Synthesis and cytotoxicity of fluorinated mannosamines

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Fluorinated carbohydrates have been widely acknowledged as useful tools for studying the mechanisms of carbohydrate-processing enzymes and carbohydrate-binding proteins, as well as for inhibiting them.[1] The similarity in size between fluorine and hydroxyl has also led to research exploring the potential of fluorosugars to modify glycan chains by inhibiting carbohydrate-processing enzymes and/or altering the balance between carbohydrate metabolites. Although this research has identified several potent metabolic inhibitors, some fluorosugars have also been found to have cytotoxic effects, which also opens up the possibility of therapeutic applications.[2]

Non-fluorinated *N*-acetylmannosamine derivatives are cytotoxic, with their cytotoxicity depending on the substitution pattern of hydroxyl groups. Among the derivatives, 3,4,6-O-acylation resulted in the most cytotoxic acylated *N*-acetylmannosamines. Conversely, the 1,3,4-O-acylated N-acetylmannosamines exhibited significantly lower cytotoxicity, indicating that the position of O-acyl, and especially the presence of a free anomeric hydroxyl, play a crucial role in cytotoxicity.[3] Ensuing research showed that similar relationships between the cytotoxicity and O-acylation pattern also apply to *N*-acetylglucosamine and -galactosamine. In our previous study, we investigated the cytotoxicity of fluorinated acylated *N*-acetylgalactosamines and glucosamines. The results revealed that the introduction of fluorine increased cytotoxicity as long as the anomeric position remained unprotected.[4] On the basis of these findings, we have decided to expand our research to include fluorinated *N*-acetylmannosamines.

The aim of the project is to synthesise mono-, di- and trifluoro analogs of *N*-acetylmannosamines. The cytotoxicity of the final products towards selected cancer cells will be determined. The key intermediates are the corresponding multiply fluorinated mannosazide thioglycosides prepared from deoxyfluorinated 1,6-anhydro-2-azido-β-D-hexopyranose precursors by ring-opening reactions with phenyl trimethylsilyl sulfide.

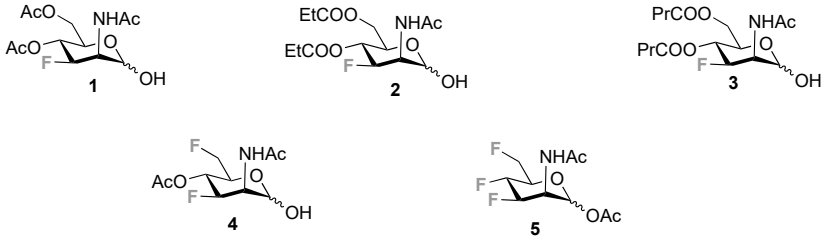

Figure 1: Structures of prepared fluorinated N-acetylmannosamine derivatives

References

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