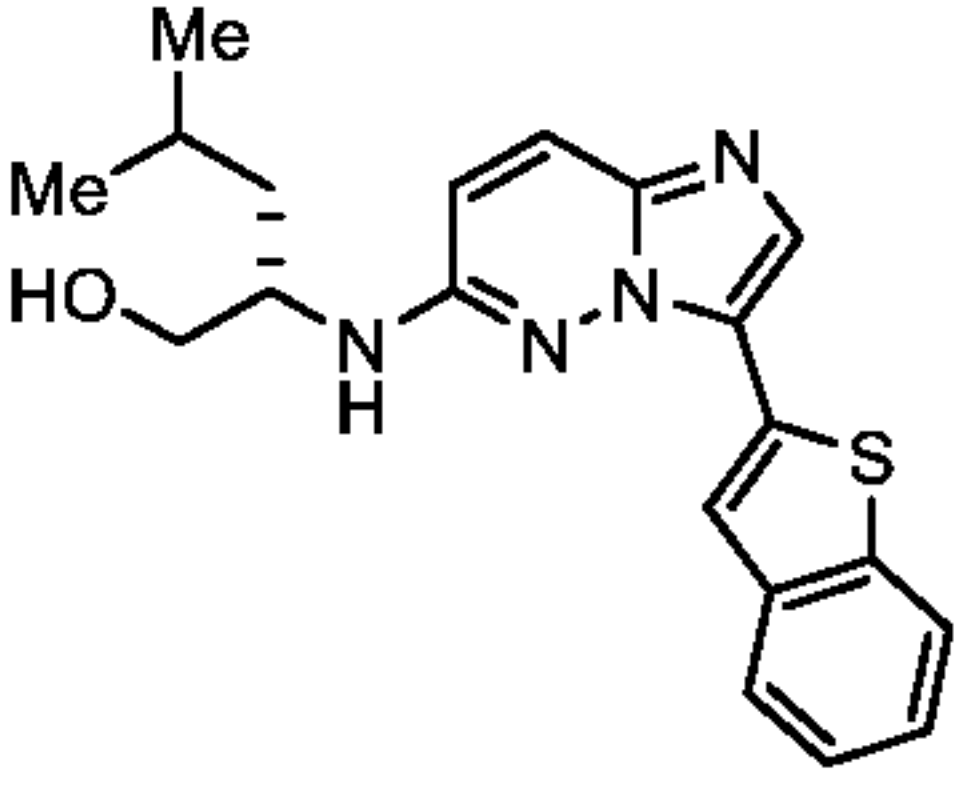
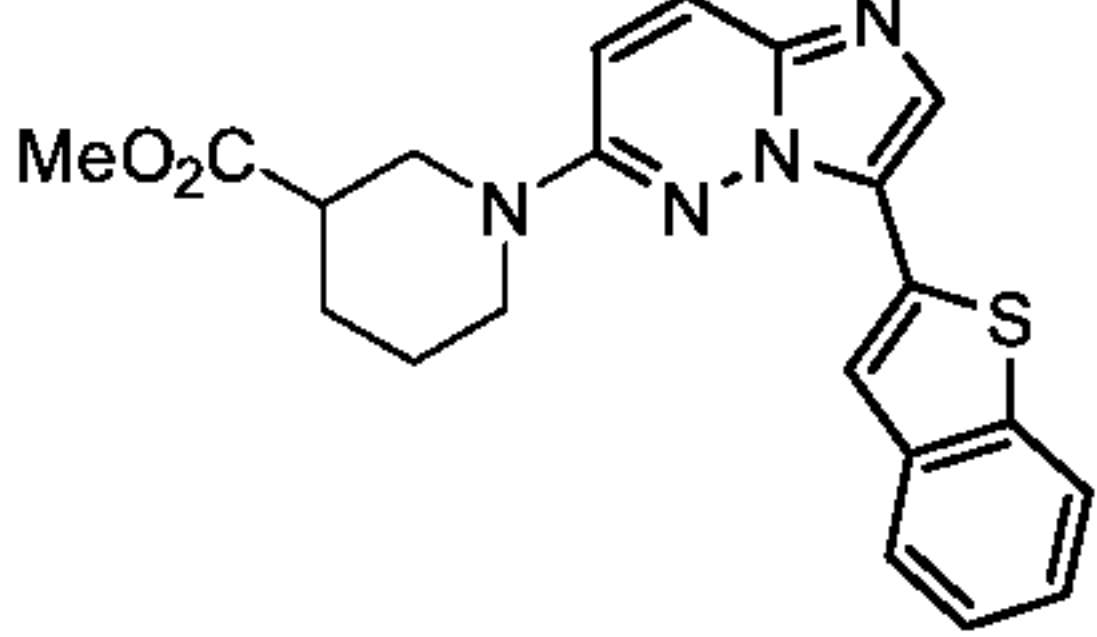
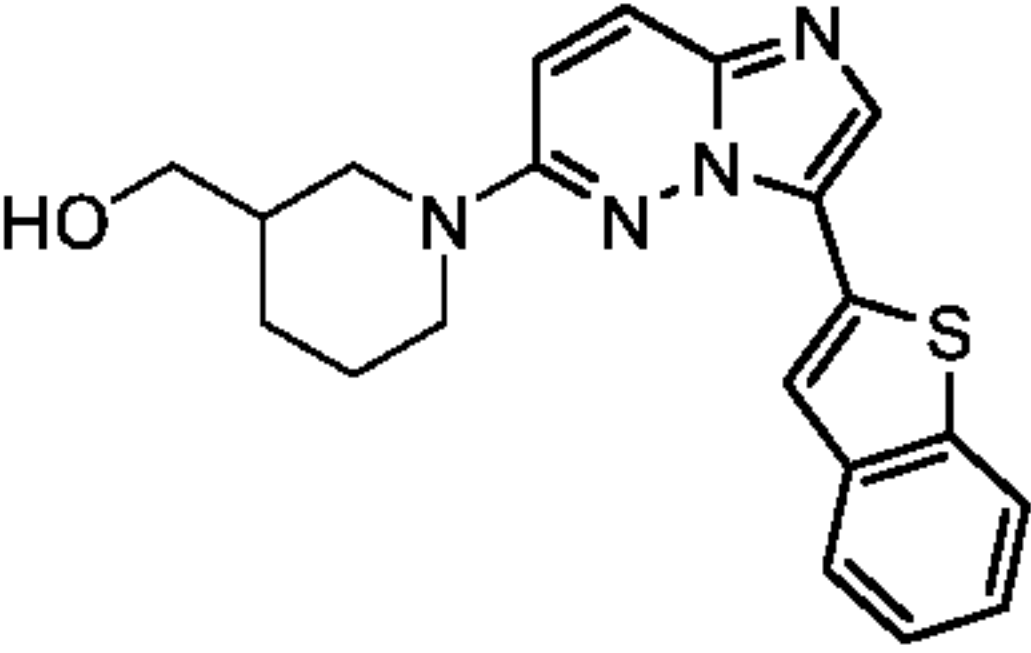
110	4-aminobutan-1-ol	4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol
119	2-(piperazin-1-yl)ethanol	2-(4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)ethanol
122	<i>cis</i> -3-aminocyclohexanol	<i>cis</i> -3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
123	<i>trans</i> -3-aminocyclohexanol	<i>trans</i> -3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
124	(S)-2-methylpentan-3-amine	3-(benzo[b]thiophen-2-yl)-N-((S)-2-methylpentan-3-yl)imidazo[1,2-b]pyridazin-6-amine
125	(R)-2-methylpentan-3-amine	3-(benzo[b]thiophen-2-yl)-N-((R)-2-methylpentan-3-yl)imidazo[1,2-b]pyridazin-6-amine
126	((R)-pyrrolidin-2-yl)methanol	((R)-1-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-2-yl)methanol
127	((S)-pyrrolidin-2-yl)methanol	((S)-1-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-2-yl)methanol
129	(R)-2-amino-4-methylpentan-1-ol	(R)-2-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-4-methylpentan-1-ol
130	(S)-2-amino-4-methylpentan-1-ol	(S)-2-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-4-methylpentan-1-ol
131	methyl piperidine-3-carboxylate	methyl 1-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)piperidine-3-carboxylate
132	(piperidin-3-yl)methanol	(1-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)piperidin-3-yl)methanol
134	4-tert-butylcyclohexanamine	N-(4-tert-butylcyclohexyl)-3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine
135	5-aminopentan-1-ol	5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)pentan-1-ol
136	3-(4-methylpiperazin-1-yl)propan-1-amine	3-(benzo[b]thiophen-2-yl)-N-(3-(4-methylpiperazin-1-yl)propyl)imidazo[1,2-b]pyridazin-6-amine
137	1-cyclohexylpiperidin-3-amine	3-(benzo[b]thiophen-2-yl)-N-(1-cyclohexylpiperidin-3-yl)imidazo[1,2-b]pyridazin-6-amine

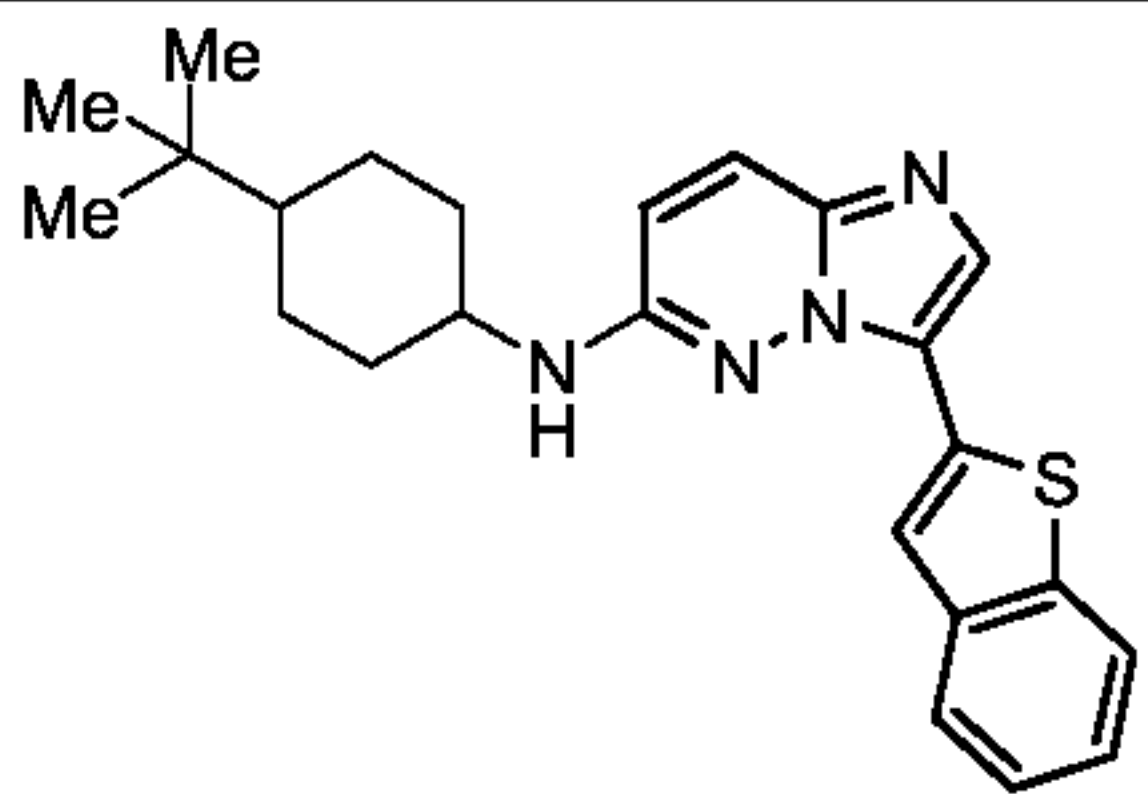
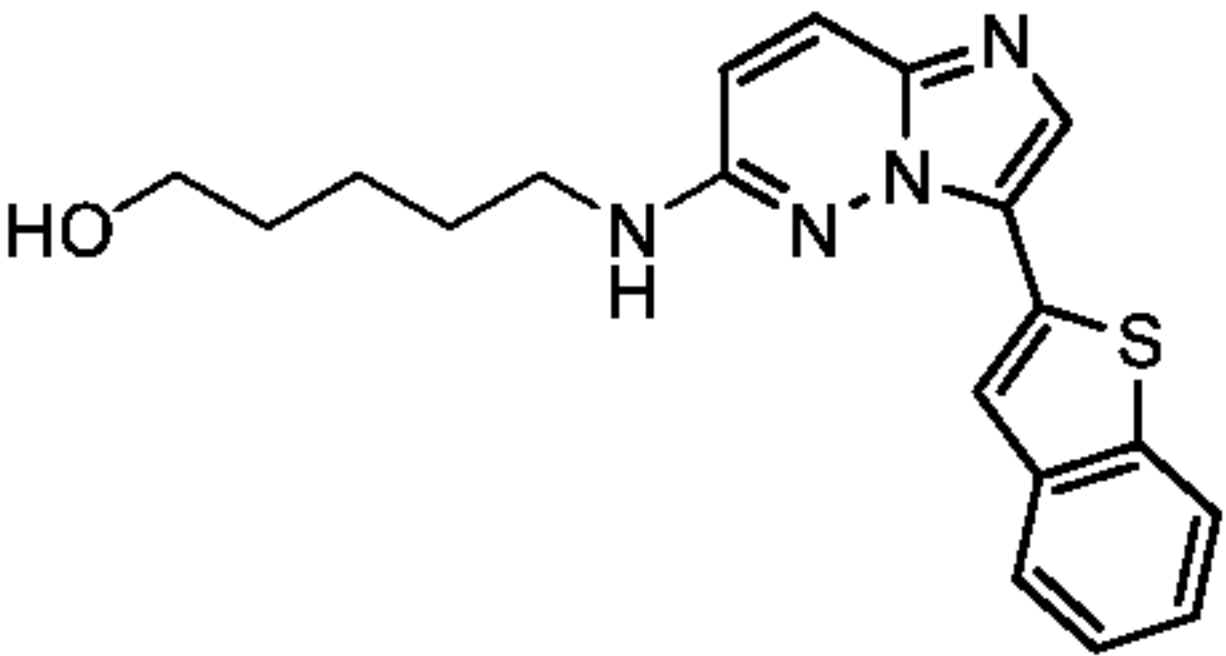
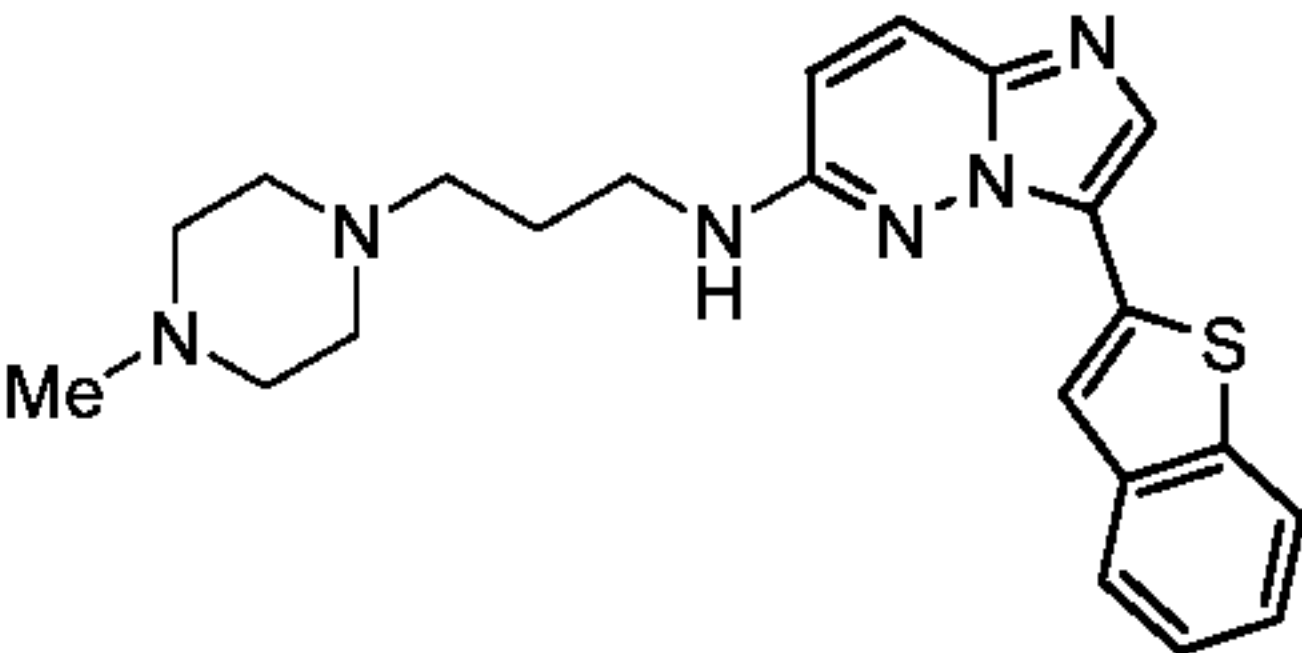
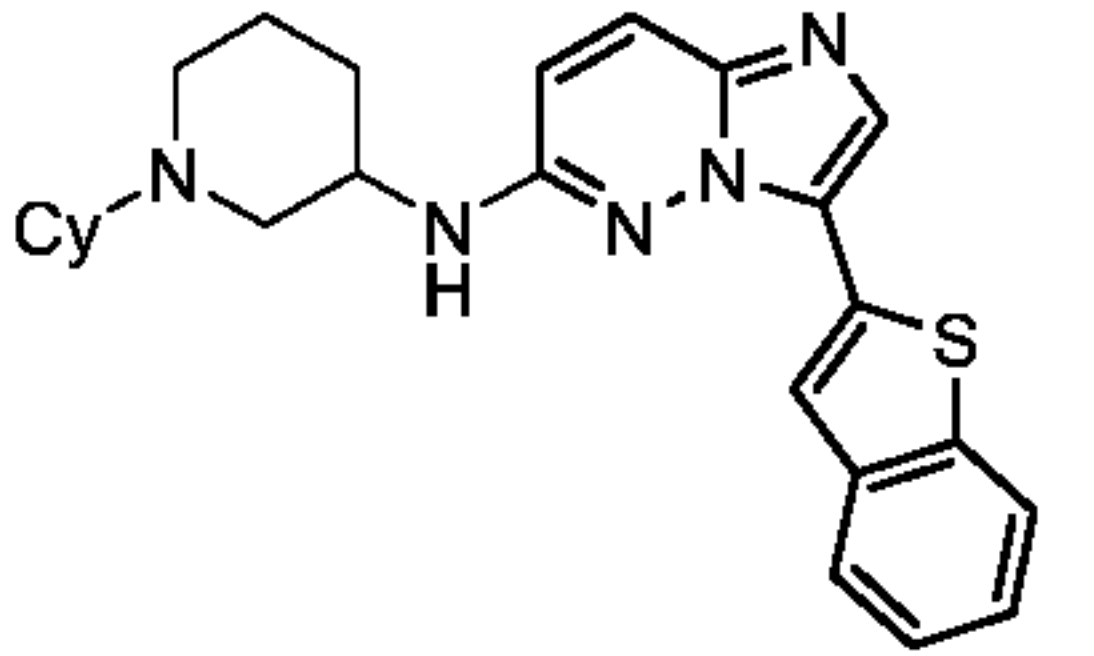
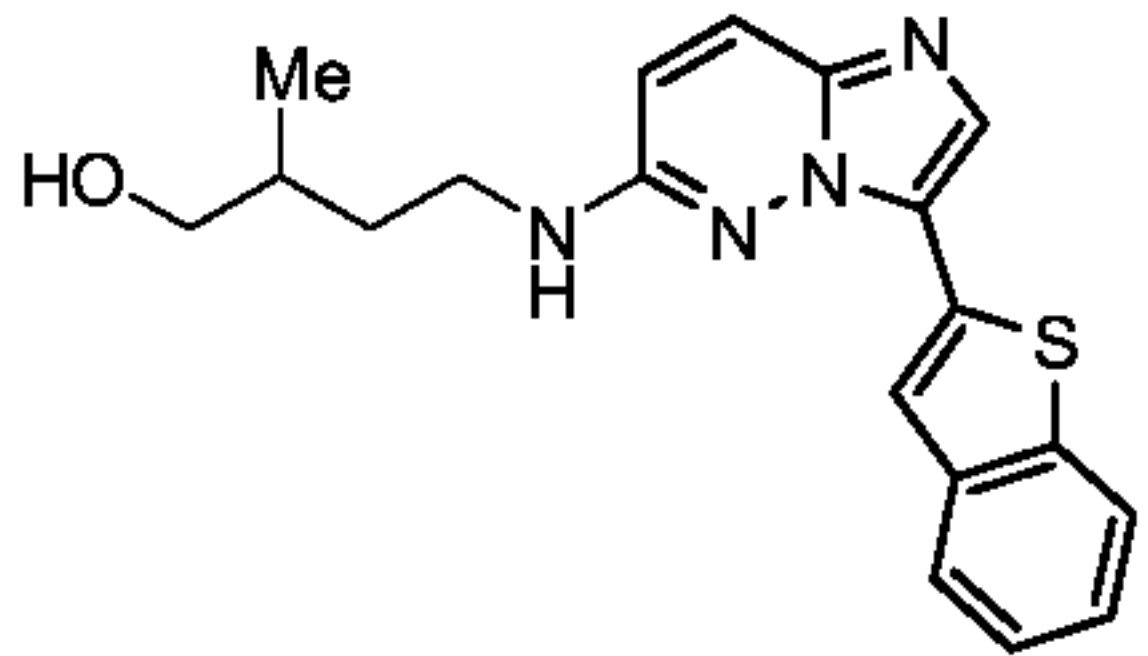
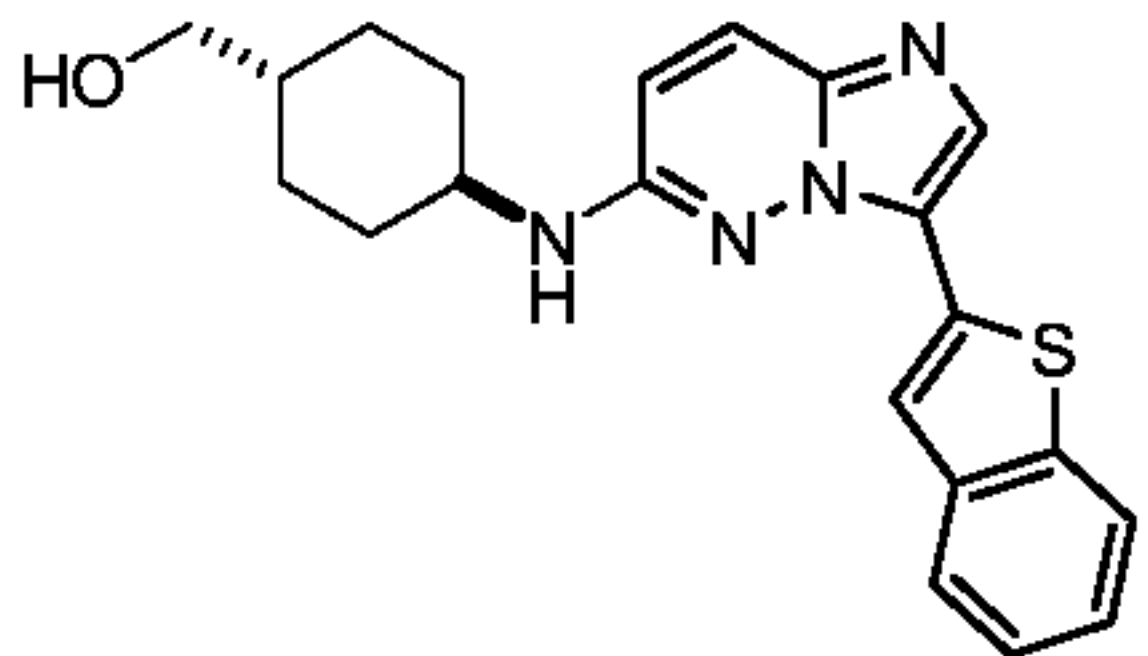
138	4-amino-2-methylbutan-1-ol	4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methylbutan-1-ol
139	<i>trans</i> -4-aminocyclohexyl)methanol	<i>trans</i> -4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexyl)methanol

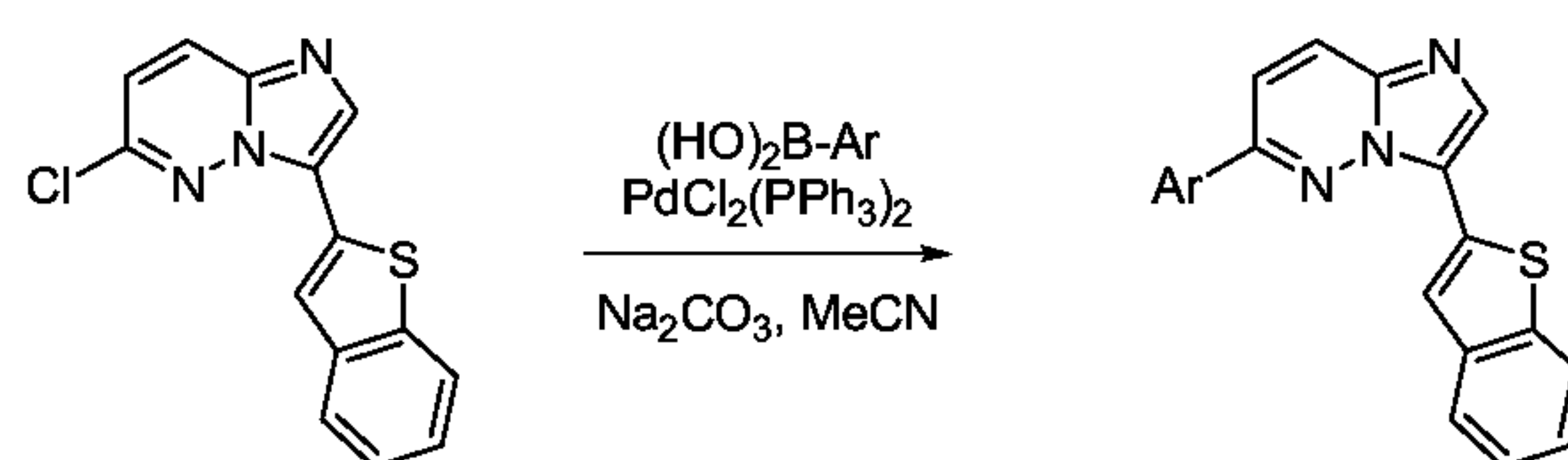
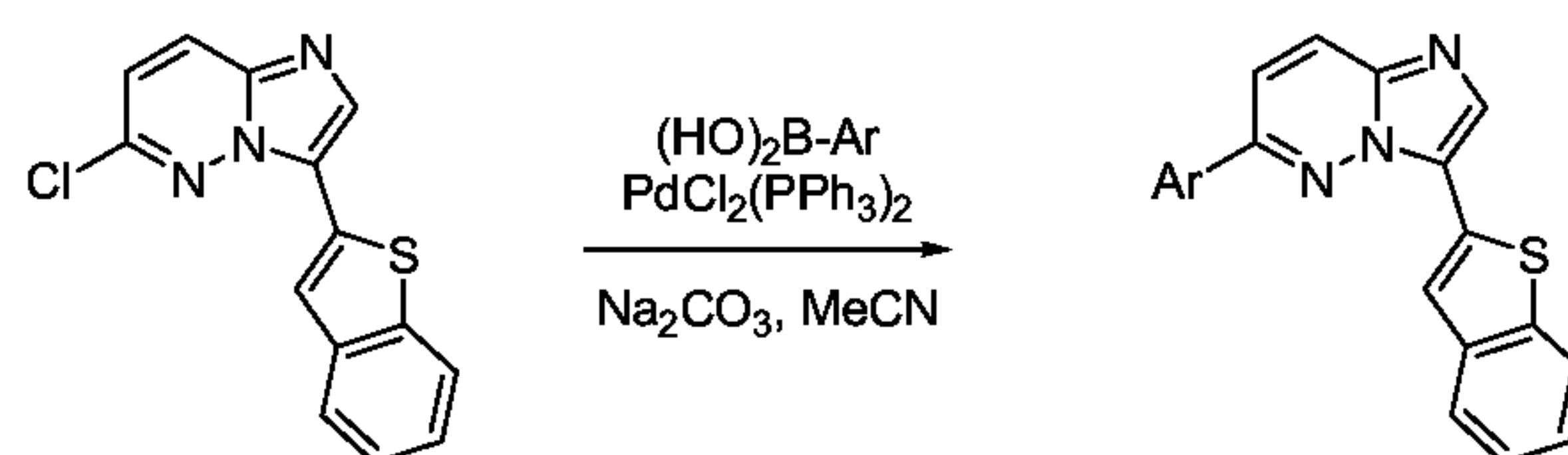
[00250] Compounds 105, 107-110, 119, 122-127, 129-132, 134-139 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 9-b**.

Table 9-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
105		<i>trans</i> -4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	365.6
107		3-(benzo[b]thiophen-2-yl)-N-methyl-N-propylimidazo[1,2-b]pyridazin-6-amine	323.6
108		2-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)ethanol	311.7
109		3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)propan-1-ol	325.6
110		4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol	339.7
119		2-(4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)piperazin-1-yl)ethanol	380.8
122		<i>cis</i> -3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	365.8

123		<i>trans</i> -3-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	365.8
124		3-(benzo[b]thiophen-2-yl)-N-((S)-2-methylpentan-3-yl)imidazo[1,2-b]pyridazin-6-amine	353.8
125		3-(benzo[b]thiophen-2-yl)-N-((R)-2-methylpentan-3-yl)imidazo[1,2-b]pyridazin-6-amine	353.8
126		((R)-1-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-2-yl)methanol	351.9
127		((S)-1-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)pyrrolidin-2-yl)methanol	351.7
129		(R)-2-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-4-methylpentan-1-ol	367.7
130		(S)-2-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-4-methylpentan-1-ol	367.6
131		methyl 1-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)piperidine-3-carboxylate	393.5
132		(1-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)piperidin-3-yl)methanol	365.8

134		N-(4-tert-butylcyclohexyl)-3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	405.7
135		5-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)pentan-1-ol	353.6
136		3-(benzo[b]thiophen-2-yl)-N-(3-(4-methylpiperazin-1-yl)propyl)imidazo[1,2-b]pyridazin-6-amine	407.5
137		3-(benzo[b]thiophen-2-yl)-N-(1-cyclohexylpiperidin-3-yl)imidazo[1,2-b]pyridazin-6-amine	432.5
138		4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methylbutan-1-ol	353.6
139		<i>trans</i> -4-(3-(benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexylmethanol	379.7

[00251] Example 10 – Synthesis of Compounds 39-40**[00252]** **Scheme 10****[00253]** **Preparation of 3-(benzo[b]thiophen-2-yl)-6-arylimidazo[1,2-b]pyridazine**

[00254] 3-(benzo[b]thiophen-2-yl)-6-chloroimidazo[1,2-b]pyridazine (50 mg, 0.175 mmol, 1.0 equiv), in acetonitrile (1.9 mL), was added the boronic ester (0.263 mmol, 1.5 equiv),

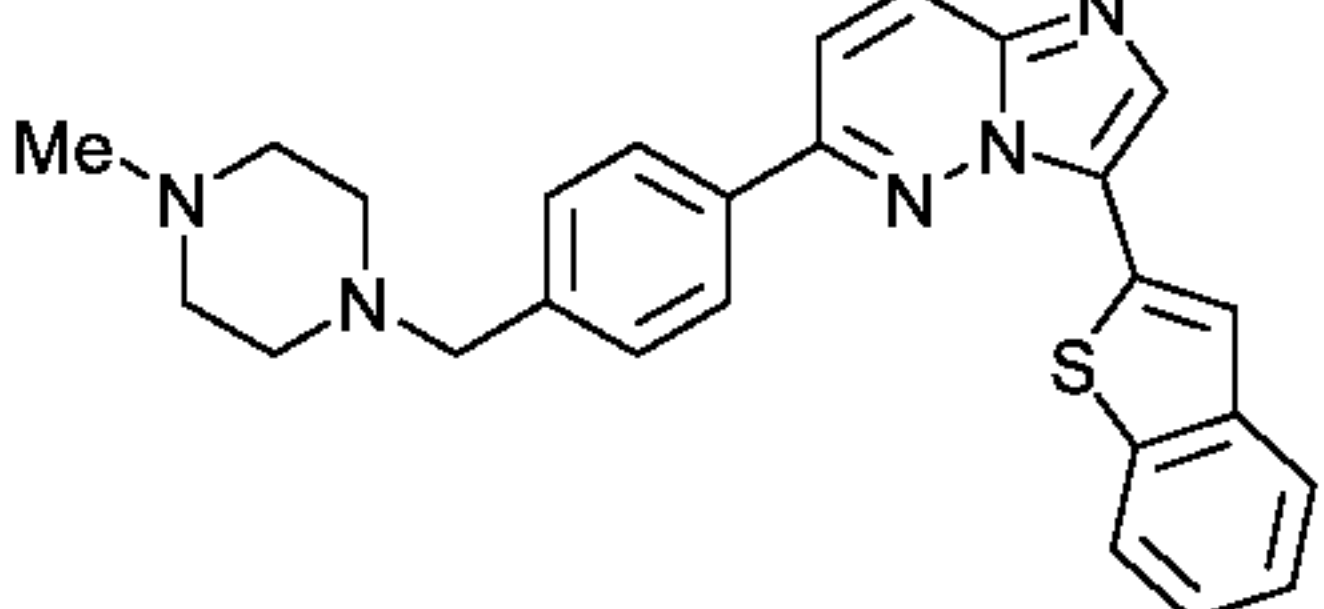
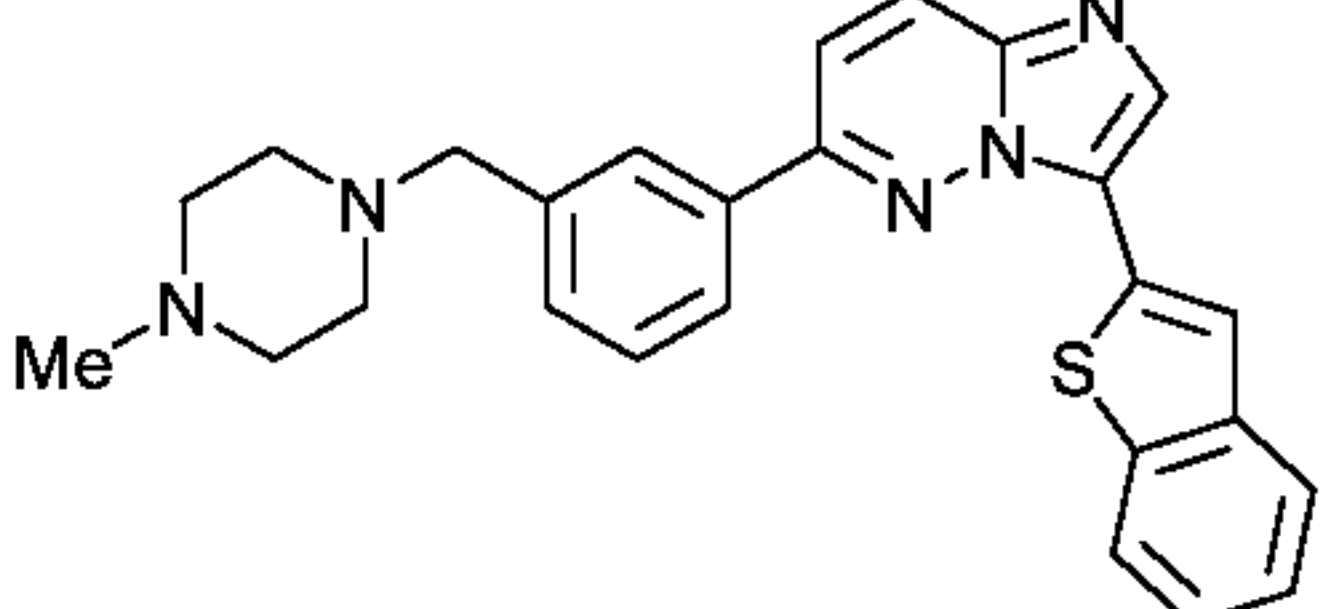
bis(triphenylphosphine)palladium(II) chloride (12 mg, 0.018 mmol, 0.1 equiv), then sodium carbonate (1.0 M aqueous solution, 10 equiv). The reaction mixture was irradiated at 150 °C for 10 min. Purification by column chromatography gave of the product.

Table 10-a

Cd.	Boronic Ester	Purified Compound Isolated
39	1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-methylpiperazine	3-(benzo[b]thiophen-2-yl)-6-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine
40	1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-methylpiperazine	3-(benzo[b]thiophen-2-yl)-6-(3-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine

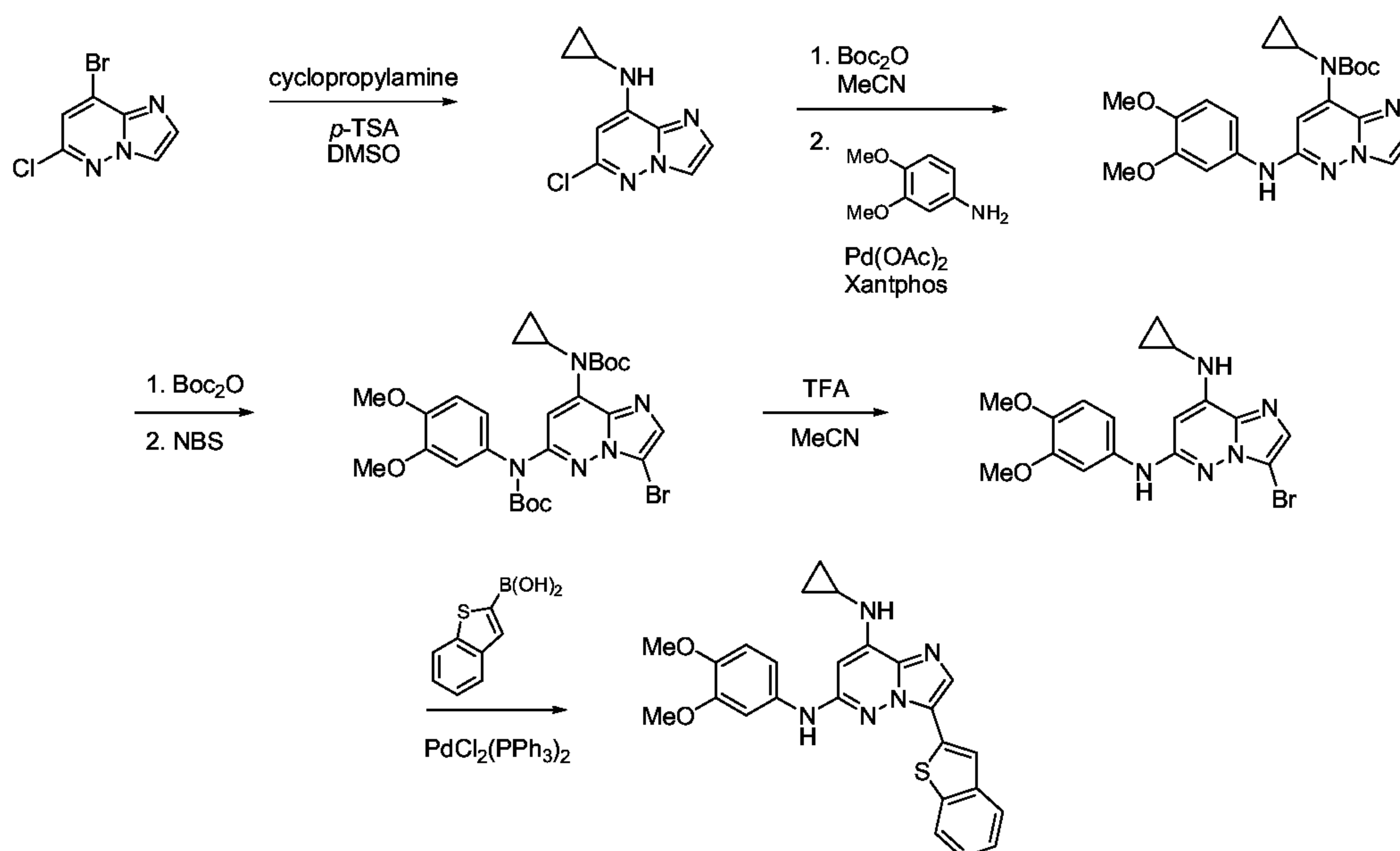
[00255] Compounds 39-40 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 10-b**.

Table 10-b

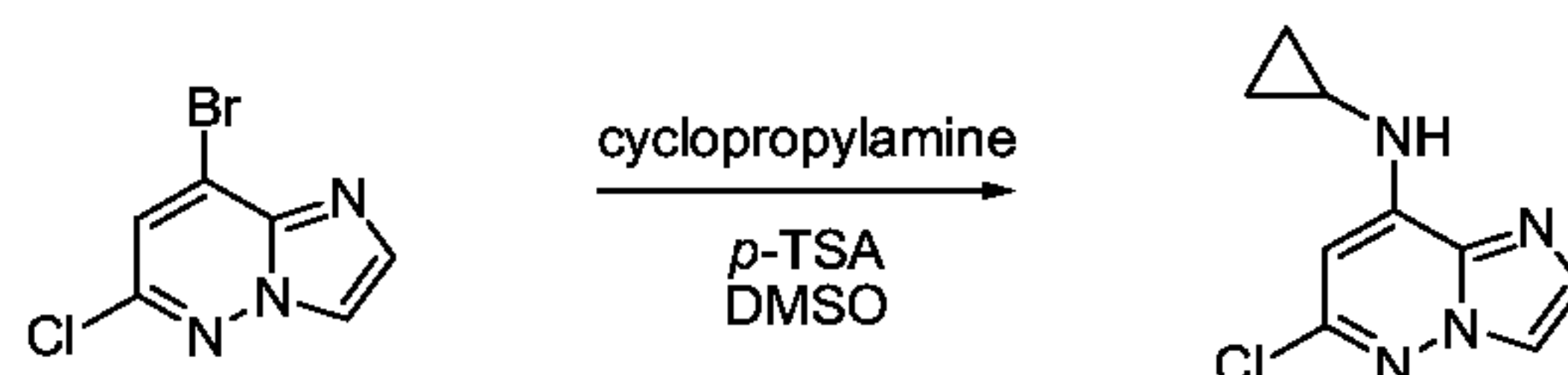
Cd.	Structure	IUPAC Name	[M+H] ⁺
39		3-(benzo[b]thiophen-2-yl)-6-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine	440.7
40		3-(benzo[b]thiophen-2-yl)-6-(3-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine	440.7

[00256] Example 11 – Synthesis of Compound 46

[00257] **Scheme 11**

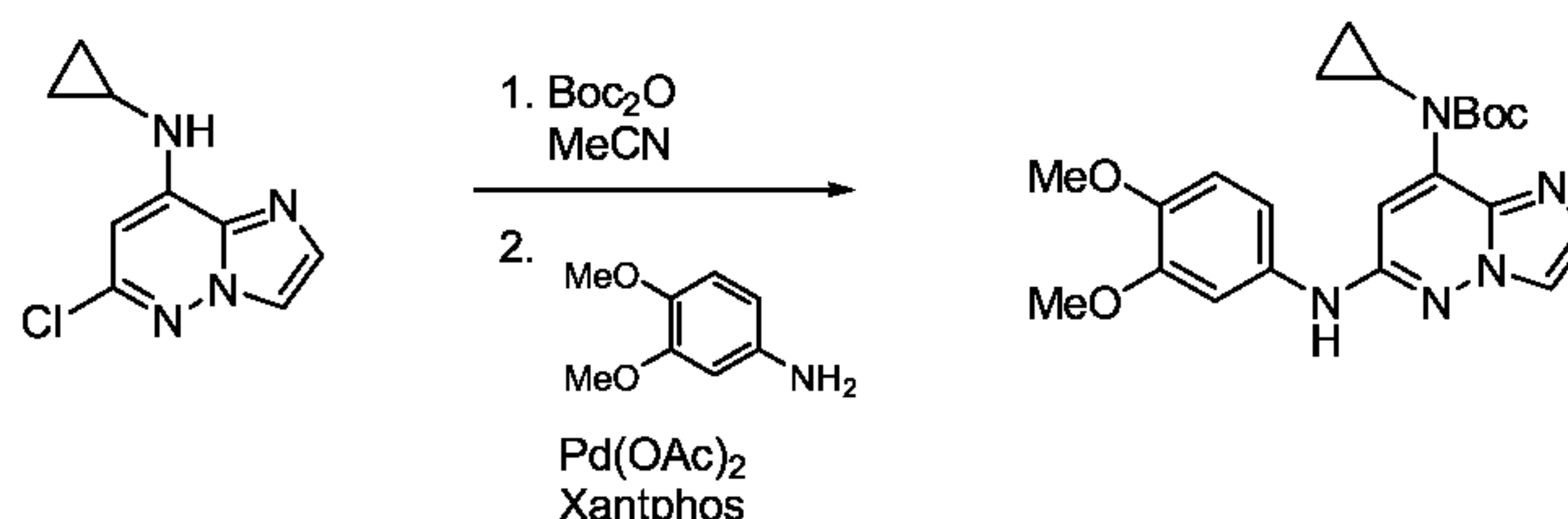


[00258] Preparation of 6-chloro-N-cyclopropylimidazo[1,2-b]pyridazin-8-amine



[00259] To a solution of 8-bromo-6-chloroimidazo[1,2-b]pyridazine (1.00 g, 3.21 mmol, 1.0 equiv) and *p*-TSA (611 mg, 3.21 mmol, 1.0 equiv) in DMSO (10.0 mL) was added cyclopropylamine (1.13 mL, 16.1 mmol, 5.0 equiv) and heated to 100 °C for 24 h. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 536 mg of the white solid, 80%.

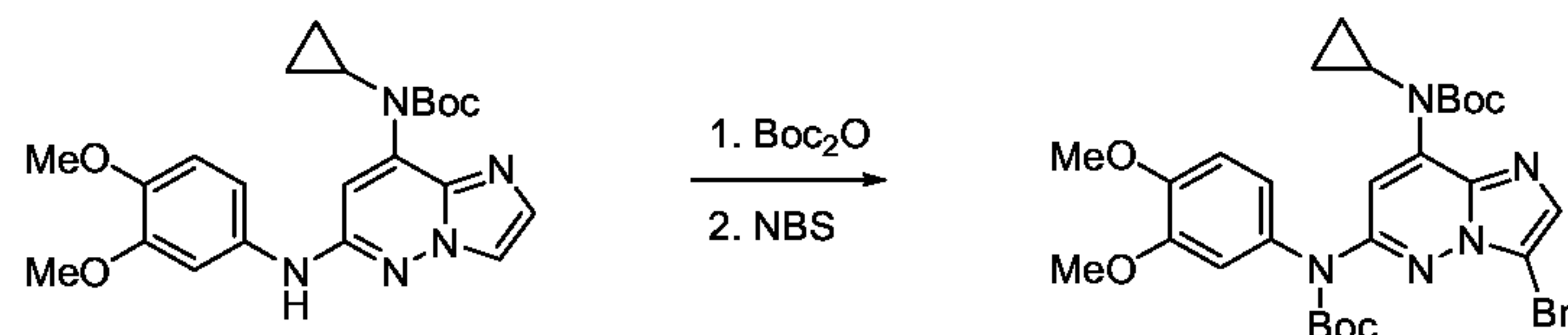
[00260] Preparation of tert-butyl 6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-8-ylcyclopropylcarbamate



[00261] To a solution of 6-chloro-N-cyclopropylimidazo[1,2-b]pyridazin-8-amine (99 mg, 0.473 mmol, 1.0 equiv) in acetonitrile (2.00 mL) was added di-*tert*-butyl dicarbonate (103 mg, 0.473 mmol, 1.0 equiv) and stirred at room temperature for 15 h. The reaction mixture was diluted with water and extracted with ethyl acetate and concentrated *in vacuo*. The crude material was diluted in dioxane (5.00 mL) and 3,4-dimethoxyaniline (109 mg, 0.709 mmol, 1.3 equiv), xantphos (55 mg, 0.0946 mmol, 0.2 equiv), palladium acetate (11 mg, 0.0473 mmol, 0.1 equiv)

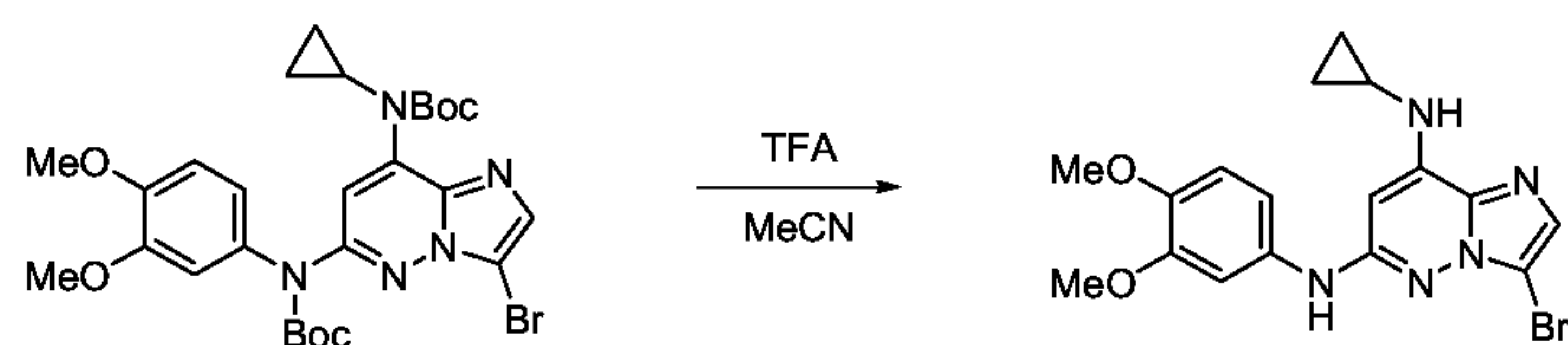
and potassium carbonate (1.31 g, 9.46 mmol, 20 equiv) was added. The reaction mixture was heated in the microwave at 150 °C for 10 minutes. Purification by column chromatography using 2% methanol in hexanes elution gave 173 mg of the brown solid, 86%.

[00262] Preparation of *bis*-Boc-protected pyridazine



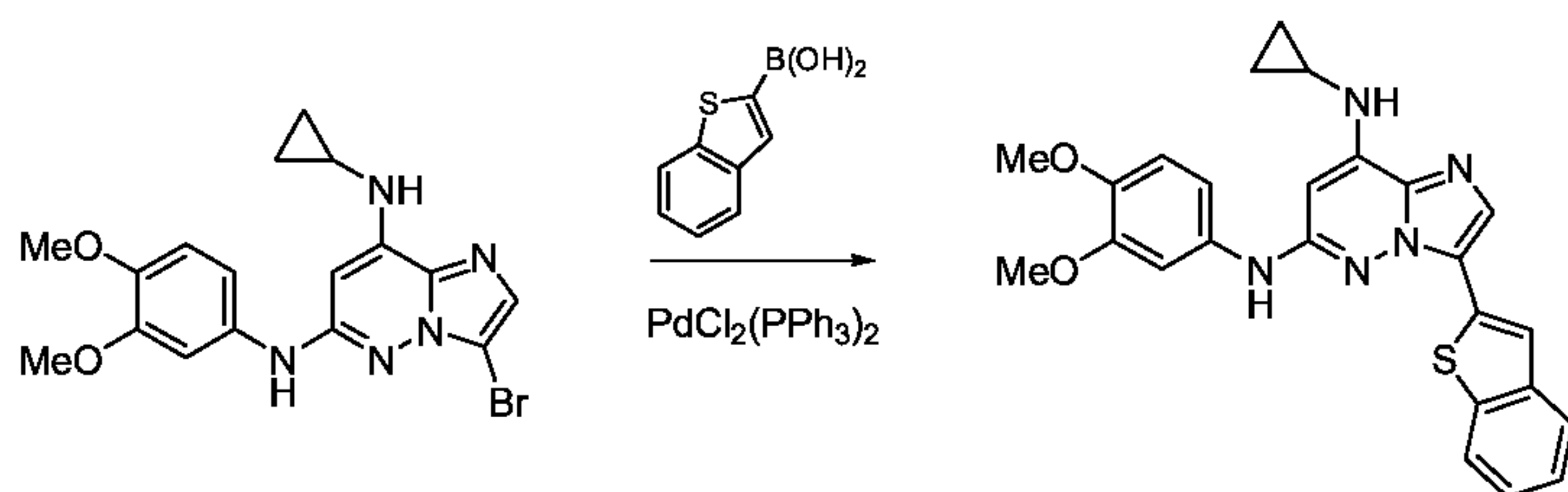
[00263] To a solution of tert-butyl 6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-8-ylcyclopropylcarbamate (173 mg, 0.407 mmol, 1.0 equiv) in acetonitrile (5.00 mL) was added di-*tert*-butyl dicarbonate (177 mg, 0.813 mmol, 2.0 equiv) and catalytic 4-dimethylaminopyridine. After 15 h, the reaction was diluted with water and extracted with ethyl acetate. The crude material was diluted in chloroform (10.0 mL) and *N*-bromosuccinimide (72 mg, 0.407 mmol, 1.0 equiv) and heated to 70 °C for 20 minutes. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 214 mg of the yellow solid, 87%.

[00264] Preparation of 3-bromo-N₈-cyclopropyl-N₆-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazine-6,8-diamine



[00265] To the *bis*-Boc-protected pyridazine (99 mg, 0.163 mmol, 1.0 equiv) in dichloromethane (5.00 mL) was added excess trifluoroacetic acid (1.00 mL) and stirred for 3 h. The reaction was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 2% methanol in hexanes elution gave 66 mg of the brown solid, 100%.

[00266] Preparation of 3-(benzo[*b*]thiophen-2-yl)-N₈-cyclopropyl-N₆-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazine-6,8-diamine

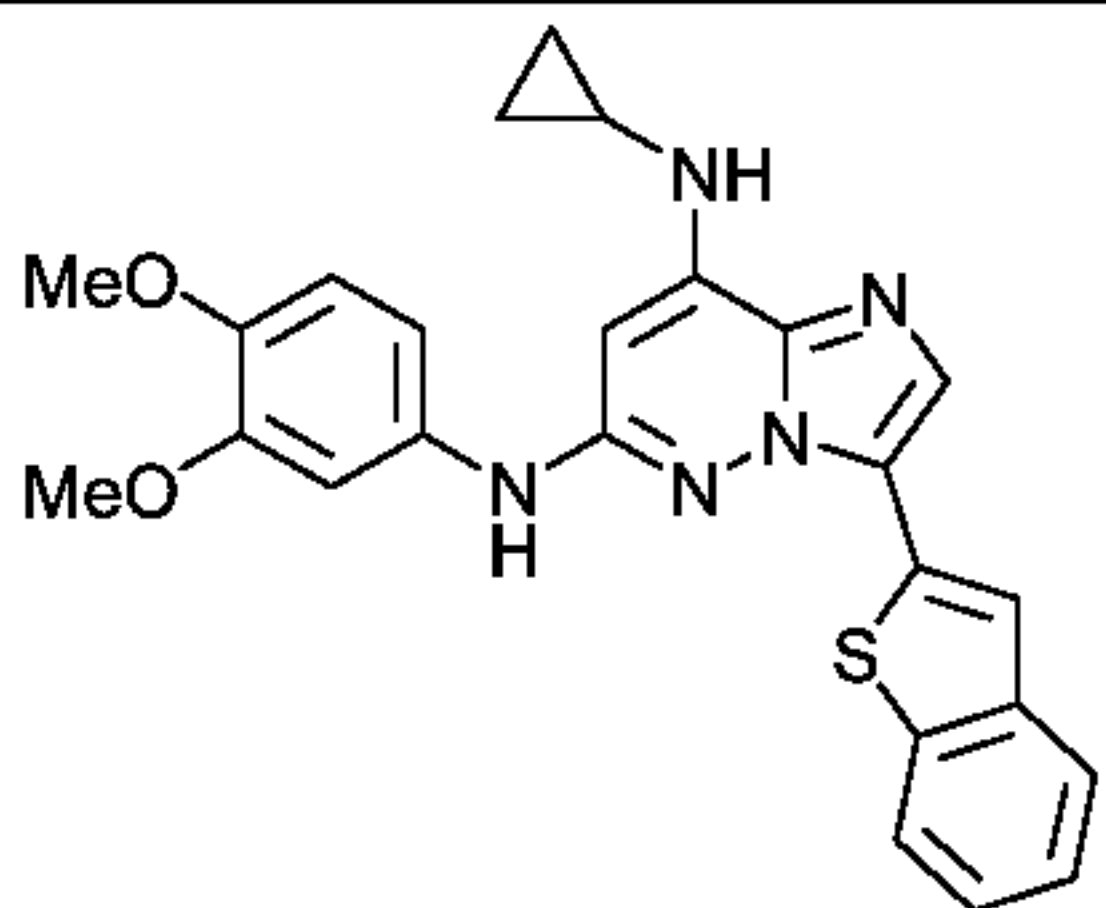


[00267] To a solution of 3-bromo-N₈-cyclopropyl-N₆-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazine-6,8-diamine (66 mg, 0.163 mmol, 1.0 equiv) in acetonitrile (1.63 mL), was added benzo[*b*]thiophen-2-yl-2-boronic acid (58 mg, 0.327 mmol, 2.0 equiv),

bis(triphenylphosphine)palladium(II) chloride (11 mg, 0.0163 mmol, 0.1 equiv), then sodium carbonate (1.63 mL, 1.0 M aqueous solution, 10 equiv). The reaction mixture was irradiated at 150 °C for 10 min. Purification by column chromatography gave 26 mg of the brown solid, 34%.

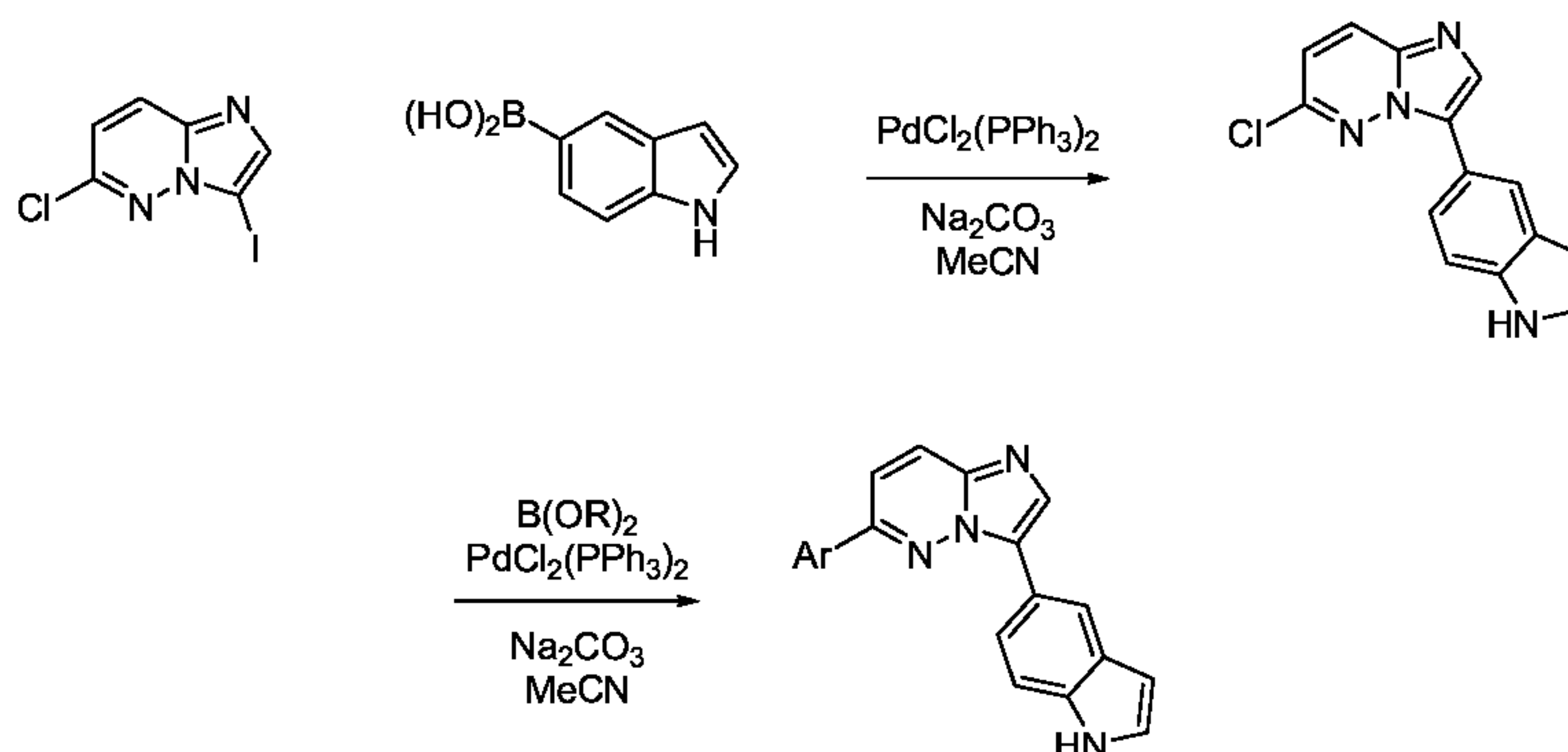
[00268] Compound 46 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 11-b**.

Table 11-b

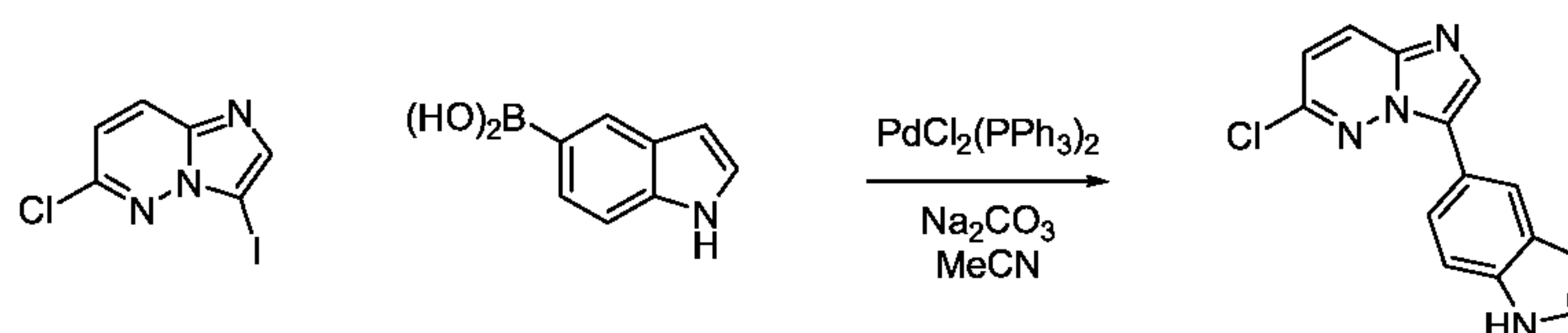
Cd.	Structure	IUPAC Name	[M+H] ⁺
46		3-(benzo[b]thiophen-2-yl)-N ₈ -cyclopropyl-N ₆ -(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazine	458.8

[00269] Example 12 – Synthesis of Compounds 49-50, 59

[00270] **Scheme 12**

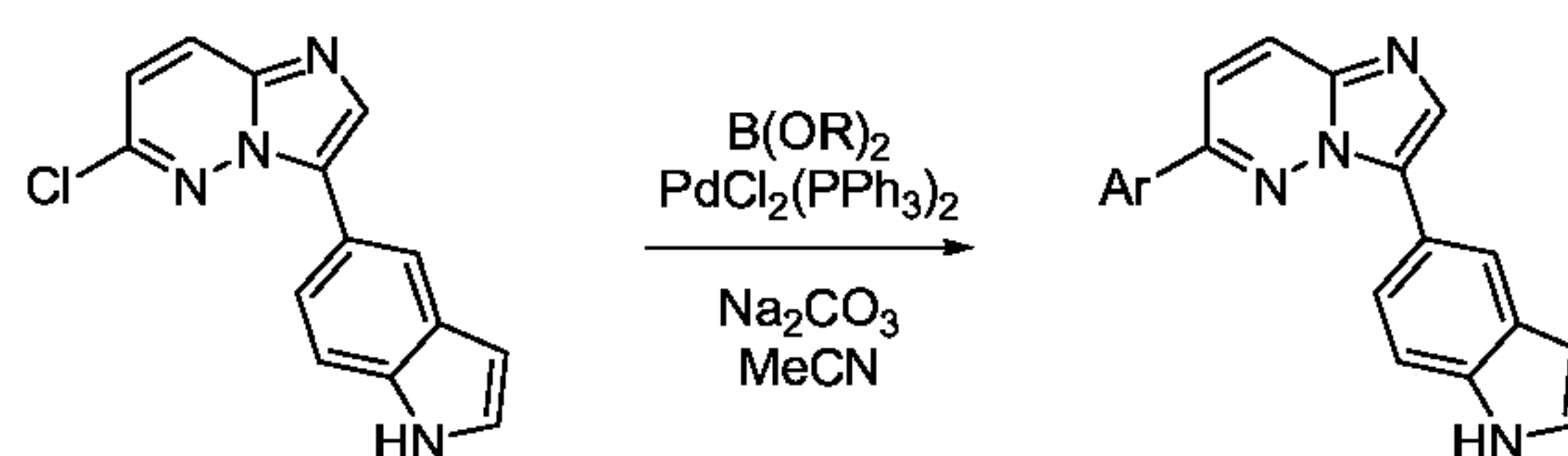


[00271] **Preparation of 6-chloro-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazine**



[00272] 6-chloro-3-iodoimidazo[1,2-b]pyridazine (1.00 g, 4.30 mmol, 1.0 equiv), in acetonitrile (20 mL), was added 1H-indol-5-yl-5-boronic acid (1.04 g, 6.45 mmol, 1.5 equiv), bis(triphenylphosphine)palladium(II) chloride (157 mg, 0.215 mmol, 0.05 equiv), then sodium carbonate (4.83 mL, 1.0 M aqueous solution, 2.0 equiv). The reaction mixture heated in the microwave at 150 °C for 20 min. Purification by column chromatography using 2% methanol in dichloromethane elutions gave 1.04 g of the white solid, 60%.

[00273] **Preparation of 3-(1H-indol-5-yl)-6-arylimidazo[1,2-b]pyridazine**



[00274] 6-chloro-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazine (60 mg, 0.223 mmol, 1.0 equiv), in acetonitrile (1.00 mL), was added boronic acid (0.241 mmol, 1.3 equiv), bis(triphenylphosphine)palladium(II) chloride (2 mg, 0.002, 0.01 equiv), then sodium carbonate (1.00 mL, 1.0 M aqueous solution). The reaction mixture heated in the microwave at 150 °C for 10 min. Purification by column chromatography using 5% methanol in hexanes elution gave the product.

Table 12-a

Cd.	Boronic Ester	Purified Compound Isolated
49	1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-methylpiperazine	3-(1H-indol-5-yl)-6-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine
50	1H-indol-5-yl-5-boronic acid	3,6-di(1H-indol-5-yl)imidazo[1,2-b]pyridazine
59	3,4,5-trimethoxyphenylboronic acid	3-(1H-indol-5-yl)-6-(3,4,5-trimethoxyphenyl)imidazo[1,2-b]pyridazine

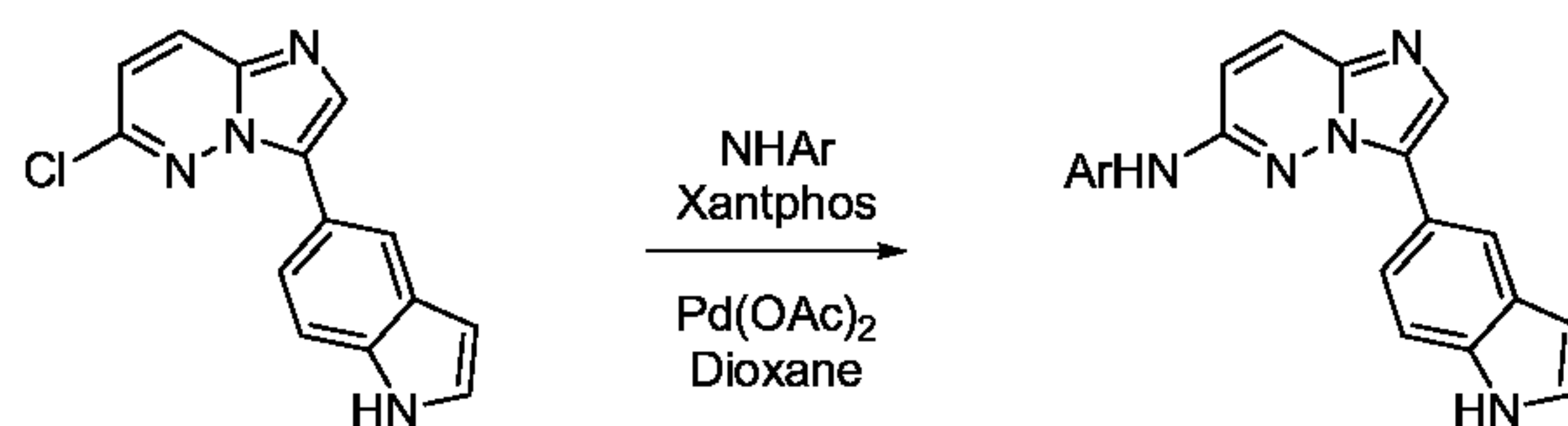
[00275] Compounds 49-50, 59 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 12-b**.

Table 12-b

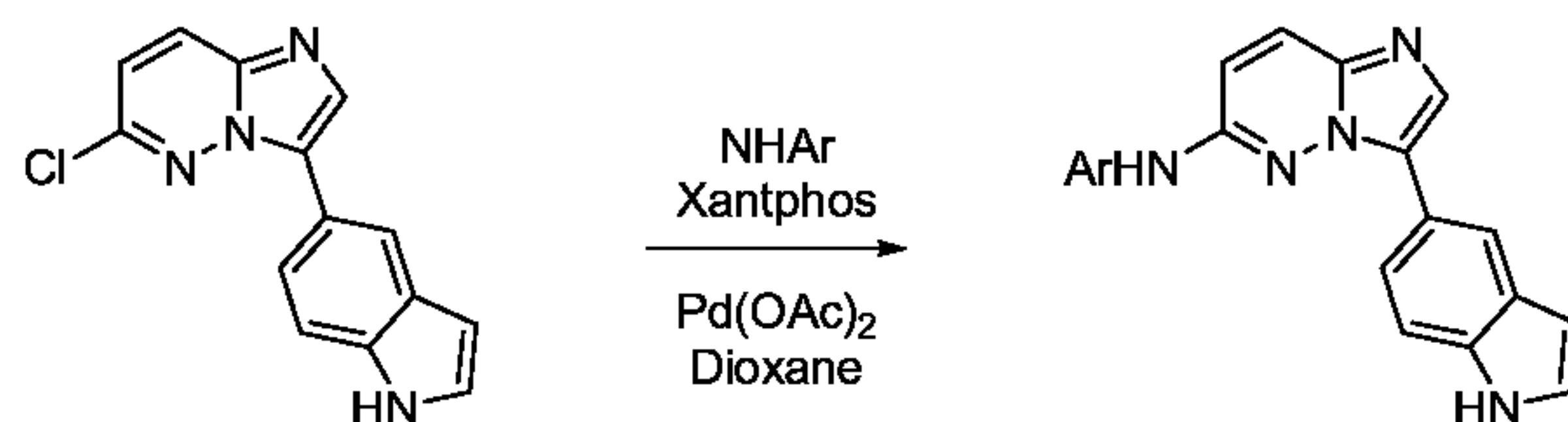
Cd.	Structure	IUPAC Name	[M+H] ⁺
49		3-(1H-indol-5-yl)-6-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine	423.6
50		3,6-di(1H-indol-5-yl)imidazo[1,2-b]pyridazine	350.6
59		3-(1H-indol-5-yl)-6-(3,4,5-trimethoxyphenyl)imidazo[1,2-b]pyridazine	401.6

[00276] Example 13 – Synthesis of Compounds 52-58, 60-61

[00277] **Scheme 13**



[00278] **Preparation of 3-(1H-indol-5-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine**



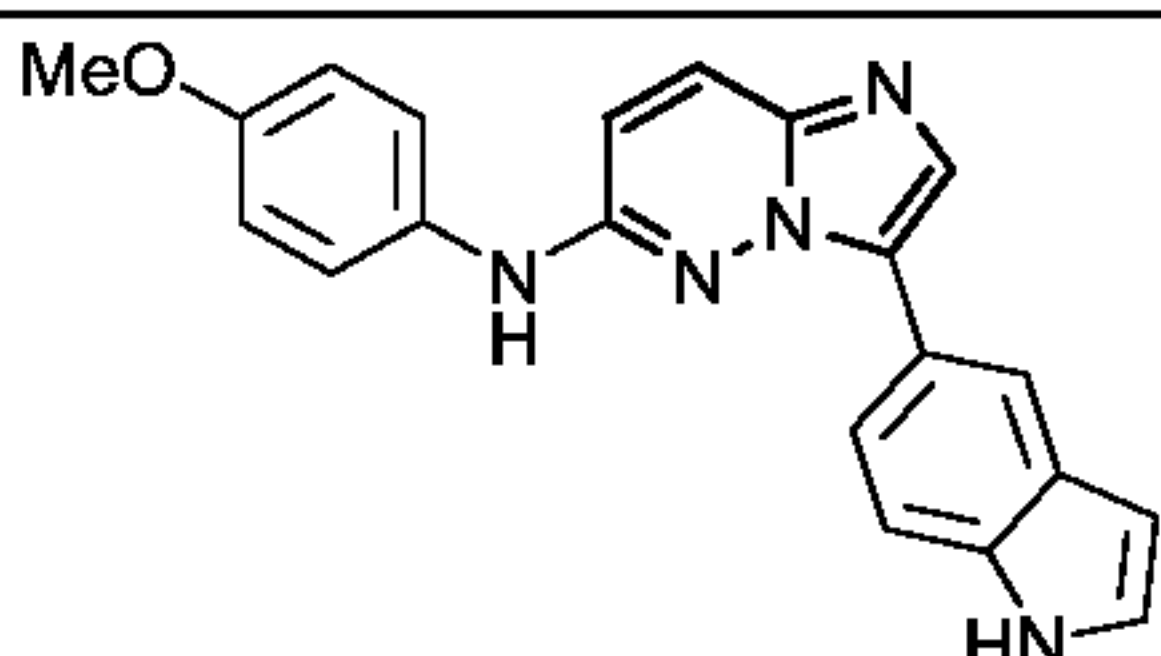
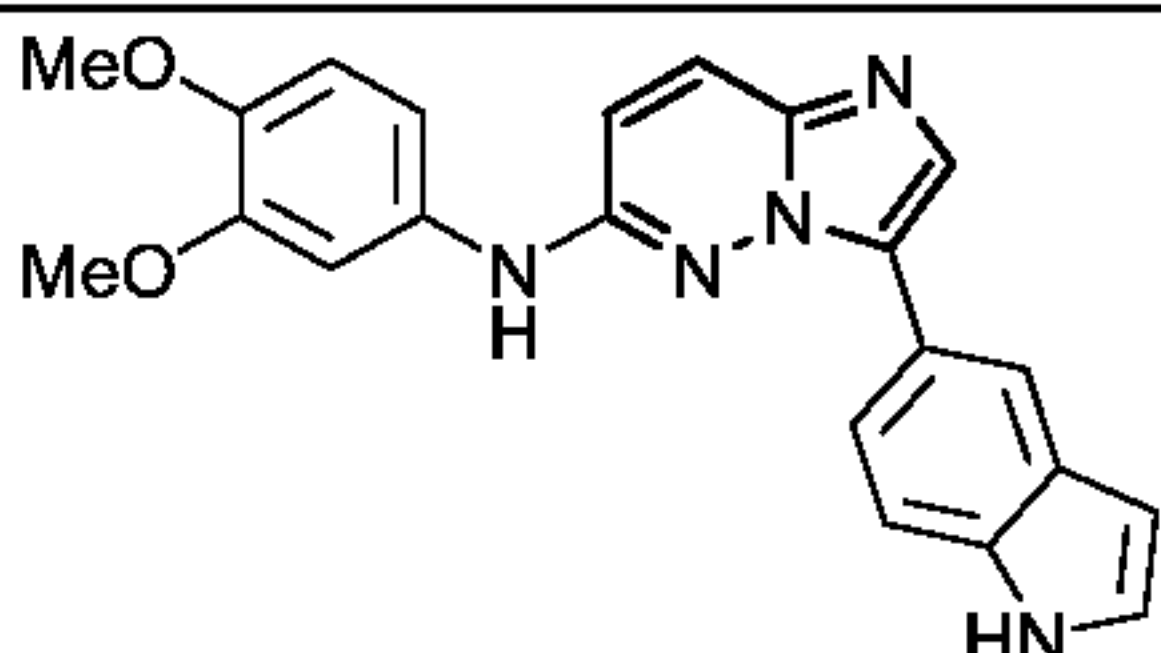
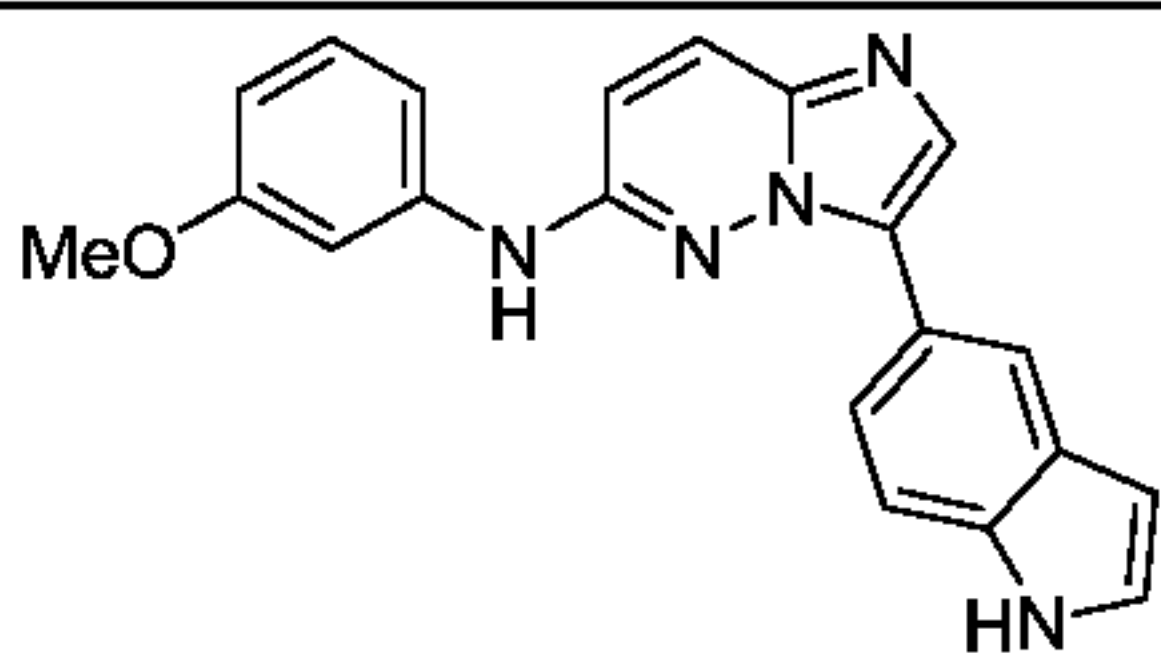
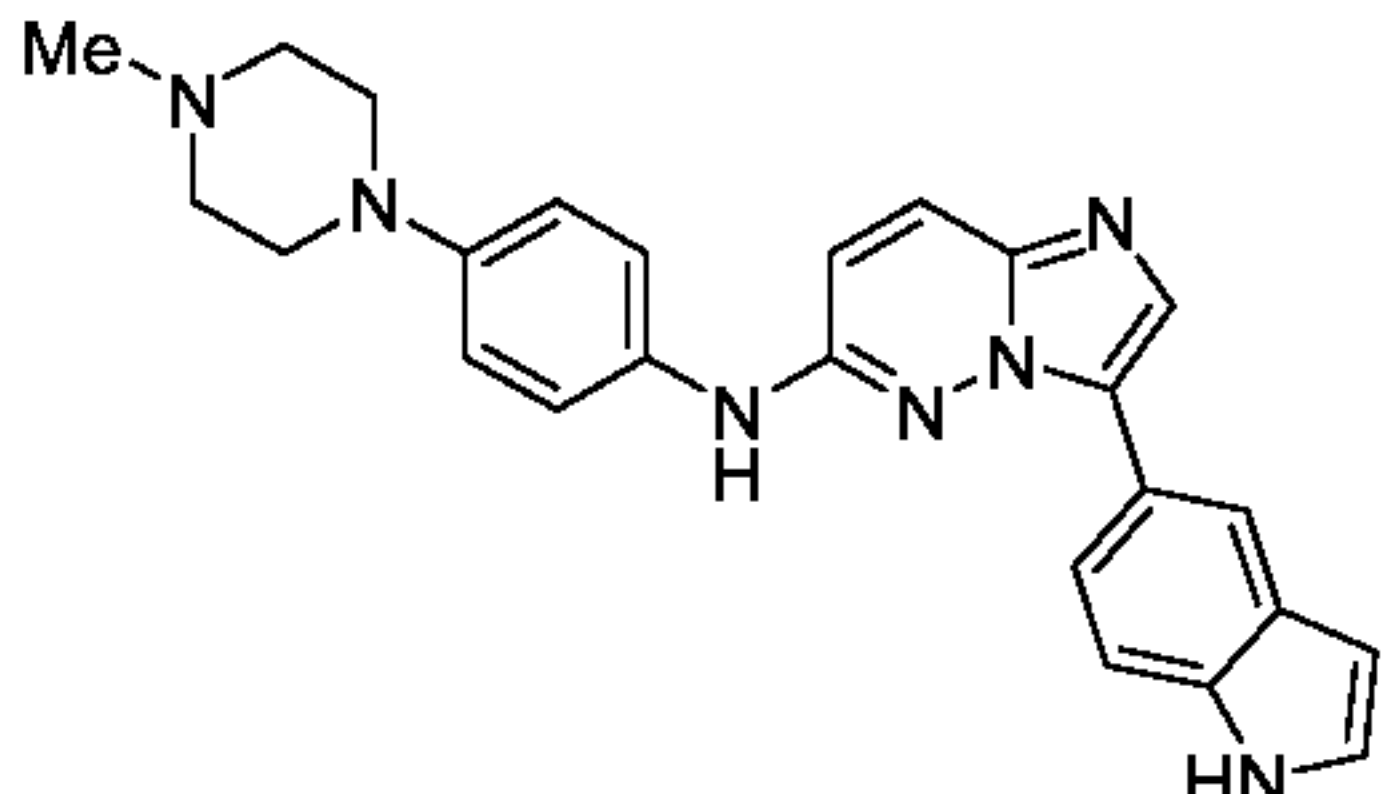
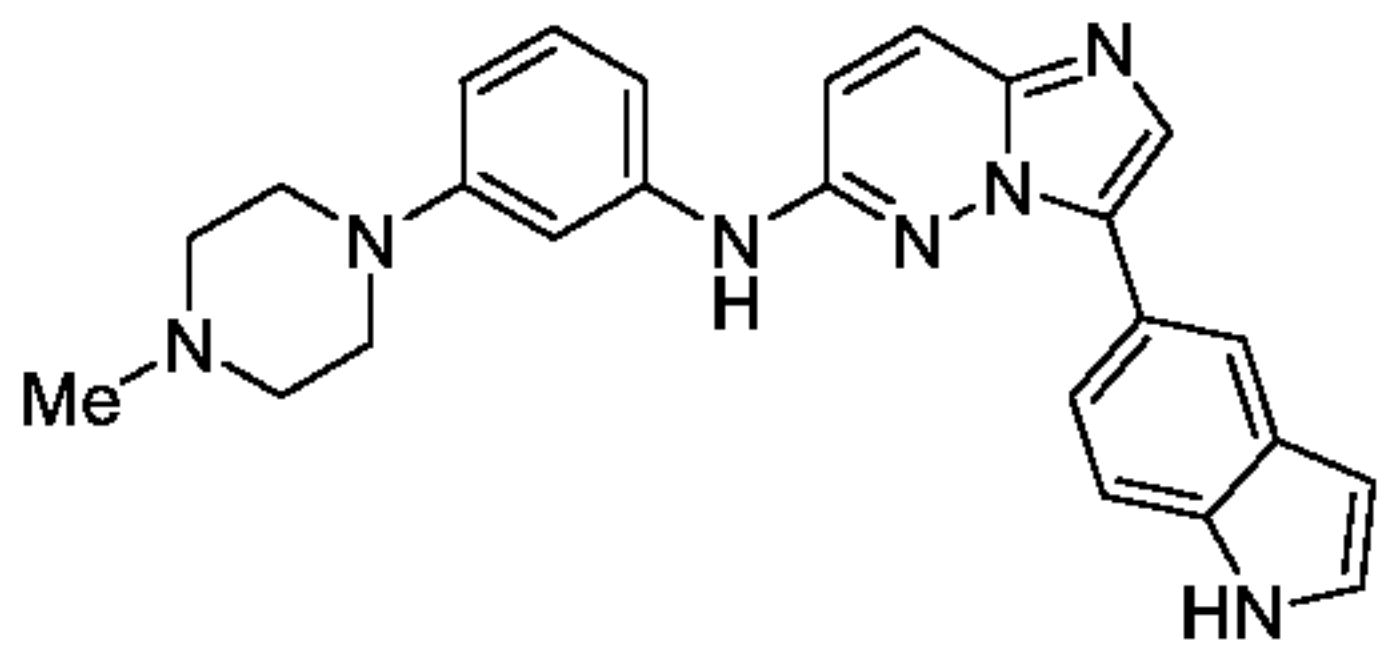
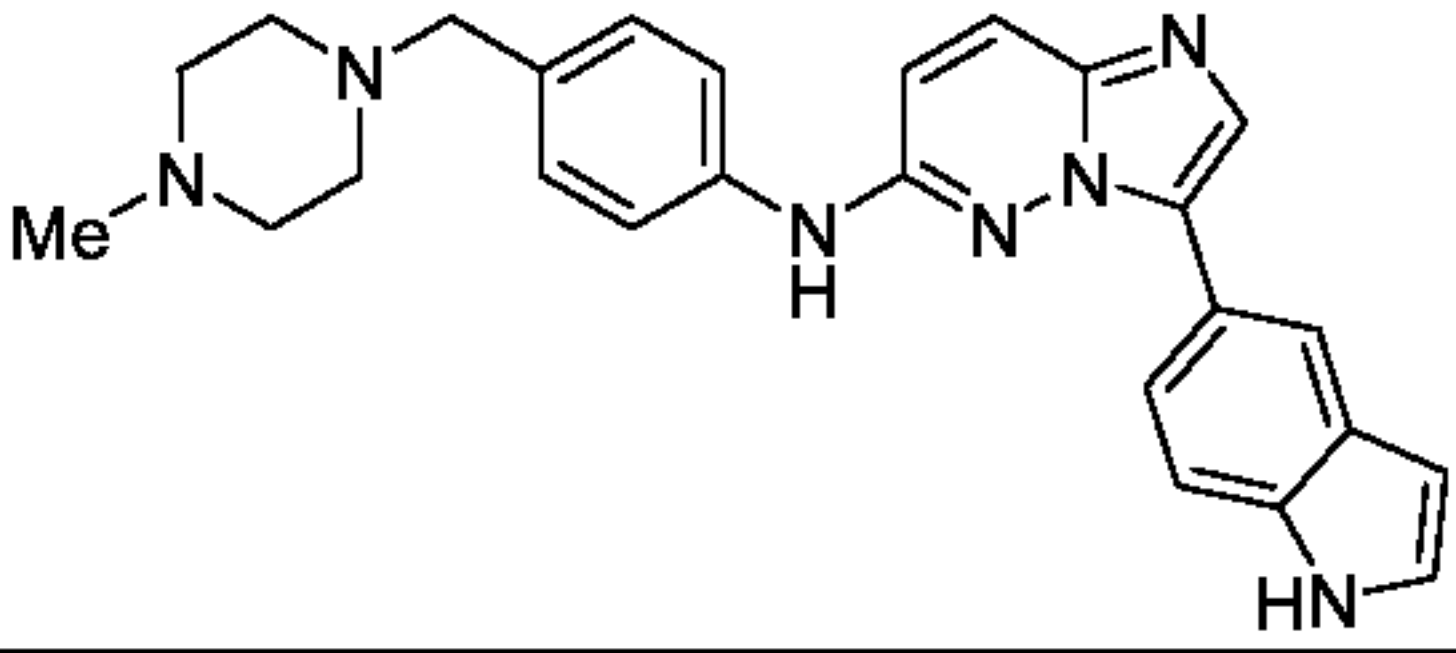
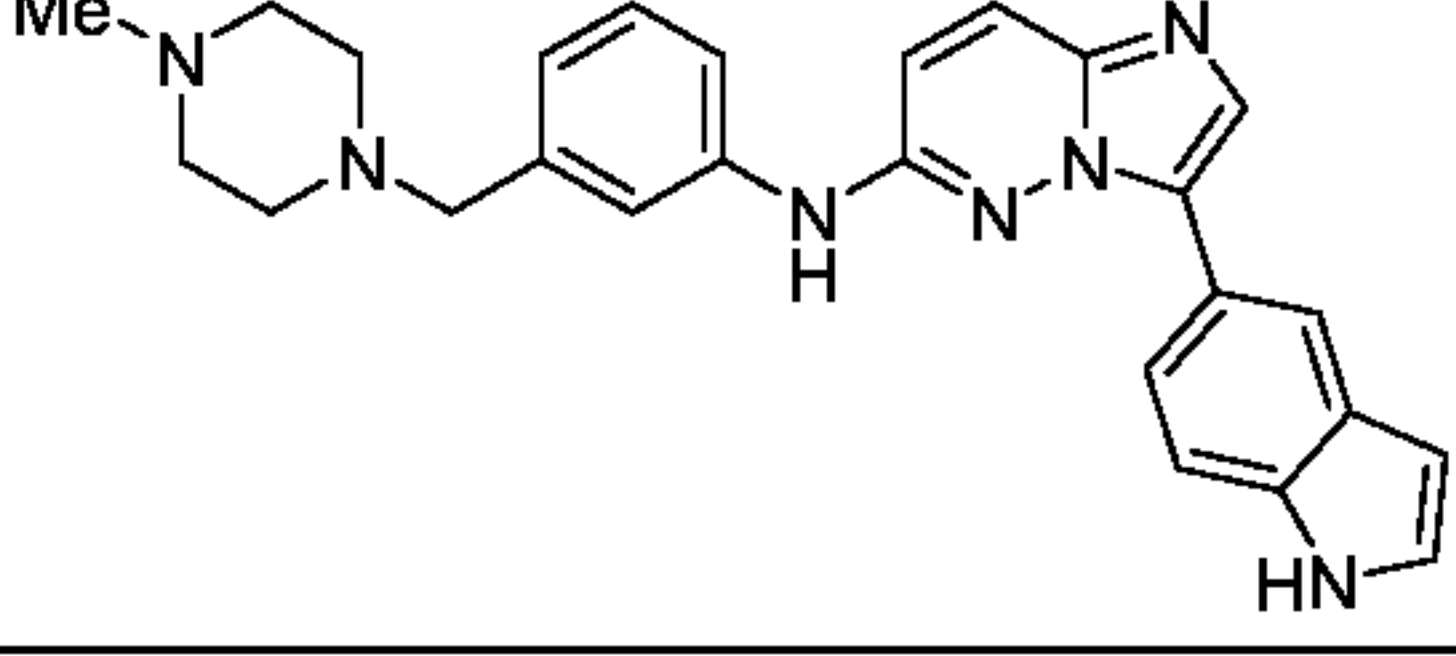
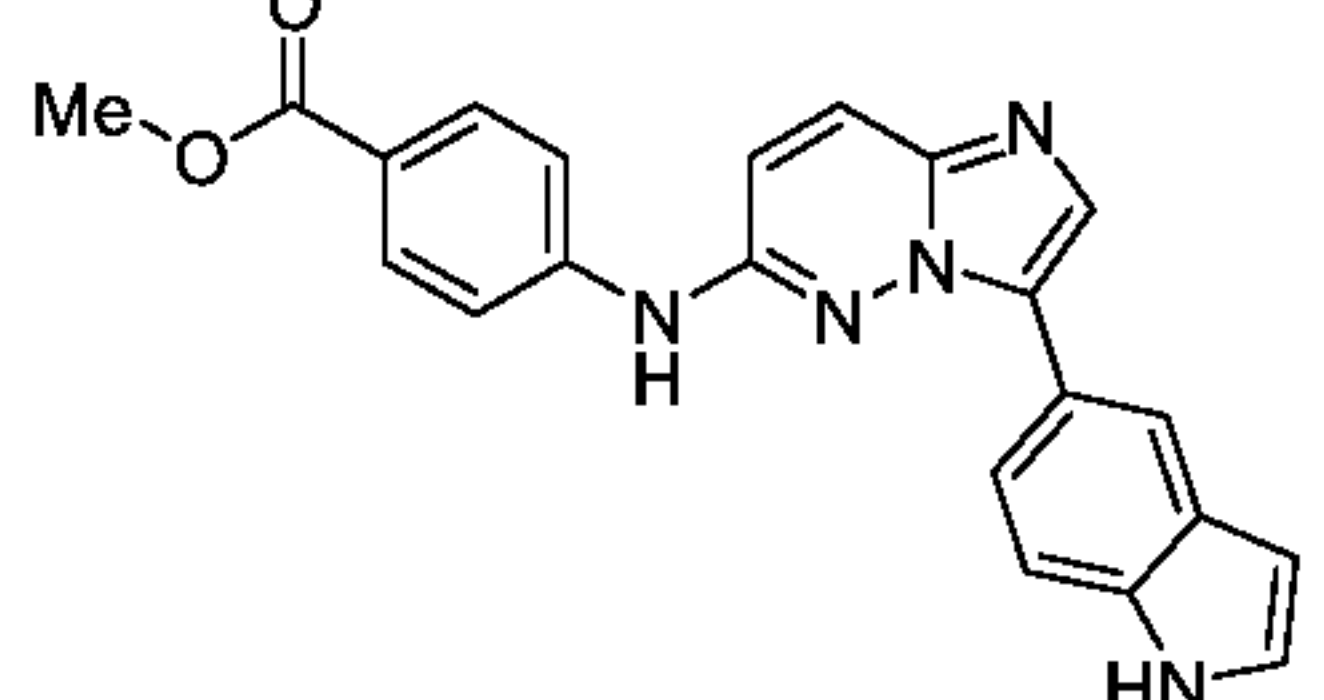
[00279] To a solution of 6-chloro-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazine (50 mg, 0.186 mmol, 1.0 equiv), xantphos (22 mg, 0.0372 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0186 mmol, 0.1 equiv), and potassium carbonate (514 mg, 3.72 mmol, 20 equiv) in dioxane (5.0 mL) was added amine (0.279 mmol, 1.5 equiv) and heated to 100 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

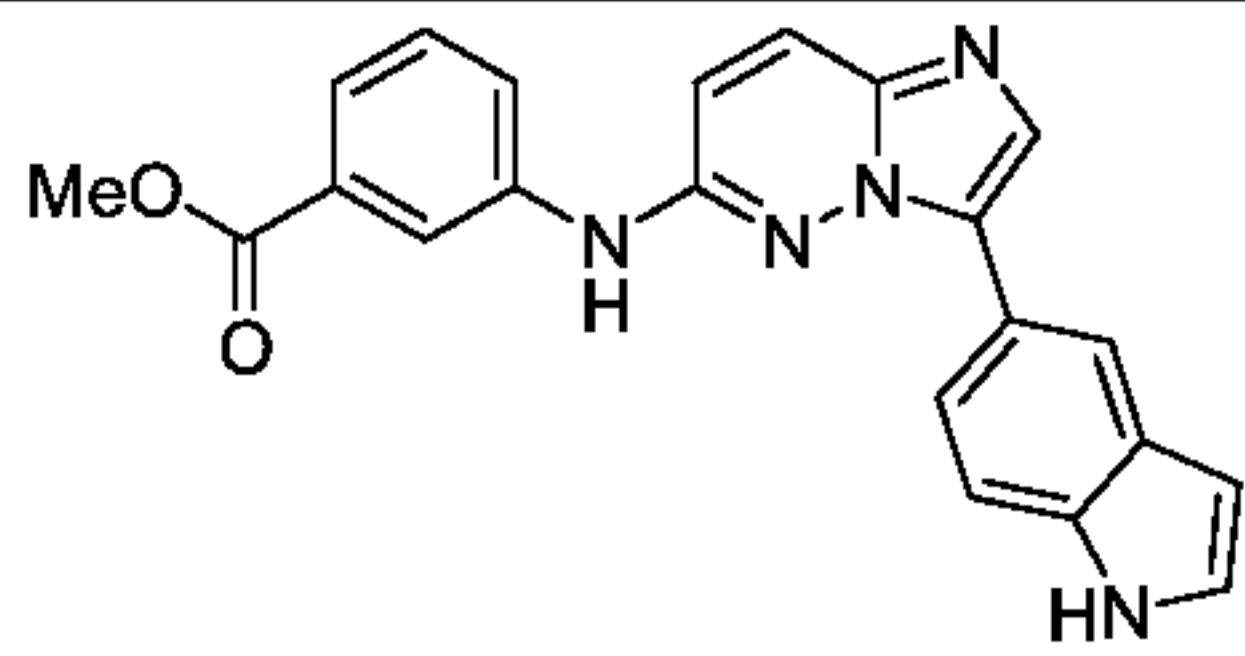
Table 13-a

Cd.	Amine	Purified Compound Isolated
52	4-methoxybenzenamine	3-(1H-indol-5-yl)-N-(4-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
53	3,4-dimethoxyaniline	3-(1H-indol-5-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
54	3-methoxybenzenamine	3-(1H-indol-5-yl)-N-(3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
55	4-(4-methylpiperazin-1-yl)benzenamine	3-(1H-indol-5-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine
56	3-(4-methylpiperazin-1-yl)benzenamine	3-(1H-indol-5-yl)-N-(3-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine
57	4-((4-methylpiperazin-1-yl)methyl)benzenamine	3-(1H-indol-5-yl)-N-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine
58	3-((4-methylpiperazin-1-yl)methyl)benzenamine	3-(1H-indol-5-yl)-N-(3-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine
60	methyl 4-aminobenzoate	methyl 4-(3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoate
61	methyl 3-aminobenzoate	methyl 3-(3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoate

[00280] Compounds 52-58, 60-61 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 13-b.

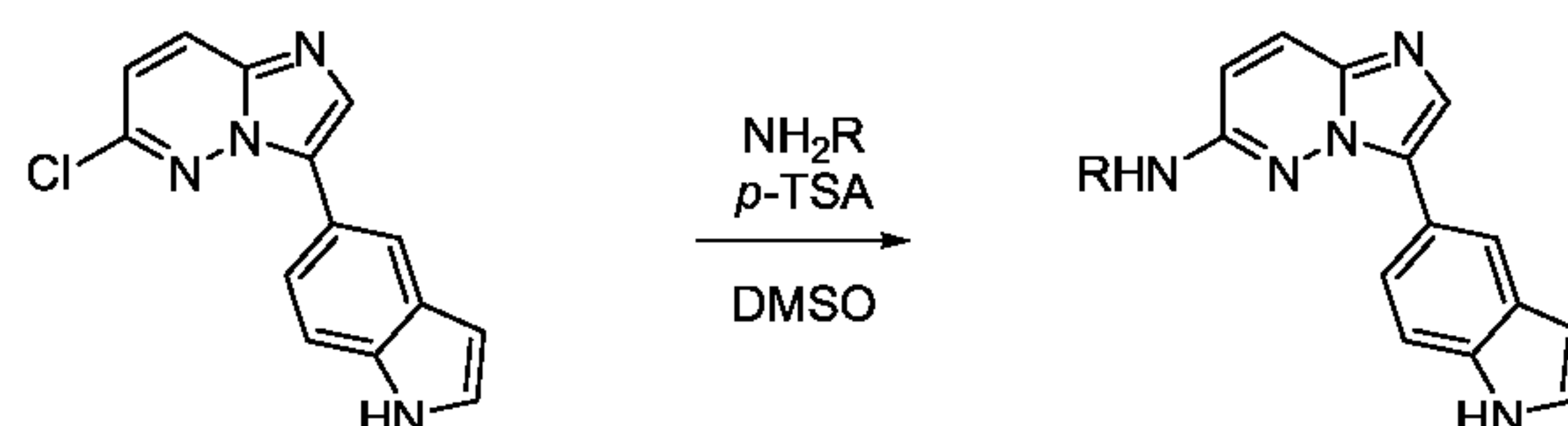
Table 13-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
52		3-(1H-indol-5-yl)-N-(4-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	356.7
53		3-(1H-indol-5-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	386.6
54		3-(1H-indol-5-yl)-N-(3-methoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	356.7
55		3-(1H-indol-5-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	424.8
56		3-(1H-indol-5-yl)-N-(3-(4-methylpiperazin-1-yl)phenyl)imidazo[1,2-b]pyridazin-6-amine	424.8
57		3-(1H-indol-5-yl)-N-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	438.8
58		3-(1H-indol-5-yl)-N-(3-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazin-6-amine	438.8
60		methyl 4-(3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoate	398.6

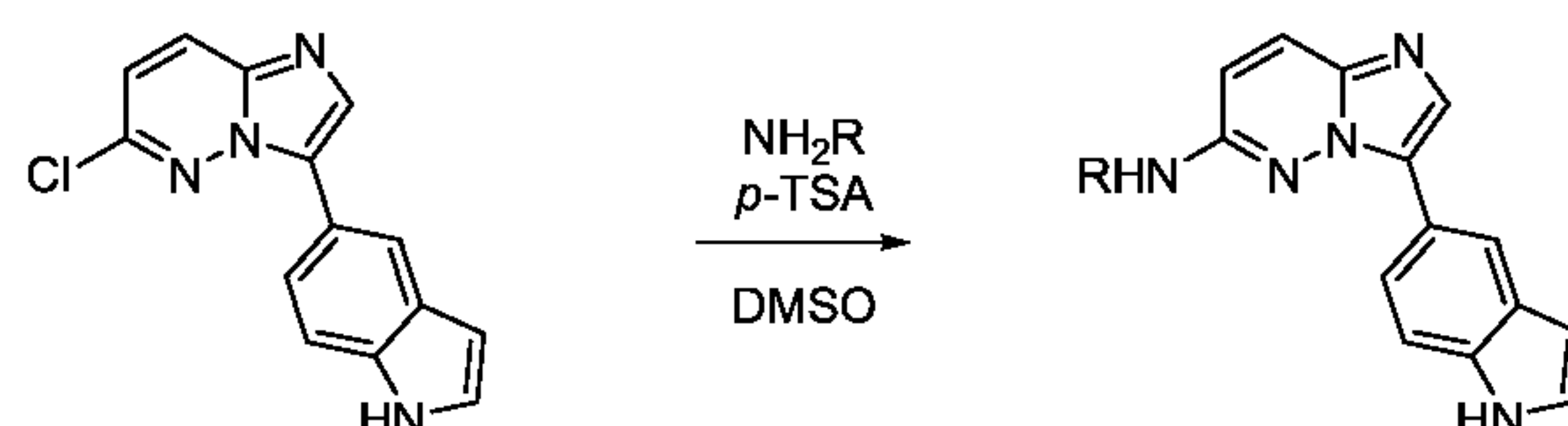
61		methyl 3-(3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoate	384.7
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[00281] Example 14 – Synthesis of Compounds 140-143, 148-150, 158

[00282] **Scheme 14**



[00283] **Preparation of 3-(1H-indol-5-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine**



[00284] To a solution of 6-chloro-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazine (150 mg, 0.500 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (95 mg, 0.500 mmol, 1.0 equiv) and amine (1.95 mmol, 4.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave the product.

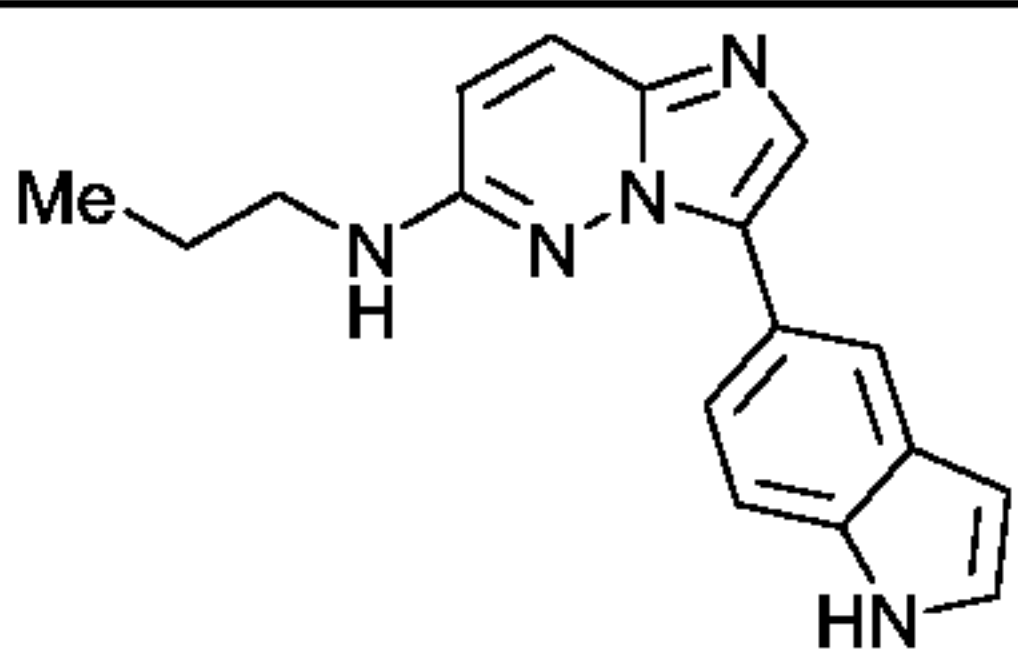
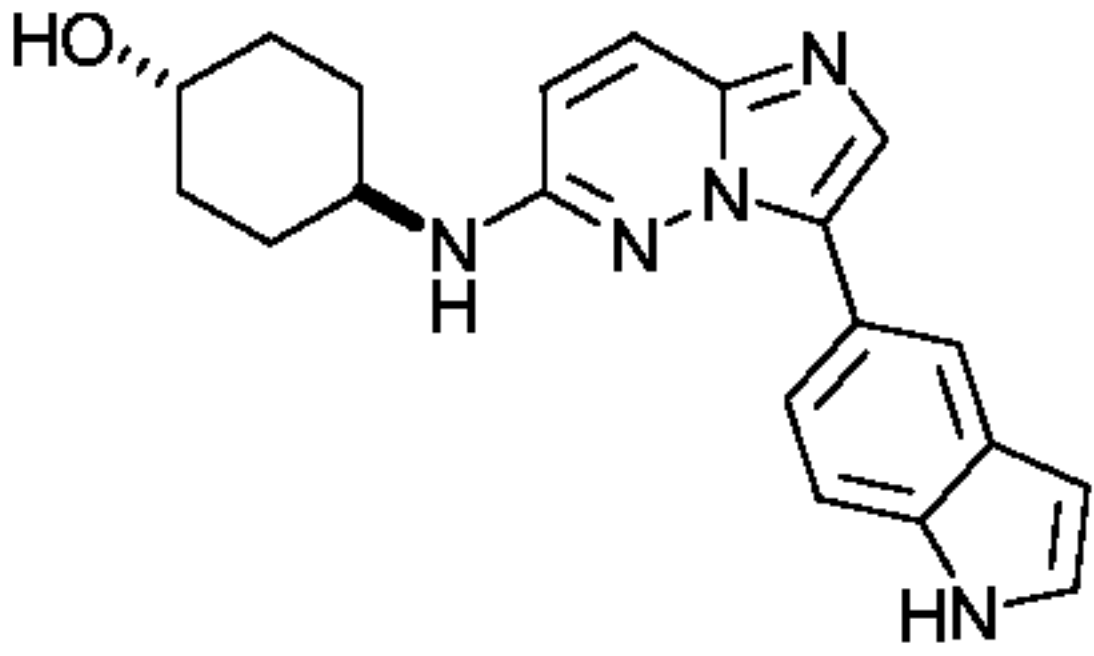
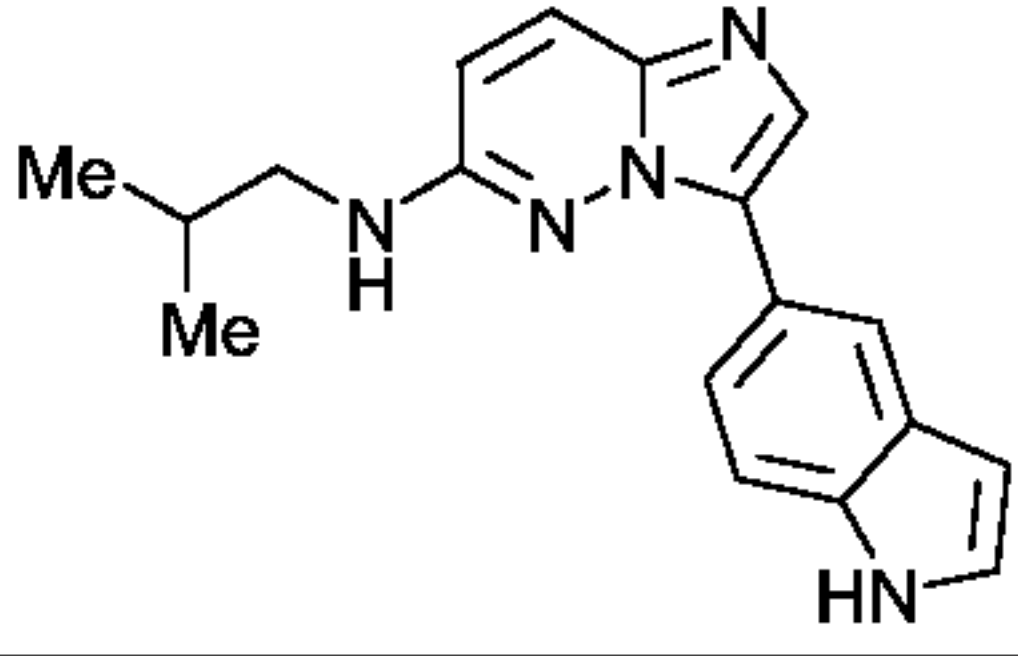
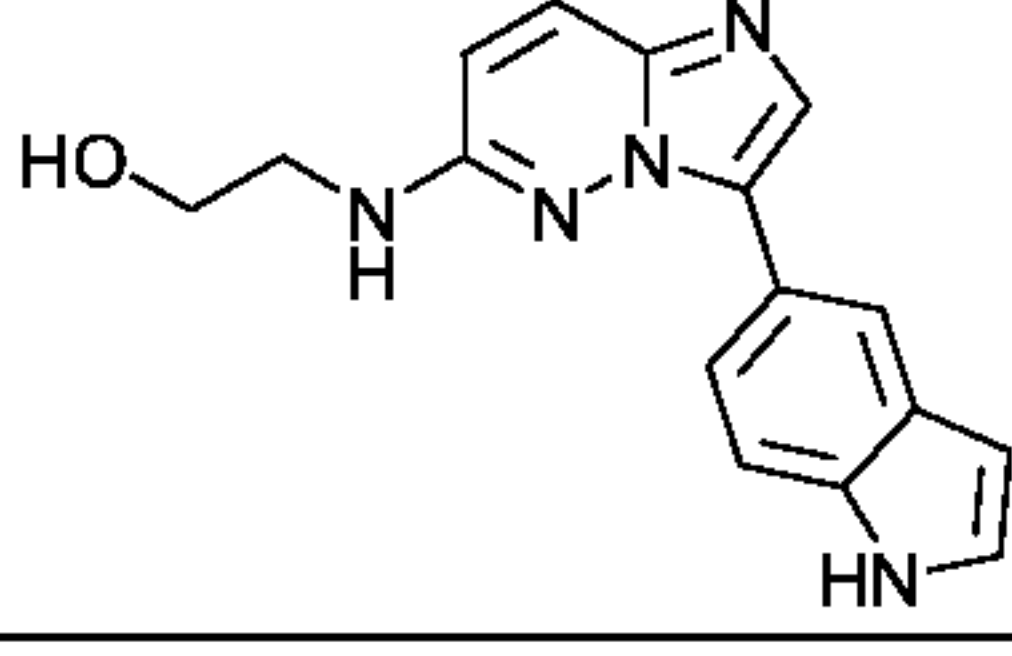
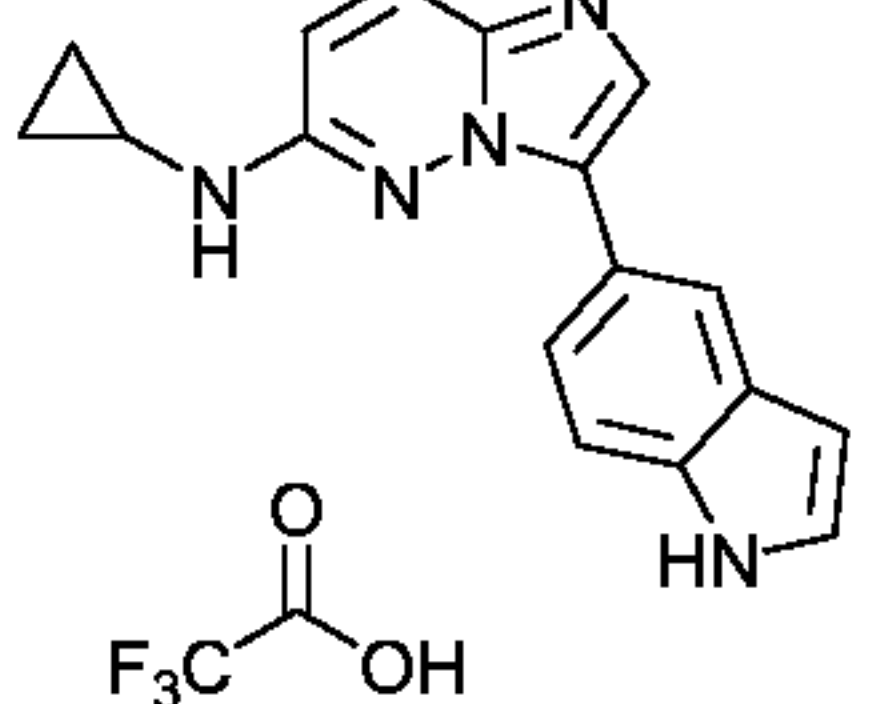
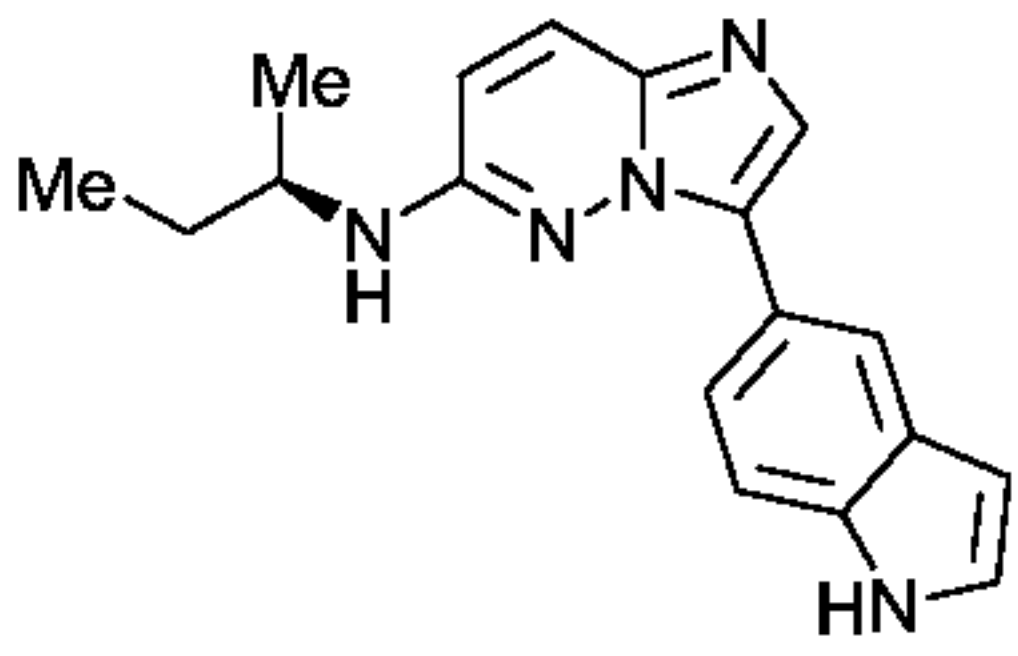
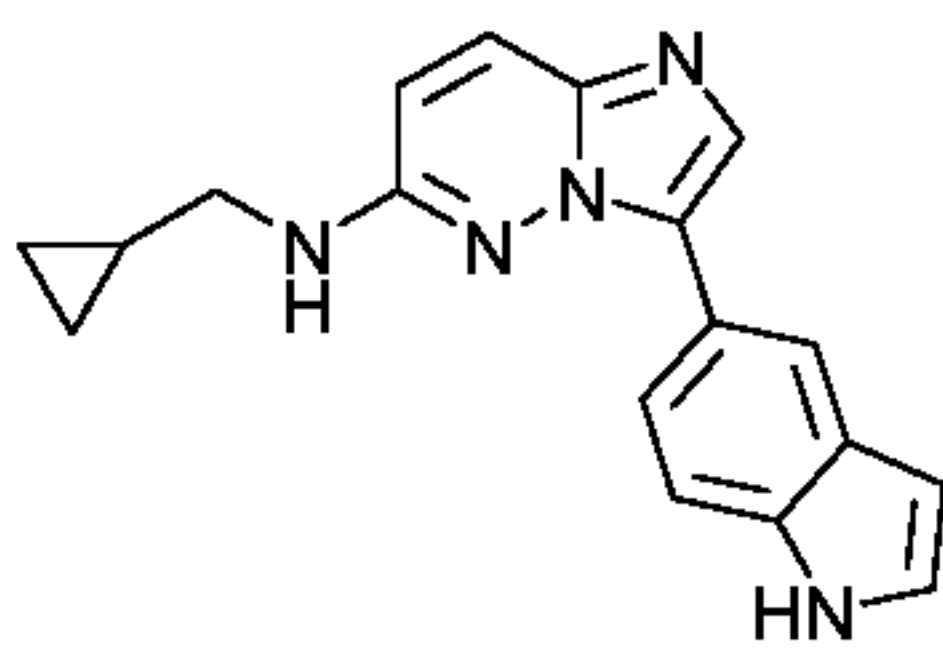
Table 14-a

Cd.	Amine	Purified Isolated Compound
140	propan-1-amine	3-(1H-indol-5-yl)-N-propylimidazo[1,2-b]pyridazin-6-amine
141	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
142	2-methylpropan-1-amine	3-(1H-indol-5-yl)-N-isobutylimidazo[1,2-b]pyridazin-6-amine
143	2-aminoethanol	2-(3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-ylamino)ethanol
148	cyclopropanamine	N-cyclopropyl-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-amine
149	(R)-butan-2-amine	N-sec-butyl-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-

		amine
150	cyclopropylmethanamine	N-(cyclopropylmethyl)-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-amine
158	N-methylpropan-1-amine	3-(1H-indol-5-yl)-N-methyl-N-propylimidazo[1,2-b]pyridazin-6-amine

[00285] Compounds 140-143, 148-150, 158 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 14-b**.

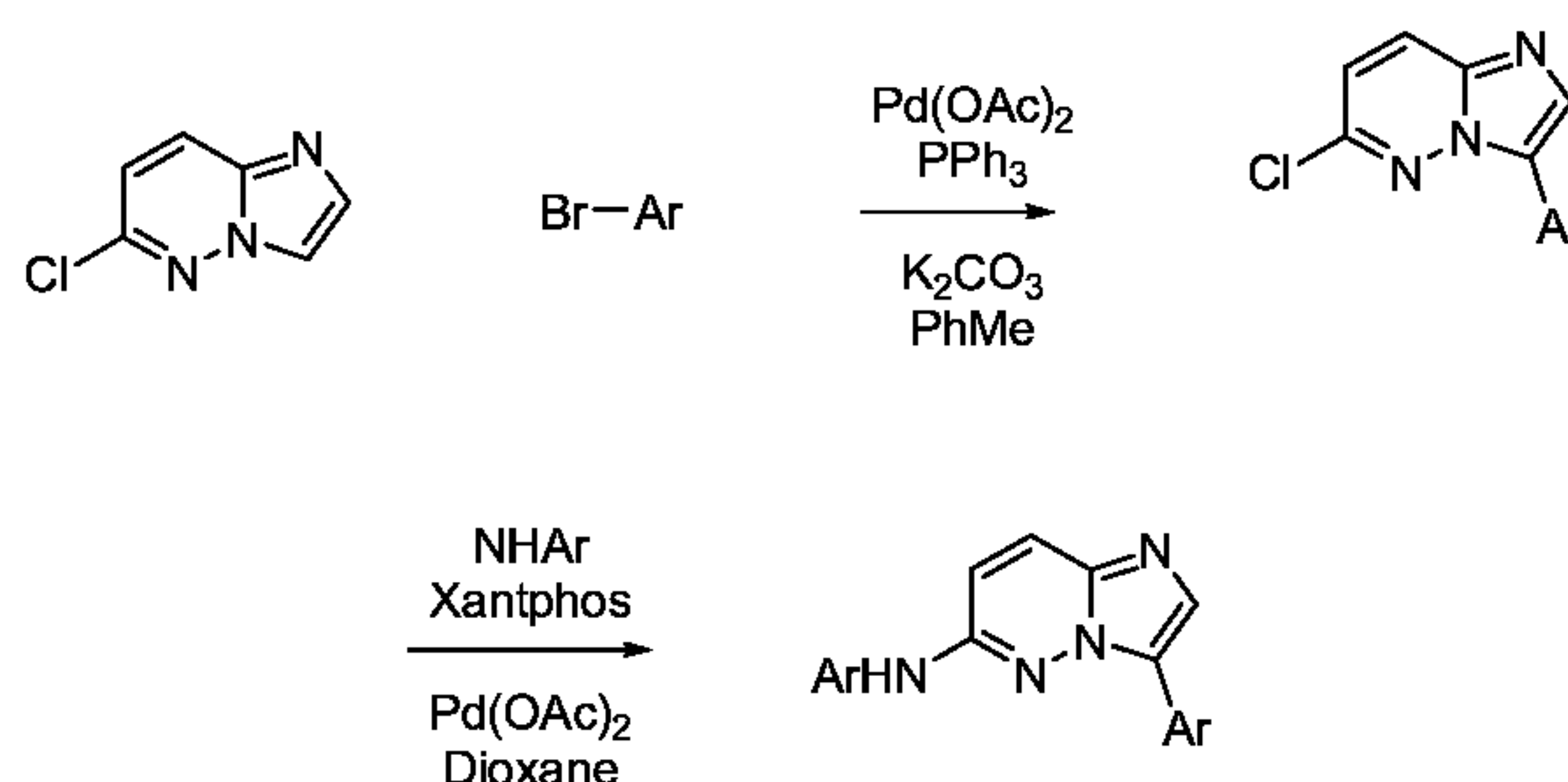
Table 14-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
140		3-(1H-indol-5-yl)-N-propylimidazo[1,2-b]pyridazin-6-amine	292.5
141		<i>trans</i> -4-(3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	348.7
142		3-(1H-indol-5-yl)-N-isobutylimidazo[1,2-b]pyridazin-6-amine	306.7
143		2-(3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-ylamino)ethanol	294.6
148		N-cyclopropyl-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-amine	290.6
149		N-sec-butyl-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-amine	306.7
150		N-(cyclopropylmethyl)-3-(1H-indol-5-yl)imidazo[1,2-b]pyridazin-6-amine	304.6

158		3-(1H-indol-5-yl)-N-methyl-N-propylimidazo[1,2-b]pyridazin-6-amine	306.7
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[00286] Example 15 – Synthesis of Compounds 62-65

[00287] Scheme 15



[00288] Preparation of 6-chloro-3-arylimidazo[1,2-b]pyridazine

[00289] To a stirred solution of 6-chloroimidazo[1,2-b]pyridazine (404 mg, 2.63 mmol, 1.0 equiv) in 10.0 mL of toluene was added aryl bromide (1.00 g, 3.95 mmol, 1.5 equiv), potassium carbonate (728 mg, 5.27 mmol, 2.0 equiv), triphenylphosphine (138 mg, 0.527 mmol, 0.2 equiv) and palladium acetate (59 mg, 0.263 mmol, 0.1 equiv). The solution was stirred to reflux for 24 h. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave the product.

[00290] Preparation of N,3-bisarylimidazo[1,2-b]pyridazin-6-amine

[00291] To a solution of 6-chloro-3-arylimidazo[1,2-b]pyridazine (50 mg, 0.179 mmol, 1.0 equiv), xantphos (21 mg, 0.0358 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0179 mmol, 0.1 equiv), and potassium carbonate (495 mg, 3.58 mmol, 20 equiv) in dioxane (5.0 mL) was added amine (0.179 mmol, 1.0 equiv) and heated to 100 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

Table 15-a

Cd.	Arylbromide	Amine	Purified Isolated Compound
62	2-bromonaphthalene	3,4-dimethoxyaniline	N-(3,4-dimethoxyphenyl)-3-(naphthalen-3-yl)imidazo[1,2-b]pyridazin-6-amine
63	2-bromonaphthalene	methyl 3-aminobenzoate	3-(3-(naphthalen-3-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid
64	2-bromo-6-fluoronaphthalene	3,4-dimethoxyaniline	3-(2-fluoronaphthalen-6-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-

			b]pyridazin-6-amine
65	2-bromo-6-methoxynaphthalene	3,4-dimethoxyaniline	3-(2-methoxynaphthalen-6-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine

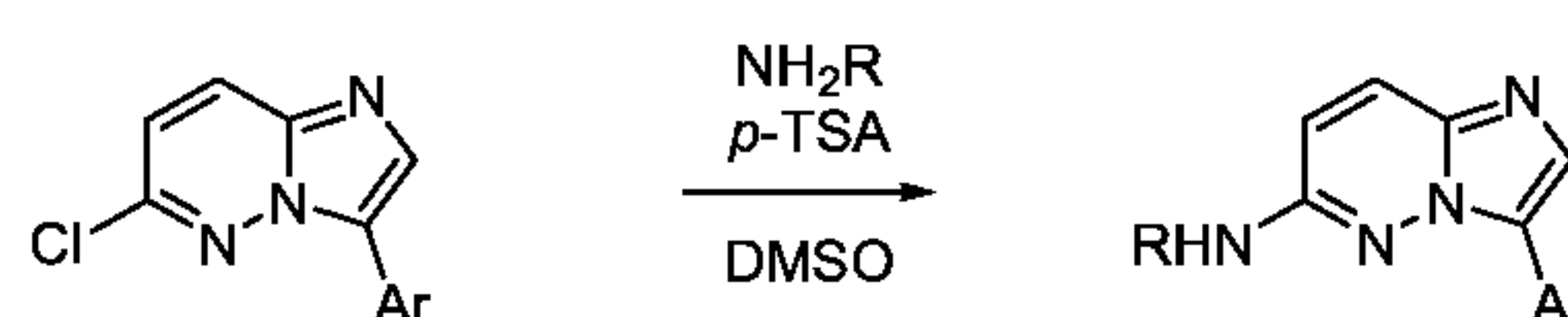
[00292] Compounds 62-65 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 15-b**.

Table 15-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
62		N-(3,4-dimethoxyphenyl)-3-(naphthalen-3-yl)imidazo[1,2-b]pyridazin-6-amine	397.6
63		3-(3-(naphthalen-3-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid	381.7
64		3-(2-fluoronaphthalen-6-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	415.8
65		3-(2-methoxynaphthalen-6-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	427.7

[00293] Example 16 – Synthesis of Compounds 160-163

[00294] **Scheme 16**



[00295] **Preparation of N-alkyl-3-aryl-1H-imidazo[1,2-b]pyridazin-6-amine**

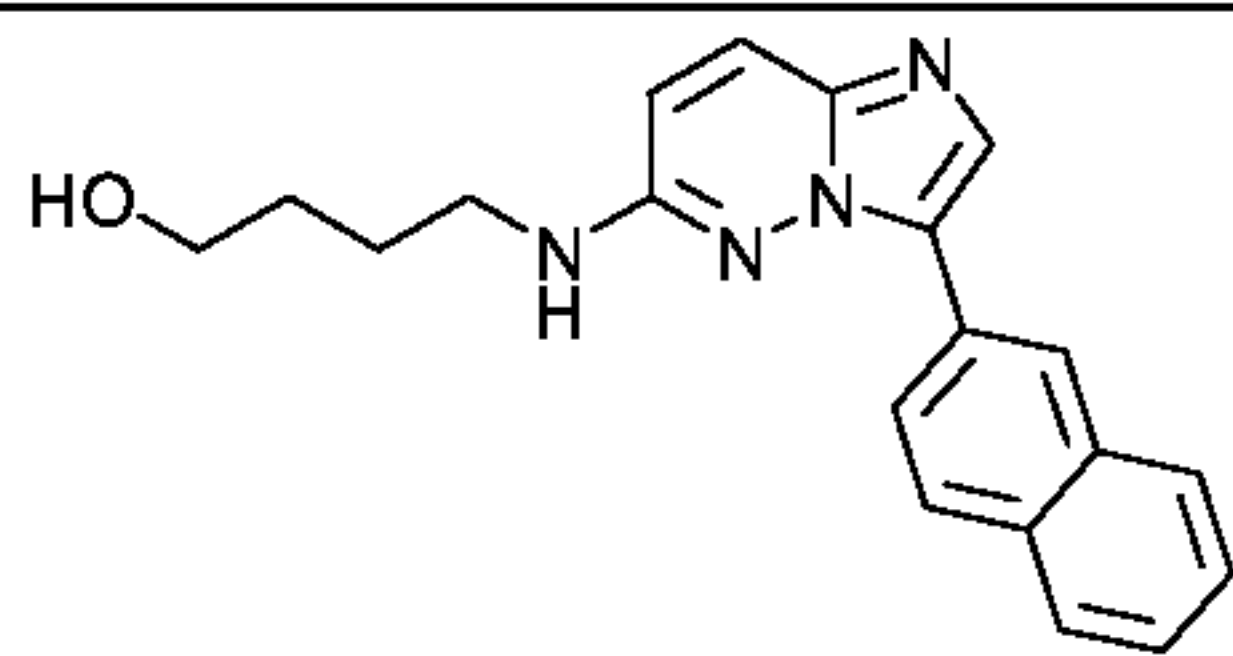
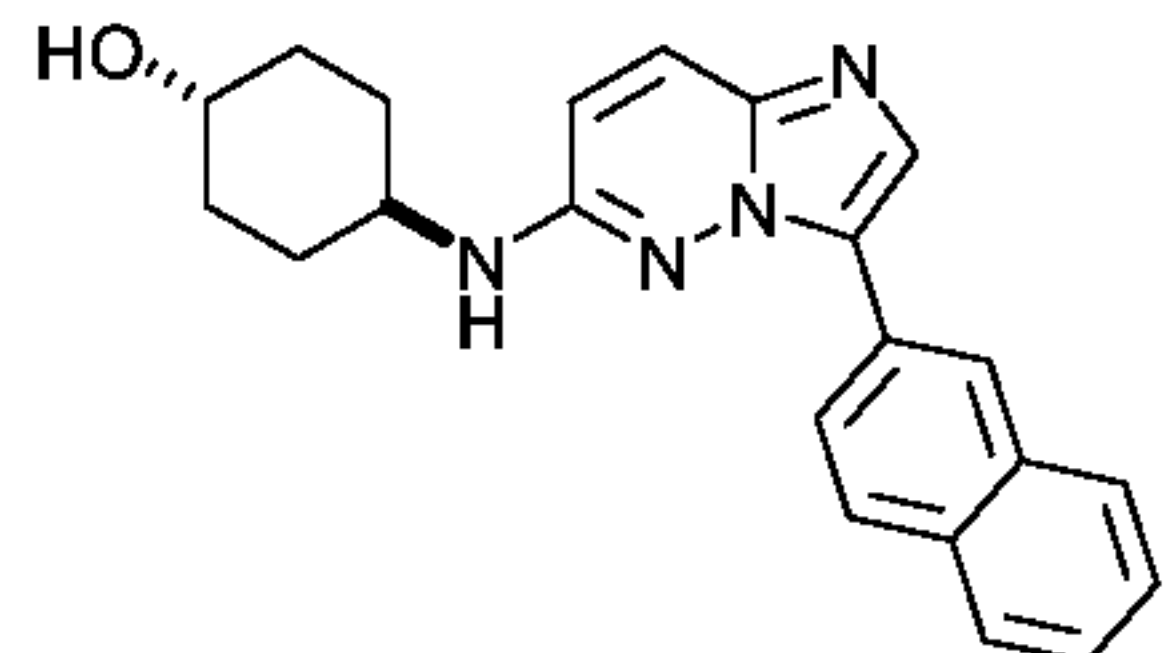
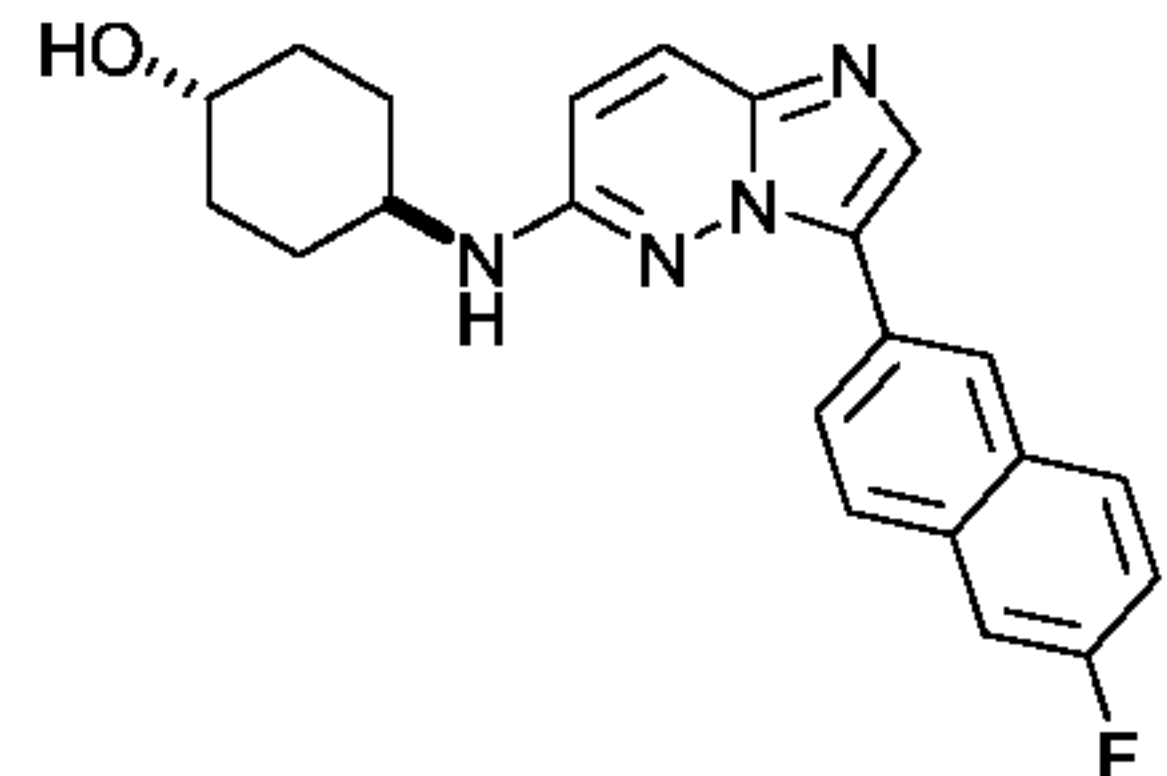
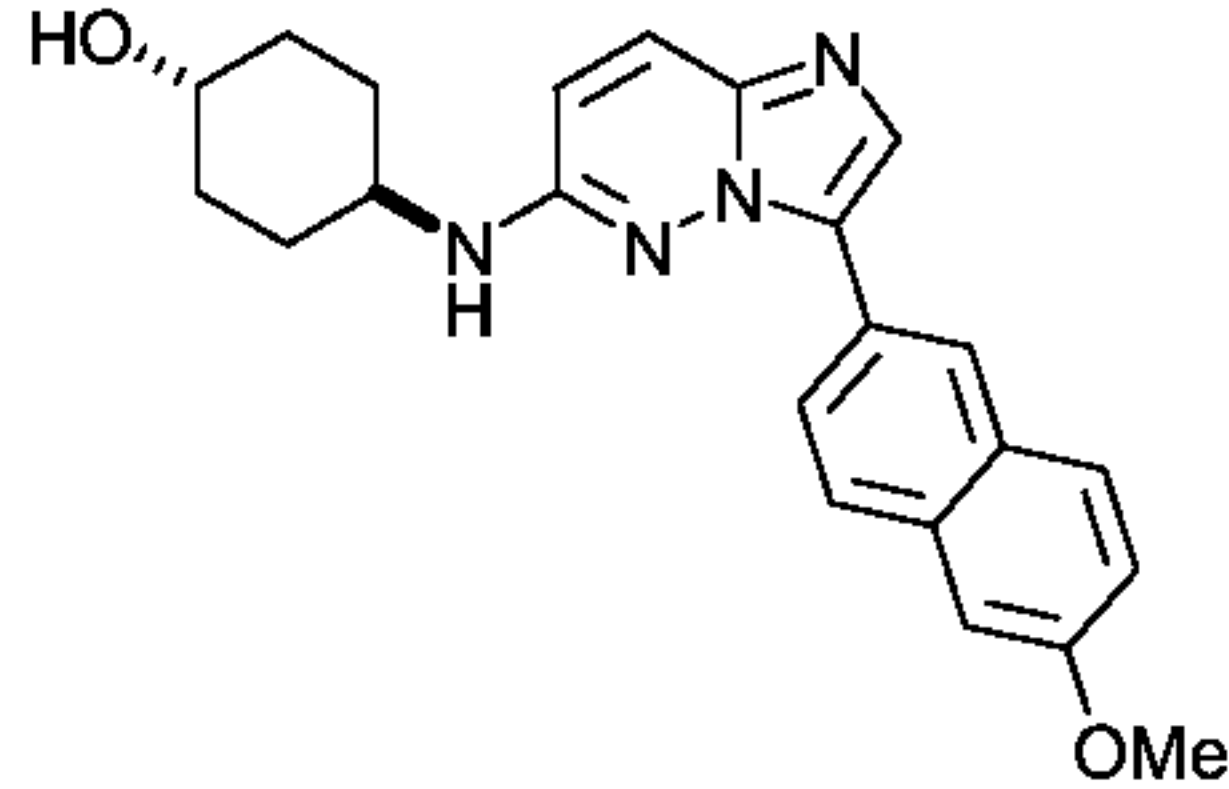
[00296] To a solution of 6-chloro-2-methyl-3-aryl-1H-imidazo[1,2-b]pyridazine (150 mg, 0.500 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (95 mg, 0.500 mmol, 1.0 equiv) and amine (1.95 mmol, 4.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave the product.

Table 16-a

Cd.	Arylbromide	Amine	Purified Isolated Compound
160	2-bromonaphthalene	4-aminobutan-1-ol	4-(3-(naphthalen-3-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol
161	2-bromonaphthalene	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(naphthalen-3-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
162	2-bromo-6-fluoronaphthalene	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(2-fluoronaphthalen-6-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
163	2-bromo-6-methoxynaphthalene	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(2-methoxynaphthalen-6-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

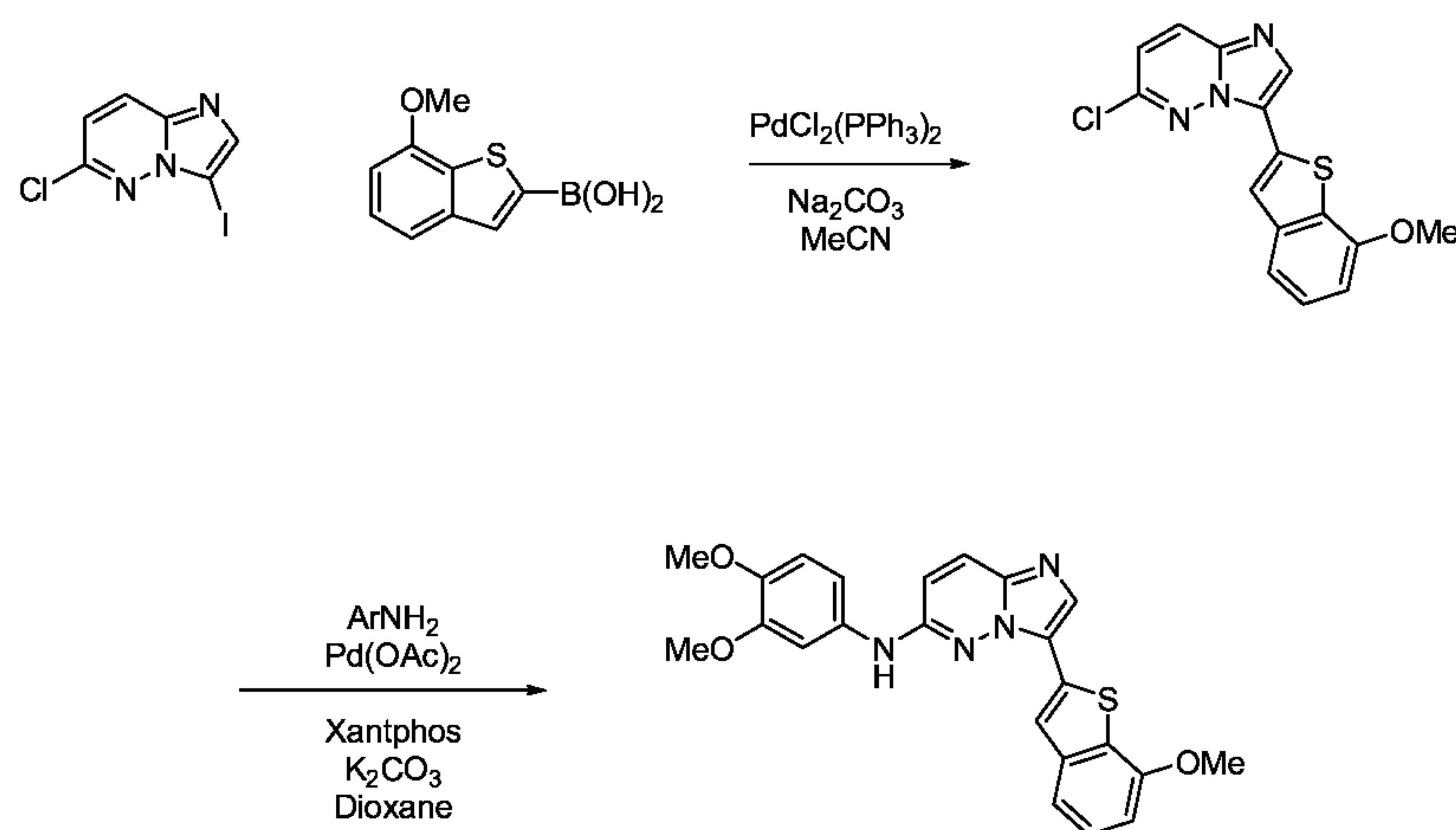
[00297] Compounds 160-163 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 16-b.

Table 16-b

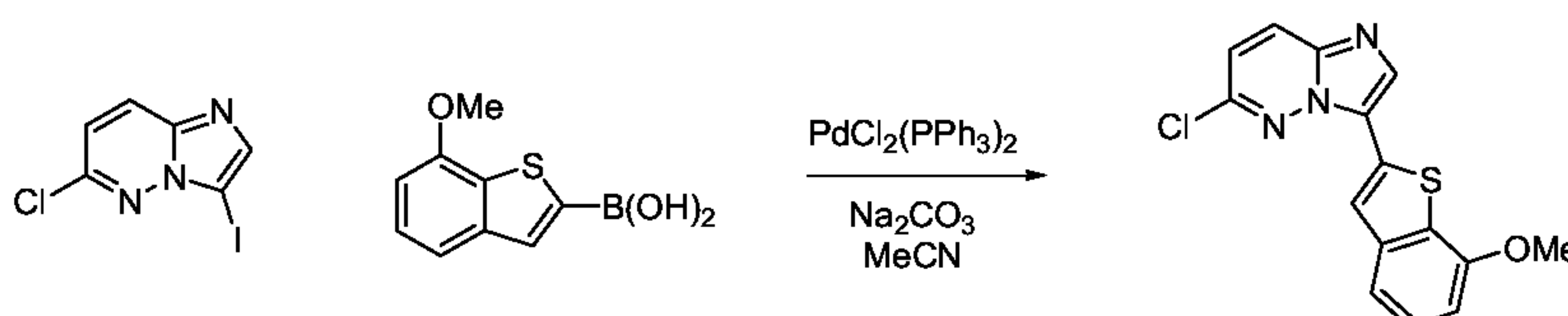
Cd.	Structure	IUPAC Name	[M+H] ⁺
160		4-(3-(naphthalen-3-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol	333.7
161		<i>trans</i> -4-(3-(naphthalen-3-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	359.8
162		<i>trans</i> -4-(3-(2-fluoronaphthalen-6-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	377.8
163		<i>trans</i> -4-(3-(2-methoxynaphthalen-6-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	389.9

[00298] Example 17 – Synthesis of Compound 68, 181-185

[00299] Scheme 17

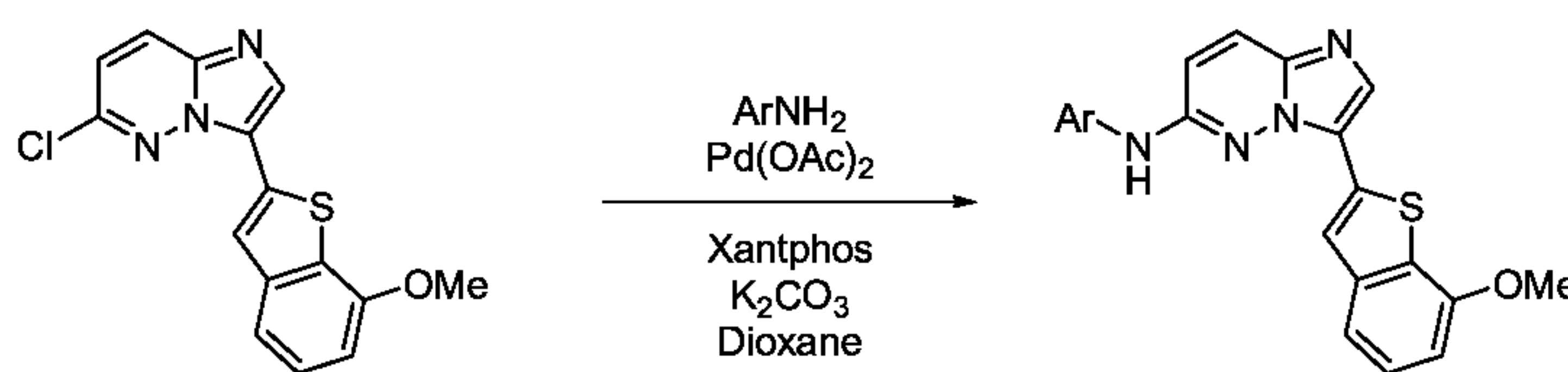


[00300] Preparation of 6-chloro-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine



[00301] To a solution of 7-methoxybenzo[b]thiophen-2-yl-2-boronic acid (49 mg, 0.237 mmol, 1.1 equiv) in acetonitrile (2.15 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (50 mg, 0.215 mmol, 1.0 equiv), palladium catalyst (8 mg, 0.0108 mmol, 0.05 equiv) and sodium carbonate (2.15 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 48 mg of the yellow solid, 70%.

[00302] Preparation of 3-(7-methoxybenzo[b]thiophen-2-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine



[00303] To a solution of 6-chloro-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (82 mg, 0.260 mmol, 1.0 equiv), xantphos (30 mg, 0.0519 mmol, 0.2 equiv), palladium acetate (6 mg, 0.0260 mmol, 0.1 equiv), and potassium carbonate (718 mg, 5.19 mmol, 20 equiv) in dioxane (5.0 mL) was added substituted aniline (48 mg, 0.312 mmol, 1.1 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

[00304] Table 17A.

Cd.	Amine	Purified Isolated Compound
68	3,4-dimethoxyaniline	3-(7-

		methoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
181	4-ethoxy-3-methoxybenzenamine	N-(4-ethoxy-3-methoxyphenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine
182	3-methoxy-4-propoxybenzenamine	N-(3-methoxy-4-propoxyphenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine
183	4-(difluoromethoxy)-3-methoxybenzenamine	N-(4-(difluoromethoxy)-3-methoxyphenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine
184	3-methoxy-4-(trifluoromethoxy)benzenamine	N-(3-methoxy-4-(trifluoromethoxy)phenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine
185	4-methoxy-3-(trifluoromethoxy)benzenamine	N-(4-methoxy-3-(trifluoromethoxy)phenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine

[00305] Compound 68, 181-185 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table x-x**.

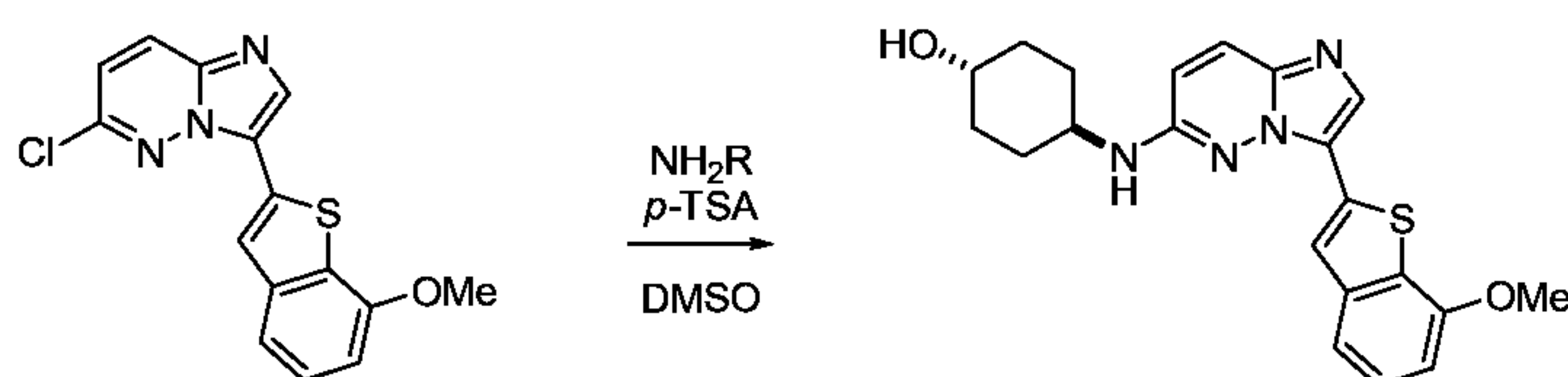
Table 17-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
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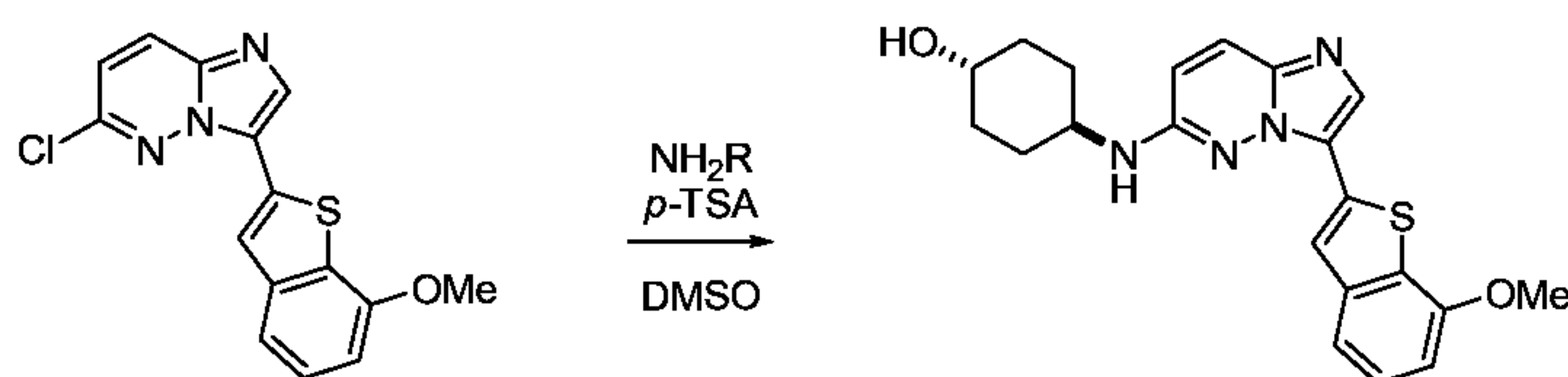
68		3-(7-methoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	433.2
181		N-(4-ethoxy-3-methoxyphenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	447.1
182		N-(3-methoxy-4-propoxyphenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	461.3
183		N-(4-(difluoromethoxy)-3-methoxyphenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	469.1
184		N-(3-methoxy-4-(trifluoromethoxy)phenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	487.1
185		N-(4-methoxy-3-(trifluoromethoxy)phenyl)-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	487.4

[00306] Example 18 – Synthesis of Compounds 170 and 200.

[00307] **Scheme 18**



[00308] Preparation of *trans*-4-(3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol



[00309] To a solution of 6-chloro-3-(6-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.111 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (30 mg, 0.111 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (0.803 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 35 mg of the yellow solid, 80%.

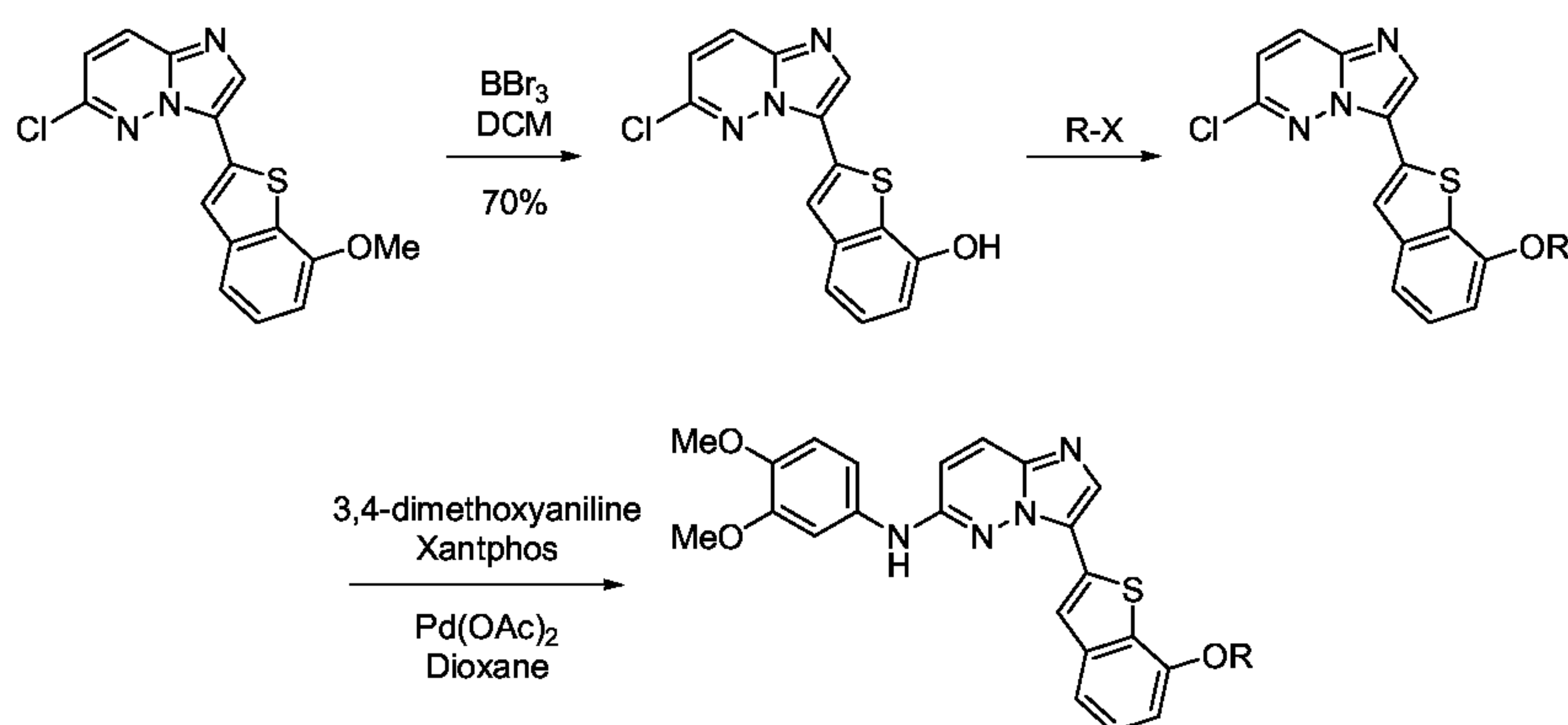
[00310] Compounds 170 and 200 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 18-b**.

Table 18-b

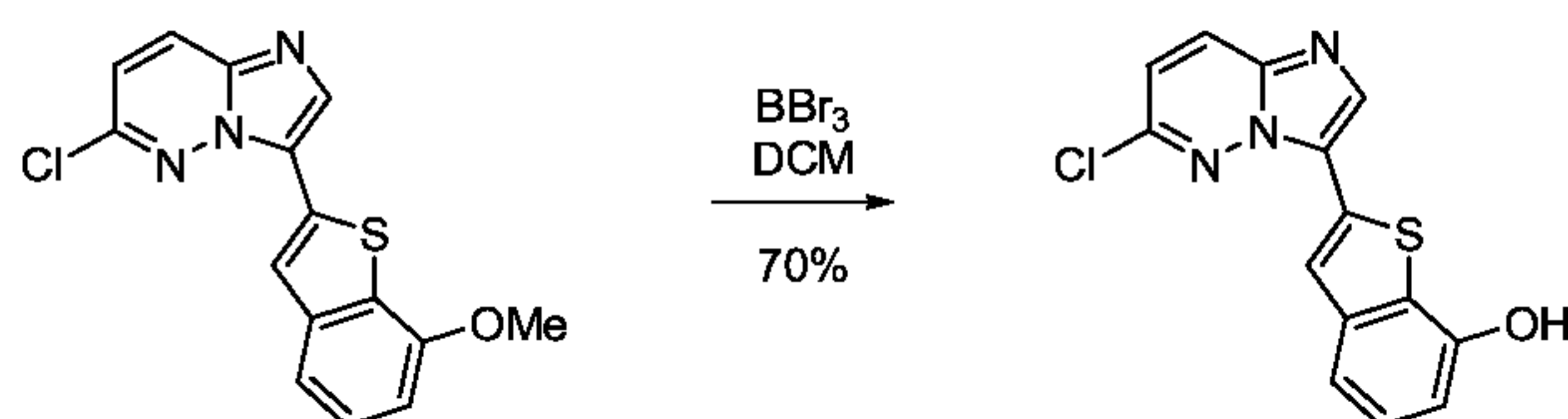
Cd.	Amine	Structure	IUPAC Name	[M+H] +
170	<i>trans</i> -4-aminocyclohexanol		<i>trans</i> -4-(3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	395.5
200	<i>trans</i> -4-methoxycyclohexylamine		<i>trans</i> -3-(7-methoxybenzo[b]thiophen-2-yl)-N-(4-methoxycyclohexyl)imidazo[1,2-b]pyridazin-6-amine	409.1

[00311] Example 19A – Synthesis of Compounds 78-81 and 186-188

[00312] **Scheme 19A**

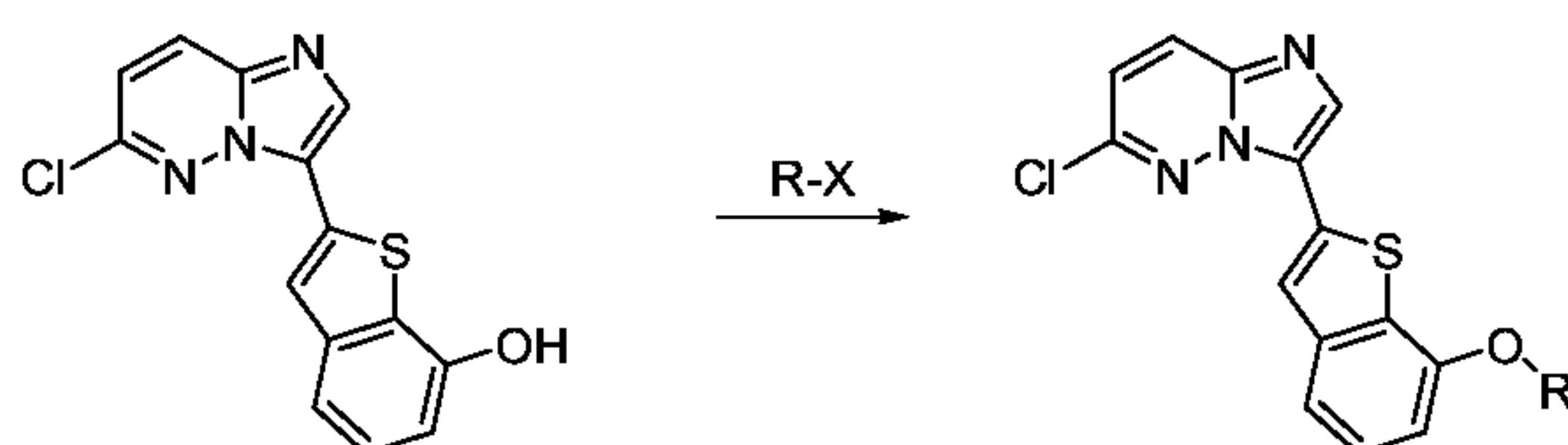


[00313] Preparation of 2-(6-chloroimidazo[1,2-b]pyridazin-3-yl)benzo[b]thiophen-7-ol



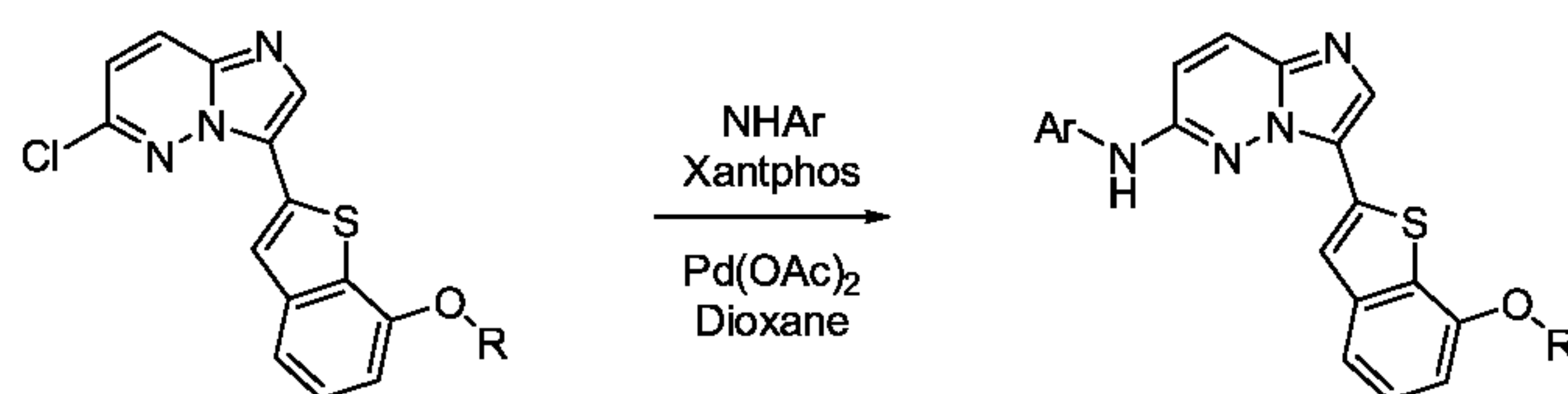
[00314] To a solution of 6-chloro-3-(7-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (103 mg, 0.326 mmol, 1.0 equiv) in dichloromethane at -78°C was added boron tribromide (2.27 mL, 1.0 M solution in dichloromethane, 7.0 equiv). The reaction mixture was stirred at the reduced temperature for 10 min then warmed to room temperature and stirred for 15 h. Methanol (2 mL) was added to quench the reaction and extracted with dichloromethane. Purification by column chromatography using 5% methanol in dichloromethane elution gave 70 mg of the yellow solid, 70%.

[00315] Preparation of 6-chloro-3-(7-alkoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine



[00316] To a solution of 2-(6-chloroimidazo[1,2-b]pyridazin-3-yl)benzo[b]thiophen-7-ol (33 mg, 0.109 mmol, 1.0 equiv) in acetone (2 mL) was added potassium carbonate (30 mg, 0.219 mmol, 2.0 equiv) and alkyl halide (0.219 mmol, 2.0 equiv) and heated to reflux for 15 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

[00317] Preparation of 3-(7-alkoxybenzo[b]thiophen-2-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine



[00318] To a solution of 6-chloro-3-(7-alkoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (38 mg, 0.109 mmol, 1.0 equiv), xantphos (0.022 mmol, 0.2 equiv), palladium acetate (0.011 mmol, 0.1 equiv), and potassium carbonate (2.19 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (0.164 mmol, 1.5 equiv) and heated to 100 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

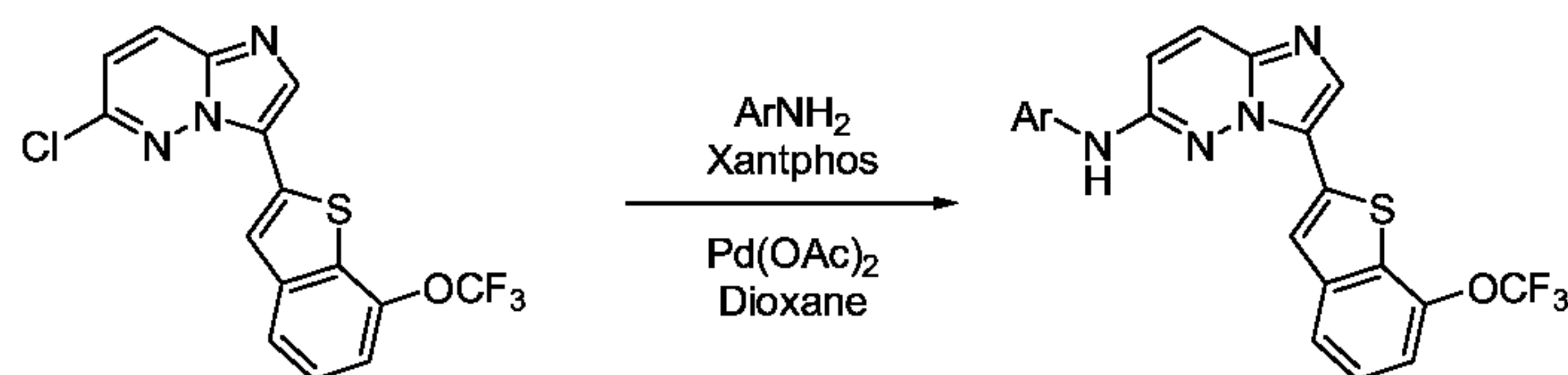
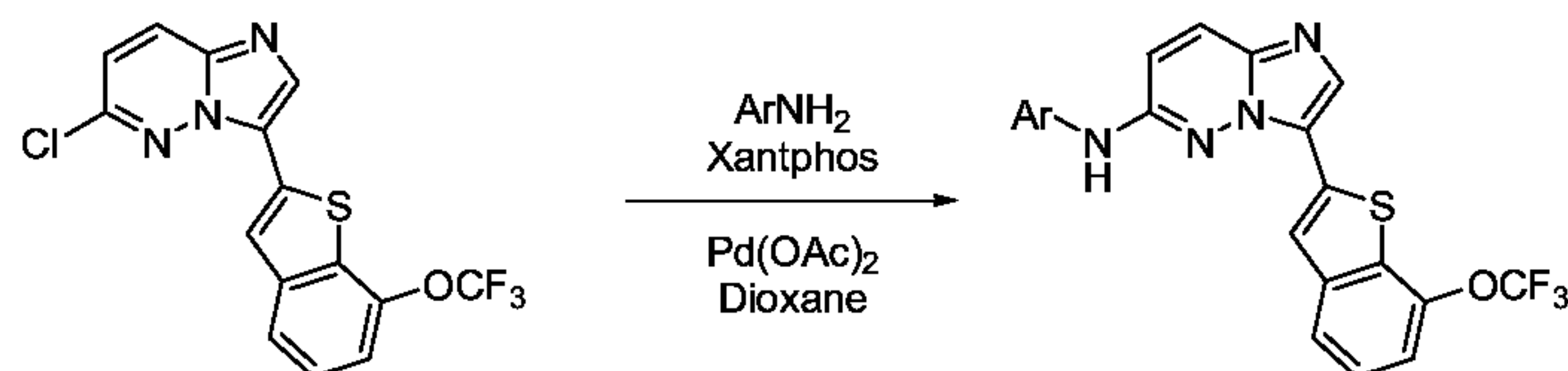
Table 19-a

Cd.	Alkyl halide	Purified Isolated Compound
78	acetyl chloride	2-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)benzo[b]thiophen-7-yl acetate
79		2-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)benzo[b]thiophen-7-ol
80	2-iodopropane	3-(7-isopropoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
81	1-iodopropane	N-(3,4-dimethoxyphenyl)-3-(7-propoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine
186	Ethyl iodide	3-(7-ethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
187	sodium 2-chloro-2,2-difluoroacetate	3-(7-(difluoromethoxy)benzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
188	trifluoroiodomethane	N-(3,4-dimethoxyphenyl)-3-(7-(trifluoromethoxy)benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine

[00319] Compounds 78-81, 186-188 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 19-A.

Table 19-B

Cd.	Structure	IUPAC Name	[M+H] ⁺
78		2-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)benzo[b]thiophen-7-yl acetate	461.3
79		2-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)benzo[b]thiophen-7-ol	419.4
80		3-(7-isopropoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	461.4
81		N-(3,4-dimethoxyphenyl)-3-(7-propoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	461.5
186		3-(7-ethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	447.2
187		3-(7-(difluoromethoxy)benzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	469.3
188		N-(3,4-dimethoxyphenyl)-3-(7-(trifluoromethoxy)benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	487.3

[00320] Example 19B – Synthesis of Compounds 189-190**[00321]** **Scheme X****[00322]** **Preparation of N-aryl-3-(7-(trifluoromethoxy)benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine**

[00323] To a solution of 6-chloro-3-(7-(trifluoromethoxy)benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (55 mg, 0.164 mmol, 1.0 equiv), xantphos (0.033 mmol, 0.2 equiv), palladium acetate (0.016 mmol, 0.1 equiv), and potassium carbonate (3.28 mmol, 20 equiv) in dioxane (5.0 mL) was added substituted aniline (0.164 mmol, 1.0 equiv) and heated to 100 °C for 2 h.

Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

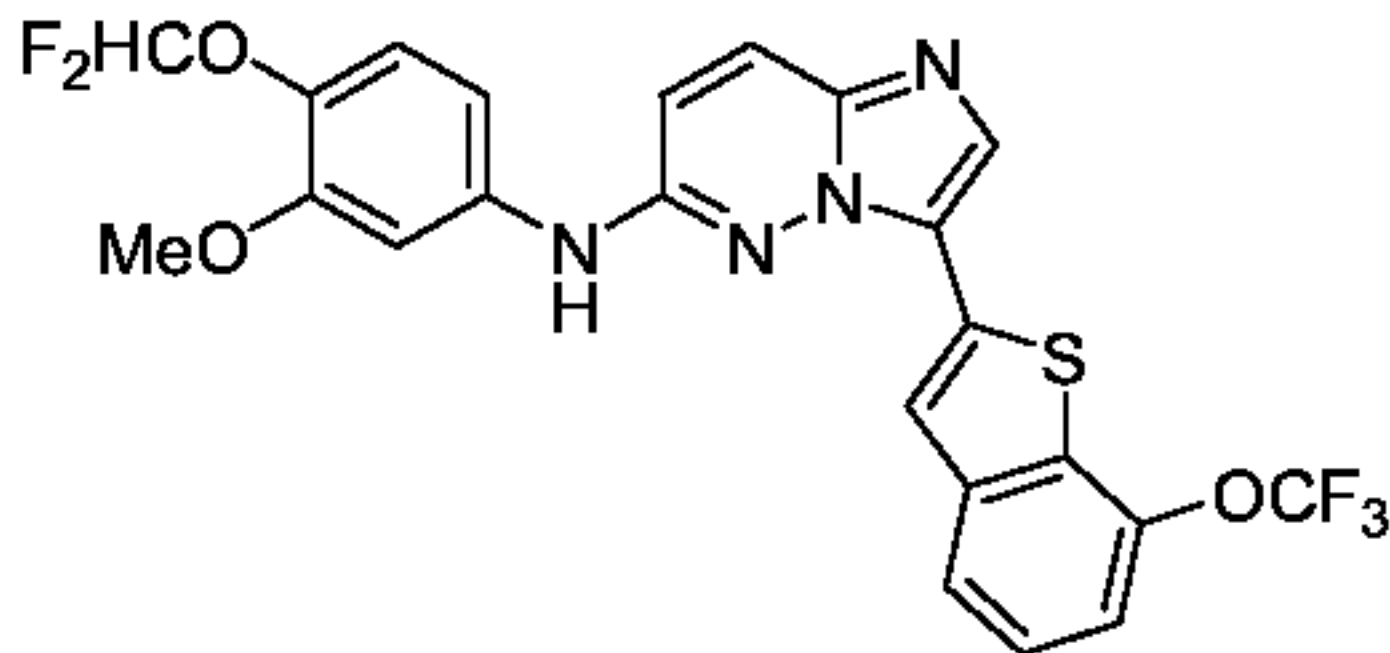
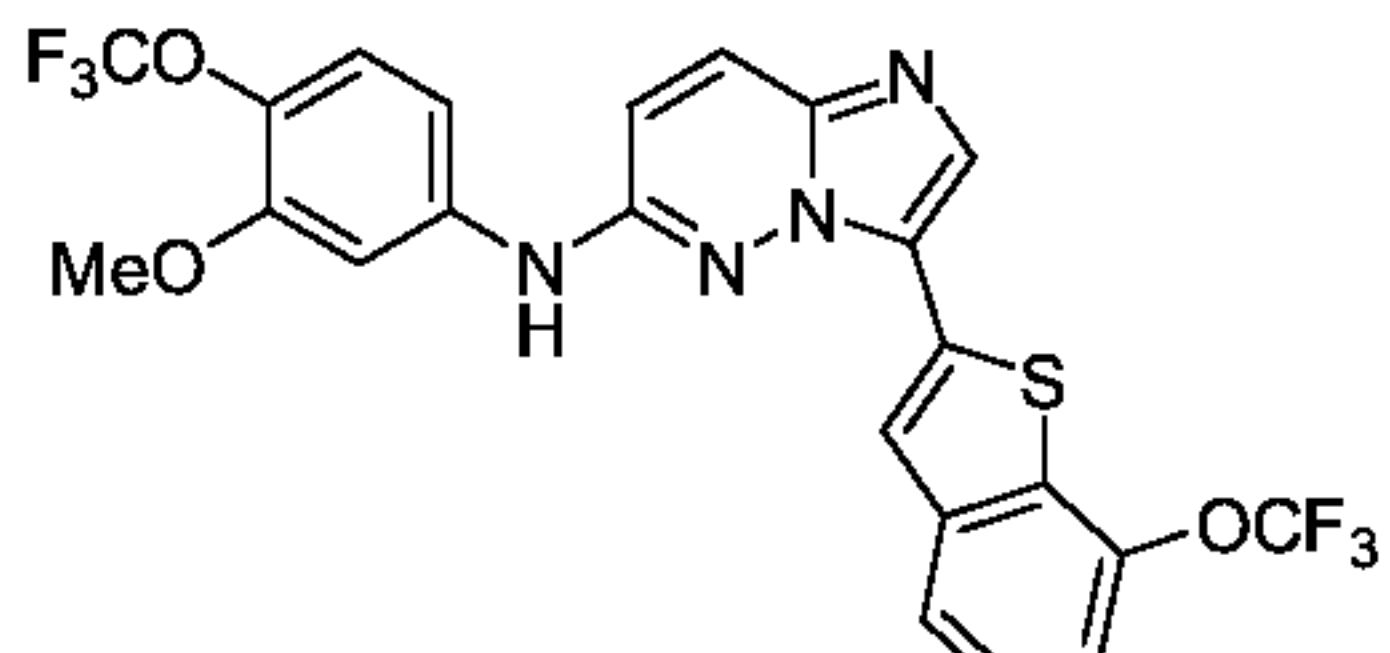
Table 19C

Cd.	Amine	Purified Isolated Compound
189	4-(difluoromethoxy)-3-methoxybenzenamine	N-(4-(difluoromethoxy)-3-methoxyphenyl)-3-(7-(trifluoromethoxy)benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine
190	N-(3-methoxy-4-(trifluoromethoxy)phenyl)-3-(7-(trifluoromethoxy)benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	N-(3-methoxy-4-(trifluoromethoxy)phenyl)-3-(7-(trifluoromethoxy)benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine

[00324] Compounds 189 – 190 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 19D**.

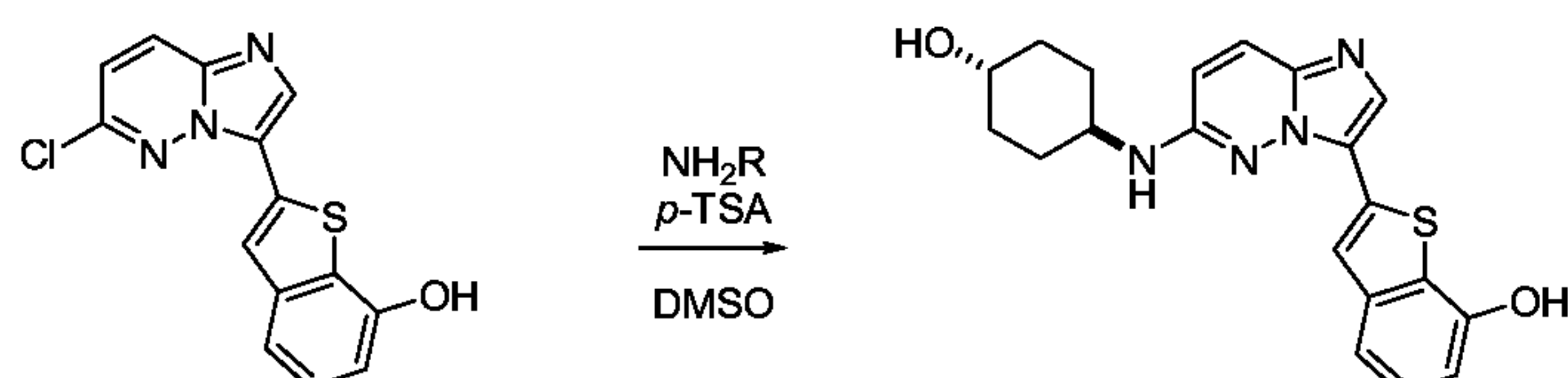
Table 19D

Cd.	Structure	IUPAC Name	[M+H] ⁺
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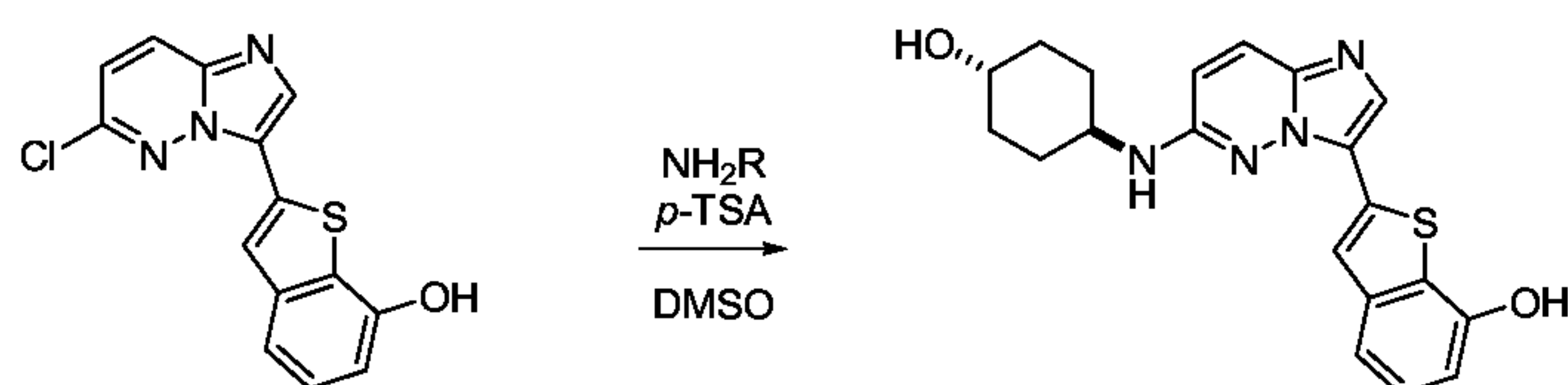
189		N-(4-(difluoromethoxy)-3-methoxyphenyl)-3-(7-(trifluoromethoxy)benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	523.1
190		N-(3-methoxy-4-(trifluoromethoxy)phenyl)-3-(7-(trifluoromethoxy)benzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	541.4

[00325] Example 20 – Synthesis of Compound 77

[00326] **Scheme 20**



[00327] **Preparation of 2-(6-*trans*-4-hydroxycyclohexylamino)imidazo[1,2-b]pyridazin-3-yl)benzo[b]thiophen-7-ol**

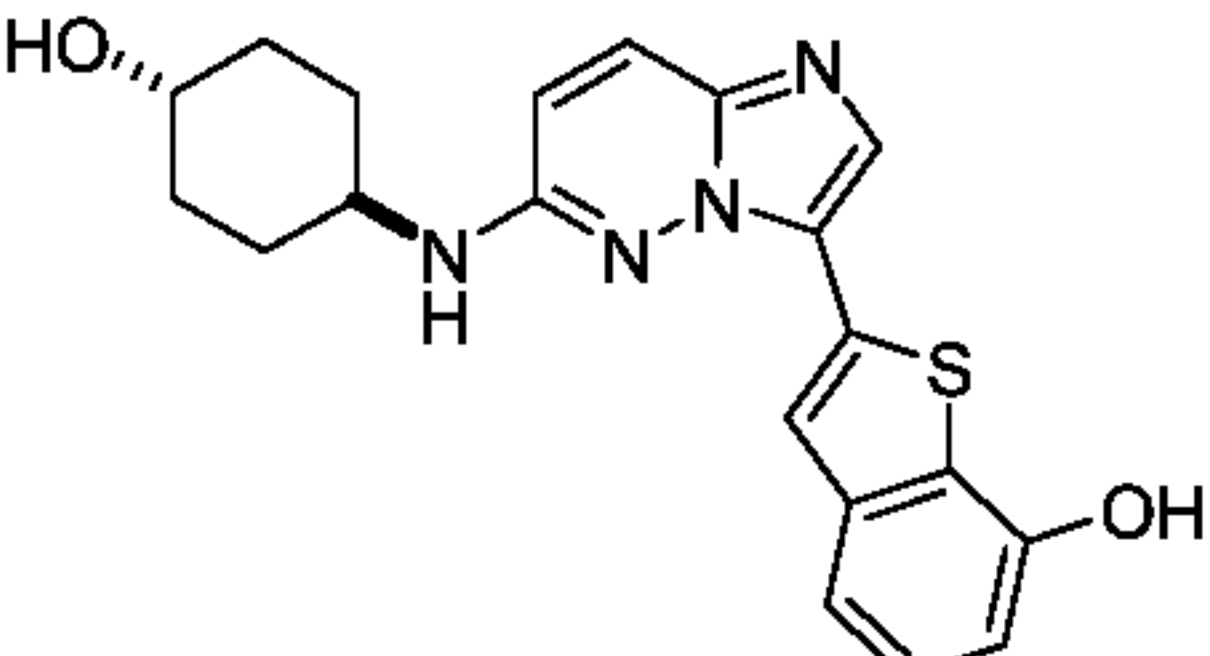


[00328] To a solution of 2-(6-chloroimidazo[1,2-b]pyridazin-3-yl)benzo[b]thiophen-7-ol (50 mg, 0.166 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (32 mg, 0.167 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (95 mg, 0.830 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 40 mg of the yellow solid, 79%.

[00329] Compound 77 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 20-b**.

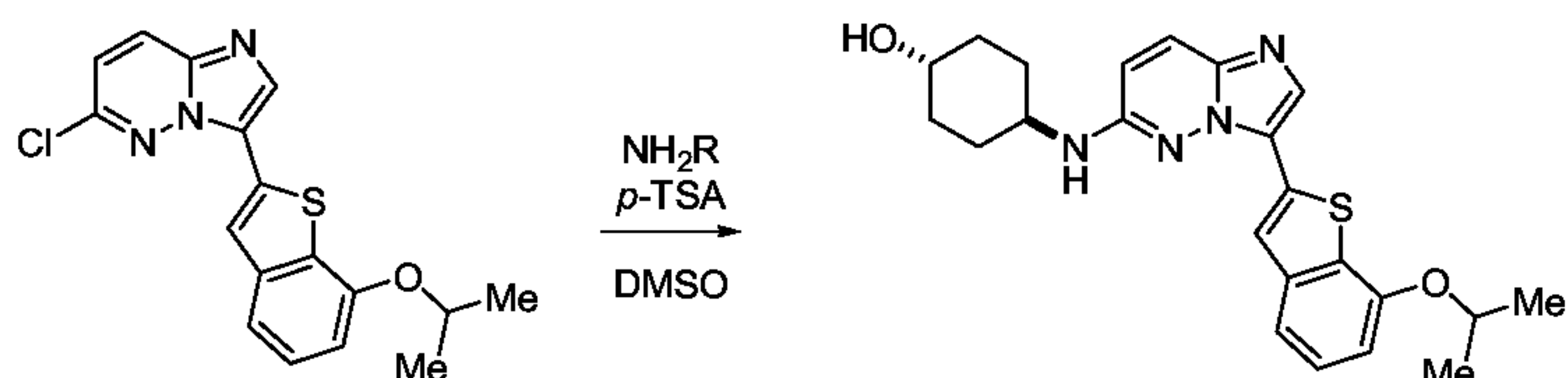
[00330] **Table 20-b**

Cd.	Structure	IUPAC Name	[M+H] ⁺
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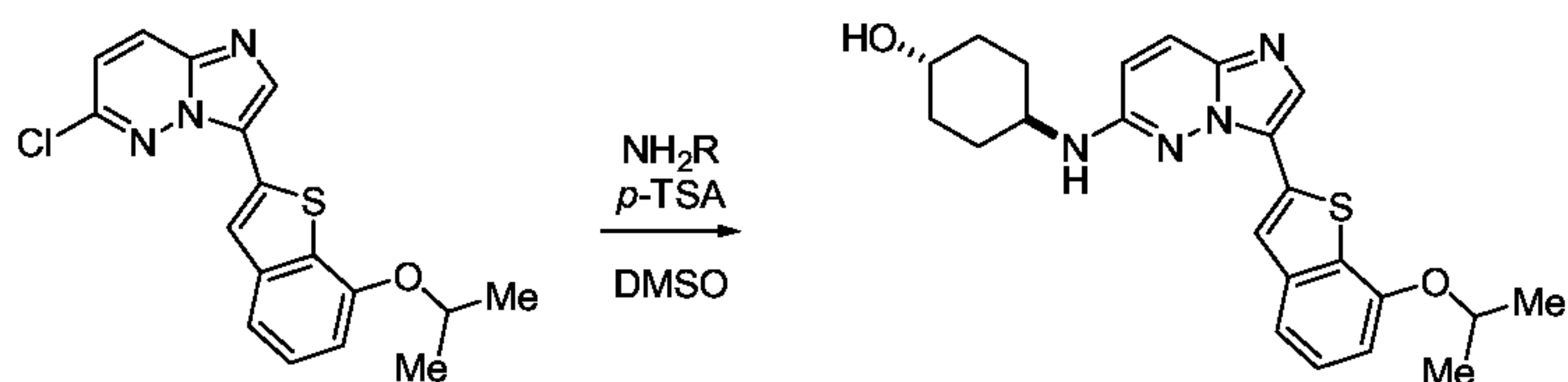
77		2-(6-(trans-4-hydroxycyclohexylamino)imidazo[1,2-b]pyridazin-3-yl)benzo[b]thiophen-7-ol	381.3
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[00331] Example 21A – Synthesis of Compound 178

[00332] **Scheme 21**



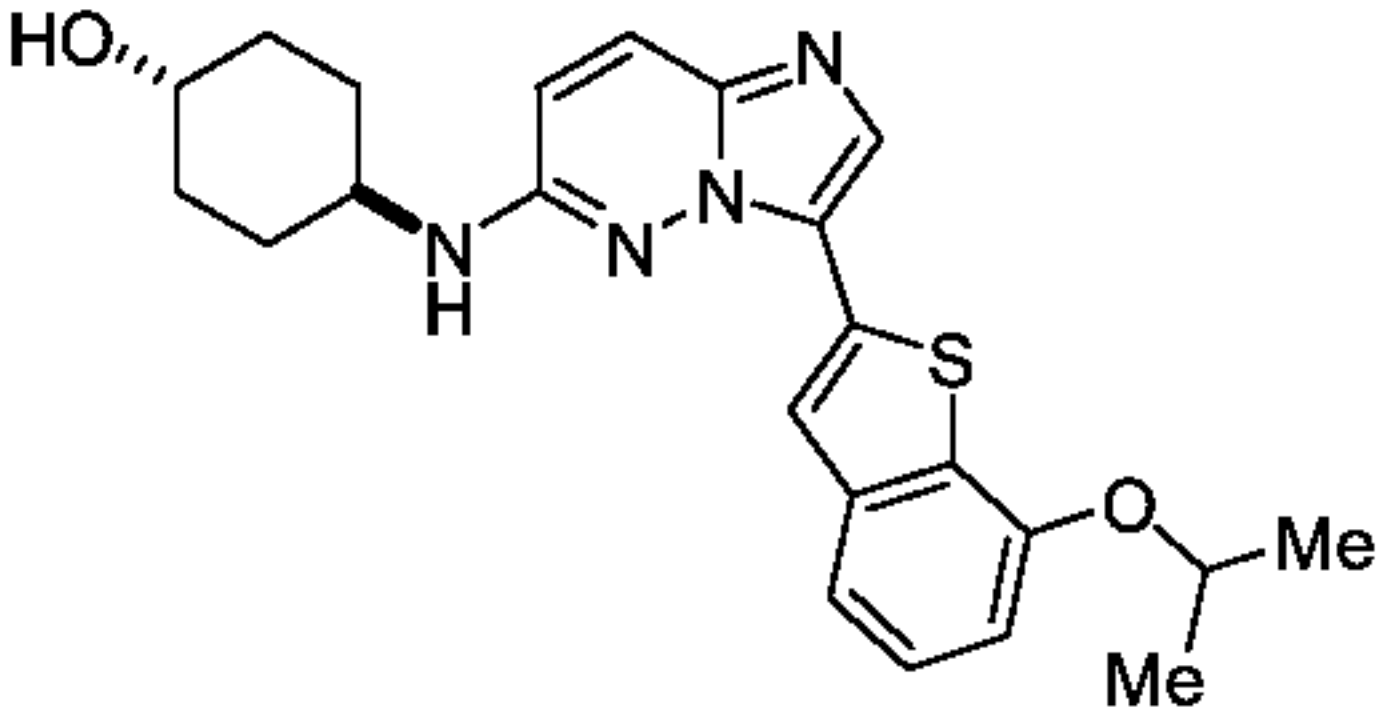
[00333] **Preparation of *trans*-4-(3-(7-isopropoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol**



[00334] To a solution of 6-chloro-3-(7-isopropoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (56 mg, 0.167 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (32 mg, 0.167 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (0.828 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 25 mg of the yellow solid, 36%.

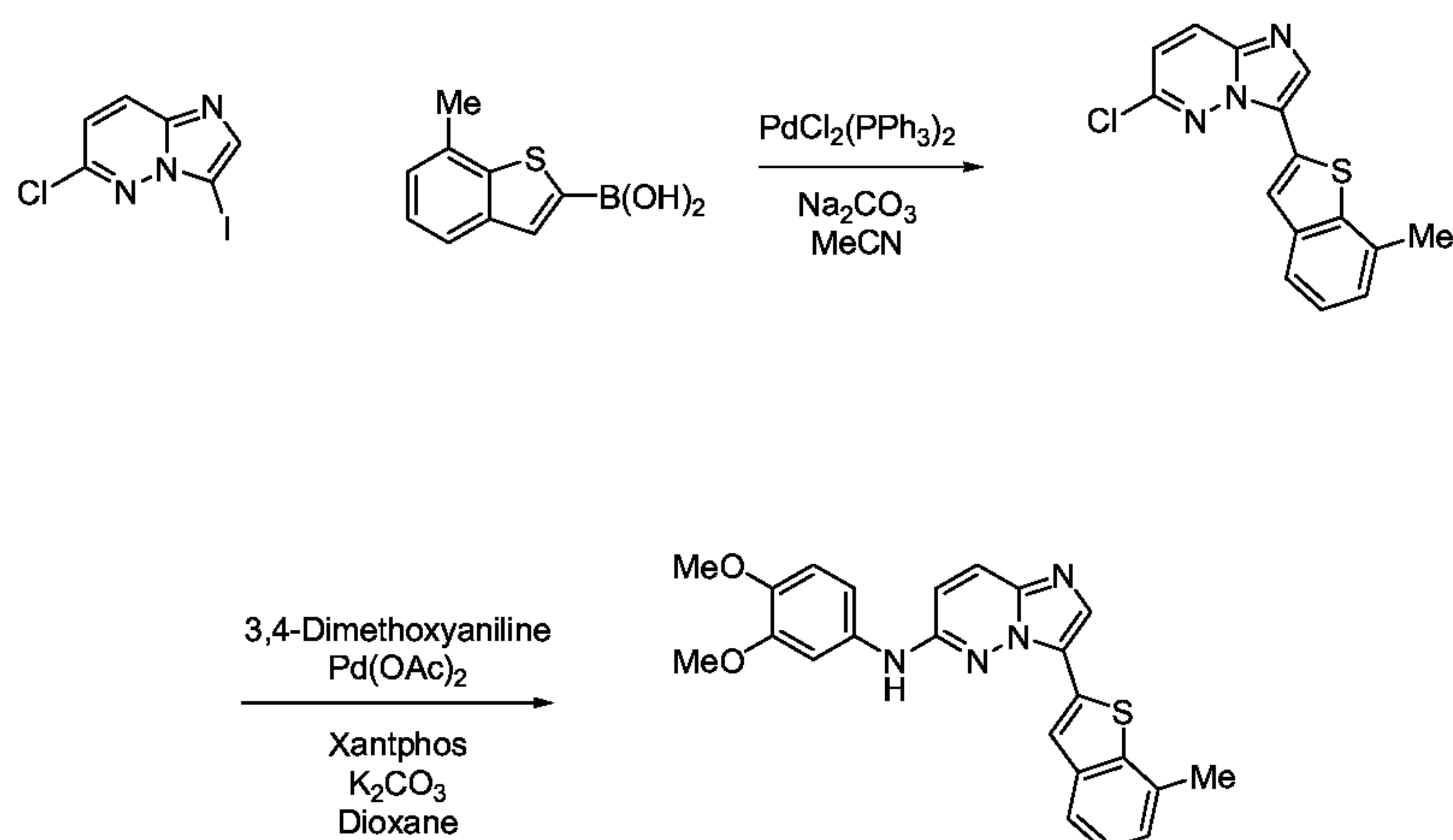
[00335] Compound 178 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 21-b**.

Table 21-b

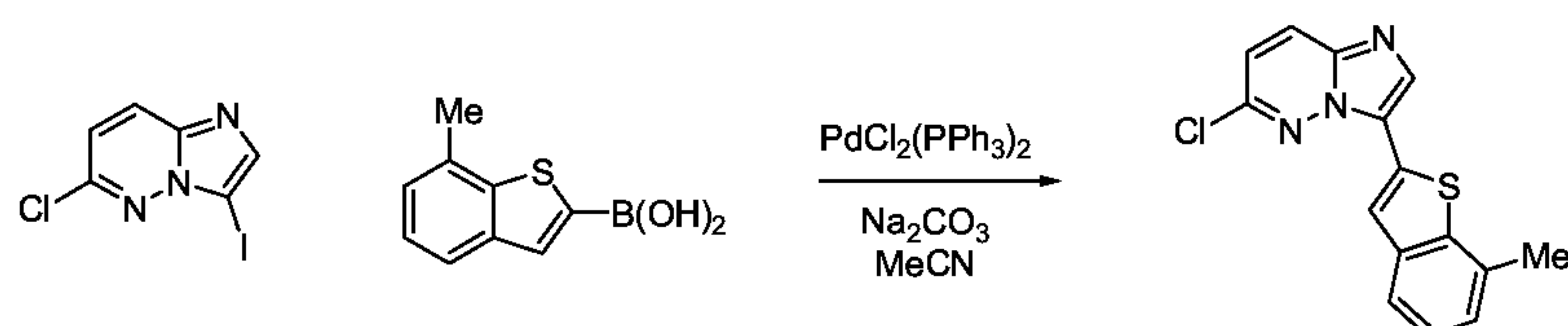
Cd.	Structure	IUPAC Name	[M+H] ⁺
178		<i>trans</i> -4-(3-(7-isopropoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	423.2

[00336] Example 21A – Synthesis of Compound 202

[00337] **Scheme 21A**

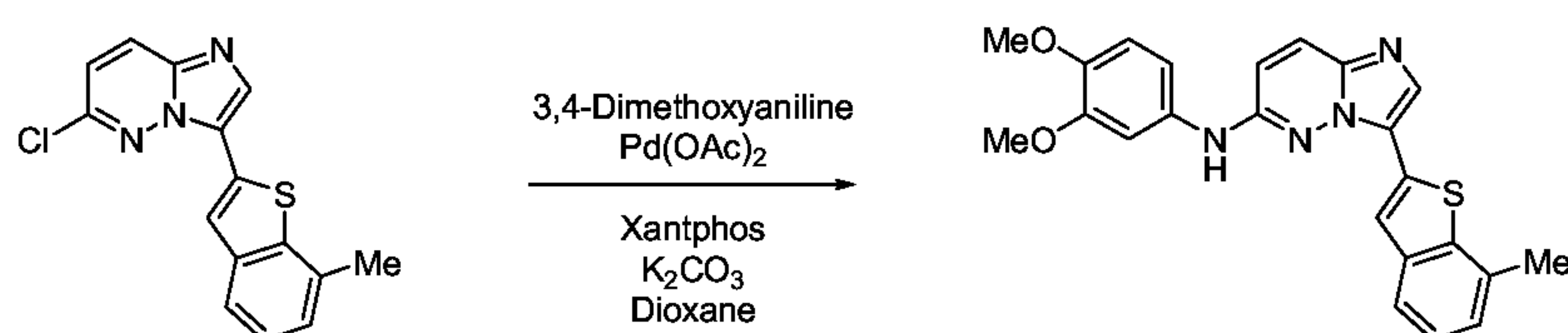


[00338] Preparation of 6-chloro-3-(7-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine



[00339] To a solution of 6-methylbenzo[b]thiophen-2-yl-2-boronic acid (100 mg, 0.521 mmol, 1.1 equiv) in acetonitrile (4.73 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (132 mg, 0.473 mmol, 1.0 equiv), palladium catalyst (35 mg, 0.0473 mmol, 0.1 equiv) and sodium carbonate (4.73 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 110 mg of the yellow solid, 78%.

[00340] Preparation of N-(3,4-dimethoxyphenyl)-3-(7-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine



[00341] To a solution of 6-chloro-3-(7-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine

(50 mg, 0.167 mmol, 1.0 equiv), xantphos (19 mg, 0.0334 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0167 mmol, 0.1 equiv), and potassium carbonate (461 mg, 3.34 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (21 mg, 0.184 mmol, 1.1 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 40 mg, 0.195 mmol of the yellow solid, 58%.

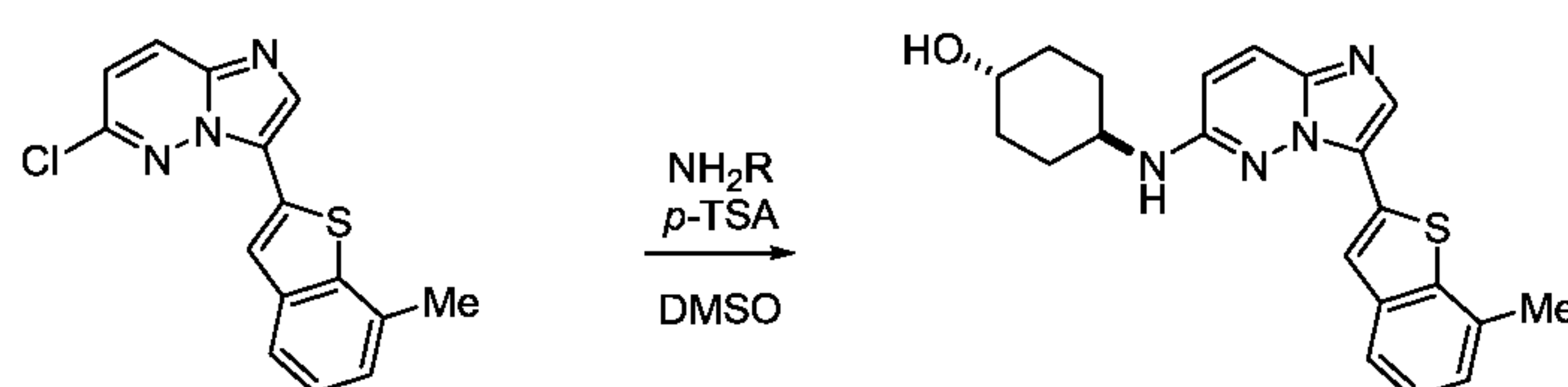
[00342] Compound 202 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 21C.

Table 21C

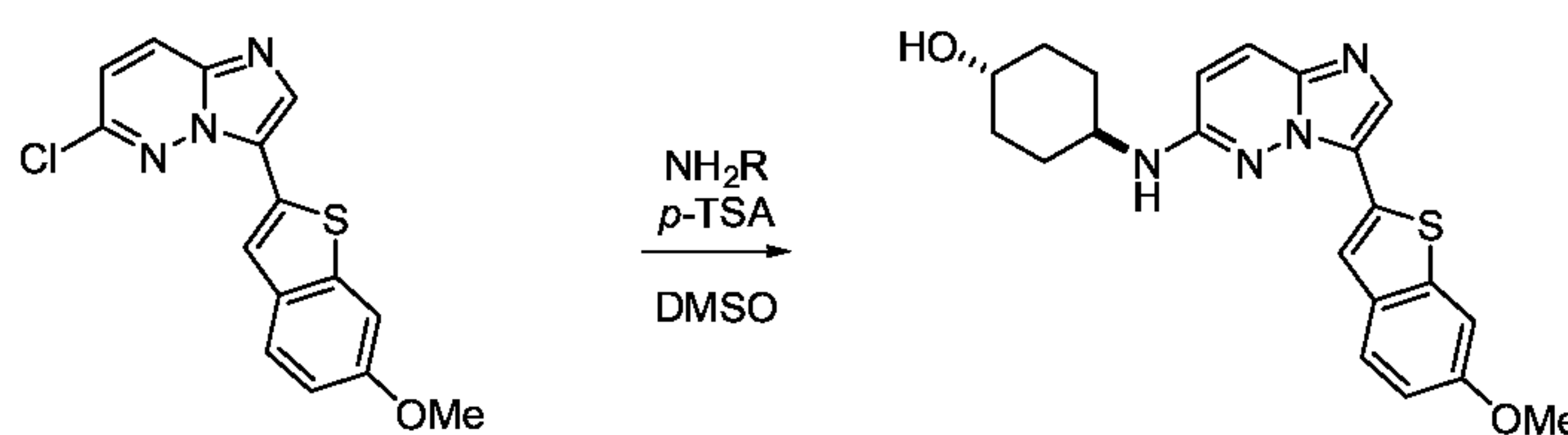
Cd.	Structure	IUPAC Name	[M+H] ⁺
202		N-(3,4-dimethoxyphenyl)-3-(7-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	416.7

[00343] Example 21B – Synthesis of Compound 203

[00344] **Scheme X**



[00345] Preparation of *trans*-4-(3-(7-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol



[00346] To a solution of 3-chloro-3-(7-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.168 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (23 mg, 0.168 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (0.840 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 32 mg of the yellow solid, 48%.

[00347] Compound 203 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 21D.

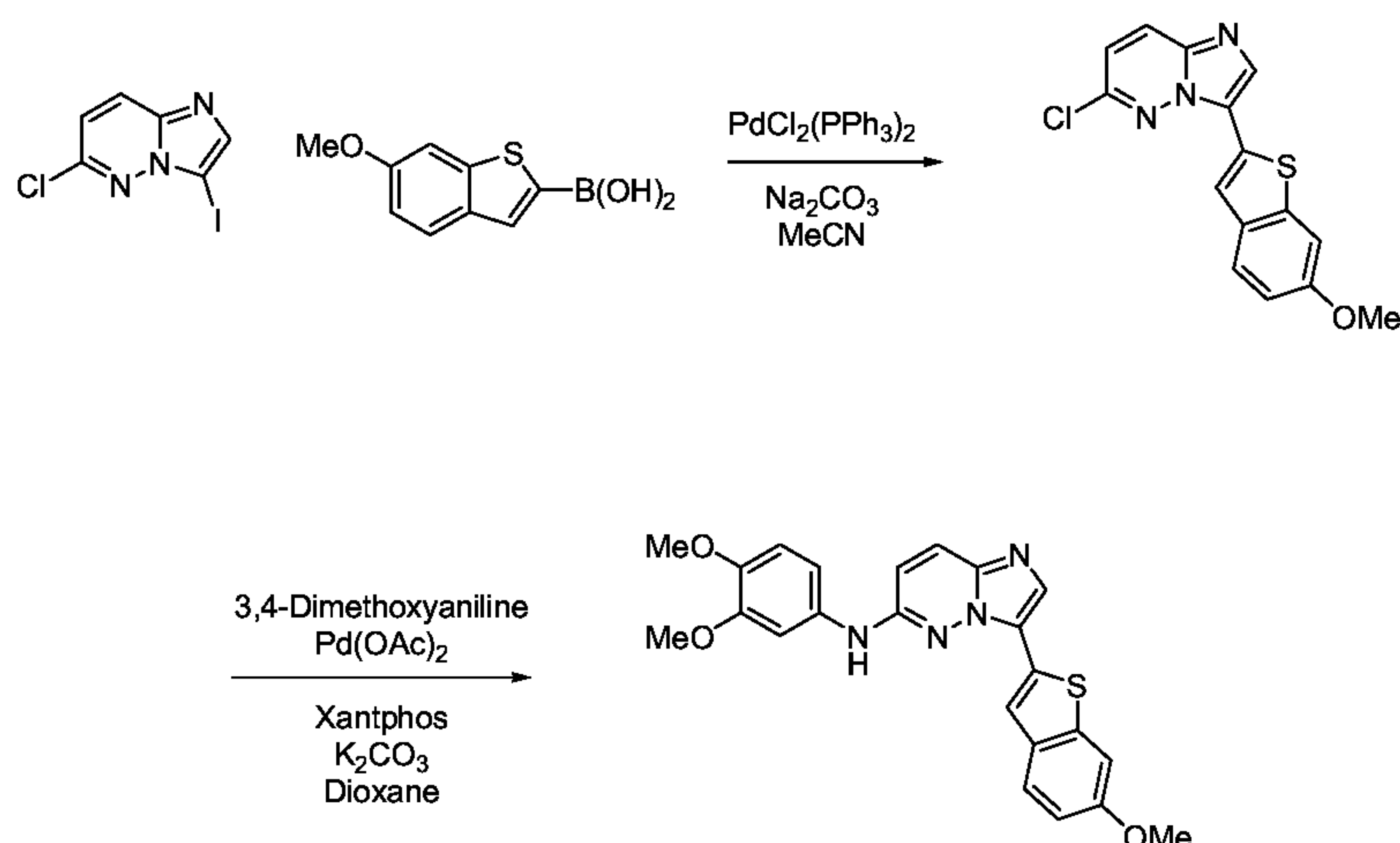
Table 21D

Cd.	Structure	IUPAC Name	[M+H] ⁺
203		<i>trans</i> -4-(3-(7-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	379.4

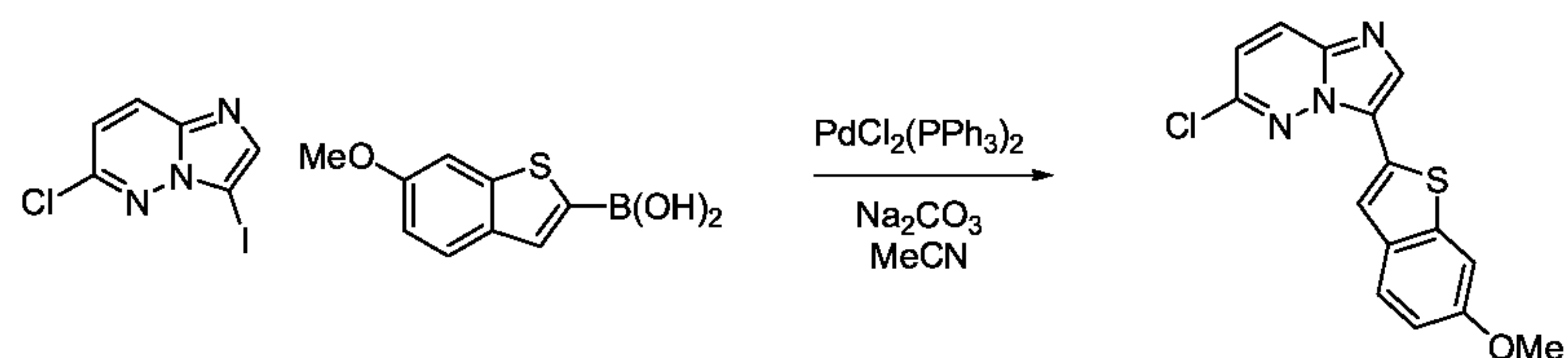
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[00348] Example 22 – Synthesis of Compound 72

[00349] **Scheme 22**

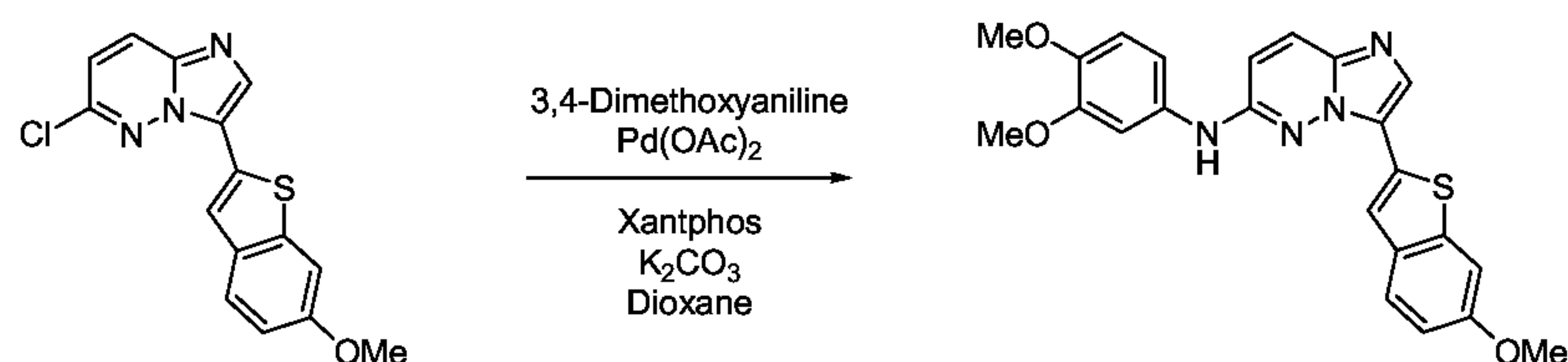


[00350] **Preparation of 6-chloro-3-(6-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine**



[00351] To a solution of 6-methoxybenzo[b]thiophen-2-yl-2-boronic acid (49 mg, 0.237 mmol, 1.1 equiv) in acetonitrile (2.15 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (50 mg, 0.215 mmol, 1.0 equiv), palladium catalyst (8 mg, 0.0108 mmol, 0.05 equiv) and sodium carbonate (2.15 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 50 mg of the yellow solid, 75%.

[00352] **Preparation of 3-(6-methoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine**

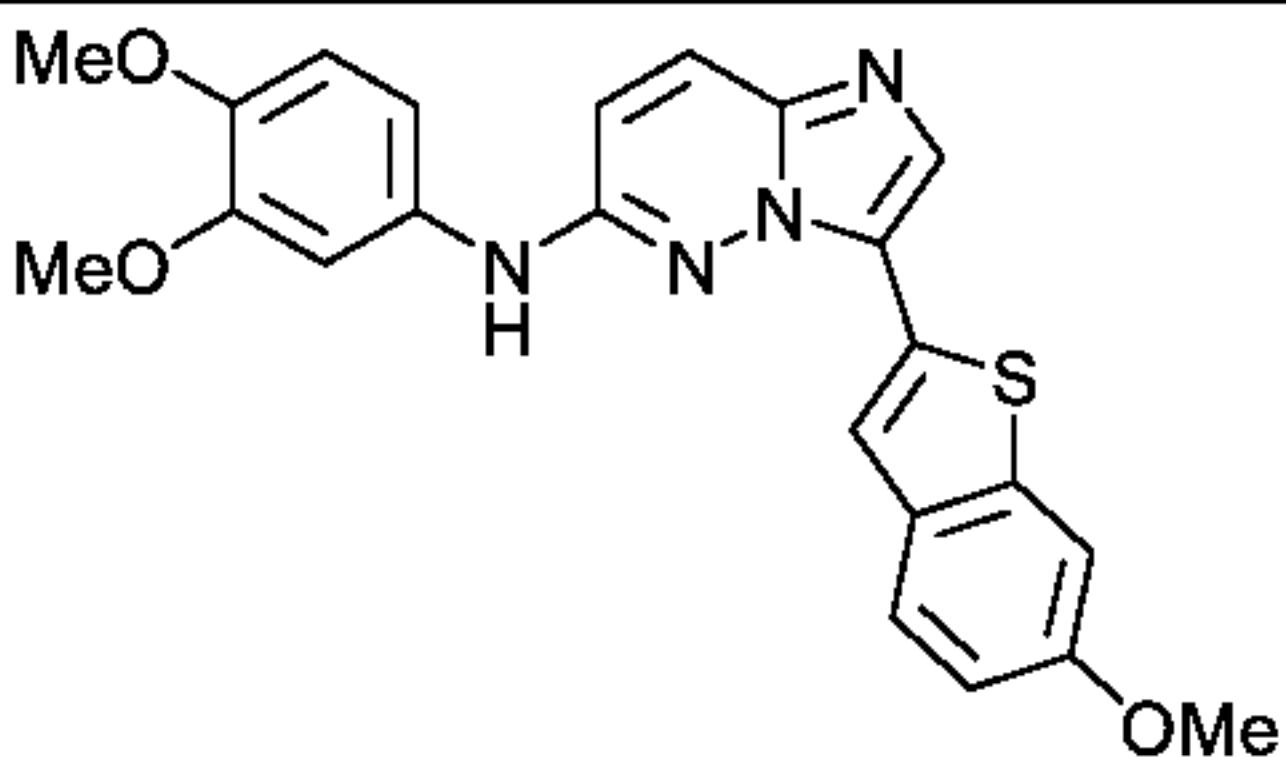


[00353] To a solution of 6-chloro-3-(6-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (82 mg, 0.260 mmol, 1.0 equiv), xantphos (30 mg, 0.0519 mmol, 0.2 equiv), palladium acetate (6 mg, 0.0260 mmol, 0.1 equiv), and potassium carbonate (718 mg, 5.19 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (48 mg, 0.312 mmol, 1.1 equiv)

and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 77 mg, 0.195 mmol of the yellow solid, 75%.

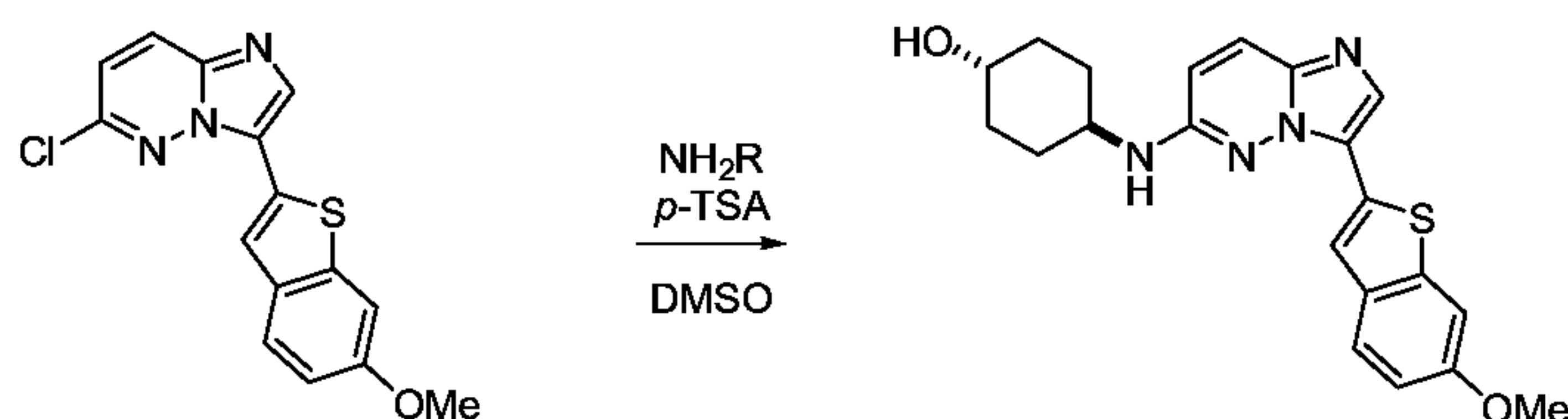
[00354] Compound 72 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 22-b.

Table 22-b

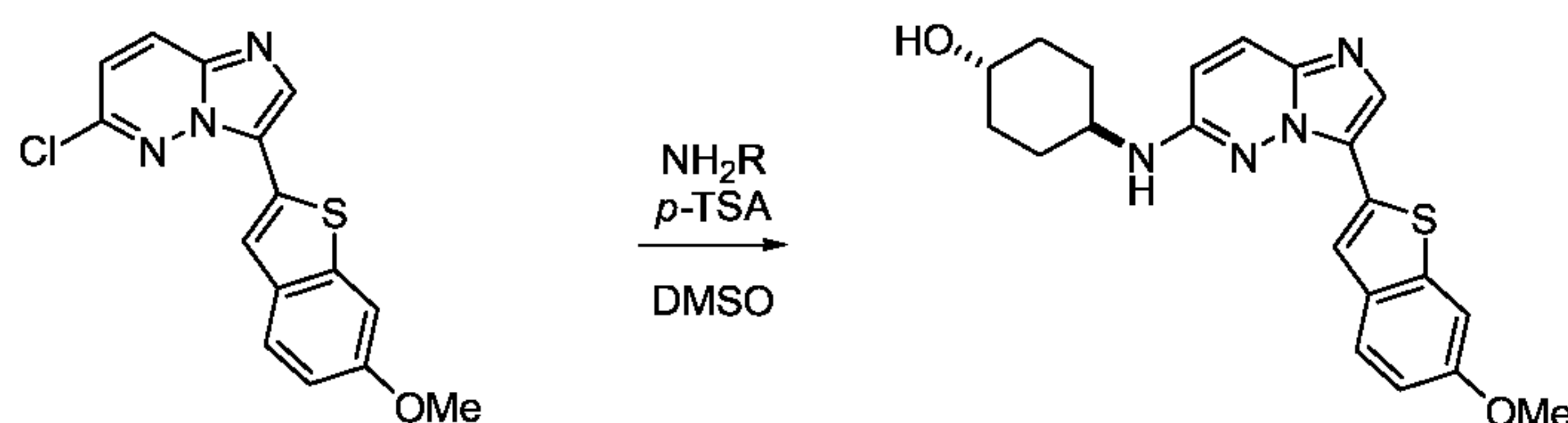
Cd.	Structure	IUPAC Name	[M+H] ⁺
72		3-(6-methoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	395.1

[00355] Example 23 – Synthesis of Compound 172

[00356] Scheme 23



[00357] Preparation of *trans*-4-(3-(6-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

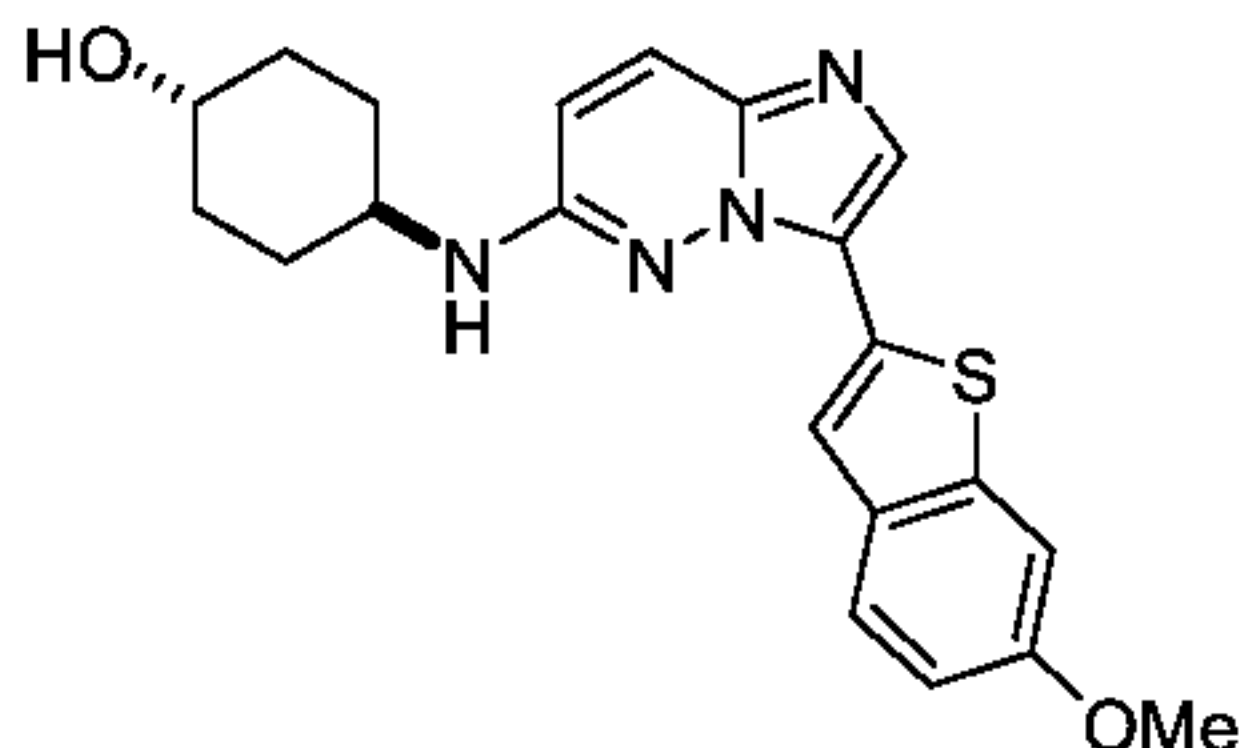


[00358] To a solution of 6-chloro-3-(6-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.111 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (30 mg, 0.111 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (0.803 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 33 mg of the yellow solid, 75%.

[00359] Compound 172 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 23-b.

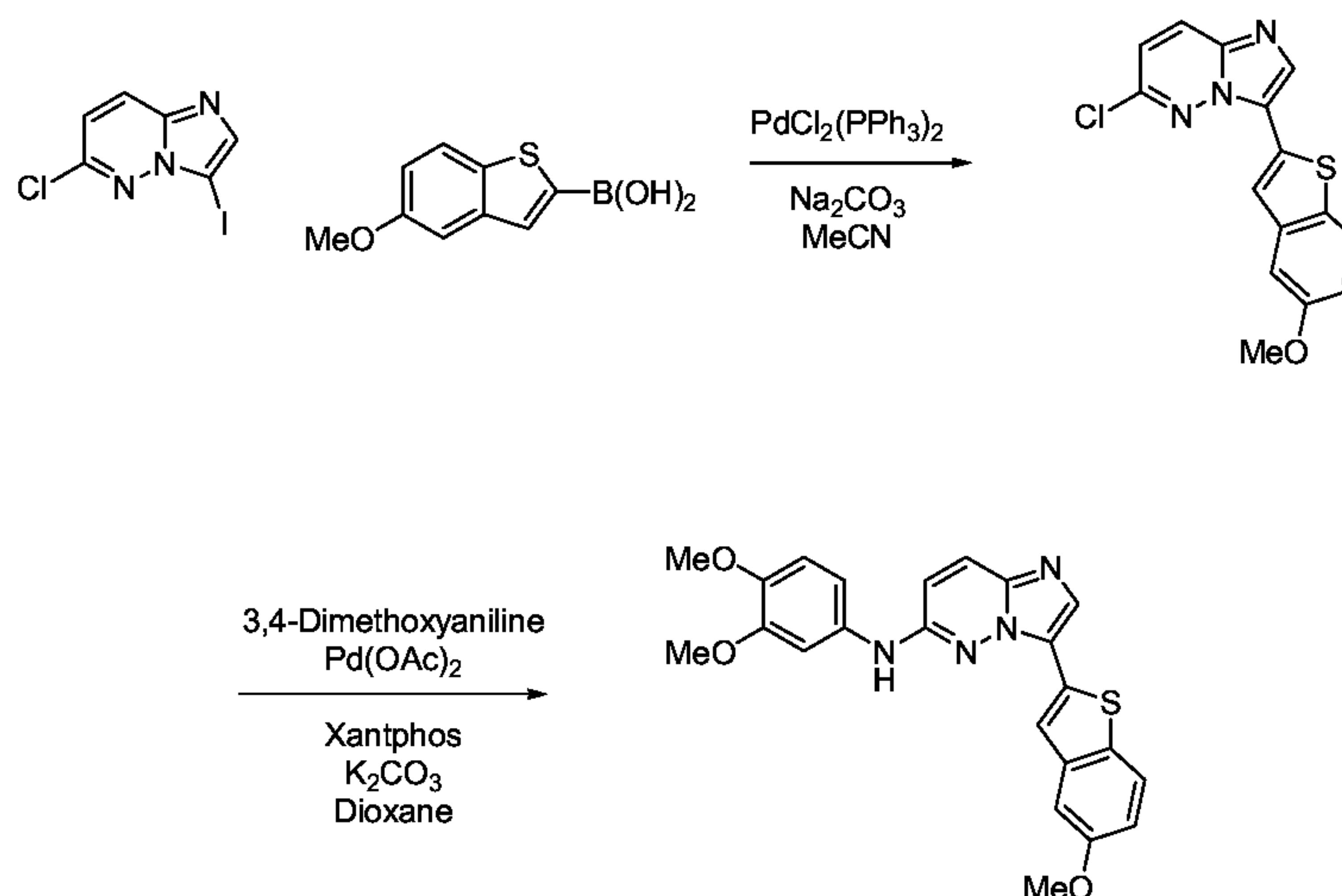
Table 23-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
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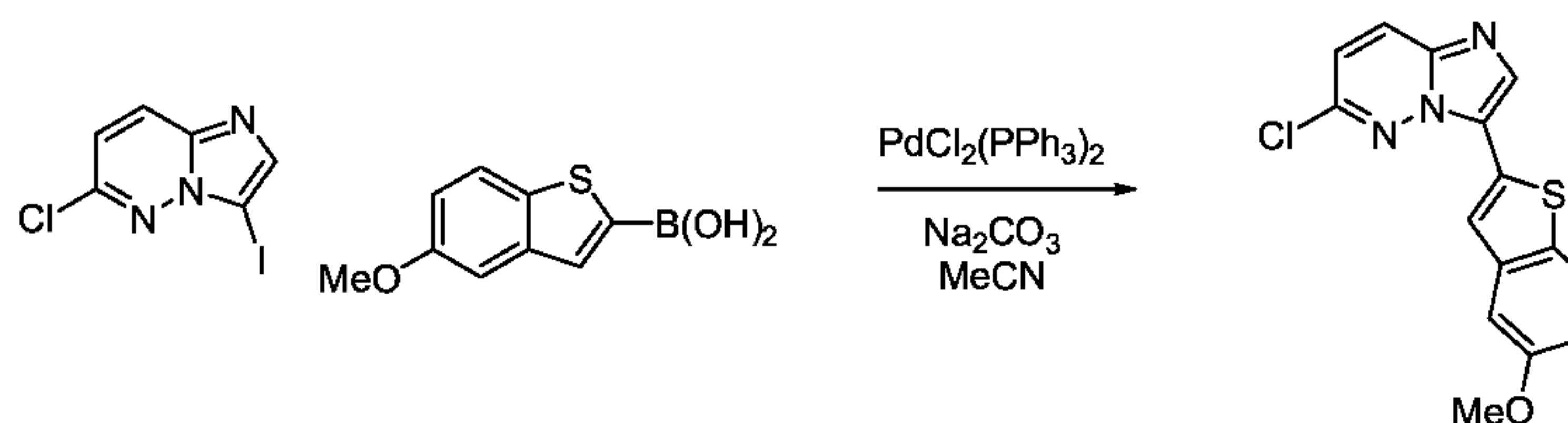
172		<i>trans</i> -4-(3-(6-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	395.1
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[00360] Example 24 – Synthesis of Compound 167

[00361] **Scheme 24**

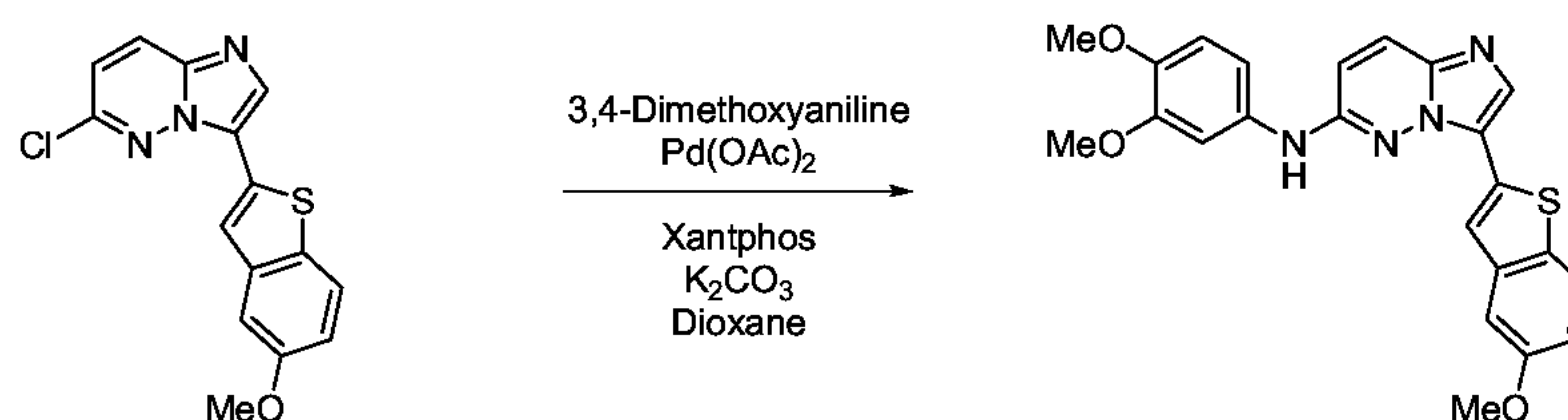


[00362] **Preparation of 6-chloro-3-(5-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine**



[00363] To a solution of 6-methoxybenzo[b]thiophen-2-yl-2-boronic acid (50 mg, 0.242 mmol, 1.1 equiv) in acetonitrile (2.15 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (56 mg, 0.220 mmol, 1.0 equiv), palladium catalyst (8 mg, 0.0121 mmol, 0.05 equiv) and sodium carbonate (2.42 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 50 mg of the yellow solid, 77%.

[00364] **Preparation of 3-(5-methoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine**



[00365] To a solution of 6-chloro-3-(5-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (80 mg, 0.254 mmol, 1.0 equiv), xantphos (29 mg, 0.0506 mmol, 0.2 equiv), palladium acetate (6 mg, 0.0254 mmol, 0.1 equiv), and potassium carbonate (700 mg, 5.06 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (47 mg, 0.304 mmol, 1.1 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 62 mg, 0.152 mmol of the yellow solid, 60%.

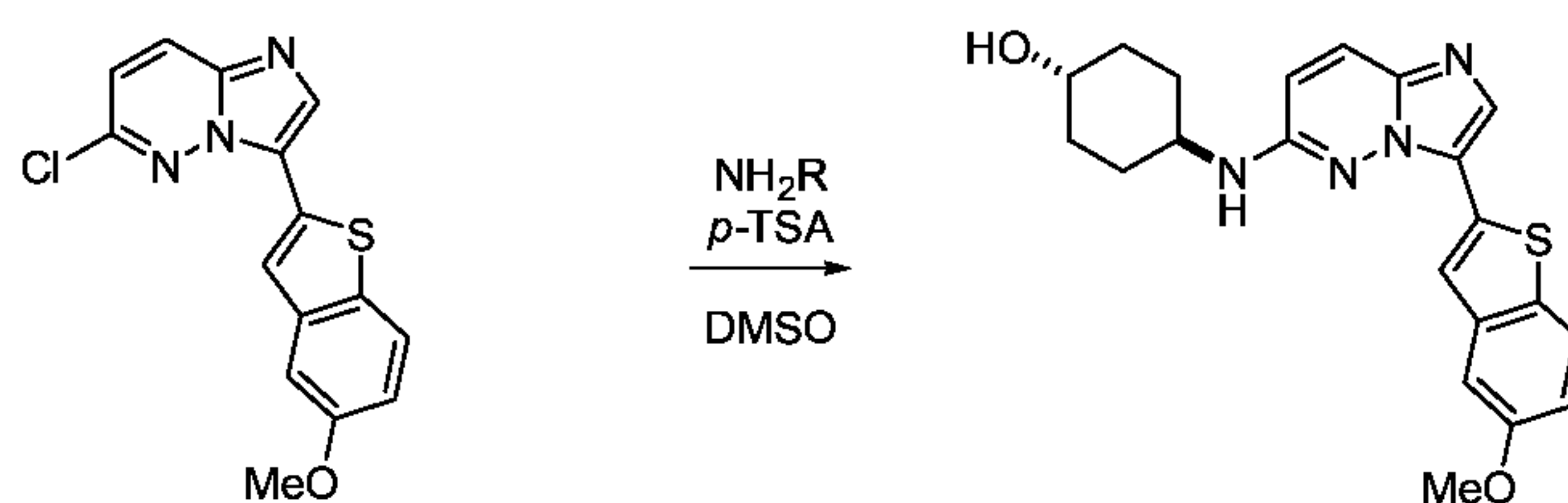
[00366] Compound 167 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 24-b**.

[00367] **Table 24-b**

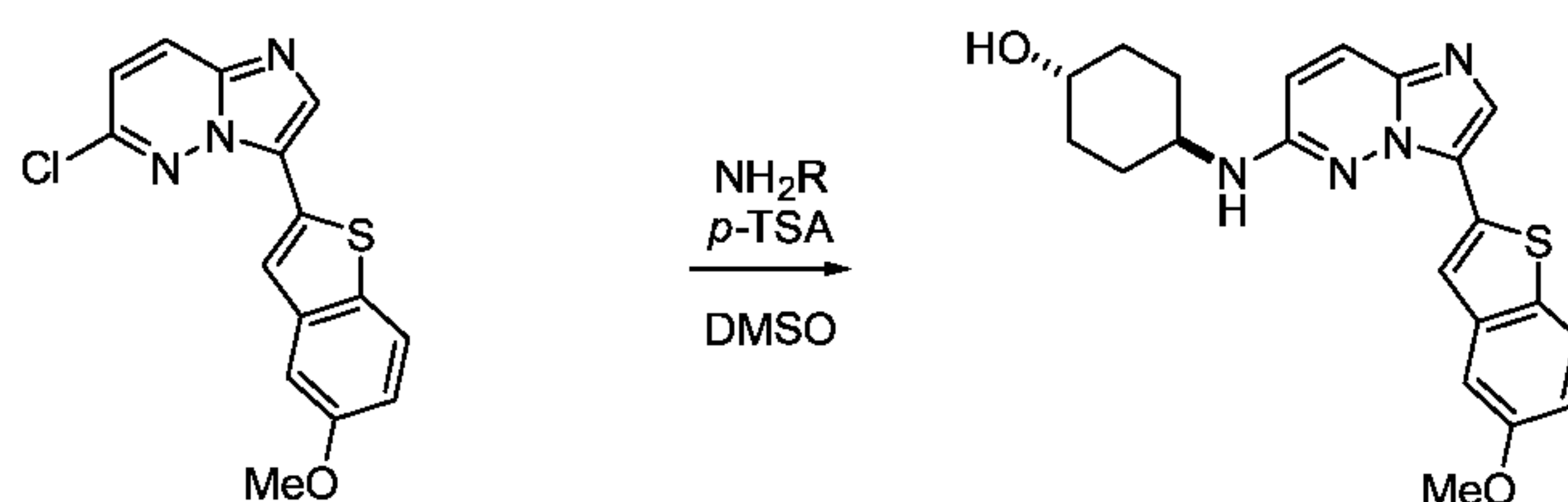
Cd.	Structure	IUPAC Name	[M+H] ⁺
167		3-(5-methoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	433.7

[00368] Example 25A – Synthesis of Compound 168

[00369] **Scheme 25A**



[00370] Preparation of *trans*-4-(3-(5-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

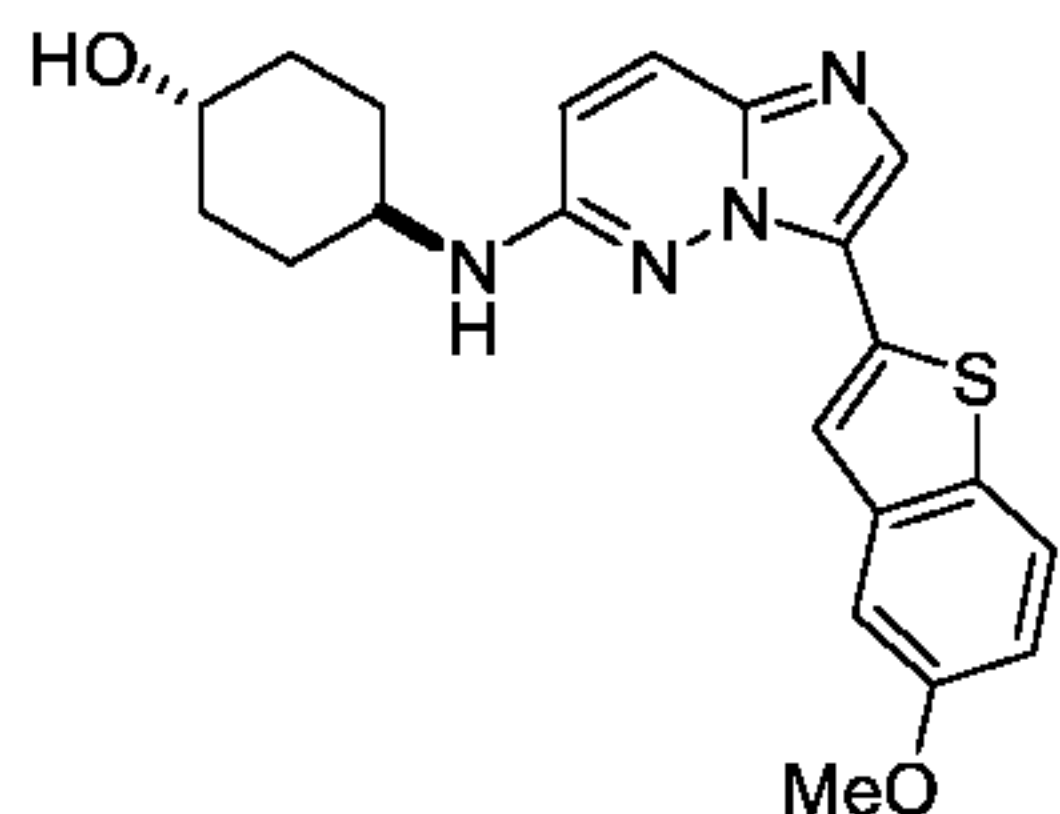


[00371] To a solution of 6-chloro-3-(5-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (47 mg, 0.151 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic

acid monohydrate (29 mg, 0.151 mmol, 1.0 equiv) and amine (0.755 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 30 mg of the yellow solid, 50%.

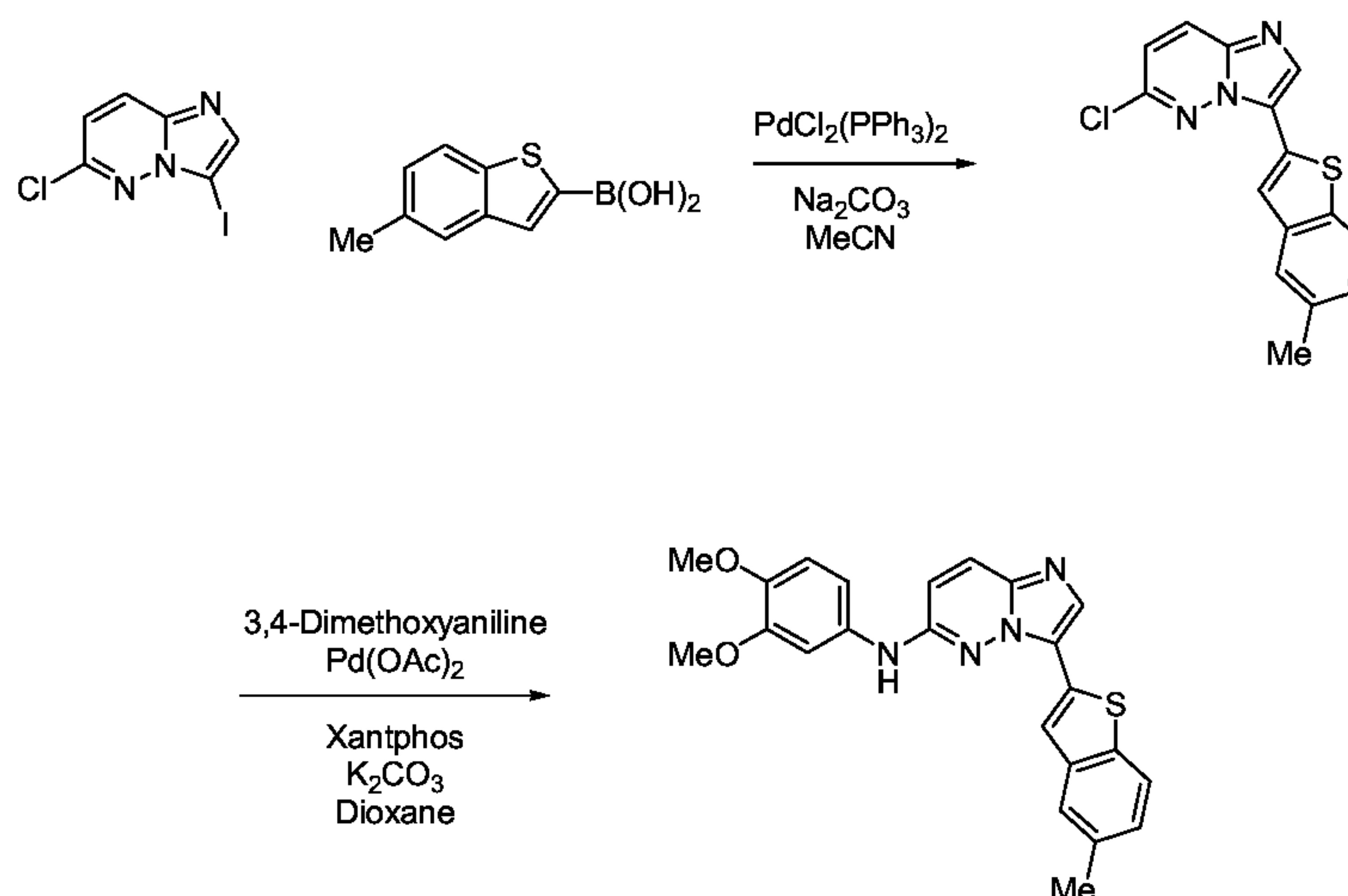
[00372] Compound 168 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 25A**.

Table 25A

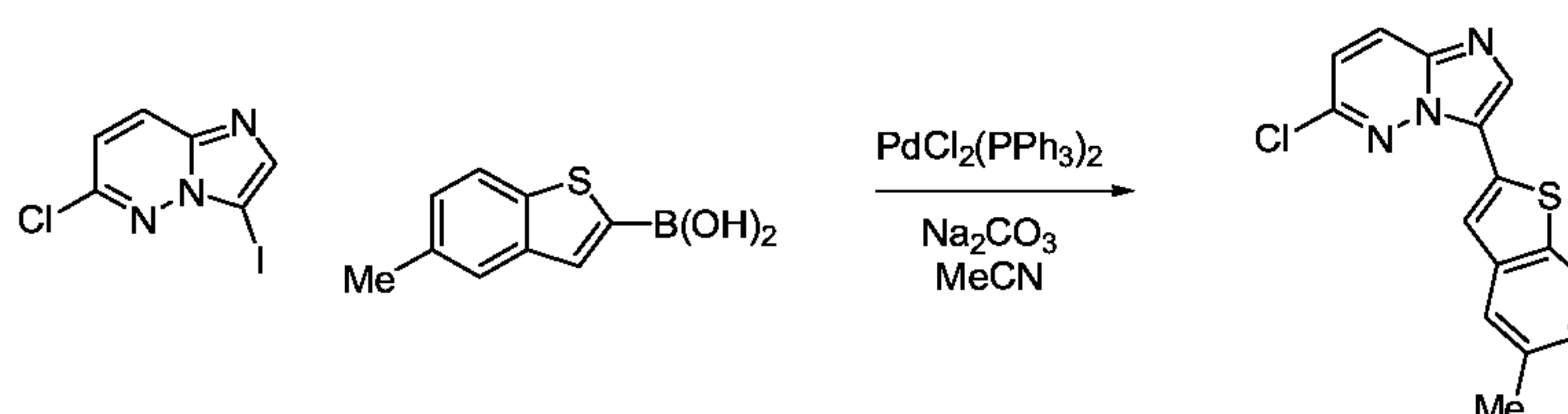
Cd.	Structure	IUPAC Name	[M+H] ⁺
168		<i>trans</i> -4-(3-(5-methoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	395.7

[00373] Example 25B – Synthesis of Compound 191

[00374] **Scheme 25B**



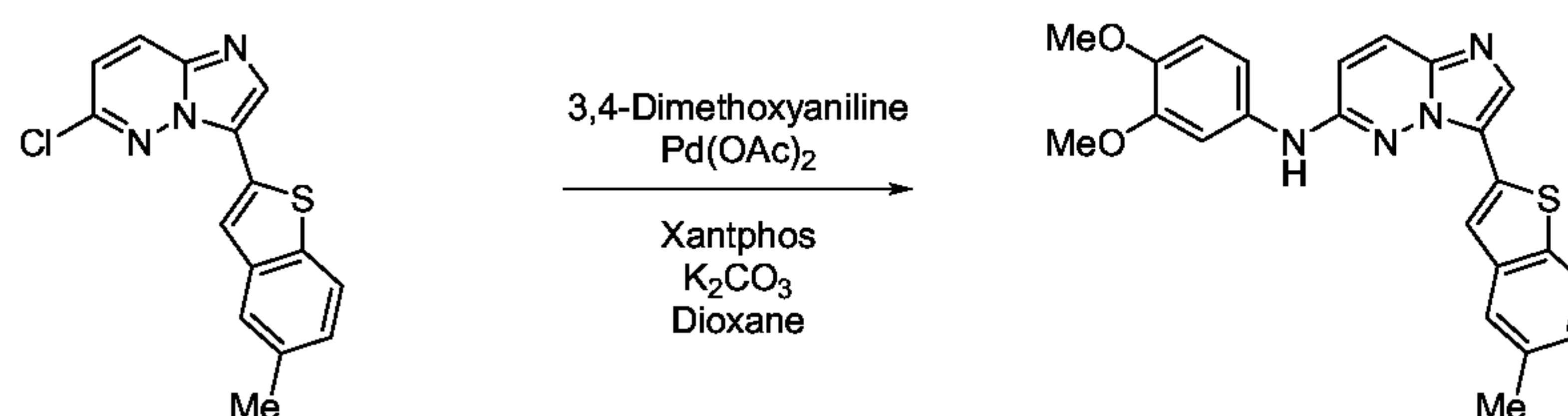
[00375] **Preparation of 6-chloro-3-(5-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine**



[00376] To a solution of 6-methylbenzo[b]thiophen-2-yl-2-boronic acid (120 mg, 0.627 mmol, 1.2 equiv) in acetonitrile (5.22 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (146 mg,

0.522 mmol, 1.0 equiv), palladium catalyst (38 mg, 0.0522 mmol, 0.1 equiv) and sodium carbonate (5.22 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 50 mg of the yellow solid 125 mg, 80%.

[00377] Preparation of 3-(5-methylbenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine



[00378] To a solution of 6-chloro-3-(5-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.168 mmol, 1.0 equiv), xantphos (19 mg, 0.0334 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0167 mmol, 0.1 equiv), and potassium carbonate (461 mg, 3.34 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (28 mg, 0.167 mmol, 1.1 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 42 mg, 0.152 mmol of the yellow solid, 60%.

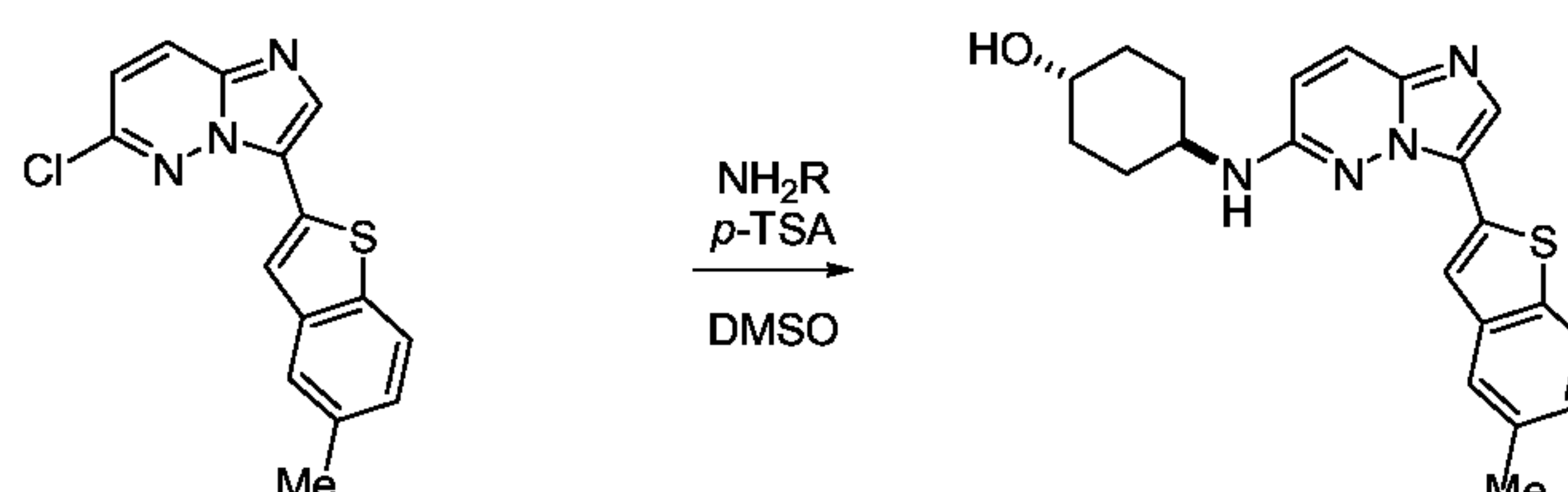
[00379] Compound 191 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 25B**.

[00380] Table 25B

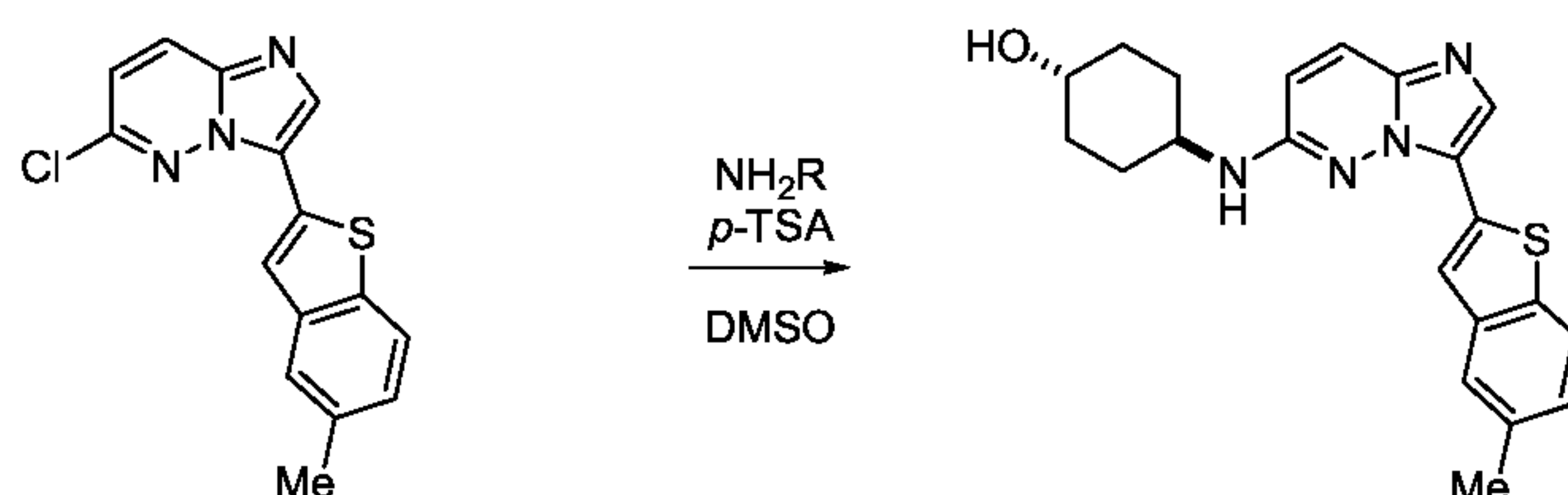
Cd.	Structure	IUPAC Name	[M+H] ⁺
191		N-(3,4-dimethoxyphenyl)-3-(5-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-amine	417.1

[00381] Example 25C – Synthesis of Compound 192

[00382] Scheme 25C



[00383] Preparation of *trans*-4-(3-(5-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol



[00384] To a solution of 6-chloro-3-(5-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.168 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (30 mg, 0.168 mmol, 1.0 equiv) and amine (0.840 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 30 mg of the yellow solid, 47%.

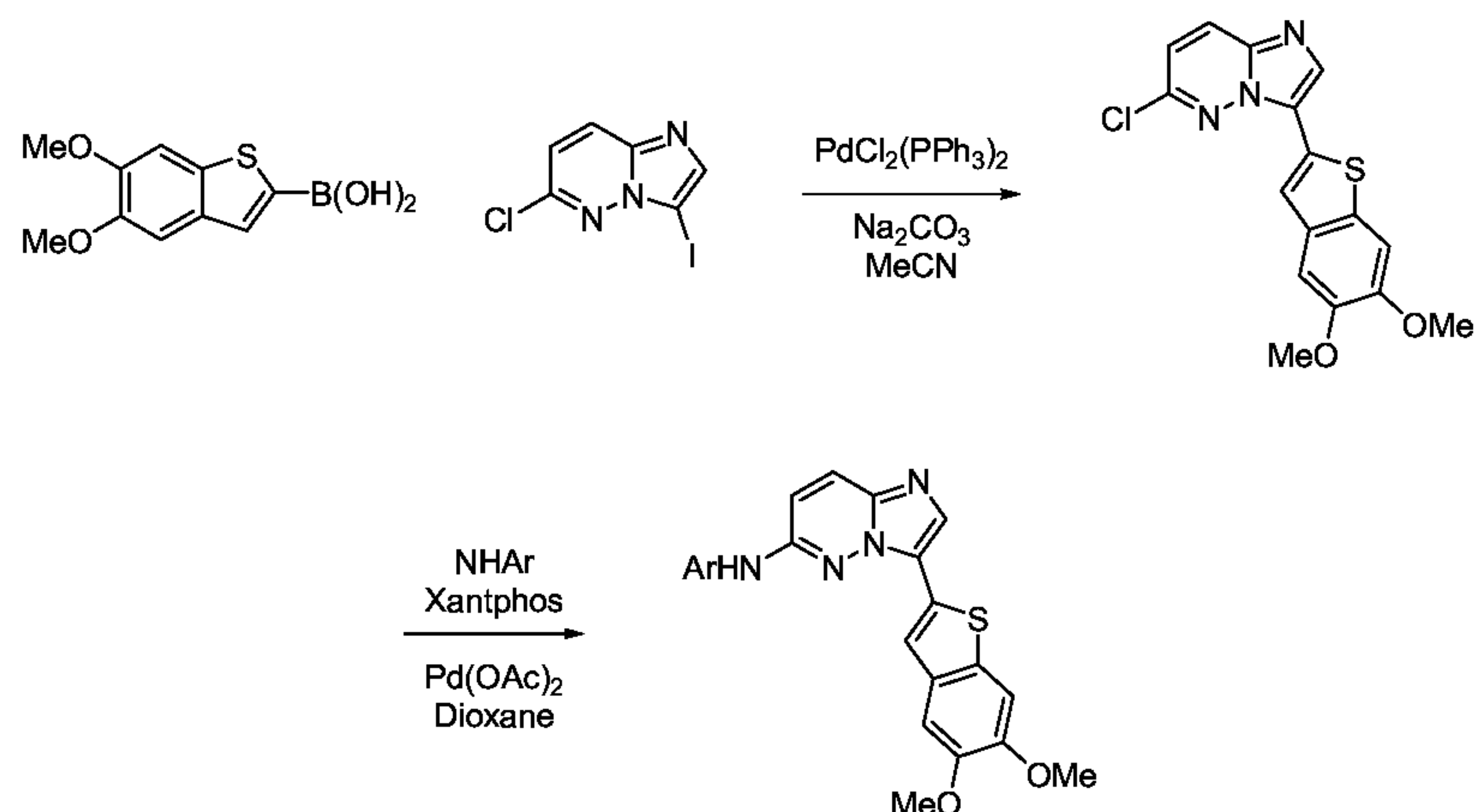
[00385] Compound 192 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 25C**.

Table 25C

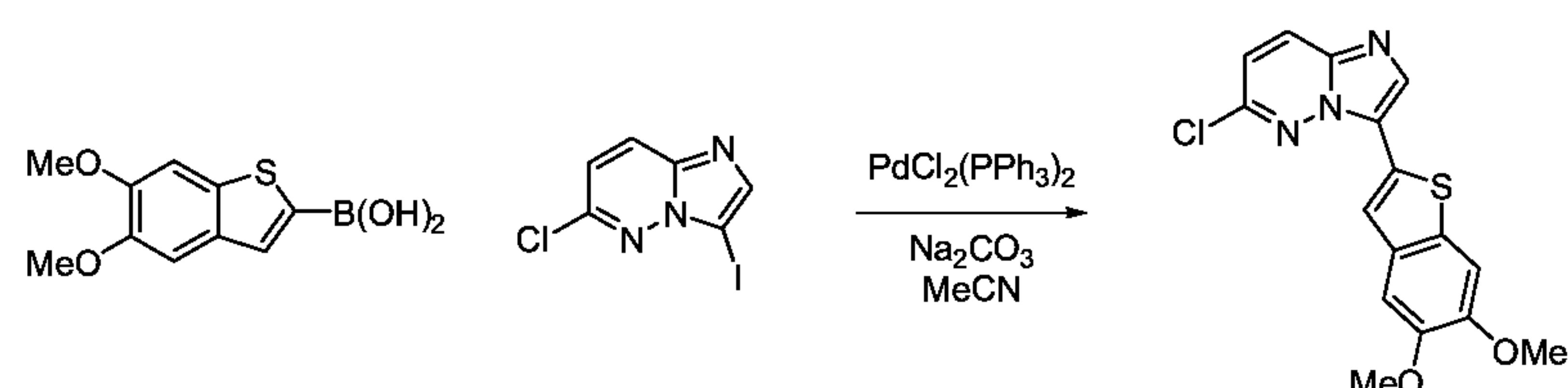
Cd.	Structure	IUPAC Name	[M+H] ⁺
192		<i>trans</i> -4-(3-(5-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	379.5

[00386] Example 26 – Synthesis of Compounds 67, 70-71

[00387] **Scheme 26**

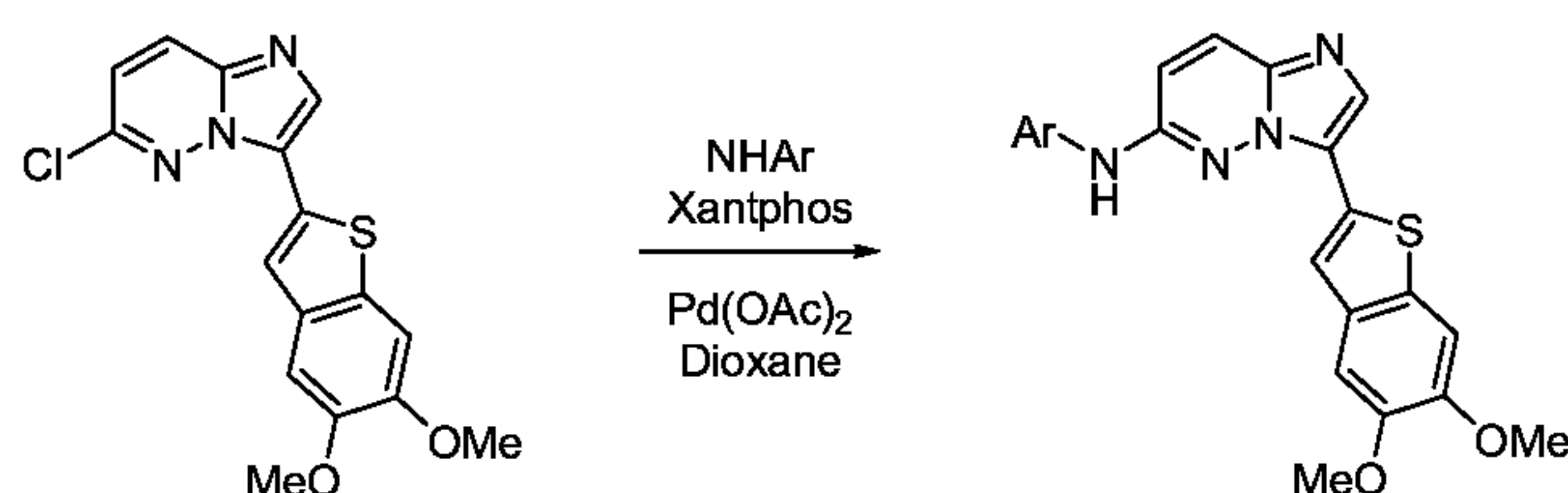


[00388] **Preparation of 6-chloro-3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine**



[00389] To a solution of 5,6-dimethoxybenzo[b]thiophen-2-yl-2-boronic acid (471 mg, 1.98 mmol, 1.3 equiv) in acetonitrile (10.0 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (425 mg, 1.52 mmol, 1.0 equiv), palladium catalyst (56 mg, 0.0760 mmol, 0.05 equiv) and sodium carbonate (10.0 mL, 1.0 M, 10.0 equiv). The solution was stirred at rt overnight. Purification using column chromatography gave 368 mg of the product, 70%: ¹H NMR (400 MHz, DMSO) δ 8.35 (s, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.06 (s, 1H), 7.63 (s, 1H), 7.47 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H).

[00390] Preparation of 3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine



[00391] To a solution of 6-chloro-3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (69 mg, 0.20 mmol, 1.0 equiv), xantphos (23 mg, 0.04 mmol, 0.2 equiv), palladium acetate (4 mg, 0.02 mmol, 0.1 equiv), and potassium carbonate (553 mg, 4.00 mmol, 20 equiv) in dioxane (5.0 mL) was added amine (0.20 mmol, 1.0 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

Table 26-a

Cd.	Amine	Pure Isolated Compound
67	3,4-dimethoxyaniline	3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine
70	3-(4-amino-2-methoxyphenoxy)propan-1-ol	3-(4-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenoxy)propan-1-ol
71	methyl 3-aminobenzoate	3-(3-(5,6-dimethoxybenzo[b]thiophen-

		2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid
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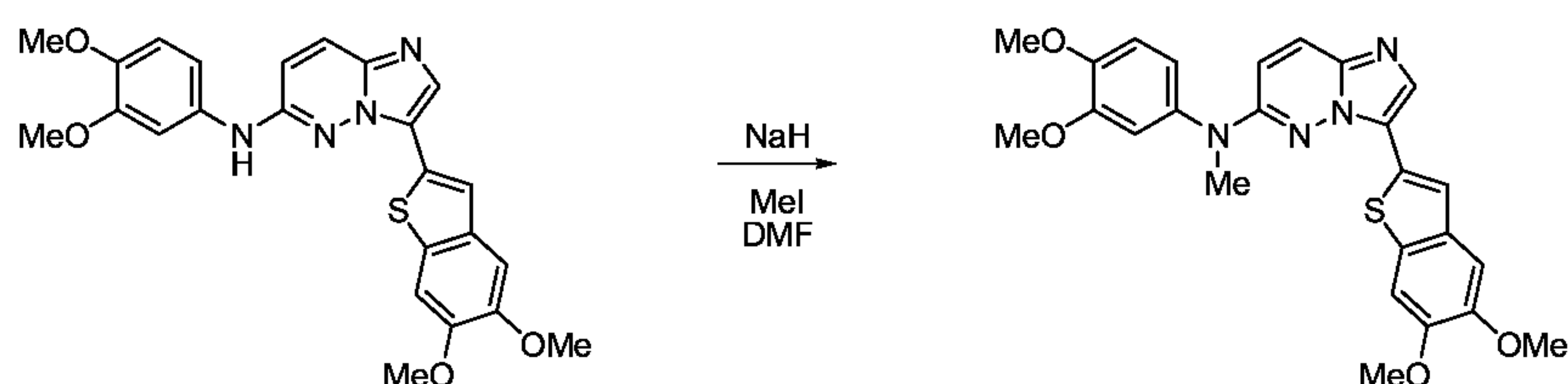
[00392] Compounds 67, 70-71 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 26-b**.

Table 26-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
67		3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	463.5
70		3-(4-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methoxyphenoxy)propan-1-ol	507.3
71		3-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)benzoic acid	447.1

[00393] Example 27 – Synthesis of Compound 75

[00394] **Scheme 27**

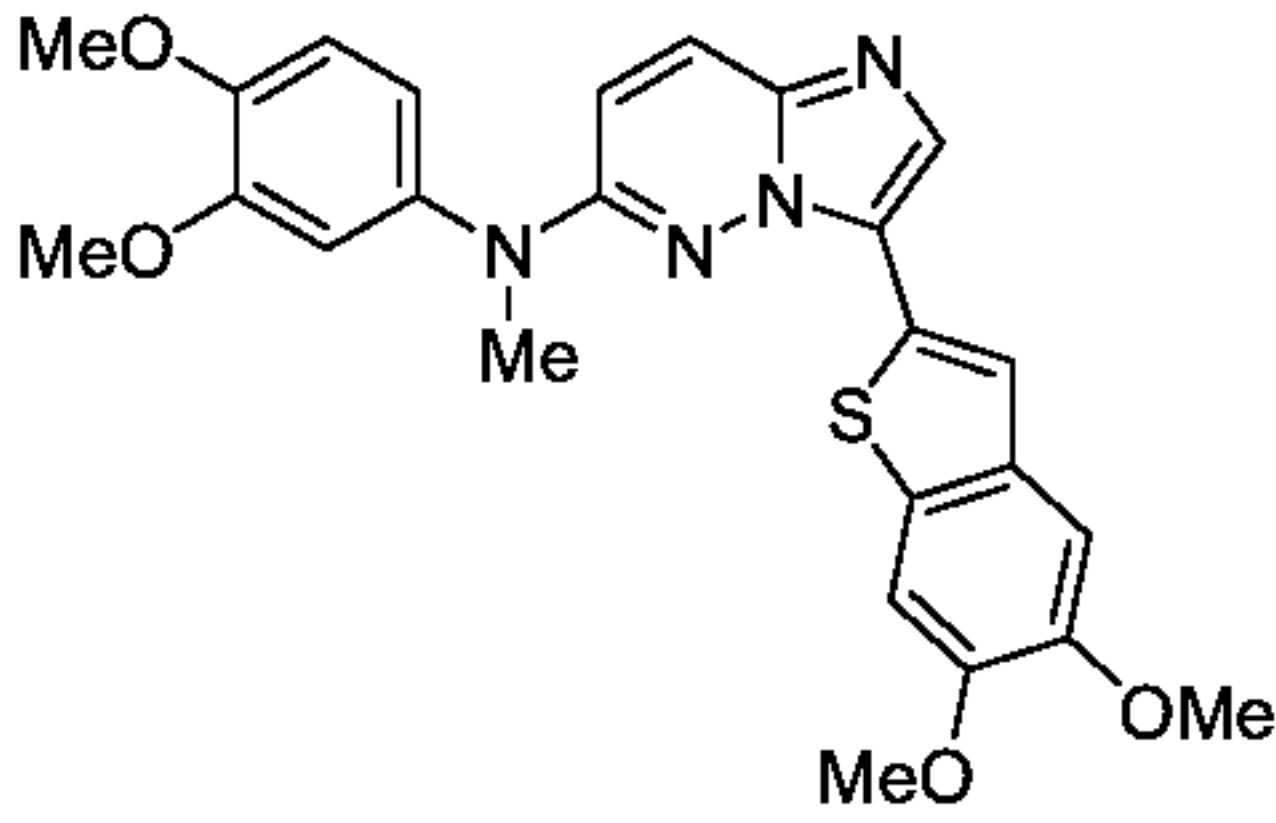


[00395] **Preparation of 3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)-N-methylimidazo[1,2-b]pyridazin-6-amine**

[00396] To a solution of 3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine (50 mg, 0.108 mmol, 1.0 equiv) in DMF (5.0 mL) was added NaH (13 mg, 0.324 mmol, 3.0 equiv) followed by iodomethane (0.07 mL, 0.541 mmol, 5.0 equiv). After 1 h, the reaction was quenched with saturated aqueous solution of ammonium chloride then extracted with ethyl acetate. Purification by column chromatography using 2% methanol in dichloromethane elution gave 30 mg of the brown solid, 58%.

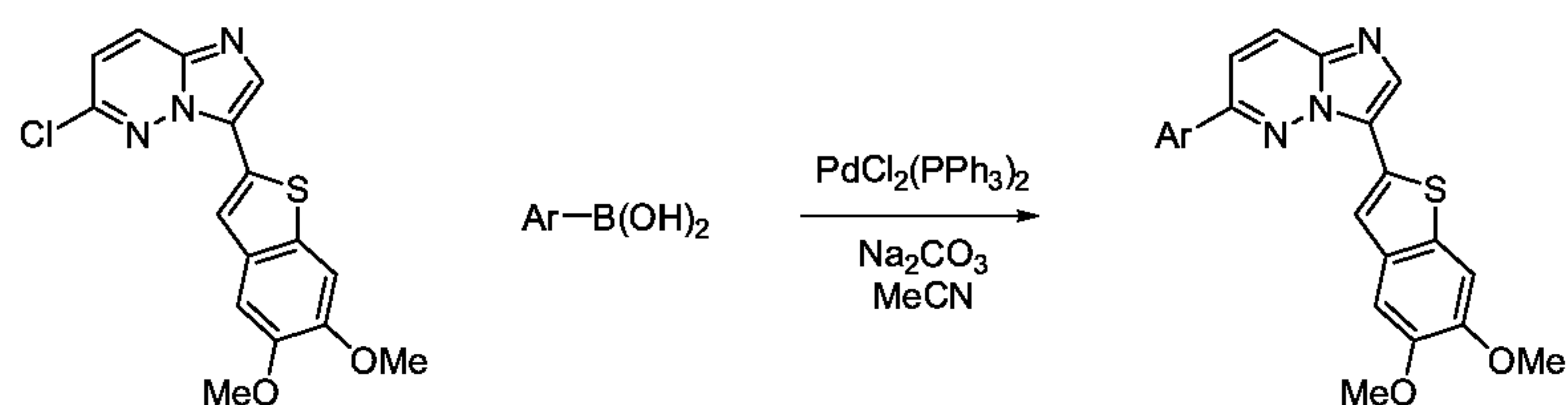
[00397] Compound 75 was physically characterized by electrospray ionization mass spectrometry. Structure and molecular mass is given below in Table 27-b.

Table 27-b

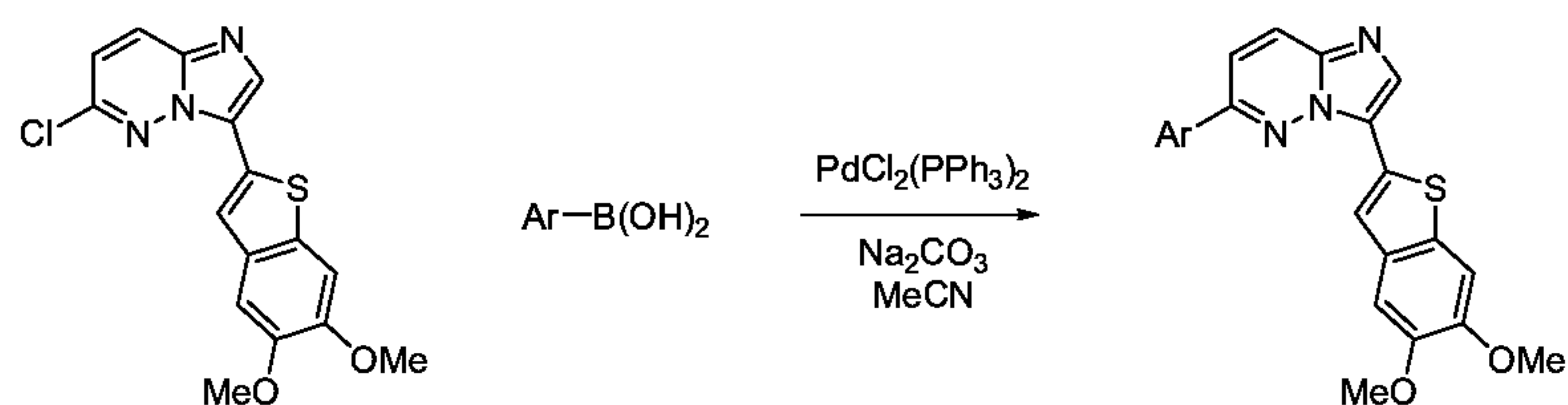
Cd.	Structure	IUPAC Name	[M+H] ⁺
75		3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)-N-methylimidazo[1,2-b]pyridazin-6-amine	477.1

[00398] Example 28 – Synthesis of Compounds 69, 73-74

[00399] **Scheme 28**



[00400] **Preparation of 3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-6-arylimidazo[1,2-b]pyridazine**



[00401] To a solution of 6-chloro-3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (100 mg, 0.289 mmol, 1.0 equiv) in acetonitrile (5.0 mL) was added boronic acid (0.376 mmol, 1.3 equiv), palladium catalyst (3 mg, 0.014 mmol, 0.05 equiv) and sodium carbonate (2.89 mL, 1.0 M, 10.0 equiv). The solution was heated in the microwave at 150 °C for 10 minutes. Purification using column chromatography gave the product.

Table 28-a

Cd.	Boronic Acid	Pure Isolated Compound
69	1H-indol-5-yl-5-boronic acid	6-(1H-indol-5-yl)-3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine
73	4-((4-methylpiperazin-1-yl)methyl)phenylboronic acid	3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-6-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine

74	3-((4-methylpiperazin-1-yl)methyl)phenylboronic acid	3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-6-(3-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine
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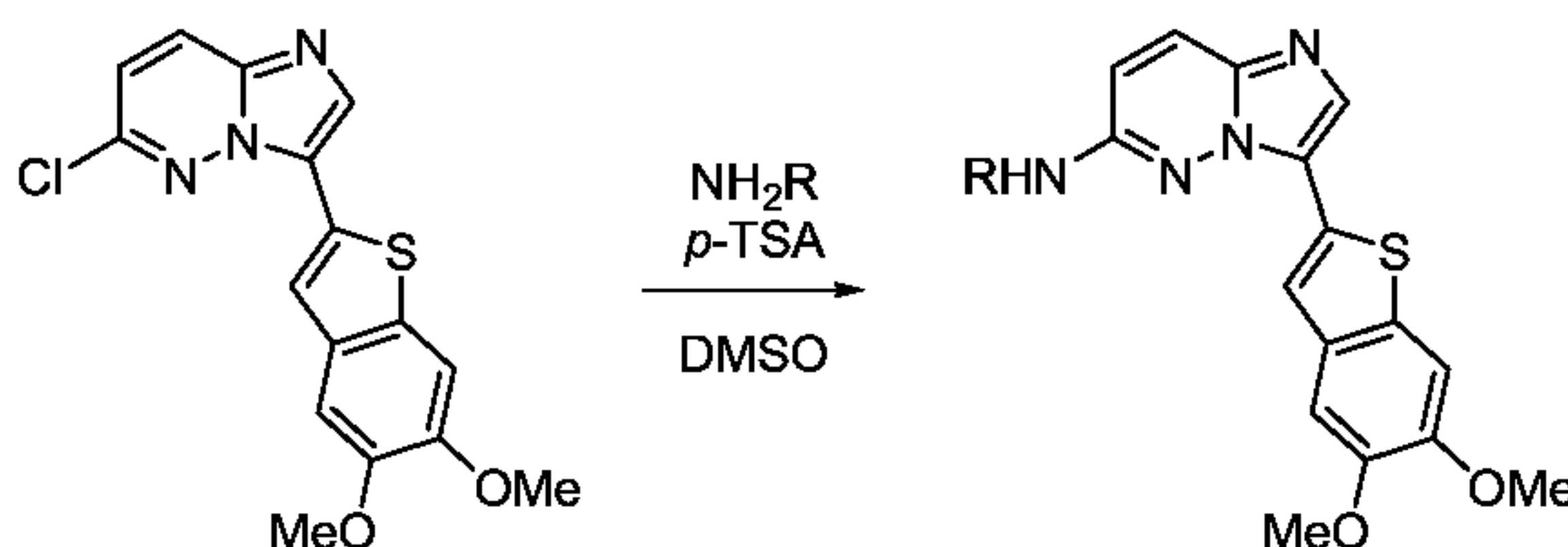
[00402] Compounds 69, 73-74 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 28-b**.

Table 28-b

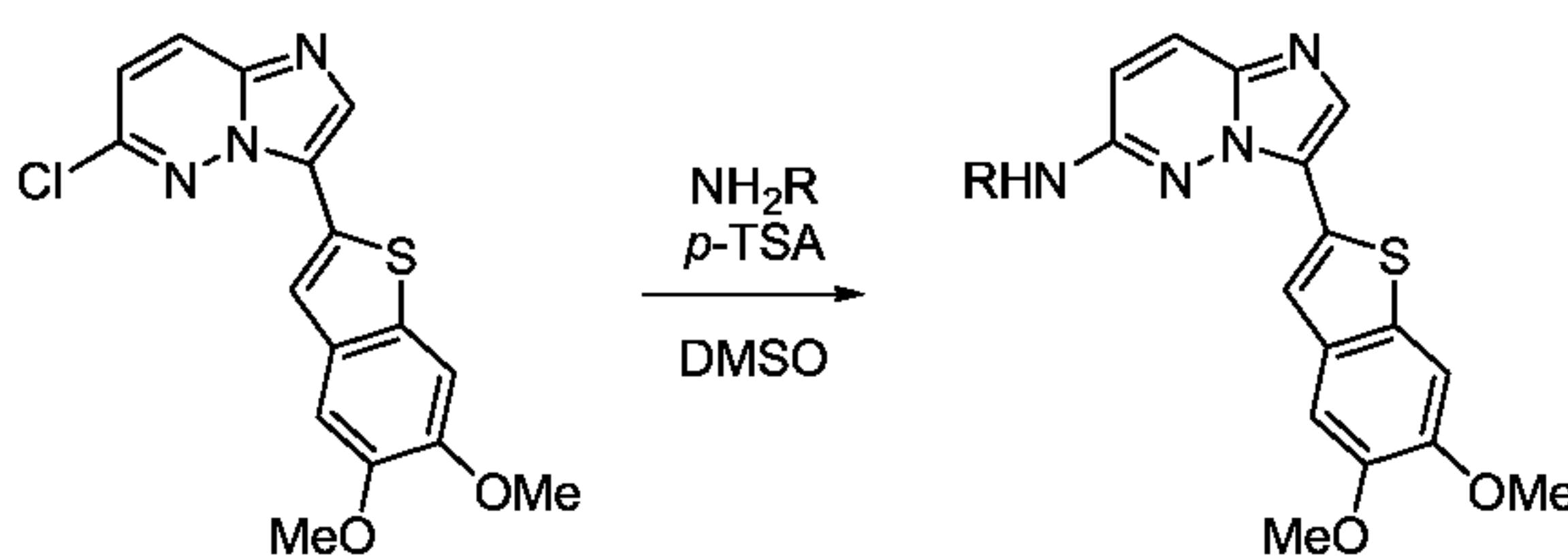
Cd.	Structure	IUPAC Name	[M+H] ⁺
69		6-(1H-indol-5-yl)-3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine	427.0
73		3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-6-(4-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine	500.2
74		3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-6-(3-((4-methylpiperazin-1-yl)methyl)phenyl)imidazo[1,2-b]pyridazine	500.3

[00403] Example 29 – Synthesis of Compounds 169, 171, 173-174

[00404] **Scheme 29**



[00405] **Preparation of 3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-alkylimidazo[1,2-b]pyridazin-6-amine**



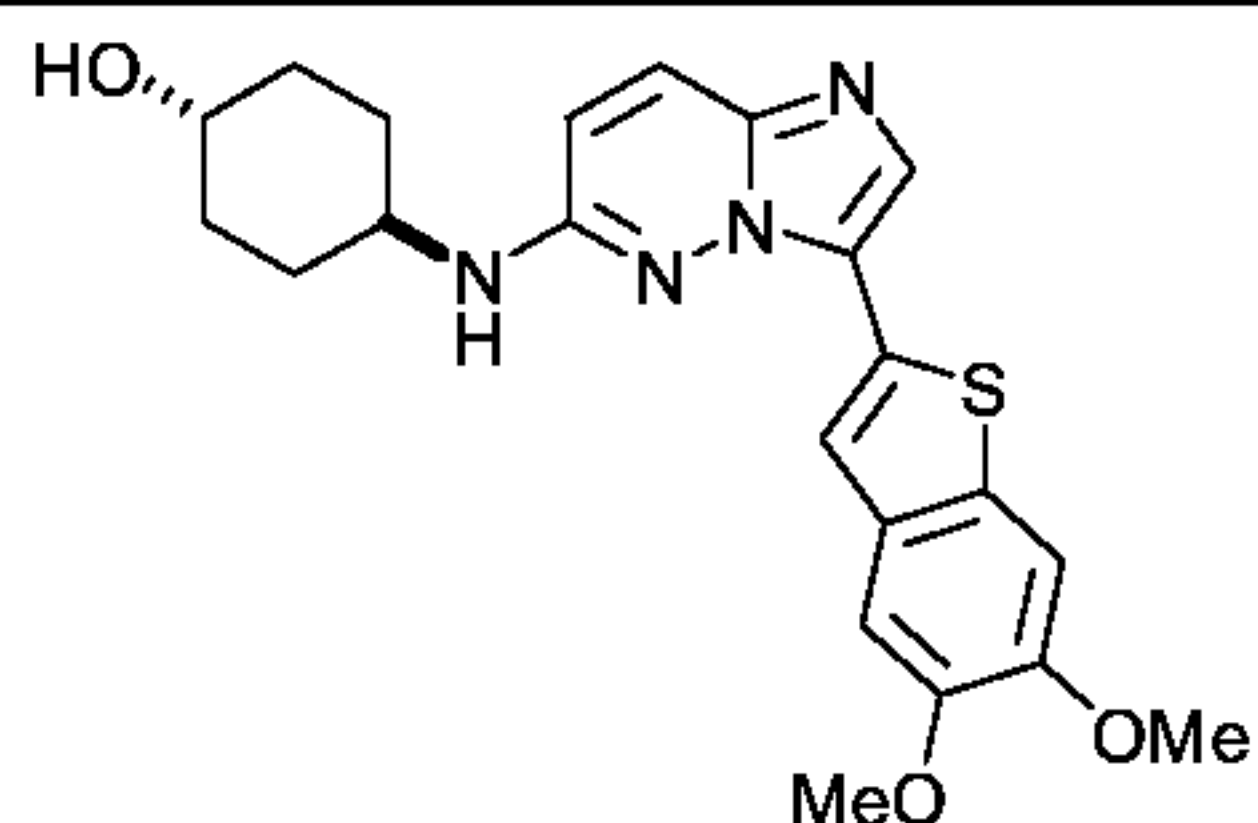
[00406] To a solution of 6-chloro-3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (311 mg, 0.899 mmol, 1.0 equiv) in DMSO (5.0 mL) was added *p*-toluene sulfonic acid monohydrate (171 mg, 0.899 mmol, 1.0 equiv) and amine (4.50 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave the product.

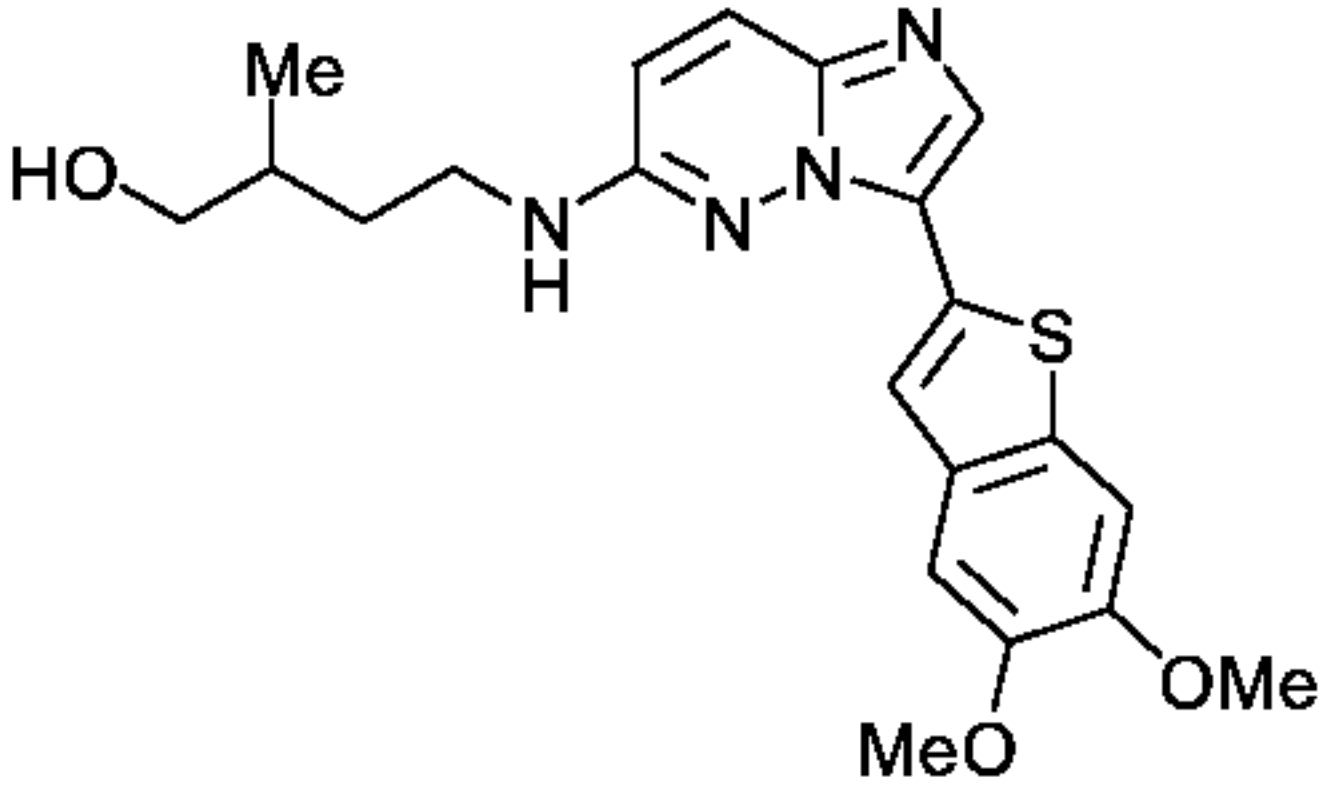
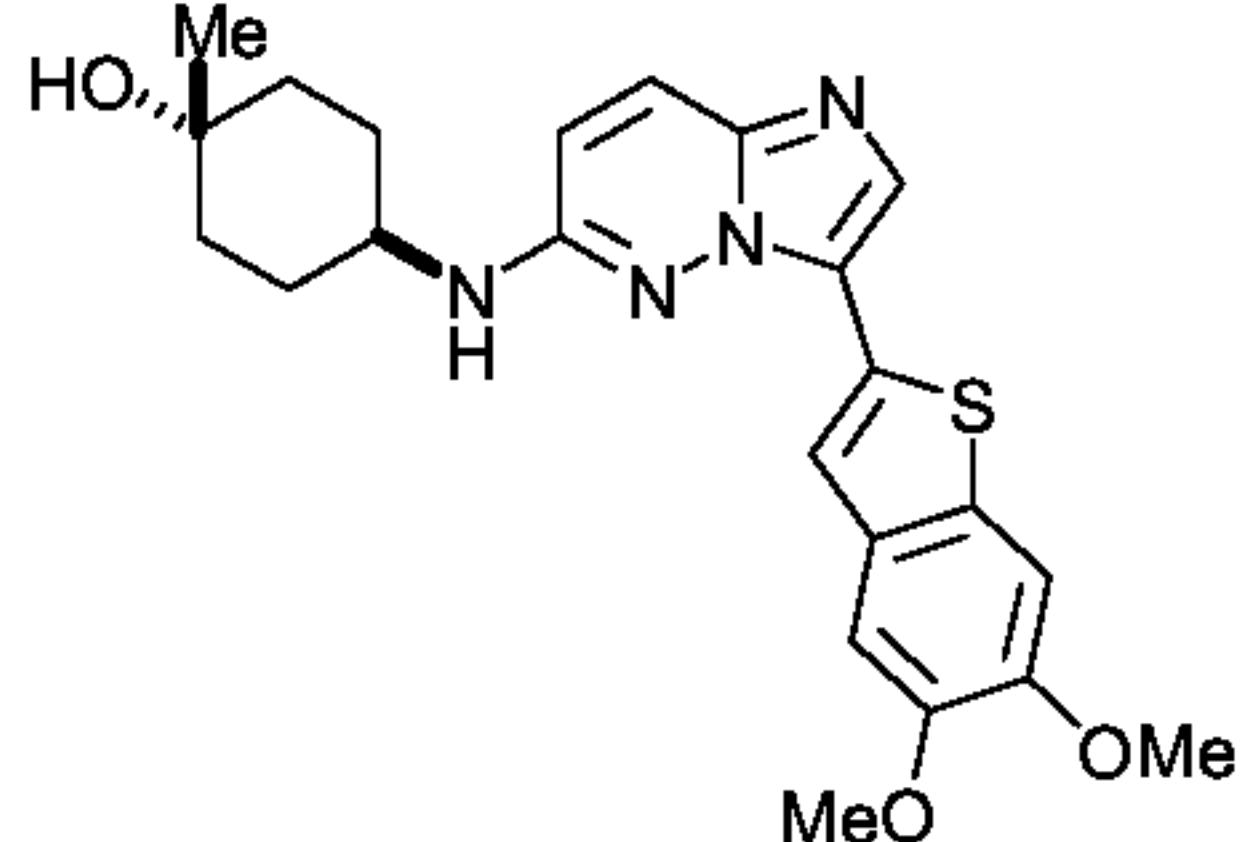
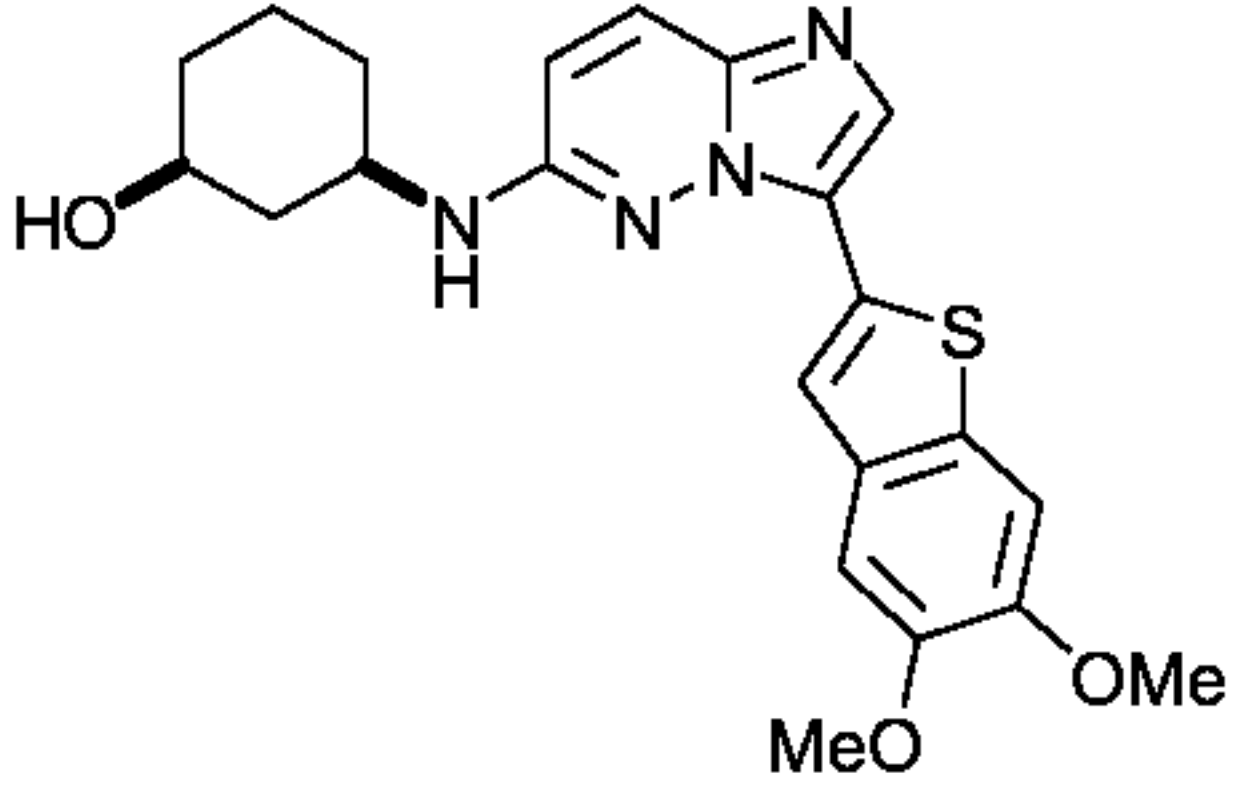
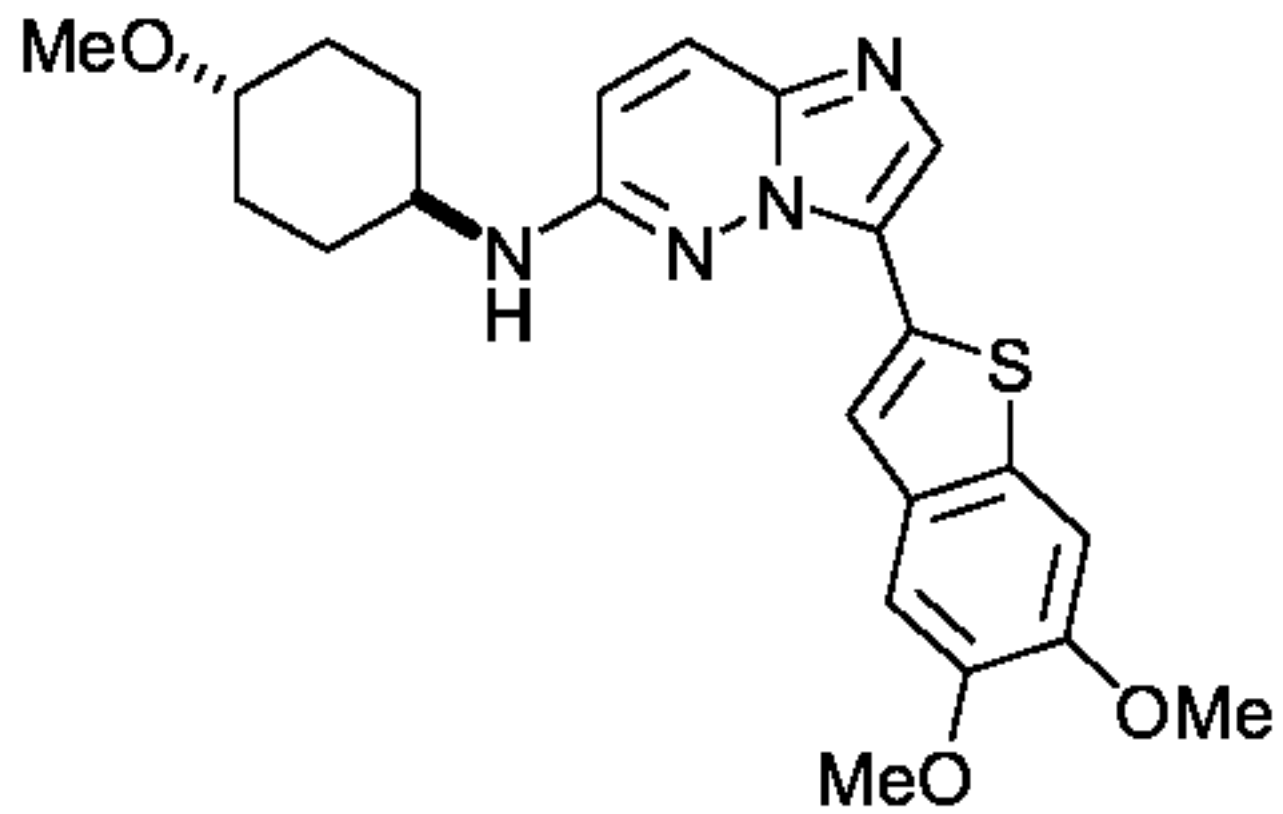
Table 29-a

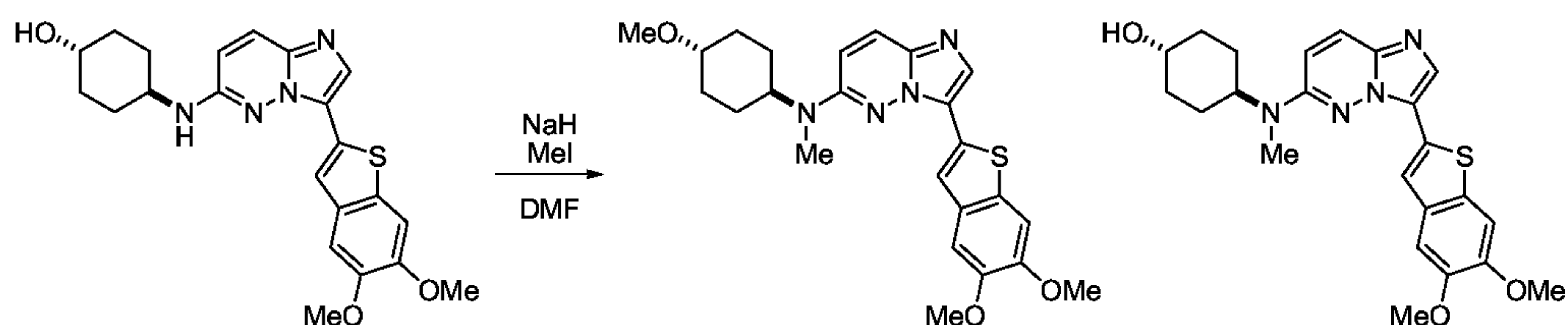
Cd.	Amine	Pure Isolated Compound
169	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
171	4-amino-2-methylbutan-1-ol	4-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methylbutan-1-ol
173	<i>trans</i> -4-amino-1-methylcyclohexanol	(1 <i>r</i> ,4 <i>r</i>)-4-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-1-methylcyclohexanol
174	3-aminocyclohexanol	3-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol
201	<i>trans</i> -4-methoxycyclohexanamine	<i>trans</i> -3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(4-methoxycyclohexyl)imidazo[1,2-b]pyridazin-6-amine

[00407] Compounds 169, 171, 173-174, 201 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 29-b**.

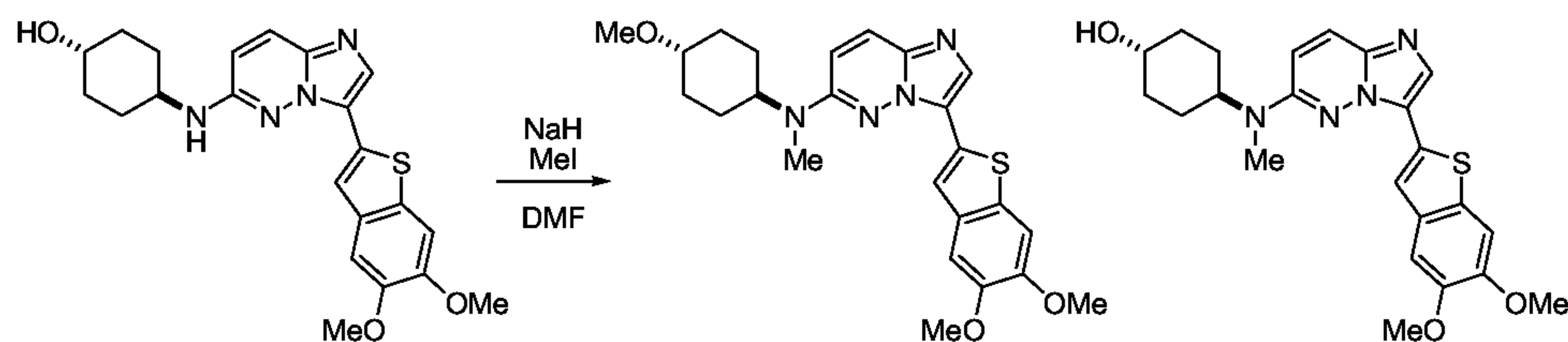
Table 29-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
169		<i>trans</i> -4-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	425.5

171		4-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-2-methylbutan-1-ol	413.3
173		(1r,4r)-4-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)-1-methylcyclohexanol	439.2
174		3-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	425.1
201		<i>trans</i> -3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(4-methoxycyclohexyl)imidazo[1,2-b]pyridazin-6-amine	439.4

[00408] Example 30 – Synthesis of Compounds 175 and 177**[00409]** **Scheme 30**

[00410] Preparation of 3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(*trans*-4-methoxycyclohexyl)-N-methylimidazo[1,2-b]pyridazin-6-amine and *trans*-4-(N-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)-N-methylamino)cyclohexanol



[00411] To a solution of *trans*-4-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol (100 mg, 0.236 mmol, 1.0 equiv) in DMF (2.00 mL) was added sodium hydride (28 mg, 0.707 mmol, 3.0 equiv) and methyl iodide (167 mg, 1.18 mmol,

5.0 equiv). After 2 h, the reaction mixture was quenched with water and extracted with ethyl acetate. Purification by column chromatography gave 30 mg (28%) of 3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(*trans*-4-methoxycyclohexyl)-N-methylimidazo[1,2-b]pyridazin-6-amine as the less polar product and 21 mg (20%) of *trans*-4-(N-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)-N-methylamino)cyclohexanol as the more polar product.

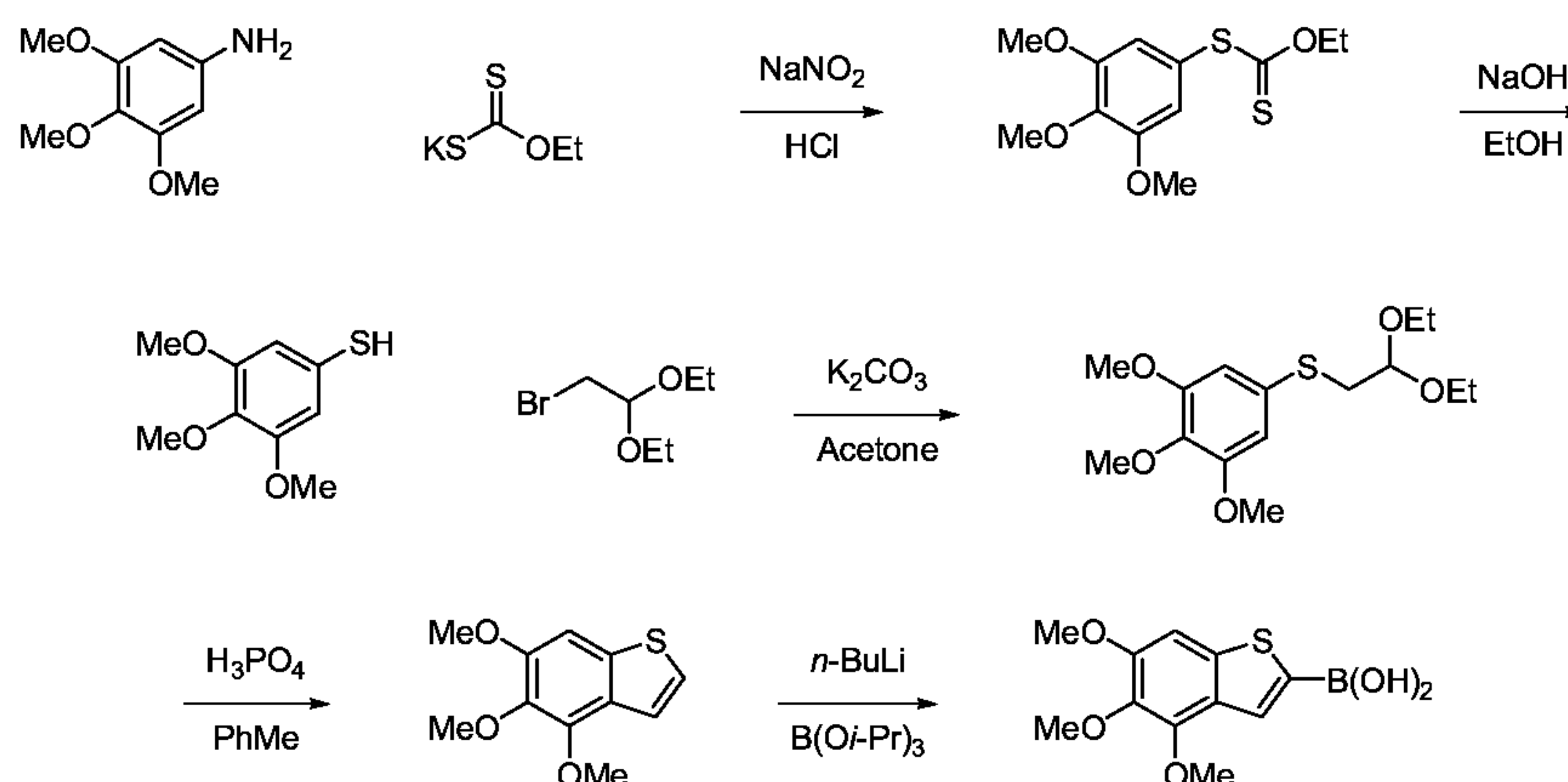
[00412] Compounds 175 and 177 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 30-b**.

Table 30-b

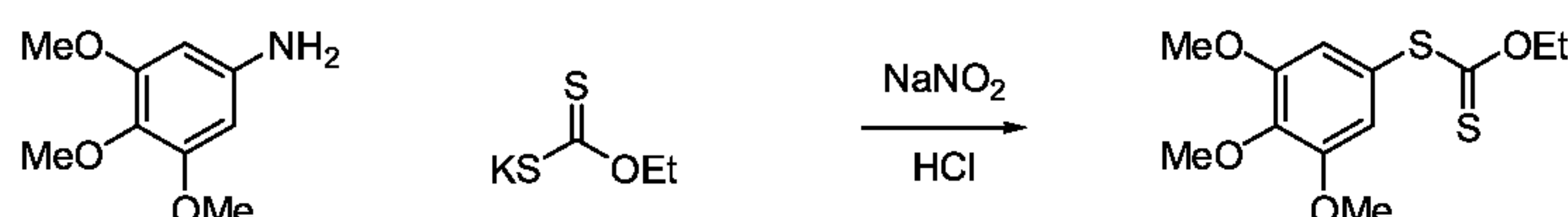
Cd.	Structure	IUPAC Name	[M+H] ⁺
175		3-(5,6-dimethoxybenzo[b]thiophen-2-yl)-N-(<i>trans</i> -4-methoxycyclohexyl)-N-methylimidazo[1,2-b]pyridazin-6-amine	453.3
177		<i>trans</i> -4-(N-(3-(5,6-dimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-yl)-N-methylamino)cyclohexanol	439.4

[00413] Example 31 – Synthesis of Compound 76

[00414] **Scheme 31**

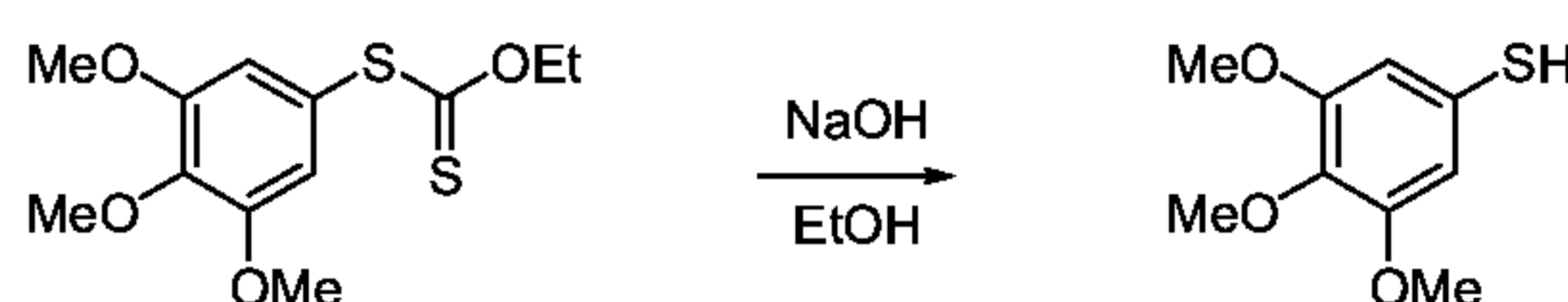


[00415] **Preparation of O-ethyl S-3,4,5-trimethoxyphenyl carbonodithioate**



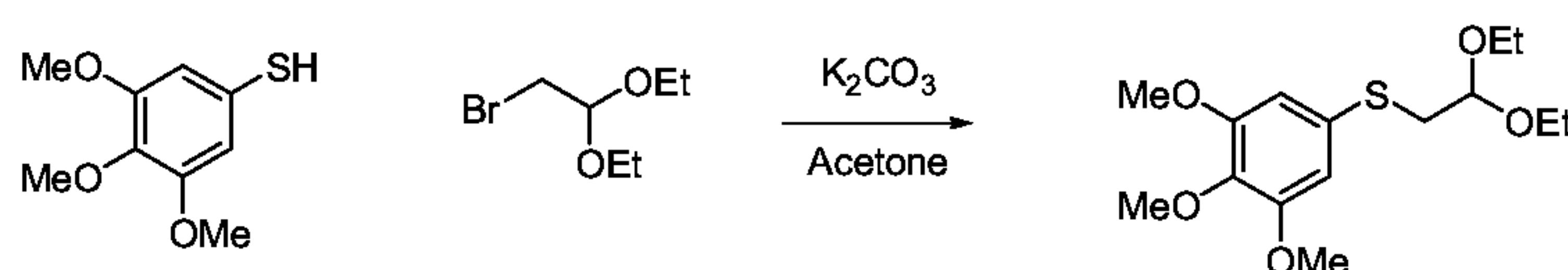
[00416] Aniline (2.00 g, 10.9 mmol, 1.0 equiv) at 0 °C was added hydrochloric acid (3 mL) and water (10 mL) followed by sodium nitrite (932 mg, 13.5 mmol, 1.25 equiv). The resulting solution was poured over potassium ethyl xanthogenate (5.35 g, 33.4 mmol, 3.0 equiv) in water (10 mL) and stirred at 50 °C for 40 minutes. Purification by column chromatography using 5% ethyl acetate in hexanes elution gave the yellow solid.

[00417] Preparation of 3,4,5-trimethoxybenzenethiol



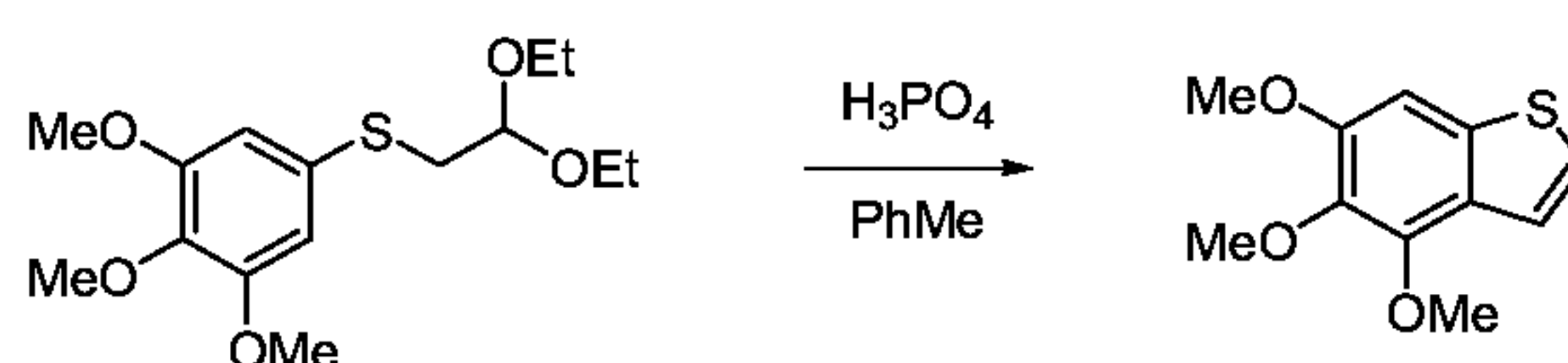
[00418] To a solution of O-ethyl S-3,4,5-trimethoxyphenyl carbonodithioate (3.45 g, 10.9 mmol, 1.0 equiv) in methanol (30 mL) was added sodium hydroxide (1.44 g, 32.8 mmol, 3.0 equiv) and heated to 60 °C for 3 h. Purification by column chromatography using 5% ethyl acetate in hexanes elution gave 1.75 g, 8.73 mmol of the yellow solid, 80% over 2 steps.

[00419] Preparation of (2,2-diethoxyethyl)(3,4,5-trimethoxyphenyl)sulfane



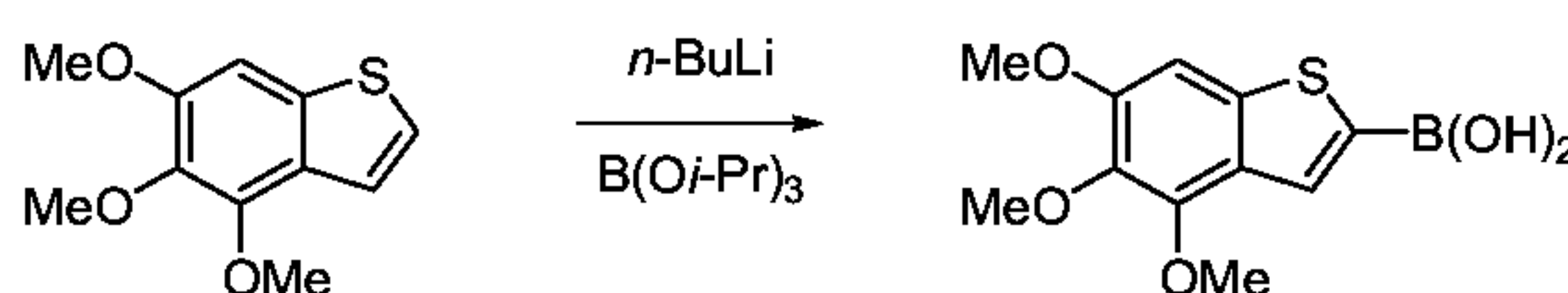
[00420] To a solution of thiophenol (1.3 g, 6.49 mmol, 1.0 equiv) in acetone (20 mL) was added potassium carbonate (1.79 g, 13.0 mmol, 2.0 equiv) and bromoacetaldehyde diethylacetal (2.56 g, 13.0 mmol, 2.0 equiv). After 15 h, the reaction mixture was filtered and concentrated. Purification by column chromatography using 5% ethyl acetate in hexanes elution gave the product.

[00421] Preparation of 4,5,6-trimethoxybenzo[b]thiophene



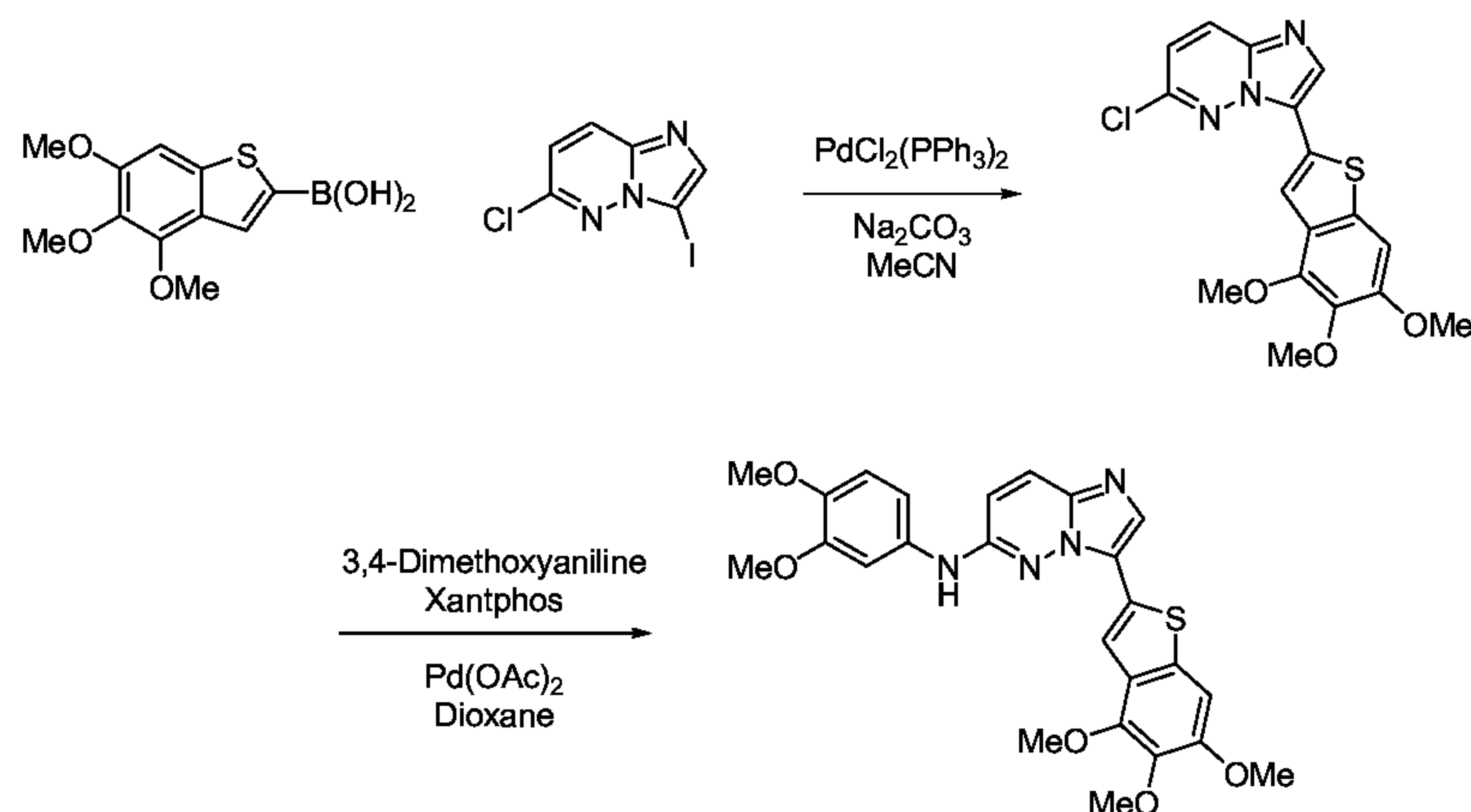
[00422] To a solution of thioether (1.00 g, 3.16 mmol, 1.0 equiv) in toluene (20 mL) was added phosphoric acid (10 mL) and heated to 110 °C. After 2 h, the reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate then concentrated. Purification by column chromatography using 5% ethyl acetate in hexanes elution gave 230 mg of the white product, 32% yield.

[00423] Preparation of 4,5,6-trimethoxybenzo[b]thiophen-2-yl-2-boronic acid

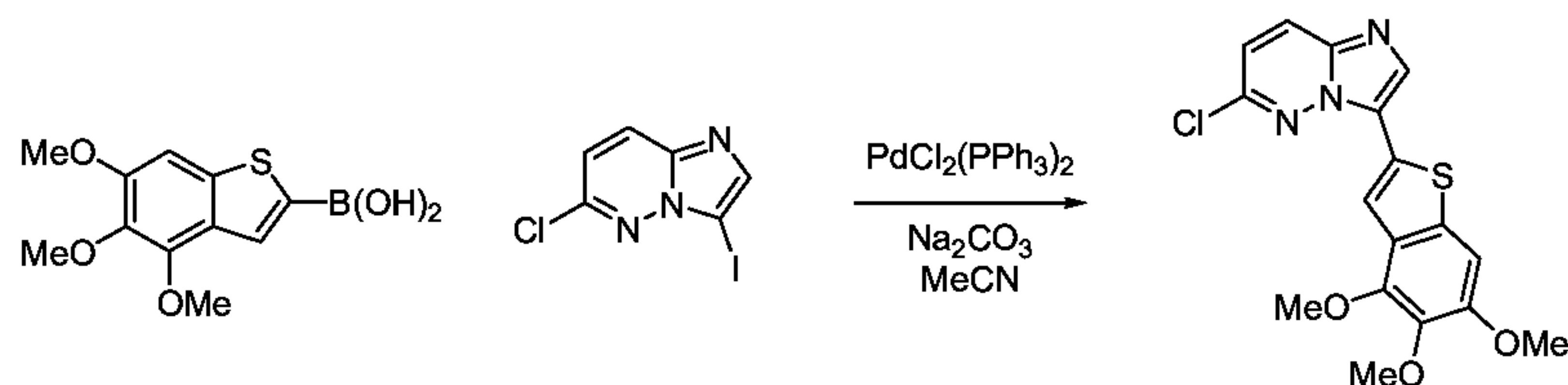


[00424] To a solution of 4,5,6-trimethoxybenzo[b]thiophene (200 mg, 0.892 mmol, 1.0 equiv) in THF (10.0 mL) at -78 °C was added *n*-BuLi (0.84 mL, 1.34 mmol, 1.5 equiv). The reaction was stirred at the reduced temperature for 1 h, then triisopropylborate (0.31 mL, 1.34 mmol, 1.5 equiv) was added and stirred at rt for 2 h. The mixture was quenched with 2N HCl and then extracted with ethyl acetate. Purification by column chromatography using 2% methanol in dichloromethane elution gave 191 mg of white solid, 80%.

[00425] Scheme 32

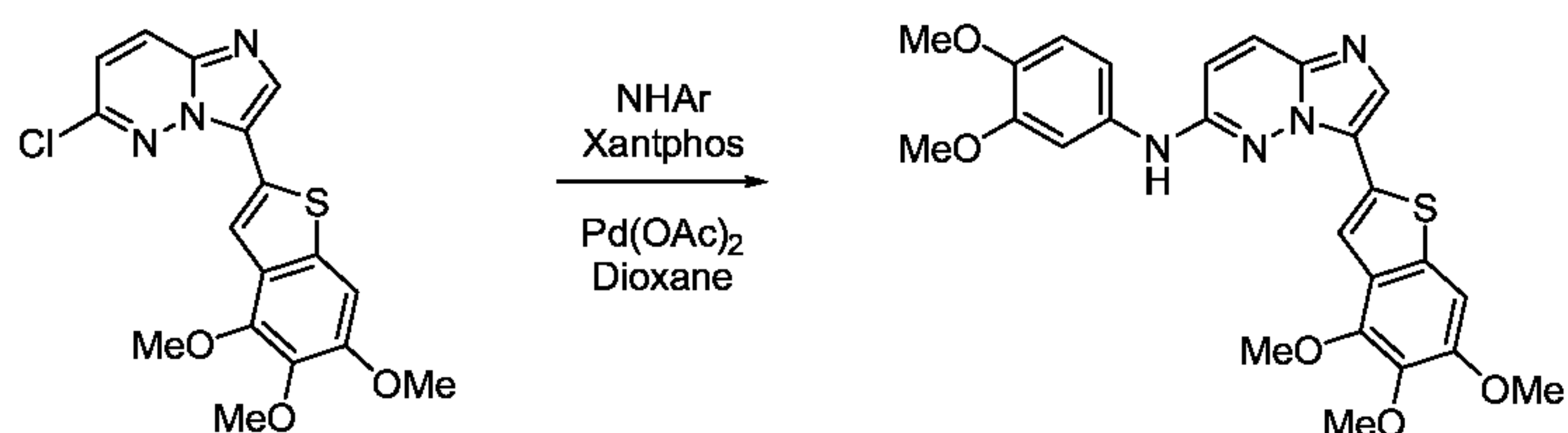


[00426] Preparation of 6-chloro-3-(4,5,6-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine



[00427] To a solution of 4,5,6-trimethoxybenzo[b]thiophen-2-yl-2-boronic acid (200 mg, 0.746 mmol, 1.3 equiv) in acetonitrile (10.0 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (160 mg, 0.574 mmol, 1.0 equiv), palladium catalyst (20 mg, 0.0287 mmol, 0.05 equiv) and sodium carbonate (5.74 mL, 1.0 M, 10.0 equiv). The solution was stirred at rt overnight. Purification using column chromatography gave 151 mg of the yellow product, 70%.

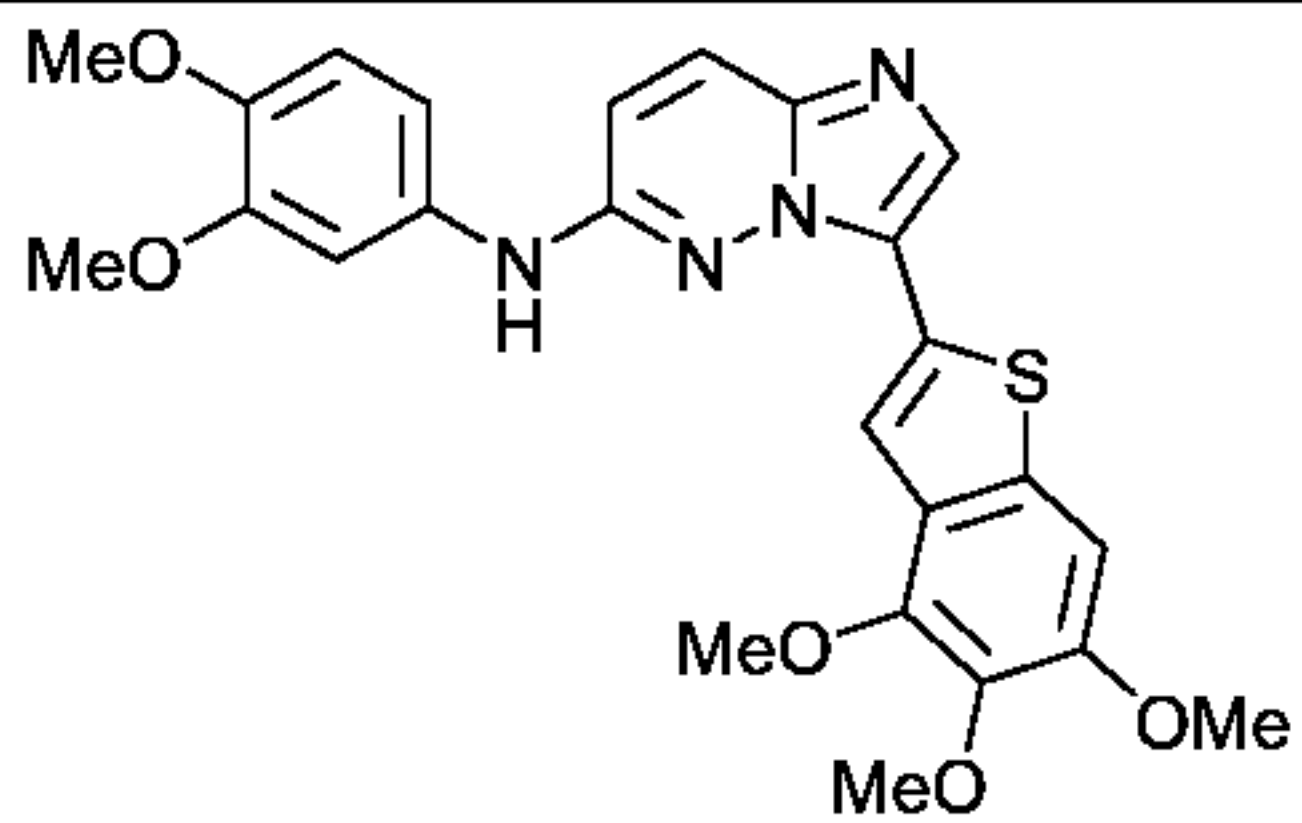
[00428] Preparation of 3-(4,5,6-trimethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine



[00429] To a solution of 6-chloro-3-(4,5,6-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.133 mmol, 1.0 equiv), xantphos (15 mg, 0.0266 mmol, 0.2 equiv), palladium acetate (2 mg, 0.0133 mmol, 0.1 equiv), and potassium carbonate (367 mg, 2.66 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (20 mg, 0.133 mmol, 1.0 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

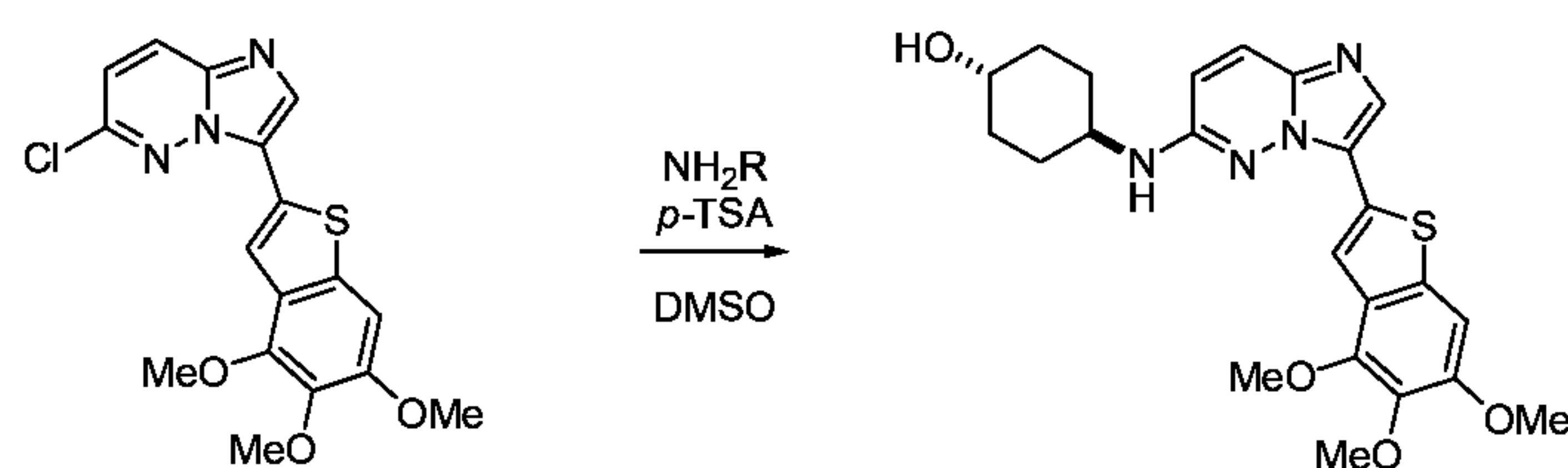
[00430] Compound 76 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 32-b.

[00431] Table 32-b

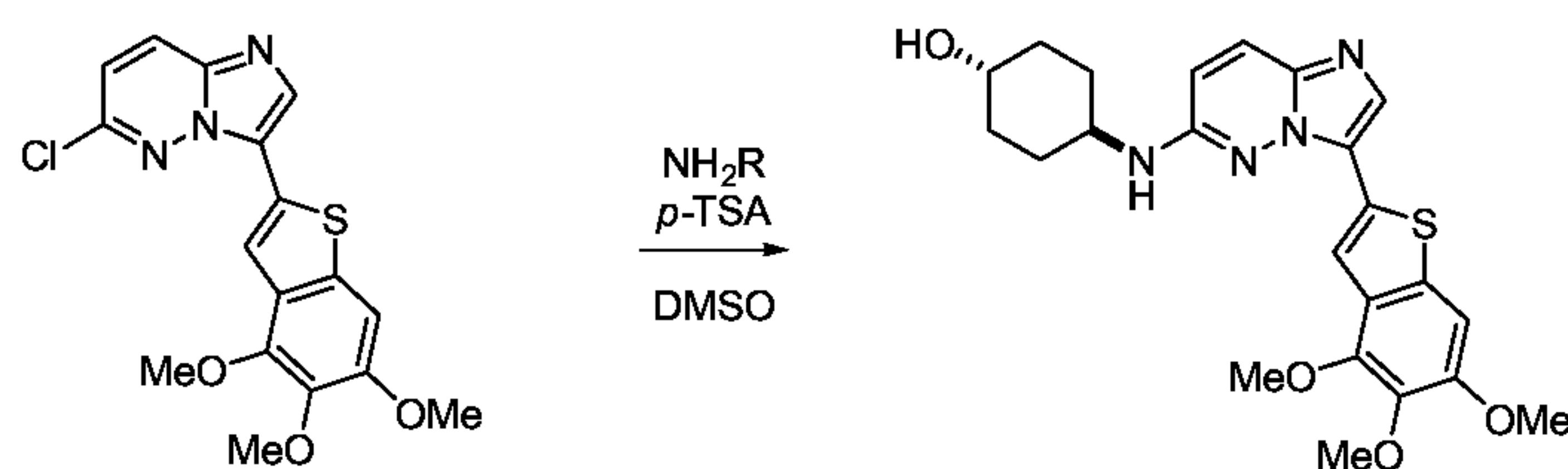
Cd.	Structure	IUPAC Name	[M+H] ⁺
76		3-(4,5,6-trimethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	493.3

[00432] Example 33 – Synthesis of Compound 176

[00433] Scheme 33

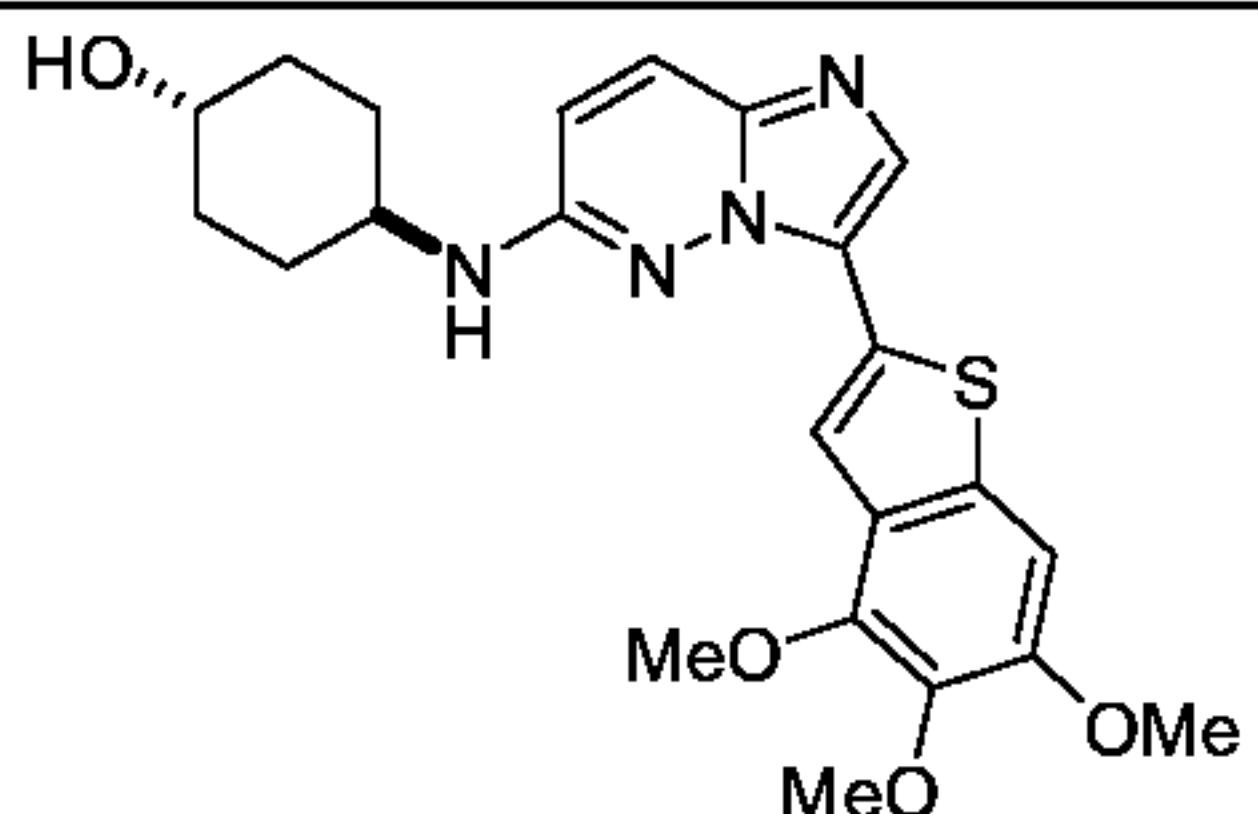


[00434] Preparation of *trans*-4-(3-(4,5,6-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol



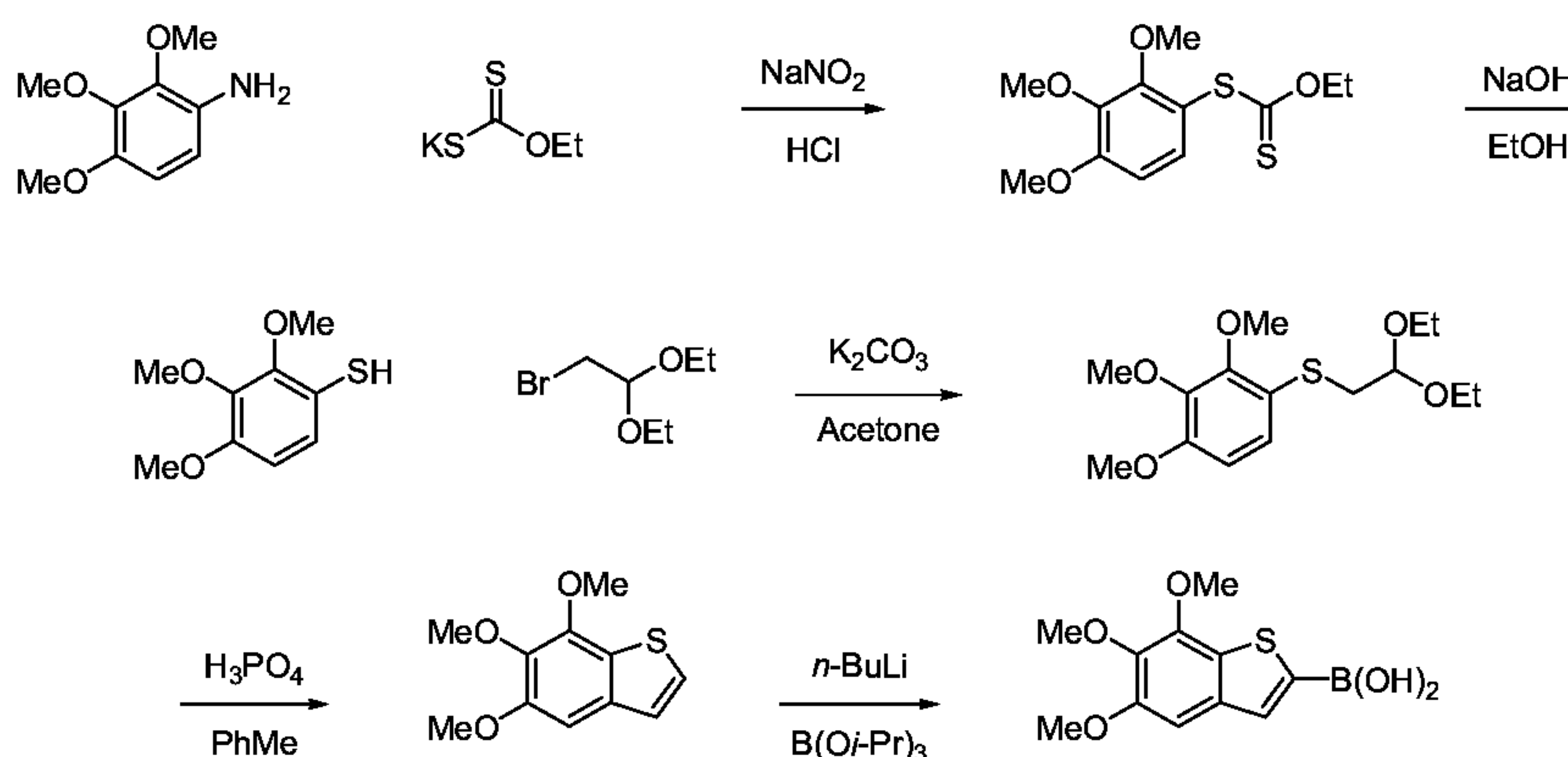
[00435] To a solution of 6-chloro-3-(4,5,6-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.133 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (25 mg, 0.144 mmol, 1.0 equiv) and amine (0.532 mmol, 4.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution 40 mg of the brown solid, 67%.

[00436] Compound 176 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 33-b.

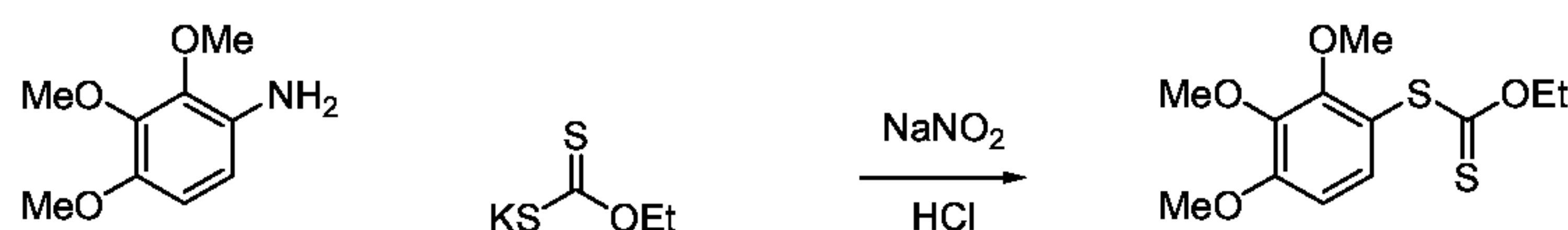
Cd.	Structure	IUPAC Name	[M+H] ⁺
176		<i>trans</i> -4-(3-(4,5,6-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	455.4

[00437] Example 34 – Synthesis of Compound 83

[00438] **Scheme 34a**

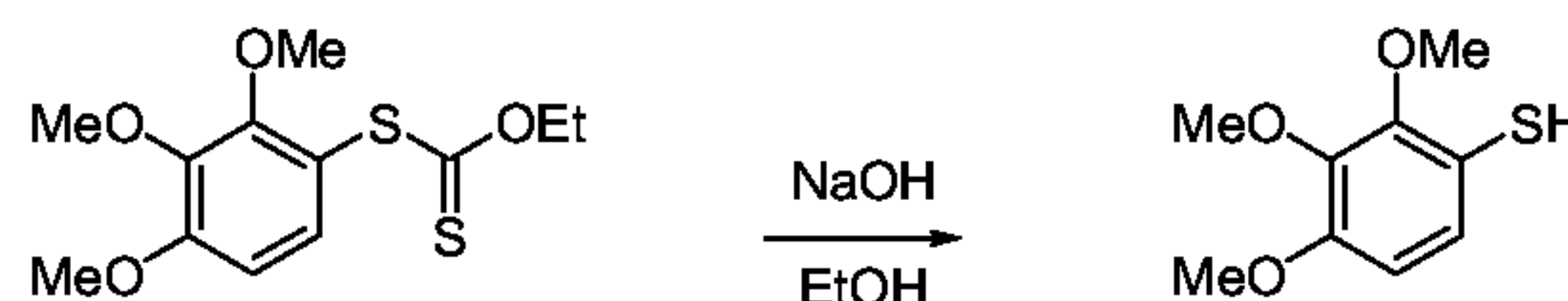


[00439] **Preparation of O-ethyl S-2,3,4-trimethoxyphenyl carbonodithioate**



[00440] Aniline (482 g, 2.63 mmol, 1.0 equiv) at 0 °C was added hydrochloric acid (0.71 mL) and water (1.86 mL) followed by sodium nitrite (227 mg, 3.29 mmol, 1.25 equiv). The resulting solution was poured over potassium ethyl xanthogenate (1.31 g, 8.06 mmol, 3.0 equiv) in water (1.50 mL) and stirred at 50 °C for 40 minutes. Purification by column chromatography using 5% ethyl acetate in hexanes elution gave the yellow solid.

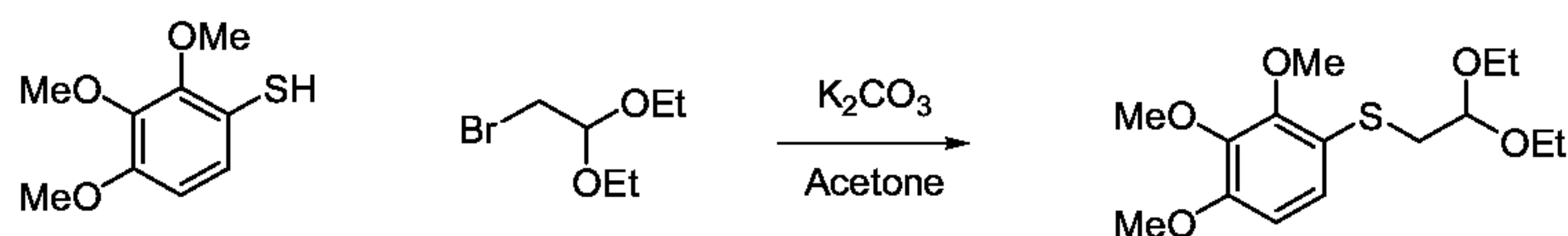
[00441] **Preparation of 2,3,4-trimethoxybenzenethiol**



[00442] To a solution of O-ethyl S-2,3,4-trimethoxyphenyl carbonodithioate (759 mg, 2.63 mmol, 1.0 equiv) in methanol (10 mL) was added sodium hydroxide (347 mg, 7.89 mmol, 3.0

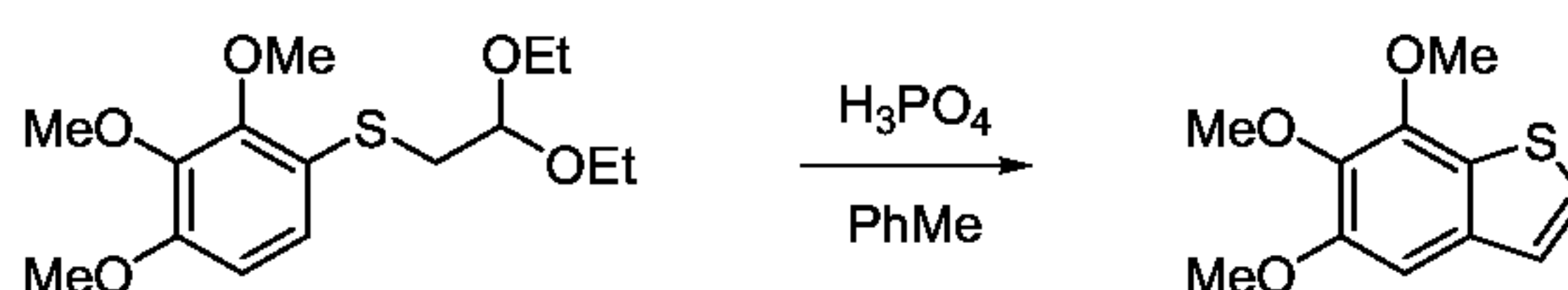
equiv) and heated to 60 °C for 3 h. Purification by column chromatography using 5% ethyl acetate in hexanes elution gave 395 mg of the yellow solid, 75% over 2 steps.

[00443] Preparation of (2,2-diethoxyethyl)(2,3,4-trimethoxyphenyl)sulfane



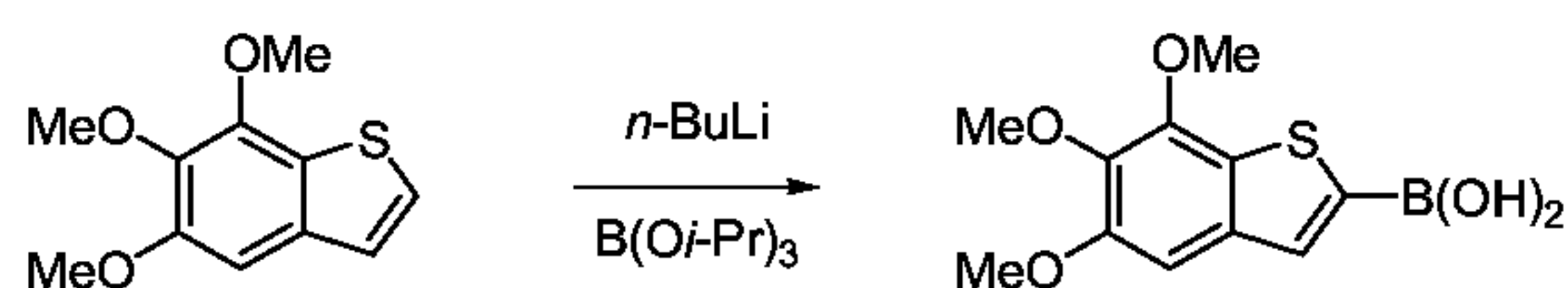
[00444] To a solution of thiophenol (1.02 g, 5.09 mmol, 1.0 equiv) in acetone (20 mL) was added potassium carbonate (1.41 g, 10.2 mmol, 2.0 equiv) and bromoacetaldehyde diethylacetal (1.57 g, 10.2 mmol, 2.0 equiv). After 15 h, the reaction mixture was filtered and concentrated. Purification by column chromatography using 5% ethyl acetate in hexanes elution gave the product.

[00445] Preparation of 5,6,7-trimethoxybenzo[b]thiophene



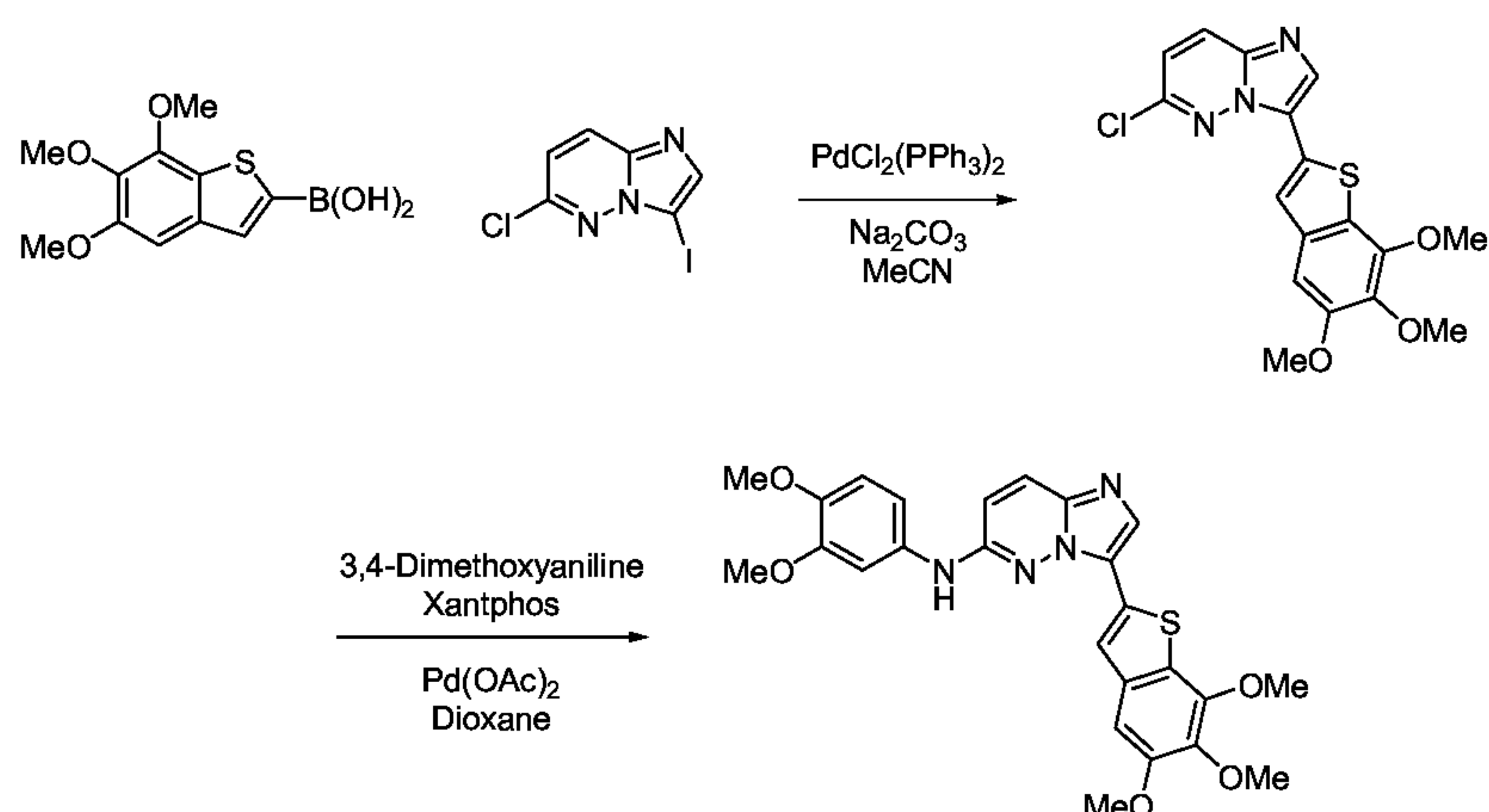
[00446] To a solution of thioether (1.03 g, 3.25 mmol, 1.0 equiv) in toluene (20 mL) was added phosphoric acid (10 mL) and heated to 110 °C. After 2 h, the reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate then concentrated. Purification by column chromatography using 5% ethyl acetate in hexanes elution gave 300 mg of the white solid, 41%.

[00447] Preparation of 5,6,7-trimethoxybenzo[b]thiophen-2-yl-2-boronic acid

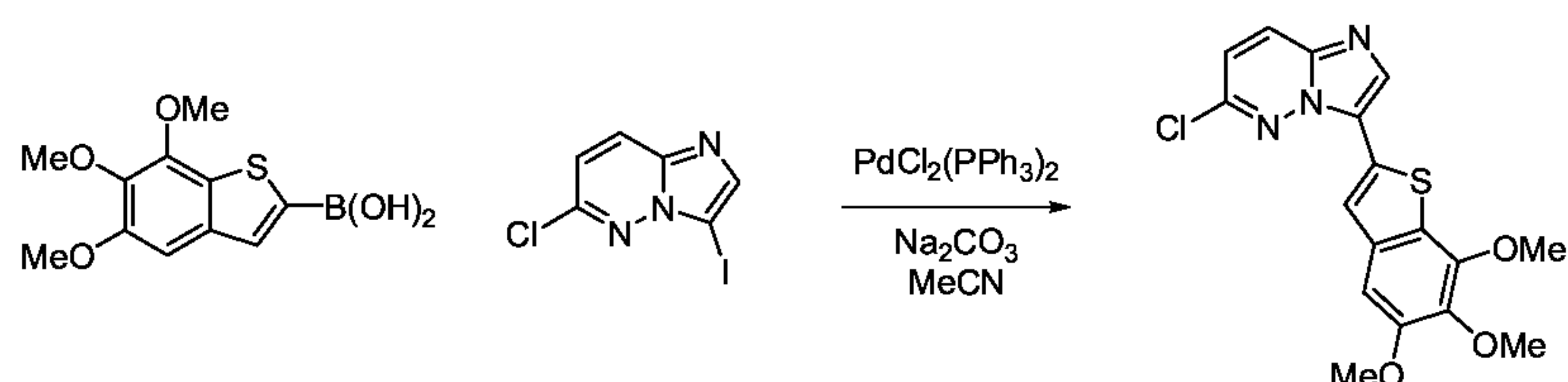


[00448] To a solution of 5,6,7-trimethoxybenzo[b]thiophene (365 mg, 1.62 mmol, 1.0 equiv) in THF (10.0 mL) at -78 °C was added *n*-BuLi (1.53 mL, 2.44 mmol, 1.5 equiv). The reaction was stirred at the reduced temperature for 1 h, then triisopropylborate (0.56 mL, 2.44 mmol, 1.5 equiv) was added and stirred at rt for 2 h. The mixture was quenched with 2N HCl and then extracted with ethyl acetate. Purification by column chromatography using 2% methanol in dichloromethane elution gave 370 mg of white solid, 85%.

[00449] Scheme 34b

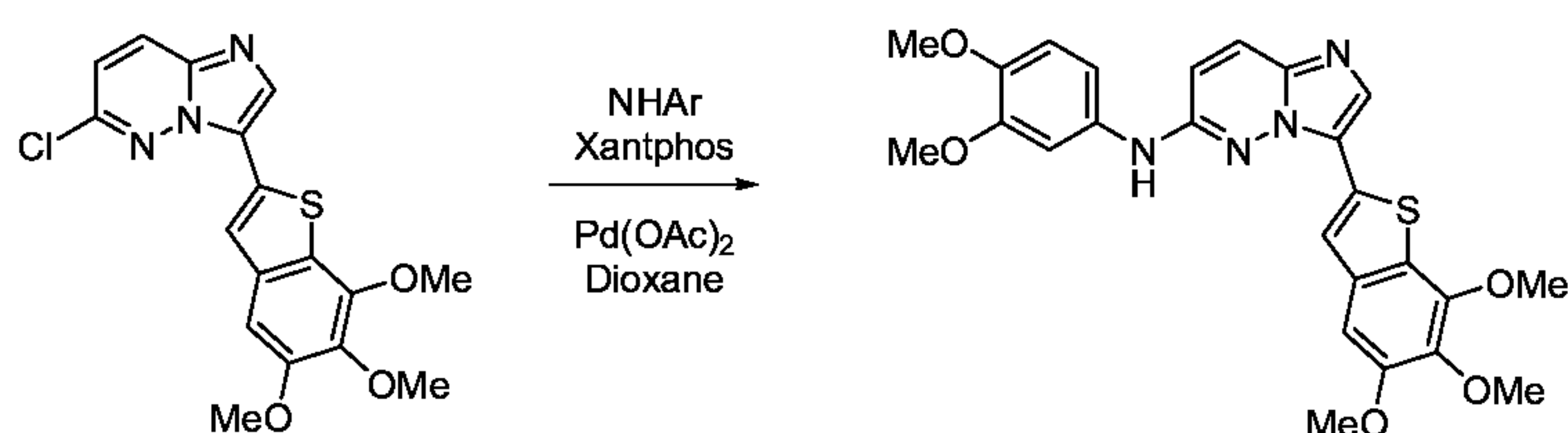


[00450] Preparation of 6-chloro-3-(5,6,7-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine



[00451] To a solution of 5,6,7-trimethoxybenzo[b]thiophen-2-yl-2-boronic acid (410 mg, 1.53 mmol, 1.3 equiv) in acetonitrile (10 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (427 mg, 1.53 mmol, 1.0 equiv), palladium catalyst (56 mg, 0.077 mmol, 0.05 equiv) and sodium carbonate (15.3 mL, 1.0 M, 10.0 equiv). The solution was stirred in the microwave at 150 °C for 10 min. Purification using column chromatography gave 368 mg of the yellow product, 64%.

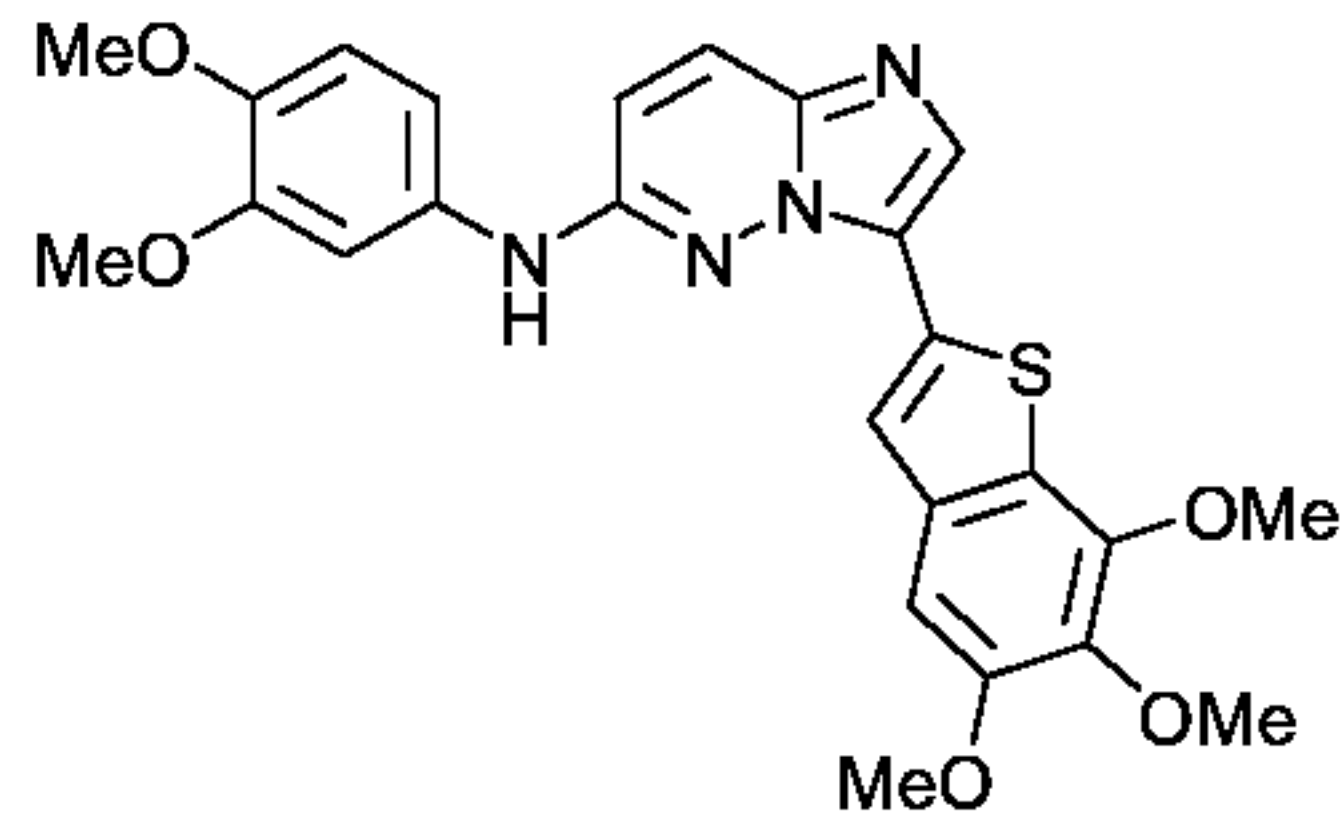
[00452] Preparation of 3-(5,6,7-trimethoxybenzo[b]thiophen-2-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine



[00453] To a solution of 6-chloro-3-(5,6,7-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.133 mmol, 1.0 equiv), xantphos (15 mg, 0.0266 mmol, 0.2 equiv), palladium acetate (2 mg, 0.0133 mmol, 0.1 equiv), and potassium carbonate (367 mg, 2.66 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (20 mg, 0.133 mmol, 1.0 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the product.

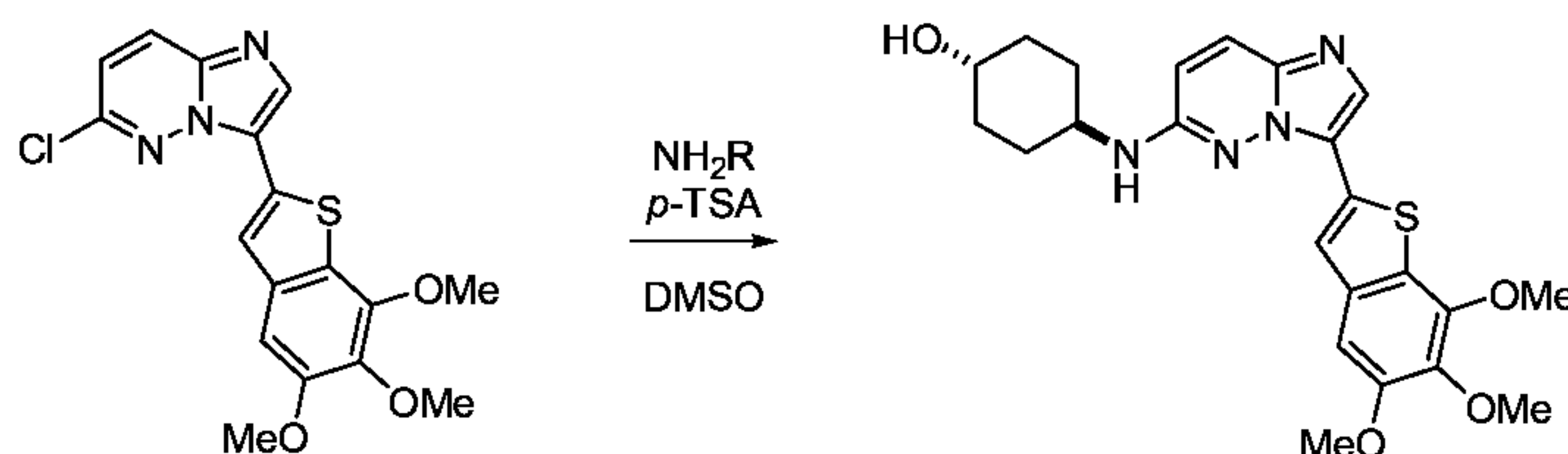
[00454] Compound 83 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 34-b.

[00455] Table 34

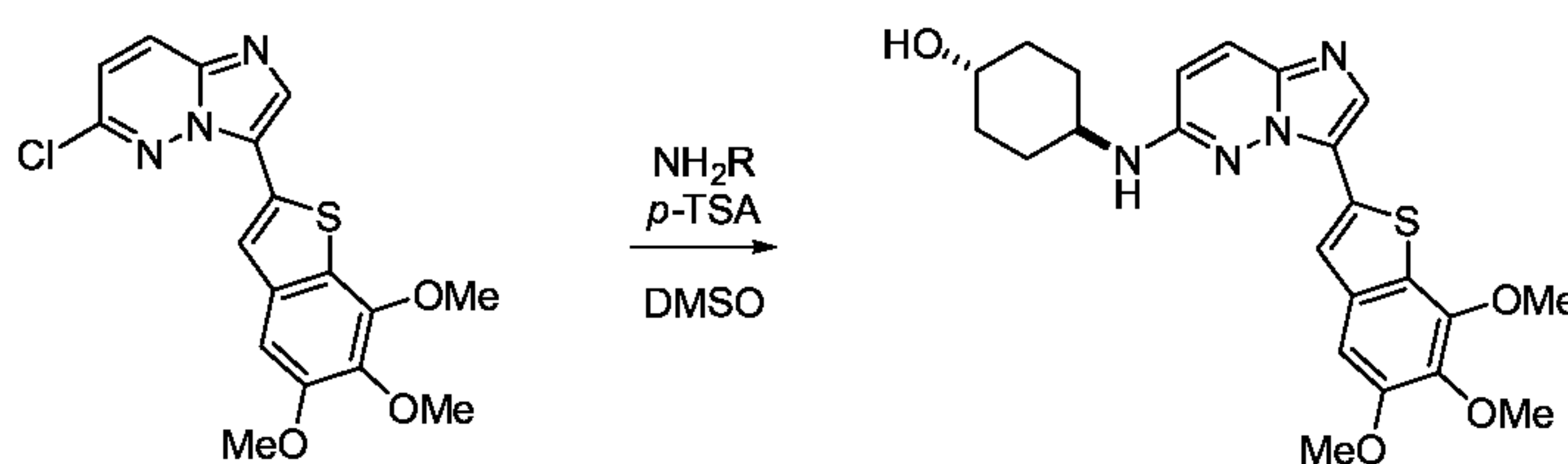
Cd.	Structure	IUPAC Name	[M+H] ⁺
83		3-(5,6,7-trimethoxybenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	492.9

[00456] Example 35 – Synthesis of Compound 179

[00457] Scheme 35



[00458] Preparation of *trans*-4-(3-(5,6,7-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

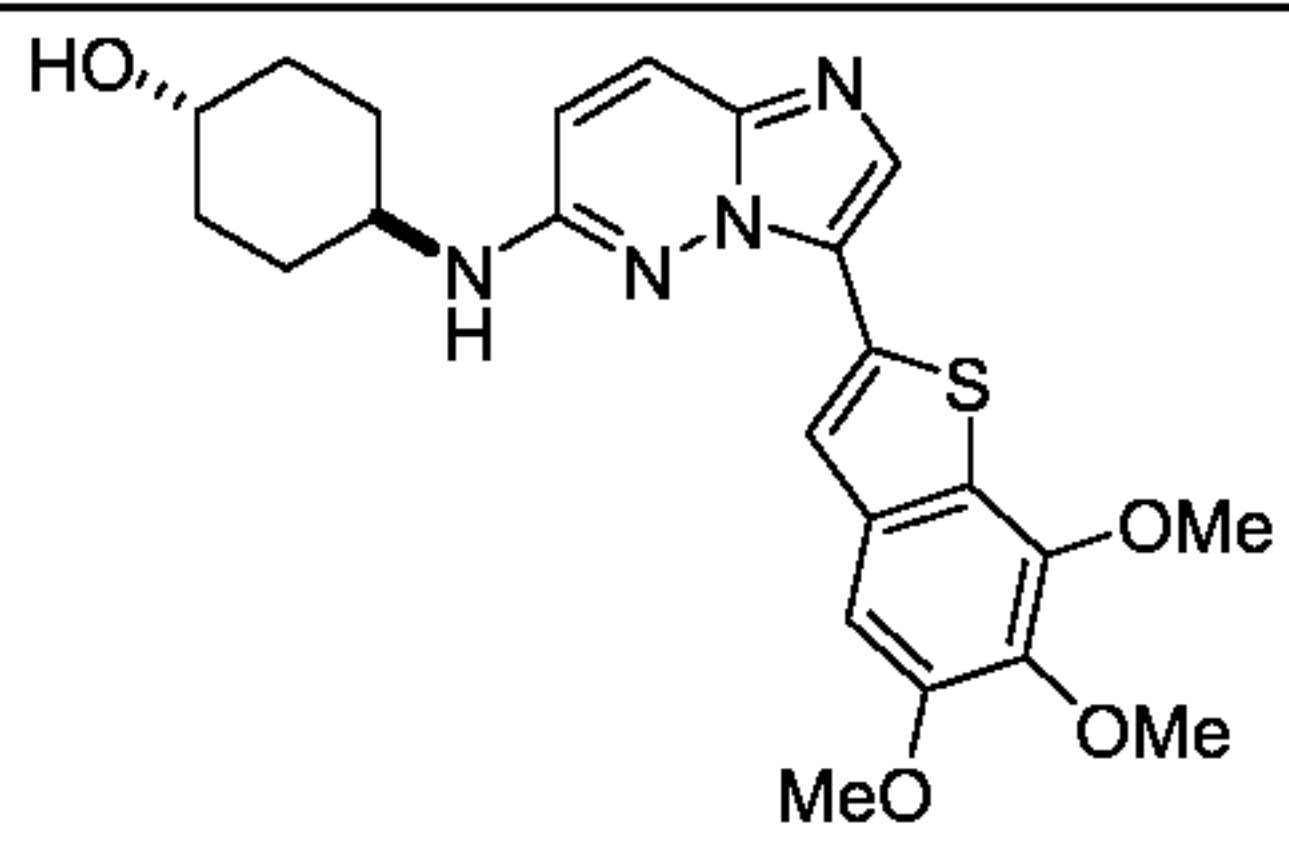


[00459] To a solution of 6-chloro-3-(5,6,7-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.133 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (25 mg, 0.144 mmol, 1.0 equiv) and amine (0.532 mmol, 4.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution 36 mg of the brown solid, 60%.

[00460] Compound 179 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 35-b.

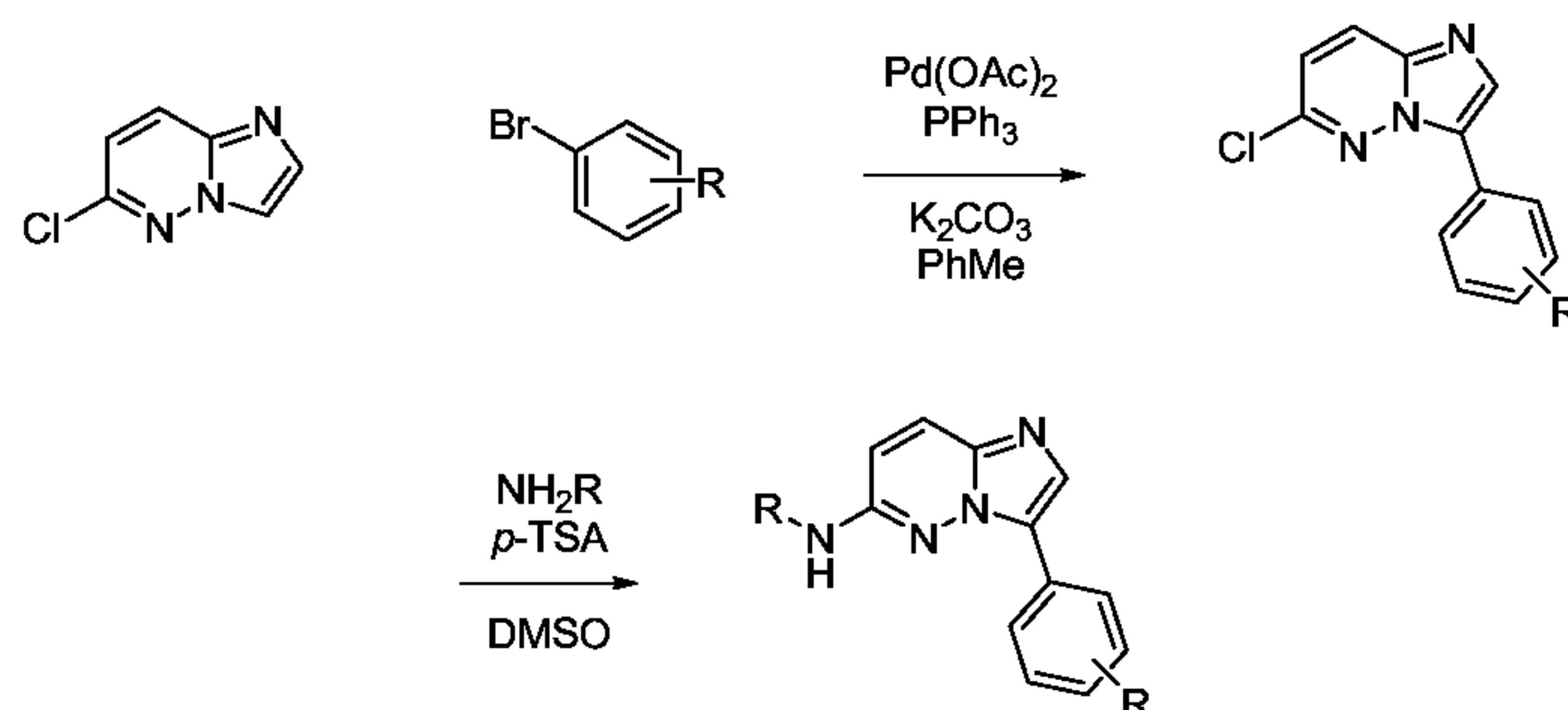
[00461] Table 35-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
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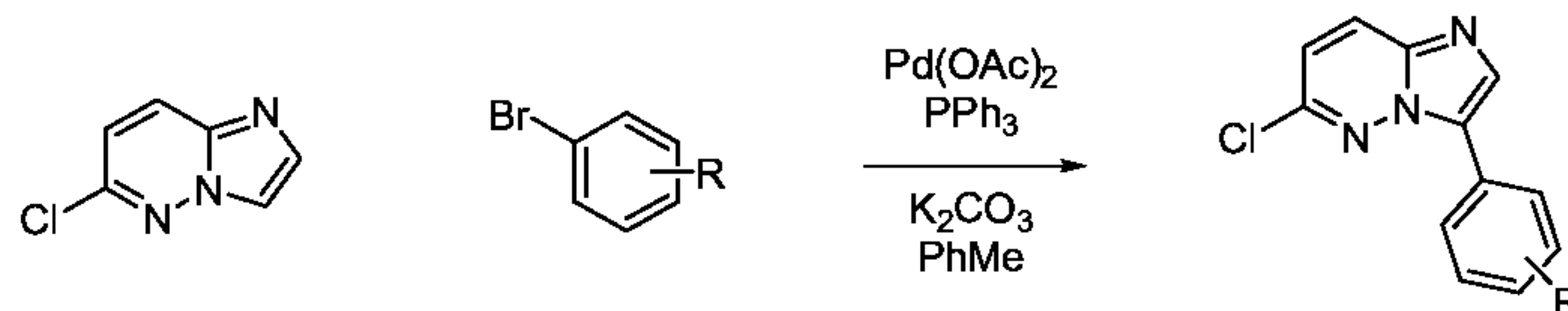
179		<i>trans</i> -4-(3-(5,6,7-trimethoxybenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	455.0
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[00462] Example 36 – Synthesis of Compounds 94-96, 99, 104

[00463] **Scheme 36**

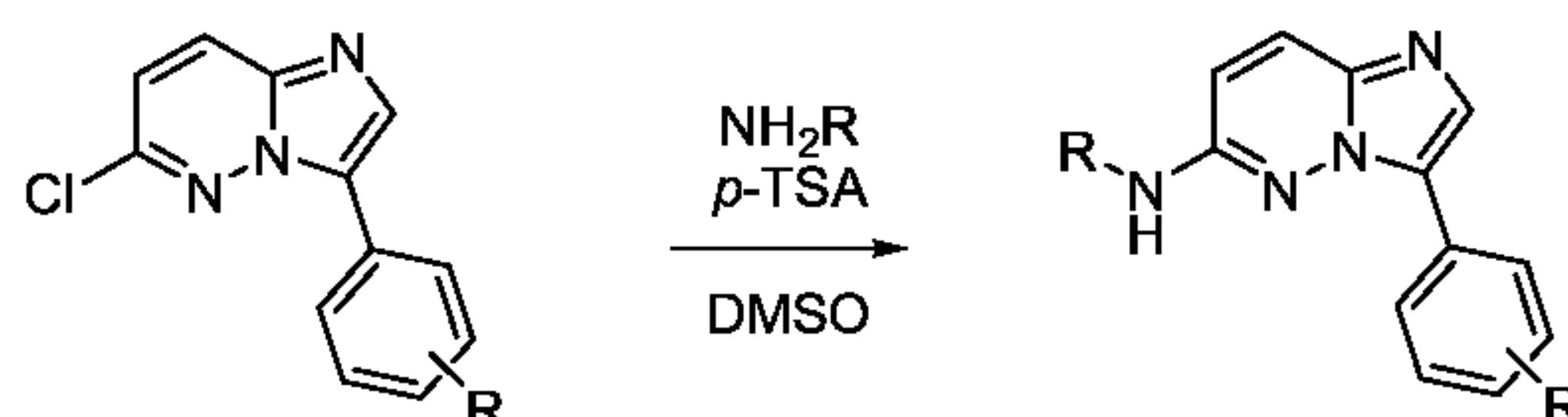


[00464] **Preparation of 6-chloro-3-arylimidazo[1,2-b]pyridazine**



[00465] To a stirred solution of 6-chloroimidazo[1,2-b]pyridazine (1.55 g, 10.1 mmol) in 10.0 mL of toluene was added aryl bromide (15.1 mmol, 1.5 equiv), potassium carbonate (2.79 g, 18.2 mmol, 2.0 equiv), triphenylphosphine (529 mg, 2.02 mmol, 0.2 equiv) and palladium acetate (227 mg, 1.01 mmol, 0.1 equiv). The solution was stirred to reflux for 24 h. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave the product.

[00466] **Preparation of N-alkyl-3-arylimidazo[1,2-b]pyridazin-6-amine**



[00467] To a solution of 6-chloro-3-arylimidazo[1,2-b]pyridazine (0.500 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (95 mg, 0.500 mmol, 1.0 equiv) and amine (1.95 mmol, 4.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave the product.

Table 3a

Cd.	Aryl bromide	Amine	Pure Isolated Compound
94	Bromobenzene	Methyl amine	N-methyl-3-phenylimidazo[1,2-b]pyridazin-6-amine
95	1-bromo-4-	Methyl amine	3-(4-methoxyphenyl)-N-

	methoxybenzene		methylimidazo[1,2-b]pyridazin-6-amine
96	1-bromo-2-methoxybenzene	Methyl amine	3-(2-methoxyphenyl)-N-methylimidazo[1,2-b]pyridazin-6-amine
99	1-bromo-3-methoxybenzene	Methyl amine	3-(3-methoxyphenyl)-N-methylimidazo[1,2-b]pyridazin-6-amine
104	5-bromo-1,2,3-trimethoxybenzene	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(3,4,5-trimethoxyphenyl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

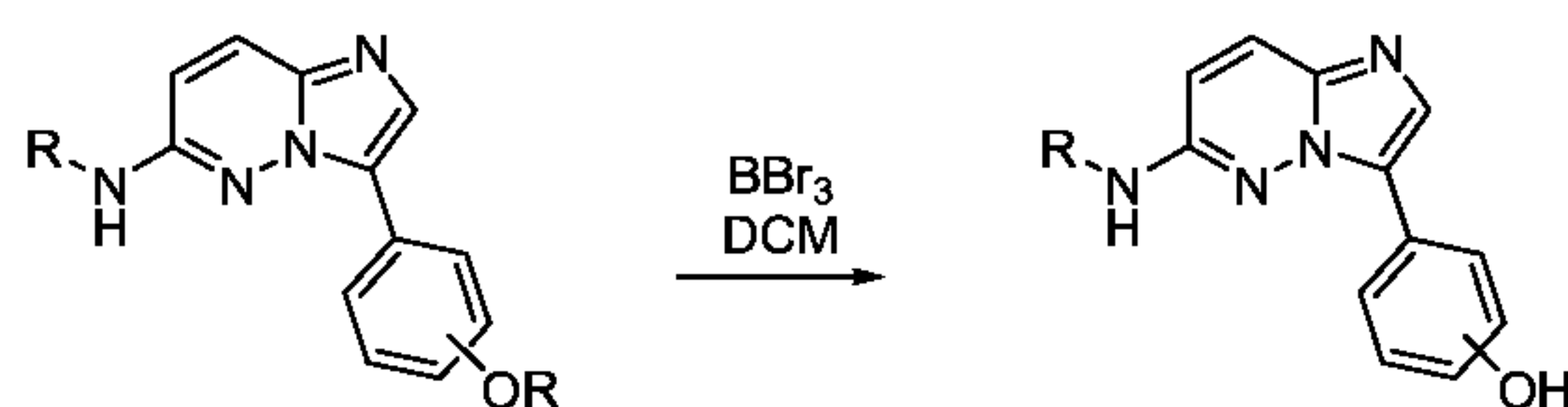
[00468] Compounds 94-96, 99, 104 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 36-b**.

Table 36-b

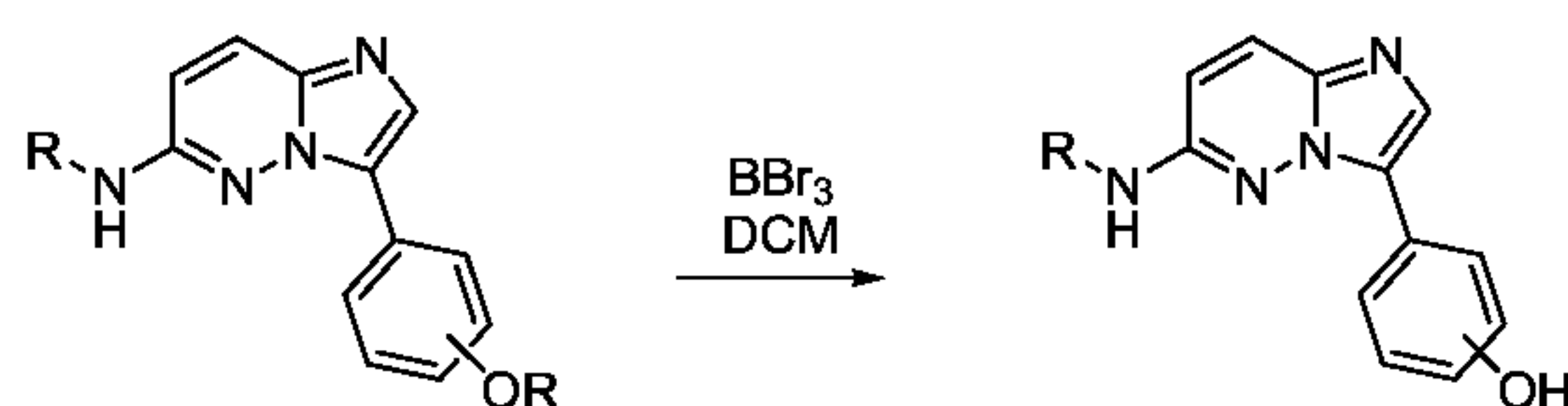
Cd.	Structure	IUPAC Name	[M+H] ⁺
94		N-methyl-3-phenylimidazo[1,2-b]pyridazin-6-amine	225.5
95		3-(4-methoxyphenyl)-N-methylimidazo[1,2-b]pyridazin-6-amine	255.6
96		3-(2-methoxyphenyl)-N-methylimidazo[1,2-b]pyridazin-6-amine	255.5
99		3-(3-methoxyphenyl)-N-methylimidazo[1,2-b]pyridazin-6-amine	255.6
104		<i>trans</i> -4-(3-(3,4,5-trimethoxyphenyl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	399.5

[00469] Example 37 – Synthesis of Compounds 97-98, 100-102

[00470] **Scheme 37**



[00471] **Preparation of 3-(hydroxyphenyl)-N-alkylimidazo[1,2-b]pyridazin-6-amine**



[00472] To a solution of 3-(alkoxyphenyl)-N-alkylimidazo[1,2-b]pyridazin-6-amine (0.197 mmol, 1.0 equiv) in dichloromethane at -78 °C was added boron tribromide (0.10 mL, 1.0 M solution in dichloromethane, 5.4 equiv). The reaction mixture was stirred at the reduced temperature for 10 min then warmed to room temperature and stirred for 15 h. Methanol (2 mL) was added to quench the reaction and extracted with dichloromethane. Purification by column chromatography using 5% methanol in dichloromethane elution gave the product.

Table 37-a

Cd.	Aryl bromide	Amine	Pure Isolated Compound
97	1-bromo-4-methoxybenzene	Methyl amine	4-(6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)phenol
98	1-bromo-2-methoxybenzene	Methyl amine	2-(6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)phenol
100	1-bromo-3-methoxybenzene	Methyl amine	3-(6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)phenol
101	1-bromo-3-methoxybenzene	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -3-(6-(4-hydroxycyclohexylamino)imidazo[1,2-b]pyridazin-3-yl)phenol
102	1-bromo-4-methoxybenzene	<i>trans</i> -4-aminocyclohexanol	<i>trans</i> -4-(3-(3,4,5-trimethoxyphenyl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

[00473] Compounds 97-98, 100-102 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 37-b.

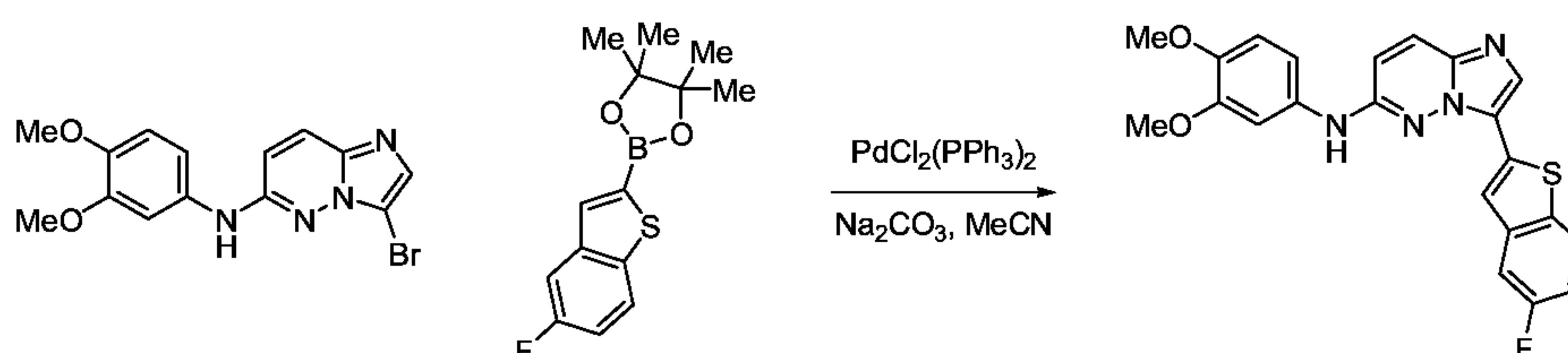
Table 37-b

Cd.	Structure	IUPAC Name	[M+H] ⁺
97		4-(6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)phenol	241.6
98		2-(6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)phenol	241.5
100		3-(6-(methylamino)imidazo[1,2-b]pyridazin-3-yl)phenol	241.6

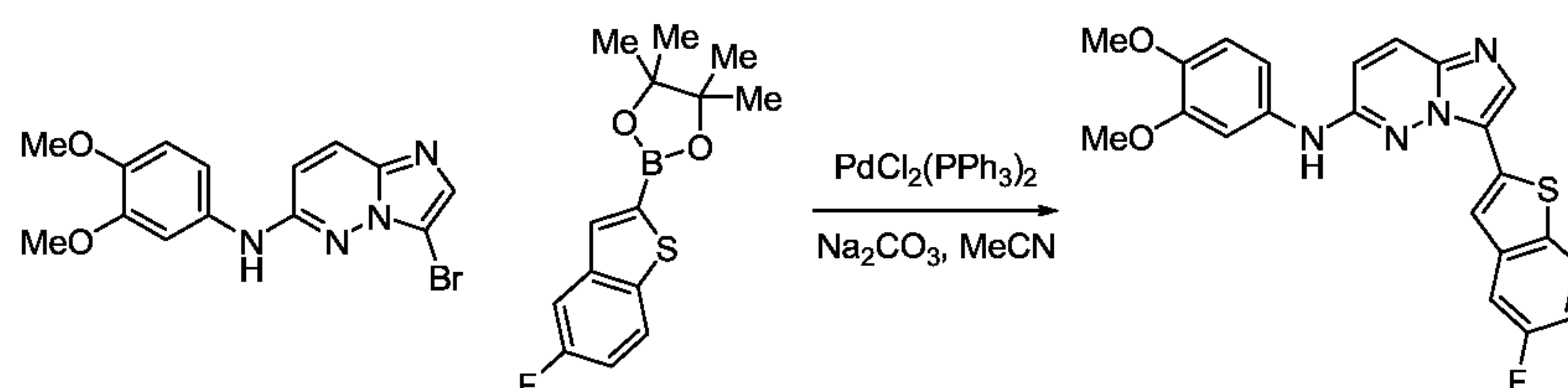
101		<i>trans</i> -3-(6-(4-hydroxycyclohexylamino)imidazo[1,2-b]pyridazin-3-yl)phenol	325.7
102		<i>trans</i> -4-(6-(4-hydroxycyclohexylamino)imidazo[1,2-b]pyridazin-3-yl)phenol	525.7

[00474] Example 38 – Synthesis of Compound 66

[00475] **Scheme 38**



[00476] **Preparation of 3-(5-fluorobenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine**



[00477] To a solution of 3-bromo-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine (118 mg, 0.338 mmol, 1.0 equiv) in acetonitrile (3.38 mL) was added 2-(5-fluorobenzo[b]thiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (122 mg, 0.439 mmol, 1.3 equiv), bis(triphenylphosphine)palladium(II) dichloride (24 mg, 0.0338 mmol, 0.1 equiv), then sodium carbonate (3.38 mL, 1.0 M aqueous solution, 10 equiv). The reaction mixture was irradiated in the microwave at 150 °C for 10 min. Purification by column chromatography gave 100 mg of the brown solid, 70%.

[00478] Compound 66 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 38-b**.

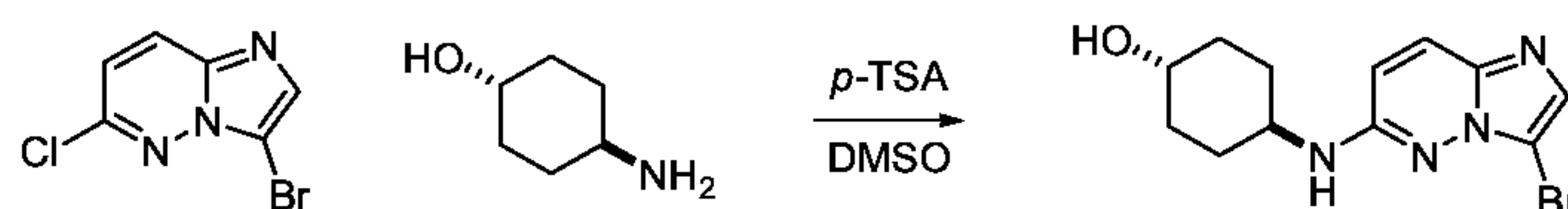
[00479] **Table 38**

Cd.	Structure	IUPAC Name	[M+H] ⁺
66		3-(5-fluorobenzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	421.8

[00480] Example 39 – Synthesis of Compound 166

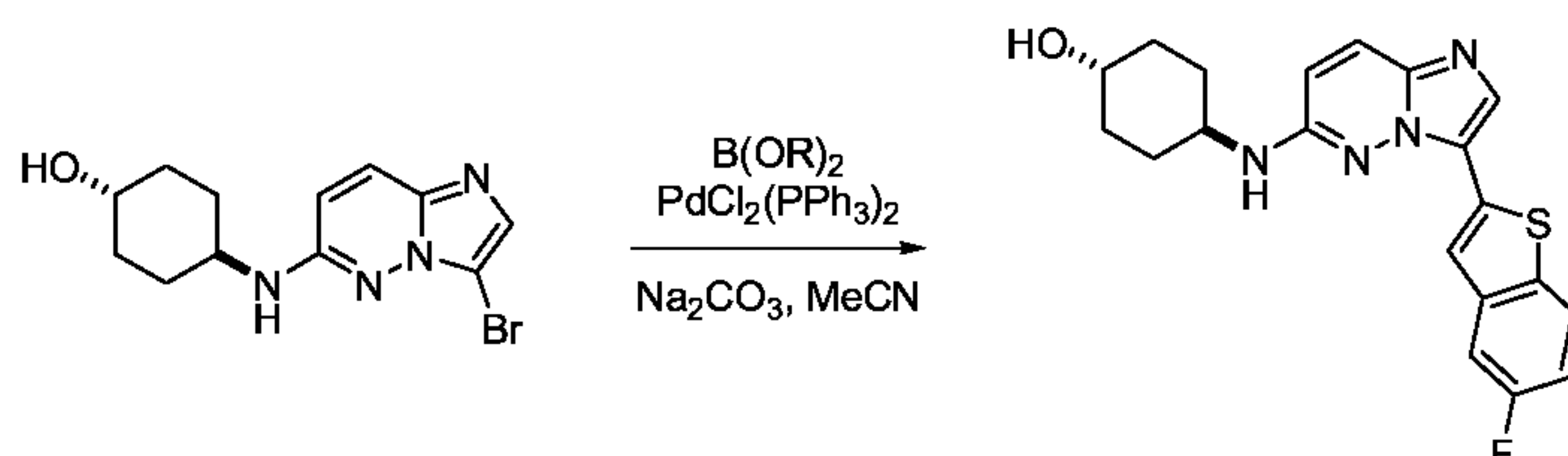
[00481] **Scheme 39**

[00482] **Preparation of *trans*-4-(3-bromoimidazo[1,2-*b*]pyridazin-6-ylamino)cyclohexanol**



[00483] To 6-chloro-3-bromoimidazo[1,2-*b*]pyridazine (1.00 g, 4.30 mmol, 1.0 equiv) and *p*-TSA (818 mg, 4.30 mmol, 1.0 equiv) in DMSO (7.00 mL) was added *trans*-4-aminocyclohexanol (1.49 g, 12.9 mmol, 3.0 equiv). The mixture was heated at 100 °C for 24 h. Purification by column chromatography using 5% methanol in dichloromethane elution gave 1.1 g of the yellow solid, 83%.

[00484] **Preparation of *trans*-4-(3-(5-fluorobenzo[*b*]thiophen-2-yl)imidazo[1,2-*b*]pyridazin-6-ylamino)cyclohexanol**



[00485] To a solution of 3-bromo-N-(3,4-dimethoxyphenyl)imidazo[1,2-*b*]pyridazin-6-amine (118 mg, 0.338 mmol, 1.0 equiv) in acetonitrile (3.79 mL) was added 2-(5-fluorobenzo[*b*]thiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (158 mg, 0.569 mmol, 1.5 equiv), bis(triphenylphosphine)palladium(II) dichloride (27 mg, 0.0379 mmol, 0.1 equiv), then sodium carbonate (3.79 mL, 1.0 M aqueous solution, 10 equiv). The reaction mixture was irradiated in the microwave at 150 °C for 10 min. Purification by column chromatography gave 90 mg of the yellow solid, 62%.

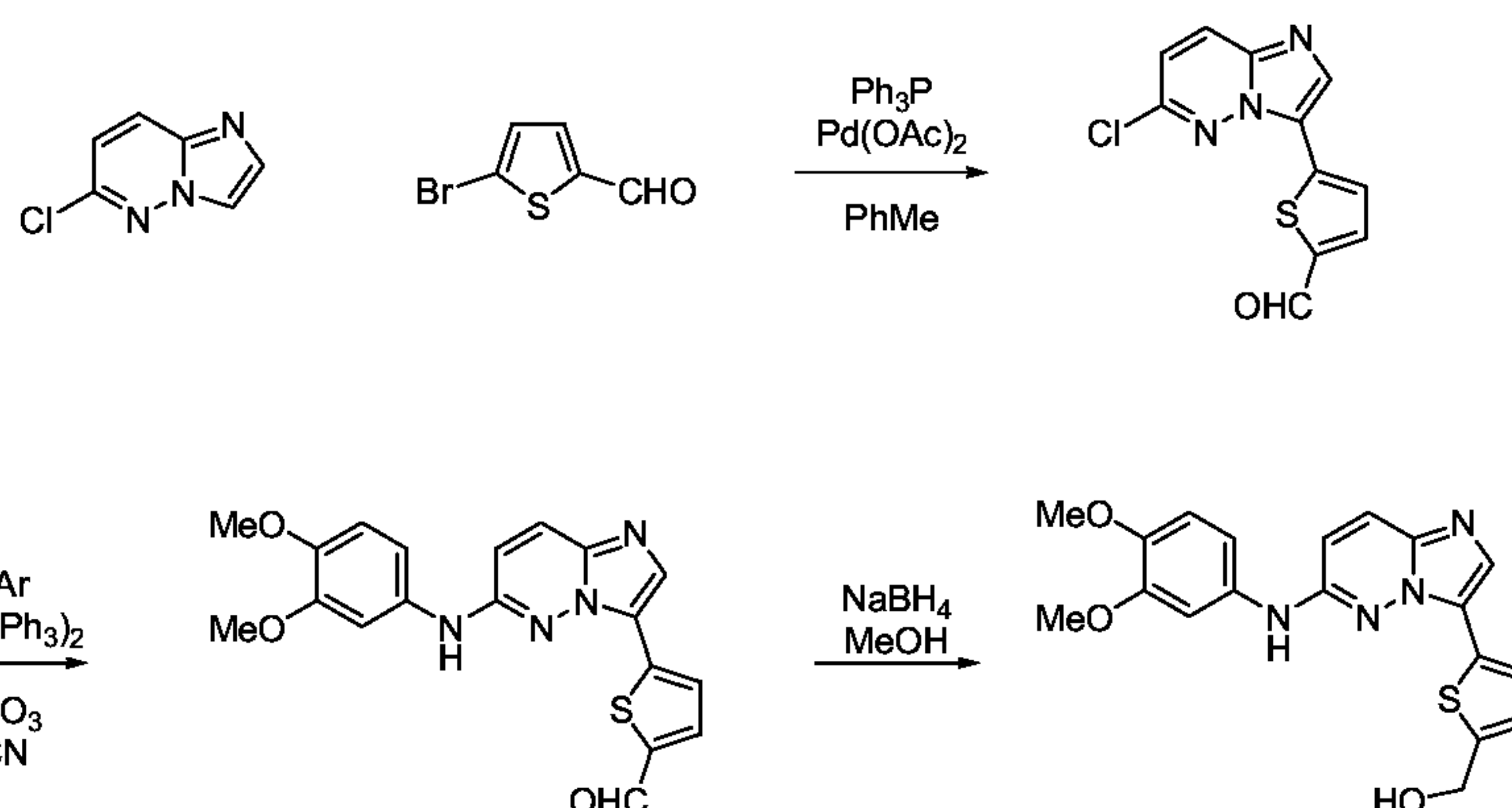
[00486] Compound 166 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 39-b.

[00487] **Table 39-b**

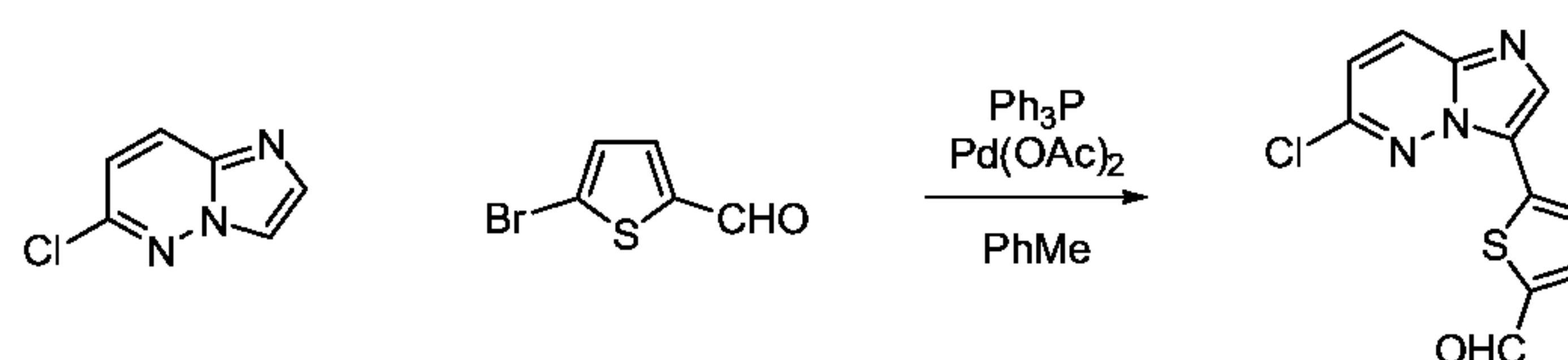
Cd.	Structure	IUPAC Name	[M+H] ⁺
166		<i>trans</i> -4-(3-(5-fluorobenzo[<i>b</i>]thiophen-2-yl)imidazo[1,2- <i>b</i>]pyridazin-6-ylamino)cyclohexanol	383.7

[00488] Example 40 – Synthesis of Compound 84

[00489] **Scheme 40**

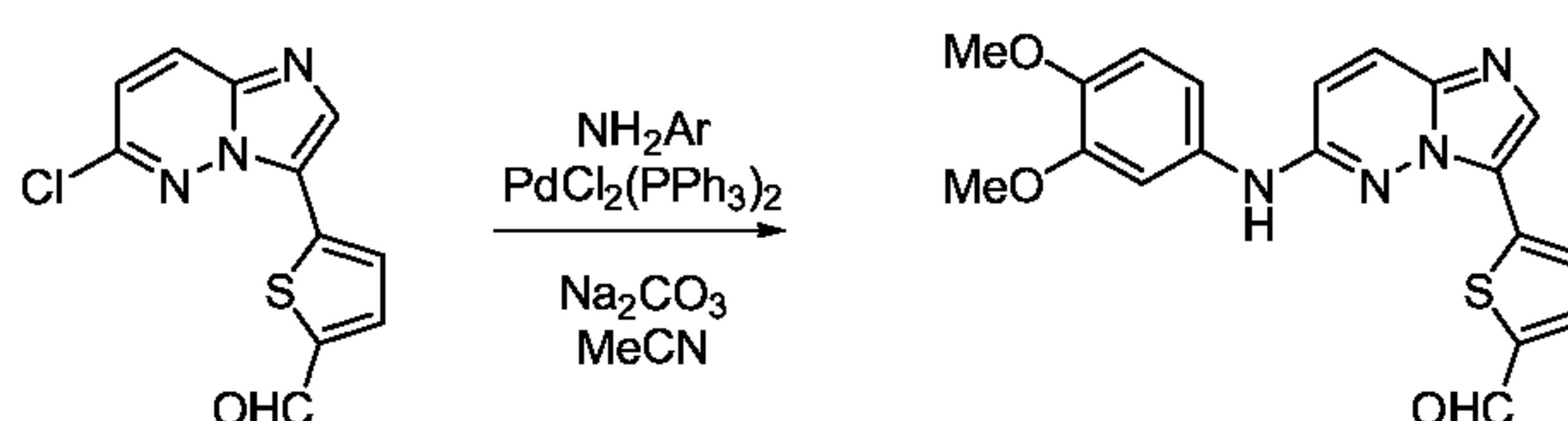


[00490] Preparation of 5-(6-chloroimidazo[1,2-b]pyridazin-3-yl)thiophene-2-carbaldehyde



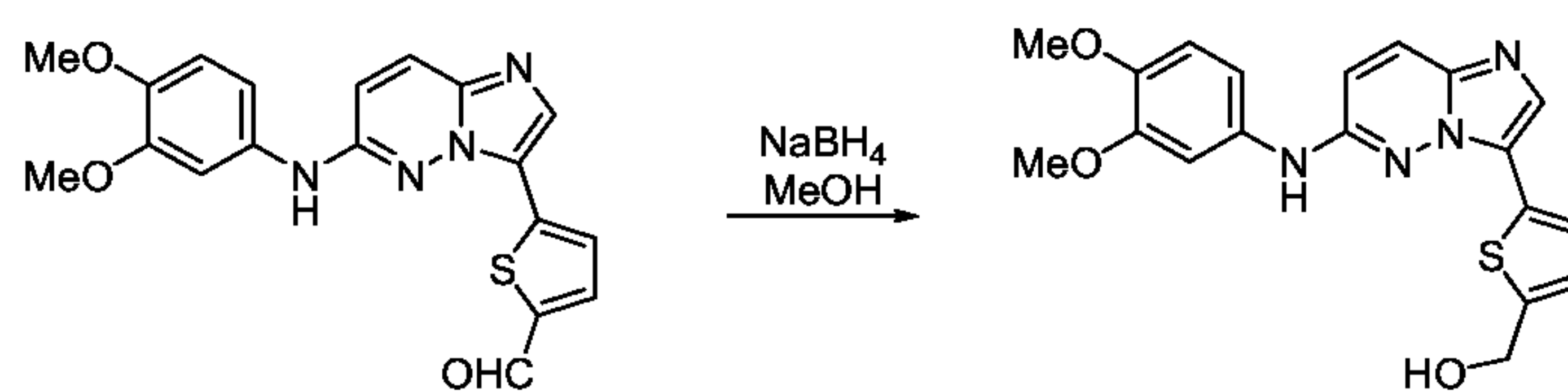
[00491] To a solution of 6-chloroimidazo[1,2-b]pyridazine (1.55 g, 10.1 mmol, 1.0 equiv) in toluene (10.0 mL) was added 5-bromothiophene-2-carbaldehyde (1.80 mL, 15.1 mmol, 1.5 equiv), potassium carbonate (2.79 g, 20.2 mmol, 2.0 equiv), triphenyl phosphine (529 mg, 2.02 mmol, 0.2 equiv) and potassium acetate (227 mg, 1.01 mmol, 0.1 equiv). The reaction mixture was heated to reflux for 24 h then diluted with water and extracted with ethyl acetate. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 1.60 g of the white solid, 60%.

[00492] Preparation of 5-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)thiophene-2-carbaldehyde



[00493] To a solution of 5-(6-chloroimidazo[1,2-b]pyridazin-3-yl)thiophene-2-carbaldehyde (200 mg, 0.758 mmol, 1.0 equiv), xantphos (88 mg, 0.152 mmol, 0.2 equiv), palladium acetate (17 mg, 0.0758 mmol, 0.1 equiv), and potassium carbonate (2.10 g, 1.52 mmol, 20 equiv) in dioxane (6.0 mL) was added 3,4-dimethoxyaniline (116 mg, 0.758 mmol, 1.0 equiv) and heated to 100 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the 100 mg of the brown solid, 35%.

[00494] Preparation of (5-(6-chloroimidazo[1,2-b]pyridazin-3-yl)thiophen-2-yl)methanol



[00495] To a solution of 5-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)thiophene-2-carbaldehyde (34 mg, 0.0894 mmol, 1.0 equiv) in methanol (5.00 mL) was added sodium borohydride (100 mg, 2.64 mmol, 30.0 equiv). After 1 h, the reaction mixture was quenched with water and extracted with ethyl acetate. Purification by column chromatography using 2% methanol in hexanes elution gave 20 mg of the brown solid, 58%.

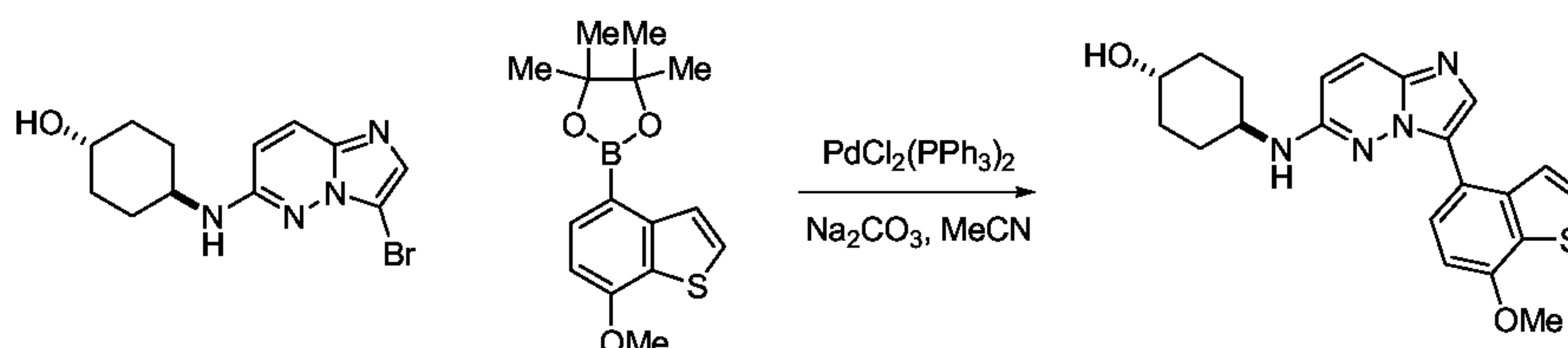
[00496] Compound 84 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 40-b**.

Table 40-b

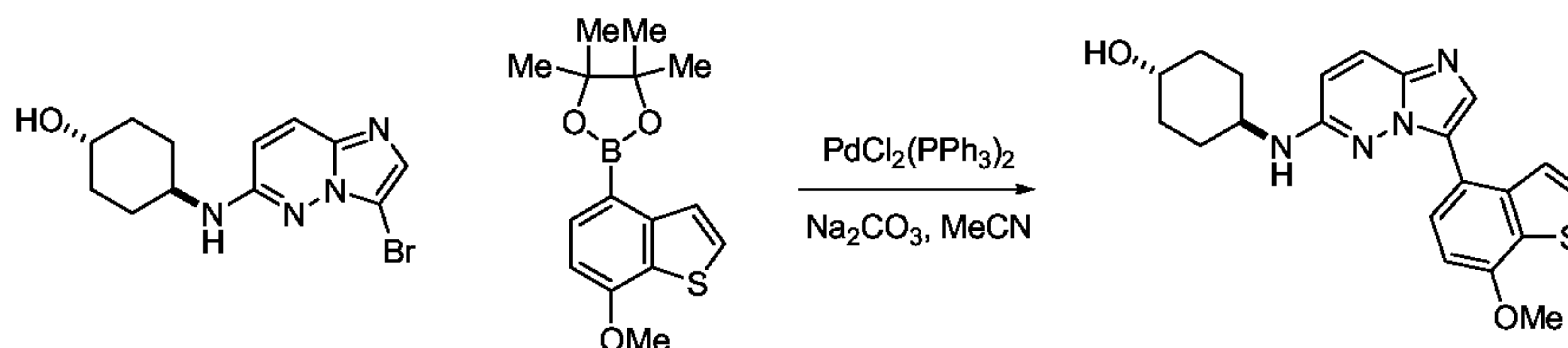
Cd.	Structure	IUPAC Name	[M+H] ⁺
84		(5-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)thiophen-2-yl)methanol	383.5

[00497] Example 41 – Synthesis of Compound 92

[00498] **Scheme 41**



[00499] Preparation of *trans*-4-(3-(7-methoxybenzo[b]thiophen-4-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol



[00500] To a solution of *trans*-4-(3-bromoimidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol (45 mg, 0.145 mmol, 1.0 equiv) in acetonitrile (1.45 mL) was added 2-(7-methoxybenzo[b]thiophen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (55 mg, 0.188 mmol, 1.3 equiv), bis(triphenylphosphine)palladium(II) dichloride (11 mg, 0.0159 mmol, 0.1 equiv), then sodium carbonate (1.45 mL, 1.0 M aqueous solution, 10 equiv). The reaction mixture was irradiated in the microwave at 150 °C for 10 min. Purification by column chromatography gave 31 mg of the yellow solid, 53%.

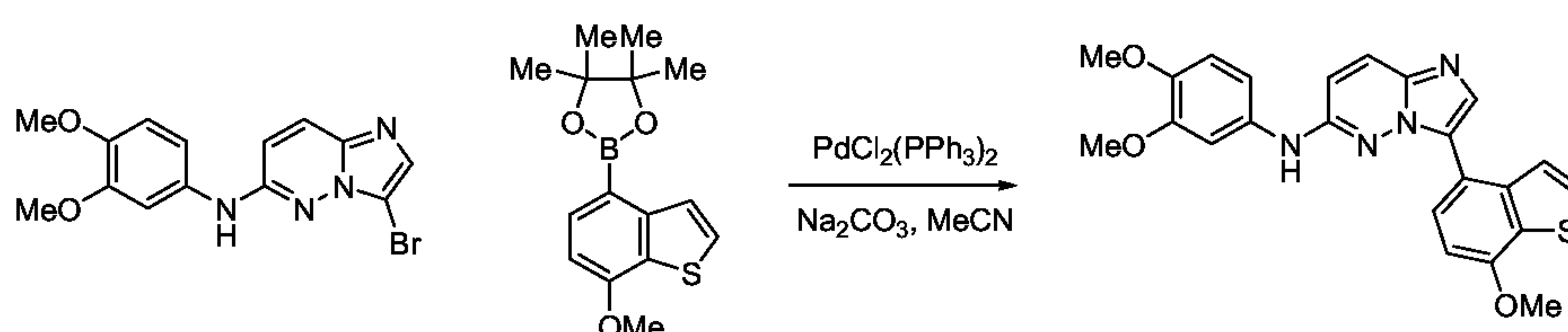
[00501] Compound 92 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 41-b.

[00502] Table 41

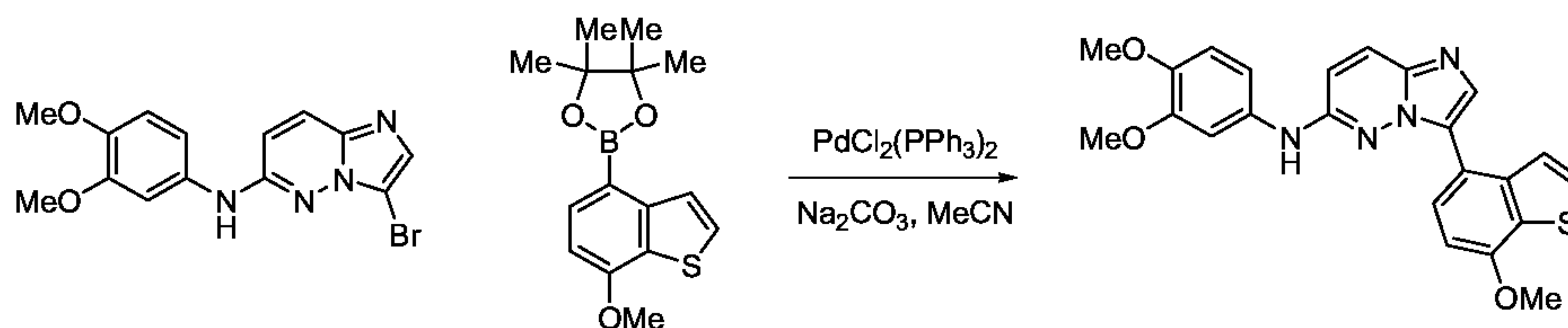
Cd.	Structure	IUPAC Name	[M+H] ⁺
92		<i>trans</i> -4-(3-(7-methoxybenzo[b]thiophen-4-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	395.0

[00503] Example 42 – Synthesis of Compound 93

[00504] Scheme 42



[00505] Preparation of 3-(7-methoxybenzo[b]thiophen-4-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine

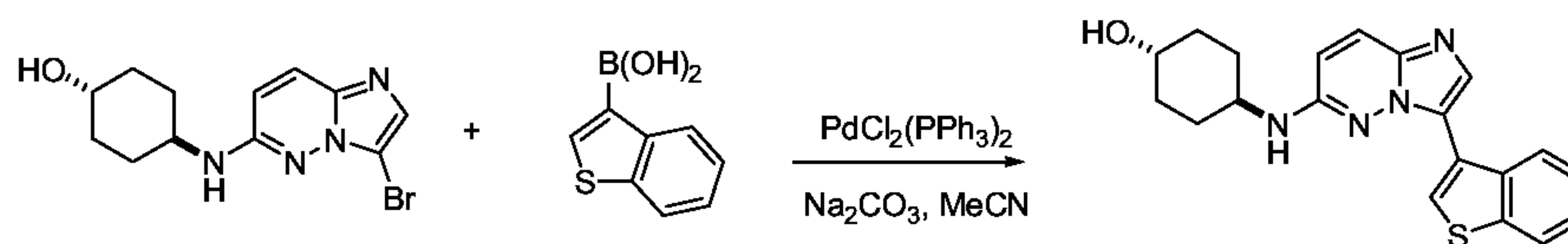
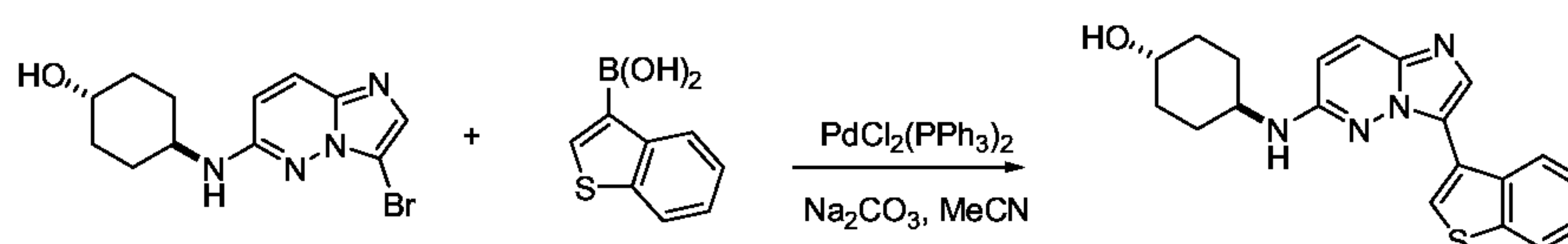


[00506] To a solution of 3-bromo-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine (43 mg, 0.123 mmol, 1.0 equiv) in acetonitrile (1.23 mL) was added 2-(7-methoxybenzo[b]thiophen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (46 mg, 0.160 mmol, 1.3 equiv), bis(triphenylphosphine)palladium(II) dichloride (9 mg, 0.0123 mmol, 0.1 equiv), then sodium carbonate (1.23 mL, 1.0 M aqueous solution, 10 equiv). The reaction mixture was irradiated in the microwave at 150 °C for 10 min. Purification by column chromatography gave 30 mg of the yellow solid, 56%.

[00507] Compound 93 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 42-b.

[00508] Table 42

Cd.	Structure	IUPAC Name	[M+H] ⁺
93		3-(7-methoxybenzo[b]thiophen-4-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-b]pyridazin-6-amine	433.1

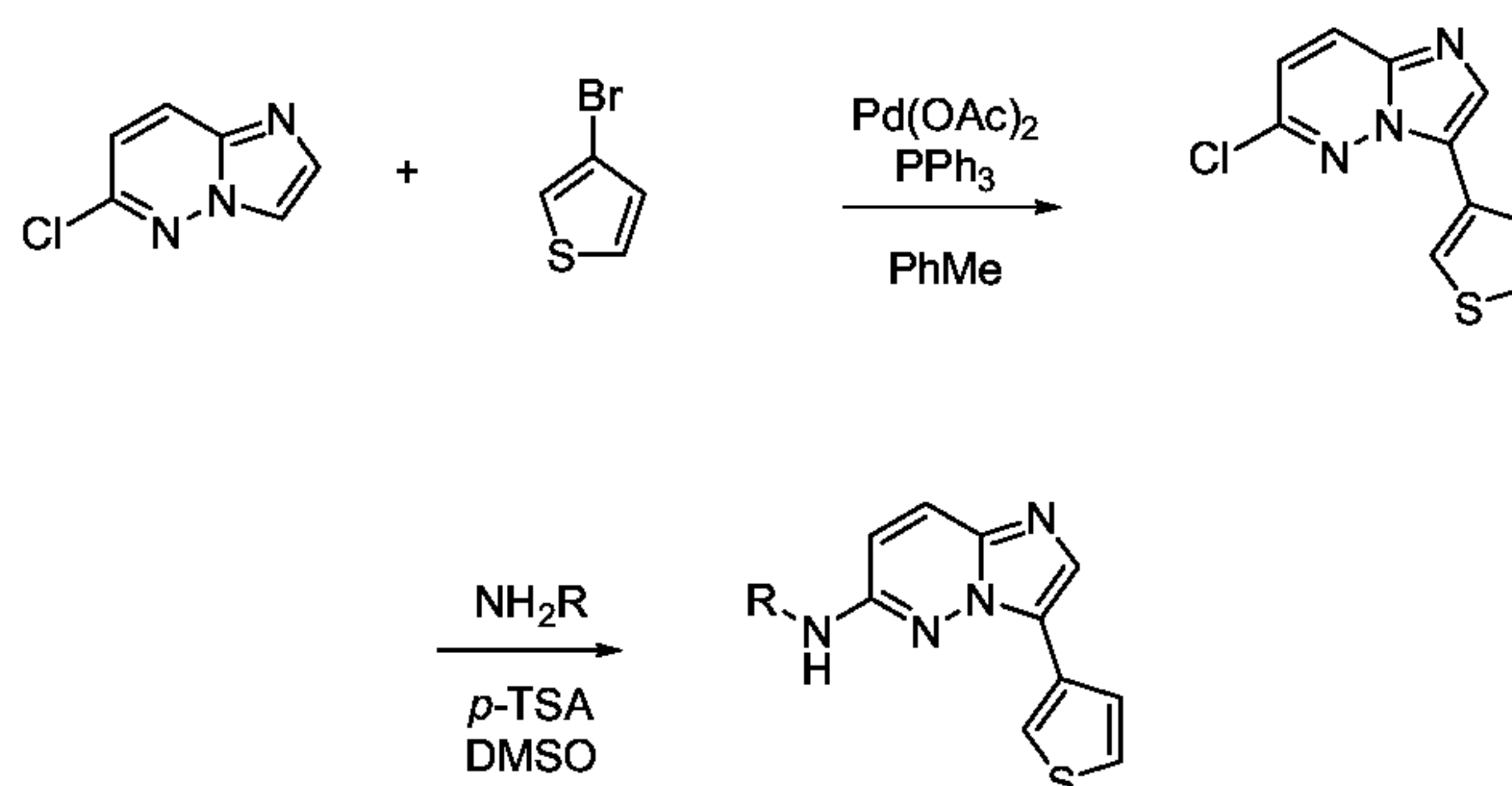
[00509] Example 43 – Synthesis of Compound 90**[00510]** **Scheme 43****[00511]** Preparation of *trans*-4-(3-(benzo[b]thiophen-3-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

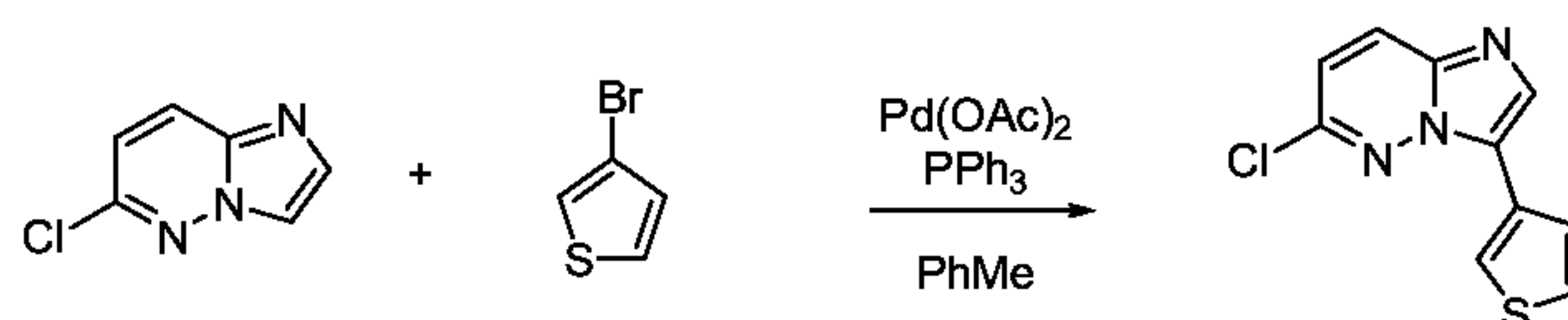
[00512] To a solution of *trans*-4-(3-bromoimidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol (50 mg, 0.159 mmol, 1.0 equiv) in acetonitrile (1.59 mL) was added benzo[b]thiophen-3-yl-3-boronic acid (117 mg, 0.239 mmol, 1.5 equiv), bis(triphenylphosphine)palladium(II) dichloride (11 mg, 0.0159 mmol, 0.1 equiv), then sodium carbonate (1.59 mL, 1.0 M aqueous solution, 10 equiv). The reaction mixture was irradiated in the microwave at 150 °C for 10 min. Purification by column chromatography gave 20 mg of the yellow solid, 36%.

[00513] Compound 90 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 43-b**.

Table 43-b

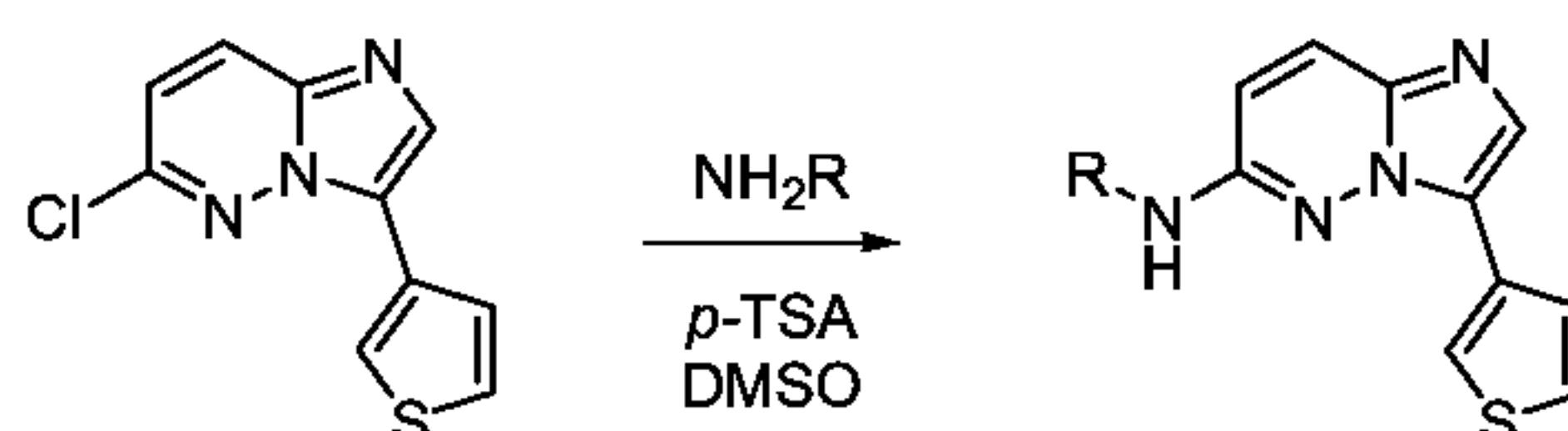
Cd.	Structure	IUPAC Name	[M+H] ⁺
90		<i>trans</i> -4-(3-(benzo[b]thiophen-3-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	365.8

[00514] Example 44 – Synthesis of Compound 91 and 180**[00515]** **Scheme 44****[00516]** Preparation of 6-chloro-3-(thiophen-3-yl)imidazo[1,2-b]pyridazine



[00517] To a solution of 6-chloroimidazo[1,2-b]pyridazine (200 mg, 1.30 mmol, 1.0 equiv) in toluene (5.00 mL) was added 3-bromothiophene (0.18 mL, 1.95 mmol, 1.5 equiv), potassium carbonate (360 mg, 2.60 mmol, 2.0 equiv), triphenyl phosphine (68 mg, 0.260 mmol, 0.20 equiv) and potassium acetate (29 mg, 0.130 mmol, 0.1 equiv). The reaction mixture was heated to reflux for 24 h. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 201 mg of the white solid, 85%.

[00518] Preparation of N-alkyl-3-(thiophen-3-yl)imidazo[1,2-b]pyridazin-6-amine



[00519] To a solution of 6-chloro-3-(thiophen-3-yl)imidazo[1,2-b]pyridazine (299 mg, 1.30 mmol, 1.0 equiv) in DMSO (5.00 mL) was added *p*-TSA (247 mg, 1.30 mmol, 1.0 equiv) and amine (6.50 mmol, 5.0 equiv) and heated to 100 °C for 24 h. Purification by column chromatography using 5% methanol in hexanes elution gave the product.

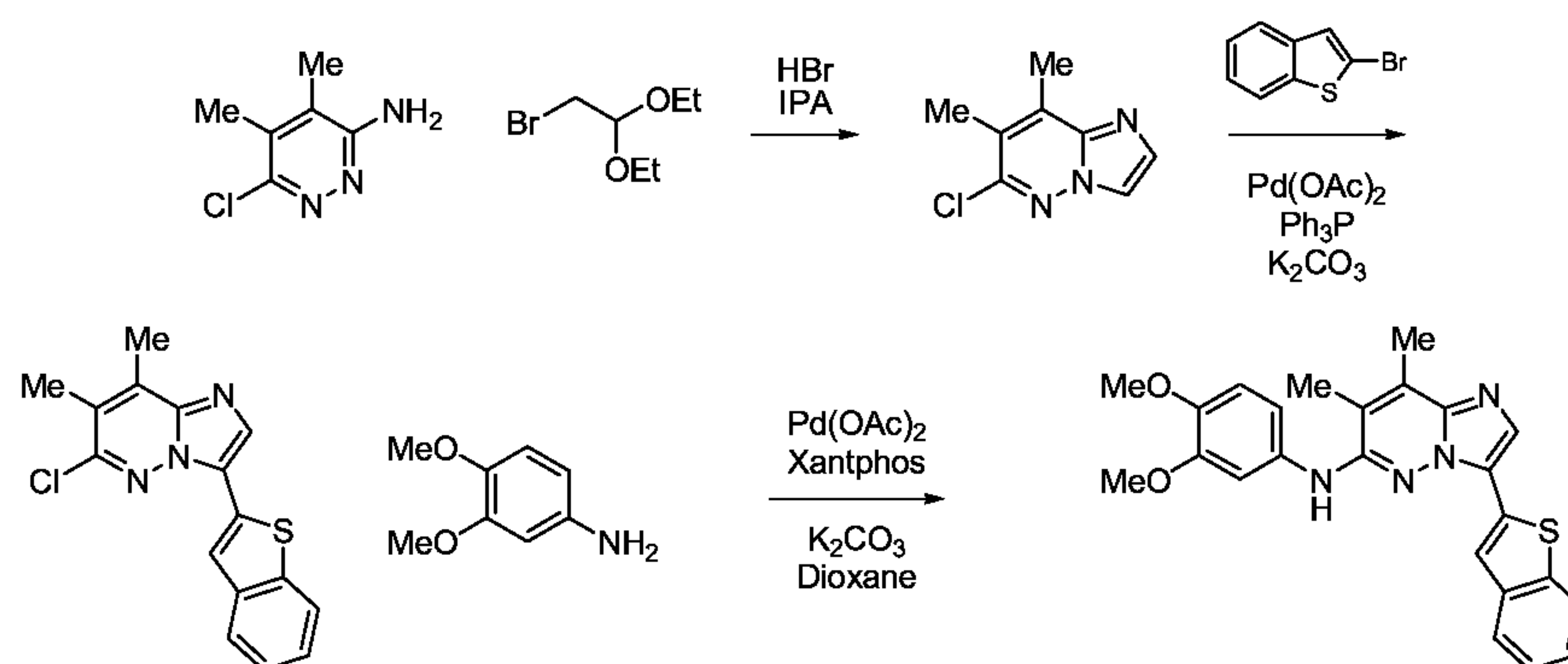
[00520] Compounds 91 and 180 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 44-b**.

[00521] Table 44-b

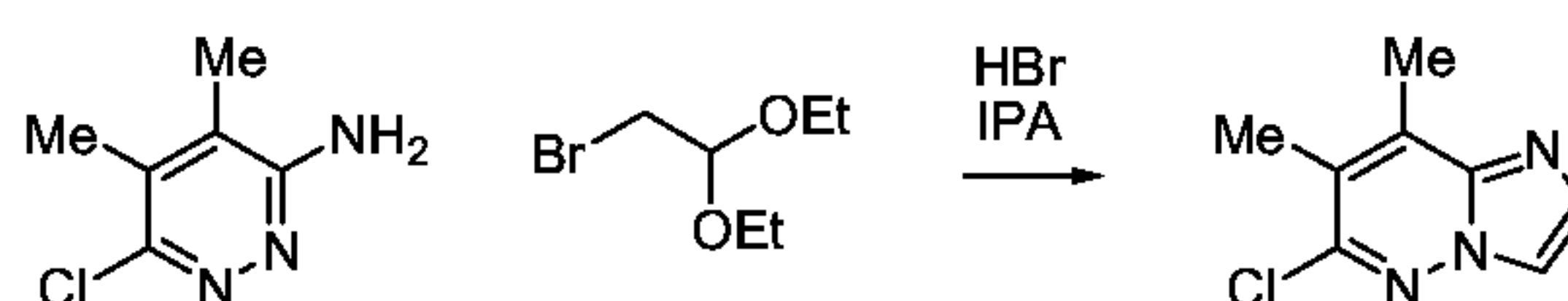
Cd.	Amine	Structure	IUPAC Name	[M+H] ⁺
91	Methylamine		N-methyl-3-(thiophen-3-yl)imidazo[1,2-b]pyridazin-6-amine	231.6
180	<i>trans</i> -4-aminocyclohexanol		<i>trans</i> -(3-(thiophen-3-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	315.6

[00522] Example 45 – Synthesis of Compound 120

[00523] **Scheme 45**

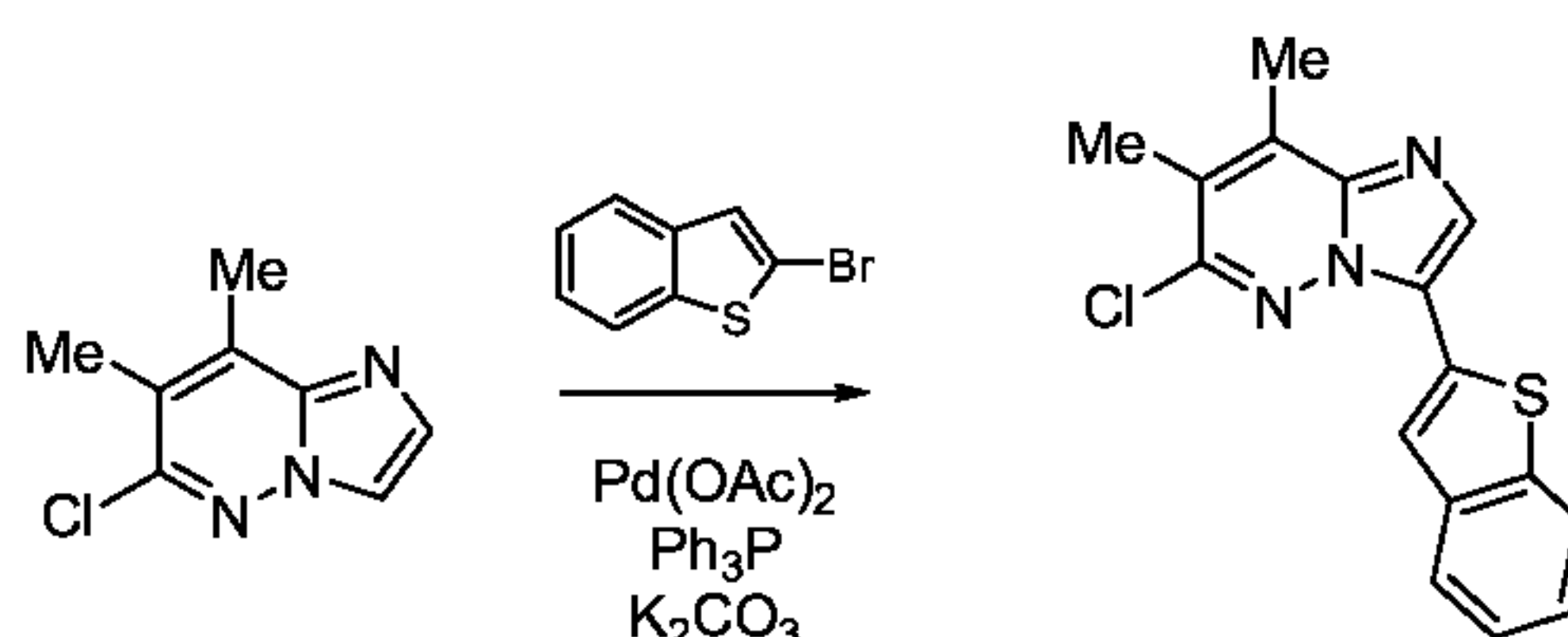


[00524] Preparation of 6-chloro-7,8-dimethylimidazo[1,2-b]pyridazine



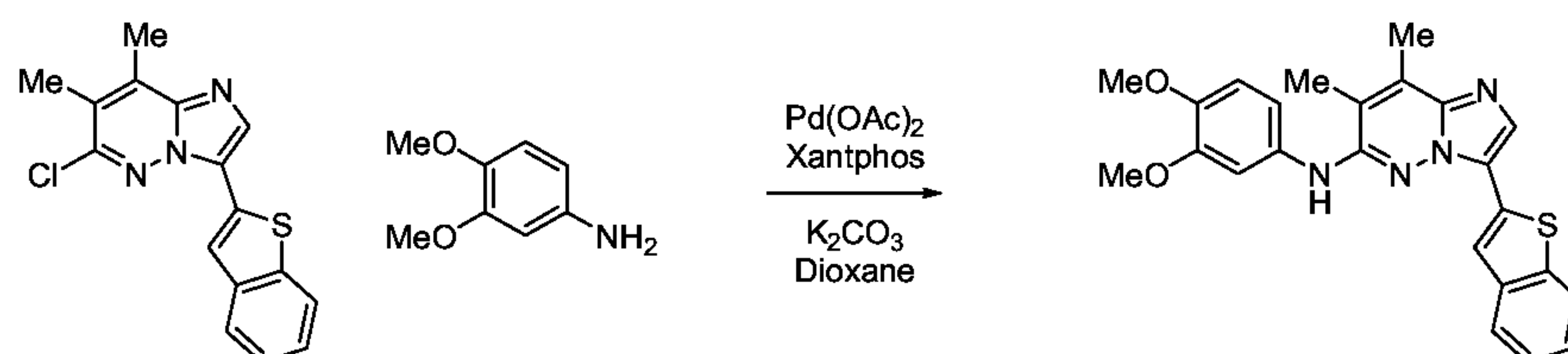
[00525] To a solution of 6-chloro-4,5-dimethylpyridazin-3-amine (2.00 g, 12.7 mmol, 1.0 equiv) in isopropanol (40 mL) was added bromoacetaldehyde diethyl acetal (5.23 mL, 34.8 mmol, 2.7 equiv), and hydrobromic acid (2.00 mL) and heated to reflux for 2 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. Purification by column chromatography using 20% ethyl acetate in hexanes elution gave 2.07 g of the white solid, 90%.

[00526] Preparation of 3-(benzo[b]thiophen-2-yl)-6-chloro-7,8-dimethylimidazo[1,2-b]pyridazine



[00527] To a solution of 6-chloro-7,8-dimethylimidazo[1,2-b]pyridazine (162 mg, 0.892 mmol, 1.0 equiv) in toluene (5.00 mL) was added 2-bromobenzo[b]thiophene (213 mg, 1.16 mmol, 1.3 equiv), potassium carbonate (247 mg, 1.78 mmol, 2.0 equiv), triphenyl phosphine (47 mg, 0.178 mmol, 0.20 equiv) and potassium acetate (20 mg, 0.0892 mmol, 0.1 equiv). The reaction mixture was heated to reflux for 24 h. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 105 mg of the white solid, 38%.

[00528] Preparation of 3-(benzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)-7,8-dimethylimidazo[1,2-b]pyridazin-6-amine



[00529] To a solution of 3-(benzo[b]thiophen-2-yl)-6-chloro-7,8-dimethylimidazo[1,2-b]pyridazine (89 mg, 0.284 mmol, 1.0 equiv), xantphos (33 mg, 0.0567 mmol, 0.2 equiv), palladium acetate (6 mg, 0.0284 mmol, 0.1 equiv), and potassium carbonate (784 mg, 5.67 mmol, 20 equiv) in dioxane (5.00 mL) was added 3,4-dimethoxyaniline (52 mg, 0.340 mmol, 1.0 equiv) and heated to 100 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave the 60 mg of the brown solid, 49%.

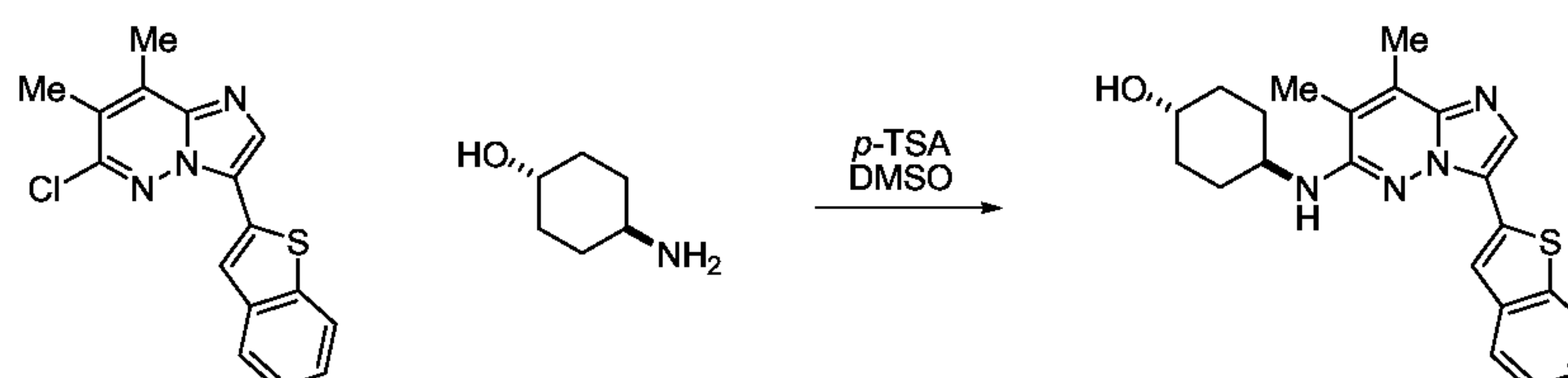
[00530] Compound 120 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 45-b.

Table 45-b

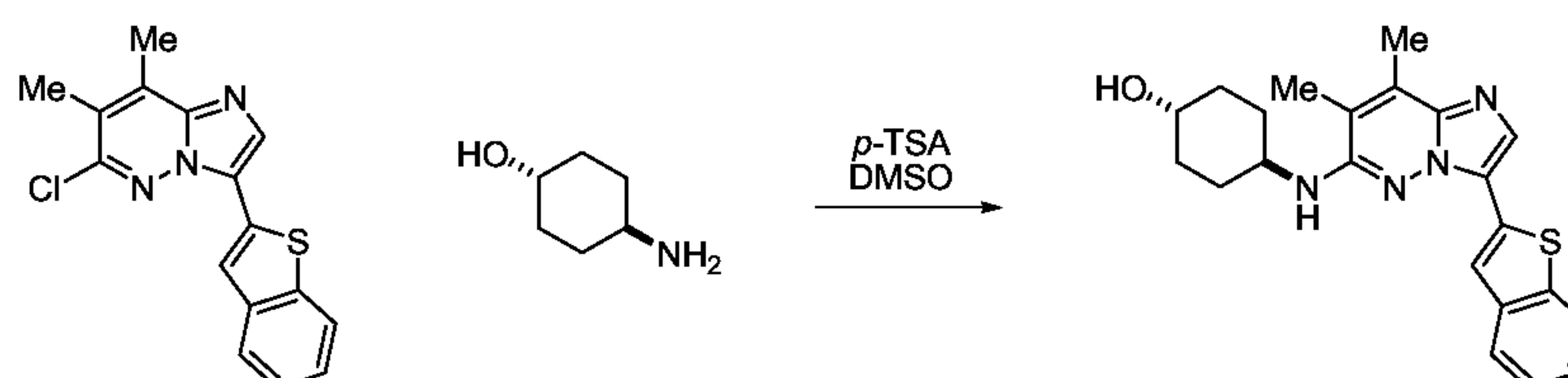
Cd.	Structure	IUPAC Name	[M+H] ⁺
120		3-(benzo[b]thiophen-2-yl)-N-(3,4-dimethoxyphenyl)-7,8-dimethylimidazo[1,2-b]pyridazin-6-amine	431.7

[00531] Example 46 – Synthesis of Compound 121

[00532] **Scheme 46**



[00533] **Preparation of *trans*-4-(3-(benzo[b]thiophen-2-yl)-7,8-dimethylimidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol**



[00534] To a solution of 3-(benzo[b]thiophen-2-yl)-6-chloro-7,8-dimethylimidazo[1,2-b]pyridazine (40 mg, 0.128 mmol, 1.0 equiv) in DMSO (1.00 mL) was added *p*-TSA (24 mg, 0.128 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (73 mg, 0.638 mmol, 5.0 equiv) and heated to 100 °C for 24 h. Purification by column chromatography using 5% methanol in dichloromethane elution gave 31 mg, 62%.

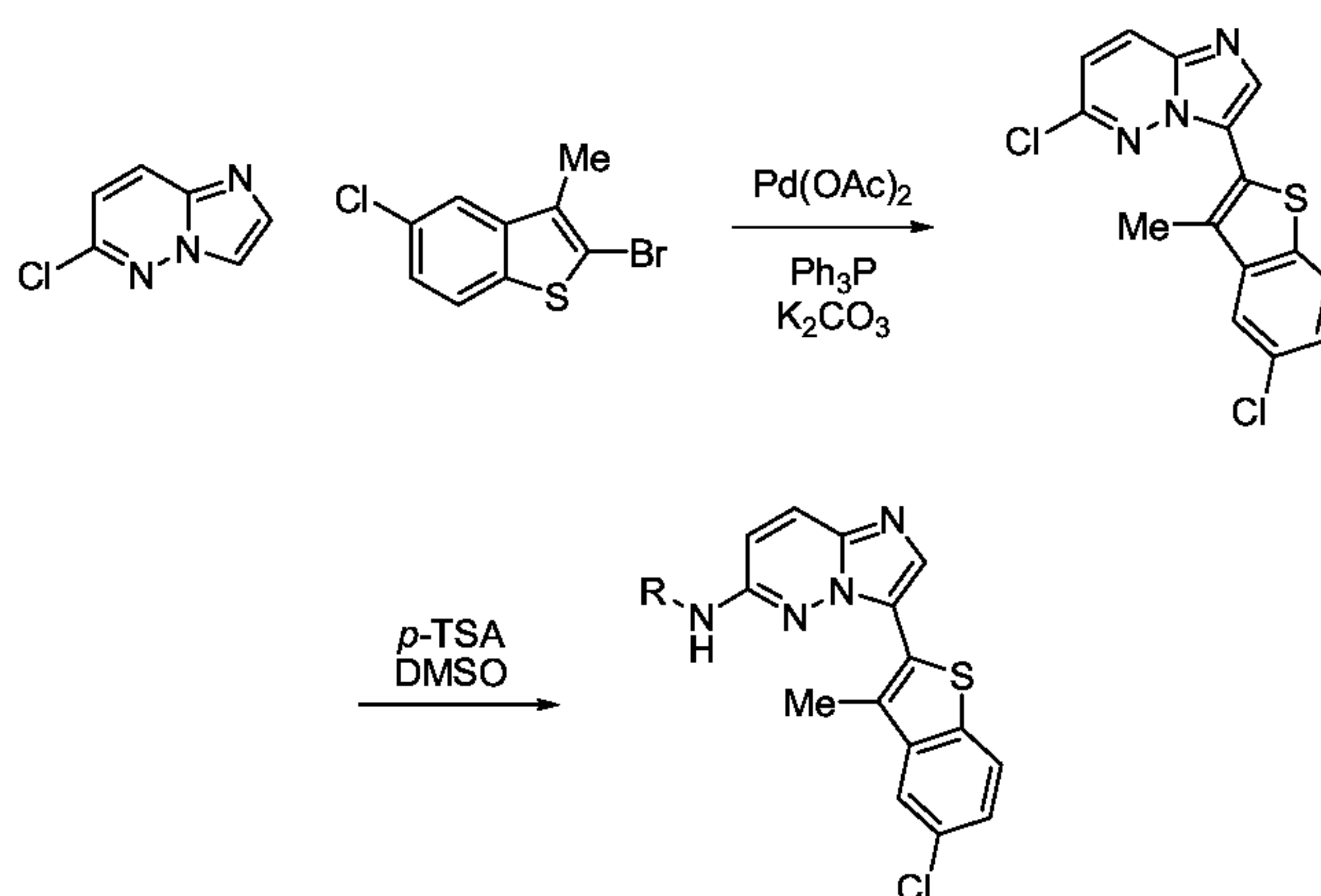
[00535] Compound 121 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 46-b.

Table 46-b

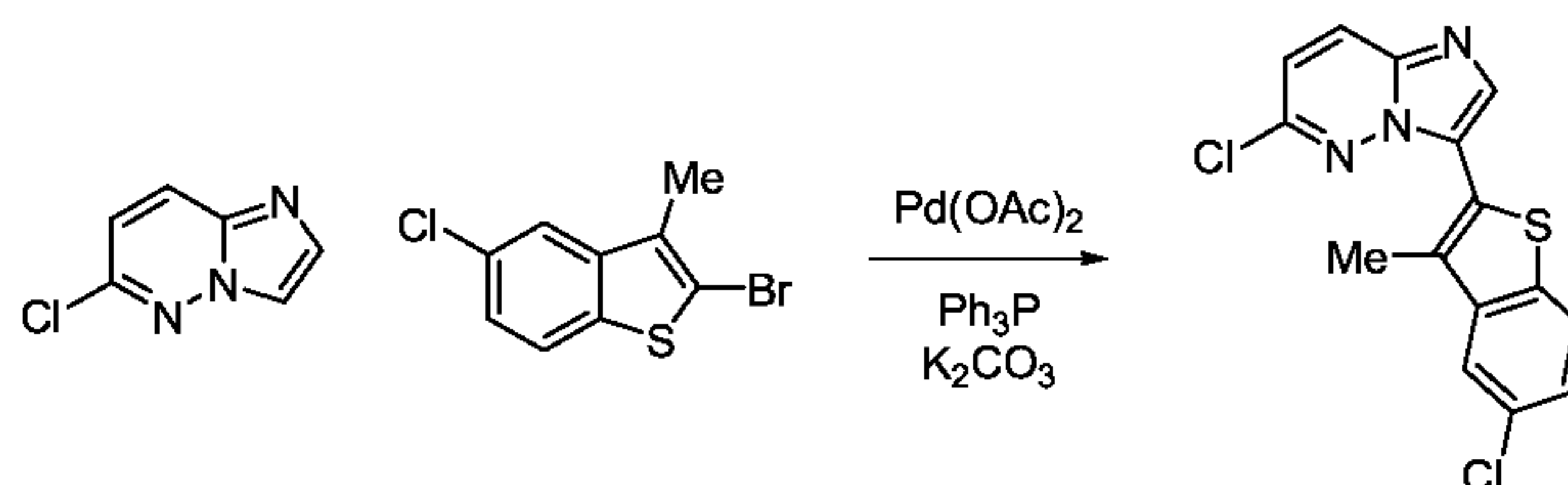
Cd.	Structure	IUPAC Name	[M+H] ⁺
121		<i>trans</i> -4-(3-(benzo[b]thiophen-2-yl)-7,8-dimethylimidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	393.7

[00536] Example 47 – Synthesis of Compounds 118 and 164

[00537] **Scheme 47**

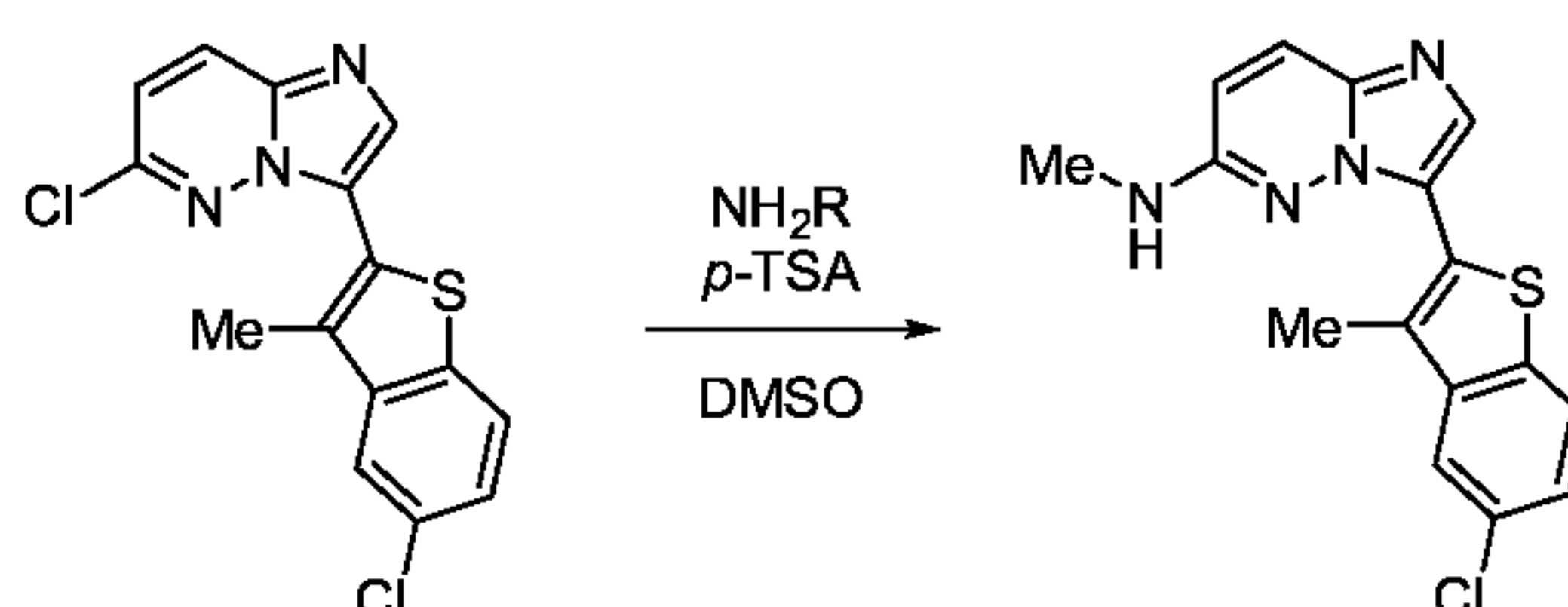


[00538] **Preparation of 6-chloro-3-(5-chloro-3-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine**



[00539] To a solution of 6-chloroimidazo[1,2-b]pyridazine (606 mg, 3.95 mmol, 1.0 equiv) in toluene (10.00 mL) was added 2-bromo-5-chloro-3-methylbenzo[b]thiophene (1.03 g, 3.95 mmol, 1.0 equiv), potassium carbonate (1.09 g, 7.90 mmol, 2.0 equiv), triphenyl phosphine (207 mg, 0.790 mmol, 0.20 equiv) and potassium acetate (89 mg, 0.395 mmol, 0.1 equiv). The reaction mixture was heated to reflux for 24 h. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 500 mg of the white solid, 38%.

[00540] **Preparation of 3-(5-chloro-3-methylbenzo[b]thiophen-2-yl)-N-alkylimidazo[1,2-b]pyridazin-6-amine**



[00541] To a solution of 6-chloro-3-(5-chloro-3-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (40 mg, 0.120 mmol, 1.0 equiv) in DMSO (1.00 mL) was added *p*-TSA (35 mg, 0.120 mmol, 1.5 equiv) and amine (2.24 mmol, 12.5 equiv) and heated to 100 °C for 24 h. Purification by column chromatography using 5% methanol in dichloromethane elution gave the product.

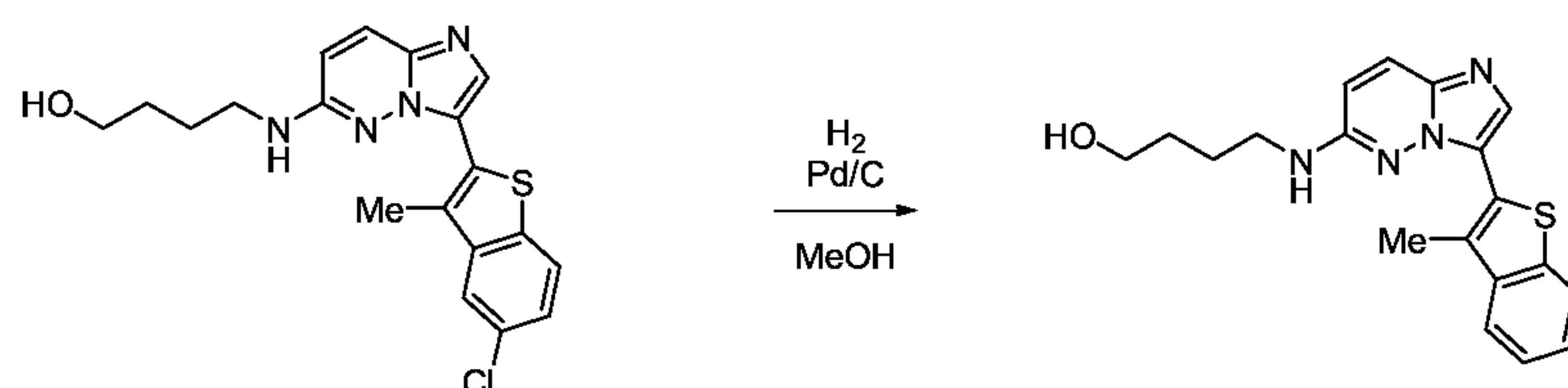
[00542] Compounds 118 and 164 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 47-b**.

Table 47-b

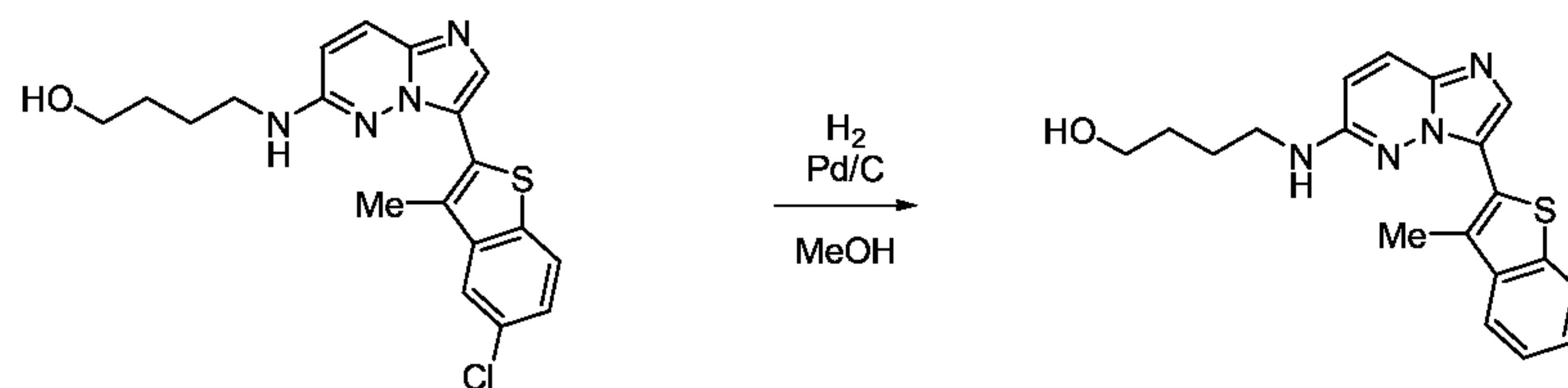
Cd.	Amine	Structure	IUPAC	[M+H] ⁺
118	4-aminobutan-1-ol		4-(3-(5-chloro-3-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol	387.6
164	<i>trans</i> -4-aminocyclohexanol		<i>trans</i> -4-(3-(5-chloro-3-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	413.8

[00543] Example 48 – Synthesis of Compound 165

[00544] **Scheme 48**



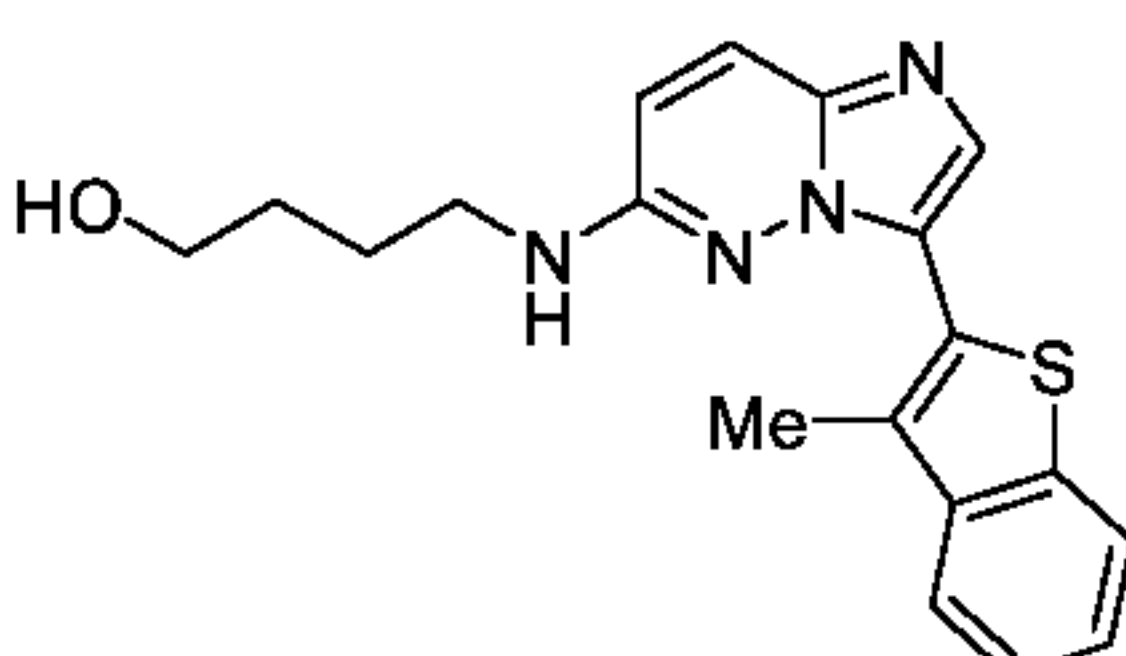
[00545] **Preparation of 4-(3-(3-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol**



[00546] To a solution of 4-(3-(5-chloro-3-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol (20 mg, 0.0517 mmol, 1.0 equiv) in methanol (2.00 mL) was added Pd/C and placed under a balloon of hydrogen. After 3 h, the reaction mixture was filtered through a plug of silica gel to provide 15 mg of the white solid, 82%.

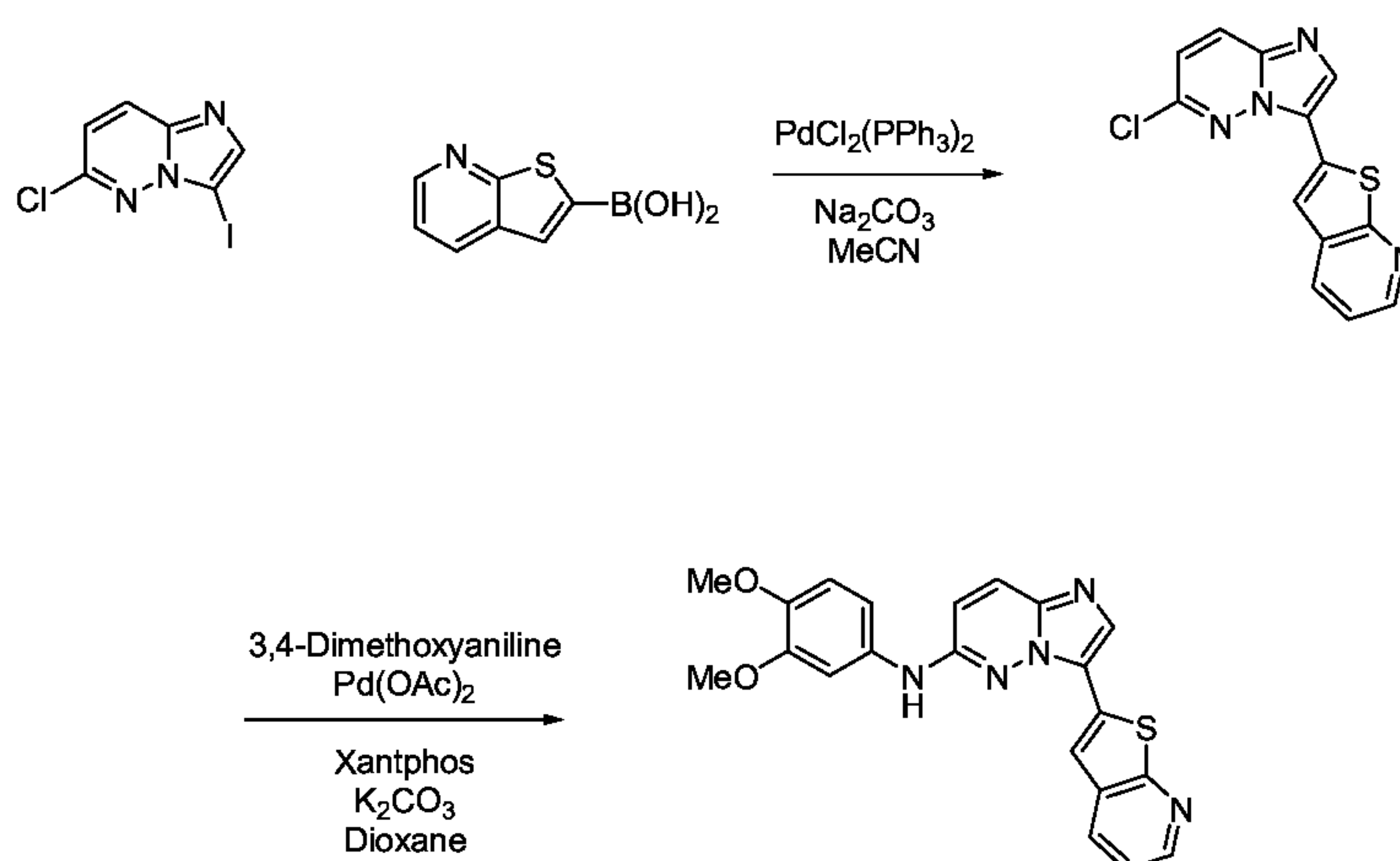
[00547] Compound 165 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 48-b.

Table 48-b

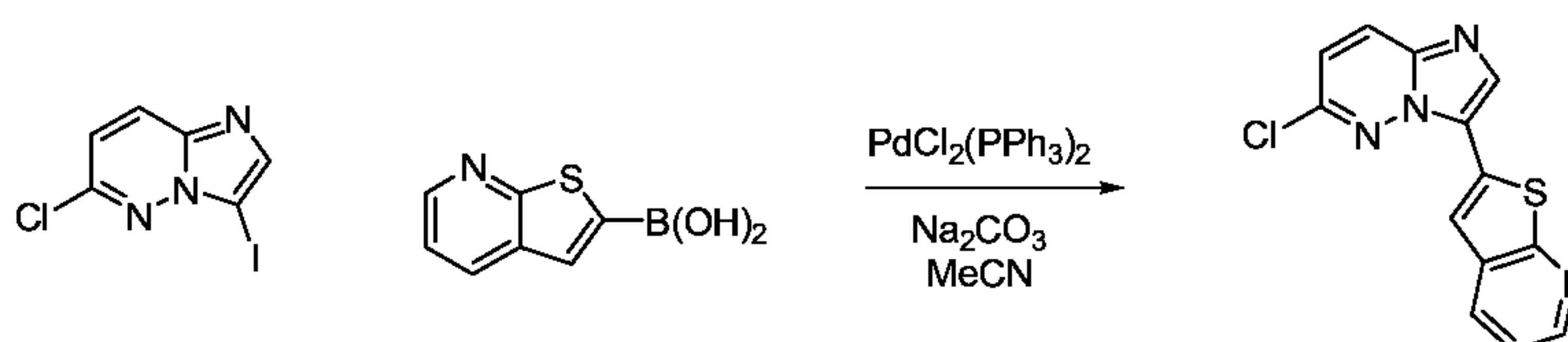
Cd.	Structure	IUPAC Name	[M+H] ⁺
165		4-(3-(3-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)butan-1-ol	355.7

[00548] Example 49 – Synthesis of Compound 204

[00549] Scheme 49

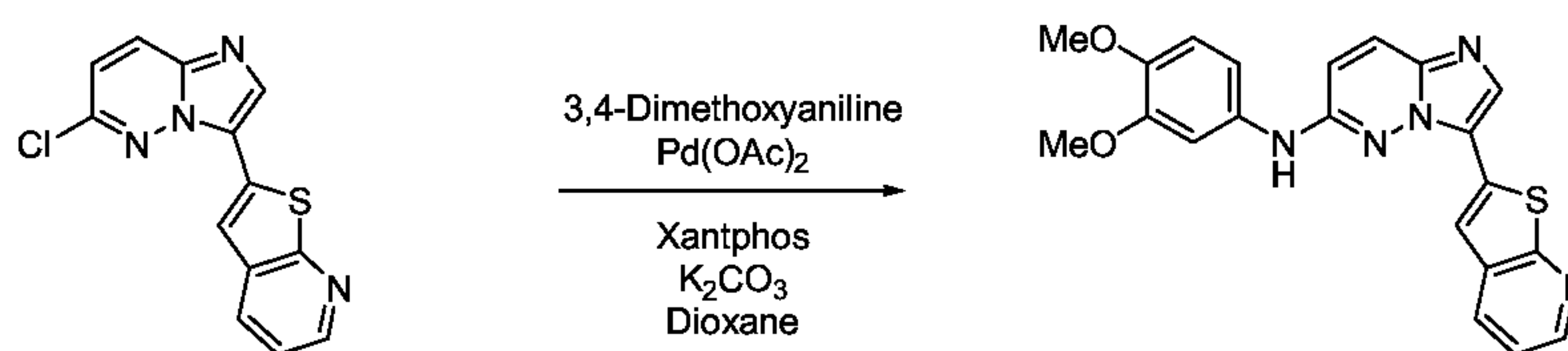


[00550] Preparation of 6-chloro-3-(7-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine



[00551] To a solution of thieno[2,3-b]pyridin-2-yl-2-boronic acid (304 mg, 1.70 mmol, 1.1 equiv) in acetonitrile (14.2 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (396 mg, 1.42 mmol, 1.0 equiv), palladium catalyst (104 mg, 0.142 mmol, 0.1 equiv) and sodium carbonate (14.2 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 350 mg of the yellow solid, 86%.

[00552] Preparation of N-(3,4-dimethoxyphenyl)-3-(thieno[2,3-b]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine



To a solution of 6-chloro-3-(7-methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]pyridazine (58 mg, 0.202 mmol, 1.0 equiv), xantphos (23 mg, 0.0405 mmol, 0.2 equiv), palladium acetate (5 mg, 0.0202 mmol, 0.1 equiv), and potassium carbonate (559 mg, 4.05 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (37 mg, 0.247 mmol, 1.2 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 42 mg, 0.195 mmol of the yellow solid, 52%.

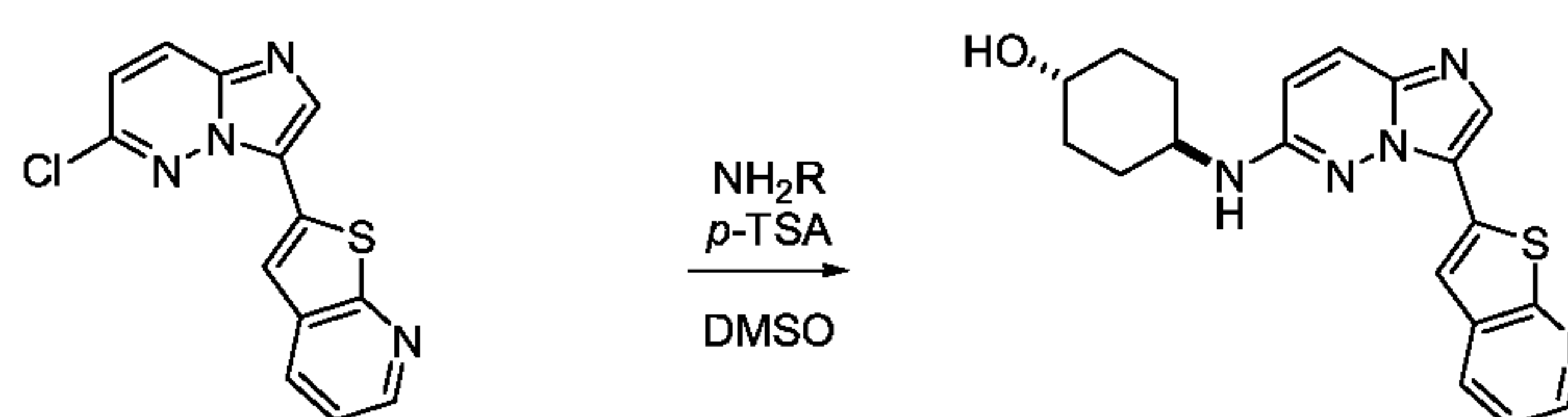
[00553] Compound 204 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table x**.

Table 49

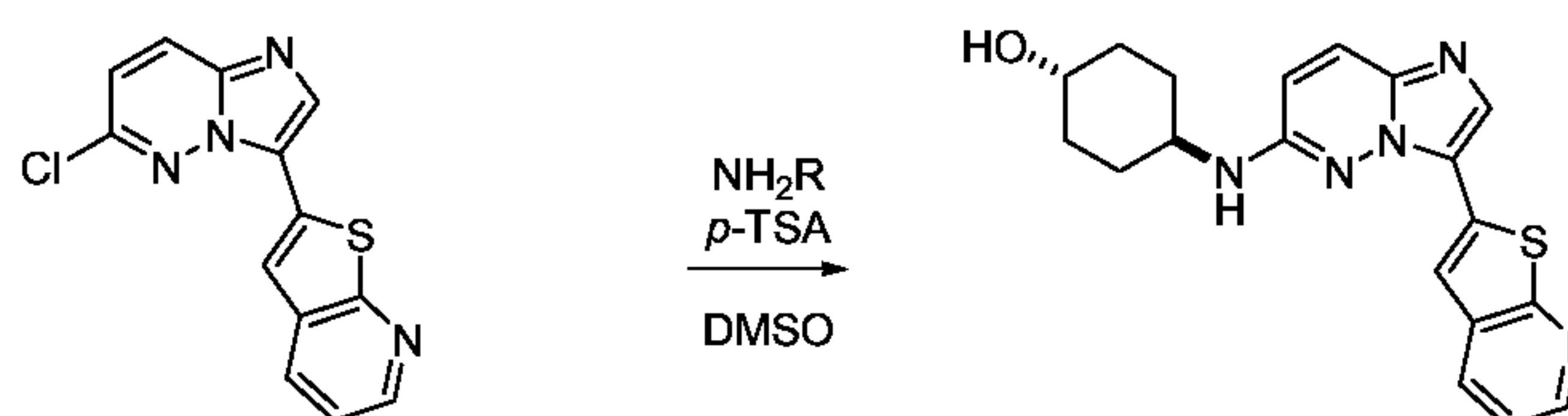
Cd.	Structure	IUPAC Name	[M+H] ⁺
204		N-(3,4-dimethoxyphenyl)-3-(thieno[2,3-b]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	404.3

[00554] Example 50 – Synthesis of Compound 205

[00555] **Scheme 50**



[00556] **Preparation of *trans*-4-(3-(thieno[2,3-b]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol**

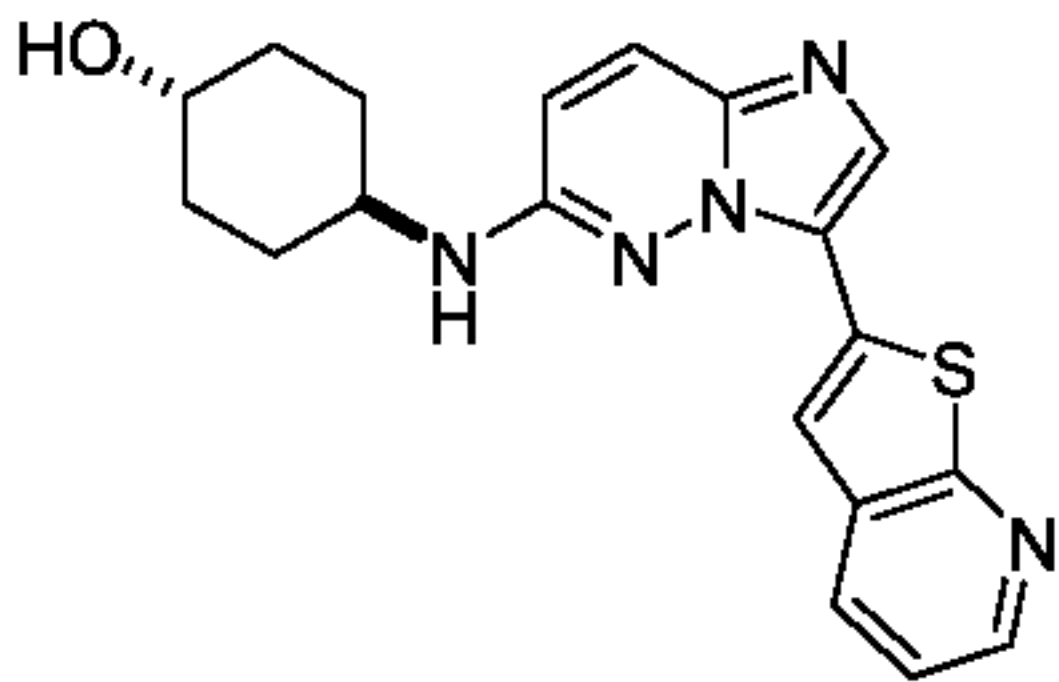


[00557] To a solution of 6-chloro-3-(thieno[2,3-b]pyridin-2-yl)imidazo[1,2-b]pyridazine (45 mg, 0.157 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (22 mg, 0.157 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (0.784 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl

acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 40 mg of the yellow solid, 70%.

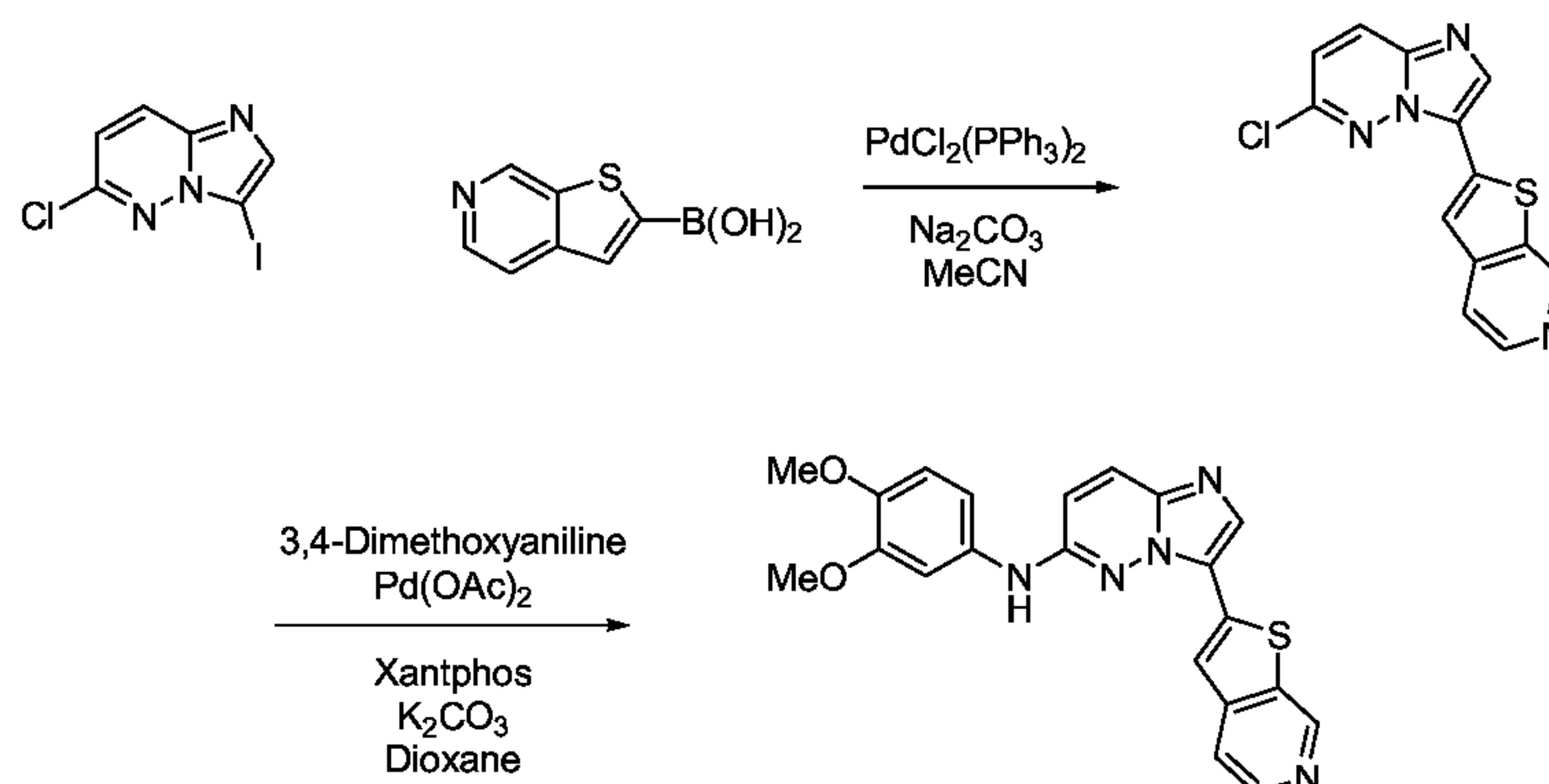
[00558] Compound 205 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 50**.

Table x

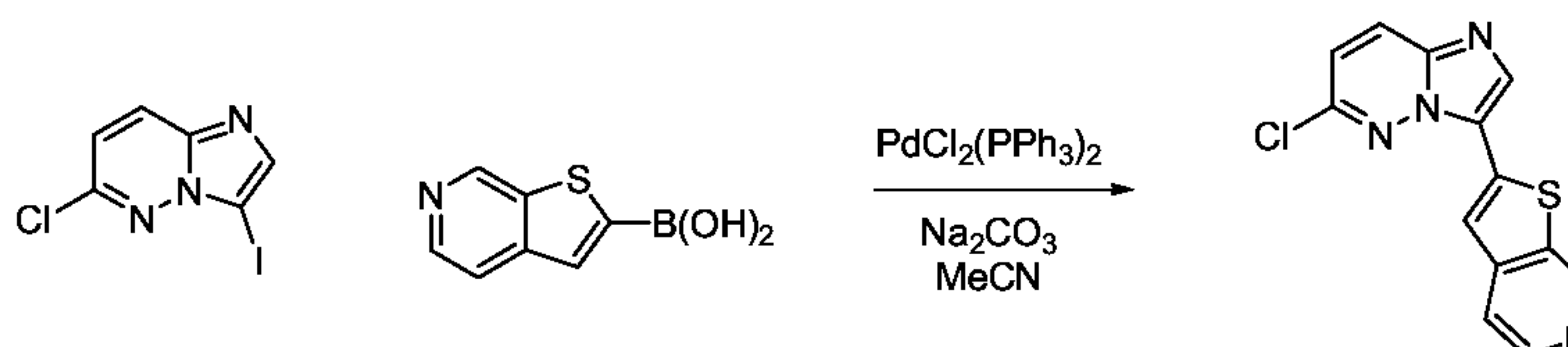
Cd.	Structure	IUPAC Name	[M+H] ⁺
205		<i>trans</i> -4-(3-(thieno[2,3-b]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	366.2

[00559] Example 51 – Synthesis of Compound 218

[00560] **Scheme 51**

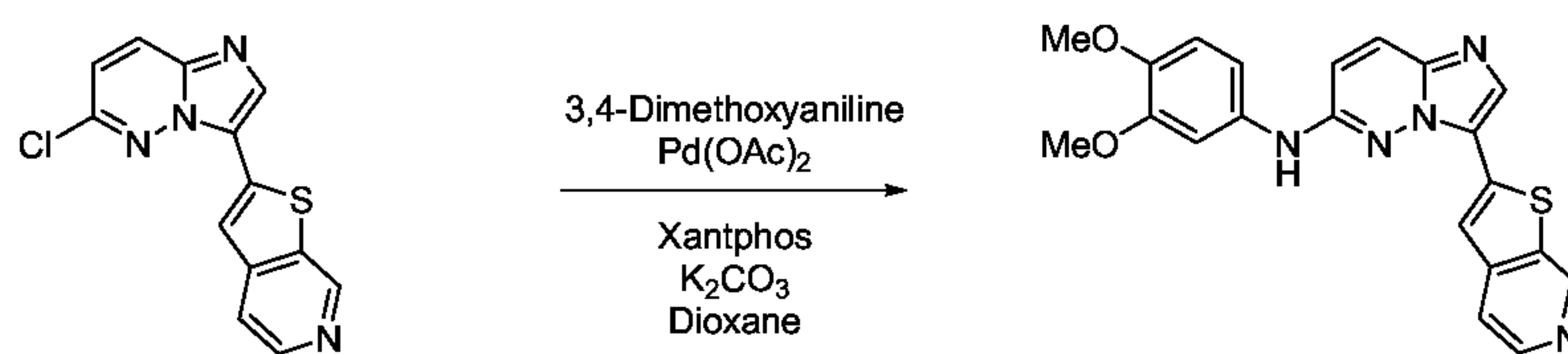


[00561] **Preparation of 6-chloro-3-(thieno[2,3-c]pyridin-2-yl)imidazo[1,2-b]pyridazine**



[00562] To a solution of thieno[2,3-c]pyridin-2-yl-2-boronic acid (265 mg, 1.48 mmol, 1.0 equiv) in acetonitrile (14.8 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (414 mg, 1.48 mmol, 1.0 equiv), palladium catalyst (108 mg, 0.148 mmol, 0.1 equiv) and sodium carbonate (14.8 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 200 mg of the white solid, 47%.

[00563] **Preparation of N-(3,4-dimethoxyphenyl)-3-(thieno[2,3-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine**



[00564] To a solution of 6-chloro-3-(thieno[2,3-c]pyridin-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.174 mmol, 1.0 equiv), xantphos (20 mg, 0.0349 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0174 mmol, 0.1 equiv), and potassium carbonate (482 mg, 3.49 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (35 mg, 0.227 mmol, 1.3 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 38 mg, of the yellow solid, 54%.

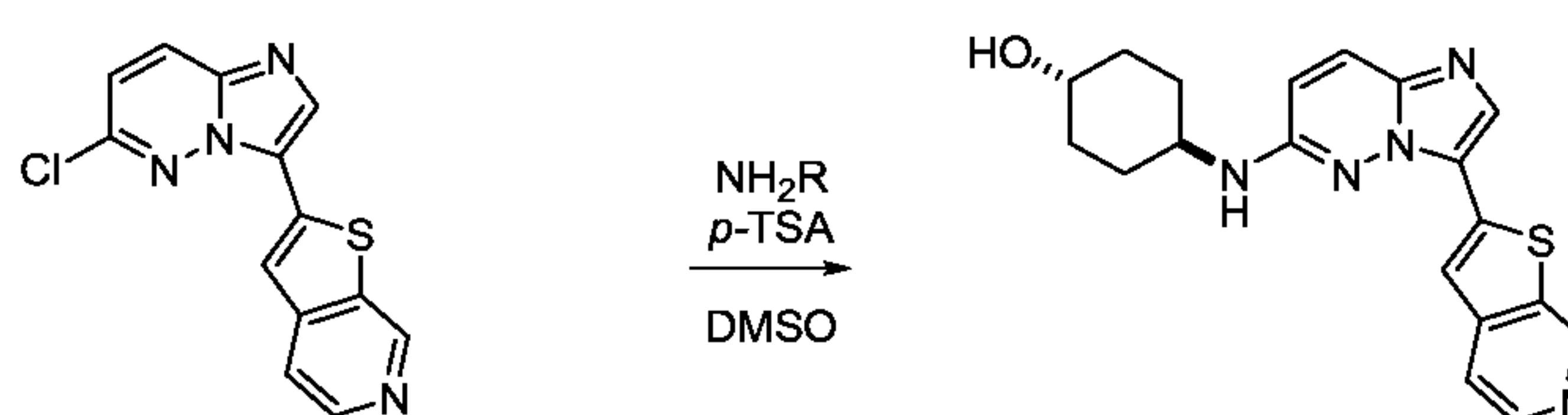
[00565] Compound 218 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 51**.

Table 51

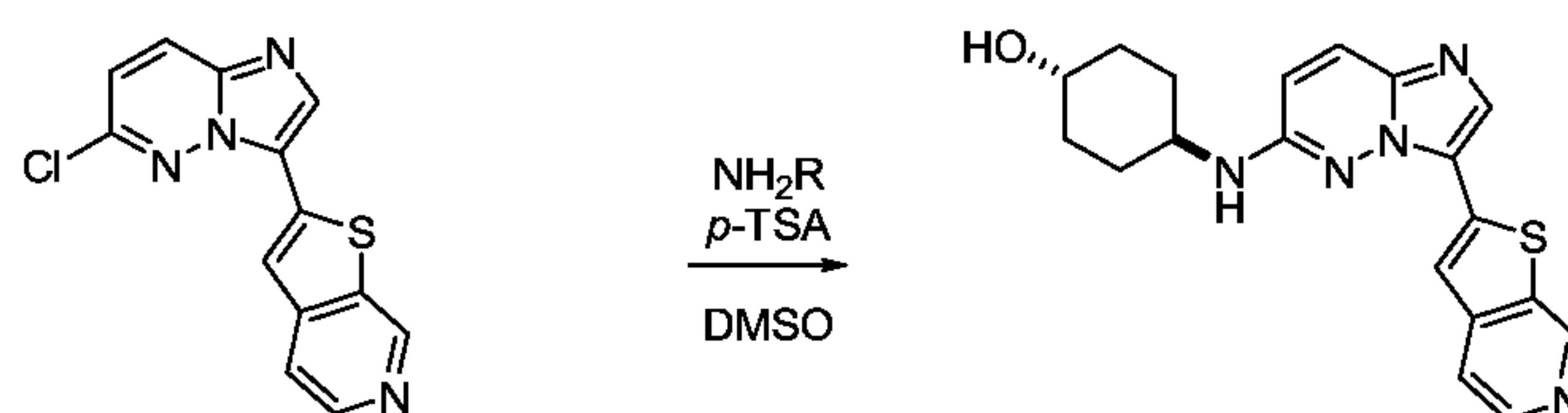
Cd.	Structure	IUPAC Name	[M+H] ⁺
218		N-(3,4-dimethoxyphenyl)-3-(thieno[2,3-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	404.5

[00566] Example 52 – Synthesis of Compound 219

[00567] **Scheme 52**



[00568] **Preparation of *trans*-4-(3-(thieno[2,3-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol**

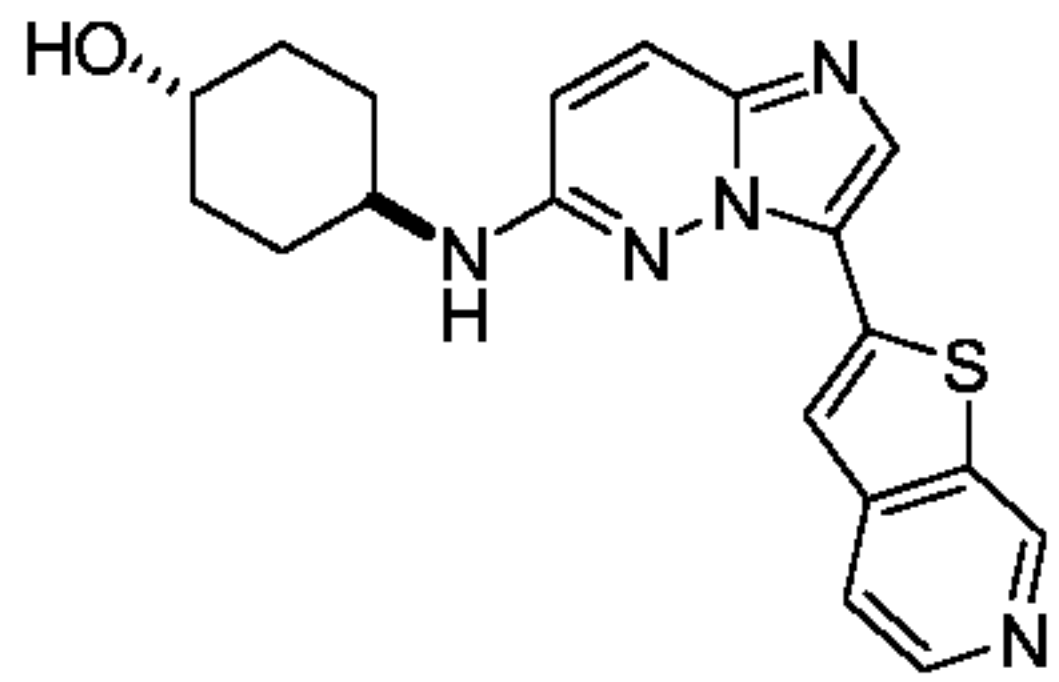


[00569] To a solution of 6-chloro-3-(thieno[2,3-c]pyridin-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.174 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (25 mg, 0.174 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (0.870 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl

acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 42 mg of the yellow solid, 67%.

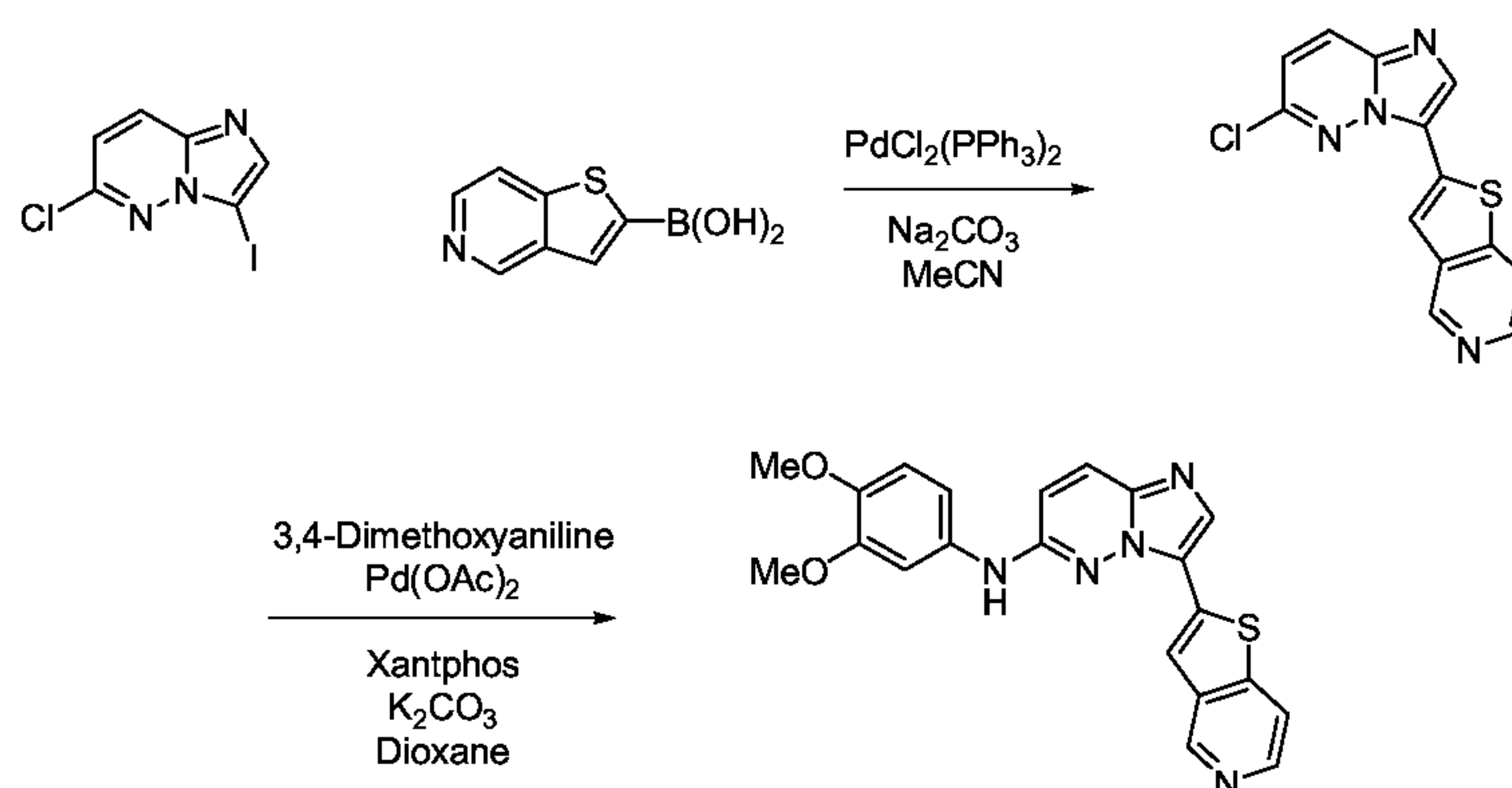
[00570] Compound 219 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 52.

Table 52

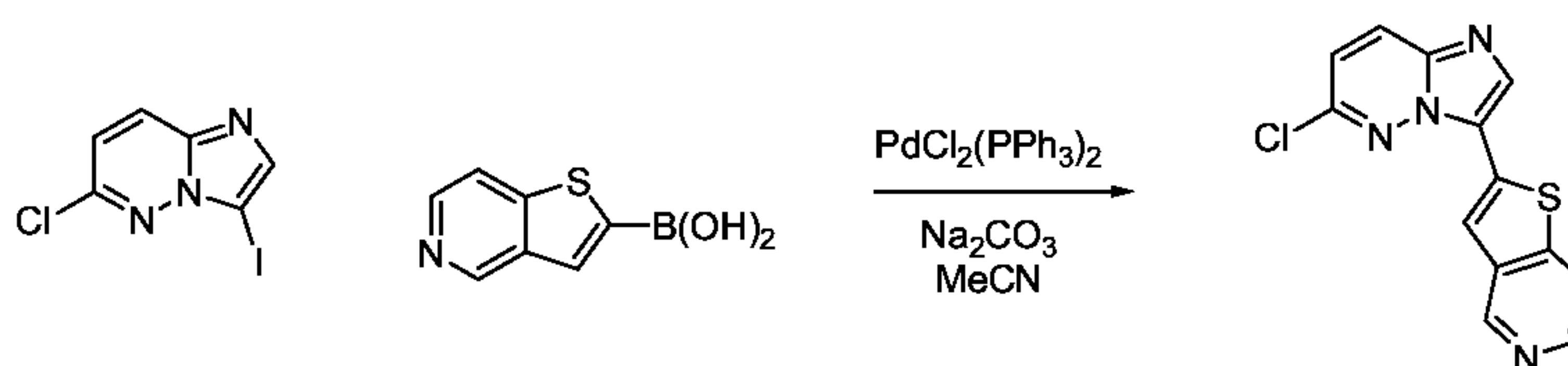
Cd.	Structure	IUPAC Name	[M+H] ⁺
219		<i>trans</i> -4-(3-(thieno[2,3-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	366.7

[00571] Example X – Synthesis of Compound 206

[00572] **Scheme 52**

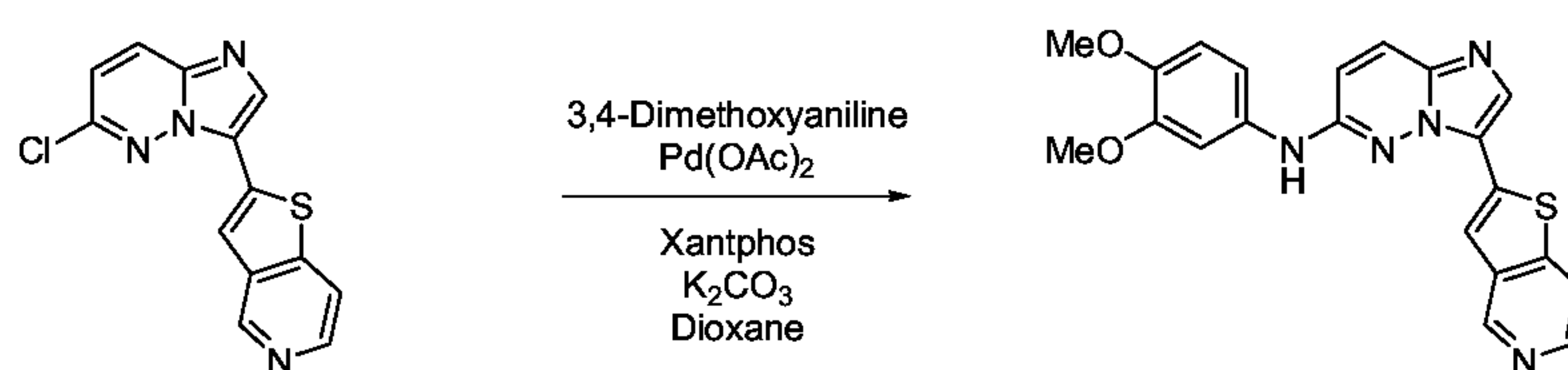


[00573] **Preparation of 6-chloro-3-(thieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazine**



[00574] To a solution of thieno[3,2-c]pyridin-2-yl-2-boronic acid (104 mg, 0.580 mmol, 1.1 equiv) in acetonitrile (5.28 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (148 mg, 0.528 mmol, 1.0 equiv), palladium catalyst (39 mg, 0.0529 mmol, 0.1 equiv) and sodium carbonate (5.28 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 101 mg of the yellow solid, 67%.

[00575] **Preparation of N-(3,4-dimethoxyphenyl)-3-(thieno[2,3-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine**



[00576] To a solution of N-(3,4-dimethoxyphenyl)-3-(thieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine (44 mg, 0.153 mmol, 1.0 equiv), xantphos (18 mg, 0.0306 mmol, 0.2 equiv), palladium acetate (3 mg, 0.0153 mmol, 0.1 equiv), and potassium carbonate (424 mg, 3.07 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (28 mg, 0.184 mmol, 1.2 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 38 mg, of the yellow solid, 62%.

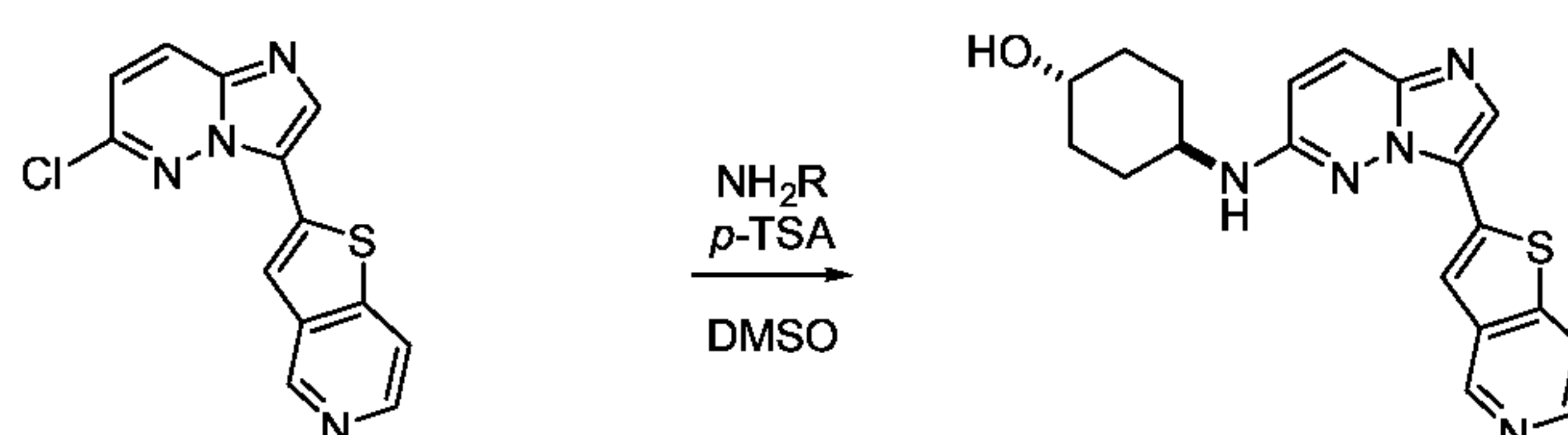
[00577] Compound 206 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 52**.

Table 52

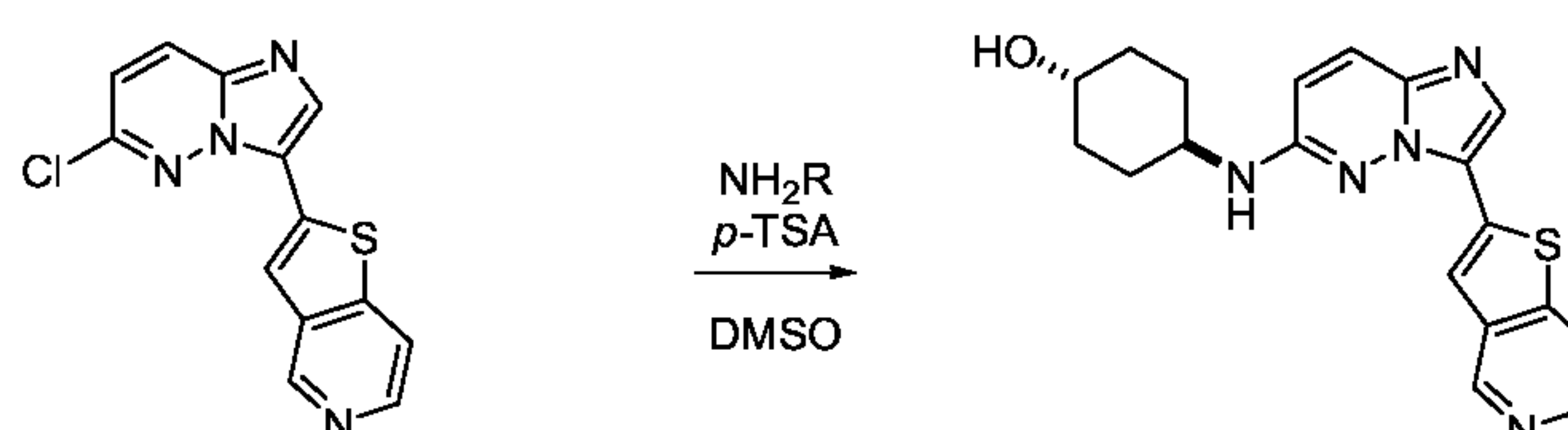
Cd.	Structure	IUPAC Name	[M+H] ⁺
206		N-(3,4-dimethoxyphenyl)-3-(thieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	404.1

[00578] Example 53 – Synthesis of Compound 207

[00579] **Scheme 53**



[00580] Preparation of *trans*-(3-(thieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

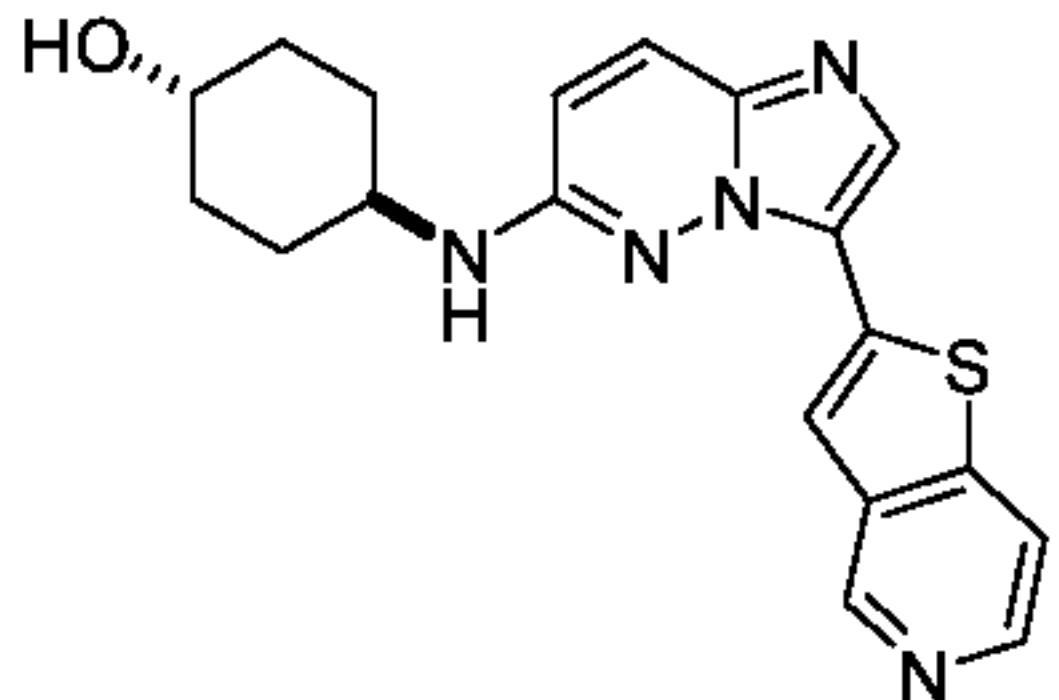


[00581] To a solution of 6-chloro-3-(thieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.174 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (25 mg, 0.174 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (0.870 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl

acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 40 mg of the yellow solid, 63%.

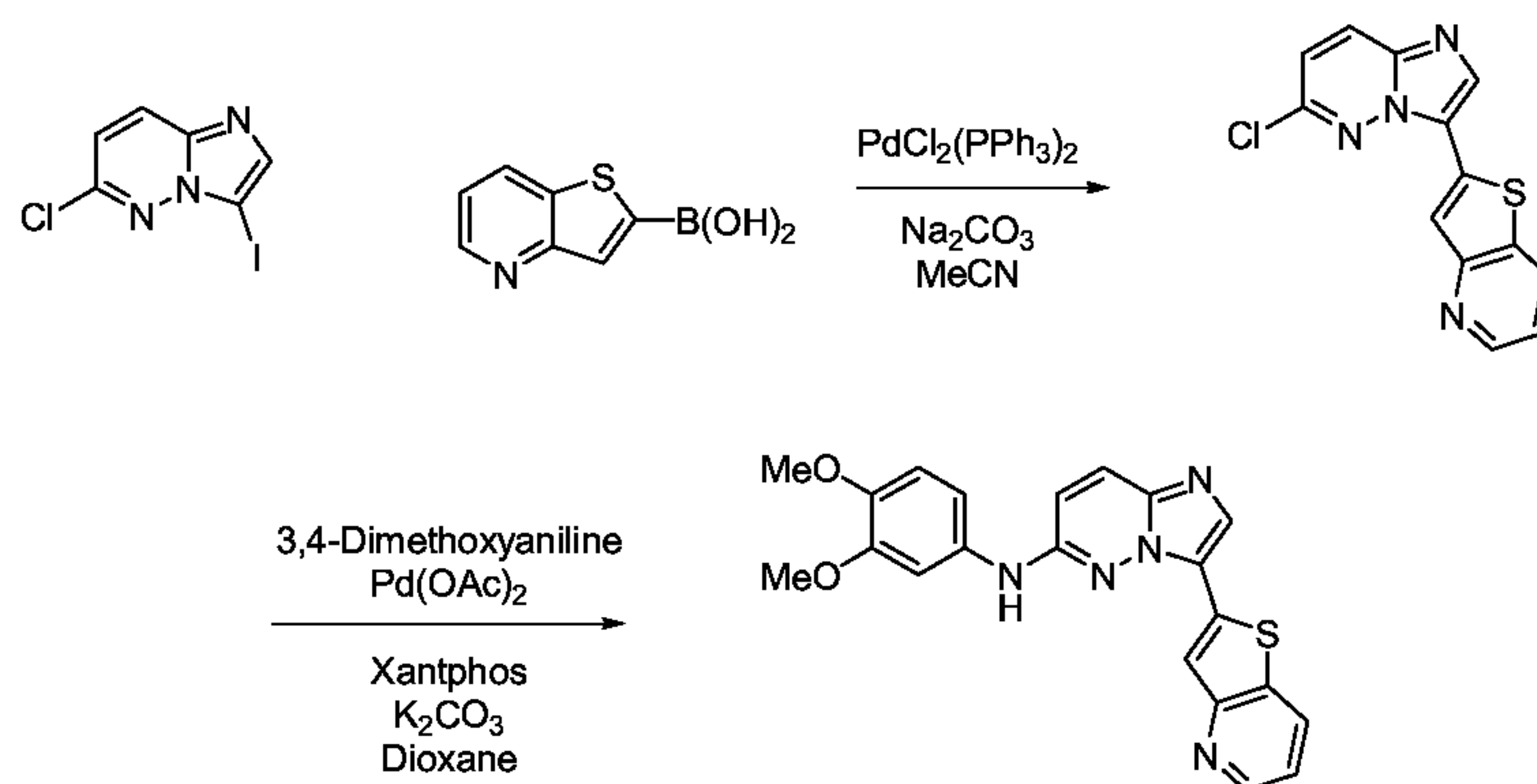
[00582] Compound 207 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 53**.

Table 53

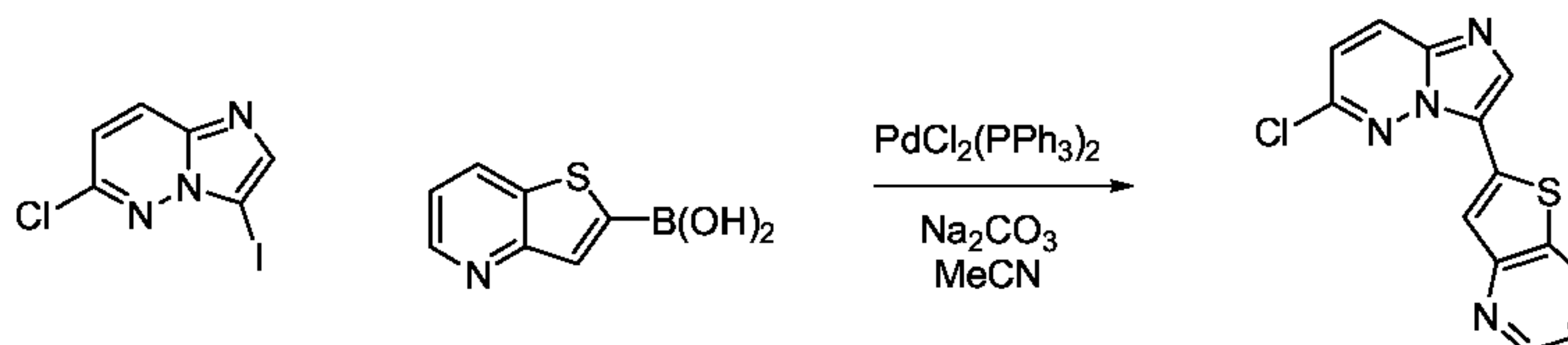
Cd.	Structure	IUPAC Name	[M+H] ⁺
207		<i>trans</i> -(3-(thieno[3,2-b]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	366.5

[00583] Example 54 – Synthesis of Compound 208

[00584] **Scheme 54**

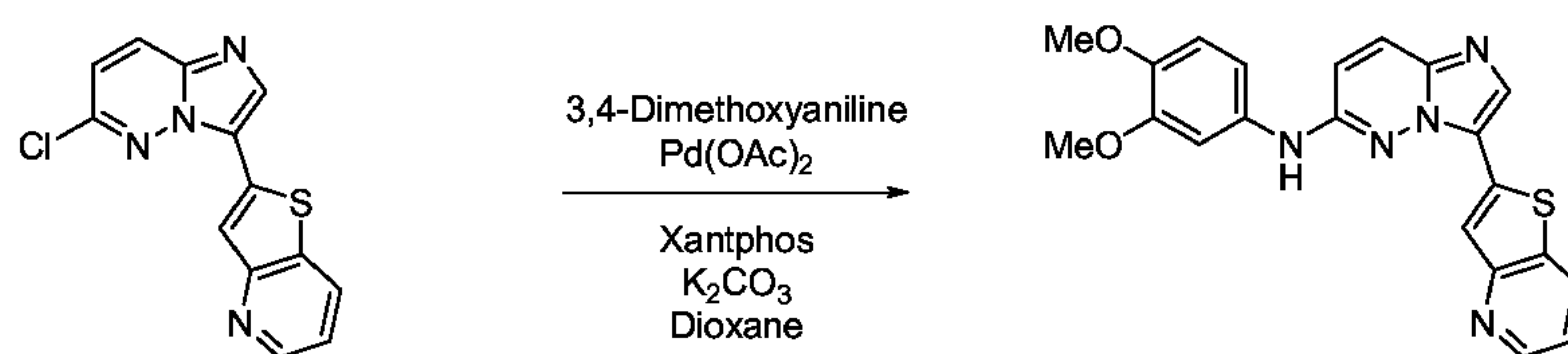


[00585] **Preparation of 6-chloro-3-(thieno[3,2-b]pyridin-2-yl)imidazo[1,2-b]pyridazine**



[00586] To a solution of thieno[3,2-b]pyridin-2-yl-2-boronic acid (104 mg, 0.580 mmol, 1.1 equiv) in acetonitrile (5.28 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (148 mg, 0.528 mmol, 1.0 equiv), palladium catalyst (39 mg, 0.0529 mmol, 0.1 equiv) and sodium carbonate (5.28 mL, 1.0 M, 10.0 equiv). The solution was stirred at 150 °C in the microwave for 10 minutes. Purification using column chromatography gave 95 mg of the yellow solid, 63%.

[00587] **Preparation of N-(3,4-dimethoxyphenyl)-3-(thieno[3,2-b]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine**



[00588] To a solution of 6-chloro-3-(thieno[3,2-b]pyridin-2-yl)imidazo[1,2-b]pyridazine (50 mg, 0.174 mmol, 1.0 equiv), xantphos (20 mg, 0.0348 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0174 mmol, 0.1 equiv), and potassium carbonate (482 mg, 3.49 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (32 mg, 0.209 mmol, 1.2 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 35 mg, of the yellow solid, 50%.

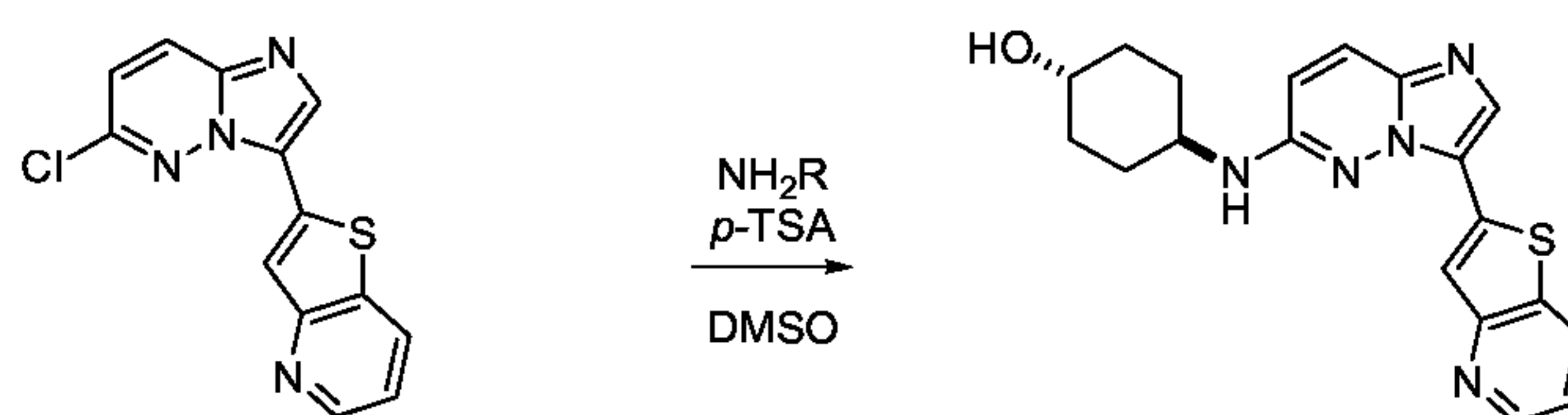
[00589] Compound 208 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 54**.

Table 54

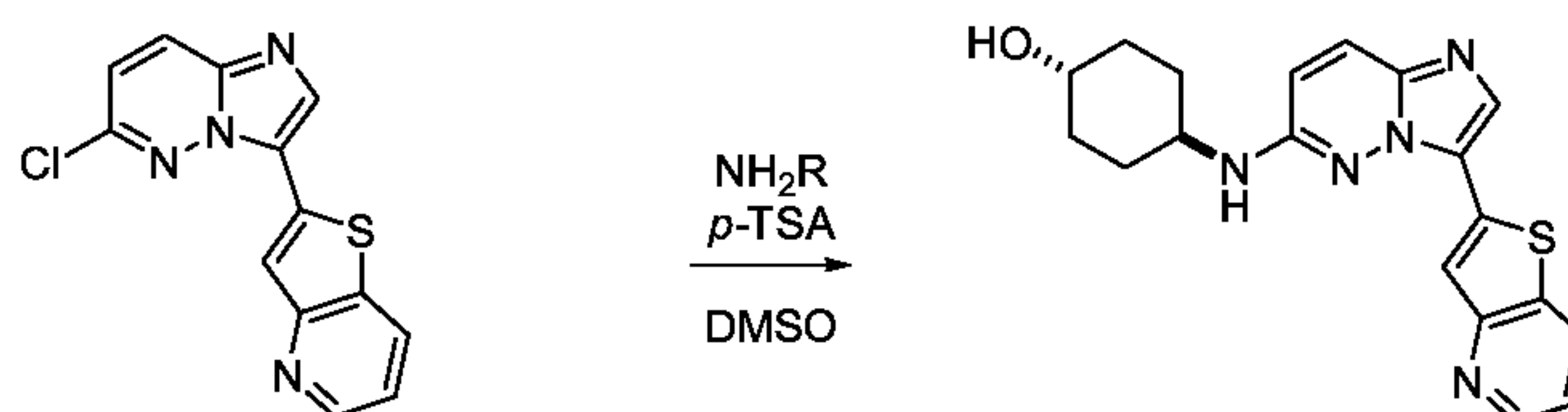
Cd.	Structure	IUPAC Name	[M+H] ⁺
208		N-(3,4-dimethoxyphenyl)-3-(thieno[3,2-b]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	404.5

[00590] Example 55 – Synthesis of Compound 209

[00591] **Scheme 55**



[00592] Preparation of *trans*-4-(3-(thieno[3,2-b]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol

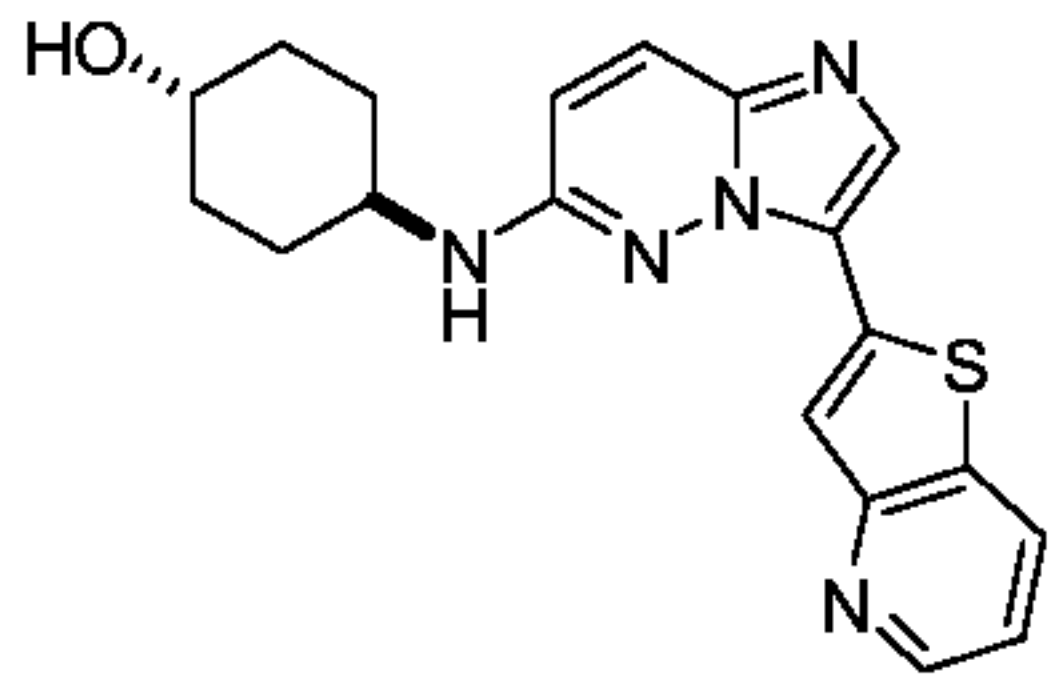


[00593] To a solution of 6-chloro-3-(thieno[3,2-b]pyridin-2-yl)imidazo[1,2-b]pyridazine (40 mg, 0.139 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (20 mg, 0.139 mmol, 1.0 equiv) and *trans*-4-aminocyclohexanol (0.695 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl

acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 40 mg of the yellow solid, 79%.

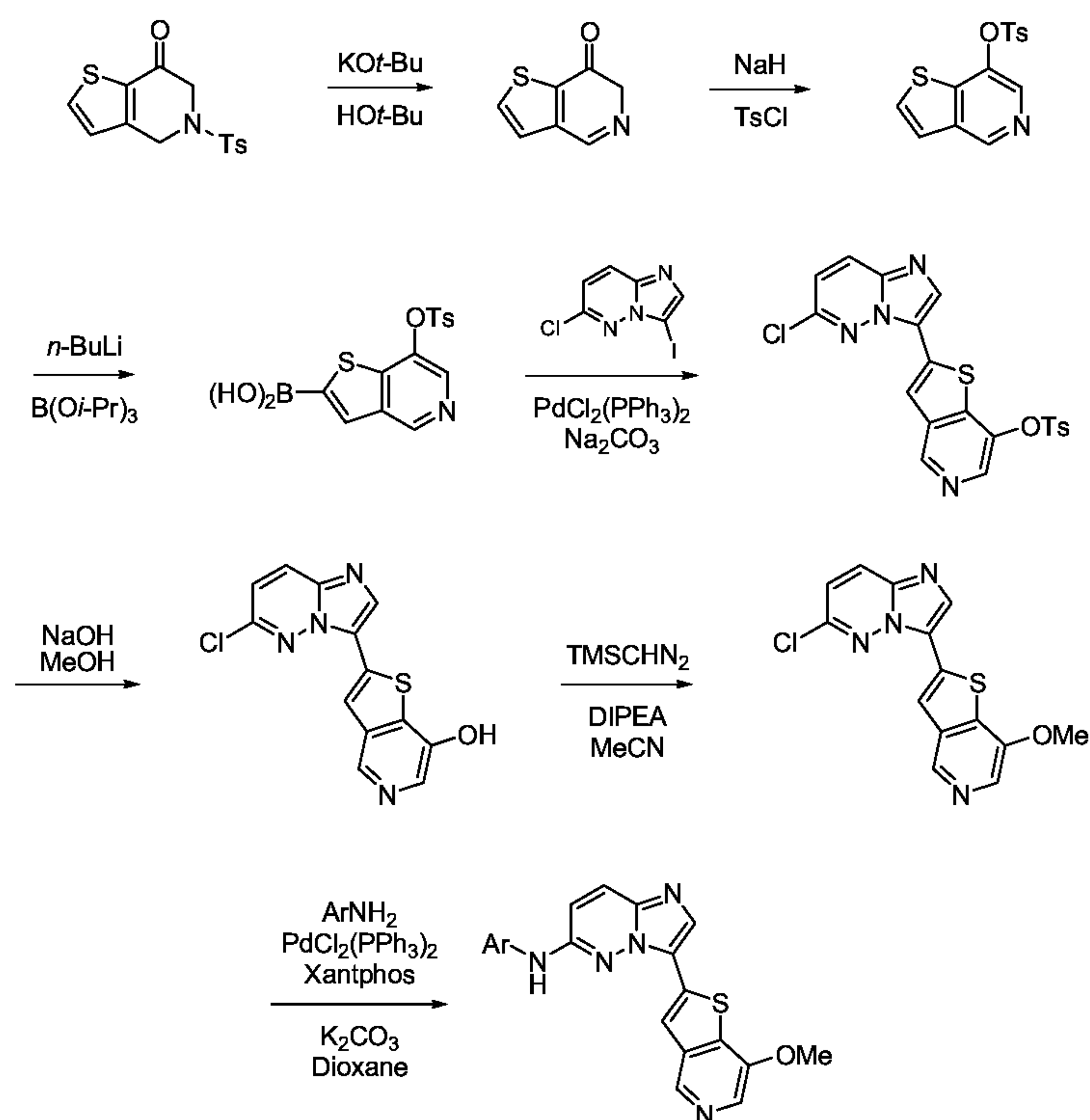
[00594] Compound 209 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 55**.

Table 55

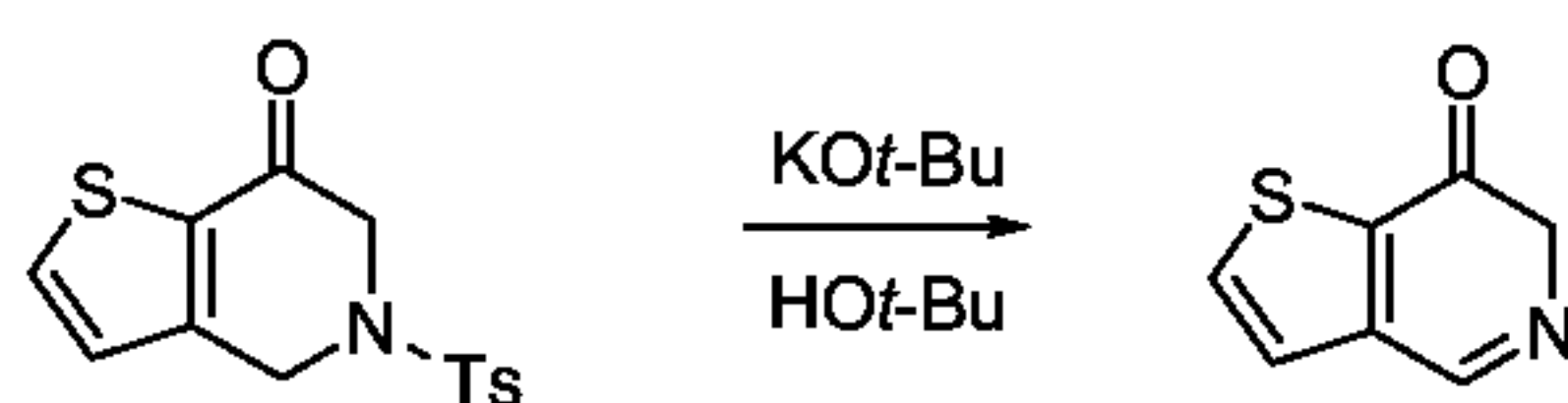
Cd.	Structure	IUPAC Name	[M+H] ⁺
209		<i>trans</i> -4-(3-(thieno[3,2-b]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	366.5

[00595] Example 56 – Synthesis of Compound 210

[00596] **Scheme 56**



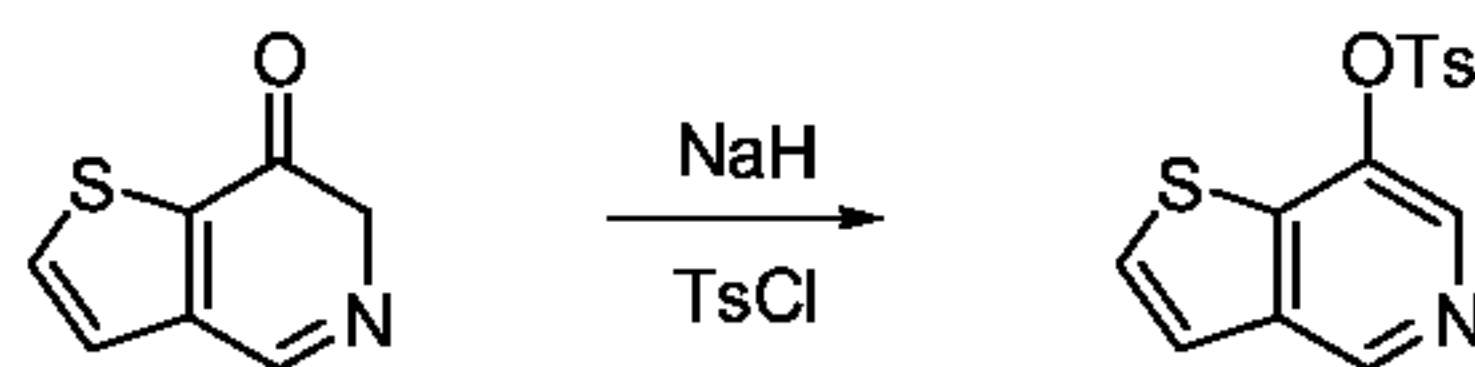
[00597] **Preparation of thieno[3,2-c]pyridin-7(6H)-one**



[00598] To a solution of 5,6-dihydro-5-tosylthieno[3,2-c]pyridin-7(4H)-one (1.24 g, 4.03 mmol, 1.0 equiv) in HOT-Bu (15.0 mL) was added KOt-Bu (904 mg, 8.06 mmol, 2.0 equiv) and heated to reflux for 2 h. The mixture was quenched with water and then extracted with ethyl

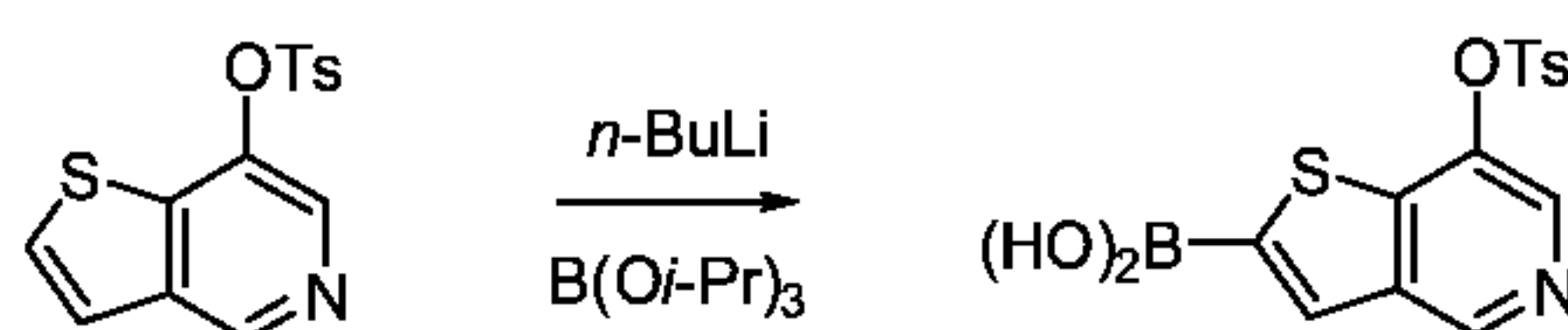
acetate. Purification by column chromatography using 50% ethyl acetate in hexanes elution gave 1.09 g of white solid, 89%.

[00599] Preparation of thieno[3,2-c]pyridin-7-yl 4-methylbenzenesulfonate



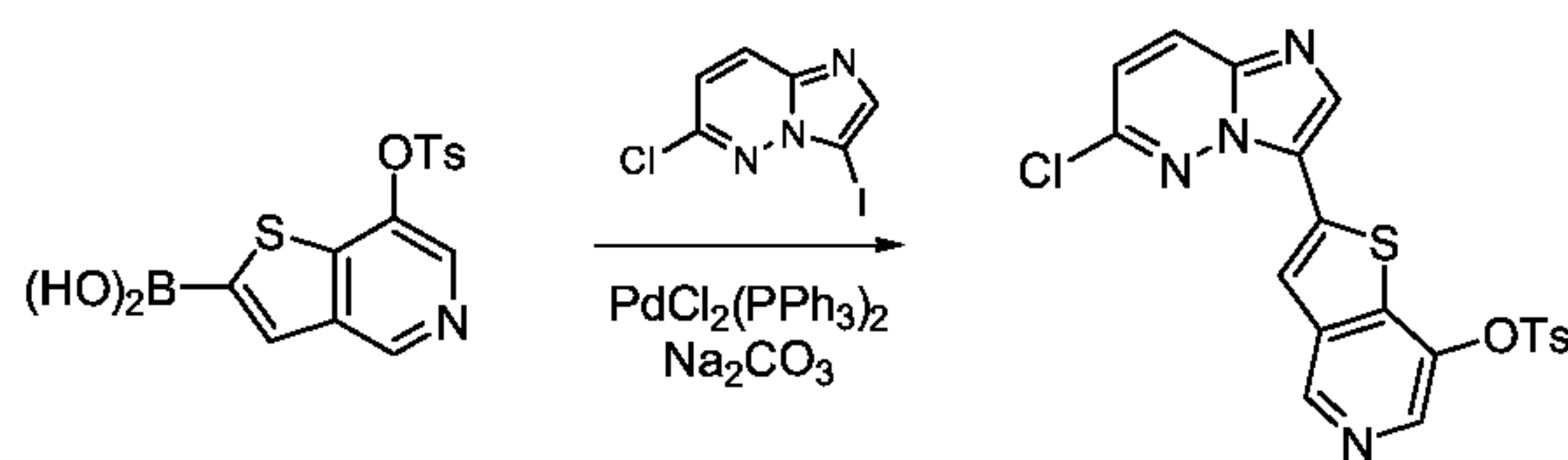
[00600] To a solution of thieno[3,2-c]pyridin-7(6H)-one (110 mg, 0.728 mmol, 1.0 equiv) in THF (5.00 mL) was added NaH (35 mg, 0.873 mmol, 1.2 equiv) followed by TsCl (180 mg, 0.946 mmol, 1.3 equiv). The reaction mixture was stirred at rt for 2 h, then quenched with water and extracted with ethyl acetate. Purification by column chromatography using 20% ethyl acetate in hexanes elution gave 180 mg of a white solid, 81%.

[00601] Preparation of 7-(4-methylbenzenesulfonyl)thieno[3,2-c]pyridin-2-yl-2-boronic acid



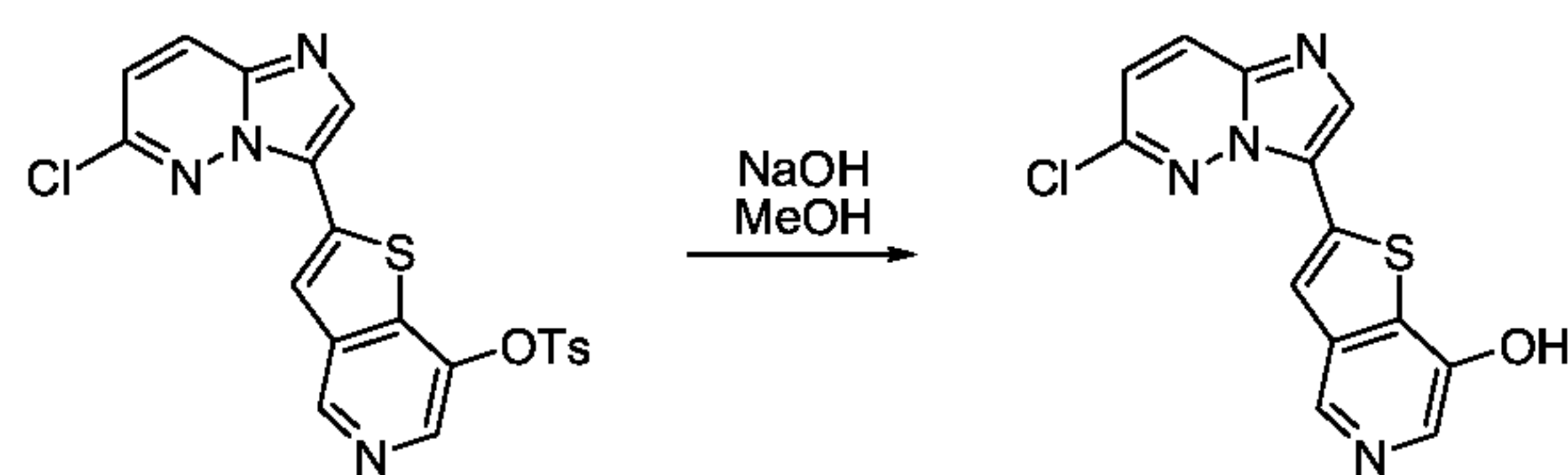
[00602] To a solution of thieno[3,2-c]pyridin-7-yl 4-methylbenzenesulfonate (1.18 g, 3.86 mmol, 1.0 equiv) in THF (20.0 mL) at -78 °C was added *n*-BuLi (3.62 mL, 5.80 mmol, 1.5 equiv). The reaction was stirred at the reduced temperature for 1 h, then triisopropylborate (1.34 mL, 5.80 mmol, 1.5 equiv) was added and stirred at rt for 2 h. The mixture was quenched with 2N HCl and then extracted with ethyl acetate. Purification by column chromatography using 2% methanol in dichloromethane elution gave 800 mg of white solid, 59%.

[00603] Preparation of 2-(6-chloroimidazo[1,2-b]pyridazin-3-yl)thieno[3,2-c]pyridin-7-yl 4-methylbenzenesulfonate



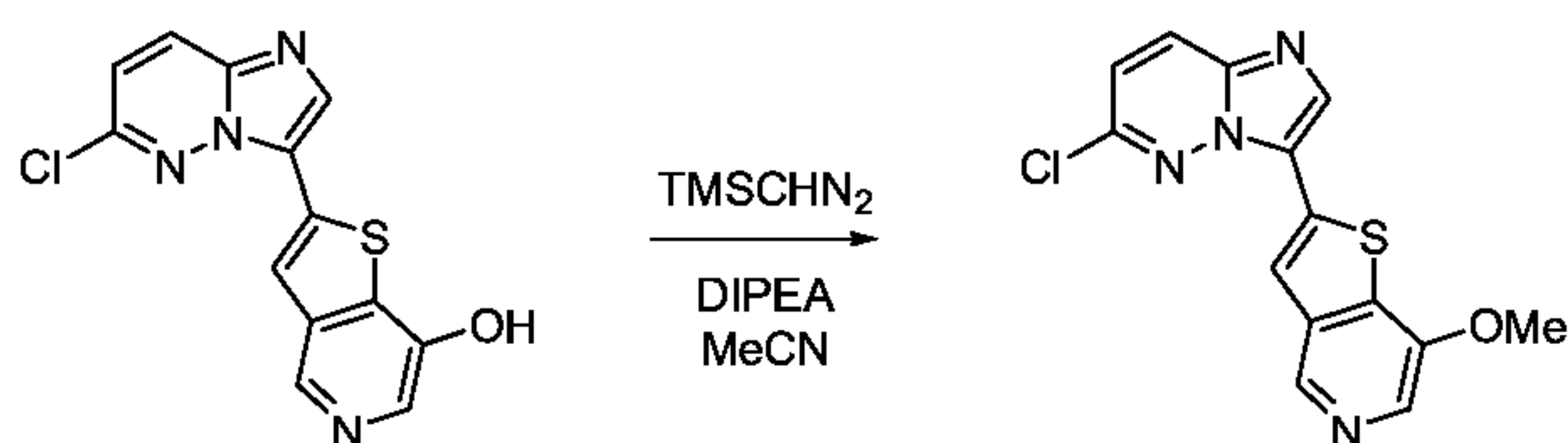
[00604] To a solution of 7-(4-methylbenzenesulfonyl)thieno[3,2-c]pyridin-2-yl-2-boronic acid (650 mg, 1.69 mmol, 1.1 equiv) in acetonitrile (16 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (473 mg, 1.69 mmol, 1.0 equiv), palladium catalyst (124 mg, 0.169 mmol, 0.1 equiv) and sodium carbonate (16.9 mL, 1.0 M, 10.0 equiv). The solution was stirred in the microwave at 150 °C for 10 min. Purification using column chromatography gave 600 mg of the yellow product, 78%.

[00605] Preparation of 2-(6-chloroimidazo[1,2-b]pyridazin-3-yl)thieno[3,2-c]pyridin-7-ol



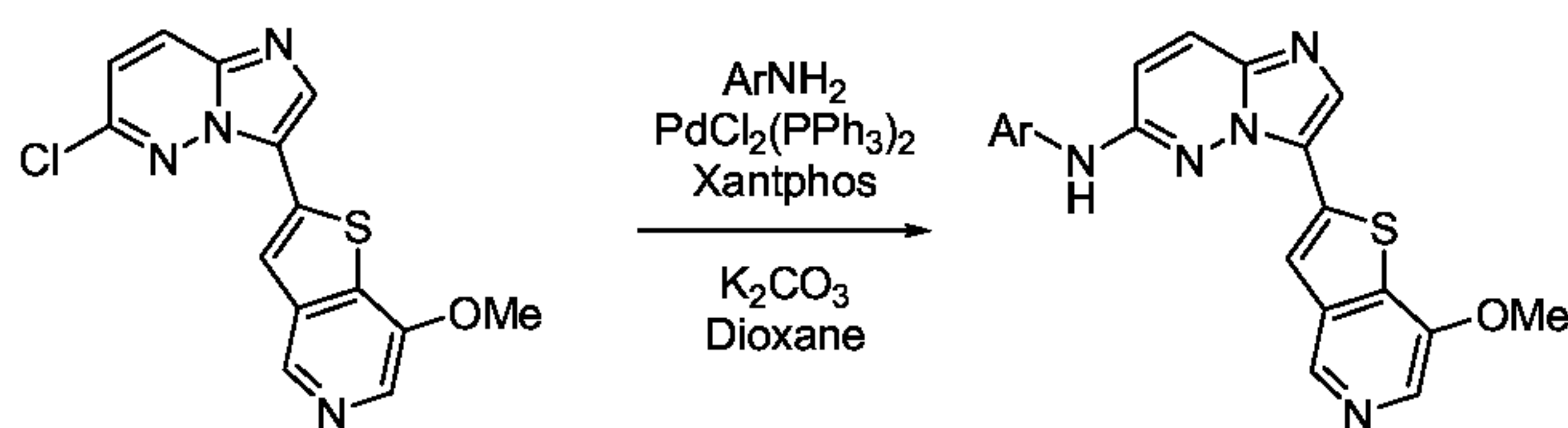
[00606] To a solution of 2-(6-chloroimidazo[1,2-b]pyridazin-3-yl)thieno[3,2-c]pyridin-7-yl 4-methylbenzenesulfonate (200 mg, 0.349 mmol, 1.0 equiv) in MeOH (5.0 mL) was added sodium hydroxide (70 microliter, 5.0 M aqueous solution, 1.0 equiv). The reaction mixture was stirred at rt for 3 h, then quenched with water and extracted with ethyl acetate. Purification using column chromatography gave 80 mg of the white product, 76%.

[00607] Preparation of 6-chloro-3-(7-methoxythieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazine



[00608] To a solution of 2-(6-chloroimidazo[1,2-b]pyridazin-3-yl)thieno[3,2-c]pyridin-7-ol (38 mg, 0.126 mmol, 1.0 equiv) in DCM (3.0 mL) and MeOH (1.0 mL) was added DIPEA (0.188 mmol, 1.5 equiv) then TMSCHN₂ (94 microliter, 0.188 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 3 h, then quenched with water and extracted with ethyl acetate. Purification by column chromatography using 20% ethyl acetate in hexanes elution gave 20 mg of the yellow solid, 50%.

[00609] Preparation of 3-(7-methoxythieno[3,2-c]pyridin-2-yl)-N-arylimidazo[1,2-b]pyridazin-6-amine



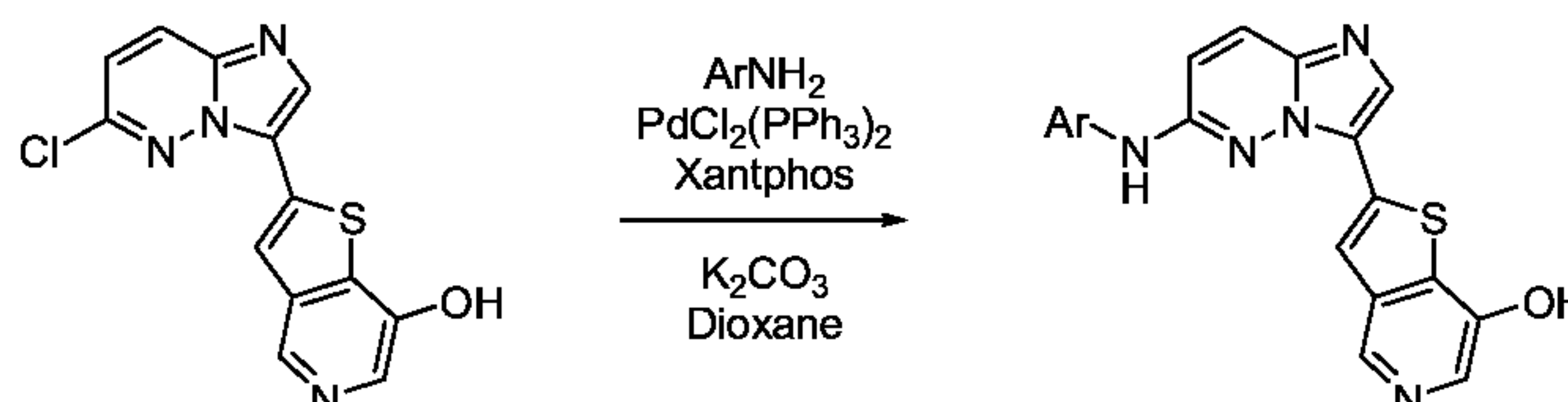
[00610] To a solution of 6-chloro-3-(7-methoxythieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazine (30 mg, 0.095 mmol, 1.0 equiv), xantphos (11 mg, 0.0189 mmol, 0.2 equiv), palladium acetate (2 mg, 0.0947 mmol, 0.1 equiv), and potassium carbonate (261 mg, 1.89 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (22 mg, 0.142 mmol, 1.5 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 28 mg, of the yellow solid, 68%.

[00611] Compound 210 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 56**.

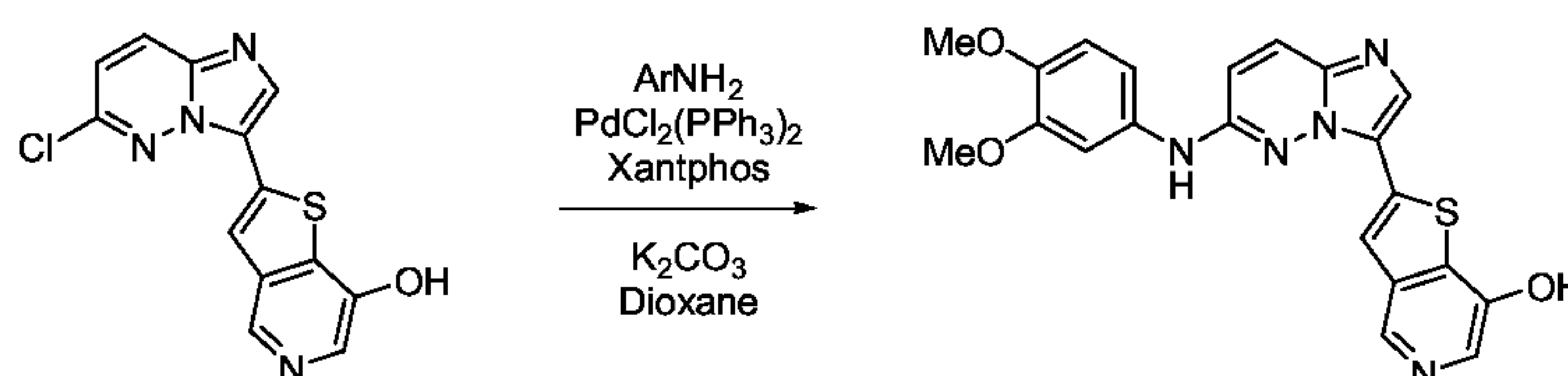
Cd.	Structure	IUPAC Name	[M+H] ⁺
210		N-(3,4-dimethoxyphenyl)-3-(7-methoxythieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	434.0

[00612] Example 57 – Synthesis of Compound 211

[00613] **Scheme 57**



[00614] **Preparation of 2-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)thieno[3,2-c]pyridin-7-ol**



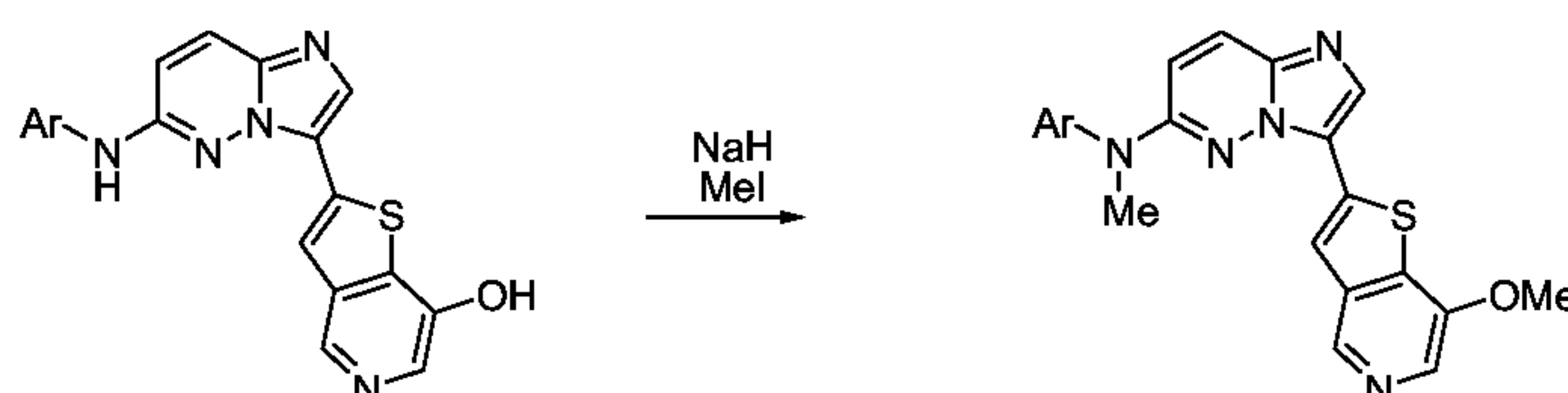
[00615] To a solution of 2-(6-chloroimidazo[1,2-b]pyridazin-3-yl)thieno[3,2-c]pyridin-7-ol (50 mg, 0.165 mmol, 1.0 equiv), xantphos (19 mg, 0.0330 mmol, 0.2 equiv), palladium acetate (4 mg, 0.0165 mmol, 0.1 equiv), and potassium carbonate (456 mg, 3.30 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (38 mg, 0.248 mmol, 1.5 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 30 mg, of the brown solid, 43%.

[00616] Compound 211 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 57**.

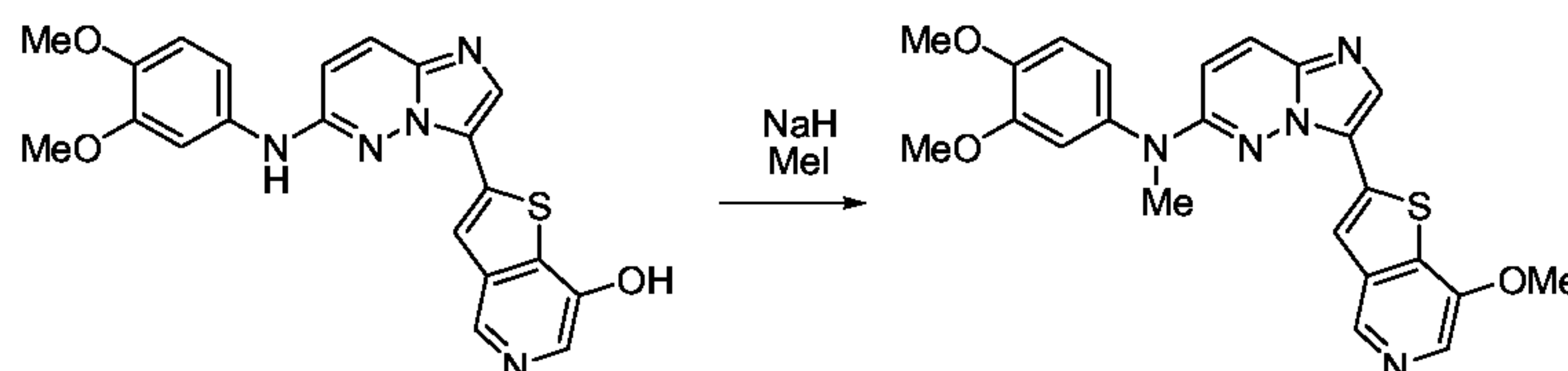
Cd.	Structure	IUPAC Name	[M+H] ⁺
211		2-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)thieno[3,2-c]pyridin-7-ol	420.5

[00617] Example 58 – Synthesis of Compound 212

[00618] **Scheme 58**



[00619] Preparation of N-(3,4-dimethoxyphenyl)-3-(7-methoxythieno[3,2-c]pyridin-2-yl)-N-methylimidazo[1,2-b]pyridazin-6-amine



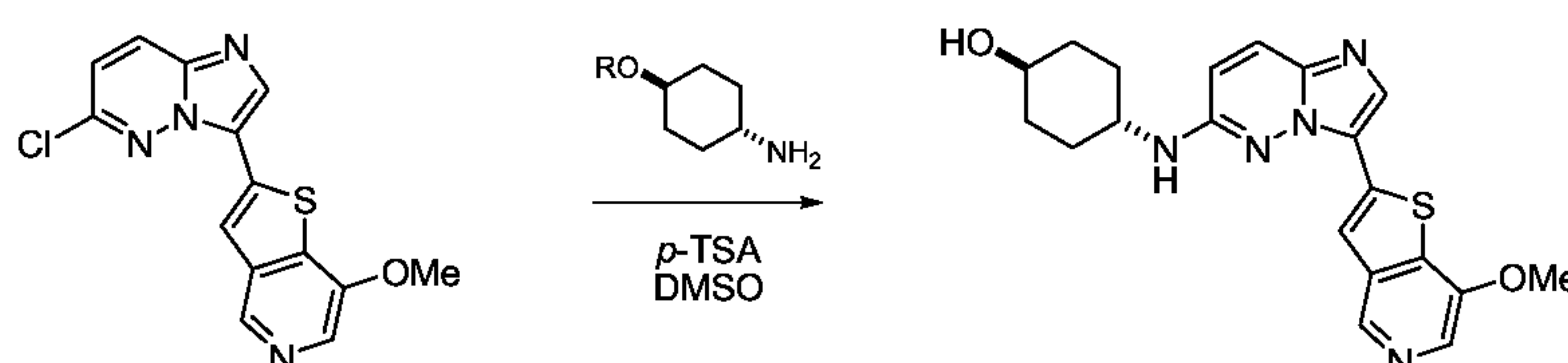
[00620] To a solution of 2-(6-(3,4-dimethoxyphenylamino)imidazo[1,2-b]pyridazin-3-yl)thieno[3,2-c]pyridin-7-ol (10 mg, 0.0238 mmol, 1.0 equiv) in THF (3.00 mL) was added NaH (30 mg, 0.750 mol, 31.5 equiv) then iodomethane (100 mg, 0.705 mmol, 30.0 equiv). The reaction mixture was stirred at rt for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 10 mg, of the yellow solid, 94%.

[00621] Compound 212 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 58**.

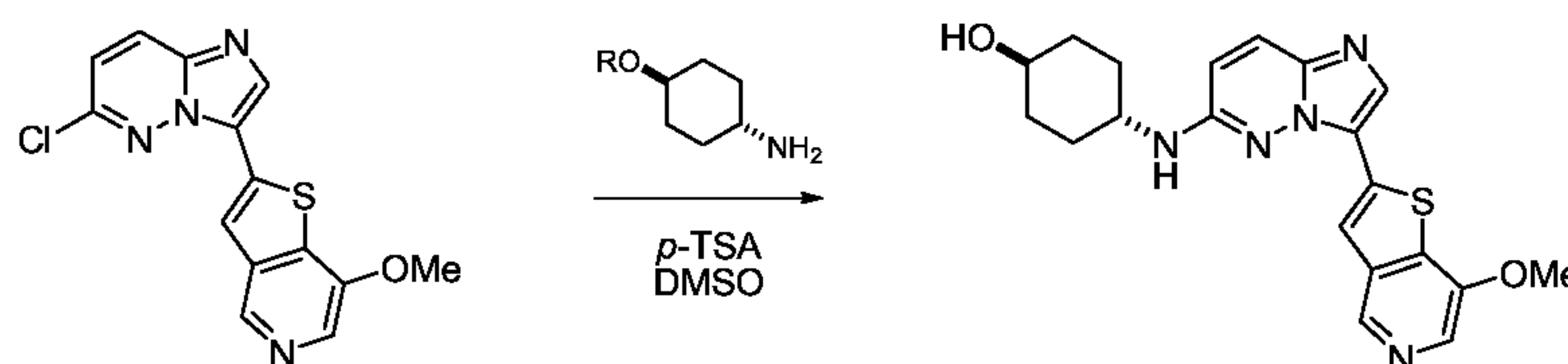
58.	Structure	IUPAC Name	[M+H] ⁺
212		N-(3,4-dimethoxyphenyl)-3-(7-methoxythieno[3,2-c]pyridin-2-yl)-N-methylimidazo[1,2-b]pyridazin-6-amine	448.1

[00622] Example X – Synthesis of Compound 213, 217

[00623] **Scheme 59**



[00624] **Preparation of N-Alkyl-3-(7-methoxythieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine**



[00625] To a solution of 6-chloro-3-(7-methoxythieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazine (20 mg, 0.0631 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (12 mg, 0.0631 mmol, 1.0 equiv) and amine (36 mg, 0.316 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 20 mg of the yellow solid, 80%.

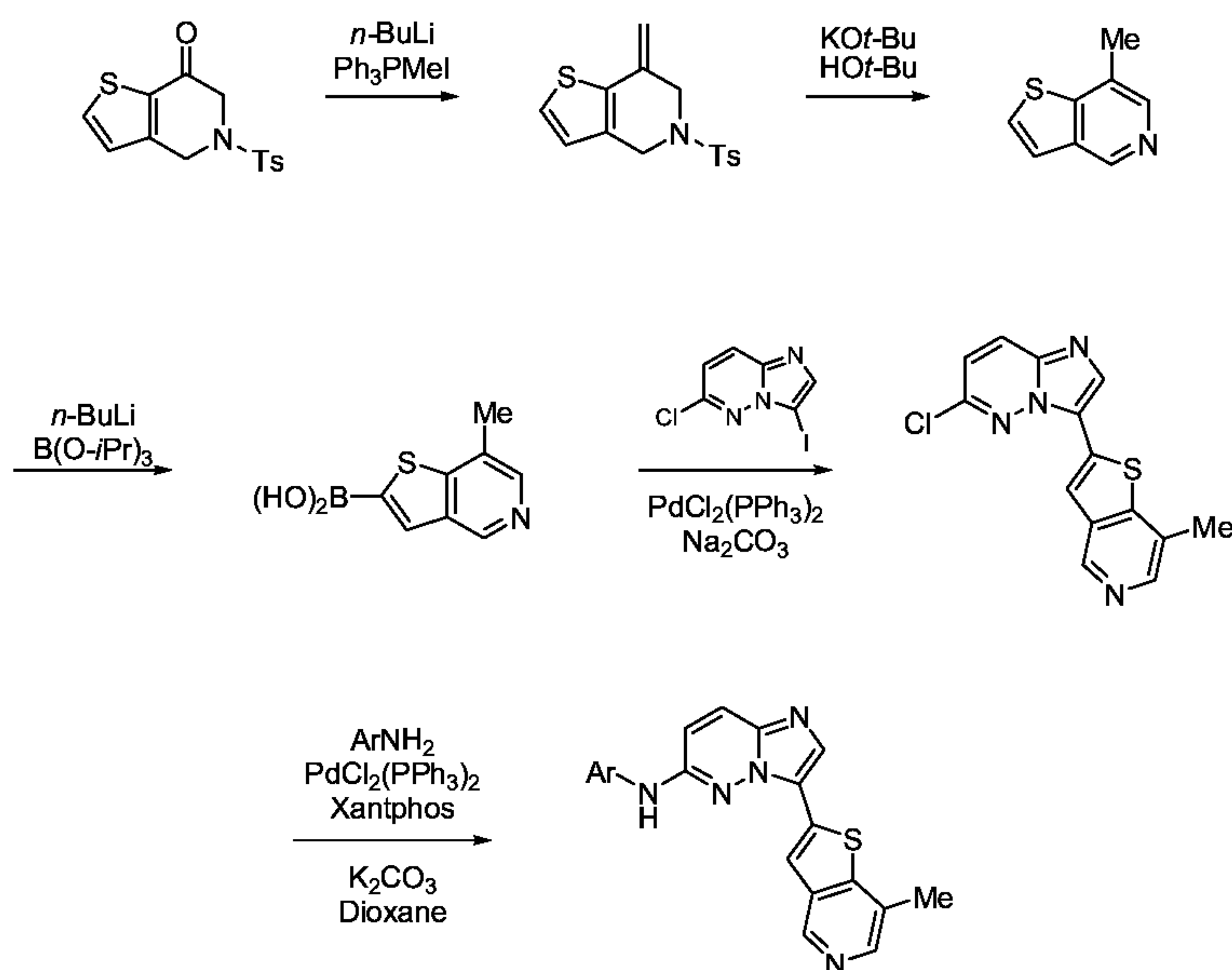
[00626] Compound 213, 217 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 59.

Table 59

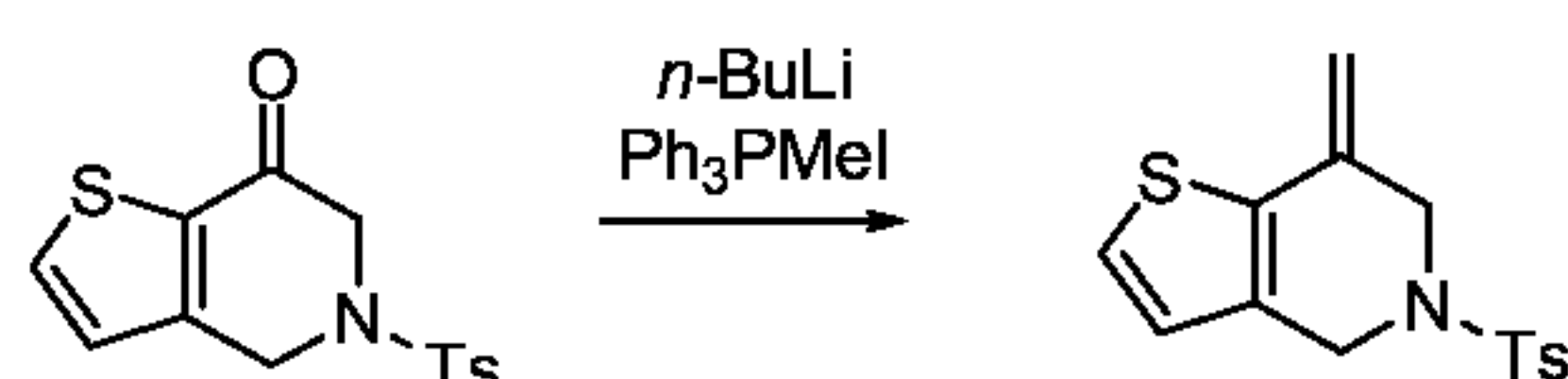
Cd.	Amine	Structure	IUPAC Name	[M+H] ⁺
213	<i>trans</i> -4-aminocyclohexanol		<i>trans</i> -4-(3-(7-methoxythieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	396.1
217	<i>trans</i> -4-methoxycyclohexanamine		<i>trans</i> -4-methoxycyclohexyl)-3-(7-methoxythieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	410.5

[00627] Example 60 – Synthesis of Compound 215

[00628] Scheme 60



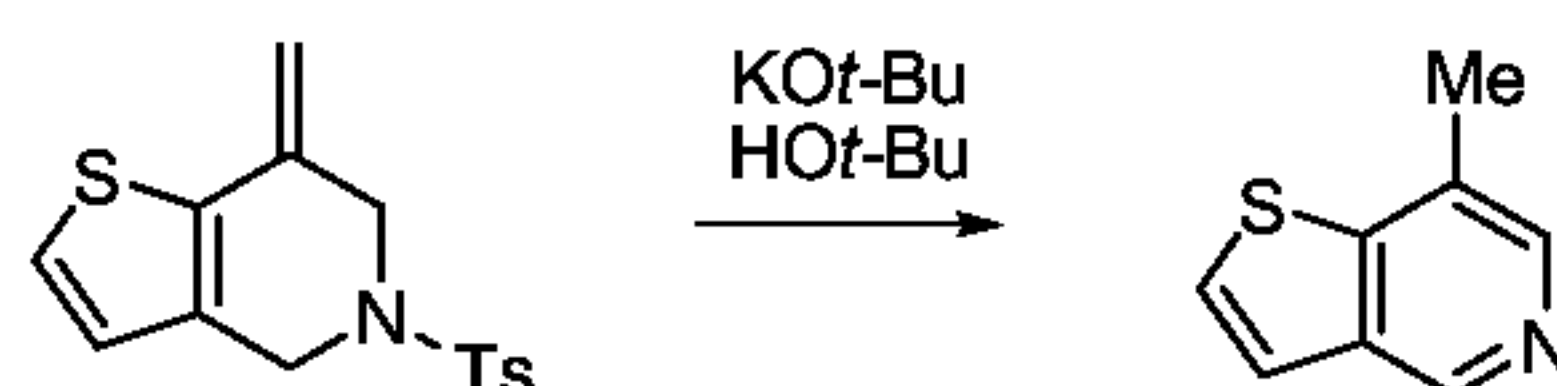
[00629] Preparation of 4,5,6,7-tetrahydro-7-methylene-5-tosylthieno[3,2-c]pyridine



[00630] To a solution of methyltriphenylphosphonium bromide (2.05 g, 5.73 mmol, 2.0 equiv) in THF (10.0 mL) at -78 °C was added *n*-BuLi (3.58 mL, 1.6 M solution, 2.0 equiv) and stirred for 30 min followed by addition of 5,6-dihydro-5-tosylthieno[3,2-c]pyridin-7(4H)-one (880 mg,

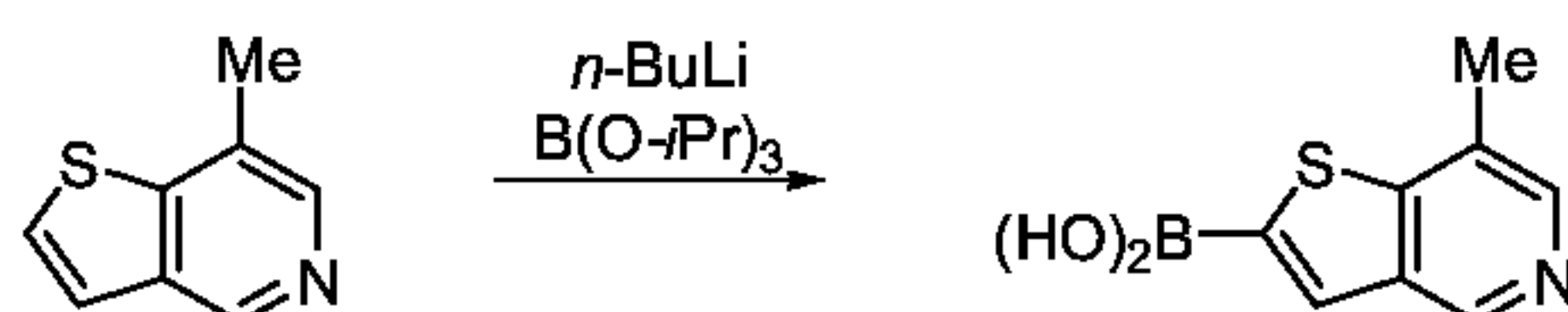
2.86 mmol, 1.0 equiv) in THF (5.00 mL). The reaction mixture was stirred at rt for 1 h, then quenched by the addition of a saturated aqueous solution of ammonium chloride. Purification by column chromatography using 5% ethyl acetate in hexanes elution gave 175 mg of the yellow solid, 20%.

[00631] Preparation of 7-methylthieno[3,2-c]pyridine



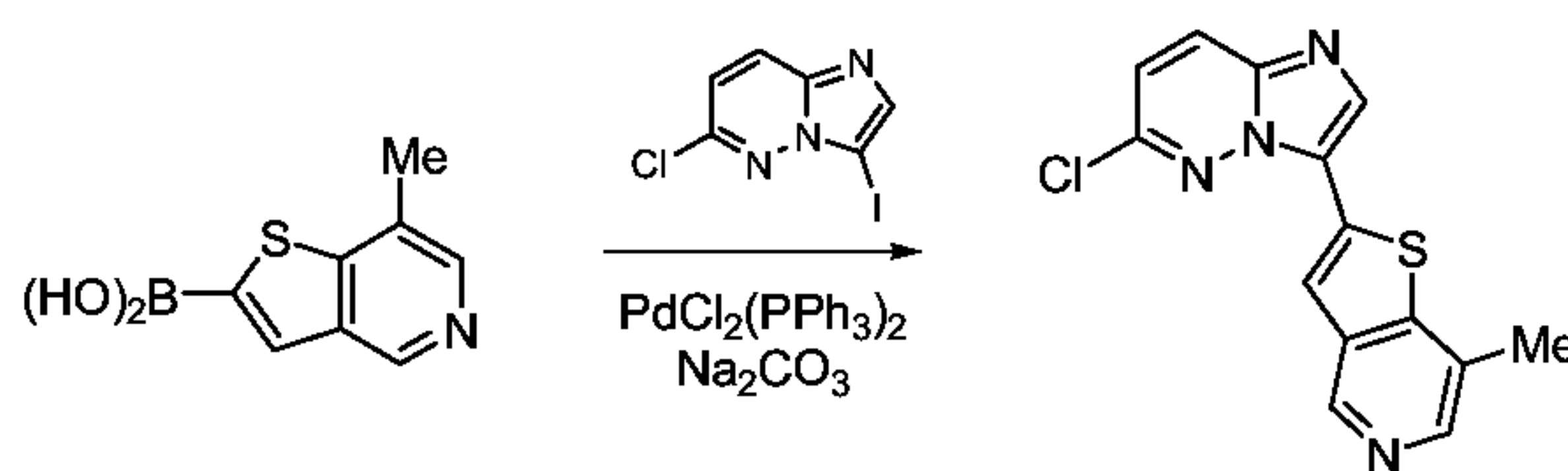
[00632] To a solution of 4,5,6,7-tetrahydro-7-methylene-5-tosylthieno[3,2-c]pyridine (150 mg, 0.491 mmol, 1.0 equiv) in HOt-Bu (5 mL) was added KOt-Bu (110 mg, 0.982 mmol, 2.0 equiv) and heated to reflux for 3 h. Purification by column chromatography using ethyl acetate elution gave 62 mg of the yellow solid, 85%.

[00633] Preparation of 7-methylthieno[3,2-c]pyridin-2-yl-2-boronic acid



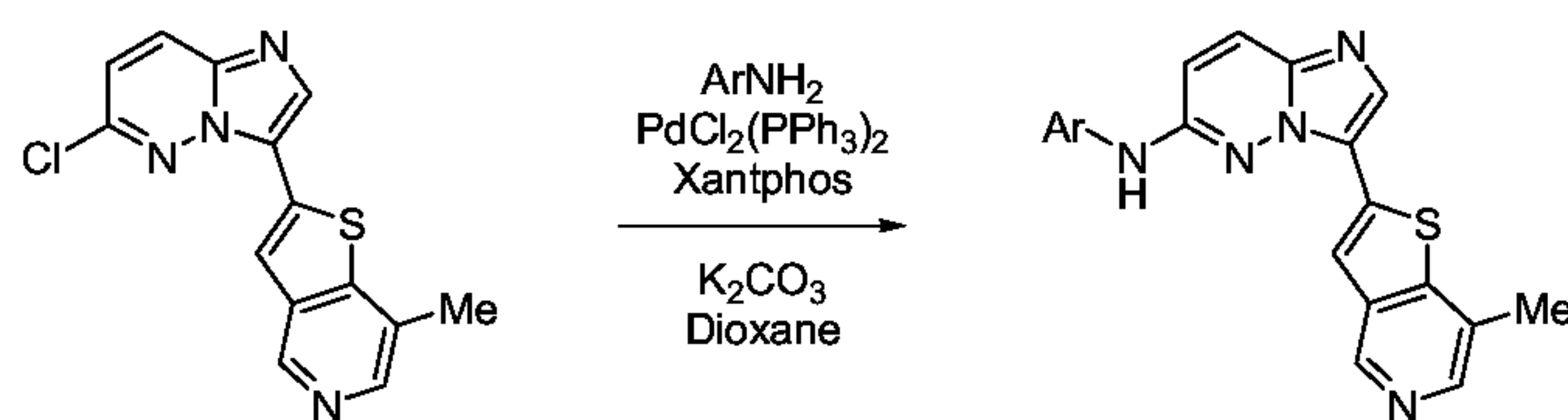
[00634] To a solution of 7-methylthieno[3,2-c]pyridine (82 mg, 0.550 mmol, 1.0 equiv) in THF (5.0 mL) at -78 °C was added *n*-BuLi (0.52 mL, 0.824 mmol, 1.5 equiv). The reaction was stirred at the reduced temperature for 1 h, then triisopropylborate (0.19 mL, 0.824 mmol, 1.5 equiv) was added and stirred at rt for 2 h. The mixture was quenched with 2N HCl and then extracted with ethyl acetate. Purification by column chromatography using 2% methanol in dichloromethane elution gave 80 mg of white solid, 75%.

[00635] Preparation of 6-chloro-3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazine



[00636] To a solution of 7-methylthieno[3,2-c]pyridin-2-yl-2-boronic acid (71 mg, 0.368 mmol, 1.0 equiv) in acetonitrile (3.68 mL) was added 6-chloro-3-iodoimidazo[1,2-b]pyridazine (103 mg, 0.368 mmol, 1.0 equiv), palladium catalyst (27 mg, 0.0368 mmol, 0.1 equiv) and sodium carbonate (3.68 mL, 1.0 M, 10.0 equiv). The solution was stirred in the microwave at 150 °C for 10 min. Purification using column chromatography gave 60 mg of the yellow product, 54%.

[00637] Preparation of N-(3,4-dimethoxyphenyl)-3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine



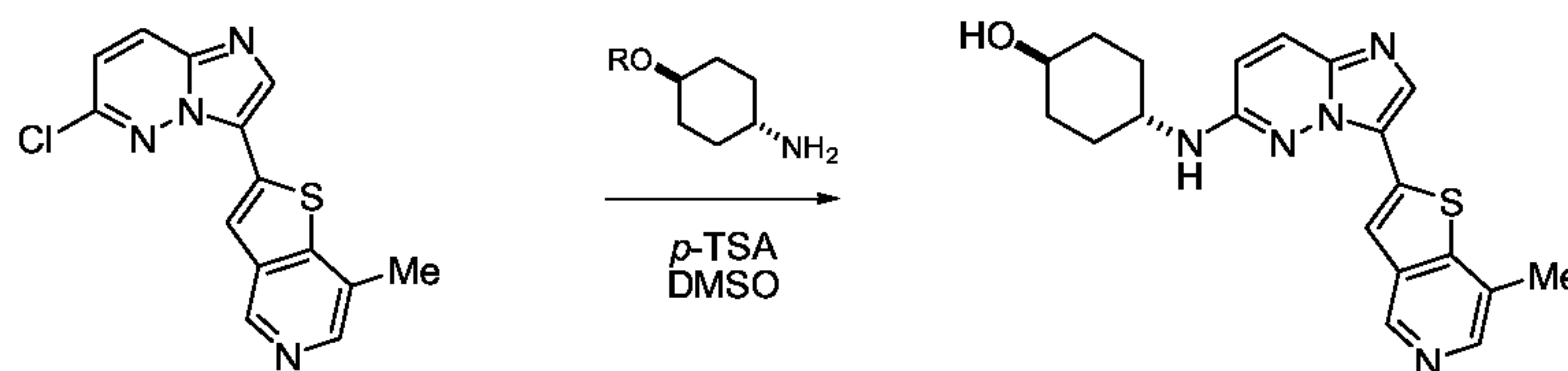
[00638] To a solution of 6-chloro-3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazine (31 mg, 0.103 mmol, 1.0 equiv), xantphos (12 mg, 0.0206 mmol, 0.2 equiv), palladium acetate (2 mg, 0.0103 mmol, 0.1 equiv), and potassium carbonate (284 mg, 2.06 mmol, 20 equiv) in dioxane (5.0 mL) was added 3,4-dimethoxyaniline (24 mg, 0.155 mmol, 1.5 equiv) and heated to 110 °C for 2 h. Purification by column chromatography using 2% methanol in dichloromethane elution gave 20 mg, of the brown solid, 47%.

[00639] Compound 214 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in **Table 60**.

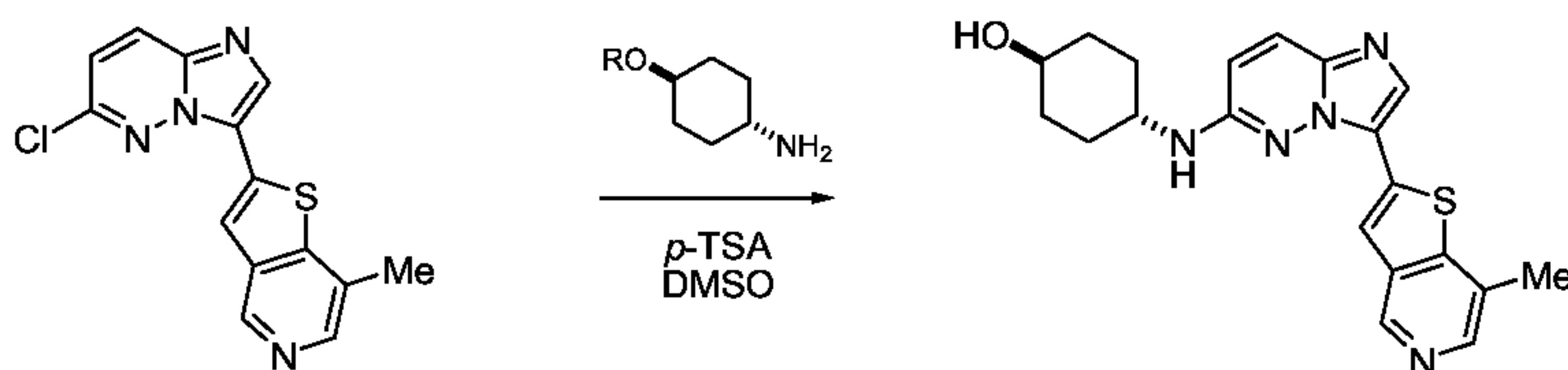
Cd.	Structure	IUPAC Name	[M+H] ⁺
214		N-(3,4-dimethoxyphenyl)-3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	418.0

[00640] Example 61 – Synthesis of Compound 215, 216

[00641] **Scheme 61**



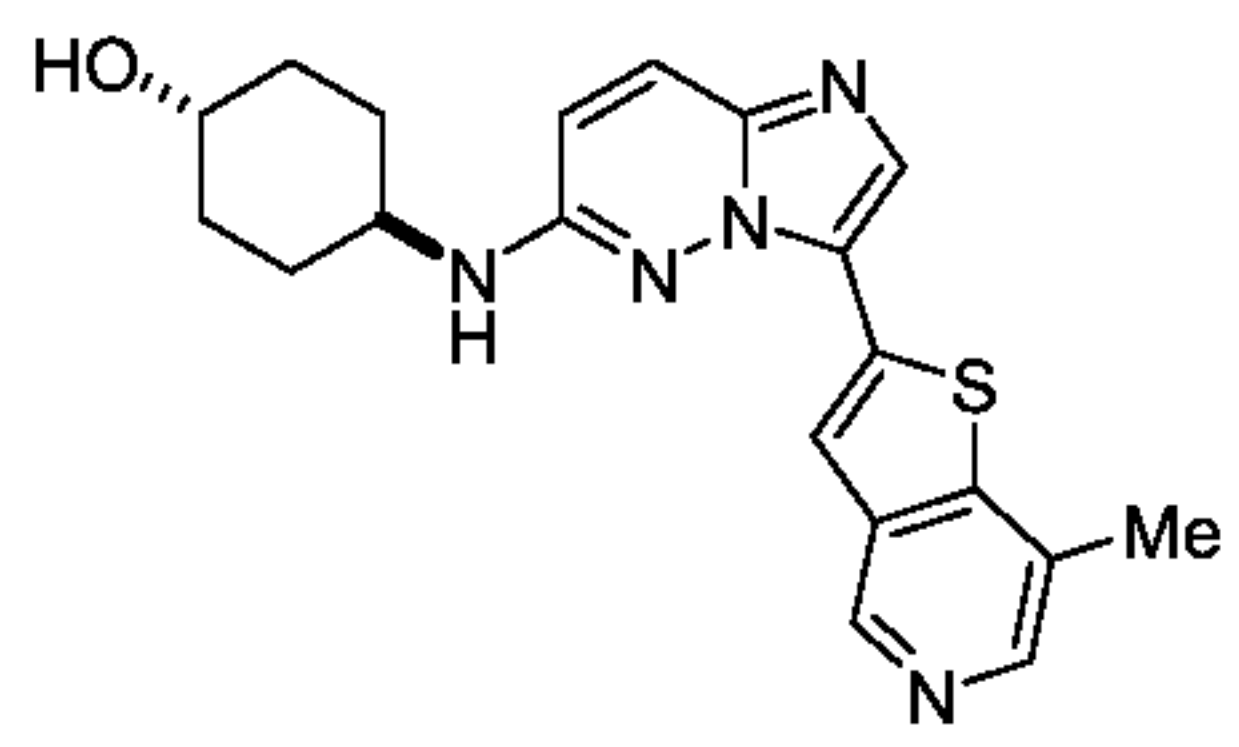
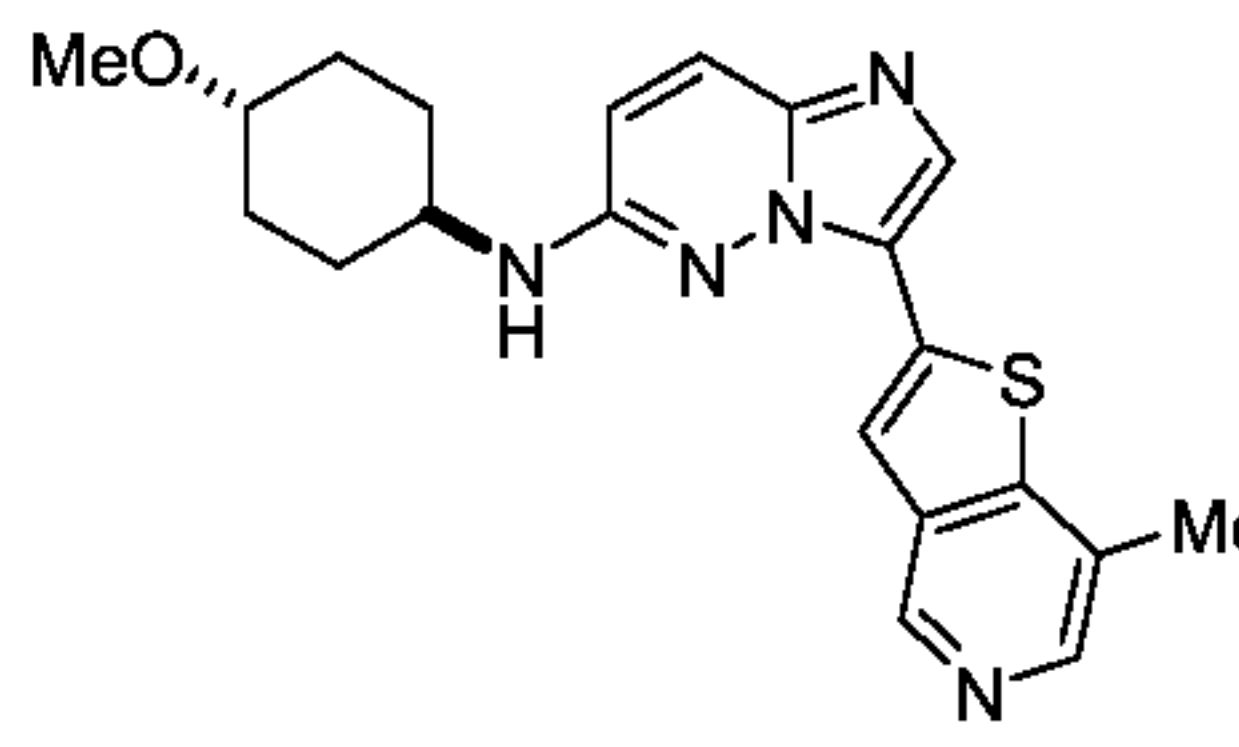
[00642] **Preparation of N-alkyl-4-(3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol**



[00643] To a solution of 6-chloro-3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazine (20 mg, 0.0665 mmol, 1.0 equiv) in DMSO (2.0 mL) was added *p*-toluene sulfonic acid monohydrate (13 mg, 0.0665 mmol, 1.0 equiv) and amine (38 mg, 0.333 mmol, 5.0 equiv) and heated to 100 °C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Purification by column chromatography using 5% methanol in dichloromethane elution gave 22 mg of the yellow solid, 87%.

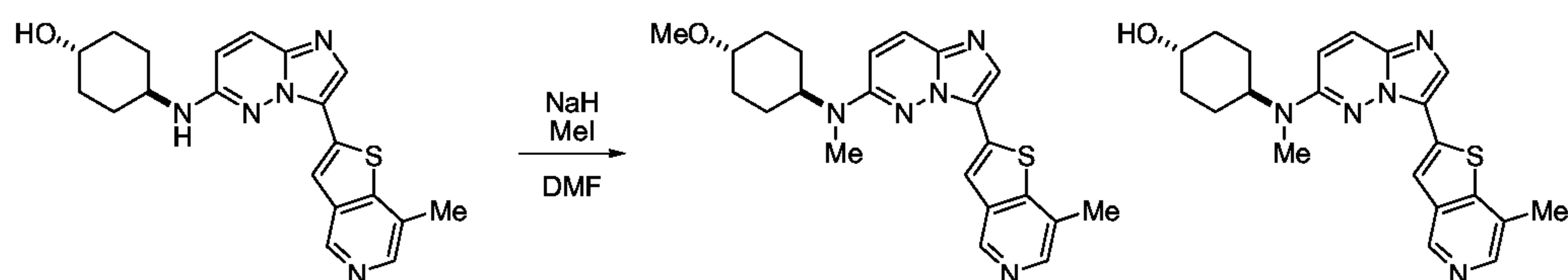
[00644] Compound 215, 216 was physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 61.

Table 61

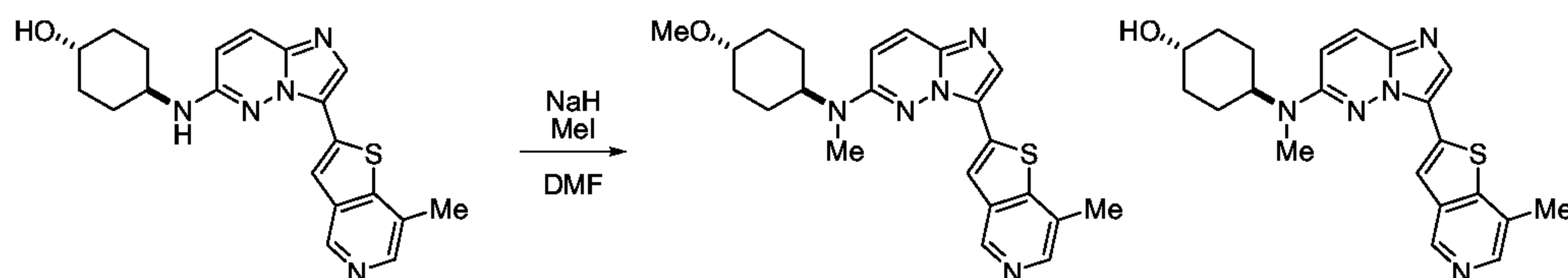
Cd.	Structure	IUPAC Name	[M+H] ⁺
215		<i>trans</i> -4-(3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol	380.5
216		<i>trans</i> -4-methoxycyclohexyl-3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine	394.5

[00645] Example 62 – Synthesis of Compounds 220, 221

[00646] Scheme 62



[00647] Preparation of *N*-((1*r*,4*r*)-4-methoxycyclohexyl)-*N*-methyl-3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine and *trans*-4-(*N*-methyl-*N*-(3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)amino)cyclohexanol



[00648] To a solution of *trans*-4-(3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-ylamino)cyclohexanol (37 mg, 0.0975 mmol, 1.0 equiv) in DMF (2.00 mL) was added sodium hydride (20 mg, 0.488 mmol, 5.0 equiv) and methyl iodide (68 mg, 0.488 mmol, 5.0 equiv). After 2 h, the reaction mixture was quenched with water and extracted with ethyl acetate. Purification by column chromatography gave 20 mg (50%) of *N*-((1*r*,4*r*)-4-methoxycyclohexyl)-*N*-methyl-3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine as the less polar product and 10 mg (25%) of *trans*-4-(*N*-methyl-*N*-(3-(7-methylthieno[3,2-c]pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)amino)cyclohexanol as the more polar product.

[00649] Compounds 220 and 221 were physically characterized by electrospray ionization mass spectrometry. Structures and molecular masses are given below in Table 62.

Table 62

Cd.	Structure	IUPAC Name	[M+H] ⁺
220		<i>N</i> -((1 <i>r</i> ,4 <i>r</i>)-4-methoxycyclohexyl)- <i>N</i> -methyl-3-(7-methylthieno[3,2- <i>c</i>]pyridin-2-yl)imidazo[1,2- <i>b</i>]pyridazin-6-amine	407.5
221		<i>trans</i> -4-(<i>N</i> -methyl- <i>N</i> -(3-(7-methylthieno[3,2- <i>c</i>]pyridin-2-yl)imidazo[1,2- <i>b</i>]pyridazin-6-yl)amino)cyclohexanol	394.5

Biochemical Assay

[00650] Biochemical Assay for the inhibition of kinase activity for MLK-3: Myelin basic protein (20 μM final concentration) is dissolved in 20 mM Hepes (pH 7.5) containing 10 μM MgCl₂, 1 μM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 μM Na₃VO₄, 2 mM DTT, and 1% DMSO. Activated MLK-3 is added and mixed (20 nM final concentration), and inhibitors are added in DMSO. ³³P-ATP (specific activity 500 μCi/μL) is delivered into the reaction mixture to initiate the reaction (ATP concentration is 50 μM) and the mixture is incubated at room temperature for 20 minutes. %Activity is determined using a proprietary HOTSPOT™ microfluidic filter binding technology. See, Expert Opin. Drug Discov. 2008 June; 3(6): 607–621.

Reported MLK-3 Activity

[00651] Activity data for selected selected MLK-3 inhibitors is displayed in Table 63. The IC₅₀ MLK-3 range is denoted as follows: + denotes activity < 5 μM, ++ denotes activity between 0.5 μM to 1 μM, and +++ denotes activity between 0.1 μM to 0.5 μM, and ++++ denotes activity < 0. 10 μM.

Table 63

COMPOUND #	IC ₅₀ MLK-3 (μM)	COMPOUND #	IC ₅₀ MLK-3 (μM)
3	+++	138	+++
4	+++	139	+++
5	++++	140	+

9	+	142	+
11	+	150	+
12	+++	158	+
13	+	160	++
14	++	161	+++
24	+++	162	++
25	++	163	++
26	+++	164	++
27	+++	166	++
28	+	167	+++
30	+	168	+++
31	+	169	++++
34	+	170	++++
39	+	171	++++
40	+	172	+++
41	++	173	++++
43	++	174	++++
44	++	175	++++
45	+	176	+++
50	+++	177	++++
53	++	178	+++
54	+	179	++++
56	++	180	+
61	+	181	+++
62	+	182	+
63	+++	183	+
67	++++	184	+
68	++++	185	+
69	++++	186	+++
70	++++	187	++
71	++++	188	+
72	+++	189	+
73	++	190	+
74	++	191	+
75	+++	192	++
76	+	193	+
77	++++	194	+
78	+++	195	+
79	++++	196	+++
80	+++	197	+++
81	++	198	+
83	+	199	+
84	+	200	++
85	++++	201	+++
86	+++	202	+
87	++++	203	+++
88	+++	204	+++
90	++	205	+++

101	+	206	++++
102	+	207	+++
105	+++	208	+
107	+	209	++
108	++	210	+
109	+++	211	+
110	+++	212	+
111	+	213	++++
119	+	214	+++
122	+++	215	++++
126	+	216	+++
127	+	217	+++
131	+	218	++++
132	++	219	+
135	+++	220	+++
136	+	221	+++

Blood Brain Barrier Penetration

[00652] Compounds disclosed herein may be evaluated in pharmacokinetic assays and models to determine absorption, distribution, metabolism, and excretion parameters. The choice and tailoring of *in vitro* and *ex vivo* assays and *in vivo* models will vary according to the route of administration/formulation, indication under study, properties of test compounds, *etc.*, as well as according to such factors as costs, availability of technology and resources, *etc.* Such parameters are well known in the fields of pharmacology and drug development. It is within the capacity of one skilled in the art to design and carry out, such work, or to outsource it to a capable third party.

[00653] Several compounds disclosed herein were evaluated in a standard murine pharmacokinetic model. Compounds were selected that exhibited reasonable solubility and metabolic stability, and good predicted blood brain barrier penetration, based on low molecular weight, a low number of hydrogen bond donors, logD within a range of from 2 to 5, and low polar surface area. For ease of analysis compounds were dissolved in 5% DMSO, 40% PEG400, and 55% to yield a nominal concentration of 2 mg/mL for intravenous administration. Compounds were administered via a single intravenous (IV) injection in CL57 BL/6 mice at 10 mg/kg in DMSO/PEG400/Saline solution. Three mice in each group were used for blood and brain collection at each time point. Blood samples (300 μ L) were collected via the retro-orbital vein predose and at 30, 60 and 180 minutes postdose. Blood samples were placed into tubes containing sodium heparin and centrifuged under refrigerated conditions at 8000 rpm for 6 minutes to separate plasma from the samples. The brain of each animal was collected after the final blood collection. The whole tissue was harvested, excised and rinsed by saline, dried by filter paper, and then placed into one tube per tissue per animal. All samples were stored at -20°C

until bioanalysis. Compound concentrations in plasma and brain homogenate were determined using a high performance liquid chromatography/mass spectrometry (HPLC/MS/MS) methods. Brain concentrations at the three hour time point for several representative compounds are disclosed below in Table 64.

Table 64

Compound #	Cbrain 3 hrs (ng/g)
URMC-099	950 (Positive Control)
CEP-1347	67
12	1280
67	566
175	1880
68	1554

Protein Kinase Selectivity: MLK-3 inhibitors previously reported in the literature are somewhat promiscuous and inhibit a large number of serine and threonine protein kinases. Compounds of the present invention that show potent inhibition on MLK-3 are very specific for MLK family kinases. For comparison, IC₅₀ values for selected compounds from the invention were compared against a diverse set of kinases for inhibition of the MLK-3 potent, brain penetrant compound, URMC-099, which is disclosed in Goodfellow, V.S., *et al.* A CNS Active, Orally Bioavailable Inhibitor of Mixed Lineage Kinase 3 for Potential Treatment of HIV Associated Neurocognitive Disorder. *Journal of Medicinal Chemistry*, 2013.

Table 51

Compounds							
Kinase/Assay	URMC-099	105	12	169	67	68	170
ABL1(T315D)	3	>10,000	>10,000	>10,000	>10,000	>10,000	>10,000
CDK2	1180	1028	19,400	8,260	>10,000	>10,000	>10,000
IKKa	591	>10,000	>10,000	>10,000	>10,000	>10,000	>10,000
IKKb	257	>10,000	>10,000	>10,000	>10,000	>10,000	>10,000
IR	200	>10,000	>10,000	>10,000	>10,000	>10,000	>10,000

[00654] Neuroprotection from HIV-1 Tat: E18 primary hippocampal neurons were plated in microfluidic chambers for 7 days in vitro (DIV). These chambers contain a cell body compartment contiguous with a series of 10um wide, 3um high, 400um long microgrooves through which axons grow into a second compartment, fluidically isolated by a hydrostatic pressure gradient. BV-2 microglial cells treated with 1µg/ml HIV-1 Tat ± test compounds (100nM) were introduced into the second compartment for 18 hours. Chambers that were exposed to BV-2 microglia treated with Tat alone had almost their entire axonal field destroyed (FIG. 1, brightfield image). Treatment with various example compounds or URMC-099 protected the axon field. The specific MLK3 inhibitor, compound 68, promoted continued

axonogenesis in the presence of Tat-activated microglia (FIG. 1, arrows). FIGS. 2 and 3 show quantifications of axon elimination in the presence of HIV tat and Compounds 169, 67, 68 and 175. (U = Control Inhibitor URM-099, previously shown to protect against effects of HIV-Tat *in vitro* and *in vivo*.)

[00655] Western blots of ICAM-5 cleavage (FIG. 4): Rat hippocampal neurons were dissected from E18 embryos and plated on 96-well plates in Neurobasal medium supplemented with B27 plus antioxidants (AO) for 24 hours and then maintained in Neurobasal supplemented with B27 minus AO for 12-14 days *in vitro* before use. Neurons were treated with vehicle or 20 mM of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist dizocilpine (MK-801) or increasing doses ranging between 10-300 nM of Compound 68 in 100 ml of modified Locke's buffer (no Mg^{2+}) for 20 minutes before adding 10 or 100 mM NMDA for 15 minutes. After NMDA treatment, the modified Locke's Buffer was replaced with Neurobasal Medium supplemented with B27 minus AO and returned to a 37°C incubator with 5% CO₂ overnight. The treated neurons were washed with ice-cold PBS and fixed in 4% PFA + 4% Sucrose for 15 minutes and then washed 3 times with PBS. The fixed neurons were then immunostained with rabbit anti-ICAM-5 polyclonal antibody and a specific fluorescent secondary antibody for Odyssey System gel imaging from Licor. Results are from 3 independent experimental replicates. In this paradigm, neurotoxicity was measured as the amount of cleaved (i.e., soluble) ICAM-5 that was released after excitotoxic injury from sublethal doses of NMDA (Guo H, Tong N, Turner T, Epstein LG, McDermott MP, Kilgannon P, Gelbard HA. Release of the neuronal glycoprotein ICAM-5 in serum after hypoxic-ischemic injury. *Ann Neurol*. 2000 Oct;48(4):590-602. PMID: 11026442; Conant K, Wang Y, Szklarczyk A, Dudak A, Mattson MP, Lim ST. Matrix metalloproteinase-dependent shedding of intercellular adhesion molecule-5 occurs with long-term potentiation. *Neuroscience*. 2010 Mar 17;166(2):508-21. doi: 10.1016/j.neuroscience.2009.12.061. Epub 2010 Jan 4. PMID: 20045450).

[00656] Synaptodendritic Beading (FIG.5): Rat hippocampal neurons were dissected from E18 embryos and plated on 12 mm glass coverslips in Neurobasal medium supplemented with B27 plus antioxidants (AO) for 24 hours and then maintained in Neurobasal supplemented with B27 minus AO for 12-14 days *in vitro* (DIV) before use. Neurons cultured for DIV 12-14 were transfected with pMAX-GFP for 12 hours and then treated with vehicle or 20 mM MK-801 and 200 nM of Compound 68 in 0.5 ml of modified Locke's buffer (no Mg^{2+}) for 20 minutes before adding 10 mM NMDA for < 5 minutes. After NMDA treatment, the neurons were washed with ice-cold PBS and fixed in 4% PFA + 4% Sucrose for 15 Minutes and then washed 3 times with PBS. The beaded and unbeaded

neurons were identified by GFP expression and quantitated per 20X field using fluorescence microscopy. Results are from three independent experimental replicates. In this paradigm, neurotoxicity is defined as the extent of synaptodendritic beading in each microscopic field (Bellizzi MJ, Lu SM, Masliah E, Gelbard HA. Synaptic activity becomes excitotoxic in neurons exposed to elevated levels of platelet-activating factor. J Clin Invest. 2005 Nov;115(11):3185-92. PMID: 16276420).

[00657] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described herein.

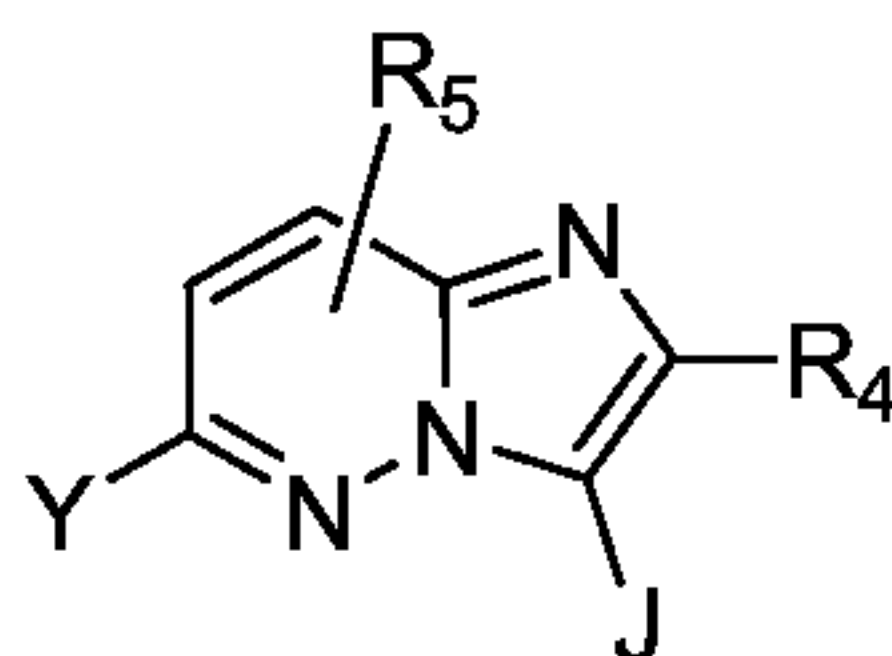
[00658] All applications, publications, patents and other references cited herein are incorporated by reference in their entirety. In case of conflict, the specification, including definitions, will control. As used herein, the singular forms “a”, “and,” and “the” include plural referents unless the context clearly indicates otherwise. Thus, for example, reference to “a peptide sequence” or a “treatment,” includes a plurality of such sequences, treatments, and so forth.

[00659] The invention is generally disclosed herein using affirmative language to describe the numerous embodiments. The invention also specifically includes embodiments in which particular subject matter is excluded, in full or in part, such as substances or materials, method steps and conditions, protocols, procedures, assays or analysis. Thus, even though the invention is generally not expressed herein in terms of what the invention does not include, aspects that are not expressly included in the invention are nevertheless disclosed herein.

[00660] Where features or aspects of the invention are described in terms of Markush groups, 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. For example, if X is described as selected from the group consisting of A, B, C, claims for X being A and claims for X being B and C are fully described. Moreover, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any combination of individual members or subgroups of members of Markush groups. Thus, for example, if X is described as selected from the group consisting of A, B, and C, and Y is described as selected from the group consisting of D, E, and F, claims for X being A and Y being D are fully described.

We claim:

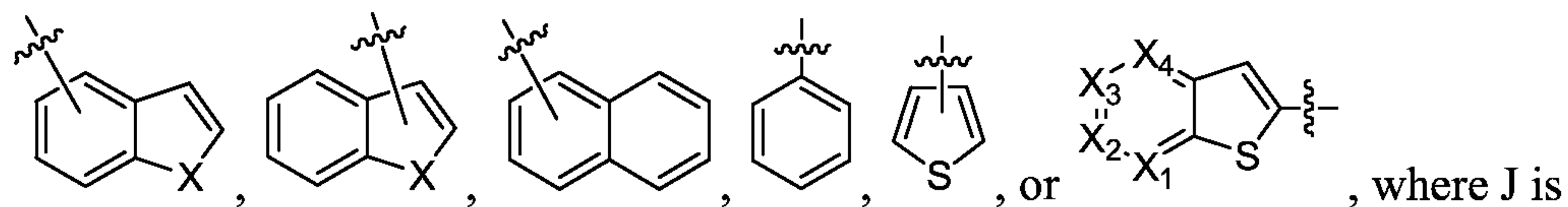
1. A compound having the structure of Formula I



I

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

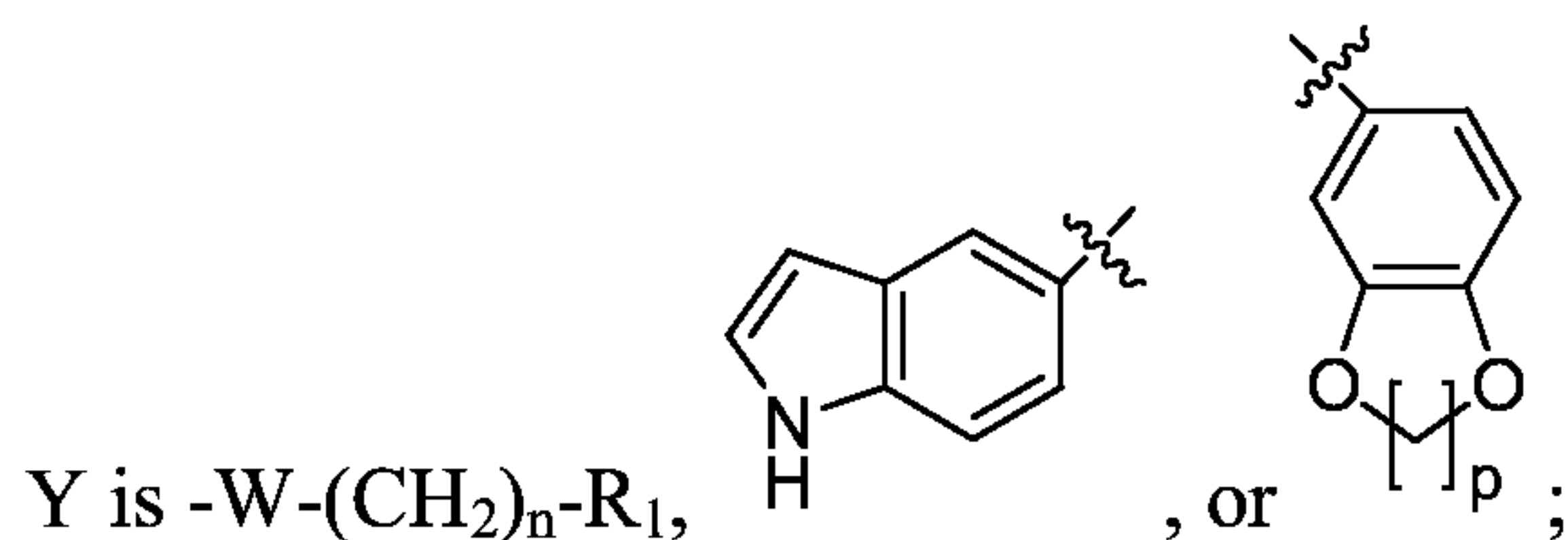
J has a structure of



optionally substituted with up to four R_{10} , each R_{10} is independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy, haloalkoxy, -OH, and -OCOR₆;

X is NR₁₂ or S;

each X₁, X₂, X₃, and X₄ is independently CH or N and wherein no more than one of X₁, X₂, X₃, and X₄ is N;



W is null, phenylene, or -NR₆-phenylene, where the NR₆ is attached to the imidazopyridazine core structure of Formula I;

R₁ is -NR₂R₃, or piperazinyl, where the nitrogen atom of the piperazinyl is optionally substituted with alkyl or alkoxy;

R₂ is H or alkyl;

R₃ is selected from the group consisting of C₂-C₁₀ alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, where any atom of R₃ is optionally substituted with one or more R₇; or R₂ and R₃ taken together with the N atom to which they are attached form a 3- to 7-membered heterocyclic ring optionally substituted with R₈;

R₄ is H or alkyl;

R₅ is H, alkyl, or NHR₉;

R₆ is H or alkyl;

each R_7 is independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkyloxy, perhaloalkoxy, halo, oxo, -OH, hydroxyalkyl, -COOR₁₁, or -O-(CH₂)_m-OH;

R_8 is alkoxy, hydroxyalkyl, or COOR₁₁;

R_9 is H, alkyl, or cycloalkyl;

R_{11} is H, or alkyl;

R_{12} is H, or alkyl;

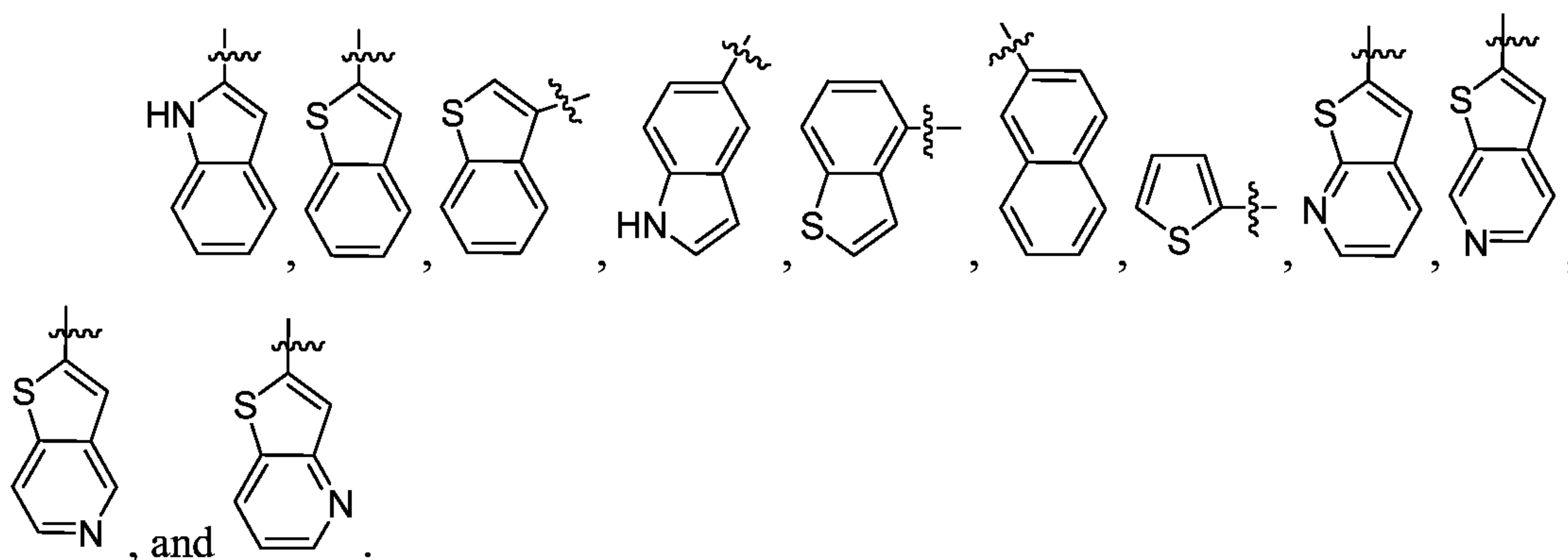
n is 0 or 1;

m is 1, 2, or 3; and

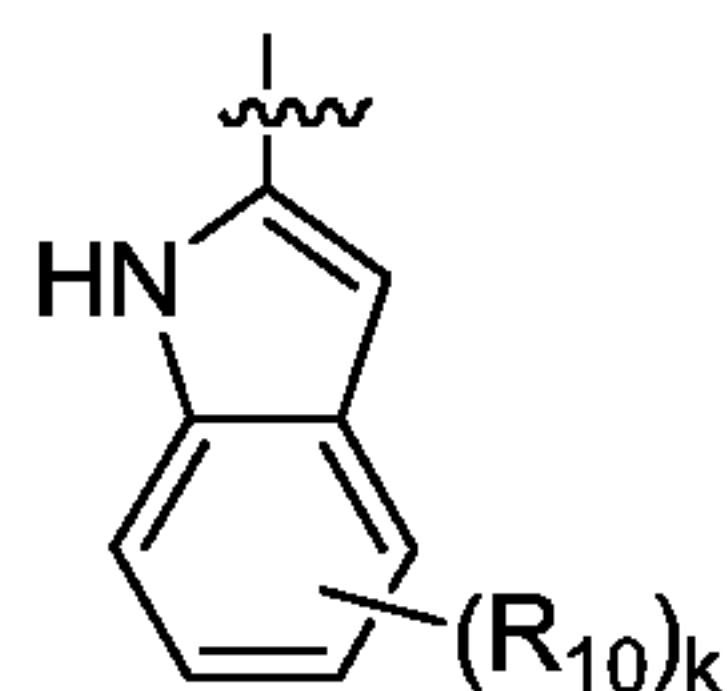
p is 1, 2, or 3;

with the proviso that if J is an unsubstituted benzothiophene, then R_3 is either aryl or heteroaryl, where any atom of R_3 is optionally substituted with one or more R_7 .

2. The compound of claim 1 wherein J is selected from the group consisting of

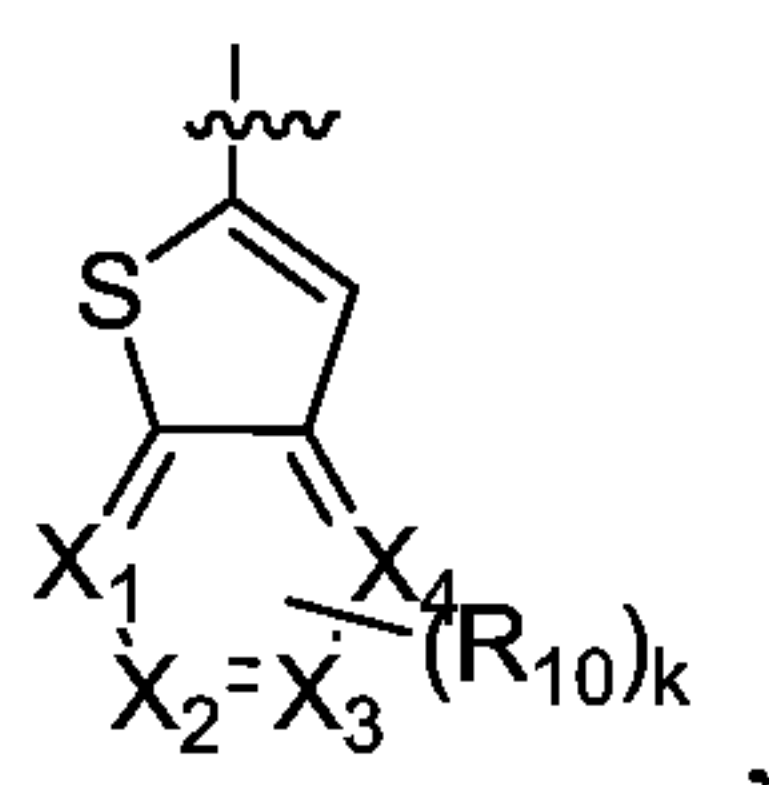


3. The compound of any of claims 1-2 wherein J is



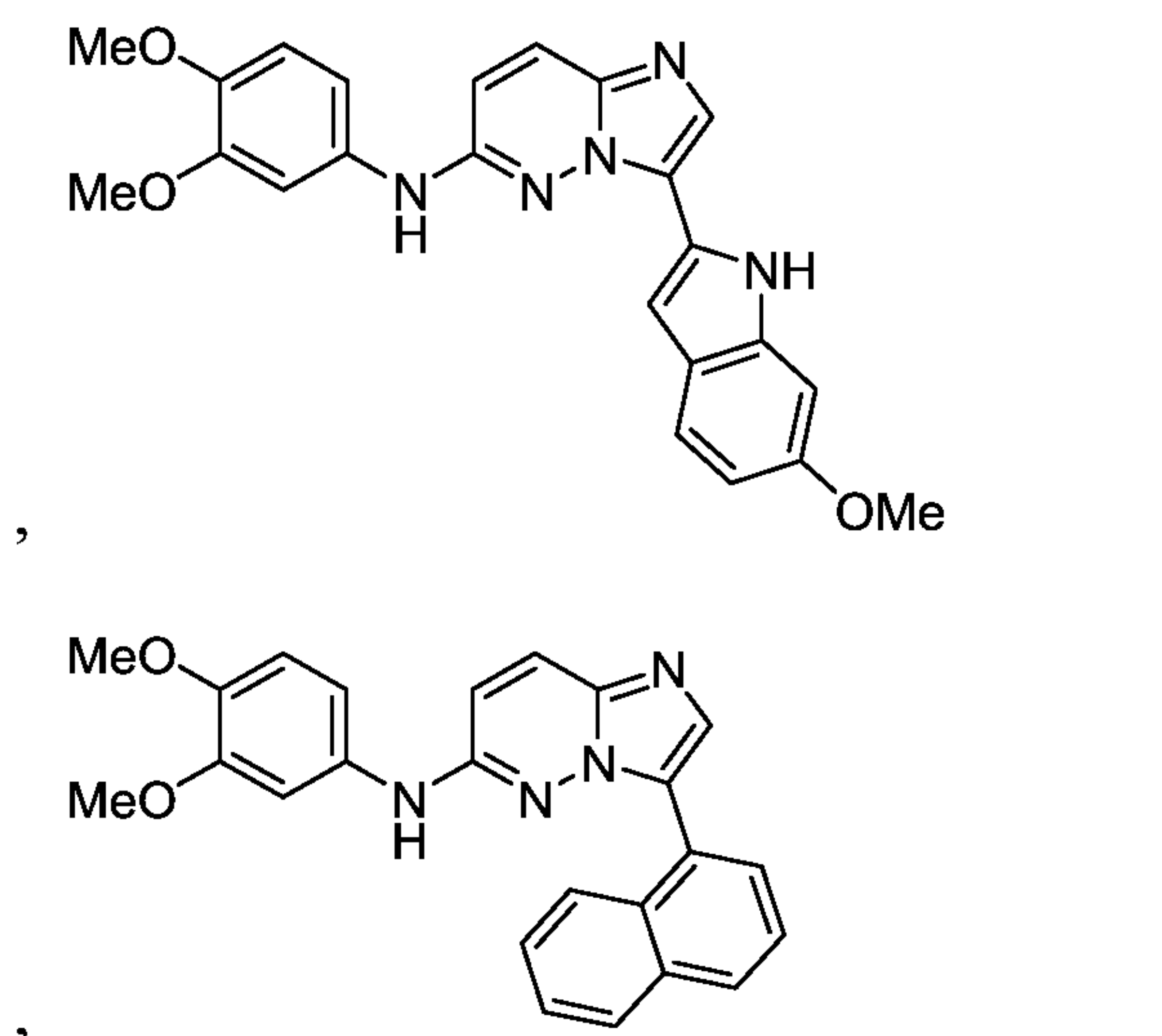
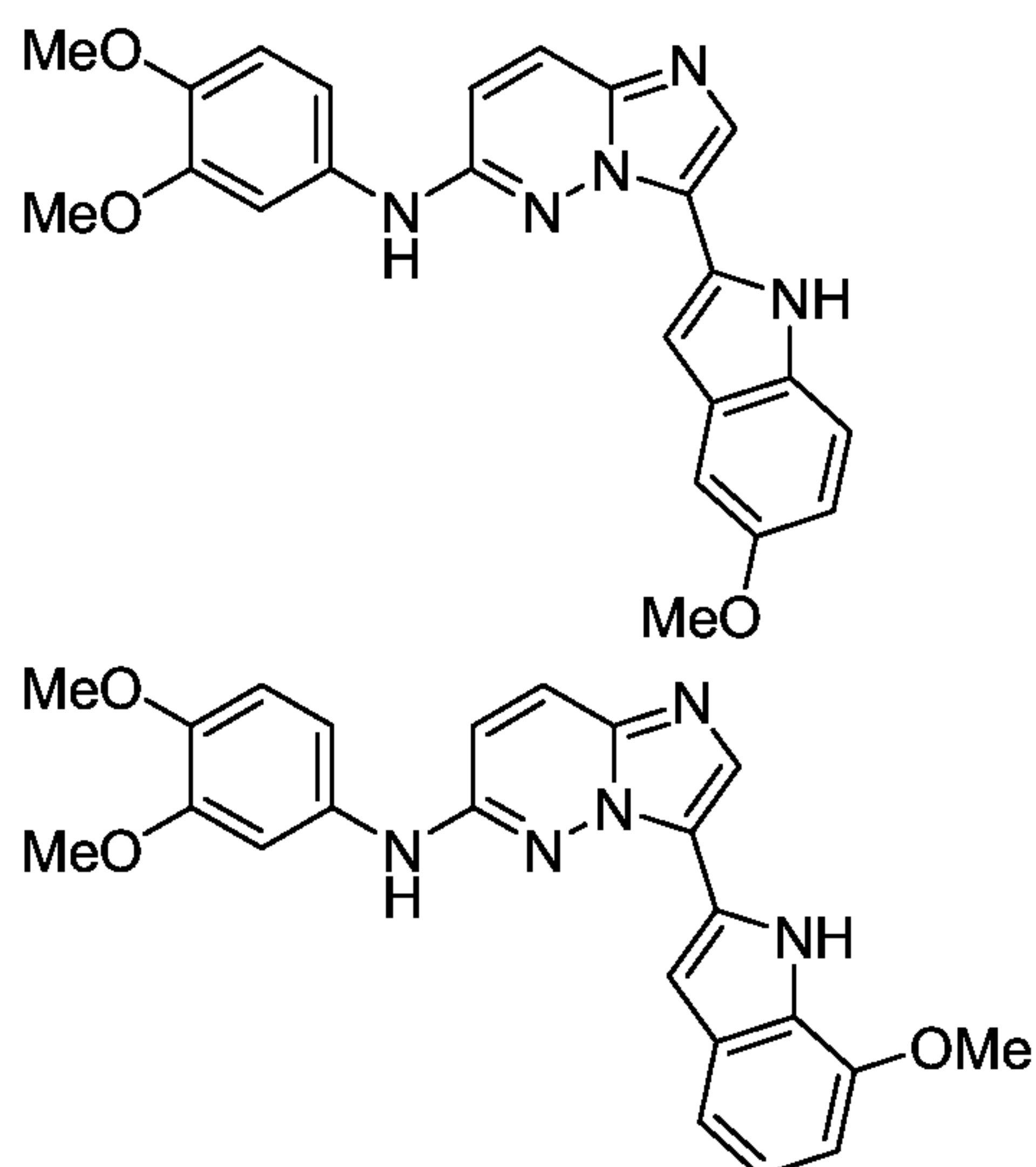
wherein each R_{10} is independently selected from the group consisting of F, Cl, -OH, methyl, methoxy, ethoxy, propoxy, isopropoxy, and -OCOCH₃; and k is 0, 1, 2, or 3.

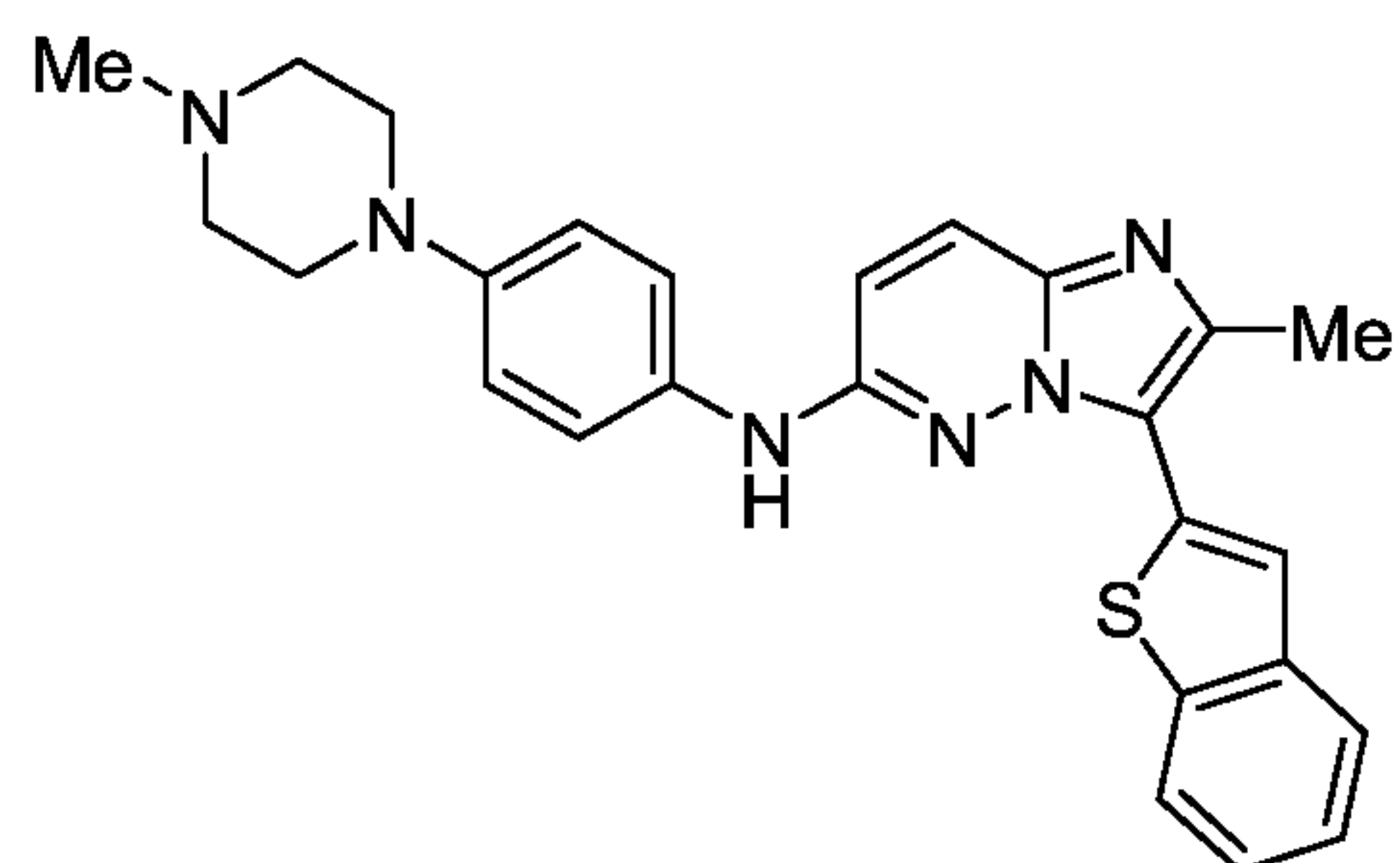
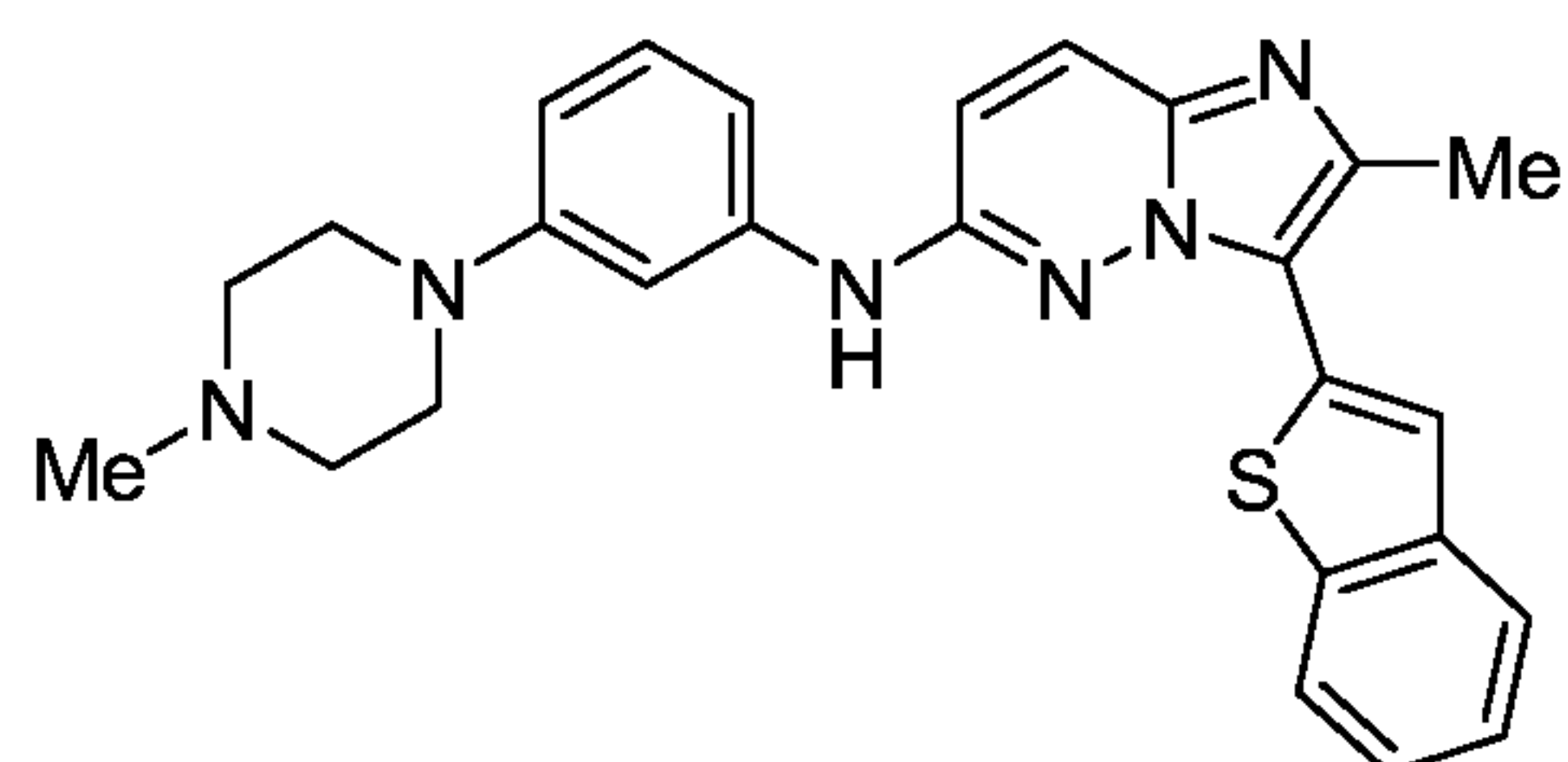
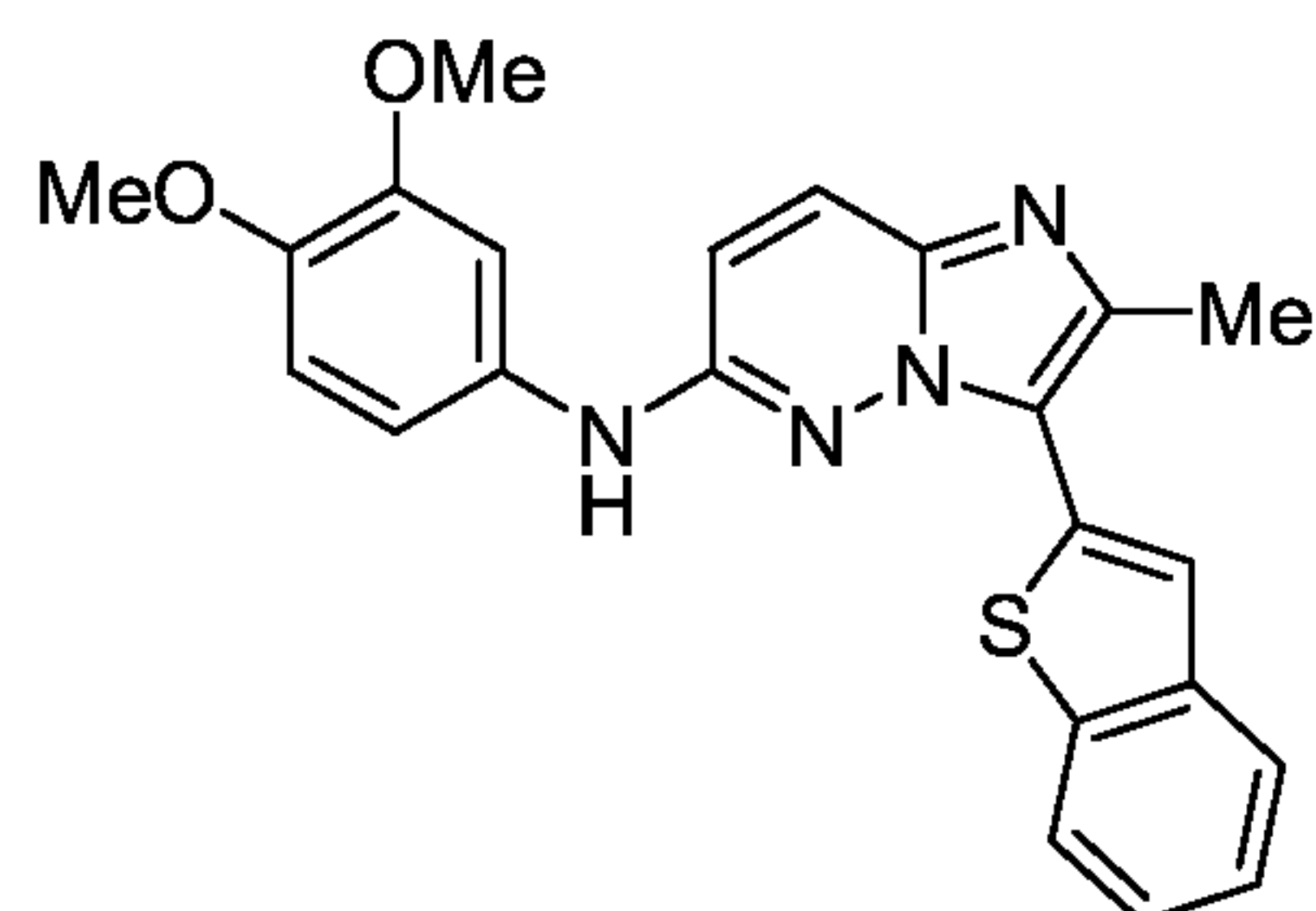
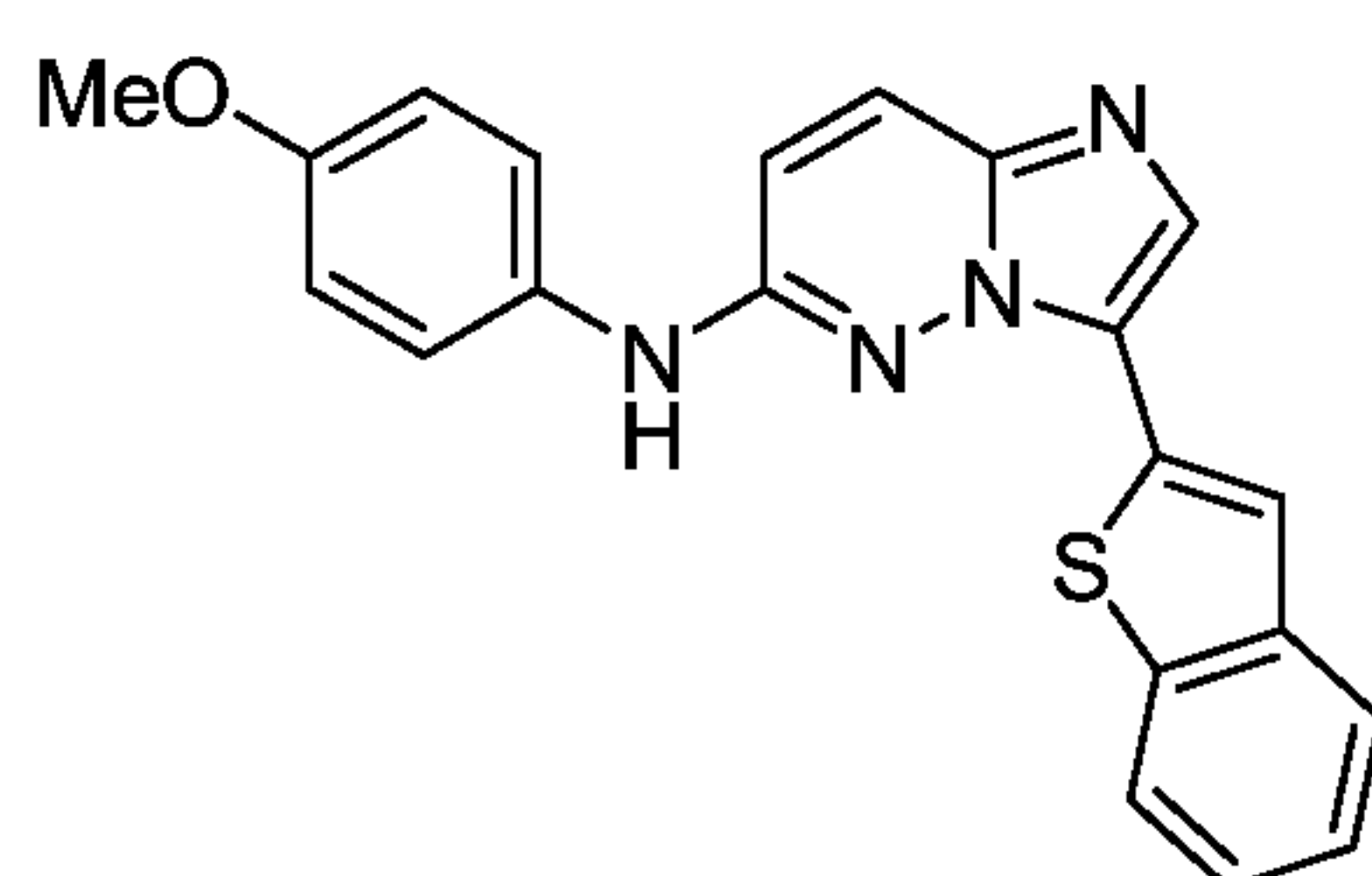
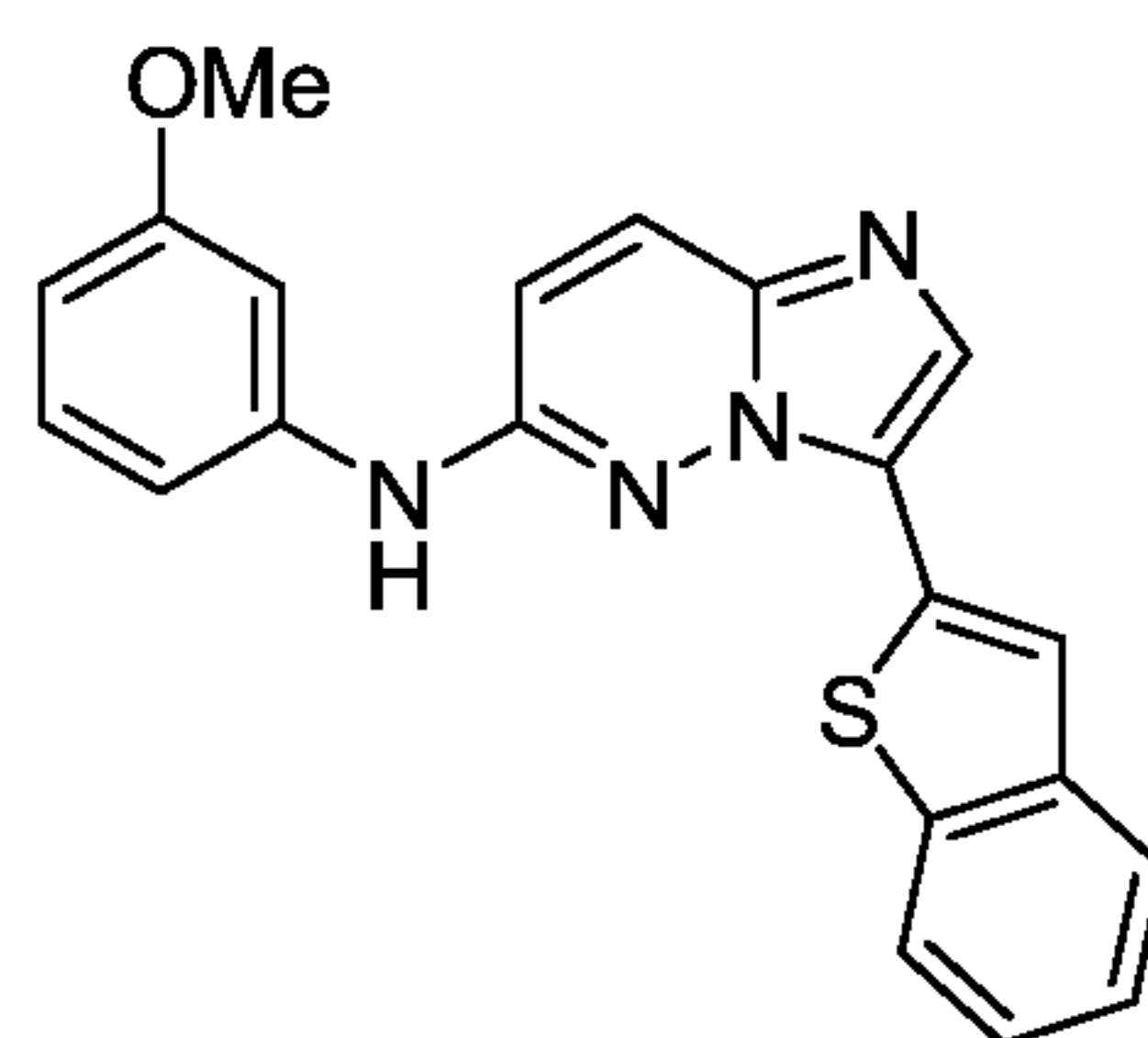
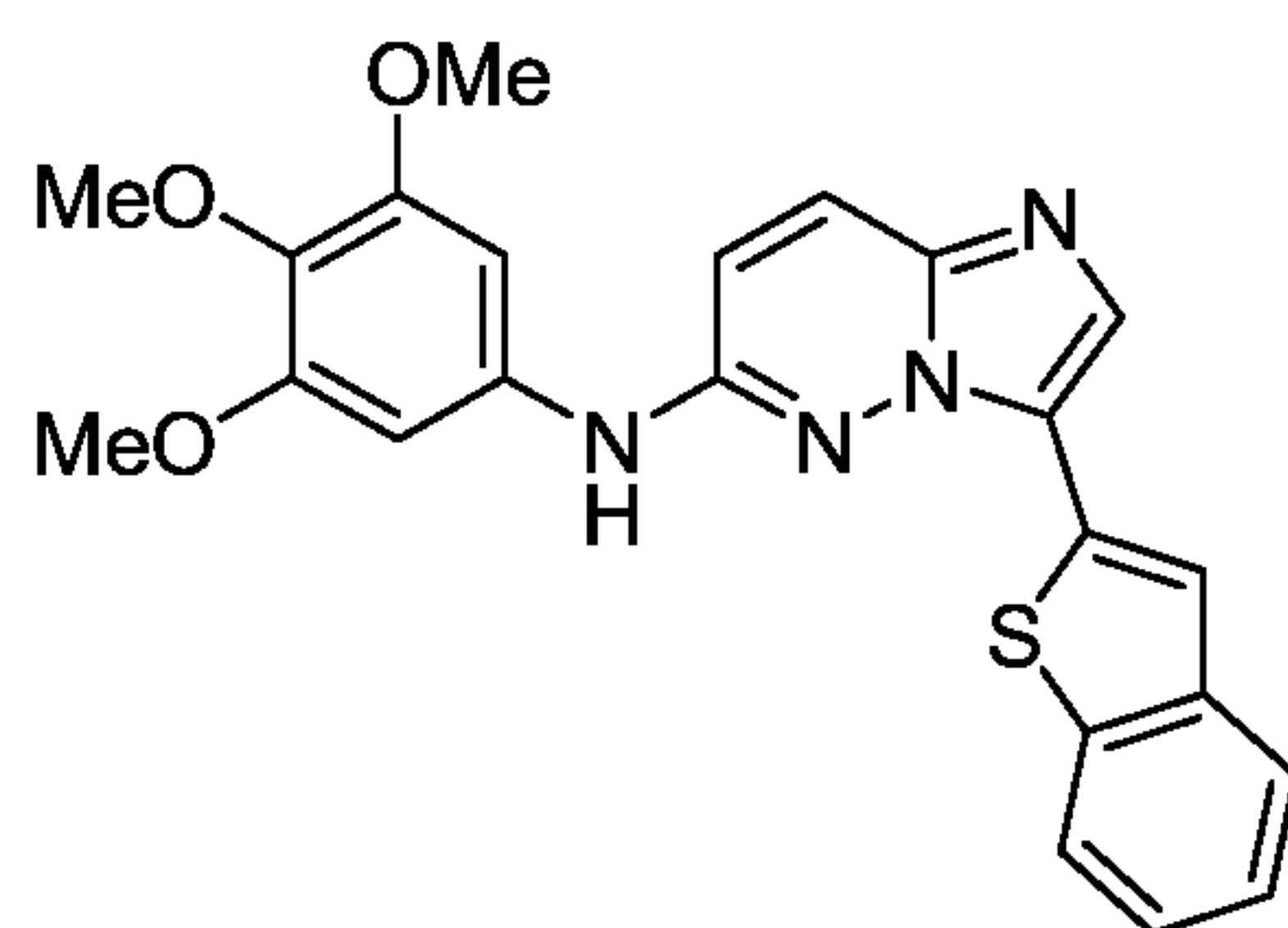
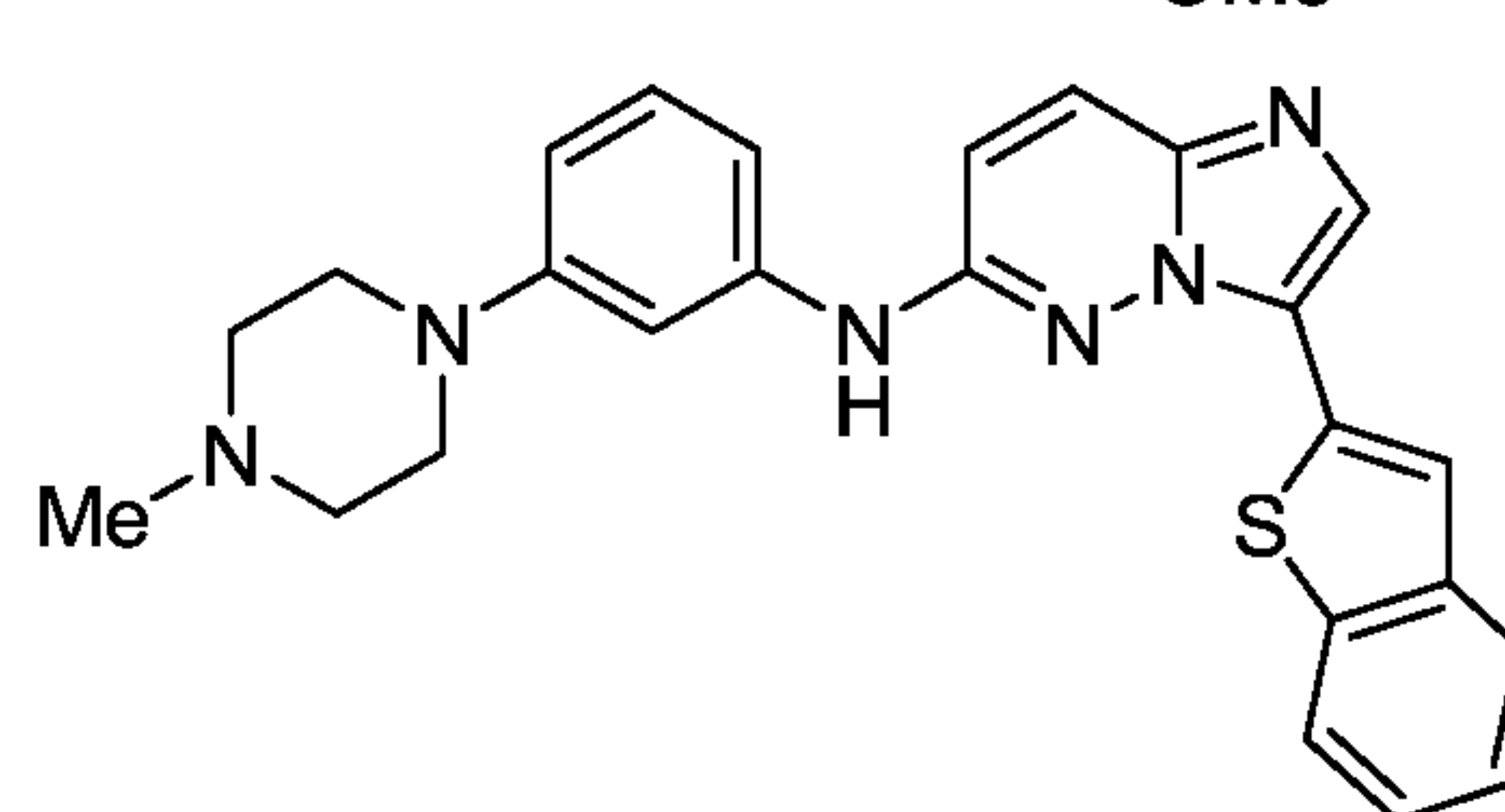
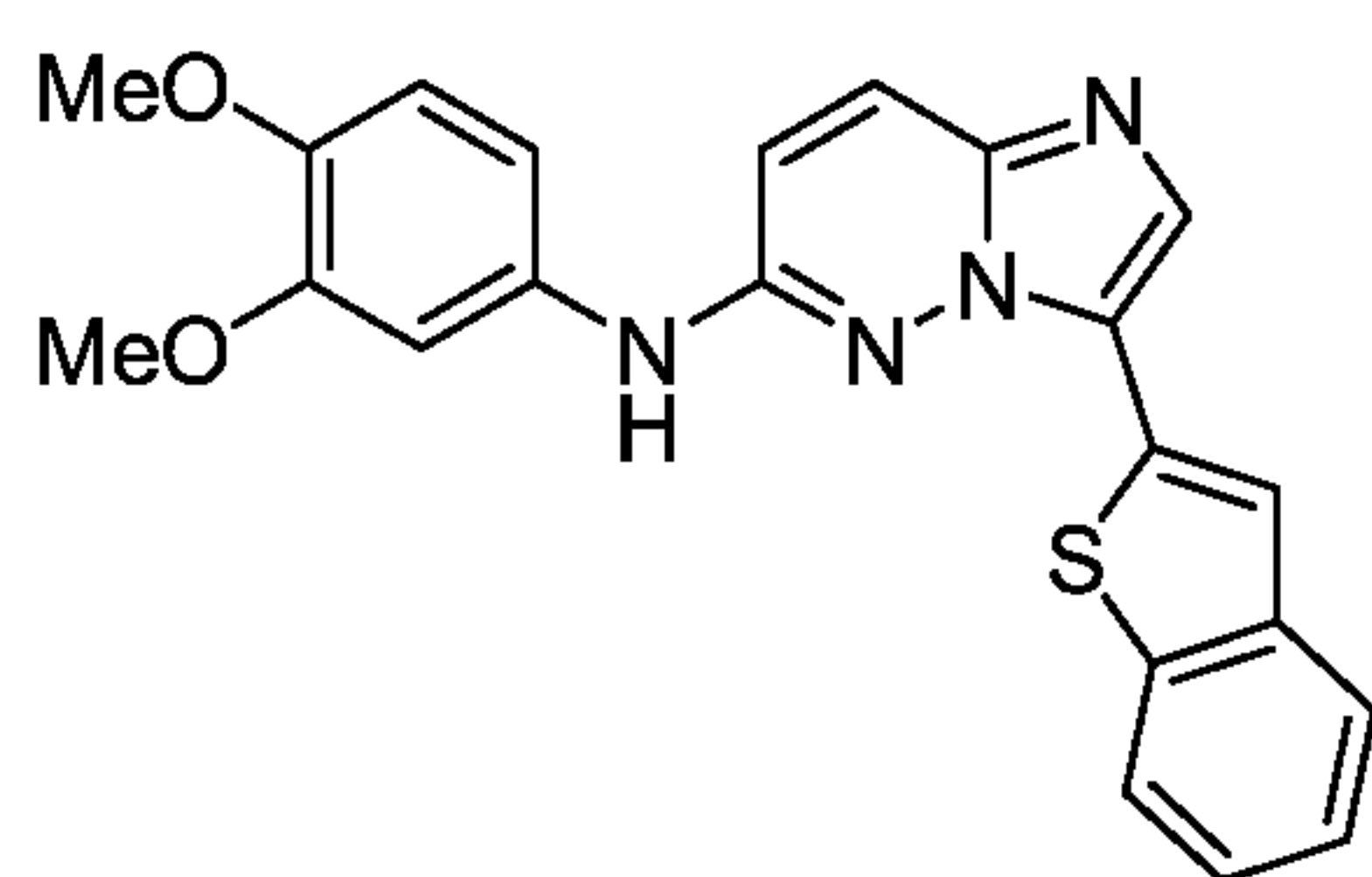
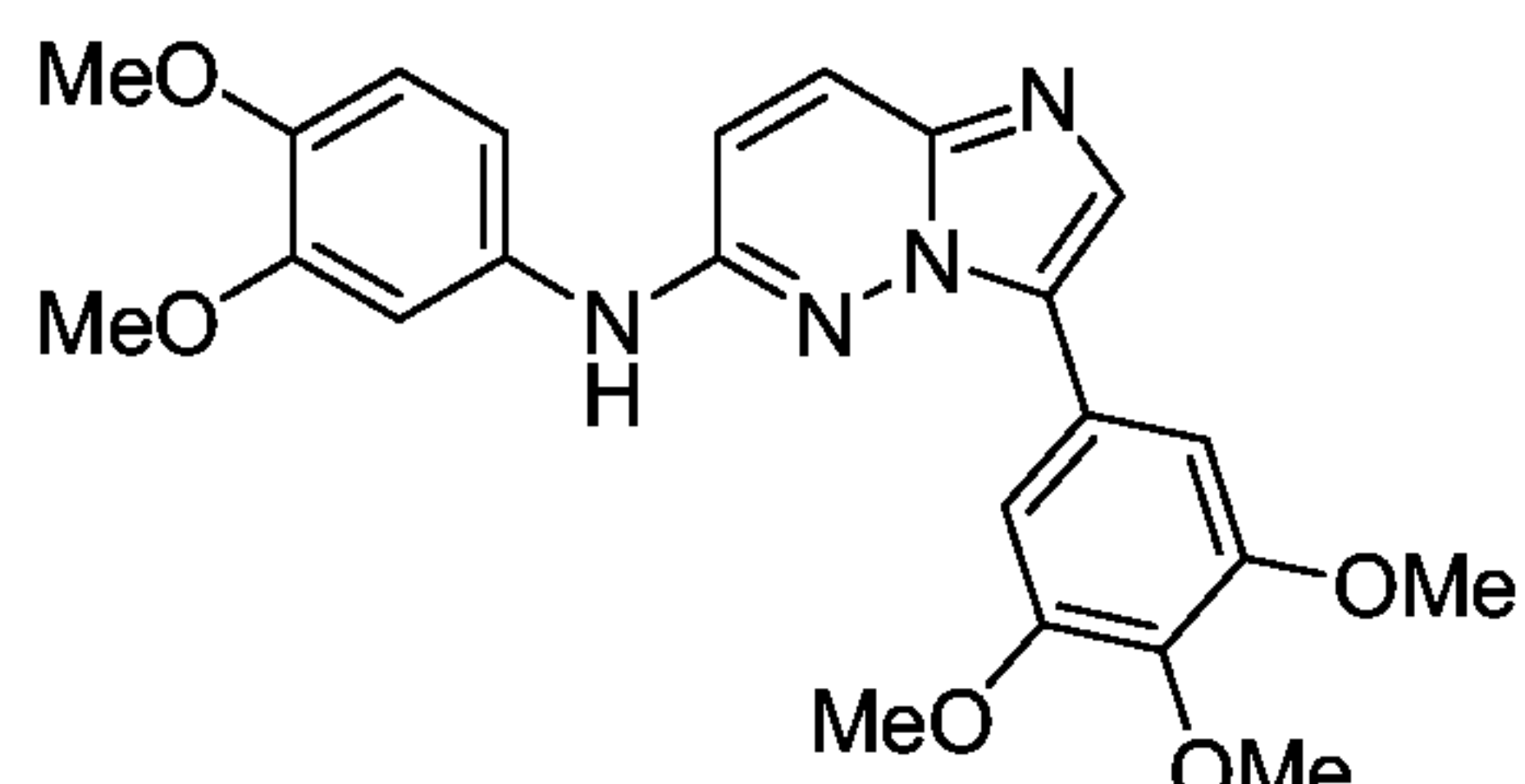
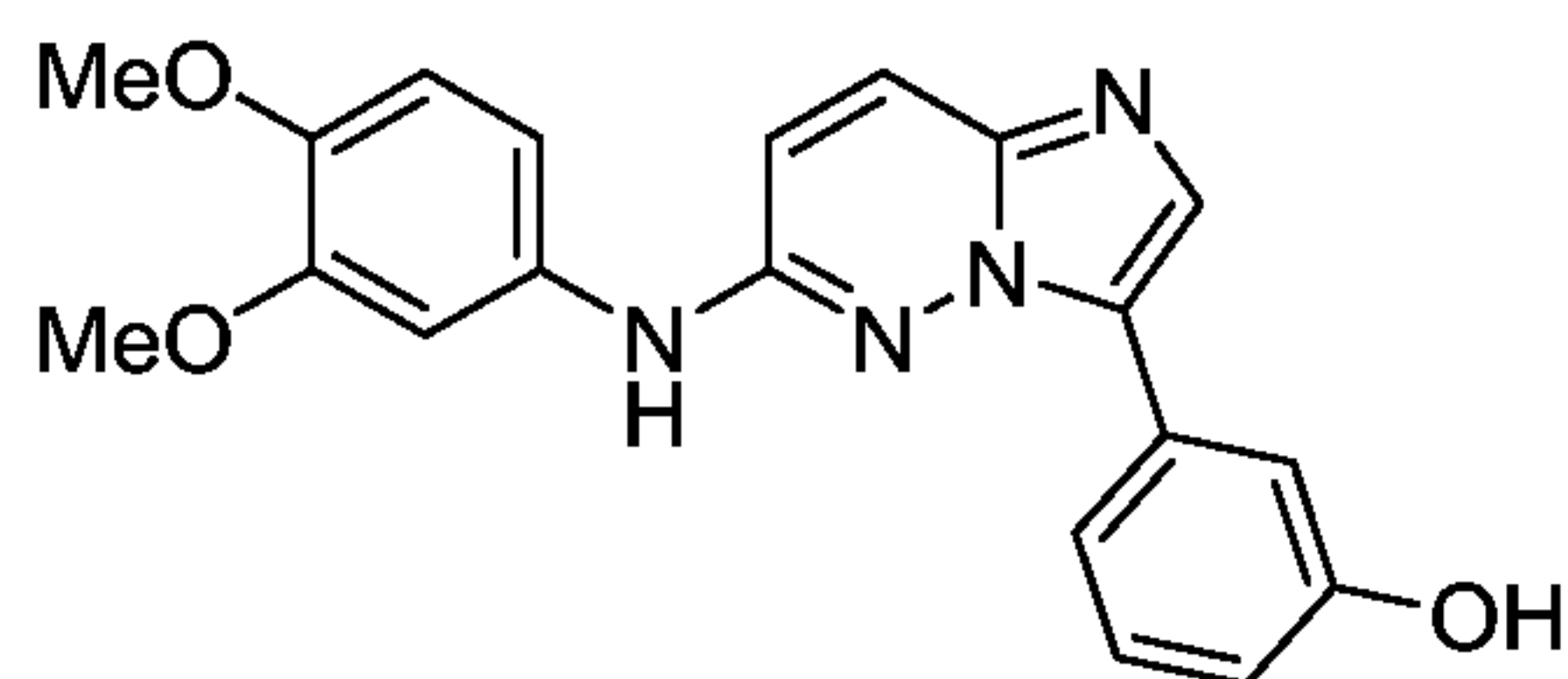
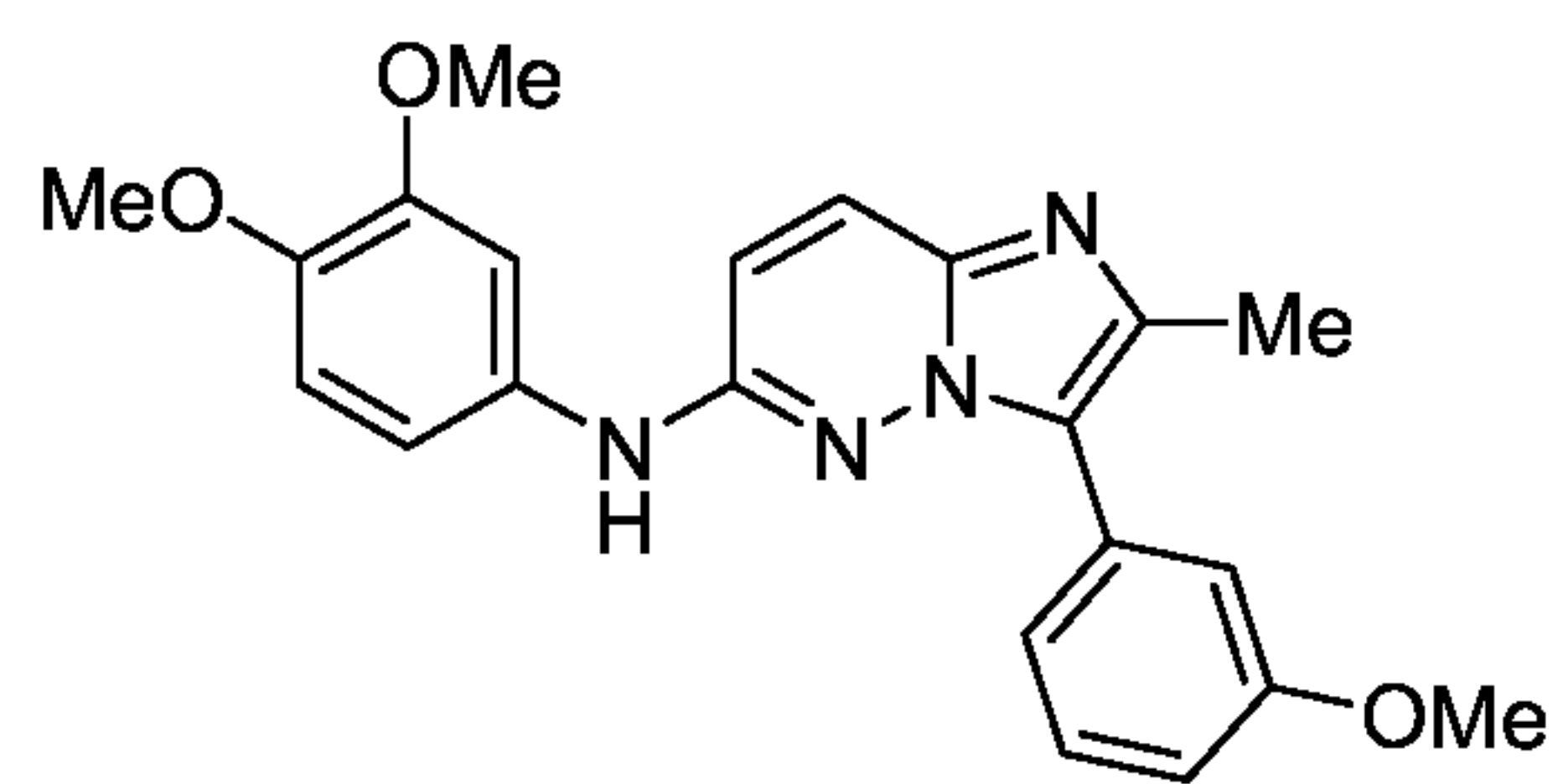
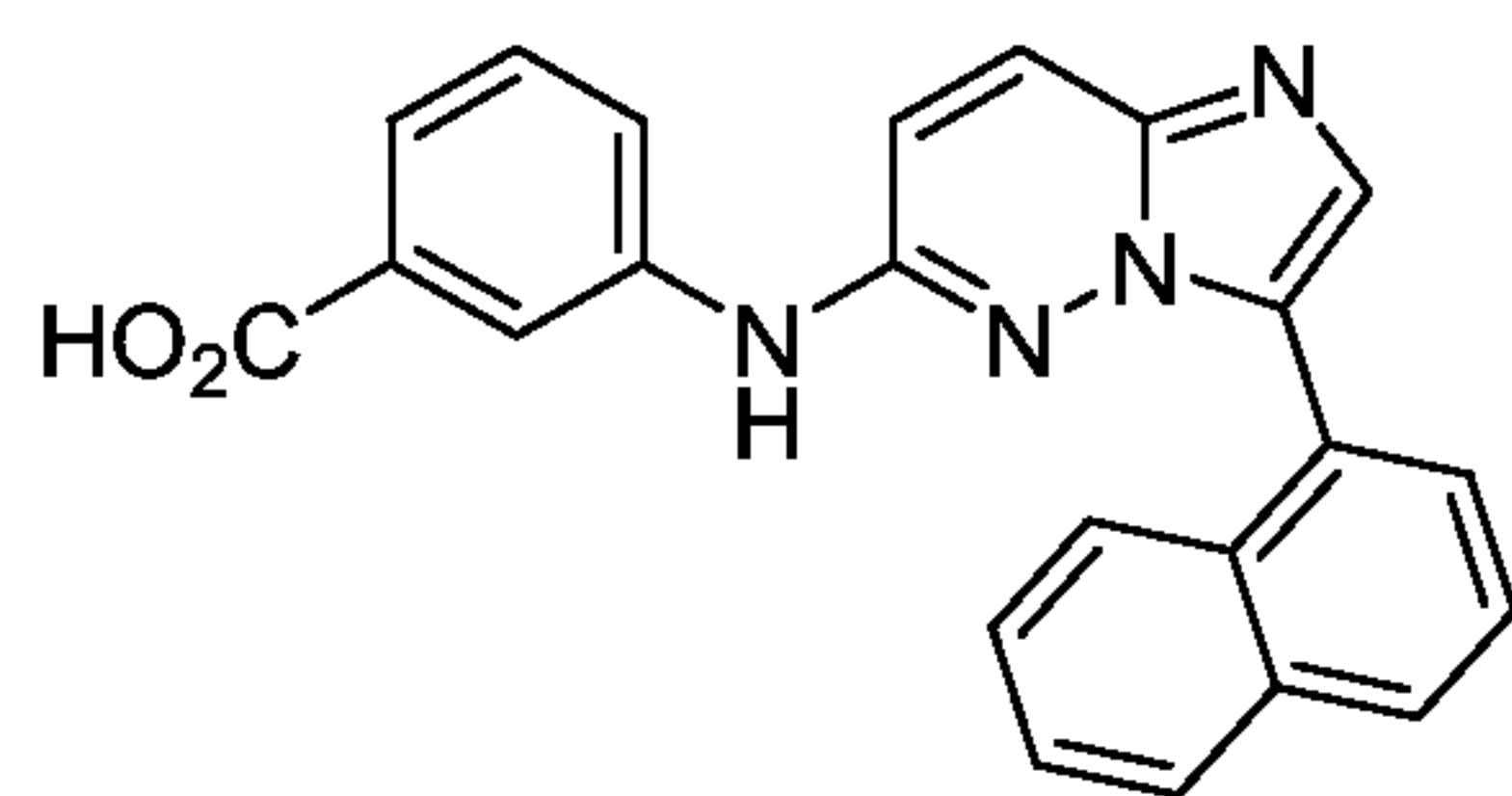
4. The compound of any of claims 1-2 wherein J is

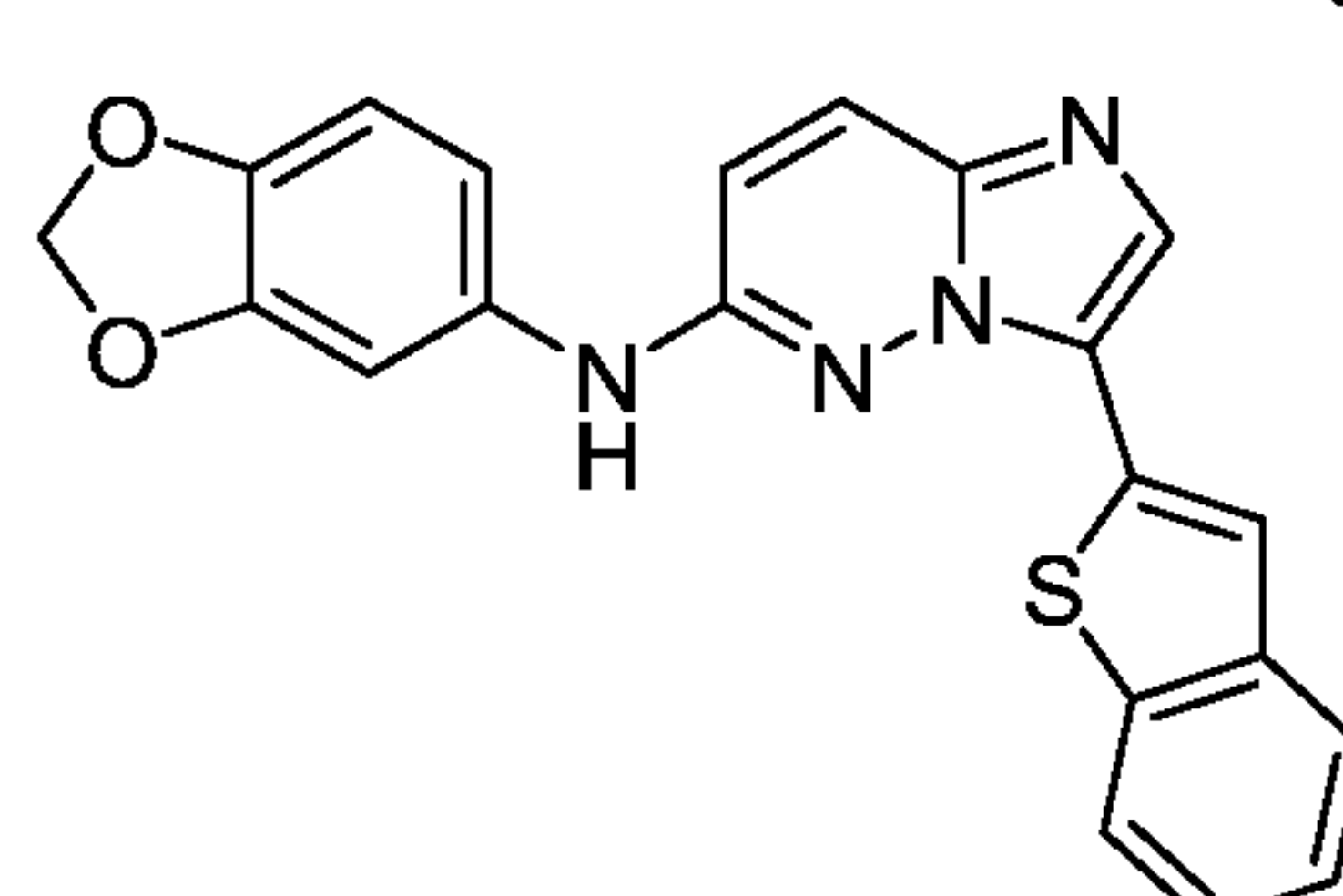
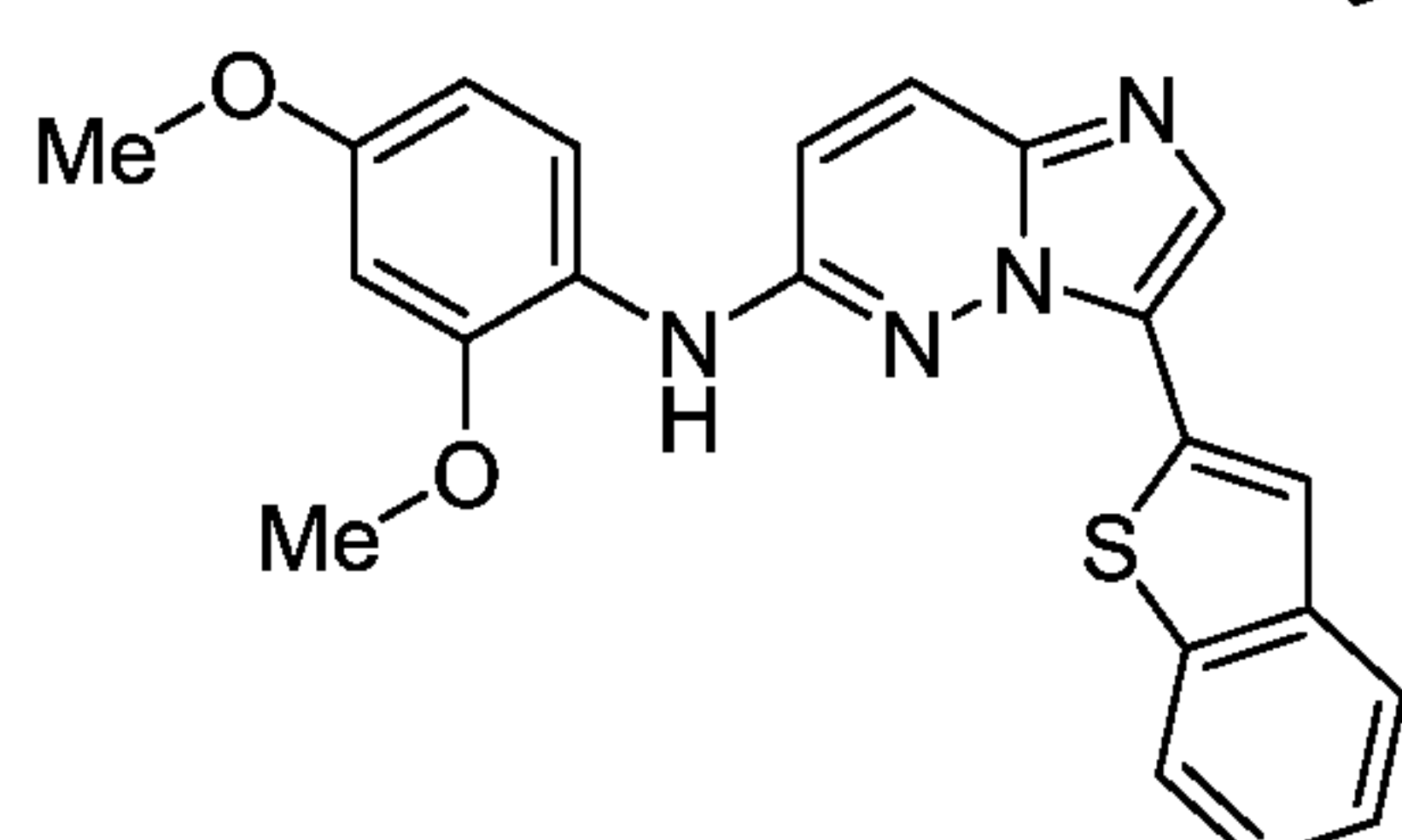
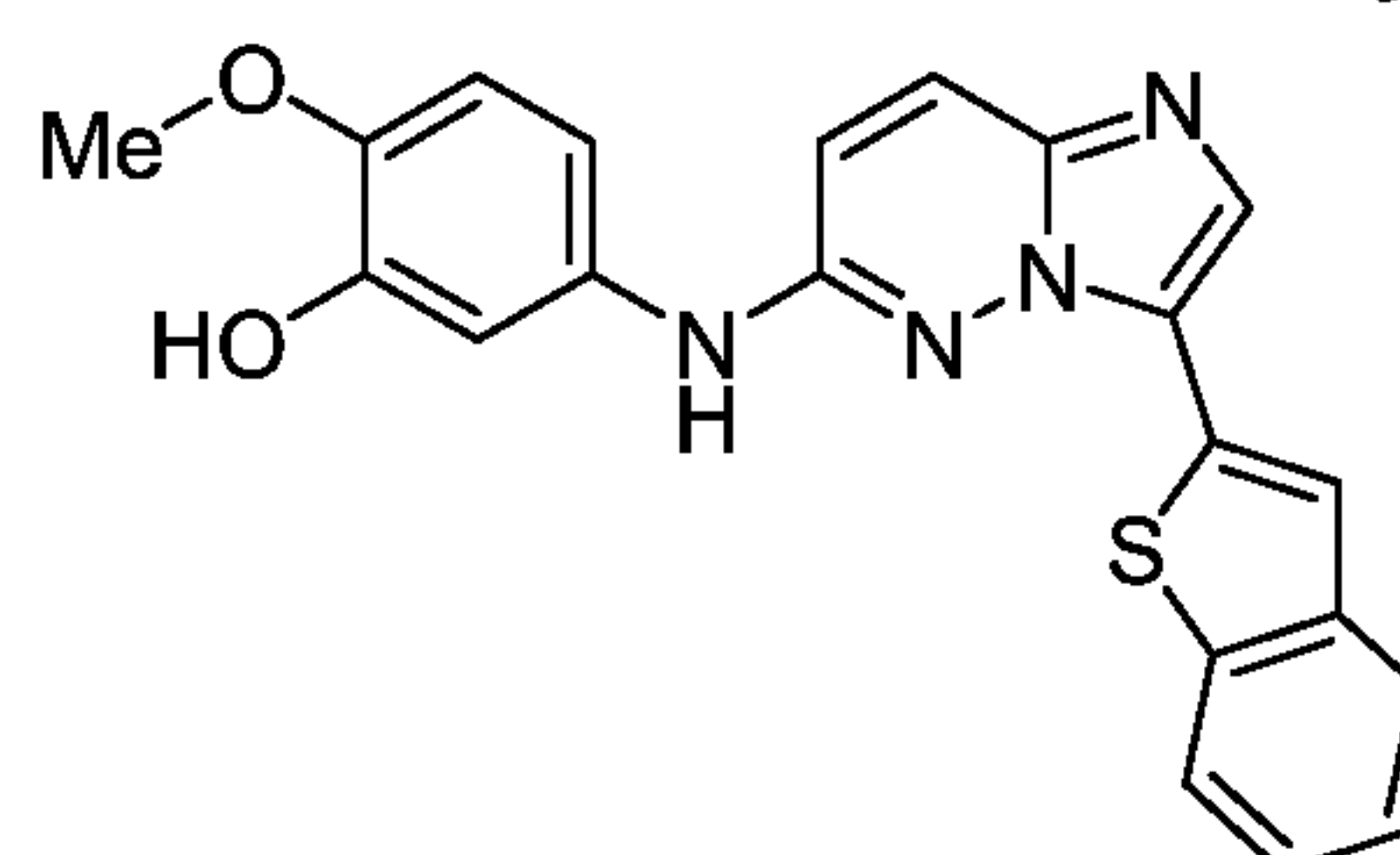
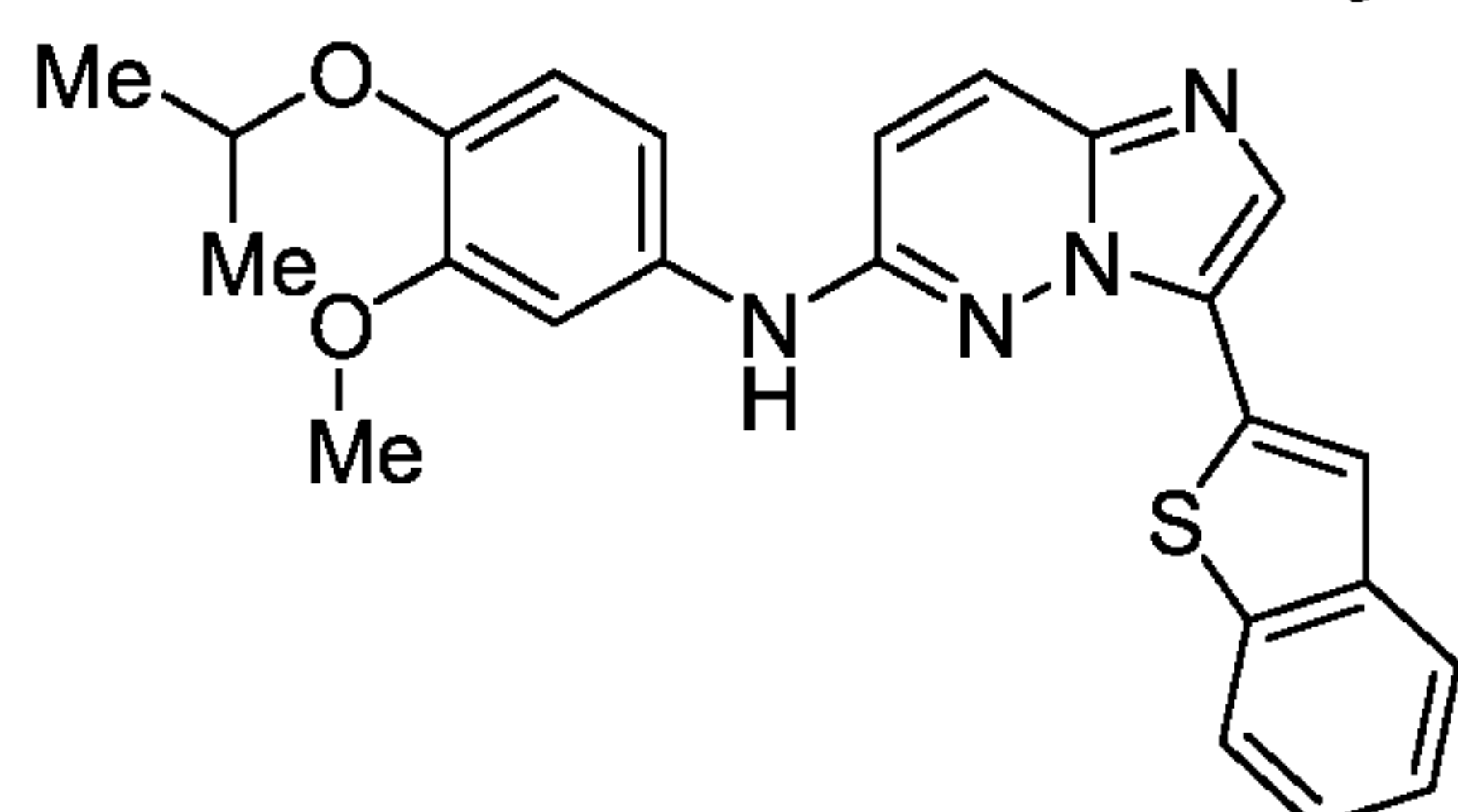
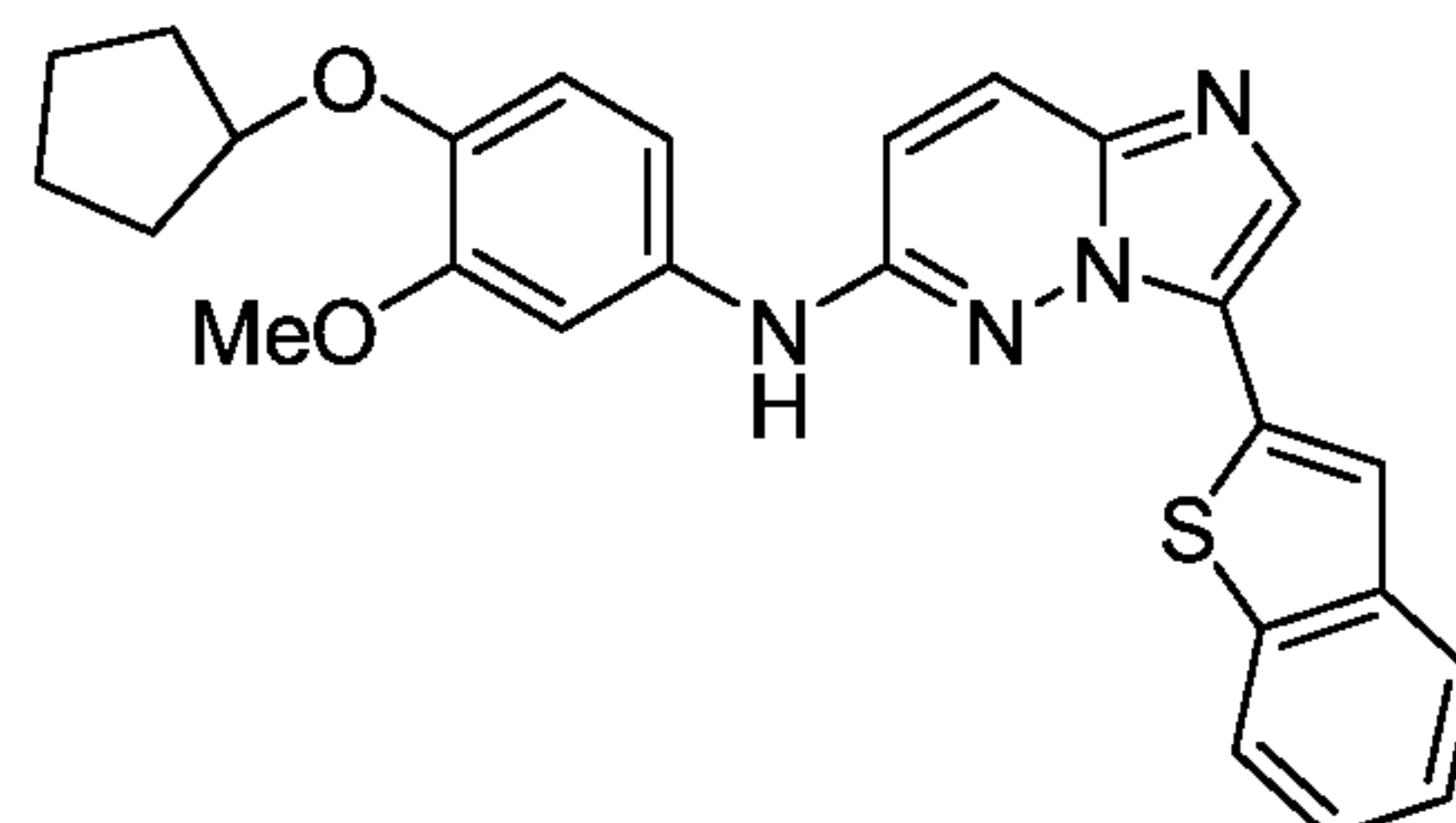
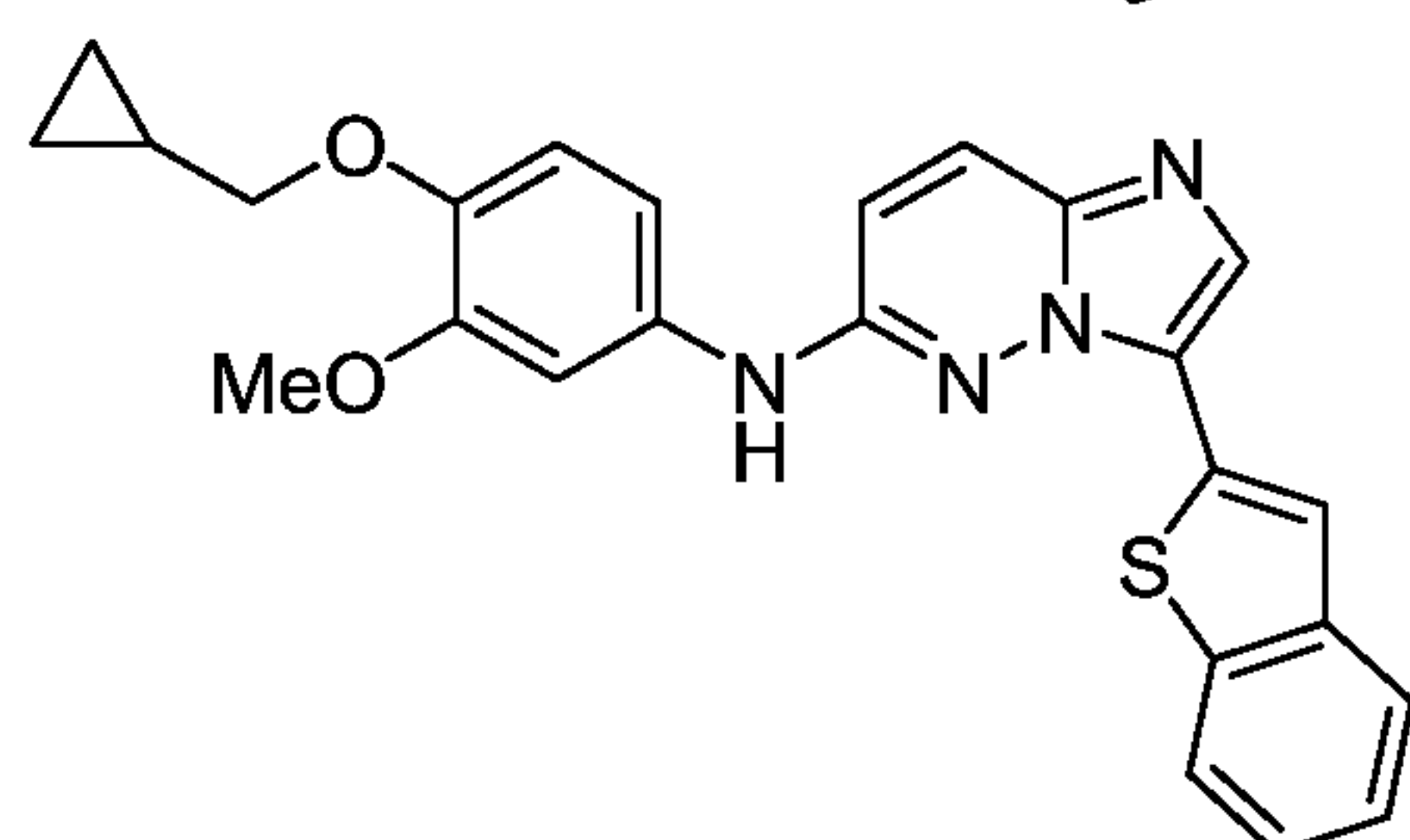
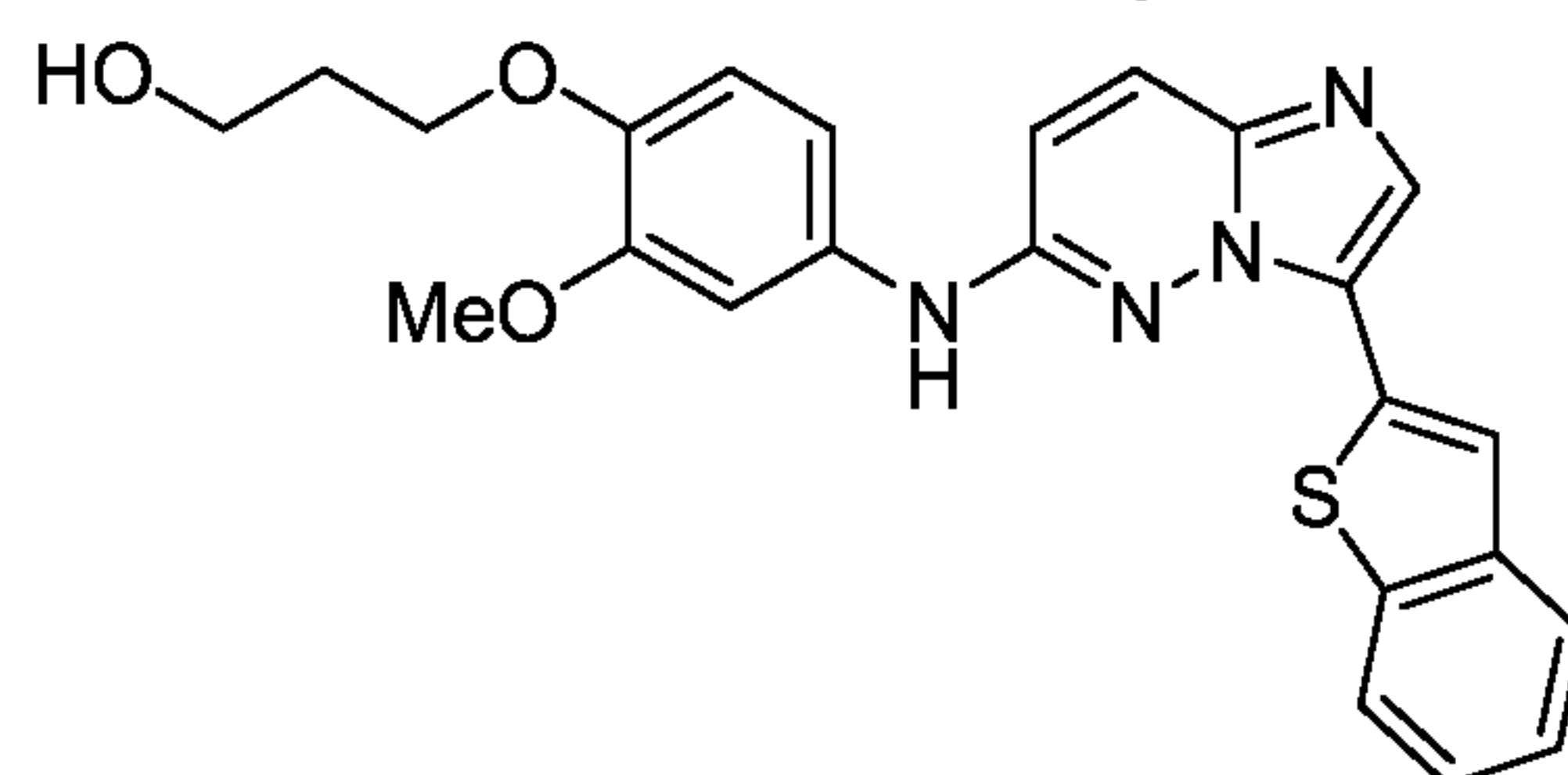
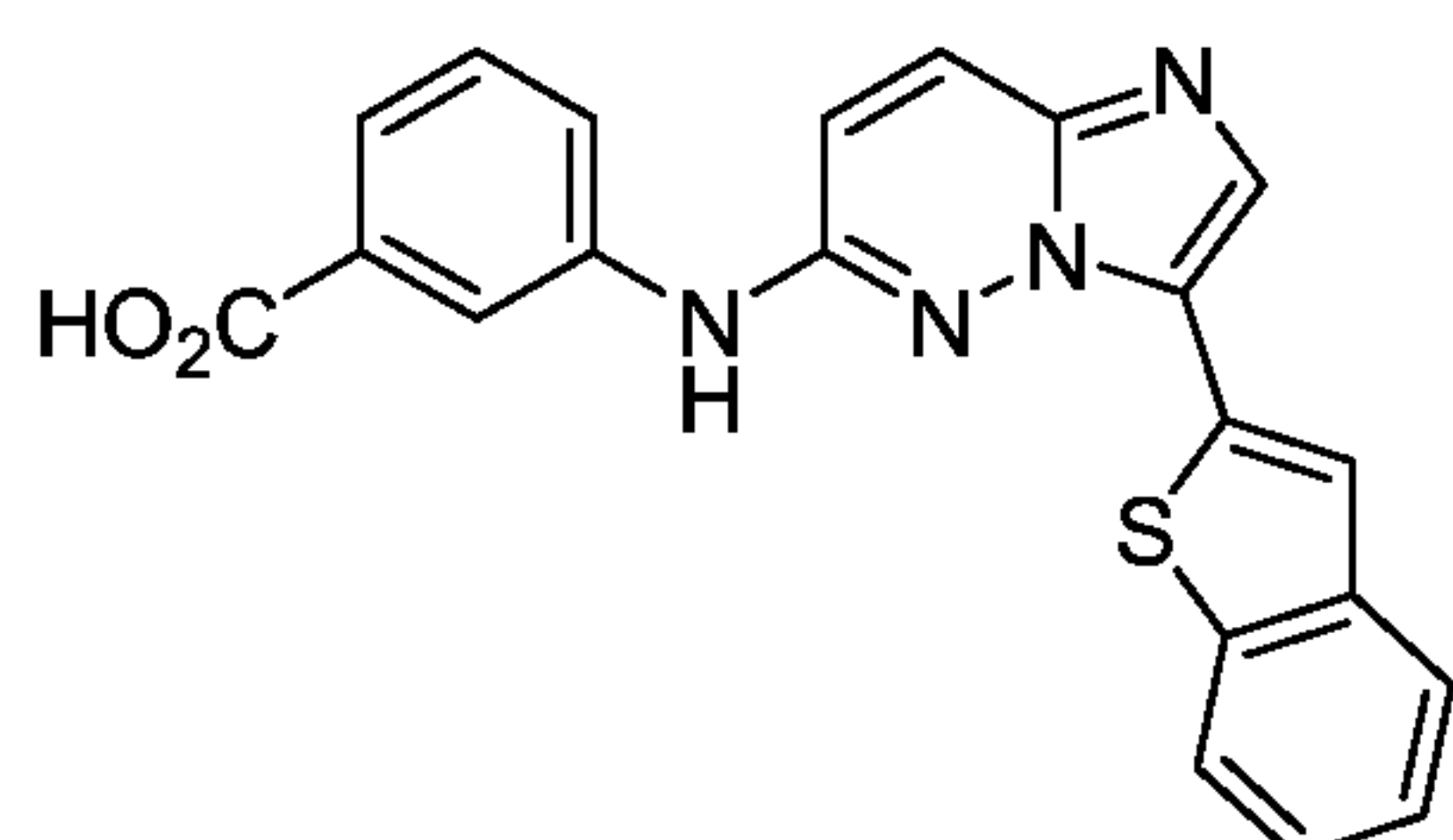
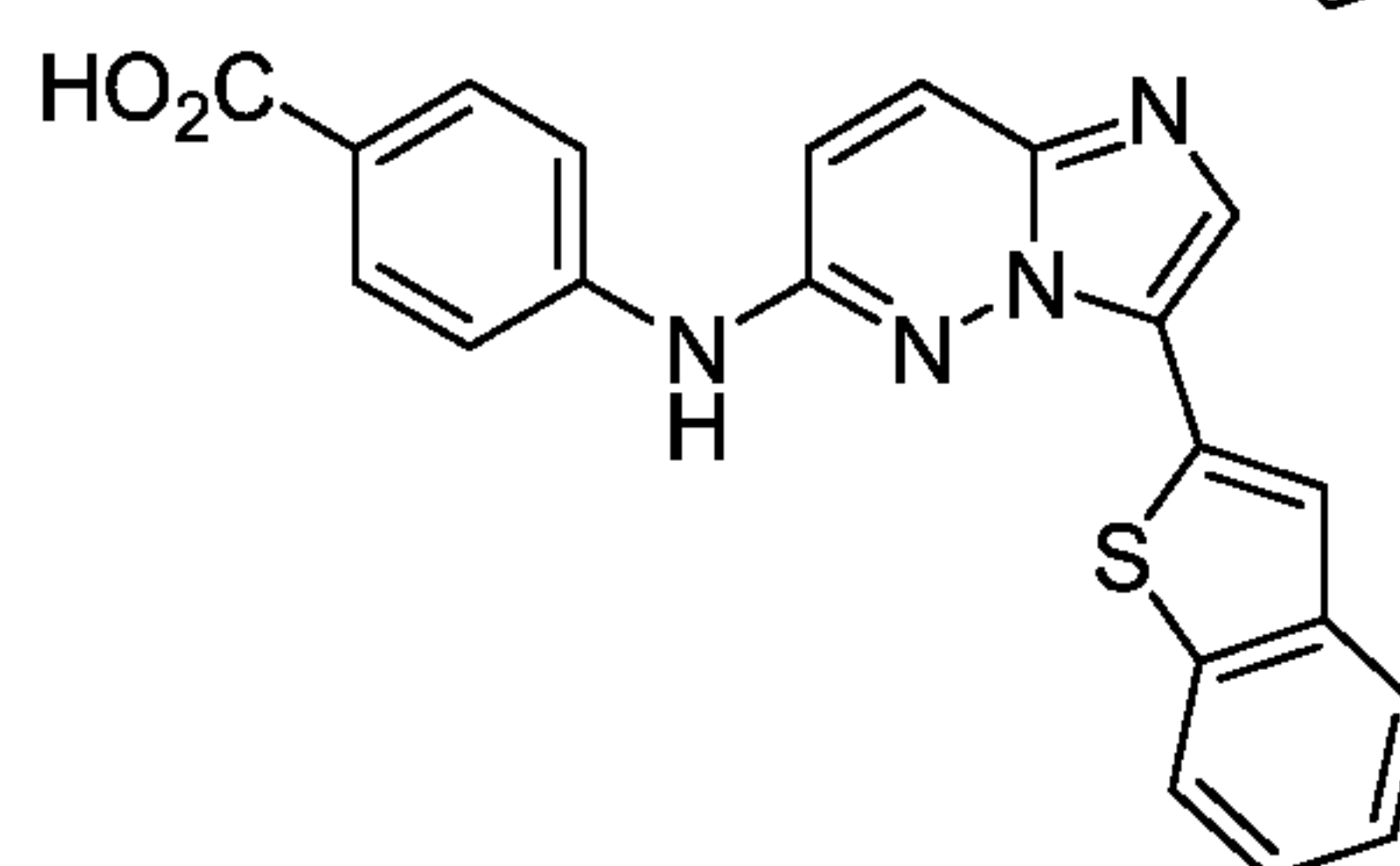
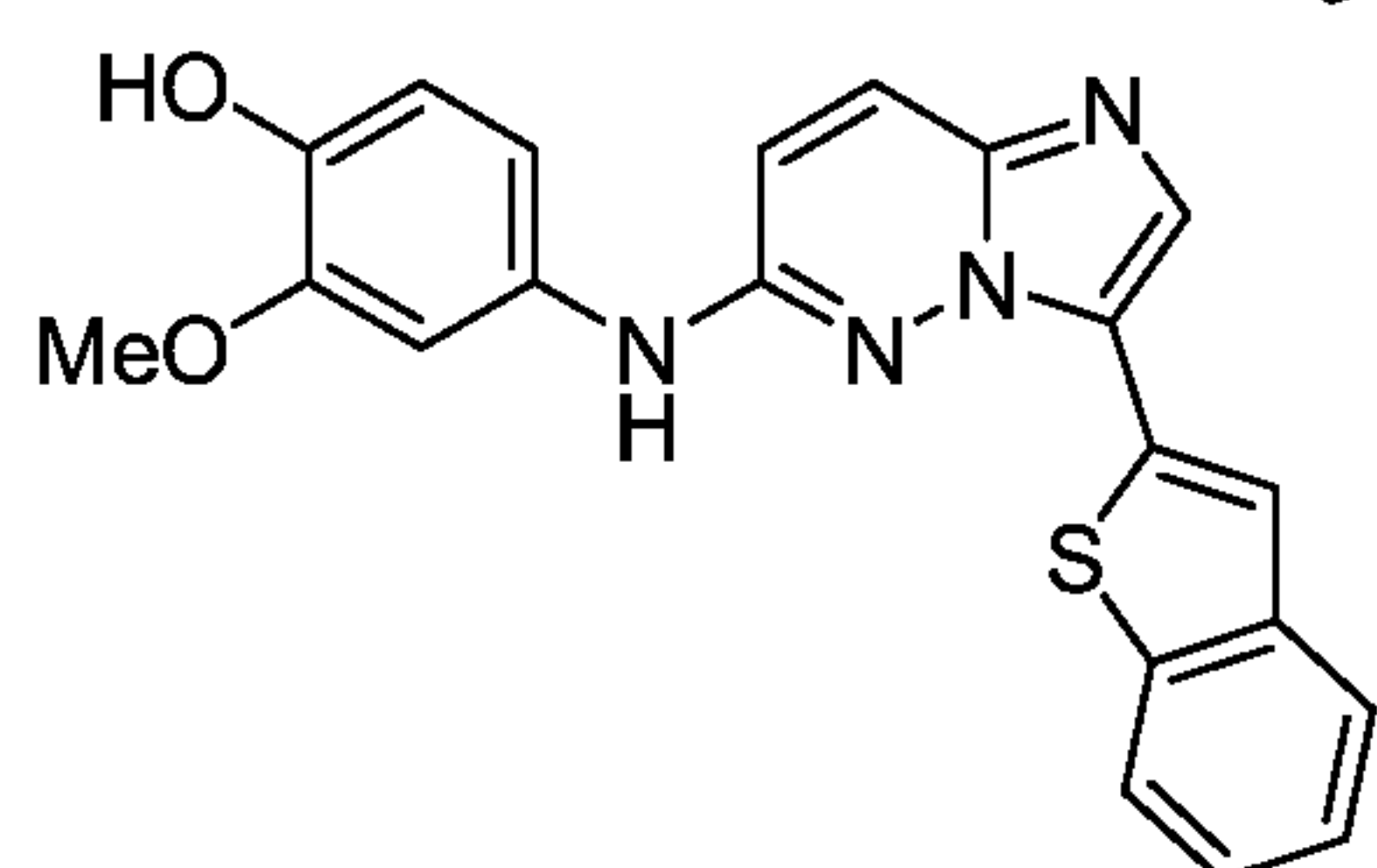
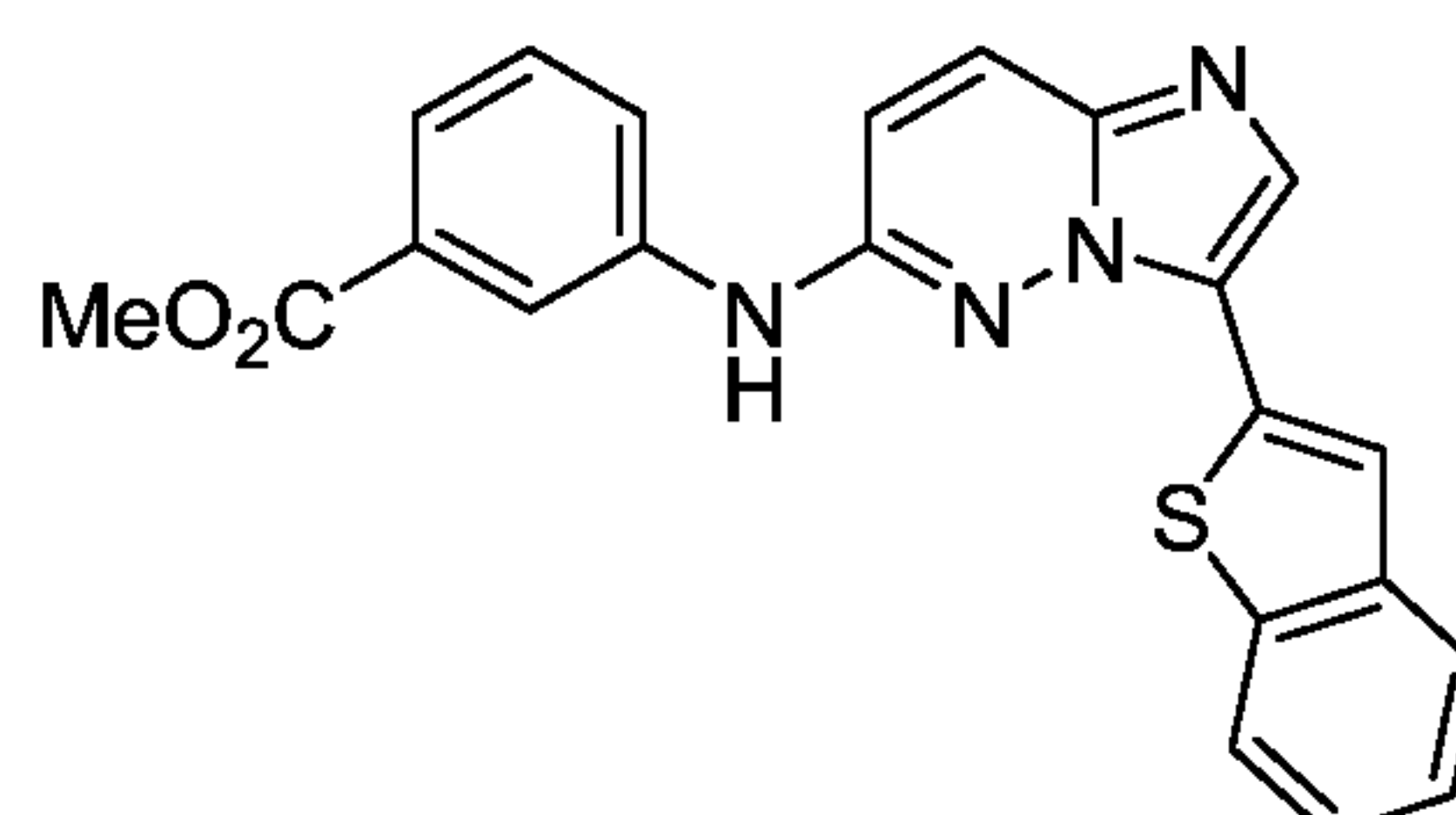
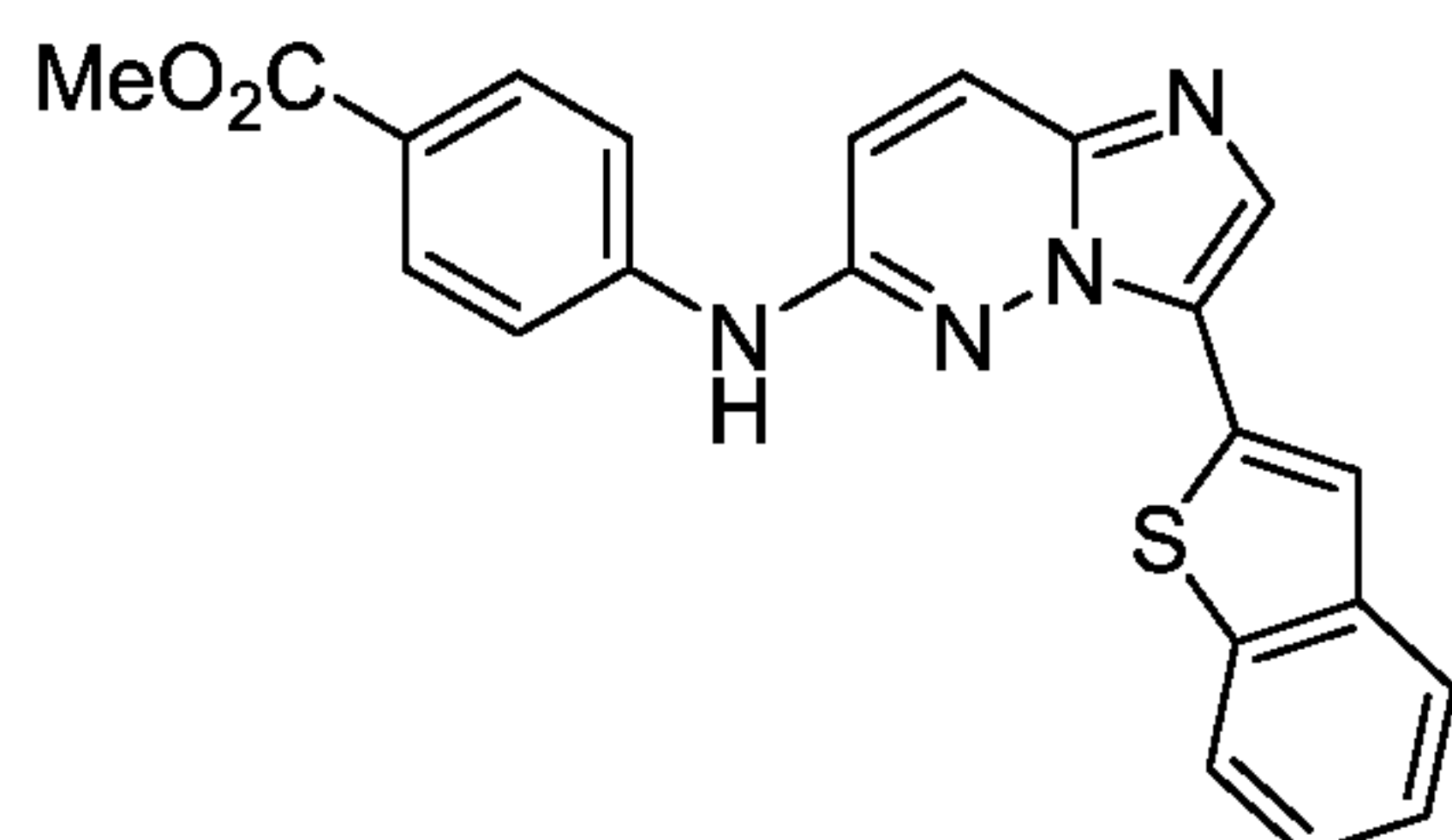
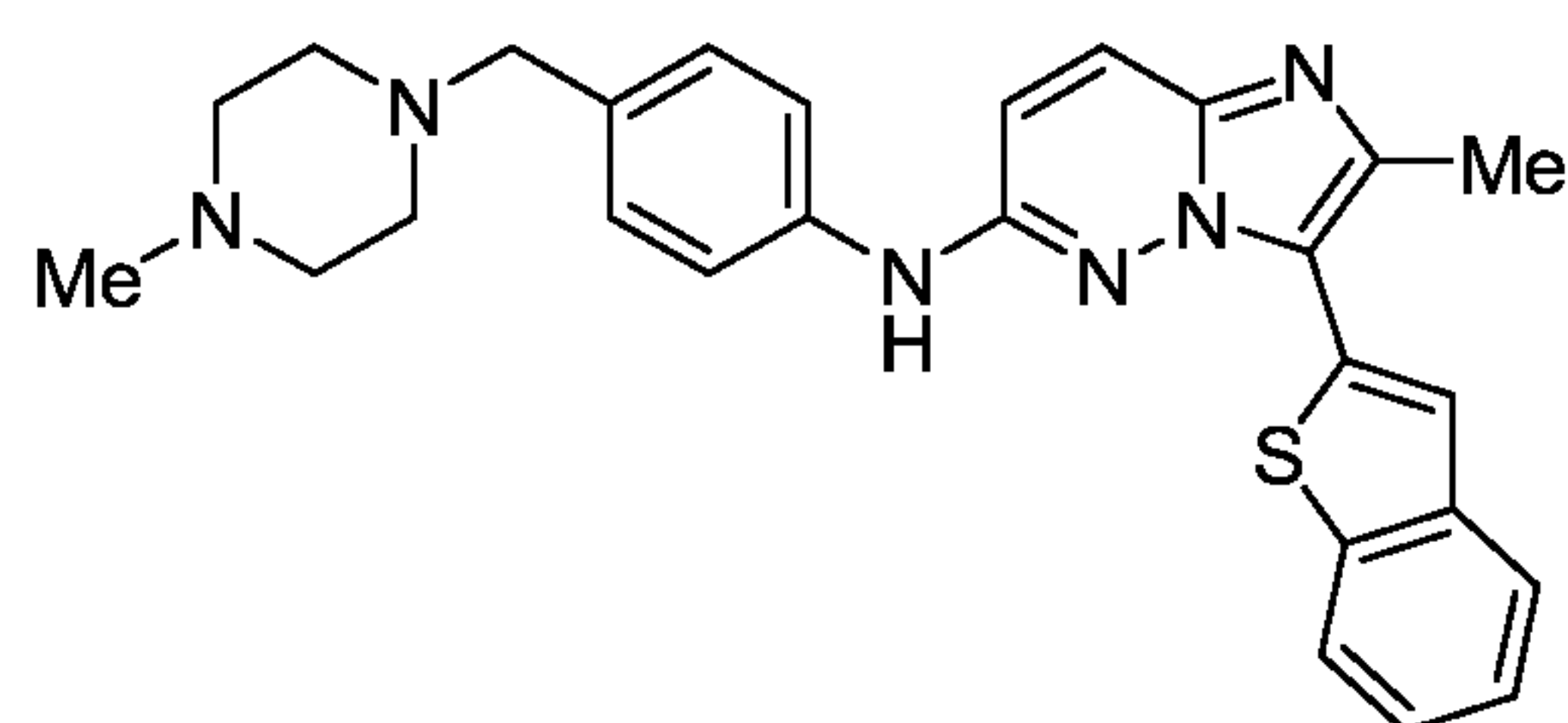
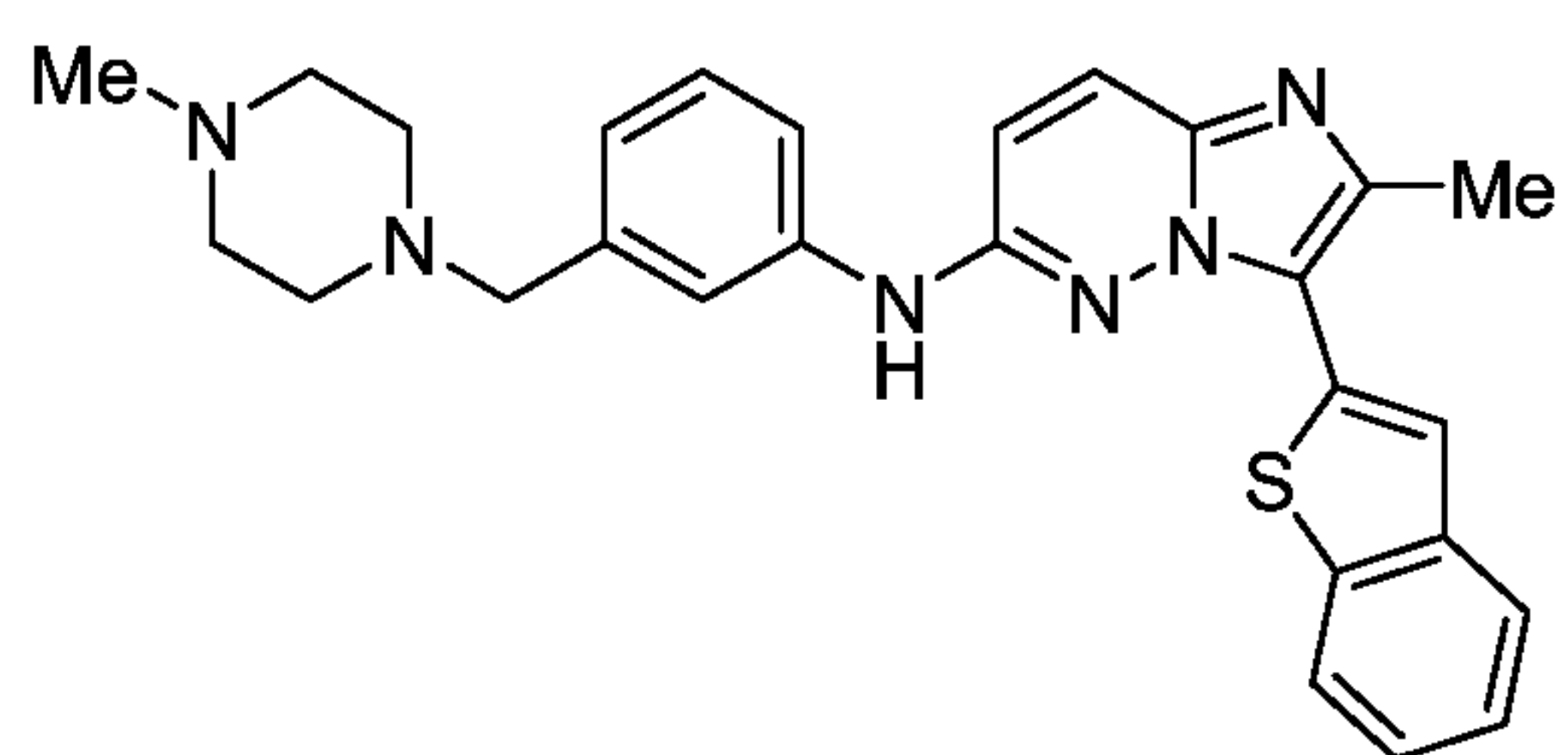


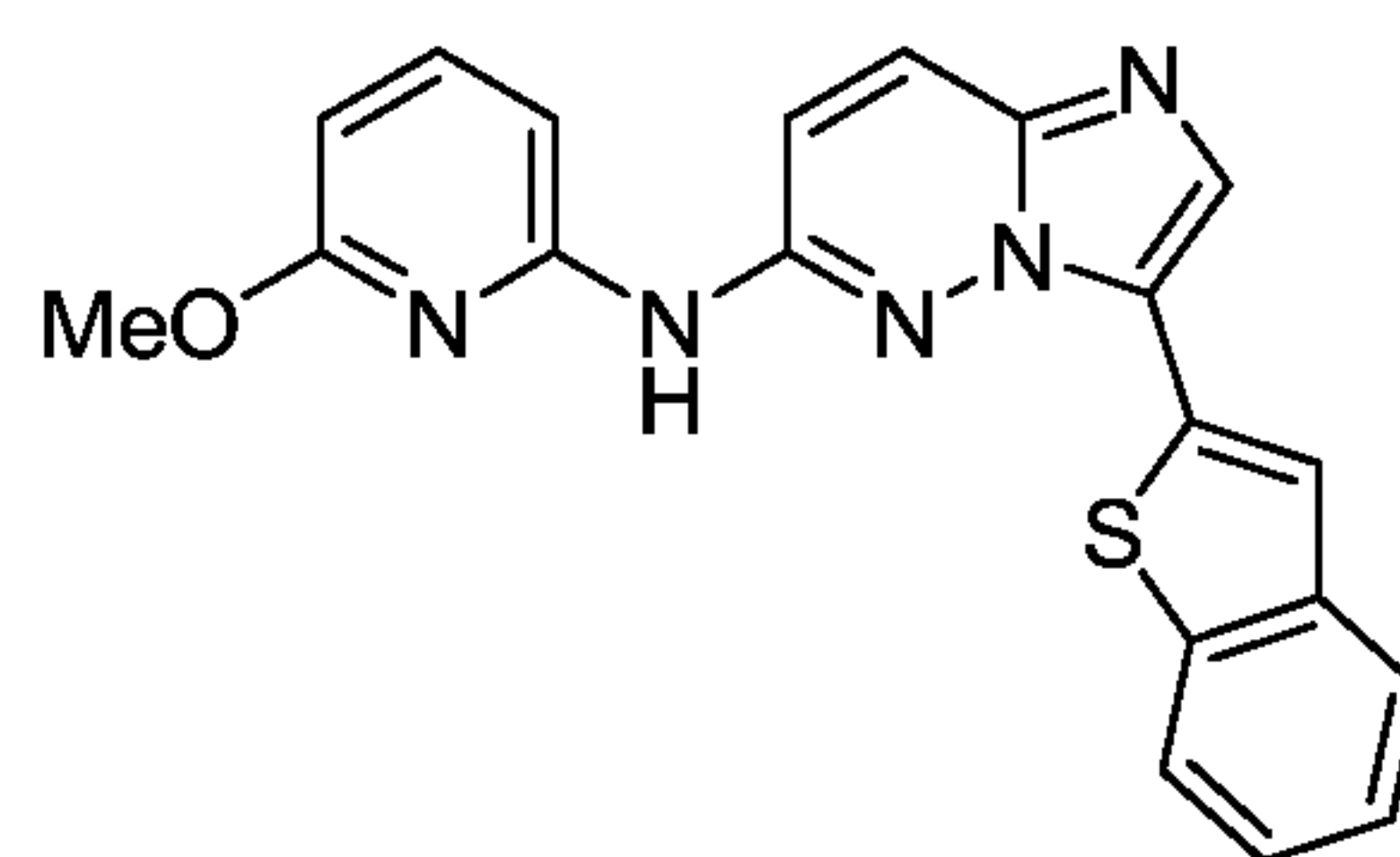
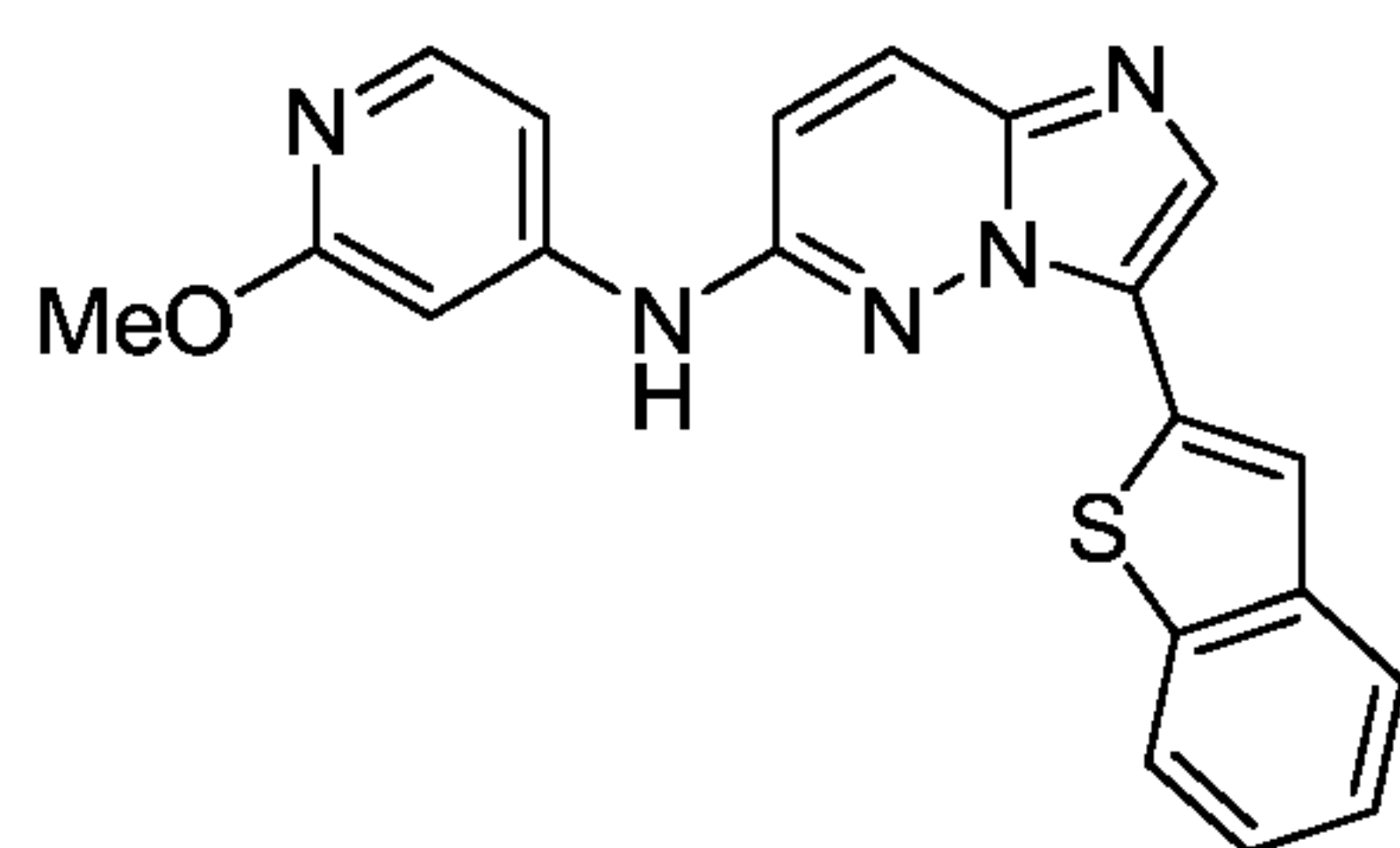
wherein each R_{10} is independently selected from the group consisting of F, Cl, -OH, methyl, methoxy, ethoxy, propoxy, isopropoxy, and -OCOCH₃; and k is 0, 1, 2, or 3.

5. The compound of any of claims 1, 2, or 4 wherein each of X_1 , X_2 , X_3 , and X_4 is CH.
6. The compound of any of claims 1, 2, or 4 wherein X_1 is N, and each of X_2 , X_3 , and X_4 is CH.
7. The compound of any of claims 1, 2, or 4 wherein X_2 is N, and each of X_1 , X_3 , and X_4 is CH.
8. The compound of any of claims 1, 2, or 4 wherein X_3 is N, and each of X_1 , X_2 , and X_4 is CH.
9. The compound of any of claims 1, 2, or 4 wherein X_4 is N, and each of X_1 , X_2 , and X_3 is CH.
10. The compound of any of claims 1-9 wherein Y is $-W-(CH_2)_n-R_1$.
11. The compound of any of claims 1-10 wherein R_1 is $-NR_2R_3$.
12. The compound of any of claims 1-11 wherein R_3 is selected from the group consisting of C_2 - C_{10} alkyl, aryl, and cycloalkyl.
13. The compound of any of claims 1-12 wherein R_3 is phenyl optionally substituted with one or more R_7 , wherein each R_7 is independently selected from the group consisting of hydroxyl, methoxy, $-COOH$, $-O-(CH_2)_m-OH$, cyclopropylmethoxy, cyclopentylmethoxy, and isopropyl.
14. The compound of any of claims 1-13 wherein each R_7 is independently selected from the group consisting of methoxy, $-COOH$, and $-O-(CH_2)_3-OH$.
15. The compound of any of claims 1-11 wherein R_3 is C_2 - C_{10} alkyl, aryl, and cycloalkyl, where any atom of R_3 is optionally substituted with one or more R_7 .
16. The compound of any of claims 1-15 wherein the compound is selected from any of:



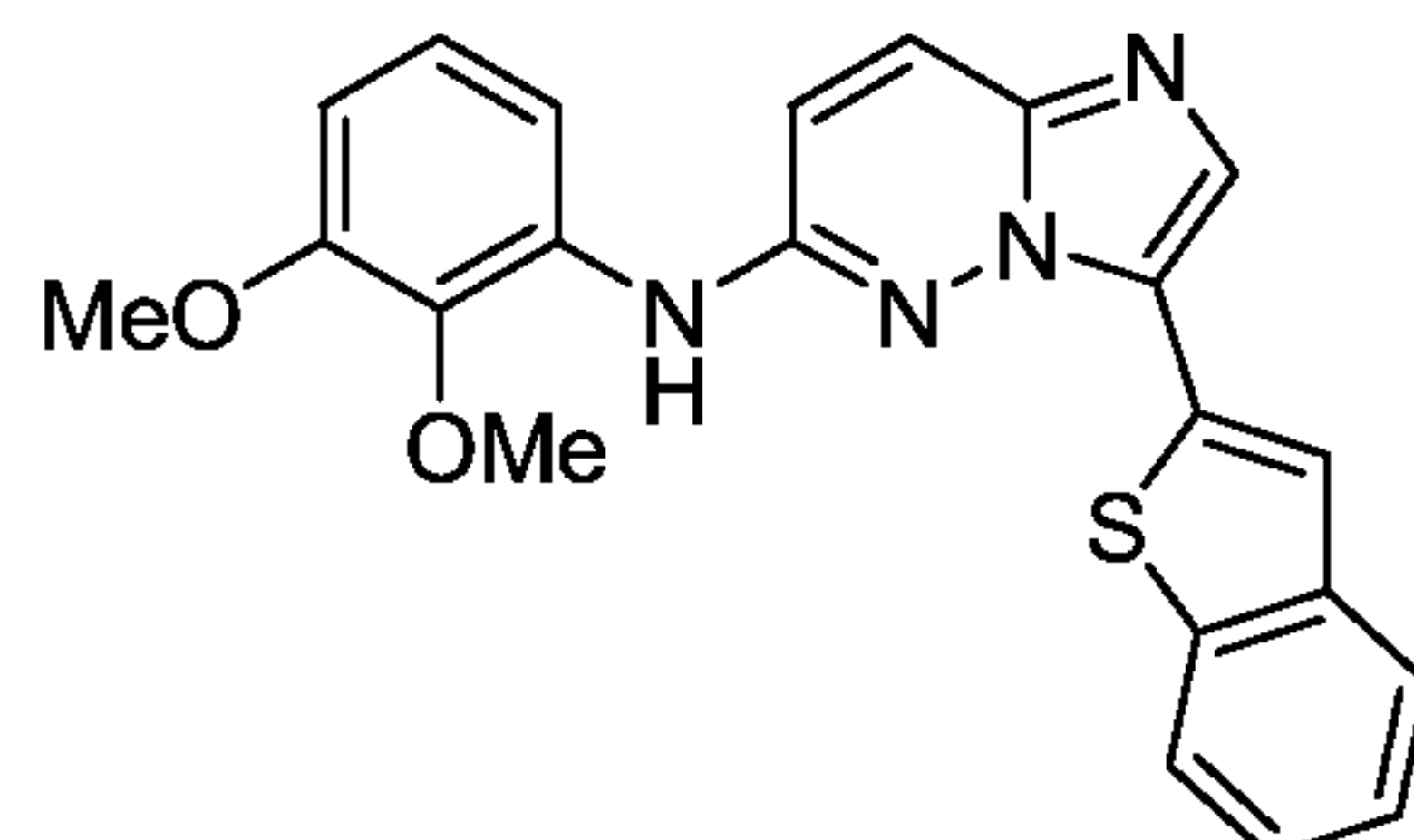
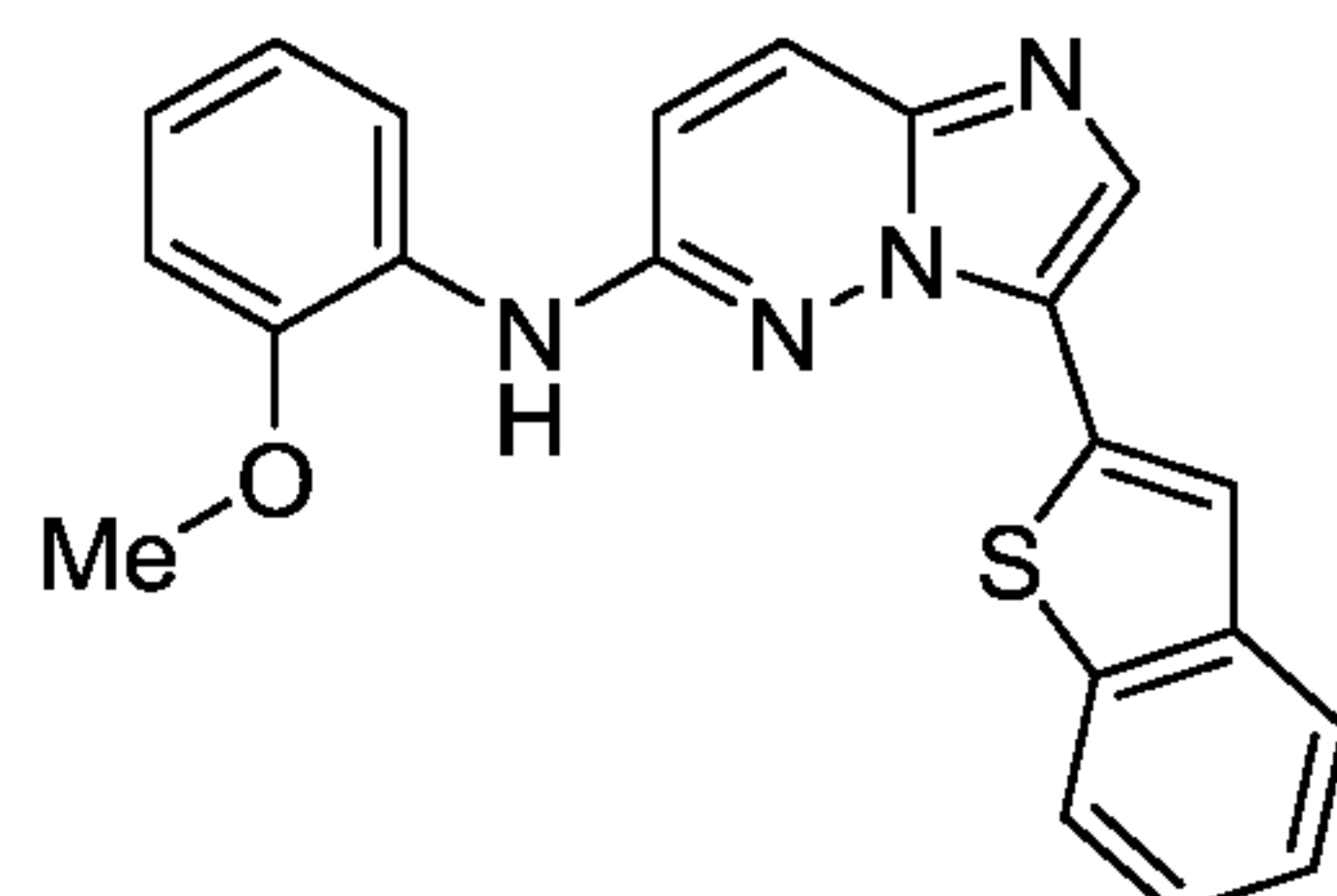






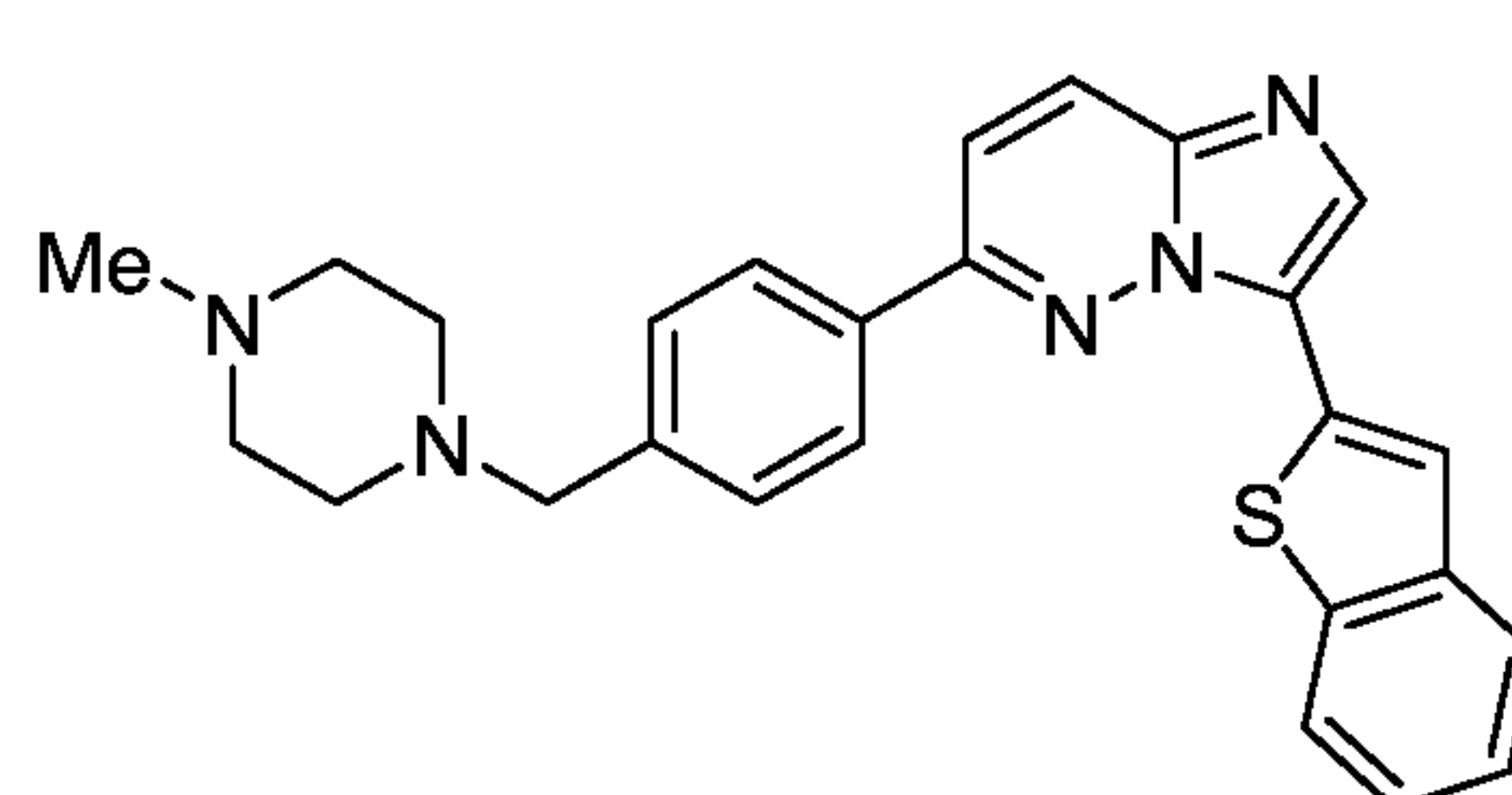
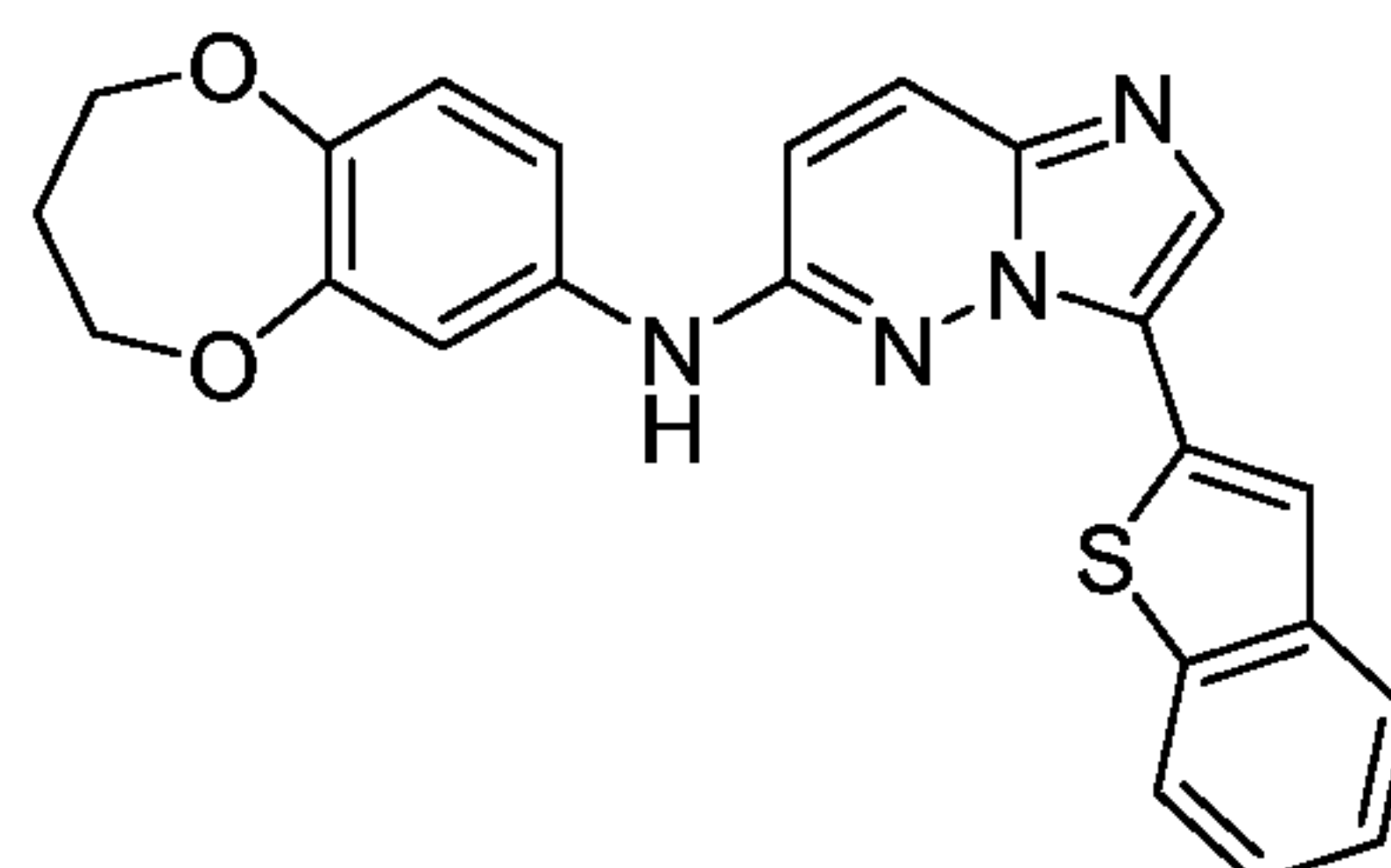
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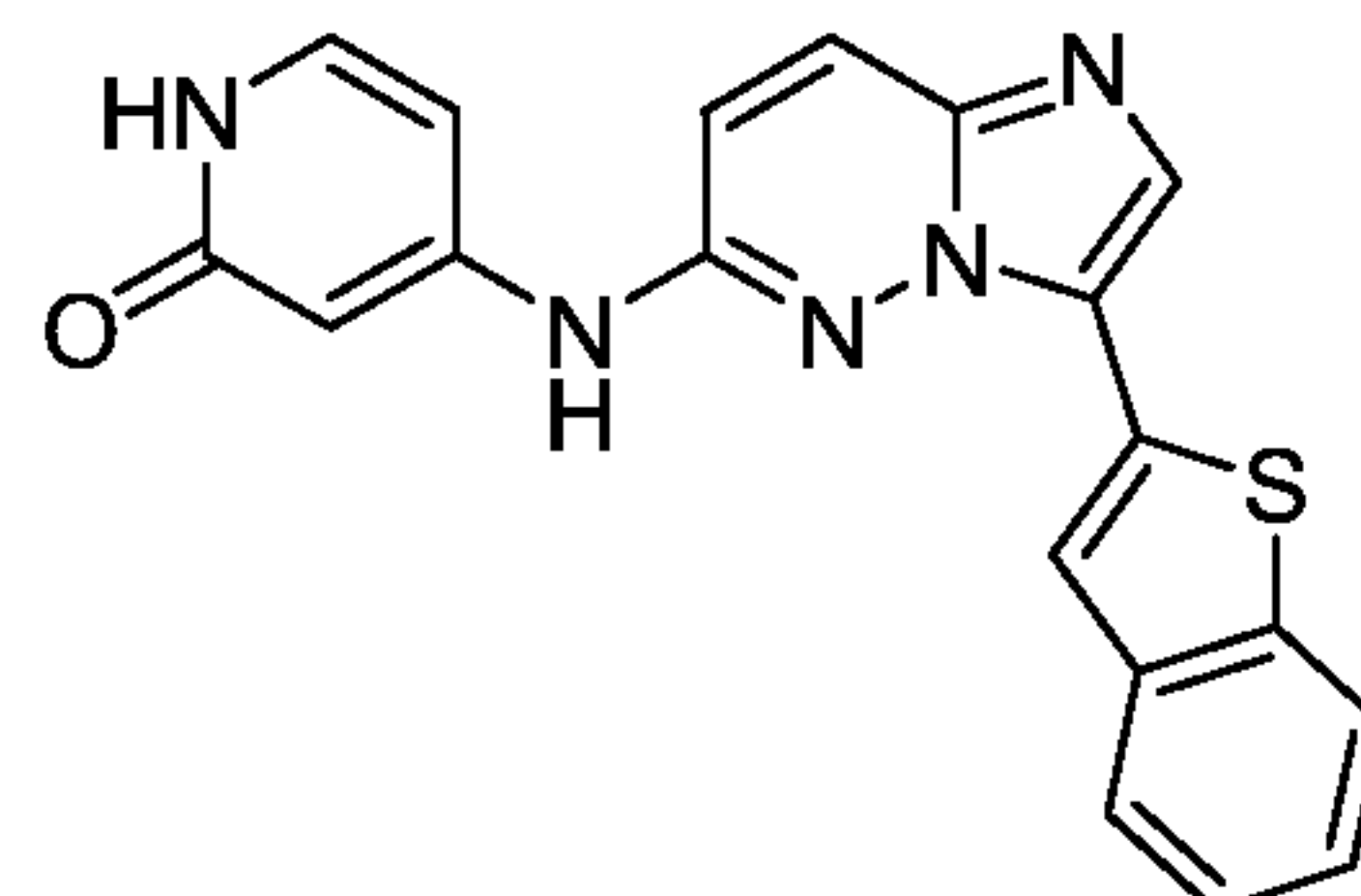
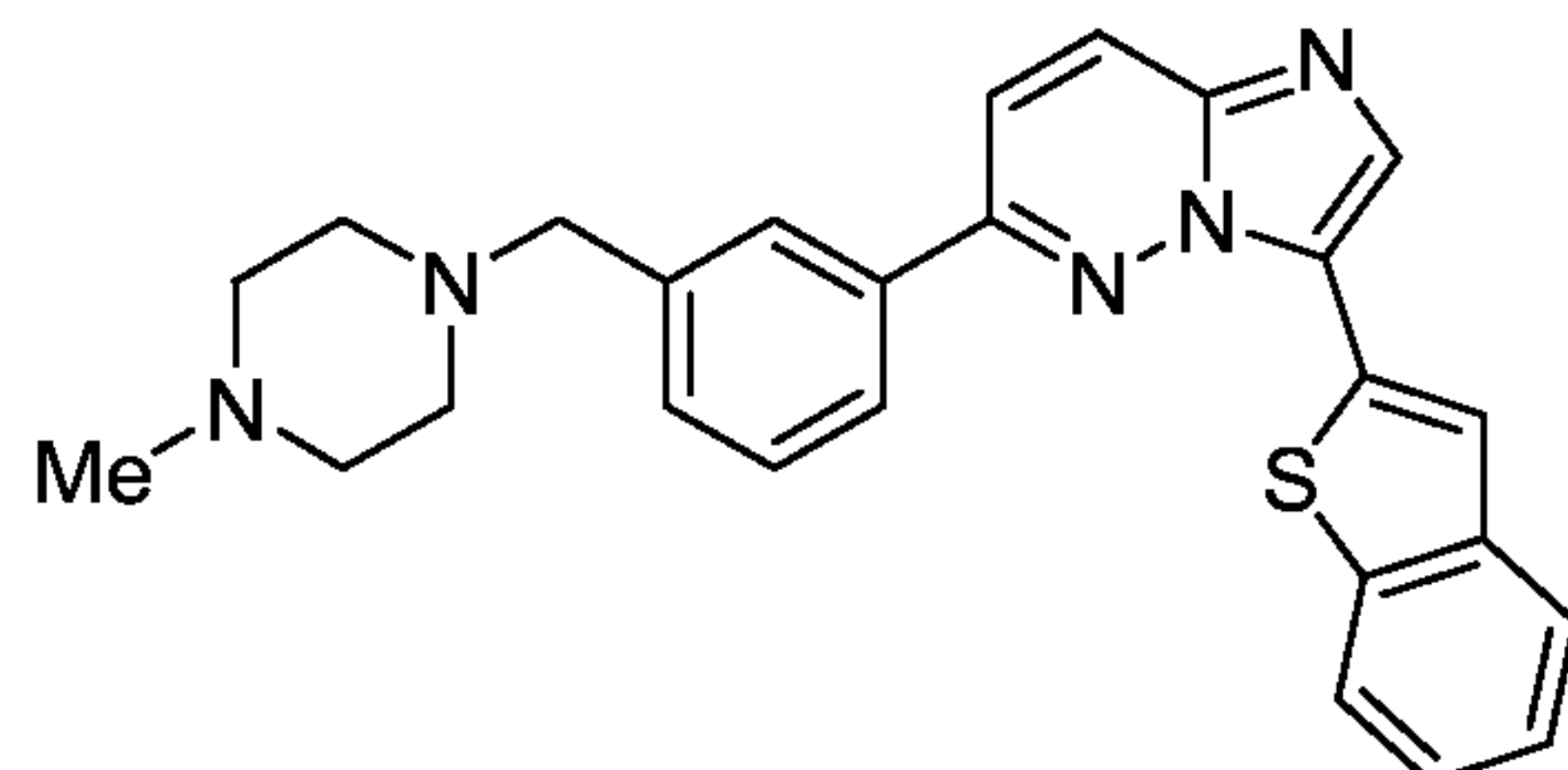
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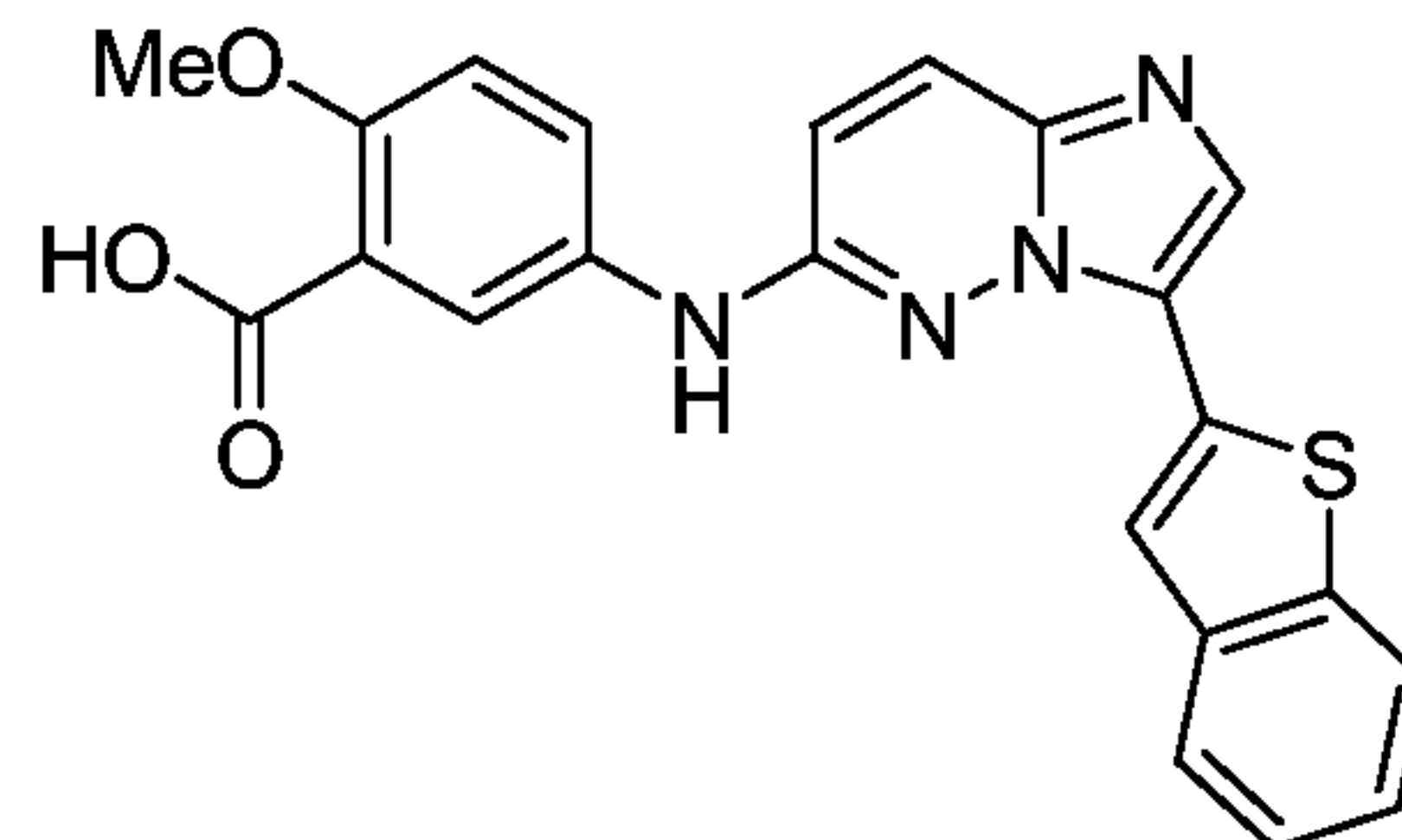
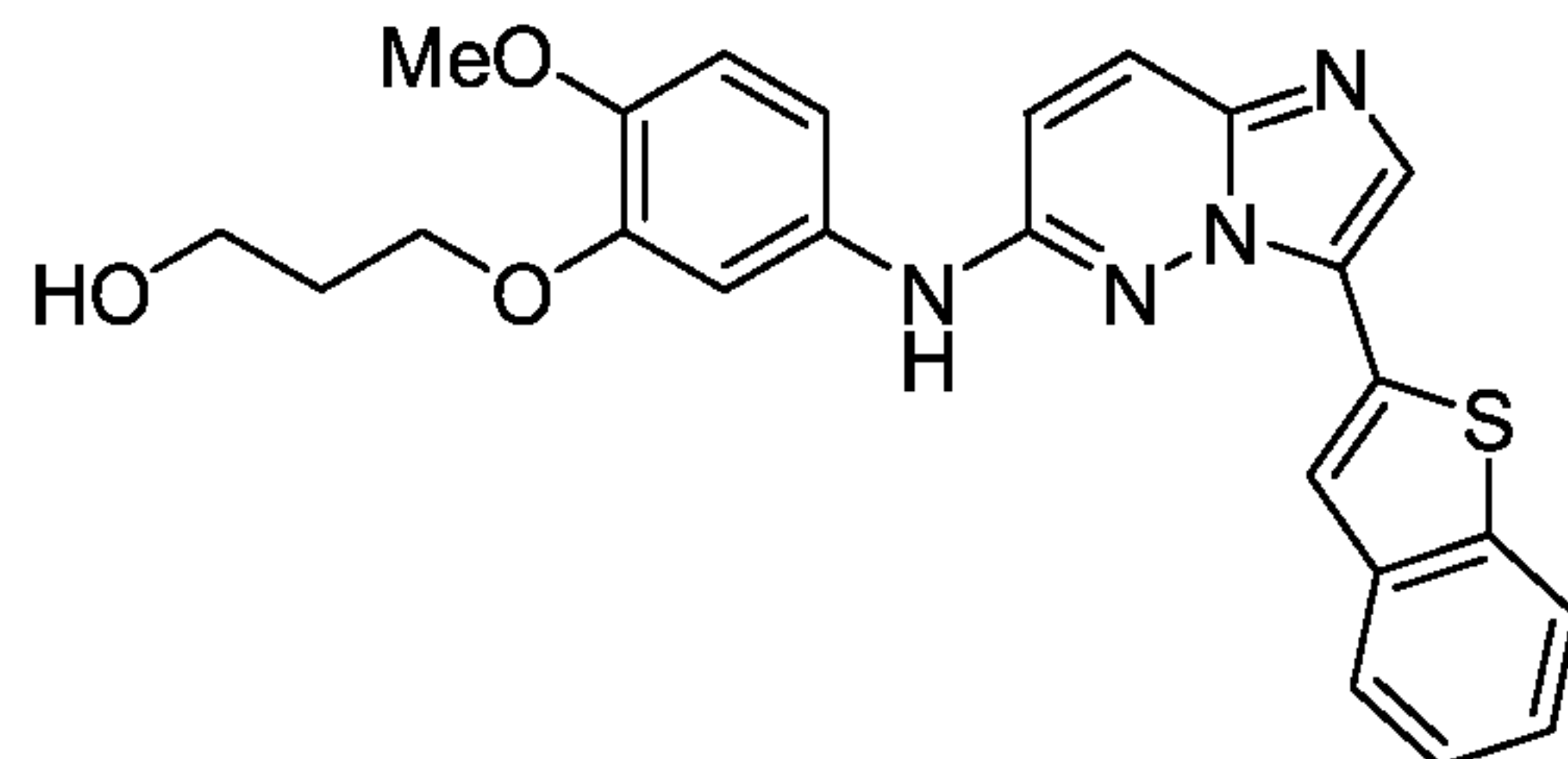
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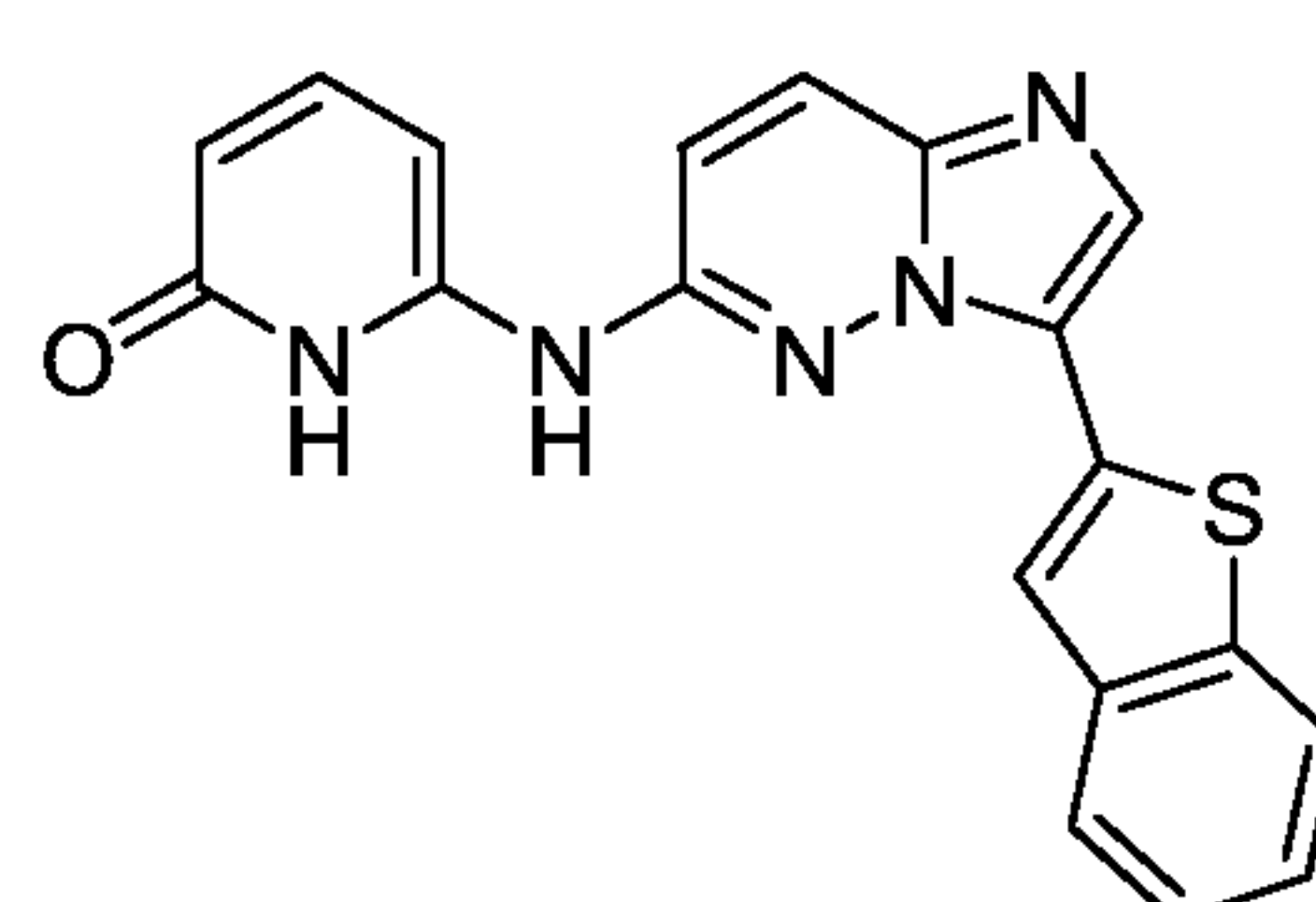
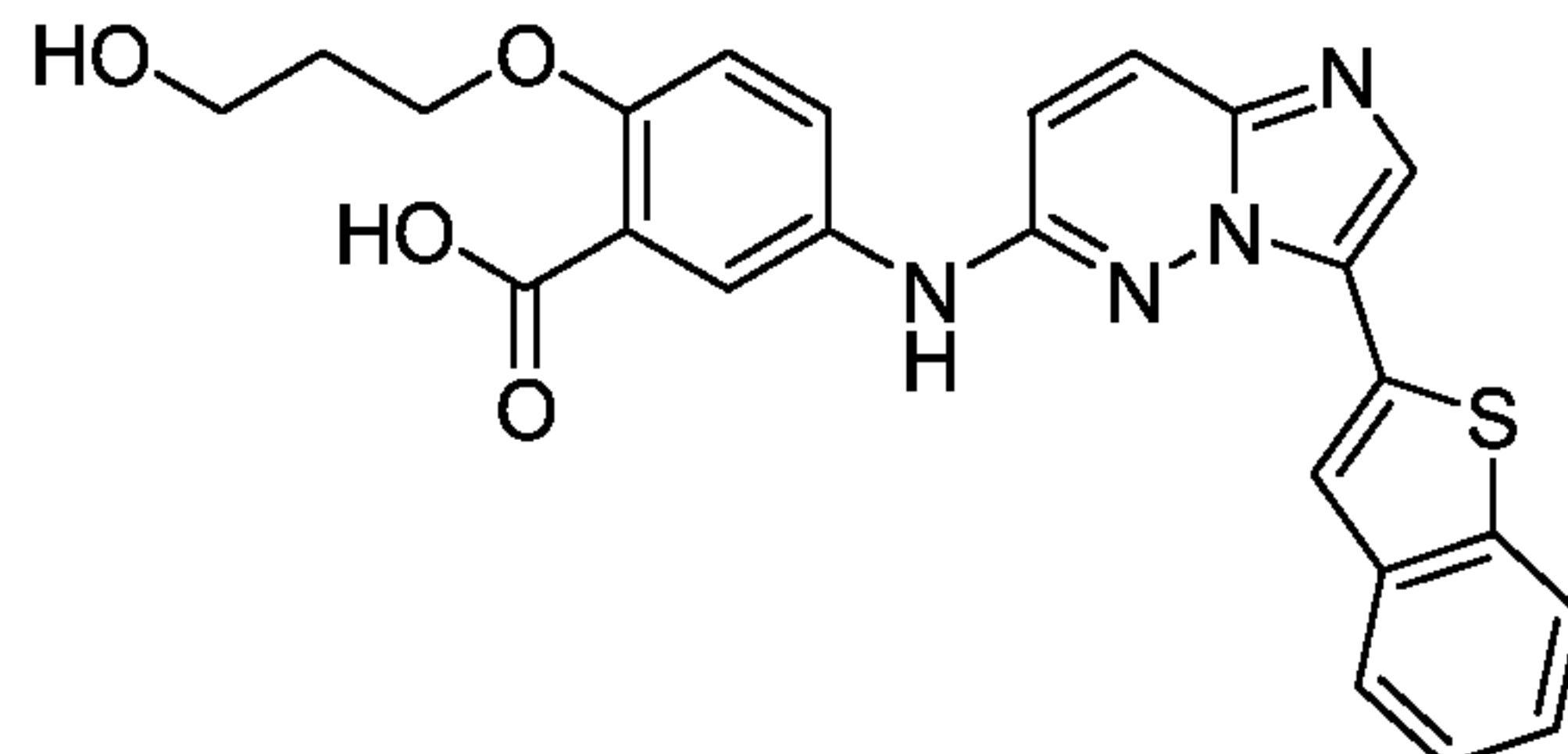
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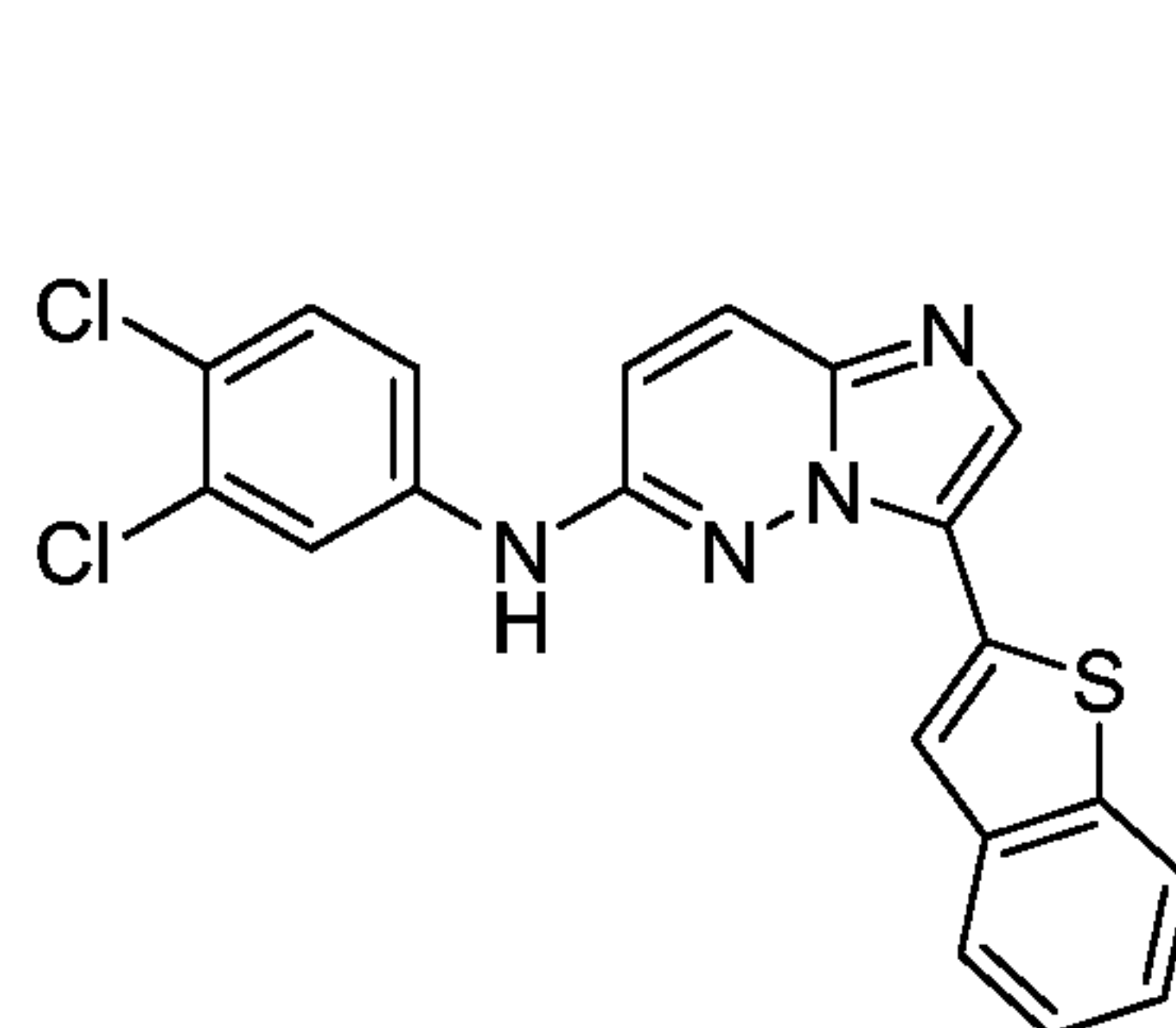
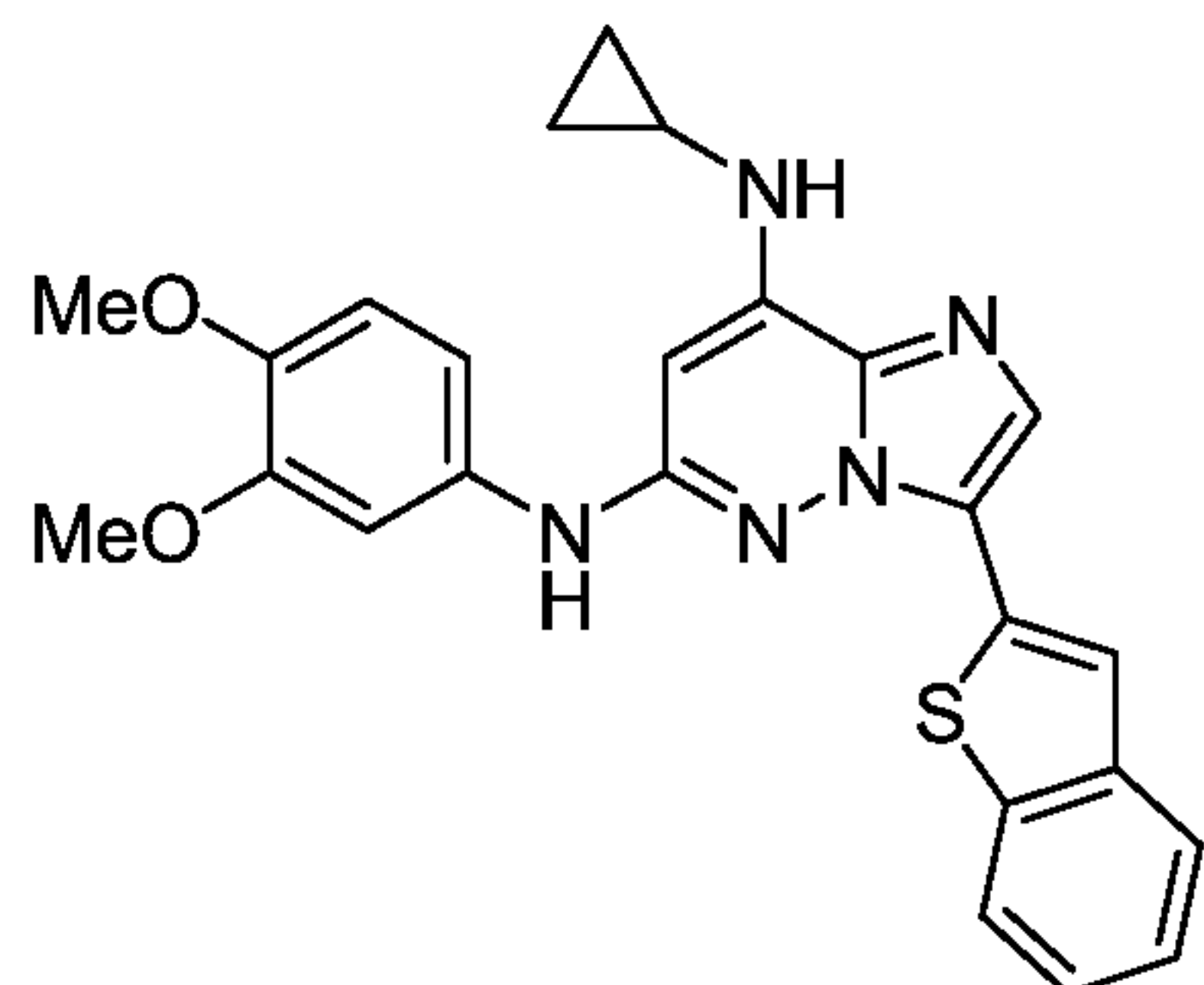
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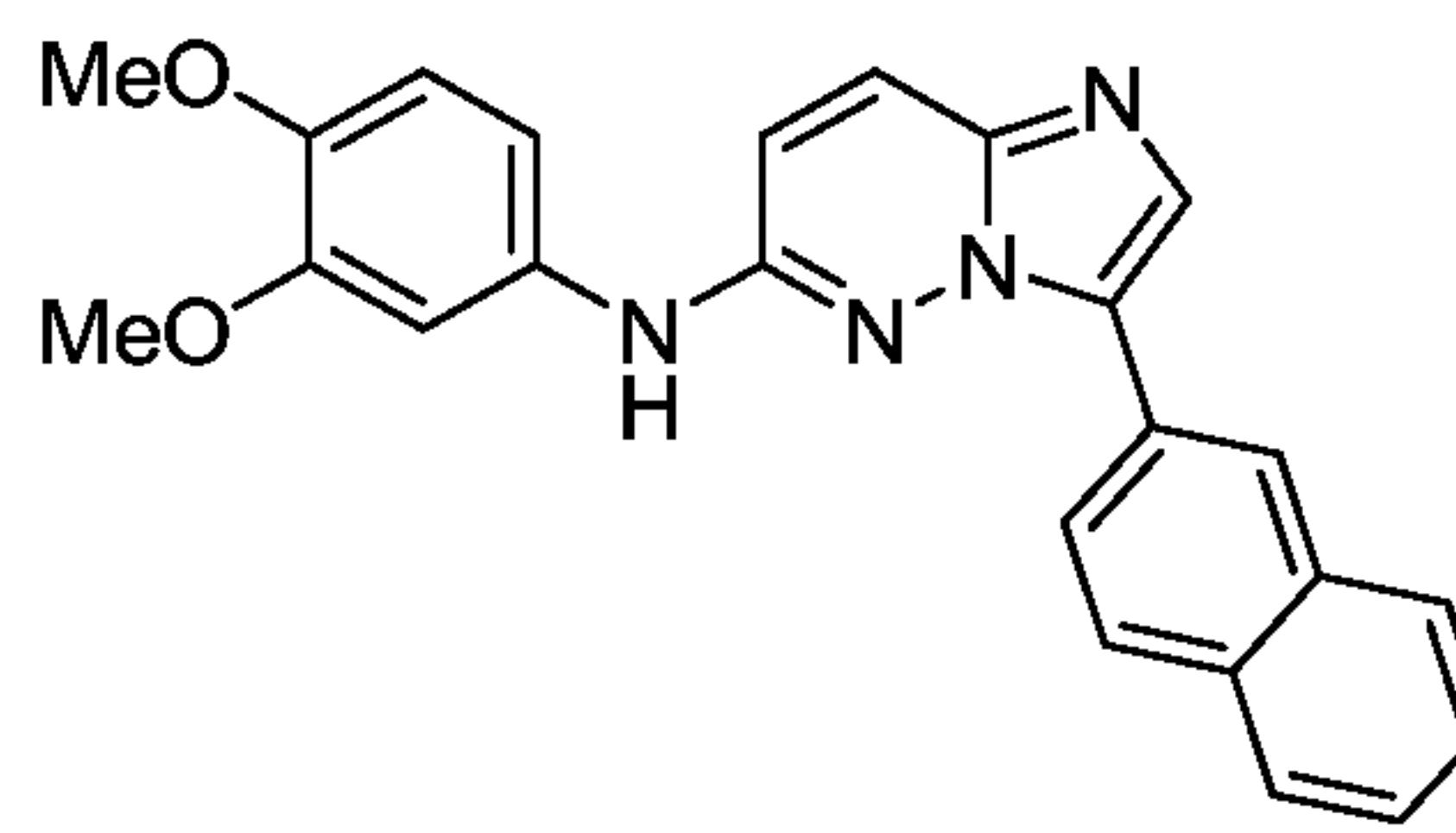
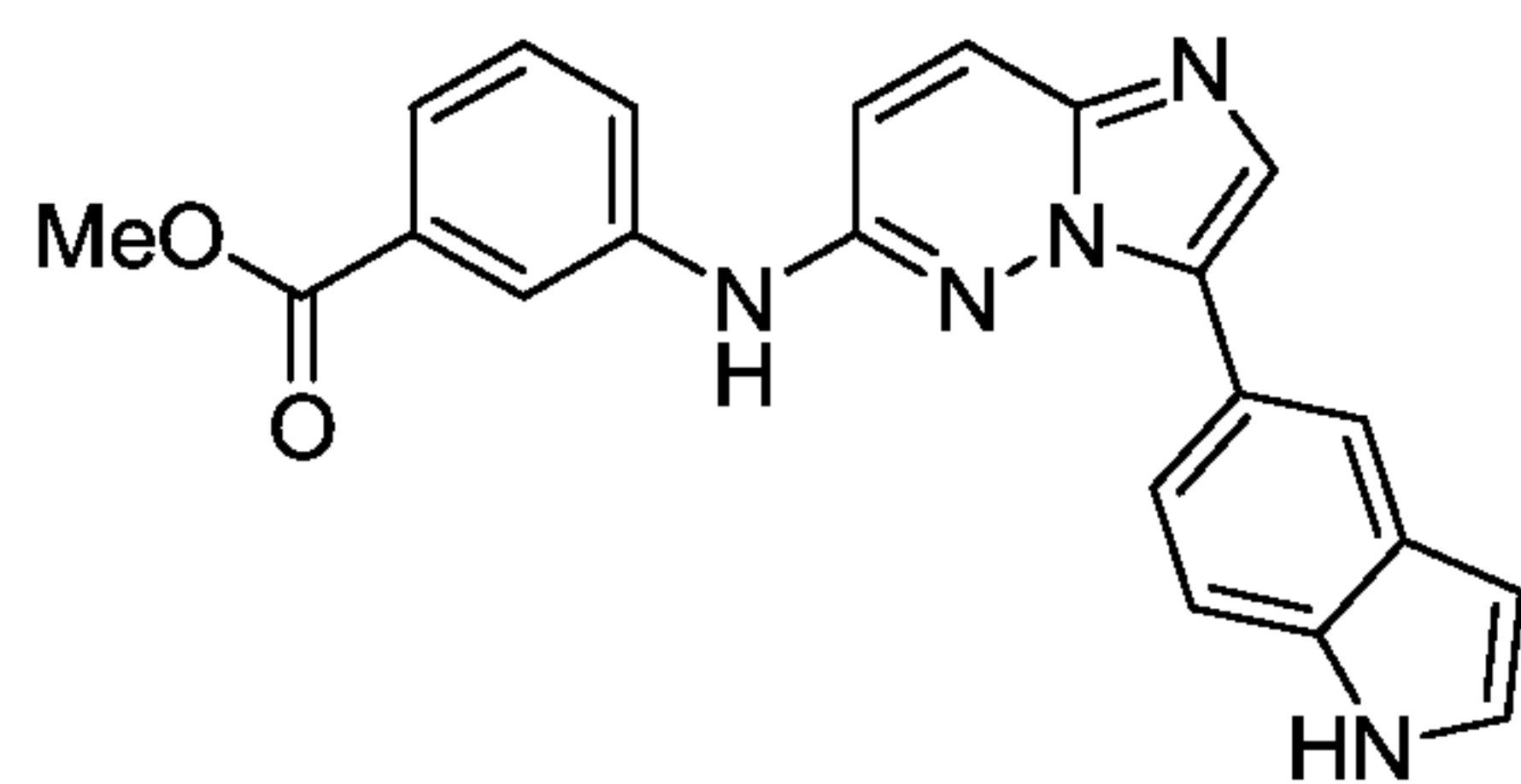
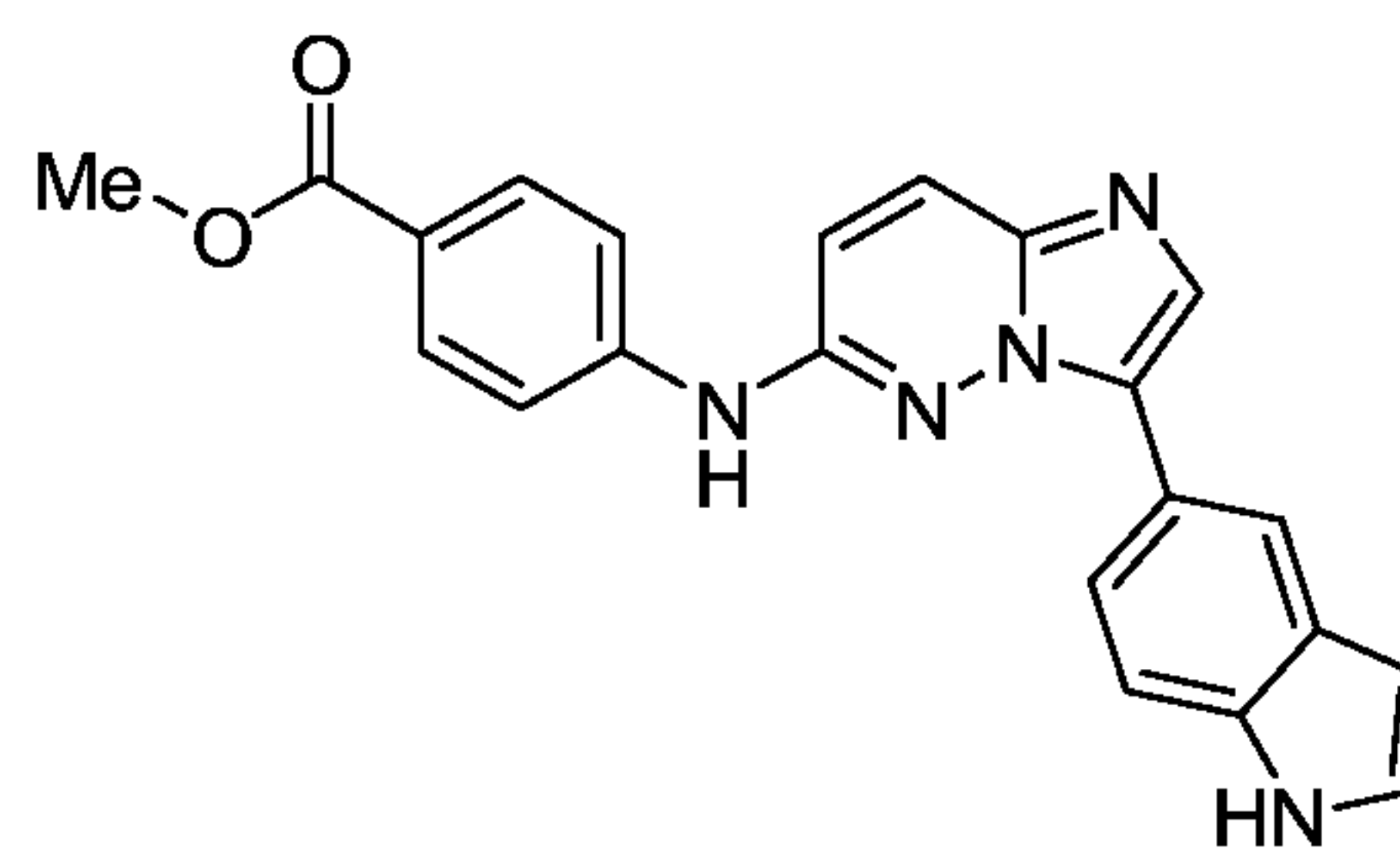
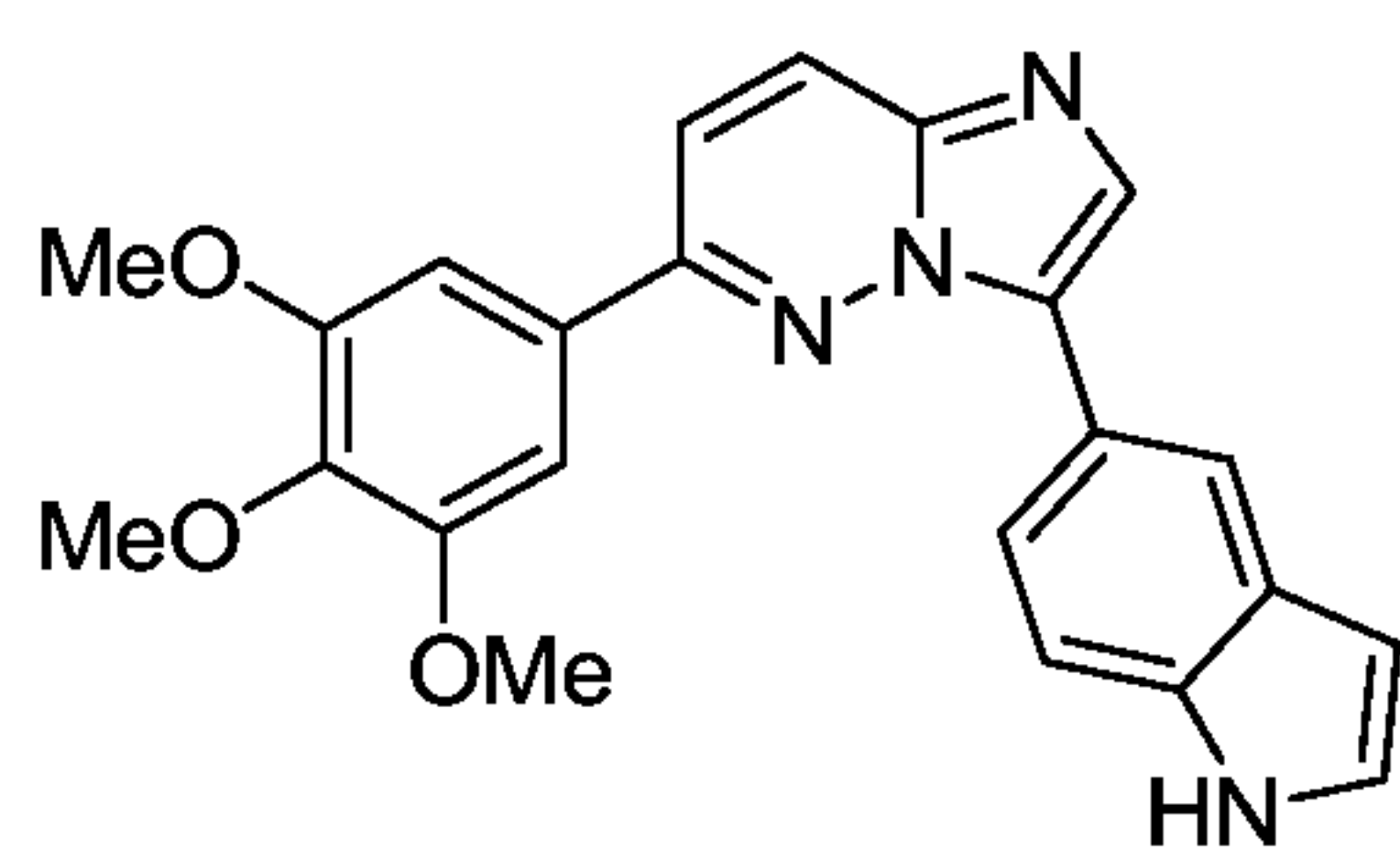
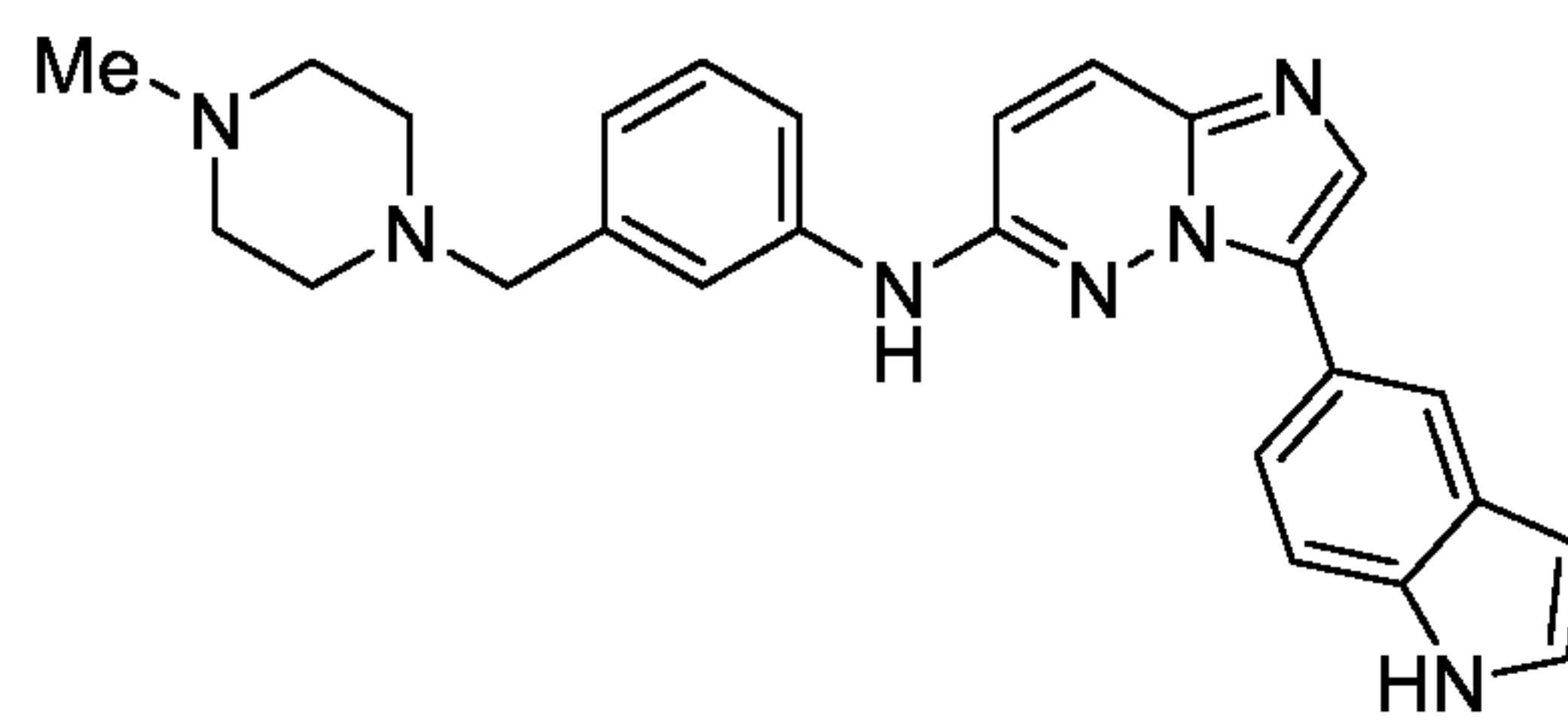
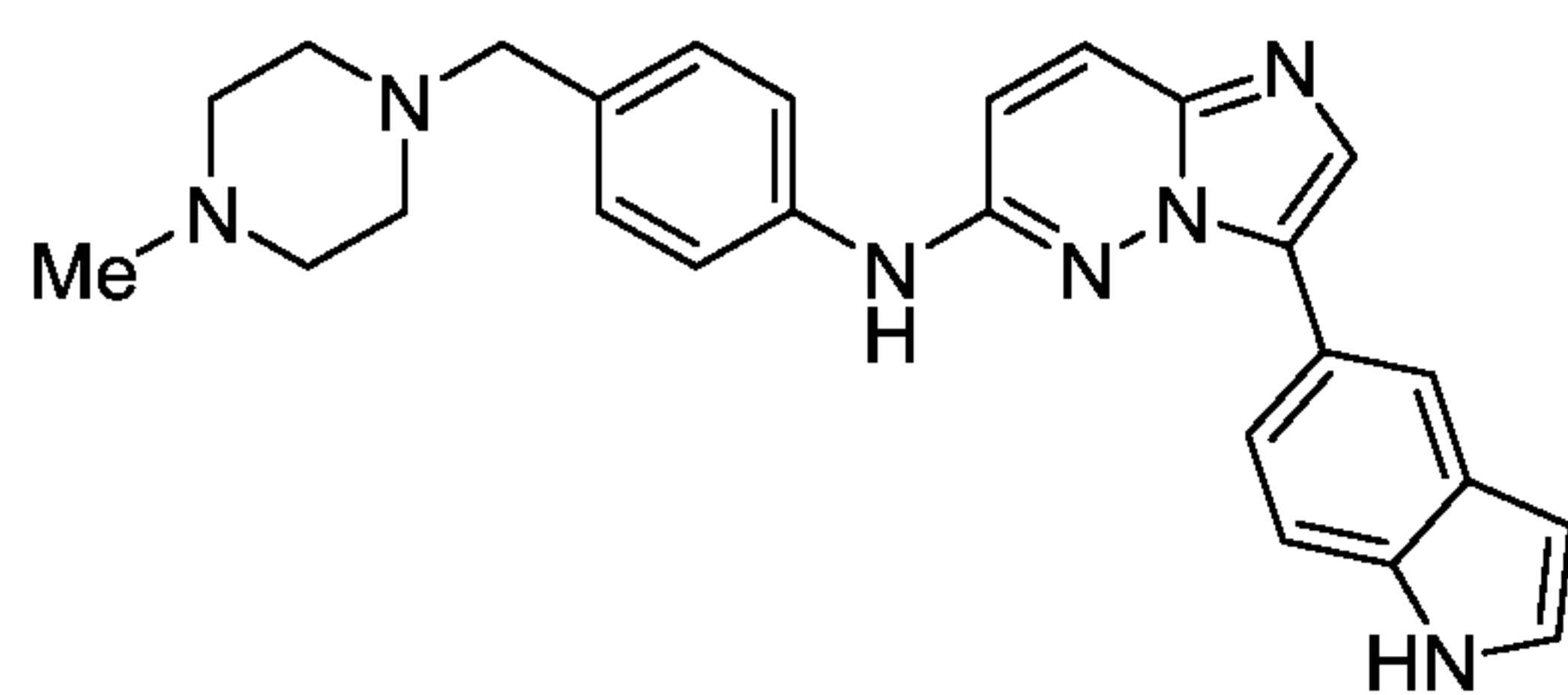
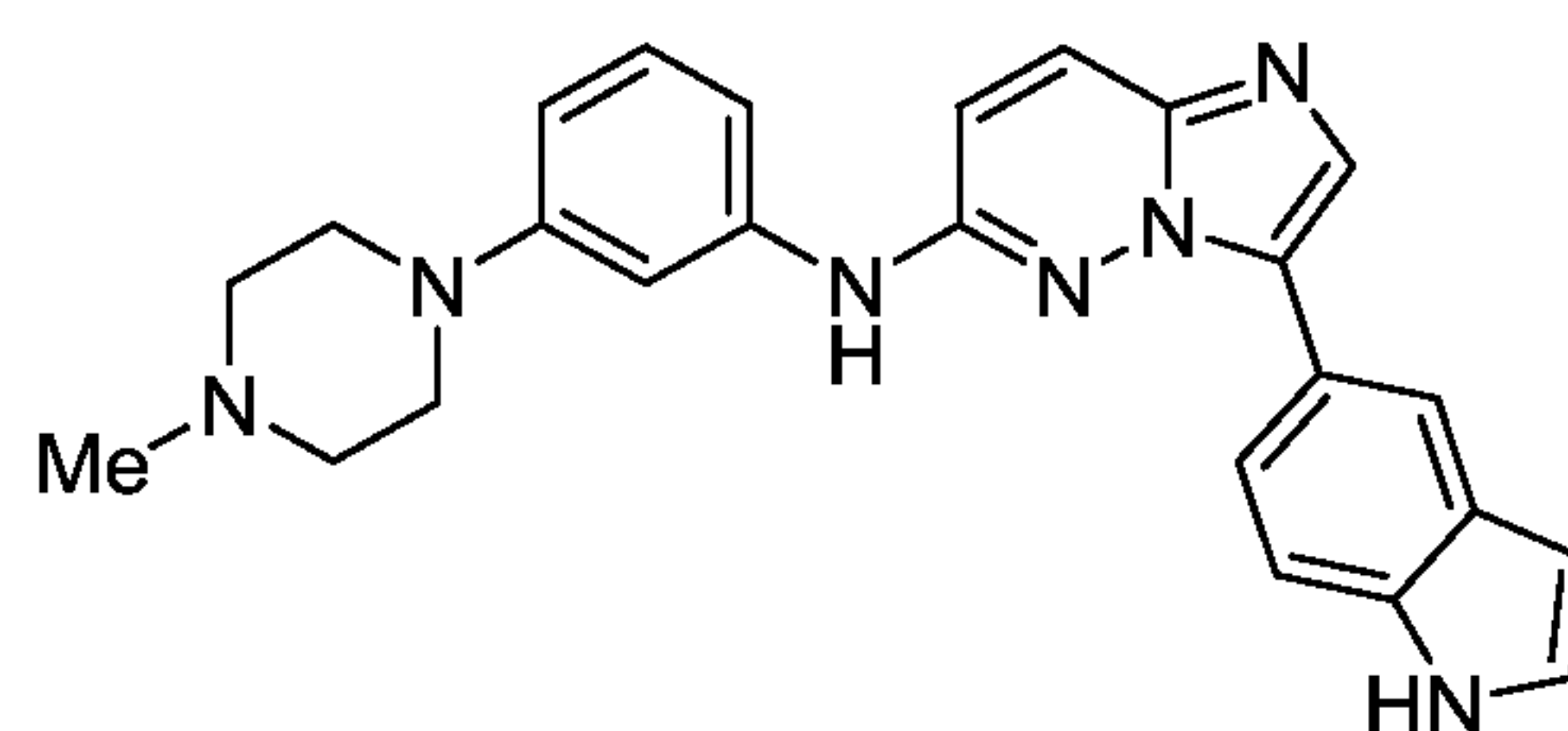
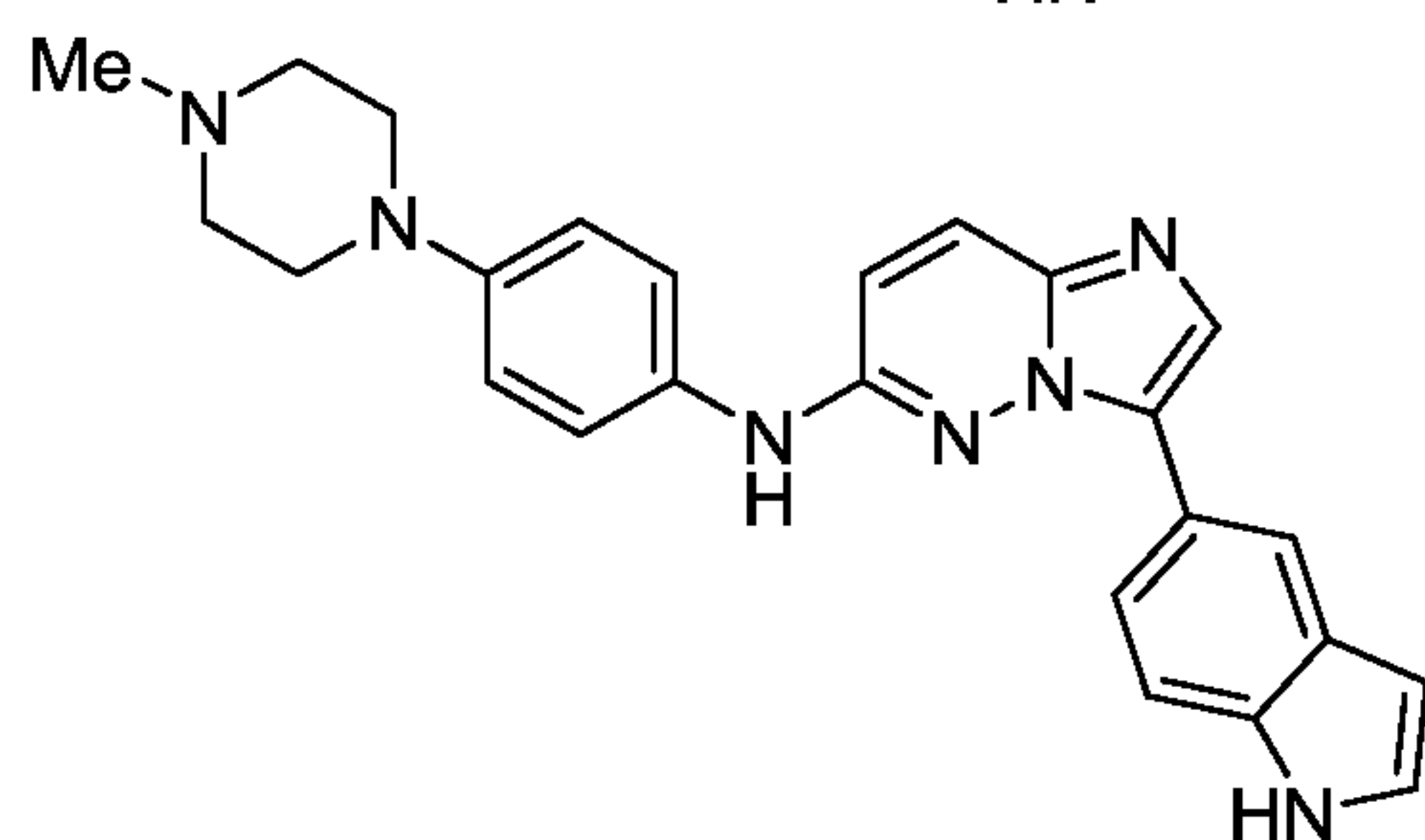
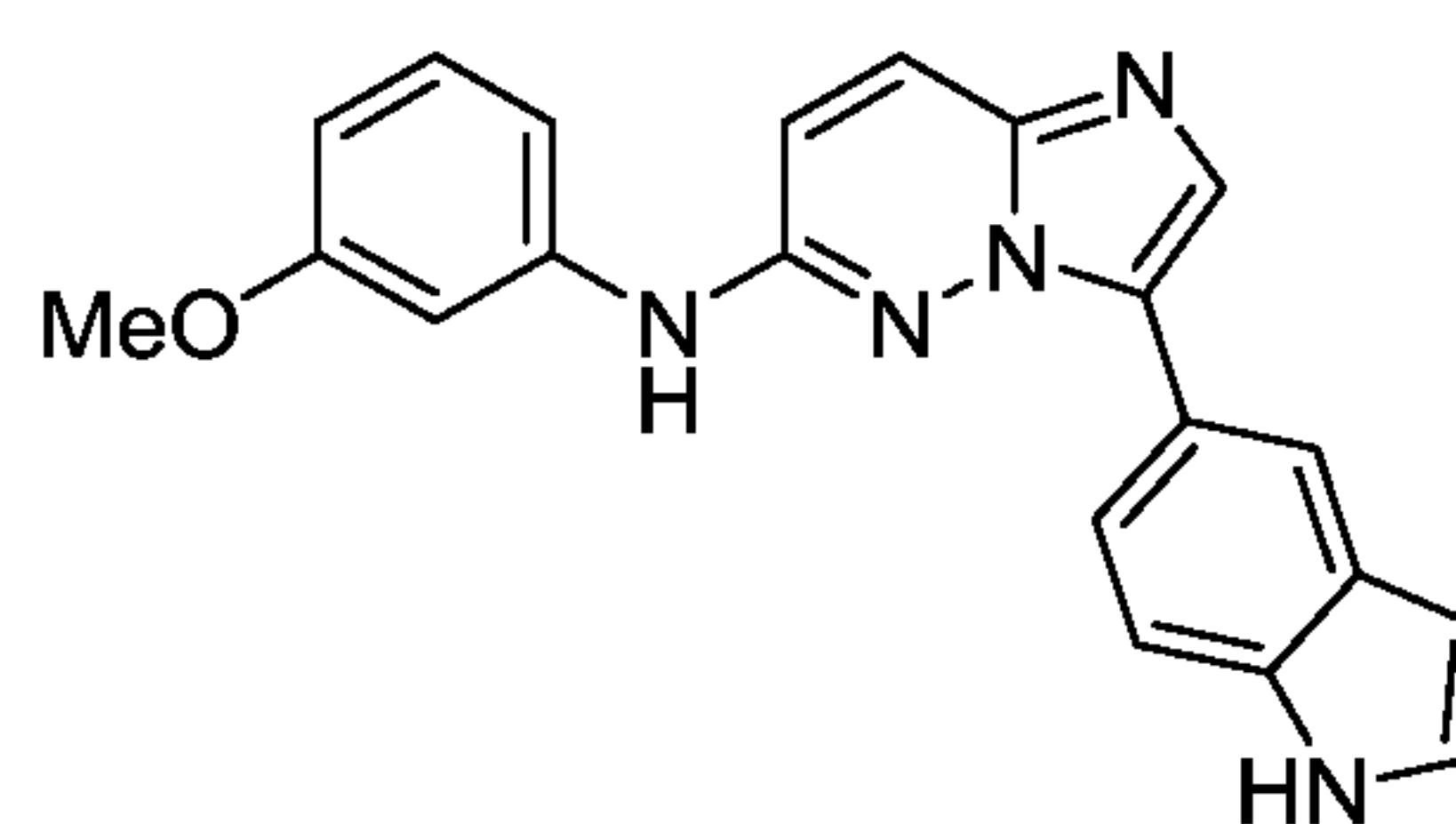
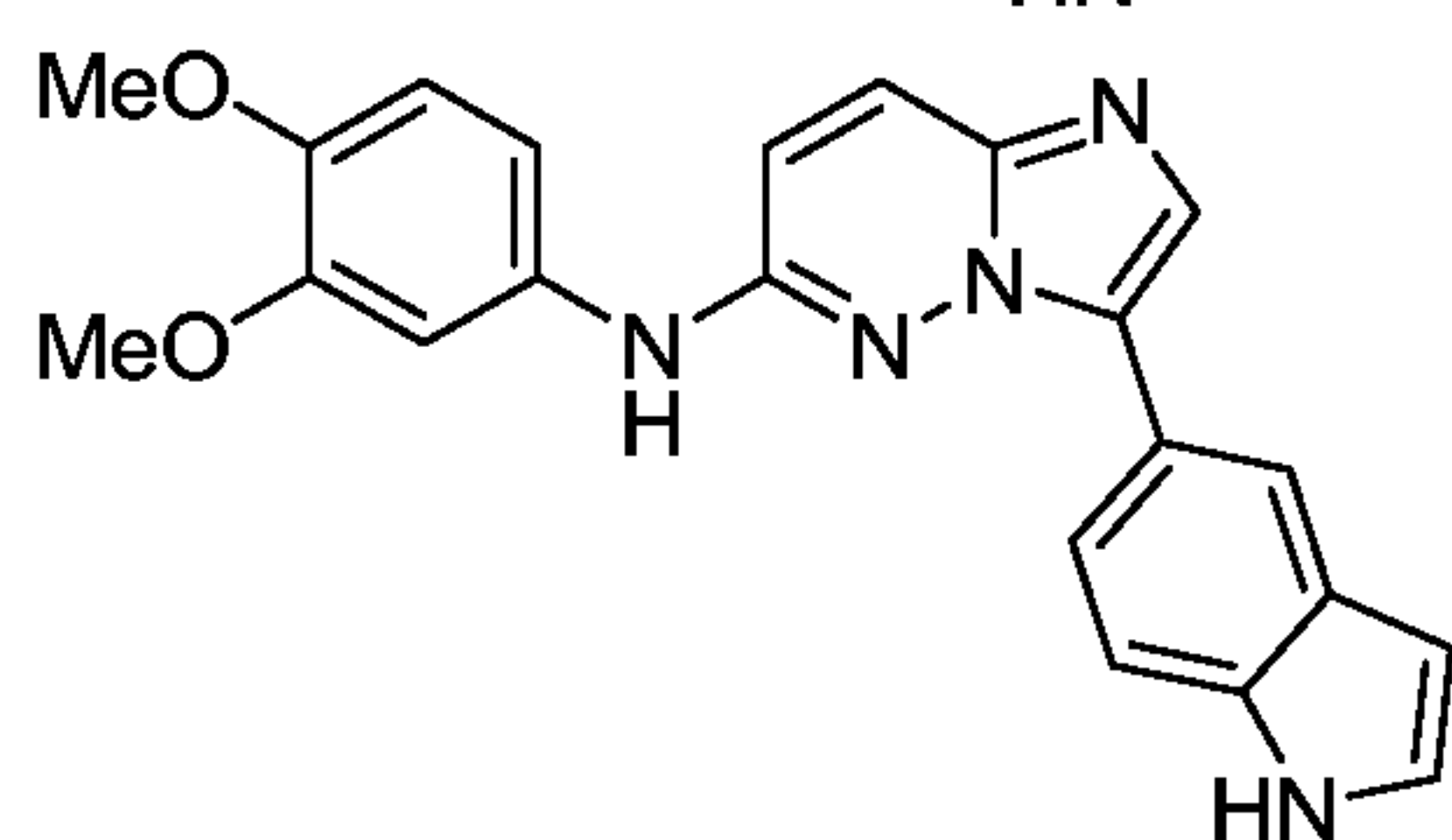
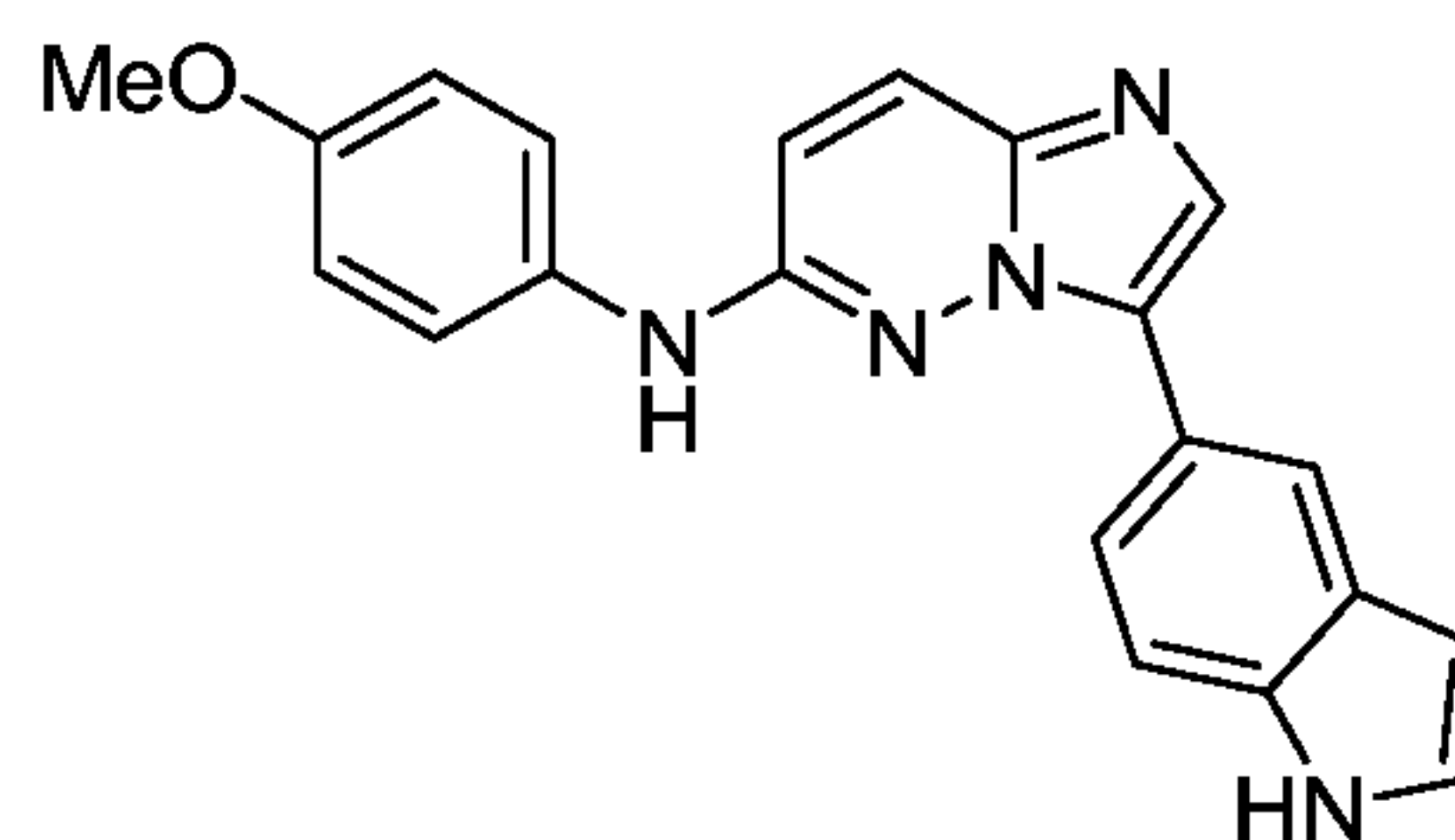
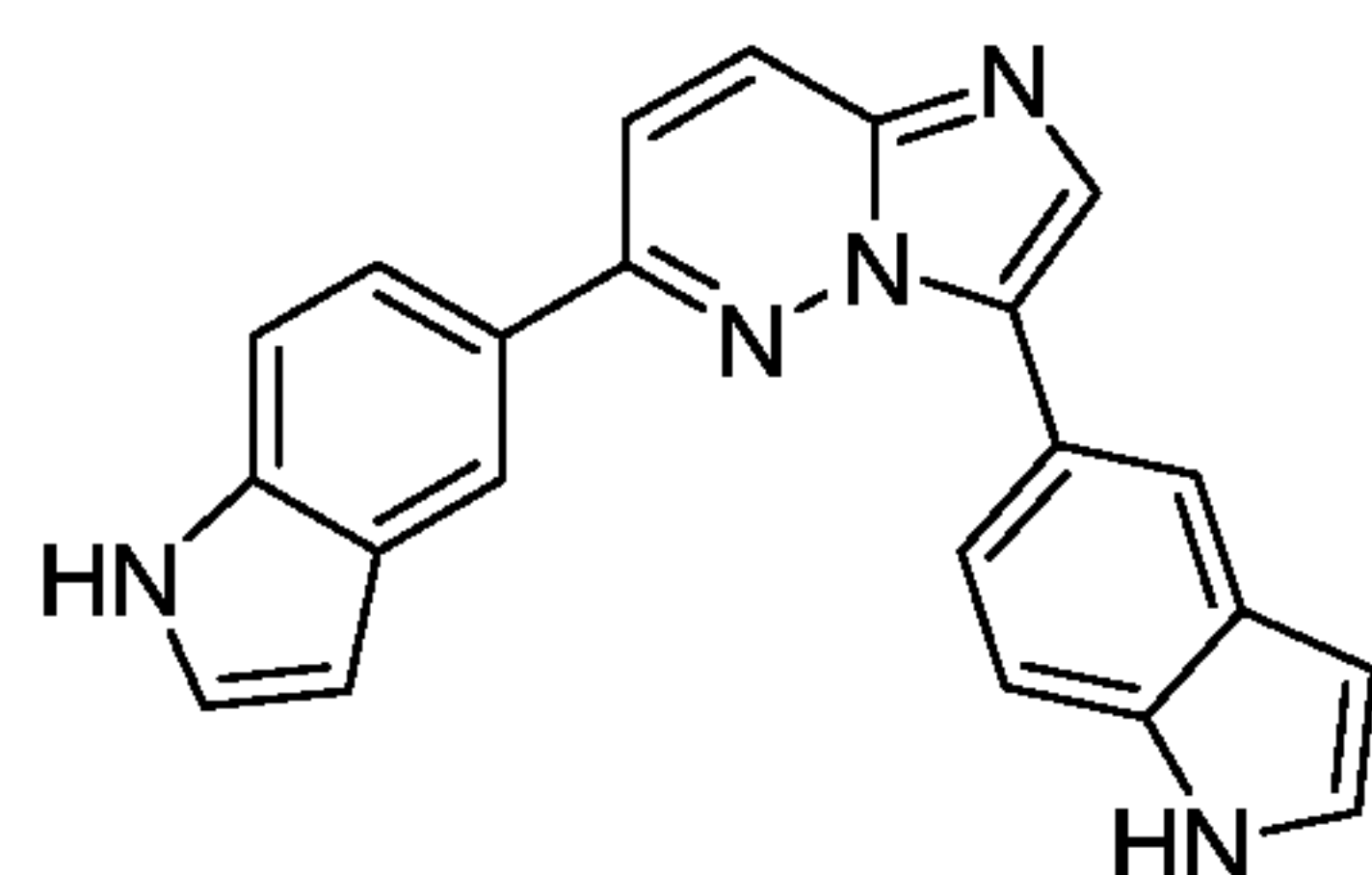
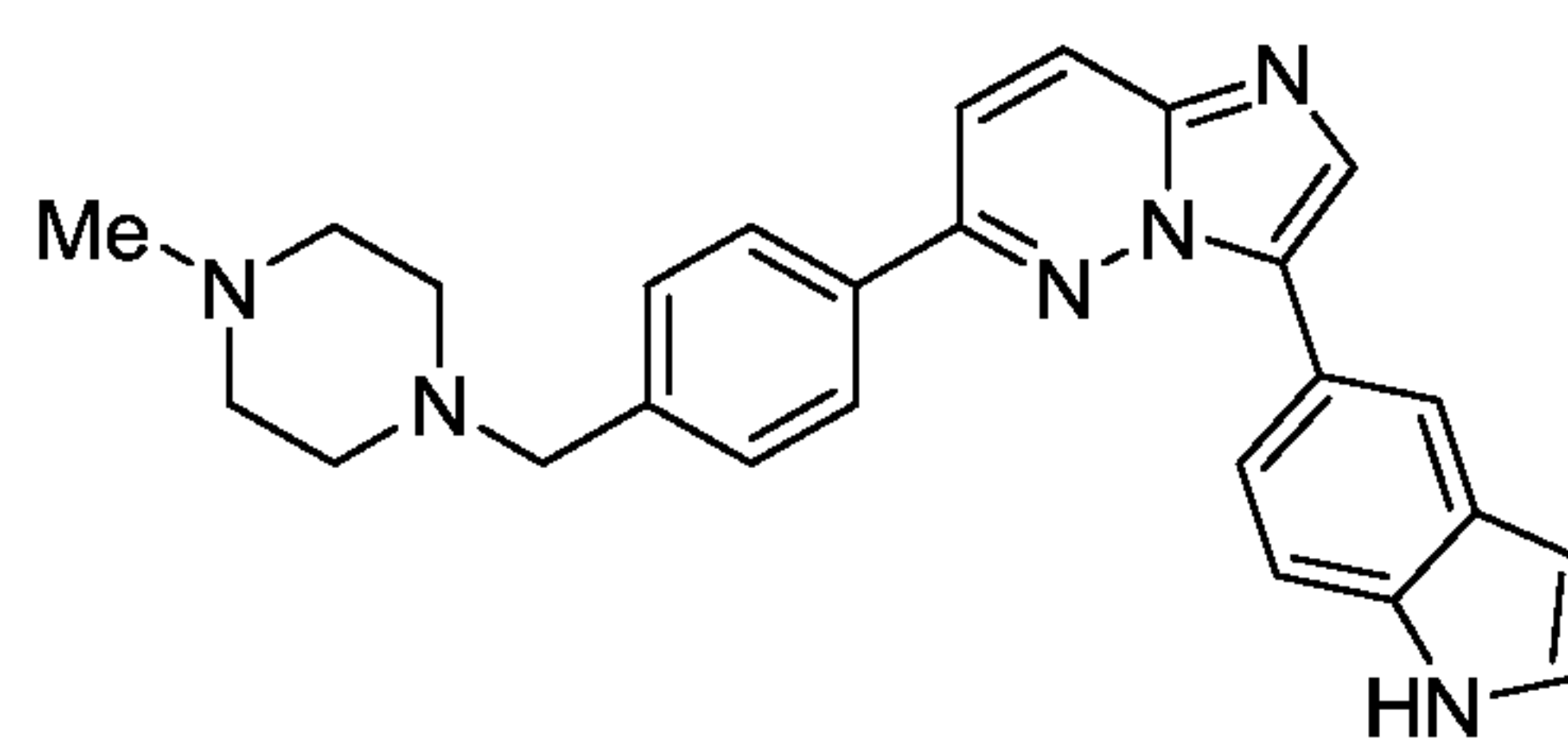
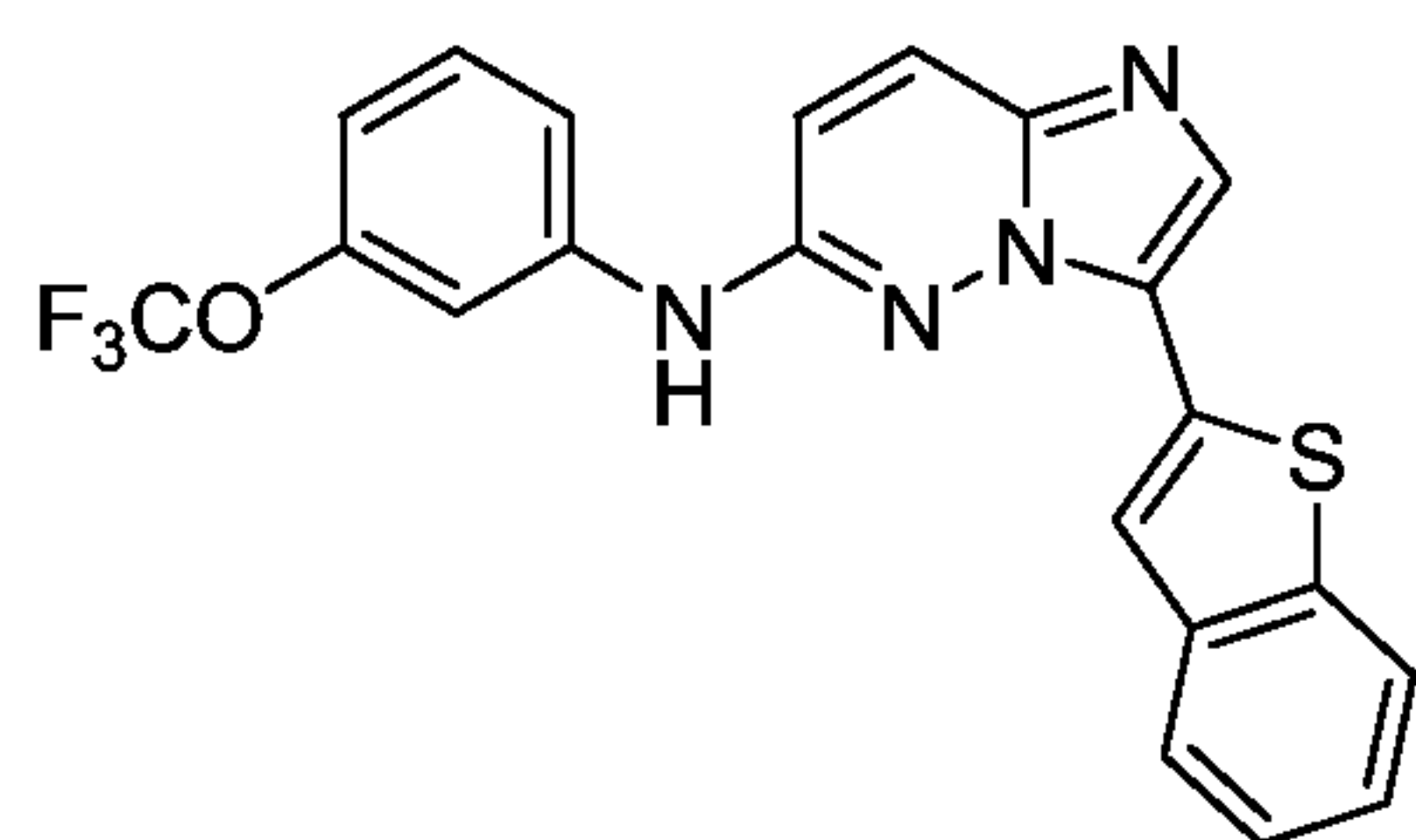
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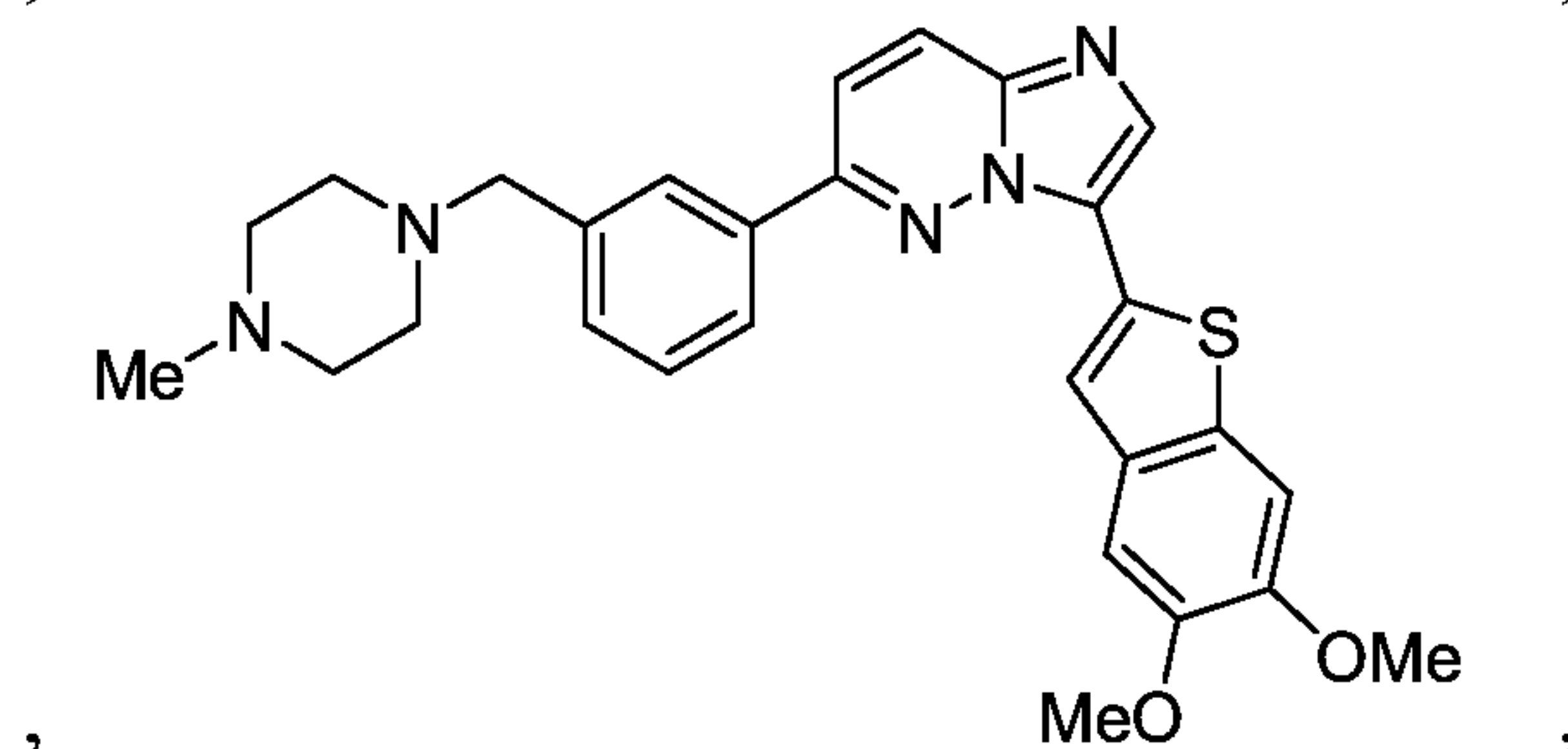
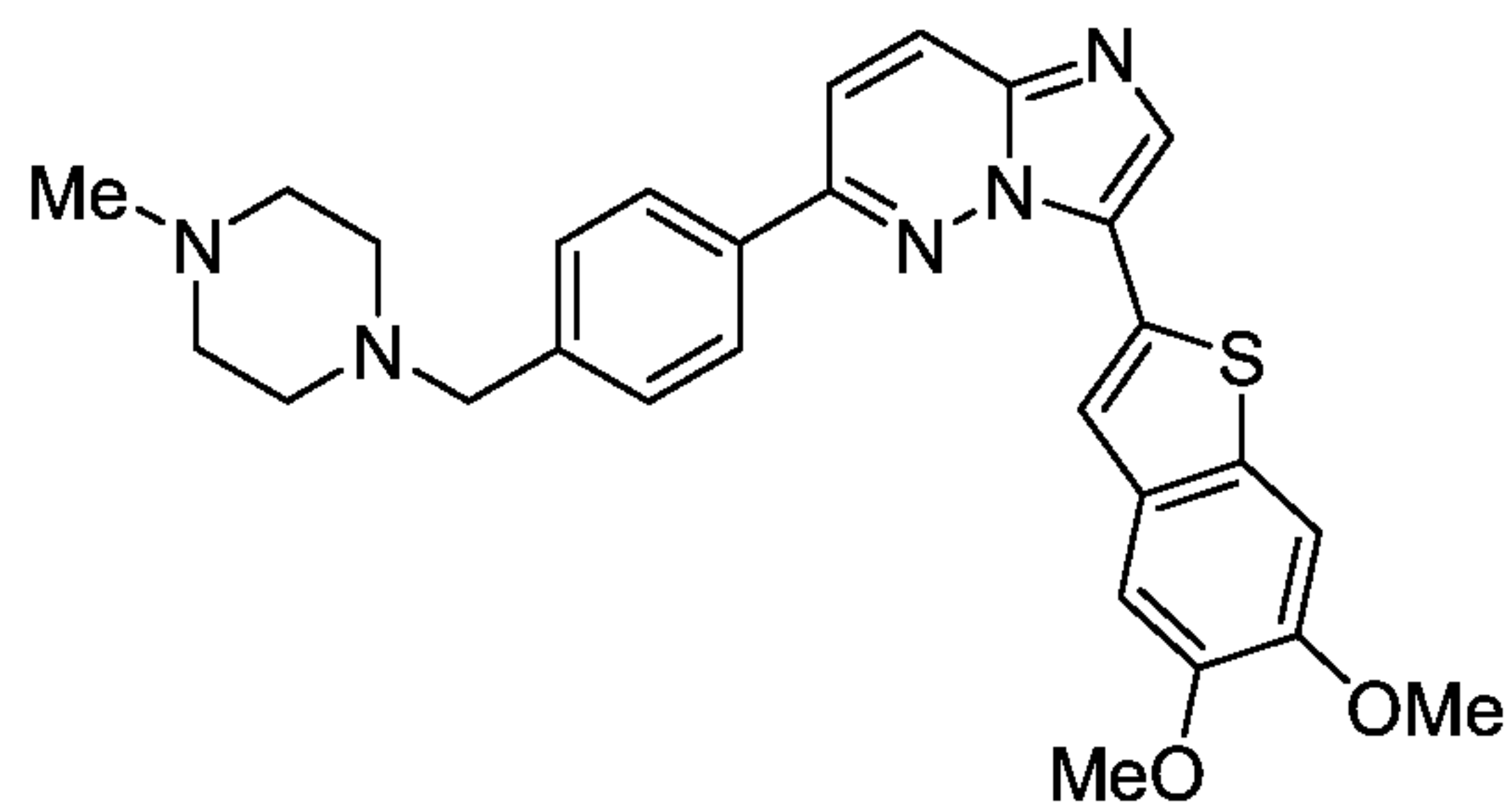
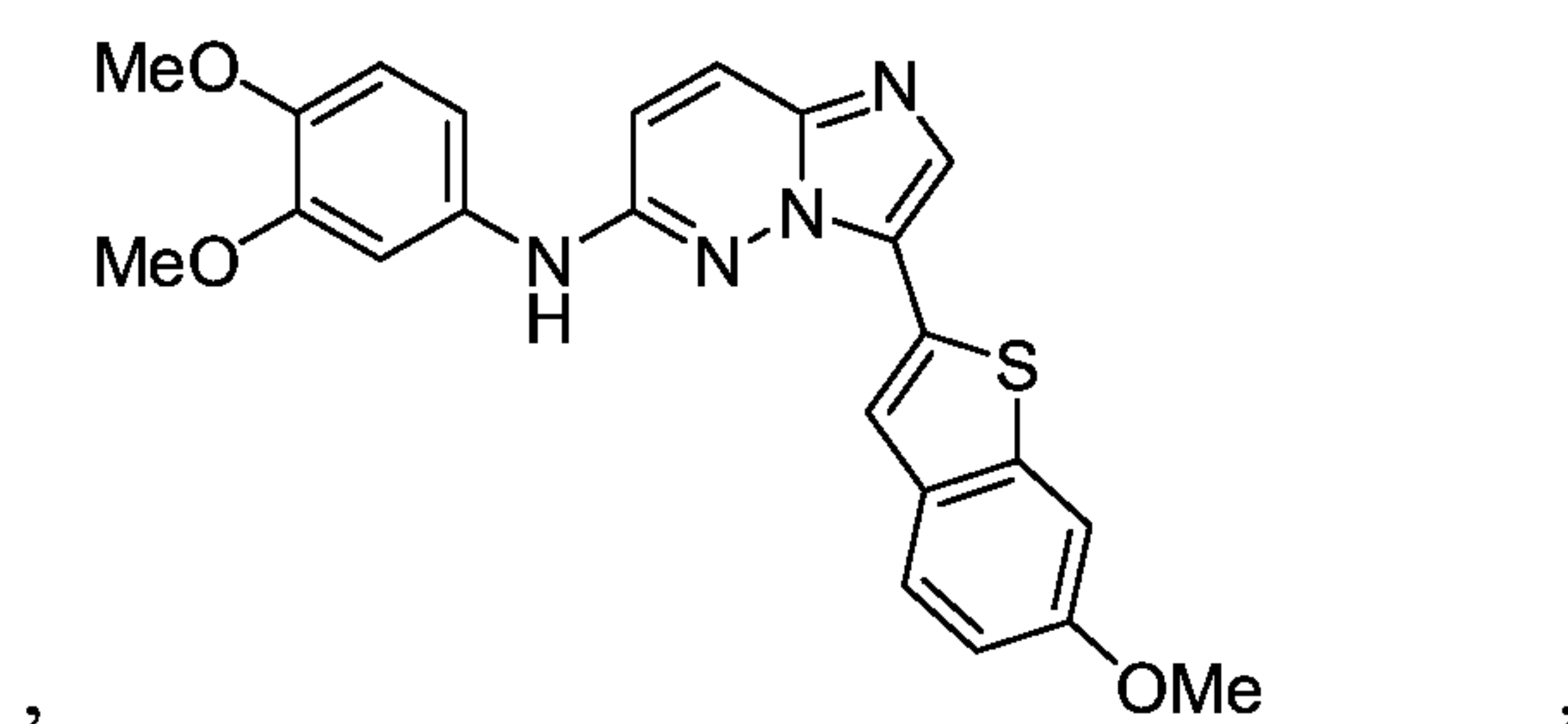
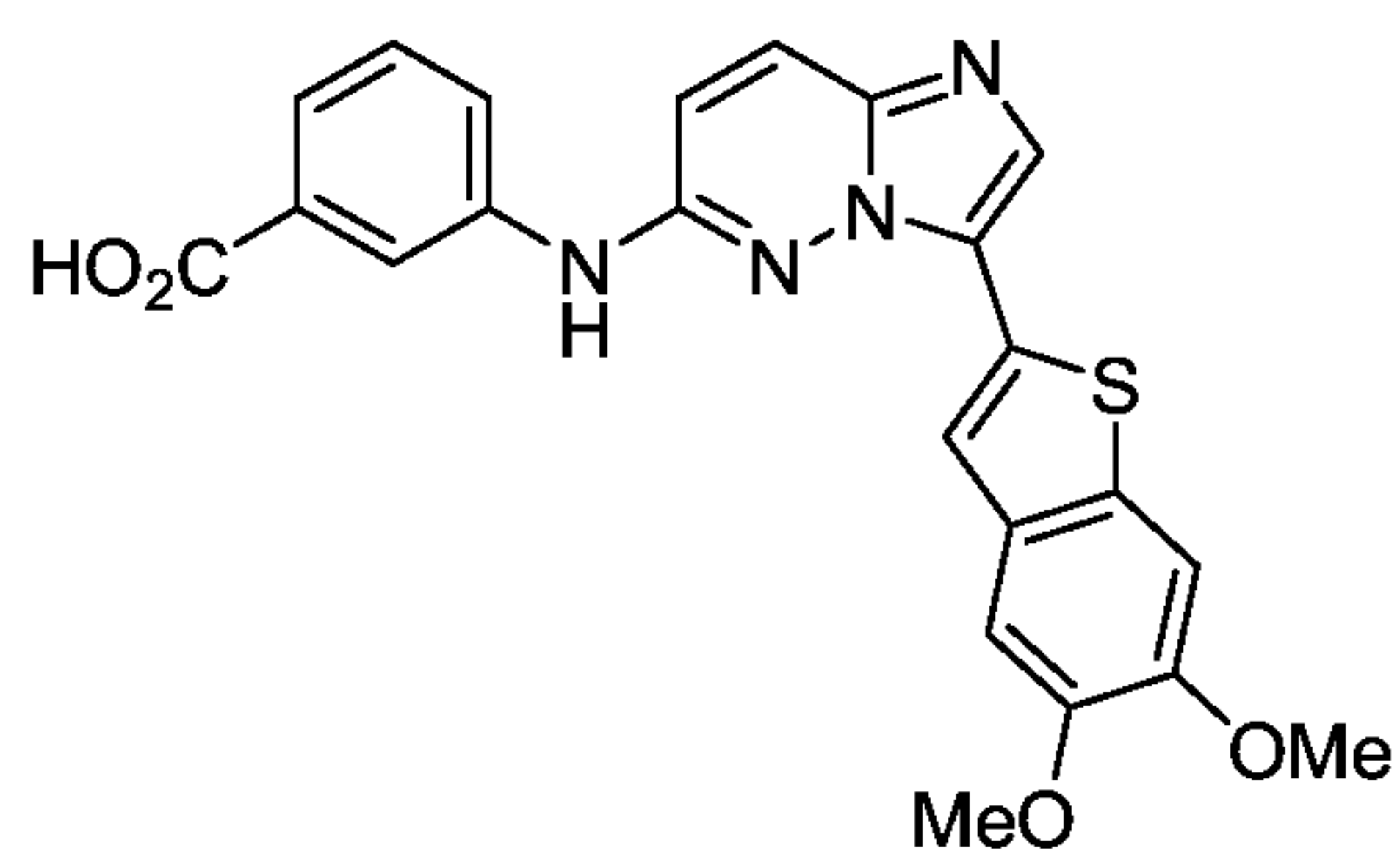
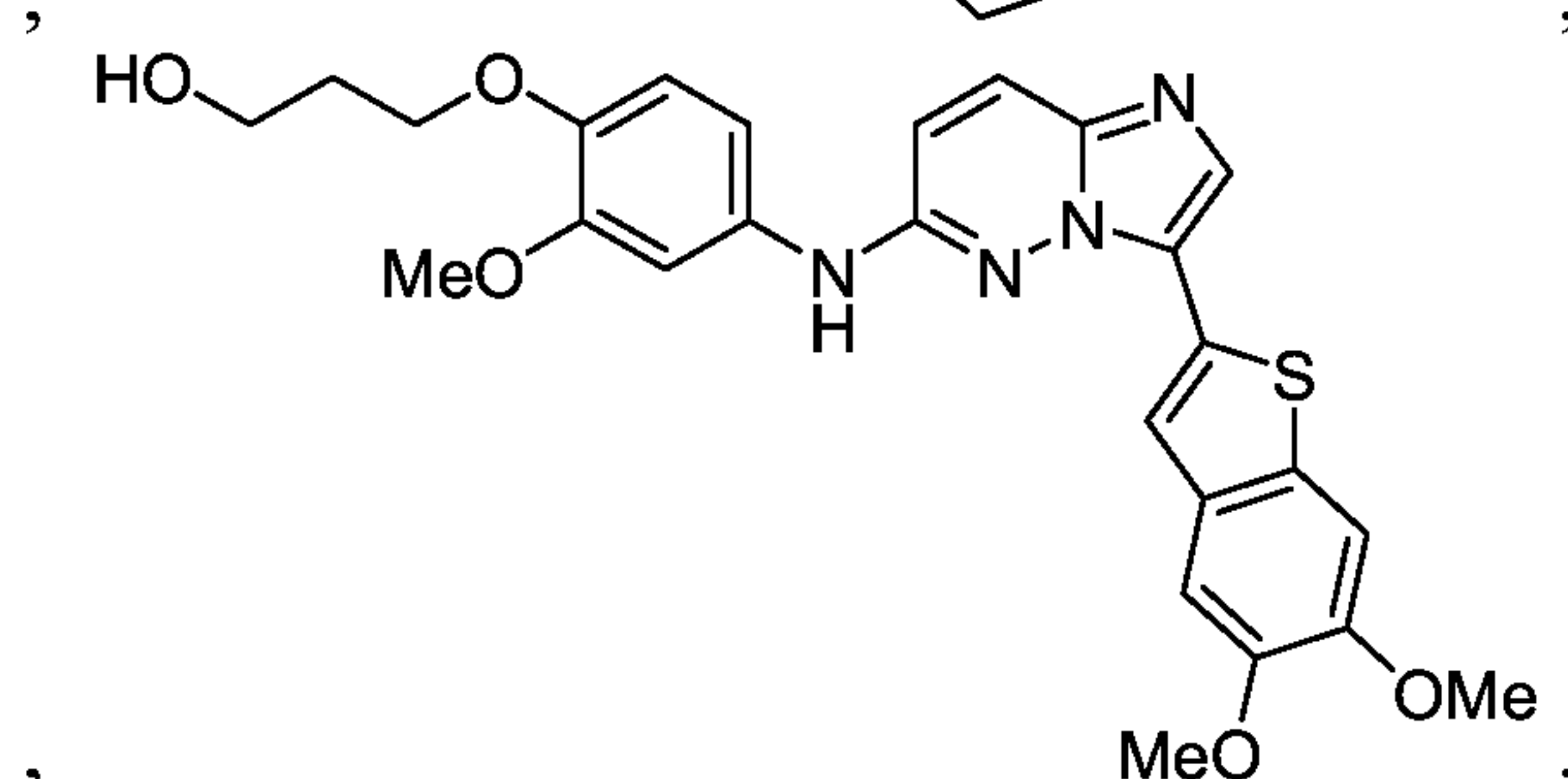
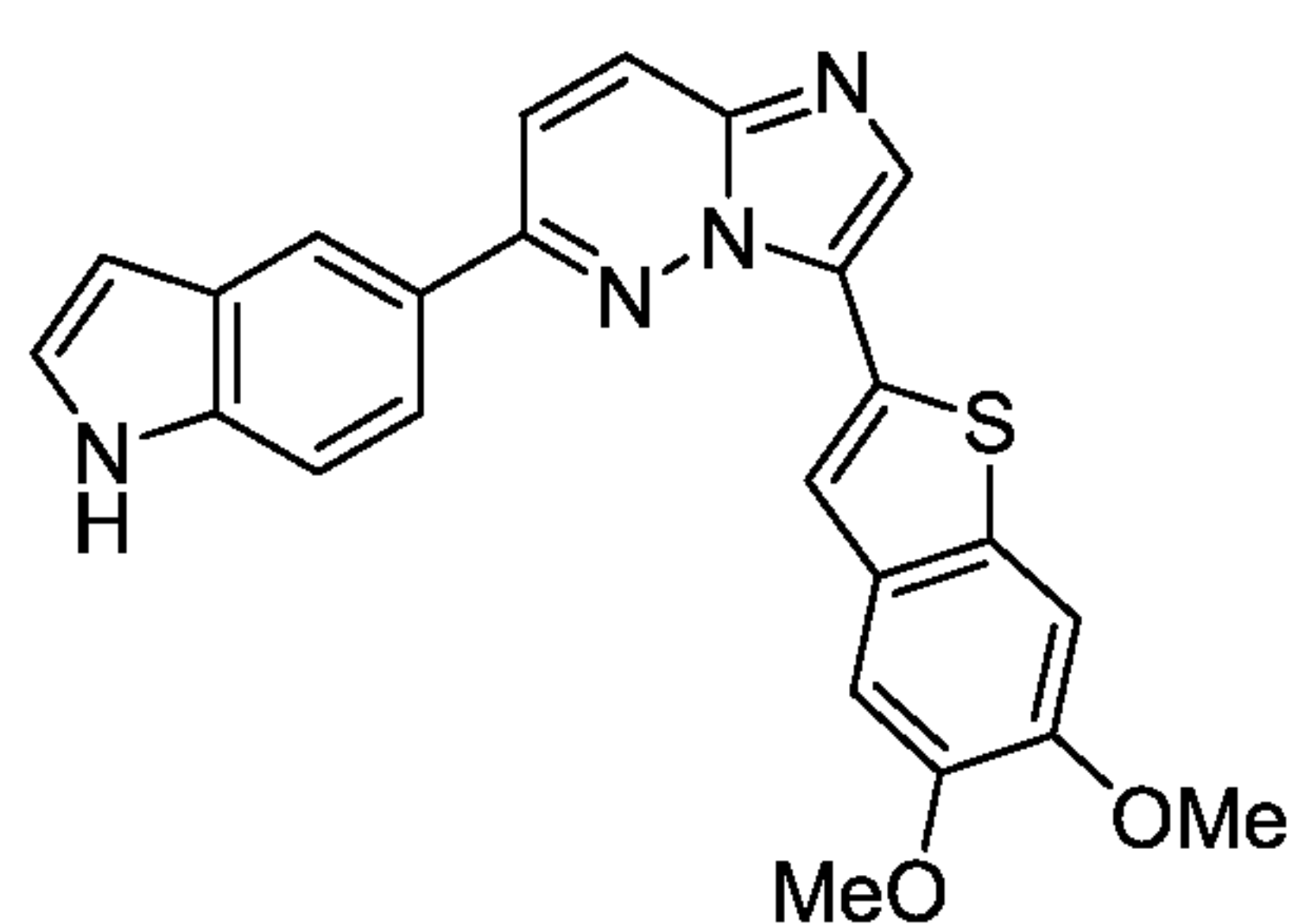
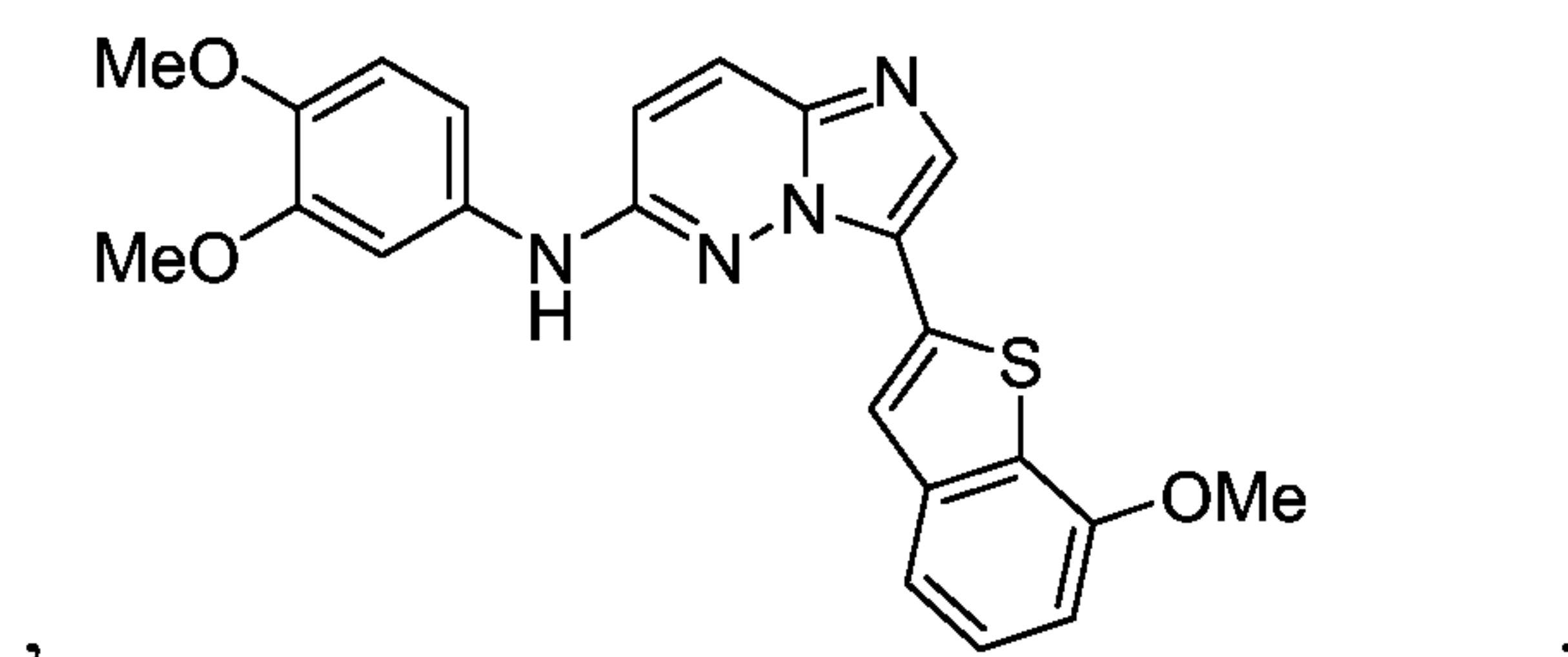
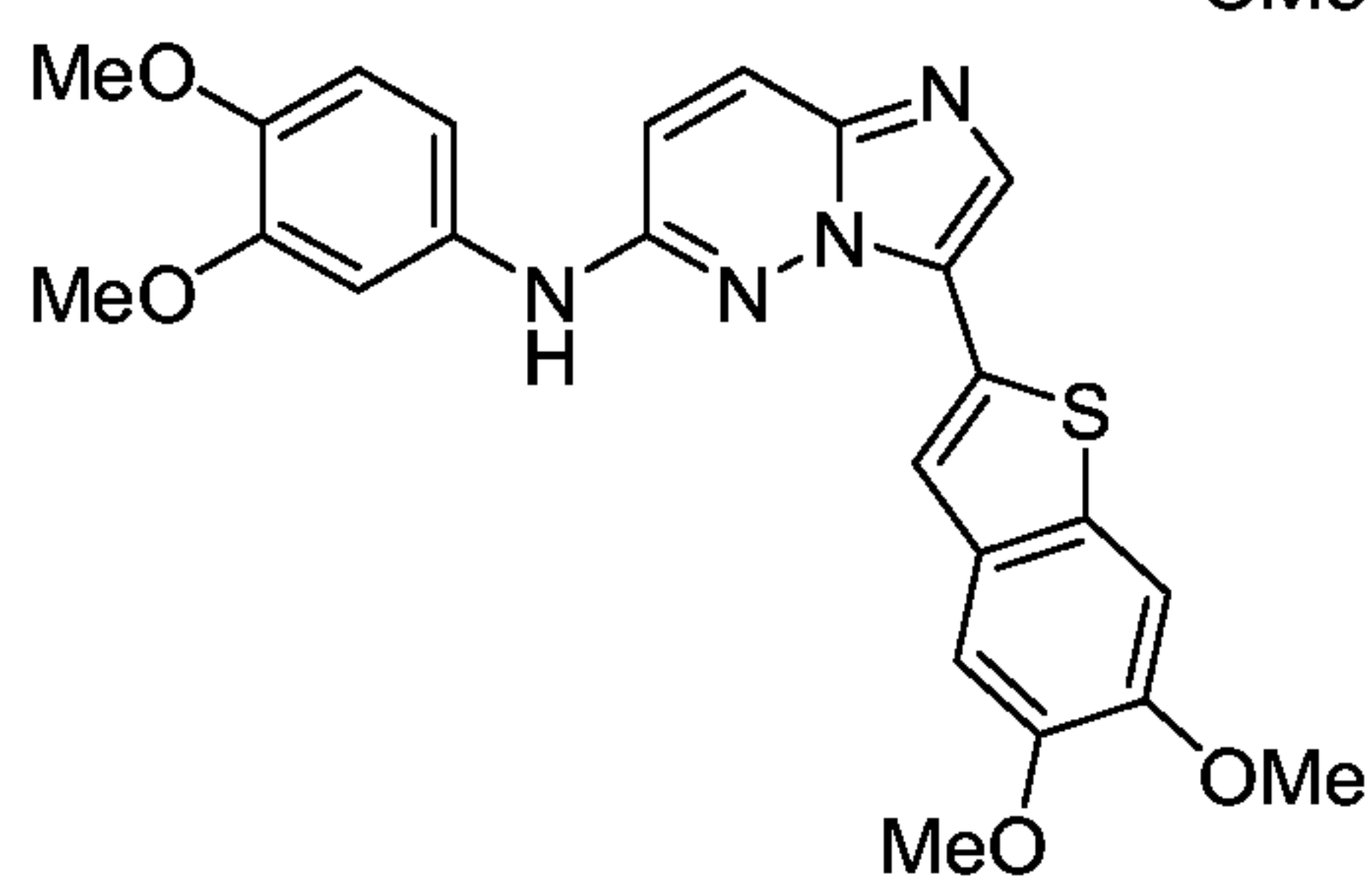
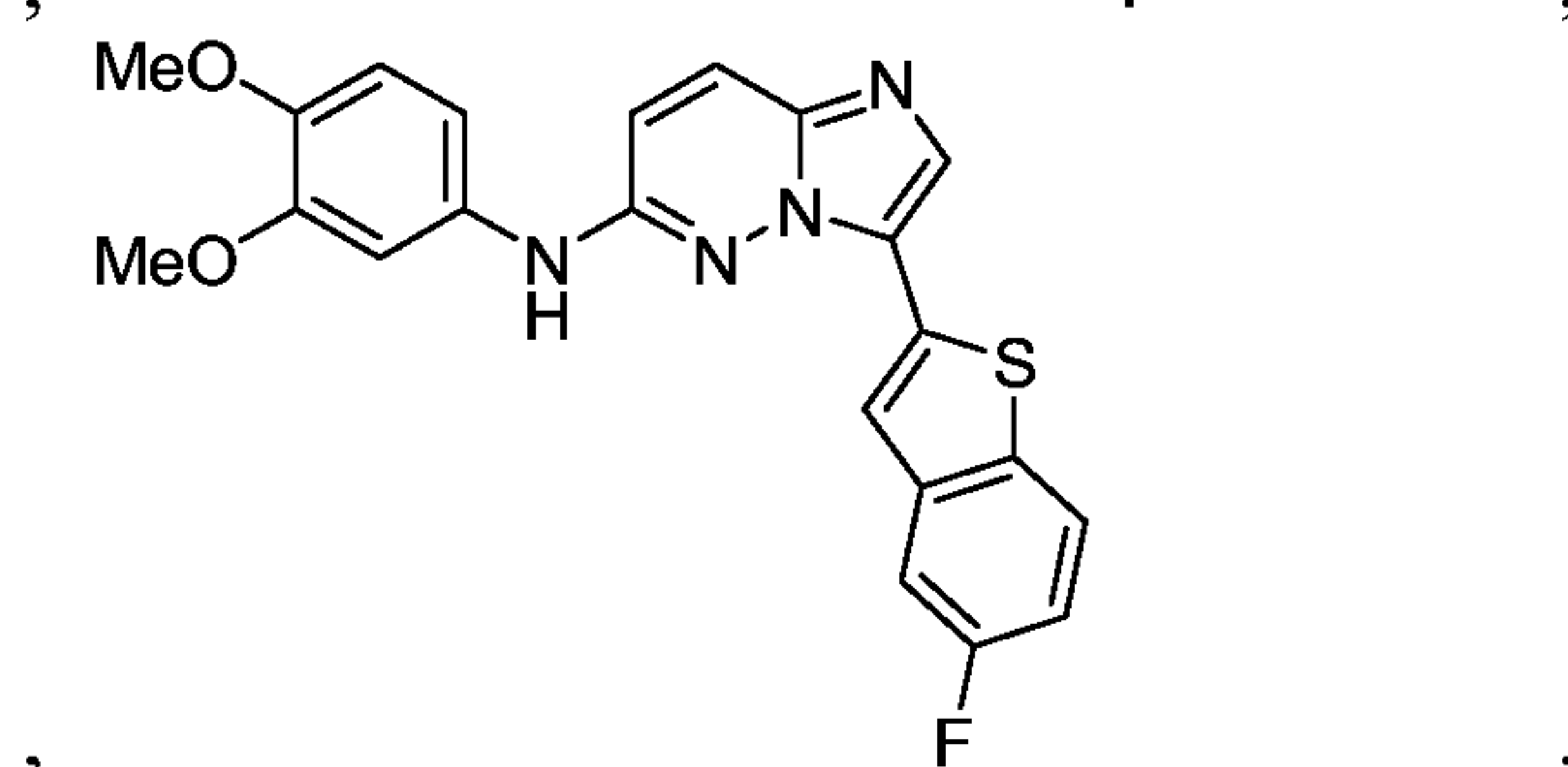
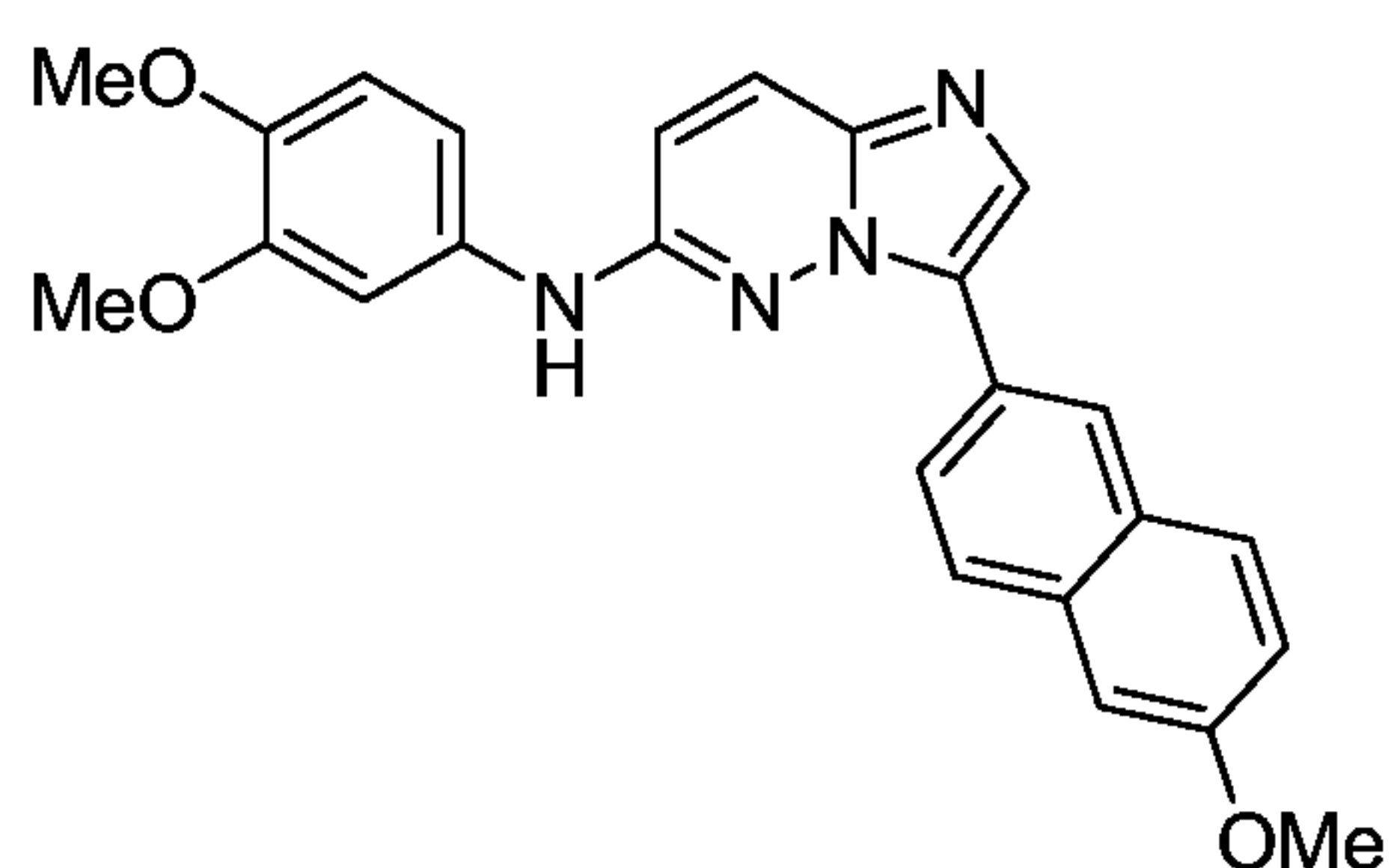
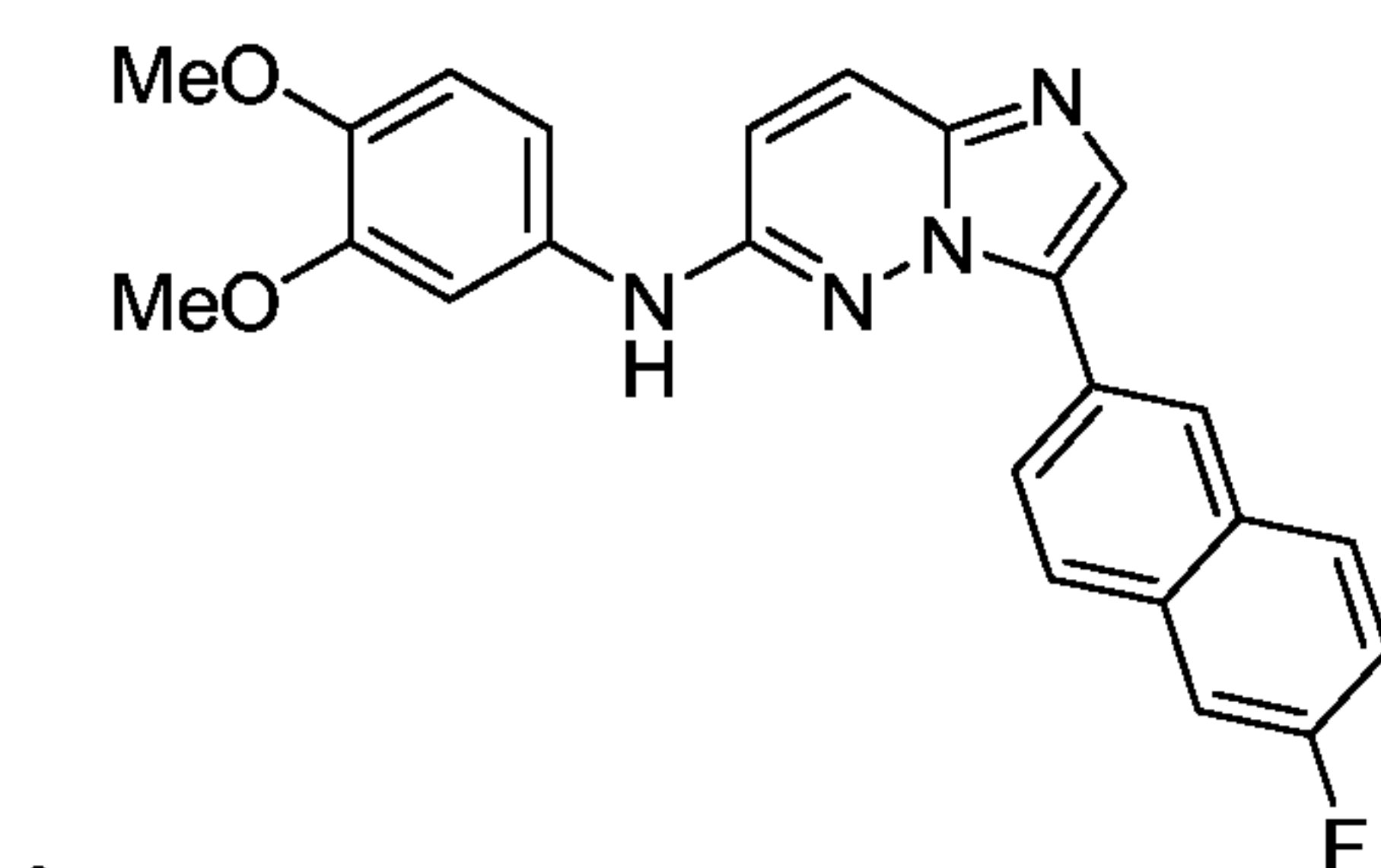
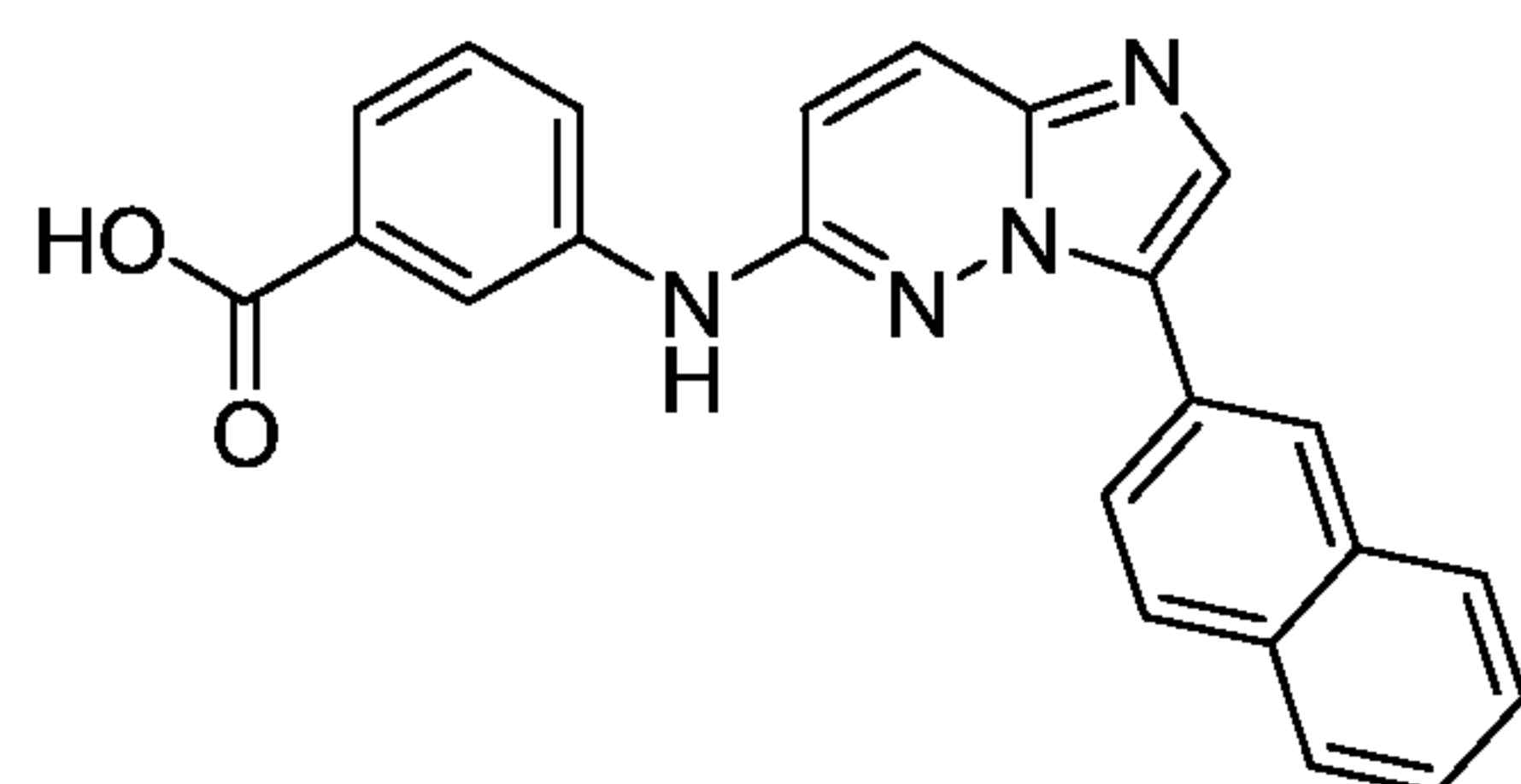
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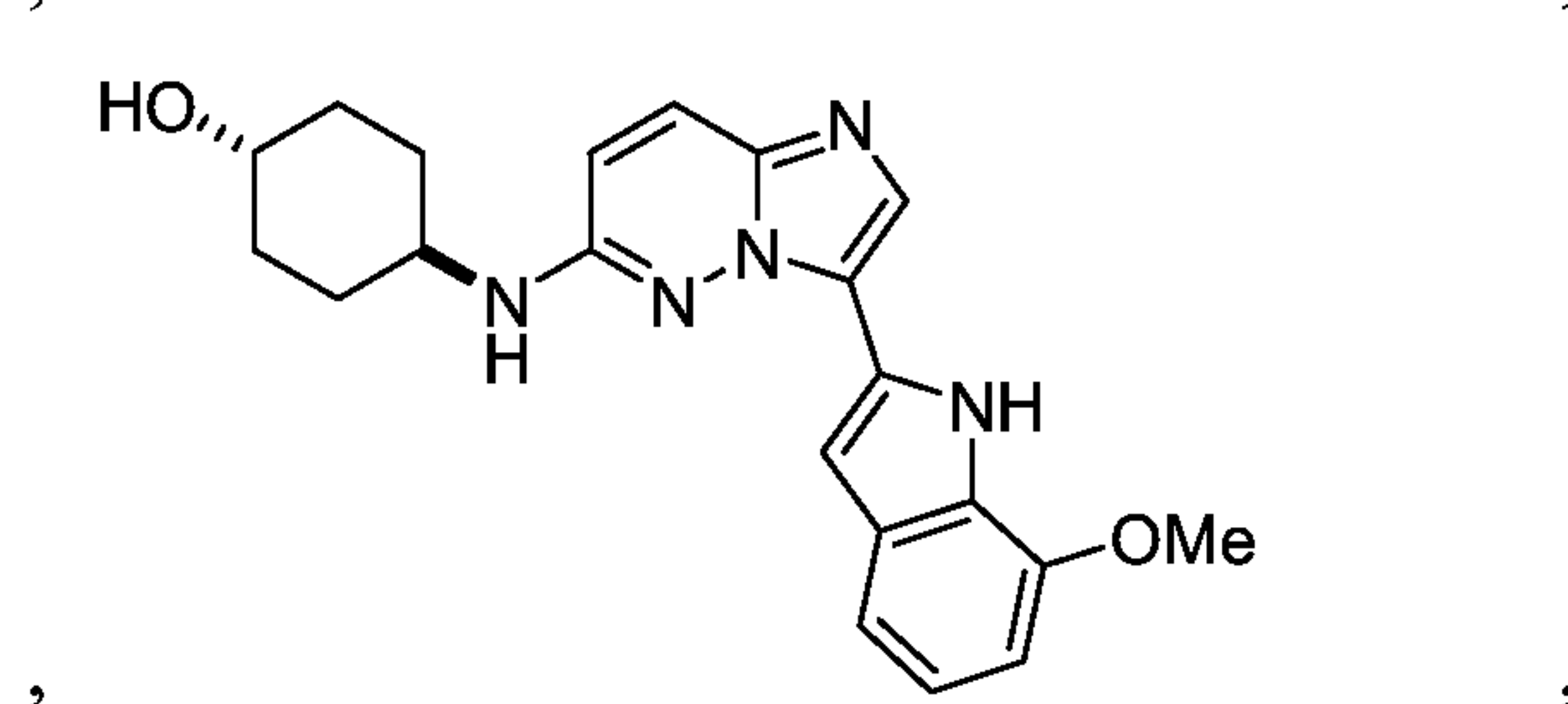
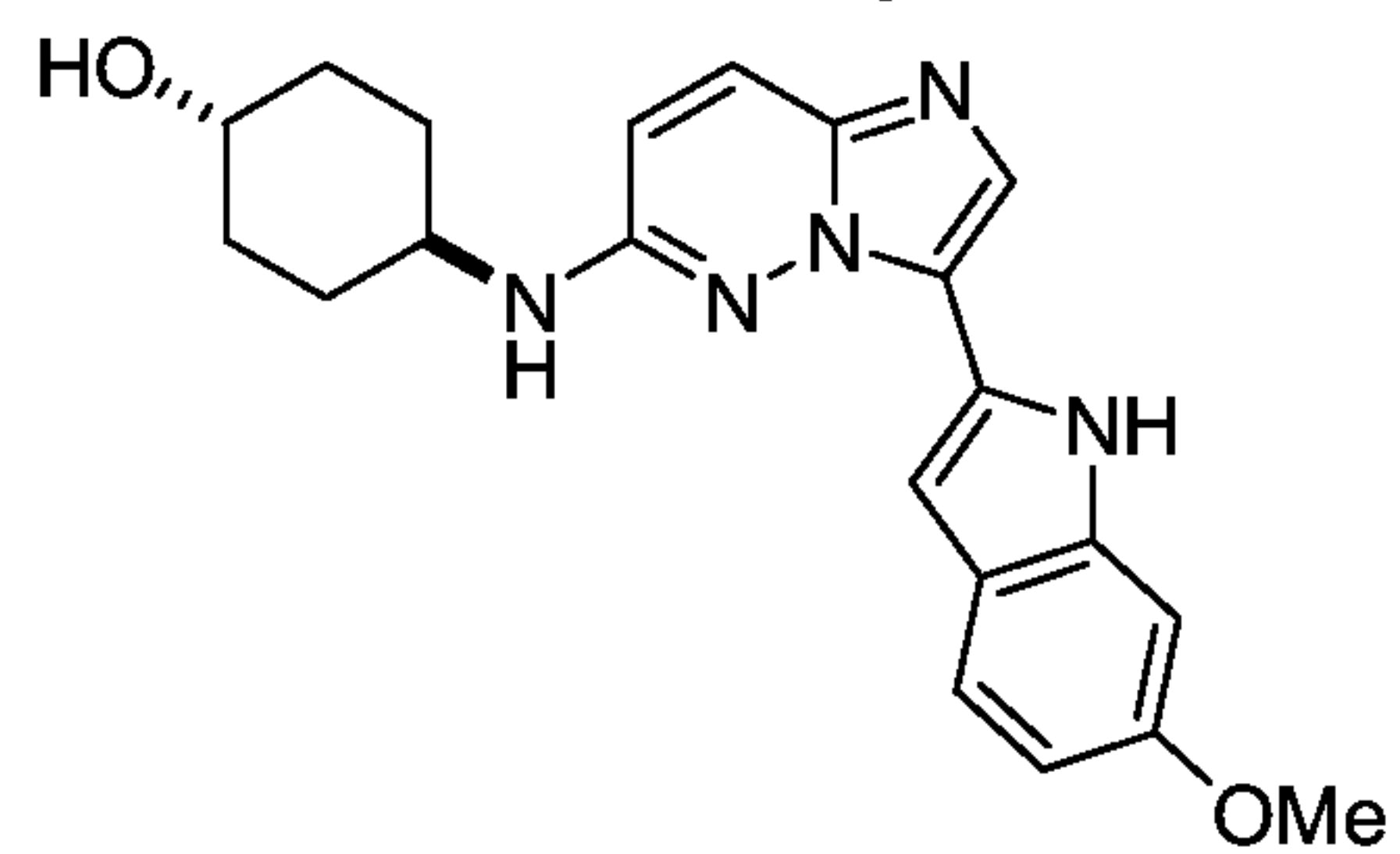
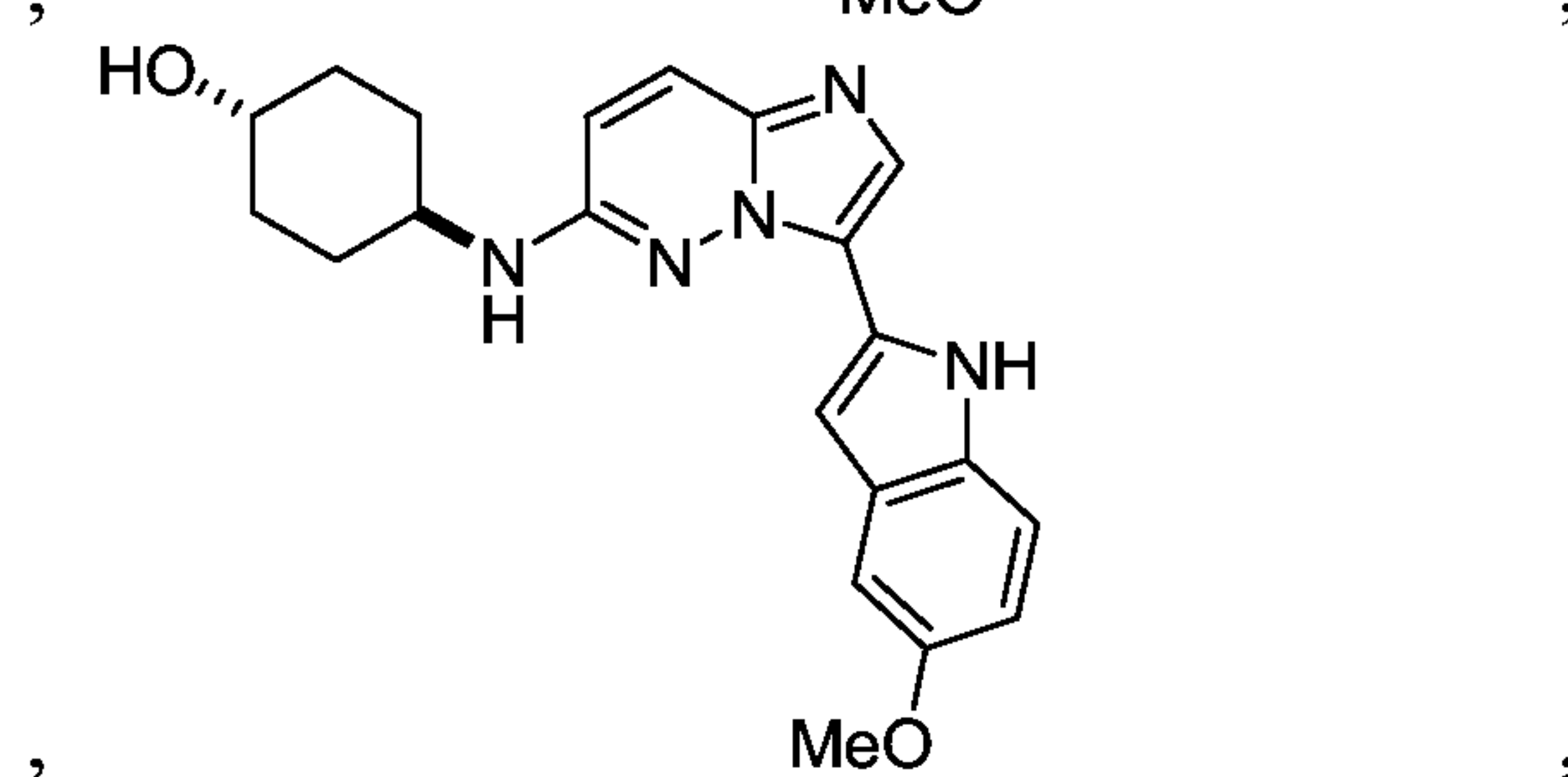
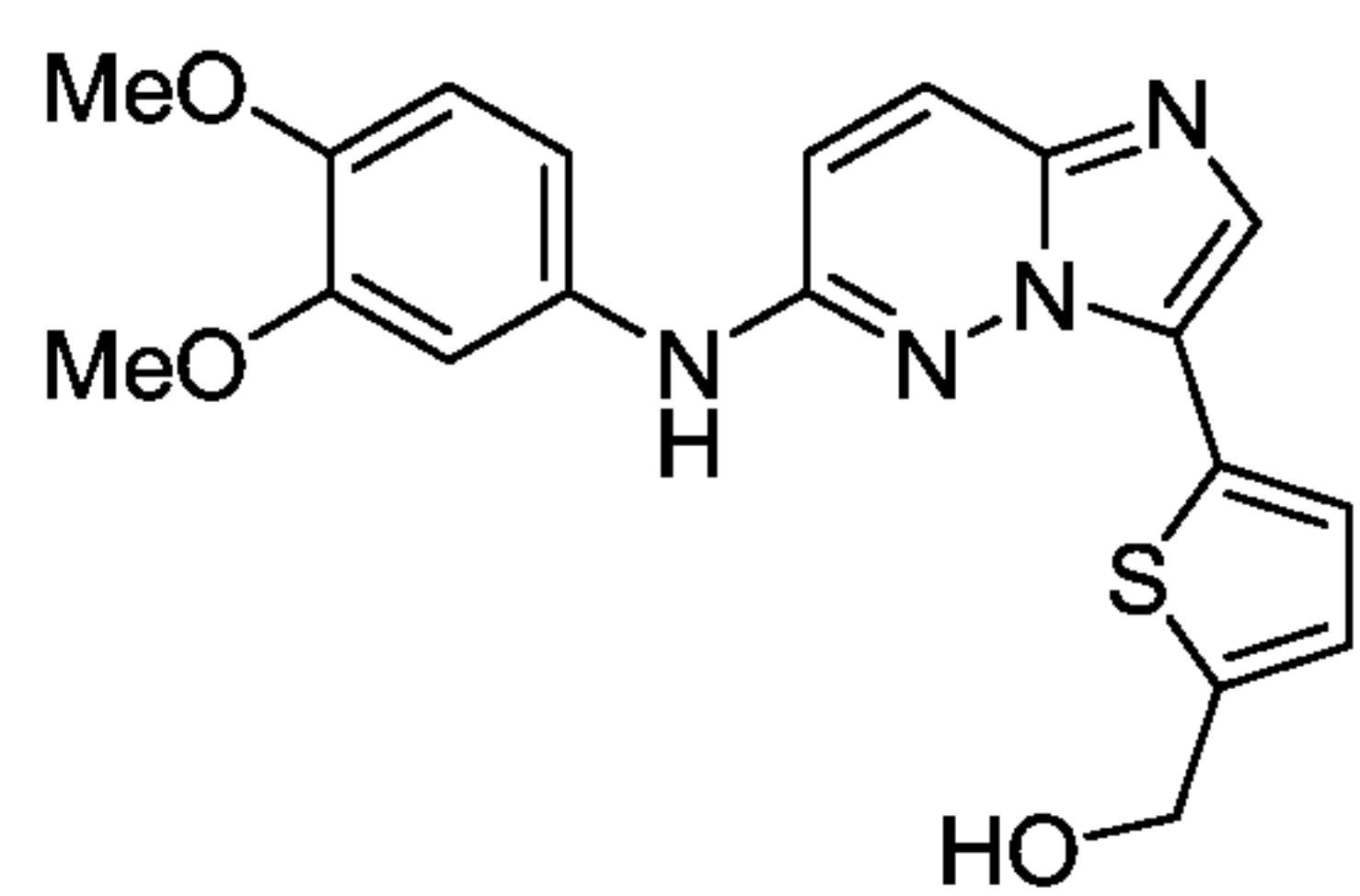
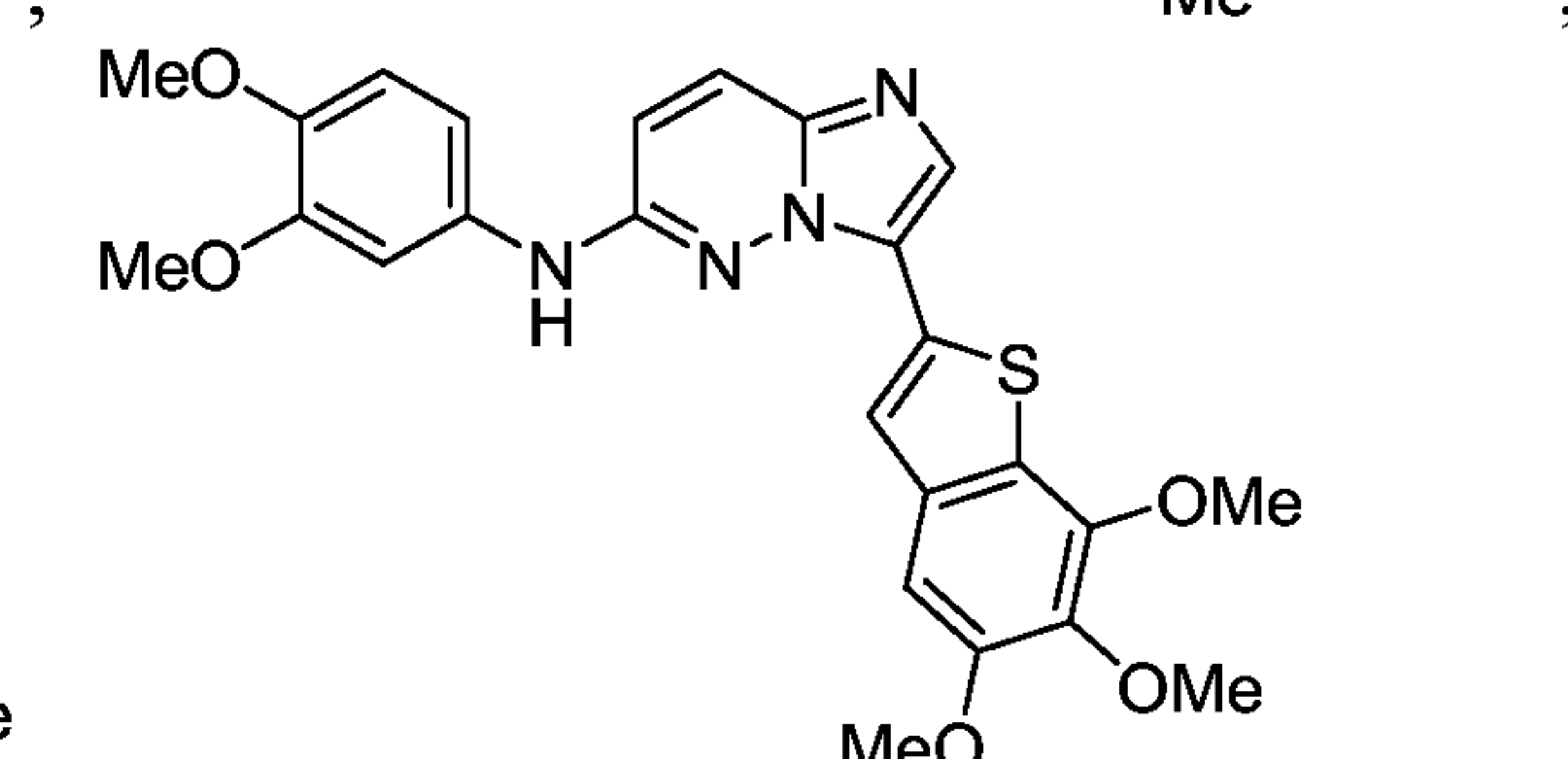
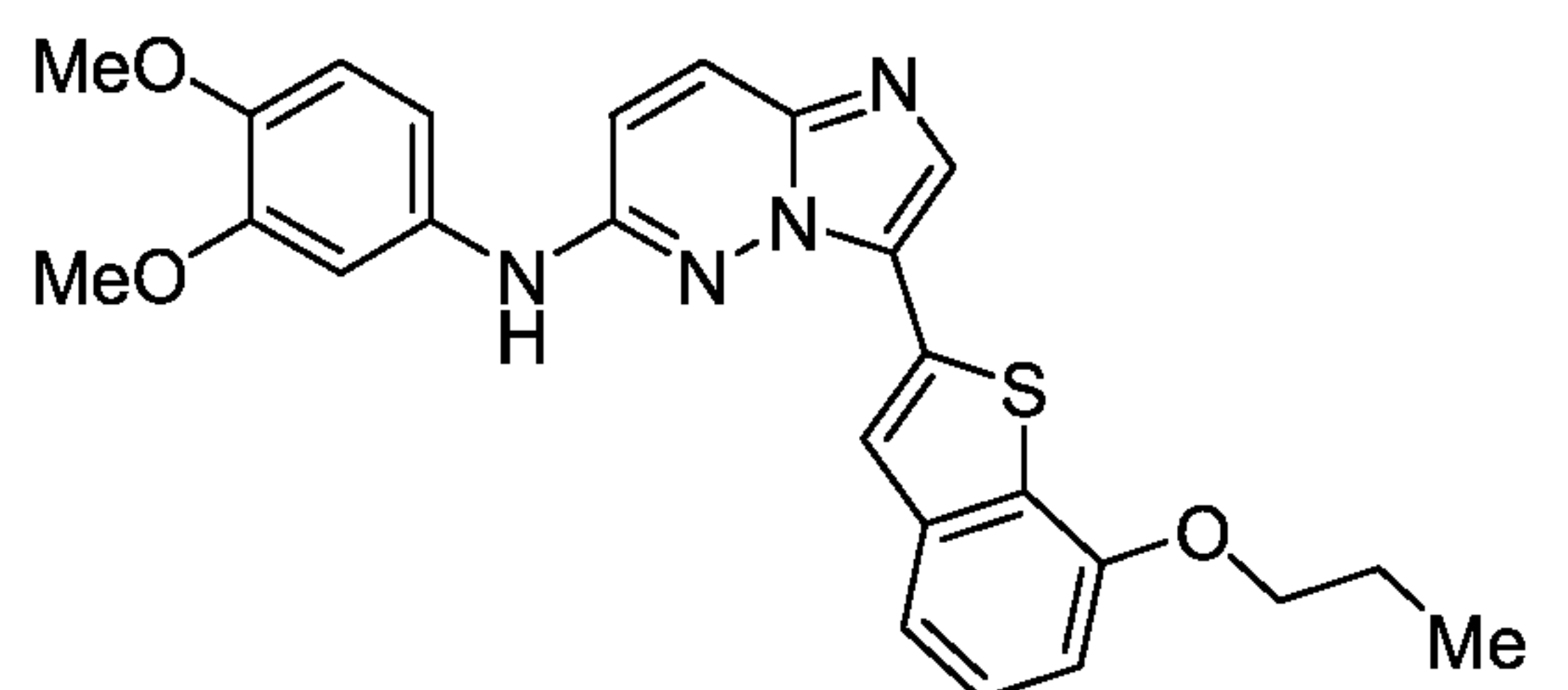
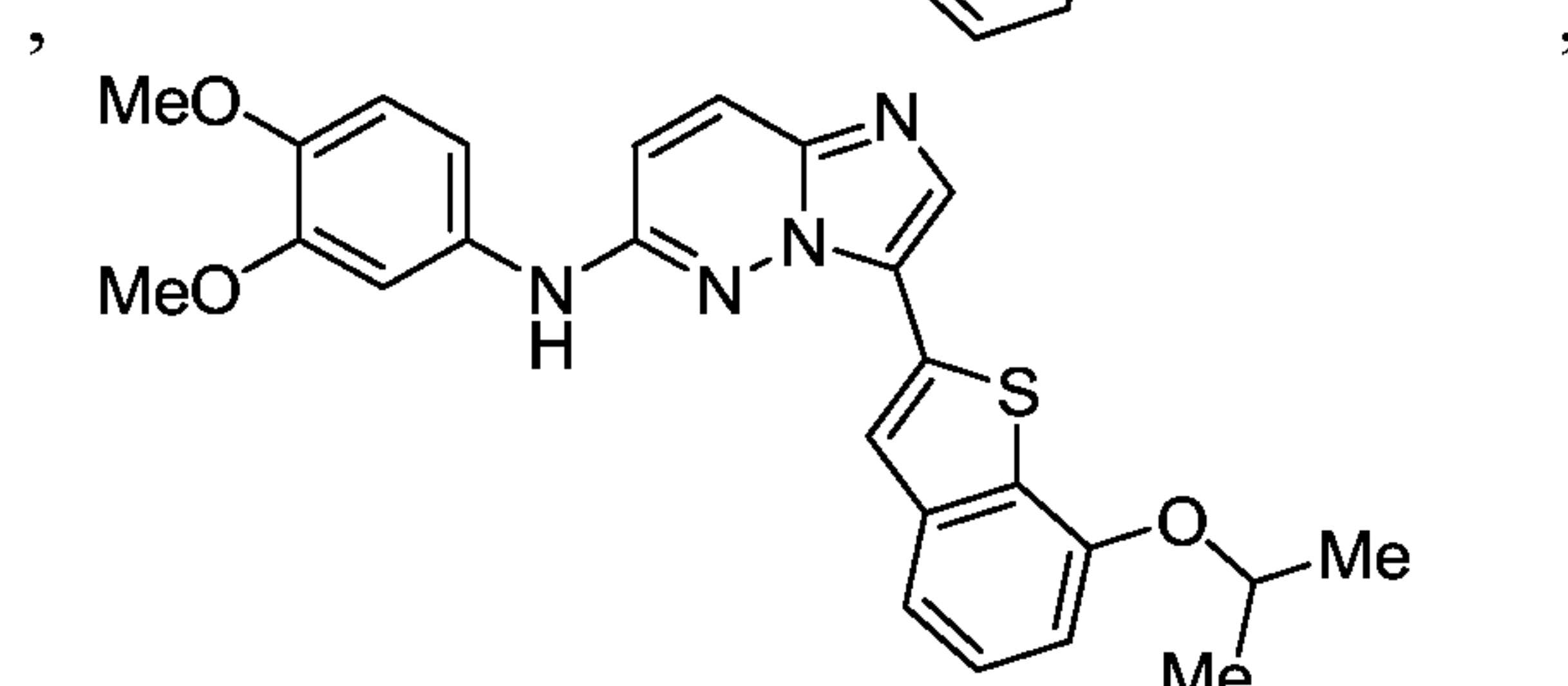
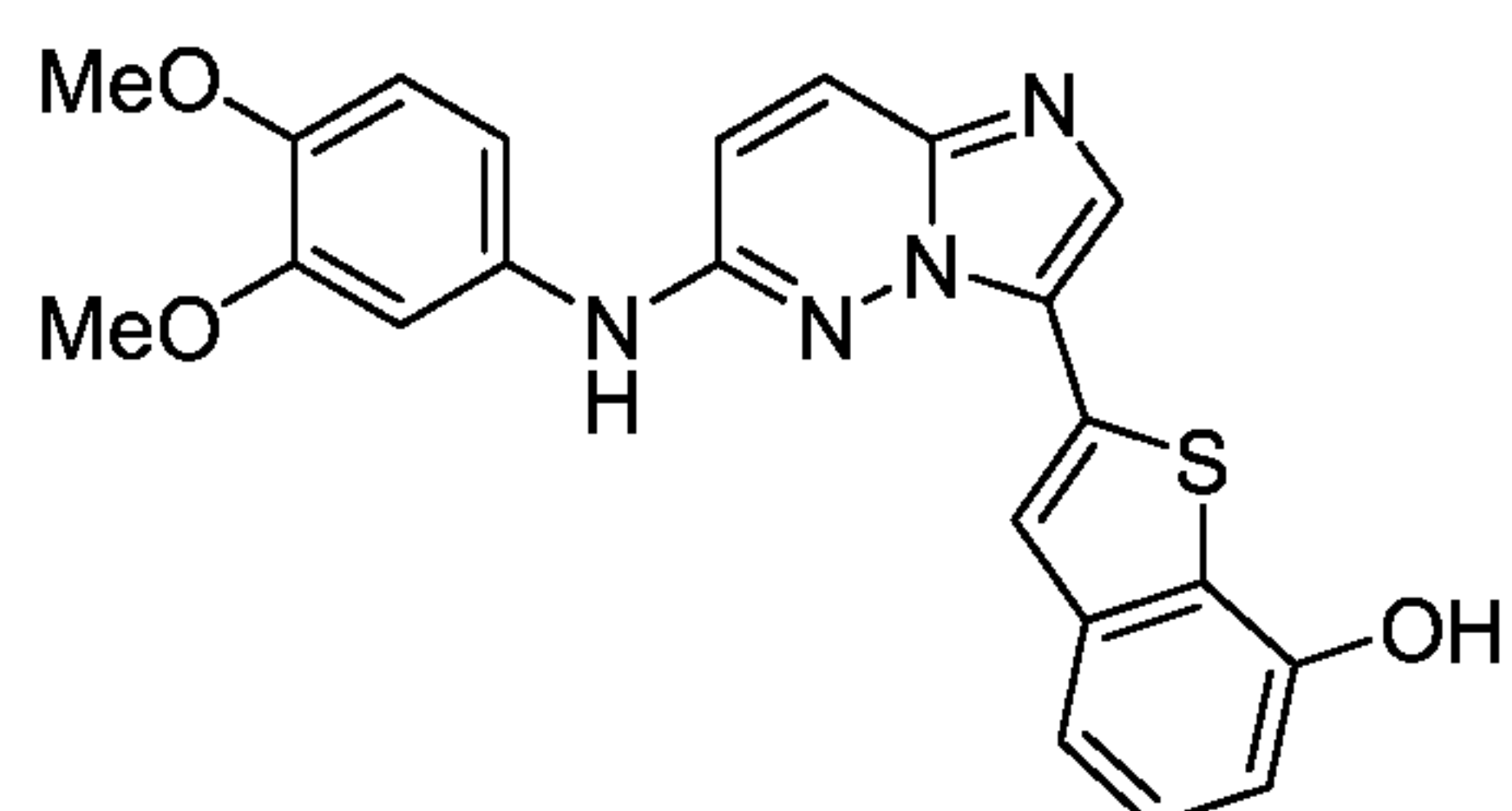
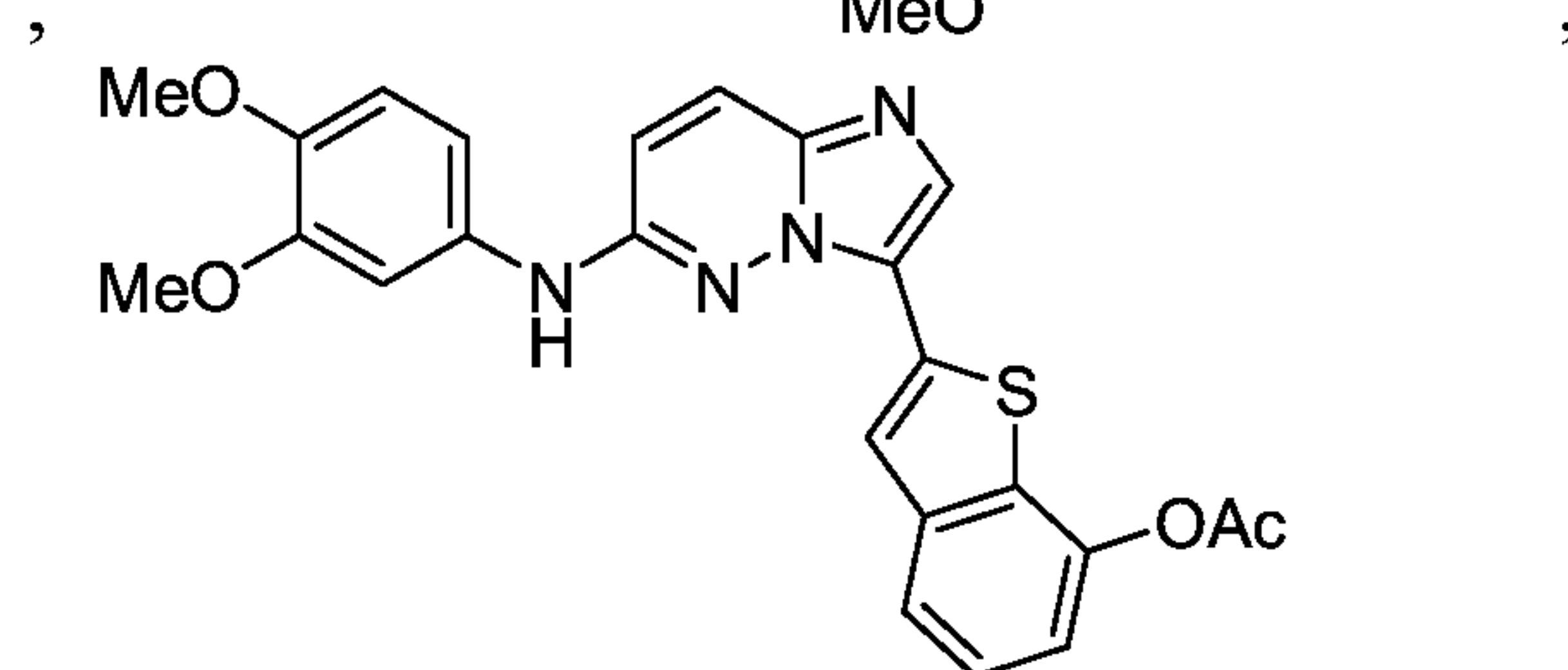
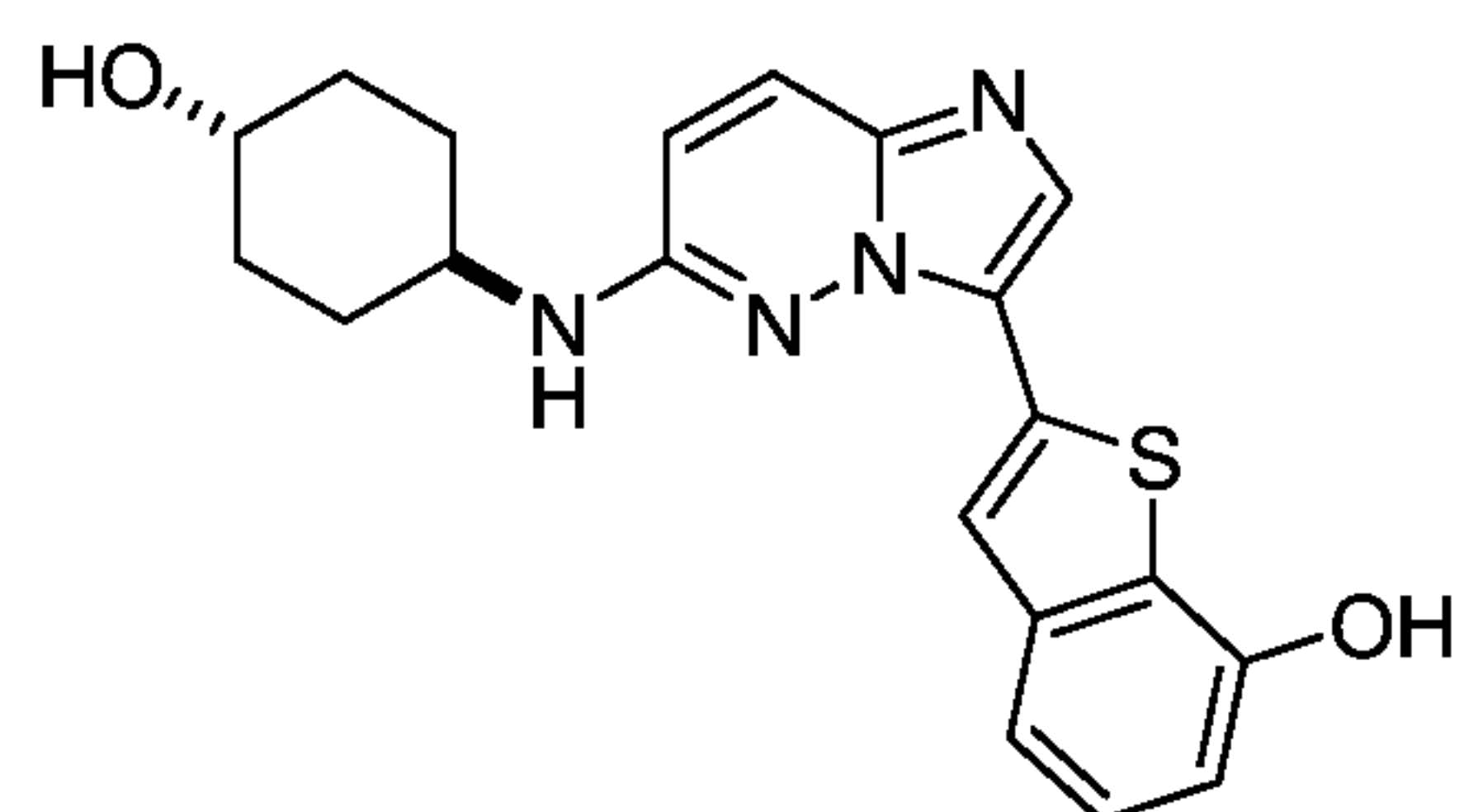
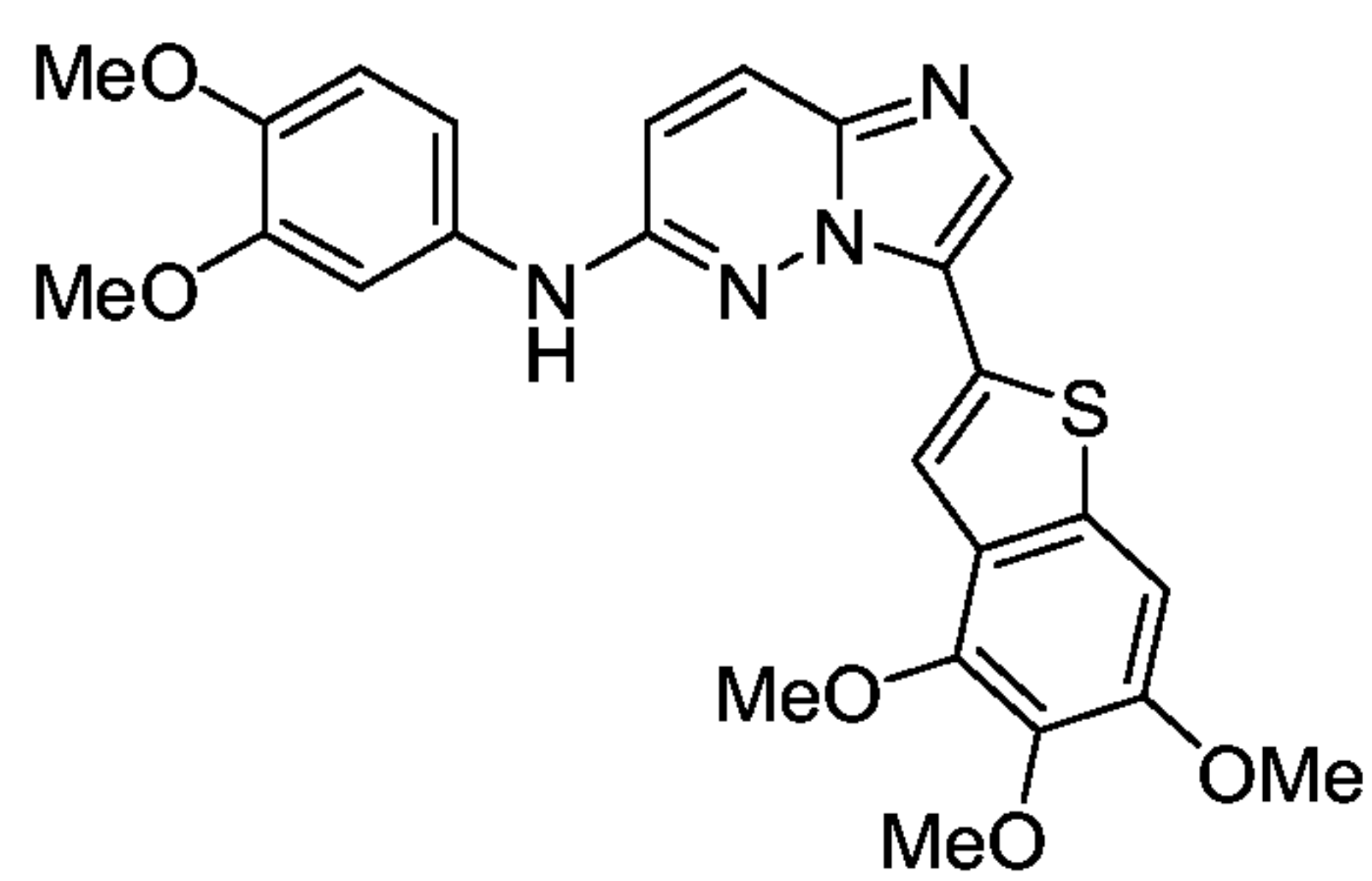
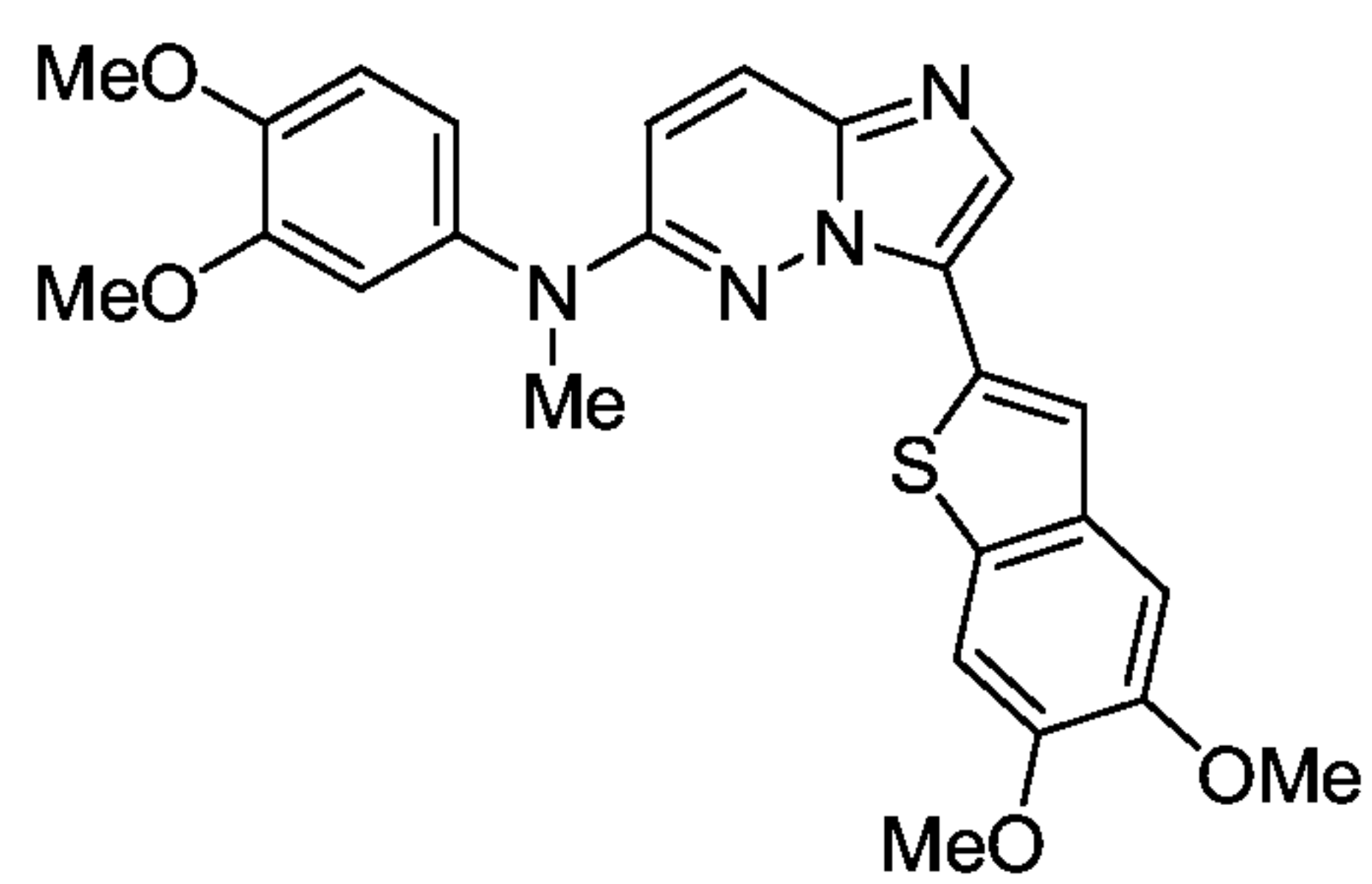


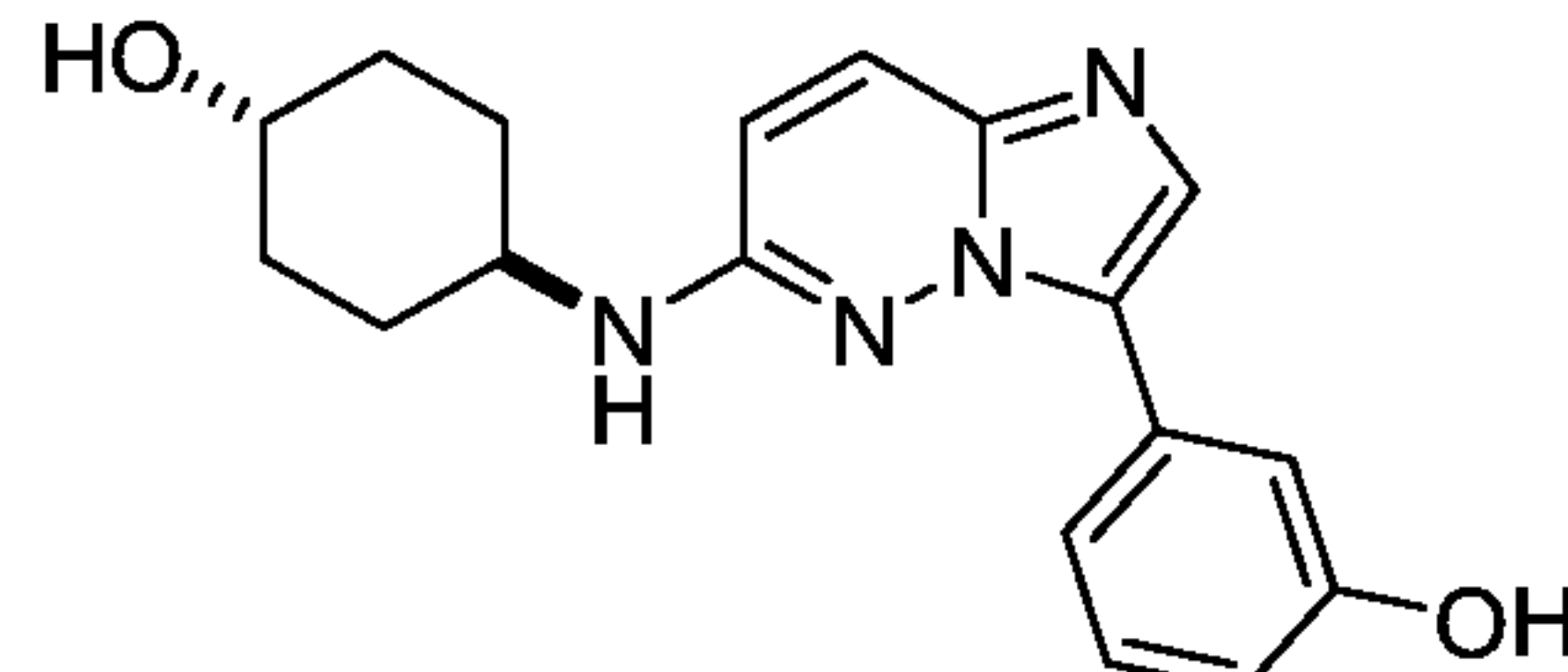
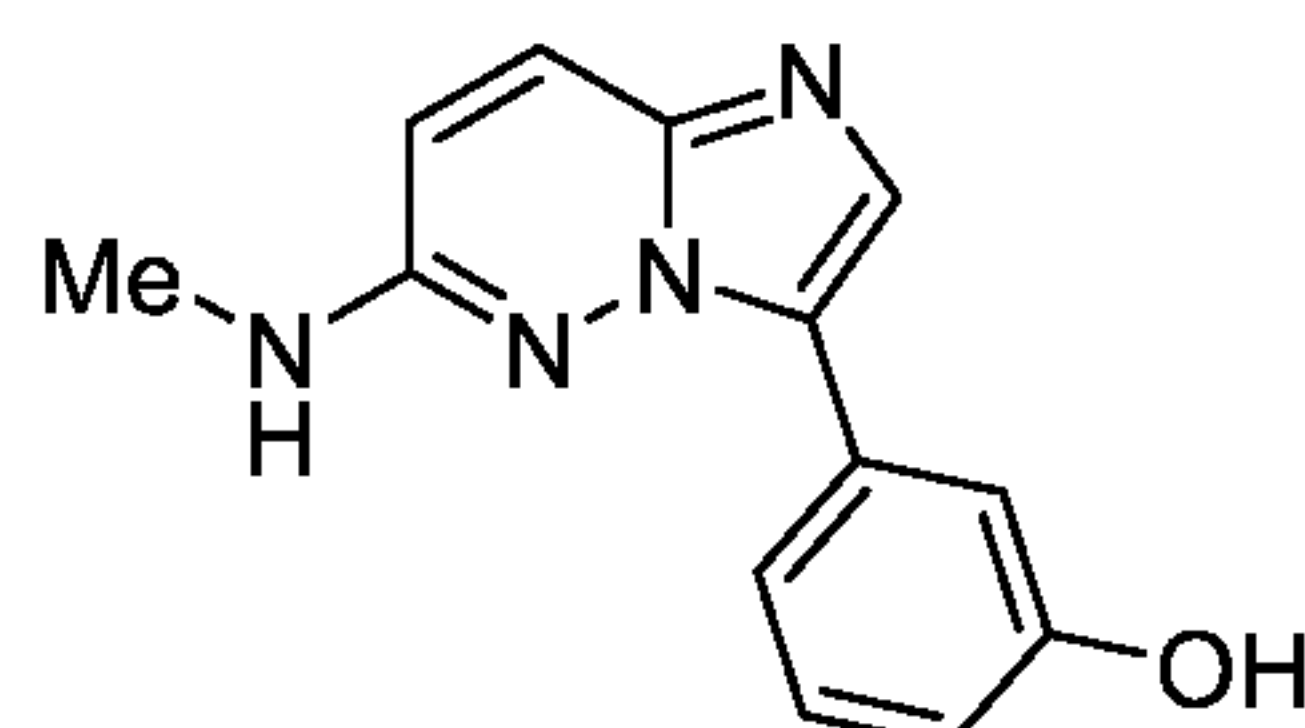
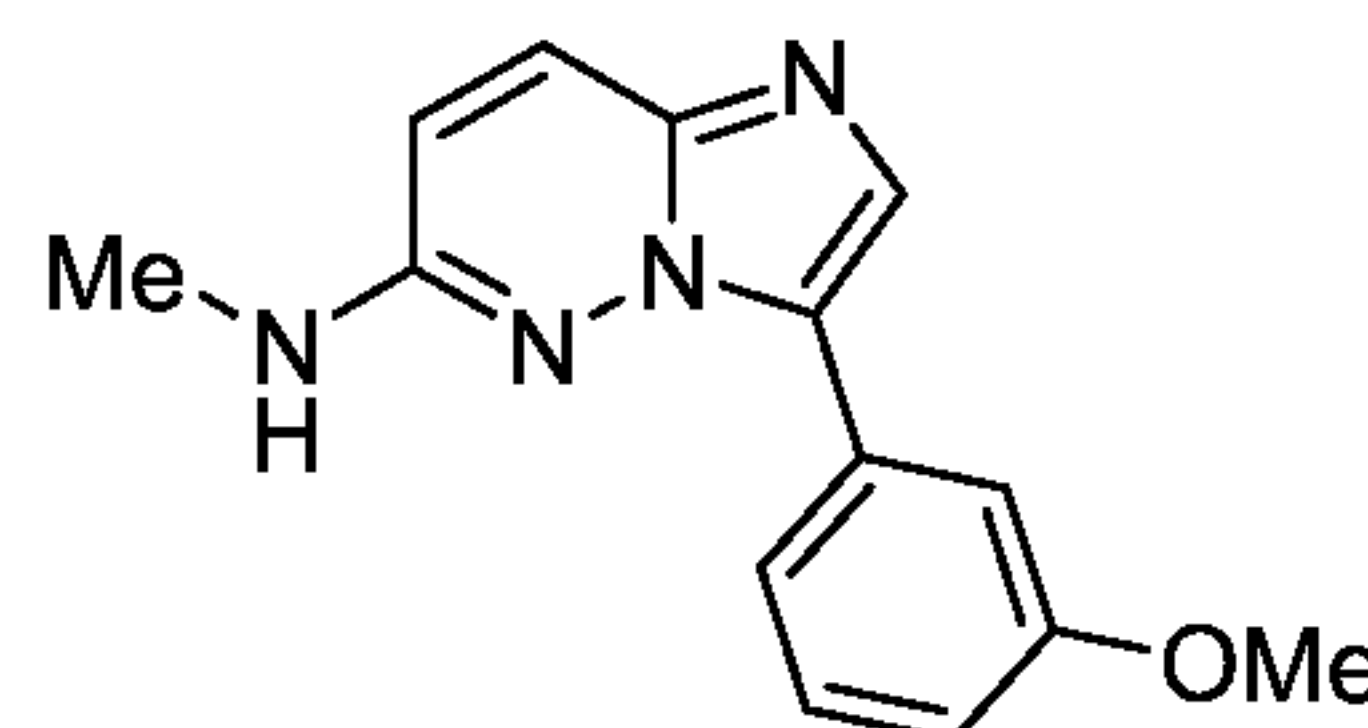
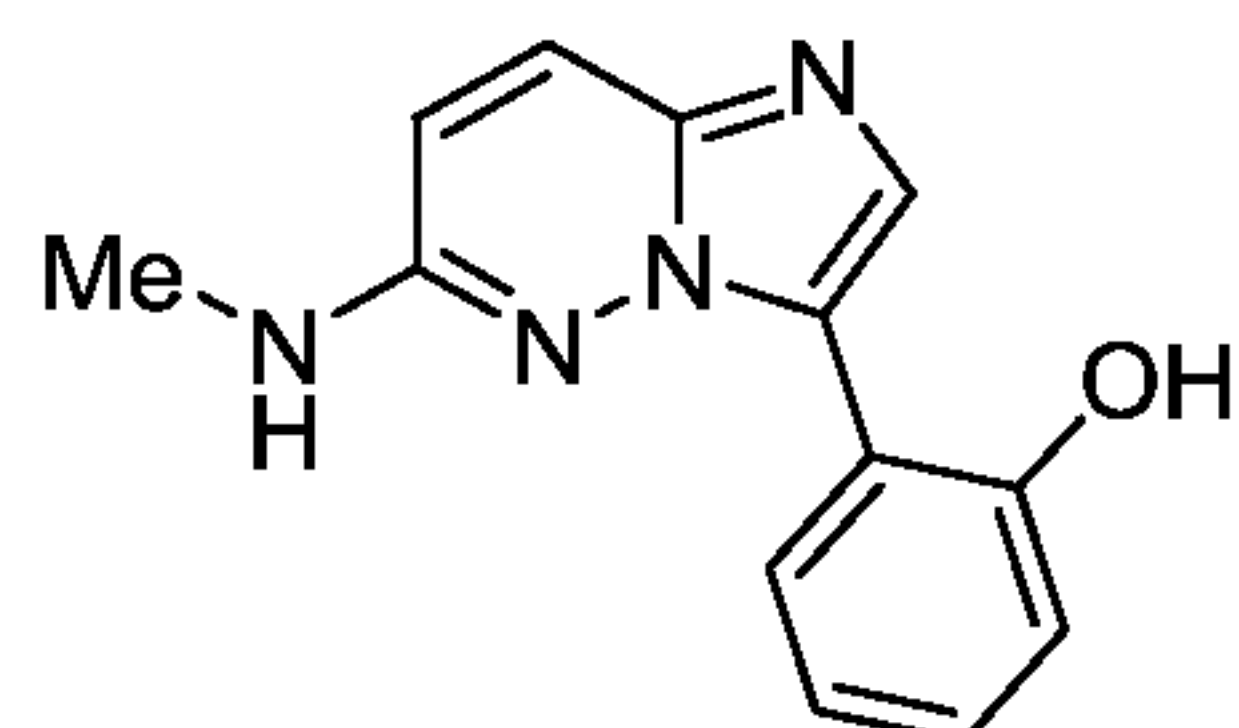
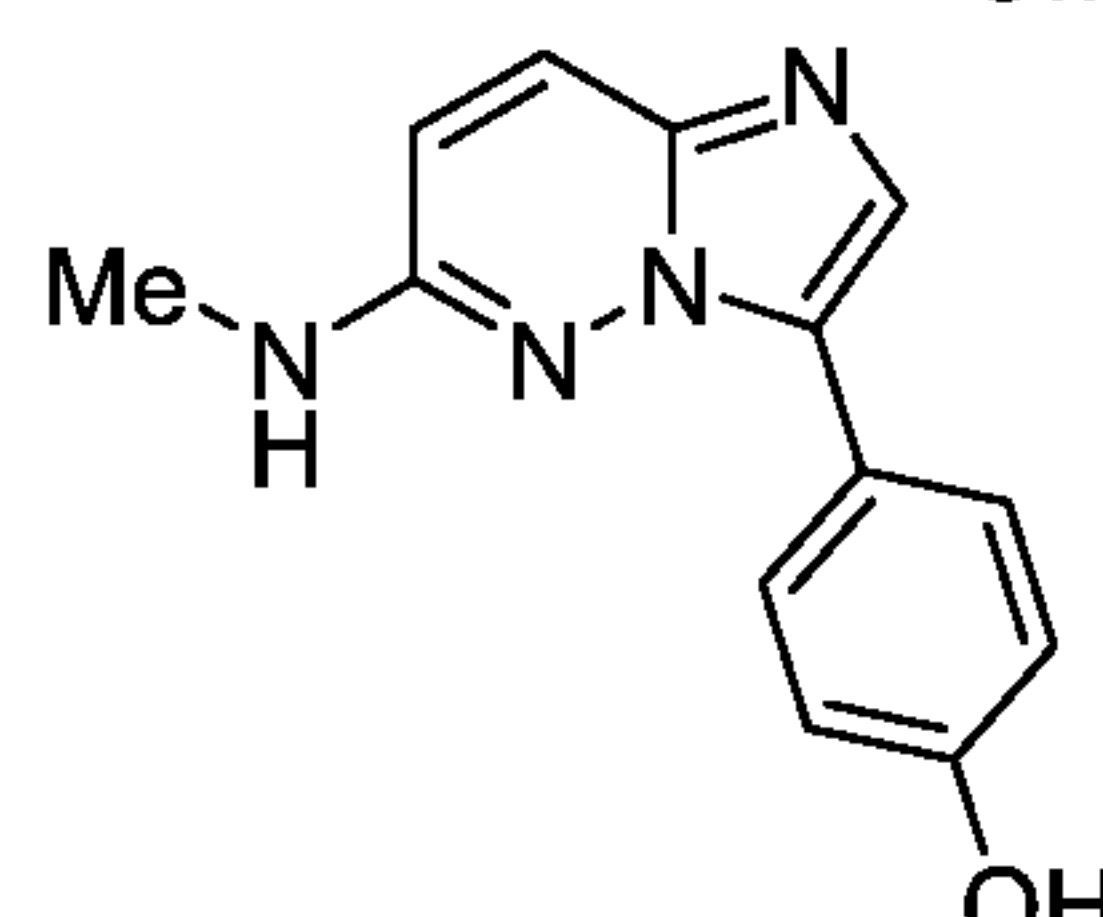
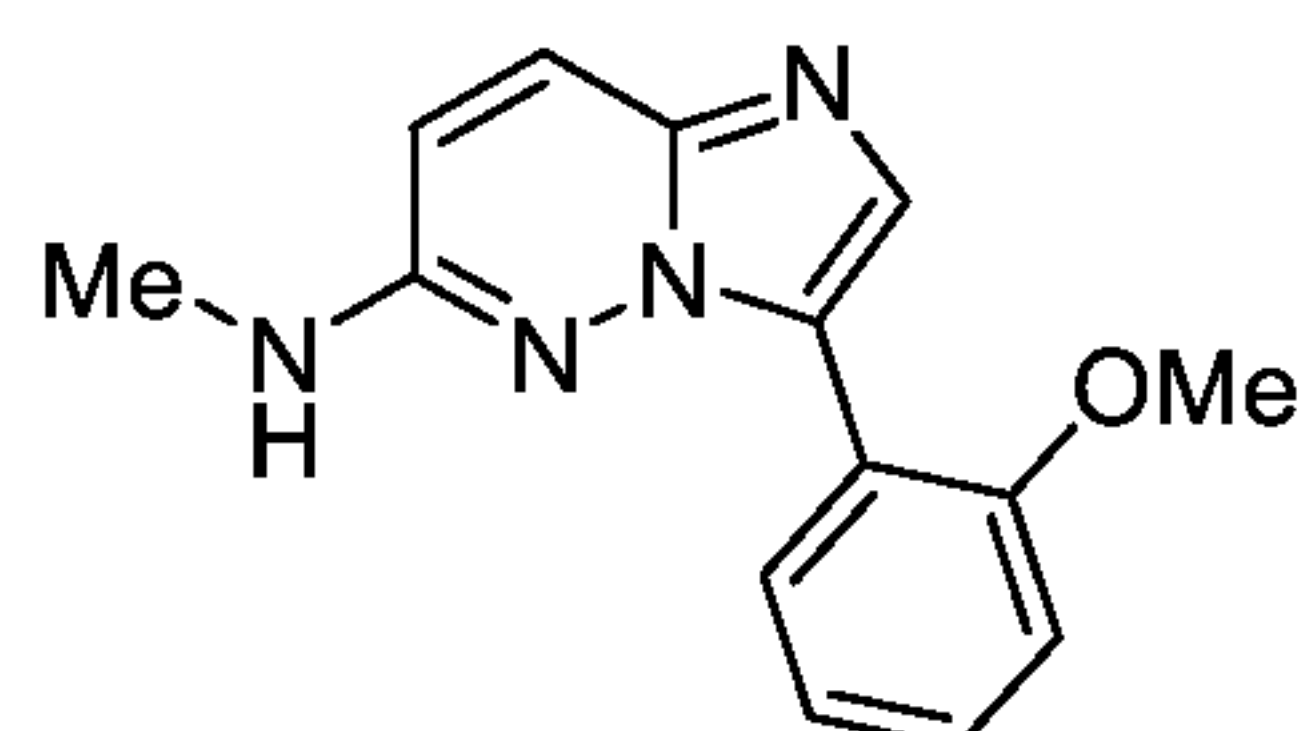
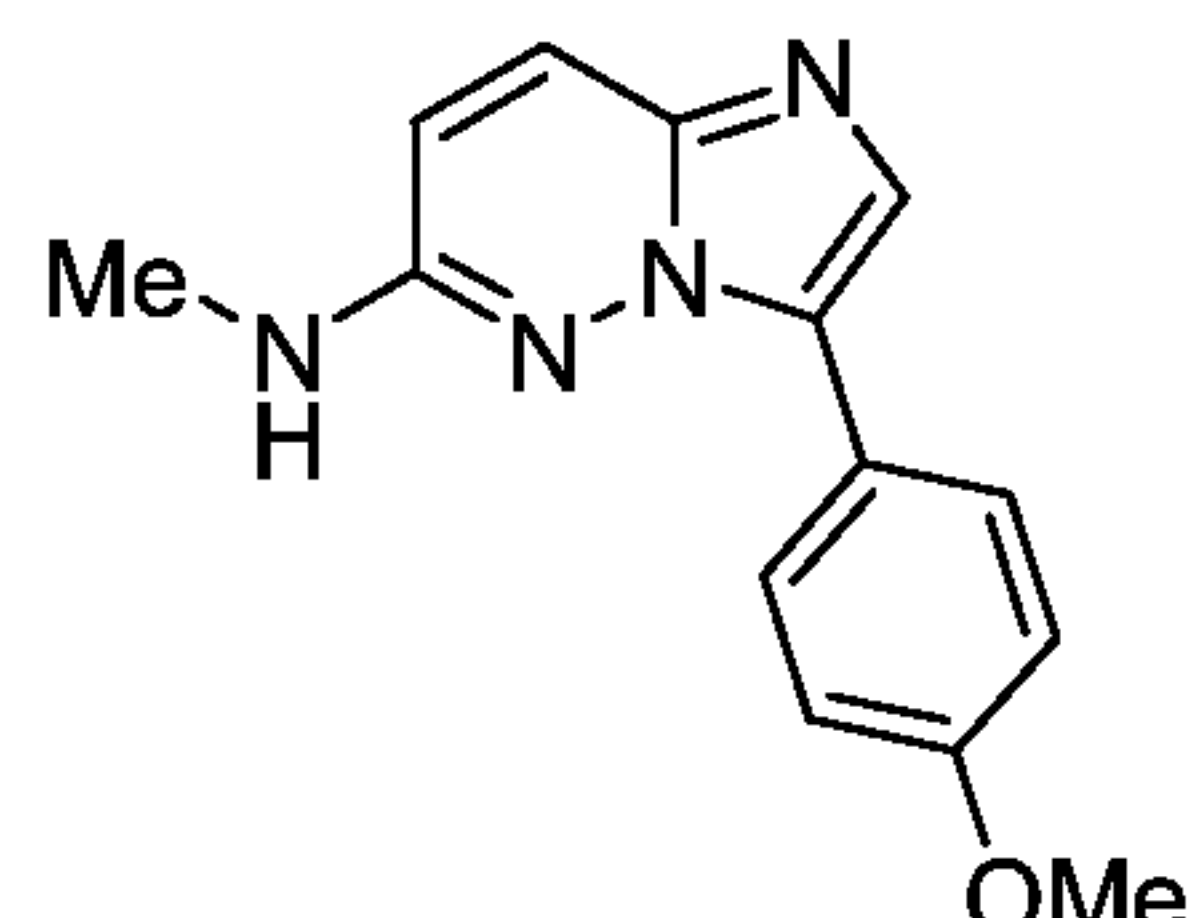
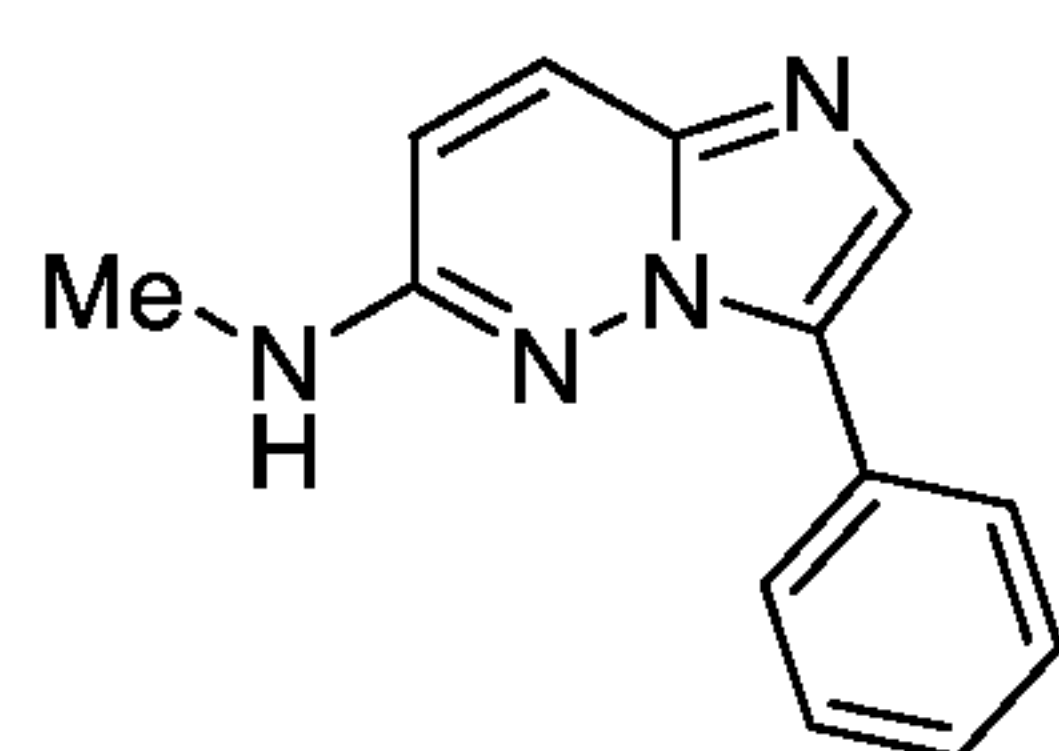
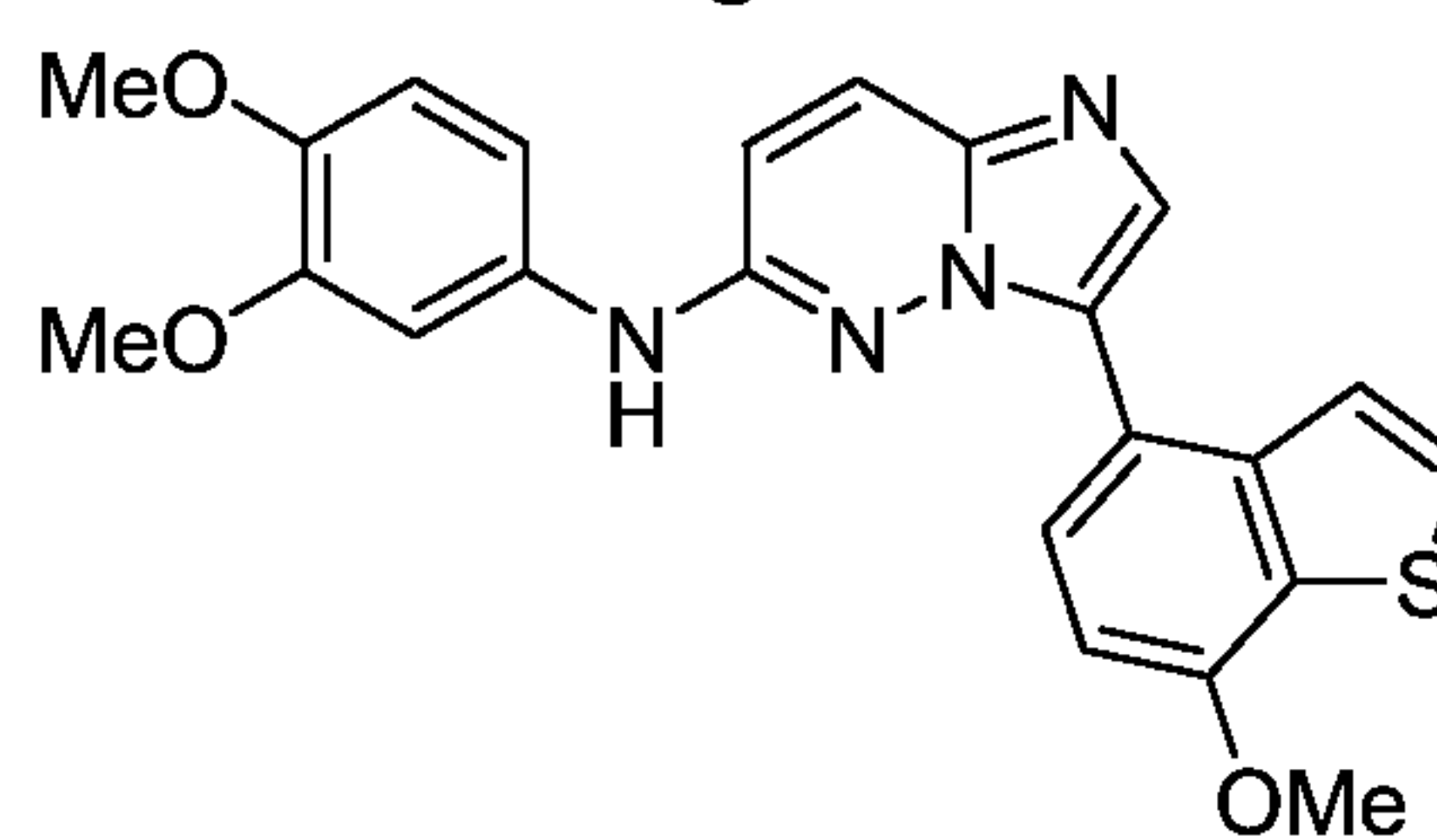
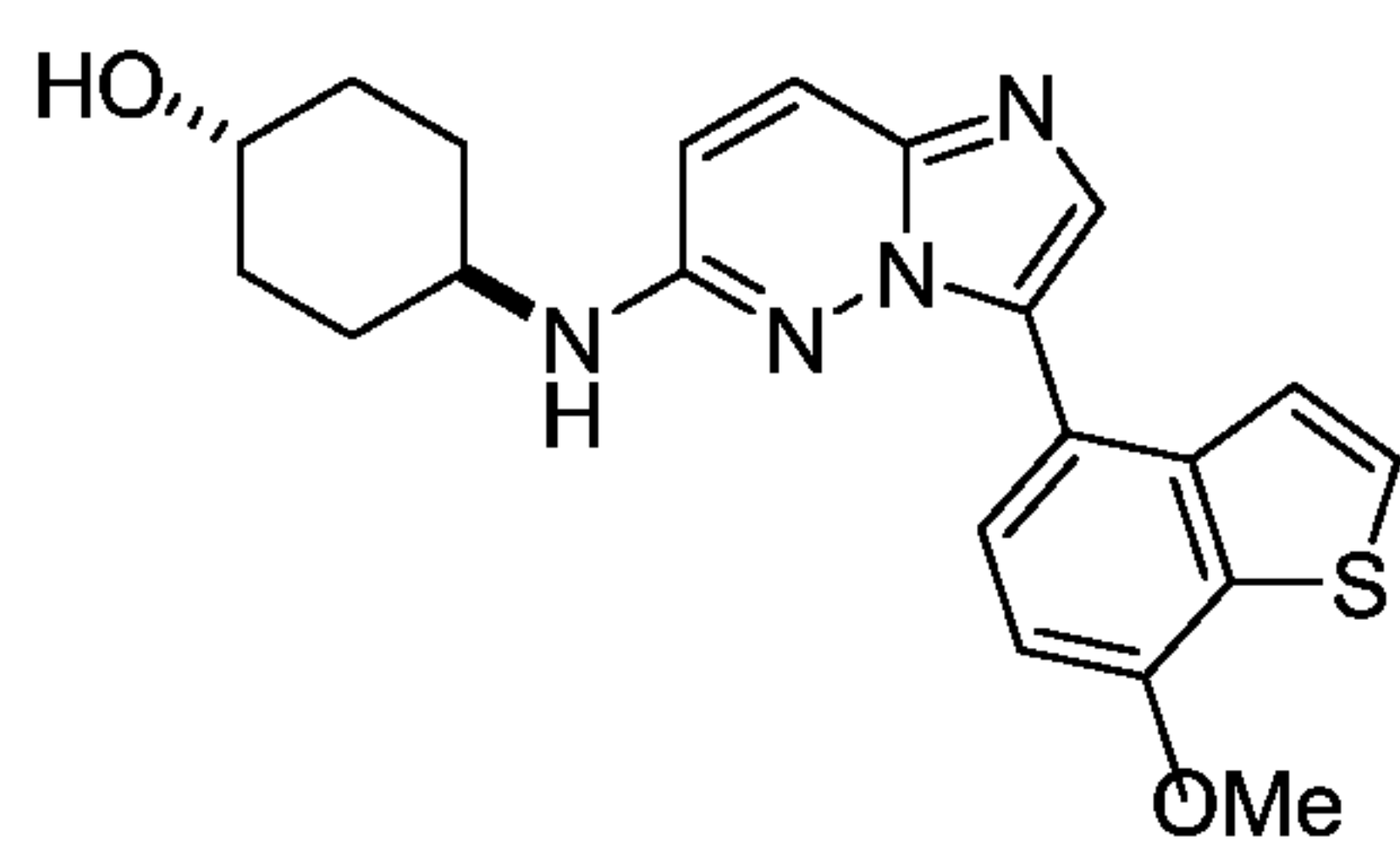
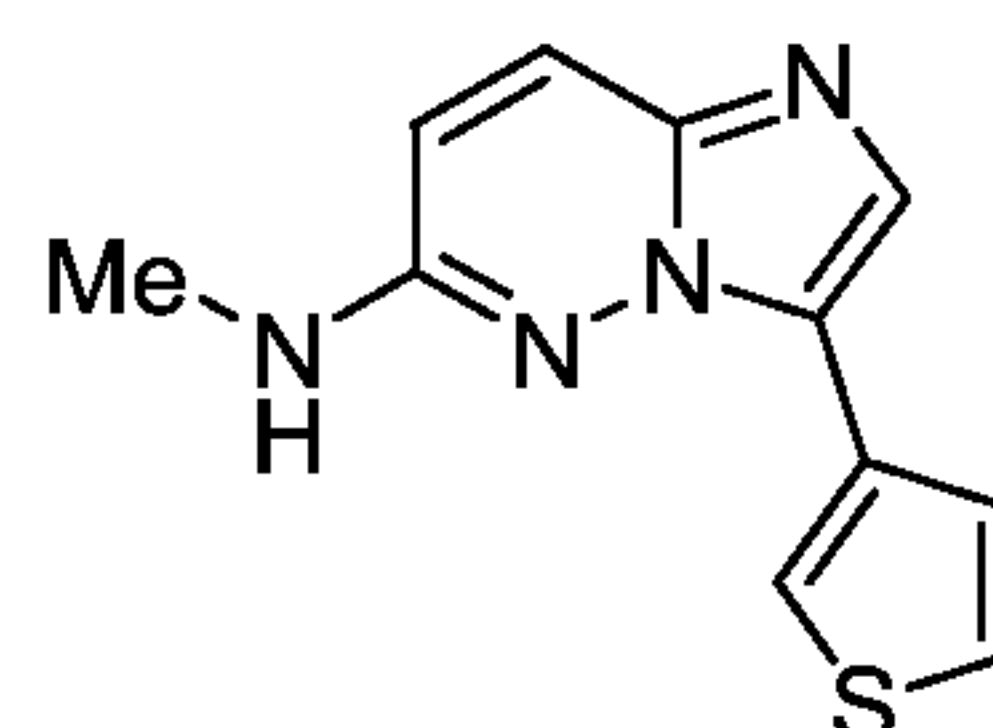
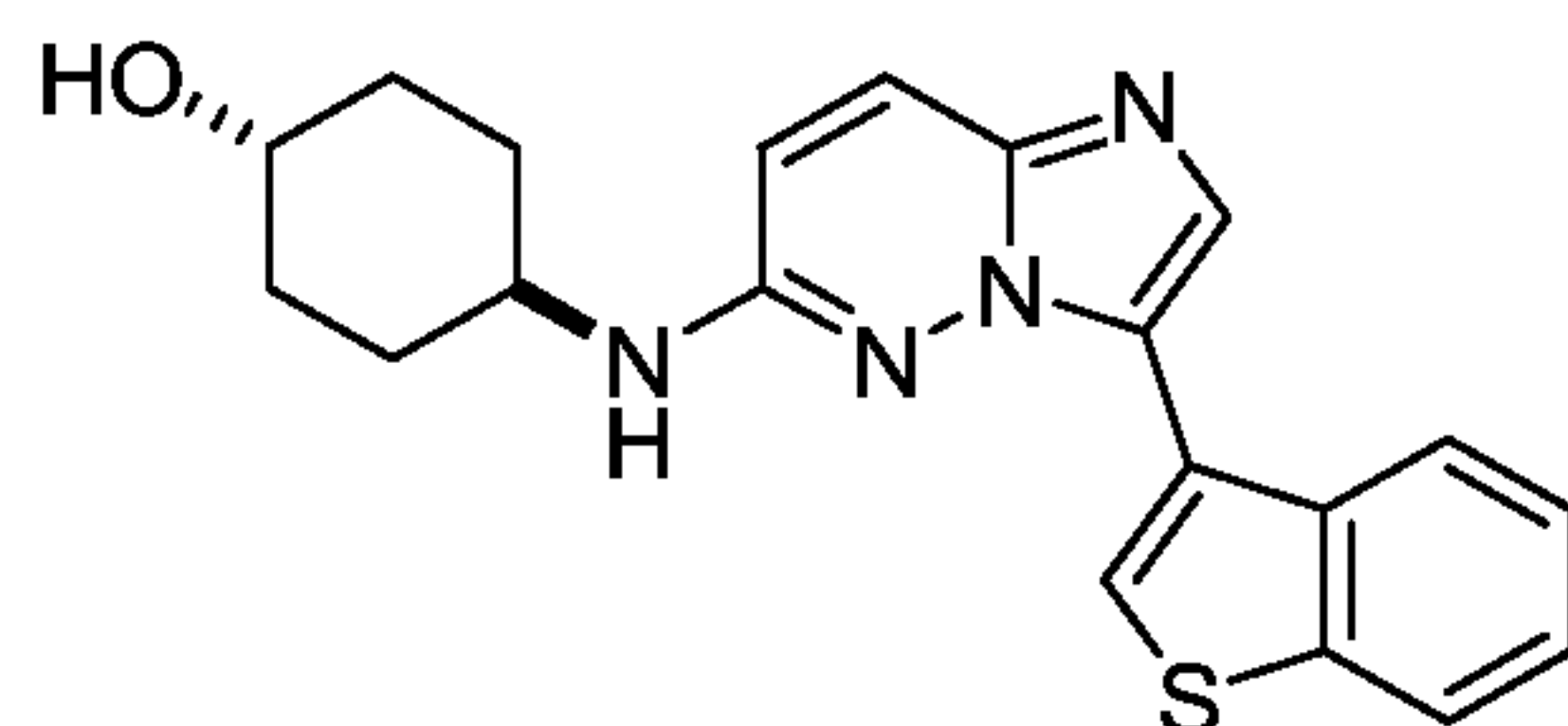
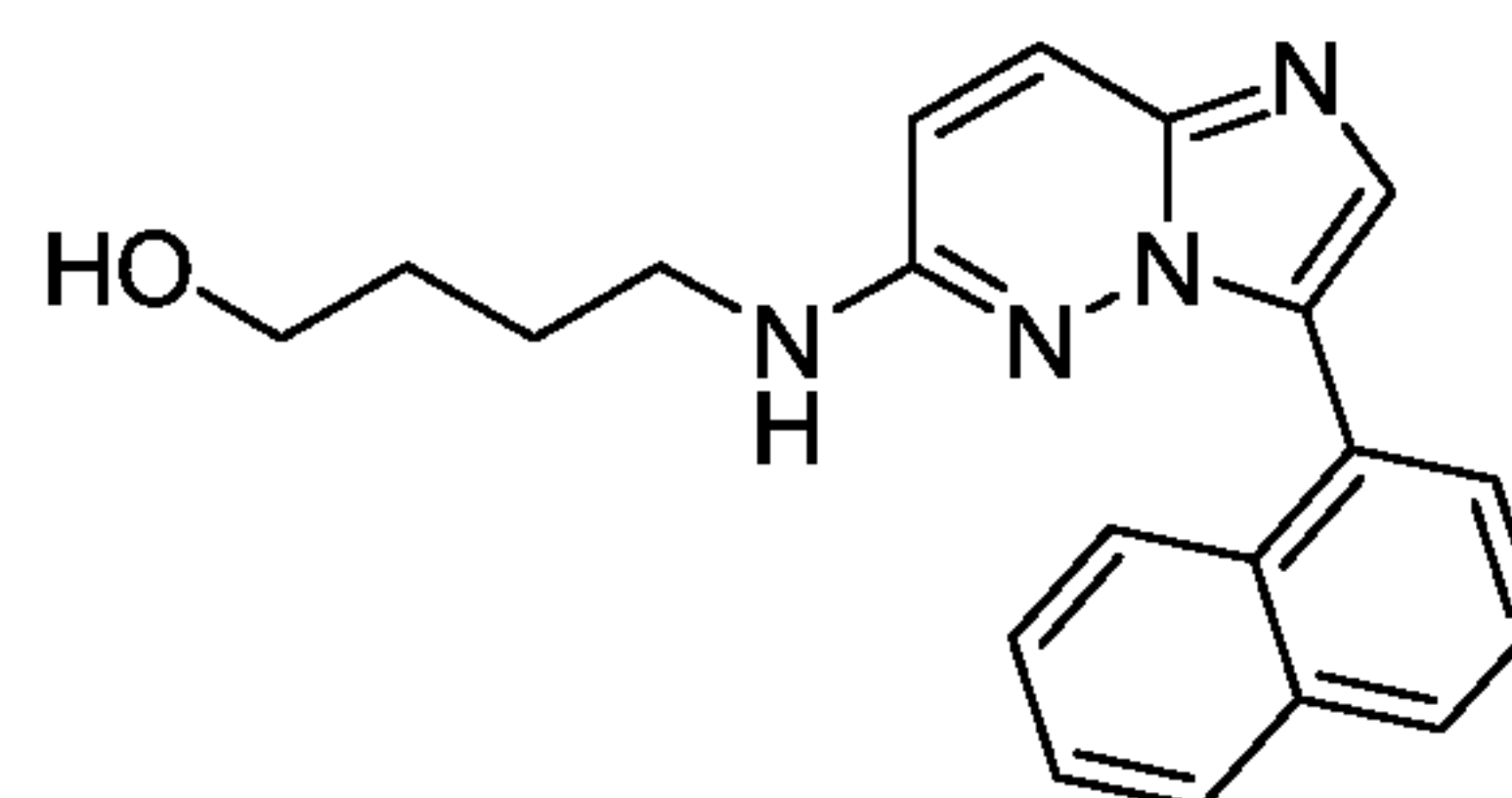
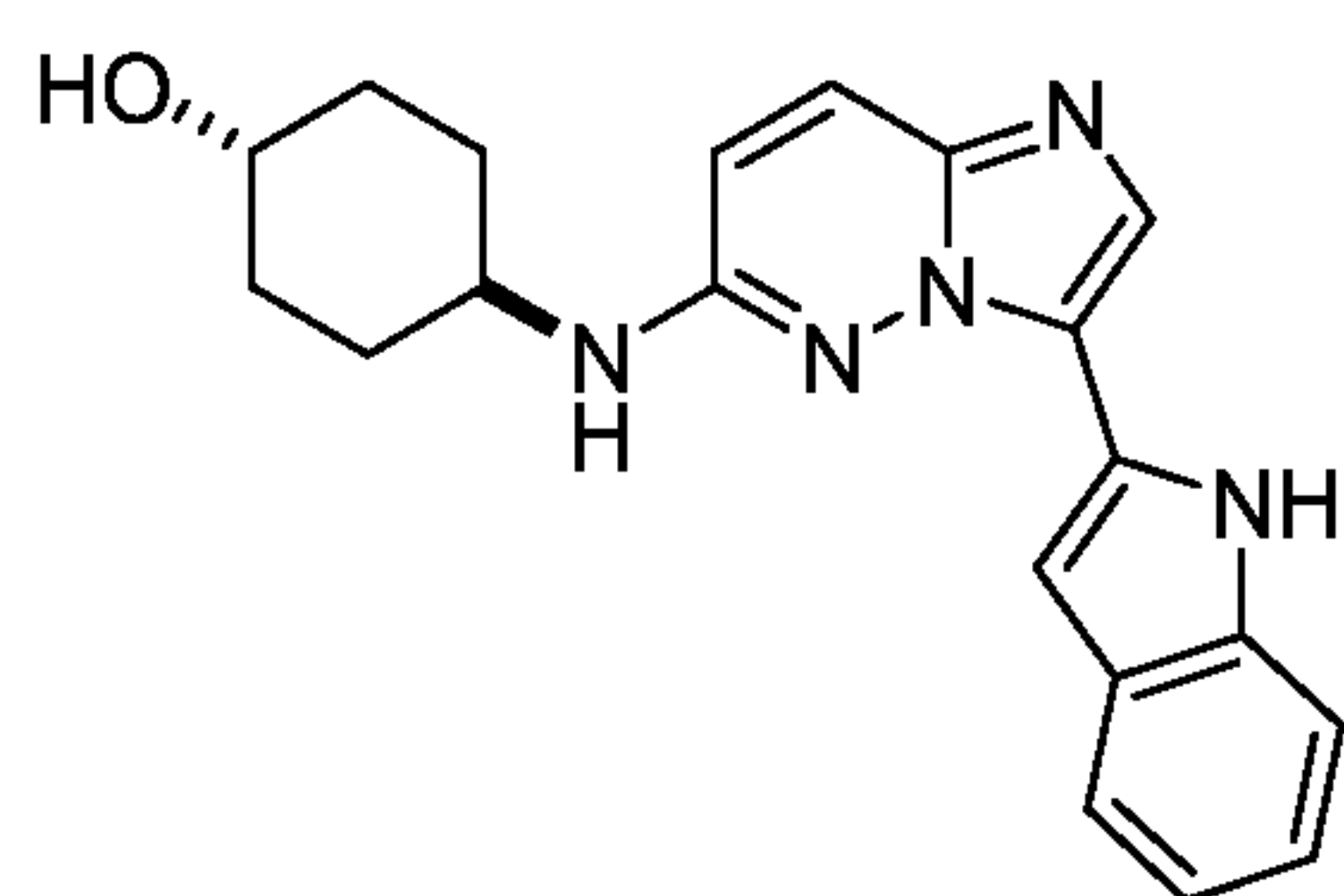
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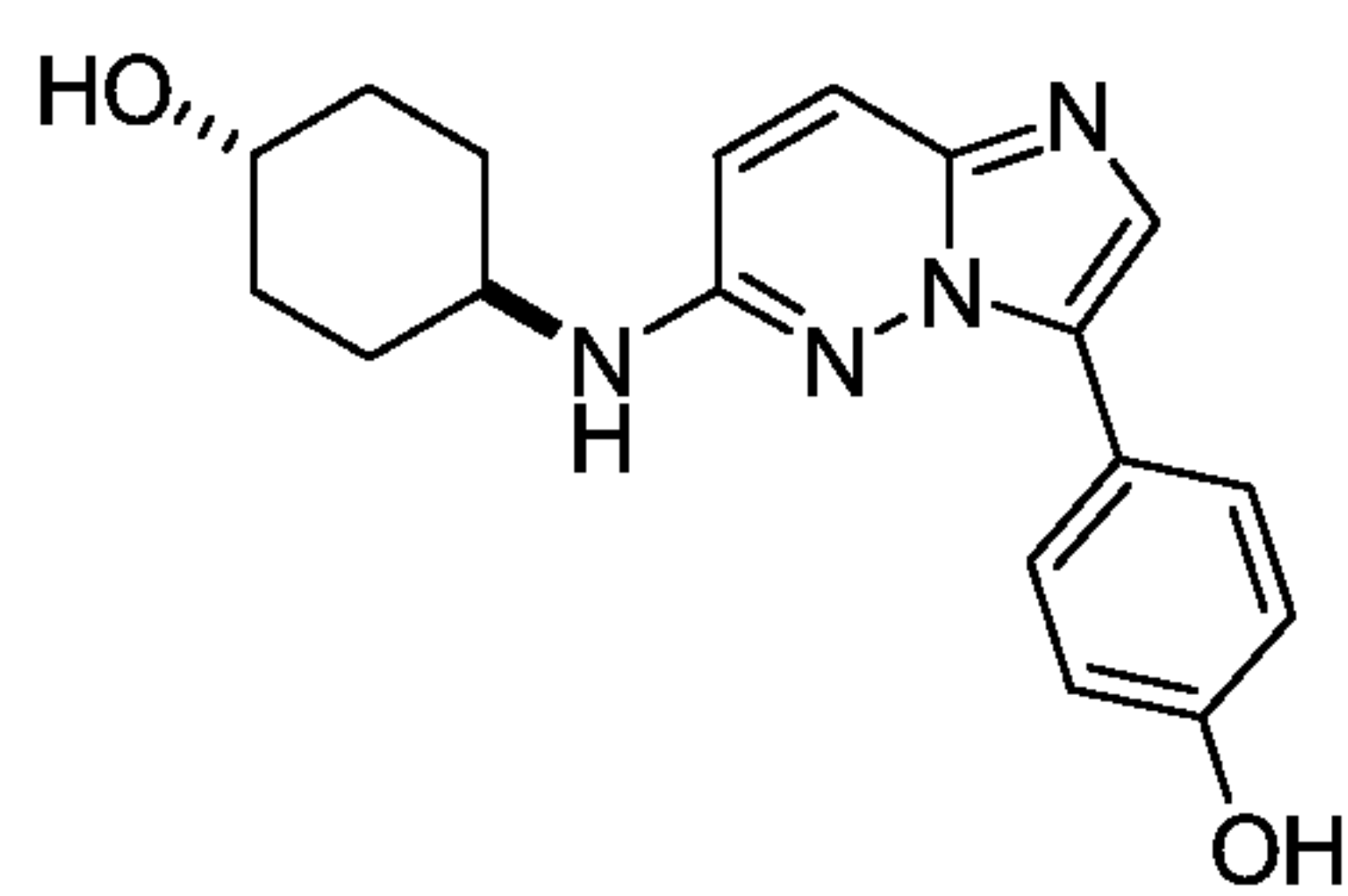
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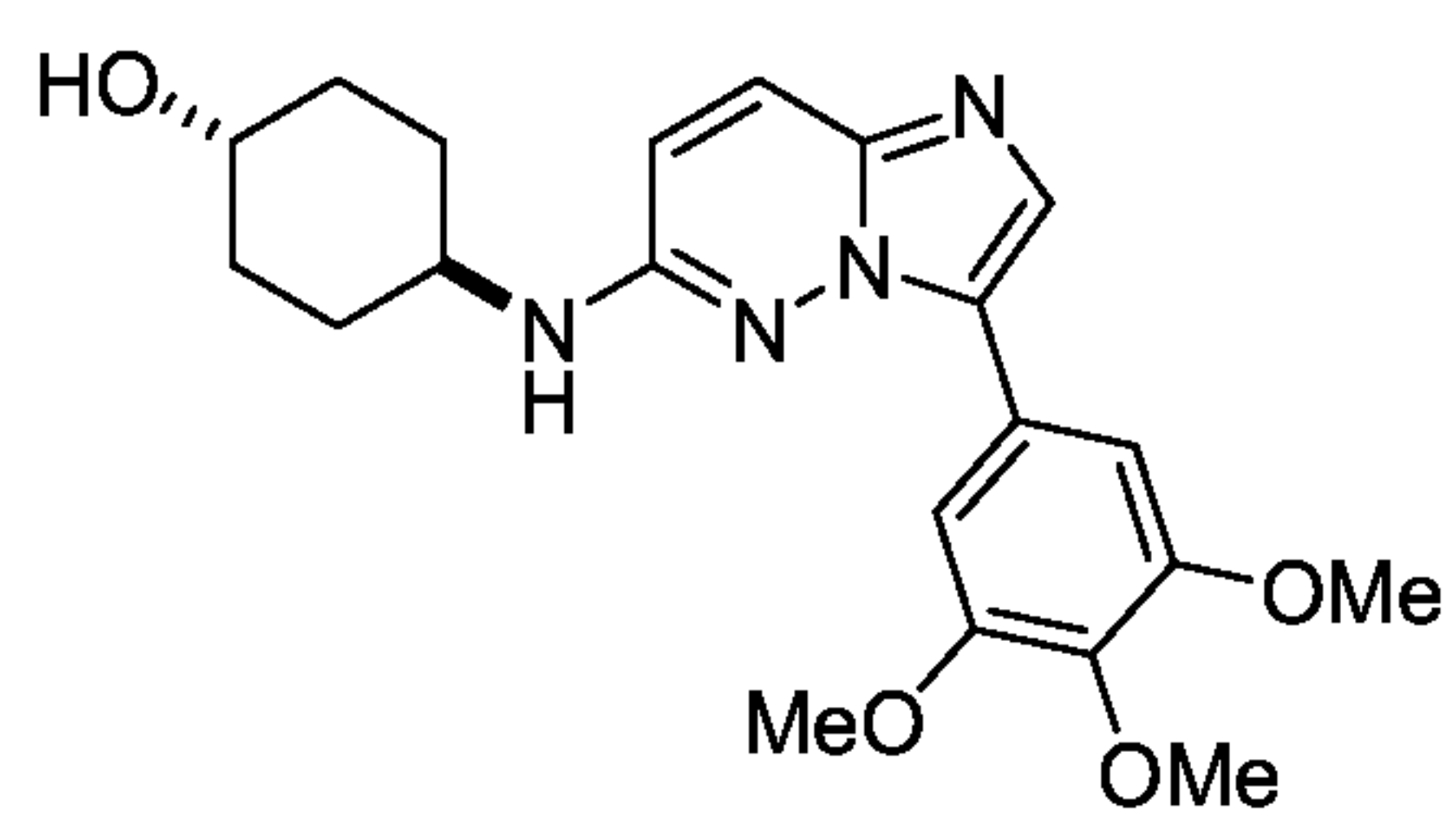




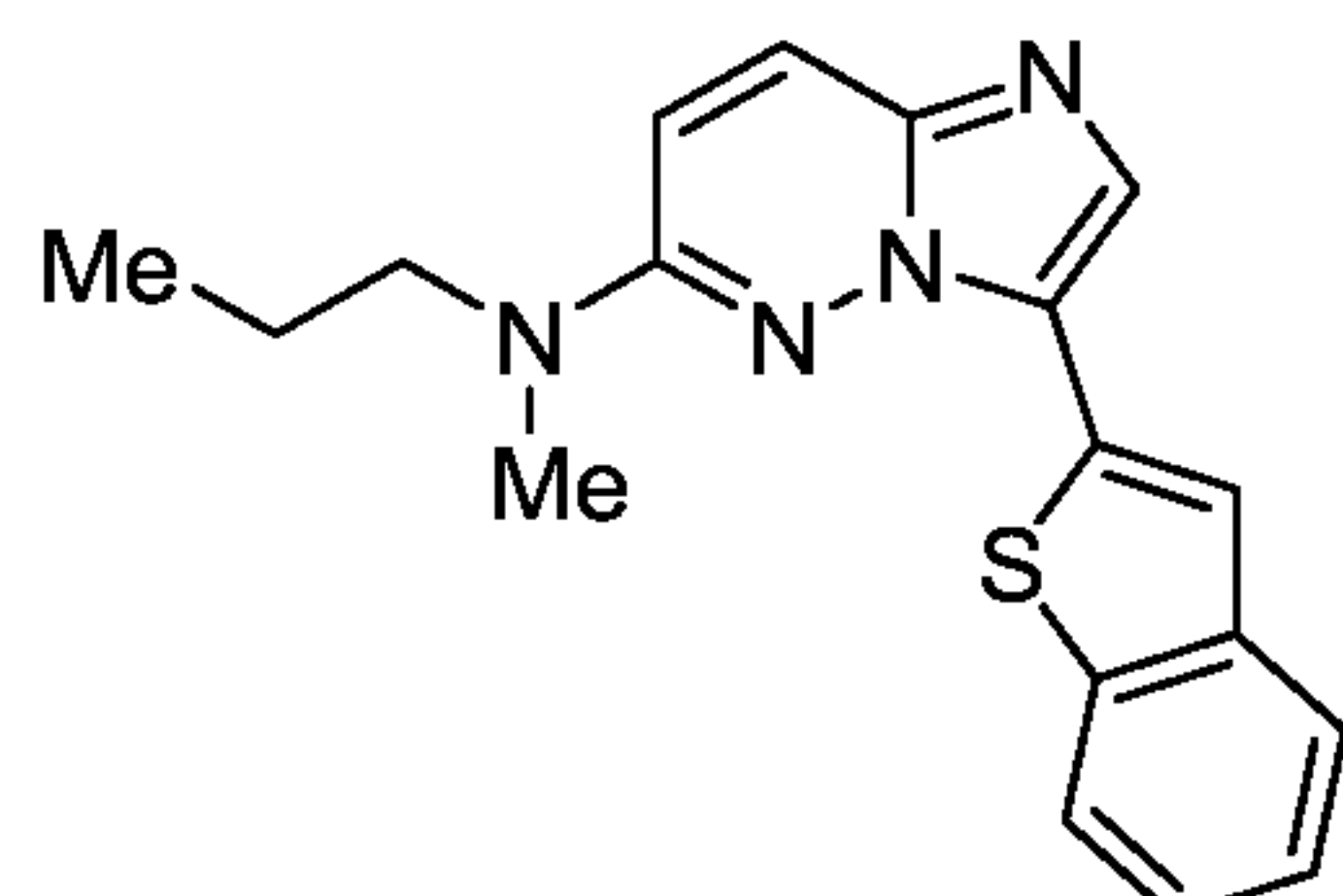




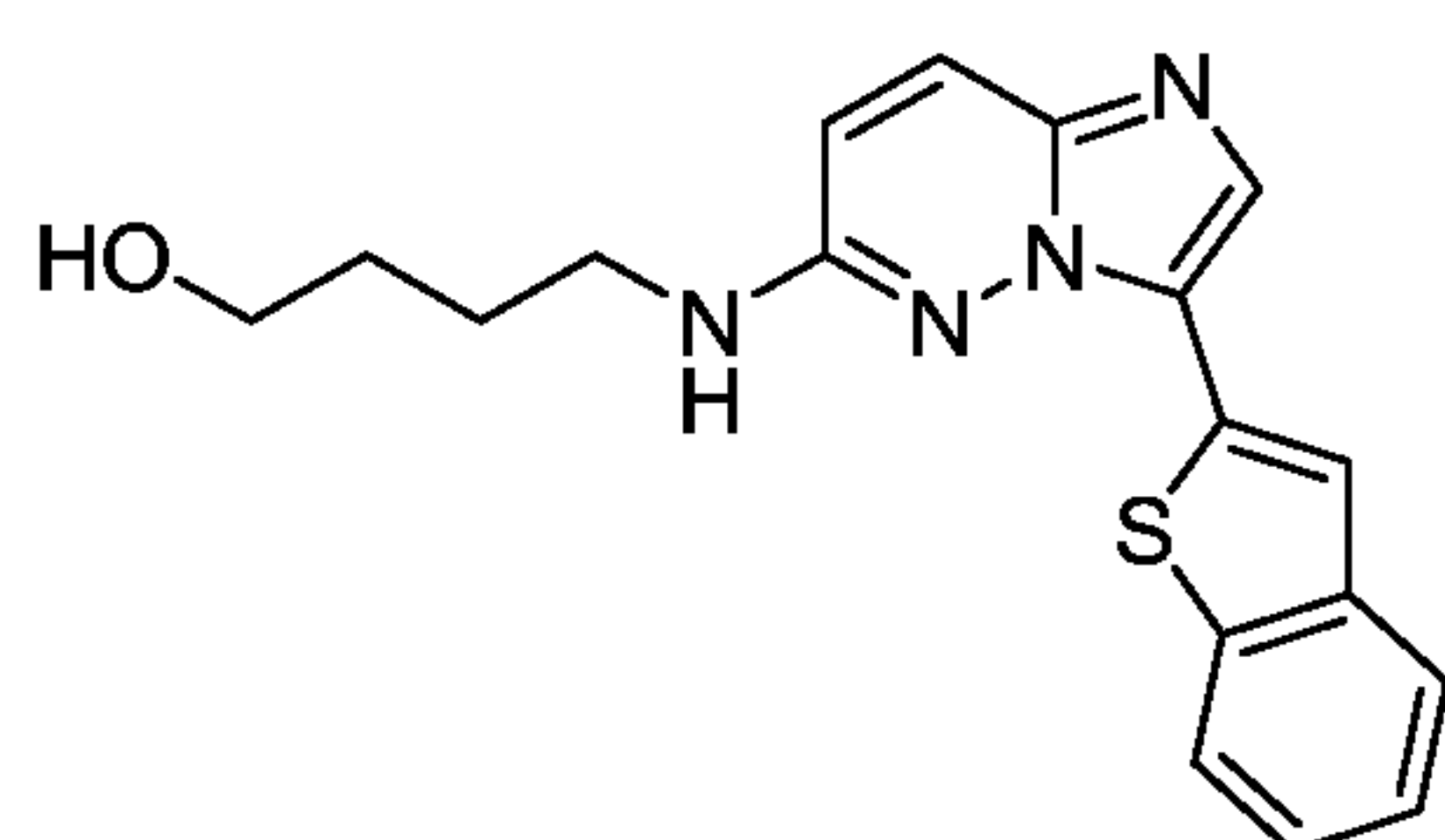
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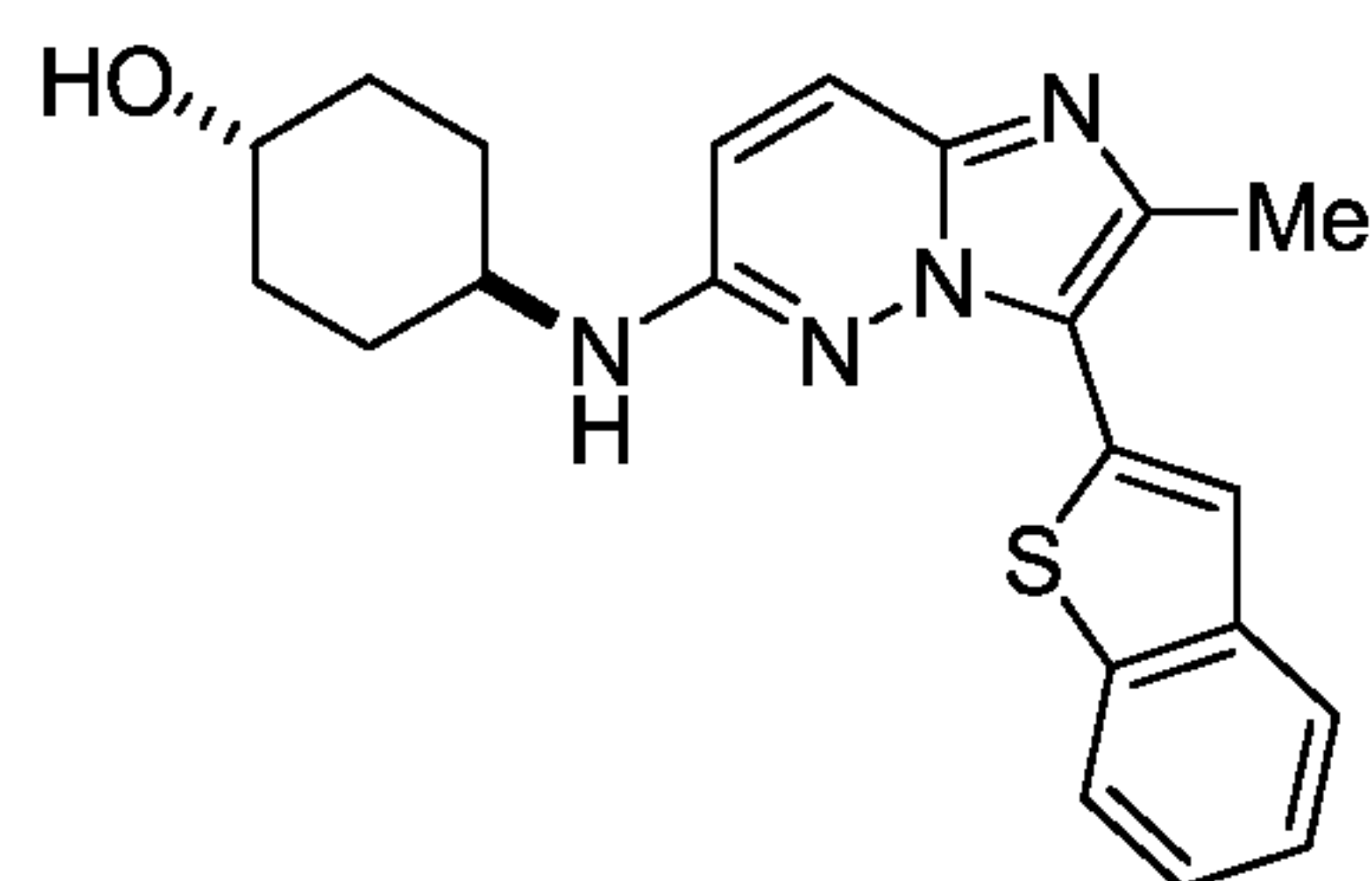
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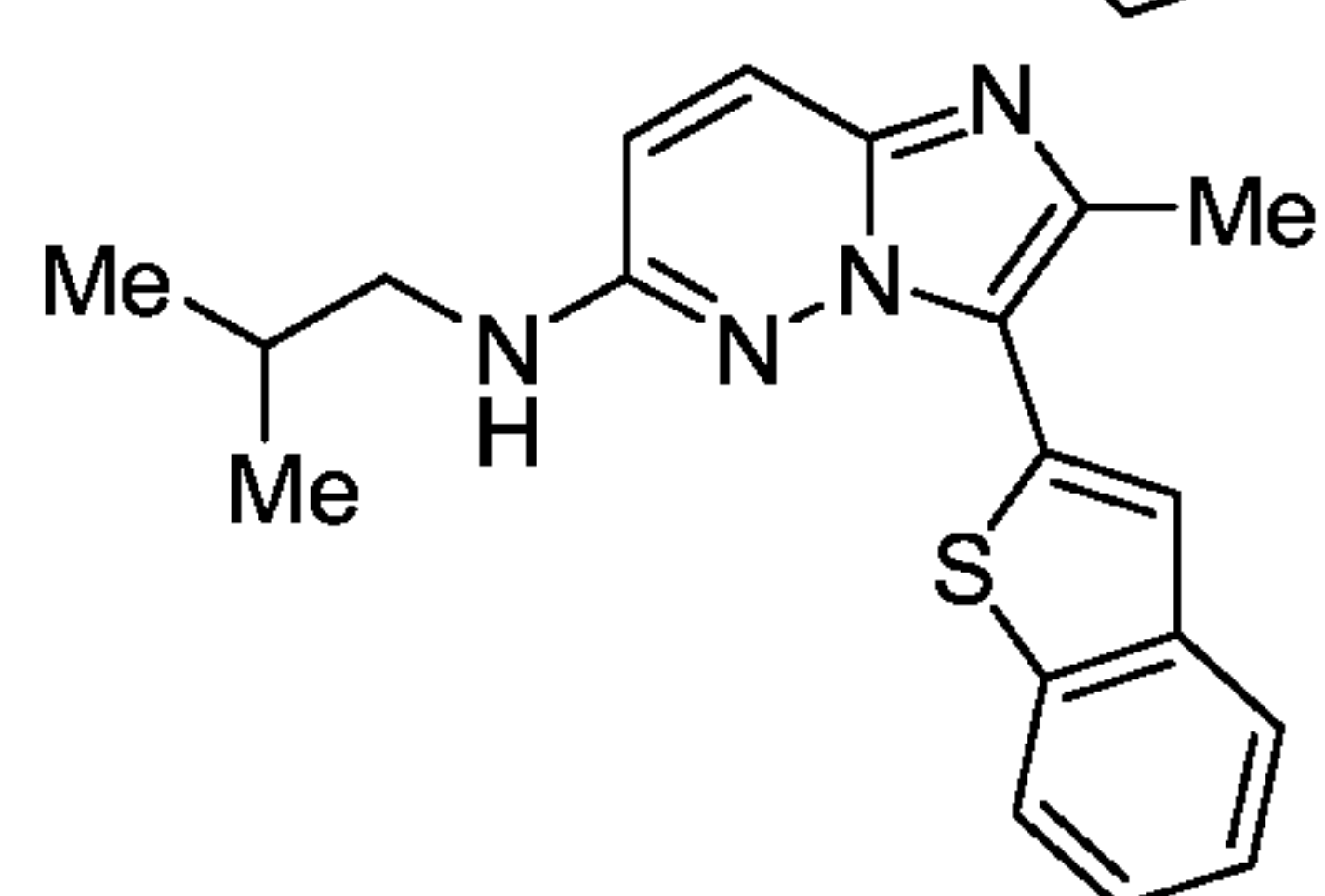
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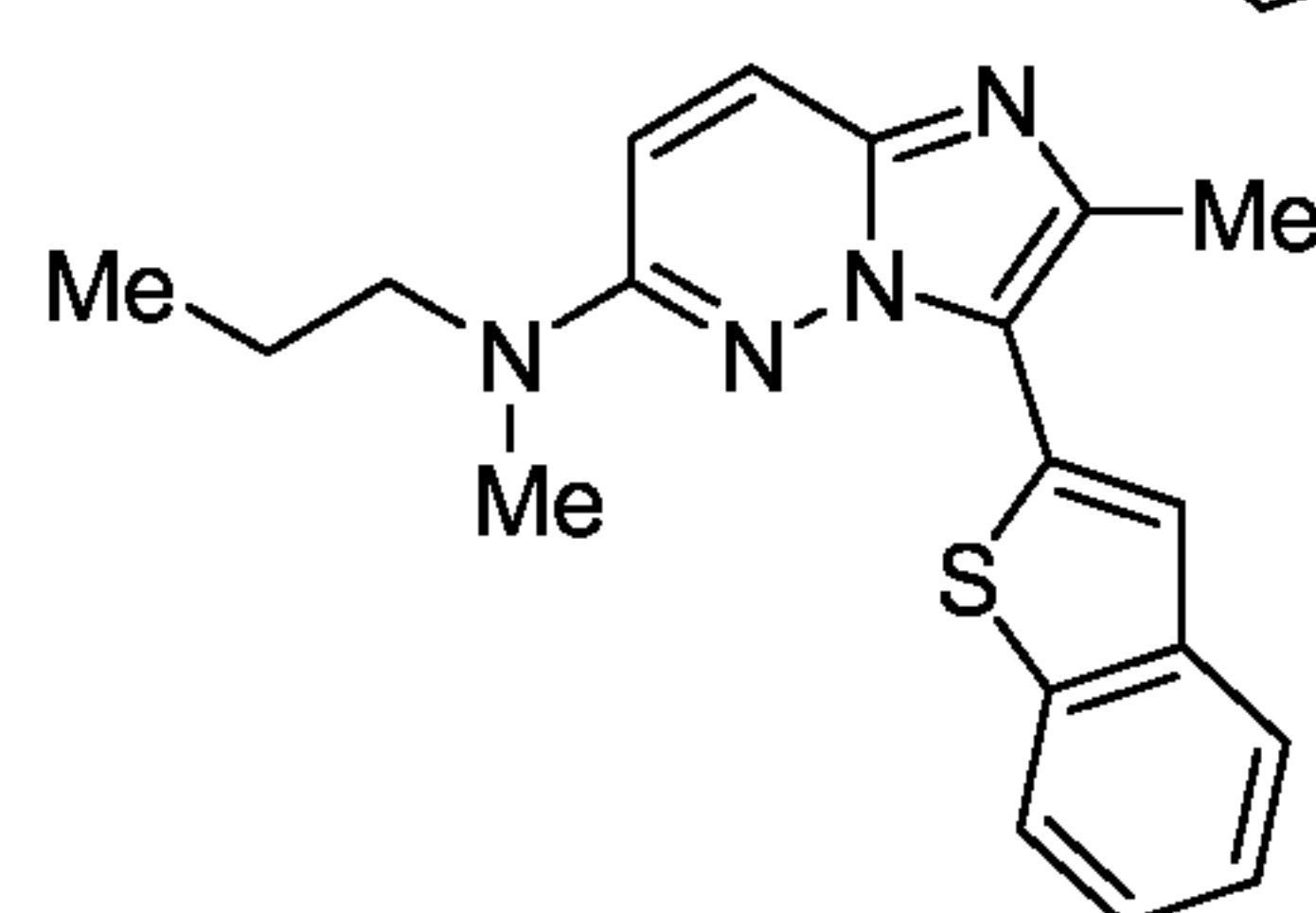
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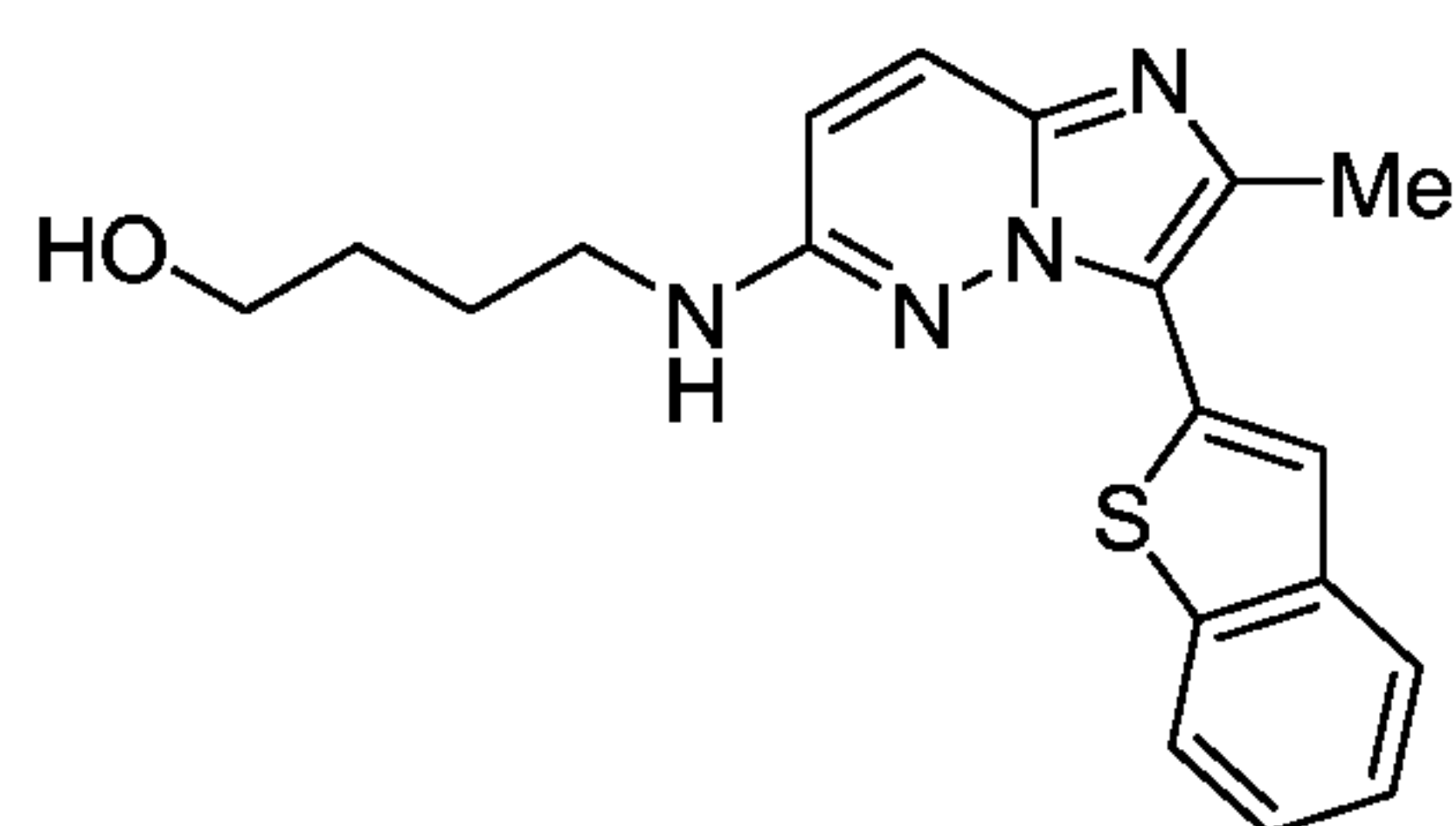
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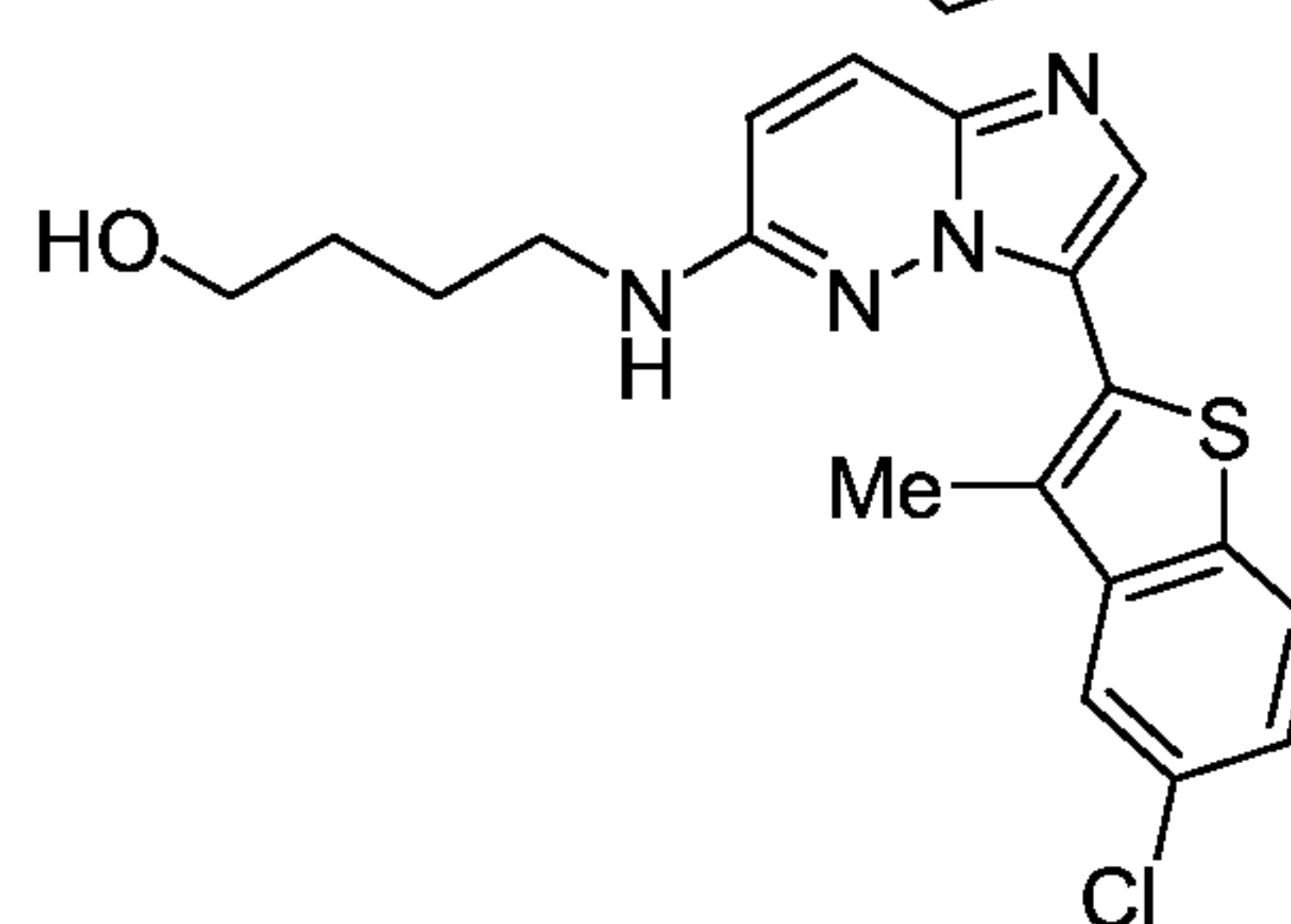
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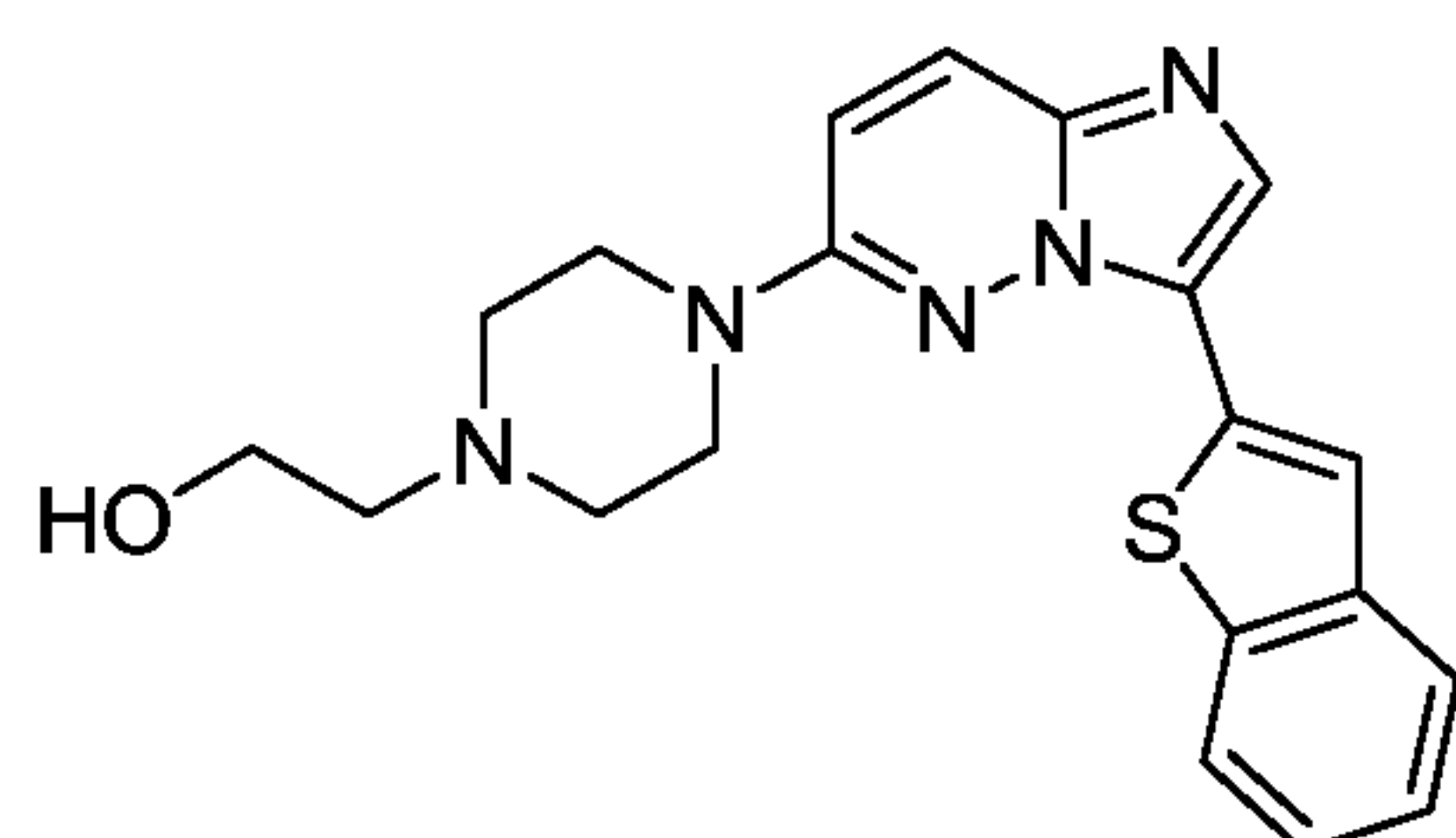
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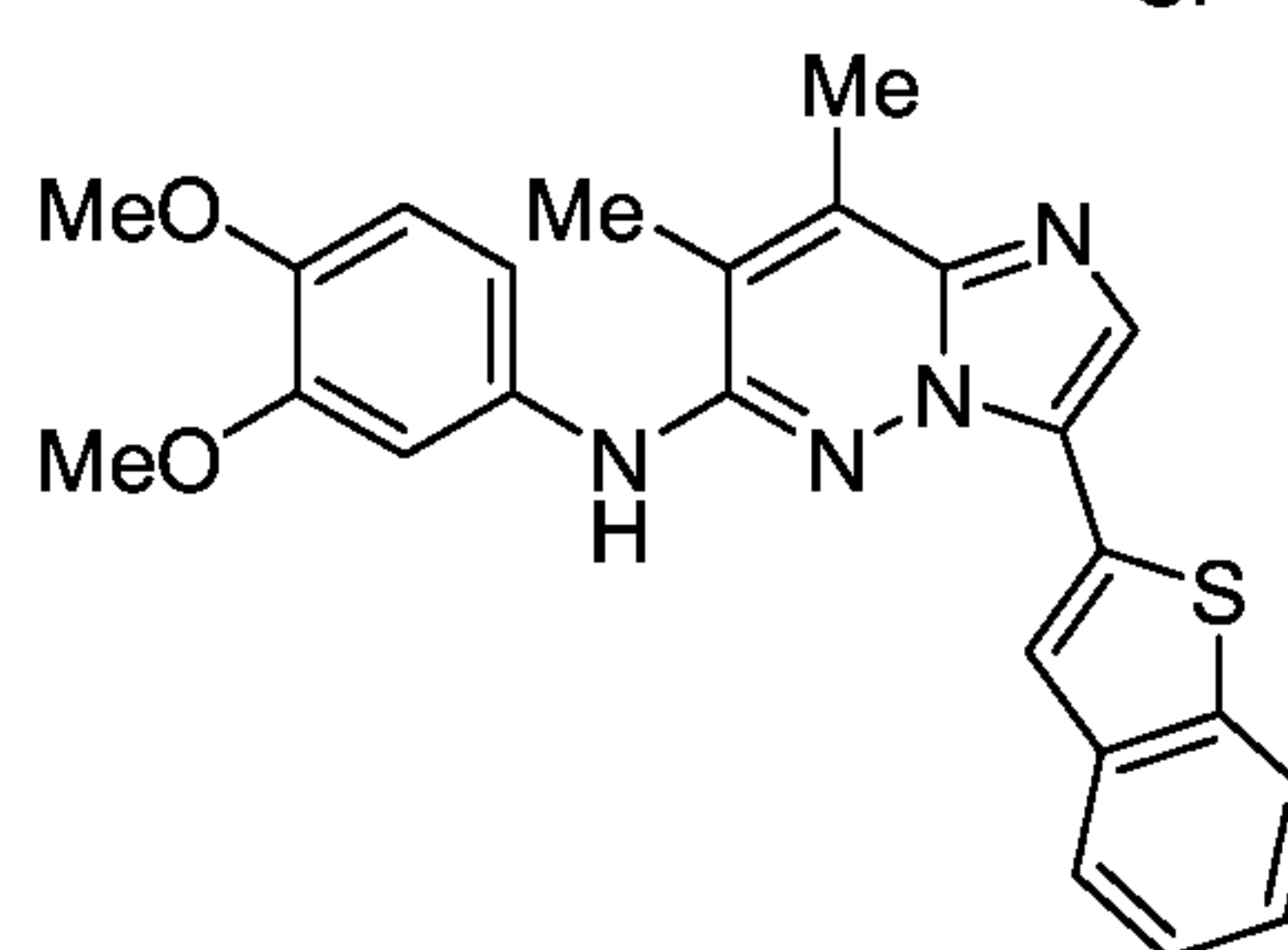
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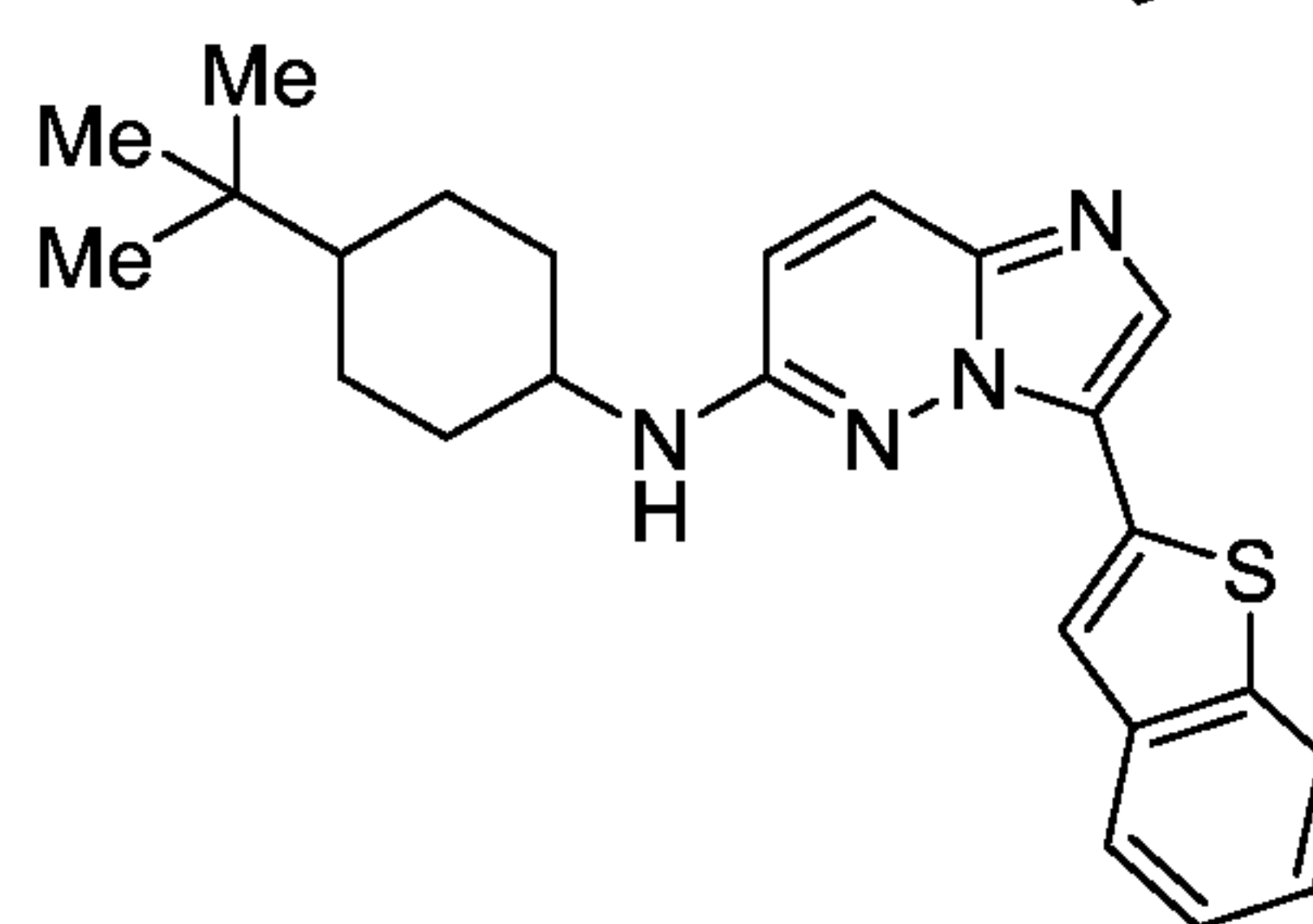
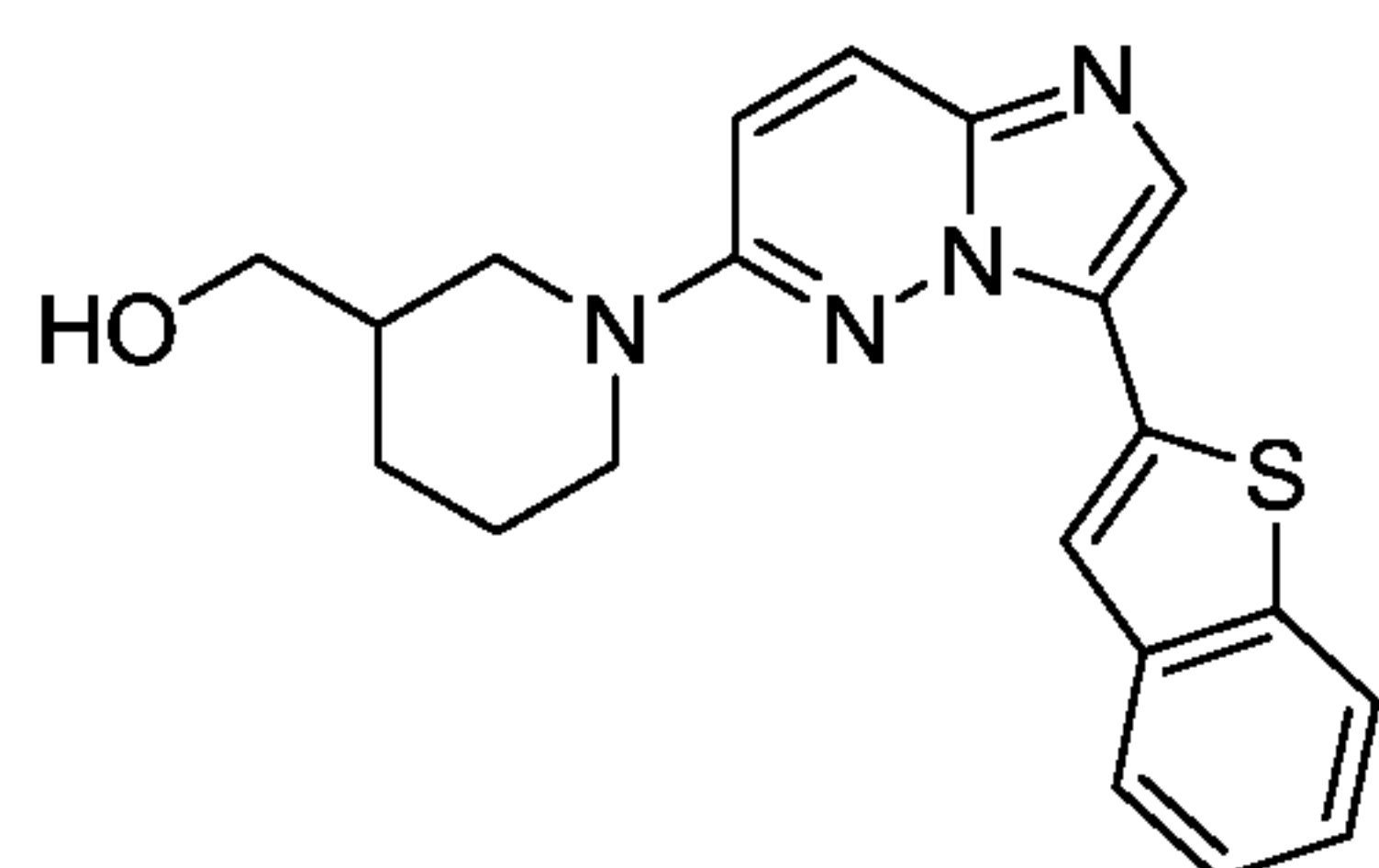
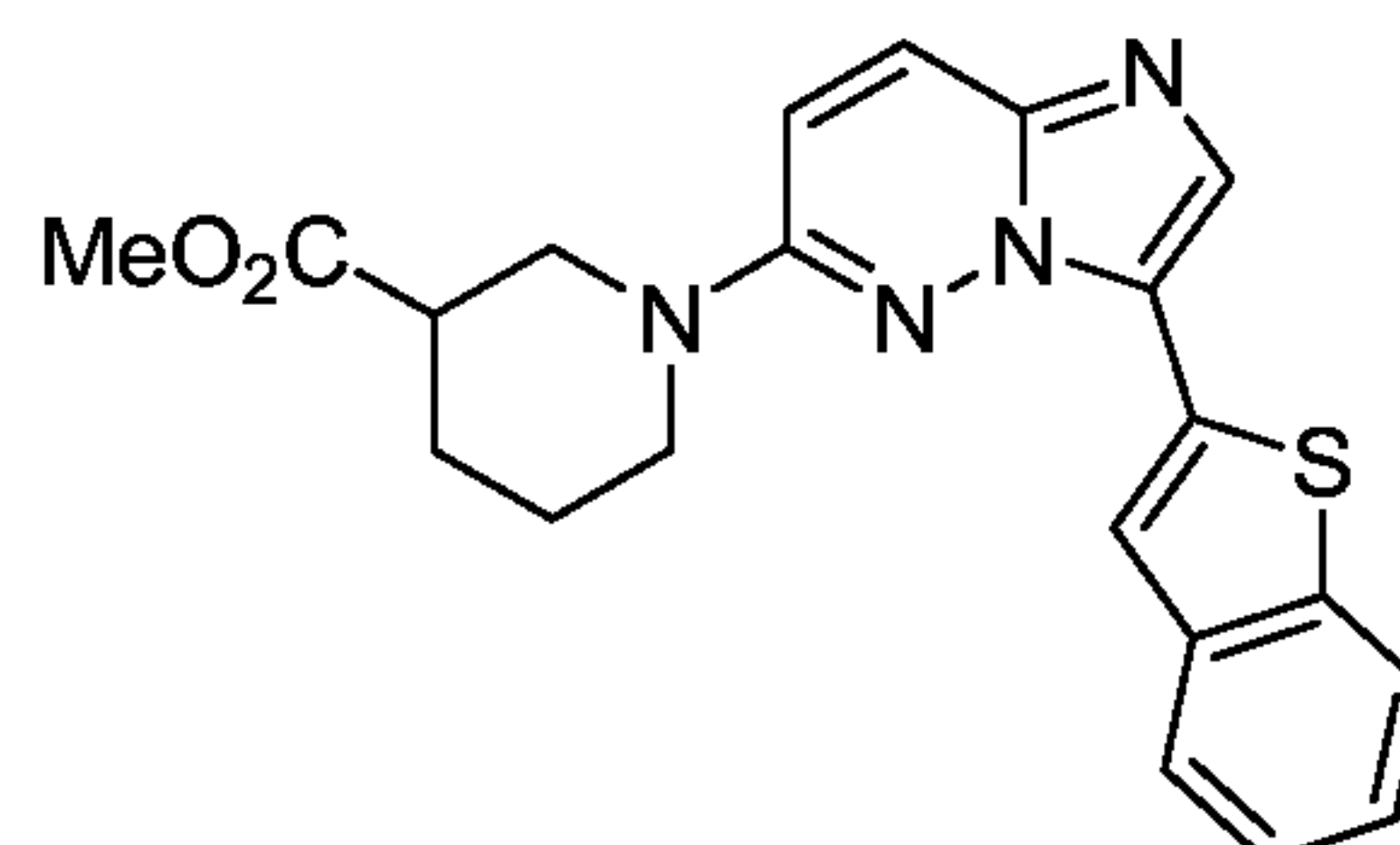
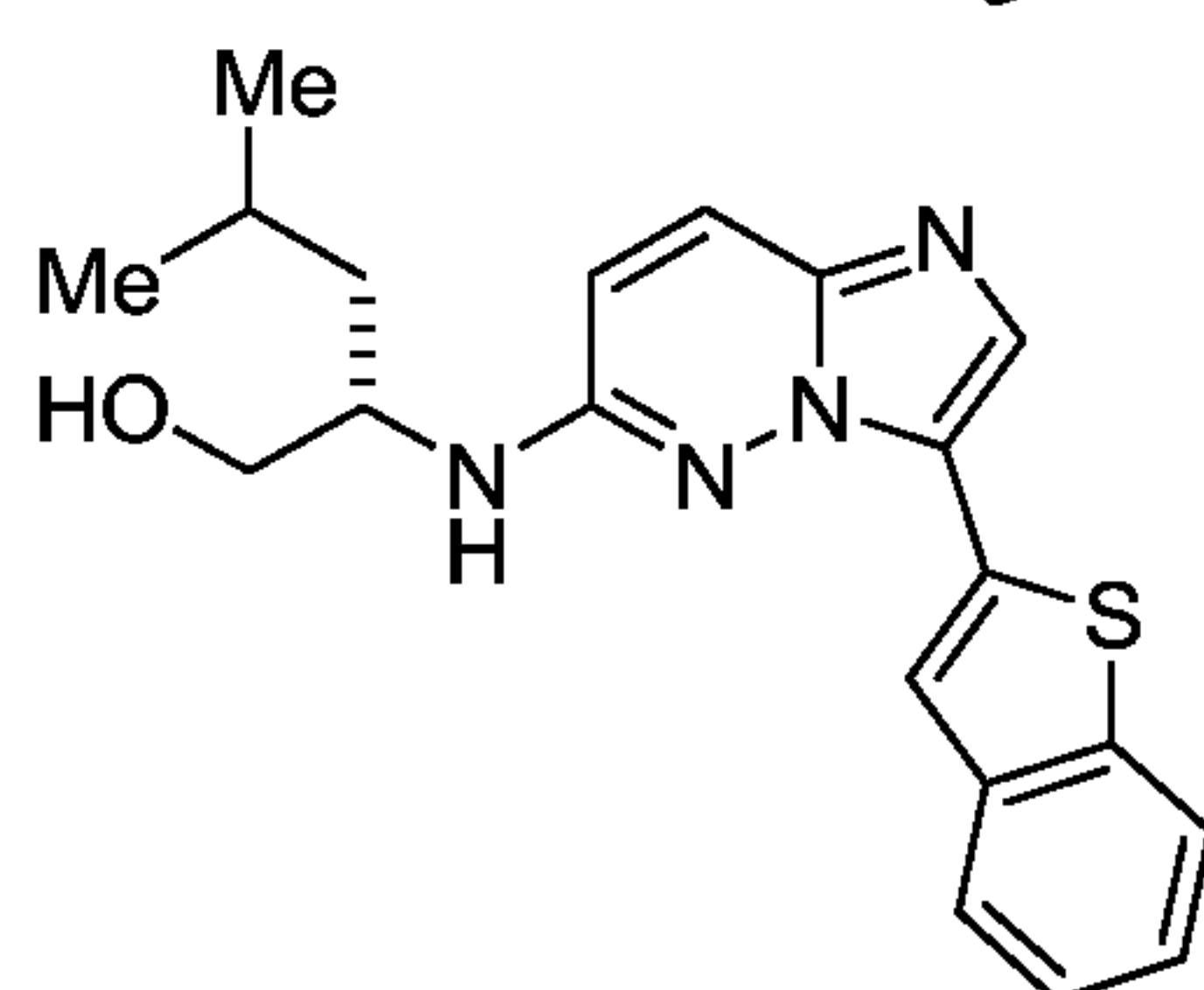
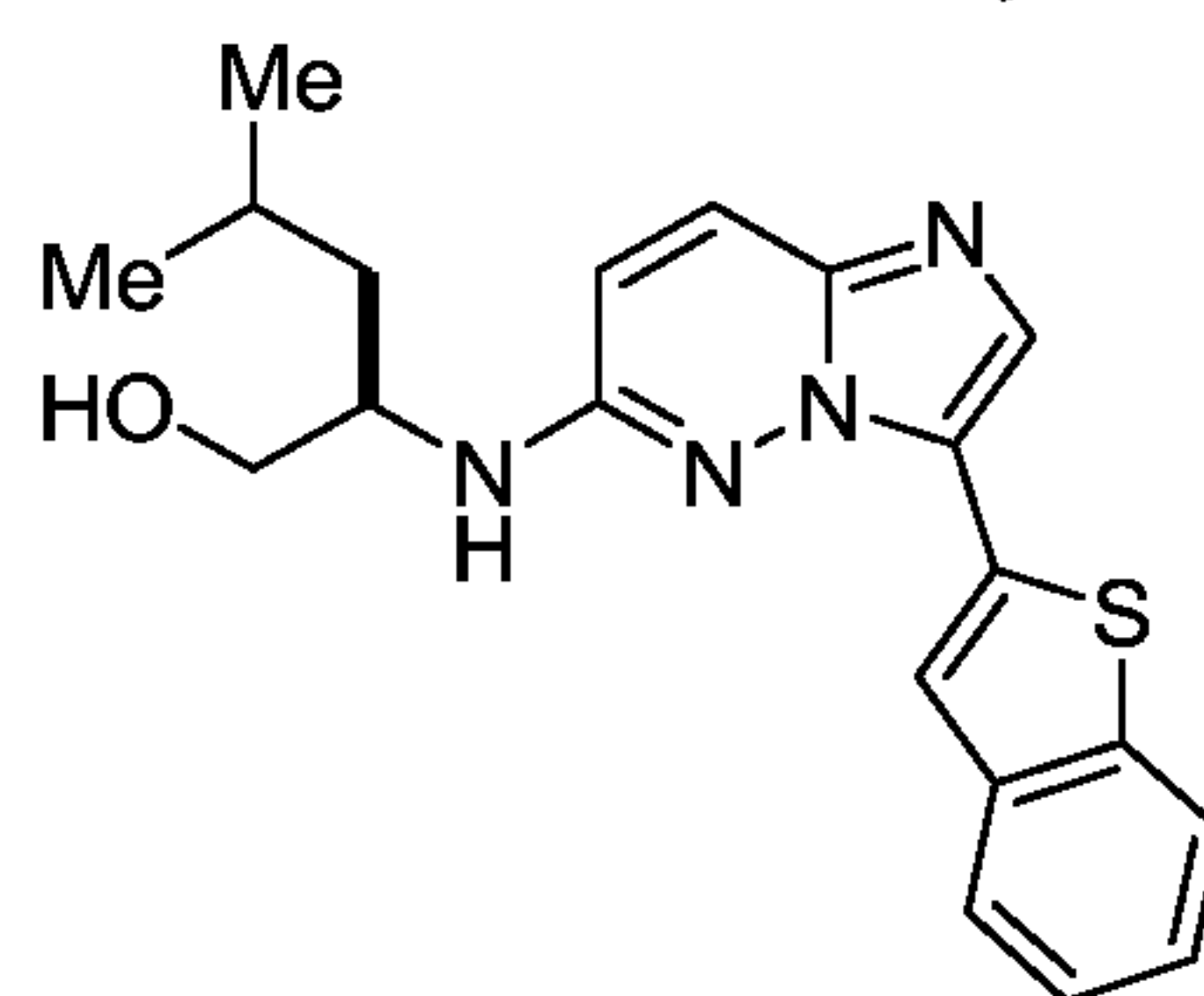
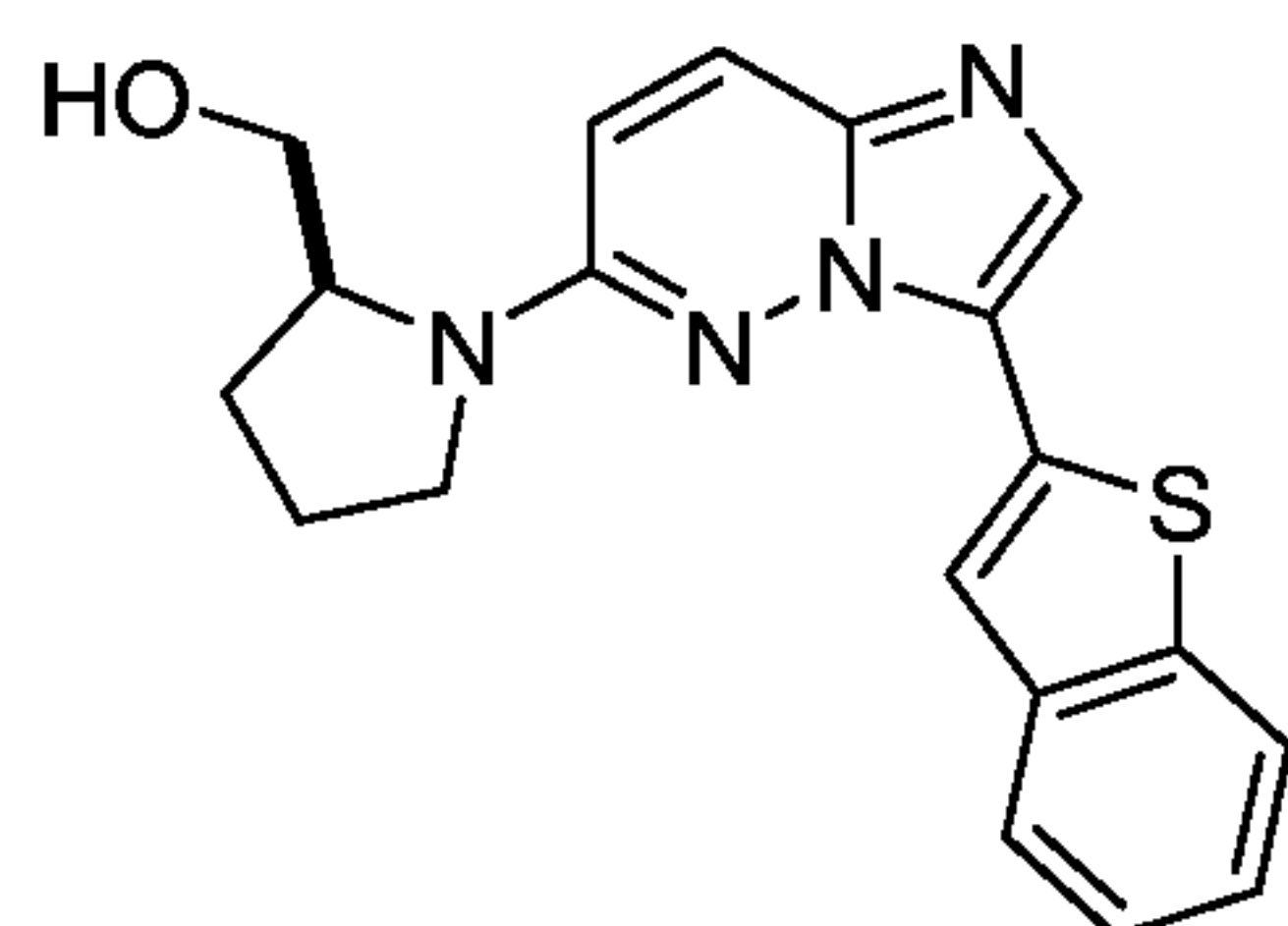
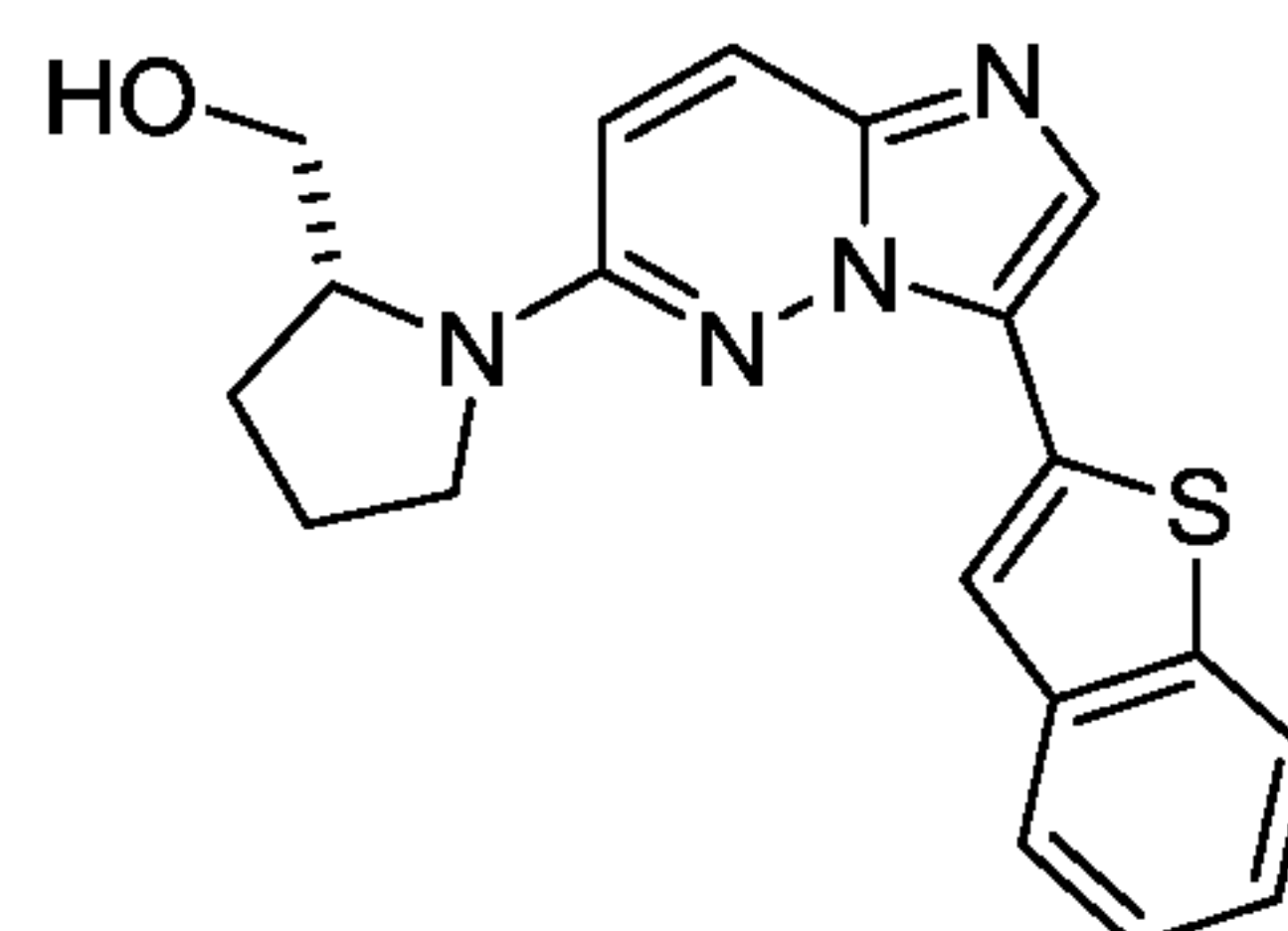
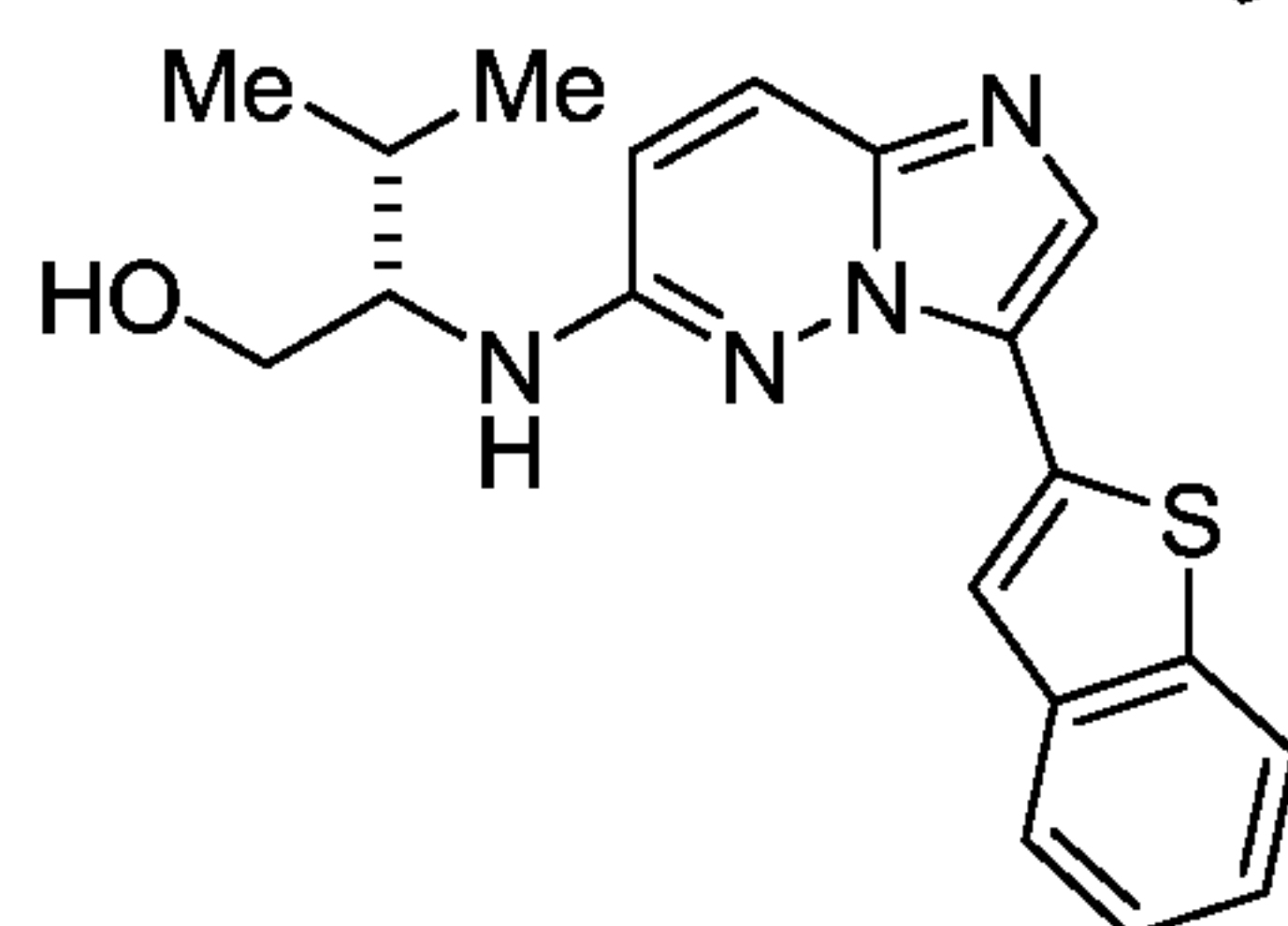
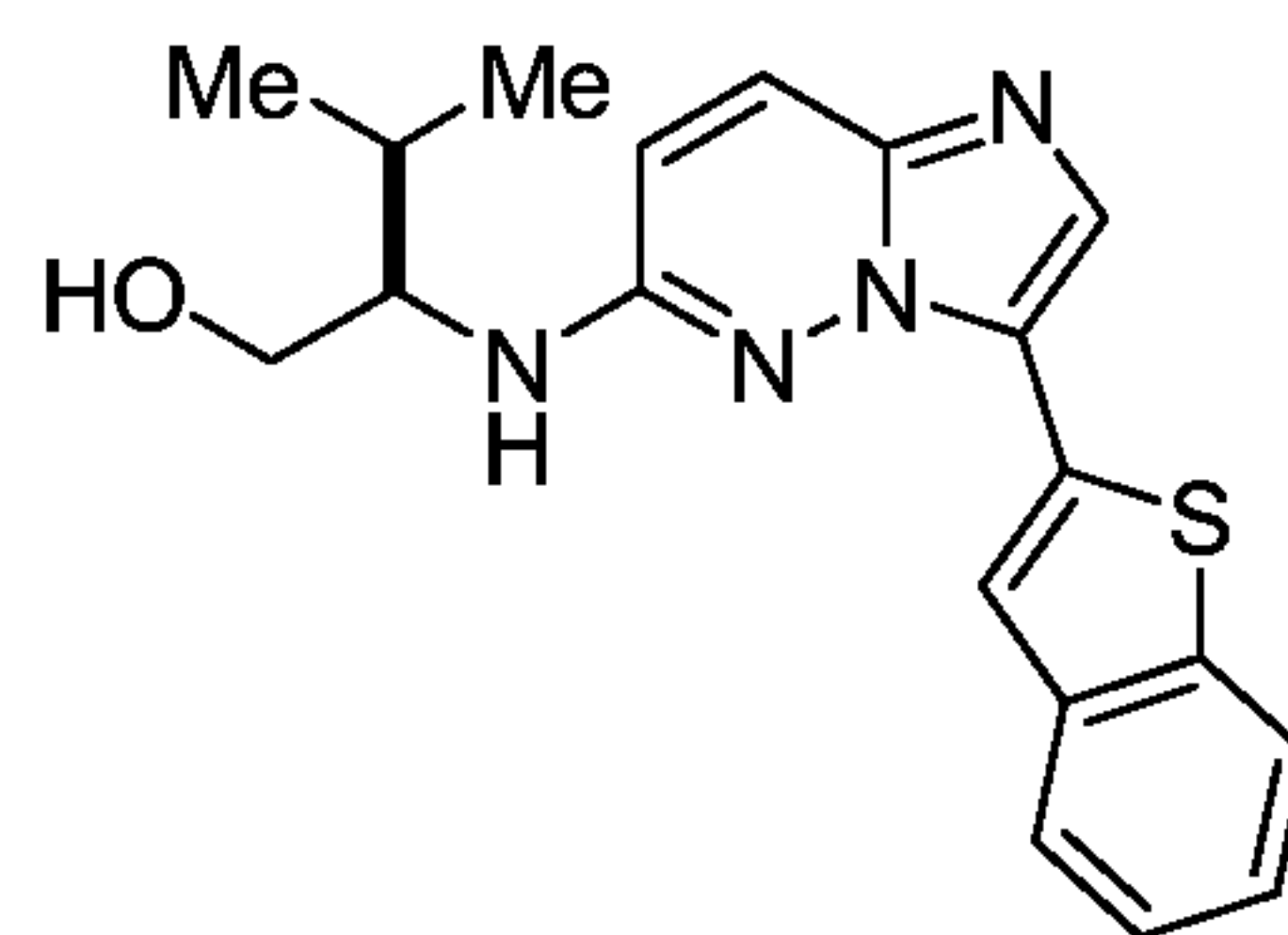
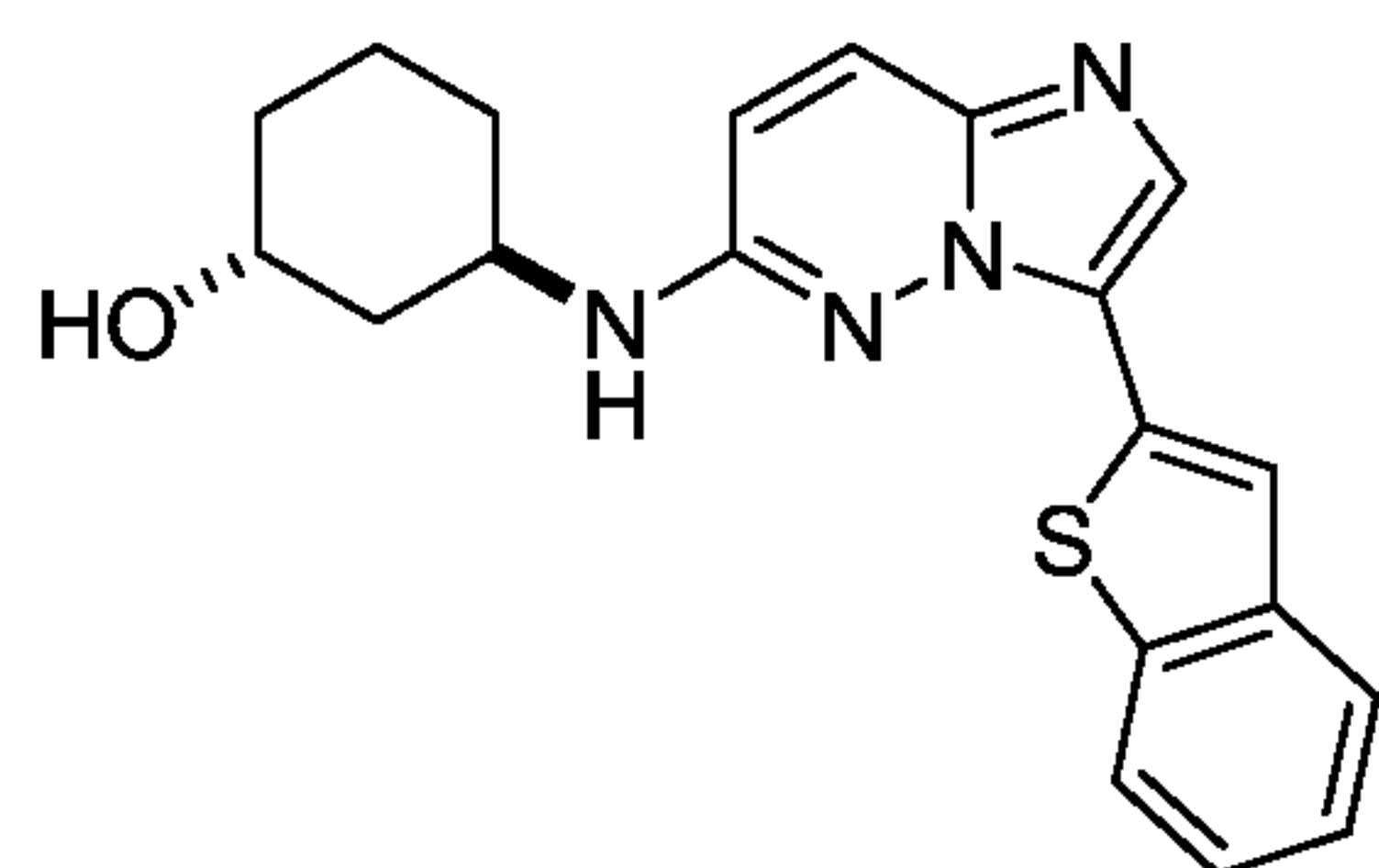
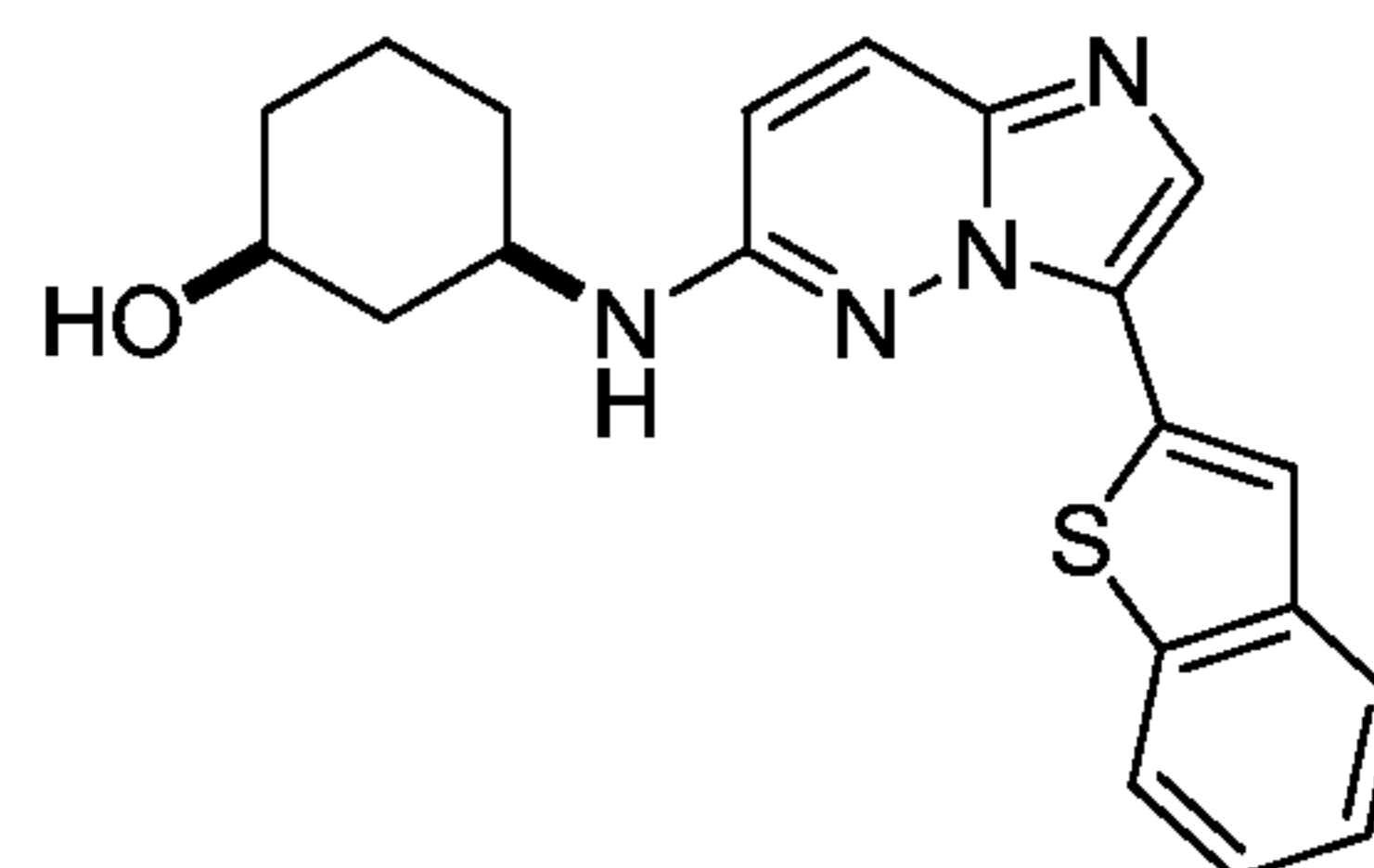
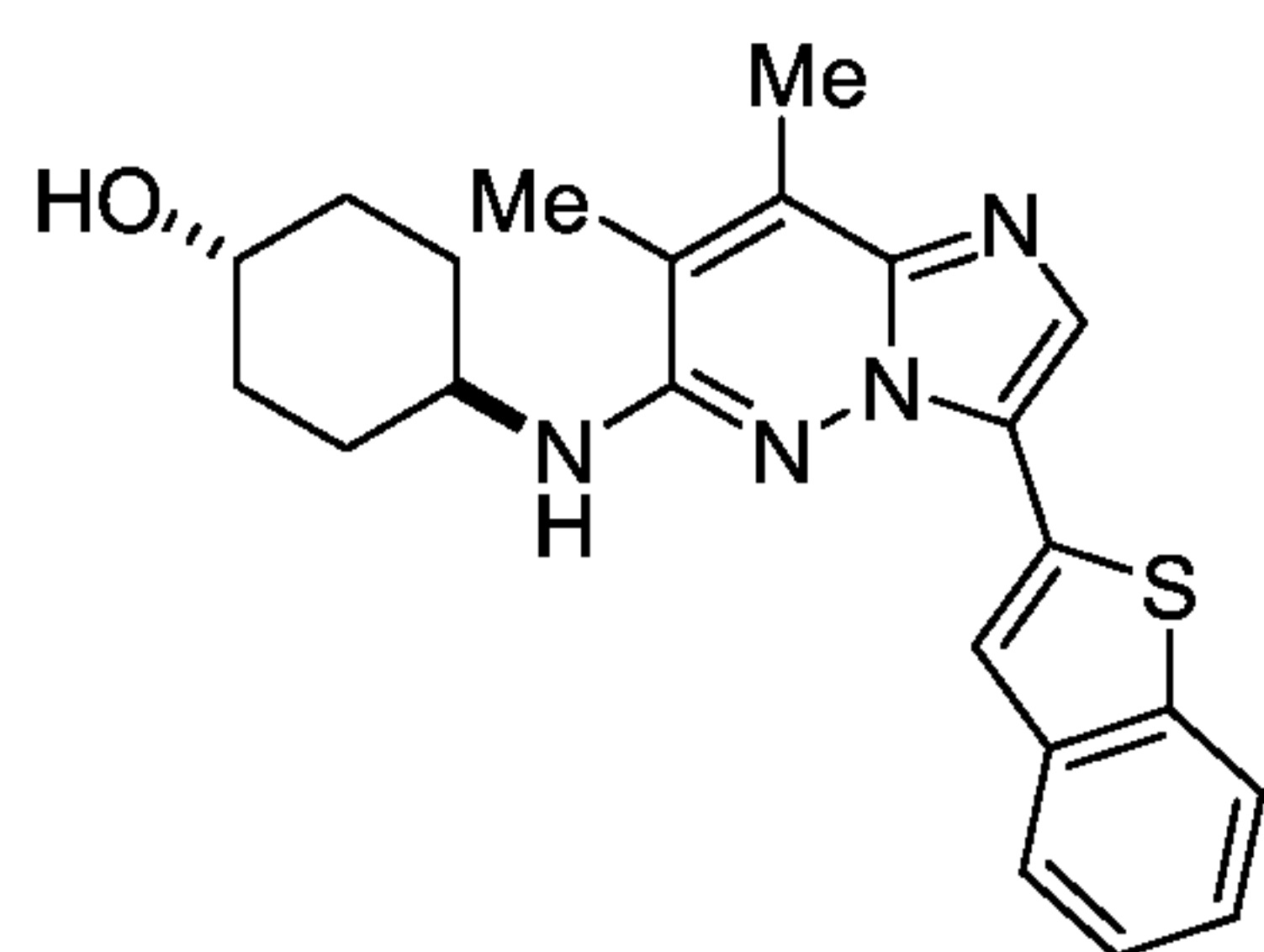
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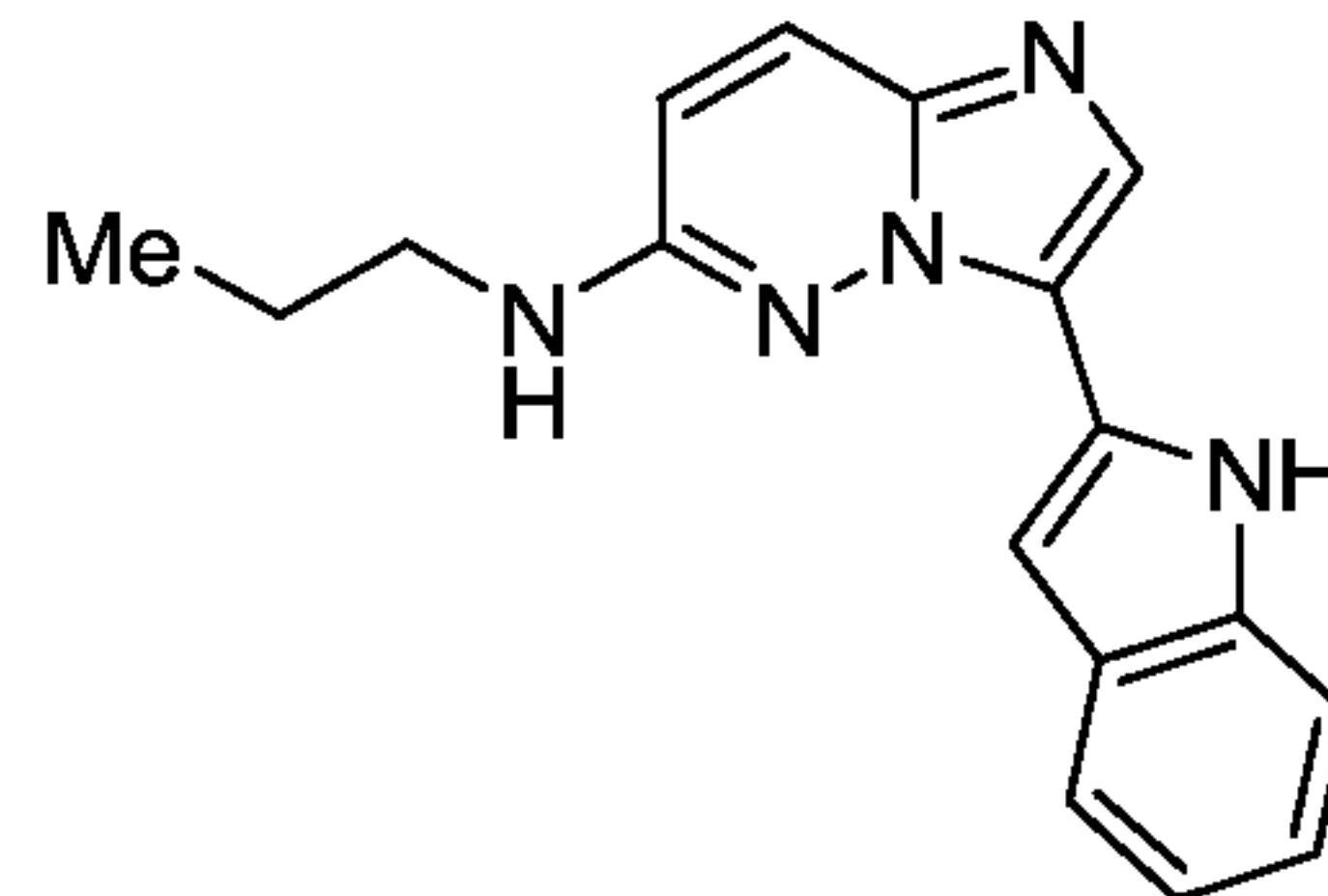
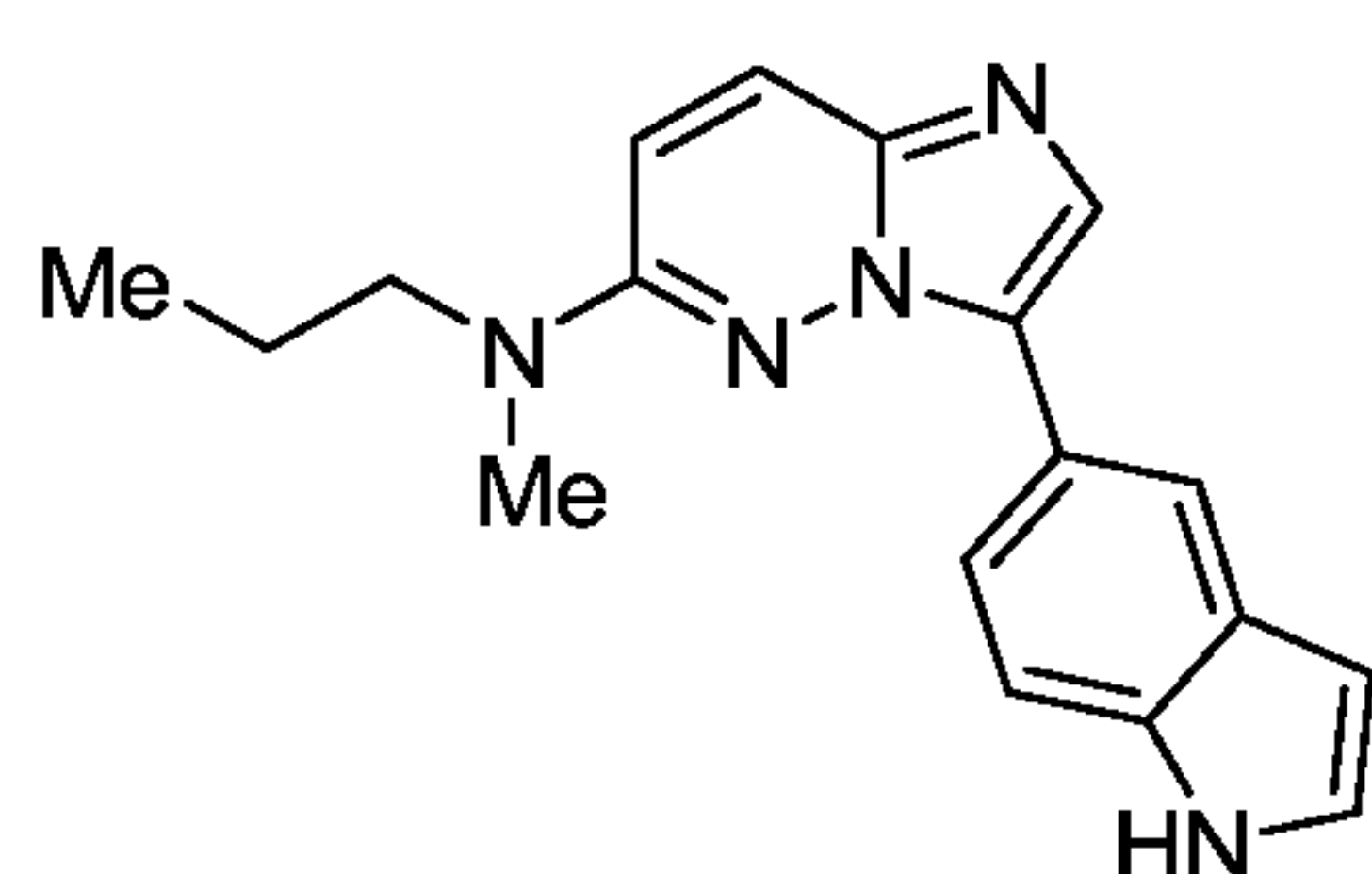
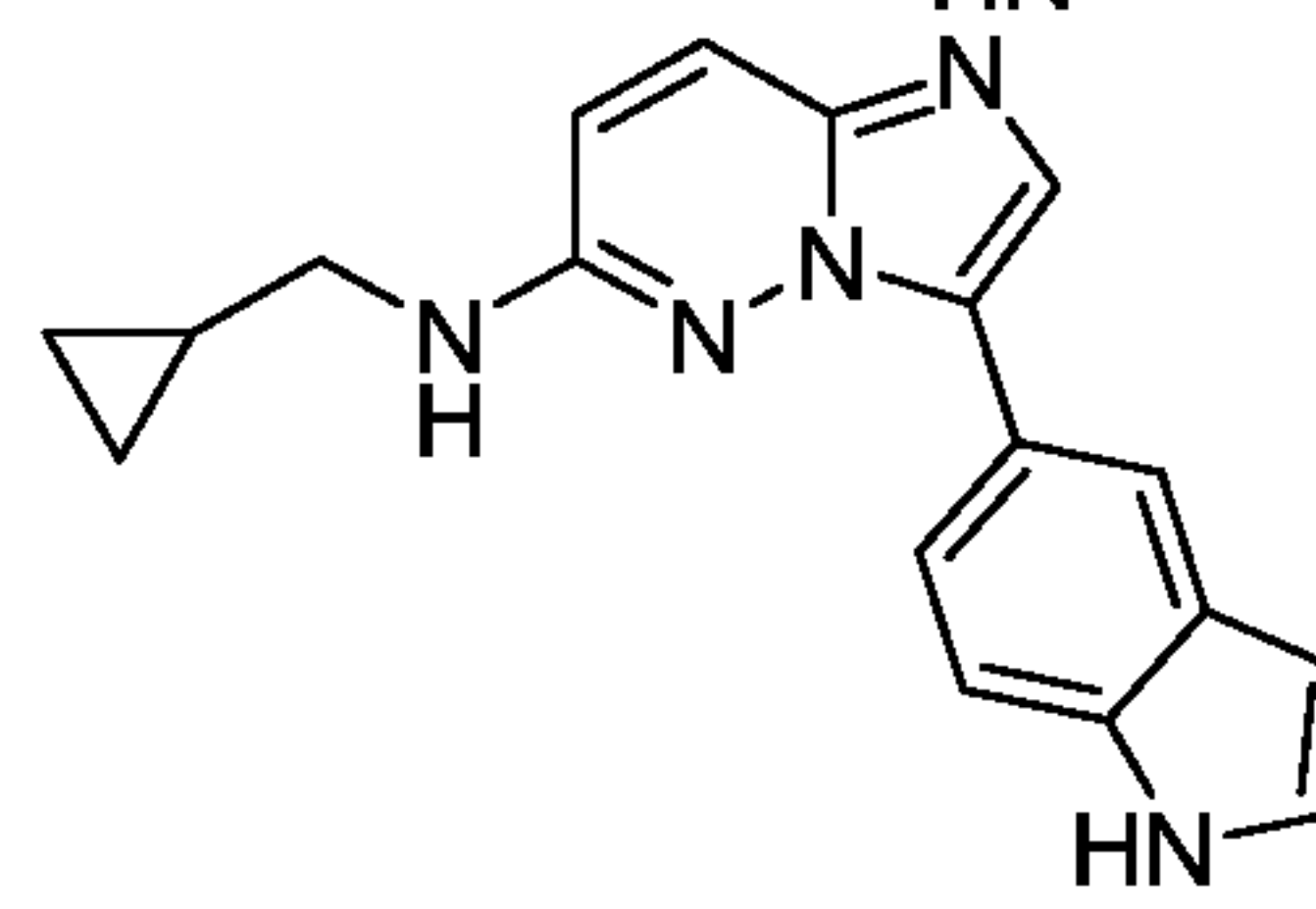
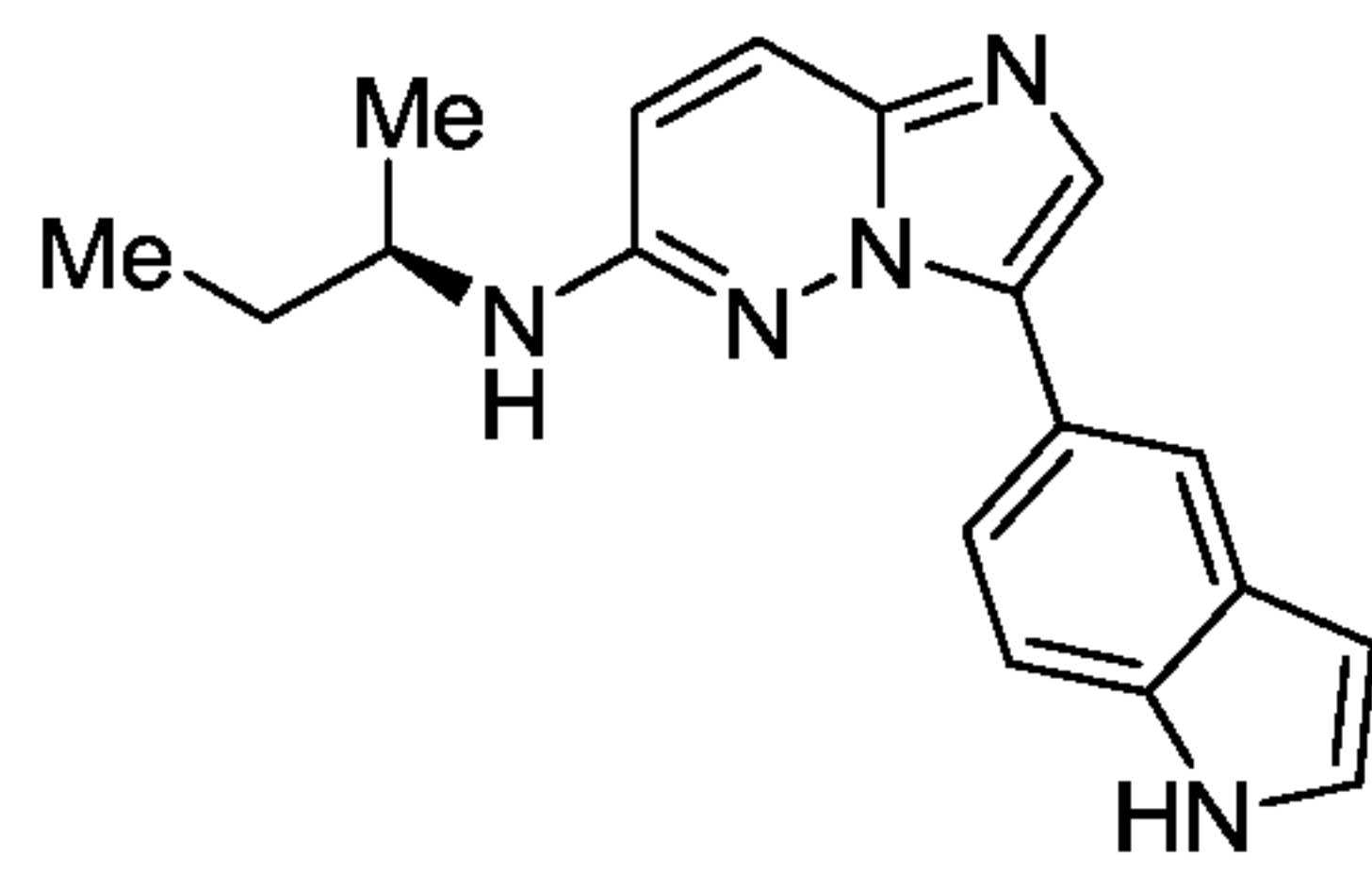
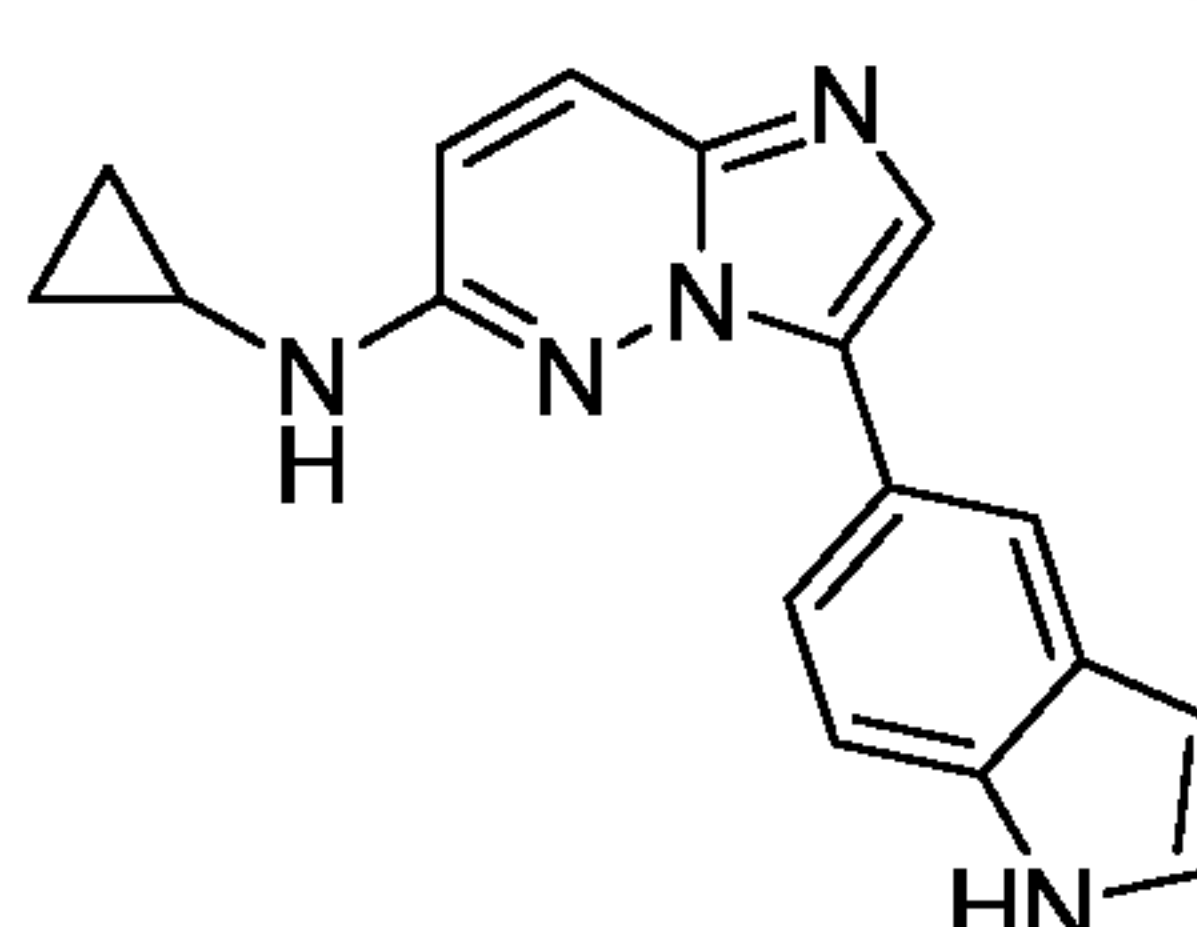
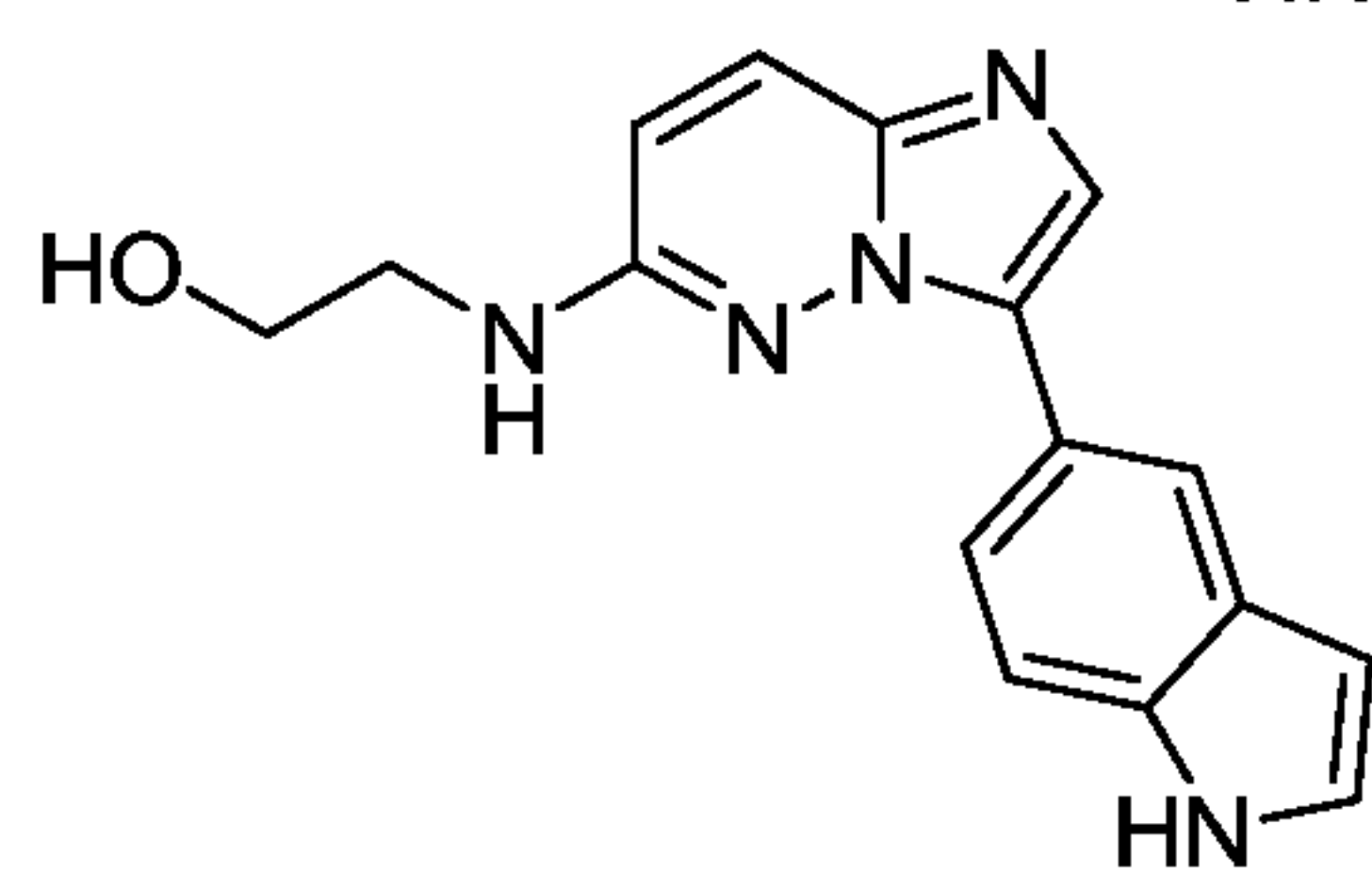
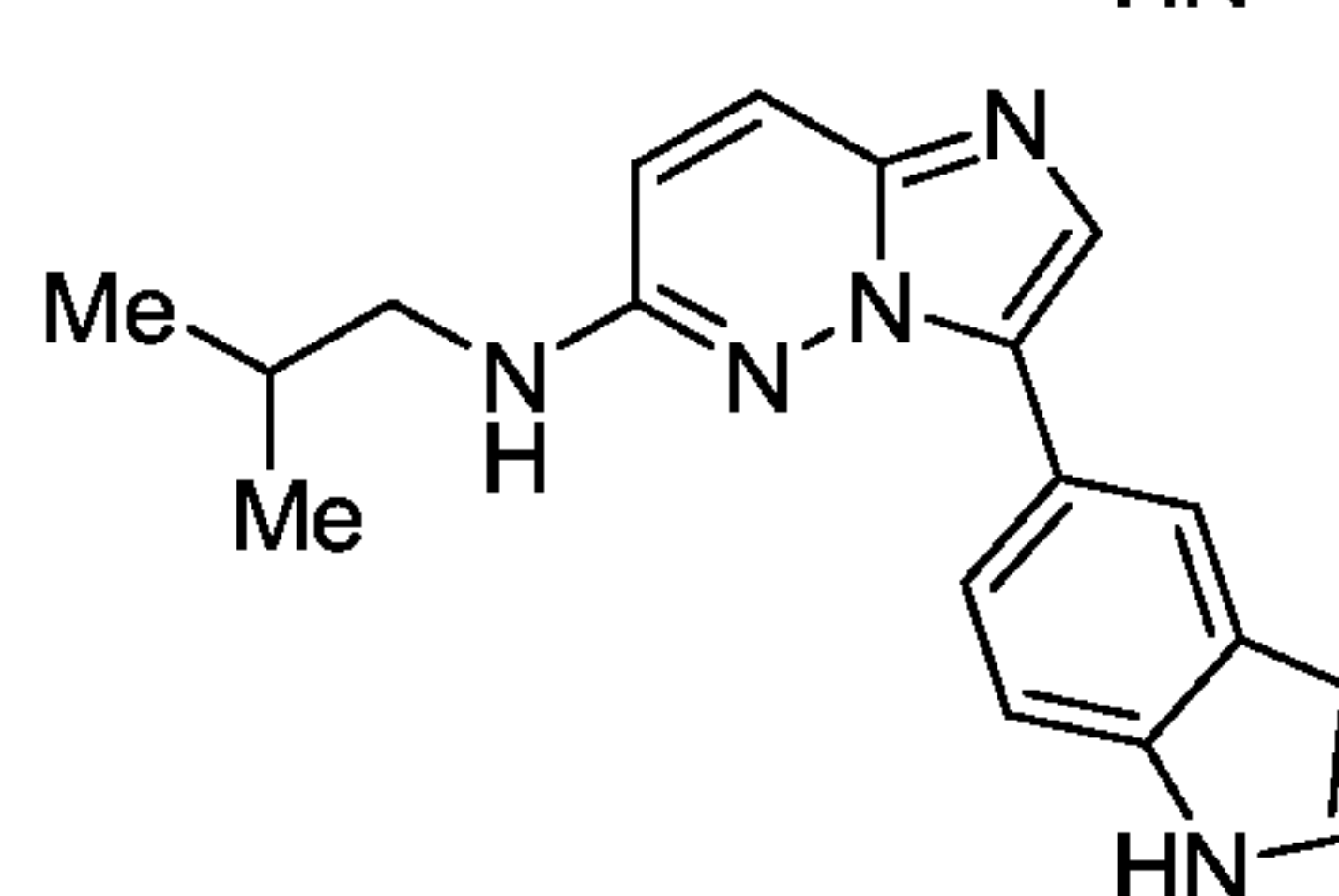
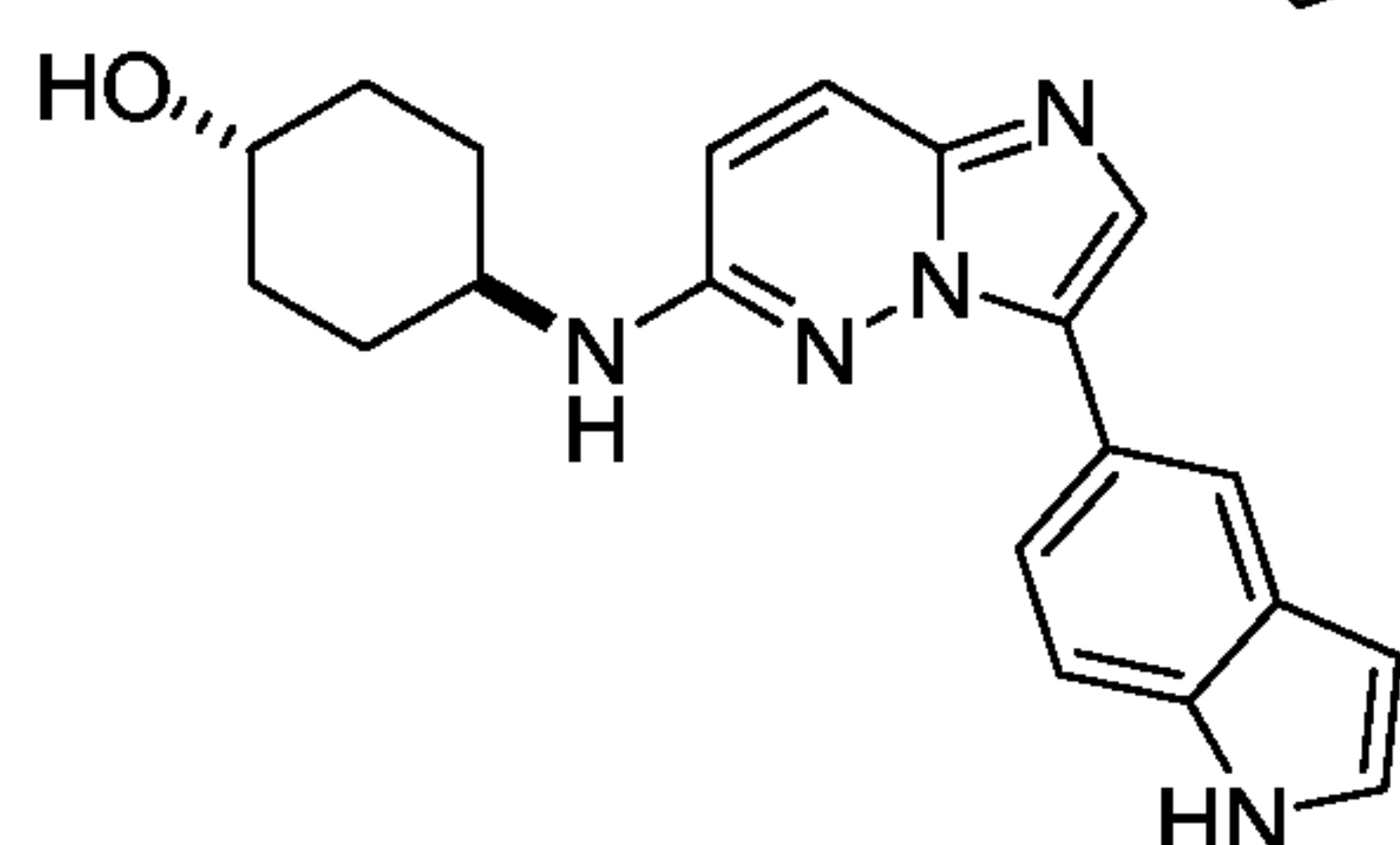
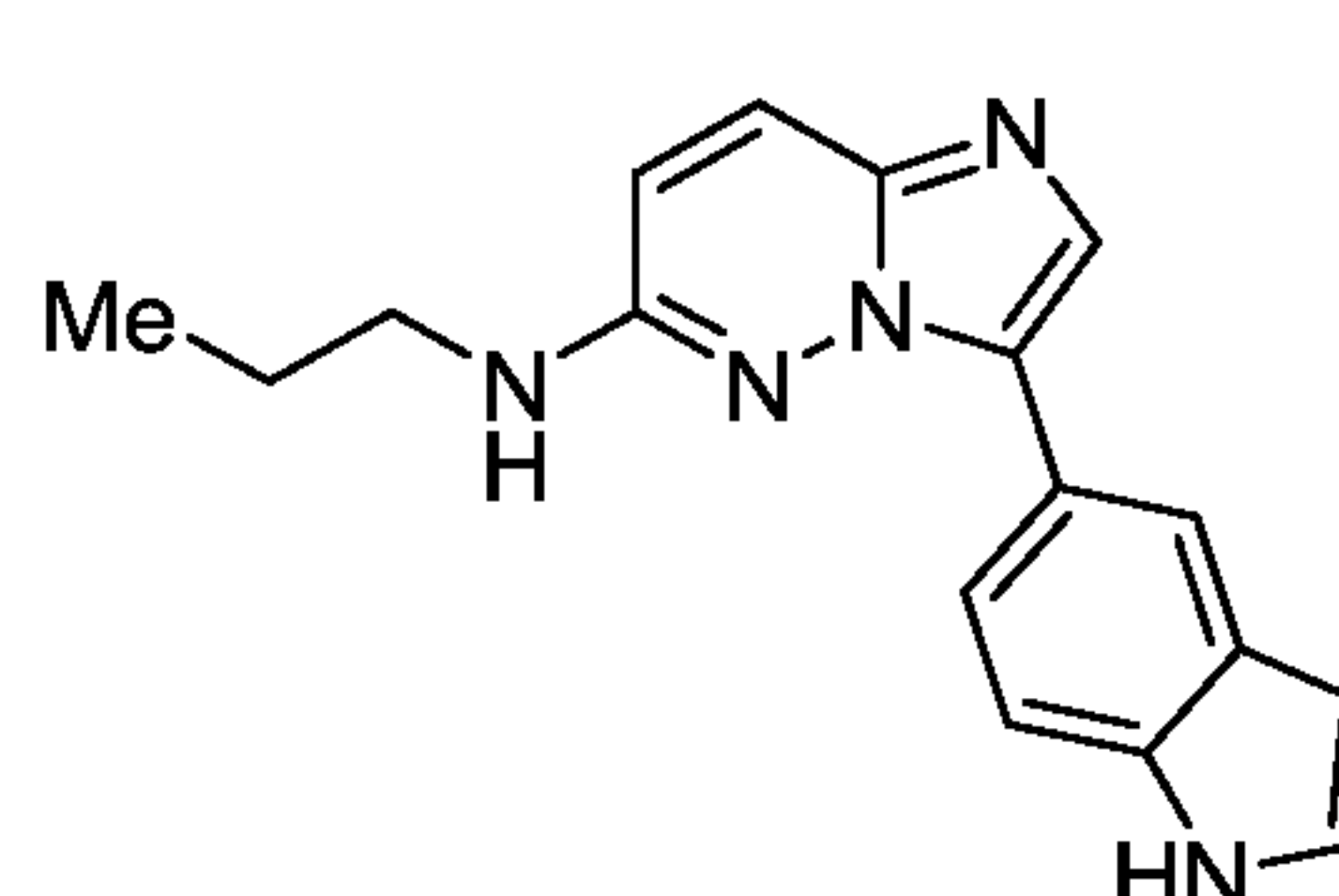
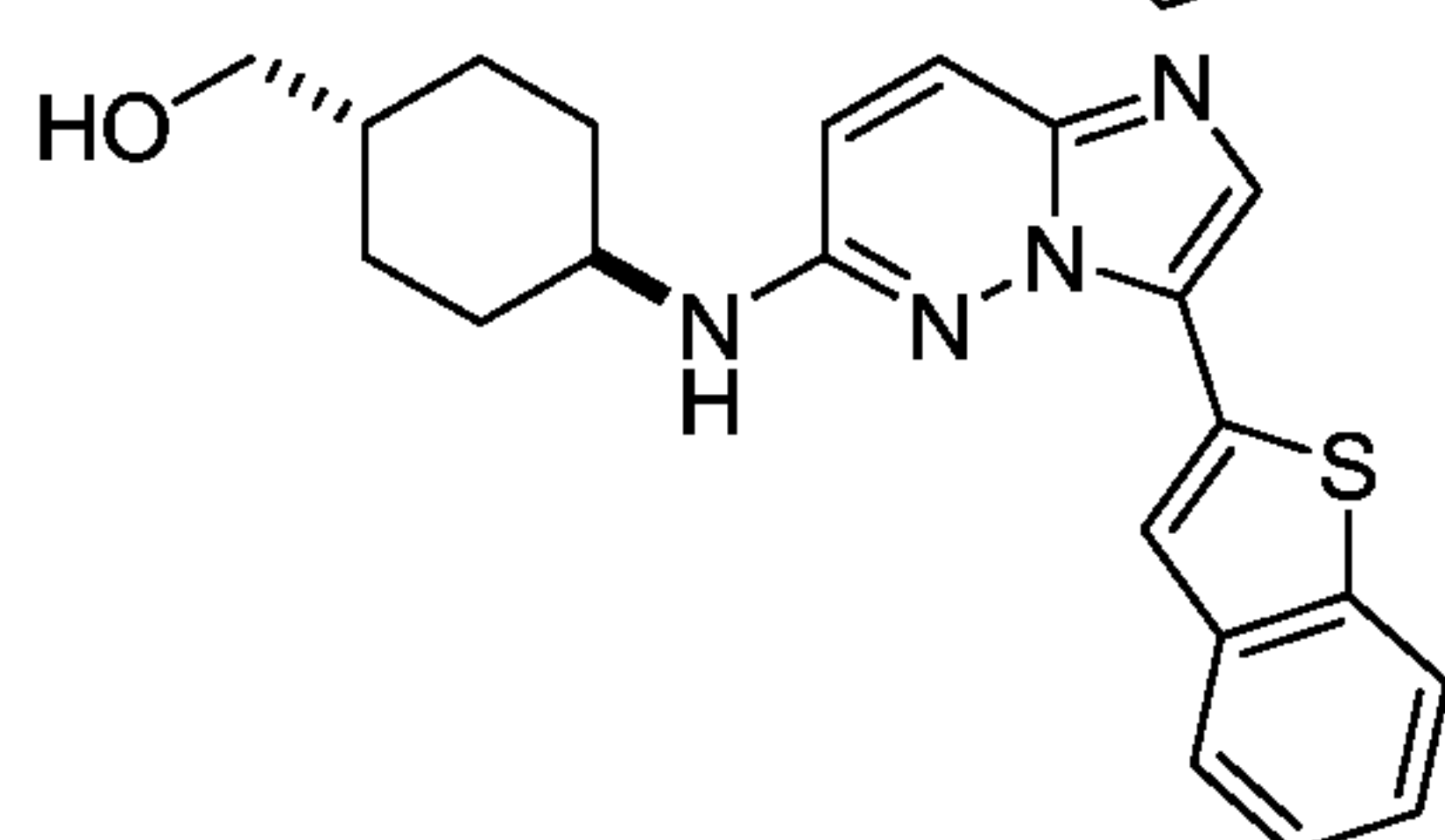
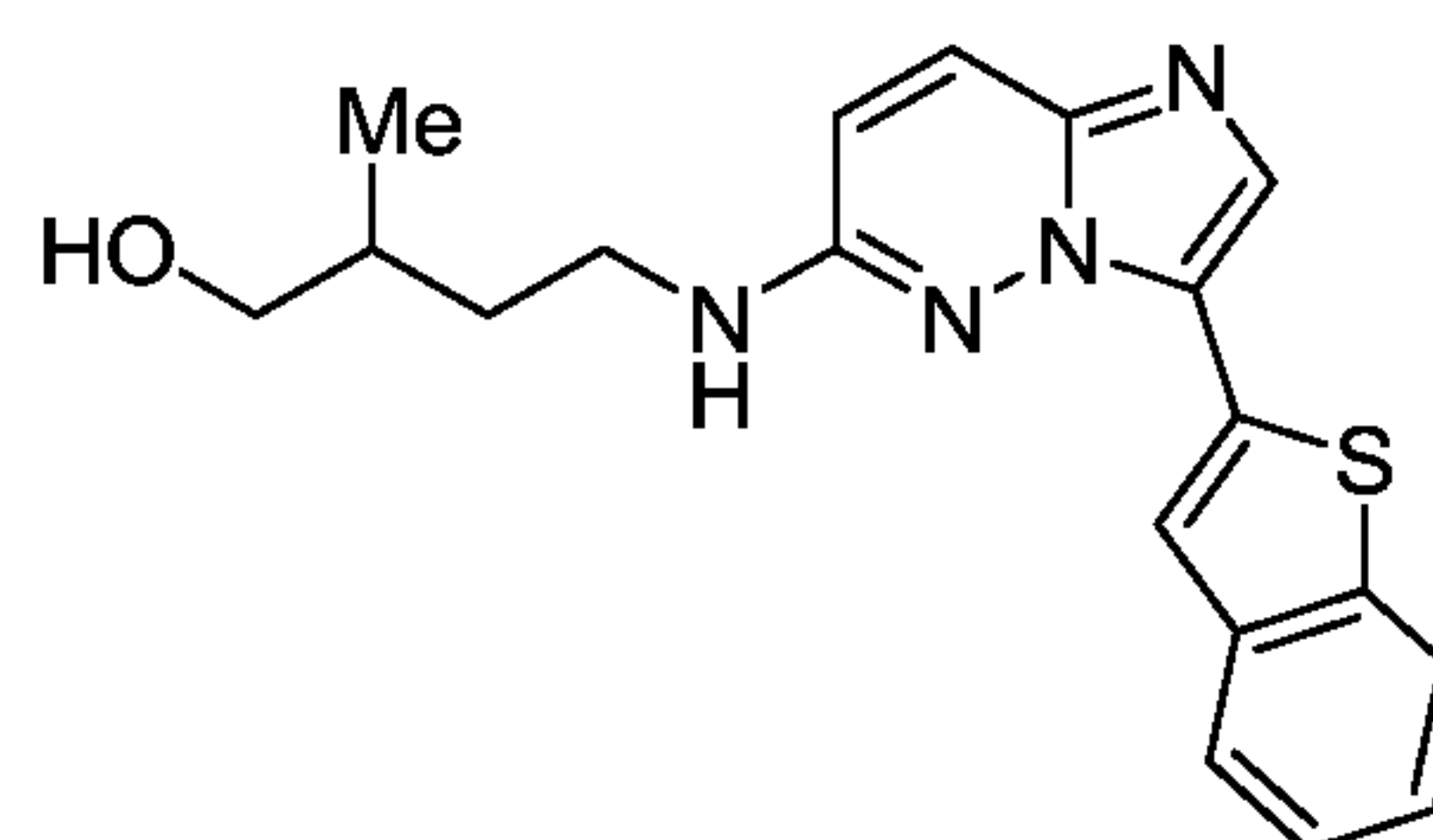
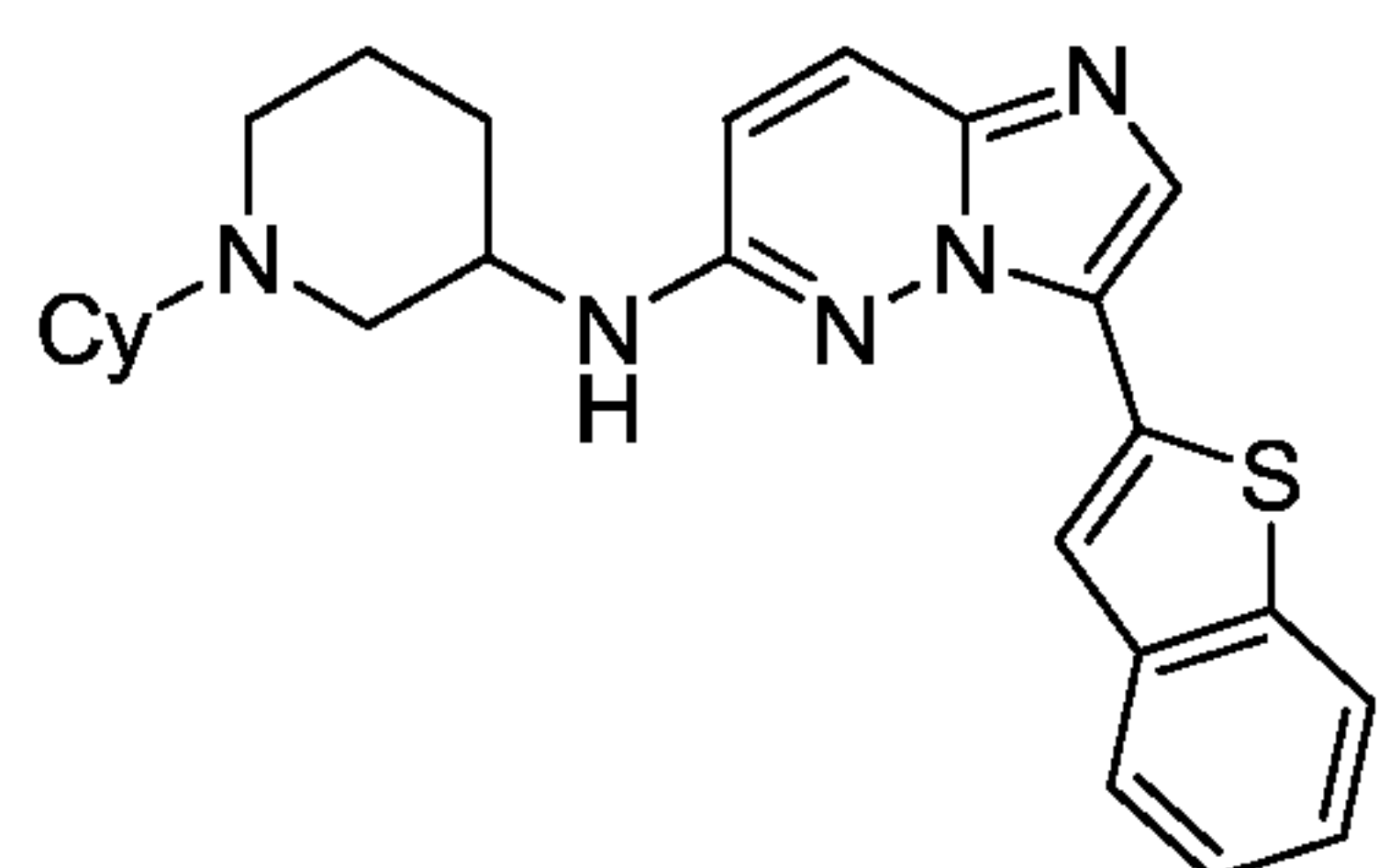
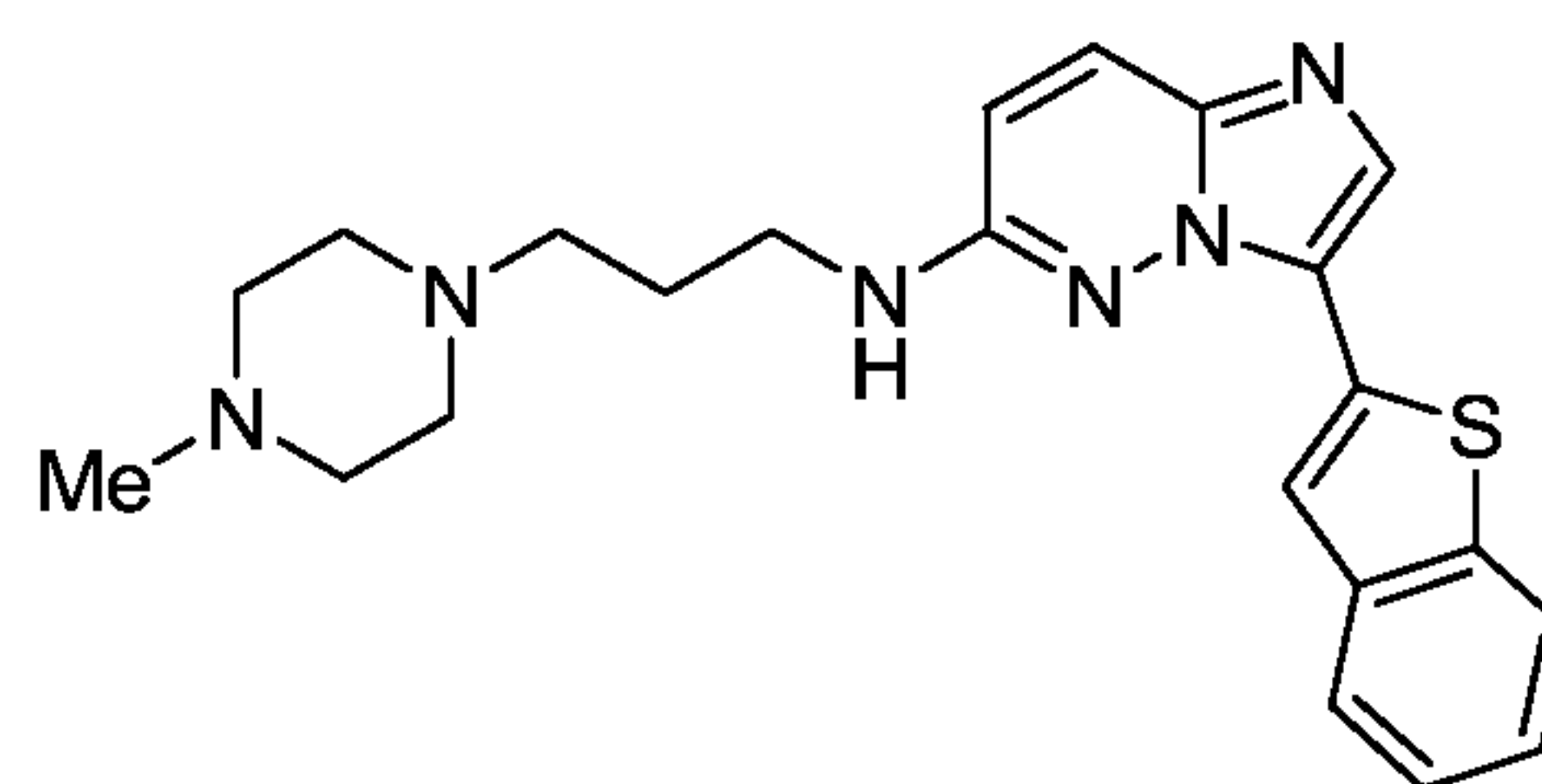
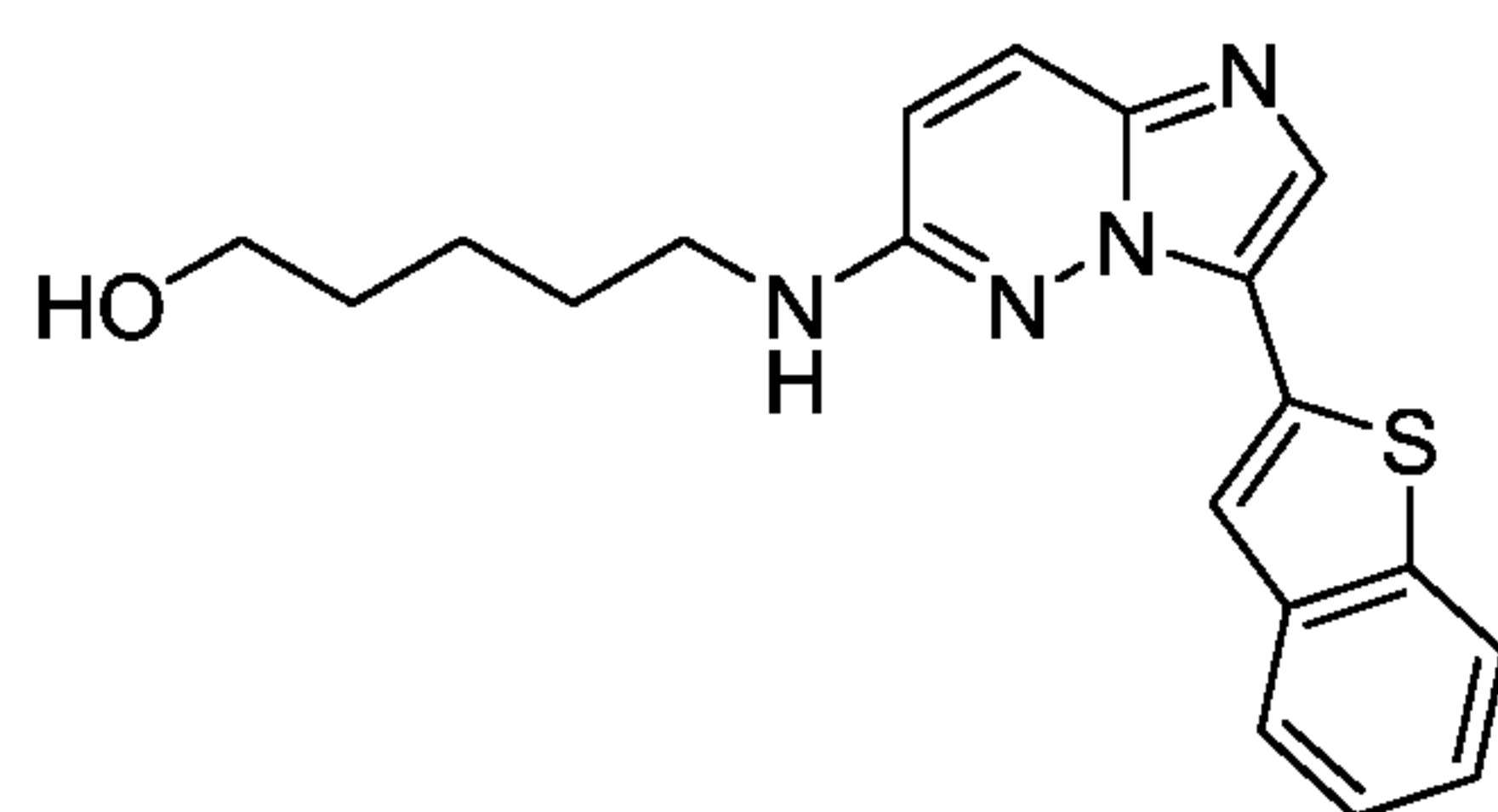


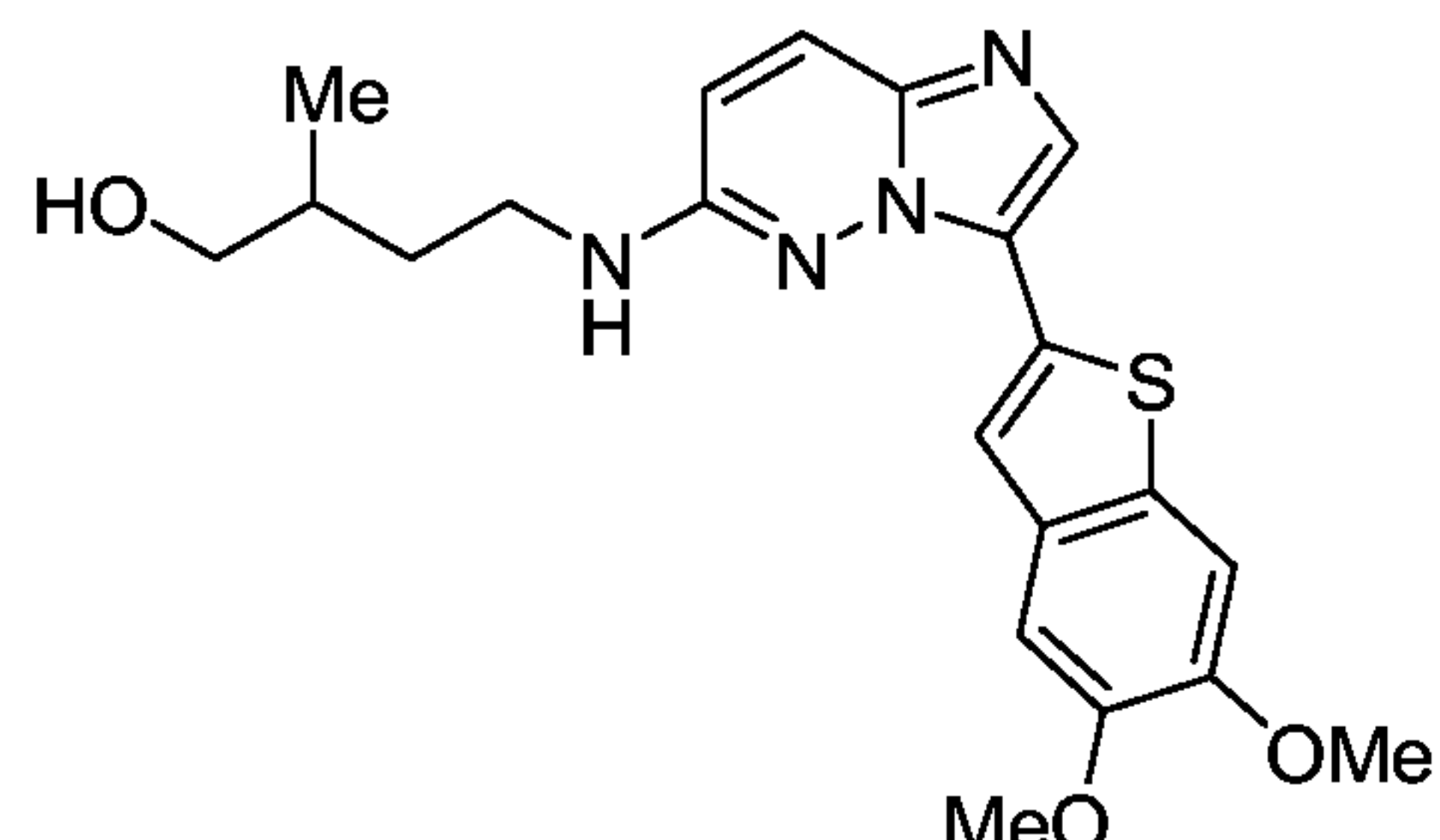
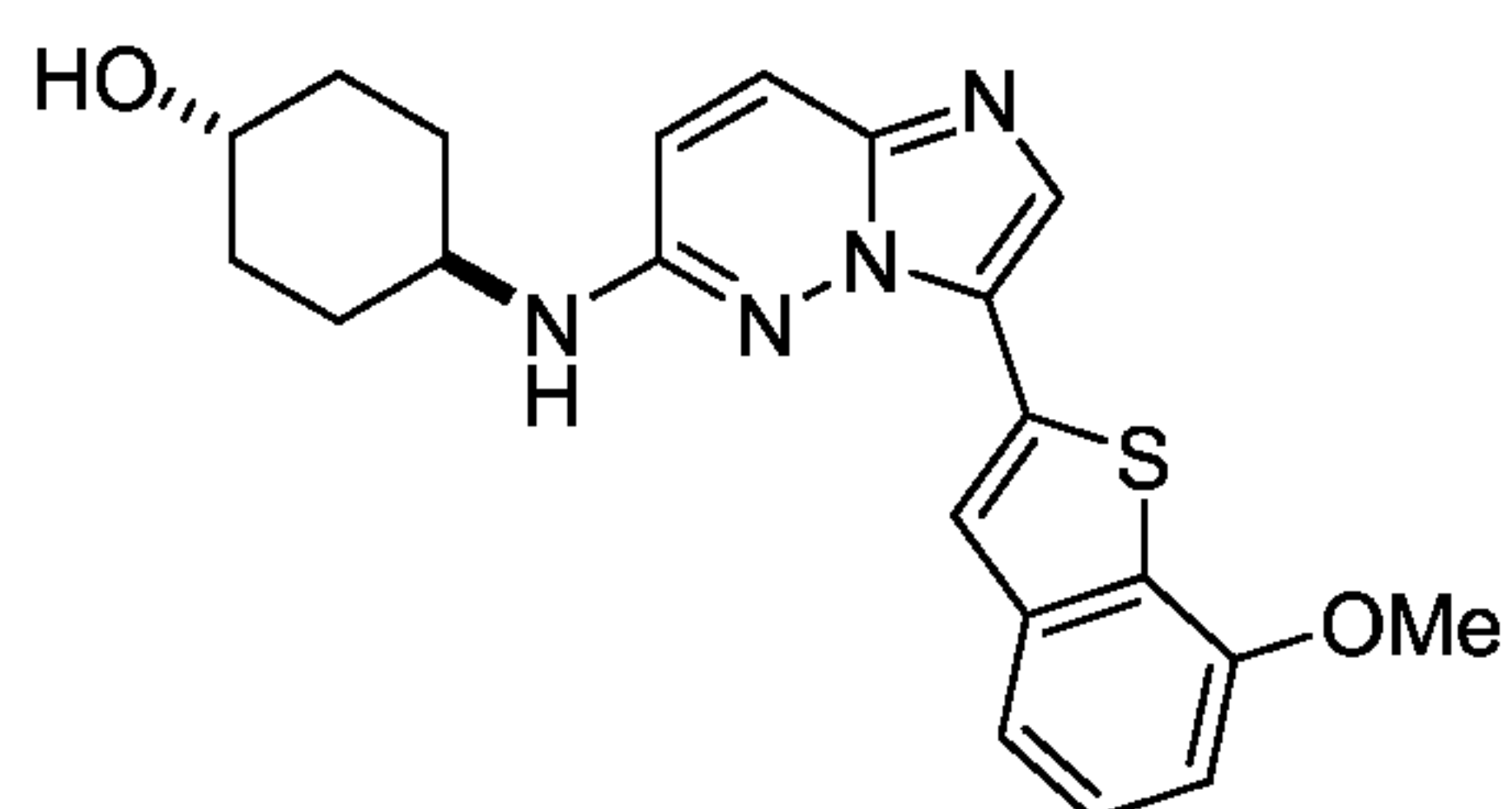
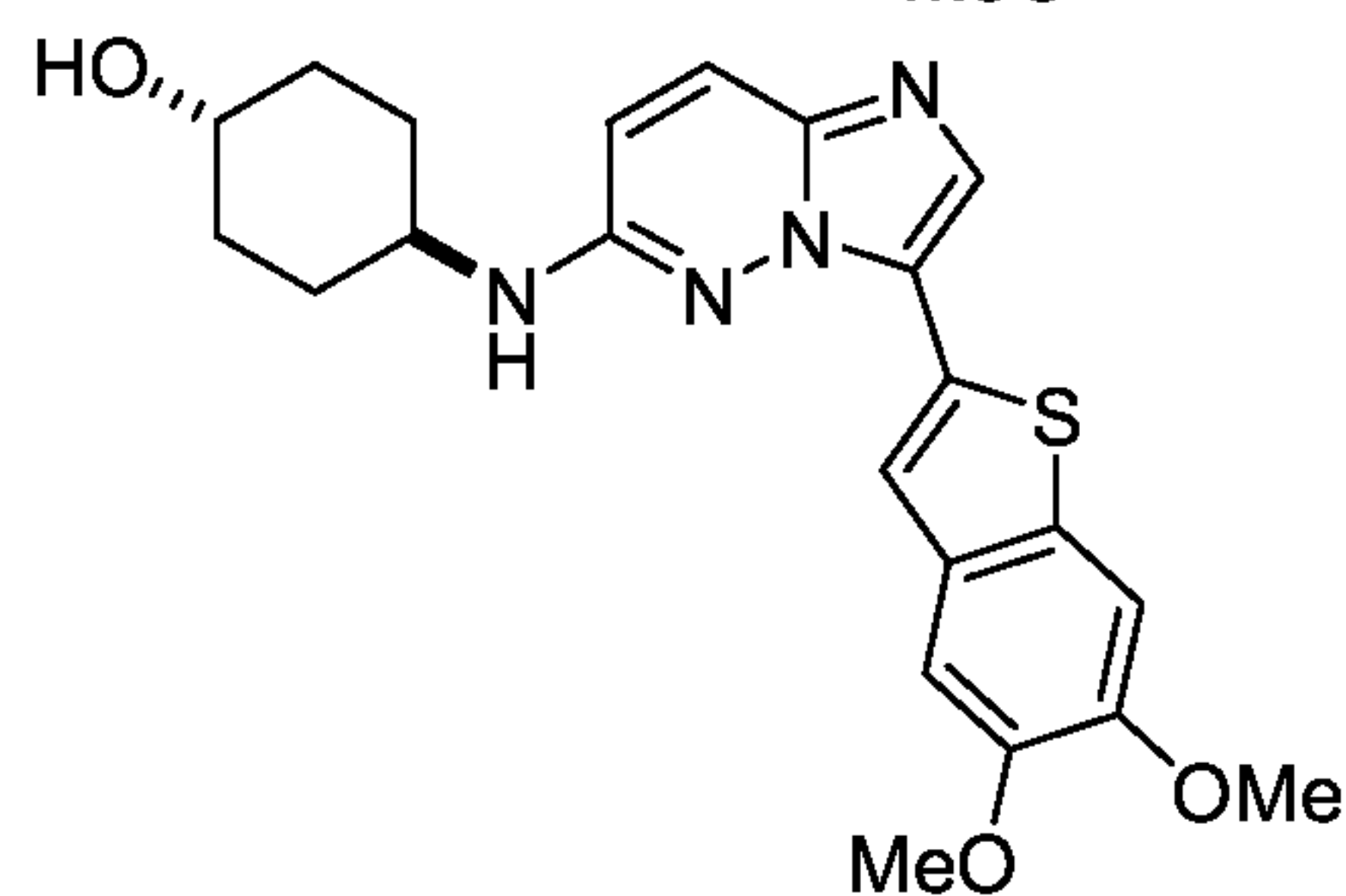
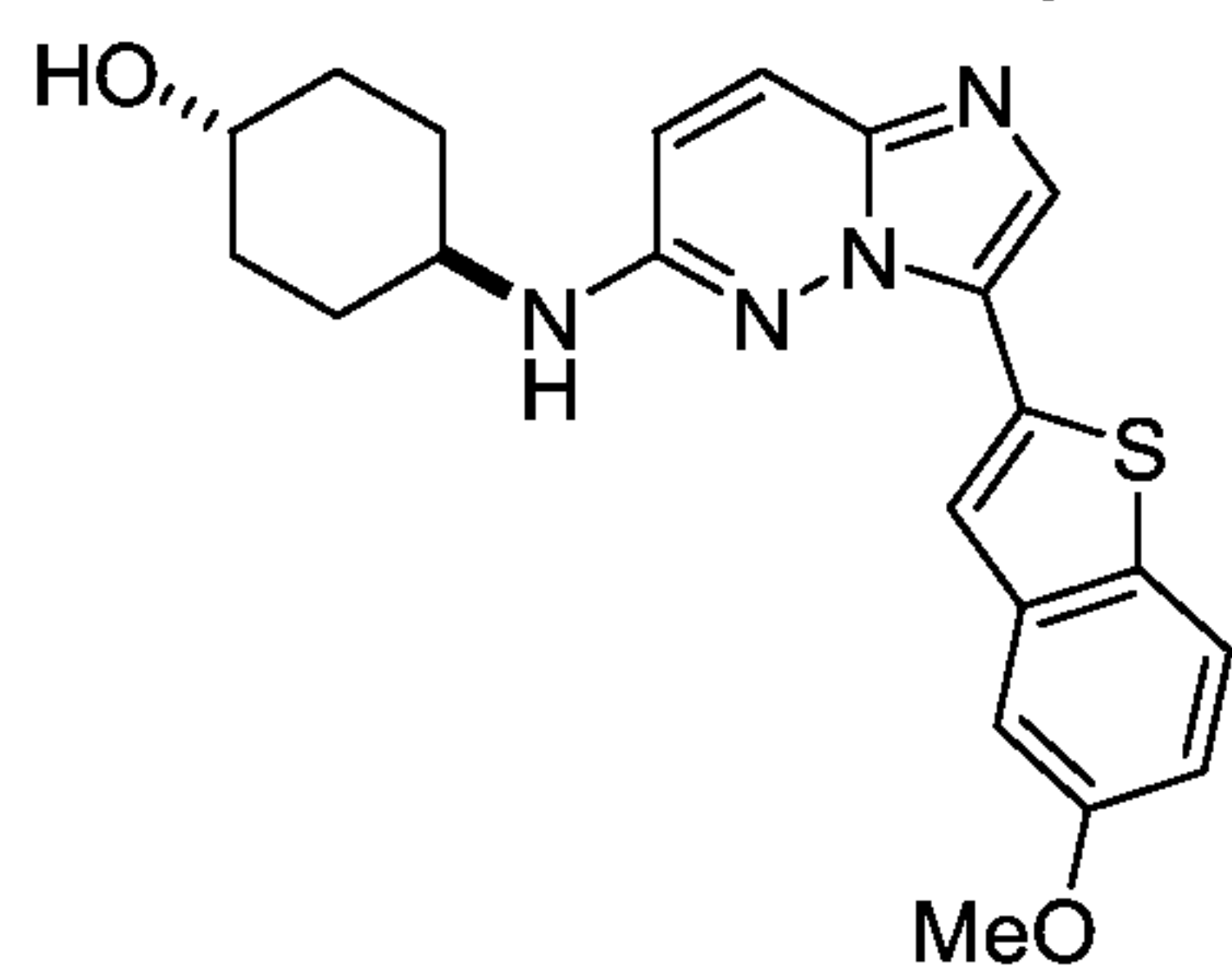
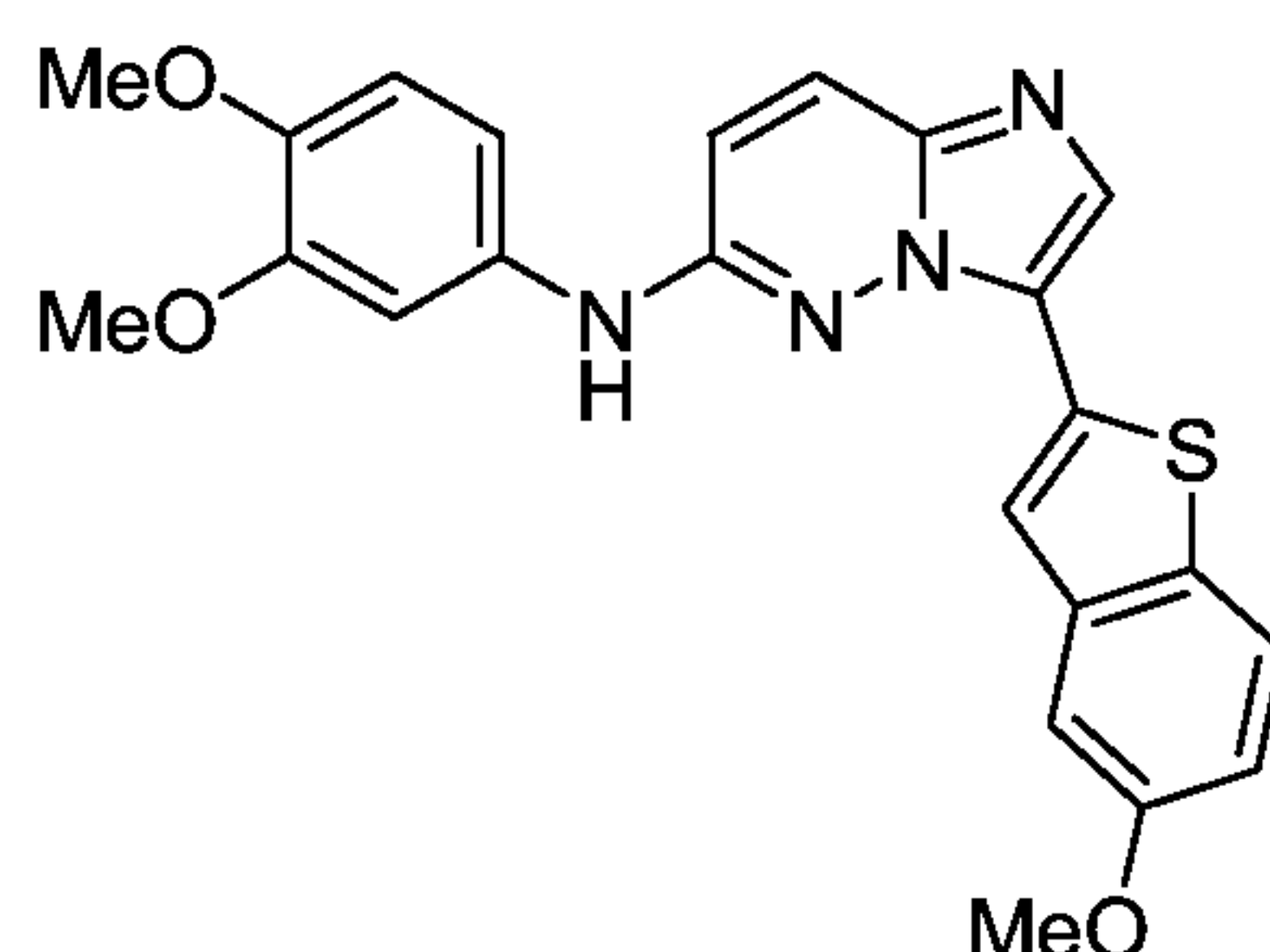
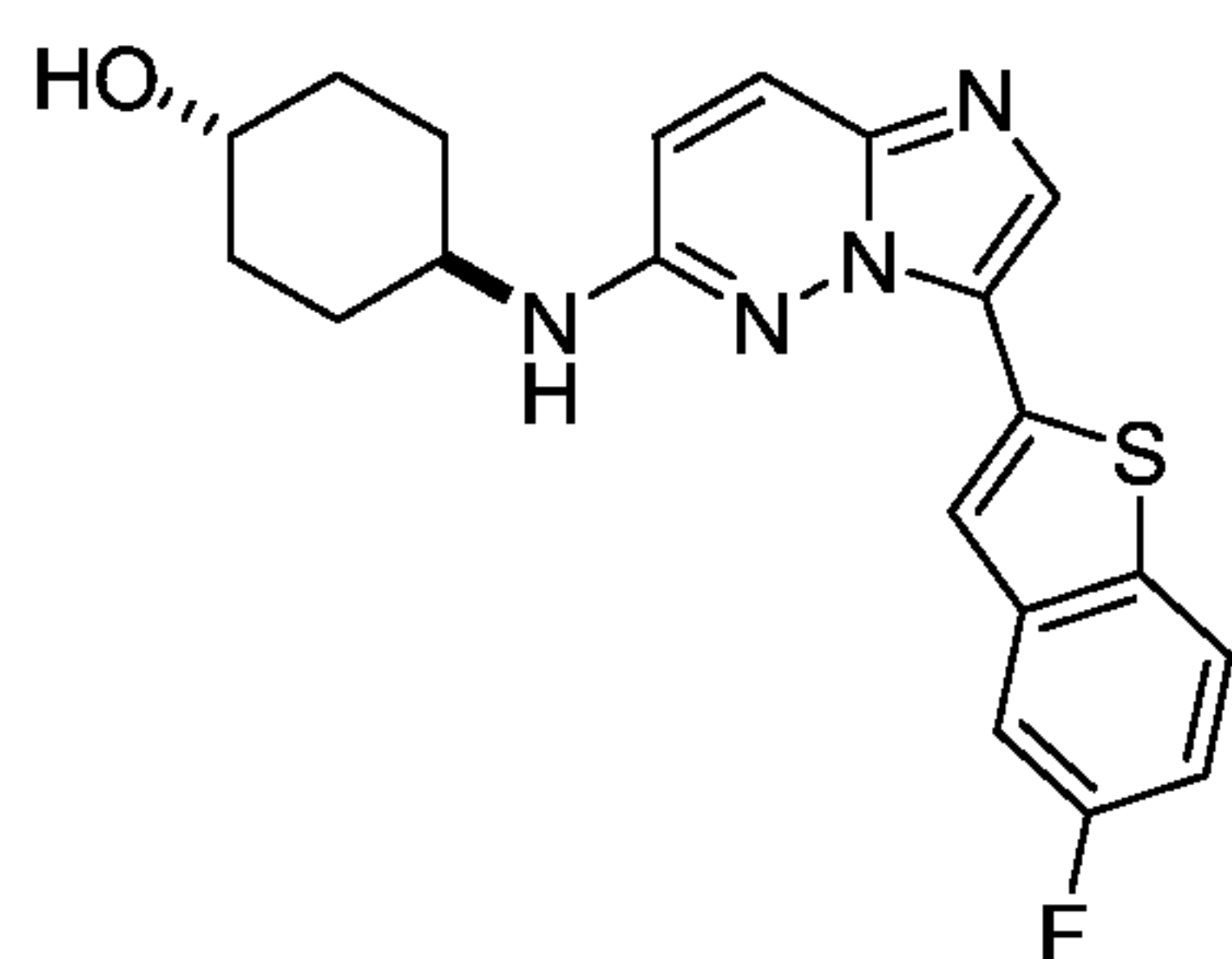
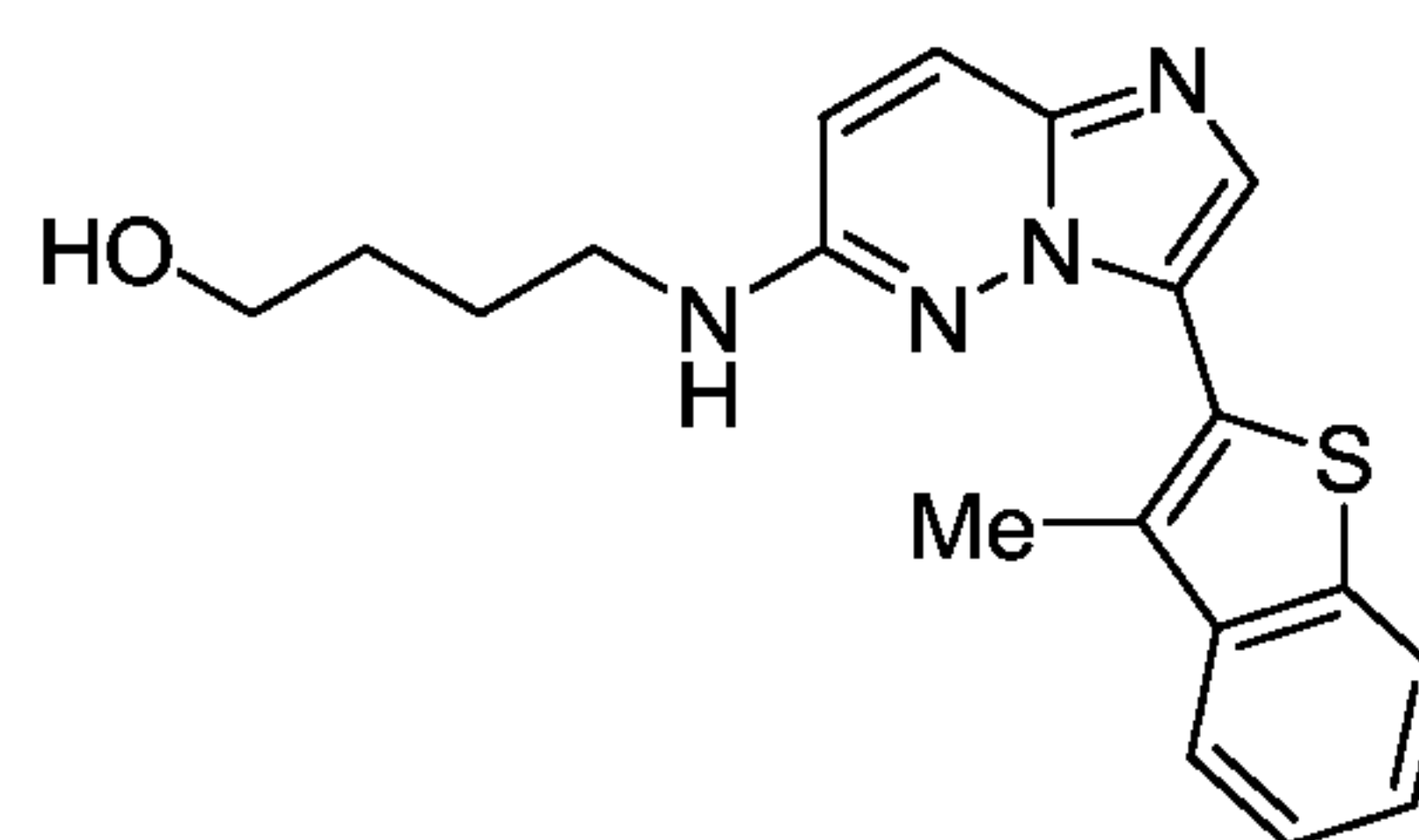
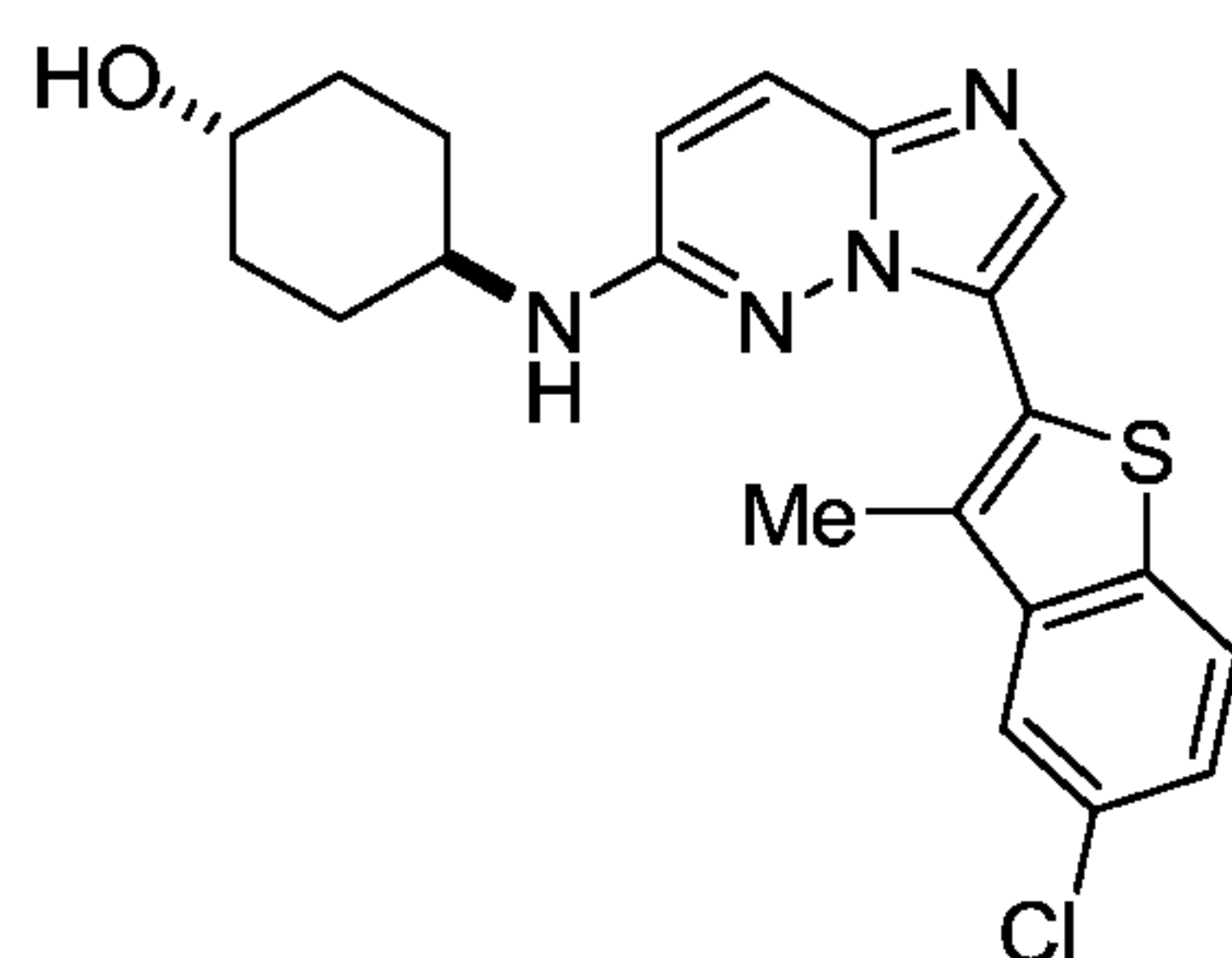
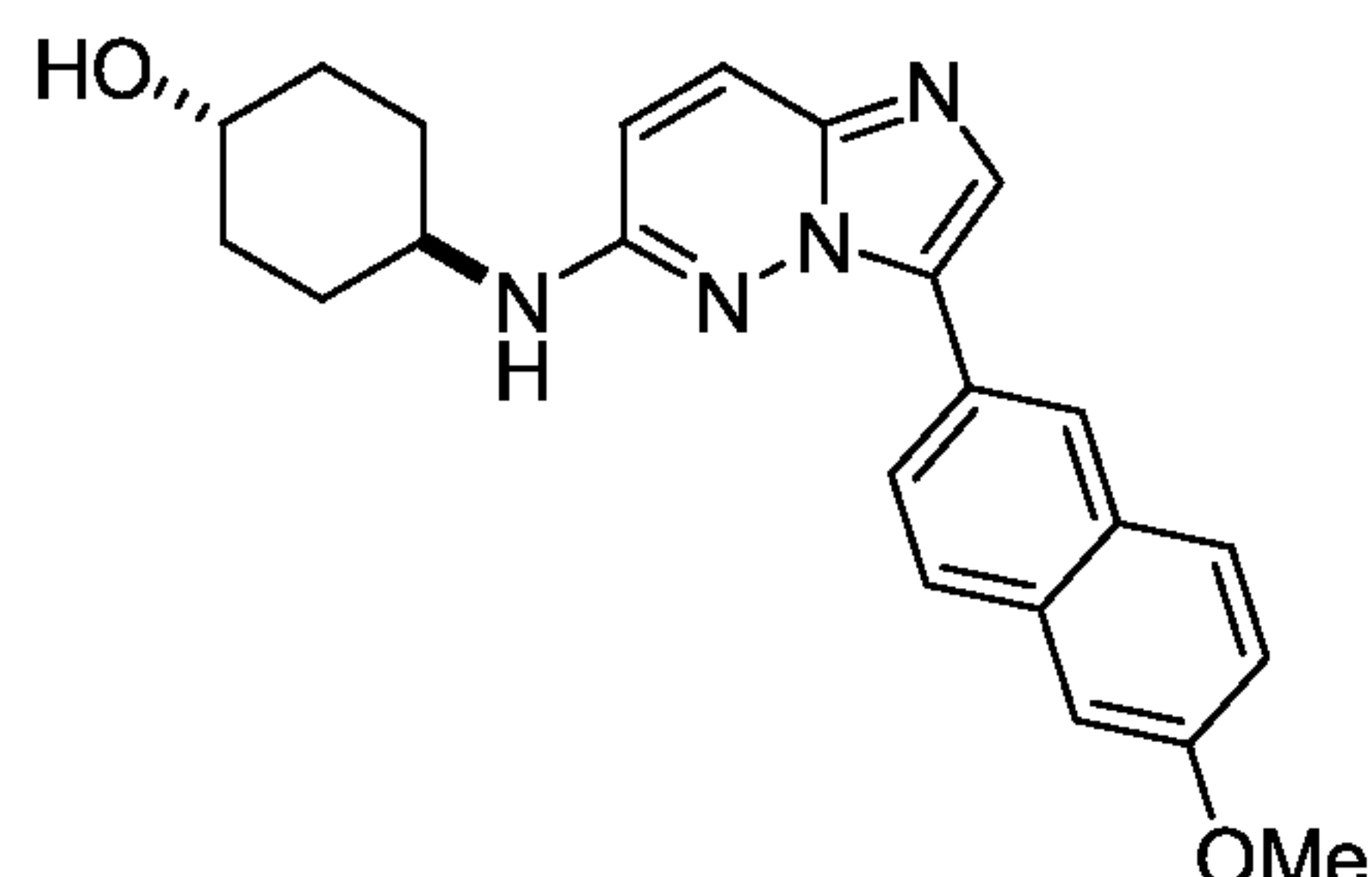
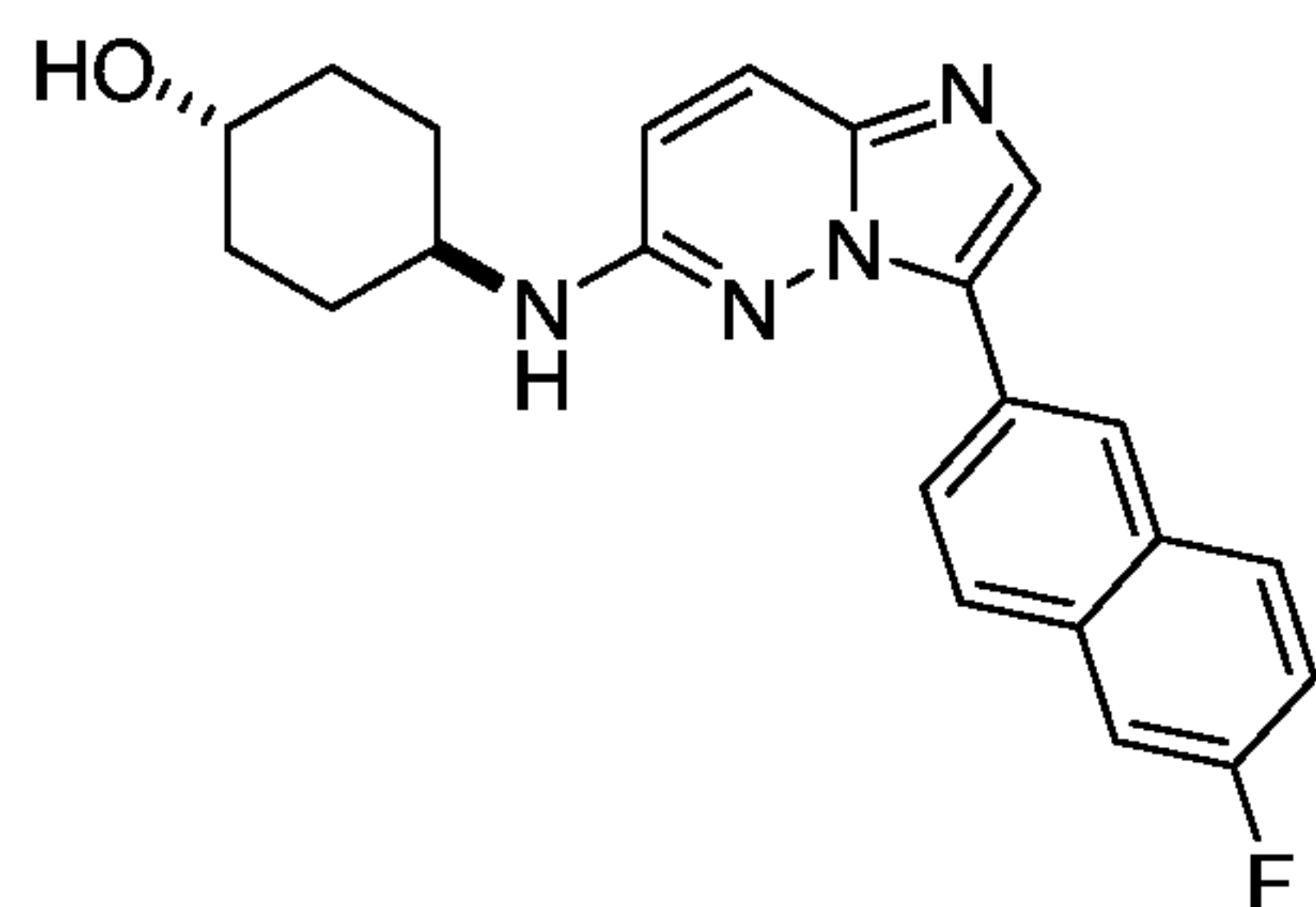
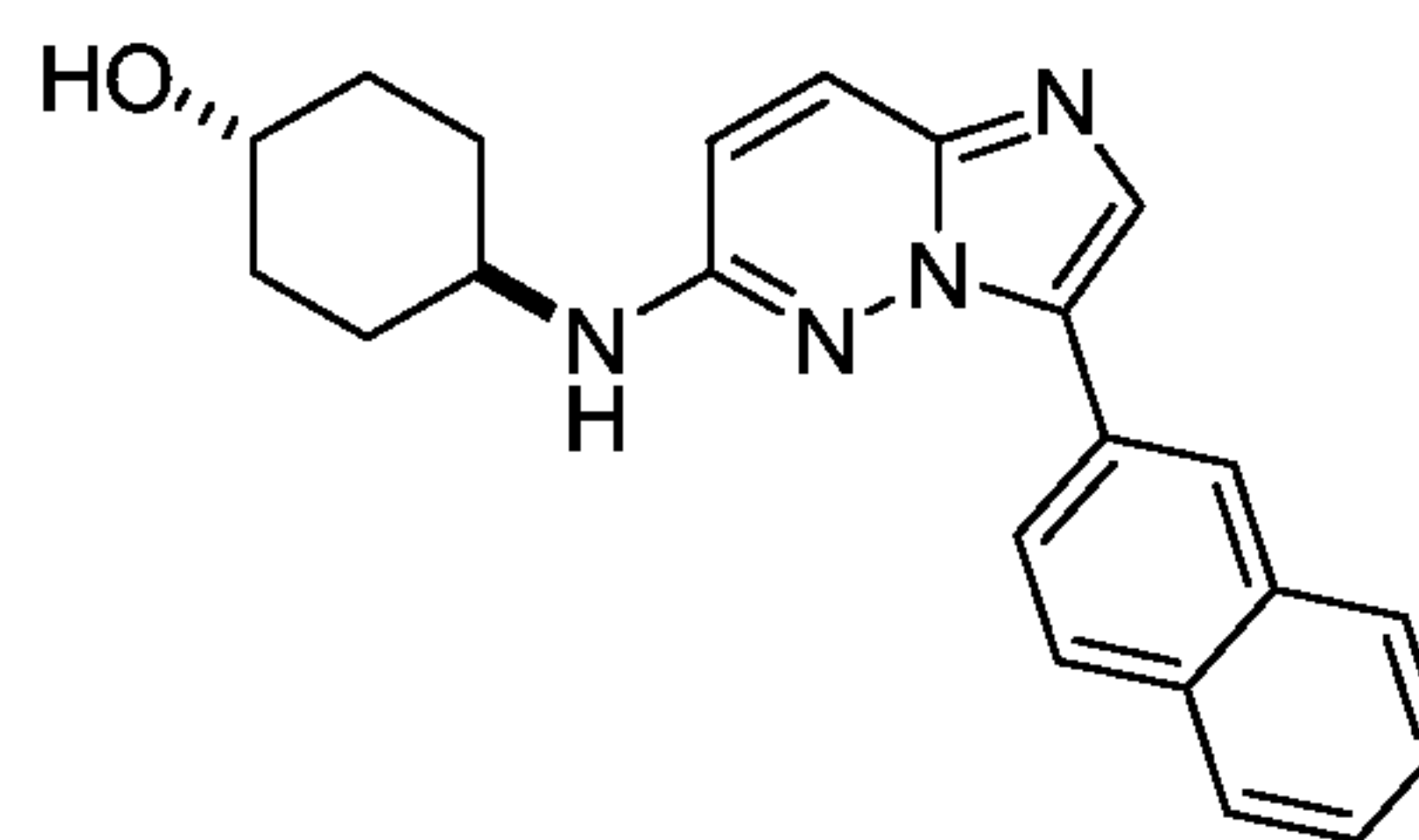
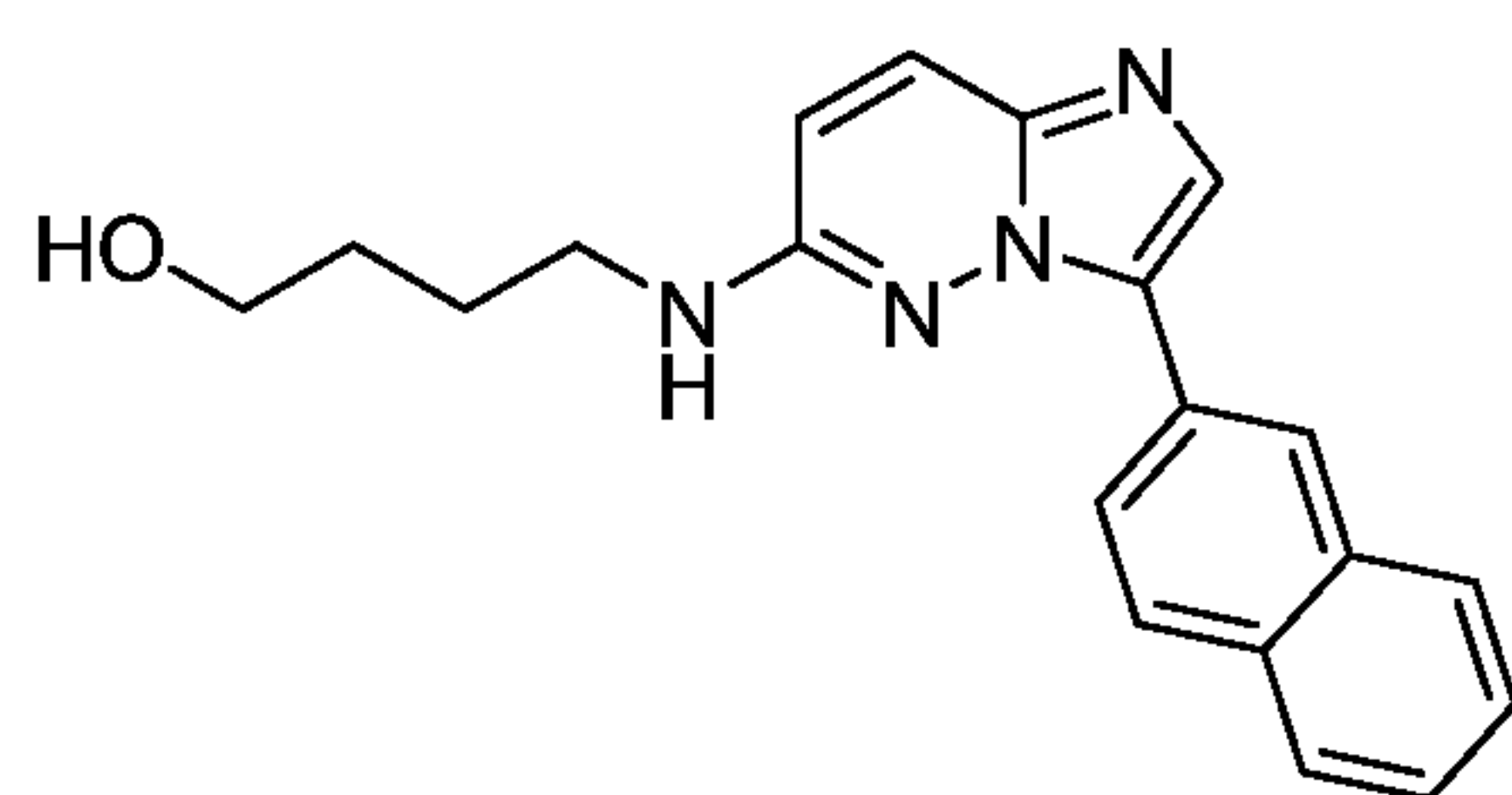
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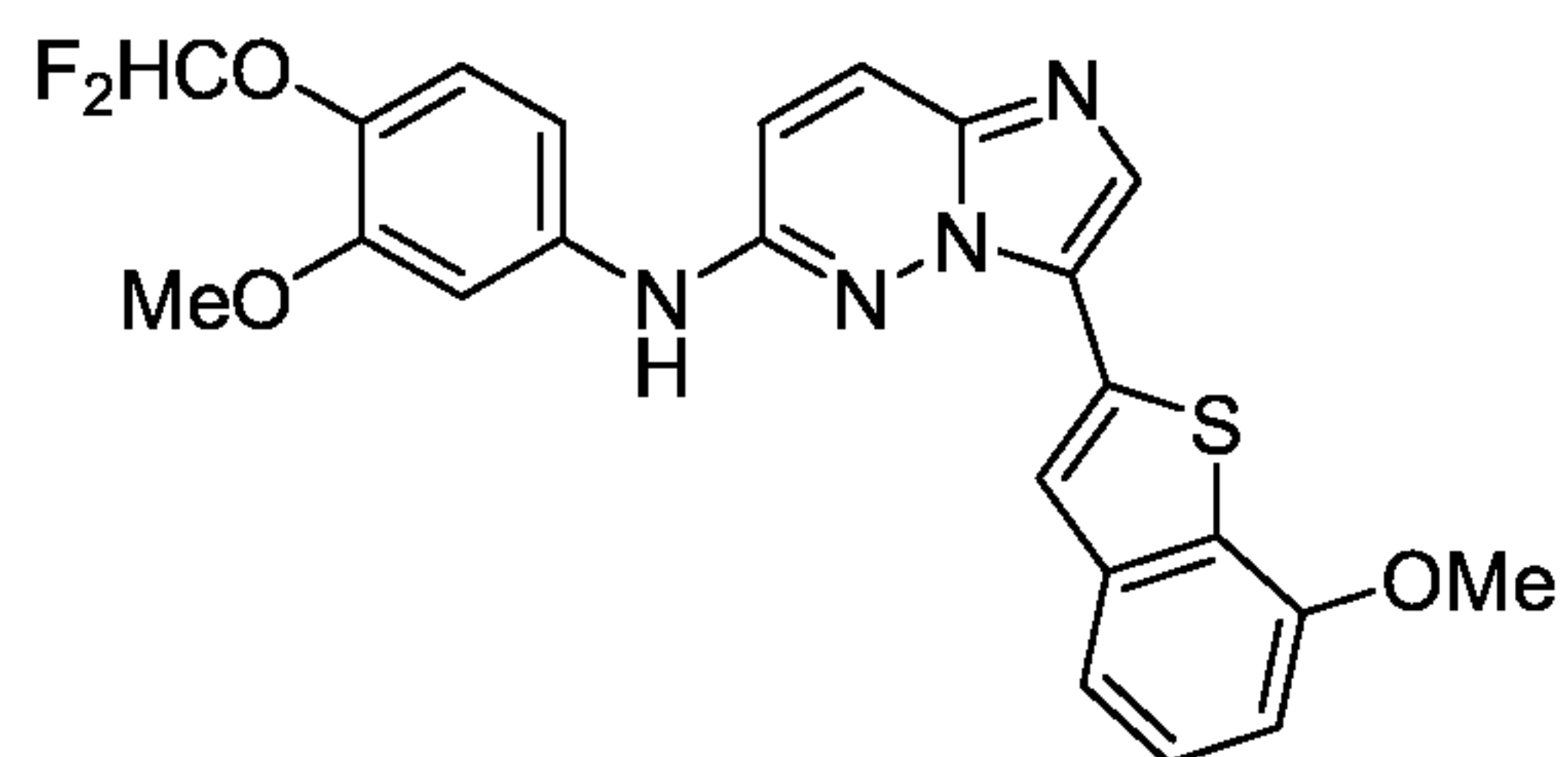
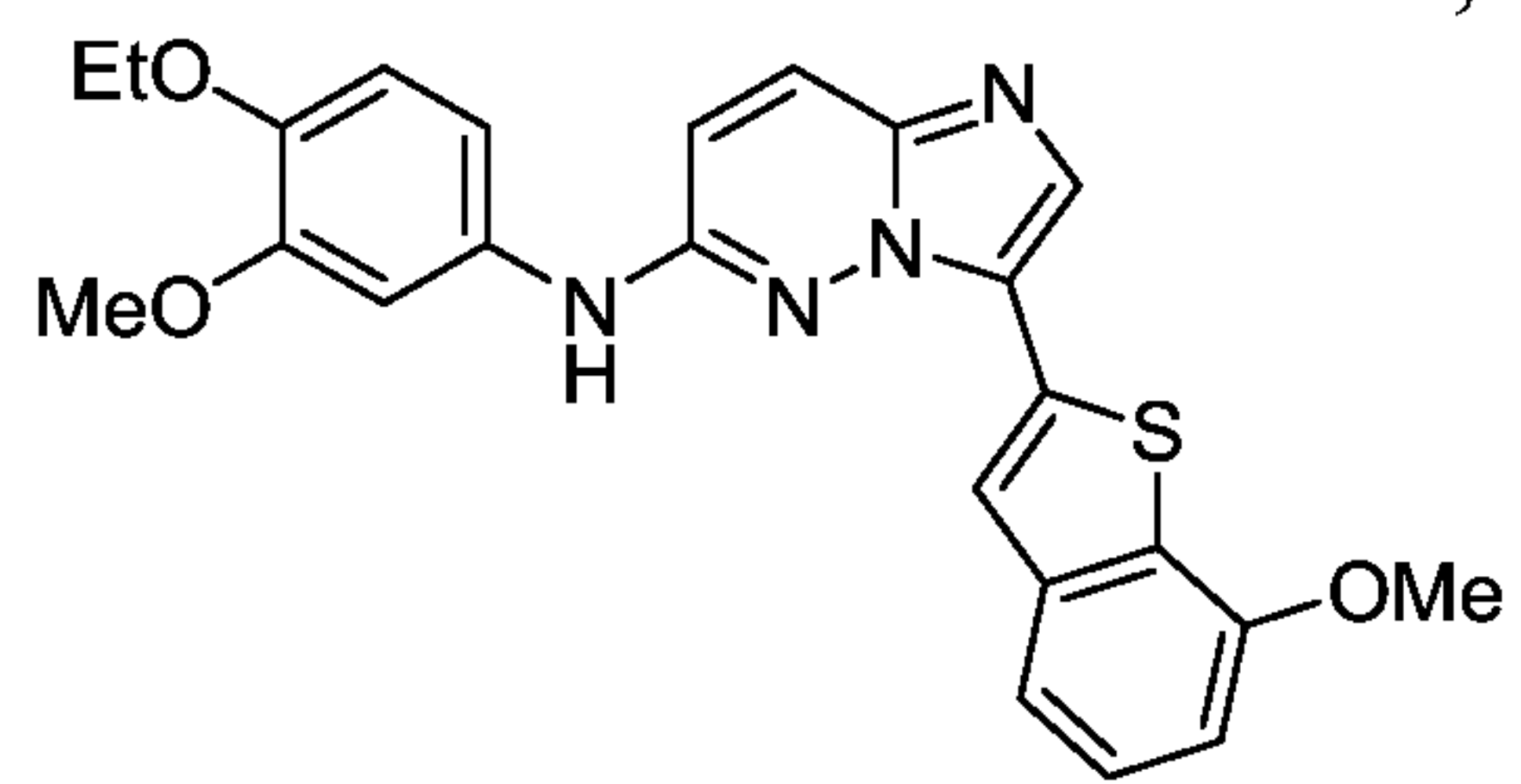
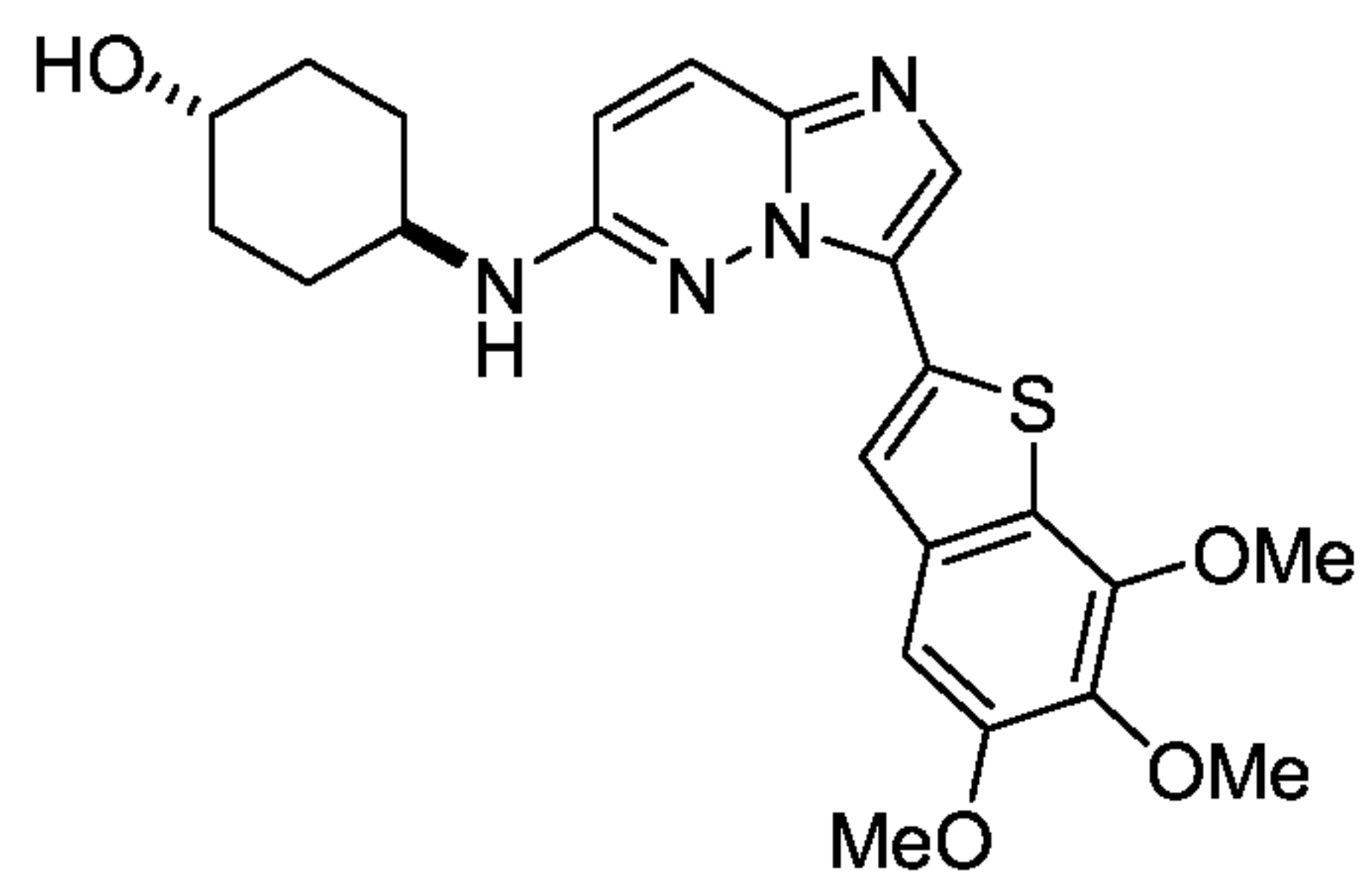
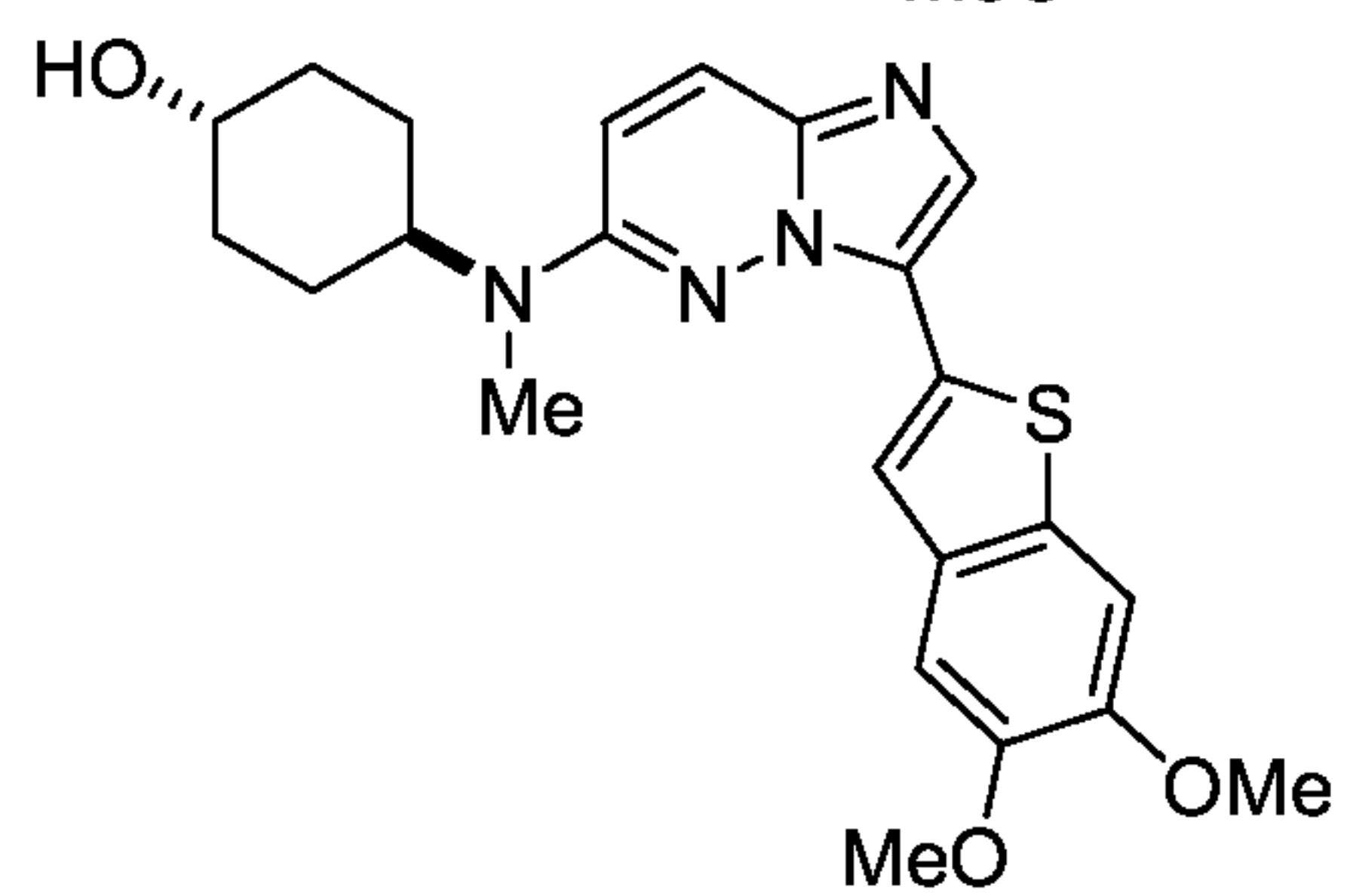
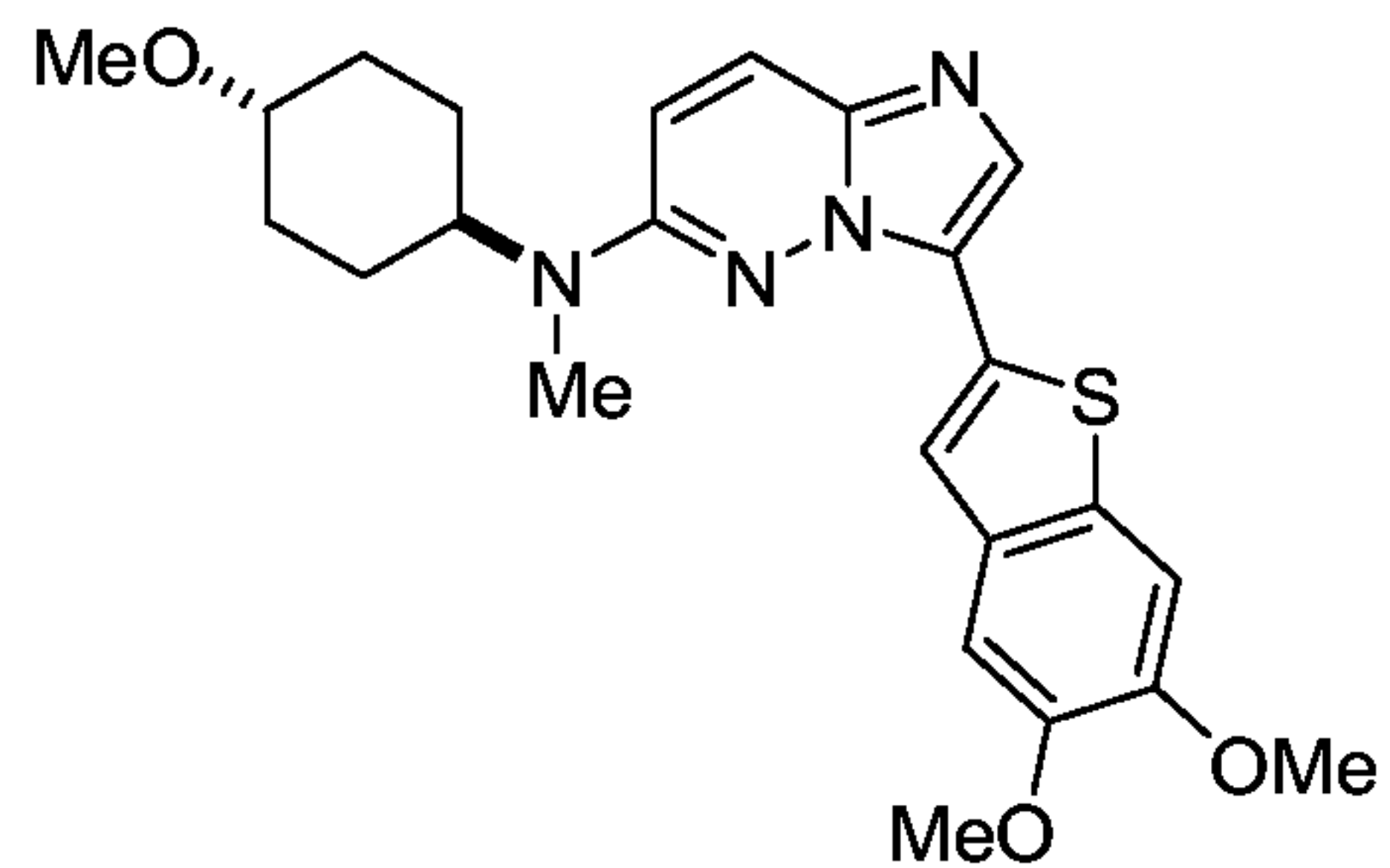
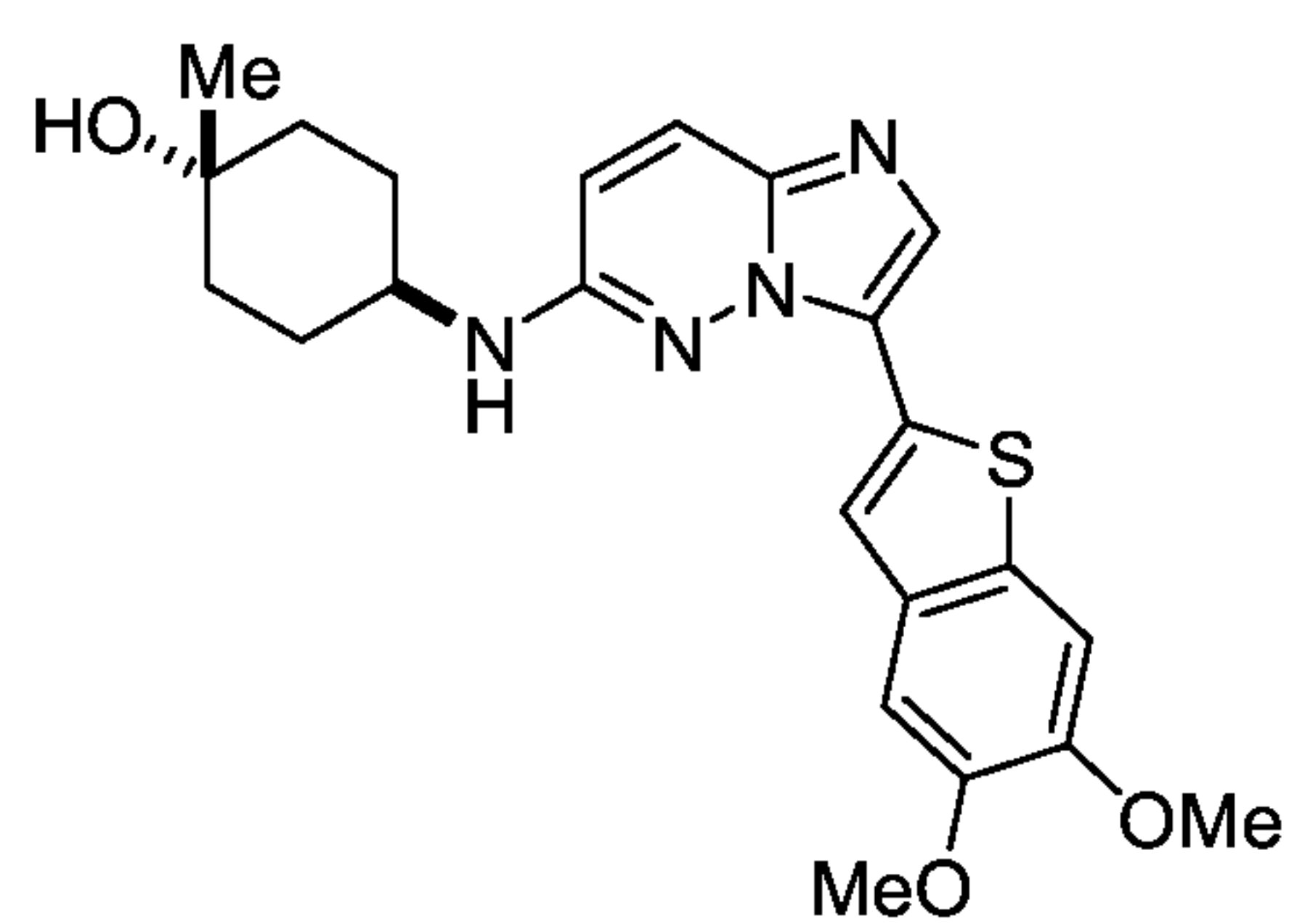
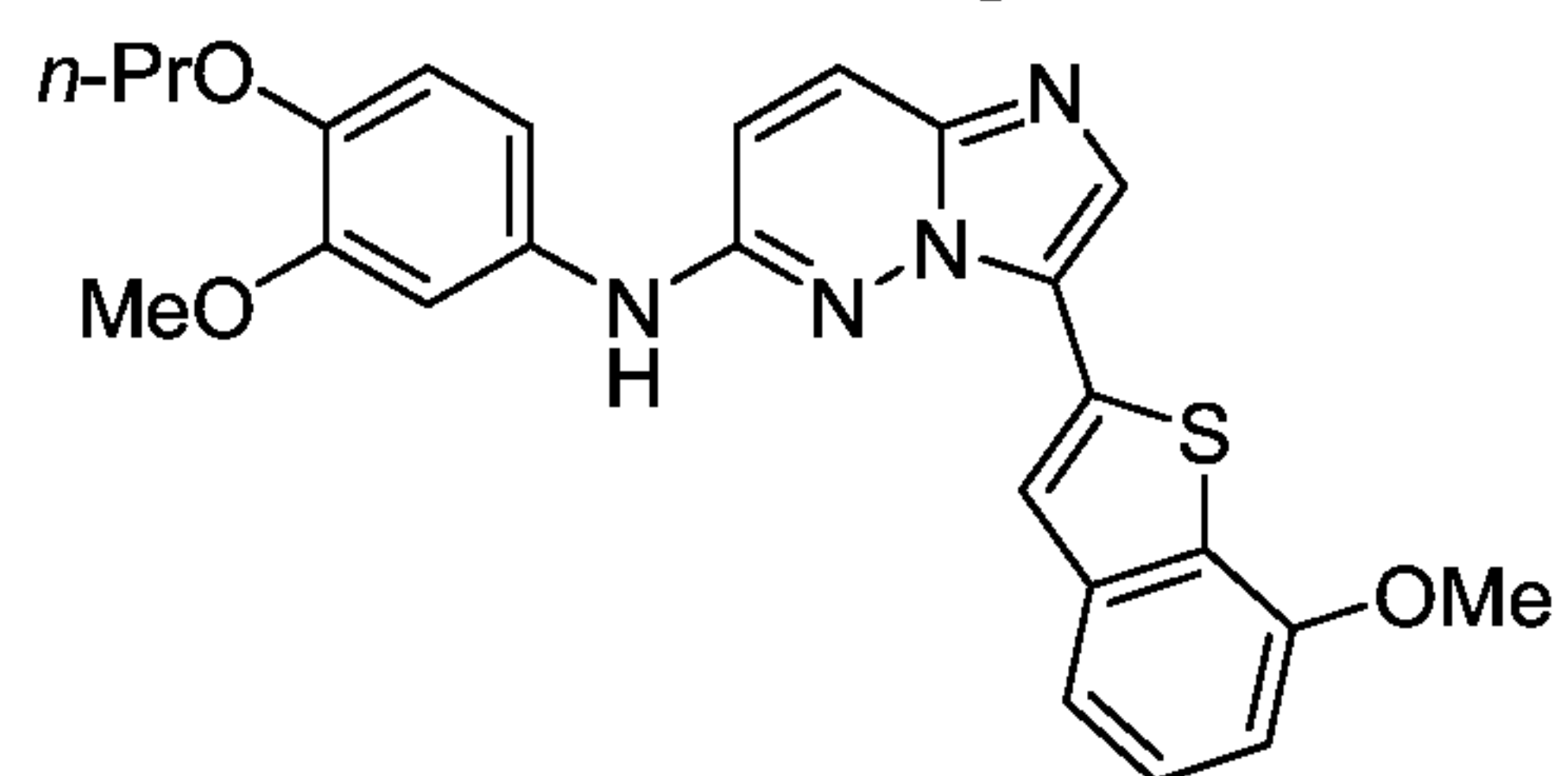
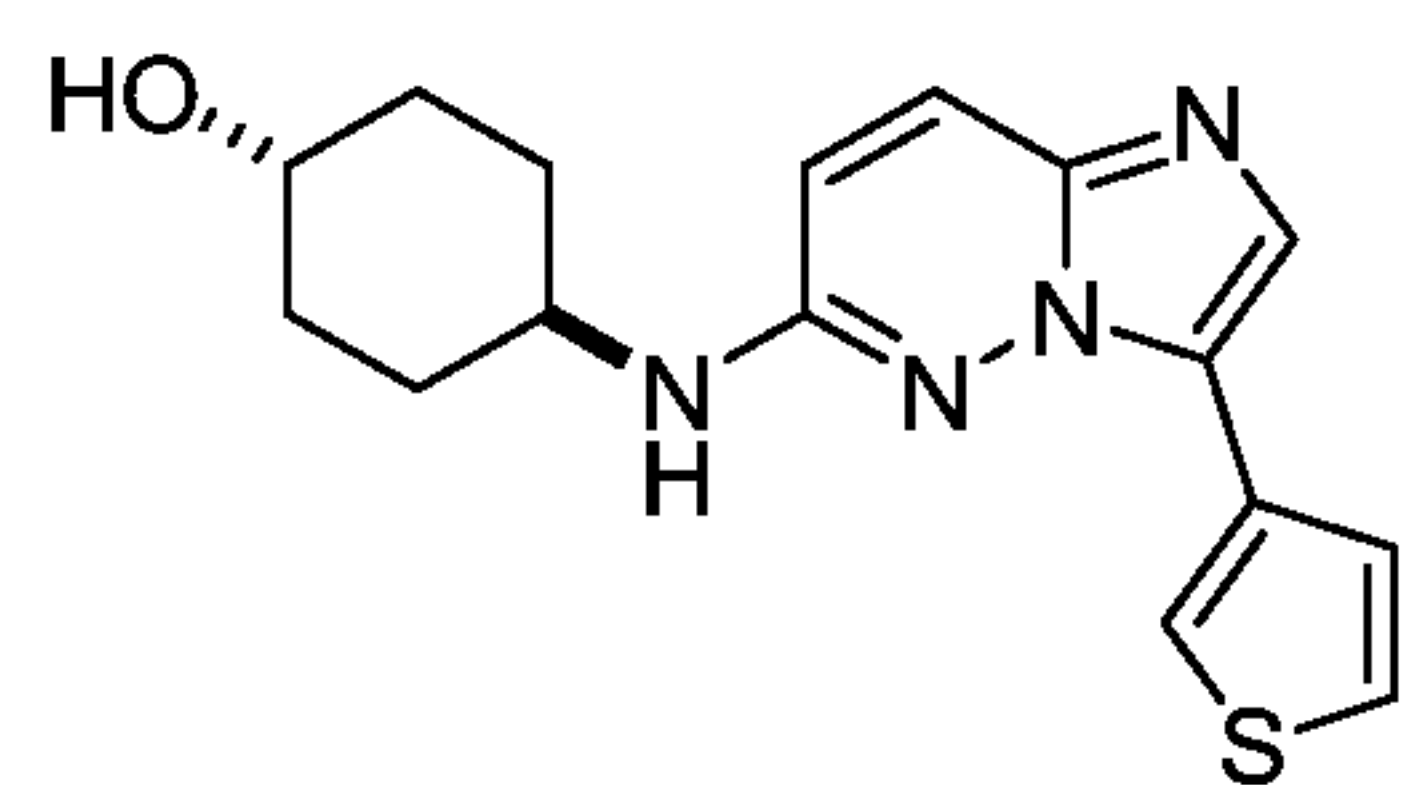
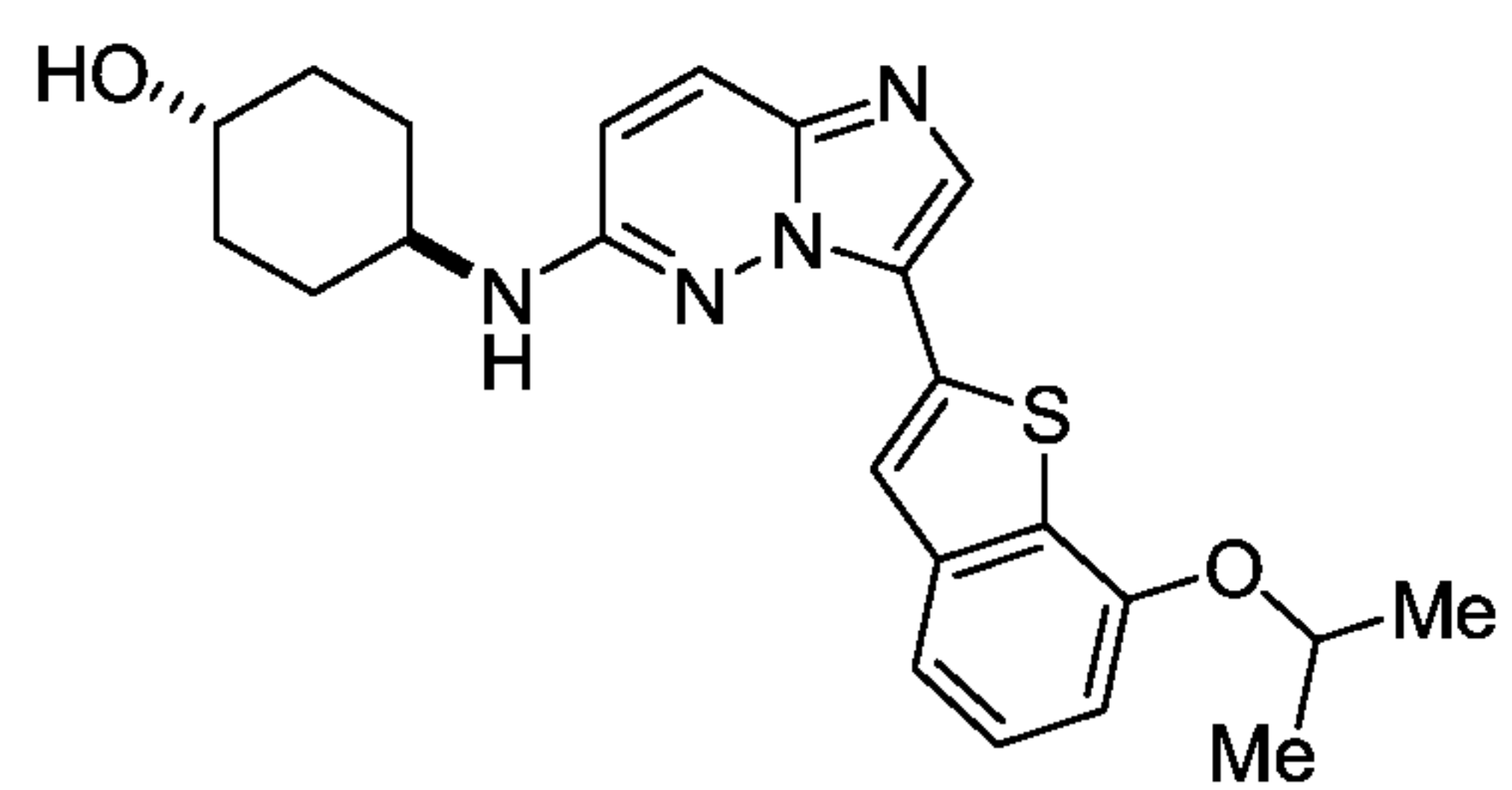
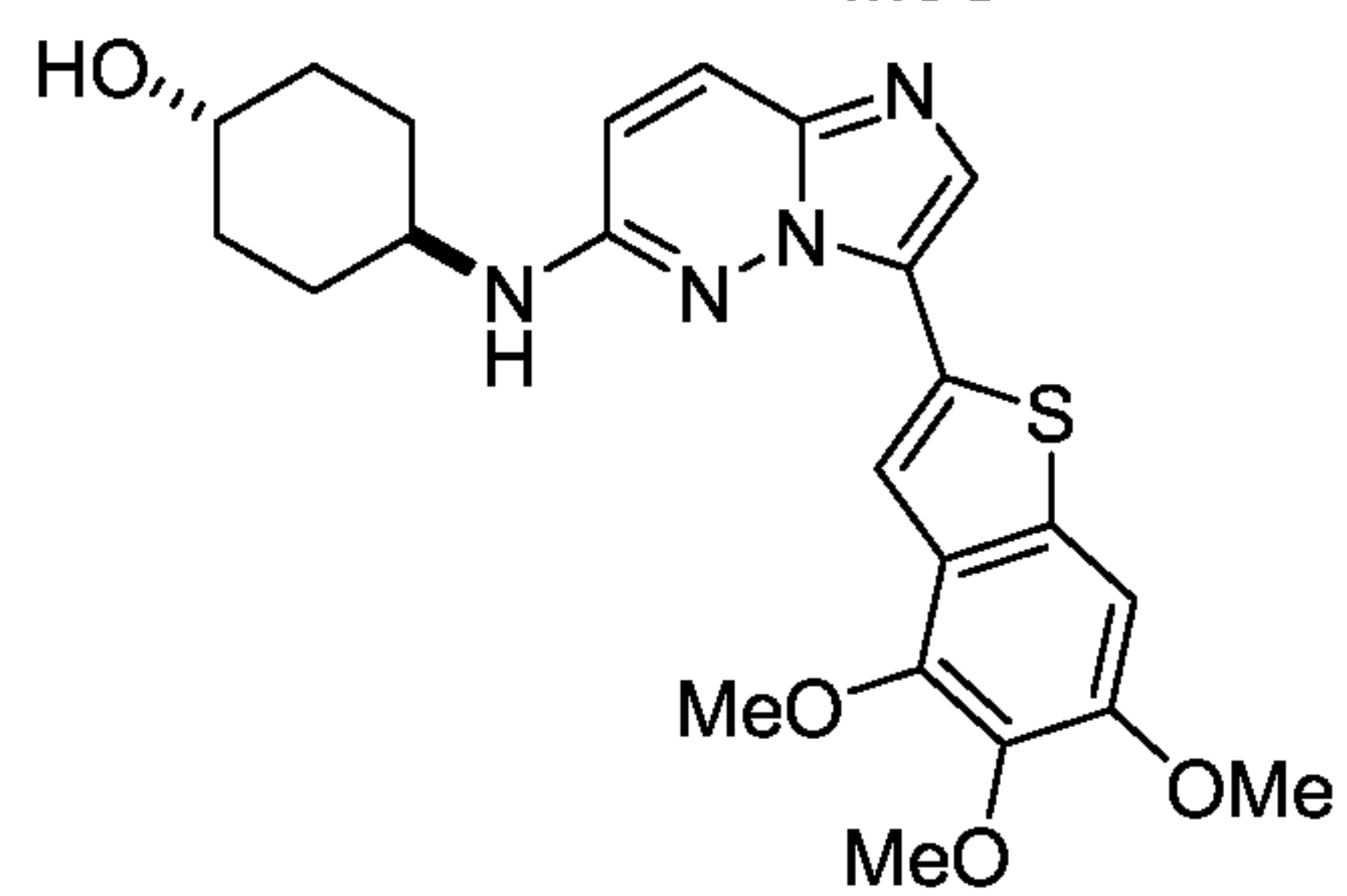
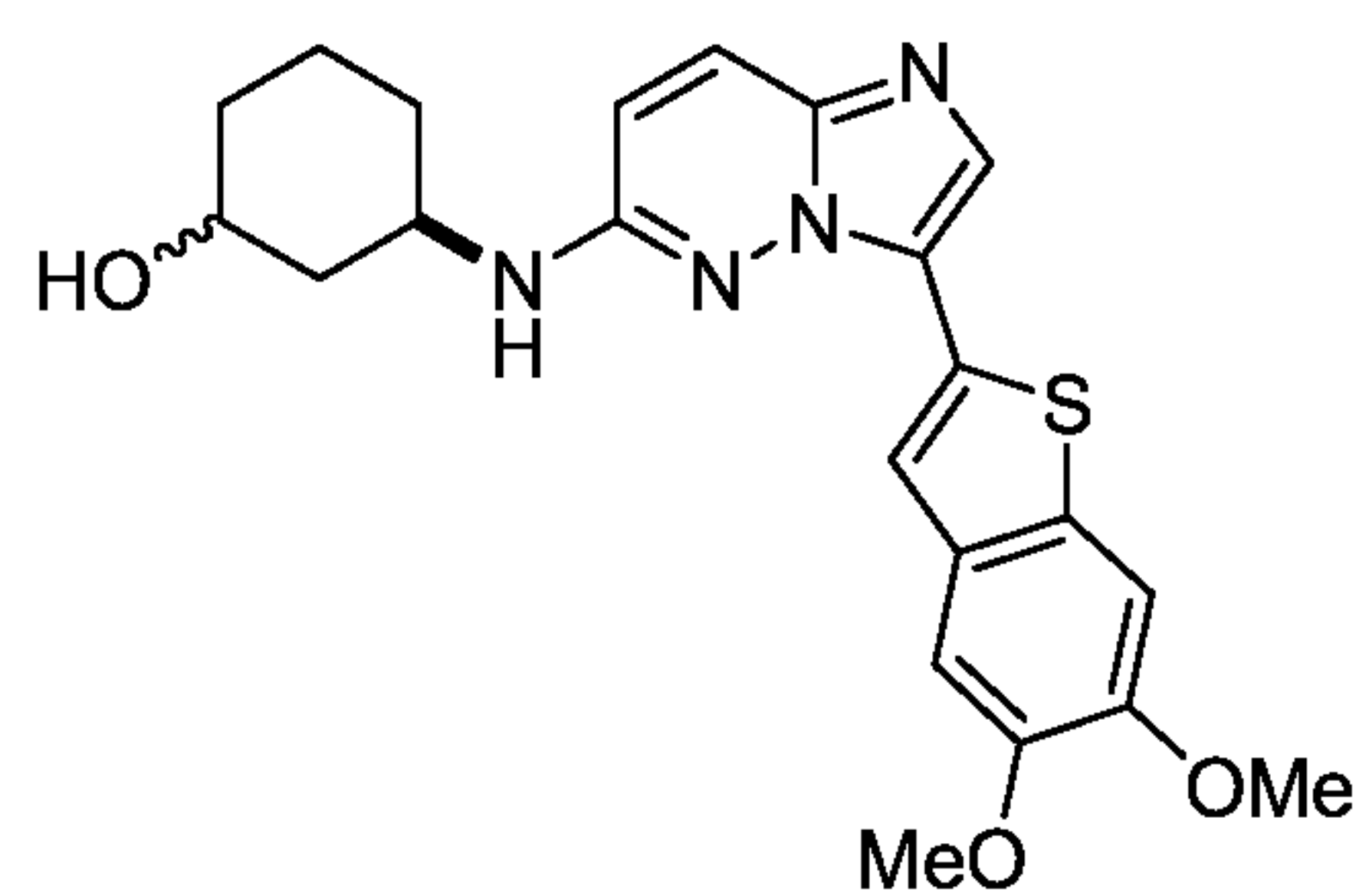
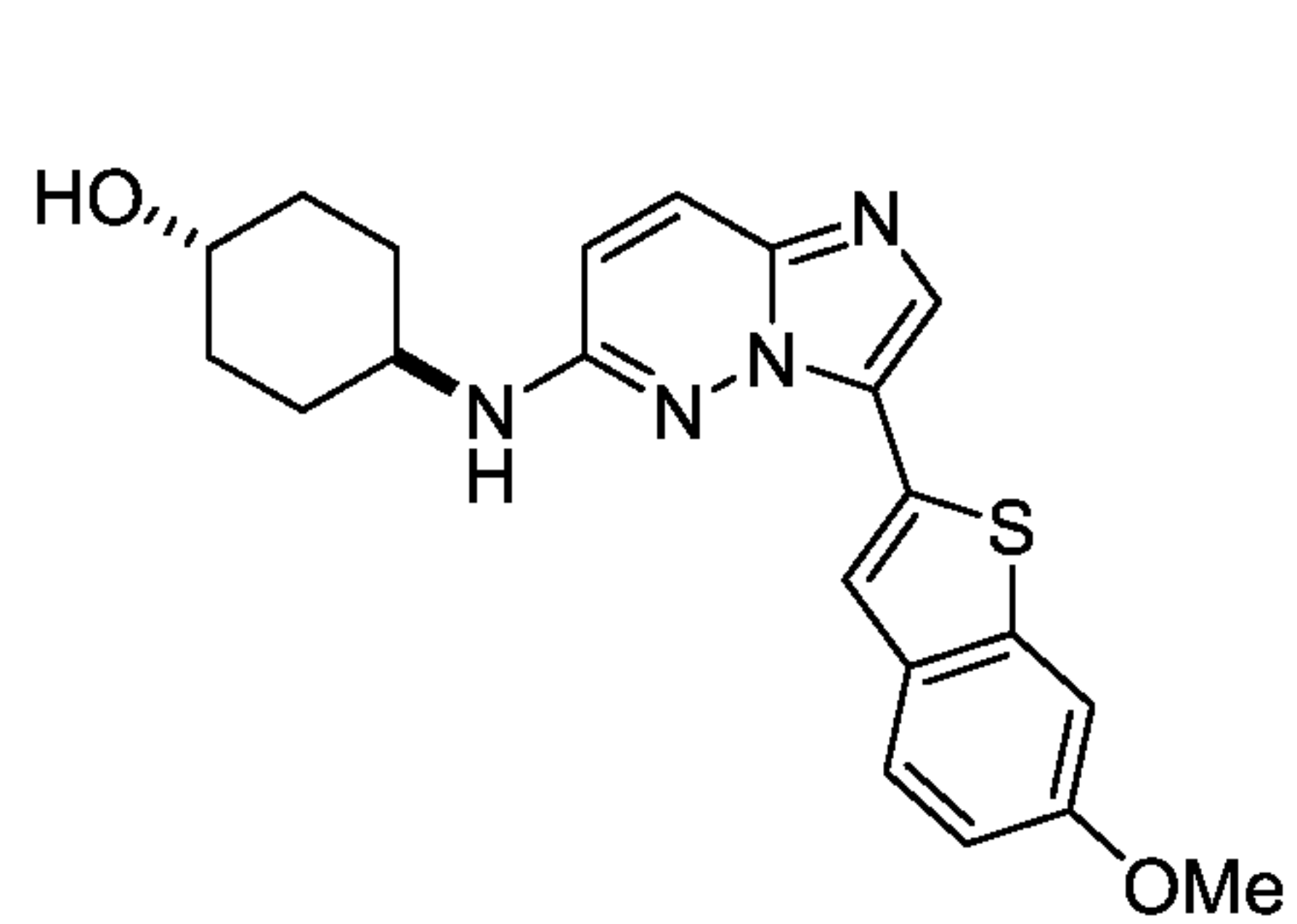


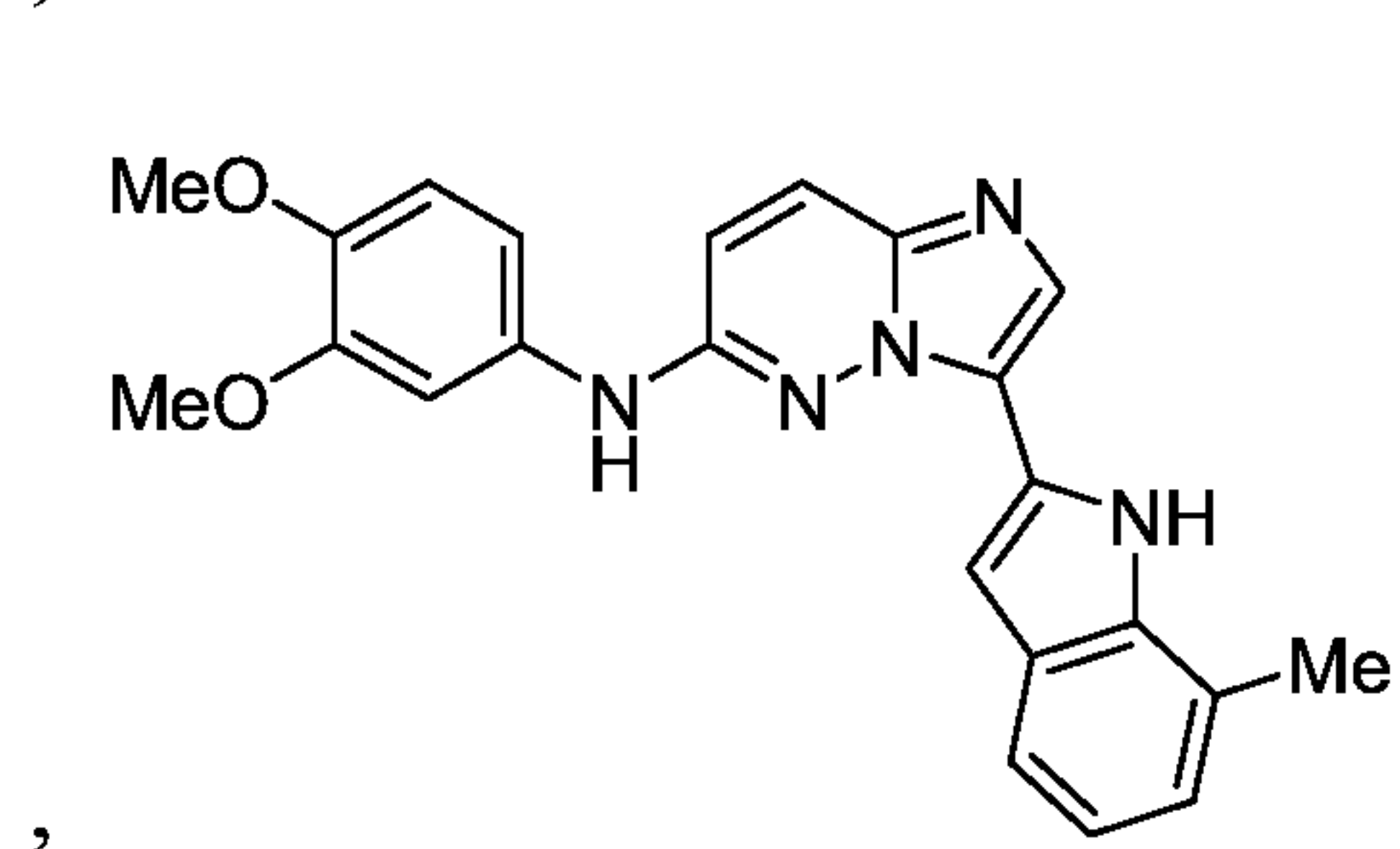
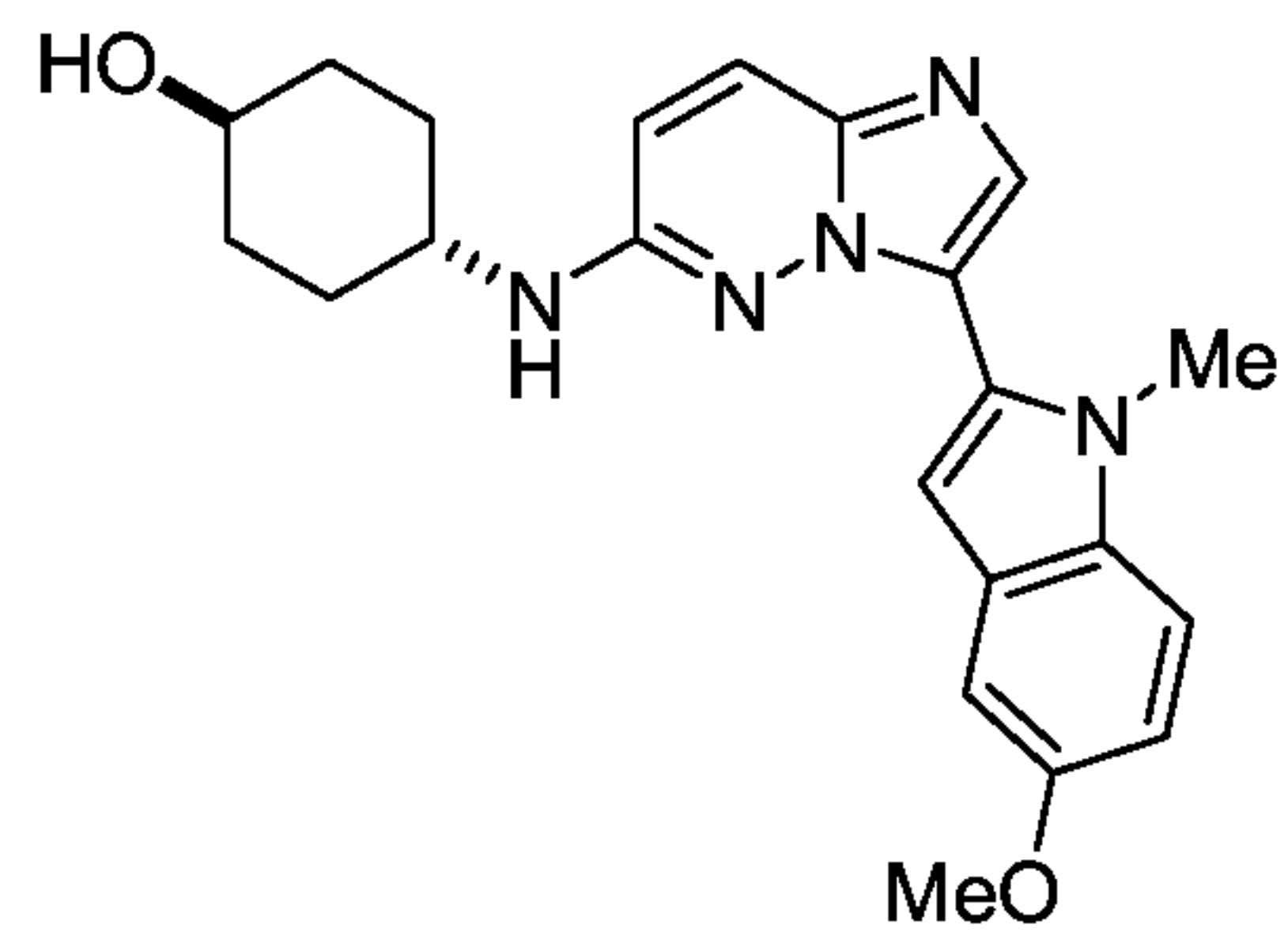
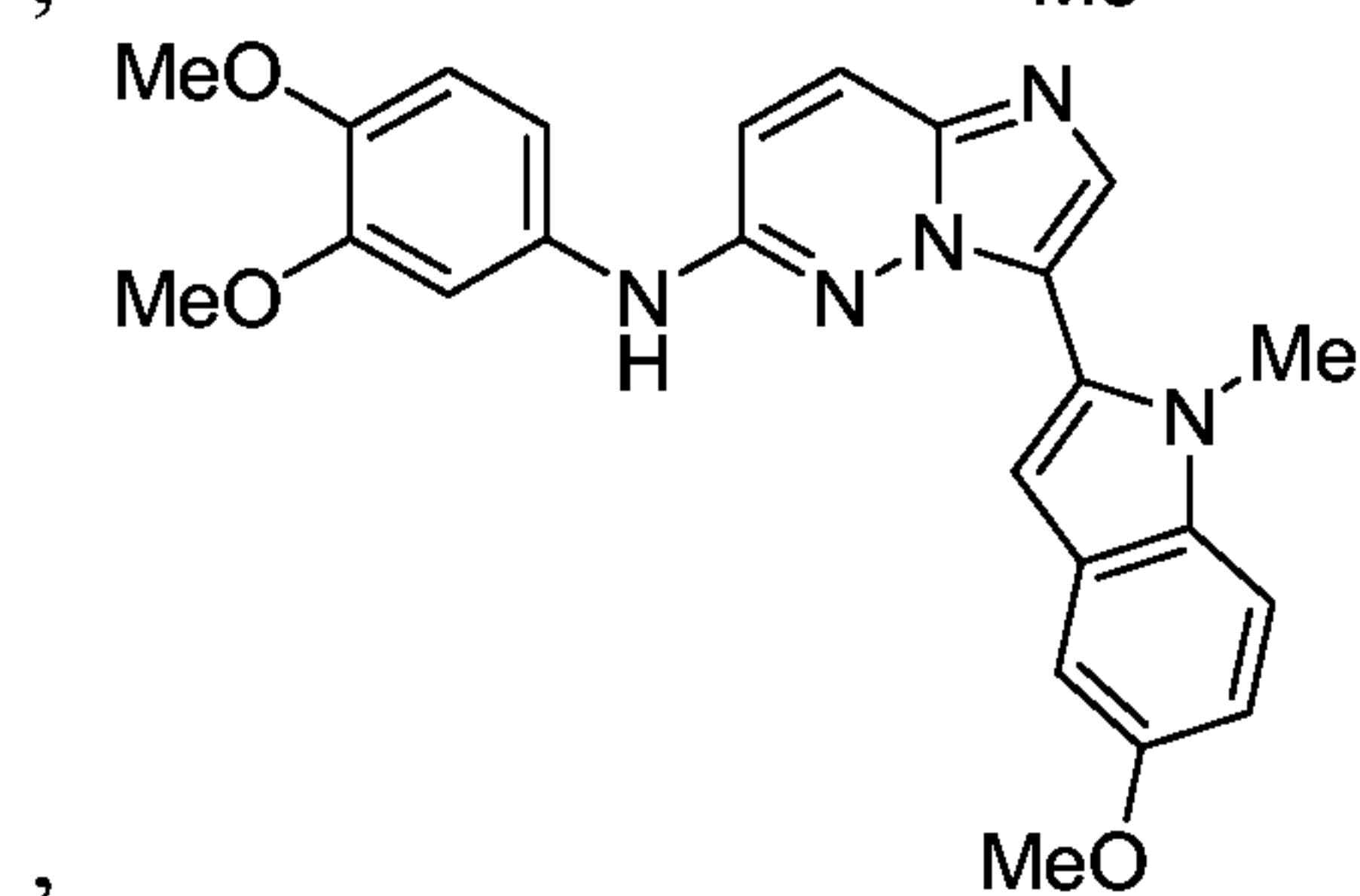
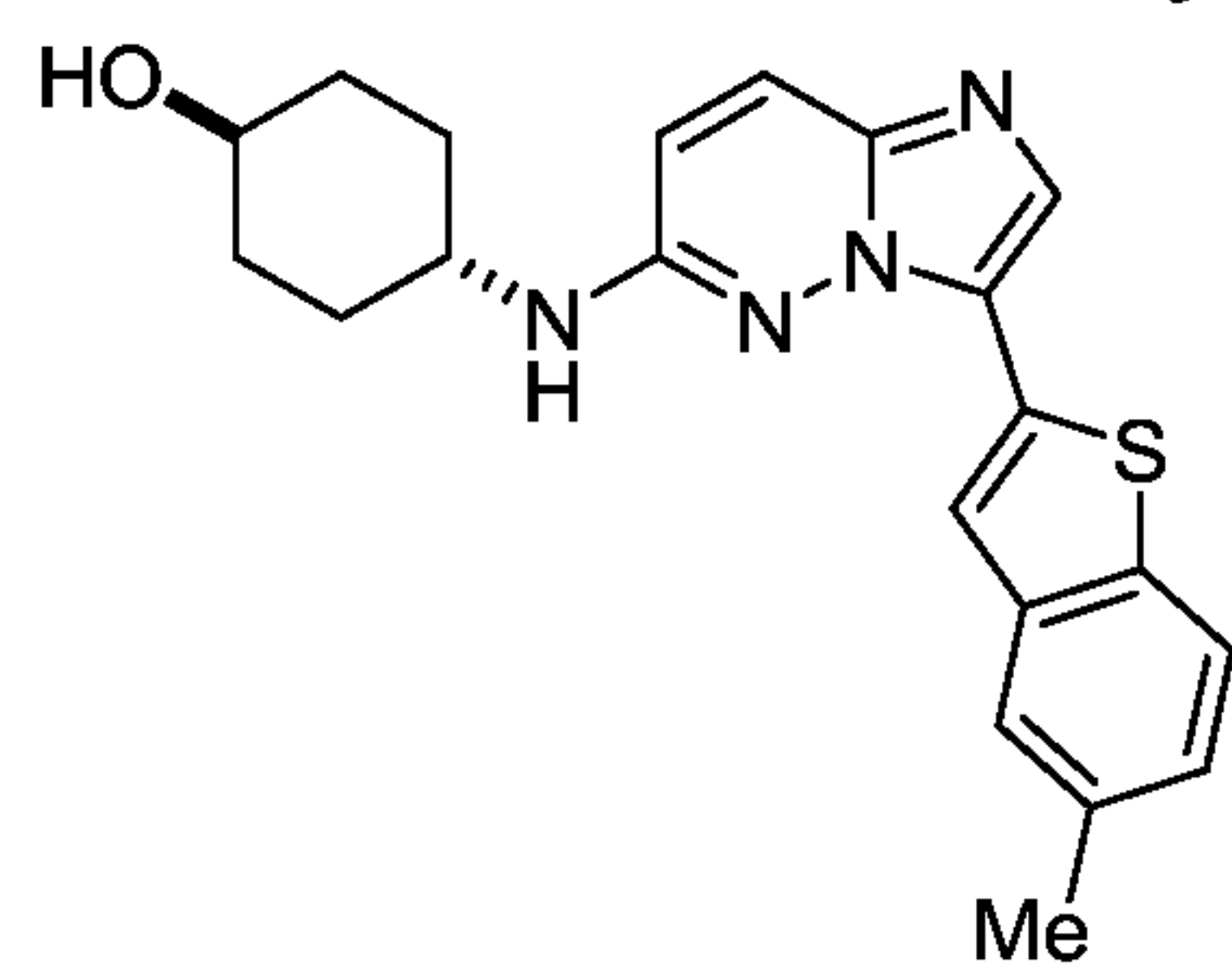
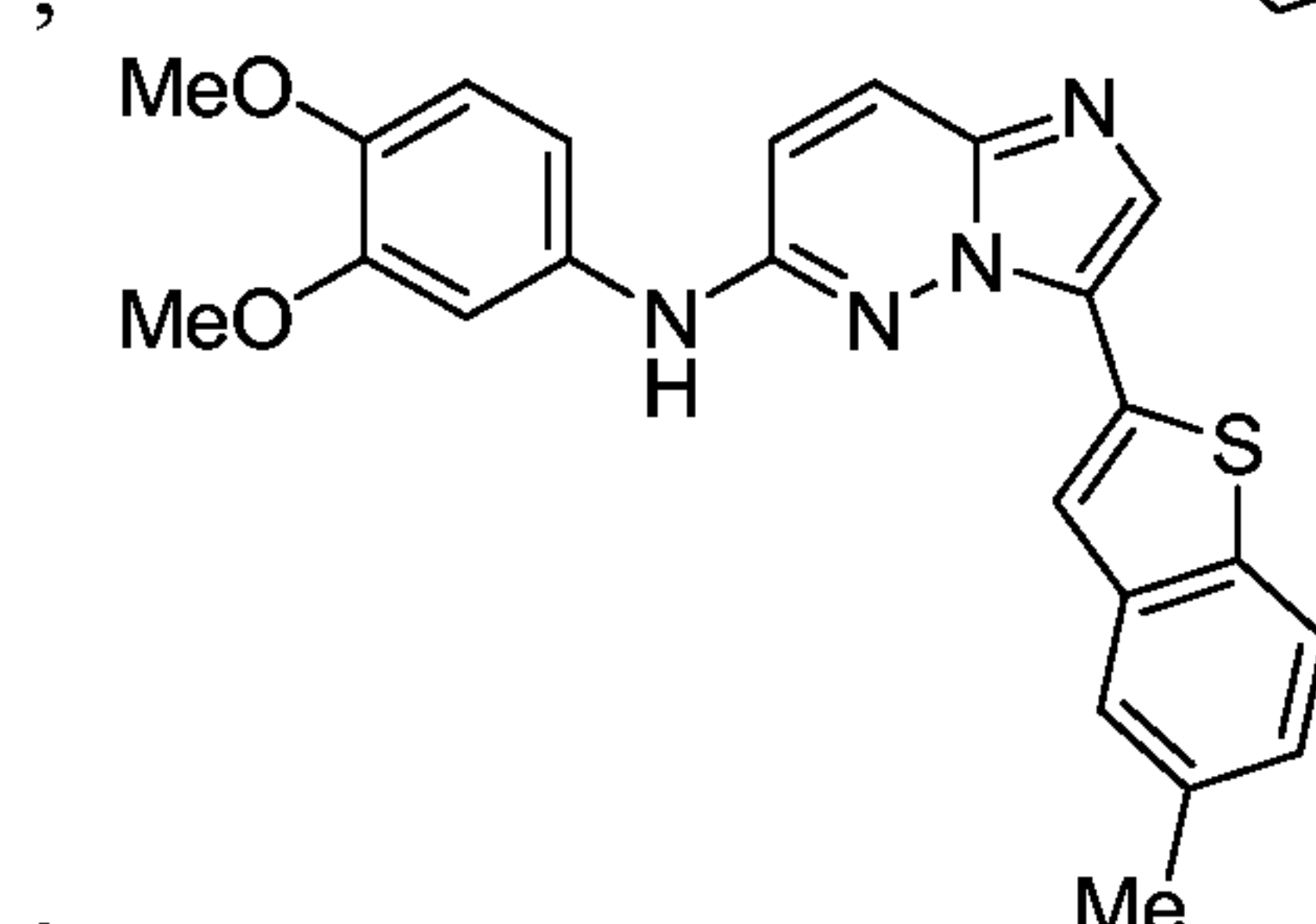
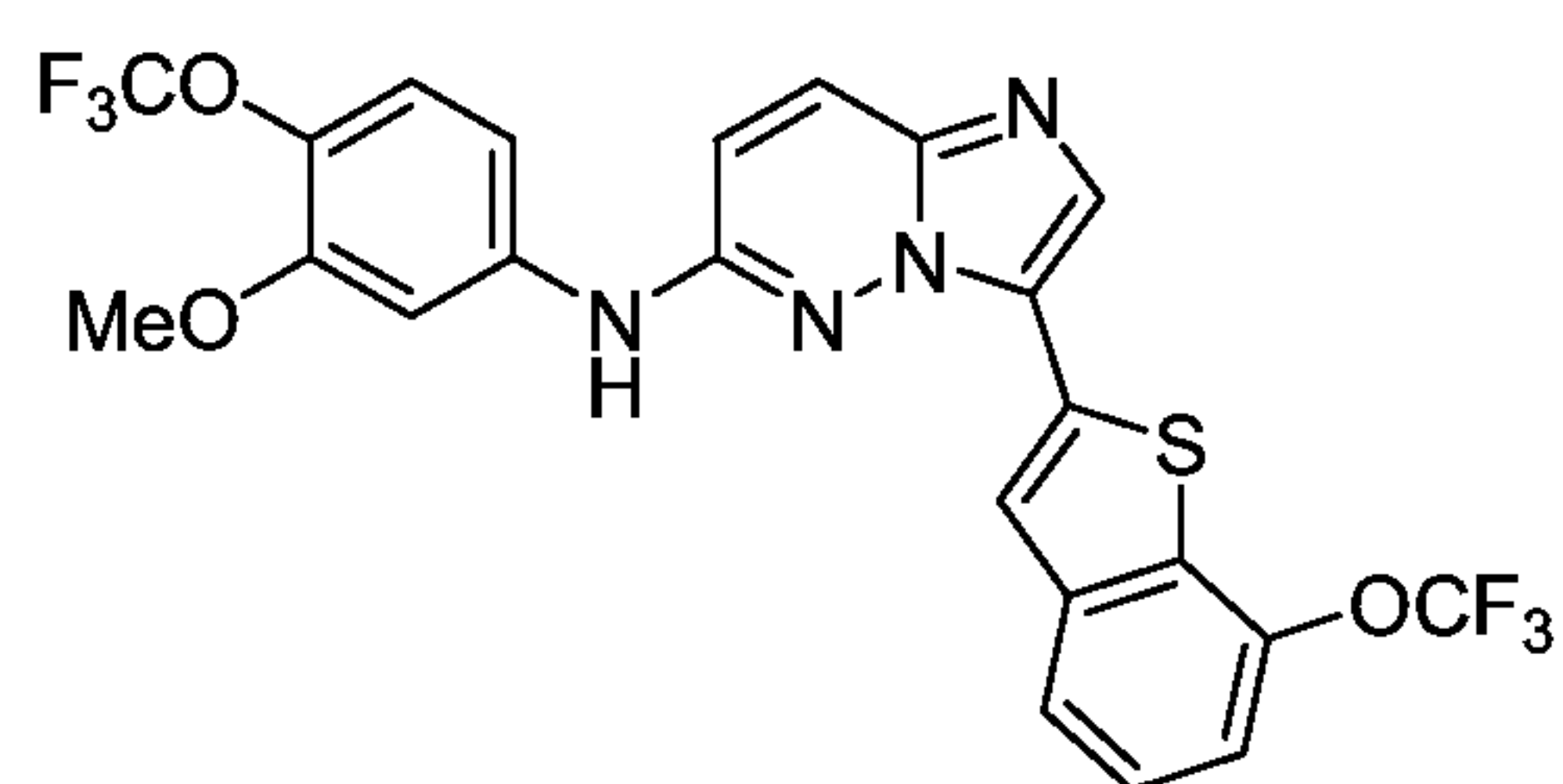
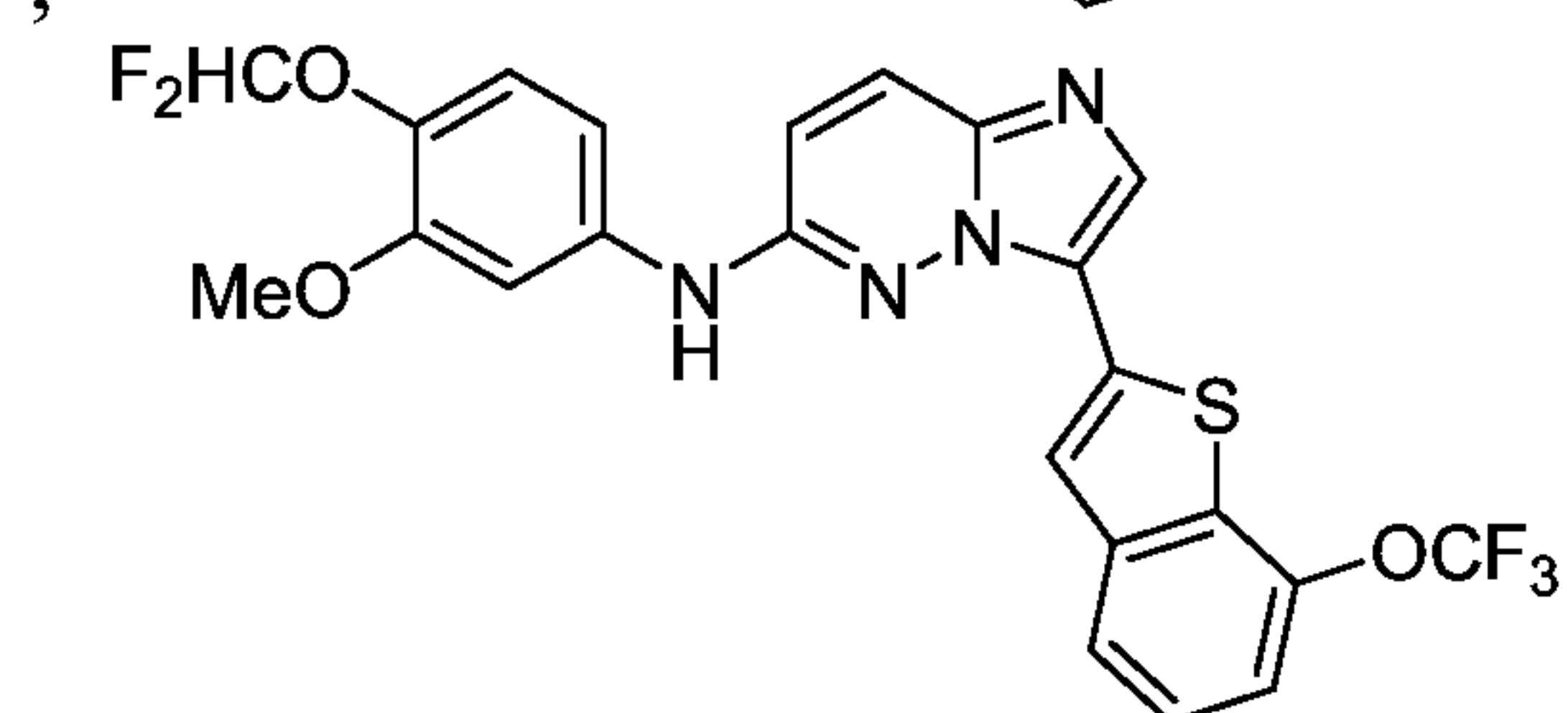
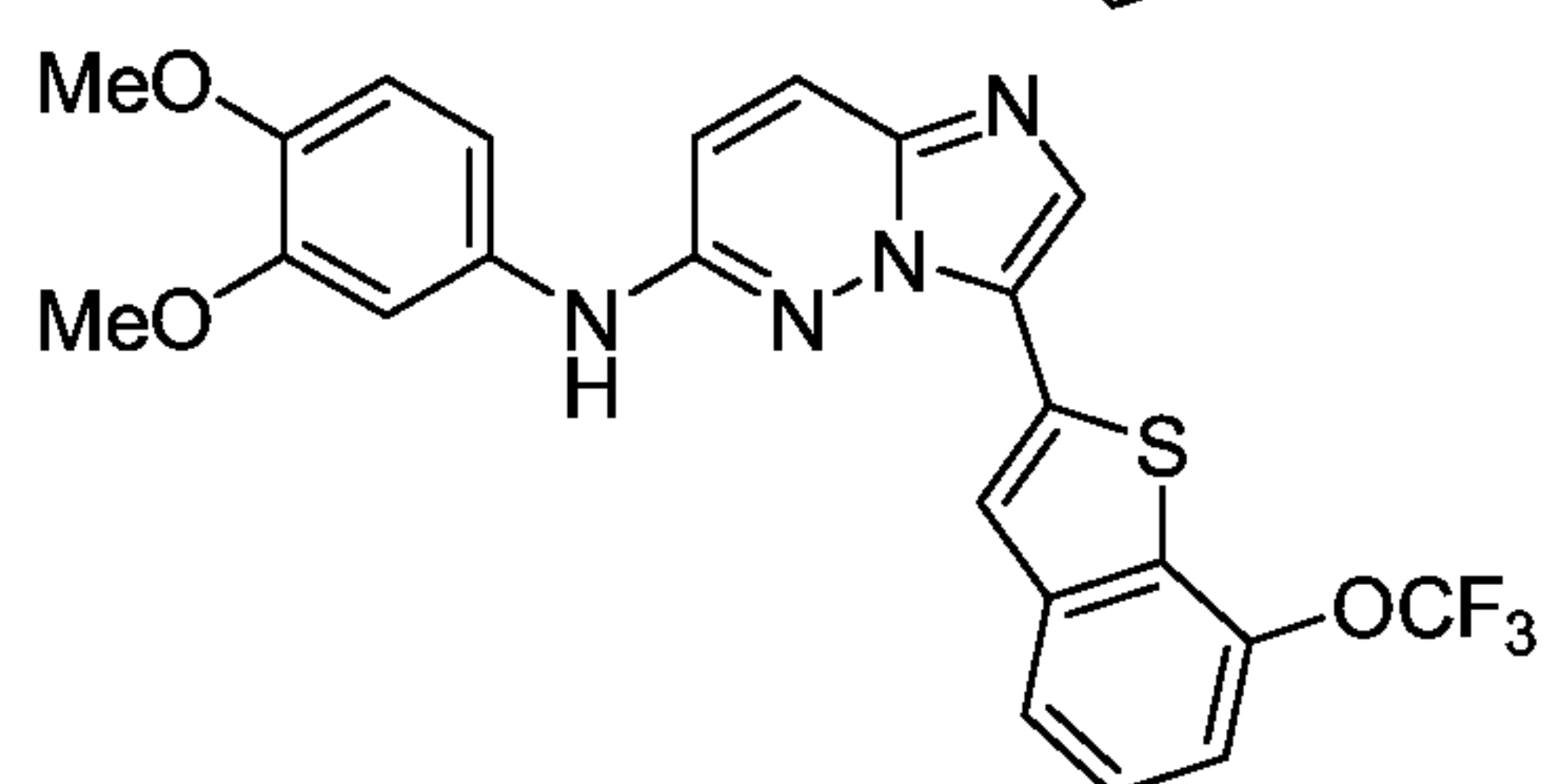
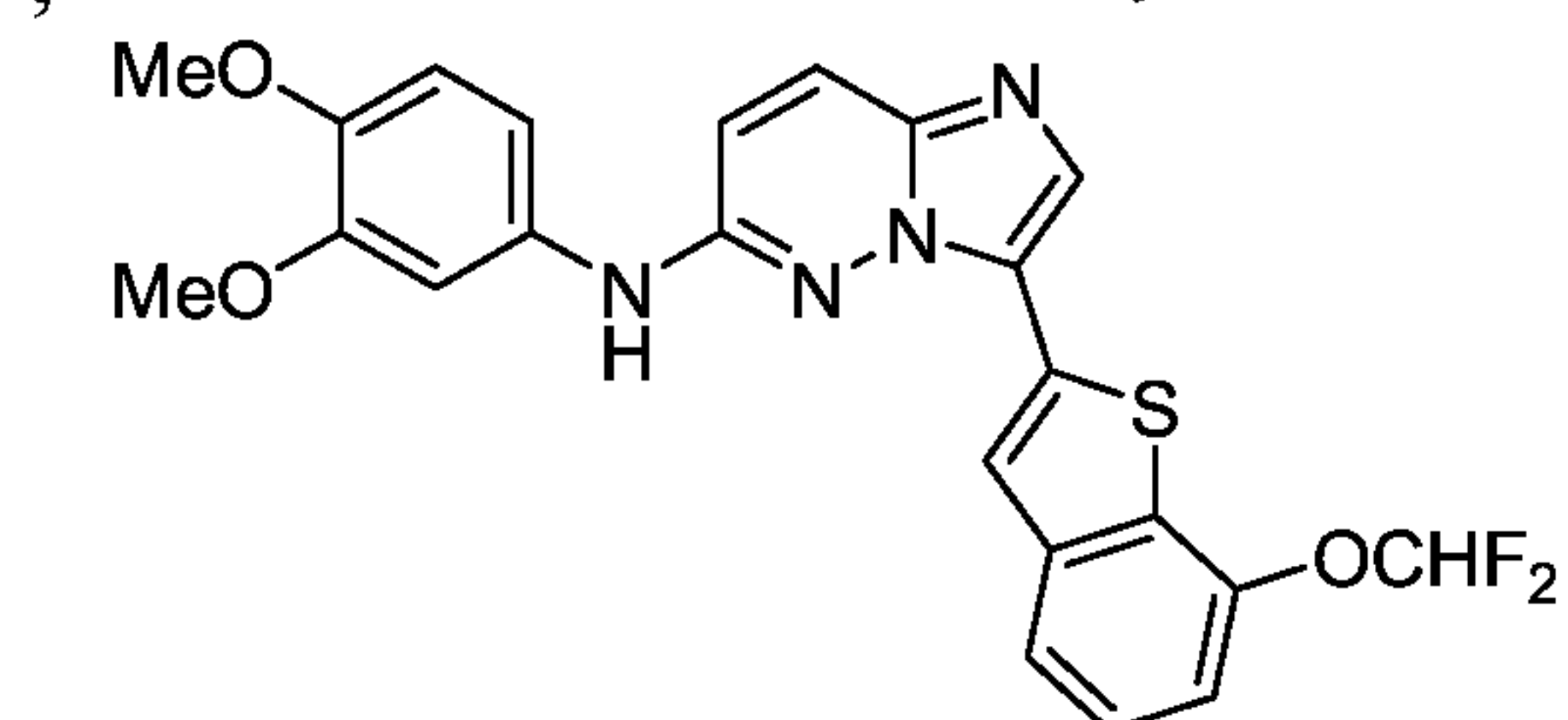
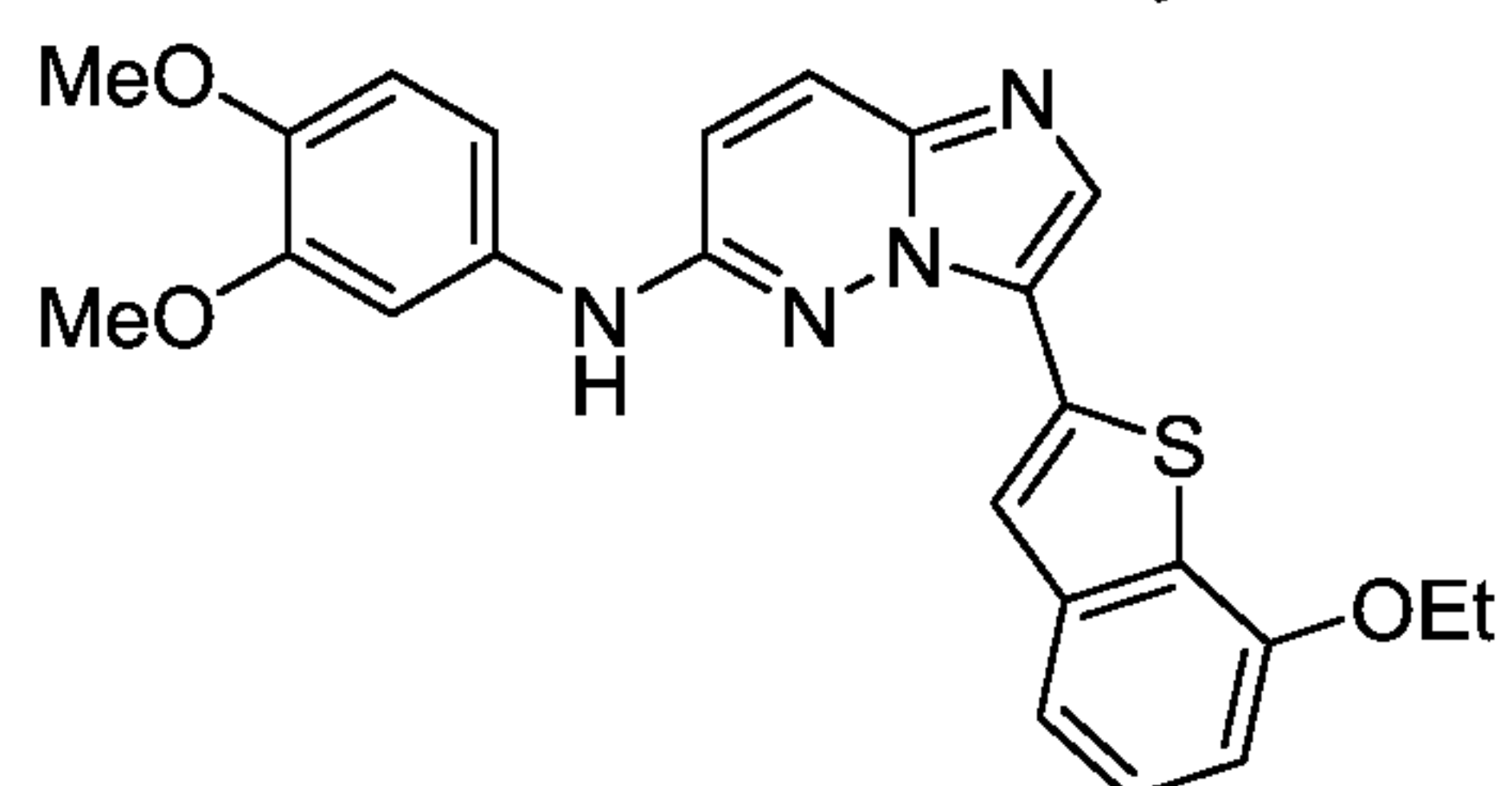
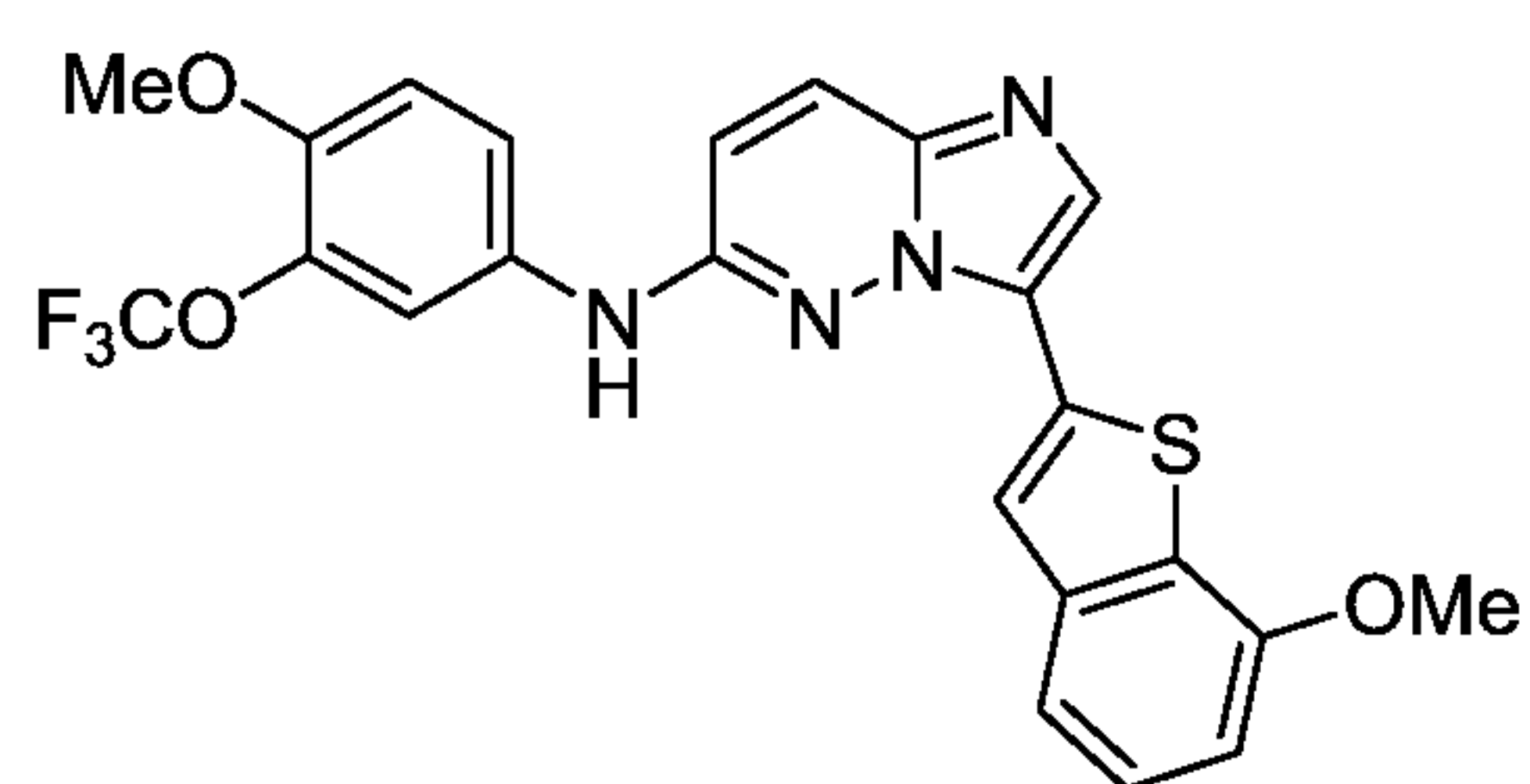
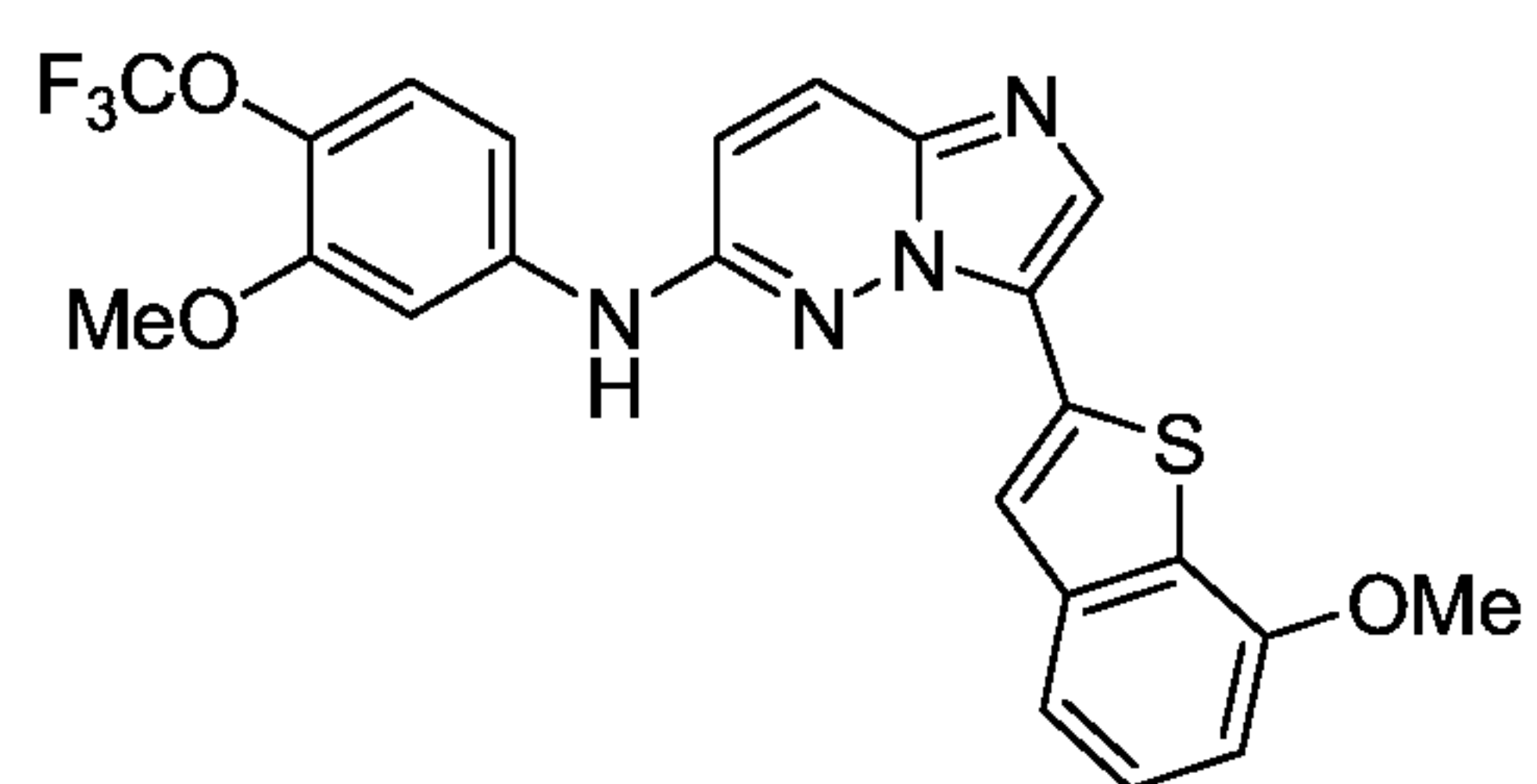
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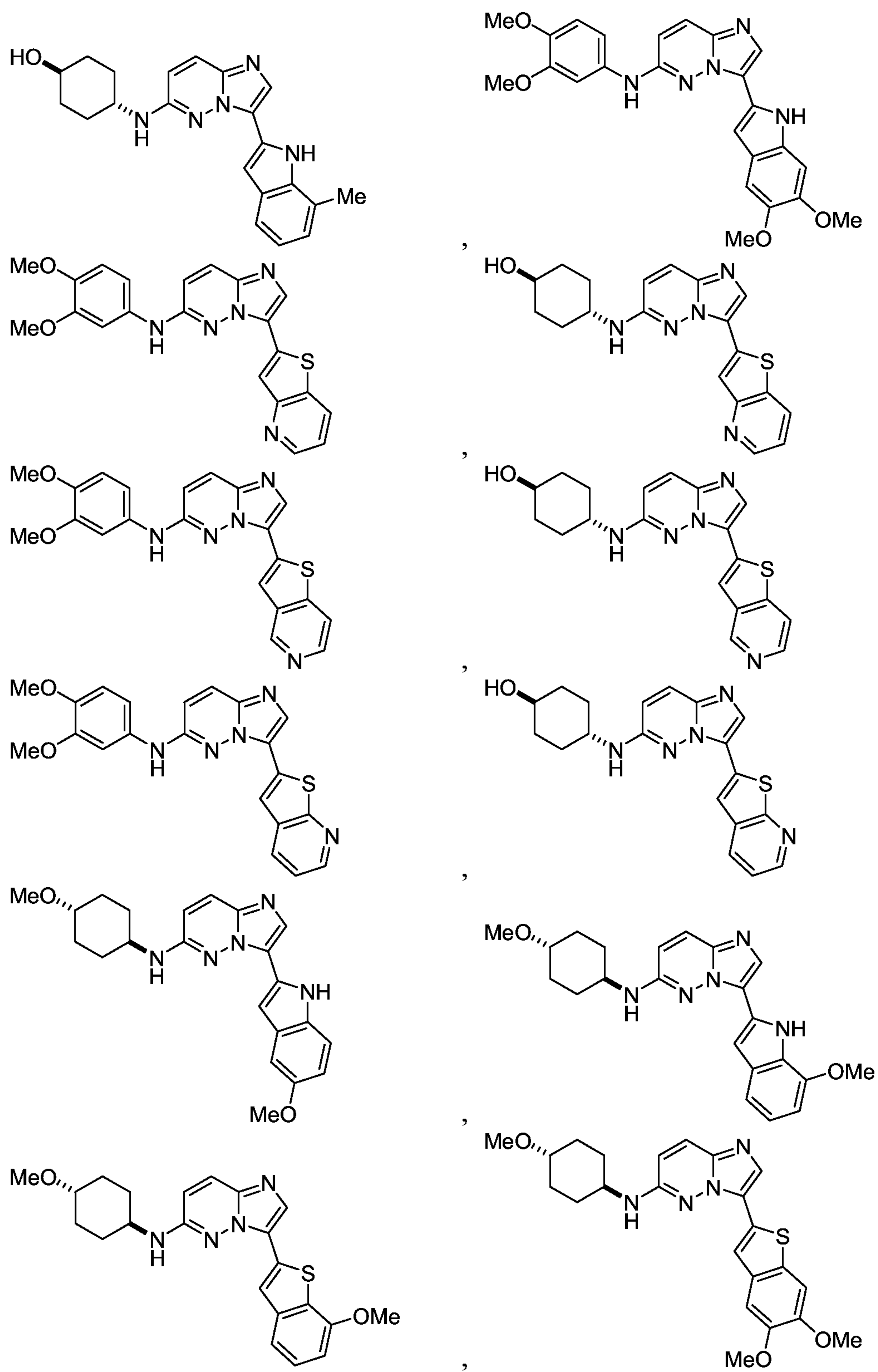


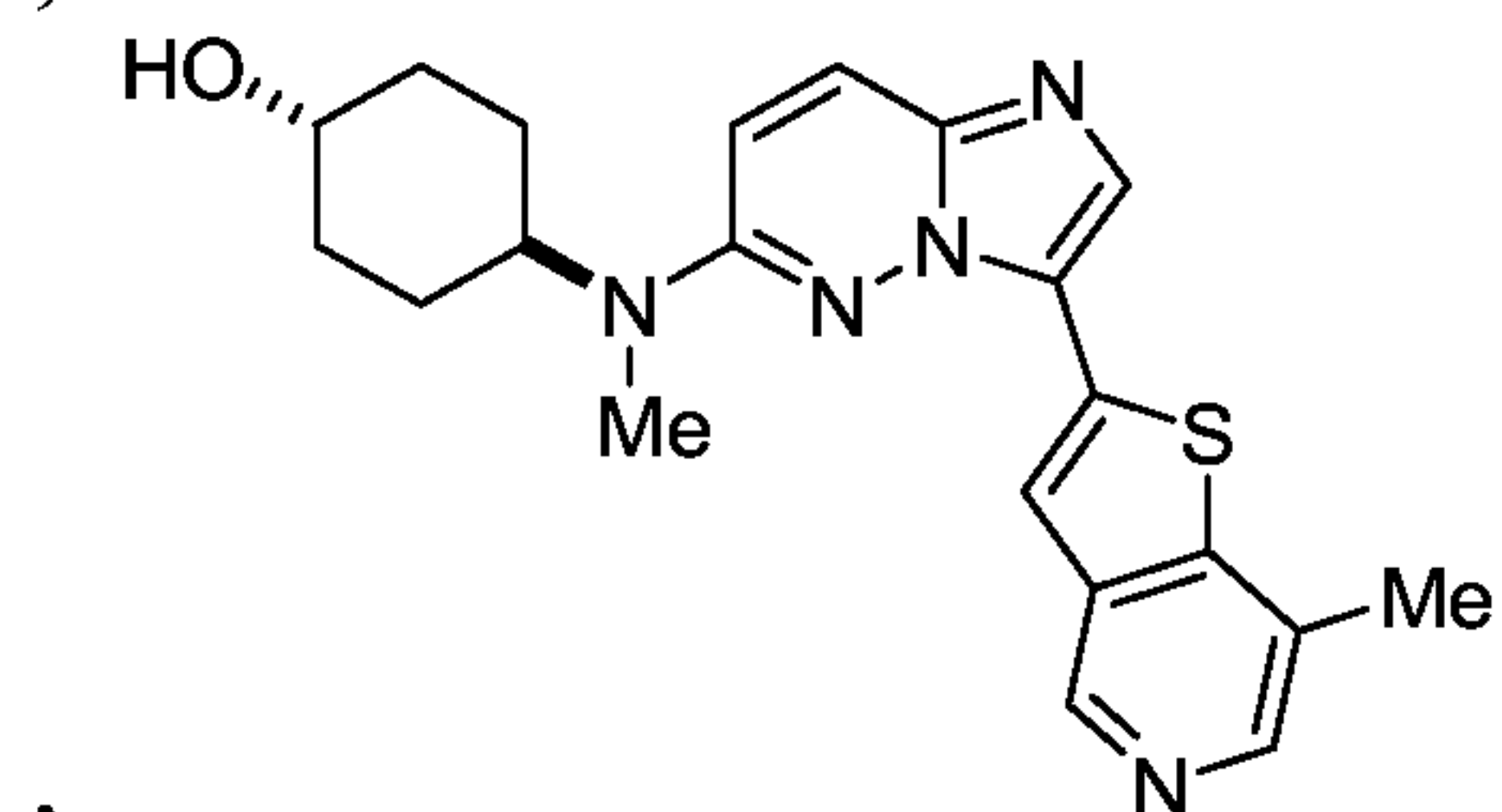
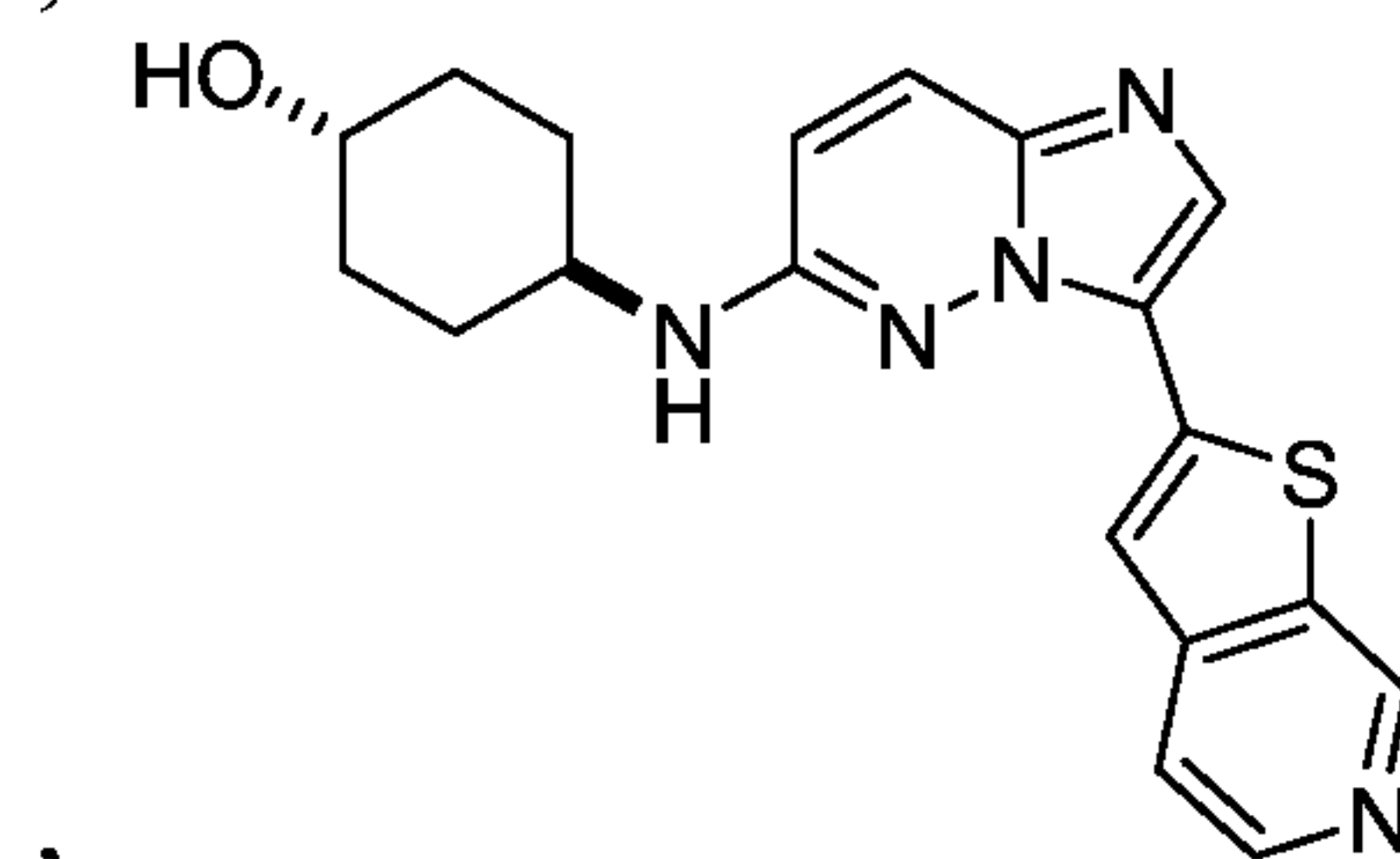
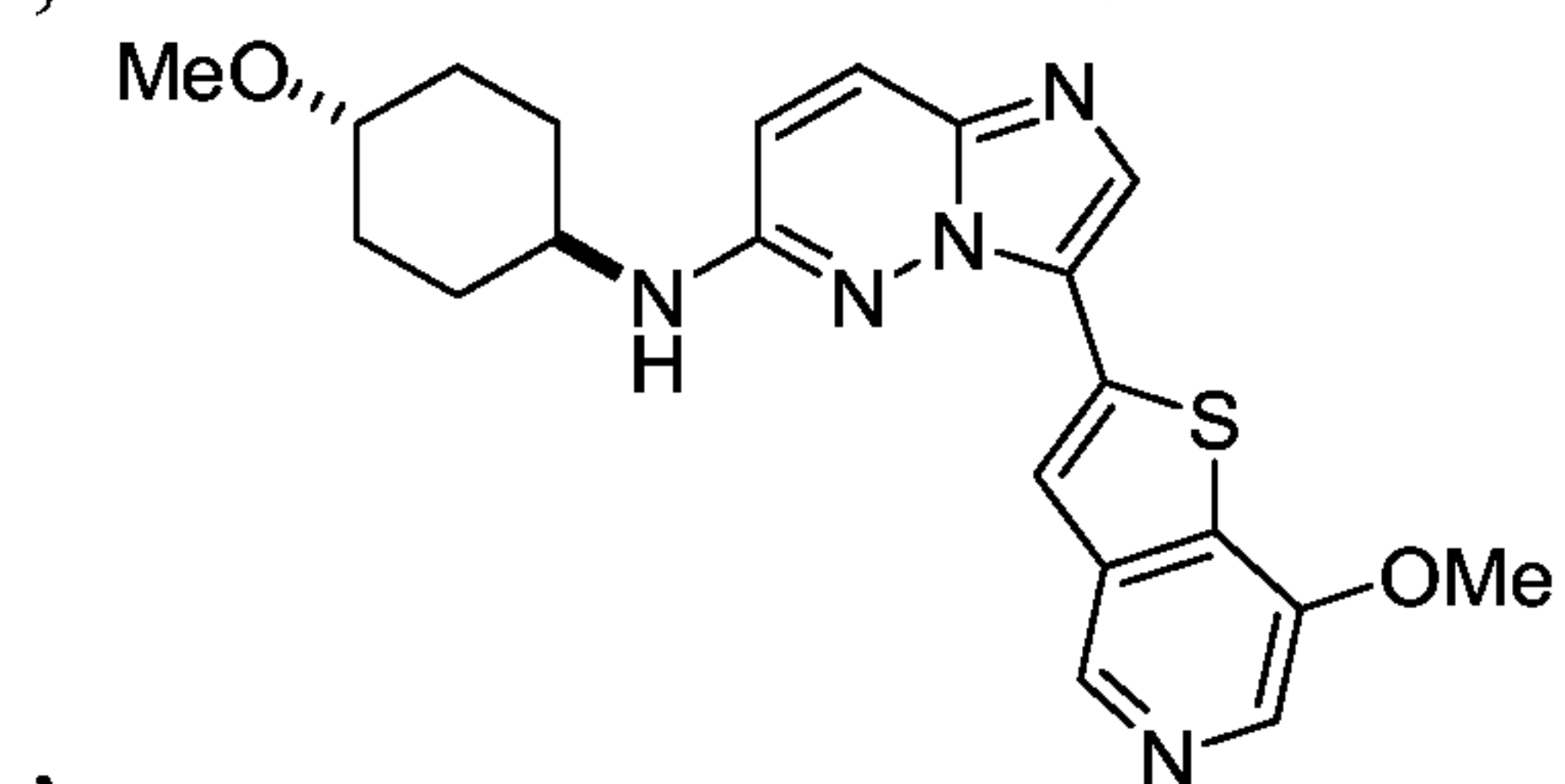
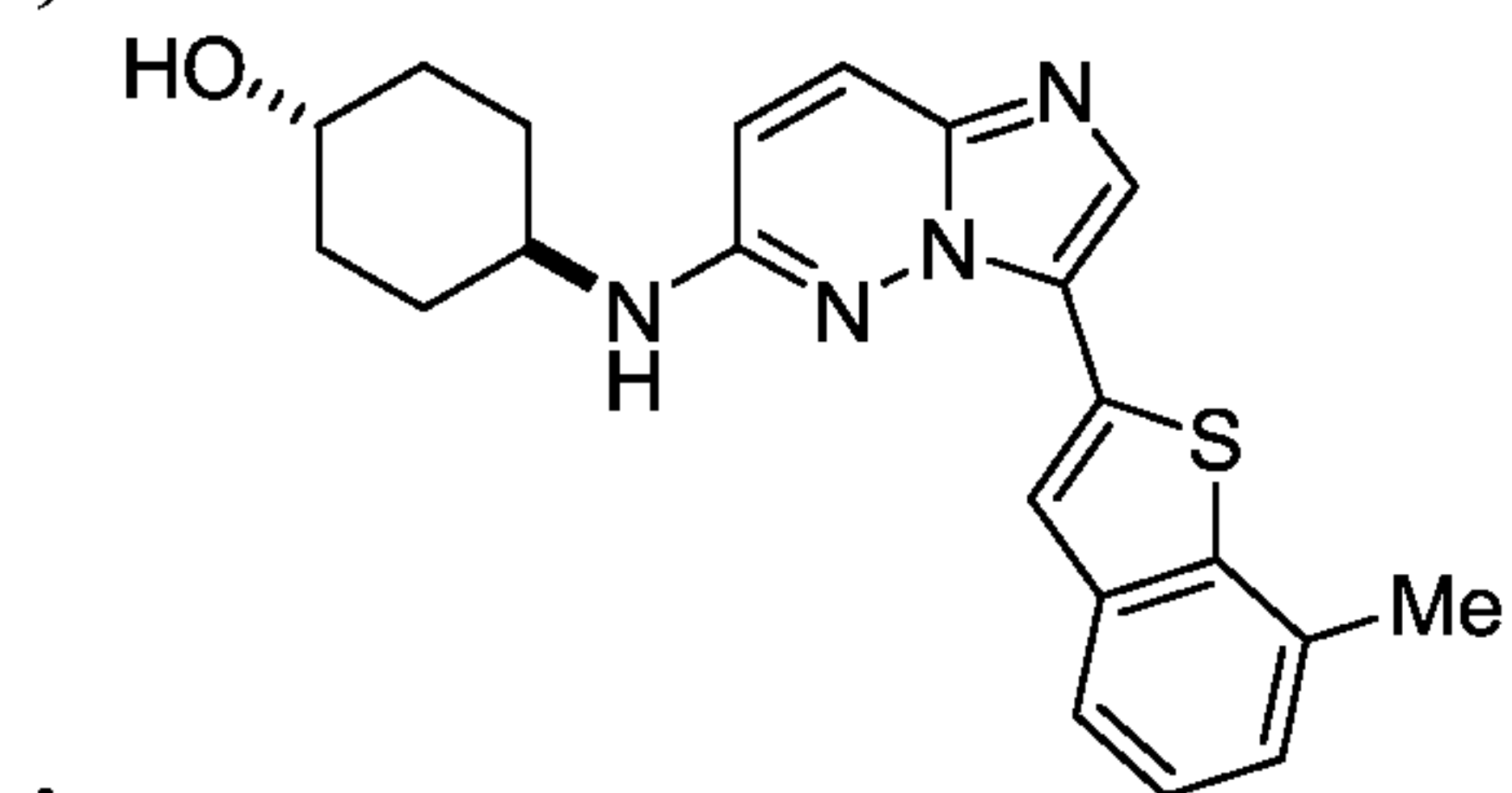
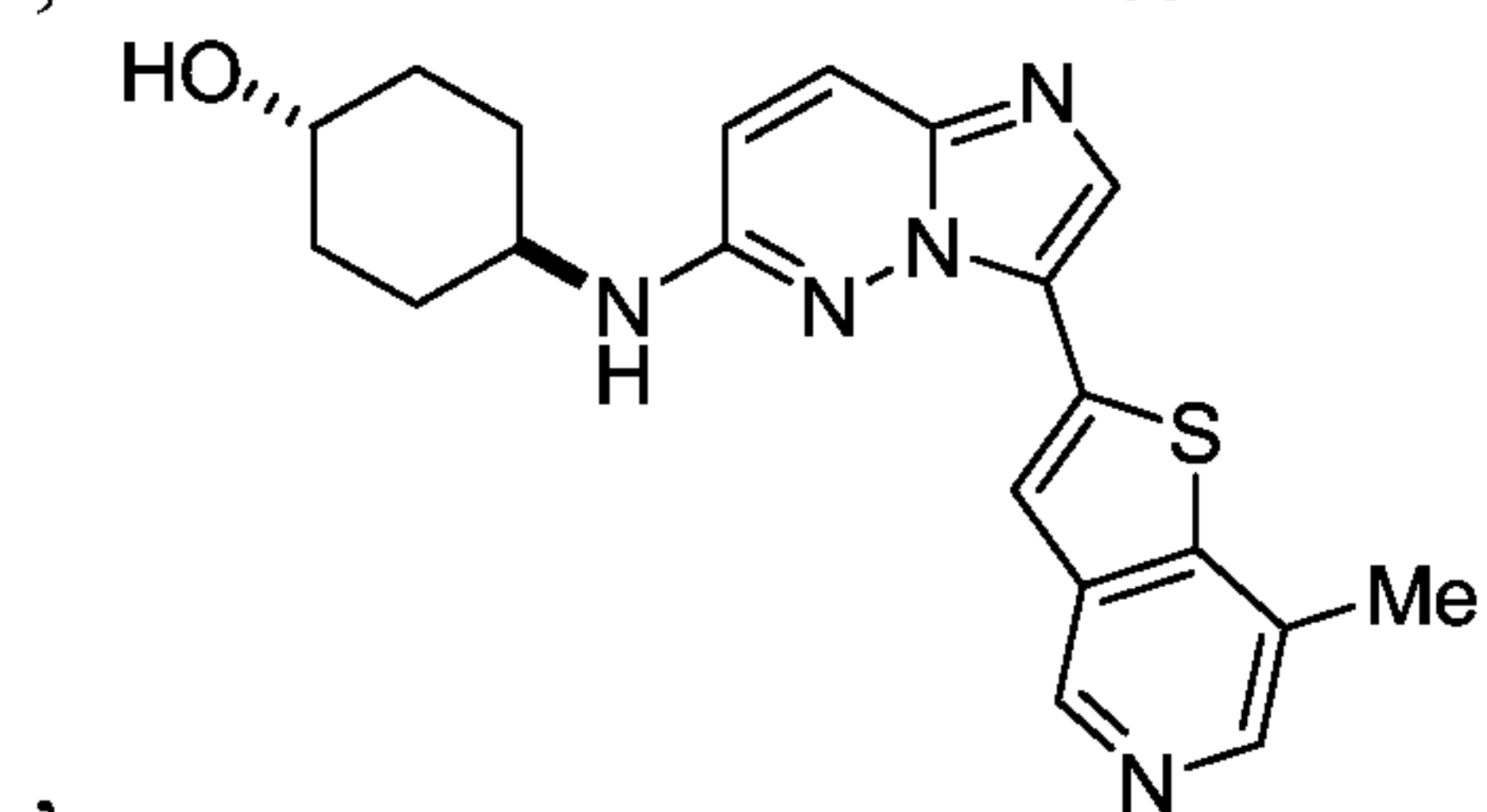
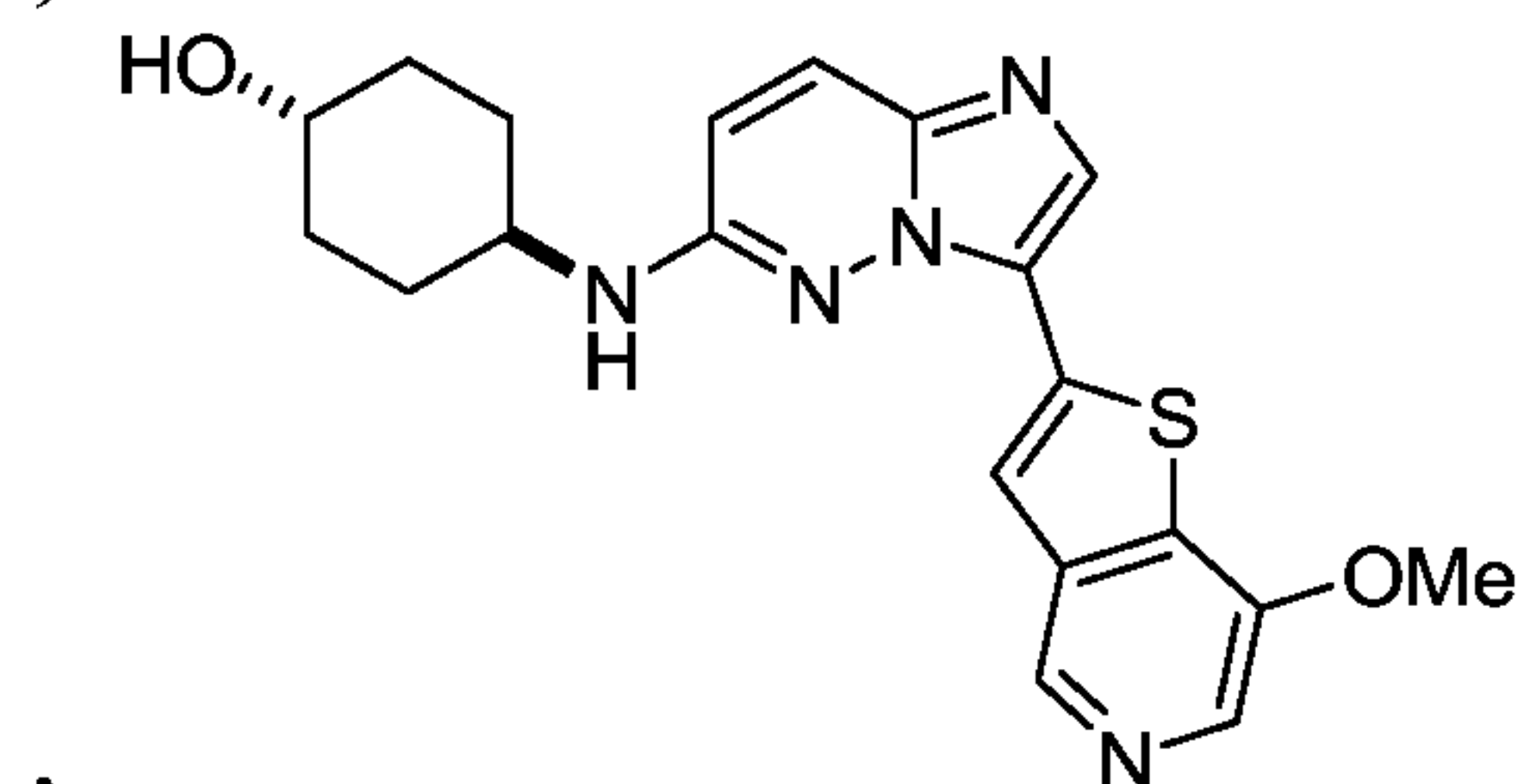
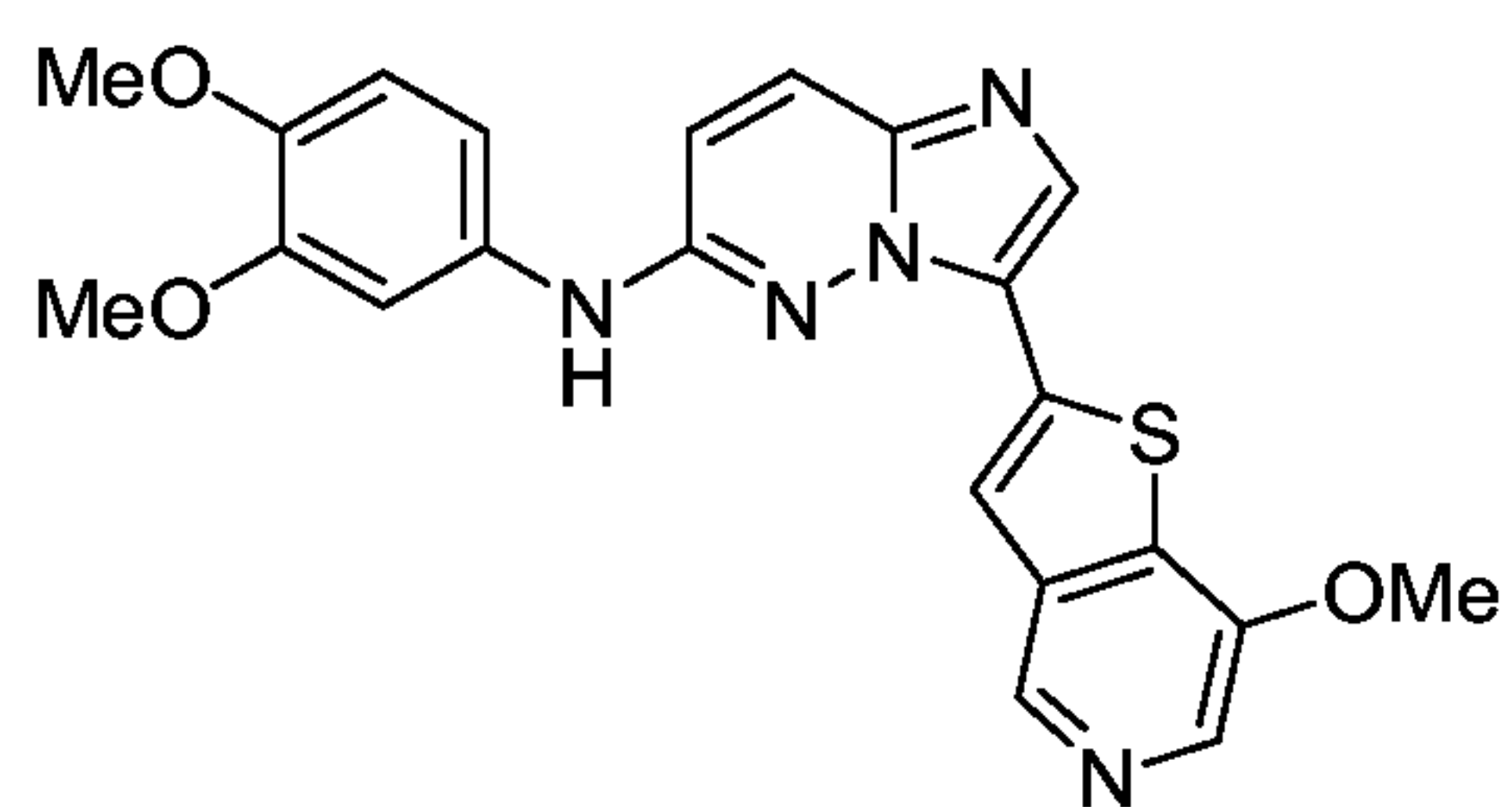
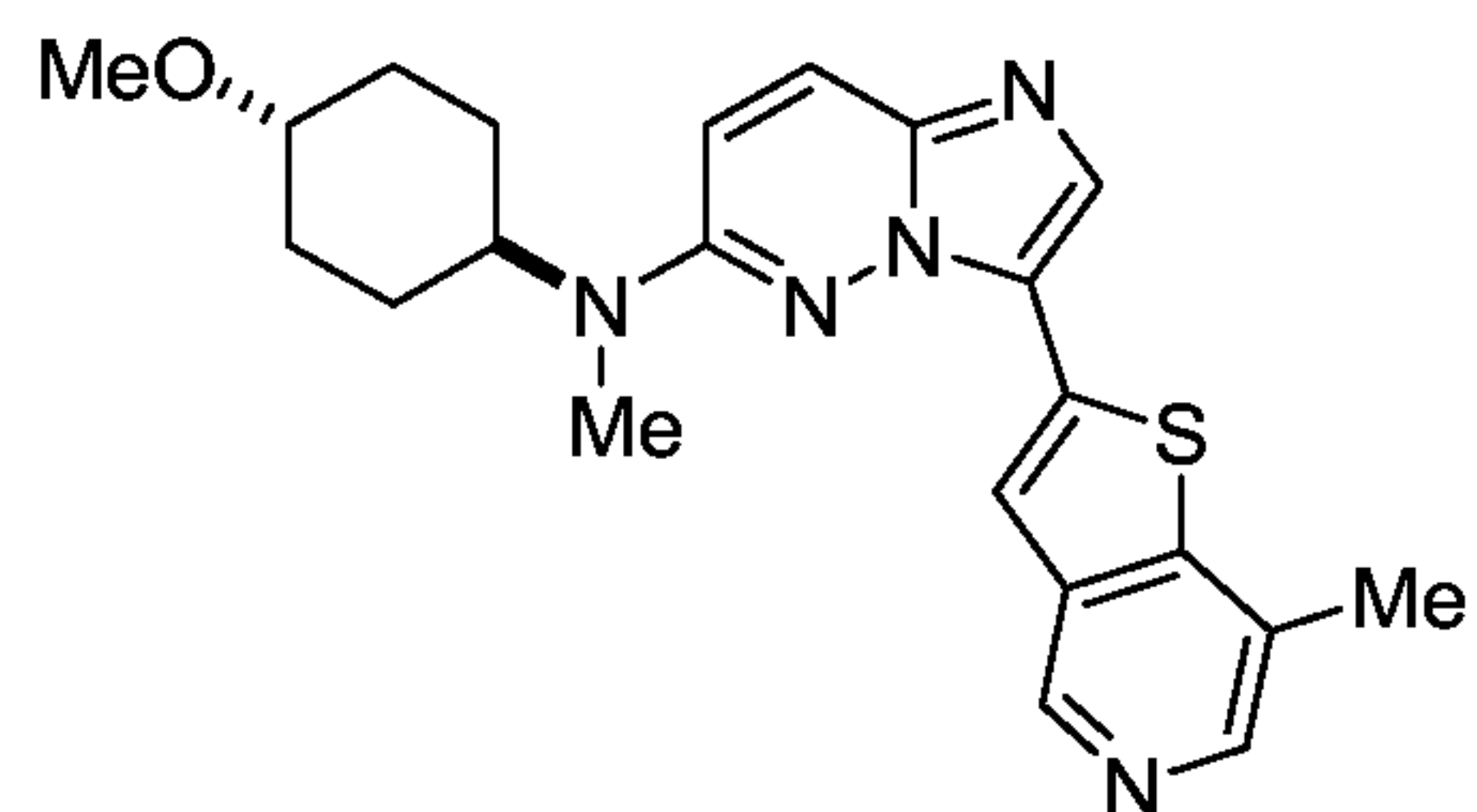
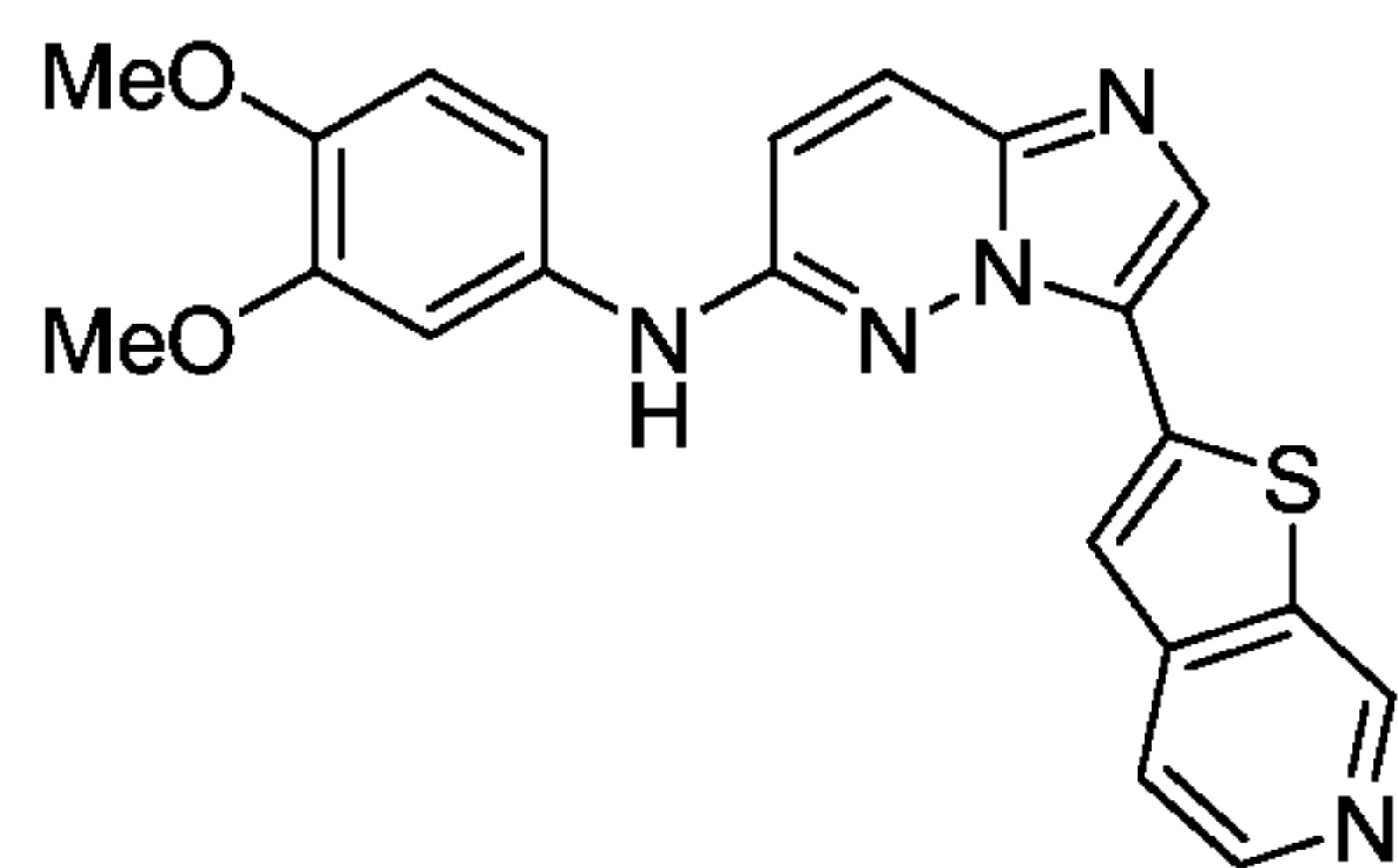
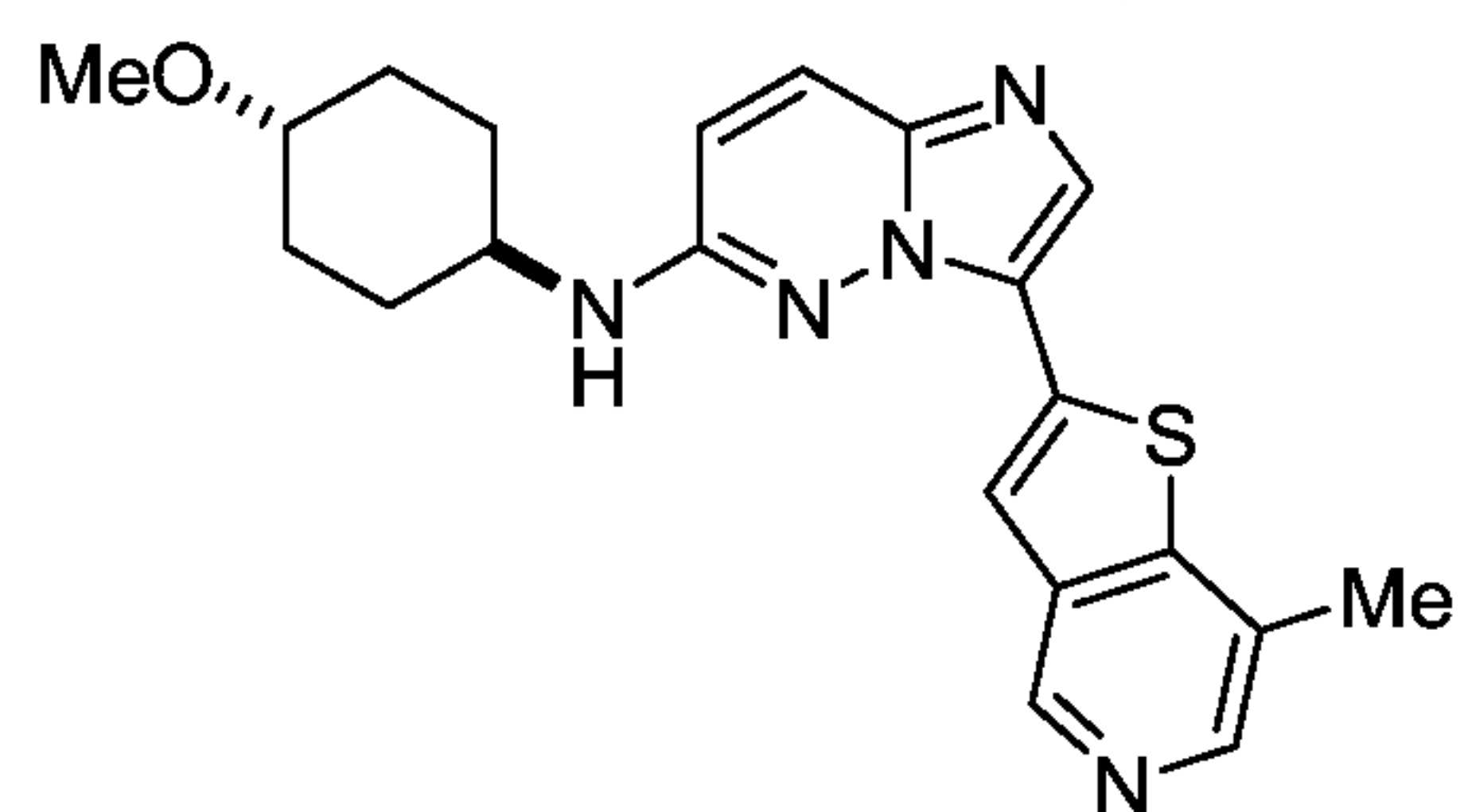
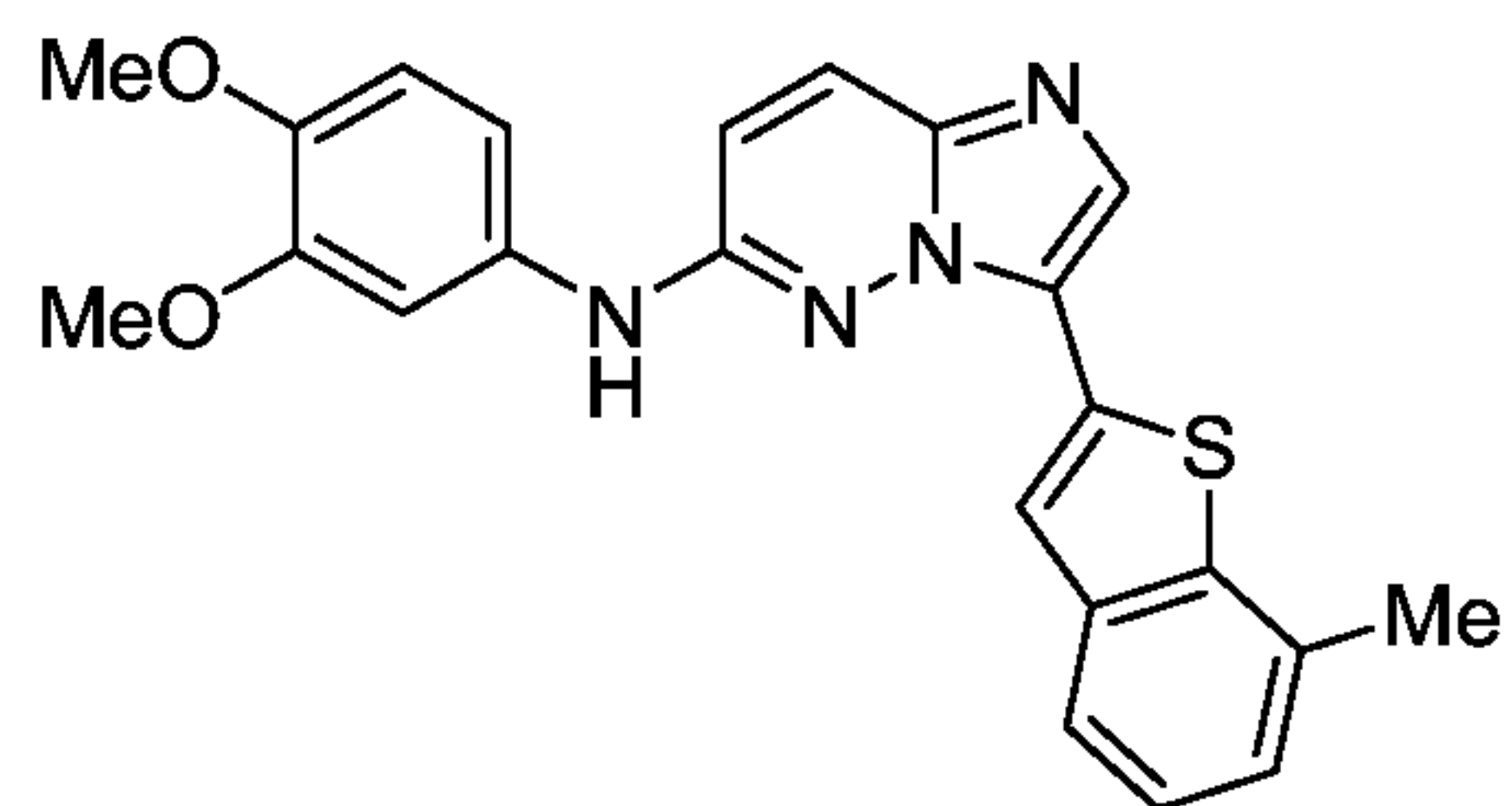
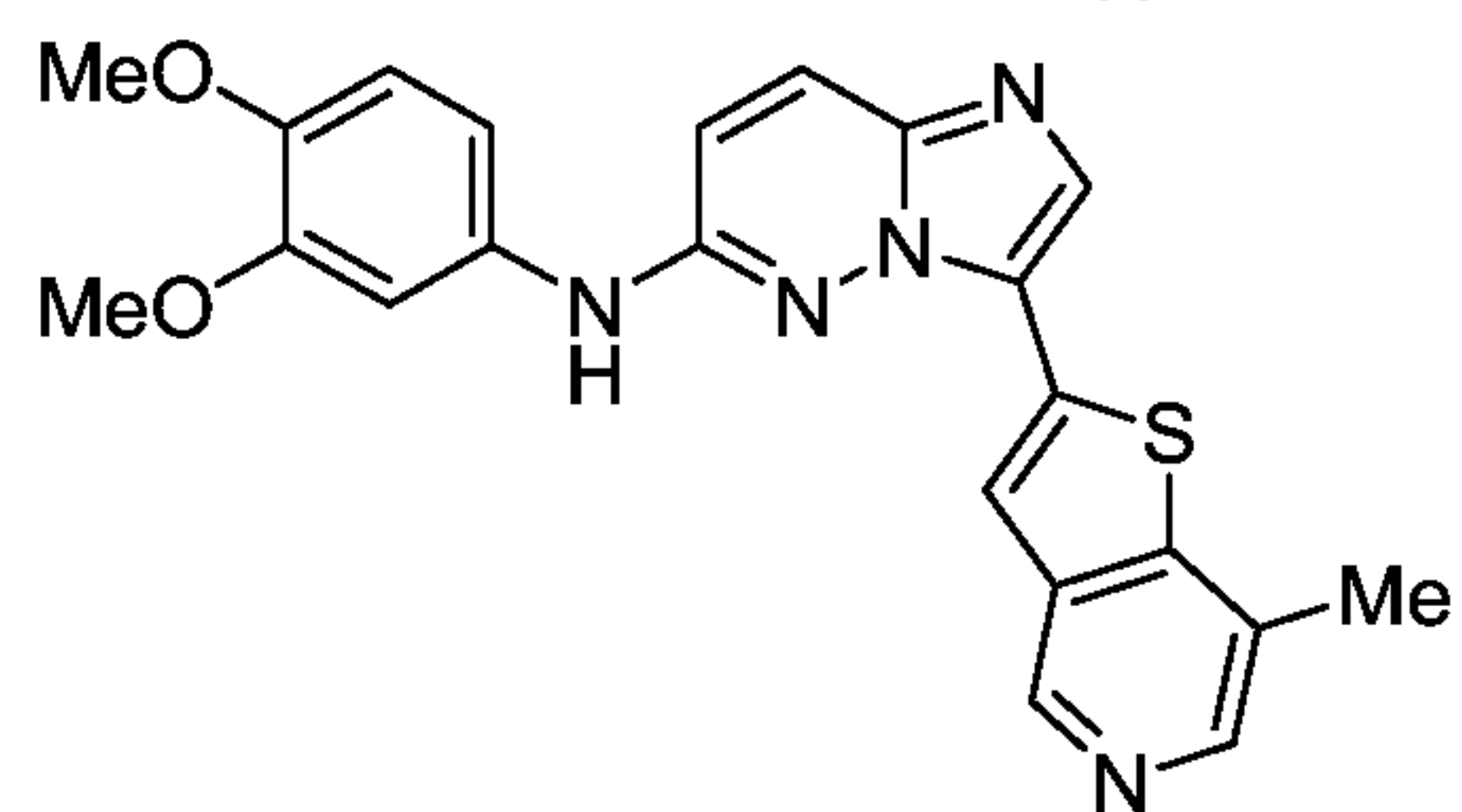
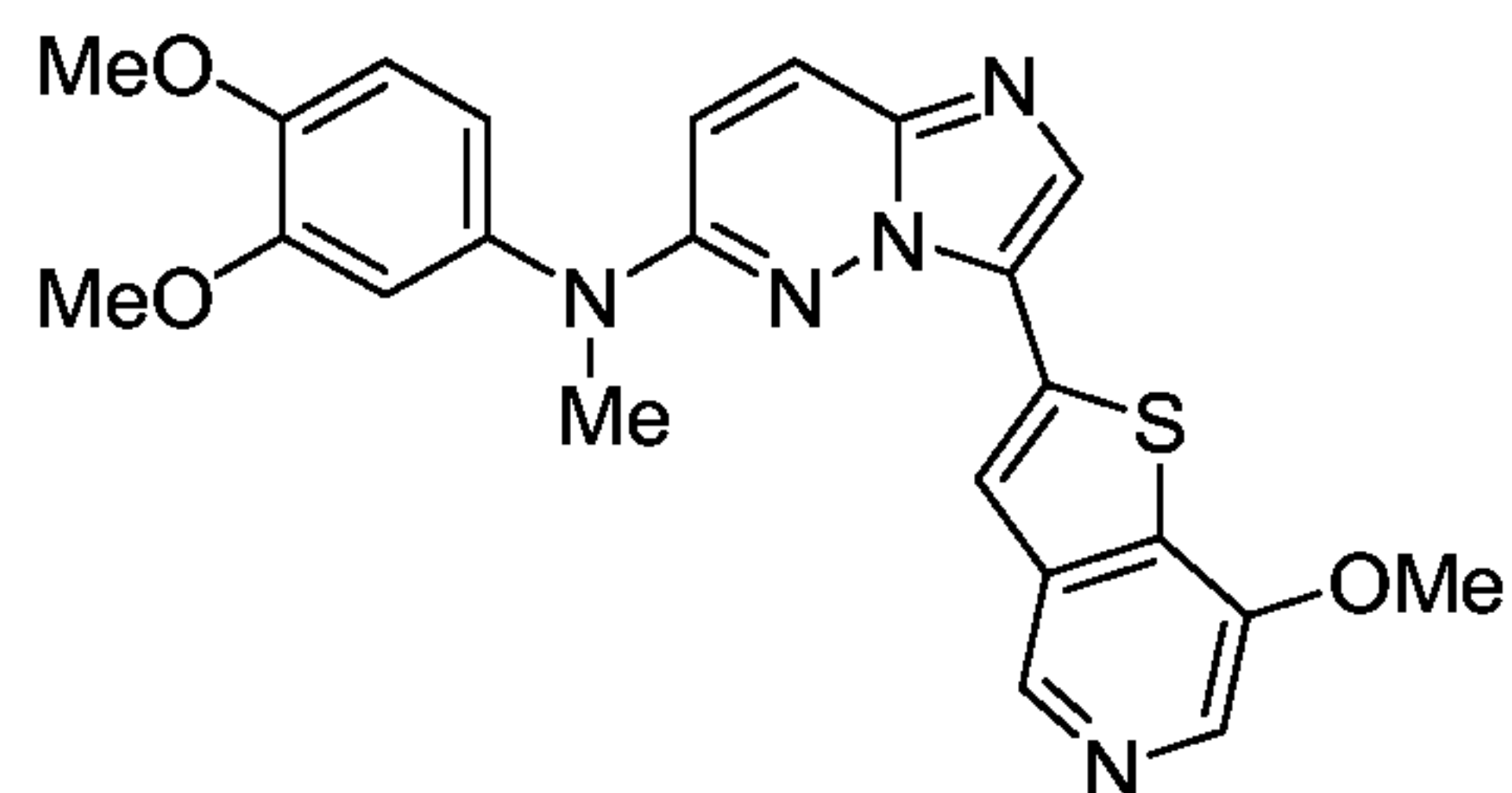
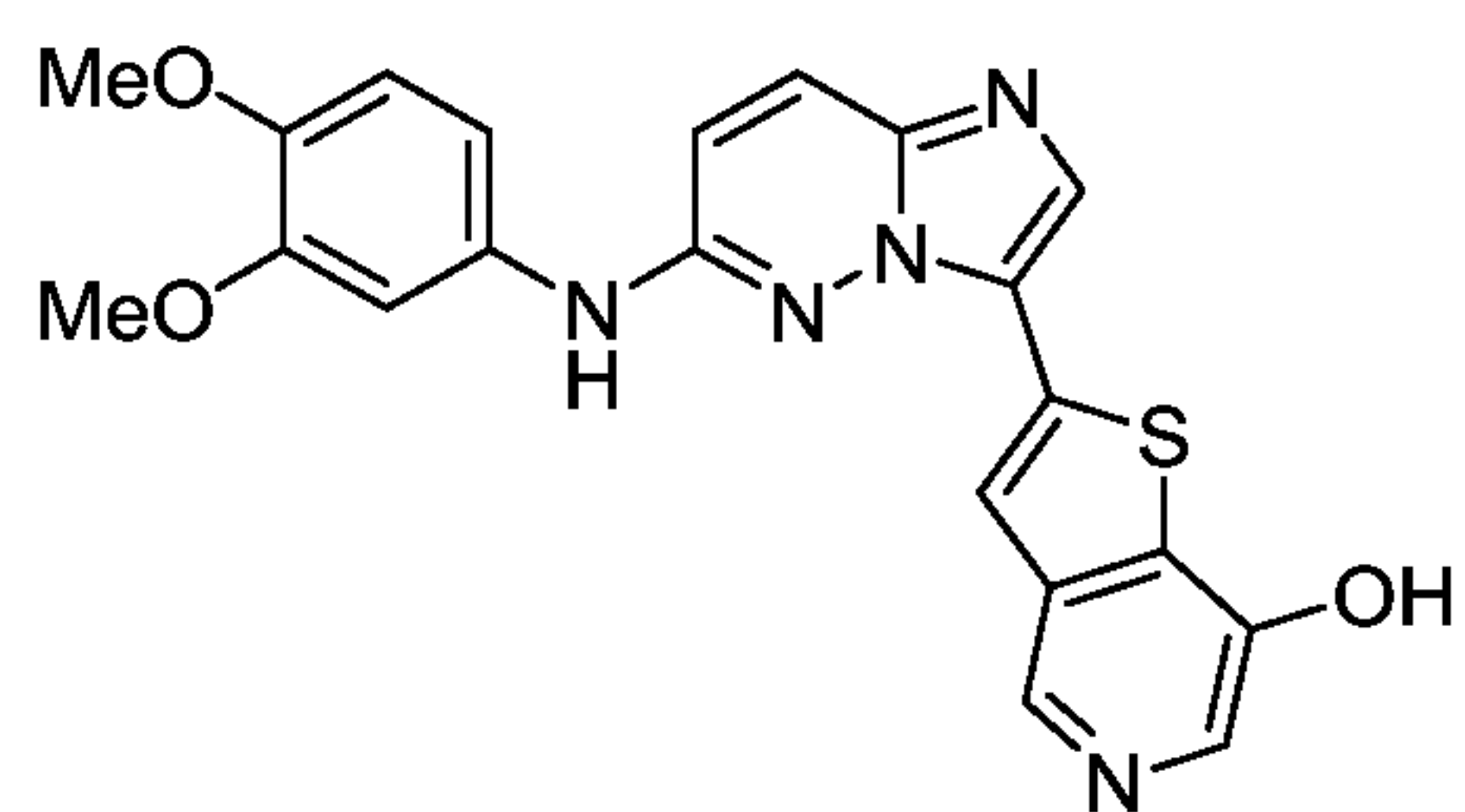






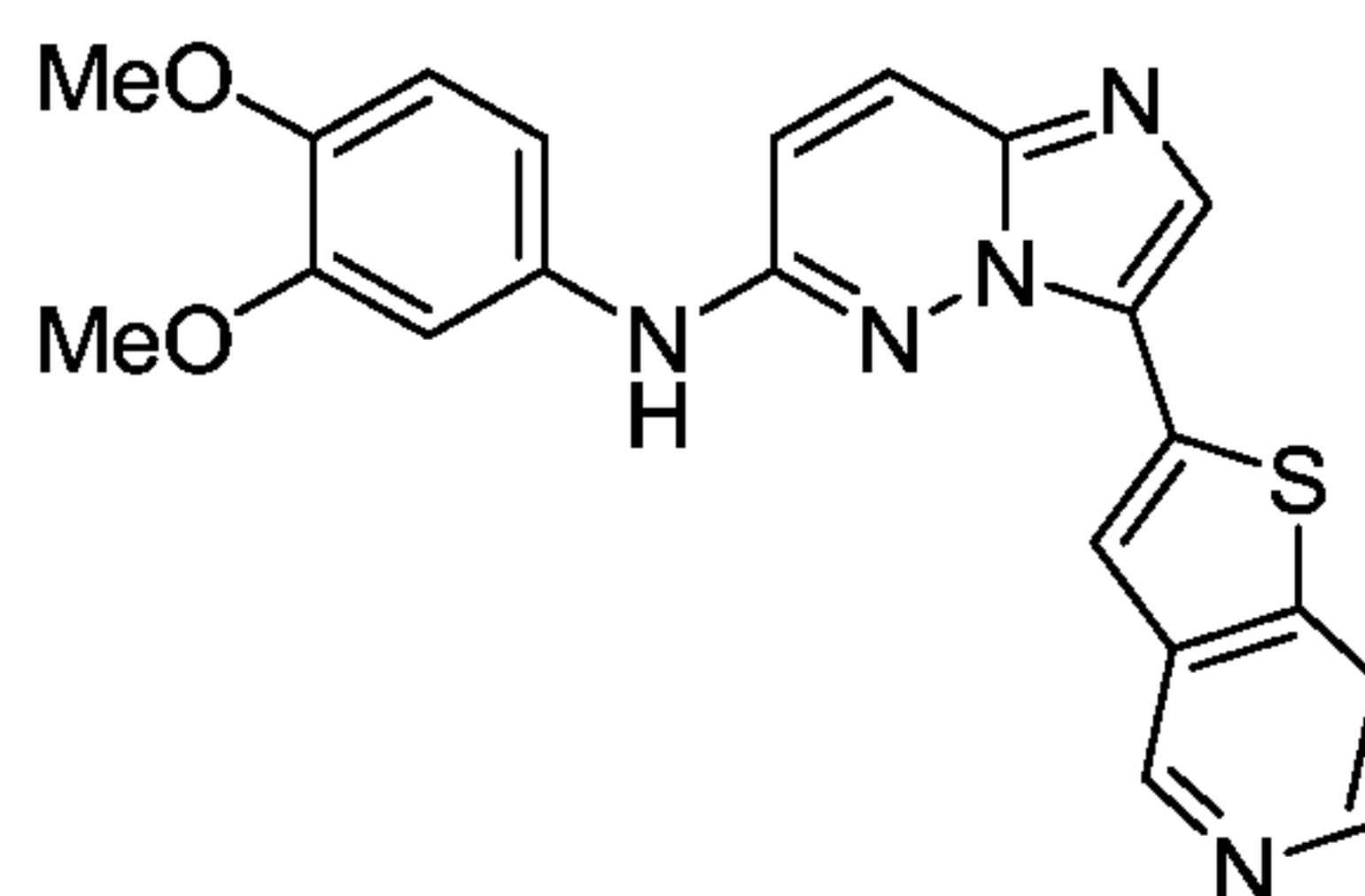
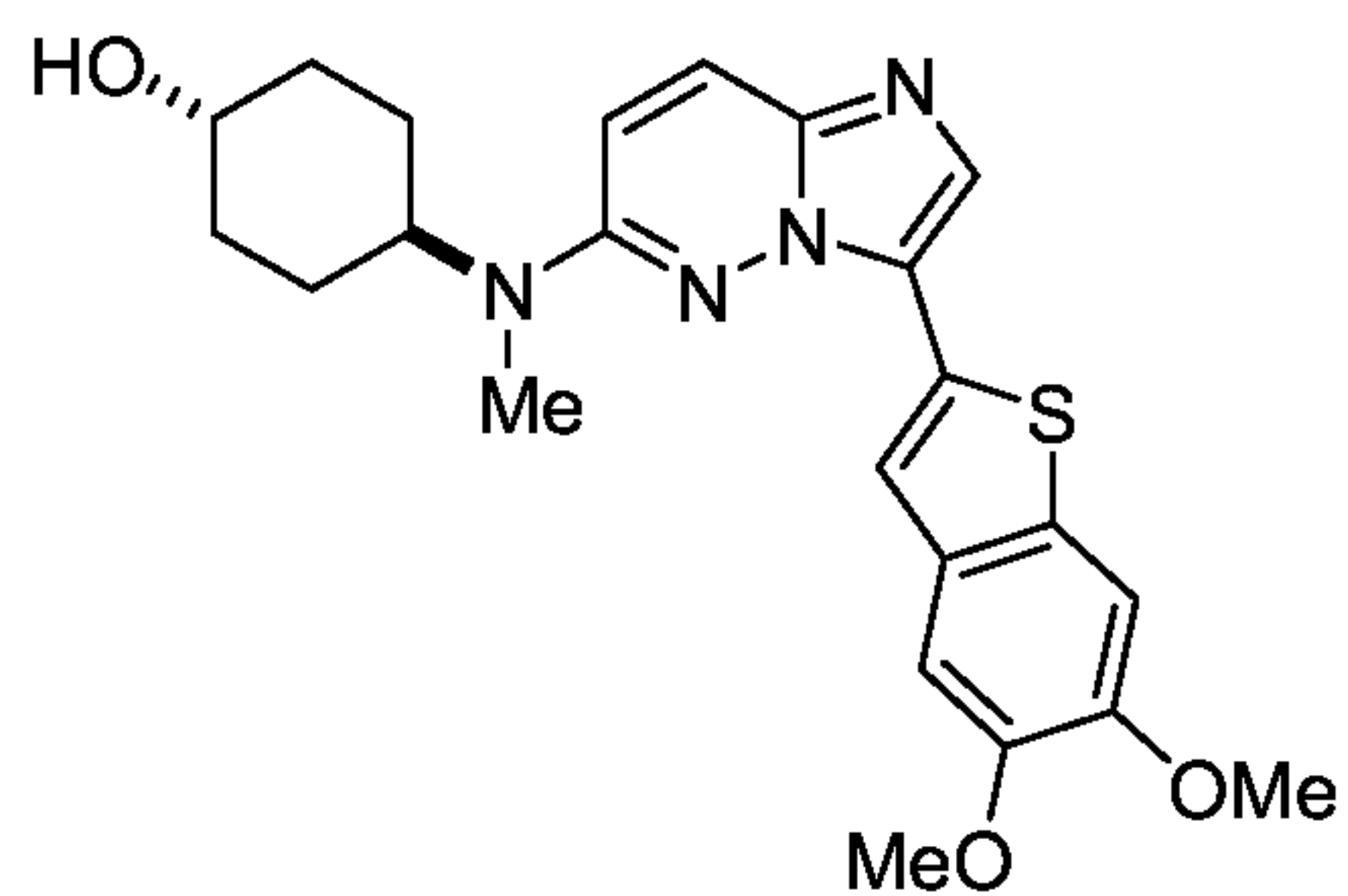
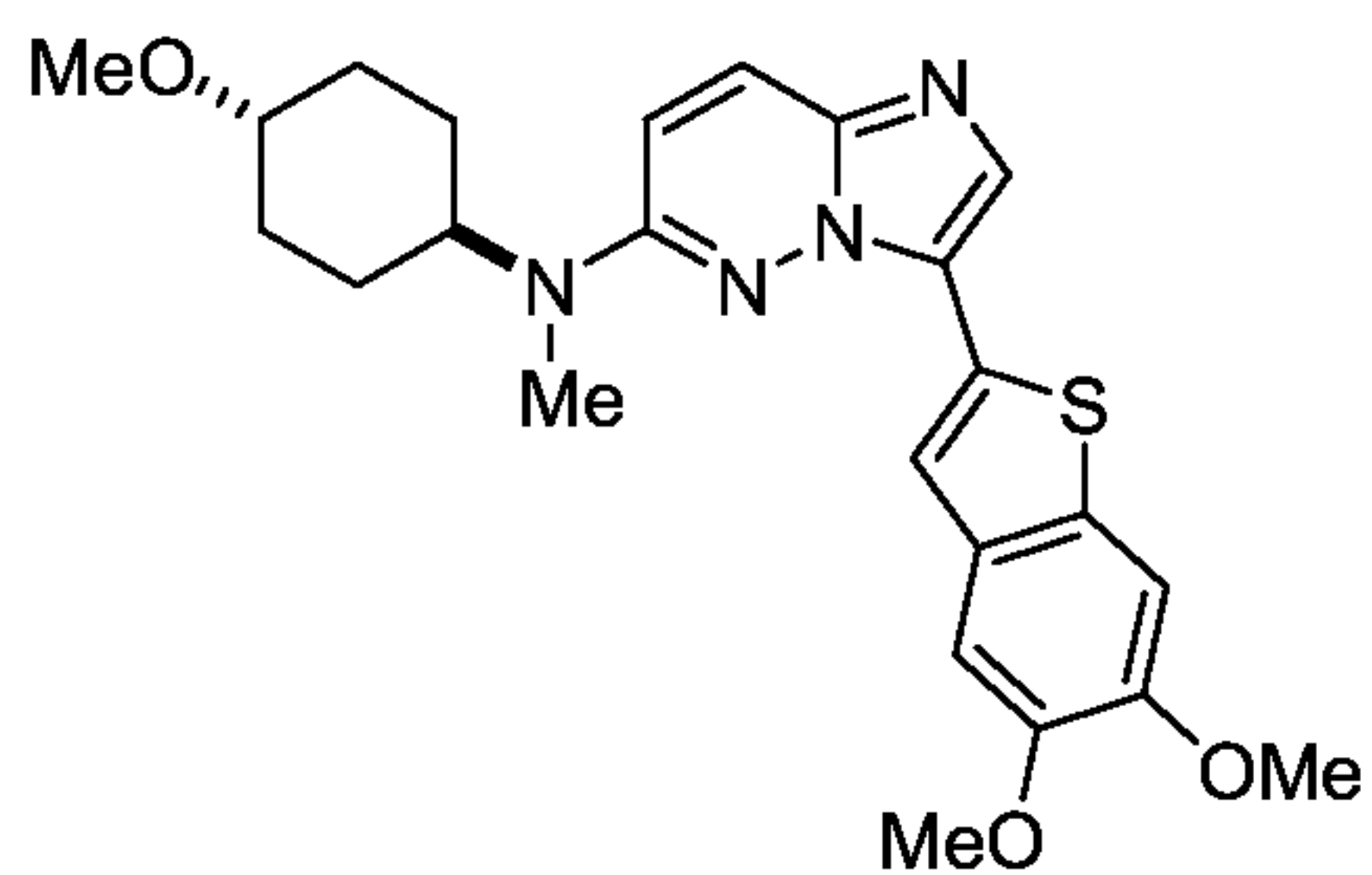
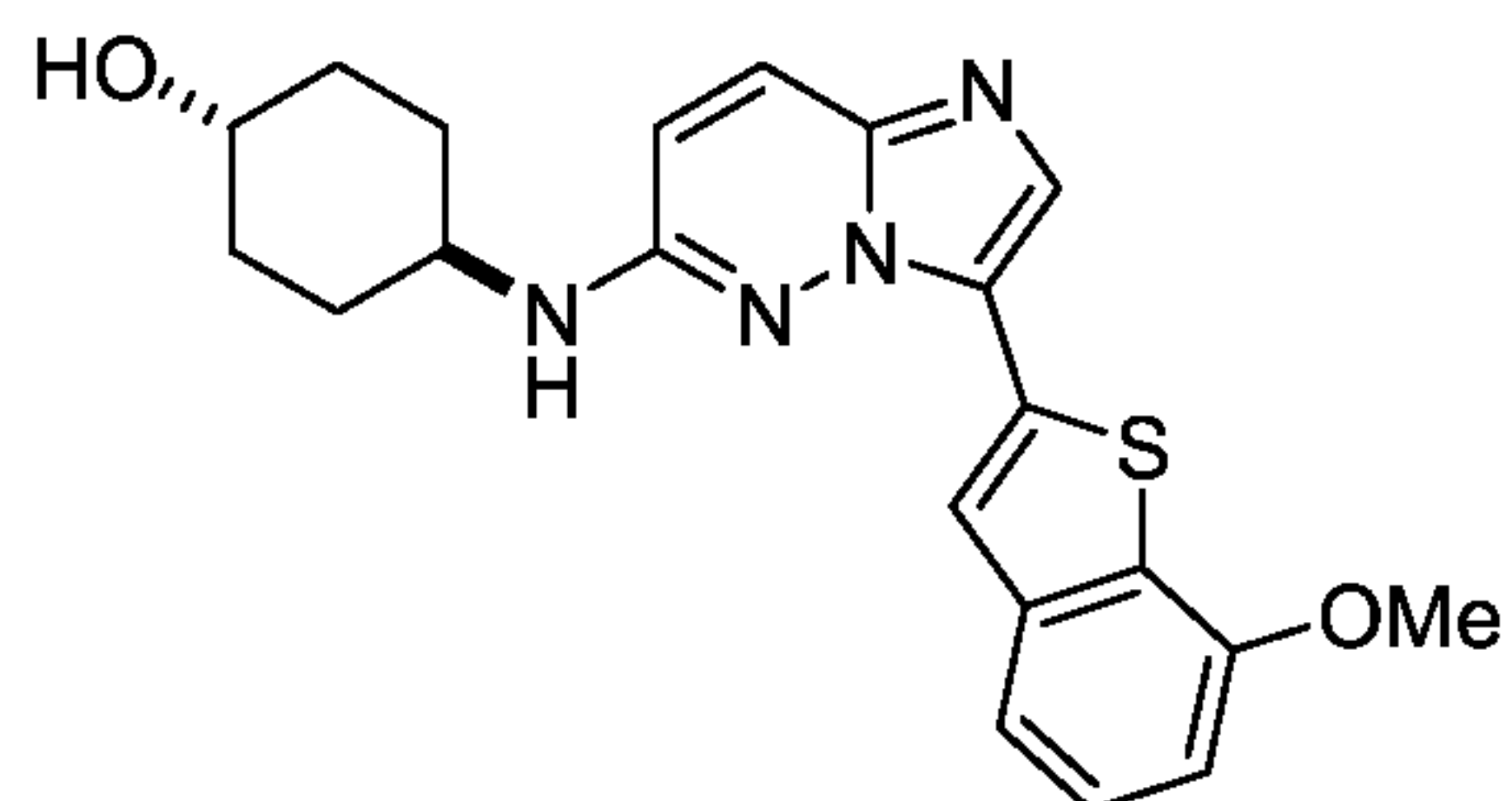
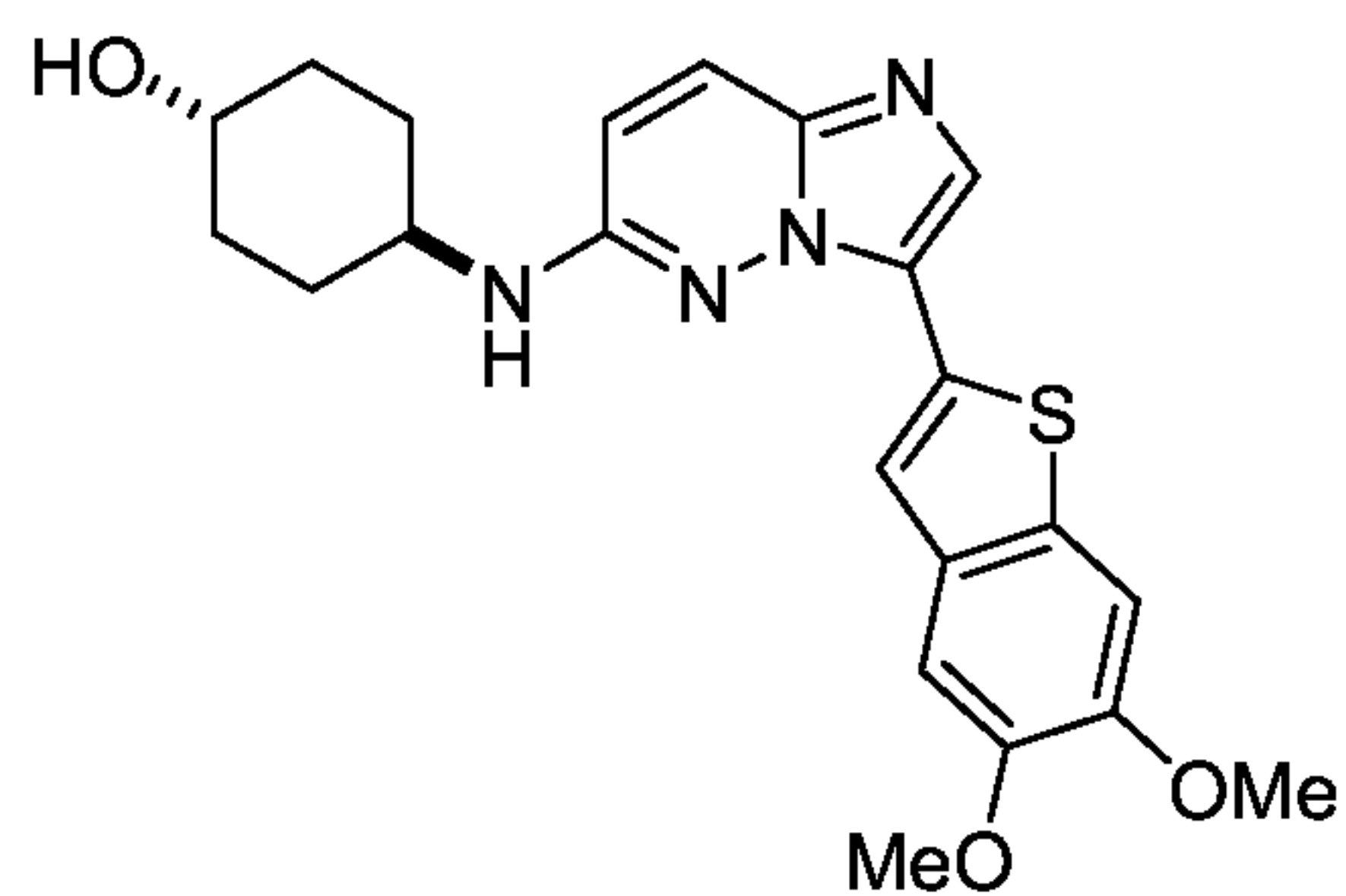
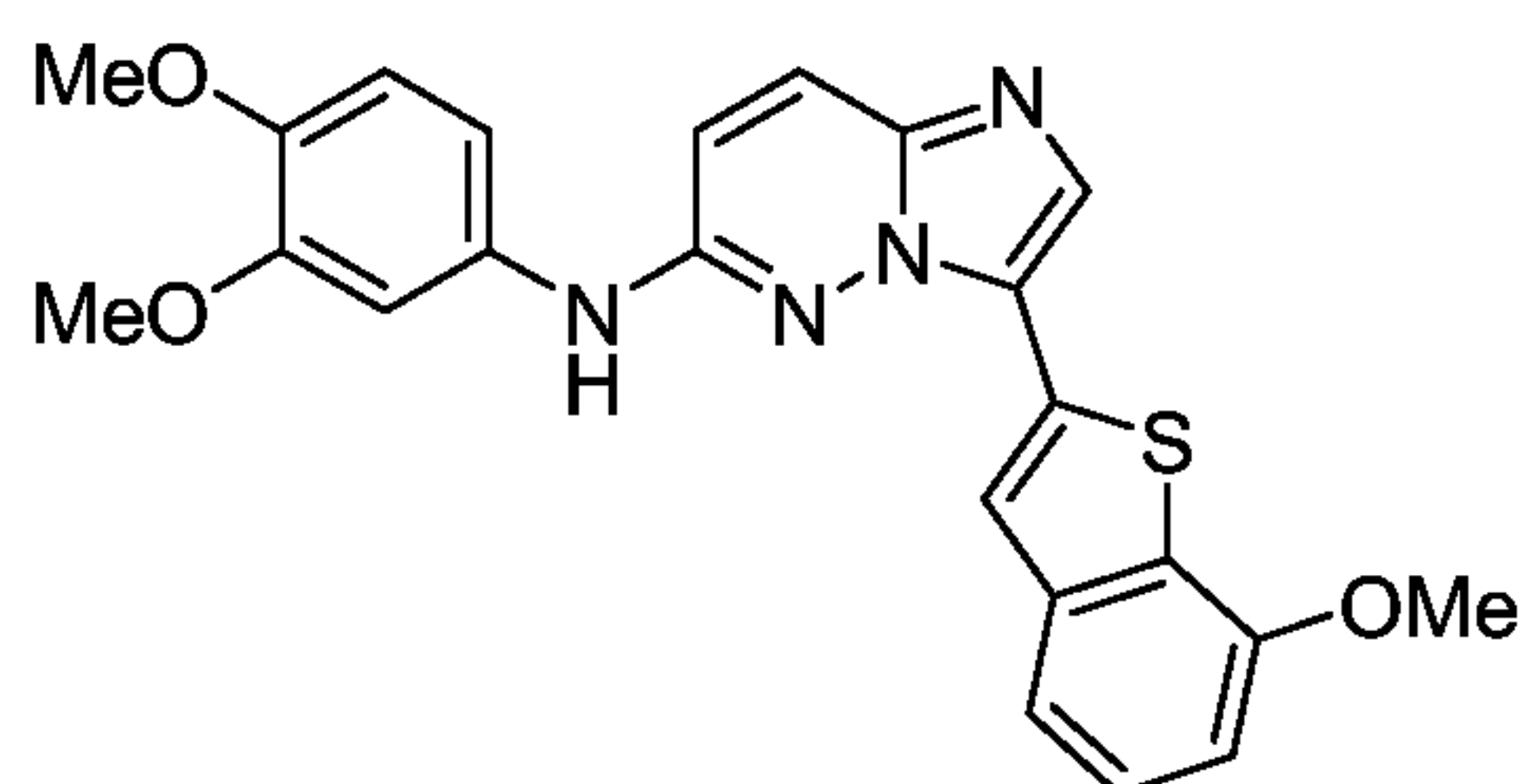
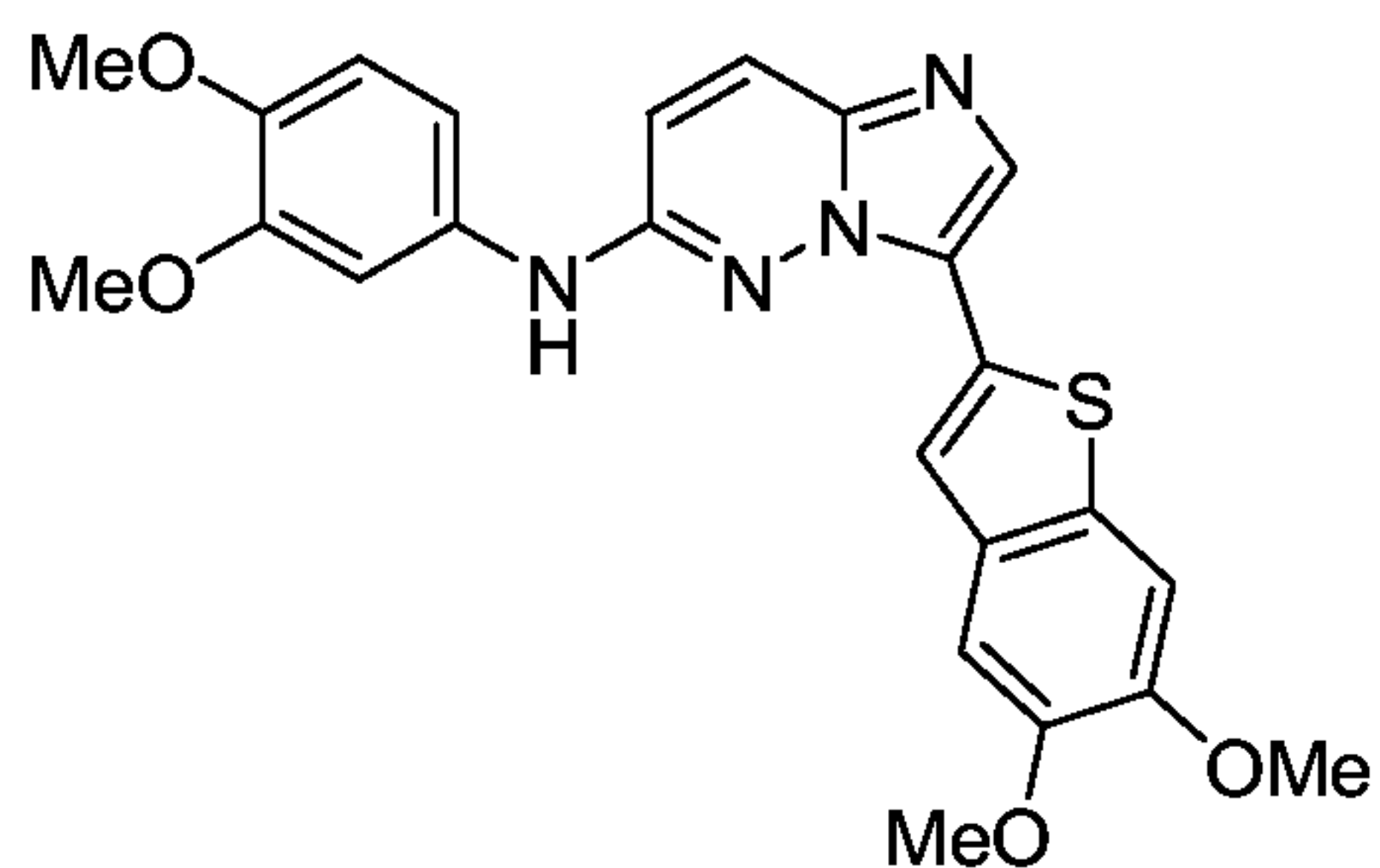
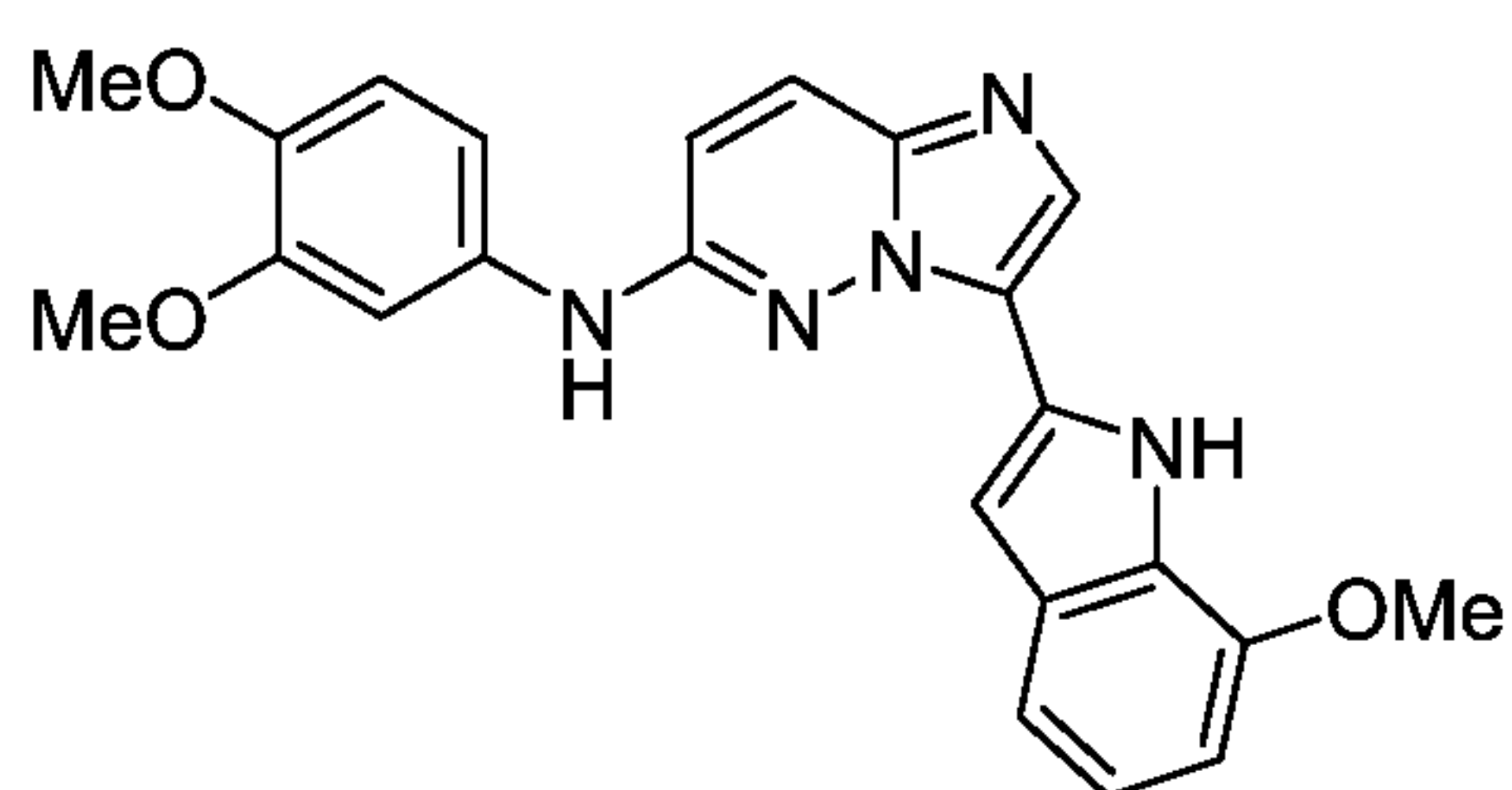
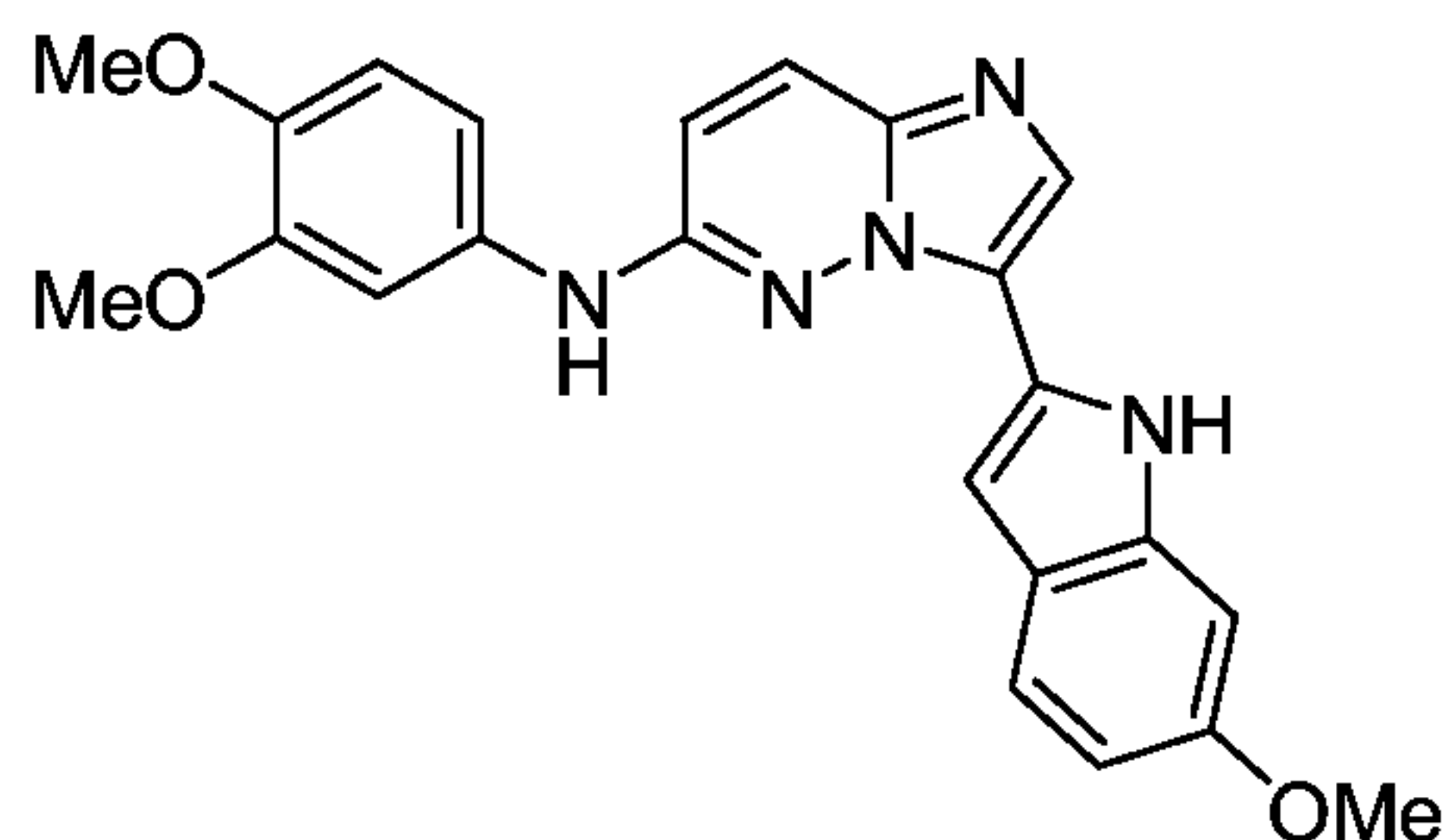
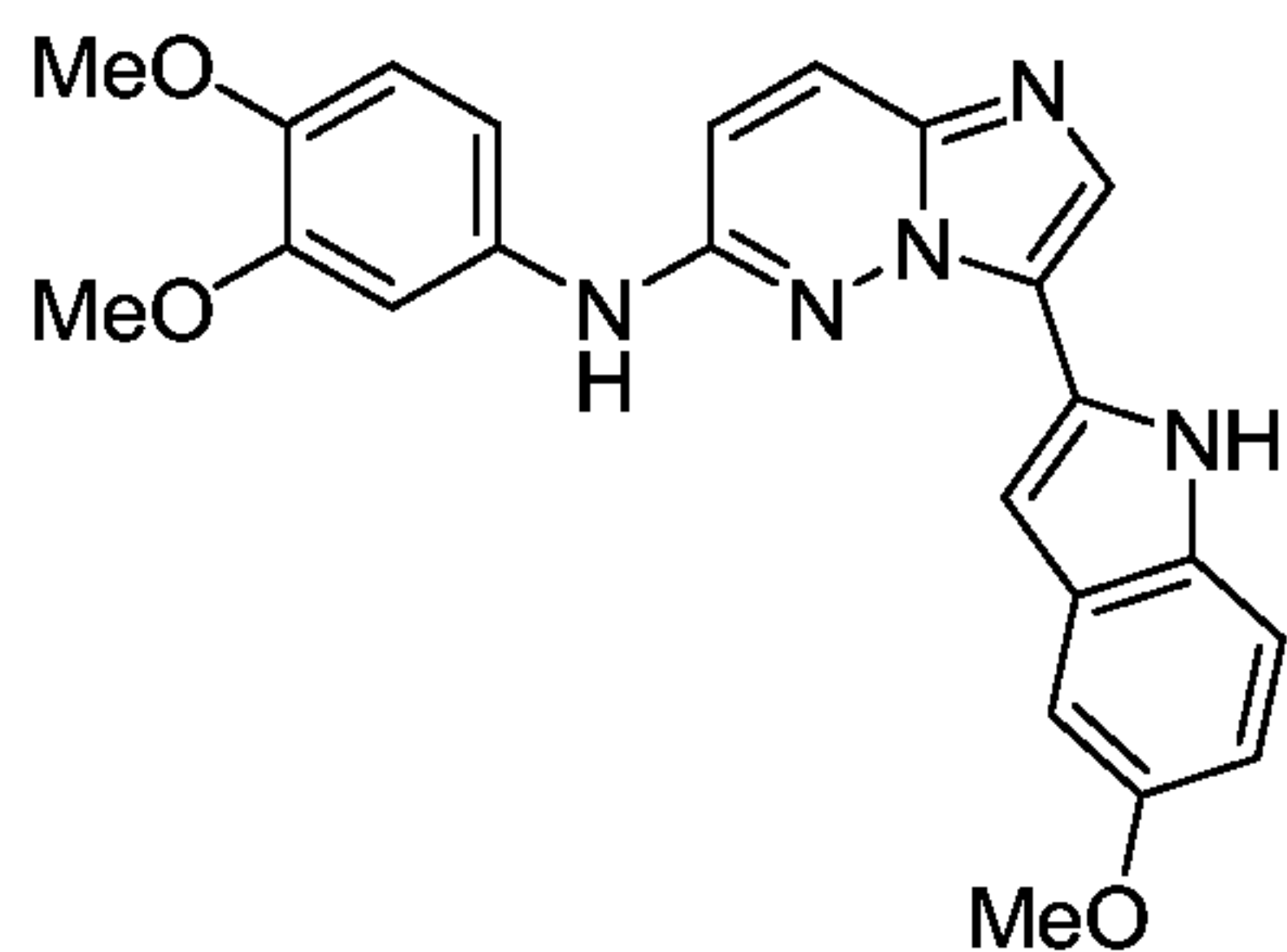


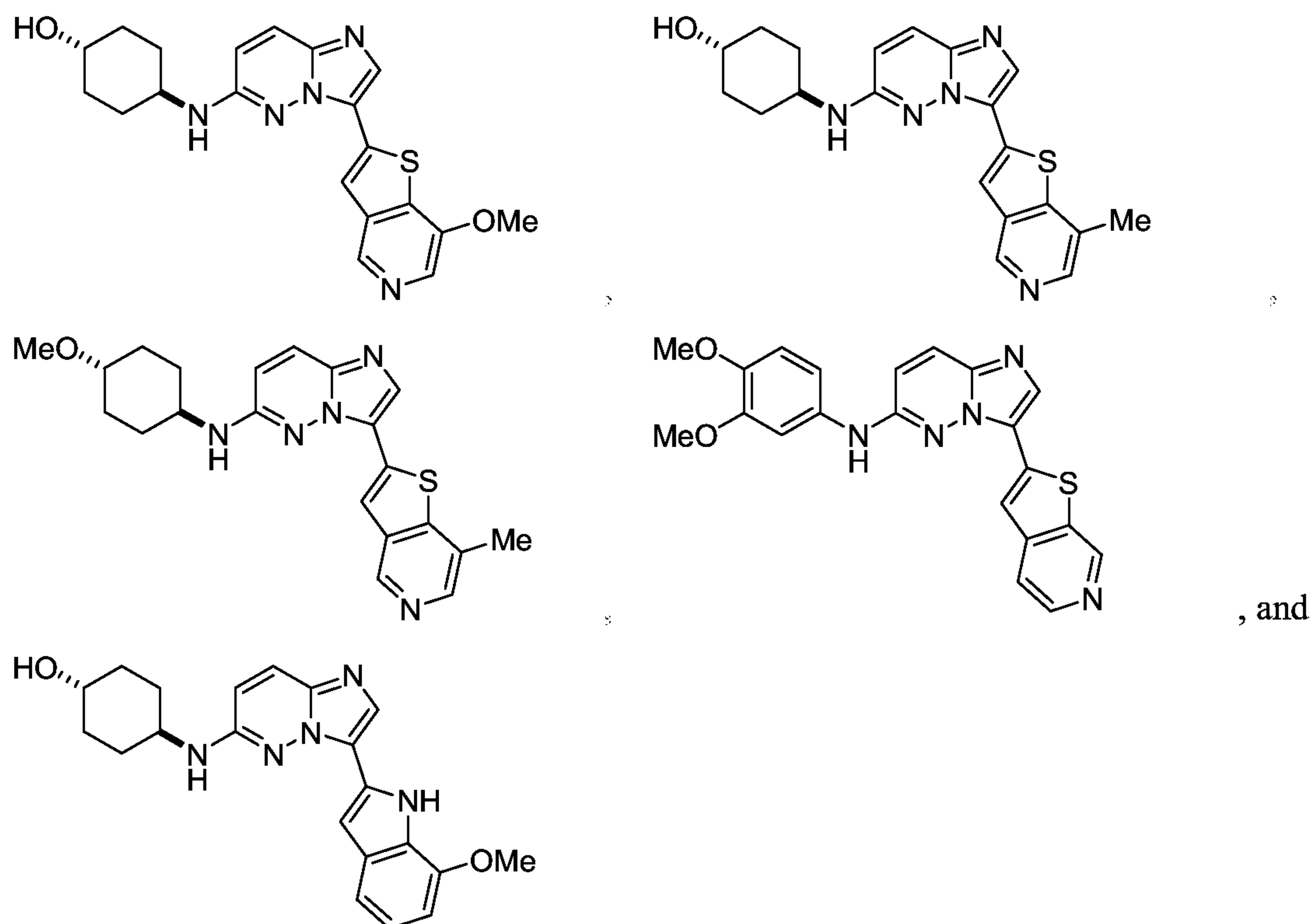




or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, isotope, or hydrate, or solvate thereof.

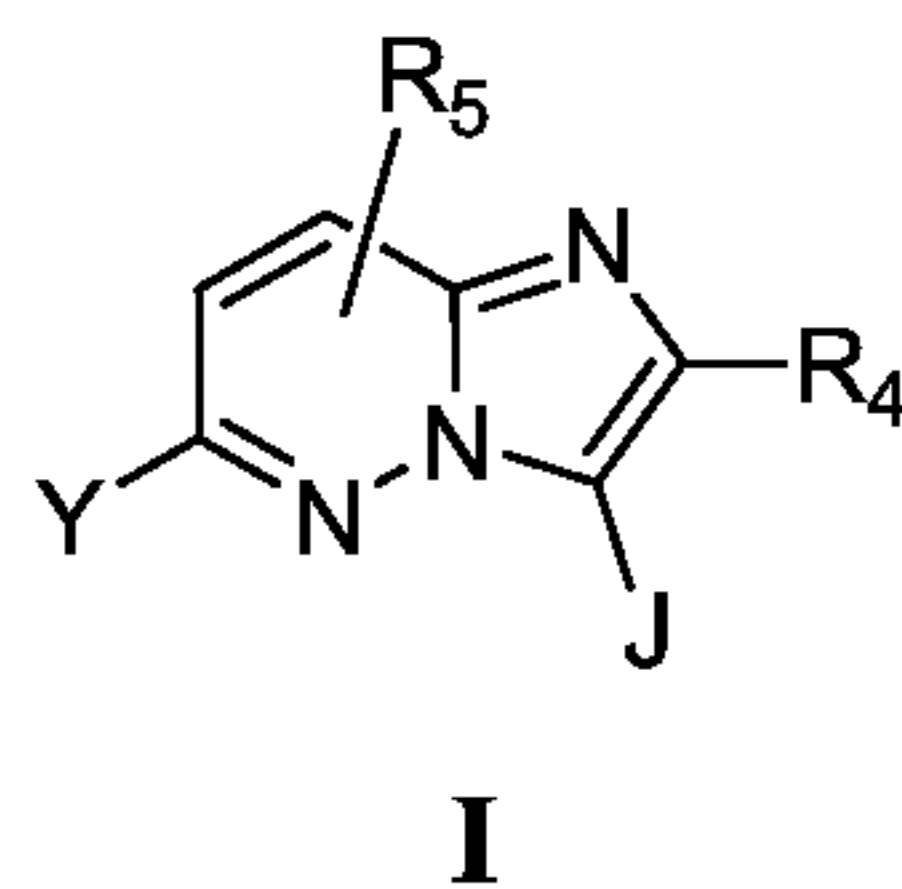
17. The compound of any of claims 1-16 wherein the compound is selected from any of:





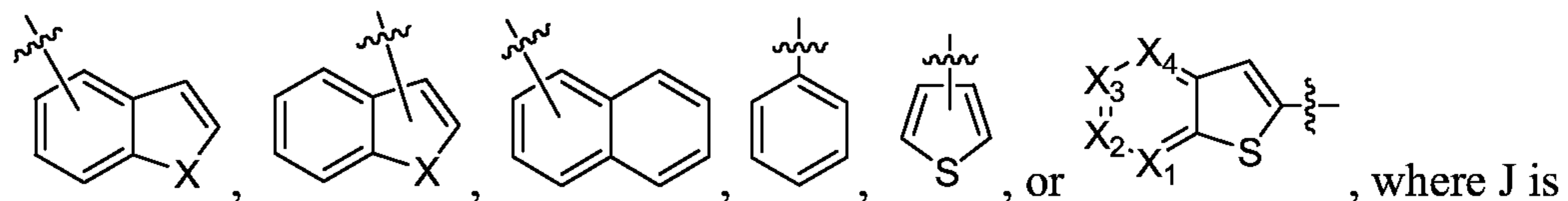
or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, isotope, or hydrate, or solvate thereof.

18. A pharmaceutical composition comprising a compound having the structure of Formula I



or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

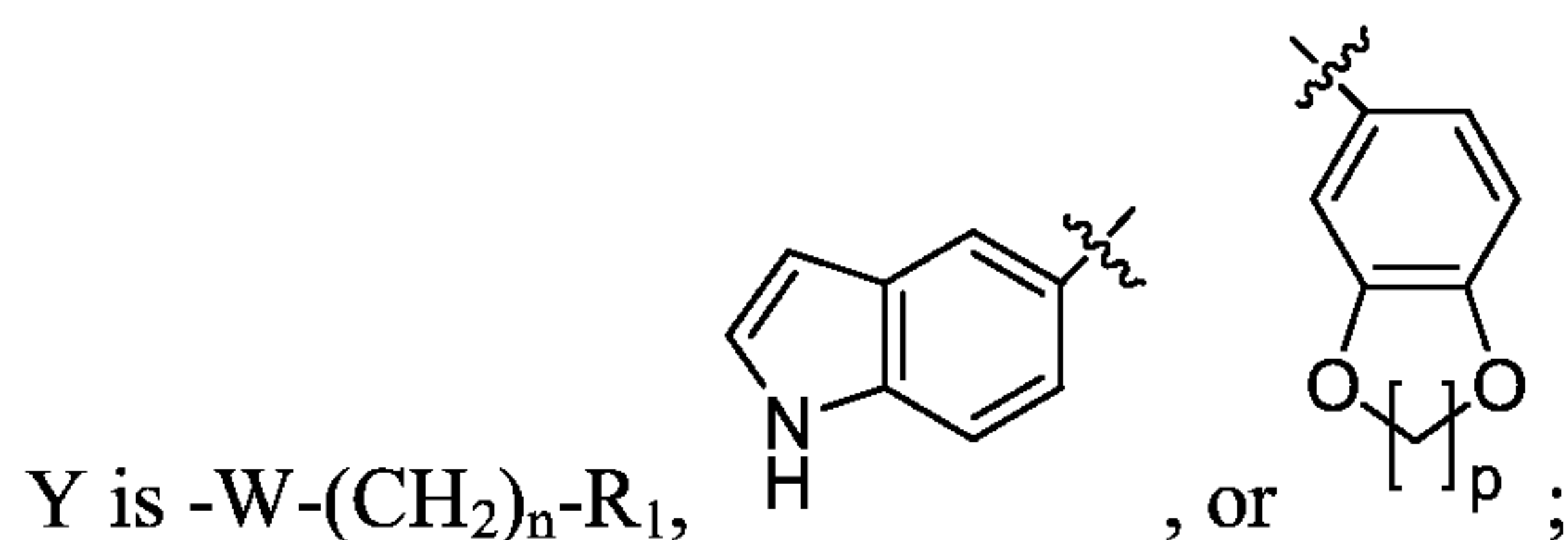
J has a structure of



optionally substituted with up to four R_{10} , each R_{10} is independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy, haloalkoxy, -OH, and -OCOR₆;

X is NR₁₂ or S;

each X_1 , X_2 , X_3 , and X_4 is independently CH or N and wherein no more than one of X_1 , X_2 , X_3 , and X_4 is N;



W is null, phenylene, or $-NR_6$ -phenylene, where the NR_6 is attached to the imidazopyridazine core structure of Formula I;

R_1 is $-NR_2R_3$, or piperazinyl, where the nitrogen atom of the piperazinyl is optionally substituted with alkyl or alkoxy;

R_2 is H or alkyl; R_3 is selected from the group consisting of C_2 - C_{10} alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, where any atom of R_3 is optionally substituted with one or more R_7 ; or R_2 and R_3 taken together with the N atom to which they are attached form a 3- to 7-membered heterocyclic ring optionally substituted with R_8 ;

R_4 is H or alkyl;

R_5 is H, alkyl, or NHR_9 ;

R_6 is H or alkyl;

each R_7 is independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkoxy, perhaloalkoxy, halo, oxo, -OH, hydroxyalkyl, $-COOR_{11}$, or $-O-(CH_2)_m-OH$;

R_8 is alkoxy, hydroxyalkyl, or $COOR_{11}$;

R_9 is H, alkyl, or cycloalkyl;

R_{11} is H, or alkyl;

R_{12} is H, or alkyl;

n is 0 or 1;

m is 1, 2, or 3;

p is 1, 2, or 3; and

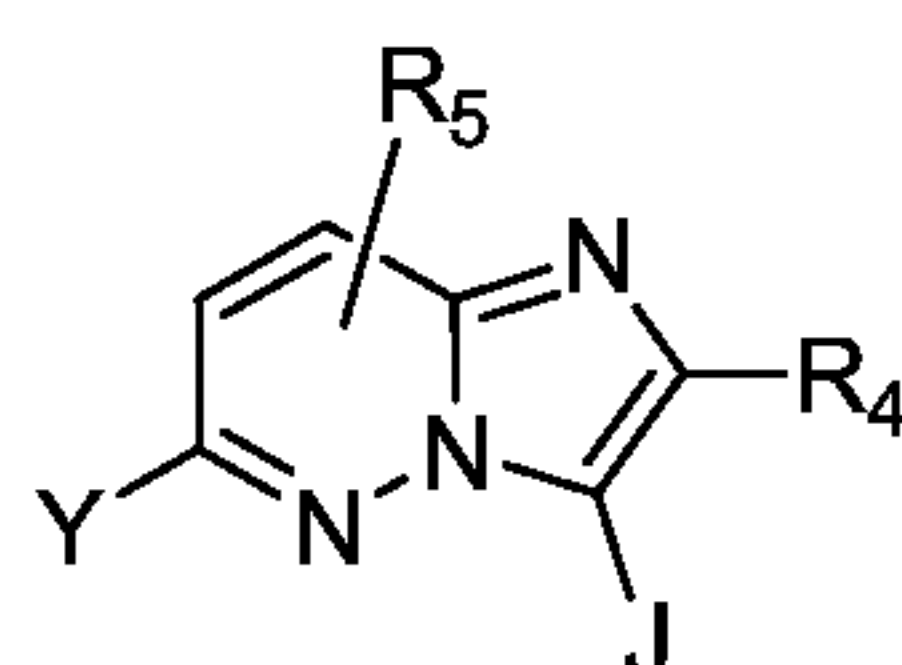
together with at least one pharmaceutically acceptable carrier, diluent or excipient.

19. A pharmaceutical composition of claim 18 wherein the compound is selected from any of compounds 3-9, 11-50, 52-102, 104, 105, 107-112, 114, 115, 118, 119-127, 129-132, 134-143, 148-150, 158-163, 166-220, and 221.

20. A pharmaceutical composition comprising the compound of claims 1-17 and a suitable excipient.

21. A pharmaceutical combination comprising the compound of claims 1-17 and a second medicament or medicaments used for the treatment of HIV infection or AIDS.

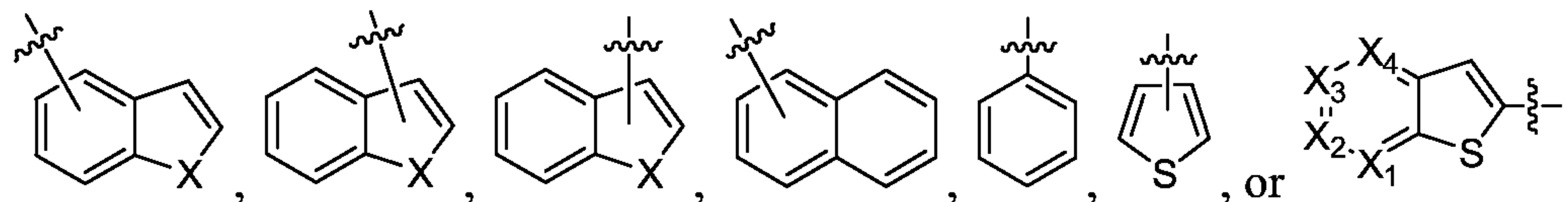
22. The pharmaceutical combination of claim 21 wherein the second medicament comprises atazanavir, ritonavir, zidovudine, lamivudine, or efavirenz.
23. A method for the preparation of a medicament useful for treating a MLK-mediated disease, wherein the medicament comprising a pharmaceutical composition of any one of claims 18-22.
24. The method of claim 23, wherein the MLK-mediated disease comprises diabetes mellitus, hyperglycemia, retinopathy, nephropathy, neuropathy, ulcers, micro- and macroangiopathies, gout and diabetic foot disease, insulin resistance, metabolic syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, peripheral inflammation, cancer, hepatitis, HIV associated neurocognitive disorders, HIV associated neuropathy, neurodegenerative disease, Alzheimer disease, cirrhotic diseases in liver or pancreas.
25. A method for treating a MLK-mediated disease comprising administering to a subject a pharmaceutical composition of any one of claims 18-22.
26. A method for treatment of a MLK-mediated disease comprising administering to a subject a therapeutically effective amount of a pharmaceutical composition comprising a compound having the structure of Formula I



I

or a pharmaceutically acceptable isomer, isotope, enantiomer, salt, ester, prodrug, hydrate or solvate thereof, wherein

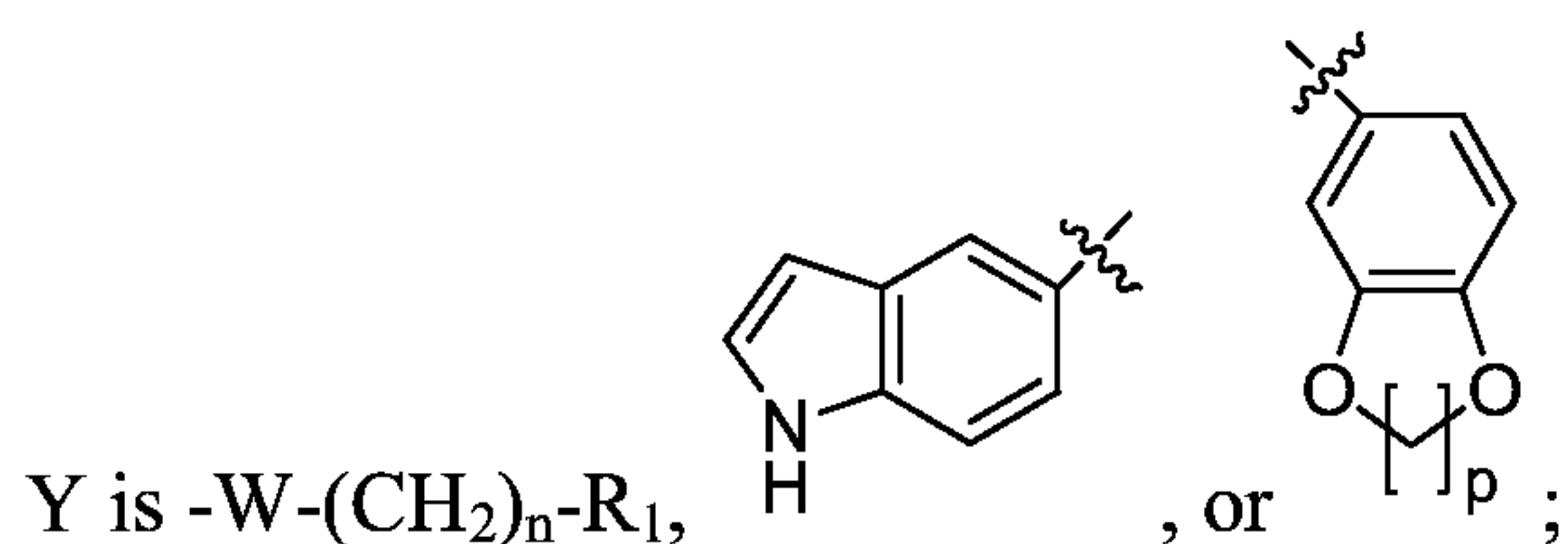
J has a structure of



where J is optionally substituted with up to four R_{10} , each R_{10} is independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy, haloalkoxy, -OH, and -OCOR₆;

X is N R₁₂ or S;

each X₁, X₂, X₃, and X₄ is independently CH or N and wherein no more than one of X₁, X₂, X₃, and X₄ is N;



W is null, phenylene, or $-NR_6$ -phenylene, where the NR_6 is attached to the imidazopyridazine core structure of Formula I;

R_1 is $-NR_2R_3$, or piperazinyl, where the nitrogen atom of the piperazinyl is optionally substituted with alkyl or alkoxy;

R_2 is H or alkyl; R_3 is selected from the group consisting of C_2 - C_{10} alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, where any atom of R_3 is optionally substituted with one or more R_7 ; or R_2 and R_3 taken together with the N atom to which they are attached form a 3- to 7-membered heterocyclic ring optionally substituted with R_8 ;

R_4 is H or alkyl;

R_5 is H, alkyl, or NHR_9 ;

R_6 is H or alkyl;

each R_7 is independently alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloalkylalkyloxy, perhaloalkoxy, halo, oxo, $-OH$, hydroxyalkyl, $-COOR_{11}$, or $-O-(CH_2)_m-OH$;

R_8 is alkoxy, hydroxyalkyl, or $COOR_{11}$;

R_9 is H, alkyl, or cycloalkyl;

R_{11} is H, or alkyl;

R_{12} is H, or alkyl;

n is 0 or 1;

m is 1, 2, or 3; and

p is 1, 2, or 3.

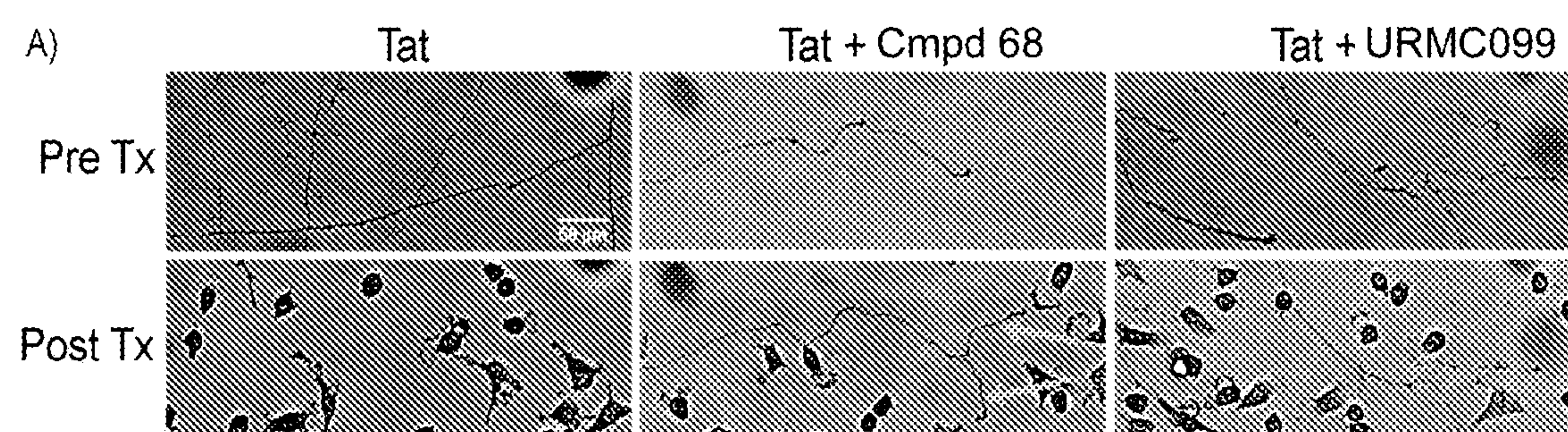
27. The method of any of claims 25 or 26 wherein the subject is a human being.

28. The method according to any of claims 25-27 wherein the MLK-mediated disease is selected from the group consisting of stroke, diabetes mellitus, hyperglycemia, retinopathy, nephropathy, neuropathy, ulcers, microangiopathies, macroangiopathies, gout, diabetic foot disease, insulin resistance, metabolic syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, peripheral inflammation, cancer, hepatitis, steatohepatitis, HIV associated neurocognitive disorder, HIV associated neuropathy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, neurodegenerative disease, cirrhotic liver disease, and cirrhotic pancreatic disease.

29. The method according to any of claims 25-28 wherein the MLK-mediated disease is selected from the group consisting of HIV associated neurocognitive disorders, HIV associated neuropathy, heart failure, cirrhotic liver disease, cirrhotic pancreatic disease, steatohepatitis, pancreatic cancer, breast cancer, Alzheimer's disease, Parkinson's disease, and neurodegenerative disease.

30. Use of the compound recited in any of claims 18-21 for preparation of a medicament for treating a MLK-mediated disease selected from the group consisting of stroke, diabetes mellitus, hyperglycemia, retinopathy, nephropathy, neuropathy, ulcers, microangiopathies, macroangiopathies, gout, diabetic foot disease, insulin resistance, metabolic syndrome, hyperinsulinemia, hypertension, hyperuricemia, obesity, edema, dyslipidemia, chronic heart failure, atherosclerosis, peripheral inflammation, cancer, hepatitis, steatohepatitis, HIV associated neurocognitive disorder, HIV associated neuropathy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, neurodegenerative disease, cirrhotic liver disease, and cirrhotic pancreatic disease.

31. Use of the compound recited in any of claims 18-21 for preparation of a medicament for treating a MLK-mediated disease selected from the group consisting of HIV associated neurocognitive disorders, HIV associated neuropathy, heart failure, cirrhotic liver disease, cirrhotic pancreatic disease, steatohepatitis, pancreatic cancer, breast cancer, Alzheimer's disease, Parkinson's disease, and neurodegenerative disease.

**FIG. 1**

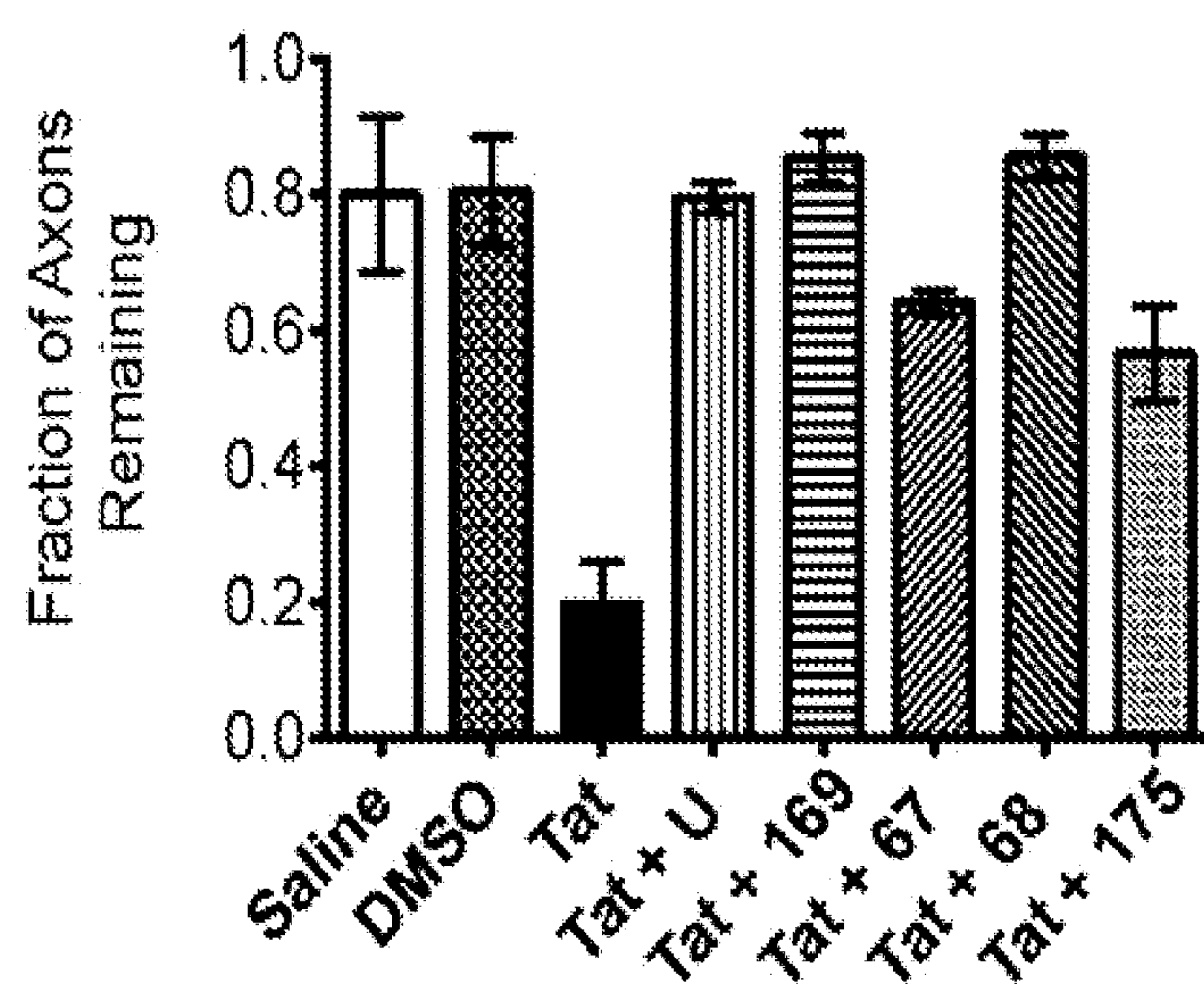


FIG. 2

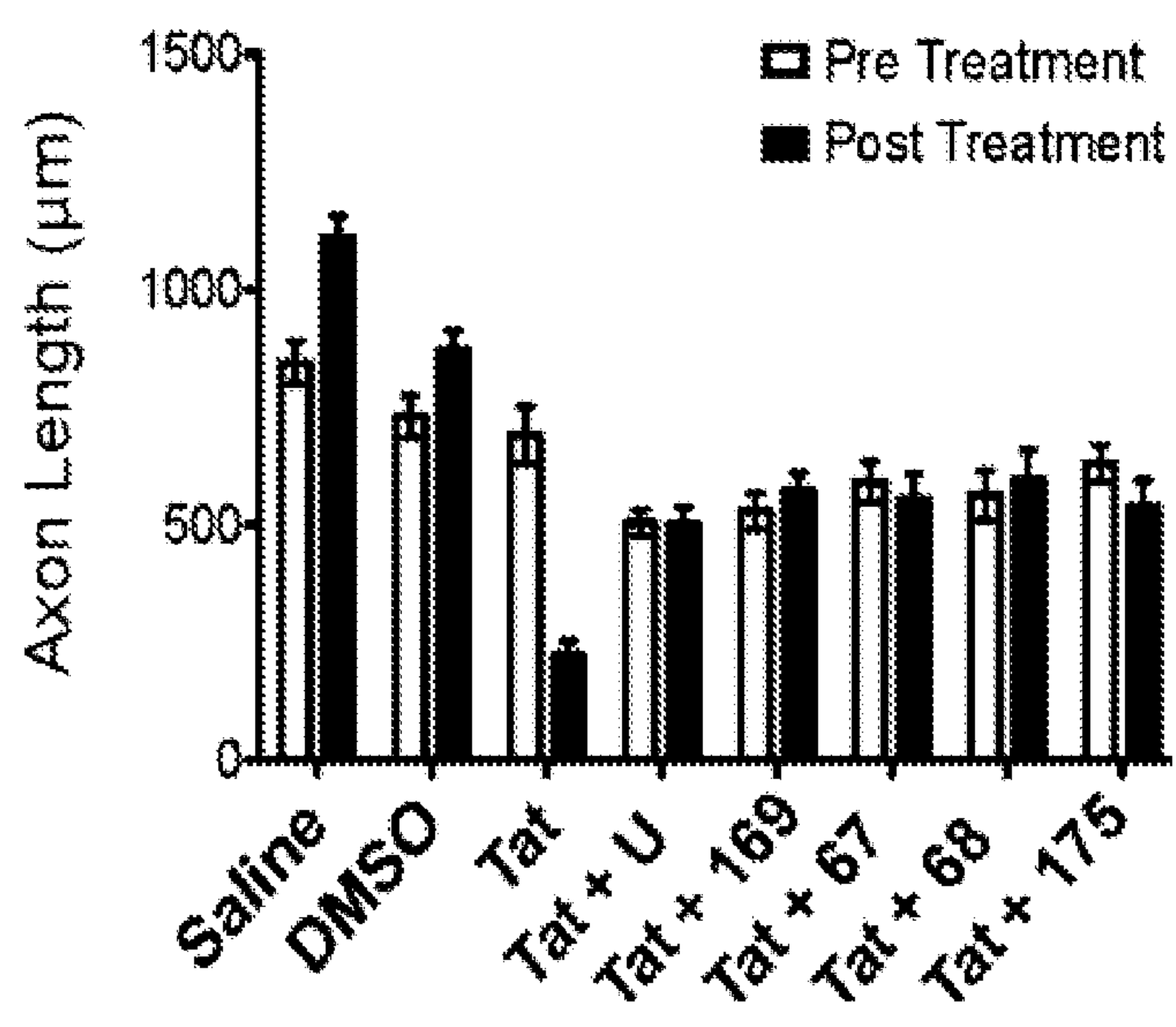
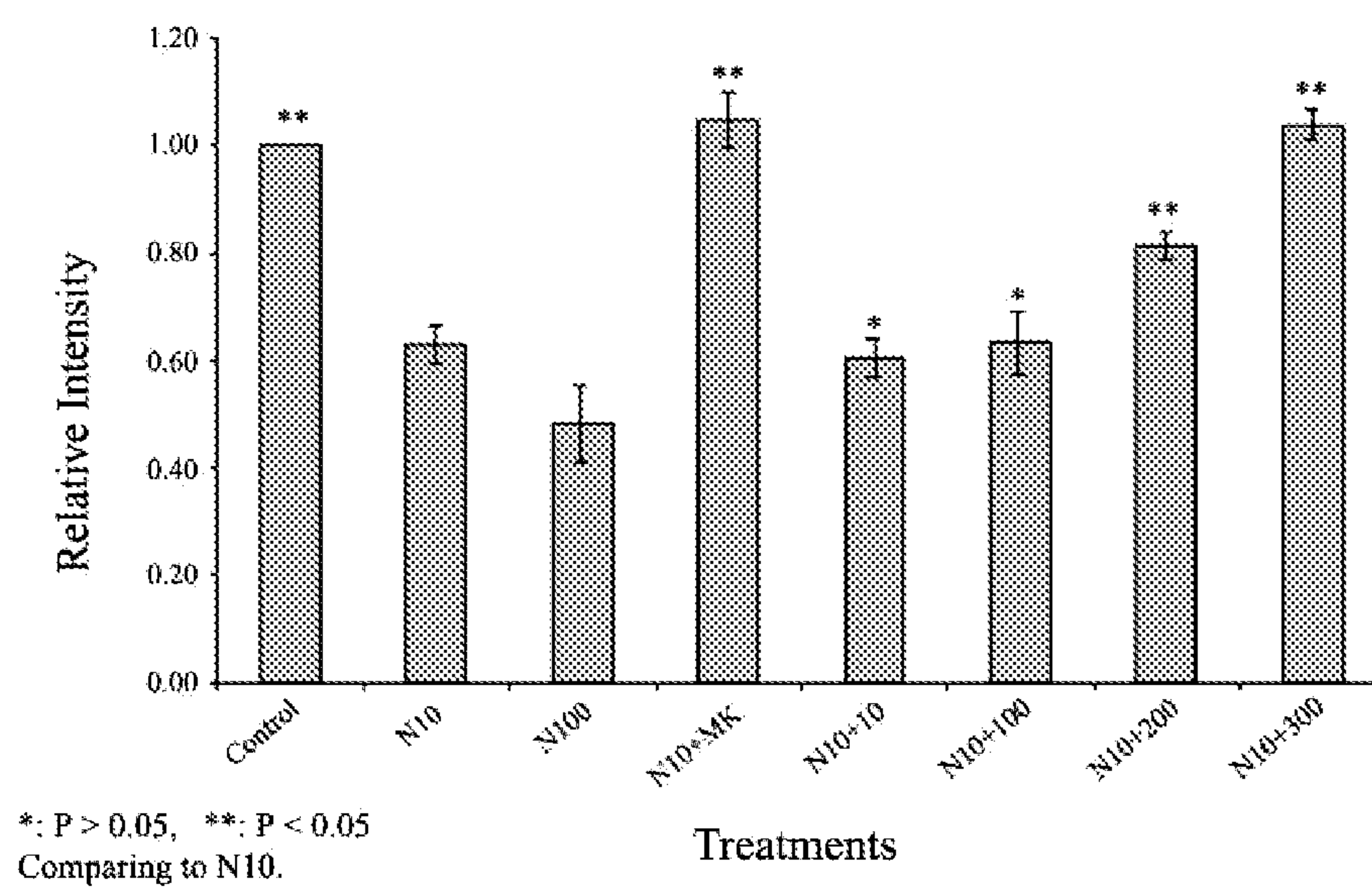
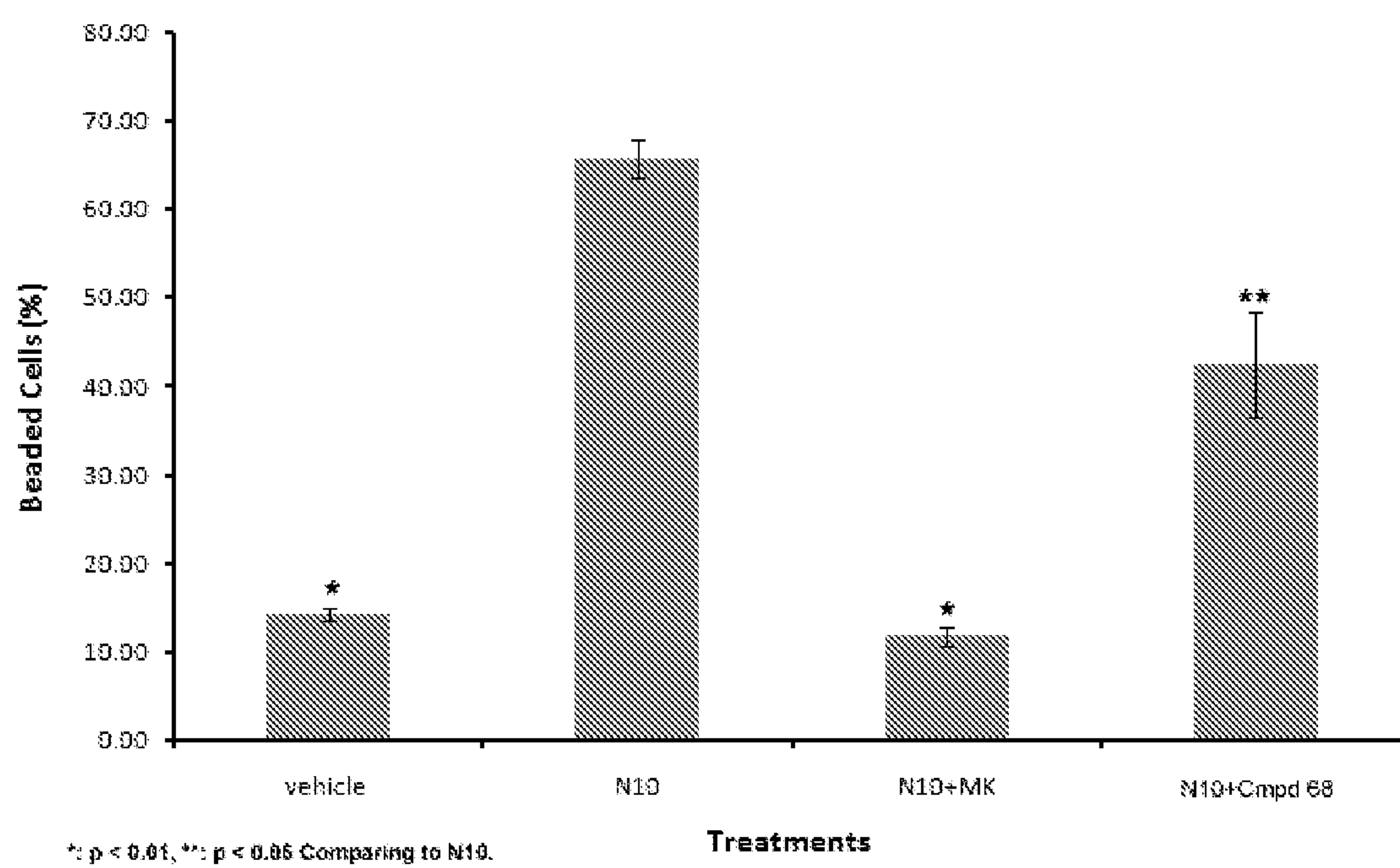


FIG. 3

**FIG. 4**

**FIG. 5**