SYNTHESIS OF 2,4-DIAMINOPYRIMIDINES AS POTENTIAL ANTIFOLATES

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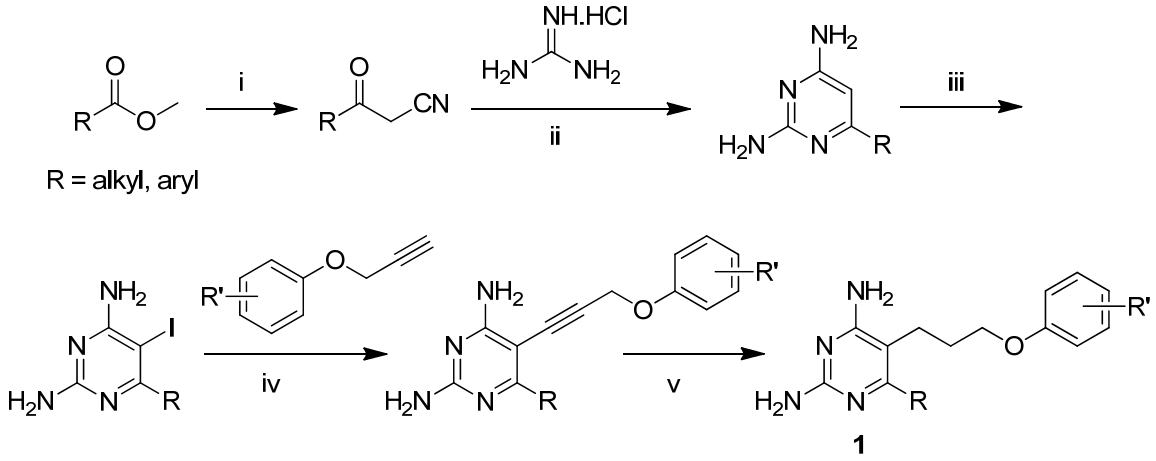
Antifolates are a class of therapeutic agents that have potential application for cancer chemotherapy and for the treatment of parasitic and bacterial infections.[1] In Africa, the parasite that causes malaria, *P. falciparum*, is responsible for 93% of malaria deaths worldwide.[2] Substituted 2,4-diaminopyrimidines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

We have previously prepared a series of dihydrotriazines that displayed potent activity against *P. falciparum* DHFR (*Pf*DHFR).[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.



Scheme 1: i) MeCN, *t*BuOK, IPA, 2-MeTHF; ii) *t*BuOK, 2-MeTHF, 100W, 100°C; iii) HIO_3, H_2SO_4/H_2O; iv) $Pd(PPh_3)Cl_2$, CuI, DIPEA, DMF; v) H_2, Pd/C, EtOH

[1] J Feeney; *Angew. Chem. Int. Ed.*, **2000**, *39*, 290 - 312

[2] WHO World Malaria Report 2018, https://www.who.int/malaria/publications/world-malaria-report-2018/report/en/

[3] ACU Lourens, D Gravestock, RL van Zyl, HC Hoppe, N Kolesnikova, S Taweechai, Y Yuthavong, S Kamchonwongpaisan and AL Rousseau; *Organic & Biomolecular Chemistry*, **2016**, *14*, 7899-7911.