



Azaindoles in Medicinal Chemistry

Key Points

- May provide higher binding affinity than and superior physiochemical properties

Overview

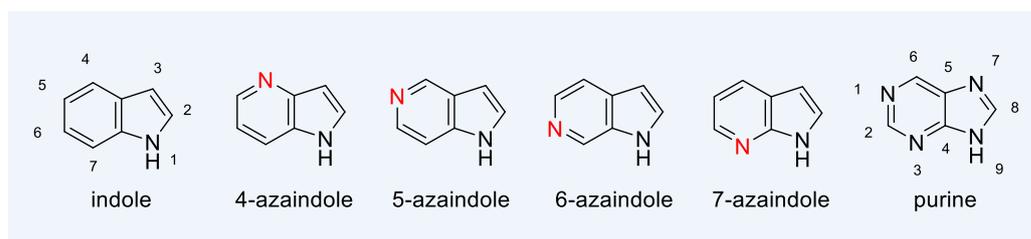
Azaindoles, fruitful scaffolds in the field of kinase inhibitors and others, may provide higher binding affinity than and superior physiochemical properties to its indole prototypes. Many synthetic methods exist to prepare all four possible azaindoles. Thanks to their widespread applications in medicinal chemistry, many azaindole intermediates are nowadays commercially available, greatly reducing the time and resources required to prepare azaindole-containing compounds.

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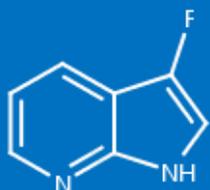
Azaindoles, also known as pyrrolopyridines, are bioisosteres for both indole and purine systems. Depending on the position of the nitrogen atom, they are 4-azaindole, 5-azaindole, 6-azaindole, and 7-azaindole, respectively. Rare in nature, azaindoles are privileged structures in medicinal chemistry—addition of a nitrogen atom to the indole ring in a prospective drug could potentially modulate its potency and physicochemical properties, as well as creating novel intellectual property space. They have found extensive utility in drug discovery, especially in the field of kinases, a class of particularly fruitful drug targets.



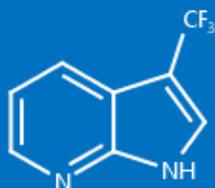
Azaindole-containing Drugs

Two azaindole-containing drugs currently on the market include Plexxikon's BRAF inhibitor vemurafenib (Zelboraf, **1**) and Abbvie's Bcl-2 inhibitor venetoclax (Venclexta, **2**). Both 7-azaindole-containing molecules are cancer drugs discovered from the fragment-based drug discovery (FBDD) strategy.

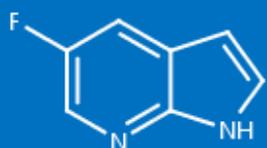
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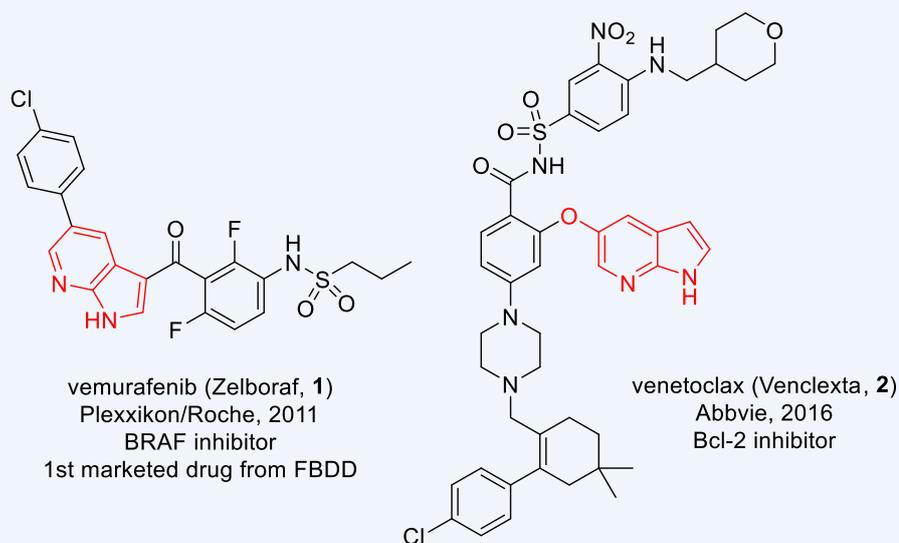
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Plexxikon's vemurafenib (Zelboraf, **1**) was the first marketed drug discovered employing the FBDD (or scaffold-based drug design) strategy under the guidance of co-crystallography. No sooner than the BRAF V600E mutant allele as a cancer target became known in 2002, Plexxikon began pursuing this target because BRAF^{V600E} is the most frequent oncogenic protein kinase mutation known and exists only in tumors that are dependent on the well-known RAF/MEK/ERK pathway.

A library of 20,000 fragment compounds with molecular weights ranging from 150 to 350 (fewer than 8 hydrogen bond donors and acceptors and few rotatable bonds) was screened at a concentration of 200 μ M. One of the 238 high throughput screening (HTS) hits, binding to the ATP site, 7-azaindole co-crystallized with a kinase called proviral integration site of moloney murine leukemia virus-1 (PIM1) enzyme while 3-aniliny-7-azaindole **3** also co-crystallized with PIM1 with an IC₅₀ value of approximately 100 μ M for PIM1. The 7-azaindole scaffold **3** represented a general framework capable of presenting *two hydrogen bonding interactions with the kinase hinge region*. Minor variation afforded benzyl-7-azaindole **4**, which co-crystallized with another kinase fibroblast growth factor receptor-1 (FGFR1) with an IC₅₀ value of 1.9 μ M for FGFR1. Structure–activity relationship (SAR) investigations led to PLX4720 (**5**),¹ which was a potent and selective (including wide-type B-Raf and many other kinases) BRAF^{V600E} inhibitor with an IC₅₀ value of 13 nM.

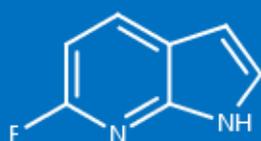
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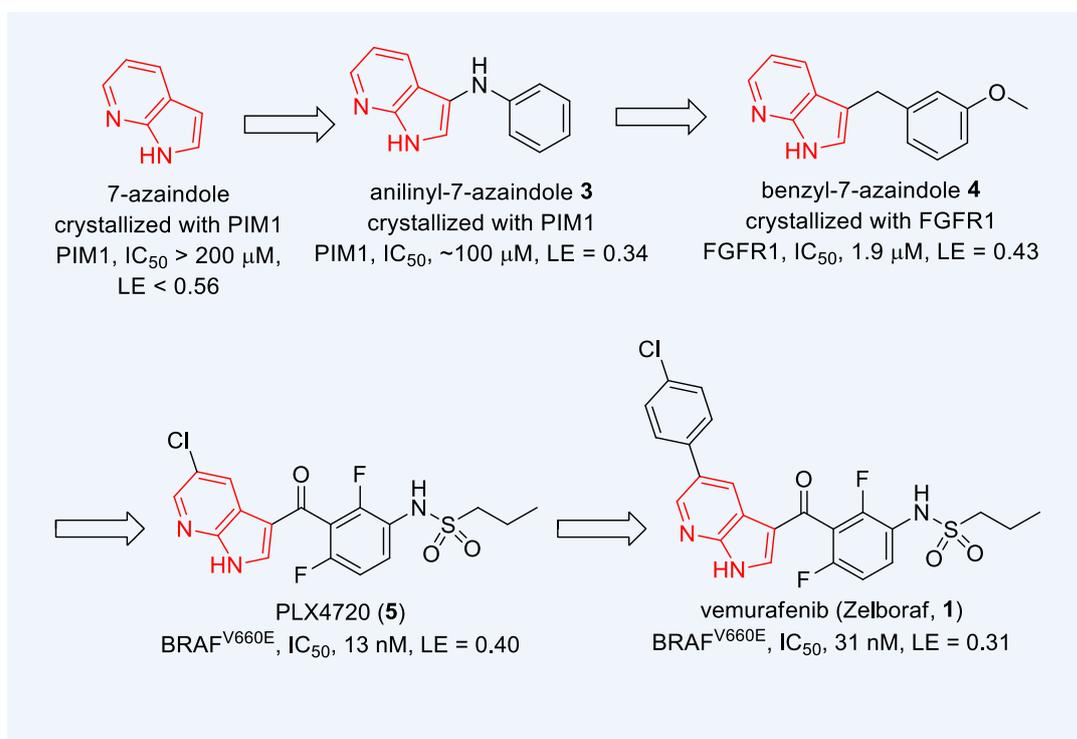


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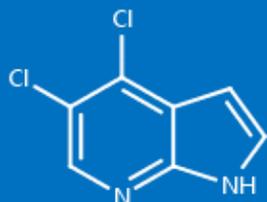


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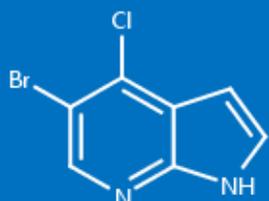
Installation of a chlorophenyl fragment to replace the 5-chlorine atom on the 7-azaindole core of **5** led to vemurafenib (**1**).² Vemurafenib (**1**) displays similar potency for BRAF (31 nM) and c-RAF-1 (48 nM) and selectivity against other kinases, including wide-type B-Raf (100 nM). It was chosen for development over **5** because its pharmacokinetic properties scaled more favorably in beagle dogs and cynomolgus monkeys. The FDA approved vemurafenib (Zelboraf, **1**) for the treatment of BRAF-mutant metastatic melanoma in 2011.³



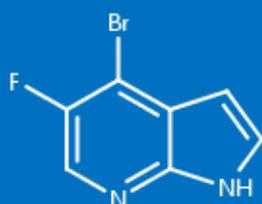
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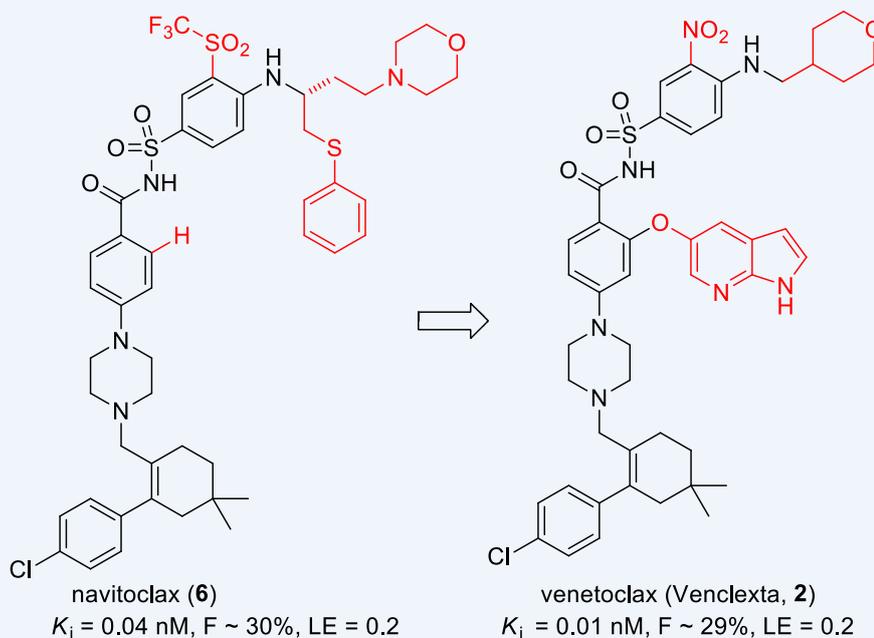


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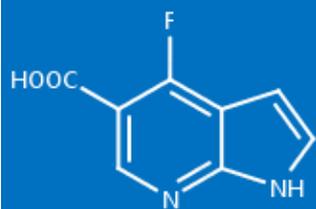


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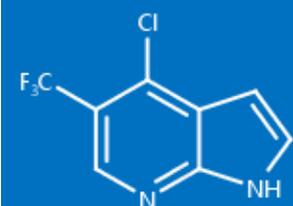
Abbvie's B-cell lymphoma 2 (Bcl-2) inhibitor venetoclax (Venclexta, **2**) was discovered employing the FBDD strategy as well. Instead of the co-crystallography tactic, "SAR by NMR" method was key to generate their fragment hits. From initial screening a 10,000 compound library with MW < 215 at 1 mM concentration, *p*-fluorophenyl-benzoic acid emerged as one of the first-site (P1) ligands. Later on, screening a 3,500 compound library with MW ~ 150 at 5 mM concentration identified the second site (P2) ligand 5,6,7,8-tetrahydro-naphthalen-1-ol.⁴ A protracted and winding road consisting of identifying the third binding site (P3), designing away from serum deactivation from domain II of human serum albumin (HSA-III) binding, boosting oral bioavailability, and removing a potential nitro structural alert cumulated to the discovery of navitoclax (**6**) as a potent and orally bioavailable Bcl-2 inhibitor.⁵ Eventually, the fourth binding site (P4) was identified and 7-azaindole ether filled P4 site and captured an additional hydrogen bond, giving rise to venetoclax (Venclexta, **2**) as a potent, selective (against Bcl-x_L, Bcl-w, and Bcl-1), and orally bioavailable Bcl-2 inhibitor. In 2016, it was approved by the FDA for treating chronic lymphocytic leukemia (CLL) with the 17p deletion.⁶



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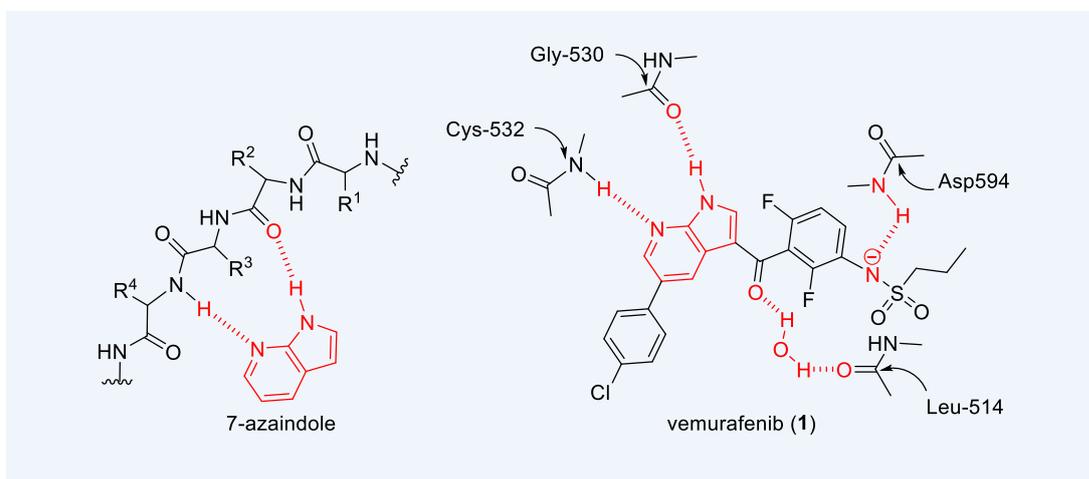
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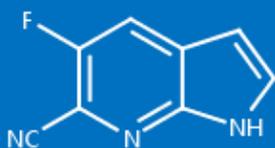
Azaindoles in Drug Discovery

In terms of utility in drug discovery, 7-azaindoles are the most frequently used, followed by 6-azaindoles, whereas 4-, and 5-azaindoles are less frequently encountered in the literature.⁷ Azaindoles have found widespread applications in the design of kinase inhibitors. This is probably not surprising considering azaindoles are structurally similar to the adenine fragment of adenosine triphosphate (ATP), which is critical to the phosphorylation process, the key function of kinases. Kinase inhibitors mimic ATP and bind to the catalytic domain, making azaindoles especially valuable scaffolds in this field.

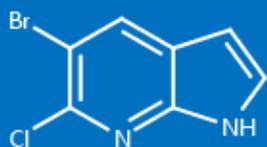


The pyridine N atom and its pyrrole NH of the 7-azaindole ring provide a hydrogen bond acceptor and donor, respectively to make bidentate hydrogen bonds with the kinase's hinge-binding region. Analysis of many 7-azaindole-containing kinase inhibitors revealed that 7-azaindole may bind to kinases in three modes: normal, flipped, and non-hinge binding modes.⁸ Vemurafenib (**1**), for instance, has the pyridine N of its 7-azaindole scaffold serving as a hydrogen bond acceptor, and forming a hydrogen bond with the NH of BRAF's backbone amide of cysteine-532 (Cys-532) near the hinge region, which overlaps with the ATP-binding site. Meanwhile, its pyrrole NH serves as a hydrogen bond donor, making contact with glycine-530 (Gly-530)'s carbonyl oxygen to form another hydrogen bond. The hydrogen bonding of azaindole, which is tightly confined within the adenine-binding region of the ATP pocket, to the hinge residues anchors the structure.¹

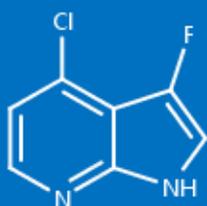
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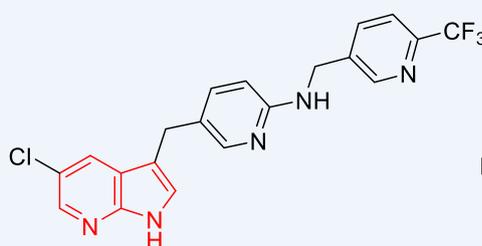


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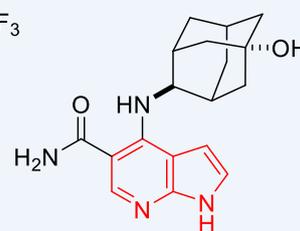


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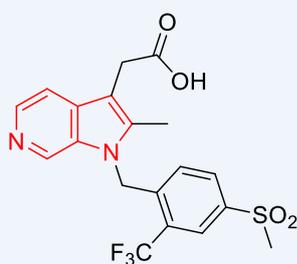
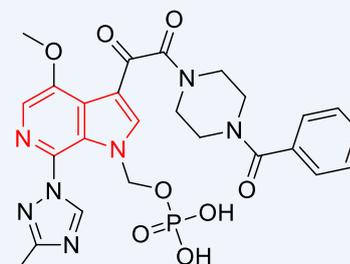
Plexxikon's encore pexidartinib (**7**), a colony-stimulating factor-1 receptor (CSF-1R) kinase inhibitor for treating tenosynovial giant-cell tumor, emerged from their old hit benzyl-7-azaindole PLX070 (**4**).⁹ Pexidartinib (**7**)'s phase III clinical trials completed in 2018. Astellas's peficitinib (**8**), a Janus kinase-3 (JAK3) inhibitor developed for the treatment of rheumatoid arthritis (RA), also contains a 7-azaindole framework.¹⁰ Two 6-azaindole-containing drugs in phase III trials include fevipiprant (**9**), a potent and selective prostaglandin D₂ (DP₂) receptor antagonist for the treatment of asthma¹¹ and BMS's fostemsavir (**10**), an human immunodeficiency virus type 1 (HIV-1) attachment inhibitor for treating AIDS.¹²



pexidartinib (**7**)
Plexxikon, phase III
CSF-1R inhibitor



peficitinib (**8**)
Astellas, phase III
JAK3 inhibitor

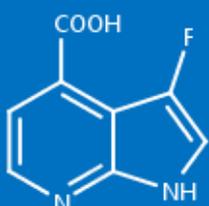
fevipiprant (**9**)fostemsavir (**10**)

The abundance of 6- and 7-azaindole-containing drugs shown here thus far does not imply only 6- and 7-azaindoles are useful in medicinal chemistry. A plethora of 4-, and 5-azaindole-containing drugs are current going through the pipelines of phase I and phase II clinical trials.¹³ Even more of them are in preclinical investigations.

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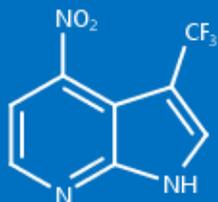
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en route to the discovery of fostemsavir (**10**), systematic replacement of each of the unfused carbon atoms in the phenyl ring of the indole moiety by a nitrogen atom provided four different azaindole derivatives that displayed a clear SAR for antiviral activity and all of which displayed marked improvements in pharmaceutical properties.¹⁴ The prototype indole **11** was a potent, non-cytotoxic inhibitor of HIV-1 in cell culture using a pseudo-virus (LAI strain) assay and displayed high permeability in a Caco-2 assay (Pc 169 nm/s at pH 6.5). But it exhibited a relatively short half-life when incubated in human liver microsomes (HLMs, $t_{1/2}$ = 16.9 min) and low crystalline solubility of 16 $\mu\text{g/mL}$ at 25 °C and at pH 6.5 in an aqueous buffer solution. For azaindoles, 4-azaindole **12** and 7-azaindole **15** had better efficacy than that of indole **11**; while 5-azaindole **13** and 6-azaindole **14** saw their efficacy reduced in comparison to the parent indole **11**. Conspicuously, all four possible azaindoles **12–15** uniformly displayed enhanced solubility by more than 25-fold (419 to 936 $\mu\text{g/mL}$) over that of the prototype indole **11**. They all displayed enhanced metabolic stability as measure by half-life in HLM (38.5 to > 100 min).

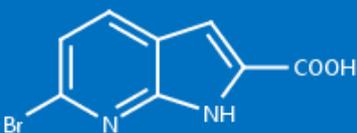


Compound	EC ₅₀ (μM)	HLM, $t_{1/2}$ (min)	Caco-2 (nm/s)	Solubility (mg/mL)	pK _a	Log <i>D</i> at pH 6.5
11	4.85	16.9	169	0.016	10.0	1.9
12	1.56	> 100	76	0.932	9.0, 5.8	0.9
13	576.90	> 100	19	0.419	6.2, 9.8	1.2
14	21.55	38.5	< 15	0.487	6.0, 9.3	1.5
15	1.65	49.5	168	0.936	2.0, 9.7	1.8

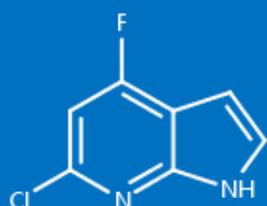
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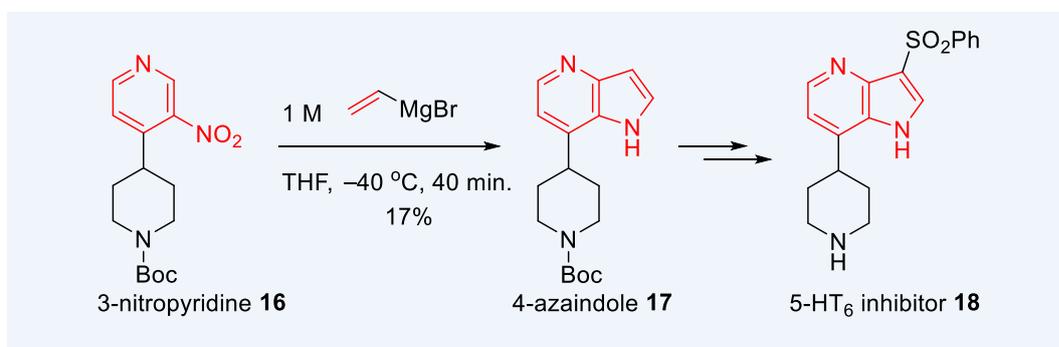
This case offers a glimpse of azaindole derivatives' ability to provide superior physiochemical properties to the parent indole compound. Azaindoles can also offer an additional hydrogen bond acceptor, which may translate to higher binding affinity, higher potency, and enhanced efficacy.

Synthesis of Some Azaindole-containing Drugs

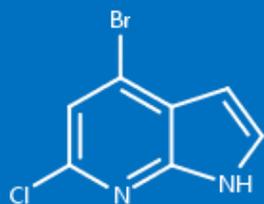
Because pyridine ring is electron-deficient, many classic indole synthesis methods do not work as well to synthesize azaindoles. For instance, the Fischer indole synthesis generally gives poor yields using pyridyl hydrazines and it also requires harsh conditions. There are tactics to circumvent pyridine's electron-deficiency by addition of electron-pushing group such as methoxyl and methylsulfide groups. In contrast, the Bartoli reaction and the Batcho–Leimgruber reaction have proven to be productive in preparing azaindoles.

a Bartoli Reaction

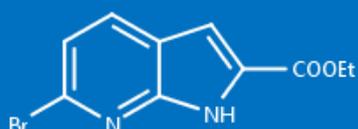
Although discovered only 20 years ago, the Bartoli reaction has found more and more applications in indole and azaindole synthesis. Applying the classic Bartoli conditions, 3-nitropyridine **16** was converted to 4-azaindole **17** in 17% yield, which was then transformed to 5-HT₆ inhibitor **18** as a potential treatment of schizophrenia.¹⁵



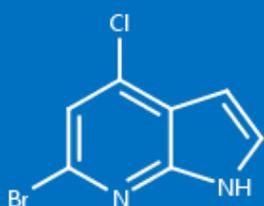
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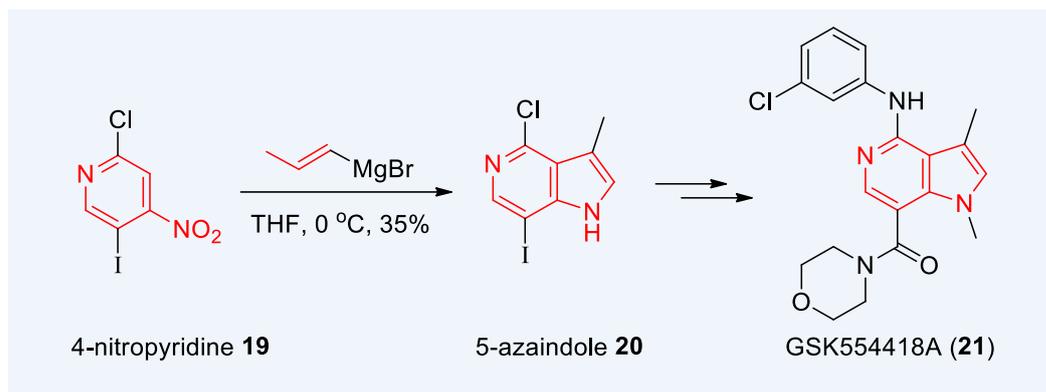


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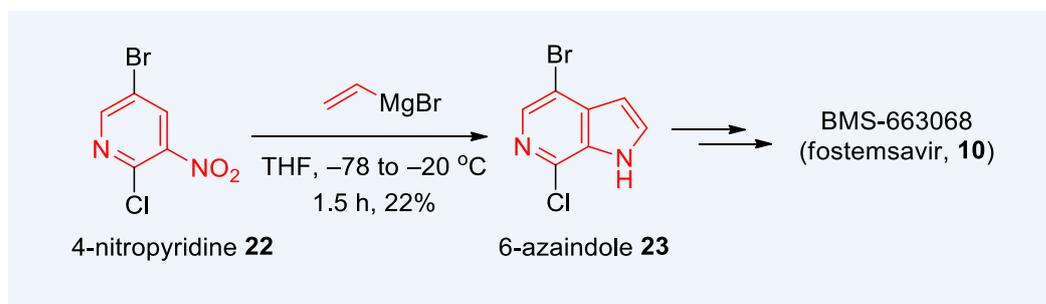


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The Bartoli reaction of 4-nitropyridine **19** with propenylmagnesium bromide produced 5-azaindole **20** in a 35% yield. 5-Azaindole **20**, in turn, was eventually converted to a brain penetrant cannabinoid receptor 2 (CB2) agonist GSK554418A (**21**) as a potential treatment of chronic pain.¹⁶

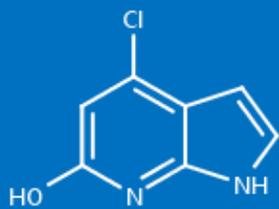


For the discovery route to prepare fostemsavir (**10**), 4-nitropyridine **22** underwent the Bartoli reaction with vinylmagnesium bromide to assemble the 6-azaindole scaffold **23**.¹⁴

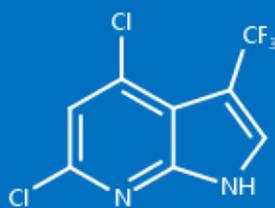


Notwithstanding its low yields, the Bartoli reaction is adequate for the medicinal chemists to synthesize the desired azaindole analogs.

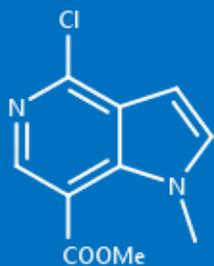
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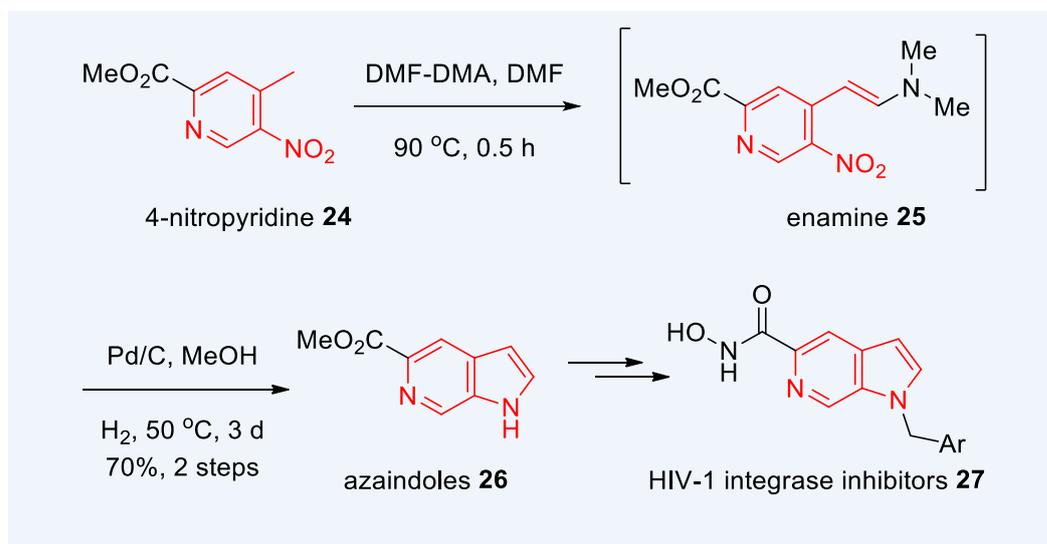
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b. Batcho–Leimgruber Reaction

Pfizer constructed 6-azaindole core structure using the Batcho–Leimgruber reaction to prepare a series of azaindole hydroxamic acids **27** as HIV-1 integrase inhibitors. The Batcho–Leimgruber reaction involved treating 4-nitropyridine **24** with *N,N*-dimethylformamide dimethyl acetal [DMF-DMA, Me₂NCH(OMe)₂] to afford enamine intermediate **25**, which was reduced via palladium-catalyzed hydrogenolysis to give 6-azaindole **26**. The 6-azaindole scaffold **26** was then transformed to potent HIV-1 integrase inhibitors **27** after further functional group manipulations.¹⁷

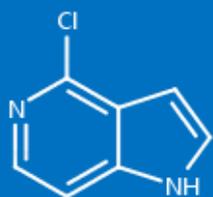


The Process Chemistry at BMS developed an enabling preparation route employing the Batcho–Leimgruber reaction for their first scale-up campaign. Thus, 3-nitropyridine **28** was converted to intermediate enamine **29**, which underwent an Ullman coupling with NaOMe to afford enamine **30**. Palladium-catalyzed hydrogenation reduced the nitro group and led to 6-azaindole **31**, which was further manipulated to deliver fostemsavir (**10**).¹⁸

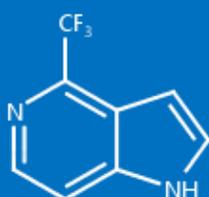
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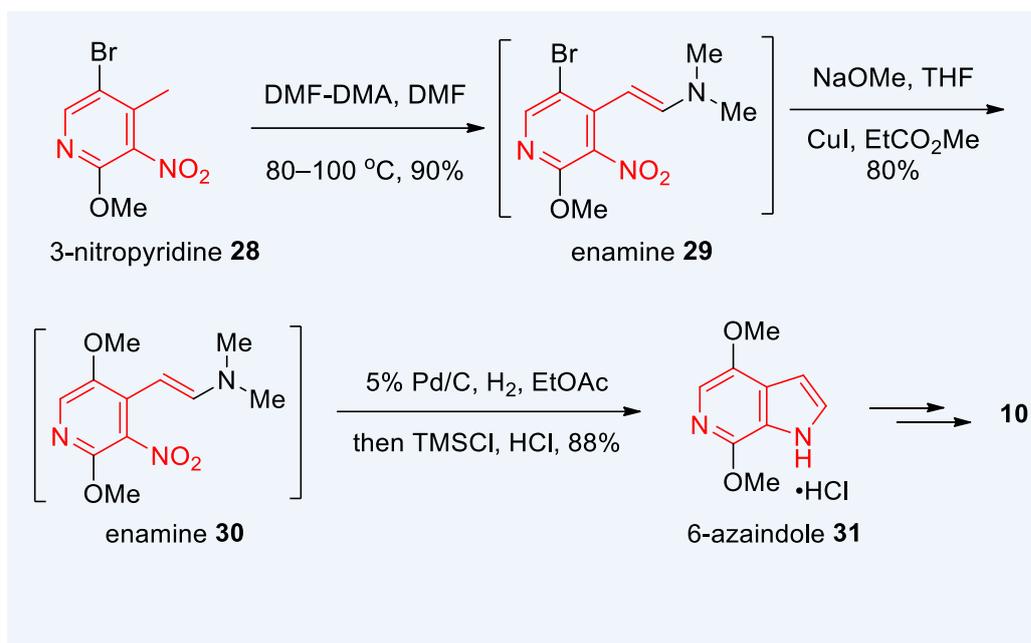
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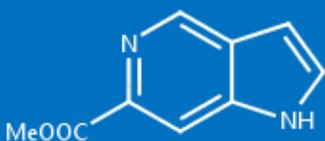


c. Radical Aromatization

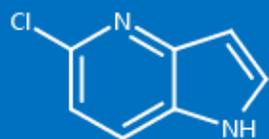
The Process Chemistry at BMS made a herculean effort to develop a commercial route to manufacture fostemsavir (**10**). Baran dubbed it an example of the majesty of chemistry.

3-Ketopyrrole **32**, assembled using a Pietet–Spengler cyclization, was exposed to methanesulfonic acid (MSA) and trimethylorthoformate [TMOF, $\text{CH}(\text{OMe})_3$] in methanol to prepare methyl enol ether **33**. In the same pot, addition of cumene hydroperoxide (CHP) initiated a radical aromatization process with the concomitant elimination of the sulfonate group to afford 6-azaindole **34**.¹⁹ Functionization of the 7-position involved oxidation of 6-azaindole **34** with H_2O_2 and methyltrioxorhenium (MTO, MeReO_3) as the catalyst to make 6-azaindole *N*-oxide **35**. Treatment of **35** with PyBroP in the presence of K_3PO_4 in trifluoromethyl toluene (TFT), followed by addition of NaOH in isopropyl alcohol (IPA), generated 7-bromo-6-azaindole **36**, which was converted to fostemsavir (**10**) in due course.

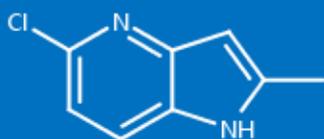
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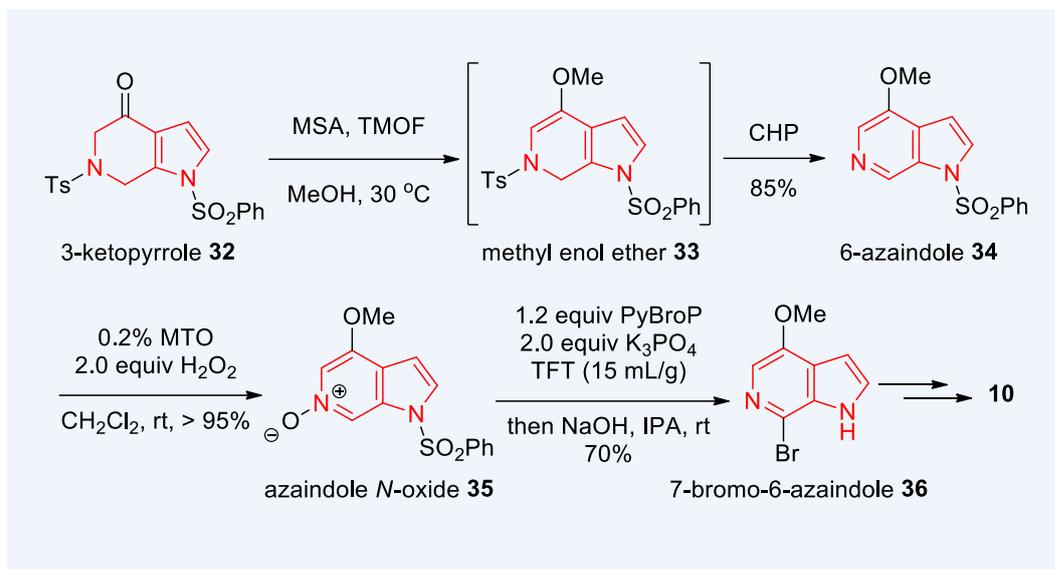
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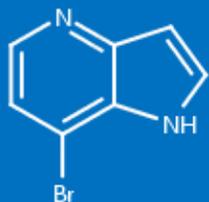
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*d. Suzuki Coupling*

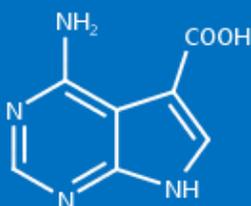
As azaindoles find more and more applications in drug discovery, many advanced azaindole intermediates are now commercially available as building blocks. Here, only azaindole-boron intermediates are highlighted as their widespread utility in Suzuki coupling reactions.

Commercially available 7-azaindole-2-boronic acid **36** coupled with bromide **37** under standard Suzuki coupling conditions to assemble adduct **38**, which was eventually manipulated to a covalent EGFR inhibitor **39**. This particular drug and its analogs with a rigidized hinge binding motif act as single digit inhibitors of clinically relevant EGFR L858R/T790M and L858R/T790M/C797S mutants.²⁰

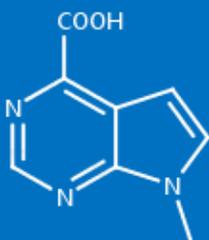
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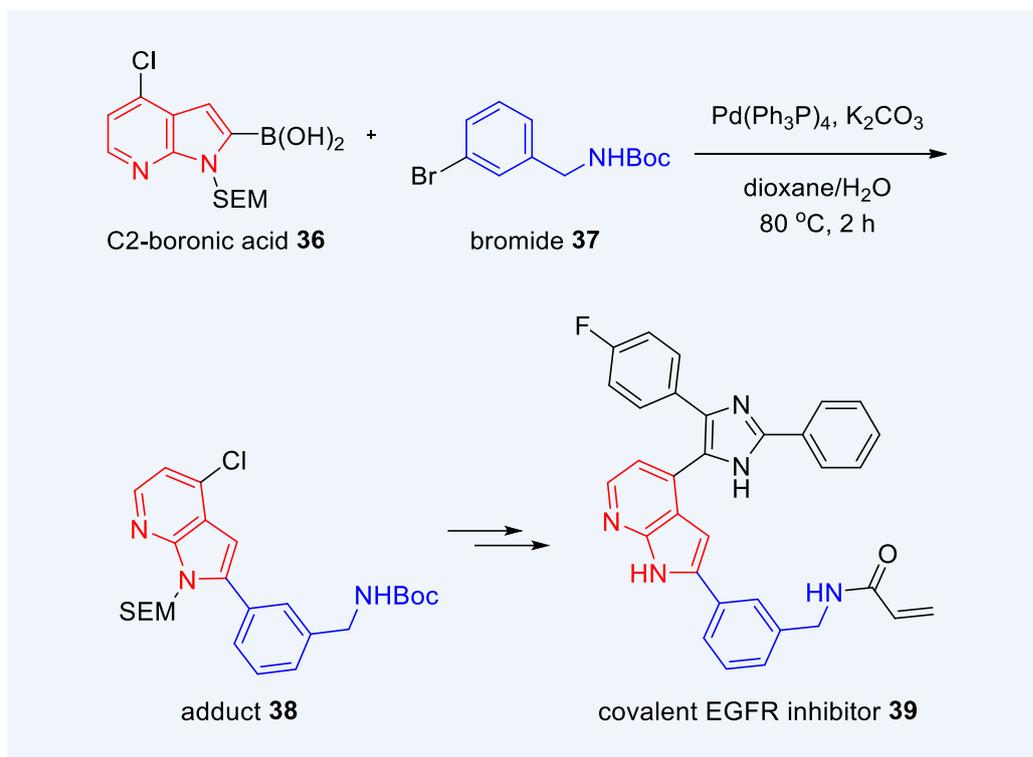
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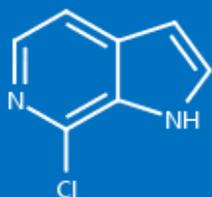


A Suzuki coupling reaction was carried out between commercially available 7-azaindole-3-boronate ester **40** (PB00509) and chloropyrimidine **41** to assemble adduct **42**. Oxidation of the sulfide on **42** gave the corresponding sulfone as a good leaving group, which was then displaced with a primary amine to deliver **43** as a cyclin-dependent kinase-2/9 (CDK2/9) inhibitor.²¹

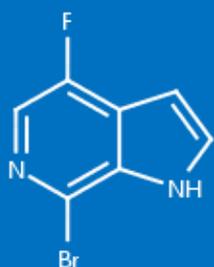
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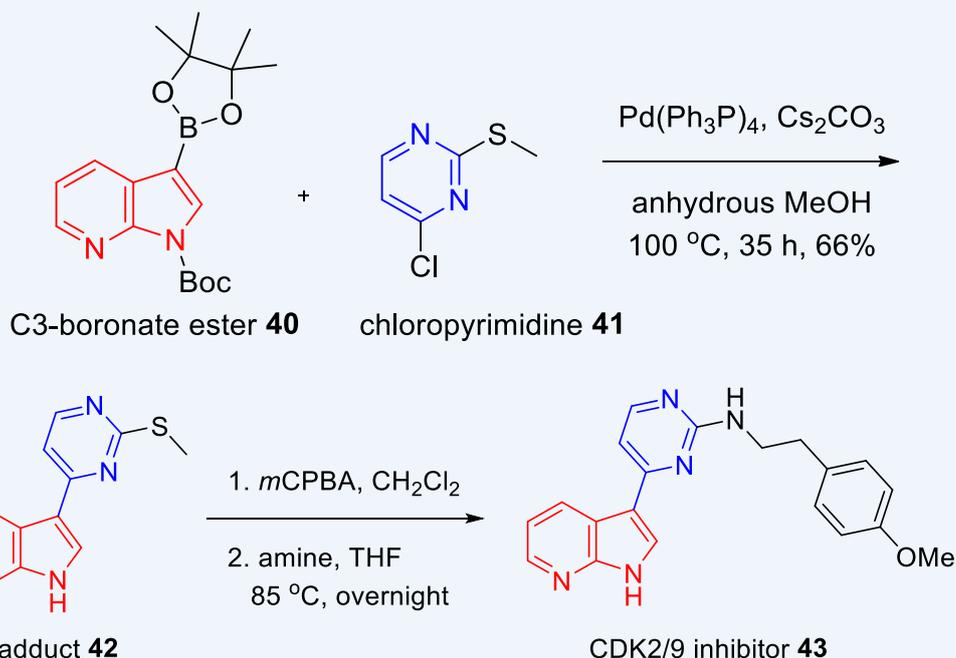
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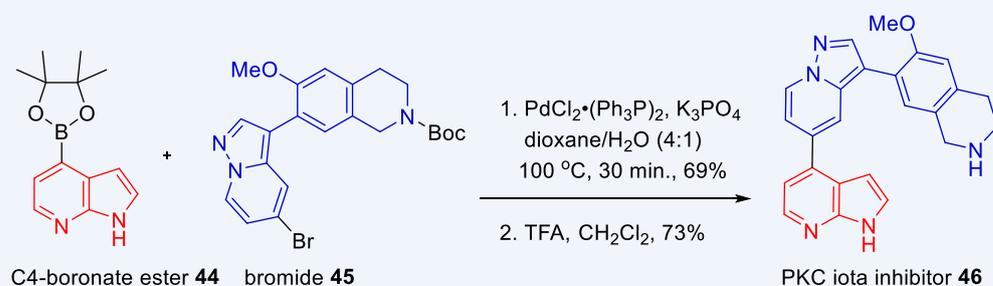
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A selective protein kinase C iota (PKC ι) inhibitor **46** was discovered using the FBDD approach. Interestingly, the fragment expansion employed 4-bromo-7-azaindole as the starting point. In the course of SAR investigations, commercially available 7-azaindole-4-boronate ester **44** was coupled with aryl bromide **45** to deliver **46** after acidic deprotection.²²

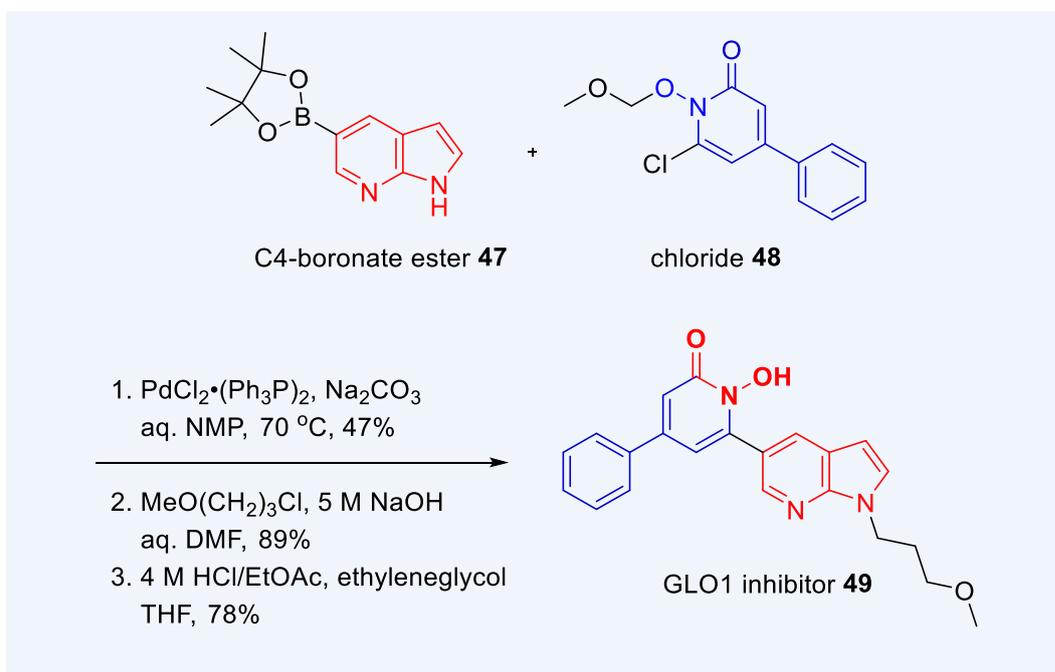




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Glyoxalase I (GLO1) is a zinc enzyme that isomerizes glutathione (GSH) and methylglyoxal to lactic thioester. GLO1 inhibitors have potential as treatment for cancer and other diseases. Synthesis of GLO1 inhibitor **49** entails a Suzuki coupling between C4-boronate ester **47** and chloride **48**, followed by two more steps. Although hidden in a ring on **49**, the cyclic hydroxamic acid, that chelates with the catalytic zinc cation, is a structural alert similar to other linear hydroxamic acids. Here, the nitrogen on the pyridine of the 7-azaindole core forms a hydrogen bond with a water molecule in a hydrogen bond network.²³



e. Sonogashira reaction

A Sonogashira reaction was key to assemble the 7-azaindole core of Merck's focal adhesion kinase (FAK) inhibitors.²⁴ Coupling between 3-iodopyridine **50** and *para*-fluorophenylacetylene prepared alkyne **51**, which was exposed to KO*t*-Bu to afford 7-azaindole **52**. Selective C4-chlorination of 7-azaindole **52** required a two-step sequence involving *m*CPBA oxidation to form *N*-oxide **53**, followed by treatment with POCl₃ to give rise to 4-chloro-7-azaindole **54**, which was then converted to FAK inhibitor **55** in several additional steps.



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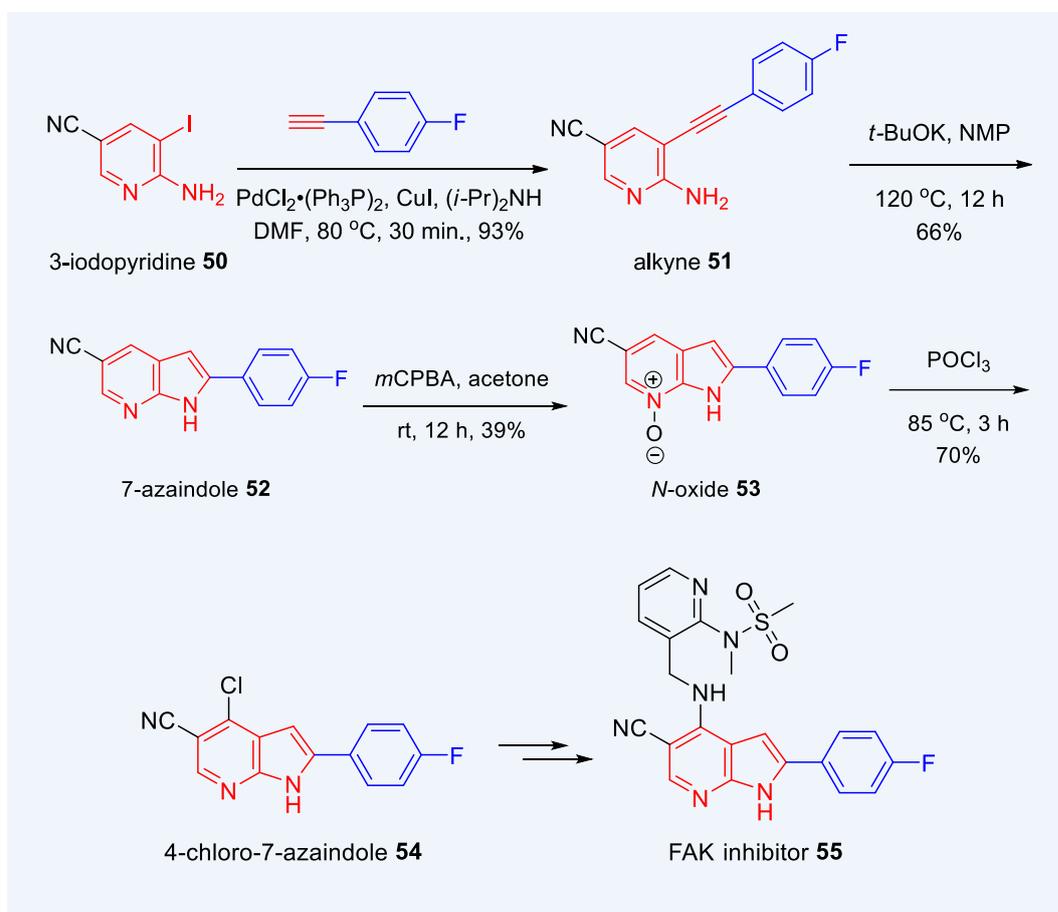
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In addition to what we have discussed here, many additional synthetic methods exist for making all four possible azaindoles.²⁵

In summary, azaindoles, fruitful scaffolds in the field of kinase inhibitors and others, may provide higher binding affinity than and superior physiochemical properties to its indole prototypes. Many synthetic methods exist to prepare all four possible azaindoles. Thanks to their widespread applications in medicinal chemistry, many azaindole intermediates are nowadays commercially available, greatly reducing the time and resources required to prepare azaindole-containing compounds.

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