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A Review on Pyridazine, A Magically Active Moiety Among the Heterocyclic Compounds for Drug Designing

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ABSTRACT:

The wide spectrum activity of the pyridazine moiety makes them substantially an active compound in new drug design. The experimental data obtained in the current study explains pyridazine and its derivatives are pharmacologically active and are being used in various disorders and diseases with a few side effects. The two adjacent nitrogen atoms in the structure along with the various aromatic and alkyl side chains containing the halogen atoms have shown potent biological activity, even with the physical properties pyridazine shows the most unique properties. The extent of the study involves exploring the various activities of the pyridazines.

KEY WORDS: Pyridazine; Anti-inflammatory; Anti-cancer; Antiepileptic; Antimicrobial

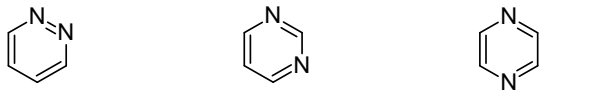
INTRODUCTION

As most of the naturally available compounds are heterocyclic by their chemical structure, hetero compounds play an important role in drug design. Pyridazines among the heterocyclic compounds drew much attention, as their occurrence in nature is quite less and are not easily produced by biochemical transformation exceptionally to other heterocyclic compounds[1]. Phthalazines are one among the diazine derivatives containing two sp2 -hybridized nitrogen atoms in adjacent within their structures, there are the three basic diazines which are Pyrazine, Pyridazine, and Pyrimidine Fig.1[2]. The presence of nitrogen-containing heterocyclic core makes pyridazine a potential active compound with a wide range of immense biological functionalities[3].

The different substitutions have led to a variety of agrochemical[4] and pharmacological activities among them some reported applications are antihypertensive[5], anti-inflammatory[6], anticonvulsant[7], antimicrobial[8], anti-tubercular[9], and anticancer agents[10]. Pyridazine ring containing drugs that are available in the clinical practice with different pharmacological action and are as follows Levosimendan for CHF treatment, Emorfazone used for the treatment of inflammation, Zardaverine used as an anti-asthmatic agent, Pyridomycin as an antifungal agent, a cytotoxic agent such as Azamerone and Cirratiomycin, Antrimvcin which are peptide antibiotic[11].

Among the heterocyclic diazine compound, phthalazine is also one and is also referred to as benzopyridazine or benzo-ortho-diazine. Phthalazine-1(2H)-one and 2,3-dihydro phthalazine-1,4-dione are phthalazines moiety that is important in the diazine[12]. Nevertheless, this moiety also exhibited various pharmacological actions such as azelastine, an antihistamine used to treat allergic rhinitis. Recent studies showed that some of the pyridazine derivatives are more selective inhibitors of the enzymes such as cGMP phospho di-esterase (PDE), aldose reductase (Zopolrestat), and also used in the prevention of retinopathy, neuropathy, and cataract formation in diabetes. Apresoline containing hydralazine derivative used in the treatment of hypertension during pregnancy,

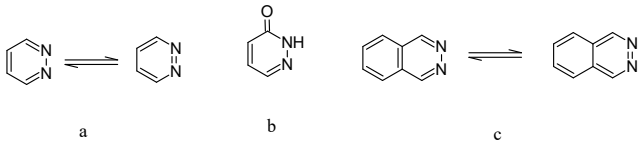
indolidan bemoradan that are antihypertensive, pimobendan used in congestive heart failure, milrinone a cardiotonic, imazodan and zardaverine which are PDE3 inhibitor, minaprine an antidepressant, and olaparib an anticancer[13].



(a) Pyridazine (b) Pyrimidine (c) Pyrazine

Scheme 1. Structure of diazines.

Pyridazinones which is the oxygen atom attached derivatives of the pyridazine ring at position 3 have an elegant interest in biological activity hence it is also called the wonder nucleus, which shows different activity with a broad range of substitutions that have a potential activity [14].



a b c

Scheme 2. Structure of (a) Pyridazine, (b) Pyridazinone, (c) Phthalazine.

RESULTS AND DISCUSSION

Physical properties

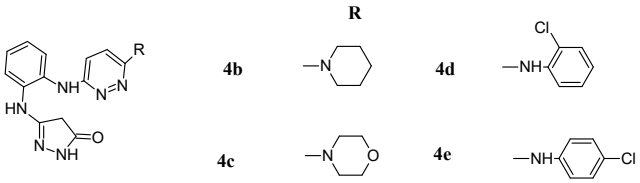
Pyridazine is a liquid having an odor like pyridine and melts at -8^{0}C. They are also known as orthodiazine having molecular formula $C_4H_4N_2$ and their molecule weighs is 80.09g. They have an unusually high boiling point (208^{0}C at 760 mm, 87^{0}C at 14mm, and 48^{0}C at 1mm) compared to benzene (bp 80^0 C) and pyridine (bp 115^0 C). They are readily soluble in water because of the availability of lone pair of electrons on the nitrogen atom and thus they are completely miscible with water and alcohol, soluble in benzene but it is insoluble in cyclohexane and ligroin [15].

2.2. *Biological activity*

2.2.1. *Anti-inflammatory activity*

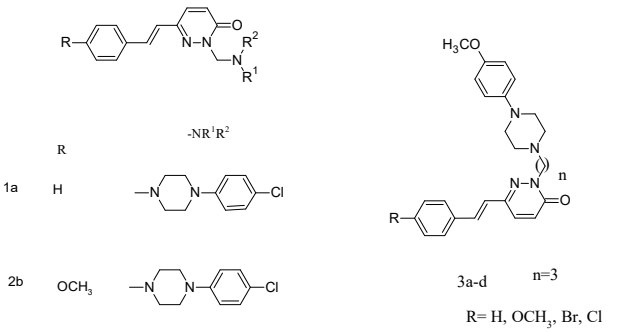
Due to a harmful stimulus, the human body triggers a biological immune response to counteract that stimulus, the process which is known as Inflammation. Inflammation can be characterized by a simple reaction such as redness, swelling, heat, pain, and loss of sensation to complex cell-mediated reactions, which could be acute or chronic and could also damage the host cell itself[16]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely utilized against inflammatory mediators during the treatment of inflammation, these agents act by inhibiting cyclooxygenase enzyme (COX-1 and COX-2) or lipoxygenase, but due to their gastrointestinal side effects, the quest for various other compounds with similar activity along with fewer side effect can be seen[17]. Pyridazine and their derivative such as pyridazinones are well known for their potent anti-inflammatory action and are reported, some among them are;

Khalil et al. reported anti-inflammatory activity of a series of pyrazolone–pyridazine conjugates. The compounds 4b-e showed their activity in the docking studies which was included with drug diclofenac as a standard against cyclo-oxygenase 2 enzyme. The ability of compounds to protect against physiological agents such as TNF-α and IL-6 were evaluated. The compounds were also included in acute ulcerogenic activity with analgesic and anti-inflammatory activity. The results of the test revealed that compounds 4c and 4e were potent and non-ulcerogenic[18].



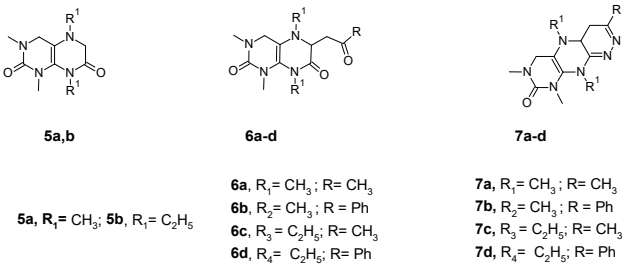
Scheme 3. Pyridazine with analgesic and anti-inflammatory activity.

The synthesis of different pyridazine and pyridazinone derivatives by Saeed et al. revealed that synthesized series of compounds are having anti-inflammatory activity studied carrageenan-induced paw edema method using Indomethacin as standard drug for comparison and the compounds 1a and 2b containing 4-chlorophenylpiperazine in their structure displayed a potent anti-inflammatory effect, along with better gastric profile, with this a series of compounds 3a-d with 6-arylethenylpyridazinone group linked to the 4-methoxyphenylpiperazine showed higher activity than indomethacin with low ulcerogenic compounds. The compounds 1a and 3d also exhibited a high COX-2 inhibition effect in *in-vitro* which was reported on the data obtained by the measurement of COX-2 cells in the macrophages lysate by ELISA[19].



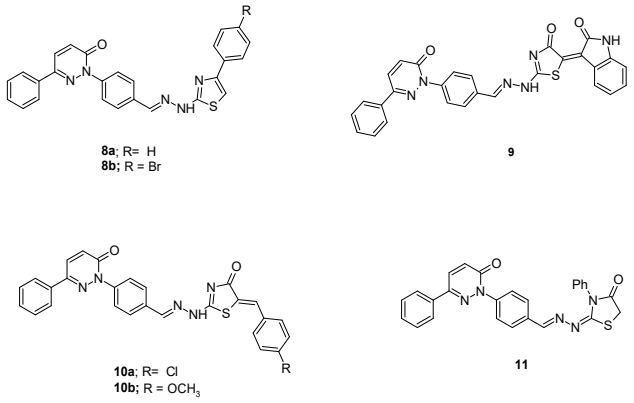
Scheme 4. pyridazines with anti-inflammatory and low ulcerogenic activity

Abu-Hashem et al. reported the synthesis of a unique series of novel isoxazole, pyridazine, pyrimidopyrazine derivatives were prepared and they were assessed for the analgesic and anti-inflammatory activities, where isoxazole derivatives 5a-f were found to inhibit both the early stages (serotonin and histamine) of inflammatory mediators and late-stage mediators of inflammation (bradykinins and prostaglandins) which were studied taking diclofenac sodium as the standard. They showed anti-inflammatory activity and also to a lesser extent analgesic activity. The biological activity of other derivatives was also reported which shows that pyrimidopyrazines are effective against inflammation and pyridazine ring modification did not improve the activity[20].



Scheme 5. Pyrimidopyrazine, pyridazine compounds with anti-inflammatory activity.

A series of the compound that was synthesized by Khan et al., reported the cyclooxygenase (COX)-2 inhibitory action and gastric safety profile of novel pyridazines. The in-vitro activity of synthesized compounds 8a (3.76%), 8b (6.39%), compound 9(3.70%), 10 (4.85%), and 11(9.16%) were examined, with indomethacin (6.60%) and celecoxib (4.92%) (indomethacin as an ulcerogenic and non-specific inhibitor of COX enzymes) and a reduction % in edema was reported. The results obtained determined that among the synthesized compounds 4-phenyl thiazole derivative was more potent and decreased with incorporation of bromine atom in the compound exhibited better inhibition of COX-2 in contrast to COX-1. 8a, 8b, 10 and 11 compounds did not produce any ulcers after administration. Molecular docking of the mentioned compounds was studied and the interacting residues were also determined and were reported[21].



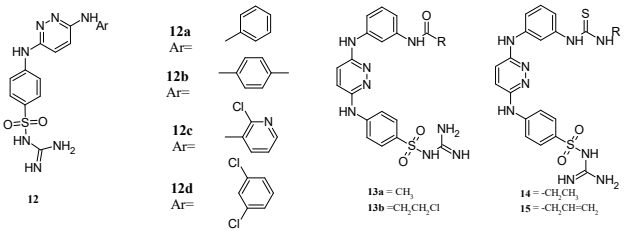
Scheme 6. Pyridazines (8a-11) with COX inhibitory activity.

2.2.2. *Anti-cancer activity*

Cancer is a leading disease-causing of more deaths around the world, around 10 million deaths were reported in 2020. Cancer is defined by the production of abnormal cells in the body, these cells are devoid of the normal apoptotic pathway or cell cycle that makes them divide without any control and can infiltrate and destroy normal body tissue, The causes are considered to person's genetic factor and other external agents including; physical agents inducing cancer are ultraviolet and other ionizing radiation, chemical carcinogens such as asbestos, components of tobacco, aflatoxins, arsenic, and biological carcinogens includes infections from certain viruses, bacteria, or parasites. The usage of alcohol, tobacco, unhealthy diet, physical inactivity, and exposure to pollution to a larger extent is the risk factors [22,23].

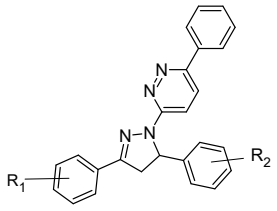
Cancer treatment mainly involves cytotoxic agents that kill all rapidly dividing cells, certain times both tumor and normal cells which could cause other ill side effects to the body. The main goal is to find a treatment module that kills cancer or tumor cells only and causes no or few side effects[24]. Various pyridazine derivatives synthesized from 3,4-dichloropyridazine and sulfaguanidine which were reported by Elmeligie et al., these compounds evaluated for the *in-vitro* antitumor activity. The study included the usage of colon cancer cell line (HCT-116) and breast cancer cell line (MCF-7) by applying sulforhodamine B stain colorimetric assay with standard antitumor drug imatinib which acts as a VEGFR inhibitor. All the derivatives were reported to possess cytotoxic activity, allylthiourea-derived compound among them has shown the activity that has more potent activity than imatinib. The presence

of the chlorine atom increases the activity of the compound in the case of breast cells whereas the same compound exhibits moderate activity with colon cancer cell line. The synthesized compounds from the *in-vitro* studies were also evaluated for the *invivo* activity, compounds 12a, b, c, d, 13a, b, 14, and 15 (Figure-7) were found to produce the activity comparable to the imatinib[25].



Scheme 7. Pyridazine moiety with anticancer activity**.**

In the view of safety and the selectivity of anticancer drug targeted therapy is a special type of chemotherapy, novel hybrids of pyridazine-pyrazoline were synthesized by Ahmed et al., where the compounds with the substituted chlorine atom were synthesized along with fluorine and another alkyl, and methoxy groups. Data of the synthesized compounds demonstrated different growth inhibition levels, in the screening of anticancer activity with cell lines of ovarian cancer IGROVI1, breast cancer cell line T-47D, renal cancer cell line CAKI-1, and UO-31. Using standard drug Erlotinib against human EGFR the IC_{50} of the compounds was determined, the compounds showed an inhibitory effect of 5.5-0.65 µM. cell cycle analysis and Annexin V-FITC apoptosis assay and effects on the levels of Bax, Bcl-2, and active caspase-3 were also reported in the study. The compounds 16, 17,18 (figure-8) were also studied for the molecular docking which exhibited the best docking score free energy, the compounds exhibited promising anticancer activity[26].



16,17,18

R_1= 2-Cl

R_2= H,2-F,3-OCH_3,3-CH_3-4-F

Scheme 8. Novel hybrid pyridazine-pyrazoline with different substitutions have different growth inhibition activity levels.

In further studies, the compound's activity with 1,4-disubstituted phthalazines has a promising effect on the cancer cell and is an active cytotoxic agent. cytotoxic activity of targeted compounds against human liver cancer cell line (Bel-7402) and human fibrosarcoma cell line (HT-1080) was studied by El-Helby et al., With two different cancer cell line anti-proliferative activity of the compounds were examined, the results were expressed as growth inhibitory concentration (IC_{50}) and compounds 19a, 19b, 20b and 20c exhibited the highest activity compared to sorafenib[27].

19a,b

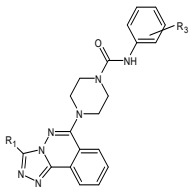
$R^1 = C_6H_{11}$, $R = C_6H_5$.

20a-c

R^2= C_2H_5, R= C_3H_7, R= C_6H_5

Scheme 9. Pyridazine compounds with VEGFR-2 inhibitor activity.

Phthalazine derivatives with 1,2,4-triazole moieties reported by Ding-qi et al, which were had piperazinyl and acetyl group linkers to targeted compound moieties, also the same moieties were studied for their effect on the cell life cycle and also apoptosis, among the reported twenty compounds one compound 21h containing difluoro phenyl was found to be more active[28].



21a-m

21a: R_1 =H, R_3= 4-F
21b: R_1 =H, R_3= 4-Cl
21c: R_1 =H, R_3= 4-OCH_3
21d: R_1 =H, R_3= 4-CF_3
21e: R_1 =H, R_3= 2-F
21f: R_1 =Ph, R_3= 4-Cl
21g: R_1 =Ph, R_3= 3-CF
21h: R_1 =Ph, R_3= 2-F
21i: R_1 =CH_3, R_3= 4-F
21i: R_1 =CH_3, R_3= 4-F
21j: R_1 =CH_3, R_3= 4-Cl
21k: R_1 =CH_3, R_3= 4-OCH_3
21l: R_1 =CH_3, R_3= 4-CF_3
21m: R_1 =CH_3, R_3= 2-F

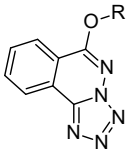
Scheme 10. Cytotoxic active pyridazine compounds.

2.2.3. *Antiepileptic activity*

Epilepsy is a disorder of CNS characterized by its transient occurrences and dysrhythmia with signs or symptoms, which can be manifested as loss of consciousness or with or without characteristic body movement. It may be either provoked or unprovoked, based on which it is classified into two large categories partial and generalized seizures. About 60 to 70% of seizures are controlled by antiepileptic medications available[29,30]. Some of the currently available medications such as dapsone, levodopa, methyldopa, nitrofurantoin, etc, have a risk of hemolytic anemia. Thus, the search for novel antiepileptic drugs is

continued and some of the potentially reported discoveries are mentioned here[31].

In the view of safety and efficacy, an attempt was made by Xian Sun et al., where they reported the synthesis of a series of 6-alkoxy-tetrazole[5,1-a] phthalazine derivatives. These derivatives were tested for their potential action against convulsion and neurotoxicity. The results showed that the pharmacological activity of most of the compounds exhibited a potent effect on their median effective doses with the standard reference being carbamazepine. All the compounds synthesized showed anticonvulsive activity at a concentration of 300mg/kg while a few derivatives are potential even at the concentration of 200mg and 100mg/kg[32].

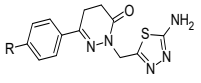


22a-22o

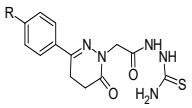
22a = C_2H_5
22b = i-C_3H_7
22c = n-C_4H_9
22d = n-C_5H_1
22e = n-C_6H_{13}
22f = n-C_7H_{15}
22g = n-C_8H_{17}
22h = C_6H_5
22i = C_6H_4(p-CH_3)
22j = C_6H_4(o-CH_3)
22k = C_6H_4(m-CH_3)
22l = C_6H_4(p-F)
22m = C_6H_4(p-Cl)
22n = C_6H_4(p-Br)
22o = C_6H_3(2,4-Cl_2)

Scheme 11. Tetrazole containing pyridazines with anticonvulsive effect.

Thiadiazol containing pyridazinones derivatives were reported with muscle relaxant and anticonvulsive effects by Sharma et al., the aryl pyridazinones synthesized exhibited a potential pharmacological activity, among the synthesized compounds 23d and 23e showed the protection of 82.75% and 85.44% against tonic limb extensor phase in maximal electrode shock which was a promising result in the development[33].



23a-e



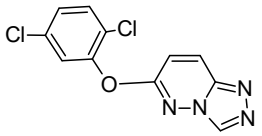
24a-e

a, OCH_3
b, C_2H_5
c, CH_3
d, H
e, Cl

Scheme 12. Thiadiazol containing pyridazinones.

An alkoxy derivative at the position of 6 in pyridazine substituted with various other groups exhibited the anticonvulsive effect with the lowest toxicity along with a very low dose of 17.3mg and protective index of 22.0 than that of the reference compound, the study reported by Guan et al., also exhibited compound 25 have a much better margin of safety also[34].

Scheme 13. Alkoxy pyridazine with anticonvulsive activity.



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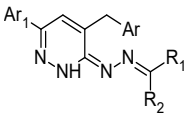
2.2.4. *Antimicrobial Activity*

Microbes are the organism that are closely associated with humans as they found trillions of numbers in the body which make outnumbering the human cells by 10 to 01. Even though they exist in a large number only less than 1% of them are known to cause infections or diseases to humans. These pathogenic microbes can cause a mild infection such as cold and cough to severe such as measles and malaria. To overcome the diseases and to maintain health intact antimicrobials agents are used[35,36].

Various pyridazine or derivatives of pyridazines have shown antimicrobial activity such as 1-[4-2(2-methoxybenzyl)-6-aryl pyridazine-3(2H)-ylidene) a series of the compound, and the compound 26d hydrazone derivative showed the highest biological activity against gram-positive bacteria (Staph aureus and Strep faecalis) and gram-negative (E coli and pseudomonas aeruginosa) with reference tetracycline in the study that was reported by Kandile et al., [37].



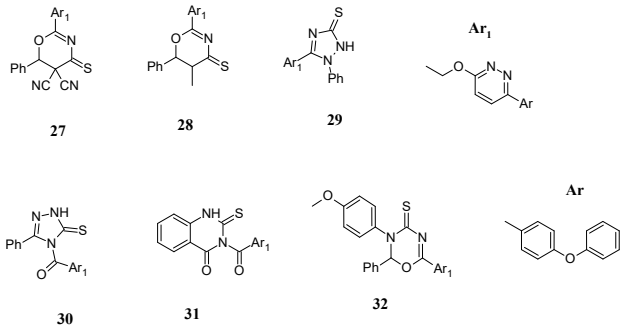
26d

26a-d

R_1	R_2
ph	C_4H_5-COOH(O)

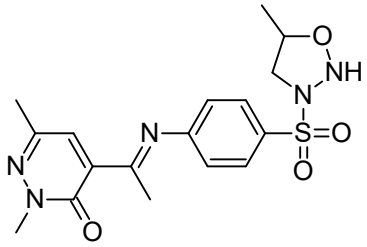
Scheme 14. Aryl pyridazine exhibiting antimicrobial activity.

In the study reported by Behalo et al., a series of [6-(4-phenoxy phenyl) pyridazine-3-yloxy] acetyl isocyanate possessing different nucleophilic reagents have exhibited the potent activity against the gram-positive bacteria (Staph cocci and Bacillus subtilis), gram-negative bacteria (E coli and Klebsiella bacilli) and antifungal activity (candida Albicans and Aspergillus niger) by agar diffusion method. The compounds 27, 28, 29 were active against gram-negative bacteria while 30, 31, 32 were highly active against gram-positive [38].



Scheme 15. Pyridazine moieties with antibacterial activity.

From the past decades, with the literatures, we came to know that sulpha drugs are potential antimicrobial [39]. Based on this Mohamed et al., reported the compounds with pyridazine-3(2H)-ones, 3-chloropyridazines, and pyridazine-3(2H)-thiones derivatives which were treated with sulpha drug (sulphamethoxazole). And the synthesized moieties were evaluated for antimicrobial activity against gram-positive (Staphylococcus aureus, Bacillus subtilis) and gram-negative bacteria (E. coli, Pseudomonas aeruginosa, and Yersinia enterocolitica)[40].



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Scheme 16. Pyridazine derivative with thiones.

CONCLUSION

Pyridazines among the heterocyclic compounds with the simplest basic nucleus have the potential activity for various diseases and disorders when substituted with different compounds. Drugs that are available in the market have pyridazine nuclei in their structures such as pimobendan, zardaverine, emorfazone, indolidan, and levosimendan. The study of various literature has given the knowledge that most of the pyridazine with aryl substituents, triazoles, or the presence of the electronegative group on the substitution increases the activity much more than the straight chains, further, the drugs available in the market have been established the potency for the various pyridazine moieties.

By the knowledge obtained from the above stated literatures it came to know that N-substituted aryl groups in the position of 1, or 2 possess anti-inflammatory activity by inhibiting COX enzymes. Around the active moiety diazene substituted with higher number of hetero atoms having a lone pair of electrons shows potential cytotoxic activity. The cyclo-tri and di-aza derivatives have a prominent effect in CNS activity that are helpful in treating disorder such as seizures. Even though plenty of compounds are being synthesized and researched extensively, there is more probability of getting a new compound with the help of structure-activity relation.

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this article.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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