QSAR Study of Dihydropyrimidinone C-5 Amides as the Selective $\alpha_{1b}$-Receptor Antagonists

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The $\alpha_{1b}$-antagonistic activity of dihydropyrimidinone C-5 amides is analyzed through the Fujita-Ban and Hansch approaches. The analyses have helped to ascertain the role of different substituents in explaining the observed antagonistic activity of these analogues. From both approaches, it is predicted that the more hydrophobic X-substituents and the phenyl or 2-cyanophenyl substituents at the 4-position of the piperidine ring are beneficial in raising the $\alpha_{1b}$-receptor antagonist action of a compound. Likewise, the presence of F at R₄ (the para-position of either phenyl or 2-cyanophenyl ring) further helps in augmenting it. The positions R₁ and R₃ of the dihydropyrimidinone ring are in favour of Me and H respectively. In addition, a non hydrogen-bond acceptor substituent at R₂ is least preferred. Substituents at position R₄ of this ring, however, by either H or CH₂OMe leads to better potency compounds.

Benign prostatic hyperplasia (BPH) is the progressive enlargement of the prostate gland especially in the older age of male population. The mechanical component of this disorder is due to increased prostatic mass, which is attributed to 5α-dihydrotestosterone. The dynamic component of BPH is due to endogenous adrenergic tone, which also restricts flow through the urethra. It was shown that adrenergic receptor antagonists, specially, $\alpha_{1}$-type ($\alpha_{1}$-AR) antagonists, can also relieve symptoms of BPH by relaxing lower urinary tract tissue, thus reducing prostatic and urethral tone. These agents were initially developed for treatment of hypertension, and thus their efficacy in the treatment of BPH is balanced against a small, but significant, incidence of side effects, such as orthostatic hypotension, which is considered as the critical disadvantage in BPH patients.

Three subtypes of $\alpha_{1}$-receptors, $\alpha_{1A}$, $\alpha_{1B}$ and $\alpha_{1D}$ have, recently been identified with varying tissue distributions and their corresponding cloned counterparts are termed as $\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$ respectively. The $\alpha_{1A}$-receptors are mainly present in lower urinary tract tissue, and are less prevalent in the vasculature. Thus, agents that selectively inhibit $\alpha_{1A}$-receptors over $\alpha_{1B}$ and $\alpha_{1D}$ should display a better therapeutic profile, particularly in terms of cardiovascular effects and for BPH. Soon after the cloning and expression of the three different $\alpha_{1}$-receptor subtypes, the calcium channel blocker nilidipine was shown to be a potent antagonist of the $\alpha_{1A}$-receptor subtype. Several modifications of the nilidipine structure have been extensively documented which maintained their selectivity towards $\alpha_{1A}$-receptor subtype. The success of such modifications suggests that the exact structure of the central heterocycle in nilidipine is not critical and that the other mode of attachment of the piperidine containing side chain via amide bond formation of the dihydropyrimidinone (DHP) C-5 carboxylate might also provide potent and selective compounds. These newly prepared compounds were more selective for the $\alpha_{1A}$- over $\alpha_{1B}$- and $\alpha_{1D}$-receptors and also lessened effects on the cardiovascular system. The analogues may, therefore, be better $\alpha_{1A}$-receptor antagonists for the treatment of BPH. The aim of this communication is to establish the quantitative structure-activity relationship (QSAR) study, which may provide the rationale for drug-design and helps in exploring the possible mechanism of action.

*For correspondence
MATERIALS AND METHODS

The reported compounds\textsuperscript{13}, given by the general structure in fig. 1, with their $\alpha_{1a}$-antagonist activity and relevant physicochemical parameters are listed in Table 1. For present work, however, the hydrophobic parameter, $\pi$ and the hydrogen-bond acceptor parameter, $HA$ were only found appropriate and the same were taken from the compilation of Hansch et al.\textsuperscript{14}. Besides these parameters, some indicator variables were also used to account for the effect of some specific binary variations. The derived most significant QSAR equations were further subjected to a validation test\textsuperscript{12} by the leave-one-out (LOO) method. This method creates a number of modified data sets by taking away one compound from the parent data set in such a way that each observation is taken away once and once only. Then one model is developed for each reduced data set and the response values of the deleted observations are predicted from the model. The squared difference between predicted and actual values are added to give the predictive residual sum of squares (PRESS). The cross-validation index, CVI was then calculated from the ratio of PRESS to the sum of squares of the response values, SSY. A value $< 0.1$, obtained for this index, indicates an excellent model. Both the Fujita-Ban and the Hansch type of calculations were carried out for these compounds.

In the Fujita-Ban approach\textsuperscript{13}, which is based on an additivity principle, the biological activity, $BA_f$ for $fh$ compound is expressed as: $BA_f = \Sigma a_j X_j + \mu ... 1$ where, $X_j$ has a value of 1 if a substituent is present at $fh$ position and 0 if not. Similarly, $a_j$ is the contribution of the $fh$ substituent (generally hydrogen) to $BA_f$ and $\mu$ is the theoretical biological activity of the reference compound of the series. The reference compound is usually (but not necessarily) the unsubstituted congener. The linear equations generated, using Eqn. 1, were solved by the method of least squares for the values of unknowns, $a_j$ and $\mu$.

RESULTS AND DISCUSSION

Twenty-eight data points were used in the construction of the Fujita-Ban matrix with compound 23 as the parent congener. The frequency of occurrence of certain groups at a given position of parent compound in three of the congeners, e.g., 20, 24 and 25 of Table 1 was one, and as per the requirement of statistical significance, these data-points were dropped in the construction of Fujita-Ban matrix. A total number of 28 linear equations in 10 unknowns including $\mu$ were generated and were solved by the method of least squares. The solutions obtained thereon are summarized in Table 2. The resulting statistical parameters of this study are: $n = 28$, $R = 0.965$, $s = 0.293$, $F(10,17) = 22.707$ where, $n$, $R$, $s$ and $F$ are respectively the number of data points, the multiple correlation coefficient, the standard deviation and the $F$-ratio between the variances of calculated and observed activities. These parameters, therefore, tune to highly significant results as the $F$-value mentioned above is significant at 99% level [$F_{10,17}(0.01) = 3.59$] and the $R^2$-value accounts for 93% of the variance between the observed and the predicted $pK_a$ values. The predicted $pK_a$ values, obtained by adding the requisite substituents contributions to $\mu$, are also in close agreement with the observed ones (Table 1). The substituents (incorporated at various positions of the parent moiety) that make higher positive contributions to activity may be used to design more active compounds of the series in future. It may further be inferred that only the substituent Me at $R_7$, H at $R_9$, H or CH$_3$OMe at $R_9$, and C–CN moiety at Y–$R_7$, relative to the substituents in the parent compound, 23 are predicted to enhance activity while the remaining variations at these sites lead to detrimental effect.

It is important to note that the Fujita-Ban approach cannot extrapolate beyond the substituents used in the training set whereas the Hansch approach, attempted next, can do so. The steps of the development of the final QSAR are described through follow up correlations. In this approach, the binary variations at different positions are accounted for by a number of indicator variables such as $IR_1$, $IR_2$, $IR_3$, $IR_4$, $IYR_1$, and $IR_5$. Each of these are arbitrarily assigned a value 1 if the indicated position contains respectively Me, Me, CF$_3$, CN, N and F, and a value 0 for hydrogen and otherwise. Thus, for the same set of data points and with the above indicator variables, the MRA leads to following correlation equations.

$$K_a = 9.709 \pm 0.28 IR_2 + 0.086 \pm 0.34 IR_3 \pm 2.008 \pm 0.30 IR_5 - 176 \pm 0.27 I_{YR} - 0.998 \pm 0.36 I_{YR}$$

Fig. 1: The derivatives of dihydroptymidinone C-5 amide.
### Table 1: QSAR Results for Dihydropyrimidinone C-5 Amides at the $\alpha_1$-Receptor.

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*The binding profile $K_1$ expressed as $pK_1$ on molar scale represents the displacement of [125I]HEAT from human cloned $\alpha_1$-receptor, expressed in CHO cells; taken from Ref. [10].$^{b}$ calculated using Fujita-Ban method; $^c$ calculated using Eqn. 7; $^d$ calculated using Eqn. 11; $^e$ the outlier compound of present study.

November - December 2003 Indian Journal of Pharmaceutical Sciences 597
+0.147(±0.29)/R_{x}, n = 28, R = 0.952, s = 0.304, F(6,21) = 34.114... 2.

\[ pK_r = 9.710 - 0.075(±0.32)/R_{x} - 2.003(±0.29)/R_{s} - 0.189(±0.24)/R_{x} - 1.001(±0.35)/IYR_{x} + 0.135(±0.26)/IYR_{s} \]

\[ pK_r = 9.709 - 1.996(±0.28)/R_{s} - 0.188(±0.23)/R_{x} - 1.001(±0.34)/IYR_{s} + 0.124(±0.25)/IYR_{x} \]

\[ n = 28, R = 0.952, s = 0.292, F(4,23) = 42.795 \ldots 3 \]

\[ pK_r = 9.662 - 1.949(±0.28)/R_{s} - 0.966(±0.34)/IYR_{s} + 0.106(±0.26)/IYR_{x} \]

\[ n = 28, R = 0.948, s = 0.298, F(3,24) = 70.513 \ldots 5 \]

\[ pK_r = 9.805 - 2.007(±0.28)/R_{s} - 0.179(±0.23)/R_{x} - 1.095(±0.28)/IYR_{s} \]

\[ n = 28, R = 0.950, s = 0.290, F(3,24) = 74.684 \ldots 6 \]

\[ pK_r = 9.747 - 1.961(±0.27)/R_{s} - 1.048(±0.27)/IYR_{s} \]

\[ n = 28, R = 0.947, s = 0.295, F(2,25) = 107.676, CVI = 0.001 \ldots 7 \]

The stepwise deletion of different independent variables is shown through Eqns. 3 to 6, which lead us to conclude that these are incongruous for present study. In Eqn. 7 the F-test values accounts for 90% of the variance between the observed and predicted \( pK_r \) values and the F-value remains significant at 99% level \([F_{x}=0.01]=5.57\). Also, the independent variables used in this equation are mutually virtually orthogonal \((IR_{s} \text{ versus } IYR_{x}, r=0.125)\) and a low value obtained for CVI has expressed an excellent model. Thus Eqn. 7 has emphasized the importance of only two variations in the parent moiety. Substituents such as Me or CHOMe rather than CF_{3} at R_{x} are preferred. Likewise, the incision C-H or C-CN instead of N at Y-R_{x} is beneficial in raising the potency of a compound. Extending the data set for the entire set of compounds of Table 1, the MRA results in a slightly inferior correlation Eqn. 8.

\[ pK_r = 9.649 - 1.882(±0.35)/R_{s} - 0.970(±0.35)/IYR_{s} \]

\[ n = 31, R = 0.901, s = 0.378, F(3,28) = 60.713 \ldots 8 \]

which now accounts for 81% of the variance with the \( F \)-value significant at 99% level. This equation may, however, be improved further by considering additional parameters, susceptible to account for other variations of the parent structure. Amongst various attempted parameters governing the electronic, steric and hydrophobic nature of the substituents of these preoccupied positions, the hydrogen-bond acceptor property due to R_{x} and hydrophobicity due to X-substituents emerged as the best alternatives. Inclusion of each of these variables in the analysis resulted successively into correlation Eqns. 9 and 10.

\[ pK_r = 9.700 + 0.271(±0.48)p_{x} - 1.923(±0.36)/R_{x} - 1.011(±0.35)/IYR_{x} \]

\[ n = 31, R = 0.905, s = 0.379, F(3,27) = 40.700 \]

\[ pK_r = 9.716 - 0.825(±0.40)HA_{x} - 1.936(±0.30)/R_{s} - 1.023(±0.30)/IYR_{x} \]

\[ n = 31, R = 0.933, s = 0.320, F(3,27) = 60.798 \ldots 10 \]

The statistical parameters of Eqn. 10 are significantly improved in comparison to Eqns. 8 and 9, indicating the importance of the HA_{x} parameter rather than the \( p_{x} \). However both the parameters, considered together, contributed significantly to improve the results further. The same is shown in Eqn. 11.

### TABLE 2: DERIVED SUBSTITUENTS CONTRIBUTIONS TO \( \alpha_{1a} \)-RECEPTOR ANTAGONIST ACTIVITY.

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Parent Contribution, \( \mu = 9.658(±0.35) \).

### TABLE 3: THE INTERCORRELATION MATRIX AMONGST THE INDEPENDENT VARIABLES OF EQN. 11^a.

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<td>0.101</td>
<td>0.101</td>
</tr>
<tr>
<td>( \pi_{x} )</td>
<td></td>
<td>1.000</td>
<td>0.227</td>
<td>0.227</td>
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<tr>
<td>IR_{s}</td>
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<td>0.139</td>
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<tr>
<td>IYR_{x}</td>
<td></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
</tbody>
</table>

^a The matrix elements are the r-values, which satisfy the orthogonality conditions among the predictor variables.
\[ pK_y = 9.811 - 0.920(\pm 0.39) \Delta \text{HA}_y + 0.460(\pm 0.39) \pi_y - 2.012(\pm 0.29) R_y - 1.099(\pm 0.29) \gamma R_y, \ n = 31, R = 0.943, s = 0.303, F(4, 26) = 51.784, CVI = 0.002... 11. \]

This Eqn. 11 accounted for 89% of the variance and reflected the parametric requirement that may explain the in vitro binding activities of the congeners at \( \alpha_{1a} \)-receptor. The \( F \)-value obtained is significant at 99% level \( [F_{30}(0.01) = 4.14] \) for the entire data set of the present study. The mutual orthogonality conditions among the independent variables of Eqn. 11 are shown in Table 3 and the calculated \( pK_y \) values that closely resemble the observed ones are listed in Table 1. Additionally, the low value obtained for CVI has also expressed an excellent statistical model. It is now evident from Eqn. 11 that the substituents of X-position having higher hydrophobic character, in addition to Me or CH\(_2\)OMe at R\(_y\) and C–H or C–CN at Y–R\(_y\) serve to augment the binding activity of a compound. Hydrogen-bond donor substituents at R\(_y\) may, however, lead to detrimental effects on potency. From both the approaches, it appeared that the more hydrophobic substituents at X (the 4-position of piperidine) improve \( \alpha_{1a} \)-receptor antagonist action of a compound. The Fujita-Ban study, in conformity with this, assigned a negative contribution to a less hydrophobic substituent such as CN relative to H. The position is, therefore, required to remain either unsubstituted or be occupied by a more hydrophobic substituent. The positions R\(_1\) and R\(_3\) of the dihydropyrimidinone ring are best occupied by Me and H respectively as the contributions obtained for them are positive. However, these are too small to make any significant improvement in the \( \alpha_{1a} \)-potency of a compound. Both of these positions are, therefore, retained vacant in the Hansch type of correlation analysis. Similarly, H or CH\(_2\)OMe, present at R\(_y\)-position of this ring contributed positively relative to CH\(_3\) and helps in improving the potency, while CF\(_3\) at this position with a high negative contribution causes detrimental effect to it. The indicator variable \( IR_y \), considered in the Hansch type of analysis, has further acclaimed it. The indicator variable \( IYR_y \) chosen for the incision in phenyl ring, attached to 4-position of piperidine, does not favour N relative to C–H (Eqn. 11). Thus, 2-pyridyl substituents are less preferred than either phenyl or 2-cyanophenyl derivatives. This was further accredited by the Fujita-Ban approach, wherein the contribution obtained for N is highly negative. The other variation such as presence of F or H, at R\(_y\), of the phenyl ring does not seem to contribute to improve the significance of correlations in the Hansch type of study. The Fujita-Ban study, on the other hand, assigned negative contribution to H relative to F predicting that the latter substituent at para-position of phenyl ring would be slightly advantageous. The same may be explored in future analogue design and synthesis.

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REFERENCES

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