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A Review on Synthesis and Biological Activities of Magic Moiety: Pyridazinone

A.M. Isah [a], H.B. Bature [a], S. Yahaya [b], I.I. Bandi [c], B. Magaji [d], A.U.Muhammad [e]

[a]: Department of Pure and Environmental Chemistry, Usmanu Danfodiyo University, Sokoto, 888222, Nigeria
[b]: Department of Energy and Applied Chemistry, Usmanu Danfodiyo University Sokoto
[c]: Central Advanced Science Laboratory Complex, Usmanu Danfodiyo University Sokoto
[d]: Department of Pure and Applied Chemistry, Kebbi State University of Science and Technology Alieru
[e]: Department of Chemistry, Shehu Shagari College of Education, Sokoto
Email: abdulalim.muhammad@udusok.edu.ng

ABSTRACT

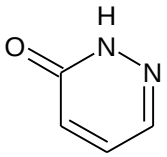
Over the past decades, the bulk of chemists' interests have been on heterocyclic compounds and their various derivatives as well as their applications in the pharmaceutical and chemical fields. Pyridazinones are six-member heterocyclic compounds, containing 2 nitrogen atoms positioned at adjacent sites. Pyridazin-3-one, a saturated or unsaturated form of pyridazine with carbonyl group on third carbon, has been considered as a magic moiety which possesses almost all types of biological activities. In this work; we compiled and discussed the biological applications of pyridazinone and its derivatives in addition to its general synthetic pathway.

Key words: Pyridazinone, Biological activity, synthesis

INTRODUCTION

Over the past decades, the widespread of chemists' interests have been on heterocyclic compounds and their numerous derivatives as well as their applications in the pharmaceutical and chemical fields. Research regarding many kinds of heterocyclic compounds, such as, tetrahydroquinolines (Xu *et* al., 2014), benzotriazole (Li *et al.,* 2012), diazepine (Smith *et al.,* 2014), pyridazine (Abida *et al.,* 2019), thiazole (Sashidhara *et al.,* 2014), pyrimidine (Meisenbach and Allmendinger, 2003 and Pérez-Balado *et al.,* 2007), has been the subject of several topical studies. During recent years, pyridazinones have been a subject of rigorous exploration due to their wide band of pharmacological activities (Youness Boukharsa *et al.,* 2014) and their easy functionalization at ring, which makes them effective compounds for scheming and development of novel pharmacotherapeutic agents (Abida *et al.,* 2019).

Pyridazinones are the derivatives of pyridazine which belong to an important group of heterocyclic compounds (Asif, 2017). Pyridazinones are six-member heterocyclic compounds, containing 2 nitrogen atoms located at adjacent positions. Pyridazin-3-one, a saturated or unsaturated form of pyridazine with carbonyl group on third carbon, has been considered as a wonder nucleus which possesses almost all types of biological activities. The structures of Pyridazinone is given below:



Pyridazinone Akhtar *et al.,* 2016

The synthesis of pyridazinone derivatives and investigation of their chemical and biological activities have increased more prominence in recent years. Pyridazinones show wide band of biological activities in the literature (Asif *et al.,* 2019 and Abida *et al.,* 2019). Considerable number pyridazine and pyridazinone derivatives represent a vital class of biologically active compounds and possess interesting wide band of biological activities as they are established to be as potent inodilators (Kumar *et al.,* 2010; Lee *et al.,* 2010), vasorelaxants (Abouzid *et al.,* 2010; Costas *et al.,* 2010; Guerrero *et al.,* 2008) and potent cardiotonic agents (Amin *et al.,* 2008; Wang *et al.,* 2009; Wang *et al.,* 2008, Husain *et al.,* 2011). They displayed also anticonvulsant (Edith *et al.,* 2009; Sivakumar *et al.,* 2009; Siddiqui *et al.,* 2006), vasodilatory (Demirayak *et al.,* 2009; Bansal *et al.,* 2009), antihypertensive (Siddiqui

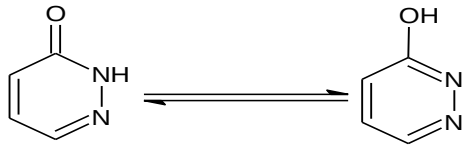
et al., 2002; Ogretir *et al.*, 2002; Vergelli *et al.*, 2007), antimicrobial (Sotelo *et al.*, 2002; Sayed *et al.*, 2002), anti-inflammatory (Gokce *et al.*, 2001; Dogruer *et al.*, 2003; Frolov *et al.*, 2004; Banoglu *et al.*, 2004, Husain *et al.*, 2011), antibacterial, antifungal, antiviral, antitubercular, anti-HIV (Husain *et al.*, 2011), herbicidal (Han *et al.*, 2002), insecticidal and fungicidal (Dang *et al.*, 2020) activities. Some of 6-aryl 3(2H) pyridazinones are well known as potent analgesics (Okcelik *et al.*, 2003, Husain *et al.*, 2011), antiplatelet (Sotelo *et al.*, 2002; Coelho *et al.*, 2004) and anticancer agents (Malinka *et al.*, 2004, Husain *et al.*, 2011) as well as other projected biological and pharmacological activities.

TAUTOMERISM

The concept of tautomerisations is known as tautomerism. It results in the formal migration of a hydrogen atom or proton, accompanied by a shift of a single bond and its adjacent double bond (Scheme 1)

Scheme 1

Emamian *et al.* (2014) reported a theoretical study of the solvent effects on the tautomerization process of the simplest pyridazinone into pyridazol.

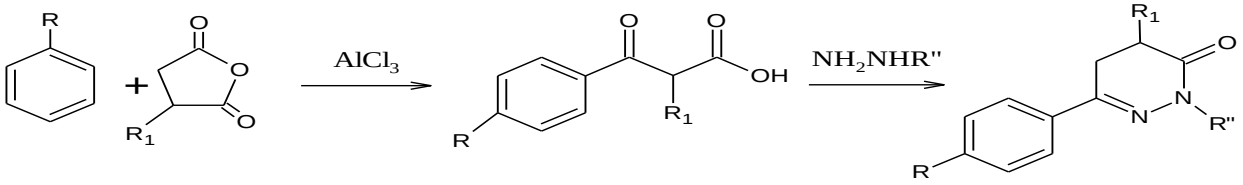


Pyridazin-3(2H)-one Pyridazin-3-ol (Boukharsa *et al.*, 2014)

SYNTHESIS OF PYRIDAZINONES

1. From 1,4 ketoesters or ketoacids

Addition of a hydrazine molecule to an anhydride or to 1, 4 ketoesters or ketoacids achieves pyridazinones.

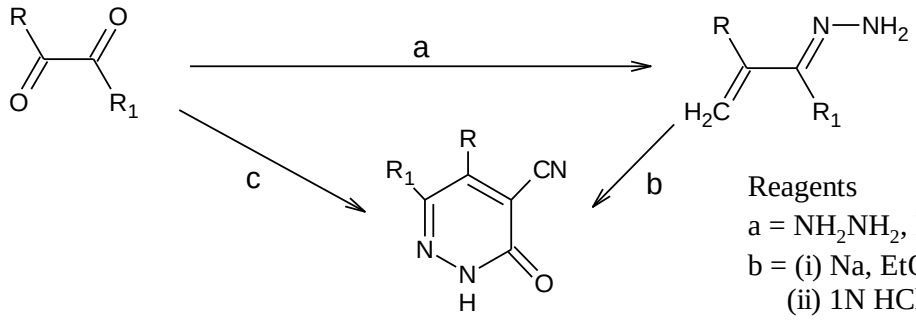


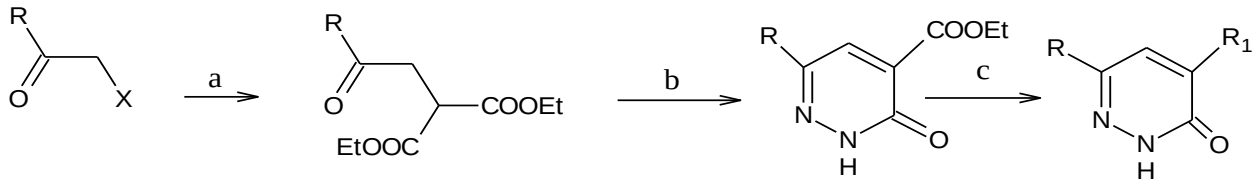
R= Different substituted ary derivatives
R_1= H, CH_3
R"= H, Phenyl, Substituted phenyl, different heterocyclic groups

2. Synthesis from monohydrazones and diethylmalonate derivatives

General Procedure for the Preparation of Monohydrazones

Commercially available 1, 2-dicarbonyl compounds (and are easily prepared following standard methods) and a suspension of the corresponding diketone in absolute EtOH containing an excess of $NH_2NH_2.H_2O$ is heated at reflux temperature after which the solution is cooled then the formed solid can be isolated by filtration and purified by recrystallization from the appropriate solvent or by column chromatography using the appropriate eluents.

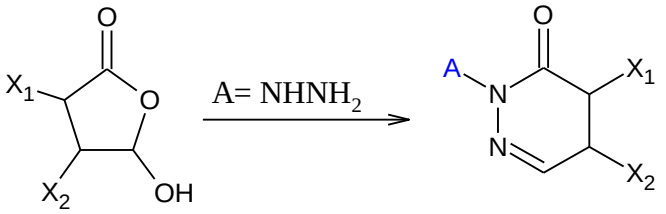




X= Cl, Br
(a)= diethylmalonate, K_2CO_3, KI
(b)= NH_2NH_2, EtOH
(c)= Br_2, AcOH

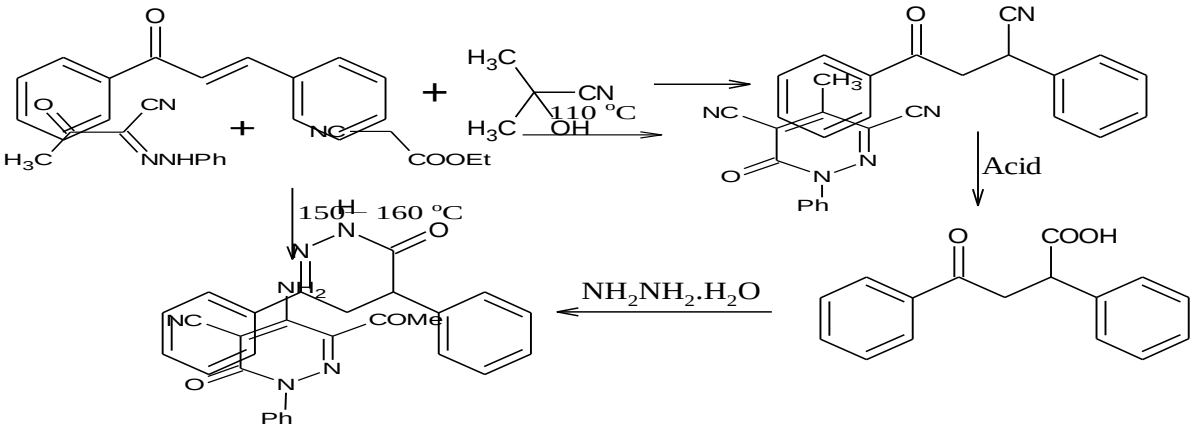
3. Direct ring synthesis

Most preparation of the pyridazinone derivatives depend on the nucleophilic substitution of the starting material of these derivatives, prepared from mucochloric acids. 4,5-dihalo-3(2H)-pyridazinone derivatives were prepared by different reaction such as direct ring synthesis, alkylation, and halogen-exchange reaction.



A= H, Ph, Py, Bu
X_1= X_2= Cl, Br

In a simple new method, 4-(*o*-hydroxyphenyl)-3-(2H)-pyridazinones can be prepared by 1,3-dipolar cycloaddition of the in situ prepared diarylnitrilimines and 3- arylidine-2(3H) benzofuranones



All these compounds are prepared by the reaction of mucohalo acid with the corresponding hydrazine (Asif *et al.*, 2010)

APPLICATIONS OF PYRIDAZINONE

Numerous properties of pyridazinone derivatives have been well recognized for decades, and their attachments with other heterocycles or metal ions often perfect the performances depending on the type of substituent and position of attachments. For its adaptability, pyridazinone is largely applied in pharmaceutical and agricultural; here, we present them distinctly.

1. Applications in Pharmaceutical Chemistry

A great number of pyridazinone and its derivatives have been described to have various pharmacological properties such as antiviral, antiparasitic, antitubercular, anticonvulsant, analgesic, and antisecretory activities. Furthermore, much curiosity has also been focused on the antibiotic (including antibacterial and antifungal), anti-inflammatory and anticancer activities exhibited by compounds incorporating other heterocyclic systems. Below are some of its applications:

i. Pyridazinones as antitubercular agents

In their work; Husain *et al.,* 2011 synthesized series of pyridazinone derivatives and evaluate it against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) and found that 5-(4-hydroxy-3-methoxybenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone showed best antitubercular activity among the synthesized compounds with *MIC*-12.5 µg/mL. Four other compounds, 5-(4-nitrobenzyl)-3-(4-chloro-phenyl)-1,6-dihydro-6-pyridazinone, 5-(4-hydroxybenzyl)-3-(4-chlorophenyl)-1,6-dihydro-6-pyridazinone, 5-(4-nitrobenzyl)-3-(4-methylphenyl)-1,6-dihydro-6-pyridazinone and 5-(4-hydroxy-3-methoxybenzyl)-3-(4-methylphenyl)-1,6-dihydro-6-pyridazinone were also notable in their antitubercular action with *MIC*-25 µg/mL. Rests of the compounds showed *MIC*-values of 50 µg/mL. Pyridazinones derived from 4-chloro-furanones were found to have better activity than those derived from 4-methyl-furanones. Disubstituted phenyl rings at 5th position of pyridazinone ring showed better antitubercular activity than unsubstituted or mono-substituted phenyl rings. Among the mono-substituted phenyl rings at 5th position of pyridazinone ring, presence of nitro group showed substantial antitubercular activity (Husain *et al.,* 2011).

Some pyridazinone and phthalazinone derivatives carrying N-(phenylsulfonyl) acetohydrazide moiety at position 2 of these rings displayed antitubercular activity against *M. tuberculosis* H37 Rv. Unsubstituted compounds were more active than after the substitution of chlorine at the *para* position in the phenyl ring (Abida *et al.,* 2019).

ii. Pyridazinones as antibacterial and antifungal agents

The 5-Thioxo-1,2,4-triazole containing a pyridazinone side chain is a perfect heterocyclic system for antifungal activity. The 6- substituted phenyl-2-[{(4-substituted phenyl-5-thioxo)-1,2,4-triazol-3-yl}-methyl]-2,3,4,5-tetra hydro pyridazin-3-one compounds displayed antifungal activity against *C. albicans, Trichophyton rubrum, Aspergillus flavus, A. niger* and *Penicillium citrinium.* The chloro substituent compound displayed the supreme activity against all the fungal species. The two electronegative groups of Cl surge the activity of 1,2,4-triazole. A series of 6-anthracenepyridazinones containing indolyl moieties from indole to 6- anthracene-4-oxo-2-butenoic acid displayed antibacterial activity A series of 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-oxadiazoles displayed fungicidal activity against wheat leaf rust, *Puccinia recondita* and their activity was influenced by the nature of the substituents. The structure and activity relationship of the compounds, pyridazinone-substituted 1,3,4-thiadiazoles and the pyridazinone-substituted 1,3,4-oxadiazoles, 1,3,4- oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring. Pyridazinone derivatives, corresponding dithio derivatives, thio derivatives and chloro derivatives displayed antimicrobial and antifungal activities. Various metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2H-pyridazin-3-one displayed antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi. The Cd(II) and Ni(II) complexes displayed selective and effective activities against one Gram-positive bacterium *S. aureus*, one Gram-negative bacterium *P. putida* and against two yeast *C. albicans* and *C. tropicalis* in contrast to poor activity observed other microorganisms (Abida *et al.,* 2019)

iii. Pyridazinones as anticonvulsants agents

The pyridazinones ring system settles with prominent feature for anticonvulsant activities. In order to discover the activity, various 6-arylpyridzinones were synthesized, characterized and tested and were found to display anticonvulsant activity. 5-substitutedbenzylidene-6- methyl-4,5-dihydropyridazinones, some 6-(substituted phenyl)-4,5-dihydropyridazinones and 6-(substituted phenyl)-pyridazinones demonstrated anticonvulsant activity against MES induced seizures. Compounds having an electron withdrawing group on the phenyl ring display substantial anticonvulsant activity. The 1-substituted-1,2-dihydro-pyridazine-3,6-diones were found to unveil anticonvulsant activity. Maximum protection against MES induced seizures was shown by the compound 1-[3-(2-aminophenylamino)- 2-hydroxypropyl)-1,2-dihydropyridazine-3,6-dione, 2-hydroxy-3-piperazin1-yl-propyl)-1,2-dihydro-pyridazine-3,6-dione and 1-[2- hydroxy-3-imidazol-1-yl-propyl)-1,2-dihydro-pyridazine-3,6-dione. But all these compounds failed to protect the animals from pentylenetetrazole (Metrozol) induced seizures. A series of 6-aryl-3-(hydroxyl poly methylene amino) pyridazines derivatives were verified for anticonvulsant activity against MES and bicuculline-induced seizures; and neurotoxicity. Phenobarbital, diphenylhydantoin, carbamazepine, and sodium valproate were used as standard antiepileptic drugs. The activities were affected by either varying the aryl ring in the 6-position of the pyridazine ring or by modifying the 3-amino side chain. Compounds with a phenyl ring in the 6-position of the pyridazine ring and 4-hydroxy piperidine side chain in the 3-position of the pyridazine ring seemed crucial for activity. Substituting the phenyl ring with a Cl in the 2-position led to upsurge in activity (Abida *et al.,* 2019)

iv. Pyridazinones as anti-inflammatory agents

Various derivatives of pyridazinones incorporating a 3-(2H)-pyridazinone ring have been described for their anti-inflammatory activity. Among the various pyridazinone derivatives, 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone (emorfazone) is currently being marketed in Japan as an analgesic and anti-inflammatory drug. In recent years a number of pyridazinone derivatives have been synthesized and found to display anti-inflammatory activity (Takaya *et al.*, 1979).

N-substituted 4, 6-diaryl-3-pyridazinones were synthesized through a Mannich reaction involving formaldehyde and N-arylpiperazine and alkyl halides. It was investigated that the introduction of arylpiperazinomethyl moiety in the 2-position of the pyridazinone ring resulted in the most potent anti-inflammatory activities. From 19 derivatives only two derivatives which produced a good level of anti-inflammatory activity at 200 mg/kg (Rubat *et al.* 1989).

Matsuda *et al.,* synthesized some novel 5,6-bis(4-methoxyphenyl)-2H-pyridazin-3-one derivatives as anti-inflammatory agents. These derivatives evaluated for their inhibitory activity against interleukin-1 beta (IL-1β). The observations suggested that a planar substituent at the 2- position of the pyridazinone ring seems to be favourable activity (Matsuda *et al*., 2001).

Chintakunta*et al*., prepared some new 3-O-substituted benzyl pyridazinone derivatives and were found to display significant anti-inflammatory activity. Among the compounds synthesized, three compounds have shown in vitro COX-2 selectivity. These co mpounds have been evaluated for their in vivo potential using carrageenan-induced rat paw edemaassay (Chintakunta *et al.,* 2002).

Siddique *et al.,* has synthesized a series of 6-(substituted aryl)-2,3,4,5-tetrahydro-3-thiopyridazinones by using Friedel-Craft's acylation of appropriate hydrocarbons. The substituents in the phenyl group at 6-position of the thiopyridazinone ring have been found to exert variable effect on the anti-inflammatory activity. Presence of p-isobutyl, p-phenyl, p-phenoxy, p-methoxy and p-ethoxy group was found to enhance the said activity (Siddique *et al.*, 2004).

The anti-inflammatory profile of [6-(3,5-dimethyl-4-dhloropyrazole-1-yl)-3(2H)-pyridazinon-2-yl]acetamides were investigated by Sukuroglu*et al*., by using the carrageenan-induced hind paw edema method, the method of Kasahara (kasahara*et al*., 1985) was followed. The amide derivatives exhibited (at 100mg/kg) potent anti-inflammatory activity as indometacin. The N-octyl derivative especially showed the highest anti-inflammatory activity comparable to indometacin. The tests of these compounds are indicating that these are exerting their anti-inflammatory activities through the mechanisms that involve the inhibition of chemical mediators such as histamine and serotonin and also presumably the COX isoforms (Sukiroglu *et al*., 2005).

Abouzid and Bekhit reported the design, synthesis, and pharmacological properties of a series of arylethenylpyridazinones and arylethylpyridazinone derivatives from the corresponding aryloxohexenoic and aryloxohexanoic acids respectively. The synthesized compounds were tested for their anti-inflammatory activity in carrageenan-induced rat paw edema model. One compound demonstrated the greatest in vivo activity with ED_{50} equal to 17 μmol compared with celecoxib with no ulceration on the gastric mucosa (Abouzid and Bekhit, 2008).

Gokce et al., synthesised 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted benzal) hydrazone derivatives and evaluated their anti-inflammatory activity. The structures of compounds were elucidated by spectral and elemental analysis. 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) (Gokce *et al.,* 2009).

Ahmad *et al.,* synthesised a series of 6-aryl-2-(*p*-sulfamylphenyl)-4,5-dihydropyridazin-3(*2H*)-ones by condensation of the appropriate β-aroylpropionic acid and 4-hydrazinobenzenesulfonamide hydrochloride in ethanol and tested them for anti-inflammatory activity by carrageenan-induced hind paw edema method. Celecoxib (20mg/kg) was used as standard. All test drugs were administered orally at dose of 20mg/kg b.o. Structure–activity relationship studies showed that the introduction of lipophilic groups such as methyl and ethyl at the *para* position of the phenyl group attached at C-6 of dihydropyridazinone led to a significant decrease in the activity (Ahmad *et al.,* 2010).

Bashir *et al.,* synthesised seven novel 6-aryl-2-(p-sulfamoylphenyl)-4,5-dihydropyridazin-3(2H)-ones and evaluated them for anti-inflammatory activity by carrageenan-induced hind paw edema method. Celecoxib (20mg/kg) was used as standard. All test drugs were administered orally at dose of 20mg/kg b.o. Compound exhibited anti-inflammatory activity comparable to that of celecoxib (at 5h). These compounds did not produce any ulceration in gastric region (Bashir *et al.,* 2011).

Many studies have been focused on pyridazine and pyridazinone compounds as non-steroidal anti-inflammatory drugs (NSAIDs), which possess analgesic and anti-inflammatory activities very low ulcerogenicity. Among the different pyridazine and pyridazinone derivatives, 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone (emorfazone) is being marketed as pentoil and nandron in Japan as analgesic and anti-inflammatory drug. The 4-amino-2-methyl-6-phenyl-5-vinyl-3(2H)-pyridazinone was seven time more potent than emorfazone. Antinociceptive activities exhibited by the compounds having 2-substituted4,5-functionalized 6-phenyl-pyridazinones, some compounds were found more potent than Emorfazone. The 4,5-dihalo, 5-arylidene and 4-carbamoyl pyridazinones and 3-oxo-5-benzylidene-6-methyl-(4H)-2-substituted pyridazines possess analgesic activities (Abida *et al.,* 2019).

v. Pyridazinones as analgesic agents

Piaz *et al.* synthesized a series of 2-substituted 4,5-functionalized 6-phenyl-3(2H)-pyridazinones. The Antinociceptive activities were evaluated in the mouse abdominal constriction model. Single dose studies showed that compound were most active. Two compounds caused a reduction in the number

of abdominal constrictions of 60 and 79%, respectively and thus both compounds appeared to be more active than Emorfazone at this dose level using this method of assessing Antinociceptive protection (Piaz *et al.*,1996).

A series of 4-phenyl-6-aryl-2-[3-(arylpiperazin-1-yl)propyl] pyridazin-3-ones related to trazodone have been synthesized and evaluated for analgesic activity. In the phenylquinone-induced writhing test, most compounds have been found several times more potent than acetaminophen and noramidopyridine (Rohet *et al.,* 1996).

Giovannoni *et al.,* prepared a number of [(3-chlorophenyl)piperazinylpropyl] pyridazinones and the corresponding isoxazolopyridazinones. They were tested for their analgesic activity. The investigated compounds showed antinociceptive properties in the mouse hot-plate test (thermal nociceptive stimulus) (Giovannoni *et al.,* 2003).

The compound 4-amino-5-heteocyclic-pyridazinones were synthesized by Giovannoni*et al.,* and tested for their analgesic activity. All the derivatives were evaluated in the experimental model of the abdominal constriction test in mice in which a painful chemical stimulus was applied. Four compounds were found potent because they were able to induce a potent antinociceptive effect at a dose of 3 mg/kg po (Giovannoni *et al.,* 2007).

A series of 4-amino-5-vinyl-3(2H)-pyridazinones and analogues were synthesized and their antinociceptive effect was evaluated in the mouse abdominal constriction model. Several of the novel compounds showed ED_{50} values in the range 6–20 mg/kg/sc and demonstrated to be able to completely protect all the treated animals from the effect of the noxious stimulus at 30 mg/kg/sc. SAR studies confirmed the essential role played by an amino or substituted amino function at position 4 and by a vinyl group at position 5 of the diazine system (Vergelli *et al.,* 2007).

A new series of 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted benzal)hydrazone derivatives were synthesized as analgesic and anti-inflammatory agents. Three compounds were exhibited more potent analgesic activity than ASA (Gokce *et al.,* 2009).

Malinka *et al.,* synthesised a series of N2-{2-[4-aryl(benzyl)-1-piperazinyl(piperidinyl)]ethyl}pyrrolo[3,4-d]pyridazinones and related derivatives were synthesized as potential analgesic agents. Analgesic activity of the compounds was investigated in the phenylbenzoquinone induced 'writhing' and 'hot plate' test in mice and at radioligand binding assay. At 'writhing' test all compounds, without exception, were more active than acetylsalicylic acid (ASA) with ED_{50} values ranging from 0.04 to 11 mg/kg (i.p.) (ED_{50} for ASA-39.15 mg/kg). Analgesic effect at the 'hot plate' test was observed for three compounds at the dose 3-5 times higher than that of morphine (ED_{50}-3.39 mg/kg). At radioligand binding assay of one compound exhibited affinity for the m-opioid receptors similar to that of Tramadol (Malinka *et al.,* 2011).

vi. Pyridazinones as anti-platelet agents

The need to prevent thrombus formation without impairing haemostasis has spurred extensive research aimed at the development of non-thrombotic haemostatic agents and platelet aggregation inhibitors. The cyclic adenosine monophosphate (c-AMP) phosphodiesterase III (PDE III) has been one of the most studied targets in the search for new Antiplatelet agents. Among the extensive family of PDE III inhibitors, compounds containing the 3(2H)-pyridazinone ring have been widely studied (Bristol *et al.,* 1984, Sircar *et al.,* 1986).

Sotelo *et al.,* prepared a series of 4,5-disubstituted -6-phenyl-3(2H)-pyridazinones which examined for platelet aggregation inhibitory activities on washed human platelets using the turbidimetric method of born and thrombin as inducer of platelet aggregation. Comparison of these results with the Antiplatelet activity of the 5-substituted-6-phenyl-3(2H)-pyridazinones shows that the introduction of a substituent at position 4 of these compounds produces an increase in the platelet inhibitory activity; this effect is particularly significant in compounds. A slight increase in activity was observed within the series due to the modification of the alkoxy group in the ester function; the isopropyl derivative is the most active (Sotelo *et al.,* 2002).

Coelho *et al.,* have been synthesized some 5-alkylidenepyridazine-3-ones derivatives with four point diversity and all the derivatives were evaluated as platelet aggregation inhibitors. Several derivatives eliciting Antiplatelet activity in the low micromolar range (1μM) were identified. Structure – activity relationships studies on these compounds revealed the key molecular determinants of this new family of antiplatelet agents: (a) two ester groups in the alkoxy moieties; (b) lipophilic substituents at the N2 position of the pyridazin-3-one. The preliminary results of a pharmacological study aimed at determining the mechanism of action of a set of representative compounds revealed that, unlike other pyridazinones, the documented antiplatelet effect is not a consequence of a PDE-III inhibitory activity (Coelho *et al.,* 2007).

vii. Pyridazinones as anti-cancer

5-Hydroxy-3(2H)-pyridazinone derivatives were investigated as inhibitors of genotype 1 HCV NS5B polymerase. Lead optimization led to the discovery of compound, which displayed potent inhibitory activities in biochemical and replicon assays, good stability toward human liver microsomes (HLM $t_{1/2}$> 60 min), and high ratios of liver to plasma concentrations 12 h after a single oral administration to rats (Li *et al.,* 2008).

Pau *et al.,* Designed as a new group of tricyclic molecules containing the thienocycloheptapyridazinone ring system, a number of 2*N*-substituted-hexahydrothienocycloheptapyridazinone derivatives were synthesized and their biological activity evaluated. Among the synthesized compounds, two derivatives were found to possess cytotoxic activity against non-small cell lung cancer and central nervous system cancer cell lines (Pau *et al.,* 2009).

Polyfunctional tetrahydro-2H-pyrano[3,2-c]pyridazin-3(6H)-one derivatives were synthesized and biologically evaluated as novel anticancer agents. Three compounds showed antiproliferative activity against the SK-BR-3 breast cancer cell line. Importantly two compounds showed the highest efficacy, being approximately 30-fold more potent against SK-BR-3 (IC_{50} 0.21 and 0.15 mM, respectively) compared to other cancer cell lines tested. These compounds form the foundation for further investigation in our continuing efforts to develop potent anticancer agents (Al-Tel, 2010).

A series of 6-aryl-2-(*p*-sulfamylphenyl)-4,5-dihydropyridazin-3(*2H*)-ones were synthesized by condensation of the appropriate β-aroylpropionic acid and 4-hydrazinobenzenesulfonamide hydrochloride in ethanol and tested for anti-cancer activity. According to the protocol of the National Cancer Institute (NCI) *in vitro* disease-oriented human cells screening panel assay, one compoundshowed 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 (Ahmad *et al.*, 2010).

Jiang *et al.,* evaluated Thieno[3,2-b]pyrrole[3,2-d]pyridazinones as Activators of the Tumor Cell Specific M2 Isoform of Pyruvate Kinase. SAR evaluations involved changes directly to the heterocyclic core structure while retaining the standard 2-fluorobenzyl substitution from the pyridazinone ring amide. Steric expansions of the methyl group at the 2-position of the thiophene ring were typically well tolerated [for instance the ethyl and isopropyl analogues (AC_{50} = 100 nM, maximum response = 105%) and (AC_{50} = 142 nM, maximum response= 106%) (Jiang *et al.,* 2010).

Abd El-Ghaffar *et al.,* synthesised and evaluated anti-tumor activities of some new pyridazinones containing the 2-phenyl-1*H*-indolyl moiety. Three different human cancer cell lines were used: MCF7 (breast carcinoma cell line), HEPG2 (hepatocellular carcinoma cell line), HCT116(colon carcinoma cell line). Cytotoxicity and IC_{50}values was evaluated (Abd El-Ghaffar *et al.,* 2011).

viii. Effects on Cardiovascular system

The inotropic and vasodilatory properties of 4,5-dihydro-6-phenylpyridazinones are well recognized. Pyridazinone derivatives like SK&F-93741, its normethyl derivative and levosimendan possess a substituted amino group at *para*-position of 6- phenyl ring and have arose as potent cardiotonic agents with dual inotropic and vasodilatory actions. These pyridazinone based cardiotonics have guaranteed in the treatment of congestive heart failure (CHF). The potency of pyridazinone based cardiotonics result from varying *para*-substituents of the phenyl ring attached to 4-position of pyridazinone. However, position 2 of the pyridazinone ring remains unmapped. Moreover, arylsubstituted-4,5-dihydropyridazinones such as imazodan are described to display ionotropic properties similar to milrinone and amrinone. Pyridazinones combine positive inotropics and vasodilating properties (Abida *et al.,* 2019).

2. Applications in Agriculture

i. Pyridazinones as insecticidal agents

Li et al., synthesized and evaluated series of novel pyridazinone derivatives to ascertain their insecticidal activity. The Initial bioassy test disclosed that these compounds displayed mild or moderate activity against Oriental armyworm at 200mg L^{-1} (Li *et al.,* 2012).

In their work; Huang *et al.,* evaluated the effect of oxadiazolyl 3(2H)-pyridazinone (ODP), a new insect growth regulator, on growth of larvae of the armyworm, Pseudaletia separata Walker (Lepidoptera: Noctuidae) in comparison to the insecticide, toosendanin, a tetranortriterpenoid extracted from the bark of Melia toosendan that has multiple effects on insects. The digestive physiological properties of these compounds on insects were investigated by feeding them maize leaves dipped in these compounds. The results displayed that ODP inhibited the growth of *P. separata* significantly, causing a decelerated development and a lengthy larval period, smaller body size and inactive behavior, delayed pupation and a reduced eclosion rate of pupae and adults. Huang *et al.,* concluded that, the regulatory action of ODP on larval growth development was similar to that of toosendanin; both could be used to decrease the growth of insect populations (Huang *et al.,* 2008)

ii. Pyridazinones as herbicidal agents

Karapetian *et al.,* in their work studied the photochemical activity of chloroplasts and Chlorella in order to establish the site of pyridazinone herbicides action on the photosynthetic electron transport chain. They find out that these compounds analogous to diuron possess an inhibition activity. The inhibiting effect is observed at herbicide concentration of 5 x 10(-6) M and is maximal at 10(-4) M. However, in contrast to diuron the herbicides enhance the msec afterglow in Chlorella cells; besides, even at concentration as high as 10(-4) M they only partly block photosynthetic oxygen evolution and the light-induced change of pH. Pyridazinone herbicides hinder the delay of light-off delta F at-196 degrees C more efficiently than diuron. (Karapetian *et al.,* 1981).

The inhibition site of the phenylpyridazinone herbicide, norflurazon [SAN 9789, 4-chloro-5-(methylamino)-2-(3-trifluoromethylphenyl)-pyridazin-3(2*H*)one] was determined in a cell-free carotenogenic enzyme system from a mutant strain of *Phycomyces blakesleeanus* (Mucoraceae). The presence of norflurazon resulted in a reduced flow of radioactivity from [2-^{14}C]mevalonic acid to phytoene and β-carotene, whereas an increased incorporation occurred in the C_{30} terpenoids, squalene, and ergosterol. Furthermore, radioactivity accumulated in geranylgeranyl pyrophosphate. Since no radioactivity was found in prephytoene pyrophosphate and the radioactivity in phytoene decreased upon addition of norflurazon, this herbicide exerts its primary inhibitory action on the reaction catalyzed by phytoene synthetase. The nonbleaching phenylpyridazinone BAS 13761 [4-chloro-5-methoxy-2-phenyl-pyridazin-3(2*H*)-one] did not show this effect (Sandman *et al.,* 1980).

CONCLUSION

Pyridazinone derivatives are biologically important compounds with group on third carbon on pyridazine ring. Pyridazinone is a wonder nucleus due to its ability to give almost all types of biological activities such as such as analgesic, anti-inflammatory, antimicrobial, antiulcer, antidepressants, anticonvulsant, antiplatelet, antithrombotics, anticancer, antidiabetic, antihypertensive, antitubercular and various other types of activities.

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