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## SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-((1-METHYL-1H-PYRROL-2-YL)METHYLENE)INDOLIN-2-ONE DERIVATIVES AS POTENT ANTICANCER ACTIVE AGENTS

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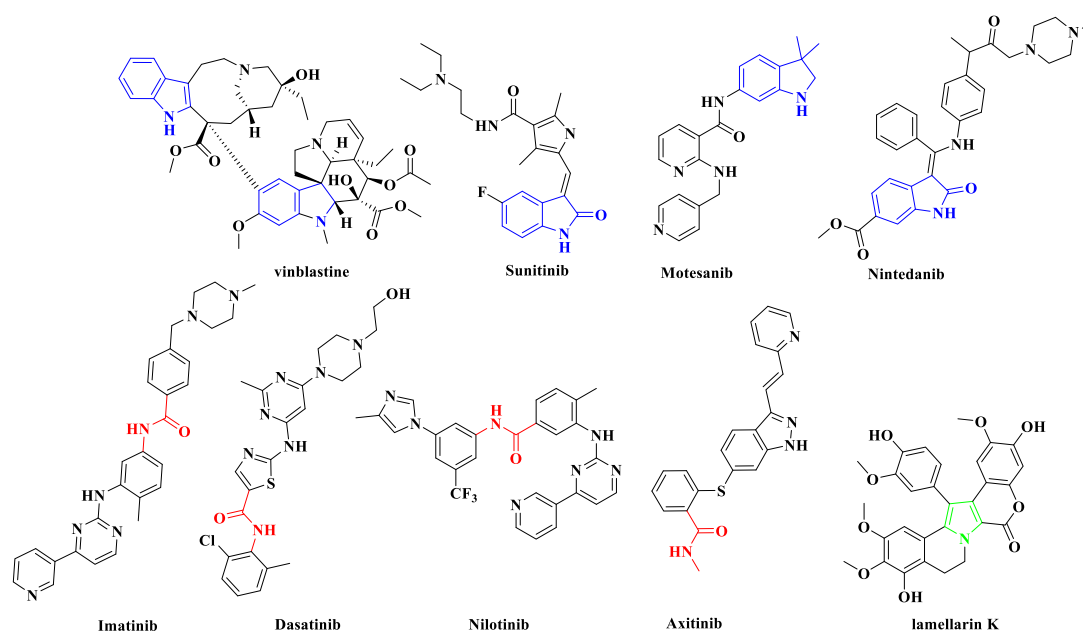
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**Abstract** – A series of 3-((1-methyl-1H-pyrrol-2-yl)methylene)indolin-2-one derivatives were designed, synthesized, and evaluated for their inhibition activities against four tumor cells *in vitro*. These compounds were fully characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS. Antitumor experiments indicated that some compounds exhibited significant inhibition activities against SMMC-7721. Especially, the IC<sub>50</sub> values of **7k** and **7l** (IC<sub>50</sub> = 8.08 ± 0.95 μM, IC<sub>50</sub> = 3.01 ± 0.61 μM) demonstrated the best antitumor activities against SMMC-7721 (human hepatoma cell lines) than the positive agents Sunitinib (IC<sub>50</sub> = 8.27 ± 0.40 μM). Likewise, their structure-activity relationship (SAR) was studied.

## INTRODUCTION

Cancer is a serious threat to human life and health with high mortality. Thus, developing anticancer drugs with high efficiency and showing minimal side effects remains a challenge in drug development. Indole also known as benzopyrrole, is a parallel compound of pyrrole and benzene. Indole and its congener derivatives widely occurred in plants, animals and microbial hormones.<sup>1</sup> The indole derivatives have attracted a great deal of interest because of their antibacterial,<sup>2</sup> antifungal,<sup>3</sup> anti-inflammatory,<sup>4</sup> antihistamine,<sup>5</sup> antioxidant,<sup>6</sup> anti-diabetes,<sup>7</sup> anti-virus,<sup>8</sup> anticholinesterase<sup>9</sup> and antitumor agents.<sup>10</sup> In view of the fine biological activity of indole structure, many indole derivatives have been used in the field of

medicine, natural and synthetic products with potent bioactivity profile. For instance, the anti-mitotic vinblastine isolated from Vinca plant has been widely used to treat a variety of cancers, including Hodgkin's disease, non-Hodgkin's lymphoma, Kaposi's sarcoma, breast cancer and testicular cancer;<sup>11</sup> the small molecule kinase inhibitor Sunitinib<sup>12</sup> was developed by the American company Prifzer and was approved by the FDA in 2006; the clinical phase III experimental PDGF and RKit oncoprotein oral inhibitor Motesanib<sup>13</sup> developed by Takeda Bio Development Center Limited; VEGFRs, PDGFRs and FGFRs<sup>14</sup> growth factor inhibitor Nintedanib was developed by Boehringer Ingelheim of Germany. Among different biologically active small molecules, the amide structure is a well-known and an important substructure with different biological and pharmacological properties.<sup>15-18</sup> N-H is a relatively active proton which can increase the polarity of the molecule and the water solubility of the drug to some extent because of carbonyl group structure. When a molecule binds to a protein, -CONH- readily forms a hydrogen bond with a residue in the biomacromolecule to enhance the efficacy of the drug. There are currently many amide-containing drugs for clinical applications: Imatinib,<sup>19</sup> a small molecule inhibitor for the treatment of chronic myelogenous leukemia; the small molecule tyrosine kinase inhibitor Dasatinib<sup>20</sup> approved by the FDA in 2006; Nilotinib,<sup>21</sup> a second-generation tyrosine kinase inhibitor for the treatment of chronic leukemia; vascular endothelial growth factor receptor (VEGFR) kinase inhibitor Axitinib.<sup>22</sup> Many of the compounds containing the pyrrole have some pharmacological activity. Especially, lamellarin showed strong cytotoxicity in multidrug-resistant (MDR) tumor cells. Furthermore, lamellarin K effectively increased its anticancer effect on tumor cells by inhibiting the release of *p*-glycoprotein (Figure 1).<sup>23</sup>

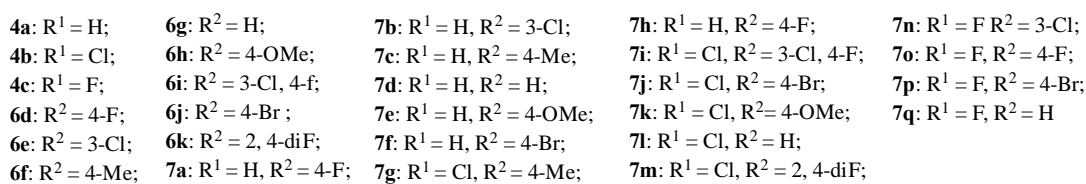
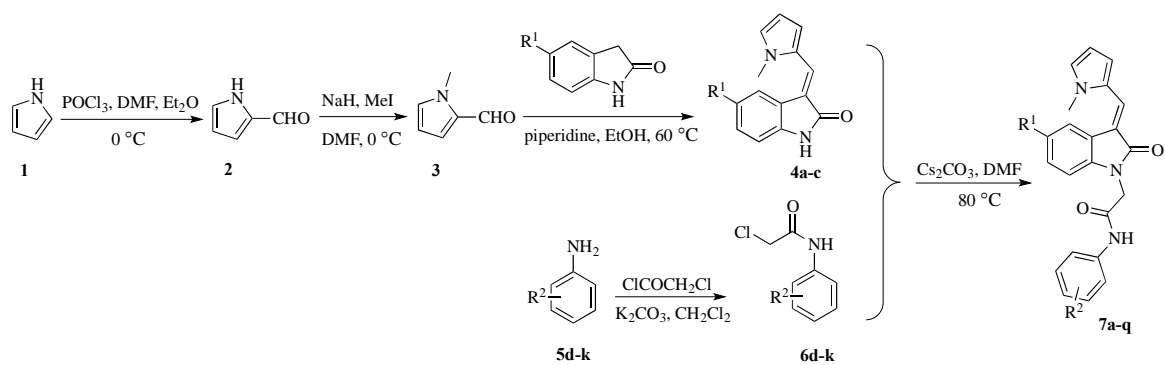


**Figure 1.** The structures of vinblastine, Sunitinib, Motesanib, Nintedanib, Imatinib, Dasatinib, Nilotinib, Axitinib and lamellarin K

Molecular hybridization is a strategy for designing new drug molecules based on the recognition of pharmacodynamic subunits in the molecular skeleton of two or more known biologically active derivatives. According to this strategy, the pyrrole was introduced into C-3 position of the indoles and the biologically active phenyl and amide fragments were introduced into the N-position of the indoles (Scheme 1). The total of 17 novel indole heterocyclic compounds were designed and synthesized. Further, the anticancer activity of the target compounds were evaluated against A549 (human non-small cell lung cancer cell lines), PC-3 (human prostate cancer cell lines), K562 (human chronic myeloid leukemia cell lines) and SMMC-7721 (human hepatoma cell lines) cancer cell lines by using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide).

## RESULTS AND DISCUSSION

**Chemistry.** The synthetic route of the target compounds **7a–q** was shown in Scheme 1. First, 1-methyl-1*H*-pyrrole-2-carbaldehyde (**3**) is obtained by Vilsmeier-Haack reaction and methylation of pyrrole (**1**).<sup>24,25</sup> Then the intermediates **4a–c**<sup>26</sup> were based on the mixture of indolin-2-one and 1-methyl-1*H*-pyrrole-2-carbaldehyde heated under reflux at 60 °C using piperidine as a catalyst and anhydrous ethanol as a reaction solvent to form a condensation reaction. Next, the intermediates **6d–k**<sup>27</sup> were obtained by amidation of chloroacetyl chloride and aniline substituted with various groups with K<sub>2</sub>CO<sub>3</sub> as an acid scavenger and dichloromethane as a solvent in an ice bath. The target compounds **7a–q** were obtained by the nucleophilic substitution reaction of intermediate **4a–c** and intermediate **6d–k** at 80 °C using DMF as solvent and K<sub>2</sub>CO<sub>3</sub> as acid binding agent. Reactions were monitored by thin layer chromatography (TLC) plates. The chemical structures of the compounds synthesized were elucidated on the basis of <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS. The characteristic hydrogen atoms of the target compounds were assigned to the <sup>1</sup>H NMR spectrum as follows. The single peak at  $\delta$  10–11 was the signal of active hydrogen on CONH, and the single peak at  $\delta$  4.5–5.0 was the signal of two hydrogens on the methylene group connected to N atom by NCH<sub>2</sub>CON, and the single peak at  $\delta$  3.6–3.9 was the signal of three hydrogens on NMe on the pyrrole. The measured value of the HRMS [M+H]<sup>+</sup> of the target compounds was consistent with the theoretical value within the tolerance ( $\pm$  0.0030) in the HRMS spectrum. The detailed physical and analytical data was given in experimental part.



**Scheme 1.** Synthetic routes of the target compounds **7a–q**

The antitumor biological activity evaluation results of 17 newly synthesized compounds **7a–q** *in vitro* (shown in Table 1) indicated that these compounds exhibited certain inhibitory activities against SMMC-7721, PC-3, A549 and K562. At concentration of 10  $\mu\text{mol/L}$ , compounds **7h**, **7g**, **7k**, **7l**, **7m**, and **7p** had a relatively high inhibition rate to SMMC-7721, PC-3, A549 and K562 tumor cells. The  $\text{IC}_{50}$  of four cells were measured for the six compounds, and the results were shown in Table 2. These compounds were determined by the MTT method, and Sunitinib was used as a positive drug for comparison. The test results were shown in Table 2. Clearly, compounds **7k** and **7l** ( $\text{IC}_{50} = 8.08 \pm 0.95 \mu\text{M}$ ,  $\text{IC}_{50} = 3.01 \pm 0.61 \mu\text{M}$ ) displayed higher antiproliferative activity than Sunitinib ( $\text{IC}_{50} = 8.27 \pm 0.40 \mu\text{M}$ ), respectively. According to the activity data and compound structures in Tables 1 and 2, preliminary SARs were proposed based on biological results. The type and position of the substituents on the indole and benzene rings had a certain effect on the inhibitory activity of tumor cells. Comparing compound **7a** to **7t**, when the fifth substituent on the indole was a chlorine atom, it was more beneficial to increase the activity of the compound. Comparing compound **7g** to **7l**, it was found that benzene ring with amide structure containing an electron-donating group such as a methyl group or a methoxy group had a good antiproliferative activity. Comparing the compound **7h** with **7m**, the results showed that the more electron-withdrawing substituents on the benzene ring, the worse inhibitory activity against SMMC-7721.

**Table 1.** Inhibition against cancer cell lines of target compounds **7a–q** at 10  $\mu\text{mol/L}$ <sup>a</sup>

Compounds	Inhibition rate/%			
	SMMC-7721	PC-3	A549	K562
<b>7a</b>	10.23±3.75	8.56±3.40	-16.63±2.78	-11.71±8.01
<b>7b</b>	23.62±4.24	11.62±3.11	-4.37±9.68	24.37±3.59
<b>7c</b>	23.33±3.18	20.89±5.05	3.70±12.1	24.11±6.50
<b>7d</b>	17.08±4.08	21.48±7.44	16.19±2.77	20.22±3.94
<b>7e</b>	48.43±0.74	4.44±3.86	-0.28±9.38	-3.49±5.37
<b>7f</b>	2.12±6.99	14.44±3.35	-4.15±13.26	12.41±2.30
<b>7g</b>	63.28±0.45	37.31±4.22	36.10±2.92	36.27±4.08
<b>7h</b>	53.03±0.09	6.71±10.73	41.11±1.29	42.52±3.53
<b>7i</b>	42.37±13.58	10.29±8.69	19.48±4.67	27.75±4.27
<b>7j</b>	1.85±2.34	5.79±3.26	7.93±0.18	9.54±7.72
<b>7k</b>	63.03±0.54	69.96±0.90	46.85±2.56	22.39±1.12
<b>7l</b>	77.51±0.73	38.33±2.59	60.36±0.57	26.03±0.55
<b>7m</b>	42.91±3.01	25.58±2.38	28.12±6.67	12.69±6.26
<b>7n</b>	28.99±10.19	28.44±1.19	5.66±6.43	9.49±4.27
<b>7o</b>	39.09±0.90	28.26±3.53	33.58±1.37	21.37±0.41
<b>7p</b>	42.55±4.70	35.68±3.26	45.24±6.49	33.76±2.90
<b>7q</b>	27.32±2.65	24.25±4.81	22.07±9.76	24.04±2.91
Sunitinib <sup>b</sup>	51.86±2.21	94.29±1.35	84.15±1.74	84.01±2.43

<sup>a</sup>Average of three independent experiments. <sup>b</sup>Sunitinib was used as positive control.

**Table 2.** *In vitro* antiproliferative activity data of compounds

Compounds	Cytotoxicity (IC <sub>50</sub> $\mu\text{mol/L}$ ) <sup>a</sup>			
	SMMC-7721	PC-3	A549	K562
<b>7h</b>	9.37±2.60	121.80±9.04	16.86±1.02	38.21±10.85

<b>7g</b>	8.53±0.51	30.99±4.63	23.35±3.24	32.92±0.91
<b>7k</b>	8.08±0.95	10.86±0.81	9.36±0.24	~
<b>7l</b>	3.01±0.61	16.03±3.19	9.23±3.25	~
<b>7m</b>	14.65±2.10	~	~	~
<b>7p</b>	11.61±0.47	~	13.98±2.03	16.74±0.75
Sunitinib <sup>b</sup>	8.27±0.40	3.05±0.13	5.8±0.11	4.73±0.75

<sup>a</sup>Average of three independent experiments. <sup>b</sup>Sunitinib was used as positive control.

In summary, we have prepared a series of derivatives of pyrrole-indolin-2-one possessing various amide structures. The biological results *in vitro* demonstrated that all the target compounds exhibited moderate to potent antitumor activities. Especially compounds **7l** and **7k** showed higher activity than Sunitinib against SMMC-7721. The results of a structure-activity relationship study showed a compound having a 5-chloroindole and an amide structure containing an electron-donating group such as a methyl group or a methoxy group had a good antiproliferative activity. Eventually, in view of the results obtained above, the **7l** and **7k** compounds were of great value for further investigation as new antitumor agents.

## EXPERIMENTAL

**General methods.** All commercially available reagents were purchased from commercial sources and used as received. Products were visualized by UV on TLC plates (silica gel 60 F254). Melting points (uncorrected) were determined on X-4 digital display micro melting point mete. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were measured on a Bruker Avance spectrometer at 600 MHz and 101 MHz in DMSO-*d*<sub>6</sub> solutions, respectively. Splitting patterns in the <sup>1</sup>H NMR spectra are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-T of Micromass spectrometer.

### General procedure for the synthesis of *N*-methylpyrrole-2-carbaldehyde (**3**):

Step 1: Pyrrole (**1**) (20.0 g, 0.30 mol) was added dropwise to a stirred solution of POCl<sub>3</sub> (50.00 g, 0.33 mol) and DMF (24.0 g, 0.33 mol) in dry Et<sub>2</sub>O (100 mL) at 0 °C. The mixture was stirred at room temperature overnight. After the reaction was over, the mixture was added to 10 volumes of a saturated aqueous NaHCO<sub>3</sub> solution. Extracted with EtOAc, extract were washed with brine, then dried over Na<sub>2</sub>SO<sub>4</sub>, and finally the solvent was evaporated under reduced pressure, the resulting product was used directly in the next step (yield: 15.5 g, 55.4%).

Step 2: Pyrrole-2-carbaldehyde (10.00 g, 0.10 mol) was added to a suspension of dry NaH (5.0 g, 0.20 mol) in 300 mL DMF with stirring. After 30 min, MeI (16.4 g, 0.12 mol) was added to the mixture and then stirred at room temperature for 30 min. After the reaction was completed, the mixture was then cooled, and the mixture was poured into water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and then evaporated to give *N*-methylpyrrole-2-carbaldehyde (yield: 10.2 g, 89.4%).

**General procedure for the synthesis of compounds 4a–4c:**

In a 25 mL single-neck round bottom flask, anthrone (15.00 mmol), *N*-methylpyrrole-2-carbaldehyde (18.02 mmol) and 15 mL of EtOH were sequentially added. Then, 2 drops of piperidine were added, and the reaction was continued for 6 h in an oil bath at 60 °C. The reaction was followed by TLC. After the reaction, the brown solid sediment, which was filtered, washed twice with water and dried to give a crude product which was recrystallized from THF. A brown solid was obtained (yield: 73.5%), and the intermediates **4a–4c** were obtained by the same synthesis and purification method.

**General procedure for the synthesis of compounds 6d–6k:**

In a 25 mL single-neck round bottom flask, substituted aniline **5d–5k** (5.9 mmol), potassium carbonate (11.81 mmol) and 15 mL CH<sub>2</sub>Cl<sub>2</sub> were added in sequence, and chloroacetyl chloride (8.85 mmol) was slowly added dropwise while stirring in an ice bath. The reaction was continued for 1 h, and the reaction was carried out for 3 h at room temperature. The reaction was followed by TLC. After the reaction was completed, the solvent was evaporated under reduced pressure, and washed three times with water, and the solid was filtered, dried, and recrystallized from EtOAc to give a light purple fine needle (yield: 91.3%). Other intermediates **6d–6k** were also obtained by the same synthesis and purification method.

**General procedure for the synthesis of compounds 7a–7q:**

Intermediates **6d–6k** (2.23 mmol), cesium carbonate (3.34 mmol) and 5 mL DMF were added in a 25 mL one-neck round bottom flask, and stirred at room temperature for 2 h. Intermediate **3a–3h** (2.68 mmol) and potassium iodide (0.1 mmol) were then added and placed in an oil bath at 80 °C for 6–12 h. The reaction was followed by TLC. After the end of the reaction, the reaction mixture was poured into six times its volume of water, and then dilute hydrochloric acid was added until the pH was between 3–4. The crude final product was suction filtered, washed several times with cold water and then dried in the infrared. The product was recrystallized from THF and petroleum ether (yield: 53.5%). Other target compounds **7a–7q** were obtained by the same synthesis and purification method.

**(*E*)-*N*-(4-Fluorophenyl)-2-(3-((1-methyl-1*H*-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)acetamide**

**(7a)**. Light yellow solid, yield: 60%, mp 180–185 °C; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.44 (s, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.64–7.59 (m, 2H), 7.58 (s, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.21 (dd, *J* = 4.8, 2.1 Hz, 1H), 7.17 (dd, *J* = 12.5, 5.3 Hz, 2H), 7.12 (d, *J* = 3.7 Hz, 1H), 7.06–7.01 (m, 2H), 6.34 (dd, *J* = 3.6,

2.7 Hz, 1H), 4.65 (d,  $J = 6.1$  Hz, 2H), 3.80 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  169.02, 166.70, 143.09, 140.82, 133.73, 131.15, 129.60, 129.24, 128.15, 124.45, 123.77, 122.28, 122.18, 121.69, 119.90, 119.23, 118.13, 116.40, 110.20, 109.45, 43.53, 34.75. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{19}\text{FN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$  376.1456, found 376.1452.

**(E)-N-(3-Chlorophenyl)-2-(3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)acetamide**

**(7b).** Light brown solid, yield: 47%, mp 172–176 °C;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  10.63 (s, 1H), 8.07 (d,  $J = 7.6$  Hz, 1H), 7.80 (d,  $J = 2.0$  Hz, 1H), 7.57 (s, 1H), 7.49–7.46 (m, 1H), 7.36 (t,  $J = 8.1$  Hz, 1H), 7.27 (td,  $J = 7.8, 0.7$  Hz, 1H), 7.22 (d,  $J = 1.8$  Hz, 1H), 7.13 (dd,  $J = 11.3, 2.7$  Hz, 2H), 7.06–7.02 (m, 2H), 6.35 (dd,  $J = 3.8, 2.7$  Hz, 1H), 4.67 (s, 2H), 3.80 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  168.89, 166.56, 142.95, 140.62, 133.60, 131.04, 129.49, 129.12, 128.01, 124.33, 123.67, 122.16, 122.06, 121.55, 119.75, 119.07, 117.98, 116.28, 110.08, 109.32, 43.38, 34.62. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{19}\text{ClN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$  392.1160, found 392.1155.

**(E)-2-(3-((1-Methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-N-(p-tolyl)acetamide (7c).** Light brown solid, yield: 45%, mp 178–180 °C;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  10.28 (s, 1H), 8.07 (d,  $J = 7.6$  Hz, 1H), 7.58 (s, 1H), 7.49 (d,  $J = 8.0$  Hz, 2H), 7.27 (t,  $J = 7.7$  Hz, 1H), 7.21 (dd,  $J = 4.0, 1.9$  Hz, 1H), 7.12 (d,  $J = 7.0$  Hz, 3H), 7.04 (ddd,  $J = 11.0, 7.8, 3.5$  Hz, 2H), 6.35 (dd,  $J = 3.7, 2.3$  Hz, 1H), 4.64 (d,  $J = 6.0$  Hz, 2H), 3.80 (s, 3H), 2.25 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  168.87, 165.82, 143.10, 140.76, 136.71, 132.86, 129.67, 129.43, 129.27, 129.11, 128.05, 124.26, 122.10, 122.05, 121.57, 119.91, 119.59, 116.23, 110.06, 109.88, 109.32, 43.32, 34.63, 20.92. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_2$   $[\text{M}+\text{H}]^+$  372.1707, found 372.1703.

**(E)-2-(3-((1-Methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-N-phenylacetamide (7d).** Light brown solid, yield: 47%, mp 185–189 °C;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  10.40 (s, 1H), 8.07 (d,  $J = 7.6$  Hz, 1H), 7.63–7.56 (m, 3H), 7.32 (t,  $J = 7.8$  Hz, 2H), 7.27 (t,  $J = 7.6$  Hz, 1H), 7.22 (s, 1H), 7.12 (d,  $J = 2.7$  Hz, 1H), 7.09–7.01 (m, 3H), 6.38–6.32 (m, 1H), 4.66 (d,  $J = 5.5$  Hz, 2H), 3.86 (d,  $J = 6.4$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  168.77, 166.45, 142.84, 140.57, 133.48, 130.90, 129.35, 128.99, 127.90, 124.20, 123.52, 122.03, 121.93, 121.44, 119.65, 118.98, 117.88, 116.15, 109.95, 109.20, 43.28, 34.50. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_2$   $[\text{M}+\text{H}]^+$  358.1550, found 358.1544.

**(E)-N-(4-Methoxyphenyl)-2-(3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)acetamide**

**(7e).** Light yellow solid, yield: 54%, mp 181–184 °C;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  10.22 (s, 1H), 8.06 (d,  $J = 7.6$  Hz, 1H), 7.57 (s, 1H), 7.50 (d,  $J = 8.9$  Hz, 2H), 7.27 (t,  $J = 7.6$  Hz, 1H), 7.22 (s, 1H), 7.11 (d,  $J = 3.1$  Hz, 1H), 7.03 (dd,  $J = 18.3, 7.8$  Hz, 2H), 6.89 (d,  $J = 9.0$  Hz, 2H), 6.36–6.33 (m, 1H), 4.61 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  168.87, 165.53, 155.78, 143.06, 132.32, 129.43, 129.12, 128.02, 124.26, 122.11, 121.55, 121.10, 119.87, 116.23, 114.38, 110.06, 109.30, 56.50, 55.60, 34.62. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_3$   $[\text{M}+\text{H}]^+$  388.1556, found 388.1551.



**(E)-N-(4-Bromophenyl)-2-(3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)acetamide**

**(7f)**. Light brown solid, yield: 37%, mp 182–187 °C; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.51 (d, *J* = 3.9 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.57 (dd, *J* = 5.2, 3.6 Hz, 3H), 7.54–7.47 (m, 2H), 7.24–7.15 (m, 2H), 7.12 (d, *J* = 3.2 Hz, 1H), 7.06–7.01 (m, 2H), 6.37–6.32 (m, 1H), 4.66 (d, *J* = 6.1 Hz, 2H), 3.85 (d, *J* = 6.7 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 168.88, 166.31, 142.97, 140.65, 138.54, 132.13, 130.57, 129.48, 129.11, 128.02, 124.33, 123.43, 122.15, 121.51, 119.76, 116.29, 115.54, 110.08, 109.31, 43.38, 34.62. HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>19</sub>BrN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 436.0655, found 436.0653.

**(E)-2-(5-Chloro-3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-N-(*p*-tolyl)acetamide**

**(7g)**. Light brown solid, yield: 55%, mp 191–196 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.47 (d, *J* = 2.9 Hz, 1H), 8.03 (s, 1H), 7.53–7.42 (m, 2H), 7.39–7.32 (m, 2H), 7.22 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 2H), 7.00 (d, *J* = 14.4 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.42 (dd, *J* = 4.3, 2.2 Hz, 1H), 4.60 (s, 2H), 3.91 (s, 3H), 2.30 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 168.80, 165.75, 143.03, 140.69, 136.64, 132.79, 129.60, 129.36, 129.20, 129.04, 127.98, 124.19, 122.03, 121.98, 121.50, 119.84, 119.52, 116.16, 109.99, 109.81, 109.25, 43.25, 34.56, 20.85. HRMS (ESI) *m/z* calcd for C<sub>23</sub>H<sub>21</sub>ClN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 406.1317, found 406.1313.

**(E)-2-(5-Chloro-3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-N-(4-fluorophenyl)-acetamide (7h)**

Light brown solid, yield: 64%, mp 210–215 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.46 (s, 1H), 8.33 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.79 (s, 1H), 7.66–7.60 (m, 2H), 7.29–7.25 (m, 1H), 7.24–7.13 (m, 3H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.29 (dd, *J* = 4.0, 2.4 Hz, 1H), 4.67 (s, 2H), 3.93 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 168.73, 166.41, 142.80, 140.53, 133.44, 130.86, 129.31, 128.95, 127.86, 124.16, 123.48, 121.99, 121.89, 121.40, 119.61, 118.94, 117.84, 116.11, 109.91, 109.16, 43.24, 34.46. HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>18</sub>ClFN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 410.1066, found 410.1061.

**(E)-2-(5-Chloro-3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-N-(3-chloro-4-fluorophenyl)acetamide (7i)**

Light brown solid, yield: 58%, mp 205–209 °C; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.44 (s, 1H), 8.33 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.00 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.78 (s, 1H), 7.65–7.58 (m, 2H), 7.27–7.24 (m, 1H), 7.21 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.16 (d, *J* = 1.7 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.29 (dd, *J* = 4.0, 2.4 Hz, 1H), 4.66 (d, *J* = 4.5 Hz, 2H), 3.92 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 168.64, 166.32, 142.71, 140.44, 133.35, 130.77, 129.22, 128.86, 127.77, 124.07, 123.39, 121.90, 121.80, 121.31, 119.52, 118.85, 117.75, 116.02, 109.82, 109.07, 43.15, 34.37. HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>17</sub>Cl<sub>2</sub>FN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 444.0676, found 444.0689.

**(E)-N-(4-Bromophenyl)-2-(5-chloro-3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-acetamide (7j)**

Light brown solid, yield: 44%, mp 212–217 °C; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.50 (s, 1H), 8.00 (d, *J* = 6.5 Hz, 1H), 7.63 (s, 1H), 7.56 (d, *J* = 8.6 Hz, 3H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.35–7.31 (m, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 2.8 Hz, 1H), 4.66 (s,

2H), 3.87 (d,  $J = 6.8$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  168.54, 166.12, 141.71, 138.49, 132.14, 130.27, 128.44, 127.84, 126.04, 123.17, 121.51, 121.10, 118.62, 116.79, 115.57, 110.52, 110.28, 43.46, 34.68. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{17}\text{Cl}_2\text{FN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$  470.0265, found 470.0099.

**(E)-2-(5-Chloro-3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-N-(4-methoxyphenyl)-acetamide (7k).** Light brown solid, yield: 60%, mp 203–205 °C;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  10.21 (s, 1H), 8.31 (d,  $J = 3.3$  Hz, 1H), 7.99 (s, 1H), 7.78 (s, 1H), 7.50 (d,  $J = 8.8$  Hz, 2H), 7.26 (s, 1H), 7.21 (dd,  $J = 8.3, 1.4$  Hz, 1H), 6.98 (d,  $J = 8.3$  Hz, 1H), 6.89 (d,  $J = 8.9$  Hz, 2H), 6.29 (d,  $J = 2.5$  Hz, 1H), 4.63 (s, 2H), 3.92 (s, 3H), 3.72 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  168.53, 165.62, 155.75, 139.34, 132.35, 131.41, 127.02, 126.52, 125.99, 125.13, 121.49, 121.06, 116.73, 115.51, 114.37, 110.26, 110.03, 56.50, 43.17, 34.74. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{21}\text{ClN}_3\text{O}_3$   $[\text{M}+\text{H}]^+$  470.0265, found 470.0099.

**(E)-2-(5-Chloro-3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-N-phenylacetamide (7l).** Light brown solid, yield: 55%, mp 213–215 °C;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  10.36 (s, 1H), 8.32 (d,  $J = 3.1$  Hz, 1H), 8.00 (s, 1H), 7.79 (s, 1H), 7.59 (d,  $J = 7.9$  Hz, 2H), 7.32 (t,  $J = 7.7$  Hz, 2H), 7.26 (s, 1H), 7.22 (d,  $J = 8.2$  Hz, 1H), 7.06 (t,  $J = 7.2$  Hz, 1H), 7.00 (d,  $J = 8.3$  Hz, 1H), 6.29 (s, 1H), 4.67 (s, 2H), 3.93 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  168.89, 167.42, 143.09, 139.74, 129.46, 129.14, 128.86, 128.14, 127.83, 127.42, 124.27, 122.20, 122.13, 121.78, 120.15, 116.25, 110.12, 109.32, 43.00, 34.72. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{17}\text{ClN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$  392.1160, found 392.1155.

**(E)-2-(5-Chloro-3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-N-(2,4-difluorophenyl)-acetamide (7m).** Light brown solid, yield: 50%, mp 220–225 °C;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  10.19 (s, 1H), 8.31 (d,  $J = 2.9$  Hz, 1H), 7.99 (d,  $J = 1.9$  Hz, 1H), 7.83 (dd,  $J = 15.2, 8.9$  Hz, 1H), 7.65–7.58 (m, 1H), 7.46–7.41 (m, 1H), 7.35 (dd,  $J = 14.3, 5.8$  Hz, 1H), 7.22 (dd,  $J = 8.3, 1.9$  Hz, 2H), 6.98 (d,  $J = 8.3$  Hz, 1H), 6.29 (dd,  $J = 3.8, 2.4$  Hz, 1H), 4.73 (s, 2H), 3.92 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  168.80, 166.48, 142.87, 140.60, 133.51, 130.93, 129.38, 129.02, 127.93, 124.23, 123.55, 122.06, 121.96, 121.47, 119.68, 119.01, 117.91, 116.18, 109.98, 109.23, 43.31, 34.53. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{17}\text{ClF}_2\text{N}_3\text{O}_2$   $[\text{M}+\text{H}]^+$  428.0972, found 428.0968.

**(E)-N-(3-Chlorophenyl)-2-(5-fluoro-3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-acetamide (7n).** Light brown solid, yield: 53%, mp 209–212 °C;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  10.57 (s, 1H), 8.31 (dd,  $J = 4.0, 1.2$  Hz, 1H), 8.00 (dd,  $J = 7.4, 1.9$  Hz, 1H), 7.79 (s, 2H), 7.46 (d,  $J = 8.3$  Hz, 1H), 7.38–7.33 (m, 1H), 7.27 (d,  $J = 6.6$  Hz, 1H), 7.21 (dd,  $J = 8.3, 2.0$  Hz, 1H), 7.13 (d,  $J = 7.4$  Hz, 1H), 7.09 (t,  $J = 6.3$  Hz, 1H), 7.00 (d,  $J = 8.3$  Hz, 1H), 6.29 (dd,  $J = 3.9, 2.5$  Hz, 1H), 4.68 (d,  $J = 3.4$  Hz, 2H), 3.93 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  168.58, 166.64, 140.58, 139.20, 133.61, 131.48, 131.04, 129.33, 127.02, 126.52, 126.08, 125.23, 123.67, 121.53, 119.07, 117.95, 116.80, 115.36, 110.29, 110.04, 43.32, 34.74. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{18}\text{ClFN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$  410.1066, found 410.1061.

**(E)-2-(5-Fluoro-3-((1-methyl-1H-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-N-(3-fluorophenyl)-**

**acetamide (7o).** Light brown solid, yield: 44%, mp 172–176 °C; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.42 (s, 1H), 8.31 (d, *J* = 3.1 Hz, 1H), 7.83–7.78 (m, 1H), 7.74 (s, 1H), 7.65–7.58 (m, 2H), 7.25 (s, 1H), 7.16 (t, *J* = 8.8 Hz, 2H), 7.05–6.98 (m, 1H), 6.96 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.28 (d, *J* = 2.4 Hz, 1H), 4.65 (s, 2H), 3.91 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 168.58, 166.64, 140.58, 139.20, 133.61, 131.48, 131.04, 129.33, 127.02, 126.52, 126.08, 125.23, 123.67, 121.53, 119.07, 117.95, 116.80, 115.36, 110.29, 110.04, 43.32, 34.74. HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>18</sub>F<sub>2</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 394.1362, found 394.1358.

**(*E*)-*N*-(4-Bromophenyl)-2-(5-fluoro-3-((1-methyl-1*H*-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-acetamide (7p).** Light brown solid, yield: 33%, mp 218–223 °C; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.50 (s, 1H), 8.30 (d, *J* = 3.0 Hz, 1H), 7.80 (dd, *J* = 9.1, 1.6 Hz, 1H), 7.74 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.25 (s, 1H), 7.12 (d, *J* = 4.5 Hz, 1H), 7.06–6.94 (m, 2H), 6.30–6.25 (m, 1H), 4.66 (s, 2H), 3.86 (d, *J* = 6.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 168.90, 166.58, 142.97, 140.70, 133.61, 131.03, 129.48, 129.12, 128.03, 124.33, 123.65, 122.16, 122.06, 121.57, 119.78, 119.11, 118.01, 116.28, 110.08, 109.33, 43.41, 34.63. HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>18</sub>FBrN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 454.0561, found 454.0562.

**(*E*)-2-(5-Fluoro-3-((1-methyl-1*H*-pyrrol-2-yl)methylene)-2-oxoindolin-1-yl)-*N*-phenylacetamide (7q).** Light brown solid, yield: 65%, mp 220–223 °C; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.36 (s, 1H), 8.32 (d, *J* = 1.0 Hz, 1H), 7.80 (d, *J* = 9.2 Hz, 1H), 7.74 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.25 (s, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 9.0 Hz, 1H), 6.98–6.94 (m, 1H), 6.30–6.26 (m, 1H), 4.66 (s, 2H), 3.91 (s, 3H). <sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>) δ 166.26, 166.13, 139.21, 136.92, 131.26, 129.29, 126.70, 124.90, 123.93, 121.39, 119.57, 116.28, 113.32, 110.21, 109.35, 106.49, 43.32, 34.69. HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>19</sub>FN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 376.1456, found 376.1451.

**Biological assays.** The test compounds were dissolved in an appropriate amount of dimethyl sulfoxide (DMSO) to obtain a solution of known concentration prior to the experiment, and then were diluted to concentrations ranging from 0.625 μM to 10 μM with culture medium. Then, the cells in the exponentially growing were trypsinized and plated at a density of 3×10<sup>4</sup> cells/mL in a 96-well plate, cultured at 37 °C in a 5% CO<sub>2</sub>-supplemented atmosphere for 24 h, and then treated with various concentrations of the test compounds for 48 h. The control group was treated only with complete medium. Then 20 μL MTT solution (5 mg/mL) was added to each well, incubated for 4 h, the medium was carefully aspirated, and the formazan crystals were dissolved in 150 μL DMSO for each well. All measurements were performed in three times and had triplicate samples in each time. Error bars were calculated from standard deviation from the mean. The absorbance of each well was measured at a test wave length of 490 nm by using a microplate reader to obtain a sample signal. Using the Graphpad Prism software package, the IC<sub>50</sub> value for the anticancer activity of each compound was calculated based on the corresponding absorbance values.

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