Quantitative Evaluation of Bioisosteres in Drug Design

Arabi, A.A.[1]

[1]Department of Life & Environmental Sciences, Zayed University, PO Box 144534, Abu Dhabi, United Arab Emirates.

Drug design is fraught with challenges. The biological activity of a drug molecule can be considerably affected even with the minor changes in its structure. However, among the common substitutions in drug molecules that lead to adjusted pharmacokinetic and pharmacodynamic properties without affecting the biological activity is bioisosterism. Using the quantum theory of atoms in molecules (QTAIM), this study highlights a newly discovered indicator to evaluate quantitatively the similarities among nonclassical bioisosteres, namely carboxilyc acid, tetrazole [1], squarate [2], sulfonamide [3], isoxazole, oxadiazole, oxazolidinedione, and thiazolidinedione groups. The bioisosteric groups had remarkably close average electron densities regardless of the capping group or the protonation state of the molecule (see Figure below). The electrostatic potential maps, which represent the classical qualitative approach of explaining the bioisosteric activity, or in other words the "key & lock" interactions between the receptor and the drug, did not show the similarities in some cases.

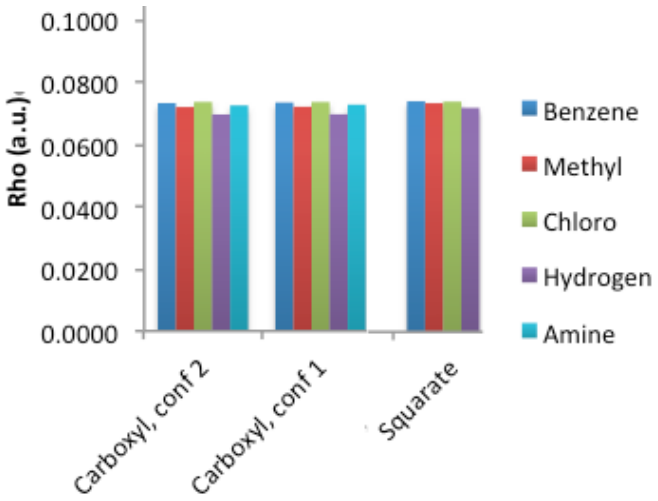

Figure 1 *Average electron densities (AED) of the bioisosteres carboxyl group (in two conformers) and squarate. The AEDs are reported for the bioisosteric groups capped with five different groups (phenyl, methyl, chloro, hydrogen, and amine).*

[1] CF Matta, AA Arabi, DF Weaver; *European journal of medicinal chemistry* **2010**, 45 (5), 1868-1872.
[2] AA Arabi, CF Matta, *Future medicinal chemistry* **2016**, 8 (4), 361-371.
[3] AA Arabi, *Future medicinal chemistry* **2017**, 9 (18), 2167-2180.