Quantitative Evaluation of Bioisosteres in Drug Design

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1. Abstract

Drug design is fraught with challenges as small differences in the structure of a molecule can significantly affect the biological activity of the drug. Bioisosteres are groups that can be interchangeably used to adjust pharmacokinetic and pharmacodynamic properties without affecting the biological activity of the drug. While electrostatic potential (ESP) maps are typically used to show the similarity in the "key & lock" interactions between the receptor and the drug, EPM is limited to qualitative comparisons. It is worth having a tool for quantitative comparisons of bioisosteres, especially nonclassical bioisosteres which are groups that vary in many aspects including numbers of atoms, types of atoms, 3D structures, and volumes. Using the quantum theory of atoms in molecules (QTAIM), this study presents a quantitative evaluation of the similarities among non-classical bioisosteres of carboxylic acid, namely isoxazole, tetrazoleone, oxadiazole, oxazolidinedione, and thiazolidinedione groups. The bioisosteric groups had remarkably close average electron densities regardless of the capping group (methyl, phenyl, hydrogen, chlorine, and amine) or the protonation state of the molecule (anionic or neutral), which was not otherwise obvious using ESP maps. The strength of this quantitative tool is in its potential to predict new bioisosteres based on the similarities in the average electron densities.

2. Introduction

Every drug is a molecule, but not every molecule is a drug. Minor changes in a drug molecule may cause drastic changes in its activity. One of the noticeable substitutions in drug design is the bioisosteric replacement where the chemical properties of the molecule significantly change while the biological activity remains intact. Examples of bioisosteres in the literature include classical and non-classical ones. The classical bioisosteres are isoelectronic at the valence shell. This isoelectronic factor is typically the accepted attribution to the similarities in the biological activity of drug molecules that involve substituted classical bioisosteres. The case with non-classical bioisosteric replacements is not as trivial as the common factor among them is not obvious. Typically, the similarity in the electrostatic potentials (ESP) is considered as the common factor for non-classical bioisosteres. Relying exclusively on ESP for explaining the similarity in the biological activity of non-classical bioisosteres has some gaps. One of the gaps evolves around the qualitative aspect of this tool, which introduces possibilities of bias in deciding whether similarities are depicted or not. Another gap is the occasional failure in exhibiting similarities for known bioisosteres as shown in reference [1]. It is thus crucial to have a quantitative tool to evaluate bioisosteres [2]. The average electron density (AED) tool, has been developed and tested on several cases ([1] and references therein). This tool is based on the partitioning of the molecule into atomic basins using the QTAIM partitioning scheme [3]. The property of a bioisosteric

group is the sum of the properties of the atoms constituting this group. The average electron density of a bioisosteric group is given by:

$$\rho = \frac{\sum_i N_i}{\sum_i V_i}$$

where N_i is the electron population of each atom i, and V_i is the volume of each atom i. This tool was tested on tetrazole, methylsquarate and sulphonamide. It was proven that all bioisosteres had AEDs similar to that of carboxylic acid. The purpose of this paper is to investigate the similarities in the average electron densities of other non-classical bioisosteres of carboxylic acid, namely, isoxazole, tetrazoleone, oxadiazole, oxazolidinedione, and thiazolidinedione. Isoxazole is part of the cycloserine drug molecule which is an antibiotic used to treat tuberculosis. Oxadiazole is found in oxolamine which is used as a cough suppressant. Oxazolidinedione is used in anticonvulsants. Thiazolidinediones are used is oral hypoglycemic drugs to improve insulin action. Tetrazoleone is tested as bioisostere in the anti-hypertensive drug, telmisartan [4]. This papers also looks at the effect of the protonation level of the bioisosteric group and the alteration of the capping group for each bioisostere. The protonation level is a reflection of the change in pH of the medium, and the use of various capping groups helps investigating the similarity in the average electron density regardless of the environment (drug) where the bioisosteric substitution takes place.

3. Methodology

Molecules were optimized in the gas phase using G09. The level of theory used was B3LYP/ 6–311++ G(d,p)// B3LYP/ 6–311++ G(d,p) with ultrafine pruned (99,590) grids and 'tight' self-consistent field optimization criteria. The symmetry in the molecule is disregarded in the optimization. Electron densities and molecular electrostatic energies were generated using the same level of theory with triple zeta Pople basis set. Vibrational frequency analysis was completed to confirm that the optimized geometries have no imaginary frequencies, in other words they are not transition states.

The AIMAll package was used for atomic integrations based on the quantum theory of atoms in molecules (QTAIM). The range of the Lagrangian values is micro- to milli- atomic units. The inter-atomic basins are delimited by zero-flux surfaces, and the outer limit of the atomic basins are defined at an isodensity envelope of 0.001 a.u..

Molecules were considered in the neutral and deprotonated (monovalent anionic form) to account for the change in pH of the medium. The protonated and anionic forms of the bioisosteric moieties of carboxylic acid (isoxazole, tetrazoleone, oxadiazole, oxazolidinedione, and thiazolidinedione) are capped with five different groups (phenyl, methyl, chloro, hydrogen, and amine). Different conformers of the protonated carboxylic acid group were considered.

4. Results and Discussion

In this study, the AED of non-classical bioisosteres of carboxylic acid were considered. The bioisosteres covered here are cyclic and open chain. The molecular electrostatic potential maps were also computed. As shown in the Figure 1 below, regardless of the bioisostere, its conformer, or the capping group used in the molecule, the average electron densities values are similar with an average of 0.072 ± 0.001 atomic units (a.u.). The small standard deviation of 1.4% reflects the precision of the tool in determining the similarity among the listed bioisisteres. This distinguished result is not coincidental given that the AED values of the capping groups varied by more than 80%. One strength of this tool, apart from its ability to precisely quantify the similarity, is its applicability to bioisosteres regardless of their protonation state. Another strength of this AED tool its ability to distinguish between cyclic and open chain non-classical bioisosteres.

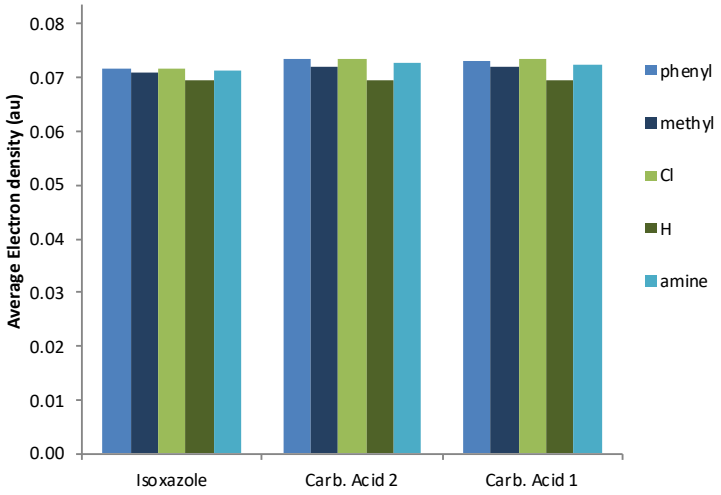

Figure 1 *Average electron densities (AED) of the bioisosteres carboxyl group (in two conformers) and the isoxazole. The AEDs are reported for the bioisosteric groups with five different capping groups (phenyl, methyl, chloro, hydrogen, and amine).*

The combination of ESP and AED allows to visualize the similarity for a qualitative assessment of a "key & lock" complementarity, and it also allows to measure quantitatively this similarity for a more rigorous distinguishing of bioiosteres. Figure 2 below shows the similarity in the molecular ESP maps of the isoxazole bioisostere with five different capping groups. The similarity in the disposition of three negative lobes (two of which are merged in the case of the amine capping group) confirms the similar interaction of the bioisosteric group with a given receptor. This reinforces the conclusion that bioisosteres would retain their similarity regardless of the drug where the bioisosteric substitution takes place. It is worth noting that the similarity in the ESP maps, in some other cases, was not as obvious, i.e. the evaluation of bioisosteres would be either ambiguous or biased.

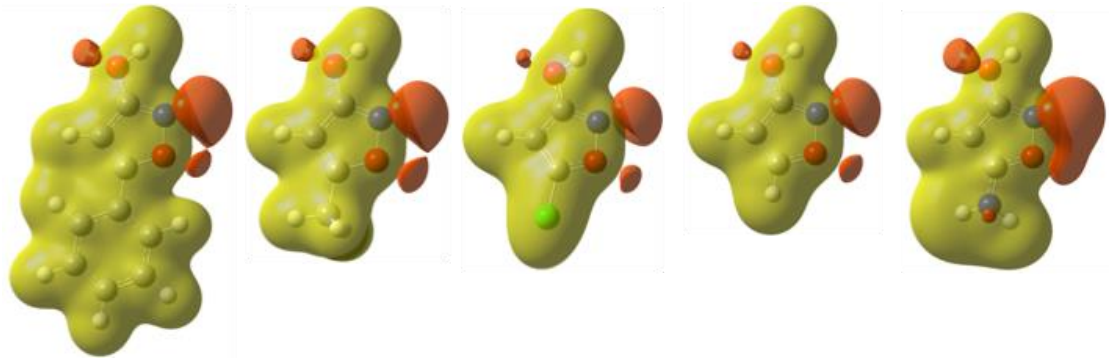

Figure 2 *ESP maps of isoxasole with five different capping groups (phenyl, methyl, chloro, hydrogen, and amine; from left to right). Red indicates negative and yellow indicates positive values of ESP.*

5. Conclusions

In conclusion, using the quantum theory of atoms in molecules partitioning scheme, this paper validates the precision of the computational AED tool in quantifying the similarity among bioisosteres. In particular, this tool was validated for five non-classical bioisosteres of carboxylic acid, namely isoxazole, tetrazoleone, oxadiazole, oxazolidinedione, and thiazolidinedione. The study was repeated under various conditions: a change in environment mimicked by substituting five different capping groups (phenyl, methyl, chloro, hydrogen, and amine), and a change in pH mimicked by varying the protonation state of the molecule (neutral and anionic). In all cases, the AED proofed to be accurate in predicting the bioisosteric similarity, with an average of 0.072 ± 0.001 a.u.. This AED tool complements the ESP tool, but it also provides more quantitative information that will be useful for the development of artificial intelligence algorithms in order to predict new bioisosteres.

6. References

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