INTERNATIONAL JOURNAL OF PHARMACEUTICAL CHEMISTRY RESEARCH
eISSN: 2278 – 8700

REVIEW ARTICLE

Mini review on Antimicrobial and anticancer activities of pyridazin-3-thiones derivatives

Mohammad Asif

Department of Pharmacy, Guru Ram Das (PG) Institute of Management and Technolgy, Dehradun, (Uttarakhand), 248009, India

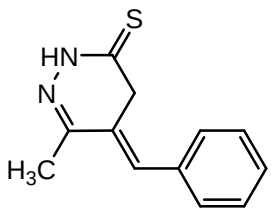
Corresponding author: Mohammad Asif

ABSTRACT:
The pyridazin-3-thiones derivatives were mainly exhibited for the antimicrobial activity. The anti-microbial activities exhibited against various microbial strains sach as Staphylococcus aureus, Escherichia coli, Bacillus subtillis and Candida albicans. Some pyridazin-3-thiones derivatives were also tested as anticancer agents. The pyridazin-3-thiones derivatives were exhibited significant both antimicrobial and anticancer activities.
Keywords: Pyridazin-3-thiones, Anti-microbial, pyridazinones, pyridazine, antitumor activity.

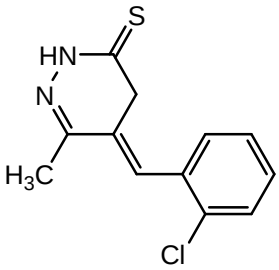
INTRODUCTION

The chemistry of pyridazines and their derivatives has received considerable attention owing to their synthetic and effective biological importance. The pyridazine derivatives are known for their therapeutic potentials. Pyridazines have been reported to possess antimicrobial, antituberculosis, antifungal, anticancer, antihypertensive, herbicidal, anti-inflammatory, anti-HIV, antioxidant, antihistaminic, antinociceptive, anthelmintic, antidiabetic, cardiotonic, antifungal, anti-hepatitis C virus, protein tyrosine phosphatase inhibitors activities and also as humans rhinovirus inhibitors and other properties are also reported [1-10]. They also have an immense potential in agricultural science as plant growth regulators and crop protection agents. The incorporation of different groups or moieties increases biological activities and thus it was of value to synthesize some heterocyclic derivatives having different groups or moieties in the same molecules. Several derivatives of pyridazine incorporating different groups have been shown to display a wide spectrum in biological and therapeutic areas [11-15]. Encouraged by these reports, we study pyridazine derivatives and their biological activities.

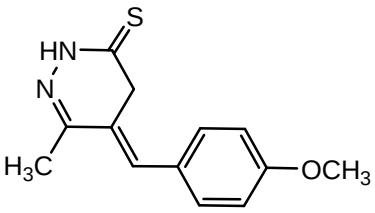
Biological activity: The pyridazin-3-thiones containing the group sulfur have important pharmacological activities but they have mainly antimicrobial (antibacterial and antifungal) and also have anticancer activity [16-20].



1



2

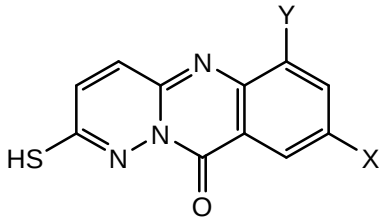


3

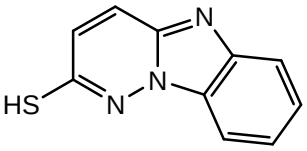
Antimicrobial activity: The acute toxicity study showed that the synthesized derivatives are tolerated. Indeed, the limit dose of 1500 mg.kg-1 intraperitoneally caused no lethality until 14 days. Lethal dose 50 (LD50) is probably more than 1500 mg/kg. The compounds (**1-3**) were tested for antibacterial activity against certain pathogenic bacteria gram positive *Staphylococcus aureus*,

Bacillus subtillis, gram negative *Escherichia coli* and antifungal activity against *Candida albicans.* Thus only the derivative **2** showed significant activity against *S. aureus* and *E. coli.* The presence of an electron attractor groups on the aromatic ring as chloro group is favorable for that activity. The derivative **3** containing the aromatic ring substituted by an electron donor by mesomeric effect (-OCH_3) inhibit the activity. In the case of *C. albicans* chloro group is not necessary, since the derivatives **1** and **2** have similar activity, however the (-OCH_3) group inhibits the activity. In conclusion, among the synthesized product **2** has a significant antimicrobial activity; in addition the acute toxicity study showed that this derivative has a low toxicity [21].

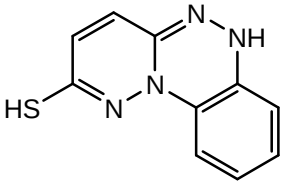
The benzimidazolo-pyridazine thione, and 1,2,4-benzotriazinopyridazinethione, imidazo-[1,2-b]-pyridazinethione, 1,2,4-triazolo[4,3-b]pyridazine-thione derivatives were testes their antimicrobial activity. These compounds possess a highly response against gram-positive and gram negative bacteria as well as fungi.



4a X=Y=H
4bX=Y=Br
4cX=Br,Y=H

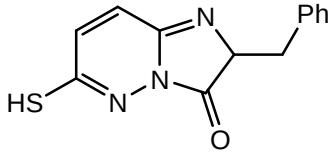


5

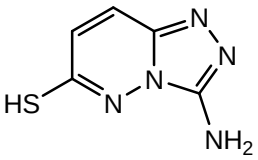


6

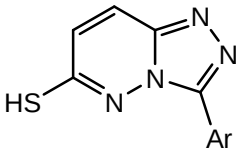
4a-c



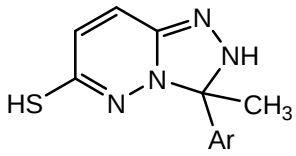
7



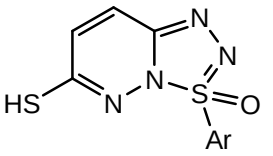
8



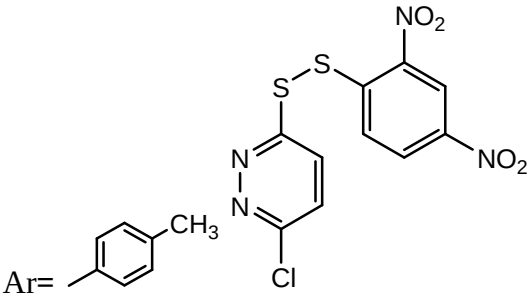
9a Ar=C_6H_4-Cl-*p*; **9b9b**Ar= -C_6H_5



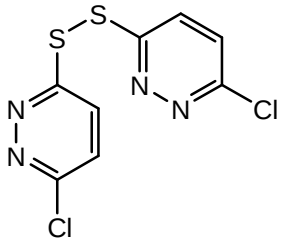
10a Ar= -C_6H_5; **10b** Ar=C_6H_4-NO_2-*m*



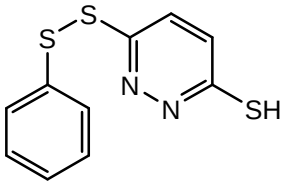
11



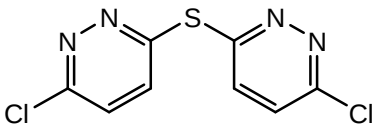
12



13



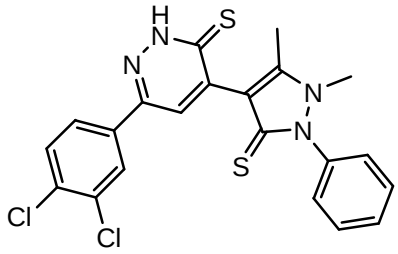
14



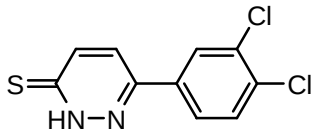
15

The compounds (**4-15**) have been tested for their antibacterial activity against *Staphylococcus aureus* ATCC6538P, *Bacillus subtilis* ATCC6633, *Pseudomonas aurignosa* ATCC9027, and *Echerichia coli* ATCC8739 and antifungal activity against *Candida albicans* ATCC2091, *Aspergillus niger*,at a concentration of 500 μg/mL in DMF. Ampicillin and mycostatin, at a concentration 500 μg/mL, were used as standard against bacteria and fungyi, respectively. From the data, it is clear that compounds (**4a**), (**6**) and (**11**) possess high activity, while compounds (**5**), (**8**), (**10b**), and (**13**) possess moderate activity against grampositive strains. As far as gram-negative microorganisms are concerned, compounds (**4a**), (**11**), and (**13**) showed high activity while

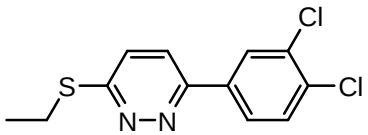
compounds (**5**), (**9a**), and (**12**) displaymoderate activity. Compounds (**11**) and (**14**) also exerted high activity while compounds (**4a**), (**5**), (**6**), and (**10b**) have moderate activity against fungi [22].



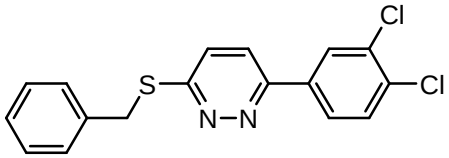
(**16**)



(**17**)

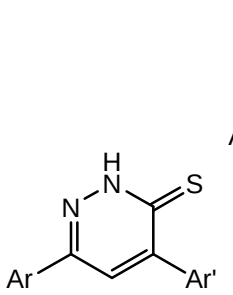


(**18a**)

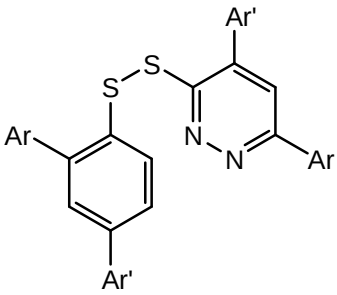


(**18b**)

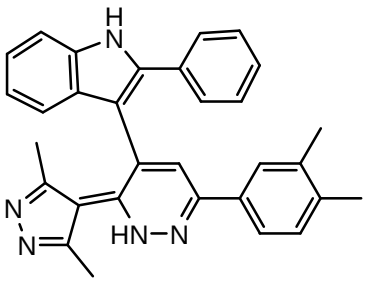
Some of the compounds showed antimicrobial and antifungal activities. The antimicrobial activity of the prepared compound **16** was tested. The compound **16** possess high activity against Gram positive strains. As far as Gram negative microorganisms are concerned, compound **16** display moderate activity and compounds **18a** moderate activity against fungi [23].



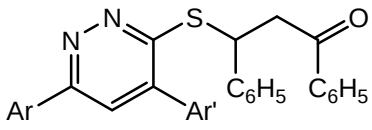
19



20

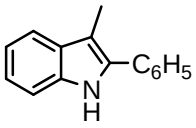


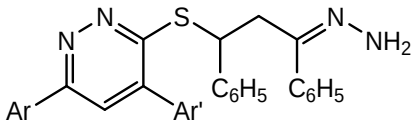
21



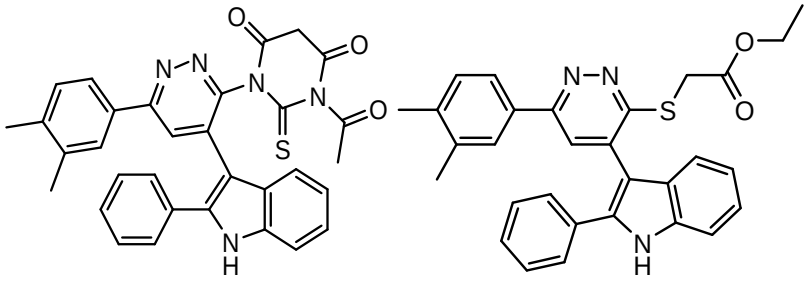
22

Ar=3,4-$(CH_3)_2C_6H_3$ Ar'=

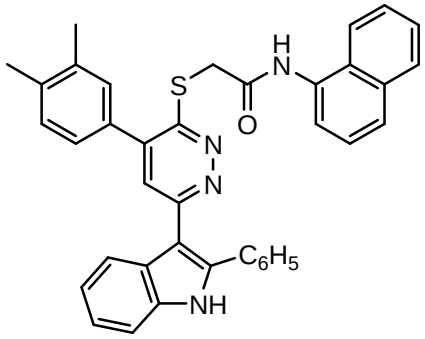


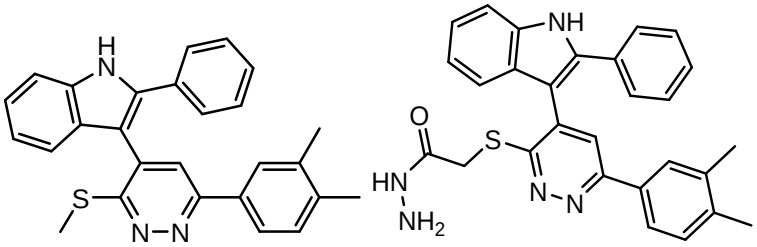


23

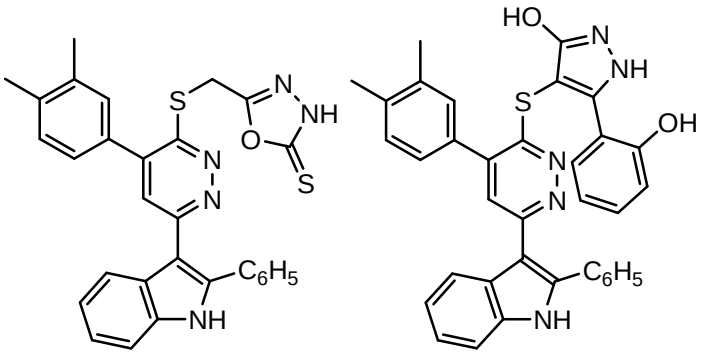


24 **25**





26 **27** **28**



29 **30**

Anticancer Activity: Cytotoxicity activity of the synthesized compounds (**19-30**), Cytotoxicity against different human cancer cell lines in vitro for evaluation of anti-tumor cytotoxicity of compounds **22** and **27**, three different human cancer cell lines were used: MCF7 (breast carcinoma cell line), HEPG2 (hepatocellular carcinoma cell line), HCT116 (colon carcinoma cell line) cytotoxicity and IC_{50} values of the tested. Compounds **22** and **27** are the compounds of lowest IC_{50} which means that they are the most effective cytotoxic drugs, accordingly compounds **27** can be used as very potent cytotoxic drug for colon carcinoma cell, while **22** as moderate cytotoxic drug for colon and liver carcinoma cell respectively, while the remaining compounds are very weak cytotoxic drug. A series of **22** and **27** compounds have different anti-tumar effects and IC_{50} values of them were discussed. Compounds **27** can be used as very potent cytotoxic drug for colon carcinoma cell, while **22** as moderate cytotoxic drug for colon and liver carcinoma cell respectively, while the remaining compounds are very weak cytotoxic drug.

CONCLUSION:

6-Chloropyridazin-3(2*H*)-thione (**1**) has been shown to be a useful building block for the synthesis of some dropyridazino[6,1-b]quinazolin-10-ones, 1,2,4-benzotriazinopyrid-azinethione, imidazo[1,2-b]pyridazinethione, 1,2,4-triazolo[4,3-b]pyridazinethione, and disulfide. Some of these compounds possess a highly response against gram-positive and gram-negative bacteria as well as fungi. Prompted by these observations and in continuation to work on the synthesis of new thiopyridazine compounds, the use of pyridazin-3(2*H*)-thione to evaluate their biological activities manly antimicrobial and anticancer activities.

REFERENCES

1. Rathish I.G., Kalim J., Shamim A., Sameena B., Alam M.S., Akhter M., Pillai K.K., Ovais S., Samim M. Synthesis and evaluation of anticancer activity of some novel 6-aryl-2-(psulfamylphenyl)-pyridazin-3(2H)-ones. Eur. J. Med. Chem., 2012, 49, 304-309.
2. Sotelo E., Coelho A., and Raviña E., Pyridazine derivatives: still–based approaches in the synthesis of 5-substituted -6-phenyl-3(2H)-pyridazinone. Chem. Pharm. Bull. 2003, 51 (4), 427-430.
3. Mangalagiu II. Recent achievements in the chemistry of 1,2-diazines. *Curr Org Chem,* 15(5), 730–752, 2011.
4. Asif M, Singh A, Lakshmayya. *In-vivo* Anticonvulsant and *In-vitro* Antimycobacterial activities of 6-aryl pyridazine-3(*2H*)-one derivatives. *Am J Pharmacolog Sci*, 2014, Vol 2, Issue 1, 1-6.
5. Asif M, Singh A, Lakshmayya. *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*, 2013, vol 9, Issues 1, 67-80.
6. Asif M, Singh D, Singh A. Analgesic Activity of Some 6-Phenyl-4-Substituted Benzylidene Tetrahydro Pyridazin-3(*2H*)-ones. *Global J Pharmacol*, 2011, Vol 5 Issue 1, 18-22.
7. R. M. Butnariu and I. I. Mangalagiu. New pyridazine derivatives: synthesis, chemistry and biological activity. *Bioorg & Med Chem*, 17(7), 2823–2829, 2009.
8. X. Han, Y. H. Hong, Z. H. U. You Quan, Z. X. Mao LIU Bim, H. U. Fang Zhong, and Y. H. Zheng. Synthesis and herbicidal activities of novel 4-(3-trifluoromethylphenyl)-2H-pyridazin-3-one derivatives. *Science China Chem*, 53(1), 157–166, 2010.
9. R. B. Tucaliuc, I. M. Risca, G. Drochioiu, and I. Mangalagiu, "Biological effect of some new pyridazine derivatives on wheat in germination experiments," *Romanian Biotechnol Lett*, 13(4), 3837–3842, 2008.

10. Al. I. Cuza., 2009. New Pyridazine Derivatives: Synthesis, Chemistry and Biological Activity. Bioorg Med. Chem., 17(7): 2823-2829.
11. Palazzo, E., M.G. Rimoli, M. De. Chiaro, F. Guida, D. Melisi, A. Curcio, V.de. Novellis, I. Marabese, F. Rossi and E. Albignente, 2010. Intra-periaqueductal grey microinjections of an imidazo [1,2-b]pyridazine derivative, DM2, affects rostral ventromedial medulla cell activity and shows antinociceptive effect.; Neuropharmacology, 58(3): 660-667.
12. Kim, M.J., J. Lee, S.Y. Kang, S.H. Lee, E.J. Son, M. E. Jung, S.H. Lee, K.S. Song, M.W. Lee, H,K. Han, J. Kim and J. Lee, 2010. Novel C-aryl glucoside SGLT2 inhibitors as potential antidiabetic agents: Pyridazinylmethylphenyl glucoside congeners.; Bioorg Med. Chem. Lett, 20(11): 3420-3425.
13. Asif M, Singh A, Siddiqui AA. The effect of pyridazine compounds on the cardiovascular system. *Med Chem Res*, 2012, Vol 21, 3336–3346. Impact Factor 1.61
14. Asif M, Singh A. Exploring potential, synthetic methods and general chemistry of pyridazine and pyridazinone: A brief introduction. *Inter J Chem Tech Res*, 2010, Vol. 2, Issue 2, 1112-1128.
15. Asif M. Antifeedant, herbicidal and molluscicidal activities of pyridazinone compounds. *Mini Rev in Org Chem*, 2013, Vol.10 Issue 2, 113-122.
16. Holler S, Tüchler M, Belaj F, Veiros LF, Kirchner K, Mösch-Zanetti NC. Thiopyridazine-Based Copper Boratrane Complexes Demonstrating the Z-type Nature of the Ligand. Inorg Chem. 2016 55(10):4980-91.
17. Rostkowska H, Lapinski L, Reva I, Almeida BJ, Nowak MJ, Fausto R. UV-induced hydrogen-atom transfer in 3,6-dithiopyridazine and in model compounds 2-thiopyridine and 3-thiopyridazine. J Phys Chem A. 2011; 115(44): 12142-9.
18. Xing X, Chang LC, Kong Q, Colton CK, Lai L, Glicksman MA, Lin CL, Cuny GD. Structure-activity relationship study of pyridazine derivatives as glutamate transporter EAAT2 activators. Bioorg Med Chem Lett. 2011; 21(19):5774-7.
19. Fathy A. Yassin, Amal F. Seleim. Synthesis and reactions of 5-phenylpyrido-[3,2-d]-pyridazin-8(7*H*)-one derivatives. Der Pharma Chemica, 2013, 5(3):1-7.
20. Dyck B, Markison S, Zhao L, Tamiya J, Grey J, Rowbottom MW, Zhang M, Vickers T, Sorensen K, Norton C, Wen J, Heise CE, Saunders J, Conlon P, Madan A, Schwarz D, Goodfellow VS. A thienopyridazinone-based melanin-concentrating hormone receptor 1 antagonist with potent in vivo anorectic properties. J Med Chem. 2006; 49(13):3753-6.
21. Benmoussa A, El harti J, Ansar M, Bouchrik M, Zahidi A, Cherrah Y, Bouklouze A, Taoufik J. Synthesis and Antimicrobial Properties Of Some Pyridazin-3-Thiones Derivatives. Inter J Pharm Tech Res, 4(4), 1591-1594, 2012.
22. Abd El-Salam NA, Mostafa MS, Ahmed GA, Alothman OY. Synthesis and Antimicrobial Activities of Some New Heterocyclic Compounds Based on 6-Chloropyridazine-3(2*H*)-thione. Journal of Chemistry, 2013, Article ID 890617, 8 pages. http://dx.doi.org/10.1155/2013/890617.
23. G.H. Sayed, A.A. Hamed, G.A. Meligi, W.E. Boraie and M. Shafik. The Use of 4-(3,4-Dichlorophenyl)-4-Oxo-2-(4-Antipyrinyl)-Butanoic Acid in the Preparation of Some New Heterocyclic Compounds With Expected Biological Activity. Molecules 2003, 8, 322-332.
24. Abd El-Ghaffar NF, Kadah MS, Sayed GH, Radwan AM, Abd Elal SN. The use of pyridazine thione derivative in the preparation of some new heterocyclic compounds with expected antitumor activity. J Chem & Pharm Res, 2012, 4(10): 4562-4569.