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PAPER

A novel acid-catalyzed C5-alkylation of oxindoles using alcohols†

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A novel C5-alkylation of oxindoles using alcohols as alkylating agents under acid catalysis is described for the first time. The reactions of various benzylic, allylic and propargylic alcohols are studied to obtain the corresponding 5-substituted oxindoles in good yields.

Introduction

In recent years, alcohols have been gaining prominence as alkylating agents towards green and atom-economic practices since they generate only water as a by-product in the reaction.[1–4] The availability and ease of preparation also makes them an attractive source. Amongst these, benzylic, allylic and propargylic alcohols have received significant attention from synthetic organic chemists due to the stability of their carbocations. The utility of these alcohols as alkylating agents in several C–C bond,[2] C–N bond[3] and C–O bond[4] formations has been demonstrated under different reaction conditions. We also have successfully established the efficacy of alcohols for the alkylation of sulfonamides, 4-hydroxy coumarins, hydrazones and 1,3-dicarbonyl compounds under acid catalysis.[5] As a part of the ongoing program on the use of alcohols as alkylating agents in our laboratory, we found it interesting to study the alkylation of oxindoles. Recently, the C3-alkylation of *N*-methyl oxindole with alcohols in the presence of metal catalysts in a basic medium, has been reported.[6]

Oxindole derivatives are one of the important classes of heterocyclic compounds and known to possess a wide range of biological activities including anti-inflammatory, anti-angiogenic, anti-cancer, tyrosine kinase A inhibition and cyclooxygenase inhibition.[7] Many of these compounds have generated substantial pharmaceutical interest.[8] For instance, Sunitinib (SU11248) as anti-cancer drug, Tenidap for the treatment of arthritis, Ziprasidone for Schizophrenia and Ropinirole, a dopamine agonist, for Parkinson's disease, are being used (Fig. 1). Several research groups have aimed towards identification of more potent oxindole derivatives with variation of the substitution on specified positions.[9] Therefore, the development of new methods for the substitution of oxindole to generate new molecular entities is very important. The present work focuses in this direction and reports the first acid-catalyzed alkylation of oxindoles with alcohols.

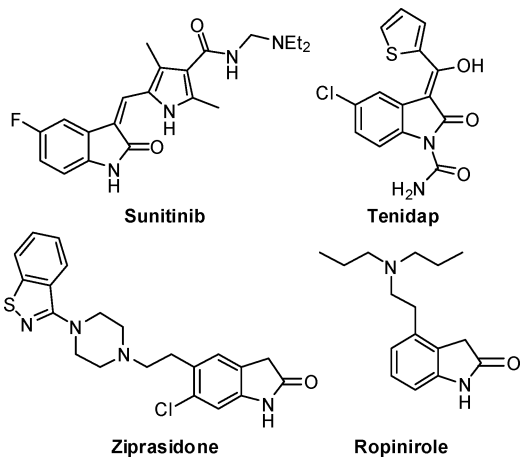

Fig. 1 Structure of representative oxindole-based drugs.

Results and discussion

As an initial experiment, oxindole (**1a**) was treated with 4-methoxybenzyl alcohol (**2a**) under the influence of *p*TSA (5 mol%) in nitromethane at room temperature. However, it was observed that under these conditions the reaction does not take place. On the other hand, when the reaction temperature is increased to 90 °C, the starting material completely disappears on TLC after 7 h. The spectral data of the isolated product revealed that the alkylation takes place on the benzene ring of oxindole, but not at the C3-position (active methylene) as we anticipated (Scheme 1). Extensive 1D and 2D NMR data (^{1}H (DQFCOSY, TOCSY and NOESY) and ^{13}C NMR (DEPT)) have established the resonance assignments.

The results have suggested that the alkylation occurred at the C5-position of oxindole to give compound **3aa** in 74% yield along with 17% of dialkylated product **3aa′**. The unambiguous NOE

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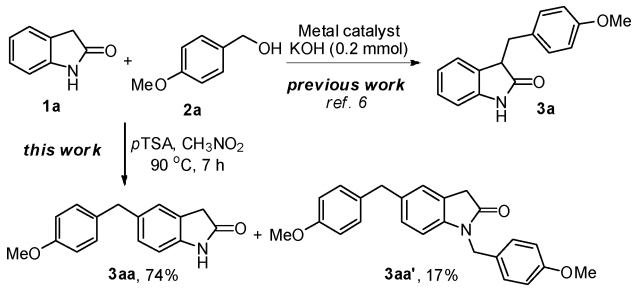
† Electronic supplementary information (ESI) available: DEPT-135, NOESY spectra for compound **3aa**, **3ba** and ^{1}H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c0ob01144d



Scheme 1 Reactions of oxindole with **2a**.

pattern with H_b–H_c, H_c–H_f, H_d–H_e and H_e–H_a cross-peaks has confirmed the conformation of **3aa** and the alkylation at the C5-position, as shown in Fig. 2. The present result is an interesting distinction from the earlier known methods,[6] where the basic reaction medium in the presence of metal catalyst provided the C3-alkylated product **3a** from the same starting materials (Scheme 1). The basis for this result is that under acid-catalyzed Friedal–Crafts conditions alcohols are prone to generate carbocations which participate in the C5-alkylation of oxindole. Whereas the reaction sequence in basic medium in the presence of metal catalyst is dehydrogenation of alcohol–Knoevenogel-type condensation–hydrogenation to give the C3-alkylated product.[6]

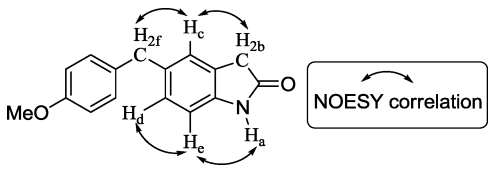
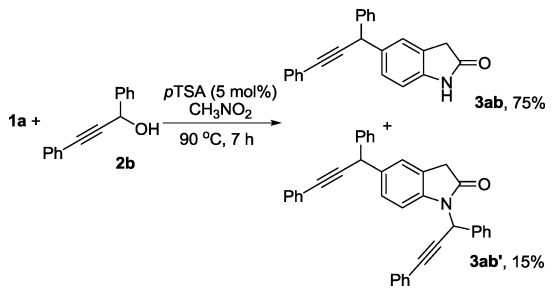


Fig. 2 nOe correlations observed in compound **3aa**.

To further confirm the C5-alkylation, a different benzylic alcohol **2b** was used as an alkylating agent for the alkylation of **1a**, which also successfully provided the 5-alkylated product **3ab** in 75% yield, along with 15% *N*-alkylated product **3ab′** (Scheme 2).



Scheme 2 C5-Alkylation of oxindole (**1a**) with **2b**.

Although there are methods known for the C5-substituion of oxindoles such as bromination, nitration and acylation *etc.*,[10] no literature precedent is available for direct C5-alkylation of oxindoles. Commonly, C5-alkylation has been accomplished in a two-step sequence of acylation followed by reduction.[11] Hence, the above result of C5-alkylation in one step is a useful method and we decided to further explore the C5-alkylation of oxindoles with various alcohols under acid catalysis. However, as oxindole (**1a**) gives mono- and dialkylated products, *N*-methyl oxindole (**1b**) was used as the substrate for more studies (Table 1). Accordingly, **1b** was subjected to alkylation using 4-methoxybenzyl alcohol (**2a**) in nitromethane using *p*TSA (5 mol%) at 90 °C. The reaction resulted in the formation of 5-alkylated product **3ba** in 92% yield, which was fully characterized. Next, we examined a variety of alcohols, including benzylic, allylic and propargylic, under *p*TSA-catalyzed conditions. From the results of Table 1, the protocol has been proven to be useful for the alkylation of *N*-methyl oxindole with secondary benzylic alcohols **2c** and **2d** to give the corresponding 5-benzylated *N*-methyloxindole products **3bc** and **3bd** in good yields (entries 3 and 4, Table 1). Cinnamyl alcohol **2e** and another allylic alcohol **2f** also provided the 5-alkylated products **3be** and **3bf** in 91% and 92% yields, respectively (entries 5 and 6, Table 1). Interestingly, benzylic propargyl alcohols **2b** and **2g** and a non-benzylic propargyl alcohol **2h** are also found to be equally effective as agents for the C5-alkylation of **1b** under the depicted reaction conditions (entries 2, 7 and 8, Table 1). Furthermore, heterocyclic based benzyl alcohols **2i** and **2j** have also provided the corresponding 5-alkylated *N*-methyl oxindoles **3bi** and **3bj** in 96 and 95% yields, respectively (entries 9 and 10, Table 1). However, the aliphatic alcohol **2k** didn't participate in the alkylation reaction with **1b** (entry 11, Table 1).

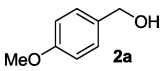
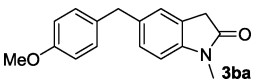
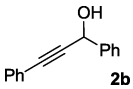
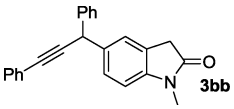
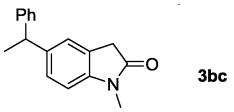
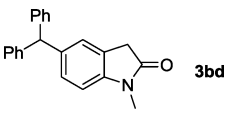
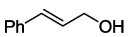
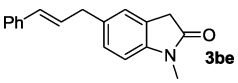
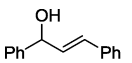
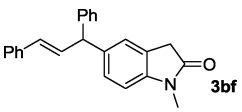
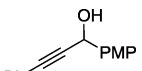
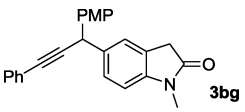
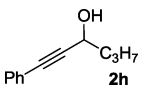
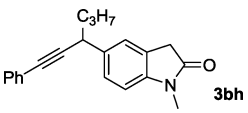
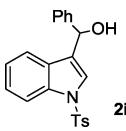
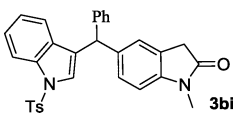
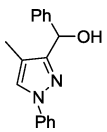
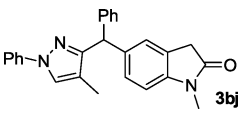
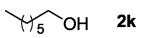
To include more diversity in the substrates, differently substituted oxindoles were next subjected to the alkylation reaction with benzylic alcohol **2b** under the described reaction conditions (5 mol% of *p*TSA, CH_3NO_2, 90 °C) and the results are summarized in Table 2. To our realization, 6-chloro *N*-methyl oxindole (**1c**) has undergone alkylation with **2b** to afford the 5-propargylated product **3cb** in 92% yield (entry 1, Table 2). *N*-Benzylated oxindoles **1d** and **1e** successfully provided the corresponding products **3db** and **3eb** in 94% and 95% yields, respectively (entries 2 and 3, Table 2). Attractively, *N*-methyl 3-benzyloxindole (**1f**) has also participated in C5-alkylation with **2b** to give the product **3fb** in 93% yield (entry 4, Table 2).

In light of the above findings, we became interested in testing the reactivity of the C5-alkylated oxindoles with aldehydes to achieve the corresponding 3-alkenyl derivatives, which are one of the important classes of bio-active compounds among the oxindole family. Thus, the reaction of **3ba** with pyrrole-2-carboxaldehyde **4a** has been examined using the known method, which resulted in successful formation of condensed product **5a** in 87% yield (entry 1, Table 3). Compound **3ab** also afforded the products **5b** and **5c** from the reaction with pyrrole-2-carboxaldehyde (**4a**) and benzaldehyde (**4b**) in high yields (entries 2 and 3, Table 3).

Finally, various readily available acid catalysts have been tested for the C5-alkylation of **1b** with **2b** and the desired product **3bb** was observed in good yield regardless of the catalyst tried (Table 4). Interestingly, $BF_3{\cdot}Et_2O$, I_2 and $FeCl_3$ were found to catalyse the reaction at room temperature (entries 1, 4 and 5, Table 4).

The above success of the reactions at room temperature[12] led us to verify the selective C5-alkylation of unprotected oxindole (**1a**). Thus, the reaction of **1a** with **2a** was carried out in the presence of $BF_3{\cdot}Et_2O$ (5 mol%) at room temperature and to our delight exclusively C5-alkylated product **3aa** was obtained in 91% yield (entry 1, Table 5). A similar result was obtained in the case of I_2 as well as $FeCl_3$ (entry 2 and 3, Table 5). Further, selective C5-alkylated product **3ab** was also accomplished from the reaction of **1a** with **2b** at room temperature (entries 4 to 6, Table 5).

Table 1 C5-Alkylation of *N*-methyl oxindole (**1b**) with various alcohols[a]

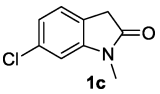
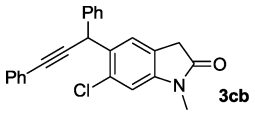
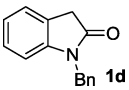
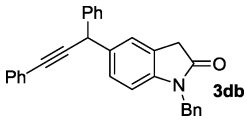
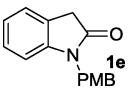
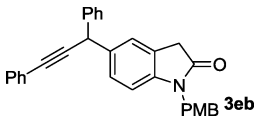
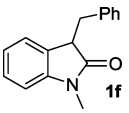
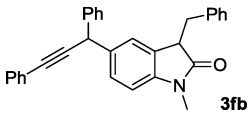
Entry	Alcohol	Time/h	Product[b]	Yield (%)[c]
1	 **2a**	7	 **3ba**	92
2	 **2b**	5	 **3bb**	93
3	 **2c**	8	 **3bc**	92
4	 **2d**	7	 **3bd**	93
5	 **2e**	7	 **3be**	91
6	 **2f**	6	 **3bf**	92
7	 **2g**	7	 **3bg**	90
8	 **2h**	10	 **3bh**	88
9	 **2i**	5	 **3bi**	96
10	 **2j**	5	 **3bj**	95
11	 **2k**	36	no reaction	—

[a] Reaction conditions: *p*TSA (5 mol%), CH_3NO_2, 90 °C. [b] All the products were characterized by ^1H, ^{13}C NMR and mass spectra. [c] Isolated yields after column chromatography.

Conclusions

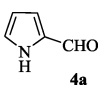
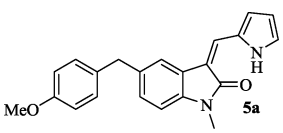
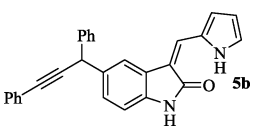
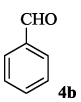
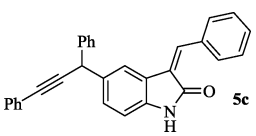
In summary, we have demonstrated an unprecedented C5-alkylation of oxindoles in the presence of an acid catalyst. The striking feature that has been revealed from the present studies is the use of alcohols as alkylating agents in this new method towards a greener and atom economic protocol. A variety of alcohols such as benzylic, allylic and propargylic alcohols were successfully utilized as alkylating agents. Furthermore, the synthesis of C3-alkenyl derivatives using the products obtained from the present method has also demonstrated. We believe that this selective C5-alkylation method, leaving C3 untouched, may find applications.

Table 2 C5-Alkylation of substituted oxindoles with **2b**[a]

Entry	Substituted oxindole	Time/h	Product[b]	Yield (%)[c]
1	 **1c**	5	 **3cb**	92
2	 **1d**	5	 **3db**	94
3	 **1e**	5	 **3eb**	95
4	 **1f**	6	 **3fb**	93

[a] Reaction conditions: *p*TSA (5 mol%), CH_3NO_2, 90 °C. [b] All the products were characterized by ^1H, ^{13}C NMR and mass spectra. [c] Isolated yields after column chromatography.

Table 3 Synthesis of 3-alkenyl derivatives from **3ba** and **3ab**[a]

Entry	C5-alkylated oxindole	Aldehyde	Time/h	Product[b]	Yield (%)[c]
1	**3ba**	 **4a**	5	 **5a**	87
2	**3ab**	**4a**	5	 **5b**	85
3	**3ab**	 **4b**	6	 **5c**	90

[a] Reaction conditions: piperidine (5 mol%), EtOH, reflux. [b] All the products were characterized by ^1H, ^{13}C NMR and mass spectra. [c] Isolated yields after column chromatography.

Experimental

General

All the solvents and reagents were purified by standard techniques; reactions were performed in oven-dried round bottom flasks; crude products were purified by column chromatography on silica gel (60–120 mesh). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to a methanolic acidic solution of *p*-anisaldehyde, an aqueous solution of potassium permanganate ($KMnO_4$) or an ethanolic solution of ninhydrin followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on a rotary evaporator at 40–45 °C. IR spectra were recorded on Perkin– Elmer 683, Nicolet Nexus 670 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solvent on Varian Gemini 200, Bruker AV-300 and Varian Innova 500 NMR spectrometers. Chemical shifts were reported in parts per million (ppm) with respect to internal TMS. Coupling constants (J) are quoted in hertz (Hz). Mass spectra were obtained on Finnigan MAT1020B, micromass VG 70–70H or Agilent technologies LC/MSD trapSL spectrometer operating at 70 eV using direct inlet system. Starting materials **1b**, **1c**, **1d**, **1e** and **1f**.[13]

General experimental procedure for C5-Alkylation of oxindoles. To a mixture of oxindole (**1**) (1.0 mmol) and alcohol (**2**) (1.0 mmol)

Table 4 C5-Alkylation of *N*-methyl oxindole (**1b**) with **2b** to obtain **3bb** under various acid catalysts[a]

Entry	Acid catalyst[b]	Temperature	Time/h	Yield (%)[c]
1	$BF_3{\cdot}Et_2O$	r.t.	3.5	93
2	$B(C_6F_5)_3$	90 °C	5	94
3	$ZnCl_2$	90 °C	5	92
4	I_2	r.t.	4	91
5	$FeCl_3$	r.t.	4	92
6	Amberlyst-15	90 °C	5	90

[a] Reactions were carried out in CH_3NO_2 on 0.1 mmol scale. [b] 5 mol% of the catalyst used. [c] Isolated yields after column chromatography.

Table 5 Selective C5-alkylation of unprotected oxindole (**1a**)[a]

Entry	Alcohol	Acid catalyst[b]	Time/h	Product	Yield (%)[c]
1	**2a**	$BF_3{\cdot}Et_2O$	4	**3aa**	91
2	**2a**	I_2	4	**3aa**	90
3	**2a**	$FeCl_3$	4	**3aa**	88
4	**2b**	$BF_3{\cdot}Et_2O$	3.5	**3ab**	94
5	**2b**	I_2	3.5	**3ab**	90
6	**2b**	$FeCl_3$	3.5	**3ab**	89

[a] Reactions were carried out in CH_3NO_2 on 0.1 mmol scale at room temperature. [b] 5 mol% of the catalyst used. [c] Isolated yields after column chromatography.

in nitromethane (20 mL), *p*-toluenesulfonic acid (5 mol %) was added and the reaction mixture was stirred at 90 °C for the given time (Table 1 and 2). After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and evaporated *in vacuo*. The crude compound was purified by column chromatography on silica gel using ethyl acetate and hexanes as eluent to give the corresponding alkylated products (**3**).

Spectral data for all new compounds

5-(4-Methoxybenzyl)indolin-2-one (3aa). Light brown solid; Mp: 174–178 °C; R_f 0.42 (hexanes/EtOAc = 1 : 1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (br s, 1H), 7.03 (d, 2H, J = 8.4 Hz), 6.99–6.95 (m, 2H), 6.77 (d, 2H, J = 8.4 Hz), 6.73 (d, 1H, J = 7.5 Hz), 3.81 (s, 2H), 3.72 (s, 3H), 3.41 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.6, 157.9, 140.4, 135.8, 133.3, 129.6, 129.6, 128.1, 125.5, 125.1, 113.9, 113.9, 109.4, 55.2, 40.6, 36.2; IR (KBr): ν_{max} 3432, 2919, 1702, 1513, 1244, 1029 cm^{-1}; MS (ESI): m/z 276.0 (M+Na)$^+$; HRMS-ESI (m/z): calcd for $C_{16}H_{16}NO_2$ (M+H)$^+$: 254.1176, found 254.1164.

1,5-Bis(4-methoxybenzyl)indolin-2-one (3aa′). Light brown solid; Mp: 129–133 °C; R_f 0.67 (hexanes/EtOAc = 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, 2H, J = 8.6 Hz), 6.99 (d, 3H, J = 8.3 Hz), 6.92 (d, 1H, J = 7.9 Hz), 6.76 (t, 4H, J = 8.6 Hz), 6.58 (d, 1H, J = 7.9 Hz), 4.78 (s, 2H), 3.81 (s, 2H), 3.75 (s, 6H), 3.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 158.9, 157.9, 142.3, 135.8, 133.2, 129.6, 129.6, 128.7, 128.7, 127.8, 127.8, 124.8, 124.8, 114.0, 114.0, 113.8, 113.8, 108.8, 55.1, 55.1, 43.1, 40.5, 35.7; IR (KBr): ν_{max} 3383, 2921, 1702, 1510, 1245, 1176, 1028, 809 cm^{-1}; MS (ESI): m/z 396.3 (M+Na)$^+$; HRMS-ESI (m/z): calcd for $C_{24}H_{24}NO_3$ (M+H)$^+$: 374.1751, found: 374.1735.

5-(1,3-Diphenylprop-2-ynyl)indolin-2-one (3ab). Brown solid; Mp: 108–112 °C; R_f 0.50 (hexanes/EtOAc = 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.47–7.16 (m, 12H), 6.82 (d, 1H, J = 7.9 Hz), 5.11 (s, 1H), 3.46 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 141.7, 141.3, 136.1, 131.6, 131.6, 128.6, 128.6, 128.2, 128.2, 128.0, 127.7, 127.7, 127.4, 126.9, 125.7, 124.2, 123.3, 109.6, 90.0, 85.0, 36.2, 29.6; IR (KBr): ν_{max} 3190, 2869, 1707, 1488, 1325, 756, 692 cm^{-1}; MS (ESI): m/z 324.1 (M+H)$^+$; HRMS-ESI (m/z): calcd for $C_{23}H_{18}$ NO (M+H)$^+$: 324.1383, found: 324.1383.

1, 5-Bis(1,3-diphenylprop-2-ynyl)indolin-2-one (3ab′). Yellow liquid; R_f 0.76 (hexanes/EtOAc = 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, 1H, J = 7.3 Hz), 7.50–7.13 (m, 21H), 6.93–6.82 (m, 2H), 5.08 (s, 1H), 3.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 140.9, 136.1, 135.6, 131.8, 131.8, 131.6, 131.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.3, 128.3, 128.3, 128.1, 128.1, 128.1, 128.0, 127.7, 127.7, 127.7, 127.0, 126.9, 126.9, 124.8, 123.9, 111.2, 90.0, 86.9, 84.9, 83.4, 45.7, 43.3, 35.6, 29.6; IR (KBr): ν_{max} 33417, 2921, 1715, 1446, 1029, 679 cm^{-1}; MS (ESI): m/z 514.2 (M+H)$^+$; HRMS-ESI (m/z): calcd for $C_{38}H_{28}NO$ (M+H)$^+$: 514.2165, found: 514.2144.

5-(4-Methoxybenzyl)-1-methylindolin-2-one (3ba). Yellow solid; Mp: 88–92 °C; R_f 0.22 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09–6.98 (m, 4H), 6.78 (d, 2H, J = 8.4 Hz), 6.68 (d, 1H, J = 7.9 Hz), 3.87 (s, 2H), 3.77 (s, 3H), 3.44 (s, 2H), 3.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 157.9, 143.3, 135.8, 133.3, 129.6, 129.6, 129.6, 127.9, 124.8, 113.8, 113.8, 107.8, 55.1, 40.6, 35.7, 26.1; IR (KBr): ν_{max} 3390, 2912, 1712, 1511, 1245, 1026, 811 cm^{-1}; MS (ESI): m/z 290.8 (M+Na)$^+$; HRMS-ESI (m/z): calcd for $C_{17}H_{18}$ NO_2 (M+H)$^+$: 268.1332, found: 268.1332.

5-(1,3-Diphenylprop-2-ynyl)-1-methylindolin-2-one (3bb). Yellow liquid; R_f 0.21 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45—7.11 (m, 12H), 6.67 (d, 1H, J = 7.9 Hz), 5.10 (s, 1H), 3.40 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 144.0, 141.7, 136.2, 131.5, 131.5, 128.6, 128.6, 128.1, 128.1, 128.0, 127.6, 127.6, 127.2, 126.8, 124.9, 123.9, 123.2, 107.9, 90.0, 84.9, 43.3, 35.7, 26.1; IR (KBr): ν_{max} 3453, 2923, 2363, 1715, 1611, 1496, 1280, 769 cm^{-1}; MS (ESI): m/z 338.1 (M+H)$^+$; HRMS-ESI (m/z): calcd for $C_{24}H_{20}$ NO (M+H)$^+$: 338.1539, found: 338.1528.

1-Methyl-5-(1-phenylethyl)indolin-2-one (3bc). Light yellow liquid; R_f 0.40 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.01 (m, 7H), 6.68 (d, 1H, J = 8.1 Hz), 4.09 (q, 1H, J = 7.1 Hz), 3.42 (s, 2H), 3.17 (s, 3H), 1.61 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 146.3, 143.3, 140.8, 128.3, 128.3, 127.3, 127.3, 126.7, 126.0, 124.6, 123.7, 107.7, 44.3, 35.7, 26.1, 21.9; IR (KBr): ν_{max} 3616, 2964, 1711, 1496, 1347, 1093, 772 cm^{-1}; MS (ESI): m/z 252.1 (M+H)$^+$; HRMS-ESI (m/z): calcd for $C_{17}H_{18}$ NO (M+H)$^+$: 252.1383, found: 252.1386.

5-Benzhydryl-1-methylindolin-2-one (3bd). Brown solid; Mp: 144–148 °C; R_f 0.40 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.14 (m, 6H), 7.10–6.89 (m, 6H), 6.69 (d, 1H, J = 7.9 Hz), 5.49 (s, 1H), 3.45 (s, 2H), 3.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 143.8, 138.3, 129.2, 129.2, 129.2, 129.2, 129.2, 128.7, 128.7, 128.3, 128.3, 128.3, 128.3, 128.3, 126.3, 126.3, 125.4, 107.7, 56.4, 35.7, 26.1; IR (KBr): ν_{max} 3409, 1714, 1495, 1338, 803, 698 cm^{-1}; MS (ESI): m/z 335.9 (M+Na)$^+$; HRMS-ESI (m/z): calcd for $C_{22}H_{20}$ NO (M+H)$^+$: 314.1539, found: 314.1545.

5-Cinnamyl-1-methylindolin-2-one (3be). Yellow liquid; R_f 0.23 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.06 (m, 7H), 6.80–6.66 (m, 1H), 6.46–6.21 (m, 2H), 3.54–3.42 (m, 4H), 3.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 143.3, 137.2, 134.2, 130.9, 129.1, 128.4, 128.4, 127.7, 127.0, 125.9, 124.7, 124.1, 122.2, 107.8, 38.8, 35.6, 26.1; IR (KBr): ν_{max} 3454, 2924, 2097, 1705, 1497, 1098 cm^{-1}; MS (ESI): m/z 264.1 $(M+H)^+$; HRMS-ESI (m/z): calcd for $C_{18}H_{18}NO$ $(M+H)^+$: 264.1383, found: 264.1387.

5-(1,3-Diphenylallyl)-1-methylindolin-2-one (3bf). Light yellow solid; Mp: 119–123 °C; R_f 0.23 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.02 (m, 12H), 6.86–6.59 (m, 2H), 6.34 (d, 1H, J = 15.8 Hz), 4.87 (d, 1H, J = 7.3 Hz), 3.49 (s, 2H), 3.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 143.6, 143.4, 137.8, 137.0, 128.4, 128.4, 128.4, 128.4, 128.4, 27.9, 127.8, 127.3, 126.4, 126.2, 126.2, 124.7, 124.6, 124.2, 122.2, 107.8, 53.7, 35.7, 26.1; IR (KBr): ν_{max} 3022, 1718, 1495, 1094, 979, 747 cm^{-1}; MS (ESI): m/z 362.1 $(M+Na)^+$; HRMS-ESI (m/z): calcd for $C_{24}H_{22}NO$ $(M+H)^+$: 340.1696, found: 340.1690.

5-(1-(4-Methoxyphenyl)-3-phenylprop-2-ynyl)-1-methylindolin-2-one (3bg). Yellow liquid; R_f 0.20 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.40 (m, 2H), 7.33–7.20 (m, 7H), 6.81 (d, 2H, J = 8.6 Hz), 6.71 (d, 1H, J = 8.3 Hz), 5.08 (s, 1H), 3.78 (s, 3H), 3.46 (s, 2H), 3.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 158.4, 143.9, 136.5, 133.8, 131.5, 131.5, 128.6, 128.6, 128.1, 128.1, 127.9, 127.9, 127.1, 123.8, 123.8, 113.9, 113.9, 107.8, 90.3, 84.8, 55.2, 42.4, 35.7, 26.1; IR (KBr): ν_{max} 3621, 3054, 2830, 2223, 1700, 1500, 1345, 1247, 759 cm^{-1}; MS (ESI): m/z 368.1 $(M+H)^+$; HRMS-ESI (m/z): calcd for $C_{25}H_{22}NO_2$ $(M+H)^+$: 368.1645, found: 368.1648.

1-Methyl-5-(1-phenylhex-1-yn-3-yl) indolin-2-one (3bh). Yellow liquid; R_f 0.29 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.37 (m, 1H), 7.37–7.18 (m, 5H), 6.99 (t, 1H, J = 7.5 Hz), 6.80–6.70 (m, 1H), 3.78 (t, 1H, J = 7.5 Hz), 3.49 (s, 3H), 3.21 (s, 2H), 1.85–1.69 (m, 2H), 1.58–1.44 (m, 2H), 0.97 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 143.7, 136.6, 133.2, 131.5, 129.9, 128.1, 127.7, 126.7, 124.1, 123.5, 122.2, 107.8, 91.5, 83.1, 40.1, 37.7, 35.6, 26.0, 20.4, 13.7; IR (KBr): ν_{max} 3059, 2959, 1716, 1612, 1369, 1085, 755 cm^{-1}; MS (ESI): m/z 304.1 $(M+H)^+$; HRMS-ESI (m/z): calcd for $C_{21}H_{22}NO$ $(M+H)^+$: 304.1696, found: 304.1698.

1-Methyl-5-(phenyl (1-tosyl-*1H*-indol-3-yl)methyl)indolin-2-one (3bi). Light yellow solid; Mp: 135–139 °C; R_f 0.18 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, 1H, J = 8.3 Hz), 7.66 (d, 2H, J = 8.3 Hz), 7.29–7.18 (m, 6H), 7.10–6.95 (m, 6H), 6.84 (s, 1H), 6.67 (d, 1H, J = 7.9 Hz), 5.43 (s, 1H), 3.41 (s, 2H), 3.18 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 144.8, 143.9, 142.1, 136.3, 135.6, 135.0, 129.7, 129.7, 129.7, 128.6, 128.6, 128.6, 128.6, 128.1, 128.1, 126.7, 126.7, 126.7, 126.7, 125.6, 124.7, 124.7, 123.1, 120.4, 113.7, 107.9, 48.0, 35.7, 26.1, 21.5; IR (KBr): ν_{max} 3407, 1711, 1497, 1369, 1174, 1093, 750, 679 cm^{-1}; MS (ESI): m/z 528.8 $(M+Na)^+$; HRMS-ESI (m/z): calcd for $C_{31}H_{27}N_2O_3S$ $(M+H)^+$: 507.1737, found: 507.1745.

1-Methyl-5-((4-methyl-1-phenyl-*1H*-pyrazol-3-yl)(phenyl)-methyl)indolin-2-one (3bj). Yellow solid; Mp: 83–87 °C; R_f 0.14 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, 2H, J = 7.7 Hz), 7.37–7.01 (m, 11H), 6.70 (d, 1H, J = 7.9 Hz), 5.25 (s, 1H), 3.45 (s, 2H), 3.19 (s, 3H), 2.06 (s. 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 148.8, 143.2, 139.9, 137.5, 129.1, 129.1, 129.1, 128.49, 128.4, 128.4, 128.4, 128.4, 128.0, 127.0, 127.0, 126.4, 125.5, 124.7, 118.2, 118.2, 107.8, 46.9, 35.7, 26.1, 12.3; IR (KBr): ν_{max} 2924, 1709, 1498, 1355, 755 cm^{-1}; MS (ESI): m/z 394.0 $(M+H)^+$; HRMS-ESI (m/z): calcd for $C_{26}H_{24}N_3O$ $(M+H)^+$: 394.1914, found: 394.1926.

6-Chloro-5-(1, 3-diphenylprop-2-ynyl)-1-methylindolin-2-one (3cb). Brown solid; Mp: 104–108 °C; R_f 0.37 (hexanes/EtOAc = 7 : 3); ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.47–7.38 (m, 5H), 7.33–7.22 (m, 6H), 6.77 (s, 1H), 5.69 (s, 1H), 3.42(s, 2H), 3.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 145.0, 140.4, 133.1, 132.2, 131.6, 131.6, 128.5, 128.5, 128.2, 128.2, 128.1, 127.6, 127.6, 126.9, 125.6, 125.6, 109.0, 109.0, 89.4, 84.5, 39.6, 35.3, 26.2; IR (KBr): ν_{max} 3066, 1708, 1490, 1366, 1100, 971, 758 cm^{-1}; MS (ESI): m/z 372.1 $(M+H)^+$; HRMS-ESI (m/z): calcd for $C_{24}H_{19}ClNO$ $(M+H)^+$: 372.1150, found: 372.1146.

1-Benzyl-5-(1, 3-diphenylprop-2-ynyl)indolin-2-one (3db). Brown solid; Mp: 145–149 °C; R_f 0.42 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.14 (m, 17H), 6.62 (d, 1H, J = 7.7 Hz), 5.09 (s, 1H), 4.85 (s, 2H), 3.56 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 143.1, 141.6, 136.1, 135.7, 131.6, 131.6, 128.6, 128.6, 128.6, 128.6, 128.1, 128.1, 128.0, 127.6, 127.6, 127.5, 127.3, 127.3, 127.2, 126.9, 124.9, 124.0, 123.2, 108.8, 90.0, 84.9, 43.7, 43.3, 35.7; IR (KBr): ν_{max} 3419, 2923, 1700, 1489, 1343, 1177, 690 cm^{-1}; MS (ESI): m/z 436.1 $(M+Na)^+$; HRMS-ESI (m/z): calcd for $C_{30}H_{23}NONa$ $(M+Na)^+$: 436.1672, found: 436.1694.

5-(1, 3-Diphenylprop-2-ynyl)-1-(4-methoxybenzyl)indolin-2-one (3eb). Light brown solid; Mp: 149–153 °C; R_f 0.34 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.16 (m, 14H), 6.78 (d, 2H, J = 8.6 Hz), 6.64 (d, 1H, J = 8.3 Hz), 5.09 (s, 1H), 4.77 (s, 2H), 3.73 (s, 3H), 3.52 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 159.0, 143.2, 141.7, 136.1, 131.6, 131.6, 128.7, 128.7, 128.6, 128.6, 128.6, 128.2, 128.2, 128.0, 127.9, 127.7, 127.7, 127.1, 126.9, 124.9, 124.0, 114.0, 114.0, 108.8, 90.0, 84.9, 55.2, 43.3, 43.2, 35.8; IR (KBr): ν_{max} 33382, 2930, 1698, 1489, 1249, 1178, 1027, 754, 693 cm^{-1}; MS (ESI): m/z 444.1 $(M+H)^+$; HRMS-ESI (m/z): calcd for $C_{31}H_{26}NO_2$ $(M+H)^+$: 444.1958, found: 444.1949.

3-Benzyl-5-(1, 3-diphenylprop-2-ynyl)-1-methylindolin-2-one (3fb). Yellow liquid; R_f 0.25 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47–7.38 (m, 2H), 7.34–7.18 (m, 9H), 7.13–6.99 (m, 5H), 6.83–6.76 (m, 1H), 6.67–6.62 (m, 1H), 5.03 (d, 1H, J = 5.0 Hz), 3.67–3.60 (m, 1H), 3.45–3.40 (m, 1H), 3.13 (d, 3H, J = 3.3 Hz), 2.90–2.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0, 142.9, 141.7, 137.5, 135.7, 131.5, 131.5, 129.3, 128.5, 128.5, 128.1, 128.1, 128.1, 128.1, 128.1, 127.9, 127.5, 127.2, 127.1, 126.7, 126.4, 124.4, 124.2, 123.3, 107.7, 89.9, 84.9, 47.1, 43.2, 36.6, 26.1; IR (KBr): ν_{max} 3421, 2926, 1711, 1617, 1492, 1089, 756, 696 cm^{-1}; MS (ESI): m/z 428.1 $(M+H)^+$; HRMS-ESI (m/z): calcd for $C_{31}H_{26}NO$ $(M+H)^+$: 428.2009, found: 428.2006.

Compounds **5a** to **5c** have been prepared using the known procedure: ref. 14

(*Z*)-3-((*1H*-Pyrrol-2-yl)methylene)-5-(4-methoxybenzyl)-1-methylindolin-2-one (5a). Yellow solid; Mp: 119–123 °C; R_f 0.53

(hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.44 (brs, 1H), 7.35 (s, 1H), 7.28 (s, 1H), 7.16–7.10 (m, 3H), 7.04 (dd, 1H, J = 7.7, 0.9 Hz), 6.8 (d, 2H, J = 8.6 Hz), 6.80–6.70 (m, 2H), 6.39–6.33 (m, 1H), 3.94 (s, 2H), 3.78 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 157.9, 135.3, 133.5, 129.9, 129.7, 129.7, 129.7, 127.3, 126.0, 124.9, 124.8, 120.0, 118.3, 116.4, 113.9, 113.9, 111.4, 107.8, 55.2, 40.8, 26.1; IR (KBr): ν_{max} 3403, 2928, 1659, 1511, 1239, 1087, 1034, 743 cm^{-1}; MS (ESI): m/z 345.2 (M+H)$^+$; HRMS-ESI (m/z): calcd for $C_{22}H_{21}N_2O_2$ (M+H)$^+$: 345.1598, found: 345.1602.

(*Z*)-3-((*1H*-Pyrrol-2-yl)methylene)-5-(1,3-diphenylprop-2-ynyl)-indolin-2-one (5b). Yellow solid; Mp: 244–246 °C; R_f 0.57 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.30 (s, 1H), 10.89 (s, 1H), 7.71 (d, 2H, J = 13.5 Hz), 7.54–7.46 (m, 4H), 7.40–7.18 (m, 8H), 6.88–6.82 (m, 2H), 6.33 (brs, 1H), 5.39 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 169.2, 142.1, 137.7, 134.9, 131.3, 131.3, 129.4, 128.6, 128.6, 128.6, 128.6, 128.6, 127.3, 127.3, 126.7, 126.5, 126.1, 125.7, 125.5, 122.6, 120.6, 117.6, 116.4, 111.4, 109.5, 91.0, 84.0, 42.3; IR (KBr): ν_{max} 3166, 1669, 1340, 1127, 754 cm^{-1}; MS (ESI): m/z 401.2 (M+H)$^+$; HRMS-ESI (m/z): calcd for $C_{28}H_{21}N_2O$ (M+H)$^+$: 401.1648, found: 401.1633.

(*Z*)-3-Benzylidene-5-(1, 3-diphenylprop-2-ynyl)indolin-2-one (5c). Yellow solid; Mp: 100–103 °C; R_f 0.64 (hexanes/EtOAc = 7 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (br s, 1H), 7.79–7.73 (m, 2H), 7.61–7.54 (m, 2H), 7.38–7.17 (m, 14H), 6.87 (d, 1H, J = 7.9 Hz), 5.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 141.7, 140.3, 139.5, 138.0, 135.6, 134.4, 133.3, 131.9, 131.6, 131.6, 130.0, 129.7, 129.2, 129.2, 128.6, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.7, 126.9, 125.3, 122.6, 110.2, 89.9, 84.9, 43.2; IR (KBr): ν_{max} 3028, 1702, 1610, 1476, 1264, 694 cm^{-1}; MS (ESI): m/z 412.2 (M+H)$^+$; HRMS-ESI (m/z): calcd for $C_{30}H_{22}NO$ (M+H)$^+$: 412.1696, found: 412.1711.

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