Bioisosteres of Carboxylic Acid in Drug Design

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1. Abstract

In pharmaceuticals, pharmacokinetic and pharmacodynamic properties can be altered, without affecting the biological activity of the drug, through the substitution of bioisosteric groups. In order to pinpoint the reason why bioisosteres can reserve the biological activity of the drug, molecular and atomic properties of several bioisosteres of carboxylic acids are tested. The bioisosteres include tetrazol-5-one, oxadiazole, oxazolidinedione and thiazolidinedione, all of which were capped with five different groups (phenyl, methyl, chloro, hydrogen and amine). The molecules were considered in their neutral and anionic forms to capture the effect of pH changes. The atomic properties considered are the average electron densities, which can be obtained using the quantum theory of atoms in molecules (QTAIM). The molecular properties are the electrostatic potential maps (EPM). While the electrostatic potential maps showed similar topology and disposition of the lobes in the molecules, the similarity could be assessed only qualitatively. However, the average electron densities are accurate quantitative tools to measure the similarity, which was remarkable among the bioisosteric groups.

2. Introduction

Bioisosteric substitutions in drug design are highly valuable as their substitutions allows for a wide range of pharmacokinetic and pharmacodynamic alterations without affecting the biological activity of the drug. Classical bioisosteres are isoelectronic at the valence shell, but non-classical bioisosteres vary in many aspects and often do not share a common quantitative value. In fact, non-classical bioisosteres have different compositions in the number of atoms, their 3 D distribution, the types of the atoms, their volumes, their charges, etc. Thus, the question is: "what allows non-classical bioisosteres to maintain the same biological activity?" The answer to this question can be addressed at the molecular level by assessing the electrostatic potential maps of the molecules and by looking for similarities in the topology and distribution of positive and negative lobes and therefore, by postulating similar interactions of a given receptor with the substituted drug molecules with bioisosteres. This question could be also answered using a more robust quantitative tool, which is the evaluation of the average electron density of the bioisosteric moiety within a molecule. In order to be able to compute properties of parts of molecules, the molecules need to be partitioned into atomic basins using schemes such as the Hershfield or the QTAIM models. In this study the QTAIM [1] is used to partition the molecule into atomic basins delimited by bond paths from the inner sides and isodensity envelopes from the outer side of the molecule. The bond paths are a set of points that form a line that has maximum electron

density in space between two atoms, and the flux of the gradient vector field along this path is null. Once the atoms are divided into basins, atomic properties can be evaluated. Properties of moieties in a molecule (or a group of atoms within a molecule) would thus be the sum of the atomic properties of each of the atoms in the moiety. For example, the charge of a bioisosteric group in a drug molecule ($q_{bioisostere}$) is the sum of the charges of each atom (i) in this group (q_i) as follows.

$$q_{bioisostere} = \sum_i q_i$$

The average electron density (ρ) is the ratio of the electron density (N) over the volume (V) (ρ = N/V).

The average electron densities and electrostatic potential maps of several bioisosteres of carboxylic acid have been assessed ([2] and references therein). The bioisosteres highlighted in this abstract are tetrazol-5-one, oxadiazole, oxazolidinedione and thiazolidinedione. Tetrazoleone can be used as a bioisosteric substitution of carboxylic acid in telmisartan (an anti-hypertensive drug) [3]. Oxadiazole is a bioisostere in cough suppressant such as oxolamine. Oxazolidinedione bioisosteric substitutions are observed in anticonvulsants, and thiazolidinediones are bioisosteres in drugs for improving the action of insulin. In order to understand the effect of the drug environment, i.e. the effect of the rest of the drug molecule on the properties of the bioisosteric moieties, the latter were capped with five different groups: phenyl, methyl, chloro, hydrogen and amine. In addition, to account for the changes in pH depending on where is the target of the drug, the molecules are considered in their neutral and anionic forms. There is a total of 80 molecules considered in this study (4 bioisosteres x 2 states neutral/anionic x 5 substituents).

3. Methodology

Density functional theory, namely B3LYP in combination with a Pople triple zeta basis set was used to optimize all the molecules in the gas phase. The Gaussian G16 was used with ultrafine pruned grids and 'tight' self-consistent field optimization criteria. The wavefunction files were obtained at the B3LYP/ 6–311++ G(d,p) level. To confirm that the molecules did not optimize to a transition state, vibrational analysis was completed to check for the absence of an imaginary frequency.

The range of the Lagrangian values from the QTAIM analysis completed using AIMALL is micro- to milli- atomic units. The isodensity value of the outer envelope used is 0.002 au.

The four bioisosteres (tetrazol-5-one, oxadiazole, oxazolidinedione and thiazolidinedione) were capped with five different groups (phenyl, methyl, chloro, hydrogen and amine) and optimized in their neutral form and mono-anionic form. To account for the high diversity in the environment of a drug molecule, the capping groups were chosen to span a wide range of

electronegativities. The deprotonation site was determined based on the pK_a values.

4. Results and Discussion

The results below illustrate how each of the atomic average electron densities and the molecular electrostatic potential maps can be used to assess the similarity in the non-classical bioisosteres tetrazol-5-one, oxadiazole, oxazolidinedione and thiazolidinedione. Figure 1 below shows that the AED of the neutral molecules is identical to two decimal places (between 0.090 au and 0.091 au). Similarly, the AED of the anionic molecules range between 0.087 au and 0.088 au. These remarkable similarities suggest that the AED could be used as a tool to quantify the similarities among bioisosteres, and it could also differentiate between the neutral and anionic states of the molecule. The small standard deviations reported in Figure 1 illustrate that the changes in the environment of the drug, i.e. in the capping group of the molecule in this case, have a minimal effect on the values of the AED. This suggests that the AED tool has the advantage of being a common tool for bioisosteres irrespective of which drug they are part of, in addition to the advantage of distinguishing the neutral from the anionic states.

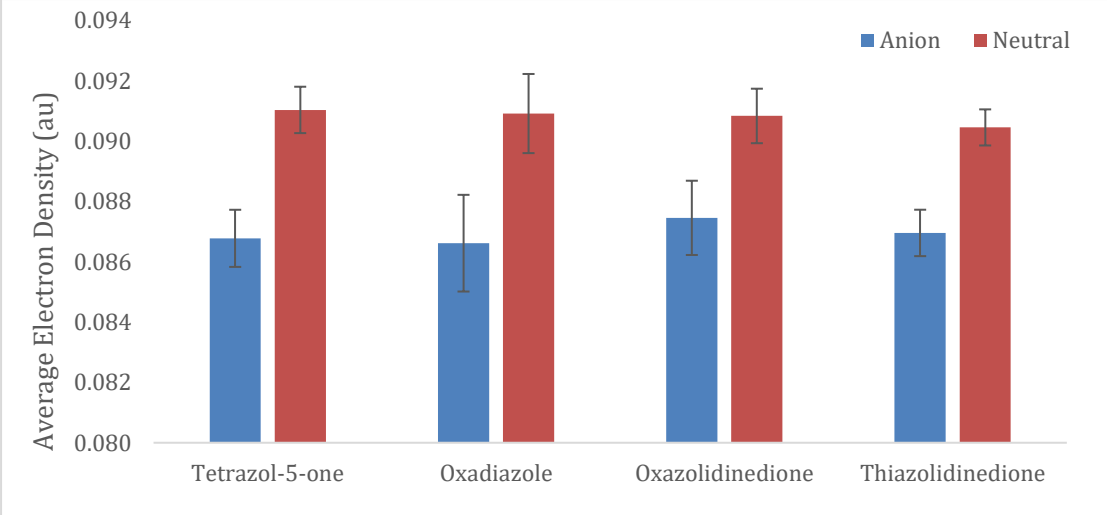

Figure 1 *Average electron densities (AED) of the bioisosteres tetrazol-5-one, oxadiazole, oxazolidinedione and thiazolidinedione in their neutral and anionic forms. The AED are averaged over the five different capping groups (phenyl, methyl, chloro, hydrogen and amine).*

Although the AED tool is robust in quantifying the similarity among the studied bioisosteres, complementing it with the qualitative electrostatic potential maps is an added strength. The EPM is a visualizing tool that helps picturing the "key & lock" complementarity between the drug and its receptor. Figure 2 depicts the EPM of the neutral (left) and anionic (right) molecules. This figure shows that the EPM are also good at distinguishing the state of the molecules. They also show that the variation in the capping groups does not have any significant effect on the dispositions of the negative lobes and the topology of the EPM. Therefore, these bioisosteres

would have similar interactions with a given receptor irrespective of which drug molecule they are part of.

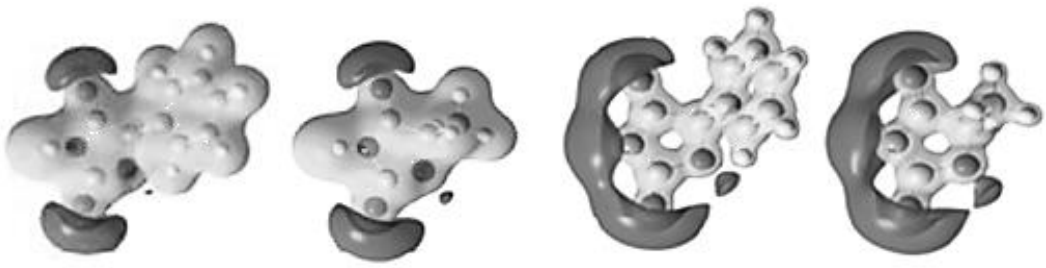

Figure 2 *Electrostatic potential maps of oxazolidinedione as follows: neutral with phenyl capping group (at isodensity 0.04 au), neutral with methyl capping group (at isodensity 0.04 au), anion with phenyl capping group (at isodensity 0.2 au) and anion with methyl capping group (at isodensity 0.2 au). The lobes in dark grey represent negative electrostatic potentials.*

5. Conclusions

In conclusion, the similarity of the bioisosteres tetrazol-5-one, oxadiazole, oxazolidinedione and thiazolidinedione could be explained using the visual similarity in the EPM, and could be more robustly justified using the average electron density quantitative tool. The difference in the environment of the drug does not seem to matter significantly on the similarity assessed using both quantitative and qualitative tools. Both tools seem to differentiate the state of the drug (neutral vs. anionic) depending on the pH. The power of the proposed quantitative tool is its potential use to discover new bioisosteres via various machine learning algorithms.

6. References

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