Antiviral prostanoid libraries

The prostaglandin family constitutes one of the most pharmacologically active low molecular weight chemical classes in existence. A library of prostanoid analogues has been prepared on a soluble polymer support and used to find novel inhibitors of a herpes family virus (Soluble-polymer supported synthesis of a prostanoid library: identification of antiviral activity, K.J. Lee et al., Org. Lett., 1, (1999), 1859-1862).

A ‘parallel pool’ library strategy was employed in which small pools of compounds were modified through a number of different functionalisation reactions. Starting with the enone (i) attached to a soluble polystyrene support, a number of different ω- and α-chains were added to generate the library (ii). Cleavage of the products from the support with fluoride ions permitted biological evaluation of the library pools, and deconvolution of active pools gave the identity of active single analogues.

The library of prostanoids was screened for their ability to inhibit the replication of murine cytomegalovirus (CMV), and the analogue (iii) was discovered as the most potent. Although an order of magnitude less potent than ganciclovir, the most frequently used anti-CMV agent, this level of activity has encouraged the preparation of other structurally related prostanoids in a second generation library to further the search for more active agents.

Cysteine protease libraries

Cysteine proteases are characterised by the presence of a key nucleophilic cysteine residue in the active site of the enzyme that attacks the carbonyl of the hydrolysed substrate amide bond. Various cysteine proteases are known to have physiological functions that make them suitable as targets for pharmacological intervention. Examples include calpains implicated in neurodegeneration, cathepsin K linked to osteoporosis and caspases which are possibly involved in apoptosis.

Various mechanism-based inhibitors have been designed, many of which depend on a electrophilic group such as a carbonyl or Michael acceptor that can covalently link to the nucleophilic thiol group of the critical cysteine. A recent publication describes a versatile route to ketone-based cysteine protease inhibitors that permits maximal variation of the ketone structure (General solid-phase method for the preparation of mechanism-based cysteine protease inhibitors, A. Lee et al., J. Am. Chem. Soc., 121, (1999), 9907-9914).
A chloromethyl ketone, readily prepared in one pot from N-protected amino acids, was linked to the solid support by reaction with a hydrazine linker. The tethered carbazate (iv) could then be derivatised by nucleophilic displacement of the chloride, and further functionalisation of the deprotected amine. A range of products (v) can be made, without racemisation of the α-chiral centre, and ultimately liberated from the solid support in 40 to 100% overall yields. Library preparation using this methodology is currently ongoing and the products will be evaluated against representative cysteine proteases.

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**Orally active GPIIb/IIIa antagonists**

Several serious cardiovascular conditions such as unstable angina and myocardial infarction are associated with platelet aggregation, atherosclerotic plaque formation and ultimately, thrombosis. In the process of thrombus formation, the final critical step is the adherence of the protein fibrinogen to the activated membrane-bound glycoprotein IIb/IIIa. Compounds that can compete with fibrinogen for the platelet glycoprotein receptor are potential antithrombotic agents. In the search for orally active agents that have the potential to be used for chronic cardiovascular care, a group from the R.W. Johnson Pharmaceutical Research Institute have used combinatorial chemistry to optimise a prototype fibrinogen receptor antagonist (Potent, orally active GPIIb/IIIa antagonists containing a nipecotic acid subunit. Structure-activity studies leading to the discovery of RWJ-53308. W.J. Hoekstra et al., *J. Med. Chem.* 42, (1999), 5254-5265).

Solid-phase parallel synthesis, employed in the preparation of around 250 analogues of compound (vi), led to the discovery of RWJ-53308 (vii). This compound is an active anti-platelet agent that can be administered both intravenously and orally, and which has a good...
duration of action. The compound has been successfully progressed through human phase II clinical trials.

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