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QSAR Study of Dihydropyrimidinone C-5 Amides as the Selective α_{1a}-Receptor Antagonists

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The α_{1a}-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 α_{1a}-receptor antagonist action of a compound. Likewise, the presence of F at R_4 (the *para*-position of either phenyl or 2-cyanophenyl ring) further helps in augmenting it. The positions R_1 and R_3 of the dihydropyrimidinone ring are in favour of Me and H respectively. In addition, a non hydrogen-bond acceptor substituent at R_3 is least preferred. Substituents at position R_6 of this ring, however, by either H or CH_2OMe 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[1]. The mechanical component of this disorder is due to increased prostatic mass, which is attributed to 5α-dihydrotestosterone[2]. The dynamic component of BPH is due to endogenous adrenergic tone, which also restricts flow through the urethra[2]. It was shown that adrenergic receptor antagonists, specially, α_1-type (α_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 α_1-receptors, α_{1A}, α_{1B} and α_{1D} have, recently been identified[3] with varying tissue distributions and their corresponding cloned counterparts are termed as α_{1a}, α_{1b} and α_{1d}, respectively[4]. The α_{1A}-receptors are mainly present in lower urinary tract tissue, and are less prevalent in the vasculature[5]. Thus, agents that selectively inhibit α_{1A}-receptors over α_{1B} and α_{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 α_1-receptor subtypes, the calcium channel blocker niguldipine was shown to be a potent antagonist of the α_{1a}-receptor subtype. Several modifications of the niguldipine structure have been extensively documented[6-9] which maintained their selectivity towards α_{1a}-receptor subtype. The success of such modifications suggests that the exact structure of the central heterocycle in niguldipine 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[10] were more selective for the α_{1a}- over α_{1b}- and α_{1d}-receptors and also lessened effects on the cardiovascular system. The analogues may, therefore, be better α_{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.

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MATERIALS AND METHODS

The reported compounds[10], given by the general structure in fig. 1, with their α_{1a}-antagonist activity and relevant physicochemical parameters are listed in Table 1. For present work, however, the hydrophobic parameter, π and the hydrogen-bond acceptor parameter, *HA* were only found appropriate and the same were taken from the compilation of Hansch *et al.*[11]. 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[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[13], which is based on an additivity principle, the biological activity, BA_i for ith compound is expressed as: $BA_i \approx \Sigma\, a_j X_{ij} + \mu$ ... 1 where, X_j has a value of 1 if a substituent is present at jth position and 0 if not. Similarly, a_j is the contribution of the jth substituent (generally hydrogen) to BA_i and μ 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 μ.

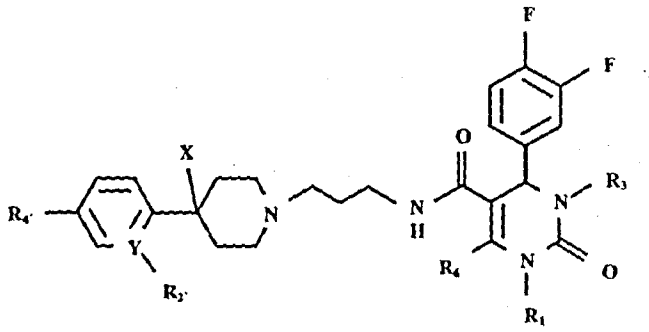

Fig. 1: The derivatives of dihydropyrimidinone C-5 amide.

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 μ 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: $n = 28$, $R \approx 0.965$, $s = 0.293$, $F(10,17) = 22.707$ 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_i values. The predicted pK_i values, obtained by adding the requisite substituents contributions to μ, 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_1, H at R_3, H or CH_2OMe at R_6 and C–CN moiety at Y–R_2, 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_3, IR_6, I_X, IYR_2 and IR_4. 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.

$$K_i = 9.709 - 0.032(\pm 0.28)IR_1 - 0.069(\pm 0.34)IR_3 - 2.008(\pm 0.30)IR_6 - 176(\pm 0.27)I_X - 0.998(\pm 0.36)IYR_2$$

TABLE 1: QSAR RESULTS FOR DIHYDROPYRIMIDINONE C-5 AMIDES AT THE α_{1a}-RECEPTOR.

R_1	R_3	R_6	X	Y–R_2	R_4	HA_3	IR_6	π_X	$IYR_{2'}$	pK_i(M).			
										Obsd[a]	Cald[b]	Cald[c]	Cald[d]
Me	H	Me	H	C–H	F	0	0	0.00	0	9.74	9.67	9.75	9.81
Me	Me	Me	H	C–H	F	0	0	0.00	0	9.74	9.67	9.75	9.81
Me	H	H	CN	C–H	F	0	0	–0.57	0	9.92	9.68	9.75	9.55
H	H	H	H	C–CN	H	0	0	0.00	0	9.89	9.85	9.75	9.81
H	H	Me	H	C–CN	H	0	0	0.00	0	9.60	9.56	9.75	9.81
H	H	CF_3	H	C–CN	H	0	1	0.00	0	7.70	7.69	7.79	7.80
H	H	CH_2OMe	H	C–CN	H	0	0	0.00	0	9.38	9.71	9.75	9.81
H	H	H	H	C–H	F	0	0	0.00	0	9.77	9.96	9.75	9.81
H	H	Me	H	C–H	F	0	0	0.00	0	9.41	9.66	9.75	9.81
H	H	CF_3	H	C–H	F	0	1	0.00	0	7.72	7.80	7.79	7.80
H	H	CH_2OMe	H	C–H	F	0	0	0.00	0	9.62	9.82	9.75	9.81
H	H	H	H	C–CN	F	0	0	0.00	0	10.15	10.08	9.75	9.81
H	H	Me	H	C–CN	F	0	0	0.00	0	9.77	9.79	9.75	9.81
H	H	CF_3	H	C–CN	F	0	1	0.00	0	8.38	7.92	7.79	7.80
H	H	CH_2OMe	H	C–CN	F	0	0	0.00	0	9.85	9.95	9.75	9.81
H	H	H	H	N	H	0	0	0.00	1	8.60	8.86	8.70	8.71
H	H	Me	H	N	H	0	0	0.00	1	8.59	8.56	8.70	8.71
H	H	CF_3	H	N	H	0	1	0.00	1	6.30	6.69	6.74	6.70
H	H	CH_2OMe	H	N	H	0	0	0.00	1	9.35	8.72	8.70	8.71
H	H	H	OH	C–H	F	0	0	–0.67	0	9.04	–[e]	–[e]	9.50
H	H	H	CN	C–H	F	0	0	–0.57	0	9.77	9.67	9.75	9.55
H	H	H	CN	C–CN	H	0	0	–0.57	0	9.80	9.56	9.75	9.55
H	Me	Me	H	C–H	F	0	0	0.00	0	9.85	9.66	9.75	9.81
Me	COMe	Me	H	C–H	F	1	0	0.00	0	8.66	–[e]	–[e]	8.89
Me	CO_2Me	Me	H	C–H	F	1	0	0.00	0	9.12	–[e]	–[e]	8.89
Me	H	Me	H	C–CN	F	0	0	0.00	0	9.92	9.80	9.75	9.81
Me	H	Me	CN	C–CN	F	0	0	–0.57	0	9.22	9.51	9.75	9.55
Me	H	Me	CN	C–H	F	0	0	–0.57	0	9.41	9.38	9.75	9.55
Me	H	H	CN	C–CN	F	0	0	–0.57	0	9.74	9.80	9.75	9.55
Me	Me	H	CN	C–CN	F	0	0	–0.57	0	9.52	9.80	9.75	9.55
Me	H	H	H	C–CN	F	0	0	0.00	0	10.17	10.09	9.75	9.81

[a]The binding profile K_i, expressed as pK_i on molar scale, represents the displacement of [^{125}I]HEAT from human cloned α_{1a}-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.

$+0.147(\pm0.29)IR_4$, $n = 28$, $R = 0.952$, $s = 0.304$, $F(6,21) = 34.114$... 2.

$pK_i = 9.710 - 0.075(\pm0.32)IR_3 - 2.003(\pm0.29)IR_6 - 0.189(\pm0.24)I_X - 1.001(\pm0.35)IYR_2 + 0.135(\pm0.26)IR_4$, $n = 28$, $R = 0.952$, $s = 0.297$, $F(5,22) = 42.795$ ... 3

$pK_i = 9.709 - 1.996(\pm0.28)IR_6 - 0.188(\pm0.23)I_X - 1.001(\pm0.34)IYR_2 + 0.124(\pm0.25)IR_4$, $n = 28$, $R = 0.952$, $s = 0.292$, $F(4,23) = 55.482$... 4

$pK_i = 9.662 - 1.949(\pm0.28)IR_6 - 0.966(\pm0.34)IYR_2 + 0.106(\pm0.26)IR_4$, $n = 28$, $R = 0.948$, $s = 0.298$, $F(3,24) = 70.513$... 5

$pK_i = 9.805 - 2.007(\pm0.28)IR_6 - 0.179(\pm0.23)I_X - 1.095(\pm0.28)IYR_2$, $n = 28$, $R = 0.950$, $s = 0.290$, $F(3,24) = 74.684$ ... 6

$pK_i = 9.747 - 1.961(\pm0.27)IR_6 - 1.048(\pm0.27)IYR_2$, $n = 28$, $R = 0.947$, $s = 0.295$, $F(2,25) = 107.676$, $CVI = 0.001$... 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 R^2-value accounts for 90% of the variance between the observed and predicted pK_i values and the F-value remains significant at 99% level [$F_{2,25}(0.01)=5.57$]. Also, the independent variables used in this equation are mutually virtually orthogonal (IR_6 versus IYR_2, 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 CH_2OMe rather than CF_3 at R_6 are preferred. Likewise, the incision C–H or C–CN instead of N at Y–R_2, 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.

TABLE 2: DERIVED SUBSTITUENTS CONTRIBUTIONS TO α_{1A}-RECEPTOR ANTAGONIST ACTIVITY.

Position	Substituent	Contribution
R_1	Me	0.010 (±0.29)
R_3	H	0.006 (±0.33)
R_6	CF_3	1.868 (±0.33)
	CH_2OMe	0.157 (±0.33)
	H	0.294 (±0.25)
X	CN	0.292 (±0.29)
Y–R_2	C–CN	0.125 (±0.24)
	N	0.867 (±0.42)
R_4	H	0.234 (±0.32)

Parent Contribution, $\mu = 9.658(\pm0.35)$.

$pK_i = 9.649 - 1.882(\pm0.35)IR_6 - 0.970(\pm0.35)IYR_2$, $n = 31$, $R = 0.901$, $s = 0.378$, $F(3,28) = 60.713$... 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_3– 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.

$pK_i = 9.700 + 0.271(\pm0.48)\pi_X - 1.923(\pm0.36)IR_6 - 1.011(\pm0.36)IYR_2$, $n = 31$, $R = 0.905$, $s = 0.379$, $F(3,27) = 40.700$ 9

$pK_i = 9.716 - 0.825(\pm0.40)HA_3 - 1.936(\pm0.30)IR_6 - 1.023(\pm0.30)IYR_2$, $n = 31$, $R = 0.933$, $s = 0.320$, $F(3,27) = 60.798$... 10

The statistical parameters of Eqn. 10 are significantly improved in comparison to Eqns. 8 and 9, indicating the importance of the HA_3 parameter rather than the π_X. However both the parameters, considered together, contributed significantly to improve the results further. The same is shown in Eqn. 11.

TABLE 3: THE INTERCORRELATION MATRIX AMONGST THE INDEPENDENT VARIABLES OF EQN. 11[a].

	HA_3	π_x	IR_6	IYR_2
HA_3	1.000	0.155	0.101	0.101
π_x		1.000	0.227	0.227
IR_6			1.000	0.139
IYR_2				1.000

[a]The matrix elements are the r-values, which satisfy the orthogonality. conditions among the predictor variables.

pK_i = 9.811 −0.920(±0.39)HA_3 +0.460(±0.39)π_X − 2.012(±0.29)IR_6 −1.099(±0.29)IYR_2. 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 α_{1a}-receptor. The F-value obtained is significant at 99% level [$F_{4,26}(0.01)$ =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_i 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_2OMe at R_6 and C–H or C–CN at Y–R_2. serve to augment the binding activity of a compound. Hydrogen-bond donor substituents at R_3 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 α_{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 α_{1a}-potency of a compound. Both of these positions are, therefore, retained vacant in the Hansch type of correlation analysis. Similarly, H or CH_2OMe, present at R_6-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_6, considered in the Hansch type of analysis, has further acclaimed it. The indicator variable IYR_2. 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_4. 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 later 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

1. Berry, S.J., Coffey, D.S., Walsh, P.C. and Ewing, L.L., **J. Urol.**, 1984, 132, 474.
2. Steers, W.D. and Zorn, B., In; Bone, R.C. Eds., Disease-a-Month, Mosby-Year Book, Inc., St Louis, 1995, 36.
3. Heible, J.P., Bylund, D.B., Clarke, D.E., Eikenburg, D.C., Langer, S.Z., Lefkowitz, R.J., Minneman, K.P. and Ruffolo, R.R., **Pharmacol. Rev.**, 1995,47, 267.
4. Price, D.T., Schwinn, D.A., Lomasney, J.W., Allen, L.F., Caron, M.G. and Lefkowitz, R.J., **J. Urol.**, 1993, 250, 546.
5. Forray, C., Bard, J.A., Wetzel, J.M., Chiu, G., Shapiro, E., Tang, R., Lepor, H., Hartig, P.R., Weinshank, R.L., Branchek, T.A. and Gluchowski, C., **Mol. Pharmacol.**, 1994, 45, 703.
6. Nagarathnam, D., Miao, S.W., Lagu, B., Chiu, G., Fang, J., Murali Dhar, T.G., Zhang, J., Tyagarajan, S., Marzabadi, M.R., Zhang, F., Wong, W.C., Sun, W., Tian, D., Wetzel, J.M., Forray, C., Chang, R.S.L., Broten, T.P., Ransom, R.W., Schorn, T.W., Chen, T.B., O'Malley, S.S., Kling, P., Schneck, K., Bendeskey, R., Harrell, C.M., Vyas, K.P. and Gluchowski, C., **J. Med. Chem.**, 1999, 42, 4764.
7. Murali Dhar, T.G., Nagarathanam, D., Marzabadi, M.R., Lagu, B., Wong, W.C., Chiu, G., Tyagrajan, S., Miao, S.W., Zhang, F., Sun, W., Tian, D., Shen, Q., Zhang, J., Wetzel, J.M., Forray, C., Chang, R.S.L., Broten, T.P., Schorn, T.W., Chen, T.B., O'Malley, S.S., Ransom, R.W., Scheneck, K., Bendesky, R., Harrell, C.M., Vyas, K.P., Zhang, K., Gilbert, J., Pettibone, D.J., Patane, M.A., Bock, M.G., Freidinger, R.M. and Gluchowski, C., **J. Med. Chem.**, 1999, 42, 4778.
8. Wong, W.C., Sun, C., Lagu, B., Tian, D., Marzabadi, M.R., Zhang, F., Nagarathnam, D., Miao, S.W., Wetzel, J.M., Peng, J., Forray, C., Chang, R.S. L., Chen, T.B., Ransom, R.W., O'Malley, S.S., Broten, T.P., Kling, P., Vyas, K.P., Zhang, K. and Gluchowski, C., **J. Med. Chem.**, 1999, 42, 4804.
9. Lagu, B., Tian, D., Nagarathnam, D., Marzabadi, M.R., Wong, W.C., Miao, S.W., Zhang, F., Sun, C., Chiu, G., Fang, J., Forray, C., Chang, R.S.L., Ransom, R.W., Chen, T.B., O'Malley, S.O., Zhang, K., Vyas, K.P. and Gluchowski, C., **J. Med. Chem.**, 1999, 42, 4794.
10. Barrow, J.C., Nantermet, P.G., Selnick, H.G., Glass, K.L., Rittle, K.E., Gilbert, K.F., Steele, T.G., Homnick, C.F., Freidinger, R.M., Ransom, R.W., Kling, P., Reiss, D., Broten, T.P., Schorn, T.W., Chang, R.S.L., O'Malley, S.S., Olah, T.V., Ellis, J.D., Barrish, A., Kassahun, K., Leppert, P., Nagarathnam, D. and Forray, C., **J. Med. Chem.**, 2000, 43, 2703.
11. Hansch, C. and Leo, A.J. In; Substituent Constants for Correla-

tion Analysis in Chemistry and Biology, John Wiley, New York, 1979, 48.
12. Wold, S., **Quant. Struct.-Act. Relat.**, 1991, 10, 191 and references therein.
13. Fujita, T. and Ban, T., **J. Med. Chem.**, 1971, 14, 148.