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Preparation and Evaluation of Potent Pentafluorosulfanyl-Substituted Anti-Tuberculosis Compounds

Garrett C. Moraski,*[a] Ryan Bristol,[a] Natalie Seeger,[a] Helena I. Boshoff,[b] Patricia Siu-Yee Tsang,[b] and Marvin J. Miller*[c]

The global fight to stop tuberculosis (TB) remains a great challenge, particularly with the increase in drug-resistant strains and a lack of funding to support the development of new treatments. To bolster a precarious drug pipeline, we prepared a focused panel of eight pentafluorosulfanyl (SF_5) compounds which were screened for their activity against *Mycobacterium tuberculosis* (Mtb) H37Rv in three different assay conditions and media. All eight compounds had sub-micromolar potency, and four displayed MICs <100 nM. Seven compounds were evaluated against non-replicating and mono-drug-resistant Mtb, and for their ability to inhibit Mtb within the macrophage. The greatest potency was observed against intracellular Mtb (MIC <10 nM for three compounds), which is often the most challenging to target. In general, the SF_5-bearing compounds were very similar to their CF_3 counterparts, with the major differences observed being their in vitro ADME properties. Two SF_5-bearing compounds were found to have greater protein binding than their corresponding CF_3 counterparts, but were also less metabolized in human microsomes, resulting in longer half-lives.

Introduction

One third of the human population is currently infected with tuberculosis (TB).[1] TB is one of the greatest modern global health threats, with an estimated 1.8 million deaths per year (including 0.4 million deaths resulting from TB among people with HIV).[1] As an air borne pathogen, TB is exceedingly easy to spread; consequently, 10.4 million people contracted TB in 2015 alone.[1] *Mycobacterium tuberculosis* (Mtb) is the causative bacterium of TB and can be traced back some 70000 years ago as an infectious agent among humans in Africa.[2] Mtb is increasingly becoming drug resistant to all currently used anti-TB agents with an estimated 580000 new multidrug-resistant TB (MDR-TB) cases observed in 2015 (480000 MDR-TB cases plus 100000 rifampicin-resistant TB).[1] Totally drug-resistant strains also are spreading throughout the population, perpetuating TB's dominance as a global health threat.[3]

We have previously disclosed the imidazo[1,2-*a*]pyridine-3-carboxamides (IAPs) as a promising series of anti-tubercular agents endowed with great potency,[4] tunable pharmacokinetics[5] and in vivo efficacy.[6] Other groups have also identified similar imidazo[1,2-*a*]pyridine-3-carboxamides as potent Mtb inhibitors[7] and three groups (GSK, Novartis, and Institute Pasteur Korea) have published their related hit-to-lead medicinal chemistry efforts.[8] In vivo efficacies using the acute[8a–c] and chronic[6a] murine infection models of tuberculosis have been reported for multiple imidazo[1,2-*a*]pyridine-3-carboxamides (**1**–**4**, Figure 1). With little doubt, IAPs are an attractive class for TB drug development as exemplified by Q203 (**2**), which is currently undergoing clinical development.[9]

We also previously reported that imidazo[2,1-*b*]thiazole-5-carboxamides (ITAs) have in vitro anti-tuberculosis properties very similar to that of the structurally similar IAPs, with compounds **5** and **6** sharing nanomolar potency, low toxicity, and the same target (QcrB) as the IAPs.[10] Subsequently, Lu et al.

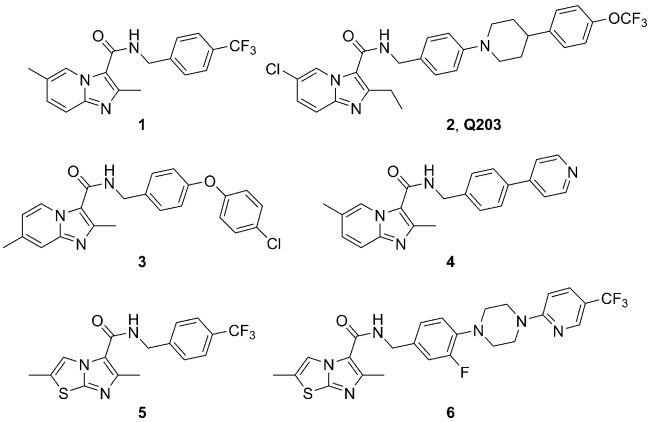


Figure 1. Previously published imidazo[1,2-*a*]pyridine-3-carboxamides **1**–**4** and imidazo[2,1-*b*]thaizole-5-carboxamides **5** and **6**.

[a] *G. C. Moraski, R. Bristol, N. Seeger*
Department of Chemistry and Biochemistry, 103 Chemistry and Biochemistry, Montana State University, Bozeman, MT, 59717 (USA)
E-mail: garrett.moraski@montana.edu

[b] *Dr. H. I. Boshoff, Dr. P. S.-Y. Tsang*
Tuberculosis Research Section, Laboratory of Clinical Infectious Diseases (LCID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), 33 North Drive, Bethesda, MD 20892 (USA)

[c] *Prof. Dr. M. J. Miller*
Department of Chemistry and Biochemistry, University of Notre Dame, 347 Nieuwland Hall of Science, Notre Dame, IN, 46556 (USA)
E-mail: mmiller1@nd.edu

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/cmdc.201700170.

profiled the ITAs as potential leads against Mtb with compounds analogous to Q203.[11] Many of the more attractive compounds from the IAP or ITA series bear either a trifluoromethyl (CF_3) or trifluoromethoxy (OCF_3) substituent. These moieties are also important components of several TB clinical candidates (pretomanid, Q203, TBA354, BTZ043, PTBZ169, Figure 2) and one recently approved TB agent (delamanid, Figure 2).

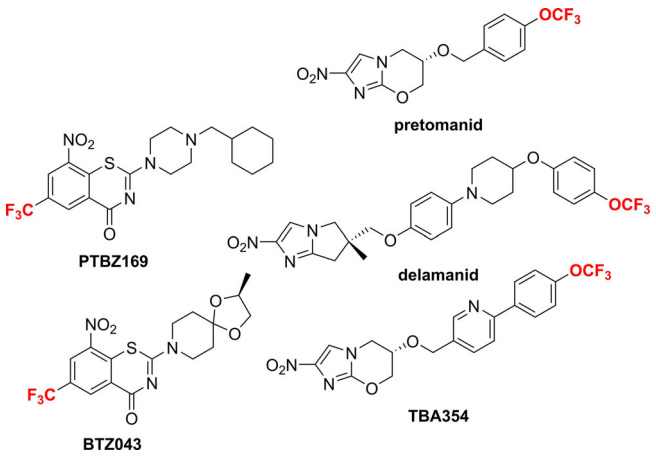


Figure 2. Trifluoromethyl- and trifluoromethoxy-substituted TB clinical candidates (pretomanid, PTBZ169, BTZ043, and TBA354) and approved drug (delamanid).

The pentafluorosulfanyl (SF_5) group, a bioisostere of the CF_3 and OCF_3 groups, has been gaining greater attention and increased reported usage within the literature.[12] The SF_5 group is large, very electronegative, lipophilic, and more resistant to acid hydrolysis than either CF_3 or OCF_3.[12] While, SF_5-bearing building blocks are typically $>5\times$ more expensive than the analogous CF_3 compounds, they are particularly attractive to medicinal chemists due to their reported effects on slowing rates of metabolism.[13] To the best of our knowledge, there are no reported TB inhibitors bearing the pentafluorosulfanyl moiety and certainly none within the IAP or ITA chemical classes reported to date. This knowledge gap attracted our attention, and herein we report the syntheses and studies of IAP and ITA anti-tubercular compounds featuring the pentafluorosulfanyl (SF_5) moiety.

Results and Discussion

Our target compounds (**13**–**20**, Figure 3) were inspired by two previously profiled trifluoromethyl containing compounds **1**[8a] and **5**,[10] chosen because of their impressive potency (MIC = 0.004 and 0.03 μM, respectively), low toxicity (IC_{50} >25 μM), and acceptable clog*P* values (4.48 and 4.46, respectively; Table 1). Syntheses of our related SF_5-bearing targets (**13**–**20**, Figure 3) began with preparation of the desired imidazo[1,2-*a*]pyridine-3-carboxylic acid (general structure, **7**) and 2,6-dimethylimidazo[2,1-*b*]thiazole-5-carboxylic acid (**8**) cores by following established literature procedures.[4, 10] Straightforward amide bond formation was accomplished by an EDC-mediated coupling with the commercially available 3-(pentafluorosulfur)-benzylamine (**9**) and 4-(pentafluorosulfur)benzylamine (**10**) (Scheme 1).

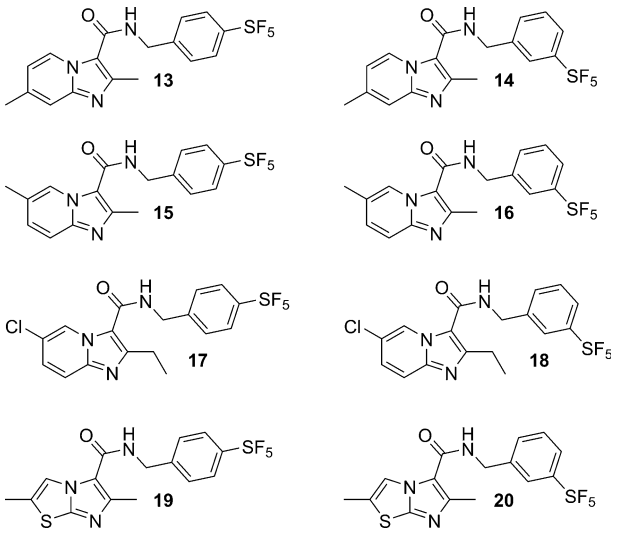


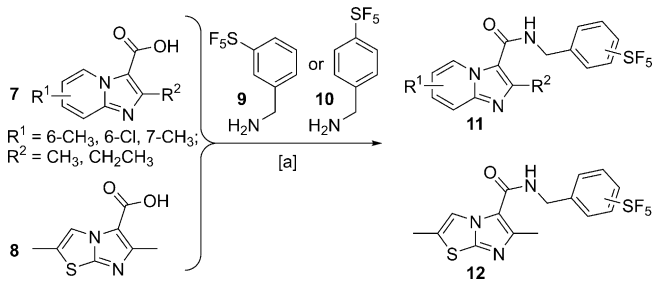
Figure 3. Eight pentafluorosulfanyl compounds (**13**–**20**) prepared for biological evaluation.

Table 1. Anti-TB activity of compounds **13**–**20** against *M. tuberculosis* strain H37Rv, Mtb *cyd* knockout strain and toxicity evaluation as compared with previously reported compounds **1**, **2**, **5** and controls *para*-aminosalicylic acid, linezolid, and rifampicin.

Compd	clog*P*[a]	MIC_{MABA} [μM][b]	MIC_{dual} [μM][c]	MIC_{cydKO} [fold Δ][d]	IC_{50} HepG2 Glu/Gal [μM][e]
1	4.48	0.004	0.009	10	>25/>25
2, Q203	7.62	0.013[f]	0.005	6.5[f]	>25/>25
5	4.46	0.034[f]	0.140	1.5[f]	>25/>25
13	4.83	0.030	0.250	15	>25/>25
14	4.83	0.230	0.650	10	>25/>25
15	4.83	0.007	0.014	10	>25/>25
16	4.83	0.310	0.200	15	>25/>25
17	5.58	0.010	0.014	19	>25/>25
18	5.58	0.310	0.280	10	>25/>25
19	4.81	0.078	0.400	15	>25/>25
20	4.81	0.630	NT[g]	10	>25/14.1
PAS[h]	1.06	0.300	NT	−2	NT/NT
LIN[i]	0.17	1.20	NT	1.5	>25/>25
RIF[j]	3.71	0.010	0.012	1	NT/NT

[a] Calculated by ChemDraw Professional 16.0 (PerkinElmer). [b] Lowest concentration of drug leading to at least 90% decrease in bacterial growth after two weeks by MABA in a GAST/Fe medium. [c] Lowest concentration of drug preventing bacterial growth in a 7H9/Tween/OADC medium readout by fluorescence and optical density after five days.[4b] [d] Lowest concentration of drug leading to at least 90% decrease in bacterial growth after two weeks in the *cyd* knockout (KO) stain in GAST/Fe medium after two weeks by MABA. [e] Cytotoxicity against mammalian HepG2 cells in glucose and galactose expressed as the concentration required to inhibit 50% growth. [f] Taken from reference [10]. [g] Not tested. [h] *para*-Aminosalicylic acid. [i] Linezolid. [j] Rifampicin. All values reported are the average of three individual measurements.

These eight SF_5-containing compounds (**13**–**20**, Figure 3) were screened for their anti-TB activity and toxicity (Table 1). Potency was determined as the minimal inhibitory concentration (MIC) to decrease the growth of *Mycobacterium tuberculo-*



Scheme 1. Syntheses of pentafluorosulfanyl compounds of Makrush structures **11** and **12**. *Reagents and conditions*: a) EDC·HCl (1.1 equiv), **9** or **10** (1 equiv), DMAP (1.1 equiv), CH_3CN, 12 h.

sis H37Rv by at least 90%. Three different assays were used: the microplate Alamar Blue assay (MABA),[7b] a dual RFU and OD readout,[4b] and a screen against the Mtb *cyd* gene knockout (*cyd*KO) strain containing a genetic deletion inactivating the second oxygen-dependent terminal oxidase, cytochrome bd oxidase[7b] (see Supporting Information for assay details). This alternative oxidase compensates for inhibition of the QcrB component of the menaquinol cytochrome *c* oxidase by compounds such as Q203. Thus, increased susceptibility of the *cyd*KO strain to inhibitors of Mtb growth suggests that the compound under investigation targets the QcrB subunit.[7b] Screens were carried out against Mtb grown in different media (GAST and 7H9), and the potency of compounds was assessed with different readouts (optical and RFU) and at different time points (14 or 5 days), thereby avoiding the pitfalls of a single screen. Toxicity was expressed as the inhibitory concentration at 50% (IC_{50}) relative to human-derived HepG2 cells grown on galactose and glucose. Compounds that show strong inhibition in galactose but not in glucose media may inhibit mammalian mitochondrial function,[14] as an off-target toxicity.

The lowest MICs of our target SF_5-containing compounds (**13**–**20**) were all sub-micromolar, with two (**15** and **17**) having potency in the low nanomolar range (MIC of 7 and 10 nM, respectively) similar to that of rifampicin (MIC of 10 nM) and related imidazo[1,2-*a*]pyridine-3-carboxamide clinical candidate Q203 (MIC of 5 nM; Table 1). All compounds showed no toxicity to the HepG2 cells in either glucose or in galactose media ($IC_{50} > 25$ μM) except for **20**, which had an IC_{50} of 14 μM in the galactose media (Table 1). When screened against the Mtb *cyd*KO strain, all compounds showed at least a 10-fold increase in potency, suggesting that QcrB is likely the target.[7b, 10] The trend of greater potency against this mutant strain was similarly observed with compounds **1** and **2** (Q203), two compounds that were reported to specifically inhibit the QcrB enzyme.[8a,c] Additionally, as expected, none of the negative controls (*para*-aminosalicylic acid (PAS), linezolid (LIN) or rifampicin (RIF) showed any significant potency enhancement in the *cyd*KO stain.

As a consequence of the excellent potency and low toxicity of seven of these compounds (**13**–**19**), their aqueous solubility, minimum bactericidal concentration (MBC)[15] and activity under low oxygen (non-replicating) conditions[16] were determined (Table 2, see Supporting Information for assay details).

Table 2. In vitro assessment of compounds **13**–**19** for solubility, activity against *M. tuberculosis* strain H37Rv under non-replicating conditions, and intracellular macrophage Mtb plus toxicity toward macrophage, as compared with previously reported compounds **1**, **2**, and **5**.

Compd	Aq. sol. [μM][a]	LORA [μM][b]	MBC [μM][c]	$MIC_{intracell.}$ [μM][d]	$THP\text{-}1_{tox.}$ [μM][e]
1	200	0.39	> 0.14	< 0.098	> 25
2, Q203	100	1.3	> 0.02	< 0.098	> 25
5	200	5.6	0.14	< 0.098	> 25
13	200	1.1	> 1.2	< 0.098	> 25
14	200	200	13	0.27	> 25
15	200	0.62	> 0.3	< 0.098	> 25
16	200	200	0.38	0.39	24
17	200	0.88	> 0.21	< 0.098	9.8
18	200	200	23	0.29	> 25
19	200	83	> 6.5	0.15	23

[a] Relative solubility of compounds determined in 7H9/Tween/OADC medium using turbidity as a measure. [b] Mtb H37Rv grown under hypoxic conditions was assessed using the low oxygen recovery assay.[16] [c] Bactericidal activity was assessed against Mtb H37Rv grown under aerobic conditions in 7H9/Tween/OADC medium. Viable cell counts were measured over three weeks of exposure to determine the rate of kill.[15] [d] Activity of compounds against intracellular bacteria was determined by measuring viability in infected THP-1 cells after three days in the presence of test compounds.[17] [e] Cytotoxicity toward eukaryotic cells was determined using the THP-1 human monocytic cell line.

In addition, because Mtb is unique in its ability to reside in macrophages, identifying compounds that can target Mtb within that intracellular compartment is of great interest.[17] To assess intracellular potency, THP-1 cells were infected with Mtb H37Rv and potency was determined along with cytotoxicity toward these macrophage-like cells.

All seven compounds (**13**–**19**) had outstanding aqueous solubility (200 μM, the highest concentration tested), greater than diethylstilbestrol (125 μM, the assay standard). Indeed, their aqueous solubility was twice that of clinical candidate Q203 (100 μM), which suffers from a very high clog*P* of 7.6 and molecular weight > 500 Da, constituting two Rule of Five violations.[18] Additionally, all these compounds could be dissolved in DMSO to prepare stock solutions at 10 mM, demonstrating good organic solubility. As with many other compounds known to inhibit QcrB, the MBC of compounds **13**, **15**, **17**, **18**, **19** and comparative compounds **1** and **2** were 10-fold higher than their MICs, classifying these compounds as bacteriostatic. However, compounds **14**, **16**, and **18** did produce a 2-log bacterial growth kill in 21 days, resulting in MBC values of 13, 0.38, and 23 μM, respectively, suggesting that these compounds, like rifampicin, are slowly bactericidal. All three compounds have a *meta*-SF_5 moiety and **16** demonstrated time dependent inhibition (see Supporting Information S1). Under anaerobic, non-replicating conditions, there was notable loss in potency relative to replicating conditions, wherein compounds **13**, **15**, **17** and **19** had MICs of 1.1, 0.62, 0.88 and 83 μM, respectively, and compounds **14**, **16**, and **18** were inactive (> 200 μM). Due to their mechanism of action, both metronidazole and rifampicin are active under anaerobic conditions (MIC of 197 and 0.02 μM, respectively). These compounds demonstrate their best activity against H37Rv Mtb-infected macrophages with

MICs <10 nM for **13**, **15**, and **17** and <400 nM for the rest, which is similar to isoniazid (MIC of 370 nM). Only compound **17** showed any notable cytotoxicity to the macrophage itself with an IC_{50} of 10 μM. However, its therapeutic window of >100 abates any real concern, particularly when compared with staurosporine (IC_{50} of 0.017 μM). This significant increase in activity against Mtb within the macrophage has been previously noted with the imidazo[1,2-*a*]pyridine-3-carboxamides,[19] but this is the first demonstration of imidazo[2,1-*b*]thiazole-5-carboxamides acting likewise.

Because drug resistance is a major issue, seven compounds (**13**–**19**) were evaluated against a panel of mono-drug-resistant Mtb strains (fluoroquinolone, isoniazid and rifampicin strains, Table 3). The activity against these five mono-drug-resistant Mtb strains was outstanding for **15** and **17** (MIC <100 nM) and impressive for **13** and **19** (MIC <650 nM). Interestingly, these compounds share a *para*-SF_5 moiety whereas the *meta*-SF_5 compounds were less potent against these drug-resistant strains (MICs ranging from 0.4 to 7 μM). When screened against two health relevant non-tuberculous mycobacteria (*Mycobacterium avium* and *Mycobacterium abscessus*) only **14** and **19** showed activity against *M. avium* (MICs of 200 μM; see Supporting Information).

To determine whether the incorporation of the SF_5 moiety could enhance ADME properties, the in vitro plasma protein binding, CaCo-2 permeability, cytochrome P450 inhibition, and microsomal stability of two of the most promising compounds (**18** and **19**) were determined for comparison with CF_3-bearing compounds **1** and **5** (Table 4). Not surprisingly, the SF_5 compounds with the higher clog*P* values also had greater protein binding, with **18** being the most protein bound at 99.9% (clog*P* of 5.6) and **1** the least at 99% (clog*P* of 4.5; Table 4). The increased protein binding of **18** over **1** is due to replacement of the 2,6-dimethyl groups of **1** with 2-ethyl and 6-Cl groups in **18**, as well as replacement of the CF_3 with the SF_5 moiety. Compounds **5** and **19** (which differ by a CF_3 or SF_5)

Table 3. In vitro assessment of compounds **13**–**19** against five drug-resistant strains of Mtb as compared with previously reported compounds **1**, **2**, and **5**.

Compd	MIC [μM]				
	FQ res[a]	INH res1[b]	INH res2[c]	RIF res1[d]	RIF res2[e]
1	0.013	0.028	0.011	0.0061	0.0058
2, Q203	0.0055	0.0065	0.0034	0.0018	0.0055
5	0.86	0.50	0.32	0.16	0.36
13	0.36	0.070	0.24	0.079	0.52
14	2.5	3.4	4.0	1.3	0.13
15	0.021	0.044	0.011	0.0060	0.016
16	2.7	3.1	2.4	0.35	7.2
17	0.083	0.051	0.021	0.0089	0.022
18	2.9	2.9	2.7	1.5	0.5
19	0.33	0.60	0.39	0.26	0.64
INH[f]	0.34	>200	>200	0.160	0.370
RIF[g]	0.043	0.027	0.013	3.2	>50
LEV[h]	91	3.97	5.83	3.43	3.83

[a] Fluoroquinolone-resistant strain derived from H37Rv Mtb with a *gyrA* mutation (D94N). [b] Isoniazid-resistant strain derived from H37Rv Mtb with a *katG* mutation (Y155*=truncation). [c] Isoniazid-resistant strain ACTCC35822. [d] Rifampicin-resistant strain derived from H37Rv Mtb with a *ropB* mutation (S522L). [e] Rifampicin-resistant strain ACTCC35838. [f] Isoniazid. [g] Rifampicin. [h] Levofloxacin.

Table 4. In vitro ADME assessment of compounds **18** and **19** as compared with previously reported compounds **1** and **5**.

	18	**19**	**1**	**5**
Plasma fraction bound [mean %][a]	99.9	99.7	99.0	99.1
Caco-2 P_{app} [10^{-6} cm s^{-1}][b]				
Mean A→B (1 h)	1.09	6.35	11.1	10.6
Mean B→A (1 h)	3.65	8.35	9.92	9.67
Mean A→B (2 h)	1.99	12.1	21.5	19.1
Mean B→A (2 h)	5.61	8.1	12.8	12.7
Efflux ratio (average)	3.16	0.988	0.745	0.788
Cytochrome P450 inhibition IC_{50} [μM][23]				
CYP2B6	8.4	>20	>20	>20
CYP2C8	14.4	>20	>20	>20
CYP2C9	10.4	14	14.7	19.2
CYP2C19	10.6	13.5	>20	18.7
CYP2D6	6.5	13.4	>20	>20
CYP3A4[c]	8.4	>20	13	>20
CYP3A4[d]	>20	>20	12.5	>20
Human liver S9 microsomes[24]				
CL [μL min^{-1} mg^{-1}]	89.7	175	167	406
$t_{1/2}$ [min]	25.8	13.3	13.8	5.7

[a] Plasma protein binding for each test compound was determined by equilibrium dialysis.[21] [b] Permeability using a Caco-2 cell monolayers in both directions.[22] For A→B permeability, test compounds were added to the apical side of the Caco-2 monolayer, and compound transport to the basal side was monitored. For B→A permeability, test compounds were added to the basal side of the Caco-2 monolayer, and compound transport to the apical side was monitored. Assays were run for 1 or 2 h in duplicate. [c] CYP3A4 drug–drug interaction (DDI) assay including midazolam.[23e] [d] CYP3A4 DDI assay including testosterone.[23e]

have a 0.6% difference in protein binding which clearly indicates that incorporation of the SF_5 does increase protein binding.

Because the ability of ChemDraw to accurately calculate log*P* values is uncertain (particularly for SF_5-bearing compounds), we place greater importance on the experimentally determined CaCo-2 values as an approximation of absorption (Table 4). Here we found that tested compounds (**19**, **1** and **5**) had apparent permeability rate coefficients (P_{app}) higher than atenolol and more like propranolol (see Supporting Information). Atenolol and propranolol have known human absorption of 50% and 90% respectively.[25] These three compounds all had lower CaCo-2 efflux ratios (<1, average of the 1 and 2 h assays) than the standards (see Supporting Information). While compound **18** had the highest efflux ratio (3.2), it was only slightly greater than propranolol (1.7) but significantly lower than talinolol (93.9, a known P-glycoprotein substrate with blood brain barrier transport). In the cytochrome P450 (CYP) panel, the SF_5-bearing compounds showed more CYP inhibition than the CF_3 compounds (**1** and **5**), but their IC_{50} values were all high ($>6\,\mu M$) relative to their MICs (<400 nM; Table 4).

Metabolic stability within human microsomes is even more important and in this evaluation the SF_5-bearing compounds (**18** and **19**) were superior to the CF_3-bearing compounds when not considering free drug fraction. For example, **18** had much lower clearance and, in turn, a longer half-life than **1** (25.8 compared with 13.8 min, respectively; Table 4). This increase in half-life imparted by the SF_5-moiety was even more pronounced between compounds **19** and **5** (13.5 relative to 5.6 min, respectively) which differ only in their *para* substitution (Table 4). Should the in vivo pharmacokinetics of the SF_5 compounds be determined, we anticipate that they could have better exposure than **1**[8a] based on their greatly increased half-lives (despite their lower free drug fraction).

Conclusions

Each of the eight pentafluorosulfanyl compounds had noticeable differences in their spectrum of activity against Mtb. Compounds **13**, **15** and **17** were the most potent against replicating, non-replicating, drug-resistant and intracellular Mtb but were not bactericidal (by MBC). Compounds **14**, **18**, and **16** were less potent in the various Mtb assays but were bactericidal, with **16** being particularly potent (MBC = 380 nM). Compound **19** was one of the only compounds that could inhibit *M. avium* (MIC = 200 μM), and **20** displayed the most cytotoxicity in Hep2G cells (IC_{50} 14 μM).

Because lipophilicity plays a critical role in medicinal chemistry, the lipophilic efficiency (LipE) values[20] of the best compounds should be considered to normalize potency relative to lipophilicity. The LipE (or ligand-lipophilicity efficiency, LLE) values for **13**, **15** and **17** (3.06, 3.51 and 2.53, respectively) were greatly improved relative to that of the TB clinical candidate Q203 (**2**, LipE = 1.23) but not as high as the first line drug treatment rifampicin (LipE = 4.63) or the CF_3-bearing analogue **1** (LipE = 3.94).

In head-to-head comparisons, the SF_5-bearing compounds **15** and **19** were very much like their analogous CF_3-bearing compounds **1** and **5.** They were only slightly less potent against replicating Mtb (7 and 4 nM for **15** vs. **1**; 78 and 34 nM for **19** vs. **5**, respectively; Table 1). Compounds **15** and **19**, like **1** and **5**, had high aqueous solubility (>200 μM), no toxicity to HepG2 cells (>25 μM), impressive intracellular potency (from <98 nM to 150 nM) and even similar MIC shifts against the *cyd*KO strain (which is suggestive of compounds having the same mechanism of action). Some differences appear when comparing their MBCs, and potency against non-replicating and drug-resistant Mtb. Interestingly, we found some compounds to be weakly (**14**, **18**) or strongly (**16** and **5**) bactericidal by MBC determination (13, 23, 0.38, 0.14 μM, respectively). This is surprising as most compounds that inhibit the QcrB subunit are bacteriostatic. We are investigating whether these compounds might inhibit an additional target within the respiration pathway to explain this difference. The ITA SF_5-bearing compounds **15** and particularly **19** were generally less potent than the CF_3 counterparts **1** and **5** when comparing their MBCs, and potency against non-replicating and drug-resistant Mtb.

A particularly important attribute of these compounds was their enhanced intracellular potency combined with a lack of toxicity to the macrophage. This is especially important considering that a major habitat for Mtb is within the host's acidic macrophage where drug penetration is difficult.

Lastly, compounds **18** and **19** had good in vitro ADME properties including longer half-lives than similar CF_3-bearing compounds (**1** and **5**). While longer in vitro half-lives do not always translate in vivo, the improved pharmacokinetics are encouraging for the further evaluation of these SF_5-containing compounds.

Experimental Section

Biology: The minimum inhibitory concentration (MIC) values were determined using *M. tuberculosis* H37Rv and *cyd*KO Mtb.[7b] Screening was done with the microplate Alamar Blue assay (MABA) according to published procedures and also by a dual readout assay in different media.[4b] For a full description of the biological assays, see Supporting Information.

Chemistry: All anhydrous solvents, reagent grade solvents for chromatography and starting materials were purchased from either Aldrich Chemical Co. (Milwaukee, WI, USA) or Fisher Scientific (Suwanee, GA, USA) unless otherwise noted. Water was distilled and purified through a Milli-Q water system (Millipore Corp., Bedford, MA, USA). General methods of purification of compounds involved the use of silica purchased from Silicycle (Quebec City, QC, Canada) and/or recrystallization. The reactions were monitored by TLC on pre-coated Merck 60 F_{254} silica gel plates and visualized using UV light (254 nm). All compounds were analyzed for purity by HPLC and characterized by ^1H and ^{13}C NMR using a Bruker 300 MHz NMR and/or a Bruker Avance III 500 MHz NMR spectrometer, equipped with a Prodigy cryoprobe and SampleJet™ automatic sample loading system. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak in the corresponding spectra; chloroform $\delta = 7.26$ ppm and $\delta = 77.23$ ppm, methanol $\delta =$ 3.31 ppm and $\delta = 49.00$ ppm and coupling constants (*J*) are report-

ed in hertz (Hz) (where s = singlet, bs = broad singlet, d = doublet, dd = double doublet, bd = broad doublet, ddd = double doublet of doublet, t = triplet, tt = triple triplet, q = quartet, m = multiplet; a = apparent) and analyzed using MestReC NMR data processing. ^{19}F NMR spectra were run without a standard and are uncorrected. Mass spectra values are reported as *m/z*. Melting points were measured on a Thomas–Hoover capillary melting point apparatus and are uncorrected. HPLC HRMS analyses were carried out on a Dionex RSLC (UPLC) System with a Bruker MicroTOF-Q II, using a Dionex Acclaim RSLC 120 C_{18}, 2.2 um, 120 Å, 2.1×100 mm column run at 40 °C. Mobile phases: HPLC-grade acetonitrile with 0.1% formic acid at a flow rate of 0.5 mL min^{-1} and UV detection at 254 nm. A gradient for a 20 min run was from 0.0 to 2.0 min B = 10%; at 18.0 min B = 100%, at 18.1 min B = 10%, and the run finished at 20 min with B = 10%; flow rate: 0.4 mL min^{-1}. High-performance liquid chromatography analyses for checking purity (> 95% area) of compounds were performed on Dionex HPLC as described above and by HRMS. All final compounds were found to have > 95% purity by HPLC unless otherwise noted. All reactions were conducted under argon unless otherwise noted. Solvents were removed in vacuo on a rotary evaporator. Abbreviations: *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl); 4-(dimethylamino)pyridine (DMAP).

2,7-Dimethyl-*N*-(4-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (13): 2,7-Dimethylimidazo[1,2-*a*]pyridine-3-carboxylic acid[4a] (CAS: 81438-53-1, 150 mg, 0.79 mmol) was dissolved in 7 mL of dry CH_3CN and then EDC·HCl (181 mg, 0.95 mmol) was added and the reaction stirred for 10 min at room temperature in a round-bottom flask under argon. Next 4-(pentafluorosulfur)benzylamine (CAS: 771573-35-4, 202 mg, 0.87 mmol) and DMAP (116 mg, 0.95 mmol) were added sequentially and the reaction was stirred for 12 h under argon. The reaction mixture was concentrated in vacuo. The resulting residue was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (2×), 5% aqueous acetic acid solution (2×), brine and then dried over sodium sulfate. The drying agent was removed by filtration and organics were concentrated in vacuo. The resulting residue was purified by recrystallization with hot CH_3CN to give 180 mg of 2,7-dimethyl-*N*-(4-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (**13**, 56% yield) as a white solid; mp: 186–187 °C; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.20 (d, J = 7.1 Hz, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.40 (s, 1H), 6.77 (d, J = 7.1 Hz, 1H), 6.51 (bs, 1H, NH_2), 4.72 (d, J = 5.9 Hz, 2H), 2.69 (s, 3H), 2.41 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = 84.4 (penta, J = 150.0 Hz, 1F), 63.0 ppm (d, J = 150.07 Hz, 4F); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 175.33, 161.38, 153.14 (penta, J = 17.3 Hz), 145.55, 144.20, 142.58, 140.08, 127.90, 127.31, 126.51 (penta, J = 4.6 Hz), 116.66, 114.38, 42.77, 21.33, 15.81 ppm; HRMS (EI), $[M+1]^+$ calcd for $C_{17}H_{17}F_5N_3OS$, 406.1007, found 406.0969; HPLC t_R = 9.2 min gradient B, > 99% pure.

2,7-Dimethyl-*N*-(3-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (14): 2,7-Dimethylimidazo[1,2-*a*]pyridine-3-carboxylic acid[4a] (CAS: 81438-53-1, 100 mg, 0.52 mmol) was dissolved in 5 mL of dry CH_3CN and then EDC·HCl (82 mg, 0.57 mmol) was added and the reaction stirred at room temperature for 10 min in a round-bottom flask under argon. 3-(Pentafluorosulfur)benzylamine (CAS: 771573-34-3, 134 mg, 0.57 mmol) and DMAP (77 mg, 0.63 mmol) were added sequentially and the reaction was stirred for 12 h under argon. The reaction mixture was concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (2x), 5% aqueous acetic acid solution (2×), brine and then dried over sodium sulfate. The drying agent was removed by filtration and the organic solvent was concentrated in vacuo. The resulting residue was purified by recrystallization with hot CH_3CN to give 111 mg of 2,7-dimethyl-*N*-(3-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (**14**, 52% yield) as a white solid; mp: 149–150 °C; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.25 (d, J = 7.1 Hz, 1H), 7.77 (s, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.33 (s, 1H), 7.59–7.41 (m, 2H), 6.78 (d, J = 7.1, 1H), 6.32 (bs, 1H, NH_2), 4.75 (d, J = 6.0 Hz, 2H), 2.68 (s, 3H), 2.42 ppm (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = 84.4 (penta, J = 149.5 Hz, 1F), 62.9 ppm (d, J = 150.00 Hz, 4F); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.02, 154.41 (penta, J = 17.2 Hz), 144.90, 143.20, 140.88, 139.95, 131.07, 129.28, 127.57, 125.42 (penta, J = 4.6 Hz), 125.21 (penta, J = 4.6 Hz), 117.05, 115.44, 114.11, 43.09, 21.57, 15.86 ppm; HRMS (EI), $[M+1]^+$ calcd for $C_{17}H_{17}F_5N_3OS$, 406.1007, found 406.0999; HPLC t_R = 8.9–8.9 min gradient B, 98% pure.

2,6-Dimethyl-*N*-(4-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (15): 2,6-Dimethylimidazo[1,2-*a*]pyridine-3-carboxylic[4c] (CAS: 81438-52-0, 150 mg, 0.79 mmol) was dissolved in 7 mL of dry CH_3CN and then EDC·HCl (181 mg, 0.95 mmol) was added and the reaction was stirred at room temperature for 10 min in a round-bottom flask under argon. 4-(Pentafluorosulfur)benzylamine (CAS: 771573-35-4, 202 mg, 0.87 mmol) and DMAP (116 mg, 0.95 mmol) were added sequentially and the reaction was stirred for 12 h under argon. The reaction mixture was concentrated in vacuo. The resulting residue was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (2×), 5% aqueous acetic acid solution (2×), brine and then dried over sodium sulfate. The drying agent was removed by filtration and the organic solvent was concentrated in vacuo. The resulting residue was purified by recrystallization with hot CH_3CN to give 180 mg of 2,6-dimethyl-*N*-(4-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (**15**, 56% yield) as a white solid. mp: 176–177 °C; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.21 (s, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.2 Hz, 1H), 6.33 (bs, 1H, NH_2), 4.73 (d, J = 5.9 Hz, 2H), 2.69 (s, 3H), 2.34 ppm (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = 84.5 (penta, J = 150.0 Hz, 1F), 63.0 ppm (d, J = 150.05 Hz, 4F); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.02, 154.41 (penta, J = 17.0 Hz), 144.90, 139.95, 131.07, 129.28, 127.57, 125.42 (penta, J = 4.7 Hz), 125.23 (penta, J = 4.7 Hz), 117.05, 115.44, 114.11, 43.09, 21.57, 15.86 ppm; HRMS (EI), $[M+1]^+$ calcd for $C_{17}H_{17}F_5N_3OS$, 406.1007, found 406.1010; HPLC t_R = 9.3 min gradient B, > 99% pure.

2,6-Dimethyl-*N*-(3-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (16): 2,6-Dimethylimidazo[1,2-*a*]pyridine-3-carboxylic acid[4c] (CAS: 81438-52-0, 100 mg, 0.52 mmol) was dissolved in 5 mL of dry CH_3CN and then EDC·HCl (82 mg, 0.57 mmol) was added and the reaction stirred for 10 min at room temperature in a round-bottom flask under argon. 3-(Pentafluorosulfur)benzylamine (CAS: 771573-34-3, 134 mg, 0.57 mmol) and DMAP (77 mg, 0.63 mmol) were added sequentially and the reaction was stirred for 12 h under argon. The reaction mixture was concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (2×), 5% aqueous acetic acid solution (2×), brine and then dried over sodium sulfate. The drying agent was removed by filtration and organic solvent was concentrated in vacuo. The resulting residue was purified by recrystallization with hot CH_3CN to give 75 mg of 2,6-dimethyl-*N*-(3-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (**16**, 35% yield) as a white solid; mp: 143–144 °C; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.19 (s, 1H), 7.77 (s, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.60–7.45 (m, 3H), 7.21 (d, J = 9.1 Hz, 1H), 6.34 (bs, 1H, NH_2), 4.76 (d, J = 6.0 Hz, 2H), 2.70 (s, 3H), 2.36 ppm (s, 3H);

^{19}F NMR (282 MHz, $CDCl_3$) $\delta = 84.4$ (penta, $J = 149.5$ Hz, 1F), 62.3 ppm (d, $J = 150.00$ Hz, 4F); ^{13}C NMR (126 MHz, $CDCl_3$) $\delta =$ 160.96 154.42 (penta, $J = 17.3$ Hz), 143.15, 142.64, 139.90, 132.15, 131.05, 129.25, 126.28, 125.41 (penta, $J = 4.6$ Hz), 125.22 (penta, $J =$ 4.6 Hz), 124.80, 115.71, 114.59, 43.62, 18.49, 15.73 ppm; HRMS (EI), $[M+1]^+$ calcd for $C_{17}H_{17}F_5N_3OS$, 406.1007, found 406.1004; HPLC $t_R = 9.2$–9.3 min gradient B, > 99% pure.

6-Chloro-2-ethyl-*N*-(4-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (17): 6-Chloro-2-ethylimidazo[1,2-*a*]pyridine-3-carboxylic acid[8e] (CAS: 1216142-18-5, 150 mg, 0.66 mmol) was dissolved in 7 mL of dry CH_3CN and then EDC·HCl (153 mg, 0.80 mmol) was added and reaction stirred at room temperature for 10 min in a round-bottom flask under argon. 4-(Pentafluorosulfur)benzylamine (CAS: 771573-35-4, 171 mg, 0.73 mmol) and DMAP (98 mg, 0.80 mmol) were added sequentially and the reaction was stirred for 12 h under argon. The reaction was concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (2×), 5% aqueous acetic acid solution (2×), brine and then dried over sodium sulfate. The drying agent was removed by filtration and the organic solvent was concentrated in vacuo. The resulting residue was purified by silica gel column (CH_2Cl_2/EtOAc solvent gradient) or by recrystallization with hot CH_3CN to give 115 mg of 6-chloro-2-ethyl-*N*-(4-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (**17**, 39% yield) as a white solid. mp: 191–192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 9.50$ (s, 1H), 7.75 (d, $J = 8.6$ Hz, 2H), 7.55 (d, $J = 9.5$ Hz, 1H), 7.46 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 9.5$ Hz, 1H), 6.30 (bs, 1H, NH_2), 4.74 (d, $J = 5.9$ Hz, 2H), 3.01 (q, $J = 7.5$, 7.5, 7.5 Hz, 2H), 1.43 ppm (t, $J = 7.5$, 7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) $\delta =$ 84.4 (penta, $J = 150.1$ Hz, 1F), 63.0 ppm (d, $J = 150.1$ Hz, 4F); ^{13}C NMR (126 MHz, $CDCl_3$) $\delta = 161.12$, 153.28 (penta, $J = 17.4$ Hz), 144.08, 142.22, 129.20, 127.88, 126.64 (penta, $J = 4.7$ Hz), 126.38, 122.33, 116.61, 115.11, 42.89, 23.47, 13.28 ppm; HRMS (EI), $[M+1]^+$ calcd for $C_{17}H_{16}ClF_5N_3OS$, 440.0541, found 440.0574; HPLC $t_R =$ 12.8–12.9 min gradient B, > 99% pure.

6-Chloro-2-ethyl-*N*-(3-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (18): 6-Chloro-2-ethylimidazo[1,2-*a*]pyridine-3-carboxylic acid[8e] (CAS: 1216142-18-5, 100 mg, 0.45 mmol) was dissolved in 5 mL of dry CH_3CN and then EDC·HCl (69 mg, 0.45 mmol) was added and reaction was stirred at room temperature for 10 min in a round-bottom flask under argon. 3-(Pentafluorosulfur)benzylamine (CAS: 771573-34-3, 114 mg, 0.49 mmol) and DMAP (65 mg, 0.53 mmol) were added sequentially and the reaction was stirred for 12 h under argon. The reaction mixture was concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (2×), 5% aqueous acetic acid solution (2×), brine and then dried over sodium sulfate. The drying agent was removed by filtration and the organic solvent was concentrated in vacuo. The resulting residue was purified by recrystallization with hot CH_3CN to give 71 mg of 6-chloro-2-ethyl-*N*-(3-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide (**18**, 36% yield) as a white solid; mp: 146–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 9.49$ (s, 1H), 7.77 (s, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.63–7.43 (m, 4H), 7.33 (d, $J = 9.4$ Hz, 1H), 6.36 (bs, 1H, NH_2), 4.76 (d, $J = 5.9$ Hz, 2H), 3.02 (q, $J = 7.5$, 7.5, 7.5 Hz, 2H), 1.42 ppm (t, $J = 7.5$, 7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) $\delta = 84.6$ (penta, $J = 149.8$ Hz, 1F), 62.8 ppm (d, $J = 150.00$ Hz, 4F); ^{13}C NMR (126 MHz, $CDCl_3$) $\delta = 160.37$, 154.43 (penta, $J =$ 17.2 Hz), 144.11, 148.43, 142.47, 139.43, 131.12, 130.59, 129.36, 126.46, 125.38 (penta, $J = 4.7$ Hz), 123.33, 118.03, 115.66, 43.30, 22.68, 13.30 ppm; HRMS (EI), $[M+1]^+$ calcd for $C_{17}H_{16}ClF_5N_3OS$, 440.0541, found 440.0570; HPLC $t_R = 12.2$ min gradient B, > 99% pure.

2,6-Dimethyl-*N*-(4-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[2,1-*b*]thiazole-5-carboxamide (19): 2,6-Dimethylimidazo[2,1-*b*]thiazole-5-carboxylic acid[10] (150 mg, 0.76 mmol) was dissolved in 7 mL of dry CH_3CN and then EDC·HCl (196 mg, 0.92 mmol) was added and the reaction was stirred at room temperature for 10 min in a round-bottom flask under argon. Next 4-(pentafluorosulfur)benzylamine (CAS: 771573-35-4, 196 mg, 0.84 mmol) and DMAP (112 mg, 0.92 mmol) were added sequentially and the reaction was stirred for 12 h under argon. The reaction was concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (2×), 5% aqueous acetic acid solution (2×), brine and then dried over sodium sulfate. The drying agent was removed by filtration and the organic solvent was concentrated in vacuo. The resulting residue was purified by recrystallization with hot CH_3CN to give 131 mg of 2,6-dimethyl-*N*-(4-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[2,1-b]thiazole-5-carboxamide (**19**, 42% yield) as a white solid. mp: 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.96$ (s, 1H), 7.73 (d, $J = 8.7$ Hz, 2H), 7.44 (d, $J = 8.3$ Hz, 2H), 6.17 (bs, 1H, NH_2), 4.69 (d, $J = 6.0$ Hz, 2H), 2.59 (s, 3H), 2.42 ppm (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) $\delta = 84.5$ (penta, $J =$ 150.1 Hz, 1F), 63.0 ppm (d, $J = 150.04$ Hz, 4F); ^{13}C NMR (126 MHz, $CDCl_3$) $\delta = 160.21$, 153.20 (penta, $J = 17.4$ Hz), 149.47, 142.82, 142.47, 128.01, 127.94, 127.78, 126.56 (penta, $J = 4.7$ Hz), 118.44, 118.34, 117.70, 42.95, 15.99, 14.04 ppm; HRMS (EI), $[M+1]^+$ calcd for $C_{15}H_{15}F_5N_3OS_2$, 412.0571, found 412.0519; HPLC $t_R = 11.8$ min gradient B, 99% pure.

2,6-Dimethyl-*N*-(3-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[2,1-*b*]thiazole-5-carboxamide (20): 2,6-Dimethylimidazo[2,1-*b*]thiazole-5-carboxylic acid acid[10] (100 mg, 0.51 mmol) was dissolved in 5 mL of dry CH_3CN and then EDC·HCl (72 mg, 0.46 mmol) was added and the reaction was stirred at room temperature for 10 min in a round-bottom flask under argon. 3-(Pentafluorosulfur)benzylamine (CAS: 771573-34-3, 118 mg, 0.51 mmol) and DMAP (68 mg, 0.55 mmol) were added sequentially and the reaction was stirred for 12 h under argon. The reaction was concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (2×), 5% aqueous acetic acid solution (2×), brine and then dried over sodium sulfate. The drying agent was removed by filtration and the organic solvent was concentrated in vacuo. The resulting residue was purified by recrystallization with hot CH_3CN to give 109 mg of 2,6-dimethyl-*N*-(3-(pentafluoro-λ^6-sulfanyl)benzyl)imidazo[2,1-*b*]thiazole-5-carboxamide (**20**, 57% yield) as a white solid; mp: 123–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta =$ 7.97 (s, 1H), 7.74 (s, 1H), 7.69 (d, $J = 8.2$ Hz, 1H), 7.55–7.43 (m, 2H), 6.07 (bs, 1H, NH_2), 4.72 (d, $J = 6.0$ Hz, 2H), 2.59 (s, 3H), 2.44 ppm (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) $\delta = 84.6$ (penta, $J = 150.0$ Hz, 1F), 63.1 ppm (d, $J = 150.03$ Hz, 4F); ^{13}C NMR (126 MHz, $CDCl_3$) $\delta =$ 159.56, 154.45 (penta, $J = 17.0$ Hz), 144.09, 143.39, 139.56, 131.81, 131.12, 126.45, 125.39 (penta, $J = 4.6$ Hz), 123.37, 118.05, 115.72, 43.23, 22.72, 13.31 ppm; HRMS (EI), $[M+1]^+$ calcd for $C_{15}H_{15}F_5N_3OS_2$, 412.0571, found 412.0533; HPLC $t_R = 11.7$–11.8 min gradient B, 99% pure.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: drug resistance · imidazo[1,2-*a*]pyridines · imidazo[2,1-*b*]thiazoles · *Mycobacterium tuberculosis* · pentafluorosulfanyl

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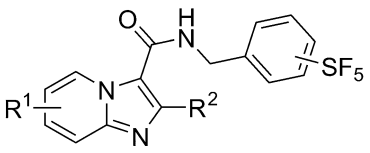
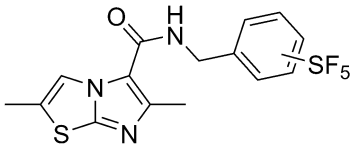
FULL PAPERS

A focused set of pentafluorosulfanyl (SF_5) compounds were prepared and evaluated against *Mycobacterium tuberculosis* (Mtb) H37Rv in multiple assays. Overall, the compounds demonstrated great potency against replicating Mtb, particularly within the macrophage. However, in other evaluations (non-replicating Mtb, drug-resistant Mtb, minimum bactericidal concentration, and toxicity) these compounds began to show differences between each other.



13-17; MIC_{MABA}= 7 – 310 nM



19, 20; MIC_{MABA}= 78 – 630 nM

G. C. Moraski, R. Bristol, N. Seeger, H. I. Boshoff, P. S.-Y. Tsang, M. J. Miller**

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Preparation and Evaluation of Potent Pentafluorosulfanyl-Substituted Anti-Tuberculosis Compounds