1. Current literature highlights

1.1. 1,3,4-Oxadiazole analogues as tyrosinase inhibitors

Polyphenol oxidase, or tyrosinase, is a multi-functional copper-containing enzyme that catalyses the $\alpha$-hydroxylation of monophenols and the oxidation of $\alpha$-diphenols into $\alpha$-quinones. Tyrosinase is a key enzyme for melanin biosynthesis and thus tyrosinase inhibitors could be clinically useful for treating some dermatological disorders associated with melanin hyperpigmentation. Recent work has focussed on the synthesis of a small library in solution of 2,5-disubstituted-1,3,4-oxadiazoles. 1

The 1,3,4-oxadiazoles were synthesised using microwave-assisted combinatorial synthesis. Several hydrazides were treated with a range of carboxylic acids in the presence of phosphorous oxychloride to afford 2,5-disubstituted-1,3,4-oxadiazoles of general structure (i). One-pot microwave-assisted syntheses were carried out in a reaction time of 6–16 minutes, whereas under traditional reflux, a reaction time of 4–10 hours was required for conversion. When the library compounds were screened for $\alpha$-diphenolase inhibitory activity of tyrosinase using L-DOPA as substrate, a number of moderately active compounds were discovered. One of the most potent compounds isolated was (ii) which possessed an IC$_{50}$ of 2.18 $\mu$M. This work has identified a novel series of tyrosinase inhibitors and SAR that indicates that electronegative substitution is essential for activity. These compounds serve as a starting point for the ultimate clinical development of a potential treatment for skin disorders.

1.2. NPY5 receptor antagonists derived from iterative parallel chemistry design

Neuropeptide Y (NPY), a 36 amino acid neuropeptide, is a member of the pancreatic polypeptide family. Antagonists of the NPY5 receptor cause the reduction of food intake in animal feeding models and thus such agents have been targeted as potential anti-obesity drugs. Recent work has combined a topological similarity approach in virtual screening, likely to deliver compounds with similar binding affinity to the seed compound, with a pure 3D pharmacophore approach more likely to deliver structural novelty, but with the potential penalty of reduced binding affinity. 2

From this work, 632 pre-existing compounds were chosen from a corporate compound collection and screened for antagonist activity at the mouse NPY5 receptor. From this set upon screening, 31 compounds had an IC$_{50}$ < 10 $\mu$M, with (iii) possessing an IC$_{50}$ of 40 nM. This compound was also active at 10 mg/kg ip in a mouse feeding model. Hit compound (iii) then underwent two rounds of optimisation using parallel solution phase synthetic chemistry preparing approximately 140 compounds.

A number of active NPY5 receptor antagonists were discovered. One of the most potent was (iv) with an IC$_{50}$ of
2.8 nM. The authors have sought to yield a balance between maintaining the pharmacophoric pattern and shape of the parent compounds whilst concomitantly allowing for topological variability of the scaffold.

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

2.1. Solid-phase synthesis

A solid-phase synthesis has been developed to make a thymidinyl and 2'-deoxyuridinyl Ugi library starting from 5'-azidonucleosides loaded onto polystyrene butyl diethylsilane (PS-DES) resin. A 1344 member library was synthesised for anti-bacterial screening.3

A robust solid-phase approach to cyclic guanidines based on the Staudinger protocol has been reported. Convenient isolation and good yields of the desired products (34–84%) along with the diversity of the targeted molecules are distinctive features of the resultant library.4

A novel solid-phase method for the synthesis of 4-methyl-pyrido[2,3-d]pyrimidin-7-one compounds with two diversity points has been described and used to generate 126 compounds in good yield and purity.5

A mild and improved method for the synthesis of thiethers has been developed, and used in an example of a one-pot, solid-phase synthesis.6

A new method for the synthesis of functionalised biaryl α-ketophosphonic acids has been developed. The key step involves the use of sodium bromobenzoyl phosphonates to react with polymer-bound boronic acids via microwave-assisted aqueous Suzuki coupling.7

2.2. Solution-phase synthesis

A novel traceless route to 3,5-disubstituted-1,2,4-triazoles on PEG polymers has been described, which allows the incorporation of two elements of diversity. This method provided a library of 3,5-disubstituted-1,2,4-triazoles with high yields and purity.8

A mild and highly efficient one pot–one step condensation and/or condensation–cyclisation of various acids to amides and/or oxazolines using Deoxo-Fluor reagents has been described and used for parallel reactions of various free fatty acids with 2-amino-2,2-dimethyl-1-propanol.9

A simple and straightforward methodology for the parallel, solution-phase synthesis of a new series of S-DABO derivatives bearing aromatic substituents at the C2 and C6 positions, has been developed.10

2.3. Scaffolds for combinatorial libraries

A parallel synthetic strategy to the 9-aminoacridine scaffold of the classical anti-malarial drug quinacrine has been presented. The route allows ready variation of the two diversity elements present in this class of molecules – the tricyclic aromatic heterocyclic core, and the disubstituted diamine sidechain – and a library of 175 compounds was designed.11

2.4. Solid-phase supported reagents

A novel heterogeneous combination of a formate reagent and palladium catalyst co-immobilised on a resin support has been developed and shown to be highly efficient and recyclable for transfer hydrogenation of alkenes, imines, nitroarenes and 1,2-dicarbonyl compounds.12

1,3,4-Oxadiazoles can be rapidly and efficiently synthesised from a variety of carboxylic acids and acid hydrazides in one simple step using commercially available PS-PPh3 resin combined with microwave heating.13

A series of polar group functionalised polystyrene-supported phosphine reagents have been examined as catalysts in the aza-Morita–Baylis–Hillman reactions of N-tosyl arylimines and a variety of Michael acceptors with the aim of identifying the optimal polymer/solvent combination.14

New polystyrene-bound perfluoroalkyl sulphonic acids and their ytterbium salts have been prepared, and used as catalysts in multicomponent reactions (MCRs) for the efficient synthesis of homoallylic amines or amides.15

The utility of both soluble (non-cross-linked) and insoluble (cross-linked) polystyrene-supported triphenylarsine reagents has been examined. These reagents were prepared by standard radical polymerisation methodology and used in palladium-catalysed homocoupling reactions of aryl halides.16

A polymer-supported palladium(II) salen-type complex has exhibited catalytic activity in the cross-coupling reaction of various aryl bromides and heteroaryl bromides with phenylboronic acid in a mini-continuous flow reactor system at elevated temperatures in a phosphine-free system. To demonstrate the utility of the system, a diversity of aryl and heteroaryl bromides were studied.17

A chiral N-sulphonylated α-amin acid monomer derived from (S)-tryptophan was copolymerised with styrene and divinylbenzene under radical polymerisation
conditions to give a polymer-supported N-sulphonyl-(S)-tryptophan. Treatment of the polymer-supported chiral ligand with 3,5-bis(trifluoromethyl)phenyl boron dichloride afforded a polymeric Lewis acid catalyst effective for asymmetric Mukaiyama aldol reaction of silyl enol ethers and aldehydes.\(^1^8\)

A family of polystyrene-supported amino alcohols, characterised by a high catalytic activity in alkylation transfer from zinc to formyl groups has been successfully tested in the enantioselective addition of phenyl zinc reagents to aldehydes to afford chiral diarylmethanols.\(^1^9\)

Co-polymerised 4-bromopolystyrene has been converted to a range of polymer-supported reagents and scavengers by bromine–magnesium exchange using Oshima’s trialkylmagnesate complex followed by quenching with a variety of electrophiles. Mitsunobu, halogenation and Wittig reactions were explored to assess the utility of the resins for target oriented and diversity oriented synthesis.\(^2^0\)

Starting from Merrifield resin, various polymer-bound diazonium salts have been prepared, and upon treatment with amino acid esters, the corresponding diazo-acetic esters were formed following basic cleavage.\(^2^1\)

2.5. Novel resins, linkers and techniques

A cross-linked polyacrylamide hydrogel that displays large swelling properties in both organic solvents and water has been shown to serve as a scaffold for the photosensitiser haematoporphyrin. Upon exposure to light, the resulting resin efficiently generates singlet oxygen which can then react with appropriate substrates.\(^2^2\)

Cross-linked polystyrene (PS) with polytetrahydrofuran (PTHF) chains has been prepared for use in solid phase organic synthesis (SPOS). These PS–PTHF resins exhibited good swelling characteristics across a wide spectrum of polar and non-polar solvents and were used in the synthesis of 3-methyl-1-phenyl-2-pyrazolin-5-one, which requires β-ketoester formation at low temperature.\(^2^3\)

A column based flow system has been developed in which a cinchona alkaloid based reagent/catalyst solid-phase promotes the asymmetric α-chlorination of acid chlorides to afford highly optically active α-chloroesters in high enantiomeric excess and in good yields.\(^2^4\)

2.6. Library applications

A 2,3-diphenylpropionic acid library for seeking a VLA-4 antagonist has been synthesised on solid-phase.\(^2^5\)

A library of acylhydrzone iron chelators was synthesised and tested for its ability to inhibit the growth of a chloroquine-resistant strain of Plasmodium falciparum.\(^2^6\)

The solid-phase synthesis of a series of 3-substituted indolizine-1-carbonitrile derivatives has been reported and some display activity against MPtpA/MPtpB phosphatases involved in infectious diseases.\(^2^7\)

Evaluation of the CCK<sub>1</sub> SAR in a series of diarylpyrazole antagonists was conducted in a matrix synthesis format revealing additive (Free–Wilson) and non-additive SAR. This use of additive QSAR modelling in conjunction with combinatorial libraries represents a unique approach to the evaluation of SAR interactions between the variables of any combinatorial matrix.\(^2^8\)

The synthesis of combinatorial libraries of a CCK<sub>1</sub> receptor antagonist by solid-phase synthesis on Kenner ‘safety catch’ resin has been described.\(^2^9\)

The synthesis of kinase targeted libraries based on the thienopyrazole scaffold has been reported and several analogues have been identified as submicromolar inhibitors of KDR.\(^3^0\)

Pulvinones were synthesised (>180) in arrays and evaluated as inhibitors of early stage cell wall biosynthesis enzymes MurA–MurD. Several pulvinones inhibited Mur enzymes and demonstrated antibacterial activity against Gram-positive bacteria including methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus faecalis, and penicillin-resistant Streptococcus pneumoniae.\(^3^1\)

A small library of cyclic RGD pentapeptide mimics incorporating stereoisomeric 5,6- and 5,7-fused bicyclic lactams have been synthesised, and found to contain high-affinity ligands for the α<sub>v</sub>β<sub>3</sub> integrin.\(^3^2\)

Fourier transform ion cyclotron resonance mass spectrometry has been employed to screen a combinatorially generated natural product-based library for binding affinity to bovine carbonic anhydrase II. The fungal natural product 3-chloro-4-hydroxyphenylacetamide was the library template, with 11 secondary amide analogues of this template constituting the combinatorial library.\(^3^3\)

References

Further reading

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


Sparano, B. A.; Koide, K. A strategy for the development of small-molecule-based sensors that strongly fluoresce when bound to a specific RNA. *Journal of the American Chemical Society* 2005, 127 (43), 14954–14955.


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