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Synthesis, Fungicidal, and Insecticidal Activities of β-Methoxyacrylate-Containing *N*-Acetyl Pyrazoline Derivatives

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1-Acetyl-3,-5-diarylpyrazolines have received considerable interests from the fields of medicinal and agricultural chemistry due to their broad spectrum of biological activities. To discover new lead compounds exhibiting both fungicidal and insecticidal activities, a series of pyrazoline derivatives were designed and synthesized by introducing the β-methoxyacrylate pharmacophore into the scaffold of 1-acetyl-3,5-diarylpyrazoline. The fungicidal activities against *Pseudoperoniospora cubensis*, *Sphaerotheca fuliginea*, *Botrytis cinerea*, and *Rhizoctonia solani* and the insecticidal activities against *Aphis medicagini*, *Nilaparvata legen*, *Mythima separata*, and *Tetranychus cinnabarnus* were screened. The most potent compound **13**, 1-aceto-3-{*m*-[*o*-(*E*-1-methoxycarboxyl-2-methoxy)-1-yl]benzyloxy}phenyl-5-(benzo-[1,3]-dioxolyl)-4,5-dihydro- pyrazoline, was identified. Its fungicidal IC_{50} values against *P. cubensis* and *S. fuliginea* are 26.6 and 57.6 μg mL^{-1}, respectively, while its insecticidal LC_{50} value against *M. separata* is 26.6 μg mL^{-1}. These results indicated that compound **13** could be used as a lead for further developing new pyrazoline type products exhibiting both fungicidal and insecticidal activities.

KEYWORDS: 3,5-Diarylpyrazoline; β-methoxyacrylate; fungicide; insecticide

INTRODUCTION

Recently, increasing interests have been focused on the pyrazoline derivatives because of their broad spectrum of biological activities (*1*−*6*). Among the existing various pyrazoline type derivatives, 1-acetyl-pyrazolines have been identified as one of the most promising scaffold. In the field of medicinal chemistry, 1-acetyl-pyrazoline derivatives were found to display anticancer and anti-inflammatory activities. For example, as shown in **Scheme 1**, compound **1** as a monoamine oxidase inhibitor has been proved to be effective in treating Alzheimer's disease (AD), which accounts for most cases of dementia that are diagnosed after the age of 60 years of life (*7*). Compound **2** (**Scheme 1**) is an inhibitor of kinesin spindle protein (KSP) with potential use for the treatment of cancer (*8*).

In the early 1970s, pyrazoline type derivatives were found to be associated with insecticidal activity (*9*), and some compounds such as **3** (code, PH 60-41) and **4** (code, PH 60-42) were known to effectively control insects with unique mode of action. Unfortunately, these compounds did not yield commercial insecticide products due to their unfavorable toxicity profiles and environmental properties. Therefore, synthesis efforts in this area focused on improving the toxicological and environmental-fate properties of the compounds while maintaining high insecticidal activity. A notable example is compound **5** (code, RH342) from Rohm and Haas, which was reported to have high insecticidal activity, low mammalian toxicity, and a rapid rate of degradation in the environment. Further efforts at DuPont led to the discovery of a new crop insecticide, indoxacarb, which is the first commercialized pyrazoline type sodium channel blocker (*10*).

In past decade, strobilurin fungicides have been widely and rapidly adopted due to the advantages such as novel mode of action, wide spectrum of biological activities, low toxicity toward mammalian cells, and favorable profiles to human safe (*11*−*16*). In addition, pyrazoline type derivatives with fungicidal activity were patented by Rohm and Haas in 1999 (*17*) but have not yielded commercial products so far. The above-mentioned facts indicate that *N*-acetyl-3,5-diarylpyrazoline is a very promising scaffold with broad spectrum biological activities. Hence, to search for novel lead compounds for crop protection, as shown in **Scheme 2**, we designed the titled compounds **6**−**39** by introducing the β-methoxyacrylate pharmacophore into the *N*-acetyl-3,5-diarylpyrazoline scaffold, which will be expected to exhibit both insecticidal and fungicidal activities due to the coexistence of two kinds of pharmacophores.

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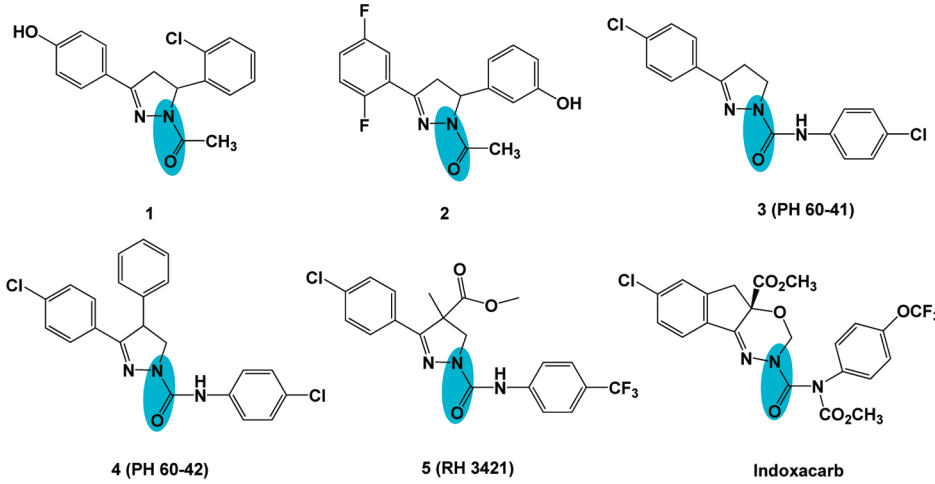
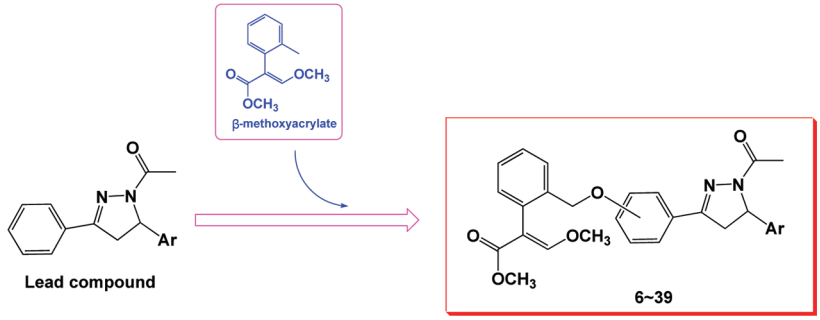
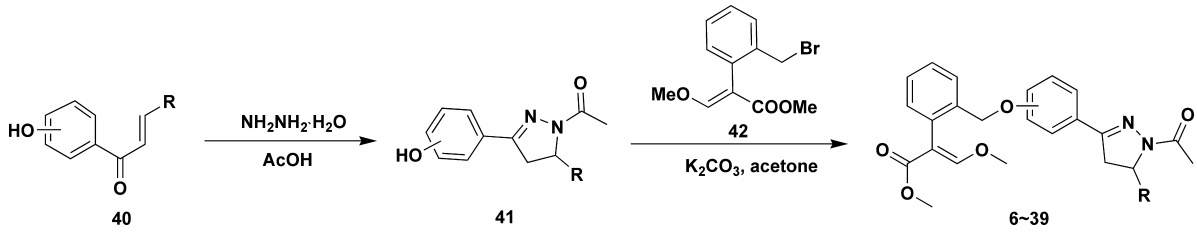
Scheme 1



Scheme 2. Design Strategy of the Title Compounds



Scheme 3



MATERIALS AND METHODS

Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification while all solvents were redistilled before use. ^{1}H NMR spectra were recorded on a Mercury-Plus 400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal reference. MS spectra were determined using a Trace MS 2000 organic mass spectrometry. Elementary analyses were performed on a Vario EL III elemental analysis instrument. Melting points were taken on a Buchi B-545 melting point apparatus and are uncorrected. Intermediates **40**, **41**, and **42** were prepared according to the reported methods (*6, 18*), and the detailed procedure and characterization data for intermediate **41** can be found in the Supporting Information.

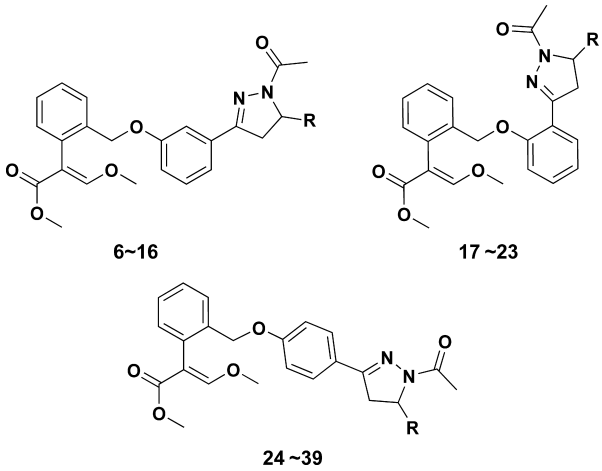
General Procedure for the Synthesis of Target Compounds 6−39. A 1.1 mmol amount of pyrazolines **41** and 0.16 g (1.2 mmol) of anhydrous K_2CO_3 in dry acetone (8 mL) were stirred and refluxed for 0.5 h, followed by the addition of 0.28 g (1.0 mmol) of (*E*)-methyl 2-[2-(bromomethyl)-phenyl]-3-methoxyacrylate **42**. The reaction was continued for 5−8 h under reflux. The resulting mixture was cooled to room temperature and filtered off by suction, and the solvent was evaporated to give the crude product followed by chromatography purification on silica using a mixture of petroleum ether and ethyl acetate (12:1) as an eluent to give the target compounds in yields of 61−89%.

Data for 6. Yield, 63%; mp 116−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H, $COCH_3$), 3.11 [dd, J = 5.0 Hz, J = 17.8 Hz, 1H, 4-H_a (refer to one of the protons of methylene in the pyrazoline ring, the same as the following)], 3.69−3.77 [m, 4H, 4-H_b (refer to the other protons of methylene in the pyrazoline ring, the same as the following), $COOCH_3$], 3.82 (s, 3H, =CH-O$\underline{CH_3}$), 5.00 (s, 2H, CH_2), 5.79 (dd, J = 5.0 Hz, J = 11.8 Hz, 1H, Ar-CH), 6.93−6.96 (m, 1H, ArH), 7.03−7.14 (m, 3H, ArH), 7.17−7.31 (m, 4H, ArH), 7.33−7.36 (m, 3H, ArH), 7.53 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =$\underline{CH}$-OCH_3). EI MS: m/z (%) 503 ([M + 1]$^+$, 13), 502 (M$^+$, 13), 297 (29), 256 (55), 205 (30), 204 (64), 145 (100), 144 (54), 116 (26), 114 (27), 102 (34), 101 (25). Anal. calcd for $C_{29}H_{27}FN_2O_5$: C, 69.31; H, 5.42; N, 5.57. Found: C, 69.14; H, 5.52; N, 5.64.

Data for 7. Yield, 83%; mp 83−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.46 (s, 3H, $COCH_3$), 3.01 (dd, J = 4.6 Hz, J = 17.8 Hz, 1H, 4-H_a), 3.65−3.72 (m, 4H, 4-H_b, $COOCH_3$), 3.81 (s, 3H, =CH-O$\underline{CH_3}$), 3.85 (s, 3H, Ar-OCH_3), 4.99 (s, 2H, CH_2), 5.83 (dd, J = 4.6 Hz, J = 11.8 Hz, 1H,Ar-CH), 6.87−6.93 (m, 3H, ArH), 7.01 (d, J = 7.6 Hz, 1H, ArH), 7.17−7.27 (m, 4H, ArH), 7.33 (t, J = 4.0 Hz, 3H, ArH), 7.53 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =$\underline{CH}$-OCH_3). EI MS: m/z (%) 514 (M$^+$, 7), 267 (11), 204 (94), 176 (17), 174 (15), 146 (26), 145 (100), 144 (29), 131 (14), 130 (13), 115 (11), 102 (10). Anal. calcd for $C_{30}H_{30}N_2O_6$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.26; H, 5.89; N, 5.17.

Data for 8. Yield, 81%; mp 145−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H, $COCH_3$), 3.13 (dd, J = 4.6 Hz, J = 17.8 Hz, 1H, 4-H_a), 3.66−3.73 (m, 4H, 4-H_b, $COOCH_3$), 3.79 (s, 3H, Ar-OCH_3), 3.82 (s, 9H, 2 × Ar-OCH_3, =CH-O$\underline{CH_3}$), 5.01 (s, 2H, CH_2), 5.50 (dd, J = 4.8 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.42 (s, 2H, ArH), 6.96 (t, J =

Table 1. Structures and Fungicidal Activities of Compounds **6**−**39**



		200 μg mL^{-1} (in vivo)[a]	
compd	R	*P. cubensis*	*S. fuliginea*
6	2-FC_6H_4	++++	−
7	2-$MeOC_6H_4$	+++	+++
8	3,4,5-$(MeO)_3C_6H_2$	−	−
9	4-*t*-BuC_6H_4	+++	−
10	4-ClC_6H_4	+	−
11	3-FC_6H_4	−	−
12	2-BrC_6H_4	+++++	−
13	3,4-$OCH_2O-C_6H_3$	+++++	++++
14	thiophen-2-yl	+++++	−
15	4-$EtOC_6H_4$	+++++	−
16	4-MeC_6H_4	+++++	−
17	4-EtC_6H_4	+++++	−
18	4-ClC_6H_4	−	−
19	3,4-$(Me)_2C_6H_3$	−	−
20	3,4-$(OMe)_2C_6H_3$	−	−
21	3-$MeOC_6H_4$	−	−
22	3,4-$Cl_2C_6H_3$	−	−
23	4-BrC_6H_4	−	−
24	thiophen-2-yl	++	+
25	4-EtC_6H_4	+++++	−
26	3,4-$OCH_2O-C_6H_3$	+++++	−
27	4-ClC_6H_4	+++++	−
28	3,4,5-$(MeO)_3C_6H_2$	−	−
29	2-FC_6H_4	−	−
30	4-MeC_6H_4	−	−
31	4-BrC_6H_4	−	−
32	2,4-$Cl_2C_6H_3$	−	−
33	3-FC_6H_4	−	−
34	3,4-$Me_2C_6H_3$	−	−
35	4-FC_6H_4	−	−
36	3-$MeOC_6H_4$	++	−
37	4-$MeOC_6H_4$	−	−
38	4-*t*-BuC_6H_4	−	−
39	4-$EtOC_6H_4$	−	−
	Kresoxim-methyl	++++	+++++

[a] Rating system for the inhibition percentage: +++++, 100%; ++++, ≥90%; +++, ≥80%; ++, ≥70%; +, ≥60%; and −, <60%.

3.0 Hz, 1H, ArH), 7.17−7.20 (m, 1H, ArH), 7.28−7.35 (m, 5H, ArH), 7.53 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3). EI MS: *m*/*z* (%) 574 (M^+, 3), 205 (19), 204 (18), 160 (11), 146 (19), 144 (100), 131 (20), 130 (19), 114 (19), 103 (20), 101 (12). Anal. calcd for $C_{32}H_{34}N_2O_8$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.65; H, 6.08; N, 4.80.

Data for 9. Yield, 89%; mp 79−81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (s, 9H, t-Bu), 2.42 (s, 3H, $COCH_3$), 3.14 (dd, J = 4.0 Hz, J = 18.0 Hz, 1H, 4-H_a), 3.65−3.72 (m, 4H, 4-H_b, $COOCH_3$), 3.81 (s, 3H, =CH-OCH_3), 5.01 (s, 2H, CH_2), 5.57 (dd, J = 4.4 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.94 (d, J = 4.4 Hz, 1H, ArH), 7.13−7.22 (m, 3H, ArH), 7.27−7.35 (m, 7H, ArH), 7.54 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3). EI MS: *m*/*z* (%) 540 (M^+, 8), 315 (23), 294 (20), 293 (13), 205 (29), 204 (19), 160 (12), 146 (16), 144 (100), 130 (10), 114 (22), 102 (12). Anal. calcd for $C_{33}H_{36}N_2O_5$: C, 73.31; H, 6.71; N, 5.18. Found: C, 73.60; H, 6.52; N, 5.35.

Data for 10. Yield, 79%; mp 149−151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H, $COCH_3$), 3.10 (dd, J = 5.0 Hz, J = 17.8 Hz, 1H, 4-H_a), 3.68−3.75 (m, 4H, 4-H_b, $COOCH_3$), 3.81 (s, 3H, =CH-OCH_3), 5.00 (s, 2H, CH_2), 5.54 (dd, J = 4.4 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.96 (t, J = 4.6 Hz, 1H, ArH), 7.15−7.20 (m, 3H, ArH), 7.28−7.35 (m, 7H, ArH), 7.53 (t, J = 4.6 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3). EI MS: *m*/*z* (%) 518 (M^+, 3), 204 (35), 178 (13), 172 (15), 145 (100), 130 (45), 128 (13), 116 (13), 114 (52), 102 (44), 101 (36). Anal. calcd for $C_{29}H_{27}ClN_2O_5$: C, 67.11; H, 5.24; N, 5.40. Found: C, 67.22; H, 5.19; N, 5.20.

Data for 11. Yield, 78%; mp 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H, $COCH_3$), 3.11 (dd, J = 4.4 Hz, J = 17.6 Hz, 1H, 4-H_a), 3.68−3.75 (m, 4H, 4-H_b, $COOCH_3$), 3.82 (s, 3H, =CH-OCH_3), 5.00 (s, 2H, CH_2), 5.56 (dd, J = 4.4 Hz, J = 12.0 Hz, 1H, Ar-CH), 6.90−6.97 (m, 4H, ArH), 7.02 (d, J = 8.0 Hz, 1H, ArH), 7.17−7.22 (m, 2H, ArH), 7.28−7.34 (m, 4H, ArH), 7.54 (t, J = 4.6 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3). EI MS: *m*/*z* (%) 503 ([M + 1]$^+$, 2), 502 (M^+, 2), 298 (51), 256 (78), 254 (39), 204 (99), 171 (23), 160 (100), 145 (88), 144 (91), 114 (25), 102 (25). Anal. calcd for $C_{29}H_{27}FN_2O_5$: C, 69.31; H, 5.42; N, 5.57. Found: C, 69.06; H, 5.15; N, 5.33.

Data for 12. Yield, 61%; mp 141−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H, $COCH_3$), 3.01 (dd, J = 4.6 Hz, J = 17.8 Hz, 1H, 4-H_a), 3.71 (s, 3H, $COOCH_3$), 3.79−3.87 (m, 4H, 4-H_b, =CH-OCH_3), 4.99 (s, 2H, CH_2), 5.87 (dd, J = 4.8 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.93 (dd, J = 3.0 Hz, J = 5.8 Hz, 1H, ArH), 7.03 (d, J = 8.0 Hz, 1H, ArH), 7.12 (d, J = 8.0 Hz, 1H, ArH), 7.19 (dd, J = 3.0 Hz, J = 5.8 Hz, 1H, ArH), 7.23−7.28 (m, 3H, ArH), 7.34 (t, J = 4.0 Hz, 3H, ArH), 7.53 (t, J = 4.4 Hz, 1H, ArH), 7.57−7.59 (m, 2H, =CH-OCH_3, ArH). EI MS: *m*/*z* (%) 564 ([M + 2]$^+$, 18), 562 (M^+, 18), 315 (23), 278 (20), 204 (79), 178 (20), 176 (50), 160 (45), 144 (100), 130 (65), 128 (45), 114 (62), 102 (88). Anal. calcd for $C_{29}H_{27}BrN_2O_5$: C, 61.82; H, 4.83; N, 4.97. Found: C, 61.73; H, 4.56; N, 4.75.

Data for 13. Yield, 87%; mp 83−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H, $COCH_3$), 3.10 (dd, J = 4.4 Hz, J = 17.6 Hz, 1H, 4-H_a), 3.64−3.72 (m, 4H, 4-H_b, $COOCH_3$), 3.82 (s, 3H, =CH-OCH_3), 5.00 (s, 2H, CH_2), 5.49 (dd, J = 4.6 Hz, J = 11.4 Hz, 1H, Ar-CH), 5.92 (s, 2H, OCH_2O), 6.67 (s, 1H, ArH), 6.73 (d, J = 1.6 Hz, 2H, ArH), 6.95 (t, J = 3.2 Hz, 1H, ArH), 7.19 (dd, J = 3.4 Hz, J = 5.4 Hz, 1H, ArH), 7.28−7.35 (m, 5H, ArH), 7.54 (t, J = 4.6 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3). EI MS: *m*/*z* (%) 528 (M^+, 5), 324 (18), 323 (30), 280 (73), 204 (100), 189 (30), 177 (23), 175 (27), 163 (25), 160 (35), 144 (88), 130 (17). Anal. calcd for $C_{30}H_{28}N_2O_7$: C, 68.17; H, 5.34; N, 5.30. Found: C, 68.16; H, 5.10; N, 5.24.

Data for 14. Yield, 72%; mp 63−64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.39 (s, 3H, $COCH_3$), 3.31 (dd, J = 3.6 Hz, J = 18.0 Hz, 1H, 4-H_a), 3.64−3.71 (m, 4H, 4-H_b, $COOCH_3$), 3.81 (s, 3H, =CH-OCH_3), 5.01 (s, 2H, CH_2), 5.89 (dd, J = 3.4 Hz, J = 11.0 Hz, 1H, Ar-CH), 6.90−7.01 (m, 3H, ArH), 7.18 (t, J = 6.0 Hz, 2H, ArH), 7.29−7.34 (m, 5H, ArH), 7.53 (d, J = 5.2 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3). EI MS: *m*/*z* (%) 491 ([M + 1]$^+$, 16), 490 (M^+, 69), 431 (85), 388 (100), 368 (33), 341 (27), 330 (30), 286 (26), 285 (32), 243 (27), 145 (39). Anal. calcd for $C_{27}H_{26}N_2O_5S$: C, 66.10; H, 5.34; N, 5.71. Found: C, 66.17; H, 5.57; N, 5.56.

Data for 15. Yield, 86%; mp 104−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.39 (s, 3H, $COCH_3$), 3.12 (dd, J = 4.4 Hz, J = 17.6 Hz, 1H, 4-H_a), 3.64−3.72 (s, 4H, 4-H_b, $COOCH_3$), 3.81 (s, 3H, =CH-OCH_3), 3.99 (dd, J = 6.8 Hz, J = 14.0 Hz, 2H, OCH_2CH_3), 5.00 (s, 2H, CH_2), 5.54 (dd, J = 4.4 Hz, J = 11.2 Hz, 1H, Ar-CH), 6.82 (d, J = 8.4 Hz, 2H, ArH), 6.95 (t, J = 5.6 Hz, 1H, ArH), 7.14 (d, J = 8.4 Hz, 2H, ArH), 7.18 (dd, J = 3.4 Hz, J = 5.8 Hz, 1H, ArH), 7.28−7.36 (m, 5H, ArH), 7.54 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3). EI MS: *m*/*z* (%) 529 ([M + 1]$^+$, 24), 528 (M^+, 84), 281 (30), 253 (11), 205 (37), 177 (11), 145 (100), 131 (29), 128 (11), 115 (21), 103 (39). Anal. calcd for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.47. Found: C, 72.73; H, 6.52; N, 5.21.

Data for 16. Yield, 84%; mp 85−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H, Ar-CH_3), 2.40 (s, 3H, $COCH_3$), 3.12 (dd, J =

4.6 Hz, J = 17.8 Hz, 1H, 4-H_a), 3.65−3.72 (m, 4H, 4-H_b, $COOCH_3$), 3.81 (s, 3H, =CH-OCH_3), 5.00 (s, 2H, CH_2), 5.54 (dd, J = 4.8 Hz, J = 12.0 Hz, 1H, Ar-CH), 6.93−6.96 (m, 1H, ArH), 7.10−7.20 (m, 4H, ArH), 7.18 (t, J = 4.4 Hz, 1H, ArH), 7.26−7.29 (m, 2H, ArH), 7.31−7.35 (m, 3H, ArH), 7.53 (dd, J = 3.2 Hz, J = 5.6 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3). EI MS: m/z (%) 499 ($[M + 1]^+$, 6), 498 (M^+, 24), 294 (27), 293 (35), 252 (47), 251 (66), 204 (57), 161 (11), 146 (13), 144 (100). Anal. calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 72.17; H, 5.95; N, 5.51.

Data for 17. Yield, 76%; mp 58−59 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, J = 4.0 Hz, 3H, CH_2CH_3), 2.40 (s, 3H, $COCH_3$), 2.59 (dd, J = 7.4 Hz, J = 14.8 Hz, 2H, CH_2CH_3), 3.12 (dd, J = 4.6 Hz, J = 12.0 Hz, 1H, 4-H_a), 3.64−3.72 (m, 4H, 4-H_b, $COOCH_3$), 3.81 (s, 3H, =CH-OCH_3), 5.00 (s, 2H, CH_2), 5.55 (dd, J = 4.2 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.94 (d, J = 4.6 Hz, 1H, ArH), 7.13−7.21 (m, 6H, ArH), 7.27−7.33 (m, 4H, ArH), 7.53 (t, J = 4.6 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3). EI MS: m/z (%) 513 ($[M + 1]^+$, 12), 512 (M^+, 53), 308 (56), 266 (33), 264 (47), 236 (25), 145 (100), 131 (21), 115 (21), 102 (27). Anal. calcd for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.47. Found: C, 72.51; H, 6.56; N, 5.22.

Data for 18. Yield, 67%; mp 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.38 (s, 3H, $COCH_3$), 3.27 (dd, J = 4.0 Hz, J = 18.8 Hz, 1H, 4-H_a), 3.66 (s, 3H, $COOCH_3$), 3.76 (s, 3H, =CH-OCH_3), 3.81 (dd, J = 12.0 Hz, J = 18.4 Hz, 1H, 4-H_b), 5.00 (s, 2H, CH_2), 5.46 (dd, J = 4.2 Hz, J = 11.8 Hz, 1H, Ar-CH), 6.88 (d, J = 8.4 Hz, 1H, ArH), 6.99 (t, J = 6.6 Hz, 1H, ArH), 7.16 (dd, J = 8.0 Hz, J = 13.2 Hz, 3H, ArH), 7.22−7.34 (m, 5H, ArH), 7.38 (d, J = 7.6 Hz, 1H, ArH), 7.56 (s, 1H, =CH-OCH_3), 7.87 (d, J = 7.6 Hz, 1H, ArH). EI MS: m/z (%) 518 (M^+, 2), 206 (10), 205 (69), 146 (22), 145 (100), 130 (18), 114 (13), 103 (15). Anal. calcd for $C_{29}H_{27}ClN_2O_5$: C, 67.11; H, 5.24; N, 5.40. Found: C, 66.83; H, 5.26; N, 5.10.

Data for 19. Yield, 79%; mp 139−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.19 (s, 3H, Ar-CH_3), 2.20 (s, 3H, Ar-CH_3), 2.39 (s, 3H, $COCH_3$), 3.29 (dd, J = 4.4 Hz, J = 18.8 Hz, 1H, 4-H_a), 3.66 (s, 3H, $COOCH_3$), 3.77 (s, 3H, =CH-OCH_3), 3.84 (dd, J = 12.0 Hz, J = 18.8 Hz, 1H, 4-H_b), 5.00 (s, 2H, CH_2), 5.44 (dd, J = 4.4 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.85 (d, J = 8.4 Hz, 1H, ArH), 6.93−7.05 (m, 4H, ArH), 7.16 (d, J = 7.6 Hz, 1H, ArH), 7.24−7.30 (m, 3H, ArH), 7.40 (d, J = 7.6 Hz, 1H, ArH), 7.57 (s, 1H, =CH-OCH_3), 7.89 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H, ArH). EI MS: m/z (%) 513 ($[M+1]^+$, 12), 512 (M^+, 87), 306 (20), 264 (63), 205 (40), 204 (42), 160 (16), 146 (27), 145 (100), 144 (72), 131 (57), 102 (25). Anal. calcd for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.47. Found: C, 72.91; H, 6.43; N, 5.24.

Data for 20. Yield, 83%; mp 74−76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H, $COCH_3$), 3.32 (dd, J = 4.2 Hz, J = 18.2 Hz, 1H, 4-H_a), 3.66 (s, 3H, $COOCH_3$), 3.77 (s, 3H, =CH-OCH_3), 3.78−3.86 (m, 7H, 4-H_b, 2 × Ar-OCH_3), 5.00 (s, 2H, CH_2), 5.46 (dd, J = 4.0 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.75−6.78 (m, 3H, ArH), 6.87 (d, J = 8.4 Hz, 1H, ArH), 6.99 (t, J = 7.4 Hz, 1H, ArH), 7.17 (d, J = 7.6 Hz, 1H, ArH), 7.27−7.33 (m, 3H, ArH), 7.40 (d, J = 7.6 Hz, 1H, ArH), 7.57 (s, 1H, =CH-OCH_3), 7.88 (dd, J = 1.4 Hz, J = 7.8 Hz, 1H, ArH). EI MS: m/z (%) 546 ($[M + 2]^+$, 21), 544 (M^+, 94), 513 (10), 296 (27), 204 (32), 145 (27), 144 (100), 130 (33), 114 (19), 102 (20). Anal. calcd for $C_{31}H_{32}N_2O_7$: C, 68.37; H, 5.92; N, 5.14. Found: C, 68.18; H, 6.03; N, 5.17.

Data for 21. Yield, 74%; mp 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H, $COCH_3$), 3.27 (dd, J = 4.2 Hz, J = 18.6 Hz, 1H, 4-H_a), 3.66 (s, 3H, $COOCH_3$), 3.76−3.88 (m, 7H, 4-H_b, =CH-OCH_3, Ar-OCH_3), 4.99 (s, 2H, CH_2), 5.47 (dd, J = 4.4 Hz, J = 12.0 Hz, 1H, Ar-CH), 6.75−6.80 (m, 3H, ArH), 6.85 (d, J = 8.0 Hz, 1H, ArH), 6.98 (t, J = 7.6 Hz, 1H, ArH), 7.15−7.33 (m, 5H, ArH), 7.40 (d, J = 7.6 Hz, 1H, ArH), 7.57 (s, 1H, =CH-OCH_3), 7.89 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H, ArH). EI MS: m/z (%) 516 ($[M + 2]^+$, 14), 514 (M^+, 54), 335 (14), 268 (37), 266 (95), 177 (39), 173 (27), 172 (43), 164 (33), 160 (32), 159 (50), 146 (27), 145 (100), 130 (74), 114 (53), 102 (41), 101 (42). Anal. calcd for $C_{30}H_{30}N_2O_6$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.88; H, 6.14; N, 5.41.

Data for 22. Yield, 63%; mp 91−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H, $COCH_3$), 3.26 (dd, J = 5.2 Hz, J = 18.0 Hz, 1H, 4-H_a), 3.66 (s, 3H, $COOCH_3$), 3.77 (s, 3H, =CH-OCH_3), 3.88 (dd, J = 12.0 Hz, J = 17.6 Hz, 1H, 4-H_b), 5.00 (s, 2H, CH_2), 5.49 (dd, J = 5.0 Hz, J = 11.8 Hz, 1H, Ar-CH), 6.87−6.96 (m, 2H, ArH), 7.05−7.21 (m, 3H, ArH), 7.27−7.42 (m, 5H, ArH), 7.56 (s, 1H, =CH-OCH_3), 7.86 (d, J = 2.8 Hz, 1H, ArH). EI MS: m/z (%) 554 ($[M + 2]^+$, 7), 552 (M^+, 10), 206 (34), 205 (100), 177 (30), 173 (31), 145 (76), 144 (97), 130 (72), 114 (53), 103 (58), 102 (22). Anal. calcd for $C_{29}H_{26}ClN_2O_5$: C, 62.94; H, 4.74; N, 5.06. Found: C, 62.73; H, 4.79; N, 5.13.

Data for 23. Yield, 66%; mp 76−78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.38 (s, 3H, $COCH_3$), 3.27 (dd, J = 3.8 Hz, J = 18.6 Hz, 1H, 4-H_a), 3.66 (s, 3H, $COOCH_3$), 3.76−3.85 (m, 4H, 4-H_b, =CH-OCH_3), 4.99 (s, 2H, CH_2), 5.44 (dd, J = 4.0 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.87 (d, J = 8.8 Hz, 1H, ArH), 6.99 (t, J = 7.4 Hz, 1H, ArH), 7.07−7.18 (m, 4H, ArH), 7.25−7.34 (m, 4H, ArH), 7.46 (d, J = 8.4 Hz, 1H, ArH), 7.57 (s, 1H, =CH-OCH_3), 7.87 (d, J = 7.6 Hz, 1H, ArH). EI MS: m/z (%) 564 ($[M + 2]^+$, 6), 562 (M^+, 7), 207 (10), 206 (20), 205 (95), 178 (16), 177 (20), 173 (17), 160 (19), 145 (60), 144 (100), 130 (44), 114 (32), 102 (34), 101 (14). Anal. calcd for $C_{29}H_{27}BrN_2O_5$: C, 61.82; H, 4.83; N, 4.97. Found: C, 61.91; H, 4.54; N, 5.11.

Data for 24. Yield, 64%; mp 124−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H, $COCH_3$), 3.29 (dd, J = 4.0 Hz, J = 17.6 Hz, 1H, 4-H_a), 3.62−3.71 (m, 4H, 4-H_b, $COOCH_3$), 3.82 (s, 3H, =CH-OCH_3), 5.02 (s, 2H, CH_2), 5.88 (dd, J = 3.6 Hz, J = 11.2 Hz, 1H, Ar-CH), 6.89−6.94 (m, 3H, ArH), 7.00 (d, J = 3.6 Hz, 1H, ArH), 7.15−7.20 (m, 2H, ArH), 7.32−7.34 (m, 2H, ArH), 7.51 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3), 7.65 (d, J = 8.4 Hz, 2H, ArH). EI MS: m/z (%) 491 ($[M + 1]^+$, 6), 490 (M^+, 16), 286 (26), 244 (28), 243 (35), 241 (25), 204 (100), 172 (19), 146 (23), 145 (50), 144 (99), 114 (23), 102 (14). Anal. calcd for $C_{27}H_{26}N_2O_5S$: C, 66.10; H, 5.34; N, 5.71. Found: C, 65.94; H, 5.18; N, 5.51.

Data for 25. Yield, 75%; mp 79−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, J = 3.8 Hz, 3H, CH_2CH_3), 2.40 (s, 3H, $COCH_3$), 2.60 (dd, J = 7.6 Hz, J = 14.8 Hz, 2H, CH_2CH_3), 3.12 (dd, J = 4.0 Hz, J = 17.6 Hz, 1H, 4-H_a), 3.64−3.71 (m, 4H, 4-H_b, $COOCH_3$), 3.83 (s, 3H, =CH-OCH_3), 5.01 (s, 2H, CH_2), 5.55 (dd, J = 4.2 Hz, J = 11.4 Hz, 1H, Ar-CH), 6.74 (d, J = 8.4 Hz, 1H, ArH), 6.92 (d, J = 7.6 Hz, 2H, ArH), 7.10−7.19 (m, 3H, ArH), 7.32 (dd, J = 4.4 Hz, J = 9.2 Hz, 2H, ArH), 7.51 (dd, J = 7.2 Hz, J = 11.2 Hz, 2H, ArH), 7.59 (s, 1H, =CH-OCH_3), 7.65 (d, J = 8.8 Hz, 2H, ArH). EI MS: m/z (%) 512 (M^+, 10), 308 (61), 307 (36), 266 (81), 265 (89), 204 (91), 161 (24), 144 (100), 130 (27), 114 (63), 104 (38), 102 (28). Anal. calcd for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.47. Found: C, 72.87; H, 6.03; N, 5.49

Data for 26. Yield, 89%; mp 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H, $COCH_3$), 3.08 (dd, J = 4.4 Hz, J = 17.6 Hz, 1H, 4-H_a), 3.63−3.71 (m, 4H, 4-H_b, $COOCH_3$), 3.83 (s, 3H, =CH-OCH_3), 5.01 (s, 2H, CH_2), 5.48 (dd, J = 4.0 Hz, J = 11.6 Hz, 1H, Ar-CH), 5.91 (s, 2H, OCH_2O), 6.67 (s, 1H, ArH), 6.74 (d, J = 8.0 Hz, 2H, ArH), 6.92 (d, J = 8.8 Hz, 2H, ArH), 7.19 (t, J = 4.4 Hz, 1H, ArH), 7.34 (dd, J = 3.4 Hz, J = 5.8 Hz, 2H, ArH), 7.51 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3), 7.63 (d, J = 8.8 Hz, 2H, ArH). EI MS: m/z (%) 529 ($[M + 1]^+$, 20), 528 (M^+, 100), 323 (22), 295 (11), 281 (37), 165 (11), 145 (37), 144 (21), 115 (11), 102 (13). Anal. calcd for $C_{30}H_{28}N_2O_7$: C, 68.17; H, 5.34; N, 5.30. Found: C, 67.89; H, 5.06; N, 5.13.

Data for 27. Yield, 73%; mp 86−89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H, $COCH_3$), 3.08 (dd, J = 4.4 Hz, J = 17.6 Hz, 1H, 4-H_a), 3.66−3.74 (m, 4H, 4-H_b, $COOCH_3$), 3.84 (s, 3H, =CH-OCH_3), 5.01 (s, 2H, CH_2), 5.53 (dd, J = 4.4 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.93 (d, J = 8.8 Hz, 2H, ArH), 7.14−7.20 (m, 3H, ArH), 7.28−7.35 (m, 4H, ArH), 7.51 (t, J = 4.6 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH_3), 7.63 (d, J = 8.8 Hz, 2H, ArH). EI MS: m/z (%) 518(M^+, 2), 316 (19), 315 (21), 314 (41), 313 (49), 272 (77), 271 (100), 205 (38), 204 (41), 145 (67), 144 (53), 114 (47), 102 (22). Anal. calcd for $C_{29}H_{27}ClN_2O_5$: C, 67.11; H, 5.24; N, 5.40. Found: C, 66.93; H, 5.02; N, 5.27.

Data for 28. Yield, 71%; mp 223−225 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H, $COCH_3$), 3.12 (dd, J = 4.6 Hz, J = 17.8 Hz, 1H, 4-H_a), 3.65−3.74 (m, 4H, 4-H_b, $COOCH_3$), 3.79 (s, 3H, Ar-OCH_3), 3.81 (s, 6H, 2 × Ar-OCH_3), 3.83 (s, 3H, =CH-OCH_3), 5.01 (s, 2H, CH_2), 5.49 (dd, J = 4.6 Hz, J = 11.8 Hz, 1H, Ar-CH), 6.81 (d, J =

8.4 Hz, 1H, ArH), 6.93 (d, J = 8.4 Hz, 2H, ArH), 7.19 (dd, J = 3.4 Hz, J = 5.8 Hz, 1H, ArH), 7.32−7.35 (m, 2H, ArH), 7.51 (t, J = 4.6 Hz, 1H, ArH), 7.57 (s, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.64 (d, J = 9.2 Hz, 2H, ArH). EI MS: *m/z* (%) 575 ([M + 1]$^+$, 7), 574 (M$^+$, 12), 370 (21), 369 (47), 327 (30), 250 (27), 218 (34), 205 (45), 203 (40), 144 (100), 130 (19). Anal. calcd for $C_{32}H_{34}FN_2O_8$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.67; H, 5.99; N, 5.00.

Data for 29. Yield, 77%; mp 151−153 °C.^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.43 (s, 3H, COCH$_3$), 3.09 (dd, J = 4.8 Hz, J = 18.0 Hz, 1H, 4-H$_a$), 3.68−3.73 (m, 4H, 4-H$_b$, COOCH$_3$), 3.82 (s, 3H, =CH-OCH$_3$), 5.01 (s, 2H, CH$_2$), 5.78 (dd, J = 4.6 Hz, J = 11.8 Hz, 1H, Ar-CH), 6.92 (d, J = 8.4 Hz, 2H, ArH), 7.02−7.13 (m, 3H, ArH), 7.17−7.23 (m, 2H, ArH), 7.34 (dd, J = 4.0 Hz, J = 5.2 Hz, 2H, ArH), 7.50 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.63 (d, J = 8.4 Hz, 2H, ArH). EI MS: *m/z* (%) 502 (M$^+$, 17), 298 (26), 256 (32), 255 (30), 253 (23), 204 (72), 161 (17), 144 (100), 114 (19), 102 (12). Anal. calcd for $C_{29}H_{27}FN_2O_5$: C, 69.31; H, 5.42; N, 5.57. Found: C, 69.46; H, 5.38; N, 5.48.

Data for 30. Yield, 83%; mp 73−75 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.30 (s, 3H, Ar-CH$_3$), 2.39 (s, 3H, COCH$_3$), 3.10 (dd, J = 4.6 Hz, J = 17.8 Hz, 1H, 4-H$_a$), 3.64−3.72 (m, 4-H$_b$, 4H, COOCH$_3$), 3.82 (s, 3H, =CH-OCH$_3$), 5.01 (s, 2H, CH$_2$), 5.52 (dd, J = 4.6 Hz, J = 11.8 Hz, 1H, Ar-CH), 6.92 (d, J = 8.8 Hz, 2H, ArH), 7.09−7.12 (m, 4H, ArH), 7.17−7.20 (m, 1H, ArH), 7.32−7.35 (m, 2H, ArH), 7.51 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.63 (d, J = 8.8 Hz, 2H, ArH). EI MS: *m/z* (%) 498 (M$^+$, 10), 294 (51), 250 (39), 252 (55), 206 (28), 204 (36), 161 (24), 146 (40), 144 (100), 131 (20), 130 (31), 115 (25), 102 (20). Anal. calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 72.41; H, 6.07; N, 5.46.

Data for 31. Yield, 76%; mp 78−80 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.42 (s, 3H, COCH$_3$), 3.09 (dd, J = 4.4 Hz, J = 17.6 Hz, 1H, 4-H$_a$), 3.66−3.74 (m, 4H, 4-H$_b$, COOCH$_3$), 3.84 (s, 3H, =CH-OCH$_3$), 5.02 (s, 2H, CH$_2$), 5.51 (dd, J = 4.4 Hz, J = 12.0 Hz, 1H, Ar-CH), 6.85 (d, J = 8.8 Hz, 1H, ArH), 6.93 (d, J = 8.8 Hz, 2H, ArH), 7.14−7.20 (m, 3H, ArH), 7.31−7.39 (m, 3H, ArH), 7.50 (t, J = 4.6 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.63 (d, J = 8.4 Hz, 2H, ArH). EI MS: *m/z* (%) 564 ([M + 2]$^+$, 23), 562 (M$^+$, 18), 317 (14), 315 (11), 204 (17), 178 (10), 145 (27), 144 (100), 130 (24), 114 (28), 102 (25), 101 (13). Anal. calcd for $C_{29}H_{27}BrN_2O_5$: C, 61.82; H, 4.83; N, 4.97. Found: C, 61.74; H, 4.72; N, 5.05.

Data for 32. Yield, 69%; mp 108−110 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.45 (s, 3H, COCH$_3$), 2.98 (dd, J = 4.4 Hz, J = 17.6 Hz, 1H, 4-H$_a$), 3.72 (s, 3H, COOCH$_3$), 3.77−3.84 (m, 4H, 4-H$_b$, =CH-OCH$_3$), 5.01 (s, 2H, CH$_2$), 5.83 (dd, J = 4.2 Hz, J = 11.4 Hz, 1H, Ar-CH), 6.91 (d, J = 8.4 Hz, 2H, ArH), 6.98 (d, J = 8.4 Hz, 1H, ArH), 7.16−7.19 (m, 2H, ArH), 7.30−7.34 (m, 2H, ArH), 7.40 (d, J = 1.6 Hz, 1H, ArH), 7.51 (t, J = 4.8 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.62 (d, J = 8.4 Hz, 2H, ArH). EI MS: *m/z* (%) 554 ([M + 1]$^+$, 6), 553 (M$^+$, 26), 544 (57), 296 (22), 205 (75), 204 (68), 145 (39), 144 (100), 130 (32), 114 (27), 102 (28). Anal. calcd for $C_{29}H_{26}Cl_2N_2O_5$: C, 62.94; H, 4.74; N, 5.06. Found: C, 63.16; H, 5.02; N, 5.32.

Data for 33. Yield, 61%; mp 135−137 °C.^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.40 (s, 3H, COCH$_3$), 3.08 (dd, J = 3.4 Hz, J = 17.4 Hz, 1H, 4-H$_a$), 3.66−3.73 (m, 4H, 4-H$_b$, COOCH$_3$), 3.83 (s, 3H, =CH-OCH$_3$), 5.01 (s, 2H, CH$_2$), 5.55 (dd, J = 4.4 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.91−6.94 (m, 4H, ArH), 7.01 (d, J = 7.6 Hz, 1H, ArH), 7.17−7.20 (m, 1H, ArH), 7.28−7.34 (m, 3H, ArH), 7.51 (t, J = 4.2 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.63 (d, J = 8.8 Hz, 2H, ArH). EI MS: *m/z* (%) 502 (M$^+$, 13), 298 (61), 256 (67), 255 (58), 254 (34), 225 (20), 205 (31), 204 (45), 160 (48), 144 (100), 130 (24), 114 (21), 102 (19). Anal. calcd for $C_{29}H_{27}FN_2O_5$: C, 69.31; H, 5.42; N, 5.57. Found: C, 69.57; H, 5.20; N, 5.34.

Data for 34. Yield, 88%; mp 88−90 °C.^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.20 (s, 3H, Ar-CH$_3$), 2.21 (s, 3H, Ar-CH$_3$), 2.40 (s, 3H, COCH$_3$), 3.11 (dd, J = 4.4 Hz, J = 17.6 Hz, 1H, 4-H$_a$), 3.63−3.71 (m, 4H, 4-H$_b$, COOCH$_3$), 3.82 (s, 3H, =CH-OCH$_3$), 5.01 (s, 2H, CH$_2$), 5.50 (dd, J = 4.4 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.94 (dd, J = 7.4 Hz, J = 15.8 Hz, 4H, ArH), 7.06 (d, J = 7.6 Hz, 1H, ArH), 7.18 (d, J = 4.8 Hz, 1H, ArH), 7.32−7.34 (m, 2H, ArH), 7.50 (t, J = 4.6 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.63 (d, J = 8.8 Hz, 2H, ArH). EI MS: *m/z* (%) 513 ([M + 1]$^+$, 7), 512 (M$^+$, 9), 307 (20), 265 (15), 264 (14), 205 (26), 204 (25), 172 (13), 146 (27), 145 (49), 144 (100), 131 (21), 130 (14), 114 (13). Anal. calcd for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.47. Found: C, 72.54; H, 6.13; N, 5.48.

Data for 35. Yield, 68%; mp 84−86 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.39 (s, 3H, COCH$_3$), 3.08 (dd, J = 4.6 Hz, J = 17.4 Hz, 1H, 4-H$_a$), 3.66−3.73 (m, 4H, 4-H$_b$, COOCH$_3$), 3.83 (s, 3H, =CH-OCH$_3$), 5.01 (s, 2H, CH$_2$), 5.54 (dd, J = 4.4 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.92−7.01 (m, 4H, ArH), 7.19 (dd, J = 4.4 Hz, J = 8.8 Hz, 3H, ArH), 7.32−7.35 (m, 2H, ArH), 7.51 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.64 (d, J = 8.4 Hz, 2H, ArH). EI MS: *m/z* (%) 503 ([M + 1]$^+$, 9), 502 (M$^+$, 28), 255 (25), 204 (19), 146 (26), 144 (100), 131 (24), 114 (23), 102 (23). Anal. calcd for $C_{29}H_{27}FN_2O_5$: C, 69.31; H, 5.42; N, 5.57. Found: C, 69.04; H, 5.63; N, 5.30.

Data for 36. Yield, 82%; mp 75−77 °C.^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.40 (s, 3H, COCH$_3$), 3.10 (dd, J = 4.4 Hz, J = 17.6 Hz, 1H, 4-H$_a$), 3.64−3.72 (m, 4H, 4-H$_b$, COOCH$_3$), 3.77 (s, 3H, Ar-OCH$_3$), 3.82 (s, 3H, =CH-OCH$_3$), 5.01 (s, 2H, CH$_2$), 5.52 (dd, J = 4.2 Hz, J = 11.8 Hz, 1H, Ar-CH), 6.75−6.81 (m, 3H, ArH), 6. 92 (d, J = 8.8 Hz, 2H, ArH), 7.17−7.24 (m, 2H, ArH), 7.32−7.34 (m, 2H, ArH), 7.50 (t, J = 4.6 Hz, 1H, ArH), 7.52 (s, 1H, =CH-OCH$_3$), 7.63 (d, J = 8.8 Hz, 2H, ArH). EI MS: *m/z* (%) 514 (M$^+$, 5), 311 (12), 310 (48), 309 (32), 268 (67), 267 (58), 266 (53), 204 (56), 161 (26), 146 (24), 144 (100), 131 (28), 114 (50), 103 (22). Anal. calcd for $C_{30}H_{30}N_2O_6$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.04; H, 6.14; N, 5.26.

Data for 37. Yield, 79%; mp 77−80 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.38 (s, 3H, COCH$_3$), 3.10 (dd, J = 4.2 Hz, J = 17.4 Hz, 1H, 4-H$_a$), 3.63−3.71 (m, 4H, 4-H$_b$, COOCH$_3$), 3.76 (s, 3H, =CH-OCH$_3$), 3.83 (s, 3H, Ar-OCH$_3$), 5.01 (s, 2H, CH$_2$), 5.52 (dd, J = 4.0 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.83 (d, J = 8.0 Hz, 2H, ArH), 6. 93 (d, J = 8.0 Hz, 2H, ArH), 7.14−7.20 (m, 3H, ArH), 7.33 (t, J = 4.4 Hz, 2H, ArH), 7.51 (t, J = 4.2 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.64 (d, J = 8.4 Hz, 2H, ArH). EI MS: *m/z* (%) 515 ([M + 1]$^+$, 9), 514 (M$^+$, 40), 310 (39), 268 (29), 267 (54), 204 (44), 146 (22), 144 (100), 130 (22), 130 (14), 114 (17), 102 (17). Anal. calcd for $C_{30}H_{30}N_2O_6$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.75; H, 6.42; N, 5.47.

Data for 38. Yield, 86%; mp 112−114 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.27 (s, 9H, t-Bu), 2.41 (s, 3H, COCH$_3$), 3.12 (dd, J = 4.4 Hz, J = 17.2 Hz, 1H, 4-H$_a$), 3.64−3.72 (m, 4H, 4-H$_b$, COOCH$_3$), 3.83 (s, 3H, =CH-OCH$_3$), 5.01 (s, 2H, CH$_2$), 5.56 (dd, J = 4.0 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.92 (d, J = 8.8 Hz, 2H, ArH), 7.13−7.20 (m, 3H, ArH), 7.30−7.34 (m, 4H, ArH), 7.51 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.63 (d, J = 8.8 Hz, 2H, ArH). EI MS: *m/z* (%) 540 (M$^+$, 7), 293 (15), 204 (51), 176 (13), 145 (100), 130 (31), 116 (12), 114 (33), 102 (38). Anal. calcd for $C_{33}H_{36}N_2O_5$: C, 73.31; H, 6.71; N, 5.18. Found: C, 73.16; H, 6.68; N, 5.07.

Data for 39. Yield, 87%; mp 67−69 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.38 (t, J = 7.0 Hz, 3H, OCH$_2$CH$_3$), 2.38 (s, 3H, COCH$_3$), 3.11 (dd, J = 3.8 Hz, J = 17.4 Hz, 1H, 4-H$_a$), 3.63−3.71 (m, 4H, 4-H$_b$, COOCH$_3$), 3.84 (s, 3H, =CH-OCH$_3$), 3.98 (dd, J = 7.0 Hz, J = 14.2 Hz, 2H, OCH$_2$CH$_3$), 5.01 (s, 2H, CH$_2$), 5.52 (dd, J = 4.0 Hz, J = 11.6 Hz, 1H, Ar-CH), 6.82 (d, J = 8.8 Hz, 2H, ArH), 6.93 (d, J = 8.8 Hz, 2H, ArH), 7.13 (d, J = 8.4 Hz, 2H, ArH), 7.19 (dd, J = 3.4 Hz, J = 5.8 Hz, 1H, ArH), 7.32−7.35 (m, 2H, ArH), 7.51 (t, J = 4.4 Hz, 1H, ArH), 7.59 (s, 1H, =CH-OCH$_3$), 7.64 (d, J = 9.2 Hz, 2H, ArH). EI MS: *m/z* (%) 528 (M$^+$, 8), 281 (18), 205 (64), 204 (68), 146 (26), 145 (100), 144 (70), 131 (20), 114 (23), 102 (18). Anal. calcd for $C_{31}H_{32}N_2O_6$: C, 70.44; H, 6.10; N, 5.30. Found: C, 70.39; H, 6.21; N, 5.06.

X-ray Diffraction. A yellow plate of **12** (0.20 mm × 0.10 mm × 0.10 mm) was mounted on a quartz fiber. Cell dimensions and intensities were measured at 293 K on a Bruker SMART CCD area detector diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å); θ_{max} = 25.00; 12589 measured reflections; 4569 independent reflections (R_{int} = 0.1063) of which 2421 had $|F_o| > 2|F_o|$. Data were corrected for Lorentz and polarization effects and for absorption (T_{min} = 0.7377; T_{max} = 0.8548). The structure was solved by direct methods using SHELXS-97 (*19*); all other calculations were performed with Bruker SAINT System and Bruker SMART programs (*20*). Full-matrix least-squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.2000P)^2 + 0.0000P]$ gave final values of R = 0.1680, ωR

Table 2. Insecticidal Activities of Compounds **9**, **10**, **13**, **16**, and **17**

		500 μg mL^{-1} (in vivo)[a]		
		M. separata		
compd	R^1		LC_{50} (μg mL^{-1})	*T. cinnabarnus*
9	4-*t*-BuC_6H_4	+++++		++++
10	4-ClC_6H_4	+++++		−
13	3,4-OCH_2O-C_6H_3	+++++	26.6	−
16	4-MeC_6H_4	++++		−
17	4-EtC_6H_4	+++++		−
	chlorfenapyr	+++++	18.5	

[a] Rating system for the death percentage: +++++, 100%; ++++, ≥90%; +++, ≥80%; ++, ≥70%; +, ≥60%; and −, <60%.

= 0.4824, and GOF(F) = 1.773 for 386 variables and 2650 contributing reflections. The maximum shift/error = 0.000(3), and max/min residual electron density = 1.201/−1.297 e Å^{-3}. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Evaluation of Fungicidal Activities. The in vivo fungicidal preventive activities of compounds **6**−**16**, **17**−**23**, and **24**−**39** against cucumber *Pseudoperoniospora cubensis*, *Sphaerotheca fuliginea*, *Botrytis cinerea*, and *Rhizoctonia solani* were tested according to the procedure described previously (*21*−*23*). Cucumber plants were grown under greenhouse conditions (T = 20 ± 5 °C, RH = 90 ± 10%) in plastic planting pots (6 cm diameter × 10 cm). The tested compounds dissolved in acetone/distilled water (1:4 v/v) containing Tween 80 (0.4 μg mL^{-1}) at the given concentration were sprayed over the plant. One day later, the cucumber plants were inoculated by a spore suspension. One week later, the symptoms were examined. Three replicates were done for each concentration. The inhibition percentage was expressed as the mean of values obtained in three independent experiments. The results are listed in **Table 1**, in which the inhibition percentage was expressed as the mean of values obtained in three independent experiments. Kresoxim-methyl, a commercial fungicide, was used as a control.

Evaluation of Insecticidal Activities. The insecticidal test of compounds **6**−**16**, **17**−**23**, and **24**−**39** were carried out according to the previous procedure (*24*−*26*) with the following insect species: *Aphis medicagini*, *Nilaparvata legen*, *Mythima separata*, and *Tetranychus cinnabarnus*. These insects were reared in a room maintained at 25 (±1) °C, 60 (±5)% relative humidity, and 14 h light photoperiod. Stock solutions of each test compound were prepared in acetone at a concentration of 1.0 g L^{-1} and then diluted to the required test concentrations with water containing Triton X-100 (0.1 mL L^{-1}). Groups of 10 insects of each species were transferred to glass Petri dishes and sprayed with test solutions using a Potter sprayer. After air drying, they were kept in a room for normal cultivation. The mortality was determined in 72 h by the number and size of live larvae in the treated bottles relative to that in the untreated controls. In the case of *N. lugen*, rice seedlings (second semester) were dipped in the test solution for 5 s, air-dried, and then placed in a large test tube. Each test rube contained 20 seedlings. Twenty insects (fifth instar) were introduced into the tube, and the mouth of the tube was covered with white cheesecloth. The tube was kept at room temperature, and the number of live and dead insects was counted after 72 h. In a control experiment, carried out under the same conditions, 1 mL of acetone was applied on each insect. All experiments and the respective controls were carried out in three replicates, and the data were subjected to probit analysis. The results were shown in **Table 2**, and Chlorfenapyr was used as a control.

RESULTS AND DISCUSSION

Synthetic Chemistry and Structure Characterization. The synthetic route for the target compounds is outlined in **Scheme 3**. The starting materials chalcones **40**, which were prepared in good yields according to our previously reported method (*18*), reacted with hydrazine monohydrate in acetate acid to afford the key intermediates pyrazolines **41**. Then, compound **41** reacted with (*E*)-methyl 2-[2-(bromomethyl)phenyl]-3-methoxyacrylate **42** to afford the target compounds **6**−**39** in yields of 61−89%.

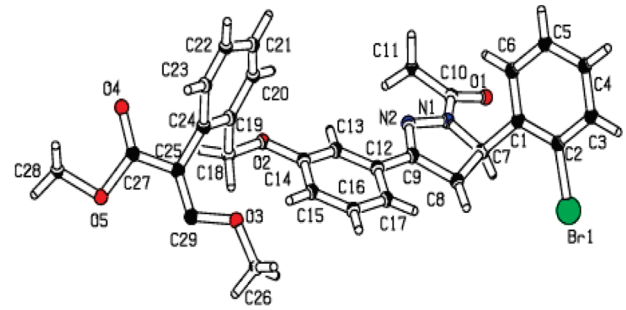


Figure 1. Molecular structure of **12**.

The structures of all of the target compounds were characterized by ^{1}H NMR, EI-MS spectrum, and elemental analyses. In addition, the crystal structure of **12** was determined by X-ray diffraction analyses. As shown in **Figure 1**, the β-methoxyacrylate group adopts an *E*-configuration and the dihedral angle of the pyrazoline and the 2-bromobenzene planes showed a gauche conformation with an angle of 73.41° that is affected by the bulky acetyl group.

Biological Activities and Structure−Activity Relationships. The results of in vivo fungicidal activities of compounds **6**−**39** against *P. cubensis*, *S. fuliginea*, *B. cinerea*, and *R. solani* were listed in **Table 1**. For the convenience of structure−activity relationship analysis, according to the relative position of the pyrazoline ring and the β-methoxyacrylate pharmacophore, compounds **6**−**16**, **17**−**23**, and **24**−**39** were defined as *meta*-derivatives, *ortho*-derivatives, and *para*-derivatives, respectively. Although it seems impossible to extract an obvious structure−activity relationship from the data shown in **Table 1**, we can conclude clearly that all compounds did not exhibit fungicidal activity against *B. cinerea* and *R. solani* at the concentration of 200 μg mL^{-1} (data not included). In addition, *ortho*-derivatives also did not shown obvious fungicidal activity against *P. cubensis* and *S. fuliginea* at the same concentration. In most cases, *meta*-derivatives displayed higher fungicidal activity against *P. cubensis* than *para*-derivatives, for example, compounds **6** and **29** (R = 2-FC_6H_4), **9** and **38** (R = 4-*t*-BuC_6H_4), **14** and **24** (R = thiophen-2-yl), **15** and **39** (R = 4-EtOC_6H_4), and **16** and **30** (R = 4-MeC_6H_4). However, *meta*-derivative **10** (R = 4-ClC_6H_4) showed lower fungicidal activity against *P. cubensis* than the corresponding *para*-derivative **27**.

It is shown in **Table 1** that, within the series of *meta*-derivatives, only compound **13** (R = 3,4-$OCH_2OC_6H_3$) displayed excellent fungicidal activities (≥90%) against both *P. cubensis* and *S. fuliginea* at the concentration of 200 μg mL^{-1}. Therefore, the IC_{50} values of compound **13** were determined and the commercial product Kresoxim-methyl was used as a control. It was found that the IC_{50} values of compound **13** against *P. cubensis* and *S. fuliginea* are 26.6 and 57.6 μg mL^{-1}, respectively, while the IC_{50} values of Kresoxim-methyl against *P. cubensis* and *S. fuliginea* are 24.1 and 1.6 μg mL^{-1}. These results indicated that compound **13** displayed comparable fungicidal activity with Kresoxim-methyl against *P. cubensis*.

The in vivo insecticidal activities of compounds **6**−**39** against *A. medicagini*, *N. legen*, *M. separata*, and *T. cinnabarnus* were tested, and only compounds **9**, **10**, **13**, **16**, and **17** were found to be active. It was found that compounds **9**, **10**, **13**, and **17** did not display insecticidal activity against *A. medicagini* and *N. legen* (data not shown) but showed excellent insecticidal activity against *M. separata* at the concentration of 500 μg mL^{-1} as

shown in **Table 2**. It is very interesting that compound **13** displayed both fungicidal activity and insecticidal activity. Therefore, we carried out further insecticidal activity assay for compound **13**, and it was found that the LC_{50} value of compound **13** against *M. separata* is 26.6 μg mL^{-1}, while that of the commercial control chlorfenapyr is 18.5 μg mL^{-1}.

In conclusion, by introducing the β-methoxyacrylate pharmacophore into the scaffold of *N*-acetyl-3,5-diarylpyrazoline, a pyrazoline type lead exhibiting both fungicidal and insecticidal activities was successfully identified. The fungicidal IC_{50} values of the most potent compound **13**, 1-aceto-3-{*m*-[*o*-(*E*-1-methoxycarboxyl-2-methoxy)-1-yl]benzyloxy}phenyl-5-(benzo[1,3]dioxol-6-yl)-4,5-dihydropyrazoline, were 26.6 and 57.6 μg mL^{-1} against *P. cubensis* and *S. fuliginea*, respectively. Meanwhile, compound **13** was also found to display good insecticidal activity against *M. separata* with a LC_{50} value of 26.6 μg mL^{-1}. These results indicated that compound **13** could be used as a lead for further developing new pyrazoline type candidates bearing both fungicidal and insecticidal activities.

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Supporting Information Available: Characterization data including ^{1}H NMR, MS, and melting points for the intermediate **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

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