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A Systemic Review on Oxazolidinones as Anti-Tubercular Agents and Antibacterial Agent

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Priyanka B. Gorde *, Kalyani Kale, Manish A. Raskar

Department of Pharmaceutical Chemistry, Dr. Vithalrao Vikhe Patil College of Pharmacy Ahmednagar, India.

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ABSTRACT

TB drug development pipeline represents varied structural classes of molecules. Oxazolidinones represent synthetic antibacterial agents with a unique mechanism of action having a wide spectrum of activity, oral bioavailability, and well-established SAR. They act by inhibiting translation at the initiation phase of protein synthesis. Linezolid was the first oxazolidinone to reach the market in the year 2000 for the treatment of methicillin-resistant staphylococcal and vancomycin-resistant enterococcal infections. Oxazolidinones have shown very good anti-mycobacterial activities. Several oxazolidinones are currently in development for their possible use in TB therapy. Oxazolidinones are classified based on C-ring modifications. DuP-721 was the first oxazolidinone having good anti-TB activity. Linezolid, sutezolid and AZD5489 are in clinical devel- opment. Several other C-ring modifications have shown promising results. The usefulness of these oxazolidinones in drug-resistant TB is already established. Toxicity, especially myelosuppression, has been an im-important limiting factor for their development.

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*) [1], accounts for the death of 1.5 million people; 360, 000 of whom were Human Immunodeficiency Virus (HIV) positive and 9.0 million new cases in 2013 [2]. Latent TB infection in the *Mtb* infected (LTBI) people increases the possibility of reactivation of this deadly disease [3,4]. The current year 2015 marks the 132nd anniversary of Robert Koch's discovery of the tubercle bacillus *Mtb* [5]. Most of the first-line drugs were discovered in the 1950s and 1960s. For nearly a half-century, TB patients lacked new drugs to be available for treatment until Bedaquiline was launched at the end of 2012, which was approved to treat multidrug-resistant tuberculosis (MDR-TB, resistant strains to isoniazid (INH) and rifampicin, RIF) [6]. The development of drug resistance, rise of multi- and extensively-drug resistant TB (MDR-TB and XDR-TB: more insusceptible to any fluoroquinolone and one of three injectable drugs) strains, and the long duration required for the treatment of TB, make it imperative to develop novel leads against TB. The devastating effect of HIV co-infection has led to an urgent need for the development of new, fast-acting, and more efficient anti-mycobacterial drugs. An ideal drug candidate is required to act on a novel target and also be effective against the resistant *Mtb* strains [7].

Current anti-TB drugs target bacterial cell wall synthesis, protein synthesis, and fatty acid synthesis [8]. The therapeutic regimen for the treatment of TB involves first-line drugs such as isoniazid (INH), rifampicin (R), pyrazinamide (Z), ethambutol (E), streptomycin (S), and rifabutin (Rfb), second-line drugs such as kanamycin (Km), amikacin (Amk), capreomycin (Cm), viomycin (Vim), ciprofloxacin (Cfx), levofloxacin (Lfx), ofloxacin (Ofx), *para*-aminosalicylic acid (Pas), D-cycloserine (Dcs), teridizone (Trd), ethionamide (Eto), prothionamide (Pto) and thioacetazone (Thz), and third-line drugs such as clofazimine (Cfz), amoxicillin plus clavulanate (Amx/Clv), linezolid (Lzd) in combination regimens to treat MDR-TB or XDR-TB [2,9,10]. Directly observed treatment short-course strategy (DOTS) provides a cure rate of > 95% for the treatment of drug-sensitive TB with initial treatment for two months with four drugs (INH, R, Z, and E) and subsequent four months treatment with two drugs (INH and R). Drug-resistant TB requires the use of second-line toxic drugs for a longer duration (18-24 months or more) of time. The coinfection of TB with HIV further complexes the problem leading to morbidity and mortality [11]. The currently employed drugs have many

potential side effects viz. Z causes hepato- toxicity and gout because of a decrease in uric acid secretion in urine, INH causes peripheral neuropathy in fast acetylators and hepatotoxicity in slow acetylators, RIF causes orange discoloration of body fluids such as lymph, saliva, lacrimal fluid, sputum, sweat, and urine because of dye characteristics and E causes optical neuritis or retrobulbolar neuritis, aminoglycosides causes ototoxicity and nephrotoxicity [8]. In total, none of the anti-TB drugs is devoid of hazardous side effects. This, in deed, enhances the need for the development of novel chemical entities and novel anti-tubercular agents.

Apart from these, several classes of molecules are in different stages of development (Table **1**) providing some promise [10]. This review highlights the progress made by oxazolidinones a new structural class of anti- biotic. First oxazolidinone linezolid was approved in the year 2000 for the treatment of methicillin-resistant staphylococcal and vancomycin-resistant enterococcal infections [12]. Since then there is spurred interest in research in this area [13,14]. Considering their promising activity against *M. tuberculosis* the search for molecules as potential anti-TB agents is pursued. This review highlights the developments in oxazolidinones as anti-TB agents, the only review highlighting these developments appeared in 2006 [15].

ANTI-TB DRUG PIPELINE

New chemotherapeutics active against multidrug-resistant *M. tuberculosis* are urgently needed. Despite the urgent need for new anti-tubercular drugs, few are on the horizon. To combat the problem of emerging drug resistance, structurally unique chemical entities that inhibit new or novel targets will be required. The Novel Chemical Entities (NCEs) which have distinguished potential to be drug candidates for the treatment of TB are represented in (Table **1**) with their chemical class, mode of action, *in vitro* activity, and current clinical status. These NCEs are represented in (Fig. **1**) with their trivial names.

TB Alliance with the help of the University of Auckland and University of Illinois-Chicago has developed nitroimidazoles such as PA-824 (**1**) and delamanid(OPC67683) (**2**) a new drug class for drug-sensitive and drug-resistant *Mtb* [16]. TBA-354 (**3**) is a next-generation nitroimidazole for TB treatment with demonstrated advantages over the first-generation compounds and entered clinical testing in 2015 [17]. Currently, in phase III clinical trial treatment of drug-sensitive TB in four months, a possible replacement of

E/INH by fluoroquinolone moxifloxacin (**4**) and E by fluoroquinolone gatifloxacin (**5**) is being established [18]. Bedaquiline (**7**) is a diarylquinoline class anti-TB drug approved by the US FDA for the treatment of MDR-TB [19]. It has been recognized as the first anti-TB drug to interfere with bacterial energy metabolism [20]. SQ109 (**8**) a 1,2-ethylenediamine derived from E through combinatorial synthesis is under clinical development [21]. A phase IIa clinical trial for LL3858 (**10**) a pyrrole derivative developed by Lupin Limited has shown the potential for the treatment of tuberculosis [22]. Linezolid or PNU-100766 (**11**), sutezolid or PNU-100480 (**12**), and AZD5847 (**13**) are the only oxazolidinones which have reached phase II of the clinical trial. AZD5847, a next-generation oxazolidinone, is having bactericidal action and has completed Phase I clinical trials [23]. Rifapentine has entered in a clinical trial, in 2008 with a view of the evaluation of antimicrobial activity and safety in which several doses of rifapentine are substituted for rifampin [17]. BDM31343 (**15**) has been evolved as an emerging drug candidate among 1,2,4-oxadiazoles and is currently under preclinical trial [24]. BTZ043 (**16**) has shown excellent whole cell-based activity (1 ng/mL) among nitrophenyl derivatives with a completely novel mechanism of action [25]. Various diversified NCEs too have the potential to become anti-mycobacterial drugs such as PBTZ169 (**18**), TBI-166 (**19**), CPZEN-45 (**20**), SQ641 (**21**), Q203 (**22**), and **23** are under preclinical trial. Other NCEs such as 377790 (**24**), C215 (**25**), A039 (**26**), and AU1235 (**27**) have been identified as active anti-tubercular hits, and their respective biological targets are also well elaborated [26,27].

Table No. 1: Different chemical classes of NCEs for TB in clinical pipeline.

Entry	Chemical Class	Drug Candidate	Mode of action	*In vitro* Activity (MIC)	Clinical Status [17]	Refs.
1	Nitroimidazole	PA-824 (**1**)	Bactericidal action by intracellular NO release[28]	0.015-0.25 μg/mL	III	[29]
		TBA-354 (**3**)	Same as that of PA 824	0.004 μM	I	[30]
		Delamanid (OPC67683) (**2**)	Inhibits mycolic acid synthesis	0.006-0.024 μg/mL	III	[31]

Table 1) contd….

Entry	Chemical Class	Drug Candidate	Mode of action	*In vitro* Activity (MIC)	Clinical Status [17]	Refs.
2	Fluoroquinolone	Moxifloxacin (**4**)	Inhibits *Mtb* DNA topoisomerase II[32]	0.12-0.5 μg/mL	III	[33]
		Gatifloxacin (**5**)	Inhibits *Mtb* DNA topoisomerase II[32]	0.007-0.12 μg/mL	III	[34]
		DC-159a (**6**)	Inhibits *Mtb* DNA topoisomerase II	0.12 mg/L	Preclinical	[35]
3	Diarylquinoline	Bedaquiline (**7**) (TMC207 or R207910) (**7**)	Target subunit c of *Mtb* ATP synthase	0.004-0.07 μg/mL	Approved (Nov. 2012)[6]	[20]
4	Diamine	SQ109 (**8**)	Cell wall synthesis inhibitor (targets MmpL3)[36]	0.7-1.56 μM	II	[21]
		SQ609 (**9**)	Cell wall synthesis inhibitor	4 μg/mL	Preclinical	[37]
5	Pyrrole	LL3858 (**10**)	Not yet known	0.25 μg/mL	IIa	[38]
6	Oxazolidinones	Linezolid (PNU-100766) (**11**)	Protein synthesis inhibitor[39]	0.50 μg/mL	II	[40]
		Sutezolid (PNU- 100480) (**12**)	Protein synthesis inhibitor	0.5- 4 μg/mL	IIa	[41]
		AZD5847 (**13**)	Protein synthesis inhibitor	0.13-1 μg/mL	IIa	[42]
7	Rifamycin	Rifapentine (**14**)	Inhibition of bacterial RNA synthesis via inhibiting DNA-dependent RNA polymerase[8]	$\leq$ 0.25 mg/L	II	[43]
8	1,2,4-Oxadiazole	BDM31343 (**15**)	EthR inhibitor	-	Preclinical	[24]
		BTZ043 (**16**)		1 ng/mL	Preclinical	[25]

9	Nitrophenyl derivatives	DNB1 (**17**) PBTZ169 (**18**)	DprE1 inhibitor	0.072 μg/mL ≤0.19 ng/mL		[25] [44]
10	Riminophenazines	TBI-166 (**19**)	-	0.016 μg/mL	Preclinical	[45]
11	Caprazene Nucleoside	CPZEN-45 (**20**)	GlcNAc-1-phosphate transferase WecA	0.2-1.56 μg/mL	Preclinical	[46]
12	Capuramycin	SQ641 (**21**)	Inhibition of translocase I[47]	1 μg/mL	Preclinical	[48]
13	Imidazopyridine	Q203 (**22**)	Inhibition of cytochrome bc_1 subunit (qcrB)	2.7 nM	Preclinical	[49]
14	Nitrofuran isoxa- zolines	**23**	-	6 μg/mL	Preclinical	[50]
15	Nitro-triazole	377790 (**24**)	DprE1 inhibitor	IC_{50}: 0.5 μM	-	[26]
16	Benzimidazole	C215 (**25**)	MmpL3 Inhibitor	IC_{90}: 16 μM	-	[26]
17	Substituted Imidazole	A039 (**26**)	Glycerol dependent *Mtb* growth inhibitor	IC_{90}: 1.5 μM	-	[26]
18	Adamantyl urea derivative	AU1235 (**27**)	MmpL3 Inhibitor[47]	0.03 μM	-	[27]

Mrrow toxicity in these molecules, which led to the termination of this project. However, scientists at the Upjohn Company (now Pharmacia) continued to work on this class of molecules to find an antibiotic active against Gram-positive pathogens with better activity and safety profiles [55].

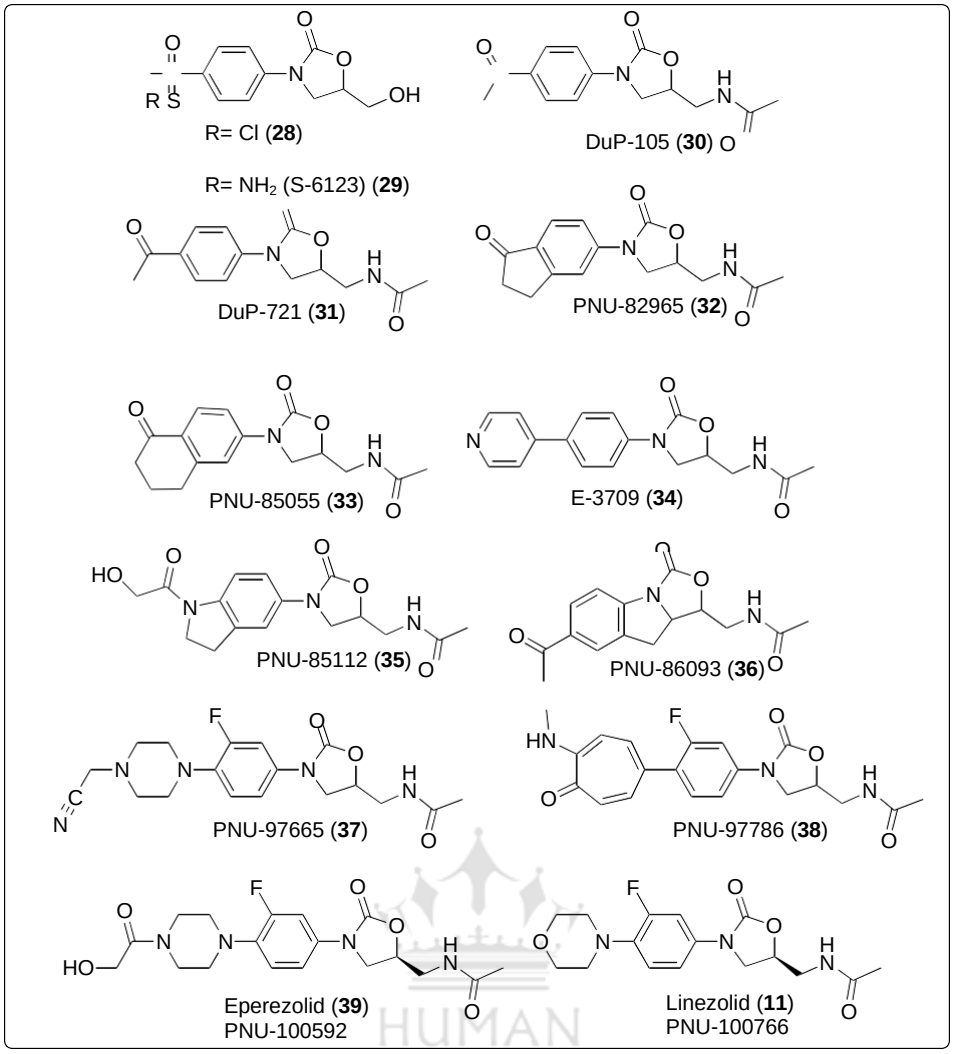


Figure No. (2): Development of oxazolidinones.

DuP 721 was used as one of the leads for these studies. The annulations of the acetyl moiety of DuP 721 resulted in PNU- 82965 (**32**) and PNU-85055 (**33**). PNU-82965 was found to have a better safety profile than DuP 721. This study helped in further progress in this area using PNU-82965 as a new lead having better safety profile to give PNU-85112 (**35**) and PNU-86093 (**36**). PNU-85112 exhibited excellent safety profile as well as activity comparable to DuP 721.

Another development in this area took place wherein the scientists at Pharmacia modified the DuPont lead molecule E-3709 (**34**) to PNU-97665 (**37**) [56]. PNU-97665 (piperzinylphenyloxazolidenones), PNU-85112 (indolinyloxazolidinones) and PNU-97786.

(**38**) (troponylphenyloxazolidinones) now represented the three classes of compounds

having the potential for further development. However, the better solubility, pharmacokinetics and easy synthesis of piperzinyl- phenyloxazolidenones over the other two classes of molecules led to their selection for further development. Two molecules PNU-100592 (eperezolid **39**) and PNU-100766 (linezolid **11**) were developed by Upjohn and were tested in Phase I clinical trials of which linezolid proceeded further in the development and finally introduced in the market in the year 2000, with the brand name Zyvox [12].

Mechanism of Action

Oxazolidinones are synthetic antibiotics with a unique mechanism of action acting on the 50S ribosomal subunit of bacteria inhibiting the protein synthesis with no cross resistance with the existing class of antibacterial agents [57,58]. The bacterial protein synthesis involves the four main steps the initiation, elongation, termination and recycling [59]. In the Initiation process constituent small (30S) and large (50S) ribosomal subunits combine to form a 70S ribosome and the mRNA start codon is accurately positioned with the initiator tRNA at the ribosomal P-site for the peptide bond formation. During the elongation phase, an elongation factor Tu (EF-Tu) delivers the aminoacylated tRNA (aa-tRNA) to the A-site of the ribosome in complex with GTP. Following this peptide-bond formation occurs between the amino acids attached to the A- and P-sites tRNAs, leading to the transfer of the amino acid from the P-site tRNA to the aa-tRNA in the A-site. Translocation phase involves the movement of tRNAs from the A- and P-sites to the P- and E-sites this is aided by EF-G. The elongated peptide exits through the exit tunnel in 50S subunit to the cytoplasm. Stop codon finally terminates the elongation cycle liberating the polypeptide chain from the ribosome. The components are then recycled for the next round of translation initiation.

Linezolid (oxazolidinone) binds at the A site of *50S peptidyl-transferase* centre (PTC) where it takes the space typically occupied by the aminoacyl residue of the A-site bound aminoacyl-tRNA. This binding inhibits the peptide-bond formation between the A- and P-site tRNAs. Further oxazolidinones are also thought to influence P-site tRNA positioning during initiation step [39,60-62].

To reveal the possible mechanism of action of linezolid against *M. tuberculosis*, recently a group of scientist has performed commercial oligonucleotide microarrays to analyse

the genome-wide transcriptional changes. They found that a number of important genes were significantly regulated that are involved in various pathways, such as protein synthesis, sulfite metabolism, and genes involved in the cell envelope and virulence [63] Important Attributes of Oxazolidinone as Anti- Bacterial Agents: [64,65].

Antibiotics with unique mechanism of action with no cross resistance with the existing class of antibacterial agents [57,58].

Good activity against Mycobacteria and Gram-positive bacteria.

Excellent oral and parenteral bioavailability making them ideal candidates for pharmaceutical development.

Activity in *in vivo* animal models when administered by oral or parenteral route.

Well established SAR for this totally synthetic class of compounds. A more classified[55] pharmacophoric features are presented in Fig. (**3**).

Availability of crystal structure with the known inhibitor (linezolid) important for structure aided drug design [39].

CHEMICAL CLASSES OF ANTI-TB OXA- ZOLIDINONES

Phenyl Oxazolidinones

DuP 721

DuP 721 and DuP 105 were the early representation of the oxazolidinone class developed at DuPont that showed wide anti-bacterial activity [66,67]. In the year 1991, Ashtekar *et al.* for the first time decided to test DuP 721, an orally active oxazolidinone, against *M. tuberculosis* strains ($H_{37}Rv$) susceptible and resistant to conventional drugs. These strains were inhibited when DuP 721 was used in the concentration range of 1.25-4.

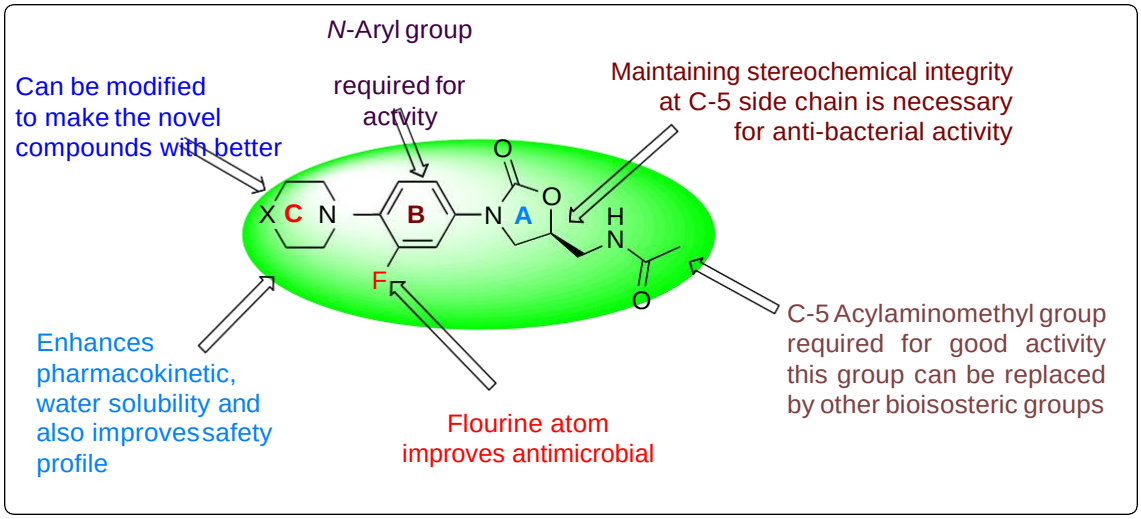


Figure No. (3): Important attributes of oxazolidinone as anti-bacterial agents [55].

μg/mL using *in vitro* assay. The activity was also confirmed in the *in vivo* mice model [68]. Moreover, the population of the drug resistant organism in the study was < 1 in 10^{10} fulfilling one of the objectives of TB treatment drug regimen. This study for the first time highlighted the activity of this class of compounds against *M. tuberculosis* and realised hope for the dis- covery of molecules which will be active against the drug resistant strains. However, this study did not high- light the effect on exact killing of intracellular and ex- tracellular organisms. This marked the actual beginning of the study of anti-TB potential for this class of molecules. DuP 721 was found to be less active than INH or RIF in the murine model [12]. The discovery of lethal bone marrow toxicity in drug safety studies performed at DuPont in rat models led to the termination of further development of DuP 721.

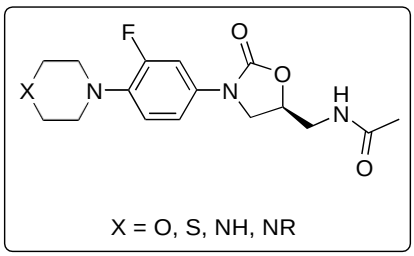


Figure No. 4: Piperazylphenyl/Morpholinylphenyl/Thiomorpholy- nylphenyl oxazolidinones

_N_-Piperazinylphenyl/ Morpholinylphenyl/ Thio- morpholynylphenyl Oxazolidinones

Linezolid and Eperezolid

Eperezolid **39** and Linezolid **11** are the early examples of the oxazolidinones to reach the clinical testing. Scientists at Pharmacia & Upjohn, Inc. tested linezolid and eperezolid against various clinical isolates of bacteria *in vitro*. Both have shown an activity against a wide range of bacteria including *M. tuberculosis* and the Gram-positive anaerobes.

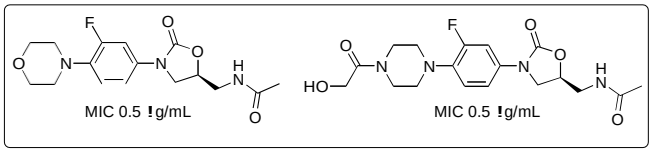


Figure No. 5: Early oxazolidinones to reach clinical testing.

With the MIC of 0.50 μg/mL, both were found effective against drug susceptible and resistant strains of mycobacteria [12,69]. Moreover, both have shown no cross-resistance with conventional anti-TB agents. These were also active against non-tuberculous mycobacteria [65]. In the murine test system, eperezolid was found to be less active than Linezolid against *M. tuberculosis* [12]. Linezolid has 100% oral bioavailability with $t_{1/2}$ of 5.4 h. It has shown severe side effects like bone marrow suppression (myelosuppression), optic and peripheral neuropathy and anemia [70]. Although Linezolid is a very good mycobacterial agent its high cost, high daily dosing requirement and toxicity (myelosuppression) in long term usage limits its usefulness for TB treatment [40]. Considering its high activity against *M. tuberculosis*, as well as with those strains that are resistant to conventional anti-mycobacterial drugs, the potential role of this agent in the treatment of tuberculosis is still under clinical investigation [40].

Fortune *et al.* observed the usefulness of linezolid in treating MDR-TB when used with other drugs in combination. However, the toxicity associated with long term uses persisted. To minimize the toxicity they have suggested 300 mg twice daily dosing than the 600 mg single daily dosing [71]. Park *et al.* found the daily 600 mg dose along with 4 standard combination drugs to be useful in the treatment of intractable or XDR-TB. Although dose reduction reduced the hematological side effects and the total cost of the therapy, its neurotoxic effect persisted [72].

Von der Lippe *et al.* carried out an important drug combination study. In this study, linezolid was found to be very effective when used in combination therapy with other anti-TB drugs for the treatment of MDR-TB. After the introduction of linezolid within 10–37 days, the cultures were negative. The irreversible peripheral neuropathy and bone marrow suppression however led to withdrawal of this treatment in some patients [73].

Schecter *et al*. studied the usefulness of linezolid for MDR-TB and XDR-TB. Considering the toxicity of linezolid they have studied the effect of 600 mg daily dose (the FDA approved 1200 mg daily dose). In addition they have used vitamin B6 supplements to attenuate the bone marrow toxicity of the drug. This study concluded that the use of linezolid under proper monitoring is a promising way to treat drug-resistant TB [74].

A small group of patients having chronic XDR-TB not treatable by any available chemotherapeutic option were treated with the 600 mg per day dosing for four months followed by 600/300 mg daily dosing for 18 months. This study also found the usefulness of the linezolid with the caution of its adverse reactions. How- ever, the necessity to carry out further studies to find out the correct dose of linezolid sufficient for potency with minimum toxicity was advised [70]. Another study showed that linezolid has a potential anti-mycobacterial activity. Using the DNA microarray analysis, it was found that linezolid affected several vital genes involved in diverse pathways in *M. tuberculosis*. More importantly, this study highlighted one of the possible reasons behind the effectiveness of linezolid against *M. tuberculosis* [63].

In one of the meta-analyses, it was further observed that the linezolid was useful in the treatment of complicated DR-TB and XDR-TB while the need to monitor the adverse effects during the treatment was highlighted [75].

In conclusion, linezolid holds the promise in drug-resistant TB therapy and is now recommended off-label as a third-line agent in combination regimens; [10] however, the studies carried out were limited to a small number of patients. Therefore, further studies are warranted in this area.

PNU-100480 (Sutezolid)

Barbachyn *et al.* have synthesized novel oxazolidinones with potent anti-mycobacterial

activity (Fig. **6**) [41]. At Upjohn Co. they have synthesized thiomorpholine derivatives of oxazolidinones such as PNU-100480 **12**, U-101603 **40,** and U-101244 **41**. The *in vitro* activity of PNU-100480 (≤ 0.125 μg/mL) and U-101603(≤ 0.125 μg/mL) was found to be more than that of standard drug isoniazid (0.2 μg/mL) whereas U- 101244 was found to be less active (0.5 μg/mL) against the $H_{37}Rv$. These compounds also exhibited potent *in vitro* activity against multiple isolates of *M. avium* complex (MIC_{90}: 4 μg/mL). Pharmacokinetics and metabolism study of PNU-100480 had shown that it is well absorbed orally but with significant first-pass metabolism to sulfoxide (U-101603) and lesser extent sulfone metabolite (U-101244). Both of these metabolites exhibited potent anti-mycobacterial activity. It was found to be safe and well tolerated when studied in ex- perimental rats. PNU-100480 was tested *in vivo* using *M. tuberculosis* mouse infection model. Wherein it has shown comparable activity (100 mg/kg) as that of isoniazid (25 mg/kg) [41]. This result was duly confirmed by Cynamon *et al.* demonstrating that PNU- 100480 has a better activity than linezolid [12]. Drug- drug interaction of PNU-100480 is low because it did not inhibit CYP3A4 enzyme. Further, Williams *et al.* have performed the anti-TB activity of PNU-100480 relative to that of linezolid and their observations were similar to that of earlier. It is also observed that PNU- 100480 enhances the activity of conventional anti-TB drugs when given in combination with them [76]. Walis *et al.* performed phase I clinical trial study on 19 healthy volunteers [77] and found that all doses of PNU-100480 were safe and well tolerated in humans [77,78]. Some subjects have shown GI and CNS symptoms and one has shown colitis starting from abdominal cramping, diarrhea, elevated leukocyte count followed by heme-positive stool [79]. Pharmacokinetics study of PNU-100480 revealed that 1000 mg dose is well absorbed [77] and the optimized dose is 600 mg twice in a day [79]. The T_{max} for drug in plasma is 1-2 h under fasting conditions [78]. Bactericidal activity of PNU-100480 and linezolid occurred at twice the concentration of MIC in whole blood cell. In human, metabolism of PNU-100480 is less extensive than mice. PNU-100480 has superior bactericidal activity than linezolid in human [77]. Further study revealed that MPS IC_{50} for PNU-100480 (600 mg twice in a day) was similar to that of linezolid (300 mg twice in a day) [78]. Concentration of sulfoxide metabolite in human is four times than that of the parent compound but the metabolite is less active than the parent compound [79,80]. PNU-100480 is 17 fold more potent (80% of activity) for killing intracellular *M. tuberculosis* than its metabolite.

RBx 7644 and RBx 8700 (Ranbaxy compounds)

Rattan and co-workers from the Ranbaxy research laboratories have synthesized compounds with 4- substituted piperazinyl ring (Fig. **7**) [81]. The *in vitro* activity testing identified two most active anti-bacterial compounds RBx-8700 **42** (0.25 µg/mL) and RBx-7644.

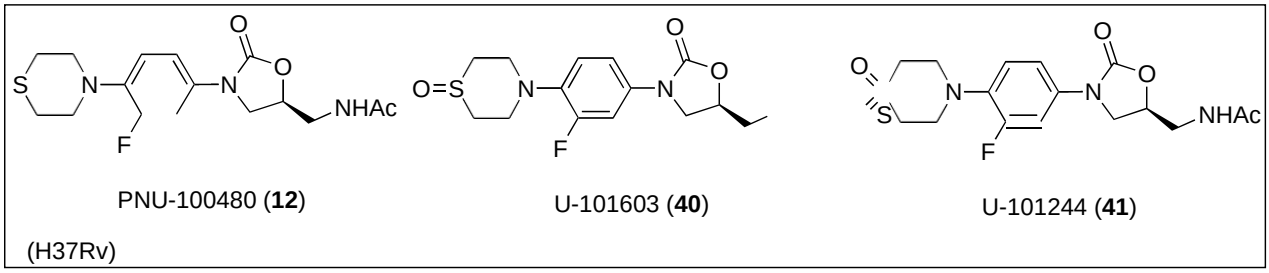


Figure No. 6: Novel oxazolidinones with potent anti-mycobacterial activity.

43 (16 µg/mL). Further, the activity of these compounds was investigated against *M. tuberculosis* infected murine macrophage model [82]. When tested against INH and RIF resistant strains it was found that RBx-8700 is a good compound for further development with MIC_{90} of 1 µg/mL against MDR strains. It was also found to be active against *M. avium* complex with MIC_{90} with 0.5 µg/mL. It showed bactericidal activity at 0.5 µg/mL, comparable with rifampicin at 0.25 µg/mL. Further, it was found to be non-cytotoxic at 100 µg/mL (alamar blue assay) [82]. The study also showed that the RBx-8700 is effective in combination therapy with the standard anti-TB drugs. This study concluded that this molecule has an excellent intracellular activity, which is very important for TB therapy.

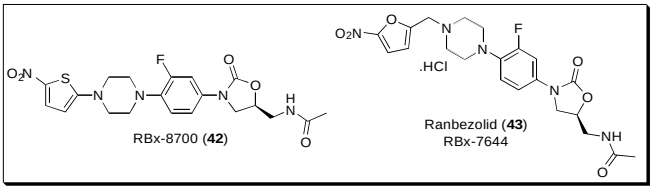


Figure No. 7: Compounds with 4-substituted piperazinyl ring synthesized by Ranbaxy research laboratories.

Further, RBx-8700 was found to have the MIC of 1 µg/mL in the *in vitro* assay against *M. tuberculosis* iso- lates resistant to both INH and RIF and MIC of 0.5 µg/mL against *M. tuberculosis* isolates resistant to either INH or RIF [83]. Since the last report on this

molecule in year 2006, no reports on its progress are available in literature.

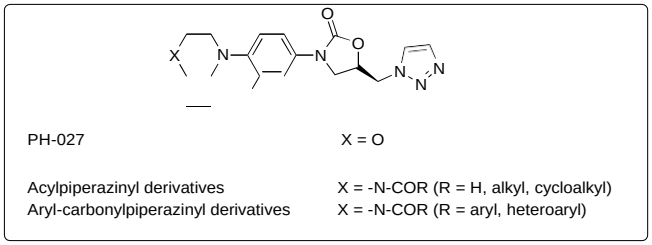


Figure no 8. 5-substituted oxazolidinones demonstrated by O. A. Phillips *et al.* [84-87].

5-Triazolylmethyl N-Piperazinylphenyloxa- zolidinones

Synthesis and antibacterial activity of 5-substituted oxazolidinones have been demonstrated by O. A. Phil- lips *et al.* (Fig. **8**). The compounds have shown anti-TB activity with the IC_{90} of <0.2–100 μg/mL against the $H_{37}Rv$. 4*N*-acylpiperazinyl derivatives showed IC_{90} ranging from >0.2–0.422 μg/mL, 4*N*-aryl- carbonylpiperazinyl derivatives showed IC_{90} ranging from <0.2–2.103 μg/mL and 4*N*-arylsulfonyl derivatives, which are the least active and showed IC_{90} ranging from 5.469–100 μg/mL. Methanesulfonylpiperaz- inyl derivative **44a** was found to be the most active with IC_{90} of <0.2 μg/mL.

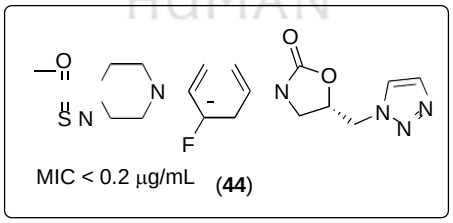


Figure No. 9: Methanesulfonylpiperazinyl/morpholinyl derivative 44.

On the basis of the selectivity index (≥10), compounds are selected for *in vivo* testing. Preliminarily, they have measured bioavailability of the selected compounds and further shortlisted few compounds for *in vivo* efficacy in reducing bacterial load (log_{10} CFU reduction) in lungs and spleen of mice. PH-027 (**44b**) with morpholino ring emerged as the best compound from these series but it is not as active (1.1 μg/mL) as linezolid (0.37 μg/mL) or isoniazid (0.014 μg/mL). The low bioavailability may be the reason for poor *in vivo* activity [88].

Arylsulfonamido Conjugated Oxazolidinones

Kamal *et al.* [89,90] have synthesized new arylsul- fonamido conjugated oxazolidinones **45** and conjugated benzothiadiazines **47** by modifying the C-5 side chain. Similarly, conjugated benzothiadiazines **46** are synthesized by modifying 4-position of *N*-phenylpiperazine ring of oxazolidinones (Fig. **10**). These oxazolidinones were evaluated for *in vitro* anti- TB activity. Three compounds **48**, **49** and **50** (Fig. **11**) were found active at MIC of 1 μg/mL better than the linezolid (2 μg/mL). Compounds **49** and **50** were found to be non-cytotoxic when tested for cytotoxicity assay using HFF cells (IC_{50} >100 μM) [89].

The same group has further synthesized diarylpyr- roleoxazolidinone conjugates at 4-piperazinyl position with C5 acetamide **51** or triazole conjugates **52** (Fig. **12**). The MIC for these compounds in the *in vitro* assay ranged from 2 to > 6.25 μg/mL. The most active compound **53** showed MIC of 2 μg/mL against the susceptible H_{37}Rv *Mtb* strain and MIC of 4 and 8 μg/mL against rifampicin resistant and XDR strains respectively. However, it was found to be less active than linezolid. These compounds were found to be non-cytotoxic. They have also performed docking study for these compounds in 50S ribosome unit to gain insight into the binding and mechanism of action of these com-

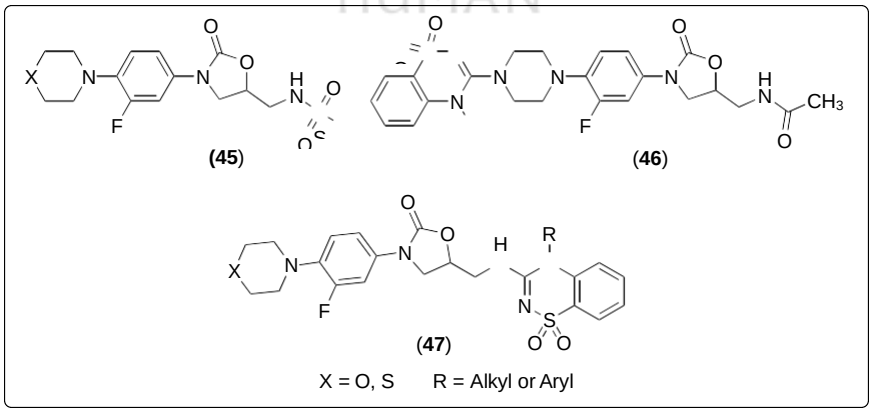


Figure No. 10: Novel arylsulfonamido conjugated oxazolidinones.

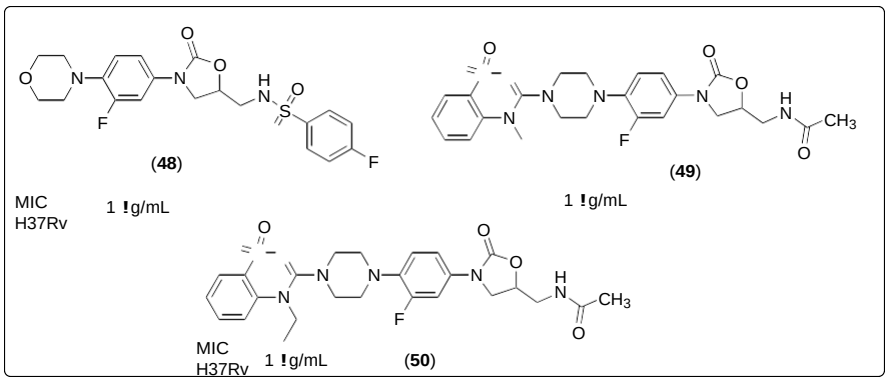


Figure No. 11: Active arylsulfonamido conjugated oxazolidinones.

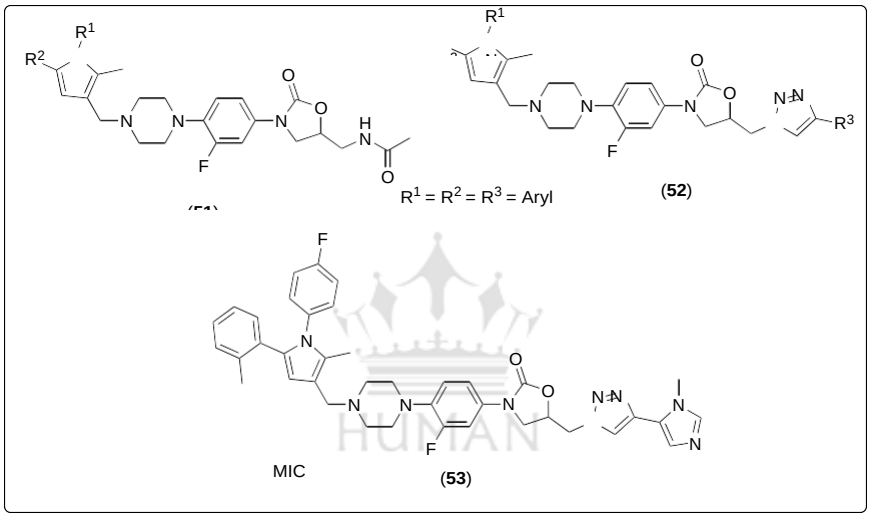


Figure No. 12: Diarylpyrroleoxazolidinone conjugates at 4-piperazinyl position with C5 acetamide 7 or triazole conjugate compounds [90,91]. No further development in this series has been noticed.

Sy142 and Sy144

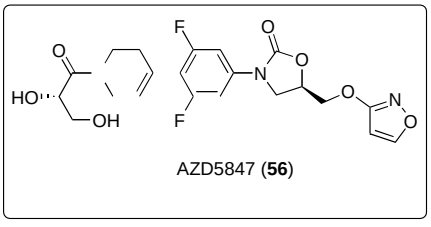
Gong *et al.* synthesized a series piperazinyl phenyl oxazolidinones by varying the substitutions on piperaz- inyl nitrogen that were found to have as potent antibacterial activity [92]. These compounds have shown good *in vitro* and intracellular anti-TB activity [93]. Compounds Sy142 (**54**) and Sy144 (**55**) were the most active with the MIC value of 0.5 μg/mL equal to as that of linezolid (Fig. **13**). Several other less active molecules were also identified than these two compounds. The structure-activity relationship (SAR) studies found that the bulky or polar substitutions on the morpholinyl

nitrogen can cause the decrease in activity giving the guideline for further modifications in this type of compounds yridinyl Phenyl Oxazolidinones.

A group of researchers [97] has synthesized a new oxazolidinone nucleus having pyridine-heterocycle. Vera-Cabrera *et al*. have tested these compounds for anti-tubercular activity. The most active compound A-7867 **59** showed MIC_{90} of 0.125 μg/mL (Fig. **15**).

3. Tetrahydropyridinylphenyl Oxazolidinone

Astra Zeneca has developed a new oxazolidinones with improved activity (Fig. **14**) [94]. AZD2563, initially developed for treating Gram-positive infection, was renamed as AZD5847 **56** for its anti-TB activity exploration. It has better safety and efficacy profile than linezolid [42]. *In vitro* bactericidal activity against both extracellular and intracellular *M. tuberculosis* was found to be better than that of linezolid. Moreover, it was found to be suitable combination agent with the conventional anti-TB drugs as its efficacy is additive when used in combination with them supporting its clinical utility. It has MIC of 1.0 μg/mL against various strains of Mycobacteria including drug sensitive and resistant strains [42]. In the chronic TB mouse model it's *in vivo* efficacy was superior to that of linezolid but inferior to that of sutezolid [42]. AZD5847 has completed phase I study in 2011 and it is in phase IIa clinical trial [95,96]. However, it has also some serious side effects like vision loss, anaemia and painful damage to the peripheral nervous system [70]. It was well tolerated in short term study with no serious side effects like GI events and reduction in WBC and RBC count. In a recent study however it was observed that AZD5847 or its prodrug has no activity or low modest activity in the *in vivo* SS18b model while the other clinical oxazolidi- nones such as linezolid and sutezolid are active. Further Sutezolid was found to be the most active in this study and highlighted its promise in the combination study. However, this study gave the setback for the development of AZD5847 [96].



AZD5847 (**56**)

Figure No. 14: Tetrahydropyridinylphenyl oxazolidinone.[98]. This compound was found more active (MIC 0.0312-0.5 μg/mL) than the linezolid (MIC 0.25-4 μg/mL) in the *in vitro* assay against the various clinical isolates of *Mtb*. In another study [99] tedizolid (DA- 7157) **58** was tested *in vitro* assay against the ninety-five clinical isolates of *Mtb* which included the resistant strains and this molecule has inhibited all of them (MIC ≤ 0.5 μg/mL). It was found to be more active than linezolid and less active that DA-7867. Tedizolid phosphate (DA-7218), prodrug of tedizolid, also showed similar MIC as of tedizolid [99]. This research group also tested tedizolid and DA-7867 against rapidly and slowly growing twenty-nine reference species of Mycobacteria. MIC for both compounds ranged from 1 to 8 μg/mL which was much better than that of linezolid (4-32 μg/mL) [100].

Bae *et al.* has studied the pharmacokinetics of tedizolid and its phosphate prodrug in rats both by oral and IV route. This study has shown that both compounds exhibit dose-proportional pharmacokinetics by both routes [101]. However, none of the studies has been carried out to check the *in vivo* efficacy of these three compounds. Tedizolid was approved, in 2014 by the USFDA to treat bacterial skin infections [102].

Spiropiperazinyloxazolidinones

Miller *et al*. have synthesized spiropiperazinyloxa- zolidinone and evaluated the synthesized compounds for *in vitro* anti-bacterial and anti-tubercular activity (Fig. **16**). The most active compounds **61** and **62** showed activity of 19 and 24 μM respectively, which was less than linezolid 0.4 μM (MIC, 0.135 μg/mL) [103].

Azabicyclooctanyloxazolidinone

Bhattarai *et al.* [104,105] have reported 3- azabicyclo[3.3.0]octanyloxazolidinones **63** with oxime or cyano group substituent at C-7 position of the azabi- cyclo ring having comparable or higher activity than linezolid against M. tuberculosis (Fig. **17**). The activity ranged from 0.5 to 1 µg/mL except one compound which was active at 2 µg/mL. Compound **64,** one of the most active compounds from this series was further found to have no CYP metabolism mediated liabilities,

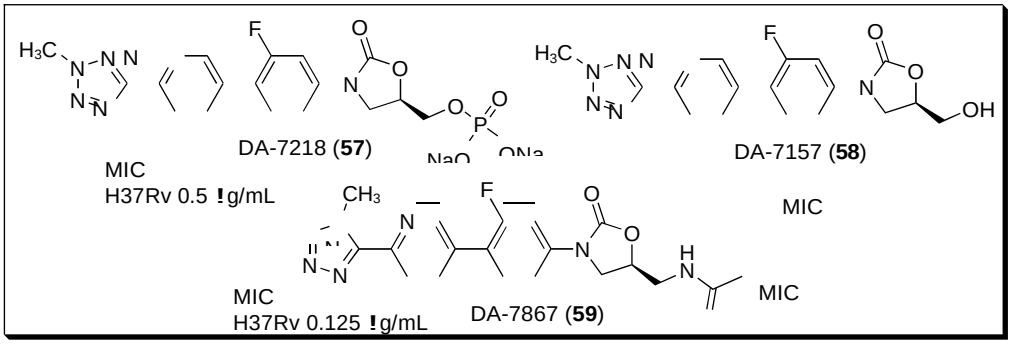


Figure No. (15): Pyridinyl phenyl oxazolidinones.

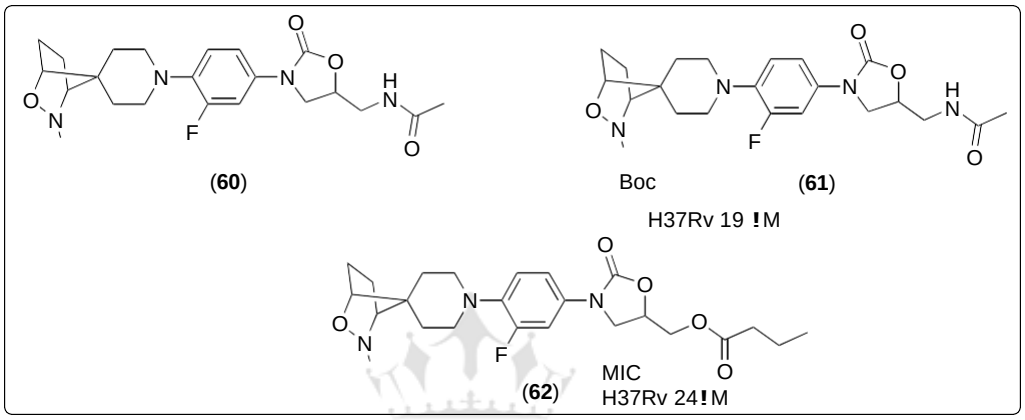


Figure No. (16): Spiropiperazinyloxazolidinone

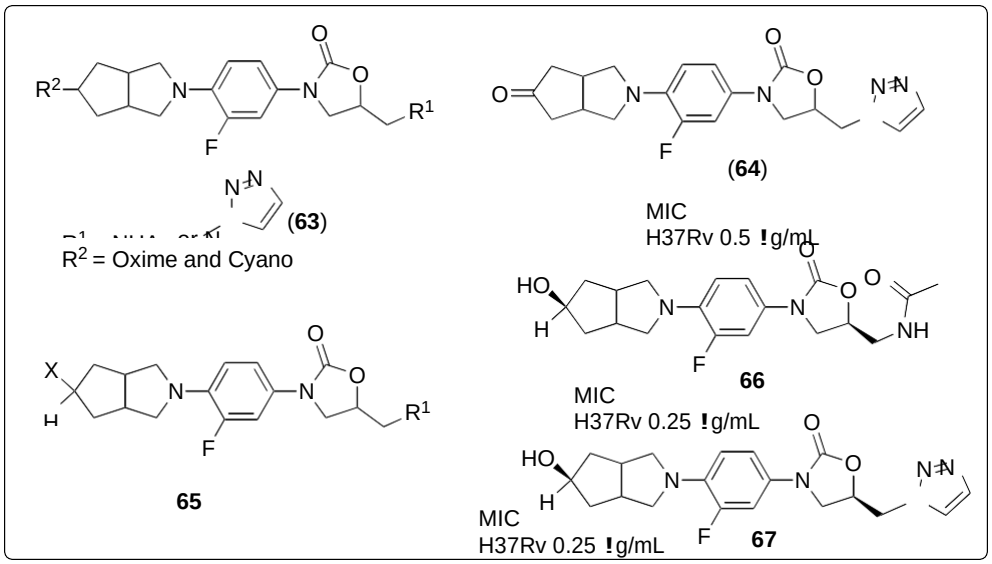


Figure No. (17): 3-Azabicyclo[3.3.0]octanyloxazolidinones.

it has the stability in human microsome and has low activity against hERG channel indicating its cardiac safety. Recently, the same research group has reported new stereoselective C-7 oxygen or nitrogen substituted oxazolidinones **65** in continuation with their earlier work. This resulted in the new potent compounds having the activity of two to four folds greater than the linezolid. Alcohols **66** and **67** were four fold active(MIC, 0.25 µg/mL) than linezolid. Further docking studies revealed the possible reason for their activity over linezolid. Interaction of C-ring hydroxy group in the binding pocket was proposed to be responsible for the better activity of these alcohols. The active compounds displayed better selectivity, CYP-profiles, microsomal stability (human), safety and pharmacology [106].

Bis-oxazolidinones

Ang *et al.* [107] have synthesized bis-oxazolidinone compounds and tested them for anti-TB activity in whole cell based assay (Fig. **18**). Several active compounds were found with the MIC of 0.125- 0.25 µg/mL. The active compounds showed no cytotoxicity and good selectivity. The compound **68** was the best amongst all the synthesized compounds with high potency (0.125 µg/mL) and excellent selectivity index SI (> 40,000). Moreover, they have established the preliminary SAR for this class of compounds (Fig. **18**). However, they were less active against MDR and XDR strains of M. tuberculosis; this loss in activity was attributed to the presence of efflux pumps or non-ribosomal alterations.

Pyrrolidinyl Phenyl Oxazolidinones

Paget and Hlasta at Johnson & Johnson have synthesized pyrrolidinyl oxazolidinones (Fig. **19**) and they were found to have good antibacterial activity [108,109]. The compounds RWJ-334181 and RWJ- 337813 were found to be useful anti-TB agents in the*in vitro* and *in vivo* assays. The compound RWJ- 334181 was equally potent as that of linezolid and the compound RWJ-337813 was less active than linezolid [110]. No further details are available on their development.

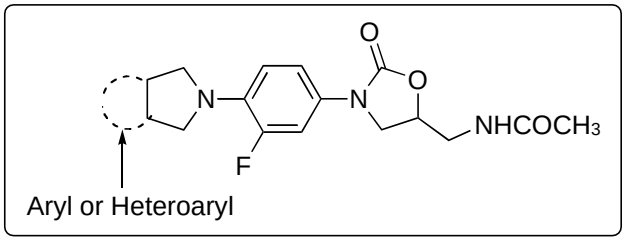


Figure No. (19): Pyrrolidinyl oxazolidinones.

SUMMARY AND CURRENT CLINICAL STATUS OF OXAZOLIDINONES AS ANTI-TB AGENTS

All the diversified oxazolidinone scaffolds reported for anti-mycobacterial activity are collectively represented in Table **2** along with their *in vitro* activity and clinical status.

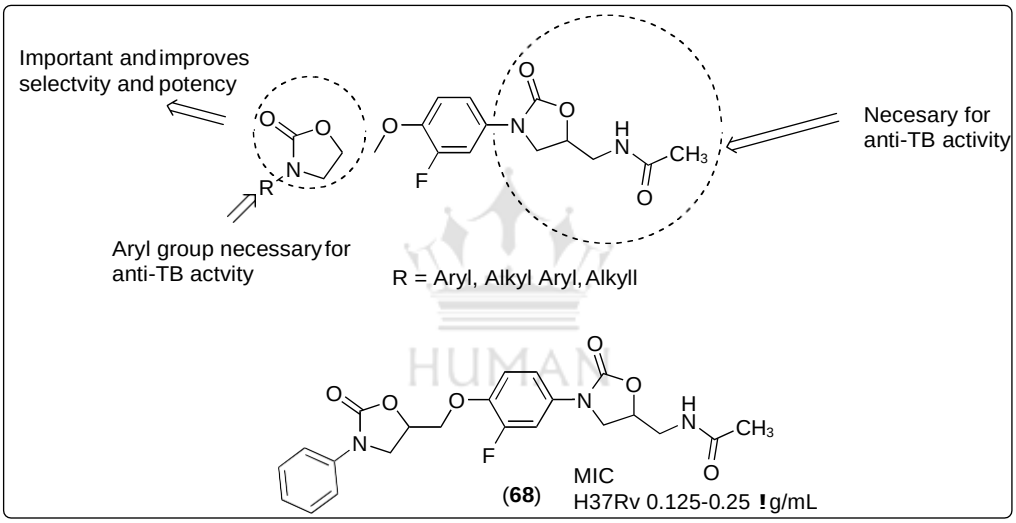


Figure No. (18): Bis-oxazolidinone compounds.

Table No. 2: Summary and current status of oxazolidinones as anti-mycobacterial agents.

Entry	Chemical Class	Trivial Names	*In vitro* Activity (MIC)	Clinical Status [17]	Refs.
1	Phenyl Oxazolidinones	DuP-721 (**31**)	1.25-4 μg/mL	-	[68]
	Piperazylphenyl/	Eperezolid (**39**)	0.25 μg/mL	-	[12]
2	Morpholinylphenyl/ Thiomorpholynylphenyl	Linezolid (**11**)	0.5 μg/mL	IIb	[12]
		PNU-100480 (**12**)	1 μg/mL	IIa	[12]
	Oxazolidinones	U-101603 (**40**)	$\leq$ 125 μg/mL	-	[41]
Entry	**Chemical Class**	**Trivial Names**	***In vitro* Activity (MIC)**	**Clinical Status [17]**	**Refs.**
		U-101244 (**41**)	$\leq$ 125 μg/mL	-	[41]
		RBx-7644 (**42**)	16 μg/mL	-	[82]
		RBx-8700 (**43**)	0.25 μg/mL	-	[82]
		44a	IC_{90} < 0.2 μg/mL	-	[85]
		48	1 μg/mL	-	[89]
		49	1 μg/mL	-	[89]
		50	1 μg/mL	-	[89]
		53	2 μg/mL	-	[90]
		Sy142 (**54**)	0.5 μg/mL	-	[93]
		Sy144 (**55**)	0.5 μg/mL	-	[93]

3	Tetrahydropyridinylphenyl oxazolidinone	AZD5847 (**56**)	1 μg/mL	IIa	[42]
4	Pyridinyl phenyl oxazolidinones	DA-7218 (**57**)	0.5 μg/mL	-	[99]
		DA-7157 (**58**)	0.5 μg/mL	-	[99]
		DA-7867 (**59**)	0.125 μg/mL	-	[98]
5	Spiropiperazinyloxazolidinones	**61**	19 μM	-	[103]
		62	24 μM	-	[103]
6	Azabicyclooctanyloxazolidinone	**64**	0.5 μg/mL	-	[105]
		66	0.25 μg/mL	-	[106]
		67	0.25 μg/mL	-	[106]
7	Bis-oxazolidinones	**68**	0.125-0.25 μg/mL	-	[107]
8	Pyrrolidinyl Phenyl Oxazolidinones	RWJ-334181	Equipotent or up to twice as potent as linezolid	-	[110]
		RWJ-337813	25-50% as active as linezolid	-	[110]

CONCLUSION

Oxazolidinones represent synthetic antibacterial agents with a unique mechanism of action having good spectrum of activity, oral bioavailability and well-established SAR. All these properties make them ideal candidates for pharmaceutical development. Their potent activity against *M. tuberculosis* and their established usefulness in the treatment of drug resistant TB has brought a new hope for TB treatment. The crystal structure data and their established SAR suggest that the C-ring can be modified to bring new oxazolidinones with better activity and safety profile. Several research groups have

developed novel oxazolidinones by C-ring modification. Some of them have shown excellent activity and safety profile. Several molecules were synthesized in this pursuit. Some have failed to live up with the challenge and some have built confidence and are in different stages of development. Linezolid, sutezolid and AZD5847 represent the promise in this direction. Certainly, oxazolidinones hold a promise for TB drug discovery with sutezolid developed by Pfizer leading this race.

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