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Routes to drug design via bioisosterism of carboxyl and sulfonamide groups

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Research Article

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Future Medicinal Chemistry

Routes to drug design via bioisosterism of carboxyl and sulfonamide groups

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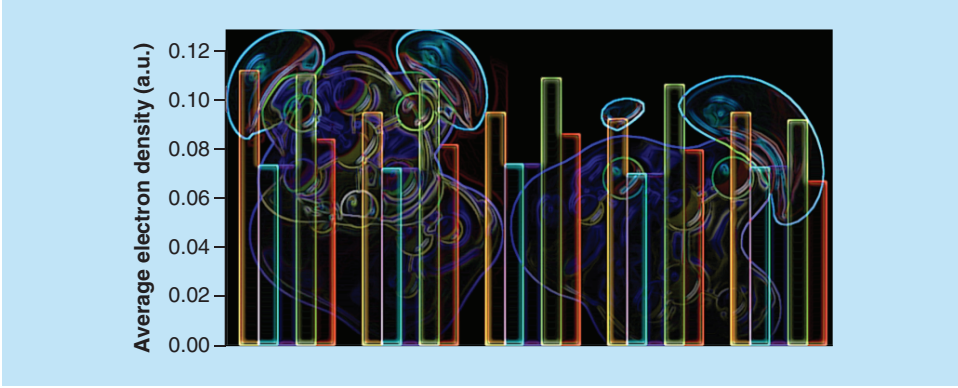
Aim: The similarity in the biological function of the bioisosteric pair, carboxyl and sulfonamide functional groups, is studied using the quantitative tool, average electron density of the bioisosteric moiety in drug molecules and the qualitative tool, electrostatic potential. **Results/methodology:** Five different capping groups (methyl, phenyl, chlorine, hydrogen and amine) were considered to investigate the effect of the environment on the properties of the bioisosteres. The molecules were considered in their neutral and anionic forms to account for the change in pH depending on the medium of the drug–receptor interactions. **Conclusion:** The new developed approach, average electron density, is not only advantageous as a qualitative descriptor, it is also more consistent compared with the conventionally accepted method, electrostatic potential, especially for the anions.



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Keywords: average electron density through the quantum theory of atoms in molecules • bioisosteres • carboxyl and sulfonamide • electrostatic potential of neutral and anionic molecules in drug design

Bioisosterism is the replacement of functional groups in a drug molecule while keeping similar biological properties [1,2]. Bioisosteres are useful to enhance the physiochemical [3–9], pharmacological [10–16] and pharmacodynamics/pharmacokinetic properties of drugs [17–26]. For example, tetrazole has been studied as a bioisostere of carboxylic acid in the treatment of the neurodegenerative Alzheimer's disease [3,5]. The substitution with tetrazole, for example, in β-site amyloid precursor protein cleaving enzyme 1 inhibitors, is mandatory to avoid the difficulty in crossing the blood–brain barrier which is highly hydrophobic [27,28]. Bioisosteres are classified as classical if the functional groups are isoelectronic [29]; otherwise they are nonclassical with groups that could possibly differ in the number of atoms, the 3D structure, the volumes and the number of valence electrons [30]. While the similarity is obvious for classical bioisosteres, it is not for the nonclassical ones. Often, bioisosterism is explained by looking at similarities in the molecular electrostatic potentials (ESPs) [30–32]. Recently, there have been two studies where two examples of nonclassical bioisosteres were explained using a new quantitative descriptor, namely the average electron densities, defined as the ratio of the total electron population of the bioisosteric group to its volume [32,33].

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Table 1. Comparison of some chemical and physical properties of 1,1,1-trichloro-N-methylmethanesulfonamide and acetic acid.

Property	1,1,1-trichloro-N-methylmethanesulfonamide	Acetic acid
Number of atoms in the bioisostere	9	4
Molecular shape of the bioisostere	Open chain	V-shaped
Monoisotopic MW (g mol^{-1})	210.90	60.02
Number of hydrogen bond acceptors	3	3
Number of hydrogen bond donors	1	1
LogP	1.3	-0.2
Polar surface are ($Å^2$)	55	37

Data taken from [39,40].

In the first study, the authors looked at the carboxylate and tetrazole anion with three different environments, that is, with methyl, hydrogen, and chlorine as capping groups. In all cases, the average electron densities of the bioisosteres were identical up to three decimal places, 0.066 a.u. [32]. The second set of bioisosteres considered was methylsquarate and acetic acid [33]. In this study, the authors looked at the neutral and the ionic forms of the molecules, with four different capping groups, namely methyl, hydrogen, chlorine, and a phenyl ring. The quantitative similarity in the average electron densities of the bioisosteric groups was obvious for all cases considered. The authors have also concluded that the illustrative molecular ESPs failed at showing the similarities in the dispositions of the positive and negative lobes for the bioisosteres in the anionic forms.

The partitioning of a molecule into atomic basins using the quantum theory of atoms in molecules (QTAIM) [34–36] allows the evaluation of properties of atoms in molecules, and subsequently bioisosteres in drug molecules. In QTAIM, the zero flux surfaces separate atoms into their own atomic basins. Then by operating different mathematical operators on the atomic basins, followed by numerical integrations, atomic properties of atoms in molecules can be evaluated. These properties include, volumes, charges, electron densities, areas, and average electron densities.

In this study the bioisosterism of the sulfonamide and the carboxyl groups will be investigated using molecular ESPs and average electron densities. A carboxyl group could be substituted by a sulfonamide bioisostere [37] in angiotensin II receptor antagonists [38]. The efficacy of the drug as the carboxylic acid group is replaced with the sulfonamide group increases by a factor of three. The IC_{50} (nM) drops from 275 with the carboxylic acid to 100 with the sulfonamide group. Squarate and tetrazole, which are other common bioisosteres of carboxyl, have IC_{50} (nM) of 25 and 3, respectively. According to the IC_{50} (nM), tetrazole has the highest efficacy, yet squarate is a better bioisostere as it reduces the blood pressure in hypertensive cases.

Table 1 summarizes some of the differences in the chemical and physical properties of acetic acid and 1,1,1-trichloro-N-methylmethanesulfonamide [39,40]. The pK_a of acetic acid (4.76) is smaller than that of a sulfonamide with $-CF_3$ as an R group (6.3) [41]. Thus, 1,1,1-trichloro-N-methylmethanesulfonamide is more acidic than acetic acid and gives its sulfonamide proton more readily. Both acids will, however, deprotonate at physiological pH of 7.4.

Methodology

Geometry optimization was completed in the gas phase using the Gaussian 09 package [42]. The density functional theory (DFT) [43,44] B3LYP functional [45–47] was used with an augmented triple-ζ Pople basis set with diffuse functions, a level of theory denoted by B3LYP/6–311++G(d,p)//B3LYP/6–311++G(d,p). The same level of theory was used to generate electron densities and molecular ESPs. The molecules were confirmed to be minima by checking for the absence of imaginary frequencies. The numerical integrations in G09 were evaluated using ultrafine pruned (99,590) grids. The 'tight' self-consistent field (SCF) and optimization criteria were imposed while disregarding symmetry in the molecule.

The atomic integrations were completed according to QTAIM using the AIMAll package [48]. The Lagrangian values of all atoms varied from 10^{-7} to 10^{-3} a.u. The limits for the volumes of the atomic basins were defined by the internal zero-flux interatomic surfaces within the molecular interior and up to the 0.001 a.u. isodensity envelope for the external atoms.

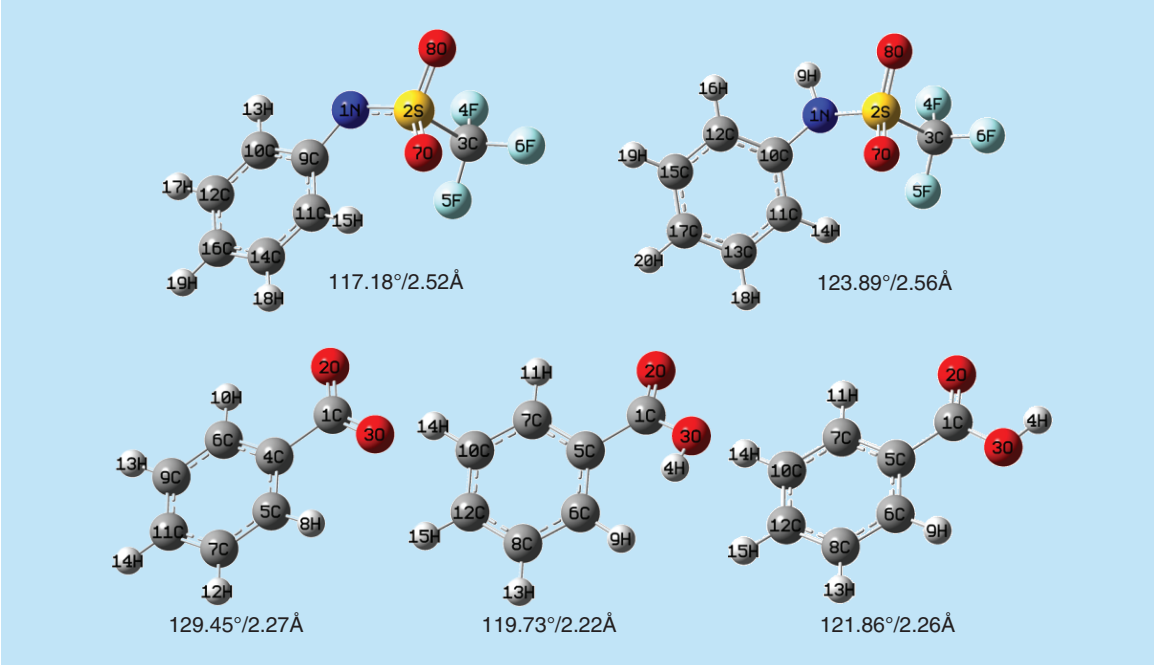


Figure 1. Optimized geometries with the labeled atoms of the anionic (left) and neutral (right) forms of two bioisosteres (-SO_2NCF_3-/-SO_2NHCF_3 on the top and-CO_2^-/-CO_2H at the bottom) capped with a phenyl ring.
Conformer 1 of the carboxylic bioisostere is displayed in the middle and conformer 2 is on the right. The numbers below each molecule refer to angle/distance measurements, that is, ∠OSO/d_{OO} (top) and ∠OCO/d_{OO} (bottom).

The protonated bioisosteres, R-SO_2NHCF_3 and R-CO_2H, and their corresponding anionic forms, R-$SO_2NCF_3^-$ and R-CO_2^- have been considered with five different capping groups, R = CH_3-, H-, Cl-, C_6H_5-, or NH_2-. The capping elements hydrogen and chlorine were chosen as two elements with significantly different electronegativities. The methyl group is the simplest R group that can be used as a capping group; the phenyl ring and the amine group were chosen because they are ubiquitous in drug molecules. In the case of the amine capping group, the hydrogen on the middle nitrogen is more acidic than the hydrogen atoms on the terminal amine. Thus, upon deprotonation, the NH_2-$SO_2NCF_3^-$ is considered.

Results & discussion

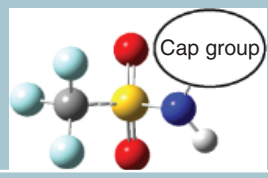
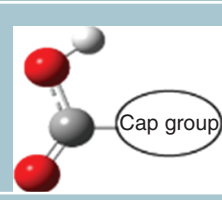
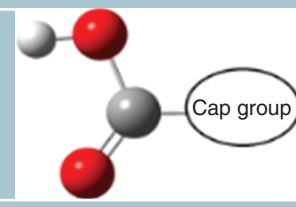
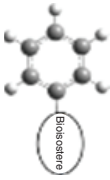
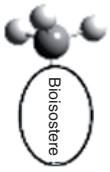
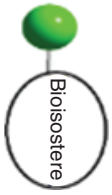
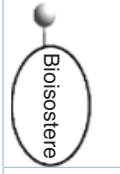
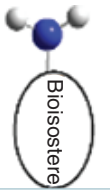
Figure 1 displays the optimized geometries of the neutral and anionic forms of the bioisosteres capped with a phenyl group. The OSO angle of the sulfonamide is wider in the neutral form (124°) compared with the ionic form (117°) and the OO distance is consequently longer in the neutral molecule by 0.04 Å. This observation is reversed in the carboxyl group: the OCO angle is wider in the acetate (129°) compared with both conformers of acetic acid (120° and 122°). The OO distances are consistently bigger (but not proportionally) for wider OCO angles. Two conformers are considered because they are both equally populated according to Boltzmann distribution [33], yet they might have significantly different biological interactions with the receptor. This is because of the orientation of the hydrogen in the carboxylic group, which can either enter the active site or remain oriented away from it.

Average electron densities of the bioisosteric groups in the neutral molecules

The properties for the protonated sulfonamide and both conformers of carboxylic acid capped with five different R groups are listed in Table 2. The atomic properties of all the atoms in all the molecules considered in this study are listed in detail in the Supplementary Information. The sums of properties for the bioisosteric groups or the capping groups (listed in Tables 2 & 3) are obtained by summing the corresponding properties of all the atoms constituting each group.

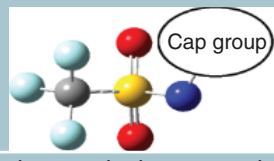
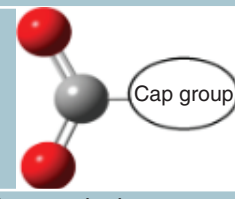
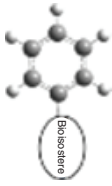
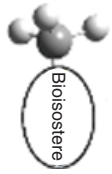
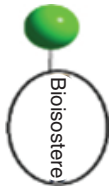
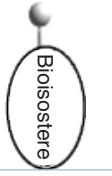
Regardless of the capping group, the average electron densities of the two conformers of the carboxyl group are identical to three decimal places; they vary only by a maximum of 0.0002 a.u., for example, from 0.0732 and 0.0734 for the carboxyl conformers 1 and 2 of benzoic acid, respectively (see Table 2). This slight variation is

Table 2. Properties of the neutral sulfonamide bioisostere (left), carboxyl conformer 1 (middle) and carboxyl conformer 2 (right) capped with a phenyl ring, methyl group, chlorine, hydrogen, and an amine group (listed sequentially).

	Neutral molecules														
															
	Group	N (a.u.)	V (a.u.)	<ρ> (a.u.)	q (a.u.)	Group	N (a.u.)	V (a.u.)	<ρ> (a.u.)	q (a.u.)	Group	N (a.u.)	V (a.u.)	<ρ> (a.u.)	q (a.u.)
	$\Sigma_{bioisostere}$	73.48	657.29	0.1118	-0.48	$\Sigma_{bioisostere}$	23.16	316.46	0.0732	-0.16	$\Sigma_{bioisostere}$	23.11	314.93	0.0734	-0.11
	$\Sigma_{capping\ group}$	40.52	595.39	0.0681	0.48	$\Sigma_{capping\ group}$	40.84	728.96	0.0560	0.16	$\Sigma_{capping\ group}$	8.92	231.73	0.0385	0.08
	$\Sigma_{bioisostere}$	73.47	773.94	0.0949	-0.47	$\Sigma_{bioisostere}$	23.15	321.83	0.0719	-0.15	$\Sigma_{bioisostere}$	23.11	320.88	0.0720	-0.11
	$\Sigma_{capping\ group}$	8.53	205.85	0.0414	0.47	$\Sigma_{capping\ group}$	8.85	216.16	0.0410	0.15	$\Sigma_{capping\ group}$	8.89	217.47	0.0409	0.11
	$\Sigma_{bioisostere}$	73.12	770.03	0.0950	-0.12	$\Sigma_{bioisostere}$	22.80	309.94	0.0736	0.20	$\Sigma_{bioisostere}$	22.80	310.07	0.0735	0.20
	$\Sigma_{capping\ group}$	16.88	207.51	0.0814	0.12	$\Sigma_{capping\ group}$	17.20	221.47	0.0777	-0.20	$\Sigma_{capping\ group}$	17.20	221.51	0.0776	-0.20
	$\Sigma_{bioisostere}$	73.42	794.98	0.0924	-0.42	$\Sigma_{bioisostere}$	23.08	331.86	0.0695	-0.08	$\Sigma_{bioisostere}$	23.05	331.12	0.0696	-0.05
	$\Sigma_{capping\ group}$	0.58	28.72	0.0200	0.42	$\Sigma_{capping\ group}$	0.92	46.94	0.0196	0.08	$\Sigma_{capping\ group}$	0.95	49.17	0.0194	0.05
	$\Sigma_{bioisostere}$	73.12	770.56	0.0949	-0.12	$\Sigma_{bioisostere}$	22.71	313.44	0.0725	0.29	$\Sigma_{bioisostere}$	22.71	312.40	0.0727	0.29
	$\Sigma_{capping\ group}$	8.88	170.59	0.0521	0.12	$\Sigma_{capping\ group}$	9.29	176.84	0.0525	-0.29	$\Sigma_{capping\ group}$	9.29	179.14	0.0519	-0.29
	Average bioisostere	73.32	753.36	0.0978	-0.32	Average bioisostere	22.98	318.71	0.0721	0.02	Average bioisostere	22.95	317.88	0.0722	0.05
	SD bioisostere	0.19	54.68	0.0079	0.19	SD bioisostere	0.21	8.55	0.0016	0.21	SD bioisostere	0.19	8.42	0.0016	0.19
	Average capping group	15.08	241.61	0.0526	0.32	Average capping group	15.42	278.07	0.0494	-0.02	Average capping group	9.05	179.80	0.0457	-0.05
	SD capping group	15.35	210.93	0.0237	0.19	SD capping group	15.33	261.73	0.0213	0.21	SD capping group	5.75	75.70	0.0214	0.18

The properties include electron population, volume up to the 0.001 a.u. isodensity envelope, average electron density, and electric charge, all in atomic units. The average properties and the SDs are also included.
a.u.: Atomic units; <ρ>: Average electron density; N: Electron population; SD: Standard deviation; q: Electric charge; V: Isodensity envelope.

Table 3. Properties of the sulfonamide anion (left) and the carboxylate (right) capped with a phenyl ring, methyl group, chlorine, hydrogen, and an amine group (listed sequentially).

	Anionic molecules									
										
	Group	**N (a.u.)**	**V (a.u.)**	**<ρ> (a.u.)**	**q (a.u.)**	**Group**	**N (a.u.)**	**V (a.u.)**	**<ρ> (a.u.)**	**q (a.u.)**
	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	73.25 40.75	665.88 609.77	0.1100 0.0668	-1.25 0.25	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	22.81 41.19	272.17 618.68	0.0838 0.0666	-0.81 -0.19
	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	73.29 8.71	675.35 174.12	0.1085 0.0500	-1.29 0.29	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	22.87 9.13	280.17 186.28	0.0816 0.0490	-0.87 -0.13
	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	72.89 17.11	669.94 177.15	0.1088 0.0966	-0.89 -0.11	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	22.10 17.90	256.81 243.25	0.0861 0.0736	-0.10 -0.90
	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	73.32 0.68	691.42 26.59	0.1060 0.0256	-1.32 0.32	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	22.89 1.11	288.05 46.12	0.0795 0.0241	-0.89 -0.11
	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	72.94 9.05	793.59 185.90	0.0919 0.0487	-0.94 -0.05	$\Sigma_{bioisostere}$ $\Sigma_{capping\ group}$	22.59 9.41	339.58 198.13	0.0665 0.0475	-0.59 -0.41
	Average bioisostere SD bioisostere	73.14 0.20	699.24 53.63	0.1051 0.0075	-1.14 0.20	Average bioisostere SD bioisostere	22.65 0.33	287.36 31.40	0.0795 0.0077	-0.65 0.33
	Average capping group SD capping group	15.26 15.39	234.71 219.86	0.0575 0.0263	0.14 0.21	Average capping group SD capping group	15.75 15.41	258.49 214.44	0.0521 0.0193	-0.35 0.33

The properties include electron population, volume up to the 0.001 a.u. isodensity envelope, average electron density, and electric charge, all in atomic units. The average properties and the SD are also included.
a.u.: Atomic units; <ρ>: Average electron density; N: Electron population; SD: Standard deviation; q: Electric charge; V: Isodensity envelope.

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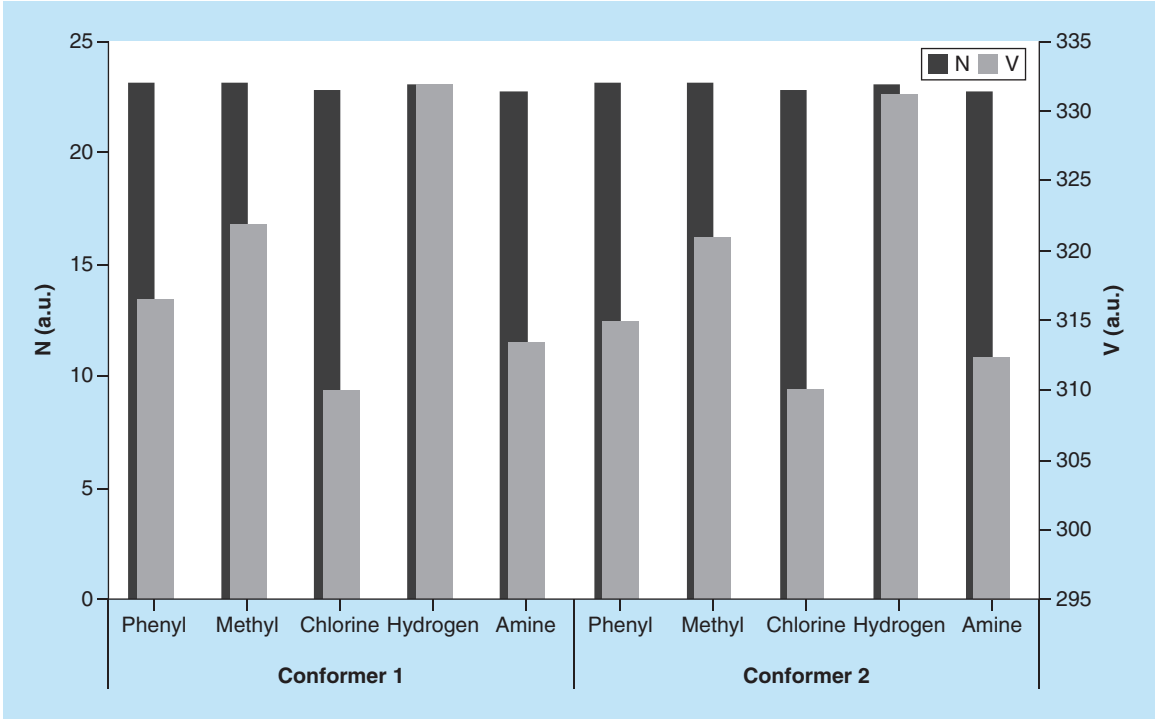

Figure 2. Electron populations and volumes of the carboxyl bioisostere in both conformers capped with five different capping groups.
a.u.: Atomic units; N: Electron population; V: Volume.

mainly a result of a change in the volume and not a change in the electron population (see Figure 2), as the latter is minimal to the point that electron populations are actually identical for both conformers in the cases of the chlorine (22.80 e^-), and the amine (22.71 e^-) capping groups. This suggests that QTAIM captures the similarity of an identical carboxyl groups by the similarity in electron populations, yet it differentiates their 3D arrangements (conformational changes) by the slight variations in their volumes, for example, 313.44 $bohr^3$ and 312.40 $bohr^3$ for the carboxyl groups when capped with amine. The change in the average electron densities as a result of changing the capping group is more pronounced (compared with changing conformations), where these values range from a minimum of 0.0695 a.u. (H-COOH, conformer 1) to a maximum of 0.0736 a.u. (Cl-COOH, conformer 1).

Considering only the methyl, chlorine, and amine capping groups, the average electron density (AED) of the sulfonamide bioisostere is $0.0949 \pm 3.2 \times 10^{-5}$ a.u. (with a volume of 771.51 ± 2.12 $bohr^3$). This AED decreases slightly to 0.0924 a.u. with the hydrogen capping atom (as the volume of the bioisostere expands slightly to 794.98 $bohr^3$) and it increases significantly to 0.1118 a.u. with the phenyl capping group (as the volume of the bioisosteres shrinks by ~14.8% to 657.29 $bohr^3$). Again, the electron population of the sulfonamide remains almost constant, in all cases, at an average of 73.32 ± 0.19 e^-.

As depicted in Figure 3, the charge of the carboxyl bioisostere alternates between positive and negative depending on the capping group (e.g., +0.20 with chlorine vs -0.15 e^- with methyl), and in some cases its value varies slightly depending on the conformational change (e.g., -0.16 e^- vs -0.11 e^- in conformers 1 and 2 of benzoic acid). The charge of the sulfonamide group is always negative, but varies in magnitude from -0.12 e^- when capped with chlorine or amine to -0.46 ± 0.03 e^- when capped with phenyl, methyl, and hydrogen.

Overall, the sulfonamides have an average electron population of 73.32 ± 0.19 e^-, an average volume of 753.36 ± 54.68 $bohr^3$ and an average AED of 0.0978 ± 0.0079 a.u.; while the corresponding values for the carboxyl group (averaged over both conformers) are 22.79 ± 0.19 e^-, 318.29 ± 8.01 $bohr^3$ and 0.0722 ± 0.0015 a.u., respectively. Excluding the outlier of sulfonamide capped with a phenyl group, on average, the AED of the carboxyl group (0.0722 ± 0.0015 a.u.) are smaller by 23.4% compared with the AED of the sulfonamide bioisostere (0.0943 ± 0.0013 a.u.).

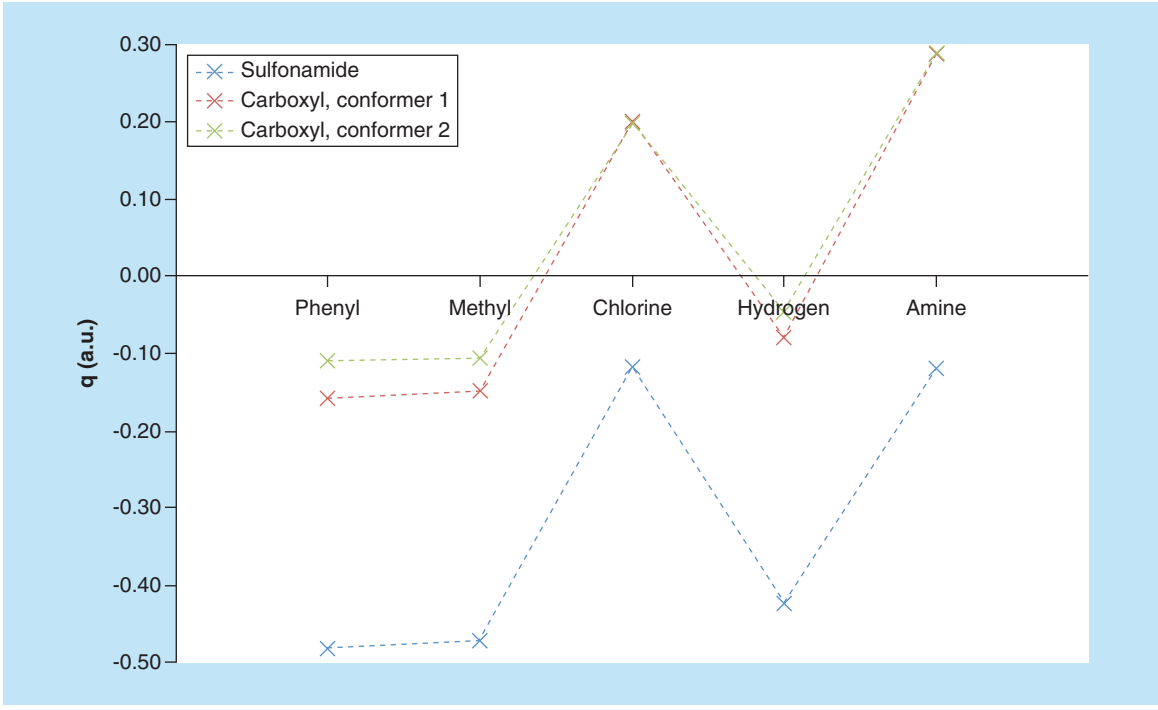

Figure 3. Charge of the carboxyl (both conformers) and sulfonamide bioisosteres capped with five different capping groups.
a.u.: Atomic units; q: Charge.

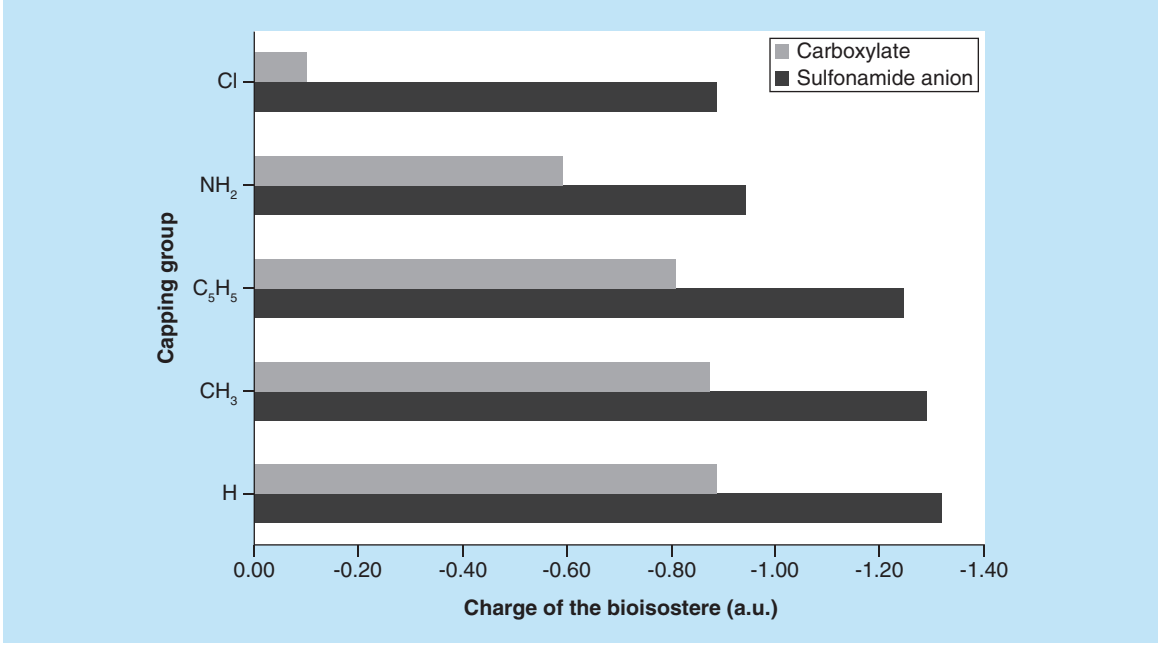

Figure 4. Charge of the carboxylate and sulfonamide anion bioisosteres capped with five different capping groups.
a.u.: Atomic units.

Average electron densities of the bioisosteric groups in the anionic molecules

The charges in Table 3 and Figure 4 show that the carboxylate group does not carry a full negative charge, it is partially negatively charged, and the rest of the charge is distributed on the capping group. The sum of both partial

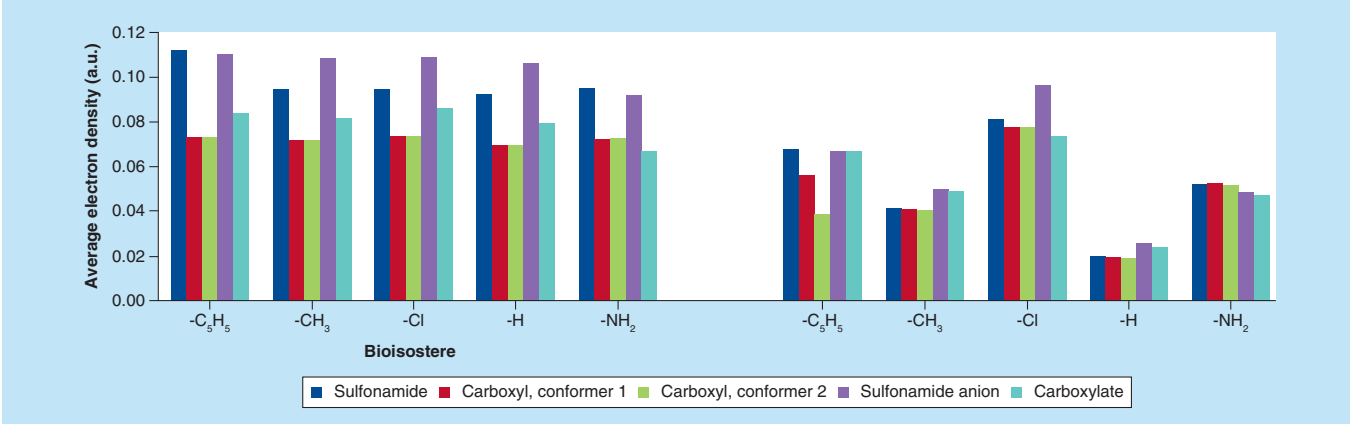

Figure 5. Average electron densities of the bioisosteres with five different capping groups (left set) and the average electron density of the five capping groups (right set).
a.u.: Atomic units.

charges, for the bioisostere and the capping group, always adds to unity, as it should. Depending on the capping group, the partial charge of the carboxylate group is in the following order (where the capping group is indicated in parentheses): -0.89 e^- (H) > -8.7 e^- (methyl) > -8.1 e^- (phenyl) > -0.59 e^- (amine) > -0.1 e^- (Cl). The sulfonamide anion group withdraws more charge than the carboxylate; in some cases its charge exceeds unity leaving a partial positive charge on the capping group in such a way the sum of the charges for the entire molecule adds to -1. The ranking of the charges, depending on the capping group is as follows: -1.32 e^- (H), -1.29 e^- (methyl), -1.25 e^- (phenyl), -0.94 e^- (amine) and -0.89 e^- (Cl). Even though the sulfonamide anion carries more negative charge than the carboxylate, they both follow the same ranking trend with the five capping groups as shown in Figure 4.

The average AED for sulfonamide anion capped with five different groups is 0.1051 ± 0.0075 a.u., with the range being from 0.0919 to 0.1100 a.u. (see Table 3). The small standard deviation in the AED indicates that, irrespective of the capping group, the AED property is transferable. In other words, regardless of which drug it is used with, a given bioisostere would have a similar AED. A similar observation is made for the carboxylate, where the AED values range from 0.0795 to 0.0861 a.u., with the amine-capped bioisostere being an outlier with an AED of 0.0665 a.u. For the carboxylate anion, the average AED is 0.0795 ± 0.0077 a.u. (or 0.0827 ± 0.0028 a.u. if the amine capping group is excluded, i.e., 21.3% smaller than the average AED for the sulfonamide anion case). Again, the variation is more because of the volumes than it is of the electron populations which span a very narrow range of 22.10–22.89 a.u. for the carboxylate and 72.89–73.32 a.u. for the sulfonamide anion. Overall, it is important to note that the AED of the carboxylate is smaller than that of the sulfonamide anion by 24.4%. This difference cannot be judged as small or large as there are no references to compare with. However, it is worth noting that the similarity in the bioisosteres is remarkable as it is captured up to 75.6% despite all the changes in the number and identities of the atoms (eight atoms in the sulfonamide including one S and three Cl vs three atoms in the carboxylate), the structure of the bioisosteres and many other properties listed in Table 1. More prominently, it is worth appreciating this 75.6% similarity in AED given (as will be shown below) the substantial difference observed in the classic way of assessing bioisosteres using ESP.

AED of the bioisosteric groups in the neutral compared with the anionic molecules

The average AED in the carboxyl group (0.0722 a.u., average over both conformers) versus the carboxylate group (0.0795 a.u.) are off by only 9.2% (see Figure 5) which is a very small deviation to be compared with a much more pronounced difference in the ESP (as will be explained in the last section). Those of the sulfonamide (0.0978 a.u.) and sulfonamide anion (0.1051 a.u.) are off by a small percent of 6.9% (see Figure 5). The ratio of $AED_{sulfonamide}/AED_{carboxyl}$ = 1.35 and $AED_{sulfonamide\ anion}/AED_{carboxylate}$ = 1.32, which are similar up to 97.8%. These small variations in the AED between the neutral and anionic bioisosteres suggest that, regardless of the pH of the biological medium (i.e., irrespective of the protonation state), the AED can still be used as a tool to identify and describe bioisosteres.

The most important comparison in this study is between the AED values of the carboxyl and the sulfonamide bioisosteres; they are off by 26.2%. Those of the anion counterparts are off by 24.4% (see Figure 5). These differences are not necessarily minimal. Nonetheless, the AED descriptor is not only valuable for a quantitative assessment (that cannot otherwise be obtained with traditional evaluators, i.e., ESPs), it is also more reliable than ESP in identifying similarities between anionic bioisosteres (as will be described below in the last section). It is worth mentioning that the 75.6% similarity between the bioisosteric groups, while not maximal, is not coincidental because, even for identical capping groups, the AED is not the same. For example, the AED of the chlorine with the sulfonamide anion bioisostere is 0.0966 a.u., while it is 0.0736 a.u. with the carboxylate, that is, a difference of 23.8% for one single identical atom (not even a group of atoms). This conclusion is supported by the findings of the previous study in reference [32].

Figure 5 clearly shows (in the left set) that the bioisosteres have similar AED values irrespective of their identity, charge, conformer, or capping group. The AED values of the sulfonamide and sulfonamide anions are consistently higher than those of the carboxyl and carboxylate bioisosteres. However, they remain comparable within 75.6% as discussed above. This similarity is not intuitive given the difference in the atomic and structural composition of the carboxyl and sulfonamide bioisosteres. This similarity is not coincidental either, as can be obvious from the right side where the AED of the five chosen capping groups (with different atomic and structural composition) vary a lot more drastically compared with the variations in the AED of the bioisosteres, for example, the AED of the hydrogen with sulfonamide is 70.5% smaller than that of the phenyl ring with sulfonamide. This similarity in the AED of the carboxyl and sulfonamide bioisosteres is deemed to be valuable in explaining bioisosterism because, as will be shown in the last section, the similarity between bioisosteres is not necessarily clear from the qualitative molecular ESPs, which are commonly used to explain the resemblance in the biological activity of these different bioisosteres.

Molecular ESP of the neutral & anionic molecules

Molecular ESPs were first introduced in the 1970 [49], and they are ubiquitously used for the identification of electrophilic and nucleophilic sites for predicting reactivities and gaining more insight about the directions of interactions, and thus mechanisms of various processes [50–54]. The molecular ESP, $V(\mathbf{r})$, is given by:

$$V(\mathbf{r}) = \sum_{A} \frac{Z(A)}{|\mathbf{R}(A) - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d\mathbf{r}'$$

where $Z(A)$ is the atomic number, $\mathbf{R}(A)$ is the position vector of nucleus A, $\mathbf{r}$ is the position vector of the point at which $V(\mathbf{r})$ is evaluated and $\rho(\mathbf{r}')$ is the electron density at a position vector $\mathbf{r}'$.

The ESPs in Figure 6 clearly depict the similarity in the disposition of the red lobes, for any given bioisostere, with the five different capping groups. The red lobes of the sulfonamide bioisostere are almost symmetric in size and shape. The ESP of both conformers of the carboxyl group have two lobes with one being a lot bigger in size and different in shape than the other. However, the disposition of these lobes varies slightly from being adjacent, in conformer 1, with a separating distance of roughly 3.3 Å; to being across two sides of the molecule, in conformer 2, with a separating distance of roughly 5.1 Å (i.e., ~1.5-times the separation in conformer 1). While the ESP varies more with different conformers compared with different capping groups, the AED showed the opposite trend (as discussed above).

The ESP of the sulfonamide is closer to that of the carboxyl group in conformer 1 than conformer 2. The distance, on average across all capping groups, between the lobes in conformer 1 (3.31 Å) is 18.9% smaller than that between the lobes of the sulfonamides (4.08 Å). It is, however, 25% larger in conformer 2 (5.09 Å) compared with the sulfonamides. This percent difference matches with the 26.2% difference in the AED of the carboxyl and the sulfonamide bioisosteres.

It is noticeable, by glancing at the ESP of the anionic molecules shown in Figure 7, that there are no clear similarities in the disposition of the red lobes between the bioisosteres. The sulfonamide anions have three lobes as opposed to only two lobes for the carboxylates (the carboxylate capped with a chlorine is an exception where the C-Cl bond, 2.9 Å, is much more stretched than the average C-Cl bond, 1.7 Å, suggesting that the Cl-COO^- optimized to a CO_2 molecule and a chloride anion where the big red lobe of the ESP is accumulated). It could be argued that only two of the lobes of the sulfonamide enter the active site of the receptor, but it would not be clear,

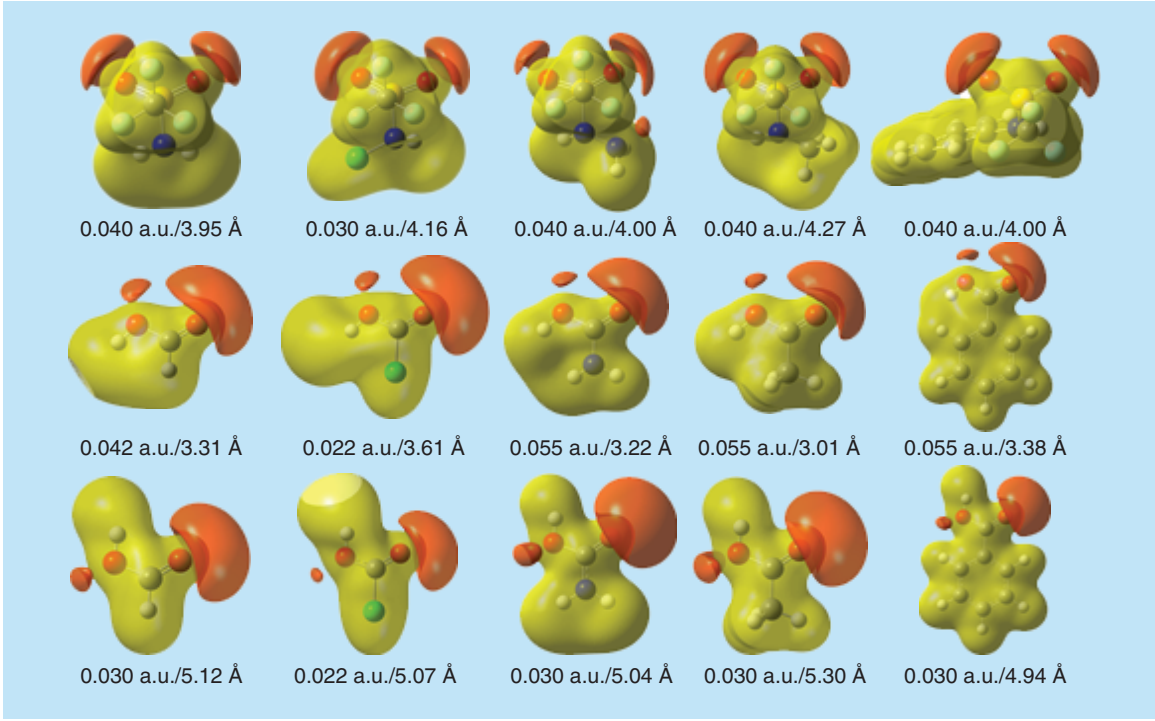

Figure 6. Electrostatic potential surfaces of the neutral bioisostere $^{-}SO_2NHCF_3$ (top), $^{-}CO_2H$, conformer 1 (middle) and $^{-}CO_2H$, conformer 2 (bottom) with the hydrogen, chlorine, amine, methyl and phenyl capping groups (from left to right). Red is for negative and yellow is for positive values of the electrostatic potential. The numbers displayed in Å represent the distance between the centers of the negative lobes in red. The isodensity value is reported, in atomic unit, for each molecule.

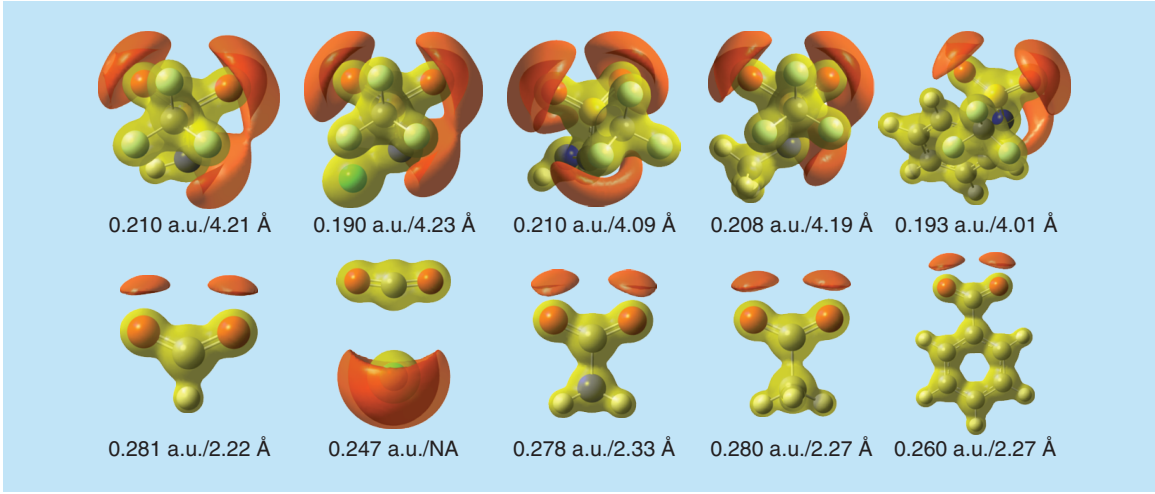

Figure 7. Electrostatic potential surfaces of the anionic bioisostere $^{-}SO_2NCF_3^{-}$ (top) and $^{-}CO_2^{-}$ (bottom) with the hydrogen, chlorine, amine, methyl and phenyl capping groups (from left to right). Red is for negative and yellow is for positive values of the electrostatic potential. The numbers displayed in Å represent the distance between the centers of the negative lobes in red. The isodensity value is reported, in atomic unit, for each molecule.

based on the ESP, which two lobes will enter the active site. Even if the two upper lobes are assumed to enter the active site, the average distance between these lobes is 4.1 Å; which is 1.8-times wider than that of the carboxylates (2.3 Å), that is, a difference of 43.9% in the distance between the lobes of the two bioisosteres. Thus, by simply looking at the ESP, it is difficult to strictly confirm a 'lock-and-key' complementarity between the bioisosteres at a

given receptor. This is to be compared with the 24.4% difference in the AED of the carboxylates and sulfonamides. Therefore, for assessing bioisosteric similarities, the AED descriptor is likely more accurate and more consistent than the ESP tool. Another advantage of the AED is that it can quantify both the similarity in the bioisosteres and the difference in the capping groups (as shown in Figure 5), which is not otherwise possible with the ESP.

Comparison of the ESP of the bioisosteric groups in the neutral & the anionic molecules

The neutral carboxyl groups (both conformers) and the anionic carboxylate group share the same number of red lobes (see Figures 6 & 7), and a similar 3D topology, but only to a certain extent. The lobes of the neutral carboxyl group have different sizes and shapes while they are perfectly symmetric in carboxylate. The distance between the lobes vary from 3.3 Å and 5.1 Å in conformers 1 and 2 (respectively) to 2.3 Å in carboxylate. While the similarity between the neutral and the anionic forms is not noticeably obvious with ESP, the AED of both forms were off by only 9.2% (as described above). The similarity between the ESP of sulfonamide and sulfonamide anion is even less pronounced (see Figures 6 & 7 for comparison). The neutral molecules have two lobes as opposed to three lobes in the anionic form. It is worth noting, however, that the distance between the two upper lobes in the sulfonamide anion is identical (4.1 Å, on average) to that of the neutral sulfonamide group. The AED values of the neutral and anionic sulfonamides are off by only 6.9%.

Conclusion

In this study, the bioisosterism between carboxyl and sulfonamide groups is explored quantitatively using the new descriptor, average electron densities and qualitatively using molecular ESPs. The bioisosteres were capped with five different groups, namely a phenyl ring, methyl and amine groups, and chlorine and hydrogen atoms to understand the effect of the environment on the properties of the bioisosteres. The molecules were considered in their protonated and deprotonated forms as their status depends on the pH of the biological medium they are in.

The results suggest that AED is a more consistent quantitative descriptor for bioisosteres compared with the illustrative qualitative ESP descriptor. The topology of the ESP of the neutral molecules shows similarity in having two lobes of negative values at slightly different positions. The separation of these lobes is off by 25% for the sulfonamide compared with the carboxyl group, which is aligned with the 26.2% difference of the AED of these bioisosteres. However, the ESP of the sulfonamide anion and the carboxylate bioisosteres had different topologies, where the former had three lobes of negative values and the latter had only two. While the ESP of the anionic forms did not clearly show a similarity for the bioisosteres, the AED of these groups exhibit 75.65% similarity.

It was shown that the capping groups marginally affect the values of the AED: they are 0.0978 ± 0.0079 a.u. for the sulfonamide and 0.0722 ± 0.0015 a.u. for the carboxyl group, both capped with the five groups. The corresponding values for sulfonamide anion and carboxylate are 0.1051 ± 0.0075 a.u. and 0.0795 ± 0.0077 a.u., respectively. It was also shown that the ESP of the bioisosteres remains the same irrespective of the capping group (in both the neutral and anionic forms).

Future perspective

This study will be extended by studying more bioisosteres in order to validate the usefulness of the AED as a standard and accurate tool for evaluating bioisosteres. We hope that this will then permit us to predict new bioisosteres that are hitherto unknown in the literature. The discovery of new bioisosteres would be an important advance in the field of drug discovery and design.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/suppl/10.4155/fmc-2017-0136.

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Summary points

- Average electron density (AED) is a more consistent quantitative descriptor for bioisosteres compared with the illustrative qualitative electrostatic potential (ESP) descriptor.
- The average AED of the neutral bioisosteres, sulfonamide and carboxyl, capped with five different groups (-C_5H_5, -CH_3, -Cl, -H and -NH_2) are 0.0978 $\pm$ 0.0079 a.u. and 0.0722 $\pm$ 0.0015 a.u., respectively.
- The average AED of the two anionic bioisosteres, sulfonamide anion and carboxylate, with the same five capping groups are 0.1051 $\pm$ 0.0075 a.u. and 0.0795 $\pm$ 0.0077 a.u., respectively.
- A given bioisostere would have a similar AED regardless of the capping group used or, in broader terms, regardless of the drug it is part of.
- The ESP of the neutral forms of the bioisosteres reveals similarity by having two and only two negative lobes. The ESP of conformer 1 of carboxyl is closer than that of conformer 2 to the ESP of sulfonamide.
- The ESP of the deprotonated bioisosteres did not reveal a clear similarity in the topology of the lobes, which makes it difficult to determine, for drug design, the bioisosterism between sulfonamide anion and carboxylate using ESP as a sole indicator.

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