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Research Article

Design, Synthesis, and Biological Activity of Oxime Ether Strobilurin Derivatives Containing Indole Moiety as Novel Fungicide

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Twenty-one novel oxime ether strobilurins containing indole moiety, which employed an indole group to stabilize the *E*-styryl group in Enoxastrobin, were designed and synthesized. The biological assay indicated that most compounds exhibited potent fungicidal activities. The structure–activity relationship study demonstrated that the synthesized methyl 3-methoxypropenoate oxime ethers 7b–e exhibited remarkably high activities among all the synthesized oxime ether compounds 7. Moreover, the fungicidal activities of methyl α-(methoxyimino)benzeneacetate oxime ethers compounds 7f–i and N-methoxy-carbamic acid methyl esters compounds 7j–m showed significant differences compared to the corresponding products of ammonolysis.

Key words: fungicidal activities, fungicide, indole, oxime ether, strobilurins

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The synthetic strobilurins, derivatives of 3-methoxypropenoic acid, are one of the most important classes of agricultural fungicide (1–4). Their discovery was inspired by a family of natural strobilurins which, although fungicidal, could not be used in agriculture because they are unstable in light and volatile (2,5). To date, several chemists have published remarkable reports on synthetic analogs of strobilurin A (Figure 1) to stabilize the triene structure of the compound (6–14).

Compounds **I** (Figure 1), reported by Rohm and Haas Company [the 4-Cl-substituted derivatives of compounds **I** were developed by Shenyang Research Institute of Chemical Industry and named Enoxastrobin (Figure 1) (10)], contain an unsaturated oxime ether group and exhibit effective fungicidal activities (7). To further stabilize the *E*-styryl group in Enoxastrobin, some novel arylcyclopropyl oxime ether compounds **II** (Figure 1), which use *trans*-arylcyclopropyl group to replace *E*-styryl group in compounds **I**, have been reported. These compounds show excellent fungicidal activities (8). In our previous study, we synthesized a series of novel indene-substituted oxime ethers **III** (Figure 1) to study structure–activity relationship of this type of compound (12,15). Benzopentatomic ring structure was used to stabilize the *E*-styryl group in Enoxastrobin. Fortunately, it was found most of the indene-substituted oxime ethers **III** exhibited effective fungicidal activity. Moreover, the fungicidal activities of some compounds **III** were better than Enoxastrobin.

Many heterocyclic compounds have shown good insecticidal or fungicidal activities, thus increasing their importance in pesticide discovery (16–23). The heterocyclic scaffold of a crop protection agent often has a positive effect on its synthetic accessibility and its physicochemical properties, driving values like lipophilicity and solubility toward the optimal balanced range regarding uptake and bioavailability (21). Heterocycles are deemed to be perfect bioisosteres of other carba- or heterocyclic rings, as well as of several different functional groups, delivering equal or even better biological efficacy through their similarity in structural shape and electronic distribution (18,21). Furthermore, the substitution of a heteroaryl group (i.e., pyridine or furane) with one of the aryl residues of the compound results in heightened biological activity (19). More importantly, environmental compatibility of the synthesized organic compounds is enhanced when heteroatoms are introduced into the carba-rings (17,18,21).

In view of all these facts and as continuation of our research on fungicidal important heterocycles, hereby, a series of novel indole-substituted oxime ethers **7** (Figure 1) utilizing a indole group as bioisostere to replace the *E*-styryl group in Enoxastrobin were synthesized in this study. The title compounds (**7**) were envisioned to retain or urther enhance their biological activity and simultaneously improve their environmental compatibility. The structure–activity relationship of this type of compound was also studied. The biological assay showed that most title compounds (**7**) maintained good fungicidal activities.

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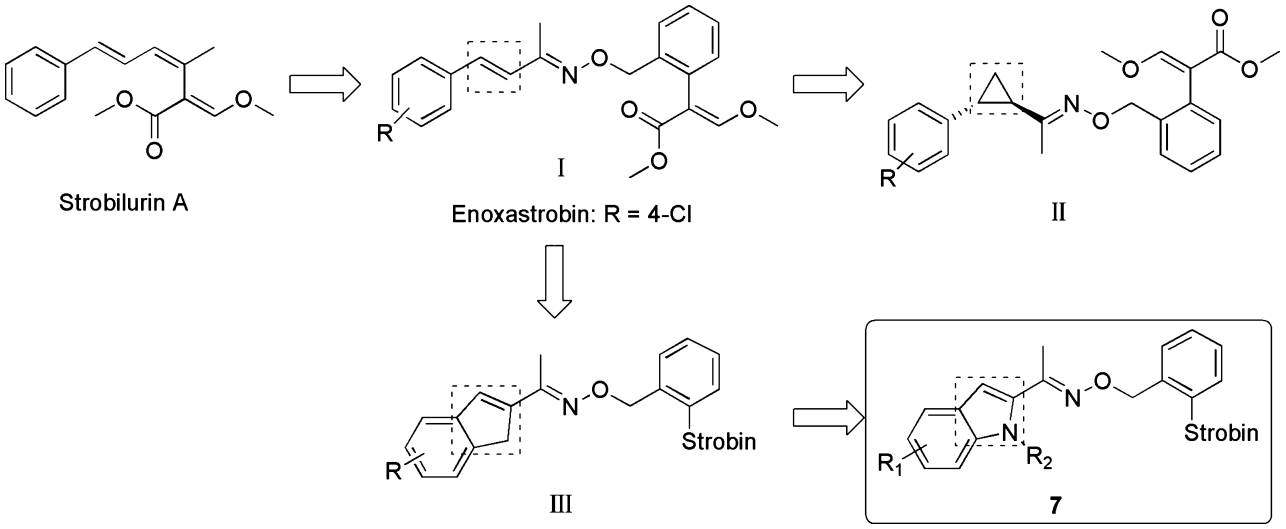


Figure 1: Structure of strobilurin **A** and its analogs.

Methods and Materials

Synthetic procedure

Oxime ether strobilurin derivatives containing indole moiety **7** were prepared by the synthetic route outlined in Scheme 1, and the reaction yields were not optimized.

General

All of the starting materials and reagents were commercially available and used without further purification, except as indicated. Silica gel (300–400 mesh) was used for column chromatography. The (*E*)-methyl 2-(2-(chloromethyl) phenyl)-3-methoxyacrylate (**A**), (*E*)-methyl 2-(2-(bromomethyl)phenyl)-2-methoxyiminoacetate (**B**), and methyl (2-(bromomethyl)phenyl)methoxycarbamate (**C**) intermediates were provided by Shenyang Research Institute of Chemical Industry. Melting points were determined with a Tech X–6 micro–melting–point apparatus made in Beijing and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 400 MHz spectrometer and Bruker 500 MHz spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. HRMS spectra were recorded on a 7.0T FT–MS.

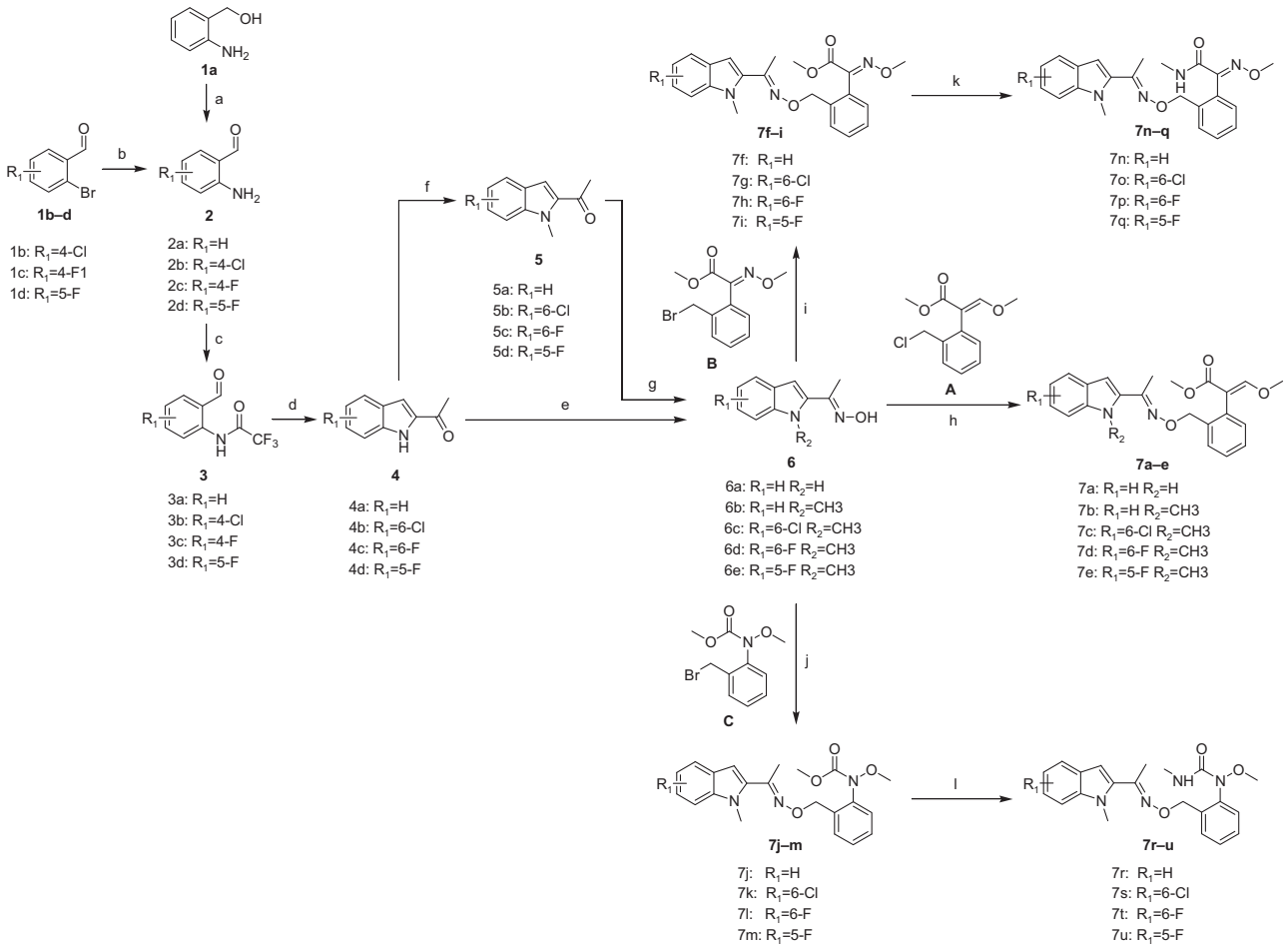
2-Aminobenzaldehyde derivatives (2a–d)

2-Aminobenzaldehyde (2a). A mixture of (2-aminophenyl)methanol (**1a**, 3.77 g, 30 mmol), MnO_2 (10.43 g, 120 mmol), and dichloromethane (50 mL) was stirred. Keep the reaction temperature at 30 °C for 18 h. After cooling to room temperature, the reaction mixture was filtrated, and the combined organic layers were concentrated under vacuum. The residue was purified by flash chromatography using a 1:6 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford 3.42 g (94.1%) intermediate 2-aminobenzaldehyde (**2a**) as yellow solid: M.P.: 37.6–38.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.11 (s, 2H, NH_2), 6.64 (d, J = 8.0 Hz, 1H, ArH), 6.72-6.77 (m, 1H, ArH), 7.28-7.33 (m, 1H, ArH), 7.48 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 9.87 (s, 1H, O=CH); ^{13}C NMR ($CDCl_3$, 100 MHz): 115.9, 116.4, 118.8, 135.2, 135.7, 149.8, 194.1.

2-Aminobenzaldehyde derivatives (2b–d). A mixture of 2-bromobenzaldehyde derivatives (**1b–d**, 20 mmol), sodium ascorbate (0.59 g, 3.0 mmol), DL-proline (0.46 g, 4 mmol), sodium azide (2.42 g, 36 mmol), DMSO (45 mL) and H_2O (5 mL) was stirred. The reaction mixture was heated to 70 °C and reacted for 4.5–12.5 h. After cooling to room temperature, the reaction mixture was poured into 200 mL of water and extracted with ethyl acetate. The combined organic layers were washed with 100 mL saturated aqueous sodium chloride solution. Then, the combined water layers were extracted with ethyl acetate. Finally, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography using a 1:12 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford 2-aminobenzaldehyde derivatives (**2b–d**) in moderate yields.

Data for 2-amino-4-chlorobenzaldehyde (2b): pale yellow solid (1.80 g, 58.1%); M.P.: 81.8–82.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.21 (s, 2H, NH_2), 6.66 (d, J = 1.6 Hz, 1H, ArH), 6.71 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.40 (d, J = 8.4 Hz, 1H, ArH), 9.82 (s, 1H, O=CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 115.8, 117.3, 117.7, 137.3, 141.9, 150.8, 193.3.

Data for 2-amino-4-fluorobenzaldehyde (2c): yellow oil (2.04 g, 73.4%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.31 (s, 2H, NH_2), 6.31 (dd, J = 10.8, 2.0 Hz, 1H, ArH), 6.42–6.47 (m, 1H, ArH), 7.46 (dd, J = 8.0, 6.4 Hz, 1H, ArH), 9.79 (s, 1H, O=CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 102.0 (d,



Scheme 1: General synthetic route for the title compounds **7**. Reagents and conditions: (a) MnO_2, CH_2Cl_2, 30 °C; (b) sodium ascorbate, DL-proline, sodium azide, DMSO, H_2O, 70 °C; (c) trifluoroacetic anhydride, azabenzene, CH_2Cl_2, rt; (d) 1-chloropropan-2-one, calcium oxide, PEG-400, 100 °C; (e, g) hydroxylamine hydrochloride, sodium acetate, H_2O, ethanol, reflux; (f) iodomethane, potassium carbonate, anhydrous acetonitrile, 70 °C; (h, i, j) potassium carbonate, anhydrous acetonitrile, reflux; (k, l) methylamine, methanol, reflux.

J_{CF} = 24.7 Hz), 105.2 (d, J_{CF} = 23.4 Hz), 116.4 (d, J_{CF} = 0.9 Hz), 139.0 (d, J_{CF} = 12.5 Hz), 152.5 (d, J_{CF} = 23.5 Hz), 167.6 (d, J_{CF} = 252.9 Hz), 192.9.

Data for 2-amino-5-fluorobenzaldehyde (2d): yellow oil (1.24 g, 44.5%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.00 (s, 2H, NH_2), 6.62 (dd, J = 9.2, 4.0 Hz, 1H, ArH), 7.06–7.12 (m, 1H, ArH), 7.18 (dd, J = 8.4, 3.2 Hz, 1H, ArH), 9.81 (s, 1H, O=CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 117.8 (d, J_{CF} = 6.6 Hz), 118.5 (d, J_{CF} = 5.2 Hz), 119.8 (d, J_{CF} = 21.2 Hz), 123.8 (d, J_{CF} = 21.2 Hz), 146.8 (d, J_{CF} = 1.2 Hz), 154.4 (d, J_{CF} = 234.5 Hz), 193.1.

2,2,2-Trifluoro-*N*-(2-formylphenyl)acetamide derivatives (3a–d)

A mixture of 2-aminobenzaldehyde derivatives (**2a–d**, 10 mmol), azabenzene (1.6 mL, 20 mmol), and dichloromethane (12 mL) was stirred on ice bath. After the temperature of the mixture was low to 4 °C, trifluoroacetic anhydride (2.4 mL, 16 mmol) was added slowly. The reaction mixture was stirred under room temperature for 1.5–12.5 h. Then, the reaction mixture was poured into 30 mL of water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography using a 1:12 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford 2,2,2-trifluoro-*N*-(2-formylphenyl)acetamide derivatives (**3a–d**) in good yields.

Data for 2,2,2-trifluoro-*N*-(2-formylphenyl)acetamide (3a). pale yellow solid (1.67 g, 76.9%); M.P.: 68.9–69.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.43 (m, 1H, ArH), 7.68-7.74 (m, 1H, ArH), 7.79 (dd, J = 7.6, 1.6 Hz, 1H, ArH), 8.68 (d, J = 8.4 Hz, 1H, ArH), 9.98 (s, 1H, O=CH), 12.19 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.0, 120.8, 122.9, 125.6, 136.4, 136.7, 138.5, 156.3, 195.9.

Data for *N*-(5-chloro-2-formylphen-yl)-2,2,2-trifluoro-acetamide (3b). pale yellow solid (2.44 g, 97.2%); M.P.: 58.5–59.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38

(dd, J = 6.4, 1.6 Hz, 1H, ArH), 7.71 (d, J = 6.4 Hz, 1H, ArH), 8.75 (d, J = 1.2 Hz, 1H, ArH), 9.94 (s, 1H, O=C-H), 12.24 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 114.2, 117.1, 121.1, 121.2, 125.9, 137.2, 139.3, 143.5, 194.8.

Data for *N*-(5-fluoro-2-formylphen-yl)-2,2,2-trifluoro acetamide (3c). pale yellow solid (2.15 g, 91.5%); M.P.: 47.6–48.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.06–7.12 (m, 1H, ArH), 7.80 (dd, J = 8.8, 6.0 Hz, 1H, ArH), 8.46 (dd, J = 11.2, 2.4 Hz, 1H, ArH), 9.93 (s, 1H, O=C-H), 12.39 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 108.8 (d, J_{CF} = 28.7 Hz), 112.9 (d, J_{CF} = 22.7 Hz), 115.6 (d, J_{CF} = 286.8 Hz), 119.7, 138.8 (d, J_{CF} = 11.6 Hz), 140.9 (d, J_{CF} = 13.5 Hz), 156.5 (d, J_{CF} = 76.0 Hz), 167.4 (d, J_{CF} = 259.6 Hz), 194.5.

Data for *N*-(4-fluoro-2-formylphen-yl)-2,2,2-trifluoro-acetamide (3d). pale yellow solid (0.23 g, 97.9%); M.P.: 96.3–97.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04–7.46 (m, 1H, ArH), 7.50 (dd, J = 7.6, 3.2 Hz, 1H, ArH), 8.72 (dd, J = 9.2, 4.8 Hz, 1H, ArH), 9.94 (s, 1H, O=C-H), 12.01 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 115.8 (d, J_{CF} = 326.9 Hz), 122.0 (d, J_{CF} = 22.7 Hz), 122.9 (d, J_{CF} = 6.9 Hz), 123.7 (d, J_{CF} = 21.9 Hz), 124.0 (d, J_{CF} = 5.5 Hz), 134.7 (d, J_{CF} = 2.9 Hz), 156.0 (d, J_{CF} = 37.9 Hz), 159.5 (d, J_{CF} = 247.2 Hz), 194.6.

1-(1*H*-indol-2-yl)ethanone derivatives (4a–d)

A mixture of 2,2,2-trifluoro-*N*-(2-formylphenyl)acetamide derivatives (**3a–d**, 9 mmol), 1-chloropropan-2-one (1.0 mL, 11 mmol), calcium oxide (1.54 g, 27 mmol), and PEG-400 (30 mL) was stirred. The reaction mixture was heated to 100 °C and reacted for 3.0–11.0 h. After cooling to room temperature, the reaction mixture was poured into 60 mL of water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography using a 1:12 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford 1-(1*H*-indol-2-yl)ethanone derivatives (**4a–d**) in moderate yields.

Data for 1-(1*H*-indol-2-yl)ethanone (4a). brown solid (1.07 g, 74.7%); M.P.: 139.7–140.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.60 (s, 3H, CH_3), 7.13–7.17 (m, 1H, ArH), 7.20 (dd, J = 2.4, 0.8 Hz, 1H, N-C=CH),7.32–7.37 (m, 1H, ArH), 7.43 (dd, J = 8.0, 0.8 Hz, 1H, ArH), 7.71 (dd, J = 8.0, 0.8 Hz, 1H, ArH), 9.24 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.2, 110.2, 112.5, 121.3, 123.4, 126.7, 127.9, 135.7, 137.7, 190.9.

Data for 1-(6-chloro-1*H*-indol-2-yl)ethanone (4b). yellow solid (1.17 g, 67.4%); M.P.: 150.3–150.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.61 (s, 3H, CH_3), 7.12 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.17 (dd, J = 2.4, 0.8 Hz, 1H, N-C=CH), 7.44–7.45 (m, 1H, ArH), 7.62 (d, J = 8.8 Hz, 1H, ArH), 9.49 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.2, 110.1, 112.4, 122.4, 124.3, 126.4, 132.6, 136.3, 138.0, 190.8.

Data for 1-(6-fluoro-1*H*-indol-2-yl)ethanone (4c). yellow solid (0.99 g, 62.1%); M.P.: 145.2–145.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.61 (s, 3H, CH_3), 7.08–7.14 (m, 1H, ArH), 7.16 (d, J = 1.2 Hz, 1H, N-C=CH), 7.34 (dd, J = 8.8, 2.0 Hz, 1H, ArH), 7.39 (dd, J = 9.2, 4.4 Hz, 1H, ArH), 9.49 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.2, 107.4 (d, J_{CF} = 23.2 Hz), 109.9 (d, J_{CF} = 5.5 Hz), 113.7 (d, J_{CF} = 9.5 Hz), 115.9 (d, J_{CF} = 26.9 Hz), 128.0 (d, J_{CF} = 10.3 Hz), 134.4, 137.0, 158.5 (d, J_{CF} = 235.7 Hz), 191.0.

Data for 1-(5-fluoro-1*H*-indol-2-yl)ethanone (4d). pale yellow solid (1.38 g, 86.6%); M.P.: 187.3–187.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.61 (s, 3H, CH_3), 7.08–7.14 (m, 1H, ArH), 7.16 (d, J = 1.2 Hz, 1H, N-C=CH), 7.34 (dd, J = 8.8, 2.4 Hz, 1H, ArH), 7.39 (dd, J = 8.8, 4.4 Hz, 1H, ArH), 9.45 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.2, 107.4 (d, J_{CF} = 23.1 Hz), 109.9 (d, J_{CF} = 5.6 Hz), 113.6 (d, J_{CF} = 9.4 Hz), 115.9 (d, J_{CF} = 26.9 Hz), 128.0 (d, J_{CF} = 10.2 Hz), 134.4, 137.0, 158.9 (d, J_{CF} = 235.7 Hz), 191.0.

1-(1-Methyl-indol-2-yl)ethanone derivatives (5a–d)

A mixture of 1-(1*H*-indol-2-yl)ethanone derivatives (**4a–d**, 10 mmol), iodomethane (2.0 mL, 32 mmol), potassium carbonate (1.38 g, 10 mmol), and anhydrous acetonitrile (10 mL) was stirred. The reaction mixture was heated to 70 °C and reacted for 33–72 h. After cooling to room temperature, the reaction mixture was poured into 30 mL of water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography using a 1:12 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford 1-(1-methyl-indol-2-yl)ethanone derivatives (**5a–d**) in good yields.

Data for 1-(1-methyl-indol-2-yl)ethanone (5a). brown solid (1.08 g, 62.4%); M.P.: 92.5–93.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.61 (s, 3H, C-CH_3), 4.07 (s, 3H, N-CH_3), 7.13–7.17 (m, 1H, ArH), 7.28 (s, 1H, N-C=CH), 7.36–7.38 (m, 2H, ArH), 7.69 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 32.5, 110.7, 112.3, 121.0, 123.2, 126.1, 126.2, 135.2, 140.4, 192.0.

Data for 1-(6-chloro-1-methyl-indol-2-yl)ethanone (5b). pale yellow solid (1.61 g, 86.4%); M.P.: 147.1–147.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.64 (s, 3H, C-CH_3), 3.95 (s, 3H, N-CH_3), 7.25 (s, 1H, N-C=CH), 7.40 (dd, J = 8.4, 2.0 Hz, 1H, ArH), 7.62 (d, J = 7.2 Hz, 1H, ArH), 7.96 (d, J = 2.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$,

100 MHz): δ 20.5, 55.4, 110.5, 126.8, 126.9, 127.4, 127.4, 132.0, 142.9, 152.3, 154.3.

Data for 1-(6-fluoro-1-methyl-indol-2-yl)ethanone (5c). yellow solid (1.58 g, 91.9%); M.P.: 106.6–107.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.59 (s, 3H, C-CH_3), 4.03 (s, 3H, N-CH_3), 6.90–6.95 (m, 1H, ArH), 7.03 (dd, J = 10.0, 2.0 Hz, 1H, ArH), 7.27 (s, 1H, N-C=CH), 7.63 (dd, J = 8.8, 5.6 Hz, 1H, ArH), 7.96 (d, J = 2.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.1, 32.7, 96.6 (d, J_{CF} = 28.2 Hz), 110.8 (d, J_{CF} = 25.5 Hz), 112.5 (d, J_{CF} = 1.2 Hz), 122.6, 124.6 (d, J_{CF} = 10.5 Hz), 136.0 (d, J_{CF} = 3.6 Hz), 140.8 (d, J_{CF} = 12.2 Hz), 162.4 (d, J_{CF} = 242.1 Hz), 191.4.

Data for 1-(5-fluoro-1-methyl-indol-2-yl)ethanone (5d). yellow solid (1.59 g, 92.5%); M.P.: 83.6–84.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.60 (s, 3H, C-CH_3), 4.05 (s, 3H, N-CH_3), 7.10–7.16 (m, 1H, ArH), 7.22 (s, 1H, N-C=CH), 7.28–7.33 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 32.7, 107.1 (d, J_{CF} = 23.0 Hz), 111.7, 111.8 (d, J_{CF} = 3.1 Hz), 115.3 (d, J_{CF} = 26.9 Hz), 126.0 (d, J_{CF} = 10.3 Hz), 136.3, 136.7 (d, J_{CF} = 71.4 Hz), 158.9 (d, J_{CF} = 235.6 Hz), 191.9.

The intermediate ethanone oximes (6a–e)

(*E*)-1-(1*H*-indol-2-yl)ethanone oxime (6a). mixture of 1-(1*H*-indol-2-yl)ethanone (**4a**, 5 mmol), hydroxylamine hydrochloride (0.52 g, 7.5 mmol), sodium acetate (0.62 g, 7.5 mmol), H_2O (4 mL), and ethanol (8 mL) was stirred under reflux for 1.0 h. After cooling to room temperature, the reaction mixture was poured into 25 mL of 0.5 M HCl (aq.) and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by recrystallization with ethyl acetate to afford 0.21 g (24.1%) (*E*)-1-(1*H*-indol-2-yl)ethanone oxime (**6a**) as white solid: M.P.: 146.9–147.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H, CH_3), 6.79–6.80 (m, 1H, N-C=CH), 7.09–7.20 (m, 1H, ArH), 7.20–7.23 (m, 1H, ArH), 7.24–7.28 (m, 1H, ArH), 7.62 (d, J = 8.0 Hz, 1H, ArH), 8.20 (s, 1H, N-OH), 8.97 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.8, 105.0, 111.3, 120.4, 121.5, 124.3, 128.3, 133.9, 137.1, 150.6.

(*E*)-1-(1-methyl-indol-2-yl)ethanone oxime (6b–e). A mixture of 1-(1-methyl-indol-2-yl)ethanone derivatives (**5a–d**, 5 mmol), hydroxylamine hydrochloride (0.52 g, 7.5 mmol), sodium acetate (0.62 g, 7.5 mmol), H_2O (4 mL), and ethanol (8 mL) was stirred under reflux for 1.0–3.0 h. After cooling to room temperature, the reaction mixture was poured into 25 mL of 0.5 M HCl (aq.) and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by recrystallization with ethyl acetate to afford (*E*)-1-(1-methyl-indol-2-yl)ethanone oxime derivatives (**6b–e**) in excellent yields.

Data for (*E*)-1-(1-methyl-indol-2-yl)ethanone oxime (6b): yellow solid (0.92 g, 98.3%); M.P.: 161.5–162.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (s, 3H, C-CH_3), 3.94 (s, 3H, N-CH_3), 6.77 (d, J = 0.8 Hz, 1H, N-C=CH), 7.08–7.13 (m, 1H, ArH), 7.26–7.29 (m, 1H, ArH), 7.31–7.34 (m, 1H, ArH), 7.59–7.63 (m, 1H, ArH), 7.83 (s, 1H, N-OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8, 33.2, 105.3, 110.1, 120.2, 121.4, 123.5, 127.3, 135.6, 139.7, 151.9.

Data for (*E*)-1-(6-chloro-1-methyl-indol-2-yl)ethanone oxime (6c): yellow solid (1.09 g, 98.2%); M.P.: 163.7–164.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.34 (s, 3H, C-CH_3), 3.91 (s, 3H, N-CH_3), 6.73 (d, J = 0.4 Hz, 1H, N-C=CH), 7.07 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.32 (d, J = 0.8 Hz, 1H, ArH), 7.50 (d, J = 8.4 Hz, 1H, ArH), 7.54 (s, 1H, N-OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6, 33.4, 105.3, 110.1, 121.0, 122.2, 125.7, 129.4, 136.3, 140.1, 151.6.

Data for (*E*)-1-(6-fluoro-1-methyl-indol-2-yl)ethanone oxime (6d): yellow solid (1.02 g, 99.0%); M.P.: 164.3–164.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H, C-CH_3), 3.88 (s, 3H, N-CH_3), 6.74 (d, J = 0.4 Hz, 1H, N-C=CH), 6.84–6.90 (m, 1H, ArH), 7.00 (dd, J = 10.0, 2.4 Hz, 1H, ArH), 7.51 (dd, J = 8.8, 5.6 Hz, 1H, ArH), 7.84 (s, 1H, N-OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 33.5, 96.3 (d, J_{CF} = 26.3 Hz), 105.4, 109.2 (d, J_{CF} = 24.7 Hz), 122.3 (d, J_{CF} = 10.2 Hz), 123.7, 136.2(d, J_{CF} = 3.9 Hz), 139.9 (d, J_{CF} = 11.9 Hz), 151.6, 161.0 (d, J_{CF} = 237.9 Hz).

Data for (*E*)-1-(5-fluoro-1-methyl-indol-2-yl)ethanone oxime (6e): yellow solid (1.01 g, 98.0%); M.P.: 158.9–159.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.34 (s, 3H, C-CH_3), 3.92 (s, 3H, N-CH_3), 6.71 (s, 1H, N-C=CH), 6.99–7.04 (m, 1H, ArH), 7.21–7.26 (m, 2H, ArH), 7.77 (s, 1H, N-OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8, 33.4, 105.0 (d, J_{CF} = 4.9 Hz), 105.8 (d, J_{CF} = 23.2 Hz), 110.8 (d, J_{CF} = 9.6 Hz), 112.0 (d, J_{CF} = 26.2 Hz), 127.3 (d, J_{CF} = 10.3 Hz), 136.3, 137.0, 151.7, 158.3 (d, J_{CF} = 233.6 Hz).

Methyl 3-methoxypropenoate oxime ethers (7a–e)

Methyl (*E*,*E*)-3-methoxy-2-(2-((((1-(1*H*-indol-2-yl)ethylidene)amino)oxy)methyl)phenyl)propenoate (7a). A mixture of (*E*)-1-(1*H*-indol-2-yl)ethanone oxime (**6a**, 0.17 g, 1.0 mmol), (*E*)-methyl 2-(2-(chloromethyl)phenyl)-3-methoxyacrylate (**A**, 0.32 g, 1.3 mmol), potassium carbonate (0.36 g, 2.6 mmol), and anhydrous acetonitrile (6 mL) was stirred under reflux for 7.0 h. After cooling to room temperature, the reaction mixture was poured into 30 mL of water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by

flash chromatography using a 1:12 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford 0.35 g (91.4%) (*E*, *E*)-methyl 3-methoxy-2-(2-((((1-(1*H*-indol-2-yl)ethylidene) amino)oxy)methyl)phenyl)propenoate (**7a**) as brown solid: M.P.: 115.7–116.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.23 (s, 3H, N=C-CH_3), 3.72 (s, 3H, C=C-OCH_3), 3.81 (s, 3H, O=C-OCH_3), 5.12 (s, 2H, O-CH_2), 6.67 (d, J = 1.2 Hz, 1H, N-C=CH), 7.03–7.12 (m, 1H, ArH), 7.16–7.22 (m, 3H, ArH), 7.31–7.35 (m, 2H, ArH), 7.49–7.51 (m, 1H, ArH), 7.60 (s, 1H, O-CH=C), 7.95–7.99 (m, 1H, ArH), 9.03 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.3, 52.1, 62.2, 74.4, 103.8, 110.9, 111.3, 120.0, 121.3, 123.8, 127.9, 128.3, 129.0, 131.2, 132.2, 134.4, 137.0, 137.4, 148.5, 160.3, 168.7; HRMS (ESI) calcd for $[C_{22}H_{22}N_2NaO_4]^+$ ($M+Na^+$): 401.1472; found: 401.1469.

Methyl 3-methoxypropenoate oxime ethers (7b–e). A mixture of the corresponding (*E*)-1-(1-methyl-indol-2-yl)ethanone oxime (**6b–e**, 1.5 mmol), (*E*)-methyl 2-(2-(chloromethyl)phenyl)-3-methoxyacrylate (**A**, 0.49 g, 2.0 mmol), potassium carbonate (0.62 g, 4.5 mmol), and anhydrous acetonitrile (9 mL) was stirred under reflux for 11.0–30.0 h. After cooling to room temperature, the reaction mixture was poured into 30 mL of water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography using a 1:12 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford the corresponding title compounds methyl 3-methoxypropenoate oxime ethers (**7b–e**) in good yields.

Data for methyl (*E*,*E*)-3-methoxy-2-(2-((((1-(1-methy-indol-2-yl)ethylidene)amino)oxy)methyl)phenyl)propenoate (7b): yellow solid (0.48 g, 81.6%); M.P.: 113.4–114.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.29 (s, 3H, N=C-CH_3), 3.66 (s, 3H, C=C-OCH_3), 3.78 (s, 3H, N-CH_3), 3.80 (s, 3H, O=C-OCH_3), 5.15 (s, 2H, O-CH_2), 6.71 (d, J = 1.2 Hz, 1H, N-C=CH), 7.05–7.09 (m, 1H, ArH), 7.15–7.18 (m, 1H, ArH), 7.21–7.25 (m, 1H, ArH), 7.26–7.36 (m, 3H, ArH), 7.48–7.51 (m, 1H, ArH), 7.56–7.59 (m, 1H, ArH), 7.58 (s, 1H, O-CH=C); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 33.2, 51.9, 62.2, 74.8, 105.0, 110.0, 110.8, 120.0, 121.2, 123.3, 127.2, 127.8, 128.1, 128.8, 131.3, 132.1, 135.7, 137.6, 139.7, 150.1, 160.1, 168.4; HRMS (ESI) calcd for $[C_{23}H_{24}N_2NaO_4]^+$ ($M+Na^+$): 415.1628; found: 415.1620.

Data for methyl (*E*,*E*)-3-methoxy-2-(2-((((1-(6-chloro-1-methy-indol-2-yl)ethylidene)amino)oxy)methyl)phenyl)propenoate (7c): yellow solid (0.49 g, 76.7%); M.P.: 107.8–108.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.27 (s, 3H, N=C-CH_3), 3.67 (s, 3H, C=C-OCH_3), 3.75 (s, 3H, N-CH_3), 3.80 (s, 3H, O=C-OCH_3), 5.15 (s, 2H, O-CH_2), 6.67 (s, 1H, N-C=CH), 7.04 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.15–7.19 (m, 1H, ArH), 7.27 (d, J = 0.8 Hz, 1H, ArH), 7.29–7.36 (m, 2H, ArH), 7.42–7.50 (m, 2H, ArH), 7.59 (s, 1H, O-CH=C); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 33.4, 51.9, 62.2, 74.9, 104.9, 110.0, 110.8, 120.8, 122.1, 125.7, 127.8, 128.1, 128.8, 129.2, 131.3, 132.1, 136.4, 137.5, 140.1, 149.8, 160.1, 168.3; HRMS (ESI) calcd for $[C_{23}H_{23}ClN_2NaO_4]^+$ ($M+Na^+$): 449.1239; found: 449.1229.

Data for methyl (*E*,*E*)-3-methoxy-2-(2-((((1-(6-fluoro-1-methy-indol-2-yl)ethylidene)amino)oxy)methyl)phenyl)propenoate (7d): pale yellow solid (0.32 g, 52.0%); M.P.: 119.0–119.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.27 (s, 3H, N=C-CH_3), 3.67 (s, 3H, C=C-OCH_3), 3.74 (s, 3H, N-CH_3), 3.80 (s, 3H, O=C-OCH_3), 5.14 (s, 2H, O-CH_2), 6.68 (s, 1H, N-C=CH), 6.81-6.87 (m, 1H, ArH), 6.94 (dd, J = 10.0, 2.0 Hz, 1H, ArH), 7.15-7.18 (m, 1H, ArH), 7.31-7.34 (m, 2H, ArH), 7.46-7.50 (m, 2H, ArH), 7.59 (s, 1H, O-CH=C); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 33.5, 51.9, 62.2, 74.8, 96.3 (d, J_{CF} = 26.3 Hz), 105.0, 108.9 (d, J_{CF} = 24.7 Hz), 110.8, 122.1 (d, J_{CF} = 10.1 Hz), 123.7, 127.8, 128.1, 128.8, 131.3, 132.1, 136.3 (d, J_{CF} = 3.8 Hz), 137.6, 139.9 (d, J_{CF} = 12.0 Hz), 149.9, 160.1, 160.8 (d, J_{CF} = 237.6 Hz), 168.4; HRMS (ESI) calcd for $[C_{23}H_{23}FN_2NaO_4]^+$ ($M+Na^+$): 433.1534; found: 433.1526.

Data for methyl (*E*,*E*)-3-methoxy-2-(2-((((1-(5-fluoro-1-methy-indol-2-yl)ethylidene)amino)oxy)methyl)phenyl)propenoate (7e): pale yellow solid (0.57 g, 92.6%); M.P.: 102.8–103.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.28 (s, 3H, N=C-CH_3), 3.67 (s, 3H, C=C-OCH_3), 3.77 (s, 3H, N-CH_3), 3.80 (s, 3H, O=C-OCH_3), 5.15 (s, 2H, O-CH_2), 6.65 (s, 1H, N-C=CH), 6.95–7.00 (m, 1H, ArH), 7.15–7.22 (m, 3H, ArH), 7.29–7.36 (m, 2H, ArH), 7.47–7.50 (m, 1H, ArH), 7.59 (s, 1H, O-CH=C); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 33.4, 51.9, 62.2, 74.9, 104.6 (d, J_{CF} = 4.9 Hz), 105.7 (d, J_{CF} = 23.2 Hz), 110.7(d, J_{CF} = 9.5 Hz), 110.8, 111.7 (d, J_{CF} = 26.3 Hz), 127.2 (d, J_{CF} = 10.3 Hz), 127.8, 128.1, 128.8, 131.3, 132.1, 136.3, 137.1, 137.5, 149.9, 158.1 (d, J_{CF} = 233.1 Hz), 160.1, 168.4; HRMS (ESI) calcd for $[C_{23}H_{23}FN_2NaO_4]^+$ ($M+Na^+$): 433.1534; found: 433.1529.

Methyl α-(methoxyimino)benzeneacetate oxime ethers (7f–i)

A mixture of the corresponding (*E*)-1-(1-methyl-indol-2-yl) ethanone oxime (**6b–e**, 1.5 mmol), (*E*)-methyl 2-(2-(bromomethyl)phenyl)-2-methoxyiminoacetate (**B**, 0.57 g, 2.0 mmol), potassium carbonate (0.62 g, 4.5 mmol), and anhydrous acetonitrile (9 mL) was stirred under reflux for 9.5–24.0 h. After cooling to room temperature, the reaction mixture was poured into 30 mL of water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography with using a 1:12 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford the corresponding title compounds methyl α-(methoxyimino)benzeneacetate oxime ethers (**7f–i**).

Data for methyl (*E*,*E*)-2-(2-((((1-(1-methyl-indol-2-yl) ethylidene)amino)oxy)methyl)phenyl)-2-methoxy imino acetate (7f). yellow solid (0.54 g, 91.6%); M.P.: 89.0–89.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.27 (s, 3H, N=C-CH_3), 3.75 (s, 3H, N-CH_3), 3.79 (s, 3H, O=C-OCH_3), 4.01 (s, 3H, N-OCH_3), 5.13 (s, 2H, O-CH_2), 6.72 (s, 1H, N-C=CH), 7.05–7.09 (m, 1H, ArH), 7.18–7.20 (m, 1H, ArH), 7.21–7.29 (m, 2H, ArH), 7.35–7.39 (m, 1H, ArH), 7.39–7.44 (m, 1H, ArH), 7.48 (dd, J = 7.6, 0.8 Hz, 1H, ArH), 7.57 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 33.1, 53.2, 64.1, 75.1, 105.2, 110.0, 120.0, 121.3, 123.4, 127.2, 128.0, 128.9, 129.1, 129.6, 130.2, 135.4, 137.0, 139.7, 150.0, 150.6, 163.6; HRMS (ESI) calcd for $[C_{22}H_{23}N_3NaO_4]^+$ (M+Na^+): 416.1581; found: 416.1565.

Data for methyl (*E*,*E*)-2-(2-((((1-(6-chloro-1-methyl-indol-2-yl)ethylidene)amino)oxy)methyl)phenyl)-2-methoxy imino acetate (7 g). pale yellow solid (0.59 g, 92.1%); M.P.: 99.0–99.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.25 (s, 3H, N=C-CH_3), 3.70 (s, 3H, N-CH_3), 3.80 (s, 3H, O=C-OCH_3), 4.02 (s, 3H, N-OCH_3), 5.12 (s, 2H, O-CH_2), 6.68 (d, J = 0.8 Hz, 1H, N-C=CH), 7.04 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.20 (dd, J = 7.2, 1.6 Hz, 1H, ArH), 7.26–7.27 (m, 1H, ArH), 7.38–7.49 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 33.4, 53.2, 64.1, 75.2, 105.1, 110.0, 120.8, 122.1, 125.7, 128.0, 128.9, 129.1, 129.3, 129.6, 130.2, 136.2, 136.9, 140.1, 149.9, 150.2, 163.6; HRMS (ESI) calcd for $[C_{22}H_{22}ClN_3NaO_4]^+$ (M+Na^+): 450.1191; found: 450.1196.

Data for methyl (*E*,*E*)-2-(2-((((1-(6-fluoro-1-methyl-indol-2-yl)ethylidene)amino)oxy)methyl)phenyl)-2-methoxy imino acetate (7h). white solid (0.55 g, 89.2%); M.P.: 123.0–124.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.24 (s, 3H, N=C-CH_3), 3.69 (s, 3H, N-CH_3), 3.80 (s, 3H, O=C-OCH_3), 4.01 (s, 3H, N-OCH_3), 5.12 (s, 2H, O-CH_2), 6.80 (d, J = 0.4 Hz, 1H, N-C=CH), 6.80–6.86 (m, 1H, ArH), 6.93 (dd, J = 10.0, 2.0 Hz, 1H, ArH), 7.20 (dd, J = 7.2, 1.2 Hz, 1H, ArH), 7.35–7.44 (m, 2H, ArH), 7.45–7.49 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0, 33.4, 53.2, 64.1, 75.1, 96.2 (d, J_{CF} = 26.2 Hz), 105.2, 109.0 (d, J_{CF} = 24.6 Hz), 122.1 (d, J_{CF} = 10.2 Hz), 123.6, 128.0, 128.9, 129.1, 129.6, 130.2, 136.0 (d, J_{CF} = 3.9 Hz), 136.9, 139.9 (d, J_{CF} = 12.1 Hz), 150.0, 150.3, 161.0 (d, J_{CF} = 237.8 Hz), 163.6; HRMS (ESI) calcd for $[C_{22}H_{22}FN_3NaO_4]^+$ (M+Na^+): 434.1487; found: 434.1492.

Data for methyl (*E*,*E*)-2-(2-((((1-(5-fluoro-1-methyl-indol-2-yl)ethylidene)amino)oxy)methyl)phenyl)-2-methoxy imino acetate (7i). pale yellow solid (0.57 g, 92.5%); M.P.: 90.5–92.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.25 (s, 3H, N=C-CH_3), 3.72 (s, 3H, N-CH_3), 3.80 (s, 3H, O=C-OCH_3), 4.01 (s, 3H, N-OCH_3), 5.12 (s, 2H, O-CH_2), 6.65 (d, J = 0.4 Hz, 1H, N-C=CH), 6.95–7.01 (m, 1H, ArH), 7.15–7.22 (m, 2H, ArH), 7.35–7.44 (m, 2H, ArH), 7.47 (dd, J = 7.6, 1.2 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 33.4, 53.2, 64.1, 75.2, 104.8 (d, J_{CF} = 4.9 Hz), 105.7 (d, J_{CF} = 23.1 Hz), 110.7 (d, J_{CF} = 9.6 Hz), 111.8 (d, J_{CF} = 26.3 Hz), 127.2 (d, J_{CF} = 10.3 Hz), 128.0, 128.9, 129.1, 129.6, 130.2, 136.3, 136.8, 136.9, 150.0, 150.3, 158.2 (d, J_{CF} = 233.4 Hz), 163.6; HRMS (ESI) calcd for $[C_{22}H_{22}FN_3NaO_4]^+$ (M+Na^+): 434.1487; found: 434.1487.

N-methoxy-carbamic acid methyl esters (7j–m)

A mixture of the corresponding (*E*)-1-(1-methyl-indol-2-yl) ethanone oxime (**6b–e**, 1.5 mmol), methyl (2-(bromomethyl)phenyl)methoxycarbamate (**C**, 0.55 g, 2.0 mmol), potassium carbonate (0.62 g, 4.5 mmol), and anhydrous acetonitrile (9 mL) was stirred under reflux for 9.5–36.0 h. After cooling to room temperature, the reaction mixture was poured into 30 mL of water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography using a 1:12 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford the corresponding title compounds *N*-methoxy-carbamic acid methyl esters (**7j–m**).

Data for (*E*)-*N*-methoxy-*N*-(2-((1-(1-methyl-indol-2-yl) ethylidene)aminooxymethyl)phenyl)carbamic acid methyl ester (7j). brown solid (0.50 g, 87.5%); M.P.: 93.5–94.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (s, 3H, N=C-CH_3), 3.76 (s, 3H, N-OCH_3), 3.77 (s, 3H, O=C-OCH_3), 3.82 (s, 3H, H-N-CH_3), 5.30 (s, 2H, O-CH_2), 6.74 (s, 1H, N-C=CH), 7.06–7.10 (m, 1H, ArH), 7.21–7.26 (m, 1H, ArH), 7.28 (d, J = 8.0 Hz, 1H, ArH), 7.35–7.40 (m, 3H, ArH), 7.54–7.57 (m, 1H, ArH), 7.58 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 33.2, 53.8, 62.3, 72.4, 105.3, 110.0, 120.1, 121.3, 123.4, 127.2, 127.5, 128.5, 129.0, 129.4, 135.4, 136.5, 137.6, 139.7, 150.6, 156.1; HRMS (ESI) calcd for $[C_{21}H_{23}N_3NaO_4]^+$ (M+Na^+): 404.1586; found: 404.1581.

Data for (*E*)-*N*-methoxy-*N*-(2-((1-(6-chloro-1-methyl-indol-2-yl)ethylidene)aminooxymethyl)phenyl) carbamic acid methyl ester (7k). yellow solid (0.47 g, 75.5%); M.P.: 98.8–99.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H, N=C-CH_3), 3.76 (s, 3H, N-OCH_3), 3.77 (s, 3H, O=C-OCH_3), 3.78 (s, 3H, H-N-CH_3), 5.29 (s, 2H, O-CH_2), 6.70 (d, J = 0.8 Hz, 1H, N-C=CH), 7.05 (dd, J = 8.4, 1.2 Hz, 1H, ArH), 7.27–7.28 (m, 1H, ArH), 7.34–7.40 (m, 3H, ArH), 7.48 (d, J = 8.4 Hz, 1H, ArH), 7.52–7.55 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 33.4, 53.8, 62.4, 72.5, 105.2, 110.0, 120.9, 122.1, 125.7, 127.6, 128.6, 129.0, 129.3, 129.4, 136.2, 136.3, 137.6, 140.1, 150.3, 156.1; HRMS (ESI) calcd for $[C_{21}H_{22}FClN_3NaO_4]^+$ (M+Na^+): 438.1191; found: 438.1188.

Data for (*E*)-*N*-methoxy-*N*-(2-((1-(6-fluoro-1-methyl-indol-2-yl)ethylidene)aminooxymethyl)phenyl) carbamic acid methyl ester (7 l). yellow oil (0.36 g, 60.1%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H, N=C-CH_3), 3.76 (s, 3H, N-OCH_3), 3.77 (s, 3H, O=C-OCH_3),

3.78 (s, 3H, H-N-CH_3), 5.29 (s, 2H, O-CH_2), 6.71 (s, 1H, N-C=CH), 6.81–6.87 (m, 1H, ArH), 6.94 (dd, J = 10.0, 2.0 Hz, 1H, ArH), 7.35–7.40 (m, 3H, ArH), 7.48 (dd, J = 8.4, 5.2 Hz, 1H, ArH), 7.53–7.55 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 33.5, 53.8, 62.4, 72.5, 96.3 (d, J_{CF} = 26.3 Hz), 105.3, 109.0 (d, J_{CF} = 24.7 Hz), 122.2 (d, J_{CF} = 10.1 Hz), 123.6, 127.6, 128.6, 129.0, 129.4, 136.0 (d, J_{CF} = 3.8 Hz), 136.4, 137.6, 140.0 (d, J_{CF} = 12.0 Hz), 150.3, 156.1, 161.0 (d, J_{CF} = 237.9 Hz); HRMS (ESI) calcd for $[C_{21}H_{22}FN_3NaO_4]^+$ (M+Na^+): 422.1487; found: 422.1486.

Data for (*E*)-*N*-methoxy-*N*-(2-((1-(5-fluoro-1-methyl-indol-2-yl)ethylidene)aminooxymethyl)phenyl) carbamic acid methyl ester (7 m). yellow oil (0.50 g, 73.5%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H, N=C-CH_3), 3.76 (s, 3H, N-OCH_3), 3.78 (s, 3H, O=C-OCH_3), 3.79 (s, 3H, H-N-CH_3), 5.30 (s, 2H, O-CH_2), 6.68 (d, J = 0.8 Hz, 1H, N-C=CH), 6.95–7.01 (m, 1H, ArH), 7.17–7.23 (m, 2H, ArH), 7.35–7.40 (m, 3H, ArH), 7.53–7.55 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 33.4, 53.8, 62.4, 72.5, 104.9 (d, J_{CF} = 4.9 Hz), 105.6(d, J_{CF} = 23.2 Hz), 110.7 (d, J_{CF} = 9.6 Hz), 111.9 (d, J_{CF} = 26.2 Hz), 127.2 (d, J_{CF} = 10.3 Hz), 127.6, 128.6, 129.0, 129.4, 136.3, 136.3, 136.8, 137.6, 150.4, 156.1, 158.2 (d, J_{CF} = 233.5 Hz). HRMS (ESI) calcd for $[C_{21}H_{22}FN_3NaO_4]^+$ (M+Na^+): 422.1487; found: 422.1481.

α-(methoxyimino)-*N*-methyl-phenylacetamide oxime ethers (7n–q)

A mixture of the corresponding methyl α-(methoxyimino) benzeneacetate oxime ethers (**7f–i**, 1 mmol) and methylamine (0.74 g, 6 mmol, 25% in water) was heated for 1.0–11.0 h in 10 mL of methanol under reflux. Then, the reaction mixture was cooled to room temperature and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography using a 1:3 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford the corresponding title compounds α-(methoxyimino)-*N*-methyl-phenylacetamide oxime ethers (**7n–q**).

Data for (*E,E*)-2-(2-((1-(1-methyl-indol-2-yl)ethylidene) aminooxymethyl)phenyl)-2-methoxyimino-*N*-methylacetamide (7n). White solid (0.28 g, 71.6%); M.P.: 163.6–164.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.26 (s, 3H, N=C-CH_3), 2.86 (d, J = 5.2 Hz, 3H, H-N-CH_3), 3.76 (s, 3H, C-N-CH_3), 3.93 (s, 3H, N-OCH_3), 5.13 (s, 2H, O-CH_2), 6.71 (d, J = 0.4 Hz, 1H, N-C=CH), 6.73–6.74 (m, 1H, NH), 7.05–7.10 (m, 1H, ArH), 7.18–7.21 (m, 1H, ArH), 7.22–7.25 (m, 1H, ArH), 7.28 (d, J = 7.6 Hz, 1H, ArH), 7.34–7.43 (m, 2H, ArH), 7.47–7.50 (m, 2H, ArH), 7.57 (d, J = 7.6 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 26.5, 33.2, 63.6, 75.2, 105.1, 110.0, 120.0, 121.2, 123.4, 127.2, 127.9, 129.1, 129.1, 129.5, 129.9, 135.5, 137.0, 139.7, 150.4, 151.6, 163.2; HRMS (ESI) calcd for $[C_{22}H_{24}N_4NaO_3]^+$ (M+Na^+): 415.1741; found: 415.1738.

Data for (*E,E*)-2-(2-((1-(6-chloro-1-methyl-indol-2-yl) ethylidene)aminooxymethyl)phenyl)-2-methoxyimino-*N*-methylacetamide (7o). Pale yellow solid (0.28 g, 65.7%); M.P.: 169.4–170.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.24 (s, 3H, N=C-CH_3), 2.88 (d, J = 5.2 Hz, 3H, H-N-CH_3), 3.71 (s, 3H, C-N-CH_3), 3.93 (s, 3H, N-OCH_3), 5.12 (s, 2H, O-CH_2), 6.66 (d, J = 0.8 Hz, 1H, N-C=CH), 6.74–6.76 (m, 1H, NH), 7.03 (dd, J = 8.4, 2.0 Hz, 1H, ArH), 7.19 (dd, J = 7.2, 1.6 Hz, 1H, ArH), 7.25–7.27 (m, 1H, ArH), 7.34–7.43 (m, 2H, ArH), 7.45–7.49 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 26.5, 33.4, 63.6, 75.3, 105.0, 110.0, 120.8, 122.1, 125.7, 127.9, 129.0, 129.2, 129.3, 129.5, 129.9, 136.4, 137.0, 140.1, 150.1, 151.6, 163.2; HRMS (ESI) calcd for $[C_{22}H_{23}ClN_4NaO_3]^+$ (M+Na^+): 449.1351; found: 449.1353.

Data for (*E,E*)-2-(2-((1-(6-fluoro-1-methyl-indol-2-yl) ethylidene)aminooxymethyl)phenyl)-2-methoxyimino-*N*-methylacetamide (7p). Yellow solid (0.25 g, 60.9%); M.P.: 167.9–168.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.24 (s, 3H, N=C-CH_3), 2.88 (d, J = 4.8 Hz, 3H, H-N-CH_3), 3.70 (s, 3H, C-N-CH_3), 3.93 (s, 3H, N-OCH_3), 5.12 (s, 2H, O-CH_2), 6.67 (d, J = 0.4 Hz, 1H, N-C=CH), 6.74–6.76 (m, 1H, NH), 6.81–6.86 (m, 1H, ArH), 6.93 (dd, J = 10.0, 2.0 Hz, 1H, ArH), 7.20 (dd, J = 7.2, 1.2 Hz, 1H, ArH), 7.36–7.41 (m, 2H, ArH), 7.45–7.49 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 26.5, 33.5, 63.6, 75.2, 96.3 (d, J_{CF} = 26.3 Hz), 105.1, 109.0 (d, J_{CF} = 24.6 Hz), 122.1 (d, J_{CF} = 10.1 Hz), 123.7, 127.9, 129.0, 129.1, 129.5, 129.9, 136.1 (d, J_{CF} = 3.8 Hz), 137.0, 139.9 (d, J_{CF} = 12.0 Hz), 150.2, 151.6, 161.0 (d, J_{CF} = 237.6 Hz), 163.2; HRMS (ESI) calcd for $[C_{22}H_{23}FN_4NaO_3]^+$ (M+Na^+): 433.1646; found: 433.1644.

Data for (*E,E*)-2-(2-((1-(5-fluoro-1-methyl-indol-2-yl) ethylidene)aminooxymethyl)phenyl)-2-methoxyimino-*N*-methylacetamide (7q). Yellow solid (0.35 g, 85.3%); M.P.: 139.0–139.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.25 (s, 3H, N=C-CH_3), 2.88 (d, J = 5.2 Hz, 3H, H-N-CH_3), 3.72 (s, 3H, C-N-CH_3), 3.93 (s, 3H, N-OCH_3), 5.13 (s, 2H, O-CH_2), 6.65 (d, J = 0.4 Hz, 1H, N-C=CH), 6.75–6.77 (m, 1H, NH), 6.95–6.70 (m, 1H, ArH), 7.16–7.22 (m, 3H, ArH), 7.34–7.43 (m, 2H, ArH), 7.47–7.49 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 26.5, 33.4, 63.6, 75.3, 104.6 (d, J_{CF} = 5.0 Hz), 105.7 (d, J_{CF} = 23.2 Hz), 110.7 (d, J_{CF} = 9.5 Hz), 111.8 (d, J_{CF} = 26.3 Hz), 127.2 (d, J_{CF} = 10.4 Hz), 127.9, 129.0, 129.1, 129.5, 129.9, 136.3, 137.0, 137.0, 150.2, 151.6, 158.1 (d, J_{CF} = 233.3 Hz), 163.1; HRMS (ESI) calcd for $[C_{22}H_{23}FN_4NaO_3]^+$ (M+Na^+): 433.1646; found: 433.1645.

1-methoxy-3-methyl-1-phenyl-ureas (7r–u)

A mixture of the corresponding *N*-methoxy-carbamic acid methyl esters (**7j–m,** 1 mmol) and methylamine (0.74 g,

6 mmol, 25% in water) was heated for 26.5–82.0 h in 10 mL of methanol under reflux. Then, the reaction mixture was cooled to room temperature and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography using a 1:3 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60–90 °C) as the eluting solution to afford the corresponding title compounds 1-methoxy-3-methyl-1-phenyl-ureas (**7r–u**).

Data for (*E*)-1-methoxy-3-methyl-1-(2-((((1-(1-methyl-indol-2-yl)ethylidene)amino)oxy)methyl)phenyl)urea (7r). Brown oil (0.16 g, 42.7%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (s, 3H, N=C-CH_3), 2.89 (d, J = 0.4 Hz, 3H, N-CH_3), 3.67 (s, 3H, C-N-CH_3), 3.83 (s, 3H, N-OCH_3), 5.36 (s, 2H, O-CH_2), 5.97–5.98 (m, 1H, NH), 6.73 (d, J = 0.4 Hz, 1H, N-C=CH), 7.06–7.10 (m, 1H, ArH), 7.21–7.26 (m, 1H, ArH), 7.27–7.29 (m, 1H, ArH), 7.31–7.38 (m, 3H, ArH), 7.51–7.55 (m, 1H, ArH), 7.58 (d, J = 8.0 Hz, 1H, ArH), 7.69–7.72 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 27.1, 33.3, 62.1, 72.5, 105.1, 110.0, 120.0, 121.2, 123.3, 125.7, 127.2, 128.2, 128.4, 129.0, 135.6, 137.1, 139.0, 139.7, 150.3, 158.5; HRMS (ESI) calcd for $[C_{21}H_{24}N_4NaO_3]^+$ (M+Na^+): 403.1741; found: 403.1738.

Data for (*E*)-1-methoxy-3-methyl-1-(2-((((1-(6-chloro-1-methyl-indol-2-yl)ethylidene)amino)oxy)methyl) phenyl)urea (7s). Pale yellow solid (0.12 g, 29.0%); M.P.: 92.9–93.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H, N=C-CH_3), 2.89 (d, J = 4.8 Hz, 3H, N-CH_3), 3.68 (s, 3H, C-N-CH_3), 3.79 (s, 3H, N-OCH_3), 5.36 (s, 2H, O-CH_2), 5.98–6.00 (m, 1H, NH), 6.69 (d, J = 0.8 Hz, 1H, N-C=CH), 7.04 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.26–7.28 (m, 1H, ArH), 7.31–7.38 (m, 3H, ArH), 7.47 (d, J = 8.4 Hz, 1H, ArH), 7.51–7.54 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 27.1, 33.5, 62.1, 72.7, 105.1, 110.0, 120.8, 122.1, 125.7, 125.7, 128.2, 128.5, 128.9, 129.2, 136.4, 136.9, 139.0, 140.1, 150.0, 158.5; HRMS (ESI) calcd for $[C_{21}H_{23}ClN_4NaO_3]^+$ (M+Na^+): 437.1351; found: 437.1345.

Data for (*E*)-1-methoxy-3-methyl-1-(2-((((1-(6-fluoro-1-methyl-indol-2-yl)ethylidene)amino)oxy)methyl) phenyl)urea (7t). Brown solid (0.21 g, 52.7%); M.P.: 99.4–101.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H, N=C-CH_3), 2.89 (d, J = 4.8 Hz, 3H, N-CH_3), 3.68 (s, 3H, C-N-CH_3), 3.77 (s, 3H, N-OCH_3), 5.35 (s, 2H, O-CH_2), 5.98–6.00 (m, 1H, NH), 6.70 (s, 1H, N-C=CH), 6.81–6.87 (m, 1H, ArH), 6.94 (dd, J = 10.0, 2.0 Hz, 1H, ArH), 7.30–7.38 (m, 3H, ArH), 7.46–7.54 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 27.1, 33.6, 62.1, 72.6, 96.3 (d, J_{CF} = 26.2 Hz), 105.2, 109.0 (d, J_{CF} = 24.7 Hz), 122.1 (d, J_{CF} = 10.1 Hz), 123.6, 125.8, 128.2, 128.5, 128.9, 136.2 (d, J_{CF} = 3.7 Hz), 137.0, 139.0, 139.9 (d, J_{CF} = 11.9 Hz), 150.1, 158.5, 161.0 (d, J_{CF} = 237.7 Hz); HRMS (ESI) calcd for $[C_{21}H_{23}FN_4NaO_3]^+$ (M+Na^+): 421.1646; found: 421.1649.

Data for (*E*)-1-methoxy-3-methyl-1-(2-((((1-(5-fluoro-1-methyl-indol-2-yl)ethylidene)amino)oxy)methyl) phenyl)urea (7u). Brown solid (0.23 g, 57.8%); M.P.: 93.7–94.4 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.33 (s, 3H, N=C-CH_3), 2.89 (d, J = 5.0 Hz, 3H, N-CH_3), 3.68 (s, 3H, C-N-CH_3), 3.81 (s, 3H, N-OCH_3), 5.36 (s, 2H, O-CH_2), 5.98 (d, J = 4.5 Hz, 1H, NH), 6.67 (s, 1H, N-C=CH), 6.96–7.00 (m, 1H, ArH), 7.17–7.22 (m, 2H, ArH), 7.31–7.38 (m, 3H, ArH), 7.51–7.53 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.4, 27.1, 33.5, 62.1, 72.7, 104.8 (d, J_{CF} = 4.9 Hz), 105.7 (d, J_{CF} = 22.9 Hz), 110.7 (d, J_{CF} = 9.6 Hz), 111.8 (d, J_{CF} = 26.3 Hz), 125.8, 127.3 (d, J_{CF} = 10.8 Hz), 128.2, 128.5, 129.0, 136.3, 137.0, 137.1, 139.1, 150.1, 158.2 (d, J_{CF} = 233.5 Hz), 158.5; HRMS (ESI) calcd for $[C_{21}H_{23}FN_4NaO_3]^+$ (M+Na^+): 421.1646; found: 421.1641.

Biological assay (24–27)

The fungicidal activities of title compounds **7** against *Pyricularia oryzae* and *Botrytis cinerea in vitro* were tested according to the following procedure: The synthesized title compounds (0.0111 g) were dissolved in 0.5 mL of DMF and then mixed rapidly with thawed potato glucose agar culture medium under 50 °C to the tested concentrations. The mixtures were poured into Petri dishes. After the dishes were cooled to room temperature, the solidified plates were incubated with 4 mm mycelium disk at 28 °C for 48 h. Water was used as the blank control. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibition rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, I is the growth inhibition rate (%), C is the control settlement radius (mm), and T is the treatment group fungi settlement radius (mm).

The fungicidal activities of title compounds **7** against *Erysiphe graminis*, *Colletotrichum lagenarium*, *Pseudoperonospora cubensis,* and *Puccinia sorghi* Schw. *in vivo* were tested according to the following procedure: The synthesized title compounds (0.0111 g) were dissolved in 0.5 mL of DMF, and then distilled water (containing 0.1% Tween-80) was added to the solution. The solution was diluted to the tested concentration and sprayed onto the plants and allowed to dry for 2 h. Twenty-four hours later, the plants were inoculated with fungal spores. Each test utilized control plants which were sprayed with a 1:1:2 (by volume) mixture of acetone, methanol, and water (containing 0.1% Tween-80) and inoculated with fungal spores. The results are percent disease control as compared to the untreated check, wherein 100 is rated as complete disease control and 0 as no disease control.

The results are listed in Tables 1 and 2. To make a judgment on the fungicidal potency of the synthesized compounds, Enoxastrobin was used as the standard.

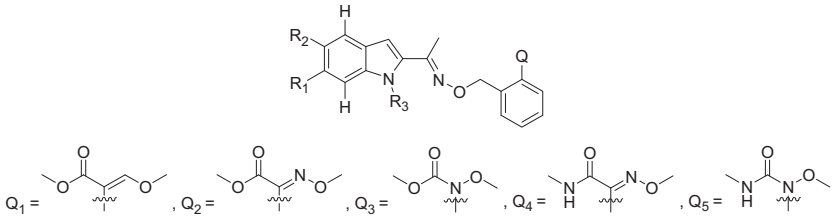
Results and Discussion

Synthetic Chemistry

The synthesis of 2-aminobenzaldehyde derivatives (**2a** and **2b**–**d**, respectively) necessitated a different synthetic plan as shown in Scheme 1, as (2-aminophenyl)methanol derivatives except (2-aminophenyl)methanol (**1a)** are too expensive comparing with 2-bromobenzaldehyde derivatives (**1b**–**d**). The intermediate 2-aminobenzaldehyde (**2a**) was provided through the oxidation reaction of (2-aminophenyl) methanol (**1a**) with 4.0 equiv of MnO_2 in the presence of dichloromethane according to the precedent literature (28, 29). The intermediate 2-aminobenzaldehyde derivatives (**2b**–**d**) were provided through the reaction of 2-bromobenzaldehyde derivatives (**1b**–**d**) with 1.8 equiv of sodium azide according to the literature (30, 31).

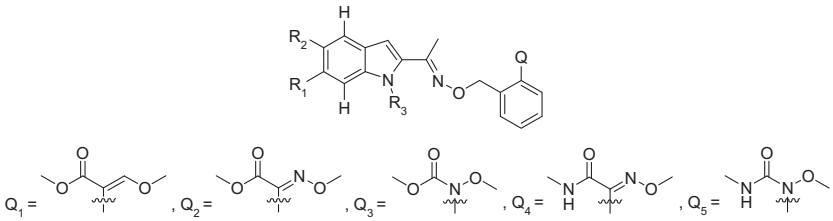
The intermediate 2,2,2-trifluoro-*N*-(2-formylphenyl)acetamide derivatives (**3a**–**d**) were prepared through the reaction of 2-aminobenzaldehyde derivatives (**2b**–**d**) with 1.6 equiv of trifluoroacetic anhydride in the presence of azabenzene and dichloromethane. Then, 2,2,2-trifluoro-*N*-(2-formylphenyl)acetamide derivatives (**3a**–**d**) were reacted with 1.2 equiv of 1-chloropropan-2-one in the presence of PEG-400 and 3.0 equiv of K_2CO_3 to afford the intermediate 1-(1*H*-indol-2-yl)ethanone derivatives (**4a**–**d**) according to previous report (32).

Table 1: Chemical structures and fungicidal activity of title compounds **7** (inhibition %)



	Substituents				Testing concentration (mg/L)					
					In vitro		*In vivo*			
					25		100			
No.	R_1	R_2	R_3	Q	*Pyricularia oryzae*	*Botrytis cinerea*	*Erysiphe graminis*	*Colletotrichum lagenarium*	*Pseudoperonospora cubensis*	*Puccinia sorghi* Schw.
7a	H	H	H	Q_1	80	80	100	100	0	98
7b	H	H	CH_3	Q_1	100	80	100	98	50	100
7c	Cl	H	CH_3	Q_1	50	80	100	100	98	95
7d	F	H	CH_3	Q_1	50	80	100	100	50	98
7e	H	F	CH_3	Q_1	100	80	100	100	75	100
7f	H	H	CH_3	Q_2	80	80	100	98	75	98
7g	Cl	H	CH_3	Q_2	80	80	100	100	0	98
7h	F	H	CH_3	Q_2	80	80	100	100	0	85
7i	H	F	CH_3	Q_2	80	80	100	90	0	98
7j	H	H	CH_3	Q_3	100	80	100	100	0	95
7k	Cl	H	CH_3	Q_3	80	80	100	100	0	95
7l	F	H	CH_3	Q_3	80	80	100	100	0	85
7m	H	F	CH_3	Q_3	80	80	100	100	0	98
7n	H	H	CH_3	Q_4	100	80	100	98	30	95
7o	Cl	H	CH_3	Q_4	100	0	100	98	45	98
7p	F	H	CH_3	Q_4	100	50	100	98	0	98
7q	H	F	CH_3	Q_4	100	0	100	100	0	98
7r	H	H	CH_3	Q_5	80	80	100	100	0	98
7s	Cl	H	CH_3	Q_5	80	50	100	98	0	95
7t	F	H	CH_3	Q_5	80	80	80	98	0	60
7u	H	F	CH_3	Q_5	100	80	85	98	0	95
Enoxastrobin					50	100	100	95	40	95

Table 2: The *in vivo* fungicidal activity of title compounds **7** (inhibition %)



	Substituents				Testing concentration (mg/L)		
					6.25		
No.	R_1	R_2	R_3	Q	*Erysiphe graminis*	*Colletotrichum lagenarium*	*Puccinia sorghi* Schw.
7a	H	H	H	Q_1	50	0	100
7b	H	H	CH_3	Q_1	95	80	90
7c	Cl	H	CH_3	Q_1	75	20	90
7d	F	H	CH_3	Q_1	90	65	90
7e	H	F	CH_3	Q_1	99	75	60
7f	H	H	CH_3	Q_2	15	30	0
7g	Cl	H	CH_3	Q_2	40	35	0
7h	F	H	CH_3	Q_2	45	25	60
7i	H	F	CH_3	Q_2	60	10	20
7j	H	H	CH_3	Q_3	85	10	40
7k	Cl	H	CH_3	Q_3	100	20	70
7l	F	H	CH_3	Q_3	95	30	90
7m	H	F	CH_3	Q_3	100	30	0
7n	H	H	CH_3	Q_4	88	0	60
7o	Cl	H	CH_3	Q_4	98	40	90
7p	F	H	CH_3	Q_4	95	70	90
7q	H	F	CH_3	Q_4	100	20	90
7r	H	H	CH_3	Q_5	40	30	85
7s	Cl	H	CH_3	Q_5	70	45	100
7t	F	H	CH_3	Q_5	///	0	///
7u	H	F	CH_3	Q_5	70	10	90
Enoxastrobin					100	85	100

81.6% of target intermediate (*E*)-1-(1*H*-indol-2-yl)ethanone oxime (**6a**) and 18.4% of by-product (*Z*)-1-(1*H*-indol-2-yl) ethanone oxime (**6a–1**, Figure 2) were produced by the reaction of 1-(1*H*-indol-2-yl)ethanone (**4a**) with 1.5 equiv of hydroxylamine hydrochloride and 1.5 equiv of sodium acetate trihydrate in the presence of a 2:1 (v/v) mixture of ethanol and water under reflux according to a previously described method (33, 34). However, it is too difficult to purify the target intermediate (*E*)-1-(1*H*-indol-2-yl)ethanone oxime (**6a**) by recrystallization from the mixture of (*E*)-1-(1*H*-indol-2-yl)ethanone oxime (**6a**) and (*Z*)-1-(1*H*-indol-2-yl)ethanone oxime (**6a–1**), leading the target compound **6a** was obtained only in the yield of 24.1%. From the best of our experiences, the presence of intramolecular hydrogen bond in the molecule of *cis*-by-product made the by-product (*Z*)-1-(1*H*-indol-2-yl)ethanone oxime (**6a–1**) stable and promoted the generation of (*Z*)-1-(1*H*-indol-2-yl)ethanone oxime (**6a–1**), which could provide proper explain to the above experimental result.

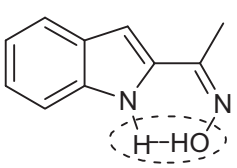


Figure 2: The structure of compound **6a–1**.

Considering the analysis of the above experimental results, the active hydrogen in the molecular of 1-(1*H*-indol-2-yl) ethanone derivatives (**4a–d**) should be protected before their oximation reaction. So the 1-(1-methyl-indol-2-yl)ethanone derivatives (**5a–d**) were produced by the reaction of 1-(1*H*-indol-2-yl)ethanone derivatives (**4a–d**) with 3.2 equiv of iodomethane and 1.0 equiv of K_2CO_3 in the presence of anhydrous acetonitrile according to the precedent literature (35).

Much to our surprise, the 1-(1-methyl-indol-2-yl)ethanone derivatives (**5a–d**) were reacted with 1.5 equiv of hydroxylamine hydrochloridean and 1.5 equiv of sodium acetate

trihydrate in the presence of a 2:1 (v/v) mixture of ethanol and water under reflux to produce (*E*)-1-(1-methyl-indol-2-yl)ethanone oxime derivatives (**6b**–**e**) in excellent yields which are more than 98%.

The title compounds (**7a**–**m**) were obtained by reaction of ethanone oximes (**6a**–**e**) with (*E*)-methyl 2-(2-(chloromethyl) phenyl)-3-methoxyacrylate (**A**), (*E*)-methyl 2-(2-(bromomethyl)phenyl)-2-methoxyiminoacetate (**B**), or methyl (2-(bromomethyl)phenyl)methoxycarbamate (**C**) in the presence of a base and solvent according to the literature protocol (15,18). The title compounds (**7n**–**q** and **7r**–**u**) were produced by ammonolysis of the corresponding title compounds methyl α-(methoxyimino)benzeneacetate oxime ethers (**7f**–**i**) and *N*-methoxy-carbamic acid methyl esters (**7j**–**m**) according to a literature protocol (8).

Biological activity and structure–activity relationship

The *in vitro* fungicidal activity results for compounds **7** against *P. oryzae* and *B. cinerea* at the concentration of 25 mg/L are listed in Table 1. The results of the preliminary bioassays were compared to those of Enoxastrobin. Compounds **7** exhibited potent fungicidal activities against the tested fungi. All the title compounds were more potent or exhibited a similar potency for *in vitro* fungicidal activities against *P. oryzae* compared to Enoxastrobin.

The *in vivo* fungicidal activity results for compounds **7** against *E. graminis*, *C. lagenarium*, *P. cubensis,* and *P. sorghi* Schw. at 100 mg/L are also listed in Table 1. Most of the compounds showed effective fungicidal activities to some extent. Almost all compounds **7** exhibited nearly 100% growth inhibition against *E. graminis*, *C. lagenarium* and *P. sorghi* Schw. but lower activities against *P. cubensis*. However, some compounds possessed better fungicidal activities against *P. cubensis* than that of Enoxastrobin.

Compounds **7** were tested *in vivo* against *E. graminis*, *C. lagenarium,* and *P. sorghi* Schw. at lower concentration (Table 2). However, findings indicated that the fungicidal activities of almost all the compounds **7** have shown a certain degree of decrease against *E. graminis*, *C. lagenarium,* and *P. sorghi* Schw. and lower than Enoxastrobin at 6.25 mg/L. But some compounds still exhibited a broad spectrum of fungicidal activities. Structure–activity relationship indicated that the synthesized methyl 3-methoxypropenoate oxime ethers **7b**–**e** exhibited remarkably high activities among all the synthesized oxime ether compounds **7**. Methyl α-(methoxyimino) benzeneacetate oxime ethers compounds **7f**–**i** possessed lower fungicidal activities against *E. graminis* and *P. sorghi* Schw. compared to the corresponding ammonolysis products α-(methoxyimino)-*N*-methyl-phenyl acetamide oxime ethers (**7n**–**q**). However, *N*-methoxy-carbamic acid methyl esters compounds **7j**–**m** exhibited better fungicidal activities against *E. graminis* but lower fungicidal activities against *P. sorghi* Schw. compared to the corresponding ammonolysis products 1-methoxy-3-methyl-1-phenyl-ureas (**7r**–**u**).

Conclusion

A series of compounds containing indole moiety were designed and synthesized by modifying the side chain of unsaturated oxime ether strobilurin fungicide Enoxastrobin. Most of these synthesized compounds showed moderate or potent fungicidal activities against the tested five fungi. The structure–activity relationship demonstrated that the synthesized methyl 3-methoxypropenoate oxime ethers **7b**–**e** exhibited remarkably high activities among all the synthesized oxime ether compounds **7**. Moreover, the fungicidal activities of methyl α-(methoxyimino)benzeneacetate oxime ethers compounds **7f**–**i** and *N*-methoxy-carbamic acid methyl esters compounds **7j**–**m** showed significant differences compared to the corresponding products of ammonolysis.

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