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In silico design of halogenated carbohydrate mimetics as potential halogen-bonding ligands

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Abstract

The molecular recognition of carbohydrates by proteins is characterized by the presence of classical hydrogen bonds stabilizing binding together with an important contribution from other intermolecular interactions conferring high specificity. [1] The design of glycomimetic ligands as modulators of protein-carbohydrate binding events is a common approach in the context of chemical glycobiology [2] and carbohydrate-based drug discovery. [3]

While a diversity of functional groups has been successfully introduced in carbohydrate structures, [2] the use of halogens has been largely neglected, except for fluorine. However, heavier halogens (X = Cl, Br, or I) can establish highly directional, R–X···B interactions with Lewis bases (B), known as halogen bonds (HaB). These interactions have been mostly explained by the presence of an electropositive site at the outermost region of X species, named sigma-hole. [4] HaB-mediated molecular recognition phenomena are widespread across biological systems and have been used as tools in medicinal chemistry, [5] amongst other fields.

In the search for novel glycomimetics with the potential to modulate carbohydrate-protein recognition via HaB interactions, we performed a quantum mechanical study on the HaB donor propensity of model halogenated carbohydrate derivatives by computing the respective molecular electrostatic potential surface maxima. This procedure allowed us to map the chemical space of halogenated sugars in terms of their potential to act as HaB interaction partners with HaB acceptor species commonly found in biomolecules and the results encourage further in silico optimization towards new halogen-bonding glycomimetic ligands.

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