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Quantitative structure–activity relationship in aziridinyl-1,4-naphthoquinone antimalarials: study of theoretical correlations by the PM3 method

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Abstract—Several molecular parameters for 2,3,5-substituted 1,4-naphthoquinones including 2-aziridinyl and 2,3-aziridinyl-1,4-naphthoquinones with antimalarial activities were obtained with the semi-empirical PM3 method. The descriptor related to the Gibbs free energy of an isodesmic equation defining the reduction of the naphthoquinones was found to have high correlation with activity. The quantitative models reported clearly show a dependence of activity on the redox potential for reduction of the naphthoquinones. Compounds with lower values of ΔG for reduction are more active than those with higher values of ΔG.

1. Introduction

Malaria is caused mainly by four species of parasitic protozoa (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*) that infect human red blood cells. Malaria is transmitted by inoculation of sporozoites during the bite of an infected female *Anopheles* mosquito. At present, at least 300,000,000 people are affected by malaria globally, and there are between 1,000,000 and 1,500,000 malaria deaths per year. The use of prophylactic drugs has been generally effective, but the disease continues to increase in many parts of the world. In addition, drug resistant malaria has become one of the most important problems in malaria control in recent years. Resistance in vivo to all antimalarial drugs has been reported.[1]

The drug arsenals for fighting malaria include many quinones and some natural products.[2,3] The quinones have been the subject of much interest for a number of years due to their various biological activities. In 1946 Wendel[4] showed that certain 2-hydroxy-3-alkyl-naphthoquinones inhibited the growth of *P. vivae* upon the influence on the respiratory and carbohydrate cycles in the parasite. Further studies proved that the toxicity of naphthoquinones to *Plasmodium* sp. is due to interaction with the mitochondrial respiratory chain.[5] This observation led Fieser and collaborators to start an extensive search for new quinones[6] aiming to discover new drugs for malaria chemotherapy. The quinones are also associated with antitumor,[7] trypanocidal,[8] molluscicidal,[9] leischmanicidal,[10] anti-inflammatory[11] and antifungal[12] activities. Among the quinones (Fig. 1) the following should be pointed out: atovaquone[13,14] (**1**), a coenzyme Q analogue which inhibits selectively *P. Vivae* by affecting the mitochondrial electron transport; lapachol[15] (**2**), present in the heartwood of the lapacho tree, *Tabebuia avellanedae* Lorentz ex. Griseb. (Bignoniaceae), and other *Tabebuia* trees native to Central and South America. These are known to possess several biological activities.[16,17] For example, it may interact with P450 reductase, producing reactive species, which promote DNA scission through the redox cycling-based generation of super-oxide anion radical;[18,19] and β-lapachone (**3**), an isomer of lapachol (**2**), which was intensely investigated for clinical use in cancer chemotherapy[20] directly target Topoisomerase I[21] and Topoisomerase II.[22] In addition, it also possesses a variety of pharmacological effects, including antibacterial, antifungal, and trypanocidal activities.

Keywords: Antimalarial; Naphthoquinone; QSAR; PM3.
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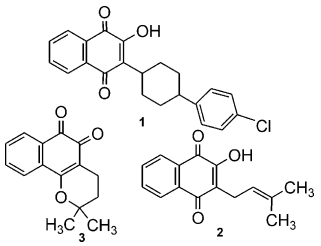


Figure 1. Examples of antimalarial naphthoquinones.

In most cases, the pharmacological activities of quinones are related to their ability to accept one and two-electron through a mixed mechanism mediated by some reductases, for example, NAD(P)H dehydrogenase or lipoamide dehydrogenase (LipDH). The cytotoxicity of quinones is often related to DNA damage by alkylation or intercalation, although cellular toxicity caused by oxidative stress, mediated by a redox process, has also been suggested. So, the search for new compounds having redox center substituted with different electronegativity is still desirable.

In a recent work by Pandey and coworkers[23] using three dimensional-quantitative structure–activity relationship (3D-QSAR) the influence of some structural features on the antimalarial activity of 63 aziridinyl-1,4-naphthoquinones was investigated. These naphthoquinones were previously synthesized and tested against chloroquine-resistant *P. falciparum* by Sartorelli and coworkers.[24] The oxygen atom at position 1 of the naphthoquinone moiety and the center of the phenyl ring were identified as the most important biophoric sites of these substances.

In an ongoing program aimed to study molecular features of antimalarial compounds,[25] the present paper aims to study the molecular descriptors for 2,3,5-substituted 1,4-naphthoquinones (**4**–**9**, Fig. 2) focusing mainly on 2-aziridinyl (**5a**–**m** and **7a**–**h**) and 2,3-aziridinyl-1,4-naphthquinones (**6a**–**s** and **8a**–**j**) prepared by Sartorelli et al.,[24] by using the semi-empirical PM3 method. We wish to discuss the effects of substituents on the redox cycle, and to correlate the molecular descriptors with the antimalarial activities that have been already reported on the literature.

2. Results and discussion

The variable capacity of quinones to accept electrons is due to the electron-attracting or electron-donating substituents at the quinone moiety, which modulate the redox properties responsible for the resulting oxidative stress. The molecular basis of quinone toxicity is the enzyme-catalyzed reduction to semiquinone radicals, which then reduce oxygen to superoxide anion radicals, thereby regenerating the quinone. The redox cycling and oxygen activation leading to increased levels of hydrogen peroxide is closely related to the quinone redox potential, since the electron density on the redox center is affected by the substituents present, as the redox potential of the resultant compounds depends on the electron density.

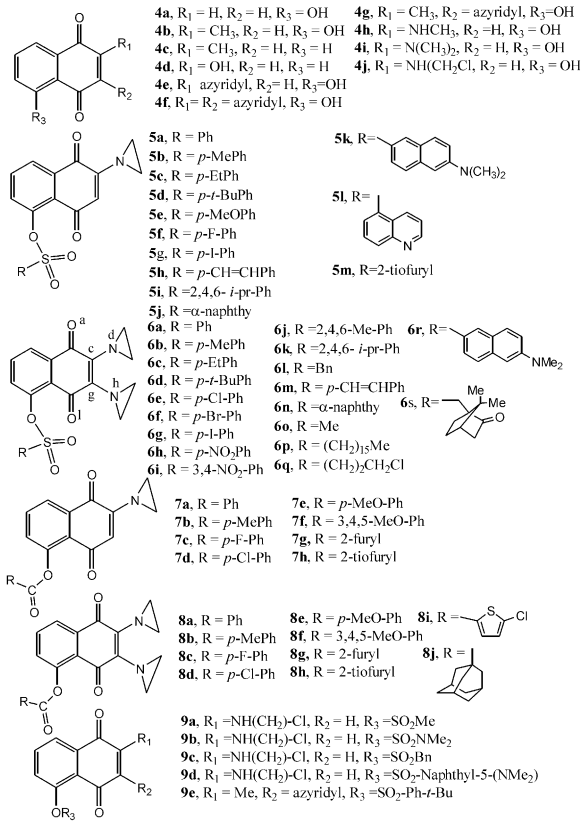


Figure 2. Antimalarial naphthoquinones synthesized and tested by Sartorelli.

Another pathway for the toxicity of quinones is the formation of interstrand cross-links by alkylation of the DNA (Fig. 3). Both pathways depend on the quinone structures, since electrochemical and bioactive properties are closely related.[26]

A relationship between redox potential and intramolecular electron transfer has been found reversible for electrochemical redox reactions mediated by quinone.[27] In a recent work, Goulart and coworkers related experimental redox potentials, obtained on Hg and glassy carbon electrodes, with trypanocidal activities.[28,29] In the case of the aziridinyl-naphthoquinones, the redox process is fundamental to enhance their action on the DNA, since reduction to hydroquinone decreases the conjugation of the nitrogen lone pair of the aziridinyl moiety. Driebergen and coworkers have found some relationships between structural parameters and their electrochemical behavior.[30]

To establish a structure–activity relationship and to ascertain the role of the redox moiety for the antimalarial activity of the naphthoquinones, we calculated several structural parameters (HOMO and LUMO energies, hardness, atomic charges, dipole moment, polarizability, molecular volume and Gibbs free energy) for a training set composed of 65 naphthoquinone analogues, namely compounds **4**–**9**, which had their antimalarial activity determined in a systematic way.[24]

The geometry of all compounds in the training set was completely optimized using the semi-empirical PM3 method.[31] For those compounds having free rotating single bonds a complete conformational analysis was undertaken in order to identify the most stable conformer. This was done by calculating the full set of conformers obtained by a complete rotation (in 30 steps) around that single bond. This led to identification of a set of minima on the potential energy surface for each compound. From these minima, the most stable one was selected for calculation of the molecular descriptors.

The molecular descriptors HOMO and LUMO energies, atomic charges on selected atoms (q_a, q_c, q_d, q_g, q_h and q_l, see Fig. 2 for index identification), dipole moment and polarizability were obtained directly from the semi-empirical PM3 calculation.[32]

Molecular volume was calculated for the optimized minimum energy geometry, using the SURFER software.[33] Hardness was defined as the energy difference between the frontier orbitals HOMO and LUMO. Finally, the Gibbs free energy (GFE) was calculated on the basis of the redox process in which the 1,4-naphthoquinones are supposed to be involved. To calculate the GFE for the redox process we defined an isodesmic equation (Scheme 1) where the 1,4-benzoquinone is used as the reference system. Thus, ΔG for the equation in Scheme 1 gives the relative standard Gibbs free energy (ΔG°) for reduction of each derivative. Due to the direct relationship between ΔG° and ε°, the redox potential, we expected that ΔG° might give us a quantitative indication of the trend of each derivative to undergo reduction as indicated in Scheme 1. Therefore, for each derivative we also calculated the reduced form necessary for the calculation of ΔG° for the equation in Scheme 1. S° for each compound was calculated using the subroutine THERMO from the MOPAC program.[34] Having ΔH° and ΔS° we calculate ΔG° at 298 K, following the relationship $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$. ΔG° was calculated in vacuum (GFE) as well as with simulation of solvent effects (GFE_{solv}), using the COSMO subroutine of MOPAC.[35] The last calculation was done using the dielectric constant of 78.4, which simulates the solvent water. All calculations, but the molecular volume, were done with the MOPAC93 set of molecular orbital program.[36] The values of the calculated descriptors are given in Table 1.

Once the molecular descriptors were available, we built up a matrix (65×15, see Table 1) that was submitted to the statistical analysis.

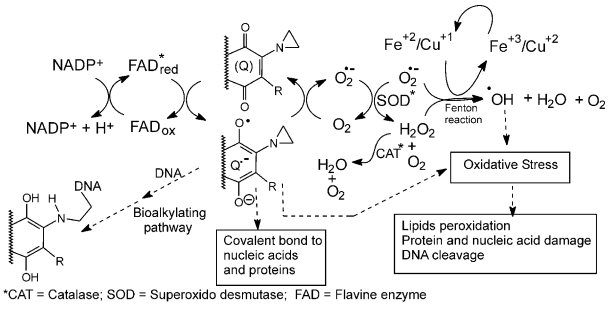
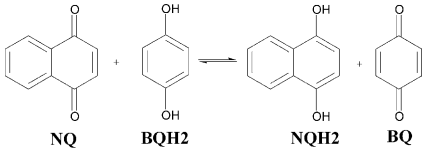


Figure 3. Formation of reactive oxygen species by redox cycling and aziridinyl bioalkylating pathway.



Scheme 1. General isodesmic equation defining the relative variation of GFE for reduction of the naphthoquinone derivative.

3. Statistical analysis

The first step in the statistical analysis was done with the Principal Component Analysis (PCA) methodology.[37] The main goals of the PCA analysis were to reduce the dimensionality of the original matrix and to identify the reduced set of molecular descriptors that retains the highest degree of information of the original data set. Initially, from each pair of highly correlated descriptors in Table 1 ($r \geq 0.8$) one was excluded. The retained descriptor was that which: (i) is highly correlated to various descriptors; (ii) has higher correlation to activity. This led to elimination of the following descriptors: q_c, q_g, q_h, hardness, molecular volume and solvated Gibbs free energy (GFE_{solv}). The plot of PC1×PC2 for the remaining set of molecular descriptors shows the same distribution pattern as that found for the original matrix. This indicates that few information was lost by elimination of those descriptors. Following with the PCA analysis it was possible to further reduce the number of representative descriptors by analysis of the autovector loadings of the most relevant PC's. A systematic procedure (one by one elimination of those descriptors having the lowest autovector loading) led to a final set of only three descriptors: LUMO, charge on atom 1 (q_l) and GFE. This reduced set of molecular descriptors retains most of the information contained in the original matrix, since a plot of PC1×PC2 gives a distribution pattern similar to that found for the original data set. The composition of PC2 for the reduced set of descriptors is mainly dominated by the GFE descriptor (autovector loading = 0.99), a first indication of the relevance of this descriptor to the discrimination of the molecules in the training set. PC1 is evenly composed of the LUMO and q_l descriptors (both autovector loading = 0.70).

From this stage up we employed multivariate regression analysis, using the BILIN software[38] to identify the best correlation between the subset of molecular descriptors (LUMO, q_l and GFE) and the activity. Three kinds of models were tested: linear, bilinear and parabolic.[39] Individual plot of each descriptor against activity revealed that only the GFE, in a parabolic or bilinear model, was able to give any significant correlation. Therefore we decided to continue investigating only the behavior of the correlation between GFE and the activity, using the parabolic and bilinear models.

Table 1. Calculated molecular descriptors HOMO, LUMO, polarizability, Q_a, Q_c, Q_d, Q_g, Q_h, Q_I, dipole moment, molecular volume, hardness, Gibbs free energy (GFE) in vacuum and Gibbs free energy (GFE) in the solvent

Subst.	HOMO	LUMO	Polariz	Q_a	Q_c	Q_d	Q_g	Q_h	Q_I	Dipole	Vol.	Hardness	GFE vacuum	GFE solvent
4a	−9.583	−1.709	13.736	−0.289	−0.130	0.123	−0.143	0.126	−0.343	0.313	220.0	−7.874	12.906	11.677
4b	−9.539	−1.659	15.073	−0.291	−0.095	−0.080	−0.165	0.129	−0.348	0.804	250.0	−7.880	13.565	12.044
4c	−10.260	−1.408	14.016	−0.294	−0.109	−0.073	−0.165	0.127	−0.297	1.719	237.0	−8.852	11.265	10.848
4d	−10.162	−1.611	13.706	−0.308	0.037	−0.213	−0.236	0.144	−0.302	2.683	223.0	−8.551	12.595	12.216
4e	−9.514	−1.623	17.876	−0.288	−0.067	−0.016	−0.220	0.136	−0.353	1.384	280.0	−7.891	13.398	12.519
4f	−8.978	−1.579	21.447	−0.287	−0.126	−0.014	−0.128	−0.024	−0.351	1.382	344.0	−7.399	16.235	14.857
4g	−9.483	−1.566	18.808	−0.294	−0.150	−0.080	−0.102	−0.007	−0.339	2.734	306.0	−7.917	13.650	13.023
4h	−9.243	−1.540	17.030	−0.300	−0.096	0.080	−0.278	0.140	−0.364	2.038	259.0	−7.703	15.081	12.713
4i	−9.198	−1.449	18.077	−0.279	−0.071	0.056	−0.276	0.141	−0.359	3.030	295.0	−7.749	11.253	11.533
4j	−9.355	−1.590	19.203	−0.295	−0.089	0.070	−0.280	0.138	−0.363	1.164	313.0	−7.765	17.316	14.487
5a	−9.548	−1.215	28.955	−0.291	−0.091	−0.017	−0.209	0.134	−0.307	3.455	435.0	−8.333	9.333	12.371
5b	−9.517	−1.216	30.417	−0.278	−0.094	−0.007	−0.204	0.134	−0.305	3.454	462.0	−8.301	8.881	12.910
5c	−9.533	−1.196	31.501	−0.292	−0.091	−0.017	−0.208	0.133	−0.307	3.925	491.0	−8.337	9.621	12.577
5d	−9.511	−1.208	33.662	−0.278	−0.094	−0.007	−0.204	0.134	−0.305	3.621	541.0	−8.303	8.670	12.097
5e	−9.532	−1.192	31.484	−0.292	−0.091	−0.017	−0.209	0.133	−0.309	4.303	473.0	−8.340	9.128	11.926
5e	−9.583	−1.314	29.237	−0.277	−0.092	−0.007	−0.206	0.134	−0.308	2.135	444.0	−8.269	8.995	12.071
5g	−9.483	−1.279	32.437	−0.277	−0.093	−0.007	−0.205	0.134	−0.307	2.609	454.0	−8.204	8.777	11.812
5h	−9.517	−1.230	33.055	−0.292	−0.091	−0.017	−0.209	0.133	−0.306	4.382	477.0	−8.287	9.591	12.396
5i	−9.599	−1.280	35.778	−0.276	−0.092	−0.005	−0.210	0.133	−0.301	4.724	599.0	−8.319	8.939	11.327
5j	−9.415	−1.265	34.810	−0.278	−0.095	−0.007	−0.202	0.133	−0.295	3.275	491.0	−8.150	8.666	12.803
5k	−9.317	−1.228	38.400	−0.279	−0.096	−0.007	−0.202	0.133	−0.294	3.672	581.0	−8.089	8.643	12.383
5l	−9.491	−1.306	34.639	−0.293	−0.090	−0.016	−0.211	0.134	−0.315	5.357	487.0	−8.185	10.747	12.618
5m	−9.567	−1.292	28.517	−0.291	−0.090	−0.017	−0.209	0.134	−0.311	3.568	415.0	−8.275	8.285	11.578
6a	−8.815	−1.146	32.348	−0.287	−0.152	−0.013	−0.121	−0.015	−0.295	3.712	489.0	−7.669	17.871	16.603
6b	−5.771	−1.062	33.885	−0.300	−0.147	0.002	−0.138	0.008	−0.296	4.920	519.0	−7.709	18.716	18.490
6c	’−8.796	−1.120	34.894	−0.287	−0.153	−0.013	−0.121	−0.015	−0.295	3.951	545.0	−7.676	13.710	15.261
6d	−8.763	−1.054	37.062	−0.300	−0.147	0.003	−0.137	0.008	−0.296	5.090	601.0	−7.709	15.894	15.156
6e	−8.835	−1.197	34.258	−0.286	−0.152	−0.013	−0.121	−0.015	−0.297	2.612	506.0	−7.638	13.905	15.365
6f	−8.816	−1.169	34.650	−0.299	−0.146	0.002	−0.138	0.008	−0.297	3.235	516.0	−7.647	15.308	15.842
6g	−8.831	−1.190	35.709	−0.286	−0.152	−0.013	−0.121	−0.015	−0.297	2.805	509.0	−7.641	14.006	15.802
6h	−8.971	−1.950	35.796	−0.283	−0.148	−0.013	−0.123	−0.017	−0.304	3.222	507.0	−7.021	14.384	16.412
6i	−9.062	−2.394	37.234	−0.293	−0.139	0.002	−0.142	0.009	−0.315	6.335	542.0	−6.668	15.317	14.519
6j	−8.728	−1.096	36.427	−0.282	−0.135	0.021	−0.136	0.004	−0.282	5.490	573.0	−7.632	16.554	16.436
6k	−8.707	−1.072	42.681	−0.299	−0.139	−0.019	−0.132	−0.016	−0.278	4.612	738.0	−7.635	14.243	13.789
6l	−8.838	−1.240	33.680	−0.296	−0.135	−0.020	−0.134	−0.014	−0.301	2.283	518.0	−7.598	14.469	13.184
6m	−8.749	−1.254	36.447	−0.301	−0.148	0.003	−0.137	0.008	−0.297	5.353	535.0	−7.495	15.093	15.816
6n	−8.769	−1.269	38.190	−0.304	−0.158	−0.004	−0.120	0.012	−0.290	4.447	554.0	−7.500	15.718	15.388
6o	−8.746	−1.194	42.227	−0.300	−0.149	0.003	−0.136	0.011	−0.302	4.503	631.0	−7.552	16.259	15.547
6p	−8.866	−1.235	25.748	−0.286	−0.150	−0.013	−0.122	−0.017	−0.301	2.194	423.0	−7.631	14.215	17.153
6q	−8.907	−1.230	42.192	−0.293	−0.141	0.001	−0.142	0.003	−0.321	3.719	848.0	−7.677	16.069	13.659
6r	−8.999	−1.356	29.603	−0.292	−0.124	−0.023	−0.149	−0.010	−0.311	3.274	500.0	−7.643	15.065	14.022
6s	−8.832	−1.162	35.663	−0.299	−0.144	0.003	−0.140	0.007	−0.308	5.448	622.0	−7.670	16.581	16.034
7a	−9.621	−1.383	26.921	−0.275	−0.087	−0.006	−0.209	0.136	−0.300	2.637	419.0	−8.238	9.711	12.073
7b	−9.630	−1.338	28.443	−0.289	−0.085	−0.017	−0.214	0.135	−0.301	1.630	447.0	−8.292	10.217	11.871
7c	−9.692	−1.426	27.270	−0.287	−0.082	−0.017	−0.215	0.136	−0.304	0.942	430.0	−8.266	10.396	11.747
7d	−9.652	−1.406	28.802	−0.286	−0.083	−0.019	−0.217	0.135	−0.305	1.917	439.0	−8.246	10.561	11.847
7e	−9.445	−1.338	29.493	−0.289	−0.084	−0.017	−0.214	0.135	−0.302	2.172	460.0	−8.107	10.301	11.973
7f	−9.325	−1.454	33.375	−0.273	−0.086	−0.005	−0.214	0.134	−0.305	5.411	534.0	−7.871	9.943	12.352
7g	−9.622	−1.354	25.219	−0.275	−0.090	−0.005	−0.209	0.135	−0.290	4.832	390.0	−8.268	9.883	10.258

(*Continued on next page*.)

Table 1 (*continued*)

Subst.	HOMO	LUMO	Polariz	Q_a	Q_c	Q_d	Q_g	Q_h	Q_I	Dipole	Vol.	Hardness	GFE vacuum	GFE solvent
7h	−9.693	−1.387	26.468	−0.287	−0.084	−0.019	−0.217	0.134	−0.304	2.534	401.0	−8.306	10.113	11.327
8a	−8.934	−1.283	30.388	−0.292	−0.123	−0.022	−0.149	0.010	−0.286	3.868	479.0	−7.651	15.266	15.305
8b	−8.884	−1.213	31.946	−0.295	−0.142	0.001	−0.140	0.003	−0.301	2.556	502.0	−7.671	16.356	15.177
8c	−8.984	−1.352	30.708	−0.291	−0.121	−0.022	−0.150	−0.010	−0.289	3.242	481.0	−7.632	15.312	15.276
8d	−8.962	−1.326	32.235	−0.292	−0.123	−0.022	−0.149	−0.010	−0.288	3.433	491.0	−7.636	15.296	15.250
8e	−8.895	−1.217	33.017	−0.295	−0.141	0.000	−0.141	0.003	−0.301	3.188	512.0	−7.678	16.261	15.050
8f	−8.973	−1.295	36.980	−0.293	−0.139	0.000	−0.144	0.005	−0.306	2.202	589.0	−7.678	15.978	14.866
8g	−8.924	−1.284	28.552	−0.282	−0.150	−0.011	−0.122	−0.022	−0.290	4.138	450.0	−7.640	14.440	15.383
8h	−8.948	−1.316	30.107	−0.282	−0.148	−0.011	−0.124	−0.021	−0.300	3.645	459.0	−7.632	14.553	14.763
8i	−8.919	−1.285	33.477	−0.283	−0.151	−0.010	−0.121	−0.021	−0.289	3.489	501.0	−7.634	14.504	14.105
8j	−8.859	−1.262	32.704	−0.279	−0.128	0.022	−0.141	0.008	−0.282	4.897	584.0	−7.597	14.624	17.337
9a	−9.223	−1.296	23.502	−0.298	−0.107	0.064	−0.259	0.136	−0.324	2.289	388.0	−7.927	13.482	13.348
9b	−9.218	−1.270	26.009	−0.298	−0.110	0.064	−0.257	0.137	−0.315	1.789	436.0	−7.948	13.466	13.522
9c	−9.213	−1.286	31.541	−0.299	−0.107	0.064	−0.258	0.136	−0.326	2.290	493.0	−7.927	13.761	13.735
9d	−9.147	−1.243	36.223	−0.291	−0.116	0.067	−0.258	0.133	−0.305	3.833	525.0	−7.904	11.486	12.986
9e	−9.263	−1.076	34.386	−0.298	−0.174	−0.060	−0.101	−0.010	−0.295	4.703	557.0	−8.187	11.892	13.117

A first attempt using all molecules in the training set resulted in the correlations shown in Eqs. 1a (parabolic) and 1b (bilinear).

$$\log 1/C = 0.0302(\pm 0.014)GFE^2 - 0.943 \times (\pm 0.37)GFE + 12.74(\pm 2.29) \quad (1a)$$
$$n = 65; \quad r^2 = 0.643; \quad s = 0.399; \quad F = 55.86$$

$$\log 1/C = -0.419(\pm 0.10)GFE + 0.431 \times (\pm 0.17)\log(\beta.10^{GFE} + 1) + 10.52 \times (\pm 1.08) \quad (1b)$$
$$n = 65; \quad r^2 = 0.677; \quad s = 0.382; \quad F = 42.78$$
$$\log\beta = -12.22$$

Successive exclusion of outliers, identified as those molecules whose residues (the difference between the calculated and the actual value of log1/C) are higher than 2*s*, leads to improved equations as shown below. In the case of the parabolic model, 14 compounds were excluded (**4c**, **4d**, **4e**, **4f**, **5c**, **5d**, **5m**, **6h**, **7f**, **9a**, **9b**, **9c**, **9d** and **9e**), resulting in a subset of 51 molecules, with statistical parameters as given in Eq. 2.

$$\log 1/C = 0.0220(\pm 0.0064)GFE^2 - 0.937 \times (\pm 0.17)GFE + 11.52(\pm 1.03) \quad (2)$$
$$n = 51; \quad r^2 = 0.918; \quad s = 0.158; \quad F = 268.17$$

Statistical parameters in Eq. 2 are considerably improved as compared to those in Eq. 1a. In the subset of 51 compounds used to obtain Eq. 2 none behaves as outlier.

In the case of the bilinear model only nine outliers (**4c**, **4d**, **4e**, **4g**, **5c**, **5d**, **5m**, **7f** and **9b**) have to be excluded from the original training set. The final subset of 56 compounds led to the statistical parameters shown in Eq. 3.

$$\log 1/C = -0.385(\pm 0.059)GFE + 0.369 \times (\pm 0.093)\log(\beta.10^{GFE} + 1) + 10.16 \times (\pm 0.62) \quad (3)$$
$$n = 56; \quad r^2 = 0.887; \quad s = 0.180; \quad F = 136.30$$
$$\log\beta = -12.18$$

In the subset of 56 compounds used to derive Eq. 3, none behaves as outlier. Therefore, we consider this as the final equation with the bilinear model. The final plot of predict IC_{50} versus experimental IC_{50} for this model including all compounds is presented in Figure 4.

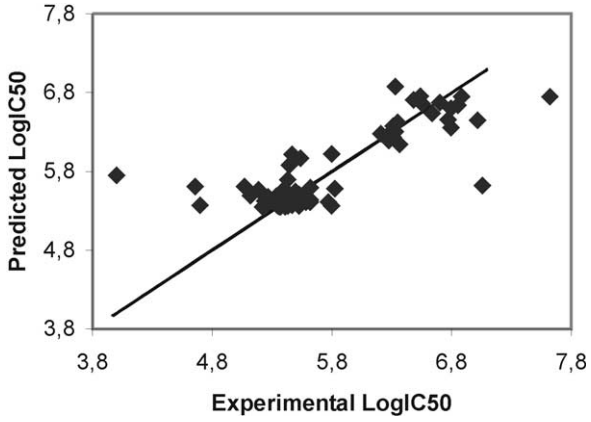


Figure 4. Plot of predicted IC_{50} versus experimental IC_{50} for the set of 65 compounds as calculated with the bilinear model (Eq. 3).

The outliers compounds excluded in both models, for example **4c** and **4d,** are among the most active compounds, what seems to be related with some special features, or conjugation of physicochemical properties, of the structures. The observed increase in antimalarial activity of some compounds appears to be related with its bioalkylation properties, which is a well known pathway for bioreductive alkylating agents in malignant cells by cross-linking DNA. As suggested by Sartorelli et al.,[24] it is also possible that some other enzymes may be a target site for these compounds.

4. Conclusions

The semiempirical PM3 molecular orbital calculations for 65 derivatives of 1,4-naphthoquinones, including 2- and 2,3-aziridinyl-1,4-naphthoquinones, furnished a set of molecular descriptors, which upon analysis by PCA and multivariate analysis indicated a variation in the activity of the compounds in the training set as a function of the GFE descriptor. Both models indicate that the most active compounds are those associated with lower GFE values, while less active ones are associated with higher GFE values. The GFE descriptor is directly related to the Gibbs free energy for the redox process represented in Scheme 1. Both the parabolic and the bilinear models clearly indicate that substituents yielding smaller ΔG° values for the equation in Scheme 1, lead to more active compounds than those yielding higher values of ΔG°. From a physichochemical point of view this can be rationalized as follows: ΔG° for the isodesmic equation in Scheme 1 is always positive (see Table 1). This means that under equilibrium conditions that equation will be shifted to the left, resulting in low concentration of the reduced form of the naphthoquinones, the active form which is able to activate oxygen or to alkylate DNA (see Fig. 3). If we assume that the antimalarial activity of naphthoquinones involves a mechanism wherein they act as oxidizing agents (Scheme 1) through the quinone moiety, we would expect that compounds leading to smaller ΔG° values would produce higher concentration of the reduced form QH_2, rendering it thereby more active. In this regards, Eqs. 2 and 3 fit very well with this hypothesis,

except for some cases where other biological mechanism of action may be also operative. Although the antimalarial potency of naphthoquinones has for long been known to be related to the redox potential of the quinone moiety, for our knowledge this is the first time when a quantitative correlation between these two quantities is given.

Finally, in this study we were able to show that 2- and 2,3-aziridinyl-1,4-naphthquinone antimalarial agents share specific molecular electronic properties related to the ability of some groups in donating or withdrawing electrons of the aromatic ring which affect the GFE (ΔG°) for the redox process. Eqs. 2 and 3 seem to represent very well this correlation and provide a guide to the chemist as to which compounds are worthy of expensive chemical synthesis.

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