



Int. J. New. Chem., 2020, Vol. 7, Issue 4, pp. 303-317.

International Journal of New Chemistry

Published online 2020 in <http://www.ijnc.ir/>.

Open Access

Print ISSN: 2645-7237

Online ISSN: 2383-188x



Review Article

Pyridazinone Compounds: A Mini review on their antifungal activities

Mohammad Asif^{1*} Abida and Md Tauquir Alam²

¹Department of Pharmacy, Himalayan Institute of Pharmacy and Research, Dehradun, (Uttarakhand), 248007, India

²Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, India

Received: 2019-11-01

Accepted: 2020-02-15

Published: 2020-03-02

ABSTRACT

Pyridazine derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. They are widely used in pharmaceuticals and agrochemicals. In view of these facts and in continuation of our interest in the chemistry of pyridazines, pyridazinones are six membered cyclic 1,2-diazine having carbonyl group at 3-position of ring system. They are widely used for industrial purposes and also exhibit a broad range of biological activities. This short review compiles examples of the most promising antibacterial activity. An overview on the antifungal activity is also described.

Keywords: Antifungal; Antibacterial; pyridazinone, phthalazinone, antimicrobial activity.

*Corresponding Author: Tel.: +91-9897088910

E-mail: aasif321@gmail.com

Introduction

Infectious diseases caused by bacteria have increased dramatically in recent years. In spite of many significant advances in antibacterial therapy, the widespread use and misuse of antibiotics have caused the emergence of bacterial resistance to antibiotics, which is a serious threat to public health. In particular, the emergence of multidrug resistant gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), and vancomycin-resistant Enterococci (VRE), has become a serious problem in the treatment of bacterial diseases[1]. Therefore, the development of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. In world up to 5% of all the infections are caused by fungi. Fungal infections in such a high risk patients progress rapidly and are difficult to diagnose and treat. Especially in the developed countries fungal infections have grown rapidly in last few decades. In recent decades, the problems of multi-drug resistant microorganisms have reached on alarming level in many countries around the world. A number of recent clinical reports describe the increasing occurrence of MRSA, VRSA, VRE and other antibiotic-resistant human pathogenic microorganisms. Infections caused by those microorganisms pose a serious challenge to the medical community and need for an effective therapy has led to a search for novel antimicrobial agents [2].

Structurally, pyridazinone (also known as 1,2-diazinone) is a six membered heterocyclic compound containing two nitrogen hetero atoms at 1 and 2 position in their cyclic ring. The carbonyl group (CO) is present at three position of ring. Pyridazinones are some of the most widely used organic compounds in recent years. They are used as dyes, intermediates in organic synthesis, and agrochemicals. Pyridazinones have also been shown to exhibit a broad range of biological activities, including antiplatelet, antihypertensive, analgesic, antimicrobial, anticancer, antihypertensives, anticonvulsant, antiviral antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, and antipyretic properties etc.[3-5] Imine groups are present in various natural, natural-derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities. In this review we present the general approaches of pyridazinones as antimicrobial agents. We also highlight the most significant examples of compounds belonging to this class, which exhibit antifungal activity to have been reported in the literature [6-8]. Many compounds carrying pyridazinone and benz-

fused pyridazinone (phthalazinone) rings are known to have different biological activities. However, some compounds bearing pyridazinone or phthalazinone rings have been reported to have antimicrobial activity [9]. Although antimicrobial agents having different structures are frequently used in the treatment of fungal infections, there is an increasing resistance to these drugs. To overcome the development of drug resistance it is necessary to synthesize a new class of antifungal compounds possessing different chemical properties from those of used commonly.

Antibacterial activities of Pyridazinones

The increase in the mortality rate associated with infectious diseases is directly related to bacteria that exhibit multiple resistance to antibiotics. The lack of effective treatments is the main cause of this problem. The development of new antibacterial agents with novel and more efficient mechanisms of action is definitely an urgent medical need. Fungal infections are not usually limited to the superficial tissues; indeed, a significant increase in life threatening systemic fungal infections has been reported. The fundamental reason for this is the increasing number of patients at risk, including those with advanced age, major surgery, immunosuppressive therapy, acquired immunodeficiency syndrome (AIDS), cancer treatment, and solid-organ and hematopoietic stem cell transplantation. The search and development of more effective antifungal agents are mandatory and some pyridazinone are known to be promising antifungal agents. Pyridazinones have been pointed to as promising antibacterial agents[3-8].

The idea of bioisosterism is one of the most successful techniques of bioactive compound design. The substitution of sulfur for oxygen in the heterocyclic ring represents an example of an approach that is commonly known as bioisosterism. The 1,3,4-oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring. In previous papers, we reported that pyridazinone-substituted 1,3,4-thiadiazole exhibited highly fungicidal activity against wheat leaf rust, *Puccinia recondite*[10-11]. On the other hand, 1,3,4-oxadiazoles exhibit a broad spectrum of biological activity. In view of these facts and in continuation of our interest on the chemistry of pyridazinones [10-11], we contemplated undertaking the synthesis of an, as yet, unreported novel di-heterocyclic compound containing both pyridazinone and 1,3,4-oxadiazole moieties in order to obtain compounds possessing better biological activity. The preliminary bioassay indicated that pyridazinonesubstituted 1,3,4-oxadiazoles exhibited fungicidal activity against wheat leaf rust, *Puccinia recondita*, just as that of pyridazinone substituted 1,3,4-thiadiazoles. Prompted by

these results, and in an attempt to establish an agrophore model and find more potent analogues, three-dimensional quantitative structureactivity relationships (3D-QSAR) analysis has been performed on both pyridazinone-substituted 1,3,4-thiadiazoles and 1,3,4-oxadiazoles by using comparative molecular field analysis (CoMFA)[12-13].

Special tetrasubstituted pyridazines are potent fungicides by promoting the tubulin polymerisation, hereby disrupting the microtubule dynamics in the fungus. They are monocyclic analogs of similar substituted triazolopyrimidines and pyridopyrazines with the same mode of action. The fungicidal activity of these pyridazines was evaluated against the plant pathogens *Botrytis cinerea* (grey mould), *Mycosphaerella graminicola* (wheat leaf blotch) and *Alternaria solani* (potato and tomato early blight). Structure-activity relationship studies revealed the importance of a methyl and a chlorine substituent next to both ring nitrogen atoms and two aryl or heteroaryl groups in the other two pyridazine positions[14].

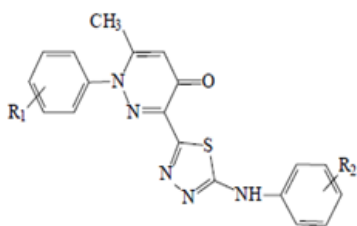
The echinocandins are a class of semisynthetic natural products that target β -1,3-glucan synthase (GS). Their proven clinical efficacy combined with minimal safety issues has made the echinocandins an important asset in the management of fungal infection in a variety of patient populations. However, the echinocandins are delivered only parenterally. A screen for antifungal bioactivities combined with mechanism-of-action studies identified a class of piperazinyl-pyridazinones that target GS. The compounds exhibited in vitro activity comparable, and in some cases superior, to that of the echinocandins. The compounds inhibit GS in vitro, and there was a strong correlation between enzyme inhibition and in vitro antifungal activity. In addition, like the echinocandins, the compounds caused a leakage of cytoplasmic contents from yeast and produced a morphological response in molds characteristic of GS inhibitors. Spontaneous mutants of *Saccharomyces cerevisiae* with reduced susceptibility to the piperazinyl-pyridazinones had substitutions in FKS1. The sites of these substitutions were distinct from those conferring resistance to echinocandins; likewise, echinocandin-resistant isolates remained susceptible to the test compounds. Finally, we present efficacy and pharmacokinetic data on an example of the piperazinyl-pyridazinone compounds that demonstrated efficacy in a murine model of *Candida glabrata* infection[15].

A series of pyridazinone analogs has been developed as potent β -1,3-glucan synthase inhibitors through structure–activity relationship study of the lead 5-[4-(benzylsulfonyl)piperazin-1-yl]-4-morpholino-2-phenyl-pyridazin-3(2H)-one (**1**). Optimization of the sulfonamide moiety led to

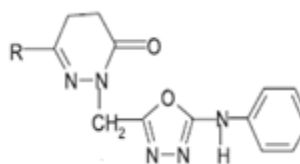
the identification of important compounds with much improved systematic exposure while retaining good antifungal activity against the fungal strains *C. glabrata* and *Candida albicans*[16]. The in vitro antibacterial and antifungal activities of the pyridazinone compounds were tested, some of the compounds have proved to have a remarkable activity against Gram positive germs, the results on *Sarcinia lutea* being spectacular[17]. Novel pyridazine derivatives, some of them displayed good antifungal activities against *G. zeae*, *F. oxysporum* and *C. mandshurica* in preliminary antifungal activity tests[18]. A series of 6-substituted phenyl-2-(3'-substituted phenyl pyridazin-6'-yl)-2,3,4,5-tetrahydropyridazin-3-ones were investigated for their in vitro antitubercular, antifungal and antibacterial activities. The results indicated that the pyridazinones have mild to potent activities with reference to their appropriate reference standards[19]. The 5-Thioxo-1,2,4-triazole containing a pyridazinone side chain is an ideal heterocyclic system for antifungal activity. The following antifungal 1,2,4-triazole derivatives are applicable in medicine like fluconazole, itraconazole and terconazole. A series of 1,2,4-triazole derivatives was evaluated for their in vitro antifungal activity[2]. New series of selenolo[2,3-c]pyridazine and pyrimido[4',5':4,5]selenolo[2,3-c] pyridazine derivatives, some of compounds were showed antibacterial and antifungal activities[20].

Some 3(2H)-pyridazinone and 1(2H)-phthalazinone derivatives were evaluated for their antibacterial activity against various gram-positive, gram-negative strains of bacteria and antitubercular activity against *M. tuberculosis* H37Rv. These compounds were generally active against *B. subtilis* and its clinical isolate. One compounds exhibited antibacterial activity, with a MIC value of 15.62µg/mL against *B. subtilis* and one other compound had the highest antitubercular activity[9]. Several 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-thia diazoles on preliminary bio-active test, exhibited high antifungal activity[21]. The tri-heterocyclic compounds containing both pyridazinone and 1,3,4-thiadiazole moieties in order to obtain compounds possessing better biological activity. 1-Aryl-1,4-dihydro-6-methylpyridazin-3-carboxy-4-one was esterified into ester, which in turn was hydrazinolysed by hydrazine hydrate to give hydrazide. The hydrazide reacted with various arylisothiocyanates resulting in the information of acylthiosemicarbazides. The preliminary biological tests showed that new compounds (**1**) gave mortality levels of 100% against *Puccinia recondita* at 500 ppm. The further study of their bio-logical activity is underway[22].

A series of 5-{3i-oxo-6'-(substituted aryl)-tetrahydropyridazin-2'-ylmethyl}-2-substituted 1,3,4-oxadiazoles, 5-[3i-oxo-6i-(substituted aryl)-tetrahydropyridazin-2'-ylmethyl]-2-amino-1,3,4-oxadiazoles. 5-[3i-oxo-6i-(substituted aryl)-tetrahydropyridazin-2iylmethyl]-2-thione-1,3,4-oxadiazoles. 5-[3i-oxo-6i-(substituted aryl)-tetrahydro pyridazin-2i-ylmethyl]-N-(substituted aryl)-2-amino-1,3,4-oxadiazoles (**2**) has been screened for antibacterial, antifungal and antitubercular activity. All the compounds are evaluated for their antibacterial activity against *E. coli*, *S. aureus*, *Micrococcus luteus* and *Klebsiella pneumoniae* at 100 µg/mL concentration. Antitubercular activity was determined using the BACTEC 460 system. All the compounds were screened at 6.25µg/mL against *M. tuberculosis* H37 Rv comparable with that of standard rifampicin and isoniazid. All the final compounds were evaluated for antifungal activity against *C. albicans*, *C. neoformans* and compared with standard drug fluconazole.² The compounds were evaluated for their antibacterial activity against *E. coli*, *S. aureus*, *Micrococcus luteus* and *Klebsiella pneumonia*, some compounds were the most active as compared to standard drugs ampicillin and chloramphenicol. In antitubercular activity, all the compounds were tested for antitubercular activity at 6.25 µg/mL concentration and showed percentage of inhibition ranging from 45 to 90%. One compound emerged as highly active analogue of the series with 91% inhibition against *M. tuberculosis* H37 Rv. The order of activity was found to be H > Cl > o-toluidine > m-xylyl > diphenyl ether. All the compounds were evaluated for antifungal activity against *C. albicans* and *C. neoformans*. Some compounds were found to be highly active as compared with the standard drug, fluconazole [2].



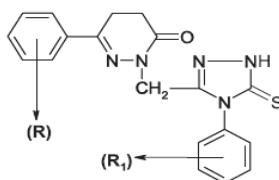
(1) R₁=p or o-Cl R₂=o-F or m-CF₃



(2) R=phenyl, m-xylyl, p-tolyl, p-phenoxyphenyl, p-chlorophenyl

Some compounds are active against Gram positive and Gram negative bacteria having unsubstituted derivatives of the series and most potent against the *S. aureus*, *M. luteus* and *M. tuberculosis* H37 Rv. For antitubercular activity, unsubstituted compounds were more active than after the substitution of chlorine at the para position in the phenyl ring. Substituted compounds potent antifungal agents against the *C. albicans*[2].

The synthetic pathway for 6-substituted phenyl-2-[(4*i*-substituted phenyl-5*i*-thioxo)-1,2,4-triazol-3-yl]-methyl]-2,3,4,5-tetrahydropyridazin-3-one (**3**) compounds was achieved by a sequence of reactions starting from respective aryl hydrocarbons and is illustrated in Scheme 1. All the compounds were tested for their in vitro antifungal activity on five fungal species, namely *Candida albicans*, *Trichophyton rubrum*, *Aspergillus flavus*, *Aspergillus niger* and *Penicillium citrinum*. The chloro substituent derivative showed the highest activity against all the fungal species. The MIC of the standard drug voriconazole was between 0.10 ñ 0.40 µg/mL against all the fungal species except *A. fumigatus*. The two electronegative groups of Cl were increasing the activity of 1,2,4-triazole. As we increased the bulky group or aromatic group on benzene ring, there was a decrease of activity. Some compounds tested in the present study were found to have significant antifungal activities against all the fungal species. The chloro substituent derivative (6-(4'-Chlorobenzene)-2-[(4'-p-chlorophenyl-5*i*-thioxo)-1,2,4-triazol-3-yl]-methyl]-2,3,4,5-tetrahydropyridazine-3-one showed the highest activity against all the fungal species. The MIC of the standard drug voriconazole was between 0.10 and 0.50 µg/mL against all the fungal species. The two electronegative groups of Cl were increasing the activity of 1,2,4-triazole. As we increased the bulky group or aromatic group on benzene ring, the activity was decreased [2].

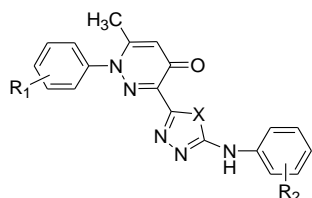


(3) R= H, CH₃, Cl, Br, OCH₃, C₆H₅O

R₁= H, p-Cl, p-Br

The tetrazolo-pyridazines and of ditetrazolophthalazine, it is given the assessment of their antimycotic activity, being noticeable a selective fungicidal action [23]. A series of novel 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-oxadiazoles (**4**), were showed fungicidal activity, based on bioisosterism. The in vivo activity against wheat leaf rust *Puccinia recondita*. These compounds were shown to be fungicidally active, and their activity was influenced by the nature of the substituents. By using the three-dimensional quantitative structureactivity relationships (3D-QSAR) method of comparative molecular field analysis (CoMFA), the structure and activity relationship of the compounds containing both

pyridazinonesubstituted 1,3,4-thiadiazoles and pyridazinone-substituted 1,3,4-oxadiazoles. The 3D-QSAR modes gave good correlation between the variations on percent inhibition and the steric-electrostatic properties. The common mode of action for the pyridazinone-substituted 1,3,4-thiadiazoles and the pyridazinone-substituted 1,3,4-oxadiazoles, which further confirms that the 1,3,4-oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring[24].



(4) X=O,S R₁= H , o-Cl, p-Cl, 2,6-Cl₂ , 2,4,5-Cl₃ , 2,4- 2CH₃

R₂= m-CF₃, o-F, H, p-OCH₃

The pyridazinone-substituted 1,3,4-oxadiazoles exhibited the same fungicidal activity as that of pyridazinonesubstituted 1,3,4-thiadiazoles. The fungicidal activity varies with the substituents of the phenyl moiety. The 3D-QSAR analyses have been performed on both pyridazinone-substituted 1,3,4-thiadiazoles and pyridazinone-substituted 1,3,4-oxadiazoles. The 3D-QSAR models gave good correlation between the variations on the percent inhibition and the steric-electrostatic properties. These results are consistent with a common mode of action for the pyridazinone-substituted 1,3,4-thiadiazoles and the pyridazinone-substituted 1,3,4-oxadiazoles, which further confirms that the 1,3,4- oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring[25].

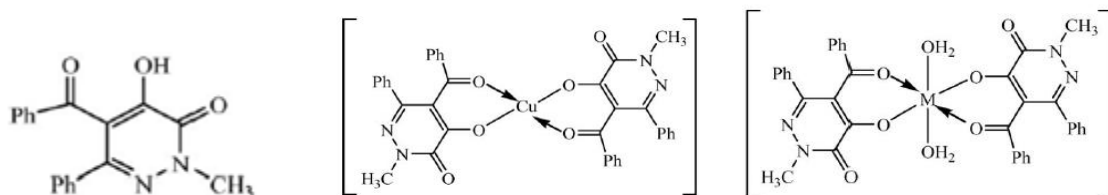
As a part of a research project on antimicrobial agents, some carbamoyl derivatives of pyridazine-N-oxides were exhibited a fairly good activity against *Trichomonas vaginalis*. The investigations concerning synthesis-structure-biological activity in the pyridazine series, the antimicrobial and antifungal tests of some pyridazinium compounds, the comparative analysis may leads to the following conclusions concerning the relation between structure and activity in the pyridazine series: The cis-isomers are always more active comparatively with similar trans-isomers. In the pyrrolopyridazine series, the saturated or partial saturated compounds have always a stronger activity as the related aromatics derivatives. The saturated, partial saturated and aromatic compounds have different selectivity. Thus, the saturated are more active on the *Pseudomonas aeruginosa* and *Candida albicans*, the partial saturated are more active on the *Staphylococcus aureus* and *Bacillus subtilis* while the aromatic compounds are active on the

Bacillus subtilis[26]. Pyridazine-derived carboxamides bearing at the ring N-atom an alkyl side-chain with a terminal carboxylic group or with a terminal acetylamino malonic ester moiety, two desaza-pyridazomycin derivatives and homologs, compounds which are structurally related to the antifungal antibiotic pyridazomycin showed antifungal activity [27]. Derivatives of two unusual classes of heterocycles, possessing structural similarities to the broad spectrum antibiotic fervenulin, were examined for in vitro antimicrobial activity. Some mesoionic pyrimido[1,2-b]pyridazine-2,4-diones and pyridazino[2,3-a]-s-triazine-2,4-diones were exhibited evidence of antimicrobial activity. Susceptibility toward attack by nucleophiles of both mesoionic pyridazino[2,3-a]-s-triazine-2,4-diones and fervenulin was observed[28].

Metal Complexes

The various metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2H-pyridazin-3-one (**5&6**) 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[29].

The pyridazin derivative compounds showed weak activity against fungi and bacteria, however, some of the prepared pyrazolo[3,4-d]pyridazine derivatives, containing chloro group, displayed higher MIC values than the above mentioned standard drugs. Metal chelation is involved in many important biological processes where the coordination can occurs between a variety of metals ions and a wide range of ligands. Many types of ligands are known and the properties of their derived metal chelates have been investigated. The complex combination with copper of pyridazin derivatives and sulfamethoxypyridazine complexes of Cu(II), Ni(II), Co(II) and Ag(I) have a considerable anti-inflammatory and antimicrobial activity against Gram-positive, Gram-negative bacteria and fungi. In this paper we report the synthesis of new Cu(II), Co(II), Cd(II), Ni(II) and Zn(II) complexes with 5-benzoyl-4-hydroxy- 2-methyl-6-phenyl-2H-pyridazin-3-one (LH). Moreover, the new complexes were tested against representative Gram-negative and Gram-positive bacteria, as well as fungi [29].



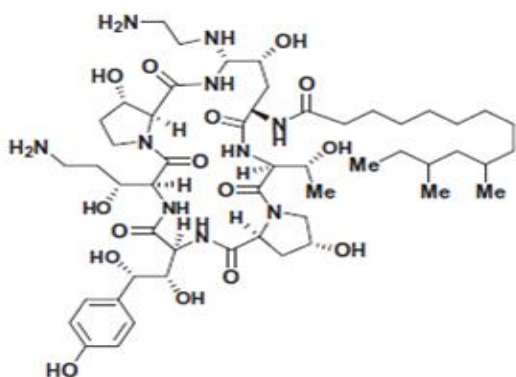
(5) Structure of the ligand (LH).

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

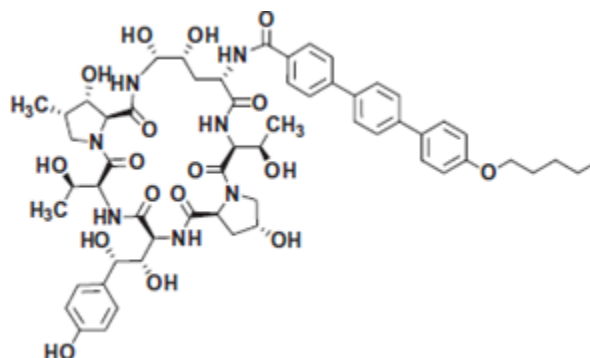
The synthesized pyridazinon complexes are very stable at room temperature in the solid state. The metal complexes are generally soluble in DMF and DMSO. Antimicrobial activities of the compounds were tested against bacteria, such as *Bacillus cereus* ATCC 7064, *S. aureus* ATCC 6538, *Escherichia coli* ATCC 4230, *Pseudomonas putida* ATCC 12633 and against human pathogenic fungi (*Candida albicans* ATCC 27541, *C. albicans* 1481, *Candida tropicalis* 1828 and *Candida krusei* 24941. Ampicillin tri hydrate for bacteria and fluconazole for fungi were used as reference drugs. The ligand showed weak activity, whereas the complex compounds had the highest antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi with MIC in the range of 0.16–0.005 mg/ml. The results of antibacterial activities indicated that slight differences between the activities of all the complex compounds against tested bacteria, except Cd (II) complex. The Cd (II) complex showed selective and effective antibacterial activity against one of the Gram-positive bacteria (*S. aureus* ATCC 6538) and one of the Gram-negative bacteria (*P. putida* ATCC 12633), also poor activity against other tested microorganisms (*E. coli* ATCC 4230 and *B. cereus* ATCC 7064). *S. aureus* ATCC 6538 strain is highly pathogenic to humans. The Cd (II) complex showed highest antibacterial activity against this bacterium compared to other tested bacterial strains.²⁹ The antifungal activities of the tested complexes against human pathogenic yeast species, the results revealed that the synthesized Cd(II) and Ni (II) complexes had promising antifungal activities against two yeast strains (*C. albicans* ATCC 27541 and *C. tropicalis* 1828) and poor activities against other yeast. These results suggested that the Cd (II) and Ni(II) complexes had effective and selective antimicrobial activities against both bacteria and yeast. Cu, Co, Ni and Zn are essential for microorganisms as trace nutrients. In contrast, Cd has not been identified as a trace nutrient and is (in fact) thought to have no beneficial roles in bacteria and fungi. Therefore, cadmium, and its derivatives are more toxic than other trace elements against microorganisms at micro or millimolar levels. Moreover, several studies reported that the organometallic compounds of the divalent cations are more toxic than their metallic forms, particularly when compared to their own inorganic equivalents. Here,

we proposed that the reason for this higher antimicrobial activity might be related to the structure of the Cd(II) complex rather than the presence of the metal form of cadmium. Also, the other cause for the effect could be bounded to the damaged of the membrane permeabilization and the membrane lipid composition. In conclusion, we have synthesized and evaluated in vitro the antimicrobial activity of the new various metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2H-pyridazin-3-one. According to the in vitro results indicated that the new various metal complexes of pyridazin-3-one had commonly of greater toxicological significance than the ligand. Especially we suggested that the Cd(II) and Ni(II) complexes might be a promising candidate of new antimicrobial agents[29].

Pyridazinone as glucan synthase inhibitors: Over the past decades, several different series of antifungal agents, such as the azoles or polyenes, have been widely used for the treatment of invasive fungal infections caused by *Candida albicans* and *Aspergillus fumigatus*. However, to overcome their off-target toxicity, fungistatic activity and emerging resistance, a new class of macrocyclic lipopeptidolactones represented by caspofungin and anidulafungin have been developed as potent fungicidal agents. The lipopeptidolactones exert their fungicidal activity through a totally different mechanism of action from the azoles and polyenes by disrupting the fungal cell wall polymer synthesis through inhibition of 1,3-glucan synthase (GS). Consequently, they have attracted considerable attention. A major drawback of this new class of compounds, however, is that they are only deliverable via the intravenous route so an orally bioavailable small molecule inhibitor is desirable. Unfortunately, only a few small molecule GS inhibitors have been reported to date. Herein, we describe the SAR optimization of a novel pyridazinone series of small molecule glucan synthase inhibitors [16].

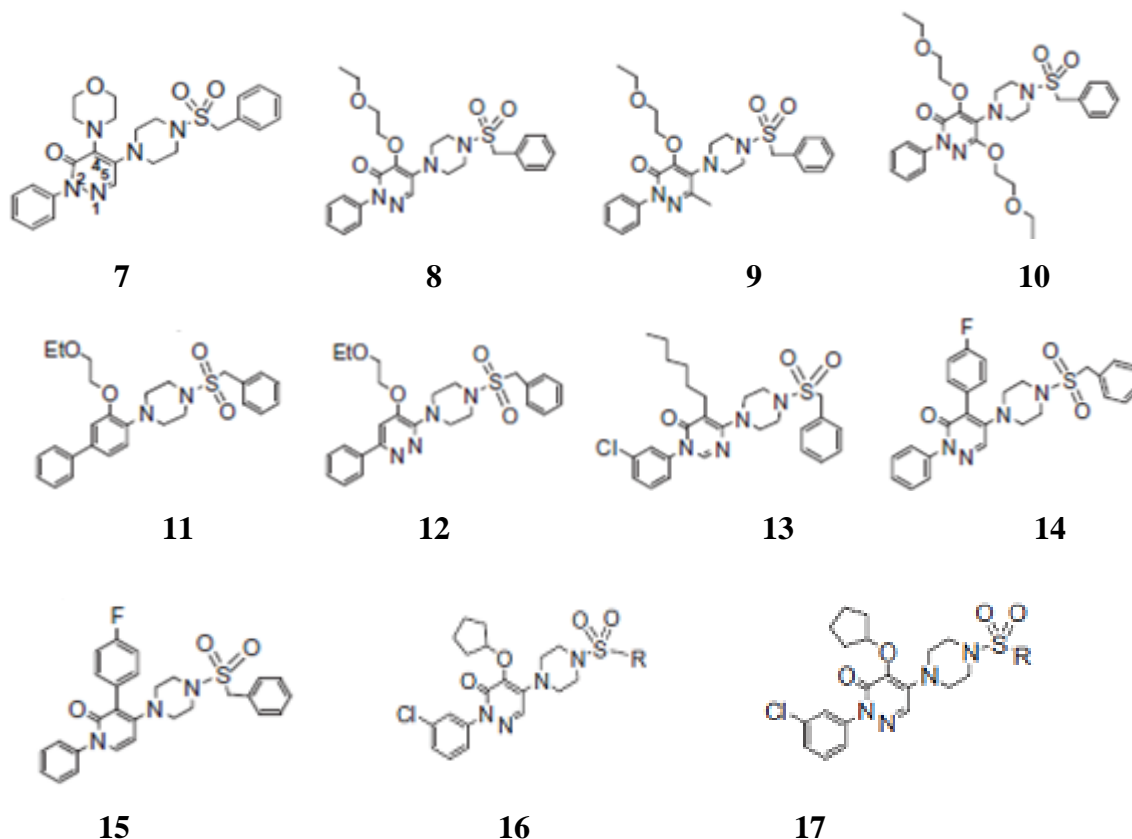


Caspofungin



Anidulafungin

Orally active antifungal compounds, compound **7** as a GS inhibitor with modest activity against the yeast strain *C. albicans* via high throughput screening. Introducing an ether or aryl chain at the C-4 position in place of the morpholine ring in **7** produces a 5- to 10-fold improvement in activity against *C. glabrata* and *C. albicans*. (compounds **8** and **14**). Further introduction of an alkyl or ether chain at the C-6 position (compounds **9** and **10**) reduces antifungal activity dramatically. While replacement of the pyridazinone core with a simple benzene or pyridazine ring (compounds **11** and **12**) removes all antifungal activity, the pyrimidin-4-one and pyridinone (compounds **13** and **15**) showed antifungal activity against fungal strain *C. glabrata*. A comparisons of several different core series demonstrated that the C-6 unsubstituted pyridazinone was the best core structure in terms of antifungal activity.¹⁶. The SAR of pyridazinone series, a cyclopentyloxy or cyclohexyloxy group at C-4 shows relatively optimal activity in combination with a 3-F/Cl substituted phenyl group at the N-2 position. Since, the sulfonamide moiety on the right side of the structure was shown to be essential for antifungal activity. A large variety of sulfonamide groups have been introduced into the pyridazinone (**16**). Simple and substituted alkyl sulfonamides and aryl sulfonamides (compounds **16**) displayed relatively low activity against *C. albicans* except for the thienyl compound. The benzyl compound and benzothiazolmethyl compound exhibited the best antifungal activity. Activity against fungal strains *C. glabrata* and *C. albicans* was increased 20- to 50-fold in comparison to the morpholine compound. Extension of the benzyl sulfonamide to the phenethyl or phenylpropyl resulted in a decrease in antifungal activity. Functional groups such as F, Me, CF₃, CN, and CO₂Et were also introduced into the benzene ring (compounds **17**), but did not show any improvement over compound **16** in rat pharmacokinetic studies. An alternative approach is to improve the hydrophilicity of the benzylsulfonamide series by introducing polar group on the sulfonamide benzene ring since this type of substitution on other parts of the molecule is not tolerated. Substitution on the phenyl ring with hydrophilic groups such as a boronic acid in **17**, or a nitro group in all displayed no improvement in rat blood levels. Introduction of a carboxylic acid group in **17** gave some improvement in rat PK but lost antifungal activity. Only substitutions at the ortho and para position retain good antifungal activity [16].



Conclusion: Pyridazinone have been widely explored for industrial applications. However, the biological activity of this class of compounds deserves further investigation. This becomes clear when plant pathogens are considered. Although the research on this subject is incipient, a number of reports disclosing the effects of the pyridazinones on the pathogens of clinical interest have recently been increasing.³⁰ Pyridazinones have been shown to be promising leads for the design of more efficient antimicrobial agents. Advances in this field will require analyses of the structure–activity relationships of the Pyridazinones as well as the mechanism of action of these compounds. Further optimization of the chemical synthesis can possibly lead to more active molecules against fungal infections. Since all twelve compounds showed promising results, studies to establish their *in vivo* efficacy will be carried in the future.

Acknowledgements: The authors are thankful to the College of Pharmacy, GRD (PG) Institute of Management and Technology, Dehradun, India for technical assistance and facilities.

REFERENCES

- [1] Asif M, Singh A, Ratnakar L. *J. Pharm. Res.*, 4, 664 (2011).
- [2] Siddiqui AA, Ahamad SR, Mir MS, Hussain AS, Raish M, Kaur R. *Acta. Pol. Pharm.*, 65, 223 (2008).
- [3] Asif M, Singh A, Lakshmayya. *Am J. Pharmacol. Sci.*, 2, 1 (2014).
- [4] Asif M, Singh A, Lakshmayya. *Iran. J. Pharm. Sci.*, 9, 67 (2013).
- [5] Asif M, Singh A, Lakshmayya, Husain A, Siddiqui AA. *Lett. Drug. Design. Discov.*, 10, 651 (2013).
- [6] Asif M, Singh A, Lakshmayya. *Chronicle. Young. Scientist.*, 4, 1 (2013).
- [7] Asif M, Anita Singh A, Siddiqui AA. *Med. Chem. Res.*, 21, 3336(2012).
- [8] Asif M, Singh A. *Int. J. Chem. Tech. Res.*, 2, 1112 (2010).
- [9] Dogruer DS, Onkol T, Ozkan S, Ozgen S, Sahin MF. *Turk. J. Chem.*, 32, 469 (2008).
- [10] Zou, X.-J, Jin, G.-Y, Zhang, Z.-X. *J. Agric. Food. Chem.*, 50, 1451 (2002).
- [11] Zou, X.-J, Jin, G.-Y, Yang, Z. *Chem. J. Chin. Univ.*, 23, 404 (2002).
- [12] Zou, X.-J, Jin, G.-Y. *Chin. Chem. Lett.*, 12, 419 (2001).
- [13] Cramer, R. D, Pattern, D. E, Bunce, J. D. *J. Am. Chem., Soc.*, 110, 5959(1988).
- [14] Lamberth C, Trah S, Wendeborn S, Dumeunier R, Courbot M, Godwin J, Schneiter P. *Bioorg. Med. Chem.*, 20, 2803 (2012).
- [15] Walker SS, Xu Y, Triantafyllou I, Waldman MF, Mendrick C, Brown N, Mann P, Chau A, Patel R, Bauman N, Norris C, Antonacci B, Gurnani M, Cacciapuoti A, McNicholas PM, Wainhaus S, Herr RJ, Kuang R, Aslanian RG, Ting PC, Black TA. *Antimicrob. Agents. Chemother.*, 55, 5099 (2011).
- [16] Zhou G, Ting PC, Aslanian R, Cao J, Kim DW, Kuang R, Lee JF, Schwerdt J, Wu H, Herr RJ, Zych AJ, Yang J, Lam S, Wainhaus S, Black TA, McNicholas PM, Xu Y, Walker SS. *Bioorg. Med. Chem. Lett.*, 21, 2890 (2011).
- [17] Butnariu RM, Mangalagiu II. *Bioorg. Med. Chem.*, 17, 2823 (2009).
- [18] Wu J, Song B, Chen H, Bhadury P, Hu D. *Molecules.*, 14, 3676 (2009).
- [19] Islam M, Siddiqui AA, Rajesh R, Bakht A, Goyal S. *Acta. Pol. Pharm.*, 65, 441-447(2008).
- [20] Abdel-Hafez SH. *Eur. J. Med. Chem.*, 43, 1971 (2008).

- [21] Zou, X.-J, Jin, G.-Y. *Chin. J. Pestic. Sci.*, 3, 17(2001).
- [22] Zou, X.-J, Jin, G.-Y, Yang, Z. *Chin. J. Appl. Chem.*, 18, 599 (2001).
- [23] Rogut O, Ștefănescu E, Apreutesei A. *Rev. Med. Chir. Soc. Med. Nat. Iasi.*, 107, 868 (2003).
- [24] Zou X-J, Lai L-H, Jin G-Y, Zhang Z-X. *J. Agric. Food. Chem.*, 50, 3757 (2002).
- [25] Zou XJ, Jin GY. *Chinese. Chem. Lett.*, 12, 419 (2001).
- [26] Ungureanu M, Mangalagiu I, Grosu G, Petrovanu M. *Ann. Pharm. Fr.*, 55, 69 (1997).
- [27] Easmon J, Heinisch G, Holzer W, Matuszczak B. *Arch. Pharm. (Weinheim).*, 328, 307 (1995).
- [28] Coburn RA, Carapellotti RA. *J. Pharm. Sci.*, 65, 1505 (1976).
- [29] Sonmez M, Berber I, Akbaş E. *Eur. J. Med. Chem.*, 41, 101 (2006).
- [30] Islam M, Siddiqui AA, Rajesh R. *Acta. Pol. Pharm.*, 65, 353 (2008).

How to Cite This Article

Mohammad Asif Abida, Md Tauquir Alam, “Pyridazinone Compounds: A Mini review on their antifungal activities” *International Journal of New Chemistry.*, 2020; 7(4), 303-317. DOI: 10.22034/ijnc.2020.115500.1058.