Pyridazines in Drug Discovery

Key Points

- Serve a bioisostere of hetaryl rings such as pyridine, pyrimidine, and pyrazine.
- Boost a drug's aqueous solubility
- Facilitate formation of crystalline, water-soluble solid salts

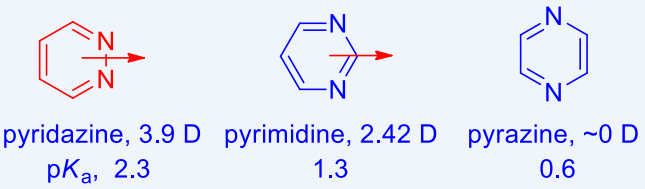
Overview

Pyridazine motif has been employed in drug discovery to (a) serve a bioisostere of hetaryl rings such as pyridine, pyrimidine, and pyrazine. Furthermore, aminopyridazines can be used as carboxamide and amine surrogates; (b) boost a drug's aqueous solubility; and (c) facilitate formation of crystalline, water-soluble solid salts.

PharmaBlock

PharmaBlock designs and synthesizes over 728 Pyridazines and 132 Pyridazine products are in stock. CLICK HERE to find detailed product information on webpage.

Although not too many pyridazine-containing drugs are on the market, it has been argued that pyridazines should be considered privileged structures.[1] As a phenyl bioisostere, pyridazine's two nitrogen atoms are capable of forming hydrogen bonds with target proteins. Pyridazine has also been frequently employed as an isostere of pyridine, pyrimidine and pyrazine in drug discovery. In addition, aminopyridazines can be used as carboxamide and amine surrogates. Among the three diazines shown below, pyridazine is the most polar due to concentration of electronegative nitrogen lone pairs on one side of the molecule. As a consequence, pyridazine could help boosting aqueous solubility of a drug. It often aides formation of crystalline, water soluble salts as well.[2]



Dipole Moments (D = Debye) and pK_a's of Diazines

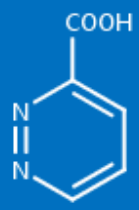
Pyridazine-containing Drugs

Only a few pyridazine-containing drugs are currently on the market. Sulfamethoxy-pyridazine (**1**) is an old sulfa drug. Ciba's hydralazine (Apresoline, **2**) is an old anti-hypertensive, but its safety profile is sub-ideal because of several side effects. Since its “naked” hydrazine was considered the culprit of toxicity and is a conspicuous structural alert under today's standards, it was masked by as a hydrazine-carboxylate to afford cadralazine (**3**).

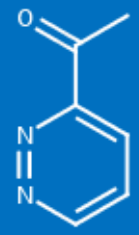
Minaprine (Cantor, **4**) is an old anti-depressant only marketed in France. Like most reversible monoamine oxidase (MAO) inhibitors, minaprine (**4**) has many side effects and it was withdrawn in 1996.

Considering so many aromatic heterocycles have made appearances in kinase inhibitors, it is surprising that no pyridazine-containing kinase inhibitor has made its way to market. Xcovery's anaplastic lymphoma kinase (ALK) inhibitor ensartinib (X-396, **5**) is currently in phase II clinical trials.

PharmaBlock Products

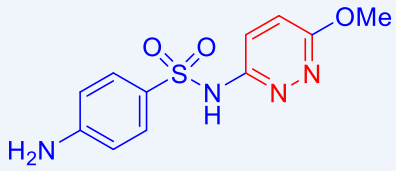


PB00522

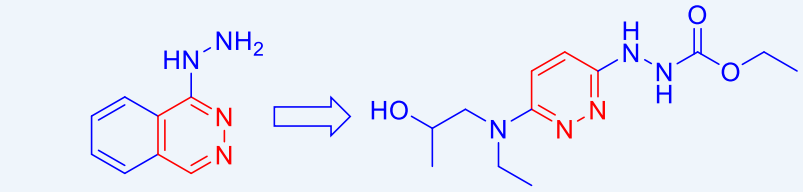


PB00390

Takeda's relugolix (Relumina, **6**) is the latest entry of pyridazine-containing drugs just approved in 2019 for the treatment of uterine fibroids. It is a gonadotropin-releasing hormone (GnRH) receptor antagonist.

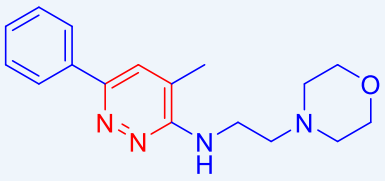


sulfamethoxypyridazine (**1**)

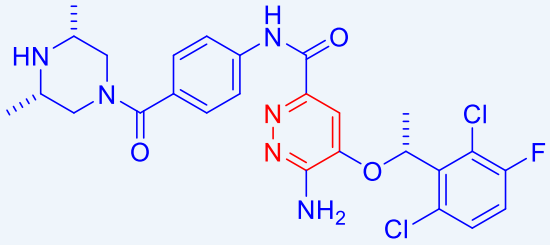


hydralazine (Apresoline, **2**)
Ciba, 1949
anti-hypertensive

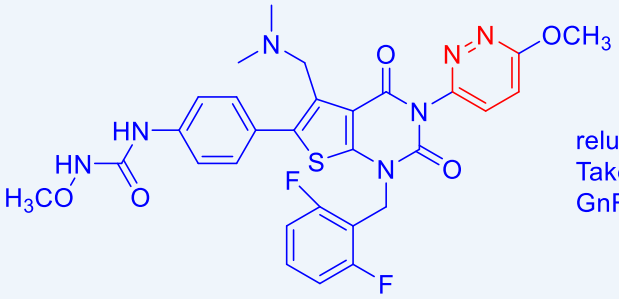
cadralazine (**3**)
anti-hypertensive



minaprine (Cantor, **4**)
anti-depressant (France)
reversible MAO-A inhibitor
withdrawn in 1996

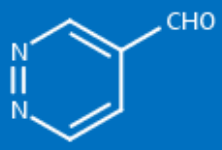


ensartinib (X-396, **5**)
Xcovery
ALK inhibitor

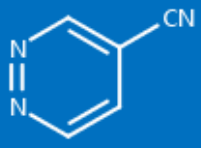


relugolix (Relumina, **6**)
Takeda, 2019
GnRH receptor antagonist

PharmaBlock Products



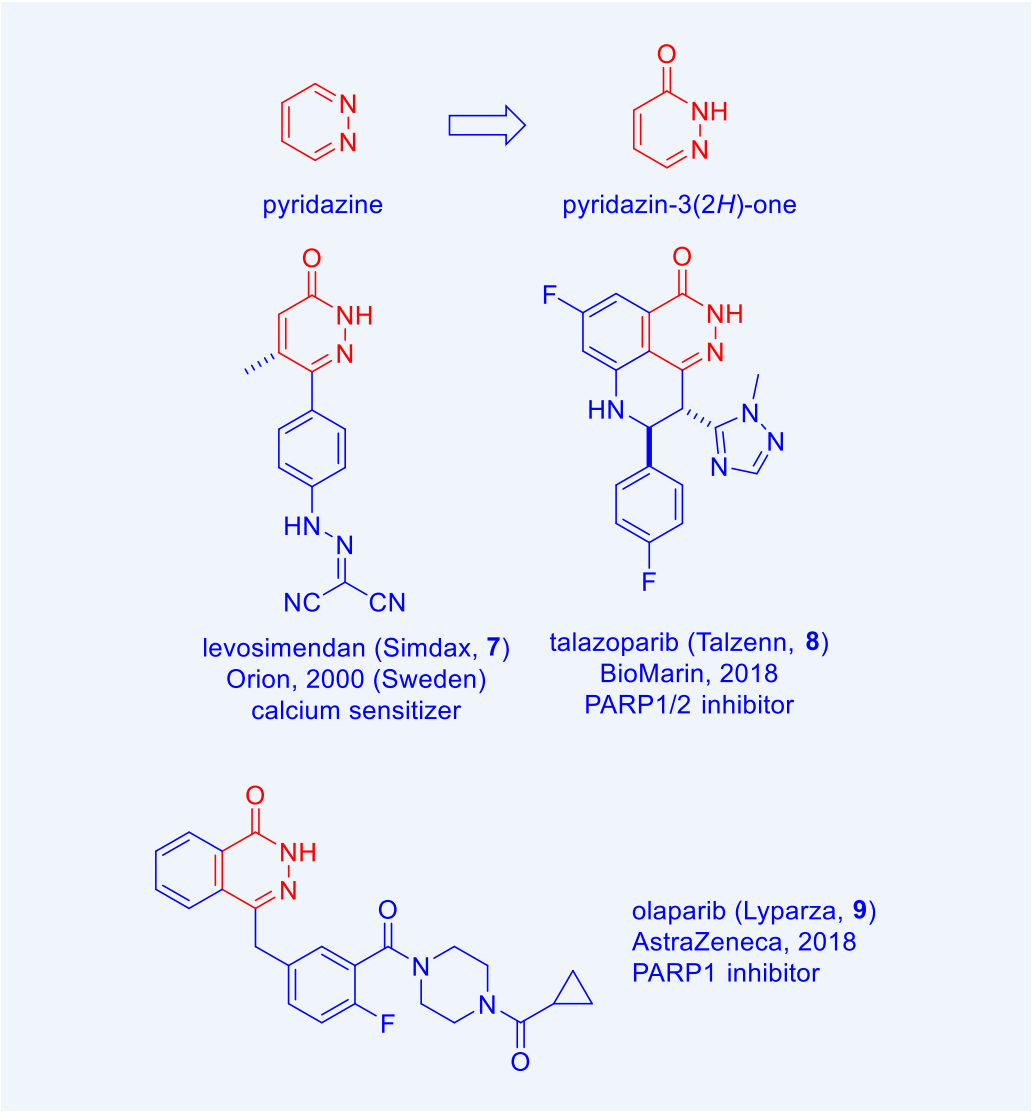
PB00345



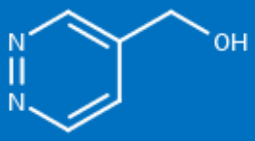
PB00350

A pyridazine derivative, pyridazone [pyridazin-3(2*H*)-one], has made appearances in several drugs. Orion's levosimendan (Simdax, **7**) was approved 2000 in Sweden for the treatment of congestive heart failure (CHF). It functions as a calcium sensitizer. In addition, BioMarin's phthalazin-1(2*H*)-one-containing talazoparib (Talzenna, **8**) is a poly(ADP-ribosyl) polymerase (PARP)-1/2 inhibitor approved by the FDA in 2018 for the treatment of germ line BRCA-mutated, HER2-negative, locally advanced or metastatic breast cancer.

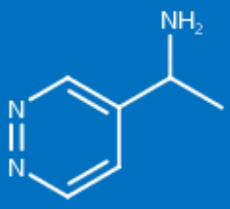
Similar to that of talazoparib (**8**), AstraZeneca's PARP-1 inhibitor olaparib (Lyparza, **9**) also contains a phthalazin-1(2*H*)-one motif.



PharmaBlock Products

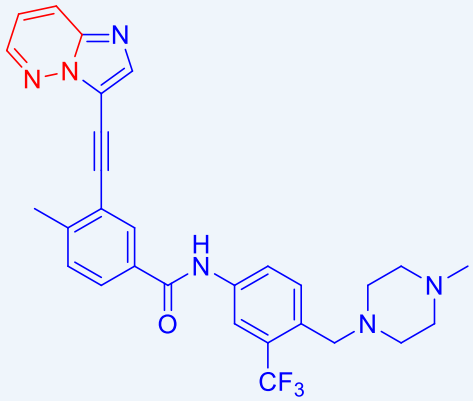


PB00349



PB00347

On the other hand, bicyclic fused pyridazines have showed up as fragments of many drugs. Since it is not the focus of this review, only one example is given here. Ariad's ponatinib (Iclusig, **10**) was approved by the FDA in 2012 for the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). It is a dual Bcr-abl/vascular endothelial growth factor receptor (VEGFR) inhibitor. CML with the T315I mutation is resistant to imatinib (Gleevec). Ponatinib (**10**), along with several second-generation Bcr-Abl inhibitors such as dasatinib (Sprycel, BMS, 2006), nilotinib (Tasigna, Novartis, 2007) and bosutinib (Bosulif, Pfizer, 2012), has been designed to be effective against T315I-mutant CML.



ponatinib (Iclusig, **10**)
Ariad, 2012
Bcr-abl/VEGFR inhibitor

Pyridazines in Drug Discovery

Pyridazine motif has been employed to boost a drug's aqueous solubility and facilitate formation of crystalline, water soluble salts. Furthermore, pyridazine may serve as a bioisostere for many heterocycles such as pyridine, pyrazine, pyrimidine, etc.

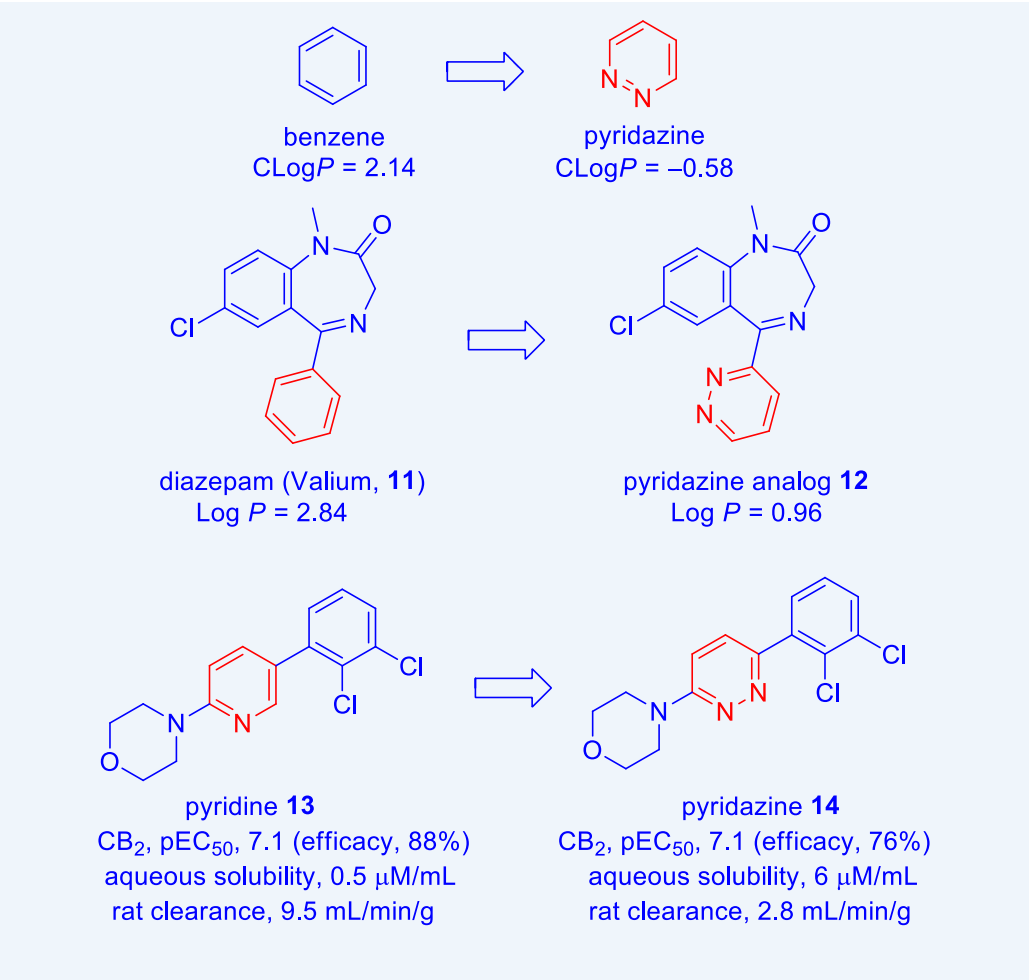
PharmaBlock Products

PBN20120707

PBU2143

a. ***Boost a drug's aqueous solubility***

As an isostere of the phenyl ring (Clog *P* = 2.14), the pyridazine fragment (Clog *P* = –0.58) is significantly less lipophilic than the former as indicated by their respective Clog *P* values. Diazepam (Valium, **11**), a g-aminobutyric acid $(GABA)_A$ receptor modulator, was one of the most successful minor tranquilizers, even garnered the nickname of "Mother's Little Helper". With a log *P* value of 2.84, it is quite lipophilic with a low aqueous solubility. In contrast, its corresponding pyridazine analog **12** has a log *P* value of 0.96, which translates to boosted aqueous solubility.



PharmaBlock Products

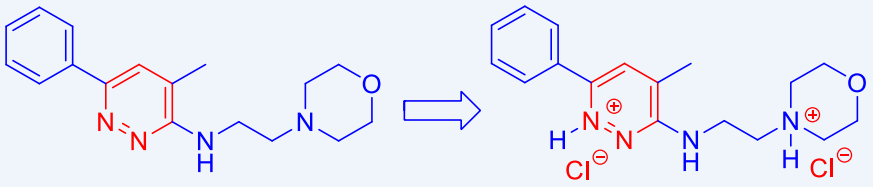
PBTQ2569

PB06152

Naturally occurring cannabinoids, such as D^9-teterahydracannabinol (THC), act as agonists of three G-protein coupled receptors (GPCRs): cannabinoid receptor type-1 (CB_1R) and type-2 (CB_2R), and GPR55. A series of 3-amino-6-aryl-pyridazines have been identified as CB_2R agonists with high efficacy and selectivity against the CB_1R. While pyridine **13** had an abysmal aqueous solubility of 0.5 μM/mL with high *in vitro* metabolism, its diazine analog, pyridazine **14**, saw a 12-fold boost of aqueous solubility (6 μM/mL). Diazines, including pyridazine **14**, also showed more favorable metabolic stability in comparison to the pyridine prototype **13**. Moreover, in the presence of two basic nitrogen atom on the pyridazine ring, formation of salt becomes possible, which may further enhance the drug's aqueous solubility. For instance, the HCl salt of pyridazine **14** has a solubility of 120 μg/mL.[3]

b. ***Facilitate formation of crystalline, water-soluble solid salts***

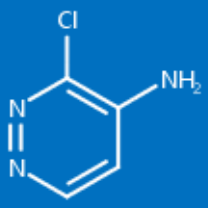
An old antidepressant, minaprine (**4**), acts on both forms of monoamine oxidase: MAO-A and MAO-B. The free base of minaprine (**4**) is an oily, water-insoluble liquid. In stark contrast, its di-hydrochloride salt **4'** is a white, crystalline, water-soluble solid power.[4]



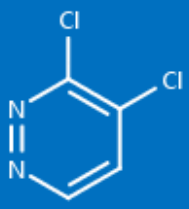
minaprine (**4**), free base
oily, water-insoluble liquid

minaprine-di-HCl **4'**, white,
water-soluble crystalline power

PharmaBlock Products



PB97710

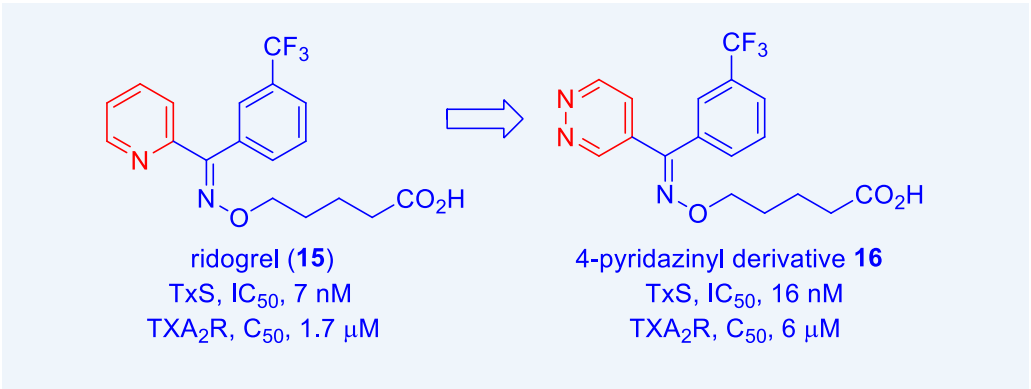


PB05235

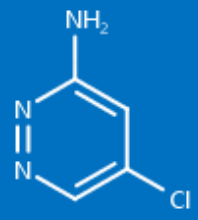
c. As a bioisostere of hetaryl rings

The pyridazine motif has been employed as a bioisostere for phenyl and hetaryl rings including pyridine, pyrazine, and pyrimidine, etc.

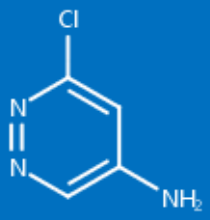
Ridogrel (**15**) is an anti-platelet that functions as a combined thromboxane A_2 receptor (TXA_2R) antagonist and thromboxane synthase (TxS) inhibitor. Bioisosteric replacement of the 3-pyridyl moiety (**15**, IC_{50}, 7 nM) with 2-pyrazinyl (IC_{50}, 6 nM), 4-pyridazinyl (**16**, IC_{50}, 16 nM), and 5-pyrimidyl (IC_{50}, 39 nM) analogs inhibited TxS with comparable potency in gel-filtered human platelets. Meanwhile, the three diazines 2-pyrazinyl (IC_{50}, 11 μM), 4-pyridazinyl (**16**, IC_{50}, 6 μM), and 5-pyrimidyl (IC_{50}, 1.5 μM) analogs tested to have comparable potency in blocking the TXA_2R in comparison to the prototype **15** (IC_{50}, 1.7 μM). At the end, testing of inhibition of collagen-induced platelet aggregation in human platelet-rich plasma with 2-pyrazinyl, 4-pyridazinyl (**16**), or 5-pyrimidinyl analogs of ridogrel (**15**) indicated that these heteroaromatic moieties may serve as bioisosteric substitutes of a 3-pyridyl group in dual-acting anti-platelet agents.[5]



PharmaBlock Products



PB05523

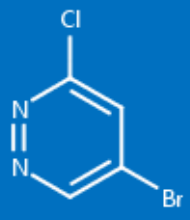


PBN20120790

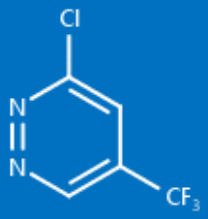
Janus kinases (JAKs) are intracellular tyrosine kinases that mediate the signaling of numerous cytokines and growth factors involved in the regulation of immunity, inflammation, and hematopoiesis. There are four members of the Janus kinase family: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). In response to the stimulation of these receptors, the Janus kinases phosphorylate signal transducer and activator of transcription (STAT) proteins, which then dimerize, translocate to the nucleus and activate gene transcription. As a member of the JAK family of non-receptor tyrosine kinases, TYK2 plays an important role in mediating the signaling of pro-inflammatory cytokines including IL-12, IL-23, and type 1 interferon. Therefore, selective TYK2 inhibitors may be treatment of autoimmune diseases.

In an effort to identify a new *allosteric* TYK2 JH2-binding scaffold, BMS screened their corporate compound collection by utilizing a scintillation proximity assay (SPA) and identified nicotinamide **17** as a potent TYK2 JH2 inhibitor. Unfortunately, in the IL-23 and IFNα-stimulated reporter assays, **17** was not selective over the catalytic (JH1) domains of the four JAK family members. Furthermore, **17** was found to be fairly promiscuous, inhibiting 85 of 261 kinases tested by at least 50% (at 1 μM concentration) in the homogeneous time-resolved fluorescence (HTRF) assay. Extensive structure–activity relationship (SAR) investigations eventually led to the discovery of pyridazinyl derivative **18** as the clinical candidate. Allosteric inhibitor **18** provided robust inhibition in a mouse IL-12-induced IFNγ pharmacodynamic model as well as efficacy in an IL-23 and IL-12-dependent mouse colitis model. These results demonstrated the ability of TYK2 JH2 domain binders to provide a highly selective alternative to conventional TYK2 *orthosteric* inhibitors.[6]

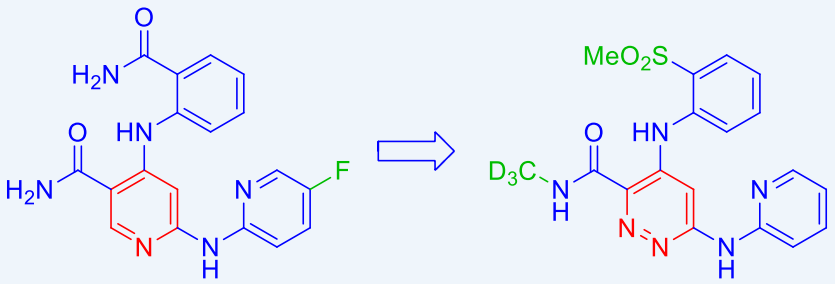
PharmaBlock Products



PB1130503



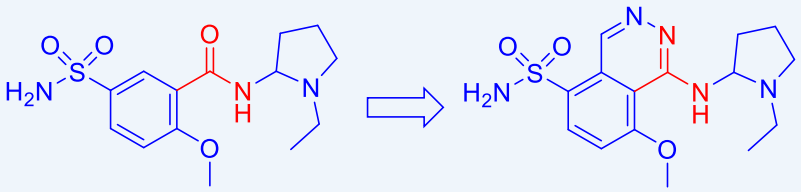
PBLJ0612



pyridyl derivative **17**
$K_{i,app}$ = 0.06 nM
TYK2 JH2 IC_{50} = 0.46 nM
TYK2/JAK1/JAK2 kinase domain
IC_{50} = 15/26/24 nM
IFNα IC_{50} = 37 nM

pyridazinyl derivative **18**
$K_{i,app}$ = 0.07 nM
TYK2 JH2 IC_{50} = 0.53 nM
TYK2/JAK1/JAK2 kinase domain
IC_{50} = >50/>40/>50 nM
IFNα IC_{50} = 27 nM

Perhaps a more “exotic” form of isostere for amide, aminopyridazine successfully served to expand the SAR of sulpiride (Dogmatil, **19**), an antipsychotic drug. *Wermuth and coworkers replaced* sulpiride (**19**)'s carboxamide with aminopyridazine and arrived at Do-754 (20, K_i = 3.9 nM), which showed a higher affinity toward target protein than its prototype 1**9** (K_i = 7.6 nM).[7]

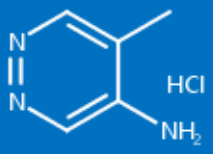


sulpiride (Dogmatil, **19**)
K_i = 7.6 nM

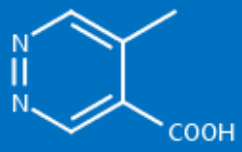
Do-754 (**20**)
K_i = 3.9 nM

Synthesis of Some Pyridazine-containing Drugs

PharmaBlock Products



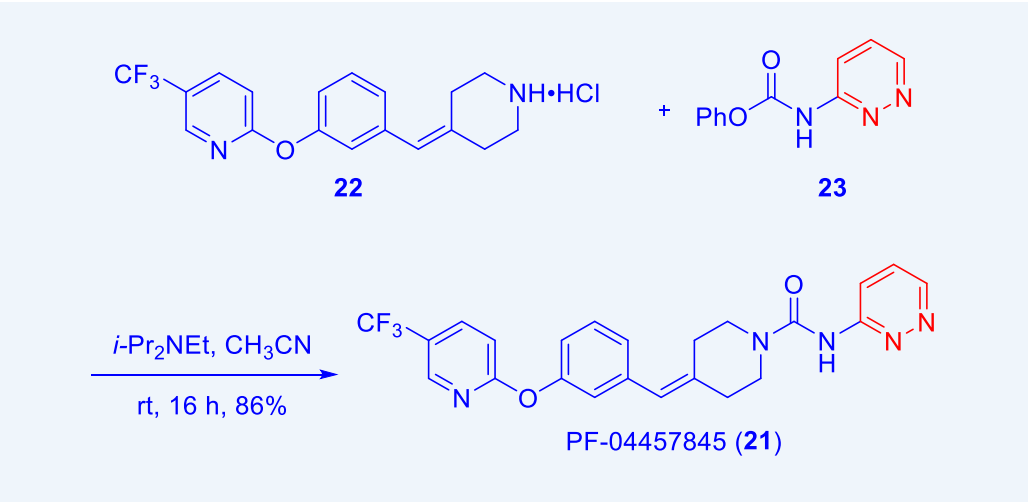
PBSQ8080-1



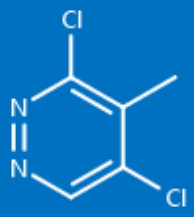
PB03306

Fatty acid amide hydrolase (FAAH) is an integral membrane serine hydrolase responsible for the degradation of fatty acid amide signaling molecules such as endocannabinoid anandamide (AEA), which has been shown to possess cannabinoid-like analgesic properties. FAAH belongs to the amidase class of enzymes, a subclass of serine hydrolases that have an unusual Ser_{241}–Ser_{217}–Lys_{142} catalytic triad since the Ser–His–Asp catalytic triad is more common among hydrolyses. Pfizer discovered PF-04457845 (**21**), a highly potent and selective FAAH inhibitor that reduces inflammatory and non-inflammatory pain. Mechanistic and pharmacological characterization of PF-04457845 (**21**) revealed that it is an irreversible covalent inhibitor involved in carbamylation of FAAH's catalytic Ser_{241} nucleophile, which results in four products including inactive covalently modified FAAH, a serine, a lysine, and by-product pyridazin-3-amine as the leaving group.[8]

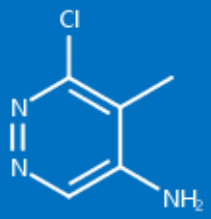
Preparation of PF-04457845 (**21**) is quite straight forward. Reaction between benzylidenepiperidine hydrochloride salt **22** and phenyl pyridazin-3-ylcarbamate (**23**) in the presence of the Hünig base provided urea **21**.[8]



PharmaBlock Products

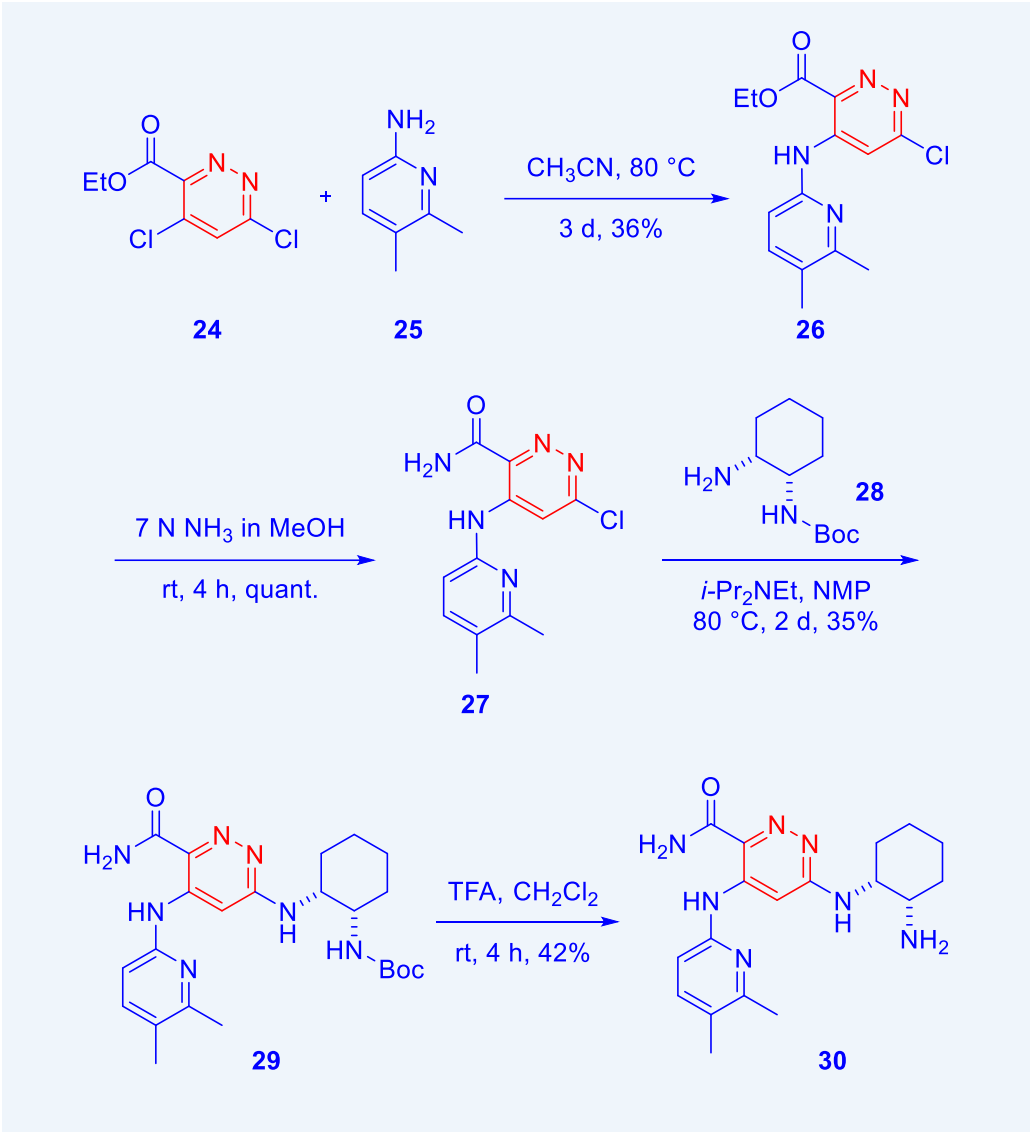


PBU0815



PBSQ8072

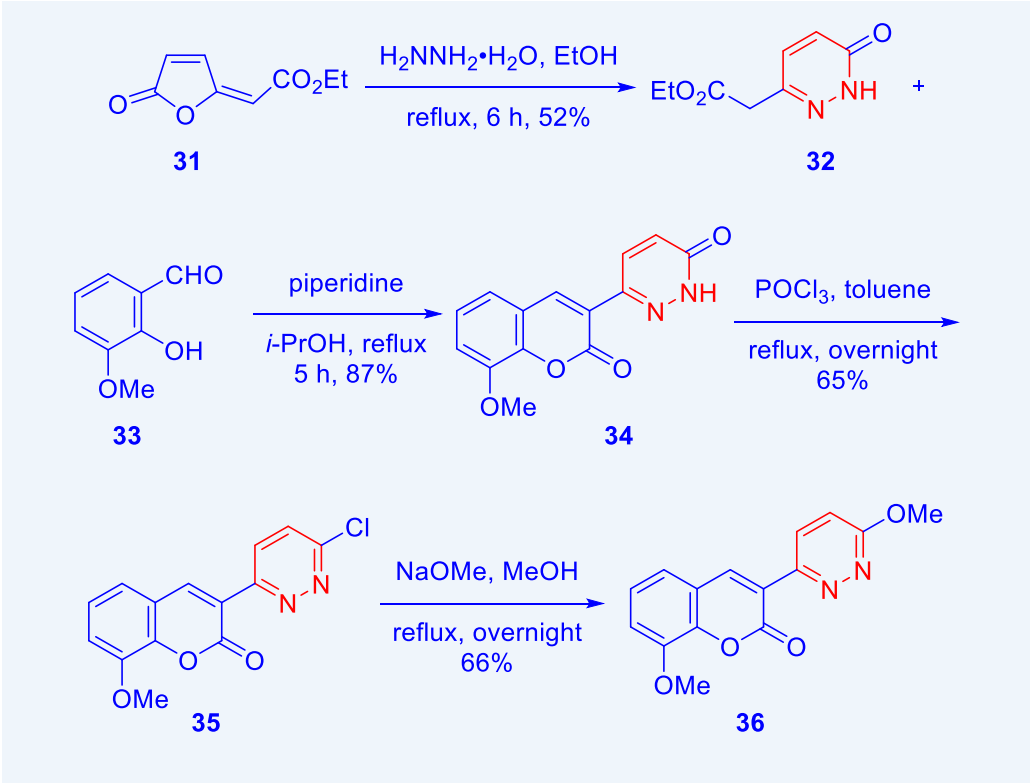
Pyridazine amide **30** is an orally efficacious inhibitor of cell spleen tyrosine kinase (Syk). Its synthesis began with an S_NAr displacement of dichloropyridazine ester **24** with pyridyl aniline **25** to assemble adduct **26**. Conversion of ester on **26** to amide **27** was accomplished with ease by using 7 N ammonia in methanol. Finally, another S_NAr reaction between **27** and *tert*-butyl [(1*S*,2*R*)-2-aminocyclo-hexyl]-carbamate (**28**) produced adduct **29**, which was deprotected to offer pyridazine amide **30** as a potent Syk inhibitor.[9]



PharmaBlock is recognized for its outstanding capability in the design, synthesis, production and commercialization of novel building blocks for use throughout the drug R&D process.

- 80,000+ building blocks
- 16,000+ in stock in both USA and China
- 20,000+ supplied within two weeks
- 1,000+ SAR tool kits
- Novel building blocks designed upon daily monitoring on recent researches and patents
- Keep optimizing cost effective route for better price and sustainable supply
- Fast delivery of custom synthesis
- Enabling technologies of flow chemistry, biocatalysis, photochemistry, electrosynthesis, and fluorination, etc.
- Commercial production with GMP compliance

3-Pyridazinyl-coumarin **36** is a selective and reversible monoamine oxidase B (MAO-B) inhibitor, a potential drug for treating Parkinson's disease (PD) and Alzheimer's disease (AD). Its pyridazinone intermediate **32** may be prepared by condensation of ethyl (*E*)-2-(5-oxofuran-2(5*H*)-ylidene)acetate (**31**) with hydrazine hydrate. Another condensation between ester **32** and a-hydroxyl-phenol **33** in the presence of piperidine then assembled the pyridazinyl-coumarin hybrid **34** in good yield. Refluxing pyridazinone **34** with excess $POCl_3$ then gave rise to pyridazinyl chloride **35**, which was then converted to the final MAO-B inhibitor **36** via an S_NAr reaction with sodium methoxide.[10]

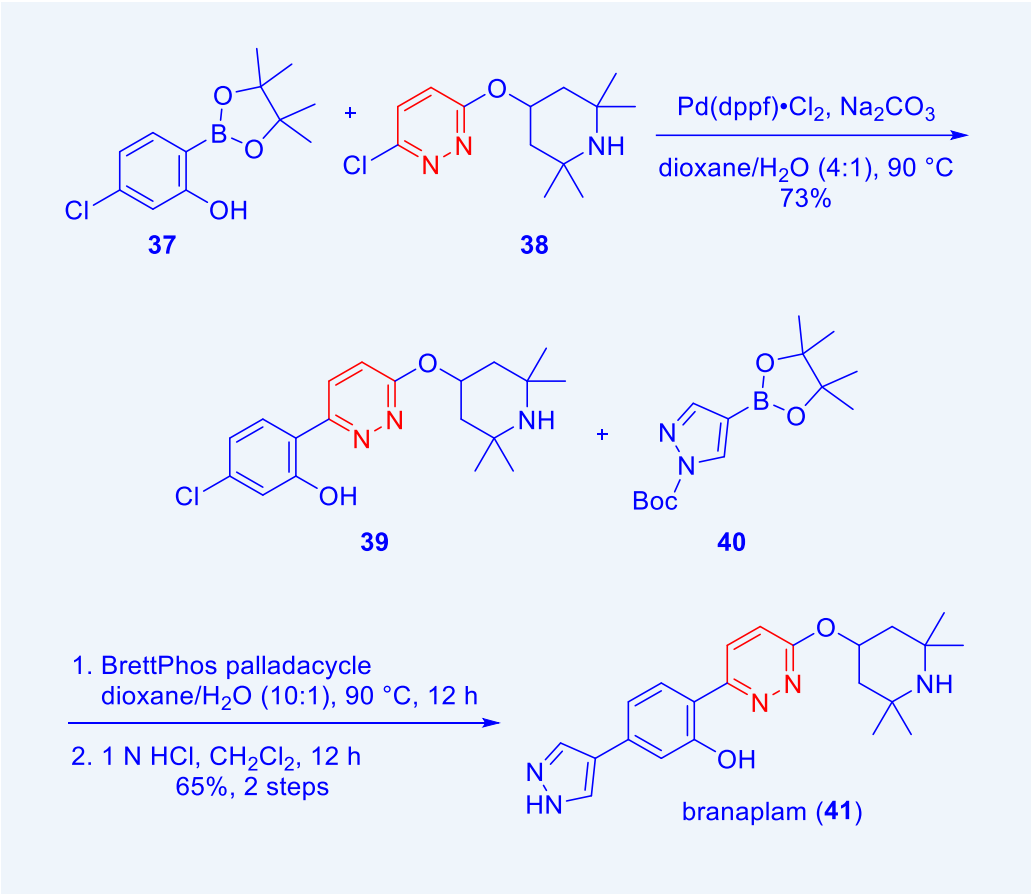


As a potential treatment of spinal muscular atrophy (SMA), branaplam (**41**) is a splicing modulator of survival motor neuron-2 (SMN2). *En route* to its synthesis, intermediate **39** was obtained from the Suzuki coupling between pinacol boronic ester **37** and pyridazinyl chloride **38**. Subsequently, another Suzuki coupling between **39** and pinacol boronic ester **40** was followed by an HCl-promoted deprotection to deliver SMN2 modulator **41**.[11]

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, pyridazine motif has been employed in drug discovery to (a) serve a bioisostere of hetaryl rings such as pyridine, pyrimidine, and pyrazine. Furthermore, aminopyridazines can be used as carboxamide and amine surrogates; (b) boost a drug's aqueous solubility; and (c) facilitate formation of crystalline, water-soluble solid salts.

References

1. Wermuth, C. G. *MedChemComm* **2011,** *2*, 935–941.
2. Jaballah, M. Y.; Serya, R. T.; Abouzid, K. *Drug Res.* **2017,** *67*, 138–148.
3. Gleave, R. J.; Beswick, P. J.; Brown, A. J.; Giblin, G. M.; Goldsmith, P.; Haslam, C. P.; Mitchell, W. L.; Nicholson, N. H.; Page, L. W.; Patel, S.; Roomans, S.; Slingsby, B. P.; Swarbrick, M. E. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 465–468.
4. Kan, J. P.; Mouget-Goniot, C.; Worms, P.; Biziere, K. *Biochem. Pharmacol.* **1986,** *35*, 973–978.
5. Heinisch, G.; Holzer, W.; Kuntz, F.; Langer, T.; Lukavski, P.; Pechlaner, P.; Weissenberger, H. *J. Med. Chem.* **1996,** *39*, 4058–4064.
6. Moslin, R.; Zhang, Y.; Wrobleski, S. T.; Lin, S.; Mertzman, M.; Spergel, S.; Tokarski, J. S.; Strnad, J.; Gillooly, K.; McIntyre, K. W.; Zupa-Fernandez, A.; et al. *J. Med. Chem.* **2019,** *62*, 8953–8972.
7. *Rognan, D.; Sokokoff, P.; Mann, A.; Martres, M.-P.; Schwartz, J.-C.; Costentin, J.; Wermuth, C. G. Eur. J. Pharmacol.* **1990,** *189*, 59–70.
8. Johnson, D. S.; Stiff, C.; Lazerwith, S. E.; Kesten, S. R.; Fay, L. K.; Morris, M.; Beidler, D.; Liimatta, M. B.; Smith, S. E.; Dudley, D. T.; et al. *ACS Med. Chem. Lett.* **2011,** *2*, 91–96.
9. Lucas, M. C.; Bhagirath, N.; Chiao, E.; Goldstein, D. M.; Hermann, J. C.; Hsu, P.-Y.; Kirchner, S.; Kennedy-Smith, J. J.; Kuglstatter, A.; Lukacs, C.; et al. *J. Med. Chem.* **2014,** *57*, 2683–2691.
10. Costas-Lago, M. C.; Besada, P.; Rodriguez-Enriquez, F.; Vina, D.; Vilar, S.; Uriarte, E.; Borges, F.; Teran, C. *Eur. J. Med. Chem.* **2017,** *139*, 1–11.
11. Cheung, A. K.; Hurley, B.; Kerrigan, R.; Shu, L.; Chin, D. N.; Shen, Y.; O'Brien, G.; Sung, M. J.; Hou, Y.; Axford, J.; et al. *J. Med. Chem.* **2018,** *61*, 11021–11036.