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Sugar–amino acid cyclic conjugates as novel conformationally constrained hydroxyethylamine transition-state isosteres

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ABSTRACT

Hydroxyethylamine (HEA) isosteres have previously been shown to display a multitude of biomedical applications. In fact, the first protease inhibitor, saquinavir is an HEA based peptidomimetic. Herein we describe an easy-to-operate synthetic route to a series of carbohydrate-based conformationally constrained hydroxyethylamine (HEA) isosteres featuring amino acid side chains, starting from D-glucose. This class of novel sugar–amino acid-tethered conformationally restricted HEA systems may have bearing in practical application, particularly in the development of conformationally restricted protease inhibitors.

Recent years have witnessed the design and development of a number of protease inhibitor—systems which mimic the transition-state of the protease's actual substrate.[1] Protease inhibitors can be obtained by the isosteric replacement of the scissile peptide bond.[2] One of the most important transition-state isosteres developed so far is the hydroxyethylamine motif (HEA, Fig. 1).[3] Ever since the successful development of the first protease inhibitor based on transition-state simulation principle, the amount of attention given to this class of compounds has increased manifolds.[4] The HEA isosteres have already been proven to be promising candidates for various curative programs—in conditions varying from contagious malaria to the deadly AIDS and many others.[5] Success of using this moiety as a peptide bond replacement can be readily understood by the number of HEA-based drugs which have been available in the market that includes saquinavir, indinavir, nelfinavir and amprenavir which are the FDA approved protease inhibitors (PIs). Several other therapeutically significant HEA isosters are known for their potential for treating cancer, Alzheimer's disease and nosocomial infections.[3a,4,6]

In continuation of our ongoing programmes directed toward the development of novel HEA isosteres,[7] and robust peptide secondary structure scaffolds,[8] herein we describe a general synthetic route, starting from the readily available D-glucose, to access carbohydrate-based conformationally constrained hydroxyethylamine (HEA) isosteres featuring amino acid side chains.

As per the literature precedents, the structural modulations of HEA isosteres can be achieved by amino acid variations, changing the side chain lengths and composition and introducing conformational constraints on the backbone, which would often enhance the binding affinity of the ligands (Fig. 2).[9]

A carbohydrate-based starting material was chosen herein owing to the enormous scope of its functionalization and ready avail-

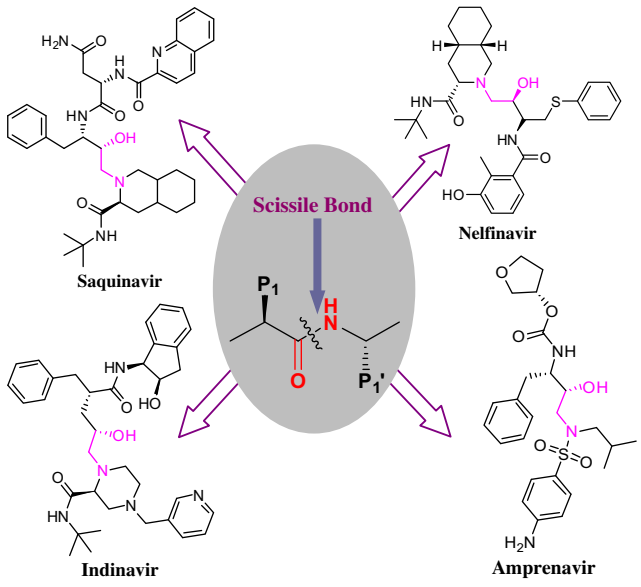

Figure 1. Selected FDA approved protease inhibitors (PIs) wherein the scissile peptide bond has been modified with an HEA moiety.

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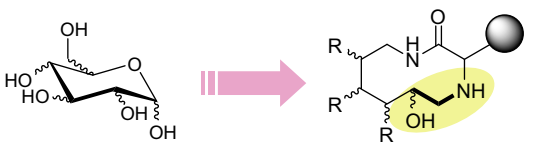

Figure 2. Design strategy to form conformationally constrained carbohydrate derived macrocyclic HEA isosteres featuring amino acid side chain.

baility,[10] as well as the ease of tuning of the ring size of these constrained HEA isosteres. The design strategy illustrated herein is a straightforward one which makes use of established synthetic protocols. The main challenge of our synthetic strategy was the formation of the 10-membered macrocycle which was finally achieved through a two-step 1,2 acetonide deprotection *cum* reductive amination process. The constrained HEA isosteres were synthesized in an overall thirteen steps starting from D-glucose (Scheme 1).

To synthesize the carbohydrate-based conformationally constrained HEA isosteres **9a–c**, we began with D-glucose which was transformed into the tosyl analog **5** in four steps, following the known protocols reported in the literature.[11] The tosyl protected furanose sugar **5** furnished the azide displaced product **6** in excellent yield upon heating it at 50 °C in DMF containing NaN_3.[12] Benzyl protection of the two secondary hydroxyl groups was carried out by reacting with benzyl bromide in THF, having NaH as the base and TBAI as a phase transfer catalyst affording the di-benzyl ether **7**. The furanose **7** was then subjected to selective azide reduction using triphenylphosphine/water followed by coupling with different BOC-protected amino acids to furnish **8a–c** in very good yields.[13] The 1,2 acetonide protected furanose sugar bearing amino acid side chains were then subjected to a two-step TFA-assisted acetonide cleavage followed by reductive amination in the presence of $NaBH_3CN$. The crude secondary amine was then protected using BOC anhydride in water as a solvent. Finally the benzyl groups were removed using 20% $Pd(OH)_2$ in methanol at 150 psi under hydrogen atmosphere for 16 h to furnish the macrocyclic HEA isosteres **9a–c**.[14]

It is noteworthy that at some stage during the formation of the 10-membered macrocyclic ring from the amino acid coupled furanose precursor, a water molecule got associated with the molecule, as clearly evident from their spectral data (vide infra), which is a common feature in carbohydrates and their analogs bearing multiple hydroxyl groups.[15]

In summary, this work has provided an elegant synthetic route to access amino-acid-tethered carbohydrate conjugates, which may eventually find potential application in the development of conformationally restricted HEA isosteres. The synthetic strategy reported herein is a convenient and straightforward one starting from the readily available D-glucose. The generality of this synthetic strategy has been demonstrated by the introduction of three different amino acid residues into the carbohydrate cyclic frame work.

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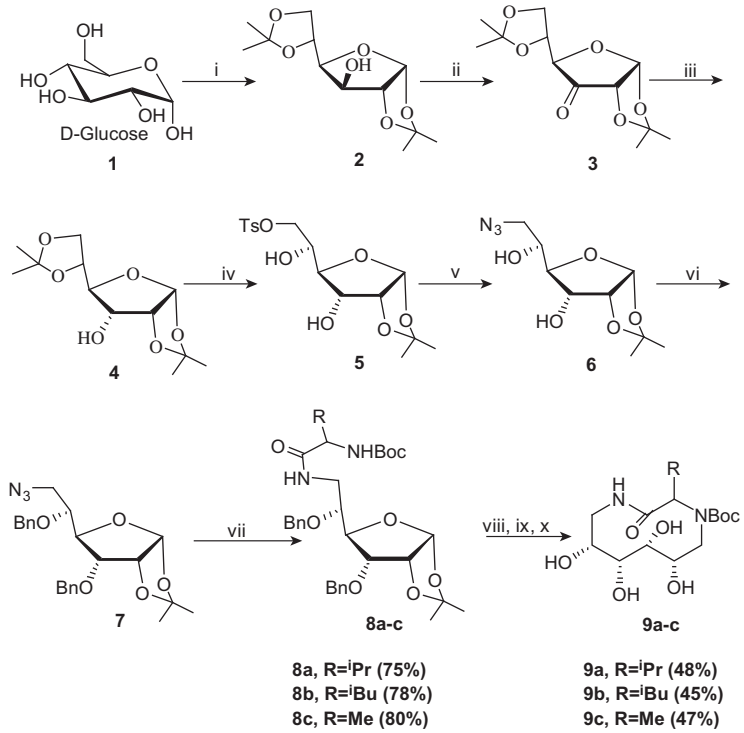
Supplementary data

Supplementary data (general experimental procedures, ^1H, ^{13}C, DEPT-135 NMR spectra and ESI mass spectra of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.086.



Scheme 1. Reagents and conditions: (i) H_3PO_4, $ZnCl_2$, acetone, reflux, 36 h, 43%; (ii) PDC, DCM, Ac_2O, 2 h, 95%; (iii) $NaBH_4$, EtOH, 2 h, 70%; (iv) (a) 80% aq AcOH, 8 h, 92%, (b) Bu_2SnO, $CHCl_3$, TsCl, 5 h, 86%; (v) NaN_3, DMF, 0 °C, 10 h, 94%; (vi) NaH, BnBr, TBAI, THF, 2.5 h, 68%; (vii) (a) TPP, THF–H_2O, rt, 3 h, (b) HBTU, DIPEA, BOC-amino acids, CH_3CN, 10 h; (viii) (a) 80% aq TFA, 30 h, (b) $NaBH_3CN$, AcOH, 40 h; (ix) BOC_2O, H_2O, 12 h; (x) H_2, $Pd(OH)_2$, MeOH, 150 psi, 16 h.

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13. *tert-Butyl-1-(2-(benzyloxy)-2-((3aR,5R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)ethyl amino)-3-methyl-1-oxobutan-2-ylcarbamate(**8a**):*
Representative procedure: PPh_3 (1.11 g, 4.23 mmol, 1.5 equiv) was added to a solution of 1,2-*O*-isopropylidene-3,5-di-*O*-benzyl-6-azido-α-D-allofuranose **7** (1.2 g, 2.82 mmol, 1 equiv) in 4:1 (v/v) THF:H_2O mixture (15 ml) and was stirred for 3 h. THF was then completely evaporated and the residue was extracted with ethyl acetate, dried over anhy. Na_2SO_4 and was concentrated under reduced pressure. The residue containing the crude amine (1.22 g, 3.05 mmol, 1 equiv) was dissolved in acetonitrile containing Boc ^{L}Valine (0.729 g, 3.36 mmol, 1.1 equiv). To the resulting mixture at 0 °C, HBTU (1.5 g, 3.97 mmol, 1.3 equiv) was added followed by the addition of DIPEA (1.04 mL, 6.11 mmol, 2 equiv) and the mixture was allowed to stir at room temperature for 10 h. The reaction mixture was then taken into ethyl acetate, sequentially washed with aq $NaHCO_3$ and $KHSO_4$, dried over anhy. Na_2SO_4, concentrated under reduced pressure and was finally purified by column chromatography to furnish a white solid. Yield 1.35 g (75%); mp: 73–75 °C; $[\alpha]_D^{28}$: 333.3 (c = 0.6, $CHCl_3$); IR ($CHCl_3$) ν cm^{-1}): 3436, 3018, 2299, 1666, 1369, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 10H), 6.24 (br s, 1H), 5.71–5.69 (d, J = 3.66 Hz, 1H), 4.96–4.92 (d, J = 8.59 Hz, 1H), 4.81–4.54 (m, 5H), 4.24–4.19 (m, 1H), 3.99–3.92 (m, 1H), 3.82–3.75 (m, 2H), 3.68–3.55 (m, 1H), 3.29-3.22 (m, 1H), 2.07–2.00 (m,1H), 1.80 (s, 1H), 1.58 (s, 3H), 1.44 (s, 9H), 1.36 (s, 3H), 0.89–0.85 (d, J = 6.82 Hz, 3H), 0.79–0.76 (d, J = 6.82 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.3, 155.5, 138.2, 137.1, 128.4, 128.3, 128.0, 127.8, 127.6, 112.9, 103.9, 79.7, 77.2, 77.1, 75.9, 72.9, 71.9, 59.7, 39.2, 30.7, 28.2, 26.7, 26.5, 19.0, 17.3; ESI-MS: 599.2980 (M+H)$^+$, 621.2883 (M+Na)$^+$, 637.2506 (M+K)$^+$; Elemental Anal. Calcd for $C_{33}H_{46}N_2O_8$: C, 66.20; H, 7.74; N, 4.68. Found: C, 66.32; H, 7.82; N, 4.48.
14. *(6R,7R,8R,9S)-tert-Butyl-6,7,8,9-tetrahydroxy-2-isopropyl-3-oxo-1,4-diazecane-1-carboxylate monohydrate (**9a**):*
Representative procedure: Valine coupled furanose sugar **8a** (0.34 g, 0.56 mmol, 1 equiv) was taken in a 25 mL two-neck round bottomed flask containing 6 mL aq trifluoro acetic acid (80%) and the reaction mixture was stirred for 30 h at rt The residue (0.4 g, 0.73 mmol, 1 equiv) obtained after evaporation of TFA at reduced pressure was then taken into methanol and $NaBH_3CN$ (0.13 g, 2.1 mmol) was added followed by the addition of AcOH (0.04 mL, 0.73 mmol, 1 equiv) at 0 °C. The reaction mixture was then allowed to come to rt and was further stirred for 40 h. Methanol was then evaporated under reduced pressure and the aq layer was washed with ethyl acetate, followed by neutralization with saturated $NaHCO_3$. The neutralized aq layer thus obtained was subsequently extracted with dichloromethane. The organic layer was concentrated and the crude product obtained was carried forward for the next reaction without further purification. To the crude free amine (0.13 g, 0.30 mmol, 1 equiv), BOC anhydride (0.33 g, 1.5 mmol, 5 equiv) was added followed by water (3 mL) and the resulting mixture was stirred for 12 h, when a sticky material settled down, which was taken into DCM, washed sequentially with aq $KHSO_4$ and $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure to obtain a residue whose benzyl groups were subjected to hydrogenolysis using 20% $Pd(OH)_2$ in methanol at 150 psi under hydrogen atmosphere for 16 h to furnish **9a**, which was then purified using preparative TLC to furnish the pure product as an off white fluffy solid. Yield over three steps (48%); mp: 82–85 °C; $[\alpha]_D^{28}$: −7.07° (c = 5.09, $CHCl_3$); IR (Nujol) ν (cm^{-1}): 3323, 2922, 2359, 1633, 1454, 1163, 727; ^{1}H NMR (500 MHz, CD_3OD): δ = 3.94–3.93 (m, 2H), 3.89 (br s, 1H), 3.85–3.79 (m, 2H), 3.72–3.70 (m, 2H), 3.61–3.58 (m, 1H), 3.45–3.42 (m, 1H), 3.37 (br s, 1H), 2.14–2.10 (m, 1H), 1.51 (s, 9H), 1.02–1.01 (d, J = 6.60 Hz, 3H), 0.99–0.98 (d, J = 6.88 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 175.2, 158.1, 80.7, 74.8, 74.4, 74.3, 72.6, 64.3, 61.8, 43.2, 31.9, 28.8, 19.8, 18.4; ESI-MS: 381.2047 (M+H)$^+$, 403.1407 (M+Na)$^+$; Elemental Anal. Calcd for $C_{16}H_{32}N_2O_8$: C, 50.51, H, 8.48, N, 7.36. Found: C, 50.35; H, 8.40; N, 7.60.
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