

SUPPORTING INFORMATION

FOR

Hit-to-Lead Optimisation of a Novel Class of Potent, Broad-Spectrum Trypanosomacides

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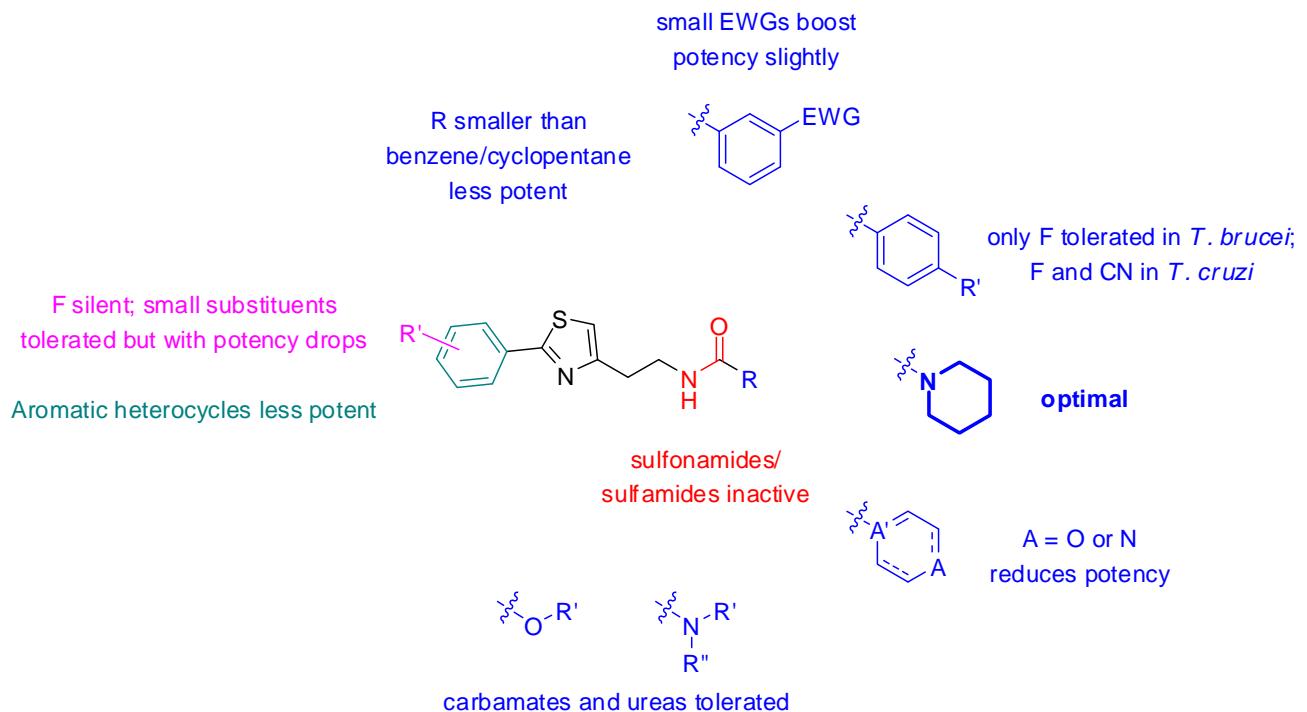
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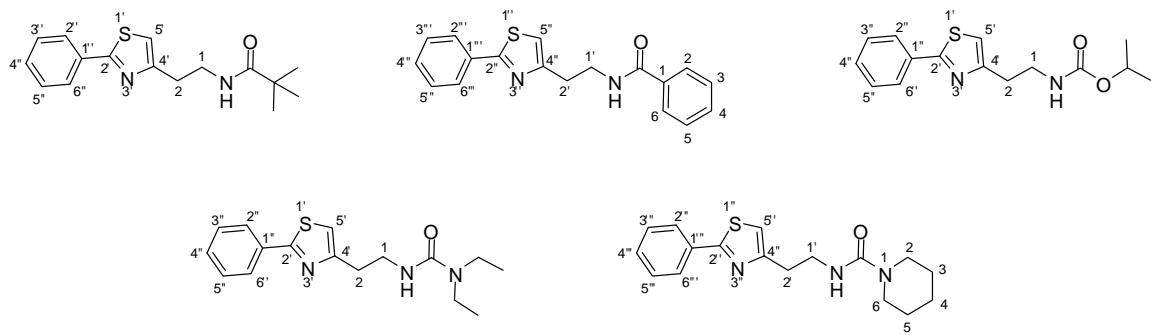
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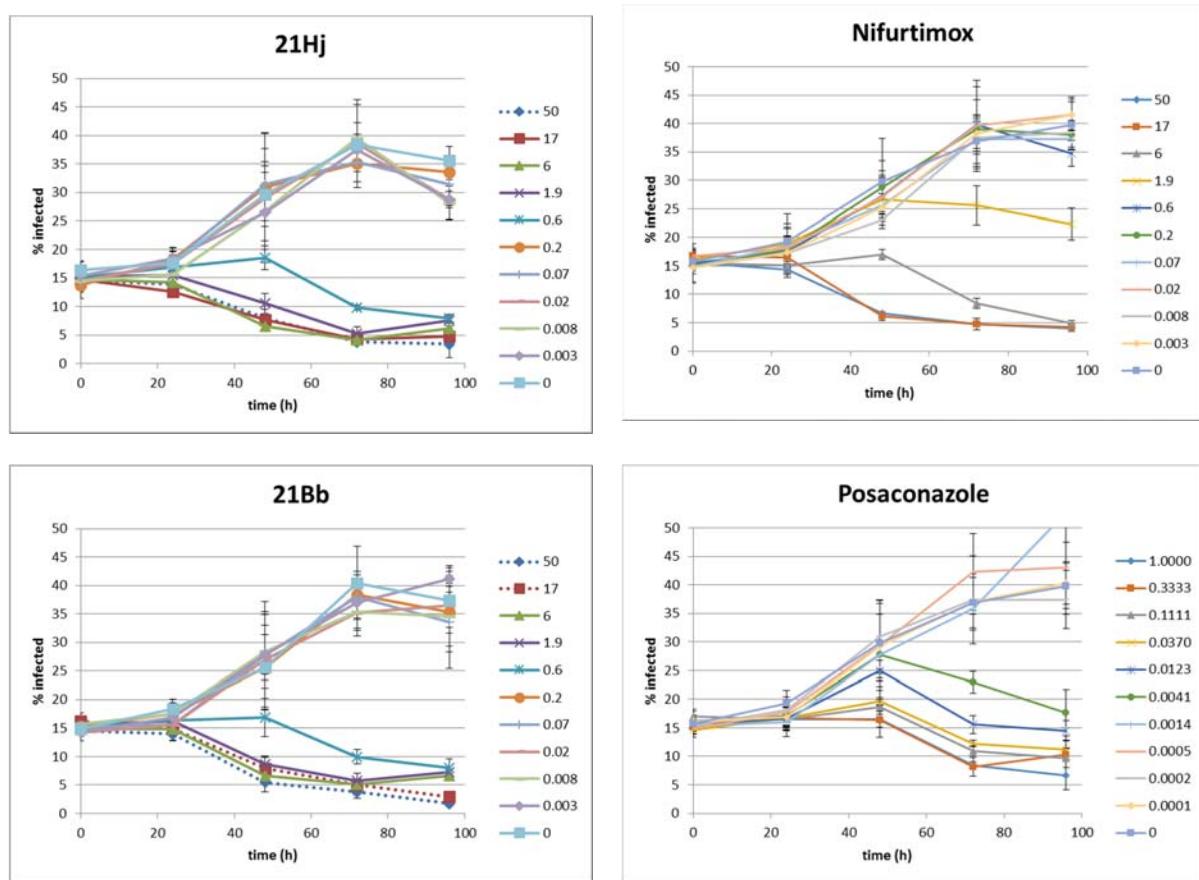
Supplementary Figure 1. SAR summary diagram



Supplementary Figure 2. Exemplar compound numbering schemes

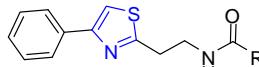
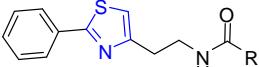


Supplementary Figure 3. Intracellular *T. cruzi* rate-of-kill profiles.

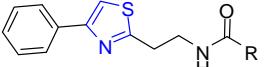
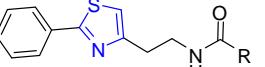


Rate-of-kill against intracellular *T. cruzi* amastigotes was determined as described.¹ Plots show kill profiles over 96 h at ten compound concentrations (shown on right in μM). Concentrations at which host cell toxicity was seen are represented by dotted lines.

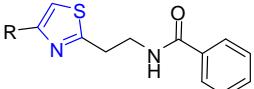
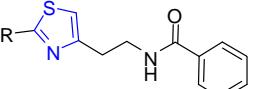
Supplementary Table 1. Comparison of regioisomeric thiazoles from Tidwell *et al.*² and the current work (RHS modifications).

				
	Current work			
R	<i>T. b. rhodesiense</i>	<i>T. b. rhodesiense</i>	<i>T. b. brucei</i>	<i>T. cruzi</i>
	0.63	0.078	0.25	0.40
	0.46	0.42	0.47	—
	0.38	0.21	0.19	0.50
	1.42		0.77	—
	0.48		1.5	—
	1.5		0.42	—
	35		n.i.	—
	53		n.i.	40
	0.17		0.13	0.79
	41		n.i.	0.40
	0.27			
	0.16			
	1.6		0.76	2.5
	17		14	40
	2.0		1.6	6.3
	1.7		1.1	—
	0.48		0.8	2.0
	0.26		0.35	0.40
	0.19		0.23	—

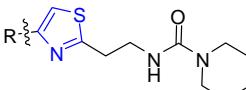
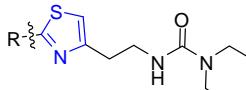
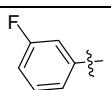
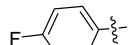
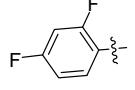
Supplementary Table 1 continued...

				
		Current work		
R	T. b. rhodesiense	T. b. rhodesiense	T. b. brucei	T. cruzi
	0.13	0.046	0.050	0.32
	0.020		0.028	0.039
	0.51		0.69	3.2
	0.052		0.091	0.12

Supplementary Table 2. Comparison of regioisomeric thiazoles from Tidwell *et al.*² and the current work (LHS modifications).

			
		Current work	
R	T. b. rhodesiense	T. b. brucei	T. cruzi
	3.6	1.1	6.3
	4.6	2.7	40
	10	3.1	32
	1.6	1.5	—

Supplementary Table 2 continued...

			
		Tidwell and co-workers	Current work
R	<i>T. b. rhodesiense</i>	<i>T. b. brucei</i>	<i>T. cruzi</i>
	0.0090	0.026	—
	0.012	0.024	0.030
	0.0099	0.024	0.020

References

- (1) De Rycker, M.; Thomas, J.; Riley, J.; Brough Stephen, J.; Miles Tim, J.; Gray David, W. Identification of trypanocidal activity for known clinical compounds using a new *Trypanosoma cruzi* hit-discovery screening cascade. *PLoS Negl. Trop. Dis.* **2016**, *10*, e0004584.
- (2) Patrick, D. A.; Wenzler, T.; Yang, S.; Weiser, P. T.; Wang, M. Z.; Brun, R.; Tidwell, R. R. Synthesis of novel amide and urea derivatives of thiazol-2-ethylamines and their activity against *Trypanosoma brucei rhodesiense*. *Bioorg. Med. Chem.* **2016**, *24*, 2451-2465.