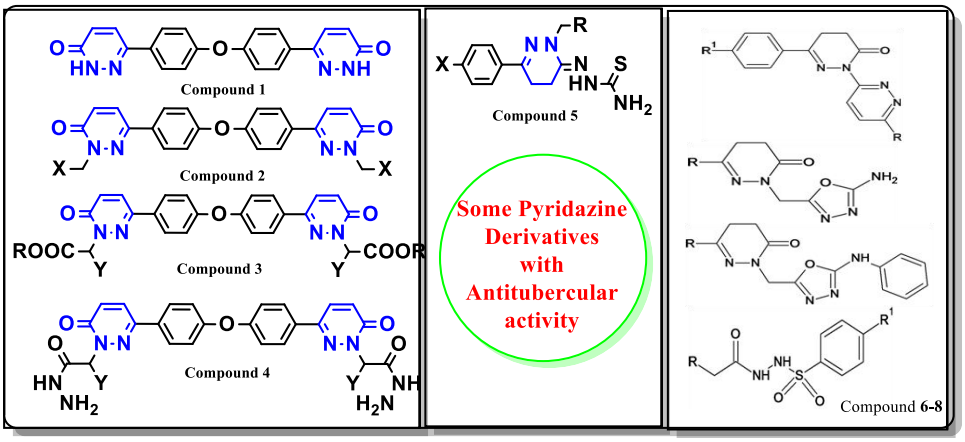
An Overview of Anti-Tubercular Activity of Some Pyridazine Compounds

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Graphical Abstract



Abstract

Tuberculosis, sometimes known as TB, is an infectious illness caused by various mycobacteria strains, the most prevalent of which is Mycobacterium tuberculosis (*Mtb*). TB is the most common contagious bacterial agent-related cause of death globally. According to the World Health Organization (WHO), about one-third of the world's population is infected with *Mtb*, with two billion people worldwide affected. As a result, despite the availability of effective anti-TB medications, tuberculosis remains a severe worldwide public health problem, necessitating the ongoing search for novel anti-TB therapies and therapy regimens. Preexisting anti-TB medications have been modified considerably, resulting in the development of innovative, effective, and non-toxic anti-TB agents. Despite more than a century of research, tuberculosis (TB) remains the most common infectious illness in humans, with an estimated 9 million new cases and 1.5 million deaths each year. The anti-tubercular effects of a novel family of nitrogen-containing heterocyclic compounds known as substituted-pyridazines were investigated. Some of these derivatives were discovered to be active against Mycobacterium TB, and their antitubercular activities were compared to those of Rifampicin, Pyrimethamine, and Cycloserine, which are all conventional antitubercular medications. These findings were backed up by the fact that pyridazine derivatives looked to be a new leading antitubercular structure, making it a viable candidate for further therapeutic development.

Keywords: Antitubercular, Heterocyclic, Pyridazine, New Drugs.
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1. INTRODUCTION

Infectious diseases caused by microbes have increased dramatically in the last few decades. The widespread use and misuse of antibiotics have caused the emergence of bacterial resistance, which is a serious problem in the treatment of bacterial diseases to human health. To overcome the development of drug resistance it is necessary to synthesize a new class of antimicrobial compounds possessing different chemical properties from those commonly used. Pyridazine belongs to an important group of heterocyclic compounds containing two nitrogen atoms in a six-member ring, both nitrogen atoms are present in adjacent positions and attached with the single bond is the most favorable form. In recent years there has been an increased interest in the pyridazine ring system. To explore the activities associated with the structural moiety -CH=N-NH-CH_2-or -CH =N-NH-CO-CH- and various substitutions.The biological and pharmacological actions of nitrogen-containing heterocyclic molecules are varied [1-2]. Pyridazine derivatives are a common heterocyclic molecule in medicinal chemistry because they offer a wide range of biological properties and uses, including antimicrobial [3-4], anti-inflammatory and analgesic [5-6], anti-HIV [7],antiplasmodial [8], antitubercular [9], antibacterial [10], anticonvulsant [11,12], COX inhibitor [13],antidiabetic [14], antihypertensive [15], anticancer [16-17], blood platelet aggregationinhibitors [18], antidepressants, anxiolytic [19,20], antioxidant [21], antitumor [22,23],antifungal and other anticipated activities [24]. They are also used as intermediates for drugs and agrochemicals because of their action, these compounds have been successfully used as systemic agricultural fungicides (against mildews and rusts of cereal grains, fruits, and vegetables) and against both systemic and topical fungal diseases in humans and domestic animals. The pyridazine moieties are regarded favored structures based on the foregoing discoveries, and as a result, they have piqued the curiosity of synthetic organic chemists. In 2006, the World Health Organization (WHO) proposed "The Stop TB Strategy." The goal of this plan is to minimize the worldwide burden of tuberculosis through 2015. The mission also promotes the creation of novel and effective instruments for TB prevention, diagnosis, and treatment. The major goal is to eliminate tuberculosis as a public health hazard by 2050 [25,26]. Multi-drug-resistant (MDR) TB has emerged globally in the last 20 years, followed by extended drug-resistant (XDR) TB, and, most recently, strains resistant to all anti-TB medications. MDR-TB is caused by mycobacteria resistant to at least Isoniazid (INH) and Rifampicin (RIF), as well as any fluoroquinolone and one of the three injectable drugs, capreomycin, kanamycin, and amikacin. XDR-TB is caused by mycobacteria resistant to RIF and INH, any fluoroquinolone, and one of the three injectable drugs, capreomycin, Drug resistance poses a serious challenge to TB control since it enhances the risk of a return to a time when medications are no longer effective [27-30]. The rapid growth of MDR and XDR *Mtb* strains has considerably contributed to the rise in TB cases and has fueled the hunt for novel treatment medications to battle the disease [32-34]. Furthermore, TB therapy has become even more difficult for AIDS patients, where the prevalence of TB and subsequent fatalities has increased by more than 10% in the last two decades (TB is currently the top cause of death among HIV patients) [35,36]. Only one new

medicine against *Mtb* has been created in the previous 45 years (Bedaquiline, code designations TMC-207 and R-207910), and even this has several negative effects [37]. As a result, one of medicinal chemistry's top priorities is to find novel anti-TB medications that are effective against *Mtb*. Because of *Mtb*'s adaptability, fighting tuberculosis is a tough, complex, and time-consuming undertaking.

Several tactics are now being utilized to produce novel anti-TB medicines [38-40]. One strategy for creating new anti-TB medications is to look for novel structures that the TB organism has never seen before, particularly for the treatment of MDR- and XDR-TB [41]. Many investigations have been conducted on nitrogen heterocyclic (5 and 6-member rings) pharmacophores with a hydrazone (or isostere) component [41-42]. The diphenyl ether nucleus is a key scaffold found in a variety of synthetic and natural derivatives with diverse pharmacological properties, including anti-TB action [44]. Anti-TB action has been shown in certain pyridine and diazine compounds [42-43]. The inclusion of certain pyridazine or pyrimidine moieties in the molecule inhibits *Mtb* to a significant degree [44,45].

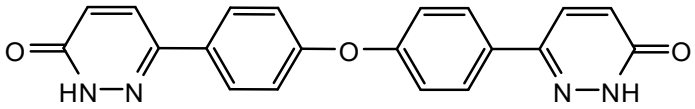
2. Pyridazinone Derivatives and Antitubercular Activity

The presence of a*llyl-* or *methylene-carboxyalkyl*groups at the *N-1* position of the pyridazine moiety also contributes to the anti-TB activity. As a part of ongoing research, aiming at the synthesis of novel biologically active compounds with anti-TB activity, namely *N1*-substituted-diphenyl ether*bis*-pyridazine.Pyridazinones, 6,6'-(Oxybis(4,1-phenylene))bis-(2-allylpyridazin-3(*2H*)-one) ***(2a)*** and Diethyl 2,2'-(3,3'-oxybis(4,1-phenylene))bis(6-oxopyridazine-3,1(*6H*)-diyl)) diacetate ***(3b)***compounds were evaluated for *in vitro* anti-TB activity against *M. tuberculosis* H37Rv. Any compound with an IC_{90} value of ≤10 μg/mL is considered 'active' for anti-TB activity. The MIC is defined as the lowest concentration affecting a reduction in fluorescence of 90% relative to controls. MIC screening was conducted for *Mtb*37Rv, isoniazid (INH)-resistant *M. tuberculosis*, rifampin (RMP)-resistant *Mtb*, and ofloxacin-resistant *Mtb*.Encouraged by the promising anti-TB activity of *N1*-substituted pyridazine derivatives, *N1*-substituted *bis*-pyridazine derivatives retain a significant activity against *Mtb*. In this respect, a new anti-TB nitrogen heterocycle, namely *N1*-substituted-diphenyl ether-*bis*-pyridazine (BP) was synthesized to combine the properties of the pharmacophore units: two pyridazine scaffolds, a diphenyl ether nucleus (act a linker between the two pyridazine units) and, *N1*-substituted side chains (*allyl-, propargyl- methylene-carboxyalkyl-* and *methylene-carbohydrazone*-). The two pyridazine units and the diphenyl ether moiety contribute to their potential anti-TB activity, while the *N1*-substituted side chains allow enough mobility (via the methylene group) to ensure a good interaction with the putative binding site.

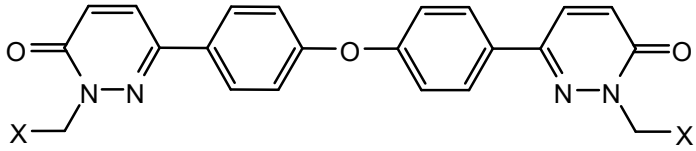
3. Biological Activity and Mechanism of Action

Tuberculosis (TB) is a contagious disease infecting one-third of the world's population and killing between 2 and 3 million people each year. The increase in TB incidence during recent years is largely due to the AIDS epidemic and also the emergence of multidrug-resistant (MDR-TB) strains. The treatment of MDR-TB has become a major concern worldwide. Therefore, recent efforts have been directed toward exploring new, potent antimycobacterial agents with low toxicity profiles when compared with currently marketed drugs. Many compounds carrying pyridazinone rings have been reported to have antimycobacterial activity. The obtained compounds were

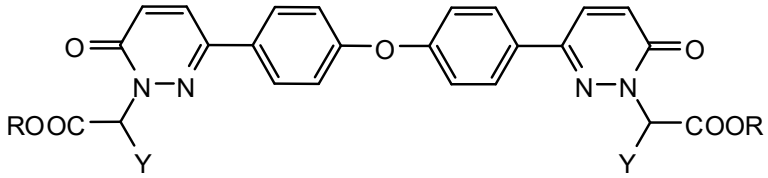
evaluated for *in vitro* anti-TB activity against *Mtbs*. The primary cycle High Throughput Screening (HTS) was conducted against *Mtb*H37Rv [9,16]. Compounds were tested, typically from 100µg/mL to 0.195µg/mL. Rifampicin, Pyrimethamine, Isoniazid, Ethambutol, Cycloserine, and Amikacin were used as reference compounds in these assays. Compounds demonstrating a percent inhibition of bacterial growth ≥90% in the primary screen were tested in the next stage of the procedure, against *Mtb*H37Rv to determine the minimum inhibition concentration (MIC) in the MicroplateAlamarBlue Assay (MABA). IC_{90} is defined as the concentration affecting a reduction in fluorescence of 90% relative to controls. Compounds with IC90 values ≤10 µg/mL were considered active anti-TB agents (Table **1)**. Compounds **1**, **2b**, **4a**, and **4b** did not exhibit anti-TB activity (MIC >100 µg/mL); compound **2b** showed only a slightly inhibitory activity against *Mtb*(IC_{50}= 33.87); while compound **3a** showed a moderate anti-TB activity (MIC=$_{50}$µg/mL and IC50= 45.89). Notably, two compounds, **3b,** and **2a** were identified as potent inhibitors against *Mtb*, with a MIC value of 25 µg/mL (IC_{50}= 17.75) respectively 50 µg/mL (IC_{50}=18.27), in the MABA assay. Moreover, their anti-TB activity was superior to the second-line anti-TB drug Pyrimethamine (MIC=100 µg/mL) and equal to Cycloserine (MIC=25 µg/mL), Table **1**.



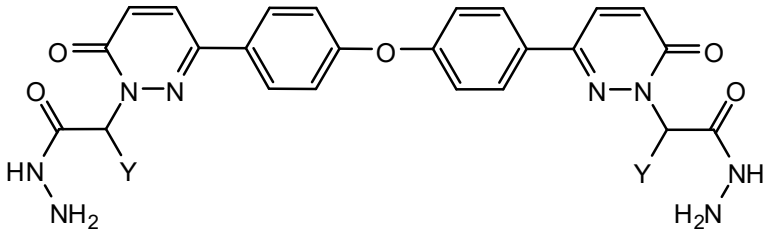
Compound **1**



Compound **2.** **2a.** X= -CH=CH_2 2**b.** X= -C≡CH



Compound **3.** **3a.** Y= -H, R= -CH_3;**3b.** Y= -H, R= -C_{2H5}; **3c.** Y= -CH_3, R= -C_{2H5}



Compounds **4**and **b. 4a.** Y= -H; **4b.** Y= -CH_3

Figure 1. Structure of *N1*-substituted-*bis*-pyridazinones.

Table 1. Anti-TB activity against *M. tuberculosis* H37Rv in the MABA assay

Compd	Antimycobacterial activity % inhibitiona (µg /mL)	IC50 (µg/mL)	IC90 (µg/mL)	MIC (µM)
2a	100(97.90), 50(97.10), 25(86.80), 2.5(9.10),6.25 (8.20), 1.56 (-9.50)	18.27	26.45	50
3a	100(96.80), 50(92.30), 25 (-11.40), 12.5(-16.40)	45.89	49.51	50
2b	100(83.70), 50(75.70), 25(35.90), 12.5(-12.70)	33.87	>100	NA
3b	25(92.10), 6.25 (-14.20), 1.56(-9.60)	17.75	24.27	25
4b	100(18.70), 50(20.70), 25(8.00), 0.4(-16.00)	>100	>100	NA
4a	100(6.60), 50(-0.30), 25(-0.30), 1.56(-12.00)	>100	>100	NA
1	100(0.30), 50(4.60), 25(4.30), 12.5(-0.30)	>100	>100	NA
Cycloserine	100(97.70), 50(96.30), 25(93.90), 12.5(51)	12.47	13.49	25.00
Pyrimethamine	100(95.60), 50(69.70), 25(26.70)	37.35	74.96	100.00
Amikacin	5, 2.5, 1.25(98), 0.63(97.30), 0.31, 0.16(96), 0.08(79.80)	0.07	0.08	0.16
Isoniazid	5, 2.5, 1.25(94), 0.63(93.90), 0.31(92.90)	0.18	0.29	0.31
Ethambutol	100(90.00), 50, 25, 12.5(89), 6.25 (86.60), 3.13 (84.30), 1.56 (69.10)	<1.56	32.79	12.50
Rifampicin	5, 2.5, 1.25, 0.63, 0.31, 0.16(99.50), 0.08(97.60), 0.04(91.90),0.02(61.20)	0.02	0.02	0.04

aAnti-TB activity was typically determined at concentrations 100, 50, 25, 12.5, 6.25, 3.13, 1.56, 0.79, 0.4, and 0.2 µg/mL; NA- Not applicable: compound not used in the assay.

After initial dose-response testing, compounds **2a** and **3b** were found promising in primary TB assay. The MIC screening was conducted for *Mtb*H37Rv, isoniazid (INH)-resistant *Mtb*, rifampin (RMP)-resistant *Mtb*, and ofloxacin (OFX)-resistant *Mtb*. MBC, LORA, and intracellular drug screening assays were conducted using only *Mtb*H37Rv. The MIC for each compound was determined by testing ten, two-fold dilutions in the following concentration ranges: 75.00 to 0.146µg/mL for MIC, 75.00, 7.50, and 0.75µg/mL for macrophage and MTT. Like in the earlier case, a MIC value is reported as the lowest concentration (µg/mL) of a drug that visually inhibited the growth of the organism. In addition, the percentage of inhibition at the MIC has been provided (Table **2)**. The MIC value for both compounds was 9.38µg/mL and the percentage of inhibition at the MIC concentration was 49% for **3b** and 86% for **2a**, respectively suggesting that compound **2a** was potent against replicating *Mtb*. The obtained data against drug-resistant strains reinforce the previous results, suggesting that **2a** was potent against drug-resistant strains too. The oxofloxacin-resistant *Mtb*had MIC 2.34 µg/mL for **2a** and 4.69 µg/mL for **3b** and the percentage of inhibition was 85% for **2a** and 71% for **3b**, respectively rifampin-resistant *Mtb*had MIC 0.59 µg/mL (49%) for **2a** and MIC 4.69 µg/mL (52%) for **3b** and, finally, INH resistant *Mtb*had MIC 2.34 µg/mL for both compounds and the percentage of

inhibition was 53% for **3b** and 44% for **2a**, respectively [45].

Table 2. MIC and MBC results

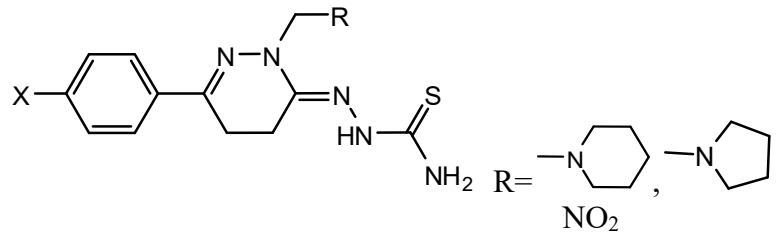
Compd.	MIC H37Rv (µg/mL)	Inha, %	MBC H37Rv (µg/mL)	MIC INH-Rb (µg/mL)	Inh, %	MIC RMP-Rc (µg/mL)	Inh, %	MIC OXF-Rd (µg/mL)	Inh, %
2a	9.38	86	25	2.34	44	0.59	49	2.34	85
3b	9.38	49	NA	2.34	53	4.69	52	4.69	71
Rifampin (pos control)	0.049	63	1.56	0.02	56	NAe	NA	0.05	80
Isoniazid (pos control)	NA	NA	NA	NA	NA	0.02	92	NA	NA

Inha- Percent inhibition at the MIC concentration; INH-Rb- Isoniazid resistance; RMP-Rc- Rifampin resistance; OFX-Rd- Oxofloxacin resistance; NAe- Not applicable: compound notused in the assay; NA- Not applicable: colony counts above the established rejection value of ≥ 40; Inh- inhibition.

The MBC assay determines whether a drug's mechanism of action is bacteriostatic or bactericidal. This is important because bactericidal drugs can potentially shorten the standard treatment regimen which is a minimum of 6 months for TB. The MBC is defined as the lowest concentration (µg/mL) of compound exhibiting 99.9% kill over the same period used to determine the MIC. Minimum bactericidal concentration (MBC) values greater than 16 times the MIC typically indicate antimicrobial tolerance. The established rejection value of ≥40 colonies for the MBC assay was based on the calculated concentration of *Mtb*in the MIC plates. The MBC value for **2a** was 25µg/mL and CFU was 18, suggesting a low antimicrobial tolerance and a bactericidal mechanism of action. The MBC value for **3b** being above the established rejection value of ≥40 colonies indicates antimicrobial tolerance.

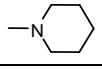
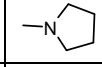
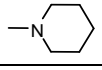
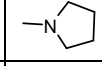
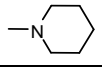
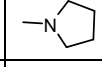
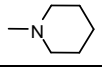
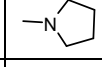
The MTT (3-(4,5-dimethyl thiazolyl)-2,5-di-phenyltetrazolium bromide) cell proliferation evaluated intracellular drug effectiveness. This is important because *Mtb*can survive inside macrophages which contributes to treatment failure and disease relapse. The assay is performed by exposing the macrophages to *Mtb* and then incubating the infected macrophages in the presence of a variety of test compounds. Each compound was tested in duplicate, using 3 concentrations, and rifampin was used as the positive control drug. A drug cytotoxicity control plate assay (MTT proliferation) was also conducted in parallel using uninfected macrophages to confirm that concentrations utilized for testing were not toxic to the macrophages. Drug cytotoxicity is reported as cell proliferation or percentage of viability. These results suggested that compounds **2a** and **3b** are active against intracellular *Mtb*and again, **2a** is more potent. The MTT viability for compounds **2a** and **3b**, is almost equal to low concentrations to control drug rifampin, and lower to mid and high concentrations. These results suggest that compounds **2a** and **3b** have low toxicity, and their activity against *Mtb*is not due to the cytotoxicity of the compound itself. Taking into consideration the above present results, some SAR correlations occur. Comparative with other pyridazine derivatives [41-43], the presence of a diphenyl ether-*bis*pyridazine skeleton seems to be favorable for anti-TB activity. We may also notice a certain

influence of the side chains of the *N1*-substituted nitrogen from BP molecules, the activity decreasing in order: vinyl >carboxyalkyl>ethynyl>carbohydrazone> hydrogen. Some important hints concerning the mechanism of action are also suggested. The fact that ethyl-carboxy- BP **3b** has a significant anti-TB activity while methyl-carboxy**3a** is significantly less active, in conjunction with the fact that the vinyl-BP **2a** has also a very good anti-TB activity, suggesting that the presence of two atoms hydrocarbon skeleton is favorable for activity. We believe that this should be somehow related to the mechanism of action, a good interaction of BP molecule with the putative binding site being facilitated by the presence of these two atoms hydrocarbon skeleton [45].The biologically active molecules [46], (*E*)-2-(6-(4-substituted phenyl)-2-(piperidin/ pyrolidin-1ylmethyl)-4,5-dihydropyridazine-3(*2H*)-ylidene)hydrazine carbothioamide or hydrazones**(5a-p)** to investigate their anti-TB activities by using the resazurinmicrotiter assay plate method against *Mtb*. The pyridazinone moiety in the present study has been reported to possess a wide variety of biological activities [47]. In particular, a large number of pyridazinones are well-known as intermediates for drugs and agrochemicals.



(E)-2-(6-(4-substituted phenyl)-2-(piperidin/pyrrolidin-1ylmethyl)-4,5-dihydro pyridazine-3(*2H*)-ylidene)hydrazine carbothioamide **(5a-p):**

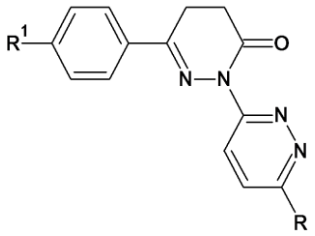
Table 2. Anti-TB activity results of the synthesized compounds (5a-p)

S. No	R	X	MIC (µg/ml)	Zone of inhibition in Mm 150 µg/ml	S. No	R	X	MIC (µg/ml)	Zone of inhibition in Mm 150 µg/ml
5a		H	3.2	21	**5i**		H	1.9	16
5b		4-Cl	3.4	29	**5j**		4-Cl	2.8	18
5c		4-F	3.0	25	**5k**		4-F	2.5	17
5d		4-Br	2.7	27	**5l**		4-Br	2.7	23
5e		4-I	2.5	23	**5m**		4-I	2.8	25
5f		4-CH_3	2.8	23	**5n**		4-CH_3	2.4	21
5g		4-OCH_3	2.4	25	**5o**		4-OCH_3	2.3	22
5h		4-NO_2	1.5	30	**5p**		4-NO_2	1.7	31
Rifampicin			1.1	38					

The series of hydrazone derivatives with pyridazine moiety were screened for anti-TB activity against *Mtb.* The data obtained by anti-TB screening, reveals that several compounds showed inhibitory activity against *Mtb*in primary screening assays at a concentration of 1.56-200 µg/ml. The compounds **5h, 5n, 5m, 5g, 5j, 5l**, and **5p** were shown to be active against the *Mtb,* whereas the other compounds **5a, 5b, 5c, 5d, 5f, 5i, 5k, 5e**, and **5o** are found to be moderately active against *Mtb*. The potency of the compounds can be explained on the basis substitution pattern of the aromatic nucleus and the presence of five-member heterocycles. The pyrrolidine nucleus with an electron-donating group exhibits a synergic effect against *Mtb*. This may may be due to an increase in the lipophilicity of the compounds.A series of dihydropyridazin-3(*2H*)-ylidene)hydrazine carbothioamide derivatives were synthesized and screened for their anti-TB activities. Some of the compounds showed inhibitory activity against *Mtb*in primary screening assays. The compounds **5h, 5n, 5m, 5g, 5j**, and **5e were** found to be active against *Mtb.* The dihydropyridazin-3(*2H*)-ylidene)hydrazine carbothioamide derivatives.

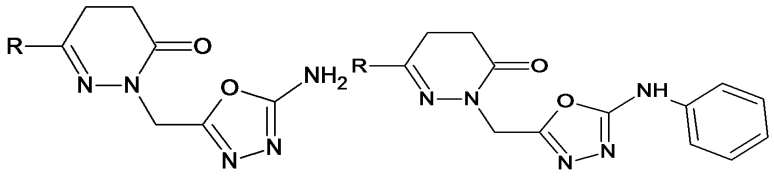
The compounds **2a** and **3b**, suggest that these BP compounds were potent against both replicating and non-replicating *Mtb*. Notably, the MBC and CFU values for **2a** indicate a bactericidal mechanism of action, which could be a supplementary asset in anti-TB fighting for this compound. The intracellular (macrophage) drug screening indicates that these compounds are active against both extracellular and intracellular organisms. The MTT assay illustrates that compounds **2a** and **3b** have low toxicity, and their activity against *Mtb*is not due to the cytotoxicity of the compound itself. The SAR correlations suggest that the presence of a diphenyl ether-*bis*-pyridazine skeleton seems to be favorable for anti-TB activity. It was also noticed a certain influence of the side chains of the *N1*-substituted nitrogen from BP molecules. Moreover, the presence of a two atoms hydrocarbon skeleton as a terminal group on the *N1*-substituted seems to facilitate a good interaction of BP molecule with the putative binding site, these compounds being the most active. The potent bioactivity of compound **2a** must be highlighted because of its lack of toxicity, its remarkable activity against replicating and nonreplicating*Mtb*, its bactericidal mechanism of action and, intracellular drug effectiveness. Overall, the BP derivatives especially compound **2b**, appeared as an attractive new chemical entity due to their interesting properties, which makes it a very promising anti-TBlead for further drug development.The anti-TB activity of a novel family of nitrogen heterocycles, N1-substituted-diphenyl ether-bis-pyridazine, was investigated (BP). The chemical route, which involves a N-alkylation of the BP heterocycle, is simple, efficient, and straightforward. X-ray examination showed that the structure of the eight novel BP heterocycle scaffolds produced was unambiguous [45,46]. Two BP compounds, **2a** and **3b**, are powerful inhibitors of *Mtb*, with anti-TB effectiveness superior to the second-line anti-TB medication Pyrimethamine and equal to Cycloserine, according to high throughput screening.

A series of 6-substituted phenyl-2-(3'-substituted phenyl pyridazin-6'-yl)-2,3,4,5-tetrahydropyridazin-3-ones (**6a-e**) were reported mild to potent in vitro antitubercular, antifungal and antibacterial activities their appropriate reference standards [48].



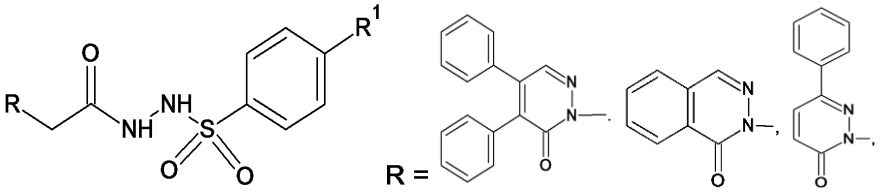
6 a-e R= -C_6H_5, 4-$CH_3C_6H_5$, 3,5-$(CH_3)_2$- C_6H_5, $C_{11}H_9O$, -$(C_6H_5)_2$ R^1= H, 3,5-$(CH_3)_2$, 4-Cl-, 4-Br, C_6H_5, p-CH_3, C_6H_5O-

A series of 5-{3'-oxo-6'-(substituted aryl)-2',3',4',5'-tetrahydropyridazin-2'-ylmethyl-2-substituted 1,3,4-oxadiazole (**7a-d &7a'-d'**) were exhibited antibacterial, antifungal and antitubercular activities. The antitubercular activity was determined using the BACTEC 460 system. These compounds were screened at 6.25 µg/mL against M. tuberculosis H37 Rv and comparable with that of standard rifampicin and Isoniazid and antifungal activity against *C. albicans* and *C. neoformans*by using the cup-plate method and zone of inhibition (mm) of each compound compared with standard drug fluconazole [49].



(**7a-d &7a'-d'**) R= Phenyl, p-tolyl, p-phenoxy phenyl, p-chlorophenyl

In addition, some pyridazinone derivatives (**8a-c**) carrying *N*-(phenyl sulfonyl) acetohydrazide moiety at position 2 of these rings were active against *M. tuberculosis*. Unsubstituted compounds were more active than after the substitution of chlorine at the para position in the phenyl ring. Some 3(*2H*)-pyridazinone derivatives were generally active against both gram-positive and gram-negative strains of bacteria as well as *M. tuberculosis* [50].



A lot of research work on pyridazine derivatives has been done in the past. This heterocyclic moiety possesses almost all types of pharmacological activities. The small and simple pyridazine nucleus is present in compounds involved in the research aimed at evaluating new products that possess interesting biological activities, such as analgesic, anti-inflammatory, antisecretory, antiulcer, antidepressants, anxiolytics, sedative-hypnotics, anti-convulsants, antiplatelets, antithrombotics, antitumor, cardiotonic, vasodilators, antiarrhythmics, antidiabetic, antitubercular agents etc. The present review is focused on the pyridazine derivatives with potential activities that have been developed.

2. CONCLUSION

The literature reveals that pyridazines or pyridazinone have diverse biological potential. The CNS, antimicrobial, and cardiotonic activities are the most

encouraging activities for the researchers. The research as anticonvulsant, anticancer, antitubercular, analgesic, anti-inflammatory, etc. has given positive results. This diversity in the pharmacotherapeutic response profile has attracted the attention of many researchers to explore this nucleus due to its multiple potential against several activities.After that pyridazinone derivatives have been studied extensively and found to have diverse chemical reactivity also. By the present scenario, it can be concluded that pyridazine has great potential which remains to be disclosed to date. The biological profile of these generations of pyridazinones represents much progress with regards.Pyridazinones further drew our attention because of their easy functionalization at various ring positions, which makes them attractive synthetic building blocks for designing and developing novel pyridazine-based pharmacotherapeutic agents.

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