comparison. Insulin is degraded in the GI tract by several enzymes, including trypsin, chymotrypsin and elastase. The protective effect of the delivery system towards enzymatic attack of insulin by these three enzymes was evaluated *in vitro*. In these studies, the incorporated insulin was almost completely degraded in the dosage form without CMC–BBI and CMC–Ela, whereas ~50% of the insulin remained intact in the delivery system containing the polymer–inhibitor conjugates[4]. The release rate of insulin from the dosage form was also studied *in vitro* and a slow release was observed in artificial intestinal fluid (pH 7.1).

To determine the efficacy of the insulin delivery system, an *in vivo* study was performed in which diabetic Balb/C mice were dosed with the insulin drug delivery system tablets[4]. Even though the CMC–BBI and CMC–Ela inhibitor conjugates only account for 20% of these drug delivery systems, the bioavailability of orally administered insulin from this formulation was significantly improved. Basal glucose levels of diabetic mice were reduced by 20–40% when dosed with the insulin drug delivery system. This effect appears 4 h after administration and is maintained for ~80 h, then gradually returns to initial values. In comparison, tablets without insulin had no effect on the blood glucose level, indicating that the effect is not caused by the CMC–BBI/CMC–Ela formulation itself. Oral administration of insulin in aqueous ascorbic acid solution also had no influence on blood glucose levels.

Mechanism of action

There are presumably several reasons that this drug delivery system increases the oral bioavailability of insulin. Luminally secreted enzymes must penetrate the polymeric network of the tablet to degrade the embedded insulin. The PCP–cysteine conjugate is capable of forming intermolecular as well as intramolecular disulfide bonds within the polymeric network, thereby contributing stability to the dosage form. The reactive thiol groups of PCP–Cys contribute to a mucoadhesive effect that is twice that of PCP itself, presumably from thiol or disulfide exchange reactions with cysteine-rich mucin glycoproteins. The high stability of the carrier matrix allows for a prolonged release of the drug, over ~10 h *in vitro*. Once released, the inhibitory effects of CMC–BBI and CMC–Ela also provide the insulin with some protection from the action of proteolytic enzymes. Of course, the therapeutic window for insulin is narrow and rodent studies do not always extend well to human patients, but this could prove to be a good starting point for an oral insulin delivery system.

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Combinatorial chemistry

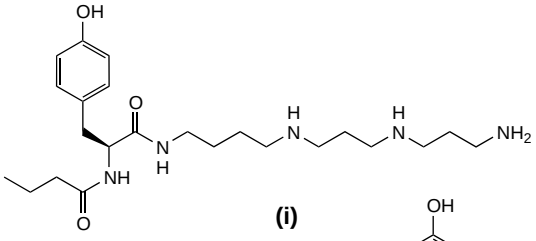
Philanthotoxin analogues

Philanthotoxins, a group of non-competitive antagonists of ionotropic receptors, are composed of long-chain polyamines connected to a relatively nonpolar headgroup via an amide bond. Recently, interest in the medicinal chemistry and pharmacology of philanthotoxins has been highlighted by the observation that the specificity of their antagonist action on various classes of ionotropic receptors can be achieved by modification of the polyamine portion of the molecule. Thus, natural and synthetic toxins **(i)** are known to antagonize various types of nicotinic acetylcholine receptors (nAChRs) and ionotrophic glutamate receptors (iGluRs) with similar potency. However, analogues in which the secondary amino groups are replaced by methylene groups or oxygen atoms **(ii)**, exhibit enhanced antagonist activity on mammalian muscle-type nAChR and Torpedo nAChR but are inactive on several types of iGluR.

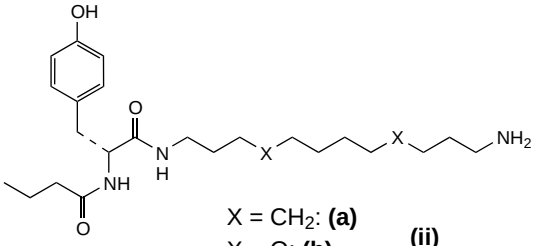
Previous structure–activity investigations of synthetic analogues containing a symmetrical spermine moiety or closely related polyamine, which have been tested on iGluR and nAChR, emphasize the importance of the hydrophobic character of the headgroup. By contrast, no information regarding the influence of the structure of the headgroup on the potency of philanthotoxin analogues lacking inner basic sites is available.

In an effort to produce SARs in such series, a library of compounds was synthesized to test whether compounds that lack the inner basic sites bind to nAChR in a similar fashion[1]. A library of 18 individual compounds was synthesized on trityl chloride solid phase. Of those compounds tested that lacked the inner basic sites, all were inactive when tested on rat brain non-NMDA receptors. The success of this library protocol lies in increasing the understanding of the SAR of antagonism of nAChR by

 PII: S1359-6446(01)01871-2



(i)



X = CH_2: **(a)**
X = O: **(b)**

(ii)

philanthotoxin analogues lacking inner basic sites.

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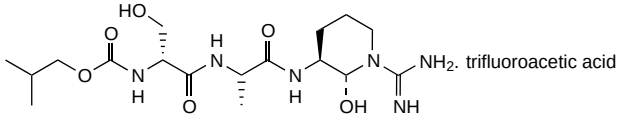
Urokinase inhibitors

Urokinase-type plasminogen activator (u-PA) is one of the two major endogenous plasminogen activators catalyzing the conversion of the zymogen plasminogen to the fibrinolytic protease plasmin. The primary role of u-PA is to generate plasmin in events involving the degradation of the extracellular matrix. Localization of u-PA on the cell surface is achieved by binding to urokinase plasminogen activator receptor (u-PAR), which is attached to the cell membrane via its glycosyl phosphatidyl inositol (GPI) anchor. Recent advances in the elucidation of the u-PA–u-PAR system's function have led to an increased understanding of the role this enzyme has in angiogenesis, cell invasion and cancer metastasis. Efforts are focused on the development of selective direct and mechanism-based synthetic u-PA inhibitors as potential therapeutic targets for cancer, arthritis and pathological angiopathies[2]. A library of 11 peptidyl arginine-based compounds were synthesized in solution. One of the most potent compounds isolated was **(iii)**, which had an IC_{50} of 23.1 nM against human urokinase enzyme, with 63-fold selectivity against human plasmin enzyme, and >100-fold selectivity against human t-PA enzyme. This work has provided further delineation of the active-site requirements of u-PA, and should help the discovery of potent and selective inhibitors.

(iii)



. trifluoroacetic acid

2 Nolan, T.G. *et al.* (2000) Synthesis and biological activity of peptidyl aldehyde urokinase inhibitors. *Bioorg. Med. Chem. Lett.* 10, 983–987

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