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Letter

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Spirocyclic and Bicyclic 8-Nitrobenzothiazinones for Tuberculosis with Improved Physicochemical and Pharmacokinetic Properties

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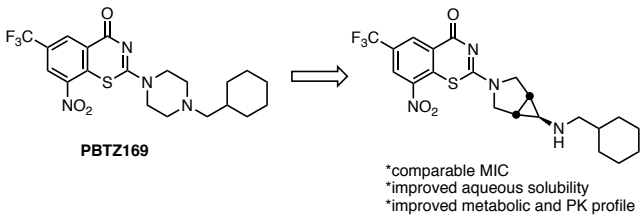


Supporting Information Placeholder

ABSTRACT: 8-Nitrobenzothiazinones (BTZs) typified by the second-generation analogue PBTZ169 are a new class of antitubercular agents. The activity of BTZs and lipophilicity are tightly coupled since the molecular target DprE1 is located in the mycobacterial cell envelope. A series of analogues was designed to address the notorious insolubility of the BTZs while preserving the required lipophilicity. This was accomplished by decreasing the molecular planarity and symmetry through bioisosteric replacement of the piperazine moiety of PBTZ169 with spirocyclic and bicyclic diamines. Several promising compounds with improved aqueous solubilities were identified with potent antitubercular activity. Compound **5** was identified as the most promising candidate based on its excellent antitubercular activity (MIC of 32 nM), more than 1000-fold improvement in solubility, 2-fold lower clearance in mouse and human microsomes relative to PBTZ169, and promising pharmacokinetic parameters.

Keywords: benzothiazinone, tuberculosis, antitubercular, spirocyclic

Tuberculosis (TB) is an infectious disease mainly caused by members of *Mycobacterium tuberculosis* (*Mtb*) complex.[1] In 2017, more than 10 million people were actively infected by TB and approximately 1.6 succumbed to the disease. The current treatment regimen for drug-susceptible TB involves 6–9 months of the first-line TB drugs isoniazid, rifampicin, ethambutol, and pyrazinamide. The lengthy treatment course is necessary to eliminate the various bacterial subpopulations that exhibit differential drug sensitivity including dormant bacilli which are phenotypically drug resistant. Consequently, the emergence of drug resistance TB (DR-TB) caused by either multidrug or extensively drug resistant *Mtb* strains represents a global health crisis.

The 8-nitrobenzothiazinones (BTZs) represent an entirely new class of compounds with a fascinating history and mechanism of action first identified by Ute Möllmann as biotransformation products of dithiocarbamates, which in turn had been initially synthesized by Vadim Makarov.[2, 3] The benzothiazinones are mechanism-based inhibitors of the flavoenzyme DprE1 and are bioactivated by the dihydroflavin cofactor $FADH_2$ through reduction of the C-8 nitro group to a nitroso intermediate that covalently reacts with Cys387 in the enzyme active site to form a semi-mercaptal enzyme-inhibitor adduct (**Figure 1**).[4] With support from the NM4TB consortium led by Stewart Cole, Makarov developed a concise synthesis of the BTZs and carried out an extensive SAR campaign culminating in the synthesis of the second-generation candidate PBTZ169.[5] This promising compound possesses extraordinary whole-cell activity with a minimum inhibitory concentration (MIC) of ~ 1 nM against drug-sensitive (DS) and drug-resistant (DR) *Mtb* strains, displays strong synergism with other TB drugs, is potently bactericidal, and significantly shortens therapy in a TB mouse relapse model.[5] While impressive, PBTZ169 does have liabilities emanating from its extremely poor solubility (<0.01 μg/mL at pH 7.4 in 1× PBS buffer at 37 °C) that portend poor membrane penetration. This may affect oral bioavailability (F) and volume of distribution (V_d), neither of which have been

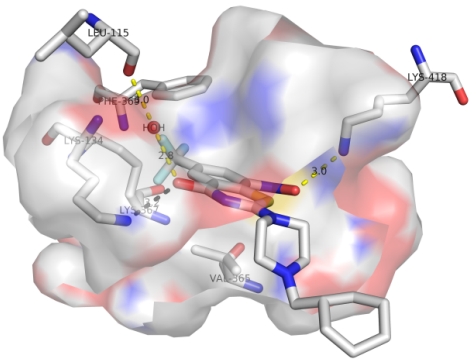


Figure 1. Binding mode of PBTZ169 to the target DprE1 (PDB code: 4NCR).

The structure-activity relationships (SAR) of the benzothiazinones reveal a strong positive correlation between

lipophilicity and activity, consistent with location of the target DprE1, which is found in the periplasmic space of the mycobacterial cell wall.[6] Consequently, introduction of polar functional groups to modulate solubility is unlikely to be successful without adversely impacting potency. Disruption of molecular symmetry and planarity is an alternate strategy to improve aqueous solubility.[7,8] The 6-trifluormethyl-8-nitrobenzothiazinone heterocycle must be strictly maintained and even subtle alterations obliterate activity providing limited opportunities to disrupt planarity in this portion of the molecule. On the other hand the piperazine substituent appears substantially more tolerant to modification.[5] Indeed, many structural modifications at position 2 of BTZ core have been reported.[4,5,9-18] Based on these SAR requirements, we initially elected to replace the central piperazine moiety with a wide variety of bioisosteric spirocyclic and bicyclic diamines that preserve the overall lipophilicity, but disrupt the molecular symmetry and/or planarity of PBTZ169 (Figure 2).

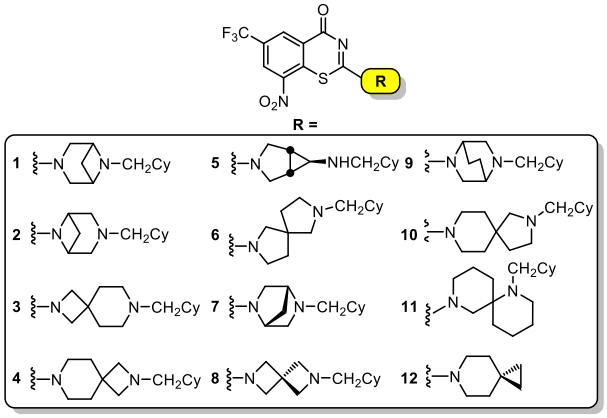
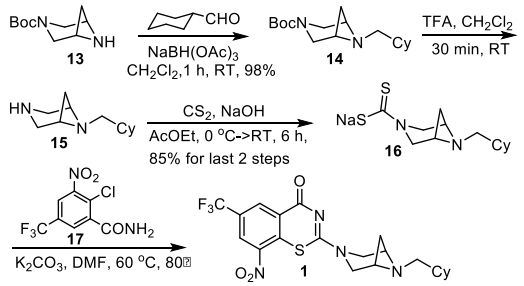


Figure 2. Proposed analogues in this study containing bioisosteric replacements of the piperazine moiety.

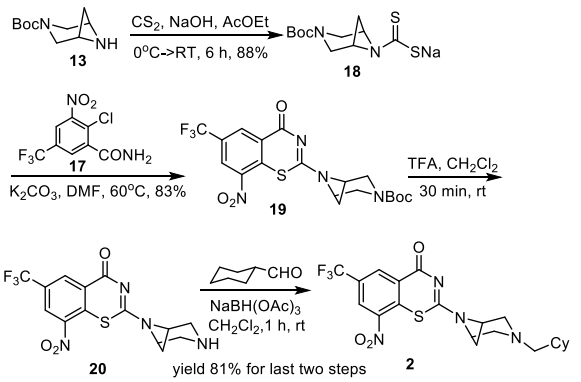
We initially conceived of a series of closely related bicyclic and spirocyclic analogues to reduce planarity. A representative synthesis is illustrated in Scheme 1 for compound **1**. Reductive amination[19] of Boc-3,6-diazabicyclo[3.1.1]heptane **13** and cyclohexane carboxaldehyde with $NaBH(OAc)_3$ afforded **14** that was subsequently deprotected by trifluoroacetic acid to furnish **15**. Reaction with carbon disulfide in aqueous NaOH yielded **16.**[20] Nucleophilic aromatic substitution of **16** with 2-chlorobenzamide derivative **17** followed by intramolecular cyclization provided **1** in 80% yield that was purified by silica gel chromatography.[13] Consistent with a decrease in planarity, the melting point of **1** (mp 126–128 °C) was significantly decreased compared to PBTZ169 (mp 176–178 °C).[5] Compounds **3–4** and **6–12** were prepared in analogous fashion as described in the Supporting Information.

Scheme 1. Representative Synthesis of Analog **1.**



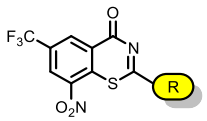
For compound **2** and **5** we employed an alternate synthetic route due to low yields in the final cyclization step with **17**. Boc-3,6-diazabicyclo[3.1.1]heptane **13** was elaborated to **18** via reaction with carbon disulfide in aqueous NaOH.[2] Nucleophilic aromatic substation of **18** with **17** followed by cyclization smoothly provided **19**. TFA-mediated deprotection of the Boc group furnished **20** and reduction amination with cyclohexane carboxaldehyde yielded **2** in 81% yield. Spirocyclic analogue **2** was recrystallized (mp 122–124 °C) from EtOH–EtOAc (1:1, *v/v*). Analogue **5** was prepared analogously as described in the Supporting Information.

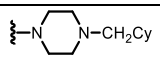
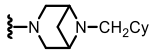
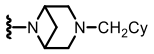
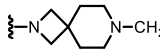
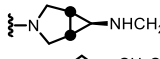
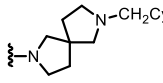
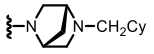
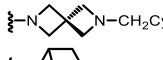
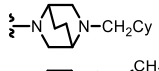
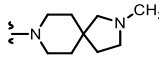
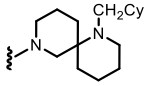
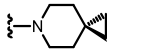
Scheme 2. Representative Synthesis of Piperazine Analog **2**.



All compounds were evaluated for whole-cell activity against *M. tuberculosis* strains H37Rv, CDC1551, and Erdrman in 7H9 medium to determine minimum inhibitory concentrations (MICs) that resulted in complete inhibition of observable growth. The MICs were nearly identical for all *M. tuberculosis* strains and MIC data for strain H37Rv are shown in Table 1 (MICs for CDC1551 and Erdman were equal to or 4-fold lower than H37Rv, Table S2). The MICs ranged by nearly two-orders of magnitude from 16–1024 nM. To track physicochemical properties, we calculated the lipophilic ligand efficiency (LLE) and logP of each analogue. Spirocycle **12** is the most potent analogue with an MIC of 16 nM followed by compounds **5** and **9** with MICs of 32 nM and compound **7** whose MIC is 64 nM. Among these analogues, only **12** has an improved LLE relative to PBTZ169 due to an overall decrease in clogP, whereas **5**, **7**, and **9** all have lower LLEs primarily attributed to their decreased activity. Examination of the structure–activity relationships (SAR) reveal analogues containing conservative modifications to the piperazine nucleus are generally better tolerated, whereas more extreme modifications resulted in substantial decrease in activity. Thus, the 4,4- 4,6- 5,5-, 5,6- and 6,6-spirocycles in **3**, **4**, **6**, **8**, **10** and **11** were poorly tolerated resulting in nearly 64–512-fold losses in potencies compared to PBTZ169. Based on the outstanding whole-cell activities, we selected compounds **5**, **7**, **9** and **12** for further evaluation.

Table 1. MIC_{90} and clogP of **1–12.**



Compounds	R	MIC (nM)	clogP[a]	LLE[b]
PBTZ169		2	4.6	4.1
1		128	4.4	2.5
2		128	4.4	2.5
3		1024	4.3	1.7
4		512	4.3	2.0
5		32	4.1	3.4
6		256	4.7	1.9
7		64	4.4	2.8
8		256	3.9	2.7
9		32	5.0	2.5
10		128	4.9	2.0
11		1024	5.4	0.6
12		16	3.2	4.6

[a]Calculated $log_{10}P$ (clogP) was determined by ChemDraw Professional version 16.0; [b]Lipophilic ligand efficiency (LLE) was calculated from the equation: LLE= $log_{10}MIC$-$clog_{10}P$.

The objectives of our study were to improve aqueous solubility, thus selected compounds **5**, **7**, **9** and **12** were examined for their kinetic solubility in phosphate-buffered saline pH 7.4 by LC-MS/MS and the results are shown in Table 2 along with the experimentally determined melting points (mp) and total polar surface areas (tPSA). Compound **7** displayed the highest solubility (14.6 µg/mL) that was 1600-fold greater than PBTZ169 while **5**, **9**, and **12** also showed marked improvements in solubility. The solubility did not show obvious correlation with the molecular descriptor tPSA or melting points.

Table 2. Solubility, melting points and tPSA of **5**,**7**,**9** and **12**.

Compounds	Solubility (µg/mL)	mp (°C)	tPSA
PBTZ169	$< 1 \times 10^{-2}$	183–185	87.7
5	4.8 ± 0	110–112	96.5
7	14.6 ± 0.1	>250	87.7
9	$< 2.9 \times 10^{-2}$	209–211	87.7
12	0.30 ± 0.02	192–194	84.5

[a]tPSA was calculated by Chembiodraw Ultra version 15.0.

We performed *in vitro* metabolic stability studies for compounds **5**, **7**, **9** and **12** in parallel with PBTZ169, using both mouse and human liver microsomes (MLM and HLM). The results are shown in Table 3. Compound **5** has the lowest intrinsic clearance in both MLM and HLM that is nearly 2-fold lower than PBTZ169 while **9** behaves similarly to PBTZ169. However, compounds **7** and **12** were rapidly metabolized in MLMs, but displayed improved stability in HLMs relative to PBTZ169. We also measured plasma protein binding (PPB) and showed all compounds exhibited nearly quantitative PPB with compound **5** having a slightly improved free fraction of 0.5% versus 0.1% for PBTZ169. Given the high PPB, it was not surprising that all compounds exhibited high plasma stability. Based on these results, we selected compound **5** for evaluation of vivo pharmacokinetic parameters in ICR mice.

Table 3. Microsomal stability, plasma protein binding and plasma stability of compounds **5**, **7**, **9**, **12** and PBTZ169.

	$t_{1/2}$ (min)		Cl_{int} ($\mu L \cdot min^{-1} \cdot mg^{-1}$)		PPB (%)	Plasma Stability (%)
	MLM	HLM	MLM	HLM		
PBTZ169	34.4	43.0	20.1	16.5	99.9	88.7
5	65.2	76.6	10.6	9.05	99.5	91.4
7	7.05	26.6	98.4	26.1	99.6	81.9
9	27.3	30.6	25.4	22.7	99.9	102
12	8.33	43.0	83.3	16.1	99.4	93.3

The in vivo PK profile of compound **5** was evaluated in ICR mice after intravenous (i.v.) (2 mg/kg) and oral (p.o.) (10 mg/kg) administration (Table 4). Compound **5** displays a useful PK profile with a 27% oral bioavailability and a high volume of distribution (V_d) that is offset by moderate-to-high clearance resulting in a terminal elimination half life of 2.5 h. Makarov and co-workers only dosed PBTZ169 orally at 25 mg/kg and observed similar exposure as measured by the area-under-the curve (AUC) assuming linear PK and a slightly shorter terminal elimination half-life.[5]

Table 4. Pharmacokinetic parameters for compound **5** in ICR mice following intravenous (2 mg/kg) and oral (10 mg/kg) administration.

PK parametersa	Compound **5**	
	p.o.	i.v.
C_{max} ($ng \cdot mL^{-1}$)	195 ± 61	483 ± 143
$t_{1/2}$ (h)	2.19 ± 0.29	2.53 ± 0.25
MRT (h)	3.09 ± 0.09	2.24 ± 0.23
AUC ($ng \cdot h \cdot mL^{-1}$)	791 ± 338	576 ± 54
Clint ($mL \cdot min^{-1} \cdot kg^{-1}$)	-	58.2 ± 5.7
Vd ($L \cdot kg^{-1}$)	-	12.8 ± 2.5
F (%)	27.4 ± 11.7	-

[a]C_{max}: maximum concentration of drug in blood plasma; $t_{1/2}$: the elimination half-life of drug; MRT: mean residence time; AUC: area under the curve; Cl_{int}: hepatic clearance; V_d: apparent volume of distribution; F: oral bioavailability.

In conclusion, we designed and synthesized a series of benzothiazinones with spirocyclic and bicyclic isosteres of the

piperazine to improve physicochemical properties by disruption of molecular planarity. Compound **5** containing the azabicyclo[3.1.0]hexan-3-amine emerged as the most promising analogue based on its improved solubility, enhanced microsomal stability, and lower PPB compared to PBTZ169. In addition, compound **5** had a respectable pharmacokinetic profile with an oral bioavailability of 27% and high volume of distribution.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedure, biochemical methods, LC-MS/MS method, and ^{1}H and ^{13}C NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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