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Synthesis and evaluation of quinazolinone-eugenol hybrids as new compounds with trypanocide and leishmanicide potential

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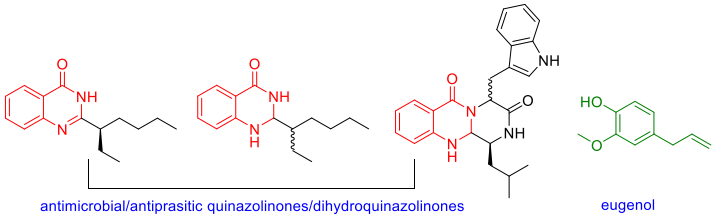
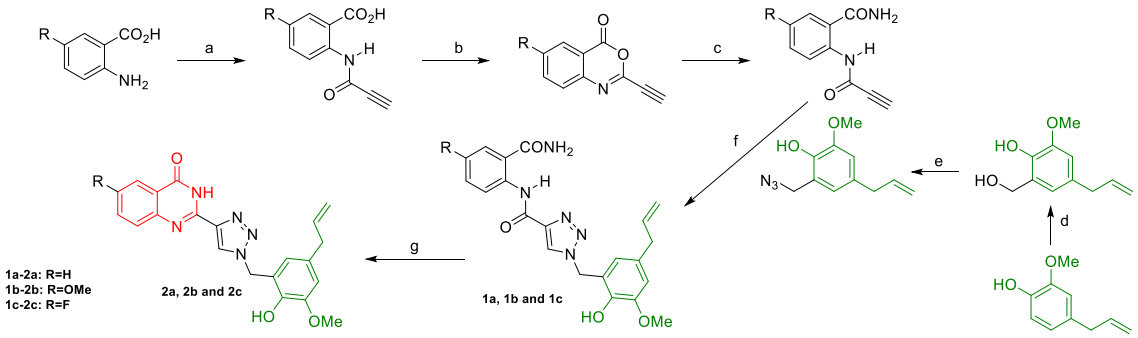
ABSTRACT

The search for new therapeutic agents against neglected tropical diseases is one of the most frequent branches of academic research for new drug candidates. Natural products are a very rich source for obtaining new compounds with therapeutic potential[1]. Very often, they are explored in the construction of hybrids that may bring together the potential of the individual compounds. Then, given the need of better drugs against trypanosomiasis and leishmaniosis, we designed new molecular hybrids based on marine quinazolinones and eugenol, a natural phenolic compound[2]. Following reports on the antiparasitic and antimicrobial activity of quinazolinones[3] and eugenol derivatives, we expected that the union of these pharmacophores could generate biologically relevant substances.



The designed compounds were obtained by classical synthetic procedures and using triazole click chemistry to link both pharmacophores. Nine intermediates and final products were then evaluated *in vitro* against *Trypanosoma brucei* and *Leishmania infantum.* Three compounds (**1b**, **1c** and **2c)** showed activity against *T. brucei* with IC_{50} 11.7-16.4 μM. Intermediate **1c** showed anti-*Leishmania* activity (IC_{50} 7.5 μM) and was six times less cytotoxic against normal cells. The antiparasitic potential of these compounds indicates that their structural framework may be interesting for future optimization.



a) propinoyl chloride, TEA, DCM, 0°C; b) Ac_2O, 130 °C; c) NH_4OH, EtOH, 25 °C; d) NaOH, H_2CO, H_2O, 25°C; e) $SOCl_2$, K_2CO_3, DMF, 0°C, then NaN_3, DMSO, 25°C; f) $CuSO_4.5H_2O$, sodium ascorbate, THF/ H_2O, 25°C; g) NaOH, H_2O, EtOH, reflux, 1 hour.

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