Recent Developments in Antitubercular Drugs

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Abstract: This review article describes the current TB drugs, their merits and demerits as well as the new promising anti-TB agents such as diarylquinolines, oxazolidinones and nitroimdiazoles. It also includes the future development of new antitubercular agents according to the potential drug targets of *Mycobacterium tuberculosis* and structure-activity relationship studies on important anti-TB drugs.

Key Words: Tuberculosis, *Mycobacterium tuberculosis*, anti-tubercular drugs, drug targets, structure-activity relationship.

INTRODUCTION

Tuberculosis (TB) is the leading cause of mortality worldwide, infecting about 9.2 million people and kills approximately 2.0 million people annually [1]. In 2006 of these, 0.7 million TB cases and 0.2 million deaths were in HIV-positive people [1]. The organisms responsible for the disease are the tubercle bacilli, *Mycobacterium tuberculosis*, *Mycobacterium tuberculosis complex* including *Mycobacterium bovis* and *Mycobacterium africanum* [2]. Due to discovery of effective antimycobacterial agents between 1950 and 1970s, viz., ethambutol, isoniazid, pyrazinamide, rifampicin and streptomycin, and reduction in poverty, there was drastic decrease in the number of TB cases, especially in developed countries. However, since 1980s, the number of TB cases throughout the world has been increasing rapidly due to the emergence of multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB) [3]. The MDR forms of the disease are more often fatal and are difficult and expensive to treat [4]. The situation has recently been complicated by the association of TB with HIV in sub-Saharan Africa and many developing countries and also the HIV epidemic in many parts of the World [5]. In the case of acquired drug resistance only second-line drugs (e.g. capreomycin, cycloserine, kanamycin, ethionamide) have to be used which have significant side effects with approximately 50% cure rate. However, fluoroquinolones such as ofloxacin, norfloxacin can be used which are safer than above-mentioned second-line drugs but have the disadvantage of expense [6]. There have been no anti-TB drugs introduced in the past 30 years. Thus, there is an urgent need to search for and develop new, effective and affordable anti-TB drugs.

Two review articles on antitubercular drugs have been published recently. The article by Tomioka [7] briefly reviewed some recent findings on the pharmacological status of rifamycin derivatives and fluoroquinolones. It also described other types of new agents, such as oxazolidinones, nitroimidazoles, 2-pyridone, riminophenazines and diarylquinolines, which are being developed as anti-TB drug along with future development of new antitubercular drugs according to potential pharmacological targets. The second article by Janin, Y.L. [8] described the drugs currently used in antituberculosis treatment and the most advanced compounds undergoing clinical trials. The article also provided a description of mechanism of action of advanced compounds along with other series of inhibitors known to act on related biochemical targets, reported in last 10 years. Very recently a comprehensive review article has been published which described the present status of the development of new antitubercular agents such as nitroimidazoles, diarylquinolines and oxazolidinones and the future development of new antitubercular drugs discussed according to potential pharmacological targets of *M. tuberculosis* and drug design based on structure-activity relationship (SAR) analysis [9].

The present article includes concrete description of the clinical status of various anti-tubercular drugs as well as drugs that are under development. In addition the developments of new anti-tubercular drugs are being discussed with respect to the molecular targets and SARs.

RIFAMPIN AND ITS ANALOGUES

This group of drugs inhibits bacterial RNA synthesis by binding to β-subunit of the DNA-dependent polymerase. Various modifications were performed on the core structure of rifampin, **1** to obtain more effective analogues such as rifapentine **2**, rifabutine **3** and rifalazil (Fig. **1**) [10]. Rifapentine was approved in 1998 for the treatment of TB. It appears to be safe and is currently being evaluated in phase III trials for the treatment of latent TB [11]. Recently a controlled phase 3 clinical trial was conducted to compare the efficacy of rifapentine/isoniazid to daily rifampin/pyrazinamide in preventing TB with pulmonary TB in Brazil. The study involved a total of 399 patients. In this study rifapentine/ isoniazid was better tolerated than rifampin/pyrazinamide and was associated with good protection against TB. Rifapentine/isoniazid weekly for 12 weeks is likely a promising therapy for latent TB infection [12]. Rifalazil (RZL), a new semi-synthetic rifampin derivative with a long half life, is highly active against *M. tuberculosis*, *M. avium*. RZL is more active than rifampin or rifabutin against *M. tuberculo-*

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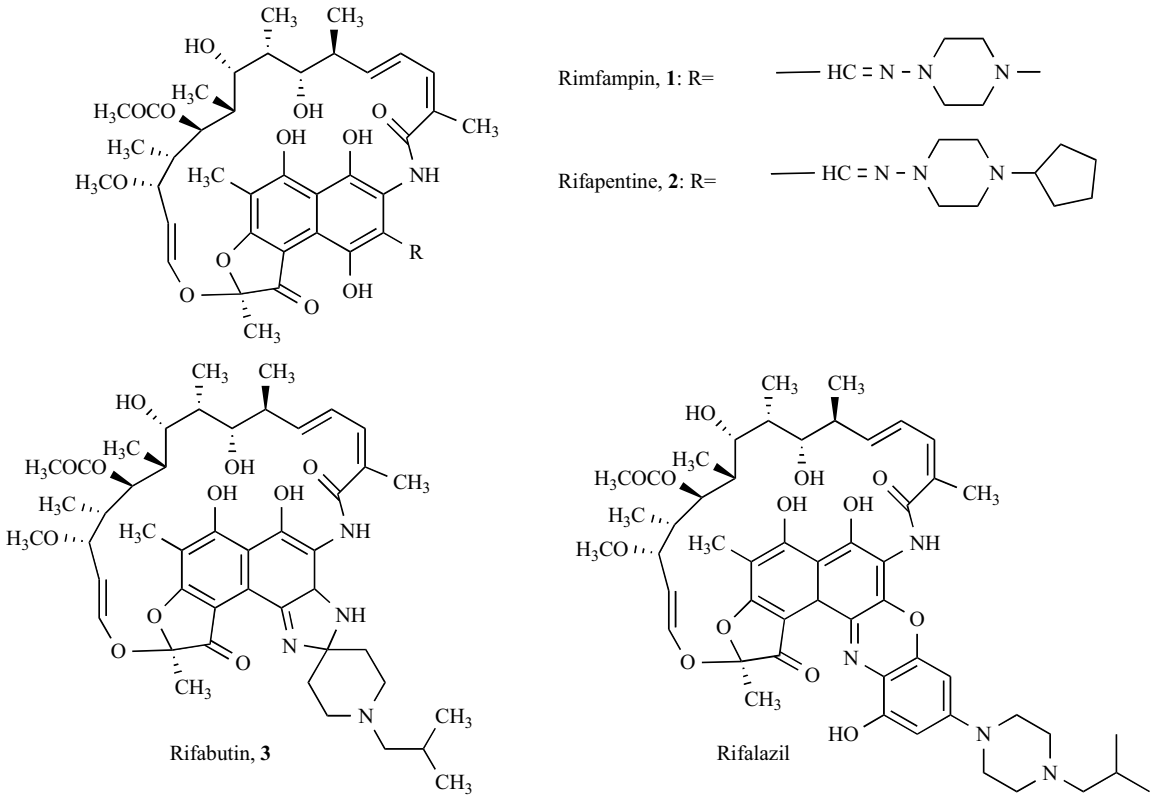


Fig. (1). Chemical structures of rifampin and its derivatives.

sis in mice both *in vivo* and *in vitro* [13]. Rifampin-resistant strains confer cross resistance to all rifamycins including RZL which limits its use in the treatment of rifampin-resistant TB [14]. A safety study in humans showed that although RZL at doses of 10 and 25 mg was safe, a dose of 100 mg produced flu-like symptoms and a transient dose-dependent decrease in white blood cell and platelet counts, and did not show better efficacy than rifampin [15].

FLUOROQUINOLONES

There are at least 25 various fluoroquinolone antibacterials spanning over four generations reported in the literature that are used for treatment. These compounds originated from the impurity obtained during synthesis of chloroquine and first commercial quinolone was nalidixic acid. The various quinolones addressed the issues of side effects, pharmacokinetics, simplified dosing and extended the activity spectrum to many bacteria including mycobacteria [16, 17]. This class of antibiotics has been proven as an indispensable treatment of MDR-TB. In this review only the few currently used fluoroquinolones are described. The fluoroquinolones such as ciprofloxacin, **4**, ofloxacin, **5**, levofloxacin, **6**, sparfloxacin, **7**, gatifloxacin, **8**, moxifloxacin, **9** and sitafloxacin, **10** should be included in the regimen. The extensive SAR study on fluoroquinolones carried out at N-1 and N-1to C-8 bridge positions led to the development of the compounds **4-10** (Fig. **2**) which are being used clinically [17]. The N-1 cyloproply moiety was first optimized with ciprofloxacin and this change enhanced the anti-Gram negative potency compared to norfloxacin. The cyclopropyl moiety became common for long time thereafter in quinolone structure modifications tions with potency being modulated by changing the substituents at C-5, C-7 and C-8. Among these ciprofloxacin withstood all the challenges of drug development and remains a market leader. In the N-1 to C-8 bridged family of quinolones C-8 substituent is linked to an N-ethyl moiety at N-1 resulting in the tricyclic family of quinolones. This resulted in restricted rotation of the ethyl group and introduced a chiral atom in the structure. From this member, racemic ofloxacin was marketed and became popular. Subsequently it was replaced by its resolved *S*-analogue levofloxacin which is one of the present marketed fluoroquinolones. Rigification of N-1 substituent in this way resulted in significant enhancement in the anti-Gram positive activity. The nature of the atom attached at C-8 seems comparatively unimportant as C, O and S bioisosteres possess similarly significant antibacterial activity [17]. The mechanism of action of fluoroquinolones is dual inhibition of topoisomerase-II (an ATP-dependent DNA gyrase) and in most Gram positive bacteria, an ATP-dependent topoisomerase-IV. In case of *M. tuberculosis* they inhibit topoisomerase-II as topoisomerase-IV is absent in this pathogen [18]. 22 different fluoroquinolones were tested for their inhibitory effect on topoisomerase-II. The results of the *in vitro* assay showed that a correlation (R_2 = 0.9) exists between their inhibition of topoisomerase-II and effect on growth of *M. tuberculosis*. The six quinolones, **4** and **6-10** along with clinafloxacin, **11** were among the best inhibitors according to this investigation [18]. Recently the compound **12**, with novel side chain (Fig. **2**) has been patented and it was found to be 10 times more active against *M. tuberculosis* than some of the currently used quinolones [19]. The compound **12** or its analogue is undergoing preclinical trial as an antitubercular drug under the name DW-224.

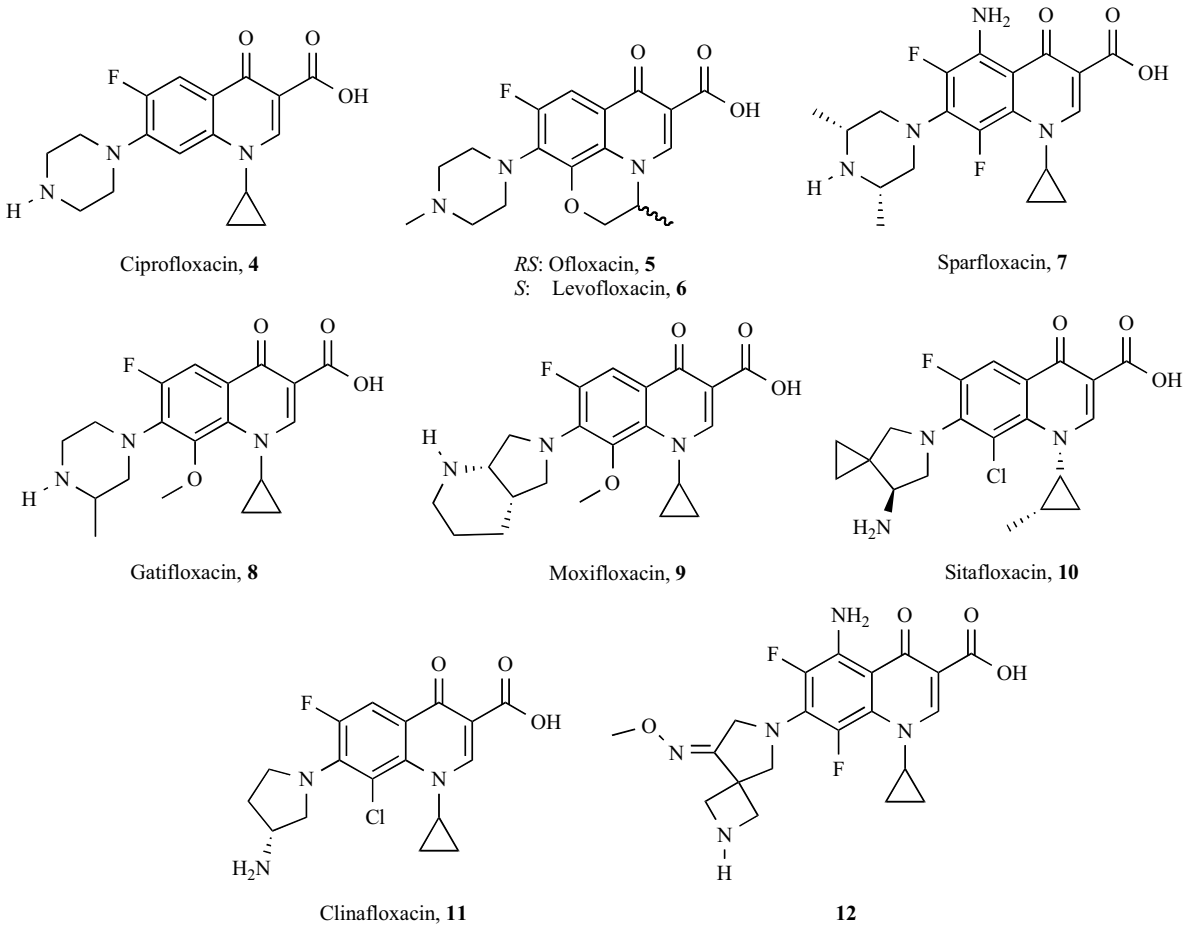


Fig. (2). Chemical structures of fluoroquinolones.

Other quinolones reported recently for their antimycobacterial potential [20, 21]. Gatifloxacin is being developed by OFLOTUB Consortium, The European Commission, WHO TDR and Lupin Ltd. and it is currently undergoing phase 3 clinical trials [22]. It is the first TB agent to reduce the pulmonary TB therapy to four-month duration. Moxifloxacin is undergoing phase 2 and 3 clinical trials by CBC TBTC, John Hopkins University and UK MRC. The TB Alliance and Bayer are jointly pursuing clinical development for tuberculosis [22].

OXAZOLIDINONES

Oxazolidinones are a new group of antibiotics and linezolid is the first oxazolidinone available. The first oxazolidinone was developed by EI DuPont de Nemours and Co. Inc. in 1978, was synthesized because of its activity against certain plant pathogens. Nine years later two oxazolidinones, DuP 721 and DuP 105, were synthesized as antibacterials against human pathogens [23]. However, because of their toxicity, the development of these antibacterials was stopped. Upjohn laboratories (latterly Pharmacia and now Pfizer), in 1996, developed two non-toxic derivatives of these drugs, a morpholine derivative linezolid, **13**, and a piperazine derivative eperezolid, **14** (Fig. **3**) [24]. Linezolid is active against *Staphylococcus aureus*, *Enterococci*, *Streptococcus pneumoniae* and gram-positive anaerobic bacteria. Linezolid has been approved by FDA for the treatment of skin infections caused by methicillin-resistant *S. aureus* (MRSA). The activity of this oxazolidinone along with new oxazolidinones against *Mycobacterium tuberculosis* is comparable with that of the first line anti TB agents. Oxazolidinones may be useful for the treatment of multi -drug resistant strains. Oxazolidinones bind to the 50S ribosomal subunit and they have no affinity to the 30S subunit. Oxazolidinones have the close binding site with the chloramphenicol and lincomycines at the 50S ribosomal subunit. Unlike chloramphenicol and lincomycine, oxazolidinones do not inhibit peptidyl transferase. Oxazolidinones also do not inhibit formation of fMet-tRNA or elongation or termination steps [25, 26]. It is observed that oxazolidinones inhibit formation of initiation complex of 30S subunit, fMet-tRNA, mRNA, GTP and initiation factors 1-3 [27]. A detail SAR study was conducted on the oxazolidinones with respect to their antibacterial properties at Pharmacia. The extensive research work at Pharmacia led to improved SAR than that reported by Dupont earlier. The most significant finding of this SAR was that a suitable electron-donating amino group on the phenyl ring can confer an excellent antibacterial activity while helping to maintain a good safety profile (Fig. **4**). Another important finding of this investigation was the identification of the potentiating effect of one or two fluorine atoms flanking the morpholine or piperazine ring [28]. This class of compounds were also tested for their anti-tubercular effect and several active compounds were reported [29, 30]. More detail clinical trials are

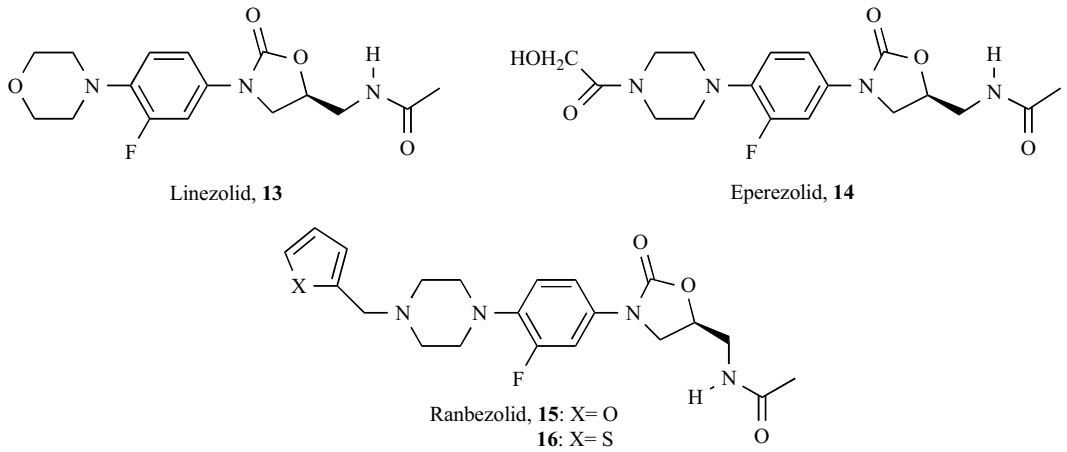


Fig. (3). Chmical structures of Oxazolidinones.

needed with better oxazolidinones in order to assess their anti-tubercular activity. The most recent oxazolidinone is ranbezolid/R Bx 7644, **15**, (Fig. **3**) which has undergone phase I clinical trial in 2004 [31, 32]. This compound exhibited excellent antibacterial spectrum and its effect on *M. tuberculosis* was reported along with its thiophene analogue, **16** [33, 34].

NITROIMIDAZOLES

The effect of bicyclo nitro-bearing imidazoles was studied on *M. tuberculosis* and led to the lead molecule PA-824, **17** [35]. The preclinical study with PA-824 (Fig. **5**) in murine models demonstrated a good activity on resistant strains [36] and the TB alliance is currently conducting phase 1 clinical trials of PA-824 [22, 37]. Further a series of structurally related nitroimidazo[2,1-b]oxazoles has been prepared and one of the compounds, OPC-67683, **18**, (Fig. **5**) is undergoing phase 2 clinical trials conducted by Otsuka Pharmaceuticals, Japan [17, 32]. It may possess treatment-shortening potential as it synergizes *in vitro* with rifampicin and pyrazinamide. OPC-67683 is effective against MDR-TB and showed no cross-resistance to first line TB therapy [38]. It exhibited quite low minimum inhibitory concentration (MIC) value, in the range of 0.006–0.024 μg/ml against *M. tuberculosis in vitro*. OPC-67683 showed dose-dependent effect on intracellular *M. tuberculosis* H37Rv after a 4-hr pulsed exposure with MIC value of 0.1 μg/ml whereas rifampicin showed MIC value of 3 μg/ml in the same assay. The combination of OPC-67683 with rifampicin and pyrazinamide exhibited remarkably quick eradication of viable TB bacilli in the lung in comparison to the standard regimen consisting of rifampicin, isoniazid, ethambutol and pyrazinamide. Thus, it has a potential to be developed as TB drug [39]. The exact mechanism of action of this type of agents is not reported yet. However one study proposed the possible mechanism of action of PA-824 recently. A bioreductive activation of the nitroimidazooxazine- bearing PA-824 by a combination of the low redox potential F420-dependent glucose-6-phosphate dehydrogenase and previously unstudied protein (Rv3547) acting as the electron transfer mediator, has been suggested [40]. This compound inhibited the biosynthesis of mycolic acid at the stage of methoxy and keto-mycolic acid synthesis [41].

PLEUROMUTILIN ANTIBIOTICS

Valdemulin and tiamulin are used in veterinary medicine, targets 50S ribosome subunit [42, 43]. Renewed interest in this class of antibiotics led to the design and synthesis of more active molecules such as **19**, (Fig. **6**) which is active against bacterial strains resistant to valdemulin [44, 45].

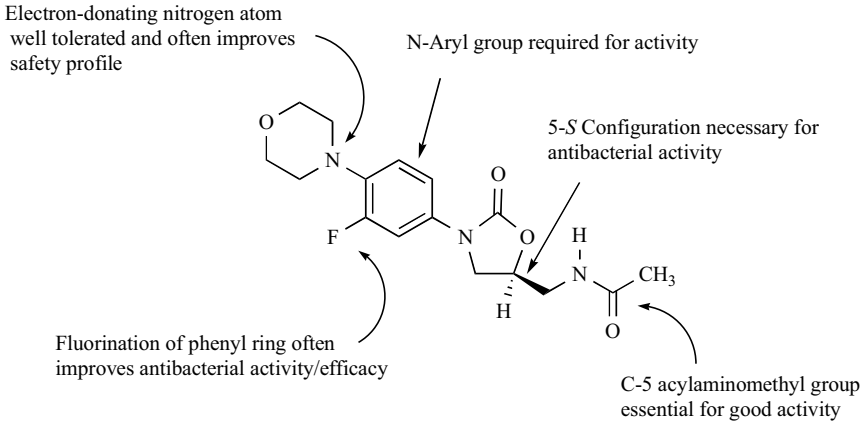
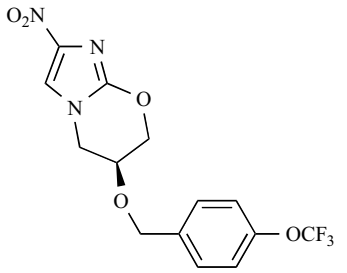
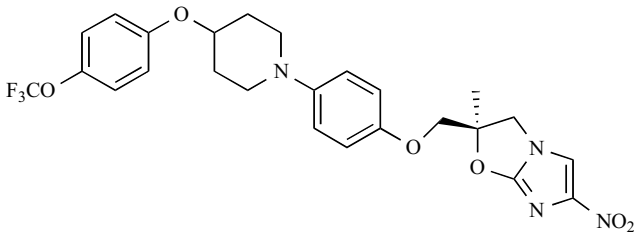


Fig. (4). SAR of Oxazolidinones.



PA-824, **17**



OPC-67683, **18**

Fig. (5). Chmical structures of Nitroimidazopyrans.

Other analogues of pleuromutilin including compound **20**, (Fig. **6**) have been patented for their antimycobacterial properties [46].

INHIBITORS OF PROTON PUMP F_0F_1 H^+ ATPASE

Diarylquinolines: A series of diarylquinolines (DARQs) with potent *in vitro* activity against several mycobacteria including *M. tuberculosis* was reported [47]. About 20 molecules of the DARQ series were reported to possess MIC below 0.5 μg/ml against *M. tuberculosis* H37Rv. Structurally and mechanistically DARQs are different from both fluoroquinolones and other quinoline classes including mefloquine and its analogues. One of the major structural differences between DARQs and other quinolines is the specificity of the functionalized lateral chain at C3' borne by the DARQs. The most active compound of this series, R207910 (**21,** Fig. **7**), is a pure enantiomer with two asymmetric carbons. This compound showed very potent activity against *M. tuberculosis* H37Rv and six antibiotic susceptible strains and exhibited MIC values in the range of 0.03 to 0.12 μg/ml whereas rifampicin and isoniazid exhibited MIC values 0.5 and 0.12 μg/ml. R207910 demonstrated similar *in vitro* efficacy against *M. tuberculosis* clinical isolates resistant to anti-TB drugs isoniazid, rifampicin, ethambutol, streptomycin, pyrazinamide and moxifloxacin. It did not inhibit *M. tuberculosis* DNA gyrase, the target for quinolones. R207910 appeared to be specific inhibitor of *M. tuberculosis* as it showed much higher MIC values against several other Gram negative and Gram positive bacteria.

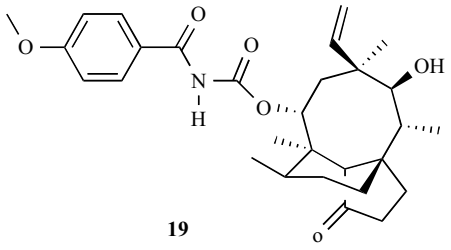
The target and mechanism of action of R207910 are different than that of all other anti-TB agents. It inhibited ATP synthase of *M. tuberculosis*, which leads to ATP depletion and imbalance in pH homeostasis, which in turn decreases survival of the bacillus. There is no cross resistance with other anti-TB drugs due to its separate mechanism of action. R207910 also exhibited anti-tubercular activity *in vivo* in animal murine TB model. It was found to be more active in this model than rifampicin [48].

Human studies with R207910 have shown good tolerability during a limited exposure period and plasma levels were around 8 times higher than those in mice. Human pharmacokinetics of this molecule seems to reflect good oral absorption and sustained plasma levels. The combination of low MIC values, a distinct mechanism of action, early and late bactericidal activity, and pharmacokinetic profile makes R207910 a promising TB drug candidate [47]. It was initially identified by Johnson and Johnson and subsequently developed by Tibotec Pharmaceuticals Ltd. (TMC207) where it is undergoing phase 2a clinical trials in both drug sensitive and drug resistant TB [48].

The antimalarial mefloquine, **22**, is also reported to be the inhibitor of *M. tuberculosis* and it inhibits the proton pump F_0F_1 H^+ ATPase of *S. pneumoniae* [49]. Few analogues of mefloquine were synthesized and among them compound, **23**, also found to inhibit the proton pump F_0F_1 H^+ ATPase of *S. pneumoniae* [49]. This led to the further SAR studies of mefloquine analogues and the more active hydrazone derivative of mefloquine, **24**, was reported [50]. For the quinoline derivatives such as **25** (Fig. **7**) reported during last four years, no mechanism of action explained so far. Thus, further studies are required to establish the hypothesis that these compounds act by inhibiting mycobacterial proton pump F_0F_1 H^+ ATPase.

FtsZ TARGET

The FtsZ protein is the bacterial tubulin homologue and is crucial for cell division [51]. Thus, tubulin polymerization



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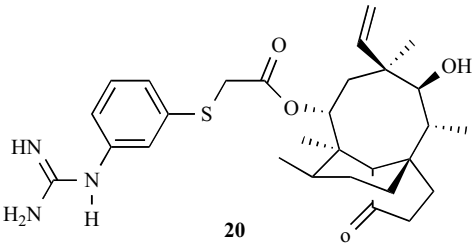

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Fig. (6). Chemical structures of pleuromutilin antibiotics.

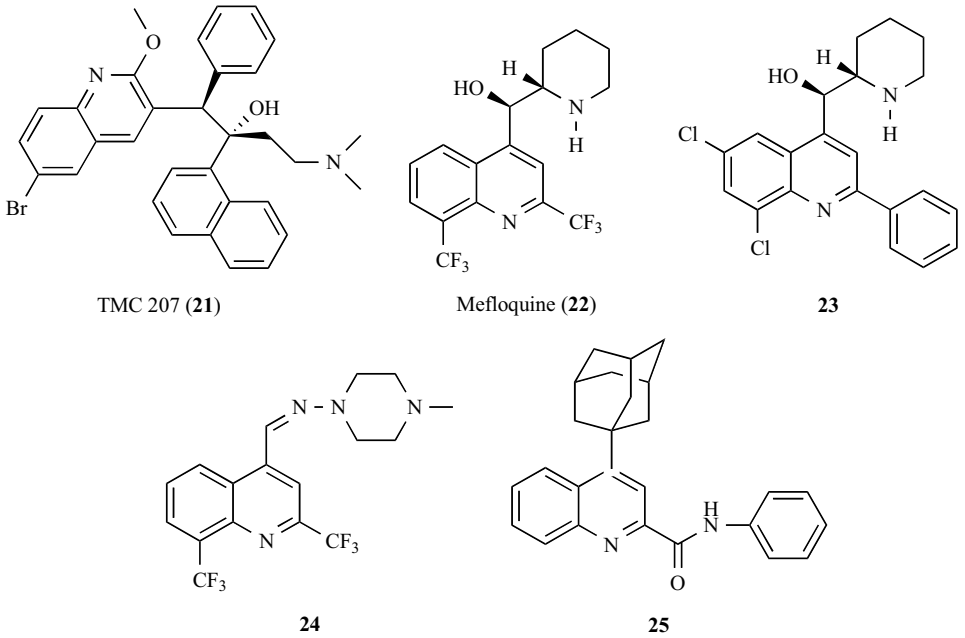

Fig. (7). Chemical structure of quinolines reported as proton pump F0F1 H+ ATPase inhibitors.

inhibitors were tested on mycobacterial growth [52, 53]. The thioether-bearing compound, **26**, (Fig. **8**) was reported as bacterial cytokinesis inhibitor [54]. A taxane derivative with a similar diphenylthioether moiety was also reported to inhibit *M. tuberculosis* growth [55]. The biochemical processes regulating *M. tuberculosis* functions of this protein are still unknown.

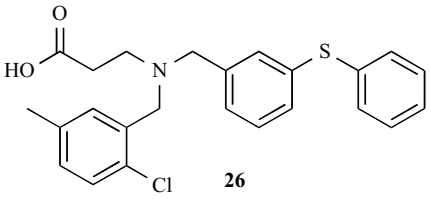

Fig. (8). Chemical structure of thioether compound which inhibit FtsZ protein.

SIGNALLING KINASE INHIBITORS

A series of antimycobacterial salicylanilides were reported which inhibit signal transduction system in mycobacteria [56]. Inhibition of this regulatory system remains a significant research field as a regulation of this type is involved in the virulence of *M. tuberculosis* in mice. At least eleven eukaryotic-like protein serine-threonine kinases (Pkn A to L) involved in signal transduction were identified in *M. tuberculosis* h37Rv genome [57]. The generic kinase inhibitor, **27**, (Fig. **9**) and other complex compounds have shown to inhibit the growth of some mycobacteria and this result provided fresh impetus for the research on more specific inhibitors [58, 59]. Benzoquinoxaline compounds such as **28** (Fig. **9**), were patented for their inhibition on PKnB, PknG and PknH as well as for their effect on mycobacterial growth [60]. Mycobacterial tyrosine phosphatase inhibitors, which were secreted by mycobacteria, have been suggested as the new target for the research on new antimycobacterial agents [61].

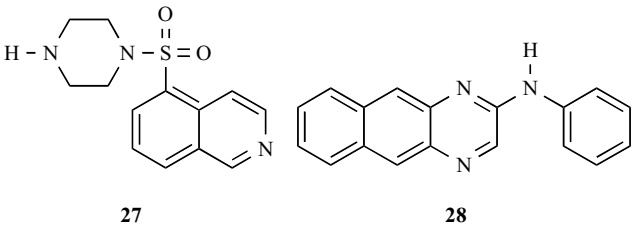

Fig. (9). Chemical structure of Signalling Kinase inhibitors.

MYCOBACTERIAL CYTOCHROME P450 MONO-OXYGENASE INHIBITORS

The azole group of antifungal agents such as clotrimazole, **29**, and econazole, **30** (Fig. **10**); have been reported to inhibit growth of *M. tuberculosis* [62-64]. The likely target of these compounds in mycobacteria is the P450 monooxygenase homologue to the eukaryotic 14α-sterol demethylases and that the imidazole moiety is binding the iron of these haem-containing enzymes [65]. The X-ray derived structures of this enzyme were obtained [66] and econazole was reported to have antitubercular activity *in vivo* on a murine model [67]. The recently reported X-ray structure of a *M. tuberculosis* P450 CYP121-fluconazole complex, led to specific structure activity relationship study [68]. Compound, **31** (Fig. **10**), having the 2,4-dichloro and 4-chlorophenyl pattern has a slightly better activity than the compounds **29** and **30** [69]. The 3D-QSAR and comparatie molecular field analysis have been performed on various pyrrole derivatives with MIC values of 0.5 to > 250 μg/ml [70]. The pyrrole series of antimycobacterials such as compounds, **32** and **33** (Fig. **10**) and other imdiazole-containing derivatives are inhibitors of *M. tuberculosis* cytochrome P450 mono-oxygenases. In these studies it has been reported that replacement of the piperazine moiety of BM-212 by a thiomorpholine ring improved its antimycobacterial activity. Moreover, a new compound, 1-(4-fluorophenlyl)-2-methyl-3-(thiomorpholin-4-yl)

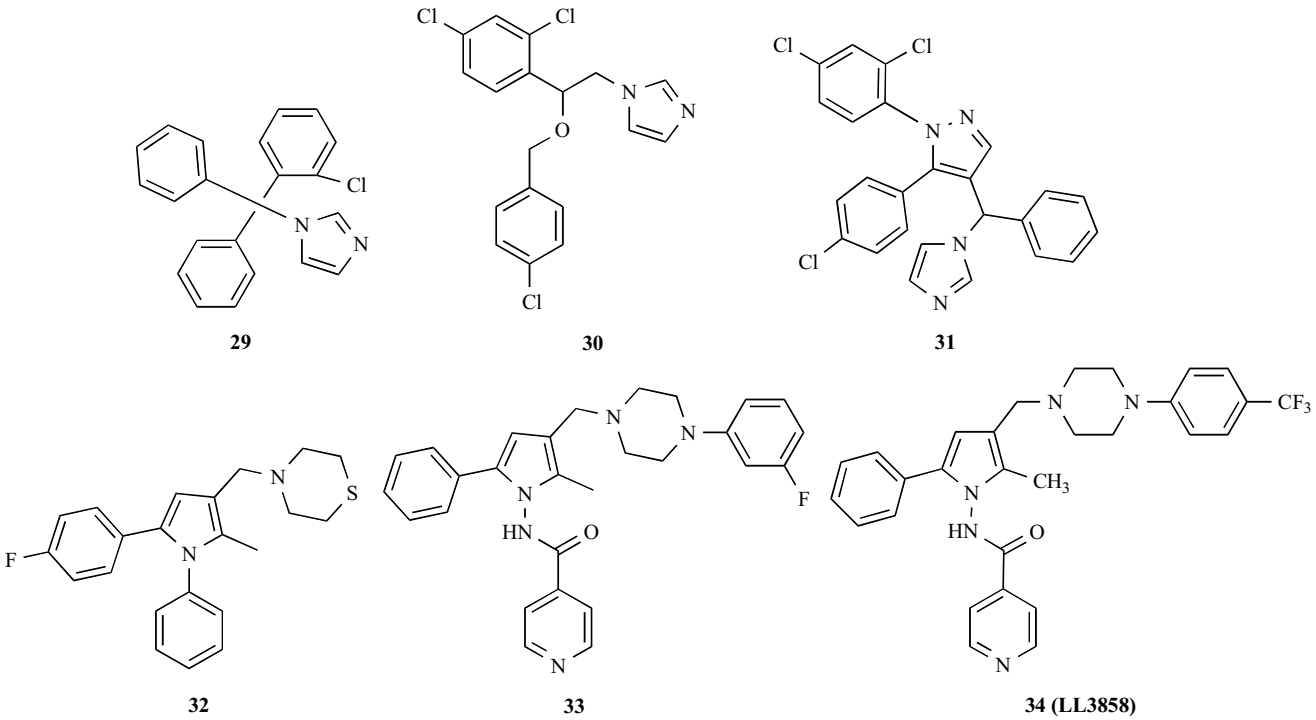

Fig. (10). Chemical structures of Mycobacterial cytochrome P450 monooxygenase inhibitors.

methyl-5-(4-methylphenyl)-1H-pyrrole having potent anti-TB activity with MIC of 0.4 μg/ml and very high protection index (maximum nontoxic dose/MIC) was obtained by performing SAR analysis on diarylpyrrole derivatives of BM-212 [71, 72]. The pyrrole LL3858 (**34,** Fig. **10**) is being developed by Lupin Pharmaceuticals Ltd. and being evaluated in multidose phase 1 trial involving healthy volunteers in India. The activity of pyrroles against *M. tuberculosis* was first reported by Deidda *et al*. [73] in 1998. The most potent pyrrole reported was BM212, 1,5-diaryl-2-methyl-3-(4-methylpieprazin-1-yl)methyl prrole with MICs in the range, 0.7-1.5 μg/ml against several strains of *M. tuberculosis*. The mechanism of action for this class of compounds is not established yet. Based on the work of Deidda *et al*. Lupin, India synthesized a series of pyrroles, one of which (LL3858) is currently in clinical development for the treatment of TB [Abstract presentation[1]]. This compound showed potent activity in mouse model of TB. In combination with currently used anti-tubercular drugs, LL3858 is reported to sterilize lungs and spleen of infected animals in shorter time than conventional therapy [Abstract presentation[2]].

DIAMINE SQ109

SQ109 [N-adamantan-2-yl-N'-(3,7-dimethylocta-2,6-dienyl)-ethane-1,2-diamine] **35** (Fig. **11**) , is the most recent compound to enter phase 1 clinical trials for TB and is being developed by Sequella. It is originally intended to be an improvement of ethambutol, but structurally different than ethambutol and different in its intracellular target suggest it may be a novel antimycobacterial agent and not an ethambutol analogue. SQ109 was identified as the most potent compound in the synthesized library of compounds with the 1,2-diamine pharmacophore of ethambutol [74, 75]. SQ109 exhibited MIC value in the range of 0.1 – 0.63 μg/ml and it showed 2- to 2.5-log reduction in the counts of colony-forming units in the lung and spleen in mice [76].

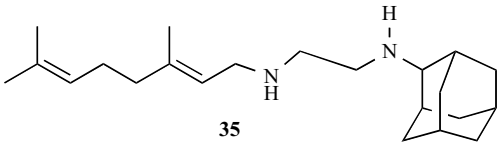

Fig. (11). Chemical structure of Diamine SQ 109.

Other types of compounds reported with significant anti-*M. tuberculosis* (MTB) activity (MIC values ≤ 2 μg/ml) are enumerated in Table **1**.

CONCLUSION

So far enormous efforts were made to develop rifamycin derivatives and quinolones for multi-drug regimens of MDR-TB, which can replace first-line anti-tubercular drugs. But, the physicians are not satisfied with the therapeutic outcome of these drugs, as they have some serious drawbacks. The therapeutic efficacy of new rifamycins (rifabutine, rifapentine) against MDR-TB is limited because the majority of rifampicin-resistant MTB isolates easily acquires high cross-resistance. Further, the usefulness of fluoroquinolones is

[1] Arora, S. K.; Sinha, N.; Sinha, R. K.; Uppadhayaya, R. S.; Modak, V. M.; Tilekar, A. Synthesis and *in vitro* anti-mycobacterial activity of a novel anti-TB composition LL4858 [abstract F-1115]. In: Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC). Washington, DC: American Society for Microbiology, **2004**:212.

[2] Sinha, R. K.; Arora, S. K.; Sinha, N.; Modak, V. M. *In vivo* activity of LL4858 against *M. tuberculosis* [abstract F-1116]. In: Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC). Washington, DC: American Society for Microbiology, **2004**:212.

Table 1. Reported Anti-MTB Compounds with Significant Activity

Compound	Reported anti-TB Activity	Ref.
9-Benzylpurines	MIC: 0.39 μg/ml against MTB.	[77]
9-Sulfonylated-6-mercaptopurines	Good to moderate anti-MTB activity *in vitro* (MIC: 0.39 μg/ml) and SDR-MTB (mic: 0.78 μg/ml)	[78]
2'-Monosubstituted INH derivatives	Excellent *in vitro* activity against RIF-resistant MTB (MIC: 0.05 μg/ml)	[79]
6-Arylpurines	Good *in vitro* activity against MTB (MIC: 0.78 μg/ml)	[80]
Quinoxaline 1,4-dioxide derivatives	Good *in vitro* activity against MTB (MIC: 0.39 μg/ml)	[81, 82]
2-Alkoxycarbonyl-amino pyridine	Good *in vitro* activity against MTB (MIC: 0.25 μg/ml) Target: FtsZ	[83]
Chloropyrimidines	Good *in vitro* activity against MTB (MIC: 0.78 μg/ml)	[84]
Hydantoins Arylidene aromatic derivatives	Good *in vitro* activity against MTB (MIC: 0.8 μg/ml) Comparable with RIF	[85]
Peptide deformylase inhibitors N-formyl hydroxylamine	Good *in vitro* activity against MDR-MTB and SDR-MTB (MIC: 0.03-2.0 μg/ml)	[86]
N-alkyl urea hydroxamic acids	Good *in vitro* activity against MDR-MTB and SDR-MTB (MIC: 0.03-1.0 μg/ml)	[87]
Capuramycin analogues RS-112997, RS-124922, RS-118641	Moderate to good *in vitro* activity against MDR-MTB (MIC: 0.5-2.0 μg/ml), target: cell wall synthesis Active against MDR-MTB infection in mice	[88]
Cyclic thiazolyl peptide Nocathiacin	Excellent *in vitro* activity against MTB (MIC ≤ 0.008 μg/ml), Good *in vitro* activity against MAC a (MIC: 0.06-0.25 μg/ml)	[89]
Alkyl α-(5-aryl-1,3,4 -thiadiazole-2ylthio) -acetates/propionates	Good to moderate *in vitro* activity against MTB (MIC: 0.78-6.25 μg/ml)	[90, 91]
Pyrazolyl-2-methanethiones	Good *in vitro* activity against MTB (MIC: 0.9 μg/ml)	[92]
N,N-dialkyl sulfenamides/sulfonamides	Good *in vitro* activity against MTB (MIC: 0.9 μg/ml)	[93]
Tetracycline derivatives	Good *in vitro* activity against MTB (MIC: 0.2 μg/ml)	[94]
Phenyl/pyridylthiourea analogues	Good *in vitro* activity against MDR-MTB (MIC: 0.05 μg/ml)	[95]
Oxadiazole mannich bases	Good *in vitro* activity against MDR-MTB (MIC: 0.9 μg/ml)	[96]
Oxazolyl/thiosemicarbazone analogues	Excellent *in vitro* activity against MTB (MIC: 0.05 μg/ml)	[97]
Ag(I) cyclamate	Good *in vitro* activity against MTB (MIC: 0.45 μg/ml)	[98]
6-(2-Furyl)-9-(p-methoxy- benzyl)purines	Good *in vitro* activity against MTB (MIC: 0.2 μg/ml)	[99]

MTB: Mycobacterium tuberculosis, MDR: multi-drug resistant, RIF: Rifampin, SDR: single-drug resistant.

somewhat limited because of quinolone-resistant MTB strains are now rapidly increasing. Thus, there is an urgent need to develop new anti-TB drugs with no cross-resistance to any existing drugs, and especially to develop drugs with potent bactericidal activity against MTB including dormant MTB, for effective treatment of TB. Currently few drug molecules such as diarylquinoline TMC-207, nitroimidazopyran PA-824, nitroimidazooxazole OPC-67683, linezolid and pyrrole LL-3858 are undergoing clinical trials. It is strongly needed to discover novel anti-TB drugs acting on novel drug targets and in particular it is necessary to develop molecules which are potently bactericidal against dormant MTB, in order to shorten the duration of directly observed treatment strategy (DOTS) of TB patients and to eliminate the reservoir of MTB in developing countries.

As described in the present review, a number of compounds have been synthesized and screened as candidates for new anti-TB drugs, and some compounds are now being developed as a new class of antitubercular drugs. In this context, the efforts should also be made to search and develop

promising candidates from natural products, as majority of existing drugs used to treat infectious diseases due to common bacteria are based on natural products. For example, some high molecular weight natural products such as pleuromutilins, fulleropyrrolidines, granulysin (a protein) have been developed as a source of new antimycobacterial drugs. It need to be emphasized that the most important goal of chemotherapy of TB associated with HIV, is to develop highly effective but low-cost drugs that can be used globally to treat this deadly disease combination.

ABBREVIATIONS

DARQs	=	Diarylquinolines
DOTS	=	Directly observed treatment strategy
MDR-TB	=	Multi-drug resistant *Mycobacterium tuberculosis*
MIC	=	Minimum inhibitory concentration
MRSA	=	Methicillin-resistant *Staphylococcus. aureus*
MTB	=	*M. tuberculosis*
Pkn	=	Protein serine-threonine kinases
RZL	=	Rifalazil
SAR	=	Structure-activity relationship
TB	=	Tuberculosis

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