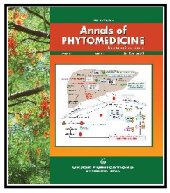
Annals of Phytomedicine 12(2): 423-429, 2023

DOI: http://dx.doi.org/10.54085/ap.2023.12.2.52

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

# Quantitative structure activity relationship studies of some quinoline derivatives of angiotensin II receptor inhibitors

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**Article Info**

**Article history**
Received 10 June 2023
Revised 29 July 2023
Accepted 30 July 2023
Published Online 30 December 2023

**Keywords**
k-nearest neighbor
Quinoline
Ang II receptor
3D descriptors
AT1 receptor

**Abstract**

The aim of this study is to develop 3D-QSAR models to validate the antihypertensive activity of quinoline derivatives and insight into the requirements for the improvement of activity for the designing of more potent analogues of new therapeutic agents. 3D-QSAR analysis models were developed and validated with good performance and robustness of the molecular modeling studies. We proceeded to develop a 3D-QSAR model, utilizing the k-nearest neighbor method. The 3D model exhibited a fit with values of cross validated $q^2$ (0.6923), correlation coefficient $r^2$ (0.7351), and external predictive ability of pred_r2 (0.7015). The value of pred_$r^2$ was obtained for the test set and gave better results, with a value of 0.7015, which means 70% predictive power for the external test set. The 3D-QSAR models explore the structural requirements for improving activity, for the better understanding of features required for selectivity of the activity.

## 1. Introduction

Angiotensin II (Ang II) is an active octapeptide and a potent vasoconstrictor in the renin-angiotensin-aldosterone system (RAAS), which is produced *in vivo* from angiotensin I by the angiotensin-converting enzyme (ACE). Regulators of the RAAS have been found to be effective for the treatment of hypertension and congestive heart failure, and they continue to be one of the most active areas of drug discovery (Aulakh *et al.,* 2007). Angiotensin II type 1 receptor ($AT_1$) is a GPCR that regulates all known physiological functions of angiotensin II, a peptide hormone product of the renin angiotensin system (Gasparo *et al.,*2000). Hypertension is a complex disorder and a significant threat to the general population's health (Misra *et al.,* 2023). Hypertension is a common and major health problem and accounts for 6% of death worldwide (Jabeen *et al.,* 2022). Overall 1.13 billion people worldwide have hypertension, most of them living in low-and middle-income countries (Gupta *et al.,* 2022; Sharma and Kohli, 2023). Benzylimidazole-5-acetic acid compounds were reported by the Takeda laboratories (Furukawa *et al.,* 1982). Losartan is the widely used drug and numerous modifications to its chemical structure have generated a large number of candesartan, tasosartan, telmisartan, irbesartan and olmesartan, all of which have been used clinically (Carini *et al.,* 1991; Kubo *et al.,* 1993; Ries *et al.,* 1993; Ferrari *et al.,* 1994; Brousil and Burke, 2003). QSAR studies have been demonstrated to be an effective computational tool in understanding the correlation between the structure of molecules and their activities (Wang *et al.,* 2007). For the development of molecular field analysis has been applied to evaluate specific contributions of steric and electrostatic field effects necessary for the activity (Ajmani *et al.,* 2006). Three-dimensional (3D) structure for $AT_1$ receptor, a rational design of antagonists for this receptor using a structure-based approach is not feasible (Tuccinardi *et al.,* 2006).The main objective of this study is to develop 3D-QSAR models to validate the antihypertensive activity of quinoline compounds and identify optimal structural characteristics for the design of new compounds.

## 2. Materials and Methods

All the quinoline derivatives used in this experiment were obtained from the research conducted by Bradbury (Bradbury *et al.,*1992). The structures and corresponding activity values of the compounds are presented in Table 1 and lead compounds show Figure 1. For the purpose of 3D QSAR analysis, chemical structures of all the compounds have been drawn using the builder module in Molecular Design Suite 3.5 software package(Vlife, 2004). In alignment method (Ajmani *et al.,*2006), a template structure used as a basis for alignment of a set of molecules. The training and test sets using the sphere exclusion algorithm (Golbraikh and Tropsha, 2002). Another stepwise forward variable (Darlington, 1990), genetic algorithms (Holland, 1992) and simulated annealing (Zheng and Tropsha, 2000) based feature selection procedures create new 3D models and can explain the situation more effectively. Using Tripos force field (Clark *et al.,* 1989) and Gasteiger and Marsili charge type (Gasteiger and Marsili,1980) electrostatic, steric and hydrophobic field descriptors were calculated with cut-offs of 10.0 and 30.0 kcal/mol. The steric, electrostatic and hydrophobic interaction energies were computed at the lattice points of the grid using a methyl probe of charge +1. This resulted in calculation of 4500 field

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descriptors (1500 for each electrostatic, steric and hydrophobic) for all the compounds in separate columns.

The method of validation was employed to using leave-one-out method (Cramer *et al.,* 1988). The $q^2$ was calculated using the equation which describes the internal stability of a model.

$$q^2 = 1\frac{\Sigma(y_i - \hat{y}i)^2}{\Sigma(yi - y\,mean)^2}$$

where, the actual and predicted activity of the $i^{th}$ molecule in the training set, respectively, and $y_{mean}$ is the average activity of all molecules in the training set.

The pred_$r^2$ value formula is expressed as follows:

$$pred_{-r2} = 1 - \frac{\Sigma(y_i - \hat{y}i)^2}{\Sigma(yi - y\,mean)^2}$$

**Table 1: Structure and activities of quinoline derivatives with biological activities**

| Com. | $R^1$ | $R^2$ | $R^3$ | Y–Z | A | X | $IC_{50}$ [a] | $pIC^b_{50}$ |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | H | H | $OCH_2$ | COOH | N | 0.18 | 6.74 |
| 2 | Et | H | H | $OCH_2$ | COOH | N | 0.17 | 6.76 |
| 3 | Pr | H | H | $OCH_2$ | COOH | N | 0.60 | 6.22 |
| 4[c] | Bu | H | H | $OCH_2$ | COOH | N | 3.10 | 5.50 |
| 5 | H | H | H | $OCH_2$ | Tetrazol-5-yl | N | 6.30 | 5.20 |
| 6[c] | Me | H | H | $OCH_2$ | Tetrazol-5-yl | N | 0.016 | 7.79 |
| 7 | Et | H | H | $OCH_2$ | Tetrazol-5-yl | N | 0.031 | 7.50 |
| 8[c] | Me | H | H | $OCH_2$ | Tetrazol-5-yl | CH | 90.0 | 4.04 |
| 9 | Me | Me | H | $OCH_2$ | Tetrazol-5-yl | N | 4.6 | 5.33 |
| 10 | Me | H | H | $OCH(CH_3)$ | Tetrazol-5-yl | N | 0.040 | 7.39 |
| 11 | Me | H | H | $SCH_2$ | Tetrazol-5-yl | N | 0.37 | 6.43 |
| 12[c] | Me | H | H | CH=CH | Tetrazol-5-yl | N | 1.30 | 5.88 |
| 13 | Me | H | H | $CH_2CH_2$ | Tetrazol-5-yl | N | 0.27 | 6.56 |
| 14 | Et | - | 5-Me | $OCH_2$ | - | - | 0.013 | 7.88 |
| 15 | Et | - | 5-Cl | $OCH_2$ | - | - | 0.12 | 6.92 |
| 16 | Et | - | 5-CN | $OCH_2$ | - | - | 0.060 | 7.22 |
| 17[c] | Me | - | 6-Me | $OCH_2$ | - | - | 0.47 | 6.32 |
| 18 | Me | - | 6-Cl | $OCH_2$ | - | - | 1.20 | 5.92 |
| 19 | Et | - | 6-CN | $OCH_2$ | - | - | 0.36 | 6.44 |
| 20 | Et | - | 6-$CF_3$ | $OCH_2$ | - | - | 0.86 | 6.06 |
| 21 | Et | - | 6-COOMe | $OCH_2$ | - | - | 0.066 | 7.18 |
| 22 | Et | - | 6-OMe | $OCH_2$ | - | - | 0.022 | 7.65 |
| 23 | Et | - | 6-O-*i*-Pr | $OCH_2$ | - | - | 0.026 | 7.58 |
| 24[c] | Et | - | 6-$CH_2CH_2$ F | $OCH_2$ | - | - | 0.007 | 8.15 |
| 25 | Et | - | 6-$CH_2CF_3$ | $OCH_2$ | - | - | 0.026 | 7.58 |
| 26 | Et | - | 7-Me | $OCH_2$ | - | - | 0.14 | 6.85 |
| 27[c] | Et | - | 7-Cl | $OCH_2$ | - | - | 0.16 | 6.79 |
| 28 | Et | - | 7-CN | $OCH_2$ | - | - | 0.46 | 6.33 |
| 29 | Et | - | 7-OMe | $OCH_2$ | - | - | 0.22 | 6.65 |
| 30 | Me | - | 8-Me | $OCH_2$ | - | - | 0.31 | 6.50 |
| 31[c] | Et | - | 8-Cl | $OCH_2$ | - | - | 0.14 | 6.85 |
| 32 | Et | - | 8-$CF_3$ | $OCH_2$ | - | - | 2.00 | 5.69 |
| 33 | Et | - | 8-OMe | $OCH_2$ | - | - | 0.96 | 6.01 |

[a] $IC_{50}$ or inhibition of specific binding of [$^{125}$I] AII to a guinea pig adrenal membrane preparation.

[b] -log $IC_{50}$ to generate equation.

[c] Indicates the compounds considered in the test set in 3D QSAR.

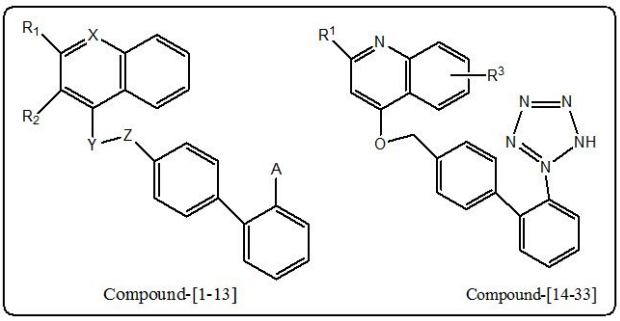


**Figure 1: Lead Compounds.**

## 3. Results

The 3D-QSAR studies were carried out using k-nearest neighbor molecular field analysis method was used in conjunction with stepwise (SW), simulated annealing (SA) and genetic algorithm method (GA) for selection of variables, followed by partial least squares to obtain the 3D models. The plot of the k-nearest neighbor molecular field analysis shows the relative position and ranges of the corresponding important electrostatic, steric and hydrophobic fields in the model provide guidelines for new molecule design. 3D QSAR model 1 shows a $q^2$ (cross validated $r^2$) of 0.6483 with five descriptors; namely, S_806, H_897, S_404, S_479 and E_736. Molecular field analysis was used to create the 3D-QSAR model using k-nearest neighbour method, showing correlative and predictive activity in terms of $q^2$ (cross validated $r^2$) and pred_$r^2$ (0.6724). As the $q^2$ is used as a measure of reliability of prediction, the correlation coefficient suggests that 3D model is accurate. Model 2 showed $q^2$ (cross validated $r^2$) of 0.6923 with five descriptors; namely, E_348, E_566, H_366, S_594 and E_736. A non-cross validated $r^2$ of 0.7629, F value of 60.116 and number k of 4 were observed with this model. The steric, electrostatic and hydrophobic contributions were 25, 50 and 25%, respectively, and exhibited good external prediction with pred_$r^2$ of 0.7015. QSAR model is considered to be predictive, if the following conditions are satisfied: $r^2 > 0.6$, $q^2 > 0.6$ and pred_$r^2 > 0.5$. Statistical significance of the model indicated by $Z_{score}$ value of 2.8975. The parameters involved in the selected model (steric and electrostatic) and the calculated activity by model 3 (GAkNN-MFA) are given in Table 2. Figure 4 shows the contribution plot for steric and electrostatic interactions in lattice. The good internal prediction of the model was confirmed by $q^2$ 0.6398 external prediction power was confirmed by pred_$r^2$ 0.564. The above all model is validated by predicting the biological activities of the test molecules, as indicated in Table 3.

**Table 2: Summary of 3D QSAR models**

| S.No. | Statistical parameter | 3D QSAR result | | |
|---|---|---|---|---|
| | | SW-PLS Model 1 | SA-PLS Model 2 | GA-PLS Model 3 |
| 1 | $q^2$ | 0.6483 | 0.6923 | 0.6398 |
| 2 | pred_$r^2$ | 0.6724 | 0.7015 | 0.5641 |
| 3 | $q^2$_se | 0.3306 | 0.3598 | 0.3986 |
| 4 | pred_$r^2$se | 0.3287 | 0.4366 | 0.5163 |
| 5 | F test | 49.273 | 60.116 | 33.132 |
| 6 | $N_{training}$ | 25 | 25 | 25 |
| 7 | $N_{test}$ | 8 | 8 | 8 |
| 8 | Contributing descriptors | S_806, S_404, S_479, E_736, H_897 | E_348, E_566,H_366, S_594 ,E_736 | E_752, S_330 |

**Table 3: Observed and predicted activity of quinoline derivatives**

| S.No | $pIC_{50}$ | SW-PLS Model-1 | | SA-PLS Model-2 | | GA-PLS Model-3 | |
|---|---|---|---|---|---|---|---|
| | | Pred. | Res. | Pred. | Res. | Pred. | Res. |
| 1 | 6.74 | 6.25 | 0.49 | 7.21 | -0.47 | 5.98 | 0.76 |
| 2 | 6.76 | 6.27 | 0.49 | 6.49 | 0.27 | 6.14 | 0.62 |
| 3 | 6.22 | 5.92 | 0.3 | 6.85 | -0.63 | 5.94 | 0.28 |
| 4 | 5.5 | 5.11 | 0.39 | 4.97 | 0.53 | 6.08 | -0.58 |
| 5 | 5.2 | 4.83 | 0.37 | 4.6 | 0.6 | 4.88 | 0.32 |
| 6 | 7.79 | 8.17 | -0.38 | 7.26 | 0.53 | 7.24 | 0.55 |
| 7 | 7.5 | 7.18 | 0.32 | 7.94 | -0.44 | 6.92 | 0.58 |
| 8 | 4.04 | 3.82 | 0.22 | 3.52 | 0.52 | 4.43 | -0.39 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 9 | 5.33 | 4.87 | 0.46 | 5.69 | -0.36 | 4.95 | 0.38 |
| 10 | 7.39 | 6.89 | 0.5 | 7.81 | -0.42 | 7.8 | -0.41 |
| 11 | 6.43 | 6.12 | 0.31 | 6.68 | -0.25 | 6.1 | 0.33 |
| 12 | 5.88 | 5.52 | 0.36 | 5.49 | 0.39 | 5.43 | 0.45 |
| 13 | 6.56 | 6.11 | 0.45 | 6.15 | 0.41 | 7.06 | -0.5 |
| 14 | 7.88 | 7.53 | 0.35 | 8.29 | -0.41 | 8.11 | -0.23 |
| 15 | 6.92 | 6.7 | 0.22 | 7.26 | -0.34 | 6.46 | 0.46 |
| 16 | 7.22 | 7.35 | -0.13 | 7.74 | -0.52 | 7.61 | -0.39 |
| 17 | 6.32 | 5.9 | 0.42 | 6.86 | -0.54 | 6.12 | 0.2 |
| 18 | 5.92 | 5.78 | 0.14 | 5.47 | 0.45 | 5.67 | 0.25 |
| 19 | 6.44 | 6.14 | 0.3 | 6.23 | 0.21 | 6.89 | -0.45 |
| 20 | 6.06 | 5.93 | 0.13 | 5.55 | 0.51 | 6.44 | -0.38 |
| 21 | 7.18 | 7.69 | -0.51 | 7.44 | -0.26 | 7.62 | -0.44 |
| 22 | 7.65 | 7.24 | 0.41 | 7.1 | 0.55 | 8.09 | -0.44 |
| 23 | 7.58 | 7.87 | -0.29 | 8.13 | -0.55 | 7.63 | -0.05 |
| 24 | 8.15 | 8.5 | -0.35 | 7.88 | 0.27 | 8.49 | -0.34 |
| 25 | 7.58 | 7.07 | 0.51 | 7.12 | 0.46 | 7.86 | -0.28 |
| 26 | 6.85 | 6.57 | 0.28 | 6.57 | 0.28 | 7.04 | -0.19 |
| 27 | 6.79 | 6.22 | 0.57 | 6.53 | 0.26 | 6.92 | -0.13 |
| 28 | 6.33 | 5.79 | 0.54 | 6.17 | 0.16 | 5.76 | 0.57 |
| 29 | 6.65 | 6.06 | 0.59 | 6.36 | 0.29 | 6.84 | -0.19 |
| 30 | 6.5 | 7.1 | -0.6 | 6.08 | 0.42 | 6.08 | 0.42 |
| 31 | 6.85 | 7.28 | -0.43 | 7.06 | -0.21 | 7.33 | -0.48 |
| 32 | 5.69 | 6.16 | -0.47 | 5.78 | -0.09 | 5.42 | 0.27 |
| 33 | 6.01 | 5.51 | 0.5 | 5.82 | 0.19 | 6.3 | -0.29 |

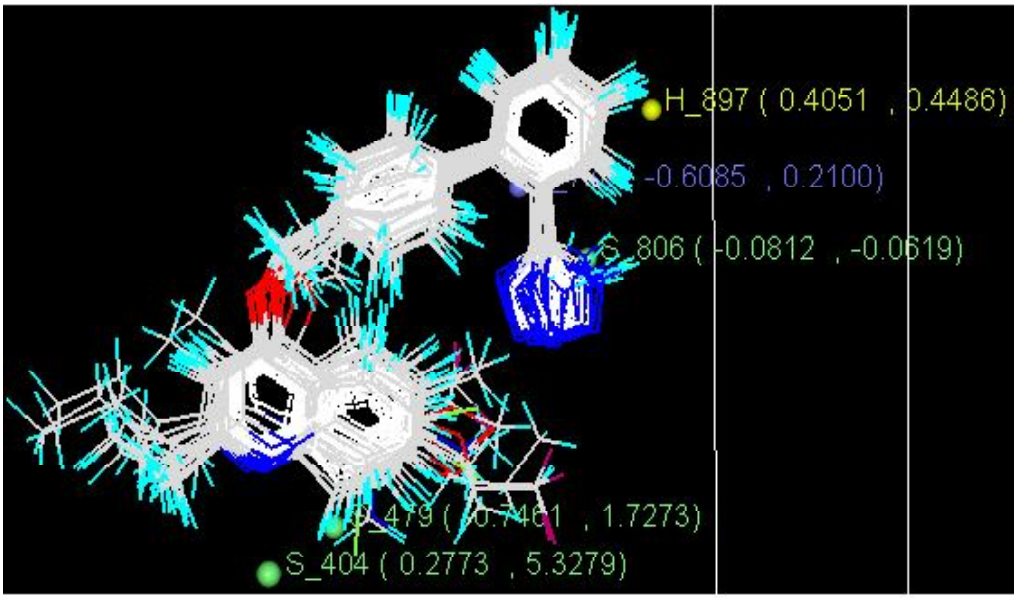


**Figure 2(a): Contour plots of model -1.**

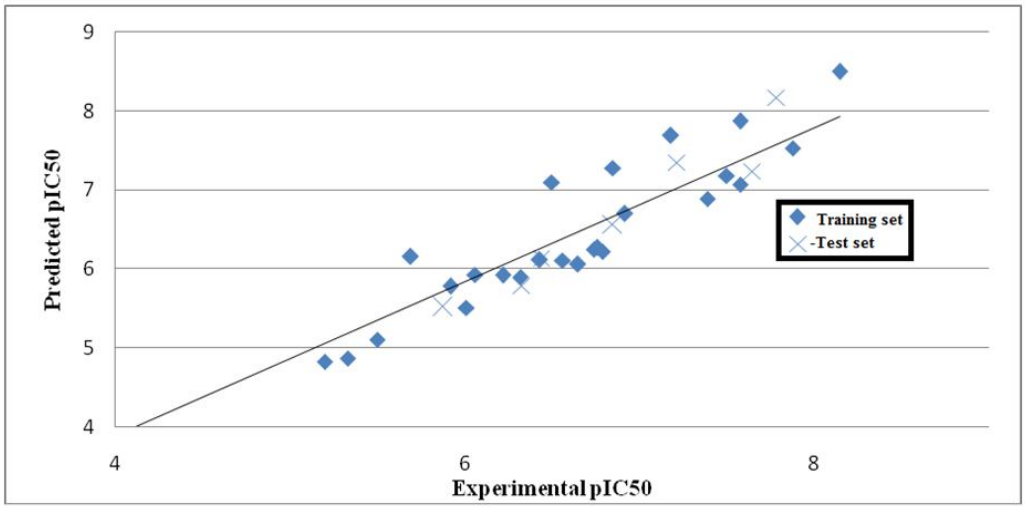


**Figure 2(b): Graph for observed *vs.* predicted activity of model-1.**

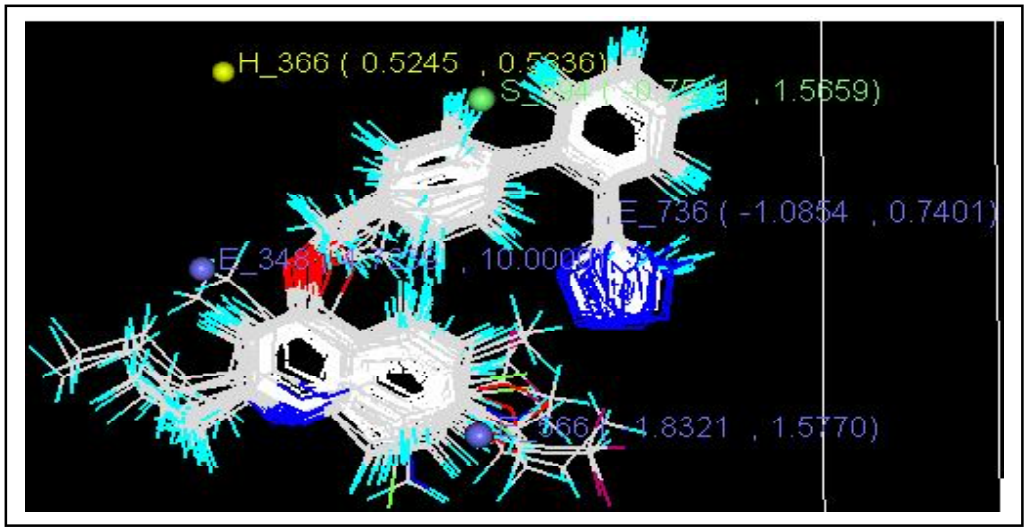


**Figure 2(c): Contour plots of model -2.**

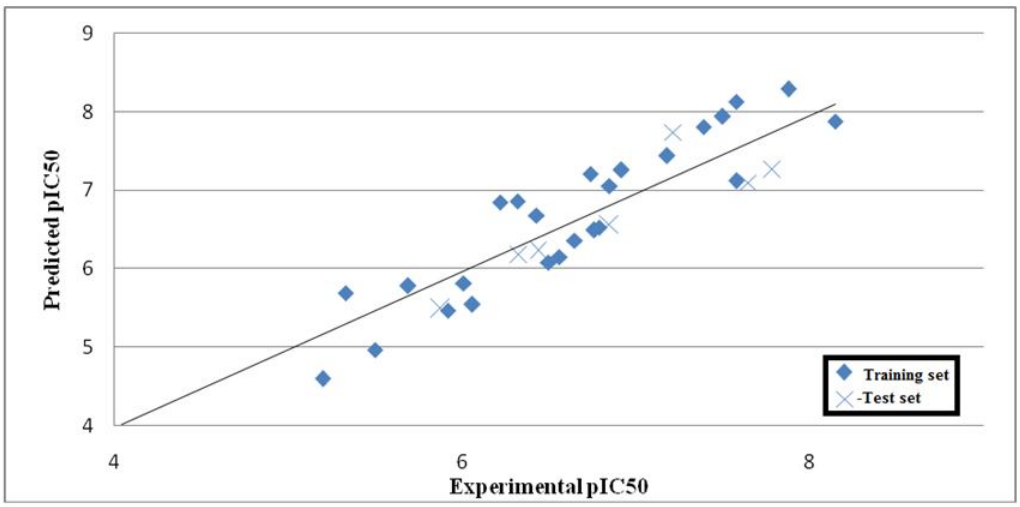


**Figure 2(d): Graph for observed *vs.* predicted activity of model-2.**

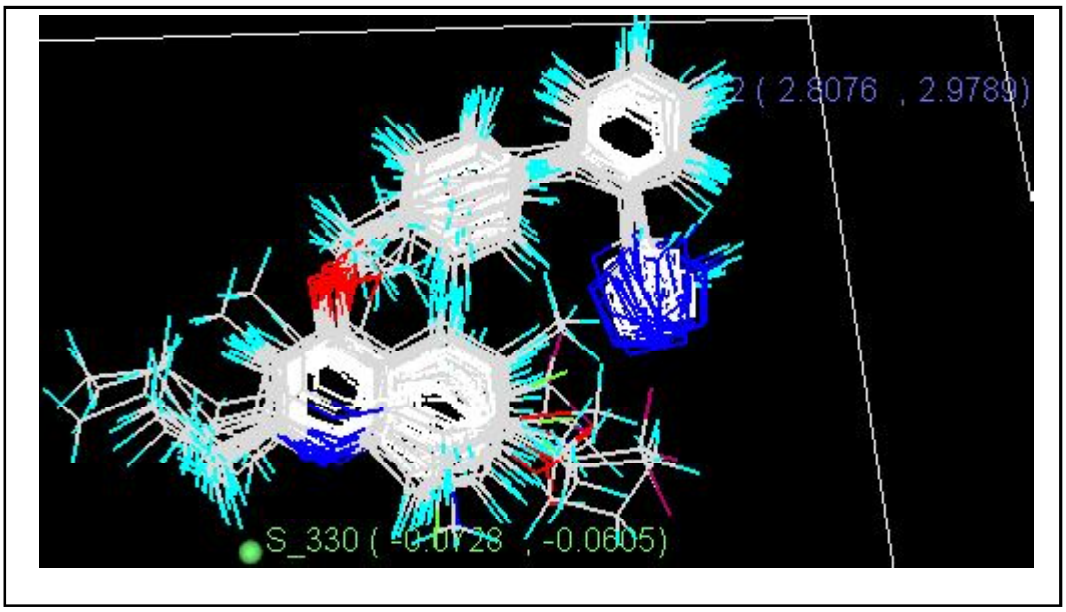


**Figure2(e): Contour plots of model -3.**

## 4. Discussion

QSAR studies (k-nearest neighbor molecular field analysis) were done using template alignment method to investigate the effect of electrostatic, steric and hydrophobic descriptors on angiotensin II $AT_1$ receptor activity of quinoline derivatives. From 3D-QSAR model 1, it is observed that electrostatic descriptor like E_736 (-0.6085) with negative values is near from R1 and R2 position of the quinoline ring. This indicates that electronegative groups are favour in this position is preferred in that region and presence of electronegative groups enhance the activity of quinoline derivatives (compound 14, 18, 20, 27, and 31) (Figure 2(a). Electronegative substituents at R1 and less steric bulk with electropositive substituents at R3 were found to be favourable for activity. The presence of steric descriptors S_404 (0.2773) and S_479 (0.7461) with positive values is also near from the R1 position and R3 of the ring which indicates that more bulky groups substituents are favourable on this position and presence of more bulky group increases the activity. The presence of H_897 (0.4051) positive coefficients represent near biphenyl regions of hydrophobic potential is favour for increase in activity and hence more hydrophobic substituent group is preferred in that moiety. Hydrophobic groups such as, $C_6H_5$,$CH_3$ were preferred at the position of generated data point H_897 at the moiety. The methyl group ($-CH_3$) is electron donating in nature, making the molecule more reactive (Kushwaha *et al.,* 2022). The plot of experiment versus predicted activities for the compounds is represented in Figure 2(c). In the 3D model-2, steric descriptors S_594 (0.7501) with negative coefficients represent regions of less steric tolerance; less bulky group is favourable in this region. The presence of E_348 (0.1769) and E_566 (1.8321)) electrostatic field with positive coefficients represent regions where electropositive groups are favourable at R1 position. The next electrostatic descriptor with negative coefficient E_736 (-1.0854) around biphenyl position of the ring corroborates that electronegative group is preferred at biphenyl position of quinoline ring. The negative values of electrostatic descriptors suggested that the essential of electronegative group like hydroxyl, nitro, chlorine, fluorine, bromine and iodine groups at the R1 position of the ring for maximum activity. The larger blue colour descriptors near R3 indicate that an electron withdrawing group is of beneficial to the activity in this position. Compounds with chlorine at the R3 position had more potential than those with methoxy, methyl, and ethyl at the same position. The next descriptor hydrophobic with positive coefficient H_366 (0.5245) is away from the ring and possibly it has not effect on the activity. The graphical representations and model summary of QSAR models results for activity are shown in Figure 2(c) and Table 2. The plot of observed versus predicted activities for the compounds is represented in Figure 2(d). The steric and electrostatic points considered in 3D model 3 is shown in the Figure 2(e), no contribution of any hydrophobic parameters according to model. 3D model determined by partial least squares with a $q^2$ (0.6398) of 64% and a predictivity for the external test set (pred_$r^2$ =0.5641) of about 56 %. The external predictability of the above 3D-QSAR model using the test set was determined by pred_$r^2$, which is 0.5641. The electrostatic descriptor generated was E_752 shown in map (Figure 2e). This is indicated that the electropositive groups like methyl and ethyl were essential for activity. The steric descriptor S_330 with negative coefficients at R3 ring indicates that bulky groups are unfavourable on this position and presence of bulky groups would decrease the activity of these compounds. QSAR study showed that small, hydrophobic and electron-withdrawing substituents seem to be better at the R1 position, whereas it is obvious that small electron-withdrawing substituents are favourable at the R3 position in the ring.

## 5. Conclusion

In the present study, we developed significant and predictive 3D QSAR models for angiotensin II $AT_1$ receptor activity of quinoline derivatives. The model was validated by cross-validation and external test set prediction. The present study reveals that presence of steric descriptor groups at R3 position and bulky groups at R3

position of quinoline moiety enhance the activity. Electronegative substituents at R1 and less steric bulk with electropositive substituents at R3 were found to be favourable for activity. The results revealed that the appropriate small, electron-withdrawing and hydrophobic group on R3 might help enhance activity, while the small and electron-withdrawing group on R1 and R3 would be favoured for activity. The novelty of this QSAR study is not only that the structural requirements for activity have been explored in this work, but the developed models have also been used for design of new molecules with possible potent antihypertensive activity.

## Acknowledgements

The author wishes to express gratitude to V-Life Science Technologies Pvt. Ltd for providing the software for the study.

## Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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**Citation** **Mukesh Chandra Sharma and Dharm Veer Kohli (2023). Quantitative structure activity relationship studies of some quinoline derivatives of angiotensin II receptor inhibitors. Ann. Phytomed., 12(2):423-429. http://dx.doi.org/10.54085/ap.2023.12.2.52.**