European Journal of Biological Sciences 8 (4): 142-157, 2016
ISSN 2079-2085

DOI: 10.5829/idosi.ejbs.2016.142.157

A Mini Review on Antimicrobial Activities of Different Substituted Pyridazinone Derivatives

Mohammad Asif

Department of Pharmacy, GRD (P.G) Institute of Management and Technology, Dehradun, 248009, India

Abstract: The effective methods have been developed for the preparation under mild conditions of novel pyridazine derivatives from the easily accessible starting materials. All the synthesized compounds were fully characterized. Various pyridazinone compounds were synthesized and tested for their antibacterial against various Gram positive and Gram negative bacterial strains such as *Staphylococcus aureus*, *Bacillus cereus, B. subtilis, Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Escherichia coli, Micrococcus luteus, S. flexneri* and *Klebsiella pneumonia* and antifungal activities on some fungal species, namely *Candida albicans, C. neoformans, Trichophyton rubrum, Aspergillus flavus, Aspergillus niger, G. zeae*, *F. oxysporum* and *C. mandshurica* and *Penicillium citrinum.* The results indicated that the synthesized pyridazine compounds have mild to potent antibacterial and antifungalactivities with reference to their appropriate standard reference drugs.

Key words: Antimicrobial · Antibacterial · Antifungal · Pyridazinones · Phthalazinone · Synthesis

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. Therefore, the development of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. The available antibacterial compounds still have some of the disadvantages. These are microbial resistance, associated disorders like GIT disturbances and dose required may be high [1-10].

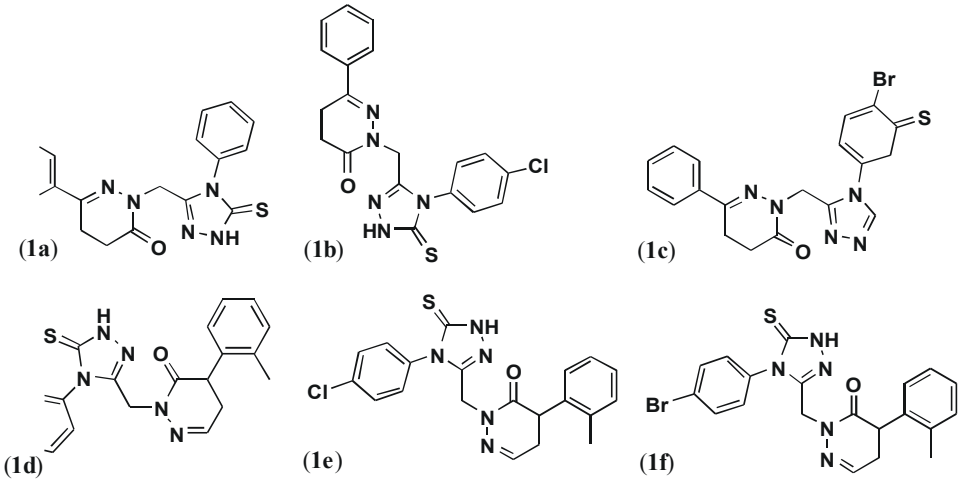
In world up to 5% of all the infections are caused by fungi. Fungal infections in such a high risk patients progress rapidly and are difficult to diagnose and treat. Especially in the developed countries fungal infections have grown rapidly in last few decades. Although antimicrobial agents having different 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. Many human illnesses are caused by infections with microbes like viruses or bacteria or fungi. Amongst those various illnesses, certain bacterial, viral and fungal infections are more common because of their tendency to develop new strains under any circumstances and developing resistance against the available drugs. This stimulated the scientists for development of novel molecules to combat these illnesses. Infectious microbial disease remains a pressing problem worldwide, because microbes have resisted prophylaxis or therapy longer than any other form of life [8-12].

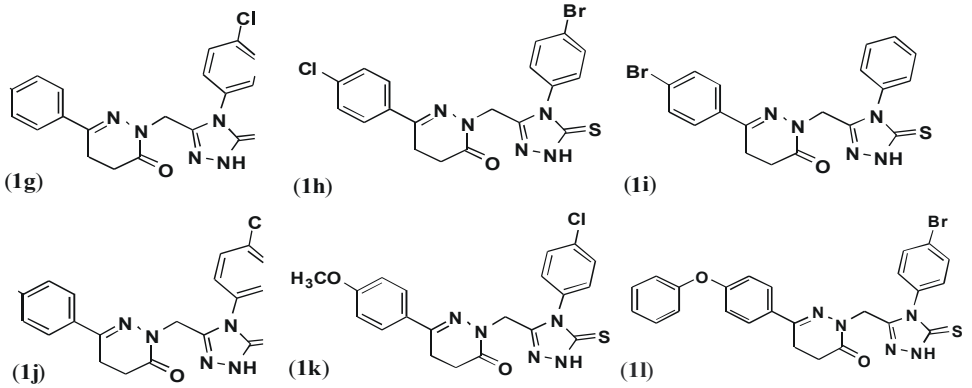
Pyridazine is an important compound of heterocyclic compounds, containing two nitrogen atoms at 1 and 2 positions in a six membered ring. Pyridazin-3-one, saturated or unsaturated form with carbonyl group on

Corresponding Author: Mohammad Asif, Department of Pharmacy, GRD (P.G) Institute of Management and Technology, Dehradun, 248009, India. E-mail: aasif321@gmail.com.

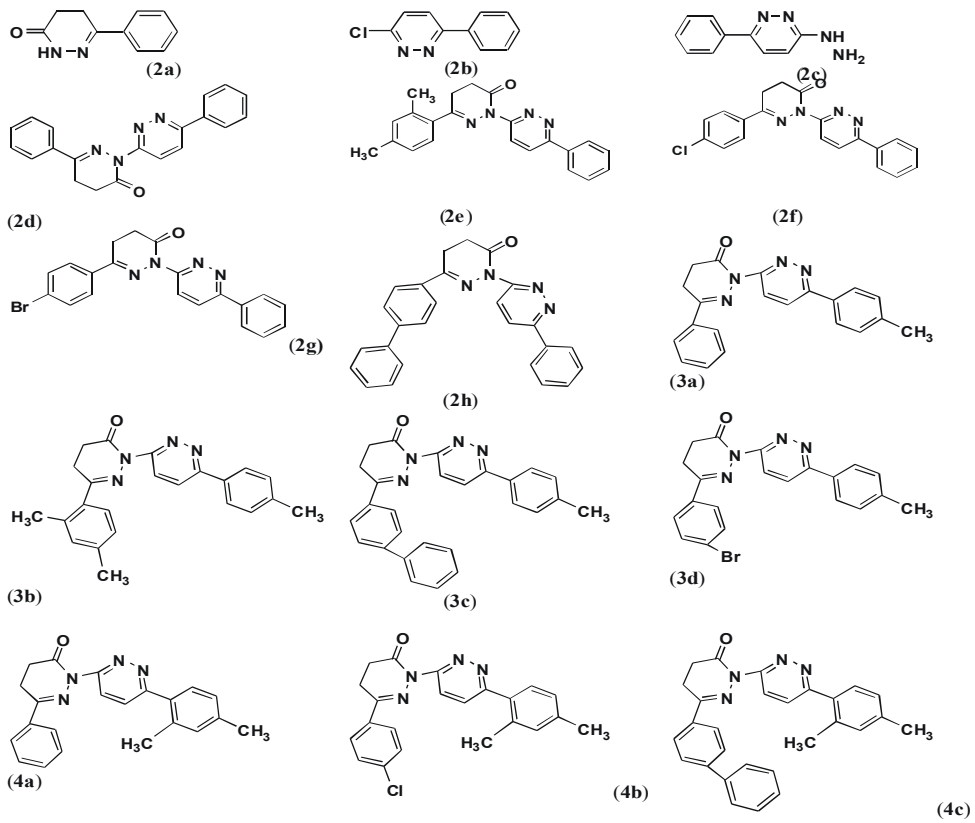
third carbon, has been considered as a magic moiety, which possesses diverse set of biological activities [12-15]. The pyridazine nucleus represents a versatile scaffold to develop new pharmacologically active compounds. Pyridazine and its derivatives are noteworthy for their physiological and biological importance. Medicinal chemists are working on pyridazines due to their wide range of biological activities. Many pyridazine and related analogue were found to possess valuable properties such as antiangiogenic, anticancer, anti-inflammatory, antimicrobial, analgesic, antidepressant, antihypertensive, antithrombotic, antitubercular, antifungal, phosphodiesterase-4 (PDE4) inhibitors are effective anti-inflammatory, selective COX-2 inhibitors, antipyretic, antidiabetic, antifeedant, insecticidal activities, antihypertensive, antiplatelet, diuretics and anticonvulsant activities [16-22]. Besides they exhibit antiviral activity against the replication of human immunodeficiency virus, inhibit human picorna viruses, protein kinase and acyl coenzyme A: cholesterol acyltransferase. Many pyridazine derivatives are well known to possess a wide range of bioactivities and are often employed as plant virucides, fungicides, insecticides and herbicides. They have immense potential in agricultural science as plant growth regulators and crop protection agents. In addition, pyridazinones act as core nucleus in various drugs like Sulmazole, Levosimendan, Amipizone, Indolidan, Imazodan, Pimobendan, Emorfazone, Zardaverine, Milrinone etc. [23-30].Many compounds carrying phthalazinone rings are known to have different biological activities such as antimicrobial, cardiotonic, molluscicidal and herbicidal, antiplatelet, antihypertensive, analgesic and anti-inflammatory actions. However, some compounds bearing pyridazinone or phthalazinone rings have been reported to have antimicrobial activity [31-35]. In view of above facts and inspired by the research going on pyridazinone derivatives, particularly in relation to microbial infections, various pyridazines have been synthesized. These observations contemplated us to synthesize some new derivatives of pyridazinones with a view to discover, design and explore their optimized biological activities with desired structures.

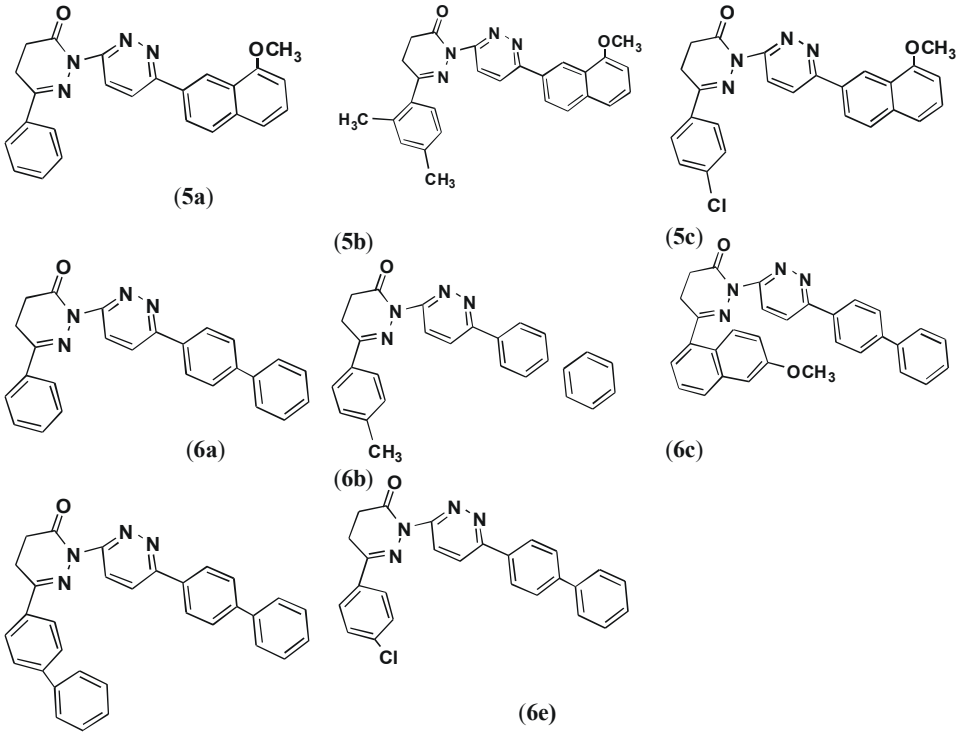
Antimicrobial Activities of Pyridazinone Compounds: The 6-substituted phenyl-2-[{(4'-substituted phenyl-5'-thioxo)-1,2,4-triazol-3-yl}-methyl]-2,3,4,5-tetrahydropyridazin-3-one compounds (1a-1l) were tested for their *in vitro* antifungal activity on five fungal species, namely *Candida albicans, Trichophyton rubrum, Aspergillus flavus, Aspergillus niger* and *Penicillium citrinum.* The6-Substituted-2-{[(4'-substituted-phenyl-5íthioxo)-1,2,4-triazol-3-yl]-methyl]-2,3,4,5-tetrahydro-pyridazin-3-one derivatives (1a-1l) were found to have significant antifungal activities against *C. albicans, T. rubrum, A. flavus, A. niger* and *P. citrinium* fungal species. The chloro substituent derivative (1g) showed the highest activity against all the fungal species. The MIC of the standard drug voriconazole was between 0.10 and 0.50 ìg/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 as in case of compound 1l. These pyridazinone compounds showed comparable results with standard drug voriconazole [36].





Various substituted pyridazinone derivatives (2a-2h), 6-substituted phenyl-2-(3'-substituted phenyl pyridazin-6'-yl)-2,3,4,5-tetrahydropyridazin-3-ones (3a-d, 4a-c, 5a-c and 6a-e) were investigated for their antifungal and antibacterial activities. The synthesized compounds have mild to potent activities with reference to their appropriate reference standards. The final synthesized compounds were evaluated for their antibacterial activity against *E. coli, S. aureus, Micrococcus luteus* and *Klebsiella pneumonia*. The results of antibacterial evaluation show that all compounds have comparable activity against the bacterial strains. Compounds 2e, 3b and 4a are the most active derivatives, which show significant activity against the bacteria comparable to standard drug, ampicillin and chloramphenicol. All the final compounds were evaluated for antifungal activity against *C. albicans* and *C. neoformans* by using cup-plate method in the Sabouraud agar medium. The zone of inhibition (mm) of each compound was determined and compared with standard drug ñ fluconazole. The compounds 3b and 3b were found to be active derivatives of this series against the microorganisms used. Compounds 2e, 3b and 4a are active against Gram positive and Gram negative bacteria. Compounds 3b and 4b exhibited potent antifungal activity [37].



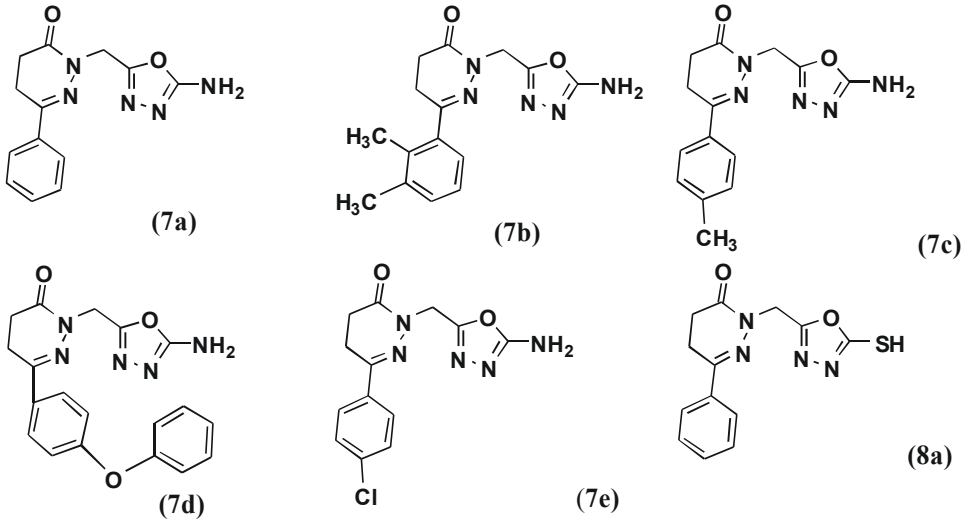


(5a) (5b) (5c)

(6a) (6b) (6c)

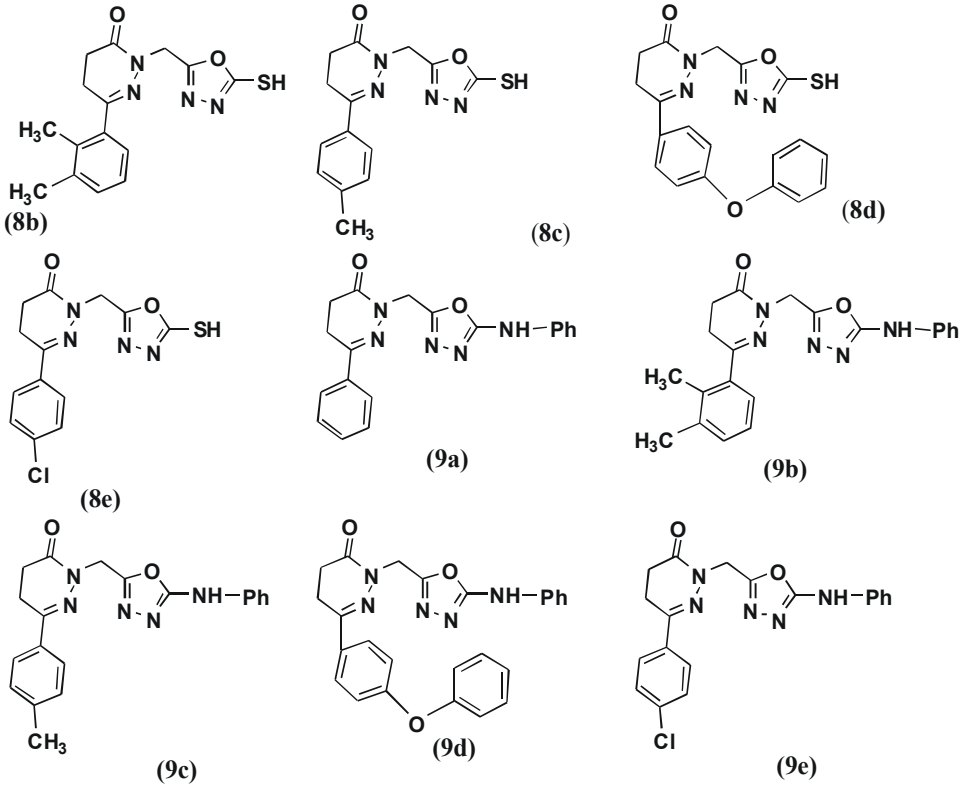
(6d) (6e)

A series of 5-{3'-oxo-6'-(Substitutedaryl)-2',3',4',5'-tetrahydropyridazin-2'-ylmethyl}-2-substituted-1,3,4-oxadiazole compounds (7a-e, 8a-e and 9a-e) were screened for antibacterial and antifungal activity. All the compounds are evaluated for their antibacterial activity against *E. coli, S. aureus, Micrococcus luteus* and *Klebsiella pneumoniae*. All the final compounds were evaluated for antifungal activity against *C. albicans* and *C. neoformans* and compared with standard drug fluconazole.The synthesized compounds were evaluated for their antibacterial activity against *E. coli, S. aureus, M. luteus* and *K. pneumonia*. Compound (7e) and (9e) are the most active derivatives as compared to that of standard drugs ampicillin and chloramphenicol. All the synthesized final compounds were evaluated for antifungal activity against *C. albicans* and *C. neoformans* and compared with standard drug fluconazole. Compounds 7b, 8b and 9b were found to be highly active as compared with the standard drug, fluconazole. Compounds 7a and 9a are active against Gram positive and Gram negative bacteria. Both the compounds are unsubstituted derivatives of the series and most potent against the *S. aureus* and *M. luteus*. Compounds 7b, 8b and 9b are potent antifungal agents against the *C. albicans* [38].

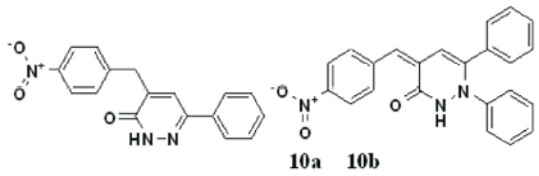


(7a) (7b) (7c)

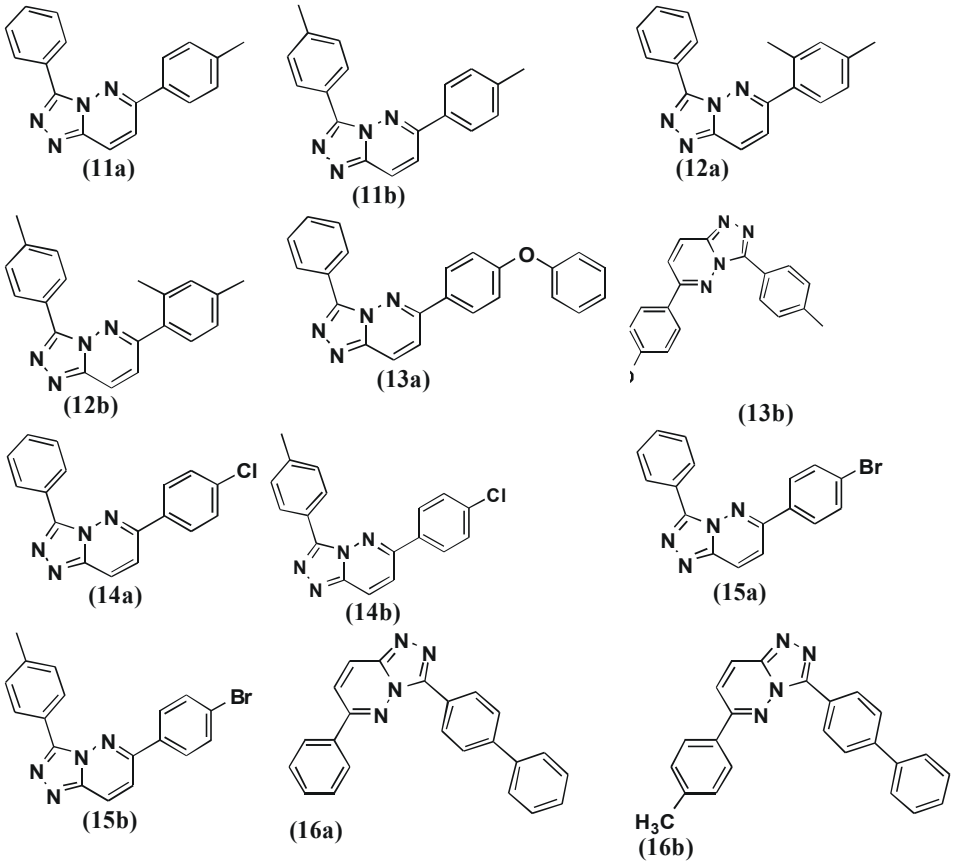
(7d) (7e) (8a)



Compounds 4-(4-Nitrobenzyl)-6-phenylpyridazin-3(2*H*)-one (10a) and4-(4-Nitrobenzylidene)-1,2-dihydro-1,6-diphenylpyridazin-3(4*H*)-one (10b) were screened for their antimicrobial activity against Gram positive bacteria; *B. subtilis*, *B. cereus* and *S. aureus* and Gram negative bacteria; *E. coli*, *P. aeruginosa*and fungus *C. albicans* and results were compared with the reference antibiotics. Both compounds have no antimicrobial activity against *B. cereus*, *S. typhimurium* and *P. aeruginosa*. Both compounds were showed activity against *E. coli* (Gram negative) and *S. aureus* (Gram positive). Both tested compounds have low antibacterial or antifungal activities [39].

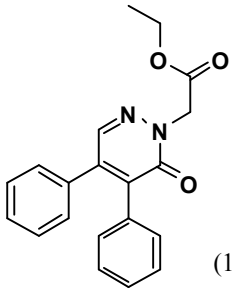


A series of 3-substituted phenyl-6-substituted phenyl(1,2,4)triazolo(4,3-b) pyridazine compounds (11a-b, 12a-b, 13a-13b, 14a-b, 15a-b and 16a-b) were investigated for their *in vitro* antifungal and antibacterial activities. The results indicated that the synthesized compounds have mild to potent activities with reference to their appropriate reference standards. These compounds were evaluated for their antibacterial activity against *E.coli, S.aureus, Micrococcus luteus* and *Klebsiella pneumoniae*. The results of antibacterial test exhibit that all compounds having comparable activity against the bacterial strains. Compounds 11b, 12b and 13b are the most active derivatives, which show significant activity against these bacteria comparable to standard drug, ampicillin and chloramphenicol. All the final compounds were evaluated for antifungal activity against *C. albicans* and *C. neoformans*. The zone of inhibition (mm) of each compound is determined and compared with standard drug fluconazole. The compounds 12a, 12b and 14b were found to be active derivatives of this series against the microorganisms. Compounds 2b, 3b and 4b are active against Gram positive and Gram negative bacteria. Compound 12a, 12b and 14b are potent antifungal drugs [40].

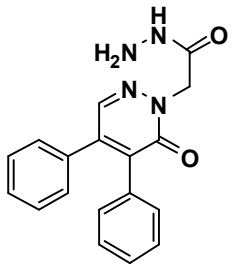


Some 3(2H)-pyridazinone and 1(2H)-phthalazinone derivatives (17,18, 19a-e, 20) were evaluated for their antibacterial activity against various Gram-positive and Gram-negative strains of bacteria. The results showed that the synthesized compounds were generally active against *B. subtilis* and its clinical isolate. Among the target compounds, compound 20c exhibited the best antibacterial activity, with a MIC value of 15.62*i*g/mL against *B. subtilis.* Compound 21e had the highest antimycobacterial activity. These compounds were tested *in vitro* for antibacterial activity against Gram-positive *S. aureus*, methicillin-resistant *S. aureus* (MRSA, clinical isolate), *B. subtilis*, *B. subtilis* (Clinical isolate), Gramne gative *E. coli* and *E. coli* producing extended spectrum β-lactamase, *P. aeruginosa*and *P. aeruginosa* (Clinical isolate) bacteria using broth microdilution. Sulfanilamide, sulfamethoxazole and ampicillin were used as references. None of the target compounds had activity against Gram-negative bacteria. The target compounds were generally active against *B. subtilis* and its clinical isolate. When the chemical structures of the active compounds were taken into consideration, it was determined that 1(2H)-phthalazinone (21a-e) and 4,5-dipheyl-3(2H)-pyridazinone derivatives (20a-e) were more active than 6-phenyl-3(2H)-pyridazinone derivatives (19a-19e) against *B. subtilis* and its clinical isolate. While compounds 20b, 20d, 20e, 21a, 21c and 21e were as active as sulfanilamide against *B. subtilis* clinical isolate, compounds 19d and 21b were as active as sulfanilamide against both *B. subtilis* and its clinical isolate. Compounds 20a and 20c were 2 times as active as sulfanilamide against *B. subtilis* clinical isolate and their antibacterial activity was 50% of that of sulfamethoxazole against *B. subtilis* clinical isolate. Compound 21a was 2 times as active as sulfanilamide against *B. subtilis* and its activity was equal to that of sulfamethoxazole against *B. subtilis*. Compound 21d was as active as sulfamethoxazole against *B. subtilis* and its antibacterial activity was 50% of that of sulfamethoxazole against *B. subtilis* clinical isolate. Moreover, this compound was 2 times as active as sulfanilamide against both *B. subtilis* and its clinical isolate. Among the target compounds, compound 20c exhibited the best antibacterial activity, with a MIC value of 15.62*i*g/mL against *B. subtilis.* Moreover, this derivative was the only compound that was active as ampicillin, with a MIC value of 31.2 *i*g/mL against *S. aureus*[41].

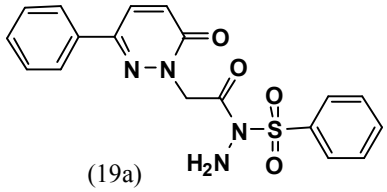
(17)

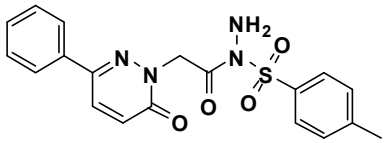


(18)

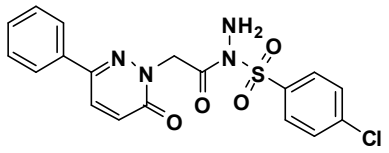


(19a)

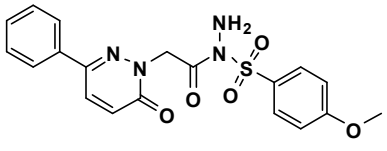




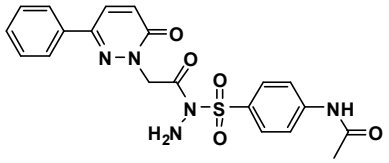
(19b)



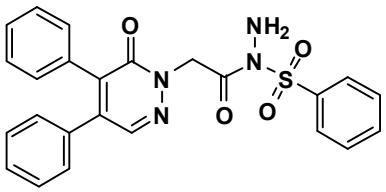
(19c)



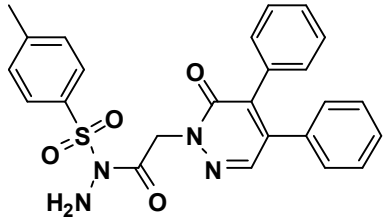
(19d)



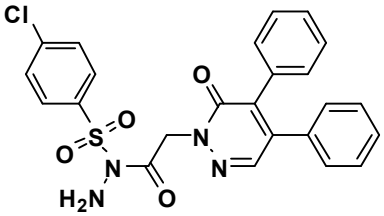
(19e)



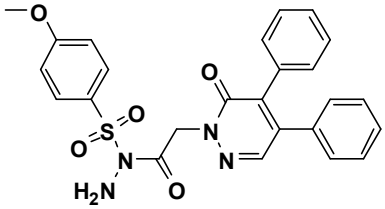
(20a)



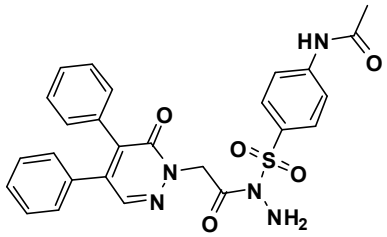
(20b)



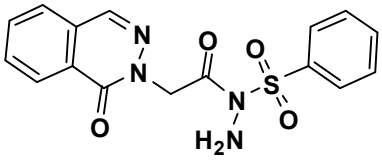
(20c)



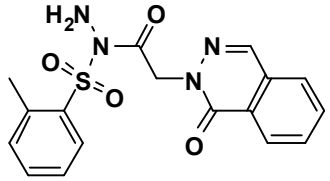
(20d)



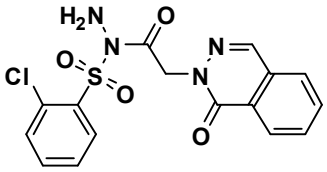
(20e)



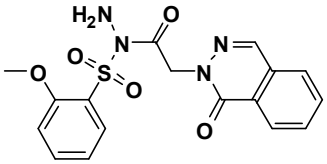
(21a)



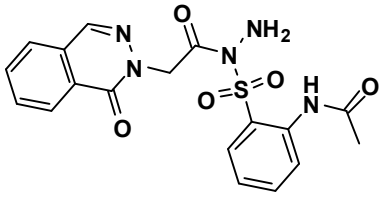
(21b)



(21c)



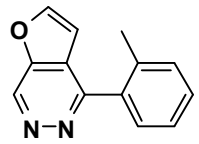
(21d)



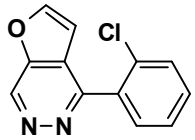
(21e)

The 4-aryl furo pyridazines (22a-b), Based on these findings it was considered valuable to incorporate furan ring in pyridazine framework as in 22a-b, which might enhance the biological activity. Herein we are reporting the conversion of 1-aroyl-hydrazones 3a-b to the corresponding pyridazines 22a-b using PPE in good yield. The antibacterial screening results have shown that chloro substituted compounds 22b exhibit, growth inhibitory activity more relevant than that of the reference compound. Even in case of antifungal activity chloro substituted compounds showed growth inhibitory activity more relevant than that of the reference drug. The compound 22a-b was screened for antimicrobial activity using cup plate method. The activity was carried out against three pathogenic bacteria, *B. Cereus, S. Aureus* and *E. Soli* and two fungal cultures, *F. Solani, Aspergillus Favus*. The standard drugs used were Chloromycetin and Griseofulvin. The compound was tested in dimethyl formide. Further compounds with chloro group have shown more antibacterial and antifungal activities [42].

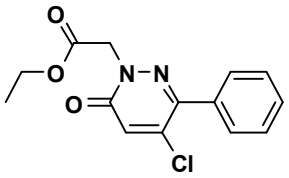
(22a)



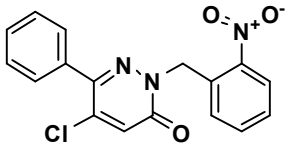
(22b)



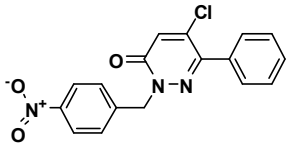
An effective method has been developed for the preparation under mild conditions of novel pyridazine derivatives exhibited antifungal activities and some of them displayed good antifungal activities against *G. zeae*, *F. oxysporum* and *C. mandshurica* in preliminary antifungal activity tests. These synthesized compounds showed weak to good antifungal activities against the tested fungi at 50ig/ml. Compounds 23d, 23e and 25b were shown to inhibit the growth of *G. zeae* at 45.1, 43.8 and 40.4%, respectively; compounds 23d, 23f and 26c exhibited good activities on *F. oxysporum* at 38.2, 44.2 and 43.1%, respectively while compounds 23d, 23e and 23h inhibited the growth of *C. mandshurica* at 43.5, 40.6 and 47.8%, respectively. These figures were slightly lower than those of hymexazol. It should be noted that compounds 23h, 26b and 26c showed good activities on *G. zeae* at 50.3, 57.9 and 60.5%, respectively; compounds 23e and 23h exhibited the growth of *F. oxysporum* at 53.2 and 50.9% respectively and compound 7c exhibited good activity on *C. mandshurica*. Amongst the four compounds 23e, 23h, 26b and 26c that exhibited similar activities as that of hymexazol on their corresponding fungi, the last two showed considerable promise. Although, a definite structure activity relationship could not be established with the limited experimental data and available compounds, it appears that incorporation of oxadiazole or thiadiazole unit through thiolinto parent pyridazine derivative and subsequent oxidation of the resulting product to sulfone 26 might have a positive influence to enhance antifungal activity of the designed compounds. In this study, a mild and effective method for the preparation of 21 novel pyridazine derivatives were undertaken by employing mucochloric acid and benzene as the starting materials. The compounds were subjected to fungicidal activities *in vitro* against *G. zeae*, *F. oxysporum* and *C. mandshurica*. The results showed that the synthesized pyridazine compounds possessed weak to good antifungal activities against the tested fungi, among which, compounds 23e, 23h, 26b and 26c displayed good antifungal activities. Further studies are currently underway to establish a definite structure activity relationship [43].



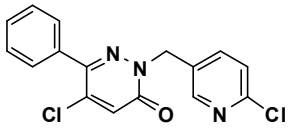
(23a)



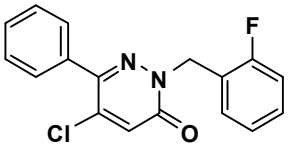
(23b)



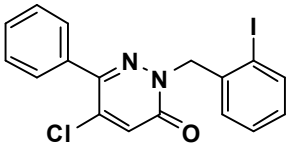
(23c)



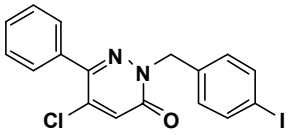
(23d)



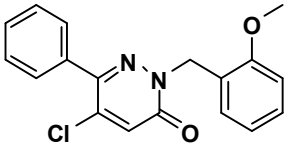
(23e)



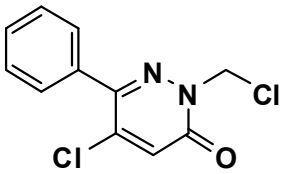
(23f)



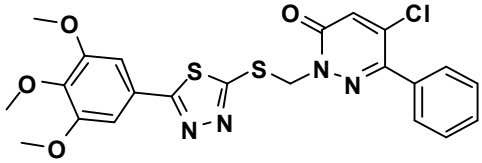
(23g)



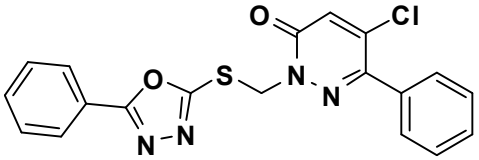
(23h)



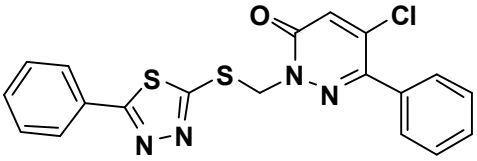
(24)



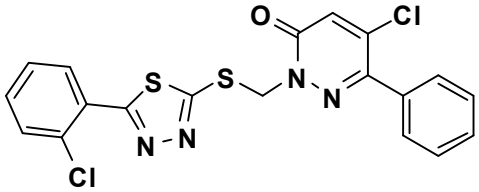
(25a)



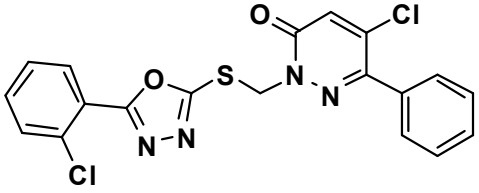
(25b)



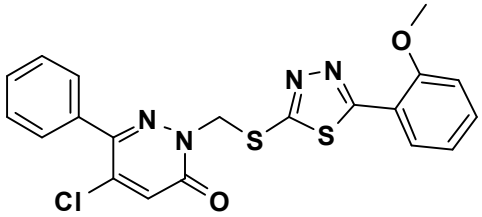
(25c)



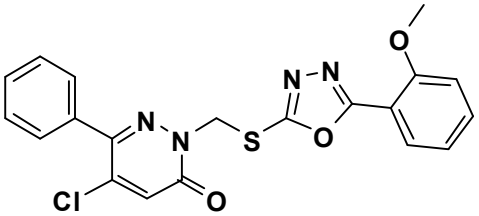
(25d)



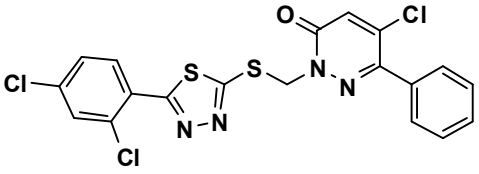
(25e)



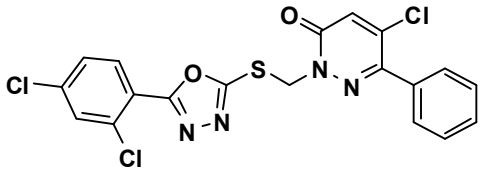
(25f)



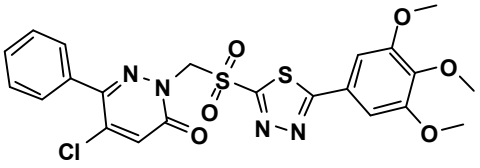
(25g)



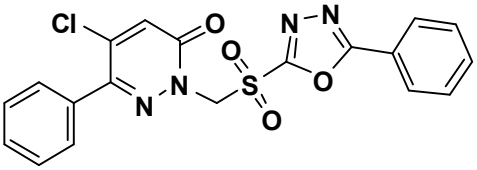
(25h)



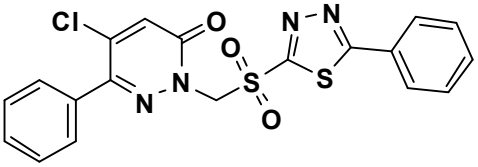
(25i)



(26a)

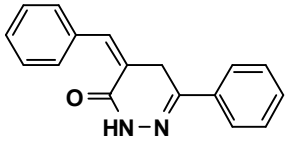


(26b)

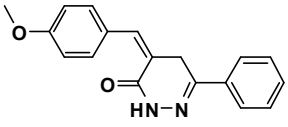


(26c)

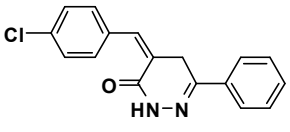
Some derivatives of pyridazinone (27a-e) were synthesized andtheir anti-bacterial activity wastested as antimicrobial agents against *S. aureus* (MTCC 737), *S. epidermidis* (MTCC 3615), *P. aeruginosa* (MTCC 424) and *E. coli* (MTCC 1687). The concentration of the test compound used was 50 mg/ml and ampicillin was taken as the standard drug. Compounds 27c and 27e showed excellent activity against *E. coli* and *P. aeruginosa* when tested at 50 mg/ml concentration taking ampicillin as the standard. From the above results, it may be concluded that the derivatives of pyridazinone possess moderate to potent antimicrobial activity when compared to standard, ampicillin [44].



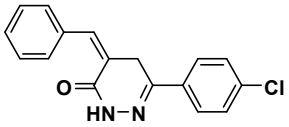
(27a)



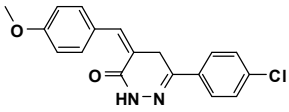
(27b)



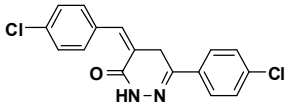
(27c)



(27d)

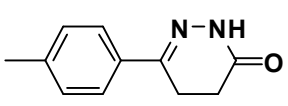


(27e)

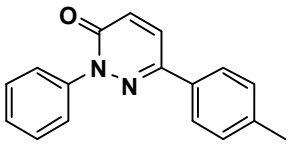


(27f)

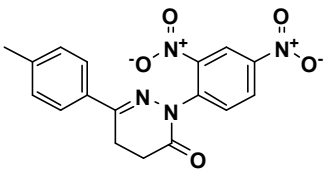
The designing of selected 6-(4-methylphenyl)-4,5-dihydropyridazin-3(2*H*)-one, 6-(4-benzyl phenyl)-4,5-dihydropyridazin-3(2H)-one and 6-(4-phenoxyphenyl)-4,5-dihydro-pyridazin-3(2H)-one derivatives were tested as *in-vitro* anti-bacterial agents, compound no. III *j* was found to be most effective against Gram positive strains*S. aureus* and *B. cereus* whereas compound no. III *n* was found to be most effective against Gram negative strains*E. coli* and *S. flexneri*. Four microbial strains were selected on the basis of their clinical importance in causing diseases in humans. Two Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538 P) and *Bacillus cereus* ATCC 11770) and two Gram-negative bacteria (*Escherichia coli* 01547 NCTC 12980 & *Shigella flexneri* ATCC 9199) were used for evaluation of antimicrobial activity of the compounds. Levofloxacin, Meropenem and Vancomycin were used as a standard. The zone of inhibition produced against the test bacterium, compound 28j was found to be most effective against *S. aureus* and *B. cereus* (Gram-positive) showing the maximum zone of inhibition and 28n was found to be most effective against *E. coli* and *S. flexneri* (Gram-negative) showing maximum zone of inhibition [45].



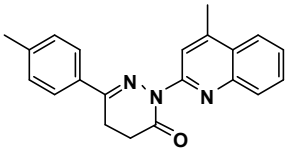
(28a)



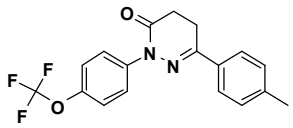
(28b)



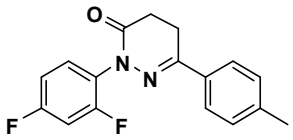
(28c)



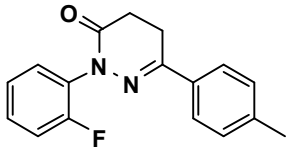
(28d)



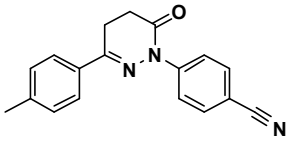
(28e)



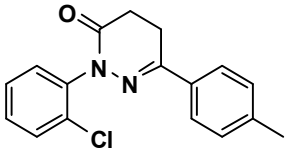
(28f)



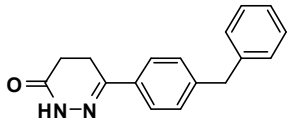
(28g)



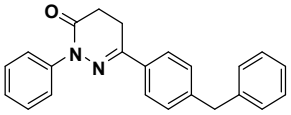
(28h)



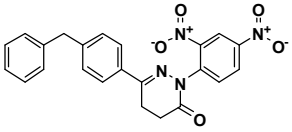
(28i)



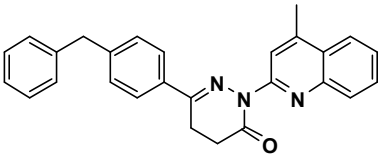
(28j)



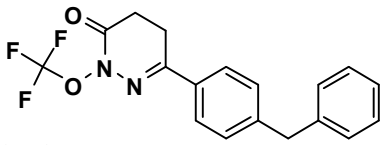
(28k)



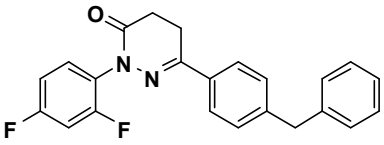
(28l)



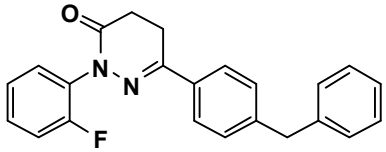
(28m)



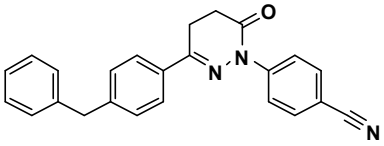
(28n)



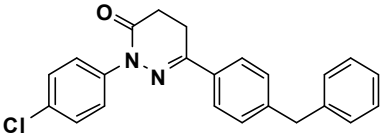
(28o)



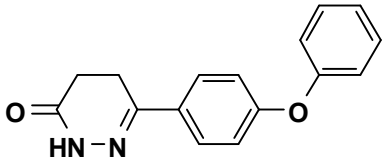
(28p)



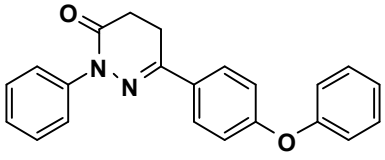
(28q)



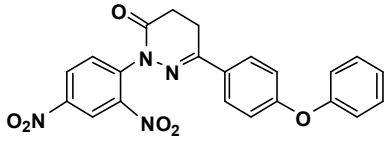
(28r)



(28s)

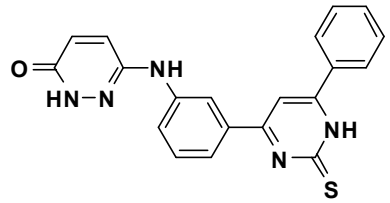


(28t)

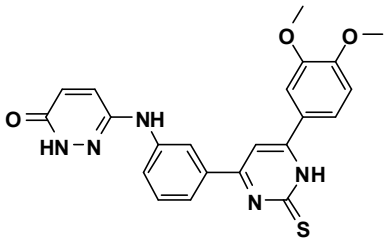


(28u)

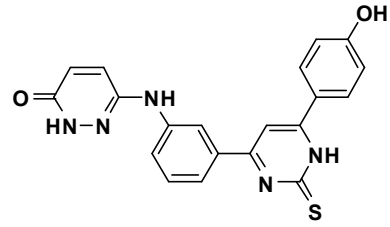
Several substitute pyridazine compounds (29a-d) were screened for their antimicrobial activity. Most of the compounds showed significant antibacterial and antifungal activities. All of the synthesized compounds were screened for their antimicrobial activity against the Gram –ve bacteria *Escherichia coli* (ATCC 8739) and Gram +ve bacteria *Staphylococcus aureus (ATCC6538*), in addition to their antifungal activity against *Aspergillus Niger* (ATCC16404) and *Candida albicans* (ATCC10231). Compounds29a, 29c and 3i show highly efficient antibacterial activity against *S. aureus* (*ATCC* 6538) more than Penicillin standard. Compounds 29g, 29h, 29i and 29l showed antifungal activities more than reference antifungal. Many synthesized compounds werealso found to be efficient equivalent to standard, e. g. Penicillin, Griseofulvin [46].



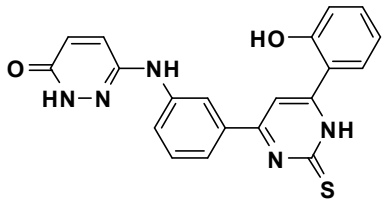
(29a)



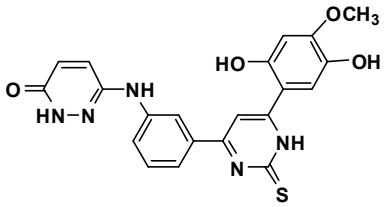
(29b)



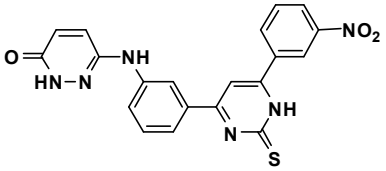
(29c)



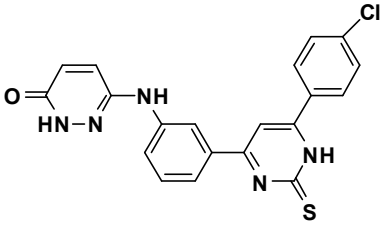
(29d)



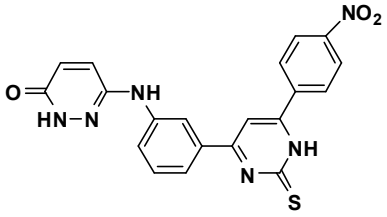
(29e)



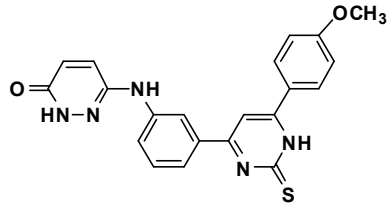
(29f)



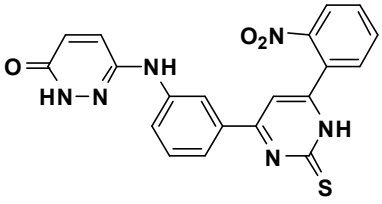
(29g)



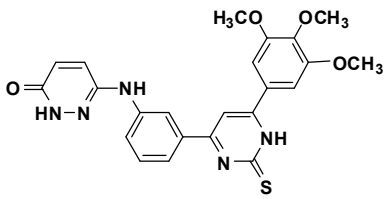
(29h)



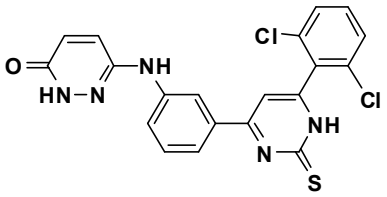
(29i)



(29j)



(29k)



(29l)

Further optimization of the chemical synthesis can possibly lead to more active molecules against fungal infections. The pyridazinones have diverse potential, further drew attention because of their easy functionalization at various ring positions insisted us to work on designing and development of novel pyridazine as anti-microbial agents. Therefore, the experimental study justifies the therapeutic application of the pyridazinone moiety in the present era. Since all twelve compounds showed promising results, studies to establish their *in vivo* efficacy will be carried in the future.

DISCUSSION

Pyridazinone nucleus exhibited immense pharmacological activities. The simple pyridazinone nucleus is present in compounds which are evaluatedfor new products that possess some remarkable pharmacological activities, such as anti-inflammatory, cardiotonic, antihypertensive, analgesic, anti-platelet aggregation, vasodilatory, antidiabetic and anticonvulsant. This review focuses on pyridazinones which possess potential activities that are new in development. The pyridazinones have diverse potential, further drew attention because of their easy functionalization at various ring positions insisted us to work on designing and development of novel pyridazine as anti-microbial agents [47-53]. The synthesized compounds showed very encouraging results. As a part of research project, the knowledge gained by various literatures has suggested that substituted pyridazine which possess good pharmacological activity with lower toxicities.So substituting or adding a new moiety to the parent lead compound thus by making gradual changes in the structure of compound resulting gradual change in physicochemical properties and biological activities of drug.

CONCLUSIONS

From the literature review we find that pyridazine derivatives was found to be having activity like anti-hypertensive, antiproliferative, anti-inflammatory activity and anti-fungal activity. Therefore it was aimed to synthesize the novel series of pyridazine and its derivatives and to evaluate the biological activities of newly synthesized compounds. Pyridazines occupy a distinct and unique place in our life. This hetero cyclic moiety has great biological and medicinal significance. A large array of pyridazine drugs possesses a variety of medicinal properties. Pyridazines have been shown more importance properties in the field of synthetic organic chemistry. The method used in the synthesis of newer pyridazine was found good because all products obtained have moderate to good percentage yield. Many of newer pyridazines were shown antimicrobial activities.

ACKNOWLEDGMENTS

The Authors are thankful to GRD(PG)IMT, Dehradun, Uttarakhand, India for providing technical support during the study.

REFERENCES

1. Asif, M. and A. Singh, 2013. Lakshmayya. The development of structurally different new antitubercular molecules containing pyridazine ring system. Chron. Young Scientists, 4(1): 1-8.
2. Shamroukh A.H., AE. Rashad, NA. Marsok, AH. El-Sayed, JA. Micky, H.M.I. Abdallah and F.M.E. Abdel-Megeid, 2016. Synthesis and Biological Evaluation of Some 1, 2, 4-Triazoles and [1,2,4]Triazolo[4, 3-*b*]-Pyridazine Derivatives. World J. Chem., 11(1): 01-08.
3. Carmellino, M.L., G. Massolini, G. Pagani, F. Zani and G. Leri, 1993. Fungicidal and genotoxic activity of new substituted pyridazinones. Farmaco, 48(10): 1427-1438.
4. Wang, Z., Mwang and X. Yao, 2012. Design, synthesis and antiviral activity of novel pyridazines. Eur J. Med. Chem., 54: 33-41.

5. Abdelrazek, F.M., F.A. Michael and A.E. Mohamed, 2006. Synthesis and molluscicidal activity of some 1,3,4-triaryl-5-chloropyrazole, pyrano-[2,3-c]pyrazole, pyrazolylphthalazine and pyrano[2,3-d]thiazole derivatives. Arch. Pharm., 339(6): 305-312.
6. Abouzid, K., M. A. Hakeem, O. Khalil and Y. Makla, 2008. Pyridazinone derivatives: Design, synthesis and *in vitro* vasorelaxant activity. Bioorg & Med Chem, 16: 382–389.
7. Abubshait, S.A., 2007. An efficient synthesis and reactions of novel indolylpyridazinone derivatives with expected biological activity. Molecules, 12(1): 25-42.
8. Asif, M., S. Anita, Lakshmayya, A.A. Siddiqui and A. Husain, 2011 Anti-inflammatory and Antinociceptive Activities of 6-phenyl (3'-imino-benzylidene)-4-benzylidene-2,3,5-trihydro-3-(2H)-pyridazin-3-one Compounds. Acta Pharm Sci., 53: 563-575.
9. Asif, M., A. Anita Singh and A.A. Siddiqui, 2012. The effect of pyridazine compounds on the cardio-vascular system. Med Chem Res., 21: 3336-3346.
10. Asif, M., A. Singh, Lakshmayya, A. Husain and A.A. Siddiqui, 2013. Anticonvulsant and antitubercular activities of 6-Phenyl/Biphenyl-4-yl-2-[2-(pyridin-2-ylamino)-ethyl]-and6-(Biphenyl-4yl)-2-(2N-subtituted amin-1-yl)-ethyl derivatives of 4,5-dihyropyridazin-3(2H)-one. LettDrug Design & Discov, 10(7): 651-660.
11. Asif, M., A. Singh and Lakshmayya, 2013. Analgesic and anti-inflammatory activities of several 4-substituted-6-(3'-nitrophenyl)pyridazin-(2H)-3-one derivatives. Brazil J. Pharm Sci., 49(4): 903-909.
12. Asif, M., A. Singh and Lakshmayya, 2011. Anticonvulsant activity of 4-(Substituted Benzylidene)-6-(3-nitrophenyl)-4,5-dihydropyridazin-3(2H)-ones against maximal electro shock induced seizure. Middle-East J Scientific Res., 9(4): 481-485.
13. Asif, M., A. Singh and Lakshmayya, 2014. In-vivo Anticonvulsant and In-vitro Antimycobacterial activities of 6-aryl pyridazine-3(2H)-one derivatives. Am J. Pharmacolog Sci., 2(1): 1-6.
14. Asif, M., A. Singh and Lakshmayya, 2013. In-vivo anticonvulsant and In-vitro Antitubercular activity of methyl indole derivative of some 6-aryl-4,5-dihydropyridazin-3(2H)-ones their expected anticonvulsant mechanisms. Iranian J. Pharm Sci., 9(1): 67-80.
15. Asif, M. and A. Singh, 2010. Exploring potential, synthetic methods and general chemistry of pyridazine and pyridazinone: A brief introduction. Inter J Chem Tech Res, 2(2): 1112-1128.
16. Asif, M., D. Singh and A Singh, 2011. Analgesic activity of some 6-phenyl-4-substituted benzylidenetetrahydro pyridazin-3(2H)-ones. Global J. Pharmacol., 5(1): 18-22.
17. Asif, M., 2013. Antifeedant, herbicidal and molluscicidal activities of pyridazinone compounds. Mini Rev in Org Chem, 10(2): 113-122.
18. Asif, M., 2014. The Study of Pyridazine Compounds o nProstanoids: Inhibitors of COX, cAMP Phosphodiesterase and TXA2 Synthase. Journal of Chem, http://dx.doi.org/10.1155/2014/703238.
19. Bansal, R., D. Kumar and R. Carron, 2009. Synthesis and vasodilatory activity of some amide derivatives of 6-(4-carboxymethyloxyphenyl)-4,5-dihydro-3(2H)-pyridazinone. Eur J. Med. Chem., 44: 4441–4447.
20. Cao, S., G.H. Song, Y.C. Qu, N. We, D. Lu, Li and Q.C. Huang, 2005. Synthesis and biological activity of 5-(3'-aryl-2'-oxo-5'-oxazolidinylmethoxy)-3(2H)pyridazinones. Chin. J. Appl. Chem., 22: 448- 450.
21. Cignarella, G., D. Barlocco, S. Villa, M.M. Curzu, G.A. Pinna, A. Lavezzo and A. Bestetti, 1992. Tricyclic 3-(2H)-pyridazinone derivatives. Synthesis and evaluation of their antisecretory and antiulcer activity, Eur J. Med. Chem., 27: 819-823.
22. Dumas, J.P, S.J. Boyer, J.A. Dixon, T.K. Joe, H.C.E. Kluender, W. Lee, D. Nagarathnam, R.N. Sibley and N. Su, 2004. Preparation of substituted pyridines and pyridazines with angiogenesis inhibiting activity for pharmaceutical use as antitumor agents. US Patent 6689883, [Chem.Abstr., 140: 163891].
23. Gokce, M., G. Bakir, M.F. Sahin, E. Kupeli and E. Yesilada, 2005. Synthesis of new Mannich bases of arylpyridazinones as analgesic and anti-inflammatory agents. Arzneimittelforschung, 55(6): 318-325.
24. Guan, L.P., X. Sui, X.Q. Deng, Y.C. Quan and Z.S Quan, 2010. Synthesis and anticonvulsant activity of a new 6-alkoxy-[1,2,4]triazolo[4,3-b]pyridazine. Eur J. Med. Chem, 45: 1746-1752.
25. Hu, F.Z., G.F. Zhang, Y.Q. Zhu, X.M. Zou, B. Liu and H.Z. Yang, 2007. Synthesis and biological activity of 3-aryloxy-6-(3,5-dimethyl-1H-pyrazol-1-yl)-pyridazine. Chin. J. Org. Chem., 27: 758-762.

26. Javed, K., S. Yaseen, R. Bashirand P. Rathore, 2013. Synthesis, antiproliferative and anti-inflammatory activities of some novel 6-aryl-2-(p-(Methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-ones. Eur J Med Chem, 67: 352-358.
27. Kawano, Y., H. Nagayaand M. Gyoten, 2000. Preparation of fused pyridazine compounds as drugs. WO Patent 2000020417, 2000.Chem. Abstr., 132: 265202.
28. Li, R.D., X. Zhai, Y.F. Zhao, S. Yu and P. Gong, 2007. Synthesis and anti-tumor activities of a novel series of tricyclic 1-anilino-5H-pyridazino[4,5-b]indoles. Arch. Pharm., 340: 424-428.
29. Liu, W.D., Z.W. Li, Z.Y. Li, X.G. Wang and B.D. Gao, 2005. Synthesis and biological activity of methyl N-methoxy-N-[2-(1,6-dihydro-1-substituent-6-oxo-pyridazin-3-yloxymethyl)phenl] carbamates. Chin. J. Org. Chem., 25: 445-448.
30. Malinka, W., A. Redzicka and O. Lozach, 2004. New derivatives of pyrrolo[3,4-d] pyridazinone and their anticancer effects. Farmaco, 59(6): 457-462.
31. Murty, M.S.R. and R. Rao, 2012. Synthesis and preliminary evaluation activity studies of novel 4-(Aryl/heteroaryl-2-ylmethyl)-6-phenyl-2-[3-(4-substituted-piperazine-1-yl)propyl] pyridazine-3(2H)-one derivatives as anticancer agents. Med Chem Res, 21: 3161-3169.
32. Siddiqui, A.A., R. Mishra, M. Shaharyar, A. Husain, M. Rashid and P. Pal, 2011. Triazole incorporated pyridazinones as a new class of antihypertensive agents: Design, synthesis and in vivo screening. Bioorg & Med Chem lett, 21: 1023-1026.
33. Somila, K. and S. Sarverwari, 2012. Synthesis and biological evaluation of some pyridazinone derivatives. Inter. J. Res. Pharm & Chem., 2(2): 2231-2781.
34. Sonmez, M., I. Berber and E. Akbas, 2006. Synthesis, antibacterial and antifungal activity of some new pyridazinone metal complexes. Eur. J. Med. Chem., 41(1): 101-105.
35. Sotelo, E. Fraiz, N. Yáñez, M. Terrades, V. Laguna, R. Cano and E. Ravina 2002. Pyridazines, Part XXIX: Synthesis and Platelet Aggregation Inhibition Activity of 5-Substituted-6-phenyl-3(2H)-pyridazinones. Novel aspects of their biological actions. Bioorg. Med. Chem., 10: 2873 2882.
36. Siddiqui, A.A., S.A. Ahamad, M.S. Mir, S.A. Hussain, M. Raish and R. Kaur, 2008. Synthesis and *in-vitro* antifungal activity of 6-substituted-phenyl-2-{[(4'-substituted phenyl-5'-thioxo)-1,2,4-triazol-3-yl]-methyl}-2,3,4,5-tetrahydro-pyridazin-3-one derivatives. Acta Pol Pharm-Drug Res,. 65(2): 223-228.
37. Islam, M., A.A. Siddiqui and R. Rajesh, 2008. Synthesis, antitubercular, antifungal and antibacterial activities of 6-substituted phenyl-2-(3;-substituted phenyl pyridazin-6'-yl)-2,3,4,5-tetrahydropyridazin-3-one. Acta Pol Pharm-Drug Res., 65(3): 353-362.
38. Islam, M., A.A. Siddiqi, R. Rajesh, A. Bakht and S. Goyal, 2008. Synthesis and antimicrobial activity of some novel oxadiazole derivatives. ActaPolPharm-Drug Res., 65(4): 441-447.
39. El-Shehry, M.F., K.M. Abu-Zied, E.F. Ewies, S.M. Awad and M.E. Mohram, 2013. Synthesis of some novel azaheterocycles utilizing 3-(4-nitrobenzylidene)-5-phenylfuran-2(3H)-one with expected antimicrobial activity. Der Pharma Chemica, 5(5): 318-326.
40. Islam, M. and A.A.H. Aljaiyash, 2013. Synthesis, antifungal and antibacterial activities of 3-substituted phenyl-6-substitutedphenyl-(1,2,4)-triazolo-(4,3-b)-pyridazines. Der Pharm Lett, 5(5): 27-34.
41. Dogruer, D.S., T. Onkol, S. Ozkan, S.Ozgen and MF. Sahin, 2008. Synthesis and Antimicrobial Activity of Some 3(2H)-Pyridazinone and 1(2H)-Phthalazinone Derivatives. Turk J Chem., 32: 469-479.
42. Singh, A.K. and N.K. Srivastav, 2012. Synthesis and Antimicrobial Activity of 4-aryl furo Pyridazines. J. Nepal Chem. Soc., 30: 66-70.
43. Wu, J., B. Song, H. Chen, P. Bhadury and D. Hu, 2009. Synthesis and Antifungal Activity of 5-Chloro-6-Phenylpyridazin-3(2H)-one Derivatives. Molecules, 14: 3676-3687.
44. Alang, G., R. Kaur, A. Singh, P. Budhlakoti and A. Singh, 2011.Synthesis, characterization and anti-bacterial activity of certain 2,3,4,5-tetrahydropyridazinone analogues. Turk J. Pharm. Sci., 8(1): 71-80.
45. Khokra, S.L., S. Seth, B. Saharan and Ankita, 2014. Designing, synthesis and biological evaluation of novel pyridazinone derivatives. Pharmacophore, 5(4): 517-534.
46. Tupare, S.D. and RP. Pawar, 2015. Synthesis and microbial evaluation of some newer 6-(3-(1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-yl) phenyl amino) pyridazin-3(2H)-one via a novel chalcone series. Eur J Pharm & Med Res., 2(4): 750-756.
47. Sukuroglu, M., E. Kupeli, E. Banoglu, S. Unlu, E. Yesilada and M.F. Sahin, 2006. Synthesis and analgesic activity of some 4,6-disubstituted-3(2H)-pyridazinone derivatives. Arzneimittelforschung, 56(5): 337-345.
48. Trah, S., C. Lamberth and S. Wedeborn, 2008. Novel pyridazine derivatives. WO Patent 2008049584.; [Chem. Abstr. 2008, 148, 495967].

49. Xu, H., X.M. Zou, Y.Q. Zhu, B. Liu, H.L. Tao, X.H. Hu, H.B. Song, F.Z. Hu, Y. Wang and H.Z. Yang, 2006. Synthesis and herbicidal activity of novel alpha, alpha, alpha-trifluoro-m-tolyl pyridazinone derivatives. Pest Manag. Sci., 62(6): 522-530.
50. Yang, H.Z., H. Xu, X.H. Hu, X.M. Zou, B. Liu, Y.Q. Zhu and F.Z. Hu, 2007. Method for preparation of 3-substituted aminopyridazine derivatives with herbicidal activity.CN Patent 101058563, 2007; [Chem. Abstr., 147, 541889].
51. Yang, H.Z., H. Xu, X.M. Zou, F.Z. Hu, B. Liu and X.F. Yang, 2005. Method of preparation 4-substituted phenyl pyridazine compounds as herbicide. CN Patent 1676518, [Chem. Abstr. 2005, 144, 412521].
52. Zou, X.J., G.Y. Jin and Z.X. Zhang, 2002. Synthesis, fungicidal activity and QSAR of pyridazinone-thiadiazoles. J. Agric. Food Chem., 50: 1451-1454.
53. Zou, X.J., L. H. Lai, G.Y. Jin and Z.X. Zhang, 2002. Synthesis, fungicidal activity and 3D-QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. J. Agric. Food Chem., 50: 3757-3760.