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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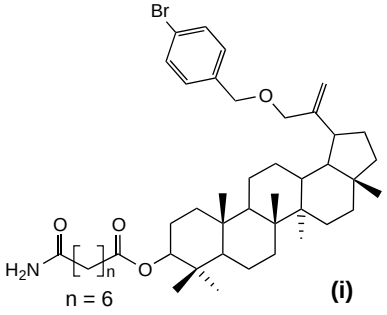
Combinatorial chemistry

Antimalarial agents

Natural products represent promising scaffolds for diversification using combinatorial chemistry techniques because they have been selected by nature for their ability to undergo transformations in 3D space. Library construction around such scaffolds offers the potential for both lead discovery and optimization. Usually, however, such diversification is functional-group-based with the original structure of the template unchanged. Terpenoids are often isolated in significant quantities from natural sources, and a wide array have been isolated and characterized. The lupane-type of triterpenoids and their derivatives represent a unique and important class of biologically active natural product.

An example is the pentacyclic triterpenoid lupeol [lup-20(29)-en-3β-ol] obtained from the stem bark of *Crataeva nurvula*, which is of interest because of its demonstrated wide spectrum of biological activity, such as anticalciuric and antimalarial activity against chloroquine-resistant *Plasmodium falciparum*. Recent work has used template-directed synthesis of libraries based upon lupeol with the aim of increasing the antimalarial activity of compounds contained within the library [1].

Two libraries totalling 96 individual compounds were synthesized on Rink/Sieber amide solid phase resin. Compounds were evaluated for their antiparasitic activity by evaluating their minimum inhibitory concentration (MIC) against *P. falciparum in vitro*. One of the most active compounds was **i**, which possessed a MIC of 13.07 μM, compared with the MIC value of 117 μM for lupeol. This work has produced compounds with a 7- 9-fold increase in antimalarial activity, compared to lupeol using combinatorial chemistry techniques, and this approach warrants further investigation to optimize this lead structure.



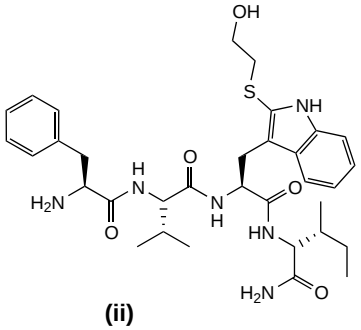
(i)

1 Srinivasan, T. *et. al.* (2002) Solid-phase synthesis and bioevaluation of lupeol-based libraries as antimalarial agents. *Bioorg. Med. Chem. Lett.* 12, 2803–2806

Motilin agonists

Motilin, a single-chain peptide of 22 amino acid residues, was isolated from endocrine cells in the gastrointestinal (GI) mucosa of various species. Although the biological function of motilin has not been fully elucidated, the peptide is known to stimulate GI motility in several species. Motilin has been suggested to have physiological relevance to several gastrointestinal symptoms, including early satiety, abdominal distension, nausea, vomiting and anorexia. Although motilin agonists have been suggested to be effective in the treatment of such symptoms, the detailed mechanisms of motilin agonistic action after binding to the motilin receptor (MTL-R) have yet to be explored. The discovery of small-molecule agonists could stimulate new studies on the biological and physiological mechanism of motilin, and perhaps lead to the discovery of new drugs for the treatment of patients with hypomotility symptoms [2].

A small library of 11 compounds was constructed on *p*-methylbenzhydrylamine substituted polystyrene resin and the compounds tested for binding activity to MLT-R and for rabbit smooth-muscle contractile activity. One of the most potent compounds isolated was **ii**, which



(ii)

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possessed a binding affinity IC_{50} value of 570 nM, and an EC_{50} value of 14.1 μM in the contractile assay, demonstrating that the N-terminal tetrapeptide can act as a motilin agonist *in vivo*. This work has generated rapid SARs against MLT-R, and these studies will hopefully stimulate further work on the elucidation of the biological and physiological mechanism of motilin and assist in developing remedies for motilin-associated diseases.

2 Haramura, M. *et. al.* (2002) Design and synthesis of novel tetra-peptide motilin agonists. *Bioorg. Med. Chem.* 10, 1805–1811

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