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HYDROGEN BOND DESCRIPTORS FOR USE IN DRUG DESIGN: HYDROXAMIC ACIDS

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ABSTRACT

Hydrogen bond is important parameters in chemistry, biology and material science. The hydrogen bond is most important kind of molecular interaction, which influences the drug solubility, bodily transport and docking to active sites. The hydroxamic acid functionality –NOH.C=O, is the outstanding chemical feature of these molecules and is responsible for their biological and medicinal properties. The partition coefficient of five hydroxamic acids have been measured in octanol-water $P_{(O/W)}$ and chloroform-water, $P_{(Cl/W)}$ systems using shake-flask method. The log $P_{(O/W)}$ and log $P_{(Cl/W)}$ are found in the range 0.3916 to 0.7224 and 0.1284 to 0.5460, respectively. The hydrogen bond descriptors are also computed from the lipophilicity data. The values obtained for hydrogen bond donor acidity are in the range 0.6732 to 1.0189 and hydrogen bond acceptor basicity is in the range 2.4054 to 3.0718. Based on these data determined, hydroxamic acids prove to be drug like molecules as proposed by Lipinski et al in the rule of five.

Keywords: *Hydroxamic acid, hydrogen bond descriptors, log $P_{(O/W)}$, log $P_{(Cl/W)}$.*

INTRODUCTION

Lipophilicity is a fundamental physicochemical property in drug discovery [1-3] and is usually expressed by the logarithm of the 1-octanol/water partition coefficient [4] log $P_{(O/W)}$. Lipophilicity have found wide application in quantitative structure-activity relationships (QSARs), where they have proved useful as conventionally used hydrophobic parameters for the analysis of the biological activity of solute and the design of new active molecules [5]. Hydrogen bond is known to play a major role in many properties affecting drug design. Hydroxamic acids constitute an important class of organic bioligand [6], with the hydroxamic acid moiety, -NOH.C=O, a constituted of antibiotics, antifungal agents, food additives, drug, tumor inhibitors and growth factors [7-9].

The above facts motivated to take the present investigation in which five N-aryl hydroxamic acids with general formula R_1-CO-NR_1-OH (where R_1 and R_2 are phenyl as substituted phenyl groups) to determine partition coefficient of molecule in octanol, chloroform/water systems further hydrogen bond donor and hydrogen bond acceptor strengths of hydroxamic acids are obtained from experimental data.

EXPERIMENTAL SECTION

Synthesis of hydroxamic acids

Hydroxamic acids were synthesized in the laboratory following the procedure reported in the literature[10]. These were purified by recrystallization from benzene thrice and dried in vacuum over phosphorous pentoxide. The purity was ascertained by comparing M.P. and I.R. spectra with the literature value[11]. The experimental analysis was determined with a Vario-EL analysis apparatus.

Measurement of partition coefficient

Partition coefficient of five hydroxamic acids was determined in two solvent systems by shake-flask method[12] using 1-Octanol/water system and chloroform/water system. Before the partitioning of hydroxamic acids, 1-octanol/chloroform and water were saturated with each other. The desired hydroxamic acid (5mg) was dissolved in octanol/chloroform was shaken with water of ratio 1:2 v/v on a mechanical shaker 24 hrs. After separation the absorbance of the 1-octanol/chloroform phase was measured using Elico UV Visible spectrophotometer at λ_{max}. The values of ($P_{org/w}$) is calculated from the following equation,[13],

$$\mathbf{P_{(Organic\ solvent/water)} = A_f / A_i - A_f \times V_{org}/V_W} \quad [1]$$

Where,

A_i = Absorbance of hydroxamic acid in organic phase before partitioning,

A_f = Absorbance of hydroxamic acid in organic phase after partitioning,

V_{org} = Volume of organic phase,

V_w = Volume of water phase.

RESULTS AND DISCUSSION

Lipophilicity (log P) is representing by logarithm of partition coefficient in octanol/chloroform-water systems. The value of partition coefficient and logarithm of partition coefficient in octanol/chloroform-water system are listed in Table 1.

HYDROXAMIC ACIDS	LIPOPHILICITY		
	log $P_{(O/W)}$	**log $P_{(Cl/W)}$**	**log $P_{(O/Cl)}$**
N-phenyl-2-bromobenzo-	0.7224	0.1284	0.5941
N-phenyl-2-methylbenzo-	0.5726	0.5014	0.0712
N-phenyl-4-methylbenzo-	0.7031	0.5460	0.1570
N-phenyl-2-nitrobenzo-	0.4784	0.0629	0.4156
N-phenyl-3-nitrobenzo-	0.3916	0.3460	0.0455

Table I. Lipophilicity of hydroxamic acids

Hydrogen bond descriptors

The most important characteristic feature of hydroxamic personality are presence of hydrogen bond acceptor and donor sites. It consists of only one HBD site that is hydrogen of hydroxyl group, where as nitrogen, hydroxyl oxygen and carbonyl-oxygen are three HBA sites. The hydrogen bond descriptors are represented by the effective hydrogen bond donor acidity εα and acceptor basicity, εβ.

Hydrogen bond donor acidity of hydroxamic acids

The HBD strength of hydroxamic acids calculated by following the expression as[18],

$$\log P_{(O/Cl)} = -1.0(0.01V_x) + 3.20\varepsilon\alpha - 0.03 \quad [2]$$

$$\log P_{(O/Cl)} = \log P_{(O/W)} - \log P_{(Cl/W)} \quad [3]$$

where, $\log P_{(O/Cl)}$ is the 1-octanol-chloroform partition coefficient, log $P_{(O/W)}$ is the octanol-water partition coefficient, log $P_{(Cl/W)}$ is the chloroform-water partition coefficient and V_X is the molar volume. The values of log $P_{(O/W)}$ of five hydroxamic acids are reported in Table I.

Hydrogen bond acceptor basicity of hydroxamic acids

The hydrogen bond acceptor basicity of hydroxamic acids will be obtained from the equation [19],

$$\log P_{(O/W)} = 3.67(0.01V_x) - 0.040(0.1\mu^2) - 0.0\varepsilon\alpha - 3.00\varepsilon\beta + 0.24 \quad [5]$$

Where, μ is molecular dipole moment is obtained by linear co-relation between (n^2-1/n^2+2) vs. 1/T, following the Debye equation[20],

$$\frac{n^2 - 1}{n^2 + 2} = \frac{4\pi N_0 \rho P_0}{M} + \frac{4\pi N_0 \rho \mu^2}{3kTM} \quad [6]$$

Where, No is Avogadro No. (6.023 X 10^{23} gm atom), K is Boltzmann constant (1.38 X 10^{-16}erg/k/mole) and T is absolute temperature (303.15K). The values of εα, εβ and μ are given in Table II.

HYDROXAMIC ACIDS	HYDROGEN BOND DESCRIPTORS				
	α	**β**	**π_x**	**μ X 10^{-24}**	**Vx**
N-phenyl-2-bromobenzo-	1.0189	3.0653	-0.4039	0.7690	264.6959
N-phenyl-2-methylbenzo-	0.6732	2.4054	-0.5537	1.0198	207.0318
N-phenyl-4-methylbenzo-	0.7009	3.0718	-0.4232	0.7695	206.6203
N-phenyl-2-nitrobenzo-	0.8803	2.8228	-0.6479	0.9138	238.3391
N-phenyl-3-nitrobenzo-	0.7162	2.6618	-0.7347	0.9363	221.9693

Table II. Hydrogen bond parameters of hydroxamic acids.

CONCLUSION

The molecular weight of hydroxamic acids, MW, I (291.09), II (227.06), III (227.06), IV (258) and V (258) and HBA sites = 3 and HBA sites = 1 and are log P ≤ 5. Based on the data obtained in present investigation proved that the hydroxamic acids are drug like molecule follows "Lipinski rule of 5". The rule states that most drug like molecule may have log P ≤ 5, MW ≤ 500, HBA sites ≤ 10 and HBD sites ≤ 5. Thus this drug like molecules can be used in the design of lead generation libraries.

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