1. Current literature highlights

1.1. Incorporating heterocycles into peptoid libraries

Peptoids have been investigated in a library format for many years, as they are readily synthesised on solid-support using a two step synthesis: acylation of a growing amine-terminated chain with an activated halo-carboxylic acid, and then displacement of the halide with a primary amine. They are versatile, in that the prime source of diversity is an almost inexhaustible supply of primary amines, and the final products are metabolically stable and can be readily analysed by tandem mass spectrometry. A recent publication has taken this basic concept and increased the potential diversity of peptoid libraries by incorporation of heterocyclic components.\(^1\)

With the chemistry thus optimised, these new heterocycle-containing peptoids were prepared within the context of a one-bead one-compound (OBOC) library. A library of heptamers was prepared where the sixth position was diversified by the inclusion of the oxazole or thiazole monomer in place of the usual bromoacetic acid. The final library of 128 compounds was analysed by MS-MS fragmentation of the compounds cleaved by TFA from 20 beads picked at random.

The successful analysis of peptoid products led to the design and incorporation of other heterocyclic scaffolds, such as a 1,4 substituted pyrazine (4) and a 1,2-substituted furan (5). An OBOC library of 16,384 compounds incorporating all of the new heterocyclic monomers was prepared on Rink resin and the quality of the library assessed by examining the cleaved products from 24 beads.

This approach has demonstrated a convenient way of increasing the diversity of peptoid OBOC libraries, and the preparation of other heterocyclic building blocks is currently in progress.

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

2.1. Solid-phase synthesis

An efficient approach for the parallel solid phase synthesis of isoxazole and isoxazoline derivatives has been developed. The isoxazoles and isoxazolines were constructed through a 1,3-dipolar cycloaddition reaction of nitrile oxides, with resin-bound alkynes or alkenes. This methodology presents a new alternative to the diversity oriented synthesis of disubstituted isoxazoles and isoxazolines different from existing routes which are limited in structural diversity.\(^2\)
2.2. Solution-phase synthesis

A green, operationally simple and highly efficient one-pot three-component approach for the synthesis of spiro[indoline-3,4’-thiopyranol][2,3-b]indole] derivatives has been developed by the domino reaction of indoline-2-thione, isatin and ethyl cyanoacetate or malononitrile in ethanol at 80 °C for just 20 min. The protocol provides short reaction time, excellent yields, operational simplicity and formation of three new bonds in one operation from easily available starting materials and would be suitable for the generation of a library of relevant natural products.  

A convenient synthetic protocol for the synthesis of imidazo[1,2-a] pyridine has been developed by employing the one-pot three-component Ugi reaction. In addition, these products also exhibit interesting fluorescence properties, which makes the products useful as fluorescent probes. Mild reaction conditions, non-aqueous work-up procedure, good yields, short reaction time, and no need of chromatographic separation are some of the salient features of the present protocol, that may provide access to a diverse array of imidazoheterocyclic scaffolds.  

2.3. Scaffolds and synths for combinatorial libraries

No papers this month.

2.4. Solid-phase supported reagents

A recent paper describes an investigation into a solid phase based method for no carrier-added nucleophilic [18F]fluorination of aromatic compounds via de-diazofluorination. A variety of substituted aryl diazonium cations were immobilised using a sulphonate-functionalised ion exchange resin and labelled with [18F]fluoride ion by Balz–Schiemann like thermal decomposition in the presence of no carrier-added [18F]fluoride ion. Similarly, a chloromethyl-bearing (Merrifield) resin was modified using piperazine to provide the means for covalent immobilisation of diazoniun ions. The resin bound 1-(arylidiazonyle) piperazines obtained were used as substrates for a Wallach reaction with hydrogen [18F]fluoride.  

A very rapid, convenient, and general method for the synthesis of α-oxo thioyanates has been described by using clay-supported ammonium thiocyanate. The procedure avoids the use of additional catalyst, solvent, aqueous work-up and the yields are high. Moreover, the method is applicable for a variety of aryl, heteroaryl, alkyl α-halo carbonyls, β-keto tosylates, α-halo β-dicarbonyl, α-tosyl, β-dicarbonyl, alkyl halide, and alkyl tosylates.

2.5. Novel resins, linkers and techniques

The development of a novel fluorene-type anchor support molecule and a liquid-phase peptide synthesis protocol has been reported. Using this support molecule, the synthesis of a protected peptide with a free carboxyl group has been carried out by repeated coupling/deprotection reactions and isolation by simple precipitation. Cleavage is performed under mild acidic conditions to release the products in good yield and purity.  

A modular synthesis of photocleavable peptides has been developed. Peptide based kinase substrates were modified on solid support with a traceless linker derived from 1-(2-nitrophenyl)propargyl alcohol and coupled to azide functionalised cell-penetrating peptides using Cu(I) catalysed click chemistry.

2.6. Library applications

Among matrix metalloproteinases (MMPs), gelatinases MMP-2 (gelatinase A) and MMP-9 (gelatinase B) play a key role in a number of physiological processes such as tissue repair and fibrosis. A recent report describes the identification, design and synthesis of new gelatinase inhibitors with appropriate drug-like properties and a good profile in terms of affinity and selectivity. Using an in silico protocol and innovative and versatile solid phase approaches, a series of 4-thiazolylindinyl-N-hydroxyurea carboxamide derivatives have been identified. Some compounds showed a potent inhibitory activity against gelatinase B and good selectivity over other MMPs.  

A series of fluorobenzylated di- and tripeptides as potential leads for the development of molecular probes for imaging of COX-2 expression have been prepared using standard Fmoc-based solid-phase peptide synthesis. All peptides were assessed for their COX-2 inhibitory potency and selectivity profile in a fluorescence-based COX binding assay. Fluorobenzylated tripeptide FB-Phe-Cys-Ser-OH was further used in molecular modelling docking studies to determine the binding mode within the active site of the COX-2 enzyme.  

A recent paper describes the first structure-based activity prediction model for benzothiadiazines against various genotypes of HCV NS5b polymerase. The model was applied for structure-based fragment hopping by screening a library designed by reaction enumeration. A top scoring hit was used to generate a focused library such that it has lower topological polar surface area than the original class ligands and thus better pharmacokinetic properties. After that, experimental validation was carried out by the synthesis of this library and its biological evaluation which yielded compounds that exhibit EC50 ranging from 1.86 to 23 μM.  

A library of 32 novel glycoconjugate thiourea-bridged benzene sulphonamides has been synthesised from the reaction of glycosyl isothiocyanates with a panel of simple benzene sulphonamides. Compounds were investigated for their ability to inhibit the enzymatic activity of five human carbonic anhydrase (hCA) isozymes: hCA I, II and membrane-associated isozymes IX, XII and XIV. From this library several inhibitors displayed excellent potency-selectivity profiles for transmembrane anchored CAs over off-target CA I and II.  

A phosphite–phosphoroamidite and diphasphoroamidite ligand library was employed in the Cu-catalysed allylic substitution of a range of cinnamyl-type substrates using several organometallic nucleophiles. Results indicated that selectivity depended strongly on the ligand parameters, the nature of the leaving group of the substrate and the alkylating reagent. Good enantioselectivities (up to 76%) and activity combined with high regioselectivities were obtained.

References

Further reading

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


Donald JR, Wood RR, Martin SF. Application of a sequential multicomponent assembly process/huisgen cycloaddition strategy to the preparation of libraries of 1,2,3-triazole-fused 1,4-benzodiazepines. ACS Combinatorial Science 2012;14(2):135–43.


