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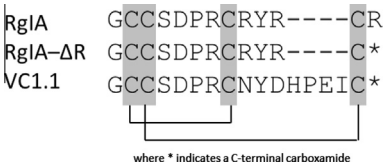
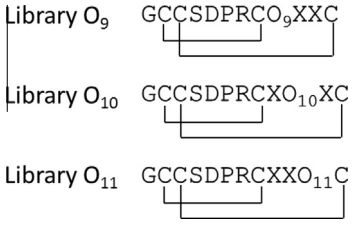
1. Current literature highlights

1.1. Novel antinociceptive α-conotoxin analogues from a synthetic combinatorial library

Marine cone snails generate venoms which consist of a naturally-occurring combinatorial mixture of peptides that can swiftly immobilise prey animals. The venoms are complex in that each species of snail can express thousands of individual peptides, many of which have been characterised and shown to be ligands of various ion channels and receptors. Amongst these venom peptides, the α-conotoxins are selective for nicotinic acetylcholine receptors (nAChRs). Their unique structures are based on the formation of two peptide loops (denoted *m*- and *n*- respectively) which are maintained by the presence of two highly conserved disulphide bonds. Although the peptide sequences in each of the two loops varies greatly, two α-conotoxins, RgIA and Vc1.1, have been shown to be efficacious in treating pain in animal models. Both these peptides share an Asp-Pro-Arg motif in the *m*-loop which is presumed to be essential for nAChR activity. Deletion of the C-terminal Arg residue of RgIA to give RgIA-ΔR has no effect on this activity. As other peptides possessing the Asp-Pro-Arg motif but variable *n*-loops have different analgesic activity and selectivity, it is hypothesised that these properties can be modified by the peptide sequence of the *n*-loop. A recent study has used combinatorial chemistry to explore variability in the *n*-loop in a series of synthetic analogues of RgIA-ΔR.[1]



The α-conotoxin positional-scanning synthetic combinatorial library was made up of three individual sub-libraries defined as O_9, O_{10}, and O_{11} respectively. Each sub library had a mixture of 22 natural and non-natural amino acids mixed in two positions (X), and one defined amino acid in the remaining third (O) position. The amino acids employed comprised natural amino acids plus the addition of norleucine, aminoisobutyric acid, hydroxyproline and norvaline. Each sub library was thus generated as 22 mixtures each of 484 peptides giving a total library size of 10,648 possible individual conotoxin sequences. The library was synthesised using Boc-based solid phase peptide chemistry on resin beads contained in polypropylene tea bags. After completion of each library mixture, the sample was cleaved from the resin with HF, and oxidised in a pH 8.2 buffer to ensure formation of the intramolecular disulphide bonds. Conditions employed have been reported to be optimal for the formation of the *m*- and *n*-loops in the conotoxin structure.



The activity of the peptides in the library was determined by the use of the 55 °C warm water tail-withdrawal assay. Mice were assessed for antinociceptive activity every 10 min following icv administration of a 30 μg dose of the individual library mixture samples. The latency to tail withdrawal adjusted by each animal's baseline response, summed over 12 time points indicated which amino acids contributed to the most active conotoxin structures. In particular, Asn, Val and Trp in position O_9, Ile, Nle, Gln and Arg in position O_{10} and Phe, Gly and Nle in position O_{11} appeared to promote antinociceptive activity. The 36 conotoxin analogues representing the combinatorial set of these residues were prepared and individually tested, resulting in the identification of six analogues with summed antinociceptive effects similar to RgIA-ΔR. These compounds were advanced to further examination of antinociceptive, respiratory and locomotor effects.

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

2.1. Polymer supported synthesis

No papers this month.

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2.2. Solution-phase synthesis

A facile, one-pot, pseudo four-component catalyst- and solvent-free synthesis of novel benzopyrano[2,3-*b*]pyridines has been achieved by Michael addition of various naphthols to iminocoumarin derivatives. The iminocoumarins were obtained from Knoevenagel condensation of salicylaldehydes with malononitrile, which can be attacked by another molecule of malononitrile to afford the title products. The advantages of this procedure are mild reaction conditions, high yields of products, generality, short reaction times and operational simplicity with the potential for generating new libraries.[2]

An efficient one-pot method for the synthesis of 2,3-disubstituted benzo[*b*]furans from commercially available 2-iodophenols, terminal acetylenes and aryl iodides has been developed utilising Sonogashira reaction conditions. After an initial Sonogashira coupling of the 2-iodophenol with the terminal alkyne, cyclisation involving the aryl iodide provided the 2,3-disubstituted benzo[*b*]-furan in good to excellent yields. The use of microwave irradiation shortens the reaction times and minimises the side products. This methodology is especially useful for the construction of libraries of highly substituted benzo[*b*]furans and their analogues.[3]

2.3. Scaffolds and synthons for combinatorial libraries

No papers this month.

2.4. Solid-phase supported reagents

A novel ferrocene-tethered polymer-supported ionic liquid phase catalyst has been synthesised and successfully applied to the intramolecular O-arylation of *o*-iodoanilides to give the corresponding benzoxazoles. The catalyst was easily recovered by simple filtration that greatly simplified the purification step and resulted in quantitative yields, without ionic liquid impurities in the products.[4]

2.5. Novel resins, linkers and techniques

2,2-Bipyridines having β-lactoside, β-D-glucoside, β-D-galactoside, and *N*-acetyl-β-D-glucosaminide substituents were prepared and then complexed with ferrous ion to afford trivalent glycoclusters having tris-bipyridine ferrous complex cores. Each glycocluster provides a dynamic combinatorial library composed of four diastereomeric stereoisomers (Δ*mer*, Δ*fac*, Λ*mer*, and Λ*fac*) whose ratios depend on their relative stabilities. CD spectral analyses of these glycoclusters showed that various cations (Na^+, Mg^{2+}, K^+ or Ca^{2+}) enriched the Δ-forms of the glycocluster containing β-lactosides and *N*-acetyl-β-D-glucosaminides possibly by cation-induced intramolecular carbohydrate–carbohydrate interactions.[5]

Lower cyclic oligomers C_2–C_5 of a family of naphthalenophane formaldehyde acetals C_n have been isolated and characterised, the dimer being obtained in two atropisomeric forms, *syn*-C_2 and *anti*-C_2, as confirmed by X-ray analysis. The investigated cyclophanes showed interesting recognition properties towards electron-poor guests ($K \approx 10^5\ M^{-1}$ for association of the guanidinium ion with C_3 in chloroform). A library of macrocycles was generated by acid catalysed transacetalation of C_n in chloroform, but the dynamic nature of the system was spoiled by the occurrence of irreversible reaction pathways promoted by the relatively easy formation of extended benzyl-like carbocations.[6]

2.6. Library applications

A rapid, inexpensive and high yielding method has been developed for the synthesis of 1,8-dioxodecahydroacridines using Amberlite IR-120H as a reusable catalyst under open air. These compounds were designed as potential inhibitors of sirtuins and prepared via the MCR of 5,5-dimethyl-1,3-cyclohexanedione, (hetero)aryl aldehydes and (hetero)aromatic amines under mild conditions. Overall, the MCR described could be useful in constructing a library of small molecules based on the 1,8-dioxodecahydroacridine framework leading to the identification of novel inhibitors of sirtuins.[7]

6-Oxo and 6-thio analogues of purine have been prepared based on the initial activity from a small, diverse purine library against *Mycobacterium tuberculosis* (Mtb). Certain 6-oxo and 6-thio-substituted purine analogues described showed moderate to good inhibitory activity. N^9-substitution apparently enhances the antimycobacterial activity in the purine series, and several 2-amino and 2-chloro purine analogues were also synthesised with moderate inhibitory activity against Mtb.[8]

The synthesis of four different libraries of overall 23 N3-substituted thymidine (dThd) analogues, including eleven 3-carboranyl thymidine analogues (3CTAs), has been reported. The latter compounds are potential agents for Boron Neutron Capture Therapy (BNCT) of cancer. The linker between the dThd scaffold and the *m*-carborane cluster at the N3-position of the 3CTAs contained amidinyl-, guanidyl-, tetrazolylmethyl-, or tetrazolyl groups to improve human thymidine kinase 1 (hTK1) substrate characteristics and water solubilities compared with first generation 3CTAs.[9]

Analogues of potent the CaMKinase II inhibitor, CaM-KNtide, have been prepared to explore new structural requirements for inhibitory activity. CaMKII inhibition by CaM-KIINα is dependent on a minimal region of 19 amino acids. In this recent publication, a library of potential inhibitors of CaMKII was prepared, and analysis of the homologous CaM-KIINβ showed that a 17-mer peptide (CN17β) was the shortest sequence that still retained useful inhibitory potency, and Ala substitution of almost any residue of CN17β dramatically reduced potency.[10]

A small library of dihydropyrimidin-2-ones (DHPMs) has been synthesised and evaluated for their potency to block iodide entrapment in rat thyroid cells. Synthesis was achieved using the multicomponent Biginelli reaction, and 12 compounds were tested for the inhibition of sodium iodide symporter (NIS) in a cell-based assay. One newly synthesised derivative exhibited a remarkably strong activity, with a half-maximum inhibitory concentration value (IC_{50}) of 65 pM. This study provides new insights for the development of anti-thyroid drugs, as well as for the synthesis of novel pharmacological tools designed to investigate iodide transport mechanisms at cellular and molecular levels.[11]

Large combinatorial libraries of N-substituted peptides would be an attractive source of protein ligands, because these compounds are known to be conformationally constrained, whereas standard peptides or peptoids are conformationally mobile. A recent paper reports an efficient submonomer solid-phase synthetic route to these compounds and demonstrates that it can be used to create high quality libraries. A model screening experiment and analysis of the hits indicates that the rigidity afforded by the stereocentres is critical for high affinity binding.[12]

Neuromyelitis optica (NMO) is an autoimmune inflammatory disorder of the central nervous system. In most NMO patients, autoantibodies to the water channel protein Aquaporin 4 (AQP4) are present at high levels and are thought to drive pathology by mediating complement-dependent destruction of astrocytes. The application of recently developed chemical library screening technology to identify a synthetic peptoid that binds anti-AQP4 antibodies in the serum of NMO patients has been reported. This finding validates, in a well-defined human disease, that synthetic, unnatural ligands for the antigen-binding site of a disease-linked antibody can be isolated by high-throughput screening.[13]

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