Bicyclic Pyridines Containing Ring-junction Nitrogen in Drug Discovery

Key Points

- May boost binding to target proteins and elevate potency
- Reducing metabolic liabilities, and create novel chemical space and intellectual properties

Overview

With four imidazo[1,2-*a*]pyridine-containing drugs and one pyrazolo[1,5-*a*]pyridine-containing drug on the market, bicyclic pyridines containing ring-junction nitrogen are privileged structures in medicinal chemistry. With two nitrogen atoms with potential to serve as hydrogen bond acceptors, imidazopyridines and pyrazolopyridines may boost binding to target proteins and elevate potency. In addition, these structures have found utility in FBDD, covalent inhibitors, reducing metabolic liabilities, and creating novel chemical space and intellectual properties. With many of the advanced intermediates now commercially available, they will find more and more applications in drug discovery.

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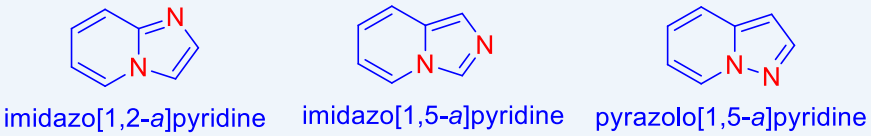
PharmaBlock designs and synthesizes over 795 bicyclic pyridines and 162 bicyclic pyridine products are in stock. CLICK HERE to find detailed product information on webpage.

There are three classes of bicyclic pyridines that contain a ring-junction nitrogen: imidazo[1,2-*a*]pyridines, imidazo[1,5-*a*]pyridines, and pyrazolo[1,5-*a*]pyridines. Their utility in drug discovery and preparations are reviewed by Larry Yet in a chapter in his excellent book: *Privileged Structures in Drug Discovery, Medicinal Chemistry and Synthesis.*[1]



Bicyclic Pyridine-containing Drugs

There are at least four imidazo[1,2-*a*]pyridine-containing drugs and one pyrazolo[1,5-*a*]pyridine-containing drug currently on the market.

Synthélabo's alpidem (Anaxyl, **1**) is a γ-aminobutyric acid ($GABA_A$) agonist specifically used for treating anxiety approved in France in 1991. Its close analog zolpidem (Ambien, **2**), also a $GABA_A$ agonist, is a blockbuster drug to treat insomnia because, unlike alpidem (**1**), zolpidem (**2**) has sedative effect. It is highly bioavailable (70%) with a short duration of action ($t_{1/2}$ = 2 h). In contrast, alpidem (**1**) has a half-life of 19 h, a testimony to the fact that its two chlorine atoms are more resistant to CYP450 metabolism in comparison to the two methyl groups on zolpidem (**2**).[2] Two similar imidazo[1,2-*a*]pyridine-based $GABA_A$ agonists saripidem and necopidem were investigated in clinical trials but did not gain government approval for marketing. Olprinone (Coretec, **3**) is a cardiotonic agent only available in Japan. It is a phosphodiesterase-3 (PDE3) inhibitor with positive ionotropic and vasodilator effects.[3] On the other hand, minodronic acid (Recalbon, **4**) is the third generation bisphosphonate oral drug to treat loss of bone density for diseases such as osteoporosis.

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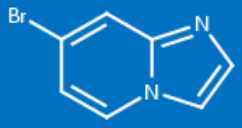

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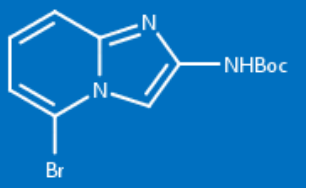

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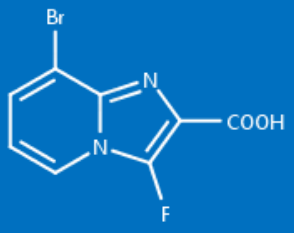

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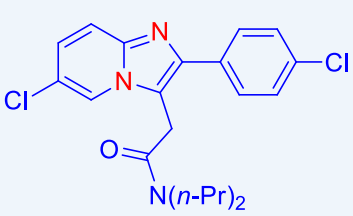
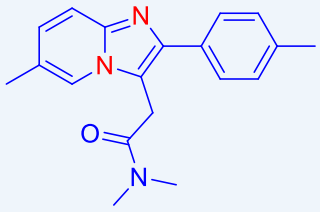
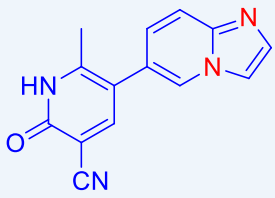
Finally, ibudilast (Ketas, **5**) has the pyrazolo[1,5-*a*]pyridine core structure. Only available in Japan for treating asthma and stroke, it is a neuroimmune modulator. It is a pan-PDE inhibitor with activities against PDE-3, PDE-4, PDE-10, and PDE-11. Other more PDE-4 selective inhibitors include roflumilast (*Daliresp*) for treating chronic obstructive pulmonary disease (COPD) and apremilast (Otezla) for treating plaque psoriasis.[4]



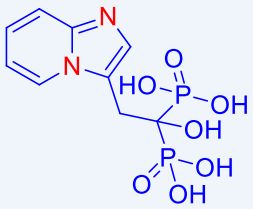
alpidem (Anaxyl, **1**)
Synthelabo, 1991
GABA agonist



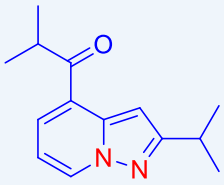
zolpidem (Ambien, **2**)
Sanofi-Aventis, 1992
GABA agonist



olprinone (Coretec, **3**)
Eisai, 1996
PDE3 inhibitor



minodronic acid (Recalbon, **4**)
Ono/Astellas, 2009
bisphosphonate



ibudilast (Ketas, **5**)
Kyorin, 1992
PDE inhibitor

Bicyclic Pyridines in Drug Discovery

Receptor interacting protein kinase-2 (RIPK2) is an intracellular serine/threonine/tyrosine kinase, a key signaling partner, and an obligate for nucleotide-binding oligomerization domain-containing protein 2 (NOD2). Employing virtual library screening (VLS), He and colleagues chose pyrazolo[1,5-*a*]pyridine **6** as their starting point among other hits because although it had only micro-molar (1.5 μM) activity, it exhibited attractive ligand efficiency (LE = 0.32) and lipophilic efficiency (LiPE = 3.5). Guided by structure-based drug design (SBDD) combined with extensive structure–activity relationship (SAR) investigations, they arrived at imidazo[1,2-*a*]pyridine **7**, which was potent and selective with excellent oral bioavailability. In both *in vitro* and *in vivo* assays, imidazo[1,2-*a*]pyridine **7** showed activities in suppressing cytokine secretion upon activation of the NOD2:RIPK2 pathway.[5]

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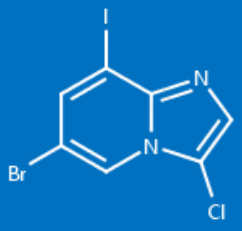

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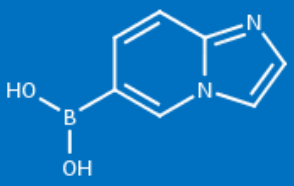

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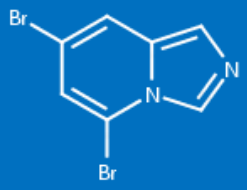

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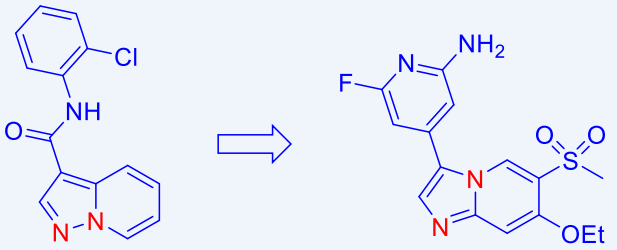

6, RIPK2, IC_{50} = 1.5 μM
CLogP = 2.31
LE = 0.32, LiPE = 3.5

7, RIPK2, IC_{50} = 3 nM

The imidazo[1,2-*a*]pyridine core structure was used as an isostere of imidazo[1,2-*a*]pyrimidine to reduce metabolism mediated by aldehyde oxidase (AO). Pfizer identified imidazo[1,2-*a*]pyrimidine **8** as a full antagonist of the androgen receptor (AR) with excellent *in vivo* tumor growth inhibition (TGI) in castration-resistant prostate cancer (CRPC). Regrettably, compound **8**'s core structure imidazo[1,2-*a*]pyrimidine moiety was rapidly metabolized by AO. Indeed, heteroaryls, such as imidazo[1,2-*a*]pyrimidines, are versatile synthetic building blocks commonly used in medicinal chemistry because they are often capable of binding to diverse biological targets with high affinity and providing useful pharmacological activities. In addition, electron-deficient heteroaryls are often resistant to CYP-450-mediated metabolism. However, an electron-deficient nature may also make the ring carbons susceptible to nucleophilic attack by aldehyde oxidase (AO), particularly when they are adjacent to heterocyclic nitrogen(s). Guided by an AO protein structure-based model, Pfizer chemists discovered that imidazo[1,2-*a*]pyridine core structure on compound **9** (with one nitrogen atom removed from the original core structure on **8**) was clean of AO metabolism although it was more susceptible to CYP450 oxidation. Another tactic was also successful for blocking the AO metabolism by installing a methoxyl group at C29 on the imidazo[1,2-*a*]pyrimidine ring. It was speculated that C29 was the most probable AO oxidation site.[6]

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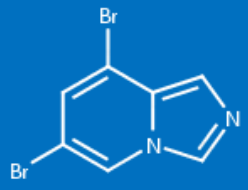

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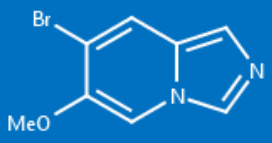

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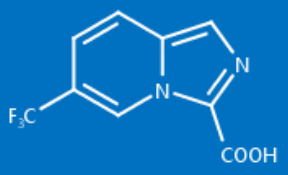

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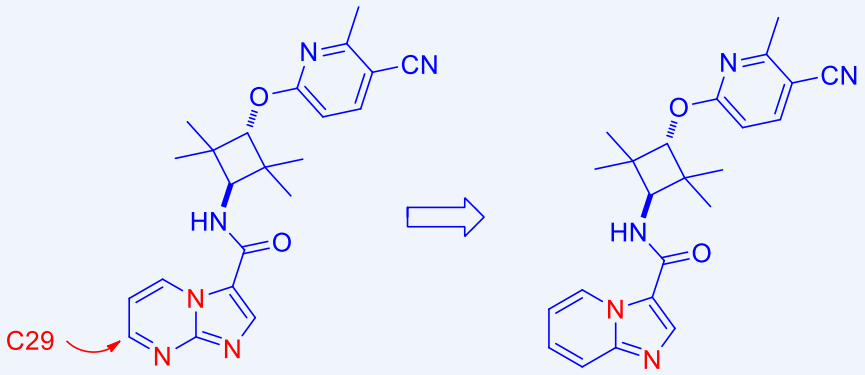

Fragment-based drug discovery (FBDD) has attracted more and more attention, especially with the FDA approval of Plexxikon's vemurafenib (Zelboraf) in 2011 and Abbvie's venetoclax (Venclexta), both of which started with fragment hits.

Astex obtained fragment **10** as a hit using a protein thermal shift assay (T_M) in their pursuit of selective discoidin domain receptors 1 and 2 (DDR1/2) inhibitors. Fragment **10** placed a chlorophenyl in the back pocket region and a pyridyl in the selectivity pocket proximal to the small gatekeeper residue (Thr701 in DDR1/2) and lacked a hinge binding moiety. With the help of crystal structures and computer-aided drug design (CADD) by overlaying with FGFR inhibitor dasatinib, Astex installed an imidazo[1,2-*a*]pyridine in place of the thiazole hinge binder. The resulting compound **11**'s imidazo[1,2-*a*]pyridine fragment indeed formed the anticipated hydrogen bonds with the hinge. More interestingly, it was demonstrated that compound **13**'s sp^3 center in the linker region can be used in conjunction with a variety of linker groups. It is potent, selective and also displays promising pharmacokinetic properties.[7]

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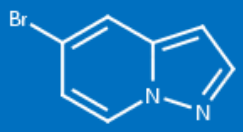

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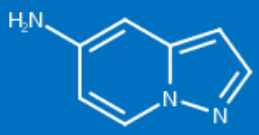

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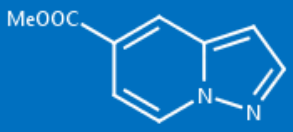

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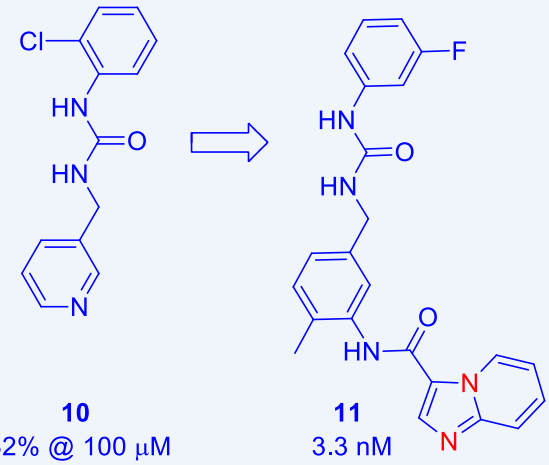

10
32% @ 100 μM

11
3.3 nM

Pyrazolo[1,5-*a*]pyridines have been employed as bioisosteres for imidazo[1,2-*a*]pyridines.

Pyrazolo[1,5-*a*]pyridine substituent was a preferred fragment of a covalent epidermal growth factor receptor (EGFR) inhibitor. EGFR inhibitors were among the earliest kinase inhibitors on the market. But resistance invariably developed and covalent inhibitors have been invented to combat the L858R and T790M mutations by taking advantage of Cys-797 at EGFR's active site. T790M mutation is also known as the gatekeeper mutation. AstraZeneca chose Dana–Farber's WZ-4002 (**12**, $LogD_{7.4} > 4.3$) as their starting point because it showed activities against EGFR's L858R and T790M double mutation (DM). In an effort to maintain activities against double mutation while reducing lipophilicity, AstraZeneca arrived at covalent inhibitor **13** with the pyrazolo[1,5-*a*]pyridine fragment. While it is less active in the exon 19 deletion activating (AM) using PC9 cell line, inhibitor **13** achieved remarkable DM/WT margin (WT stands for the wild-type enzyme with a human LoVo cell line). More importantly, it has a $LogD_{7.4}$ value of 3.6 and LLE (for DM) value of 3.4. The compound showed encouraging antitumor efficacy in H1975 double mutant and PC9 activating mutant models although it had relative poor solubility (1.6 μM) and the hERG IC_{50} of 4.2 μM.[8]

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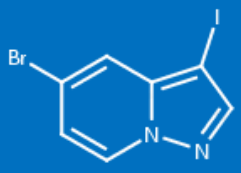

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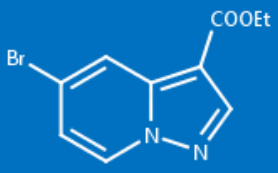

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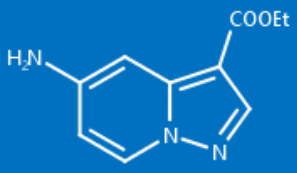

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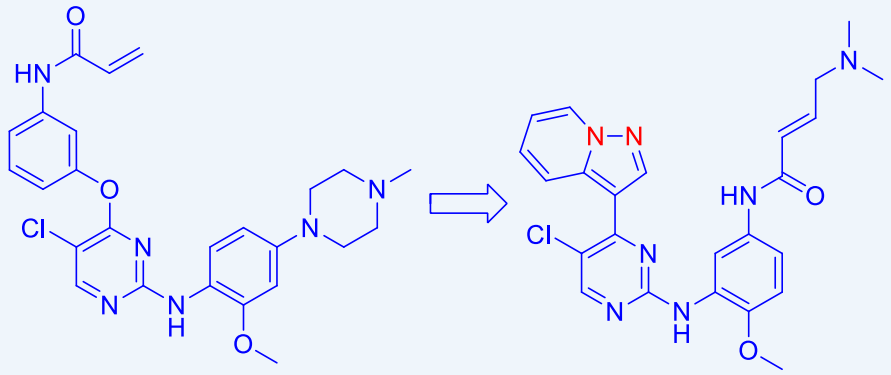
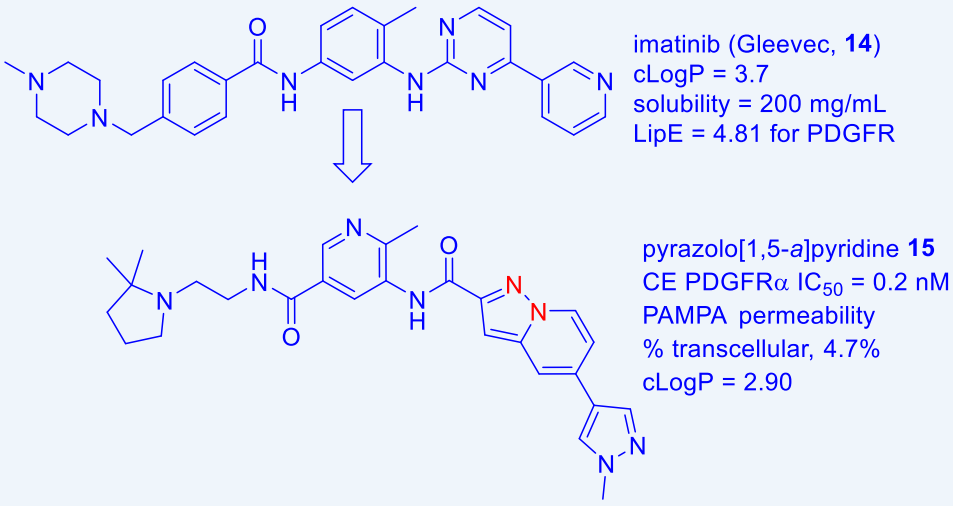


The first approved kinase inhibitor imatinib (Gleevec, **14**) inhibits a panel of kinases including bcr-abl, c-kit, and platelet-derived growth factor receptor (PDGFR). A Novartis team chose imatinib (**14**) as a starting point and employed a novel occupancy assay to directly measure target occupancy. At the end of their SAR, pyrazolo[1,5-*a*]pyridine-containing compound **15** showed 24 h occupancy of the PDGFR kinase domain after a single i.t. dose and had efficacy at 0.03 mg/kg in rat moncrotaline model for pulmonary arterial hypertension.[9]



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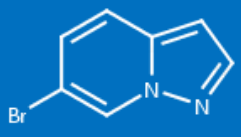

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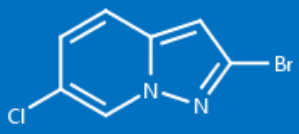

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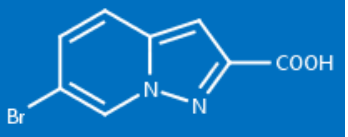

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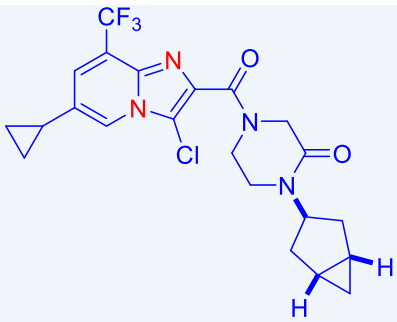
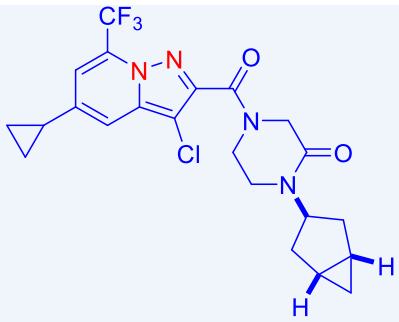
In GSK's pursuit of hepatitis C replication inhibitors targeting the viral NS4B protein, several isosteres for imidazopyridine were explored. In comparison to imidazo[1,2-*a*]pyridine **16**, pyrazolo[1,5-*a*]pyridine **17** was tested more potent in NS4B binding affinity assay for both genotype 1b and 1a.[10]



imidazo[1,2-*a*]pyridine **16**
NS4B binding affinity
GT1b, IC_{50} = 58 nM
GT1a, IC_{50} = 1.4 nM



pyrazolo[1,5-*a*]pyridine **17**
NS4B binding affinity
GT1b, IC_{50} = 4 nM
GT1a, IC_{50} = 0.1 nM

Synthesis of Some Bicyclic Pyridines

Several synthetic routes exist for making alpidem (Anaxyl, **1**). One of the earliest and more robust route began with condensation of aminopyridine **18** with α-bromoketone **19** to assemble imidazo[1,2-*a*]pyridine **20**. Installation of the dimethylaminomethyl group was accomplished using the Mannich conditions to prepare **22**, which then underwent a 3-step sequence to achieve a one-carbon homologation to afford carboxylic acid **23**. Formation of the corresponding acid chloride was followed by addition of diisopropylamine to deliver alpidem (**1**).[11]

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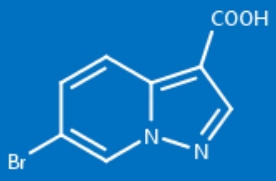

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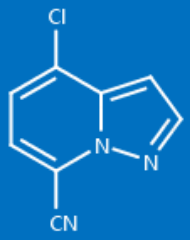

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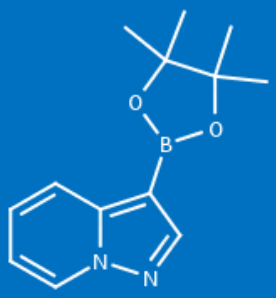

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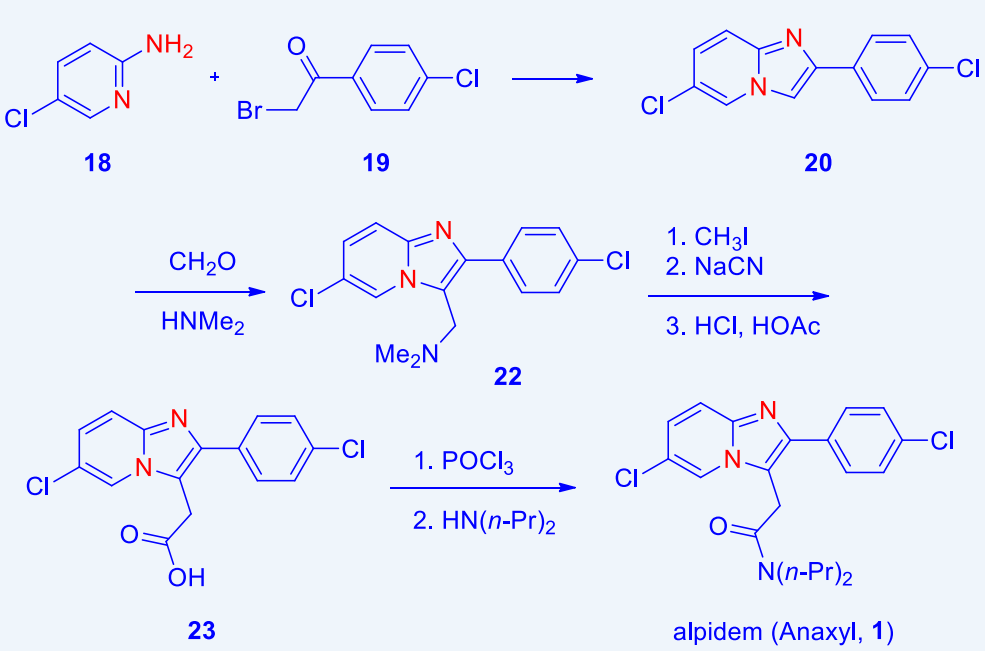
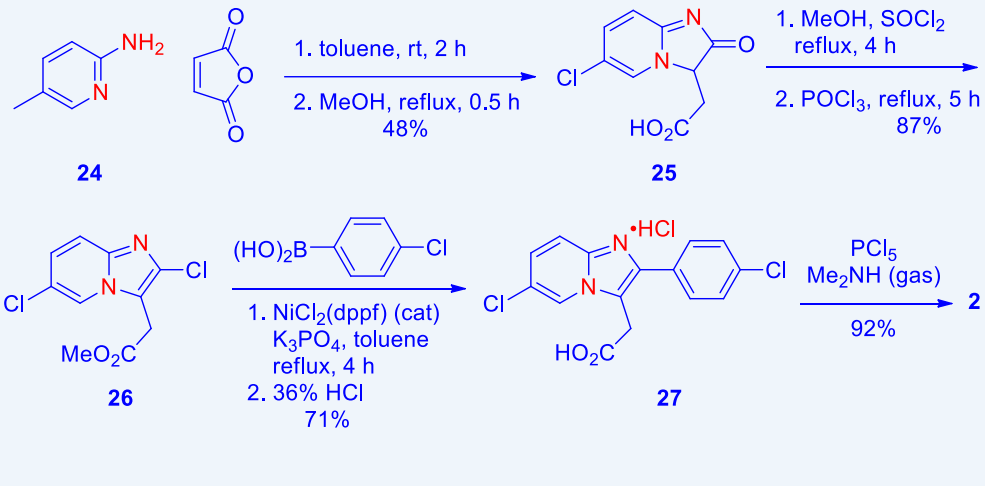


In 2019, Lei and coworkers reported a practical and scalable preparation of zolpidem (**2**) from 2-chloroimidazo[1,2-*a*]pyridine **26**. Therefore, acylation of aminopyridine **24** with maleic acid anhydride was followed an intramolecular Michael addition to assemble **25**. Methyl ester formation was followed by chlorination to provide the key intermediate, 2-chloroimidazo[1,2-*a*]pyridine **26**. Coupling of **26** with tolylboronic acid was optimally carried out using $NiCl_2$(dppf) as the catalyst to afford adduct **27**. The final step to make zolpidem (**2**) was a straightforward amide formation.[12]



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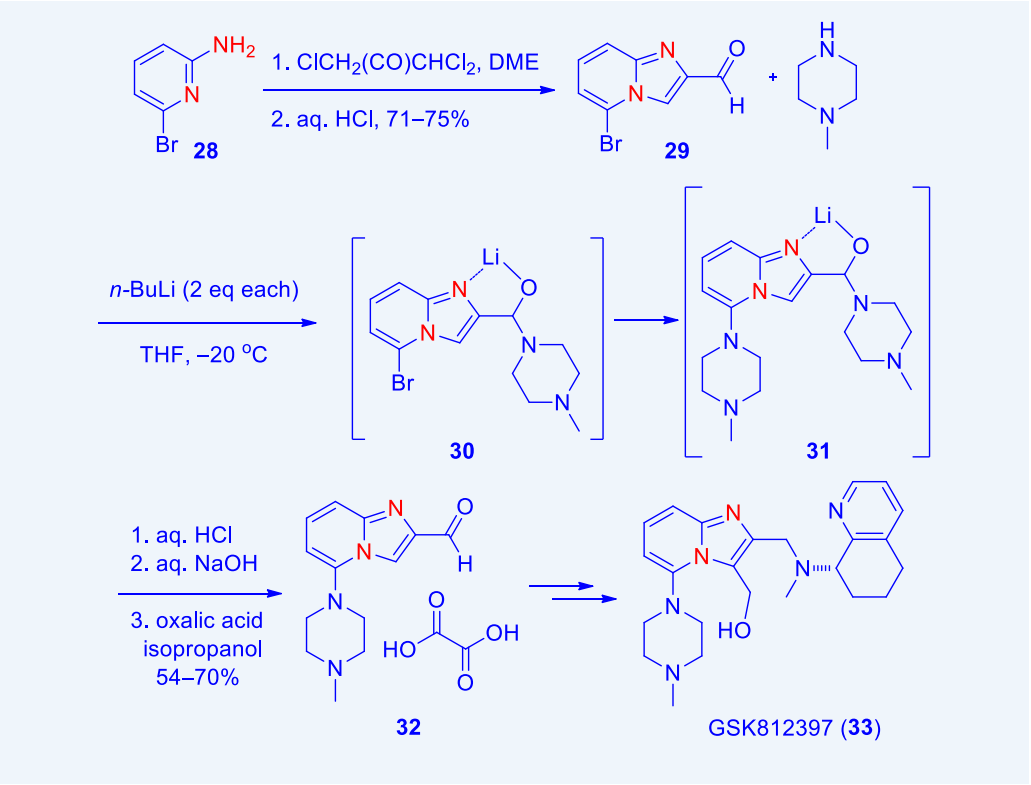
- Enabling technologies of flow chemistry, biocatalysis, photochemistry, electrosynthesis, and fluorination, etc.
- Commercial production with GMP compliance

GSK process chemistry reported a kilogram-scale synthesis of their CXCR4 antagonist GSK812397 (**33**). Condensation of 6-bromopyridin-2-amine (**28**) with 1,1,3-trichloropropan-2-one, followed by acidic hydrolysis led to 5-bromoimidazo[1,2-*a*]pyridine-2-carbaldehyde (**29**). A clever maneuver using lithiated 1-methylpiperazine gave rise to 5-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyridine-2-carbaldehyde (**32**) after applying carefully optimized workup conditions. The trick was using intermediates **30** and **31** to serve as a transient protection so that the aldehyde function was conserved without any protection and deprotection. Two additional steps then delivered GSK812397 (**33**).[13]

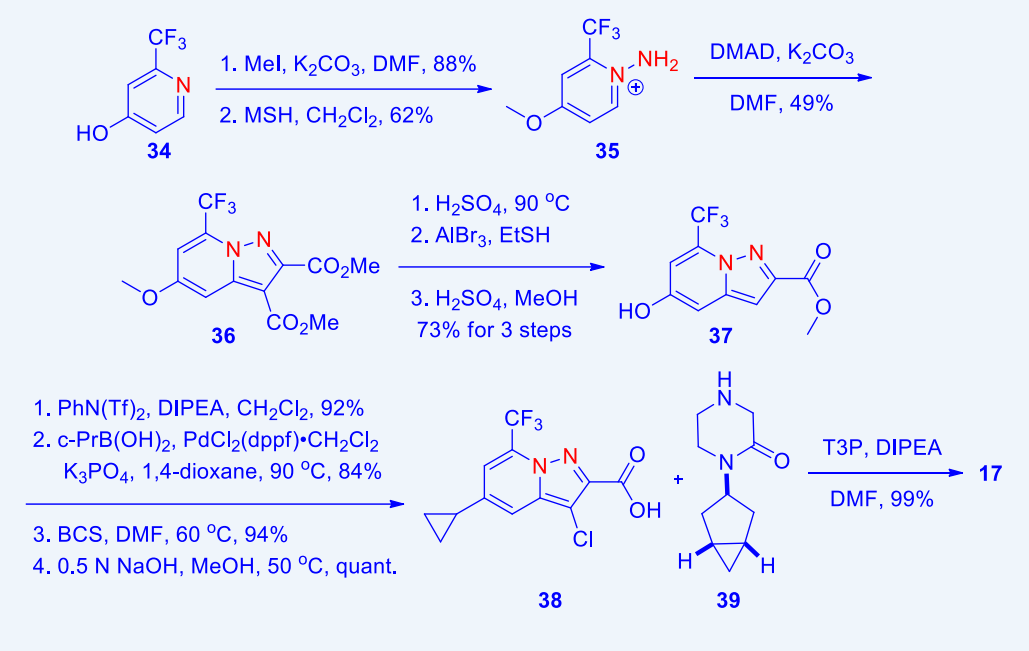


The initial route to prepare pyrazolopyridine **17** used 2-(trifluoromethyl)pyridin-4-ol (**34**) as the starting material. *O*-Methylation was followed by *N*-amination using *O*-mesitylensulfonylhydroxylamine (MSH) as the *N*-amination agent to produce hydrazine **35**. It then underwent a 1,3-dipolar cycloaddition reaction with dimethylacetylene dicarboxylate (DMAD) to give pyrazolopyridine **32** in 49% yield. A three-step sequence from **36** provided ester **37** in 73% yield. An additional four steps of transformations converted **37** to acid **38**, which subsequently was coupled with amine to deliver amide **17** in excellent yield.[10]

Contact Us

PharmaBlock Sciences (Nanjing), Inc.
Tel: +86-400 025 5188
Email: sales@pharmablock.com

PharmaBlock (USA), Inc.
Tel (PA): 1-877 878 5226
Tel (CA): 1-267 649 7271
Email: salesusa@pharmablock.com



In summary, with four imidazo[1,2-*a*]pyridine-containing drugs and one pyrazolo[1,5-*a*]pyridine-containing drug on the market, they are privileged structures in medicinal chemistry. With two nitrogen atoms with potential to serve as hydrogen bond acceptors, imidazopyridines and pyrazolopyridines may boost binding to target proteins and elevate potency. In addition these structures have found utility in FBDD, covalent inhibitors, reducing metabolic liabilities, and create novel chemical space and intellectual properties. With many of the advanced intermediates now commercially available, they will find more and more applications in drug discovery.

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