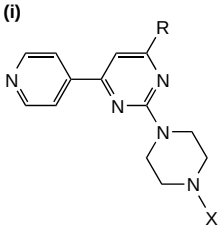
monitor

MOLECULES

Novel trisubstituted pyrimidines as potential antimalarial agents

Malaria is a tremendous problem for many tropical and subtropical countries. It is caused by several protozoan parasites, namely *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae,* and it is transmitted by female mosquitoes belonging to the *Anopheles* genus. Endemic maps indicate that *P. falciparum* and *P. vivax* account for 95% of malarial infections [1]. Although several antimalarial drugs are available (e.g. quinine, chloroquine, primaquine, cycloguanyl, pyrimethamine and proguanyl), the parasites develop resistance rapidly. Therefore, the need for new and effective drugs is high. As a part of their ongoing programme in this field, Agarwal and co-workers [2] have previously reported the antimalarial activity of series of triazines, pyrimidines and quinolines. They have synthesized new 2,4,6-trisubstituted pyrimidines [3] that were tested for their capability to inhibit the maturation (into schizonts) of ring stage *P. falciparum* parasites during a 40 h incubation. Pyrimetamine **(i)** was used as the reference compound.

(i)



a C_6H_5
b 4-Me-C_6H_4
c 4-SMe-C_6H_4
d 3,4-Me_2-C_6H_3
e 4-OMe-C_6H_4
f 2,5-OMe_2-C_6H_3
g 2,4,5-OMe_3-C_6H_2
h 3,4,5-OMe_3-C_6H_2
i 3-NO_2-C_6H_4
j 4-Cl-C_6H_4

Series 1: X = CH_3 (methyl group)
Series 2: X = $CH_2C_6H_5$ (benzyl group)
Series 3: X = C_6H_5 (phenyl ring)

The SAR clearly indicates that series **1** (X = CH_3) gives the best derivatives. Substituting the methyl group with a benzyl group (series **2**) slightly reduces the activity and substitution with a phenyl ring (series **3**) is detrimental. As far as the phenyl ring on the pyrimidine moiety is concerned (R), disubstitution at positions 3 and 4 or 2 and 5 gave the best results. By contrast, trisubstitution did not favour the activity. In particular, minimum inhibitory concentrations (MICs) of 0.5 μg/ml were seen with compounds **1d** and **1f**. In addition, nine compounds had MICs of 1 μg/ml, whereas ten compounds had MICs of 2 μg/ml. In the same test, the MIC for pyrimethamine was 10 μg/ml. On these bases, the new compounds could be considered as leads for antimalarial chemotherapy.

1 Kumar, A. (2003) Perspective in antimalarial chemotherapy. *Curr. Med. Chem.* 10, 1137–1150
2 Agarwal, A. *et al.* (2005) Synthesis of 2,4,6-trisubstituted triazines as antimalarial agents. *Bioorg. Med. Chem. Lett.* 15, 531–533
3 Agarwal, A. *et al.* (2005) Antimalarial activity and synthesis of new trisubstituted pyrimidines. *Bioorg. Med. Chem. Lett.* 15, 3130–3132

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