

28AB-ISMS35 **6-Arylpyrazine-2-carboxamides: A New Core for *Trypanosoma brucei* Inhibitors**

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From a whole-organism high throughput screen of approximately 87000 compounds against *Trypanosoma brucei brucei*, we recently identified eight new unique compounds for the treatment of human African trypanosomiasis. In an effort to understand the structure–activity relationships around these compounds, we report our results on a new class of trypanocides, the pyrazine carboxamides. Attracted by the low molecular weight (270 g·mol⁻¹) of our starting hit and its potency (0.49 μM), the SAR around the core was explored, leading to compounds having an EC₅₀ as low as 25 nM against *T. b. brucei* and being more than 1500 times less toxic against mammalian L6 and HEK293 cell lines. The most potent compounds in the series were exquisitely selective for *T. brucei* over a panel of other protozoan parasites, showing an excellent correlation with the human infective parasite *Trypanosoma brucei rhodesiense*, the most potent compound having an EC₅₀ of 24 nM. These compounds are highly drug-like and are able to penetrate the CNS, their only limitation currently being their rate of microsomal metabolism. To that effect, efforts to identify potential metabolites of selected compounds are also reported.