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# Investigation of QSAR kNN-MFA on a Series of Substituted Chromen-2-one Derivatives as FXa Inhibitors

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## ABSTRACT

Factor Xa (FXa), a trypsin-like serine protease, forms a well-known target for the development of anticoagulants. Various molecules have been reported as Factor Xa inhibitors, but most of them have pharmacokinetic issues. Quantitative understanding of the structure activity relationship of already developed inhibitors can overcome pharmacokinetic issues. With this aim, we performed development and validation of the (3D-QSAR) k-nearest neighbour molecular field analysis (kNN-MFA). The QSAR models of chromen-2-one derivatives were developed by kNN-MFA to identify an effective inhibitor of FXa. The results of QSAR study showed that more steric and electronegative groups are the important features for anticoagulant activity. The selected 3D kNN-MFA model B has a training set of 44 molecules and a test set of 20 molecules having validation (q2) and cross validation (pred_r2) values 0.7110 and 0.5947, respectively. The results of 3D QSAR models may lead to a better understanding of the design and development of novel FXa inhibitors.

**Keywords**: 3D-QSAR; kNN-MFA model; FXa; Vlife MDS; Anticoagulant.

## 1. INTRODUCTION

Anticoagulants are a class of drugs that work to prevent blood coagulation. They are used for coagulation disorders and as prophylactic in patients with mechanical heart valves as a lifelong therapy[1]. Blood Clotting is a complex process guided by bimolecular proteins, known as clotting factors. In the past decade, these clotting factors have emerged as potential targets for anticoagulant molecules[2]. Current anticoagulant therapy has various side effects such as bleeding, variable patient responses, heparin-induced thrombocytopenia (HIT) and major inability to inhibit clot-bound thrombin[3, 4, 5]. Direct inhibitors of thrombin and factor Xa (FXa) are considered better over indirect inhibitors as they can target both circulating and clot-bound thrombin[6]. FXa is an important target in coagulation cascade due to its strategic presence at the junction of both extrinsic and intrinsic pathways. Warfarin, a coumarin derivative has been the drug of choice for the prevention and treatment of arterial and venous thrombotic disorders for more than 40 years. Treatment with Warfarin becomes precarious as it has a lower therapeutic window, requiring critical dose monitoring. New oral direct FXa inhibitors like rivaroxaban and Apixaban are seen as effective and safe alternatives for warfarin. Rivaroxaban and Apixaban are approved for treatment of venous thromboembolism (VTE), prevention after elective hip or knee replacement in adults, and stroke prevention and systemic embolization in non-valvular atrial fibrillation[7, 8]. Ximelagatran is the first oral direct thrombin inhibitor; ithas confirmed efficacy for treatment of VTE, stroke prevention and recurrent coronary events after acute myocardial infarction. Unfortunately, it was withdrawn by AstraZeneca in 2006 because of liver toxicity[9, 10].

Traditional drug development methods are based on

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random screening and chance based discovery, these methods also have major disadvantages, namely, long-lasting, expensive and intellectual method. To overcome these problems, computer-assisted drug development methods have emerged in the past few decades with a fair amount of success ratio. Computational methods have proved to become a cost and time effective option for screening of potential drug-like candidates[11,12,13,14]. QSAR methods have a great importance in modern medicinal chemistry due to their ability to directly correlate molecular structure with biological activity[15,16]. 3D QSAR models by kNN-MFA method facilitate the assessment of 3D molecular fields in the region of molecules and generate relationships between these fields with the activity of molecules. In this study, we examine the role that kNN-MFA method of QSAR plays in identifying important molecular sites and their properties to aid in the development of novel FXa inhibitors.

## 2. MATERIALS AND METHODS

### 2.1. Data set and ligand preparation

Data set for the current study was taken from the literature reported by Bhatia *et al.*[1]. Structure and activity (pIC50) as mentioned in the literature are listed in Table 1. Structures of pyridyl chromen-2-one derivatives were drawn using 2D draw module of Vlife MDS 4.3. The 2D structures were converted to 3D structures and the energy was minimized. Energy minimization was carried out using Merck molecular force field (MMFF) and Gasteiger charges with 0.01 as convergence criteria (RMS gradient)[17, 18].

**Table 1. The molecules understudy**


**General Structure**

| Sr. No. | R | X | Ar | Observed Activity $pIC_{50}$ | Predicted Activity $pIC_{50}$ Model A | Predicted Activity $pIC_{50}$ Model B |
|---|---|---|---|---|---|---|
| **1#** | - | H | -- | 0.46 | 0.43 | 0.44 |
| **2** | - | $NO_2$ | -- | 0.02 | 0.41 | 0.38 |
| **3#** | 7-OH | H | -- | 0.25 | 0.31 | 0.28 |
| **4** | 7-OH | $NO_2$ | -- | 0.24 | 0.31 | 0.32 |
| **5#** | 6-$NH_2$ | H | -- | 0.47 | 0.32 | 0.35 |
| **6** | 6-$NH_2$ | $NO_2$ | -- | 0.45 | 0.50 | 0.48 |
| **7** | 8-$NO_2$ | H | -- | 0.32 | 0.42 | 0.41 |
| **8** | 8-$NO_2$ | $NO_2$ | -- | 0.16 | 0.39 | 0.38 |
| **9#** | - | H | 2-OH-$C_6H_5$ | 0.85 | 0.56 | 0.61 |
| **10** | - | H | 4-Cl-$C_6H_5$ | 0.78 | 0.72 | 0.74 |
| **11** | - | H | 4-$OCH_3$-$C_6H_5$ | 0.79 | 0.59 | 0.62 |
| **12** | - | H | $C_6H_5$ | 0.65 | 0.64 | 0.66 |
| **13** | - | H | H | 0.39 | 0.43 | 0.41 |
| **14** | - | H | 4-$(CH_3)_2$N-$C_6H_5$ | 0.66 | 0.66 | 0.65 |
| **15#** | - | H | 3,4,5-$(OCH_3)_3C_6H_5$ | 0.59 | 0.67 | 0.58 |
| **16** | - | $NO_2$ | 2-OH-$C_6H_5$ | 0.38 | 0.40 | 0.39 |
| **17#** | - | $NO_2$ | 4-Cl-$C_6H_5$ | 0.55 | 0.76 | 0.59 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **18** | - | $NO_2$ | 4-$OCH_3$-$C_6H_5$ | 0.31 | 0.42 | 0.34 |
| **19** | - | $NO_2$ | $C_6H_5$ | 0.44 | 0.36 | 0.38 |
| **20** | - | $NO_2$ | H | 0.36 | 0.41 | 0.39 |
| **21#** | - | $NO_2$ | 4-$(CH_3)_2N$-$C_6H_5$ | 0.78 | 0.82 | 0.79 |
| **22** | - | $NO_2$ | 3,4,5-$(OCH_3)_3C_6H_5$ | 0.52 | 0.47 | 0.51 |
| **23** | 7-OH | H | 2-OH-$C_6H_5$ | 0.55 | 0.53 | 0.54 |
| **24** | 7-OH | H | 4-Cl-$C_6H_5$ | 0.78 | 0.70 | 0.72 |
| **25#** | 7-OH | H | 4-$OCH_3$-$C_6H_5$ | 0.81 | 0.67 | 0.76 |
| **26#** | 7-OH | H | $C_6H_5$ | 0.68 | 0.75 | 0.69 |
| **27** | 7-OH | H | H | 0.59 | 0.51 | 0.53 |
| **28** | 7-OH | H | 4-$(CH_3)_2N$-$C_6H_5$ | 0.75 | 0.62 | 0.61 |
| **29** | 7-OH | H | 3,4,5-$(OCH_3)_3C_6H_5$ | 0.35 | 0.43 | 0.41 |
| **30** | 7-OH | $NO_2$ | 2-OH-$C_6H_5$ | 0.45 | 0.35 | 0.39 |
| **31** | 7-OH | $NO_2$ | 4-Cl-$C_6H_5$ | 0.80 | 0.61 | 0.65 |
| **32** | 7-OH | $NO_2$ | 4-$OCH_3$-$C_6H_5$ | 0.21 | 0.35 | 0.32 |
| **33** | 7-OH | $NO_2$ | $C_6H_5$ | 0.32 | 0.37 | 0.35 |
| **34** | 7-OH | $NO_2$ | H | 0.44 | 0.37 | 0.40 |
| **35#** | 7-OH | $NO_2$ | 4-$(CH_3)_2N$-$C_6H_5$ | 0.75 | 0.70 | 0.71 |
| **36** | 7-OH | $NO_2$ | 3,4,5-$(OCH_3)_3C_6H_5$ | 0.25 | 0.40 | 0.38 |
| **37** | 6-$NH_2$ | H | 2-OH- $C_6H_5$ | 0.61 | 0.66 | 0.63 |
| **38** | 6-$NH_2$ | H | 4-Cl- $C_6H_5$ | 0.77 | 0.73 | 0.75 |
| **39** | 6-$NH_2$ | H | 4-$OCH_3$- $C_6H_5$ | 0.65 | 0.70 | 0.67 |
| **40** | 6-$NH_2$ | H | $C_6H_5$ | 0.79 | 0.56 | 0.63 |
| **41#** | 6-$NH_2$ | H | H | 0.61 | 0.65 | 0.62 |
| **42#** | 6-$NH_2$ | H | 4-$(CH_3)_2N$-$C_6H_5$ | 0.78 | 0.68 | 0.70 |
| **43** | 6-$NH_2$ | H | 3,4,5-$(OCH_3)_3C_6H_5$ | 0.49 | 0.70 | 0.57 |
| **44#** | 6-$NH_2$ | $NO_2$ | 2-OH-$C_6H_5$ | 0.49 | 0.48 | 0.50 |
| **45** | 6-$NH_2$ | $NO_2$ | 4-Cl-$C_6H_5$ | 0.72 | 0.68 | 0.69 |
| **46** | 6-$NH_2$ | $NO_2$ | 4-$OCH_3$-$C_6H_5$ | 0.36 | 0.42 | 0.39 |
| **47** | 6-$NH_2$ | $NO_2$ | $C_6H_5$ | 0.39 | 0.43 | 0.41 |
| **48** | 6-$NH_2$ | $NO_2$ | H | 0.31 | 0.28 | 0.39 |
| **49** | 6-$NH_2$ | $NO_2$ | 4-$(CH_3)_2N$-$C_6H_5$ | 0.61 | 0.65 | 0.63 |
| **50** | 6-$NH_2$ | $NO_2$ | 3,4,5-$(OCH_3)_3C_6H_5$ | 0.30 | 0.28 | 0.31 |
| **51** | 8-$NO_2$ | H | 2-OH-$C_6H_5$ | 0.57 | 0.59 | 0.56 |
| **52** | 8-$NO_2$ | H | 4-Cl-$C_6H_5$ | 0.68 | 0.78 | 0.73 |
| **53** | 8-$NO_2$ | H | 4-$OCH_3$-$C_6H_5$ | 0.46 | 0.61 | 0.58 |
| **54#** | 8-$NO_2$ | H | $C_6H_5$ | 0.69 | 0.75 | 0.72 |
| **55** | 8-$NO_2$ | H | H | 0.40 | 0.38 | 0.39 |
| **56** | 8-$NO_2$ | H | 4-$(CH_3)_2N$-$C_6H_5$ | 0.83 | 0.78 | 0.80 |
| **57** | 8-$NO_2$ | H | 3,4,5-$(OCH_3)_3C_6H_5$ | 0.40 | 0.35 | 0.38 |
| **58#** | 8-$NO_2$ | $NO_2$ | 2-OH-$C_6H_5$ | 0.35 | 0.33 | 0.36 |
| **59#** | 8-$NO_2$ | $NO_2$ | 4-Cl-$C_6H_5$ | 0.65 | 0.71 | 0.69 |
| **60** | 8-$NO_2$ | $NO_2$ | 4-$OCH_3$-$C_6H_5$ | 0.18 | 0.42 | 0.37 |
| **61** | 8-$NO_2$ | $NO_2$ | $C_6H_5$ | 0.21 | 0.32 | 0.25 |
| **62** | 8-$NO_2$ | $NO_2$ | H | 0.22 | 0.37 | 0.32 |
| **63** | 8-$NO_2$ | $NO_2$ | 4-$(CH_3)_2N$-$C_6H_5$ | 0.70 | 0.81 | 0.77 |
| **64** | 8-$NO_2$ | $NO_2$ | 3,4,5-$(OCH_3)_3C_6H_5$ | 0.29 | 0.32 | 0.28 |

1. #- Indicate molecules in test set

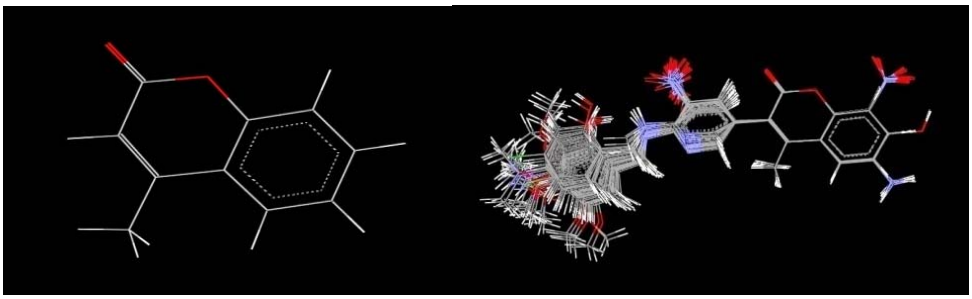

**Figure 1a: Chromen-2-one (Template) Fig. 1b: Alignment of the molecules**

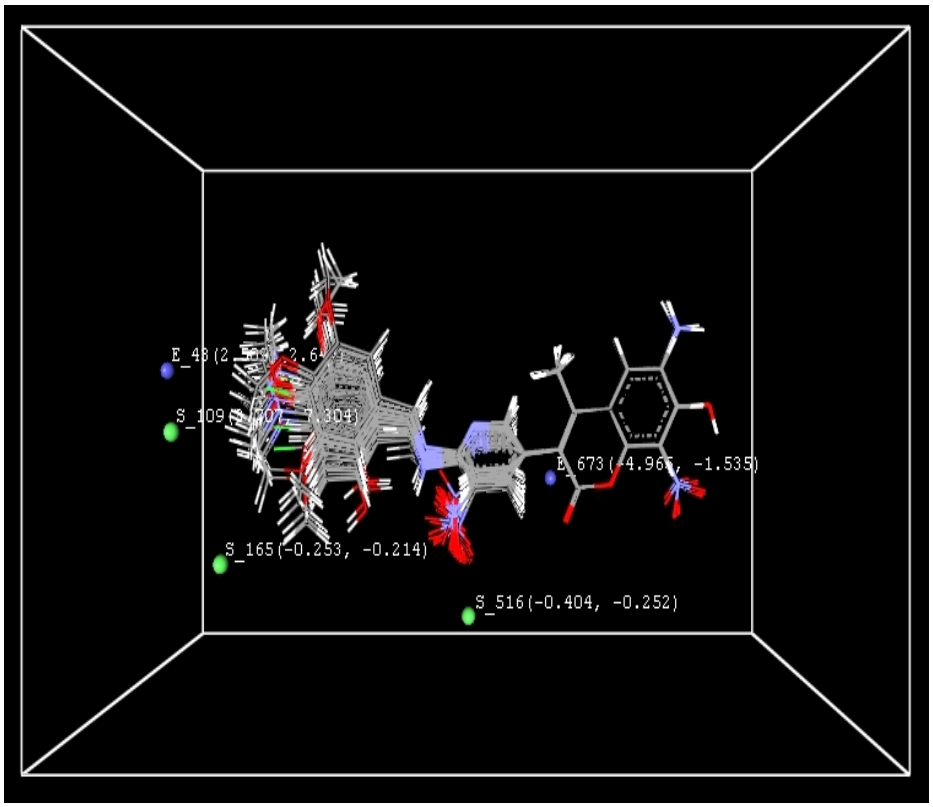


**Figure 2: Field points of QSAR model A**

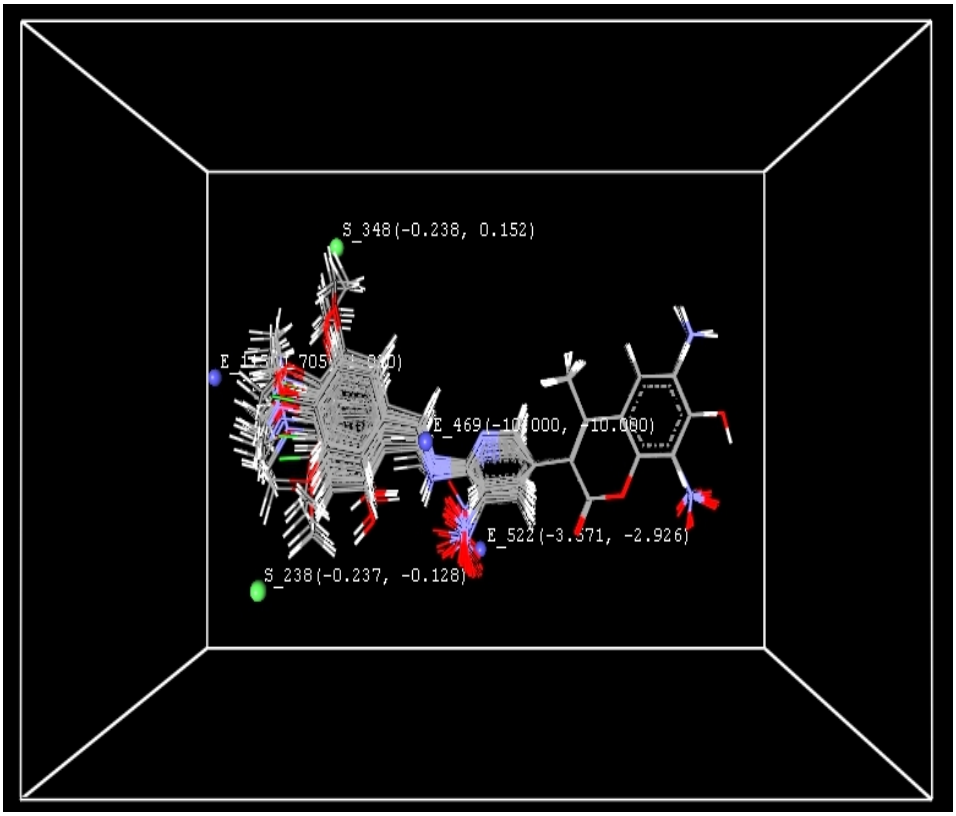


**Figure 3: Field points of QSAR model B**

## 3. ALIGNMENT OF MOLECULES

The molecules of the present dataset were aligned by the template based technique using the common structure of chromen-2-one derivatives. The template used for alignment and set of Aligned molecules are showed in Fig. 1a and 1b respectively.

## 4. DESCRIPTOR CALCULATION

The aligned molecules were subjected to descriptor calculation using 3D QSAR modules of VLife MDS[19]. A common rectangular grid was generated around the molecules and steric and electrostatic energies were computed at the lattice points using methyl probe of charge +1.

## 5. 3D-QSAR

The QSAR methods require distribution of the data sets into training and test sets. A random selection algorithm was used for dividing the data into 70:30 ratio. kNearest Neighbour method was used to generate 3D QSAR models along with simulated annealing or genetic algorithm methods. The standard kNN method was implemented simply as follows [20, 21]:

- Calculate distances between an unknown object (u) and all the objects in the training set.
- Select k objects from the training set most similar to object (u), according to the calculated distances.
- Classify object (u) with the group to which a majority of the k objects belong.
- An optimal k value is selected by the optimization through the classification of a test set of samples or by the leave-one out cross-validation.

Models having $q^2$ above 0.7 were used to check the external predictivity. The selected models having $q^2$ value above 0.7 and pred_$r^2$ value above 0.5 are shown in Table 2 and Figures 2 and 3.

**Table 2. Statistical results of 3D-QSAR kNN MFA models generated by stepwise variable selection method**

| Model No. | QSAR model Selected Descriptors | n Training set/Test set | k Nearest Neighbour | $q^2$ | Pred $r^2$ |
|---|---|---|---|---|---|
| A | E_43 (2.509 2.646) E_673 (-4.964 -1.534) S_516 (-0.403 -0.252) S_165 (-0.253 -0.214) S_109 (3.706 7.303) | 48/16 | 2 | 0.70 | 0.62 |
| B | E_115 (0.705 1.020) E_522 (-3.571 -2.926) S_348 (-0.237 0.152) S_238 (-0.236 -0.1281) E_469 (-10.000 -10.000) | 48/16 | 5 | 0.71 | 0.59 |

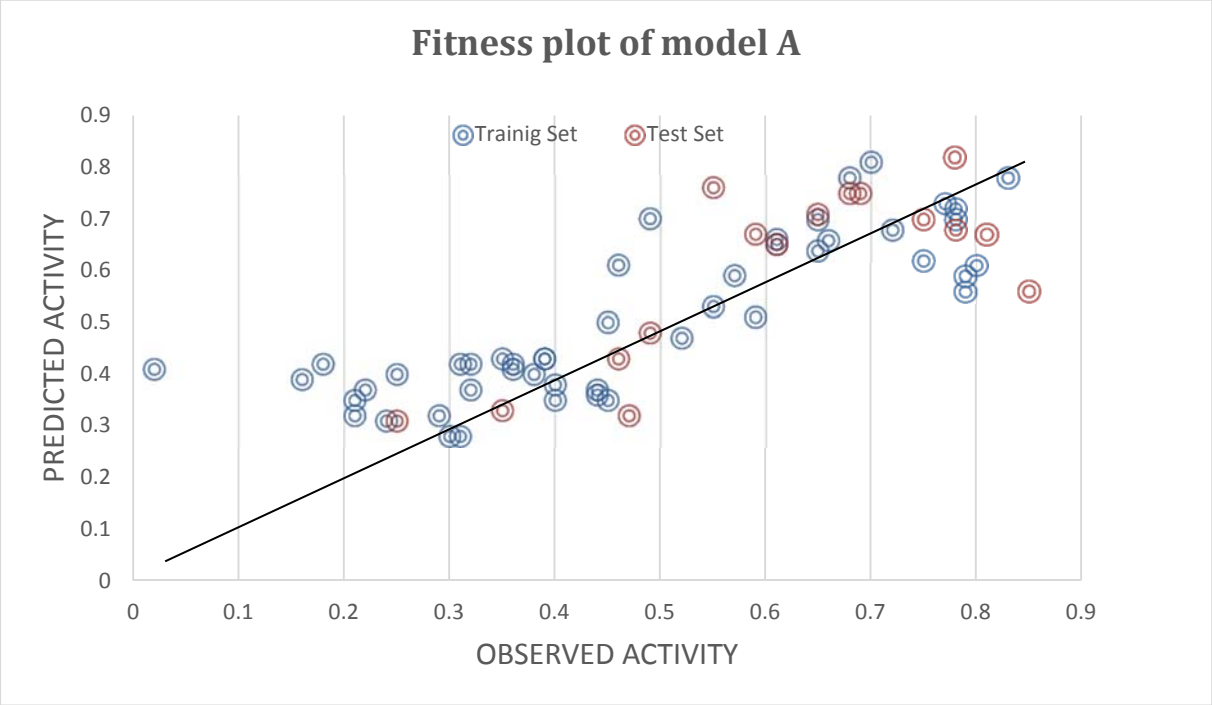


**Figure 4: Fitness plot of model A comparison of observed versus predicted activity**

## 6. RESULTS AND DISCUSSION

### 6.1. 3D-QSAR studies

In the present study, a 3D QSAR was performed on reported coumarin derivatives as anticoagulant agents. The molecules in the study were randomly divided into the training set and test set. Simulated aneling and genetic algorithm methods were used in combination with kNN to develop kNN-MFA model. The 3D-QSAR kNN-MFA model was selected based on various statistical parameters as $q^2$, pred $r^2$ as shown in Table 2.

### 6.2. Interpretation of QSAR models

The model was selected on the basis of $q^2$ and pred $r^2$ to evaluate molecular features that govern the anticoagulant potential of the selected derivatives. The $q^2$

value for model A was 0.70 and pred_$r^2$ was found to be 0.62. The fitness plot for model A is shown in Figure 4, which shows the random distribution of predicted versus observed activity of molecules. Electrostatic interaction at lattice point E_43 is positively contributing to the activity shown in blue colour, which indicates that positive electrostatic potential is complimentary for enhancing activity. Electrostatic interaction at lattice point E_673 is negatively contributing to activity, which shows negative electrostatic potential is complimentary for enhancing anticoagulant activity. Consequently, more electronegative substituents are preferred at para position of phenyl ring. The steric interaction fields shown in green lattice points S_516 and S_165 are negatively contributing to activity. Hence, less electronegative functional group is ideal at meta position of the pyridine ring, whereas steric interaction fields at lattice point S_109 is positively contributing to increasing activity. Therefore, more bulky functional substitution of group like Cl<O<F is ideal on para position of substituted benzaldehyde ring. Model B was found to be the best as the model is able to predict lager external set with better correlation, indicating the applicability of the model to external sets. The $q^2$ value for model B was 0.71m whereas pred_$r^2$ value was 0.59. The fitness plot of (model B) predicted versus observed activity of training and test sets molecules are shown in Figure 5, which displays the random distribution of activity.

The steric interaction fields represented in green lattice points as S_348, S_238 are negative, which indicates that the reduction of the steric behaviour meta positions of the Aromatic ring on the amino group of pyridine ring is conducive for activity. The electrostatic interaction fields represented in blue lattice points E_522 and E_469 are negatively contributing to activity, which indicates that negative electrostatic potential is conducive for activity. This suggests that increasing electronegative groups at 3rd position of the pyridine ring is conducive for activity. Electrostatic interaction at lattice point E_115 is positive, suggesting electrostatic interactions at para position of the phenyl ring are detrimental for the biological activity. The model provides key suggestions around various substitution sites for the design of new molecules.

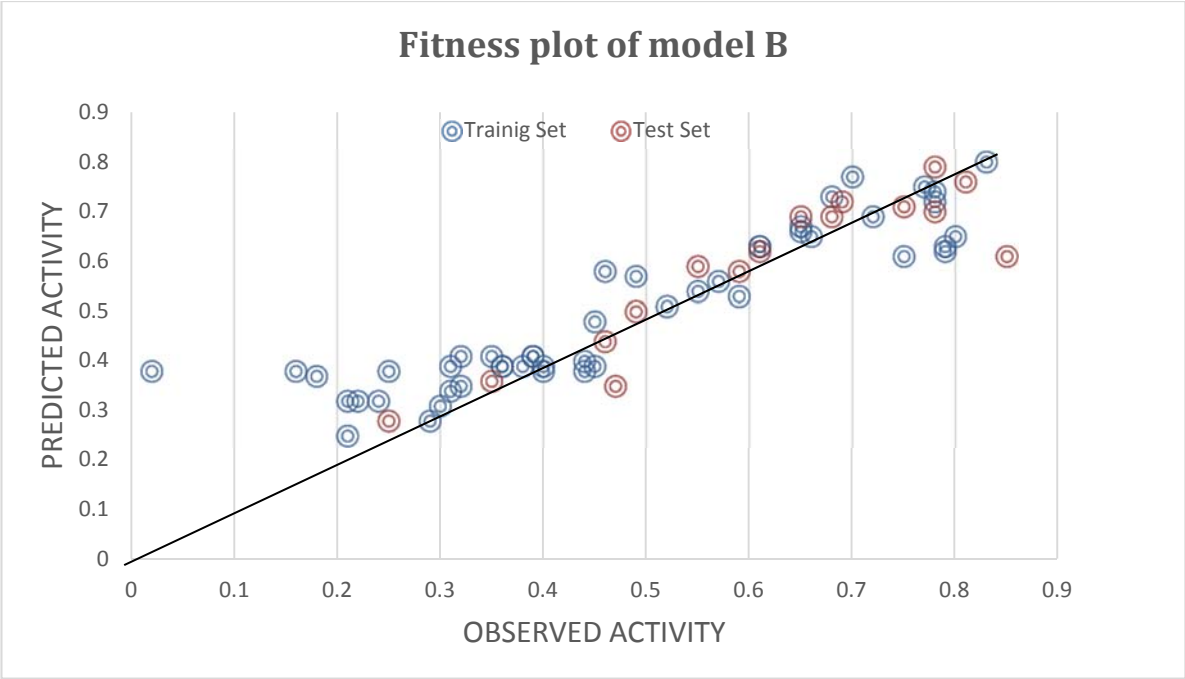


**Figure 5: Fitness plot of model B comparison of observed versus predicted activity**

## 7. CONCLUSION

Present communication is an attempt to identify structural features of chromen-2-one derivatives for this 3D-QSAR kNN-MFA. The kNN-MFA results show that substitution favouring less steric strain and more electronegativity are preferred for enhancing factor XA inhibition. Thus, the data obtained from this 3D-QSAR kNN-MFA model will be helpful for the design and development of novel lead molecules to yield potent FXa inhibitors.

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# دراسة QSAR kNN-MFA على سلسلة من مشتقات2- Chromen-1 كأنها مثبطات FXa

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مجموعة تصميم وتطوير الأدوية، قسم كيمياء الصيدلية، كلية الصيدلة بهاراتي فيديابيث، كولهابور (MH)، Bharati Vidyapeeth، كلية الصيدلة، بالقرب من Chitranagari Morewadi، Kolhapur (MH)، الهند.

## ملخص

يشكل عامل Xa (FXa) بروتين سيرين البروتيني ويشبه التريبسين، ويشكل هدفا معروفا جيدا لتطوير مضادات التخثر. وقد تم تقديم تقارير عن جزيئات مختلفة كعامل Xa باعتبارها مثبطات ولكن معظمها لديها مشاكل دوائية. يمكن باستخدام الفهم الكمي للعلاقة بين المثبطات المتقدمة التغلب على قضايا الحرائك الدوائية. بناء على ذلك، قمنا بالتطوير والتحقق باجراء تحليل ميداني جزئي (k-N-MFA) لأقرب جاري .(3D-QSAR) وتم تطوير نماذج QSAR من مشتقات chromen-2-one بواسطة kNN-MFA لتحديد مثبط فعال لـ .FXa أظهرت نتائج دراسة QSAR بأن المجموعات الأكثر استثارة إلكترونياً تشكل السمات الهامة لنشاط مضاد التخثر. يحتوي نموذج KNN-MFA ثلاثي الأبعاد على مجموعة التدريب والتي تتكون من 44 جزيء ومجموعة الاختبار التي تتكون من 20 جزيء والتي تتميز باحتوائها على صلاحية التحقق (q2) وقيم التحقق المتقاطع (pred_r2) بقيمة 0.7110 و 0.5947 على التوالي. وقد تؤدي نتائج نماذج QSAR ثلاثية الأبعاد إلى الحصول على فهم أفضل لتصميم مثبطات FXa الجديدة وتطويرها.

**الكلمات الدالة:** 3 .D-QSAR نموذج Xa kNN-MFA النشط Vlife MDS، مضاد التخثر.

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