Quantitative Structure-Activity Relationships of Renin Inhibitors

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Abstract: A review is presented on quantitative structure-activity relationships (QSARs) of renin inhibitors which have potential as antihypertensive and cardiovascular agents. They inhibit the renin, an enzyme that is involved in the rate-limiting first step of the renin angiotensin system (RAS). Most of the renin inhibitors are peptidomimetics but recently some nonpeptidomimetic renin inhibitors with low molecular weight have also been developed. In both types of renin inhibitors, the QSARs have exhibited that their inhibition activity would largely depend upon the molecular weight of the compounds, van der waals radius related parameters of the substituents, and the localized electronic effects, particularly of the side chain of the residues substituted in the peptides.

Keywords: Renin inhibitors, aspartic protease inhibitors, antihypertensive agents, pepstatin analogues, quantitative structure-activity relationships.

INTRODUCTION

Renin is a member of one of the four classes of protease enzymes: aspartic, serine, cysteine, and metallo. It is an aspartic protease. All classes of protease enzymes selectively catalyze the hydrolysis of polypeptide bonds. Aspartic proteases employ an enzyme-bound activated water molecule as the nucleophile, which attacks the amide carbonyl of the scissile bond. They generally bind 6-10 amino acid regions of their polypeptide substrates that are typically processed with the aid of two catalytic aspartic acid residues in the active site [1]. All aspartic proteases are endopeptidases and the primary sequence in them has two different Asp-Thr-Gly sequences (e.g. in Cathespin D, Asp-33, Thr-34, Gly-35-----Asp-231, Thr-232, Gly-233). Their apostructure shows these two chains running in opposite directions with a water molecule bound between two aspartates [2]. The general acid-base mechanism that is considered most likely for polypeptide hydrolysis catalyzed by aspartic proteases is depicted in Fig. (**1**) [3]. The scissile amide bond undergoes nucleophile attack by a water molecule which is itself partially activated by a deprotonated catalytic aspartic acid residue (Fig.**1a**). The protonated aspartic acid donates a proton to the amide bond nitrogen, generating a zwitterionic intermediate (Fig.**1b**) that collapses to the cleaved products (Fig.**1c**). The water molecule that binds between the enzyme (Ile50 and Ile150) and the inhibitor is thought to position a peptide substrate, stretching the peptide bond out of planarity toward a tetrahedral transition state that is stabilized by a second water molecule [4].

In addition to catalyzing amide hydrolysis, most proteases are capable of cleaving peptide bonds with sequence selectivity. This is usually accomplished by having an enzyme binding site(s) which is complimentary to one (or more) substrate residues. Standard nomenclature is used to designate substrate residues and their corresponding binding sites on the enzyme as shown in Fig. **2** [5]. Two members of the aspartic protease class of enzymes, renin and

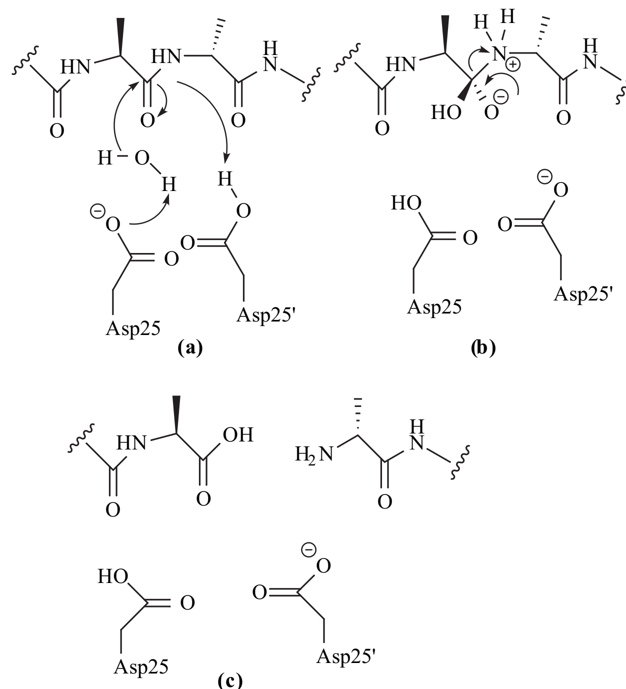

Fig. (1). Catalytic mechanism for substrate hydrolysis by aspartic proteases as suggested by Leung *et al.* [3]. The scissile amide bond undergoes nucleophile attack by a water molecule which is itself partially activated by a deprotonated catalytic aspartic acid residue (**a**). The protonated aspartic acid donates a proton to the amide bond nitrogen, generating a zwitterionic intermediate (**b**) that collapses to the cleaved products (**c**).

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HIV-1 protease, have been subjects of extensive research efforts to discover therapeutically useful inhibitors [3, 6, 7]. Renin inhibitors have potential as antihypertensive agents [8] and HIV-1 protease inhibitors have been shown to be clinically useful in the control of AIDS [9-11].

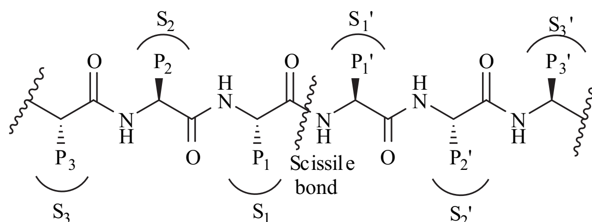
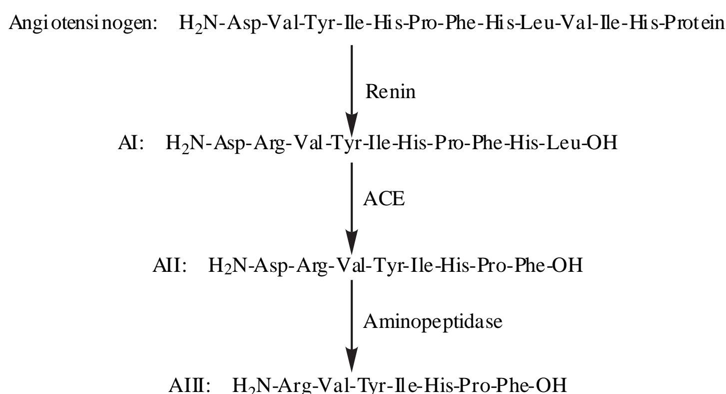


Fig. (2). A peptidic substrate of aspartic proteases. The P_1, P_2, ……P_n and $P_1{}'$, $P_2{}'$,……$P_n{}'$ are amino acid residues, and S_1, S_2,……S_n and $S_1{}'$, $S_2{}'$,……$S_n{}'$ are the corresponding binding sites at the enzyme. These nomenclatures are according to the Schechter, I.; Burger, A. *Biochem. Biophys. Res. Commun.* **1967**, 27, 157.

The renin is involved in the rate-limiting first step of the renin-angiotensin system (RAS) (Scheme **1**), hydrolyzing most of the renin inhibitors reported have been peptidomimetics that retain significant peptidic character [8,13,14] which confers low stability and poor oral bioavailability in human. Because of this, the clinical progress of renin inhibitors has been comparatively hampered. Another hurdle to the development of renin inhibitors has been the high cost of the production as compared to current hypertensives such as ACE inhibitors and AII receptor antagonists. Renin inhibitors generally need to interact with five subsites (S4-S1) of the enzyme to bind tightly and selectively compared with only three for ACE inhibitors. Consequently renin inhibitors tend to have a higher molecular weight, have more stereocenters, and are thus more expensive to manufacture.

For many years, several research groups have been involved in search of orally bioavailable inhibitors of renin. Most of the design principles for renin inhibitors were derived from the classical studies of the inhibition of fungal aspartic proteases by pepstatin (**1**) and related compounds. During most of the renin inhibitor research, the 3D structure of the renin enzyme was not known [15].



Scheme 1. Renin angiotensin system.

the α_2-globulin angiotensinogen to release the 10-residue peptide angiotensin I (AI). AI is then converted by angiotensin converting enzyme (ACE), a dipeptidylcarboxypeptidase, to an octapeptide angiotensin II (AII), which is a potent vasoconstricter, a promoter of aldosterone release (and thus sodium retention), and a trigger for a variety of other effects on kidneys, brain, and pituitary. AII, in turn, is converted to angiotensin III (AIII) by aminopeptidases. AIII produces effects similar to A II, but to a lesser extent. The whole cascade of RAS is, thus, an important area for the study of regulation of blood pressure and electrolyte homeostasis.

RENIN INHIBITORS

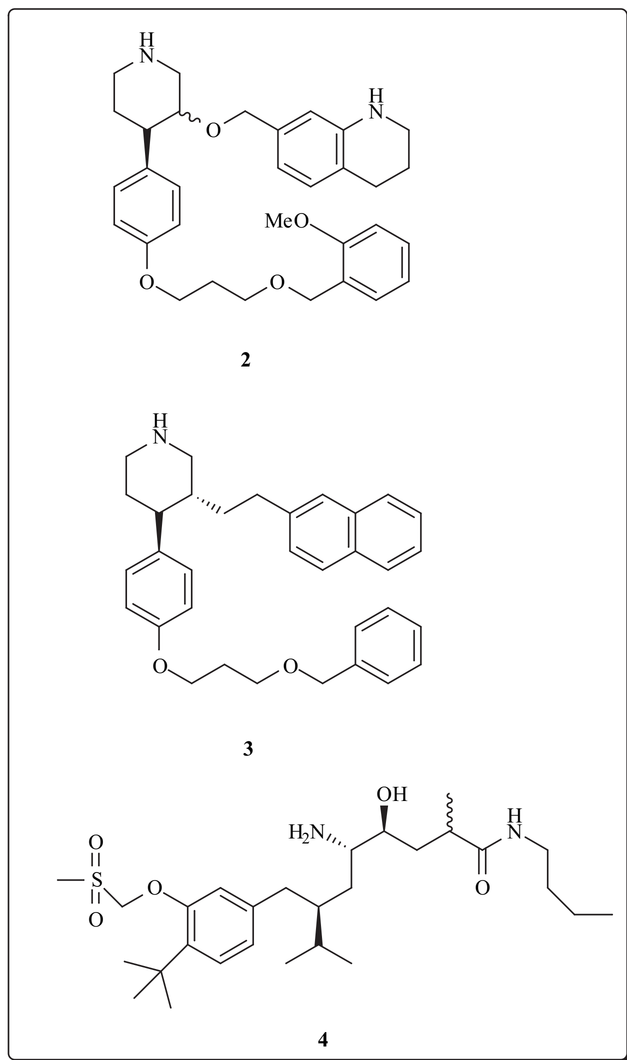
Whilst the treatment of hypertension and cardiac failure by means of ACE inhibitors has been well studied [12], renin inhibitors provide a more direct probe of the RAS, because renin has a remarkable specificity towards its substrate while ACE is relatively nonspecific. However,

Iva-Val-Val-Sta-Ala-OH

1

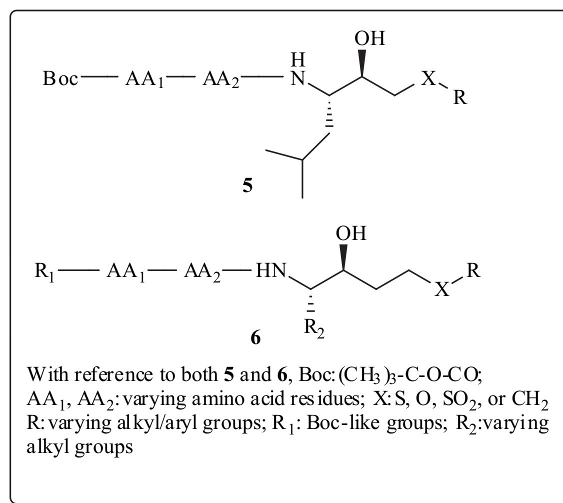
Though mostly, renin inhibitors have been developed by modifying substrate fragments from the angiotensinogen cleavage site [14], many renin inhibitors with low molecular weight, less peptidic character, and improved oral bioavailability have recently emerged. Compound **2** is a representative of a series of nonpeptidic piperidine based inhibitors of human plasma renin [16]. An X-ray crystal structure of **3** shows that protonated nitrogen of the piperidine ring is located between the two active site aspartic residues forming one hydrogen bond with each, thus fulfilling the function of the transition state isosteres present in other inhibitors [17]. The napthyl residue occupies the large hydrophobic S1/S3 subsite of renin, while the 4-phenyl ring of the inhibitor and the attached lipophilic tail disrupt a hydrogen bond between Tyr75 and Trp39 of the enzyme, lifting a portion of the flap region from the Thr72 to Ser81. This binding induces the formation of a new

hydrophobic pocket in the enzyme to accommodate the lipophilic tail and terminal phenyl group. Nonpeptidic low molecular weight compounds such as **2** and **3**, and **4** developed by Goschke *et al.* [18] represent excellent progress towards the necessary features (oral bioavailability and economic production) for a renin-inhibiting drug but may need to be more selective. The other important features, leading to therapeutically useful renin inhibitors and a deeper insight into the mechanism of renin inhibition can be derived from quantitative structure-activity relationship (QSAR) studies on renin inhibitors. An attempt is, therefore, made to present a review of all QSAR studies available on them.



QSAR RESULTS AND DISCUSSION

As a preamble to QSAR, a recent SAR study of Hamilton *et al.* [19] is of great importance. These authors found that peptidic renin inhibitors with higher lipophilicity were better absorbed from the intestine and that the compounds with ionizable functionality were less well absorbed than neutral compounds. Neutral compounds showed some dependency on molecular weight, with small compounds exhibiting better absorption. While uptake into hepatic cells was rapid regardless of partition coefficient or molecular weight, rate of appearance in bile was dependent on the molecular weight of the compounds. Most of these factors, indicated to be conducive to optimizing the bioavailability, were found to be well correlated quantitatively with the *in vitro* activities of the renin inhibitors. Gupta *et al.* [20] reported a QSAR study on two small series of peptide analogues of angiotensinogen with novel Leu replacements at the scissile amide bonds (**5**) [21] and with a scissile amide bond modified with a hydroxyethylene isostere and the valine amide bond replaced with a biosteric substituent (**6**) [22]. For both the series, the activity of the compounds against purified human renin was found to have excellent correlations with molecular weight and some indicator variables as shown by Equations (1) (for **5**) and (2) (for **6**).



With reference to both **5** and **6**, Boc: $(CH_3)_3$-C-O-CO; AA_1, AA_2: varying amino acid residues; X: S, O, SO_2, or CH_2 R: varying alkyl/aryl groups; R_1: Boc-like groups; R_2: varying alkyl groups

$$\log(1/IC_{50}) = 1.410(\pm 0.375)\,MW - 0.941(\pm 0.320)\,D_1 - 0.575(\pm 0.333)\,D_2 - 1.844$$
$$n = 31,\ r = 0.92,\ s = 0.31,\ F_{3,27} = 46.05 \quad (1)$$

$$\log(1/IC_{50}) = 0.752(\pm 0.413)\,MW + 1.673(\pm 0.415)\,D + 1.155$$
$$n = 20,\ r = 0.98,\ s = 0.26,\ F_{2,17} = 187.44 \quad (2)$$

In both the equations, IC_{50} refers to the molar concentration of the inhibitor leading to 50% inhibition of the enzyme activity. Among the statistical parameters, n refers to the number of data points, r is the correlation coefficient, s is the standard deviation, F is the F-ratio between the variances of calculated and observed activities, and the figures within the parentheses with ± sign refer to 95% confidence intervals. Both Equations (1) and (2) had exhibited the significant dependence of the activity on the molecular weight (MW). The indicator variable D_1 in Equation (1) was used with a value of 1 for X = SO_2 and D_2 was used with a value of 1 for an R-group containing an aromatic moiety. The significant negative coefficients of both these variables indicated that an SO_2 group present at the terminus and/or an aromatic group present at the far end of the molecule will not be conducive to the activity. Both could be assumed to have some steric effects.

In **6**, R_2 was either an isobutyl group as in **5** or a *c*-hexylmethyl group. The effect of a *c*-hexylmethyl group relative to an isobutyl group was accounted for by an

indicator variable D with a value of 1 for the former and zero for the latter. A highly positive coefficient of this variable in Equation (2) suggested that a *c*-hexylmethyl group will have about 50 times better effect than an isobutyl group. This difference in effect can be attributed to the larger size of the *c*-hexylmethyl group, because of which it might have better dispersion or hydrophobic interaction with some active site of the enzyme than the isobutyl group.

In a series of pepstatin analogues with the general formula A-X-Y-Sta-Ala-Sta-R, where A and R are protecting groups like Boc and OH, respectively, X and Y are amino acid residues, and Sta stands for statine [(*3S*,*4S*)-4-amino-3-hydroxy-6-methylheptanoic acid], Nisato *et al.* [23] performed a Free-Wilson analysis and reported, with a value of r = 0.979, that most favourable to the activity were the Y amino acid residues in the order: valine > cyclopentylglycine > norvaline > histidine. These authors also identified the crucial physiochemical parameters of Y that were important for the activity. They were the NMR chemical shift of the α-carbon, inductive effect, and van der Waals radius-related parameter.

We made a Fujita-Ban analysis [24] (a modified Free-Wilson analysis) on a series similar to **6** and studied by Dellaria *et al.* [25] against purified human renal renin and found that the most active compound in the series could be the one represented by **7**.

We also performed the Fujita-Ban analysis on two nonpeptidic series of renin inhibitors (**8** and **9**) reported by Baker *et al.* [26] for their *in vitro* enzyme inhibition activity against purified and plasma renin. The analysis revealed that the most active compound in the series of **8** could be the one that will have R = EtO, X = O, $R_1 = CH_2Ph$ (*S*), and R_2 = butyl, and in the series of **9** the one that will have $R_1=CH_3O$ or CH_3OCH_2O like group, X = NH, and R_2 = butyl. In both the series, thus, R_2 = butyl was found to give the best effect. The R_2 was varied from one- to four-carbon atom alkyl groups, out of which the group of the largest size appeared to produce the best effect. When this butyl group was replaced by a still larger group, *c*-hexylmethyl group, as in **6** and **7**, the activity was found to be further improved. This suggests that at R_2-position a highly bulky group would be conducive to the activity. At the start of the molecular chain, a group like Boc [$(CH_3)_3C$-O-CO], CH_3O,or CH_3OCH_2O is found to favour the activity. In these groups, the oxygen atom(s) appear to play some significant role in the binding, probably by forming the hydrogen bonds with some groups in the enzyme (possibly histidine or water in the S4 site [26])

Charton [27] had made a QSAR study on several series of peptidic renin inhibitors (**10-17**) derived from residues 8 to 11 of angiotensinogen or from pepstatin.

10. Boc-Phe-AaX[9]-NHCH (*c*Hx)CHOHCH$_2$SO$_n$-R (purified human renin) [25]

AaX = His, Ala, Leu, Phe, Thr, Ser, Hse, (Bzl)Thr, (BzlO$_2$C)Orn, (BzlO$_2$C) Lys, (Ac)Lys

R = any alkyl group; n = 0, 1, 2

$$\log (1/EC_{50}) = 7.13 (\pm 3.08)\ \sigma_{1,X} - 0.766 (\pm 0.261)\ n_{H,X} + 0.638 (\pm 0.236)\ I_X + 3.48 (\pm 1.83)\ \alpha_R + 1.87 (\pm 0.944)\ \nu_R - 3.04 (\pm 0.724)$$

$$n = 18,\ r = 0.845,\ s = 0.39,\ F_{5,12} = 6.00 \qquad (3)$$

11. Boc-Phe-His-Sta-Leu-NH-Y (human plasma renin) [28]

Y = any phenylalkyl group

$$\log (1/IC_{50}) = 2.71 (\pm 1.52)\ \Sigma\sigma_{1,Y} - 4.79(\pm 0.964)\ \Sigma\sigma_Y + 0.255(\pm 0.106)\ \Sigma n_{n,Y} + 0.727 (\pm 0.154)\ n_{cf} + 0.755 (\pm 0.193)\ n_{1,Y} - 1.35 (\pm 0.273)\ n_{2,Y} + 2.06 (\pm 0.462) n_{3,Y} - 2.80 (\pm 0.402)$$

$$n = 13,\ r = 0.966,\ s = 0.19,\ F_{7,5} = 9.95 \qquad (4)$$

12. Boc-Phe-AaX[9]-NHCH(CH$_2$-R)CHOH-CH$_2$CH$_2$WZ (purified human renal renin) [28]

AaX = Ala, His, Leu, Phe; R = an alkyl group; W=O, CO, S, SO$_2$ like group;

Z = alkyl/phenylalkyl group

$$\log (1/IC_{50}) = 1.97 (\pm 0.764)\ \alpha_X + 0.479 (\pm 0.125)\ n_{HnI,X} + 1.34 (\pm 0.106) n^*_R + 0.164 (\pm 0.044)\ n_{O,W} - 1.44 (\pm 0.206)$$

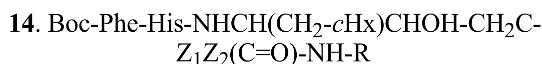
$$n = 17,\ r = 0.993,\ s = 0.13,\ F_{5,11} = 243.20 \qquad (5)$$

13.A-(C=O)-Phe-AaX[9]-NHCH(CH$_2$-R) CHOH-CH$_2$(C=CH$_2$)(C=O)-NH-B

(purified human renal renin) [22]
AaX = Ala, His, Leu, Phe; A= any alkoxy group; B = R/RNMe$_2$ (R = an alkyl group)

$$\log (1/IC_{50}) = 2.11 (\pm 0.497)\ \nu_X + 0.499 (\pm 0.225)\ \nu_B + 0.989 (\pm 0.235) n^*_R - 0.680 (\pm 0.170)\ n_{HnI,X} - 13.50 (\pm 3.08)\sigma_{1,B} - 4.07 (\pm 0.385)$$

$$n = 20,\ r = 0.956,\ s = 0.33,\ F_{5,14} = 29.53 \qquad (6)$$



14. Boc-Phe-His-NHCH(CH_2-*c*Hx)CHOH-CH_2C-Z_1Z_2(C=O)-NH-R

(purified human renal renin) [29]

Z_1, Z_2 = OH, Me, CH_2N_3, CH_2Cl, CH_2NH_2 like group; R= any alkyl group

$$\log(1/IC_{50}) = 2.42 (\pm 0.528)\, \sigma_{1,Z1/Z2} - 0.984 (\pm 0.454)\, v_{Z1/Z2} - 1.01 (\pm 0.198)\, n_{cf} - 0.786 (\pm 0.210)$$

$$n = 9,\ r = 0.941,\ s = 0.28,\ F_{3,5} = 13.01 \qquad (7)$$

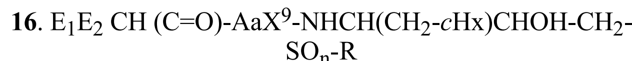
15. Boc-Phe-AaX^9-NHCH(CH_2-*i*Pr)CHOH-CH_2-U-Z

(purified human renal renin) [21]

AaX = His, Ala; U = S, O, SO_2, CH_2; Z = alkyl/phenylalkyl group

$$\log(1/IC_{50}) = 0.878 (\pm 0.181)\, I_{His} + 1.25 (\pm 0.477)\, v_W - 0.118 (\pm 0.069)\, n_{n,W} - 1.06 (\pm 0.279)$$

$$n = 26,\ r = 0.779,\ s = 0.42,\ F_{3,22} = 11.32 \qquad (8)$$



16. E_1E_2 CH (C=O)-AaX^9-NHCH(CH_2-*c*Hx)CHOH-CH_2-SO_n-R

(purified human renal renin) [25]

AaX = His, Ala; E_1 = group like Bzl, BzlOCH-R, $PhCH_2$, PhO, etc.;

E_2 = group like H, NH_2, BZl, or RO_2CNH; R = any alkyl group

$$\log(1/IC_{50}) = 5.99 (\pm 1.80)\sigma_{1,X} + 4.31 (\pm 0.60)\, \sigma_{1,E2} - 7.96 (\pm 1.42)\, \alpha_X + 4.44 (\pm 1.03)\, A_{E2} + 16.90 (\pm 3.47)\, v_X - 12.68 (\pm 2.47)$$

$$n = 16,\ r = 0.973,\ s = 0.21,\ F_{5,10} = 35.11 \qquad (9)$$

17. Q-AaX^1-AaX^2-Sta-Ala-Sta-CO_2-R (enriched human plasma renin) [23]

AaX^1, AaX^2 = a variety of amino acid residues including His, Val, Phe, Gln, etc.
Q = Boc, Iva, Cbz, or Ac group; R= any alkyl group

$$\log(1/IC_{50}) = 7.51 (\pm 1.29)\, \sigma_{1,X} + 1.97 (\pm 0.522)\, \alpha_X + 0.314 (\pm 0.107)\, n_{H,X} - 0.898 (\pm 0.254)\, I_X + 3.49 (\pm 0.569)\, v_X - 1.20 (\pm 0.238)\, v_Q - 8.64 (\pm 0.524)$$

$$n = 34,\ r = 0.867,\ s = 0.34,\ F_{6,27} = 13.69 \qquad (10)$$

In all the series **10-17**, AaX^n refers to an amino acid residue with side chain X (n in it refers to the position in angiotensinogen or pepstatin). In the QSAR equations derived for them (Eqs.3-10), the various variables have their meanings as follows:

σ_1: localized electrical effect parameter identical to electronic inductive effect parameter σ_I.

α: polarizability parameter defined as $\alpha = (MR_X - MR_H)/100$, where X is any substituent and MR is molar refractivity index

v: van der Waals radius relative to hydrogen atom.

n_H: hydrogen bonding parameter, referring to number of NH and/or OH bonds present in a group.

n_n: number of lone pair of electrons present on O or N in the group.

I: a parameter accounting for the effect of an ionic side chain with a value of 1 for charged moiety and zero for neutral moiety

n_{HnI}: for His, the parameters n_H, n_n, and I each takes the value of 1. n_{HnI} therefore refers to a combination of these three.

n_O: number of oxygen atoms bonded to sulfur in SO_n group (n_O = n)

n*: an indicator variable used for alkyl group R, having a value of 1 for R = *c*Hx and zero for R = *i*Pr

I_{His}: an indicator parameter used specifically for His residue. In **15**, AaX^9 is either His or Ala. I_{His} has a value of 1 for the former and zero for the latter.

n_{cf}: an indicator parameter to account for the configurational effect. In Equation (4) obtained for **11**, it stands for the chirality of C (in Y) bonded to NH. In Equation (7) obtained for **14**, it stands for the chirality of C in –CHOH– moiety.

n_1, n_2, n_3: In Equation (4) derived for **11**, these parameters refer to branching in first three carbon atoms in Y-substituents.

Now these equations suggest that so far AaX residues are concerned their side chain X may produce variety of effects. Equation (3) suggests that it can have a favourable local electrical effect ($\sigma_{1,X}$) and if it is a charged group an additional electronic effect can be had (I) due to some electrostatic interaction of it with the receptor. However, a negative coefficient of the parameter $n_{H,X}$ indicated that if the side chain has any hydrogen bonding group like NH or OH, it will not be advantageous to the activity. For a residue like His, Equation (6) obtained for **13** suggests, through a negative coefficient of parameter $n_{HnI,X}$, that its side chain can have an adverse effect not only because of having a hydrogen bonding group (NH), but also because of having a lone pair on both the nitrogens of the ring and being a charged species. However, these properties of His appear exceptionally to be advantageous for the activity of **12** (Eq.5) and as compared to Ala, His appears to be better in **15** as exhibited by I_{His} parameter in Equation (8). The side chain of any residue, however, appears to produce strong localized electrical effect (Eqs. 3, 9, and 10). It can also affect the activity through its various other properties such as its molecular size accounted for by v_X (Eqs. 6, 9, and 10) and molar refractivity accounted for by α_X(Eqs.5,

9, and 10). However, while v_X exhibits uniformly a positive effect of the molecular size in each case, the α_X exhibits a positive effect of molar refractivity only in the series of **12** and **16** (Eqs. 5 and 9) and a negative effect in the series of **17** (Eq.10). This negative effect may be due to misorientation of the side chain towards the active site of the enzyme where it should make a dispersion interaction.

Equations (3)-(10) exhibit that for most of the other substituents, too, in the peptides, the molecular size and molar refractivity play the important roles in the activity of the compounds, though the coefficients of α or v may be somewhere positive and somewhere negative. The positive and negative roles of these parameters can be attributed to the relative orientations of the groups towards the active site of the enzyme.

Occasionally, in some cases a few more parameters have been found to govern the activity, e.g., in **11** and **15** the n_n parameter describing the number of lone pairs on oxygen and nitrogen in a group (Eqs 4 and 8), in **11** and **14** the parameter n_{cf} describing the configuration of a particular carbon atom (Eqs. **4** and **7**), in **11** n_1, n_2, n_3 accounting for the branching at carbon atoms in Y-substituent, and in **12** n_O denoting the number of oxygen atoms bonded to sulfur atom in W group. All such parameters seem to have their incidental effects, which are also not very consistent, e.g. n_n has a positive coefficient in Equation (11) and a negative coefficient in Equation (8). Thus the most important characteristics of the substituents governing the activity seem to be their electronic nature and their molecular size. The electronic nature appears to be important particularly for the side chain of the residues and the molecular size for the other substituents in the peptides. Almost similar properties have been indicated, as already discussed, to be crucial for the activity by Nisato *et al.* [23] from Free-Wilson analysis on pepstatin analogues.

Thus, in conclusion, it can be said that the activity of renin inhibitors is primarily governed by the electronic factors and molecular size of the substituents. The electronic factors include the localized electrical effect that may influence the electrostatic interaction, if any, between the substituent and receptor, the hydrogen bonding, and the lone-pair effect. The molecular size may be responsible for dispersion interaction or for some steric effects.

These QSARs have not exhibited any explicit dependence of activity on lipophilicity, which governs the permeability of the compound through the lipoid membrane and the hydrophobic interaction of the molecule with the receptor. It can be, therefore, assumed that all renin inhibitors may have almost equal permeability through the membrane and have a definite hydrophobic interaction with a fixed site of the enzyme.

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