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Pharmacologically Active Molecules Bearing the Pyridazinone Ring as Main Scaffold

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Abstract

Pyridazines are organic compounds in which benzene has nitrogen atoms instead of two carbon atoms. The pyridazine structure is one of the heteroaromatic rings that can be developed for drug design. Pyridazinone analogues are found in the structure of drugs with different activities. This core is of interest to medicinal chemists because of its diverse pharmacological activities. In this review, some of the antibacterial and antifungal, analgesic and anti-inflammatory, anticancer, cardiovascular and anticholinesterase compounds with pyridazinone structure are mentioned.

1. Introduction

Pyridazine nucleus represent a versatile structure for developing new pharmacologically active compounds. The heterocyclic nitrogen structure is often added to the structure of compounds with extensive biological activities and also can be used to bind other pharmacophore groups (Gökçe *et al.*, 2004; Akhtar *et al.*, 2016; Özdemir *et al.*, 2017; Alagöz *et al.*, 2019; Asif, 2019; Asif *et al.*, 2020)

While naming 3-(2*H*)-piridazinone and its derivatives, numeration is performed as follows (Figure 1).

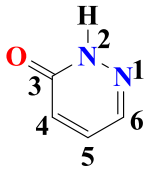

Figure 1. Structure of 3(2*H*)-pyridazinone

It is stated in the number two position that there is tautomer balance due to the free hydrogen in the nitrogen atom in 3(2*H*)-pyridazinone derivatives that do not contain any substituents (7,8). When the IR and UV spectral data of 3(2*H*)-pyridazinones are evaluated, it is seen that they are mostly in the oxo form. (Figure 2) (Lapinski *et al.*, 1990; Matrai, 1997).

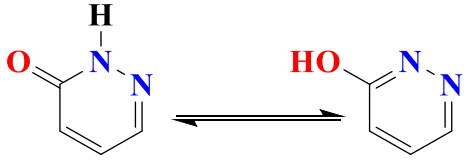

Figure 2. Tautomerism of 3(2*H*)-pyridazinone (Lapinski *et al.*, 1990; Matrai, 1997)

The 3(2*H*)-pyridazinone compounds that do not carry substituents in the ring nitrogen atom are weak acids, which form strong bases or salts with ammonia and amines (Katritzky & Boulton, 1968).

Most pyridazinone compounds are synthesized from carbonyl compounds. The first pyridazinone compound was synthesized in 1886 by Fischer, and the reaction was carried out from levulinic acid phenylhydrazone (Figure 3) (Lenhert & Castle, 1973).

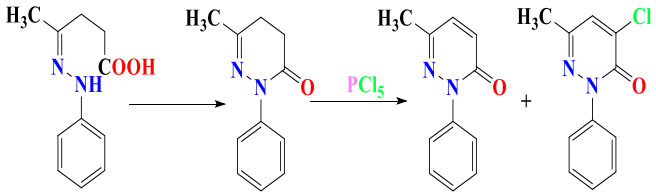

Figure 3. Synthesis scheme of 3(2*H*)-pyridazinone (Lenhert & Castle, 1973)

One of the most common methods of obtaining pyridazinone is the reaction of maleic acid derivatives or their mono- and di-substituted derivatives with hydrazine. Although maleic anhydride is commonly used in these reactions, maleic acid and its ester and acid halide derivatives are also used. The 3(2*H*)-piridazinone structure can also be obtained by modification of pyridazine derivatives. By hydrolysis of halogen or alkoxyl groups in the pyridazine ring, pyridazinone compounds having carbonyl structure are reached; however, it is reported that tautomeric structures may occur in these reactions (Lintholter *et al.*, 1961; Özçelik *et al.*, 2019).

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Numerous pharmacological activity studies have been carried out on compounds bearing 3(2*H*)-pyridazinone structure and in these studies the compounds carrying this skeleton. It has been reported that they have many biological activities such as anti-inflammatory, analgesic, antihypertensive, cardiotonic, antiplatelet, anticholinesterase, antibacterial, antifungal, antitumoral and herbicide effects. (1,2,12-15,17-20) (Cunha *et al*., 2003; Akhtar *et al.*, 2016; Alagöz *et al*., 2019; Özçelik *et al*., 2019; Özdemir *et al*., 2019[a]; Özdemir *et al*., 2019[b] ;Özdemir *et al*., 2020).

For example, the pyridazinone derivatives are known as drugs with interesting effects on the cardiovascular system due to their inhibition of platelet aggregation and their antihypertensive and cardiotonic properties (Table 1).

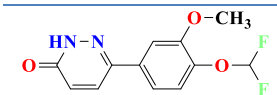
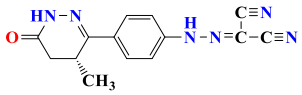
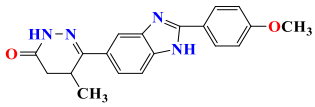
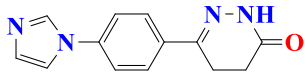
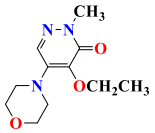
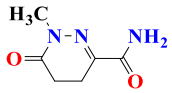
2. Biological Activity of Pyridazinone Derivatives

2.1. Antibacterial and antifungal 3(2*H*)-pyridazinones

Antimicrobial infections are a leading cause of mortality and morbidity in many countries around the world. Literature reports that many compounds bearing 3(2*H*)-pyridazinone rings exhibit antibacterial and antifungal activity.

In a study of the synthesis of a series of new compounds bearing an N'-benzylidene acetohydrazide group at the 2nd position of the 3(2*H*)-pyridazinone ring, the antimycobacterial, antibacterial and antifungal activities of the compounds were investigated. It has been reported that 2-[4-(4-chlorophenyl)-6-(morpholin-4-yl)-3-oxo-(2*H*)-pyridazin-2-yl]-N'-(4-tert-butylbenzylidene) acetohydrazide (**1**) and 2-[4-(4-chlorophenyl)-6-(morpholin-4-yl)-3-oxo-(2*H*)-pyridazin-2-yl]-N'-(4-chlorobenzylidene) acetohydrazide (**2**) are effective against both Gram (+) and Gram (-) bacteria and more than one of the synthesized compounds are active against E. coli ATCC 35218 (Figure 4) (Şüküroğlu *et al.*, 2012).

Table 1. Some drugs with pyridazinone ring used in treatment

Formula	Active compound	Activity
	Zardaverine	Cardiotonic
	Levosimendan	Vasodilator
	Pimobendan	Vasodilator
	Imazodan	Cardiotonic
	Emorfazone	Analgesic
	Medazonamid	Antitussive

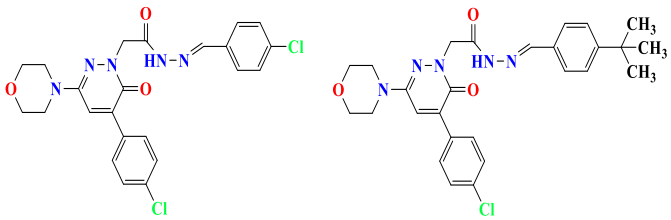


Figure 4. Structure of **1** and **2** (Şüküroğlu *et al.*, 2012)

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Nagle *et al.* studied the antibacterial activity of thymol and the pyridazinone derivatives with the thymol structure (3-14) (Figure 5), which they synthesized, against E. coli and S. aureus by the agar well diffusion method and the antifungal activities against A. niger and P. marneffei with ciprofloxacin and fluconazole. They reported that all compounds had good bactericidal and fungicidal effects. In this study, molecular modeling studies of the compounds against the enzymes glucosamine-6-phosphate synthase and A. niger phytase were also performed, and the compounds were shown to have high binding affinity to the receptors (Nagle *et al.*, 2013).

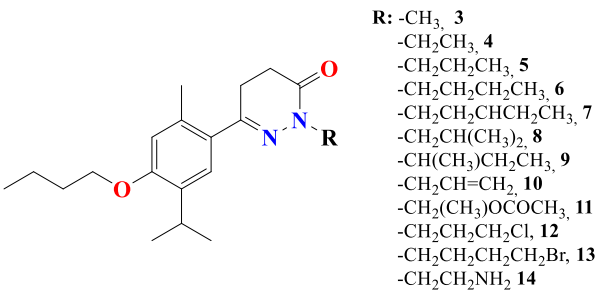

Figure 5. Structure of pyridazinone thymol complexes (Nagle *et al.*, 2013)

Several pyridazinone derivatives were synthesized by Sönmez *et al.* They synthesized different metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2*H*-pyridazin-3-one and evaluated them for their antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi using the microdilution method (Figure 6). According to the results of their studies, the Cd (II) (15) and Ni (II) (16) complexes were selective against a Gram-positive bacterium (*Staphylococcus aureus* ATCC 6538), a Gram-negative bacterium (*6H* ATCC 12633) and two yeasts (*Candida albicans* ATCC 27541 and *Candida tropicalis* 1828) (Sönmez *et al.*, 2006).

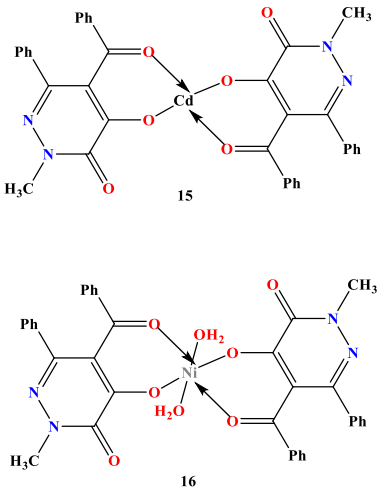

Figure 6. Structure of metal complexes pyridazinones (Sönmez *et al.*, 2006)

Sallam *et al.* were synthesized using the new N-substituted 6-aryl-pyridazin-3(2*H*)-ones bearing 1,3,4-thiadiazolyl moiety at 4-position, using the aza-Michael adduct as the building block. Finally, the compounds were tested for their antimicrobial activity in vitro, and many of them showed promising biocidal activities. According to the results, the compounds carrying only thiadiazole in C-4 of the pyridazinone ring were generally more active against all microbial strains except *P. aeruginosa* and *C. albicans*, and the carbamoyl or thiocarbamoyl group in N-2 enhanced the activity. The compound carrying the acetyl at the 2nd position (**17**) among the synthesized substituted pyridazine-3(2*H*)-one series showed the best antibacterial activity against *S. Racemosum* (Figure 7) (Sallam *et al.*, 2016).

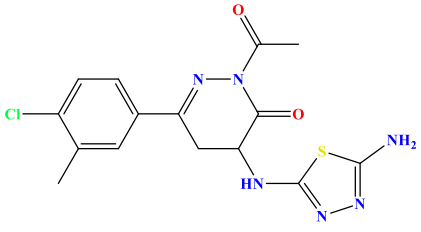

Figure 7. Structure of **17** (Sallam *et al.*, 2016)

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2.2. Analgesic and anti-inflammatory 3(*2H*)-pyridazinones

Analgesic and anti-inflammatory activity studies on 3(2*H*)-pyridazinone derivatives gained importance in the 19th and 20th centuries. Emorfazone, which was marketed in the late 1980s under the names Pentoil and Nandron as an analgesic and anti-inflammatory drug, is a compound with a 3(2*H*)-pyridazinone ring. (Figure 8) (Heinisch & Frank, 1990).

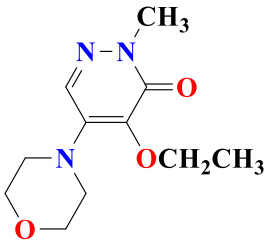

Figure 8. Structure of emorfazone (Heinisch & Frank, 1990)

In the literature, the analgesic and anti-inflammatory effects of 6-substituted 3(2*H*)-pyridazinone derivatives have been investigated. In a study, the analgesic and anti-inflammatory activities of 6-substituted-3(2*H*)-pyridazinone compounds consisting of ten compounds were evaluated using the phenylbenzokinone-induced twitch (PBQ) test and the carrageenan-induced claw edema test. Four of the compounds have been reported to show a significant analgesic effect at 200 mg/kg dose without ulcerogenic effect and acute toxicity. In addition, the researchers reported that the compound 6-[4-(2-fluorophenyl)piperazin-1-yl]-3(2*H*) pyridazinone (Dubey & Bhosle 2015) which they synthesized showed antiinflammatory activity similar to the standard drug, indomethacin (Figure 9) (Gökçe *et al*., 2004).

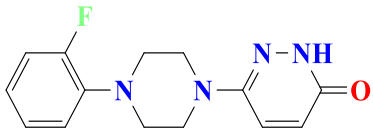

Figure 9. Structure of **18** (Gökçe *et al.*, 2004)

Husain *et al*. synthesized pyridazinone derivatives as safer anti-inflammatory compounds than existing drugs, and also investigated the analgesic, ulcerogenic and lipid peroxidation effects of the compounds. In studies of anti-inflammatory activity compared with ibuprofen, the compounds 5-(4-fluorobenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone 19 and 5-(4-chlorobenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone 20 were found to be most active (Figure 10) (Husain *et al.*, 2011).

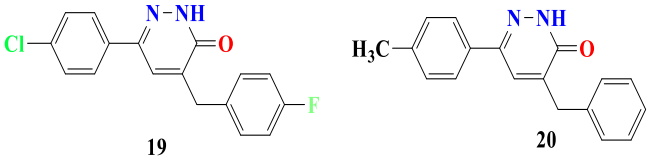

Figure 10. Structure of **19** and **20** (Husain *et al.*, 2011)

Barberot *et al.* developed two pyridazinone derivative compound groups as potential PDE4 inhibitors and evaluated their anti-inflammatory effects (Figure 11). The researchers added alkoxy or catechol portions on the scaffold, when designing compounds of group A from the 5-arylidenetetronates or levulinic acid derivatives. This is because molecules containing dialkoxyphenyl are selective inhibitors of PDE4 and therefore it is desirable to form hydrogen bonds with a glutamine residue behind the catalytic region. The researchers also based the design of group B compounds on the PDE4 inhibitor pyridazinone derivatives made by

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Pieretti and Dal Piaz in 1998 (DalPiaz *et al.*, 1998; Barberot *et al*., 2018).

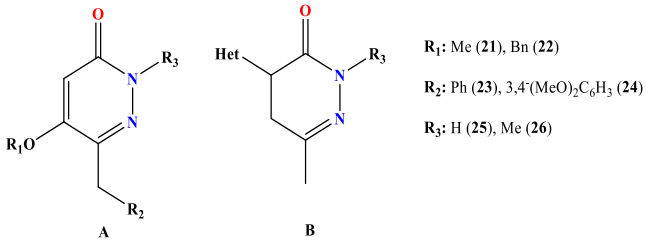

Figure 11. Structure of A and B derivatives (DalPiaz et al., 1998; Barberot *et al*., 2018)

In these studies, pyridazinones fused with heterocyclic nuclei (thiophene or isoxazole) have been developed as possible anti-inflammatory agents (Figure 12) (DalPiaz *et al.*, 1998; Barberot *et al.*, 2018).

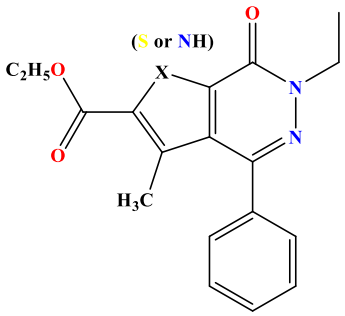

Figure 12. Structure of pyridazinone with thiophene (DalPiaz et al., 1998; Barberot et al., 2018)

Therefore, Barberot *et al.* offered a certain degree of conformational freedom between the pyridazinone scaffold and the heterocyclic moiety in their derivatives to investigate whether these restricted conformations affect the action and selectivity on PDE4. Among these derivatives, B-group compounds belonging to the 4,5-dihydropyridazinones have shown promising activity and selectivity toward PDE4 isoenzymes and have been reported to reduce IL -8 production by human primary polymorphonuclear cells (Barberot *et al.*, 2018).

Eman et al. designed and synthesized a series of pyridazinone derivatives bearing an aryl or pyridyl moiety linked via an ethenyl compound at position 6 and screened the compounds for preferential inhibition of COX -1 isoforms of COX -2. Nine of the compounds showed extremely potent COX -2 inhibitory activity with IC50 values in the nanomolar range. They also clearly showed selective COX -2 inhibition with selectivity indices (SI) ranging from 4 to 38. In particular, compounds 29, 30, 31, and 32 (Figure 13) showed the most important COX-2 inhibitory effect with IC50 values in the range of 15.56-19.77 nM. (Ahmed *et al.*, 2019).

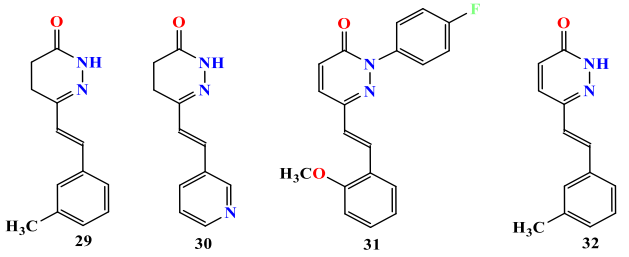

Figure 13. Structure of **29**, **30**, **31** and **32** (Ahmed *et al.*, 2019)

The researchers also tested the anti-inflammatory effects of these four compounds using the in vivo method of carrageenan-induced rat paw edema and ulcerogenic responsibility. At the end of these studies, compounds 30, 31, and 32 showed superior anti-inflammatory activity compared to indomethacin and celecoxib, and none of the compounds showed gastric ulcer-inducing activity. In further studies, compound 29 was found to be equivalent to celecoxib in the second hour after oral administration and showed an anti-inflammatory effect equivalent to

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indomethacin in the fourth hour. The compound showed mild hyperemia in vivo compared with indomethacin and celecoxib (Ahmed *et al*., 2019).

3-O-substituted benzylpyridazinone compounds were synthesized by Chintakunta *et al.* and evaluated for their cyclooxygenase inhibitory activity and COX -2 selectivity. The three of these compounds (33, 34 and 35) showed COX -2 selectivity in vitro (Figure 14). These compounds were evaluated for their in vivo potential using carrageenan-induced paw edema in rats. Compound 33 showed 32% anti-inflammatory activity at a dose of 30 mg/kg. (Chintakunta *et al.*, 2002).

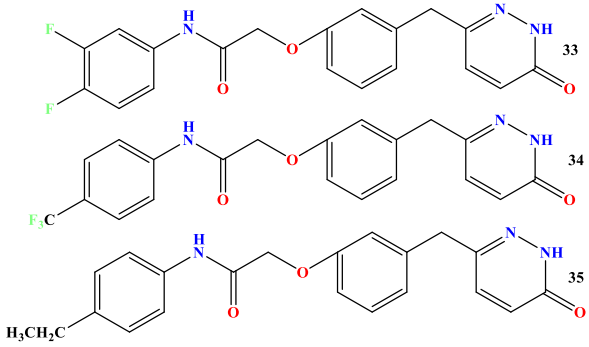

Figure 14. Structure of **33**, **34** and **35** (Chintakunta *et al.*, 2002)

In another study in which antipyrin and pyridazinone derivatives (**36**) were synthesized, the analgesic and anti-inflammatory activities of the compounds obtained were evaluated against aspirin and indomethacin reference drugs, respectively, using p-benzoquinone-induced cleavage test and carrageenan-induced paw edema test methods, and some of the compounds were more potent than reference drugs. Side effects potentials of the compounds were also investigated and no ulcerogenic side effects were found (Baytaş *et al*., 2012).

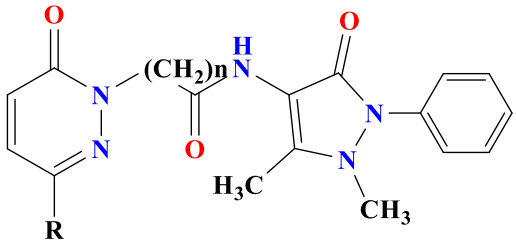

Figure 15. Structure of **36** (Baytaş *et al.*, 2012)

In a similar study in which 4-substituted-phenylhydrazine derivative substituents (**37**) containing lactam nitrogen are synthesized, then, analgesic and anti-inflammatory activities of the compounds against aspirin reference drug, using p-benzoquinone-induced cleavage test and carrageenan-induced paw test methods are evaluated. The compounds are reported to have analgesic and anti-inflammatory effects without ulcerogenic side effects (Figure 16) (Tiryaki *et al*., 2013).

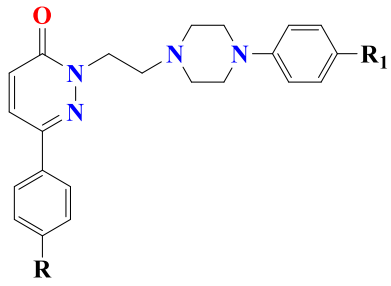

Figure 16. Structure of **37** (Tiryaki *et al*., 2013)

2.3. Anticancer 3(*2H*)-pyridazinones

According to the World Health Organization, cancer is one of the most dangerous diseases affecting a large part of the world's population. There are agents that work through different mechanisms to treat a variety of cancers. However, the major drawback of these drugs is that they also have cytotoxic effects on normal cells due to their lack of selectivity for cancer cells. Various researchers have synthesized antitumor agents with pyridazinone. As a result, many

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pyridazinone-based antiproliferative agents have been developed by researchers (Akhtar *et al.*, 2016; Gong *et al.*, 2018).

A series of novel pyridazinone derivatives with benzenesulfonamide moiety were designed and synthesized by Rathish *et al*. to investigate their anticancer activity against human cancer cell lines such as leukemia, non-small cell lung cancer, colon, melanoma, ovarian, and breast cancer cell lines. They found that compound 38 (Figure 17) showed remarkable activity against SR (leukemia) and NCI-H522 (non-small cell lung cancer) with a GI50 value of less than 0.1 mM (Rathish *et al.*, 2012).

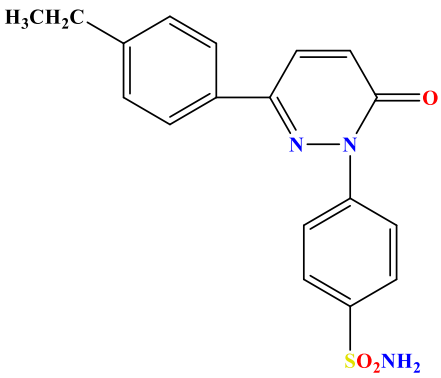

Figure 17. Structure of **38** (Rathish *et al*., 2012)

Additionally, in another study, Bruel *et al.* showed that a series of pyridazino[4,5-b]indole derivative compounds showed anticarcinogenic activity against colorectal adenocarcinoma (Caco2), hepatocellular carsinoma (Huh-7), breast carcinoma (MDA-MB-231), colorectal carcinoma (HCT-116), lung carcinoid (NCI-H727) and prostate carcinoma (PC3) cell lines. The researchers found that compound 39 of the compounds they synthesized was the most active compound with an IC50 value of 0.091 mM (Figure 18). In these studies, 3(2*H*)-pyridazinone derivatives were shown to possess anticarcinogenic potency and could be effective for cancer treatment (Bruel *et al.*, 2012).

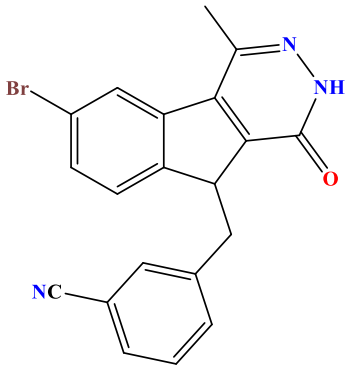

Figure 18. Structure of **39** (Bruel *et al.*, 2012)

Ahmad *et al.* found a series of 6-aryl-2-(p-sulfamoylphenyl)-4,5-dihydropyridazine-3(2*H*)-one compounds **40** (Figure 19) from condensation of β -aroilpropanoic acid and 4-hydrazinobenzenesulfonamide hydrochloride and investigated their effect on SR (leukemia), BT-549 (breast cancer), HL-60 (TB) (leukemia) and NCI-H522 (non-small cell lung cancer) cell lines. They reported that the compounds had a high antitumor effect at a concentration of less than 2 µM (Ahmad *et al.*, 2010).

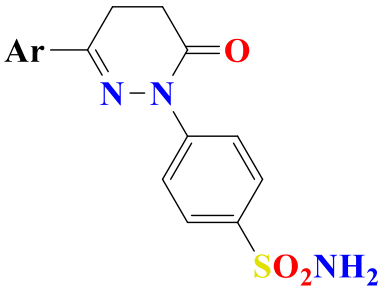

Figure 19. Structure of **40** (Ahmad *et al.*, 2010)

The multifunctional tetrahydro-2*H*-pirano [3,2-c] pyridazine-3(6*H*)-one derivatives have been synthesized by Al-Tel *et al.* and evaluated as new biological anticancer agents. Compounds 41 and 42

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(Figure 20) showed the highest potency, about 30 times stronger against SK-BR -3 (IC50 0.21 and 0.15 mM, respectively) compared to other cancer cell lines tested. In addition, these two compounds showed about 295 times less toxicity to the normal breast cell line MCF10A compared to SKBR-3 breast cancer cells (Al-Tel, 2010).

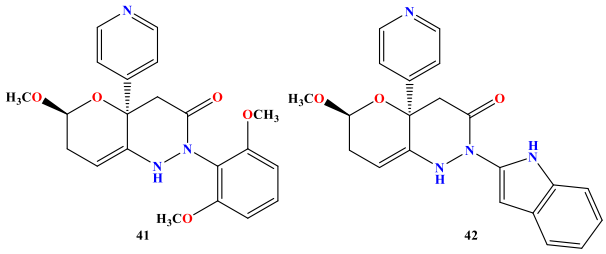

Figure 20. Structure of **41** and **42** (Taleb & Al-Tel, 2010)

Gong *et al.* identified a new compound IMB5043 (**43**) (Figure 21), a thiophenylated pyridazinone that exerts cytotoxicity against cancer cells through cell-based screening models. In this study, the researchers who investigated the antitumor efficacy and possible mechanism of 43 reported that MTT analysis inhibited the proliferation of various human cancer cell lines, especially hepatocarcinoma cells SMMC-7721. IMB5043 was observed to block cell cycle, induce cell apoptosis and inhibit migration and invasion of SMMC-7721 cells with G_2/M arrest. It has been reported that activity results are confirmed by comet assay and γ-H2AX focus formation, as well as IMB5043 causing DNA damage and activating ATM, Chk2 and p53 by phosphorylation (Gong *et al.*, 2018).

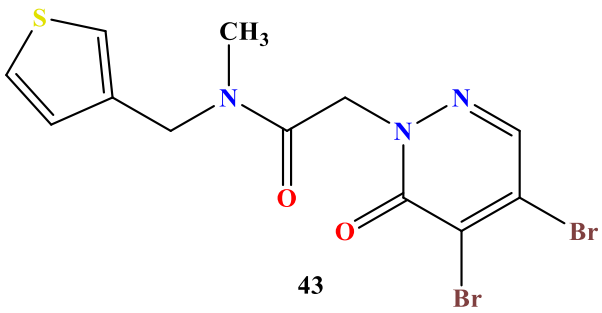

Figure 21. Structure of **43** (Gong *et al.*, 2018)

In a 2020 study, Floresta *et al.* targeted the enzyme aspartate aminotransferase via a computational repurposing approach to small pyridazinone molecules (figure 22) with their in silico screening study using pharmacophores and structure-based models. They reported that the use of pyridazine-based analogues that inhibit this enzyme in cancer therapy could open up pharmacological opportunities for the search for new drugs (Floresta *et al.*, 2020).

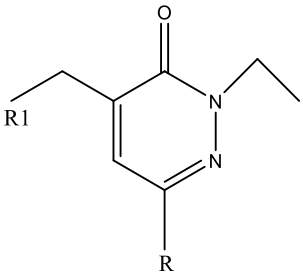

Figure 22. Structure of small pyridazinone molecules (Floresta *et al.*, 2020)

In a 2020 study, Özdemir *et al*. synthesized N'-(substituted benzylidene)-2-(3-(3-fluoro-4-methoxy-phenyl)-6-oxopyridazin-1(6*H*)-yl)-acetohydrazide derivatives in a study they conducted and investigated the antiproliferative effect of these compounds on HCT116 cell lines. They found that the compounds were a good pro-inflammatory factor alone or also after serotonin simulation in the gut (Özdemir *et al*., 2020).

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Today, there are pyridazinone derived drug molecules such as levosimendan, pimobendan, zardaverine, and imazodan that are used to treat cardiovascular disease. Zardaverine has a bronchodilator effect, inhibits the enzyme phosphodiesterase (PDE), and exerts a positive inotropic effect on cardiac muscles (Bansal & Thota, 2013).

Levosimendan, marketed under the name Simadex, is an effective drug for the treatment of congestive heart failure. Levosimendan both increases calcium sensitivity and acts as a PDE enzyme inhibitor at high doses. Although the mechanism of levosimendan is not precisely known, it is known to have a vasodilatory effect by affecting smooth muscle contraction and regulatory proteins. (Kaşıkçıoğlu & Cam 2006).

Pimobendan, another vasodilator and inotropic drug molecule with pyridazinone structure, shows its effect by inhibiting PDE enzyme and increasing calcium sensitivity in cardiac muscle cells (Fitton & Brogden 1994).

Pyridazinon compounds show antihypertensive activity due to their relaxing effect on vascular smooth muscle. In a study involving the synthesis of new 6-substituted and 2,6-disubstituted pyridazinone derivatives (Figure 23), the vasodilating effects of the compounds obtained were investigated, and it was reported that most of the compounds showed lower effects than the reference drug milrinone at micromolar concentrations (32.5-78.25 μM). The N,O-dibenzyl derivatives were found to be the most active compounds, whereas the derivatives containing a hydroxyl group were inactive even at concentrations greater than 100 μM (Costas *et al.*, 2010).

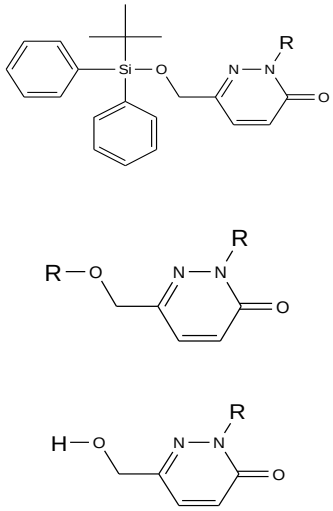

Figure 23. Structure of 6-substituted and 2,6-disubstituted pyridazinone derivatives (Costas *et al.*, 2010)

In a 2011 study, Siddiqui *et al.* synthesized 6-(substituted phenyl)-2-(4-substituted phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-one derivatives (figure 24) as new compounds and investigated the antihypertensive effect of the compounds by using a non-invasive technique with the Tail Cuff method,and reported that they showed significant antihypertensive effect compared to the standard drugs hydralazine and propranolol (Siddiqui *et al.*, 2011).

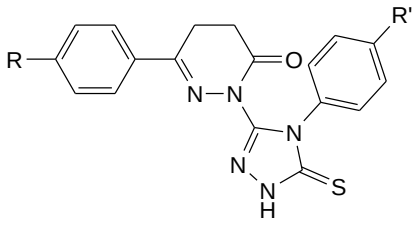

Figure 24. Structure of pyridazinone with triazole structure (Siddiqui *et al.*, 2011)

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Imran and Abida summarized the cardiovascular effects of 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone derivatives in their review article in 2016 and mentioned that they can be used as very effective agents with cardiovascular effects in the clinic. (Imran & Abida, 2016).

İsmail *et al.* synthesized 6-fluoroarylpyridazinone derivative compounds in their study in 2021 and obtained compounds with more potent vasodilating activity than prazosin, and the formula of the most potent compound is given below (figure 25) (Ismail *et al*., 2021).

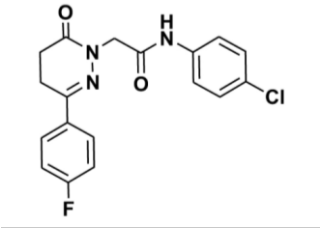

Figure 25. Structure of 6-fluoroarylpyridazinone derivative (Ismail *et al.*, 2021)

2.4. Cholinergic Systems 3(2*H*)-Pyridazinones

Anticholinesterase Effective 3(2*H*)-Pyridazinones

Acetylcholinesterase is an enzyme that catalyzes the breakdown of acetylcholine, which functions as a neurotransmitter. Alzheimer's disease (AD) is a complex neurodegenerative disorder of the central nervous system. It is estimated that nearly 36 million people worldwide suffer from Alzheimer's disease today, and this number would increase to approximately 66 million by 2030 if breakthroughs are not made. Acetylcholinesterase (AChE), a serine protease, is responsible for the hydrolysis of acetylcholine and plays a fundamental role in impulse transmission by terminating the action of the neurotransmitter acetylcholine at cholinergic synapses and the neuromuscular junction (Sharma, 2019).

Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), two important enzymes belonging to the serine hydrolase enzyme group, are generally known as cholinesterases. The main role of the enzyme acetylcholinesterase is to catalyze the hydrolysis of acetylcholine at cholinergic synapses. The role of butyrylcholinesterase is not as clear as that of acetylcholinesterase, as it hydrolyzes other esters in addition to acetylcholine. Cholinesterase inhibitors, which increase the amount of acetylcholine in synapses by preventing the hydrolysis of acetylcholine, are used to treat neuromuscular diseases such as glaucoma, myasthenia gravis, and Alzheimer's disease (Imramovsky *et al*., 2013).

In a 2010 study, Özçelik *et al.* reported that the AChE/BChE inhibitor Ethyl 6-[(substituted phenylpiperazin]-3(2*H*)-pyridazinon-2-yl-propionate and 6-[(substituted phenylpiperazin]-3(2*H*)-pyridazinon-2- ilpropionohydrazide derivatives were synthesized. The activities of the compounds were evaluated by comparison with galantamine, which is used to treat Alzheimer's disease. 6-[4-(3-Trifluoromethylphenyl)-piperazine]-3(2*H*)-pyridazinon-2-yl-propionate (Figure 26) proved to be the most active compound in inhibiting the enzymes acetylcholinesterase and butyrylcholinesterase (Özçelik *et al*., 2010).

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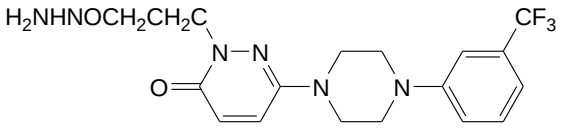

Figure 26. Structure of propionate derivative pyridazion (Özçelik *et al*., 2010)

In similar studies with 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(substituted/non-substituted benzal)-hydrazone and N'-[(4-substituted phenyl)sulfonyl]-2-[4-(substituted phenyl)-piperazine]-3(2*H*)-pyridazinone-2-yl-acetohydrazide derivatives, the anticholinesterase activity of the compounds at 0.05 mM, 0.1 mM, 0.2 mM, 0.25 mM, and 0.5 mM concentrations by the Ellman method (Önkol *et al.*, 2013). It has been reported that 6-(3-chlorophenyl)-3(2*H*)-pyridazinone-2-acetyl-2-(3-methoxy-4-hydroxy benzal)hydrazone and N'-[(4-trifluoromethylphenyl)sulfonyl]-2-[4-(2-fluorophenyl)piperazine]-3(2*H*)-pyridazinone-2-yl acetohydrazide (figure 27) were the most active compounds, and that N'-[(4-trifluoromethylphenyl)sulfonyl]-2-[4-(2-fluorophenyl)-piperazine]-3(2*H*)-pyridazinon-2-yl acetohydrazide has a higher activity than galantamine (Utku *et al.*, 2011).

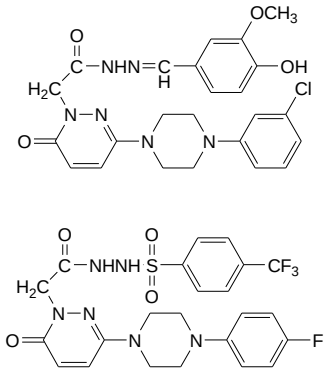

Figure 27. Structure of hydrozone and acetohydrazide derivative pyridazinones (Önkol *et al.*, 2013; Utku *et al*., 2011)

In a 2013 study, Xing *et al.* synthesized 2,6-disubstituted pyridazinone derivatives and investigated in vitro AChE/BChE inhibitory effects of the compounds by molecular modeling studies. As a result of the study, the pyridazinone compound with 6-ortho-tolylamino and N-ethyl-N-isopropylacetamide substituted piperidine (Figure 28) groups were found to have high acetylcholinesterase inhibitory activity and was AChE/BChE selective in vitro (Xing *et al*., 2013).

In a 2013 study, Xing *et al.* synthesized a new 2,6-disubstituted pyridazinone derivative compound and investigated the inhibitory effect of AchE and obtained a lead compound with high AChE/BuchE selectivity. The 6-ortho tolylamino substituent showed a π-π interaction and a "magic methyl" effect. The interaction of the 4-substituted piperidine group with the CAS binding site has been reported. Through docking studies, they reported that these pyridazinone derivatives have dual binding sites and can function (Figure 29) (Xing *et al.*, 2013).

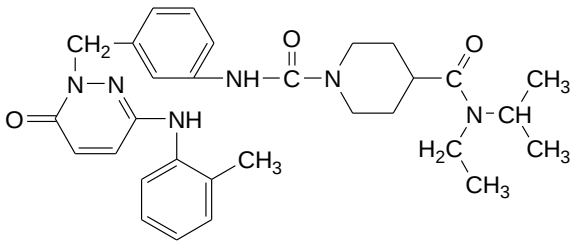

Figure 28. Structure of N-ethyl-N-isopropylacetamide substituted piperidine (Xing *et al.*, 2013)

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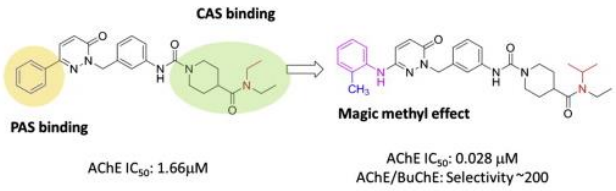

Figure 29. Pyridazinone derivatives binding sites (Xing et al., 2013)

In a 2017 study, Özdemir *et al.* synthesized 18 compounds of 3(2*H*)-pyridazinone derivatives and reported that 3-methyl/methoxybenzalhydrazone derivatives showed high AChE inhibitory activity, while 3-methyl and 2-methoxybenzalhydrazone derivatives showed high BchE inhibitory activity. 6-[4-(3,4-Dichlorophenyl)piperazin-1-yl-]-3(2*H*)-pyridazinone 2-acetyl-2-(3-methylbenzal)hydrazone is a potent dual acetylcholinesterase inhibitor. The 3,4-dichlorophenyl group in the structure occupies the choline-binding pocket and has strong π-π-stacking against the aromatic side chain W86 and weak interactions with E202 and the catalytic residue H447. The piperazine ring occupies the entrance of the acyl linker pocket and the constriction site below PAS, which is in contact with the aromatic side chains Y124, Y337, and F338. Via the carbonyl oxygen of the pyridazinone ring, it formed a direct H-bond to F295 backbone NH and a water-mediated H-bond to R296 backbone NH. The pyridazinone ring interacts with the domain PAS, while Y341 makes a π-π interaction with the aromatic side chain. The 3-methylbenzene ring interacts hydrophobically with the PAS domain (Özdemir *et al.*, 2017).

In the 2019 study by Özçelik *et al.* reported that 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(nonsubstituted/4-substituted) benzenesulfonohydrazide derivatives have BchE inhibitory effects (Özçelik *et al*., 2019).

In a 2019 study, Dundar *et al.* synthesized 6-oxo-3-substituted pyridine-1-(6*H*)methyl)carbamate derivatives and reported that these compounds have BuchE inhibitory effects. They reported that short alkyl chain carbamate derivatives have high eqBuchE inhibitory effect, aromatic carbamate derivatives have both EeAchE and eqBuchE inhibitory effects. They reported that the 6-(2-methoxyphenyl)pyridazin-3(2*H*)-one scaffold (Figure 30) is important for the design and development of selective BuChE inhibitors. The double-acting compounds that show inhibition of AChE and BuChE interact with the CAS and PAS domains and are compatible with the EeACHE binding site. The pyridazinone and phenyl rings adjacent to the carbamate moiety project beyond the CAS domain and are stabilized by a hydrogen bond between the carbonyl oxygen and the PHE295 backbone and by π-π-stacking contacts with TYR337, respectively (Dündar *et al.* 2019).

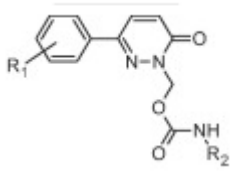

Figure 30. Structure of 6-(2-methoxyphenyl)pyridazin-3(2*H*)-one derivatives (Dündar *et al*., 2019)

In the 2014 study by Sharma *et al.* a series of 2-(2-(3-(4-chlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)yl)acetyl)hydrazine carbotioamide and 2-((5-amino-1,3, 4-thiadiazol-2-yl)methyl)-6-(4-chlorophenyl)-4,5-dihydropyridazine-3(2*H*)-one derivatives were synthesized, and evaluated for anticonvulsant activity and muscle relaxant activity.

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It has been reported that 2-(2-(3-(4-chlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl)acetyl)hydrazinecarbothioamide and 2-((5-amino-1,3,4-thiadiazole) -2-yl)methyl)-6-(4-chlorophenyl)-4,5-dihydropyridazin-3(2*H*)-one (Figure 31) showed anticonvulsant effects in the maximal electroshock seizure test at 50 mg/kg dose and in the pentylenetetrazole seizure test at 100 mg/kg dose (Sharma *et al.* 2014).

In a 2019 study, Kılıç *et al.* synthesized diphenyl-2-(2-(4-substitutedpiperazin-1-yl)ethyl)pyridazin-3(2*H*)-one derivatives compounds and reported that some of these compounds are promising compounds as acetylcholine estarase inhibitors due to their dual effects (Kılıç *et al.*, 2019)**.**

2.5. Other Biological Activities of 3(2*H*)-Pyridazinones

In addition to the above-mentioned activities, compounds bearing pyridazinone ring also have antiplatelet, antidiabetic, antimycobacterial and insecticidal effects. In the thesis study on pyridazinone compounds, the antiplatelet effects were investigated by synthesizing twenty-six new compounds, including 2-[6-phenyl-3(2*H*)-pyridazinon-2-yl]ethanamide, 2-[6-(4-methylphenyl)-3(2*H*)-pyridazinon-2-yl]ethanamide, 2-[6-(4-chlorophenyl)-3(2*H*)-pyridazinon-2-yl]ethanamide, 2-[6-(4-nitrophenyl)-3(2*H*)-pyridazinon-2-yl]ethanamide derivatives, and compounds ethyl 2-(6-(4-nitrophenyl)-pyridazin-3(2*H*)-on-2-yl)acetate and 2-(6-(4-nitrophenyl)-pyridazin-3(2*H*)-on-2-yl)acetic acid (Figure 32) (Özçelik, 2008).

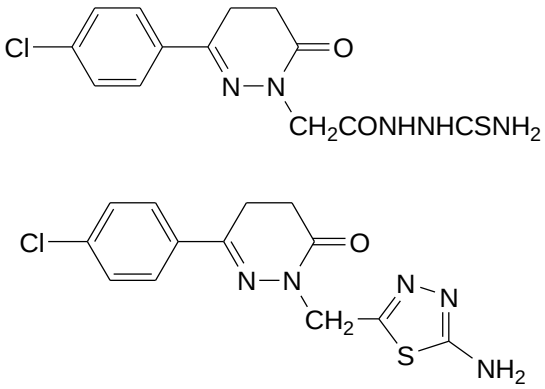

Figure 31. Structure of 2-(2-(3-(4-chlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl)acetyl)hydrazinecarbothioamide and 2-((5-amino-1,3,4-thiadiazole) -2-yl)methyl)-6-(4-chlorophenyl)-4,5-dihydropyridazin-3(2*H*)-one (Sharma *et al.* 2014)

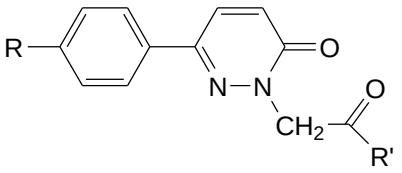

Figure 32. Structure of pyridazinone derivatives (Özçelik, 2008)

In a 2010 study, Thota and Bansal investigated their antiplatelet activities by synthesizing 6-(4-(substituted-amino)phenyl)-4,5-dihydro-3(2*H*)-pyridazinone derivatives. They reported that compounds (6-(4-(2-hydroxybenzylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one and 6-(4-(1*H*-indol-3-ylmethylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (Figure 33) showed potent activity results like the aspirin standard (Thota & Bansal, 2010).

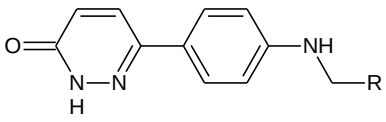

Figure 33. Structure of pyridazinone derivatives (Thota & Bansal, 2010)

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In a 2009 study, Rathish *et al.* synthesized 15 new pyridazinone substituted benzenesulfonylurea derivatives (Figure 34) and examined their antidiabetic effects in rats by glucose tolerance test. Almost all compounds showed a significant blood glucose-lowering effect at a dose of 20 mg/kg compared to the control group (Rathish *et al*., 2009).

In the 2016 study by Cao *et al.* a new series of pyridazinone-substituted analogues were designed and synthesised and evaluated for their in vitro antineuropathic pain activity. Compound 318 (Figure 35) showed strong affinity for the s1 receptor (K_is1=1.4 nM) and excellent selectivity not only toward the s2 receptor (1366-fold). These profiles suggest that compound 318 may be a new class of drug candidates for the treatment of neuropathic pain. (Cao *et al.*, 2016).

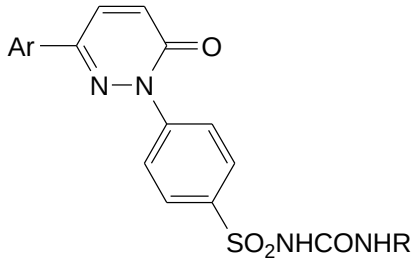

Figure 34. Structure of pyridazinone substituted benzenesulfonylurea derivatives (Rathish *et al.*, 2009)

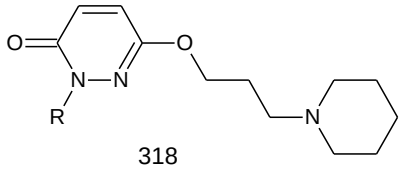

Figure 35. Structure of compound 318 (Cao *et al.*, 2016)

α_1 –AR substypes and $5HT_{1A}$ receptors

In a 1997 study, Corsana *et al.* reported that 3(2*H*)-pyridazinone derivative compounds with 1-phenyl-4-piperazine alkyl scaffold showed selectivity for α1a subtype. In particularly 4-(2-methoxyphenoxyethyl)-1-piperazinyl and 1-(2-furonyl)piperazine groups showed α1a selective antagonist effects and showed similar α1a-AR receptor binding profile with 5-methylurapidil (Corsano *et al*., 1997).

In a 2006 study, Betti *et al.* reported that the chemical structure should contain three hydrophobic substituents, a hydrogen bond acceptor group, and a positive ionized group in their pharmacophoric model study for the α1 –AR antagonist effect. As a result of this study, they reported that the arylpiperazinylalkylpyridazanone (Figure 36) scaffold for α1 - AR antagonist action exhibited remarkable selectivity for both α2 - AR and 5HT1 AR. It has been reported that the ortho-alkoxy structure in the phenyl ring attached to the arylpiperazine group enhances the affinity (Betti *et al.*, 2006).

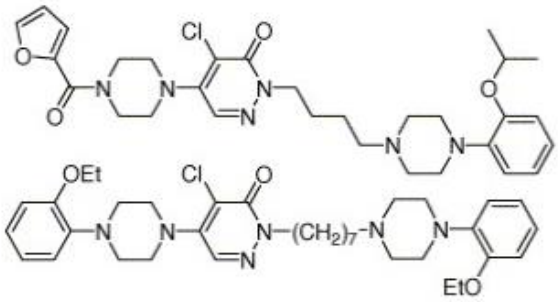

Figure 36. Structure of arylpiperazinylalkylpyridazanone derivatives (Betti *et al*., 2006) In a 2019 study, Allerton *et al.* synthesized compounds bearing the pyridazinone core, resulting in the identification of the compound

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bearing the CF3 group as a potent, partial functional 5-HT2C agonist with excellent selectivity toward 5-HT2B and other aminergic GPCRs (Allerton *et al.*, 2009).

3. Conclusion

In recent years, studies on 3(2*H*)-pyridazinone derivatives with various pharmacological activities have increased. The synthetically prepared 3(2*H*)-pyridazinone derivatives are used in a variety of activity studies. The treatment of diseases that place a heavy burden on the economies of developed and developing countries in terms of treatment processes and patient care will provide economic relief to government budgets and make an important contribution to public health. Therefore, studies on the 3(2*H*)-pyridazinone scaffold will continue in the future.

Conflicts of interest

The author declares no conflicts of interest related to this study.

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