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Design and Synthesis of Novel 3,5-Substituted Indolin-2-one Derivatives

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In this paper, twelve novel 3,5-substituted indolin-2-one derivatives were designed and synthesized based on indolin-2-one. The structures of the new compounds have been confirmed by ^{1}H NMR, HR-MS and IR spectra analysis. This study provides a new method for development of indolin-2-one derivatives.

Keywords: 3-Substituted indolin-2-ones, Benzamides, Synthesis.

INTRODUCTION

Indolin-2-one derivatives are important structures and have a wide range of biological activities, such as antiinflammatory[1], antibacterial[2], antifungal[3], anticancer[4] and regulating receptor kinase[5]. The indolin-2-one skeleton can be found in many prevalent natural products (rhyncophylline, paraher-quamide *e.g.*,)[6,7]. Over the past decade, various methods for the synthesis of these biologically active compounds have been developed[8-10].

In 1995, Tenida **1** (Fig. 1), a derivative of 3-benzylidene indolin-2-one developed by Pfizer, was marketed in Spain and Holland as a novel non-steroidal antiinflammatory drug.

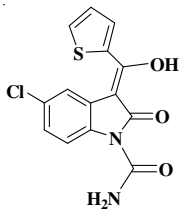
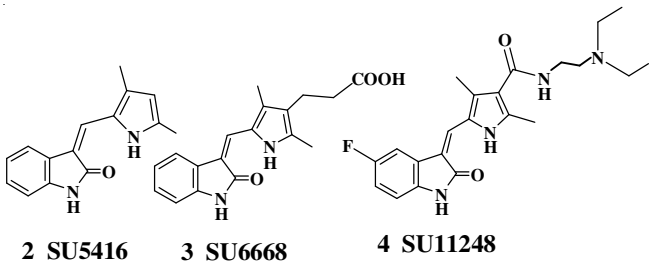


Fig.1. Structure of Tenida **1**

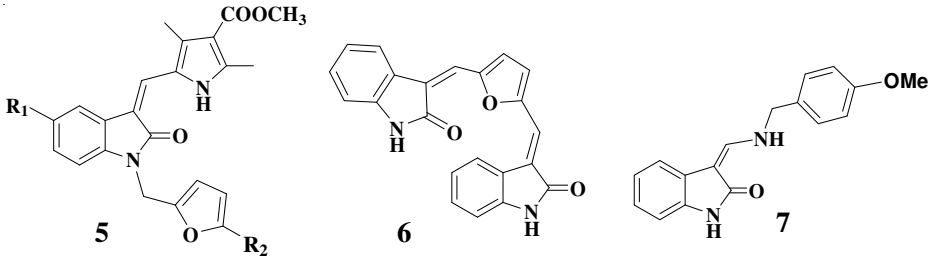
As antitumor drugs, 3-benzylidene indolin-2-one derivatives SU5416[8] **2**, SU6668[9] **3** and SU11248[10] **4** (Fig. 2) have been used in clinical trial. In 2006, SU11248 was approved to market by the FDA.



2 SU5416 **3 SU6668** **4 SU11248**

Fig. 2. Structure of compounds **2**, **3** and **4**

Recently, the researchers have paid more attention on 3-benzylidene indolin-2-one derivatives[11-15]. Wen *et al.*[11] have reported that 1-furfuryl-3-substituted indolin-2-one derivatives **5** (Fig. 3) which have good antitumoral activity *in vitro*. Shinobu *et al.*[12] have studied on hydroxyindole derivatives as Pim-1 kinase inhibitors and indicated that compound **6** (Fig. 3)



5 **6** **7**

Fig. 3. Structure of compounds **5**, **6** and **7**

have strong anticancer activity. Hyeon *et al.*[13] have found that 3-(4-methoxy-benzylaminomethylene)-1,3-dihydroindole-2-one **7** (Fig. 3) showed EC_{50} (50 % inhibition concn. of cell growth) of 269.2 μM for *T. gondii* and 75 % *anticoccdial* activity (after 9 days post infection).

Rindhe *et al.*[14] reported that indolin-2-ones **8** (Fig. 4) exhibited significant antimicrobial activity. Watanabe *et al.*[15] have studied that indolin-2-one derivatives may serve as a new molecular scaffold for developing novel NFT imaging agents and the compound **9** (Fig. 4) showed the highest affinity.

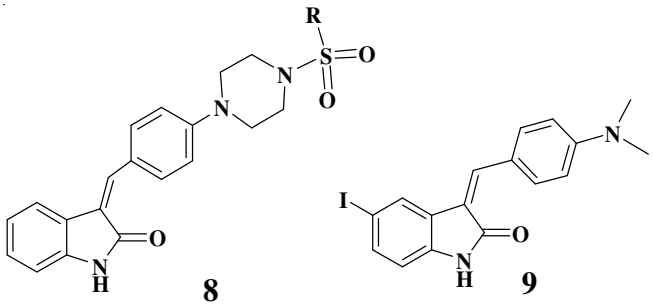


Fig. 4. Structure of compounds **8** and **9**

To search biologically active molecules of indolin-2-one derivatives, twelve new 5-substituted 3-benzylidene derivatives of indolin-2-one **10** (Fig. 5) have been designed and synthesized in our lab. Compared with previous compounds, the new target compounds which have different structure framework may have new biological activity. The synthesis route of target compounds was shown in **Scheme-I**.

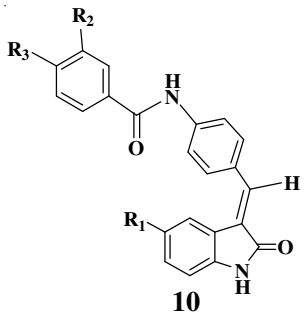
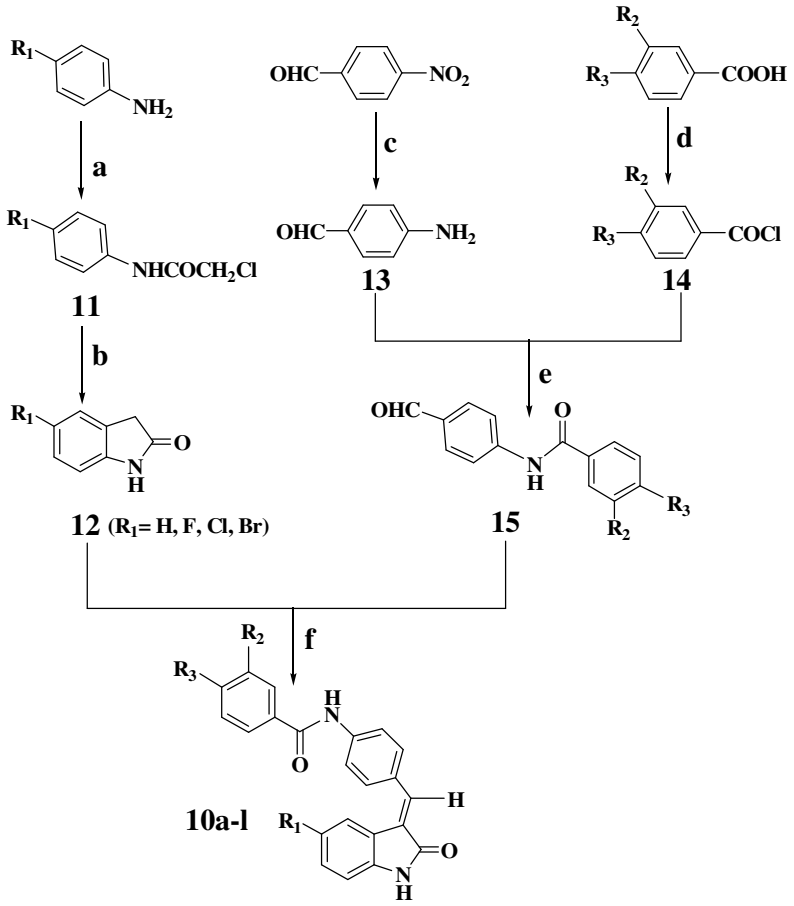


Fig. 5. Structure of target compound **10**

EXPERIMENTAL

All reagents and solvents used in this study were procured 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.



10a: R_1= H, R_2= H, R_3= H
10b: R_1= H, R_2= CH_3, R_3= H
10c: R_1= H , R_2= H, R_3= Cl
10d: R_1= F, R_2= H, R_3= H
10e: R_1= F, R_2= CH_3, R_3= H
10f: R_1= F, R_2= H, R_3= Cl
10g: R_1= Cl, R_2= H, R_3= H
10h: R_1= Cl, R_2= CH_3, R_3= H
10i: R_1= Cl, R_2= H, R_3= Cl
10j: R_1= Br, R_2= H, R_3= H
10k: R_1= Br, R_2= CH_3, R_3= H
10l: R_1= Br, R_2= H, R_3= Cl

Scheme-I: Reagents and conditions: (a) $ClCH_2COCl$, K_2CO_3, CH_2Cl_2, rt 3-5 h; (b) $AlCl_3$, 220 °C, 1 h; (c) $SnCl_2$, EtOH, 70 °C, 2 h; (d) $SOCl_2$, reflux, 1 h; (e) EtOAc, K_2CO_3, rt, 4-6 h; (f) Piperidine, EtOH, reflux, 3-5 h

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 DMSO-d_6 or $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. Melting point was recorded on XRC-1 apparatus and the thermometer was uncorrected.

Synthesis of intermediate 5-substituted indolin-2-ones 12a-d: The compound **12a** was prepared from 4-substituted anilines according to literature procedures[16] with some modifications. Yield: 82 % (81.3 %[16]). **12b**, **12c** were prepared by the similar method as **12a**, yield: 83-85 %. **12d** was prepared by bromination of compound **12a** with NBS according the literature[17]. The melting point, ^{1}H NMR and IR spectra of **12a-d** that were in accordance with previous report[18].

Synthesis of *p*-aminobenzaldehyde 13: *p*-Aminobenzaldehyde was obtained by the reduction of *p*-nitrobenzaldehyde according the literature[19], Data of melting points and NMR spectra were in excellent agreement with the literature data. Because of the instability of **13**, the dried extract (EtOAc) containing *p*-aminobenzaldehyde was directly used to prepare compounds **15a-c**.

Synthesis of intermediate compounds 15a-c: Substituted benzoyl chloride **14** was prepared *via* refluxing substituted benzoic acid (0.02 mol) with $SOCl_2$ (10 mL). After cooling, the mixture was evaporated under reduced pressure to afford the liquid **14a-c**, yield: 98-99 %.

The compound **14** (0.02 mol) in anhydrous ethyl acetate (10 mL) was added dropwise to a solution of *p*-aminobenzaldehyde **13** in dried ethyl acetate (0.02 mol, 40 mL) and K_2CO_3 (0.05 mol, 3.24 g) at room temperature. After 4-6 h, water (50 mL) was poured into the reaction flask and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to give crude product. The crude material was chromatographed on silica gel using petroleum ether/ethyl acetate (4:1 v/v) as eluent to afford the pure product **15a-15c**.

***N*-(4-Formylphenyl)benzamide (15a)[20]:** Yellow solid, m.p. 122-124 °C, yield: 82 %, ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ = 9.96 (s, 1H), 8.03 (s, 1H), 7.84-7.93 (m, 6H), 7.60 (t, 1H, *J* = 7.2 Hz), 7.53 (t, 2H, *J* = 8.0 Hz). IR (KBr, ν_{max}, cm^{-1}): 3437, 2831, 2739, 1695, 1658, 1596, 1523, 1451, 1259, 1167, 1099, 1024, 826, 802, 683, 651. HR-MS (ESI): Calcd for $C_{14}H_{10}NO_2$ $[M-H]^+$: 224.0712, Found: 224.0713.

***N*-(4-Formylphenyl)-3-methylbenzamide (15b):** Yellow solid, m.p. 126-128 °C, yield: 76.9 %, ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ = 9.94 (s, 1H), 8.09 (s, 1H), 7.87 (q, 4H, *J* = 8.0 Hz), 7.65-7.70 (m, 2H), 7.38 (d, 2H, *J* = 4.8Hz), 2.43 (s, 3H). IR (KBr, ν_{max}, cm^{-1}): 3481, 2851, 1677, 1586, 1417, 1397, 1372, 1267, 838, 808, 806, 771, 737, 676, 645. HR-MS (ESI): Calcd for $C_{15}H_{12}NO_2$ $[M-H]^+$: 238.0868, Found: 238.0860.

4-Chloro-*N*-(4-formylphenyl)benzamide (15c)[21]: yellow solid, m.p. 180-182 °C, yield: 74.8 %, ^{1}H NMR (400 MHz; $CDCl_3$; TMS): δ = 9.95 (s, 1H), 8.06 (s, 1H), 7.91 (d, 2H, *J* = 8.4 Hz), 7.84 (d, 4H, *J* = 8.8 Hz), 7.49 (d, 2H, *J* = 8.4 Hz). IR (KBr, ν_{max}, cm^{-1}): 3443, 2963, 2848, 1690, 1654, 1596, 1532, 1486, 1329, 1262, 898, 843, 820, 794, 752. HR-MS (ESI): Calcd for $C_{14}H_9NO_2Cl$ $[M-H]^+$: 258.0322, Found: 258.0316.

Synthesis of the target compounds 10(a-l): A solution of compound **12** (2 mmol), compound **15** (2.4 mmol), piperidine (2 mmol, 0.17 g) in EtOH (15 mL) was stirred at 90 °C under nitrogen for 3-5 h. After the mixture cooled, the precipitate was filtered, washed with cold ethanol and dried in vacuum oven to give the target compounds **10(a-l)**.

4-[(*E*)-(2-Oxoindolin-3-ylidene)methyl]-*N*-phenylbenzamide (10a): Yellow solid, yield: 85 %, m.p. 212-214 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.62 (s, 1H), 10.52 (s, 1H), 8.47 (d, 2H, *J* = 8.4 Hz), 7.98 (d, 2H, *J* = 7.6 Hz), 7.91 (d, 2H, *J* = 8.4 Hz), 7.77 (s, 1H), 7.70 (d, 2H, *J* = 7.6 Hz), 7.63 (t, 1H, *J* = 7.2 Hz), 7.56 (t, 2H, *J* = 7.2 Hz), 7.20 (t, 1H, *J* = 7.6 Hz), 6.99 (t, 1H, *J* = 7.6 Hz), 6.83 (d, 1H, *J* = 7.6 Hz). IR (KBr, ν_{max}, cm^{-1}): 3378, 2921, 1684, 1650, 1614, 1581, 1521, 1467, 1258, 1095, 1025, 837, 785, 747. HR-MS (ESI): Calcd for $C_{22}H_{15}N_2O_2$ $[M-H]^+$: 339.1134, Found: 339.1124.

4-[(*E*)-(2-Oxoindolin-3-ylidene)methyl]-*N*-*m*-tolylbenzamide (10b): Yellow solid, yield: 82.8 %, m.p. 214-216 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.62 (s, 1H), 10.48 (s, 1H), 8.47 (d, 2H, *J* = 8.4 Hz), 7.91 (d, 2H, *J* = 8.4 Hz), 7.77 (d, 3H, *J* = 10.8 Hz), 7.70 (d, 2H, *J* = 7.6 Hz), 7.45 (d, 2H, *J* = 6.8 Hz), 7.20 (t, 1H, *J* = 7.6 Hz), 6.99 (t, 1H, *J* = 7.6 Hz), 6.83 (d, 1H, *J* = 7.6 Hz), 2.42 (s, 3H). IR (KBr, ν_{max}, cm^{-1}): 3366, 3271, 2920, 1682, 1647, 1622, 1584, 1524, 1467, 1315, 1264, 1178, 830, 786. HR-MS (ESI): Calcd for $C_{23}H_{16}N_2O_2$ $[M-H]^+$: 353.1290, Found: 353.1280.

***N*-(4-Chlorophenyl)-4-[(*E*)-(2-oxoindolin-3-ylidene)-methyl]benzamide (10c):** Yellow solid, yield: 81.7 %, m.p. 242-244 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.60 (s, 2H), 8.01 (d, 2H, *J* = 8.4 Hz), 7.95 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 2H, *J* = 8.4 Hz), 7.66 (d, 3H, *J* = 8.4 Hz), 7.60 (s, 1H), 7.24 (t, 1H, *J* = 7.6 Hz), 6.87 (t, 2H, *J* = 8.0 Hz). IR (KBr, ν_{max}, cm^{-1}): 3446, 3079, 2876, 1705, 1668, 1647, 1594, 1516, 1485, 1462, 1364, 1324, 1258, 1096, 1015, 841, 779, 750. HR-MS (ESI): Calcd for $C_{22}H_{14}N_2O_2Cl$ $[M-H]^+$: 373.0744, Found: 373.0735.

4-[(*E*)-(5-Fluoro-2-oxoindolin-3-ylidene)methyl]-*N*-phenylbenzamide (10d): Yellow solid, yield: 81.4 %, m.p. 246-248 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.63 (s, 1H), 10.55 (s, 1H), 8.48 (d, 2H, *J* = 8.4 Hz), 7.98 (d, 2H, *J* = 7.6 Hz), 7.92 (d, 2H, *J* = 8.4 Hz), 7.85 (s, 1H), 7.62 (t, 2H, *J* = 8.0 Hz), 7.56 (t, 2H, *J* = 7.6 Hz,), 7.02 (t, 1H, *J* = 8.4 Hz), 6.80 (dd, 1H, *J* = 8.4, 4.4 Hz). IR (KBr, ν_{max}, cm^{-1}): 3293, 2920, 2850, 1675, 1650, 1574, 1520, 1486, 1375, 1267, 1121, 1017, 899, 801, 694. HR-MS (ESI): Calcd for $C_{22}H_{14}N_2O_2F$ $[M-H]^+$: 357.1040, Found: 357.1034.

4-[(*E*)-(5-Fluoro-2-oxoindolin-3-ylidene)methyl]-*N*-*m*-tolylbenzamide(10e): Yellow solid, yield: 86.4 %, m.p. 248-250 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.63 (s, 1H), 10.51 (s, 1H), 7.96 (d, 2H, *J* = 8.4 Hz), 7.74-7.80 (m, 4H,), 7.67 (s, 1H), 7.45 (d, 2H, *J* = 5.6 Hz), 7.37 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.10 (td, 1H, *J* = 2.4, 8.8 Hz), 6.87 (dd, 1H, *J* = 4.8, 8.8 Hz), 2.42 (s, 3H). IR (KBr, ν_{max}, cm^{-1}): 3426, 3297, 2923, 2850, 1701, 1653, 1593, 1520, 1473, 1406, 1324, 1242, 1083, 1007, 836, 732. HR-MS (ESI): Calcd for $C_{23}H_{16}N_2O_2F$ $[M-H]^+$: 371.1196, Found: 371.1184.

***N*-(4-Chlorophenyl)-4-[(*E*)-(5-fluoro-2-oxoindolin-3-ylidene)methyl]benzamide (10f):** Yellow solid, yield: 80.4 %, m.p. 254-256 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ =

10.75 (s, 1H), 10.61 (s, 1H), 8.00-8.04 (m, 2H), 7.95-7.98 (m, 2H), 7.76 (dd, *J* = 2.4, 8.8 Hz), 7.65 (d, 2H, *J* = 8.8 Hz), 7.30 (dd, 1H, *J* = 2.0, 8.0 Hz), 6.96 (dd, 1H, *J* = 2.0, 8.4 Hz), 6.90 (dd, 1H, *J* = 2.0, 6.4 Hz). IR (KBr, ν_{max}, cm^{-1}): 3443, 1704, 1651, 1592, 1521, 1480, 1319, 1263, 1095, 1012, 840, 755. HR-MS (ESI): Calcd for $C_{22}H_{13}N_2O_2ClF$ $[M-H]^+$: 391.0650, Found: 391.0657.

4-[(*E*)-(5-Chloro-2-oxoindolin-3-ylidene)methyl]-*N*-phenylbenzamide (10g): Yellow solid, yield: 81.7 %, m.p. 250-252 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.77 (s, 1H), 10.55 (s, 1H), 8.46 (d, 2H, *J* = 8.8 Hz), 7.98 (d, 2H, *J* = 7.2 Hz), 7.92 (d, 2H, *J* = 8.4 Hz), 7.83 (s, 1H), 7.74 (t, 1H, *J* = 8.4 Hz), 7.62 (t, 1H, *J* = 6.4 Hz), 7.56 (t, 2H, *J* = 7.6 Hz), 7.05 (dd, 1H, *J* = 2.0, 8.4 Hz), 6.83 (d, 1H, *J* = 2.0 Hz). IR (KBr, ν_{max}, cm^{-1}): 3431, 1683, 1655, 1614, 1578, 1527, 1479, 1450, 1325, 1262, 1067, 1029, 838, 813, 758, 700. HR-MS (ESI): Calcd for $C_{22}H_{14}N_2O_2Cl$ $[M-H]^+$: 373.0744, Found: 373.0735.

4-[(*E*)-(5-Chloro-2-oxoindolin-3-ylidene)methyl]-*N*-*m*-tolylbenzamide (10h): Yellow solid, yield: 82.4 %, m.p. 252-254 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.76 (s, 1H), 10.51 (s, 1H), 7.98 (d, 2H, *J* = 8.4 Hz), 7.71-7.80 (m, 4H), 7.69 (s, 1H), 7.59 (d, 1H, *J* = 2.0 Hz), 7.43 (d, 2H, *J* = 7.2 Hz), 7.30 (dd, 1H, *J* = 2.4, 8.4 Hz), 7.05 (dd, 1H, *J* = 2.0, 8.0 Hz), 2.43 (s, 3H). IR (KBr, ν_{max}, cm^{-1}): 3407, 3265, 2926, 2850, 1707, 1685, 1647, 1581, 1517, 1454, 1251, 1204, 1096, 1064, 802, 722, 640. HR-MS (ESI): Calcd for $C_{23}H_{16}N_2O_2Cl$ $[M-H]^+$: 387.0901, Found: 387.0893.

4-[(*E*)-(5-Chloro-2-oxoindolin-3-ylidene)methyl]-*N*-(4-chlorophenyl)benzamide (10i): Yellow solid, yield: 80.7 %, m.p. 256-258 °C, ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.75 (s, 1H), 10.62 (s, 1H), 7.95-8.04 (m, 4H), 7.76 (dd, 2H, *J* = 2.4, 8.4 Hz), 7.69 (s, 1H), 7.65 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 1H, *J* = 2.0 Hz), 7.30 (dd, 1H, *J* = 2.0, 8.4 Hz), 6.97 (dd, 1H, *J* = 2.4, 8.4 Hz). IR (KBr, ν_{max}, cm^{-1}): 3423, 2929, 2856, 1710, 1669, 1600, 1533, 1517, 1454, 1410, 1261, 1102, 1004, 838, 805, 757, 646. HR-MS (ESI): Calcd for $C_{22}H_{13}N_2O_2Cl_2$ $[M-H]^+$: 407.0354, Found: 407.0346.

4-[(*E*)-(5-Bromo-2-oxoindolin-3-ylidene)methyl]-*N*-phenylbenzamide (10j): Yellow solid, yield: 84 %, m.p. 270-272 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.71 (s, 1H), 10.52 (s, 1H), 7.97 (m, 4H), 7.72-7.75 (m, 3H), 7.68 (s, 1H), 7.61 (t, 1H, *J* = 7.2 Hz), 7.56 (t, 2H, *J* = 7.6 Hz), 7.41 (d, 1H, *J* = 8.0 Hz), 6.86 (d, 1H, *J* = 8.0 Hz). IR (KBr, ν_{max}, cm^{-1}): 3430, 2926, 2917, 2850, 1701, 1650, 1593, 1511, 1463, 1403, 1250, 1201, 1172, 817, 707, 640. HR-MS (ESI): Calcd. for $C_{22}H_{14}N_2O_2Br$ $[M-H]^+$: 417.0239, Found: 417.0237.

4-[(*E*)-(5-Bromo-2-oxoindolin-3-ylidene)methyl]-*N*-*m*-tolylbenzamide (10k): Yellow solid, yield: 83.7 %, m.p. 274-276 °C. ^{1}H NMR (400 MHz; d_6-DMSO, TMS): δ = 10.76 (s, 1H), 10.52 (s, 1H), 7.98 (d, 2H, *J* = 8.4 Hz), 7.92 (d, 1H, *J* = 8.4 Hz), 7.72-7.80 (m, 4H), 7.68 (s, 1H), 7.44 (m, 3H), 6.86 (d, 1H, *J* = 8.4 Hz), 2.41 (s, 3H). IR (KBr, ν_{max}, cm^{-1}): 3436, 3268, 2917, 2850, 1707, 1673, 1646, 1588, 1460, 1320, 1244, 1104, 1005, 815, 733, 640. HR-MS (ESI): Calcd for $C_{23}H_{16}N_2O_2Br$ $[M-H]^+$: 431.0395, Found: 431.0393.

4-[(*E*)-(5-Bromo-2-oxoindolin-3-ylidene)methyl]-*N*-(4-chlorophenyl)benzamide (10*l*): Yellow solid, yield: 82.3 %, m.p. 280-282 °C. ^{1}H NMR (400MHz; d_6-DMSO, TMS): δ = 10.74 (s, 1H), 10.60 (s, 1H), 8.03 (d, 2H, *J* = 8.0 Hz), 7.97 (d, 2H, *J* = 8.4 Hz), 7.74 (d, 2H, *J* = 8.4 Hz), 7.71 (s, 1H), 7.65 (t, 3H, *J* =8.8 Hz), 7.42 (d, 1H, *J* = 8.0 Hz), 6.86 (d, 1H, *J* = 8.4 Hz). IR (KBr, ν_{max}, cm^{-1}): 3426, 3173, 2917, 2847, 1698, 1669, 1590, 1508, 1492, 1463, 1457, 1258, 1175, 1087, 1023, 846, 754, 646. HR-MS (ESI): Calcd for $C_{22}H_{13}N_2O_2BrCl$ $[M-H]^+$: 450.9849, Found: 450.9847.

RESULTS AND DISCUSSION

Compounds **14a-c** were prepared *via* refluxing substituted benzoic acid with $SOCl_2$. According the literature[20,21], the synthesis of compound **15** and its analogues generally involved four steps: the protection of *p*-nitrobenzaldehyde as dioxolanes, the reduction of nitro group, amidation and deprotection of the formyl group. In this study, compound **15** was synthesized by two procedures: the reduction of *p*-nitrobenzaldehyde and amidation, we used EtOAc as solvent and K_2CO_3 as alkali in the amidation, the total yield is 74-82 %.

The target compounds **10a-l** were synthesized by substituted aldehydes (**15a-c**) and 5-substituted indolin-2-ones (**12a-d**) in the presence of piperidine. The molar ratio of aldehydes, indolin-2-ones and piperidine is 1.2 : 1.0 : 1.0. Most of the compounds need not to be recrystallized, the yields are over 80 %. According to the literature[22], The chemical shifts for the protons at the C-2' and C-6' positions in the phenyl ring at the C-3 position of the 3-(substituted benzylidenyl)indolin-2-ones were around 7.85-8.53 ppm for the Z isomer but 7.45-7.84 ppm for the E isomer. The chemical shifts for the protons at the C-2' and C-6' positions in the phenyl ring of target compounds are consistent with that of the related E isomers reported.

Conclusion

Twelve new 3,5-substituted indolin-2-one derivatives (**10a-l**) bearing substituted benzamide moiety have been synthesized with good yield. The target compounds were confirmed by 1H NMR, HR-MS and IR spectra analysis. The biological activities of these new compounds need to be further researched. This study may lay the foundation for further research on modification and reformation of indolin-2-ones.

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