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Synthesis and Quantitative Structure−Activity Relationships of Oxanilates as Chemical Hybridizing Agents for Wheat (*Triticum aestivum* L.)‡

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Chemical hybridizing agents (CHAs) can facilitate two-line breeding in heterosis programs of crops. Twenty-seven oxanilates having different aromatic substitutions were synthesized and screened as CHAs on two genotypes of wheat, PBW 343 and HD 2733, during two *Rabi* (winter) seasons, 2000−01 and 2001−02. The oxanilates prepared by thermal condensation of anilines with diethyl oxalate or by acylation with ethoxycarbonyl methanoyl chloride were sprayed at 1000 and 1500 ppm at the premeiotic stage of wheat, when the length of the emerging spike of the first node was 7−8 mm. Pollen sterility and spikelet sterility were measured in each treatment. Ethyl oxanilates **5**, **6**, and **25,** containing 4-F, 4-Br, and 4-CF_3 aromatic substituents, respectively, induced greater than 98% spikelet sterility, the desired level, at 1500 ppm. Quantitative structure−activity relationship analysis revealed a direct relationship between F_p and molecular mass but an inverse relationship between MR, E_S, and R in influencing the bioactivity. Several F_1 hybrids were developed using **5**, and at least one showed heterosis.

KEYWORDS: Chemical hybridizing agents (CHAs); *Triticum aestivum* L. wheat; male sterility; oxanilates; ethyl *N*-aryl carbamoyl methanoate; QSAR

INTRODUCTION

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, 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 hybridizing 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.

CHAs facilitate cross-breeding in plant species with perfect flowers by selectively sterilizing male sex cells or by interrupting microsporogenesis to prevent self-pollination and to promote fertilization by an outside pollen source. Unlike the cytoplasmic-genetic male sterile system, the CHAs have unique advantages of saving time and labor (*1*), since no restorer−maintainer lines are required (*2*), and any profitable heterotic combination is significant. Recently, Clofencet [2-(4-chlorophenyl)-3-ethyl-2,5-dihydro-5-oxo-4-pyridazinecarboxylic acid potassium salt] has been registered as a CHA for wheat (*3*). Oxanilates and related thio and thiono analogues have been reported to induce male sterility in maize and barley (*4*), but their effect on wheat, rice, and chickpea is not known. Furthermore, there is a need to develop very potent analogue(s) by a proper structure optimization.

In a program of design and development of potential CHAs, we have undertaken the synthesis of several *N*-acylanilines, amino acid analogues, and pyridones at the Indian Agricultural Research Institute, New Delhi, India. Encouraging results have been obtained with the field trials of a few *N*-acylanilines on rice (*5*, *6*) wheat (*7*, *8*), and chickpea (*9*). Quantitative structure−activity relationship (QSAR) analysis is a powerful tool for unraveling the essential structural features governing bioactivity. To the best of our knowledge, QSAR has not been applied in the design of CHAs. We now report the synthesis, spectroscopic data, and QSAR analysis of 27 oxanilates, including 15 new compounds, as potential CHAs for wheat.

MATERIALS AND METHODS

Chemicals and Reagents. Substituted anilines and diethyl oxalate were procured from Aldrich Chemical Co. Inc. Isoproturon [3-(4-isopropylphenyl)-1,1-dimethylurea] was isolated from a formulation (50 WP) obtained from the Division of Agronomy of this institute. Xylene used in this study was of rectified grade.

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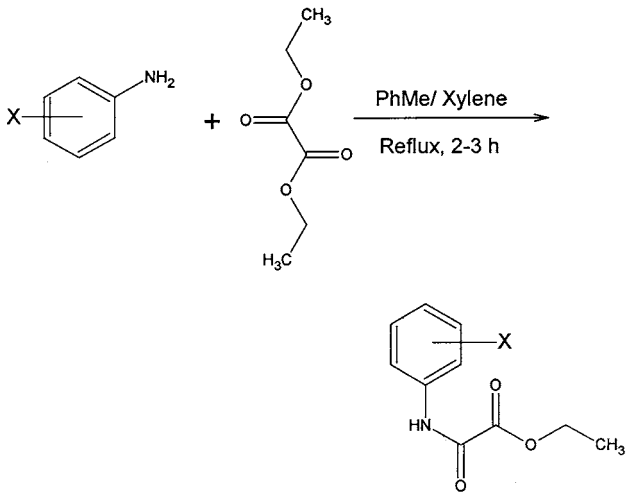

Figure 1. General synthesis of meta- and para-substituted oxanilates.

Chromatography and Spectroscopy. IR spectra (ν_{max} in cm^{-1}) were recorded on a Nicolet Impact 400 FT-IR spectrometer using a potassium bromide (KBr) disk, scanning from 625 to 4000 cm^{-1}. 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 (parts per million) 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 GC−MS (GC-8000 coupled with an EI mass detector MD-800) with a 30-m × 0.32-mm-i.d., OV-17 capillary column, 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 h, using hexane−ethyl acetate (4:1) as the developing medium. GC data were recorded on a HP Series-II GC using a FID detector and a 10-m × 0.53-mm-i.d., 0.25-μm, OV-1 megabore column with the injector temperature maintained at 250 °C and the oven temperature programmed from 80 to 250 °C at 9.9 °C/min. The carrier gas used was N_2, at a flow rate of 30 mL/min.

Melting points (mp) were determined by using a sulfuric acid bath and are uncorrected. Elemental analysis of the synthesized compounds was carried out using a Euro Vector elemental analyzer (model no. EA3011).

General Procedure for the Synthesis of Oxanilates (1, 3−6, 8−14, 16−19, 21, 22, 24−27). The following method illustrates the general scheme of synthesis of the title compounds using different substituted anilines and diethyl oxalate.

Aniline (0.025 mol, 2.3 mL), diethyl oxalate (0.03 mol, 4.06 mL), and toluene (50 mL) were mixed together in a 100-mL round-bottomed flask fitted with a Dean−Stark apparatus. The mixture was refluxed for 45 min, and ethanol was collected as an azeotrope. The reaction was cooled to 90 °C to let the product solidify, triturated with boiling ethanol, and refrigerated to allow for recrystallization of **1**. TLC and GC were used to monitor the course of the reaction shown in **Figure 1**. The duration of the reaction, yield, and physicochemical characteristics of the products thus prepared were as follows:

*Ethyl Oxanilate **(1).*** White crystalline solid; yield 4.2 g (87%); mp 71−72 °C; TLC R_f 0.56; GC t_R 11.32 min; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 6 Hz, 3H, $-OCH_2CH_3$), 4.35 (q, J = 6 Hz, 2H, $-OCH_2$), 7.50 (m, 2H, H_a, H_a'-aromatic), 7.20 (m, 3H, H_b, H_b', and H_c-aromatic), 8.85 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 193 (M^+, 7), 120 (53), 106 (24), 92 (25), 77 (23), 59 (16), 58 (100). Elemental analysis, found C, 62.3; H, 5.8; N, 7.3 ($C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25).

*Ethyl 3′-Fluorooxanilate **(3)***. A white crystalline solid was obtained from the reaction between 3-fluoroaniline and diethyl oxalate for 3 h; yield 4.28 g (81%); mp 86−88 °C (lit. mp 83−88 °C) (*4*); TLC R_f 0.54; GC t_R 10.66 min; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 6 Hz, 3H, $-OCH_2CH_3$), 4.40 (q, J = 6 Hz, 2H, $-OCH_2$), 6.80 (m, 1H, H_c-aromatic), 6.90 (m, 1H, H_b-aromatic), 7.40 (m, 1H, H_a-aromatic), 7.70 (m, 1H, H_a'-aromatic), 9.20 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 211 (M^+, 15), 138 (52), 137 (27), 124 (12), 111 (37), 110 (100), 109 (21), 95 (48), 83 (85), 82 (17), 75 (27), 63 (16), 57 (47).

*Ethyl 3′-Chloro-4′-fluorooxanilate **(4)***. A white crystalline solid was obtained from the reaction for 2 h; yield 4.78 g (89%); mp 130−131 °C (lit. mp 130−131 °C) (*4*); TLC R_f 0.49; GC t_R 13.63 min; ^{1}H NMR ($CDCl_3$) δ 1.50 (t, J = 6 Hz, 3H, $-CH_3$), 4.50 (q, J = 6 Hz, 2H, $-OCH_2$), 7.80 (m, 1H, H_a-aromatic), 7.20 (m, 2H, H_b, H_b'-aromatic), 9.01 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 245 (M^+, 12), 171 (22), 173 (10), 174 (6), 172 (20), 147 (6), 146 (33), 145 (22), 144 (100), 129 (16), 131 (5), 119 (15), 117 (45), 109 (49), 108 (45), 93 (15), 92 (15), 91 (11), 83 (7), 82 (16), 81 (15), 63 (10), 57 (23), 56 (15).

*Ethyl 4′-Fluorooxanilate **(5)***. A white crystalline solid was obtained from the reaction for 30 min; yield 4.75 g (90%); mp 118−119 °C (lit. mp 118.5 °C) (*4*); TLC R_f 0.50; GC t_R 7.82 min; ^{1}H NMR ($CDCl_3$) δ 1.65 (t, J = 6 Hz, 3H, $-CH_3$), 4.70 (q, J = 6 Hz, 2H, $-OCH_2$), 7.40 (t, J = 6 Hz, 2H, H_b, H_b'-aromatic), 7.95 (d, J = 6 Hz, 1H, H_a-aromatic), 8.10 (d, J = 6 Hz, 1H, H_a'-aromatic), 9.44 (s, 1H, NH); IR 3333 (as. NH str), 1698 (C═O ester str.), 1640 (amide-I band, C═O str.), 1400 (CF str.), 1295 (aromatic secondary δ_{CH}); EI-MS *m*/*z* (relative intensity) 211 (M^+, 100), 139 (18), 138 (93), 137 (72), 110 (92), 75 (12), 83 (32), 63 (5).

*Ethyl 4′-Bromooxanilate **(6)***. A white crystalline solid was obtained from the reaction between 4-bromoaniline and diethyl oxalate for 2 h; yield 5.11 g (75%); mp 152−153 °C (lit. mp 152−153 °C) (*4*); TLC R_f 0.50; GC t_R 15.64 min; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 6 Hz, 3H, $-CH_3$), 4.45 (q, J = 6 Hz, 2H, $-OCH_2$), 7.65 (m, 4H, aromatic), 9.12 (s, 1H, NH); IR 3332 (as. NH str), 1702 (C═O ester str.), 1695 (amide-I band, C═O str.), 560 (−C Br str.); EI-MS *m*/*z* (relative intensity) 273 (M^+, 81), 271 (84), 200 (76), 199 (100), 198 (82), 197 (89), 172 (82), 170 (82), 92 (24), 91 (66), 90 (28), 76 (27), 75 (25), 64 (38), 63 (52).

*Ethyl 3′-Chlorooxanilate **(8)***. White crystals were obtained from the reaction of diethyl oxalate with *m*-chloroaniline for 2 h; yield 3.61 g (78%); mp 110 °C; TLC R_f 0.52; GC t_R 9.67 min; ^{1}H NMR ($CDCl_3$) δ 1.50 (t, J = 6 Hz, 3H, $-CH_3$), 4.45 (q, J = 6 Hz, 2H, $-OCH_2$), 7.30 (m, 1H, H_c-aromatic), 7.35 (t, J = 6 Hz, 1H, H_b-aromatic), 7.55 (t, J = 6 Hz, 1H, H_a-aromatic), 7.75 (t, 1H, H_a'-aromatic), 9.10 (s, 1H, NH); IR 3331 (as. sec. NH str), 1710 (C═O ester str), 1709 (amide-I band, C═O str), 1295 (aromatic sec. CN_δ), 707 (C−Cl str); EI-MS *m*/*z* (relative intensity) 227 (M^+, 73), 156 (33), 154 (100), 153 (37), 129 (12), 128 (18), 126 (50), 125 (6), 113 (12), 111 (36), 101 (5), 100 (7), 99 (17), 91 (8), 90 (10), 76 (7), 75 (21), 64 (8), 63 (14). Elemental analysis, found C, 52.9; H, 4.5; N, 6.2 ($C_{10}H_{10}ClNO_3$ requires C, 52.76; H, 4.43; N, 6.15).

*Ethyl 2′,6′-Dichlorooxanilate **(9)***. A white crystalline solid was obtained from the reaction of 2,6-dichloroaniline with diethyl oxalate for 3 h; yield 4.85 g (82%); mp 86−88 °C; TLC R_f 0.45; GC t_R 4.05 min; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 6 Hz, 3H, $-CH_3$), 4.15 (q, J = 6 Hz, 2H, $-OCH_2$), 7.10 (m, 2H, H_b, H_b'-aromatic), 7.00 (m, 1H, H_c-aromatic), 9.40 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 262 (M^+, 95), 161 (59), 90 (26), 75 (23), 73 (42), 72 (24), 65 (29), 63 (100), 62 (68), 61 (55), 60 (28), 52 (75). Elemental analysis, found C, 45.9; H, 3.5; N, 5.4 ($C_{10}H_9Cl_2NO_3$ requires C, 45.83; H, 3.46; N, 5.34).

*Ethyl 4′-Chlorooxanilate **(10)***. White flakes were obtained from the reaction for 2 h; yield 4.89 g (86%); mp 152−153 °C (lit. mp 151−154 °C) (*4*); TLC R_f 0.45; GC t_R 9.27 min; ^{1}H NMR ($CDCl_3$) δ 1.52 (t, J = 6 Hz, 3H, $-CH_3$), 4.60 (q, J = 6 Hz, 2H, $-OCH_2$), 7.65 (d, J = 6 Hz, 2H, H_b, H_b'-aromatic), 7.95 (d, J = 6 Hz, 2H, H_a, H_a'-aromatic), 9.36 (s, 1H, NH); IR 3332 (as. NH str.), 1703 (C═O ester str), 1702 (amide-I band, C═O str), 1296 (aromatic sec. CN_δ), 713 (C−Cl str); EI-MS *m*/*z* (relative intensity) 229 (31), 227 (M^+, 95), 156 (27), 155 (44), 154 (83), 153 (87), 149 (20), 140 (16), 129 (14), 128 (34), 127 (48), 126 (100), 125 (12), 113 (8), 111 (24), 101 (10), 99 (32), 75 (27), 73 (13), 64 (11), 63 (21).

*Ethyl 2′-Methoxyoxanilate **(11)***. 2-Anisidine and diethyl oxalate were refluxed in xylene for 3 h to furnish light brown crystals; yield 4.34 g (86%); mp 96 °C, TLC R_f 0.52; GC t_R 9.92 min; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, J = 3 Hz, 3H, $-CH_3$), 3.88 (s, 3H, $-OCH_3$), 4.32 (q, J = 6 Hz, 2H, $-OCH_2$), 6.85 (m, 3H, H_b, H_b', H_c-aromatic), 8.25 (dd, 1H, H_a'-aromatic), 9.23 (s, 1H, NH); IR 3346 (as. sec. NH str.), 2836 (methyl CH str.), 1716 (C═O ester str), 1702 (amide-I band, C═O str), 1302 (aromatic sec. CN_δ), 763 (aromatic CN_δ due to ortho substitution); EI-MS *m*/*z* (relative intensity) 224 (M^+, 10), 223 (8), 151

(10), 150 (100), 149 (42), 136 (7), 135 (44), 123 (8), 122 (31), 120 (11), 108 (13), 94 (24), 92 (19), 79 (10), 77 (12), 65 (18). Elemental analysis, found C, 59.2; H, 5.9; N, 6.3 ($C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27).

*Ethyl 3′-Methoxyoxanilate (**12**).* 3-Anisidine and diethyl oxalate were refluxed in xylene to furnish creamy white powders of **12**; yield 4.01 g (86%); mp 98 °C; TLC R_f 0.43; GC t_R 10.13 min; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 3 Hz, 3H, $-CH_3$), 3.91 (s, 3H, $-OCH_3$), 4.60 (q, J = 6 Hz, 2H, $-OCH_2$), 7.00 (dd, 1H, H_c-aromatic), 7.48 (m, 1H, H_b'-aromatic), 7.55 (m, 1H, H_a'-aromatic), 7.60 (m, 1H, H_a-aromatic), 9.22 (s, 1H, NH); IR 3346 (as. sec. NH str.), 2837 (methyl CH str.), 1703 (C═O ester str.), 1700 (amide-I band, C═O str), 1302 (aromatic sec. CN_δ), two bands, i.e., 862 and 762 (aromatic CN_δ due to meta substitution); EI-MS *m*/*z* (relative intensity) 223 (M^+, 89), 151 (11), 150 (100), 149 (66), 136 (8), 123 (19), 122 (39), 107 (60), 95 (15), 94 (7), 93 (6), 92 (18), 77 (29), 65 (8), 64 (15). Elemental analysis, found C, 59.3; H, 5.9; N, 6.3 ($C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27).

*Ethyl 4′-Methoxyoxanilate (**13**).* 4-Anisidine and diethyl oxalate were refluxed for 1.5 h to provide creamy white powders of **13**; yield 3.96 g (84.93%); mp 112−113 °C (lit. mp 112−113 °C) (*4*); TLC R_f 0.34; GC t_R 13.06 min; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 6 Hz, 3H, $-CH_3$), 4.35 (q, J = 6 Hz, 2H, $-OCH_2$), 3.75 (s, 3H, $-OCH_3$), 6.85 (dd, J = 6 Hz, 2H, H_b, H_b'-aromatic), 7.50 (dd, J = 6 Hz, 2H, H_a, H_a'-aromatic), 8.90 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 223 (M^+, 16), 150 (7), 149 (100), 136 (99.9), 135 (26), 134 (22), 123 (7), 122 (82), 108 (19), 106 (15), 95 (41), 80 (34), 79 (23), 77 (20), 65 (15), 53 (16), 52 (22).

*Ethyl 2′,4′-Dimethoxyoxanilate (**14**).* Grayish-white crystals were obtained from the reaction of 2,4-dimethoxyaniline with diethyl oxalate for 3 h in xylene; yield 4.27 g (76%); mp 86−88 °C; TLC R_f 0.46; GC t_R 11.30 min; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 6 Hz, 3H, CH_3), 3.80 (ds, 6H, OCH_3), 4.40 (q, J = 6 Hz, 2H, OCH_2), 6.70 (m, 2H, H_b, H'_b-aromatic), 8.10 (m, 1H, H_a-aromatic), 9.40 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 253 (M^+, 65), 179 (94), 165 (91), 164 (100), 138 (32), 110 (36), 107 (34), 95 (33), 79 (54), 53 (33), 52 (35). Elemental analysis, found C, 57.0; H, 6.0; N, 5.6 ($C_{12}H_{15}NO_5$ requires C, 56.91; H, 5.97; N, 5.53).

*Ethyl 3′-Nitrooxanilate (**16**).* 3-Nitroaniline and diethyl oxalate were refluxed for 3 h in xylene to furnish deep yellow crystals; yield 3.33 g (56%); mp 96−98 °C; TLC R_f 0.65; GC t_R 12.22 min; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 6 Hz, 3H, CH_3), 4.30 (q, J = 6 Hz, 2H, OCH_2), 7.50 (m, 2H, H_c, H_b'-aromatic), 7.95 (m, 1H, H_a'-aromatic), 8.40 (t, 1H, H_a-aromatic), 9.10 (s, 1H, NH); IR 3335 (as. sec. NH str), 2994 (methyl CH str), 1703 (C═O ester str), 1728 (amide-I band), 1532 (sym. $ArNO_2$ str), 784 (aromatic δ_{CH} due to meta substitution); EI-MS *m*/*z* (relative intensity) 238 (M^+, 58), 166 (41), 165 (100), 164 (15), 159 (17), 149 (29), 148 (15), 138 (35), 137 (36), 91 (37), 77 (15), 76 (38), 75 (26), 65 (20), 64 (31), 63 (30). Elemental analysis, found C, 50.5; H, 4.4; N, 11.9 ($C_{10}H_{10}N_2O_5$ requires C, 50.42; H, 4.23; N, 11.76).

*Ethyl 4′-Nitrooxanilate (**17**).* 4-Nitroaniline and diethyl oxalate were refluxed for 2 h in xylene to furnish yellow crystals; yield 4.98 g (84%); mp 144−145 °C; TLC R_f 0.45; GC t_R 11.35 min; ^{1}H NMR ($CDCl_3$) δ 1.50 (t, J = 6 Hz, 3H, CH_3), 4.45 (q, J = 6 Hz, 2H, OCH_2), 8.10 (m, 4H, aromatic), 10.80 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 238 (M^+, 53), 166 (64), 165 (100), 149 (33), 138 (45), 137 (39), 108 (24), 92 (37), 80 (19), 76 (44), 75 (30), 65 (15). Elemental analysis, found C, 50.5; H, 4.3; N, 11.8 ($C_{10}H_{10}N_2O_5$ requires C, 50.42; H, 4.23; N, 11.76).

*Ethyl 2′,4′-Dinitrooxanilate (**18**).* 2,4-Dinitroaniline and diethyl oxalate were refluxed together in xylene for 3 h (as shown in **Figure 1)** to furnish deep yellow crystals; yield 4.62 g (72%); mp 140 °C dec; TLC R_f 0.42; GC t_R 16.15 min; ^{1}H NMR ($CDCl_3$) δ 1.60 (t, J = 6 Hz, 3H, CH_3), 4.50 (q, J = 6 Hz, 2H, OCH_2), 8.10 (m, 2H, H_b, H_b'-aromatic), 9.00 (m, 1H, H_a-aromatic), 10.90 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 285 (M^+, 1), 183 (26), 153 (50), 79 (24), 65 (25), 64 (48), 63 (62), 62 (33), 53 (18), 52 (100). Elemental analysis, found C, 42.5; H, 3.3; N, 14.9 ($C_{10}H_9N_3O_7$ requires C, 42.41; H, 3.20; N, 14.84).

*Ethyl 3′-Methyloxanilate (**19**).* 3-Toluidine and diethyl oxalate were refluxed in toluene for 3 h to furnish a grayish-white powder; yield 3.92 g (75%); mp 58−59 °C (lit. mp 58.5 °C) (*4*); TLC R_f 0.28; GC t_R 6.20 min; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 6 Hz, 3H, CH_3), 2.25 (s, 3H, $ArCH_3$), 4.28 (q, J = 6 Hz, 2H, OCH_2), 6.80 (m, 1H, H_c-aromatic), 7.10 (m, 1H, H_b'-aromatic), 7.30 (m, 2H, H_a, H'_a-aromatic), 9.38 (s, 1H, NH); IR 3360 (as. sec. NH str), 2870 (methyl CH_{str}), 1719 (C═O ester str), 1700 (amide-I band), 1306 (aromatic sec. δ_{CH}); EI-MS *m*/*z* (relative intensity) 207 (M^+, 69), 134 (100), 106 (41), 91 (53), 77 (17), 65 (17).

*Ethyl 3′-Cyanooxanilate (**21**).* A grayish-white crystalline solid was obtained from the reaction between 3-aminobenzonitrile and diethyl oxalate for 3 h; yield 3.81 g (71%); mp 144 °C (lit. mp 144 °C) (*4*); TLC R_f 0.48; GC t_R 14.22 min; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 6 Hz, 3H, CH_3), 4.35 (q, J = 6 Hz, 2H, OCH_2), 7.45 (m, 2H, H_c, H_b'-aromatic), 7.95 (m, 2H, H_a, H'_a-aromatic), 9.00 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 218 (M^+, 18), 145 (73), 144 (19), 118 (70), 117 (100), 102 (46), 90 (82), 65 (11), 64 (42), 62 (12).

*Ethyl 4′-Cyanooxanilate (**22**).* A white crystalline solid was obtained from the reaction between 4-aminobenzonitrile and diethyl oxalate for 2.5 h; yield 4.19 g (78%); mp 189 °C; TLC R_f 0.72; GC t_R 14.45 min; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 6 Hz, 3H, CH_3), 4.40 (q, J = 6 Hz, 2H, OCH_2), 7.25 (m, 2H, H_b, H_b'-aromatic), 7.70 (m, 2H, H_a, H'_a-aromatic), 9.00 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 218 (M^+, 19), 145 (71), 144 (24), 118 (70), 117 (100), 116 (21), 102 (55), 91 (29), 90 (79), 89 (16), 76 (21), 75 (27), 65 (13), 64 (32), 63 (49), 62 (18), 51 (20). Elemental analysis, found C, 60.6; H, 4.7; N, 12.9 ($C_{11}H_{10}N_2O_5$ requires C, 60.55; H, 4.62; N, 12.84).

*Ethyl 3′-(Trifluoromethyl)oxanilate (**24**).* Grayish-white crystals of **24** were obtained from the reaction between 3-(trifluoromethyl)aniline and diethyl oxalate for 2.5 h; yield 4.70 g (73%); mp 122 °C (lit. mp 122 °C) (*4*); TLC R_f 0.66; GC t_R 11.03 min; ^{1}H NMR ($CDCl_3$) δ 1.50 (t, J = 6 Hz, 3H, CH_3), 4.40 (q, J = 6 Hz, 2H, OCH_2), 7.45 (m, 2H, H_c, H_b'-aromatic), 8.15 (m, 2H, H_a, H'_a-aromatic), 10.30 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 261 (M^+, 27), 249 (7), 207 (12), 189 (100), 188 (36), 187 (12), 161 (77), 145 (22), 141 (52), 140 (31), 105 (13), 101 (16), 91 (75), 83 (85), 75 (86), 73 (13), 65 (31), 59 (51), 54 (27).

*Ethyl 4′-(Trifluoromethyl)oxanilate (**25**).* A white crystalline solid of **25** was obtained from the reaction between 4-(trifluoromethyl)aniline and diethyl oxalate for 2 h; yield 5.22 g (81%); mp 139−141 °C (lit. mp 137−142 °C) (*4*); TLC R_f 0.66; GC t_R 10.78 min; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 6 Hz, 3H, CH_3), 4.35 (q, J = 6 Hz, 2H, OCH_2), 7.35 (m, 2H, H_b, H_b'-aromatic), 7.85 (m, 2H, H_a, H'_a-aromatic), 8.85 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 261 (M^+, 5), 207 (4), 188 (9), 145 (7), 59 (12), 58 (100).

*Ethyl 4′-Ethyloxanilate (**26**).* White crystals were obtained from the reaction between 4-ethyl aniline and diethyl oxalate for 2.5 h; yield 3.97 g (73%); mp 56−57 °C (lit. mp 55−58 °C) (*4*); TLC R_f 0.67; GC t_R 4.56 min; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 6 Hz, 3H, CH_2CH_3), 1.40 (t, J = 6 Hz, 3H, OCH_2CH_3), 2.60 (q, J = 6 Hz, 2H, CH_2), 4.32 (q, J = 6 Hz, 2H, OCH_2), 7.08 (dd, 2H, H_b, H_b'-aromatic), 7.45 (dd, 2H, H_a, H'_a-aromatic), 9.15 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 221 (M^+, 26), 145 (71), 148 (26), 118 (70), 147 (45), 132 (75), 120 (99), 106 (28), 103 (21), 93 (44), 91 (62), 79 (25), 78 (48), 77 (72), 65 (25), 58 (100), 52 (49), 51 (60).

*Ethyl 4′-Isopropyloxanilate (**27**).* A white powder was obtained from the reaction between 4-isopropylaniline and diethyl oxalate for 3 h (as shown in **Figure 1**); yield 3.65 g (63%); mp 103−104 °C; TLC R_f 0.35; GC t_R 5.09 min; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 7H, $CH(CH_3)_2$), 2.55 (t, J = 6 Hz, 3H, OCH_2CH_3), 4.30 (q, J = 6 Hz, 2H, OCH_2), 7.15 (m, 2H, H_b, H_b'-aromatic), 7.55 (m, 2H, H_a, H'_a-aromatic), 9.25 (s, 1H, NH). Elemental analysis, found C, 66.4; H, 7.3; N, 6.0 ($C_{13}H_{17}NO_5$ requires C, 66.36; H, 7.28; N, 5.95).

General Procedure for the Synthesis of Ortho-Substituted Anilates (2, 7, 15, 20, and 23). The following example illustrates the general scheme of synthesis of the title compounds using ortho-substituted anilines and the corresponding esters.

To 2-fluoroaniline (0.25 mol, 2.78 mL), ethoxycarbonyl methanoyl chloride (0.25 mol) in $CHCl_3$ (10 mL) was dispensed drop by drop under stirring at ≤10 °C. After the addition of acid chloride, the aliquot was left overnight at room temperature for completion of reaction. It was poured into ice-cold water (100 mL), and then the $CHCl_3$ layer

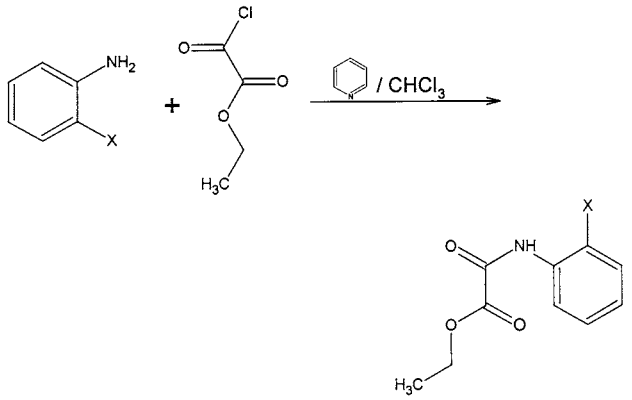

Figure 2. General synthesis of ortho-substituted oxanilates (**2**, **7**, **15**, **20**, and **23**).

was washed with $NaHCO_3$ solution once followed by water and dried over anhydrous Na_2SO_4. On evaporation of $CHCl_3$, the product was obtained as a white solid which was recrystallized from ethanol to furnish milky white crystals of ethyl 2′-fluorooxanilate (**Figure 2**).

Ethyl 2′-Fluorooxanilate (2). Yield 4.91 g (93%); mp 103 °C; TLC R_f 0.63; GC t_R 4.79 min; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 6 Hz, 3H, CH_3), 4.35 (q, J = 6 Hz, 2H, OCH_2), 7.20 (m, 3H, H_b, H_b', and H_c-aromatic), 7.50 (m, 1H, H_a-aromatic), 9.15 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 211 (M^+, 14), 139 (40), 111 (100), 91 (18), 84 (45), 83 (63), 64 (41), 63 (36), 57 (59), 52 (23), 50 (16). Elemental analysis, found C, 56.9; H, 4.8; N, 6.6 ($C_{10}H_{10}$ FNO_3 requires C, 56.87; H, 4.77; N, 6.63).

Ethyl 2′-Chlorooxanilate (7). Compound **7** was obtained from 2-chloroaniline (as shown in **Figure 2)** as a white crystalline solid; yield 5.17 g (91%); mp 108 °C; TLC R_f 0.52; GC t_R 8.63 min; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 6 Hz, 3H, CH_3), 4.45 (q, J = 6 Hz, 2H, OCH_2), 7.25 (m, 3H, H_b, H_b', and H_c-aromatic), 8.65 (d, J = 6 Hz, 1H, H_a-aromatic), 9.60 (s, 1H, NH); IR 3368 (as. sec. NH str), 1719 (C═O ester str), 1718 (amide-I band), 1308 (aromatic sec. CN_δ), 755 (aromatic δ_{CH} due to ortho substitution), 749 (C−Cl str.); EI-MS *m*/*z* (relative intensity) 229 (22), 227 (M^+, 70), 193 (10), 192 (91), 156 (33), 154 (100), 153 (32), 140 (18), 129 (14), 128 (30), 127 (47), 126 (86), 120 (12), 99 (32), 90 (30), 75 (17), 73 (10), 65 (7), 64 (12), 63 (18). Elemental analysis, found C, 52.8; H, 4.5; N, 6.2 ($C_{10}H_{10}$ $ClNO_3$ requires C, 52.76; H, 4.43; N, 6.15).

Ethyl 2′-Nitrooxanilate (15). Reaction of 2-nitroaniline and ethoxycarbonyl methanoyl chloride gave a deep yellow crystalline solid; yield 5.36 g (90%); mp 116 °C; TLC R_f 0.56, GC t_R 10.53 min; ^{1}H NMR ($CDCl_3$) δ 1.58 (t, J = 6 Hz, 3H, CH_3), 4.60 (q, J = 6 Hz, 2H, OCH_2), 7.50 (m, 1H, H_c-aromatic), 7.90 (m, 1H, H_b'-aromatic), 8.55 (t, 1H, H_b-aromatic), 9.11 (t, 1H, H_a'-aromatic), 10.36 (s, 1H, NH); IR 3309 (as. sec. NH str), 1741 (C═O ester str.), 1728 (amide-I band), 1515 (as. $ArNO_2$ (N−O)$_2$ str.), 1340 to 1278 (sym. $ArNO_2$ (N−O)$_2$ str), 1302 (aromatic sec. CN_δ), 860 (CN str for $ArNO_2$), 739 (aromatic δ_{CH} due to ortho substitution); EI-MS *m*/*z* (relative intensity) 238 (M^+, 74), 192 (24), 165 (100), 164 (18), 149 (13), 148 (57), 138 (17), 122 (18), 121 (86), 118 (21), 105 (17), 103 (18), 93 (10), 92 (75), 91 (92), 90 (92), 64 (38), 63 (40), 80 (25), 78 (30), 77 (16), 76 (12), 66 (20), 65 (37). Elemental analysis, found C, 50.5; H, 4.3; N, 11.8 ($C_{10}H_{10}$ N_2O_5 requires C, 50.42; H, 4.23; N, 11.76).

Ethyl 2′-Cyanooxanilate (20). 2-Aminobenzonitrile, following the reaction shown in **Figure 2**, gave **20** as a white buff solid; yield 4.62 g (86%); mp 143−144 °C; TLC R_f 0.45, GC t_R 13.78 min; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 6 Hz, 3H, CH_3), 4.40 (q, J = 6 Hz, 2H, OCH_2), 7.40 (m, 2H, H_c, H_b'-aromatic), 8.15 (m, 2H, H_a and H_b-aromatic), 9.75 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 218 (M^+, 26), 146 (14), 145 (73), 144 (22), 118 (14), 117 (100), 116 (21), 102 (59), 91 (31), 90 (78), 89 (18), 76 (18), 75 (26), 64 (36), 63 (46), 62 (19), 51 (22). Elemental analysis, found C, 60.6; H, 4.7; N, 12.8 ($C_{11}H_{10}$ N_2O_5 requires C, 60.55; H, 4.62; N, 12.84).

Ethyl 2′-(Trifluoromethyl)oxanilate (23). White crystalline solid; yield 5.28 g (82%); mp 132−134 °C; TLC R_f 0.67; GC t_R 6.35 min; ^{1}H NMR ($CDCl_3$) δ 1.50 (t, J = 6 Hz, 3H, CH_3), 4.40 (q, J = 6 Hz, 2H, OCH_2), 7.20 (m, 1H, H_c-aromatic), 7.60 (m, 3H, H_a', Hb, and H_b'-aromatic), 8.85 (s, 1H, NH); EI-MS *m*/*z* (relative intensity) 261 (M^+, 31), 188 (77), 168 (22), 161 (30), 160 (100), 117 (100), 145 (87), 140 (76), 133 (32), 125 (31), 114 (61), 113 (71), 109 (26), 95 (37), 91 (30), 83 (36), 75 (36), 69 (48), 63 (46), 51 (27). Elemental analysis, found C, 50.6; H, 3.9; N, 5.4 ($C_{11}H_{10}$ F_3NO_3 requires C, 50.58; H, 3.86; N, 5.36).

Field Trials. *Variety*. Two high-yielding varieties of bread wheat (*Triticum aestivum* L.), PBW 343 and HD 2733, recommended for timely sowing in the North Western Plain Zone of India, were chosen for the evaluation of chemical induction of male sterility.

Experimental Layout. The field trials were conducted in two *Rabi* (winter) seasons, November 2000−April 2001 and November 2001−April 2002. The experiment was laid out in randomized block design in three replicates. Randomization was done independently for the subplots in each of the three replicates. Seeds of both of the wheat varieties were sown using a seed drill in November, using 100 kg of N, 60 kg of P_2O_5, and 40 kg of K_2O following a 100 kg/ha seed rate at IARI. The 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 which included recommended fertilizer schedule, timely weeding, and other cultural operations. Five irrigations were done at different stages of crop growth, viz., crown root initiation, late tillering, late jointing, flowering, and dough stage.

Field Applications. The test chemicals were sprayed at both 1000 and 1500 ppm as an oil-in-water emulsion containing cyclohexanone (1%) and polyoxyethylene sorbitan monooleate (FW ≈ 1200) (Tween-80) as emulsifier (0.02%) at the premeiotic stage (60 days after sowing), when the length of the spike emerging out from the first node was 7−8 mm (*10*). 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. During spraying, the innermost two lines were covered by polyethylene to ensure that chemicals did not fall on the plants of the pollinator lines. As the degree of synchrony of flowering varied with the variety, care was taken to tag the treated tillers at the appropriate stage. Ten spikes of each treated plot were covered with rainproof paper bags to prevent out-crossing at the pre-emergent stage, when awns were just emerging. The remaining ear heads were left uncovered.

Observations Made. *Pollen Sterility*. Anthers from three or four florets were smeared together over a drop of acetocarmine (1%) or KI (2%) in iodine and examined under a light microscope (*6*). From the stain test, it was seen that the sterile grains were transparent, thereby confirming the disintegration of cytoplasm and nucleus in the sterile pollen. In contrast, fertile pollen from control plots was stained uniform deep red or blue, depending on the stain, confirming the induction of male sterility in various treatments.

Spikelet Sterility. Ten each of bagged and unbagged spikes including one control were harvested at maturity. To study the floret sterility, the number of fertile (filled) and sterile (unfilled) grains was counted, and the percent male sterility was computed as percent inhibition of seed set in bagged spikes of treated plants. Percent sterility is calculated from the following formula:

$$\% \text{ sterility} = (S_c - S_f)/S_c \times 100$$

where S_c is the number of seeds per spikelet in bagged spikes of control plants and S_f is the number of seeds per spikelet in bagged spikes of treated plants.

Quantitative Structure−Activity Relationship Study (QSAR): Descriptor Variables. The following descriptor variables were used for aromatic substituents: electronic parameters, Swain−Lupton field constant (F) (*11*), Hammett constant (σ_m, σ_p), σ^+, R (*12*, *13*), Taft steric parameter (E_s), molecular weight (MW), Verloop−Hoogenstraaten multidimensional steric parameters L and B_4 (*14*, *15*), hydrophobic parameters π and π^2, and other parameters such as molar refractivity (MR), δ ^{13}C, chemical shift values of C atoms containing NH moiety with reference to various substituents (*17*, *18*), and index variable. The steric parameters E_s, MR, L, and B_4 were designated according to their position on the phenyl ring with a subscript indicating ortho, meta, or

Table 1. Percent Spikelet Sterility of CHAs Tested in *Rabi* (Winter) 2000–01 and 2001–02

		spikelet sterility (%) in genotypes at 1000 and 1500 ppm spray concentrations							
		2000–01				2001–02			
		PBW 343		HD2733		PBW 343		HD 2733	
oxanilates	aromatic substituents	1000	1500	1000	1500	1000	1500	1000	1500
1	H	79.91	90.11	80.39	90.76	77.99	84.18	79.92	86.35
2	2-F	48.85	59.77	47.6	59.12	54.76	68.13	56.58	70.99
3	3-F	27.91	37.16	27.71	37.75	32.78	50.04	37.48	55.81
4	3-Cl, 4-F	64.85	72.00	64.21	67.75	71.56	77.91	72.52	77.11
5	4-F	89.90	97.86	90.53	97.3	99.54	99.97	99.59	99.99
6	4-Br	86.34	97.04	86.1	95.54	98.76	99.96	99.12	99.97
7	2-Cl	23.95	37.43	24.26	38.54	28.62	50.25	34.17	56.37
8	3-Cl	15.77	29.93	14.17	29.66	20.03	44.25	24.48	50.07
9	2,6-Cl_2	20.23	26.56	21.21	28.13	24.71	41.56	31.24	48.98
10	4-Cl	44.00	64.73	43.29	64.7	49.67	72.09	52.44	74.95
11	2-OMe	55.91	68.87	54.94	67.67	66.39	78.02	69.21	78.75
12	3-OMe	14.16	23.45	11.95	23.73	18.34	39.07	22.35	45.86
13	4-OMe	70.74	79.06	70.10	76.52	77.69	84.39	78.38	85.76
14	2,4-$(OMe)_2$	51.78	58.65	49.92	58.78	55.34	63.43	56.49	68.49
15	2-NO_2	34.26	50.86	32.06	48.78	39.44	61.00	41.66	63.64
16	3-NO_2	11.28	14.77	11.71	21.59	15.31	32.13	22.12	44.34
17	4-NO_2	63.09	69.55	62.99	70.99	70.41	79.06	70.85	81.57
18	2,4-$(NO_2)_2$	72.48	77.58	71.94	77.62	79.57	82.37	79.94	84.12
19	3-Me	1.92	3.73	2.28	3.77	5.49	23.29	13.07	31.69
20	2-CN	63.04	76.82	61.48	75.32	68.95	81.43	69.45	82.56
21	3-CN	52.75	65.97	54.74	63.01	57.13	71.74	62.28	72.71
22	4-CN	82.49	93.85	83.29	95.20	91.31	96.63	92.65	98.46
23	2-CF_3	69.52	80.36	68.76	88.41	76.4	84.59	77.19	93.03
24	3-CF_3	78.91	91.86	82.42	93.13	87.2	94.86	91.72	96.81
25	4-CF_3	88.69	97.14	89.70	97.10	98.44	99.57	99.47	99.98
26	4-Et	12.86	6.32	8.32	2.66	11.28	18.48	12.89	20.18
27	4-^{i}Pr	9.70	3.84	4.44	5.27	7.64	9.41	8.77	10.09
control (without spray)		0.04	0.04	0.02	0.02	0.02	0.02	0.02	0.02
emulsion control		0.25	0.34	0.33	0.46	0.26	0.46	0.34	0.49
CD ($P = 0.05$)		2.03		1.78		0.59		0.54	

para, as the case may be. Thus, $E_{s(o)}$ denotes Taft's steric parameter for the ortho substituents, $E_{s(m)}$ that for the meta substituents, and $E_{s(p)}$ that for the para substituents. Thirty-two independent variables were used in constructing the correlation matrix. The independent variables, which were found orthogonal to each other, were minimized. In cases containing two substituents, additive nature of MR and Es was presumed. The mean percent spikelet sterility caused by test oxanilates tested at 1500 ppm on wheat variety PBW 343 in *Rabi* (winter) 2001−02 was transformed into sin arc and used as the dependent variable (Ms %).

Multiple Linear Regression (MLR) Analysis. The independent variables were used in generating MLR equations by autocorrelation using the computer software package SPSSPC (Version 9.1). None of the independent variables appearing in the equations was restrained to be orthogonal.

RESULTS AND DISCUSSION

Synthesis. The various *N*-acylanilines were prepared by the thermal condensation of respective anilines with diethyl oxalate. In the case of some ortho-substituted anilines, the yield obtained by this method was low, and therefore the *N*-acylanilines of this type were prepared by N-acylation using ethoxycarbonyl methanoyl chloride.

Spectral Analysis. IR spectra showed characteristic peaks for symmetrical NH stretching vibrations at 3339 ± 16 cm^{-1} for oxanilates. The C═O stretching vibration of ester was centered at 1711 ± 12 cm^{-1}. The characteristic features of proton magnetic resonance spectra were the presence of a triplet around δ 1.30 ppm (in ethyl 3′-nitrooxanilate) to as high as δ 1.65 ppm (in ethyl 4′-fluorooxanilate) and a quartet centered at δ 4.15 ppm in ethyl 2′,6′-dichlorooxanilate to δ 4.70 ppm in ethyl 4′-fluorooxanilate. The anilide NH proton appeared as a broad singlet ranging from δ 8.85 ppm in simple oxanilates to δ 10.90 ppm in ethyl 2′,4′-dinitrooxanilate. The substituents at ortho and para positions caused deshielding, the highest effect of δ 10.80 ppm by the 2,4-dinitro group, followed by the para nitro group having the chemical shift of δ 10.36 ppm.

Spikelet Sterility. The results of induction of spikelet sterility on bread wheat caused by test chemicals at two test concentrations on two genotypes for two winter seasons are given in **Table 1**. All the test chemicals showed significant induction of spikelet sterility at both of the test concentrations on both of the genotypes tested. The results, which were dose-dependent, were consistent in a two-year field trial. There was no marked variation in the response of two genotypes. The para-substituted oxanilates, **5**, **6**, **25**, and **22**, containing F, Br, CF_3, and CN, respectively, were found to be the best in that order when considered across two test concentrations, two genotypes, and two-year trial data. The other substituents at the para position influenced the activity in the order OMe > NO_2 > Cl. The disubstituted analogues **4**, **9**, **14**, and **18** were found to be inferior to their respective mono(para)substituted ones generally. The ortho analogues performed next best in all cases except in CF_3 substitution, wherein meta (**24**) was found to be better than ortho (**23**). Alkyl substitution in oxanilates **19**, **26**, and **27** 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 levels of activity. From a practical point of view, the percent spikelet sterility induced must not be less than 98%. Three compounds, **5**, **6**, and **25**, containing fluoro, bromo, and trifluoromethyl substituents in the para position, respectively, met the above criterion at the 1500 ppm test concentration.

Table 2. Chemical Descriptors for Aromatic Substituents in Ethyl Oxanilates

R	π	σ_m	σ_p	δ ^{13}C	σ^+_p	MR	E_S	F	R	L	B_4
H	0.00	0.00	0.00	128.5	0.00	3.09	0.00	0.00	0.00	7.18	3.00
2-F	0.12	0.00	0.06	114.2	0.00	0.92	–0.46	0.43	0.39	2.65	1.35
3-F	0.13	0.34	0.00	129.4	0.00	0.92	–0.46	0.43	0.39	2.65	1.35
4-F	0.12	0.00	0.06	124.1	–0.07	0.92	–0.46	0.43	0.39	2.65	1.35
4-Br	1.01	0.00	0.23	127.0	0.15	8.88	–1.16	0.44	–0.22	3.83	1.95
2-Cl	0.71	0.00	0.23	128.7	0.00	6.03	–0.99	0.41	–0.19	3.52	1.80
3-Cl	0.76	0.37	0.00	129.5	0.00	6.03	–0.97	0.41	–0.19	3.52	1.80
4-Cl	0.71	0.00	0.23	126.5	0.11	6.03	–0.97	0.41	–0.19	3.52	1.80
2-OMe	–0.02	0.00	–0. 27	114.1	0.00	7.87	–0.55	0.26	–0.56	3.98	2.87
3-OMe	0.11	0.12	0.00	129.5	0.00	7.87	–0.55	0.26	–0.56	3.98	2.87
4-OMe	–0.02	0.00	–0.27	120.7	–0.78	7.87	–0.55	0.26	–0.56	3.98	2.87
2-NO_2	–0.28	0.00	0.78	124.2	0.00	7.36	–2.52	0.67	8.39	3.44	2.44
3-NO_2	0.10	0.71	0.00	129.8	0.00	7.36	–2.52	0.67	8.39	3.44	2.44
4-NO_2	–0.28	0.00	0.78	134.7	0.79	7.36	–2.52	0.67	8.39	3.44	2.44
3-Me	0.56	–0.07	0.00	129.2	0.00	5.65	–1.24	–0.04	–0.18	3.00	2.04
2-CN	–0.30	0.00	0.66	132.6	0.00	6.33	–0.51	0.51	0.15	4.23	1.60
3-CN	–0.32	0.56	0.00	129.9	0.00	6.33	–0.51	0.51	0.15	4.23	1.60
4-CN	–0.21	0.00	0.66	133.5	0.66	6.33	–0.51	0.51	0.15	4.23	1.60
2-CF_3	0.88	0.00	0.54	125.2	0.00	5.02	–2.40	0.38	0.16	3.30	2.41
3-CF_3	1.09	0.43	0.00	128.8	0.00	5.02	–2.40	0.38	0.16	3.30	2.41
4-CF_3	0.88	0.00	0.54	131.7	0.61	5.02	–2.40	0.38	0.16	3.30	2.41
4-Et	1.08	0.00	–0.15	125.2	–0.30	10.3	–1.31	–0.05	–0.15	4.11	2.97
4-^{i}Pr	1.64	0.00	–0.15	125.9	–0.28	14.96	–1.71	–0.05	–0.19	4.11	3.16

Quantitative structure−activity relationship analysis was carried out using sin arc-transformed spikelet sterility percent as the dependent variable and the physicochemical parameters of the substituents listed in **Table 2** as independent variables. Six multiple regression equations were obtained with multiple *R*-values of 0.7 and above. Only the best equation is given below:

$$\text{Ms (sin arc \%)} = 39.59F_p - 2.86\sum\text{MR} + 0.67\text{MW} - 5.11D - 2.57\sum R - 16.91\sum\pi - 64.28$$

$$n = 27,\ R = 0.91,\ s = 8.78,\ F = 16.99\ (p = 0.00)$$

where n is the number of test compounds used, R is the multiple correlation coefficient, s is the standard error, F is Fisher's ratio at the p value, and p is the probability value (here, it is almost zero).

The observed bioactivity could thus be explained by the above equation containing the Swain−Lupton field constant (F_p), molar refractivity (MR), molecular weight (MW), an index variable (D) signifying the position of aromatic substituents, the Swain−Lupton resonance constant (R), and a hydrophobic parameter (π). The individual contributions of the independent variables to R^2 were 27.29, 22.19, 8.17, 8.23, 8.29, and 7.13%, respectively. The direct involvement of F_p, MR, and $\sum E_s/\sum R$ with the target bioactivity implies that both electronic and steric factors in that order have a positive effect on the activity. The direct influence of molecular weight (MW) can be inferred to indicate a preference for molecules with less volatility. The negative sign of the MR, D, and π coefficients indicates the inverse relationship with the bioactivity. In other words, the less the hydrophobic character, the higher will be the percent sterility. Chemicals with high water solubility would be preferred. In fact, many of the CHAs reported in the literature are either free acids or alkali salts of carboxylic acids (*4*). It is thus possible to carry out lead optimization of aromatic substitution of oxanilates as CHAs using the best equation obtained in the present study.

In a pilot study, 13 F_1 hybrids were produced using ethyl 4′-fluorooxanilate (**5**) and have shown encouraging primary seed characteristics, namely test weight, average seed set per spike, and high percent of germination. One of them was found to out-yield its parents in a preliminary agronomic evaluation.

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