Heterocyclic hydrazone derivatives as potential antitubercular agent against *Mycobacterium tuberculosis*

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Tuberculosis disease has been recognized as one of the most dangerous diseases due to its high mortality level to the human population in the world. That problem becomes worse when the antitubercular drug resistance has been reported. Heterocyclic hydrazone derivatives, unique nitrogen-based organic compounds, have been reported for their pivotal role in the biological activity, especially on the antitubercular agent against Mycobacterium tuberculosis $H_{37}Rv$. This review summarizes the up to date review of hydrazone derivatives application as the potential antitubercular agent. The effect of substituents and the presence of the heterocyclic moieties on the antitubercular activity were discussed.

Key Words: *Hydrazone; Heterocyclic; Antitubercular; Mycobacterium tuberculosis*

INTRODUCTION

Tuberculosis is one of the deadliest diseases in the world. Tuberculosis disease was generated by Mycobacterium tuberculosis infection on the lung [1-3]. World Health Organization (WHO) reported that tuberculosis disease gave mortality level as similar to human immunodeficiency virus (HIV) in 2014 [4]. In 2017, tuberculosis disease caused mortality of 1.3 million people in the world [5]. Furthermore, the treatment of tuberculosis disease is expensive, takes long time, and the efficiency of the treatment process is still unsatisfied. That problem became worst since the drug resistance has been reported toward general used drugs such as isoniazid, rifampicin and fluoroquinolone [6].

Recently, WHO launched "End Tuberculosis Strategy" to reach a world with a zero death from tuberculosis disease [5]. Many efforts are on that WHO policy, such as developing a rapid and efficient tuberculosis diagnosis and developing an effective treatment process. To reach an effective treatment process, a potential antitubercular drug should be developed [7]. Many researchers are synthesizing and developing the new antitubercular drug based on the available lead compounds and the computational analysis, such as quantitative structure-activity relationship (QSAR) models and molecular docking studies. QSAR is a computational technique which used to predict the physicochemical properties and biological activity of the unknown compounds based on the multi-regression analysis from the previously reported active compounds. While molecular docking is a computational method to predict and visualize the orientation and interaction of the docked compound to the protein receptor [8].

Hundreds of antitubercular agents have been evaluated and proposed, such as hydrazone, diarylquinoline, nitroimidazole, oxalidinone, and benzothiazinone compounds. Hydrazone derivatives have been thoroughly investigated over the past several years due to their wide biological activities. The present of azomethine (R_1-HN-N=CR_2R_3) functional group contributes to several biological activities, such as antibacterial, antimalarial, antifungal, and antitubercular agents [9-12]. Because of their unique and high biological activity, many researchers are investigating and developing hydrazone derivatives especially to be used as the antitubercular agent. This review summarizes the up to date review of hydrazone derivatives application as the potential antitubercular agent against Mycobacterium tuberculosis $H_{37}Rv$.

Hydrazone derivatives can be prepared through 3 synthesis methods, i.e. Japp-Klingemann coupling (reaction between beta-keto acids and aryl diazonium salts), condensation reaction between hydrazine (R-NH-NH_2) and carbonyl (R_1R_2C=O) compounds, and *N*-arylation of hydrazine derivative with aryl halide [13,14]. However, condensation reaction between hydrazine and carbonyl compounds is commonly used because it is simple, easy and high-yield method [15]. Condensation reaction between hydrazine and carbonyl compound can be performed in acidic condition (Figure 1). Either sulfuric acid or glacial acetic acid is commonly used in a catalytic amount in the alcoholic solvent to accelerate the formation of the hydrazone as the product and give higher reaction yield [16]. In our previous work, a series of 2-thiophenecarboxylic acid hydrazone derivatives have been synthesized using this method and the products were obtained in 90-96% yield [14].

In this review, we summarize the up to date application and investigation of heterocyclic hydrazone derivatives as the antitubercular agent against *Mycobacterium tuberculosis* $H_{37}Rv$. The effect of substituents, as well as the presence of the heterocyclic moieties on the hydrazone derivatives toward their antitubercular activity, were discussed.

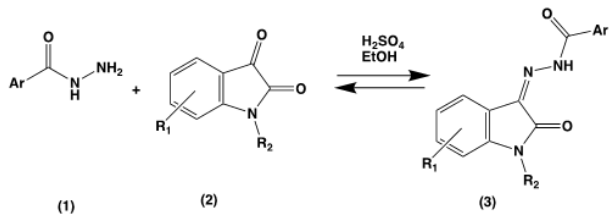

Figure 1) *Condensation reaction between hydrazine and carbonyl compounds to form hydrazone derivatives [14]*

Antitubercular activity of hydrazone derivatives

Since the preparation of hydrazone derivatives is easy and the reaction yield is very high, it is interesting to evaluate the hydrazone derivatives as the antitubercular agent against *Mycobacterium tuberculosis* $H_{37}Rv$. Telvekar et al. have prepared *N'*-benzylidine benzofuran-3-carbohydrazide (Figure 2) (compound **4**) and it shows antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ with minimum inhibition concentration (MIC) equals to

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7.56 µM [17]. Torres et al. synthesized hydrazone derivatives (compound **5**) and (compound 6) from isoniazid and 6-fluoro-3-formyl-2-methyl-2-methylquinoxaline-1,4-dioxide as the starting materials. Compound **5** and **6** gave MIC value 0.58 and 0.81 µM, respectively, against *Mycobacterium tuberculosis* $H_{37}Rv$, which is remarkable [18]. Paven et al. reported that either *N'*-(di(pyridine-2-yl)methylene)isonicotinohydrazide (compound **7**) or *N'*-(4-oxo-4-phenylbut-2-en-2-yl) isonicotinohydrazide (compound **8**) gave higher MIC value (3.13 µM) [19]. In 2009, Sriram et al. found that 2-isonicotinoyl-N-(2-trifluoromethyl)phenyl)hydrazinecarbothiomide (compound **9**) gave 0.58 µM as the MIC value [20], while Elhakeem et al. reported the synthesis of *N'*-(4-(4-chlorophenyl)-3-phenylthiazol-2(3H)-ilydene)isonicotinohydrazide (compound **10**) which gave 9.77 µM as the MIC value [3]. A series of 2-oxo-2,3-dihydro-1H-3-indolilydene-pyridine carboxylic acid compounds show antitubercular activity, in which compound **11** with R = methyl and ethyl gave 10.3 µM as the lowest MIC value among them [19-21]. Novel hydrazone derivatives derived from benzoyl hydrazide and substituted isatin have been synthesized and evaluated as the antitubercular agent against *Mycobacterium tuberculosis* $H_{37}Rv$. From the evaluation of their antitubercular assay, it was found that the 4-bromo-*N'*-(5-chloro-1-(4-chlorobenzyl)-2-oxoindolyn-3-ilydene)benzohydrazide (compound **12**) gave 12.4 µM as the MIC value [22,23].

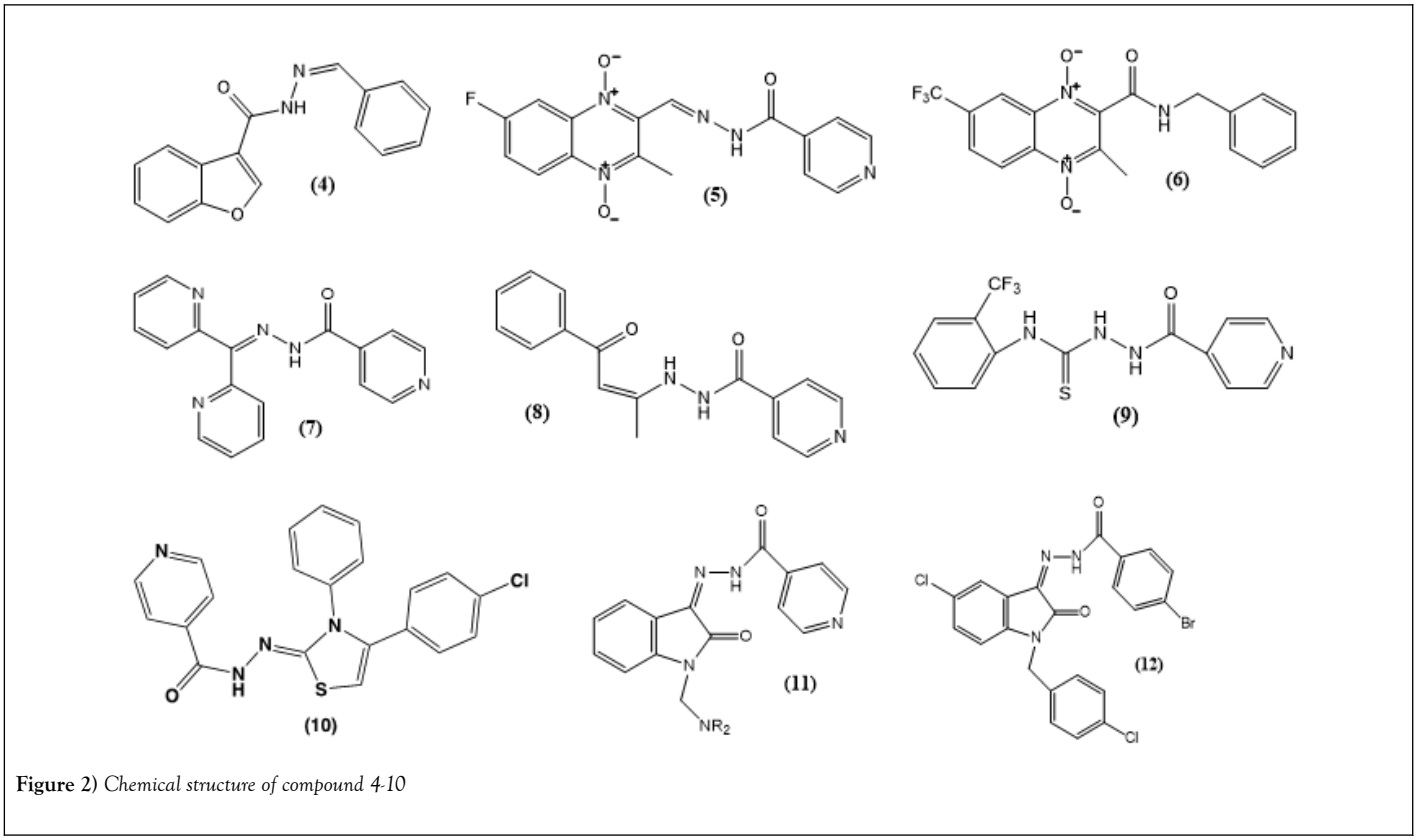

Figure 2) *Chemical structure of compound 4-10*

Fifteen novel hydrazone derivatives have been prepared from *N'*-benzylidene isonicotinohydrazide as the starting material by Kumar et al. and among them, compound **13** exhibit the best antitubercular activity with 0.59 µM as the MIC value [24]. Compound **14** was prepared from the condensation reaction between isoniazid and 3-ethoxysalicilaldehyde and it was found that the MIC value of compound **14** is 14.0 µM [25], while *N'*-(5-bromo-2-oxoindolyn-3-ilydene)-6-(4-fluorophenyl)-2-methylnicotinohydrazide (compound **15**) gave 13.8 µM as the MIC value against *Mycobacterium tuberculosis* $H_{37}Rv$ [26]. Sinha et al. synthesized hydrazone derivatives (compound **16**) from *N'*-arylidene-N-[2-oxo-2-(4-arylpiperazin-1-yl)ethyl]hydrazide and isoniazid as the starting materials and they were evaluated as the antitubercular agent. It was found that compound **16** gave the lowest MIC value (2.28 µM) [27].

Sixty-six compounds of indole-2,3-dion-3-thiosemicarbazone derivatives have been prepared. Among all of the synthesis compounds, *N*-butyl-2-(5-methyl-2-oxoindolyn-3-ilydene)hydrazine carbothioamide (compound **17**) and *N*-(4-bromophenyl)-2-(1-(morpholinomethyl)-2-oxo-5-(trifluoromethoxy)indolin-3-ilydene)hydrazine carbothioamide (compound **18**) exhibit antitubercular activity with 2.24 and 2.67 µM as the MIC value against *Mycobacterium tuberculosis* $H_{37}Rv$ [28]. Condensation reaction between isatin derivatives and isoniazid have been thoroughly investigated because the hydrazone products gave potential antibacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$. Saxena et al. synthesized 9 hydrazone compounds from isatin and isoniazid through condensation reaction (Figure 3). The biological assay results show that *N'*-(1-benzyl-5-methyl-2-oxoindolin-3-ilydene)-4-chlorobenzohydrazide (compound **19**) gave the MIC value equals 15.5 µM [23]. Aboul-Fadl et al. synthesized 142 hydrazone derivatives from the substituted isatin and isoniazid compounds. Compound **20** and **21** exhibit a high antitubercular activity with 1.00 and 0.38 µM as the MIC values, respectively [1]. On the other hand, *N'*-(1-(4-bromophenyl)ethylidene)-2-(3-(4-(4-fluorophenyl)piperazin-1-yl)-6-oxopiridazine-1(6H)-yl)aceto-hydrazide (compound **22**) has been successfully synthesized and it gave 9.48 µM as the MIC value [29]. While *N'*-((5-nitrofuran-2-yl)methylene)-2-(phenylthio)benzohydrazide (compound **23**) gave the half maximum inhibitory concentration (IC_{50}) value at 7.92 µM [30]. In our previous study, six hydrazone derivatives have been synthesized from isatin and 2-thiophenecarboxylic acid hydrazide as the starting materials through condensation reaction (Figure 1). We reported that bromo substituents on R_1 and R_2 (compound **24**) show the best antitubercular activity amongst the other products [14].

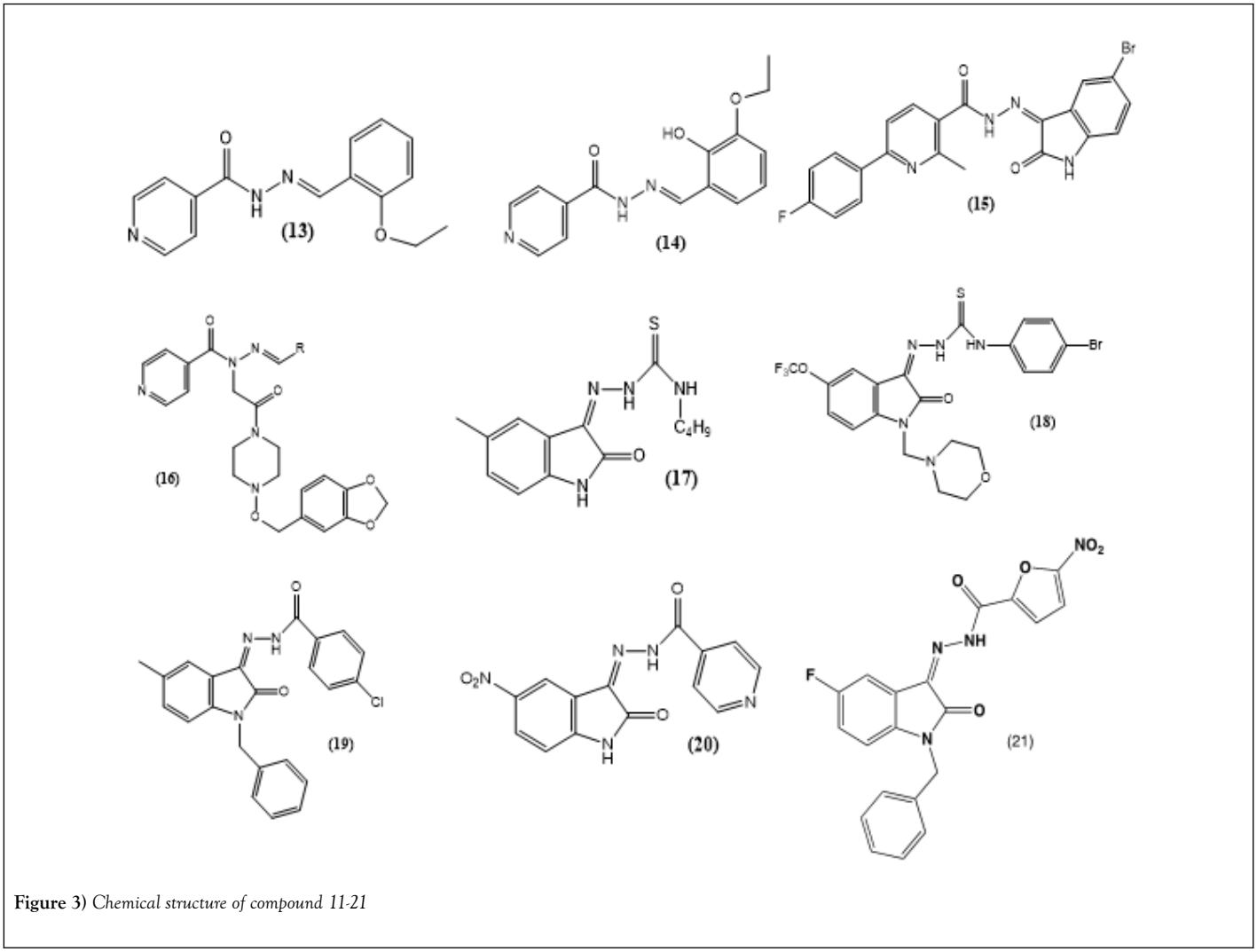

Figure 3) *Chemical structure of compound 11-21*

TABLE 1 The summary of antitubercular activity of hydrazone derivatives

Compound	MIC (μM)
4	7.56
5	0.58
6	0.81
7	3.13
8	3.13
9	0.58
10	9.77
11	10.3
12	12.4
13	0.59
14	14
15	13.8
16	2.28
17	2.24
18	2.67
19	15.5
20	1
21	0.38
22	9.48
23	7.92
24	72.8
25	36.6
26	69.6
27	0.09
28	0.02
29	1.21
30	4.84

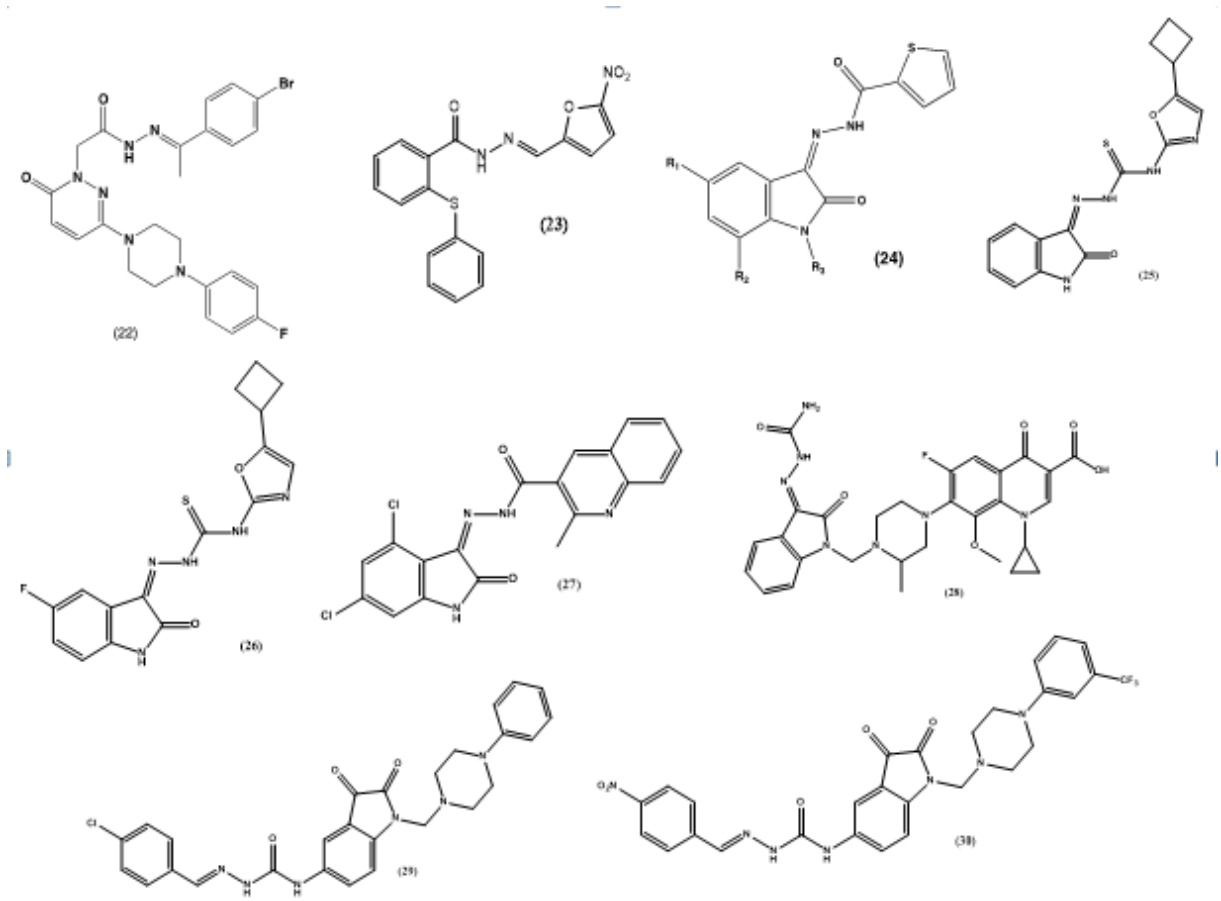

Figure 4) *Chemical structure of compound 22-30*

Twenty oxazole-thiosemicarbazone derivatives have been prepared and evaluated for *in vitro* and *in vivo* assays against *Mycobacterium tuberculosis* $H_{37}Rv$ by Sriram et al. All the oxazole-thiosemicarbazone derivatives gave medium to high antitubercular activities with MIC values from 0.05 to 25.00 μg/mL. Moreover, some of them were more biologically active than the first-line antitubercular agents such as rifampicin and isoniazid compounds. It is important to note that the resistance indexes of oxazole-thiosemicarbazone derivatives against *Mycobacterium tuberculosis* $H_{37}Rv$ were around 1, demonstrating that oxazole-thiosemicarbazone derivatives have no cross-resistance with the first-line antitubercular agents [30]. However, when isatin moiety is exist on the oxazole-thiosemicarbazone derivatives, i.e. compound **25** and **26** (Figure 4), they show a weak antitubercular activities against *Mycobacterium tuberculosis* $H_{37}Rv$. The MIC values for compound **25** and **26** is 36.6 and 69.6 μM, respectively [31]. Other series of isatin-quinoline hybrids were also evaluated for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ by Maddela et al. The isatin-quinoline hybrids exhibit excellent activities against *Mycobacterium tuberculosis* $H_{37}Rv$ with MIC value ranging from 0.09 μM, and minimum bactericidal concentration (MBC) ranging from 0.30 μM. The QSAR revealed that the presence of electron-withdrawing substituents remarkably increased the antitubercular activity of the hybrids.

The most potent hybrids, i.e. compound **27** gave 0.09 and 0.30 μM as the MIC and MBC value, respectively. The antitubercular activity of compound 27 was found as same potent as isoniazid compound with 0.03 and 0.05 μM as the MIC and MBC values. Due to that potential antitubercular activity, compound **27** was further evaluated for its susceptibility on 16 pan-susceptible, 2 rifampicin-resistant and 2 poly-drug resistant *Mycobacterium tuberculosis* clinical isolates. The obtained results demosntrate that compound **27** (0.33-1.50 μM as the MIC value) was almost as potent as isoniazid (0.22-1.82 μM as the MIC value) against pan-susceptible and rifampicin-resistant strains. It was also found that compound **27** exhibits excellent activities against poly-drug resistant *Mycobacterium tuberculosis* clinical isolates with MIC in a range of 0.08 to 0.75 μM [32]. Another form of isatin hybrid, i.e. gatifloxacin-isatin hybrids exhibited promising antitubercular activities against *Mycobacterium tuberculosis* $H_{37}Rv$ (MIC: 0.0125 to 0.78 μg/mL) and they were more potent than gatifloxacin (MIC: 3.12 μg/mL) as the starting material. Compound **28** was reported to be the most active compound with MIC of 0.02 μM against *Mycobacterium tuberculosis* $H_{37}Rv$ on the *in vitro* assay, which is 64 times more active than its parent drug (gatifloxacin). Moreover, compound **28** has no toxicity property to Vero cell up to 0.11 M concentration, and the SI value (ratio between

IC_{50} and MIC) of compound **28** was more than 1250. The isatin-semicarbazone derivatives (compound **29** and **30**) were found as highly active compounds against both *Mycobacterium tuberculosis* $H_{37}Rv$ strains with MIC of 1.21 and 4.84 μM, respectively. Some of them were more potent than the first-line anti-TB agents. It is interesting to notice that when either chloro or nitro group on the phenyl ring are exist, those hybrids generate better antitubercular activities against *Mycobacterium tuberculosis* $H_{37}Rv$ strain. Isatins with N_1 position substituted by *N*-trifluoromethyl piperazine (compound **29**, MIC: 1.21 μM) or *N*-phenyl piperazine (compound 30, MIC: 4.84 μM) exhibit remarkable antitubercular activities against *Mycobacterium tuberculosis* $H_{37}Rv$, while those with N_1 position substituted by dimethylamino or pyrrolidine ring decreased the antitubercular activities. Compound **29** showed a promising antibacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ with MIC value of 1.21 μM, which were more active with isoniazid and four times more potent than rifampicin (MIC: 30.4 μM).

Effect of the heterocyclic as the substituent and the molecular docking

Table 1 lists the antitubercular activity of the reported hydrazone derivatives. Even though a comprehensive comparison is difficult to be explained, however, a simple comparison was given to evaluate the effect of the existence of the heterocyclic ring moieties. From Table 1, either furan or oxazole aromatic ring shows a weak antitubercular activity on compound **4**, **23** and **25-26** [**17, 30, 31**]. Quinoxaline moiety gave 0.58 and 0.81 μM for compound **5** and **6**, respectively, demonstrating that they are critical for antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ [18]. Quinoline substituent gave high MIC value as represented by compound **27** [32]. While pyridine substituent shows good antitubercular activity (compound **7-10**, **13-14**) in which the presence of trifluoromethyl functional group on compound 9 enhance the antitubercular activity to 0.58 μM as the MIC value [**3, 19, 20, 24, 25**]. Piperidine and thiophene aromatic ring did not give significant MIC value as indicated by compound **16**, **22** and **23** [**27, 29, 30**]. Isatin derivatives exhibit good antitubercular activity (compound **11**, **12**, **15**, **17-21** and **25-30**) [**1, 21-23, 26, 28, 31-34**]. Among them, compound **28** gives the lowest MIC value (0.02 μM) or exhibits the highest antitubercular activity due to the combination of isatin and fluoroquinolone moieties [33].

Molecular docking is one of the common methods to visualize and identify the interaction between drug compound and the protein receptor. The 2-trans-enoyl-acyl carrier protein reductase, called as InhA has been deeply investigated as the protein receptor because it is produced by *Mycobacterium tuberculosis* and involved in the *Mycobacterium tuberculosis* type II fatty acid biosynthesis pathway. Once the antitubercular drug is able to bind the active site of InhA and inhibit the enzymatic reaction, the biosynthesis of mycolic acids (as a major component of mycobacterial membrane) was disturbed. Because of that inhibition, there are two responses, i.e. bacteriostatic and bactericidal actions. Bacteriostatic action is an action which is generated by drug compound to inhibit the cell growth of bacteria, while bactericidal action is an action to kill and destroy the bacteria due to the presence of drug compound [**35**]. Wang et al. reported that the antitubercular activity against InhA receptor commonly related to the presence of hydrogen bonding between NH of hydrazone with carboxylate residue of Ser94, phi-phi stacking between aromatic ring and phenyl group of Phe41 and also dipole-dipole interaction between bromo substituent and either Gly14 or Gln66 residue [**36**]. On the other hand, Atta et al. stated that the hydrogen bonding between sulfur and Gly14 and/or Ser20 is important for antitubercular activity. Furthermore, it was reported that the presence of pyridine aromatic ring could inhibit InhA through hydrogen-phi interaction with Gly14 residue [**35**]. More et al. reported that -NH- of hydrazone is able to bind with Tyr158 through hydrogen bonding [**37**]. Similar results were obtained by Angelova et al. which evaluate the pyrazole-hydrazone derivatives. The pyrazole-hydrazone derivatives are able to form hydrogen bonding with Tyr158 residue of InhA. Moreover, they found that hydrogen-phi interaction between the pyrazole-hydrazone derivatives with Phe149 and Met161 influenced the antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ [**38**]. From those reports, it can be concluded that either hydrazone and heterocyclic ring moieties are pivotal for the antitubercular activity. A further heterocyclic hydrazone derivative design needs to consider those interactions to obtain a potential antitubercular agent against *Mycobacterium tuberculosis* $H_{37}Rv$.

CONCLUSION

This review summarizes the up to date review of hydrazone derivatives over the past several years because they served as a potential antitubercular agent against *Mycobacterium tuberculosis* $H_{37}Rv$ strain. The effect of some functional groups, especially heterocyclic moiety has been discussed and their role has been evaluated through molecular docking studies. The molecular docking results confirmed that heterocyclic hydrazone derivatives gave a high antitubercular activity due to the suitable interaction with InhA as the protein receptor.

CONFLICT OF INTEREST

Authors declare there is no conflict of interest.

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