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Exploring the influence of fluorine substitution on tuning the hydrogen bonding properties using theoretical and spectroscopic methods

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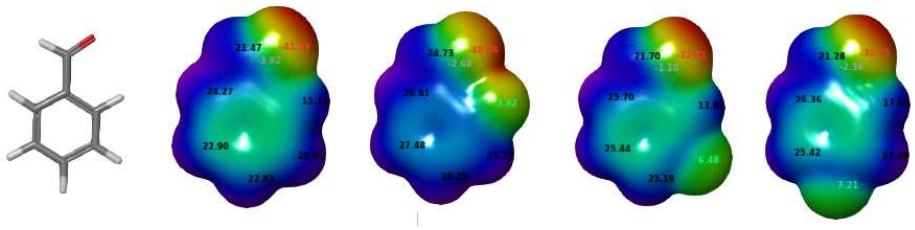
Fluorine substitution affects to a number of different properties of molecules i.e.: electrical charges of neighboring atoms, pK_a perturbation, conformational changes, basicity/acidity and bioavailability, toxicity, modulation of lipophilicity and metabolic stability [1-3].
Since the 1950s, over 150 fluorinated drugs have been released to market and now make up approx. 20% of all pharmaceuticals, with even higher records for agrochemicals (up to 30%) [4].

Herein, we present the effect of fluorine substitution on electrostatic surface potential (ESP) and atomic charge distribution for a series of benzene derivatives with hydrogen bond donors/acceptor (HBD/A) substituents (-OH, $-NH_2$, -CHO, $-OCH_3$, $-SCH_3$) using DFT/B97-1 method and cc-pVTZ-pp++ basis set. Next, the influence of fluorination on the strength of the hydrogen bond was investigated for fluorinated series of aniline – methanol dimers using the same DFT and basis set combination and FTIR spectroscopy.



The results confirmed the impact of fluorine on the acidity of the functional groups, in particular, the effect was the most significant for *para*-substitution. Interestingly, the strength of hydrogen bonds depend on the position of the fluorine substitution in the ring. The obtained results can be used in rational drug design and the lead modification in order to improve its activity as well as pharmacokinetics and pharmacodynamics properties.

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[2] O'Hagan D, *Understanding organofluorine chemistry. An introduction to the C–F bond, 2007,*
[3] Gillis EP. et al., *J. Med. Chem.* 58 (2015) 8315-8359,
[4] Zhou P. et al., *J. Chem. Inf. Model*. 49 (2009) 2344-2355.

Acknowledgements:
This study was partially supported by the statutory funds of the Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland.