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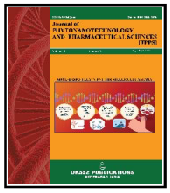

Original Article : Open Access

Exploring the molecular structural requirements of 3, 4, 5-trisubstituted triazoles and imidazotriazole analogues as angiotensin II receptor using molecular modeling approach

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Abstract

This work presents the development of a quantitative structure-activity relationship model to predict the antihypertensive activity of 3,4,5-trisubstituted 4H-1,2,4-triazoles and a related series of 3H-imidazo [1,2-b] [1,2,4] triazoles derivatives. These 4H-1,2,4-triazole and 3H-imidazo [1,2-b][1,2,4] triazoles derivatives were divided into a training set of fifty-two compounds and a test set of thirty-three compounds. The best 2D model with multiple linear regressions, giving a square correlation coefficient of 0.8173, cross-validated squared correlation coefficient of 0.7524, and predictable ability of 0.8836, and the 3D model produced good predictive models with a cross-validated correlation coefficient of 0.7994 and external test set 0.7005 values using the stepwise variable selection k-nearest neighbor molecular field analysis approach. The results will serve as a basis for the future design of potent molecules for angiotensin II AT1 receptor for antihypertensive agents.

1. Introduction

Angiotensin II is the most important endocrine ligand in the renin - angiotensin system (RAS), contributing to the development of several cardiovascular diseases including hypertension (Karnik *et al*., 2015). The renin-angiotensin-aldosterone system is intricately involved in the pathophysiology of several diseases, including hypertension, congestive heart failure, and chronic kidney disease of all types, including diabetic nephropathy (Hernández-Hernández *et al.,* 2002). The presence of two subtypes of angiotensin II receptors were pharmacologically recognized based on the sensitivity to the first orally active nonpeptide angiotensin II receptor antagonist (Bumpus *et al.,*1991). Angiotensin II receptor blockers represent a class of effective and well tolerated orally active antihypertensive drugs. Activation of AT_1 receptor leads to vasoconstriction, stimulation of the release of catecholamines and antidiuretic hormone and promote growth of vascular and cardiac muscle (Maggioni, 2006). Losartan was the first drug of this class marketed, shortly followed by valsartan, irbesartan, telmisartan, candesartan, eprosartan and others on current investigation. All these drugs have the common properties of blockading the AT_1 receptor, thereby relaxing vascular smooth muscle, increase salt excretion, decrease cellular hypertrophy and induce antihypertensive effect without modifying heart rate or cardiac output (Cernes *et al.,* 2011). Quantitative structure - activity relationships (QSAR) have come into widespread use for the prediction of various molecular properties and biological responses. The different topological descriptors can be used in place of experimentally derived descriptors in QSARs for prediction of properties (Gute and Basak,1997). The field of computational medicinal chemistry comprises computational approaches for the design, the development and the synthesis of pharmacologically active compounds (Schneider, 2011). QSAR models are essential to optimize the structure that gives the desired biological activities (Hellberg *et al.,* 1987). This approach could predict the biological activity of newly designed derivatives and being made these derivatives should be synthesized and tested. Imidazole moiety is a scaffold that is not only synthetically important but also possesses a wide range of promising biological activities. The series of eighty-five 3,4,5-trisubstituted 4H-1,2,4-triazoles and a related series of 3H-imidazo [1,2-b][1,2,4] triazoles derivatives was used for multiple linear regression model generation using the VLife MDS 3.5 software package. Different 2D physicochemical descriptors were used as independent variables and were correlated with angiotensin II AT_1 receptor antagonist's activity. We used the k nearest neighbor and pharmacophore methods to study the relationship of the structure and biological activity, which provide a theoretical basis for the further structural optimization of these compounds. These steric, electrostatic and hydrophobic field descriptors are useful for the better understanding of molecular modeling studies of these series of compounds in terms of ligand-receptor interactions.

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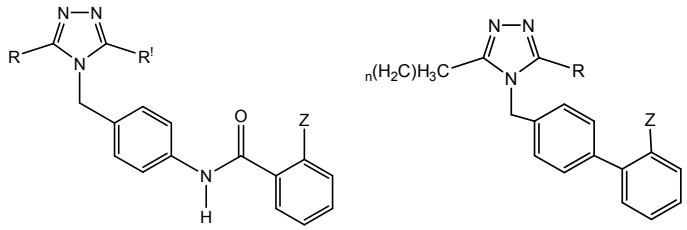
Table 1: Structures of triazole and imidazotriazole derivatives and their activity



S. No.	R	R'	Z	IC_{50} [a]	pIC_{50} [b]	Dataset
1	Bu	Ph	COOH	930	6.03	Training
2	EtS	Ph	COOH	1900	5.72	Training
3	PrS	Ph	COOH	1600	5.79	Training
4	Bu	4-pyridyl	COOH	1400	5.85	Training
5	Bu	3-pyridyl	COOH	1700	5.76	Test
6	Bu	2-furyl	COOH	1000	6.00	Training
7	EtS	CH_2Ph	COOH	1000	6.00	Training
8	PrS	CH_2Ph	COOH	380	6.42	Test
9	PrS	$(CH_2)_2Ph$	COOH	75	7.12	Training
10	PrS	$(CH_2)_3Ph$	COOH	320	6.49	Test
11	PrS	CH_2SPh	COOH	1200	5.92	Training
12	EtS	CH_2OMe	COOH	5200	5.28	Training
13	EtS	CF_3	COOH	4800	5.31	Training
14	PrS	CF_3	COOH	2100	5.67	Test
15	Bu	SCH_2CO_2Me	COOH	330	6.48	Training
16	Bu	$SCH_2CONHMe$	COOH	720	6.14	Training
17	Bu	SCH_2CO_2H	COOH	770	6.11	Training
18	Bu	$S(CH_2)_2OH$	COOH	480	6.31	Test
19	Bu	$SCH(Et)CO_2Me$	COOH	300	6.52	Test
20	Bu	SCH_2COPh	COOH	190	6.72	Training
21	Bu	SPh	COOH	60	7.22	Training
22	Bu	SCH_2Ph	COOH	15	7.82	Test
23	Bu	$S(CH_2)_2Ph$	COOH	70	7.15	Training
24	Pr	SCH_2Ph	COOH	120	6.92	Test
25	Bu	SCH_2Ph(2-Me)	COOH	14	7.85	Training
26	Bu	SCH_2Ph(3-Me)	COOH	32	7.49	Test
27	Bu	SCH_2Ph(4-Me)	COOH	7.6	8.11	Training
28	Bu	SCH_2Ph(2-Cl)	COOH	30	7.52	Test
29	Bu	SCH_2Ph(3-Cl)	COOH	26	7.58	Test
30	Bu	SCH_2Ph(4-Cl)	COOH	6.8	8.16	Training
31	Bu	SCH_2Ph(3-OMe)	COOH	21	7.67	Training
32	Bu	SCH_2Ph(4-OMe)	COOH	3	8.52	Test
33	Bu	$SOCH_2Ph$(4-OMe)	COOH	7.4	8.13	Training

34	Bu	$SCH_2Ph(2\text{-}CN)$	COOH	60	7.22	Test
35	Bu	$SCH_2Ph(4\text{-}CF_3)$	COOH	42	7.37	Test
36	Bu	SCH_2(P-naphthyl)	COOH	49	7.30	Training
37	Bu	$SCH(CO_2Me)Ph$	COOH	6.1	8.21	Training
38	Bu	$SCH(CO_2H)Ph$	COOH	20	7.69	Test
39	Bu	$SCH_2Ph(2\text{-}CO_2Me)$	COOH	14	7.85	Training
40	Bu	$SCH_2Ph(2\text{-}CO_2H)$	COOH	3.3	8.48	Test
41	Bu	$SCH_2Ph(3\text{-}CO_2Me)$	COOH	30	7.52	Training
42	Bu	$SCH_2Ph(3\text{-}CO_2H)$	COOH	15	7.82	Training
43	Bu	$SCH_2Ph(4\text{-}C1)$	CN_4H	6.8	8.16	Test
44	Bu	$SCH_2Ph(4\text{-}OMe)$	CN_4H	4.1	8.38	Test
45	Bu	$SOCH_2Ph(4\text{-}C1)$	CN_4H	33	7.48	Training
46	Bu	$SOCH_2Ph(4\text{-}OMe)$	CN_4H	28	7.55	Training
	R	**Z**				
47	H	SCH_2CO_2Me	COOH	540	6.26	Training
48	H	SH	COOH	860	6.06	Test
49	H	$SCMe_3$	COOH	890	6.05	Training
50	H	SMe	CN_4H	310	6.50	Training
51	H	SCH_2CHMe_2	CN_4H	72	7.14	Test
52	H	SCH_2-Cyclohexyl	CN_4H	36	7.44	Training
53	H	SPh	CN_4H	100	7.00	Training
54	H	SCH_2Ph	CN_4H	7.1	8.14	Test
55	H	$S(CH_2)_2Ph$	CN_4H	35	7.45	Training
56	H	$SCH_2Ph(2\text{-}Me)$	CN_4H	17	7.76	Training
57	H	$SCH_2Ph(2\text{-}Cl)$	CN_4H	110	6.95	Test
58	H	$SCH_2Ph(4\text{-}Cl)$	CN_4H	98	7.008	Training
59	H	$SCH_2Ph(4\text{-}Cl)$	CN_4H	24	7.61	Test
60	H	$SCH_2Ph(4\text{-}Cl)$	CN_4H	94	7.02	Training
61	H	$SCH_2Ph(2\text{-}NO_2)$	CN_4H	130	6.88	Test
62	H	$SCH_2Ph(4\text{-}NO_2)$	CN_4H	6.6	8.18	Training
63	H	$SCH_2Ph(3\text{-}OMe)$	CN_4H	94	7.02	Test
64	H	$SCH_2Ph(4\text{-}OMe)$	CN_4H	31	7.50	Training
65	H	$SCH_2Ph(4\text{-}CO_2Me)$	CN_4H	120	6.92	Training
66	H	$SCH_2Ph(4\text{-}CO_2H)$	CN_4H	24	7.61	Test
67	H	$SCH_2Ph(2\text{-}CO_2Me)$	CN_4H	90	7.04	Training
68	H	$SCH_2Ph(2\text{-}CO_2H)$	CN_4H	1.5	8.82	Test
69	H	$SCH_2Ph(2\text{-}CH_2OH)$	CN_4H	36	7.44	Training
70	H	$SCH_2Ph(2\text{-}CN_4H)$	CN_4H	1.4	8.85	Test
71	H	SO_2Me	CN_4H	400	6.39	Training
72	H	$SOCH_2Ph(4\text{-}Cl)$	CN_4H	11	7.95	Test
73	H	$SO_2CH_2Ph(4\text{-}Cl)$	CN_4H	48	7.31	Training

74	H	$SOCH_2Ph(4\text{-}NO_2)$	CN_4H	8.9	8.05	Training
75	H	$SOCH_2Ph(4\text{-}OMe)$	CN_4H	50	7.30	Test
76	H	$SOCH_2Ph(2\text{-}CO_2Me)$	CN_4H	40	7.39	Training
77	H	$SOCH_2Ph(2\text{-}CO_2H)$	CN_4H	10	8.00	Test
78	H	OCH_2Ph	CN_4H	370	6.43	Training
79	H	$O(CH_2)_2Ph$	CN_4H	63	7.20	Test
80	H	$NHCH_2Ph$	CN_4H	28	7.55	Training
81	H	$NHCH_2Ph(4\text{-}Cl)$	CN_4H	140	6.85	Training
82	H	$NHCH_2Ph(4\text{-}OMe)$	CN_4H	780	6.10	Test
83	H	$CONHCH_2Ph$	CN_4H	57	7.24	Training
84	H	$CON(Me)CH_2Ph$	CN_4H	89	7.05	Training
85	H	CON(Me)Ph	CN_4H	350	6.45	Training

[a]IC_{50} or inhibition of specific binding of [^{125}I] Ang II AT_1 receptor rabbit aorta, [b]-log IC_{50} to generate equation.

2. Materials and Methods

In this work, the dataset of the activities of eighty-five compounds were selected from the synthesized series of 3,4,5-trisubstituted 4H-1,2,4-triazoles and 3H-imidazo[1,2-b][1,2,4] triazole as angiotensin II AT_1 receptor antagonists (Ashton *et al.,*1993). The molecular structures of the studied molecules with their activity for eighty-five derivatives are presented in Table 1. All experimental activity values IC_{50} were converted to pIC_{50}. 2D structures of all the eighty-five compounds were sketched and converted into 3D structures using VLife molecular design suite software package (VLife MDS, 2010). The training set comprises fifty-two compounds and the test set consists of thirty-three compounds (Golbraikh and Tropsha, 2002). The minimization was terminated when the distance dependent dielectric constant of 1.0 and the convergence criterion of 0.01 kcal/mol Å (Halgren, 1996). A large number of theoretical 2D individual descriptors such as molar refractivity, molecular weight, partition coefficient, volume, estate numbers, polar surface area, element count, dipole moment have been computed. The physicochemical descriptors include 239 physicochemical parameters, 700 alignment type parameters and 99 atom type count descriptors were calculated. Energy minimized structures of molecules were aligned by the template-based method (Ajmani *et al.,* 2006). The template structure imidazotriazole ring is shown in Figure 1. The alignment of all molecules is shown in Figure 2.

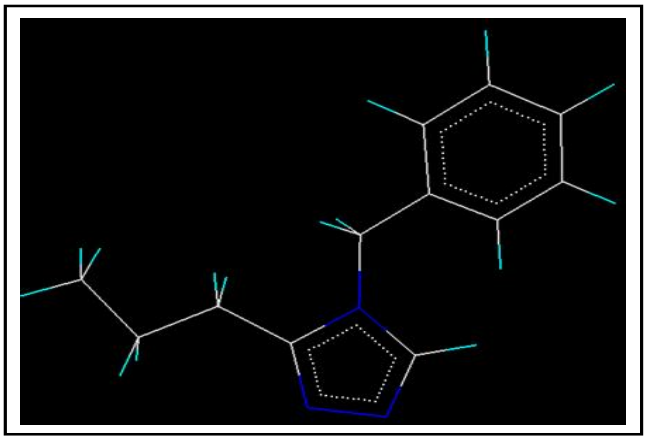


Figure 1: Stereo view of the template.

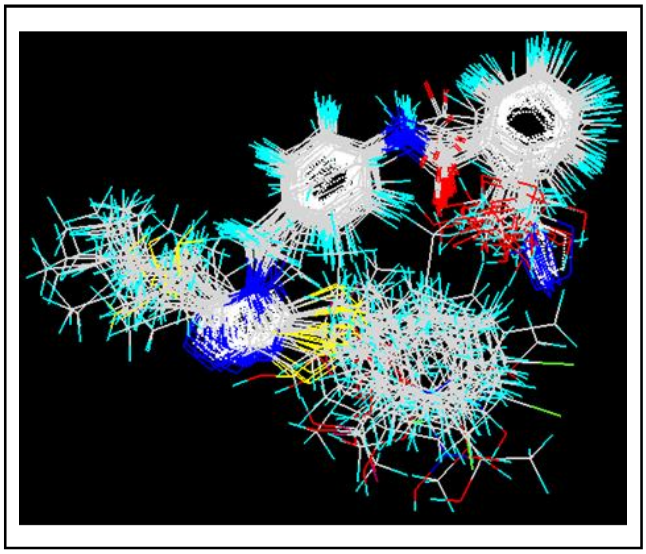


Figure 2: Stereo view of the alignment of the dataset.

The position of each atom is important for k nearest neighbor study because the descriptors calculation is based on the 3D space grid. To derive the k nearest neighbor molecular field analysis descriptor fields, a 3D cubic lattice with grid spacing of 2 Å in x, y, and z dimensions was created to encompass the aligned molecules. The descriptors were calculated using a sp3 carbon probe atom with a van der Waals radius of 1.52 Å and a charge of + 1.0 with a default cut-off energy value of ± 30 kcal/mol to generate steric, electrostatic and hydrophobic fields. The steric, electrostatic and hydrophobic energy values were truncated at a default value of ± 30 kcal/mol (Clark *et al.,* 1989). This resulted in the calculation of 4500 field descriptors (1500 for each electrostatic, steric and hydrophobic) for all the compounds in separate columns. The pharmacophore model was developed using the MolSign module of VLife molecular design suite. The pharmacophore model consisting of a set of three-dimensional attributes essential for the bioactive ligand was generated using a minimum of four pharmacophoric features, 10 Å as the tolerance limit and 30 Å as the maximum allowed distance (Sharma *et al.,* 2014; Sharma, 2015).

Table 2: Unicolumn statistics of activity for training and test set compounds

Dataset	Average	Max.	Min.	Std.Dev	Sum
2D- QSAR					
Training	11.783	16.322	5.278	0.971	144.58
Test	9.680	7.2788	3.176	0.895	59.48
3D-QSAR					
Training	16.216	19.187	7.321	1.785	185.31
Test	12.873	10.965	6.017	1.154	74.32

3. Results

In the present study, partial least squares applied with stepwise variable selection method was used to develop 2D and 3D QSAR models of 3,4,5-trisubstituted 4H-1,2,4-triazoles derivatives based on steric, electrostatic and hydrophobic fields. Statistical measures used for the evaluation of models were the number of compounds in the regression coefficient r^2, the F-test (Fischer's value) for statistical significance F, the cross-validated correlation coefficient q^2 and the standard error of estimation r^2 and q^2. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. Predicted squared regression (pred_r^2) and standard error of predicted squared regression (pred_r^2se) to estimate the predictive potential of the models respectively, standard error (r^2_se) representing absolute measure of quality of fit, and standard error of cross-validated square correlation coefficient (q^2_se). A value of r^2_pred greater than 0.5 indicates the good predictive capacity of the model. A uni column statistics for training set and test set were generated to check correctness of selection criteria for trainings and test set molecules (Table 2). The frequency of use of a particular descriptor in the population of equations indicated the relevant contributions of the descriptors (Table 3). Model-1 shows good squared correlation coefficient (r^2) of 0.8173 explains 81% variance in biological activity. The low standard error of r^2_se 0.3117 demonstrates accuracy of the model. The F test value of 61.487 shows the overall statistical significance level to be 99.99% of the model. Cross validated squared correlation coefficient of this model was 0.7524, which shows the good internal prediction power of this model. Another parameter for predictivity of test set compound is high pred_r^2 0.7813 and low pred_r^2se 0.6431, which is showing good external predictive power of the model. The plots of observed activity vs predicted activity values of pIC_{50} are shown in Figure 3.

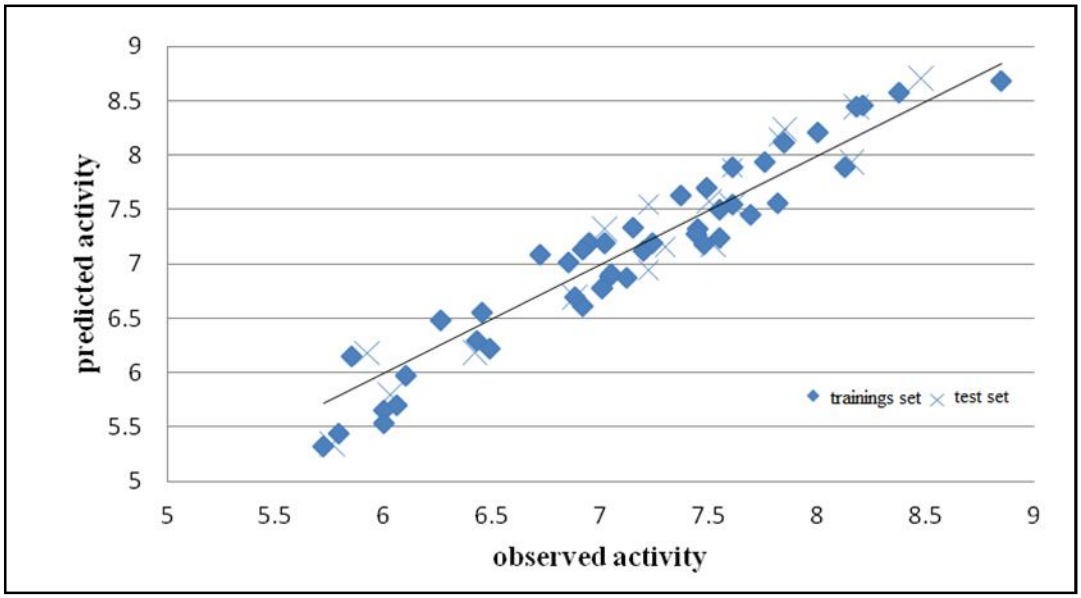


Figure 3: Relation between observed versus predicted activity for 2D model 1.

Model-2 shows good squared correlation coefficient (r^2) of 0.7819 explains 78% variance in biological activity. The low standard error of r^2_se 0.3799 demonstrates accuracy of the model. This model also indicates statistical significance 99.9% with F values 77.32. Cross validated squared correlation coefficient of this model was 0.7014, which shows the good internal prediction power of this model. Another parameter for predictivity of test set compound is high pred_r^2 0.7539 and low pred_r^2se 0.6825, which is showing good external predictive power of the model. The 3D QSAR model-3 showed significant correlation coefficient q^2 of 0.7994, standard error of predicted squared regression of 0.3952, r^2 for external test set 0.7360, degree of freedom 33 and k nearest neighbour of 4 and external predictability of the model using the test set was determined by pred_r^2, which is 0.7005. The points generated in 3D QSAR model 3 are S_735,- S_1130, E_912 and H_1007 that is, steric,

electrostatic and hydrophobic interaction respectively (Figure 4). The plots of observed activity vs predicted activity values of pIC_{50} are shown in Figure 5. Model 4 was found to be statistically most significant, especially with respect to the internal predictive ability 0.7251 of the model. 3D QSAR models were selected based on value of statistical parameters and the best 3D QSAR models have a q^2_se of 0.4192 and pred_r^2 of 0.6831. The points generated in 3D QSAR model 4 are S_498, E_790, E_1005 and H_1236 that is, steric, electrostatic and hydrophobic interaction respectively (Figure 6). The pharmacophore model was built using the Molsign module of VLife MDS. For five-point pharmacophore identification tolerance limit set up to 20 Å and max distance allowed between two features, set the value to 5 Å. This model, containing chemical functionalities such as hydrogen bond donor, hydrogen bond acceptor, hydrophobic, aliphatic, negative ionisable, positive ionizable and aromatic carbon centre can serve as an effective search filter for virtual screening.

Table 3: Statistical parameters of models

2D Model-1	pIC_{50}=-0.7695(±0.3440) Polar surface area (Including sulfur atom) -0.1662(±0.0363) T_2_F_4+0.4752(±0.1829) T_C_O_1+0.2606(±0.1448) H-donor countOptimum Components=5, $N_{Training}$ = 52, N_{Test}= 33, r^2= 0.8173, q^2= 0.7524, F test =61.487,r^2_se =0.311, q^2_se= 0.643,pred_r^2 = 0.7813, pred_r^2se = 0.6431.
2D Model-2	pIC_{50} = 0.3585(±0.0493) 5ChainCount-0.4984(±0.2319) T_O_S_6 -0.9598 (±0.6402) T_S_Cl_6+ 0.2076(±0.0243) T_C_S_2Optimum Components=5, $N_{Training}$ = 52, N_{Test}= 33, r^2= 0.7819, q^2= 0.7014, F test =77.32, r^2_se = 0.564, q^2_se= 0.643, pred_r^2 = 0.7539, pred_r^2se = 0.682.
3D Model-3	pIC50= -1.7695+ H_1007(0.3705,0.4404)+ E_912 (2.0154,2.1266)+ S_735 (-0.6671,3.1985)- S_1130 (30.0000 30.0000)k Nearest Neighbour= 4; $N_{Training}$ = 52, N_{Test}= 33, Optimum Components = 4, DF = 33, q^2 = 0.7994, q^2_se = 0.2306, pred_r^2 = 0.7005, pred_r^2se = 0.3952
3D Model-4	pIC50= 0.5138- E_790 (-1.8662 , -0.9458) - E_1005 (-1.2756,-0.0455) + H_1236 (0.1093, 0.4918)- S_498 (-0.5820 ,-0.2431)k Nearest Neighbour= 4; $N_{Training}$ = 52, N_{Test}= 33, Optimum Components = 4, DF =31,q^2 = 0.725,F test=51.37,q^2_se =0.419, pred_r^2= 0.6831,pred_r^2se = 0.642

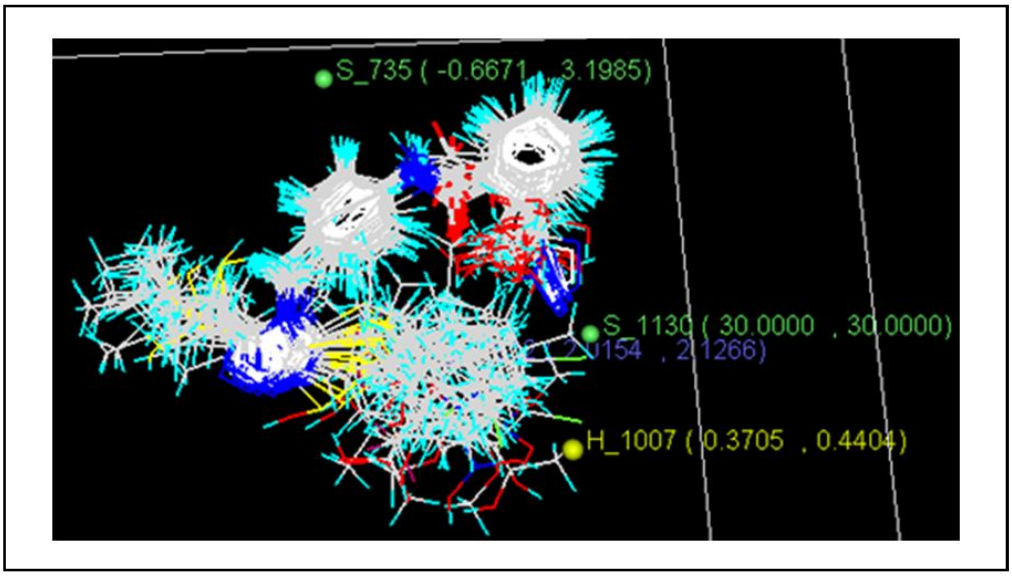


Figure 4: Contribution plot of steric, electrostatic field and hydrophobic interactions 3D model 3.

Table 4: Observed activities and predicted activities of compounds by models

Comp.	pIC_{50}	2D-Model-1		2D-Model-2		3D Model-3		3D Model-4	
		Pred.	Res.	Pred.	Res.	Pred.	Res.	Pred.	Res.
1	6.03	5.7925	0.2375	5.6961	0.3339	6.3029	-0.2729	6.1815	-0.1515
2	5.72	5.3215	0.3985	5.9012	-0.1812	5.8989	-0.1789	5.6776	0.0424
3	5.79	5.4423	0.3477	5.3022	0.4878	5.9973	-0.2073	5.2945	0.4955
4	5.85	6.1466	-0.2966	5.6301	0.2199	6.0223	-0.1723	5.6921	0.1579
5	5.76	5.3463	0.4137	5.2826	0.4774	5.3218	0.4382	5.4689	0.2911
6	6.00	5.6488	0.3512	5.7606	0.2394	6.3063	-0.3063	5.6853	0.3147
7	6.00	5.5331	0.4669	5.6847	0.3153	6.4062	-0.4062	5.7793	0.2207

8	6.42	6.1845	0.2355	6.5732	-0.1532	6.2011	0.2189	6.0708	0.3492
9	7.12	6.8776	0.2424	7.3802	-0.2602	6.8571	0.2629	6.9356	0.1844
10	6.49	6.2154	0.2746	6.6196	-0.1296	6.1901	0.2999	6.3056	0.1844
11	5.92	6.1799	-0.2599	5.7156	0.2044	6.0917	-0.1717	5.6258	0.2942
12	5.28	4.9227	0.3573	4.9955	0.2845	5.0119	0.2681	5.1998	0.0802
13	5.31	5.5952	-0.2852	5.3562	-0.0462	5.1383	0.1717	5.3134	-0.0034
14	5.67	6.0101	-0.3401	5.3124	0.3576	5.3808	0.2892	5.2604	0.4096
15	6.48	6.7994	-0.3194	6.7297	-0.2497	6.6701	-0.1901	6.2732	0.2068
16	6.14	5.8473	0.2927	5.9357	0.2043	6.0261	0.1139	6.2671	-0.1271
17	6.11	6.2862	-0.1762	5.7751	0.3349	6.3948	-0.2848	5.8628	0.2472
18	6.31	5.9904	0.3196	5.4856	0.8244	6.4782	-0.1682	6.1662	0.1438
19	6.52	6.7805	-0.2605	6.6544	-0.1344	6.3489	0.1711	6.2203	0.2997
20	6.72	7.0852	-0.3652	6.4218	0.2982	6.4565	0.2635	6.3303	0.3897
21	7.22	7.5456	-0.3256	7.3584	-0.1384	6.9308	0.2892	6.8176	0.4024
22	7.82	8.1674	-0.3474	7.6536	0.1664	7.5572	0.2628	7.4958	0.3242
23	7.15	7.3296	-0.1796	6.7891	0.3609	6.9068	0.2432	6.8371	0.3129
24	6.92	6.6097	0.3103	7.2194	-0.2994	6.7181	0.2019	6.6458	0.2742
25	7.85	8.2375	-0.3875	7.5602	0.2898	7.5128	0.3372	7.6949	0.1551
26	7.49	7.6951	-0.2051	7.3893	0.1007	7.2838	0.2062	7.2018	0.2882
27	8.11	8.3844	-0.2744	7.9782	0.1318	7.8735	0.2365	8.2619	-0.1519
28	7.52	7.3673	0.1527	7.0217	0.4983	7.2429	0.2771	7.1141	0.4059
29	7.58	7.1705	0.4095	7.4491	0.1309	7.2503	0.3297	7.2398	0.3402
30	8.16	8.4675	-0.3075	8.3191	-0.1591	8.0572	0.1028	7.9463	0.2137
31	7.67	7.3876	0.2824	7.4654	0.2046	7.2835	0.3865	7.1995	0.4705
32	8.52	8.8265	-0.3065	8.3275	0.1925	8.2762	0.2438	8.1972	0.3228
33	8.13	7.8847	0.2453	8.3088	-0.1788	7.9648	0.1652	8.2462	-0.1162
34	7.22	6.9448	0.2752	7.3879	-0.1679	6.8607	0.3593	7.0176	0.2024
35	7.37	7.6237	-0.2537	7.0416	0.3284	7.5473	-0.1773	7.1223	0.2477
36	7.30	7.1571	0.1429	7.3885	-0.0885	7.0121	0.2879	7.5958	-0.2958
37	8.21	8.4584	-0.2484	7.9764	0.2336	8.3623	-0.1523	8.0983	0.1117
38	7.69	7.4557	0.2343	7.7215	-0.0315	7.2604	0.4296	7.5069	0.1831
39	7.85	8.1162	-0.2662	7.4981	0.3519	7.6946	0.1554	7.5742	0.2758
40	8.48	8.7016	-0.2216	8.6986	-0.2186	8.1957	0.2843	8.2958	0.1842
41	7.52	7.1742	0.3458	7.0669	0.4531	7.2482	0.2718	7.3595	0.1605
42	7.82	7.5522	0.2678	8.1854	-0.3654	7.6159	0.2041	7.4473	0.3727
43	8.16	7.9366	0.2234	8.0325	0.1275	8.3492	-0.1892	7.8583	0.3017
44	8.38	8.5755	-0.1955	8.6972	-0.3172	8.2142	0.1658	8.1916	0.1884
45	7.48	7.1766	0.3034	7.6538	-0.1738	7.6853	-0.2053	7.1918	0.2882
46	7.55	7.2338	0.3162	7.7146	-0.1646	7.1148	0.4352	7.3425	0.2075
47	6.26	6.4763	-0.2163	6.3378	-0.0778	5.9942	0.2658	6.0594	0.2006
48	6.06	5.6985	0.3615	6.1169	-0.0569	6.1869	-0.1269	6.0948	-0.0348
49	6.05	6.2759	-0.2259	5.8675	0.1825	6.1093	-0.0593	6.2276	-0.1776

50	6.50	6.7042	-0.2042	6.3294	0.1706	6.5849	-0.0849	6.4127	0.0873
51	7.14	7.2258	-0.0858	6.8511	0.2889	6.9861	0.1539	7.1882	-0.0482
52	7.44	7.6931	-0.2531	7.5018	-0.0618	7.3079	0.1321	7. 3362	0.1038
53	7.00	6.8642	0.1358	7.1365	-0.1365	6.9883	0.0117	7.0983	-0.0983
54	8.14	7.8321	0.3079	7.8524	0.2876	8.1965	-0.0565	8.0157	0.1243
55	7.45	7.316	0.134	7.3943	0.0557	7.6304	-0.1804	7.7286	-0.2786
56	7.76	7.9416	-0.1816	7.8194	-0.0594	7.8477	-0.0877	7.8207	-0.0607
57	6.95	7.1951	-0.2451	7.0568	-0.1068	6.7643	0.1857	6.7453	0.2047
58	7.008	6.7816	0.2264	7.1413	-0.1333	7.2891	-0.2811	6.7193	0.2887
59	7.61	7.8841	-0.2741	7.8285	-0.2185	7.8519	-0.2419	7.5335	0.0765
60	7.02	7.1968	-0.1768	6.9649	0.0551	6.7834	0.2366	6.8974	0.1226
61	6.88	6.6941	0.1859	6.6897	0.1903	6.9938	-0.1138	6.8392	0.0408
62	8.18	8.4481	-0.2681	8.2681	-0.0881	8.2479	-0.0679	7.9844	0.1956
63	7.02	7.3174	-0.2974	6.7173	0.3027	6.9394	0.0806	7.0935	-0.0735
64	7.50	7.5762	-0.0762	7.6285	-0.1285	7.4291	0.0709	7.5482	-0.0482
65	6.92	7.1287	-0.2087	6.8913	0.0287	6.8189	0.1011	7.1433	-0.2233
66	7.61	7.5418	0.0682	7.8244	-0.2144	7.6988	-0.0888	7.6514	-0.0414
67	7.04	6.8809	0.1591	6.915	0.125	7.1291	-0.0891	6.7719	0.2681
68	8.82	9.0659	-0.2459	8.7448	0.0752	8.9756	-0.1556	8.6823	0.1377
69	7.44	7.2751	0.1649	7. 5502	-0.1102	7.5879	-0.1479	7.2789	0.1611
70	8.85	8.6831	0.1669	9.1429	-0.2929	8.6476	0.2024	8.9873	-0.1373
72	6.39	6.2574	0.1326	6.1882	0.2018	6.4514	-0.0614	6.5321	-0.1421
72	7.95	8.1056	-0.1556	7.7462	0.2038	7.6063	0.3437	7.8649	0.0851
73	7.31	7.3879	-0.0779	7.4577	-0.1477	7.4865	-0.1765	7.1309	0.1791
74	8.05	8.2216	-0.1716	8.1497	-0.0997	7.9468	0.1032	8.1635	-0.1135
75	7.30	7.1896	0.1104	7.5725	-0.2725	7.5971	-0.2971	7.1607	0.1393
76	7.39	7.4879	-0.0979	7.2905	0.0995	7.1789	0.2111	7. 2063	0.1837
77	8.00	8.2147	-0.2147	8.1974	-0.1974	8.1582	-0.1582	6.8326	1.1674
78	6.43	6.2968	0.1332	6.6485	-0.2185	6.8546	-0.4246	6.1912	0.2388
79	7.20	7.1176	0.0824	6.9829	0.2171	7.4096	-0.2096	7.6264	-0.4264
80	7.55	7.4968	0.0532	7.2665	0.2835	7.4271	0.1229	7.3213	0.2287
81	6.85	7.0143	-0.1643	6.7253	0.1247	6.9385	-0.0885	7.11738	-0.267
82	6.10	5.9683	0.1317	5.9581	0.1419	5.8427	0.2573	6.1639	-0.0639
83	7.24	7.1958	0.0442	7.3252	-0.0852	7.0415	0.1985	7.2997	-0.0597
84	7.05	6.9085	0.1415	7.1892	-0.1392	7.1649	-0.1149	6.8153	0.2347
85	6.45	6.5493	-0.0993	6.3271	0.1229	6.6861	-0.2361	6.2876	0.1624

4. Discussion

The derived Model-1 shows good correlation between biological activity and parameters polar surface area, T_2_F_4, T_C_O_1 and H donor count as the correlation coefficient 0.87 and the model explains about 87% variance in activity. Model-1 also shows a positive correlation with polar surface area (including sulfur atom), T_C_O_1, and H donor count and a negative correlation with T_2_F_4. As a positive contributing descriptor, polar surface area (including sulfur atom) is an signifies total polar surface area including sulphur plays a most important role in determining activity and descriptor signifies the total polar surface area including sulphur in postion imidazo and triazoles R^1 and Z. This suggests that substituents such as -SPhCl,-$SCH_2Ph(-OMe)$ and $SCH_2Ph(-CF_3)$ would increase the activity. The descriptor influencing activity T_2_F_4 is directly proportional to the activity and indicates that increase in the count of number of double bounded atoms (any double bonded atom, T_2) separated from fluorine atom by four bonds in a molecule will lead to positive effect on the activity. The other descriptor T_C_O_1 are inversely proportional which indicates that the presence of methoxy, ethoxy and carbonyl increase in the number of bonds between two carbon atoms at the part R, R^1 and Z position end may be detrimental for biological activities. The positive correlation of polar surface area including sulfur atom shows that polar groups like hydroxyl and methoxy at R^1 are important for activity. Its positive contribution shows a detrimental effect of an R and R^1 methyl group on activity. The predicted activities of the compounds by the above model are shown in Table 4.

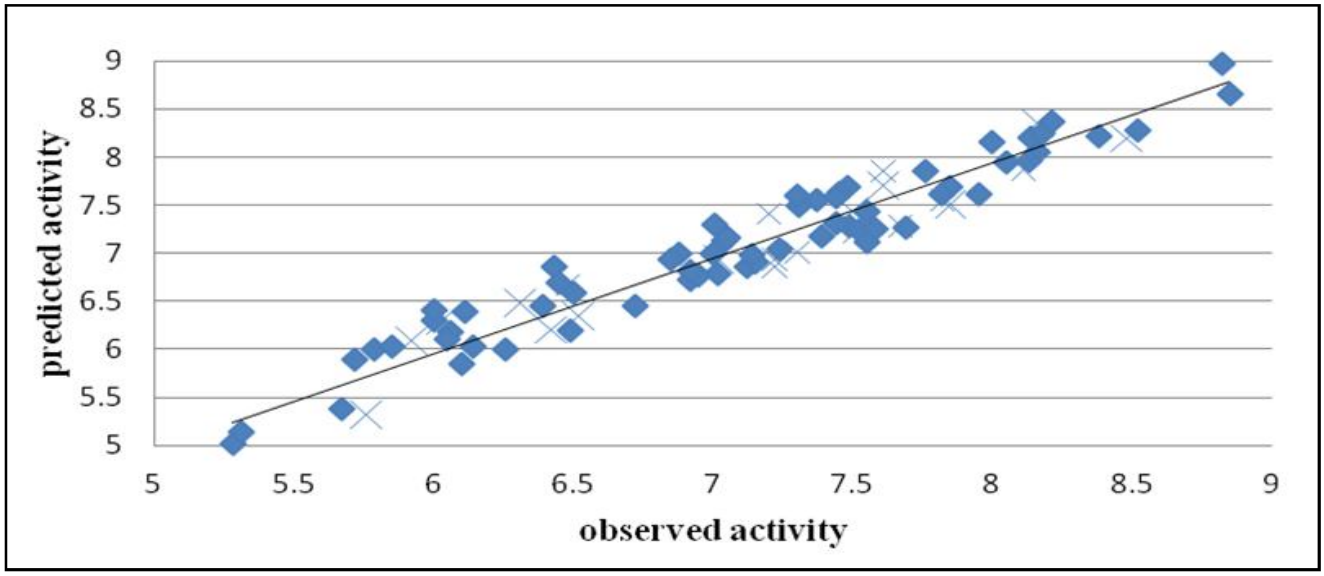


Figure 5: Comparison of observed activity versus predicted activity for 3D Model-3.

Model-2 also shows with descriptor 5 Chain Count is a number of five membered compounds in a ring, like imidazole and tetrazole variant substituents in triazole is conducive to activity. The tetrazole group in the biphenyl portion role in biological activity of compounds. The descriptor T_C_S_2 count of number of double bounded atoms (*i.e.*, any double bonded atom, T_2) separated from any other double bonded atom by 2 bonds in a molecule in favour increase activity R position of ring. The positive contribution of descriptor T_S_Cl_6 number of sulphur atoms separated from chlorine atom by six bond distance in a molecule and show that presence of sulphur group 1,2,4-triazole such as compound number 28, 29 and 30 position is enhanced for the activity. The positive contribution of next important alignment independent descriptor T_O_S_6 count of number of oxygen atoms (single double or triple bonded) separated from sulphur atom by six bond distance in a molecule position of 4H-1, 2, 4-triazole is favourable for the activity. The stepwise variable selection method resulted in significant 3D Model-3 and Model-4. The model- 3 shows steric descriptors S_735 (-0.6671,3.1985) showed that negative steric potential is favourable for activity, and less bulky substituents group should be considered in that position at R2 position. The electrostatic data point generated was E_912 (2.0154,2.1266) electropositive groups like methyl, ethyl and butyl group for activity. The hydrophobic field descriptor H_1007 (0.3705,0.4404) has positive range indicates that positive hydrophobic is favorable for activity at the R and Z position. Positive value of steric descriptor S_1130 (30.0000, 30.0000) showed that favourable and bulkier group is to prefer in that R and Z position triazole moiety.

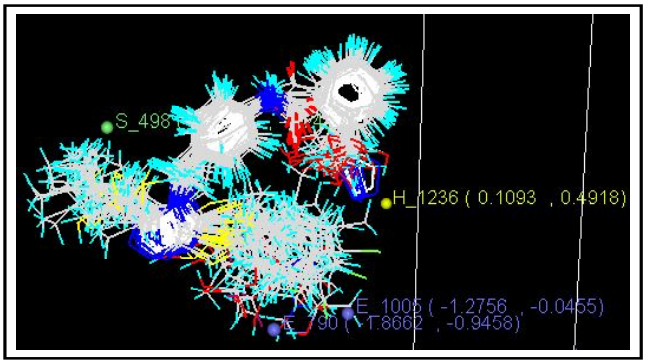


Figure 6: Contribution plot of steric, electrostatic field and hydrophobic interactions 3D model 4.

3D model 4 showed electrostatic field descriptor E_790 and E_1005 (-1.2756, -0.0455) with negative coefficient indicates that electron donating groups are favourable at the R and Z ring of triazoles moiety and more electronegative groups are preferred in that position.

Electron donating groups like amines, methoxy may increases the activity and electron withdrawing groups like Br, Cl may significantly decrease the activity. The steric descriptor S_498 (-0.5820, -0.2431) indicates less bulky group were required at R position. The hydrophobic descriptor H_1236 (0.1093,0.4918) surrounding of ring indicate that hydrophobic substitution at the RÈ and Z positions will decrease activity. The obtained pharmacophore model information shows that the five features used were two AroC feature (aromatic), one HAc (hydrogen bond acceptor), and one negative ionizable (NegC) features (Figure 7). The average RMSD of the pharmacophore alignment of each two molecules is 0.4752 Å. Distance (59HDr-57HAc) = 4.7697 Distance (59HDr-56NegC) =7.3787 Å, Distance (59HDr 16O) = 4.7697 Distance (56NegC 16O) = 3.4608 Å, Distance (57HAc 33C) = 3.8406 Å, Distance (57HAc 9C) = 4.5775 Å, Distance (16O 22C) =4.5921Å, Distance (56NegC 22C) = 4.7913 Å, Distance (22C 59HDr) = 4.3521 Å.

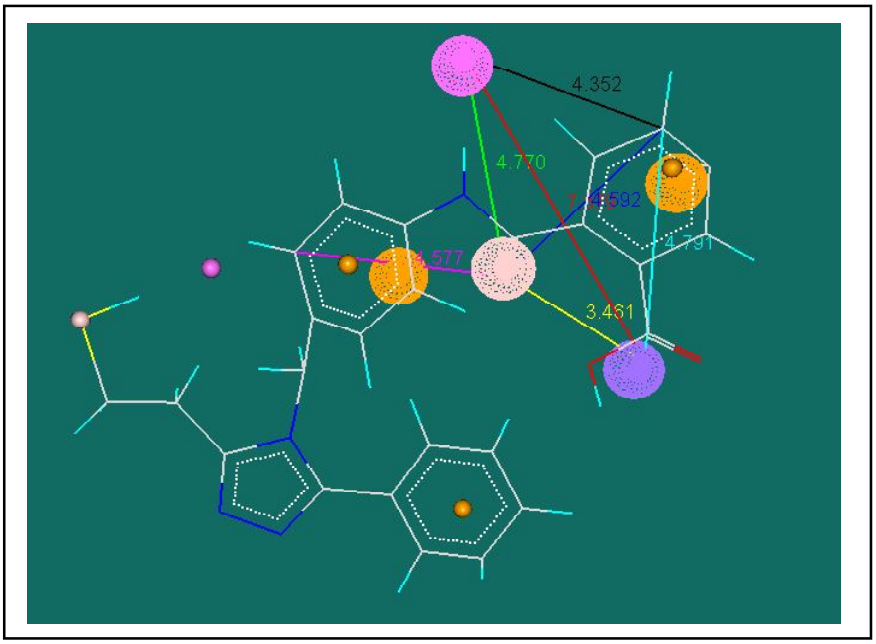


Figure 7: Distance based pharmacophore model.

5. Conclusion

The combined QSAR analysis provides useful insight into the structural basic moiety for the series of derivatives as to improve their potency 3,4,5-trisubstituted 4H-1,2,4-triazoles and a related series of 3H-imidazo [1,2-b] [1,2,4] triazoles angiotensin II receptor. 2D-QSAR model was found that properties like polar surface area, T_2_F_4, T_C_O_1, and hydrogen donor count contributes around the moiety to increase activity whereas 3DQSAR model shows that substitution of less bulky, hydrophobic, electropositive and electronegative substitutions are preferable for better antihypertensive activity. In models shows the bulky, electron withdrawing, substituents at the chain of R^1 and Z position would be favourable. Furthermore, these results would be of great value in optimizing the discovery of new candidate antihypertensive drugs in the future before their synthesis.

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Conflict of interest

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

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