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Synthesis and solid state study of pyridine- and pyrimidine-based fragment libraries

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ABSTRACT

A library of pyridines and pyrimidines has been synthesised in excellent yields employing microwave and flow chemistry methodologies. Work-up bottlenecks have been facilitated substantially by the use of supported reagents and many of the final compounds have been studied in the solid state by single crystal X-ray diffraction.

Pyridines and pyrimidines are privileged structures found in diverse bioactive molecules, including anticancer agents, CNS acting drugs and antivirals.[1] A number of these bioactive molecules are associated with a piperazine unit, which can add water solubility as well as act as a linker to attach other binding motifs (Fig. 1).[2]

We report here a parallel synthetic route to a library of pyridines and pyrimidines, many of which contain a piperazine group. Our methods include the use of microwave-assisted organic synthesis (MAOS),[3] flow chemistry[4] and supported resins,[5] and are applicable to fragment-based drug discovery, since the molecules, in general, obey the 'rule of three'.[6] The synthetic efforts have been supported by solid state studies; in principle this could be used to generate coordinates for docking studies of the products into enzymes/receptors for drug discovery.

2-Bromo-5-nitropyridine (**1**) was found to be a useful starting point for the chemistry herein. Reaction of **1** with cyclic amines **2** and base, in a microwave apparatus, afforded coupled products **3**. The Boc-protected analogue **3a** was deprotected with TFA affording **3b**. Catalytic reduction of compounds **3** gave the amines **4**. The addition of 1.2 equiv of different aryl, alkyl or heterocyclic acid chlorides to compound **3b** in the presence of PS-NMM (polymer-supported *N*-methylmorpholine) (Scheme 1) as a base furnished the corresponding amide derivatives **5a–g** in good to excellent yields as yellow solids, after treatment with a nucleophilic

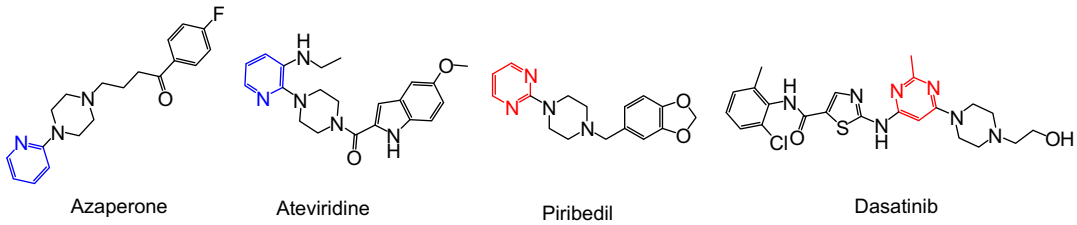

Figure 1. Bioactive piperazine-linked pyridines (blue) and pyrimidines (red).

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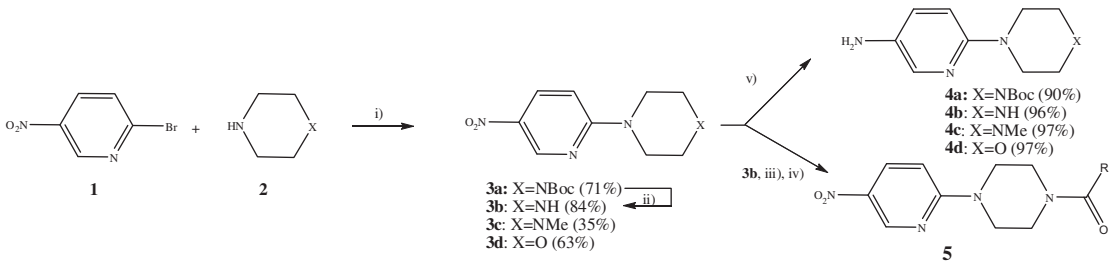
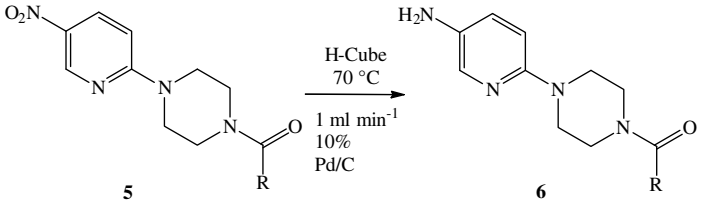
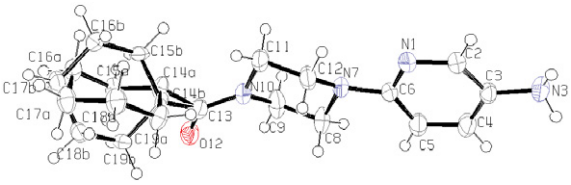


Product	R	Isolated yield (%)[a]
5a	CH_3	90
5b	C_6H_5	56
5c	Cy	98
5d	4-FC_6H_4	99
5e	4-$CH_3OC_6H_4$	99
5f		94
5g		95

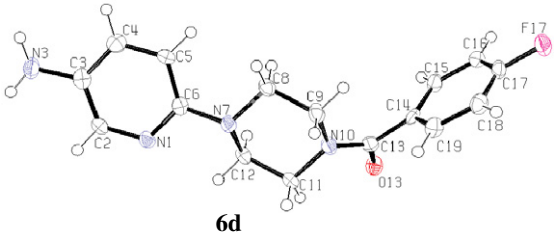
Scheme 1. Synthesis of amines **4** and amides **5**. Reagents and conditions: (i) Na_2CO_3, H_2O, MW, 150 °C, 15 min; (ii) TFA; (iii) RCOCl, CH_2Cl_2, PS-NMM; (iv) PS-trisamine; (v) H-Cube; 70 °C, Pd/C. [a]Isolated yield after chromatography.



Product	R	Isolated yield (%)[a]
6a	CH_3	97
6b	C_6H_5	93
6c	Cy	93
6d	4-FC_6H_4	95
6e	4-$CH_3OC_6H_4$	96
6f		97
6g		91



6c



6d

Scheme 2. Synthesis of amines **6**. [a]Isolated yield after chromatography.