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Theoretical evaluation of medicinal properties for some of N-aryl-3-hydroxypyridine-4-ones derivative compounds

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Abstract

Nowadays, the bidentate ligands 3-hydroxypyridin-4-ones (HPOs) as orally active iron chelating agents have been demonstrated to possess potentials for the treatment of some of the human diseases such as iron-overload in thalassaemia patients and malaria. In this research, a series of HPOs with different substitutes and positions were theoretically investigated in order to extract and predict their partition coefficient values (LogP) which were experimentally determined in an aqueous/octanol system. The effective electronic parameters on logP were also investigated. The results show that the type of method, basis set, and the solvent do not basically affect on the logP values. But some parameters such as hydrophobicity, polarizability, and orbital electronic charge density (HOMO and LUMO) are effective on logP values.

Keywords: Hydroxypridinone, partition coefficient, chelating agent, density functional theory

Introduction

3-Hydroxypyridin-4-ones (HPOs) iron chelators have properties which would properly suit the chelation of iron in vivo by the use of oral route. These properties include a high specificity and selectivity for iron (III) and the neutral charge possession in the iron-free and iron-complexed forms, allowing both forms of the chelators to cross biologic membranes. So far, there are several HPO ligands which have been widely investigated for iron chelation, both in iron-overloaded animal models and in thalassaemia patients [1]. A wide range of human studies has

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centered on the simple 1,2-dialkyl derivatives, such as 1,2-dimethyl-3-hydroxypyridin-4-one (Deferipro- ne or L1, Figure 1, marketed by Apotex Inc. Toronto, Canada, as Ferripox ^{TM}) [2].

L1 is an effective compound for removing iron from iron overloaded animals and humen but can also be associated with some disadvantages. One of the major reasons for the limited efficacy of L1 in the clinical applications is that it would rapidly conjugate with glucuronic acid under vivo conditions and, it is worth mentioning that, high doses must be utilized in order to achieve clinically useful levels of iron excretion [3].

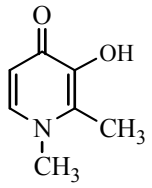


Figure 1. Structure of Deferiprone (L1)

Despite these limitations, this class of the chelators has a considerable potential as orally active iron chelators [4]. Some derivatives, such as N-carboxyethyl derivatives, have also the highest affinity towards Fe(III), Al(III) and Ga(III) ions. The binding affinity of HPOs with these metal ions and their hydrophilic characters decreases with the increase in the size of the alkylic chain [5]. It is interesting that the absolute stabilities of the complexes of Al^{3+} and Ga^{3+} with 1-ethyl-3-hydroxy-2-methyl pyridin-4-one ligand are similar and both are also greater than that of the iron(III) complex [6]. In addition to the potential treatment of iron overload in thalassaemic patients, HPOs would also have other clinical applications centered on iron removal [3,7].

The ability of these compounds to remove aluminum (Al) from Al-loaded rats using microdialysis, especially aluminum mobilization in alzheimer and renal dialysis patients, were studied [8-10].

3-Hydroxypyridin-4-ones containing basic side chains have been investigated for antimalarial activity as orally active iron (III) chelating agents [11]. The antibacterial and antifungal activities of some derivatives of 3-hydroxypyridinones and 3-hydroxypyranones with metal chelating ability have also been investigated [12].

High daily doses of *N*-alkylated HPOs will be required for the treatment of patients who suffer from iron overload, and consequently it is important to establish whether the selected ion chelators have toxic effect on human or not. The presence of o-alkyl functions does not influence the affinity constant in the interaction between

pyridinones and either iron(III) or copper(II). Therefore, the presence of these groups must create steric congestion, whereby the ligand is unable to approach the copper atom at the active site of tyrosinase in a bidentate fashion [13]. In order to investigate further ligands which are able to scavenge iron effectively at low concentrations, other derivatives of this type of compounds namely *N*-aryl-3-hydroxypyridin-4-one derivatives were synthesized [14]. The factor of lipophilicity has a key role in biological action of each drug. In fact, the absorption, distribution, storage and elimination of drugs depend on their lipophilicity. The 1-octanol/water partition coefficient (K_{part}) is a generally accepted physico-chemical parameter for characterization of lipophilicity.

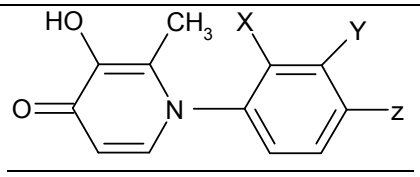
The lipophilic efficiency, logP, of a drug indentifies that how the drug can easily reach its intended target in the body, how strong an effect it will have once it reaches its target, and how long it will remain in the body in an active form. logP is one of the criterion used in medicinal chemistry to assess the druglikeness of a given molecule, and used to calculate, a function of potency and LogP that evaluate the quality of research compounds [15]. Besides, a given compound lipophilic efficiency is defined as the pIC50 (or pEC50) of interest minus the logP of the compound.

The quantitative relationship between chemical structure and biological activity has received considerable attention in the fields of pharmacology and drug development. More recently, quantitative structure-activity relationships (QSARs) [16] have been used for predicting chemical toxicity. It represents an attempt to correlate structural or property descriptors of compounds with activities. These physicochemical descriptors, which include parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods. Activities used in QSAR include chemical measurements and biological assays. QSAR are currently being applied in many disciplines, with many relations to drug design and environmental risk assessment. The objective of this study is to evaluate the role of substituents in *N*-aryl positions of the set of 3-hydroxypyridin-4-ones (Figure 2) on the hydrophobicity in order to predict the liphobilic efficiency of this class of the pharmaceutical drugs and new compounds design with the mentioned potential applications. Two computational softwares including Dragon [17] and

Hyperchem [18] were applied in order to identify their efficiency and abilities in prediction of drug properties of such compounds. Finally, we recognized that there is a relationship between quantum chemical parameters and logP for molecules 1-16.

Computational method

All calculations and geometry optimization for each molecule were obtained by HF and DFT at the level of B3LYP with 6-31G* and 6-31G** basis sets [19]. Computational calculations have been performed both in the gas phase and in the water and octanol phases in Gaussian 98 [20]. The restricted method was used for the systems. The geometry of all molecules under investigation was determined by optimizing all geometrical variables without any symmetry constraints. The harmonic frequencies were computed from analytical derivatives for all species in order to define the minimum-energy structures. The effect of solute-solvent interaction was taken into account via the self-consistent reaction field (SCRF) method [21]. The pharmaceutical descriptors were evaluated from Dragon 5.5 and HyperChem 7.0 software.



NO	X	Y	Z	NO	X	Y	Z
1	H	H	H	9	H	F	H
2	Br	H	H	10	H	H	F
3	H	Br	H	11	OH	H	H
4	H	H	Br	12	H	OH	H
5	Cl	H	H	13	H	H	OH
6	H	Cl	H	14	COOH	H	H
7	H	H	Cl	15	H	COOH	H
8	F	H	H	16	H	H	COOH

Fig 2. Entitled N-arylhydroxypyridinones derivatives

Results and discussion

Some of electronic parameters and descriptors including electronic energy, E_{HOMO}, E_{LUMO}, dipole moment, polarizability, hydrophobicity and logP values for the compounds 1-16 were calculated in the gas, water and octanol phases. The obtained results have been represented in Figures 3 and 4. Some of the obtained data have been collected in Table 1 beside that of the experimental logP values for some of synthesized compounds 1-16. By noting the variational bahaviour of the calculated electronic parameters, it was observed that the substituted Cl as a donor group at the para position of the aryl, compound 7, leads to a high approximately changes in the electronic energy of L1.

Moreover, the trend of the effect of the different substituted groups at different positions of the aryl on the electronic energy in the gas phase is as follows:

para-Cl<<Br<orto- and mata-Cl<COOH≈OH≈F<<H

This trend is like the water and octanol phases except that of para-Cl substitution. The substituted groups lead to low and high effect on the HOMO and LUMO orbitals, respectively, compared to L1. For example, para-Br, compound 4, leads to high decreasing HOMO, and para-OH, compound 13, leads to increases HOMO in the gas phase. All of the substituted groups decrea LUMO. The trend for varying HOMO and LUMO is as follows:

HOMO (in the gas phase): para-Br <<COOH <Cl≈ orto- and mata-Br≈OH<F<H<para-OH

HOMO (in water and octanol phases): COOH<Cl≈Br≈OH<F<H<para-OH

LUMO: COOH<Cl≈Br≈OH<F<H

For the dipole moment, such systematic trend was not observed for the compounds 1-16 respect to L1. This quantity depends on the substitution position of the aryl group. The hydrophobicity, HY, of the L1 would be changed by the substitution of the donor and acceptor groups in the aryle functional group. The substituted Halogen leads to decrease the HY and OH and the substituted COOH leads to increase the HY. Thus, the halogens which act as the acceptor groups cause increasing solubility of the compounds in the water, and the other groups which act as the donor groups decreas the solubility. All of substituted groups on the aryl which in turn cause increasing the polarizability of the L1. It means the deformation of the compounds 2-16 in an electric field, is easier than L1.

The logP values were calculated by two scaling method in Dragon software, Ghose-Crippen logP (alogP) [20] and Moriguchi logP (mlogP) [21], and in HyperChem by B3LYP/6-31G* in the gas phase. The pictorial

description of the values has been represented in Figure 2.

All of the extracted logP values from HyperChem software which were negative mean that all of these compounds must be hydrophobic, and all of the extracted values from Dragon software which were positive show that these compounds must be lipophilic. The computed hydrophobicity values adapt with logP values for the lipophilic compounds including the halogen substituent, and for the hydrophobic compounds including OH and COOH groups.

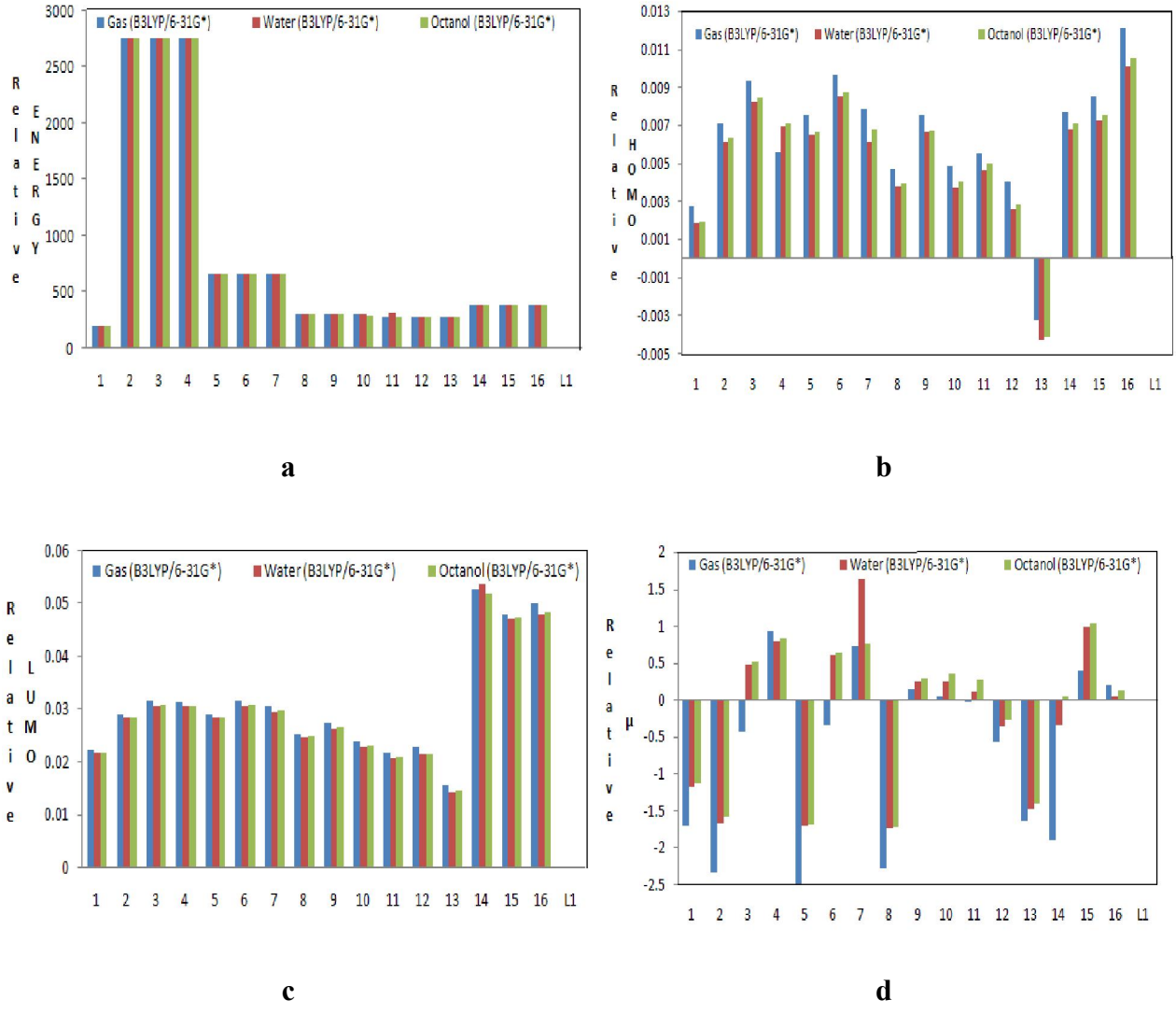


Figure 3. Electronic parameters and descriptors including (a) relative electronic energy, (b) relative HOMO, (c) relative LUMO, and (d) relative dipole moment respect to L1, for the compounds 1-16 and L1 calculated by B3LYP/6-31G* in the gas, water and octanol phases

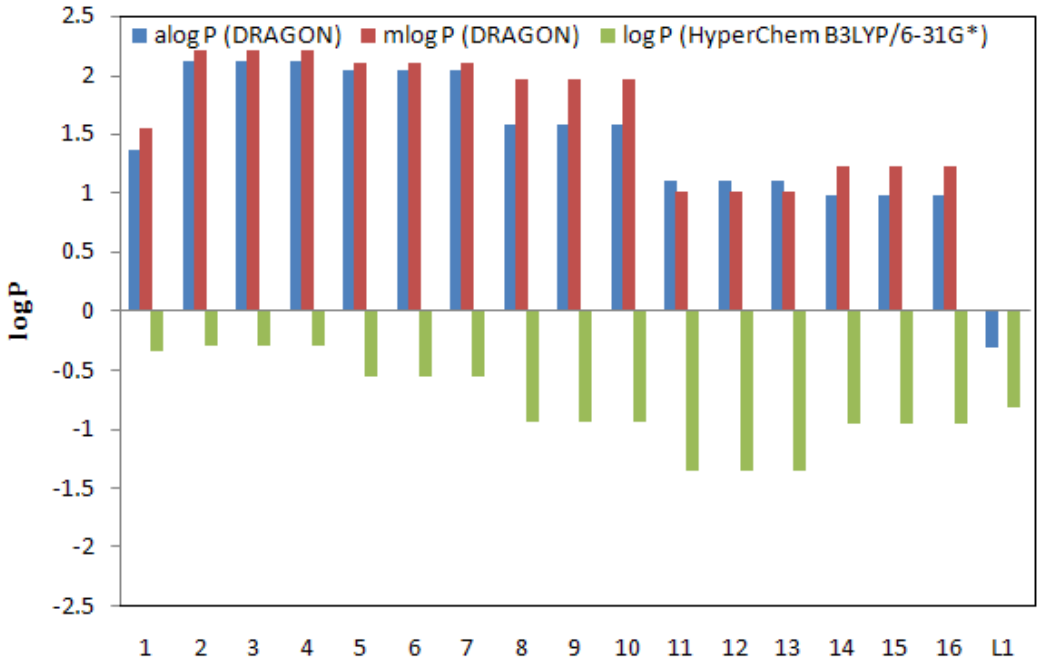


Figure 4. LogP values for the compounds 1-16 and L1 evaluated from HyperChem and DRAGON soft-wares including Ghose-Crippen logP (alogP) [22] and Moriguchi logP (mlogP) [23], in the gas phase

The main objective of this research is to find a relationship between quantum chemical parameters and logP for molecules 1-16. Since the studied compounds are designed on the base of the synthesized compounds such as L1, 1, 6, 12, 15 and 16, we should operate directly to predict logP by finding an equation to fit the experimental [24] and theoretical data for the other molecules close to the structure of the designed molecules. The molecular structures were optimized by DFT at the level of B3LYP/6-31G* and the results of obtained parameters such as E_{HOMO}, E_{LUMO}, energy gap, dipole moment and polarizability have been listed in Table 1. The multilinear regression equation which can be derived from the linear model, approximates logP:

$$LogP=constant+a*E_{HOMO}+b*E_{LUMO}+c*Gap+d*\mu+e*\alpha+f*S+g*M$$

Multiple regressions were performed on logP of the mentioned six compounds derived of L1 by using experimental logP data in Table 1. This equation is as follows with R^2=0.9885 and S=0.1208,

$$\text{Log P}=-10.2676(\pm1.3620)+1.892983(\pm0.2617)*\text{Gap}-0.00476(\pm0.0011)*\alpha+0.0125(\pm0.0131)*S$$

Table 1. Some of gas phase calculated electronic parameters and descriptors including molecular weight (M), E_{HF}, E_{HOMO}, E_{LUMO} (in Hartree), gap energy, dipole moment, polarizability, surface area (S), logP values at B3LYP/6-31G* level of theory compared with experimental logP [24], and calculated logP from the analysis regression by QSAR method for the compounds 1-16 and L1

No	M	E_{HF}	E_{HOMO}	E_{LUMO}	Gap (ev)	μ (Debye)	α (a.u.)	S ($^{O}A^{2}$)	logP	$logP_{exp}$	$logP_{reg}$
1	201	-669.04	-0.2000	-0.0425	4.28	7.69	21.58	261.2	-0.34	1.008	1.016
2	281	-3240.12	-0.2044	-0.0493	4.22	8.31	165.20	311.5	-0.29		0.841
3	281	-3240.15	-0.2066	-0.0517	4.21	6.41	166.58	304	-0.29		0.731
4	281	-3240.14	-0.2829	-0.0515	6.29	5.04	170.60	282.2	-0.29		4.376
5	235.5	-1128.61	-0.2048	-0.0492	4.23	8.48	157.97	324.1	-0.56		1.060
6	235.5	-1128.64	-0.2069	-0.0518	4.22	6.32	158.77	301.6	-0.56	0.748	0.747
7	235.5	-1128.64	-0.2051	-0.0508	4.20	5.25	192.91	296.7	-0.56		0.482
8	219	-768.26	-0.2020	-0.0455	4.26	8.25	146.72	328	-0.94		1.208
9	219	-768.28	-0.2048	-0.0477	4.27	5.83	146.03	272.7	-0.94		0.549
10	219	-768.27	-0.2021	-0.0442	4.29	5.93	145.77	284.6	-0.94		0.740
11	217	-744.23	-0.2028	-0.0420	4.37	5.99	149.23	288.2	-1.36		0.918
12	217	-744.26	-0.2013	-0.0431	4.30	6.55	150.07	266.9	-1.36	0.544	0.513
13	217	-744.26	-0.1940	-0.0359	4.30	7.61	151.34	300.3	-1.36		0.921
14	245	-857.57	-0.2050	-0.0730	3.59	7.88	168.47	300.3	-0.95		-0.504
15	245	-857.61	-0.2058	-0.0682	3.74	5.58	164.49	284.6	-0.95	-0.284	-0.394
16	245	-857.61	-0.2094	-0.0702	3.79	5.78	174.72	294.2	-0.95	-0.366	-0.240
L1	139	-477.36	-0.1973	-0.0201	4.82	5.98	86.21	63.02	-0.81	-0.770	-0.763

This equation shows that the dominant molecular parameters for the partition coefficient are the gap energy, polarizabilty, and surface area. There is a clear relationship between the increase in logP by increasing the energy gap and the size of the molecule and

decreasing the polarizabilty. The P-values for the energy gap, polarizability and surface area parameters are 0.019, 0.050 and 0.007, respectively. Figure 5 shows the correlation between experimental and calculated logP obtained from above equation for six substituted L1 compounds. By using this relationship and the data in Table 1, logP of the titled compounds (1-16) were calculated and listed in Table 1.

Conclusion

The LogP values for these compounds were obtained with two program softwares, DRAGON 5.5 and HyperChem 7. All of the extracted logP values from hyperchem software were negative which means that all of these compounds must be hydrophobic, besides, all of these extracted values from dragon software were positive which means that these compounds must be lipophilic. With attention to hydrophobicity values computed from dragon sofware, we showed that for evaluation of the logP values for the lipophilic compounds including the halogen substituent, the hyperchem software is suitable, and for evaluation of logP values for the hydrophobic-compounds including OH and COOH groups, the dragon software is suitable.

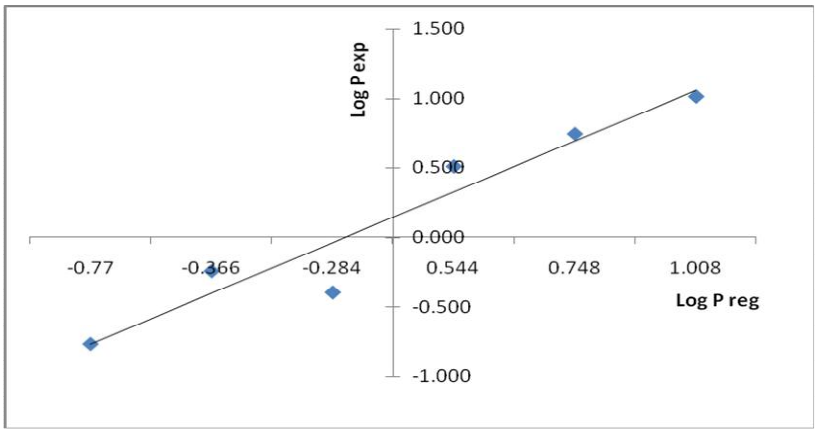


Fig 5. The correlation between experimental and calculated logP obtained from evaluated multilinear regression equation for L1 and 1, 6, 12, 14 and 15 substituted L1 compounds

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