Journal of Enzyme Inhibition, Vol. 16, pp. 331–338
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Quantitative Structure–activity Relationship Study of Novel α_{1a}-selective Adrenoceptor Antagonists

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(Received 28 November 2000)

Two series of compounds were recently reported as novel α_{1a}-selective adrenoceptor antagonists. In the first series, a dihydropyrimidone moiety is attached to a 4-phenyl piperidine containing side chain, while in the second, it is linked to a 4-substituted phenyl piperazine containing side chain. These compounds having potential for the treatment of benign prostatic hyperplasia, a urological disorder in the older age male population, were subjected to a quantitative structure–activity relationship study. The analysis has helped to ascertain the role of different substituents in explaining the observed binding potencies of these analogues. In the first category of compounds, three sites R_1, R_2, and X were varied and from the quantitative structure–activity relationship, it emerged that X- and R_1-substituents having respectively, the high values of field and resonance effects may lead to more potent α_{1a}-antagonists. The substituent of R_2, being either CH_3 or C_2H_5, does not add to improve the activity and thus the site, at present, becomes redundant. This site may, however, be explored for some additional substituents in future. In the second series of compounds, the phenyl ring, linked to a piperazine moiety at the end of a side chain, was substituted with various groups onto different positions. From derived significant correlations, it appeared the less polar and/or bulky substituents at the *meta*- and *para*-positions and a more hydrophobic substituent at the *para*-position are advantageous.

Keywords: Quantitative structure–activity relationship (QSAR); Selective antagonists of α_{1a}-adrenoceptor; Hansch analysis; Analogues of dihydropyrimidone

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a urological disorder, especially in the older age male population. This causes a variety of obstructive and irritative symptoms including hesitancy in starting the urine flow, poor stream of urine flow, dribbling, nocturia, increased frequency of urination, and a large residual volume.[1–3] Earlier studies revealed[4,5] that a combination of mechanical constriction of the urethra due to increased prostatic mass and a dynamic

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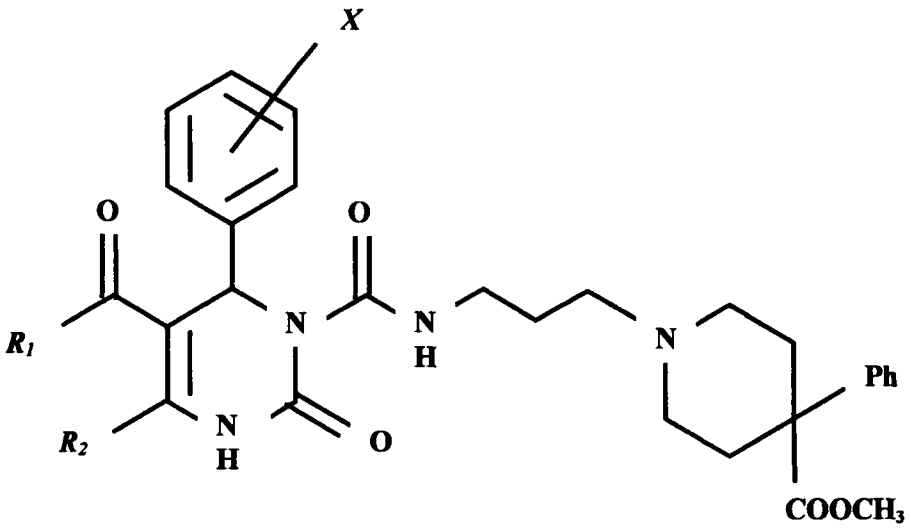

FIGURE 1 Structures of dihydropyrimidones linked to a 4-phenylpiperidine containing side chain.

component associated with increased nonadrenergic tone in the hyperplasic prostate may result in obstructive symptoms related to BPH. α_1-Adrenoceptor antagonists such as tetrazosin[6] and doxazosin,[7] currently in use for the treatment of BPH, are associated with a number of side effects such as orthostatic hypotension, dizziness, asthenia and nasal congestion.[8] The associated side effects of these drugs are possibly due to their inability to discriminate between the α_1-receptors in the vascular and lower urinary tracts. The predominant α_1-receptor subtype in the prostate is α_{1a}, which controls the smooth muscle tone.[9] Thus an α_{1a}-selective adrenoceptor antagonist may provide symptomatic relief without causing some of the above mentioned side effects. For this reason, several α_{1a}-antagonists exhibiting uroselectivity have been reported in the last decade.[10–14] More recently, two new series of compounds have been identified as novel α_{1a}-selective adrenoceptor antagonists with potential for the treatment of BPH.[15,16] In both of these series, a dihydropyrimidone moiety is attached to differently substituted side chains. In the first series, it is linked to a 4-phenylpiperidine containing side chain (Fig. 1), while in the second, it is linked to a 4-substituted phenyl piperazine containing side chain (Fig. 2). The initial structure–activity relationship (SAR) studies on these series were, however, directed to only alteration of the substituents at various positions of the structure. Although these studies resulted into the discovery of lead compounds, no rationale has yet been provided to reduce the trial-and-error factors. Hence, a quantitative SAR (QSAR) on these analogues was conducted since QSAR not only provides the rationale for drug design but also illuminates the possible mechanism of action of drugs.

MATERIALS AND METHOD

The QSAR analysis was made on two reported series of novel α_{1a}-selective adrenoceptor antagonists. The compounds along with their activity values for α_{1a}-receptor subtypes are compiled in Tables I and II. This activity profile, considered as a dependent variable, was subjected to multiple regression analysis (MRA) using some physicochemical parameters as independent variables. The most appropriate

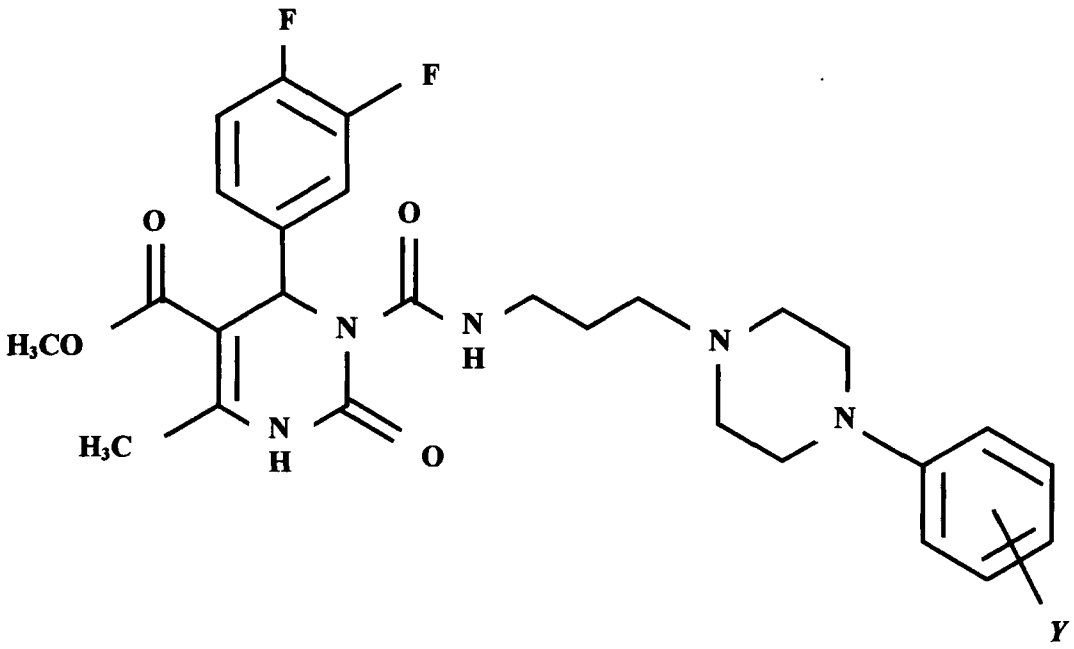

FIGURE 2 Structures of dihydropyrimidones linked to a 4-substituted phenyl piperazine containing side chain.

parameters were found to be the field constant *F*, the resonance parameter *R*, the electronic parameter σ, the molar refraction parameter MR (scaled to 0.1), hydrogen donor parameter HD and the hydrophobic parameter π. The values of these parameters were taken from the literature.[17] The activity profiles of these compounds for the aforesaid receptor subtype

TABLE I QSAR parameters and binding profiles of substituted dihydropyrimidinones linked to a piperidine containing side chain (See Fig. 1 for structures)

Compound No.	R_1	R_2	X	$\sum F$	$R(R_1)$	HD (R_1)	$pK_i(\alpha_{1a})$	
							Observed*	Calculated Eq. (3)
1	OCH_3	CH_3	4-NO_2	0.67	−0.51	0	9.30	9.34
2	OH	CH_3	4-NO_2	0.67	−0.64	1	8.00†	9.11
3	OC_2H_5	CH_3	4-NO_2	0.67	−0.44	0	9.52	9.47
4	NH_2	CH_3	4-NO_2	0.67	−0.68	1	9.15	9.04
5	$NHCH_3$	CH_3	4-NO_2	0.67	−0.74	1	8.68	8.93
6	OCH_3	C_2H_5	4-NO_2	0.67	−0.51	0	9.10	9.34
7	NH_2	C_2H_5	4-NO_2	0.67	−0.68	1	9.30	9.04
8	$NHCH_3$	C_2H_5	4-NO_2	0.67	−0.74	1	8.92	8.93
9	OCH_3	CH_3	4-CH_3	−0.04	−0.51	0	8.10	7.92
10	OCH_3	CH_3	4-Cl	0.41	−0.51	0	8.35	8.82
11	OCH_3	CH_3	3-Cl	0.41	−0.51	0	8.96	8.82
12	OCH_3	CH_3	4-F	0.43	−0.51	0	8.92	8.86
13	OCH_3	CH_3	3-F	0.43	−0.51	0	8.82	8.86
14	OCH_3	CH_3	3,4-F_2	0.86	−0.51	0	10.00	9.73
15	OCH_3	CH_3	2,4-F_2	0.86	−0.51	0	9.70	9.73

* The binding profile K_i, expressed as pK_i, on a molar scale, represents the displacement of [^{3}H]prazosin from cloned human receptors; taken from Ref. [15].
† The outlier compound in the present study.

TABLE II QSAR parameters and binding profiles of dihydropyrimidinones linked to a 4-substituted phenyl piperazine containing side chain (See Fig. 2 for structures)

Compound No.	*Y*	HD_2	σ_3	MR_{3+4}	π_4	$pK_i(\alpha_{1a})$	
						Observed*	Calculated Eq. (8)
1	H	0	0.00	0.206	0.00	9.70	9.81
2	4-Cl	0	0.00	0.706	0.71	9.10	9.14
3	4-OCH_3	0	0.00	0.890	−0.02	7.85	7.88
4	4-$COCH_3$	0	0.00	1.221	−0.55	6.37	6.41
5	3-Cl	0	0.37	0.706	0.00	9.15	8.41
6	3-CF_3	0	0.43	0.605	0.00	8.31	8.69
7	3-NO_2	0	0.71	0.839	0.00	7.92	8.04
8	2-CH_3	0	0.00	0.206	0.00	9.52	9.81
9	2-Cl	0	0.00	0.206	0.00	9.70	9.81
10	2-OH	1	0.00	0.206	0.00	9.22	9.40
11	2-OCH_3	0	0.00	0.206	0.00	10.00	9.81
12	2-OC_2H_5	0	0.00	0.206	0.00	10.00	9.81
13	2-CH_3,4-OCH_3	0	0.00	0.890	−0.02	7.80	7.88
14	2-CN	0	0.00	0.206	0.00	10.00	9.81
15	2-$COOCH_3$	0	0.00	0.206	0.00	9.70	9.81
16	2-$CONH_2$	1	0.00	0.206	0.00	9.59	9.40

*See footnotes under Table I; taken from Ref. [16].

were obtained as a binding constant K_i by displacement of [^{3}H]prazosin from cloned human receptors. For the present work, the same are expressed as pK_i on the molar scale.

RESULTS AND DISCUSSION

Table I lists the compounds where the alteration in substituents were made at R_1, R_2 and *X* and none at the 4-phenylpiperidine containing side chain. Employing the most appropriate parameters the MRA yielded the correlation shown in Eq. (1)

$$pK_i(\alpha_{1a}) = 2.013(\pm 0.438)\sum F - 0.533(\pm 0.202) \times HD(R_1) + 7.996$$
$$n = 15,\ r = 0.810,\ s = 0.353,\ F(2, 12) = 11.485 \quad (1)$$

where n is 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 ±data within the parentheses are 95% confidence intervals. The field constant $\sum F$, summed for the 2-, 3- and 4-*X* substituents, reflects the electronic type of interaction at the receptor and is more intrinsic in nature compared to the electronic parameter, σ. Likewise, HD (R_1) characterizes the hydrogen donating nature of R_1-substituents. It is important to note that for the position R_2 there were only two types of substituents and inclusion of an indicator variable, accounting for such binary variation, could not further improve the above equation. It may, therefore, be inferred that the presence of either CH_3 or C_2H_5 at R_2 is equally tolerable and does not add to improve the activity of a compound. From the derived statistical parameters of Eq. (1), it is evident that the r^2-value accounts only for 66% of variance in the observed activity values and the F-value stands significant at 99% level [$F_{2,12}(0.01) = 6.93$]. Using the above equation, the calculated $pK_i(\alpha_{1a})$ values for the congener 2, largely deviated from the observed ones. Ignoring this compound the MRA, therefore, returned much a improved

correlation as seen in Eq. (2).

$$pK_i(\alpha_{1a}) = 2.013(\pm 0.308)\sum F - 0.331(\pm 0.152) \times HD(R_1) + 7.996$$
$$n = 14,\ r = 0.892,\ s = 0.248,\ F(2,11) = 21.505 \quad (2)$$

The F-value, still significant at 99% level [$F_{2,10}(0.01) = 7.56$] is increased and ±data within parentheses are lowered. In addition, the significantly improved r-value now accounts for 80% of variance in observed activity values. When the hydrogen-donor parameter HD, in the above equation, was replaced by the resonance parameter, R, a slightly better correlation was further obtained, Eq. (3)

$$pK_i(\alpha_{1a}) = 2.011(\pm 0.279)\sum F + 1.792(\pm 0.647) \times R(R_1) + 8.910$$
$$n = 14,\ r = 0.910,\ s = 0.228,\ F(2,11) = 26.561 \quad (3)$$

which accounts for 83% of the variance. Both the $\sum F$ and $R(R_1)$ variables are poorly inter-correlated ($\sum F$ vs. $R(R_1)$; $r = 0.229$), satisfying the required orthogonal condition between the variables used in this equation. The above equation reveals that X- and R_1-substituents having respectively, the higher field and less negative resonance parametric values may result in more potent α_{1a}-antagonists. The calculated $pK_i(\alpha_{1a})$ values, using Eq. (3) and listed in Table I, are in close agreement with the observed ones. The lone compound **2**, having a carboxyl acid functionality on dihydropyrimidinone moiety seems to display an unusual behavior. Using Eq. (3), its calculated pK_i value equals 9.11 which is much higher than the observed one (Table I). The outlier behavior of this congener may be attributed to the fact that due to the highly degradable nature of an acid group, the R_1-site may not properly bind to the receptor. Further, the selection of R, instead of the *HD* parameter, for R_1-substituents seems to be more appropriate because the resulting correlation in it (Eq. (3)) is more significant than Eq. (2). Also these parameters are perfectly correlated to each other as shown by Eq. (4)

$$R(R_1) = -0.207(\pm 0.015)HD(R_1) - 0.503$$
$$n = 14,\ r = 0.969,\ s = 0.026,\ F(1,12) = 183.411 \quad (4)$$

A parallelism is, therefore, obtained between the R and HD parameters of R_1-substituents.

The compounds listed in Table II have substitutional variations in the 4-phenyl piperazine containing side chain attached to the dihydropyrimidone moiety. For these analogues, it was suggested[16] that the presence of an *ortho*-substituted electron-withdrawing group on the phenyl ring would decrease the basicity of the proximal piperazine nitrogen that might be essential for high binding affinity to the α_{1a}-receptor. But if this line of reasoning was correct, it would be expected that the order of binding affinity would parallel the electron-withdrawing nature of the substituents present on the phenylpiperazine (i.e. $NO_2 > CN > COOCH_3 > CONH_2$). The binding data, however, are not consistent with such a hypothesis and the situation became clearer when an exhaustive search for quantifying parameters pertaining to different positions was carried out. One of the most significant correlations obtained in such identified parameters, in the initial attempt, is given by Eq. (5)

$$pK_i(\alpha_{1a}) = -0.403(\pm 0.175)HD_2 - 2.693(\pm 0.284)\sigma_3 - 2.855(\pm 0.186)MR_4 + 1.002(\pm 0.252)\pi_4 + 10.101$$
$$n = 16,\ r = 0.984,\ s = 0.219,\ F(4,11) = 82.933 \quad (5)$$

where the subscripted numerals associated with the hydrogen donor HD, electronic σ, molar

refraction MR and hydrophobic π parameters represent respectively, the *orhto-*, *meta-* and *para*-positions of the phenyl ring. The *r*-value of this equation accounted for 97% of the variance and the *F*-value is significant at 99% [$F_{4,11}(0.01) = 5.67$]. The correlation Eq. (5), obtained in four independent variables using 16 data points only may, however, have misled the QSAR results. To avoid this situation, an attempt was further made to reduce the number of independent variables. A number of different parameters for 2-, 3- and 4-positions were attempted in such a way that the resulting final equation should maintain a high level of statistical significance. To this end, the molar refraction parameter MR_3 (for *meta*-position), which is perfectly correlated with the parameter σ_3, emerged as one of the best alternative parameter. The correlation between σ_3 and MR_3 is given by correlation Eq. (6)

$$MR_3 = 0.968(\pm 0.049)\sigma_3 + 0.107$$
$$n = 16,\ r = 0.982,\ s = 0.041,$$
$$F(1, 14) = 388.767 \qquad (6)$$

This hints that the *meta*-substituents may also be engaged in polar and/or steric interaction. Thus, replacing the σ_3 with MR_3 in Eq. (5) and considering the same number of data points, the MRA gave the correlation Eq. (7)

$$pK_i(\alpha_{1a}) = -0.395(\pm 0.239)HD_2 - 2.598(\pm 0.394) \times MR_3 - 2.844(\pm 0.254)MR_4 + 1.006(\pm 0.343)\pi_4 + 10.359$$
$$n = 16,\ r = 0.970,\ s = 0.299,$$
$$F(4, 11) = 43.388 \qquad (7)$$

where the coefficients of both the MR_3 and the MR_4 variables have emerged nearly equal in magnitude and similar in signs. These two variables may, therefore, be added up and the resulting correlation is described by Eq. (8)

$$pK_i(\alpha_{1a}) = -0.405(\pm 0.233)HD_2 - 2.792(\pm 0.234) \times \sum MR_{3+4} + 1.020(\pm 0.334)\pi_4 + 10.384$$
$$n = 16,\ r = 0.969,\ s = 0.291,$$
$$F(3, 12) = 60.822 \qquad (8)$$

As hinted by the statistical parameters, the level of significance of Eq. (8) is still very high. The r^2-value has accounted for 94% of the variance and the *F*-value remained significant at 99% level [$F_{3,12}(0.01) = 5.95$]. Also the variables used in deriving this equation, are mutually orthogonal (HD_2 vs. $\sum MR_{3+4}$; $r = 0.310$, HD_2 vs. π_4; $r = 0.013$, $\sum MR_{3+4}$ vs. π_4; $r = 0.218$). Further the calculated pK_i values, using the above equation, are found to be in close agreement with the observed ones (Table II). From Eq. (8), it appears that the hydrogen-donor, rather than the electron-withdrawing substituents (according to the earlier suggestion) at the *ortho*-position of the phenyl ring are adding negatively to the binding affinity for the α_{1a}-receptor. For this reason, substituents like OH, $CONH_2$ etc., at this position, seem to be least preferred. Similarly, the less polar and/or bulky substituents at the *meta-* and *para*-positions (governed by the parameter $\sum MR_{3+4}$) and the more hydrophobic *para*-substituents are advantageous in improving the binding affinity of a compound. It is important to mention here that the consideration of the HD_2 variable in Eq. (8) for only two (compounds **10** and **16** in Table II) out of sixteen data points seems to impose a severe limitation on its selection and creates doubt on the predictive power of this equation. Such a situation is often observed with newly reported compounds where the design of derivatives has not been carried out properly with respect to a later QSAR study. At this stage however, it appears that either the parameter HD_2 or the accuracy in the observed biological data of the

TABLE III Derived correlations in the cross validation procedure to check the predictive power of statistical Eq. (8). $pK_i(\alpha_{1a}) = -\alpha HD_2 - \beta\sum MR_{3+4} + \gamma\pi_4 + \delta$

Equation No.	α	β	γ	δ	n	r	s	F_{n-k-1}	DC^*
1	0.404(±0.242)	2.783(±0.256)	1.022(±0.348)	10.382	15	0.966	0.303	50.977	3
2	0.373(±0.241)	2.745(±0.248)	1.038(±0.341)	10.344	15	0.968	0.297	54.533	11
3	0.400(±0.242)	2.751(±0.294)	0.951(±0.452)	10.372	15	0.943	0.303	29.562	4
4	0.373(±0.241)	2.745(±0.248)	1.038(±0.341)	10.344	15	0.968	0.297	54.533	12
5	0.421(±0.257)	2.809(±0.276)	1.012(±0.363)	10.404	14	0.965	0.316	45.611	1,3
6	0.388(±0.258)	2.768(±0.271)	1.029(±0.358)	10.363	14	0.967	0.310	47.770	9,11
7	0.477(±0.222)	2.843(±0.227)	0.995(±0.313)	10.468	14	0.976	0.272	67.541	6,8
8	0.331(±0.251)	2.682(±0.264)	1.062(±0.348)	10.289	14	0.967	0.302	48.475	12,14
9	0.389(±0.172)	2.925(±0.187)	0.986(±0.243)	10.396	13	0.986	0.211	106.228	1,3,5
10	0.388(±0.271)	2.746(±0.297)	1.033(±0.376)	10.358	13	0.964	0.326	39.458	9,11,13
11	0.454(±0.236)	2.810(±0.248)	1.007(±0.327)	10.438	13	0.975	0.284	57.847	6,8,12
12	0.382(±0.254)	2.758(±0.286)	1.033(±0.357)	10.355	13	0.968	0.308	45.087	8,12,14
13	0.381(±0.284)	2.653(±0.385)	0.912(±0.517)	10.333	12	0.927	0.341	16.255	1,4,7,11
14	0.389(±0.285)	2.723(±0.326)	1.040(±0.397)	10.355	12	0.961	0.344	32.631	3,7,12,15
15	0.350(±0.175)	2.846(±0.192)	1.014(±0.243)	10.340	12	0.987	0.211	100.498	5,7,11,15
16	0.420(±0.255)	2.760(±0.275)	1.027(±0.343)	10.394	12	0.974	0.296	48.598	6,8,12,14

*Deleted compounds (for numbers see Table II).

compounds under consideration may be doubtful. A compound having a substituent like −OH or −COOH, under prevailing conditions of pH etc., may undergo ionization before reaching the actual site of action and may elicit an unexpected biological response. Such is the case with compound **10** where the reported activity value may therefore be suspected to entail an error. In order to ensure the validity of the HD_2 parameter, attempts to replace it with various electronic and bulk determining parameters failed. However, eliminating it from parametric space resulted in a slightly inferior correlation Eq. (9).

$$pK_i(\alpha_{1a}) = -2.661(\pm 0.238)\sum MR_{3+4} + 1.071(\pm 0.357)\pi_4 + 10.270$$
$$n = 16,\ r = 0.961,\ s = 0.312,$$
$$F(3, 12) = 77.949 \qquad (9)$$

Thus looking at the wider scope of correlation Eq. (8), the cross-validation test was further performed to derive a number of correlations by eliminating one, two, three and four random data points. In all such test data subsets compounds **10** and **16** were retained. A few of such correlations, along with eliminated data points, are listed in Table III. In all the subsets the statistical significance of correlations are maintained which corroborates the predictive power of correlation Eq. (8). The guidelines mentioned above may, therefore, be very helpful in designing more potent compounds of this series. In addition, the different kind of parameters which have emerged for varying functions on the compounds may provide valuable information regarding interactive sites present on the receptor, which in turn may provide a guide to the future synthesis of new α_{1a}-selective antagonists.

Acknowledgements

The financial assistance provided by the UGC, Regional Office, Bhopal is thankfully acknowledged.

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