Letter

Discovery of Fluorine-Containing Benzoxazinyl-Oxazolidinones for the Treatment of Multidrug Resistant Tuberculosis

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ACS Med. Chem. Lett., **Just Accepted Manuscript** • DOI: 10.1021/acsmedchemlett.7b00068 • Publication Date (Web): 12 Apr 2017

Discovery of Fluorine-Containing Benzoxazinyl-Oxazolidinones for the Treatment of Multidrug Resistant Tuberculosis

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KEYWORDS Antitubercular agents, fluoro-benzoxazinyl-oxazolidinones, structure-activity relationships, drug-resistant tuberculosis (DR-TB)

ABSTRACT: A novel series of fluorine-containing benzoxazinyl-oxazolidinones were designed and synthesized as anti-drug-resistant tuberculosis agents possessing good activity and improved pharmacokinetic profiles. Compound **21** exhibited not only outstanding *in vitro* activity with a MIC value of 0.25−0.50 μg/mL against drug-susceptible $H_{37}Rv$ strain and two clinically isolated drug-resistant *mycobacterium tuberculosis* strains, but also acceptable *in vitro* ADME/T properties. Moreover, this compound displayed excellent mouse pharmacokinetic profiles with an oral bioavailability of 102% and a longer elimination half-life of 4.22 h, thereby supporting further optimization and development of this promising lead series.

Tuberculosis (TB), one of the top 10 causes of death worldwide in 2015[1], is caused by the infection of *Mycobacterium tuberculosis* (MTB). In recent years, the emergence of multidrug-resistant tuberculosis (MDR-TB), extensively drug-resistant tuberculosis (XDR-TB), totally drug-resistant tuberculosis (TDR-TB) and even co-infections with HIV create a serious global challenge for treatment of this fatal disease[2,3]. The prolonged treatment of TB, adverse drug reactions and drug-drug interactions are commonly encountered, especially to the second-line medicines and in HIV co-infected individuals on antiretroviral treatment. Consequently, there is a pressing need for new anti-tuberculosis agents effective against drug-resistant TB[4,5]. The current situation even necessitates the re-engineering and repositioning of some old drug families to achieve effective control.

The oxazolidinones is a new class of antibacterial protein synthesis inhibitors that block translation through a unique mechanism by binding to 23S RNA in the 50S ribosomal subunit of bacteria[6,7]. Linezolid[8,9] (Figure 1), the first marketed oxazolidinone developed to treat gram-positive bacterial infection with a dose of 600 mg twice daily in adults, has an off-label use to treat complicated MDR-TB and XDR-TB with improved outcome[10,11]. In addition, sutezolid[12] (Figure 1) is undergoing clinical studies for tuberculosis treatment, making the oxazolidinones a class likely to play a key role in future TB treatment regimens. However, prolonged treatment with linezolid is associated with serious neuropathies and myelosuppression which is mediated by dose- and time-dependent inhibition of mitochondrial protein synthesis (MPS)[13,14]. Hence it is still needed to develop new oxazolidinones with acceptable safety margins through enhancing efficacy and reducing toxicity.

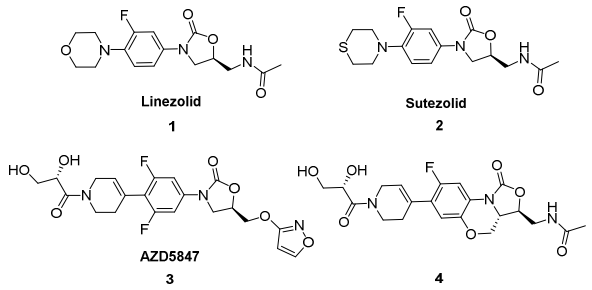


Figure 1. Structures of representative oxazolidinones for TB treatment.

Considering the very short half-life (less than one hour) of linezolid after oral administration in mouse[15], the drug-like scaffold-tricyclic fused benzoxazinyl-oxazolidinone developed by Yang and co-workers[16,17] has attracted our great interest, due to its benefits regarding pharmacokinetics profile. Additionally, the tetrahydropyridine moiety of AZD5847[18] (Figure 1) provided a possibility to reduce molecular planarity and increase molecular hydrophilicity[19]. To our delight, our first fluoro-benzoxazinyl-oxazolidinone compound **4** containing acetylaminomethyl side chain from linezolid and dihydroxypropinoyl tetrahydropyridine moiety from AZD5847 demonstrated good anti-TB activity with MIC 0.48 μg/mL against

MTB $H_{37}Rv$ and very low Vero cytotoxicity with an IC_{50} of more than 64 μg/mL. Herein, we disclose the synthesis, biological evaluation and preliminary structure-activity relationship (SAR) studies from the hit-to-lead optimization of these novel fluorine-containing benzoxazinyl-oxazolidinones bearing a tetrahydropyridine moiety.

As shown in Scheme 1, the synthetic routes for target compounds **4**, **17-41** were outlined. The synthesis of the key intermediates **Ia-f**, **IIa** and **IIIa-c** is summarized in Scheme S1 and Scheme S2 (Supporting Information). The desired compounds **24**, **26**, **28**, and **36-41** were obtained through nucleophilic substitution reaction of respective intermediates with 2-bromoethanol. The intermediate **Ia** reacted with cyclopropanecarbonyl chloride to give compound **18**. The remaining acylated target compounds were prepared by condensation reaction of respective intermediates with different carboxylic acids. Among them, compounds **22** and **23** were obtained as a hydrochloride form by the deprotection of Boc group using HCl in EtOAc.

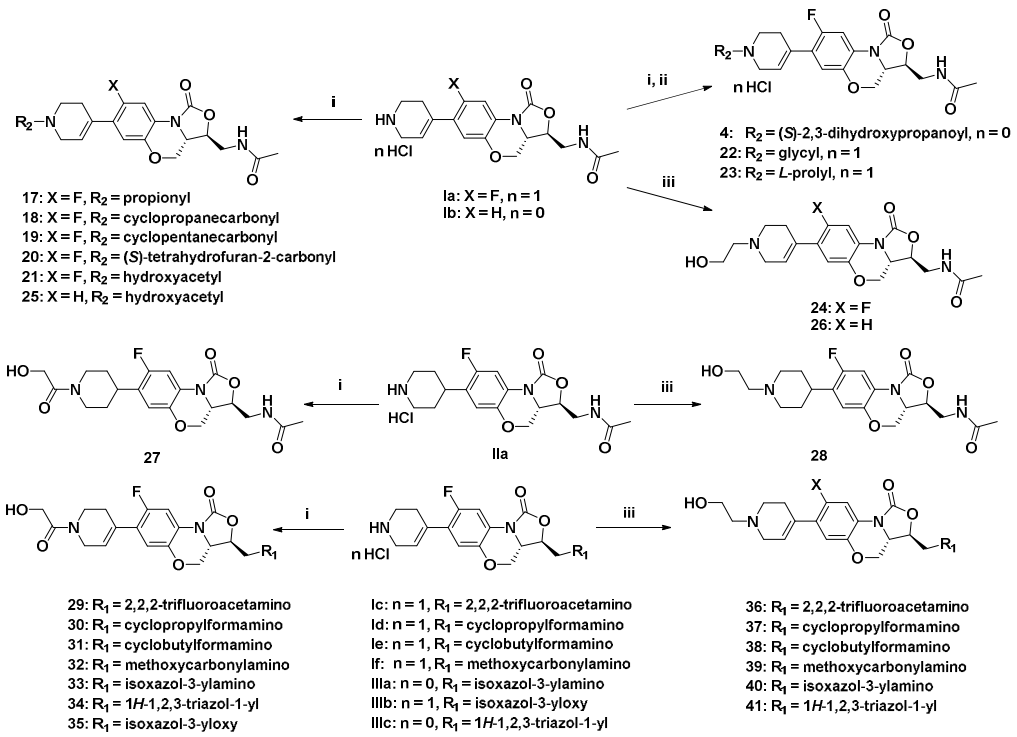
All the target compounds were evaluated for their activity against MTB $H_{37}Rv$ using the microplate alamar blue assay (MABA)[20]. The MIC was defined as the lowest concentration effecting a reduction in fluorescence of ≥90% relative to the mean of replicate bacterium-only controls. The compounds with MIC less than 5 μg/mL were further tested for mammalian cell cytotoxicity using Vero cells measured as a concentration inhibiting 50% growth (IC_{50}) as compared to a no-treatment control. Table 1 summarizes the biological data for 26 new benzoxazinyl-oxazolidinones derivatives. Linezolid and AZD5847 were used as reference compounds.

Inspired by the observation that the privileged scaffold of tricyclic fused benzoxazinyl-oxazolidinone could increase the antibacterial activity and improve pharmacokinetic properties[16], compound **4** was prepared to investigate the effect of this scaffold on anti-tuberculosis activity. To our delight, as shown in Table 1, compound **4** displayed the same anti-TB activity as linezolid but superior to that of AZD5847. In addition, this compound exhibited low toxicity. With the encouraging observation, a preliminary structure-activity relationship (SAR) investigation was carried out to seek the optimal R_2 and R_1 substituents in this new fluorine-containing benzoxazinyl-oxazolidinone scaffold.

Keeping the tricyclic fused scaffold (section B) and the traditional C-5 acetylaminomethyl side chain (section C), which plays a very important role in linezolid and sutezolid[21], our initial exploration of the hit compound **4** was focused on the modification of section A (Table 1) to identify the optimum R_2 substituent. A variety of different substituents including acyclic and cyclic alkylated acyl with or without hetero atoms were evaluated at this position. Unfortunately, the results revealed that R_2 without polar substituent like hydroxyl or amino (**17-19**) or with a bulkier group (**20**, **23**) caused a more than 10-fold loss of potency. However, replacement of the chiral (*S*)-2,3-dihydroxypropanoyl group with simple achiral 2-hydroxyacetyl group (**21**) or even 2-hydroxyethyl group (**24**) displayed equipotent activity compared to the hit compound **4**. Compound **22** bearing glycyl group also displayed good activity. From results described above, it appeared that a small flexible hydrophilic group is beneficial for the anti-tuberculosis activity.

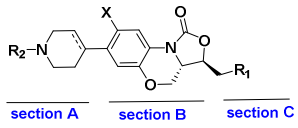
As such, the 2-hydroxyacetyl group or 2-hydroxyethyl group in section A and acetylamino group in section C were selected as optimized fragments to probe the impact of the fluorine on the benzene ring and the double bond in the

Scheme 1. Synthesis of the Target Compounds 4 and 17-41.



Reagents and conditions: (i) cyclopropanecarbonyl chloride, Et_3N, DCM, rt for **18**; carboxylic acids, EDCI, HOBt, Et_3N, DMF, rt for the others; (ii) HCl/H_2O, 0 °C to rt for **4**; HCl/EtOAc, 0 °C to rt for **22-23**; (iii) 2-bromoethanol, Et_3N, DMF, 100 °C.

Table 1. Structures, Anti-tuberculosis Activity, Cytotoxicity, and Selectivity Index (SI) Values for Target Compounds



Compd	R_2	R_1	X	Double bond	MIC (μg/mL)	IC_{50} (μg/mL)	SI[a]
4			F	Y	0.483	>64	133
17			F	Y	6.357		
18			F	Y	6.404		
19			F	Y	7.940		
20			F	Y	5.525		
21			F	Y	0.391	>64	164
22[b]			F	Y	0.732	>64	87
23[b]			F	Y	7.125		
24			F	Y	0.578	>64	111
25			H	Y	0.725	13.76	19
26			H	Y	2.645	26.77	10
27			F	N	3.814	>64	17
28			F	N	14.602		
29			F	Y	1.159	>64	55

Compd	R_2	R_1	X	Double Bond	MIC (μg/mL)	IC_{50} (μg/mL)	SI[a]
30			F	Y	1.868	>64	34
31			F	Y	1.680	>64	39
32			F	Y	0.999	>64	64
33			F	Y	1.044	>64	61
34			F	Y	10.900		
35			F	Y	>32		
36			F	Y	1.916	>64	33
37			F	Y	0.473	>64	135
38			F	Y	1.104	>64	58
39			F	Y	2.223	57.43	26
40			F	Y	0.980	>64	65
41			F	Y	7.956		
AZD5847					1.023	>64	62
Linezolid					0.304	>64	197

[a]Selectivity index (SI) = IC_{50}(Vero)/MIC. [b]Using in the form of hydrochloride.

tetrahydropyridine ring on potency and cytotoxicity. As exhibited in Table 1, compound **26** bearing 2-hydroxyethyl group displayed 5-fold less potency than compound **24**. Although compound **25** still exhibited moderate anti-TB activity with MIC 0.725 μg/mL compared to compound **21** (MIC 0.391 μg/mL), these two fluorine-free compounds **25** and **26** showed higher cytotoxicity (**25** vs **21**, **26** vs **24**). Interestingly, almost all compounds listed in Table 1 with fluorine on the benzene ring exhibited very low cytotoxicity, no matter what the MIC values are. The advantage of fluorine on the benzene ring in this tricyclic scaffold was confirmed, consistent with the general SAR studies results of oxazolidinone. Replacement of the 4-tetrahydropyridine with 4-piperidine caused a significant loss of activity (**27** vs **21**, **28** vs **24**). This result demonstrated that the double bond is required for potency.

Although it is well-established that C-5 acetylaminomethyl group in linezolid is essential for good antibacterial activity, further explorations on the C-5 side chain (section C) in this new tricyclic fused oxazolidinone were also undertaken. Different C-5 side chain moieties like trifluoroacetamino (**29** and **36**), methyl carbamate (**32** and **39**), aminoisoxazole (**33** and **40**), hydroxyisoxazole (**35**), [1,2,3]tirazole (**34** and **41**), cyclopropanecarboxamide (**30** and **37**) and cyclobutanecarboxamide (**31** and **38**), had been introduced to replace the acetylamino group in section C. Most compounds showed good to moderate potency with MIC values 0.473-2.223 μg/mL. However, analogues with [1,2,3]tirazole (**34** and **41**), hydroxyisoxazole (**35**) completely lost the anti-TB activity. The results revealed

Table 2. *In Vitro* Activity of the Selected Compounds against Drug Resistant Tuberculosis

Compd	MIC (μg/mL) ($H_{37}R_v$)	MIC (μg/mL) (16892[a])	MIC (μg/mL) (16802[b])
4	0.483	0.25	1.00
21	0.391	0.25	0.50
22	0.732	0.25	2.00
24	0.578	0.50	2.00
37	0.473	0.50	1.00
INH	0.037	>40	2.50
RFP	0.057	>40	20.0

[a]Resistance to isoniazid (INH) and rifampicin (RFP). [b]Resistance to isoniazid, rifampicin, streptomycin, ethambutol, and levofloxacin.

Table 3. Representative Properties of Compound 21

HepG2 Cytotoxicity IC_{50}(μg/mL)	hERG K^+ inhibition IC_{50}(μM)	MPS[a] inhibition IC_{50}(μM)	Caco-2 Papp ($\times10^{-6}$cm/s)	MLM[b] Substrate remaining (%)[d]	MLM[b] Stability[e]	HLM[c] Substrate remaining (%)[d]	HLM[c] Stability[e]
> 64	> 30	9.19	4.14±0.57	102.0	stable	103.0	stable

[a]Mitochondrial protein synthesis. [b]Mouse liver microsome. [c]Human liver microsome. [d]Substrate concentrations were determined in incubations with NADPH after 30 min and normalized to concentrations at time zero. [e]Stability was determined without the NADPH cofactor.

Table 4. Mouse Pharmacokinetic Properties of Compound 21

Compd	Route	Dose (mg/kg)	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$[a] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$MRT_{(0-\infty)}$[b] (h)	Clearance (mL/h/kg)	F[c] (%)
21	po	100	30.0	2	4.22	122	4.12		102
	iv	10	11.4	0.03	8.23	12	2.54	836	

[a]Plasma elimination half-life. [b]Mean residence time. [c]Bioavailability.

that N-H is essential for the maintenance of activity.

As a result of their high potency against $H_{37}Rv$ strain and superior selectivity index values, five compounds including **4**, **21**, **22**, **24** and **37** were selected to investigate their anti-DR-TB activity. As summarized in Table 2, all tested compounds displayed high *in vitro* potency to 16892 strain (MDR-TB). More importantly, compound **21** also exhibited good activity against 16802 strain (XDR-TB), supporting it to move forward for further evaluation.

To develop a deeper understanding of compound **21**'s druggability, more profiling was performed. As depicted in Table 3, compound **21** exhibited high IC_{50} value against HepG2 cell, indicating a lack of toxicity to hepatic cells. Notably, this compound showed almost no inhibition of the hERG K^+ channel using the patch clamp technique. Due to the main adverse effect of myelosuppression during the long-term use of linezolid, likely related to inhibition of mitochondrial protein synthesis (MPS)[13], the *in vitro* MPS inhibition activity was conducted to predict myelosuppression risk. Compound **21** showed a comparable inhibition activity (IC_{50} 9.19 μM) with linezolid (IC_{50} 8.71 μM). This outcome suggested that **21** and linezolid have a similar safety profile in terms of myelosuppression risk. Regarding the *in vitro* physicochemical properties, compound **21** showed good membrane permeability and excellent metabolic stability against mouse and human liver microsomes. These data therefore indicate that compound **21** may exhibit favorable *in vivo* PK performance. Indeed the PK of **21** in Balb/c mouse was outstanding (Table 4), with high maximal plasma concentration (C_{max} = 30.0 μg/mL), high plasma exposure ($AUC_{0-\infty}$ = 122 μg·h /mL), long elimination half-life ($t_{1/2}$ = 4.22 h) and excellent oral bioavailability (F = 102%) after oral administration.

In summary, a new series of fluorine-containing benzoxazinyl-oxazolidinones were prepared and characterized. Preliminary exploration of structure-activity relationships on the scaffold revealed that the fluorine atom on the benzene ring has dual function in improving activity and reducing toxicity. Compound **21** displayed promising anti-tuberculosis activity against drug-sensitivity $H_{37}Rv$ and drug-resistant strains (MIC = 0.25~0.50 μg/mL) and an adequate preliminary *in vitro* safety profiles with negligible cytotoxicity and cardiotoxicity. Importantly, compound **21** exhibited notable oral bioavailability (102%) in mouse as well as relatively long half-life, which may help to reduce the dosage and frequency of medication and improve patient compliance. Hence, compound **21** as a promising anti-tuberculosis potential lead compound, warranting further evaluation, will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

Experimental procedures, compounds characterization, minimum inhibitory concentration assay, in vitro ADME/T and PK evaluation. (PDF)

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Funding Sources

The research is supported in part by the National Science & Technology Major Project of China (Grant 2015ZX09102007-013), the National Natural Science Foundation of China (Grant 81502917), and the Fundamental Scientific Research Fund of Institute of Materia Medica (Grant 2014CX15).

Notes

The authors declare no competing financial interest.

ABBREVIATIONS

ADME/T, absorption, distribution, metabolism, excretion, and toxicity; Boc, *tert*-butoxycarbonyl; DCM, dichloromethane; DMF, *N*,*N*-dimethylforamide; EDCI, 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; PK, pharmacokinetic

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