**Plecanatide, a superior analog of uroguanylin, as an oral drug candidate for treatment of gastrointestinal functional disorders and diseases**

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**BACKGROUND**

Agonists of guanylate cyclase-C (GC-C) are emerging as a new class of drug candidates for treatment of gastrointestinal (GI) disorders and diseases. Uroguanylin (UG) and guanylin (GN) are physiological natriuretic peptides that bind and activate GC-C receptors expressed on the epithelial cells lining the GI mucosa, leading to production of cyclic guanosine monophosphate and promoting electrolyte and water secretion needed for normal bowel movements. While UG cooperatively regulates GC-C receptors in a pH-dependent physiological mechanism to regulate water secretion, the E. coli enterotoxin ST Pierce activators GC-C in an uncontrolled and pH-independent manner, resulting in excessive fluid secretion to cause Traveller’s diarrhoea. Spatial conformation of UG assumes several distinct topoisomers in aqueous solution and only one of those is biologically active. Consequently, large scale manufacturing and purification of UG becomes difficult and cost prohibitive. Thus, functional homologues of UG may have the advantage as drugs for normalising bowel movements with less likelihood of causing severe diarrhoea. Objective of this study was to identify an analog of UG with superior physiological properties for the treatment of chronic constipation (CC) and irritable bowel syndrome-constipation (IBS-c).

**METHODS**

Strategies used to design new analogs: Number of strategies such as thermal bond energy calculations, 3-D structure modeling, structural activity relationships and molecular dynamics were utilized to design new analogs of UG. New analogs were selected based on their promise to initiate cGMP synthesis and affinities to bind GC-C receptors expressed on T84 cells. Plecanatide (SP-304), being the most potent analog, was further evaluated for its stability against digestion in simulated gastric fluids.

**RESULTS**

Fig 1 Primary structures of plecanatide, uroguanylin and other agonists of GC-C receptors

![Image](image1)

An optimal volume of water secretion into the intestinal lumen is essential for normal bowel movement.

Fig 2 Plecanatide and uroguanylin stimulate water secretion in the lumen of the proximal intestine to normalize bowel movement

![Image](image2)

Like UG, activity of plecanatide might also be regulated by the mucosal acidity of the GI tract.

**DISCUSSIONS**

The distance between Asp3 and Ala11 is larger (10Å) in uroguanylin as compared to that in plecanatide (4Å) in urusguanylin as compared to that in plecanatide (4Å) in plecanatide highlighting the structural change of plecanatide in more rigid and stable state with Glu3 as in plecanatide minimizes topoisomer formation. Plecanatide is by far the most potent and stable analog of uroguanylin as an oral drug candidate for treatment of gastrointestinal functional disorders and diseases. Plecanatide was found to be the most potent analog of UG to stimulate cyclic cGMP synthesis in T84 cell.

**CONCLUSIONS**

- Plecanatide is by far the most potent and stable analog of uroguanylin to stimulate cGMP synthesis in T84 cells.
- Like uroguanylin, the activity of plecanatide to stimulate cGMP synthesis is modulated by pH. First three amino acids (Asn-Asp-Glu) at the N-terminal and Leu at the C-terminal of plecanatide are crucial for its activity and stability.
- Oral administered plecanatide acts primarily in the proximal intestine to stimulate fluid secretion.
- Data suggest that the site of action of plecanatide is likely to be in the proximal region of the gastrointestinal tract.
- Repeated oral doses of plecanatide increased stool consistency in monkeys, suggesting that the drug is pharmaceutically active.