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3D-QSPR STUDY ON HYDROGEN BOND STRENGTH OF HYDROXAMIC ACIDS: KEY ROLE OF STERIC AND ELECTROSTATIC FACTORS USING THE kNN-MFAMETHOD

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ABSTRACT

Hydrogen bonding is critical for drug efficacy, impacting factors like absorption, distribution, metabolism, and excretion (ADME) and receptor binding. Hydroxamic acids, low-toxicity, and therapeutically diverse compounds were tested for lipophilicity and hydrogen bond strength. LogP (2.5120-2.8383), hydrogen bond donor (HBD) strength (1.880-3.740), and acceptor (HBA) strength (0.8350-1.271) were calculated. For the prediction of HBD and HBA strengths, we employed k-nearest neighbor molecular field analysis (kNN-MFA), and the best predictions for HBD and HBA were obtained from SWkNN-MFA models. The 3D-QSPR models revealed that hydrogen bond strength was largely influenced by steric and electrostatic conditions. These data are valuable for engineering hydroxamic acid derivatives with improved hydrogen bonding interactions and enhanced therapeutic potential.

Keywords PBHA**,** Hydroxamic Acids, Liphophilicity, Hydrogen Bond Strength, 3DQSPR, kNN-MFA

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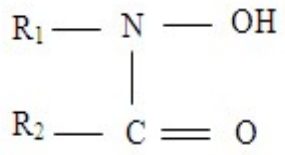
INTRODUCTION

These hydrogen bonds are the basis of many biological and chemical systems, controlling molecular structure, function, and behaviour. These weak interactions in biochemistry and pharmacology are what enable intermolecular recognition and catalyse key molecules, such as between a drug and its biological target.[1-3] The modeling and decipherment of hydrogen bond energies - which are necessary for the design and synthesis of drugs - require accurate prediction and knowledge of their energies.[4-8] The effect of hydrogen bonds on the chemistry of drugs is enormous: they affect drug activity, selectivity, permeability, and solubility.[9-14] So the search for and optimisation of hydrogen bonding interactions is one of the central aims of drug design to produce safe and effective drugs.[15,16] Hydroxamic acids, I are a class of weak organic acids widely distributed in plant tissues, bacterial and fungal metabolites, and complex molecules. Owing to their significance in numerous applications within modern society, hydroxamic acids are among the most extensively studied compounds. Since Lossen's discovery over a century ago, a vast body of research has focused on the design, preparation, structure-activity relationships (SAR), utilization, and potential applications of hydroxamic acids.[17] These compounds exhibit inhibitory activity against a variety of enzymes, including ureases[18-20], peroxidases[21-23], and matrix metalloproteinases.[24-28]



I

Some hydroxamic acids are currently accepted therapeutic agents, such as desferrioxamine B (II) for iron overload treatment, ibupraxam (III) for anti-inflammatory and analgesic purposes, and adrafinal (IV) as an α-adrenergic agonist and antidepressant.

Numerous Quantitative structure-activity relationships (QSAR) studies have highlighted the crucial role of hydrogen bonding interactions in modeling specific target activities.[29] Hydrogen bonding parameters employed in QSAR can be either experimentally derived or computationally calculated.

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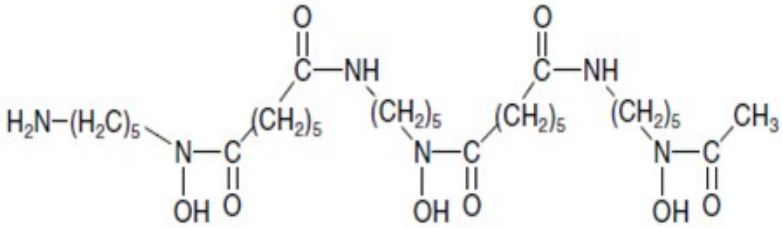

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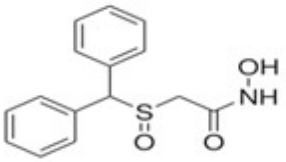

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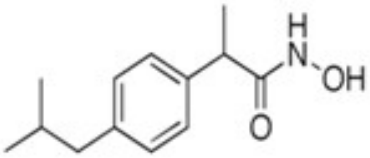

IV

QSPR has proven to be a valuable computational tool for elucidating the structure-property relationships of molecules.[30] Hydrogen bonds play a crucial role in molecular recognition within biological systems, significantly influencing drug-target interactions. While extensive research has explored hydrogen bonding in various contexts, a critical gap remains in understanding the specific hydrogen bonding properties of hydroxamic acids, a class of compounds with diverse biological activities. This study aims to bridge this gap by determining the lipophilicity of five hydroxamic acid derivatives using the shake flask method, evaluating their hydrogen bond strength within the context of drug design, and employing the kNN-MFA approach to generate 3D-QSPR(Quantitative structure-property relationships) models that predict the hydrogen bond strengths of these hydroxamic acids. This research will provide valuable insights into the structure-activity relationships of hydroxamic acids, aiding in the design and optimization of drug candidates with improved potency and selectivity.

EXPERIMENTAL

Material

1-Octanol, Chloroform, and Ammonium metavanadate were purchased from Sigma-Aldrich (USA). Concentrated Hydrochloric acid was purchased from Merck, India.

General Procedure

Synthesis of Hydroxamic Acids

Hydroxamic acids were synthesized in the laboratory following the procedure reported in the literature.[31] These were purified by recrystallization from benzene three times and dried in a vacuum over phosphorus pentoxide. Their purity was confirmed by comparison with literature values.[32]

Lipophilicity by Shake Flask Method

The 1-Octanol and Chloroform used were saturated with double-distilled water. The hydroxamic acids (10-15 mg) were dissolved in saturated 1-Octanol/Chloroform and shaken with 1-Octanol/water and Chloroform/water (1:2 v/v) on a mechanical shaker for 24 hours. Following the shaking, the samples were allowed to stand in a stirred water bath for at least 2-4 hours. Subsequently, the phases were separated and examined using a UV-Vis spectrophotometer (model UV-1900i, Shimadzu Corporation, Japan) following the vanadium(V) method.[33]

Data Set
A total of 30 hydroxamic acids were selected, 24 from the literature[34-36] and 6 from the current studies. The hydrogen bond donor and hydrogen bond acceptor strength were listed in Table-5.

Molecular Modeling
3D-QSPR studies were performed using Vlife MDS 3.0 software. The compounds were built in the software. Partial atomic charges, required for the calculation of electrostatic interactions, were computed using the Gasteiger-Marsili charge type and a dielectric constant value of 1.0.

Alignment Rules
In the present study, molecules were superimposed using template alignment. Two templates were used: (a) the hydroxamic acid functional group (Template I, Fig.-1a); and (b) the hydroxamic acid functional group and phenyl ring atoms (Template II, Fig.-1b).

(a) (b)

Fig.-1: The Template-Based Alignment was used for Superimposition

MFA Analysis
A common rectangular grid was generated around each molecule. Steric and electrostatic interaction energies were computed at each lattice point using a methyl probe with a charge of +1. These interaction energy values were used to generate relationships and, as descriptors, to determine the proximity between molecules. In the following discussion, the term "descriptor" refers to these field values at the lattice points.

k-Nearest Neighbor (kNN) Method
The kNN methodology employs a simple distance-learning approach, classifying an unknown member based on the majority class among its k-nearest neighbors in the training set. Proximity is determined using an appropriate distance metric (e.g., a molecular similarity measure calculated from field interactions of the molecular structures). Variables and optimal k values were selected using various methods, including kNN-MFA with stepwise (SW) variable selection, kNN-MFA with simulated annealing(SA), and kNN-MFA with a genetic algorithm(GA), as described by Subhash *et al.*[37]

RESULTS AND DISCUSSION

Partition Coefficients, P(O/W)
The partition coefficient P(O/W) of the parent compound, PBHA, and nine hydroxamic acid derivatives between the organic phase (1-octanol/chloroform) and water were determined using eqn.-1.[38]

$$P\ (O/W) = Af\ /Ai - Af \times Vo/Vw \qquad (1)$$

Where, Ai = Absorbance of hydroxamic acids in the organic (1-octanol/chloroform) phase before partitioning.
Af = Absorbance of hydroxamic acids in the organic (1-octanol/chloroform) phase after partitioning.
Vo= Volume of organic (1-octanol/chloroform) phase.
Vw = Volume of water phase.
P (O/W) = Partition coefficient between organic (1-octanol/chloroform) and water
The lipophilicities of hydroxamic acids are given in Table-1.

Hydrophobic Substituent, π_X

Hydrophobic constituent constant, π_X, for the hydroxamic acid derivatives was calculated using eqn.- 2.[39]

$$\pi_X = \log Px - \log P_H \quad (2)$$

Where,

π_X is the logarithm of partition coefficient of the function X.

P_X is for N-phenylbenzohydroxamic acid (PBHA),

P_H is the hydroxamic acid derivative.

The data on the hydrophobic constituent constant is listed in Table-1.

Hydrogen Bond Donor Strength, εα

The hydrogen bond donor strength of the hydroxamic acids was calculated using eqn.-3, as proposed by Taft and Leo.[40]

$$\log P(O/Cl) = -1.0(0.01Vx) + 3.20\ \varepsilon\alpha - 0.03 \quad (3)$$

Where,

Vx = solute's molar volume

ε = total of the multifunctional groups' effective interactions.

α = HBD's strength

$$\log P(Cl/W) = \log P(O/W) - \log P(Cl/W)$$

Hydrogen Bond Acceptor Strength, εβ

The hydrogen bond acceptors' strength of the hydroxamic acids was calculated using eqn.-4, as proposed by Leo and Hoekman.[41]

$$\log P(O/W) = 3.67(0.01Vx) - 0.040(0.1\mu^2) - 0.0\varepsilon\alpha - 3.00\varepsilon\beta + 0.24 \quad (4)$$

Where,

Vx=Molar volume of hydroxamic acids.

β=HBA strength/capacity.

Molecular volume and dipole moment were calculated from Chemoffice, Chambridgesoft, UK, and values obtained were reported in Table-2. The observed data on hydrogen bond strength are listed in Table-5.

Table-1: Lipophilicities of Hydroxamic Acids

S. No.	Hydroxamic Acid	log P(O/W)	logP(Cl/W)	logP(O/Cl)
1.	N-phenylbenzo-	2.5120	2.4700	0.0420
2.	N-phenylpalmito-	2.7569	2.4556	0.3013
3.	N-phenylenantho-	2.7869	2.3885	0.3984
4.	N-p-chlorophenylcarpito-	2.6787	2.3771	0.3016
5.	N-p-chlorophenylundecane-	2.5736	2.3874	0.1862
6.	N-m-chlorotetrabutylbenzo-	2.8383	2.5366	0.3017

Table-2: Hydrophobic Substituent, Molecular Volume (MV in 10^2 cm^3/mol) and Dipole Moment (μ in debye) of Hydroxamic Acids

S.No.	Hydroxamic Acid	π_X	MV	μ
1.	N-phenylbenzo-	-	195.24	4.5660
2.	N-phenylpalmito-	0.3521	375.62	3.4620
3.	N-phenylenantho-	0.3821	224.40	3.4460
4.	N-p-chlorophenylcarpito-	0.2738	274.80	3.7730
5.	N-p-chlorophenylundecane-	0.1688	291.61	4.5500
6.	N-m-chlorotetrabutylbenzo-	0.4339	274.96	5.8430

3D-QSPR Approach

3DQSPR-kNNMFA Model for Hydrogen Bond Strength

Steric and electrostatic descriptors for 30 hydroxamic acids were calculated using the Gasteiger-Marsili charge method and a dielectric constant of 1.0 within the 3D-QSAR model of Vlife MDS 3.0 software. Descriptors exhibiting no variation were excluded. A sphere exclusion algorithm was used to divide the

dataset into a training set (n=24) and a test set (n=6). The 3D-QSPR kNN-MFA model generated using the hydroxamic acid functional group (Template I; Figure 1a) demonstrated good internal predictivity (q^2 = 0.5624) and good external predictivity (pred_r^2 = 0.7305). The 3D-QSPR kNN-MFA model generated using the hydroxamic acid functional group and phenyl ring atoms (Template II; Fig.-1b) showed internal predictivity (q^2 = 0.7700) and external predictivity (pred_r^2 = 0.4927).

3DQSPR-kNNMFA Model for Hydrogen Bond Donor Strength of Hydroxamic Acids

The kNN-MFA models generated using the hydroxamic acid functional group as a template were selected for SAR analysis and further investigation. The SWkNN-MFA model, developed using one steric descriptor and its 2k-nearest neighbors (k=2), exhibited internal validation (q^2 = 0.5624) and external validation (pred_r^2 = 0.7305). The SAkNN-MFA model, incorporating one steric and one electrostatic field descriptor with its 3 k-nearest neighbors (k=3), showed poor internal predictivity (q^2 = 0.4987) and poor external predictivity (pred_r^2 = 0.2484). The GAkNN-MFA model, generated using three steric and one electrostatic field descriptor with its 5 k-nearest neighbors (k=5), also displayed poor internal predictivity (q^2 = 0.1932) and poor external predictivity (pred_r^2 = -0.2685). A comparison of the 3D-QSPR kNN-MFA models generated for hydrogen bond donor strength of the hydroxamic acids is presented in Table-3.

Table-3: Comparison of the kNNMFA Models Generated for Hydrogen Bond Donor Strength of Hydroxamic Acids

Parameter/molecule	SWkNN-MFA	SAkNN-MFA	GAkNN-MFA
q^2	0.5624	0.4987	0.1932
Pred_r^2	0.7305	0.2484	-0.2685
k	2	3	5
Descriptors	S_1565	E_367, S_1185	E_1287, S_1490,S_120,S_724

A plot of the kNN-MFA model illustrates the relative positions and ranges of the important electrostatic and steric fields, indicating their favorable or unfavorable effects on activity. Specifically, a negative electrostatic field (higher electronegativity) is associated with increased activity, while a positive electrostatic field (lower electronegativity) is associated with decreased activity. Similarly, a negative steric field (greater steric bulk) correlates with decreased activity, and a positive steric field (less steric bulk) correlates with increased activity.

The points contributing to the SWkNN-MFA model (Fig.-2) were used to explain the SAR of the molecules in this study. For the hydroxamic acid analogs, one point, representing steric interactions, was identified as essential for the SWkNN-MFA model. The steric field value at point S_1565 ranged from -0.001 to -0.001. This negative range suggests that greater steric bulk at this location is unfavorable for increasing hydrogen bond donor strength.

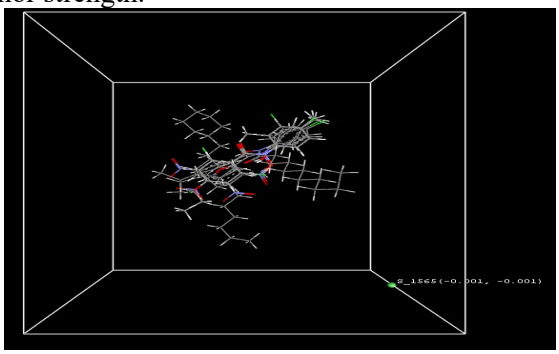

Fig.-2: Distribution of Chosen Points in SWkNN-MFA for the Hydroxamic Acid Analogues with Test Set Molecules For Hydrogen Bond Donor Strength

3DQSPR-kNNMFA for Hydrogen Bond Acceptor Strength of Hydroxamic Acids

The SWkNN-MFA model, developed using one steric and one electrostatic field descriptor with its 2k-nearest neighbors (k=2), demonstrated internal validation (q^2 = 0.6533) and external validation (pred_r^2 = 0.6632). The SAkNN-MFA model, incorporating one steric field descriptor with its 2k-nearest neighbors (k=2), showed poor internal predictivity (q^2 = 0.2458) and poor external predictivity (pred_r^2 = 0.4147).

The GAkNN-MFA model, generated using two steric and two electrostatic field descriptors with its 4k-nearest neighbors (k=4), also displayed poor internal predictivity (q^2 = 0.3452), although it showed reasonable external predictivity (pred_r^2 = 0.6288). A comparison of the 3D-QSPR kNN-MFA models generated for hydrogen bond acceptor strength of the hydroxamic acids is presented in Table-4.

Table-4: Comparison of the kNNMFA Models Generated for Hydrogen Bond Acceptor Strength of Hydroxamic Acids

Parameter/molecule	SWkNN-MFA	SAkNN-MFA	GAkNN-MFA
q^2	0.6533	0.2458	0.3452
Pred_r^2	0.6632	0.4147	0.6288
k	2	2	4
Descriptors	S_84, E_1496	S_521	S_733, S_1586, E_761, E_868

The points contributing to the SWkNN-MFA model (Fig.-3) were used to explain the SAR for hydrogen bond acceptor strength. For the hydroxamic acid analogs, two points were identified as essential for the SWkNN-MFA model: one contributing through steric interactions and the other through electrostatic interactions. The steric field value at point S_84 ranged from -0.0005 to -0.0004. This negative range suggests that greater steric bulk at this location is unfavorable for hydrogen bond acceptor strength. The electrostatic field value at point E_1496 ranged from -0.0512 to -0.0444. This negative range indicates that a more negative electrostatic potential is favorable for increased activity.

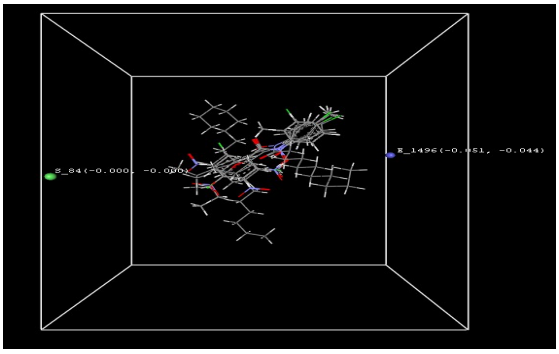

Fig.-3: Distribution of Chosen Points in SWkNN-MFA for the Hydroxamic Acid Analogues with Test Set Molecules for Hydrogen Bond Acceptor Strength

Table-5: Hydrogen Bond Strength of Hydroxamic Acids

S. No.	Hydroxamic Acid	HBA strength, εα			HBA strength, εβ		
		Observed	Calculated	Observed-Calculated	Observed	Calculated	Observed-Calculated
1	N-phenylbenzo-	1.3500	0.6635	0.6865	0.5600	2.7595	-2.1995
2	N-phenylpalmito-	3.7400	1.0740	2.6660	1.2710	1.6197	-0.3487
3	N-phenylenantho-	1.8800	0.7775	1.1025	0.8350	2.7645	-1.9295
4	N-p-chlorophenylcarpito-	2.5300	0.8590	1.6710	0.9620	2.1750	-1.2130
5	N-p-chlorophenyl undecane-	2.7620	0.9191	1.8429	1.0040	2.1950	-1.1910
6	N-m-chlorotetrabutylbenzo-	2.4520	0.9188	1.5332	0.9630	2.7595	-1.7965
7	N-phenylcinnamo-	2.0300	1.4905	0.5395	0.7800	2.7595	-1.9795
8	N-phenyl-2-furo-	1.5330	1.2617	0.2713	0.6330	2.4450	-1.8120
9	N-p-tolyl-2-furo	1.2400	1.5205	-0.2805	0.6400	1.3100	-0.6700
10	N-phenyl-p-chlorobenzo-	1.7000	0.6000	1.1000	0.6700	1.4565	-0.7865
11	N-phenyl-p-methoxybenzo-	1.9900	0.6150	1.3750	0.7600	1.8700	-1.1100
12	N-phenyl-p-nitrobenzo-	2.3600	0.8840	1.4760	0.8500	2.3175	-1.4675
13	N-phenyl-2-chlorobenzo-	2.4000	0.8841	1.5159	1.5600	2.1325	-0.5725
14	N-phenyl-4-ethoxybenzo-	2.5300	0.7890	1.7410	1.7200	2.1250	-0.4050
15	N-phenyl-2,4-dichlorobenzo-	2.3600	0.7470	1.6130	1.0480	1.9960	-0.9480
16	N –o-tolylbenzo-	1.6900	0.9440	0.7460	0.6600	2.2410	-1.5810

17	N-o-tolyl-p-methylbenzo-	1.9760	1.2115	0.7645	0.6150	2.7639	-2.1489
18	N-o-tolyl-o-nitrobenzo-	2.3400	0.6950	1.6450	0.6170	2.2800	-1.6630
19	N-o-tolyl-p-nitrobenzo-	2.2600	0.5600	1.7000	0.6360	2.1750	-1.5390
20	N-o-tolyl-p-chlorobenzo-	2.5500	0.8050	1.7450	1.6700	1.8200	-0.1500
21	N-o-tolyl-p-ethoxybenzo-	2.6900	1.2935	1.3965	1.7100	1.7761	-0.0661
22	N-p-tolylbenzo-	1.8500	0.9190	0.9310	0.7200	1.9350	-1.2150
23	N-p-tolyl-o-methylbenzo-	1.9290	0.6000	1.3290	0.6240	1.7050	-1.0810
24	N-p-tolyl-m,m-dinitrobenzo-	2.8290	0.8565	1.9725	0.7100	2.2060	-1.4960
25	N-p-tolyl-p-ethoxybenzo-	2.7000	0.6000	2.1000	1.7700	2.1233	-0.3533
26	N-p-tolyl-o-chlorobenzo-	2.1420	1.0055	1.1365	0.8630	2.0277	-1.1647
27	N-p-tolyl-o-nitrobenzo-	2.2700	1.7400	0.5300	0.8770	2.7645	-1.8875
28	N-p-chlorophenyl-p-methoxybenzo-	2.2750	0.8570	1.4180	1.0780	1.5400	-0.4620
29	N-p-chlorophenylbenzo-	1.3800	0.5965	0.7835	0.5600	1.7745	-1.2145
30	N-m-chlorophenylbenzo-	1.9400	0.9640	0.9760	0.6400	2.6950	-2.0550

A test set for hydrogen bond donors are 7,14,16,19,20, and 23.
B test for hydrogen bond acceptors are 1,14,16,19,20, and 23.

CONCLUSION

The hydrogen bond acceptor strengths of N-phenylbenzohydroxamic acid and its five analogs ranged from 0.560 to 1.644, while the hydrogen bond donor strengths ranged from 1.352 to 5.080. A three-dimensional quantitative structure-property relationship (3D-QSPR) model for the hydrogen bond strength of hydroxamic acids was developed based on the k-nearest neighbor method. Temple-based alignment using the hydroxamic acid functional group yielded better results. Statistically, the SWkNN-MFA model performed better than the SAkNN-MFA and GAkNN-MFA models for evaluating the hydrogen bond donor strength of novel hydroxamic acid analogs. The SWkNN-MFA model performed better than the SAkNN-MFA and GAkNN-MFA models for predicting the hydrogen bond acceptor strength of novel hydroxamic acid molecules. The plot of the SWkNN-MFA model for hydrogen bond strength shows that the negative ranges of steric and electrostatic potential reveal that bulky and more electronegative substituents at the respective sites are important for designing new hydroxamic acids with increased hydrogen bond strength.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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