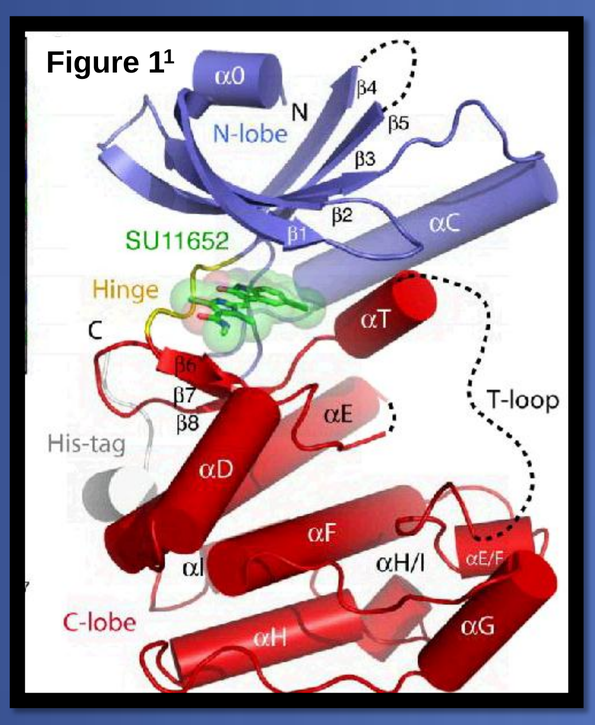
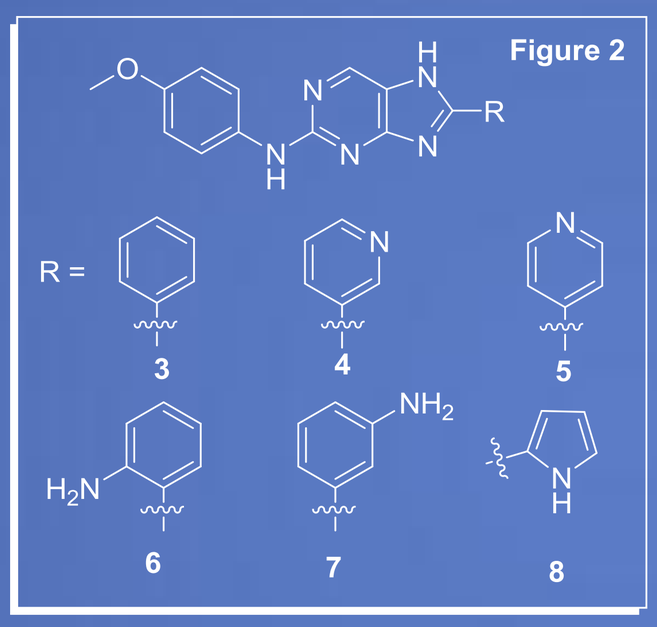
Design, Synthesis and Biological Evaluation of Nek2 Kinase Inhibitors as Antitumour Agents

James Pickles
Newcastle Cancer Centre, School of Chemistry, Bedson Building, Newcastle University, Newcastle upon Tyne, NE1 7RU

1 Introduction:

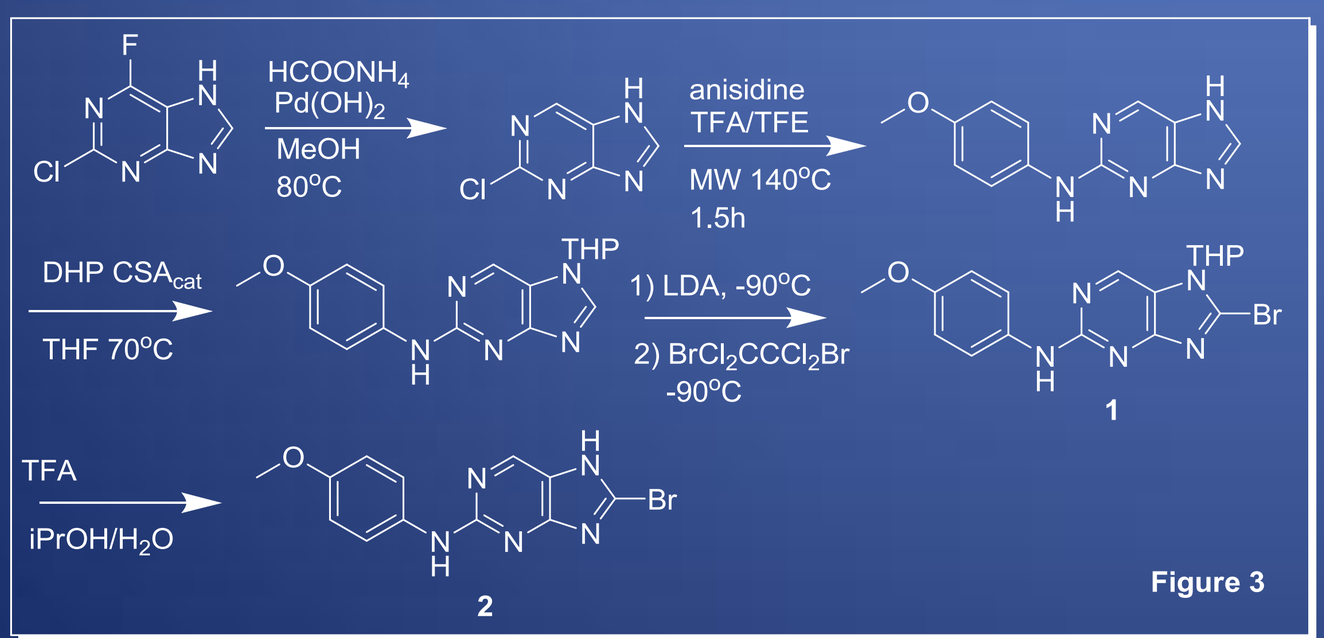
Nek2 kinase (figure 1) is an enzyme that is over-expressed in some cancers. Inhibition of Nek2 reduces tumour growth, making it a target for designing a new drug. Our aim was to synthesise six potential Nek2 inhibitors (figure 2).





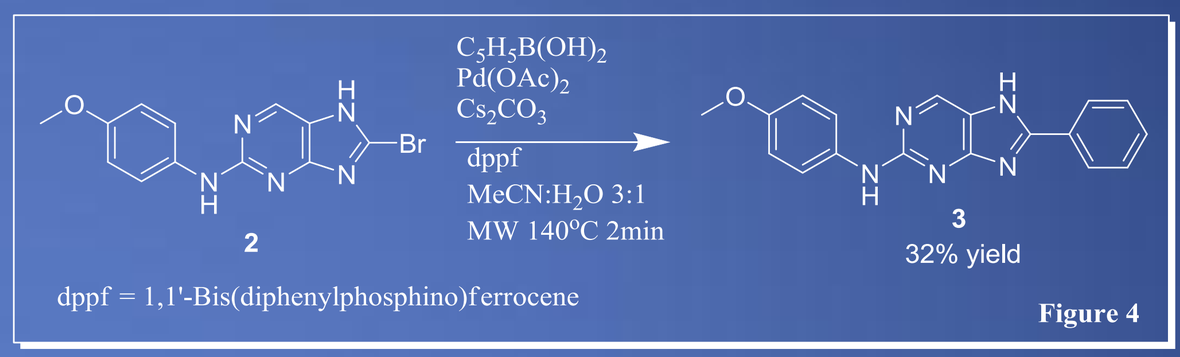
2

The synthetic approach (figure 3) gave the bromopurines **1** and **2**. Suzuki reactions were carried out on the THP-protected compound (**1**), but a mixture of THP-protected and deprotected products was isolated. Therefore Suzuki reactions were repeated with **2**.



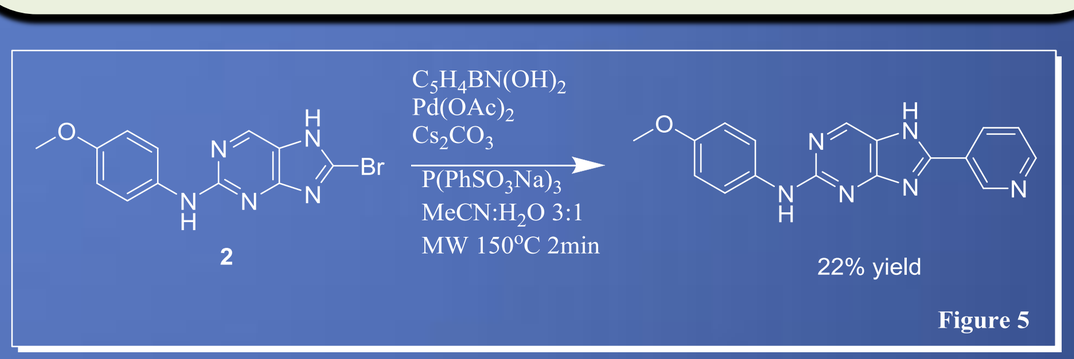
3

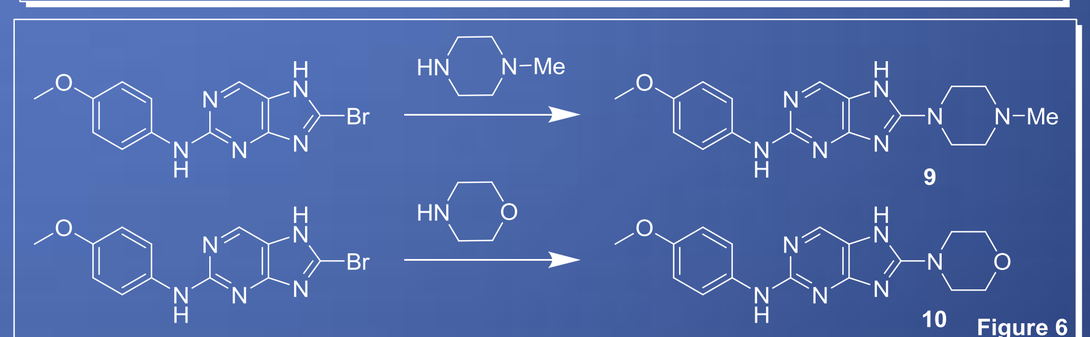
The synthetic approach (figure 4) produced the 8-phenylpurine (**3**) (32% yield).



4

Pyridine derivatives **4** and **5** were obtained in low yields (figure 5), whilst attempts to obtain the pyrrole derivative (**8**) failed. Treatment of **2** with several amines produced **9** and **10** (figure 6).





5 Conclusion:

The original targets proved challenging to synthesise. The phenyl compound (**3**) was isolated, as was an 8-oxo guanine species. Suitable conditions for four other targets were determined. Compounds that were successfully produced and characterised, will be tested for their inhibitory activity against the Nek2 kinase.

Acknowledgements: Thanks to Professors B T Golding and R J Griffin for giving me the opportunity to work on this project, and for project supervision. I would also like to thank Dr Benoit Carbain for help and advice. I also thank Newcastle University for the funding.

[1] P. Rellos *et al,* Structure and Regulation of the Human Nek2 Centrosomal Kinase, *J. Biol. Chem.,* 2007, **282,** *6833-6842*