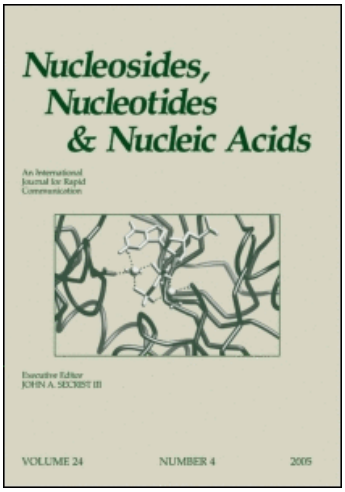


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Purine Based Combinatorial Chemistry: Solution Phase Simultaneous Addition of Functionalities. Iterative Deconvolution by Orthogonal Protection to a Single Compound with Potent Antibacterial Activity

A. S. Fraser[a]; A. M. Kawasaki[a]; P. D. Cook[a]
[a] Department of Medicinal Chemistry, Isis Pharmaceuticals, Inc., Carlsbad, California

To cite this Article Fraser, A. S. , Kawasaki, A. M. and Cook, P. D.(1999) 'Purine Based Combinatorial Chemistry: Solution Phase Simultaneous Addition of Functionalities. Iterative Deconvolution by Orthogonal Protection to a Single Compound with Potent Antibacterial Activity', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 1087 — 1089
To link to this Article: DOI: 10.1080/15257779908041654
URL: http://dx.doi.org/10.1080/15257779908041654

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 1087–1089 (1999)

PURINE BASED COMBINATORIAL CHEMISTRY: SOLUTION PHASE SIMULTANEOUS ADDITION OF FUNCTIONALITIES. ITERATIVE DECONVOLUTION BY ORTHOGONAL PROTECTION TO A SINGLE COMPOUND WITH POTENT ANTIBACTERIAL ACTIVITY.

A. S. Fraser*, A. M. Kawasaki and P.D. Cook
Department of Medicinal Chemistry, Isis Pharmaceuticals, Inc., 2292 Faraday Avenue, Carlsbad, California 92008

We have recently described a method to prepare combinatorial chemistry libraries by solution phase simultaneous addition of functionalities (SPSAF).[1-2] SPSAF has been used to create libraries based on the purine heterocycle. The nucleophilic sites (secondary nitrogens) in the planer heteroaromatic purine scaffold were built in via linkers. Thus, to continue the use of electophilic functionalities, as in previous libraries, a bifunctional nucleophilic linker was required. Piperazines readily served this purpose. Nucleophilic displacement of the chloro groups on 2,6-dichloropurine with piperazines provides reactive, constrained secondary amines for combinatorialization (Figure **1**, **1**). An additional piperazine was placed in the 9-position by alkylation of 2,6-dipiperazinylpurine. In this manner, the functionality that differentiates each pool (sublibrary) could be placed last in the synthetic scheme (fix last concept).[1]

Synthesis of a tri-substituted nucleophilic scaffold (Figure **1**, **1**) and the simultaneous combinatorilization (SPSAF) of the 2 and 6 piperazinyl nigrogen groups (positions **B** and **C**, Figure **1**, **1**) with five electrophilic functionality sets, each set giving rise to a library. The t-Boc protecting group was removed and the library divided into individual fractions and fixed with appropriate functionalities to provide 43 sub-libraries (total of 2725 tri-substituted purines). All 43 sub-libraries were examined for antibacterial activity by minimum inhibitory concentration (MIC) assays against *S. pyogenes and E.*

Figure 1
Tri-Substitued Purine Scaffold

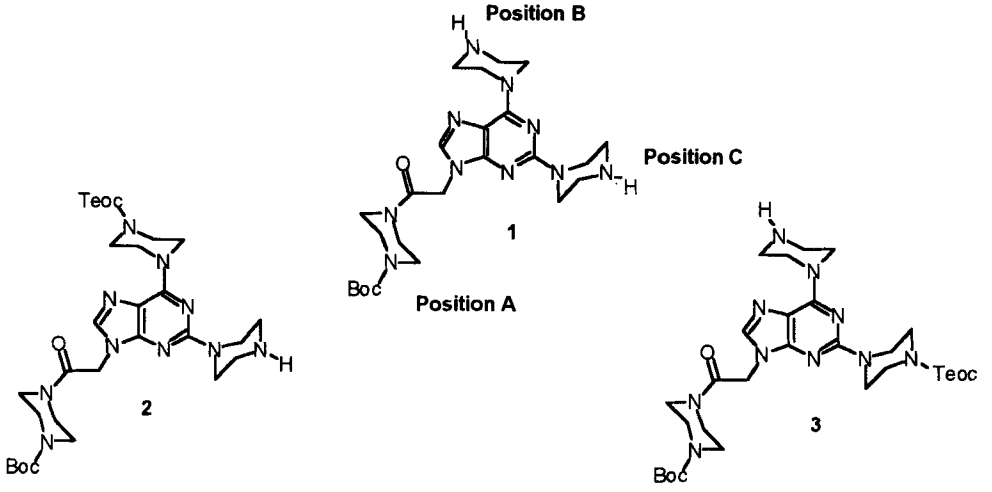
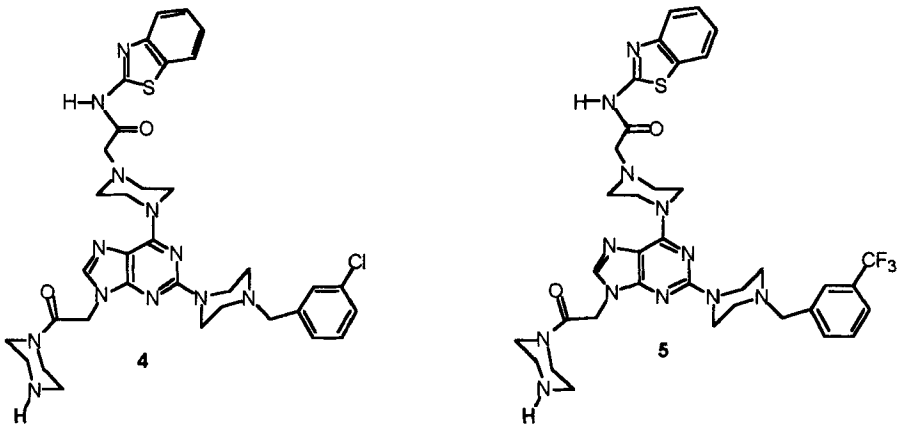


Figure 2
Active compounds
from Iterative Deconvolution



coli imp- and in select cases a *C. albicans* yeast specificity assay. The biological activity for the first round produced one sublibrary as a candidate for deconvolution. The iterative solution phase deconvolution using orthagonally protected scaffolds **2** and **3** (Figure **1**) resulted in two active compounds, **4** and **5** (Figure **2**). Compounds **4** and **5** exhibit a potent broad based antibacterial profile against several known pathogens (*S. pyogenes S. aureus, K. pneumoniae*) and both compounds show a possible two fold enhanced activity compared to the parent sublibrary of 100 compounds.

Acknowledgments: Supporting work by Laura Wilson-Lingardo, Lisa M. Risen, Larry Blyn and Jacqueline R. Wyatt with biological assays is greatly appreciated.

REFERENCES:

1. An, H.; Cummins, L. L.; Griffey, R. H.; Bharadwaj, R.; Haly, B. D.; Fraser, A. S.; Wilson-Lingardo, L.; Risen, L. M.; Wyatt, J. R.; Cook, P. D. *J. Am. Chem. Soc.* **1997**, *119*, 3696-3708.
2. An, H.; Haly, B.D.; Fraser, A. S.; Guinosso, C.J.; Cook P.D. J. Org. Chem. **1997**, *62*, 5156-5164.