Asian Journal of Chemistry Vol. 17, No. 2 (2005), 877–881

QSAR Studies of 1,2-Cyclomethylene Carboxylic Monoamide Hydroxamic Derivatives

N.D. GALPALLI* and S.C. CHATURVEDI
Modern College of Pharmacy, Sector 21, Yamunanagar Nigdi, Pune-411 044, India
E-mail: niranjanwins@yahoo.com

A series of monoamide derivatives of *cis* and *trans*-1,2-cyclohexane dicarboxylic acids bearing hydroxamic group in the side chain molecules as potential ACE inhibitors were subjected to QSAR analysis. The QSAR equations indicate that mostly electronic and shape parameters are responsible for the variation in biological activity. Molecular shape analysis suggests that there is less difference in NCOSV while comparing biological activity with reference compound. The so obtained and validated models bring important structural insight to aid the design of novel class of non-amino acid ACE inhibitors.

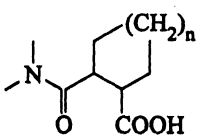
Key Words: QSAR studies, Hydroxamic derivatives.

INTRODUCTION

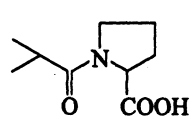
Clinical success of angiotensin converting enzyme (ACE) inhibitors in hypertension and in congestive heart failure is well established[1, 2]. Several potential new clinical applications of these agents have been under investigation in the past years[3] and there is convincing evidence coming out to support novel indications for ACE inhibitors such as diabetic nephropathy[4], myocardial infarction, cardiac hypertrophy, vascular proliferation, and cognitive disorders[5].

The basic structure of ACE inhibitors is a dipeptide or acylamino acid derivative bound to a Zn-ligand functional group (sulfhydryl, carboxyl or phosphoryl). These groups, according to a frequently used classification, chemically mark out the three corresponding classes of ACE inhibitors, while an acylamino acid moiety in the carboxyl terminal portion[6] is a feature common to all ACE inhibitors of each class.

In this research, the hypothesis has been made that a monoamidic residue of a 1,2 cyclohexane dicarboxylic acid (**1**) could be an alternative structure to the acylproline moiety (**2**) which is the carboxyl-terminal portion of various ACE inhibitors.



1



2

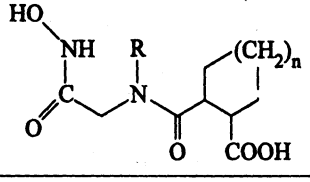
The structure **1** seems indeed able both to mimic the distance between C=O and COOH groups and produce the same rigidity of the system **2**, which are two important geometrical parameters for the inhibition of ACE.

The aim of this study was to find 3D QSAR models with good correlation between molecular structure and biological activity. Such an effort would facilitate the discovery of novel class of non-amino acid ACE inhibitors.

EXPERIMENTAL

In the present study, Silicon Graphics Indigo XZ employing Cerius[2] software (Version 3.5) workstation was used. Structures of all compounds (Table-1) were sketched using 3D-sketcher module of the Cerius[2]. The biological data was acquired from Turbanti *et al*[7].

TABLE-1
BIOLOGICAL ACTIVITY AND STRUCTURE OF 1,2-CYCLOMETHYLENE CARBOXYLIC MONOAMIDIC HYDROXAMIC DERIVATIVE



S.No.	R	IC_{50} (nM)	$-\log IC_{50}$ (nM)
ACE 1	H	3.000	5.5228
ACE 2	H	1.500	5.8239
ACE 3	CH_3 (1S, 2R *cis*)	0.007	8.1549
ACE 4	C_2H_5 (1R, 2S *cis*)	1.800	5.7447
ACE 5	CH_3 (1S, 2S *trans*)	23.500	4.6289
ACE 6	CH_3 (1R, 2R *trans*)	0.024	7.6197
ACE 7	C_2H_5 (1S, 2R *cis*)	0.028	7.5528
ACE 8	C_2H_5 (1R, 2S *trans*)	2.900	5.5376
ACE 9	C_2H_5 (1S, 2S *trans*)	2.900	5.5376
ACE 10	C_2H_5 (1R, 2R *trans*)	0.014	7.8538
ACE 11	nC_3H_7 (*cis*)	0.400	6.3979
ACE 12	nC_3H_7 (*trans*)	0.150	6.8239
ACE 13	iC_3H_7 (*trans*)	0.500	6.3010
ACE 14	C_2H_5 (*cis*)	75.000	4.1249
ACE 15	C_2H_5 (*trans*)	97.000	4.0132
ACE 16	H (*cis*)	10.000	5.0000
ACE 17	CH_3 (*trans*)	1.400	5.8538
ACE 18	CH_3 (*cis*)	11.000	4.9586
ACE 19	Captopril	0.003	8.5220

The energy calculations were done using universal force field. All the structures were energy minimized by standard minimizer algorithms. In the minimization process, first steepest descent (SD) method was used to eliminate the bad contacts, after which more accurate minimizing methods like conjugate gradient (CG) and truncated Newton-Raphson (N—R) methods were used[8]. Most stable conformations for each compound were generated and its analysis was performed using GRID method. These conformers were used for calculating other physicochemical parameters. Semiempirical quantum mechanical calculations were performed using modified neglected differential overlap (MNDO) method. The Austin model 1 (AM1) Hamiltonian of molecular orbital package (MOPAC) module was used for calculating atomic charges and electron density on various atoms. The Connolly surface (solvent accessible area) of the lowest energy conformers of each molecule was computed and viewed on a SGI IRIS Indigo using the programme Cerius[2] with probe radius (1.04 Å), dot density (8.0 Å) and VDW scale factor (1.0)[9]. The other parameters for all the compounds were calculated by standard procedure[9].

The following descriptors were calculated for 3D-QSAR study (values of only those descriptors which found place in the equations are given in Table-2).

TABLE-2
CALCULATED DESCRIPTOR VALUES FOR THE SERIES

S.No.	Cedensity[a]	N charge[b]	Nedensity[c]	Apol[d]	Density[e]	Dip-Mopac[f]	Sr[g]	Ncosv[h]	HBD[i]
ACE 1	3.70	–0.377	4.37	8051	1.14	4.54	0.42	70.06	4
ACE 2	3.69	–0.377	4.37	8051	1.13	4.69	1.45	72.02	4
ACE 3	3.69	–0.321	4.32	8564	1.11	5.49	1.24	71.02	3
ACE 4	3.69	–0.313	4.31	8564	1.11	5.65	0.57	78.08	3
ACE 5	3.69	–0.319	4.31	8564	1.12	3.46	0.78	77.92	3
ACE 6	3.68	–0.322	4.32	8564	1.12	3.77	1.26	76.78	3
ACE 7	3.68	–0.307	4.30	9077	1.09	5.38	1.69	70.07	3
ACE 8	3.69	–0.317	4.31	9077	1.09	6.04	1.71	96.73	3
ACE 9	3.69	–0.323	4.32	9077	1.09	3.80	1.60	96.97	3
ACE 10	3.69	–0.316	4.31	9077	1.09	4.92	1.71	95.26	3
ACE 11	3.69	–0.319	4.31	9590	1.07	6.84	1.71	111.3	3
ACE 12	3.69	–0.318	4.30	9590	1.07	3.40	0.77	114.94	3
ACE 13	3.68	–0.320	4.32	9590	1.07	5.62	0.77	102.94	3
ACE 14	3.68	–0.311	4.31	8644	1.09	4.87	0.76	62.54	2
ACE 15	3.69	–0.315	4.31	8131	1.10	4.72	1.73	76.46	2
ACE 16	3.69	–0.361	4.36	8503	1.10	6.21	1.64	72.47	3
ACE 17	3.69	–0.316	4.31	8051	1.12	4.56	0.57	48.74	3
ACE 18	3.68	–0.365	4.36	7990	1.11	3.96	1.61	76.17	3
ACE 19	3.68	–0.113	4.11	7990	1.10	3.50	0.55	65.66	2

[a]Cedensity, [b]Ncharge, [c]Nedensity, [d]Atomic polarizibilty, [e]density, [f]Dipole-molecular orbital package, [g]superdelocalizability, [h]non-common overlap steric volume, [i]hydrogen bond donor.

The correlation between the biological activity and physicochemical parameters was found through stepwise multiple regression analysis and genetic function approximation. The statistical measures used in this study are correlation coefficient (r), squared correlation coefficient (r^2), Fischer's value and standard deviation.

RESULTS AND DISCUSSION

When all the calculated parameters and –log IC_{50} of the compounds were subjected to stepwise multiple parameter regression analysis and GFA analysis. The following significant equations (1) and (2) were obtained by GFA analysis.

$$-\log IC_{50} = 158.96 - 0.04 * \text{col N cosv} + 0.026 * \text{col PMI-Y} - 30.20 * \text{col Nedensity} + 1.18 * \text{col H-bond donor}$$

$$n = 19,\quad r^2 = 0.832,\quad Cvr^2 = 0.673,\quad F = 17.30 \qquad (1)$$

$$-\log IC_{50} = 101.15 + 80.34 * \text{col density} - 0.53 * \text{col DIPOLE-MOPAC} + 0.004 * \text{col Apol} + 17.90 * \text{col Ncharge} - 0.048 \text{ col Ncosv}$$

$$n = 19,\quad r^2 = 0.854,\quad Cvr^2 = 0.72,\quad F = 15.315 \qquad (2)$$

The following significant equations (3) and (4) were obtained by stepwise multiple regression analysis.

$$-\log IC_{50} = 492.68 - 108.71 * \text{col Cedensity} - 17.73 * \text{col Nedensity} + 1.96 * \text{col HOMO-MOPAC} - 0.37665 * \text{col Foct} + 5.23 * \text{col Fo}$$

$$n = 19,\quad r^2 = 0.727,\quad Cvr^2 = 0.534,\quad F = 6.93 \qquad (3)$$

$$-\log IC_{50} = 112.49 - 27.21 * \text{col Nedensity} + 2.0094 * \text{col H-bond donor} + 0.837 * \text{col Sr } 0.0268 * \text{col Cosv} + 5.23 * \text{col Fo}$$

$$n = 19,\quad r^2 = 0.718,\quad Cvr^2 = 0.592,\quad F = 8.893 \qquad (4)$$

The QSAR study shows that all the equations have 99% significance. The significant value is larger than the tabulated values. QSAR equations indicate the mostly electronic and shape parameters are responsible for variation in biological activity.

One single electronic parameter Nedensity accounts for maximum biological activity. Considering equations (1) and (2), we find that equation (1) suggests better correlation ($r^2 = 0.832$) between parameters and biological activity. The r^2 accounts for 83.2% variance in activity values. Equation (2) has still better correlation ($r^2 = 0.854$) between parameters and biological activity. The r^2 (2) 85.4% variance in activity values. Of the equations that have been presented equation (1) is most significant. It explains the correlation between biological activity and Ncosv of the compounds. Maximum biological activity is influenced by this parameter alone. Since the coefficient of Ncosv is negative in this equation, it can be interpreted that biological activity is more for compounds which have very less difference in Ncosv as compared to reference compound.

Considering the above equations, (1) and (2) can be used for theoretical prediction of a novel class of non-amino acid ACE inhibitors.

ACNOWLEDGEMENTS

The authors are thankful to M/s Torrent Research Center, Bhat, Gandhi Nagar for providing access to molecular modeling software facilities and to Director, SGSITS, Indore, for providing necessary facilities for this work. The author NDG is thankful to CSIR, New Delhi for Senior Research Fellowship.

REFERENCES

1. M.A. Ondetti, *Circulation*, **77**, 174 (1988).
2. B. Waeber, J. Nussberger and H.R. Brunner, in: N.M. Kaplan, B.M. Brenner and J.H. Laragis (Eds.), New Therapeutic Strategies in Hypertension, Raven Press, New York, p. 97 (1989).
3. S.E. O'Connor, *Drug News Paerspect*, **3**, 133 (1990).
4. M. Stornello, E.V. Valvo and L. Scapellato, *Nephron*, **58**, 52 (1991).
5. T.M. Barnes, N.M. Barnes, B. Costall, J. Coughlan, E. Kelly, R.J. Naylor, D.M. Tomkins and T.J. Williams, *Cardiovasc. Pharmacol.*, **19**, S63 (1992).
6. In ACE inhibitors of lactamic structure the acylamino acid moiety is mimicked by the carboxyl-substituted lactamic ring.
7. L. Turbanti, G. Cerbai, C. Di Bugno, R. Giori, G. Garzelli, M. Criscuoli, A.R. Renzetti, A. Subissi and G. Bramanti, *J. Med. Chem.*, **36**, 699 (1993).
8. K. Hugo, *Quant. Struct. Act. Relat.*, **13**, 285 (1994).
9. Cerius^2 version 3.5, Biosym/Molecular Simulations Inc., 9685 Scranton Road, California, USA, 92121-3752.

(*Received*: 27 May 2004; *Accepted*: 8 December 2004) AJC-4020