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New pyrazolopyrimidine and triazolopyrimidine derivatives with potential activity anti-*P. falciparum*

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Highlights

Eight pyrazolopyrimidine and triazolopyrimidine derivatives were synthesized in 12-30% overall yield and in vitro evaluated against *P. falciparum*. Compound **13** was the most potent pyrazolopyrimidine derivative of the series with an IC_{50} value of 0.063 µM.

Resumo/Abstract

During our search for new compounds against malaria, we have demonstrated the importance of triazolopyrimidine prototype **I** with an IC_{50} value of 0.023 µM against *P. falciparum.*[1] In another series, we have showed the importance of quinolinic derivatives linked to benzenesulfonamide moiety by 3 or 4 methylene carbons as the most promising derivative (IC_{50} = 0.09 µM), which is lower than that of chloroquine (CQ) (IC_{50} = 0.46 µM) and, when *in vivo* evaluated against *P. berghei,* compound **II** inhibited parasitemia by 49% (10 mg/kg).[2] Based on that, a new series of triazolopyrimidine and pyrazolopyrimidine derivatives (**6-13**) was designed (Figure **1**).

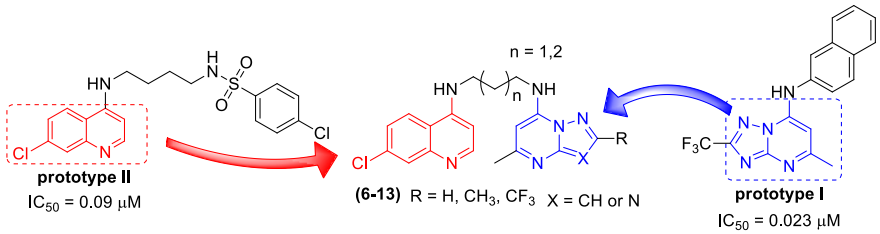
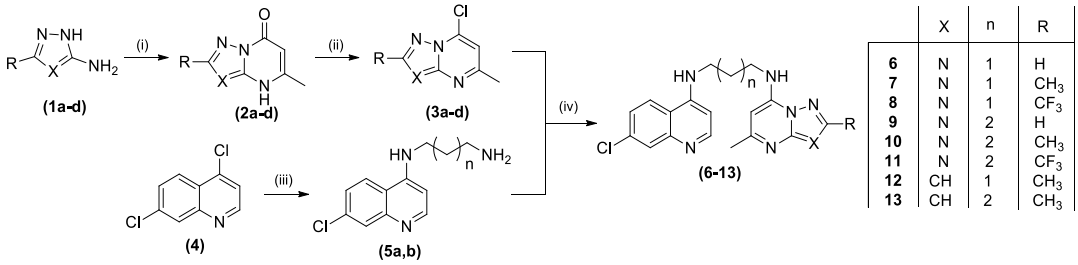


Figure 1. Design of compounds **6-13**.

Reaction of **1a-c** and **1d** with ethyl acetoacetate produced the derivatives **2a-c** and **2d**, respectively**,** in 71-95% yield. After, **2a-d** were treated with $POCl_3$ under reflux to obtain **3a-d** in 51-70% yield.[1] The synthesis of **5a,b** was achieved by the reaction of **4** with appropriate diamines, under reflux for 4h, with 86-90% yield. Finally, the reaction of **3a-d** and **5a,b** in ethanol produced the compounds of interest **6-13** in 40-50% yield.



	X	n	R
6	N	1	H
7	N	1	CH_3
8	N	1	CF_3
9	N	2	H
10	N	2	CH_3
11	N	2	CF_3
12	CH	1	CH_3
13	CH	2	CH_3

Reagents and conditions: (i) ethyl acetoacetate, AcOH, toluene, reflux, 24h; (ii) $POCl_3$, reflux, 3h; (iii) diamine, reflux, 4h; (iv) ethanol, reflux, 6h.

Figure 2: Synthesis of compounds **6-13**.

Compounds **6-13** were tested against *P. falciparum* (3d7 strain - chloroquine-sensitive) and had their cytotoxicity profile determined against human hepatocarcinoma cells (HepG2) (Table 1). Derivative **13** was the most potent compound in the series with an IC_{50} value 0.063 µM and an excellent selectivity index (SI >1570).

Table 1. Biological evaluation results against *P. falciparum* 3d7-chloroquine-sensitive strain

	IC_{50} (µM)	MCL_{50} (µM)	SI		IC_{50} (µM)	MCL_{50} (µM)	SI
6	3,19 ± 0,06	>100	>31	**11**	0,31 ± 0,04	>25	>81
7	0,84 ± 0,02	110 ± 10	131	**12**	0,145 ± 0,003	>50	>345
8	0,6725 ± 0,0005	113 ± 2	168	**13**	0,0635 ± 0,0005	>100	>1570
9	0,62 ± 0,08	99 ± 6	160	**CQ**	0,03		
10	0,25 ± 0,03	>25	>100				

(1) Boechat, N. et al. *Molecules*, **2012**, 17, 8285-8302.
(2) Pinheiro, L. C. S. et al. *Bioorg. Med. Chem.*, **2015**, 23, 5979-5984.

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