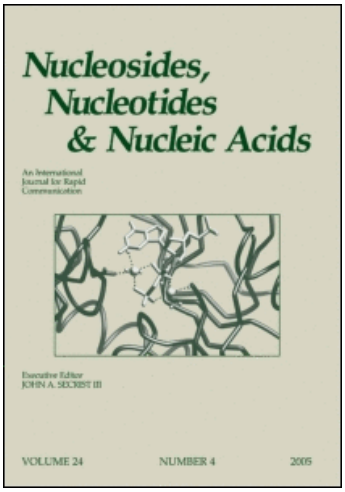

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Solution Phase Combinatorial Chemistry. Purine- and Pyrimidine-Based Libraries with Antibacterial Activity via Solution Phase Simultaneous Addition of Functionalities

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SOLUTION PHASE COMBINATORIAL CHEMISTRY. PURINE- AND PYRIMIDINE-BASED LIBRARIES WITH ANTIBACTERIAL ACTIVITY VIA SOLUTION PHASE SIMULTANEOUS ADDITION OF FUNCTIONALITIES

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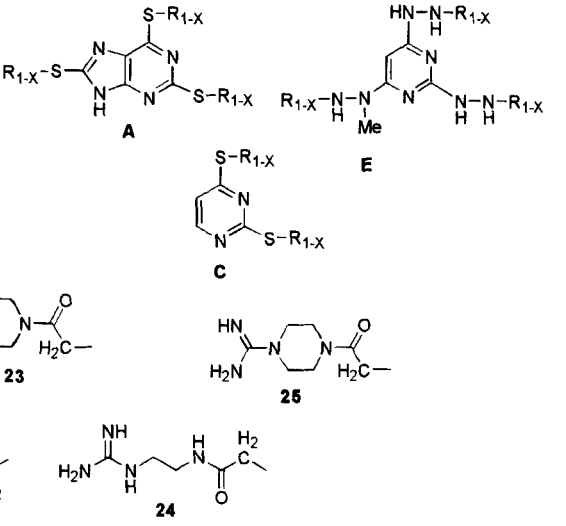
ABSTRACT: We have effectively used the SPSAF method with purine and pyrimidine based scaffolds to rapidly generate diverse libraries with antibacterial activity. Deconvolution via HPLC fractionation resulted in libraries with reduced complexity (2-10 compounds), a number of which retained good antibacterial activity.

In recent years the area of drug discovery has been greatly impacted by the emerging field of combinatorial chemistry.[1] Obviously the technology provides a tool for streamlining the process of lead development, but also less appreciated is the potential for discovery of novel pharmacophores. To date, the most common method for preparing libraries of small organic molecules has been via solid phase, either as parallel synthesis of single compounds or as mixtures.[2] Recently solution phase chemistry has been used to the same end. Of late we have reported a process of preparing chemical libraries by adding a mixture of functionalities to a single scaffold with several reactive sites in solution,[3] a process which has been labeled SPSAF (solution phase simultaneous additon of functionalities).

Application of SPSAF with purine and pyrimidine based scaffolds and diverse functionalities provided seven first round libraries (complexities of 25, 49, or 125) which displayed activity in bacterial growth inhibition assays. The amino- and guanidino-containing groups **22-25,** in conjunction with the quinoline moiety **21,** functionalized onto purine and pyrimidine scaffolds appeared to be key to the inhibitory activity. Deconvolution by HPLC fractionation of libraries A8 based on scaffold A, C3 based on

Library	$R_{1\text{-}X}$
A8	21, 22, 23, 24, 25
C3	21, 22, 23, 24, 25
E1	21, 22, 23, 24, 25
E2	13, 21, 22, 23, 24



scaffold C, and E1 and E2 both based on scaffold E afforded fractions of reduced complexity (2-10) which retained good antibacterial activity (2-10, 20, 3-10, 3-10 μM, respectively). Mass spectrometry enabled characterization of library fractions with respect to composition of the members, however, the regiochemistry of substitution was not determined. Thus, to address this issue the next phase of deconvolution will involve MS/MS and/or multidimensional NMR analysis of structure.

Thus, we have effectively used the SPSAF method with purine and pyrimidine based scaffolds to rapidly generate diverse libraries with antibacterial activity. Deconvolution via HPLC fractionation resulted in libraries with reduced complexity (2-10 compounds), a number of which retained good antibacterial activity.

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