Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

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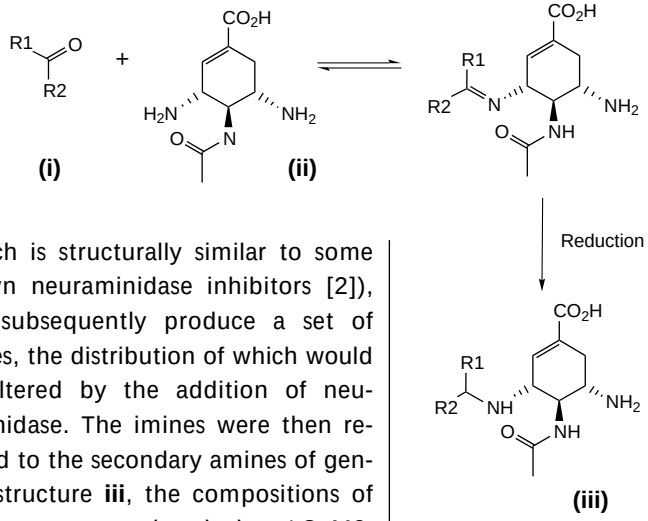
Combinatorial chemistry

Neuraminidase inhibitors from dynamic combinatorial libraries

Dynamic combinatorial chemistry (DCC) is a new approach to the integration of combinatorial chemistry and screening and is based on the shift of chemical equilibrium in a mixture of interconverting components, driven by a molecular target. This process results in the selective formation of one or a few mixture components that form the strongest noncovalent complexes to the target. The successful application of DCC to the discovery of new ligands for biological targets relies on the synergy of several factors: use of reversible reactions that are compatible with aqueous media, availability of functional diversity of library building blocks and robust methods of mixture analysis. The first use of ketones as the building blocks of dynamic libraries has been reported by Eliseev *et al.* [1].

The structures of library components that are selected and amplified by the target reveal building block combinations that can be used to generate highly active inhibitors with properties that at least match those of commercial drugs. Neuraminidase, a key enzyme in influenza virus propagation, has been used to exemplify the DCC approach.

A mixture of 22 ketones (**i**) was used to equilibrate the scaffold, diamine (**ii**)

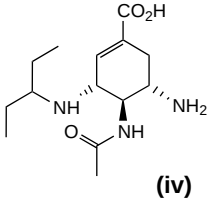


(which is structurally similar to some known neuraminidase inhibitors [2]), and subsequently produce a set of imines, the distribution of which would be altered by the addition of neuraminidase. The imines were then reduced to the secondary amines of general structure **iii**, the compositions of which were analyzed by LC–MS. Addition of the enzyme target resulted in a dramatic amplification of selected amine peaks – the binding properties of the amines (**iii**) (as measured by K_i values) correlated well with their amplification in the DCC experiment, with one of the most potent compounds synthesized being **iv,** with a K_i of 85 nM. This work has provided neuraminidase inhibitors that are more potent than the native forms and, thus, the DCC approach outlined here warrants further investigation.

TNF-α inhibitors

One of the earlier approaches to combining the design and synthesis of combinatorial libraries with biological screening efforts was the split-pool method for the synthesis of a library, and subsequent assay of its mixtures for biological activity. Although valuable, the full potential of the method was limited by high levels of false positives, which were due, in part, to the additive effects arising from the screening of mixtures.

A programme using an aroyloxy proline scaffold has been undertaken, with the aim of generating a diverse collection of combinatorial libraries for screening [3]: a 1728-member split-pool library was synthesized in mixtures of 48 on TentaGel SRam NH_2 solid phase resin



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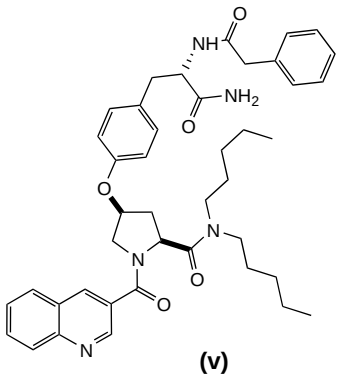

(v)

(a commercial amine resin, from Advanced ChemTech, http://www. peptide.com). The library compounds were screened in a functional assay designed to identify inhibitors of tumour necrosis factor (TNF)-α signalling – the addition of TNF-α to A549 cells in the presence of actinomycin D causes the cells to undergo apoptosis, a crucial part of cellular homeostasis that, if left unchecked, could contribute to disease states such as sepsis or reperfusion injury. TNF-α is also a pro-inflammatory cytokine and is known to have a role in inflammatory diseases, such as rheumatoid arthritis, psoriasis and inflammatory bowel disease.

Several active mixtures were obtained upon screening and, following deconvolution of one of these, compounds were resynthesized in solution, purified and re-screened in the apoptosis assay. One of the most potent compounds isolated was **v**, having an IC_{50} value of 8.1 μM. This work has generated rapid SAR, based on a novel tyrosine-proline peptidomimetic scaffold and, thus, should be explored further.

1 Eliseev, A.V. *et. al.* (2003) Ketones as building blocks for dynamic combinatorial libraries: highly active neuraminidase inhibitors generated via selection pressure of the biological target. *J. Med. Chem.* 46, 356–358

2 Lew, W. *et. al.* (2000) Discovery and development of GS 4104 (oseltamivir): an orally active influenza neuraminidase inhibitor. *Curr. Med. Chem.* 7, 663–672

3 Jackson, R. W. *et. al.* (2003) Identification of TNF-α inhibitors from a split-pool library based on a tyrosine-proline peptidomimetic scaffold. *Bioorg. Med. Chem. Lett.* 13, 205–208

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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 Steve Carney, Editor, *Drug Discovery Today*, Elsevier, 84 Theobald's Road, London, UK WC1X 8RR. tel: +44 207 611 4132, fax: +44 207 611 4485, e-mail: DDT @elsevier.com

Contributions to *Profiles*

We welcome contributions for the *Profiles* series, which gives a commentary on promising lines of research, new technologies and progress in therapeutic areas. Articles should provide an accurate summary of the essential facts together with an expert commentary to provide a perspective. Brief outlines of proposed articles should be directed to the *Monitor* Editor (see below). Articles for publication in *Monitor* are subject to peer review and occasionally may be rejected or, as is more often the case, authors may be asked to revise their contribution. The *Monitor* Editor also reserves the right to edit articles after acceptance.

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