Pyridine, A Privileged Scaffold in Drug Discovery —The Magic of Phenyl–Pyridyl Switch

Key Points

- A good bioisostere for the phenyl fragment
- Boosting biochemical potency
- Fixing CYP450 liability
- Elevating permeability

Overview

The nitrogen atom on pyridine has a profound impact on its physiochemical properties, making pyridine a good bioisostere for the phenyl fragment. The phenyl–pyridyl switch may improve a drug's *in vitro* binding affinity, *in vitro* functional affinity, *in vitro* PK/ADME profile, *in vitro* safety profile, and *in vivo* pharmacological profile.

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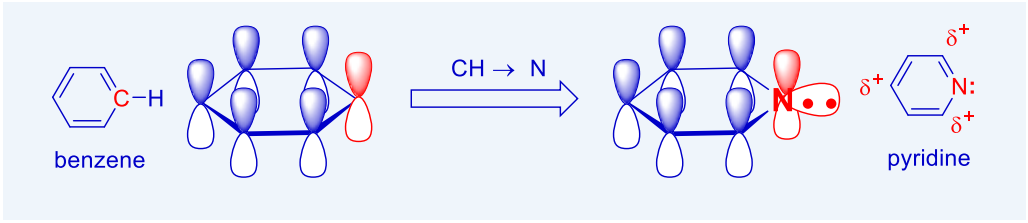
PharmaBlock designs and synthesizes over 5226 Pyridines, and 1059 Pyridine products are in stock. A list of featured Pyridine derivatives is attached at the end of this whitepaper. CLICK HERE to find detailed product information on webpage.

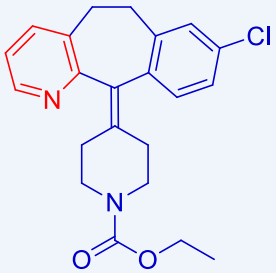
With 6 π-electrons, pyridine is an electron-deficient aromatic heterocycle containing a ring nitrogen atom. The aromatic π-electron system does not require participation of the lone pair of electrons on the nitrogen atom. The ring nitrogen is more electronegative than the ring carbons, making the two α-ring carbons and the γ-ring carbon more electropositive than otherwise would be expected from benzene.



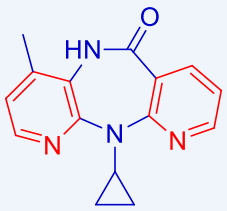
In the context of medicinal chemistry, replacement of a CH group with an N atom on a phenyl ring may influence a drug's molecular and physicochemical properties, as well as its intra- and intermolecular interactions that can translate to improved pharmaceutical profiles.

Pyridine-containing Drugs

The FDA has approved over 60 pyridine-containing drugs, making pyridine a privileged scaffold, only eclipsed by (72) piperidine-containing drugs. We showcase only 8 representative examples here for brevity.



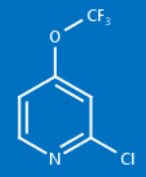
loratadine (Claritin, **1**)
Schering–Plough, 1993
H_1 receptor antagonist



nevirapine (Viramune, **2**)
Boehringer Ingelheim, 1996
NNRTI

Schering–Plough's antihistamine franchise dominated the allergy drug market for decades. Its non-sedating histamine receptor-1 (H_1) antagonist loratadine (Claritin, **1**), containing one pyridine ring, was one of the most popular treatment for allergy without central nervous system (CNS) side effects. Its carbamate moiety is key to retard it brain penetration and the 8-chlorine atom blocks a probable site of metabolism and offers a longer duration of action[1]—since pyridine is electron-deficient, the phenyl ring is oxidized more readily by cytochrome P450 (CYP) in liver. Nevirapine

PharmaBlock Products



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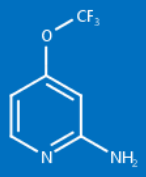

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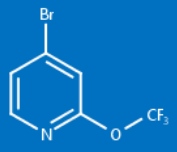

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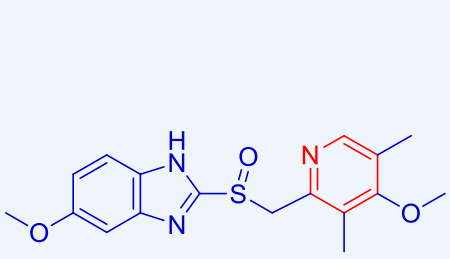
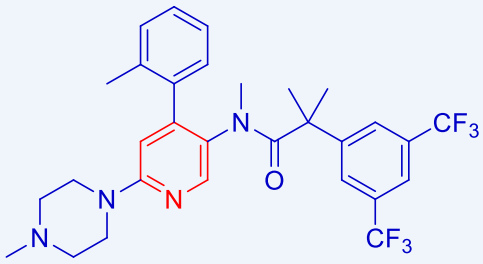
(Viramune, **2**), Boehringer Ingelheim's non-nucleoside human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitor (NNRTI) for treating AIDS, contains two pyridine rings. It adopts a "butterfly-like" conformation when binding to the allosteric site of the reverse transcriptase enzyme. Although the corresponding N11-ethyl derivative was more potent (IC_{50}, 35 nM) than nevirapine (**2**, IC_{50}, 84 nM) in both enzymatic and cellular assays and more soluble, the N11-cyclopropyl analog nevirapine (**2**) was selected as the drug candidate because it was more bioavailable due to the fact that cyclopropane was more resistant to metabolism while the ethyl group was more prone to undergo dealkylation.[2]

The pyridine motif is indispensable to the biological activities of AstraZeneca's proton pump (H^+,K^+-ATPase) inhibitor omeprazole (Prilosec, **3**) as a treatment of peptic ulcer. The lone pair electrons on pyridine is the "engine" to start the "omeprazole cycle". Indeed, the "omeprazole cycle" begins by nucleophilic attack of protonated benzimidazole by the N atom of pyridine to form a benzimidazoline intermediate.[3] In a sense, omeprazole (**2**) is a pro-drug, only becoming active when protonated. On the other hand, Roche's netupitant (**4**, Akynzeo when combined with palonosetron, a $5HT_3$ receptor antagonist) is a nerokinin-1 (NK-1) receptor antagonist for the treatment of nausea and vomiting caused by chemotherapy or surgery.[4]



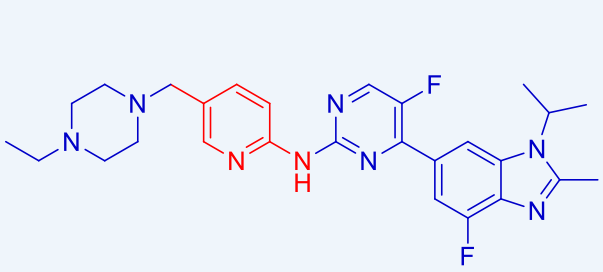
omeprazole (Prilosec, **3**)
AstraZeneca, 1998
proton pump inhibitor



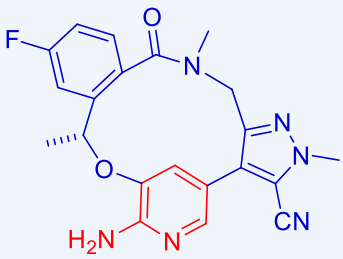
netupitant (Akynzeo, **4**)
Roche, 2015
NK-1 receptor antagonist

Kinase inhibitors are the most fruitful class of medicines as targeted cancer drugs during the last three decades. Half a dozen of them possess the pyridine fragment, which include Lilly's cyclin-dependent kinase (CDK)4/6 inhibitor abemaciclib (Verzenio, **5**)[5] and Pfizer's anaplastic lymphoma kinase (ALK) inhibitor lorlatinib (Lorbrena, **6**). The case of lorlatinib (**6**) serves as a clever medicinal chemistry maneuver that converting linear ALK inhibitor crizotinib (Xalkori) to macrocycle may offer superior physicochemical properties. As the first-in-class ALK inhibitor, crizotinib (Xalkori) has little CNS exposure. Guided by structure-based

drug design (SBDD), lipophilicity efficiency (LipE), and physical property-based optimization, Pfizer discovered macrocyclic lorlatinib (**6**), which has good absorption, distribution, metabolism, and excretion (ADME), low propensity for P-glycoprotein (pgp) 1-mediated efflux, and good passive permeability with significant CNS exposure. It is thus suitable for treating metastasized brain tumors.[6]



abemaciclib (Verzenio, **5**)
Lilly, 2017
CDK4/6 inhibitor



lorlatinib (Lorbrena, **6**)
Pfizer, 2018
ALK inhibitor

The latest entries of pyridine-containing drugs on the market may be exemplified by Janssen's androgen receptor (AR) antagonist apalutamide (Erleada, **7**)[7] for treating castration-resistant prostate cancer (CRPC) and Agios' isocitrate dehydrogenase 1 (IDH1) inhibitor ivosidenib (Tibsovo, **8**) for treating IDH1-mutant cancers such as acute myeloid leukemia (AML).[8] The structure of apalutamide (**7**), discovered by Jung's group at UCLA in the 2000s, is similar to that of enzalutamide (Xtandi, developed by Medivation and approved in 2012), also discovered by Jung. However, in murine xenograft models of metastasized-CRPC (mCRPC), apalutamide (**7**) demonstrated greater antitumor activity than enzalutamide. Furthermore, apalutamide (**7**) penetrates less effectively the BBB (blood-brain barrier) than enzalutamide, suggesting that the chance of developing seizures may be less than with enzalutamide. At the end, the fact that both Janssen and Medivation were able to secure intellectual properties for their respective AR antagonists also speaks volume of the power of phenyl–pyridyl switch. Finally, Agios' ivosidenib (**8**) is the first-in-class IDH1 inhibitor, approved hot on the heel of FDA approval of their IDH2 inhibitor enasidenib (Idhifa, incidentally, also contains two pyridine rings), another first-in-class cancer drug.

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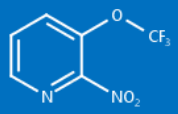

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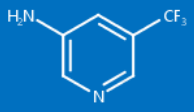

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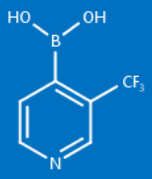

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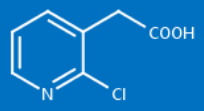

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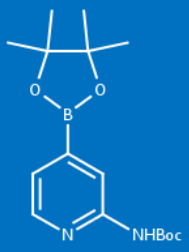

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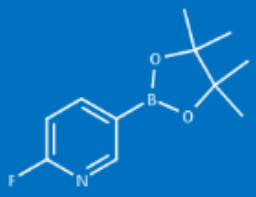

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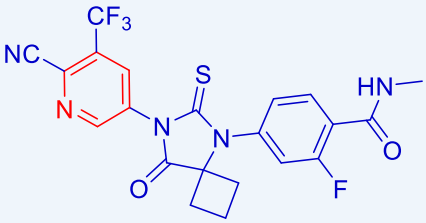
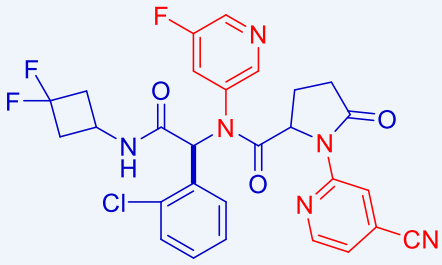


apalutamide (Erleada, **7**)
Janssen, 2018
androgen receptor antagonist



ivosidenib (Tibsovo, **8**)
Agios, 2018
IDH1 inhibitor

Pyridines in Drug Discovery

In 2017, Pennington and Moustakas published an excellent review on "The Necessary Nitrogen Atom" covering the influence of pyridine as a bioisostere for the phenyl fragment (dubbed as the N scan SAR strategy).[9] The phenyl–pyridyl switch may have profound impact on a drug's *in vitro* binding affinity; *in vitro* functional affinity; *in vitro* PK/ADME profile; *in vitro* safety profile; and *in vivo* pharmacological profile. Here only a few interesting examples are highlighted.

a. Boosting Biochemical Potency

Replacing a phenyl ring with a pyridine offers a nitrogen atom as a hydrogen bond acceptor, which may make contact with the target, forming a hydrogen bond in addition to a subtle change in π-stacking. The consequence may be higher binding affinity and better biochemical potency.

Phenyl-linked sulfonamide **9** as a dual mammalian target of rapamycin (mTOR) and phosphoinositide 3-kinase-α (PI3Kα) inhibitor was not very potent (mTOR, IC_{50} = 1,500 nM; PI3Kα, IC_{50} = 48 nM). A partial N-scan on the phenyl scaffold of **9** identified pyridyl-linked sulfonamide **10** displaying 140- and 30-fold improved potency toward mTOR and PI3Kα, respectively (mTOR, IC_{50} = 11 nM; PI3Kα, IC_{50} = 1.6 nM). An X-ray cocrystal structure revealed that the pyridyl N atom engaging in a hydrogen bond with an ordered water molecule located between Tyr867 and Asp841 in the affinity pocket of the enzyme.[10]

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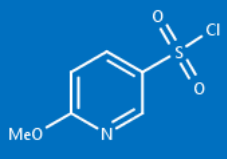

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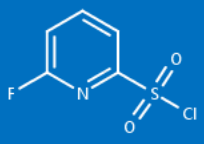

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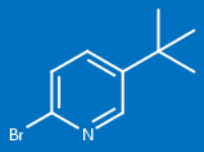

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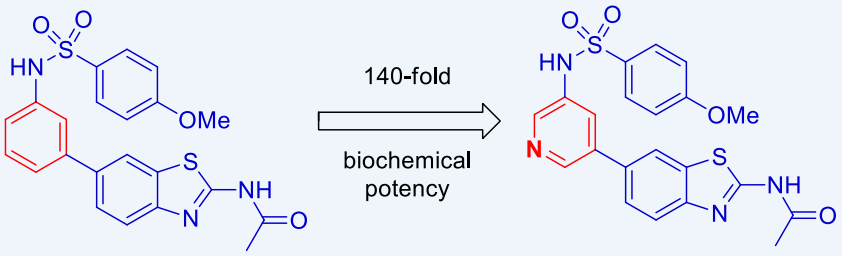
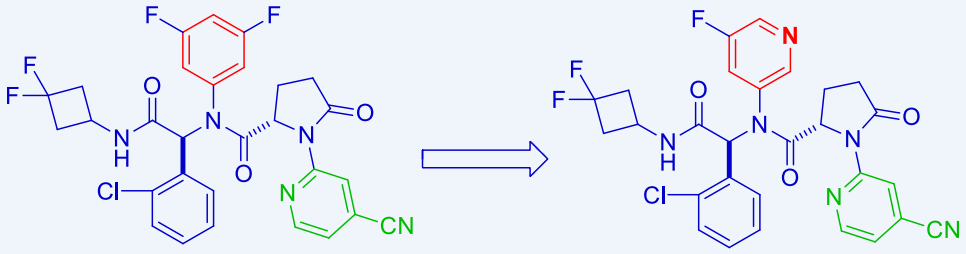


phenyl-linked sulfonamide **9**
mTOR IC_{50} = 1,500 nM
PI3Kα K_i = 48 nM

pyridyl-linked sulfonamide **10**
mTOR IC_{50} = 11 nM
PI3Kα K_i = 1.6 nM

b. Fixing CYP450 Liability

One of Agios' IDH1 inhibitors AGI-14100 (**11**) looked largely promising as a drug candidate with a good profile of single-digit nM potency in enzyme and cell-based assays and desired metabolic stability. However, assessment in the human pregnane X receptor (hPXR) screen indicated that it was potentially a CYP 3A4 inducer. hPXP activation by AGI-14100 (**11**) was approximately 70% of rifampicin, a known strong CYP 3A4 inducer. Miraculously, changing one of the two C–F bonds with an N atom embedded in the ring led to ivosidenib (Tibsovo, **12**) with two pyridine rings and a balance of desirable properties: good enzyme and cellular potency, good stability in human liver microsomes (HLM), reduced hPXPR activation, good permeability, and low efflux ratio (E_h).[8] It is small wonder that it eventually became an FDA-approved drug.



AGI-14100 (**11**)	ivosidenib (Tibsovo, **12**)
enzyme IC_{50}, 6 nM	12 nM
cellular IC_{50}, 1 nM	8 nM
E_h 0.23	0.15
hPXR activation (% of rifampicin at 1/10 μM):	
69/70	2/21

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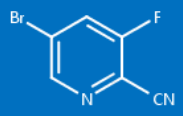

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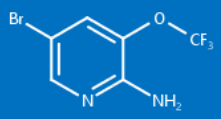

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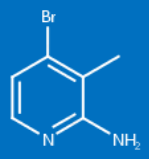

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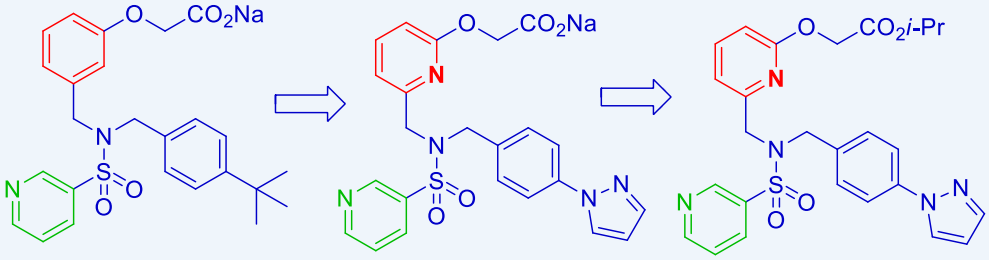
c. Elevating Permeability

Pfizer's CP-533,536 (**13**) is a selective and non-prostanoid EP2 receptor agonist (EP2 stands for prostaglandin E2). Switching one CH to N led to omidenepag (OMD, **14**), which was 15-fold more potent than its progenitor **13**. However, OMD (**14**)'s cell membrane permeability was insufficient and the rate measured with the parallel artificial membrane permeability assay (PAMPA) was 0.9×10^{-6} cm/s. The isopropyl ester prodrug, omidenepag isopropyl (OMDI, **15**), gratifyingly, had adequate cell membrane permeability with a rate of 2.8×10^{-5} cm/s. After showing efficacy in lowering intraocular pressure (IOP) following ocular administration in ocular normotensive monkeys, omidenepag isopropyl (**15**) was selected as a clinical candidate for the treatment of glaucoma.[11]



Some may consider "cheating" to use ester prodrug **15** to further boost the drug's cellular permeability. A *bona fide* example of permeability improvement via phenyl–pyridyl switch may be found in Lundbeck's endeavor in their tricyclic thiazolopyrazole derivatives as metabotropic glutamate receptor 4 (mGluR4) positive allosteric modulators (PAMs). Phenyl aniline **16** displayed weak PAM activity and poor permeability in PAMPA. Nitrogen scan afforded 3-pyridyl aniline **17** with > 190-fold increase of permeability although at the price of losing potency. The 2-pyridyl aniline saw > 30-fold improvement in permeability and a 10-fold increase in potency, but its kinetic solubility was low. Eventually, the corresponding 2-pyrimidyl aniline derivative had a good balance of potency, permeability, and solubility.[12] In this case, one more nitrogen atom is good, two more are even better!

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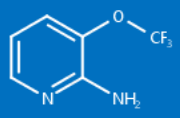

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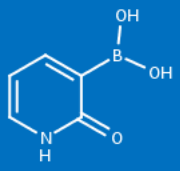

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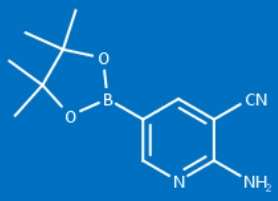

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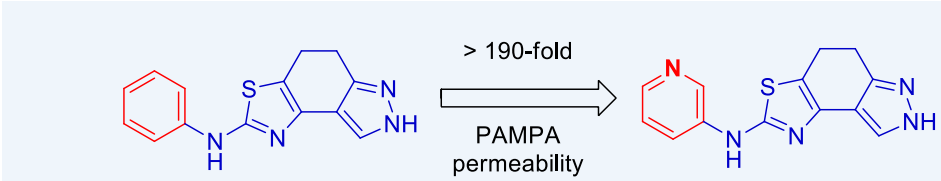


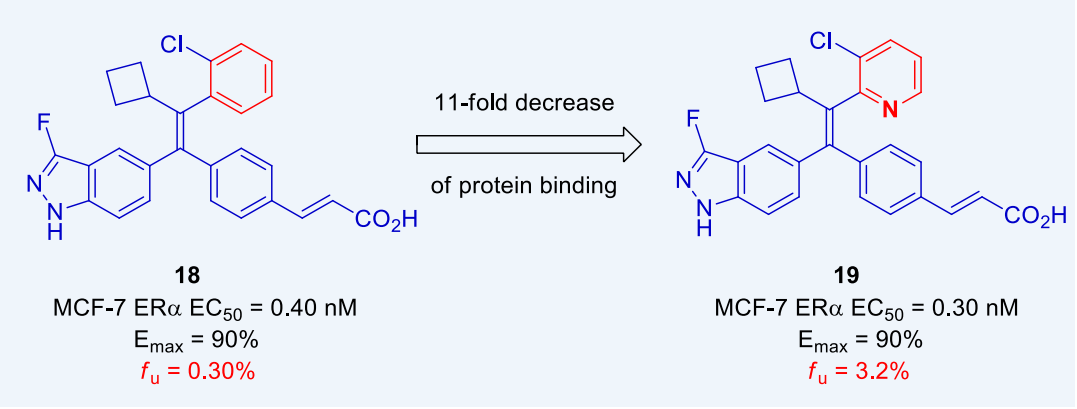
phenyl aniline **16**
mGlu4 EC_{50} = 2.2 μM
P_{app}(A→B) < 0.10x10^{-6} cm/s

3-pyridyl aniline **17**
mGlu4 EC_{50} > 10 μM
P_{app}(A→B) = 19x10^{-6} cm/s

d. Addressing Protein Binding Issue

The phenyl–pyridyl switch has been employed to fix protein binding (plasma protein shift) issues. For example, olefin **18** as a selective estrogen receptor degrader (SERD) had an excellent potency toward lowering steady-state ERα levels but was highly protein-bound in diluted mouse plasma (f_u = 0.30%). The phenyl–pyridyl switch offered several pyridyl analogs. One of them, 2-pyridyl **19** exhibited an 11-fold lower protein binding (f_u = 3.2%). Apparently, reduction of the molecule's lipophilicity was beneficial in reducing protein binding.[13]

Again, many useful examples on the merits of the phenyl–pyridyl switch may be found in Pennington's scholastic 2017 JMC review.[9]



18
MCF-7 ERα EC_{50} = 0.40 nM
E_{max} = 90%
f_u = 0.30%

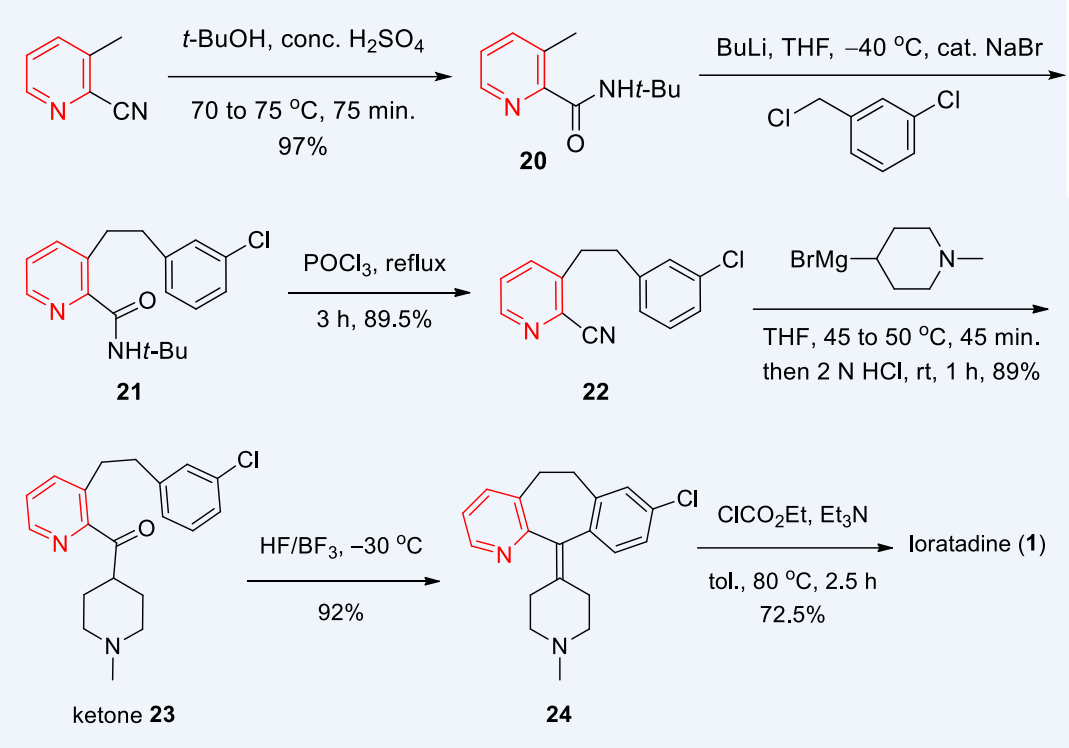
19
MCF-7 ERα EC_{50} = 0.30 nM
E_{max} = 90%
f_u = 3.2%

Synthesis of Some Pyridine-containing Drugs

*a. Loratadine (Claritin, **1**)*

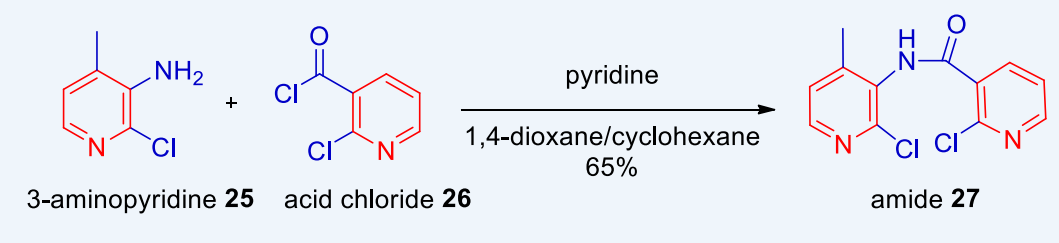
Schering–Plough's synthesis of loratadine (**1**) commenced with a Ritter reaction of 3-methylpicolinonitrile in *t*-butanol with the aid of concentrated H_2SO_4 as catalyst to prepare *N*-(*tert*-butyl)-3-methylpicolinamide (**20**) as a means of masking the nitrile group. After treating **20** with 2 equivalents of BuLi, the resulting intensely purple colored dianion underwent an S_N2 reaction with *m*-chlorobenzyl chloride to assemble adduct **21**. Refluxing **21** in $POCl_3$ restored the original nitrile functionality on **22**, which was then treated with *N*-methyl-piperidinyl Grignard reagent to produce ketone **23**

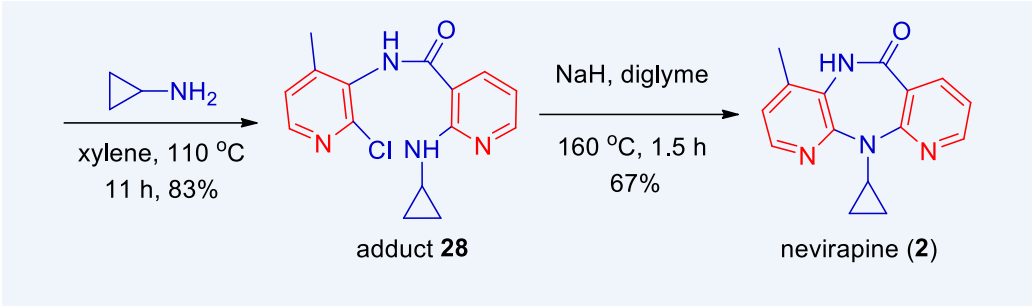
after acidic hydrolysis of the imine intermediate. Superacid cyclodehydration of ketone **23** employing HF/BF_3 delivered the C8-chloro-tricyclic **24**. Superacid HF/BF_3 was key to the success for regioselectivity with minimal C10-chloro isomer formation. The penultimate derivative **24** was then treated with 3 equivalents of ethyl chloroformate to deliver antihistamine **1**.[14]



*b. Nevirapine (Viramune, **2**)*

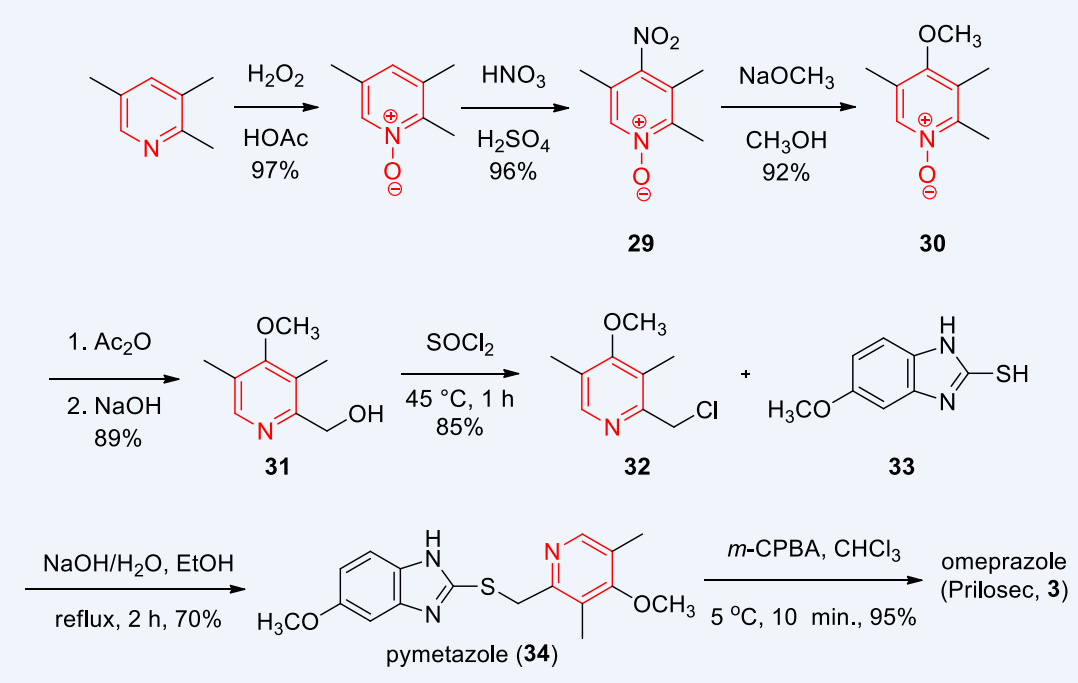
The precursor for one of the syntheses of nevirapine (**2**) was 3-aminopyridine **25**, which was prepared from reduction of the corresponding 3-nitropyridine analog. Coupling **25** with acid chloride **26** resulted in bis-pyridyl-amide **27**. Subsequent S_NAr reaction between **27** and cyclopropylamine gave adduct **28** in 83% yield. Such an excellent regioselectivity favoring the chloride on the right is a reflection of its attachment to an electron-withdrawing carbonyl group. Finally, adduct **28**, on cyclization under basic conditions at 160 °C, afforded nevirapine (**2**) in 67% yield.[15]





*c. Omeprazole (Prilosec, **3**)*

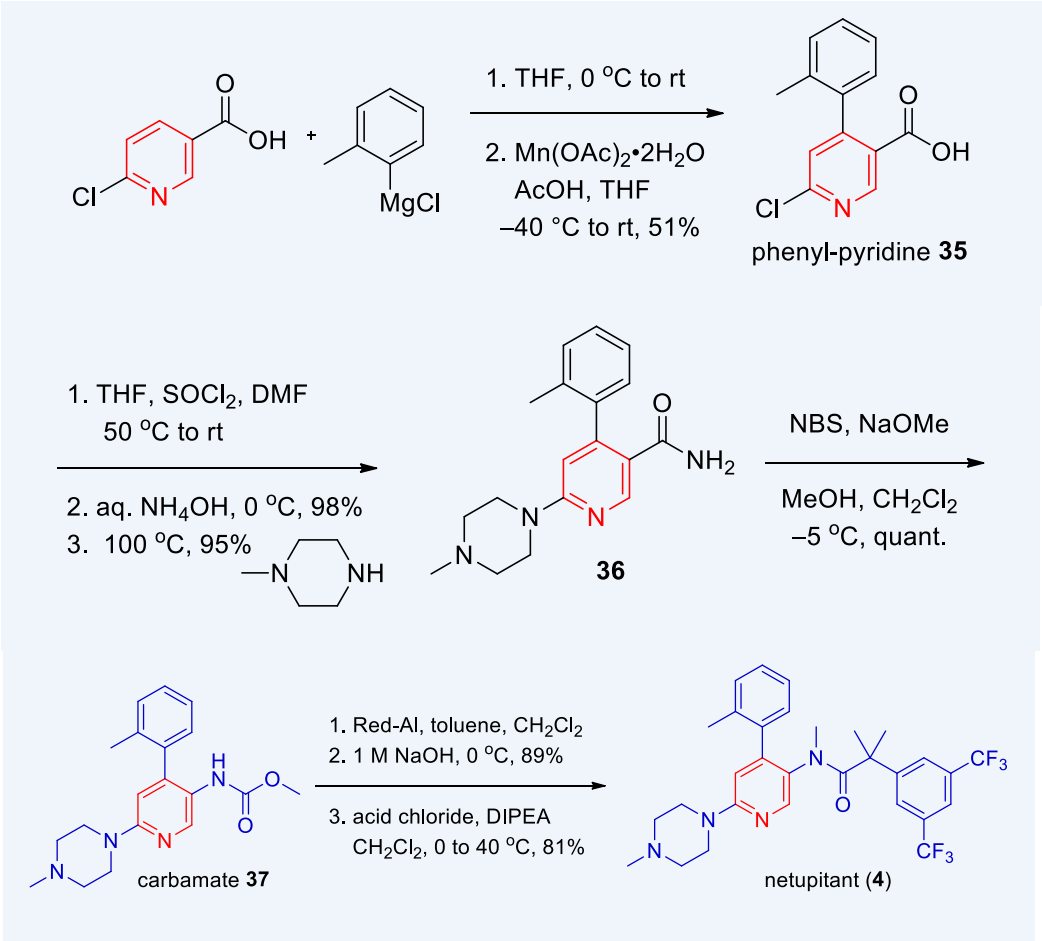
One of the syntheses of omeprazole (Prilosec, **3**) employed 2,3,5-trimethylpyridine as its starting material, which underwent an oxidation and subsequent nitration to produce 4-nitro-pyridine *N*-oxide **29**. S_NAr replacement of the nitro group with NaOMe afforded 4-methoxy-pyridine *N*-oxide **30**. The Boekelheide reaction entailing treatment of *N*-oxide **30** with acetic anhydride offered hydroxymethyl-pyridine **31** after basic hydrolysis of the acetate intermediate. Chlorination of alcohol **31** led to chloride **32**, which was coupled with thiol **33** to assemble pymetazole (**34**). Oxidation of sulfide **34** then delivered omeprazole (**3**).[16]



*d. Netupitant (**4**)*

Roche's preparation of netupitant (**4**) was initiated by a conjugate addition of *o*-tolylmagnesium chloride to 6-chloronicotinic acid to afford the corresponding dihydropyridine intermediate, which was then oxidized to

phenyl-pyridine **35**. Converting its carboxylic acid to the corresponding primary carboxamide was followed by an S_NAr displacement of the chlorine with 1-methylpiperazine to give tri-substituted pyridine **36**. The Hoffmann rearrangement of **36** was initiated by NBS to produce carbamate **37**, which was then reduced to the corresponding methylaniline and treated with the requisite acid chloride to deliver netupitant (**4**).[17]



*e. Abemaciclib (Verzenio, **5**)*

As the first step for a route to Lilly's CDK4/6 inhibitor abemaciclib (**5**), a reductive amination between 6-bromonicotinaldehyde and 1-ethylpiperazine led to adduct **38**. Conversion of the bromide to the corresponding amine employing Hartwig's procedure—a combination of LiHMDS and $Pd_2(dba)_3$ with the aid of CyJohnphos as the ligand led to aminopyridine **39** after acidic hydrolysis. A Buchwald–Hartwig coupling of **39** with chloropyrimidine **40** then produced abemaciclib (**5**).[18]

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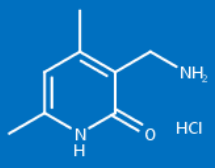

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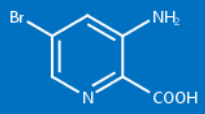

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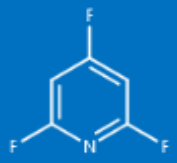

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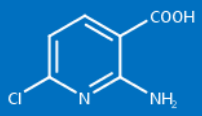

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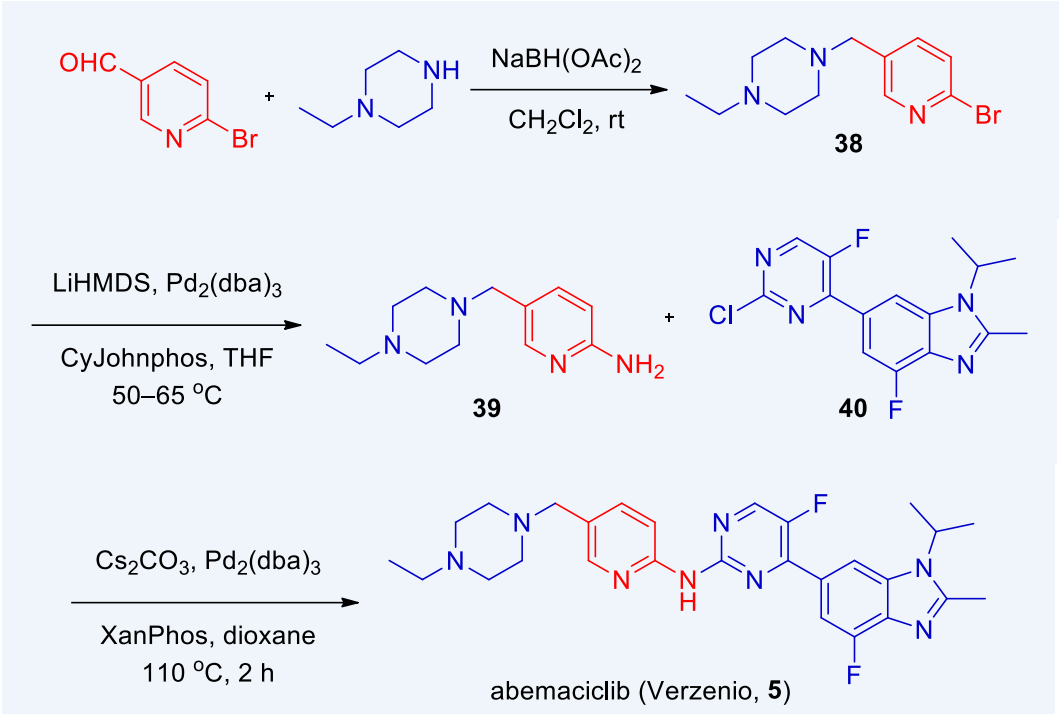
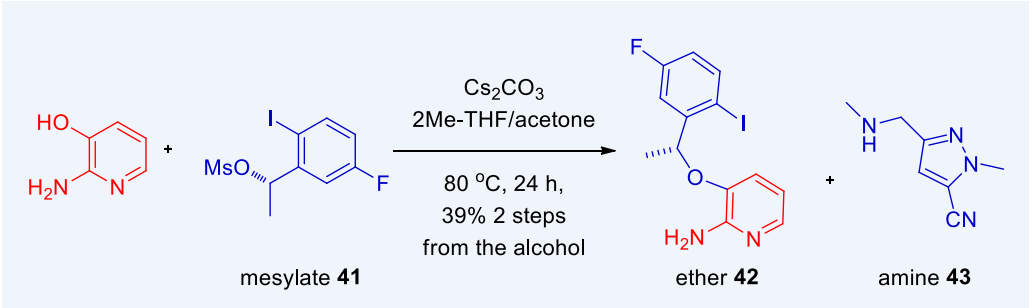


*f. Lorlatinib (Lorbrena, **6**)*

Pfizer's synthesis of lorlatinib (**6**) started with an S_N2 displacement of mesylate **41** with 2-aminopyridin-3-ol to prepare ether **42**, which coupled with amine **43** under palladium-catalyzed carbonylation conditions to assemble amide **44**. Regioselective bromination was readily achieved to install 5-bromopyridine **45** since the pyridine ring became quite electron-rich under the influence of two strongly electron-donating substituents. Because the intramolecular Heck reaction did not work well in the presence of "naked" C2-amine group, it had to be protected as bis-acetamide **46**, which was then cyclized to deliver lorlatinib (**6**) after acidic deprotection.[6]



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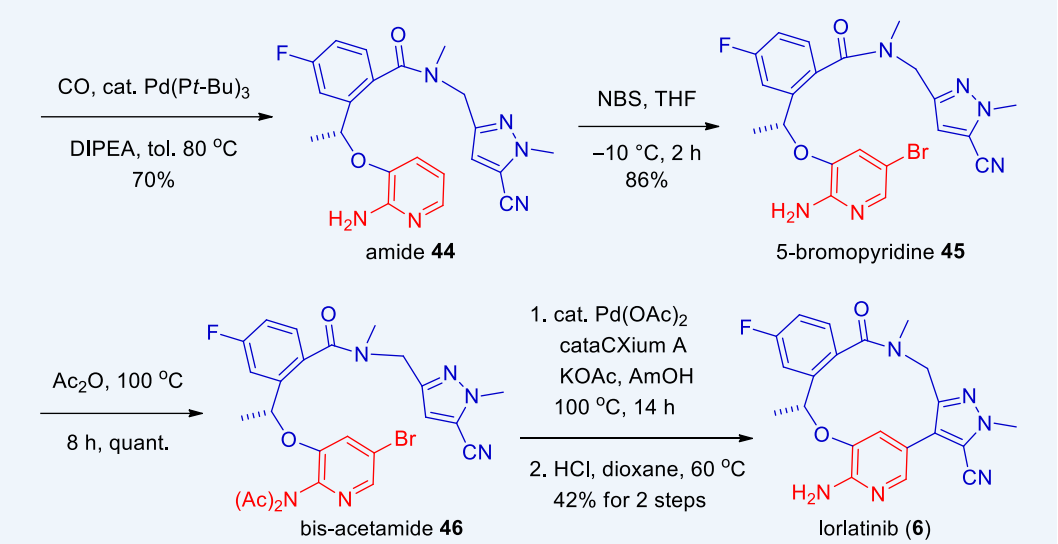
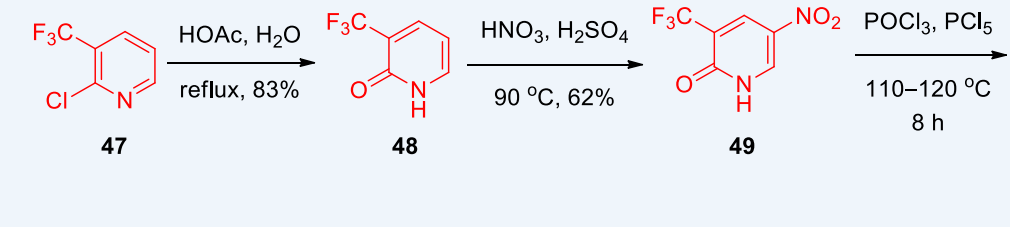


*g. Apalutamide (Erleada, **7**)*

Hydrolysis of commercially available 2-chloro-3-(trifluoromethyl)pyridine (**47**) was Jung's first step toward apalutamide (**7**) to afford pyridone **48**, which offered requisite reactivity and regioselectivity for nitration to produce 5-nitropyridone **49**. Refluxing **49** with a mixture of $POCl_3$ and PCl_5 restored the chloropyridine functionality on **50**, which was then reduced to 6-chloro-5-(trifluoromethyl)pyridin-3-amine (**51**). The choice of Raney nickel as the catalyst for hydrogenation was a wise one because a palladium-based catalyst would have caused concurrent dechlorination. After Boc protection of the amine as **52**, an S_NAr reaction took place to install 6-cyano-pyridine on **53**, which underwent an acidic deprotection to unmask the amine on **54**. Transformation of **54** to isothiocyanate **55** was accomplished by treating **54** with thiophosgene. Coupling between isothiocyanate **55** and aniline **56** then delivered apalutamide (**7**) after acidic hydrolysis.[19]



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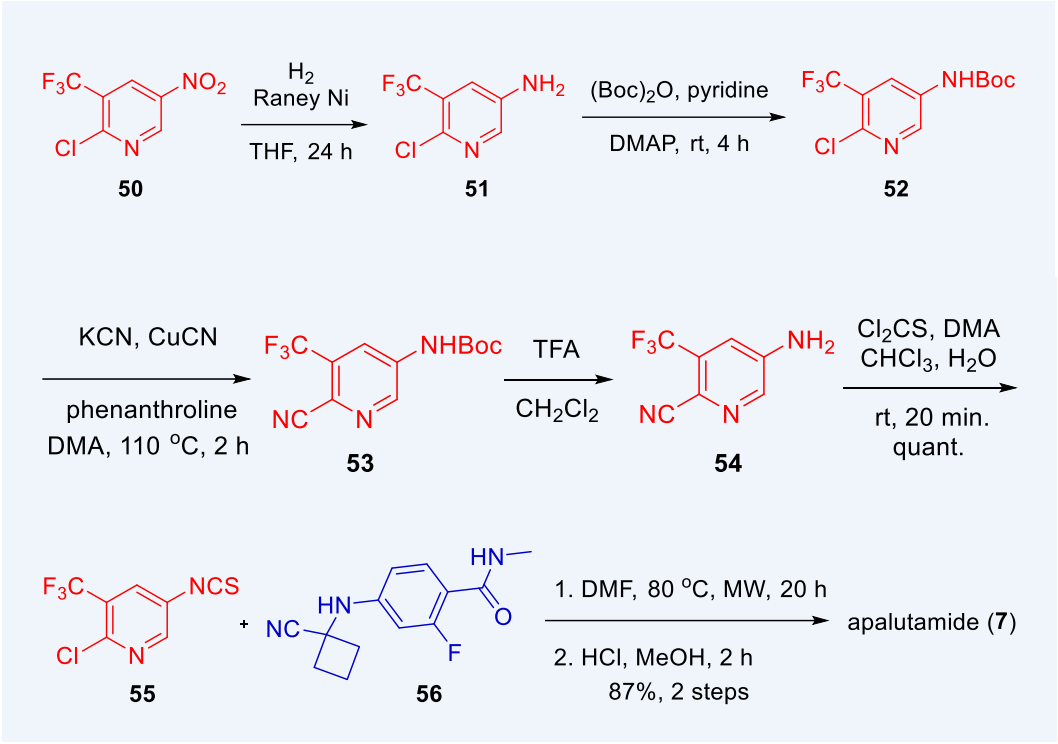

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