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SYNTHESIS OF POTENTIAL PEPTIDOMIMETICS BASED ON HIGHLY SUBSTITUTED GLUCOSE AND ALLOSE SCAFFOLDS.

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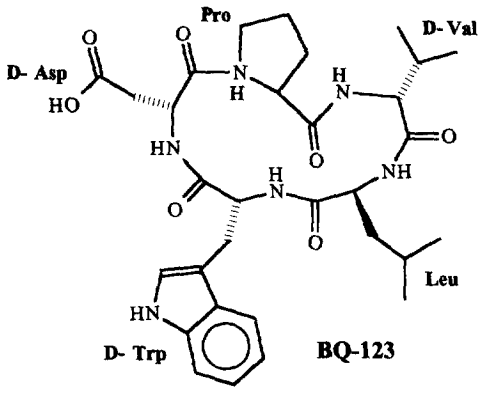
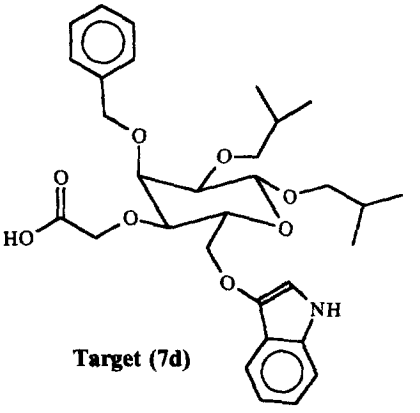
Abstract : A series of eight potential peptidomimetics has been synthesised based on the use of *gluco-* and *allo-* carbohydrate derivatives as scaffolds to support appropriate side-chains which mimic the D- and L-aminoacid residues of the cyclic peptide endothelin antagonist **BQ123**.

The use of peptide ligands as drugs is often compromised by numerous factors including : (1) most peptides have low metabolic stability towards proteolysis in the GI tract and in serum, (2) peptides are often very poorly absorbed after oral dosing and (3) peptides are rapidly excreted *via* both liver and kidneys. For these reasons there is currently wide interest in peptidomimetics. One possible approach is mimicking of peptide molecules using non-peptide based scaffoldings which may maintain aminoacid like side chains in the required spatial geometry to mimic the biological activity of the target peptide.[1] The use of sugars as scaffolds, is an area that has previously been examined. We were interested in CNS penetrating mimics of the highly constrained cyclic-peptide endothelin antagonist **BQ123**, which when injected directly into the brain has been shown [2] to prevent the often fatal early cerebral vasospasm which follows a subarachnoid haemorrhage. **BQ123** given intra-venously is inactive in this model. The three dimensional structure and solution conformation of **BQ123** have been studied in detail.[3] The solution conformation of **BQ123** involves a type-II beta-turn, and an inverse gamma turn, probably stabilised by an internal hydrogen bond, resulting in a single well defined dominant



BQ-123



Target (7d)

Figure 1

conformation in solution. Molecular modelling comparisons [4] of **BQ123** and various sugar based potential mimics showed that for both *gluco-* and *allo-* based molecules a good overlap of functional groups was possible in a low energy conformation. From these studies we identified a series of target molecules based on the use of these sugar scaffolds, and we report here the synthesis and biological activity of these molecules.

Molecular modelling [4] indicated that attachment of an indole or potential indole mimic (*eg* 2-naphthyl group) directly at the 6-position of the sugar skeleton, together with an isobutyl ether at the anomeric position, in the β-configuration, gave a good match to both the D-tryptophan and L-leucine side chains of **BQ123**. The D-aspartic acid side chain could be effectively mimicked by an acetic acid side chain, placed in an equatorial position at C-4. The remaining D-valine side-chain of **BQ123** could then be matched by either an isopropyl or isobutyl ether, equatorially disposed at C-2. Finally the volume occupied by the proline ring which is "fused" onto the cyclic peptide could be filled by an O-benzyl group at C-3, either equatorially or axially disposed

Figure 2a , Stereoscopic view of target compound **7d.**

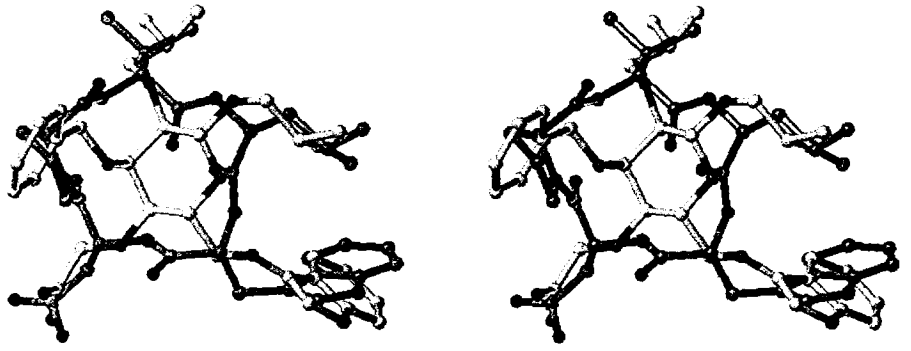


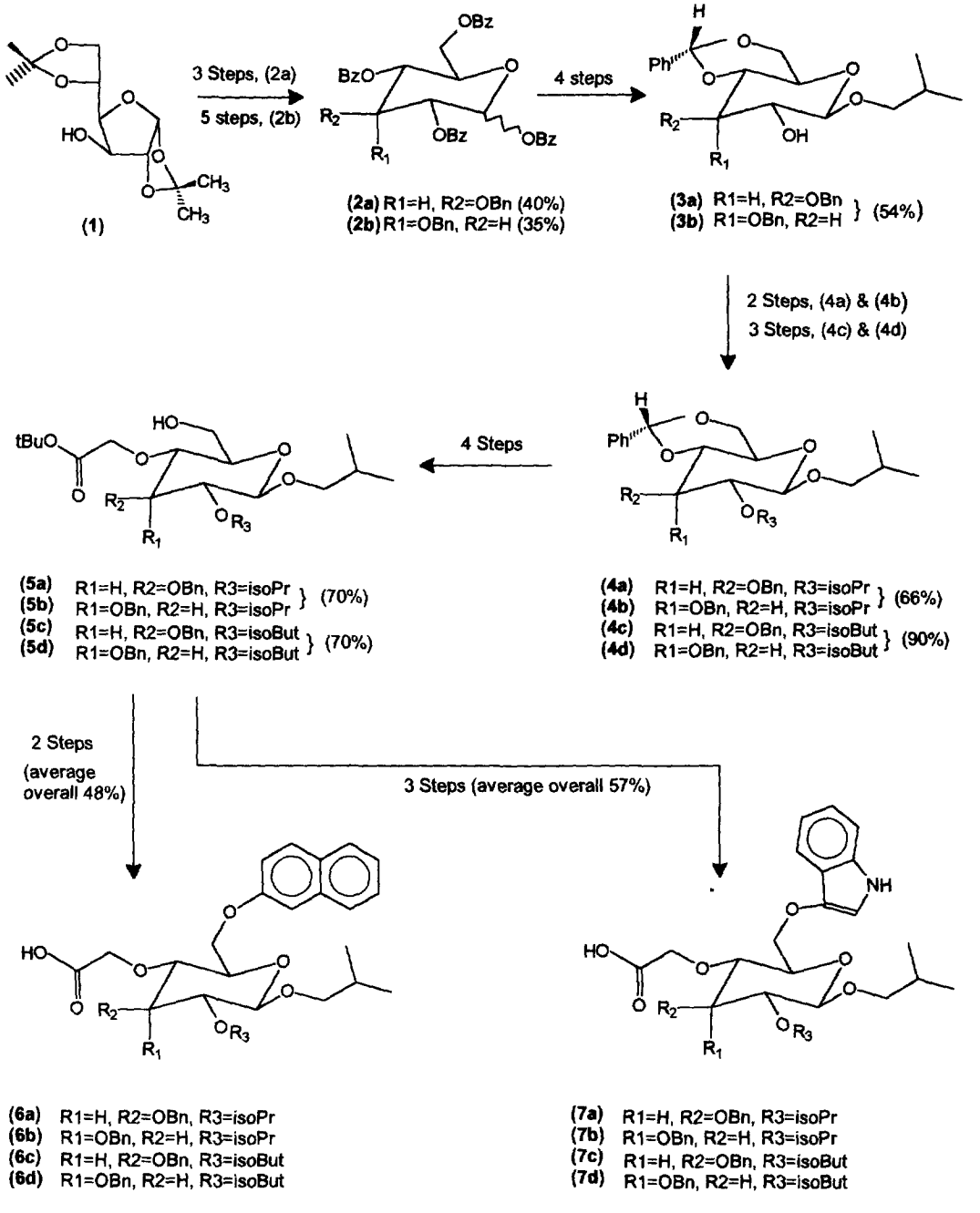
Figure 2b, Stereoscopic view of superposition of **BQ123** and compound **7d**.

(depending on the overall low energy conformation chosen for matching), thus giving either a glucose or allose based stereochemistry respectively. These observations are illustrated by the stereoscopic view of the target compound **7d**, *Figure 2a*, and the stereoscopic view of the superposition of **7d** with the low energy conformation of **BQ123**, *Figure 2b*.

We therefore embarked on the synthesis of the eight derivatives shown in *Scheme 1*, **6a-d** and **7a-d**, and the structure of one representative molecule amongst these targets is shown in *Figure 1*, together with the structure of the cyclic peptide **BQ123** for comparison.

Both the *gluco*-(**6a,6c,7a,7c**) and *allo*-(**6b,6d,7b,7d**) series of derivatives were synthesised from the same commercially available starting material, diisopropylidene D-glucofuranose **1**, *Scheme 1*. Direct benzylation [5] of the free OH group in **1** using NaH/BnBr (86%) followed by acidic hydrolysis of the two isopropylidene groups (100%), and benzoylation [6] of the resulting tetrol using BzCl/pyridine gave the fully protected D-glucose derivative **2a** (60%). Alternatively, oxidation of the free OH group of **1** to the ketone with PCC [7] (80%) followed by stereoselective reduction with $NaBH_4$/THF [8] gave the epimeric alcohol (85%), which was treated in an identical manner to the glucose derivative, to give the fully protected D-allose derivative **2b**, in a similar overall yield.

Bromination of **2a** and **2b** proceeded most efficiently [9] with $TiBr_4$ in $CHCl_3$ (76%) [10] and subsequent glycosylation using 2-methyl-1-propanol in the presence of $HgO/HgBr/CaSO_4$ [11,12] gave the β-glycosides selectively and in good yields (90%). Basic hydrolysis of the benzoyl groups using NaOMe/MeOH [13] furnished the corresponding triols (92%), which were protected as the benzylidene acetals **3a** and **3b** by treatment with benzaldehyde dimethylacetal and *p*TSA in CH_3CN (86%).[14] Alkylation of **3a** and **3b** with methallyl bromide/NaH in THF (89%) followed by selective reduction of the olefin using NaOAc and benzene sulphonylhydrazide in DME/H_2O [15] gave the isobutyl ethers **4c** and **4d**. In order to prepare the corresponding isopropyl ethers, we developed a novel synthetic approach ; firstly **3a** and **3b** were treated with acetic anhydride in pyridine to give the corresponding acetates (95%). Subsequent reaction with the Petasis reagent ($Ti(Cp)_2Me_2$) [16,17] gave the corresponding enol ethers (78%), which were efficiently reduced using H_2 over $Pd/BaSO_4$ 10% to the isopropyl ethers **4a** and **4b** (90%). [18] Solvolysis of the benzylidene acetals of **4a-d** using MeOH/I_2 (100%), [19] was followed by temporary protection of the primary OH groups as their trityl ethers using $(Ph)_3CCl$/pyridine at reflux (100%). Alkylation of the remaining free OH at C-4 using NaH/DMF and *tert*-butyl bromoacetate (78%), followed by removal of the trityl group using an acidic ion-exchange resin in MeOH [20] then gave the four primary alcohols **5a-d** (90%). Each of these four alcohols was then converted separately into its corresponding 2-naphthyl and 3-indolyl ether. Thus we obtained our eight target compounds. The four target compounds bearing a 2-naphthyl group as a potential indole mimic were prepared directly from **5a-d** by a Mitsunobu reaction with 2-naphthol in THF (60%),[21] followed by basic hydrolysis of the *tert*-butyl ester group using LiOH/MeOH, giving the target carboxylic acids **6a-d** (80%).



Yields are given as overall yields for the multi-step transformations shown. Average yields are given for multiple examples involving identical transformations.
See text for reagents and conditions.

Scheme 1

In order to prepare the four indole derivatives, the free primary alcohol groups of compounds **5a-d** were converted into the corresponding triflates using Tf_2O/pyridine/CH_2Cl_2 (98%) [22] and the triflate group was displaced with 3-hydroxy-N-acetyl indole [23] in acetone/DMF using $CsCO_3$ as base (89%). [24] Finally basic hydrolysis using LiOH/MeOH as for the 2-naphthyl derivatives, removed both the *t*-butyl ester and the N-acetate protecting groups, giving the four target carboxylic acids **7a-d** (65%).[25]

The target molecules were examined for their interaction with human derived endothelin receptors using standard protocols [26]. To our profound disappointment, no significant binding to endothelin receptors was observed for any of these eight target molecules.

This lack of activity presumably results from the increased conformational mobility of the side chains of these molecules compared to the highly rigid structure of **BQ123**. This result stands in stark contrast to the good biological activity observed at somatostatin receptors[1b,1c] for highly flexible sugar derived peptidomimetics. Future studies should therefore address the question of potentially reducing the number of accessible conformations for this type of sugar derived analogue if potent endothelin antagonists are to result.

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26) Compounds were tested for their interactions (agonist or antagonist) with human ET_A and ET_B receptors by CEREP, Le Bois l'Eveque, BP-1 Celle l'Evescault, France, 86600.

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