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Synthesis and assessment of catechol diether compounds as inhibitors of trypanosomal phosphodiesterase B1 (TbrPDEB1)

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ABSTRACT

Human African trypanosomiasis (HAT) is a parasitic neglected tropical disease that affects 10,000 patients each year. Current treatments are sub-optimal, and the disease is fatal if not treated. Herein, we report our continuing efforts to repurpose the human phosphodiesterase 4 (hPDE4) inhibitor piclamilast to target trypanosomal phosphodiesterase TbrPDEB1. We prepared a range of substituted heterocyclic replacements for the 4-amino-3,5-dichloro-pyridine headgroup of piclamilast, and found that these compounds exhibited weak inhibitory activity of TbrPDEB1.

Human African trypanosomiasis (HAT) is a neglected tropical disease caused by the parasites *Trypanosoma brucei gambiense* and *T. b. rhodesiense*. Together, over 60 million people in 36 countries in sub-Saharan Africa are at risk, with approximately 10,000 infections annually.[1] HAT is fatal unless treated and the four drugs approved for this indication: pentamidine, suramin, eflornithine, and melarsoprol, are inadequate for a variety of reasons, including cost, toxicity, and lack of oral bioavailability. For instance, melarsoprol is especially toxic as it induces reactive encephalopathy in 5–10% of patients, killing approximately half of them.[2] As such, new medicines are desperately needed but pharmaceutical companies tend to deprioritize diseases such as HAT due to an inability to recover research costs from the extremely poor who are the most affected by the disease.

In order to speed up the drug discovery process, a drug repurposing approach[3] has been taken against two *T. brucei* phosphodiesterases (PDEs), TbrPDEB1 and TbrPDEB2.[4–6] Simultaneous RNAi knockdown of both is fatal,[7] suggesting that small molecule inhibitors of these enzymes could be useful interventions.[4,8] Humans have 11 PDEs that have been well explored, producing numerous clinical drug candidates.[9] The catalytic domains of human PDEs

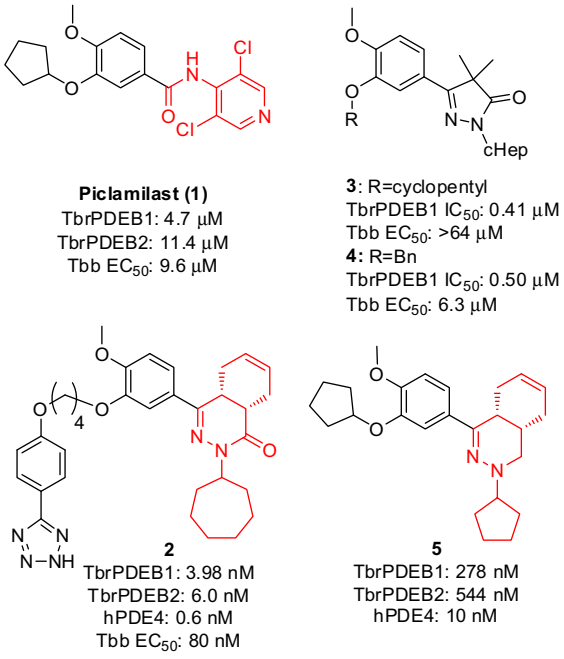

Figure 1. Headgroup replacement rationale based upon related TbrPDEB1 inhibitor chemotypes.

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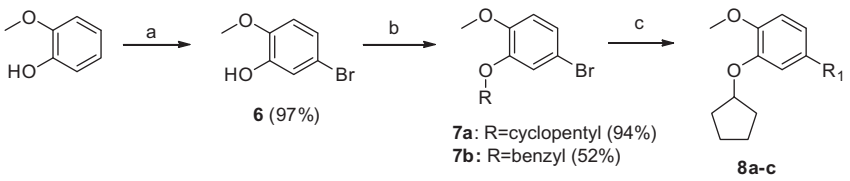
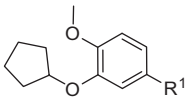
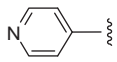
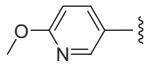
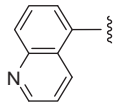


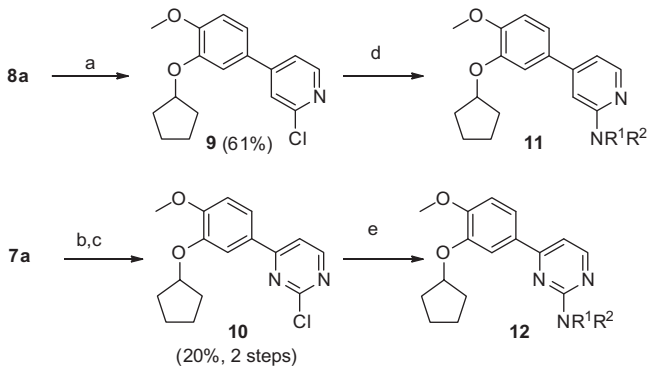
Scheme 1. Synthesis of **8a–c**. Reagents and conditions: (a) (i) TFAA, *t*-BuOK, MeCN, rt, 45 min, (ii) NBS, MeCN, rt, o/n; (b) ROH, PPh_3, DEAD, toluene, rt, 2 h; (c) R-$B(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, toluene/EtOH/H_2O (4:1:1), 105 °C, o/n.

Table 1
Aryl analogs tested against TbrPDEB1



Compound	R^1	TbrPDEB1 (% inh)[a]
8a		18.7 ± 10.7[b]
8b		7.6 ± 2.6
8c		69.1 ± 13.9

[a] Data shown are average of 3 replicate independent experiments.
[b] Replicate of 5 independent experiments.

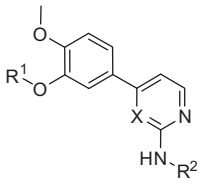


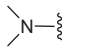
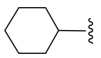
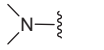
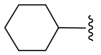
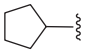
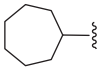
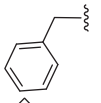
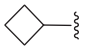
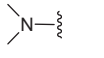
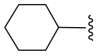
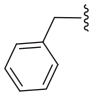
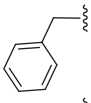
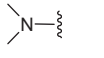
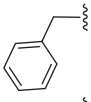
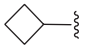
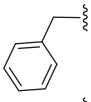
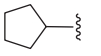
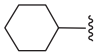
Scheme 2. Synthesis of **11** and **12**. Reagents and conditions: (a) (i) *m*-CPBA, $CHCl_3$, 0 °C to rt, o/n, (ii) $POCl_3$, TEA, $CHCl_3$, MW, 100 °C, 1 h; (b) *n*-BuLi, then bis-(pinacolato)diborane, −78 °C to rt, o/n; (c) 2,4-dichloropyrimidine, Na_2CO_3, PPh_3, $Pd_2(dba)_3$, tol/EtOH/H_2O (4:1:1), 105 °C, o/n; (d) R^1R^2NH, DIEA, NMP or DMF, MW, 250 °C, 1 h; (e) R^1R^2NH, DIEA, NMP or DMF, 80 °C, o/n.

are 30–35% homologous to those of the parasite enzymes TbrPDEB1 and TbrPDEB2. Recent crystallographic evidence confirms that there are key regions of the trypanosomal protein that may allow for selective inhibition over human PDEs.[10] We previously reported that human PDE4 inhibitor piclamilast (**1**) represents a promising lead series for optimization towards selective TbrPDEB inhibitors,[4] and others have shown analogous catechol-derived inhibitors to have high potency against the trypanosomal enzyme.[8,11] In this Letter, we describe our efforts to explore replacements for the 2,6-dichloro-4-pyridylamide headgroup of **1** by assessing their potency against TbrPDEB1.

Our rationale for focusing first on the headgroup region of **1** is shown in Figure 1. The optimization of phthalizinones as human

Table 2
Pyridine and Pyrimidine analogs tested against TbrPDEB1



Compound	R^1	R^2	X	TbrPDEB1[a] (% inh)
11a			C	34.0 ± 22.8
11b			C	27.1 ± 6.1
12a			N	15.8 ± 21.2
12b			N	29.8 ± 0.3
12c			N	12.7 ± 17.9
12d			N	20.6 ± 8.8
12e			N	32.9 ± 6.0
12f			N	3.9 ± 0.5
15a			C	48.0 ± 3.1
15b			C	28.4 ± 2.8
15c			C	7.2 ± 33
16a			N	14.5 ± 20.5
16b			N	16.1 ± 22.8
16c			N	21.8 ± 4.6[b]
16d			N	23.2 ± 10.9