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Review Article

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Pyridazin-3(*2H*)-ones: Synthesis, reactivity, applications in pharmacology and agriculture

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ABSTRACT

Pyridazinone derivatives constitute an important class of heterocyclic in drug discovery. The interesting groups of this compound have diverse biological activities such as antibacterial, antifungal, anti-inflammatory, anticancer, anti-tubercular, antihypertensive and analgesic activities. Interestingly, It also shows insecticide and herbicide activity. In the present review, our main interest is to emphasize the various synthetic molecules of pyridazinone analogs along with their pharmacological significance which is also presented.

Keywords: Pyridazinone, heterocyclic, biological activities

INTRODUCTION

Over the past decades, the bulk of chemists' interests have been on heterocyclic compounds and their various derivatives as well as their applications in the pharmaceutical and chemical fields. Research concerning many kinds of heterocyclic compounds, such as, tetrahydroquinolines [1], benzotriazole [2], diazepine [3], pyridazine [4], thiazole [5], pyrazole [6], pyrimidine [7, 8], has been the subject of numerous recent studies. During recent years, pyridazinones have been a subject of intensive research owing to their wide spectrum of pharmacological activities like antibacterial [9], antifungal [10], anti-HIV [11], anticancer [12], analgesic & anti-inflammatory [13-15], anticonvulsant [16], cardiotonic [17], antihypertensive [18, 19], and antiulcer activities [20]. A substantial number of pyridazinones have been reported to possess a wide variety of agrochemical such as insecticide, acaricide [21-23] and herbicide activities [24, 25].

This review covers updated information in the synthesis and reactivity of pyridazinones and their derivatives. It also shows important properties, applications in pharmacological and agrochemical fields.

- **Physicochemical properties**

Pyridazin-3(2H)-one **(Figure 1)** refers to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a six-membered ring structure composed of four carbon atoms, one oxygen atom and two nitrogen atoms in adjacent positions.

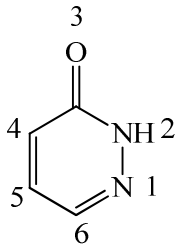
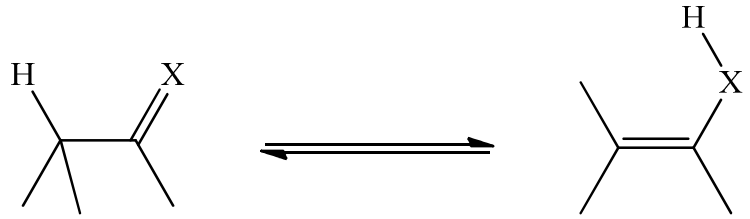


Figure 1: Numbering of the pyridazin-3(2H)-one ring system

Molecular Formula	$C_4H_4N_2O$
Molecular Weight	96.09 g/mol
Melting Point	98-104 °C
Boiling Point	101 °C (lit.) at 1.5 mmHg
Appearance	Solid

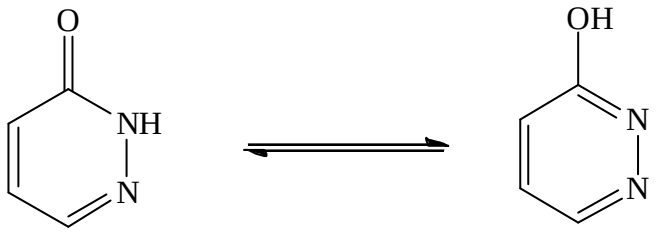
- **Tautomerism of pyridazinone**

The concept of tautomerizations is called tautomerism, which results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and its adjacent double bond **(Scheme 1)** [26-28].



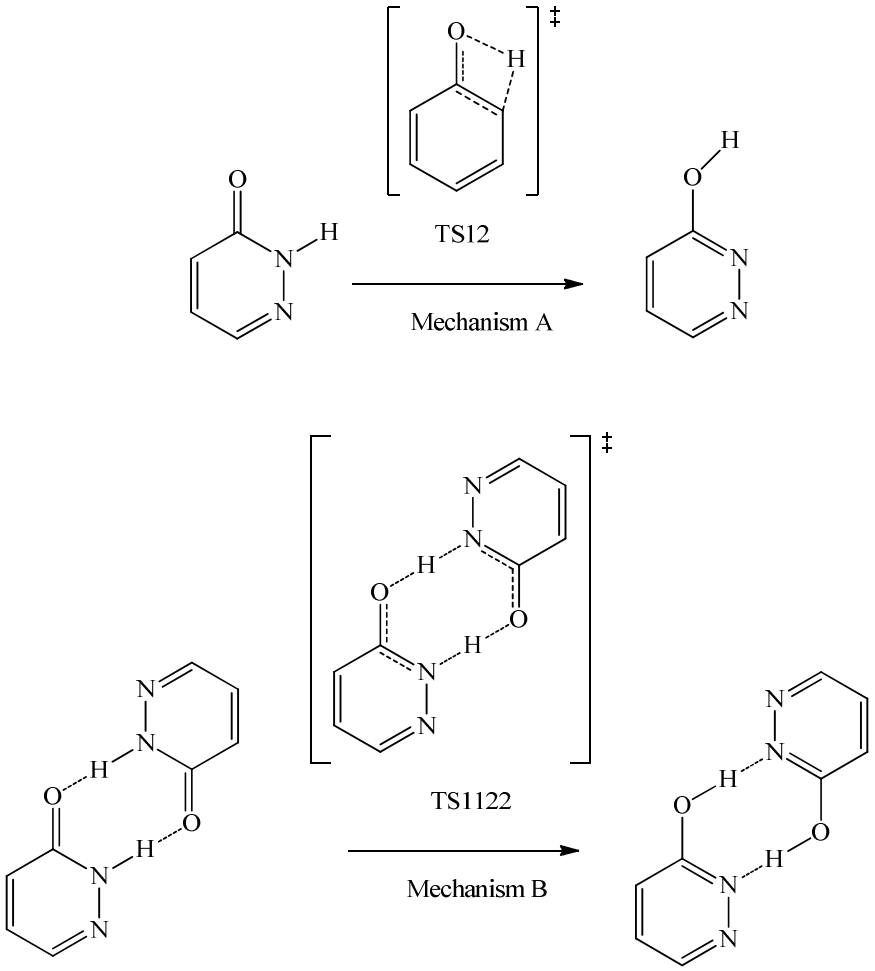
Scheme 1: Tautomerism

Saeed Reza Emamian et al. [29] reported a theoretical study of the solvent effects on the tautomerization process of the simplest **pyridazinone 1** into **pyridazol 2**, using DFT methods at the B3LYP/6-311++G** level of theory **(Scheme 2)**. In the gas phase two mechanisms for the hydrogen transfer have been investigated. Two of them were taken into consideration in this process: **(i)** one in which the hydrogen is directly transferred from the nitrogen to the oxygen atom through the synchronous **TS12** (transition state12); and **(ii)** another one in which a double hydrogen transfer takes place via **TS1122** (transition state1122) upon formation of the corresponding dimer **(Scheme 3)**. The former requires a very high activation energy of 42.64 kcal/mol as a consequence of the strain associated with the formation of the four-membered **TS12**, while the latter requires a much lower activation energy, 14.66 kcal/mol. A combined explicit and implicit solvation model, for protic and aprotic polar solvents, is used in order to analyze the solvent effects on the tautomerization. This study allows the establishment of the requirement to use protic polar solvents in order to reduce the high activation energy associated with TS12.



Pyridazin-3(2H)-one (1) **Pyridazin-3-ol (2)**

Scheme 2: The tautomeric equilibrium investigated in this work

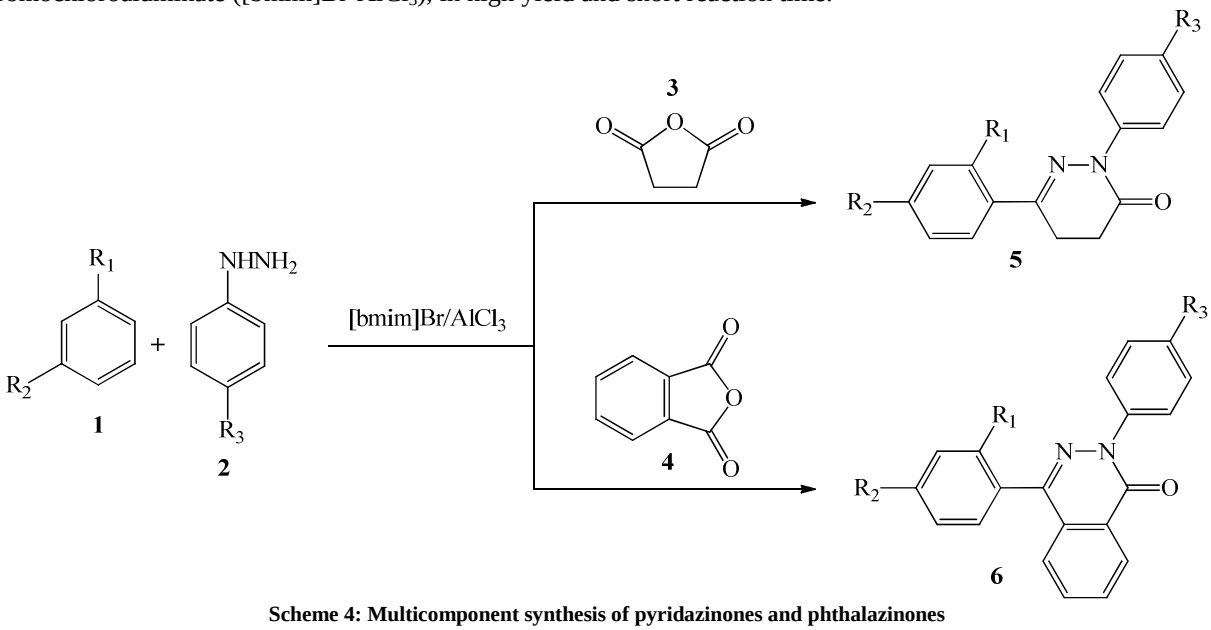


Scheme 3: Direct hydrogen transfer (mechanism A) and indirect hydrogen transfer (mechanism B) are involved in the gas phase tautomerization of pyridazinone 1 into pyridazol 2

A. SYNTHESIS AND REACTIVITY OF PYRIDAZIN-3(2H)-ONE

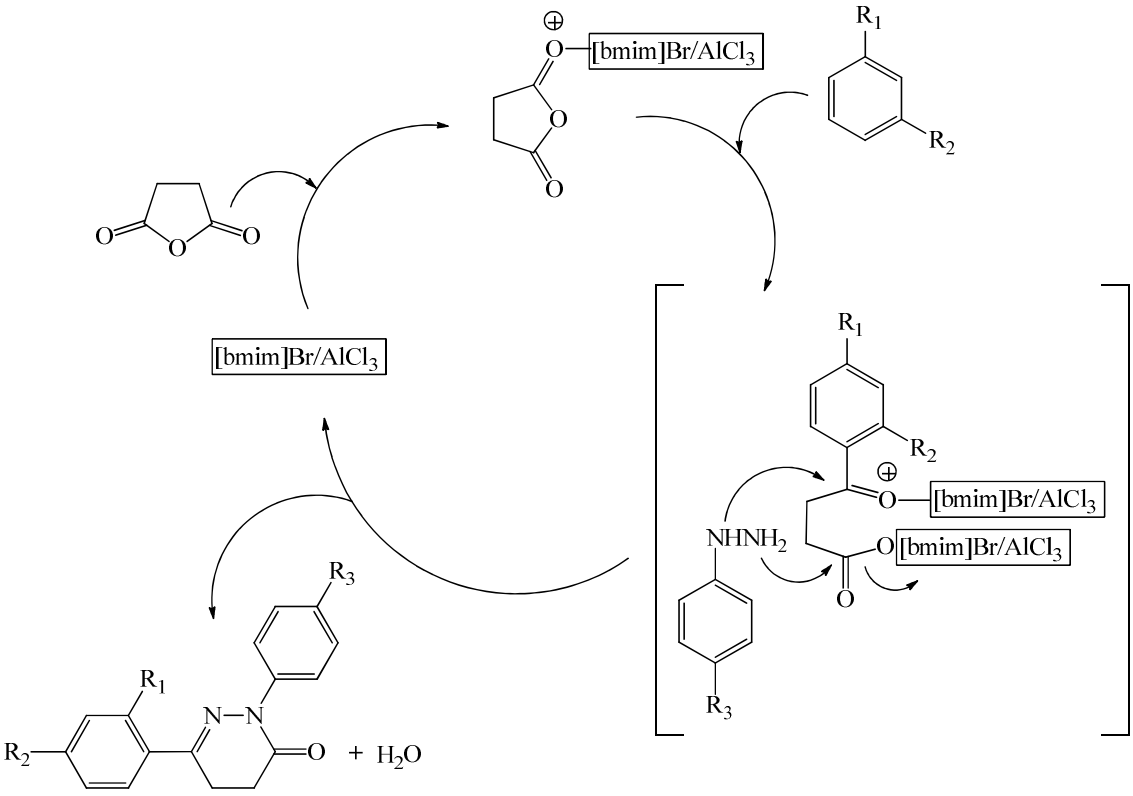
1. Synthesis of pyridazin-3(2H)-one

Several methods have been used for the synthesis of pyridazinone. Leila Zare et al. [30] reported the first ultrasound-promoted multicomponent synthesis of pyridazinones **5** and phthalazinones **6** from arenes **1**, cyclic anhydrides **3**, **4** and $ArNHNH_2$ **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.

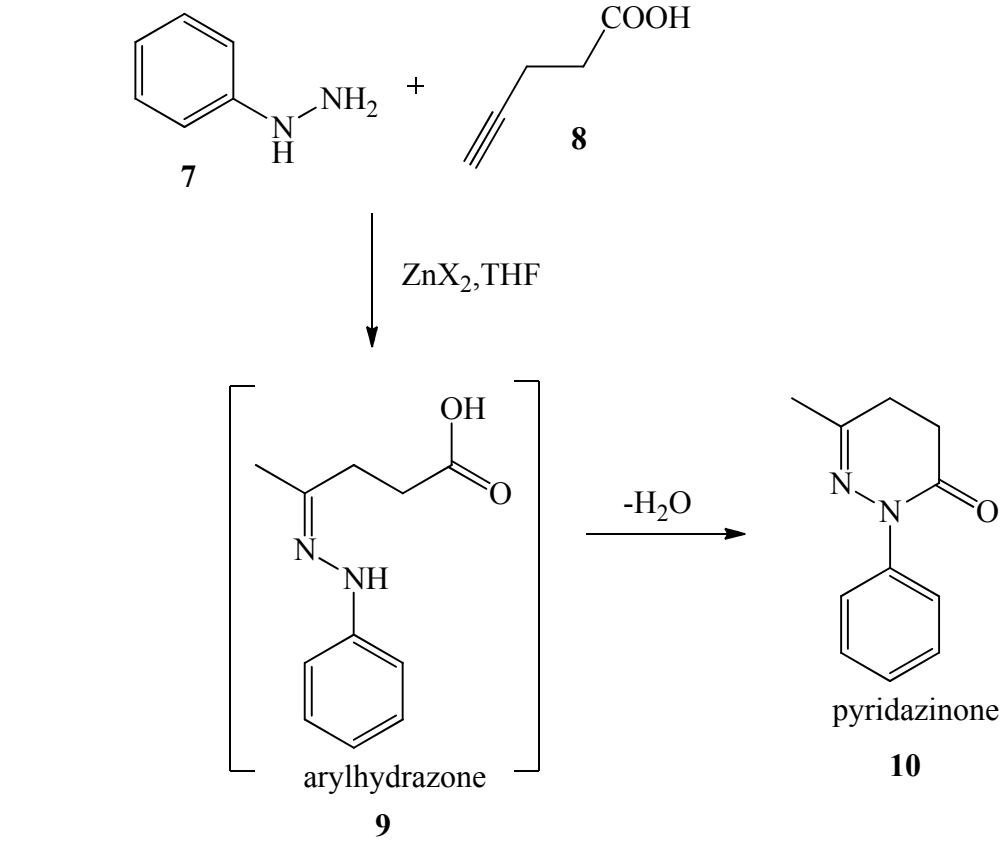


Scheme 4: Multicomponent synthesis of pyridazinones and phthalazinones

The mechanism of reaction [30] 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 5)**. For these reasons, the [bmim]Br/AlCl3 use as a catalyst, because of its environmental compatibility, reusability, operational simplicity, no toxicity, non-corrosiveness, low cost and ease of isolation.



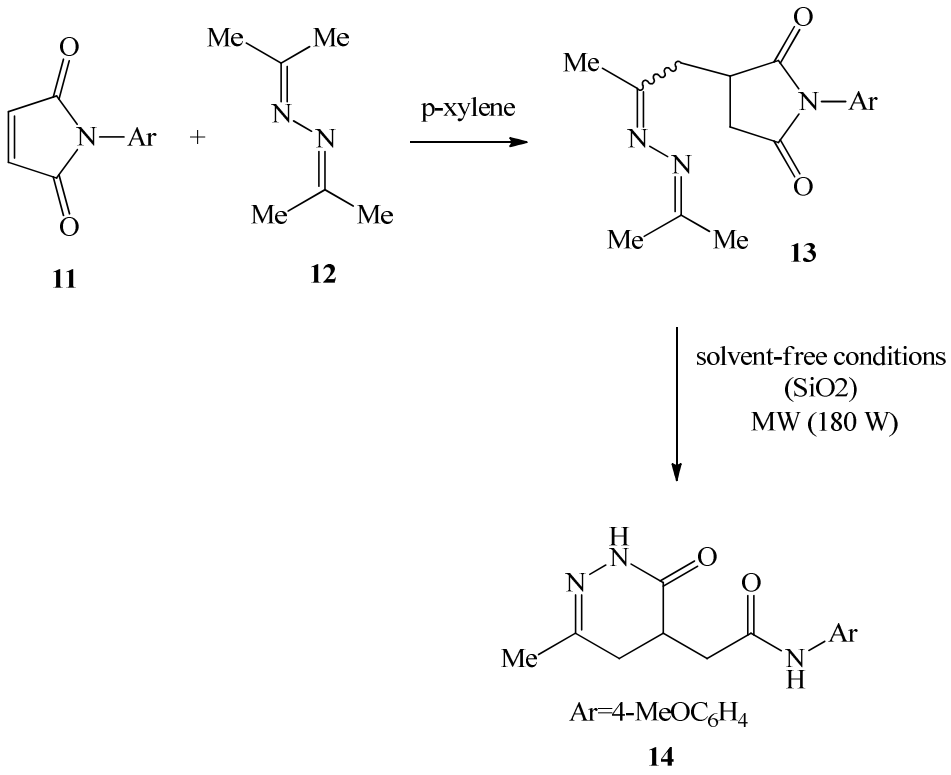
Scheme 5: Proposed mechanism for the multicomponent synthesis of pyridazinones and phthalazinones



Scheme 6 : Synthesis of pyridazinone

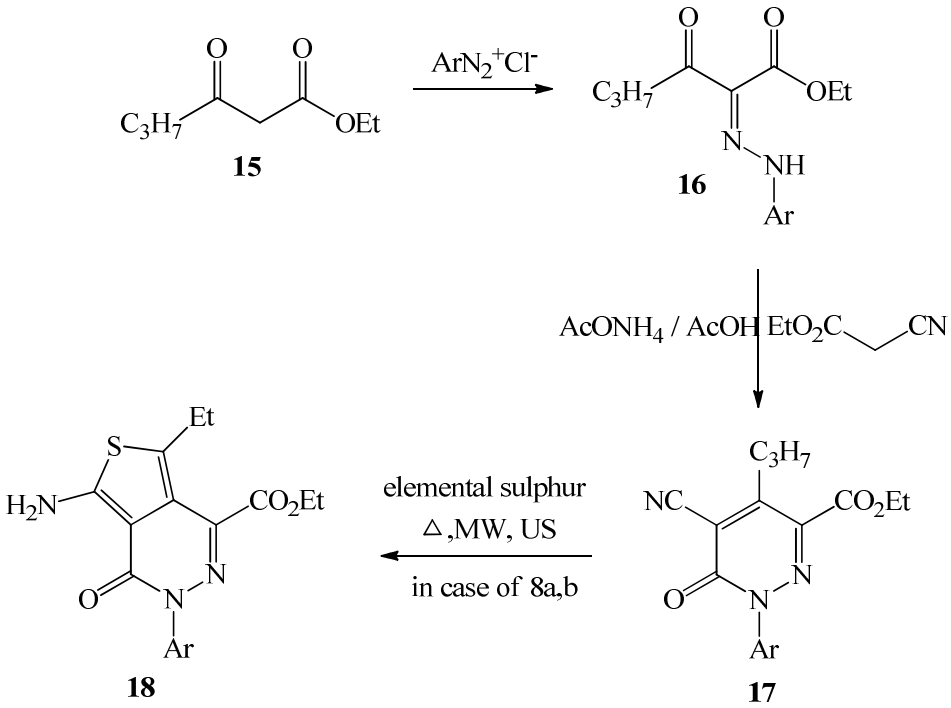
In addition, Karolin AlexIn et al. [31] have developed a novel method for the synthesis of 6-methyl-2-phenyl-4,5-dihydropyridazin-3(2H)-one **10** based on domino hydrohydrazination and condensation reactions. Phenylhydrazine **7** react with 4-pentynoic acid **8** in the presence of 1 equiv $ZnCl_2$ to give the corresponding pyridazinone in a one-pot process in moderate to good yields.

In this study, Alexander V. Stepakov et al. [32] demonstrated a new approach to the synthesis of 4-(N-aryl)carbamoylmethyl-4,5-dihydropyridazin-3(2H)-ones **14** by reaction of N-aryl substituted maleimide **11** with azines **12**. In some cases, Michael addition intermediates **13** 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.



11 **12** **13** **14**

Scheme 7: Synthesis of 4,5-dihydropyridazin-3(2H)-ones

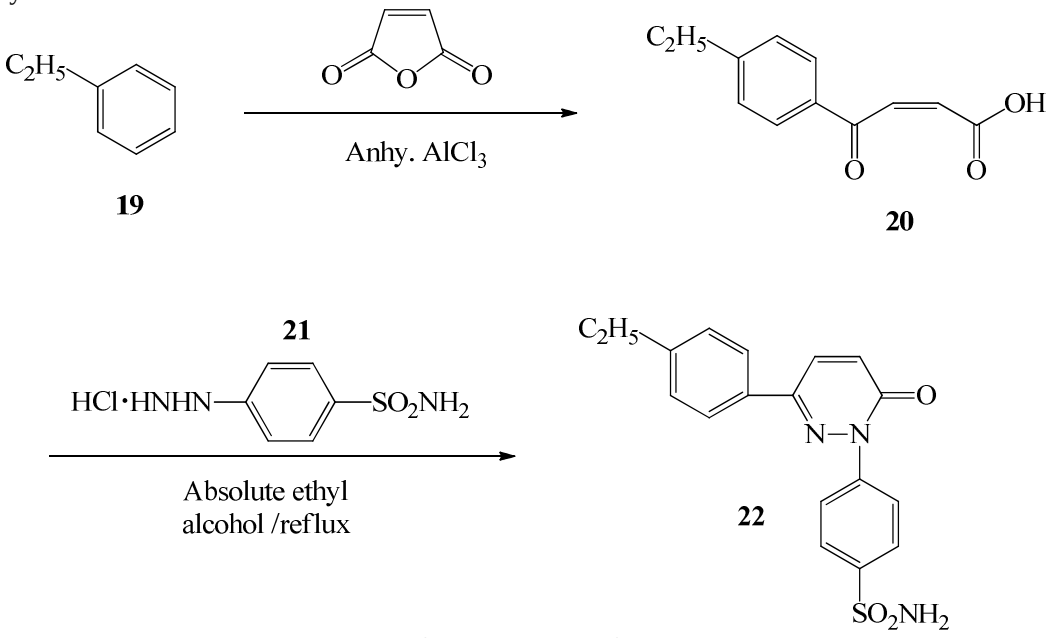


15 **16** **17** **18**

Scheme 8: Synthesis of thieno[3,4-d]pyridazinones

In 2010, A novel environmentally benign methodology for the synthesis of thieno[3,4-d]pyridazinones **18** has been developed by Khadijah M. Al-Zaydi [33], avoiding volatile and toxic organic solvents. This neat reaction under both microwave and ultrasound irradiations gave excellent yield of products with lesser reaction time.

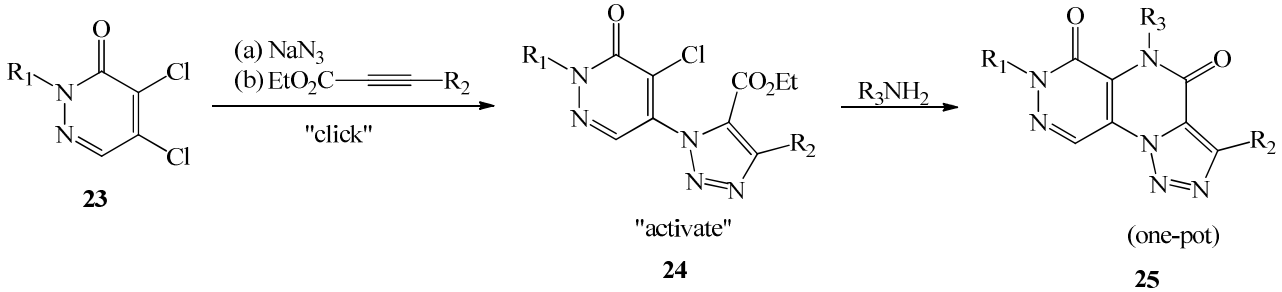
Additionally, I.G. Rathish et al. [34] synthesized a series of novel pyridazinone derivatives bearing benzenesulfonamide moiety **22** by the condensation of appropriate aroylacrylic acid **20** and 4-hydrazinobenzenesulfonamide hydrochloride **21** in ethanol in 9.1-16.2% yield. The b-aroylacrylic acids **20** were obtained by a Friedel Craft's acylation through reported methods [35, 36]. The purity of the compounds was checked by TLC.



Scheme 9: Synthesis of 6-aryl-2-benzenesulfonamide-pyridazinones

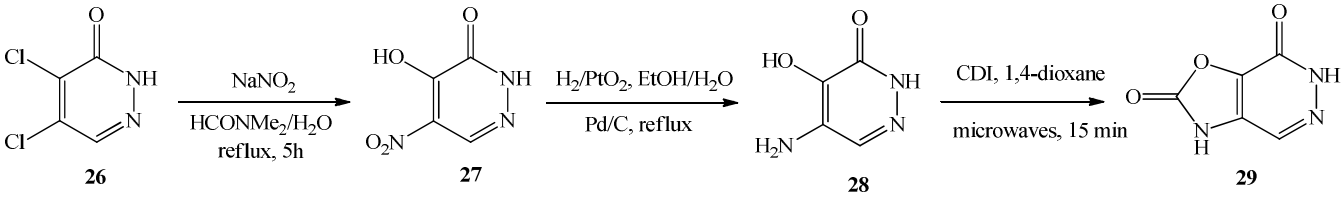
2. Reactivity of pyridazin-3(2H)-ones

Recently, Wenyuan Qian et al. [37] reported the preparation of substituted [1,2,3]triazole-fused pyrazinopyridazindione tricycles **25** 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 **24** 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 **25** framework. As a result, a total of five new bonds and two new rings are formed in a highly organized fashion in one pot.

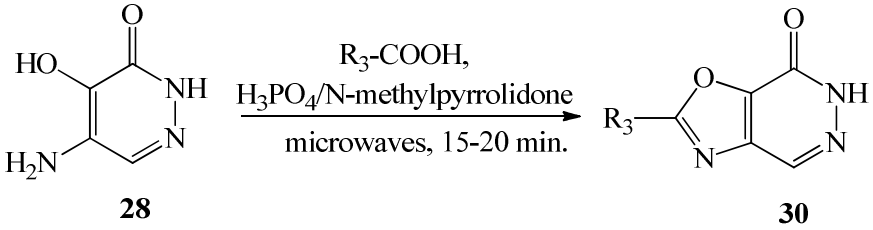


Scheme 10: synthesis of [1,2,3]triazole-fused pyrazinopyridazindione tricycles by a 'click and activate' approach

In 2004, a convenient and versatile synthetic approach to novel 1,3-oxazolo[4,5-d]pyridazine-2(3H),7(6H)-diones **29 (schema 11)** and 1,3-oxazolo[4,5-d]pyridazine-7(6H)-ones **30 (schema 12)** is developed by Eugene B. Frolov. et al. [38] The oxazole ring was formed upon reaction of 5-amino-4-hydroxy-3(2H)-pyridazinone **28** with various carboxylic acid derivatives using a microwave-assisted procedure, which favors the reaction time and purity of the resulting products.

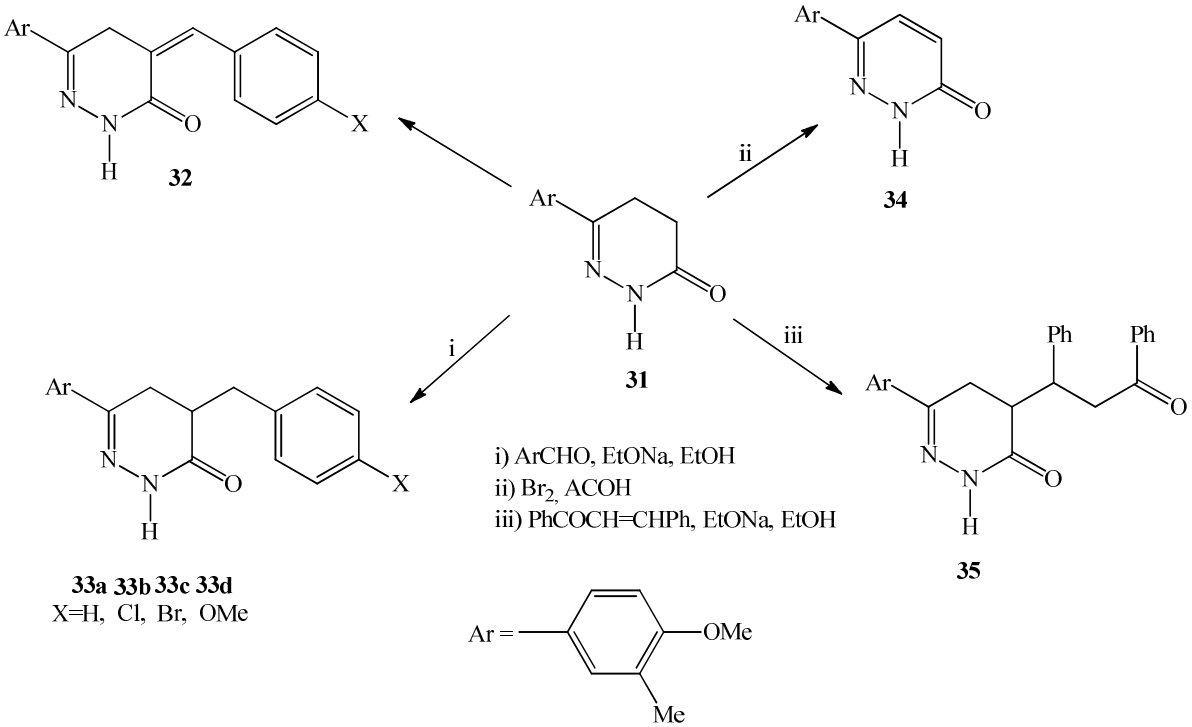


Scheme 11: Synthesis of 1,3-oxazolo[4,5-d]pyridazine-2(3H),7(6H)-diones



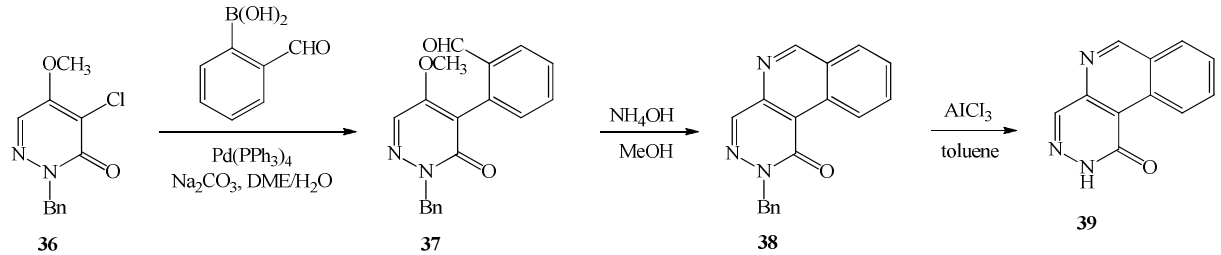
Scheme 12: Synthesis of 1,3-oxazolo[4,5-d]pyridazine-7(6H)-ones

Additionally, Soliman's group [39] reported 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 **31**, 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 **31** with aromatic aldehydes in the presence of sodium ethoxide affords the corresponding 4-substituted benzyl pyridazinones **33a-d**, which are the tautomers of 4-arylidene derivatives **32a-d**. The dihydropyridazinone **31** underwent dehydrogenation upon treatment with bromine/acetic acid mixture to give **34**. Pyridazine **35** has been synthesized upon the reaction of pyridazinone **31** with 1,3-diphenyl-2-propen-1-one under the Michael addition reaction.



Scheme 13: Synthesis of 4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone derivatives

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 **39** were prepared by Zsuzsanna Riedl et al. [40] through the cyclization of the biaryl Suzuki-Miyaura coupling products from the reaction of 2-benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one **36** with 2-formylphenylboronic acid afforded the corresponding biaryl products **37** which were cyclized with ammonia. Removal of the *N*-benzyl protective group in position 2 yielded the unsubstituted tricyclic pyridazinones **39**.



36 **37** **38** **39**

Scheme 14: Synthesis of pyridazino[4,5-*c*]isoquiniolinone by Suzuki cross-coupling reaction

B. APPLICATION OF PYRIDAZINONE

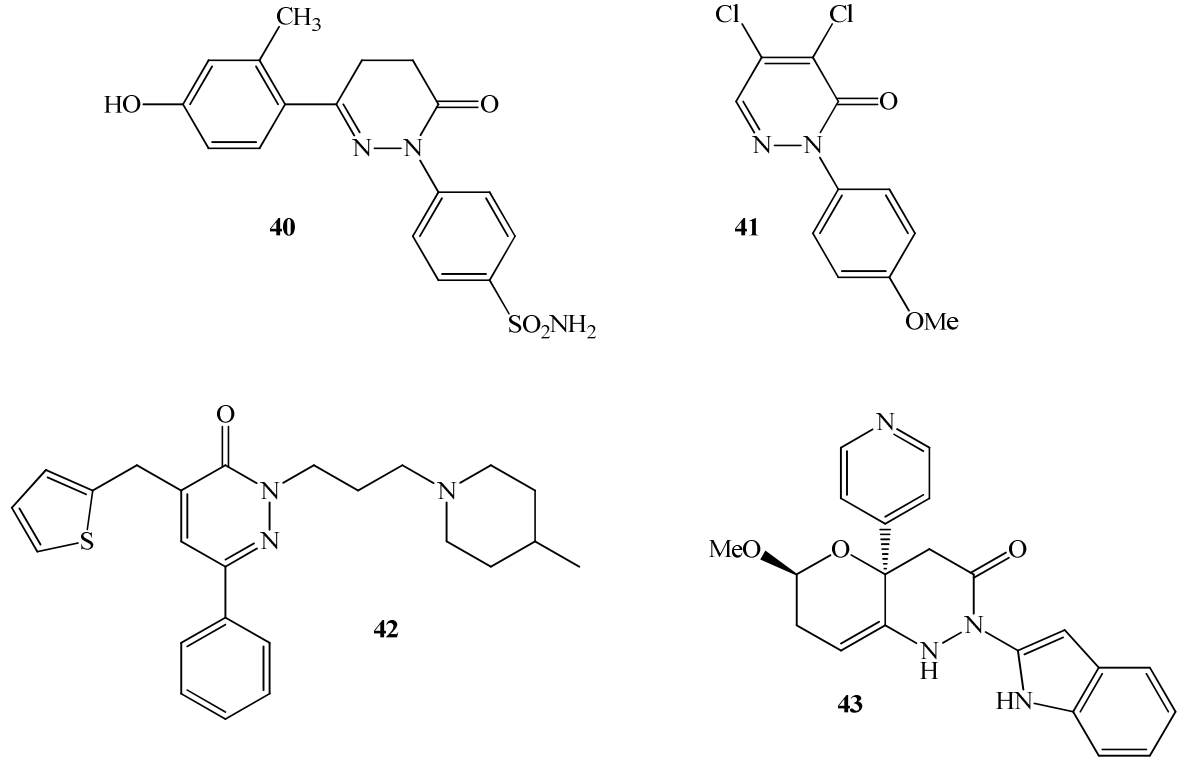
Multiple properties of pyridazinone derivatives have been well documented for decades, and their attachments with other heterocycles or metal ions often ameliorate the performances depending on the type of substituent and position of attachments. For its versatility, pyridazinone is broadly applied in pharmaceutical and agricultural; herein, we introduce them separately.

1. Applications in Pharmaceutical Chemistry

A large number of pyridazinone and its derivatives have been reported to possess diverse pharmacological properties such as antiviral, antiparasitic, antitubercular, anticonvulsant, analgesic, and antisecretory activities. Moreover, much interest has also been focused on the antibiotic (including antibacterial and antifungal), antiinflammatory, and anticancer activities displayed by compounds incorporating other heterocyclic systems. Due to the different activities pyridazinone possess, we classify them as follows:

- **Anticancer Activity**

There are numerous reports available in the literature, which indicate the potential anticancer effects of pyridazinones **(figure 2)**.



40 **41** **42** **43**

Figure 2: Structures of various pyridazinones exhibiting anticancer Activity

Shamim Ahmad et al. [41] synthesized a series of 6-(4-Hydroxy-2-Methylphenyl)-2-(p-sulfamylphenyl)-4,5-dihydropyridazine-3(2H)-one by condensation of the appropriate β-aroylpropionic acid and 4-hydrazinobenzenesulfonamide hydrochloride in ethanol and tested for anti-cancer, anti-inflammatory, and antimicrobial actions. Compound **40** showed high activity against HL-60 (TB) (leukemia), SR (leukemia), NCI-H522 (non-small-cell lung cancer), and BT-549 (breast cancer) with a GI50 value of less than 2 μM. In addition, the p-methoxydichloropyridazone **41** [42] displayed a good inhibition of tumour growth in mice for the resistant MAC 16 cell line. Additionally, Murty's group [43] synthesized a series of new pyridazin-3(2H)-one derivatives. All the compounds were evaluated for their cytotoxicity toward five human cancer cell lines of different origins viz HeLa

(Cervical), SKBR3 (Breast), HCT116 (Colon), A375 (Skin) & H1299 (Lung). The compounds **42** exhibited good to moderate activity. In 2010, Taleb H. et al. [44] reported the development of a novel tetrahydro-2H-Pyrano[3,2-c]Pyridazin-3(6H)-one. The compound **43** showed a good antiproliferative activity against the SK-BR-3 breast cancer cell line.

- **Anti-inflammatory, analgesic and antinociceptive activities**

Great attention has been paid to the compounds containing a pyridazin-3(2H)-one moiety, due to their potential biological activities as anti-inflammatory, analgesic and antinociceptive agents **(figure 3)**.

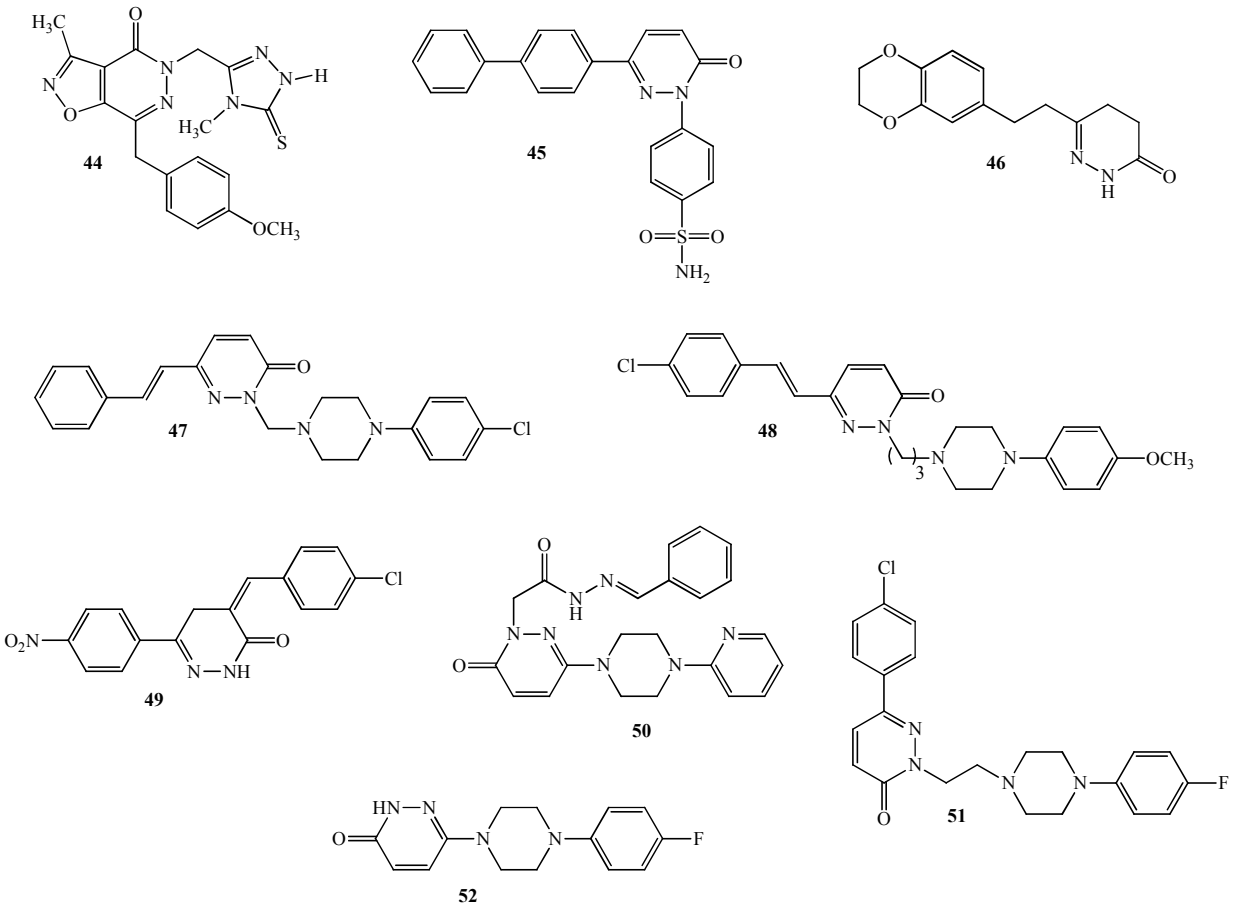


Figure 3: Structures of various pyridazinones bearing analgesic, anti-inflammatory and antinociceptives activities

In this study, eighteen new isoxazolo[4,5-d]pyridazin-4(5H)-one derivatives [45] were synthesized and tested for anti-inflammatory activity in vitro (COX-1/COX-2, 5-LOX) and in vivo (rat paw edema assay). The most potent compound **44** exhibited the best anti-inflammatory profile by inhibiting. In addition to that, the 6-(4′-Phenylphenyl)-2-(4-sulfamoylphenyl)-4,5-dihydropyridazin-3(2H)-one **45** [46] were prepared and evaluated for their anti-inflammatory activity in carrageenan-induced rat paw edema model. This compound **45** exhibited anti-inflammatory activity comparable to that of celecoxib (at 5 h). In another study, Compound **46** demonsstrated the greatest in vivo activity with ED50 equal to 17 µmol compared with celecoxib with no ulceration on the gastric mucosa [47]. M. M. Saeed et al. [48] synthesized several series of pyridazine and pyridazinone derivatives and tested, in vivo, for their anti-inflammatory and ulcerogenic properties against indomethacin, as a reference compound. Compounds **47** and **48** have shown a potent anti-inflammatory activity more than indomethacin with rapid onset of action and safe gastric profile. In the MTT assay in vitro, both compounds were identified as potent and selective COX-2 inhibitors. In 2012, Mohammad Asif [49] synthesized a series of 6-(m-Nitrophenyl)-4-sustituted benzylidene-4,5-dihydropyridazin-3(2H)-Ones. This compound **49** showed significant analgesic activity when compare to control group and were found less potent than reference drug aspirin. Same 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted benzal)hydrazone derivatives have been synthesized and evaluated for analgesic and anti-inflammatory activities by Gokce et al. [50] as analgesic and anti-inflammatory. The structures of compounds were elucidated by spectral and elemental analysis. The Compound **50** showed good analgesic activity than acetylsalicylic acid (ASA). Also these derivatives demonstrated anti-inflammatory activity as well as standard compound indomethacin. Side effects of the compounds were examined on gastric mucosa. None of the compounds showed gastric ulcerogenic effect compared with reference nonsteroidal anti-inflammatory drugs (NSAIDs). Recently, Tiryaki et al. [13]

reported the synthesis and pharmacological evaluation of 2,6-disubstituted-3(2H) pyridazinone derivatives. The compound **51** showed the best analgesic and anti-inflammatory activities without causing any gastric effect in stomachs of tested animals. A series of 3-pyridazinones carrying morpholino, arylpiperidino and arylpiperazino moiety in the position 6 [51] were synthesized and evaluated for antinociceptive activity. In the modified Koster test in mice 4-(4-fluorophenyl) piperazine **52** was found the most active compound than aspirin in the antinociceptive activity test. In another study, Deniz S. Dogruer et al. [52] report the synthesis of a novel series. All the compounds (at 100 mg/kg dose) have been found more potent than aspirin.

- **Antihypertensive activity**

Many research groups have been interested in 3(2H)-pyridazinones for the development of potential antihypertensive agents.

6-(4-Ethylphenyl)-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one [53] were synthesized in order to determine their antihypertensive properties by non-invasive method using Tail Cuff method. The compound **53** showed good antihypertensive activity. A number of 6-(substituted phenyl)-2-(4-substituted phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2H)-one derivatives [54] were synthesized and evaluated for antihypertensive activities by non-invasive method using Tail Cuff method. The compound **54** showed appreciable antihypertensive activity comparable with that of standard hydralazine and propranolol.

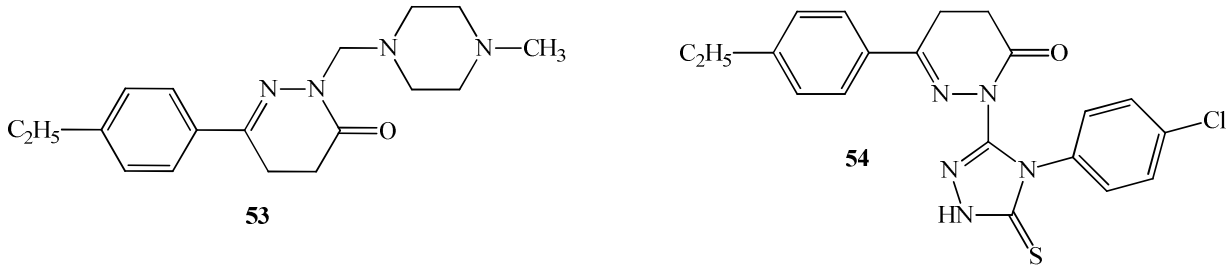


Figure 4 : Pyridazinones as antihypertenseur agents

- **Antimicrobial activity**

Recently, Didem Tiryaki et al. [13] synthesized of some new 2,6-disubstituted-3(2H)-pyridazinone derivatives and screened for their antibacterial and antifungal activities against some pathogenic strains. These compounds might be relatively good candidates to develop better antifungal agents against C. albicans and C. krusei. In addition, some 6-(4-Chlorobenzoyl)-2-substituted-3-oxo-2,3-dihydropyridazine-4-carboxylic acid ethyl ester derivatives [55] were synthesized and evaluated for antimicrobial activity. The compound **55** were found to exhibit strong inhibitory effects on the growth of Gram-positive bacteria especially *Bacillus subtilis*, comparable to ampicillin, which was used as the reference compound.

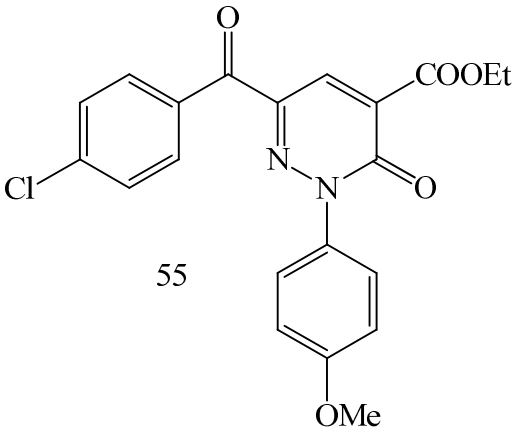


Figure 5: Pyridazinones as antimicrobial agents

The new various metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2H-pyridazin 3-one were synthesized. All the complexes were evaluated for their antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi using microdilution procedure. The **Cd(II)** and **Ni(II)** complexes exhibited selective and effective activities against one Gram-positive bacterium (*Staphylococcus aureus* ATCC 6538), one Gram-negative bacterium (*Pseudomonas putida* ATCC 12633) and against two yeast (*Candida albicans* ATCC 27541 and *Candida tropicalis* 1828) in contrast to poor activity observed other microorganisms [56].

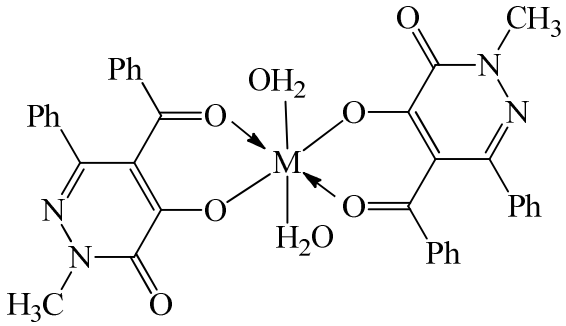


Figure 6: Supposed structure of the M (II) complexes

- **Inhibitors of Hepatitis C virus (HCV) NS5B polymerase**

In this study, 4-(1,1-Dioxo-1,4-dihydro-1λ6-benzo[1,4]thiazin-3-yl)-5-hydroxy-2H-pyridazin-3-one [57] analogs were discovered as a novel class of inhibitors of HCV NS5B polymerase. Structure-based design led to the identification of compound **56** that displayed potent inhibitory activities in biochemical and replicon assays (1b IC50 < 10 nM; 1b EC50 = 1.1 nM) as well as good stability toward human liver microsomes (HLM t1/2 > 60 min).

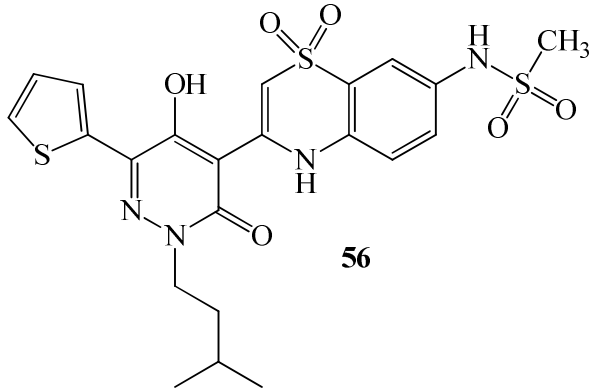


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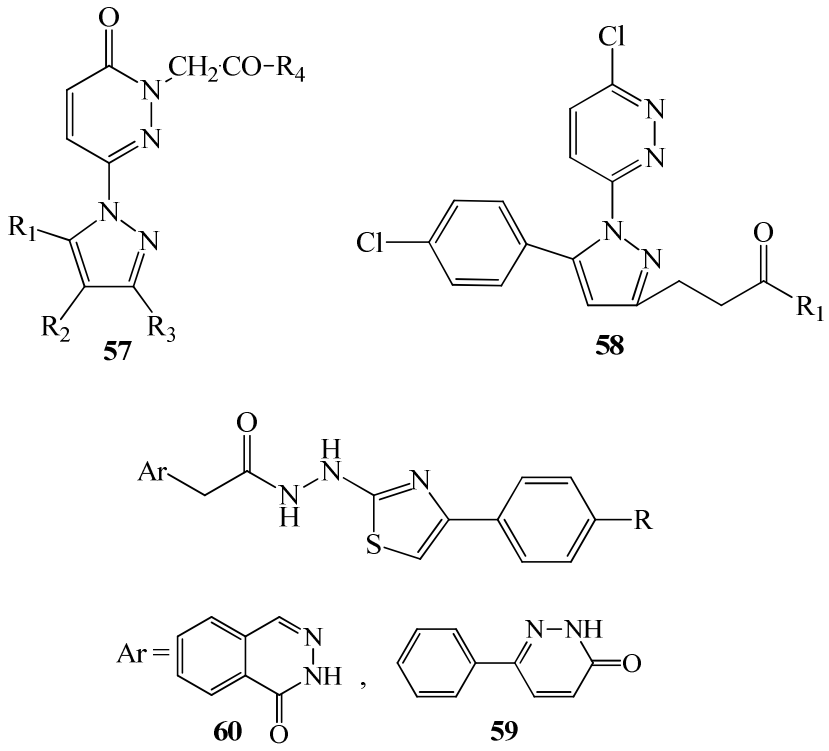
Figure 7: Pyridazinones as HCV NS5B polymerase inhibitors



57 **58** **60** **59**

Figure 8: Pyridazinones as antioxidants agents

- **Antioxidant Activity**

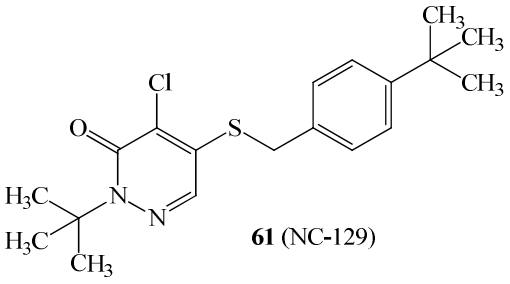
Antioxidants are compounds that can delay, inhibit, or prevent the oxidation of materials that can be oxidized by scavenging free radicals and help in diminishing oxidative stress. Based on these findings a series of 2H-pyridazine-3-one **57** and 6-chloropyridazine **58** [58] analogues was tested in vitro on superoxide formation and effects on lipid peroxidation were determined against α-tocopherol. Most of the compounds have strong inhibitory effect on superoxide anion (between 84% – 99%) at 10^{-3} M concentration. In addition, these compounds showed similar activity to α-tocopherol at 10^{-3} M concentrations. In another study, Cem Yamalı et al. [59] synthesized of some 3(2H)-pyridazinone **59** and 1(2H)-phthalazinone **60** derivatives and tested for antioxidant properties. Almost all the synthesized compounds showed excellent activity with inhibition values in the range of 89.22 ± 0.31–93.29 ± 0.21 %, better than that of reference compound ascorbic acid (31.83 ± 2.01) at 10 µM concentration, particularly in the DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay.

2. Applications in Agromedicine Chemistry

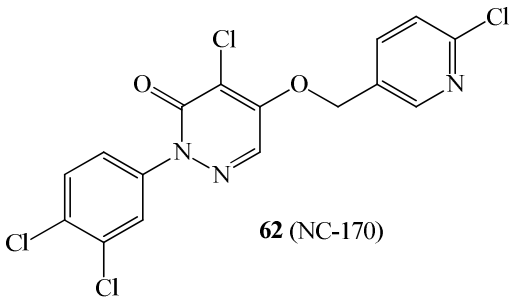
Pyridazinones have been used in numerous applications in the fungal, weed, and insect control sectors of agriculture.

- **Applications as insecticides and acaricides**

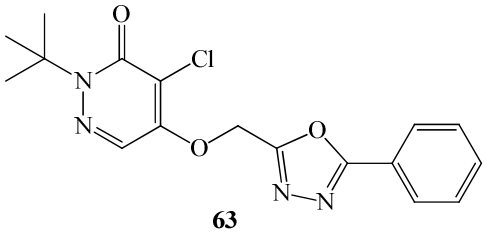
The search for new, specific acaricides, which has been conducted mainly by research-based agrochemical companies, has resulted in a number of compounds providing selective mite control. For example, NC-129 (pyridaben) **61**, a pyridazinone derivative, is a new acaricide and insecticide discovered by Nissan Chemical Industrial, Ltd. Japan, for controlling mites and some insects such as white flies, aphids and thrips [60]. NC-170 **62** is a highly selective juvenoid, and it strongly inhibits metamorphosis in planthopper when topically applied to midpenultimate larvae [61]. In addition, a total of 20 new oxadiazolyl 3(2H)-pyridazinones were synthesized by Song Cao et al. [62]. The bioassay tests show that some compounds exhibited good antifeedant activity on the Asiatic corn borer *Ostrinia furnacalis* (Guenee) compared with commercial azadirachtin. The feeding deterrency of **63** was 57% at 500 mg/kg concentration.



61 (NC-129)



62 (NC-170)



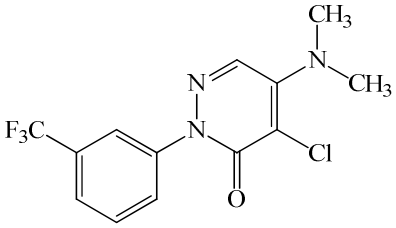
63

Figure 9: Pyridazinones as insecticides and acaricides agents

- **Applications as herbicide**

Bean, G. A. et al. [25] reported the influence of two pyridazinone herbicides 4-chloro-5-(dimethylamino)-2-α,α,α-trifluro-m-tolyl-3(2H)-pyridazinone and 4-chloro-5-(dimethylamino)-2-phenyl-3(2H)-pyridazinone represented by structures **64, 65**, respectively, on aflatoxin production by aspergillus flavus and A. parasiticus. This influence was studied in liquid media. Mycelia production was not affected by 20, 40 or 60 ug of herbicide per ml; however, aflatoxin production by A. parasiticus was higher in media with herbicide, whereas A. flavus produced lower aflatoxin levels. Pyrazon **66** or PCA (amino-5-chloro-4-phenyl-pyridazin-3(2H)-one) appears for several years among the herbicides and a number of publications concerning the behavior of pyrazon in the soil. Smith and Meggitt [63] reported that pyrazon remains the only observable metabolite, this metabolite is also more persistent than the parent compound. These same authors, student movement pyrazon in the field [64], have shown that two months after application of 2.7 kg / ha, 80 to 100% of the herbicide were in the top five centimeters of soil. The study Smith & Meggitt [65] also performed on the adsorption of pyrazon appear that there is a strong correlation (r = 0.9) between the adsorbed amount and the rate of soil organic matter. In a study conducted in comparison with

aldicarb [2-methyl-2-(methylthio) propionaldehyde O-(methyl carbamoyl) oxime] **67** to show pyrazon resisted well to the training by leaching [66].



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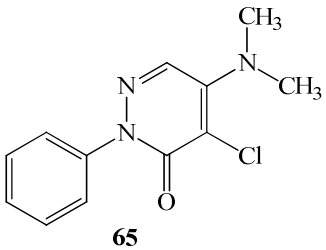
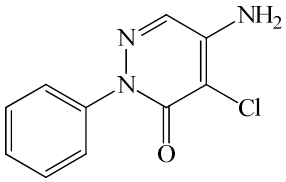
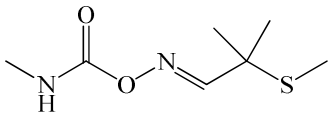


65



66



67

Figure 10: Pyridazinones as herbicides agents

CONCLUSION

Pyridazinones has been a subject of intensive research. This heterocyclic moiety has great biological significance. A vast literature has been accumulated over the years and chemistry of pyridazinone continues to be a blossoming field. The anticancer, anti-inflammatory, analgesic, antinociceptive, antimicrobial and antihypertensive activities are the most encouraging activities for the chemists, pharmacologists and researchers. Ultimately, the research on insecticides, acaricides and herbicides activities has given positive results. In this review, we have investigated the synthesis and biological activity of various pyridazinone derivatives, mainly focusing on the most potent molecules which exhibited the higher biological profile.

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