Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 3307–3310

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Aryl C-Glycosides: Physiologically Stable Glycomimetics of Sialyl Lewis X.

Takeshi Kuribayashi, Nobuyuki Ohkawa, Susumu Satoh*

Exploratory Chemistry Research Laboratories, Sankyo Co. Ltd. ,
2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710 JAPAN

Received 31 August 1998; accepted 7 October 1998

Abstract:

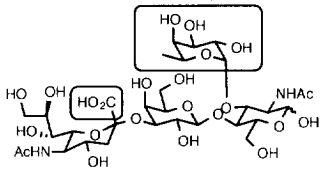
In the course of the search for physiologically stable, structurally simple, and low molecular weight sLeX mimetics, aryl C-glycosides with carboxylic acid functionality **2** were found to be extremely potent inhibitors against L- and P-selectins with IC_{50} in the low μM range.

Keywords: Antiinflammatories; Glycosides; Lectins; Mimetics.

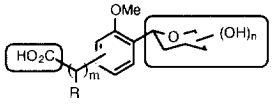
Leukocyte adherence to vascular endothelium is a critical process that contributes to the pathogenesis of inflammation. Cellular interactions mediated by adhesion molecules expressed on both leukocytes and endothelial cells are required for the movement of leukocytes out of the vascular flow into surrounding tissues. Several sets of adhesion molecules have been implicated in this adhesion and migration process, including the selectins, a family of carbohydrate-binding proteins, which mediate the early stage of adhesion cascade [1-3].

The ligands for selectins have been described by several groups to be glycoproteins with a number of terminal sialyl Lewis X (sLeX) tetrasaccharides **1** [4].

Inhibitors of these interaction have been evaluated for their therapeutic potential in several acute and chronic inflammatory diseases, ischemia-reperfusion injury, septic shock, asthma, rheumatoid arthritis, cancer metastasis and angiogenesis [5-9].



1



2

PII: S0960-894X(98)00607-6

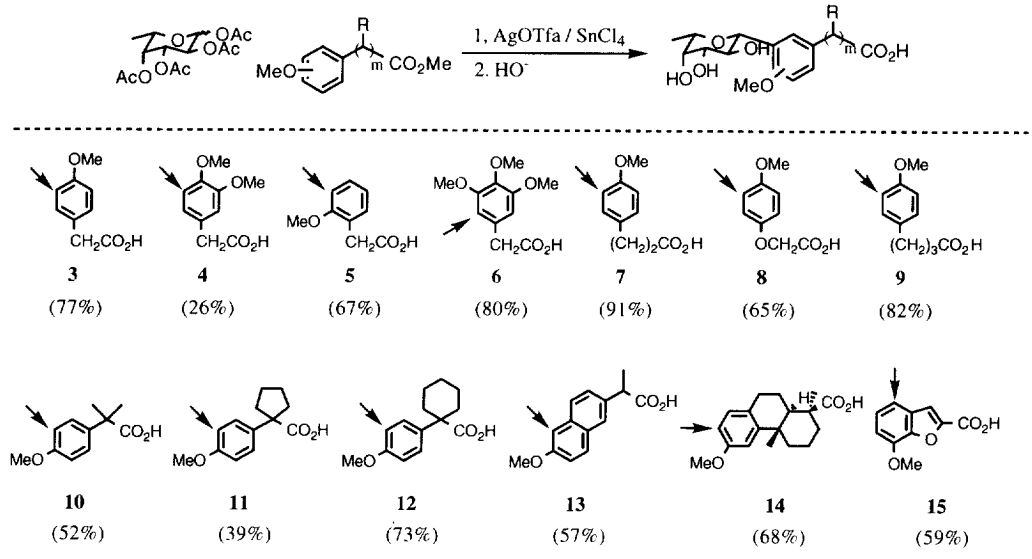
Information on a large number of structurally different mimetics of sLeX has been published during the last several years [10-20]. The structure-activity studies and the molecular modeling studies on sLeX have revealed that the sialyl carboxylic acid, the fucose residue, and to a lesser extent the 4- and 6-OH of galactose play an essential role in selectin binding [21-27].

In the course of the search for physiologically stable, simple, and lower molecular weight sLeX mimetics, aryl C-glycosides with carboxylic acid functionality **2** were designed in which the aromatic ring functions as a scaffold on which acid and fucose residues are positioned in an appropriate spatial arrangement.

The advantage of these compounds as sLeX glycomimetics is that they are stable toward acid and enzymatic digestion and that they potentially have a high oral availability because of their favorable balance of lipophilicity, based on the aromatic ring, and hydrophilicity, based on the sugar moiety. Moreover, their simple preparation by the aryl C-glycosidation reaction [28] makes it possible to synthesize a number of diverse compounds easily and to investigate the structure-activity relationship.

The aryl C-glycosides synthesized by the simple aryl C-glycosidation using tin(IV) chloride ($SnCl_4$) and silver trifluoroacetate (AgOTfa) [28] followed by hydrolysis are summarized in Table 1.

Table 1: Summary of Aryl C-Glycosides with Carboxylic Acid Group.



The figures in parenthesis are the yields of aryl C-glycosidation and the arrow shows the position on which the fucose moiety was introduced.

All compounds were evaluated in a competitive cell-free ELISA assay [29] that measures inhibition of selectin-IgG chimeras binding to sLeX coating 96 wells. Although none of the compounds showed a remarkable activity towards E-selectin, some of them exhibited excellent inhibitory activity towards L- and P-selectins, as shown in Table 2.

It is of interest to note that in spite of the C-β-bonding, which is different from the O-α bonding of fucose in sLeX, of the sugar moiety to the aromatic ring, these glycosides were found to be quite potent inhibitors for L- and P-selectins but not for E-selectin. The difference of the binding activity between the E-selectin and L- and P-

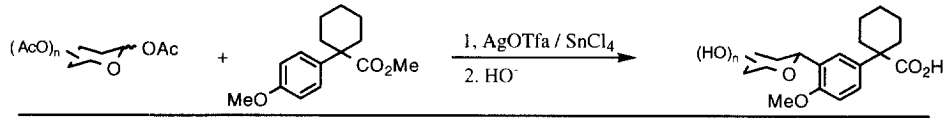
Table 2. The Result of ELISA Assay.

	ELISA (IC_{50}, mM)			
Compounds	**3**	**6**	**9**	**12**
E-selectin	>1.0	>1.0	>1.0	>1.0
L-selectin	0.003	0.114	0.170	0.106
P-selectin	0.001	0.040	0.005	0.007

selectins is due to the difference of ligand specificity among the selectins [30], which might be elucidated to some extent by the study on the recognition site of the E-selectin crystal structure and the P-selectin model [31].

Encouraged by these results, replacement of the sugar moiety focused on compound **12** was examined next (Table 3).

Table 3: Replacement of Sugar Moiety on Compound 12.



16	**18**	**19**	**20**	**21**
D-Fuc (77%)	D-Gal (35%)	D-Ribo (31%)	D-Xyl (54%)	L-Rham (54%)

The figures in parenthesis are the yields of aryl C-glycosidation.

Table 4. The Result of ELISA Assay.

	ELISA (IC_{50}, mM)			
Compounds	**12**	**18**	**20**	**21**
E-selectin	>1.0	>1.0	>1.0	>1.0
L-selectin	0.106	0.001	0.011	0.035
P-selectin	0.007	0.003	0.008	0.022

D-Fucose replacement (compound **16**) resulted in a complete loss of the binding affinity in all three selectin binding assays. Of note is the fact that not only the L-fucose derivative (**12**) but the other sugar congeners like D-xylose (**20**), L-rhamnose (**21**), D-galactose (**18**) as well exhibited agonistic activity towards P-selectin and showed a higher potency towards L-selectin (Table 4).

Although a large number of sLeX mimetics have been reported, to our knowledge this is the first example that shows low μM inhibitory activity on the binding affinity towards L- and P-selectins with such simple, low molecular weight, and physiologically stable sLeX mimetics.

Further optimization to afford structural flexibility and to identify additional binding sites are currently in progress.

Acknowledgment

We are grateful to Dr. S. Swiedler, Dr. R. Larsen, Dr. M. B. Anderson, Dr. K. Holme and coworkers in Glycomed (ex-address 860 Atlantic Ave., CA, USA) for their courtesy measurement of the ELISA on the collaboration of our cell adhesion project.

References

1. Springer, T. A. *Cell* **1994,** *76,* 301.
2. Buckley, C. D.; Simmons D. L. *Molec. Med. Today* **1997,** 449.
3. Kansas G. S. *Blood* **1996,** *88,* 3259.
4. Varki, A. *Proc. Natl. Acad. Sci. USA.* **1994,** *91,* 7390.
5. Giannis, A. *Angew. Chem. Int. Ed. Engl.* **1994,** *33,* 178.
6. Mulligan, M. S.; Paulson, J. C.; Frees, S. D.; Zheng, Z. L.; Lowe, J. B.; Ward, P. A. *Nature* **1993,** *364,* 149.
7. Boschelli, D. H. *Exp. Opin. Invest. Drugs.* **1994,** *3,* 861.
8. Lowe, J. B.; Ward, P. A. *J. Clin. Invest.* **1997,** *99,* 822.
9. Parekh, R. B.; Edge, C. J. *Trends Biotechnol.* **1994,** *12,* 339.
10. Kogan, T. P.; Dupré, B.; Keller, K. M.; Scott, I. L.; Bui, H.; Market, R. V.; Beck, P. J.; Voytus, J. A.; Revelle, B. M.; Scott, D. *J. Med. Chem.* **1995,** *38,* 4976.
11. Dupré, B.; Bui, H.; Scott, I. L.; Market, R. V.; Keller, K. M.; Beck, P. J.; Kogan, T. P. *Bioorg. Med. Chem Lett.* **1996,** *6,* 569.
12. Allanson, N. M.; Davidson, A. H.; Martin, F. M. *Tetrahedron Lett.* **1993,** *34,* 3945.
13. Ragan, J. A.; Cooper, K. *Bioorg. Med. Chem. Lett.* **1994,** *4,* 2563.
14. Narasinga, R. B. N.; Anderson, M. B.; Musser, J. H.; Gilbert, J. H.; Schaefer, M. E.; Foxall, C.; Brandley, B. K. *J. Biol. Chem.* **1994,** *269,* 19663.
15. Bänteli, R.; Ernst, B. *Tetrahedron Lett.* **1997,** *38,* 4059.
16. Birkbeck, A. A.; Ley, S. V.; Prodger, J. C. *Bioorg. Med. Chem Lett.* **1995,** *5,* 2637.
17. Kaila, N.; Yu, H. -A.; Xiang, Y. B. *Tetrahedron Lett.* **1995,** *31,* 5503.
18. Woltering, T. J.; Weitz-Schmidt, G.; Wong, C. -H. *Tetrahedron Lett.* **1996,** *37,* 9033.
19. Lin, C. -C.; Shimazaki, M.; Heck, M. -P.; Aoki, S.; Wang, R.; Kimura, T.; Ritzèn, H.; Takayama, S.; Wu, S. -H.; Weitz-Schmidt, G.; Wong, C. -H. *J. Am. Chem. Soc.* **1996,** *118,* 6826.
20. Bamford, M. J.; Bird, M.; Paul, M.; Gore, P. M.; Holmes, D. S.; Priest, R.; Prodger, J. C.; Saez, V. *Bioorg. Med. Chem. Lett.* **1996** *6,* 239.
21. Larkin, M.; Ahern, T. J.; Stoll, M. S.; Shaffer, M.; Sako, D.; O'Brien, J.; Yuen, C. -T.; Lawson, A. M.; Childs, R. A.; Barone, K. M.; Langer-Safer, P. R.; Hasegawa, A.; Kiso, M.; Larsen, G. R.; Feizi, T. *J. Biol. Chem.* **1992,** *267,* 13661.
22. Brandley, B. K.; Kiso, M.; Abbas, S.; Nikrad, P.; Srivasatava, O.; Foxall, C.; Oda, Y.; Hasegawa, A. *Glycobiology* **1993,** *6,* 633.
23. Yoshida, M.; Uchimura, A.; Kiso, M.; Hasegawa, A. *Glycoconjugate Journal* **1993,** *10,* 3.
24. Ramphal, J. Y.; Zheng, Z. -L.; Perez, C.; Walker, L. E.; DeFrees, S. A.; Gaeta, F. C. A. *J. Med. Chem.* **1994,** *37,* 3459.
25. Kiso, M.; Furui, H.; Ando, K.; Ishida, H.; Hasegawa, A. *Bioorg. Med. Chem.* **1994,** *2,* 1295.
26. Maeda, H.; Ishida.; H, Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1995,** *14,* 369.
27. Maeda, H.; Ito, K.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1995,** *14,* 387.
28. Kuribayashi, T.; Ohkawa, N.; Satoh, S. *Tetrahedron Lett.* **1998,** *39,* 4537.
29. Foxall, C.; Watson, S. R.; Dowbenko, D.; Fennie, C.; Lasky, L. A.; Kiso, M.; Hasegawa, A.; Asa, D.; Brandley, B. K. *J. Cell Biol.* **1992,** *117,* 895.
30. Rosen, S. D.; Bertozzi, C. R. *Curr. Opin. Cell. Biol.* **1994,** *6,* 663.
31. Hiramatsu, Y.; Tsujishita, H.; Kondo, H. *J. Med. Chem.* **1996,** *39,* 4547.