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PDB and CSD databases survey in searching of fluorine containing interactions

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The fluorine atom in organic compounds acting as an acceptor of hydrogen bond (H-bond) is considered controversial and remains the subject of many disputes. There is a lot of evidence for the existence of C-H· · · F-C hydrogen bonds, but for more electronegative donors, i.e. OH or NH, the H-bonds with fluorine is much less frequent and at the same time weaker than in the case when the acceptors are nitrogen, oxygen or other halogens.[1–3] No doubts that fluorine has become one of the most common elements used in the design and development of new drugs. Indeed, since the 1950s, over 150 fluorine-containing drugs have been released to the market which now make up approx. 20% of all pharmaceuticals.[4] It is important to determine the role of fluorine in the formation of hydrogen bonds in ligand-protein complexes to fully use its unique properties to improve the biological activity of compounds.

Herein, we report a statistical analysis of structural data and a detailed inspection of the geometric parameters of intermolecular hydrogen bonds of fluorine from the aromatic ring in structures deposited in the Cambridge Structural Database (CSD) and Protein Data Bank (PDB).

The results showed that indeed hydrogen bonds of fluorine with -CH donors are much more frequent than with the stronger electronegative donors (-OH, -NH). Interestingly, in the protein environment where fluorine is present in hydrophobic areas of the binding pocket it forms C-H···F-C H-bonds with leucine twice more frequently (21%) than with valine (12%), phenylalanine and isoleucine (10%).

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