A Short Review on Biological Potential Thiopyridazine Analogues

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Abstract

Pyrazidinone/thiopyrazidinone derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities such as cardiovascular properties, anti-inflammatory, analgesic, anti-diabetic, antiviral, anticancer, antimicrobial, anti-convulsant and other biological activities. Some pyrazidinithiones were tested for biological activities. Various pyrazidinone/thiopyrazidine derivatives were exhibited anti-convulsant activity against maximal electroshock seizure test, various pyrazidine-thione derivatives were exhibited antitumor activity and some thiopyrazidines were exhibited anti-microbial activity against various strains like Staphylococcus aureus, Escherichia coli, Bacillus subtilis and Candida albicans. Tricyclic ring system, pyridazino[6,1-b]quinazolin-10-ones, benzimidazolo-pyridazine thione, and 1,2,4-benzotriazino-pyridazine thione along with imidazo[1,2-b]-pyridazinethione, 1,2,4-triazolo[4,3-b] pyridazine-thione derivatives were exhibited antimicrobial activity against gram-positive and gram negative bacteria as well as fungi.

Keywords: Pyrazidinones; Anticonvulsant; Pyridazin-3-thiones; Anti-microbial; Antitumor

Introduction

The review was carried out to discuss in detail about the substituted pyridazine compounds. Heterocyclic compounds have been successfully used as antimicrobial, anticancer, anti-convulsant, hypoglycemic, antihypertensive, anti-tubercular, anti-inflammatory, analgesic, anti-viral and other useful agents. Various organo-sulfur compounds present in living and nonliving things. They occur in open chain, alicyclic, aromatic and heterocyclic compounds containing sulfur atoms or as a part of chain/ring in the structure. In this review briefly study about the structure features and biological interest of thio-pyridazine derivatives and concluded that many researches had tested on thio-pyridazine derivatives having the biological activities. The chemistry of pyridazines and their fused heterocyclic derivatives has received considerable attention due to their effective biological importance. Pyridazines have been reported to possess antimicrobial [1-3], antituberculosis [4-6], antifungal [7], anticancer [8], antihypertensive [9], herbicidal [10], anti-inflammatory [11] activities, and protein tyrosine phosphatase 1B inhibitors [12]. They also have an immense potential in agriculture science as plant growth regulators and crop protection agents [13]. The incorporation of two moieties increases biological activity of both and thus it was of value to synthesize new heterocyclic compounds having two moieties in the same molecules. Various derivatives of pyridazine incorporating other heterocyclic rings have been shown to display a wide spectrum in biological and therapeutic areas [14-18].

Biological Activities

Various pyridazine derivatives have received considerable attention due to their wide range applications. Pyridazines are reported to exhibit antibacterial, antifungal, antituberculosis, anticancer, antiepileptic, antidiabetic activities and also as human rhinovirus (HRV-3) inhibitors activities. The 6-chloropyridazin-3(2H)-thione (1) for the synthesis of pyridazines to test for their antimicrobial activities [19,20]. The 6-Chloropyridazin-3(2H)-thione (1) were used as a starting material for the synthesis of some heterocyclic compounds. Compound (1) reacts with bifunctional nucleophile like antranilic acid, 2-amino-phenol, and 2-chlorophenylhydrazine to give a tricyclic system as 2-thioxo-1,2,10-trihydroxyazidino[6,1-b]quinazolin-10-ones (2a-c), benzimidazolopyridazine thione (3), and 1,2,4-benzotriazino-pyridazinthione (4) derivatives. Imidazo [1,2-b] pyridazine-thione derivative (5) was prepared by reaction of compound (1) with phenylalanine. Other compounds were also synthesized such as 1,2,4-triazolo [4,3-b] pyridazinethione derivatives (6), (7a, b), (8a, b) and compound (9). Stirring a solution of pyridazine-3-thione (1) and 2,4-dinitrobenzenesulfonyl chloride in acetic acid give 2,4-dinitrophenyl-6-chloropyridazidylsulphide (10).

The antimicrobial activities of these compounds have been tested against Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, and Escherichia coli and antifungal activity against Candida albicans, Aspergillus niger, at a concentration of 500 µg/mL in DME. Ampicillin and mycostatin, at a concentration 500 µg/mL, were used as reference drug against bacteria and fungi, respectively. Compounds (2a), (4) and (9) possess high activity, while compounds (3), (6), (8b), and Bis (6-chloropyridazyl) disulfide (11) possess moderate activity against gram positive strains. As far as gram-negative microbes are concerned, compounds (2a), (9), and (11) showed high activity while compounds (3), (7a), and (12) display moderate activity. Compounds (9) and phenyl pyridazinylthion disulfide (12) also exerted high activity while compounds (2a), (3), (4), and (8b) have moderate activity against fungi [21]. Some of these compounds possess a highly response against gram-positive and gram-negative bacteria as well as fungi (Figure 1).

Pyridazine-thione (14) was used as a key intermediate for the preparation of numerous pyrazidine derivatives such as 3,3’-(6,6-bis(3,4-dimethylphenyl)-3,3’-bipyrazidin-4,4’-diyl)-bis(2-phenyl-1H-indole) (15), 1,2-bis(6-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl) pyridazin-3-yl) disulfane (16), 2-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl)-10H-pyrazidino[6,1-b]quinazolin-10-one (17a), 8-bromo-2-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl)-10H-pyridazino[6,1-b]quinazolin-10-one (17b), 3-(6-(3,4-dimethylphenyl)-4-(2-phenyl-1H-indol-3-yl)-pyridazin-3(2H)-ylidene)pentane-2,4-

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Received August 05, 2018; Accepted August 10, 2018; Published September 17, 2018

Citation: Asif M (2018) A Short Review on Biological Potential Thiopyridazine Analogues. Med Chem (Los Angeles) 8: 259-264. doi: 10.4172/2161-0444.1000522

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A series of pyridazines containing the 2-phenylindole at 4-position hoping to improve the antitumor activity of the compounds. Potential cytotoxicity of compounds (17a, 17b, 18, 20, 26, 30a and 30b) were tested against MCF7 (breast carcinoma cell line), HEPG2 (hepatocellular carcinoma cell line), HCT 116 (colon carcinoma cell line) [22] (Figure 2).

Cytotoxicity against different human cancer cell lines in vitro for test of anti-tumor cytotoxicity of compounds 17a, 17b, 18, 20, 26,
Figure 2: A series of pyridazines containing the 2-phenylindole at 4-position to improve the antitumor activity of the compounds. Potential cytotoxicity of compounds was tested against MCF7, HEPG2, HCT 116.
and 30b, three different human cancer cell lines were used: MCF7 (breast carcinoma cell line), HEPG2 (hepatocellular carcinoma cell line), HCT116 (colon carcinoma cell line) cytotoxicity. The survival fractions were gradually decreased as the concentration of the tested compounds was increased. It shown that 18, 20, 26, 30a, and 30b are the compounds of lowest IC50 which means that they are the most effective cytotoxic drugs, accordingly compounds 26, 30a, and 30b can be used as very potent cytotoxic drug for colon carcinoma cell, while 18 and 20 as moderate cytotoxic drug for colon and liver carcinoma cell respectively, while the remaining compounds are very weak cytotoxic drug [22].

The action of phosphorus pentasulfide on the lactam function of pyridazin-3-ones, allowed us to obtain pyridazin-3-thiones, reacting the sulfur atom with several reagents (alkyl halide, hydrazine, etc.)
hydrate) [23-25]. The action of pentasulfide on ketones led to the thione function [26,27]. Thus the reaction conducted at reflux in pyridine on pyridazin-3-ones for 4 hours lead to pyridazin-3-thiones in good yields. The acute toxicity study showed that the synthesized derivatives are tolerated. Indeed, the limit dose of 1500 mg/kg l.p caused no lethality until 14 days. No effect was observed on groups of mice after oral administration at escalating doses. We deduce that the lethal dose 50 (LD₅₀) is probably more than 1500 mg/kg. The synthesized compounds 5(1'-benzylidene)-6-methyl-(2H)-pyridazin-3-thione, 5(2'-chloro-1'-benzylidene)-6-methyl-(2H)-pyridazin-3-thione, 5(4'-methoxy-1'-benzylidene)-6-methyl-(2H)-pyridazin-3-thione (31-33) were tested for antibacterial activity against certain pathogenic bacteria by disc diffusion method using both gram positive S. aureus, B. subtilis, gram negative E. coli and antifungal activity against C. albicans. Thus only the derivative 32 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 presence of an electron acceptor groups on the aromatic ring as nitro group is not necessary, since the derivatives 31 and 32 have similar activity, however the (-OCH₃) group inhibits the activity. In conclusion, among the derivatives synthesized product 32 has a significant antimicrobial activity; in addition the acute toxicity study showed that this derivative has a low toxicity with a lethal dose 50 elevated [28] (Figure 3).

Various researches indicated that the presence of at least one aryl group, one or two electron donor atoms and/or an NH group in a special spatial arrangement is essential for antiepileptic activity. The presence of at least one aryl group, one or two electron donor atoms and/or an NH group in a special spatial arrangement seems to be necessary for antiepileptic activity. A study of anticonvulsant agents reveals that the presence of an amide moiety, cyclic or not, is present in most antiepileptic's. The pyridazine ring system agrees with this salient feature and many papers have reported antiepileptic activities of pyridazine derivatives. Hence this feature of the ring system was tapped for the presence of any anticonvulsant activity [29,30]. A series of substituted 6-aryl-2,3,4,5-tetrahydro-3-pyridazinones (34a-e) and 6-aryl-2,3,4,5-tetrahydro-3-thio-pyridazinones (35a-e) were tested for their anticonvulsant activity. The substituted 6-aryl-tetrahydro-3-pyridazone (34a-e) followed by substitution with sulphur to yield the compounds (35a-35e). All the compounds 34a-e and 35a-e were tested for anticonvulsant activity by maximal electroshock-induced seizure (MES) test. The starting dose of the test compound was 10, 25, 50 and 100 mg/Kg and standard drug Phenyltoin 25 mg/Kg, some compounds showed significant activity, rest compound were showed moderate anticonvulsant activity [31] (Figure 4).

Discussion

Because of the diversity in synthetic procedures, physiological and industrial significance, hetero cyclic chemistry has been and continues to be one of the most active areas of organic chemistry. As a result numerous heterocyclic compounds have been successfully used as antibacterial, anticancer, antiparasitic, hypoglycemic, antihypertensive, antitubercular, anti-inflammatory and anti-HIV agents. In addition, they have also been used in agriculture, plastics, polymers, dyes and textiles. Hence heterocyclic chemistry still continues to draw the attention of synthetic organic chemists and is of great scientific interest. All large number of organo-sulfur compounds occur in living and non-living object. Organo-sulfur compounds lead to the fact that some of the compounds are useful in scientific and industrial growth. During the last three decades organo-sulfur chemistry developed at a much faster pace than any other branches of organic chemistry. The pyridazin derivatives are known for their therapeutic potential such as antihypertensive and cardio tonic, antifungal and other properties are also reported [32-35]. Pyridazines containing the group sulfur have important pharmacological activities.

Conclusion

Hetero cyclic chemistry has been and continues to be one of the most active areas of organic chemistry. As a result thio-pyridazine compounds have been successfully used as antibacterial, anticancer, anticonvulsant agents. Hence thio-pyridazine still continues to draw the attention of synthetic organic chemists and is of great scientific interest. Hence it can be concluded that many researches had investigated on thio-pyridazines having the biological activities.

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