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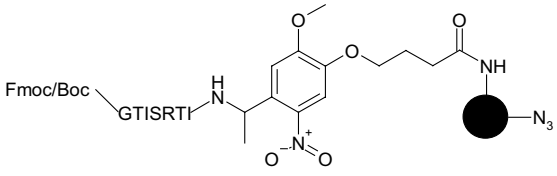
1. Current literature highlights

1.1. Metalloproteinase inhibitors

The design, preparation and screening of chemical libraries in solution or on solid phase has been used for the rapid identification of proteinase inhibitors. The benefit from the combinatorial chemistry perspective is in the synthesis of large numbers of compounds which can be screened simultaneously. In one-bead assays, the selection process to distinguish hits from non-hits can be a difficult and laborious task, rarely performed in a quantitative and reproducible manner. To overcome these problems, automated sorting machines are now available to sort spherical beads according to their fluorescent intensity. A one-bead-two-compound library of phosphinic peptides has been constructed in order to investigate the reliability of a fully automated bead sorting apparatus in selection of beads containing potent inhibitors.[1]

A solid phase library on $PEGA_{1900}$ was synthesised as a one-bead-two-compound library producing a theoretical total of 160,000 phosphinic peptide inhibitors. The $PEGA_{1900}$ resin was initially derivatised to provide two orthogonally protected reaction sites (i). The combinatorial library was generated from one reaction site whilst the other enabled the introduction of an internally quenched fluorogenic substrate. The resulting beads each carry two distinct compounds: (a) the target for molecular interaction, a randomly synthesised library member X_3X_2-GΨ[PO_2HCH_2]L$X'_2X'_3$ and with an N-substituent of acetyl, H, or H-D-Ala, linked to the support via a mass/ionisation spacer [GTISRTI], and a photolabile linker; and (b) an internally quenched fluorogenic substrate AY(NO_2)GPLGLYARK(Abz)G (-scissile bond) attached directly to the resin. Library synthesis on $PEGA_{1900}$ provided, after cleavage of compounds from the solid support, phosphinic acids which were incubated with the 65 kDa MMP-9, which penetrated into the PEGA polymer and cleaved the quenched fluorogenic substrate in beads containing no inhibitory compound. Pools of approximately 10,000 beads were automatically sorted based on a quantitative measurement of fluorescence intensity such that the whole library was sorted in a few hours.

Of those beads found to contain active constituents, ten sequences found to be active were selected for re-synthesis on PEGA 800 resin using a Rink amide linker for evaluation as MMP-9 inhibitors in solution. One of the most active compounds was (ii) which possessed a Ki for MMP-9 of 1.4 nM. These results demonstrate that potent MMP inhibitors can be identified from a one-bead-two-compound library of phosphinic peptides using a fluorescence directed automated sorting method.



(i)

AGPLGΨ[PO_2HCH_2]LYARG-NH_2

(ii)

1.2. Neuroprotective K^+ channel inhibitors

Potassium (K^+) channels play a pivotal role in electrical activity of all excitable tissues. Abnormalities in K^+ currents results in cardiovascular, neurological, renal and endocrine pathology. Pharmacological modulation of specific K^+ currents is recognised as a major strategy

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in the treatment of a broad range of disorders. However, most small-molecule modulators of K^+ channels to date affect these channels at high micromolar to millimolar concentrations and lack sufficient target specificity. Given the diversity of K^+ channels, development of more potent and specific K^+ channel drugs is a high priority for molecular pharmacology. Hindering their discovery is the traditional low-throughput capacity of ion channel assays. An approach to increase the throughput for screening K^+ channel modulators has been tried previously using yeast that functionally express mammalian K^+ channels. Yeast require K^+ and so cannot grow in low [K^+] medium when their endogenous K^+ transporters trk1 and trk2 are disrupted. However, growth of Δtrk1trk2 knockout yeast in low [K^+] medium can be rescued (genetically complemented) by mammalian Kir2.1 channel expression. Because this growth in low [K^+] medium depends on the activity of the mammalian channel, it may be possible to screen for Kir2.1 channel modulators by monitoring yeast growth.[2]

Using this approach, the authors identified a novel K^+ channel inhibitor from an initial screen of 10,000 compounds produced in a combinatorial chemistry library. The library compounds were screened as singletons in an assay based on growth of yeast that functionally expresses mammalian Kir2.1 channels. From this screening procedure, 42 potential inhibitors of Kir2.1 were identified. One compound, 3-bicyclo[2.2.1]hept-2-ylbenzene-1,2-diol was confirmed to inhibit K^+ channels in patch-clamp measurements in mammalian calls with EC_{50} values of 60 and 1 μM for Kir2.1 and Kv2.12 channels, respectively. Therefore, yeast-based screening has identified a novel neuroprotective mammalian K^+ channel inhibitor and this approach may prove useful in the search for further novel ion channels.

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

2.1. Solid-phase synthesis

A traceless solid-phase synthetic approach to isoquinolinones has been described. This method introduces both electron-donating as well as electron-withdrawing moieties on the benzene nuclei of isoquinolinones with high yields and purities.[3]

Polymer-supported isocyanides have been synthesised, from commercial Wang and HMBA-AM resins, and reacted under radical conditions with 2-mercaptoethanol and ethanethiol to give the corresponding pyrrolidine or pyroglutamic acid derivatives in good yields.[4]

The synthesis of pseudopeptides on solid supports, in order to quickly obtain modified peptides has been investigated. A convenient step-by-step synthesis of ketomethylenimino Ψ[CO–CH=N] and ketomethylenamino Ψ[CO–CH_2–NH] peptides has been described.[5]

Tripeptides containing a novel α,α-disubstituted glycine with two pyridine rings, α,α-di(2-pyridyl)glycine (2Dpy), have been synthesised by the solid-phase Ugi reaction using di(2-pyridyl)methanimine attached directly to a Rink amide resin.[6]

The traceless solid-phase synthesis of quinolines has been accomplished by treating resin-bound enol ethers with TFA and then oxidizing with manganese dioxide to give 2-substituted quinolines in high purity without the need for chromatography.[7]

Polymer-substituted dihydrofurans and tetrahydrofurans have been synthesised through polymer-supported selenium-induced intramolecular electrophilic cyclisation, followed by selenoxide *syn*-elimination or novel nucleophilic substitution cleavage of selenium resin with good yields and purities.[8]

2.2. Solution-phase synthesis

A convenient and diversity-oriented method for synthesis of the novel 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[4,5-*b*]-1,5-oxazocine-6-one skeleton and the very rarely described 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocine-6-one skeleton, featuring cyclisation using nucleophilic aromatic substitution (S_NAr) and Suzuki coupling, has been described.[9]

Olsson's one pot, three-component reaction of cyclopropylketones, aldehydes, and primary amines has been investigated for application to parallel synthesis providing an efficient synthetic route to 3-alkylidenylpyrrolidines.[10]

2.3. Scaffolds for combinatorial libraries

No papers this month.

2.4. Solid-phase supported reagents

A variety of aryl nitriles have been prepared in excellent yields from the palladium acetate catalysed coupling of aryl halides with $Zn(CN)_2$ using polymer-supported triphenyl phosphine as the ligand and dimethylformamide as solvent under microwave irradiation conditions.[11]

2.5. Novel resins, linkers and techniques

Optimization of the Heck reaction of 4-bromoacetophenone with styrene by a polymer supported, sulphur-containing palladacycle, varying six factors at a total of 28 different levels, corresponding to 5760 different possibilities has been undertaken.[12]

A rapid method for the qualitative detection of hydroxyl groups on solid-phase has been developed. The method employs *N*-methylisatoic anhydride to derivatise resin-bound substrates possessing free hydroxyl functionality, and the resultant fluorescent ester can be detected by visualisation under a standard laboratory UV lamp at 365 nm excitation.[13]

The previously proposed concept of using mixtures of two different chiral monodentate P-ligands has been extended to the asymmetric Rh-catalyzed hydrogenation

of β-acylamino acrylates with formation of chiral β-amino acid derivatives. The power of this combinatorial approach arises from the ready access to catalyst diversity without the need to synthesize new ligands.[14]

2.6. Library applications

A concise, efficient and flexible total synthesis of the potent antitumor agent TMC-69-6H has been described. The flexibility inherent to this route allows for the preparation of a focused library of analogues for biochemical evaluation with the results obtained showing that *N*-hydroxy-2-pyridone derivatives constitute a promising new class of selective phosphatase inhibitors.[15]

Screening of a combinatorial CTV-based artificial, synthetic receptor library for binding of a variety D-Ala-D-Ala and D-Ala-D-Lac containing ligands has been carried out. After screening and Edman sequencing, synthetic receptors were found containing amino acid sequences, which are either characteristic for binding dye labelled D-Ala-D-Ala or D-Ala-D-Lac containing ligands.[16]

A targeted library of small molecules has been prepared to optimise the biological activity of a lead compound, recently described as an original inhibitor of CDC25 phosphatases. Some of these compounds inhibit CDC25 in the micromolar range and therefore reinforce the interest of CDC25 as an anticancer target.[17]

A series of potent and selective inhibitors of ADAM12 have been discovered using computational screening of a focused virtual library.[18]

A solution-phase multiple-parallel synthesis approach has been employed for the preparation of 6-, 7- and 8-aryl-substituted chromenone libraries, which were screened as inhibitors of the DNA repair enzyme DNA-dependent protein kinase (DNA-PK).[19]

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