SYNTHESIS OF 2,4-DIAMINOPYRIMIDINES AS POTENTIAL ANTIFOLATES

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Antifolates are a class of therapeutic agents that have potential application for cancer chemotherapy and for the treatment of parasitic and bacterial infections\textsuperscript{[1]} In Africa, the parasite that causes malaria, \textit{P. falciparum}, is responsible for 93\% of malaria deaths worldwide\textsuperscript{[2]} Substituted 2,4-diaminopyrimidines act as antifolates by targeting the enzyme dihydrofolate reductase (DHFR)\textsuperscript{[1]}

We have previously prepared a series of dihydrotiazines that displayed potent activity against \textit{P. falciparum} DHFR (\textit{PfDHFR})\textsuperscript{[3]} Herein we report our progress on the synthesis of a series of related substituted pyrimidines 1 in a five step process (Scheme 1) from commercially available alkyl and aryl esters.

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\textbf{Scheme 1:} i) MeCN, \textit{t}BuOK, IPA, 2-MeTHF; ii) \textit{t}BuOK, 2-MeTHF, 100W, 100°C; iii) HIO\textsubscript{3}, H\textsubscript{2}SO\textsubscript{4}/H\textsubscript{2}O; iv) Pd(PPh\textsubscript{3})Cl\textsubscript{2}, Cul, DIPEA, DMF; v) H\textsubscript{2}, Pd/C, EtOH
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\textsuperscript{[1]} J Feeney; \textit{Angew. Chem. Int. Ed.}, \textbf{2000}, \textit{39}, 290 - 312
