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Synthesis and screening of 5-carbethoxy-N-aryl-4, 6-dimethyl-1,2-dihydropyrid-2-ones as chemical hybridising agents for wheat (*Triticum aestivum* L.)

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In the absence of alternative technology of hybrid development, chemical induction of male sterility-mediated technology based on chemical hybridising agents (CHAs) holds immense potential. 5-Carbethoxy-N-aryl-4,6-dimethyl-1,2-dihydropyrid-2-ones have been synthesized by the condensation between substituted anilines with ethyl isodehydracetate and evaluated as chemical hybridising agents on wheat genotypes PBW 343, HW 2046 and HD 2733 at 1000 and 1500 ppm concentration in a field trial during November 2001-April 2002. Maximum male sterility has been induced by 5-carbethoxy-N-(4-chlorophenyl)-4,6-dimethyl-1,2-dihyropyrid-2-one **10** followed closely by N-(4-fluoro phenyl)-2-pyridone **5** and N-(4-bromophenyl)-2-pyridone **6** causing $\geq$ 98 per cent induction of spikelet sterility at 1500 ppm on PBW 343. Except CF_3-containing analogues, in all cases the influence of aromatic substituents on the induction of male sterility is in the order: *para* > *ortho* > *meta*. The substituents at *para* position have a positive effect on induction of male sterility in the order: Cl (**10**) > Br (**6**) >F (**5**) > CF_3 (**25**) > CN (**22**) > OMe (**13**) > NO_2 (**17**) > ethyl (**26**). QSAR analysis reveals a positive contribution of field effect exemplified by Swain-Lupton constant F_p and molecular weight for the aromatic substitution, but negative contributions of molar refractivity MR for the side chain in influencing the bioactivity in the CHAs. These leads explain the CHA binding fit in macromolecular receptor site. The CHAs act by creating an imbalance in acid-base equilibrium in pollen mother cells resulting in dissolution of callose wall by premature callase secretion.

Keywords: Chemical hybridising agents, *Triticum aestivum* L., genotypes, spikelet sterility, QSAR

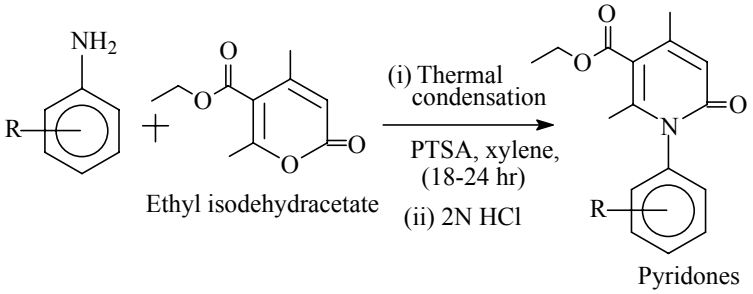
IPC: **Int.Cl.[7] C 07 D**

The production of hybrid wheat (*Triticum aestivum* L.) offers an exciting opportunity for overcoming the stagnating yield plateau of wheat in India. Exploitation of heterosis at the commercial level depends on the availability of stable male sterile lines. A viable and stable cytoplasmic-genetic male sterile system (CGMS) along with perfect restorer lines in wheat is not in place although considerable research efforts are underway. In view of this, the other option of using chemical hybridising agents (CHAs) involving two-line hybrid breeding needs to be pursued intensively. The aim is to induce physiological male sterility by spraying the plant with chemicals to induce stamen sterility without harming the pistil. The CHAs facilitate cross-breeding in plant species with perfect flowers by selectively sterilising male sex cells or by interrupting microsporogenesis to prevent self-pollination and to promote fertilisation by an outside pollen source[1]. Unlike CGMS system, the CHAs have unique advantages of saving precious time and labour since no restorer-maintainer lines are required[2]. Also, any profitable heterotic combination is apparently enormous. In a programme of design and development of potential CHAs we have undertaken the syntheses of several N-acylanilines, amino acid analogues and pyridones. Encouraging results have been obtained with the field trials of a few N-acylanilines on rice[3,4]. CHAs are important in heterosis breeding of small cereal grains like wheat for which mechanical emasculation is impractical due to the small size and close proximity of male and female reproductive organs. Ethyl oxanilates[5-8], Clofencet (Genesis, MON 21200; 2-(4-chlorophenyl)-3-ethyl-2, 5 - dihydro-5-oxo-4-pyridazinecarboxylic acid)[9], LY 195259[10] and RH 532[11] are reported to be of practical value. The search for gametocides in fifties and sixties was rather random and from the chemicals already used in agriculture such as plant

growth regulators like maleic hydrazide[12], TIBA[13], methanoproline[14], ethrel, abscisic acid and herbicides like 2,4-D[15], dalapon[16] which expectedly have strong phytotoxic response. Thus chemicals with targetted action are being now searched all over the world. Carlson has tested 1-aryl-5-carboxy-2-pyridones and their salts but not their 5-carbethoxy analogues as CHAs on small-grained cereals[17]. QSAR, a powerful tool in unraveling the structural features governing the bioactivity has not been applied in pyridones. In a programme of design and development of CHAs for crop plants, we have earlier reported the deployment of N-acylanilines in rice[3,4], wheat[6-8] and chickpea[7]. As a sequel, we report in this communication the synthesis, spectroscopic data and QSAR analysis of twenty six N-aryl-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-ones as potential CHAs for wheat.

Results and Discussion

N-Aryl-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-ones were prepared in 60-65 per cent yield by thermal condensation of respective anilines with ethyl isodehydracetate (**Scheme I**), purified by column chromatography and were characterised by their spectroscopic and elemental analysis data. In the ^{1}H NMR spectra, the presence of the ethyl ester group was confirmed by the spin-spin coupling system, *viz.*, a triplet centered at δ 1.33 ± 0.06 for CH_3 and a quartet centered at δ 4.24 ± 0.04 for OCH_2. The spin-spin coupling system was A_3X_2 type with *J* values of 6 Hz. The 6-methyl protons in the heterocyclic ring appeared at δ 2.05 ± 0.14 as a sharp singlet. The chemical shift values of the methyl protons ranged from δ 1.80 in 2′-fluoro and 4′-chloropyridone to about δ 2.25 in 2′,4′-dinitro analogue. The methyl protons (CH_3) *ortho* to nitrogen atom of the pyridone ring were more shielded than 4-methyl protons surrounded as they both are by electron deficient N-aryl group as well as the ethoxycarbonyl moiety (COOEt). They appeared as a singlet at δ 1.80 (in the N-2′-fluoro aryl derivative) and at δ 2.25 in 2′,4′-dimethoxy analogue. In contrast, the other 4-methyl protons appeared slightly downfield ranging from δ 2.10 in N-2′-fluoroaryl derivative to δ 2.40 in N-4′-nitroaryl analogue. The nitro group at *para* position caused strong deshielding. The olefinic proton in the pyridone moiety appeared as a singlet at δ 5.94 ± 0.17. The chemical shift values of the olefinic proton in 3′-chloro analogue had appeared downfield by 0.26 ppm, whereas those in 2,4′-dichloro pyridone went upfield by 0.24 ppm. The substituents *viz.*, 4′-ethyl, 2,4′-dichloro and 4′-methoxy caused marked shielding due to +R effect by 0.38, 0.43 and 0.35 ppm respectively. The methoxy group at *meta*-position instead caused deshielding effect by 0.15 and 0.07 ppm for H_a and H'_a protons respectively and 0.30 ppm for H'_b proton. It was observed that the nitro substituent at *ortho*-position of the aryl moiety caused deshielding of H_c aryl proton as compared to other analogues because of its strong – M effect operating in it. In the 2′-nitro pyridone, which by its –M effect decreased electron density of the H_c-proton, thus deshielding H_c by about 1.00 ppm. Same was the case in 3′-cyano and 3′-trifluoromethyl pyridone, which by their strong electron withdrawing effect operating on H_c-aryl proton deshielded the same by 0.52 and 0.40 ppm respectively. The M^+ ion was mostly conspicuous in the EI-mass spectra of pyridones. The aryl side chain in one form or another dominated as the base peak. The general mass fragmentation is tentatively rationalized as follows. Loss of ethoxycarbonyl moiety (COOEt) led to the formation of [M-73] peak, which in turn eliminated CO from the pyridine ring with concurrent ring to give rise to [M-101] fragment and ejection of the eventual lower homologue [M-116]. A characteristic fragment [M-45] was due to the loss of ethoxy (EtO) moiety from the molecular ion. The spectra further contained lower fragments *viz.*, m/z 78, 77, 65, 64, 63 *etc*. characteristics of the aromatic skeleton.



Scheme I — Synthetic scheme of N-aryl-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-ones **1-26**.

The pyridones were screened on three wheat varieties PBW 343, HW 2046 and HD 2733 as CHAs at 1000 and 1500 ppm concentration in November 2001 to April 2002. The results of induction of spikelet sterility caused by them are given in **Table I**. Maximum male sterility was induced by 5-carb-ethoxy-N-(4-chlorophenyl)-4,6-dimethyl-1,2-dihyro-pyrid-2-one (simply *N*-(4-chlorophenyl)-2-pyridone) (**10**) followed by N-(4-fluorophenyl)-2-pyridone (**5**) and N-(4-bromophenyl)-2-pyridone (**6**) in PBW 343. They were closely followed by N-(4-trifluoromethyl phenyl)-2-pyridone (**25**), N-(4-cyanophenyl)-2-pyridone (**22**) and N-(3-trifluoromethyl phenyl)-2-pyridone (**24**). Except CF_3-containing analogues, in all cases the influence of aromatic substituents on the induction of male sterility is in the order: *para* > *ortho* > *meta*. Disubstitution at *ortho* and *para* was found to be inferior to either of the monosubstitution. The substituents at *para* position had a positive effect on induction of male sterility in the order: Cl (**10**) > Br (**6**) >F (**5**) > CF_3 (**25**) > CN (**22**) > OMe (**13**) > NO_2 (**17**) > ethyl (**26**). The trend of activity of 2-pyridones in inducing male sterility in HW 2046 and HD 2733 followed almost the same order as in PBW 343. All other 2-pyridones exhibited moderate to low degrees of induction of male sterility. Per cent pollen sterility was found to have high correlation (r = 0.9988) with the spikelet sterility. Thus, pollen sterility appears to be the direct cause of spikelet sterility. From the stain test, it was seen that the sterile grains were transparent (**Figure 1**) thereby confirming the disintegration of cytoplasm and nucleus in the sterile pollen. In

Table I — Per cent spikelet sterility induced by pyridones on wheat tested in winter 2001-02

Compd	R (Aromatic substituent as in **Scheme I**)	Genotypes					
		PBW 343		HW 2046		HD 2733	
		1500	1000	1500	1000	1500	1000 ppm
1	H	77.04	68.10	73.81	64.84	78.95	69.20
2	2-F	72.68	65.88	70.78	64.52	73.94	67.01
3	3-F	52.91	44.21	50.31	41.92	55.53	44.84
4	3Cl, 4-F	75.60	66.90	72.74	65.29	77.21	67.48
5	4-F	98.61	94.92	97.06	92.67	98.81	95.41
6	4-Br	98.44	95.02	97.63	93.96	96.73	93.69
7	2-Cl	73.73	68.60	72.24	65.43	76.55	69.27
8	3-Cl	55.69	46.88	53.06	46.13	57.66	48.18
9	2,4-Cl_2	48.09	31.38	45.97	30.00	49.66	32.71
10	4-Cl	98.88	95.07	98.02	93.77	99.35	96.39
11	2-OMe	59.68	38.46	57.99	35.78	61.38	39.93
12	3-OMe	44.54	30.70	42.09	28.13	45.40	32.86
13	4-OMe	72.63	70.84	71.87	66.80	75.53	71.37
14	2,4-diOMe	39.59	27.87	38.13	27.44	41.96	29.26
15	2-NO_2	50.07	27.91	48.37	25.78	51.23	30.22
16	3-NO_2	39.99	18.68	38.03	16.08	42.06	19.57
17	4-NO_2	67.58	56.55	64.18	54.39	70.04	56.83
18	2,4-diNO_2	35.75	16.19	34.51	14.39	36.89	17.03
19	3-Me	16.66	9.95	14.09	9.44	18.11	12.13
20	2-CN	69.96	63.51	67.98	62.17	72.33	64.04
21	3-CN	53.26	41.63	50.70	40.14	55.27	43.05
22	4-CN	89.06	81.77	85.74	79.94	90.06	82.78
23	2-CF_3	74.33	67.50	72.34	65.43	76.26	68.78
24	3-CF_3	87.15	82.37	85.31	78.97	90.04	84.56
25	4-CF_3	96.22	91.11	94.38	87.04	96.54	92.23
26	4-Et	19.74	12.35	16.43	11.05	21.29	14.94
Emulsion control		0.46	0.26	0.33	0.22	0.49	0.34
CD (p = 0.05)			1.88		2.15		1.25

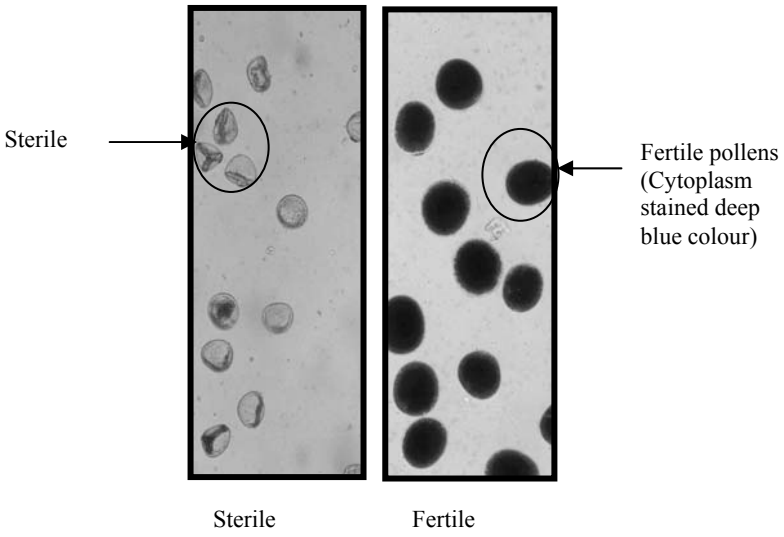


Figure 1 — Sterile pollens of wheat due to treatment of CHA *vis-à-vis* fertile pollens as revealed from KI-I_2 stain test

contrast, fertile pollens from control plots stained uniform deep blue colour in KI-I_2 stain test, thus confirming the induction of male sterility in various treatments. The absence of blue colour in sterile pollens is indicative of absence of starch. This could provide an important lead in unraveling the mode of action of the CHAs. In some cases, as apparent from the figure, the sterile pollen grains became shrivelled and the mass of cytoplasm and nucleus contracted in the pollen keeping the external pollen wall (exine) intact. The absence of any starch material in the sterile pollen grains as shown by the KI-I_2 pollen stain test could be indicative of one or other process leading to starch depletion.

QSAR Analysis

The development of an agrophore model can serve as a powerful tool in discovering new leads based on existing active chemistry. The agrophore strategy involves identifying critical structural elements responsible for activity *via* a hypothetical mode of action. There has been very little progress in the mode of action of CHAs. This situation makes CHA-agrophore development difficult, but, at the same time, it provides an opportunity to build a discovery programme focused on developing new CHAs and on elucidating CHA mode of action.

The results of induction of spikelet sterility on bread wheat (PBW 343) caused by ethyl oxanilates in N-acylanilines series at 1500 ppm concentration are shown in **Table I**. There was no marked variation in the response of different genotypes. Therefore, only the variety PBW 343 sprayed at 1500 ppm concentration was taken for QSAR analysis. The *para* substituted pyridones, containing Cl (**10**), Br (**6**) and F (**5**) respectively were found to be the best in that order when considered across three test concentrations and two year trial data. Alkyl substitution gave the least effect. It can be inferred that *para* substitution with highly electronegative groups such as F, CN or CF_3 can give rise to analogues having high level of activity. QSAR analysis in toxicology and medicine is usually carried out using log median dose as the dependent variable. It would have meant, in our case, an extremely large number of samples in field trials impossible to be handled within the constraints of resources. We have circumvented this problem by resorting to the direct use of *sin arc* transformed male sterility percent as the dependent variable because log dose is thus related in probit analysis[8]. Results of the multiple regression analysis are presented along with the statistical values (N = number of compounds; R = correlation coefficient; s = standard deviation and F = Fisher's ratio of significance index with respect to the equation). All the equations were found to be statistically significant at $P < 0.01\%$.

A set of six equations (Eqn 1-6) obtained by autoregression method anchored sum of molar refractivity values for the aromatic substituents (ΣMR) and Swain-Lupton field constant for *para* substituents (F_p) which were the major factors influencing the target activity. Stepwise auto-regression resulted into the sequential addition of Swain-Lupton resonance constant for *para* substituents (R_p) and index variable (D) for aromatic position. Eqn 1 and 2 were obtained using twenty six analogues containing three and four descriptor variables respectively.

$$Ms\ (\sin arc\ \%) = -2.69\Sigma MR + 59.00\ F_p - 3.41R_p + 64.43 \quad \ldots (1)$$

where, N = 26; R = 0.81; s = 10.37; F = 13.62

$$Ms\ (\sin arc\ \%) = -2.34\Sigma MR + 64.45\ F_p - 3.70R_p - 4.69D + 71.49 \quad \ldots (2)$$

where, N = 26; R = 0.85; s = 9.34; F = 14.13

The observed biological activity could be best explained by incorporating F_p, ΣMR, D, lnMW and ΣE_s (Eqn 5) with R = 0.94. Eqn 3 to 6 were the set of best equations obtained using 26 analogues accounting for the observed spikelet sterility with R -value ≥ 0.91.

$$Ms\ (\sin arc\ \%) = -3.21\Sigma MR + 57.18\ F_p - 3.77R_p - 5.38D + 93.98\ln Mw - 459.06 \quad \ldots (3)$$

where, N = 26; R = 0.91; s = 7.77; F = 18.38

$$Ms\ (\sin arc\ \%) = -3.32\Sigma MR + 47.47F_p - 1.74R_p - 5.10D + 173.39\ln Mw + 7.05\Sigma E_s - 904.54 \quad \ldots (4)$$

where, N = 26; R = 0.93; s = 7.01; F = 19.74

$$Ms\ (\sin arc\ \%) = -3.43\Sigma MR + 38.60\ F_p - 4.79D + 210.64\ln Mw + 10.42\Sigma E_s - 1113.06 \quad \ldots (5)$$

where, N = 26; R = 0.92; s = 7.24; F = 21.82

$$Ms\ (\sin arc\ \%) = -3.00\Sigma MR + 49.50\ F_p - 7.87D + 211.67\ln Mw + 12.19\Sigma E_s - 6.87\Sigma E_{s(m)} - 1117.35 \quad \ldots (6)$$

where, N = 26; R = 0.94; s = 6.57; F = 22.94

These equations (Eqn 3-6) tell us that the aromatic substituent must have high value of F_p but lower values of MR and R. Both electronic and steric effects exert a significant influence on the bioactivity. Inductive rather than resonance effect seemed to contribute to the activity. It is significant that the steric effect is best represented by molar refractivity rather than Verloop sterimol parameters. The direct influence of MW can be correlated with the preference for molecules with less volatility within this class.

Using Eqn 5, predicted values were generated and large deviations between predicted and observed values were observed in cases of six compounds containing 3-Me, 2-F, 3-F, 2,4-diCl, 4-Cl and 4-NO_2. The reason of these analogues showing large deviations might be that these compounds were probably not stable under field conditions. New sets of MLR equations (Eqn 7-15) were generated by resorting to "leave out" method. In one set, by leaving out 3-Me, 2-F and 3-F derivatives, the equations (Eqn 7-10) were improved with high R^2 and F values. The best equation (Eqn 10) in the data set contains five independent variables *viz.,* ΣMR, molecular weight, D, F_p and ΣEs, with R value of 0.95.

$$Ms\ (\sin arc\ \%) = -3.91\Sigma MR + 46.88F_P - 3.00R_P + 0.19\ MW + 16.46 \quad \ldots (7)$$

where, N = 23; R = 0.91; s = 7.40; F = 21.43

$$Ms\ (\sin arc\ \%) = -3.66\Sigma MR + 51.32F_P - 3.32R_P + 0.23MW - 3.62D + 9.44 \quad \ldots (8)$$

where, N = 23; R = 0.93; s = 6.55; F = 23.03

$$Ms\ (\sin arc\ \%) = -3.85\Sigma MR + 42.46F_P - 1.46R_P + 0.48MW - 3.50D + 6.58\Sigma E_S - 57.98 \quad \ldots (9)$$

where, N = 23; R = 0.95; s = 5.72; F = 26.23

$$Ms\ (\sin arc\ \%) = -4.01\Sigma MR + 34.94F_P + 0.59MW - 3.22D + 9.52\Sigma E_S - 6.32 \quad \ldots (10)$$

where, N = 23; R = 0.95; s = 5.72; F = 26.23

By leaving out 2, 4-diCl, 4-Cl and 4-NO_2 derivatives, two equations with very high R^2 and F values were obtained (Eqn 11 and 12) using twenty three analogues containing five and six descriptor variables respectively. The best equation (Eqn 11) thus obtained contained five independent variables with F-value of 31.80.

$$Ms\ (\sin arc\ \%) = -3.25\Sigma MR + 38.46F_P + 0.68MW - 4.56D + 10.20\Sigma E_S - 118.03 \quad \ldots (11)$$

where, N = 23; R = 0.95; s = 5.73; F = 31.80

$$Ms\ (\sin arc\ \%) = -2.85\Sigma MR + 30.05F_P + 0.67MW - 7.57D + 11.69\Sigma E_S - 6.58E_{s(m)} - 113.46 \quad \ldots (12)$$

where, N = 23; R = 0.96; s = 4.72; F = 40.64

Eqn 13 and 14 were obtained using 20 analogues (leaving 3-Me, 2-F and 3-F, 2, 4-diCl, 4-Cl and 4-NO_2 derivatives) and containing ΣMR, F_P and ΣR which were the major factors influencing the target activity.

$$Ms\ (\sin arc\ \%) = -3.59\Sigma MR + 40.82F_P + 74.96 \quad \ldots (13)$$

where, N = 20; R = 0.84; s = 8.96; F = 21.09

$$Ms\ (\sin arc\ \%) = -3.10\Sigma MR + 45.51F_P - 1.12\Sigma R + 72.38 \quad \ldots (14)$$

where, N = 20; R = 0.89; s = 7.87; F = 20.27

The best equation (Eqn 15) was obtained using 20 analogues refined by the 'leaveout' method and contains only four descriptor variables with R value of 0.94. Apportioning the contributions of the

descriptor variables to the R^2-term revealed that ΣMR (40%), F_p (30%), ΣR (8%) and MW (9%) were the major factors influencing the target activity. Thus, the dominating factors of the substituents are lower values of molar refractivity (MR) and resonance effect (R) and higher values of inductive effect (F_p) and molecular weight. The substituents so chosen must satisfy these criteria for enhancing the bioactivity.

$$Ms\ (\sin \text{ arc } \%) = -3.67\Sigma MR + 38.14F_P - 1.39\Sigma R + 0.26MW - 2.65 \quad \ldots (15)$$

where, N = 20; R = 0.94; s = 6.25; F = 26.71

In a competitive binding at the bioreceptor site, negative MR term could mean unfavourable conformational changes in enzyme-inhibitor complex as compared to favourable conformational changes caused by the enzyme-substrate complex. It is known that molar refractivity would explain better than sterimol parameters for representing bulk rather than directional effects. The direct involvement of Swain-Lupton field constant for *para*-substitution (F_p) with the target bioactivity in the best equation (Eqn 15) implied that inductive (field or polar) rather than resonance effect (R) of the substituent is the key factor influencing the induction of male sterility. It can be inferred that *para*-substitution with highly electronegative groups such as F or Br withdraw the electron cloud by inductive effect (-I effect) from the aromatic as well as heterocyclic ring of the most active CHAs, thus acting as the nucleophilic centre of the molecules resulting in high level of activity. Swain and Lupton studied the inverse correlation of F_p and R in the form of the equation *viz.*, $\sigma_p = \alpha F + R$, where σ_p is the Hammett constant for *para*-substitution and α is a constant. It has generally been assumed that a positive coefficient with a molar refractivity (MR) term in a correlation equation suggests a binding action *via* dispersion forces. Such binding could produce a concomitant conformation change in a macromolecular binding site. If the conformational change favoured the process under study, one would certainly expect a positive coefficient; with the detrimental, a negative coefficient could result for the MR term. The leads derived from the present study can be valuable in exploring the primary site and mode of action of these CHAs.

In a related study, 2,6-bis (trifluoromethyl)-4-hydroxy pyridine-3-carboxylates were identified as the potent CHAs for wheat[18]. 3-D QSAR method of comparative molecular field analysis (CoMFA) of pyridazine group of CHAs was carried out and there are many common findings with the present study. They found that the observed sterility rates were generally higher for the carboxylate anions than their esters. In pyridones too, this trend was discernible. The acidic *p*H generated by the hydrolysis of 5-carbethoxy-N-aryl-4,6-dimethyl-1,2-dihydropyrid-2-ones to their respective acids results in a spurt of callase (1,3-β-glucanase) secretion by the tapetal cells of pollen. The callase in turn results in premature dissolution of microsporocyte callose wall during the early stages of meiosis (meiotic I prophase) with the breakdown of microspore mother cells. Decrease in steric bulk in the aromatic region has been unanimously predicted to favour enhancement of induction of male sterility in the RH0007 family as well as the analogous 5,6-dimethyl-N-aryl-3-carboxy pyrid-4-ones[19]. The present QSAR analysis would thus facilitate the development of more potent analogues.

Experimental Section

Substituted anilines and ethyl isodehydracetate were procured from local chemical dealers and Aldrich Chemical Co. Inc. ^{1}H NMR spectra were recorded on a Varian EM-360, 60 MHz spectrometer using tetramethylsilane (TMS) as an internal reference. Chemical shifts are reported in δ (ppm) values relative to TMS, and *J* - values are expressed in hertz (Hz). Mass spectra were recorded under electron-impact (70 eV) conditions using a FISONS TRIO 1000 (HRGC Mega-2 coupled with EI-mass detector) with capillary column (30 m, HP-1, 0.32 mm i.d.) using helium (He) as the carrier gas at a flow rate of 2 mL/min. Thin layer chromatography (TLC) was performed on 250 μm silica gel G plates, preactivated at 100°C for 2 hr and using hexane-ethyl acetate (4:1) as developing medium. All test compounds gave correct elemental analyses using Euro Vector elemental analyzer (Model No. EA3011).

Synthesis of N-aryl-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-ones (1-26). Various substituted anilines (0.03 mole), *p*-toluene sulfonic acid (0.3 g) and ethyl isodehydracetate (0.015 mole, 2.94 mL) were suspended in xylene (15 mL). The reaction mixture was brought to reflux, and the water collected as an azeotrope in a Dean-Stark trap. The reaction was monitored by TLC using ethyl acetate-hexane (2:3) as the developing solvent. After 18-24 hr, the aliquot was cooled, washed with dilute hydrochloric

acid (2N) followed by water (30% v/v) to remove excess aniline and dried over anhyd. Na_2SO_4. Xylene was then removed *in vacuo*, leaving the crude product, which was purified by column chromatography using silica gel (**Scheme I**). The column was eluted with acetone-hexane (4:6) to get the pure compounds **1-26** mostly as dark-brown oils.

N-phenyl-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-ones (1): Yield 5.28 g (65%); TLC R_f 0.20; GC R_t 13.98 min. Anal. Found: C, 70.9; H, 6.4; N, 5.2. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%; ^{1}H NMR ($CDCl_3$): δ 1.40 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.00 (s, 3H, =C(CH_3) N-), 2.20 (s, 3H, -C (CH_3)=), 4.30 (q, *J*= 6Hz, 2H, OCH_2), 6.20 (s, 1H, = CH-), 6.90 (m, 1H, H_c-aromatic), 7.20 (m, 2H, H_b, H'$_b$-aromatic), 7.43 (m, 2H, H_a, H'$_a$-aromatic); EI-MS: m/z (%) 271(M^+, 17), 226(14), 214(35), 198(18), 197(14), 170(21), 168(18), 154(15), 143(9), 128(11), 118(41), 78(14), 77(100), 65(10), 53(15), 52(21), 51(35).

N-(2′-fluorophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (2): Yield 5.37 g (62%); TLC R_f 0.30; GC R_t 10.66 min. Anal. Found: C, 66.5; H, 5.6; N, 4.8. $C_{16}H_{16}$ FNO_3 requires C, 66.4; H, 5.6; N, 4.8%; ^{1}H NMR ($CDCl_3$): δ 1.20 (t, *J* = 6Hz, 3H, OCH_2CH_3), 1.80 (s, 3H, =C(CH_3) N-), 2.10 (s, 3H, -C (CH_3)=), 4.20 (q, *J*, = 6Hz, 2H, OCH_2), 6.00 (s, 1H, = C(H)-), 7.35 (m, 4H, aromatic); EI-MS: m/z (%) 289 (M^+, 39), 267 (27), 239 (32), 198 (28), 170 (25), 145 (99), 125 (33), 112 (44), 107 (17), 95 (36), 77 (24), 69 (100), 53 (75).

N-(3′-fluorophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (3): Yield 5.54 g (64%); TLC R_f 0.23; GC R_t 15.14 min. Anal. Found: C, 66.7; H, 5.8; N, 4.8. $C_{16}H_{16}FNO_3$ requires C, 66.5; H, 5.6; N, 4.8%; ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 6Hz, 3H, OCH_2CH_3), 1.90 (s, 3H, =C(CH_3) N-), 2.13 (s, 3H, -C(CH_3)=), 4.23 (q, *J*= 6Hz, 2H, OCH_2), 6.10 (s, 1H, = C(H)-), 6.87 (m, 2H, H_c, H_b'-aromatic), 7.10 (m, 1H, H'$_a$-aromatic), 7.35 (m, 1H, H_a-aromatic); EI-MS: m/z (%) 289 (M^+, 28), 244 (21), 232 (48), 216 (25), 215 (17), 188 (30), 186 (24), 172 (15), 146 (11), 136 (63), 95 (100), 77 (14), 75 (30), 53 (14), 52 (26).

N-(3′-Chloro-4′-fluorophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (4): Yield 5.91 g (61%); TLC R_f: 0.23; GC R_t: 18.33 min. Anal. Found: C, 59.5; H, 4.8; N, 4.3. $C_{16}H_{15}ClFNO_3$ requires C, 59.4; H, 4.7; N, 4.3%; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.20 (s, 3H, =C(CH_3) N-), 2.35 (s, 3H, -C (CH_3)=), 4.25 (q, *J* = 6Hz, 2H, OCH_2), 5.80 (s, 1H, = C(H)-), 6.90 (m, 2H, H_b, H_b'-aromatic), 7.15 (m, 1H, H_a-aromatic); EI-MS: m/z (%) 323 (M^+, 22), 280 (7), 278 (20), 268 (15), 266 (41), 252 (5), 250 (22), 231 (16), 222 (18), 186 (45), 172 (43), 170 (88), 156 (14), 146 (13), 131 (35), 129 (100), 111(11), 109 (34), 108 (15), 94 (26), 93 (27), 77(20), 67 (24), 53 (45), 52 (82), 51 (50).

N-(4′-fluorophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (5): Oil; yield 6.15 g (71%); TLC R_f 0.28; GC R_f 14.36 min. Anal. Found: C, 66.5; H, 5.7; N, 4.8. $C_{16}H_{16}$ FNO_3 requires C, 66.4; H, 5.6; N, 4.8%; ^{1}H NMR ($CDCl_3$): δ 1.40 (t, *J* = 6Hz, 3H, OCH_2CH_3), 1.90 (s, 3H, =C(CH_3) N-), 2.20 (s, 3H, -C (CH_3)=), 4.30 (q, *J* = 6Hz, 2H, OCH_2), 6.18 (s, 1H, = C(H)-), 7.05 (d, *J* = 6Hz, 2H, H_b, H'$_b$-aromatic), 7.18 (d, *J* = 6Hz, 2H, H_a, H'$_a$-aromatic); EI-MS: m/z (%) 289 (H^+, 24), 261 (5), 244 (19), 232 (51), 216 (21), 188 (21), 172 (15), 161 (9), 146 (10), 136 (66), 122 (11), 95 (100), 77 (24), 75 (34), 52 (24).

N-(4′-bromophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (6): Dark brown oil; yield 7.54 g (72%); TLC R_f 0.25; GC R_t 16.75 min. Anal. Found: C, 55; H, 4.7; N, 4.0. $C_{16}H_{16}$ $BrFNO_3$ requires C, 54.9; H, 4.6; N, 4.0%; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.20 (s, 3H, =C(CH_3) N-), 2.40 (s, 3H, -C (CH_3)=), 4.20 (q, *J* = 6Hz, 2H, OCH_2), 5.75 (s, 1H, = C(H)-), 6.88 (d, *J*= 6Hz, 2H, H_b, H_b'-aromatic), 7.45 (d, *J* = 6Hz, 2H, H_a, H_a'-aromatic); EI-MS: m/z (%) 349 (M^+, 29), 306 (15), 304 (18), 294 (23), 292 (22), 278 (18), 276 (22), 248 (13), 242 (15), 213 (40), 198 (49), 196 (68), 169 (26), 168 (100), 167 (34), 157 (78), 155 (86), 128 (22), 117 (15), 102 (18), 93 (15), 80(25), 78(26), 77(56), 76 (69), 75(45), 67(19), 65(17), 63(20), 53(30), 52(66).

N-(2′-chlorophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (7): Oil; yield 5.74 g (63%); TLC R_f 0.28; GC R_t 15.38 min. Anal. Found: C, 63; H, 5.4; N, 4.6. $C_{16}H_{16}ClNO_3$ requires C, 62.9; H, 5.3; N, 4.6 %; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.10 (s, 3H, =C(CH_3) N-), 2.30 (s, 3H, -C (CH_3)=), 4.18 (q, *J*, = 6Hz, 2H, OCH_2), 5.75 (s, 1H, = C(H)-), 7.10 (m,, 4H, aromatic); EI-MS: m/z (%) 305 (M^+, 6), 271 (15), 270 (93), 260 (24), 242 (83), 168 (54), 167 (18), 154 (42), 152 (79), 113 (39), 111 (100), 77 (38), 75 (47), 65 (17), 52 (49).

N-(3′-chlorophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (8): Yield 5.92 g (65%); TLC R_f 0.28; GC R_t 14.88 min. Anal. Found: C, 63.1; H, 5.4; N, 4.6. $C_{16}H_{16}ClNO_3$ requires C, 62.9; H, 5.3; N, 4.6 %; ^{1}H NMR ($CDCl_3$): δ 1.37 (t, *J* = 6Hz, 3H, OCH_2CH_3), 1.90 (s, 3H, =C(CH_3) N-), 2.18 (s, 3H,

-C (CH_3)=), 4.25 (q, *J* = 6Hz, 2H, OCH_2), 6.20 (s, 1H, = C(H)-), 7.10 (m, 2H, H_b', H_c-aromatic), 7.35 (m, 2H, H_a, H_a'-aromatic); EI-MS: m/z (%) 305 (M^+, 20), 260 (22), 250 (15), 248 (42), 231 (22), 213 (12), 204 (16), 169 (15), 168 (52), 154 (34), 152 (59), 113 (35), 111 (100), 77 (35), 75(52), 65(21), 53 (35), 52 (45).

N-(2,4′-dichlorophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (9): Yield 5.32 g (52%); TLC R_f 0.27; GC R_t 15.90 min. Anal. Found: C, 56.6; H, 4.5; N, 4.1. $C_{16}H_{15}Cl_2NO_3$ requires C, 56.5; H, 4.4; N, 4.1%; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.00 (s, 3H, =C(CH_3) N-), 2.20 (s, 3H, -C (CH_3)=), 4.21 (q, *J* = 6Hz, 2H, OCH_2), 5.70 (s, 1H, = C(H)-), 6.80 (m, 2H, H_b, H_b'-aromatic), 7.00 (m, 1H, H_a -aromatic).

N-(4'-chlorophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (10): Yield 6.29 g (66%); TLC R_f 0.27; GC R_t 15.78 min. Anal. Found: C, 63; H, 5.4; N, 4.6. $C_{16}H_{16}ClNO_3$ requires C, 63; H, 5.3; N, 4.6%; ^{1}H NMR ($CDCl_3$): δ 1.30 (t, *J* = 6Hz, 3H, OCH_2CH_3), 1.80 (s, 3H, =C(CH_3) N-), 2.12 (s, 3H, -C (CH_3)=), 4.22 (q, *J* = 6Hz, 2H, OCH_2), 6.13 (s, 1H, = C(H)-), 7.00 (d, *J*= 6Hz, 2H, H_b, H_b'-aromatic), 7.37 (d, *J* = 6Hz, 2H, H_a, H_a'-aromatic); EI-MS: m/z (%) 305 (M^+, 31), 262 (8), 260 (24), 250 (15), 248 (45), 234 (7), 232 (26), 231 (20), 213 (17), 204(22), 169 (14), 168 (55), 167 (16), 154 (36), 152 (69), 138 (11), 127 (12), 113 (35), 111 (100), 77 (35), 75 (58), 67 (16), 65 (17), 63 (17), 53 (30), 52 (47).

N-(2′-methoxyphenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (11): Light brown oily liquid; yield 5.42 g (60%); TLC R_f 0.11; GC R_t 15.01 min. Anal. Found: C, 67.9; H, 6.5; N, 4.6. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7%; ^{1}H NMR ($CDCl_3$): δ 1.23 (t, *J* = 6Hz, 3H, OCH_2CH_3), 1.90 (s, 3H, =C(CH_3) N-), 2.15 (s, 3H, -C (CH_3)=), 3.60 (s, 3H, ArOCH_3), 4.22 (q, *J* = 6Hz, 2H, OCH_2), 6.10 (s, 1H, = C(H)-), 6.86 (m,3H, H_b, H_b', H_c-aromatic), 7.15 (m, 1H, H_a'-aromatic); EI-MS: m/z (%) 301 (M^+, 11), 286 (12), 270 (91), 256 (25), 242 (73), 198 (16), 184 (15), 170 (19), 168 (25), 154 (16), 152 (18), 148 (40), 133 (20), 120 (21), 111 (18), 104 (12), 93 (18), 92 (45), 91 (12), 80 (23), 78 (35), 77 (100), 75 (16), 65 (25), 64 (18), 53 (26), 52 (43), 51 (30).

N-(3′-methoxyphenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (12): Light brown oily liqid; yield 5.60 g (62%); TLC R_f 0.25; GC R_t 16.21 min. Anal. Found: C, 67.9; H, 6.4; N, 4.7. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7%; ^{1}H NMR ($CDCl_3$): δ 1.20 (t, *J* = 6Hz, 3H, OCH_2CH_3), 1.95 (s, 3H, =C(CH_3) N-), 2.18 (s, 3H, -C (CH_3)=), 3.81 (s, 3H, ArOCH_3), 4.20 (q, *J* = 6Hz, 2H, OCH_2), 6.15 (s, 1H, = C(H)-), 7.35 (m,, 1H, H_c-aromatic), 7.50 (m, 2H, H_a', H_b'-aromatic), 7.58 (m, 1H, H_a-aromatic); EI-MS: m/z (%) 301 (M^+, 17), 244 (40), 228(15), 200 (25), 149(24), 123 (38), 95 (36), 91(42), 80 (43), 77(100), 65 (23).

N-(4′-methoxyphenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (13): Light brown oil; yield 5.87 g (65%); TLC R_f 0.25; GC R_t 16.25 min. Anal. Found: C, 67.9; H, 6.4; N, 4.7. $C_{17}H_{19}NO_4$ requires C, 67.9; H, 6.5; N, 4.7%; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.20 (s, 3H, =C(CH_3) N-), 2.30 (s, 3H, -C (CH_3)=), 3.70 (s, 3H, ArOCH_3), 4.23 (q, *J* = 6Hz, 2H, OCH_2), 5.83 (s, 1H, = C(H)-), 6.88 (m, 3H, H_a', H_b, H_b'-aromatic), 7.08 (m, 1H, H_a -aromatic); EI-MS: m/z (%) 301 (M^+, 27), 244 (37), 228(20), 200 (35), 148 (43), 134 (21), 123 (44), 115 (27), 108 (75), 95 (38), 92 (41), 91 (57), 81 (40), 80 (47), 79 (50), 77 (100), 69 (55), 65 (45), 55 (75).

N-(2′,4′-dimethoxyphenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (14): Dark brown oil; yield 5.06 g (51%); TLC R_f 0.24; GC R_t 16.30. Anal. Found: C, 65.3; H, 6.4; N, 4.2. $C_{18}H_{21}NO_5$ requires C, 65.2; H, 6.4; N, 4.2%; ^{1}H NMR ($CDCl_3$): δ 1.34 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.20 (s, 3H, =C(CH_3) N-), 2.35 (s, 3H, -C (CH_3)=), 3.75 (s, 3H, ArOCH_3), 4.25 (q, *J*= 6Hz, 2H, OCH_2), 5.85 (s, 1H, = C(H)-), 6.70 (m, 1H, H_c-aromatic), 7.50 (m, 2H, H_a - aromatic).

N-(2′-nitrophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (15): Yellowish brown oil; yield 4.93 g (52%); TLC R_f 0.30; GC R_t 15.54 min. Anal. Found: C, 61; H, 5.3; N, 9.0. $C_{16}H_{16}N_2O_5$ requires C, 60.8; H, 5.1; N, 8.9%; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.10 (s, 3H, =C(CH_3) N-), 2.30 (s, 3H, -C (CH_3)=), 4.21 (q, *J*=6Hz, 2H, OCH_2), 5.80 (s, 1H, = C(H)-), 7.90 (m, 1H, H_c-aromatic), 7.06 (m, 1H, H_b'-aromatic), 6.85 (m, 1H, H_b-aromatic), 6.43 (m, 1H, H_a'-aromatic); EI-MS: m/z (%) 316 (M^+, 2), 170 (35), 142 (16), 138 (47), 122 (13), 108 (23), 106 (11), 96 (16), 92 (32), 91 (40), 90 (52), 80 (29), 77 (100), 70 (26), 69 (3), 65 (37), 63 (26), 53 (23), 52 (28).

N-(3′-nitrophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (16): Yellowish brown oil; yield 5.12 g (54%); TLC R_f 0.32; GC R_t 15.26 min. Anal. Found: C, 61; H, 5.2; N, 8.9. $C_{16}H_{16}N_2O_5$ requires C, 60.8; H, 5.1; N, 8.9 %; ^{1}H NMR ($CDCl_3$): δ 1.30 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.10 (s, 3H, =C(CH_3) N-), 2.25 (s, 3H, -C (CH_3)=), 4.18 (q,

J=6Hz, 2H, OCH_2), 5.76 (s, 1H, = C(H)-), 7.00 (m, 2H, H_c, H_b'-aromatic), 6.40 (m, 1H, H_a'-aromatic), 7.40 (m, 1H, H_a-aromatic); EI-MS: m/z (%) 316 (M^+, 8), 263 (28), 219 (5), 147 (9), 138 (22), 108 (12), 91 (24), 80 (22), 77 (100), 65 (51).

N-(4′-nitrophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (17): Dark brown oil; yield 5.21 g (55%); TLC R_f 0.29; GC R_t 13.29 min. Anal. Found: C, 61; H, 5.2; N, 9.1. $C_{16}H_{16}N_2O_5$ requires C, 60.8; H, 5.1; N, 8.9%; ^{1}H NMR ($CDCl_3$): δ 1.33 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.20 (s, 3H, =C(CH_3) N-), 2.40 (s, 3H, -C (CH_3)=), 4.29 (q, *J* = 6Hz, 2H, OCH_2), 5.88 (s, 1H, = C(H)-), 7.03 (m, 3H, H_a', H_b, H_b'-aromatic), 8.00 (m, 1H, H_a-aromatic); EI-MS: m/z (%) 316(M^+, 11), 278 (9), 263 (41), 219 (5), 161 (10), 147 (18), 138 (11), 128 (15), 115 (15), 108 (43), 91 (25), 80 (25), 77 (100), 65 (47).

N-(2,4′-dinitrophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (18): Dark yellow oil; yield 5.20 g (48%); TLC R_f 0.28; GC R_t 15.78 min. Anal. Found: C, 53.2; H, 4.2; N, 11.7. $C_{16}H_{15}N_3O_7$ requires C, 53.2; H, 4.2; N, 11.6%; ^{1}H NMR ($CDCl_3$): δ 1.38 (t, *J* = 6Hz, 3H, OCH_2CH_3), 2.25(s, 3H, =C(CH_3) N-), 2.45(s, 3H, -C (CH_3)=), 4.35(q, *J* = 6Hz, 2H, OCH_2), 5.90(s, 1H, = C(H)-), 7.10(m, 2H, H_b, H_b'-aromatic), 8.00 (m, 1H, H_a-aromatic).

N-(3′-methylphenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (19): Dark brown oil; yield 4.45 g (52%); TLC R_f 0.16; GC R_t 15.29 min. Anal. Found: C, 71.7; H, 6.7; N, 5.0. $C_{17}H_{19}NO_5$ requires C, 71.6; H, 6.7; N, 4.9%; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, *J*=6Hz, 3H, OCH_2CH_3), 2.20 (s, 3H, =C(CH_3) N-), 2.22(s, 1H, ArCH_3), 2.38(s, 3H, -C (CH_3)=), 4.30 (q, *J*=6Hz, 2H, OCH_2), 5.86 (s, 1H, = C(H)-), 6.88 (m, 2H, H_c, H_b'-aromatic), 7.12 (m, 2H, H_a, H_a'-aromatic); EI-MS: m/z (%) 285 (M^+, 11), 240 (29), 228 (16), 212(11), 184(5), 195(48), 169 (34), 149(14), 121(22), 95(100), 93(72), 81(10), 67(29).

N-(2′-cyanophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (20): Dark brown oil; yield 5.41 g (61%); TLC R_f 0.48; GC R_t 17.83 min. Anal. Found: C, 68.9; H, 5.5; N, 9.5. $C_{17}H_{16}N_2O_5$ requires C, 68.9; H, 5.4; N, 9.5%; ^{1}H NMR ($CDCl_3$): δ 1.42 (t, *J*=6Hz, 3H, OCH_2CH_3), 2.12 (s, 3H, =C(CH_3) N-), 2.32(s, 3H, -C (CH_3)=), 4.26 (q, *J*=6Hz, 2H, OCH_2), 5.80 (s, 1H, = C(H)-), 6.65 (m, 2H, H_c, H_b'-aromatic), 7.10 (m, 2H, H $_a$', H_b'-aromatic); EI-MS: m/z (%) 296 (M^+, 17), 251 (15), 223 (42), 222 (43), 195 (29), 143 (6), 102 (100), 77(19), 67(10), 51 (18).

N-(3′-cyanophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (21): Dark brown oil; yield 5.76 g (65%); TLC R_f 0.49; GC R_t 19.37 min. Anal. Found: C, 69; H, 5.5; N, 9.5. $C_{17}H_{16}N_2O_5$ requires C, 68.9; H, 5.4; N, 9.5%; ^{1}H NMR ($CDCl_3$): δ 1.36 (t, *J*=6Hz, 3H, OCH_2CH_3), 1.90 (s, 3H, =C(CH_3) N-), 2.22(s, 3H, -C (CH_3)=), 4.28 (q, *J*=6Hz, 2H, OCH_2), 6.13 (s, 1H, = C(H)-), 7.42 (m, 2H, H_b', H_c-aromatic), 7.60 (m, 2H, H_a, H_a'-aromatic); EI-MS: m/z (%) 296 (M^+, 40), 251 (31), 239 (67), 223 (29), 222 (31), 195 (32), 193 (28), 179 (16), 143 (71), 102 (100), 77 (22), 75 (23), 67 (12), 53 (24), 52 (28), 51 (26).

N-(4′-cyanophenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (22): Dark brown oil; yield 6.03 g (68%); TLC R_f 0.29; GC R_t 18.2 min. Anal. Found: C, 68.9; H, 5.4; N, 9.5. $C_{17}H_{16}N_2O_5$ requires C, 68.9; H, 5.4; N, 9.5%; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, *J*=6Hz, 3H, OCH_2CH_3), 2.18 (s, 3H, =C(CH_3) N-), 2.35(s, 3H, -C (CH_3)=), 4.26 (q, *J*=6Hz, 2H, OCH_2), 5.80 (s, 1H, = C(H)-), 6.52 (m, 1H, H_b'-aromatic), 7.13 (m, 3H, H_a, H_a', H_b-aromatic); EI-MS: m/z (%) 296 (M^+, 28), 251 (18), 239 (59), 223 (30), 222 (31), 195 (31), 179 (8), 143 (63), 102 (100), 77 (28), 67 (8), 53 (12), 51 (22).

N-(2′-trifluoromethylphenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (23): Dark brown oil; yield 4.98 g (49%); TLC R_f 0.47; GC R_t 16.12 min. Anal. Found: C, 60.3; H, 4.9; N, 4.1. $C_{17}H_{16}N_2O_5$ requires C, 60.2; H, 4.8; N, 4.1%; ^{1}H NMR ($CDCl_3$): δ 1.30 (t, *J*=6Hz, 3H, OCH_2CH_3), 2.17 (s, 3H, =C(CH_3) N-), 2.33(s, 3H, C (CH_3)=), 4.22 (q, *J*=6Hz, 2H, OCH_2), 5.80 (s, 1H, = C(H)-), 6.80 (m, 2H, H_c, H_b'-aromatic), 7.00 (m, 2H, H_a', H_b-aromatic); EI-MS: m/z (%) 339 (M^+, 50), 294 (38), 282 (89), 266 (3), 265 (19), 238 (29), 186 (72), 168 (25), 145 (100), 125 (22), 95 (21), 75 (18), 69 (23), 67 (25), 53 (35), 52 (43).

N-(3′-trifluoromethylphenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (24): Dark brown oil; yield 5.69 g (56%); TLC R_f 0.35; GC R_t 13.80 min. Anal. Found: C, 60.2; H, 4.8; N, 4.1. $C_{17}H_{16}N_2O_5$ requires C, 60.2; H, 4.8; N, 4.1%; ^{1}H NMR ($CDCl_3$): δ 1.43 (t, *J*=6Hz, 3H, OCH_2CH_3), 1.88 (s, 3H, =C(CH_3) N-), 2.10(s, 3H, C (CH_3)=), 4.20(q, *J*=6Hz, 2H, OCH_2), 6.12 (s, 1H, = C(H)-), 7.30 (m, 2H, H_b', H_c -aromatic), 7.50 (m, 2H, H_a, H_a'-aromatic); EI-MS: m/z (%) 339 (M^+, 32), 294 (27), 282 (61), 266 (24), 265 (16), 238 (25), 186 (67), 168 (17), 145 (100), 125 (17), 95 (20), 77 (15), 69 (13), 53 (16), 52 (28).

N-(4′-trifluoromethylphenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (25): Dark brown oil; yield 6.10 g (60%); TLC R_f 0.34; GC R_t 14.27 min. Anal. Found: C, 60.2; H, 4.8; N, 4.1. $C_{17}H_{16}N_2O_5$

requires C, 60.2; H, 4.8; N, 4.1%; ^{1}H NMR ($CDCl_3$): δ 1.33 (t, *J*=6Hz, 3H, OCH_2CH_3), 2.15 (s, 3H, =C(CH_3) N-), 2.30(s, 3H, C (CH_3)=), 4.28(q, *J*=6Hz, 2H, OCH_2), 5.80 (s, 1H, = C(H)-),6.55 (m, 1H, H_b'-aromatic), 7.10 (m, 3H, H_a, H_a', H_b-aromatic); EI-MS: m/z (%) 339 (M^+, 15), 294 (14), 282 (31), 265 (9), 238 (19), 186 (49), 168 (14), 145 (100), 125 (17), 95 (17), 77 (14), 53 (27), 52 (50).

N-(4′-ethylphenyl)-5-carbethoxy-4,6-dimethyl-1,2-dihydropyrid-2-one (26): Dark brown oil; yield 6.20 g (69%); TLC R_f 0.15; GC R_t 15.31 min. Anal. Found: C, 72.3; H, 7.2; N, 4.7. $C_{18}H_{21}NO_5$ requires C, 72.2; H, 7.1; N, 4.7%; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, *J*=6Hz, 3H, $ArCH_2CH_3$), 1.28 (t, *J*=6Hz, 3H, OCH_2CH_3), 1.90 (s, 3H, =C(CH_3) N-), 2.15(s, 3H, C (CH_3)=), 4.20(q, *J*=6Hz, 2H, OCH_2), 4.68 (q, *J*=6Hz, 2H, ArCH_2-),6.10 (s, 1H, = C(H)-), 6.90 (d, *J*=6Hz, 2H, H_b, H_b'-aromatic), 7.05 (d, *J*=6Hz, 2H, H_a, H_a'-aromatic); EI-MS: m/z (%) 299 (M^+, 54), 271 (15), 254 (32), 242 (35), 226 (43), 225 (27), 199 (24), 198 (52), 196 (16), 182 (21), 168 (52), 154 (17), 146 (48), 130 (15), 116 (14), 105 (30), 103 (45), 91 (19), 90 (34), 79 (59), 77 (100), 65 (18), 53 (32), 52 (35).

Field Trials

The high-yielding varieties of bread wheat (*Triticum aestivum* L.) *viz.*, PBW 343, HW 2046 and HD 2733 recommended for timely sowing in North Western Plain Zone (NWPZ) of India were chosen for evaluation of chemical induction of male sterility. The field trial was conducted in *Rabi* season (November 2001-April 2002). The experiment was laid out in Randomised Block Design (RBD) in three replicates. Randomisation was done independently for the sub-plots in each of the three replicates. Seeds of the wheat varieties were sown using a seed drill in November, using 100 kg N, 60 kg P_2O_5 and 40 kg K_2O following a 100 kg/ha seed rate at Indian Agricultural Research Institute (IARI). Row to row distance was kept at 23 cm. Four rows of 2 m length were taken as a plot. Other optimum agronomic practices were also followed. For CHA evaluation, the test chemicals were sprayed at both 1000 and 1500 ppm as oil in water emulsion containing cyclohexanone (1%) and Tween-80 at premeiotic stage (60 days after sowing) when the length of the spike emerging out from the first node was 7-8 mm[20]. The spraying was carried out on three replicate plots of about 2 m lengths of two lines containing about 400 tillers, keeping the outermost two lines as pollinator lines. At the first signs of flower opening, ten spikes were cross-pollinated, using the approach method, with the male parent (HW 2045). For study of pollen sterility, anthers from three to four florets were smeared together over a drop of KI/I_2 (2%) and examined under a light microscope. To study the spikelet sterility, number of fertile (filled) and sterile (unfilled) grains was counted and per cent male sterility was computed. Ten each of bagged and unbagged spikes including one control were harvested at maturity. As soon as the seeds became plainly visible, spike length was measured and the number of seeds per spikelet was counted in both bagged and crossed-spikes. Male sterility was calculated as per cent inhibition of seed set in bagged spikes of treated plants.

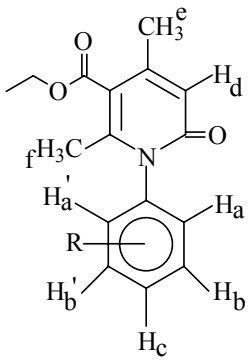
Per cent spikelet sterility was calculated from the following formula:

% Sterility = $(S_c - S_t)/S_c \times 100$ where, S_c = seeds/spikelet in bagged spikes of control plants; S_t = seeds/spikelet in bagged spikes of treated plants.

Quantitative Structure-Activity Relationship Study (QSAR)

To observe the variability in the aryl substituents in 5-carbethoxy-N-aryl-4,6-dimethyl-1,2-dihydropyrid-2-ones, various descriptor variables for aromatic substituents (electronic descriptor variables, *viz.*, Swain-Lupton field constant (F), Hammett constants (σ_m, σ_p) to define electron donating and withdrawing tendencies, partial atomic charges and electrostatic field densities, σ_p^+, Swain-Lupton resonance constant R[21,22]; steric parameters, *viz.*, Taft steric parameter (E_s), molecular weight (MW), Verloop-Hoogenstraaten multidimensional steric parameters, L and B4[23-25]; hydrophobic parameter *viz.*, π[26]; and other parameters such as molar refractivity (MR)[26] and δ ^{13}C[27,28]) dictating the biological activity (male sterility) of the CHAs were used to generate multiple linear regression equations. An index variable D for aromatic position was included with arbitrarily given values of 1, 2, and 3 for *ortho*, *para* and *meta* positions respectively[8]. To indicate the differential influences of *ortho, meta* and *para* substituents of the aromatic ring on the bioactivity of CHAs index variables were designed. The descriptors F, R, E_s, L, MR and B_4 were further split into I_o, I_m and I_p where I represents any of the variables and the subscript denotes *ortho*, *meta* and *para* positions, respectively. Additive nature of these variables was presumed for

Table II — Chemical descriptors for aromatic substituents in pyridones



R	π	σ_m	σ_p	MR	E_S	F	R
H	0.00	0.00	0.00	3.09	0.0	0.0	0.0
4-F	0.12	0.00	0.06	0.92	-0.46	0.43	0.39
4-Br	1.01	0.00	0.23	8.88	-1.16	0.44	-0.22
2-Cl	0.71	0.00	0.23	6.03	-0.99	0.41	-0.19
3-Cl	0.76	0.37	0.00	6.03	-0.97	0.41	-0.19
4-Cl	0.71	0.00	0.23	6.03	-0.97	0.41	-0.19
2-OMe	-0.02	0.00	-0.27	7.87	-0.55	0.26	-0.56
3-OMe	0.11	0.12	0.0	7.87	-0.55	0.26	-0.56
4-OMe	-0.02	0.0	-0.27	7.87	-0.55	0.26	-0.56
2-NO_2	-0.28	0.0	0.78	7.36	-2.52	0.67	8.39
3-NO_2	0.10	0.71	0.0	7.36	-2.52	0.67	8.39
4-NO_2	-0.28	0.0	0.78	7.36	-2.52	0.67	8.39
3-Me	0.56	-0.07	0.0	5.65	-1.24	-0.04	-0.18
2-CN	-0.30	0.0	0.66	6.33	-0.51	0.51	0.15
3-CN	-0.32	0.56	0.0	6.33	-0.51	0.51	0.15
4-CN	-0.21	0.0	0.66	6.33	-0.51	0.51	0.15
2-CF_3	0.88	0.0	0.54	5.02	-2.40	0.38	0.16
3-CF_3	1.09	0.43	0.0	5.02	-2.40	0.38	0.16
4-CF_3	0.88	0.0	0.54	5.02	-2.40	0.38	0.16
4-Et	1.08	0.0	-0.15	10.3	-1.31	-0.05	-0.15

disubstitution, and additional variables *viz.,* ΣI where I represents any of these variables (MR, F, R, L, B_4 and E_s) were included. The independent variables, which were found orthogonal to each other in the correlation matrix, were minimized. The "agrophore" data *viz.,* mean per cent spikelet sterility caused by pyridones tested at 1500 ppm concentration on wheat variety PBW 343 in winter 2001-02, was transformed into *sin arc* and used as the dependent variable (Ms %). Thirty three independent variables were used in constructing the correlation matrix. In case of more than one substituent, additive nature of MR and Es was presumed. The descriptor variables were used to generate stepwise multiple linear regression equations by autocorrelation using SPSS programme (version 10.0). "Leave out" method has been used to filter out the compounds showing large deviations between observed and predicted values of per cent male sterility and the MLR analysis was redone (**Table II**).

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