Chapter

Fused Pyridine Derivatives: Synthesis and Biological Activities

Huseyin Istanbullu, Gulsah Bayraktar and Merve Saylam

Abstract

Five-membered heteroaromatic ring fused pyridine derivatives are of increasing interest in drug design and medicinal chemistry. The structural similarity of many drugs (especially antiviral and anticancer ones) with DNA bases such as adenine and guanine is a key factor to explain their effectiveness. Apart from these, it is also found in the structures of substances with antituberculosis, antibacterial, antifungal, anti-inflammatory, and antimalarial activities. Another advantage of this group of compounds is their positive contribution to solubility, polarity, lipophilicity, and hydrogen bonding capacity properties of the compounds they are incorporated into. In this chapter, various bioactivities of fused pyridine derivatives will be categorized and summarized.

Keywords: fused pyridine, medicinal chemistry, furopyridines, thiazolopyridine, triazolopyridine, oxadiazolopyridine

1. Introduction

Fused pyridine heterocyclic ring derivatives are frequently used structures in drug research. Due to the vastness of the chemical space of fused pyridine derivatives, the most common fused pyridine derivatives, namely furopyridines, thienopyridines, pyrrolopyridines, oxazolopyridines, isoxazolopyridines, oxadiazolopyridines, imidazopyridines, pyrazolopyridines, thiazolopyridines, isothiazolopyridines, triazolopyridines, thiadiazolopyridines, tetrazolopyridines, selenazolopyridines, and dithiolopyridines, with their bioactivities were selected to cover in this chapter.

2. Fused pyridine derivatives

2.1 Furopyridines

Furopyridine synthesis was firstly reported almost a century ago. Since furopyridines are isosteres of benzofuran and indole cores, they are frequently encountered in the chemical structure of compounds possessing various bioactivities such as antihypertensive and antimicrobial.

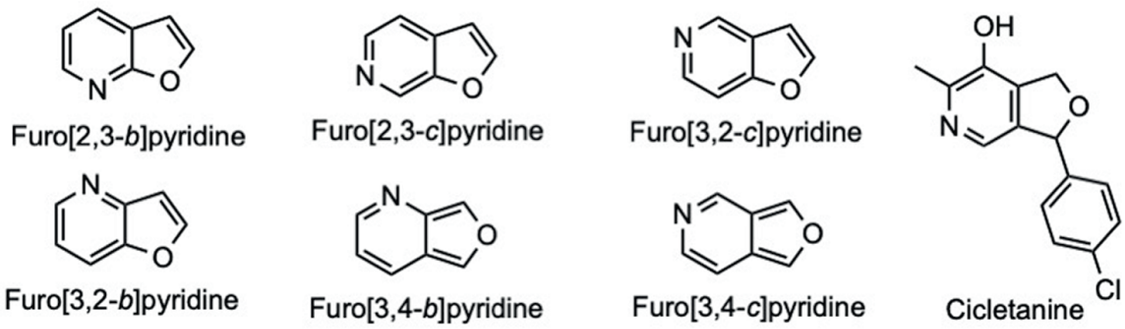

Figure 1.
Furopyridine isomeric structures and example drug molecule bearing furopyridine ring.

One of the first studies on furopyridine derivatives focused on anti-inflammatory, anti-aggregation, and anticoagulant activities [1, 2]. Sato et al. reported tetrahydrofuro[3,4-b]pyridine derivatives with coronary vasodilating activity [3]. Garay et al. examined the effect of furopyridines on the stimulation of K^+ movement across human red cells membrane [4].

On the other hand, cicletanine, a diuretic drug bearing furopyridine scaffold, used in the treatment of hypertension, also is a competitive histamine antagonist (**Figure 1**) [5, 6]. Clinical trial on its usage in hypertension with diabetes is ongoing (NCT02709031).

In addition to the activities mentioned before, there are several studies on furopyridine containing compounds with antimicrobial, anti-infective, and antiproliferative activities [7–14]. Also, furopyridine scaffold is present in a HIV protease inhibitor, L-754394 [15, 16]. Interestingly, it is also found in the structure of the antibiotic isolated from the fungus, *Cladobotryum varium* [17].

Compounds bearing furopyridine scaffold were reported in many studies as both core structure and substituent with kinase inhibitor properties, namely selective inhibitors of cdc-like kinases (CLKs), cyclin-dependent kinase (CDK2) inhibitors, and dk1, cdk2, Fyn, JNK3 kinase inhibitors [18–21].

On the other hand, furopyridine derivatives were reported possessing melanin-concentrating hormone (MCH1) receptor modulator activity and melatoninergic MT1 and MT2 receptor activity [22, 23].

In addition to these, inhibitor effect against angiogenetic targets on VEGFR2, Tie-2, and EphB4, mGluR5 noncompetitive antagonist activity, cannabinoid-1 receptor inverse agonist activity, σ receptor affinity, 5-HT1A agonists/5-HT3 antagonist activity, and 5-HT1F receptor agonist activity of various compounds bearing furopyridine fused ring were also reported [24–29].

2.2 Thienopyridines

The first report on bioactivity of thieno[3,2-b]pyridines focused on chemotherapy of parasites (*Entamoeba histolytica*) [30].

Thienopyridine ring system is an important structural element of anti-aggregation drugs (**Figure 2**). Ticlopidine, tetrahydrothieno[3,2-c]pyridine derivative, is the first reported drug with in vitro anti-inflammatory (carrageenan-induced edema) and inhibition of ADP-induced platelet aggregation activity in 1974 [2]. Then clopidogrel, having the same ring was reported in 1987 and is still on the market for antiplatelet

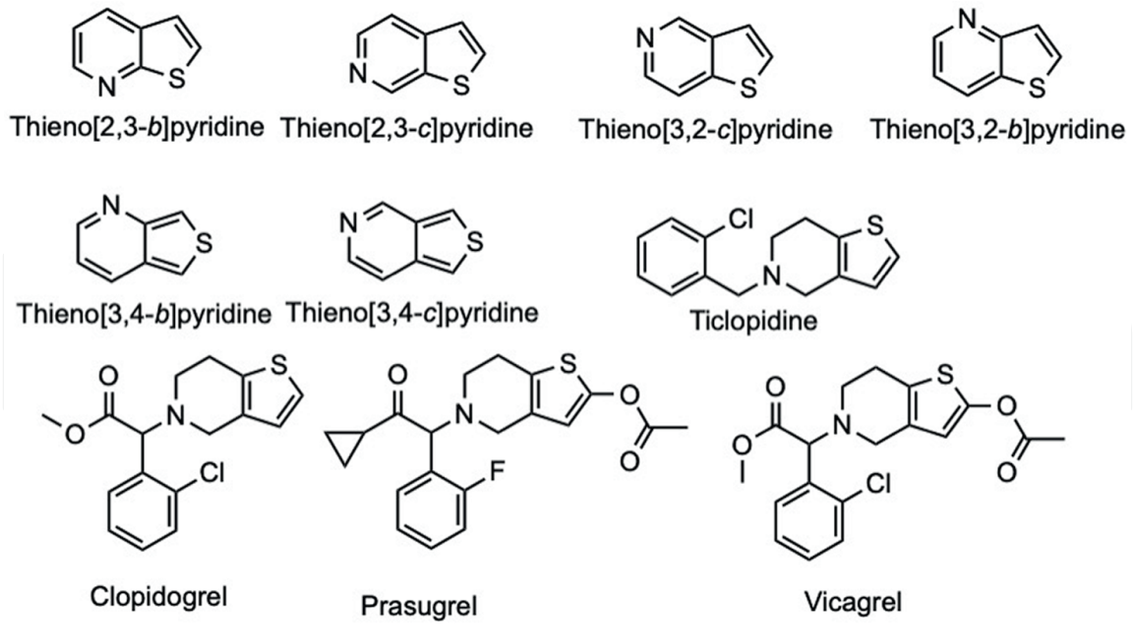

Figure 2.
Thienopyridine isomeric structures and example drug molecules bearing thienopyridine ring.

therapy [31]. Third drug of this class, prasugrel, was reported to the literature in 2000 [32]. Lastly, vicagrel was reported in 2011 to literature and is still undergoing clinical trials (NCT05162053) (**Figure 2**) [33].

On the other hand, compounds containing thienopyridine ring were reported having antimicrobial, anti-infective, antiviral, and antiproliferative effects [34–45].

Also, thienopyrimidine ring occurs either as core scaffold or a substituent in a group of kinase inhibitors such as VEGFR, EGFR, Src, Aurora, KDR, B-Raf, Pim kinases, check point 1 kinase (CHK1) IκB kinase-β (IKKβ), COT, and JAK2 inhibitors [46–56].

In addition to these, thienopyridine bearing structures are also associated with HMG-CoA reductase inhibitors, agonists for the luteinizing hormone receptor, histone lysine demethylase KDM5A Inhibitors, ubiquitin C-terminal hydrolase-L1 (UCH-L1) inhibitors, alkaline phosphatase (ALPase) activity, 5-HT1A agonists/5-HT3 antagonists, allosteric modulators of metabotropic Glu5 (mGlu5) and mGlu2 receptors, urotensin-II receptor antagonists, positive allosteric modulator targeting the M4 muscarinic acetylcholine receptor (M4 mAChR), selective inhibitors of *Plasmodium falciparum* glycogen synthase-3 (PfGSK-3), urea transporter inhibitors, and uridine diphosphate-galactose glycosyltransferase 8 (UGT8) inhibitor in the literature [28, 57–69].

2.3 Pyrrolopyridines

There are six isomeric structures of pyrrolopyridine ring, and azaindole term is also commonly used in the literature.

First reported bioactivity of pyrrolopyridine-bearing compound had been synthesized by Hooper et al. and had pyrrolo[3,2-b]pyridine scaffold with moderate antibacterial effect [70].

The first pyrrolo[2,3-b]pyridine-derived drug in literature is vemurafenib, a B-Raf enzyme inhibitor for the treatment of melanoma [71, 72]. On the other hand,

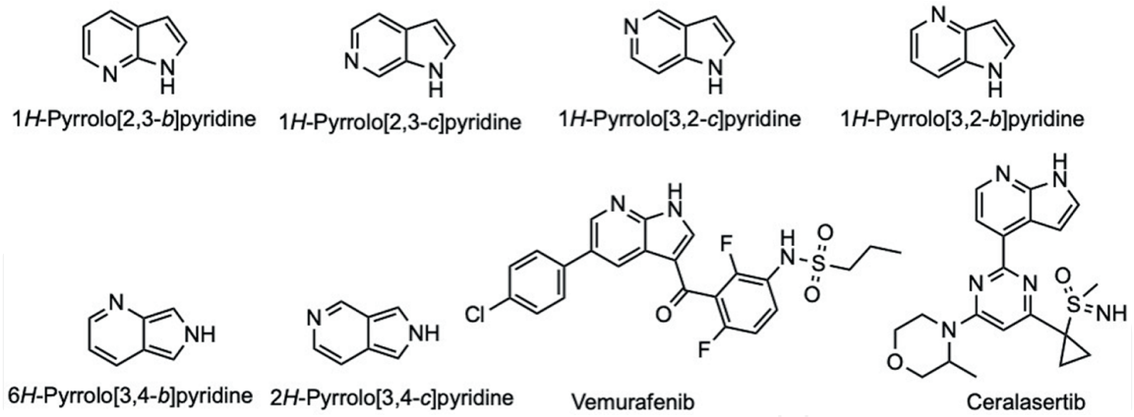

Figure 3.
Pyrrolopyridine isomeric structures and example drug molecules bearing pyrrolopyridine ring.

ceralasertib, a pyrrolo[2,3-b]pyridine-bearing compound, is under phase II trials as ATR kinase inhibitor for antineoplastic therapy (NCT04417062) (**Figure 3**) [73].

On the other hand, several studies were reported on pyrrolopyridine ring-derived compounds with antimicrobial, anti-infective, and antiviral activities [74–79].

Da Settimo et al. reported that pyrrolo[3,4-c]pyridine derivatives with local anesthetic activity and aldose reductase inhibitory properties [80].

Additionally, Kulagowski et al. found out that pyrrolo[2,3-b]pyridine derivatives showed selective D4 receptor antagonist activity [81].

As mentioned before, similar to thienopyridine ring, platelet aggregation inhibitor activity of pyrrolo[3,2-*c*]pyridine-derived scaffold was reported by Altomare et al. [82].

Moreover, antiproliferative activity of several pyrrolopyridine derivatives was investigated in many studies [83–91].

Apart from these, compounds bearing pyrrolopyridine moiety were found in various kinase inhibitors such as Met, insulin-like growth factor-1 receptor (IGF-1R), tyrosine, Aurora, Fes and Flt3 tyrosine kinases, Traf2 and Nck-interacting kinase (TNIK), Tau Tubulin Kinase 1 (TTBK1), JAK1 selective, BTK, DYRK1A, and RAF-1 dual inhibitor [92–103].

Lastly, many compounds containing fused pyrrolopyridine anologs were reported in the literature having several different bioactivities such as allosteric mGluR5 antagonist activity, diacylglycerol acyltransferase-2 inhibitors, antagonists of the G-protein-coupled chemoattractant receptor (CRTh2), in vivo TNF-a inhibitory activity, preventing protein phosphatase 2A (PP2A) inhibition, human neutrophil elastase (HNE) inhibitors, retinoic acid receptor-related orphan C2 (RORC2) inverse agonist, selective GluN2B negative allosteric modulators, 5-HT_{1F} receptor agonist, agonist of ORL-1(Opioid receptor-like) receptor, and cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptor agonist activity [104–116].

2.4 Oxazolopyridines, isoxazolopyridines, and oxadiazolopyridines

Oxazolopyridine derivatives, an aza analog of benzoxazole, have been studied extensively since the first report of their synthesis by Fraser and Tittensor in 1956 (**Figure 4**) [117]. Yet, the first bioactivity (anthelmintic and acaricidal activity) of compounds with oxazolopyridine moiety, namely oxazolo[4,5-b]pyridine, was reported nearly 20 years later by Rüfenacht et al., and then, oxazolo[5,4-b]

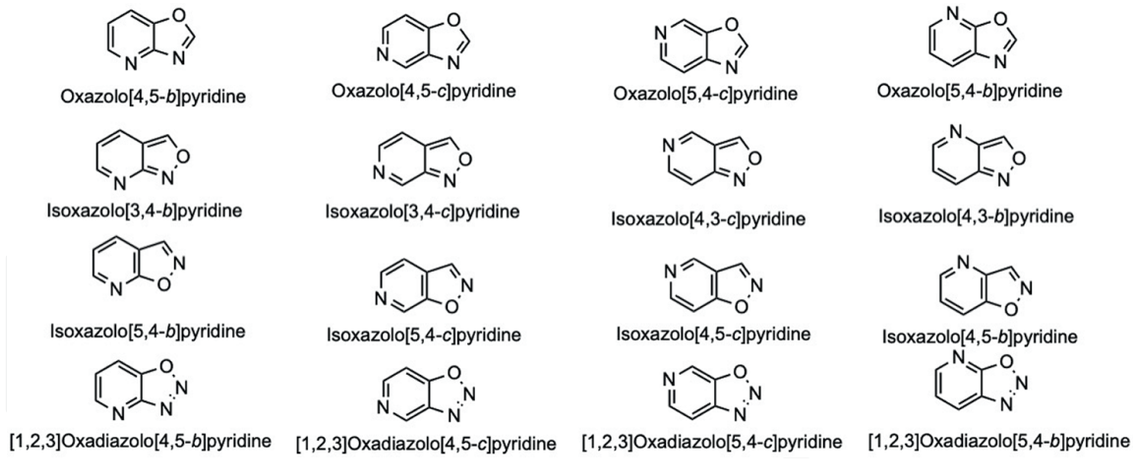

Figure 4.
Oxazolopyridine, isoxazolopyridine, and oxadiazolopyridine isomeric structures.

pyridine-bearing compounds were reported having carrageenan rat foot edema assay activity by Clark et al. [118, 119]. Later, antimicrobial, anti-infective, antiviral, and antiproliferative activities of several compounds having oxazololopyridine moiety were reported [120–124].

Additionally, various bioactivities such as fatty acid amide hydrolase (FAAH), topoisomerase II, monoamine oxidase B, GSK-3beta-, sphingomyelin synthase 2 inhibitory, SIRT1 activation, and histamine H3-receptor antagonistic activity of oxazololopyridine moiety-bearing compounds were reported in the literature [125–133].

Although the synthesis of isoxazolo[5,4-b]pyridines was reported in 1968 by Markillie, there has been a few bioactivity studies on isoxazolopyridine derivatives including GABAergic activity, HMG-CoA reductase inhibitory activity, anticancer activity, polo-like kinase inhibitor activity, and gamma-secretase modulator activity (**Figure 4**) [57, 134–138].

The synthesis of oxadiazolopyridine core was firstly reported by Bailey et al. in 1971 (**Figure 4**) [139]. Only antitumor activity and fluorescent properties of oxadiazolopyridine containing compounds were reported [140, 141].

2.5 Imidazopyridines

Imidazo[4,5-b]pyridine, the first synthesized imidazopyridine isomer, was synthesized by Takahashi and Yajima in 1946, and then analeptic activity of imidazopyridine was reported in 1965 [142, 143].

Imidazopyridines are one of the most studied fused pyridine ring systems; therefore, it is found in many drugs' structures (**Figure 5**). The various bioactivity profiles of these groups of compounds might be associated with the fact that imidazopyridines, also known as 3-deazapurines, are isosteres of purine ring.

Miroprofen, an imidazo[1,2-a]pyridine derived NSAID, has analgesic, antipyretic, and anti-inflammatory activity. Another imidazo[1,2-a]pyridine derivative, Zolpidem, is a hypnotic drug and positive GABA-A receptor modulator. Similarly, Alpidem, Necopidem, and Saripidem are other imidazo[1,2-a]pyridine containing anxiolytic drugs. Olprinone acts as a cardiotonic agent and is used in Japan. Zolimidine is a marketed anti-ulcerative drug. Minodronic acid, a bone resorption inhibitor and Sch 28080, gastric antisecretic compound, and H^+K^+-ATPase inhibitior are other imidazo[1,2-a]pyridine-bearing compounds [144–152].

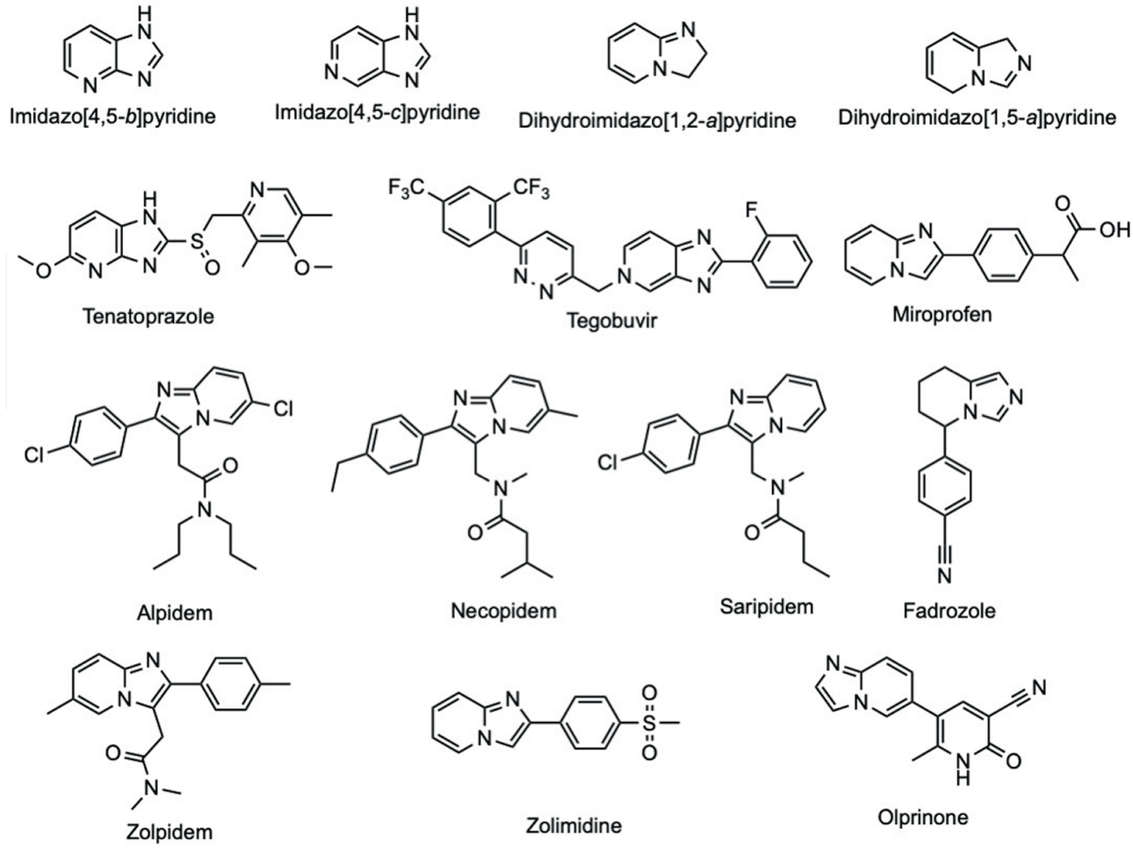

Figure 5.
Imidazopyridine isomeric structures and example drug molecules bearing imidazopyridine ring.

Imidazo[4,5-b]pyridine ring is occurred in various drugs including Vardax (sulmazole), a cardiotonic drug with positive inotropic activity, phosphodiesterase inhibition and adenosine receptor antagonist activity, and Rimegepant and Telcagepant, antimigraine drugs possessing CGRP receptor antagonists activity. Additionally, imidazo[4,5-b]pyridine-derived Tenatoprazole is reported with proton pump inhibitory activity and gastric acid secretion inhibitory properties in rats [153–158].

On the other hand, Tegobuvir, imidazo[4,5-c]pyridine-bearing compound, is used in prophylaxis and treatment of HCV infection, and Fadrozole, a Tetrahydroimidazo[1,5-a]pyridine derivative, is a nonsteroidal aromatase inhibitor for breast cancer treatment [159–162].

Moreover, there are several reports on imidazopyridine-bearing compounds possessing antibacterial, antiviral (HIV, etc.), and antiparasitic (anti-leishmanial and anti-trypanosomal) properties [163–174]. Also, imidazopyridine derivatives are often studied as anticancer agents [175–181].

The imidazopyridine scaffold has been reported in the structures of various kinase inhibitors, such as KDR kinase, calmodulin-dependent kinase II (CaMKII), Glycogen Synthase Kinase-3, cyclin-dependent kinase (CDK), Bruton's tyrosine kinase, AKT Kinase, c-Met kinase, VEGFR2 kinase, FLT3 kinase, Pan-JAK, Aurora-A kinase, phosphatidylinositol-3-kinase (PI3K) and apoptosis signal-regulating kinase 1 (ASK1) [182–195].

In addition to these bioactivities, imidazopyridine ring isomers expressed several including positive modulation of GABA-A receptor, positive allosteric modulation of metabotropic glutamate receptor 2 (mGluR2), angiotensin II receptor antagonist,

receptor-related orphan receptor gamma (RORc) inverse agonist, melanin-concentrating hormone receptor 1 (MCHR1) antagonist, anti-inflammatory, anticonvulsant, phosphodiesterase (PDE) inhibitory, platelet-activating factor antagonist, TNF-α suppressing, mammalian target of rapamycin (mTOR) inhibitory, autotaxin inhibitory, cholinesterase inhibitory, and PARP-1 inhibitory activities in the literature [196–209].

2.6 Pyrazolopyridines

The synthesis of pyrazolopyridines was reported firstly by Englert and McElvain (**Figure 6**) [210]. Shortly after the synthesis, compounds containing pyrazolopyridine moiety with anti-inflammatory, antipyretic, and analgesic activity were reported [211]. Additionally, antibacterial (against both gram-positive and gram-negative bacteria), antiviral (anti-enterovirus), and antifungal and antiparasitic (antimalarial) activity reports of pyrazolopyridine-bearing compounds were reported in the literature [212–217]. Moreover, anticancer activity of various pyrazolopyridine derivatives was investigated in many studies [218–222].

Apart from these, many kinase inhibitors, namely CDK1/CDK2, glycogen synthase kinase-3, protein kinase Cθ (PKCθ), phosphatidylinositol-3-kinases (PI3K), aurora-A kinase, pim-kinase, TYK2, ALK5 (activin receptor-like kinase 5), anaplastic lymphoma kinase (ALK), and mitogen-activated protein kinase kinase 4 (MKK4) inhibitors, have pyrazolopyridine ring in their scaffold [223–232].

Lastly, in addition to activities mentioned before, anxiolytic, adenosine A1 receptor antagonist, PDE4, PDE5, PDE9 inhibitory, mTOR inhibitory, guanylate cyclase agonist, B-Raf^{V600E} inhibitory, dopamine D3 receptor agonist, and tubulin polymerization inhibitory and cholinesterase inhibitory activity of pyrazolopyridine derivatives were reported [233–244].

2.7 Thiazolopyridines and isothiazolopyridines

Thiazolo[4,5-b]pyridine ring was synthesized by Saikachi in 1944 [245]. The first reported bioactivity of thiazolopyridine was antituberculous activity of thiazolo[4,5-c]pyridine derivatives (**Figure 7**) [246].

Antibacterial (against both gram-positive and gram-negative bacteria), antiviral, antifungal, antituberculose, and antiparasitic activity of compounds containing thiazolopyridine structure were reported [247–251]. Additionally, cytotoxic and anticancer activity of thiazolopyridine derivatives were investigated in many studies [252–255].

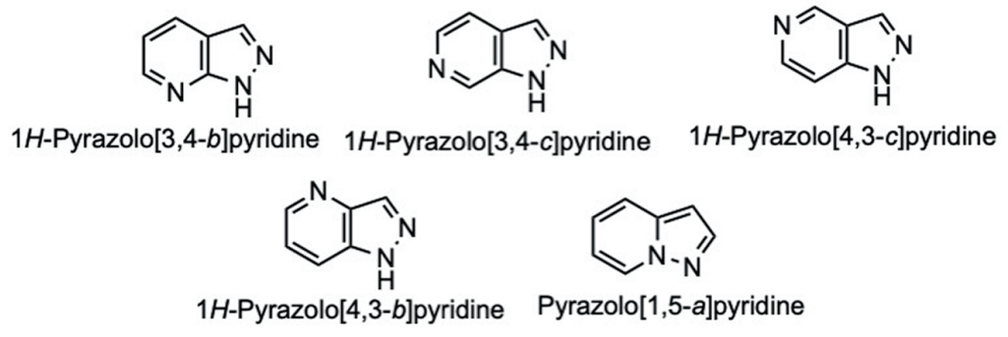

Figure 6.
Pyrazolopyridine isomeric structures.

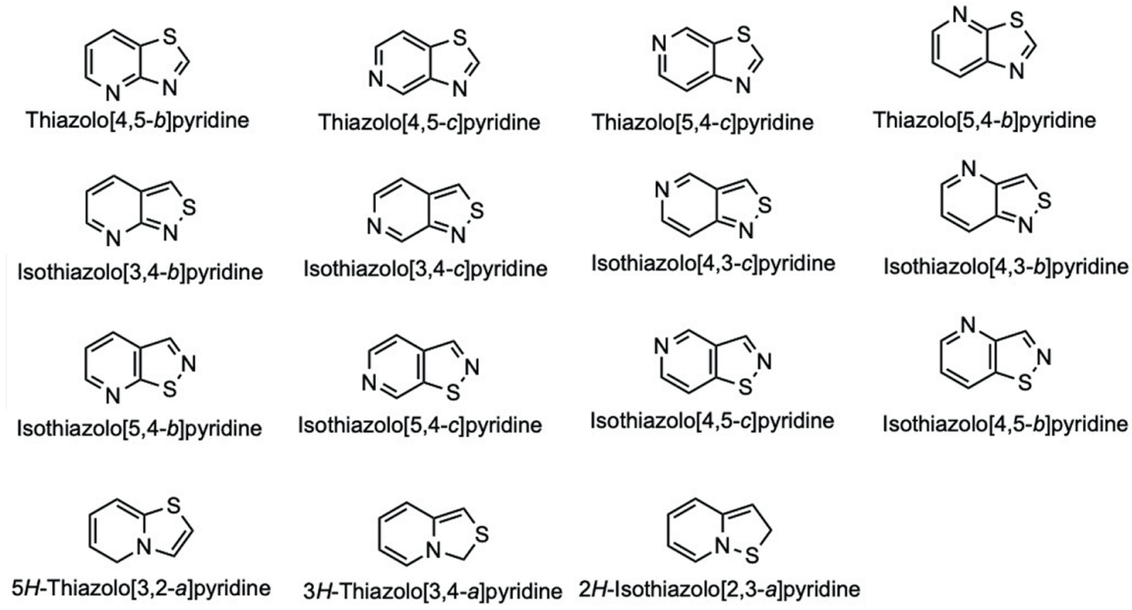

Figure 7.
Thiazolopyridine and isothiazolopyridine isomeric structures.

Moreover, there are many thiazolopyridine-bearing compounds with various bioactivity profile, such as histamine H3-receptor antagonistic activity, mGluR5—metabotropic glutamate receptor subtype 5-antagonist, sphingosine-1-phosphate (S1P) agonist, DNA Gyrase B (GyrB) ATPase inhibitor, anti-inflammatory activity, phosphoinositide 3-kinase inhibitor, and allosteric inhibitor of MALT1 [129, 256–261].

On the other hand, synthesis of isothiazolopyridines was firstly reported by Taurins and Khouw in 1997 [262]. Later, in vivo anorectic action activity of isothiazolo[5, 4-b]pyridine derivatives was reported by Malinka and Rutkowska [263]. There have been a few reports on bioactivity of isothiazolopyridine derivatives such as antitumor and radioprotective activities, in vitro antibacterial activity, analgesic activity, cyclin G-associated kinase inhibition, antiviral activity, and COX-1/2 inhibitory activity [264–269].

2.8 Triazolopyridines

Triazolopyridine scaffold is an isostere of purine ring; therefore, there are several bioactivity reports on compounds containing triazolopyridine ring.

The first report on the synthesis of (3*H*)1,2,3-triazolo[4,5-*c*]pyridine derivatives and their analeptic activity was published by Reitmann in 1936 [270].

1,2,3-Triazolo[4,5-*b*]pyridine and 1,2,3-triazolo[4,5-*c*]pyridine derivatives were reported possessing depressant, tranquilizing, anticonvulsant, and cardiovascular activities [143].

An antidepressant drug Trazodone, 1,2,4-triazolo[4,3-*a*]pyridine derivative, was first reported in 1968 and has been used commonly for the treatment of depression (**Figure 8**) [271]. In addition to its antidepressant effect, it was recently reported that trazodone inhibits tau amyloidogenesis [272].

On the other hand, several triazolopyridine-containing compounds were reported having antibacterial, antiviral, antifungal, antituberculose, and antiparasitic activity [273–278]. Additionally, triazolopyridine derivatives were investigated in many studies for their anticancer activity [279–281].

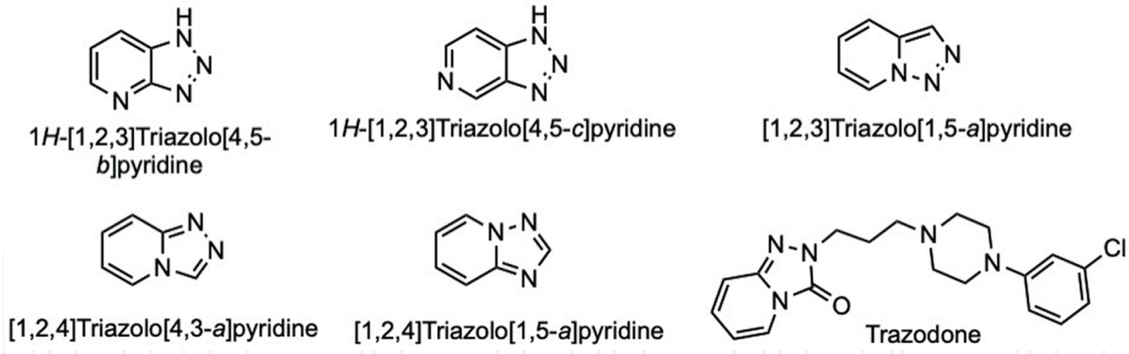

Figure 8.
Triazolopyridine isomeric structures and example drug molecule-bearing pyrrolopyridine ring.

Similar to other fused pyridine derivatives, triazolopyridine scaffold has been reported in many papers as kinase inhibitors, such as PIM kinase, JAK1, JAK2, PI3K-gama-delta, ALK-5, VEGFR2 kinase, spleen tyrosine kinase (Syk), c-met kinase, and monopolar spindle 1 (MPS1) kinase inhibitors [282–290].

Lastly, compounds containing triazolopyridine ring were evaluated for their bioactivities, such as anti-inflammatory, p38R, 11beta-hydroxysteroid dehydrogenase-type 1 (11beta-HSD-1), prolylhydroxylase domain-1 (PHD-1), myeloperoxidase, tubulin polymerization, polycomb repressive complex 2 (PRC2) inhibitory, HIV-1 allosteric inhibitor activity, mGlu receptor 2 (mGluR2) PAM, muscarinic acetylcholine receptor subtype 1 (M1) PAM, and retinoic acid receptor-related orphan nuclear receptor gama-t (RORγt) inverse agonist [174, 291–303].

2.9 The other five-membered heteroaromatic ring fused pyridine derivatives

Apart from fused pyridine derivatives mentioned before, there are several reports on five-membered heteroaromatic fused pyridine ring derivatives possessing bioactivity (**Figure 9**).

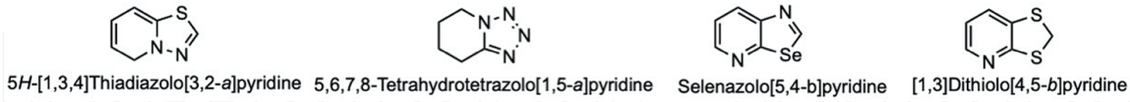

Figure 9.
Five-membered heteroaromatic ring fused pyridine derivatives.

For instance, 1,3,4-thiadiazolo[3,2-a]pyridine derivatives were reported having antimicrobial effects [304]. On the other hand, tetrahydrotetrazolopyridine scaffold was found in bovine liver-D-glucuronidase and human-alfa-L-iduronidase inhibitors [305]. Interestingly, an unusual fused pyridine derivative selenazolo[5,4-b]pyridine scaffold can highly induce apoptosis in human breast carcinoma MCF-7 cells [306]. Lastly, dithiolo[4,5-b]pyridine derivatives were reported possessing antimicrobial activity [307].

2.10 Conclusion

In conclusion, fused five-membered pyridine heteroaromatic rings are privileged scaffolds in medicinal chemistry. Therefore, selected ring systems and their bioactivities are covered in this chapter.

There are several drugs containing these heteroaromatic rings on the market, and several phase trials are ongoing on various compounds. Considering the chemical similarity between fused pyridine rings and nucleobases and amino acids, the wide variety of the bioactivity is unsurprising. The most commonly reported bioactivities of these kinds of derivatives are antimicrobial, anticancer, and kinase inhibition.

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