1. Current literature highlights

1.1. Solid-phase synthesis of a library of CB-1 receptor antagonists

Solid-phase synthesis of libraries is an effective way of creating large arrays of compounds for screening purposes, and is especially valuable when the synthetic approach allows for significant diversity to be introduced into the library. In particular, the generation of libraries containing ‘privileged scaffolds’ is a key focus as such compounds provide a disproportionate number of hits for commonly pursued targets. A recent paper describes the generation of a library of pyrazoles which have been successfully screened against the cannabinoid subtype 1 (CB-1) receptor. 1

Pyrazoles occur in a number of pharmacologically active molecules such as serotonin 5HT1A inverse agonists, COX-2 inhibitors and p38 MAP kinase inhibitors. In this particular study, 1,5-diarylpyrazole-4-carboxamides were targeted as the synthesis permitted the introduction of three points of diversity and thus contributed to the potential size and scope of the final library. In fact the final library contained over 1000 compounds and was subsequently screened against a range of GPCR targets including the CB-1 receptor. \( \text{http://dx.doi.org/10.1016/j.comche.2012.05.001} \)

The chemistry was carried out on solid support using IRORI MicroKan technology to monitor and track the individual components of the library. The synthetic approach required the introduction of the first diversity element (R\(^1\)) by loading a primary amine onto 4-formyl-3-methoxyphenoxy (FMP) resin, using a standard reductive amination step to give intermediate 1. Transacyclacylation of 1 with tert-butyl-β-ketoester, required heating in NMP with catalytic DMAP, and gave the resin-supported β-ketoamide set (2), containing the nascent R\(^2\) substituent. Conversion to the corresponding vinylogous amide, and cyclisation following reaction with an arylhydrazine, gave the products (3), containing the third (aryl) position of diversity, that could be separated from the solid support by treatment with 50% TFA in DCE. In every case examined, the authors could only observe a single regioisomeric product (4).

Using this approach, several compound arrays were generated giving thousands of analogues. LCMS analysis demonstrated that the products were present in >80% purity as determined by UV (220 nM) and light scattering detection. It was also evident that the synthetic approach was very tolerant of a wide range of substituents in each of the R\(^1\) through Ar positions. The products were screened in high throughput screening format against a library of GPCR targets, and hits were observed against several of these. In particular, several compounds showed binding affinity for the CB-1 receptor. This is an important target, as this GPCR is involved in a number of neurological processes including several linked to metabolic function.
A number of 1,5-diarylpyprazole-4-carboxamides showed activity in the range from >10 μM down to 90 nM, with a clear structure–activity relationship pattern, the most active of the series being the compound 3. Several compounds were resynthesised, purified, and some showed good IC50 values and full functional CB-1 antagonism in a GTP-γ-S assay. In conclusion, valuable SAR and active CB-1 antagonists were discovered from a library of privileged pyrazole derivatives.

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

2.1. Solid-phase synthesis

An efficient approach for the chemical synthesis of Rhesus 0-defensin-1 (RTD-1) has been described using Fmoc-based solid-phase peptide synthesis in combination with an intramolecular version of native chemical ligation. The reaction was extremely efficiently yielding natively folded RTD-1 with minimal or no purification at all, and is fully compatible with the high throughput production of chemical libraries using this peptide scaffold.

2.2. Solution-phase synthesis

A novel protocol for the rapid assembly of quinoxalinone frameworks has been demonstrated. This method combined with a soluble polymer support provides a convenient approach for the diversification of heterocyclic compounds and for easy purification via facile precipitation from the reaction mixture. The key transformation of this study involved the in situ reduction of an aromatic nitro compound, tandem lactamisation and concomitant traceless cleavage of the polymer support under microwave irradiation. This approach could potentially be used to generate drug-like small-molecule libraries for high-throughput screening.

2.3. Scaffolds and synths for combinatorial libraries

With the aim to enrich a ‘privileged structure’-based library, novel 2H-spiro[1-benzofuran-3,4’-piperidin]-1-ol scaffolds have been prepared. The method involved a key intramolecular Heck cyclisation which was successfully applied for three series of compounds, and the desired scaffolds were obtained in overall yields of 42–53%.

The synthesis of 2,5-disubstituted tetrahydrofurans from donor silylmethylcyclopropanes (without bearing an acceptor function) has been described. Their further elaboration via a wide range of synthetic transformations has been presented to highlight the potential of the method and the resulting THFs as potential scaffolds for diversity-oriented synthesis.

2.4. Solid-phase supported reagents

A magnetic nanoparticle supported N,N-diisopropylaminoacetamide (Fe3O4-DIPA) has been developed for application as a magnetic recoverable, and reusable N,N-diisopropylamidamine equivalent. The Fe3O4 nanoparticles were coated with a silica layer, followed by surface modification with 3-aminopropyltriethoxysilane. Subsequent acylation with chloroacetyl chloride and chloride displacement with diisopropylamine afforded Fe3O4-DIPA in 90% yield with a loading of 0.96 mmol/g. The reagent was used in the synthesis of amine derivatives by reactions such as sulphonylation, acylation, and N-alkylation. Fe3O4-DIPA was readily recovered by separation using a magnet and could be reused several times without significant loss of reactivity.

A polystyrene-supported Lewis acidic iron-containing ionic liquid was proved to be recyclable and efficient heterogeneous catalyst for converting CO2 into cyclic carbonate without using any organic solvent or additive. Excellent yields and selectivity were obtained under mild reaction conditions, and the catalyst could be readily recovered and reused over five times without appreciable loss of activity.

2.5. Novel resins, linkers and techniques

Many macrocyclic depsipeptides or related compounds have interesting medicinal properties and often display more favourable pharmacokinetic properties than linear analogues. However, macrocycles cannot be easily sequenced by tandem mass spectrometry, making it difficult to identify hits isolated from library screens using one bead one compound libraries. A recent report describes a strategy to solve this problem by placing a methionine in both the linker connecting the cyclic molecule to the bead as well as within the cycle itself. Treatment with CNBr both linearises the molecule at a specific position and releases the molecule from the bead, making its characterisation by tandem MALDI mass spectrometry straightforward.

2.6. Library applications

The evaluation of a comprehensive α-helix mimetic library for binding the gp41 NHR hydrophobic pocket has been reported. This approach led to the discovery of small molecule inhibitors that not only match or exceed the potency of those previously disclosed, but also exhibit effective activity in a cell–cell fusion assay.

In order to develop inhibitors of integrin α4β7, a key mediator of various inflammatory diseases, a library of cell-permeable peptides based on the biotin-R8ERY template was prepared. In this library, the tyrosine residue was modified by using the CuAAC reaction, and the peptidomectrics evaluated in a cell adhesion assay and shown to inhibit Mn2+-activated adhesion of mouse TK-1 T cells to mouse MadCAM-1.

Epigenetic modifications that govern gene expression are often overlooked in the design of artificial genetic switches. N-Methylpyrrole-N-methylimidazole (P1) hairpin polynamides are programmable small DNA binding molecules that have been studied in the context of gene regulation. Recently, the synthesis of a library of compounds generated by conjugating P1 polynamides with the chromatin-modifier, SAHA, has been described.

Through synthesis and assays with peptidyl substrates, it has been found possible to select substrates having peptidyl groups complementary against lipases. The best substrates showed a 20-
fold improved $K_a$ relative to non-peptidyl substrate, and using this information, selective inhibitors have been generated. Adamantyl ureas have been previously identified as a group of compounds active against Mycobacterium tuberculosis in culture with minimum inhibitor concentrations (MICs) below 0.1 μg/ml. These compounds have been shown to target MmpL3, a protein involved in secretion of trehalose mono-mycolate, and they also inhibit both human soluble epoxide hydrolase (hSEH) and M. tuberculosis epoxide hydrolases. In a recent study, a library of 1600 ureas (mostly adamantyl ureas) were synthesised for the purpose of increasing the bioavailability of inhibitors of hSEH. 1-Adamantyl-3-phenyl ureas with a polar para substituent were found to retain moderate activity against M. tuberculosis and one of these compounds was shown to be present in serum after oral administration to mice. A library of substituted chromenol 3,4-b-jindoles has been developed as Lamellarian analogues. Synthesis was achieved from indoles after a four-step pathway sequence involving C-3 iodonation, a Suzuki coupling, and a one pot deprotection/lactonisation step. Twenty final compounds were tested in order to determine their activity against toposomerase I and kinases, the two major biological activities of the Lamellarians.

Sinomenine is an anti-inflammatory compound clinically available for the treatment of rheumatoid arthritis (RA), but its efficacy is quite weak. In a recent study, a library of novel sinomenine-based homodimers and monomers were designed and synthesised, and their bioactivities were evaluated using RAW264.7 cells and mice. Some of the compounds possessed much more potent inhibitory effects on the production of nitric oxide, interleukin-6 and tumour necrosis factor-α than sinomenine.

References
7. Rattanaburi P, Khumraksa B, Pattarawarapan M. Synthesis and applications of para-mantyl-3-phenyl ureas with a polar

Further reading
Papers on combinatorial chemistry or solid-phase synthesis from other journals
8. Rattanaburi P, Khumraksa B, Pattarawarapan M. Synthesis and applications of para-mantyl-3-phenyl ureas with a polar...

