Bioorganic & Medicinal Chemistry 20 (2012) 2214–2220

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Generation and exploration of new classes of antitubercular agents: The optimization of oxazolines, oxazoles, thiazolines, thiazoles to imidazo[1,2-*a*]pyridines and isomeric 5,6-fused scaffolds

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ARTICLE INFO

Article history:
Received 23 December 2011
Revised 3 February 2012
Accepted 8 February 2012
Available online 16 February 2012

Keywords:
Mycobacterium tuberculosis
MDR-TB
XDR-TB
5,6-Fused heteroaromatics
Imidazo[1,2-*a*]pyridine

ABSTRACT

Tuberculosis (TB) is a devastating disease resulting in a death every 20 s. Thus, new drugs are urgently needed. Herein we report ten classes of compounds—oxazoline, oxazole, thiazoline, thiazole, pyrazole, pyridine, isoxazole, imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine and imidazo[1,2-*c*]pyrimidine—which have good (micromolar) to excellent (sub-micromolar) antitubercular potency. The 5,6-fused heteroaromatic compounds were the most potent with MIC's as low as <0.195 μM (**9** and **11**). Overall, the imidazo[1,2-*a*]pyridine class was determined to be most promising, with potency similar to isoniazid and PA-824 against replicating *Mtb* $H_{37}Rv$, clinically relevant drug sensitive, multi- and extensively resistant *Mtb* strains as well as having good in vitro metabolic stability.

1. Introduction

The battle against tuberculosis (TB, caused by the bacterium *Mycobacterium tuberculosis*, *Mtb*) has raged for millennia.[1] Throughout history, TB has claimed the lives of over one billion people and currently infects one third of the world's population. With 1.4 million deaths in 2010, TB, as a single causative agent, is the leading killer among infectious diseases.[1] The spread of TB was significantly affected with the advent of several chemotherapy agents during the mid 1900s.[2] However, since the 1980s TB has been on the rise. Presently, 8.8 million new cases are added annually.[1] The increase in cases of TB/HIV co-infection and the spread of multiple-drug resistant TB (MDR-TB, strains that are resistant to first line drugs isoniazid and rifampin) and extensively drug resistant TB (XDR-TB, strains that are resistant to isoniazid and rifampin, as well as any fluoroquinolone and at least one of three injectable second-line drugs, such as amikacin, kanamycin, or capreomycin) are making matters worse.[3] The increase in TB infection has become so alarming that the World Health Organization (WHO) declared TB a global emergency as far back as 1993.[4] More than ever, there is an urgent need to develop new antitubercular drugs to combat the spread of TB, particularly in its hard-to-kill multidrug-resistant and latent forms where, most likely, only sustained aggressive chemotherapy with a combination of drugs will stop the disease.

Our laboratory serendipitously discovered a small molecule heterocyclic TB inhibitor based on an oxazoline scaffold through broad screening of synthetic mycobactin siderophore fragments.[5] This hit was initially optimized by dehydration to an oxazole and hundreds of analogs were prepared in an effort to increase potency against *Mtb* and possibly refine ADME (absorption, distribution, metabolism and excretion) properties.[5,6] Not previously reported was that many amides and hindered benzyl ester derivates were prepared in an effort to improve the in vitro stability to rat microsomes and simulated gastric fluid. However, very little improvement was found and nearly all the amides prepared had substantially less potency against *Mtb* relative to the corresponding ester (see Supplementary data). Therefore, we were compelled to reprioritize the risk of trying to find a new metabolically robust heterocyclic class of antitubercular compounds over the optimization of oxazoline/oxazole class. Herein we report our structure activity relationship (SAR) studies starting from the serendipitous oxazoline/oxazole benzyl ester discovery[7] and leading to the identification of imidazo[1,2-*a*]pyridines as a new class of potent and metabolically robust antitubercular agents[8,9] (see Fig. 1).

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doi:10.1016/j.bmc.2012.02.025

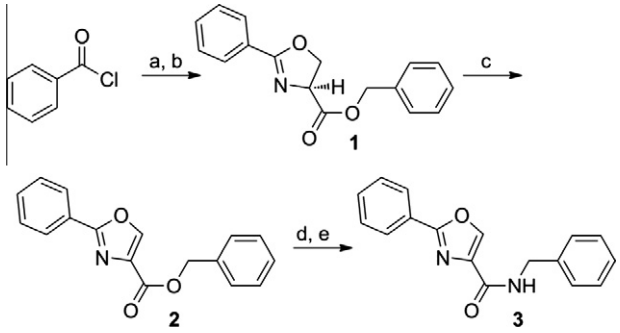
2. Results and discussion

The syntheses of the oxazoline and oxazole scaffolds started by coupling of benzoyl chloride with L-serine benzyl ester followed by the dehydrative cyclization of the resulting β-hydroxy amide with bis(2-methoxyethyl)amino-sulfur trifluoride (DAST) as reported by Wipf et al.[10] to form the oxazoline core (**1**) in 84% yield for the two steps. This oxazoline (**1**) was converted in 91% yield to the corresponding oxazole analog (**2**) by a mild $BrCCl_3$/DBU oxidation procedure[11] (Scheme 1). Hydrogenolysis of compound **2** gave the oxazole carboxylic acid intermediate which was converted to the corresponding benzyl amide (**3**) by an EDC-mediated coupling with benzyl amine (67% overall yield).

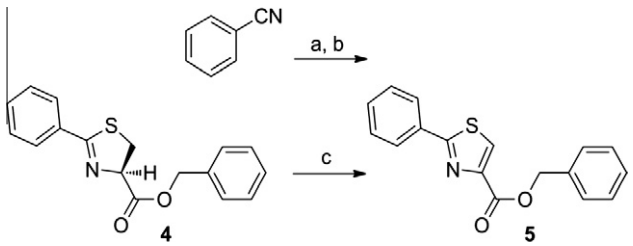
Thiazoline (**4**) was prepared by esterification of the corresponding carboxylic acid, which was obtained in 80% yield from condensation of benzonitrile and L-cysteine in a buffered aqueous methanol (pH 7.0) solution as reported Bergeron et al.[12] (Scheme 2). Subsequent oxidation with $BrCCl_3$/DBU gave the desired thiazole (**5**) in 68% yield. The pyrazole, isoxazole, pyridine and benzyl 7-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate analogs (**6**, **7**, **8**, and **9**, respectively), as well as the *N*-benzyl-7-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxamide (**10**) and *N*-benzyl-2,7-dimethylimidazo[1,2-*a*]pyridine-3-carboxamide (**12**) were formed by separate EDC-mediated coupling reactions of the commercially available carboxylic acids with benzyl alcohol or benzyl amine, respectively (see Supplementary data) in yields ranging from 26% to 80%.

Previously, we reported facile three step syntheses of various substituted *N*-benzyl imidazo[1,2-*a*]pyridine-3-carboxamides, including compound **12** that had potent antitubercular activity.[8] Herein we report that similar heterocycles, 2,7-dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (**11**), benzyl 2,6-dimethylimidazo[1,*a*]pyrimidine-3-carboxylate (**13**) and benzyl 2,5,7-trimethylimidazo[1,2-*c*]pyrimidine-3-carboxylate (**14**) can each be prepared in just a single step by condensation of benzyl 2-bromo-3-oxobutanoate with the appropriate 2-amino-heteroaromatic precursor demonstrating that these 5,6-fused heteroaromatic antitubercular agents can be made efficiently and cost effectively in respectable yields of 46–75% (Scheme 3). These compounds also exhibit notable antitubercular activity against replicating and non-replicating *Mtb* and no toxicity to VERO cells (Table 1).

Previously, we spent considerable synthetic effort to develop an understanding of the SAR of the oxazoline/oxazole benzyl ester



Scheme 1. Synthesis of oxazoline (**1**) and oxazoles (**2**, **3**) analogs. Reagents and conditions: (a) L-serine benzyl ester, DIPEA, CH_2Cl_2, 0 °C–50 °C, 14 h; (b) DAST, K_2CO_3, −78 °C, CH_2Cl_2, 1 h; (c) DBU, $BrCCl_3$, CH_2Cl_2, 0 °C to rt, 2 h; (d) H_2, Pd–C, 14 h; (e) benzyl amine, EDC, DMAP, CH_3CN, rt, 14 h.



Scheme 2. Syntheses of thiazoline (**4**) and thiazole (**5**) benzyl esters. Regents: (a) L-cysteine, $NaHCO_3$, MeOH / H_2O (pH = 7), reflux, 14 h; (b) Benzyl alcohol, EDC, DMAP, CH_3CN, room temp, 14 h; (c) DBU

scaffold (**1** and **2**) by preparing nearly a thousand analogs and screening them for activity against *Mtb* $H_{37}Rv$ (ATCC #27294) by the microplate alamar blue assay (MABA).[13] We anticipated that various benzyl amides (like **3**) would not only retain potency seen with the benzyl esters but also improve the in vitro metabolic properties of the oxazoline and oxazole scaffolds. However, such modifications were not effective (see Supplementary data). Next, we explored the closely related thiazoline/thiazole scaffolds (**4** and **5**) and found that their MIC values (13 and 6 μM, respectively, in GAS[13] media) were similar to those of the oxazoline/oxazoles (5 and 6 μM for **1** and **2**, respectively, Table 1). The thiazoline/thiazole scaffolds (**4** and **5**) were also found to be non-toxic to VERO[14] cells with IC_{50} values >128 μM, but, unfortunately, they

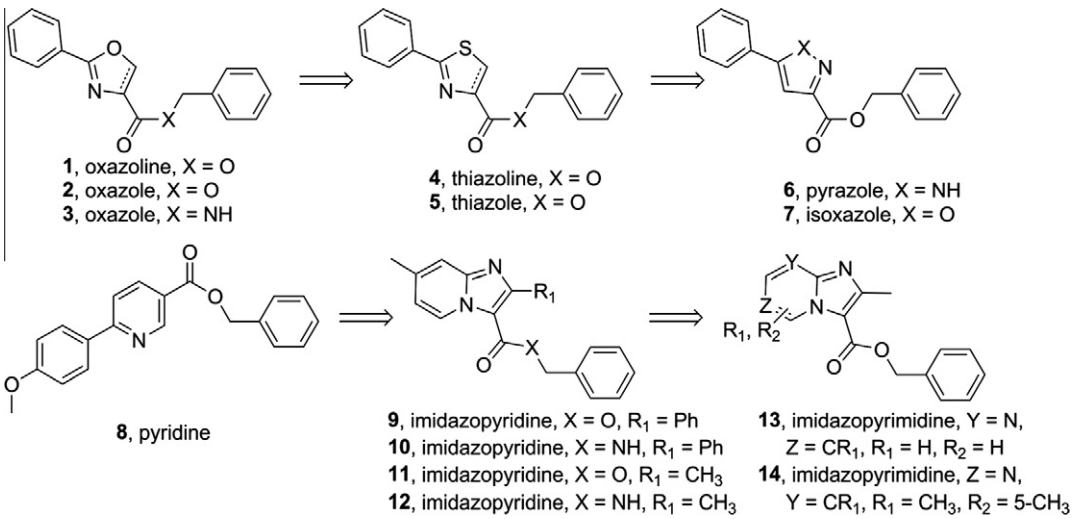
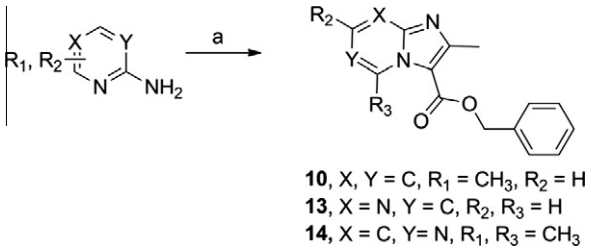


Figure 1. Various heterocyclic classes (**1**–**14**) explored for antitubercular activity.



Scheme 3. One step syntheses of benzyl 2,7-dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (**10**), benzyl 2-methylimidazo[1,2-*a*]pyrimidine-3-carboxylate (**13**) and benzyl 2,5,7-trimethylimidazo[1,2-*c*]pyrimidine-3-carboxylate (**14**). Reagents: (a) Benzyl 2-bromo-3-oxobutanoate, $NaHCO_3$, 1,2-dimethoxyethane, 110 °C, 24–36 h.

showed no improved in vitro metabolic stability (see Supplementary data). The pyrazole scaffold (**6**) gave the most ambiguous screening results showing good activity in GAS media (3.5 μM, average of three tests), but weak potency in 7H12[13] media (>38 μM, average of three tests). It is possible that the potency of the pyrazoles might be carbon source dependant, an issue experienced and described by Pethe et al. at Novartis,[15] more protein bound in the 7H12 media than the GAS or just not very soluble. Nonetheless, we purposely screened our compounds against *Mtb* $H_{37}Rv$ in at least two different types of assay media as GAS media contains glycerol-alanine-salts while the 7H12 uses palmitic acid as its carbon source. Additionally, we periodically performed assays in GAST[16] media to rule out possible iron dependence. Use

Table 1
Activity of various heterocyclic scaffolds (**1**–**14**) against replicating *Mtb* $H_{37}Rv$ in various media, against non-replicating *Mtb* 'LORA' and cytotoxicity in VERO cells

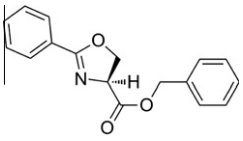
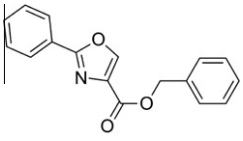
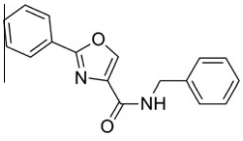
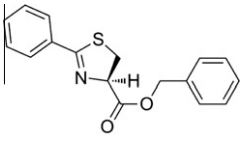
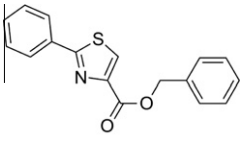
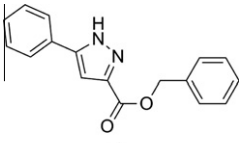
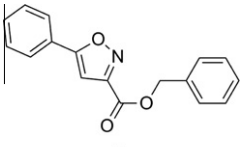
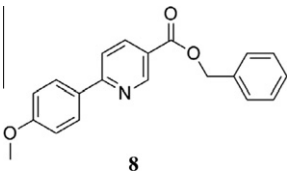
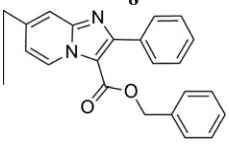
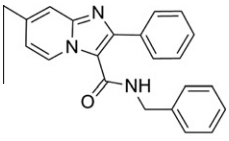
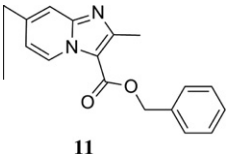
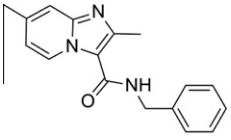
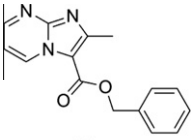
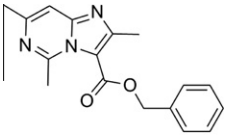
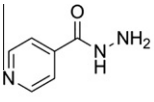
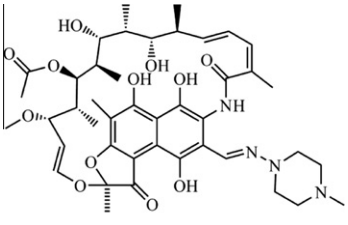
Compound	Mol Wt	Calcd Clog *P*[a]	MIC mean +/−SD (μM)[MIC range] against replicating *Mtb* in medium			LORA (μM)	VERO IC_{50} (μM)
			GAS	GAST	7H12		
 **1**	281.31	2.76	4.9 ± 1.7[2.9–6.2]	4.4 [5.7–3.7]	16.6 ± 11.1[3.8–24.0]	63	>128
 **2**	279.29	3.47	5.7 ± 2.3[0.5–7.9]	0.49 [<1–0.5]	3.9 ± 1.0[3.0–5.0]	37	121
 **3**	278.31	3.70	>65[23.1–>128]	59	>40[19.5–>50]	NT	NT
 **4**	297.37	2.94	12.9 ± 4.8[9.1–18.3]	3.5	11.6 ± 5.1[7.7–17.4]	NT	>128
 **5**	295.36	4.10	6.0 ± 4.0[1.5 - 8.5]	6.2	7.2 ± 3.0[4.0–9.8]	NT	>128
 **6**	278.31	4.54	3.5 ± 1.4[1.8–4.3]	>64	>38[15.0 - >50]	NT	>128
 **7**	279.29	4.30	2.2 ± 1.0[1.1–2.9]	NT	0.8 ± 0.01[0.7–0.8]	28.0 ± 1.3 [26.9–29.4]	>50

Table 1 (*continued*)

Compound	Mol Wt	Calcd Clog*P*[a]	MIC mean +/−SD (μM)[MIC range] against replicating *Mtb* in medium			LORA (μM)	VERO IC_{50} (μM)
			GAS	GAST	7H12		
	319.35	4.71	1.9 ± 0.6[1.5–2.5]	NT	9.5 ± 3.2[5.8–11.9]	NT	NT
8 	342.39	5.89	<0.195	NT	<0.195	21.7 ± 0.8 [21.1–22.6]	>50
9 	341.41	5.30	0.6 ± 0.1[0.5–0.7]	NT	2.9 ± 0.1[2.8–3.0]	>50	>50
10 	280.32	4.07	<0.195	NT	<0.195	34.8 ± 3.4 [31.3–38.2]	>50
11 	279.34	3.60	0.7 [0.4–1.1]	2.0 [<0.5–3.4]	2.3[1.9–2.7]	54	>128
12 	267.28	2.40	2.3 ± 0.5[1.7–2.7]	NT	4.7 ± 1.1 [3.2–5.2]	NT	>50
13 	295.34	3.40	1.1 ± 0.3 [0.9–1.4]	NT	5.3 ± 0.5 [5.0–5.9]	NT	>50
14  **Isoniazid (INH)**	137.14	−0.67	0.22 ± 0.01[0.23–0.22]	NT	0.37 ± 0.12[0.23–0.46]	>512	>128
 **Rifampin (RMP)**	822.94	6.04	0.09 ± 0.01[0.08–0.1]	0.2	0.04 ± 0.01[0.03–0.05]	2.6	113

SD, standard deviation; MIC, minimum inhibitory concentration required to inhibit the growth of 90% of organisms; NT, not tested; GAS, glycerol-alanine-salts media; GAST, iron deficient glycerol-alanine-salts with Tween 80 media; 7H12, 7H9 broth base media with BSA, casein hydrolysate, catalase, palmitic acid; LORA, low oxygen recovery assay using the *Mtb* H_{37}Rv luxAB luminescence strain; VERO, African green monkey kidney cell line to evaluate toxicity. Values reported are the average of three individual measurements.

[a] Calculated Clog*P* by ChemDraw version 12.0.

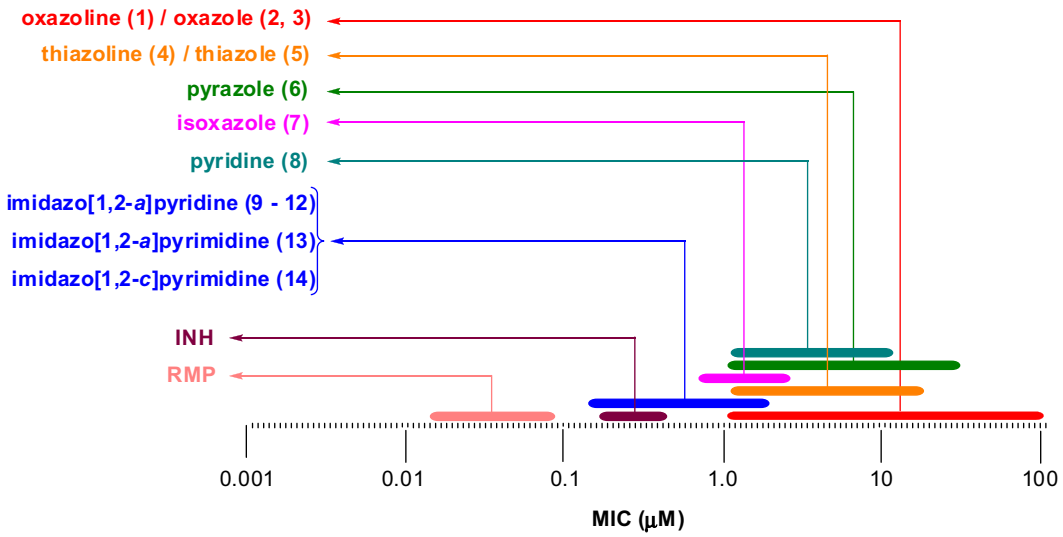


Figure 2. Comparison of the MIC range against *Mtb* $H_{37}Rv$ of the various heteroaromatic scaffolds prepared (MIC in μM).

of GAST, an iron deficient media containing glycerol-alanine-salts with Tween 80, often causes a shift in antibacterial MIC values of iron binding siderophores[17] and hydroxamate-substituted cephalosporin derivatives.[18] Though originally modeled after the oxazoline core of the mycobactin class of siderophores,[17] all of the heterocyclic classes screened appear to be non-iron dependant. The isoxazole and pyridine scaffolds (**7** and **8**) showed good potency against *Mtb* $H_{37}Rv$ (2.2 and 1.9 μM, respectively in the GAS media) that was comparable to the activity of the analogous oxazoline/oxazole and thiazoline/thiazole scaffolds, but concerns about metabolic stability of the constituent benzyl ester lingered. The isoxazole scaffold (**7**) also has been well documented as a potent antitubercular scaffold by Kozikowski et al.[19]

At this juncture we were fortunate to have made an agreement allowing for the access and screening of compounds from the Dow AgroScience (DAS) chemical bank against *Mtb*. This allowed for a deepening of our SAR studies around our oxazole and thiazole scaffolds, as well as exploration of other heterocyclic classes including various ethyl imidazo[1,2-*a*]pyridine-3-carboxylates that showed moderate activity with MIC values of 41–86 μM (see Supplementary data). These initial imidazo[1,2-*a*]pyridines screened from DAS lacked the benzyl ester that was found to improve potency in the oxazoline/oxazole scaffolds we previously explored.[5] Gratifyingly, when the benzyl ester analog (**11**) was made, a dramatic >2 orders of magnitude increase in potency was observed from an MIC of ~65 μM as the ethyl ester (**79**, in Supplementary data) to MIC <0.195 μM as the corresponding benzyl ester (**11**). In comparison, the benzyl ester oxazole (**2**), with an MIC range of 0.5–6 μM, was within an order of magnitude as potent as the corresponding ethyl ester analog (**81**, in Supplementary data) with an MIC of 8–20 μM. Therefore, simple ethyl esters do not appear to impart the sub-micromolar potency seen with the benzyl esters (see Supplementary data). Next, when the *N*-benzyl-2,7-dimethylimidazo[1,2-*a*]pyridine-3-carboxamide (**12**) was synthesized and assessed (MIC of 0.7–2.3 μM), we confirmed that extended scaffold SAR studies beyond esters had been appropriate. Indeed, the 2,7-dimethylimidazo[1,2-*a*]pyridine-3-carboxamide scaffold displayed both excellent antitubercular potency, greatly improved in vitro metabolic stability and pharmacokinetic properties relative to the oxazoline/oxazole scaffolds (as reported previously in separate publications).[5,8] The chemical dissimilarity between the oxazole and imidazo[1,2-*a*]pyridine scaffolds suggested that these compounds likely inhibited different targets, a notion that was confirmed by microarray analysis of *Mtb* $H_{37}Rv$ treated with these compounds which showed different transcriptional signatures (Ref.[8] and unpublished results). Imidazo[1,2-*a*]pyridine (**12**) had excellent in vitro stability in rat liver microsomes with 90% of compound remaining after a 15-min incubation and 100% remaining after a 15-min incubation in simulated gastric fluid[20] compared to oxazole (**2**) where only 11% remained in microsomes and 0.6% remained in the simulated gastric fluid after a 15-min incubation. In 2009, various functionalized 2-aryl-3-amino-imidazo[1,2-*a*]pyridines were reported[21] as in vitro *Mtb* glutamine synthetase inhibitors, but this publication neglected to give an assessment of these compounds versus whole cell *Mtb* $H_{37}Rv$ making it hard to compare these scaffolds for potential similarities. Previous data[8] suggested a mechanism of action distinct from inhibition of glutamine synthesis since transcriptional profiling experiments of *Mtb* $H_{37}Rv$ treated with compound **12** had suggested an effect on energy metabolism. Additionally, a set of polyfunctional imidazo[1,2-*a*]pyridines was recently disclosed[22] which displayed a broader spectrum of antibacterial activity than that which was published for our 2,7-dimethylimidazo[1,2-*a*]pyridine-3-carboxamide scaffold.[8] In comparison, we reported our class to be active against only select mycobacteria strains (*Mycobacterium kansasii*, *Mycobacterium bovis* BCG, and *Mycobacterium avium*, MIC's 1.3, 0.3, 1.3 μM, respectively) while no activity (MIC >50 μM) was seen against + the Gram positive (*Streptococcus aureus*) or Gram negative (*Escherichia coli*) organisms whereas the reported polyfunctional imidazo[1,2-*a*]pyridines did have potency against both the Gram positive and Gram negative organisms (MIC's of 0.5 and 1 μg/mL, respectively). The potency of these compounds against *M. avium* further suggested that the target was unlikely glutamine synthetase since glutamine synthetase inhibitors were found to have considerably poorer efficacy against *M. avium* due to the finding that this organism secretes only small quantities of this protein.[23]

Comparison of the MIC ranges (taken from multiple screens) of the various scaffold analogs to one another showed a positive improvement in activity with the 5,6-fused heteroaromatics (**9**–**14**), displaying potency closer to that of the first line antitubercular drug isoniazid (MIC = 0.2–0.5 μM) and significantly better than the previous explored classes (**1**–**8**) that have low micromolar potency (Fig. 2). The 5,6-fused heteroaromatics were non-toxic to the VERO cells (IC_{50} >50 μM) and some had moderate activity in

Table 2
MDR- and XDR-*Mtb* activity of compounds **2**, **5**, **11** and control PA-824 μM (MICin μg/mL)

	Compound MIC μM (μg/mL)			
	2	**5**	**11**	**PA-824**
Drug sensitive *Mtb* clinical strain #1	4.4–8.9 (1.25–2.5)	33.9 (10)	<0.04 (<0.01)	0.45–0.86 (0.16–0.31)
Drug sensitive *Mtb* clinical strain #2	2.2–4.4 (0.6–1.25)	8.5 (2.5)	<0.04 (<0.01)	>13.9 (>5)
MDR-TB resistant to HREZSKP	8.9 (2.5)	33.9 (10)	<0.04 (<0.01)	0.45–0.86 (0.16–0.31)
MDR-TB resistant to HREKP	1.1 (0.3)	4.2 (1.25)	<0.04 (<0.01)	0.45–0.86 (0.16–0.31)
MDR-TB resistant to HRERb	8.9 (2.5)	33.9 (10)	0.57 (0.16)	0.45–0.86 (0.16–0.31)
XDR-TB resistant to HRESKO	4.4 (1.25)	16.9 (5)	<0.04 (<0.01)	0.86 (0.31)
XDR-TB resistant to HREKO	8.9 (2.5)	16.9 (5)	<0.04 (<0.01)	0.22 (0.08)

*Almost no growth though up to 0.07 μM (0.02 μg/mL). MIC, minimum inhibitory concentration required to inhibit the growth of 90% of organisms; MICs were done in 7H9/glucose/glycerol/BSA/0.05% Tween 80 and the average of three individual measurements. Abbreviations: H, isoniazid; R, rifampin; E, ethambutol; Z, pyrazinamide; S, streptomycin; K, kanamycin; P, para-aminosalicylic acid; Rb, rifabutin; O, ofloxacin.

the simulated latent TB assay (LORA[16]) with compound **9** having the lowest MIC of 22 μM (isoniazid was >512 μM). Again, the 5,6-fused heteroaromatics were prepared in just a single synthetic step with the exception of compounds **10** and **12**.

Curious as to whether there would be potency against multi-drug resistant (MDR) and extensively drug resistant (XDR) *Mtb* strains, three compounds typical of their class—an oxazole (**2**), a thiazole (**5**) and an imidazo[1,2-*a*]pyridine (**11**), as well as the bactericidal nitroimidazole PA-824[24] were screened against a panel of clinical drug sensitive and drug resistant strains (Table 2). We were pleased to find that the potency determined in replicating *Mtb* H_{37}Rv (in the 7H9 media) was retained and at times improved against the drug sensitive, MDR- and XDR-*Mtb* strains screened for all three classes. Oxazole (**2**) had good potency in the lower micromolar range (MIC = 1–9 in μM) against these clinical strains, while the related thiazole (**5**) was significantly less potent having MIC values from 4 to 34 μM. The imidazo[1,2-*a*]pyridine (**11**) had potency better than that of PA-824, a clinical candidate, with MIC values of <0.04 μM against all of the clinical strains with the exception of one MDR strain (MIC = 0.6 μM) that is resistant to isoniazid, rifampin, ethambutol and rifabutin. Interestingly, there was a drug sensitive strain that showed resistance to PA-824 (MIC >14 μM) but was nonetheless inhibited by the three compound classes. This finding was surprising but may be explained by the high mutation frequency previously found for this nitroimidazole compound.[25] Imidazo[1,2-*a*]pyridine benzyl ester analog (**11**) was also slightly more potent against the clinical strains than that which was reported for imidazo [1,2-*a*]pyridine benzyl amide analog (**12**) which had MIC's of 0.07 to 2.3 μM (against a panel of twelve MDR- and XDR-*Mtb* strains).[8]

3. Conclusion

Herein we report ten classes of compounds with good (micromolar) to excellent (sub-micromolar) antitubercular potency, suggesting that there are new antitubercular compound classes yet to be found. Three 5,6-fused heteroaromatic scaffolds (imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine, and imidazo[1,2-*c*]pyrimidine) were prepared in just one synthetic step and each is amenable to further elaboration. In particular, the imidazo[1,2-*a*]pyridine class emerged as the most promising by having potency similar to isoniazid and PA-824 against replicating *Mtb* H_{37}Rv, clinically relevant drug sensitive, MDR- and XDR-*Mtb* strains (demonstrated by compound **11**), as well as good in vitro metabolic stability (demonstrated by compound **12**). It is our hope that the introduction of these various antitubercular compound classes will lower the barrier towards discovery of new antitubercular agents and inspire industry to join in the fight to combat TB.

Acknowledgments

This research was supported in part by the Intramural Research Program of the NIH, NIAID and by Grant 2R01AI054193 from the National Institutes of Health (NIH) and in part by intermediates provided from DAS. We would like to thank the University of Notre Dame, especially the Mass Spectrometry and Proteomics Facility (Bill Boggess, Michelle Joyce, Nonka Sevova), which is supported by the grant CHE-0741793 from the NIH. We thank Prof. Jennifer DuBois for regular and lasting scientific discussions. The excellent technical assistance of Baojie Wan and Yuehong Wang with antitubercular assays at UIC is greatly appreciated.

Supplementary data

Supplementary data (experimental procedures and analytical data for compounds (**1**–**14**) can be found as well as additional SAR, metabolism studies and a description of the assays used) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2012.02.025.

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