Synthesis of Phenoxyphenyl Pyridine and Pyrazine Carboxamides. Activity against *Cydia pomonella* (L.) Eggs

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Several *N*-(4-phenoxyphenyl)pyridinecarboxamides and *N*-(4-phenoxyphenyl)pyrazinecarboxamides were synthesized from commercially available material, and their ovicidal activities against *Cydia pomonella* (L.) were tested. Some of the tested products showed a moderate activity when <24-h-old eggs were sprayed using a Potter tower. A significant increase in the length of the development period of the eggs was also observed in many cases. A clear correlation between both effects was noticed: the products that produced higher mortality also produced higher increase of the length of the development. These results seem to confirm our hypothesis that these compounds could be defined as a juvenile hormone analogues.

Keywords: *Cydia pomonella; codling moth; ovicide; insecticide; carbamate; JHA; IGR*

INTRODUCTION

Codling moth [*Cydia pomonella* (L.), Lepidoptera: Tortricidae] is a major pest of apples and pears, although it can also attack other crops such as walnuts and prunes. Its world distribution closely resembles the distribution of apple trees, and it can cause heavy economic losses, depending on the climatic region. The larvae enter a fruit and fully develop inside it, rendering the fruits unmarketable, although the larvae consume only a small part of the fruit flesh (University of California Statewide IPM Program, 1991). Many different chemicals have shown efficacy against this species, both conventional insecticides (organophosphates, carbamates, pyrethroids) and insect growth regulators (chitin synthesis inhibitors, juvenile hormone analogues, molting hormone agonists). However, the environmental problems associated with the former and some resistant populations developed to the latter (Croft and Riedl, 1991) stress the need for new compounds.

With that aim, we synthesized *N*-(4-phenoxyphenyl)-2-pyridinecarboxamide (**1a**) (Figure 1), testing its ovicidal and larvicidal activities against *C. pomonella*. Considering its activity, an insect juvenile hormone-like activity was proposed (Canela et al., 1999). Although there exist many potential sites for selective disruption of endocrine function in insects (Mumby et al., 1979), it is difficult to find a clear structure−activity relationship (Schvartzapel et al., 1996). However, two hypotheses can be considered when the structure of compound **1a** is matched with the juvenile hormone 0 (**JH 0**) structure. First, the amide group from compound **1a** can match the ester group of the juvenile hormone. The introduction of an amide group instead of an ester group produced an increase of ovicidal activity against *C. pomonella* in some of the compounds tested by Gelbic

(Gelbic and Sehnal, 1973). In this case, the problem was to know how the molecule fits into the enzyme. The best way to match the ester group implies that a very huge group must fit the active site of the supposed receptor (Figure 1A). To avoid this problem, the picolinamide could interact with the active site in the other way round (Figure 1B). In this case the electrophilic carbon of both the ester and the amide group could interact with the active site of the receptor and only the pyridine moiety must fit into the active site. A second hypothesis supposes the amide group matches the epoxy moiety of juvenile hormones (Figure 1C). In both cases, an esterase or an epoxide hydrolase could be inhibited by strongly binding to the picolinamide compound. Thus, the hydrolysis of endogenous juvenile hormone could be avoided.

With these two possibilities in mind, the synthesis of a set of new compounds was formulated. First of all, we planned to study how the nitrogen position on the ring affects activity by modifying the electrophilicity of the amide carbon. Second, we increased the length of our molecule by introducing either a new amide bond or a carbamate bond. Substances containing a carbamate group are known to be among the most active juvenile hormone analogues (JHA) known (Masner et al., 1983; Wimmer et al., 1997).

EXPERIMENTAL PROCEDURES

Chemicals. 3-Pyridinecarboxylic acid (nicotinic acid), 4-pyridinecarboxylic acid (isonicotinic acid), pyrazinecarboxylic acid, 4-aminophenyl phenyl ether, 4,4′-di(aminophenyl) ether, 1,1′-carbonyldiimidazole, acetic anhydride, and triethylamine were purchased from Fluka (Sigma-Aldrich Química S.A., Alcobendas, Spain), and allyl chloroformate was purchased from Aldrich (Sigma-Aldrich Química S.A.). 2-Pyridinecarboxylic acid (picolinic acid) and silica gel 60 (0.040−0.063 mm) were purchased from Merck (Merck KGaA, Darmstadt, Germany). Fenoxycarb was a gift of CIBA-Geigy (now Novartis) and was recrystallized twice from ethyl ether saturated with hexane.

Apparatus. Synthesized compound were identified by ^{1}H NMR, IR, and MS. ^{1}H NMR spectra were recorded either with

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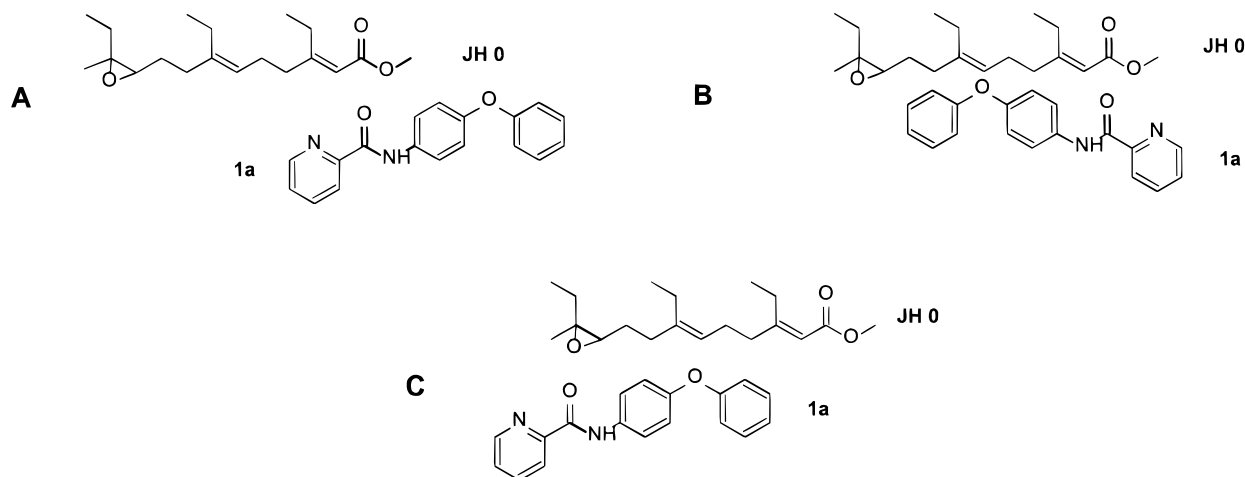
Figure 1. Possible action modes of *N*-(4-phenoxyphenyl)-2-pyridinecarboxamide (**1a**) as JH mimetic.

a Varian Gemini 200 (200 MHz) or with a Varian Unity-300 (300 MHz) spectrometer. Infrared and mass spectra were determined with Phillips PU9700 and HP5989 spectrometers, respectively.

Melting points are uncorrected.

Synthesis of 4-(4-Acetylaminophenoxy)aniline (6). 4,4′-Di(aminophenyl) ether (2.01 g, 10 mmol) was dissolved in 50 mL of dry tetrahydrofuran (THF) (Leonard et al., 1995). Then 0.945 mL (10 mmol) of acetic anhydride, dissolved in 10 mL of THF, was added dropwise to this solution. The solution was continuously stirred, and the temperature was kept below 30 °C during the addition. After 1 h, the reaction mixture was neutralized to pH 7−8 by the addition of 50 mL of water and solid NaHCO₃. The reaction mixture was extracted with ethyl acetate. The resulting organic layer was extracted with 2 M HCl. The remaining acidic aqueous solution was neutralized to pH 7−8 by addition of solid NaHCO₃ and finally extracted again with ethyl acetate. The new organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (SiO₂, 1:1 chloroform/ethyl acetate) to afford compound **6** (0.85 g, 35% yield).

Synthesis of Allyl *N*-[4-(4-Aminophenoxy)phenyl]carbamate (7). 4,4′-Di(aminophenyl) ether (2.01 g, 10 mmol) was dissolved in 50 mL of dry THF (Leonard et al., 1995), and 2.78 mL (20 mmol) of dry triethylamine (Leonard et al., 1995) was added. Next, 1.06 mL (10 mmol) of allyl chloroformate, dissolved in 10 mL of THF, was added dropwise to this solution. The solution was continuously stirred, and the temperature was kept below 30 °C during the addition. After 1 h, stirring was stopped. One hour later the reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved again in hot chloroform and then allowed to cool to room temperature. The cold organic solution was again filtered and evaporated. The residue was purified by flash chromatography (SiO₂, 93:7 chloroform/ethyl acetate) to afford compound **7** (0.77 g, 27% yield).

Synthesis of *N*-(4-Phenoxyphenyl)-2-pyridinecarboxamide (1a). Typical Procedure. 2-Pyridinecarboxylic acid (1.50 g, 12.18 mmol), 1,1′-carbonyldiimidazole (1.97 g, 12.15 mmol), and dry dimethylformamide (DMF) (Leonard et al., 1995) (25 mL) were stirred for 1 h. Then 4-aminophenyl phenyl ether (2.25 g, 12.15 mmol) dissolved in dry DMF (3 mL) was added. The mixture was stirred for 3 days. Then, 50 mL of water was added, and the resulting precipitate was collected by vacuum filtration. The solid (2.61 g, 73%) was recrystallized twice, first with chloroform and then with methanol rendering: 1.14 g of white crystals (mp 91−3 °C, 32% yield) (Canela et al., 1999).

Characterization of Phenoxyphenylanilide Derivatives. 1a: ¹H NMR (CDCl₃) δ 7.00−7.13 (m, 5H), 7.34 (m, 2H), 7.49 (ddd, 1H, *J* = 7.65, 7.83, 1.20 Hz), 7.76 (dd, 2H, *J* = 9.06, 2.25 Hz), 7.91 (dt, 1H, *J* = 7.65, 1.71 Hz), 8.30 (ddd, 1H, *J* = 7.65, 1.20, 0.93 Hz), 8.62 (ddd, 1H, *J* = 7.83, 1.71, 0.93 Hz), 10 (s, 1H); IR (KBr) 3304, 1671, 1512 cm⁻¹; MS, *m/z* 290 (100) (M⁺), 261 (4), 197 (5), 186 (8), 156 (4), 129 (5), 106 (12), 79 (95). C₁₈H₁₄N₂O₂ Anal. Calcd: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.42; H, 4.88; N, 9.64.

1b: ¹H NMR (CDCl₃) δ 7.00−7.13 (m, 5H), 7.35 (m, 2H), 7.45 (ddd, 1H, *J* = 8.18, 4.80, 0.87 Hz), 7.60 (dd, 2H, *J* = 9.00, 1.98 Hz), 8.00 (s, 1H), 8.21 (dd, 1H, *J* = 8.18, 1.71 Hz), 8.77 (dd, 1H, *J* = 4.80, 1.71 Hz), 9.09 (d, 1H, *J* = 0.87 Hz); IR (KBr) 3380, 1650, 1500 cm⁻¹; MS, *m/z* 290 (43) (M⁺), 261 (4), 184 (9), 129 (7), 106 (100), 78 (37), 51 (21); mp 154.5−156.5 °C (Tomlison, 1989).

1c: ¹H NMR (CDCl₃) δ 7.00−7.13 (m, 5H), 7.34 (m, 2H), 7.49 (ddd, 1H, *J* = 7.83, 7.65, 1.2 Hz), 7.60 (d, 2H, *J* = 8.85 Hz), 7.70 (dd, 1H, *J* = 4.41, 1.65 Hz), 7.95 (s, 1H), 8.30 (dd, 1H, *J* = 7.65, 1.62 Hz), 8.62 (dd, 1H, *J* = 7.65, 1.65 Hz), 8.80 (dd, 2H, *J* = 4.41, 1.62 Hz), 10 (s, 1H); IR (KBr) 3360, 3290, 1650, 1490 cm⁻¹; MS, *m/z* 290 (100) (M⁺) 184 (58), 129 (9), 106 (92), 78 (19); mp 146−148 °C. C₁₈H₁₄N₂O₂ Anal. Calcd: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.43; H, 4.87; N, 9.64.

1d: ¹H NMR (CDCl₃) δ 7.00−7.13 (m, 5H), 7.34 (m, 2H), 7.76 (dd, 2H, *J* = 8.97, 2.16 Hz), 8.60 (dd, 1H, *J* = 2.43, 1.50 Hz), 8.82 (d, 1H, *J* = 2.43 Hz), 9.52 (d, 1H, *J* = 1.50 Hz), 9.84 (s, 1H); 8.30 (ddd, 1H, *J* = 7.65, 1.20, 0.93 Hz), 8.62 (ddd, 1H, *J* = 7.83, 1.71, 0.93 Hz), 10 (s, 1H); IR (KBr) 3360, 1670, 1490; MS, *m/z* 291 (100) (M⁺), 211 (4), 184 (31), 107 (12), 80 (39), 53 (6); mp 158−160 °C. C₁₇H₁₃N₃O₂ Anal. Calcd: C, 70.10; H, 4.50; N, 14.42. Found: C, 70.05; H, 4.51; N, 14.40.

2a: ¹H NMR (acetone-*d₆*) δ 2.02 (s, 3H), 6.96−7.10 (m, 4H), 7.64 (d, 2H, *J* = 9.00 Hz), 7.67 (ddd, 1H, *J* = 7.68, 4.77, 1.20 Hz), 7.95 (dd, 2H, *J* = 9.06, 2.22 Hz), 8.10 (dt, 1H, *J* = 7.68, 1.71 Hz), 8.27 (dpt, 1H, *J* = 7.68, 1.20, 1.05 Hz), 8.72 (ddd, 1H, *J* = 4.77, 1.71, 1.05 Hz), 10.30 (s, 1H), 10.5 (s, 1H); IR (KBr) 3312, 3280, 1665, 1503 cm⁻¹; MS, *m/z* 347 (77) (M⁺), 305 (47), 269 (3), 214 (22), 197 (7), 151 (10), 109 (40), 79 (100), 43 (30); mp 195−197 °C. C₂₀H₁₇N₃O₃ Anal. Calcd: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.12; H, 4.94; N, 12.08.

2b: ¹H NMR (dimethyl sulfoxide-*d₆*) δ 2.02 (s, 3H), 6.96−7.05 (m, 4H), 7.45−7.60 (m, 3H), 8.27 (dd, 1H, *J* = 7.98, 1.65 Hz), 8.75 (dd, 1H, *J* = 4.77, 1.65 Hz), 9.09 (d, 1H, *J* = 2.19 Hz), 9.92 (s, 1H), 10.42 (s, 1H); IR (KBr) 3280, 3260, 1630, 1490 cm⁻¹; MS, *m/z* 347 (38) (M⁺), 305 (31), 268 (4), 214 (13), 151 (9), 106 (100), 78 (52), 43 (56); mp 243−245 °C. C₂₀H₁₇N₃O₃ Anal. Calcd: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.09; H, 4.95; N, 12.06.

2c: ¹H NMR (dimethyl sulfoxide-*d₆*) δ 2.02 (s, 3H), 6.96−6.99 (m, 4H), 7.57 (d, 2H, *J* = 9.24 Hz), 7.75 (d, 2H, *J* = 9.06 Hz), 7.84 (dd, 2H, *J* = 4.41, 1.68 Hz), 8.77 (dd, 2H, *J* = 4.41, 1.68 Hz), 9.95 (s, 1H), 10.5 (s, 1H); IR (KBr) 3260, 1640, 1490 cm⁻¹; MS, *rn/z* 347 (39) (M⁺), 305 (49), 268 (4), 214 (16), 151 (10), 106 (76), 78 (55), 43 (100); mp 269−271 °C. C₂₀H₁₇N₃O₃ Anal. Calcd: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.10; H, 4.95; N, 12.03.
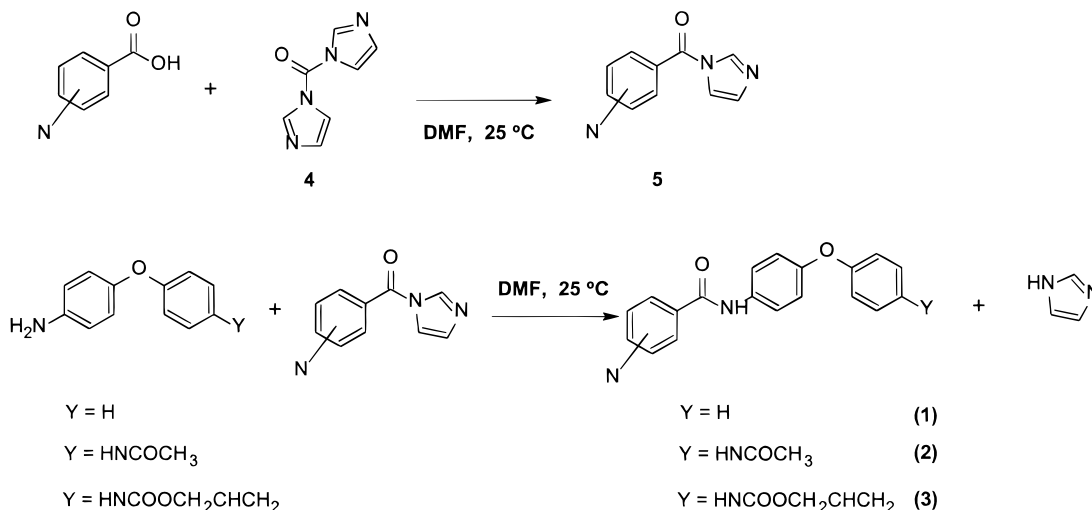
Figure 2. General synthetic route to phenoxyphenylcarboxamides.

2d: ^{1}H NMR (dimethyl sulfoxide-d_6) δ 2.02 (s, 3H), 6.96–6.99 (m, 4H), 7.57 (d, 2H, J = 9.24 Hz), 7.75 (d, 2H, J = 9.06 Hz), 8.80 (dd, 1H, J = 2.46, 1.44 Hz), 8.92 (d, 1H, J = 2.46 Hz), 9.28 (d, 1H, J = 1.44 Hz), 9.93 (s, 1H), 10.76 (s, 1H); IR (KBr) 3320, 3310, 1650, 1490 cm^{-1}; MS, m/z 348 (74) (M$^+$), 306 (100), 215 (23), 199 (5), 151 (9), 109 (40), 80 (60), 43 (38); mp 217–219 °C. $C_{19}H_{16}N_4O_3$ Anal. Calcd: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.47; H, 4.66; N, 16.03.

3a: ^{1}H NMR (CDCl$_3$) δ 4.65 (dt, 2H, J = 5.67, 1.32), 5.26 (dpq, 1H, J = 10.41, 2.61, 1.29 Hz), 5.35 (dpq, 1H, J = 17.22, 2.61, 1.29 Hz), 5.97 (ddt, 1H, J = 17.22, 10.41, 5.67 Hz), 6.64 (s, 1H), 6.95–7.05 (m, 4H), 7.36 (d, 2H, J = 8.79 Hz), 7.55 (ddd, 1H, J = 7.56, 5.97, 1.23 Hz), 7.74 (dd, 2H, J = 9.00, 2.19 Hz), 7.92 (dt, 1H, J = 7.56, 1.71 Hz), 8.35 (ddd, 1H, J = 7.56, 1.23, 1.08 Hz), 8.62 (ddd, 1H, J = 5.97, 1.71, 1.08 Hz), 10 (s, 1H); IR (KBr) 3334, 3291, 1736, 1664, 1490 cm^{-1}; MS, m/z 389 (51) (M$^+$), 304 (36), 214 (10), 106 (48), 79 (93), 41 (100); mp 139.3–141.3 °C. $C_{22}H_{19}N_3O_4$ Anal. Calcd: C, 67.86; H, 4.92; N, 10.79. Found: C, 67.79; H, 4.94; N, 10.76.

3b: ^{1}H NMR (CDCl$_3$) δ 4.65 (dt, 2H, J = 5.49, 1.47 Hz), 5.26 (dpq, 1H, J = 10.47, 3.03, 1.47 Hz), 5.35 (dpq, 1H, J = 17.25, 3.03, 1.47 Hz), 5.97 (ddt, 1H, J = 17.25, 10.47, 5.49 Hz), 6.96–7.10 (m, 4H), 7.56 (ddd, 1H, J = 7.98, 4.80, 0.87 Hz), 7.63 (d, 2H, J = 9.00 Hz), 7.86 (dd, 2H, J = 9.09, 2.25 Hz), 8.36 (dd, 1H, J = 7.98, 1.68 Hz), 8.77 (s, 1H), 8.78 (dd, 1H, J = 4.80, 1.68 Hz), 9.20 (d, 1H, J = 0.87 Hz), 9.85 (s, 1H); IR (KBr) 3290, 1702, 1652, 1507 cm^{-1}; MS, m/z 389 (29) (M$^+$), 331 (4), 304 (24), 225 (12), 214 (11), 106 (100), 78 (40), 41 (90); mp 215–217 °C. $C_{22}H_{19}N_3O_4$ Calcd: C, 67.86; H, 4.92; N, 10.79. Found: C, 67.81; H, 4.93; N, 10.76.

3c: ^{1}H NMR (acetone-d_6) δ 4.65 (dt, 2H, J = 5.46, 1.57), 5.26 (dpq, 1H, J = 10.44, 3.00, 1.59 Hz), 5.35 (dpq, 1H, J = 17.22, 3.30, 1.59 Hz), 5.97 (ddt, 1H, J = 17.22, 10.44, 5.46 Hz), 6.96–7.02 (m, 4H), 7.62 (dd, 2H, J = 9.03, 2.22 Hz), 7.86 (dd, 2H, J = 9.09, 2.25 Hz), 7.90 (dd, 2H, J = 4.41, 1.71 Hz), 8.77 (s, 1H), 8.80 (dd, 2H, J = 4.41, 1.71 Hz), 9.80 (s, 1H); IR (KBr) 3275, 1700, 1665, 1488 cm^{-1}; MS, m/z 389 (17) (M$^+$), 331 (10), 310 (27), 304 (16), 225 (34), 214 (7), 170 (6), 106 (50), 78 (22), 41 (100); mp 221–223 °C. $C_{22}H_{19}N_3O_4$ Anal. Calcd: C, 67.86; H, 4.92; N, 10.79. Found: C, 67.82; H, 4.93; N, 10.74.

3d: ^{1}H NMR (CDCl$_3$) δ 4.65 (dt, 2H, J = 5.70, 1.38), 5.26 (dpq, 1H, J = 10.41, 2.58, 1.28 Hz), 5.35 (dpq, 1H, J = 17.22, 2.58, 1.38 Hz), 5.97 (ddt, 1H, J = 17.22, 10.41, 5.70 Hz), 6.56 (s, 1H), 6.96–7.06 (m, 4H), 7.36 (d, 2H, J = 8.73 Hz), 7.71 (dd, 2H, J = 9.00, 2.22 Hz), 8.60 (dd, 1H, J = 2.46, 1.53 Hz), 8.82 (d, 1H, J = 2.46 Hz), 9.52 (d, 1H, J = 1.53 Hz), 9.64 (s, 1H); IR (KBr) 3355, 3303, 1702, 1673, 1505 cm^{-1}; MS, m/z 390 (51) (M$^+$), 305 (45), 226 (5), 215 (15), 107 (27), 79 (49), 41 (100); mp 170–172 °C. $C_{21}H_{18}N_4O_4$ Anal. Calcd: C, 64.61; H, 4.65; N, 14.35. Found: C, 64.58; H, 4.62; N, 14.34.

6: ^{1}H NMR (CD$_3$OD) δ 2.02 (s, 3H), 3.62 (br, 2H), 6.96–7.10 (m, 6H), 7.52 (d, 2H, J = 9.00 Hz); IR (KBr) 3380, 3200,

Table 1. Phenoxyanilide Derivatives Synthesized

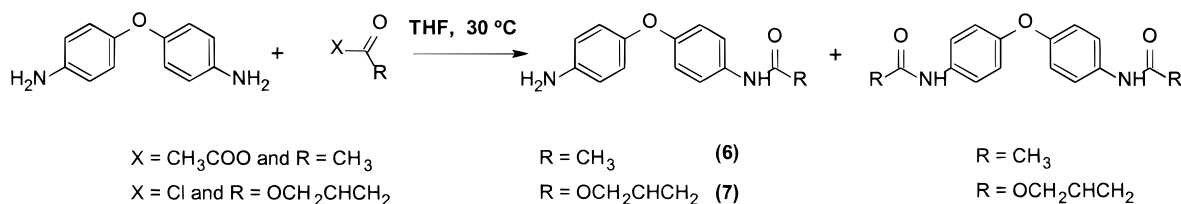| compd	X	R$_1$	% yield^a
1a	2-pyridinecarbonyl	H	32
1b	3-pyridinecarbonyl	H	26
1c	4-pyridinecarbonyl	H	23
1d	pyrazinecarbonyl	H	48
2a	2-pyridinecarbonyl	CH$_3$CONH	30
2b	3-pyridinecarbonyl	CH$_3$CONH	29
2c	4-pyridinecarbonyl	CH$_3$CONH	17
2d	pyrazinecarbonyl	CH$_3$CONH	22
3a	2-pyridinecarbonyl	CH$_2$CHCH$_2$OCONH	58
3b	3-pyridinecarbonyl	CH$_2$CHCH$_2$OCONH	50
3c	4-pyridinecarbonyl	CH$_2$CHCH$_2$OCONH	37
3d	pyrazinecarbonyl	CH$_2$CHCH$_2$OCONH	16
6	H	CH$_3$CONH	
7	H	CH$_2$CHCH$_2$OCONH	

^{a} After crystallization.

1630, 1490 cm^{-1}; MS, m/z 242 (100) (M$^+$), 200 (88), 171 (48), 108 (64), 93 (23), 80 (27), 65 (29), 43 (97); mp 129–131 °C. $C_{14}H_{14}N_2O_2$ Anal. Calcd: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.40; H, 5.80; N, 11.50.

7: ^{1}H NMR (CDCl$_3$) δ 3.62 (br, 2H), 4.65 (dt, 2H, J = 5.73, 1.38 Hz), 5.27 (dpq, 1H, J = 10.40, 2.60, 1.38 Hz), 5.36 (dpq, 1H, J = 17.20, 2.60, 1.38 Hz), 5.97 (ddt, 1H, J = 17.22, 10.38, 5.73 Hz), 6.67 (dd, 2H, J = 8.80, 2.20 Hz), 6.85 (dd, 2H, J = 8.80, 2.20 Hz), 6.91 (dd, 2H, J = 9.00, 1.60 Hz), 7.28 (dd, 2H, J = 9.00, 1.60 Hz), 7.31 (s, 1H); IR (KBr) 3380, 3300, 1704, 1490 cm^{-1}; MS, m/z 284 (100) (M$^+$), 199 (55), 171 (24), 108 (36), 41 (69); mp 99.7–101.7 °C. $C_{14}H_{14}N_2O_2$ Anal. Calcd: C, 67.60; H, 5.67; N, 9.85. Found: C, 67.62; H, 5.65; N, 9.79.

Activity on *C. pomonella* Eggs. The population of *C. pomonella* was collected from an unsprayed apple tree orchard in 1992 at Lleida (northeastern Spain) and was reared on a semisynthetic diet at room temperature under long-day conditions (Pons et al., 1994). The adults were kept in cylindrical rearing cages, where the substrate for egg laying was wax paper (Waxtex Menominee Paper Co.).

Wax paper disks (9 mm in diameter) with <24-h-old codling moth eggs were cut from the rearing cage and sprayed with 1 mL of a 5 mg/mL solution of the chemicals on pure acetone or in acetone plus 18% dimethyl sulfoxide (DMSO). The applications were done with a Potter spray tower (Potter, 1952) provided with a final nozzle, regulated at a pressure of 2 × 10^4 N m^{-2} and allowing 5 s for settlement. After drying, the disks were kept at 19 ± 1 °C in plastic Petri dishes with moist filter paper. This temperature was chosen because it was within the range for optimal development (Ferreira et al.,

X = CH$_3$COO and R = CH$_3$ R = CH$_3$ **(6)**   R = CH$_3$

X = Cl and R = OCH$_2$CHCH$_2$ R = OCH$_2$CHCH$_2$ **(7)**   R = OCH$_2$CHCH$_2$

Figure 3. General synthetic route to 4-phenoxyaniline precursors.

Table 2. Mortality and Length of Development Period of <24-h-old *C. pomonella* Eggs Topically Sprayed with 1 mL of a 5 mg/mL Solution of Phenoxyphenyl-carboxamides (Group Compounds 1)[a]

sample	mortality (%)	efficacy (%)	development period (days)
control	0.8 ± 0.30 e		9.2 ± 0.04 d
acetone	19.5 ± 0.01 d		9.3 ± 0.04 d
1d	29.2 ± 0.01 cd		9.7 ± 0.06 bc
1c	33.4 ± 0.04 bcd		10.0 ± 0.10 b
1b	40.9 ± 0.09 bc	26.3 ± 0.15 b	10.6 ± 0.02 a
1a	52.4 ± 0.31 bc	40.7 ± 0.43 b	10.8 ± 0.08 a
fenoxycarb	99.3 ± 0.27 a	99.1 ± 0.34 a	

[a] Mean and standard error of 5 replicates (20−30 eggs per replicate). Efficacy calculated by Abbott's formula. Figures followed by the same letter within the same column were not significantly different (Scheffe test, $P > 0.05$). Arcsin transformation was carried out prior to analysis.

Table 3. Mortality and Length of Development Period of <24-h-old *C. pomonella* Eggs Topically Sprayed with 1 mL of a 5 mg/mL Solution of Acetylaminophenoxy-phenylcarboxamides (Group Compounds 2)[a]

sample	mortality (%)	efficacy (%)	development period (days)
control	1.6 ± 0.26 d		9.5 ± 0.02 d
acetone + DMSO	37.4 ± 0.02 c		9.9 ± 0.00 c
2c	52.7 ± 0.50 bc		10.1 ± 0.02 c
2b	57.6 ± 0.27 bc		10.6 ± 0.07 b
2a	67.3 ± 0.20 b	47.1 ± 0.35 b	10.9 ± 0.04 a
2d	68.4 ± 0.12 b	49.1 ± 0.18 b	11.0 ± 0.04 a
fenoxycarb	100.0 ± 0.00 a	100.0 ± 0.00 a	

[a] Mean and standard error of 5 replicates (20−30 eggs per replicate). Efficacy calculated by Abbott's formula. Figures followed by the same letter were not significantly different (Scheffe test, $P > 0.05$). Arcsin transformation was carried out prior to analysis.

Table 4. Mortality and Length of Development Period of <24-h-old *C. pomonella* Eggs Topically Sprayed with 1 mL of a 5 mg/mL Solution of Allyl Phenoxyphenyl-carbamates (Group Compounds 3 and Compound 7)[a]
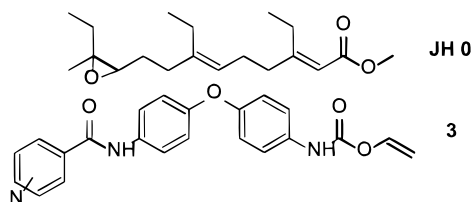
sample	mortality (%)	efficacy (%)	development period (days)
control	1.6 ± 0.27 e		9.3 ± 0.07 d
acetone	18.4 ± 0.05 d		9.4 ± 0.02 d
3d	25.3 ± 0.07 cd		9.5 ± 0.03 d
3b	34.4 ± 0.23 bcd		10.2 ± 0.05 c
3a	40.7 ± 0.25 bc	27.2 ± 0.56 bc	11.1 ± 0.05 b
7	48.1 ± 0.73 bc	35.0 ± 1.19 bc	11.3 ± 0.02 ab
3c	53.8 ± 0.55 b	42.5 ± 0.89 b	11.7 ± 0.03 a
fenoxycarb	99.5 ± 0.44 a	99.5 ± 0.52 a	

[a] Mean and standard error of 5 replicates (20−30 eggs per replicate). Efficacy calculated by Abbott's formula. Figures followed by the same letter were not significantly different (Scheffe test, $P > 0.05$). Arcsin transformation was carried out prior to analysis.

1994), and the length of development period might be sufficient to detect significant differences. The eggs were checked daily for larval emergence, until no more larvae emerged in three consecutive days. Five replicates (20−30 eggs per replicate) were carried out. Unsprayed eggs and pure acetone sprayed or acetone plus 18% DMSO sprayed eggs were used as controls. The insect growth regulator fenoxycarb (JHA) was used as a standard.

Statistical Analyses. Analysis of variance was done using the routine ANOVA of the statistical package SAS (SAS Institute Inc., 1985). Percentage of mortality was arcsin transformed [arcsinsqr (percentage mortality/100)] prior to analysis. The Scheffe test was used to separate the means, at a level of $P = 0.05$. The efficacy of each chemical was calculated by suing Abbot's formula, when the mortality was significantly different from the mortality of the acetone control. A subsequent ANOVA of the efficacy was carried out.

Molecular Calculations. Calculations were done using HyperChem release 5.0 for Windows (HyperChem Release 5.0 for Windows; Hypercube Inc., Gainesville, FL, 1996). Optimization of the different molecules was done using Molecular Mechanics (MM+) with several starting conformations, and then a semiempirical single point calculation using the AM1 parameters was carried out to obtain charges. Optimizations with MM+ were done starting with several conformations for each compound. The lowest energy conformer of each compound was used as a starting point for AM1 calculations. With juvenile hormone 0 we also optimized several starting conformations. The most extended ones gave the lower energy values. We used the lowest one to do a single-point calculation with the AM1 method. Given distances are in angrstoms and were obtained from the optimized structure.

RESULTS AND DISCUSSION

The detailed chemical reactions used to prepare all sets of compounds are shown in Figure 2. *N,N*-Carbonyldiimidazole (**4**) is a well-known reagent employed to obtain carboxylic acid derivatives through the formation of an imidazolide (**5**) (Fieser and Fieser, 1967). Although yields were moderate, this procedure was chosen on the basis of its methodological simplicity. The phenoxyphenylcarboxamide derivatives (group compounds **1**, **2**, and **3**) prepared are presented in Table 1. The two precursor

anilines employed to synthesize the two series of compounds, presenting an acetylamino (**6**) and an allyl formylamino group (**7**), were prepared according to conventional procedures (Figure 3). In both cases, the monosubstituted compound was found together with the starting material and the corresponding disubstituted compound at the end of the reaction. Purification of the crude reaction product yielded pure monoamines.

Mortality of <24-h-old *C. pomonella* eggs sprayed with the synthesized substances (Table 1) and the efficacy of these compounds are shown in Tables 2−4. Several of the tested compounds (**1a**, **1b**, **2a**, **2d**, **3a**, and **3c**) showed an ovicidal activity against *C. pomonella* eggs significantly different from that of the controls; the efficacy for these substances ranged from 26 to 50%. The efficacy of the well-known ovicide fenoxycarb was 99−100%.

Several substances also produced a significant increase in the length of the development period of the eggs 1−2 days old. Tables 2−4 show that increase is between 10 and 20%. Both effects were correlated: the products that produced higher mortality also produced higher increase in the length of the development period. The insect growth regulator effect seems to be stronger

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Figure 4. Possible action mode of allyl phenoxyphenylcarbamates (**3**) as JH mimetic.

than the biocidal effect. Thus, some products, which did not increase the mortality, increased the length of the development period.

Mortality caused by compound **1a** was lower in the tested conditions, 19 ± 1 °C, than in the conditions used in our previous work, 25 ± 1 °C (Canela et al., 1999). In that case egg hatching happens at day 5, so the available detoxification period was shorter and the activity higher.

These results seem to confirm the hypothesis presented in our previous publication (Canela et al., 1999).

In the three groups of obtained products, compounds derived from picolinic acid present activities significantly different from that of the control. However, only in the first group of derivatives is efficiency, measured as absolute value, higher than that of the other active derivative. In the other groups there is always another substance, with the nitrogen in a different ring position, with absolute values of efficiency higher than those of the corresponding picolinic derivative. This fact, and the nonexistence of statistically significant differences among the different active products, makes it difficult to draw a final conclusion about the role of the position of the nitrogen in the observed ovicidal activity.

Nevertheless, it is evident that the carbamate group (Table 4) causes an increase of the development period when the substance appears active. Considering these results, the precursor **7** (Figure 3) was tested. As Table 4 shows, such a substance presented an efficiency similar to that of the other two active products of this group, causing an elongation of the development period also.

In Figure 4 the extended structure of these substances is compared with that of the JH 0. The coincidence of the carbamate group with the carboxylate one of the juvenile hormone, as well as that of the oxirane ring with the amide, might explain the kind of observed activity. Thus, the calculated distance between the tertiary carbon supporting the epoxide group and the carbon from the carboxylic group in the JH 0 optimized conformation is 11.70 Å, very close to 11.74 Å (the distance between both carboxamidic carbons in compound **3a** optimized conformation). Moreover, positive charges are assigned to the indicated carbons in both structures. The distance between the epoxy oxygen and the carbonyl carbon at the other end (10.83 Å) in JH 0 was in the same range as that found by Katagi et al. (10.70−11.86 Å) for insect juvenile hormone III structures optimized using an MNDO program (Katagi et al., 1989). The lack of activity of some of the products tested, despite having a very similar structure, would remain without explanation. Logically, any structural modification can alter the potential surface of the molecule, varying its capacity to interact with the desired receptor or another receptor different from this.

Although the activity of the tested compounds is lower than the activity shown by fenoxycarb, two facts are pushing us to consider new modifications: (1) the similar activity between **1a** and some insect juvenile hormones (Canela et al., 1999) and (2) the clear influence on the development period of *C. pomonella* eggs. Thus, research is being carried out to examine the influence of the carbamate group as well as of the pyridine ring on the observed activity.

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