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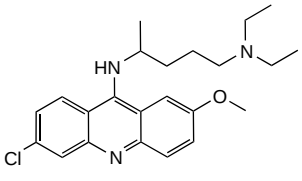
Combinatorial chemistry

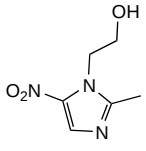
Isoflavones as antigiardial agents

Giardia lamblia is a flagellated, unicellular protozoan that causes the acute or chronic gastrointestinal disease, giardiasis, in humans. Among the most common of parasitic infections, over 200 million people are infected with *G. lamblia* throughout the world. The prevalence of diarrhoea caused by giardiasis in AIDS patients is higher than those without AIDS, due to the suppressed immunity of patients. Until 1988, quinacrine (**i**) was used to treat the disease; the current mainstay of treatment is now metronidazole (**ii**), which yields high cure rates, but also produces general toxicity and occasional drug resistance. Thus, safe efficacious novel antigiardial agents are required.

Biological evaluation of various natural products has indicated that molecules possessing a flavonoid skeleton exhibit antigiardial activity. Hence, the development of a library of isoflavone derivatives, of general structure **iii**, was envisaged as an approach to discover potent leads, while simultaneously developing SARs: Avery and co-workers prepared a library of 174 isoflavone derivatives in solution [1]. A selection of potent compounds were obtained from this library upon screening for inhibition of giardial growth, with one of the most potent compounds synthesized being **iv,** with an IC_{50} value of $<1.1\ \mu g\ mL^{-1}$. This work has provided promising antigiardial leads and, thus, represents a fruitful approach for further investigation.



(i)



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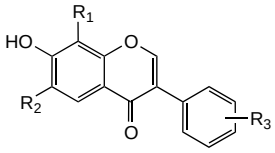
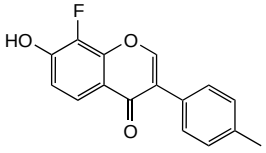


(iii)



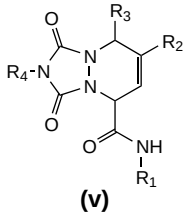
(iv)

Thrombin inhibitors

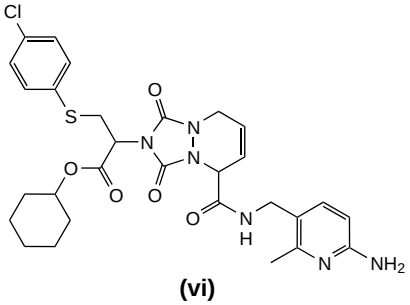
The serine protease, thrombin, has been a dominant subject of pharmaceutical research for several years. This research has produced advances in the development of highly active and selective inhibitors of thrombin. Despite these advances, however, no orally active direct thrombin inhibitor is currently widely available for the treatment of thrombotic diseases.

Recently, bicyclic β-strand mimetics have been disclosed that are useful as scaffolds for the synthesis of protease inhibitors based on the triazolopyridazine structure (**v**) [2].

More recently, new triazolopyridazine chemistry has emerged, that extends the scope of this chemical class into the synthesis of new libraries of bioactive compounds, and into rapid generation and optimization of thrombin inhibitor compounds [3]. More than 600 single compounds have been synthesized on various solid phase resins, such as Wang and chlorotrityl polystyrene resin; these have been screened for inhibition of thrombin and trypsin by fluorometric assay. Several potent inhibitors were found, one of the most potent being **vi**, which possessed a *K*i value of 0.057 nM against thrombin. This work has generated rapid SAR and potent thrombin inhibitor lead compounds.



(v)



(vi)

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