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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

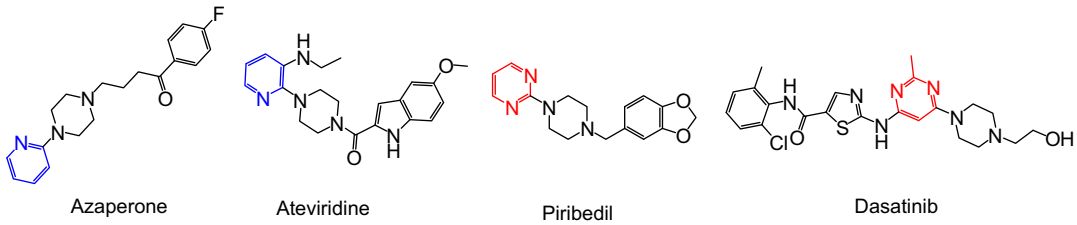

Figure 1. Bioactive piperazine-linked pyridines (blue) and pyrimidines (red).

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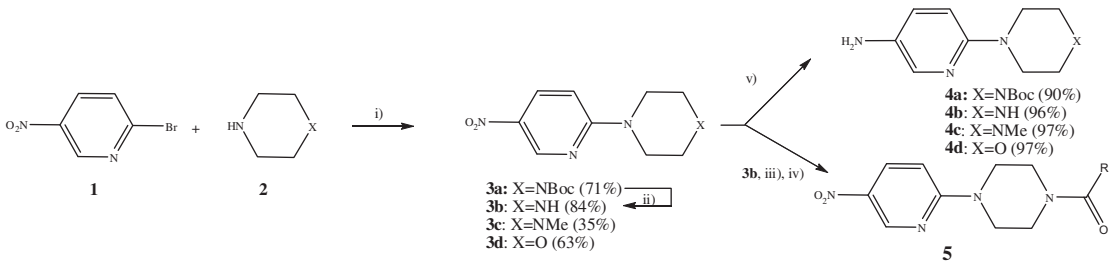
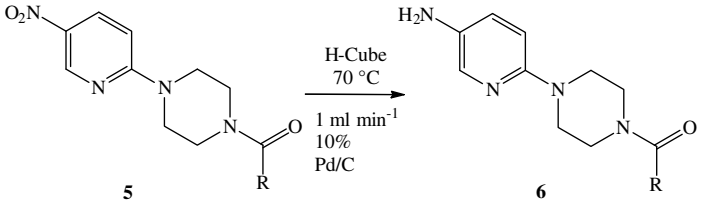
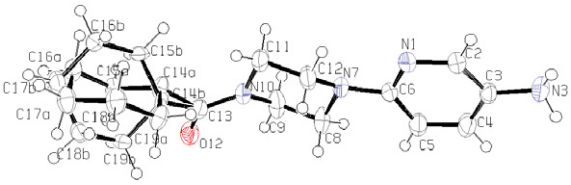


Product	R	Isolated yield (%)[a]
5a	CH_3	90
5b	C_6H_5	56
5c	Cy	98
5d	4-FC_6H_4	99
5e	4-$CH_3OC_6H_4$	99
5f		94
5g		95

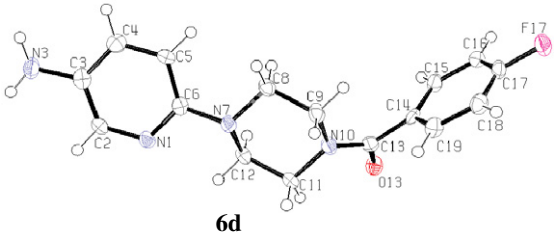
Scheme 1. Synthesis of amines **4** and amides **5**. Reagents and conditions: (i) Na_2CO_3, H_2O, MW, 150 °C, 15 min; (ii) TFA; (iii) RCOCl, CH_2Cl_2, PS-NMM; (iv) PS-trisamine; (v) H-Cube; 70 °C, Pd/C. [a]Isolated yield after chromatography.



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

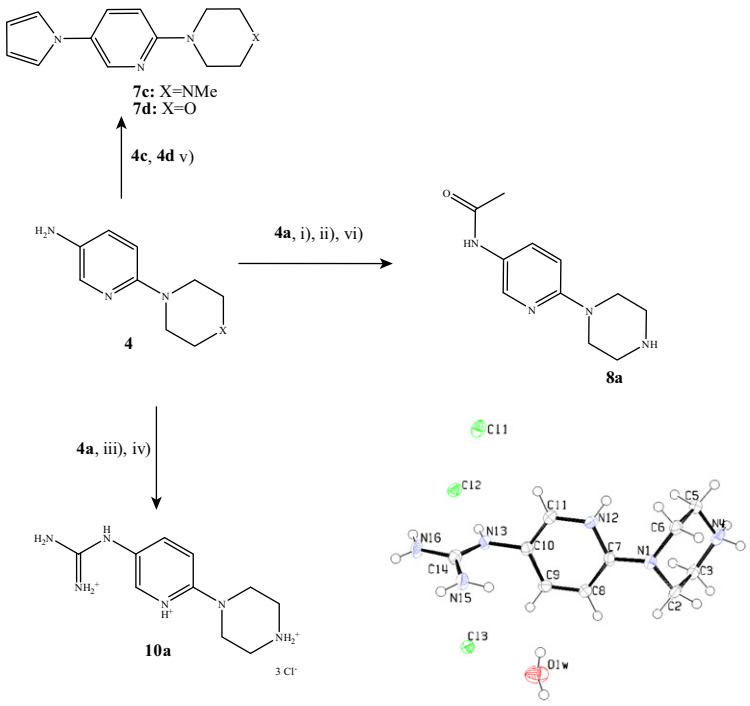


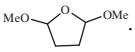
6c

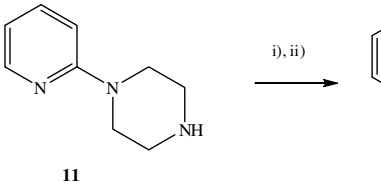


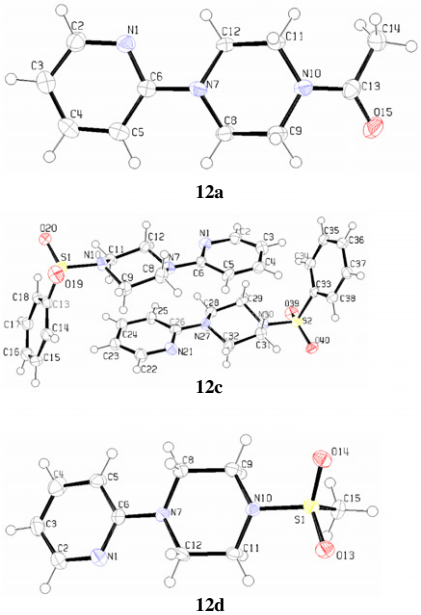
6d

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



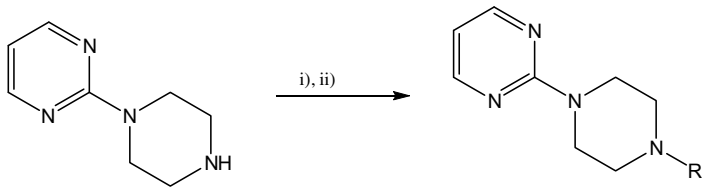
Scheme 3. Acetylation and guanylation reactions. Reagents and conditions: i) Acetyl chloride, PS-NMM, CH_2Cl_2. ii) PS-trisamine. iii) l,3-bis-(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea, PS-NMM, CH_2Cl_2, $HgCl_2$. iv) 5 M HCl, ether. v) acetic acid,  . vi) TFA.



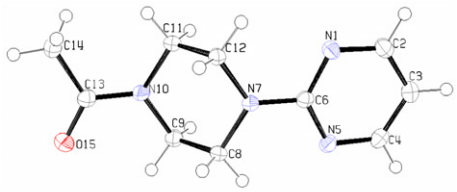


Product	R	Isolated yield (%)
12a	$COCH_3$	87
12b	COC_6H_5	76
12c	$SO_2C_6H_5$	72
12d	SO_2CH_3	83
12e		69
12f		68
12g		64
12h	COCy	80
12i	4-FC_6H_4CO	77
12j	4-$MeOC_6H_4CO$	92

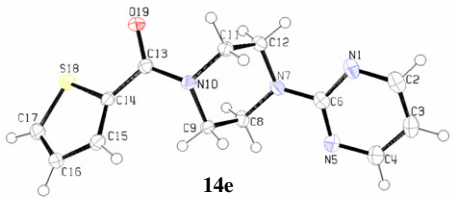
Scheme 4. Synthesis of a pyridyl piperazine library. Reagents and conditions: (i) RCl, CH_2Cl_{25} PS-NMM, rt; (ii) PS-trisamine.



13 14



14a



14e

Product	R	Isolated yield (%)
14a	$COCH_3$	94
14b	$SO_2C_6H_5$	82
14c	SO_2CH_3	81
14d		73
14e		73
14f		88
14g	COCy	76
14h	$4\text{-}FC_6H_4CO$	87
14i	$4\text{-}MeOCOC_6H_4CO$	92

Scheme 5. Synthesis of a pyrimidyl piperazine library. Reagents and conditions: (i)RCOCl, CH_2Cl_2, PS-NMM, rt; (ii) PS-trisamine.

scavenger resin, which was employed to sequester any unreacted acid chloride, necessitating a simple filtration as work-up (Scheme 1).

Reduction of nitro compounds **5** was performed in an H-cube™ with 10% Pd/C as the catalyst (Scheme 2) to afford amines **6** in excellent yields. A number of analogues were crystallised and their solid state structures determined by single crystal X-ray diffraction studies (ORTEP diagrams are shown). Analogue **6c** displayed disorder of the cyclohexyl ring in its solid state structure.

The pyrroles **7** were prepared employing a microwave-mediated cyclisation of **4c** and **4d** with 2,5-dimethoxytetrahydrofuran. Amide **8a** was obtained by standard methods using acetyl chloride as the acetylating agent followed by Boc deprotection (Scheme 3). Compound **10a** was formed by guanylation of **4a** in the presence of a mercury(II) salt followed by Boc deprotection (Scheme 3). Compound **10a** was recrystallised from methanol/toluene and a single X-ray diffraction study confirmed a protonated guanidine group (as well as pyridine and piperazine units) along with three chloride counterions and water.

We next prepared simple pyridines devoid of a nitro or amine substituent at the 5-position. In a medicinal chemistry context, this would lead to the synthesis of smaller fragments compared to compounds **5**–**10** and would enable an assessment of the effect of a lack of a substituent at the 5-pyridyl position on potential biological activity and solubility. Hence, commercially available **11** was functionalised as above to yield a range of amides and sulfonamides **12** (Scheme 4). The solid state structures of a number of derivatives were determined and the sulfonamide **12c** was found to have two independent molecules in its unit cell (see ORTEP structures below).

A similar pyrimidine library was also synthesised and the products **14** were formed in excellent yields (Scheme 5).

A diverse library of compounds has been synthesized based on the privileged pyridine, piperazine and pyrimidine structures. We have successfully employed microwave conditions for fast and efficient nucleophilic substitution reactions. A flow chemistry technique enabled efficient nitro reductions and supported resins were used in amide and sulfonamide library syntheses. This library should be appealing for use in fragment-based drug discovery, especially given the ease of incorporation of solubilising groups. Indeed, during the preparation of this manuscript we became aware of a publication outlining the synthesis of a range of bioactive analogues related to compounds **6** and **14**.[7]

Acknowledgements

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Supplementary data

Supplementary data (synthesis and spectral data (^1H and ^{13}C NMR, IR and HRMS spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.147. The X-ray structures described herein and in the supplementary data have been submitted to the CCDC and have been assigned the following numbers: **6a**, 827283; **6d**, 827284; **10a**, 827285;**12a**, 827278; **12c**, 827279; **12d**, 827282; **12e**, 827280; **12f**, 827281; **14a**, 835142; **14e**, 827281; **14f**, 835637; **14h**, 835638.

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