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MOLECULES

Pyrimidin-4-yl phenols as anti-infective agents

Parasitic diseases such as malaria have an enormous impact on global public health, particularly in developing regions of our planet. It is estimated that, with 40% of the world's population exposed to the threat of malaria, there are two million deaths each year from this disease. *Plasmodium falciparum*, one of the four species of plasmodium that affect humans, is the most prevalent and pathogenic disease-causing strain, causing the as yet untreatable and often lethal Malaria tropica.

Plasmodia resistance to antimalarial drugs is now recognized as one of the major problems facing the global eradication of malaria. Despite continuing efforts by the scientific community, an effective vaccine has yet to be discovered. The inadequacy of current drugs to treat malaria and the lack of new antimalarial drugs are limiting factors in the fight against the disease. This provides a continual and urgent need for new drugs that attack crucial targets in the malarial pathogen.

One of the targets for malarial studies to date is dihydrofolate reductase (DHFR). Inhibition of DHFR prevents DNA biosynthesis, leading to cell death. Thus, the design of novel biologically active entities specifically directed at targets in the malarial pathogen could lead to better antimalarial drugs. Traditional 'wet' medicinal chemistry is limited in its speed of compound production. To meet the need of modern drug discovery, combinatorial chemistry has been utilized to aid the drug discovery paradigm. Among small molecules, nitrogen heterocycles are an important class of compound for synthesis in a medicinal context, because they have proven utility in medicinal chemistry [1]. Along these lines, a recent communication has synthesized trisubstituted pyrimidines on solid-support as antimalarial and antimycobacterial agents [2]. The solid-phase destined for this library approach was synthesized from Merrifield resin and 4-hydroxybenzaldehyde to give **(i)**. The polymer-bound aldehyde **(i)** was further reacted with different acetophenones to give polymer-bound chalcones (general structure **ii**). These chalcones were then reacted with a range of amidines to give resin-bound pyrimidines (general structure **iii**) that, following acid (TFA) mediated cleavage from the solid phase, delivered 30 pyrimidin-4-yl phenols (general structure **iv**).

Compounds consequently produced were tested for their antimalarial activity against *P. falciparum* NF-54 strain, and for antitubercular activity against *Mycobacterium tuberculosis* H37Ra. Of the 30 compounds synthesized, 23 compounds showed *in vitro* antimalarial activity against *P. falciparum* (MICs = 0.25–2.00 μg/ml) and 16 compounds showed antitubercular activity against *M. tuberculosis* H37Ra, at a concentration of 25 μg/ml.

One of the most potent examples identified from this series was **(v)**, which displayed an MIC of 0.25 mg/ml against *P. falciparum*. This approach has identified pyrimidines that are useful new leads in antimalarial chemotherapeutic research, and further optimization work into this area is warranted.

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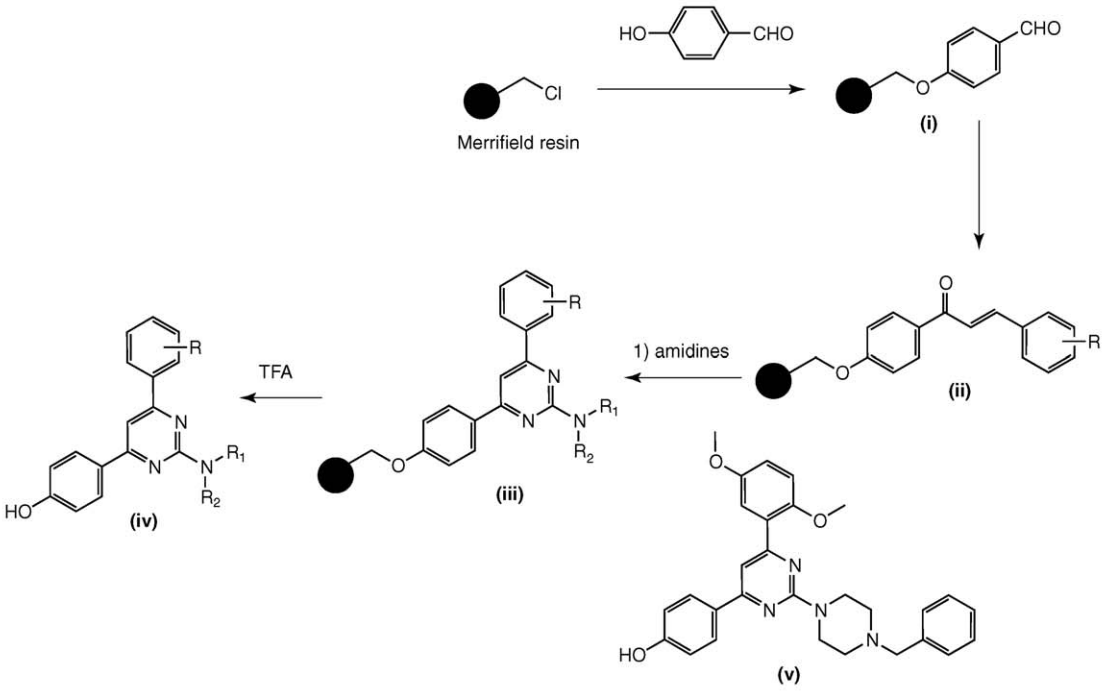

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2 Agarwal, A. *et al.* (2005) Solid support synthesis of 6-aryl-2-substituted pyrimidin-4-yl phenols as anti-infective agents. *Bioorg. Med. Chem. Lett.* 15, 4923–4926

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Free journals for developing countries

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Gro Harlem Brundtland, former director-general for the WHO, said that this initiative was "perhaps the biggest step ever taken towards reducing the health information gap between rich and poor countries".

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