Synthesis and Cytotoxicity of Fluorinated Amino Saccharides.

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Monosaccharide derivatives are gaining in importance as active or auxiliary agents in the treatment of cancer. Due to their aberrant metabolism, cancer cells have a higher uptake of monosaccharides than healthy cells. Acylated 2-amino monosaccharides with an unprotected ano-meric hydroxyl are known for their cytotoxic properties.[1]

Introducing fluorine instead of an ester group decreases the affinity of these compounds for hydrolytic enzymes, leading to greater metabolic stability and thus an increase in the cytotoxicity. Before this work, only a limited number of fluorinated acetylated amino saccharides having an unprotected anomeric hydroxyl have been prepared, some of them with promising cytotoxicity to selected cancer cell lines.[2]

This work presents the synthesis of acetyl, propionyl, and butyryl esters of monofluorinated, difluorinated, and trifluorinated analogues of *N*-acetyl-d-glucosamine and *N*-acetyl-d-galactosamine, and their cytotoxicity expressed as IC50 values against the MDA-MB-231 cancer cell line (triple-negative breast cancer) along with their IC50 values against the HEK-293 non-cancerous cell line. It was confirmed that fluorination indeed enhances cytotoxicity especially for d-galactosamine analogues. In contrast to nonfluorinated analogues, no positive correlation between the ester alkyl chain length and cytotoxicity was observed as acetyl esters and propionyl esters were sometimes more cytotoxic than butyryl esters. Computational calculations suggest that all fluorinated analogues freely permeate cell membranes.

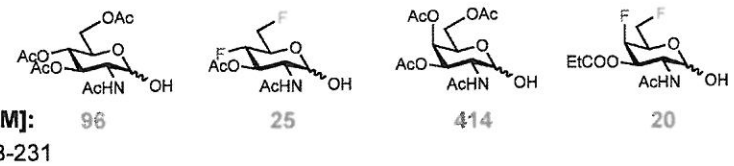

Figure 1: Selected examples of prepared nonfluorinated and deoxyfluorinated derivates and their cytotoxicity against triple negative breast cancer cell line MDA-MB-231 displayed as IC50 (μmol/L).

References

1. Aich, U.; Campbell, C. T.; Elmouelhi, N.; Weier, C. A.; Sampathkumar, S. G.; Choi, S. S.; Yarema, K. J. *ACS Chem. Biol.***2008**, *3*(4), 230–240.
2. Nishimura, S. I.; Hato, M.; Hyugaji, S.; Feng, F.; Amano, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3386–3390.