# (*E*)-3-(Aryl(arylamino)methylene)indolin-2-one derivatives: an efficient synthetic approach and evaluation of their cancer inhibitory activity

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A series of (*E*)-3-(aryl(arylamino)methylene)indolin-2-one derivatives were synthesised using an efficient synthetic approach. The method involved reaction of 3-bromo-3-(bromo(aryl)methyl)indolin-2-one with substituted anilines through nucleophilic substitution and a simultaneous elimination using $NaHCO_3$ in DMF. The anticancer activity of the products against four cell lines, HCT-116, A549, SKOV3 and MDA-MB-231, was also evaluated, and several compounds showed moderate inhibitory activity.

**Keywords:** indolin-2-one derivative, nucleophilic substitution reaction, anticancer activity

Indolin-2-one fragments can be found in many natural plants, for example, horsfiline from the traditional herb *Horsfieldia kingii*[1], and indirubin from *Indigo naturalis*[2,3], which show diverse biological activities, such as anti-angiogenesis,[4] anti-inflammatory,[5] antitumour[6] and anti-HIV[7]. Their derivatives have attracted a lot of attention, with their significant anticancer activity, as multi-target drugs.[8] Li *et al*.[9] reported that the indolin-2-one derivatives can bind with several targets related to the proliferation of cancer cells that are epidermal growth factor receptors (EGFR), fibroblast growth factor receptors (FGFR), vascular endothelial growth factor receptors (VEGFR) and platelet-derived growth factor receptors (PDGFR). *In vivo*, they can inhibit the corresponding receptor to block the growth of cancer cells.[10] Additionally, some of them have now come onto the market, including Sunitinib,[11] Vinflunine,[12] Osimertinib[13] and Nintedanib (see Fig. 1).[14]

Based on an indolin-2-one core and the precedent of the newly marketed drug Nintedanib, which has been applied to cure the symptoms of idiopathic pulmonary fibrosis (IPF)[15] with good efficacy, we designed and synthesised a series of compounds containing the indolin-2-one structure. A general method for synthesising these compounds includes the condensation reaction of indolin-2-one and trimethyl orthobenzoate, which is expensive.[16–18] Cantagrel *et al*.[19] reported another synthetic method using the reaction of 3-(chloro(phenyl)methylene)-indolin-2-one with aliphatic amines.

This paper reports a novel approach to synthesising (*E*)-3-(aryl(arylamino) methylene)indolin-2-one derivatives by reacting 3-bromo-3-(bromo(phenyl)methyl)-indolin-2-one derivatives with aniline derivatives through a simultaneous nucleophilic substitution and elimination reaction in one step using $NaHCO_3$ in DMF, which is easy to handle, with moderate to high yields. Their antitumour activities against HCT-116, A549, SKOV3 and MDA-MB-231 were evaluated and their preliminary structure–activity relationships are also discussed.

## Results and discussion

*Chemistry*

The preparation of (*E*)-3-(aryl(arylamino)methylene)indolin-2-one derivatives is illustrated in Schemes 1–3. An acyl chloride obtained from compound **1** (prepared according to the literature[20–22]) and $SOCl_2$, reacted with morpholine, piperidine and *N*-methylpiperazine to give compounds **2a–c**, which were then reduced to compounds **3a–c** under $H_2$/Pd-C.

Compounds **4a–d** were reacted with benzaldehyde to give **5a–d** in the presence of piperidine in ethanol. Compounds **6a–d** were then prepared in high yields by adding bromine in dichloromethane to solutions of **5a–d** in $CH_2Cl_2$ (Scheme 2).

Compounds **6a–d** were reacted with compounds **7a–c** or **3a–c** in DMF in the presence of $NaHCO_3$ to form the target compounds **8a–e** or **9a–g**, respectively (Scheme 3). The use of $K_2CO_3$ as base in DMF was also studied, but gave either more impurities and lower yields or even no product at all. Dibromo-compound **6** was

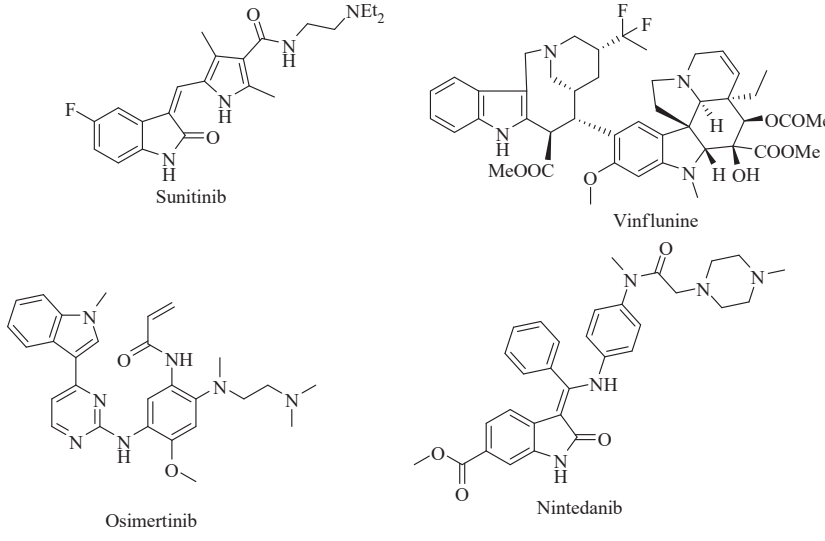


**Fig. 1** Several indole derivatives as antitumour drugs.

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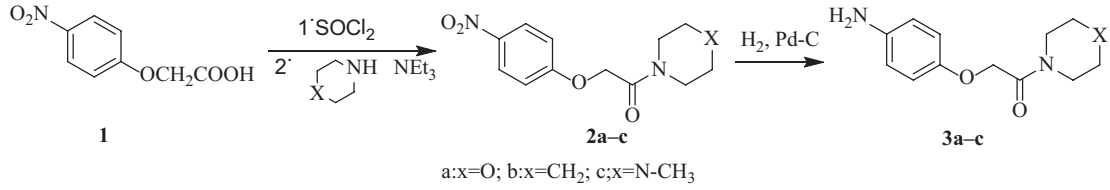
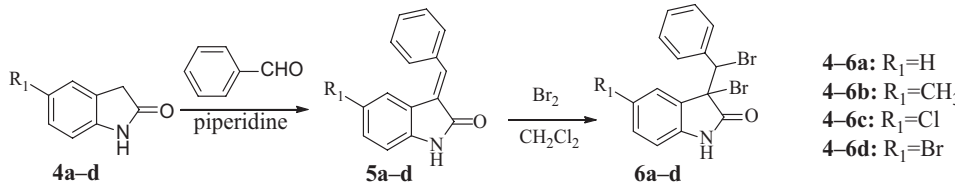
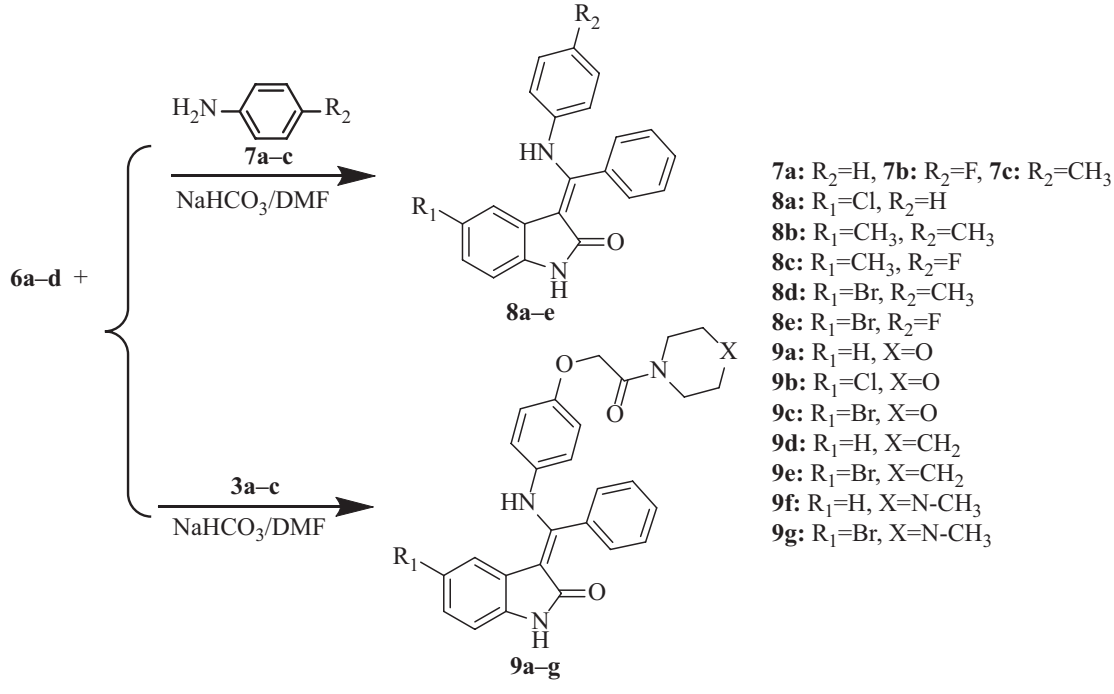



**Scheme 1** Synthetic method for 2-(4-aminophenoxy)acetamide derivatives **3a–c**.




**Scheme 2** Synthetic pathway for 3-bromo-3-(bromo(phenylmethyl))-indolin-2-one derivatives **6a–d**.




**Scheme 3** Synthetic pathway for target compounds **8a–e** and **9a–g**.

first transformed into a vinyl bromide derivative, which was then reacted with **3** or **7** very slowly, but no product was obtained. The reaction proceeded very slowly due to the $p$–$\pi$ conjugated system of the bromine atom and the C=C double bond for the intermediate of the 3-(bromo(phenyl)methylene)-indolin-2-one derivatives. As for compound **6**, nucleophilic substitution happened more easily and faster between the bromoalkane with aniline, and then the elimination reaction proceeded to form the target compound.

In the H–H COSY NMR spectrum of compound **5b**, the signal of H4 at 7.35 ppm interacted with the signal of H2′ at 7.72 ppm and that of H6′ at the phenyl group, indicating there existed an *E* configuration. Intermediate **6** has different possible stereoisomers that can be seen in the proton-NMR spectra, with signals of the NH of the indolinone and the CHBr double singlets. However, the existence of isomers does not affect the following reaction, as all raw materials are transferred to the product during the reaction. The proton-NMR signals of H4 in the indolinones of compounds **8** and **9** are located at greater than 7, according to the literature.[19] If their structures have the *Z* configuration, H4 will correlate with H2′ and H6′ of the phenyl group through NOE and the signal of H4 will be lower than 7.

In the H–H COSY NMR of compound **8d**, the signal of H4 at 7.85 ppm interacted with the signal of H3′ at 6.58 ppm and that of H5′ of the anilino group, although the intramolecular hydrogen bond that can exist between the amino group and the carbonyl group will promote the formation of the *Z* configuration, the signal of H4 of our target compounds occurred at about 7.6 ppm and, as noted in the literature,[16] the signals of H4 of similar analogues are located at 5.7–5.9 ppm. Hence, we concluded that the *E* configuration products were formed during the reaction. All of the target compounds were easily purified by recrystallisation, and their structures were confirmed by $^{1}$H NMR, $^{13}$C NMR and ESI-MS.

*Biological evaluation*

The antitumour activity *in vitro* of compounds **8a–e** and **9a–g** was evaluated by the MTT assay and compared with that of the reference drug gefitinib. Four different cancer cell lines,

**Table 1.** $IC_{50}$ values of target compounds **8a–e** and **9a–g** against tumour cells *in vitro*

| Compound | $IC_{50}$[a,b] (μM) | | | |
|---|---|---|---|---|
| | HCT116 | A549 | SKOV3 | MDA-MB-231 |
| **8a** | >50 | >50 | >50 | >50 |
| **8b** | >50 | >50 | >50 | >50 |
| **8c** | 14.5 | >50 | >50 | >50 |
| **8d** | 23.3 | 16.4 | 22.4 | 15.2 |
| **8e** | 13.6 | 15.8 | 24.8 | 30.3 |
| **9a** | >50 | >50 | >50 | 34.6 |
| **9b** | >50 | >50 | >50 | >50 |
| **9c** | >50 | >50 | >50 | >50 |
| **9d** | 20.5 | 23.3 | >50 | 23.0 |
| **9e** | 16.8 | 46.6 | >50 | 18.8 |
| **9f** | >50 | >50 | >50 | 42.1 |
| **9g** | 36.2 | ND[c] | >50 | 28.2 |
| TN[d] | 19.4 | 12.6 | >50 | 32.2 |

[a]$IC_{50}$ values represent the concentration that causes 50% growth inhibition.
[b]$IC_{50}$ values were the mean values of three repeated experiments.
[c]Not determined.
[d]TN is gefitinib.

human colonic cancer cell (HCT116), human lung cell (A549), human ovarian cancer cell (SKOV3) and human breast cancer cell (MAD-MB-231), were chosen to be tested. The results are presented in Table 1.

As can be seen from the table, **8d** and **8e** showed good inhibitory activity against all four cells, **8c** and **9e** displayed better activity than gefitinib towards HCT116, **9d** displayed the same activity as gefitinib towards HCT116, A549 and MDA-MB-231, **8e**, **9a**, **9e** and **9g** showed the same or better activity than gefitinib against MAD-MB-231, and only **8d** and **8e** showed moderate inhibitory activity against SKOV3. Other compounds showed either low or no inhibitory activity. It appears that the bromo group at position 5 of indolin-2-one promoted activity in compounds **8a–e**, and compounds containing the piperidine group could increase the activity in compounds **9a–g**.

## Conclusion

An efficient approach to synthesising (*E*)-3-(aryl(arylamino) methylene)indolin-2-one derivatives was developed and 12 target compounds were obtained in good yields. Their antitumour activity *in vitro* was evaluated by the MTT assay, and the results show that the introduction of a bromine atom in the indolin-2-one and the piperidine-containing structure appears to increase their antitumour activity. This could provide a reference for new drug development.

## Experimental

All reagents were purchased from commercial suppliers and were used without further purification unless otherwise specified. Melting points were determined by a capillary method and are uncorrected. IR spectra were recorded on a Spectrum Two Li10014 spectrometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. NMR spectra were recorded in DMSO-$d_6$ or $CDCl_3$ solutions at room temperature (20 ± 2 °C). $^1$H and $^{13}$C chemical shifts are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). ESI-MS spectra were recorded on a Bruker Esquire 3000 instrument. High-resolution mass spectra (HRMS) were obtained on a MicroTOF-Q II mass spectrometer with an ESI source (Waters, Manchester). All reactions were monitored by thin-layer chromatography (TLC) and using ultraviolet light (254 nm). As for the known compounds, melting points and $^1$H NMR spectra were confirmed by comparison with data from the previously reported literature, and the main intermediates were characterised by IR, $^1$H NMR, $^{13}$C NMR and mass spectra.

*Synthesis of N-2-(4-nitrophenoxy)acetamide derivatives* (**2a–c**)*; general procedure*

A mixture of compound **1** (10 mmol) and three drops of DMF in thionyl chloride (10 mL) was refluxed for 1.5 h. Thionyl chloride was evaporated under vacuum and $CH_2Cl_2$ (20 mL) was added. To a mixture of the heterocyclic aliphatic amine (12 mmol) and triethylamine (30 mmol) in $CH_2Cl_2$ (50 mL) the acyl chloride solution was slowly added dropwise, with constant stirring and cooling of the reaction mixture using an ice-water bath. The mixture was then stirred for 30 min at room temperature, the organic layer was separated, washed twice with salt water, dried with anhydrous sodium sulfate, and the solvent was removed to give the crude product, which was recrystallised from ethanol to give compound **2**.

*1-(Morpholin-4-yl)-2-(4-nitrophenoxy)ethanone* (**2a**): Yellow solid; yield 89%; m.p. 153–154 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.45 (s, 4H, $CH_2$), 3.61 (d, *J* = 21.4 Hz, 4H, $CH_2$), 5.08 (s, 2H, $CH_2$), 7.13 (d, *J* = 9.2 Hz, 2H, ArH), 8.20 (d, *J* = 9.2, 2H, ArH); ESI-MS *m/z*: 267.4 (M+H).

*2-(4-Nitrophenoxy1)-1-(piperidin-1-yl)ethanone* (**2b**): Yellow solid; yield 88%; m.p. 60–62 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.44 (s, 2H, $CH_2$), 1.58 (dd, *J* = 12.5, 7.2 Hz, 4H, $CH_2$), 3.34–3.48 (m, 4H, $CH_2$), 5.04 (s, 2H, $CH_2$), 7.09 (d, *J* = 9.2 Hz, 2H, ArH), 8.19 (d, *J* = 9.2, 2H, ArH); ESI-MS *m/z*: 265.2 (M+H).

*1-(4-Methylpiperazin-1-yl)-2-(4-nitrophenoxy)ethanone* (**2c**): Yellow solid; yield 84%; m.p. 213–214 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.19 (s, 3H, $CH_3$), 2.28 (d, *J* = 4.5 Hz, 2H, $CH_2$), 2.35 (s, 2H, $CH_2$), 3.44 (q, *J* = 5.2 Hz, 4H, $CH_2$), 5.06 (s, 2H, $CH_2$), 7.11 (d, *J* = 9.2 Hz, 2H, ArH), 8.20 (d, *J* = 9.2 Hz, 2H, ArH); ESI-MS *m/z*: 280.1 (M+H).

*Synthesis of 2-(4-aminophenoxy)acetamide derivatives* (**3a–c**)*; general procedure*

Compound **2** (10 mmol) in ethanol (50 mL) was hydrogenated at 0.2–0.4 MPa, catalysed by 10% Pd-C at room temperature, and recrystallised from ethanol to yield compound **3**.

*2-(4-Aminophenoxy)-1-morpholinoethanone* (**3a**): Pink solid; yield 83%; m.p. 138–139 °C (lit.[23] m.p.138 °C); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.39 (d, *J* = 4.9 Hz, 4H, $CH_2$), 3.56 (s, 4H, $CH_2$), 4.61 (s, 2H, $CH_2$), 4.64 (s, 2H, $NH_2$), 6.49 (d, *J* = 8.4 Hz, 2H, ArH), 6.65 (d, *J* = 8.1 Hz, 2H, ArH).

*2-(4-Aminephenoxy)-1-(piperidin-1-yl)ethanone* (**3b**): Oily (lit.[23] oily); yield 79%; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.40 (s, 2H, $CH_2$), 1.46–1.61 (m, 4H, $CH_2$), 3.28–3.42 (m, 4H, $CH_2$), 4.59 (s, 2H, $CH_2$), 4.62 (s, 2H, $NH_2$), 6.50 (d, *J* = 8.2 Hz, 2H, ArH), 6.65 (d, *J* = 8.2 Hz, 2H, ArH).

*2-(4-Aminophenoxy)-1-(4-methylpiperazin-1-yl)ethanone* (**3c**): Yellow solid; yield 78%; m.p. 72–73 °C (lit.[23] 73 °C); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.15 (s, 3H, $CH_3$), 2.22 (d, *J* = 4.5 Hz, 2H, $CH_2$), 2.30 (s, 2H, $CH_2$), 3.26–3.44 (m, 4H, $CH_2$), 4.62 (s, 2H, $CH_2$), 4.66 (s, 2H, $NH_2$), 6.49 (d, *J* = 8.2 Hz, 2H, ArH), 6.64 (d, *J* = 8.2 Hz, 2H, ArH).

*Synthesis of* (E)*-5-substituted-3-benzylideneindolin-2-one derivatives* (**5a–d**)*; general procedure*

A mixture of compound **4** (10 mmol), benzaldehyde (12 mmol) and a few drops of piperidine in ethanol (100 mL) was refluxed for 2 h. Part of the solvent was evaporated under reduced pressure and the residue was cooled to room temperature to crystallise the solid product, which was filtered off, washed twice with ethanol, and dried to yield compound **5**.

*(*E*)-3-Benzylideneindolin-2-one* (**5a**): Yellow solid; yield 86%; m.p. 177–178 °C (lit.[24] 178–179 °C); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.87 (t, *J* = 7.6, 8.0 Hz, 1H, ArH), 6.92 (d, *J* = 7.6 Hz, 1H, ArH), 7.23–7.28 (m, 1H, ArH), 7.48–7.58 (m, 4H, ArH), 7.69 (s, 1H, =CH), 7.72 (d, *J* = 7.2 Hz, 2H, ArH), 10.69 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 169.06, 143.41, 136.17, 134.90, 130.56, 130.05, 129.66, 129.14, 128.12, 122.75, 121.49, 121.32, 110.57; ESI-HRMS: Calcd for $C_{15}H_{11}NO$: 244.0738 ($M+Na^+$); found: 244.0729.

*(*E*)-3-Benzylidene-5-methylindolin-2-one* (**5b**): Yellow solid; yield 82%; m.p. 196–198 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.16 (s, 3H, $CH_3$), 6.78 (d, *J* = 7.6, 1H, ArH), 7.04 (d, *J* = 7.6 Hz, 1H, ArH), 7.35 (s, 1H, ArH), 7.45–7.56 (m, 3H, ArH), 7.62 (s, 1H, =CH), 7.72 (d, *J* = 7.2 Hz, 2H, ArH), 10.52 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 168.72, 143.34, 136.13, 134.68, 132.66, 130.43, 130.12, 129.58, 129.12, 128.06, 122.81, 121.35, 110.46, 20.82; ESI-HRMS: Calcd for $C_{16}H_{13}NO$: 258.0895 (M+Na$^+$); found: 258.0893.

*(*E*)-3-Benzylidene-5-chloroindolin-2-one* (**5c**): Yellow solid; yield 88%; m.p.227–229 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.89 (d, *J* = 8.4 Hz, 1H, ArH), 7.28 (dd, *J* = 8.4, 2.0 Hz, 1H, ArH), 7.41 (d, *J* = 2.0 Hz, 1H, ArH), 7.52–7.56 (m, 3H, ArH), 7.71 (d, *J* = 7.2 Hz, 2H, ArH), 7.74 (s, 1H, =CH), 10.78 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 168.66, 142.14, 138.13, 134.49, 130.51, 130.07, 129.62, 129.28, 127.36, 125.34, 122.93, 122.16, 111.93; ESI-HRMS: Calcd for $C_{15}H_{10}ClNO$: 278.0349 (M+Na$^+$); found: 278.0345.

*(*E*)-3-Benzylidene-5-bromoindolin-2-one* (**5d**): Yellow solid; yield 85%; m.p. 213–214 °C (lit.[25] 212–213 °C); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.79 (dd, *J* = 14.4, 8.0 Hz, 1H, ArH), 7.40 (t, *J* = 10.0, 8.8 Hz, 1H, ArH), 7.49–7.59 (m, 4H, ArH), 7.69 (d, *J* = 6.4 Hz, 2H, ArH), 7.74 (s, 1H, =CH), 7.96 (d, *J* = 10.4 Hz, 1H, ArH), 10.79 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 168.58, 142.55, 138.14, 134.55, 130.56, 129.67, 129.30, 128.72, 127.31, 124.96, 123.48, 113.08, 112.48; ESI-HRMS: Calcd for $C_{15}H_{10}BrNO$: 321.9843 ($^{79}$Br), 323.9823 ($^{81}$Br) (M+Na$^+$); found: 321.9840, 323.9833.

*Synthesis of 5-substituted-3-bromo-3-(bromo(phenyl)methyl)indolin-2-one derivatives* (**6a–d**)*; general procedure*

To a solution of compound **5** (5 mmol) in $CH_2Cl_2$ (100 mL), bromine (10 mmol) was slowly added dropwise at 0–5 °C, and the solution was then stirred for 3 h at room temperature. Water (50 mL) was poured into the solution and the phase was separated. The organic layer was washed with sodium thiosulfate solution to remove the extra bromine and washed further with saturated salt water (30 mL) and dried with anhydrous sodium sulfate. The organic layer was evaporated under reduced pressure to give the crude product, which was then recrystallised from ethanol to give compound **6**.

*3-Bromo-3-(bromo(phenyl)methyl)indolin-2-one* (**6a**): Yellow solid; yield 71%; m.p.193–194 °C (lit.[26] 194–195 °C); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 5.96, 5.97 (double singlet, 1H, =CH), 6.86 (d, *J* = 8.3 Hz, 1H, ArH), 7.26 (d, *J* = 6.6 Hz, 3H, ArH), 7.33–7.39 (m, 2H, CH), 7.49 (dd, *J* = 8.4, 2.0 Hz, 2H, ArH), 8.10 (d, *J* = 2.0 Hz, H, ArH), 11.01, 11.30 (double singlet, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 173.13, 141.23, 140.64, 135.15, 133.97, 130.99, 130.17, 129.89, 129.50, 128.28, 113.08, 57.78, 54.59; ESI-HRMS: Calcd for $C_{15}H_{11}Br_2NO$: 403.9085 (M+Na$^+$); found: 403.9081.

*3-Bromo-3-(bromo(phenyl)methyl)-5-methylindolin-2-one* (**6b**): Red solid; yield 76%; m.p.184–185 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.23 (s, 3H, $CH_3$), 5.86, 5.97 (double singlet, 1H, =CH), 6.80–6.86 (m, 1H, ArH), 7.17 (s, 1H, ArH), 7.27 (d, *J* = 1.4 Hz, 1H, ArH), 7.37–7.43 (dd, *J* = 5.1, 1.9 Hz, 3H, ArH), 7.49–7.59 (m, 3H, ArH), 11.03, 11.30 (double singlet, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 172.32, 141.45, 140.35, 139.86, 135.22, 133.87, 130.94, 130.11, 129.48, 128.24, 115.03, 58.12, 54.58, 21.23; ESI-HRMS: Calcd for $C_{16}H_{13}Br_2NO$: 417.9241 (M+Na$^+$); found: 417.9237.

*3-Bromo-3-(bromo(phenyl)methyl)-5-chloroindolin-2-one* (**6c**): Yellow solid; yield 80%; m.p. 175–176 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 5.87, 5.95 (double singlet, 1H, =CH), 6.82 (d, *J* = 8.4 Hz, 1H, ArH), 7.22–7.29 (m, 3H, ArH), 7.35 (d, *J* = 4.9 Hz, 2H, ArH), 7.41 (dd, *J* = 8.3, 2.1 Hz, 1H, ArH), 7.98 (d, *J* = 2.1 Hz, 1H, ArH), 10.69, 11.02 (double singlet, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 172.20, 141.51, 140.43, 139.84, 135.28, 133.91, 130.85, 130.18, 129.45, 128.43, 115.33, 58.12, 54.59; ESI-HRMS: Calcd for $C_{15}H_{10}Br_2ClNO$: 437.8695 (M+Na$^+$); found: 437.8703.

*3,5-Dibromo-3-(bromo(phenyl)methyl)indolin-2-one* (**6d**): Yellow solid; yield 75%; m.p. 170–171 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 5.86, 5.96 (double singlet, 1H, =CH), 6.86 (d, *J* = 8.3 Hz, 1H, ArH), 7.26 (d, *J* = 6.6 Hz, 3H, ArH), 7.33–7.39 (m, 2H, ArH), 7.49 (dd, *J* = 8.4, 2.0 Hz, 1H, ArH), 7.65 (d, *J* = 2.0 Hz, 1H, ArH), 11.01, 11.28 (double singlet, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 172.10, 141.22, 140.63, 135.16, 133.97, 130.99, 130.17, 129.89, 129.50, 128.42, 113.08, 57.77, 54.59; ESI-HRMS: Calcd for $C_{15}H_{10}Br_3NO$: 481.8190 ($^{79}$Br), 483.8169 ($^{81}$Br) (M+Na$^+$); found: 481.8186, 483.8163.

*Synthesis of* (E)*-5-substituted-3-(phenyl(phenylamino)methylene) indolin-2-one derivatives* (**8a–e**) *and* (E)*-5-substituted-3-(((4-heterocyclic-2-oxoethoxy)phenylamino)(phenyl)methylene)indolin-2-one derivatives* (**9a–g**)*; general procedure*

A mixture of compounds **6** (0.25 mmol) and **7** (or **3**) (0.3 mmol) and sodium bicarbonate (1.00 mmol) in DMF (50 mL) was reacted for 24 h at room temperature. The mixture was poured into water (30 mL), the solid was filtered off, washed with water, and recrystallised from methanol to yield compound **8** (or **9**).

*(*E*)-3-(Phenyl(phenylamino)methylene)-5-chloroindolin-2-one* (**8a**): Yellow solid; yield 68%; m.p. 217–218 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3384 (–NH–C=O), 1644 (C=O), 1594 (–NH–); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.57–6.72 (m, 3H, ArH), 6.93–7.05 (m, 2H, ArH), 7.07–7.27 (m, 5H, ArH), 7.36 (d, *J* = 8.7 Hz, 1H, ArH), 7.54 (dd, *J* = 8.8, 2.3 Hz, 1H, ArH), 7.72 (d, *J* = 2.3 Hz, 1H, ArH), 7.95 (s, 1H, NH), 11.84 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 162.31, 144.18, 144.03, 137.68, 134.77, 130.70, 130.57, 128.92, 127.73, 127.31, 125.68, 124.32, 122.67, 120.21, 118.96, 117.71, 117.56; ESI-HRMS: Calcd for $C_{21}H_{16}N_2ClO$: 347.0951 ([M+H]$^+$); found: 347.0955.

*(*E*)-3-(4-Methylphenylamino(phenyl)methylene)-5-methylindolin-2-one* (**8b**): Yellow solid; yield 73%; m.p. 174–177 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3364 (–NH–C=O), 1646 (C=O), 1585 (–NH–); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.25 (s, 6H, $CH_3$), 6.55 (d, *J* = 8.0 Hz, 2H, ArH), 6.86 (d, *J* = 8.0 Hz, 2H, ArH), 7.08–7.22 (m, 6H, ArH), 7.64 (d, *J* = 1.5 Hz, 1H, ArH), 7.68 (d, *J* = 1.8 Hz, 1H, ArH), 7.70 (s, 1H, NH), 10.01 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 166.12, 162.11, 151.57, 145.63, 135.58, 134.78, 131.30, 130.35, 129.98, 128.73, 127.68, 127.20, 125.18, 122.28, 120.82, 119.27, 115.49, 20.58, 20.21; ESI-HRMS: Calcd for $C_{23}H_{20}N_2O$: 341.1654 ([M+H]$^+$); found: 341.1660.

*(*E*)-3-(4-Fluorophenylamino(phenyl)methylene)-5-methylindolin-2-one* (**8c**): Red solid; yield 70%; m.p. 196–198 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3368 (–NH–C=O), 1644 (C=O), 1588 (–NH–); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.26 (s, 3H, $CH_3$), 6.52–6.64 (m, 4H, ArH), 7.08–7.22 (m, 6H, ArH), 7.63 (d, *J* = 1.5 Hz, 1H, ArH), 7.68 (d, *J* = 1.6 Hz, 1H, ArH), 7.71 (s, 1H, NH), 9.96 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 166.06, 162.09, 152.90, 145.66, 137.64, 134.84, 131.92, 130.89, 129.80, 129.25, 127.80, 127.15, 124.90, 120.41, 119.16, 119.01, 115.02, 20.72; ESI-HRMS: Calcd for $C_{22}H_{17}FN_2O$: 345.1403 ([M+H]$^+$); found: 345.1411.

*(*E*)-5-Bromo-3-(4-methylphenylamino(phenyl)methylene) indolin-2-one* (**8d**): Yellow solid; yield 70%; m.p. >250 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3360 (–NH–C=O), 1646 (C=O), 1590 (–NH–); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.12 (s, 3H, $CH_3$), 6.57 (d, *J* = 8.1 Hz, 2H, ArH), 6.83 (d, *J* = 8.0 Hz, 2H, ArH), 7.08–7.26 (m, 5H, ArH), 7.30 (d, *J* = 8.7 Hz, 1H, ArH), 7.63 (dd, *J* = 8.7, 2.2 Hz, 1H, ArH), 7.76 (s, 1H, NH), 7.85 (d, *J* = 2.2 Hz, 1H, ArH), 11.81 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 162.32, 144.35, 141.83, 138.00, 134.77, 133.14, 130.72, 129.42, 129.13, 127.78, 127.38, 127.27, 121.94, 119.31, 117.97, 113.37, 20.69; ESI-HRMS: Calcd for $C_{22}H_{17}BrN_2O$: 405.0602 ($^{79}$Br [M+H]$^+$); found: 405.0600.

*(*E*)-5-Bromo-3-((4-fluorophenylamino)(phenyl)methylene)indolin-2-one* (**8e**): Green solid; yield 66%; m.p. >250 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3368 (–NH–C=O), 1648 (C=O), 1588 (–NH–); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.55 (d, *J* = 8.0 Hz, 2H, ArH), 6.78 (d, *J* = 8.0 Hz, 2H, ArH), 7.07–7.25 (m, 5H, ArH), 7.32 (d, *J* = 8.5 Hz, 1H, ArH), 7.55 (dd, *J* = 8.8, 2.1 Hz, 1H, ArH), 7.76 (s, 1H, NH), 7.85 (d, *J* = 2.3 Hz, 1H, ArH), 11.82 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 162.32, 144.30, 141.59, 138.15, 134.67, 133.24, 131.01, 129.32, 129.10, 127.71, 127.41, 127.19, 121.90, 119.28, 117.86, 111.27; ESI-HRMS: Calcd for $C_{21}H_{14}BrFN_2O$: 409.0352, 411.0331 ([M+H]$^+$); found: 409.0348, 411.0327.

*(*E*)-3-(((4-Morpholino-2-oxoethoxy)phenylamino)(phenyl) methylene)indolin-2-one* (**9a**): Pink solid; yield 48%; m.p.

225–226 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3342 (–NH–C=O), 1646 (C=O), 1588 (–NH–), 1232 (Ar–O), 1104 ($CH_2$–O–$CH_2$); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.43 (t, *J* = 4.8 Hz, 4H, $CH_2$), 3.56 (p, *J* = 4.6 Hz, 4H, $CH_2$), 4.64 (s, 2H, $CH_2$), 6.61 (s, 4H, ArH), 7.07–7.20 (m, 6H, ArH), 7.28 (d, *J* = 8.7 Hz, 1H, ArH), 7.62 (dd, *J* = 8.7, 2.1 Hz, 1H, ArH), 7.71 (s, 1H, NH), 7.90 (d, *J* = 2.2 Hz, 1H, ArH), 11.71 (s, 1H, NH); $^{13}$C NMR (101 MHz, DMSO-$d_6$): δ 166.64, 162.36, 152.73, 144.68, 138.01, 137.61, 134.90, 133.07, 130.87, 127.74, 127.23, 127.13, 120.23, 119.70, 118.97, 117.93, 115.11, 113.28, 66.92, 66.52, 45.31; ESI-HRMS: Calcd for $C_{27}H_{25}N_4O_4$: 456.1923 ([M+H]$^+$); found: 456.1924.

*(*E*)-5-Chloro-3-((4-(2-(4-morpholinyl)-2-oxoethoxy)phenylamino)(phenyl)methylene)indolin-2-one* (**9b**): Pink solid; yield 51%; m.p. 237–239 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3336 (–NH–C=O), 1648 (C=O), 1588 (–NH–), 1232 (Ar–O), 1108 ($CH_2$–O–$CH_2$); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.43 (t, *J* = 4.8 Hz, 4H, $CH_2$), 3.55 (p, *J* = 4.5 Hz, 4H, $CH_2$), 4.64 (s, 2H, $CH_2$), 6.62 (s, 4H, ArH), 7.09–7.23 (m, 5H, ArH), 7.34 (d, *J* = 8.7 Hz, 1H, ArH), 7.52 (dd, *J* = 8.7, 2.3 Hz, 1H, ArH), 7.68 (s, 1H, NH), 7.74 (d, *J* = 2.3 Hz, 1H, ArH), 11.72 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 166.65,162.42, 152.74, 144.74, 137.82, 137.72, 134.93, 130.85, 130.38, 127.76, 127.15, 125.45, 124.27, 120.19, 119.96, 118.48, 117.75, 115.15, 66.90, 66.52, 42.08; ESI-HRMS: Calcd for $C_{27}H_{24}ClN_3O_4$: 490.1534 ([M+H]$^+$); found: 490.1535.

*(*E*)-5-Bromo-3-((4-(2-morpholinyl-2-oxoethoxy)phenylamino)(phenyl)methylene)indolin-2-one* (**9c**): Pink solid; yield 51%; m.p. >250 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3338 (–NH–C=O), 1646 (C=O), 1588 (–NH–), 1232 (Ar–O), 1104 ($CH_2$–O–$CH_2$); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.43 (t, *J* = 4.8 Hz, 4H, $CH_2$), 3.55 (p, *J* = 4.5 Hz, 4H, $CH_2$), 4.64 (s, 2H, $CH_2$), 6.61 (s, 4H, ArH), 7.08–7.21 (m, 5H, ArH), 7.28 (d, *J* = 8.7 Hz, 1H, ArH), 7.62 (dd, *J* = 8.7, 2.1 Hz, 1H, ArH), 7.70 (s, 1H, NH), 7.90 (d, *J* = 2.2 Hz, 1H, ArH), 11.71 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 166.71, 162.44, 153.12, 144.84, 139.15, 137.84, 135.60, 132.40, 130.48, 127.84, 126.99, 125.51, 124.39, 120.20, 119.98, 117.93, 117.75, 115.36, 66.90, 66.52, 45.28; ESI-HRMS: Calcd for $C_{27}H_{24}BrN_3O_4$: 534.1028 ($^{79}$Br), 536.1008 ($^{81}$Br [M+H]$^+$); found: 534.1031, 536.1013.

*(*E*)-3-((4-(2-Oxo-2-(piperidin-1-yl)ethoxy)phenylamino)(phenyl)methylene)indolin-2-one* (**9d**): Grey solid; yield 46%; m.p. 222–224 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3360 (–NH–C=O), 1640 (C=O), 1592 (–NH–), 1234 (Ar–O); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.38–1.61 (m, 6H, $CH_2$), 4.35 (t, *J* = 5.1 Hz, 4H, $CH_2$), 4.59 (s, 2H, $CH_2$), 6.61 (s, 4H, ArH), 7.07–7.22 (m, 6H, ArH), 7.28 (d, *J* = 8.7 Hz, 1H, ArH), 7.62 (dd, *J* = 8.7, 2.2 Hz, 1H, ArH), 7.70 (s, 1H, NH), 7.90 (d, *J* = 2.2 Hz, 1H, ArH), 11.70 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 166.05, 162.36, 152.89, 144.71, 138.01, 137.52, 134.90, 133.06, 130.88, 127.73, 127.23, 127.11, 120.30, 119.61, 118.96, 117.93, 115.05, 113.28, 67.27, 42.63, 26.42, 25.76; ESI-HRMS: Calcd for $C_{28}H_{27}N_3O_3$: 476.1950 ([M+Na]$^+$); found: 476.1948.

*(*E*)-5-Bromo-3-((4-(2-oxo-2-(piperidin-1-yl)ethoxy)phenylamino)(phenyl)methylene)indolin-2-one* (**9e**): Red solid; yield 50%; m.p. 204–206 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3366 (–NH–C=O), 1644 (C=O), 1592 (–NH–), 1232 (Ar–O); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.38–1.61 (m, 6H, $CH_2$), 4.35 (t, *J* = 5.1 Hz, 4H, $CH_2$), 4.59 (s, 2H, $CH_2$), 6.62 (s, 4H, ArH), 7.06–7.23 (m, 5H, ArH), 7.29 (d, *J* = 8.7 Hz, 1H, ArH), 7.60 (dd, *J* = 8.7, 2.1 Hz, 1H, ArH), 7.70 (s, 1H, NH), 7.90 (d, *J* = 2.3 Hz, 1H, ArH), 11.70 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 166.14, 163.43, 154.49, 146.61, 137.67, 137.19, 133.08, 132.87, 130.21, 129.12, 128.67, 128.36, 122.23, 120.41, 117.91, 117.33, 115.60, 114.11, 68.09, 43.27, 26.51, 25.59; ESI-HRMS: Calcd for $C_{28}H_{26}BrN_3O_3$: 534.1215 ($^{81}$Br [M+H]$^+$); found: 534.1213.

*(*E*)-3-((4-(2-(4-Methypiperazin-1-yl)-2-oxoethoxy)phenylamino)(phenyl)methylene)indolin-2-one* (**9f**): Yellow solid; yield 43%; m.p. 186–188 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3358 (–NH–C=O), 1648 (C=O), 1588 (–NH–), 1232 (Ar–O); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.17 (s, 1H, $CH_3$), 2.27 (dt, *J* = 21.9, 5.0 Hz, 4H, $CH_2$), 3.37–3.47 (m, 4H, $CH_2$), 4.61 (s, 2H, $CH_2$), 6.61 (s, 4H, ArH), 7.07–7.21 (m, 6H, ArH), 7.28 (d, *J* = 8.7 Hz, 1H, ArH), 7.62 (dd, *J* = 8.7, 2.1 Hz, 1H, ArH), 7.69 (s, 1H, NH), 7.89 (d, *J* = 2.2 Hz, 1H, ArH), 11.71 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 166.39, 162.36, 152.80, 144.70, 138.02, 137.60, 134.90, 133.07, 130.87, 127.75, 127.24, 127.14, 120.24, 119.73, 118.97, 117.94, 115.11, 113.28, 67.04, 46.13, 44.62, 41.61; ESI-HRMS: Calcd for $C_{28}H_{28}N_4O_3$: 491.2059 ([M+Na]$^+$); found: 491.2064.

*(*E*)-5-Bromo-3-((4-(2-(4-methypiperazin-1-yl)-2-oxoethoxy)phenylamino)(phenyl)methylene)indolin-2-one* (**9g**): Grey solid; yield 45%; m.p. 199–200 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3358 (–NH–C=O), 1648 (C=O), 1592 (–NH–), 1232 (Ar–O); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.18 (s, 3H, $CH_3$), 2.27 (dt, *J* = 21.6, 4.9 Hz, 4H, $CH_2$), 3.42 (d, *J* = 5.6 Hz, 4H, $CH_2$), 4.61 (s, 2H, $CH_2$), 6.61 (s, 4H, ArH), 7.08–7.21 (m, 5H, ArH), 7.28 (d, *J* = 8.8 Hz, 1H, ArH), 7.62 (dd, *J* = 8.7, 2.1 Hz, 1H, ArH), 7.70 (s, 1H, NH), 7.89 (d, *J* = 2.1 Hz, 1H, ArH), 11.71 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 166.39, 162.36, 152.80, 144.70, 138.02, 137.60, 133.07, 130.87, 127.75, 127.24, 127.14, 120.24, 119.73, 117.94, 115.11, 113.28, 67.04, 46.12, 44.62, 41.61; ESI-HRMS: Calcd for $C_{28}H_{27}BrN_4O_3$: 547.1345, 549.1324 ([M+H]$^+$); found: 547.1343, 549.1335.

*Antitumour activity test*

The antitumour activity of all of the synthesised compounds (**8a–e** and **9a–g**) against the cancer cell lines of HCT-116, A549, SKOV3 and MDA-MB-231 was measured by the MTT assay in the State Key Laboratory of Biotherapy, Sichuan University. The results were calculated as the mean values of three repeated experiments. Briefly, cells ($3 \times 10^4$ mL$^{-1}$) were seeded in 96-well plates and cultured for 24 h, followed by treatment with various concentrations of the compounds ranging from 50 μM to 1.56 μM for 48 h at 37 °C under 5% $CO_2$. Then, MTT (20 μL of 5 mg mL$^{-1}$) was added to each well and incubated for another 4 h at 37 °C, the supernatant fluid was removed, and DMSO (150 μL per well) was added for 15–20 min. Values of light absorption (OD) were measured at 570 nm with a SpectraMAX M5 microplate spectrophotometer (Molecular Devices). Gefitinib (TN) was used as the reference drug for antitumour evaluation and was also assessed under similar conditions for comparison with the tested compounds. The response parameter calculated was the $IC_{50}$ value, which corresponds to the concentration required for 50% inhibition of cell viability. The data for the antibacterial activity are presented in Table 1.

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## Electronic Supplementary Information

The ESI is available through: http://ingentaconnect.com/content/stl/jcr/2018/00000042/00000001/art00011

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