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2D-QSAR Analysis of Some Imidazole with Acylsulphonamides and Acylsulfamides as Selective AT_1 Angiotensin-II Receptor Antagonist as a Hypertensive Agent

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A series of angiotensin-II receptor antagonists of some imidazole with acylsulphonamides and acylsulfamides were subjected to 2D-QSAR analysis using Hansch analysis, by using a combination of thermodynamic, electronic and spatial descriptor. Several QSAR models were obtained using stepwise regression analysis. One model was selected on basis of the statistical values that shows better significance with biological activity. The best QSAR models were further validated by leave-one-out cross-validation method. The studies have helped to ascertain the role of different substituents in explaining the observed inhibitory activity of this analogue. From the study, it is predicted that hydrophobicity (π) at the X substitution and electronic parameter, resonance effect (r) at the R_5 and hydrogen donor effect at the X and at the R_5 substitution shows positive contribution to biological activity.

Key Words: Renin angiotensin system (RAS), Angiotensin-II receptor antagonist, Hypertension, QSAR.

INTRODUCTION

The vasoactive hormone angiotensin-II produced by the renin-angiotensin system (RAS) is a potent regulator of blood pressure, homeostasis, fluid volume and electrolyte balance in mammals[1]. The clinical success achieved by angiotensin converting enzyme (ACE) inhibitors in the treatment of hypertension and congestive heart failure has made the RAS a major focus for the discovery of novel hypertensive agents. However, ACE also has kinase activity and this lack of specificity has been implicated in the occasional side effect of ACE inhibitors such as dry cough and angiodera[3]. With the development of angiotensin-II receptor antagonist, a specific attempt to inhibit the activity of RAS has become the main pharmacological approach. There are at least two distinct angiotensin-II receptor subtypes, designated as AT_1 and AT_2[4].

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Losartan, the most advanced nonpeptide angiotensin-II antagonist, mediates its effect by blocking the angiotensin-II AT_1 receptor subtype[5]. The AT_1 receptor is G-protein coupled and mediates most of the known physiological effects of angiotensin-II, including the maintenance of blood pressure[6]. The AT_2 receptor is thought to be involved in fetal growth and adult tissue repair and remodelling, especially in cardiovascular systems. However, there are still conflicting results *in vitro* and *in vivo* as to whether AT_2 receptors limit and/or accelerate the growing process in cardiovascular tissues[7]. On extensive research we found new derivatives of angiotensin-II receptor antagonist as antihypertensive drugs. Due to our interest in various structural and new potential treatments for hypertensive disorders, we subjected some imidazoles with acylsulphonamides and acylsulfamides to 2D-QSAR analysis. QSAR is an important tool in drug designing technique[8, 9] to achieve different objective like diagnosis of mechanism of action of drug, quantitative prediction of biological activity of compound, classification of compound into various classes, optimization of lead compound and refinement of synthetic target. To achieve this target, various QSAR model have been used such as Hansch. Free-Wilson and Fujita-Ban model[10]. No QSAR studies were attempted so far in the series[11], hence it was thought worthwhile to carry out QSAR analysis for one such reported series with angiotensin-II antagonist activity, in order to identify the structural and physico-chemical requirement for binding exploit to optimize the activity.

EXPERIMENTAL

A series of 25 compounds of angiotensin-II AT_1 receptor antagonist were selected from reported work of Naylor *et al.*[11] with the basic lead structure (Fig. 1). The biological activity data IC_{50} nM were converted into the negative logarithmic dose on molar basis for QSAR analysis (Table-1). The values of appropriate physico-chemical parameters were taken directly from the compilation of Hansch and Leo[12] (Table-2). For the present studies, physico-chemical

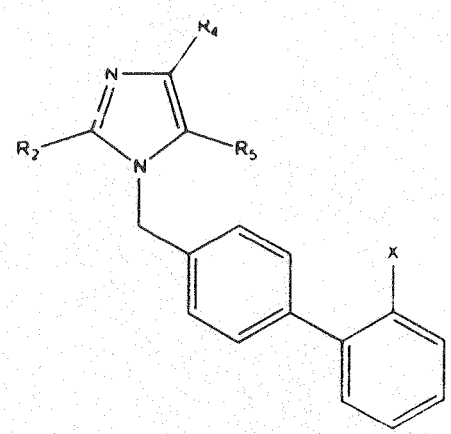

Fig. 1. Basic lead structure of imidazole with acyl sulphonamides and acyl sulfamides

parameters like hydrophobic constant (π), molar refractivity (mr), resonance constant (r), field constant (f), hammate constant (sm, sp), hydrogen donor (hd) and hydrogen acceptor (ha) were selected as independent variable and biological activity as dependent variable. Stepwise multiple regression analysis[13, 14] was performed to derive QSAR equation and in addition to advanced statistical validation procedure to select the best QSAR model from highly populated QSAR model by the software Valstat. Resulting QSAR model was assessed through a number of statistics obtained in conjunction with such calculations: correlation coefficient (r), standard deviation (s), F-test, bootstrapping (r^2), cross validation (Q^2), chance and leave-one-out method (Loo)[15] were employed for cross validation of the best equation.

TABLE-1
IN VITRO ANGIOTENSIN-II ANTAGONIST ACITIVITY OF SOME ACYL SULPHONAMIDES AND ACYL SULPHAMIDES

Compound	X	R^2	R^4	R^5	IC_{50} (nM)	$-\log IC_{50}$
ANG1	$SO_2NHCOPh$	*n*-Bu	H	COOMe	21.0	1.677
ANG2	SO_2NHCOc-Pr	*n*-Bu	H	COOMe	39.0	1.408
ANG3	$SO_2NHCOPh$	*n*-Bu	Cl	COOMe	8.8	2.090
ANG4	$SO_2NHCOPh$	*n*-Pr	Et	COOMe	0.5	2.300
ANG5	SO_2NHCOc-Pr	*n*-Pr	Et	COOMe	2.6	2.080
ANG6	$SO_2NHCOPh$	*n*-Bu	H	COOH	6.2	2.207
ANG7	SO_2NHCOc-Pr	*n*-Bu	H	COOH	5.8	2.301
ANG8	$SO_2NHCOPh$	*n*-Bu	Cl	COOH	2.0	2.698
ANG9	$SO_2NHCOPh$	*n*-Pr	Et	COOH	1.7	2.769
ANG10	SO_2NHCOc-Pr	*n*-Pr	Et	COOH	4.3	2.366
ANG11	$SO_2NHCOPh$	*n*-Pr	Et	CHO	2.4	2.019
ANG12	SO_2NHCOc-Pr	*n*-Pr	Et	CHO	12.0	1.920
ANG13	$NHSO_2NHCOPh$	*n*-Bu	H	COOMe	20.0	1.698
ANG14	$NHSO_2NHCOc$-Pr	*n*-Bu	H	COOMe	32.0	1.494
ANG15	$NHSO_2NHCO$*n*-Hept	*n*-Bu	H	COOMe	1.9	2.720
ANG16	$NHSO_2NHCOPh$	*n*-Bu	H	COOH	6.0	2.220
ANG17	$NHSO_2NHCOc$-Pr	*n*-Bu	H	COOH	7.4	2.130
ANG18	$NHSO_2NHCO$*n*-Hept	*n*-Bu	H	COOH	0.2	2.658
ANG19	Tetrazole	*n*-Bu	H	COOMe	15.0	1.823
ANG20	Tetrazole	*n*-Bu	Cl	COOMe	13.0	1.886
ANG21	Tetrazole	*n*-Bu	H	COOH	2.9	2.537
ANG22	Tetrazole	*n*-Bu	Cl	CH_2OH	50.0	1.301
ANG23	Tetrazole	*n*-Bu	Cl	COOH	7.0	1.154
ANG24	Tetrazole	*n*-Pr	Et	COOH	6.0	1.220
ANG25	Tetrazole	*n*-Pr	Et	CHO	8.0	1.096

TABLE-2
PHYSICOCHEMICAL PARAMETR VALUES FOR DIFFERENT SUBSTITUENTS

S. No.	π1	ha1	hd1	mr1	f1	r1	sm1	sp1	π4	ha4	hd4	mr4	f4	r4	sm4	sp4	π5	ha5	hd5	mr5	f5	r5	sm5	sp5	πx	hax	hdx	mrx	fx	rx	smx	spx	ba
1	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	-0.77	1	1	41.58	0.71	0.35	0.80	1	1.677
2	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	-1.59	1	1	29.75	0.66	-0.24	0.67	0.80	1.408
3	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0.71	0	0	6.03	0.41	-0.15	0.37	0.23	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	0.77	1	1	41.58	0.71	0.35	0.80	1	2.090
4	1.55	0	0	14.96	-0.06	-0.08	-0.07	-0.15	1.02	0	0	10.3	-0.05	-0.1	-0.07	-0.15	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	0.77	1	1	41.58	0.71	0.35	0.80	1	2.300
5	1.55	0	0	14.96	-0.06	-0.08	-0.07	-0.15	1.02	0	0	10.3	-0.05	-0.1	-0.07	-0.15	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	-1.59	1	1	29.75	0.66	-0.24	0.67	0.80	2.080
6	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.32	1	1	6.93	0.33	0.15	0.37	0.45	-0.77	1	1	41.58	0.71	0.35	0.80	1	2.207
7	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.32	1	1	6.93	0.33	0.15	0.37	0.45	-1.59	1	1	29.75	0.66	-0.24	0.67	0.80	2.301
8	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0.71	0	0	6.03	0.41	-0.15	0.37	0	-0.32	1	1	6.93	0.33	0.15	0.37	0.45	-0.77	1	1	41.58	0.71	0.35	0.80	1	2.698
9	1.55	0	0	14.96	-0.06	-0.08	-0.07	-0.15	1.02	0	0	10.3	-0.05	-0.1	-0.07	0.23	-0.32	1	1	6.93	0.33	0.15	0.37	0.45	-0.77	1	1	41.58	0.71	0.35	0.80	0	2.769
10	1.55	0	0	14.96	-0.06	-0.08	-0.07	-0.15	1.02	0	0	10.3		-0.1	-0.07	-0.15	-0.32	1	1	6.93	0.33	0.15	0.37	0.45	-1.59	1	1	29.75	0.66	-0.24	0.67	1	2.366
11	1.55	0	0	14.96	-0.06	-0.08	-0.07	-0.15	1.02	0	0	10.3	-0.05	-0.1	-0.07	-0.15	-0.65	1	0	6.88	0.31	0.13	0.35	0.42	-0.77	1	1	41.58	0.71	0.35	0.80	0.80	2.019
12	1.55	0	0	19.61	-0.06	-0.08	-0.07	-0.15	1.02	0	0	10.3	-0.05	-0.1	-0.07	-0.15	-0.65	1	0	6.88	0.31	0.13	0.35	0.42	-1.59	1	1	29.75	0.66	-0.24	0.67	1	1.920
13	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	-0.05	0	0	-0.15	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	-1.33	1	1	45.89	0.5	-0.08	0.48	0.80	1.698
14	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	-2.15	1	1	34.06	0.52	-0.19	0.35	0.38	1.494
15	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	0.39	1	1	54.07	0.3	-0.19	0.27	0.18	2.720
16	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.32	1	1	6.93	0.33	0.15	0.37	0.45	-1.33	1	1	45.89	0.5	-0.08	0.48	0.1	2.220
17	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.32	1	1	6.93	0.33	0.15	0.37	0.45	-2.15	1	1	34.06	0.52	-0.19	0.35	0.38	2.130
18	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.32	1	1	6.93	0.33	0.15	0.37	0.45	0.39	1	0	54.07	0.3	-0.19	0.27	0.18	2.658
19	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	-1.04	1	0	18.33	0.52	0.02	0.52	0.10	1.823
20	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0.71	0	0	6.03	0.41	-0.15	0.37	0.23	-0.01	1	0	12.87	0.33	0.15	0.37	0.45	-1.04	1	0	18.33	0.52	0.02	0.52	0.50	1.886
21	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0	0	0	1.03	0	0	0	0	-0.32	1	1	6.93	0.33	0.15	0.37	0.45	-1.04	1	0	18.33	0.52	0.02	0.52	0.50	2.537
22	2.13	0	0	19.61	-0.06	-0.11	-0.08	-0.16	0.71	0	0	6.03	0.41	-0.15	0.37	0.23	-0.13	1	1	7.19	0	0	0	0	-1.04	1	0	18.33	0.52	0.02	0.52	0.50	1.301

Parameters 1, 4, 5 and x show the physico-chemical property of substituents R_1, R_4, R_5 and x.

RESULTS AND DISCUSSION

When the 25 compounds of the series were subjected to QSAR analysis of angiotensin-II antagonist activity, out of several models, the following model gave statistically significant correlation and significant for antagonist activity.

QSAR equation is:

$$BA = [1.28157(\pm 0.396609)] + hd5[0.346299(\pm 0.147153)] + r5[3.52591(\pm 2.61622)] + pix\ [0.33544\ (\pm 0.123112)] + hdx\ [0.560287(\pm 0.172279)]$$

where $n = 25$, $r = 0.759465$, $r^2 = 0.576788$, variance = 0.131968, std = 0.363274, $F = 6.8144$

To ascertain the predictivity of QSAR model for angiotensin-II antagonist activity leave-one-out method of cross-validation was performed. The value of bootstrapping r^2, chance and Q^2 in the randomized biological activity test revealed that the result was not based on chance correlation. Structure activity data for the model are given in Table-3. Correlation matrixes for the model are given in Table-4. Figs. 2 and 3 display the graph of experimental *vs.* calculated and predicted activity of compound.

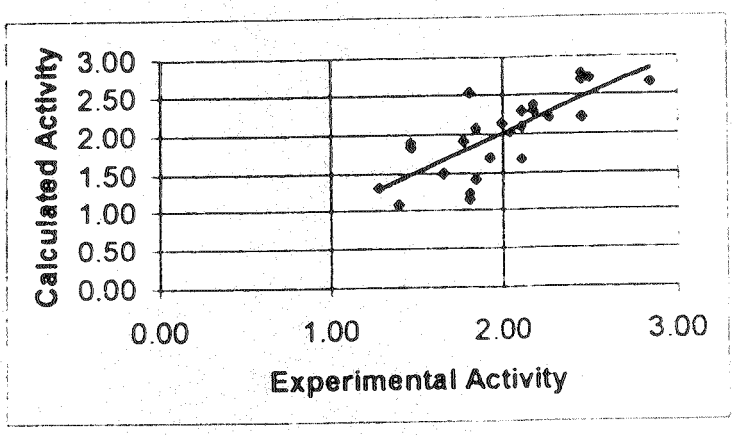

Fig. 2. Graph between experimental and calculated activity

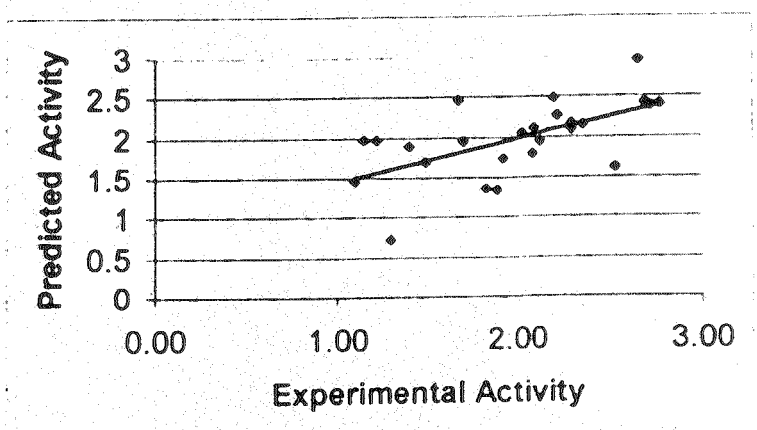

Fig. 3. Graph between experimental and predicted activity

TABLE-3
STURUCTURE ACTIVITY DATA FOR THE SELECTED MODEL FOR THE ANG-II ANTAGONIST ACTIVITY

Comp. No.	Experimental activity	Calculated activity	Residual	Predicted activity	Residual
1	1.677	2.11246	–0.43546	2.46057	–0.78357
2	1.408	1.83740	–0.42940	1.89384	–0.48584
3	2.090	2.11246	–0.02246	2.11494	–0.02494
4	2.300	2.11246	0.18754	2.09174	0.20826
5	208.000	1.83740	206.16260	1.80550	206.1945
6	2.207	2.45876	–0.25176	2.49238	–0.28538
7	2.301	2.18369	0.11731	2.16497	0.13603
8	2.698	2.45876	0.23924	2.42640	0.27160
9	2.769	2.45876	0.31024	2.41732	0.35168
10	2.366	2.18369	0.18231	2.15459	0.21141
11	2.019	2.04194	–0.02294	2.04510	–0.02610
12	1.920	1.76688	0.15312	1.74256	0.17744
13	1.698	1.92461	–0.22661	1.94817	–0.25017
14	1.494	1.64955	–0.15555	1.69249	–0.19849
15	2.720	2.50157	0.21843	2.38920	0.33080
16	2.220	2.27091	–0.05091	2.27750	–0.0575
17	2.130	1.99585	0.13415	1.95348	0.17652
18	2.658	2.84787	–0.18987	2.95170	–0.29370
19	1.823	1.46160	0.36140	1.36037	0.46263
20	1.886	1.46160	0.42440	1.34272	0.54328
21	2.537	1.80790	0.72910	1.61439	0.92261
22	1.301	1.27901	0.02199	0.739977	0.561023
23	1.154	1.80790	–0.65390	1.98145	–0.82745
24	1.220	1.80790	–0.58790	1.96394	–0.74394
25	1.096	1.39108	–0.29508	1.46299	–0.36699

TABLE-4
CORRELATION MATRIX OF QSAR MODEL FOR ANGIOTENSIN-II AT_1 RECEPTOR INHIBITION

	hd5	r5	pix	hdx
hd5	1.000000			
r5	0.132982	1.000000		
pix	0.016811	0.002561	1.000000	
hdx	0.114123	0.334434	0.033790	1.000000

$$\text{Bootstrapping } r^2 = 1.63238$$

$$\text{Chance} = 0.004$$

$$Q^2 = 0.303558$$

$$S_{press} = 0.466012$$

$$S_{DEP} = 0.41681$$

For AT_1 subtype angiotensin-II receptor, antagonistic activity study revealed that the thermodynamic parameter hydrophobicity (Pix) at substituent X on benzene ring contributes positively. Electronic parameter resonance positively contributes to angiotensin-II antagonist activity at the R_5 substitution on the imidazole ring. Hydrogen donor (hdx, hd5) at the R_5 on the imidazole ring and on the X substitution on the benzene ring contribute to the biological activity positively. The study concludes that the thermodynamic descriptor facilitates binding to the angiotensin-II receptor. Electronic parameter and hydrogen donor play an important role in the electronic interaction and hydrogen donor acceptor interaction with the selective AT_1 subtype angiotensin-II receptor.

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