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Synthesis of RGD-aPEG-lactoside, a Potential Anti-metastasis Glycoconjugate

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Abstract: The adhesive interaction between tumor cells and host cells or the extra cellular matrix plays a crucial role in metastasis. Due to the anti-metastasis effects of RGD (arginyl-glycyl -aspartic acid) and some oligosaccharides, RGD-aPEG-Lactoside was prepared which will be used on anti-metastasis.

Keywords: RGD, lactose, PEG, anti-metastasis.

In 1984, Pierschbacher[1] first reported that a peptide sequence RGD (arginyl-glycyl-aspartic acid), has inhibitory effect on platelet aggregation process. Since then, RGD motif has been extensively researched and reported by many research groups[2-4]. The results consistently indicated that peptides involving RGD sequence are active modulators of cell adhesion, which is the basis of tumor metastastic process. However, the short half-life of RGD in blood rendered it unfeasible in clinical practice. In order to solve this problem, Kawasaki[5] coupled RGD with PEG (polyethylene glycol), and the resulted hybrid maintains the activities and practically elongates its half-life in comparison with RGD[6]. On the other hand, some oligosaccharides, such as lactose and *N*-acetyllactosamine, have inhibitory effect on cell adhesion[7-11], another key process of tumor metastasis. Thus, we designed and synthesized a hybrid combining RGD and lactose with PEG as the linker, in expecting that such a hybrid could have a concerted activity against tumor metastasis *via* two different and independent inhibitory modes[12], and moreover, to develop a practical method for the synthesis of compounds with a similar structure.

A PEG lactoside **1**[13, 14] was treated with *p*-tosylsulfonyl chloride (TsCl) and the product reacted with NaN3 to afford compound **2**[15], which was then reduced via hydrogenation to give the corresponding amine **3** in a yield of 98%. Before Boc-Arg(NO_2)-Gly- Asp(OBn)-OH was coupled with aPEG β-lactoside **3**, the α-benzyl of Boc-Arg(NO_2)- Gly-Asp(OBn)-OBn must be selectively removed with aqueous LiOH. But this reaction was too complicated to give desired compound in an acceptable yield, probably due to the susceptibility of the guanidyl group of arginine. So compound **4**[16,17]

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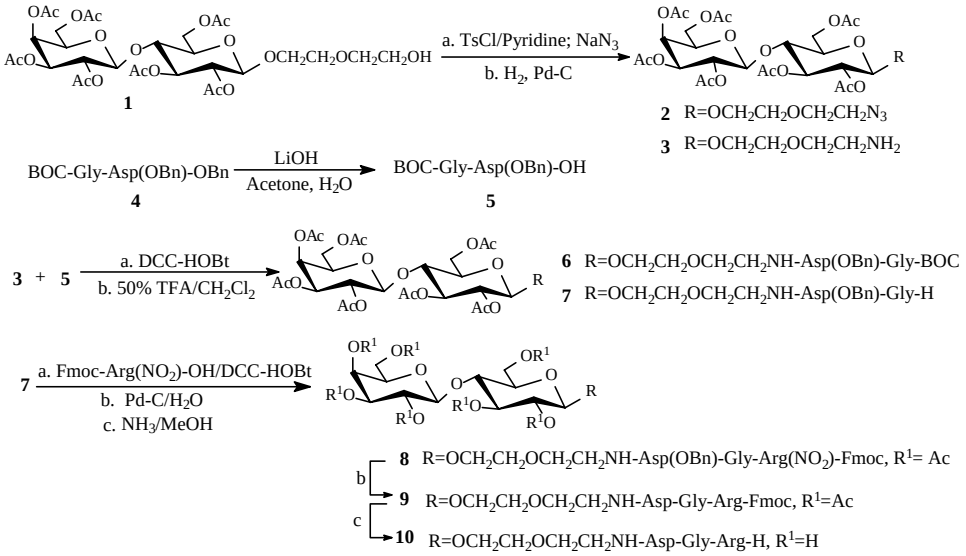
was selectively saponified in aqueous LiOH solution to give compound **5** (50%) prior to the introduction of arginine. Then aPEG β-lactoside **3** was coupled with dipeptide **5** via DCC-HOBt method to give the compound **6** in yield of 71%, which was treated with 50% trifluoroacetic acid (TFA) in dichloromethane, and then neutralized with NMM (N-methyl morpholine) to give **7**. Compound **7** was coupled with Fmoc-Arg(NO_2)-OH to give the RGD-aPEG β-lactoside backbone **8** successfully in the yield of 45%. Target compound **10**[18] was obtained by regular deprotection methods.



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18. Physical data of compound **10:** m.p.: 159.0-160.0 ^{o}C. $[\alpha]_D^{25}$ +31.4 (*c* 0.25, H_2O). ^{1}HNMR ($CDCl_3$, δppm): 1.67 (m, 2H, H_γ^{Arg}), 1.80 (m, 2H, H_β^{Arg}), 2.64 (m, 2H, H_β^{Asp}), 3.22 (t, 2H, H_δ^{Arg}), 3.34 (m,1H, H-2), 3.41 (t, 2H, $NH_2C\underline{H}_2O$), 3.54 (m,1H, H-2′), 3.60 (m, 1H, H_α^{Arg}), 4.45 (d, 1H, $J_{1',2'}$ =8.00 Hz, H-1′), 4.52 (d, 1H, $J_{1,2}$=8.50 Hz, H-1), 4.57 (m, 1H, H_α^{Asp}), 4.05~3.62 (m, 18H, H-3, H-3′, H-4, H-4′, H-5, H-5′, H-6a, 6b, H-6a′, 6b′, CH_2O, H^{Gly}). ^{13}CNMR ($CDCl_3$, δppm): 178.4 (C̲OOH), 175.5 (^{Arg}CONH), 174.1 (^{Asp}CONH), 171.7 (^{Gly}CONH), 157.4 (C=N), 103.6 (C-1′), 102.8 (C-1), 75.5 (C_α^{Arg}), 73.5 (C-2), 71.6 (C-2′), 52.3 (C_α^{Asp}), 41.2 (C_δ^{Arg}), 39.7 (NH_2CH_2O), 39.4 (C_β^{Asp}), 30.5 (C_β^{Arg}), 24.6 (C_γ^{Arg}), 79.0, 76.1, 75.0, 73.2, 70.2, 69.5, 69.4, 69.2, 61.7, 60.8, 54.3, 43.1 (C-3′, C-4′, C-5′, C-6′, C-3, C-4, C-5, C-6, 3×CH_2O, C_α^{Gly}). TOF-MS: *m/z* 758.3 $[M+1]^+$.

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