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# 3DQSAR Approach Towards the Hydroxamic Acid Analogues as Matrix Metalloproteinase Inhibitors: A Key Role of Steric and Electrostatic Factors Using kNN MFA Method

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**ABSTRACT:**
Matrix metalloproteinase-1 (MMP-1) plays a crucial role in cancer invasion and metastasis through extracellular matrix (ECM) degradation. Hydroxamic acids, known for their strong zinc-chelating ability, have emerged as potent MMP inhibitors with promising anticancer potential. However, optimizing their activity and selectivity remains a significant challenge.To address this, a three-dimensional quantitative structure-activity relationship (3D-QSAR) model was developed. This model was generated using stepwise variable selection k-nearest neighbor molecular field analysis (SW-kNNMFA), demonstrating robust internal ($q^2 = 0.7211$) and external ($pred\_r^2 = 0.6451$) validation.
The field plot derived from the developed SW-kNNMFA model indicates regions of positive electrostatic potential and positive steric potential.This suggests that, for the design of new, more active hydroxamic acid inhibitors of MMP-1, substituent groups should be less electronegative (favoring the positive electrostatic potential) and more bulky (favoring the positive steric potential) at their respective binding sites.

**KEY WORDS:** Hydroxamic Acids, MMP1, 3DQSARand kNN-MFA

## INTRODUCTION

Cancer is a serious and growing worldwide public health problem. It is characterized by uncontrolled cell proliferation, local invasion, and metastasis to other organs[1,2]. Despite considerable progress in the development of surgery, radiotherapy, and chemotherapy, the emergence of therapeutic resistance and tumor progression is still a significant limitation for patient outcome, highlighting an urgent need for the discovery of new molecular targets and drug candidates[3,4].

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that are involved in the degradation of extracellular matrix (ECM) and tissue remodeling. One of the most well-studied members of this family is Matrix Metalloproteinase-1 (MMP1), also known as interstitial collagenase. This enzyme degrades fibrillar collagens and has been implicated in several physiological and pathological processes, including wound healing, angiogenesis, tissue repair, arthritis, and cancer progression and metastasis. In particular, MMP1 has been found to be overexpressed in various cancers and to be associated with tumor cell invasion, migration, and poor prognosis. As such, MMP1 is considered to be a potential prognostic biomarker and therapeutic target for oncology[5].

Nowadays, the development and discovery of new drugs and inhibitors against cancer targets, including MMP1, is being intensively complemented with different computational and chemometric approaches. One of the most popular techniques in this field is Quantitative Structure-Activity Relationship (QSAR) modeling. QSAR is a computational method that uses statistical or machine learning techniques to establish a relationship between the chemical structure of a molecule and its biological activity. By building a QSAR model, it is possible to predict the activity profile of a compound and to identify the structural features that are responsible for its potency[6]. QSAR can be a powerful tool for the rational design and optimization of lead compounds before their synthesis and experimental testing, thus saving time and resources.

Hydroxamic acids are a class of organic compounds that contain the functional group –C(=O)NHOH. They have been studied extensively as inhibitors of metalloproteases, histone deacetylases (HDACs), and other metalloenzymes that are involved in

cancer development and progression. Hydroxamic acid derivatives are able to bind to the active site zinc ion of these enzymes with high affinity, thus inhibiting their activity[7,8]. Moreover, they have been shown to possess anticancer activity by various mechanisms, such as enzyme inhibition, epigenetic modulation, apoptosis induction, and suppression of tumor cell proliferation[9-11]. QSAR analysis has been applied successfully to the design and discovery of hydroxamic acid inhibitors of several cancer-related enzymes.

For example, QSAR models have been developed to optimize the structure-activity relationship of hydroxamic acids for anti-proliferative activity against cancer cell lines. The results of these studies have demonstrated that electronic properties, polar surface area, and hydrogen bonding potential are the most important parameters influencing the bioactivity of these compounds[12,13].

In this paper, we have described 3QSAR (three dimensional quantitative structure activity relationship) studies on some matrix metalloproteinase inhibitors.

## EXPERIMENTAL SECTION

### Data Set

In the current study, 33 hydroxamic acids used as matrix metalloproteinase (MMP) inhibitors were chosen from the literature [14]. The biological activity was expressed using inhibitory concentration 50 (IC50), the molar concentration of the compound, which can cause 50% inhibition of the MMP enzyme. For kNN-MFA QSAR studies, the biological parameter was converted into a dependent variable, log(1/C), where C is the molar concentration of the compound at IC50.

### Molecular modeling

Three dimensional quantitative structure-activity relationship (3D-QSAR) studies were conducted by using Vlife MDS 3.0 software package. The structures of all compounds were built in the software. Partial atomic charges (required for electrostatic calculations) were assigned by the Gasteiger-Marsili charge type with dielectric constant of 1.0.

### Alignment rules

In the present study, we have superimposed molecules by the hydroxamic acid functional group of the molecules as template I (figure 1).

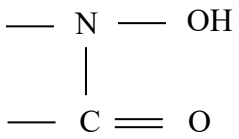



Figure1

**Figure 1. The template based alignment was used for superimposition**

### MFA analysis

A regular rectangular grid is generated about each molecule. The steric and electrostatic interaction energies are evaluated at the lattice points of this grid, with a methyl probe having a charge of +1. These interaction energy values are used as descriptors for the generation of the relationship as well as for the calculation of the molecular similarity (nearness) between the compounds. The term descriptor will, for the purposes of the following discussion, refer specifically to these field values calculated at the lattice points.

### k-Nearest Neighbor (kNN) Method

The k-Nearest Neighbor (kNN) technique is based on the simple distance-learning paradigm: an unknown member (molecule) is assigned/predicted the majority response of its k-nearest neighbors among the training set. The molecular nearness can be quantified in terms of an appropriate distance metric, for example a molecular similarity measure computed using the field interaction of the molecular structures. The best sets of variables (field points) and value of parameter k were identified using a number of variable selection methods kNN Molecular Field Analysis (kNNMFA) in conjunction with stepwise (SW) variable selection, Simulated Annealing (SA), and Genetic Algorithm (GA) as previously described by Subhash et al. [15].

## RESULT AND DISCUSSION

### 3DQSAR kNNMFA Model for sulfamate-based non-steroidal inhibitors

The steric and electrostatic descriptors of all thirty three molecules were calculated in the 3D QSAR module of Vlife MDS 3.0 software. The Gasteiger-Marsili method with the dielectric constant of 1.0 was used to compute the partial atomic charges.

Variables with zero variance in value were removed from the data set. The data set was split into a training set of 23 molecules and a test set of 10 molecules using the sphere exclusion algorithm. The 3D-QSAR kNN-MFA model was developed using the hydroxamic acid Template I (Figure 1) as a reference structure. The developed model had good $q^2$ value (0.7211) and good external prediction (pred_$r^2$ = 0.6451). A comparison of kNNMFA models built for antitumor activity of hydroxamic acids is shown in Table 2.

**Table 1. Comparison of the kNNMFA models generated for the hydroxamic acids as matrix metalloproteinase inhibitors**

| Parameter/molecule | SWkNN-MFA | SAkNN-MFA | GAkNN-MFA |
|---|---|---|---|
| **$q^2$** | 0.7211 | 0.4186 | 0.2770 |
| **Pred_$r^2$** | 0.6451 | -0.3258 | 0.1769 |
| **k** | 2 | 3 | 5 |
| **Descriptors** | E_856, S_405, S_713 | S_394, S_689 | E_343, E_831, S_647, S_1100 |

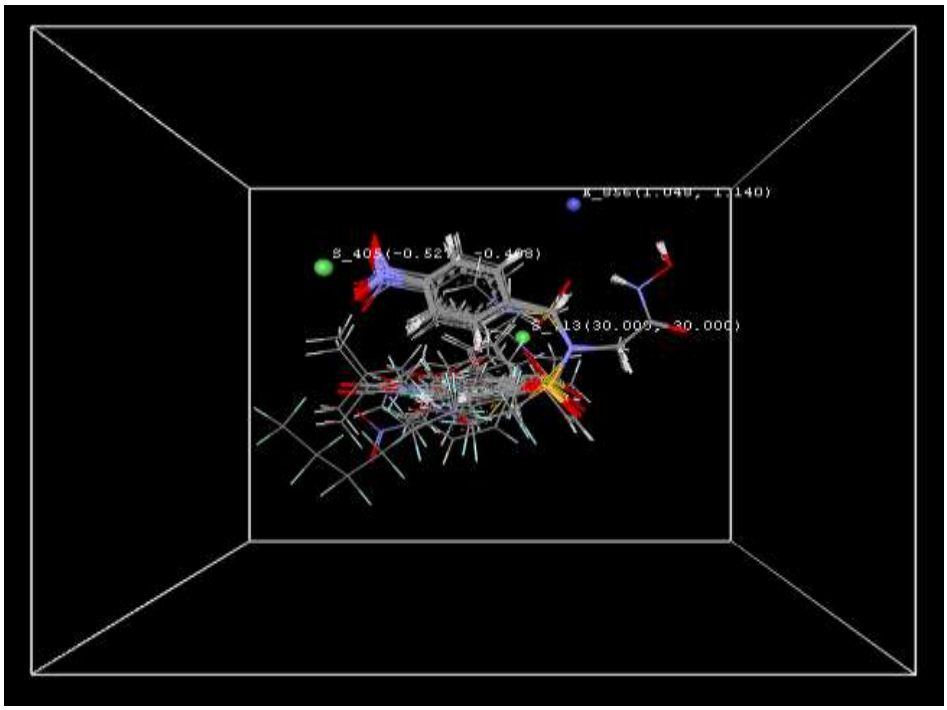


**Figure. 2 Distribution of chosen points in SWkNN-MFA for the hydroxamic acids with test set molecules for inhibitors of matrix metalloproteinase inhibitors.**

The kNN-MFA field plot visualizes the approximate positions and extents of key electrostatic and steric fields in the models and their favorable and unfavorable influence on activity. The model suggests that regions of negative steric potential (i.e., reduced steric bulk) and positive electrostatic potential (i.e., less electronegative charge) are both favorable and correspond to enhanced inhibitor activity. Regions of positive steric potential (i.e., increased bulk) and negative electrostatic potential (i.e., increased electronegative charge) are both unfavorable and lead to diminished activity.

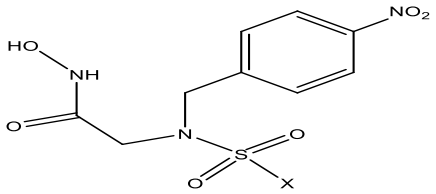
The SW-kNN-MFA model points in Figure 2 are used here to explain the SAR of the molecules investigated in this study. It is noted that four critical lattice points were identified in which descriptor distances made an important contribution to SW-kNN-MFA model predictions of hydroxamic acid analogues, one lattice point for electrostatic interactions and two lattice points for steric interactions.

For the electrostatic field value, the range of values at point E_859 was 1.0484 to 1.1403. This is an all positive range, and implies that a positive electrostatic potential in this region is not favorable to higher inhibition of MMP.

The values for the steric field were: S_405: -0.5269 to -0.4883; and S_713 : 30.0000 to 30.0000. The inclusion of a negative (S_405) and large positive (S_713) range is curious, but from the ranges provided it would seem that a positive steric potential (increased bulk) is desirable for higher MMP inhibition.

The observed and calculated inhibition values of matrix metalloproteinase by the hydroxamic acid analogues are shown in Table 2.

**Table 2. The observed and calculated inhibition of matrix metalloproteinase by hydroxamic acids analogues**




| S.No. | X | Observed | Calculated | Observed-Calculated |
|---|---|---|---|---|
| 1. | $CH_3$ | 7.1300 | 7.1550 | -0.0250 |
| 2. | $CF_3$ | 7.6800 | 7.3600 | 0.3200 |
| 3*. | $CCl_3$ | 7.6200 | 7.6345 | -0.0145 |
| 4. | n-$C_4F_9$ | 7.2100 | 7.1150 | 0.0950 |
| 5. | n-$C_8F_{17}$ | 7.1000 | 7.1700 | -0.0700 |
| 6. | $Me_2N$ | 7.5900 | 7.4050 | 0.1850 |
| 7*. | $C_6H_5$ | 7.6800 | 7.5348 | 0.1452 |
| 8*. | $PhCH_2$ | 7.6200 | 7.5348 | 0.0852 |
| 9. | 4F-$C_6H_4$ | 7.7200 | 7.5300 | 0.1900 |
| 10*. | 4Cl-$C_6H_4$ | 7.6600 | 7.4690 | 0.1910 |
| 11*. | 4Br-$C_6H_4$ | 7.6000 | 7.4657 | 0.1343 |
| 12*. | 4I-$C_6H_4$ | 7.5400 | 7.4685 | 0.0716 |
| 13. | 4$CH_3$-$C_6H_4$ | 7.5200 | 7.5100 | 0.0100 |
| 14*. | 4$NO_2$-$C_6H_4$ | 7.8200 | 7.4674 | 0.3526 |
| 15. | 3$NO_2$-$C_6H_4$ | 7.7500 | 7.4500 | 0.3000 |
| 16. | 2$NO_2$-$C_6H_4$ | 7.2300 | 7.4450 | -0.2150 |
| 17. | 3Cl-2$NO_2$-$C_6H_3$ | 7.5100 | 7.7600 | -0.2500 |
| 18. | 4AcNH-$C_6H_4$ | 7.8500 | 7.8850 | -0.0350 |
| 19. | 4BocNH-$C_6H_4$ | 7.7700 | 7.6300 | 0.1400 |
| 20. | 3BocNH-$C_6H_4$ | 7.5900 | 7.6861 | -0.0961 |
| 21*. | $C_6F_5$ | 8.5200 | 7.9517 | 0.5683 |
| 22*. | 3$CF_3$-$C_6H_4$ | 8.3000 | 7.9826 | 0.3174 |
| 23. | 3,5$Cl_2$-$C_6H_3$ | 8.0500 | 7.8850 | 0.1650 |
| 24. | 4MeO-$C_6H_4$ | 7.5500 | 7.4950 | 0.0550 |
| 25*. | 2,4,6$Me_3$-$C_6H_2$ | 7.4400 | 7.5096 | -0.0696 |

| | | | | |
|---|---|---|---|---|
| 26. | 4MeO-3BocNH-$C_6H_3$ | 7.6000 | 7.5900 | 0.0100 |
| 27. | 2HO-2,3$Cl_2$-$C_6H_2$ | 7.9200 | 7.9500 | -0.0300 |
| 28. | 3HONHCO-$C_6H_4$ | 7.3900 | 7.4050 | -0.0150 |
| 29. | 4HONHCO-$C_6H_4$ | 7.4700 | 7.5350 | -0.0650 |
| 30. | 1-Naphthyl | 7.0600 | 7.1450 | -0.0850 |
| 31. | 2-Naphthyl | 7.2100 | 7.0700 | 0.1400 |
| 32. | 5$Me_2$N-1-Naphthyl | 7.0800 | 7.1350 | -0.0550 |
| 33 | 2-Thienyl | 7.8500 | 7.6400 | 0.2100 |

.* test set .

## CONCLUSION

Cancer is a fatal condition that can affect an individual's life. The disease and all its treatment-related components, such as surgery, chemoradiotherapy, financial toxicity, unwanted side effects, psychological distress, and other demands, deplete the patients' QoL.

A k-nearest neighbor (kNN)-based Three-dimensional Quantitative Structure-Activity Relationship (3D-QSAR) model for the hydroxamic acid inhibitors of matrix metalloproteinase (MMP) was developed to aid in the development of better therapeutics. The template-based alignment technique was used to analyze these hydroxamic acid analogues.

The GA-kNN-MFA model developed in the current research was determined to be the most optimum model for the prediction of novel hydroxamic acid MMP inhibitors in comparison to the SA-kNN-MFA and SW-kNN-MFA models.

The most important model (GA-kNN-MFA) had a field plot with a positive range of electrostatic potential and a positive range of steric potential. This crucial information indicates that less electronegative substituent groups (favor positive electrostatic potential) and more bulky groups (favor positive steric potential) at the respective positions are essential for the design of new molecules with better activity as hydroxamic acid inhibitors of matrix metalloproteinase.

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