1. Current literature highlights

1.1. Parallel synthesis of gonadotrophin releasing hormone antagonists

Gonadotropin releasing hormone (GnRH), otherwise known as leuteinising hormone releasing hormone, is a decapeptide released from the hypothalamus and stimulates the release of hormones including the gonadotrophins and leuteinising hormone. Several hormone sensitive medical conditions such as prostate cancer and endometriosis have been beneficially treated by the use of peptidic GnRH antagonists and superagonists. However, the limited metabolic stability of peptides has resulted in an active search for non-peptidic small molecule ligands for this receptor. The discovery of a small molecule benzimidazole antagonist (1) with micromolar affinity for the GnRH receptor, has initiated the search for more potent compounds explored through an iterative parallel synthesis library strategy 1.

Benzimidazoles are frequently found in pharmacologically active compounds, and are often described as 'privileged' pharmaco- phores. This present study involved the development of a route based on phenylene triamines (2) that allowed the introduction of diversity into the 2-position of the product benzimidazole ring (3). After introducing a piperazine derivative onto the 3-position of the phenylene triamine, the key diversity step was the creation of 40 benzimidazoles by HATU-catalysed coupling with carboxylic acids, and then cyclisation by brief heating in acetic acid. Compounds were purified by semiprep reverse phase HPLC, to give products in 5–25% yield and were then submitted for biochemical determination. Selected compounds that demonstrated greater than 50% inhibition of the GnRH receptor at 10 μM concentration underwent a full dose response determination to give IC₅₀ values.

It was found that the most active compounds had a para-substituted phenyl ring in the 2-position of the benzimidazole, and this initiated the synthesis of a follow-up library of further 4-substituted phenyl derivatives. Several of these compounds were potent GnRH antagonists, with the compound containing a 4-tert-butylphenyl group (4) revealing an IC₅₀ value of 50 nM.

1.2. Polymer supported synthesis of a library of aryloxyalkanolamines

G-protein coupled receptors (GPCRs) represent a highly validated type of drug discovery target against which numerous successful drugs have been discovered in the last 40 years. The completion of the human genome project has revealed additional GPCRs, many of which have yet to have their function determined. It is likely that some of these will provide novel therapeutic targets. Aryloxypropanolamines (5) are a well proven structural class of compound that interact with GPCRs as agonists or antagonists, and their various biological activities make them very suitable as a chemical class for combinatorial synthesis. A recent study has described the polymer-supported synthesis of a library of aryloxypropanolamines and aryloxybutanolamines attached through an acyclic acetal linker².

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To permit the introduction of numerous diverse groups at each end of the aryloxyalkanolamines, it was envisioned that an orthogonally protected core molecule could be attached to solid support through the secondary hydroxyl group. Sequential nucleophilic substitution would permit the introduction of groups at each end of the library components.

Several different linkers have been previously explored as a method of attaching hydroxyls to a solid support. In this work, several acetal linkers were investigated as providing an appropriate balance of chemical stability for compound synthesis, and ease of cleavage from the solid support under mild acidic conditions. Ultimately linker 6 was chosen as being a low cost, high loading linker suitable for solid supported synthesis using Irori NanoKans, thus permitting the synthesis of milligram quantities of products.

Using this linker, a test library was prepared on resin, firstly in 40 mL vials for the first step, and subsequently in a 24-well plate. The key intermediate for the library synthesis (7, either enantio- mer) contained a tri-isopropylsilyl protected alcohol as well as a tosylate primed for nucleophilic substitution ultimately to give GPCR ligand products (5). Using the Irori technology, a library of 10,800 compounds was targeted, and with a success rate of 93%, 9966 were successfully obtained on an average scale of 4 µmol. Only 400 compounds required purification, with the overall purity of compounds across the library being assessed at 93%.

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

2.1. Solid-phase synthesis

No papers this month.

2.2. Solution-phase synthesis

Tetramic acid derivatives constitute an important class of nitrogen-containing heterocycles, and are key structural motifs in many natural products of terrestrial and marine origin. A novel combinatorial synthesis of tetramic acids by an Ugi/Dieckmann condensation has been described. The interesting biological and structural diversity of this class of molecules makes it a particularly interesting template for the design of compound libraries in search of small molecules that affect cellular signal.

The reaction of α-tosyloxy ketones, sodium azide, and terminal alkyynes in presence of copper(I) in aqueous polyethylene glycol afforded regioselectively 1,4-disubstituted 1,2,3-triazoles in good yield at ambient temperature. The one-pot exclusive formation of 1,4-disubstituted 1,2,3-triazoles involves in situ formation of α-azido ketones, followed by cycloaddition reaction with terminal alkyne. The generality of this one-pot method was demonstrated by synthesising an array of diverse 1,4-disubstituted 1,2,3-triazoles. A novel and efficient procedure for the synthesis of thiosemicarbazonemolecules has been achieved via a multicomponent and catalyst-free reaction of phenyl or p-chlorophenyl isothiocyanate, hydrazine, and aldehydes or ketones. The method afforded a molecular library of 20 thiosemicarbazones in good yields and short reaction time.

Methods for the synthesis of 2-substituted 2-imidazoles have been reviewed. While older, more established methods continue to be used for the preparation of these compounds, more recent reports describe techniques that provide multiple points of diversity, making them especially useful in library development for this pharmacologically-important class of compounds.

2.3. Scaffolds and syntheses for combinatorial libraries

An efficient synthesis of 2,3-dihydropyrans starting from different terminal alkyynes has been developed. The 2,3-dihydropyrans were obtained in a few minutes through a microwave-assisted multicomponent enyne cross-metathesis/hetero-Diels–Alder reaction. Starting from C-ethyl-ribofuranose, a new multicomponent approach to furanose–pyranose 1,3-C–C-linked disaccharide scaffolds was also developed.

A new and efficient method has been developed for the synthesis of novel gem-difluoromethylene-containing isocyanides. This reagent can be used as a building block for the synthesis of difluorinated pseudopeptides via the Ugi reaction.

2.4. Solid-phase supported reagents

A one-pot, two-step synthesis protocol for the conversion of Biginelli 3,4-dihydropyrimidin-2(1H)-thiones to 2-(2-hydroxy-2-arylvinyl) dihydropyrimidinoides (DHPM) derivatives via Eschenmoser sulphide contraction coupling has been described. Solution phase as well as a solid-supported protocol using solid-supported triphenylphosphine has been carried out for the decoration of the Biginelli DHMP scaffold at the C-2 position.

Clean sulphenylations are observed upon reaction of activated methylenes with phenyl succinimidyl sulphide. When working with diethyl benzylmalonate, the sulphonylated product can be selectively oxidised and thermally fragmented affording phenylsulphonic acid and diethyl benzylidenemalonate. The developed method was applied using a polymer-supported thioanisole derivative. Formation of the enedicarboxylate documents proof of principle of polymer-supported sulphones as sulphenylating agents onto activated methylenes.

The applicability of five aryl substituted m-hydrobenzoin ethers already tested in the L-Selectride mediated stereoselective reduction of phenylglyoxylates as open chain chiral auxiliaries have been further investigated via the α-alkylation of propionates, the addition of n-BuZnCl to phenylglyoxylates and the Diels–Alder reaction of acrylates with cyclopentadiene as model reactions. As up to 90% d.e. could be achieved in the solution phase, two optimised auxiliary structures were immobilised on commercially available Wang-resin and applied as a reusable solid-supported chiral auxiliaries in the same type of reactions.

2.5. Novel resins, linkers and techniques

A selective resin for linking trans-diequatorial-1,2-diols to solid support has been described. This linking was carried out under mild and aprotic conditions involving the use of trimethylsilyl methyl ether in the presence of trimethylsilyl trifluoromethanesulphonate. Cleavage from the resin was also carried out under mild conditions by treatment with dichloromethane/trifluoroacetic acid/water.

2.6. Library applications

A terpenoid-like library containing 1,4-disubstituted-(1H)-1,2,3-triazoles has been prepared by means of 1,3-dipolar cycload-
dation of geranyl and farnesyl azides with a set of terminal alkenes, in order to design a new class of potentially active anti-biofilm compounds. Two compounds were found to possess interesting activity against Pseudalteromonas sp. biofilm. This process is suitable for combinatorial chemistry of marine natural product-like compounds. A number of libraries have been produced to explore the potential of a 2,4-diaminopyridine lead. The resulting diaminopyridines proved to be potent and selective μ-opioid receptor agonists, and several rounds of lead optimisation using library chemistry identified a compound which showed efficacy in an electromyography model of neuropathic pain.

A class of small molecules displaying comparable activities with peptide ligands BAM22 and corticotatin-14 at both the human and rhesus monkey MrgX1 and MrgX2 receptors, respectively, have been discovered. A comparative study to compare solid-phase and solution-phase chemistries for the efficient synthesis of the active class, tetracyclic benzimidazoles, was undertaken. The solid-phase chemistry was found to be superior both for the synthesis of ana
glogues and for the synthesis of gram quantities.

An effective solid phase synthesis of Argifin, providing a diaminopyridine lead. The resulting diaminopyridines inhibitors, have been expanded. Sixty-six new analogues were prepared from a synthetic intermediate of Argifin, was found to be 70 times more potent as an inhibitor of Serratia marcescens chitinases B than Argifin itself.

In previous studies, several isoquinoline derivatives displaying potent anticonvulsant effects in different animal models of epilepsy were discovered. With the aim to exploit the main structure–activity relationships for this class of compound, a solution-phase parallel synthesis (SPPS) approach to new N-substituted-3,4-dihydroisoquinoline-2(1H)-carboxamides was explored. The effect of introducing different (cyclo)alkyl groups at carboxamidio moiety linked to N-2 atom of isoquinoline scaffold was investigated, and the pharmacological effects were evaluated against audiogenic seizures in DBA/2. The structure–activity relationships of acylthiocarbamates (ATCs), a new class of non-nucleoside HIV-1 reverse transcriptase inhibitors, have been expanded. Sixty-six new analogues were prepared by parallel solution-phase synthesis. In general, the potency of new ATCs was better than that of the first series and O-[2-phenyl-
limidoethoxy]-4-chlorophenyl(3-nitrobenzoyl) thiocarbamate turned out to be the most potent ATC so far synthesized with an EC50 value of 1.5 nM.