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Stereoselective synthesis and fungicidal activities of (*E*)-α-(methoxyimino)-benzeneacetate derivatives containing 1,3,4-oxadiazole ring

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Abstract—Fifteen novel (*E*)-α-(methoxyimino)-benzeneacetate derivatives, the analogues of strobilurins, which contain two pharmacophoric substructures of (*E*)-methyl methoxyiminoacetate moiety and 1,3,4-oxadiazole ring were stereoselectively synthesized. It was first found that the coupling reaction could give stereoselectively the key intermediate (*E*) and (*Z*)-methyl 2-(hydroxyimino)-2-*o*-tolylacetate **2** with a ratio of 14:1. The preliminary bioassays indicated that all the compounds **1** showed potent fungicidal activity against *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberella zeae*, *Physalospora piricola* and *Bipolaris mayclis*, and all of the tested compounds **1a**–**1o** had more potent fungicidal activities against *R. solani* than Kresoxim-methyl.

Strobilurins have been an important class of agricultural fungicides such as Kresoxim-methyl and Trifloxystrobin.[1,2] These compounds exhibit strong fungicidal activity against various fungi by binding to electron transfer at the ubiquinol-oxidation centre (Qo-site) of the bc_1-enzyme complex (complex III).[1–3] These well-known strobilurins have an (*E*)-methyl methoxyiminoacetate moiety as a common pharmacophoric substructure, isosteric with (*E*)-methyl β-methoxyacrylate group and these (*E*)-configured compounds have been shown to exhibit biological activity higher than that of the corresponding (*Z*)-stereoisomers.[1] The methods used for the synthesis of strobilurin fungicides include the lactone ring opening of phthalide,[1] the Pinner reaction of acylcyanides[4,5] and the coupling reactions assisted by organometallic reagents.[6] Although the required (*E*)-isomer generally predominates, all these approaches tend to produce mixtures of stereoisomers. On the other hand, 1,3,4-oxadiazole ring derivatives also exhibit a broad spectrum of biological activities such as fungicidal,[7,8] antimicrobial and antibacterial activities,[9] and 1,3,4-oxadiazole ring is a major pharmacophoric substructure. In view of these facts, we will have developed a new and efficient method for stereoselective synthesis of methyl (*E*)-α-(methoxyimino)-benzeneacetate and synthesized some novel analogues of strobilurins which contain both (*E*)-methyl methoxyiminoacetate and 1,3,4-oxadiazole ring moieties, methyl (*E*)-α-(methoxyimino)-2-[(5-aryl-1,3,4-oxadiazole-2-mercapto)-methyl]-benzeneacetates **1**, in order to obtain better fungicidal activities.

According to retro-synthetic analyses and the literature,[2,6] both methyl 2-oxo-2-arylacetate and methyl 2-hydroxyimino-2-arylacetate **2** are the key intermediates of the analogues of strobilurins. Our initial goal was to develop a new method for synthesis of methyl 2-oxo-2-arylacetate in which the commercially available and cheap arylamines and glyoxylic acid were used as starting material based on previous literature.[10,11] In our work, we first found that the coupling reaction between aryldiazonium salt derived from 2-methylaniline and methyl 2-(hydroxyimino)-acetate gave stereoselectively oxime **2** in 44% yield.[12] The *E*/*Z* ratio determined in the crude mixture by ^{1}H NMR spectroscopy was ca. 14:1. After further column chromatography purification, the purity of *E*-**2** could exceed 99% in

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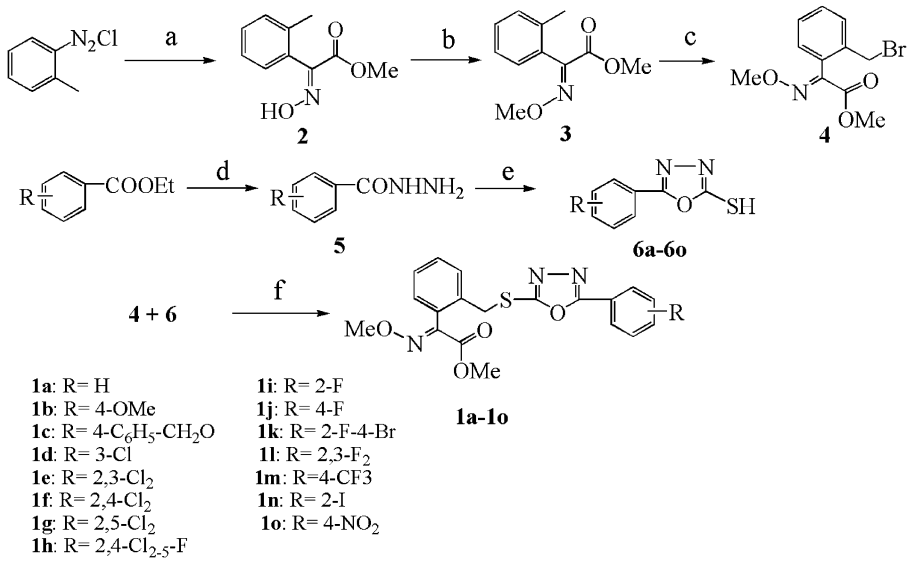
41% yield. The compound *E*-**2** was methylated by sodium hydride-dimethyl sulfate in 91% yield and successively brominated with NBS to afford oxime ether **4** in 81% yield.

The designed compounds were synthesized according to Scheme 1.The starting hydrazide **5** was obtained by prolonged heating of benzoic acid ethyl ester with hydrazine hydrate in methanol. Hydrazide **5** was reacted with carbon disulfide and potassium hydroxide, in ethanol, followed by acidification to yield 5-aryl-2-mercapto-1,3,4-oxadiazoles **6a**–**6o** (56–89%).[13] The targeted products **1a**–**1o** were synthesized by reaction of oxime ether **5** with different oxadiazoles **6a**–**6o** in the presence of $NaOCH_3$ in dry DMF (49–85%). The structures of **1a**–**1o** were confirmed by element analyses, IR, ^1H NMR, ^{13}C NMR and EI-MS spectral data.[14] The (*E*)-configurations of compounds **1** were assigned on the basis of their 2D-NOESY spectra of ^1H NMR, and the 2D-NOESY experiments all showed the absence of the cross-peak between the resonance of the $NOCH_3$ protons and that of 6-ArH.

The fungicidal activities of the title compounds **1** were tested at a concentration of 50 μg/ml by the modified method from the literature.[15] The five fungi used, *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberella zeae*, *Physalospora piricola* and *Bipolaris mayclis*, belong to the group of field fungi and were isolated from corresponding crops. The results of preliminary bioassays were compared with that of commercial agricultural fungicide, Kresoxim-methyl. As indicated in Table 1, all the compounds **1a**–**1o** showed potent fungicidal activities against all of the fungi tested, and the fluori-



Scheme 1. Stereoselective synthesis of (*E*)-α-(methoxyimino)-benzeneacetate derivatives **1**. Reagents and conditions: (a) MeO_2C–CH=NOH, $CuSO_4$–Na_2SO_3, pH 6–7; (b) NaH, Me_2SO_4; (c) NBS, CCl_4, reflux; (d) $NH_2NH_2{\cdot}H_2O$, reflux 6 h; (e) CS_2, KOH, reflux 8 h; (f) CH_3ONa /DMF, overnight.

Table 1. Fungicidal activities of (*E*)-α-(methoxyimino)-benzeneacetate derivatives **1a**–**1o** (50 μg/ml, inhibition %)

Compound	R	Inhibition %				
		Rhizoctonia solani	*Botrytis cinereapers*	*Gibberella zeae*	*Physalospora piricola*	*Bipolaris mayclis*
1a	H	92.4	97.6	79.4	94.9	88.0
1b	4-MeO	91.8	94.2	85.7	93.8	92.5
1c	4-C_6H_5-CH_2O	98.0	90.6	89.2	96.9	95.0
1d	3-Cl	94.4	85.4	96.9	92.6	90.9
1e	2,3-Cl_2	91.6	83.3	84.3	96.7	84.0
1f	2,4-Cl_2	92.6	98.8	74.3	88.9	85.7
1g	2,5-Cl_2	97.0	88.5	90.6	100	82.7
1h	2,4-Cl_2-5-F	97.8	98.8	88.6	100	81.6
1i	2-F	92.6	97.6	98.0	100	92.3
1j	4-F	97.9	100	98.6	100	91.7
1k	2-F-4-Br	97.9	100	85.7	100	92.9
1l	2,3-F_2	100	100	98.6	100	96.4
1m	4-CF_3	95.6	84.6	93.8	100	81.8
1n	2-I	90.2	96.2	98.4	96.3	86.4
1o	4-NO_2	85.9	88.5	92.5	96.3	86.4
Kresoxim-methyl		66.1	97.2	96.8	98.5	90.6

nated compounds such as **1j** and **1l** showed activity higher than that of Kresoxim-methyl. In particular, all of the tested compounds **1a**–**1o** had more potent fungicidal activities against *R. solani* than Kresoxim-methyl. These results also demonstrated that the introduction of 1,3,4-oxadiazole rings to the strobilurin fungicides might improve their fungicidal activities.

In conclusion, 15 novel (*E*)-α-(methoxyimino)-benzeneacetate derivatives were stereoselectively synthesized, and their activities were tested. All of the tested compounds showed potent fungicidal activity against all of the fungi tested, especially it was found that compounds **1a**–**1o** had higher fungicidal activities against *R. solani* than Kresoxim-methyl.

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12. Methyl 2-hydroxyimino-2-*o*-tolylacetate **2**: 3.92 g (38 mmol) methyl 2-hydroxyiminoacetate and 17 ml water were placed in a flask. To it were added 0.65 g (2.6 mmol) of cupric sulfate hydrate, 0.1 g (0. 79 mmol) of sodium sulfite, and a solution of 16 g of sodium acetate hydrate in 18 ml water. The solution is maintained at 5–10 °C and stirred vigorously. The fresh neutral diazonium salt (38 mmol) solution was then slowly introduced into the oxime solution. After the addition of the diazonium salt solution was completed, the stirring was continued for an additional hour. Then the mixture was stirred at 10–20 °C for 2 h, the reaction mixture was extracted with ether. Combined organic layers were washed with an aqueous 10% sodium bicarbonate solution then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to column chromatography using a mixture of *n*-hexane and ethyl acetate (4:1) as an eluent to obtain the compound **2**. (*Z*)-isomer (upper spot) yield: oil, 0.22 g, 3%, IR (KBr): 3353, 1728, 1620, 1445, 1314, 1032, 930, 757, 732, 670 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) $\delta = 2.36$ (3H, s, Ar-CH_3), 3.88 (3H, s, –COOMe),7.27–7.22 (3H, m, 3 × Ar-H), 7.32 (1H, d, $J = 7.8$ Hz, 6-Ar-H). (*E*)-isomer (down spot) yield: oil, 3.01 g, 41%, IR (KBr): 3349, 1732, 1622, 1443, 1310, 1034, 930, 757, 730, 696 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) $\delta = 2.23$ (3H, s, Ar-CH_3), 3.83 (3H, s, –COOMe), 7.15 (1H, d, $J = 7.8$ Hz, 3-Ar-H), 7.25–7.28 (2H, m, 2 × Ar-H), 7.33 (1H, t, $J = 7.2$ Hz, 4-Ar-H), 10.15 (1H, s, –OH).
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14. General procedure for synthesis of (*E*)-α-(methoxyimino)-benzeneacetate derivatives **1a**–**1o**: compounds **6a**–**6o** (4.6 mmol) were added to a solution of MeONa 0.25 g (4.6 mmol) in 10 ml absolute methanol and then refluxed for 0.5 h. After the methanol was removed under reduced pressure, to the residue were added dry DMF (30 ml) and 1.20 g (4.2 mmol) of compound (*E*)-**4** and then stirred at room temperature overnight. The mixture was mixed with water and extracted with ethyl ether, combined organic layers were washed with an aqueous 5% NaOH solution then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to column chromatography using a mixture of benzene and ethyl acetate (8:1) as an eluent or crystallized from absolute ether to obtain compound (*E*)-**1**.
Compound **1a**: 80%; mp 242.1–243.3 °C. IR (KBr) *v*: 3050, 2963, 1727, 1602, 1068, 1017 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) $\delta = 3.90$ (s, 3H, COOMe), 4.09 (s, 2H, $NOCH_3$), 4.41 (s, 3H, SCH_2–), 7.18 (d, $J = 7.2$ Hz, 2H, 6-ArH), 7.37–7.43 (m, 5H, 3′, 4′, 5′ and 4, 5-ArH), 7.63 (d, 2H, $J = 7.2$ Hz, 3-ArH), 7.98 (d, $J = 7.2$ Hz, 2H, 2′and 6′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.2$, 53.7, 64.4, 124.1, 127.1, 128.6, 129.1, 129.5, 130.4, 130.7, 131.0, 132.1, 134.5, 149.5, 163.7, 164.4, 166.3. MS (70 eV) *m/z* (%): 351 ($M-CH_3O^+$, 0.1), 206 (M–$HetS^+$, 3.7), 116 ($N{\equiv}CArCH_2^+$, 4.2), 105 ($ArC{\equiv}N^+$, 100), 77 (59.8), 40 (50.0). Anal. Calcd for $C_{19}H_{17}N_3O_4S$: C, 59.52; H, 4.47; N, 10.96. Found: C, 59.63; H, 4.26; N, 10.77.
Compound **1b**: 76%, mp 111.2–111.9 °C. IR (KBr) *v*: 3051, 2958, 1728, 1605, 1065, 1017 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) $\delta = 3.87$ (s, 3H, COOMe), 3.90 (s, 3H, OCH_3), 4.09 (s, 2H, $NOCH_3$), 4.39 (s, 3H, SCH_2–), 6.81 (d, $J = 8.4$ Hz, 2H, 3′ and 5′-ArH), 7.18 (d, $J = 8.4$ Hz, 2H, 2′ and 6′-ArH), 7.37–7.42 (m, 2H, 4 and 5-ArH), 7.63 (d, 2H, $J = 7.2$ Hz, 3-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.2$, 53.7, 55.9, 64.4, 115.4, 128.7, 129.1, 130.3, 130.7, 130.9, 134.6, 149.5, 162.7, 163.6, 163.7, 166.3. MS (70 eV) *m/z* (%): 413 (M^+, 6.5), 382 ($M-CH_3O^+$, 18.2), 367 ($M-HCOOCH_3^+$), 206 ($M-HetS^+$, 76.4), 131 (43.4),116 ($N{\equiv}CC_6H_4CH_2^+$, 95.2), 89 (33.5), 59 (48.1). Anal. Calcd for $C_{21}H_{19}F_3N_4O_3S$: C, 58.10; H, 4.63; N, 10.16. Found: C, 58.14; H, 4.59; N, 10.19.
Compound **1c**: 71%; mp151.9–152.1 °C. IR (KBr) *v*: 1040, 2949, 1727, 1601, 1060, 1011 cm^{-1}. ^1H NMR (600 MHz,$CDCl_1$) $\delta = 1.90$(s, 1H, COOMe), 4.09 (s, 2H, $NOCH_1$), 5.11 (s, 1H, OCH_2Ar), 4.19(s, 2H, SCH_2), 7.06 (d, $J = 8.4$ Hz, 2H, 1′ and 5′-ArH), 7.18 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.18–7.45 (m, 6H, $J = 8.4$ Hz, 5 × Ar″H and

5-ArH), 7.41 (t, $J = 7.2$ Hz, 1H, 4-ArH), 7.61 (d, 2H, $J = 7.2$ Hz, 3-ArH); 7.91 (d, $J = 7.2$ Hz, 2H, 2′ and 6′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.0$, 53.4, 64.2, 70.6, 115.5, 127.7, 128.3, 128.5, 128.7, 128.9, 130.1, 130.5, 130.7, 134.4, 136.4, 149.2, 161.6, 163.4, 163.5, 166.0. MS (70 eV) *m/z* (%): 490 (M^+, 15.8), 489 (M^+, 13.0), 443 (62.0), 206 (M−HetS$^+$, 99.7), 146 (50.7), 131 (98.1), 116 ($NCC_6H_4CH_2^+$, 100), 89 (97.9), 59 (48.3). Anal. Calcd for $C_{26}H_{23}N_3O_5S$: C, 63.79; H, 4.74; N, 8.58. Found: C, 63.82; H, 4.71; N, 8.64.

Compound **1d**: 78%, mp 126.2–126.7 °C. IR (KBr) *v*: 3055, 2965, 1725, 1601, 1065, 1017 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.91$ (s, 3H, COOMe), 4.09 (s, 3H, N–OCH_3), 4.41 (s, 2H, –SCH_2), 7.19 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.39 (t, 1H, 5-ArH), 7.41 (d, 1H,$J = 6.6$ Hz, 3-ArH), 7.43 (t, 1H, $J = 6.9$ Hz, 4-ArH), 7.49 (t, 1H, $J = 7.2$ Hz, 5′-ArH), 7.63 (d, 1H, $J = 7.2$ Hz, 4′-ArH), 7.95 (s, 1H, 2′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.2$, 53.7, 64.4, 125.2, 125.6, 127.1, 128.6, 129.2, 130.7, 130.9, 131.0, 132.1, 134.1, 135.6, 149.5, 163.7, 164.9, 165.1. MS (70 eV) *m/z* (%): 418 (M^+, 2.4), 389 (13.7), 387 (M−CH_3O^+, 40.7), 373 (35.7), 371(100), 206 (M−HetS$^+$, 69.1), 146 (20.6), 139(27.3), 116 ($N{\equiv}CC_6H_4CH_2^+$, 20.0). Anal. Calcd for $C_{19}H_{16}ClN_3O_4S$: C,54.61; H, 3.86; N, 8.23. Found: C, 54.65; H, 3.82; N, 8.27.

Compound **1e**: 80%, mp 123.2–124.3 °C. IR (KBr) *v*: 3040, 2973, 1727, 1601, 1067, 1015 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.91$ (s, 3H, COOMe), 4.10 (s, 3H, N-OCH_3), 4.42 (s, 2H, -CH_2-), 7.19 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.33 (t, 1H, 5-ArH), 7.38 (d, 1H, 3-ArH), 7.38–7.42 (m, 3H, 4′,4 and 5′-ArH), 7.68 (dd, 1H, $J = 7.8$ and 1.8 Hz, 4′-ArH), 7.89 (d,$J = 7.8$ Hz, 1H, 6′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.2$, 53.7, 64.4, 125.4, 128.1, 128.6, 129.1, 129.7, 130.3, 130.7, 130.9, 131.9, 133.6, 134.3, 135.5, 149.5, 163.7 (N=C–S), 164.1, 165.5 (COOMe). MS (70 eV) *m/z* (%): 452 (M^+, 5.2), 422 (11.8), 420 (M−$MeOH^+$, 14.2), 407 (83.5), 405 (M−$COOMe^+$, 100), 205 (15.4), 206 (M−HetS$^+$, 9.6), 173 ($diClC_6H_3C{\equiv}O^+$, 18.3), 116 ($N{\equiv}CC_6H_4CH_2^+$, 21.1), 89 (9.8), 59 (10.9). Anal. Calcd for $C_{19}H_{15}Cl_2N_3O_4S$: C, 50.45; H, 3.34; N, 9.29. Found: C, 50.48; H, 3.43; N, 9.17.

Compound **1f**: 75%, mp 108.7–109.5 °C, IR (KBr) *v*: 3065, 2982, 1726, 1599, 1060, 1010 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.91$ (s, 3H, COOMe), 4.09 (s, 3H, N–OCH_3), 4.42 (s, 2H, SH_2–), 7.19 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.37–7.43 (m, 3H, 5′, 4 and 5-ArH), 7.56 (s, 1H, 3′-ArH), 7.64 (d, 1H, $J = 7.2$ Hz, 6′-ArH), 7.87 (d, 1H, $J = 8.4$ Hz, 2′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.2$, 53.7, 64.4, 121.8, 128.1, 128.5, 129.1, 130.3, 130.7, 130.9, 131.6, 131.9, 134.2, 134.3, 138.4, 149.47, 163.7, 163.8, 165.3. MS (70 eV) *m/z* (%): 454 (M+2$^+$, 2.2), 452 (M^+, 3.8), 407 (17.2), 405 (23.6), 389 (13.7), 206 (M−HetS$^+$, 100), 175 (23.5), 173 ($diClC_6H_3C{\equiv}O^+$, 27.6), 146 (50.2), 131 (60.8), 116 ($N{\equiv}CC_6H_4CH_2^+$, 65.1), 89 (11.3), 59 (25.1). Anal. Calcd for $C_{19}H_{15}Cl_2N_3O_4S$: C, 50.45; H, 3.34; N, 9.29. Found: C, 50.49; H, 3.28; N, 9.31.

Compound **1g**: 84%, mp 106.7–107.8 °C. IR (KBr) *v*:3040, 2952, 1727, 1600, 1067, 1017 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.89$ (s, 3H, COOMe), 4.10 (s, 3H, N–OCH_3), 4.42 (s, 2H, –CH_2–), 7.19 (d, $J = 7.2$ Hz and 1.2 Hz, 1H, 6-ArH), 7.65 (d, $J = 7.2$ Hz, 1H, 3-ArH), 7.38–7.40 (m, 2H, 4′ and 5′-ArH), 7.42–7.47 (m, 3H, 4 and 5-ArH) 7.91 (d, 1H, $J = 2.4$ Hz, 6′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.21$ (NCH_3), 36.17 (SCH_2), 53.71 ($COOCH_3$), 64.43 ($NOCH_3$), 124.5, 128.6, 129.2, 130.4, 130.7, 130.9, 140.0, 131.7, 132.9, 133.6, 134.3, 149.5 (Ar-C=N), 163.5 (N=C–S), 163.7 (Ar′-C=N), 165.5 (COOMe). MS (70 eV) *m/z* (%): 452 (M^+, 3.8), 422 (11.2), 420 (M−CH_3O^+, 14.8), 407 (86.0), 405 (100), 206 (M−HetS$^+$, 63.5), 205 (94.5), 176 (30.3), 173 (39.5), 147 (35.5), 116 ($N{\equiv}CC_6H_4CH_2^+$, 42.5), 89 (17.1), 59 (16.7). Anal. Calcd for $C_{19}H_{15}Cl_2N_3O_4S$: C, 50.45; H, 3.34; N, 9.29. Found: C, 50.39; H, 3.40; N, 9.33.

Compound **1h**: 77%, mp 101.5–102.4 °C, IR (KBr) *v*: 3043, 2957, 1725, 1601, 1067, 1016 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.92$ (s, 3H, COOMe), 4.09 (s, 3H, N–OCH_3), 4.32 (s, 2H, SCH_2), 7.19 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.34 (t, $J = 7.8$ Hz, 1H, 4-ArH), 7.40 (t, $J = 8.1$ Hz, 1H, 5-ArH), 7.61 (d, $J = 6.6$ Hz, 1H, 3′-ArH), 7.64 (d, 1H, 3-ArH), 7.75 (d, $J = 7.2$ Hz, 1H, 5′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.3$, 53.7, 64.4, 118.4, 118.6, 125.9, 129.2, 130.4, 130.7, 131.0, 131.2, 132.1, 132.7, 133.0, 134.3, 149.5, 157.6, 163.7, 165.7. MS (70 eV) *m/z* (%): 470 (M+1$^+$, 1.7), 449 (9.5), 438 (M−MeO^+, 12.4), 425 (83.7), 423 (100), 407 (32.1), 405 (38.5), 206 (M−HetS$^+$, 11.5), 193 (13.9), 191 ($diClFC_6H_3C{\equiv}O^+$, 22.7), 146 (10.8), 131 (4.0), 116 ($NCC_6H_4CH_2^+$, 26.9), 89 (13.3), 59 (15.6). Anal. Calcd for $C_{19}H_{14}Cl_2FN_3O_4S$: C, 48.52; H, 3.00; N, 8.93. Found: C, 48.56; H, 3.06; N, 8.86.

Compound **1i**: 73%, mp 160.1–160.4 °C, IR (KBr) *v*:3050, 2949, 1727, 1602, 1066, 1018 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.91$ (s, 3H, $COOCH_3$), 4.01 (s, 3H, N–OCH_3), 4.42 (s, 2H, SCH_2–), 7.19 (d, $J = 6.6$ Hz, 1H, 6-ArH), 7.23 (t, $J = 9.0$ Hz, 1H, 5-ArH), 7.28 (t, $J = 7.8$ Hz, 1H, 4-ArH), 7.40 (d, $J = 7.8$ Hz, 1H, 3′-ArH), 7.41 (d, $J = 7.2$ Hz, 1H, 3-ArH), 7.52 (t, $J = 6.6$ Hz, 1H, 5′-ArH), 7.64 (d, $J = 7.2$ Hz, 1H, 6′-ArH), 7.98 (t, $J = 6.6$ Hz, 1H, 4′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.2$, 53.7, 64.4 ($NOCH_3$), 125.1, 128.6, 129.1, 130.3, 130.8, 131.1, 133.8, 133.9, 134.5, 149.5, 159.4, 161.1, 163.0, 163.7, 165.2 (Ar′–C=N). MS (70 eV) *m/z* (%): 401 (M^+, 4.81), 206 (M−ArCH=NO^+, 100), 146 (20.5), 131 (14.0), 116 ($N{\equiv}CC_6H_4CH_2^+$, 32.8), 89 (13.1), 59 (12.2). Anal. Calcd for $C_{19}H_{16}FN_3O_4S$: C, 56.85; H, 4.02; N, 10.47. Found: C, 56.79; H, 4.10; N, 10.52.

Compound **1j**: 85%, mp 93.3–93.9 °C, IR (KBr) *v*: 3230, 2984, 1727, 1600, 1064, 1014 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.90$ (s, 3H, $COOCH_3$), 4.09 (s, 3H, N–OCH_3), 4.45 (s, 2H, SCH_2–), 7.19 (m, 3H, 2′, 6′ and 6-ArH), 7.39 (t, 1H, $J = 5.7$ Hz, 4-ArH), 7.40 (t, 1H, $J = 5.7$ Hz, 5-ArH), 7.62 (d, 1H, $J = 7.2$ Hz, 3-ArH), 7.98 (dd, 2H, $J = 9.0$Hz and $J = 5.40$ Hz, 3′ and 5′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.3$, 53.7, 64.4, 116.8, 116.9, 120.4, 128.6, 129.2, 129.4, 129.5, 130.4, 130.7, 130.9, 134.5, 149.5, 164.3, 164.4 (Ar′6-C), 165.5 (COOMe), 166.0 (Ar′–C=N). Anal. Calcd for $C_{19}H_{16}FN_3O_4S$: C, 56.85; H, 4.02; N, 10.47. Found: C, 56.88; H, 4.08; N, 10.41.

Compound **1k**: 64%, mp 91.5–92.5 °C. IR (KBr) *v*: 3065, 2945, 1725, 1601, 1060, 1010 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.90$ (s, 3H, $COOCH_3$), 4.08 (s, 3H, N–OCH_3), 4.41 (s, 2H, SCH_2–), 7.17 (d, $J = 7.2$ Hz, 1H, 6-ArH), 7.37–7.44 (m, 4H, 3′, 5′, 6′ and5-ArH), 7.62 (d, 1H, $J = 7.2$ Hz, 3-ArH), 7.86 (d, 1H, $J = 8.1$ Hz, 4-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.7$ (SCH_2) 53.7 ($COOCH_3$), 64.4 ($NOCH_3$), 127.0, 127.1, 128.6, 128.7, 129.1, 130.3, 130.7, 131.5, 134.4, 149.5, 160.7, 162.5, 163.7, 165.2. MS (70 eV) *m/z* (%): 480 (M^+, 3.6), 451 (14.8), 449 (M−$COOCH_{3+}$, 12.0), 435 (11.0), 433 (81.1), 201 (25.3), 146 (12.1), 116 ($N{\equiv}CC_6H_4CH_2^+$, 25.7), 89 (11.3), 59 (11.9). Anal. Calcd for $C_{19}H_{15}BrFN_3O_4S$: C, 47.51; H, 3.15; N, 8.75. Found: C, 47.52; H, 3.18; N, 8.78.

Compound **1l**: 79%, mp 107.6–108.5 °C. IR (KBr) *v*: 3050, 2955, 1726, 1600, 1066, 1013 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.91$ (s, 3H, $COOCH_3$), 4.09 (s, 3H, N–OCH_3), 4.40 (s, 2H, SCH_2–), 7.19 (d, $J = 6.6$ Hz, 1H, 6-ArH), 7.28–7.74 (m, 5H, 3′, 4′, 5′ and 3, 4-ArH), 7.80 (d, $J = 8.4$ Hz, 1H, 6′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 35.3$, 53.7, 64.5, 116.6, 118.8, 123.8, 128.7, 129.2,

129.2, 130.3, 130.7, 131.1, 134.4, 149.5, 159.4, 161.1, 163.7, 164.6, 164.9. MS (70 eV) *m/z* (%): 419 (M^+, 1.7), 388 (14.6), 374 (100), 355 (29.3), 206 (53.3), 205 (88.4), 146 (25.7), 116 ($N{\equiv}CC_6H_4CH_2^+$, 39.3), 89 (14.9), 59 (13.3). Anal. Calcd for $C_{19}H_{15}F_2N_3O_4S$: C, 54.41; H, 3.60; N, 10.02. Found: C, 54.43; H, 3.58; N, 10.08.

Compound **1m**: 82%, IR (KBr) *v*: 3055, 2950, 1727, 1600, 1060, 1015 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 3.92 (s, 3H, COOMe), 4.10 (s, 3H, N–OCH_3), 4.45 (s, 2H, –CH_2–), 7.20 (dd, J = 7.2 Hz and J = 1.2 Hz, 1H, 6-ArH), 7.39 (t, 1H, J = 7.2 Hz, 4-ArH), 7.42 (t, 1H, J = 7.2 Hz, 5-ArH), 7.65 (d, J = 7.2 Hz, 1H, 3-ArH), 7.76 (d, 1H, J = 8.4 Hz, 2′ and 6′-ArH), 8.15 (d, 2H,J = 8.4 Hz, 3′ and 5′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 37.4, 54.2, 64.70, 126.6, 126.7, 127.1, 127.5, 128.7, 129.2, 130.4, 130.7, 130.9, 134.3, 149.8, 162.5, 161.7, 165.59. MS (70 eV) *m/z* (%): 451 (M^+, 1.8), 420 (12.0), 406 (8.2), 173($CF_3C_6H_5C{\equiv}N^+$, 100), 206 (76.4), 146 (42.8), 116 ($N{\equiv}CC_6H_4CH_2^+$, 67.2), 59 (73.1). Anal. Calcd for $C_{20}H_{16}F_3N_3O_4S$: C, 53.21; H, 3.57; N, 9.31. Found: C, 53.25; H, 3.55; N, 9.34.

Compound **1n**: 49%, IR (KBr) *v*: 3050, 2965, 1727, 1601, 1063, 1015 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 3.92 (s, 3H, COOMe), 4.09 (s, 3 H, N–OCH_3), 4.42 (s, 2H, –SCH_2), 7.19 (d, J = 7.2 Hz, 1H, 6-ArH), 7.35–7.41 (m, 2H), 7.43 (t, 1H, J = 7.5 Hz, 4-ArH), 7.61 (d, 1H, J = 7.5 Hz,3-ArH), 7.77 (d, 1H, J = 7.8 Hz, 6′-ArH), 8.04 (d, 1H, 3′-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 35.1, 53.7, 64.4, 94.5 (2′-C), 128.6, 128.7, 129.1, 129.2, 130.4, 130.8, 130.9, 131.6, 132.8, 134.4, 141.8, 149.5, 163.7, 165.1, 165.7. MS (70 eV) *m/z* (%): 509 (M^+, 0.1), 463 (8.7), 206 (M−$HetS^+$, 100), 131 (100), 116(92.5), 89 (41.3). Anal. Calcd for $C_{19}H_{16}IN_3O_4S$: C, 44.81; H, 3.17; N, 8.25. Found: 44.78; H, 3.19; N, 8.19.

Compound **1o**: 64%, IR (KBr) *v*: 3062, 2945, 1726, 1601, 1072, 1018 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 3.89 (s, 3H, COOMe), 4.08 (s, 2H, $NOCH_3$), 4.37 (s, 3H, S–CH_2), 6.90–6.95 (d, J = 8.4 Hz, 2H, 3′ and 5′-ArH), 7.17 (d, J = 7.2 Hz, 1H, 6-ArH), 7.40 (t, 1 H, J = 7.2 Hz, 4-ArH), 7.37 (t, 1H, J = 7.2 Hz, 5-ArH), 7.62 (d, 1H, J = 7.2 Hz, 3-ArH), 7.78 (d, J = 8.4 Hz, 2H, 2′ and 6-ArH). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 35.3, 53.7, 64.8, 115.1, 128.7, 129.1, 130.3, 130.7, 130.9, 134.7, 149.5, 150.1, 162.6, 163.7, 165.3. MS (70 eV) *m/z* (%): 400 (M^+, 28), 433 (M−CH_3O^+, 27.3), 229 (96.5), 206 (75.0), 171 ($CF_3C_6H_5C{\equiv}N^+$, 19.0), 131 (100), 116 (99.7), 59 (56.0). Anal. Calcd for $C_{19}H_{16}N_4O_6S$: C, 53.27; H, 3.76; N, 13.08. Found: C, 53.28; H, 3.77; N, 13.09.

15. Wang, H.-Q.; Ding, M.-W.; Liu, Z.-J. *Heteroat. Chem.* **2004**, *15*, 333, and therein reference.