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Various Chemical and Biological Activities of Pyridazinone Derivatives

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ABSTRACT

There has been an increasing interest in the chemistry of pyridazinone derivatives because of their biological significance. Pyridazinones have been reported to possess variety of biological activities like antidiabetic, anticancer, anti-AIDS, cardiovascular, antiinflammatory, anticonvulsant and cerebroprotective, analgesics, antidepressant, anticonvulsant, antiasthmatic, anti-HIV1, antimicrobial, insecticidal etc. Various compounds such as Levosimendan, Amipizone, Indolidan, Imazodan and Pimobedan are few examples of pyridazinones that are active as cardiotonic agents. The synthesis of novel pyridazinone derivatives and investigation of their chemical and biological activities have gained more importance. The biological profile of new generations of pyridazinones presents much progress with regards to the old compounds.

Keywords: Pyridazinones, Pyridazines, Drugs, Synthesis

INTRODUCTION

Pyridazinone are six-member heterocyclic compounds, 2 nitrogen atoms are present at adjacent positions. Pyridazin-3-one, a saturated or unsaturated form of pyridazine with carbonyl group on third carbon, has been considered as a magic moiety (wonder nucleus) which possess almost all types of biological activities. Pyridazinones are the derivatives of pyridazine which belong to an important group of heterocyclic compounds. The pyridazine nucleus represents a versatile scaffold to develop new pharmacologically active compounds. Diazines and their derivatives have become extremely important to the field of chemistry as well as to the general population in terms of their invaluable biological activities. Diazines contain two azomethine nitrogen atoms. There are three types of diazines. The three diazines, pyridazine, pyrimidine and Pyrazine are stable, colorless compounds, which are soluble in water [1,2]. Pyridazine derivatives represent one of the most active classes of organic compounds processing broad spectrum of biological activity. They are widely used in pharmaceuticals and agrochemicals. Pyridazine derivatives exhibit useful plant growth regulating effects. Pyridazines possess wide variety of biological activities. Recently, pyridazinone nucleus has been extensively studied in the search for new and selective medicinal agents as drugs acting on the cardiovascular system. The discovery of new series of pyridazinones possesses characteristic pharmacological and biological activities. Thus, the pyridazine and its 3-oxo derivatives, i.e., the pyridazinones have attracted a great deal of attention because of the wide spectrum of their pharmaceutical and agrochemical activities. They are widely recognized as versatile scaffolds with a diverse set of biological activities. Various pyridazinones have attracted considerable attention as they are endowed with a variety of pharmacological activities. These derivatives represent one of the most active class of compounds possessing broad spectrum of biological activity ranging from cardiovascular, antiinflammatory, antidiabetic, antidepressant, analgesic, anti-AIDS, anticancer, antimicrobial, anticonvulsant, cardiotonic, antihypertensive, analgesic, antiasthmatic, anti-HIV-1, antiproliferative, antimicrobial and insecticidal activities etc. Various pyridazinone derivatives have reached clinical trial level as biologically active agents [3-10]. Many pyridazine derivatives were reported as phosphodiesterase

inhibitors insecticidal, pesticidal and acaricidal activities. Compounds containing pyridazine moiety acts as glycosidase inhibitors influenza neuraminidase inhibitors etc. The synthesis of novel pyridazinone derivatives and investigation of their pyridazinone derivatives have chemical and biological behaviour have gained more importance in recent decades for biological, medicinal, and agricultural reason [11-14].

Pyridazines are a group of compounds formally derived from benzene by the replacement of two of the ring carbon atom by nitrogen (hence known as diazines). Depending on the position of two nitrogens, three isomeric diazines are possible with the nitrogen atoms in 1-2, 1-3, or 1-4 relationship, giving rise to the pyridazines (**a**) pyrimidine (**b**) and pyrazine (**c**) respectively. Pyridazine (1,2-diazine) has been known since the 19th century. Pyridazine is one of the important classes of compounds mainly due to their diverse pharmacological activities. This privileged structure attracts the interest of medicinal chemists as a nucleus of potential therapeutic utility. The easy functionalization at various ring positions makes them an attractive synthetic building block for designing and synthesis of new drugs. Pyridazines are widely recognized as versatile scaffolds with a diverse set of biological activities. Among pyridazine derivatives, hydroxypyridazine (Pyridazinones) form an important class of compounds mainly due to their diverse pharmacological activities. In recent years, diazines and their derivatives have become extremely important to the field of chemistry as well as to the general population in terms of their invaluable biological activities. Diazines contain two azomethine nitrogen atoms. There are three types of Diazines. The three diazines, pyridazine, pyrimidine and Pyrazine are stable, colorless compounds, which are soluble in water. There are only four ways in which a benzene ring can be fused to a diazine: cinnoline and phthalazine (Figure 1).

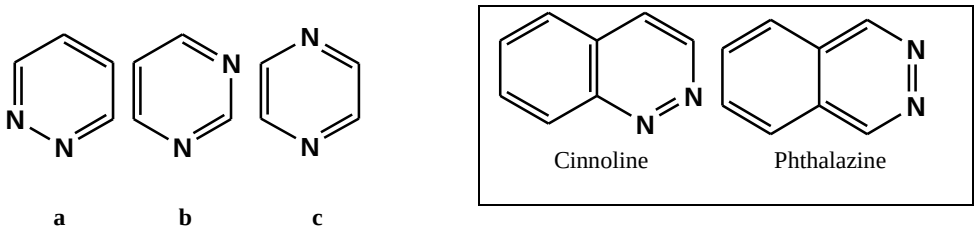


Figure 1: Diazine- cinnoline and phthalazine

Pyridazinones are the derivatives of pyridazine which belong to an important group of heterocyclic compounds containing two nitrogen atoms at 1 and 2 positions in a six member ring. In pyridazinone derivatives the amine group (NH) is suitably placed with the carbonyl group and most of the pyridazinone derivatives exhibit tautomerism. Pyridazinones exist mainly in the oxo form. This has been demonstrated in the case of pyridazinone and several of its derivatives [15]. Pyridazines and their derivatives, although known for a century, received tremendous attention with the recent discovery of medicinally useful compounds. Pyridazines are heteroaromatic, 6-membered organic compounds that are structurally important in several biologically active substances with a broad range of biological and pharmaceutical activities. The pyridazine ring system is a 1, 2-diazine or *o*- diaza benzene [16]. It is a planar molecule for having a maximum of two kekule structures (Figure 1) possible. Historically, pyridazines were first named by Knorr [17], while Fischer [18] prepared the first substituted compounds but Tauber4 was the first to synthesize the unsubstituted pyridazine (Figure 1). At room temperature, it is a colorless liquid with pyridine like odor, owing to its imine functional groups, and has a relatively high boiling point (208°C) and low melting point (-8°C). The pyridazine molecule is a π-deficient heteroaromatic compound similar to pyridine. Due to the presence of the π-deficient nitrogen aromatic heterocycles these compounds are more easily soluble in water when compared to other hydrocarbons. The basic aromatic ring system of pyridazine contains two adjacent nitrogen atoms (Figure 2) as Kekule structure for pyridazine [19,20].

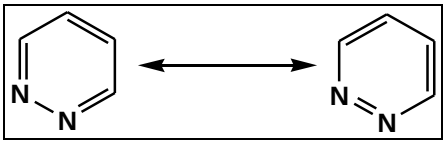


Figure 2: Kekule structure for pyridazine

Biological importance of pyridazines and pyridazinones

Pyridazine nucleus is a deficient heterocyclic system the chemistry of which has been a subject of quite a review articles. Recent literature survey has shown a number of pyridazine derivatives which have been shown to exhibit a diverse range of pharmaceutical properties such as anticancer, nephrotropic, analgesic, antidepressant, hypotensive, antianemic, antibacterial, antiaggregative and antifungal activities [1-5].

Pyridazine uses

Pyridazinones are also an important class of heterocycles that are encountered in a number of natural products. Some pyridazinone containing drugs are Chloridazon, Emorfazone, Zardaverine, Pyridaphenthion, Dimidazon etc. (Figure 3). Chloridazon is a selective herbicide from the group of pyridazine derivatives, which is used for beet cultivation. The development of non-anti-inflammatory, non-opioid agents which are able to control pain from a broad range of causes represents a primary objective in analgesic drug research. Pyridazine derivatives displaying antinociceptive activity [21], have been reported. Among this type of compounds, Emorfazone [22], which is characterized by the absence of either effects on the prostaglandin system or affinity for opioid receptors [23], emerged. Zardaverine is a pyridazinone deriative, which selectively inhibits specific phosphodiestersses (PDE). Zardaverine is shown to inhibit selectively two out of five isoenzyme classes of PDES, namely PDE III from human platelets and PDE IV from human polymorphonuclear leucocytes (PMN) with IC50 values of 0.58 and 0.17 μM, respectively [24]. Other PDE inhibitors have been shown to exhibit cardiotonic actions and are used in the treatement of cadiac failure [25].

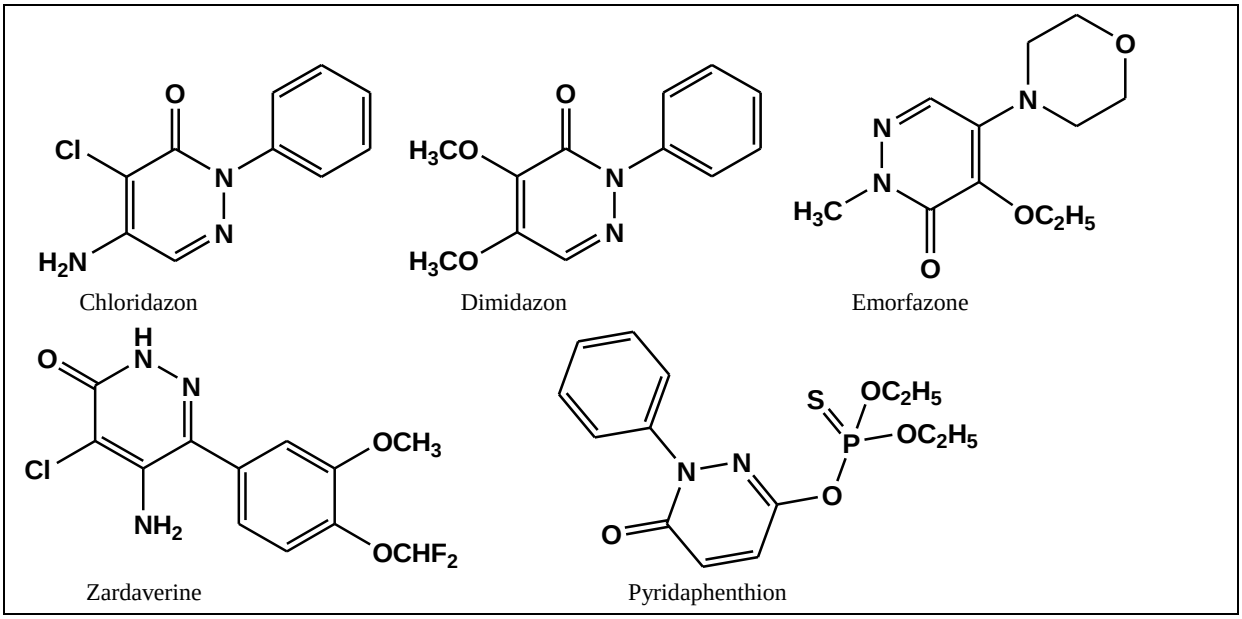


Figure 3: Structures of cholridazon, dimidazon, emorfazone, zardaverine, pyridaphenthion

Most of the biologically active compounds like Minaprine, Gabazine, and Hydralazine have pyridazine as a recurring structural component (Figure 4). Pyridazines have no household use but are mostly found in research and industry as a building block for most of the complex organic compounds [26]. Pyridazines are also useful intermediates in the synthesis of various other heterocycles and in physical organic chemistry. 3,6-Di(pyridin-2-yl)pyridazines (DPPs) are well-known ligands for the self-assembly of grid like metal complexes with copper (I) and silver (I) ions, which show unique properties [27,28]. The functionalized pyridazines are also versatile building blocks in natural-product syntheses. There are a myriad of uses for pyridazines elsewhere. Pyridazines are also known to exhibit versatile biological activities such as antibacterial, antibiotic, anti-depressant, anti-diabetic, anti-hypertensive, analgesic, anti-tumor, antiviral, nephrotropic, antiinflammatory, anti-viral, anti-cancer, anti-aggregative, anti-epileptic [29]. These compounds are also used in treating sleep disorders including insomnia and for inducing sedationhypnosis, anesthesia, sleep and muscle relaxation. The pyridazine structure is also found within a number of herbicides such as Credazine, Pyridafol and Pyridate (Figure 5) [30].

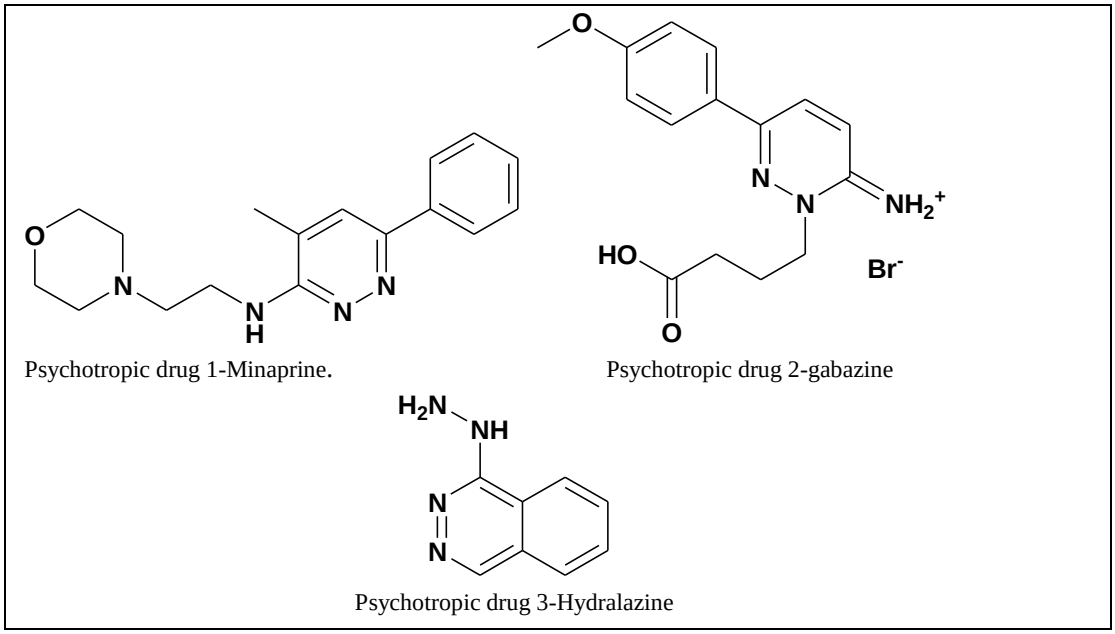


Figure 4: Biologically active compounds minaprine, gabazine, hydralazine

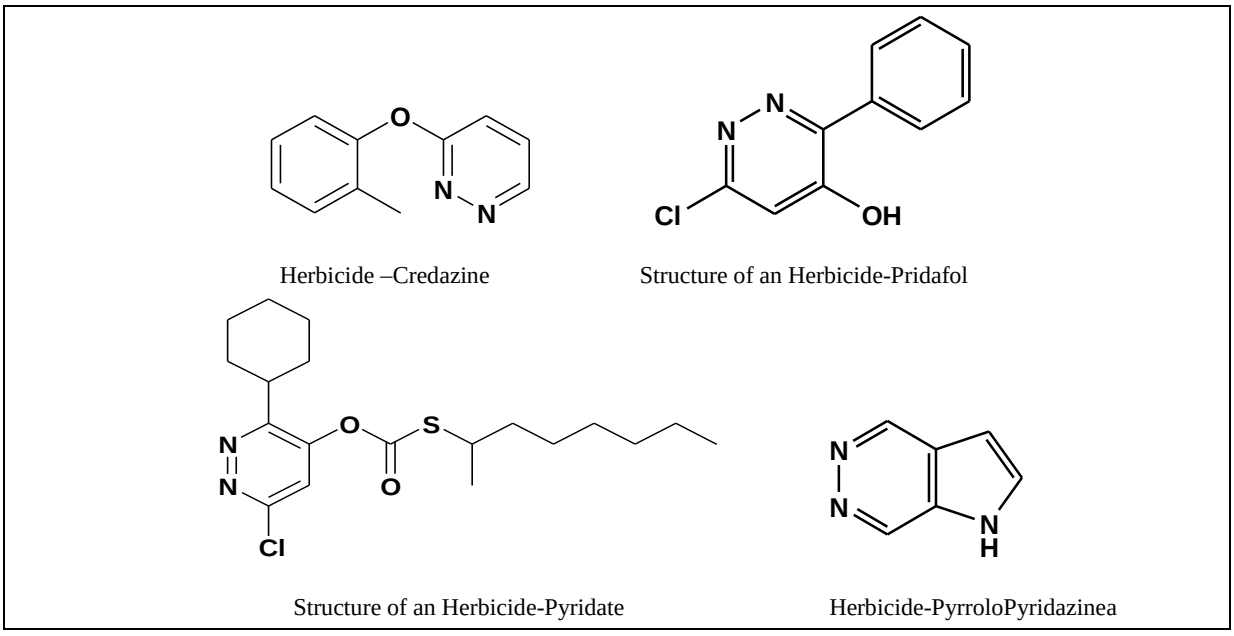
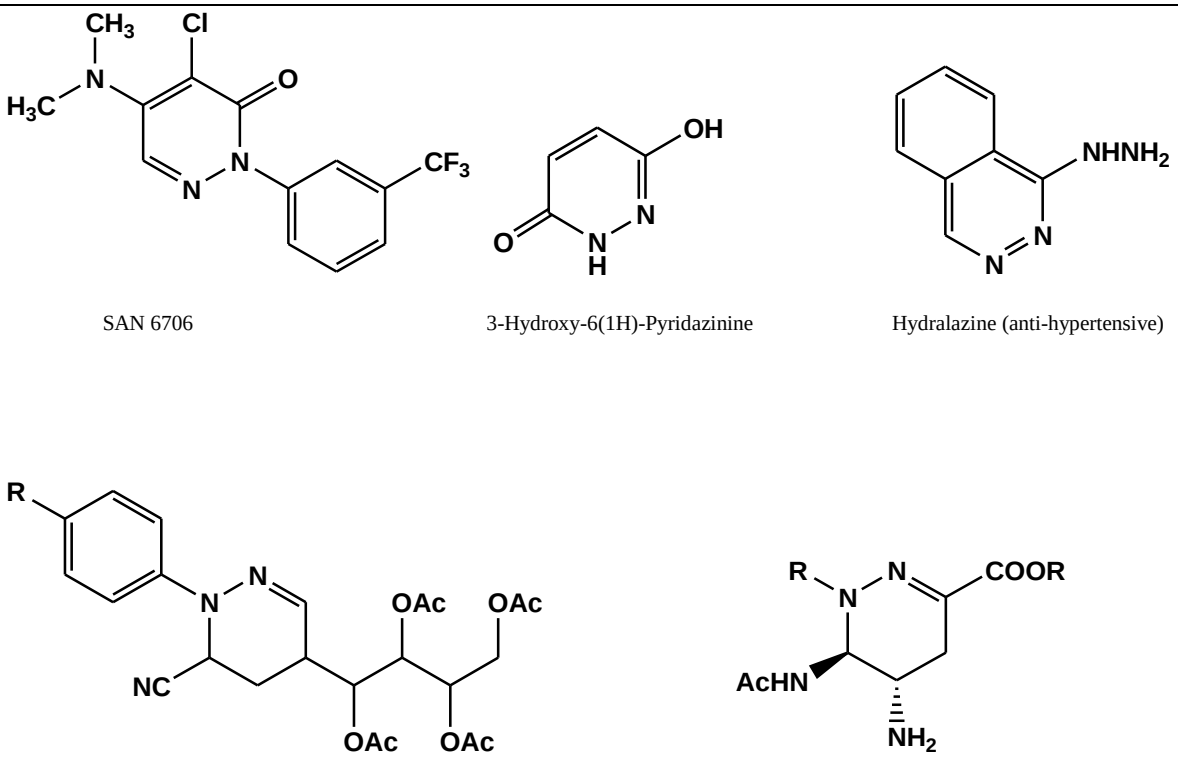


Figure 5: Structure of pyridazine is also found in herbicides – credazine, pridafol, pyridate, pyrrolo pyridazine

Additionally, pyridazines are also known for their work as efficient electron acceptors in conjugated systems, and as ligands in the synthesis of several novel coordination complexes. Above all, substituted pyridazine-based compounds are extensively investigated with regard to their versatile applications. These substituted compounds are used as stearl-CoA desaturase inhibition, and against cyclooxygenase enzyme, acetylcholine esterase, aldose reductase as inhibitors [30]. Pyridazines interfere in various regulation processes of the enzymes and find wide applications in drug design. Analogously, agricultural science takes advantage of their high biological activity, and pyridazines whose substitution patterns have been modified promote powerful fungicide properties. Among substituted pyridazines the 3-aminopyridazine unit has been proven to be interesting from pharmacological point of view. For example, Minaprine is a psychotropic drug, which is presently used as an antidepressant. Several derivatives of 3-amino pyridazines also act as selective GABA-A receptor antagonists [31]. Pyridazines are also identified as PIM kinase inhibitors, responsible for *in vitro* Anti leukemic activity. These compounds also have a rapid systemic effect on the plants and are active at very low concentrations. Some of the pyridazine derivatives

have their chemical structures related to phytohormones and some plant growth regulators. In addition, similar chemical structures occur in living cells that are involved in various biochemical reaction pathways. Some synthesized pyridazine derivatives were also used in many research fields due to their structure, stability and reactivity and their tendency to form stable compounds with useful biological properties [32]. Pyridazines can also be used as novel therapeutic agents to target Alzheimer's disease and other neurodegenerative diseases like Parkinson. Pyridazine derivatives can be used in the treatment of dermatosis, prostate cancer, and dry eye disorders. Moreover, pyridazines are pharmaceutically acceptable acid-addition salts that are used as an active component in cardiotonic compositions to increase cardiac contractility [33]. Furthermore, simple pyridazines show high halogen-free flame retardant capacity. These compounds have also been used as ligands in co-ordination chemistry unlike the N-atom donor ligands; pyridazines are not well studied from a crystal engineering perspective because of which these compounds are scarcely been explored for crystal design. Pyridazines have also been incorporated into iptycene frameworks, compounds researched for conjugated polymer sensors, high mechanical performance polymers, gas absorption/storage, and host-guest chemistry and in liquid crystals [34].

Pyridazine derivatives represent one of the most active class of organic compounds processing broad spectrum of biological activity (Figure 6). They are widely used in pharmaceuticals and agrochemicals [35,36]. Rohm-Haas company had reported that pyridazine derivatives exhibit useful plant growth regulating effects [37,38]. Compounds containing pyridazine moiety acts as antihypertensive [39], vasodilators [40], glycosidase inhibitors [41], influenza neuraminidase inhibitors etc. [42]. The most important naturally occurring diazines are the pyrimidine bases uracil, thymine and cytosine, which are constituents of the nucleic acids. Several pyrimidine nucleoside analogues have been developed as anti-viral agents. For instance Idoxuridine is used in the treatment of Herpes infections of the eye. AZT is the most widely used anti-AIDS drug. The glycosidase inhibitory activity of pyridazine derivatives containing carbohydrate side chain **1** [41]. The 1,4,5,6-tetrahydropyridazine derivatives **2** via hetero Diels-Alder reaction and evaluated as potential influenza neuraminidase inhibitors [42].



SAN 6706

3-Hydroxy-6(1H)-Pyridazinine

Hydralazine (anti-hypertensive)

1- Glycosidase inhibitory activity of pyridazine derivatives containing carbohydrate side chain

2- 1,4,5,6-rahydropyridazine derivatives via hetero Diels-Alder reaction

Figure 6: Structures of pyridazine derivatives containing broad spectrum of biological activity

The 5, 6-bis (4-methoxyphenyl)-pyridazi-3(2H)-one derivatives **3** and their ability to inhibit IL-β-production were evaluated. Some of the compounds showed potent inhibitory activity against IL-β-production in HL-60 cells stimulated with lipopolysaccharide, among the compound 4-chlorocinnamyl derivative more potent [43] (Figure 7). Palladium assisted synthesis of several 5-alkylidene-6-phenyl-pyridazin-3(2H)-ones **2** were screened for antiplatelet activity. Among these the presence of oxygenated functions (COOR, $COCH_3$) on the vinyl group gave rise to the highest activity [44].

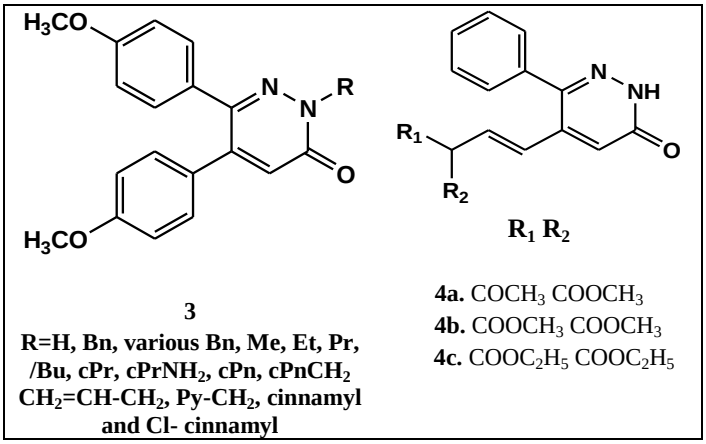


Figure 7: 5, 6-bis (4-methoxyphenyl)-pyridazi-3(2H)-one derivatives **3** and their ability to inhibit IL-β-production and presence of oxygenated functions on the vinyl group **4**

Pyridazin-3(2H)-one derivatives (Figure 8) among the series isopropoxy **5** and 4-fluorophenyl **6** derivatives exhibited potent, selective and orally active cyclooxygenase-2 (COX-2) inhibiting properties, which were highly efficacious in rat paw edema and rat pyresis models [45]. Pyridazinones-arylpiperazine derivative **7** showed a 1-adrenoceptor antagonist 4.5 folds more activity than the reference compound prazosin [46].

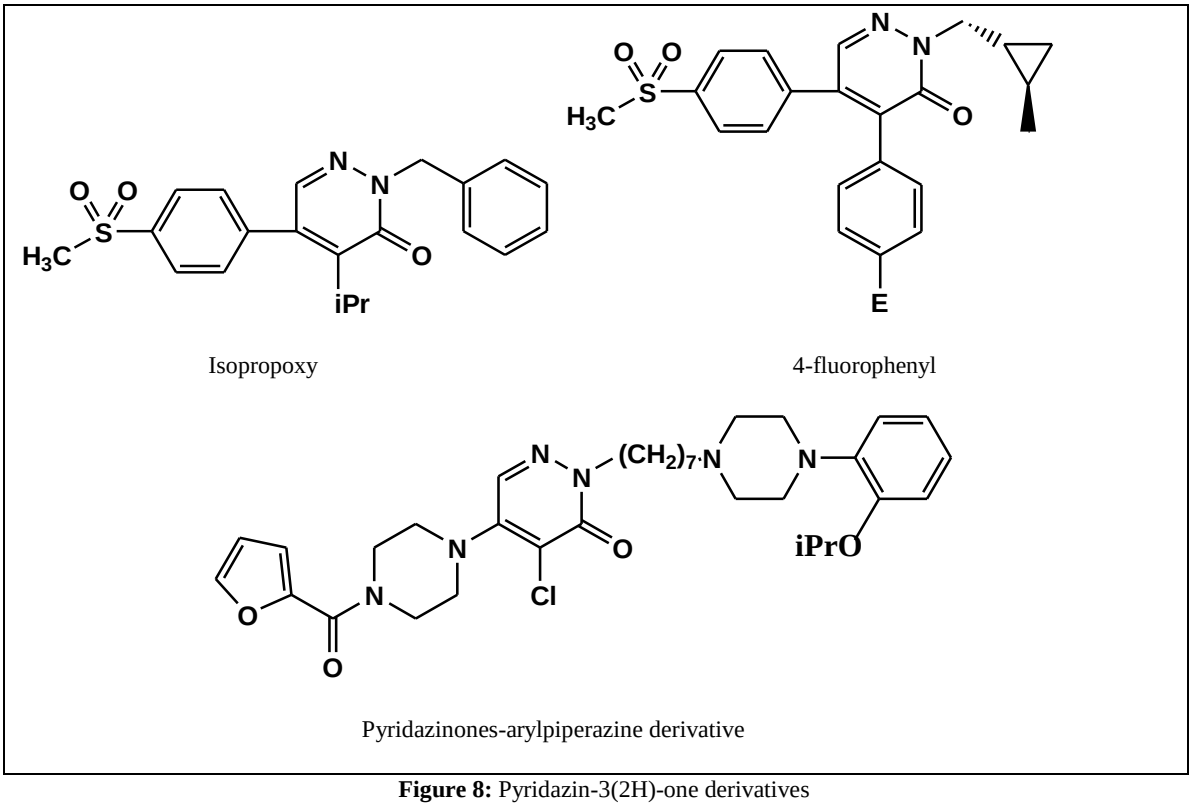


Figure 8: Pyridazin-3(2H)-one derivatives

The library of diversely substituted pyridazin-3(2H)-ones containing a 3-oxo-3'-phenylprop-l-en-l-yl **8,9** or 3'-phenylprop-2-enoyl (Figure 9)**10** fragment at position 5 has been obtained and evaluated as antiplatelet agents. They a studied preliminary SAR results by the structural modifications at positions at 2, 4 and 6 [47].

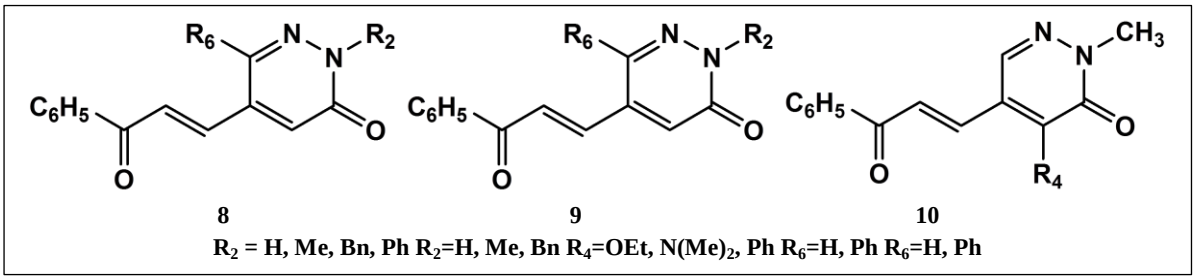


Figure 9: 3-oxo-3'-phenylprop-l-en-l-yl- 8,9 or 3'-phenylprop-2-enoyl-10

The 2-aryl-pyridazinones and screened for p38 MAP kinase inhibitor activity (Figure 10). Among the series **11,12** and **13** were found to be potent against the enzyme [48].

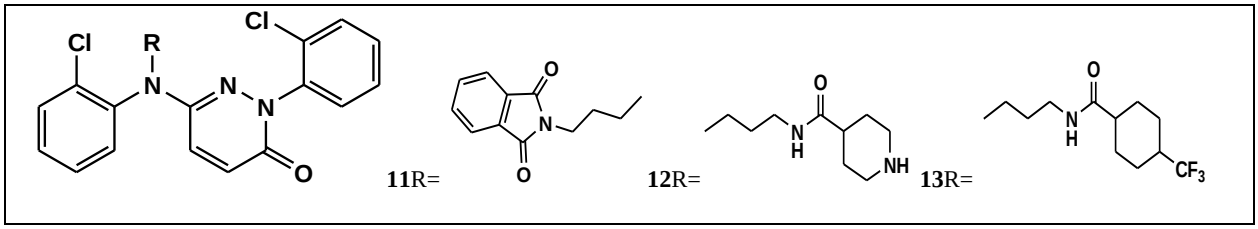


Figure 10: 2-aryl-pyridazinones containing p38 MAP kinase inhibitor activity

A set of regioisomeric 2-substituted pyridazin-3(2H)-ones (Figure 11) **14** containing a 3-oxo-3-phenylprop-l-en-l-yl fragment at either position 4,5, or 6 and 2-substituted pyridazin-3(2H)-ones **15** containing the same fragment both at positions 4 and 5 have been synthesized and identified a new highly potent platelet aggregation inhibitors [49]. The structural modifications of three groups within the generalized lead *a4*- intigrin antagonist were targeted; the arylamide, the carboxylic acid and the 5- position substitution on the pyridazin-3H-ones **16** [50].

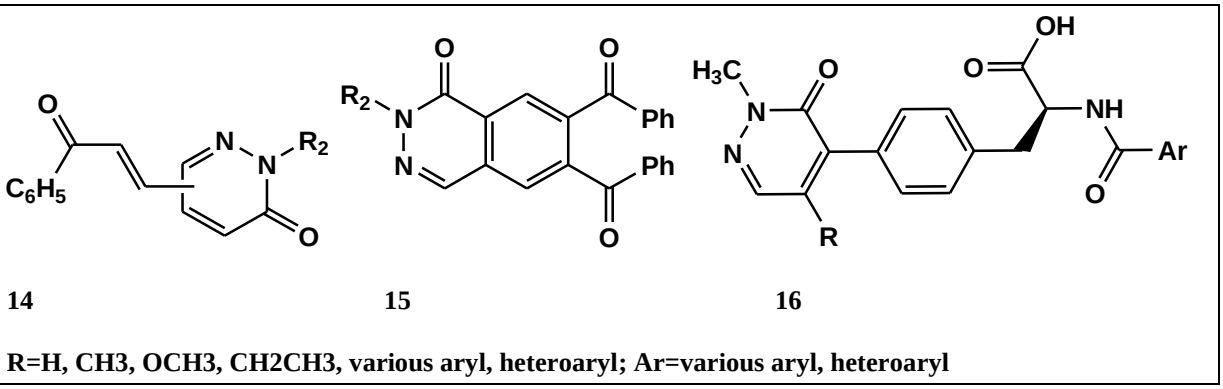


Figure 11: Regioisomeric 2-substituted pyridazin derivatives

The design and anti-inflammatory activity of a series of arylethenyl and arylethylpyridazinones from corresponding arylhexenoic and arylhexanoic acids respectively (Figure 12). Among the series **17** and **18** were more potent [51].

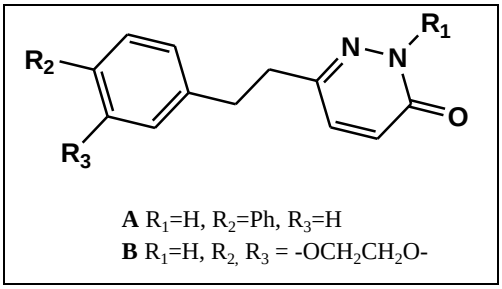
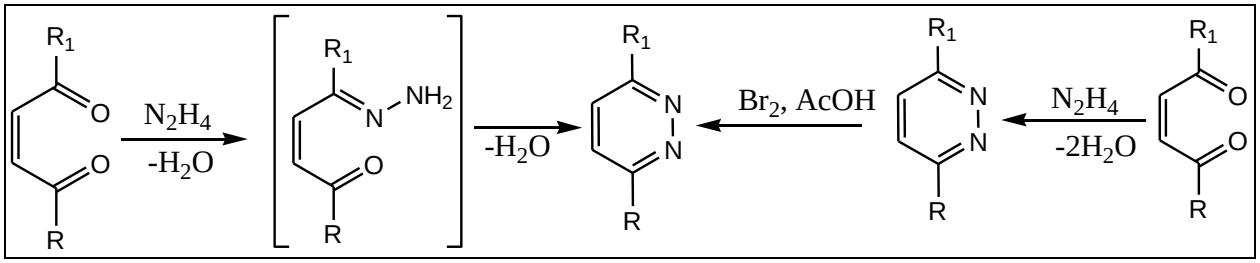


Figure 12: Arylethenyl and arylethylpyridazinones

CHEMISTRY OF PYRIDAZINES

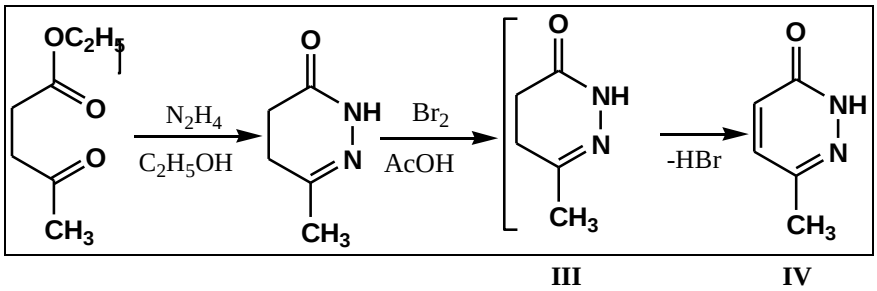
Preparation of pyridazines

Saturated and unsaturated 1,4-dicarbonyl compounds undergo cyclocondensation with hydrazine via hydrazones yielding 1,4-dihydropyridazine 4 or pyridazine (Scheme 1). Dehydrogenation of dihydropyridazines **II** to **I** is brought about by Br_2 in acetic acid [2].



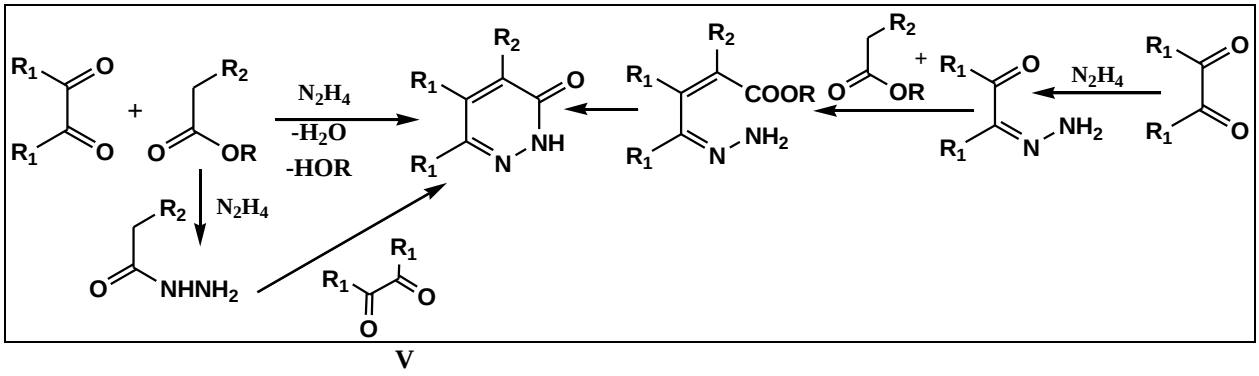
Scheme 1: 1,4-dihydropyridazine 4 or pyridazine

6-Substituted pyridazine-3-(2H)-one **IV** was synthesized by cyclocondensation of ketocarboxylic acid or their ester with hydrazine followed by dehydrogenation of the resultant dihydrocompound **III** (Scheme 2) [2].



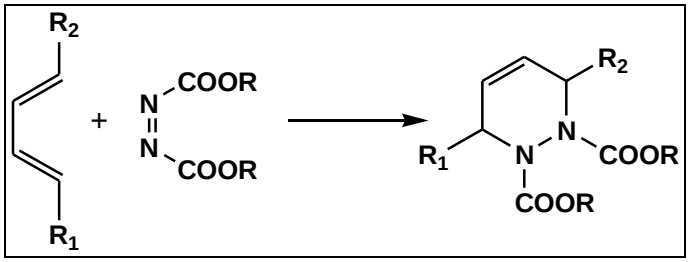
Scheme 2: Dihydrocompound resulted

The cyclocondensation of 1,2-diketones, reactive methylene esters and hydrazones leads in its simplest form as a one-pot reaction, to pyridazin-3-(2H)-ones **V** (Schmidt-Druey Synthesis). The monohydrazone of the 1,2-dicarbonyl compounds or hydrazides with a reactive CH_2 group can be employed for the pyridazin-3-(2H)-one synthesis (Scheme 3) [2].



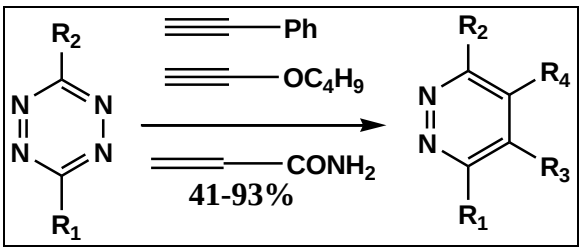
Scheme 3: Pyridazin-3-(2H)-one synthesis

Pyridazine derivatives are also obtained by [4+2] cycloaddition of 1,3-dienes with azodicarboxylic ester (Scheme 4).



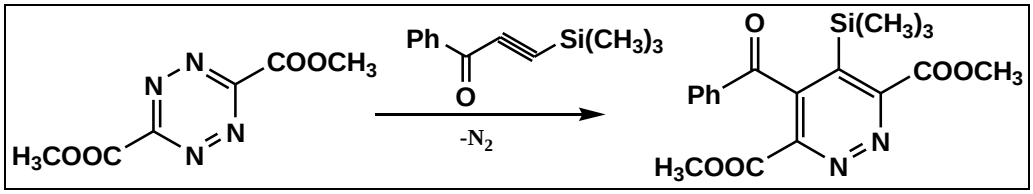
Scheme 4: Cycloaddition of 1,3-dienes with azodicarboxylic ester

A common method to synthesize pyridazines **VII** involves the inverse electron-demand Diel-Alder cycloaddition of 1, 2, 4, 5-tetrazines 8 with electron rich dienophiles (Scheme 5) [2].



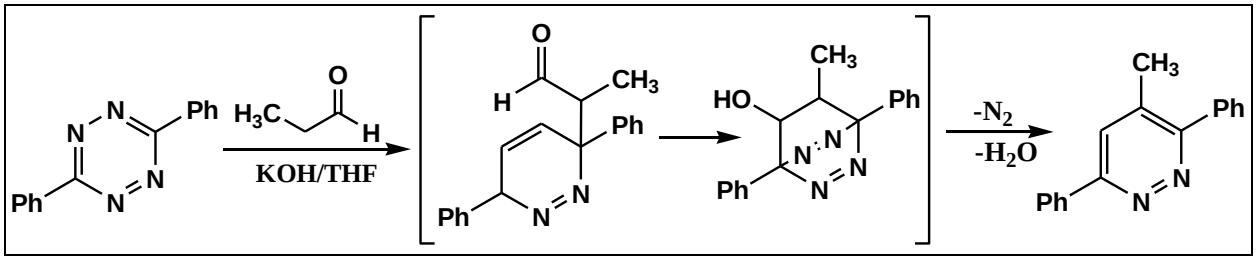
Scheme 5: 1, 2, 4, 5-tetrazines 8 with electron rich dienophiles

This process worked best when the tetrazine has electron-withdrawing substituents, but a wide range of substituents can be incorporated on the acetylene (Scheme 6).



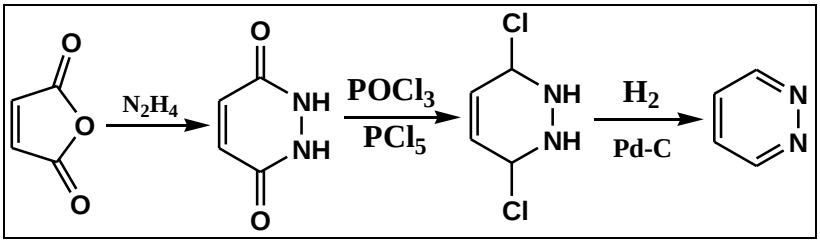
Scheme 6: Substituents incorporated on the acetylene

The addition of ketone and aldehyde enolates to tetrazines, though not a concerted process, has the same overall effect (Scheme 7).



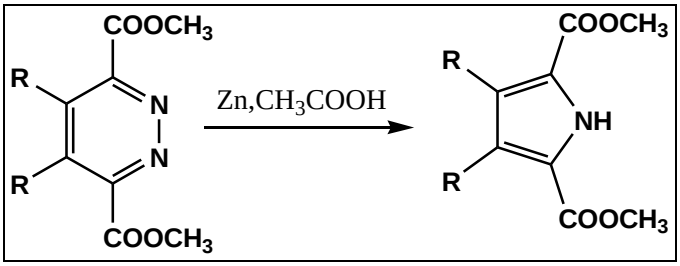
Scheme 7: Addition of ketone and aldehyde process

Pyridazine itself can be prepared from maleic anhydride. Its reaction with hydrazine yields maleic hydrazide **VIII** which is converted with POCl3/PCl5 into 3,6-dichloro pyridazine **IX**, which on reductive dehalogenation with H_2/Pd-C gives pyridazine (Scheme 8).



Scheme 8: Reductive dehalogenation with H_2/Pd-C

Interestingly, Boger and coworkers reported pyrrole synthesis when treating pyridazines to a solution of activated zinc in acetic acid (Scheme 9). This has vast importance and novelty in the field of semiconducting polypyrroles. Moreover, pyridazines serves as synthetic models and building blocks for organic and organometallic polymers which are suitable for a variety of real world applications such as Organic Light Emitting Diodes (OLEDs) and Organic Photovoltaic Cell (OPVs). Pyrrolopyridazine, which is a derivative of pyridazine, have fluorescent properties and are used in sensors, lasers, and also in vulcanization of rubber. These derivatives are also used in treatment of variety of disorders such as hypersecretion of CRF, and also show anti proliferative, anxioltic activity. In addition these compounds are also used in treatment of glaucoma [52].

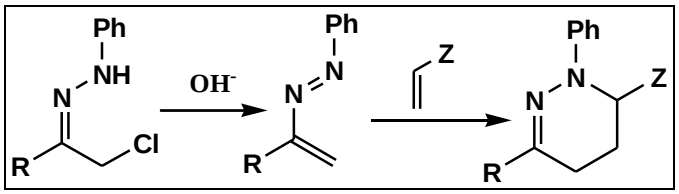


R= CH_3, C_2H_5, C_6H_5, OCH_3, $OCH_2C_6H_5$ R'=H, CH_3, $COCH_3$

Scheme 9: Boger and co-workers convert pyridazines to pyrrole**s**

Azoalkenes are potentially very versatile components in cycloadditions, and represent a useful starting point for exploring the preparation of new heterocyclic systems. Cycloaddition reaction in which azo group participates [53]. Generation of azoalkenes **X** is somewhat difficult. They are unstable and normally they are observed only in solution. The usual method of generating azoalkenes **X** is the elimination of hydrogen halide from hydrazones

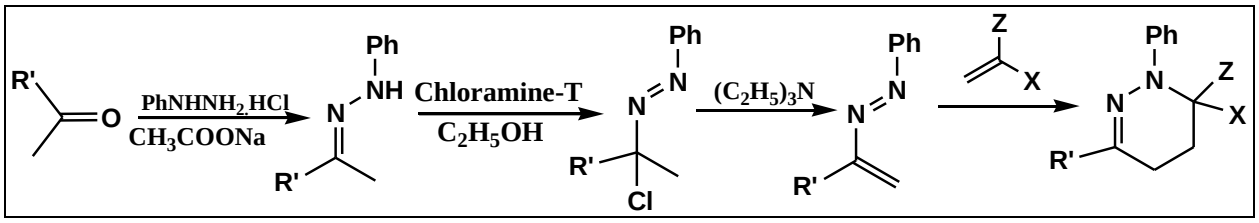
of monohaloketones in presence of base. The generated azoalkenes are trapped by alkenes to produce tetrahydropyridazine derivatives **XI** (Scheme 10) [54].



X **XI**

Scheme 10: Production of tetrahydropyridazine derivatives

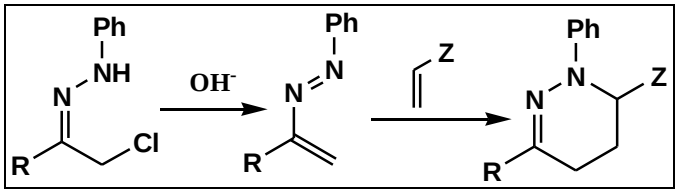
Plan of the synthesis: 1-Phenyl-3,6-disubstituted-1,4,5,6-tetrahydropyridazines were prepared by [4+2] cycloaddition reaction of azoalkenes with alkenes. The azoalkenes are generated in situ from phenyl hydrazones of ketones containing methylene group using chloramine-T as a new reagent. The starting ketohydrazones were prepared from ketones containing Methylene group by general method (Scheme 11) [55].



XII **XIII** **XIV** **XV**

Scheme 11: Preparation of ketohydrazones from ketones containing methylene group

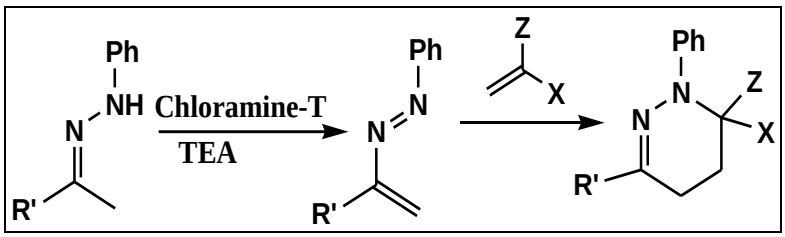
Discussion on the experiments leading to the synthesis of 1-phenyl-3,6-disubstituted-1,4,5,6-tetrahydropyridazines. The usual method for the synthesis of 3,6-disubstituted-1,4,5,6-tetrahydropyridazines involves the elimination of hydrogen halide from haloketooximes in presence of base to generate azoalkenes which undergo [4+2] cycloaddition with alkenes (Scheme 12) [54]. However azoalkenes are highly reactive and unstable, hence they are usually only generated *in situ*. The yield of cycloaddition products is often low or side reactions predominate, hence new procedure for the formation of azoalkenes remains of interest.



XVI **XVII**

Scheme 12: Cycloaddition with alkenes

Typically, the cycloaddition is carried out by refluxing an equimolecular mixture of a ketohydrazone, chloramine-T trihydrate in ethanol followed by addition of triethylamine and an alkene in ethanol at room temperature. In general 1-phenyl-3,6-disubstituted-1,4,5,6-tetrahydropyridazine derivatives are thus obtained in 65-80% yield (Scheme 13).

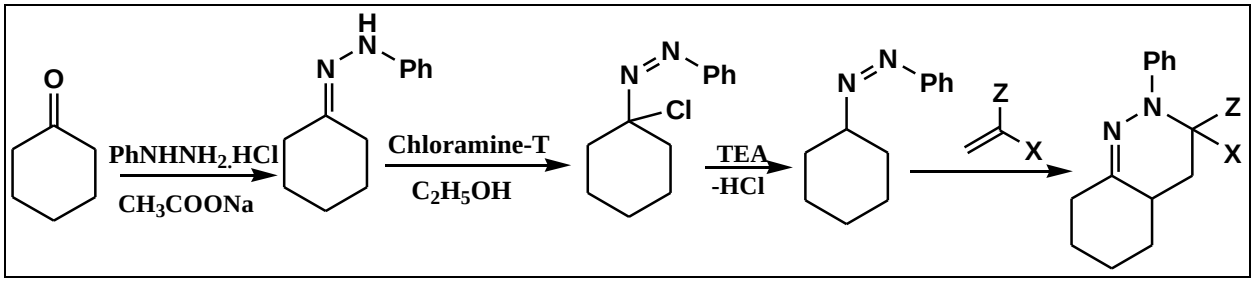


XVIII **XIX**

R=Ph, R=p-ClC$_6$H$_4$, R= p-NO$_2$C$_6$H$_4$ R=Ethyl R=Furyl; X=H, Z=Ph; X=H, Z=CN; X=CH$_3$ Z=Ph

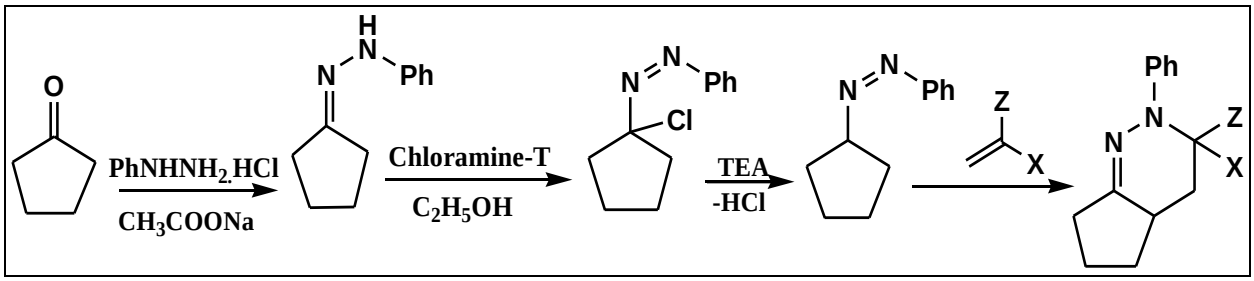
Scheme 13: Discussion on the experiments leading to the synthesis of bicyclic pyridazines

Bicyclic pyridazines were prepared by [4+2] cycloaddition reaction of azoalkenes with alkenes. The azoalkenes are generated in situ from cyclic ketohydrazones containing methylene group using chloramine-T as a new reagent. The starting cyclic ketohydrazones were prepared from cyclicketones containing *ƒ*-methylene group by general method (Schemes 14 and 15) [55].



aX=H, Z=Ph, bX=CH$_3$, Z=Ph, cX=H, Z=CN, dX=H, Z=COOC$_2$H$_5$

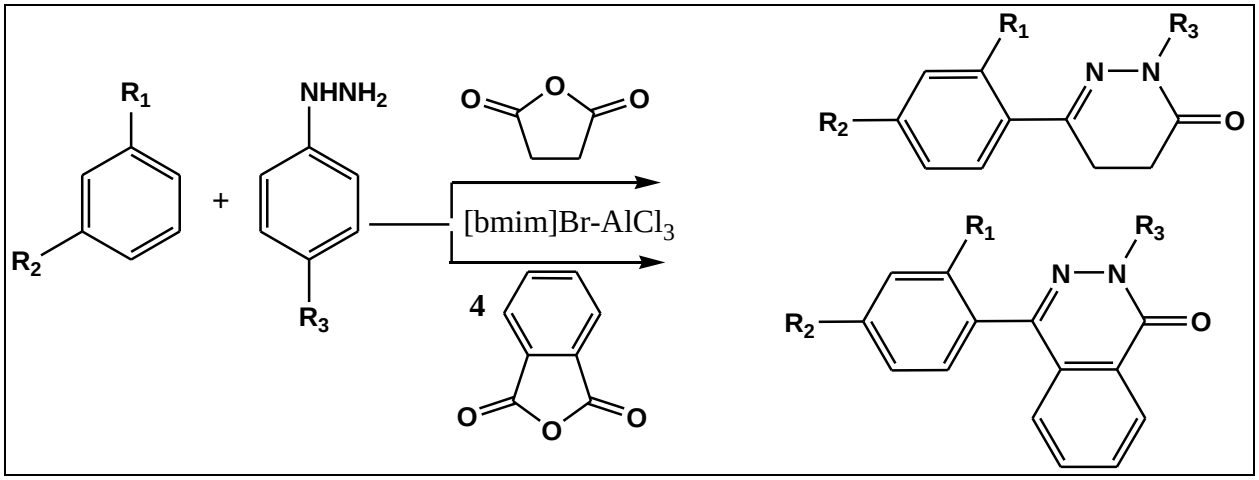
Scheme 14: Preparation of cyclic ketohydrazones from cyclicketones containing *ƒ*-methylene group



aX=H, Z=Ph, bX=CH$_3$, Z=Ph, cX=H, Z=CN, dX=H, Z=COOC$_2$H$_5$

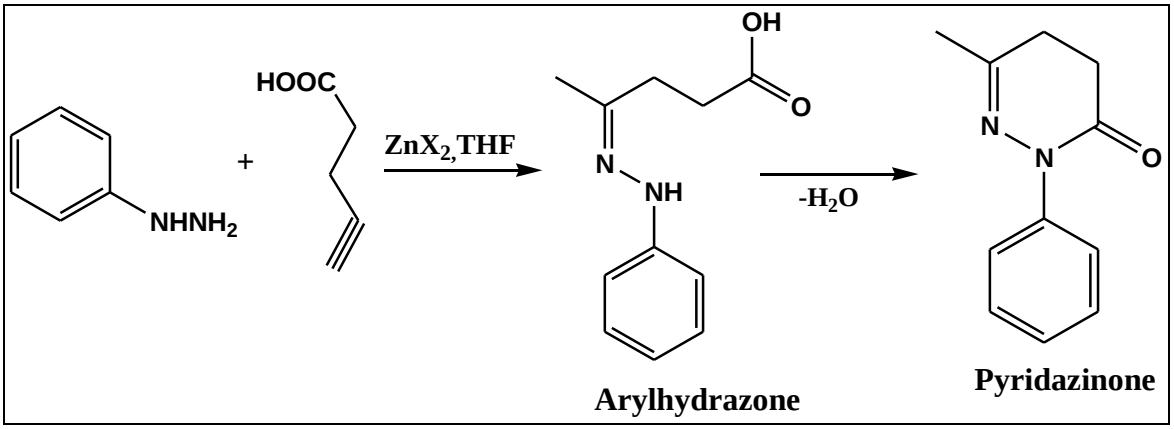
Scheme 15: Preparation of cyclic ketohydrazones from cyclicketones containing *ƒ*-methylene group

The ultrasound-promoted multicomponent synthesis of pyridazinones and phthalazinones from arenes, cyclic anhydrides and ArNHNH$_2$ in the presence of an efficient recyclable catalyst, 1-butyl-3-methylimidazolium bromochloroaluminate ([bmim] Br-AlCl$_3$), in high yield and short reaction time (Scheme 16) [56].



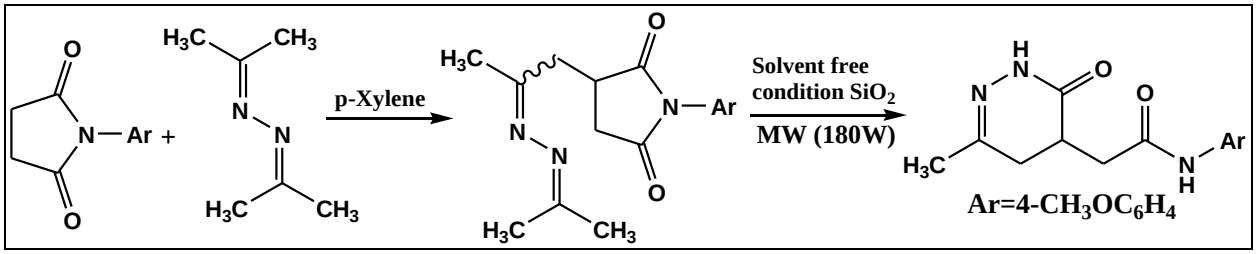
Scheme 16: Multicomponent synthesis of pyridazinones and phthalazinones

The mechanism of reaction goes through Friedel–Crafts acylation between arenes and cyclic anhydride over an efficient acidic catalyst to prepare keto-carboxylic acids. Intermolecular hydrazone formation followed by an intramolecular cyclization that led to the formation of pyridazinones and phthalazinones (Scheme 17). For these reasons, the [bmim]Br/$AlCl_3$ use as a catalyst, because of its environmental compatibility, reusability, operational simplicity, no toxicity, non-corrosiveness, low cost and ease of isolation [56].

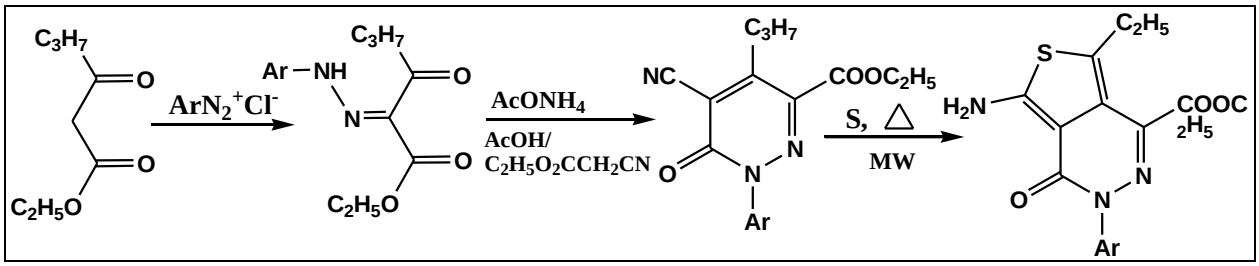


Scheme 17: Synthesis of pyridazinone

In addition, a method for the synthesis of 6-methyl-2-phenyl-4,5-dihydropyridazin-3(2H)-one based on domino hydrohydrazination and condensation reactions. Phenylhydrazine react with 4-pentynoic acid in the presence of 1 equiv $ZnCl_2$ to give the corresponding pyridazinone in a one-pot process in moderate to good yields [57]. In this study, a new approach to the synthesis of 4-(Naryl) carbamoylmethyl-4,5-dihydropyridazin-3(2H)-ones by reaction of N-aryl substituted maleimide with azines. In some cases, Michael addition intermediates were isolated, which were then converted into the corresponding 4,5-dihydropyridazin-3(2H)-ones. The reactions are operationally simple and do not require temperature manipulations or inert atmospheres (Schemes 18 and 19) [58].

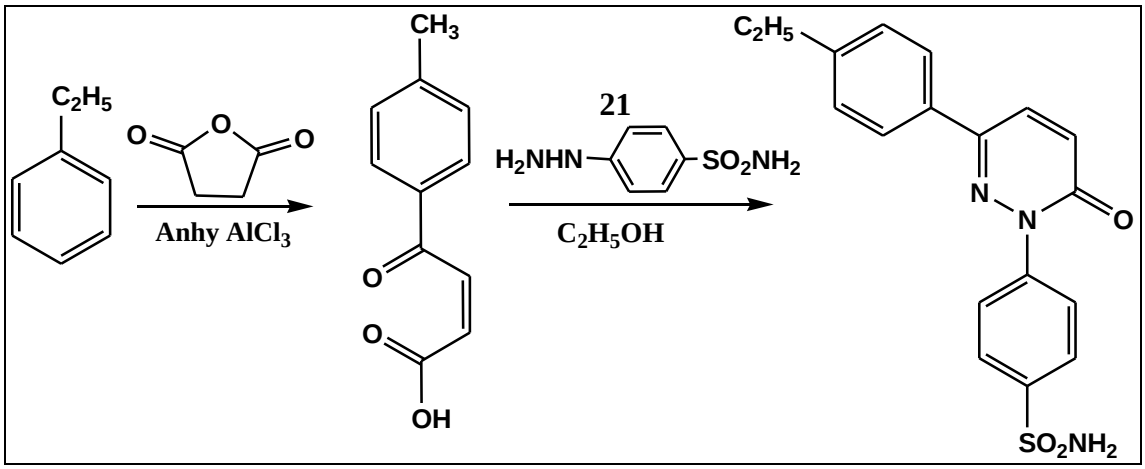


Scheme 18: Synthesis of 4,5-dihydropyridazin-3(2H)-ones



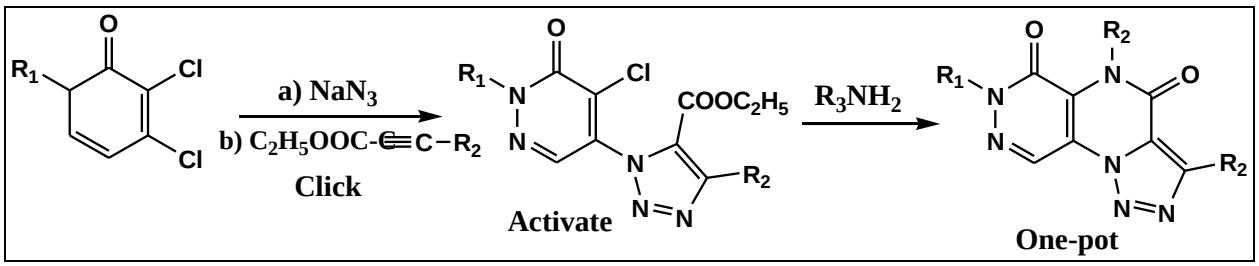
Scheme 19: Synthesis of thieno[3,4-d]pyridazinones

A environmentally benign methodology for the synthesis of thieno[3,4-d]pyridazinones has developed, avoiding volatile and toxic organic solvents. This neat reaction under both microwave and ultrasound irradiations gave excellent yield of products with lesser reaction time [59]. A series of pyridazinone derivatives bearing benzenesulfonamide moiety by the condensation of appropriate aroylacrylic acid and 4-hydrazinobenzenesulfonamide hydrochloride in ethanol [60]. The b-aroylacrylic acids were obtained by a Friedel Craft's acylation through reported methods (Scheme 20) [61,62].



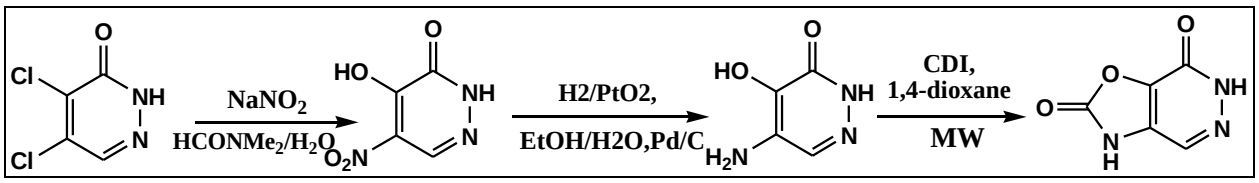
Scheme 20: Synthesis of 6-aryl-2-benzenesulfonamide-pyridazinones

Recently, the preparation of substituted [1,2,3]triazole-fused pyrazinopyridazindione tricycles by a 'click and activate' approach in a four components, stepwise condensation. In the critical step of this process, the Cu(I) catalyzed [3+2] triazole formation not only activates the neighboring group for the subsequent nucleophilic aromatic substitution, but it also anchors an ester group at the desired location for spontaneous cyclization with the nucleophile to finish the tricyclic framework. As a result, a total of five new bonds and two new rings are formed in a highly organized fashion in one pot (Scheme 21) [63].

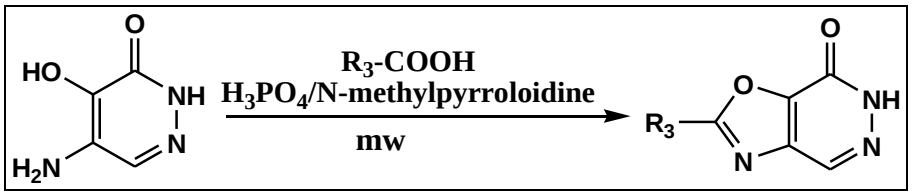


Scheme 21: Synthesis of [1,2,3]triazole-fused pyrazinopyridazindione tricycles by a 'click and activate' approach

A convenient and versatile synthetic approach to 1,3-oxazolo[4,5-d]pyridazine-2(3H),7(6H)-diones **(**Scheme 22**)** and 1,3-oxazolo[4,5-d]pyridazine-7(6H)-ones **(**Scheme 23**)** is developed [64]. The oxazole ring was formed upon reaction of 5-amino-4-hydroxy-3(2H)-pyridazinone with various carboxylic acid derivatives using a microwave-assisted procedure, which favors the reaction time and purity of the resulting products.

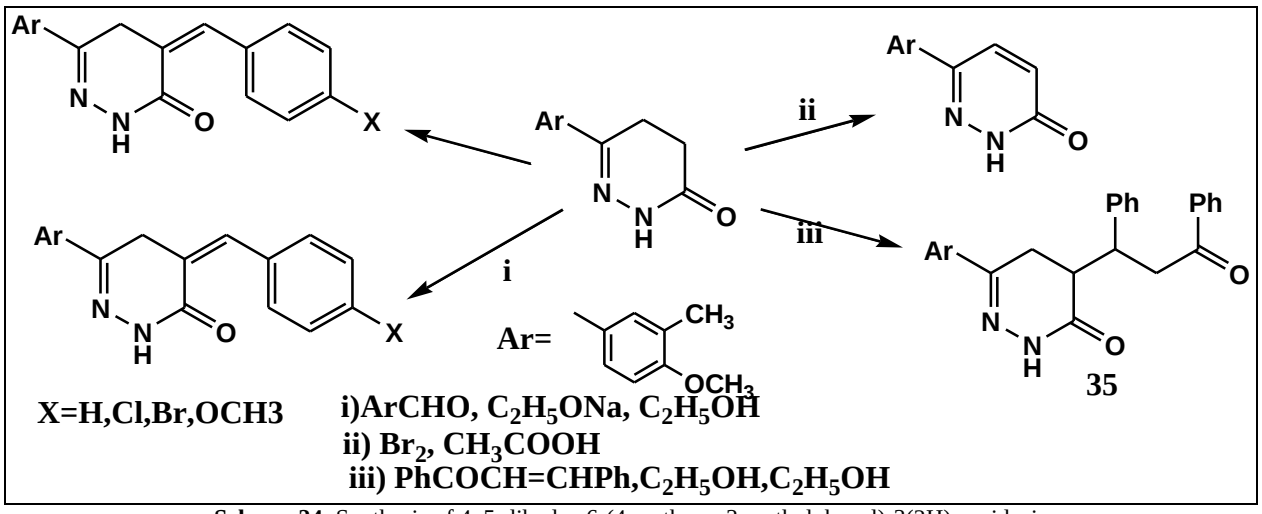


Scheme 22: Synthesis of 1,3-oxazolo[4,5-d]pyridazine-2(3H),7(6H)-diones



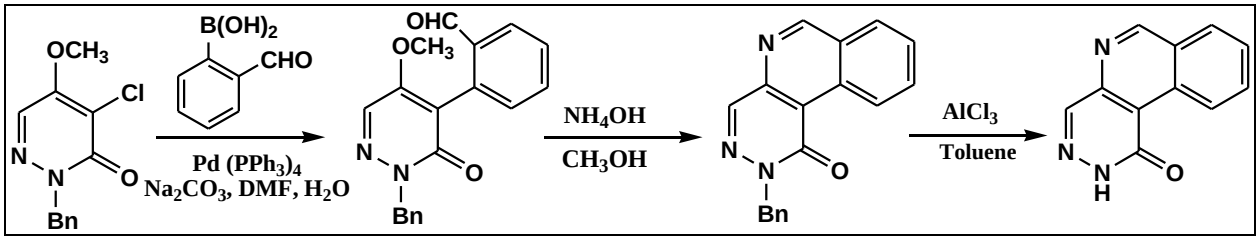
Scheme 23: Synthesis of 1,3-oxazolo[4,5-d]pyridazine-7(6H)-ones

Additionally, the synthesis of 4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone derivatives. The synthesis of the first target compound, 4,5-dihydro-6-(4-methoxy-3 methylphenyl)-3(2H)-pyridazinone, was achieved by Friedel-Crafts acylation of o-cresyl methyl ether with succinic anhydride and subsequent cyclization of the intermediary g-keto acid with hydrazine hydrate. The Condensation of compound with aromatic aldehydes in the presence of sodium ethoxide affords the corresponding 4-substituted benzyl pyridazinones, which are the tautomers of 4-arylidene derivatives. Pyridazine has been synthesized upon the reaction of pyridazinone with 1,3-diphenyl-2-propen-1-one under the Michael addition reaction [65].



Scheme 24: Synthesis of 4, 5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinones

The palladium-catalyzed cross-coupling reactions of halopyridazin-3(2H)-ones is a highly effective method for introducing different substituents in to the pyridazinone core. For example, the pyridazino[4,5-*c*]isoquiniolinone were prepared [66] through the cyclization of the biaryl Suzuki-Miyaura coupling products from the reaction of 2-benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one with 2-formylphenylboronic acid afforded the corresponding biaryl products which were cyclized with ammonia. Removal of the *N*-benzyl protective group in position 2 yielded the unsubstituted tricyclic pyridazinones (Schemes 24 and 25) [67].



Scheme 25: Synthesis of pyridazino[4,5-c]isoquiniolinone by Suzuki cross-coupling reaction

DISCUSSION

Pyridazinone derivatives have attracted the attention of medicinal chemists during the last decade due to their diverse pharmacological activities. Easy functionalization of various ring positions of pyridazinones makes them an attractive synthetic building block for designing and synthesis of new drugs. The incorporation of this versatile biologically accepted pharmacophore in established medicinally active molecules results in wide range of pharmacological effects. Pyridazinones constitute an interesting group of compounds, many of which possess wide spread pharmacological properties such as antihypertensive, platelet aggregation inhibitory, cardiotonic activities and some are also well known for their pronounced analgesic, anti-inflammatory, antinociceptive, and antiulcer activities. Recently pyridazinones have also been reported as antidiabetic, anticonvulsant, antiasthmatic, and antimicrobial agents. These encouraging reports suggest that this privileged skeleton should be extensively studied for the therapeutic benefits. Several illustrations of biological activity studies by groups of different researchers in organic scaffolds are based on the piperazine ring systems [68-80]. The effects of substitutions on piperazine nitrogen atom either by aliphatic, aromatic or heteroaromatic systems are leading to various biological activities against different microorganisms or cells, viral enzymes, and receptors. From the set

of examples, which we came across, few piperazine congeners were screened out as the most effective molecules delivering immense activity in each of the target studies. Upon varying or substituting electron-withdrawing or electron-releasing functional groups directly to the nitrogen atom of piperazine ring or on the phenyl/benzyl ring attached to the piperazine nitrogen atom, the respective biological action was found to vary in almost all cases. After careful study of numerous examples in terms of targeted molecular designs, one may have the idea to structure further classes of featured molecules, leading to an innovative drug discovery. Inspiring by the previous studies, we are intended to synthesize certain heterocyclic based piperazine derivatives which are having biologically importance using the concept of molecular hybridization. Although there are many known, effective biologically active agents for various human diseases, there is still need to improve the already used ones and also search for the new and more effective drugs. The various substitutions were chosen in order to identify the possible structure-activity relationships [81-84]. The various compounds synthesized in this way are subjected to screened for their biological activity.

CONCLUSION

The chemistry of pyridazine derivatives is of significant current interest, particularly to pharmaceutical and materials chemists who require the efficient synthesis of a diverse range of heteroaromatic derivatives for screening programmes. The pyridazine ring system is most readily assembled by the condensation of a 1,4-dicarbonyl compound with hydrazine. This article will focus on the polyfunctional pyridazine derivatives. Pyridazinone has proven to be an excellent scaffold for the synthesis of functionalised pyridazinones. Various pyridazinone derivatives have shown diverse biological activities. Most of the work on pyridazinone is focused on cardiovascular activities and as a result various pyridazinones have reached various phases of clinical trials as cardiotonic and vasodialator agents. The pyridazinones as a lead structure and as a part of central scaffold have diverse biological potential. Pyridazinone have a great potential to be disclosed till date. Pyridazinones drew attention because of their easy functionalization at various ring positions, which makes them attractive synthetic building blocks for designing and development of new pyridazine as biologically active agents. The biological profile of these new pyridazinones presents much progress with regards to the old compounds. From the plethora of pharmacological activities exhibited, pyridazinone ring derivatives serve as potential targets for further drug development.

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