Pergamon

Tetrahedron Letters 41 (2000) 10121–10125

TETRAHEDRON LETTERS

2,5-Anhydro sugar diacid and 2,5-anhydro sugar diamine based C_2 symmetric peptidomimetics as potential HIV-1 protease inhibitors

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Received 15 August 2000; revised 2 October 2000; accepted 11 October 2000

Abstract

Conformationally constrained molecular frameworks of the 2,5-anhydro sugar diacid (**9**) and 2,5-anhydro sugar diamines (**10**, **11**) were used to construct architecturally beautiful novel C_2 symmetric peptidomimetics **1**–**8**. Although none of these compounds showed any significant HIV-1 protease inhibitory activity, further refinements in design may lead to protease inhibitors based on these rigid carbohydrate-derived scaffolds.

Among the several specific targets in the cell cycle of the human immunodeficiency virus (HIV), the virally encoded homodimeric HIV-1 protease, which is an aspartyl protease required for maturation of the infectious virion, has emerged as a promising target leading to the design and evaluation of a vast array of compounds with diverse structural motifs as possible inhibitors, some of which have already been approved for the treatment of AIDS.[1–6]

We describe herein the development of a new class of compounds **1**–**8** as potential HIV-1 protease inhibitors that are based on carbohydrate–peptide hybrid structures. In this approach, identical peptide chains are anchored on both sides of a core carbohydrate motif—a C_2 symmetric 2,5-anhydro sugar diacid or sugar diamine—leading to the formation of C_2 symmetric peptidomimetics.[7] Carbohydrate-based molecular designs are increasingly drawing chemists' attention.[8,9] Detailed studies on the development of new HIV-1 protease inhibitors based on acyclic carbohydrates have recently been reported.[10–12] It is also being increasingly felt that small molecule protease inhibitors need to have restricted degrees of freedom. The success of cyclic urea based inhibitors supports this feeling.[13,14] This has prompted us to look for cyclic carbohydrate based core foundations as conformationally rigid scaffolds to build a new class of molecular frameworks as potential protease inhibitors.

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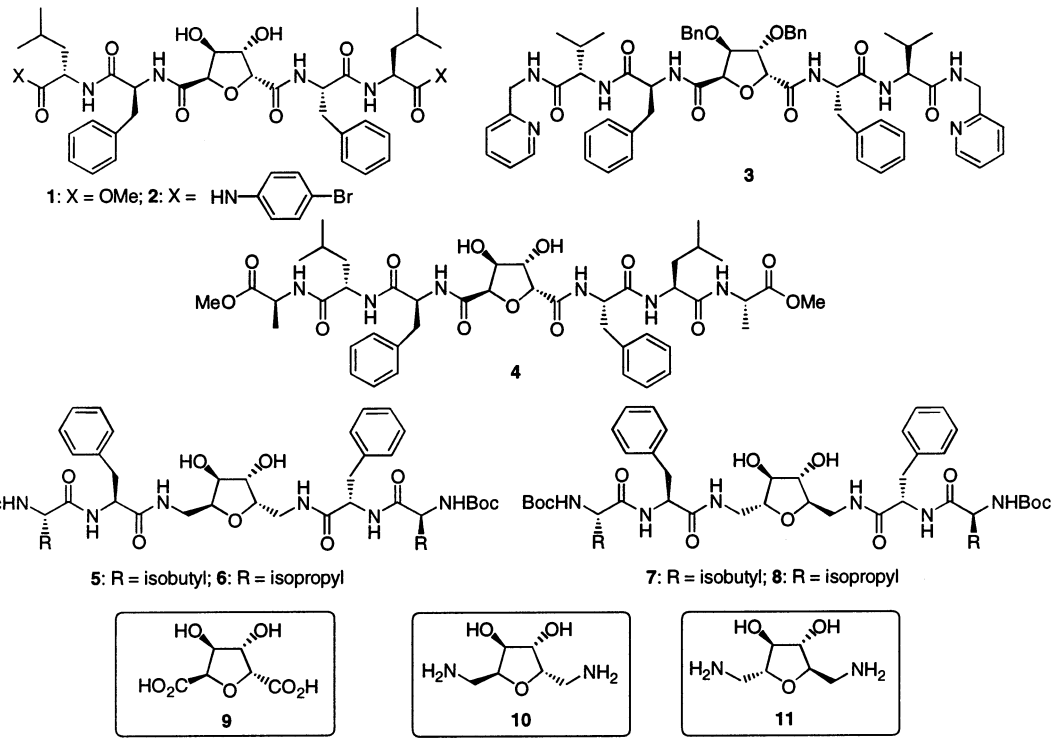
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01803-7

Two different types of cyclic carbohydrate framework—sugar diacid and sugar diamine—are employed in our designs. These molecules are 2,5-anhydro-D-idaric acid (**9**), 1,6-diamino-2,5-anhydro-1,6-dideoxy-D-iditol (**10**) and 1,6-diamino-2,5-anhydro-1,6-dideoxy-D-mannitol (**11**). The sugar diacid **9**, to the best of our knowledge, was reported for the first time by us along with the synthesis of the first sugar diacid based peptidomimetic **1**.[15] The twofold symmetry of the molecule was evident in its ^{1}H and ^{13}C NMR spectra which showed peaks for only half of the molecule. Two-dimensional NMR studies in combination with constrained molecular dynamics (MD) simulations revealed a very ordered C_2 symmetric structure for **1**, consisting of identical intramolecular H bonds at the two ends between the LeuNH→sugar-OH. A very small temperature coefficient for the LeuNH chemical shift ($\Delta\delta/\Delta T = -1.2$ ppb K^{-1}) was observed in DMSO-d_6. The presence of two '*cis*-β-hydroxycarboxyl' moieties, the core structural motif believed to be responsible for such intramolecular H bonds,[16] on two sides of the tetrahydrofuran ring nucleated identical β-turn-like structures in **1** at both ends.

To further these studies, we decided to prepare a few more C_2 symmetric peptidomimetics and examine their structures and properties, especially HIV-1 protease inhibition activities, as these compounds structurally resemble many well-established C_2 symmetric HIV-1 protease inhibitors. In this paper we describe the results of that investigation.

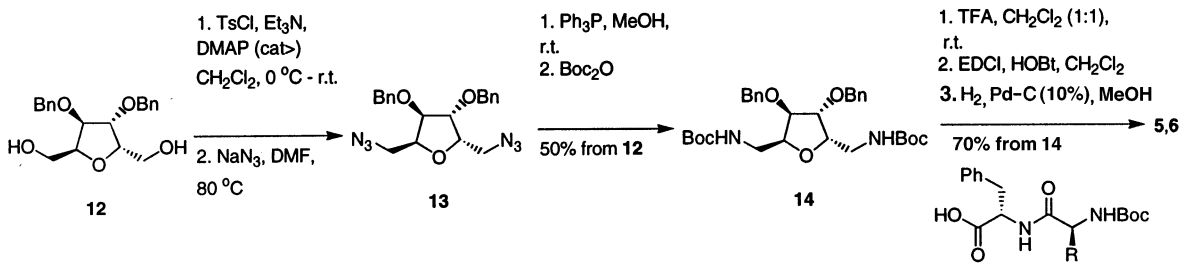


Compounds **2** and **4** were prepared in 60 and 70% yields, respectively, from **1** in two steps: saponification followed by the reaction with *p*-bromoaniline (for **2**) or H_2N–Ala–OMe (for **4**[17]) under standard solution phase peptide synthesis conditions using 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI) as coupling agents and amine-free dry DMF and/or dry CH_2Cl_2 as solvents. The synthesis of **3** was carried out following the same procedure described earlier for the synthesis of **1**.[15] The

di-*O*-benzyl derivative of 2,5-anhydro-D-idaric acid[15] (**9**) was treated with an excess of amino-terminal free peptide molecule to furnish **3** in 55% yield.

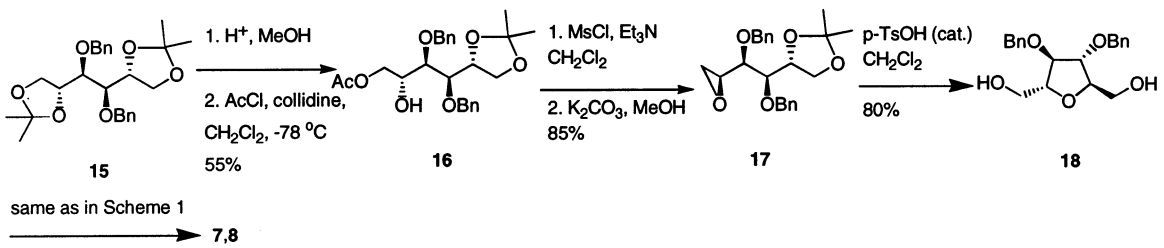
Structural studies of these molecules (**2**–**4**) did not reveal significant turn structures in solution as seen in **1**. While compounds **3** and **4** still maintained C_2 symmetric structures as shown by their NMR studies in DMSO-d_6, the *p*-bromoanilide derivative **2** lost its symmetry with each of its amide protons showing two peaks in the same solvent. Its LeuNH chemical shifts, however, exhibited low temperature coefficients of –2.1 and –2.4 ppb K^{-1} maintaining their participation in intramolecular H bonding, similar to the one observed in **1**, albeit weaker. Hydrogenation of **3** gave a complex mixture of products and its structure and properties were studied in the Bn-protected form, which showed high temperature coefficients for the amide proton chemical shifts. The temperature coefficient of the LeuNH peak in **4** was –2.8 ppb K^{-1}, indicating gradual loss in its ability to nucleate the desired secondary structure, probably due to the increased steric hindrance.

Next, we turned our attention to the remaining peptidomimetics, **5**–**8**, based on sugar diamines **10** and **11**. Syntheses of **5** and **6** were accomplished according to Scheme 1. The starting material **12**, prepared from 1,3:4,6-di-*O*-benzylidene-D-mannitol,[15] was converted to **14** in four steps—ditosylation, azidination and selective azide reduction, followed by protection in situ using Boc_2O for purification purposes giving the di-*N*-Boc-protected intermediate **14** in 50% overall yield from **12**. Purified **14** was treated with TFA in CH_2Cl_2 and peptide chains were attached at both ends using EDCI–HOBt as coupling reagents. Finally, debenzylation using H_2–Pd–C (10%) in MeOH furnished the final product **5** (and **6**) in ~70% overall yield.[18]



Scheme 1. Synthesis of **5** and **6**

Syntheses of **7** and **8** from 3,4-di-*O*-benzyl-1,2:5,6-diisopropylidene-D-mannitol (**15**) are depicted in Scheme 2. Monodeprotection gave a diol intermediate whose primary hydroxyl was selectively acylated to get a 55% yield of acetate **16**. Conversion of **16** to the terminal epoxide **17** was achieved in two steps in 86% yield. Acid-catalyzed cycloetherification of **17** went smoothly to furnish the 2,5-anhydro-D-mannitol framework **18**, which was converted to the



Scheme 2. Synthesis of **7** and **8**

diamine and finally to the desired products **7** and **8**,[19] following the procedure described above in Scheme 1.

All the sugar diamine based mimetics, **5**–**8**, had C_2 symmetric structures in solution, as determined by their ^{1}H NMR studies in DMSO-d_6, which showed peaks for only half of the molecule. However, very high temperature coefficients for all of their amide proton chemical shifts indicated the absence of any intramolecular H bonding in these molecules.

The potential of the peptidomimetics **1**–**8** as HIV protease inhibitors were evaluated using an assay protocol developed by Toth and Marshall.[20] Unfortunately, none of these compounds showed any enzyme inhibitory activities up to 2 μM inhibitor concentration. The large distances between the phenyl rings of the P1/P1′ positions are probably responsible for their low activities. Efforts are now underway to improve our designs and to prepare active HIV-1 protease inhibitors from conformationally constrained 2,5-anhydro sugar-based scaffolds.

Acknowledgements

Authors wish to thank the CSIR, New Delhi for research fellowships (to S.G. and M.H.V.R.R.) and a Young Scientist Award Research Grant (to T.K.C.).

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17. Selected physical data of **4**. R_f=0.4 (silica, EtOAc); $[\alpha]_D^{20}$ −12.8 (*c* 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.09 (d, *J*=6.8 Hz, 2H, AlaN*H*), 8.07 (d, *J*=8.5 Hz, 2H, PheN*H*), 7.72 (d, *J*=8.2 Hz, 2H, LeuN*H*), 7.28–7.19 (m, 10H, aromatic), 5.96 (d, *J*=2.8 Hz, 2H, O*H*), 4.56 (d, *J*=2.8 Hz, 2H, C2- and C5-*H*), 4.50 (ddd, *J*=10.4, 8.5, 3.4 Hz, 2H, PheαH), 4.28 (ddd, *J*=9.8, 8.2, 5.1 Hz, 2H, LeuαH), 4.23 (m, 2H, AlaαH), 4.16 (t, *J*=2.8 Hz, 2H, C3- and C4-*H*), 3.60 (s, 6H, OCH_3), 3.19 (dd, *J*=14.1, 3.4 Hz, 2H, PheβH), 2.96 (dd, *J*=14.1, 10.4 Hz, 2H, Phe$\beta H'$), 1.63 (m, 2H, LeuγH), 1.44 (ddd, *J*=13.7, 8.6, 5.1 Hz, 2H, LeuβH), 1.38 (ddd, *J*=13.7, 9.8, 5.6 Hz, 2H Leu$\beta H'$), 1.29 (d, *J*=7.3 Hz, 6H, AlaβH), 0.89 (d, *J*=7.2 Hz, 6H, LeuδH), 0.8 (d, *J*=7.2 Hz, 6H, Leu$\delta H'$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.92, 172.25, 170.51, 169.47, 135.79, 128.94, 128.91, 127.51, 83.26, 77.92, 54.19, 52.43, 51.35, 48.46, 40.39, 36.55, 24.48, 22.89, 21.72, 17.49.

18. Selected physical data of **6**. R_f=0.3 (silica, EtOAc); $[\alpha]_D^{20}$ −23.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.04 (t, *J*=5.6 Hz, 2H, sugarN*H*), 7.85 (d, *J*=8.4 Hz, 2H, PheN*H*), 7.24–7.14 (m, 10H, aromatic), 6.64 (d, *J*=9.0 Hz, 2H, ValN*H*), 5.05 (d, *J*=3.6 Hz, 2H, O*H*), 4.56 (ddd, *J*=9.2, 8.4, 5.1 Hz, 2H, PheαH), 3.91 (dt, *J*=6.8, 2.8 Hz, 2H, C2- and C5-*H*), 3.82 (dd, *J*=3.6, 2.8 Hz, 2H, C3- and C4-*H*), 3.70 (dd, *J*=9.0, 7.0 Hz, 2H, ValαH), 3.24 (ddd, *J*=13.6, 6.8, 5.8 Hz, 2H, C1- and C6-*H*), 3.12 (ddd, *J*=13.6, 6.8, 5.6 Hz, 2H, C1- and C6-*H'*), 2.94 (dd, *J*=13.7, 5.1 Hz, 2H, PheβH), 2.79 (dd, *J*=13.7, 9.2 Hz, 2H, Phe$\beta H'$), 1.81 (m, 2H, ValβH), 1.37 (s, 18H, Boc), 0.71 (d, *J*=6.6 Hz, 6H, ValγH), 0.67 (d, *J*=6.6 Hz, 6H, Val$\gamma H'$); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.38, 170.87, 155.27, 137.47, 129.11, 127.91, 126.15, 78.53, 78.06, 75.84, 59.99, 53.48, 38.29, 37.92, 30.36, 28.11, 19.02, 18.05.

19. Selected physical data of **8**. R_f=0.45 (silica, 10% MeOH in $CHCl_3$); $[\alpha]_D^{20}$ +29.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.07 (dd, *J*=6.3, 5.2 Hz, 2H, sugarN*H*), 7.81 (d, *J*=8.7 Hz, 2H, PheN*H*), 7.23–7.14 (m, 10H, aromatic), 6.65 (d, *J*=9.2 Hz, 2H, ValN*H*), 5.17 (d, *J*=3.9 Hz, 2H, O*H*), 4.60 (ddd, *J*=9.7, 8.7, 4.3 Hz, 2H, PheαH), 3.77–3.70 (m, 4H, C2-, C3-, C4- and C5-*H*), 3.69 (dd, *J*=9.2, 6.8, 1H, ValαH), 3.27 (dt, *J*=13.2, 5.2 Hz, 2H, C1- and C6-*H*), 3.19 (dt, *J*=13.2, 6.3 Hz, 2H, C1- and C6-*H'*), 2.97 (dd, *J*=13.7, 4.3 Hz, 2H, PheβH), 2.77 (dd, *J*=13.7, 9.7 Hz, 2H, Phe$\beta H'$), 1.79 (m, 2H, ValβH), 1.37 (s, 18H, Boc), 0.69 (d, *J*=6.8 Hz, 6H, ValγH), 0.64 (d, *J*=6.8 Hz, 6H, Val$\gamma H'$); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.10, 170.86, 155.27, 137.64, 129.18, 127.87, 126.11, 82.12, 78.81, 78.08, 60.10, 53.41, 41.10, 38.13, 30.41, 28.13, 19.04, 18.08.

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