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Scaffold-switching: An exploration of 5,6-fused bicyclic heteroaromatics systems to afford antituberculosis activity akin to the imidazo[1,2-*a*]pyridine-3-carboxylates

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ABSTRACT

A set of 5,6-fused bicyclic heteroaromatic scaffolds were investigated for their in vitro anti-tubercular activity versus replicating and non-replicating strains of *Mycobacterium tuberculosis* (*Mtb*) in an attempt to find an alternative scaffold to the imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidines that were previously shown to have potent activity against replicating and drug resistant *Mtb*. The five new bicyclic heteroaromatic scaffolds explored in this study include a 2,6-dimethylimidazo[1,2-*b*]pyridazine-3-carboxamide (**7**), a 2,6-dimethyl-1*H*-indole-3-carboxamide (**8**), a 6-methyl-1*H*-indazole-3-carboxamide (**9**), a 7-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-3-carboxamide (**10**), and a 5,7-dimethyl-[1,2,4]triazolo [1,5-*a*]pyrimidine-2-carboxamide (**11**). Additionally, imidazo[1,2-*a*]pyridines isomers (**2** and **12**) and a homologous imidazo[1,2-*a*]pyrimidine isomer (**6**) were prepared and compared. Compounds **2** and **6** were found to be the most potent against H_{37}Rv *Mtb* (MIC's of 0.1 μM and 1.3 μM) and were inactive (MIC >128 μM) against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*. Against other non-tubercular mycobacteria strains, compounds **2** and **6** had activity against *Mycobacterium avium* (16 and 122 μM, respectively), *Mycobacterium kansasii* (4 and 19 μM, respectively), *Mycobacterium bovis BCG* (1 and 8 μM, respectively) while all the other scaffolds were inactive (>128 μM).

Tuberculosis (TB) is a serious global health disease caused by the contagious air borne pathogen *Mycobacterium tuberculosis* (*Mtb*). In 2012, 1.3 million people died of TB and 8.6 million people fell ill of the disease.[1] For the first time in 40 years, a new TB treatment (bedaquiline) was approved in 2012[2] giving new treatment options particularly with the estimated 450,000 patients infected with multidrug resistant *Mtb*.[1] Our laboratories have had an interest in inhibiting *Mtb* with small molecule heterocyclic compounds since the serendipitous discovery of a simple synthetically attractive oxazoline scaffold[3] derived from fragment screening of an iron chelating class of compounds called the mycobactins.[4] Through an intensive structure activity relationship (SAR) campaign we improved the *Mtb* potency of the oxazolines to sub-micromolar MIC's and expanded the chemical space to include various other heterocyclic scaffolds (oxazole, thiazole, imidazole, and pyridine).[5] Further SAR effort complimented by a screening agreement with Dow AgroSciences (DAS) iteratively led to the exploration of fused heterocyclic scaffolds which resulted in the discovery of a 'hit' 5,6-fused bicyclic imidazo[1,2-*a*]pyridine.[6–8] We have since reported on the advent and advancement of various imidazo[1,2-*a*]pyridine-3-carboxamides (**1**–**3**), imidazo[1,2-*a*]pyrimidine-3-carboxamide (**5** and **6**) and a benzyl 2,5,7-trimethylimidazo[1,2-*c*]pyrimidine-3-carboxylate (**7**) with excellent in vitro potency against replicating (H_{37}Rv), as well as multi- (MDR) and extensively drug (XDR) resistant *Mtb* strains (Fig. 1).[6–8] Herein, we report our efforts on 'scaffold hopping' [9–14] to identify new heterocyclic scaffolds that will potentially retain potency against H_{37}Rv *Mtb* and subsequently have improved ADME properties while also exploring new chemical space.

The scaffold switching that was performed in this study involved moving, incorporating or removing nitrogen(s) within the 5,6-fused bicyclic framework to give a set of analogs for screening (Fig. 2). Specifically, incorporating a nitrogen at the 5-position gave the imidazo[1,2-*b*]pyridazine-3-carboxamide (**7**), removing a nitrogen from the 4-position gave the 1*H*-indole-3-carboxamide

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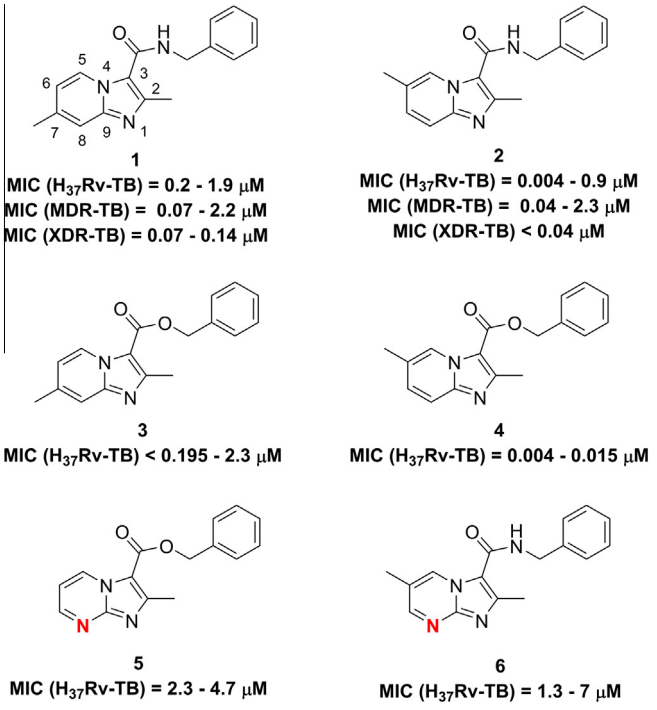
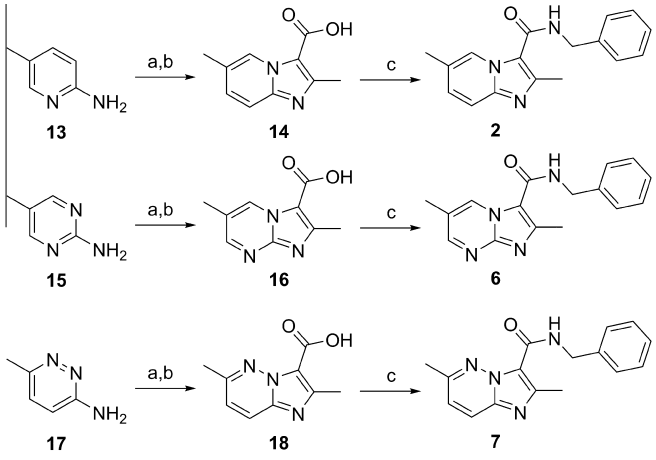


Figure 1. Previously reported imidazo[1,2-*a*]pyridines (**1**–**3**) and imidazo[1,2-*a*]pyrimidine (**5**) and two new analogs prepared for this SAR study the benzyl 2,6-dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (**4**) and the *N*-benzyl-2,6-dimethylimidazo[1,2-*a*]pyrimidine-3-carboxamide (**6**). The imidazo[1,2-*a*]pyrimidine nitrogen is denoted in red.

(**8**), moving a nitrogen from the 4-position to the 2-position gave the 1*H*-indazole-3-carboxamide (**9**), incorporating a nitrogen to the 2-position gave the triazolo[4,3-*a*]pyridine-3-carboxamide (**10**), and incorporating nitrogen at the 3 and 8-positions then moving the 3-carboxamide to the 2-position gave the triazolo[1,5-*a*]pyrimidine-2-carboxamide (**11**). We also made an isomer of compound **1** wherein we switched the adjacent 3-carboxamide with the 2-methyl group to give the imidazo[1,2-*a*]pyridine-2-carboxamide analog (**12**) (Fig. 2). These various 5,6-fused bicyclic heterocyclic scaffolds (**7**–**12**) were all searched within literature but to the best of our knowledge none of these scaffolds were found to have been screened against *Mtb* H_{37}Rv.

Syntheses of the imidazo[1,2-*a*]pyridines (**1**–**4**) and imidazo[1,2-*a*]pyrimidines (**5** and **6**) are straightforward and have been described in our previous publications[5,6,8] as well as within the Supplementary data. In brief, condensation of the appropriate



Scheme 1. Synthesis of imidazo[1,2-*a*]pyridine (**2**), imidazo[1,2-*a*]pyrimidine (**6**), and imidazo[1,2-*b*]pyridazine (**7**). Reagents and conditions: (a) (1) ethyl 2-chloroacetoacetate (for **13**) or ethyl 2-bromoacetoacetate (for **15** and **17**), DME, reflux, 48 h; (b) (1) LiOH, EtOH; (2) HCl, 56 h; (c) EDC, DMAP, benzyl amine, ACN, 16 h.

2-amino-heteroaromatic (**13** or **15**) with either ethyl 2-bromoacetoacetate (for **13**) or ethyl 2-bromoacetoacetate (for **15**) followed by saponification and acidification gave the desired imidazo[1,2-*a*]pyridine-3-carboxylic acid (**14**) or imidazo[1,2-*a*]pyrimidine-3-carboxylic acid (**15**) (Scheme 1). Both carboxylic acids were coupled with benzyl amine with EDC to give compounds **2** and **6**. In an efficient one step process, compounds **4** and **5** were prepared through condensation of the appropriate 2-amino-heteroaromatic precursor with benzyl 2-bromoacetoacetate.[5] The *N*-benzyl-2,6-dimethylimidazo[1,2-*b*]pyridazine-3-carboxamide (**7**) was synthesized in an similar method by first condensation of the 3-amino-6-methylpyridazine (**17**) with ethyl 2-bromoacetoacetate, saponification of the ethyl ester followed by acidification then coupling to the benzyl amine with EDC. By design, all of the other 5,6-fused bicyclic heteroaromatic scaffolds investigated for 'scaffold switching' were commercially available. As such, the free acids (**19**–**22**) were rapidly elaborated by EDC-mediated couplings with benzyl amine to give the desired analogs (**8**, **9**, **11** and **12**) for screening (Scheme 2). However, the *N*-benzyl-7-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-3-carboxamide (**10**) was prepared by amidation of the corresponding ethyl ester (**23**) with benzyl amine in a sealed tube at 90 °C (Scheme 2).

Table 1 summarizes the in vitro anti-TB activity of these six 'scaffold switched' 5,6-fused bicyclic heteroaromatic analogs (**6**–**12**) in two different media the glycerol–alanine–salts 'GAS'[15]

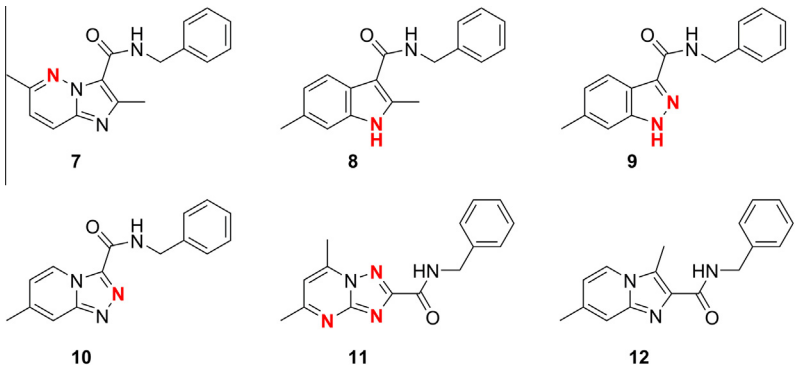


Figure 2. New 5,6-fused bicyclic heteroaromatic scaffold analogs (**7**–**12**) prepared to evaluate the effects of scaffold switching on anti-TB activity. The moving, incorporating or removing nitrogen(s) within the 5,6-fused bicyclic framework from that of the imidazo[1,2-*a*]pyridine are denoted in red.

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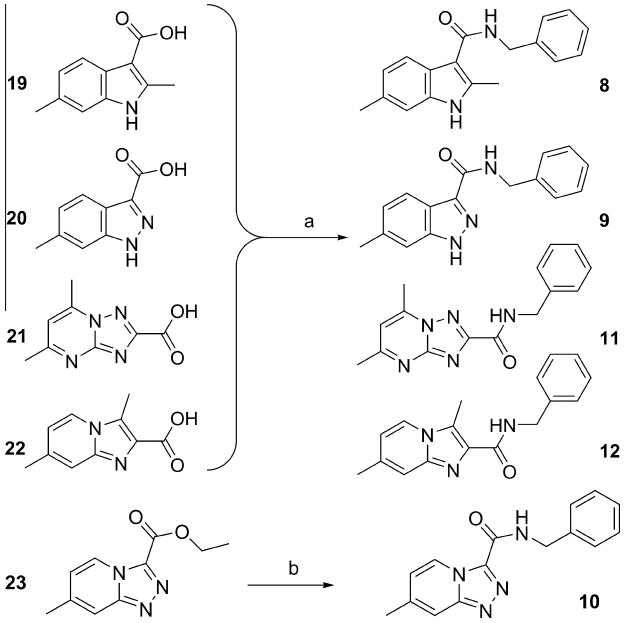
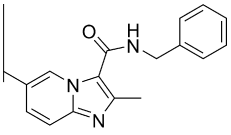
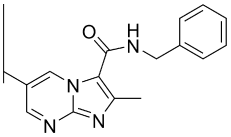
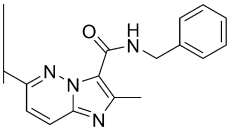
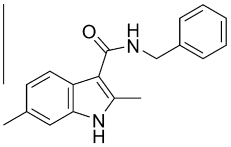
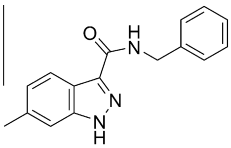


Scheme 2. Synthesis of various 5,6-fused bicyclic heterocyclic scaffold analogs (**8**–**10**) and isomeric *N*-benzyl-3,7-dimethylimidazo[1,2-*a*]pyridine-2-carboxamide (**12**). Reagents and conditions: (a) EDC, DMAP, benzyl amine, ACN, 16 h. (b) Benzyl amine, ACN, 90 °C, 56 h.

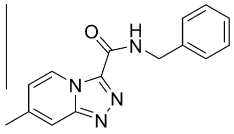
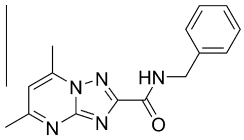
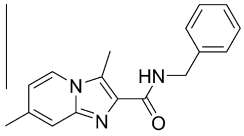
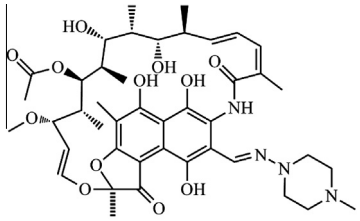
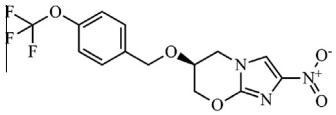
and the Middlebrook 7H12[16] and their potency against non-replicating 'latent' *Mtb* (LORA[17]) and an assessment of their toxicity by the VERO[18] assay. The most potent 5,6-fused heteroaromatics were still the imidazo[1,2-*a*]pyridine (**3**) and imidazo[1,2-*a*]pyrimidine (**6**) scaffolds with MIC's of <0.2 and 1.3 μM in the GAS media, respectively. However, it is not the imidazo[1,2-*a*]pyridine scaffold alone which imparts the majority of anti-TB activity as its isomer (**12**) was >700 times less active (MIC's of 0.1 and 70 μM, respectively). *N*-Benzyl-2,6-dimethyl-1*H*-indole-3-carboxamide (**8**), *N*-benzyl-6-methyl-1*H*-indazole-3-carboxamide (**9**) and *N*-benzyl-2,6-dimethylimidazo[1,2-*b*]pyridazine-3-carboxamide (**7**) were found to be moderately active compounds with MIC's of 44, 41 and 64 μM in the GAS media, respectively. *N*-Benzyl-7-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-3-carboxamide (**10**) and *N*-benzyl-5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-2-carboxamide (**11**) had the weakest activity with MIC's of 101 and 126 μM in the GAS media, respectively. Replacement of the 2-methyl group in compound **2** with nitrogen in compound **10** had a very negative effect (1000×) on potency (MIC of 0.1 and 101 μM, respectively). Due to the modest activity observed in most of these new scaffolds we recalculated the MIC's in terms of μg/mL and saw MIC values which are more encouraging in the GAS media and kept the same overall trends observed above (Table 1). Part of the attraction of scaffold switching is often the enhancement of ADME properties[19] which sometimes results in greater drug free fraction[20] in vivo even if analogous compounds have a lower MIC. Such ADME property enhancement was demonstrated with the imidazo[1,2-*a*]pyridines of Ramachandran et al. at AstraZeneca.[21] The SAR observed

Table 1
In vitro evaluation of compounds **2**, **6**–**12** against $H_{37}Rv$ *Mtb* in GAST media, 7H12 media and LORA as well as toxicity to VERO cells (IC_{50} in μM)

Compound	Mol Wt	Calcd *C*log*P*[a]	MIC mean ± against replicating *Mtb* in medium			LORA (μM)	VERO IC_{50} (μM)
			GAS (μM)	GAS (μg/mL)	7H12 (μM)		
 **2**	279.34	3.60	0.11 ± 0.008	0.031 ± 0.002	0.49 ± 0.004	>128	>128
 **6**	280.32	2.60	1.27 ± 0.22	0.36 ± 0.06	6.95 ± 0.15	>128	>128
 **7**	280.32	2.26	63.8 ± 1.9	17.9 ± 0.5	>128	>128	24.7
 **8**	278.35	3.73	43.8 ± 1.2	12.2 ± 0.3	>128	>128	>128
 **9**	265.31	4.02	40.8 ± 3.3	10.8 ± 0.9	>128	>128	>128

(*continued on next page*)

Table 1 (*continued*)

Compound	Mol Wt	Calcd *Clog P*[a]	MIC mean ± against replicating *Mtb* in medium			LORA (μM)	VERO IC_{50} (μM)
			GAS (μM)	GAS (μg/mL)	7H12 (μM)		
 **10**	267.31	2.85	101 ± 6.0	27 ± 1.6	>128	>128	>128
 **11**	281.31	2.20	126 ± 2.9	35.4 ± 0.8	>128	>128	>128
 **12**	279.34	3.61	70 ± 8.9	19.6 ± 2.5	>128	>128	>128
 **rifampicin**	822.95	6.04	0.11	0.09	0.06	2.6	113
 **PA-824**	359.26	2.62	0.12	0.04	0.09	4.9	>128

SD, standard deviation; MIC, minimum concentration required to inhibit growth by >90%; GAS, glycerol–alanine–salts media; 7H12, Middlebrook 7H9 broth base media with BSA, casein hydrolysate, catalase, palmitic acid; LORA, low oxygen recovery assay using the H_{37}Rv luxAB *Mtb* 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

from screening in 7H12 medium again indicated that the most potent compounds were **2** and **6** while all other compounds were inactive (MIC >128 μM). This suggests that the potency of these other 5,6-fused bicyclic heteroaromatics may be carbon source dependant, an issue that was discovered in the pyrimidine–imidazoles reported by Pethe et al.[22] or due to other medium effects.[23] The GAS medium uses glycerol–alanine–salts as the carbon source while the 7H12 medium uses palmitic acid. No activity was detected in the 'latent' *Mtb* assay (LORA, MIC >128 μM) even with compounds **2** and **6** suggesting that these compounds are only effective on replicating *Mtb*. The VERO toxicity assay also showed these compounds to be non-toxic with the exception of the *N*-benzyl-2,6-dimethylimidazo[1,2-*b*]pyridazine-3-carboxamide (**7**) which had an IC_{50} of 25 μM.

Despite varying degrees of activity observed against *Mtb* compounds **2**, **6**–**12** were all found to have a similar selectivity profile since they were inactive against representative Gram positive strains including *Staphylococcus aureus* (MIC >128 μM), Gram negative strains including *Escherichia coli* (MIC >128 μM), and the fungus, *Candida albicans* (MIC >128 μM), see Supplementary data. Additionally, when screened against various other non-tubercular mycobacteria strains only the imidazo[1,2-*a*]pyridine (**2**) and imidazo[1,2-*a*]pyrimidine (**6**) analogs had any activity and that

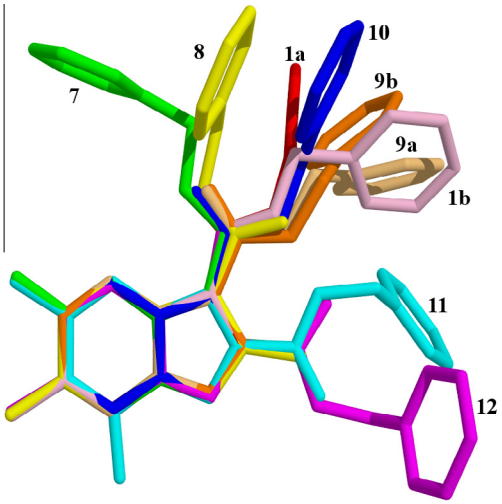


Figure 3. Overlay of the 5,6-fused bicyclic heteroaromatic scaffolds (**7**–**12**) crystal structures with potent *N*-benzyl-2,7-dimethyl-imidazo[1,2-*a*]pyridine-3-carboxamide (**1**). Legend: **1a**—red, **1b**—light pink, **7**—green, **8**—yellow, **9a**—light orange, **9b**—orange, **10**—blue, **11**—turquoise, **12**—magenta. Hydrogen atoms omitted for clarity. The nine atoms of 5,6-fused bicycle were used as template mapping atoms.

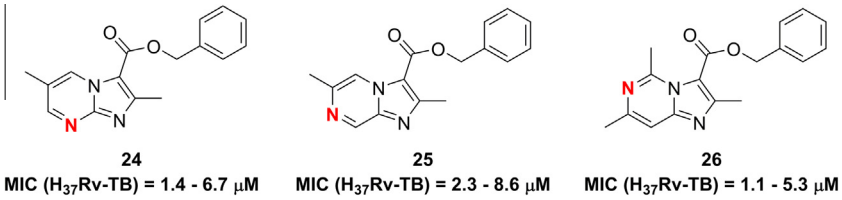


Figure 4. Positional variation of heterocyclic nitrogen.

was only against selective strains (see Supplementary data). In particular, compounds **2** and **6** inhibited *Mycobacterium avium* (MIC's of 16 and 122 μM, respectively), *Mycobacterium kansasii* (MIC's of 4 and 19 μM, respectively), *Mycobacterium bovis BCG* (MIC's of 1 and 8 μM, respectively) while all the other analogs (**7**–**12**) were inactive (>128 μM) to *Mycobacterium smegmatis*, *Mycobacterium chelonae*, *Mycobacterium marinum*, *Mycobacterium avium*, *Mycobacterium kansasii* and *Mycobacterium bovis BCG* (see Supplementary data).

It is possible that a key to understanding the varying degree of potency against *Mtb* may lie in the subtle structural or electronic effects of these various 5,6-fused heteroaromatic analogs. As such, compounds **1**, **7**–**10** were crystallized and X-ray structural studies undertaken. The resulting structures were subsequently compared with our initial imidazo[1,2-*a*]pyridine 'hit' compound **1** (Fig. 3). This information will be particularly useful once the target(s) of these compounds (presumably the QcrB gene[24]) are ultimately crystallized and these structures docked.

The overlay of the imidazo[1,2-*a*]pyridine-3-carboxamide (**1**) crystal structure with its isomeric 2-carboxamide (**12**) shows that these moieties lie in very different regions of space and this important structural difference is also reflected in their different MIC's as compound **1** is 350 times more potent than **12** (MIC's of 0.2 and 70 μM, respectively). Finally, an additional nitrogen in the 5,6-fused system did not improve activity in any scaffold other than the imidazo[1,2-*a*]pyrimidine (**6**) as the imidazo[1,2-*b*]pyridazine (**7**), triazolo[4,3-*a*]pyridine-3-carboxamide (**10**) and triazolo[1,5-*a*]pyrimidine-2-carboxamide (**11**) had the weakest activity. Curiously, in the solid state there is little correlation between the orientations of the pendant groups as can be seen in Figure 3 whereas in solution we expect them to dynamic and fluxional. It should be noted that in the solid state, compounds **2** and **9** have two crystallographically independent molecules present in the asymmetric unit. Though they are crystallographically independent, they are chemically identical. Compound **7** displays an unusual intra-molecular hydrogen-bond from the amide nitrogen to the imidazopyridine bridge nitrogen (position 4, Fig. 1). This hydrogen bond may be strong enough to persist in solution which may explain the decreased activity of this compound.

Intrigued that the imidazo[1,2-*a*]pyrimidine (**6**), which has an additional nitrogen at position 8, had retained good potency but the imidazo[1,2-*b*]pyrazine (**7**), where the additional nitrogen is at the 5 position, had poor potency, we prepared an additional compound set (**24**–**26**) to explore the effects of placing the nitrogen at the 6-(imidazo[1,2-*c*]pyrimidine) and 7-positions (imidazo[1,2-*a*]pyrazine) (Fig. 4 and expanded Fig. 8, Supplementary data). Interestingly, the MIC's of the imidazo[1,2-*c*]pyrimidine and imidazo[1,2-*a*]pyrazine compounds (**25** and **26**) were very similar to that of the analogous imidazo[1,2-*a*]pyrimidine (**24**) in that the MIC's all ranged from as low as 1–2 μM to as high as 5–9 μM when screened in either the GAS and 7H12 media for all three compounds. This suggests that placement of the nitrogen at either the 6, 7, or 8 positions retains potency much better than at the 5 position of the 5,6-fused bicyclic system, but the most potent compounds remain the imidazo[1,2-*a*]pyridines lacking any additional nitrogen as the MIC's of imidazo[1,2-*a*]pyridine compounds **3** and **4** are significantly lower than that of **24**, **25** or **26** (see Supplementary data).

In conclusion, various 5,6-fused heteroaromatic compounds were explored as potential surrogates to our previously reported imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine anti-TB scaffolds, but none of these closely related heterocycles had sub-micromolar potency. Additionally, there appears to be a great preference for imidazo[1,2-*a*]pyridine-3-carboxamide, as the imidazo[1,2-*a*]pyridine-2-carboxamides were found to be much less active. Therefore, while scaffold switching can often lead to great improvements in either potency or pharmacokinetic properties, in this study the first scaffold we discovered and reported (the imidazo[1,2-*a*]pyridine-3-carboxamides) remains the optimal scaffold for synthesis of potent 5,6-fused heteroaromatic small molecule anti-TB agents as this scaffold is the most potent and has drug-like ADME properties.[8,24,25]

Acknowledgments

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Supplementary data

CCDC 987940-987946 contains the supplementary crystallographic data for compounds (**1**, **7**–**12**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary data (experimental procedures, analytical data for compounds (**1**–**12**) and X-ray crystallization data for compounds (**1**, **7**–**12**) can be found as well as additional, SAR and description of the assays used) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.05.062.

References and notes

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