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The Diazine Trio: Pyridazine, Pyrimidine, and Pyrazine — Structure, Properties, Synthesis, Reactivity and Biological Applications

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ABSTRACT

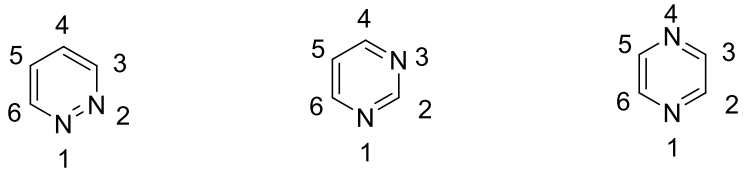
In medicinal chemistry, heterocycles, especially six-membered nitrogen-based aromatic compounds such as diazines are foundational and valuable moieties. Diazines: pyridazine, pyrimidine and pyrazine are important heterocyclic compounds with a wide range of biological applications. Although these three compounds are constitutional isomers, pyrimidine and pyrazine derivatives are found widely in nature, while pyridazines are rare. Several studies have explored the synthesis, medicinal properties, such as antimicrobial, anticancer, antiviral, and antihypertensive activities of diazines. This article reviews the chemistry—structure, properties, synthesis, and reactivity of pyridazine, pyrimidine and pyrazine derivatives. Furthermore, their biological applications were discussed to highlight their relevance to medicinal chemistry.

Keywords: Pyridazine, pyrimidine, pyrazine, diazine, synthesis, biological applications

INTRODUCTION

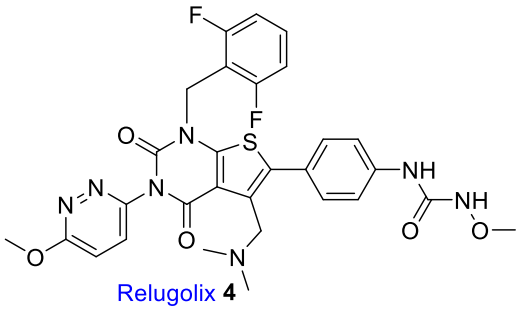
Diazines are heterocyclic dinitrogen aromatic compounds with molecular formula $C_4H_4N_2$. Diazines have three structural isomers, each containing a benzene ring in which two of the C-H fragments have been replaced with two nitrogen atoms, hence, considered as aza-analogues of benzene. The two nitrogens are in positions 1 and 2; 1 and 3; and 1 and 4 for pyridazine **1**, pyrimidine **2** and pyrazine **3** (Fig. 1.), respectively [1]. Diazines have wide range of applications in the fields of biomedical, electronics and material science. They are important components of nucleic acid bases (pyrimidine), pharmaceticals, and agrochemicals. They play a significant role in coordination chemistry as ligands. They are class of organic compounds that are found in nature and synthesised through various methods [2–5]. Pyridazine, pyrimidine and pyrazine are present in commercially available drugs. Drugs such as relugolix **4**, emarofazone **5**, mineprine **6**, and prizidilol **7** are pyridazine-based anticancer, analgesic, psychotropic, and antihypertensive drugs,

respectively (Fig. 2.). Imatinib **8**, minoxidol **9** and osimertinib **10** are primidine-based drugs. While imatinib **8** and osimertinib **10** are anticancer agents, minoxidol **9** is used in treatment of hypertensive and hair loss (Fig. 2.). Similarly, pyrazinamide **11** and amiloride **12** (Fig. 2.) are antitubercular and antihypertensive pyrazine-based approved drugs, respectively [6–8]. Primidine and pyrazine have been more thoroughly investigated than pyridazines because pyridizine rarely occurs in nature due to scarcity of their precursors, hydrazines [9].

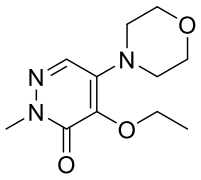


Pyridazine **1** pyrimidine **2** Pyrazine **3**

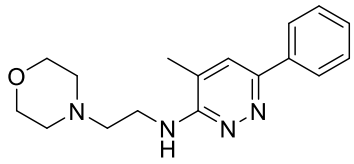
Fig. 1: Structures of diazines—pyridazine, pyrimidine and pyrazine



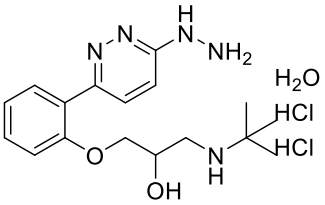
Relugolix **4**
Anti-cancer agent



Emarofazone **5**
Analgesic



Minaprine **6**
Psychotropic drug



Prizidilol 7
Antihypertensive

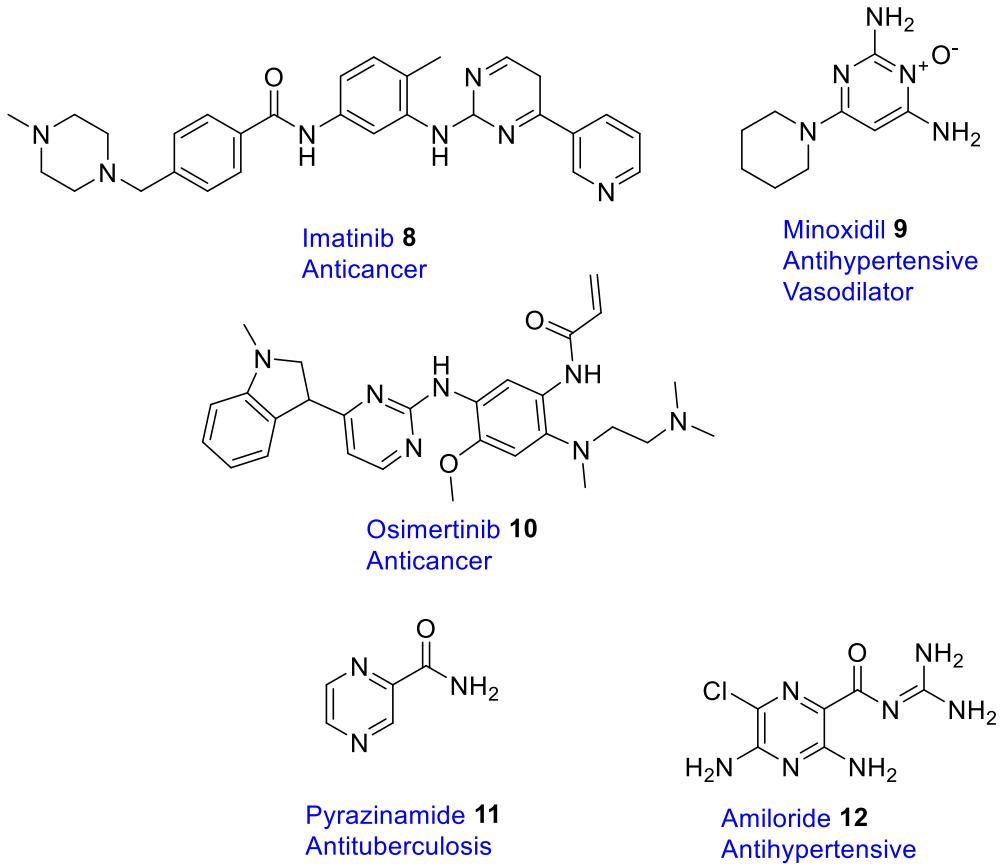


Fig. 2: Commercially available drugs bearing pyridazine, pyrimidine and pyrazine moieties

Physicochemical properties of pyridazine, pyrimidine and pyrazine

Despite their structural similarity, their positional differences cause different reactivity, utility and unique physicochemical behaviour. Pyridazine, pyrimidine and pyrazine are weak bases, far less basic than pyridine (pKa = 5.2) however, the pyridazine is the strongest base (pKa = 2.3) among them [2, 10]. The order of the acidity of their conjugate bases is pyrazine > pyrimidine > pyridazine. This order is due to the destabilization of the protonated species by the second nitrogen through inductive effect.

In pyrazines, the nitrogens are para to each other, hence less destabiliztion of the cation occurs compared to pyridine. Similarly, pyridazine has a high dipole moment (μ = 3.9), followed by pyrimidine (μ = 2.4), and lastly, pyrazine has 0 dipole moment due to it symmetrical nature [2, 4, 11]. The higher dipole moment of pyridazine lead to its improved intermolecular and intramolecular interactions, as well as interactions between molecules and proteins. Similarly, the presence of two nitrogen atoms in diazines increases the hydrophilicity of small molecules. They

are colourless, stable liquids at room temperature with appreciable boiling points. However, their boiling point trend is irregular. While pyridazine exihibits the highest boiling point (208 ºC), both pyrimidine (123 ºC) and pyrazine (115 ºC) have lower boiling points with small variation. Compared to benzene, to which they are bioisosteres, pyridazine and pyrimidine have higher boiling point than benzene (boiling point 80 ºC) due to the presence of intermolecular and intramolecular forces of attraction associated with the nitrogen atoms [4]. Their high π-deficient aromatic skeleton enables π-π stacking interactions, and two nitrogen atoms that facilitate drug-target interactions via hydrogen bonding. Compared to pyridine, the three diazines are significantly more electron deficient. The high electron deficiency makes them more susceptible to nucleophilc attack (SNAr) and less prone to electrophilic aromatic substitutions relative to benzene and pyridine. This phenomenom results from the capacity of the second nitrogen atom exerting a strong electron-withdrawing inductive (and sometimes resonance) effect, leading to less electron density around the ring carbon atoms [1, 2, 4, 12].

The electron deficiency is highest in pyrazine and pyrimidine due to para and meta-arrangement of the nitrogen, respectively. Pyridazine is slightly less than the two in terms of electron deficiency (moderate) due to the lone-pair interaction by the adjacent nitrogen. The reason for high electron deficiency in the diazines is because there is a strong resonance which leads to an effective withdrawal of electron density as the second N destabilizes the protonated form [13]. Table 1 compares the physicochemical properties of pyridazine, pyrimidine and pyrazine.

Table 1: Physicochemical properties of pyridazine, pyrimidine and pyrazine

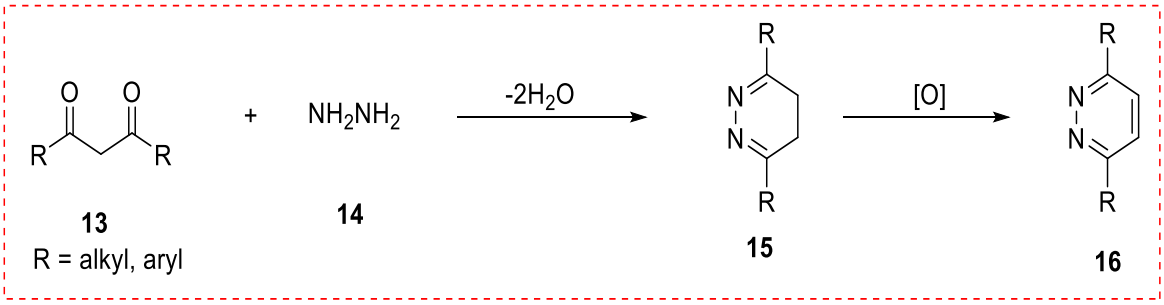
Property	Pyridazine (1,2)	Pyrimidine (1,3)	Pyrazine (1,4)
pK_a (conj. acid)	2.0	0.93	0.37
Dipole moment (D)	3.9	2.4	0
Boiling point (°C)	208	123	115
Electron deficiency	High	High	Highest
logP (Octanol/Water)	0.44	0.11	-0.19

Synthesis of diazines

Owing to their medicinal importance, several methods have been reported for the synthesis of diazines. Here are some of the most common synthetic routes.

Pyridazine

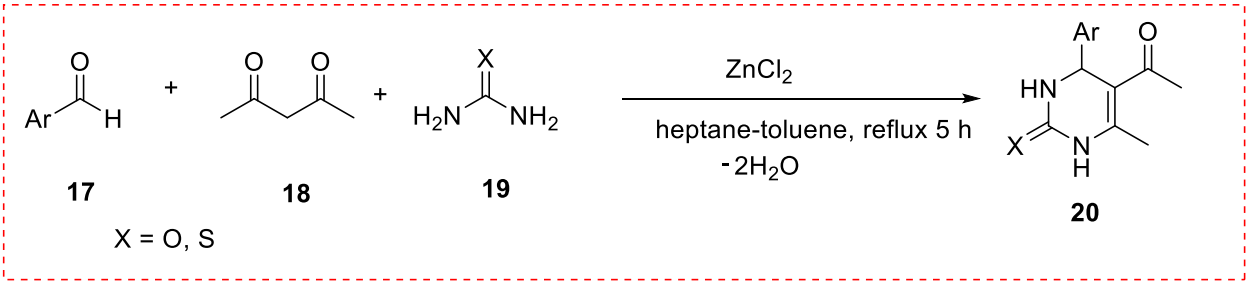
The strategy shown (**Scheme 1**) is used for the synthesis of pyridazine. It involves the reaction of 1,4-diketone **13** with hydrazine **14** to give dihydropyridazine **15**. The pyridizine **16** is finally obtained via oxidation of the dihydropyridazine **15** [9].



Scheme 1: Synthesis of pyridazine via reaction of 1,4-diketone with hydrazine

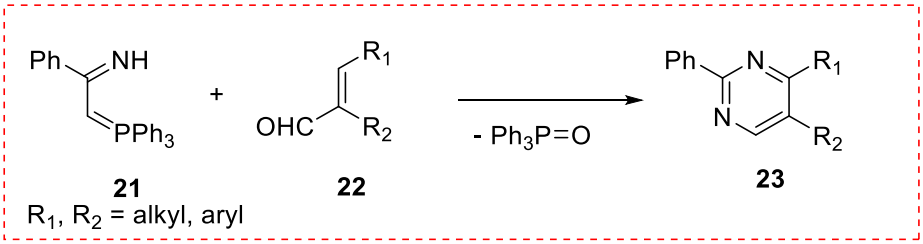
Pyrimidine

The traditional synthetic route to pyrimidine is a multicomponent process known as Biginelli reaction (**Scheme 2.**) which involves the condensation of aromatic aldehyde **17** and 1,3-dicarbonyl compounds **18** with urea or thiourea **19** in the presence of acid catalysts. This synthetic method gives good yield of the desired pyrimidine rings **20** [14].



Scheme 2: Synthesis of primidine derivatives

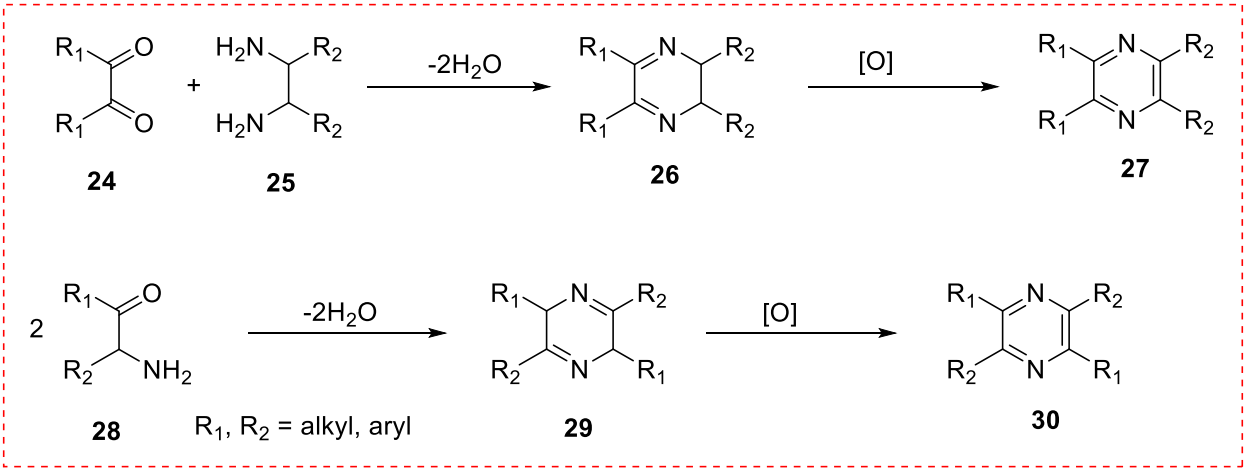
Pyrimidine scaffolds can be synthesised from the condensation of an amidine-containing substrate with an α, β-unsaturated carbonyl compound. For example, the aza-Wittig reaction of **21** with different aldehydes **22** produced pyrimidines **23 (Scheme 3)** [15].



Scheme 3: Synthesis of pyrimidine rings.

Pyrazine

The classical synthetic method for pyrazines involves the condensation of 1,2-dicarbonyl **24** with 1,2-diaminoethane **25** forming an intermediate dihydropyrazine **26**. Oxidation of dihydropyrazine **26** give pyrazines **27** in good yield (**Scheme 4.**). The oxidazing agents used are usually Copper (II) oxide and manganese oxide. Furthermore, pyrazines **30** are synthesised via self-condensation of α aminocarbonyl compound **28** leading to the formation of 3,6-dihydropyrazine intermediate **29**, subsequent oxidation yield pyrazines **30** (**Scheme 4**) [16, 17].



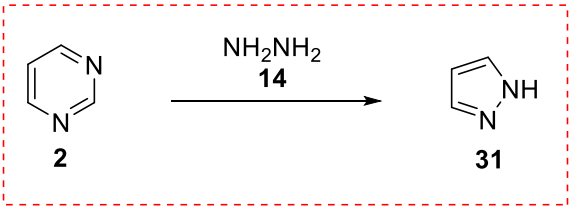
Scheme 4: Classical methods to pyrazines

Reactivity of diazines

The diazines – pyridazine, pyrimidine and pyrazine – have similar reactivities to pyridines, however, more profound. They possess an increased electron deficiency at the carbon due to the presence of two imines (two nitrogens) as such exhibit increased susceptibility and resistance to nucleophilic addition and electrophilic attack, respectively [4, 18].

Nucleophilic substitution

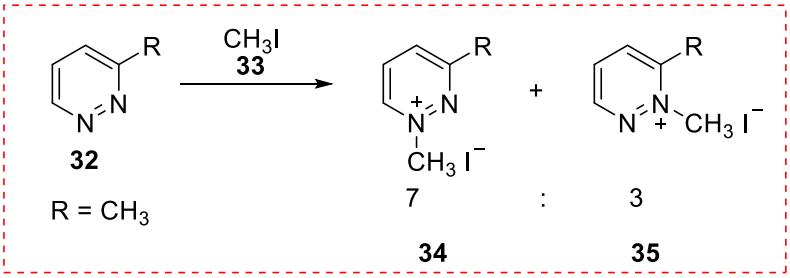
Diazines are more prone to nucleophilic attack than pyridine. Pyrimidine **2**, for example, is opened and closed to a pyrazole by hydrazine. i.e (Addition of Nucleophile Ring Opening Ring Closure) (**Scheme 5**) [18].



Scheme 5: Diazine nucleophilic substitution reaction

Electrophilic addition to Nitrogen

Electrophilic addition to nitrogen produces diazine salts. The diazines react less readily than pyridine with alkyl halides **33** forming quaternary salts **34-35** (**Scheme 6**). Among the diazines, pyridazine **32** reacts faster. The region selectivity of the reaction is determined by the nature of the substituents adjacent to nitrogen [18].

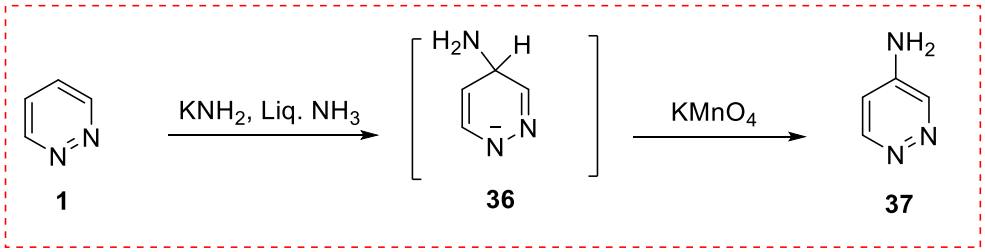


Scheme 6: Electrophilic addition to nitrogen in diazines

Substitution of Hydrogen

All three diazines undergo addition of organometallics (R-Mg, R-Li,) or amide anion at one of the neighboring carbons of the imine units generating an non-aromatic intermediate **36** that is easily

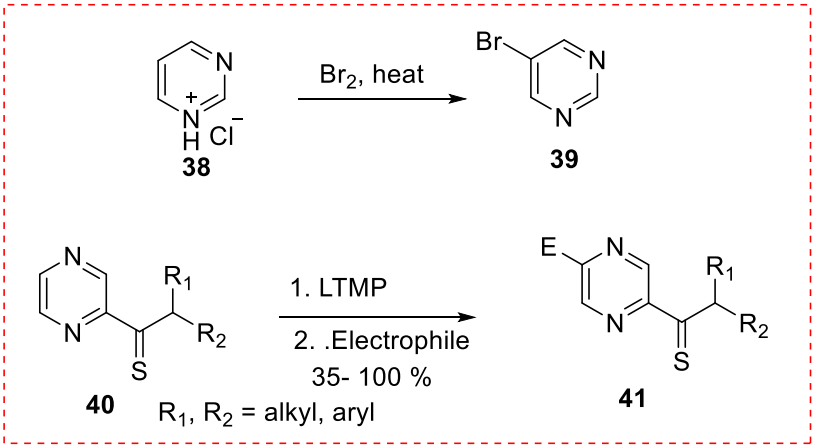
re-aromatised through nucleophilic substitution of hydrogen to form 4-aminopyridazine **37**. Example, amination reaction where amide anion adds easily leading to hydrogen substitution (**Scheme 7**) [18].



Scheme 7: Substitution of hydrogen in diazines

Electrophilic substitution at carbon

In diazines, electrophilic attack directly at carbon is rare. Pyrimidine **38** can be brominated under the conditions as pyridine leads to substitution at C-5 **39** (**Scheme 8.**). Similarly, pyrazine **40** can undergo electrophilic substitution at C-5 via lithiation and subsequent electrophilic attack on the electrophile to form compound **41**. Position 5 on diazines is important because it is the only position that is not α or ϒ to nitrogen as such it's equivalent to a β-position in pyridine [15, 18]. The reactivity trend is summarised in Table 2.



Scheme 8: Electrophilic substitution at carbon involving pyrimidine and pyrazine

Table 2: Reactivity trend

Reaction	Pyridazine (1,2)	Pyrimidine (1,3)	Pyrazine (1,4)	Pyridine (Ref.)
Electrophilic substitution	Very difficult	Very difficult	Very difficult	Difficult
Nucleophilic substitution/addition	Very easy esp. at C2/C4)	Very easy esp. at C2/C4)	Easy	Moderate

Biological applications

Pyridazine, pyrimidine and pyrazine (diazines) are important heterocylic scaffolds. Recently, much attention has been focused on their derivatives for their broad-spectrum biological activities.

Pyridazine

Pyridazine constitute essential parts of agriculture, for example, maleic hydrazide **42** and Norflurazon **43** are used as plant growth hormone and herbicide, respectively (Fig. 3.) [5]. Several pyridazine derivatives were investigated for human acetyl cholinesterase inhibitory activity among which compound N-((1-benzylpiperidin-2-yl)methyl)-5-methyl-6-phenylpyridazin-3-amine **44** was found to be 100 times more selective than the reference drug Tacrine (Fig. 3) [19].

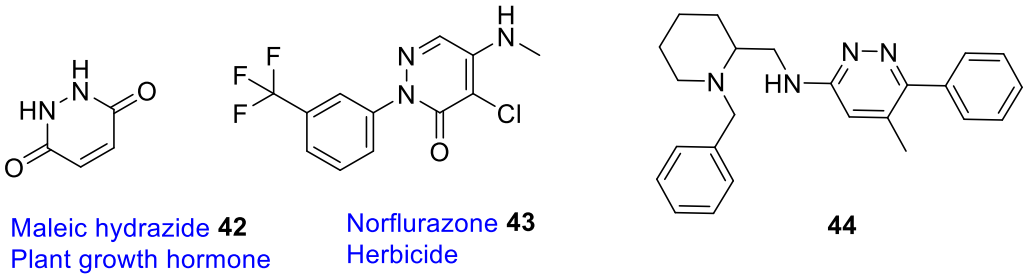


Fig. 3: Pyridazine pharmacophores

Compound **45**, a pyridazine hybrid was 100% lethal at 500 mg/L against insects: *B. tabaci* and *N. lugens* [20]. In another study, Buysse et al. reported significant insecticidal activity of compounds **46** and **47** (Fig. 4) against *M. persicae* and *A. gossypii* (LC_{50} = 13.4 mg/L; 6.4 mg/L and LC_{50} = 0.42 mg/L; 1.34 mg/L), respectively [21].

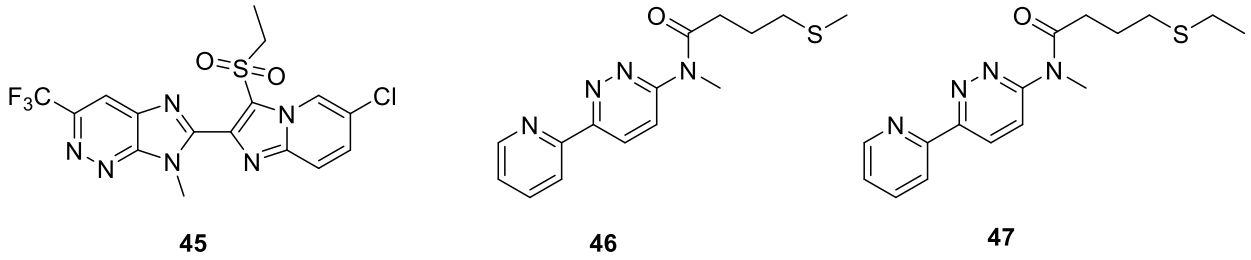


Fig. 4: Bioactive pyridazine hybrids

Pyrimidine

Pyrimidines are building blocks of DNA and RNA. Pyridazine derivatives are also widely used as starting materials in drug design and discovery [22]. A pyrimidine-based compound **48** (Fig. 5.) serves as inhibitor of acetohydroxy acid synthase (AHAS). AHAS is an enyzme that facilitates the biosynthesis of amino acids such leucine and valine [23]. In another study, furopyrimidine-based compound **49** exhibited moderate antiproliferative activity against the WiDr (colon) cancer cell line with a GI_{50} of 86 mM. Different substitutions at the phenyl ring yielded no further activity [24].

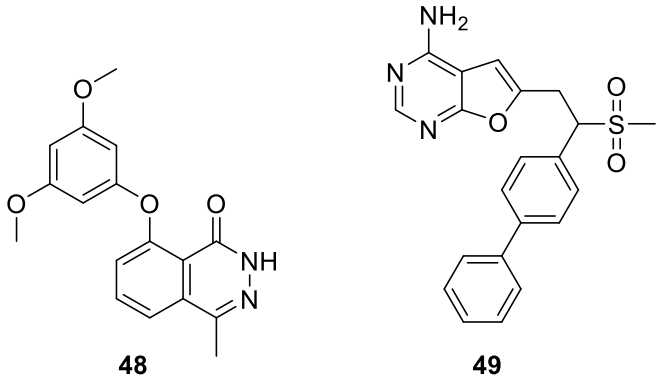
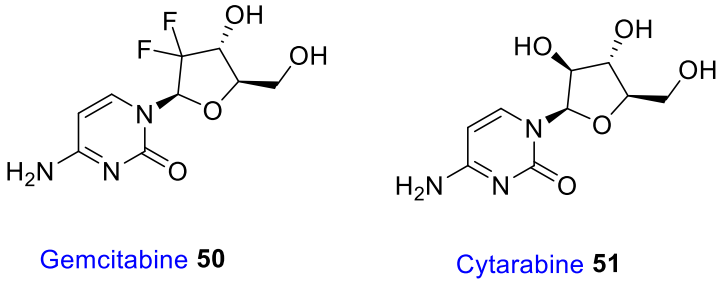


Fig. 5: Bioactive compounds containing pyrimidine moiety

In addition, pyrimidine derivatives such as gemcitabine **50** are used in treatment of various cancers such as pancreatic, breast, bladder, lung, etc. On the other hand, cytarabine **51** treats acute leukemia (Fig. 6) [25].

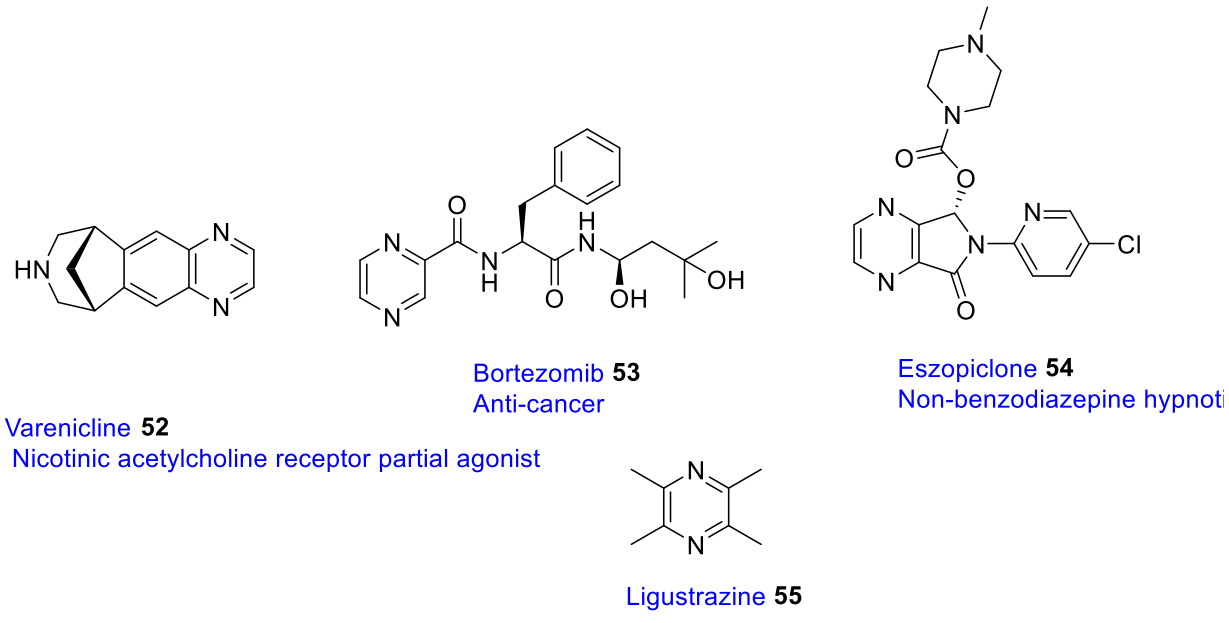


Gemcitabine **50** Cytarabine **51**

Fig. 6: Primidine-based pharmacophores

Pyrazine

Naturally occurring pyrazines fuction as pheromones, repellents and sitemarkers in some plants and insects such as bees and moths [16]. Pyrazine moiety is embeded within prominent drugs, such as varenicline **52** (Fig. 7) which used in treatment of nicotine addiction through binding to the nicotinic acetylcholine receptor at a lower level than nicotine, hence preventing it from binding [26, 27]. While bortezomib **53** inhibits proteasome, eszopiclone **54** serves as non benzodiazepine hypnotic. Ligustrazine (tetramethylpyrazine) **55** (Fig. 7.) is an active pyrazine compound found in Chuanxiong (chinese traditional medicine) used in the treatment of cardiovascular and ischemic cerebrocardiac vascular diseases [28].



Varenicline **52**
Nicotinic acetylcholine receptor partial agonist

Bortezomib **53**
Anti-cancer

Eszopiclone **54**
Non-benzodiazepine hypnoti

Ligustrazine **55**

Fig. 7: Approved drugs containing pyrazine moiety

In another study, compounds **56** and **57** (Fig. 8) exhibited potent cytotoxic effects against different human tumor cell lines including leukemia (L), colon cancer (CC), central nervous system cancer (CNSC), melanoma (M), ovarian cancer (OC), renal cancer (RC), prostate cancer (PC), and breast cancer (BC) [17]. Pyrazine-thiadiazole hybrids **58-60** (Fig. 8) demonstrated comparable antimicrobial activities to the reference drugs, chloramphenicol, cephalothin and cycloheximide. Compound **58** showed broad-spectrum activity, while **60** showed the strongest antifungal effectiveness. Moreover, *in vitro* assessment of dihydrofolate reductase (DHFR) enzyme inhibition, hybrid **60** demonstrated the highest potency (IC_{50} = 0.05 ± 0.63 µM) than reference drug, methotrexate (IC_{50} = 1.23 ± 0.51 µM)[29].

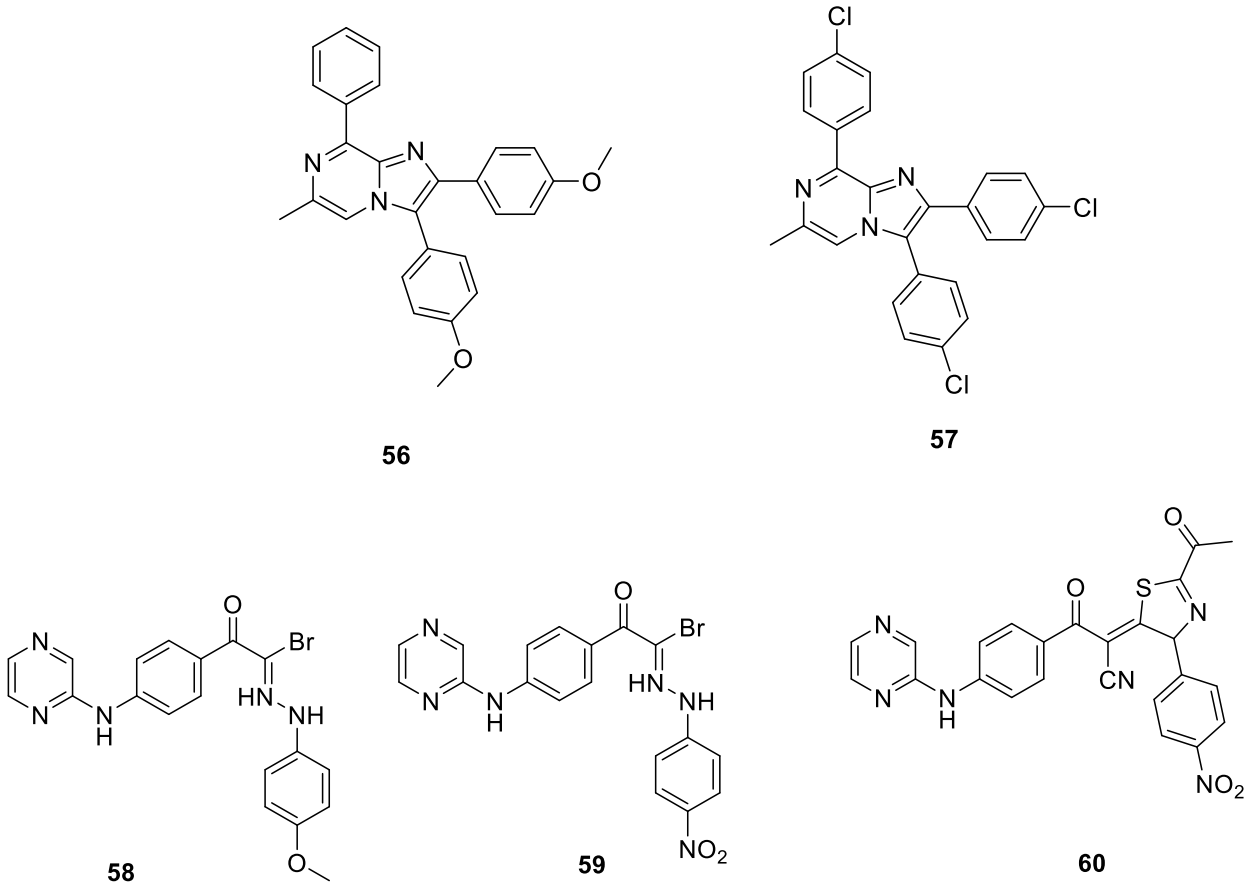


Fig. 8: Chemical structure of bioactive substituted pyrazine derivatives

Elmorsy *et al*. reported the potent antimicrobial activity of pyrazine-based compounds **61** and **62** (Fig. 9) against *E. coli* and *S. aureus* with inhibition zones of 15 mm and 18 mm, respectively. These activities were comparable to the reference drug, gentamicin [30].

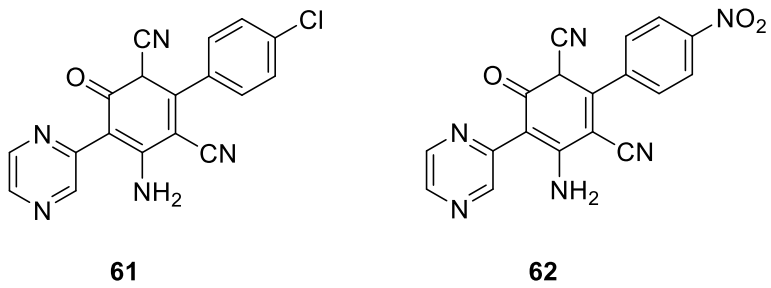


Fig. 9: Chemical structure of pyrazine derivatives

CONCLUSION

Many pyridazine, pyrimidine and pyrazine derivatives containing different substituitions have been synthesized. In this review, the importance of these derivatives was discussed systematically with the intention to serve as an update information to researchers about the interesting features—physicochemical properties, synthesis, reactivity and biological applications of the diazines. The discussion above highlighted the significance of diazines in drug design and discovery.

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