1. Current literature highlights

1.1. Parallel solution phase synthesis of uridine antibiotic analogues

Natural products offer a range of three-dimensional structural complexity that makes them highly informative when designing new compound libraries. In particular, structural variation around nucleoside structures have resulted in a range of biological properties including anticancer, antiviral and antifungal activities. A goal of a recent study has been to prepare a library of compounds based on nucleoside templates through the NIH Roadmap Program and the Molecular Libraries Probe Production Centers Network (MLPCN) [1].

Regular nucleosides that retain a 5'-hydroxyl group can generate problems however, as they can enter nucleoside metabolic pathways, as well as causing general toxicity through inhibition of DNA and RNA metabolism. Consequently, a goal of this current study was to use the 5'-substituent to introduce new chemical functionality to replace the hydroxyl and thus avoid these pitfalls. The 5'-position can be used to introduce other groups following oxidation of the hydroxyl in the starting material (1) by reaction with TEMPO-iodobenzene diacetate to a carboxylic acid (2). Alternatively, the hydroxyl can be converted to an amine (3) by conversion to a tosylate, displacement with azide and reduction by transfer hydrogenation over palladium catalyst.

Compounds 2 and 3 provide the starting points for further derivatisation to the library components. For example, the carboxylic acid in compound 2 was coupled with phenylalanine methyl ester to provide amino acid functionality in the 5'-position. The 5'-carboxylic acid (2), the 5'-amino (3), and the carboxylic acid of the phenylalanine derivative (4) provided three sites for diversification through reductive amination, sulphphonylation and peptide coupling chemistry. Following derivatisation, the acetonide protecting group was removed by treatment with 50% aqueous formic acid.
2. A summary of the papers in this month’s issue

2.1. Polymer supported synthesis

An azido-Ugi reaction involving cyclic ketones, primary amines, isonitriles, and azides has been used to give substituted tetrazole derivatives. These intermediates were then hydrolysed to the corresponding acid derivatives. Amide bond formation of this product gave fused tetrazolo[1,5-a][1,4]benzodiazepines in high yield and good diversity. Current efforts are seeking a solid supported protocol to close the ring to rapidly access large libraries of tricyclic tetrazole derivatives [2].

2.2. Solution-phase synthesis

An isocyanide-based multicomponent reaction applied to the rapid assembly of novel, biologically relevant dihydropyrrolo[1,2-a]quinazolines-amidines has been presented. Starting from 1-(2-aminophenyl)pyrroles, aldehydes, and isonitriles, and the target heterocyclic scaffold was assembled in a one-pot, operationally friendly process. With three points of diversity and formation of three chemical bonds in one step, this strategy proves to be very general, and it is envisioned that access to larger libraries of diverse analogues will be feasible [3].

A concise method has been developed for the synthesis of caroverine and its derivatives. The quinoxalinone scaffold of these compounds was constructed via the tandem nitrosation/aerobic oxidative carbon–nitrogen bond formation reaction of N-(2-chloroethyl)-2-cyano-N-phenylacetamide, followed by sequential Grignard, Finkelstein and nucleophilic substitution reactions. The paper describes the development of this strategy, the optimisation of each step and the effect of different additives on the individual reactions [4].

A simple and facile approach to highly functionalised pyrimidone derivatives and indole fused pyrimidones has been developed. The synthesis of substituted pyrimidone derivatives in moderate to good yields involves the [4+2] cycloadDITION of 1,4-dipoles generated from α,β-unsaturated imines and dimethyl acetylenedicarboxylate with isocyanates as dipolarophiles. Furthermore, the pyrimidones resulted from 2-bromophenyl isocyanate could be transformed into various indole fused pyrimidones via intramolecular palladium-catalysed Heck reaction under different conditions. All these approaches offer potential utility for library synthesis [5].

An operationally simple and facile synthesis of α-hydroxyiminooxo-β-oxodithioesters has been achieved by nitrosation of α-eno-lidithioesters. These products were further treated with internal alkynes to afford diverse 1,4-thiazin-3-ones via a domino reduction/annulation strategy under mild reaction conditions [6].

A new Staudinger/aza Wittig/Strecker multicomponent reaction sequence to give C-1-cyano iminoalditols has been developed. When applied to 5-azidodeoxy-D-xylose and D-glucose as substrates, the method leads smoothly in good yield and with excellent stereoselectivity to respectively, 1,5-dideoxy-1,5-iminov-iduro nitride and 2,6-dideoxy-2,6-imino-D-glycero-D-IDO-heptonitrile. Implementation of this MCR route to alternative azidodeoxy sugar substrates is expected to provide a variety of alternative analogues, and these promise to provide a number of interesting focussed compound libraries [7].

2.3. Scaffolds and synthons for combinatorial libraries

In the field of medicinal chemistry, the intriguing and challenging molecular architectures of nitrogen-containing heterocycles with potential bioactive properties have received significant attention from researchers engaged in the areas of natural product synthesis and heterocyclic methodology. In a recent review article, recent developments in the environmentally benign synthetic methods providing access to quinazoline and quinazolinone scaffolds with promising biological potential has been summarised [8].

2.4. Solid-phase supported reagents

A solid-supported rhodium(0) catalyst has been developed and applied to the chemo- and regio-selective reduction of nitroarenes
to their corresponding amines using hydrazine hydrate as a reducing source under mild microwave irradiation conditions. This methodology also shows excellent compatibility with a broad range of other structurally diverse reducible functional groups. The catalyst can be recovered by simple filtration and reused for 13 cycles with consistent activity [10].

A silica supported palladium catalyst has been shown to have excellent activity and reusability for the selective oxidation of alcohols to corresponding carbonyl compounds. Hydrogen peroxide was used as the oxidant in a base-free environment, and a wide range of alcohols including aliphatic alcohols were tolerated as substrates using a 0.1% loading of palladium [11].

2.5. Novel resins, linkers and techniques

No papers this month.

2.6. Library applications

By considering published structural information, high throughput biaryl lipophilic acid arrays have been designed leveraging facile chemistry to permit their synthesis. Multiple hits were rapidly identified which were of suitable prostaglandin I₂ receptor agonist potency [12].

A diverse library of bis[1,2]dithiolopyrrole derivatives has been prepared for evaluation of activity against the nucleocapsid protein of the Feline Immunodeficiency Virus (FIV). Using this target as a model for HIV, an in vitro cell culture approach has yielded nanomolar active compounds with low toxicity [13].

A library of Schiff bases has been synthesised by condensation of aromatic amines incorporating sulfonamide, carboxylic acid or carbamoylmethyl functionalities as zinc²⁺-binding groups, with aromatic aldehydes incorporating tert-butyl, hydroxy and/or methoxy groups. The corresponding amines were thereafter obtained by reduction of the imines. These compounds were assayed for the inhibition of two cytosolic human carbonic anhydrase isoenzymes, hCA I and II. The reduced Schiff bases are stable to hydrolysis and several low-nanomolar inhibitors were detected, most of them incorporating sulfonamide groups [14].

A 47-membered library of novel long-chain arylpiperazines, which contain cyclic amino acid amides in the terminal fragment have been synthesised on Rink-amide resin and evaluated for binding affinity to 5-HT₁₇ and 5-HT₁₇A receptors. Representative compounds from the library displayed high-to-low affinity for 5-HT₁₇ and 5-HT₁₇A sites. The possible interactions implicated in binding of the studied compounds to the 5-HT₁₇ receptor were supported by molecular modelling [15].

α7 Nicotinic acetylcholine receptor agonists are promising therapeutic candidates for the treatment of cognitive impairment. A novel series of α7 nAChR agonists have been investigated and results described in a recent publication. Starting from molecular docking studies on two series of molecules, an alternative scaffold was designed attempting to combine the optimal features of these previously identified urea and pyrazole compounds. A small library was synthesised in a parallel manner, affording compounds with excellent α7 nAChR activity, selectivity and a preliminary ADME profile was obtained [16].

References


Further reading

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


