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Design and Synthesis of 3-Substituted Indolin-2-one Derivatives with Methyl (*E*)-2-(3-Methoxy)acrylate Moiety

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In this article, fifteen indolin-2-one derivatives with methyl (*E*)-2-(3-methoxy)acrylate group were designed and synthesized. The structures of target compounds were confirmed by ^{1}H NMR, IR and HR-MS spectra analysis.

Keywords: Indolin-2-one, Methyl (*E*)-2-(3-methoxy)acrylate, Synthesis.

INTRODUCTION

Indolin-2-one ring system is an important pharmacophore, which can be found in many naturally occurring bioactive alkaloids such as *Welwitindolinone A*, *Spirotryprostatin A* and rhynchophylline[1-3]. Indolin-2-one derivatives are reported to exhibit broad spectrum of biological activities such as antibacterial[4], antimycobacterial[5], antifungal[6], anti-HIV[7], antiviral[8], anticonvulsant[9], anti-inflammatory[10], antitubercular[11-13] and anticancer[14].

Excellent results have been achieved after decades of research on the 3-methylene substituted indolin-2-ones. These indolin-2-one derivatives have been reported in several literatures as potent drugs to treat different diseases. For example, SU 5416[15] (Fig. 1a) and SU 6668[16] (Fig. 1b), as antitumor drugs, have been used in clinical trials. Moreover, sunitinib[17] (Fig. 1c) and methisazone[18] (Fig. 1d), as commercially available anticancer and antiviral drug, respectively, have been approved and marketed for the treatment of related diseases so far.

3-Imino substituted indolin-2-one derivatives also have effective biological activities. Pandeya *et al.*[4] reported that 3-amino indolin-2-one derivatives with pyrimidine (Fig. 2a) were significantly active against bacterial and fungi and indolin-2-one derivatives with 3-amino-2-methylmercapto quinazolin-4-(3*H*)-one (Fig. 2b) had antimicrobial, antifungal and anti-HIV activity[7]. Bari *et al.*[19] have studied that 3-imino substituted indolin-2-one derivatives bearing halogenated benzene (Fig. 2c) showed antimicrobial activity. Gudipati *et al.*[20] reported that 5-halo substituted 3-[4-(5- mercapto-1,3,4-oxadiazol-2-yl)phenylimino]indolin-2-one derivatives (Fig. 2d) contains the potent anticancer agents.

On the other hand, fungicides with methyl (*E*)-2-(3-methoxy) acrylate, such as azoxystrobin (Fig. 3a) and kresoxim (Fig. 3b), have been widely and rapidly adopted due to the advantages of novel mode of action, wide spectrum of biological activities, low toxicity toward mammalian cells and favourable profiles to human safe[21].

In this paper, fifteen compounds (**7a-7o**) have been designed and synthesized by introducing the methyl (*E*)-2-(3-methoxy) acrylate pharmacophore into the 3-imino substituted indolin-2-one structure, which will be expected to exhibit better activities than reference drugs due to the coexistence of two kinds of pharmacophores. Synthesis route of target compounds was shown in **Scheme-I**.

EXPERIMENTAL

All reagents and solvents used in this study were acquired from commercial sources without further purification. Analytical TLC was performed on silica gel GF254 and spots were visualized with ultraviolet (UV) light. The IR spectra were recorded on a Perkin-Elemer 16PC-FT spectrometer. Mass spectra (MS) were acquired with the Agilent 6210 (DOF-MAS) spectrometer (Agilent Inc., Santa Clara, CA, USA) using the electrospray ionization (ESI) method. NMR spectra were recorded on a varian Unity Inova-400 spectrometer (Varian Inc., Palo Alto, CA, USA) with $CDCl_3$ and DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the internal standard. Melting point was recorded on XRC-1 apparatus (Sichuan University Instrument Inc., Chengdu, China) and the thermometer was uncorrected.

Synthesis of compounds 2-4: Compounds **2** and **3** were prepared from 4-substituted phenylamine and chloral hydrate

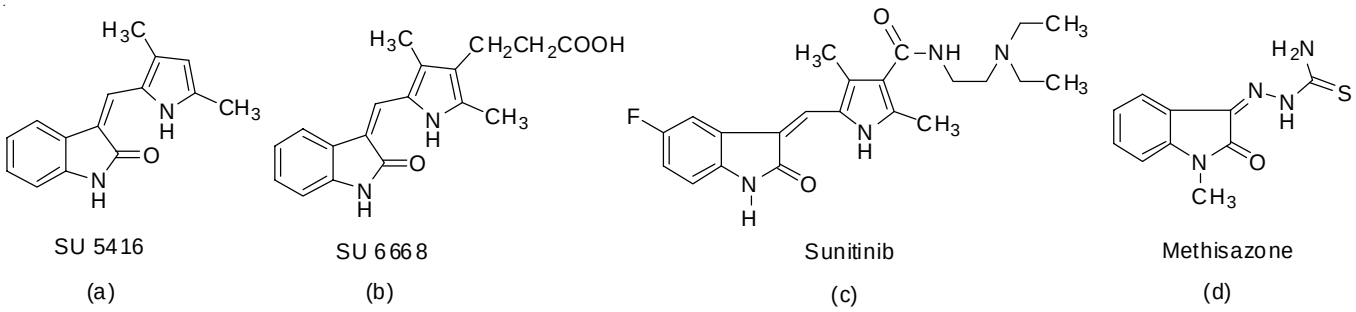


Fig. 1. Structures of SU 5416, SU6668, Sunitinib and Methisazone

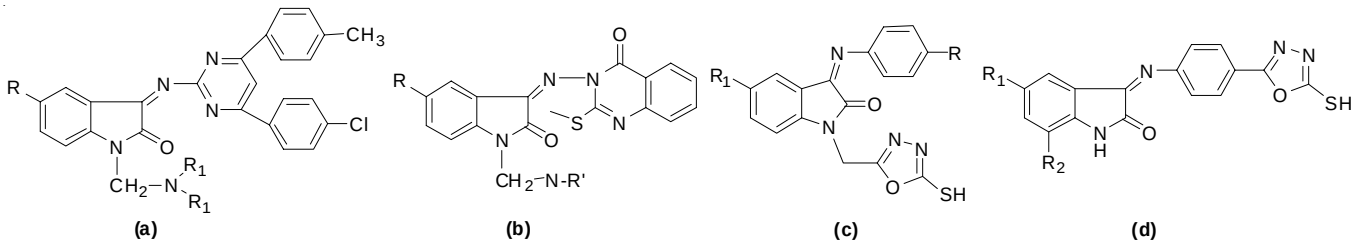
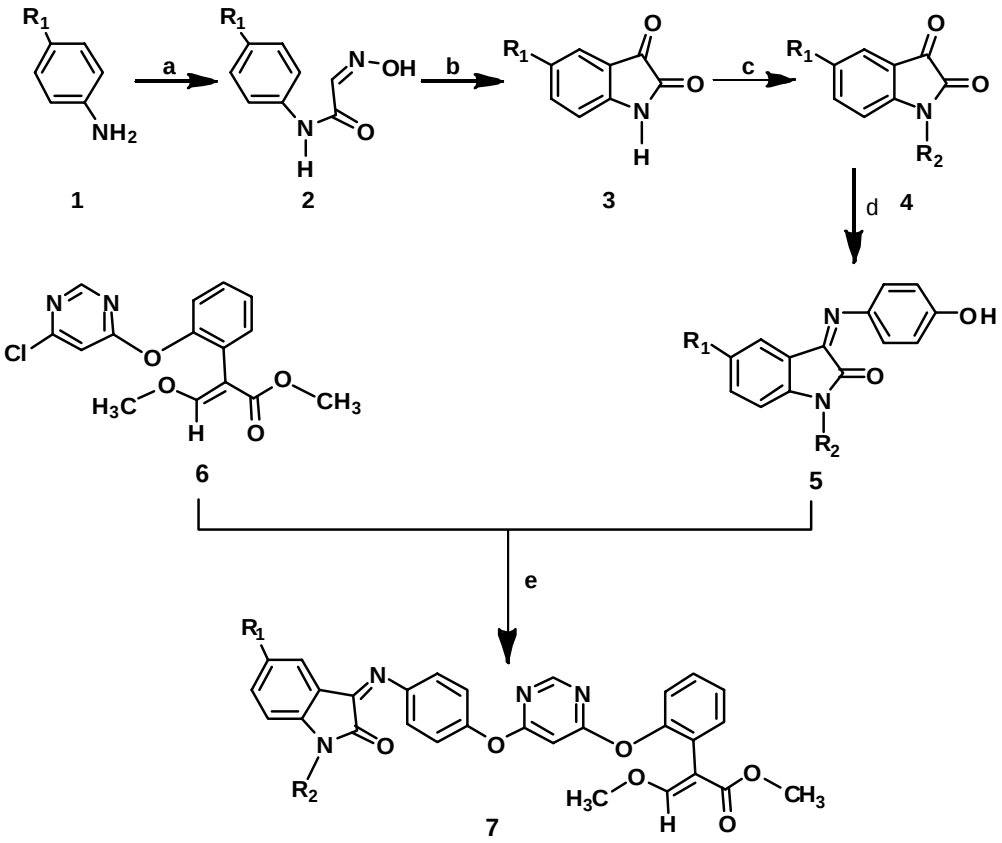


Fig. 2. Structures of indolin-2-one derivatives



7a: R_1= H, R_2= CH_2CH_3 **7f:** R_1= H, R_2= $CH_2CH_2CH_3$ **7k:** R_1= H, R_2= $CH_2CH_2CH_2CH_3$
7b: R_1= CH_3, R_2= CH_2CH_3 **7g:** R_1= CH_3, R_2= $CH_2CH_2CH_3$ **7l:** R_1= CH_3, R_2= $CH_2CH_2CH_2CH_3$
7c: R_1= F, R_2= CH_2CH_3 **7h:** R_1= F, R_2= $CH_2CH_2CH_3$ **7m:** R_1= F, R_2= $CH_2CH_2CH_2CH3$
7d: R_1= Cl, R_2= CH_2CH_3 **7i:** R_1= Cl, R_2= $CH_2CH_2CH_3$ **7n:** R_1= Cl, R_2= $CH_2CH_2CH_2CH_3$
7e: R_1= Br, R_2= CH_2CH_3 **7j:** R_1= Br, R_2= $CH_2CH_2CH_3$ **7o:** R_1= Br, R_2= $CH_2CH_2CH_2CH_3$

Reaction reagents and conditions: a. chloral hydrate, Na_2SO_4, HCl, $NH_2OH{\cdot}HCl$; b. H_2SO_4, 75°C; c. RBr, K_2CO_3, DMF, 80 °C; d. p-aminophenol, EtOH, reflux; e. K_2CO_3, DMF, 90 °C.

Scheme-1: Synthetic route of target compounds

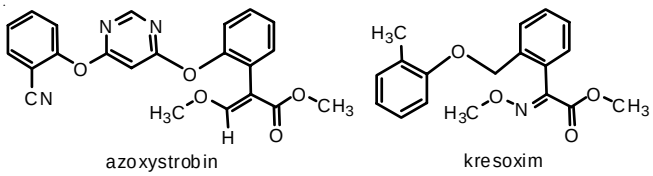


Fig. 3. Structures of azoxystrobin and kresoxim

according to literature procedures[22] with some minor modifications.

Compound **4** was prepared by the reaction of **3** with *p*-aminophenol according to the literature[23].

Melting points, ^{1}H NMR and IR spectra of compounds **2-4** were in accordance with previous report[22,23].

Synthesis of compounds 5a-5o

1-Ethyl-3-[(4-hydroxyphenyl)imino]indolin-2-one (5a): A solution of intermediate **4a** (0.83 g, 4.74 mmol) and 4-aminophenol (0.53 g, 4.88 mmol) in anhydrous EtOH (30 mL) was stirred in the presence of a catalytic amount of CH_3COOH (0.04 g, 0.67 mmol) at room temperature for 10 min, then refluxed for an additional 60 min. Evaporation of the solvent under reduced pressure yielded crude product **5a**. The crude product was successively washed with H_2O (10 mL × 3) and dried to give desired product. Purification of the crude product by column chromatography on silica gel (ether/acetone, 5:1 v/v; 0.3 % triethylamine was added) yielded pure compound **5a**. Red solid. yield: 95 %; m.p.: 206-207 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.59 (s, 1H), 7.43 (m, 1H), 7.21-7.08 (m, 2H), 6.90-6.79 (m, 5H), 3.78 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3337, 2922, 1706, 1603, 1503, 1462, 1377, 1262, 1215, 850. HR-MS (ESI): Calcd for $C_{16}H_{13}N_2O_2$ [M-H]$^-$: 265.0977; found: 265.0978.

1-Ethyl-3-[(4-hydroxyphenyl)imino]-5-methylindolin-2-one (5b): Red solid; yield: 96 %; m.p.: 203-204 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.60 (s, 1H), 7.28-7.22 (m, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.94-6.82 (m, 4H), 6.66 (s, 1H), 3.75 (q, *J* = 7.1 Hz, 2H), 2.05 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3258, 2922, 1680, 1603, 1492, 1362, 1215, 815. HR-MS (ESI): Calcd for $C_{17}H_{15}N_2O_2$ [M-H]$^-$: 279.1134; found: 279.1128.

1-Ethyl-5-fluoro-3-[(4-hydroxyphenyl)imino]indolin-2-one (5c): Red solid; yield: 91 %; m.p.: 215-217 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.68 (s, 1H), 7.37-7.28 (m, 2H), 7.21 (m, 1H), 6.90 (t, *J* = 8.2 Hz, 3H), 6.49 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.78 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3337, 2931, 1715, 1609, 1503, 1471, 1344, 1268, 1212, 823. HR-MS (ESI): Calcd for $C_{16}H_{12}N_2O_2F$ [M-H]$^-$: 283.0883; found: 283.0880.

5-Chloro-1-ethyl-3-[(4-hydroxyphenyl)imino]indolin-2-one (5d): Red solid; yield: 96 %; m.p.: 204-206 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.69 (s, 1H), 7.51 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 6.97-6.85 (m, 4H), 6.74 (d, *J* = 2.2 Hz, 1H), 3.78 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3252, 2978, 1733, 1653, 1600, 1506, 1468, 1344, 1256, 1206, 844. HR-MS (ESI): Calcd for $C_{16}H_{12}N_2O_2Cl$ [M-H]$^-$: 299.0588; found: 299.0583.

5-Bromo-1-ethyl-3-[(4-hydroxyphenyl)imino]indolin-2-one (5e): Red solid; yield: 93 %; m.p.: 190-192 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.68 (s, 1H), 7.63 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 6.99-6.84 (m, 5H), 3.77 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3272, 2969, 1689, 1606, 1500, 1471, 1336, 1262, 1212, 817. HR-MS (ESI): Calcd for $C_{16}H_{14}N_2O_2Br$ [M+H]$^+$: 345.0239; found: 345.0267.

3-[(4-Hydroxyphenyl)imino]-1-propylindolin-2-one (5f): Red solid; yield: 91 %; m.p.: 193-194 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.64 (s, 1H), 7.46 (m, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 6.93 (m, 4H), 6.88-6.85 (m, 1H), 3.75 (t, *J* = 7.1 Hz, 2H), 1.71-1.65 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3205, 2931, 1727, 1651, 1606, 1503, 1468, 1356, 1262, 1206, 841. HR-MS (ESI): Calcd for $C_{17}H_{15}N_2O_2$ [M-H]$^-$: 279.1134; found: 279.1136.

3-[(4-Hydroxyphenyl)imino]-5-methyl-1-propylindolin-2-one (5g): Red solid; yield: 92 %; m.p.: 167-169 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.61 (s, 1H), 7.27-7.22 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.95-6.83 (m, 4H), 6.67 (s, 1H), 3.69 (t, *J* = 7.1 Hz, 2H), 2.06 (s, 3H), 1.66-1.60 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3311, 2940, 1730, 1683, 1603, 1503, 1489, 1339, 1259, 1224, 844, 812. HR-MS (ESI): Calcd for $C_{18}H_{17}N_2O_2$ [M-H]$^-$: 293.1290; f ound: 293.1286.

5-Fluoro-3-[(4-hydroxyphenyl)imino]-1-propylindolin-2-one (5h): Red solid; yield: 93 %; m.p.: 198-200 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.68 (s, 1H), 7.32 (m, 2H), 7.21 (dd, *J* = 8.7, 4.3 Hz, 1H), 6.98-6.84 (m, 4H), 6.49 (m, 1H), 3.70 (t, *J* = 7.2 Hz, 2H), 1.65-1.59 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3214, 2934, 1733, 1651, 1612, 1500, 1477, 1353, 1262, 1200, 832. HR-MS (ESI): Calcd for $C_{17}H_{14}N_2O_2F$ [M-H]$^-$: 297.1040; found: 297.1036.

5-Chloro-3-[(4-hydroxyphenyl)imino]-1-propylindolin-2-one (5i) Red solid; yield: 96 %; m.p.: 176-178 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.69 (s, 1H), 7.50 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.91 (m, 4H), 6.73 (d, *J* = 2.1 Hz, 1H), 3.70 (t, *J* = 7.2 Hz, 2H), 1.65-1.59 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3387, 2934, 1733, 1603, 1500, 1468, 1353, 1256, 1200, 841. HR-MS (ESI): Calcd for $C_{17}H_{14}N_2O_2Cl$ [M-H]$^-$: 313.0744; found: 313.0745.

5-Bromo-3-[(4-hydroxyphenyl)imino]-1-propylindolin-2-one (5j): Red solid; yield: 95 %; m.p.: 154-156 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.69 (s, 1H), 7.65-7.58 (m, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 6.95-6.86 (m, 4H), 6.79-6.73 (m, 1H), 3.70 (t, *J* = 7.2 Hz, 2H), 1.65-1.59 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3328, 2928, 1704, 1595, 1500, 1462, 1347, 1271, 1203, 815. HR-MS (ESI): Calcd for $C_{17}H_{14}N_2O_2Br$ [M-H]$^-$: 357.0239; found: 357.0246.

1-Butyl-3-[(4-hydroxyphenyl)imino]indolin-2-one (5k): Red solid; yield: 93 %; m.p.: 180-182 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.59 (s, 1H), 7.42 (m, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.93-6.82 (m, 5H), 6.82-6.78 (m, 1H), 3.74 (t, *J* = 7.1 Hz, 2H), 1.63-1.57 (m, 2H), 1.35 (dd, *J* = 15.1, 7.4 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3361, 2928, 1727, 1603, 1503, 1468, 1359, 1268, 1191,

841. HR-MS (ESI): Calcd for $C_{18}H_{17}N_2O_2$ [M-H]$^-$: 293.1290; found: 293.1286.

1-Butyl-3-[(4-hydroxyphenyl)imino]-5-methylindolin-2-one (5l): Red solid; yield: 95 %; m.p.: 129-131 °C; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ (ppm) 9.60 (s, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.89 (m, 4H), 6.66 (s, 1H), 3.72 (t, *J* = 7.0 Hz, 2H), 2.05 (s, 3H), 1.58 (dd, *J* = 14.6, 7.3 Hz, 2H), 1.36-1.29 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3278, 2928, 1686, 1609, 1495, 1477, 1359, 1271, 1233, 844, 817. HR-MS (ESI): Calcd for $C_{19}H_{19}N_2O_2$ [M-H]$^-$: 307.1447; found: 307.1449.

1-Butyl-5-fluoro-3-[(4-hydroxyphenyl)imino]indolin-2-one (5m): Red solid; yield: 92 %; m.p.: 176-178 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.69 (s, 1H), 7.32 (m, 1H), 7.19 (dd, *J* = 8.7, 4.3 Hz, 1H), 6.98-6.86 (m, 4H), 6.49 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.74 (t, *J* = 7.1 Hz, 2H), 1.61-1.55 (m, 2H), 1.34 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3390, 2931, 1727, 1606, 1497, 1471, 1356, 1265, 1188, 829. HR-MS (ESI): Calcd for $C_{18}H_{16}N_2O_2F$ [M-H]$^-$: 311.1196; found: 311.1198.

1-Butyl-5-chloro-3-[(4-hydroxyphenyl)imino]indolin-2-one (5n): Red solid; yield: 96 %; m.p.: 128-130 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.69 (s, 1H), 7.50 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.91 (m, 4H), 6.77-6.71 (m, 1H), 3.74 (t, *J* = 7.1 Hz, 2H), 1.58 (dd, *J* = 14.7, 7.4 Hz, 2H), 1.34 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3275, 2925, 1686, 1600, 1559, 1477, 1350, 1256, 1233, 841, 812. HR-MS (ESI): Calcd for $C_{18}H_{16}N_2O_2Cl$ [M-H]$^-$: 327.0901; found: 327.0905.

5-Bromo-1-butyl-3-[(4-hydroxyphenyl)imino]indolin-2-one (5o): Red solid; yield: 94 %; m.p.: 144-145 °C; ^{1}H NMR (400 MHz, d_6-DMSO, TMS) δ (ppm) 9.69 (s, 1H), 7.65-7.59 (m, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.90 (m, 4H), 6.50-6.36 (m, 1H), 3.73 (t, *J* = 7.1 Hz, 2H), 1.57 (dd, *J* = 14.7, 7.4 Hz, 2H), 1.33 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3281, 2925, 1689, 1600, 1559, 1500, 1471, 1350, 1271, 1235, 838, 815. HR-MS (ESI): Calcd for $C_{18}H_{16}N_2O_2Br$ [M-H]$^-$: 371.0395; found: 371.0390.

Synthesis of compounds 7a-7o

(*E*)-Methyl 2-(2-((6-(4-((1-ethyl-2-oxoindolin-3-ylidene)-amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxy-acrylate (7a): A solution of intermediate **5a** (0.85 g, 3.18 mmol) and K_2CO_3 (4.39 g, 31.8 mmol) in 40 mL DMF were stirred at 70 °C for 0.5 h and a solution of (*E*)-methyl 2-(2-((6-chloropyrimidin-4-yl)oxy)-phenyl)-3-methoxyacrylate (1.07 g, 3.34 mmol) in DMF (10 mL) was added dropwise to the above reaction mixture. The above reaction mixture was stirred at 90 °C for 4-8 h. The mixture was cooled to room temperature and poured into saturated brine (100 mL) to give mass of solid. The solid was successively washed with H_2O (10 mL × 3) and dried to give crude product. Purification of the crude product by column chromatography on silica gel (ether/acetone, 5:1 v/v; 0.3 % triethylamine was added) yielded pure compound **7a**. Yellow solid; yield: 67 %; m.p.: 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.46 (s, 1H), 7.47 (s, 1H), 7.39 (m, 2H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 4.2 Hz, 2H), 6.26 (s, 1H), 3.87 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 3.61 (s,3H), 1.34 (t, *J* = 7.2 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3063, 2974, 2943, 2847, 1725, 1693, 1631, 1607, 1560, 1495, 1472, 1378, 1287, 1250, 1203, 1172, 1128, 1099, 1056, 1003, 878, 831, 763, 594. HR-MS (ESI): Calcd for $C_{31}H_{27}N_4O_6$ [M+H]$^+$: 551.1931; found: 551.1931.

(*E*)-Methyl 2-(2-((6-(4-((1-ethyl-5-methyl-2-oxoindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7b): Yellow solid; yield: 64 %; m.p.: 147-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.43 (s, 1H), 7.47 (s, 1H), 7.39 (m, 1H), 7.34 (m, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.21 (m, 3H), 7.15 (s, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.52 (s, 1H), 6.27 (s, 1H), 3.84 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 3.61 (s, 3H), 2.11 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3055, 2925, 2852, 1724, 1636, 1568, 1492, 1450, 1371, 1344, 1250, 1197, 1127, 1050, 988, 862, 829, 762, 653. HR-MS (ESI): Calcd for $C_{32}H_{29}N_4O_6$ [M+H]$^+$: 565.2087. Found: 565.2082.

(*E*)-Methyl 2-(2-((6-(4-((1-ethyl-5-fluoro-2-oxoindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7c): Synthesized as same as **7a**, orange solid; yield: 52 %; m.p.: 179-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.45 (s, 1H), 7.47 (s, 1H), 7.43-7.37 (m, 1H), 7.34 (m, 1H), 7.30 (m, 1H), 7.25-7.18 (m, 3H), 7.16 (s, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.83 (m, 1H), 6.51 (m, 1H), 6.29 (s, 1H), 3.86 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 3.62 (s, 3H), 1.33 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3063, 2975, 2936, 2848, 1726, 1706, 1635, 1567, 1482, 1450, 1376, 1344, 1252, 1197, 1173, 1126, 1055, 1005, 884, 858, 834, 761, 656, 561. HR-MS (ESI): Calcd for $C_{31}H_{26}N_4O_6F$ [M+H]$^+$: 569.1836; found: 569.1841.

(*E*)-Methyl 2-(2-((6-(4-((5-chloro-1-ethyl-2-oxoindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7d): Orange solid; yield: 52 %; m.p.: 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.45 (s, 1H), 7.47 (s, 1H), 7.39 (m, 1H), 7.35 (m, 2H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.23-7.13 (m, 3H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 1.9 Hz, 1H), 6.29 (s, 1H), 3.86 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 3.62 (s, 3H), 1.33 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3061, 2981, 2934, 2843, 1733, 1709, 1633, 1600, 1565, 1492, 1468, 1442, 1377, 1344, 1247, 1203, 1165, 1127, 1056, 994, 882, 832, 767, 620. HR-MS (ESI): Calcd for $C_{31}H_{26}N_4O_6Cl$ [M+H]$^+$: 585.1541; found: 585.1551.

(*E*)-Methyl 2-(2-((6-(4-((5-bromo-1-ethyl-2-oxoindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)-phenyl)-3-methoxyacrylate (7e): Orange solid; yield: 43 %; m.p.: 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.46 (s, 1H), 7.50 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.37-7.28 (m, 3H), 7.25-7.02 (m, 4H), 6.94-6.71 (m, 2H), 6.30 (s, 1H), 3.86 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 3.62 (s, 3H), 1.33 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3058, 2940, 2849, 1709, 1665, 1630, 1600, 1565, 1492, 1442, 1380, 1333, 1250, 1124, 1047, 988, 832, 767. HR-MS (ESI): Calcd for $C_{31}H_{25}N_4O_6NaBr$ [M + Na]$^+$: 651.0855; found: 651.0842.

(*E*)-Methyl 3-methoxy-2-(2-((6-(4-((2-oxo-1-propylindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)-phenyl)acrylate (7f): Orange solid; yield: 68 %; m.p.: 80-

81 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.46 (s, 1H), 7.47 (s, 1H), 7.43-7.28 (m, 4H), 7.21 (q, *J* = 4. 7 Hz, 2H), 7.15 (s, 1H), 7.12-7.05 (m, 2H), 6.92-6.85 (m, 1H), 6.84-6.76 (m, 2H), 6.27 (s, 1H), 3.82-3.71 (m, 5H), 3.61 (s, 3H), 1.83-1.72 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3058, 2928, 2872, 2849, 1721, 1633, 1603, 1568, 1492, 1447, 1383, 1359, 1250, 1203, 1130, 1097, 1050, 985, 918, 841, 753, 591, 488. HR-MS (ESI): Calcd for $C_{32}H_{29}N_4O_6$ $[M+H]^+$: 565.2087; found: 565.2090.

(*E*)-Methyl 3-methoxy-2-(2-((6-(4-((5-methyl-2-oxo-1-propylindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)acrylate (7g): Orange solid; yield: 69 %; m.p.: 72-74 °C; ^{1}H NMR (400 MHz,-$CDCl_3$, TMS) δ (ppm) 8.44 (s, 1H), 7.48 (s, 1H), 7.43-7.38 (m, 1H), 7.36-7.29 (m, 2H), 7.23-7.11 (m, 4H), 7.11-7.03 (m, 2H), 6.82-6.68 (m, 1H), 6.51 (s, 1H), 6.28 (s, 1H), 3.78-3.70 (m, 5H), 3.60 (s, *J* = 7.8 Hz, 3H), 2.10 (s, 3H), 1.81-1.70 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3058, 2934, 2869, 1721, 1565, 1489, 1447, 1383, 1350, 1250, 1203, 1124, 1053, 985, 841, 812, 762, 659, 614, 558, 511, 461. HR-MS (ESI): Calcd for $C_{33}H_{31}N_4O_6$ $[M+H]^+$: 579.2244; found: 579.2247.

(*E*)-Methyl 2-(2-((6-(4-((5-fluoro-2-oxo-1-propylin-dolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7h): Orange solid; yield: 61 %; m.p.: 81-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.45 (s, 1H), 7.47 (s, 1H), 7.43-7.35 (m, 1H), 7.34-7.28 (m, 2H), 7.25-7.18 (m, 3H), 7.13 (m, 1H), 7.08 (m, 2H), 6.82 (m, 1H), 6.50 (m, 1H), 6.29 (s, 1H), 3.80-3.72 (m, 5H), 3.62 (s, 3H), 1.76 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3058, 2940, 2875, 1709, 1636, 1565, 1480, 1450, 1383, 1330, 1250, 1200, 1130, 1100, 1053, 988, 879, 838, 767, 656, 564, 514, 461. HR-MS (ESI): Calcd for $C_{32}H_{28}N_4O_6F$ $[M+H]^+$: 583.1993; found: 583.2004.

(*E*)-Methyl 2-(2-((6-(4-((5-chloro-2-oxo-1-propylindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7i): Orange solid; yield: 65 %; m.p.: 77-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.45 (s, 1H), 7.48 (s, 1H), 7.44-7.37 (m, 1H), 7.32 (m, 3H), 7.26-7.12 (m, 3H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.81 (m, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 6.30 (s, 1H), 3.80-3.64 (m, 5H), 3.62 (s, 3H), 1.76 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3063, 2931, 2872, 2852, 1712, 1633, 1600, 1565, 1492, 1444, 1383, 1330, 1250, 1203, 1132, 1050, 988, 921, 838, 765, 606, 544, 514, 458. HR-MS (ESI): Calcd for $C_{32}H_{28}N_4O_6Cl$ $[M+H]^+$: 599.1697; found: 599.1698.

(*E*)-Methyl 2-(2-((6-(4-((5-bromo-2-oxo-1-propylindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7j): Orange solid; yield: 49 %; m.p.: 76-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.46 (s, 1H), 7.48 (dd, *J* = 8.0, 2.6 Hz, 2H), 7.43-7.37 (m, 1H), 7.36-7.28 (m, 2H), 7.25-7.11 (m, 3H), 7.12-6.99 (m, 2H), 6.86 (d, *J* = 1.9 Hz, 1H), 6.76 (m, 1H), 6.30 (s, 1H), 3.82-3.65 (m, 5H), 3.62 (s, 3H), 1.76 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3063, 2937, 2866, 1712, 1636, 1598, 1562, 1489, 1447, 1380, 1333, 1256, 1206, 1132, 1050, 991, 918, 838, 767. HR-MS (ESI): Calcd for $C_{32}H_{28}N_4O_6$ Br $[M+H]^+$: 643.1192; found: 643.1189.

(*E*)-Methyl 2-(2-((6-(4-((1-butyl-2-oxoindolin-3-ylidene)-amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxy-acrylate (7k): Orange solid; yield: 55 %; m.p.: 66-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.46 (s, 1H), 7.47 (s, 1H), 7.42-7.28 (m, 4H), 7.23-7.19 (m, 2H), 7.15 (s, 1H), 7.11-7.05 (m, 2H), 6.91-6.84 (m, 1H), 6.84-6.75 (m, 2H), 6.27 (d, *J* = 0.6 Hz, 1H), 3.80 (t, *J* = 7.4 Hz, 2H), 3.76 (s, 3H), 3.61 (s, 3H), 1.72 (m, 2H), 1.45 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3055, 2934, 2863, 1712, 1633, 1603, 1565, 1489, 1447, 1380, 1250, 1206, 1132, 1094, 1050, 985, 844, 753. HR-MS (ESI): Calcd for $C_{33}H_{31}N_4O_6$ $[M+H]^+$: 579.2244; found: 579.2240.

(*E*)-Methyl 2-(2-((6-(4-((1-butyl-5-methyl-2-oxoindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7l): Orange solid; yield: 47 %; m.p.: 59-60 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.43 (s, 1H), 7.47 (s, 1H), 7.42-7.36 (m, 1H), 7.36-7.28 (m, 2H), 7.19 (m, 4H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.75 (m, 1H), 6.51 (s, 1H), 6.27 (s, 1H), 3.81-3.73 (m, 5H), 3.61 (s, 3H), 2.10 (s, 3H), 1.71 (m, 2H), 1.44 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3055, 2952, 2928, 2866, 1712, 1562, 1486, 1444, 1380, 1344, 1250, 1200, 1127, 1053, 985, 918, 817, 765. HR-MS (ESI): Calcd for $C_{34}H_{33}N_4O_6$ $[M+H]^+$: 593.2400; found: 593.2403.

(*E*)-Methyl 2-(2-((6-(4-((1-butyl-5-fluoro-2-oxoindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7m): Orange solid; yield: 49 %; m.p.: 66-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.45 (s, 1H), 7.47 (s, 1H), 7.44-7.28 (m, 3H), 7.25-6.97 (m, 6H), 6.81 (m, 1H), 6.57-6.40 (m, 1H), 6.29 (s, 1H), 3.78 (m, 5H), 3.62 (s, 3H), 1.69 (m, 2H), 1.44 (m, 2H), 0.99 (t, *J* = 7.1 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3085, 2957, 2928, 2866, 1709, 1633, 1603, 1565, 1483, 1447, 1380, 1330, 1247, 1203, 1130, 1053, 988, 918, 823, 762. HR-MS (ESI): Calcd for $C_{33}H_{30}N_4O_6F$ $[M+H]^+$: 597.2149; found: 597.2142.

(*E*)-Methyl 2-(2-((6-(4-((1-butyl-5-chloro-2-oxoindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7n): Orange solid; yield: 40 %; m.p.: 75-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ (ppm) 8.45 (s, 1H), 7.48 (s, 1H), 7.44-7.37 (m, 1H), 7.36-7.28 (m, 3H), 7.26-7.11 (m, 3H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.80 (m, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 6.30 (s, 1H), 3.83-3.66 (m, 5H), 3.62 (s, 3H), 1.78-1.60 (m, 2H), 1.44 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3061, 2940, 2869, 1706, 1636, 1600, 1565, 1492, 1444, 1383, 1336, 1250, 1203, 1130, 1056, 991, 838, 815, 767. HR-MS (ESI): Calcd for $C_{33}H_{30}N_4O_6Cl$ $[M+H]^+$: 613.1854; found: 613.1849.

(*E*)-Methyl 2-(2-((6-(4-((5-bromo-1-butyl-2-oxoindolin-3-ylidene)amino)phenoxy)pyrimidin-4-yl)oxy)phenyl)-3-methoxyacrylate (7o): Orange solid; yield: 42 %; m.p.: 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.46 (s, 1H), 7.52-7.45 (m, 2H), 7.43-7.37 (m, 1H), 7.36-7.27 (m, 2H), 7.26-7.12 (m, 3H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 1.9 Hz, 1H), 6.76 (m, 1H), 6.30 (s, 1H), 3.82-3.70 (m, 5H), 3.62 (s, 3H), 1.75-1.64 (m, 2H), 1.44 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3061, 2940, 2866, 1709, 1633, 1600, 1562, 1492, 1439, 1380, 1330, 1250, 1203, 1130, 1050, 985, 838, 815, 762. HR-MS (ESI): Calcd for $C_{33}H_{30}N_4O_6Br$ $[M+H]^+$: 657.1349; found: 657.1339.

RESULTS AND DISCUSSION

Synthetic procedure of compounds 5: The compounds **5** were new compounds bearing C=N bond. These compounds were given in high yield by the condensation of intermediate **4** and *p*-aminophenol in the presence of a catalytic amount of glacial acetic acid. The best mole ratio of intermediate **4**: *p*-aminophenol was 1:1.05.

Synthetic procedure of compounds 7: The etherification reaction of **5** with **6** was relatively easy in basic conditions. Target compounds **7** were obtained in moderate yield according to our synthesized method. When the mole ratio of intermediate **5**, intermediate **6** and K_2CO_3 was 1: 1.05: 10, the compounds **7** were prepared in the highest yield and the excess **6** could be removed by the silica gel column easily. In addition, the reacting time of etherification was at a scale of 4-10 h based on 5-different substituent of indolin-2-one ring, 5-H substituted was the shortest and 5-Br substituted was the longest.

Purification of target compounds 7: Originally, the crude product **7** disappeared during the chromatographic purification on silica gel. Obviously, compounds **7** were decomposed. Further research shows the cleavage of carbon-nitrogen double bond of crude product **7** by the ^{1}H NMR spectrum analysis. In order to avoid the acidic separation conditions, the crude product was chromatographed on silica gel column using petroleum ether/acetone (5:1 v/v) with 0.3 % triethylamine as the mobile phase to afford the target compound **7** finally. The additional triethylamine was evaporated under reduced pressure.

Structural elucidation of compounds 7: The structure elucidation of compounds **7** was assigned on the basis of their IR, ^{1}H NMR spectral studies and mass spectra analysis. The IR spectral of compounds **7** indicated that the absorption bands at 1693-1633, 1725-1706, 2875-2843 and 3063-3055 cm^{-1} related to imino groups, carbonyl groups, aromatic C-H and methoxy groups respectively. The ^{1}H NMR spectral of compounds **7** showed the pyrimidine C-2 proton appeared at δ = 8.43-8.46 ppm as a singlet and the protons of two methoxyls also as a singlet appeared at δ = 3.60-3.62 ppm and δ = 3.76-3.78 ppm. The absorption peaks of all other protons were appeared in the expected region. Trial to detect the molecular ion peak of compounds **7** by electrospray ionization (ESI) method showed absolute error within 0.0013 compared with calculated value.

Conclusion

In conclusion, fifteen novel intermediates (**5a-5o**) and fifteen 3-substituted indolin-2-one derivatives with methyl (*E*)-2-(3-methoxy) acrylate (**7a-7o**) have been designed and synthesized. The structures of intermediates and target compounds were confirmed by ^{1}H NMR, IR and HR-MS spectra analysis. Further efforts to test biological activities of new target compounds are now in progress and will be reported in the near future.

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