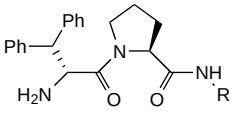
Combinatorial chemistry

Thrombin inhibitors with nonbasic P1 side-chains

Last month a paper from Merck Research Laboratories [Brady, S.F. *et al. J. Med. Chem.* (1998) 41, 401–406] was featured, in which combinatorial chemistry had been used to find thrombin inhibitors with improved pharmacokinetics. More recently, the same team have published another approach to thrombin inhibitors seeking nonbasic residues in the P1 position [Lumma, W.C. *et al. J. Med. Chem.* (1998) 41, 1011–1013].

Inhibition of the serine protease, thrombin, has been selected as a method for the treatment of diseases characterised by inappropriate thrombus formation, such as deep vein thrombosis and stroke. Many inhibitors found so far, contain a basic P1 side-chain that interacts with an aspartic acid residue at the bottom of the enzyme recognition pocket. As inhibitors with guanidine and amidine functionality have poor oral absorption, medicinal chemists have focused on the search for non-basic P1 residues.

Solid-phase parallel synthesis was used to prepare several analogues of D-diphenyl-Ala-Pro (**1**). The Boc-protected dipeptide was synthesized on Kaiser resin and cleaved from the support by reaction with a diverse range of amines. SAR studies indicated that 2,5-lipophilic substituents were preferred and that 2,5-dichlorobenzylamide (**2**), incidentally synthesized using a traditional solution-phase route, was found to be the most potent (K_i = 3 nM).



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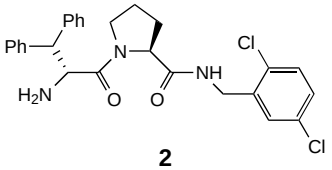
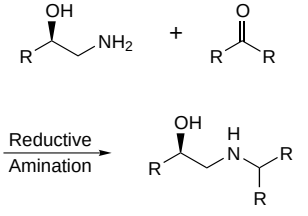


2

Library of adrenergic agents

Ligands that selectively modulate the response of β-adrenergic receptors have been successfully used to treat a range of medical conditions including angina, asthma and hypertension. It has been found that even slight modification of the central ethanolamine pharmacophore can have a dramatic effect on ligand potency or selectivity. With the intention of finding novel adrenergic ligands, an array of ethanolamine compounds (**3**) has been prepared using high-throughput solution-phase parallel synthesis [Siegel, M.G. *et al. Mol. Diversity* (1998) 3, 113–116].



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A 96-compound array was synthesized in glass vials by reductive amination of 8 ketones with 12 ethanolamines. The reactions were driven to completion by the addition of excess ketone, and a key step in the process was the removal of all non-basic products by ion exchange chromatography. This purification step led to the majority of products subsequently being obtained in good yield and near-analytical purity. The methodology is currently being used for ethanolamine SAR studies.

Simultaneous measurement of binding constants

As combinatorial chemistry methods become more effective at the rapid generation of large compound libraries, there is a need to achieve a commensurate increase in screening throughput. Various methods have been proposed for the screening of mixtures, and one method, affinity capillary electrophoresis-electrospray ionization-mass spectrometry (ACE-MS) offers the promise of simultaneous measurement of multiple binding constants [Dunayevskiy, Y.M. *et al. J. Med. Chem.* (1998) 41, 1201–1204].

Affinity capillary electrophoresis (ACE) depends on the measurement of the mobility change of a ligand when eluted with the receptor present in the electrophoretic buffer. The technique offers the opportunity to examine several substances at the same time, provided that the analytes are separated from each other, and can be unambiguously identified. Furthermore, the technique does not require an accurate knowledge of ligand concentration, nor high purity of compounds or receptor.

This recent report describes the use of ACE-MS to examine the affinity of tetrapeptides for vancomycin, measuring the dissociation constants of Fmoc-DXYA, where X is any of the 19 common amino acids (excluding Cys). The K_d values determined, whilst not greatly differing from each other, were in close agreement with binding affinities determined with individual compounds, demonstrating the advantages of a method that can simultaneously analyse compounds in mixtures.

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Emerging molecular targets

Selective CB_2 cannabinoid antagonists – potential new immune modulators?

The enigmatic failure of the immune system to attack and destroy tumor cells is a major dilemma in cancer therapy. Examples for the critical role of the immune system in cancer are the increased likelihood of cancer occurring in individuals undergoing immuno-

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