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QSAR studies on a series of N^2-aryltriazolinone biphenylsulfonamide derivatives in order to evolve potent and orally active angiotensin II receptor antagonists

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ABSTRACT

Quantitative structure activity relationship (QSAR) studies have been performed on a series of N^2 – Aryltriazolinone Biphenyl sulfonamide derivatives, using physico-chemical parameters such as hydrophobicity (π), molar refractivity (MR), field effect (F) resonance effect (R) and electronic properties. Binding affinities of these derivatives for the AT_1 and AT_2 receptor subtype of angiotensin II in human adrenal assays was found to have strong correlation with hydrophobicity (π) of the substituent at R^1 position and molar refractivity of the substituent at R^3 position. The presence of F atom at X position was also found to be important for activity.

Key words: QSAR, aryltriazolinone, antagonists.

INTRODUCTION

Renin-angiotension system or renin-angiotensin-aldosterone system is a hormone system. This system plays an important role in the regulation of blood pressure in addition to electrolyte homeostatis.[1] Angiotensin II is a major bioactive product of this system.[2] Angiotensin II causes blood vessels to constrict resulting in increased blood pressure.[3] Recent efforts have focused upon the discovery of angiotensin II receptor antagonists, Agents which block the binding of aII to its receptors.

A series of previously prepared trisubstituted 1, 2, 4 – triazolinone Biphenyl sulfonamides dual-acting AII antagonists has been taken from literature.[4]

In the present work QSAR analysis has been carried out on the same series in order to highlight the relation of different physico-chemical parameters of substituents with activity.

EXPERIMENTAL

46 compounds of N^2- Aryltriazolinone BiphenylSulfonamide series with their calculated physico-chemical parameters and angiotensin receptor antagonistic activity are given in table 1.

Values of physico-chemical parameters were taken from literature.[5] All the 46 compounds were analyzed by regression analysis with physico-chemical parameters as independent variable and negative logarithms of binding potencies as dependent variable using SYSTAT (version-12) software.[6]

It is very clear from table 2 that substituent hydrophobicity constant (π_R^1), molar refractivity (MR_R^1), field effect (F_R^1) for R^1 sustituent, molar refractivity (MR_R^2), field effect (F_R^2) for R^2 sustituent, hydrophobicity constant (π_R^3), molar refractivity (MR_R^3) for R^3 sustituent and indicator parameter Iy have considerably effective correlation with activity.

Further the inter-correlation of parameters was taken into account and highly correlated parameters were rejected. Now the parameters which have strong correlation with activity were considered for further study.

From the selected parameters selection of parameters to obtain the QSAR model was carried out using regression analysis.

RESULTS AND DISCUSSION

Regression analysis has given various equations,

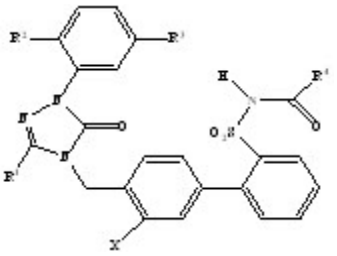
$$-\log IC_{50}\,(AT_2/AT_1) = \pi_R^1\,(-0.870) \pm 0.083 + MR_R^3\,(0.006) \pm 0.008 + Iy\,(0.334) \pm 0.189 + 0.567$$

n=46 r = 0.890 r^2 = 0.793 s = 0.251
F = 53.623 ...(1)

Where n is the number of compounds, r = correlation coefficient, r^2 = squared correlation coefficient, S = standard error of estimation, F is the value of Fisher test which denotes the statistical significance of the regression equation.

Eq. 1 with highest correlation coefficient (r

Table 1: Binding Affinities and Physicochemical Data for various N^2-Aryltriazolilone Biphenylsulphonamides for AT_2 and AT_1 Receptor subtypes of AII in Human Adrenal Tissue Preparations



C. N.	R^1	π_R^1	R^2	MR_R^2	R^3	MR_R^3	R^4	X	Ix	$-LogIC_{50}$
1.[a]	n-Bu	2.13	CF_3	5.02	NHCOEt	19.58	O(t-Bu)	H	0	-1
2.[a]	n-Bu	2.13	CF_3	5.02	NHCOEt	19.58	O(t-Bu)	F	1	-0.951
3.[a]	n-Bu	2.13	Cl	6.03	NHCOEt	19.58	O(t-Bu)	H	0	-1.332
4.[a]	n-Bu	2.13	Cl	6.03	NHCOEt	19.58	O(t-Bu)	F	1	-0.924
5.[b]	n-Bu	2.13	Cl	6.03	NHCOEt	19.58	2-Cl(C_6H_4)	F	1	-0.986
6.[b]	n-Bu	2.13	Cl	6.03	CONH(n-Bu)	28.49	2-Cl(C_6H_4)	F	1	-0.826
7.[a]	n-Bu	2.13	Cl	6.03	CONH(n-Bu)	28.49	O(t-Bu)	F	1	-0.612
8.[b]	n-Bu	2.13	Cl	6.03	NHCO(2-furyl)	27.50	O(t-Bu)	F	1	-1.113
9.[b]	n-Bu	2.13	Cl	6.03	$NHCOCH_2OEt$	26.37	O(t-Bu)	F	1	-0.643
10.[a]	n-Bu	2.13	Cl	6.03	$NHCO(CH_2)_2$ OMe	26.39	O(t-Bu)	F	1	-1.113
11.[a]	n-Bu	2.13	Cl	6.03	$CONH(CH_2)_2OMe$	26.03	O(t-Bu)	F	1	-1
12.[a]	n-Bu	2.13	Cl	6.03	CONH(n-Pr)	23.87	O(t-Bu)	F	1	-0.724
13.[b]	n-Bu	2.13	Cl	6.03	CO(n-Pr)	25.10	O(t-Bu)	F	1	-0.531
14.[a]	n-Bu	2.13	CF_3	5.02	NHCO(n-Bu)	28.85	O(t-Bu)	F	1	-0.623
15.[a]	n-Bu	2.13	CF_3	5.02	$NHCOCH_2Oet$	26.37	O(t-Bu)	F	1	-0.361
16.[a]	n-Bu	2.13	CF_3	5.02	NHCOEt	19.58	O(i-Pr)	F	1	-0.778
17.[a]	n-Bu	2.13	CF_3	5.02	NHCOEt	19.58	CH_2-(t-Bu)	F	1	-0.633

18.[a]	n-Bu	2.13	CF_3	5.02	NHCOEt	19.58	C_6H_5	F	1	-1.113
19.[a]	n-Bu	2.13	CF_3	5.02	NHCOEt	19.58	(2-F)C_6H_4	F	1	-0.748
20.[a]	n-Bu	2.13	CF_3	5.02	NHCOEt	19.58	(2-Cl)C_6H_4	F	1	-0.908
21.[a]	n-Bu	2.13	CF_3	5.02	NHCOEt	19.58	(2,5Cl_2)C_6H_3	F	1	-0.748
22.[a]	n-Bu	2.13	CF_3	5.02	NHCOPh	34.64	O(t-Bu)	F	1	-0.653
23.[a]	n-Bu	2.13	Br	8.88	NHCOEt	19.58	O(t-Bu)	F	1	-0.662
24.[b]	n-Bu	2.13	Br	8.88	NHCOPh	34.64	O(t-Bu)	F	1	-0.740
25.[b]	n-Pr	1.55	Br	8.88	NHCOPh	34.64	O(t-Bu)	F	1	-0.255
26.[b]	n-Pr	1.55	Br	8.88	NHCOEt	19.58	O(t-Bu)	F	1	-0.612
27.[b]	n-Pr	1.55	Br	8.88	NHCO(n-Bu)	28.85	O(t-Bu)	F	1	-0.707
28.[b]	n-Pr	1.55	Br	8.88	CONH(n-Bu)	28.49	O(t-Bu)	F	1	-0.477
29.[b]	n-Pr	1.55	Br	8.88	CONH(n-Bu)	28.49	(2,5Cl_2)C_6H_3	F	1	-0.113
30.[a]	n-Pr	1.55	CF_3	5.02	NHCOPh	34.64	O(t-Bu)	F	1	-0.518
31.[a]	n-Pr	1.55	CF_3	5.02	$NHCOCH_2OEt$	26.37	O(t-Bu)	F	1	-0.414
32.[a]	n-Pr	1.55	CF_3	5.02	CONH(n-Bu)	28.49	O(t-Bu)	F	1	-0.477
33.[a]	n-Pr	1.55	CF_3	5.02	CONH(n-Pr)	23.87	(2,5Cl_2)C_6H_3	F	1	-0.230
34.[b]	Et	1.02	CF_3	5.02	CONH(n-Bu)	28.49	O(t-Bu)	F	1	0.045
35.[a]	Et	1.02	CF_3	5.02	NHCO(n-Bu)	28.85	O(t-Bu)	F	1	-0.204
36.[a]	Et	1.02	Cl	6.03	NHCO(n-Bu)	28.85	O(t-Bu)	F	1	0.221
37.[b]	Et	1.02	Cl	6.03	$NHCOCH_2OEt$	26.27	O(t-Bu)	F	1	0.698
38.[a]	Et	1.02	Cl	6.03	NHCOPh	34.64	O(t-Bu)	F	1	0.397
39.[a]	Et	1.02	Br	8.88	NHCOPh	34.64	O(t-Bu)	F	1	0.698
40.[b]	Et	1.02	Br	8.88	NHCOEt	19.58	O(t-Bu)	F	1	0.301
41.[a]	Et	1.02	Br	8.88	NHCO(n-Bu)	28.85	O(t-Bu)	F	1	0
42.[a]	Et	1.02	Br	8.88	CONH(n-Bu)	28.49	O(t-Bu)	F	1	0.698
43.[b]	Et	1.02	Br	8.88	NHCO(n-Bu)	28.85	O(i-Pr)	F	1	0.522
44.[a]	Et	1.02	Br	8.88	NHCO(n-Bu)	28.85	(2,5F_2)C_6H_3	F	1	0.096
45.[a]	Et	1.02	Br	8.88	NHCO(n-Bu)	28.85	(2-F)C_6H_4	F	1	0.045
46.[a]	Me	0.56	Br	8.88	NHCO(n-Bu)	28.85	O(t-Bu)	F	1	0.305

*only the selected parameters are listed.

-Log IC_{50} is the negative logarithm of binding potencies of the compounds for AT_2 and AT_1 receptor subtypes of angiotensin II in human adrenal tissue preparation.

a- Training set compounds

b- Test set compound

Table 2: Correlation of all physico-chemical parameters with activity

	-log IC_{50} (AT_2/AT_1)	**P_R^1**	**MR_R^1**	**F_R^1**	**MR_R^2**	**F_R^2**	**MR_R^3**	**I_Y**
-log IC_{50} (AT_2/AT_1)	1							
P_R^1	-0.878	1						
MR_R^1	-0.878	0.999	1					
F_R^1	-0.734	0.884	0.869	1				
MR_R^2	0.456	-0.505	-0.503	-0.485	1			
F_R^2	0.355	-0.390	-0.391	-0.330	0.905	1		
MR_R^3	0.471	-0.453	-0.448	0.474	0.299	0.276	1	
I_Y	0.300	-0.187	-0.184	-0.204	0.137	0.098	0.274	1

=0.890) was considered to be the best model explaining 89% correlation of parameters with activity. The low standard error of estimate and a high F value suggests that the model is statistically significant.

Eq. (1) shows that the substituent hydrophobicity constant (π_R^1) for R^1 substituent has strong negative effect and molar refractivity (MR_R^3) for R^3 substituent has positive effect on activity, as their sign of coefficient indicates. The indicator

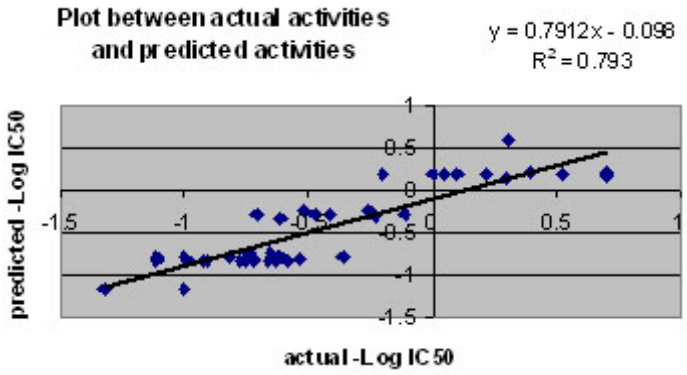


Fig. 1 Plot between actual activities and predicted activities by eq. (1) for 46 compounds

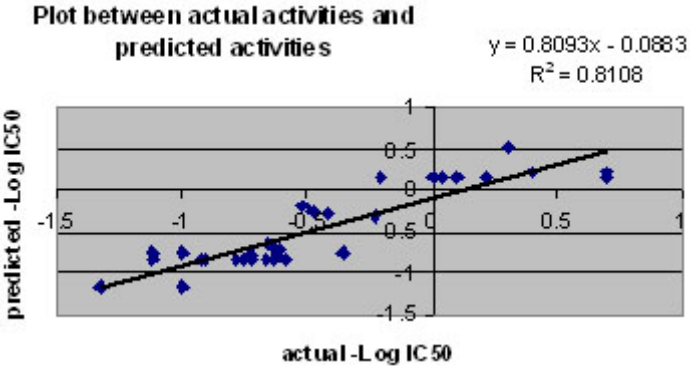


Fig. 2: Plot between actual activities and predicted activities by eq. (2) for 31 training set compounds

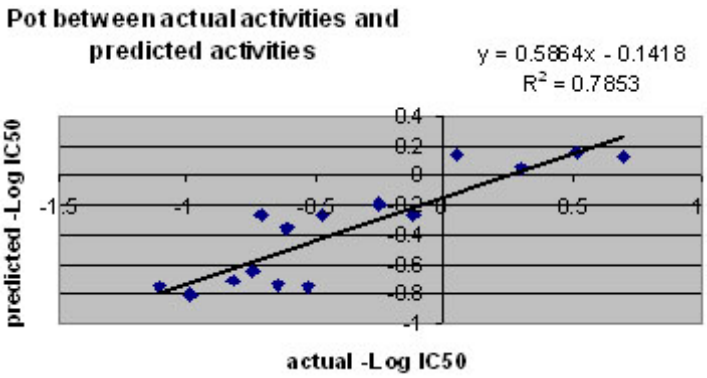


Fig. 3: Plot between actual activities and predicted activities by eq. (2) for 15 test set compounds

parameter has positive sign with its coefficient so the presence of F atom at X position is very important for activity.

The most active compounds of the series are compound number 37, 39 and 42 which have very small value of substituent hydrophobicity constant, π_{R}^{1} = 1.02 for R^1 substituent and large value of molar refractivity (MR_{R}^{3}) for R^3 substituent 26.37, 34.64 and 28.49 respectively and in these compounds F atom is present at the X position. These values complement our prediction.

External validation of generated QSAR model

A subset of 31 molecules from the total list of antagonists (1-46) was utilized as a training set for validation, (marked with footnote "a" in table 1) the remaining 23 molecules were employed as an external test set (marked with footnote "b" in table 1) for validating the QSAR model.

The eq. explaining the relation of parameters with antagonistic activities of 31 training set compounds is as follows,

$$-\log IC_{50}\ (AT_2/AT_1) = p_{R}^{1}\ (-0.777) \pm 0.108 + MR_{R}^{3}\ (0.011) \pm 0.011 + ly\ (0.348) \pm 0.187 + 0.277$$

n=31 r = 0.900 r^2 = 0.811 s = 0.244 F = 38.566 ...(2)

r_{pred} = 0.886

r_{pred} is the predicted correlation coefficient for test set compounds

Above eq. shows that π_{R}^{1}, MR_{R}^{3} and ly have 90% (r = 0.900) correlation with activity for 31 training set molecules, and 88.6% (r_{pred} = 0.886) correlation with 15 test set molecules. This validation on 15 external compounds shows that our model is reliable.

CONCLUSION

Generated and validated QSAR Model predicts that a substituent with very small value of hydrophobicity constant at R^1 position and other with large value of molar refractivity and R^3 position respectively will enhance the angiotensin II receptor antagonistic activity of compounds and the presence of F atom at X position will also give the same result.

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