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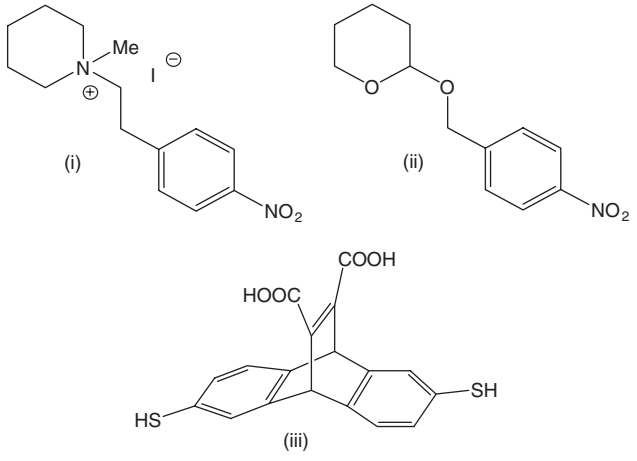
1. Current literature highlights

1.1. Acetal hydrolysis by dynamic combinatorial chemistry

Dynamic combinatorial chemistry is a technique that permits the formation of new chemical species in the presence of a template or target. As all compounds in the dynamic combinatorial library are in equilibrium with their precursors, the ratio of products can be shifted in favour of those compounds that interact most favourably with the template. This approach has been used to create novel catalysts for acetal hydrolysis.[1]

The ammonium salt (i) was reasoned to be a suitable transition state analogue (TSA) for the hydrolysis of the acetal (ii). A mixture of three disulphides were incubated with the TSA (i) under conditions that permitted both air oxidation and disulphide exchange. After 3–5 days reaction time, the mixture of products obtained showed amplification of two species compared with the equilibrium reaction mixture in the absence of the TSA. Mass spectrometry revealed these two amplified compounds to be diastereoisomeric trimers of the disulphide (iii), and repeat incubation of the precursor (iii) with the TSA (i) led to trimers constituting more than 80% of the total library material.



When the kinetics of hydrolysis of acetal (ii) were studied in the presence of the novel trimeric host molecules, consideration of k_{cat} and k_o values indicated an acceleration in hydrolysis by a factor of 2.1. This result demonstrates that dynamic combinatorial chemistry may have particular value in novel abiotic catalyst discovery.

1.2. Solid-phase synthesis of caspase 3 inhibitors

The human caspases are a group of at least 13 cysteinyl-aspartate-specific proteases which are key enzymes in the molecular pathways resulting in apoptosis. Amongst these, caspase 3 in particular appears to have a critical role in neuronal apoptosis. Peptidic inhibitors of caspase 3 have been shown to have some efficacy in models of stroke, traumatic brain/spinal chord injury, hypoxic brain damage, and cardiac ischemia/reperfusion injury. The main element of recognition for caspase-3 inhibitors is the P_1 aspartic acid residue, and the adjacent scissile amide bond can be replaced by a ketone to give irreversible inhibitors. A recent paper reports potent, selective and cell-penetrable dipeptide aspartyl inhibitors of caspase 3 prepared by solid phase synthesis.[2]

The α-methylthiobenzyl aspartyl group is a reactive electrophilic 'warhead' that is an effective inhibitor of cysteinyl proteases, but the group is difficult to synthesise requiring extensive protection-deprotection strategies. A solid phase approach addresses these issues and whilst keeping a constant P_2 valine, did allow for variation of the P_3 substitutent. An intermediate α-bromoketone

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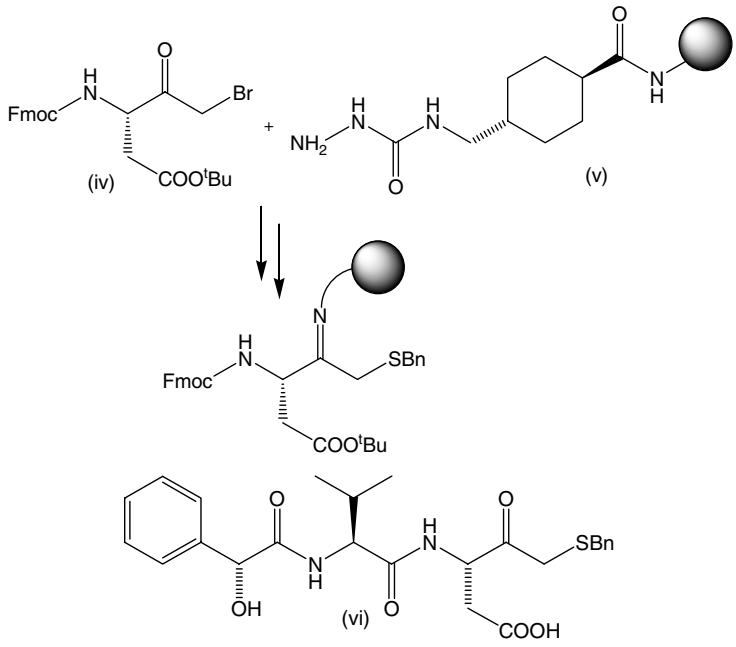

(iv) was attached to Merrifield resin previously derivatised with a hydrasemicarbazone linker (v), and the bromide displaced with benzyl mercaptan. Introduction of valine and diverse P_3 substituents generated a small array of dipeptide derivative products.

SAR investigation on the compounds prepared via this chemistry indicated that there are two distinct and mutually exclusive binding modes in the P_3 region. A hydroxyl group alpha to the amide carbonyl, as in a P_3 mandelic acid derivative (vi), gave an appreciable increase in affinity for caspase 3. However, as substituents were introduced to the phenyl ring of the mandelic acid group, any potency advantage conferred by the hydroxyl was eroded. It was presumed that a conformation that maximised lipophilic interactions on the phenyl ring did not permit the maintenance of a hydrogen bond to the α-hydroxyl group. These compounds are now being advanced to *in vivo* studies.

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

2.1. Solid-phase synthesis

A general method has been reported for the parallel solid-phase synthesis of hydroxypiperazine derivatives based on the oxidation–Cope elimination of a polymer-bound phenethylamine linker with MCPBA.[3]

A new method for the solid-phase synthesis of 6-hydroxy-2,4-diaminoquinazolines has been developed, using a solid-phase bound 6-hydroxy-2,4-dichloroquinazoline as a key intermediate.[4]

2.2. Solution-phase synthesis

A new fluorous 2-chloropyridinium hexafluorophosphate was prepared as a modified Mukaiyama condensation reagent, and has been applied to amide formation reactions. Good to excellent purities of amides were obtained after fluorous solid-phase extraction of reaction mixtures without additional chromatography.[5]

2.3. Scaffolds for combinatorial libraries

Use of *N*-protected-α-amino acid bromides for facile solid-phase synthesis of peptides (SPPS) containing extremely sterically hindered non-proteinogenic amino acids has been reported.[6]

2.4. Solid-phase supported reagents

Chiral Mn(salen) complexes axially immobilised onto insoluble polymers by phenoxy or phenyl sulphonic groups have been shown to afford comparable or even higher enantioselectivities than homogeneous Mn(salen) catalysts for the asymmetric epoxidation of various unfunctionalised olefins.[7]

Peptides with prolyl N-termini, attached to a PEG–polystyrene (TG) synthesis resin, have been tested as heterogeneous catalysts for the aldol reaction between acetone and *p*-nitrobenzaldehyde.[8]

Three phosphine-functionalised polymer resins have been used as scavengers of palladium catalysts from Buchwald–Hartwig aryl amination reactions.[9]

Through the reaction of the key synthon, 1,3-dithiane-5-methanol, with commercial resins, new polymeric reagents useful for supported organic synthesis and combinatorial chemistry have been developed. Exploiting the reactivity of position 2 in 1,3-dithiane rings, such polymeric reagents were employed in the production

of aldehydes from alkyl halides through a process entirely free from unpleasant odours.[10]

2.5. Novel resins, linkers and techniques

The iterative solution phase synthesis of a triarylamine trimer as proof of concept towards the synthesis of oligomeric materials by solid-phase synthesis has been described. The model system uses the stability of germanium linkers to nucleophilic conditions to develop efficient steps towards oligomer synthesis.[11]

Anchoring of substituted benzaldehydes to soluble and insoluble polymers allows for the synthesis of monosubstituted tetraarylporphyrins without the production of di-, tri-, and tetra-substituted porphyrin side products.[12]

2.6. Library applications

Systematic optimisation of a novel class of indole-based endothelin-converting enzyme (ECE) inhibitors by means of classical and solid-phase chemistry was undertaken and optimised compounds with low-nanomolar activity on ECE have been reported.[13]

2,2′-Dimethoxycarbonyl-4,4-dimethoxy-5,6,5′,6′-dimethylenedioxy-biphenyl (DDB) is a potent anti-HBV agent, and thus the reaction between a DDB acid chloride and serine derivatives on solid support has been studied.[14]

A series of chiral zinc catalysts containing (*R*)-3,3′-Br_2-BINOL ligand and various diimine activators, for enantioselective hetero Diels-Alder reactions of Danishefsky's diene with aldehydes, have been developed through a combinatorial approach. The reactions give the corresponding 2,3-dihydro-4*H*-pyran-4-one derivatives in excellent yields and enantioselectivities.[15]

Through parallel organic synthesis, a series of new and stable podocarpate ligands, exemplified by adamantyl- and phenylcyclohexylmethyl-podocarpic acid amides, have been discovered as agonists for Liver X receptor α and β subtypes.[16]

The solid-phase synthesis and pharmacological evaluation of a new series of small-molecule agonists of the human peroxisome proliferator-activated receptor δ (PPARδ) have been reported.[17]

A library of chiral zinc complexes formed in situ by the combination of achiral and racemic diimines with 3,3′-di(3,5-ditrifluoromethylphenyl)-BINOL and diethylzinc have been evaluated in the asymmetric addition of diethylzinc to *N*-acylimines.[18]

A stepwise library-based strategy has been employed to acquire a potent ligand for the SH3 domain of Fyn, a Src kinase family member that plays a key role in T cell activation. The library protocol created peptide/non-peptide chimeras that were able to bind to these interaction sites that are otherwise inaccessible to natural amino acid residues.[19]

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Further reading

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