Asian Journal of Chemistry Vol. 20, No. 1 (2008), 177-186

3D-QSAR Analysis of Acyl Sulfonamides and Acyl Sulfamides As AT_1 Selective Angiotensin-II Receptor Antagonists Based on Semiemperical AM_1 Calculations

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Considering the importance of developing AT_1 selective Angiotensin-II receptor antagonists in management and treatment of hypertension, the present paper explores the selectivity requirements of acyl sulfonamides and acyl sulfamides for binding with AT_1 receptor. The best triparametric equation derived for 25 compounds explains the importance of certain pharmacophoric features like lower unoccupied molecular orbital energy (E_{LUMO}), Connolly accessible area (CAA) and Non-1, 4 vander Waals forces (VDW) for Angiotensin-II receptor antagonism. The statistically significant equation has been further validated by leave one out method.

Key Words: Angiotensin converting enzyme, Rennin angiotensin system, QSAR, Angiotensin-II receptor antagonist.

INTRODUCTION

The great success of ACE inhibitors[1]: captopril, enalepril and others, which inhibit the formation of A-II from A-I in the Renin-angiotensin system (RAS)[2], led to recognition of the important role of the RAS in homeostasis of cardiovascular system. A-II, the biologically active peptide of the RAS, is a potent vasoconstrictor agent and its regulation has been achieved by inhibition of the metalloprotease ACE[2] and of the aspartyl protease renin[3]. A-II receptor antagonists have been investigated as an alternative approach in blocking the hypertensive response to endogenous A-II. They have been expected to lack adverse effects[4-7] observed with the use of ACE inhibitors. Dry cough, angioedema, aplastic anemia, conjunctivitis, headache, parenthesis and sinus tachycardia are associated side effects of ACE inhibitors[8] that are not associated with A-II receptor antagonists. The discovery by Dupont group of a series of (biphenylmethyl)

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imidazoles as nonpeptidic, potent and orally active A-II receptor antagonists has opened up a completely new field in A-II antagonists research and structure activity relationship for this class of compounds have been extensively explored[9]. One of the series reported by Naylor *et al.*[10] was found promising in terms of its structure activity data and the results of QSAR study on this series are reported here as a continuing effort in the field of drug design.

EXPERIMENTAL

The A-II receptor AT_1 antagonistic activity of acyl sulfonamide and acyl sulfamides is listed in Table-1. IC_{50} value (nanomolar concentration of the compound required for 50 % inhibition of the AT_1 activity) was transformed to pIC_{50} (negative logarithm of IC_{50}) to get the linear relationship in the QSAR equation. The 2D structures were converted to 3D structures and energy minimized using semiemperical quantum mechanics module implemented on molecular orbital package (MOPAC) version, fixing maximum iteration limit to 1000, root mean square (RMS) gradient to 0.001 kcal/mol and applying the theory of AM1 Hamiltonian using closed shell restricted wave function. 52 Descriptors were calculated for the energy minimized and geometrically optimized structures[11] from MM2 server.

The statistical quality of the models was gauged by parameters like correlation coefficient (r) or coefficient of determination (r^2), standard error of estimate (s), fisher's F-value. The level of significance of each regression term was assessed using t-test. The correlation matrix among the various predictor variables was examined regularly in order to avoid simple colinearity problem. The parameters having intercorrelation above 0.5 and those are not significant at 99.9 % confidence interval were not considered whilst deriving QSAR models. To ascertain the predictivity of the model, internal validation using leave one out (LOO) cross validation process, bootstrapping technique and randomization test were performed. Residual plots (Figs. 3 and 4) were used as diagnostic aid in identifying the outliers from the QSAR model. A data point is considered as an outlier if it has a large magnitude on any residual plot (when the residual value exceeds twice the standard error of estimate of the model). The presence of outlier was further confirmed by higher Z-score value.

RESULTS AND DISCUSSION

In order to explore the nature of interactions of R1, R2 and R3 groups with A-II receptor statistically significant QSAR models were developed. Quantitative model building was accomplished through sequential multiple regression analysis[12,13] using the method of least square in val_stat

software. This task was approached stepwise, that is successive regression equations were derived in which parameters were added, removed or replaced until r^2 and s values were optimized.

In the first step equations with single parameter were generated which shows CAA is contributing mostly with 52.38 % variance in biological activity (model 2). Com 4, 9 and 15 were omitted stepwise as outlier in model 2. Non-1, 4 VDW (model 1) and E_{LUMO} (model 3) were also contributing significantly, hence these parameters were combined in the next step for generation of equation with two parameters.

Model 1:

BA = [3.55873(± 2.82094)] + Non-1, 4 VDW* [-0.193914 (± 0.229744)]
n=25, r=0.342886, r^2=0.11757, variance=2.06571, std=1.43726, F=3.0644
Validation parameters: r^2_{bsp} =0.146595, Q^2 =-0.0657863, Spress = 1.57954, SDEP =1.51504

Model 2:

BA = [11.6091(± 12.8975)] + CAA* [-6.7798(± 8.41696)]
n=25, r=0.328956, r2=0.108212, variance=2.08762, std=1.44486, F=2.79088
Validation parameters: r^2_{bsp} = 0.197147, Q^2 =-0.216378, Spress = 1.68744, SDEP =1.61854
Optimized model 2: BA = [16.7234(± 6.93699)] +CAA [-10.1806(± 4.54232)]
n=22, r=0.723787, r^2=0.523868,variance=0.422952,std=0.650347, F=22.0052
Validation parameters: r^2_{bsp} =0.507347, Q^2 =0.376324, Spress = 0.744323, SDEP =0.709684

Model 3:

BA = [0.652975(± 2.95873)] +E_{LUMO} [-0.147548(± 0.737146)]
n=25, r=0.0862389, r^2=0.00743715, variance=2.32353, std=1.52431, F=0.172336
Validation parameters: r^2_{bsp} =0.0475373, Q^2 =-0.143578, Spress = 1.63617, SDEP =1.56936

Model 4:

BA = [3.77537(± 6.99079)] + E_{LUMO}* [-0.162963(± 0.739102)] + CAA [-0.00421026(± 0.00853729)]
n=25, r=0.229658, r^2=0.0527426, variance=2.31826, std=1.52258, F=0.612472
Validation parameters: r^2_{bsp} =0.157628, Q^2 =-0.413561, Spress = 1.85996, SDEP =1.7448
Optimized model 4: BA = [3.12844(± 5.66432)] +E_{LUMO} [0.0496105(±

*VDW = vander Waals force, CAA = Connolly accessible area
*E_{LUMO} = lower unoccupied molecular orbital energy

0.610203)] +CAA [-0.00200563(± 0.00702026)]
n=24,r=0.137064, r^2=0.0187864,variance=1.50654,std=1.22741, F=0.201034
Validation parameters: r^2_{bsp} =0.170016, Q2 = -0.650936, Spress = 1.59211, SDEP =1.48928

Model 4 is stastically insignificant due to low r, r^2, F and high s, Spress, SDEP value. Com 4 was omitted stepwise as outlier.

Model 5:

BA = [0.189313(± 2.95051)] +ELUMO [-0.257399(± 0.733507)] +Non1, 4 VDW [0.00473339(± 0.006404)]
n=25, r=0.322069, r^2=0.103728, variance=2.19348, std=1.48104, F=1.27306
Validation parameters: r^2_{bsp} =0.14994, Q^2 =-5.34124, Spress = 3.93944, SDEP =3.69552
Optimized model 5: BA = [0.306237(± 1.1816)] +E_{LUMO} [-0.241452(± 0.289632)] +Non1, 4 VDW [0.00461879(± 0.00243994)]
n=21,r=0.69437, r^2=0.48215,variance=0.304019,std=0.551379,F=8.37954
Validation parameters: r^2_{bsp} =0.527699, Q^2 =-12.1412, Spress = 2.77757, SDEP =2.57153

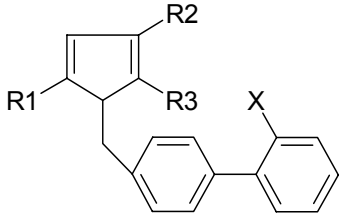
Although model 4 explains 48.21 % variance in biological activity, negative value of cross-validated Q^2 value indicates model 4 and 5 are stastically insignificant,

Model 6:

BA = [2.60907(± 2.12019)] +Non1, 4 VDW [0.0044374(± 0.00136806)] +CAA [-0.00204242(± 0.00291162)]
n=25, r=0.831831, r^2=0.691942, variance=0.102932, std=0.32083, F=24.7076
Validation parameters: r^2_{bsp} =0.590813, Q^2 =-0.215513, Spress = 0.637293, SDEP =0.597834
Optimized model 6: BA = [1.03263(± 1.80168)] +Non1, 4 VDW [0.00460584(± 0.00104642)] +CAA [6.28354e-005(± 0.00246106)]
n=24,r=0.895592, r^2=0.802085,variance=0.0594803,std=0.243886, F=42.553
Validation parameters: r^2_{bsp} =0.577708, Q^2 = 0.604565, Spress = 0.344734, SDEP = 0.322469

The derived model explains 80.20 % variance in biological activity as a function of electronic (Non 1,4 VDW) and steric parameter (CAA). Positive contribution of CAA confirms the favourable effect caused by increasing ring size at R1, R2 and R3 position of the imidazoles ring. Fairly high value of Q^2 and r^2_{bsp} and low value of Spress and SDEP suggest stastical significance of model 5. Com 4, 9, 15 and 18 were omitted stepwise as outlier.

TABLE-1
STRUCTURES AND AT_1 ANTAGONISTIC ACTIVITY OF ACYL SULFONAMIDES AND ACYL SULFAMIDES



Compd.	X	R1	R2	R3	IC_{50}	pIC_{50}
ANG 1	$SO_2NHCOPh$	*n*-Bu	H	COOMe	21.0	0.7564
ANG 2	SO_2NHCO-Pr	*n*-Bu	H	COOMe	39.0	0.6285
ANG 3	$SO_2NHCOPh$	*n*-Bu	Cl	COOMe	8.8	1.0593
ANG 4	$SO_2NHCOPh$	*n*-Pr	Et	COOMe	0.5	-3.3220
ANG 5	SO_2NHCO-Pr	*n*-Pr	Et	COOMe	2.6	2.4154
ANG 6	$SO_2NHCOPh$	*n*-Bu	H	COOH	6.2	1.2620
ANG 7	SO_2NHCO-Pr	*n*-Bu	H	COOH	5.8	1.3106
ANG 8	$SO_2NHCOPh$	*n*-Bu	Cl	COOH	2.0	3.3220
ANG 9	$SO_2NHCOPh$	*n*-Pr	Et	COOH	1.7	4.3470
ANG 10	SO_2NHCO-Pr	*n*-Pr	Et	COOH	4.3	1.5790
ANG 11	$SO_2NHCOPh$	*n*-Pr	Et	CHO	2.4	2.6315
ANG 12	SO_2NHCO-Pr	*n*-Pr	Et	CHO	12.0	0.9260
ANG 13	$NHSO_2NHCOPh$	*n*-Bu	H	COOMe	20.0	0.7680
ANG 14	$NHSO_2NHCO$-Pr	*n*-Bu	H	COOMe	32.0	0.6640
ANG 15	$NHSO_2NHCO$*n*-Hept	*n*-Bu	H	COOMe	1.9	3.5970
ANG 16	$NHSO_2NHCOPh$	*n*-Bu	H	COOH	6.0	1.2850
ANG 17	$NHSO_2NHCO$-Pr	*n*-Bu	H	COOH	7.4	1.1507
ANG 18	$NHSO_2NHCO$*n*-Hept	*n*-Bu	H	COOH	0.2	-1.4320
ANG 19	Tetrazole	*n*-Bu	H	COOMe	15.0	0.8500
ANG 20	Tetrazole	*n*-Bu	Cl	COOMe	13.0	0.8980
ANG 21	Tetrazole	*n*-Bu	H	COOH	2.9	2.1645
ANG 22	Tetrazole	*n*-Bu	Cl	CH_2OH	50.0	0.5880
ANG 23	Tetrazole	*n*-Bu	Cl	COOH	7.0	1.1832
ANG 24	Tetrazole	*n*-Pr	Et	COOH	6.0	1.2850
ANG 25	Tetrazole	*n*-Pr	Et	CHO	8.0	1.1070

Model 7:

BA = [1.40243(± 3.78317)] +E_{LUMO} [-0.169791(± 0.247565)] +CAA [-0.00117843(± 0.00483849)] +Non1, 4 VDW [0.00451285(± 0.00230863)] n=25, r=0.678048, r^2=0.459749, variance=0.276172, std=0.525521, F=5.95694

Validation parameters: r^2_{bsp} =0.477915, Q^2 =-30.0877, Spress = 3.98645, SDEP =3.65364

Optimized model 7: BA = [2.12862(± 2.45161)] +E_{LUMO} [-0.085828(±

0.163311)] +CAA [-0.00186039(± 0.00311817)] +Non1, 4 VDW [0.0046098(± 0.00148218)]
n=23, r=0.842899, r^2=0.710479, variance=0.111901, std=0.334516, F=15.5419
BA = [0.506465(± 2.02229)] +E_{LUMO} [-0.0812412(± 0.122254)] +CAA [0.000322064(± 0.00259902)] +Non1, 4 VDW [0.00478532(± 0.00111315)]
n=22, r=0.907042, r^2=0.822725, variance=0.0621511, std=0.249301, F=27.8457
Validation parameters: r^2_{bsp} =0.650178, Q^2 =0.468707, Spress = 0.431586, SDEP =0.390384

The derived model explains 82.27 % variance in biological activity as a function of electronic (Non 1, 4 VDW and E_{LUMO}) and steric parameter (CAA). Fairly high value of r^2_{bsp} and Q^2 value > 0.4 supported the predictive ability and significance of the model. Fairly high value of r, r^2, F and low value of s, Spress and SDEP suggest that model 6 is stastically more significant than model 5. Residual plot and high Z- score indicates that com 4, 9 and 17 were outlier and were omitted stepwise. Removal of these compounds result in improved r^2, r^2_{bsp} and Q^2 value.

Observed, predicted, calculated, Z score, residual value and descriptors of molecules involved in model generation and intercorrelation among descriptors are shown in Tables 2 and 3. The correlation between observed, predicted and calculated activity for training and test set molecules is given in Figs. 1 and 2.

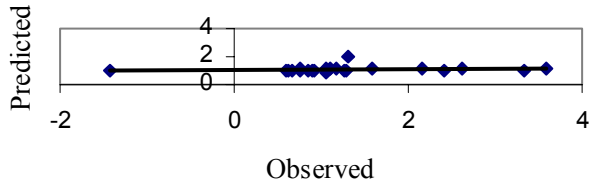


Fig. 1. Observed *vs.* predicted activity of molecules involved in model generation

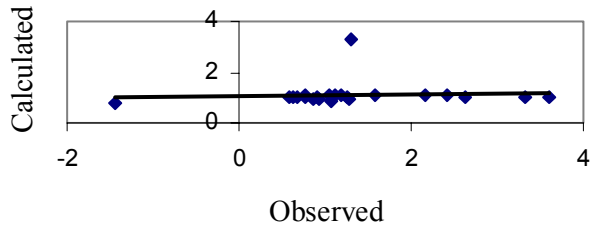


Fig. 2. Observed *vs.* calculated activity of molecules involved in model generation

TABLE-2
OBSERVED, PREDICTED, CALCULATED, RESIDUAL AND Z-SCORE VALUE OF MOLECULES INVOLVED IN MODEL GENERATION

Compd.	Obs*	Pred*	Cal*	Z-value	Res* (Obs-Cal)	Descriptors		
						E_{LUMO}	CAA	Non1,4VDW
1	0.7564	1.23600	1.17922	-0.860120	-0.47960	-4.373	790.327	-7.6156
2	0.6285	1.19970	1.17480	-1.111310	-0.57120	-4.254	731.064	-19.5935
3	1.0593	0.70368	0.80382	0.519703	0.35570	-2.418	806.143	-13.1140
4	-3.3220	1.11824	1.17480	2.523710	4.44020	-3.113	818.185	-12.6174
5	2.4154	1.15135	1.16594	0.195420	1.26400	-4.254	731.064	-19.5935
6	1.2620	1.19001	1.19546	0.234220	0.11065	-4.380	795.593	-9.4470
7	1.3106	-14.74300	3.28463	0.076027	16.05420	-4.348	724.965	-20.1431
8	3.3220	1.11781	1.14019	0.892647	2.14390	-3.070	713.028	487.7594
9	4.3470	1.18766	1.33101	2.645540	3.15930	-3.223	739.115	-12.8860
10	1.5790	1.39502	1.32790	-0.817570	0.18390	-3.986	747.082	-12.9950
11	2.6315	1.16357	1.10156	-0.678540	1.46800	-5.135	746.374	-14.1276
12	0.9260	0.97655	0.93718	-0.555730	-0.05050	-5.196	772.993	-10.1597
13	0.7680	1.12611	1.14210	0.290702	-0.35810	-4.247	805.980	-15.9959
14	0.6640	1.22434	1.22075	-0.142500	-0.56030	-3.043	767.900	-17.0638
15	3.5970	1.41714	1.34135	-0.999530	2.17980	-4.076	955.697	-17.6844
16	1.2850	0.99527	0.98061	-0.168050	0.28980	-4.352	782.690	-17.0453
17	1.1507	1.11868	1.36177	1.632960	0.03200	-4.389	715.759	-18.4856
18	-1.4320	0.94134	0.80720	-0.445910	2.37330	-4.397	951.158	-15.4062
19	0.8500	1.07457	1.08402	0.202172	-0.22450	-4.413	660.519	-7.0905
20	0.8980	1.29383	1.26596	-0.442980	-0.39580	-2.682	725.508	-4.9289
21	2.1645	1.45576	1.42052	-0.636960	0.70874	-4.417	630.201	-10.6328
22	0.5880	1.29383	1.26596	-0.442980	-0.70580	-1.741	696.864	-15.4297
23	1.1834	1.45576	1.42052	-0.636960	-0.27230	-3.269	715.138	-6.8083
24	1.0482	1.45576	1.42052	-0.636960	-0.40750	-4.067	669.297	-8.4857
25	1.1074	1.45576	1.42052	-0.636960	-0.34830	-5.183	706.634	-6.4754

Obs = observed, Pred = predicted, Cal = calculated, Res = residual

TABLE-3
CORRELATION MATRIX OF THE DESCRIPTORS USED IN DERIVED QSAR MODELS

Model 4			
	LUMO	CAA	
LUMO	1.000000		
CAA	0.077754	1.000000	
Model 5			
	LUMO	Non1,4 VDW	
LUMO	1.000000		
Non1,VDW	0.221293	1.000000	
Model 6			
	Non1,4 VDW	CAA	
Non1,4 VDW	1.000000		
CAA	0.103009	1.000000	
Model 7			
	LUMO	CAA	Non1, 4 VDW
LUMO	1.000000		
CAA	0.077640	1.000000	
Non1,4 VDW	0.214590	0.113102	1.000000

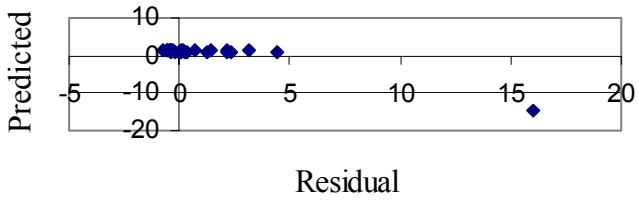


Fig. 3. Residual *vs.* predicted activity of molecules involved (with outlier)

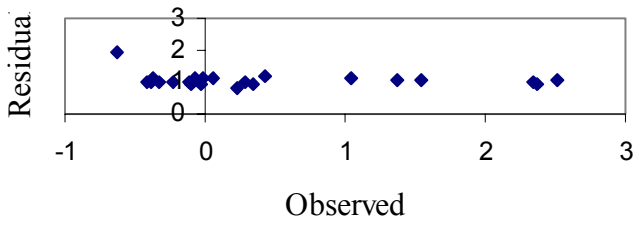


Fig. 4. Residual *vs.* predicted activity of molecules (with outlier)

Electronic parameter E_{LUMO} is a measure of electrophilicity of the molecule. When a molecule acts as a lewis acid (electron pair acceptor) in bond formation, incoming electrons are received in its LUMO. Molecules with low-lying LUMO are more able to accept electron than those with

high energy LUMO. The contribution of E_{LUMO} term suggest that electron withdrawing group at imidazole ring of the lead structure decreases the LUMO energy and in turn increases the electrophilicity of the ligands. This in turn would increase the A-II antagonistic activity. Fig. 5 shows the LUMO orbital of most active analogue of the series. Non-1, 4 VDW applies to nearly all pairs of atoms and it describes the more complex interaction between non-bonded atoms. This term has both the attractive and repulsive component. Positive contribution of this term indicates the dominating behaviour of attractive force. More the attractive force, more the legand-receptor interaction. The steric parameter Connolly surface, also called the molecular surface, is similar to the solvent-accessible surface. It is defined as the surface made by the center of the solvent sphere as it contacts the van der Waals surface. The volume enclosed by the Connolly surface is called the solvent-excluded volume. Negative contribution of CAA suggets that increasing bulk volume is not favourable for A-II receptor antagonistic activity. Connolly of most active anologue of this series is shown in Fig. 6. Hence more electrophilic and less bulky substituents enhances A-II receptor antagonistic activity.

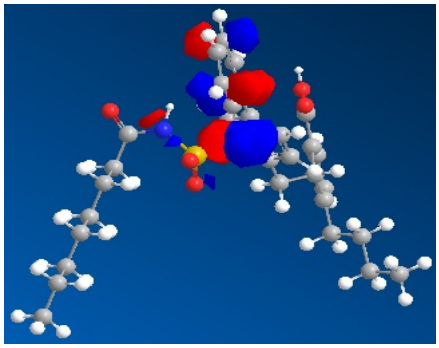


Fig. 5. LUMO (light dark colour) molecular orbitals of active member of series

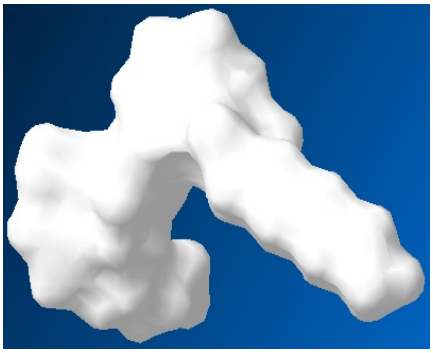


Fig. 6. Connolly molecular surface of active member of series

Conclusion

The above QSAR results may guide to design new chemical entity with high potency.

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(*Received*: 6 September 2006; *Accepted*: 5 September 2007) AJC-5804