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A Short Note on the Relationships between Electronic Structure and S-Nitrosoglutathione Reductase Inhibition by 3-[1-(4-carbamoylphenyl)-5-phenyl-1*H*-pyrrol-2-yl]propanoic acids.

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ABSTRACT

A study of the relationship between electronic structure and S-nitrosoglutathione reductase (GSNOR) inhibition by 3-[1-(4-carbamoylphenyl)-5-phenyl-1H-pyrrol-2-yl]propanoic acids was carried out. A statistically significant equation (adj-R^2=0.91, F(7,17)=34.50 (p<0.000001), SD=0.15) was obtained relating the variation of GSNOR inhibitory potency with the variation of the values of a set of local atomic reactivity indices belonging to a common skeleton. Based on the analysis of the results, a partial two-dimensional inhibitory pharmacophore was built.

INTRODUCTION

S-nitrosoglutathione reductase (GSNOR) is a class III alcohol dehydrogenase encoded by the ADH5 gene in humans that is also expressed in animals and plants [1-3]. GSNOR is involved in the control of the intracellular levels of *S*-nitrosoglutathione (GSNO) and other *S*-nitrosothiols. GSNOR reduces *S*-nitrosoglutathione to S-hydroxylaminoglutathione, which rearranges to form glutathione sulfinamide or, in the presence of GSH, forms oxidized glutathione and hydroxylamine. Through this process, GSNOR regulates the cellular concentrations of GSNO and plays an important role in regulating the levels of endogenous *S*-nitrosothiols and controlling protein *S*-nitrosylation-based signaling [2, 4-11]. GSNOR has been implicated in many biological processes, e.g. in the cardiovascular, gastro-intestinal and respiratory systems. More specifically, GSNOR may have an important function in respiratory diseases such as asthma [12-19]. As such, GSNOR emerges as a therapeutic target for a number of clinically important human diseases. For this purpose, GSNOR inhibitors have been developed [20-25]. With the aim of enlarging our knowledge about this topic we present in this paper a semiempirical quantum-chemical study of the inhibition of GSNOR by a set of 3-[1-(4-carbamoylphenyl)-5-phenyl-1*H*-pyrrol-2-yl]propanoic acids recently synthesized and tested for GSNOR inhibition [23].

MATERIALS AND METHODS

The model

As the methodology employed here to find relationships between electronic structure and inhibition constants has been extensively discussed and applied in several papers, we present here a short standard summary [26-30]. The inhibition constant, IC_{50} can be expressed as a linear relationship of the form:

$$\log(IC_{50}) = a + \sum_j \left[e_j Q_j + f_j S_j^E + s_j S_j^N \right] +$$
$$+ \sum_j \sum_m \left[h_j(m) F_j(m) + x_j(m) S_j^E(m) \right] + \sum_j \sum_{m'} \left[r_j(m') F_j(m') + t_j(m') S_j^N(m') \right] +$$
$$+ \sum_j \left[g_j \mu_j + k_j \eta_j + o_j \omega_j + z_j \varsigma_j + w_j Q_j^{\max} \right] + \sum_{K=1}^{U} O_K \qquad (1)$$

where Q_i is the net charge of atom j, S_j^E and S_j^N are, respectively, the total atomic electrophilic and nucleophilic superdelocalizabilities of Fukui et al., $F_{j,m}$ ($F_{j,m'}$) is the Fukui index of the occupied (vacant) MO m (m') located on atom j [31]. $S_j^E(m)$ is the atomic electrophilic superdelocalizability of MO m on atom j, etc. The total atomic electrophilic superdelocalizability of atom j corresponds to the sum over occupied MOs of the $S_j^E(m)$'s and the total atomic nucleophilic superdelocalizability of atom j is the sum over vacant MOs of the $S_j^N(m)$'s [32]. μ_j is the local atomic electronic chemical potential of atom j, η_j is the local atomic hardness of atom j, ω_j is the local atomic electrophilicity of atom j, ς_j is the local atomic softness of atom j, and $Q_j^{\max}$ is the maximal amount of electronic charge that atom j may accept from another site [30]. The O_K's are the orientational parameters of the substituents [28, 33]. Throughout this paper $HOMO_j$* refers to the highest occupied molecular orbital localized on atom j and $LUMO_j$* to the lowest empty MO localized on atom j [29]. They are called the local atomic frontier MOs. The application of relationship (1) has given excellent results for a great variety of drug-receptor systems (see [30, 34-46] and references therein).

Selection of the experimental data.

Molecules were selected from a set reported in Ref. [23]. The molecules are shown in Fig. 1 and Table 1. Figure 2 shows the numbering of atoms used in the LMRA. The experimental data employed in this study are the experimental GSNOR inhibition constants, IC_{50} (see Suppl. Mat. of Ref. [23])

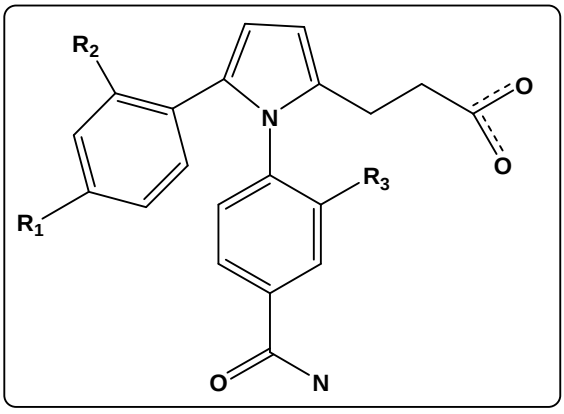

Figure 1. General formula of 3-[1-(4-carbamoylphenyl)-5-phenyl-1*H*-pyrrol-2-yl]propanoic acids.

Table 1. Selected molecules and their inhibitory activities.

Molecule	R_1	R_2	R_3	$\log(IC_{50})$ (μM)
1	H	H	H	2.76
2	H	H	Me	2.56
3	OMe	H	H	2.66
4	OMe	H	F	2.38
5	OMe	H	Cl	2.28
6	OMe	H	CF_3	2.65
7	OMe	H	Me	2.32
8	F	H	Me	2.70
9	Cl	H	Me	2.08
10	CN	H	Me	2.75
11	OH	H	Me	2.20
12	CF_3	H	Me	3.60
13	$CONH_2$	H	Me	3.59
14	1H-imidazol-1-yl	H	Me	1.30
15	Cl	MeO	Me	1.75
16	MeO	Cl	Me	2.30
17	Cl	OH	Me	1.74
18	Cl	$CONH_2$	Me	2.20
19	Cl	EtO	Me	2.23
20	Cl	PrO	Me	2.04
21	Cl	NMe_2	Me	2.54
22	Cl	NHCHO	Me	2.76
23	Cl	Cl	Me	2.20
24	Cl	F	Me	2.08
25	Cl	CF_3	Me	2.52

Calculations.

The calculation of the numerical values of the reactivity indices of Eq. 1 was carried out with Zerner's ZINDO/1 semiempirical method using the anion form of the molecules. It is worth mentioning that, after full geometry optimization, ZINDO/1 is the only quantum-chemical method producing positive nucleophilic superdelocalizabilities. ZINDO/1 gave good results when applied to the interaction of a group of 3-substituted morphinans with μ, δ and κ opioid receptors, for the inhibition of wild-type and drug-resistant HTV-1 reverse transcriptase by some thiazolidenebenzenesulfonamide derivatives and several other *in vitro* drug actions [46-52]. The statistical fitting of equation 1 was performed by means of a linear multiple regression analysis (LMRA) with the logarithm of the IC_{50} values as the dependent variable and the local reactivity indices of the atoms belonging to a common skeleton as independent variables [53]. The atom numbering of the common skeleton is depicted in Fig. 2. Hyperchem was employed for the calculation of the wave function [54]. For multiple regression analysis we employed the Statistica software [55].

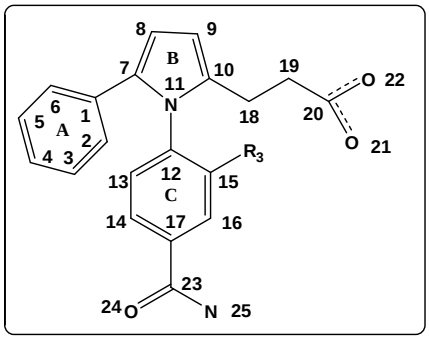

Figure 2. Numbering of atoms for the common skeleton of 3-[1-(4-carbamoylphenyl)-5-phenyl-1*H*-pyrrol-2-yl]propanoic acid analogues used in the LMRA.

RESULTS

The following equation was obtained:

$$\log(IC_{50}) = 3.47 - 1.97Q_9 - 0.84F_{11}(HOMO-1)* - 0.80F_{16}(LUMO+2)* - \\ -0.006S^E_{10}(HOMO)* - 0.26S^N_6(LUMO+1)* - \\ -0.91F_{13}(HOMO-1)* - 0.22S^N_{12}(LUMO+1)* \quad (2)$$

with n=25, R=0.95, R^2=0.03 adj-R^2=0.91, F(7,17)=34.50 (p<0.000001), outliers>2σ=0 and SD=0.15. Here, Q_9 is the net charge of atom 9, $F_j(MO_r)*$ is the Fukui index (the electron population) of MO_r at atom j and $S^N_j(MO_r)*$ is the local atomic nucleophilic superdelocalizability of MO_r at atom j. The beta coefficients and t-test for significance of coefficients of Eq. 2 are shown in Table 2. Table 3 shows that at p<0.05 there are no significant internal correlations between independent variables. Figure 3 is the plot of observed values *vs.* calculated ones. The associated statistical parameters indicate that this equation is statistically significant, explaining about the 91 % of the variation of the GSNOR inhibitory potency.

Table 2. Beta coefficients and t-test for significance of coefficients in Eq. 2.

	Beta	t(17)	p-level
Q_9	-0.43	-6.04	<0.00001
$F_{11}(HOMO-1)*$	-0.38	-5.57	<0.00003
$F_{16}(LUMO+2)*$	-0.33	-4.93	<0.0001
$S^E_{10}(HOMO)*$	-0.41	-5.76	<0.00002
$S^N_6(LUMO+1)*$	-0.32	-4.54	<0.0003
$F_{13}(HOMO-1)*$	-0.27	-3.84	<0.001
$S^N_{12}(LUMO+1)*$	-0.18	-2.70	<0.02

Table 3. Squared correlation coefficients for the variables appearing in Eq. 2.

	Q_9	$S^N_6(LUMO+1)*$	$S^E_{10}(HOMO)*$	$F_{11}(HOMO-1)*$	$S^N_{12}(LUMO+1)*$	$F_{13}(HOMO-1)*$
$S^N_6(LUMO+1)*$	0.04	1.00				
$S^E_{10}(HOMO)*$	0.02	0.01	1.00			
$F_{11}(HOMO-1)*$	0.005	0.01	0.06	1.00		
$S^N_{12}(LUMO+1)*$	0.03	0.03	0.05	0.006	1.00	
$F_{13}(HOMO-1)*$	0.03	0.04	0.001	0.06	0.02	1.00
$F_{16}(LUMO+2)*$	0.03	0.003	0.003	0.02	0.005	0.01

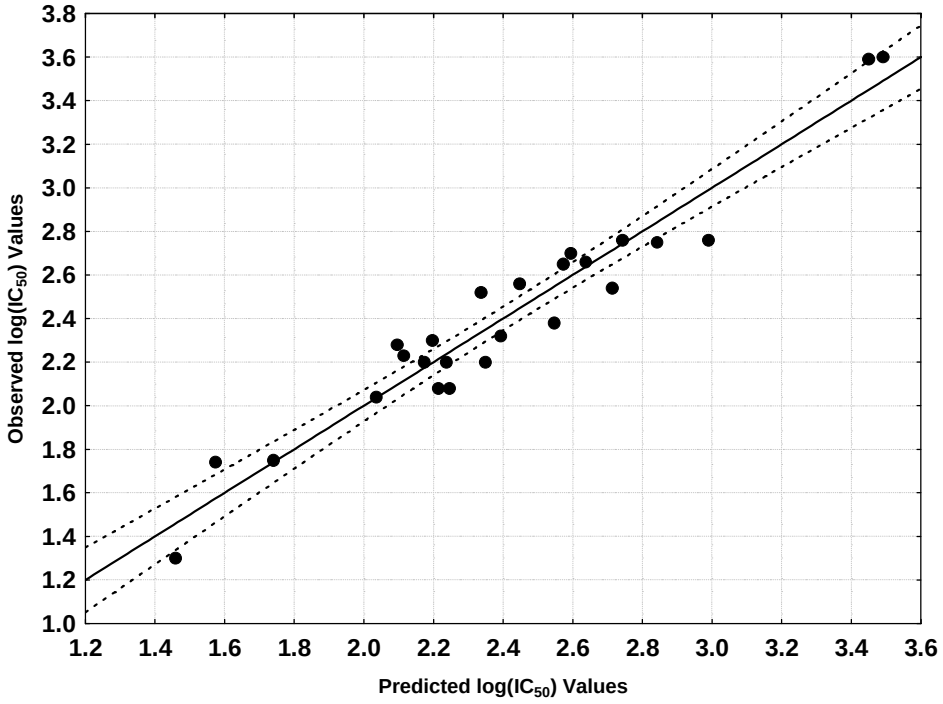

Figure 3. Plot of predicted *vs.* observed log(IC_{50}) values from Eq. 2. Dashed lines denote the 95% confidence interval.

DISCUSSION

Molecular Electrostatic Potentials

Figure 4 shows two views of the molecular electrostatic potential (MEP) of molecule 1 [54].

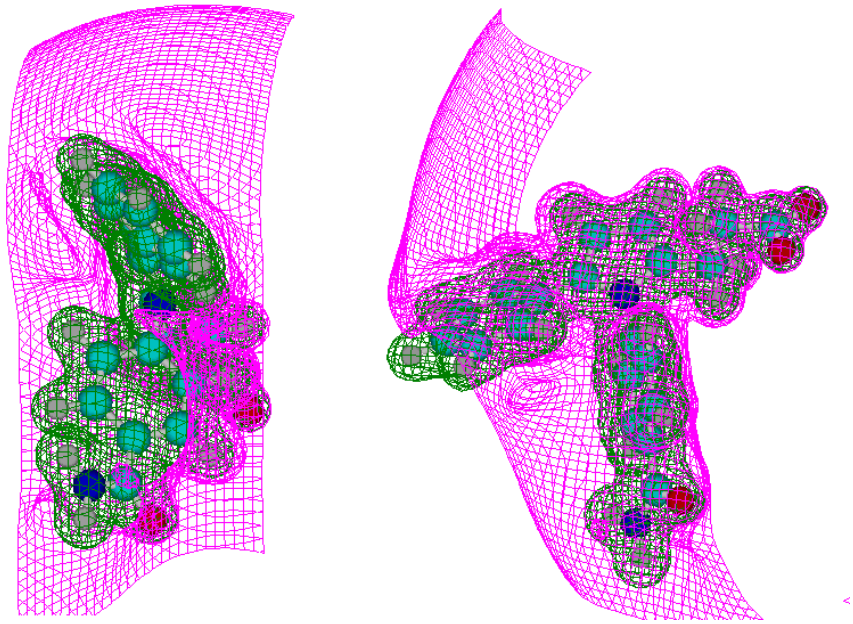

Figure 4. MEP of molecule 1. The green surface corresponds to positive MEP values and the pink one to negative MEP values.

We can see that almost all the molecule is surrounded by a negative MEP region with the exception of the left side (rings A and C, Fig. 2). The same happens for all the rest of the set. This is a direct effect of the COO^- group and is similar to anionic kynurenic acid derivatives and positively-charged β-phenylethylamine derivatives [56, 57]. As the negative MEP area is common to all the molecules studied here, we suggest that they approach GSNOR with the negative MEP area pointing toward the protein.

LMRA results

The final equations relate the *variation* of the inhibitory capacity to the *variation* of one or more local atomic reactivity indices. Thus, any index making a constant contribution will not appear in the equation. Our results indicate that, for the case analyzed, the variation of the inhibitory capacity is related to the variation of the numerical values of a set of seven local atomic reactivity indices belonging to the common skeleton. This result is very good considering the approximations made to build the model. The Beta values (Table 2) show that the importance of the variables is Q_9 > $S_{10}^E(HOMO)^*$ > $F_{11}(HOMO-1)^*$ > $F_{16}(LUMO+2)^*$ = $S_6^N(LUMO+1)^*$ > $F_{13}(HOMO-1)^*$ > $S_{12}^N(LUMO+1)^*$. $S_{12}^N(LUMO+1)^*$ and $F_{13}(HOMO-1)^*$ will not be included in the discussion because of their low p level (see Table 2). A variable-by-variable analysis indicates that a high inhibitory capacity is associated with a positive net charge on atom 9, a low electron-donor capacity of atom 10, high electron-acceptor capacities of atom 6, and high electron populations on certain molecular orbitals of atoms 11 and 13. Atom 6 is located on ring A. Its local LUMO* and (LUMO+1)* are of π nature. As an example, Fig. 5 shows the LUMO* and (LUMO+1)* of atom 6 in molecule 1 (see Fig. 2). We suggest then that atom 6, and perhaps other parts or ring A, undergo a π-π stacking interaction with an electron-donor aromatic counterpart.

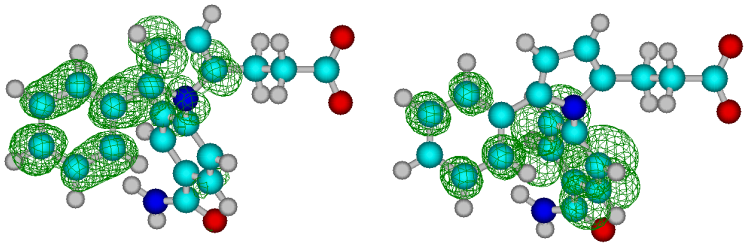

Figure 5. Local LUMO* (left, corresponding to the molecule's (LUMO+1)) and (LUMO+1)* (right, corresponding to the molecule's (LUMO+2)) of atom 6 in molecule 1.

Ring B participates in the inhibition process through, at least, atoms 9, 10 and 11. A positive net charge on atom 9 is indicative of an electrostatic interaction with a negatively-charged counterpart. A low value for $S_{10}^E(HOMO)^*$ can be obtained by lowering the corresponding $F_{10}(HOMO)^*$, by lowering the HOMO* eigenvalue or by both actions. However, the local HOMO* of atom 6 does not coincide with the molecules' HOMO. For example, in the case of molecule 1 the local HOMO* of atom 10 corresponds to the molecule's (HOMO-3) and is of π nature. Then, a low value for $S_{10}^E(HOMO)^*$ can be interpreted by suggesting that atom 10 is interacting with a counterpart in GSNOR having a high electron density that can come close to the inhibitory molecule. We lack enough information to discern if this interaction is a charge transfer or a π-π stacking interaction but we may note that the requirement of a positively charged atom 9 bonded to atom 10 can favor the approach to a region of high electron density. In the case of atom 11 (a nitrogen), its local (HOMO-1)* is well below the molecule's HOMO. For example, in molecule 1 it corresponds to the (HOMO-5) molecular MO. Our interpretation states that this atom interacts with an electron-deficient center located in GSNOR. The requirements for the three atoms of ring B are consistent among them and indirectly support the existence of a region in GSNOR to which ring B must come close to. Ring C participates in the inhibition process through at least atom 16. A high value of $F_{16}(LUMO+2)^*$ is optimal for good inhibitory capacity. In the case of atom 12, the nature of local LUMO*, (LUMO+1)* and (LUMO+2) is (σ,σ,σ) in almost all the molecules. We suggest, as a tentative explanation, that part or all of ring C interacts with a σ electron cloud located in GSNOR. Considering the fact that in a few molecules, such as molecule 1, the nature of local LUMO*, (LUMO+1)* and (LUMO+2) of atom 12 is (π,π,π), we think that the only way to clarify this point is by analyzing

more sets of similar molecules. All the above suggestions are summarized in the partial two-dimensional (2D) inhibitory pharmacophore shown in Fig. 6.

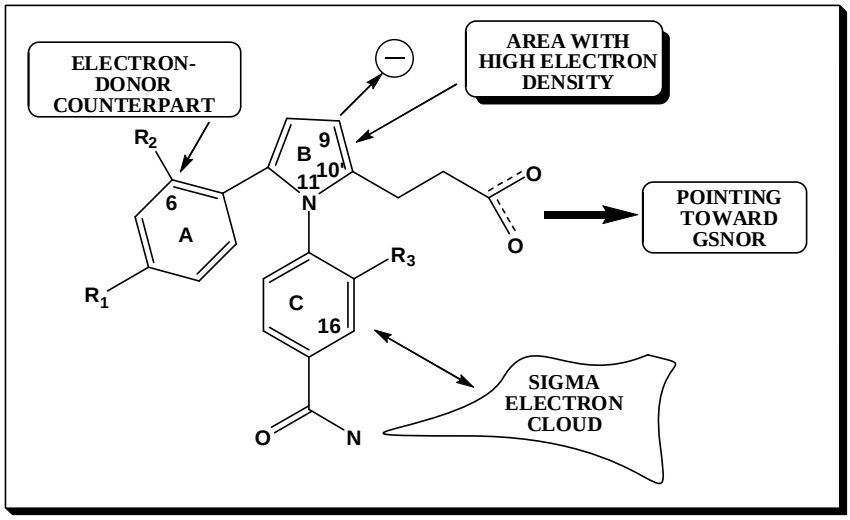

Figure 6. Partial 2D inhibitory pharmacophore for the inhibition of GSNOR by 3-[1-(4-carbamoylphenyl)-5-phenyl-1*H*-pyrrol-2-yl]propanoic acids.

Finally, let us note that Fig. 3 shows that only a few points liejust outside the 95% confidence limit, suggesting that the common skeleton used works well for this case. *S*-nitrosoglutathione reductase is involved in fundamental processes that are keys to preserve the biological integrity of living beings. In this sense, it is expected that the recognition processes must be very complex to avoid errors in substrate recognition. This is reflected in the fact that Eq. 1 has a high degree of fine orbital control that is the result of a long evolutionary process.

Some general comments about the model and calculations are pertinent. Regarding calculations, it is worth mentioning that the first successes of this method were obtained using the now old CNDO/2 semiempirical method [58-61]. There are clear theoretical reasons to abandon CNDO/2 in favor of *ab initio* methods, but to date no explanation has been provided for its success. ZINDO/1, another semiempirical approach, still shows that it can compete very well with, for example, purely statistically-based methodologies employing thousands of descriptors [51]. The other question is related to the size of most biologically active molecules. The existence of several isolated aromatic centers (i.e., not conjugated) implies that in several cases the HOMO is localized in different centers in a group of molecules. Then, if a center acts as an electron donor, it can do so employing an occupied MO different from the HOMO. This is the physical basis of the concept of local molecular orbitals. In small molecules the HOMO and LUMO are usually located on the same atomic centers, but this is only a particular case.

In conclusion, we obtained a good quality structure-activity relationship between electronic structure and GSNOR inhibitory potency for a group of 3-[1-(4-carbamoylphenyl)-5-phenyl-1*H*-pyrrol-2-yl]propanoic acids. These results should be useful to modulate the electronic structure leading to high GNSOR inhibitory activity.

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