These results strengthen the hypothesis that both the electronic nature and the location of the carbonyl group play an essential role in the functionality of this series as acetylcholine receptor agonists. The interesting profile of [(–)-**(xiii)**] makes this compound an important tool for the understanding of α7 nicotinic receptor function.


**12** De Fiebre, C.M. *et al.* (1995) Characterization of a series of anabaseine-derived compounds reveals that 3-(4)-dimethylamino-cinnamylidene derivative is a selective agonist at neuronal nicotinic α7/$^{125}$I-α-bungarotoxin receptor subtypes. *Mol. Pharmacol.* 47, 164–171

**13** Mullen, G. *et al.* (2000) (–)-spiro-[1-azabicyclo[2.2.2]octane-3,5′oxazolidin-2′-one], a conformationally restricted analogue of acetylcholine, is a highly selective full agonist at the α7 nicotinic acetylcholine receptor. *J. Med. Chem.* 43, 4045–4050



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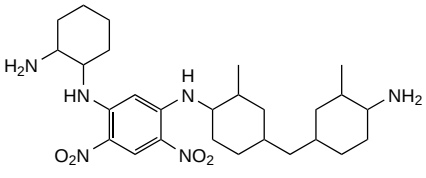
## Combinatorial chemistry

### Antibacterial compounds

Gram-positive bacteria have become increasingly resistant to antimicrobial agents, and hence multi-drug-resistant bacterial pathogens are now a major problem in clinical medicine. *Staphylococcus aureus* is a common human pathogen that has become increasingly difficult to treat because of its resistance to antimicrobial agents. Vancomycin is the main antimicrobial treatment for infections caused by *S. aureus* strains that cannot be treated with penicillinase-resistant antibiotics. The emergence of vancomycin-resistant *Enterococcus* species raises the threat of possible transfer of resistance factors to *S. aureus*. Vancomycin-resistant *Stapylococcus* clinical isolates have already been discovered in Japan. There is, therefore, a need for new antimicrobial agents.

A solution-phase approach was used to identify compounds with novel antibacterial activity[1]. A library of 4,900 compounds was prepared in mixtures of ten from a solution-phase sequential displacement of two fluorines on the 1,5-difluoro-2,4-dinitrobenzene core library template using a set of 70 amines. The mixtures of ten were tested for antibacterial activity against *S. aureus* and *E. faecalis* and several active mixtures were identified. All compounds contained within these mixtures were resynthesized as single compounds and re-tested. One of the most potent compounds isolated was **(i)**. This compound possessed a minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) against *S. aureus* of 11.09 μg ml$^{-1}$ and 22.18 μg ml$^{-1}$, respectively, and MIC and MBC values against *E. faecalis* of 5.5 μg ml$^{-1}$ and 11.0 μg ml$^{-1}$, respectively. This work could, therefore, prove useful in the further optimization of the lead compounds identified in this library for the production of more potent novel antibacterial agents.



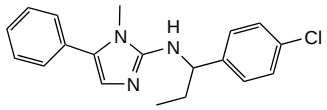

**(i)**


**1** Lam, K.S. *et al.* (2000) Solution-phase synthesis of a 1,5-dialkylamino-2,4-dinitrobenzene library and the identification of novel antibacterial compounds from this library. *J. Comb. Chem.* 2, 467–474


### $Na^+/K^+$ ATPase inhibitors

Congestive heart failure (CHF), a disease characterized by the failure of the heart to pump sufficient blood to meet the metabolic needs of the body, affects millions of people worldwide. The five-year mortality rate for CHF is almost 50%, and symptoms of the disease include peripheral oedema, tachycardia and decreased exercise capacity. Current treatments include diuretics, angiotensin-converting-enzyme inhibitors and digitoxin. Digitoxin has been shown to increase the exercise capacity of CHF patients via the inhibition of myocardial $Na^+/K^+$ ATPase, which strengthens the heart's pumping action (positive inotropy). Digitoxin plasma-concentrations, however, must be carefully maintained below the potentially life-threatening concentration of 2.0 ng ml$^{-1}$. Treatment with digitoxin is complicated further by high plasma-protein-binding and lipid solubility, which can extend the time and dosing required to achieve steady-state plasma concentrations (up to two weeks in some patients).

To develop positive inotropes with a more favourable therapeutic index, a library of aminoimidazoles was synthesized[2]. Thirteen individual compounds were synthesized in solution by condensation of a series of lithium amides with substituted heteroaryl sulfones. One of the most potent compounds isolated was **(ii),** which possessed an $IC_{50}$ value of 800 nM against the isolated myocardial $Na^+/K^+$ ATPase enzyme. This work could be useful in the future for further defining the pharmacophore required for activity against myocardial $Na^+/K^+$ ATPase.




**(ii)**


**2** Blass, B.E. *et al.* (2000) Parallel synthesis and evaluation of *N*-(1-phenylethyl)-5-phenylimidazole-2-amines as $Na^+/K^+$ ATPase inhibitors. *Bioorg. Med. Chem. Lett.* 10, 1543–1545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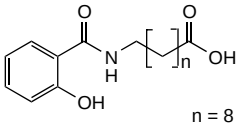
**Heparin delivery agents**

Heparin is the most commonly used anticoagulant for hospitalized patients, but it is administered only by injection because it is not absorbed following oral dosing. One approach to developing an oral heparin is to prepare and screen putative novel, oral heparin-delivery agents. The traditional approach to the elucidation of delivery agents facilitating the oral administration of heparin has been to screen a combination of one delivery agent and heparin per study group. This traditional approach requires the preparation, purification and structural identification of each delivery agent individually. Each *in vivo* study provides data on only one delivery agent. To improve the throughput in these studies, a parallel synthesis approach was investigated[3].

A library of 25 compounds in mixtures of five was prepared in solution by benzoylating a range of amino acids. Each mixture was tested in the colon of rats for its ability to facilitate the gastrointestinal absorption of heparin. Evidence of heparin delivery was indicated by an increase in blood clotting time measured by activated partial thromboplastin time (APTT). One of the most active compounds identified, when active mixtures were resynthesized as single entities, was **(iii)**, which possessed an APTT of >150 sec. This work is useful in increasing the screening throughput significantly in an *in vivo* assay, allowing the identification of delivery agents for heparin more rapidly than had been previously possible. In this case, testing of 25 compounds was achieved in just ten experiments. A traditional medicinal chemistry approach would have required 25 experiments to test 25 compounds.




**(iii)**

**3** Leone-Bay, A. *et al.* (2000) Studies directed at the use of a parallel synthesis matrix to increase throughput in an *in vivo* assay. *J. Med. Chem.* 43, 3573–3576

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## Contributions to *Monitor*

We welcome recommendations of papers for review within *Monitor*, in the fields of combinatorial chemistry, pharmacogenomics, pharmacoproteomics, bioinformatics, new therapeutic targets, high throughput screening, new drug delivery technologies and other promising lines of research. Details of recent papers or those *in press* should be directed to Dr Debbie Tranter, Editor, *Drug Discovery Today*, Elsevier Science London, 84 Theobald's Road, London, UK WC1X 8RR
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