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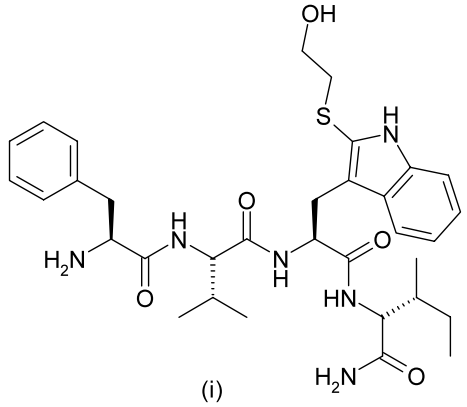
1. Current literature highlights

1.1. Motilin agonists

Motilin, a single-chain peptide of 22 amino acid residues, has been isolated from endocrine cells in the gastrointestinal (GI) mucosa of various species. Although the biological function of motilin has not been fully elucidated, it is known to stimulate GI motility and has been suggested to have physiological relevance to a number of 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.[1]



(i)

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 (i) which possessed a binding affinity IC_{50} of 570 nM, and an EC_{50} in the contractile assay of 14.1 μM, demonstrating that the N-terminal tetrapeptide can act as a motilin agonist in vivo. This work has generated rapid SAR 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.

1.2. VCAM-1 expression

Leukocyte recruitment into inflamed tissue is an essential physiologic process to remove inflammatory stimulus. However, this response itself can lead to a chronic and detrimental inflammatory process if the stimulus is not properly eliminated. Thus leukocyte recruitment itself is a key factor in the pathogenic process of inflammation. At the sites of inflammation the recruitment of leukocytes is mediated, in part, by the expression on endothelial cells of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin, that are induced in response to various cytokines such as TNF-α.

Steroids and other anti-inflammatory drugs with broad spectrum activities are effective in treating numerous diseases and inflammatory conditions. However, their long-term use often leads to unacceptable side-effects. Some leukocytes, including T cells, monocytes and eosinophils constitutively express very late antigen-4 (VLA-4), the receptor of VCAM-1, and are key effector cells in various inflammatory disorders. Tissue samples from patients have also indicated that VCAM-1 is highly expressed in many diseases. Selective inhibitors of VCAM-1 are therefore likely to have potential as therapeutic targets.[2]

A commercial library was screened giving rise to two hits (ii) and (iii) which were weak inhibitors of inducible VCAM-1 expression. Subsequent optimisation

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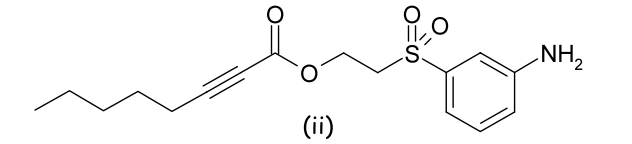
improved potency leading to (iv) as one of the most potent compounds synthesised with an IC_{50} of 2 μM. This work has indicated that α,β-unsaturated sulfones, discovered from a combinatorial library are a new series of inhibitors of inducible VCAM-1 expression and this approach warrants further investigation to optimise this lead series still further.



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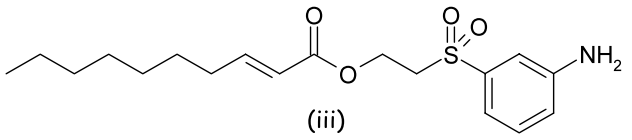
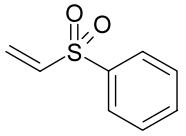


(iii)



(iv)

2. A summary of the papers in this month's issue

2.1. Solid-phase synthesis

An efficient and mild method for the reduction of aromatic nitro and azido groups on solid support using $Al/NiCl_2 \cdot 6H_2O$ and Al/NH_4Cl has been described.[3]

Deprotection of the Boc group of an amino acid attached to the Wang resin has been investigated, and several conditions, including bases, solvents and reaction time, were studied.[4]

A synthesis of new cyclopeptides via Mannich condensation on solid support with a simple work-up procedure and very good yields has been reported.[5]

A method for the detection of aromatic amines on the solid support by using chloranil has been developed. This test can detect as little as less than 5 μmol g^{-1} of primary aromatic amines attached to the resin.[6]

The use of ^{19}F NMR as a simple means to monitor reactions on a solid phase has been reported. Multi-step sequences including protection, coupling, deprotection, condensation, cycloaddition and cleavage steps are described in the case of multicomponent reactions involving fluorinated α-aminoesters, aldehydes and acid chlorides.[7]

Glycosylation reactions performed between a glycosyl donor and acceptor covalently linked to a peptide template both in the solution and solid phase have been shown to give similar yields and product distributions. The adoption of a solid phase approach opens the way for the synthesis of libraries of peptide templates in an attempt to screen for particular peptide sequences that effect complete regio- and stereochemical control during glycosidic bond formation.[8]

Diastereoselective additions of the resin-supported (*S*)-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) acetic acid to phthalimidomethyl aryl ketenes allow solid phase preparation of β^2-homoarylglycines with reasonable degrees of stereoselectivity.[9]

2.2. Solution-phase synthesis

1,3-Dipolar cycloadditions of nitrile oxide generated in situ on soluble polymer with a variety of imines has provided a library of 4,5-dihydro-1,2,4-oxadiazoles in good yields and purity.[10]

A variety of fused 3-aminoimidazoles have been synthesised by a microwave assisted Ugi three-component coupling reaction catalysed by scandium triflate in methanol as solvent. Yields of 33–93% have been achieved after just 10 min of microwave irradiation using a simple one-stage procedure.[11]

2.3. Library intermediates

The reactions of benzocyclic ketones and α-ketoacids as carbonyl components in the Biginelli reaction have been investigated to generate novel drug-like dihydropyrimidinone scaffolds suitable for further elaboration in combinatorial libraries.[12]

Anchoring of an α-amino-acid amide residue by its amine function to a carbamate resin followed by primary amide Hofmann rearrangement has resulted in a *gem*-diamino residue linked to the resin. The generated primary amine could be acylated with various carboxylic compounds offering a large variety of molecules.[13]

2.4. Novel resins and linkers

Microwave heating of high-loading TEMPO-methyl resin with functionalized styrenyl monomers affords large resin beads (>500 μm) via living free radical polymerization.[14]

The synthesis of a series of symmetrical AB_3 isocyanate-type monomers has been reported for the preparation of tri-branched dendrimers on solid-phase. This method not only allows isolable dendrimer but can generate high-loading supports and devices for multivalent presentation.[15]

The development of a versatile amine releasing linker based on the modified *o*-nitrobenzene sulfonamide protective group has been described. This new *N*-Boc-

o-nitrobenzenesulfonamide (Boc-ONBS) linker enables the elaboration on resin of primary and secondary amines by sequential substitution of the sulfonamide moiety using the Mitsunobu reaction.[16]

2.5. Solid-supported reagents

Soluble non-crosslinked polymers of *p*-vinylaniline and 3-vinyl-8-aminoquinoline-based phosphoramidites have been prepared by free radical co-polymerisation with styrene in the presence of AIBN as initiator. The corresponding $[Rh(COD)]^+$ complexes serve as recyclable catalysts for the asymmetric hydrogenation dimethylitaconate and dehydroamino acids and esters to give ee values up to 80%.[17]

Resin plugs, derivatised and loaded with palladium(0), have been used in the preparation of a Suzuki reaction based library and the removal of allyl ester protecting groups.[18]

2.6. Library applications

In an effort to identify orally bioavailable factor Xa inhibitors, two isoxazolines libraries have been prepared to scan for novel P1 ligands, resulting in 4-chloro-3-aniline being identified as a novel and potent benzamidine mimic.[19]

A new solid-phase synthesis for ET receptor antagonists suitable for automation has been described. Highly potent antagonists with excellent selectivity for ET_A were obtained.[20]

Dimeric vancomycin analogues based on a lead compound identified from a library of synthetic analogues of vancomycin have been demonstrated to have up to 60-fold greater activity than vancomycin against vancomycin-resistant *Enterococcus faecium* (VRE, VanA phenotype).[21]

Phenylalanine derivatives designed as phosphotyrosine mimetics or irreversible active site inhibitors have been synthesized, and then incorporated into a combinatorial library based on a peptidomimetic β-strand template.[22]

A library of urea compounds based on the tripeptide Phe-Trp-Lys were synthesized on solid-phase and pharmacologically characterized leading to the identification of novel melanocortin receptor agonists.[23]

Pepticinnamin E is a naturally occurring bisubstrate inhibitor of farnesyltransferase. Based on the structure of the natural product, a total of 51 analogues have been synthesised on polymeric support in 6–11-step parallel syntheses.[24]

A library of 51 analogues of the naturally occurring protein farnesyltransferase inhibitor pepticinnamin E have been investigated biologically, and several compounds with pronounced inhibitory activity were discovered with the lowest IC_{50} value reaching 1 μM.[25]

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Further Reading

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