1. Current literature highlights

1.1. Nicotinic acetylcholine receptor agonists

Polyamine toxins, a class of non-oligomeric, low molecular weight compounds isolated from the venom of spiders and wasps, are non-selective inhibitors of ionotropic receptors such as ionotropic glutamate receptors (iGluRs) and nicotinic acetylcholine receptors (nAChRs). The polyamine moiety of these toxins is considered to interact with polar or charged amino acid residues in the interior of cation-selective ion channels. It has recently been demonstrated that by modification of the polyamine portion of (i) it was possible to achieve selectivity for nAChR, as with (ii). Compound (ii) is a promising lead for the development of novel potent and selective non-competitive antagonists of nAChR.

Studies were undertaken to provide SAR within the series exemplified by (ii). A small library of seven compounds was synthesised on trityl chloride solid phase resin. The library compounds were screened for activity in the whole-cell patch-clamp assay, using human embryonic muscle-type nAChR expressed in TE671 cells. One of the most potent compounds isolated was (iii) which possessed an IC$_{50}$ of 460 nM. This work has provided novel, potent leads worthy of further investigation.

1.2. ECE Inhibitors

Endothelin-1 (ET-1), a 21 amino acid peptide, is a potent, long acting vasoconstrictor. High plasma levels are found in many clinical conditions such as congestive heart failure, subarachnoid haemorrhage and pulmonary hypertension. Endothelin is produced from its biologically inactive precursor big-ET by the Zn-endopeptidase, endothelin converting enzyme (ECE). It is thought that the inhibition of ECE-1 may allow the specific blockage of the whole ET system, and is therefore an attractive therapeutic approach. Workers at Hoffman–La Roche have attempted to improve the potency of their lead (iv) and to elucidate SAR by modifying three sites on (iv). A small library was synthesised on solid phase in an attempt to generate potent ECE inhibitors. The library compounds were evaluated for their inhibition of hECE-1. One of the most potent compounds found was (v) which possessed an IC$_{50}$ of 150 nM. This work has produced potent ECE inhibitors, and holds promise for further optimisation.
2. A summary of the papers in this month’s issue.

2.1. Solid-phase synthesis

A remarkable new entry to N-unsubstituted β-lactams using rink resin as the solid-support has been developed. A concise synthesis of a β-silylethanol anchoring group on an aminomethylated Merrifield resin has been achieved from 3-dimethyl(phenyl)silyl-5-oxohexanoic acid featuring a solid-phase silicon directed Baeyer–Villiger oxidation of a β-silylketone as the key step.

A convenient synthesis of enantiomerically pure oxindoles using a three component reaction involving 1:3 dipolar cycloaddition reaction has been achieved using solution and solid phase chemistry.

2.2. Solution-phase synthesis

A three-component synthesis of stereodefined 4-benzylidene-(or alkenylidene)-pyrrolidines from simple, readily available starting materials has been described. This one-pot process is initiated by a conjugate addition of a propargylamine to a gem-diacti1ated olefin subsequently followed by a carbopalladation involving an aryl halide (or vinyl triflate).

Tertiary amides bound to gel-type polystyrene support were reduced with LiAlH₄ to give tertiary amines with satisfactory purity, whereas the reduction of similar tertiary amides in solution gave secondary amines as main products. Synthesis of tertiary amine libraries was achieved by using this method.

2.3. Library intermediates

A glucosamine donor was selected for the solution-phase synthesis of a β-(1-6)-glucosamine pentasaccharide and proved well suited for use in the automated solid-phase synthesis of a repeating unit trisaccharide.

Glycosyl iodide donors have been used in both solid- and solution-phase syntheses yielding α-(1–6)-linked glucosyl oligomers in highly efficient protocols.

2.4. Solid-supported reagents

A butyldiethylsilyl polystyrene (PS-DES) supported ruthenium carbene is a robust, practical and easily recyclable catalyst for olefin metathesis of substituted olefins.

Cyanuric chloride was loaded onto a modified Wang resin, which was successfully used to convert carboxylic acids to their corresponding acyl chlorides. The formation of acyl chlorides were confirmed by condensation with various amines or alcohols to form the corresponding amides or esters.

2.5. Novel resins, linkers and techniques

Pyroglutamic cyclisation of glutamic acid has been used to investigate this amino acid as a linker for the attachment of alcohols. As a first example, the solid-phase synthesis of dimers on a 3,3'-diaminodiphenylmethanol has been reported.

Modification of insoluble polymers through covalent attachment of short chain soluble polymers can produce hybrids that combine some of the advantages of both types of polymers such as physical stability and solvent-like characteristics. A convenient microwave-assisted PEGylation method of Merrifield resin (MR) has been developed using focused microwave irradiation under atmospheric pressure.

2.6. Library applications

A library of tetrapeptides was evaluated for Hepatitis C Virus NS3 protease inhibitor activity in an in vitro assay system comprising the native bifunctional full-length NS3 (protease-helicase/NTPase) protein.

A series of [difluoro-(3-alkenylphenyl)-methyl]-phosphonates were prepared on non-crosslinked polystyrene, a soluble polymer support. After cleavage from the support, the resulting phosphonic acids were examined for inhibition of protein tyrosine phosphatase.

The crystal structure of a gp120/CD4/Fab17b complex was analysed leading to the design of several peptide libraries. Syntheses of tri- and tetra- and pentapeptides were performed via a solid phase synthesis methodology and were assayed against C8166 cells infected by HIV-1 IIIB and screened using a gp120 binding assay.

References

Further Reading

Papers on combinatorial chemistry or solid-phase synthesis from other journals


