Furopyridines in Drug Discovery

Key Points

- May serve as a hydrogen bond acceptor and result in additional protein–ligand interact
- May lowers the molecule's lipophilicity

Overview

As in the case of phenyl–pyridine switch, furopyridines have some advantages over the parent benzofurans. The nitrogen atom may serve as a hydrogen bond acceptor and result in additional protein–ligand interactions. Furthermore, the presence of an additional nitrogen atom also lowers the molecule's lipophilicity thus impacts its physiochemical properties such as aqueous solubility. Furopyridine building blocks have found a wide utility in drug design and drug synthesis.

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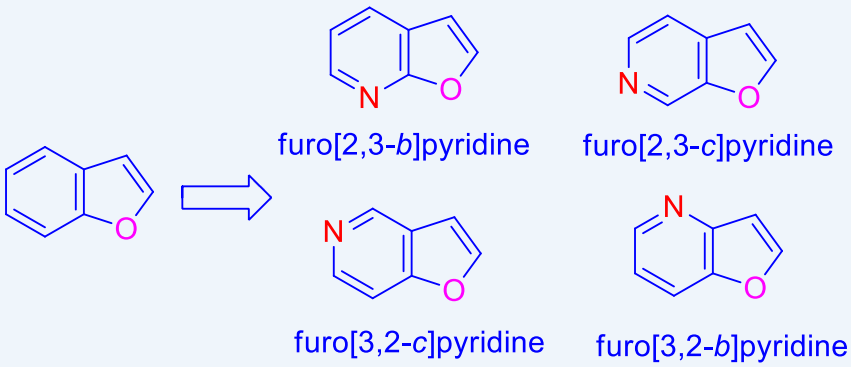
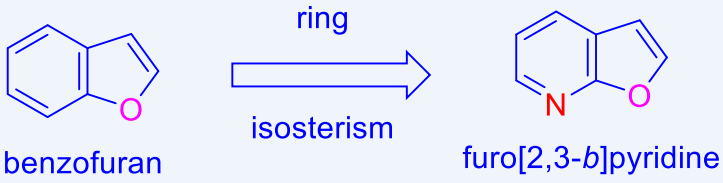
PharmaBlock designs and synthesizes over 96 Furopyridines and 9 Furopyridine products are in stock. CLICK HERE to find detailed product information on webpage.



As bioisoteres to benzofuran, four possible furopyridines exist: furo[2,3-*b*]pyridine, furo[2,3-*c*]pyridine, furo[3,2-*c*]pyridine, and furo[3,2-*b*]pyridine. Collectively they are also known as azabenzofurans. In comparison to its progenitor benzofuran, furopyridines possess an additional nitrogen atom, which may functions as a hydrogen bond acceptor. As in the case of phenyl–pyridine switch, when aligned appropriately with the target protein, azabenzofurans may gain additional protein–ligand interactions in comparison to the parent benzofurans. Furthermore, the presence of an additional nitrogen atom also lowers the molecule's lipophilicity thus impacts its physiochemical properties such as aqueous solubility.[1]



Structure	cLogP	cLogS	HBA	HBD	TPSA	MW
benzofuran	2.11	–2.78	1	0	13 Å	118
furopyridine	1.39	–2.82	2	0	26 Å	119

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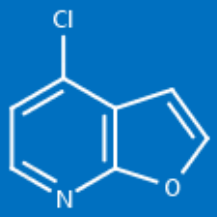

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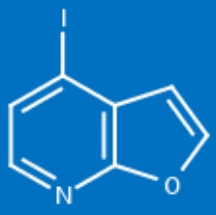

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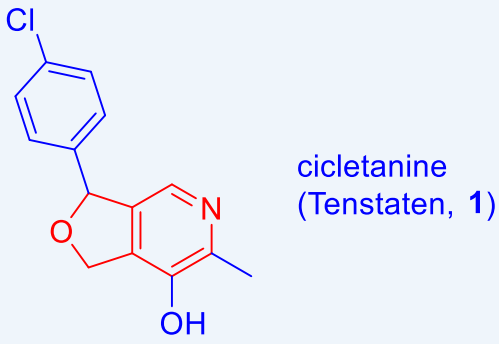
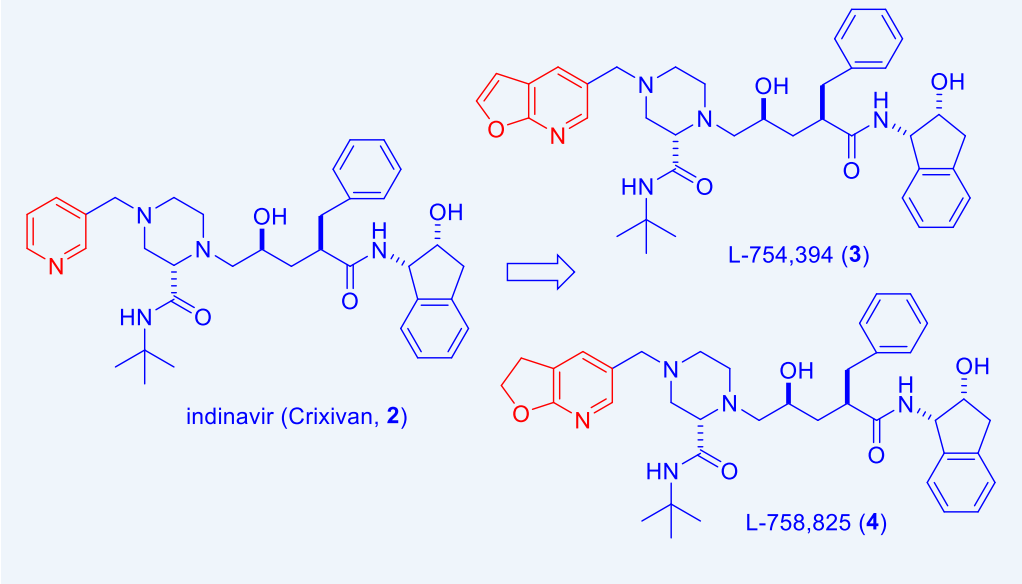
Furopyridine-containing Drugs

Ironically, no furopyridine-containing drugs, *per se*, are on the market. This may be a reflection of past difficulty in synthesizing them either as core structures or as peripheral attachments. Antihypertensive/diuretic agent cicletanine (Tenstaten, **1**) has a tetrahydrofuropyridine core structure.[2] Tetrahydrofuran moiety is more stable than the electron-rich furan toward metabolic oxidation by CYP450 (*vide infra*).



Merck's indinavir (Crixivan, **2**) was one of the first HIV protease inhibitors approved by the FDA in 1996. When its pyridine fragment was replaced with furo[2,3-*b*]pyridine, the resulting protease inhibitor L-754,394 (**3**) was tested to be an *unusually* highly potent and selective mechanism-based inhibitor (MBI, also known as suicide substrate inhibitor) of cytochrome P450 according to *in vitro* studies on the its metabolic activation.[3]



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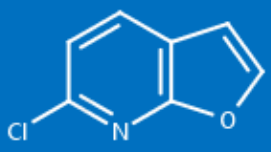

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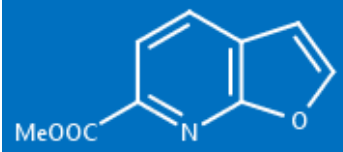

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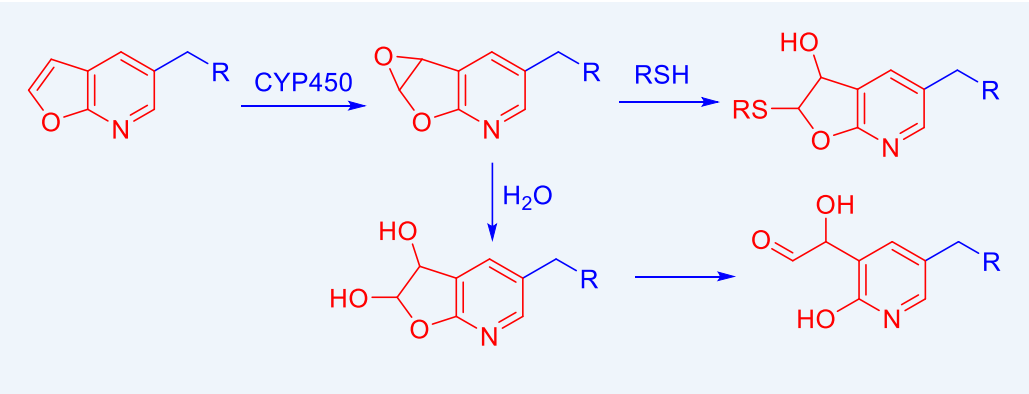
Similar to furan, the furo[2,3-*b*]pyridine motif on L-754,394 (**3**) is readily oxidized by CYP450 3A enzymes to the corresponding epoxide ring, which may be opened by nucleophiles such as water and glutathione (GSH), etc. In hepatic microsomal preparations from rats, dogs, rhesus monkeys, and humans, L-754,394 (**3**) underwent NADPH-dependent metabolic activation to generate electrophilic intermediates, which became covalently bound to cellular proteins, causing destruction of CYP450 enzymes. In contrast, neither indinavir (Crixivan, **2**), which lacks the furan ring, nor L-758,825 (**4**), which is a dihydrofuran derivative was found to act as suicide substrate inhibitors of liver microsome CYP450. Therefore, the furan ring is responsible for the metabolic activation of L-754,394 (**3**).[3] At the end, although furopyridines are prone to CYP metabolic oxidation, but they are probably less reactive than just furan or benzofuran rings because pyridine is an electron-deficient heterocycle.



Furopyridines in Drug Discovery

In one case, 7-aminofuro[2,3-*c*]pyridine **5** was one of OSI's HTS hits of TAK1 inhibitors.[4a] Transforming growth factor β receptor-associated kinase 1 (TAK1 or MAP3K7) is a serine/ threonine kinase which forms a key part of canonical immune and inflammatory signaling pathways. TAK1 inhibitors have potential to treat cancer and inflammatory diseases.

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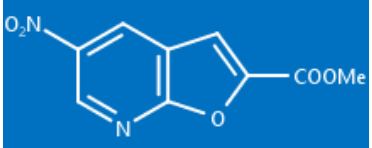

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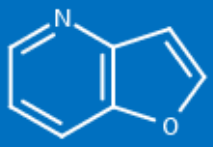
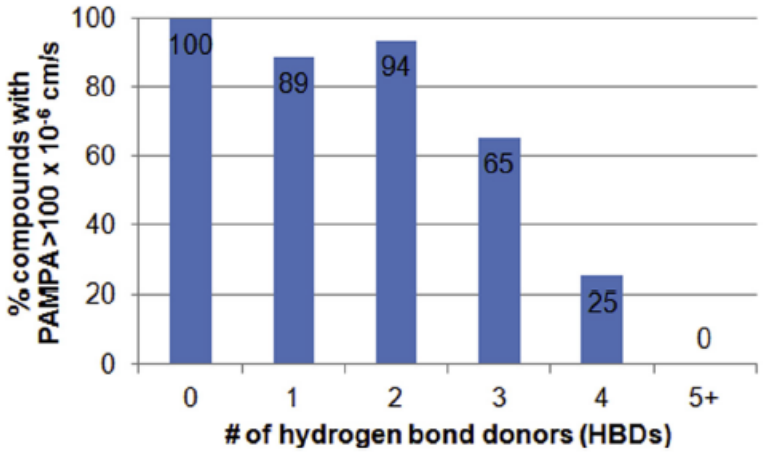


PB03288

As a mere HTS hit, compound **5** was already reasonably potent (IC_{50}, 1.2 μM). Single crystal X-ray structure revealed that the nitrogen atom on the furo[2,3-*c*]pyridine formed a hydrogen bond with the NH function provided by alanine-106 (Y106) of the TAK target protein, which helped promoting the protein–ligand binding. The geometrical vicinity between the sulfur atom on benzothiophene and the oxygen atom on furo[2,3-*c*]pyridine (2.8 Å, well within van der Waals contact distance) suggests that polarization of the sulfur atom led to positive interactions between sulfur and oxygen. In essence, polarized sulfur behaved like an NH group (S = NH!) to form an intramolecular hydrogen bond with the oxygen atom.[5]

In addition to being a promiscuous kinase inhibitor, showing > 50% inhibition of 42/192 kinases, 7-aminofuro[2,3-*c*]pyridine **5** has serious pharmacokinetics liabilities as well. The metabolic vulnerability of the sulfur atom on the benzothiophene fragment was addressed by switching to the benzothiadiazole, which still maintained the positive interaction between the sulfur and the oxygen atoms. Furthermore, as shown in the figure on top of the next page, having three hydrogen bond donors (HBDs) is detrimental to cell permeability. Capping the piperidine NH with an acetyl group led to TAK1 inhibitor **6**, which was potent (IC_{50} = 4 nM) and selective against several potentially troublesome kinases such as KDR/VEGFR2 and the cell cycle kinase Aurora B and CHK1.[4a]



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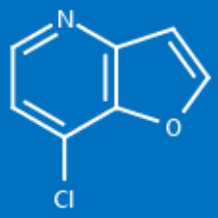

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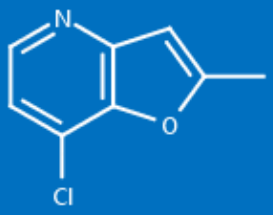

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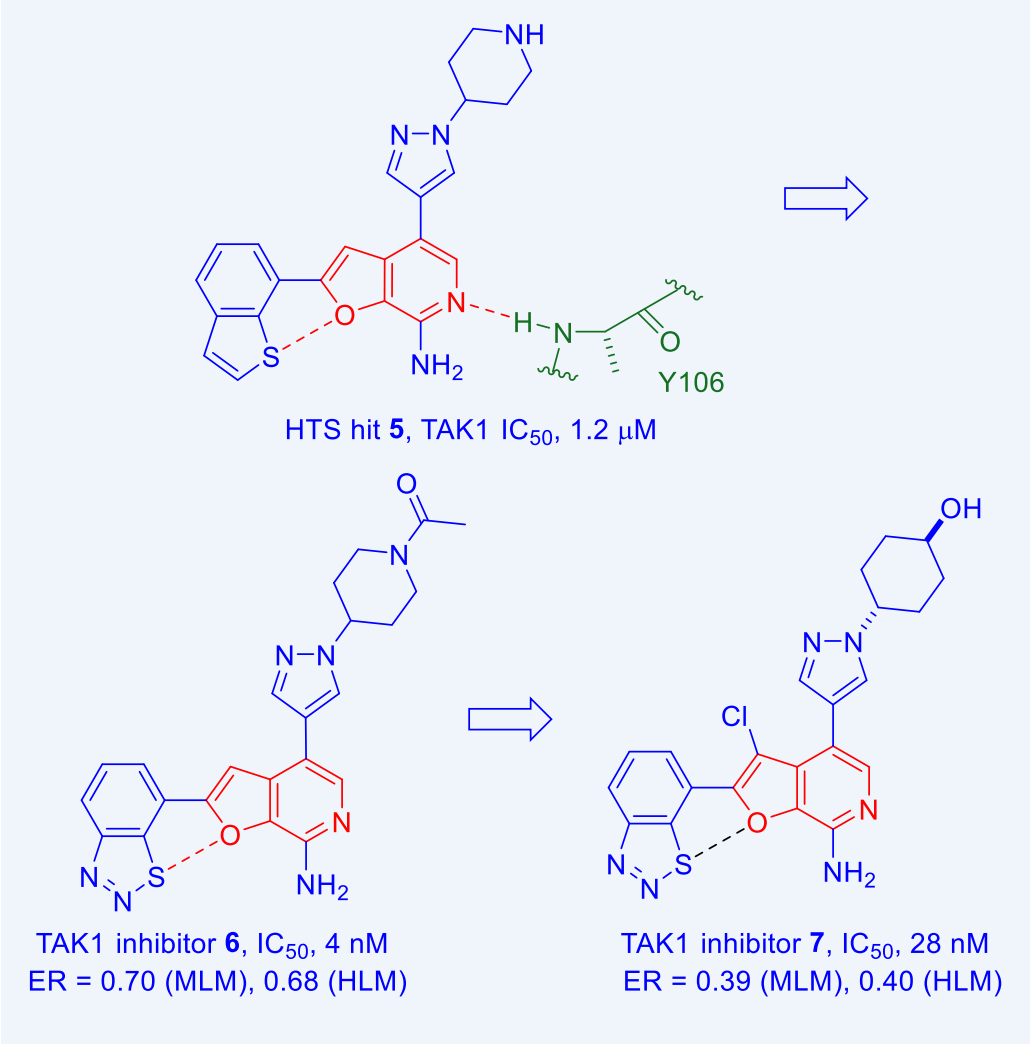

Since compound **6** still had high extraction ratios (ERs) in both mouse and human liver microsomes: 0.70 and 0.68, respectively, which presaged significant clearance and metabolism issues *in vivo*. Frustrated by their inability to replace the primary amine group without losing activity, OSI chose to install an electron-withdrawing group chlorine at the C-3 position of the furo[2,3-*c*]pyridine core structure. The maneuver killed two birds with one stone: it helped solving the metabolism and kinase selectivity problems at once. At the end, they transformed a series of potent but relatively poorly kinase selective 7-aminofuro[2,3-*c*]pyridine inhibitors of TAK1 with poor PK as represented by **5** into more selective inhibitors with excellent oral exposure, as represented by TAK1 inhibitor **7**.[4b]

OSI also had success with another furopyridine core structure on their kinase inhibitors: they discovered a series of 6-aminofuro[3,2-*c*]pyridines as potent and orally efficacious inhibitors of cMET and RON kinases.[6]

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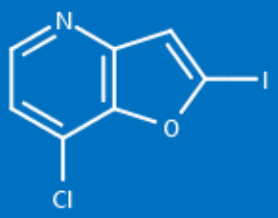

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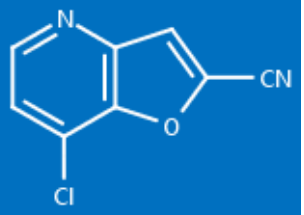
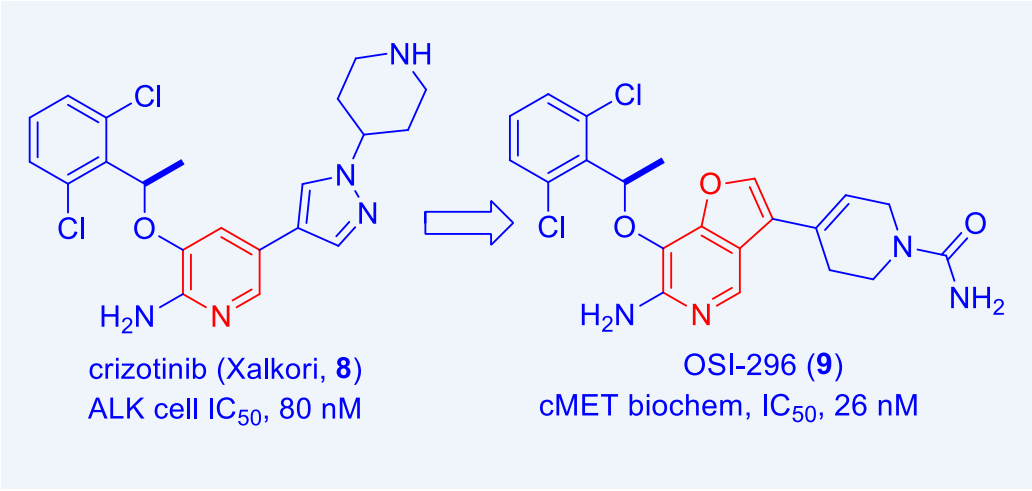


PB03291

Pfizer's anaplastic lymphoma kinase (ALK)/cMET/RON inhibitor crizotinib (Xalkori, **8**) was approved by the FDA in 2011. Its pyridine nitrogen on the 2-aminopyridine core acts as hydrogen bond acceptor for a backbone NH of the hinge region, while the 2-amino group donates a hydrogen bond to the interior hinge carbonyl, thus interacting with the same residues as ATP in a mutually exclusive fashion. OSI opted to employ 6-aminofuro[3,2-*c*]pyridine as an isostere of 2-aminopyridine and the fused additional furan retained the hinge binding but provided different vectors for substituents to interaction with the target protein. One of the derivatives, OSI-296 (**9**) was tested potent and selective with a good PK profile (> 70% bioavailability in rodents). More importantly, it showed significant tumor growth inhibition (TGI) in multiple cMET-driven xenograft models in mice at once daily doses of 50 mg/kg or less.[6]



Furopyridines have found many applications in the kinase field. Furo[2,3-*c*]pyridine-based indanone oximes were discovered as potent and selective B-Raf inhibitors.[7] Meanwhile, furo[3,2-*b*]pyridine was revealed to be a privileged scaffold for highly selective kinase inhibitors, namely CDC-like kinase (CLK) inhibitors.[8]

In another case, one particular isomer furo[2,3-*c*]pyridine helped to provide rapid brain penetration and high oral bioavailability in rat.[9]

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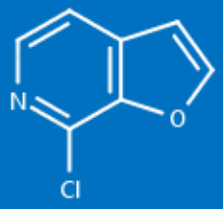

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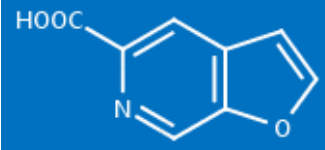
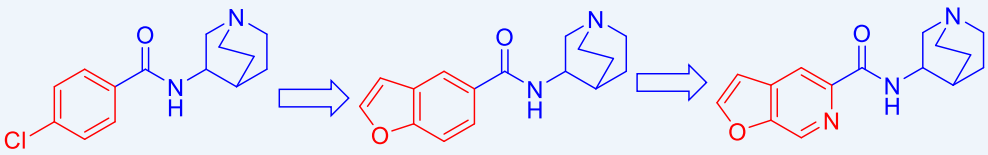
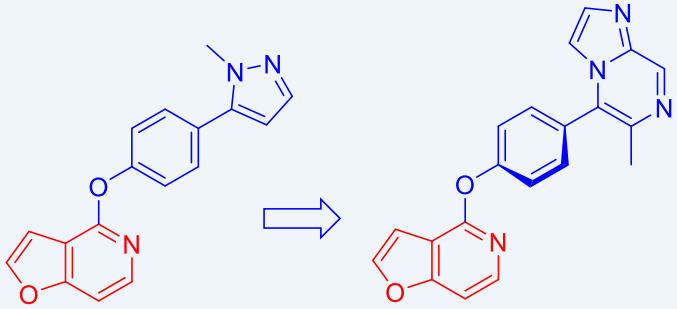


PBTQ5967

PNU-282,987 (**9**) is a potent and selective α7 neuronal nicotinic acetylcholine receptor (α7 nAChR) agonist with potential to treat cognitive deficits in schizophrenia. Regrettably, it possesses significant human ether-a-go-go (hERG) potassium channel activity. Efforts to improve its safety led to replacing *p*-chlorophenyl group with 6,5-fused analogues to afford benzofuran **10**, among others. Although benzofuran **10** stood out for its potency and stability in rat liver microsomes (RLM), furan is notorious for its tendency for metabolic activation since it is so electronic rich. Therefore, all four furopyridines including furo[2,3-*c*]pyridine **11** were prepared to mitigate the liability. Among the four furopyridines, only the furo[2,3-*c*]pyridine **11** was potent enough as an (α7 nAChR) agonist. Both **10** and **11** had reduced hERG activity. Compound **11** was also tested selective with an excellent *in vitro* profile. Moreover, it is characterized by rapid brain penetration and high oral bioavailability in rat and demonstrates *in vivo* efficacy in auditory sensory gating and novel object recognition in an *in vivo* model to assess cognitive performance.[9]



	PNU-282,987 (**9**)	benzofuran **10**	furopyridine **11**
α7-5HT$_3$, EC$_{50}$, 128 nM		47 nM	65 nM
α7 K_i	24 nM	1.6 nM	8.8 nM
hERG %block @ 20 μM, 57%		33%	29%
rat *F* (%)	74%	88%	63%
brain/plasma ratio	5.0	1.24	1.5



HTS hit **12**
D$_1$ EC$_{50}$ (cAMP):
2.3 μM, 37% E$_{max}$
D$_1$ binding K_i: 2.2 μM

PF-6256142 (**13**)
D$_1$ EC$_{50}$ (cAMP):
33 nM, 91% E$_{max}$
D$_1$ binding K_i: 12 nM

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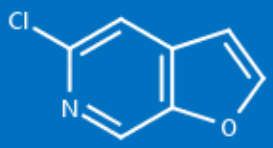
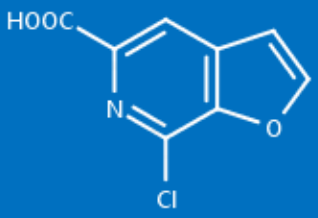


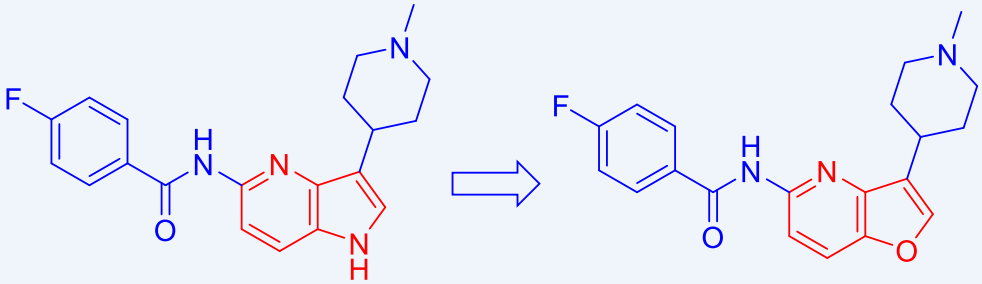
PBU1588



PBYS100884

In the past, nearly all known D_1 selective agonists are catecholamines including the only one on the market, fenoldopam (Corlopam). To avoid catechol and phenol-containing D_1 selective agonists, Pfizer carried out an HTS of three million compounds and found only one hit that fitted their requirements. The hit was furo[3,2-*c*]pyridine **12**. Extensive hit-to-lead (H2L) efforts eventually led to the discovery of atropisomer PF-6256142 (**13**), a potent and selective orthosteric agonist of the D_1 receptor that has reduced receptor desensitization relative to dopamine and other catechol-containing agonists. PF-6256142 (**13**) also has an excellent pharmacokinetics profile with an F value of 85%. It merits clinical study because in chronic diseases, such as schizophrenia and Parkinson's disease, the duration of therapeutic effect is an important component of patient quality of life.[10]

On one occasion, furopyridines helped boosting selectivity for 5-HT_{1F} receptor agonists as represented by azaindole **14**. In comparison to **14**, its furo[3,2-*b*]pyridine bioisosteres such as **15** possessed similar affinity for 5-HT_{1F} receptor and had improved selectivity for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D}. Furo[3,2-*b*]pyridine **15** may have potential as a therapeutic for acute treatment of migraine.[11]



azaindole **14**
5-HT_{1F}, K_i, 7.6 nM
ratio, 1A/1F, 7.3
ratio, 1B/1F, 160
ratio, 1D/1F, 960

furo[3,2-*b*]pyridine **15**
5-HT_{1F}, K_i, 3.1 nM
ratio, 1A/1F, 134
ratio, 1B/1F, > 1000
ratio, 1D/1F, > 1000

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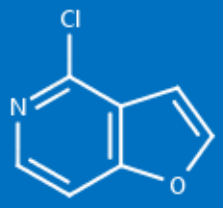

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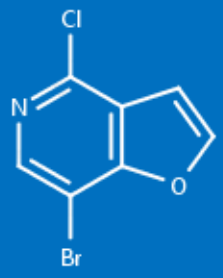

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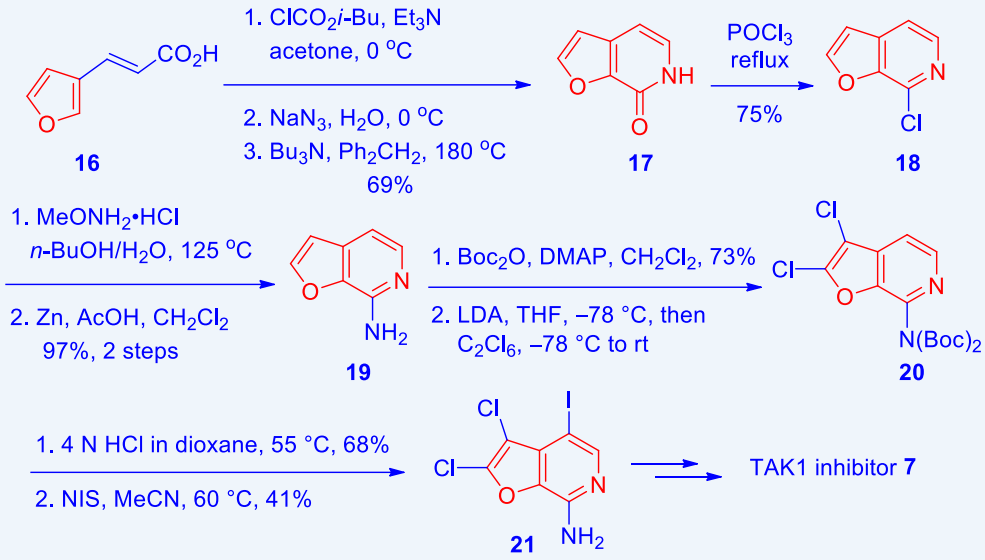
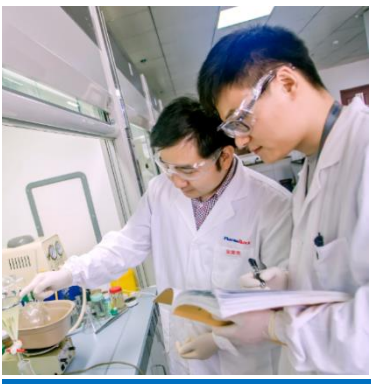
Synthesis of Some Furopyridine-containing Drugs



OSI's synthesis of their TAK1 inhibitor **7** commenced by using (*E*)-3-(furan-3-yl)acrylic acid (**16**) as the starting material. It was converted to furopyridone **17** via the intermediacy of the corresponding acyl azide, followed by the Curtius rearrangement. After conversion to the 7-chloride **18** by action of $POCl_3$, the chloride was displaced with methoxylamine. Reduction using zinc in acetic acid provided amine **19**. Protection of the amine was followed by deprotonation by LDA and quench with hexachloroethane to afford dichloride 20 when more equivalents of LDA and hexachloroethane were used. Simple removal of the Boc protection revealed the amine group, which was subsequently converted iodide **21** by action of NIS. TAK1 inhibitor **7** was prepared from iodide **21** in several additional transformations.[4]

Preparation of OSI-296 (**9**) used furopyridine **22** as the starting material. A three-step sequence involving treatment with NIS, followed by $POBr_3$, and selective reduction of the 4-bromine substituent converted furopyridine **22** 7-bromofuro[3,2-*c*]pyridine (**23**). Conversion of the 7-Br group to 7-OH and subsequent nitration at C6 provided **24**, unto which the ether bond was forged by Mitsubobu coupling with alcohol **25**. The resulting ether was then transformed to OSI-296 (**9**) in several additional steps.[6]



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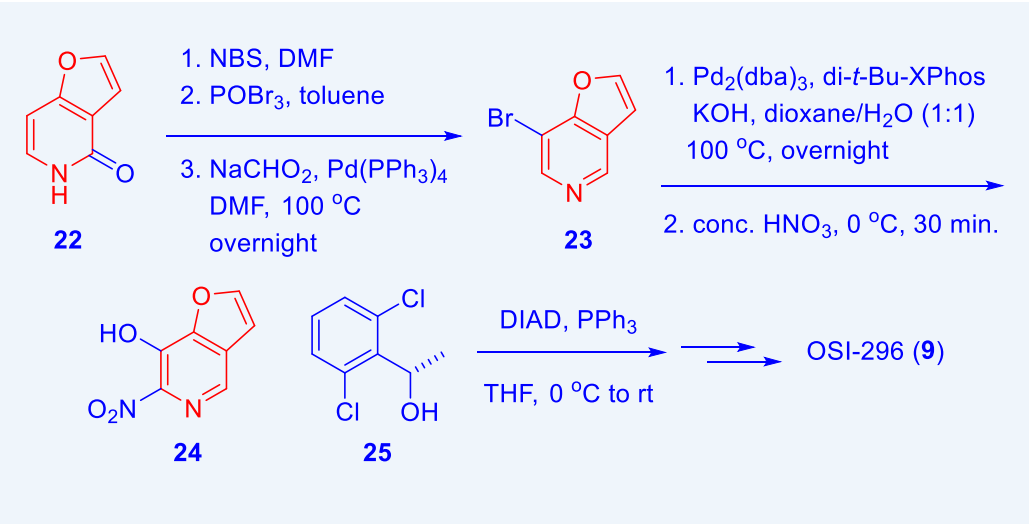
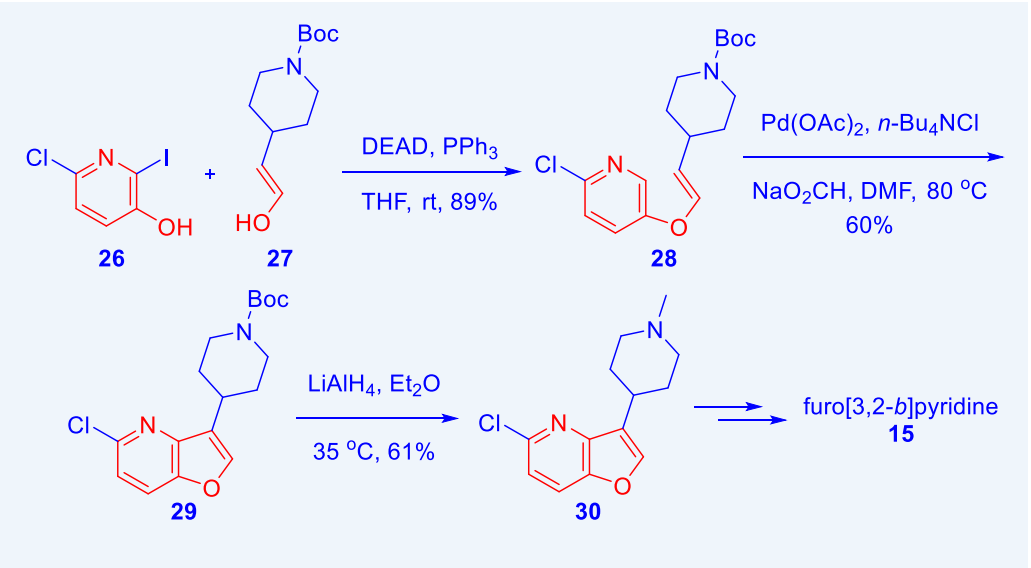
- Commercial production with GMP compliance



Liily's synthesis of the 5-HT_{1F} agonist **15** employed 6-chloro-2-iodopyridin-3-ol (**26**) as the starting material. A Mitsunobu coupling with allylic alcohol **27** yielded ether **28**. A Larock indole synthesis afforded furo[3,2-*b*]pyridine **29** in 60% yield. Reduction of the Boc protection produced the desired methyl-piperidine **30**, which was converted to furo[3,2-*b*]pyridine **15** in a few additional steps.[11]



In summary, as in the case of phenyl–pyridine switch, furopyridines have some advantages over the parent benzofurans. The nitrogen atom may serve as a hydrogen bond acceptor and result in additional protein–ligand interactions. Furthermore, the presence of an additional nitrogen atom also lowers the molecule's lipophilicity thus impacts its physiochemical properties such as aqueous solubility. Furopyridine building blocks have found a wide utility in drug design and drug synthesis.

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References

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