Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

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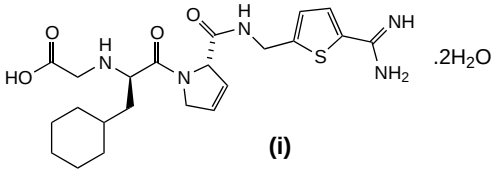
Combinatorial chemistry

Thrombin inhibitors

Thrombin is a trypsin-like serine protease that has a crucial role in blood coagulation. It cleaves soluble fibrinogen into fibrin. Subsequent polymerization of fibrin stabilizes the initially formed thrombozyte clots at the site of blood vessel damage. Undesired activation of the blood coagulation cascade can result in cardiovascular disorders, such as deep vein thrombosis, myocardial infarction, unstable angina, pulmonary embolism and ischaemic stroke. Thrombin has, therefore, become an important target for the treatment of thromboembolic diseases.

Approaches to thrombin inhibitors have centred around the D-Phe-Pro-Arg motif that mimics the natural substrate. D-Phe replaces the Phe residue in fibrinogen that normally occupies the lipophilic D pocket. The guanidine moiety of Arg, which is also present in the natural substrate, forms a salt bridge with Asp189 at the bottom of the specificity pocket of thrombin. Interactions with Ser195 in the active centre of thrombin were shown not to be essential for high affinity to the enzyme. In an effort to optimize potency and selectivity of thrombin inhibitors, a combinatorial chemistry approach was undertaken [1].

A small library was synthesized on 4-nitrophenyl carbonate Wang-resin



(i)

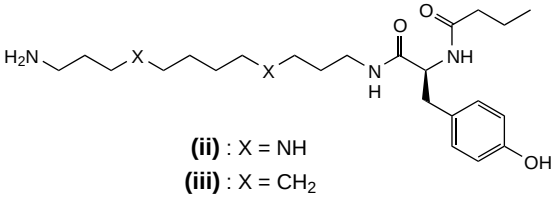
(Novabiochem, http://www.nova.ch) in an attempt to generate potent thrombin inhibitors. The library compounds were evaluated in a chromogenic assay for inhibition of thrombin. One of the most potent compounds found was **i**, which possessed a thrombin inhibition IC_{50} value of 3.6 nM. This work has produced potent thrombin inhibitors, and holds promise for further optimization.

1 Zechel, C. *et al.* (2002) Solid-phase synthesis of thrombin inhibitors. *Bioorg. Med. Chem. Lett.* 12, 1571–1573

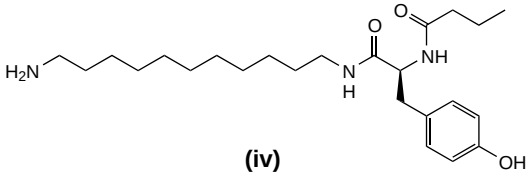
Nicotinic acetylchloline receptor agonists

Polyamine toxins are a class of nonoligomeric, low molecular weight compounds isolated from the venom of spiders and wasps that are nonselective inhibitors of ionotropic receptors, such as ionotropic glutamate receptors (iGluRs) and nicotinic acetylcholine receptors (nAChRs). The polyamine moiety of polyamine toxins is considered to interact with polar or charged amino acid residues in the interior of cation-selective ion channels. It has recently been demonstrated that, by modification of the polyamine portion of compound **ii**, it was possible to achieve selectivity for nAChR, as with compound **iii**. This compound (**iii**) is a promising lead for the development of novel potent and selective non-competitive antagonists of nAChR.

Studies were conducted to provide SAR within the series exemplified by **iii** [2]. A small library of seven compounds were



(ii) : X = NH
(iii) : X = CH_2



(iv)

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synthesized on trityl chloride solid-phase resin. The library compounds were screened for activity in the whole-cell patch-clamp assay, using human embryonic muscle-type nAChR expressed in TE671 cells. One of the most potent compounds isolated was **iv**, which possessed an IC_{50} value of 460 ± 50 nM. This work has provided novel, potent leads worthy of further investigation.

2 Stromgaard K. *et al.* (2002) Solid-phase synthesis and pharmacological evaluation of analogues of PhTX-12-A potent and selective nicotinic acetylchloline receptor antagonist. *Bioorg. Med. Chem. Lett.* 12, 1159–1162

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