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Development of flavonol and flavanone derivatives as anti-trypanosomatidic drugs

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Trypanosomatid parasites are the etiological agents of neglected tropical diseases, such as Human African Trypanosomiasis and Leishmaniasis. Dihydrofolate reductase (DHFR) is an established target for the treatment of some parasite infections, nevertheless DHFR inhibitors are poorly effective against *Leishmania* and *Trypanosoma* due to the overexpression of pteridine reductase 1 (PTR1) [1]. Since PTR1 is an enzyme unique to these parasites, it represents a promising target to fight trypanosomatidic infections. A library of natural products was assayed using target-based screening on PTR1 and phenotypic screening on parasites. Flavonols were identified as hits, and two libraries of derivatives, having either a flavonol or a flavanone core, were synthesized. Seven crystal structure of PTR1 from *Trypanosoma brucei* (*Tb*PTR1) and *Leishmania major* (*Lm*PTR1) were obtained in complex with different inhibitors [2,3]. The observed structure-activity relationship was rationalized providing the basis for further chemical modifications aimed to generate novel and high affinity anti-trypanosomatidic agents.

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