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Review Article

Various pyrrole and pyrrolidine derivatives acts as new trends in development of antimycobacterial agents

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MDR-TB.

Abstract

Pyrrole and pyrrolidine derivatives are important antimicrobial agents. Some pyrrole and pyrrolidine derivatives are under investigation for the treatment of tuberculosis and multidrug-resistant tuberculosis. In this article, study the pyrrole and pyrrolidine derivatives with anti-mycobacterial properties, mode of action and structure activity relationship studies of the pyrrole derivatives. Furthermore, we update the synthesis and activity of pyrrole and pyrrolidine derivatives as a new class of potent anti-mycobacterial agents. Furthermore, particularly interesting is their activity against MDR-TB.

1.Introduction

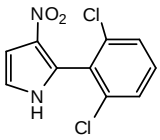
Tuberculosis (TB) is a most common infectious disease. Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains one of the biggest killers amongst the infectious diseases despite the availability of effective drugs and Bacillus-Calmette Guerin (BCG) vaccine. About one-third of world's populations are infected with *M. tuberculosis*. Every year, about 8 million of the infected people develop active TB, and about 2 million die of the disease [1]. In 2010, WHO reported that 650,000 cases of MDR-TB emerged among the world's 12 million prevalent cases of TB [2]. Streptomycin (STR) was the first drug introduced in 1944 for the treatment of TB but immediately after its opening many patients started showing resistance to this antibiotic [3,4,5]. Para-aminosalicylate (PAS) was introduced in 1946 that overcame the emergence of resistant strains [6]. A few years later, Isoniazide (INH) was developed and initial treatment with both INH and STR was even more effective. Many drugs are available, which are classified into two categories. First line therapy includes five medications: INH, pyrazinamide (PZA), ethambutol (EMB), rifampicin (RIF) and STR [7,8]. Second line therapy, which is used exceptionally in the cases of drug resistance, includes cycloserine, capreomycin, fluoroquinolones, ethionamide, PAS, thioacetazone, rifabutin, clofazimine and some macrolides [9]. The major setback in controlling TB was the emergence of multidrug resistant tuberculosis (MDR-TB). Currently, about 50 million people are estimated to be affected with MDR-TB. A few MDR strains of *M. tuberculosis* were found to be resistant to many first line agents as well as some of the second line drugs [10]. Even more frightening is the emergence of extensively drug resistant TB (XDR-TB) reported in all around the world [11]. The increased number of MDR strains, is closely related to the growing global HIV/AIDS pandemic [12]. The connection of TB and HIV infections is so dramatic that, nearly two-thirds of the patients diagnosed with TB are also HIV positive[13] and the risk of rising TB is between 20 and 37 times greater in individual living with HIV than among those who do not have HIV infection [14]. TB is the principal cause of death among HIV infected individual; more than a quarter of deaths among people living with HIV [15,16]. Furthermore, various studies showed the reciprocal deadly effect of these two conditions, since HIV infection is a major risk factor for the development of active TB which, in turn is a cofactor in the development of HIV infection [17]. The immune-suppression related to HIV infection has also caused the emergence of many opportunistic infections, including disseminated *M. avium complex* (MAC) infections [18-20]. People carrying latent infection are at a risk of reactivation and this is one of the major barriers in controlling tuberculosis. Therefore, there is an urgent need to develop novel drugs that can act against both actively growing and dormant mycobacteriums.

2. New Potential Anti-Tubercular Agents

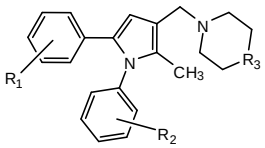
The efforts for drug development are being coordinated to bring out new, faster-acting and affordable drugs against TB. Rational development of a new anti-TB drug requires the discovery of new means to recognize the genetics and physiology of *M. tuberculosis*. In this consideration, availability of the genome sequence of *M. tuberculosis* [21] and powerful genetic tools for manipulating mycobacteria have offered valuable information about the potential targets. Many of these target has helped in designing novel therapeutic agents [22]. The new potential anti-TB agents are classified on the basis of their chemical entities. The potential drug targets compiled in this review are likely to lead to new medication with pyrrole and pyrrolidine drug that should facilitate in controlling the spread of TB.

3. Antitubercular activity of pyrrole derivatives

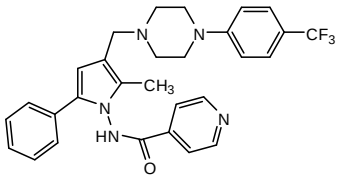
Naturally occurring pyrrolnitrin (**1a**) and its analogs were tested against *M. tuberculosis*, and the most effective exhibited an MIC of 3.9 mM [23]. Most of the compounds from this series were cytotoxic, presumably because of the nitro group. Structural optimization of pyrrolnitrin and other azole analogs led to the discovery of the more potent pyrrole, BM-212 (**1b**), exhibiting MIC values of 1.68 mM against *M. tuberculosis* [24]. BM-212 (**1b**) was also found to be effective against strains resistant to EMB, INH, amikacin, STR, RIF, and rifabutin, as well as against *M. tuberculosis* growing within a human monocyte cell line.



Pyrrolnitrin analog **1a**



1b R_1 = 4-Cl, R_2 = 4-Cl, R_3 = NCH_3; BM-212
1c R_1 = 4-F, R_2 = 4-F, R_3 = S
1d R_1 = 4-F, R_2 = 4-F, R_3= S
1e R_1, R_2 = H, R_3 = S
1f R_1=4-F, R_2= 2-F, R_3 = S
1g R_1= 4-CH_3, R_2 = 4-F, R_3=S



LL-3858 **1h**

Fig. 1: Pyrrole-based antitubercular compounds

Using BM-212 (**1b**) as a lead compound, systematic structural optimization led to the discovery of improved analogs, with similar or better activity in the range of 0.5–2 mM and an improved therapeutic index [25-28].

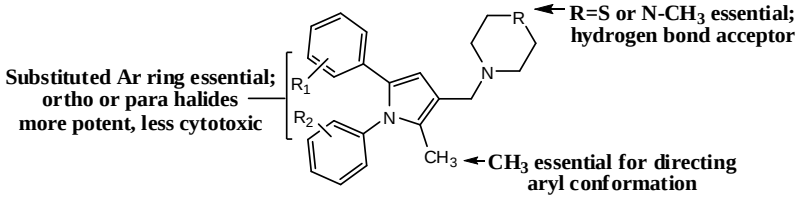
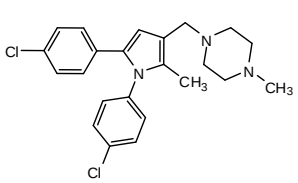


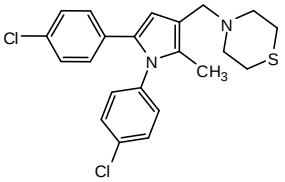
Fig. 2: Activity relationship of pyrrole compound

Based on whole cell biological activity, with aromatic groups at N_1 and C_5 and a methyl group at C_2 is an essential feature (Fig. 2). The methylene-linked thiomorpholine or N-methylpiperazine substituents at C_3 act as hydrogen bond acceptors to improve activity (**1b-g**) ([28, 29]. Thus, a 1,2,3,5-tetrasubstituted pyrrole is the pharmacophore is vital for anti-TB activity (Fig. **1**). The 2-methyl group is not involved in any pharmacophoric interaction but influences the conformation of the substituents at positions 1 and 3 of the pyrrole ring [28,29). Other pyrrole analog, LL-3858 (**1h**), a pyrrole derivative, also complies with this pharmacophore model. This compound has exhibited MIC values in the range of 0.05–0.1 mM, against *M. tuberculosis*. LL-3858 (**1h**) has been reported to sterilize the lungs and spleen of infected mice after 12 weeks of treatment, none of which relapsed after 2 months of therapy termination.

A pyrrole derivative, BM 212 [1,5-diaryl-2-methyl-3-(4-methylpiperazin-1-yl) methyl-pyrrole], displayed potent *in vitro* activity against *M. tuberculosis* [24]. The MICs were 0.7-1.5 µg/ml for drug susceptible and resistant strains of *M. tuberculosis*, suggesting there is no cross resistance with current drugs. BM 212 also exhibited good activity against nontuberculous mycobacteria including *M. avium* (MIC=0.4-3.1 mg/ml). The BM 212 showed bactericidal activity against intracellular *M. tuberculosis* in a macrophage tissue culture model (U947 cells), with MIC of 0.5 µg/ml. A series of BM 212 derivatives were made in order to improve potency [25-27]. A thiomorpholine derivative of BM 212, in which the *N*-methyl piperazino methyl moiety at the C3 position of the pyrrole ring was replaced with a thiomorpholinomethyl, was found to be more potent and less toxic than BM 212, with MIC of 0.4µg/ml against *M. tuberculosis*.



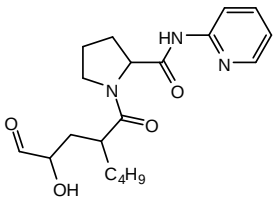
BM 212



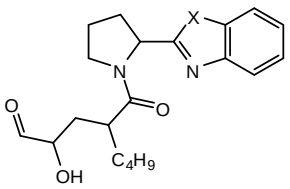
BM212 analogue

4. Pyrrole and Pyrrolidine Derivatives

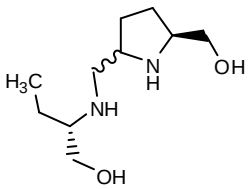
Peptide deformylase (PDF) is a key enzyme, that deformylates the *N*-formylmethionine of newly synthesized polypeptides, a key step in protein maturation. It is also identified as a validating target after the identification of LBK-611 as an anti-TB agent. In this perception, a series of LBK-611 (**2a**) derivatives were prepared by introducing benzimidazoles and benzoxazoles moieties at 2-position and peptides at N-1 position. Among all, Compounds **2b** and **2c** have shown more potent IC_{50} of 0.010, 0.013 µM respectively against *M. tuberculosis* PDF enzyme and MIC of 0.1 µg/mL and 0.15µg/mL against *M. tuberculosis* H37Rv in comparison to LBK-611. These compounds also showed promising activity of MIC 0.03, 0.06µg/mL, respectively against *M. tuberculosis* MDR strain[30]. In a different approach, three conformationally constrained ethambutol (**10**) analogues having basic skeleton of pyrrolidine and bipyrrolidine were prepared. Among these, one compound **3** with semi-rigidified EMB skeleton being the part of pyrrolidine with *cis* configuration has shown modest growth inhibition at concentrations of over 60 µg/mL, which is 30 fold less than EMB, while bipyrrolidine and *trans*-semi-rigidified EMB skeleton was found to be inactive against *M. tuberculosis* [31].



2a

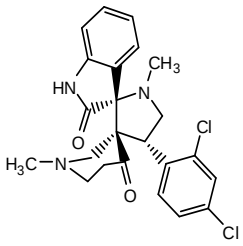


2b: X=NH 2c: X=O



3

In search of new heterocycles with anti-TB activity, two different series of spiro-compounds, 1-methyl-4-(2,4-dichlorophenyl)pyrrolo(spiro[2.3"]oxindole)spiro[3.3']-1'-methylpiperidin-4'-one (**4**) showed good activity with a MIC of 1.76 and 0.88µM against *M. tuberculosis* and MDR-TB respectively [32]. While in an another series, compound **5** showed increased potency with MIC value of 0.40 µg/mL against *M. tuberculosis* and was 4 and 15.6 times more potent than EMB and PZA, respectively [33]. Pyrrolidine containing bis-heterocyclic libraries, bis-cyclic guanidine derivative (**6**) showed preeminent potency with a MIC of 3.9 µg/mL against *M. tuberculosis* and found to be less toxic with an IC_{50} of 39.48µg/mL [34].



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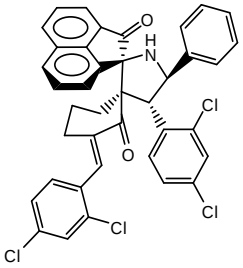

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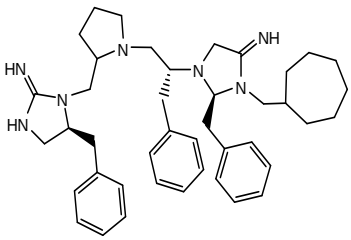

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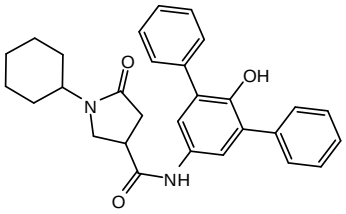
The InhA, the enoyl acyl carrier protein reductase (ENR) from *M. tuberculosis*, is a key enzyme involved in the mycobacterial fatty acid elongation cycle and has been validated as an effective anti-TB target. A series of N-substituted-2-pyrrolidine-3-carboxamides were prepared as potent InhA inhibitors. Among all, the racemic compound **7** has shown inhibition of IC_{50} 140 nM, while one of its enantiomeric excess molecules showed inhibition of IC_{50} 62 nM against InhA of *M. tuberculosis [35]*. The tetramic acid (N-substituted-2,4-pyrrolidone) molecules with structural similarity to the antibiotic reutericyclin (**8**) were screened for their antibacterial activity. Many of them have shown promising potency against Gram-positive bacteria and two compounds **8a** and **8b** showed moderate activity of MIC 12.5 µg/mL against *M. tuberculosis [36]*.



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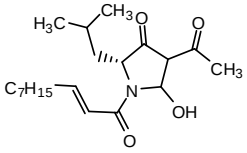

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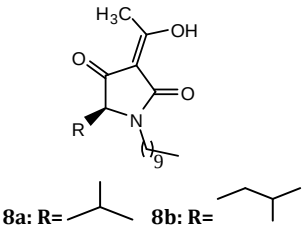
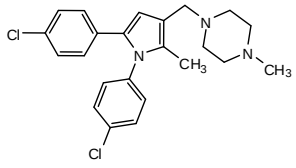


8a: R= **8b: R=**

A pyrrole derivative BM 212 **(9)** arose the attention with its very good *in vitro* activity of MIC 0.7 µg/mL against *M. tuberculosis.* Prompted by these results, a series was developed by the variation of N-1, C-3 and C-5 positions. Among all, compound **10** showed potent inhibition of MIC 0.4 µg/mL against *M. tuberculosis* and also the protection index (PI) of 20 which is more than that of BM 212 [25]. While compounds **11** [26] and **12** [27] showed comparable MIC of 1 µg/mL. Surprisingly, substitution of 4-isopropyl benzene at C-5 position and 4-fluorobenzene at N-1 position (**13**) has increased the potency with a MIC of 0.25µg/mL, which is equal to that of isoniazid (INH) [37]. While by replacing 4-isopropylbenzene with 4-methylbenzene (**14**) [28] at C-5 position of compound **13** showed decreased potency of MIC 0.4 µg/mL but lowered the toxicity.

This made the molecule a promising lead with a protection index of 160, which is greater than the anti-TB drugs INH, STR. The introducing an ethyl group at position 2 of the pyrrole nucleus by keeping both N-1 and C-5 phenyl rings, the same substituents that gave the best activity in previous 2-methyl derivatives. Among them, 1-(4-fluorophenyl)-2-ethyl-3-(thiomorpholin-4-yl) methyl-5-(4-methylphenyl)-1*H*-pyrrole (**15**) proved to be particularly active, with a MIC 0.25 µg/mL, which is better than or comparable to those of reference compounds [38]. All the above compounds (**10-15**) were also active against resistant *M. tuberculosis [39]*. In a series of pyrrole derivatives obtained by the variation of N-1, C- 2, C-3 and C-4 positions, compound **16** was found to be most potent with a MIC of 0.5µg/ml [39]. By variation of simple pyrrole at *N*-1 position, a series of *N*-(4-substituted) benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole have been prepared. Oxadiazole-2-thiol derivative (**17)** has shown moderate activity with a MIC 16 µg/mL [40].



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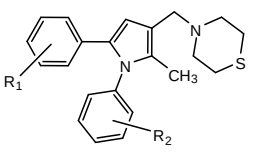
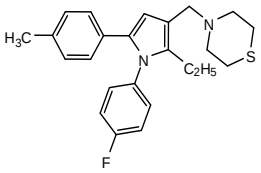


10: R_1=H, R_2=4-F
11: R_1=H, R_2=H
12: R_1=2-F, R_2=2-F
13: R_1=*i* -C_3H7, R_2=4-F
14: R_1=4-CH_3, R_2=4-F



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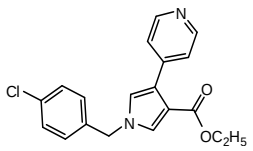

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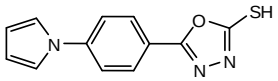

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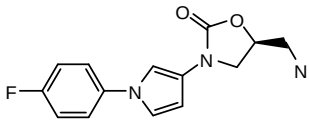
The 3-(1*H*-pyrrol-1-yl)-2-oxazolidinone analogues of PNU-100480 and evaluated their potency as an antitubercular agents. Among all, compound **18** showed 90% inhibition at 5.8 µM concentrations, which is comparable to PNU-100480 and INH [41]. Compounds (**19**) showed equal potency of MIC 0.78 µg/mL against *M. tuberculosis* [42]. The compound **20** showed MIC of 0.39 µg/mL against *M. tuberculosis* H37Rv [43]. With the same motivation, Guillon *et al*[44]. synthesized a series of pyrrolo[l,2-a]quinoxaline-2- or -4-carboxylic acid hydrazides and one compound (**21**) showed an interesting activity at 6.25 µg/mL against *M. tuberculosis* H37Rv, with a 100 percentage inhibition [44]. Two series of thiophene (**22**) [45,46], thiophene analogues displayed MIC in the range 3.12-12.5 µg/mL and benzopyrrole/pyridine analogues displayed 6.25-25 µg/mL against *M. tuberculosis* H37Rv. Whereas, hybrid of isonicotinic hydrazone of pyrrole (**23**) showed best potency of MIC ≤0.1 µg/mL against *M. tuberculosis* H37Rv and also has good selectivity index[47].



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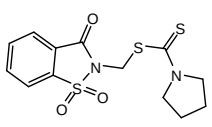

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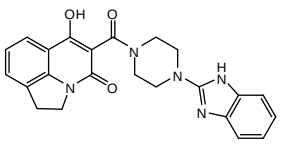

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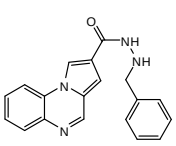

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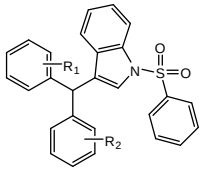

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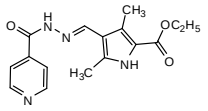

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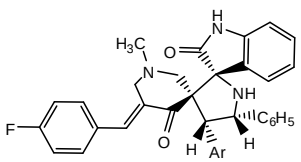
Hybridization of Spiro compound (fig **3**) and pyrrolo[2,1-b]thiazole, an unusual ring with different biological properties, particularly permitted the obtention of pyrrolothiazoles derivatives (**24**) that present a MIC of 0.007 µM against *M. tuberculosis*, being more potent than INH and Ciprofloxacin. A series of spiro-pyrrolothiazoles were evaluated for their antitubercular activity. Among all, the best potency was displayed by compound **25** with a MIC of 0.6 µM against MTB and MDR-TB [48].



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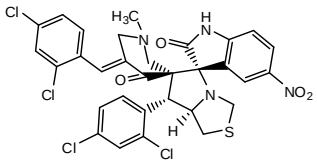

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Fig. 3: Spiro-pyrrolothiazoles derivative with anti-TB activity.

5. Discussion

Mycobacterial infections are infectious diseases of global importance. Control of TB is complicated by difficulties in administrating the long-course chemotherapy regimens, the inability to eliminate latent organisms, and increasing appearance of MDR-TB. New drugs for the control of TB are urgently needed, including developments of short-term antibiotic regimens to minimize the emergence of drug resistance and new drugs to treat MDR-TB patients and to eradicate the latent bacteria. Recent years have witnessed emergence of many new structural classes of anti-TB agents, some of which exhibit promising activities against susceptible and resistant strains of *M. tuberculosis*. In particular, the newly discovered drug with superior anti-TB activity and encouraging results from recent studies that have generated considerable excitement.

6. Conclusion

In the past several years, it has been realized that controlling TB needs two issues to be addressed, drug resistance and persistence. A better understanding of the biology of tubercle bacilli, development in mycobacterial genetic tools, high throughput drug screening and structure based drug designing have increased the prospect of identifying novel anti-tubercle agents to combat drug resistant and persistent organisms. Investigation of *M. tuberculosis* pathogenesis has entered a new era and it is anticipated that the global challenge of tuberculosis will be surmounted in near future. In conclusion, we can confirm that in general pyrrole derivatives are particularly adapted to be used as antitubercular agents. Finally, the selectivity and the consistent ability to reduce the onset of cross resistance of pyrrole derivatives, probably due to a different mechanism of action, lead them to be good candidates for further development.

Conflict of interest

The author(s) confirm that this article content has no conflicts of interest.

Acknowledgements

Declared none.

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