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New anti-tuberculosis drugs in clinical trials with novel mechanisms of action

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Tuberculosis is a major health problem worldwide, with approximately 1.7 million people dying annually from the disease. The long current drug regimen, the emergence of drug resistant strains and HIV co-infection have resulted in a resurgence in research efforts to address the urgent need for new anti-tuberculosis drugs. A number of new potential anti-tuberculosis drug candidates with novel modes of action have entered clinical trials in recent years. These agents are most likely to be effective against resistant strains. We provide a concise review of their structure-activity relationships, *in vitro* and *in vivo* activity, pharmacokinetics, mechanism of action and combination regimens.

Tuberculosis (TB) is a contagious and deadly disease that spreads through the air, which has reached pandemic proportions. According to the World Health Organisation (WHO), in 2006 there were 9.2 million new cases and 1.7 million deaths from TB around the world [1]. A significant proportion of these new cases and deaths occurs in HIV-positive people [1]. Owing to population growth, the number of new cases arising each year is increasing globally, posing a continued health and financial burden in various parts of the world, particularly Asia and Africa.

TB is caused predominantly by *Mycobacterium tuberculosis* (*M.tb*), an obligate aerobic bacillum that divides at an extremely slow rate. The chemical composition of its cell wall includes peptidoglycans and complex lipids, in particular mycolic acids, which are a significant determinant of its virulence [2,3]. The unique structure of the cell wall of *M.tb* allows it to lie dormant for many years as a latent infection, particularly as it can grow readily inside macrophages, hiding it from the host's immune system. The vast majority of TB infections are caused by *M.tb*, but other closely related mycobacteria (*M. bovis* and *M. africanum*) can also cause the disease [4,5]. When TB becomes active, it typically affects the lungs (pulmonary TB), but in around 25% of cases (immunosuppressed persons and young children) the bacteria enter the blood and infect other parts of the body, such as the pleura, the meninges, the lymphatic system, the genitourinary system and the bones and joints. Infection with HIV suppresses the immune system, rendering individuals more susceptible to TB infection, or allowing a latent infection to activate [6]. Co-infection allows faster progress of both TB and HIV [7,8].

The current first-line TB drug regimen is more than 40 years old and consists primarily of rifampicin and isoniazid. These antibiotics are effective in active, drug-susceptible TB, provided that patients complete the course. There is, however, poor patient compliance due to the cost of drugs, adverse effects, the long time required for full treatment (6–12 months) and the required number of drug doses. Non-compliance has contributed to the appearance of multi-drug resistant (MDR) and extensively drug resistant (XDR) TB strains. MDR-TB is resistant to, at least, isoniazid and rifampicin, often taking a further two years to treat with second-line drugs [9]. XDR-TB also exhibits resistance to second-line drugs including fluoroquinolones and one of capreomycin, kanamycin or amikacin, and is virtually incurable. Furthermore, common HIV/AIDS antiretroviral therapies are not compatible with the current TB regimen because of shared drug toxicities and drug interactions, for example, as a consequence of rifampicin-induced cytochrome P_{450} activation [10,11]. All the above reasons make a compelling case for the urgent need for new anti-TB drugs. In particular, shorter more effective treatments would improve patient compliance and slow down the emergence of drug resistant strains.

Research into new anti-TB drugs was at a standstill until the late 1990s, partly owing to complacency, as first-line drug treatments

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had been shown to cure TB. In addition, since the vast majority of patients are found in the developing world, there had been little incentive for investment in new anti-TB drug discovery and development. Renewed interest in this area, however, has resulted in a number of new drug candidates entering clinical trials in recent years. In this review we consider these new potential first-line anti-TB drug candidates, focusing on those with novel mechanisms of action, since these are most likely to prove effective against resistant strains.

Current anti-tuberculosis drugs

The main objectives of anti-TB drug therapy are to kill all actively metabolising bacilli in the lungs and eliminate less actively replicating and near-dormant bacilli that may otherwise cause a relapse of the disease [12]. The WHO-recommended DOTS (directly observed treatment, short course) anti-TB therapy involves the administration of four drugs: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) or streptomycin (SM), whose structures are shown in Figure 1. Treatment with these so-called first-line drugs is carried out initially over two months, leading to the destruction of bacteria in all growth stages, after which treatment continues with RIF and INH alone for four months, where any residual dormant bacilli are eliminated by RIF and any remaining RIF-resistant mutants are killed by INH [12,13]. Several excellent articles have reviewed the properties of these first-line anti-TB agents [3,9,12,14–17].

Drug-resistant bacteria have emerged, against which first-line drugs have become ineffective. Whilst resistance to a single anti-TB drug is common, affected patients respond well to standard regimens. MDR-TB, however, requires treatment for up to two years with more toxic, less active and more expensive drugs [12], usually involving any first-line drugs to which the strain is still susceptible and alternative or second-line drugs. Older agents such as ethionamide, capreomycin and para-aminosalicyclic acids can be used, as well as newer classes of drugs, such as fluoroquinolones (ofloxacin, moxifloxacin), penicillin/β-lactamase inhibitors and other members of the rifamycin class (rifabutin, rifapentine) [18].

Fluoroquinolones, such as ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin and moxifloxacin, act by inhibiting DNA topoisomerase IV and DNA gyrase [19]. Gatifloxacin and moxifloxacin, whose structures are shown in Figure 2, exhibit the highest *in vitro* activity against *M.tb* [18]. The level of resistance to fluoroquinolones, however, is limiting their use in anti-TB therapy [20].

Rifampicin (RIF), one of the most powerful first-line anti-TB drugs, has been modified to produce rifalazil, rifabutin and rifapentine, whose structures are shown in Figure 3. These agents can be given once or twice weekly, instead of daily RIF dosing because of their longer half-lives and increased *in vitro* potency [21]. The

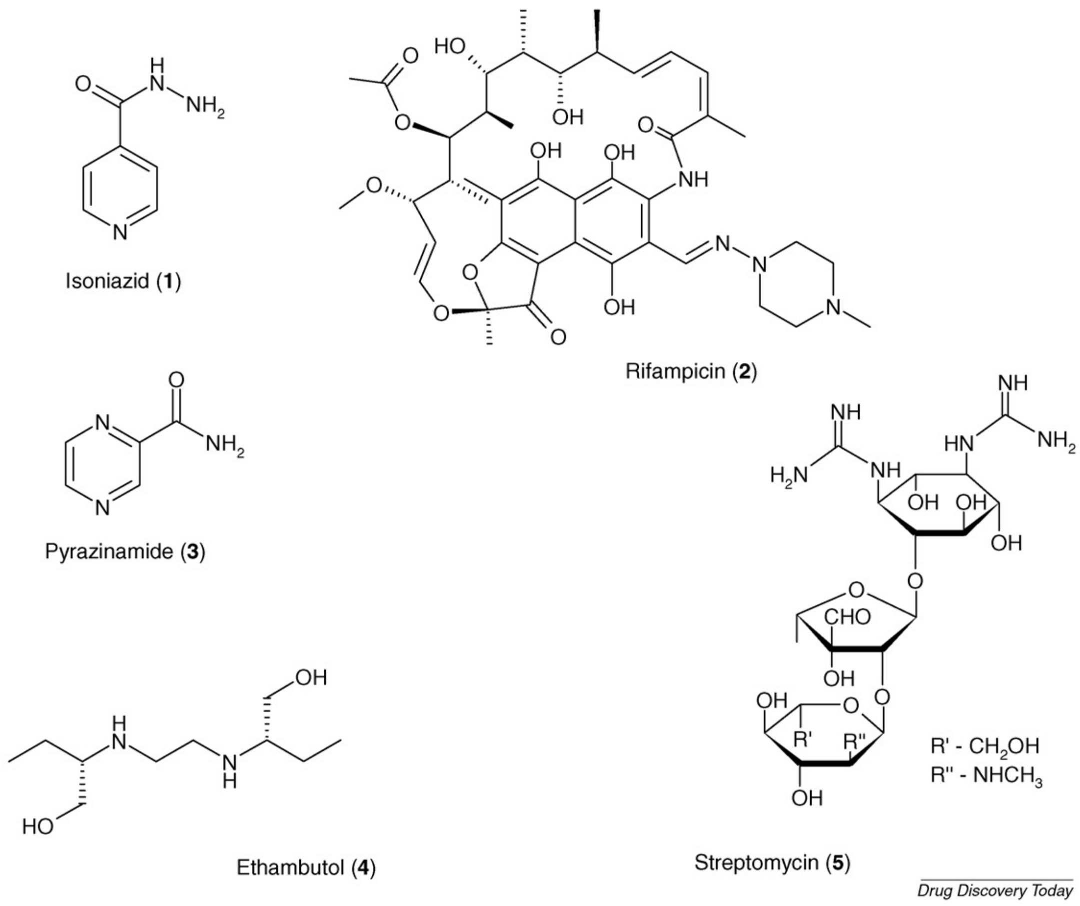

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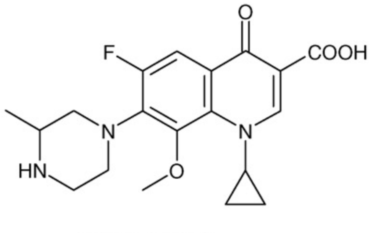
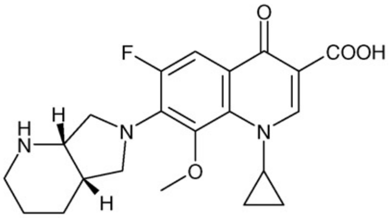
FIGURE 1

Chemical structures of first-line anti-TB drugs.



Gatifloxacin (**6**)



Moxifloxacin (**7**)

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FIGURE 2

Chemical structures of the fluoroquinolones gatifloxacin and moxifloxacin.

main problem with this class of drugs is that their common mechanism of action makes RIF-resistant *M.tb* strains cross-resistant to all rifamycins.

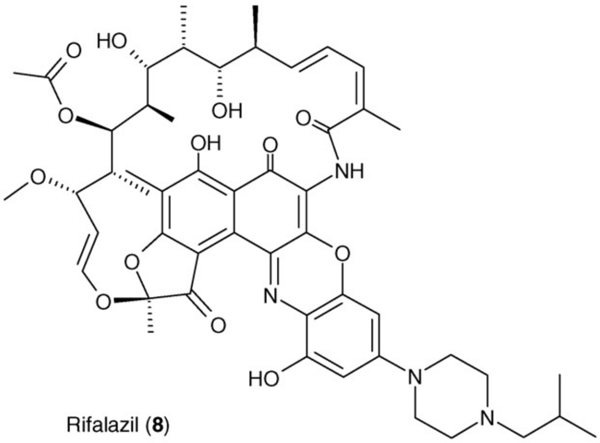
New drug candidates with novel mechanisms of action

We now consider a number of new drug candidates that have novel mechanisms of action and that are in the late stages of development.

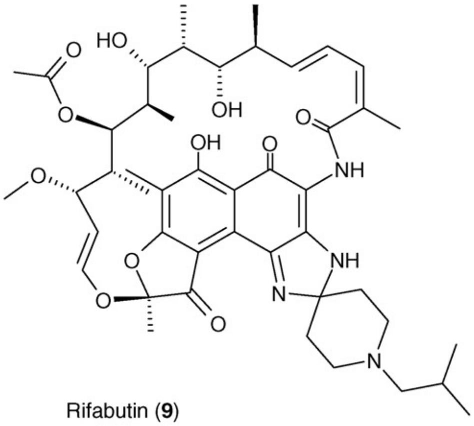
SQ109

The synthesis and screening of diamine analogues of ethambutol (EMB) has yielded a variety of compounds with activity against *M.tb*. equal or better than EMB [22], and compound SQ109, which contains unsaturated isoprenyl units and a bulky adamantyl ring (see Figure 4), was selected after *in vitro* and *in vivo* testing [23].

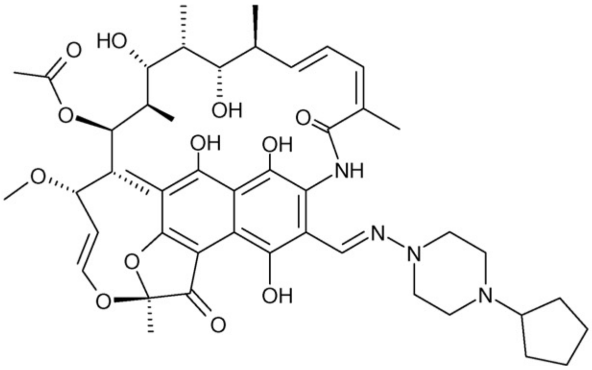
SQ109 exhibits excellent *in vitro* activity against *M.tb*, including strains resistant to EMB, INH and RIF [23]. SQ109 shows limited



Rifalazil (**8**)



Rifabutin (**9**)



Rifapentine (**10**)

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FIGURE 3

Chemical structures of the rifamycins rifalazil, rifabutin and rifapentine.

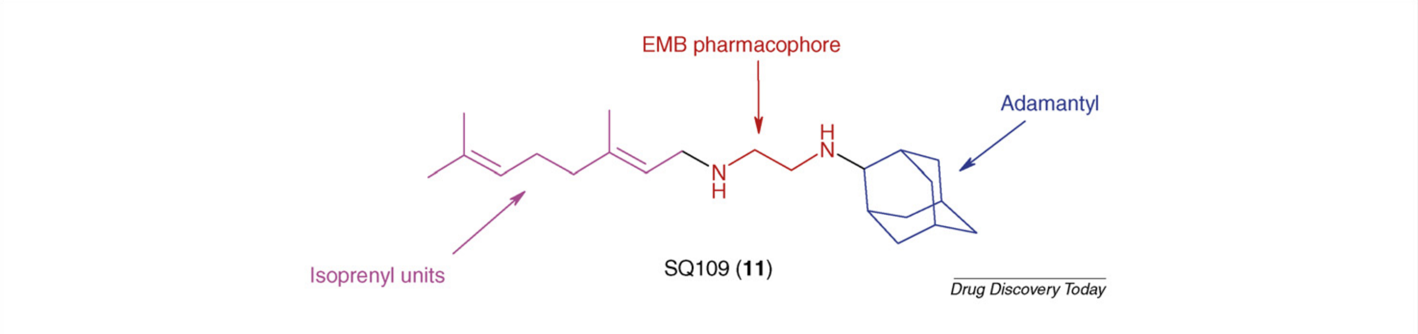

FIGURE 4

Chemical structure of SQ109, highlighting the EMB pharmacophore (red), the isoprenyl (pink) and adamantane (blue) fragments.

bioavailability, but has a large volume of distribution into various tissues, particularly the lungs, probably owing to the presence of the adamantane moiety [24]. SQ109 appears to be rapidly metabolised in the liver, and it is possible that SQ109 is in fact a prodrug [25].

The exact mechanism of action of SQ109 is not known, although it is believed to target cell wall synthesis in a different manner to EMB as SQ109 is active against EMB-resistant strains, suggesting the existence of a different specific target or activation pathway [23]. SQ109 and EMB are also different in the genes and proteins that are up or downregulated in *M.tb,* such as those implicated in fatty acid modification [26,27].

The combined administration of SQ109 and RIF or INH exhibits synergistic *in vitro* activity, with no antagonistic interactions when combined with other first-line therapies [28]. A particularly potent combination is SQ109/RIF with an inhibition of *M.tb.* growth greater than 99% at very low concentrations, and that is also effective against RIF-resistant strains [28]. It has been suggested that this synergy arises from the activation of SQ109 by RIF-induced *M.tb* cytochrome P_{450} (CYP), producing active oxidised metabolites [28]. It would be interesting to find out if this synergy is preserved with the RIF-analogue rifabutin, which activates CYP at lower levels. Experiments with mice have also shown *in vivo* synergy when SQ109 is used in combination with INH, RIF and PZA [29]. It would appear that SQ109 is a promising new drug that may shorten the duration of anti-TB regimens. The first reports of Phase Ia clinical trials, completed in 2007, describe no serious side effects and fast and extensive distribution to tissues after oral administration with a long half-life, suggesting that once-a-week dosing may be achievable [30].

PA-824

Bicyclic nitroimidazofurans have been found to be active against *M.tb*; however, the lead compound CGI 17341, whose structure is shown in Figure 5, turned out to be mutagenic [31,32]. Related bicyclic nitroimidazo[2,1-b]oxazines have been found to be equally active, but lack any unfavourable mutagenic features [33–35], with the lead compound PA-824 (see Figure 5) having been chosen on the basis of its *in vitro* and *in vivo* activity [33]. Their structure-activity relationships (SAR) are summarised in Figure 6 [36]. PA-824 is currently undergoing Phase II clinical trials [37].

PA-824 exhibits high *in vitro* activity against *M.tb* including drug resistant strains [33,38]. Importantly, it has not shown cross-resistance to other current anti-TB drugs [33] and has shown *in vitro* activity against non-replicating *M.tb* [33,38], becoming a likely candidate to treat latent TB. PA-824 has shown substantial *in vivo* activity against persistent bacilli remaining after the two months intensive phase treatment with RIF, INH and PZA [39]. PA-824 has a long half-life and appears to accumulate in the body [40], although there is not enough evidence regarding the metabolism of PA-824 that may explain these pharmacokinetic properties.

The mechanism of action of PA-824 is two-fold, as it inhibits *M.tb* cell wall lipid and protein synthesis [33]; however, since this drug is also active against non-replicating bacteria it appears that inhibition of cell wall biosynthesis cannot be its sole mode of action. PA-824 is, in fact, a prodrug that is metabolised by *M.tb* before it can exert its effect [33] and that may probably involve the bioreduction of its aromatic nitro group to a reactive nitro radical anion intermediate [41]. Drug resistance has been shown to be mediated by the loss of a specific glucose-6-phosphate dehydrogenase enzyme or of its deazaflavin cofactor F_{420}, which may provide electrons for the reductive reaction [33,42].

The replacement of INH by PA-824 in standard regimens leads to more effective treatments in mouse models [40]. Nonetheless, substitution of RIF or PZA appears to be detrimental to activity, and high relapse rates have been observed after six months of a RIF, INH and PA-824 regimen that was almost culture negative, suggesting limitations in the sterilising ability of PA-824 [40]. These problems, however, may not be relevant to humans, as PA-824 requires activation, probably nitroreduction [33,43], which would be favoured by the low redox potential environment found in human hypoxic caseous lesions, but not in mice lesions [40]. Interestingly, a combination of moxifloxacin and PA-824 appears to be particularly effective with no relapse [44]. The combination

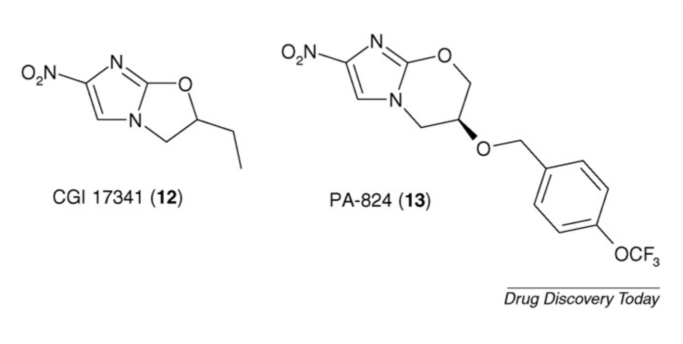

FIGURE 5

Chemical structures of CGI 17341 and PA-824.

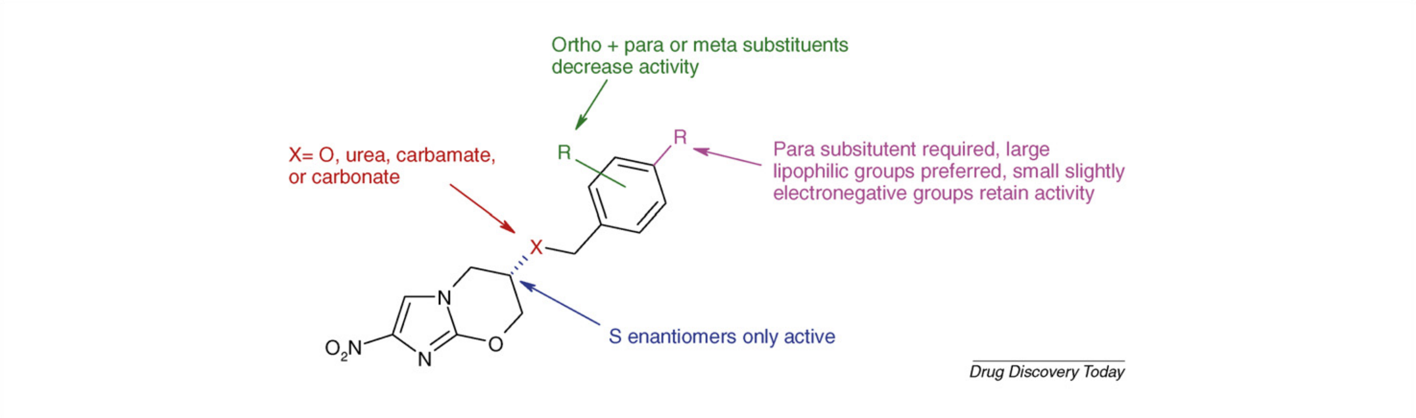

FIGURE 6

In vitro anti-Tb structure activity relationships (SAR) of the nitroimidazo[2,1-b]oxazine series (adapted from reference [36]).

of PA-824 and INH does not exhibit any synergy but is able to prevent the selection of PA-824 and INH-resistant mutants [39].

OPC-67683

The synthesis and testing of a series of 6-nitro-2,3-dihydroimidazo[2,1-b]oxazoles resulted in the discovery of OPC-67683 (see Figure 7). Figure 8 illustrates the SAR of this drug [45].

OPC-67683 exhibits excellent *in vitro* activity against drug-susceptible and resistant *M.tb.* strains and does not show cross-resistance to any current first-line drugs [46], with the evidence that infrequent and low dosing may be effective [46]. The long half-life of OPC-67683, the lack of metabolisation by CYP enzymes and its efficacy in immunocompromised mice suggest that this drug may be useful for the treatment of co-infected TB/HIV patients.

The unique structure of the cell wall of mycobacteria, rich in waxy mycolic acid, is the target of action of OPC-67683, which inhibits methoxy-mycolic and keto-mycolic acid synthesis (like INH) but at significantly lower concentrations [46]. Unlike INH, OPC-67683 does not inhibit α-mycolic acid biosynthesis [46]. It is not known whether OPC-67683 affects protein synthesis (as in the case of PA-824) or if it interacts with other *M.tb* targets. As in the case of PA-824, OPC-67683 is also a prodrug. *M.tb.* metabolises the drug and produces one main metabolite: a desnitro-imidazooxazole [46]. OPC-67683-resistant strains of *M.tb.* do not metabolise the drug to its active form [46].

The combination of OPC-67683 with the first-line drugs RIF, INH, EMB and SM does not show any antagonistic interactions, whilst synergistic interactions occur with RIF or EMB *in vitro* [46]. A combination of OPC-67683 with RIF and PZA for 2 months followed by a combination with RIF for further 2 months virtually eliminates all lung bacterial load within 3 months, totally eliminating it after 4 months in mouse models [46], thus suggesting that OPC-67683 has a powerful sterilising ability and may be effective in shorter treatments. Recently completed phase II clinical trials of OPC-67683 have been successful [47].

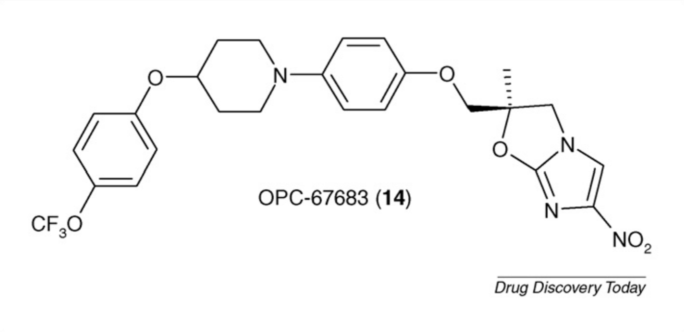

FIGURE 7

Chemical structure of OPC-67683.

TMC207

A series of diarylquinolines (DARQs) has been developed that exhibits potent *in vitro* activity against *M.tb* [48]. Subsequent *in vivo* testing of activity against *M.tb* determined that the most potent of these molecules is TMC207 [49], whose structure is seen in Figure 9 [50]. TMC207 exhibits excellent activity against drug-susceptible, MDR and XDR *M.tb* strains, with no cross-resistance to current first-line drugs [49,51]. It appears that TMC207 has greater potency against mutated drug resistant strains than to fully susceptible isolates, suggesting a unique mechanism of action [49]. Whilst TMC207-resistant *M.tb* strains have appeared, they remain fully susceptible to other anti-TB drugs such as RIF, INH, SM and EMB [49].

The use of TMC207 alone appears to be at least as effective as a combination of RIF, INH and PZA and more effective than RIF alone in mouse models [49]. TMC207 has a potent sterilising ability in guinea pigs, being 100 times more effective than the conventional combination of RIF, INH and PZA [52]. TMC207 has been determined to be well absorbed orally in humans, with a long half-life [49], which explains the effectiveness of single weekly dosing in mice. TMC207 is metabolised by CYP3A4 and, therefore, when it is administered with RIF its levels decrease significantly, making TMC207 likely to be incompatible with anti-retrovirals [53].

TMC207 acts by inhibiting *Mycobacterium* membrane-bound ATP synthase. This unique mechanism of action offers great potential as there is little similarity between the mycobacterial and human proteins encoded by the atpE gene that codes for the c subunit of ATP synthase [49], which has been identified as the specific target of TMC207 [54]. A number of mutations (I66 M and A63P) have been identified in the c subunit of TMC207-resistant strains [49,55] near the glutamate residue E61, which is involved in proton transport and is necessary for the synthesis of ATP [56]. ATP

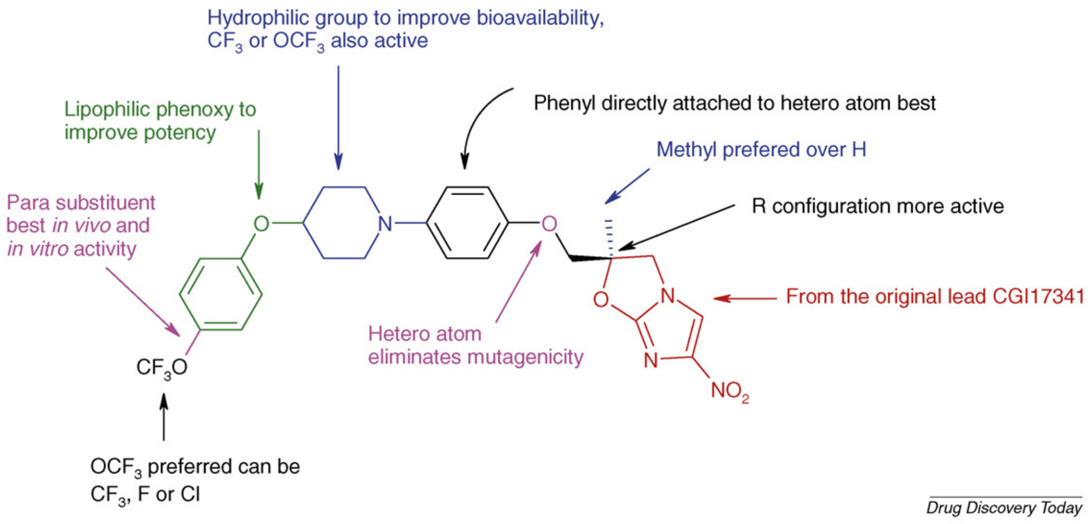

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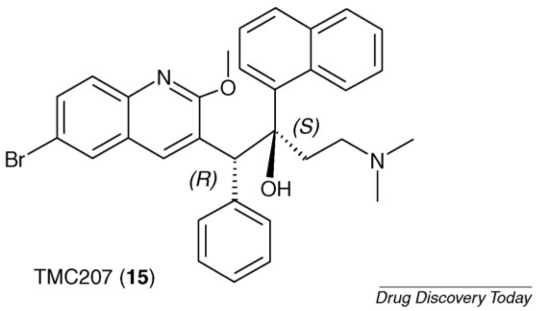
FIGURE 8

Summary of the SAR in the nitroimidazo[2,1-b]oxazole series.

synthase has two structural domains (F0 and F1) that act as a biological rotary motor: F1 is located in the cytoplasm, where it generates ATP and F0 spans the membrane and is arranged as a disc, containing one a-subunit and between 9 and 12 c-subunits. The flow of protons drives the rotation of this disc. Molecular modelling studies of *M.tb* ATP synthase have characterised the binding site of TMC207 and suggested its likely mechanism of action [56]. Normally, the sidechain of Arg-186 in the a-subunit adopts an extended conformation that reaches towards Glu-61 in the c-subunit to transfer a proton. This event leads to a conformational change in the c-subunit, making Arg-186 adopt a compact conformation and initiating a 30° rotation of the c-subunit. It is believed that the molecular mechanism of action of TMC207 is to mimic the side chain of Arg-186 [56]. TMC207 adopts a folded conformation in solution before binding owing to intramolecular hydrogen bonding [50], but this is lost upon entering the binding site, being compensated for by the creation of new hydrogen bonds with Glu-61, as shown in Figure 10. The lack of a cavity large enough to accommodate the bulky dimethyl amino group of TMC207 prevents the necessary rotation required for proton transfer, blocking ATP production. This may explain why changes in amino acids near Glu-61, as observed in the above-mentioned resistant strains, would prevent binding of the drug owing to steric factors.



TMC207 (**15**)

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FIGURE 9

Chemical structure of TMC207.

Combinations of TMC207 with current first-line drugs RIF, INH and PZA result in negative cultures in mouse models after two months [49]. In addition, a synergistic effect is observed for the combination of TMC207 and PZA, taking just two months to completely eradicate lung *M.tb* [49]. This may be due to the fact that PZA indirectly inhibits ATP synthesis [56]. A combination of TMC207 with the currently recommended MDR-TB regimen (amikacin, ethionamide, moxifloxacin and PZA) has been successful in eradicating lung and spleen infection within two months in drug-sensitive mouse model [57]. Phase IIa clinical trails have demonstrated that TMC207 is well tolerated in patients, with an appropriate activity against *M.tb.* although lower than RIF or INH monotherapy [58]. Further studies of long-term safety and efficacy in MDR-TB patients were due to start in mid-2007 [53].

Other drug candidates with potential novel mechanisms of action

There are a number of other drug molecules in clinical or pre-clinical trials, although there is limited information available. One of these compounds is the pyrrole LL-3858 (sudoterb), an INH analogue whose structure is shown in Figure 11. This drug is currently in phase I clinical trials [59,60]. Another interesting compound is OPC-37306, an active molecule that was discovered in screening studies of the inhibition of mycolic acid biosynthesis [61] and whose structure is shown in Figure 11. OPC-37306 is active against drug susceptible and resistant *M.tb* strains, and appears to be more potent than RIF in mouse models [61]. Compound FAS20013 is another drug molecule that will shortly enter clinical trials, with claims that it can eliminate more than 99% of *M.tb* (including latent bacilli) within 24 h, with no resistant strains observed so far and a good pharmacokinetic profile [62]. Other promising compounds are SQ-609 (which interferes with cell wall synthesis but whose precise target has not been identified [30]) and SQ641 (inhibitor of translocase I, an enzyme required for

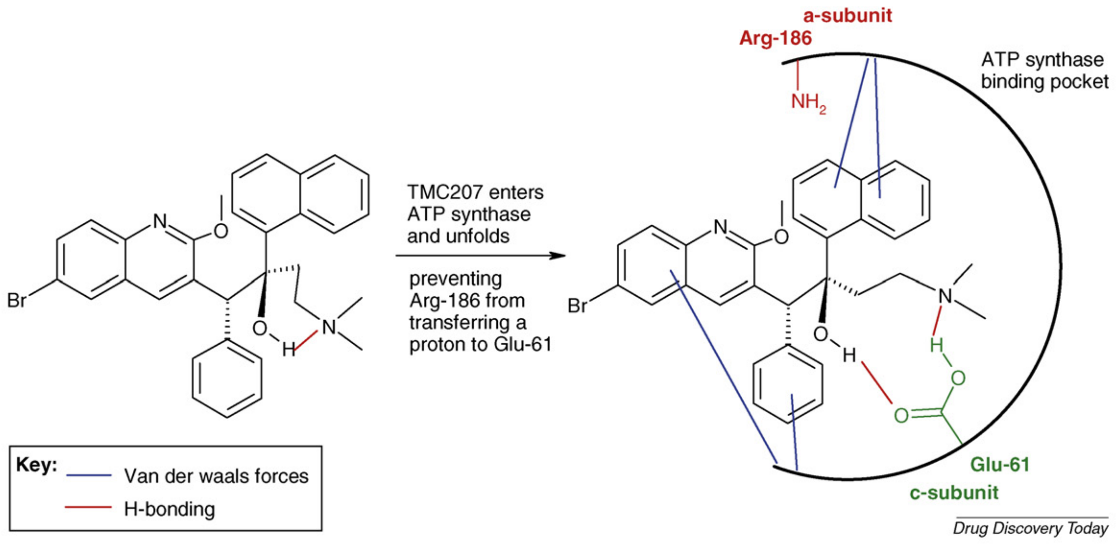

FIGURE 10

Diagram showing the interactions between TMC207 and the binding site of *M.tb* ATP synthase.

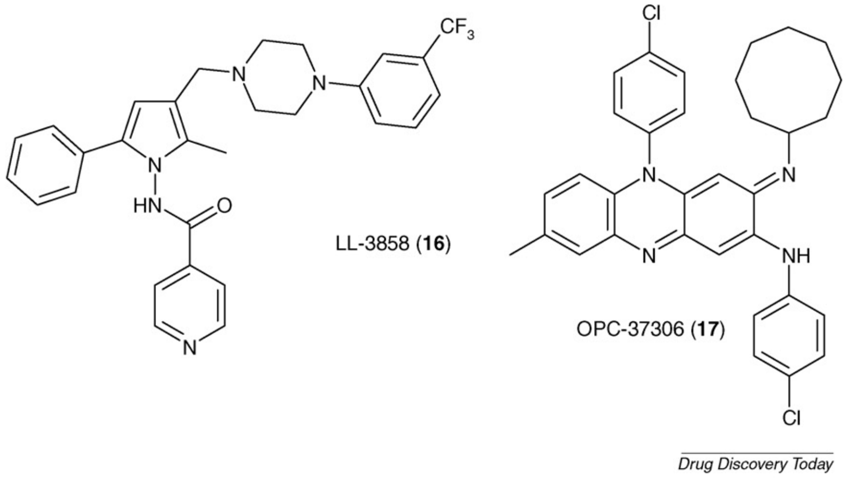

FIGURE 11

Chemical structures of other new anti-TB drug candidates: sudoterb (LL-3858) and OPC-37306.

cell wall peptidoglycan synthesis [63]), which are still in the preclinical stage [63].

Conclusions

A number of new anti-TB drugs have been developed in recent years, which have novel mechanisms of action, do not suffer from cross-resistance with existing first-line drugs, exhibit excellent activity against *M.tb*. and are likely to reduce the duration of treatment and dosing. OPC-67683 and TMC207 are the most promising of these new drugs since both are highly active against drug-resistant and susceptible strains and demonstrate excellent sterilising power. In addition, OPC-67683 may be effective in HIV/AIDS patients, whilst TMC207 may be effective against XDR-TB owing to its remarkable potent synergy with PZA. These and other developments in anti-TB drug therapy give hope that within the next decade an effective anti-TB regimen of shorter duration may be achieved.

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