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# Protecting-Group-Free Synthesis of 3-Amino-3-α-prenyl-oxindoles through the Direct Prenylation of Isatin-derived Imines

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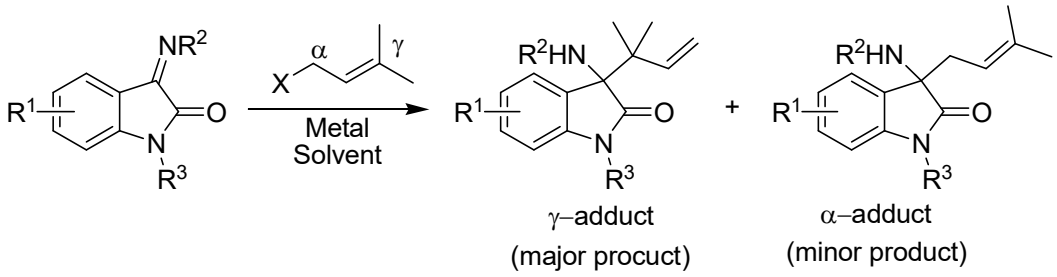
**Abstract** A zinc-mediated α-selective prenylation of isatin-derived imine using prenyl bromide as the prenyl source in a sealed tube has been developed. The protocol enables an efficient access to various 3-amino-3-α-prenyl-oxindoles from cheap and readily available chemicals in good to excellent yields. The obtained prenylated adduct can be further manipulated to other more complicated derivatives through cyclization or oxidation, which demonstrated the synthetic usefulness of this methodology. Additionally, we demonstrated that this zinc-mediated methodology is also applicable to cinnamylation and geranylation.

**Keywords:** Allylation; 3-Amino-2-oxindoles; Imines; Prenyl bromide; Zinc

## INTRODUCTION

Nitrogen-containing compounds are of great importance in the drug discovery process and more than 80% of small-molecule drugs contain at least one nitrogen atom.[1] 3-Substituted 3-amino-2-oxindoles are important structural motif in biologically active compounds.[2] In particular, 3-amino-3-allyl-2-oxindoles represent highly intriguing scaffolds, which are important precursors for the synthesis of a wide variety of bioactive compounds.[3] As a result, syntheses of this class of compounds have become an important research area and there are many reports available to synthesize them via the reactions of imines derived from isatins with allyl metal reagents.[4] However, compared to the extensive works on allylation of isatin-derived imines, the study of analogous prenylation of isatin imines for the synthesis of 3-amino-3-prenyl-2-oxindoles is far less explored because of the regioselective issue (Scheme 1).[4b,4e,5] It is well known that the prenyl fragment is a very important structural motif, which is featured in a wide variety of natural products.[6] Moreover, prenylation is critically important in the regulation of protein function[7] and the addition of a prenyl chain to an aromatic secondary metabolite often affects its pharmacological activity due to the increase in hydrophobicity of the molecule.[8] These indicate that the incorporation of a prenyl residue into a molecule may contribute to the enhancement of the biological activity, thus benefiting the drug discovery and development process.[9]




**Scheme 1.** Regioselectivity in Prenylation of Isatin-derived Imines

In 2016, Yanagisawa's group reported an α-selective prenylation of isatin imines using prenylbarium reagent.[10] To the best of our knowledge, this is the only one example in the literature of a direct α-regioselective allylation of isatin imines. Despite the success, this synthesis involved the use of metallic barium, which is of high cost and give rise to the soluble barium salts that are highly toxic to humans.[11] Meanwhile, the metallic barium also has to be carefully used because of its high reactivity, which is dangerous and may cause ignition when contact with air. On the other hand, a protecting group (such as benzyl or methyl group) at the N-1 position is necessary for oxindoles in this protocol, which limits the scope of products accessible through this reaction. In view of the significance of the prenyl moiety in the metabolism of living organisms and nitrogenous compounds in drug discovery, we envisaged that the development of a more convenient and general protocol for 3-amino-3-prenyl-2-oxindoles using N-unprotected oxindoles and cheaper and safer reagents would be of particular value.

Following our interest in the regioselective prenylation and its application[12] and the synthesis of oxindole derivatives,[13] herein we report a facile and general zinc-mediated method for the α-prenylation of isatin-derived imines in a sealed tube to afford 3-amino-3-prenyl-2-oxindoles in good to excellent yields. This protocol uses cheap and safe zinc as the mediator and readily available prenyl bromide as the prenyl source; it features high regioselectiviy, efficiency, and high yield. Moreover, a protecting group is unnecessary for isatin imines in this protocol. In addition, we have been able to expand this α-prenylation reaction of isatin-derived imine to other α-allylation reactions such as cinnamylation and geranylation, generating structurally more diverse synthetically useful α-allylated products.

## RESULTS AND DISCUSSION

We choose N-unprotected isatin imine **1a** as the model substrate for reaction condition screening. The representative results are summarized in Table 1. Taking in account that in previous works the use of polar aprotic solvents such as hexamethylphosphoramide (HMPA) or 1,3-dimethyl-2-imidazolidinone (DMI) has proven to be crucial to conduct α-regioselective prenylation,[12a,b] the reaction was performed with prenylzinc at 120 °C for 12 h in DMI initially. As expected, α-product **2a** was formed as a major product in 64% yield (entry 1). Then, other solvents such as *N,N*-dimethylformamide (DMF) (entry 2), dimethyl sulfoxide (DMSO) (entry 3), and *N,N*-dimethylacetamide (DMA) (entry 4) were investigated in order to improve the reaction yield of **2a**, and a good result was observed with DMA as solvent, affording **2a** in 77% yield. Although the above investigation and research provided a good solution for the regioselective prenylation, the problem here is that these polar aprotic solvents have significant solubility in organic solvents as well as water, and that they also act as phase-transfer agents to draw the desired products back into the aqueous layer. Consequently, the workup procedure can become very time-consuming with multiple washes and back-extractions. Thus, we investigated other conditions to overcome the limitation and eventually found that heating a THF solution of imine **1a** and prenylzinc at 120 °C in a sealed tube generated **2a** in high yield with excellent regioselectivity (entry 5). The advantage of the sealed reflux system is that it avoids the use of polar aprotic solvents commonly used in the α-prenylation process, thereby making the workup procedure and purification very simple and time-saving. To our delight, shortening the reaction time to 8 h afforded a higher yield of product **2a** at 120 °C (entry 6). Decreasing the reaction temperature to 110 °C still led to a

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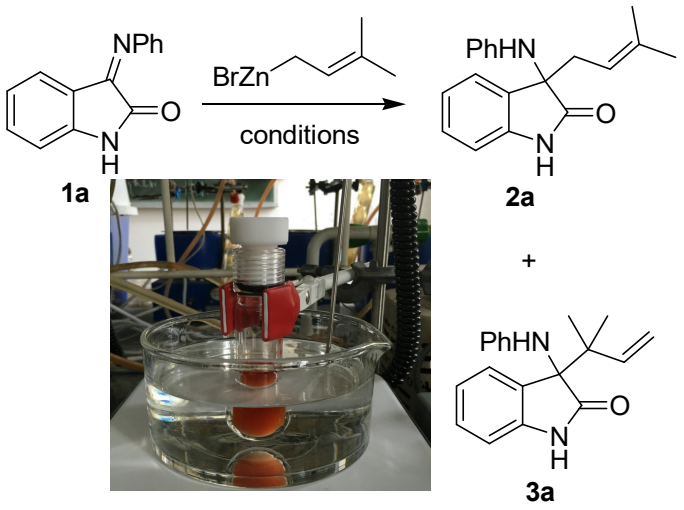
high level of α-product (85%) (entry 7). An attempt to conduct the reaction for a lower temperature resulted in the yield of **2a** dropping to 75% as well as 12% of γ-isomer **3a** (entry 8), which underlined the crucial need of the high reaction temperature for the success of the reaction.

**Table 1.** Optimization of the Reaction Conditions[a]




| entry | solvent | *T* (°C) | *t* (h) | **2a** (%)[b] | **3a** (%)[b] |
|---|---|---|---|---|---|
| 1 | DMI[c] | 120 | 12 | 64 | 0 |
| 2 | DMF[c] | 120 | 12 | 63 | 0 |
| 3 | DMSO[c] | 120 | 12 | 55 | trace |
| 4 | DMA[c] | 120 | 12 | 77 | 0 |
| 5 | THF[d] | 120 | 12 | 86 | 0 |
| 6 | THF[d] | 120 | 8 | 88 | 0 |
| 7 | THF[d] | 110 | 8 | 85 | 0 |
| 8 | THF[d] | 100 | 12 | 75 | 12 |

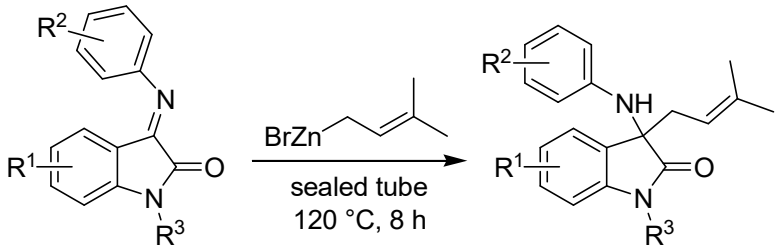
[a]Reactions were carried out with **1a** (0.5 mmol), prenyl bromide (1.0 mmol), and zinc (1.5

mmol). [b]Isolated yield. [c]Reactions were carried out in a round-bottom flask. [d]Reactions were carried out in a sealed tube.

With the optimized reaction conditions in hand, various isatin-derived imines **1b-y** were investigated, and the results are summarized in Table 2. The initial investigation of the reaction was centered on altering the substituents $R^1$ linked to the oxindoles with a free N-H group. Generally, the avoidance of protecting groups in synthesis is preferred because a protection/deprotection event lengthens the synthetic sequence, incurring costs from additional reagents, and leads to a loss of material.[14] Also, nonprotected free N-H on the oxindole allows for facile potential N-substitutions on demand. As expected, this protocol was applicable to a wide range of N-free isatin imines **1**, affording the corresponding products **2** in high yields. For example, substitution at the C5-position on the phenyl ring of imines, whether electron-donating (entries 1 and 2) or -withdrawing (entries 3 and 4) substituted, resulted in the formation of the corresponding products **2b-e** in good yields ranging from 72 to 86%. The imines containing a bromine group at the C6- or C7-position also provided the corresponding products **2f** and **2g** in 86 and 75% yields, respectively (entries 5 and 6). Subsequently, various anilines with different $R^2$ groups were used in the reaction to examine the effect of this group on the reaction. Satisfyingly, good substituent tolerance was also observed as various substitution patterns consistently gave the expected products **2h-r** in good to excellent yields (entries 7-17). It is worth noting that both strong electron-donating group ($-OCH_3$, entry 9) and strong electron-withdrawing group ($-CF_3$, entry 11) were also well tolerated, affording the corresponding products **2j** and **2l** in 80 and 71% yields, respectively.

Disubstituted aniline-derived isatin imine **1s** also delivered the desired product **2s** in satisfactory yield (entry 18). These results showed that the electronic nature and the position of the $R^2$ group have little influence on the reactivity. Finally, different protecting groups $R^3$ for the oxindole nitrogen were also screened. Small alkyl protecting groups such as methyl groups on the N-atom of oxindoles **1t-w** reacted well to give desired products **2t-w** in excellent yields (88-91%) (entries 19-22). Meanwhile, the use of a bulky protecting group such as prenyl and benzyl was also found to be compatible under the optimal conditions, affording desired product **2x** and **2y** in 82 and 89% yields, respectively (entries 23 and 24).

**Table 2.** Substrate Scope[a]




**1** **2** (α/γ > 95:5)

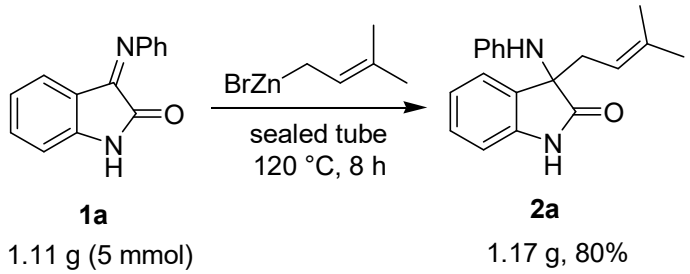
| entry | **1** | $R^1$, $R^2$, $R^3$ | **2** | yield(%)[b] |
|---|---|---|---|---|
| 1 | **1b** | 5-$CH_3$, H, H | **2b** | 83 |
| 2 | **1c** | 5-$OCH_3$, H, H | **2c** | 82 |
| 3 | **1d** | 5-F, H, H | **2d** | 72 |
| 4 | **1e** | 5-Br, H, H | **2e** | 86 |
| 5 | **1f** | 6-Br, H, H | **2f** | 86 |
| 6 | **1g** | 7-Br, 4-Br, H | **2g** | 75 |
| 7 | **1h** | H, 4-$CH_3$, H | **2h** | 88 |

| | | | | |
|---|---|---|---|---|
| 8 | **1i** | H, 3-$CH_3$, H | **2i** | 82 |
| 9 | **1j** | H, 4-$OCH_3$, H | **2j** | 80 |
| 10 | **1k** | H, 4-Br, H | **2k** | 90 |
| 11 | **1l** | H, 4-$CF_3$, H | **2l** | 71 |
| 12 | **1m** | 5-$CH_3$, 4-$CH_3$, H | **2m** | 85 |
| 13 | **1n** | 5-$CH_3$, 2-$CH_3$, H | **2n** | 83 |
| 14 | **1o** | 5-$CH_3$, 4-Cl, H | **2o** | 79 |
| 15 | **1p** | 5-$CH_3$, 4-Br, H | **2p** | 81 |
| 16 | **1q** | 5-F, 2-$CH_3$, H | **2q** | 73 |
| 17 | **1r** | 5-Cl, 4-Br, H | **2r** | 77 |
| 18 | **1s** | 5-Cl, 3,4-$Cl_2$, H | **2s** | 72 |
| 19 | **1t** | 5-Br, H, $CH_3$ | **2t** | 89 |
| 20 | **1u** | H, H, $CH_3$ | **2u** | 91 |
| 21 | **1v** | H, 4-F, $CH_3$ | **2v** | 90 |
| 22 | **1w** | H, 4-Br, $CH_3$ | **2w** | 88 |
| 23 | **1x** | H, 4-$OCH_3$, prenyl | **2x** | 82 |
| 24 | **1y** | H, H, Bn | **2y** | 89 |

[a]Unless otherwise noted, reaction conditions as for entry 6 in Table 1. [b]Isolated yield.

To exemplify the practical applicability of this protocol, a scale-up synthesis of **2a** was carried out (Scheme 2). To our delight, the reaction on the gram scale still worked very efficiently and could be scaled easily to 5 mmol and likely even larger without significantly

compromising the yield (80%) [0.5 mmol scale, 88% (entry 6 in Table 1)]. This demonstrated the applicability of this simple, protecting-group-free protocol as a useful tool in practical synthetic contexts.



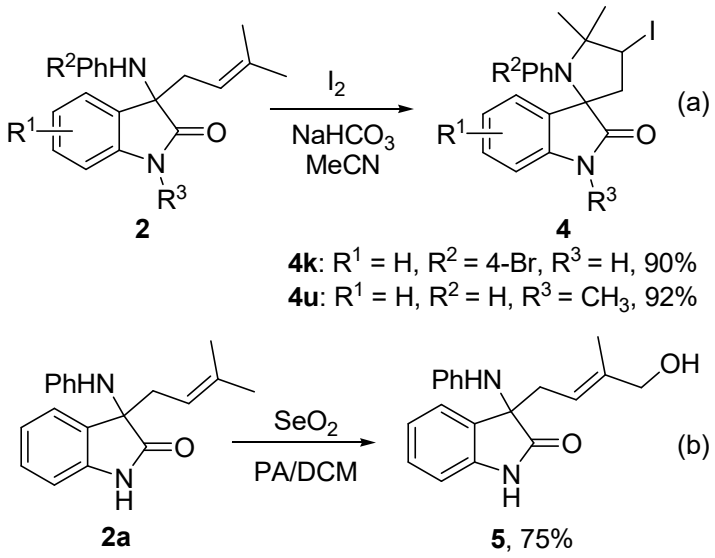

**1a**
1.11 g (5 mmol)

**2a**
1.17 g, 80%

**Scheme 2.** Gram-Scale α-Prenylation of Isatin-derived Imine **1a**

Since spirooxindoles bearing a nitrogen heterocycle at the C3-position form the basic skeleton of many natural products and therapeutic agents,[15] and they are generally more effective at inhibiting cancer cell proliferation than oxygen- or sulfur-containing heterocyclic C3-substituted molecules,[16] we believe that the preparation of their analogs would be useful for structure-activity relationship studies. Therefore, we randomly chose several N-unprotected and N-protected 3-amino-3-prenyl-2-oxindoles **2** for the synthesis of spirooxindoles containing a five-membered nitrogen heterocycle to further investigate the synthetic utility of this protocol. It was found that compounds **2k** and **2u** cyclized smoothly to the spiro pyrrolidine oxindoles **4k** and **4u** in yields of 90 and 92%, respectively, and an additional iodine atom was incorporated which could be a synthetic handle for further diversification of the spirooxindole scaffold (Scheme 3a). Then, other transformations of this 3-amino-3-prenyl-2-oxindole were also explored (Scheme 3b). For instance, the reaction of **2a** with selenium dioxide in the presence of pivalic acid (PA) in dichloromethane underwent the oxidation to afford 4-(indolin-3-yl)-2-methylbut-2-en-1-ol (a commonly found structural

motif in several bioactive natural products[17]) **5** in 75% yield. All of these applications demonstrated the usefulness of compound **2**, although they are very elementary.

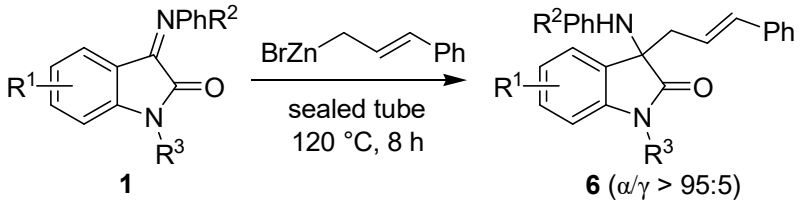



**Scheme 3.** Synthetic Applications

Encouraged by the above success, we further evaluated other 3-substituted allylmetal reagents, such as cinnamylzinc bromide, in the reaction with isatin-derived imines (Table 3). The results showed that cinnamyl-type compound also worked well for various isatin imines bearing different $R^1$ and $R^2$ groups with a free N-H group (entries 1-6 and 9), as well as different N-protecting groups $R^3$ such as methyl (entry 7) and benzyl (entry 8) groups under the reaction conditions. The previous study clearly demonstrated that 3-amino-3-α-cinnamyl-2-oxindoles are important build blocks for the synthesis of psychotrimine, a trimeric indole alkaloid.[3b] Therefore, the direct formation of α-cinnamylated products has great potential in quick construction of complex skeletons in indole alkaloids because it overcomes the regioselectivity problem with the previous cinnamylation of isatin imines,[18] which provides the incentive for the development of a new and simple entry into

psychotrimine.[3b]

**Table 3.** α-Selective Allylation of Imines **1** with Cinnamyl Bromide



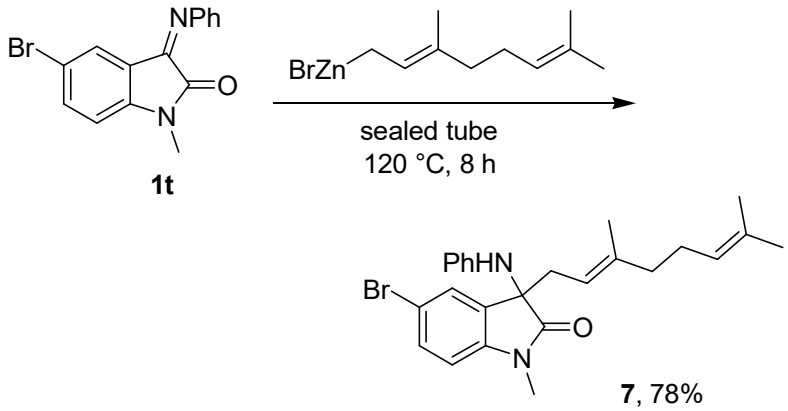

**1** **6** (α/γ > 95:5)

| entry | **1** | $R^1$, $R^2$, $R^3$ | **6** | yield (%)[a] |
|---|---|---|---|---|
| 1 | **1a** | H, H, H | **6a** | 90 |
| 2 | **1e** | 5-Br, H, H | **6e** | 88 |
| 3 | **1j** | H, 4-$OCH_3$, H | **6j** | 72 |
| 4 | **1k** | H, 4-Br, H | **6k** | 86 |
| 5 | **1l** | H, 4-$CF_3$, H | **6l** | 87 |
| 6 | **1q** | 5-F, 2-$CH_3$, H | **6q** | 88 |
| 7 | **1v** | H, 4-F, $CH_3$ | **6v** | 81 |
| 8 | **1y** | H, H, Bn | **6y** | 82 |
| 9 | **1z** | 5-Br, 4-$CH_3$, H | **6z** | 80 |

[a]Isolated yields of reactions performed on 0.5 mmol scale.

Finally, we extended our methodology toward geranylation of isatin imines, which also generally leads to the formation of γ-regioselective product.[5] Under the similar conditions with the above prenylation and cinnamylation, the corresponding α-geranylation product **7** was obtained in 78% yield by simple treating compound **1t** with geranylzinc bromide in a

sealed tube at 120 °C for 8 h (Scheme 4).




**Scheme 4.** Reaction of Isatin Imine **1t** and Geranylzinc Bromide

## CONCLUSIONS

In summary, we have developed a general and efficient method for zinc-mediated regioselective prenylation of isatin imines, which enables the simple and direct synthesis of various 3-amino-3-α-prenyl-oxindoles. Furthermore, we have demonstrated that this protocol is also applicable to other allylation reactions of isatin imines such as cinnamylation and geranylation. As a related application, several 3-amino-3-α-prenyl-oxindoles have been neatly transformed into spiro pyrrolidine oxindole and 4-(indolin-3-yl)-2-methylbut-2-en-1-ol, which further demonstrated the synthetic utility of this methodology.

## EXPERIMENTAL SECTION

**General Methods.** IR spectra were recorded with a FTIR spectrophotometer. $^{1}$H NMR and $^{13}$C NMR spectra were recorded at 400 and 100 MHz in $CDCl_3$ or DMSO-$d_6$ with chemical shifts (δ) given in parts per million relative to TMS as an internal standard. Multiplicities are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; etc.

Coupling constants (*J*) are given in hertz. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) and time-of-flight (TOF) mass analysis.

**General Procedure for the Synthesis of α-Adduct 2.** Prenyl bromide (1.0 mmol) was added to a suspension of activated zinc powder (1.5 mmol) in dry THF (5 mL); the reaction mixture was stirred for 1 h at room temperature. The solution was filtered through a Schlenk filter and kept under $N_2$ for the following reaction. Isatin-derived Imines **1** (0.5 mmol) and prenylzinc bromide prepared above were added to a 15 mL sealed tube. The resulting mixture was sealed and submerged into a 120 °C silicon oil bath. After 8 h, the solution was cooled to room temperature and the product was purified by column chromatography (3/1 petroleum ether/ethyl acetate) to afford α-product **2**.

**3-(3-Methylbut-2-en-1-yl)-3-(phenylamino)indolin-2-one (2a).** White solid (128 mg, 88% yield); mp 186-188 ºC. IR (KBr, ν, $cm^{-1}$) 3317, 1708. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.58 (s, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 6.94-6.86 (m, 4H), 6.45 (t, *J* = 7.3 Hz, 1H), 6.26 (s, 1H), 6.18 (d, *J* = 8.0 Hz, 2H), 4.84 (t, *J* = 7.2 Hz, 1H), 2.62-2.54 (m, 2H), 1.53 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 179.3, 147.0, 141.7, 135.7, 130.8, 129.0, 129.0, 123.9, 122.1, 117.0, 116.8, 113.6, 110.1, 64.4, 38.6, 26.2, 18.2. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O$ $[M - H]^-$ 291.1497; found 291.1512.

**5-Methyl-3-(3-methylbut-2-en-1-yl)-3-(phenylamino)indolin-2-one (2b).** White solid (127 mg, 83% yield); mp 193-195 ºC. IR (KBr, ν, $cm^{-1}$) 3330, 1713. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.49 (s, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.94 (s, 1H), 6.88 (t, *J* = 7.5 Hz, 2H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.45 (t, *J* = 7.2 Hz, 1H), 6.25 (s, 1H), 6.19 (d, *J* = 8.1 Hz, 2H), 4.81 (t, *J* = 6.9 Hz, 1H), 2.56 (d, *J* = 7.3 Hz, 2H), 2.20 (s, 3H), 1.54 (s, 3H), 1.37 (s, 3H). $^{13}$C NMR

(100 MHz, DMSO-$d_6$) δ 183.9, 151.7, 144.0, 140.4, 135.6, 135.6, 134.0, 133.8, 129.2, 121.6, 118.3, 114.6, 69.1, 43.4, 30.9, 25.9, 22.9. HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O$ [M − H]$^-$ 305.1654; found 305.1650.

**5-Methoxy-3-(3-methylbut-2-en-1-yl)-3-(phenylamino)indolin-2-one (2c).** White solid (132 mg, 82% yield); mp 188-190 ºC. IR (KBr, ν, cm$^{-1}$) 3390, 1707. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.42 (s, 1H), 6.89 (t, $J$ = 7.4 Hz, 2H), 6.79 (s, 2H), 6.73 (s, 1H), 6.46 (t, $J$ = 7.3 Hz, 1H), 6.25 (s, 1H), 6.20 (d, $J$ = 8.1 Hz, 2H), 4.85 (t, $J$ = 6.9 Hz, 1H), 3.65 (s, 3H), 2.61-2.55 (m, 2H), 1.55 (s, 3H), 1.37 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 183.8, 160.1, 151.7, 140.4, 139.6, 137.0, 133.8, 121.8, 121.7, 118.4, 115.4, 115.3, 69.5, 60.5, 43.3, 31.0, 23.0. HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_2$ [M − H]$^-$ 321.1603; found 321.1588.

**5-Fluoro-3-(3-methylbut-2-en-1-yl)-3-(phenylamino)indolin-2-one (2d).** White solid (112 mg, 72% yield); mp 197-199 ºC. IR (KBr, ν, cm$^{-1}$) 3350, 1715. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.62 (s, 1H), 7.04 (t, $J$ = 9.0 Hz, 1H), 6.99 (d, $J$ = 8.1 Hz, 1H), 6.91 (t, $J$ = 7.8 Hz, 2H), 6.90-6.85 (m, 1H), 6.48 (t, $J$ = 7.2 Hz, 1H), 6.30 (s, 1H), 6.19 (d, $J$ = 8.4 Hz, 2H), 4.84 (t, $J$ = 7.0 Hz, 1H), 2.65-2.24 (m, 2H), 1.55 (s, 3H), 1.37 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 179.2, 158.6 ($J$ = 236.0 Hz), 146.8, 137.9 ($J$ = 2.2 Hz), 136.1, 133.0 ($J$ = 8.0 Hz), 129.1, 116.5, 115.3 ($J$ = 23.3 Hz), 113.6, 111.6 ($J$ = 24.3 Hz), 111.0, 110.9, 64.9, 64.9 ($J$ = 2.2 Hz), 38.4, 26.1, 18.1. HRMS (ESI) m/z calcd for $C_{19}H_{18}FN_2O$ [M − H]$^-$ 309.1403; found 309.1432.

**5-Bromo-3-(3-methylbut-2-en-1-yl)-3-(phenylamino)indolin-2-one (2e).** White solid (159 mg, 86% yield); mp 221-224 ºC. IR (KBr, ν, cm$^{-1}$) 3341, 1710. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.77 (s, 1H), 7.40 (dd, $J$ = 8.2, 2.0 Hz, 1H), 7.26 (d, $J$ = 1.9 Hz, 1H), 6.93 (t, $J$

= 7.9 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.50 (t, *J* = 7.3 Hz, 1H), 6.35 (s, 1H), 6.20 (d, *J* = 7.9 Hz, 2H), 4.86 (t, *J* = 7.3 Hz, 1H), 2.66-2.57 (m, 2H), 1.55 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 178.8, 146.7, 141.0, 136.3, 133.4, 131.7, 129.2, 126.7, 117.3, 116.4, 114.1, 113.5, 112.1, 64.7, 38.4, 26.1, 18.1. HRMS (ESI) m/z calcd for $C_{19}H_{19}BrN_2NaO$ [M + Na]$^+$ 393.0578; found 393.0569.

**6-Bromo-3-(3-methylbut-2-en-1-yl)-3-(phenylamino)indolin-2-one (2f).** White solid (159 mg, 86% yield); mp 251-253 ºC. IR (KBr, ν, cm$^{-1}$) 3322, 1711. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.74 (s, 1H), 7.12-7.05 (m, 2H), 7.09 (s, 1H), 6.91 (t, *J* = 7.8 Hz, 2H), 6.48 (t, *J* = 7.2 Hz, 1H), 6.31 (s, 1H), 6.17 (d, *J* = 8.1 Hz, 2H), 4.85 (t, *J* = 7.2 Hz, 1H), 2.64-2.52 (m, 2H), 1.56 (s, 3H), 1.37 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 178.5, 146.1, 142.8, 135.6, 129.6, 125.2, 124.2, 120.9, 116.7, 115.9, 113.0, 112.4, 63.7, 37.7, 25.6, 17.6. HRMS (ESI) m/z calcd for $C_{19}H_{19}BrN_2NaO$ [M + Na]$^+$ 393.0578; found 393.0572.

**7-Bromo-3-((4-bromophenyl)amino)-3-(3-methylbut-2-en-1-yl)indolin-2-one (2g).** White solid (179 mg, 75% yield); mp 184-186 ºC. IR (KBr, ν, cm$^{-1}$) 3350, 1726. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.94 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.13-7.18 (m, 3H), 6.90 (t, *J* = 7.7 Hz, 1H), 6.62 (s, 1H), 6.12 (d, *J* = 8.8 Hz, 2H), 4.84 (t, *J* = 7.2 Hz, 1H), 2.63-2.57 (m, 2H), 1.55 (s, 3H), 1.33 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 178.2, 145.4, 140.4, 135.9, 131.7, 131.5, 131.2, 123.4, 122.4, 115.6, 115.0, 107.7, 102.3, 65.0, 38.0, 25.6, 17.6. HRMS (ESI) m/z calcd for $C_{19}H_{17}Br_2N_2O$ [M − H]$^-$ 448.9687; found 448.9693.

**3-(3-Methylbut-2-en-1-yl)-3-(p-tolylamino)indolin-2-one (2h).** White solid (135 mg, 88% yield); mp 172-174 ºC. IR (KBr, ν, cm$^{-1}$) 3344, 1712. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.56 (s, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* =

7.7 Hz, 1H), 6.73 (t, *J* = 7.8 Hz, 1H), 6.28 (d, *J* = 7.4 Hz, 1H), 6.14 (s, 1H), 6.12 (s, 1H), 5.88 (d, *J* = 8.0 Hz, 1H), 4.83 (t, *J* = 7.3 Hz, 1H), 2.59-2.53 (m, 2H), 2.01 (s, 3H), 1.53 (s, 3H), 1.36 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 179.3, 146.9, 141.7, 137.8, 135.6, 130.9, 129.0, 128.9, 123.9, 122.1, 117.9, 116.9, 114.8, 110.5, 110.0, 64.4, 38.6, 26.2, 21.7, 18.2. HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O$ [M − H]$^-$ 305.1654; found 305.1659.

**3-(3-Methylbut-2-en-1-yl)-3-(m-tolylamino)indolin-2-one (2i).** White solid (126 mg, 82% yield); mp 190-192 ºC. IR (KBr, ν, cm$^{-1}$) 3316, 1710. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.58 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 1H), 6.29 (d, *J* = 7.4 Hz, 1H), 6.16 (s, 1H), 6.12 (s, 1H), 5.89 (dd, *J* = 8.1, 1.9 Hz, 1H), 4.84 (t, *J* = 7.3 Hz, 1H), 2.64-2.52 (m, 2H), 2.02 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 179.3, 146.9, 141.7, 137.8, 135.7, 130.9, 129.0, 128.9, 123.9, 122.1, 117.9, 116.9, 114.8, 110.5, 110.0, 64.4, 38.6, 26.2, 21.7, 18.2. HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O$ [M − H]$^-$ 305.1654; found 305.1661.

**3-((4-Methoxyphenyl)amino)-3-(3-methylbut-2-en-1-yl)indolin-2-one (2j).** White solid (129 mg, 80% yield); mp 146-148 ºC. IR (KBr, ν, cm$^{-1}$) 3312, 1708. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.50 (s, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 8.8 Hz, 2H), 6.17 (d, *J* = 8.8 Hz, 2H), 5.82 (s, 1H), 4.83 (t, *J* = 7.2 Hz, 1H), 3.54 (s, 3H), 2.59-2.52 (m, 2H), 1.53 (s, 3H), 1.37 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 179.0, 151.2, 141.2, 140.4, 134.9, 130.5,128.4, 123.4, 121.5, 116.5, 114.7, 114.0, 109.5, 64.5, 55.0, 38.0, 25.6, 17.6. HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_2$ [M − H]$^-$ 321.1603; found 321.1625.

**3-((4-Bromophenyl)amino)-3-(3-methylbut-2-en-1-yl)indolin-2-one (2k).** White solid (167

mg, 90% yield); mp 204-206 ºC. IR (KBr, ν, $cm^{-1}$) 3305, 1709. $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 10.64 (s, 1H), 7.22 (t, $J$ = 7.6 Hz, 1H), 7.12 (d, $J$ = 7.3 Hz, 1H), 7.05 (d, $J$ = 8.8 Hz, 2H), 6.93 (t, $J$ = 7.5 Hz, 1H), 6.88 (d, $J$ = 7.7 Hz, 1H), 6.53 (s, 1H), 6.14 (d, $J$ = 8.8 Hz, 2H), 4.83 (t, $J$ = 7.1 Hz, 1H), 2.63-2.56 (m, 2H), 1.53 (s, 3H), 1.35 (s, 3H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 178.9, 146.2, 141.6, 135.9, 131.6, 130.1, 129.2, 123.9, 122.2, 116.6, 115.5, 110.3, 108.0, 64.4, 38.5, 26.2, 18.2. HRMS (ESI) m/z calcd for $C_{19}H_{18}BrN_2O$ $[M - H]^-$ 369.0603; found 369.0614.

**3-(3-Methylbut-2-en-1-yl)-3-((4-(trifluoromethyl)phenyl)amino)indolin-2-one (2l).** White solid (128 mg, 71% yield); mp 162-164 ºC. IR (KBr, ν, $cm^{-1}$) 3324, 1716. $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 10.72 (s, 1H), 7.26-7.22 (m, 3H), 7.13 (d, $J$ = 7.2 Hz, 1H), 7.04 (s, 1H), 6.96-6.90 (m, 2H), 6.29 (d, $J$ = 8.6 Hz, 2H), 4.84 (t, $J$ = 7.3 Hz, 1H), 2.66-2.56 (m, 2H), 1.54 (s, 3H), 1.35 (s, 3H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 178.5, 150.0, 141.7, 136.1, 129.8, 129.4, 126.4 ($J$ = 3.7 Hz), 125.5 ($J$ = 268.4 Hz), 123.9, 122.3, 116.9 ($J$ = 31.8 Hz), 116.7, 116.4, 113.0, 110.4, 64.3, 38.4, 26.2, 18.2. HRMS (ESI) m/z calcd for $C_{20}H_{18}F_3N_2O$ $[M - H]^-$ 359.1371; found 359.1361.

**5-Methyl-3-(3-methylbut-2-en-1-yl)-3-(p-tolylamino)indolin-2-one (2m).** White solid (136 mg, 85% yield); mp 173-175 ºC. IR (KBr, ν, $cm^{-1}$) 3371, 1706. $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 10.42 (s, 1H), 7.00 (d, $J$ = 7.8 Hz, 1H), 6.93 (s, 1H), 6.75 (d, $J$ = 7.8 Hz, 1H), 6.69 (d, $J$ = 8.2 Hz, 2H), 6.11 (d, $J$ = 8.2 Hz, 2H), 6.01 (s, 1H), 4.81 (t, $J$ = 6.9 Hz, 1H), 2.54 (d, $J$ = 7.3 Hz, 2H), 2.20 (s, 3H), 2.04 (s, 3H), 1.53 (s, 3H), 1.37 (s, 3H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 178.8, 144.1, 138.7, 134.9, 130.5, 130.2, 128.9, 128.6, 124.8, 123.9, 116.4, 113.3, 109.2, 64.0, 38.8, 25.6, 20.6, 19.8, 17.6. HRMS(ESI) m/z calcd for $C_{21}H_{25}N_2O$ [M +

H]$^+$ 321.1967; found 321.1971.

**5-Methyl-3-(3-methylbut-2-en-1-yl)-3-(o-tolylamino)indolin-2-one (2n).** White solid (133 mg, 83% yield); mp 158-160 ºC. IR (KBr, ν, cm$^{-1}$) 3371, 1705. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.02-6.97 (m, 3H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.72 (t, *J* = 7.7 Hz, 1H), 6.55 (t, *J* = 7.3 Hz, 1H), 5.78 (d, *J* = 8.0 Hz, 1H), 5.30 (t, *J* = 7.7 Hz, 1H), 4.38 (s, 1H), 2.70-2.57(m, 2H), 2.26 (s, 3H), 2.23 (s, 3H), 1.78 (s, 3H), 1.72 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 180.6, 143.3, 138.5, 137.1, 132.2, 130.9, 130.2, 129.1, 127.0, 124.4, 122.6, 118.0, 116.0, 111.4, 110.3, 64.0, 39.3, 26.2, 21.2, 18.1, 17.6. HRMS(ESI) m/z calcd for $C_{21}H_{23}N_2O$ [M − H]$^-$ 319.1810; found 319.1813.

**3-((4-Chlorophenyl)amino)-5-methyl-3-(3-methylbut-2-en-1-yl)indolin-2-one (2o).** White solid (134 mg, 79% yield); mp 190-192 ºC. IR (KBr, ν, cm$^{-1}$) 3319, 1713. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.54 (s, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.95 (s, 2H), 6.93 (s, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.50 (s, 1H), 6.18 (d, *J* = 8.0 Hz, 2H), 4.79 (t, *J* = 6.9 Hz, 1H), 2.56 (d, *J* = 7.2 Hz, 2H), 2.21 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 183.5, 150.7, 144.0, 140.5, 135.8, 135.0, 134.2, 133.5, 129.2, 125.2, 121.5, 119.7, 114.8, 69.2, 43.3, 30.9, 25.9, 22.9. HRMS (ESI) m/z calcd for $C_{20}H_{21}ClN_2NaO$ [M + Na]$^+$ 363.1240; found 363.1230.

**3-((4-Bromophenyl)amino)-5-methyl-3-(3-methylbut-2-en-1-yl)indolin-2-one (2p).** White solid (156 mg, 81% yield); mp 202-204 ºC. IR (KBr, ν, cm$^{-1}$) 3322, 1715. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.50 (s, 1H), 7.03-6.98 (t, 3H), 6.90 (s, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.48 (s, 1H), 6.10 (d, *J* = 8.9 Hz, 2H), 4.76 (t, *J* = 7.4 Hz, 1H), 2.52 (d, *J* = 7.3 Hz, 2H), 2.17 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 178.7, 146.3, 139.2, 135.8,

131.6, 131.1, 130.2, 129.5, 124.4, 116.7, 115.5, 110.0, 107.9, 64.4, 38.5, 26.2, 21.1, 18.2. HRMS (ESI) m/z calcd for $C_{20}H_{20}BrN_2O$ $[M - H]^-$ 383.0759; found 383.0766.

**5-Fluoro-3-(3-methylbut-2-en-1-yl)-3-(o-tolylamino)indolin-2-one (2q).** White solid (118 mg, 73% yield); mp 190-192 ºC. IR (KBr, ν, $cm^{-1}$) 3352, 1713. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 10.62 (s, 1H), 7.00-6.94 (m, 2H), 6.89 (d, $J$ = 7.2 Hz, 1H), 6.83-6.80 (m, 1H), 6.62 (t, $J$ = 7.5 Hz, 1H), 6.40 (t, $J$ = 7.3 Hz, 1H), 5.57 (d, $J$ = 8.1 Hz, 1H), 4.89 (t, $J$ = 7.3 Hz, 1H), 4.82 (s, 1H), 2.66-2.57 (m, 2H), 2.13 (s, 3H), 1.54 (s, 3H), 1.43 (s, 3H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 179.1, 158.7 ($J$ = 235.9 Hz), 144.0, 137.7 ($J$ = 1.6 Hz), 136.9, 133.0 ($J$ = 7.6 Hz), 130.5, 126.9, 123.4, 117.8, 116.5, 115.4 ($J$ = 23.3 Hz), 113.6, 111.6 ($J$ = 24.3 Hz), 111.1, 111.0 ($J$ = 7.9 Hz), 64.5 ($J$ = 1.4 Hz), 38.7, 26.2, 18.2, 18.0. HRMS (ESI) m/z calcd for $C_{20}H_{20}FN_2O$ $[M - H]^-$ 323.1560; found 323.1571.

**5-Chloro-3-((4-bromophenyl)amino)-3-(3-methylbut-2-en-1-yl)indolin-2-one (2r).** White solid (156 mg, 77% yield); mp 197-199 ºC. IR (KBr, ν, $cm^{-1}$) 3324, 1716. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 10.76 (s, 1H), 7.24 (dd, $J$ = 8.3, 2.1 Hz, 1H), 7.12 (d, $J$ = 2.0 Hz, 1H), 7.05 (d, $J$ = 8.8 Hz, 2H), 6.86 (d, $J$ = 8.3 Hz, 1H), 6.56 (s, 1H), 6.10 (d, $J$ = 8.8 Hz, 2H), 4.79 (t, $J$ = 7.2 Hz, 1H), 2.62-2.52 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 178.5, 146.0, 140.6, 136.5, 132.4, 131.8, 129.1, 126.4, 124.0, 116.2, 115.5, 111.8, 108.3, 64.7, 38.2, 26.1, 18.1. HRMS (ESI) m/z calcd for $C_{19}H_{17}BrClN_2O$ $[M - H]^-$ 403.0213; found 403.0194.

**3-(3,4-Dichlorophenylamino)-5-chloro-3-(3-methylbut-2-enyl)indolin-2-one (2s).** White solid (142 mg, 72% yield); mp 209-211 ºC. IR (KBr, ν, $cm^{-1}$) 3362, 1723. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 10.89 (s, 1H), 7.31 (dd, $J$ = 8.2, 1.9 Hz, 1H), 7.20 (s, 1H), 7.18 (s, 1H), 6.92 (d,

*J* = 8.3 Hz, 1H), 6.88 (s, 1H), 6.34 (d, *J* = 2.6 Hz, 1H), 6.16 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.82 (t, *J* = 7.1 Hz, 1H), 2.67-2.54 (m, 2H), 1.55 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 182.8, 151.5, 145.3, 141.5, 136.6, 136.1, 135.7, 134.2, 131.3, 128.9, 123.2, 120.7, 119.2, 118.6, 116.6, 69.4, 42.8, 30.9, 22.9. HRMS (ESI) m/z calcd for $C_{19}H_{16}Cl_3N_2O$ $[M - H]^-$ 393.0328; found 393.0352.

**5-Bromo-1-methyl-3-(3-methylbut-2-enyl)-3-(phenylamino)indolin-2-one (2t).** White solid (170 mg, 89% yield); mp 169-171 ºC. IR (KBr, ν, cm$^{-1}$) 3342, 1704. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.52 (d, *J* = 9.1 Hz, 1H), 7.31 (s, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.91 (t, *J* = 7.7 Hz, 2H), 6.49 (t, *J* = 7.3 Hz, 1H), 6.40 (s, 1H), 6.10 (d, *J* = 8.0 Hz, 2H), 4.76 (t, *J* = 7.1 Hz, 1H), 3.17 (s, 3H), 2.66-2.56 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 181.8, 151.3, 147.3, 141.4, 137.4, 136.6, 134.0, 131.0, 122.2, 120.9, 119.6, 118.3, 115.9, 69.2, 43.2, 31.4, 30.8, 22.9. HRMS(ESI) m/z calcd for $C_{20}H_{21}BrN_2NaO$ $[M + Na]^+$ 407.0735; found 407.0717.

**1-Methyl-3-(3-methylbut-2-en-1-yl)-3-(phenylamino)indolin-2-one (2u).** White solid (139 mg, 91% yield); mp 168-170 ºC. IR (KBr, ν, cm$^{-1}$) 3330, 1713. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.52 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 1.7 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.90 (t, *J* = 7.8 Hz, 2H), 6.49 (t, *J* = 7.3 Hz, 1H), 6.38 (s, 1H), 6.10 (d, *J* = 8.1 Hz, 2H), 4.76 (t, *J* = 7.4 Hz, 1H), 3.17 (s, 3H), 2.67-2.55 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 176.4, 145.9, 142.0, 136.0, 132.1, 131.2, 128.6, 125.7, 116.8, 115.6, 114.2, 113.0, 110.5, 63.8, 37.8, 26.0, 25.5, 17.5. HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2NaO$ $[M + Na]^+$ 329.1630; found 329.1626.

**3-((4-Fluorophenyl)amino)-1-methyl-3-(3-methylbut-2-en-1-yl)indolin-2-one (2v).** White

solid (146 mg, 90% yield); mp 132-135 ºC. IR (KBr, ν, $cm^{-1}$) 3329, 1713. $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 7.32 (t, $J$ = 7.7 Hz, 1H), 7.18 (d, $J$ = 7.3 Hz, 1H), 7.07 (d, $J$ = 7.7 Hz, 1H), 7.01 (t, $J$ = 7.4 Hz, 1H), 6.72 (t, $J$ = 8.9 Hz, 2H), 6.29 (s, 1H), 6.11-6.08 (m, 2H), 4.74 (t, $J$ = 7.0 Hz, 1H), 3.16 (s, 3H), 2.60-2.57 (m, 2H), 1.51 (s, 3H), 1.33 (s, 3H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 177.4, 156.2 ($J$ = 230.9 Hz), 143.4 ($J$ = 1.4 Hz), 143.3, 136.0, 129.9, 129.3, 123.5, 122.9, 116.5, 115.5 ($J$ = 21.9 Hz), 114.7 ($J$ = 7.3 Hz), 109.1, 64.6, 38.6, 26.5, 26.1, 18.1. HRMS (ESI) m/z calcd for $C_{20}H_{21}FN_2NaO[M + Na]^+$ 347.1536; found 347.1528.

**3-((4-Bromophenyl)amino)-1-methyl-3-(3-methylbut-2-en-1-yl)indolin-2-one (2w).** White solid (169 mg, 88% yield); mp 146-148 ºC. IR (KBr, ν, $cm^{-1}$) 3337, 1717. $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 7.33 (t, $J$ = 7.6 Hz, 1H), 7.17 (d, $J$ = 7.2 Hz, 1H), 7.09 (d, $J$ = 7.8 Hz, 1H), 7.04-7.00 (m, 3H), 6.60 (s, 1H), 6.05 (d, $J$ = 8.8 Hz, 2H), 4.74 (t, $J$ = 7.2 Hz, 1H), 3.17 (s, 3H), 2.64-2.57 (m, 2H), 1.51 (s, 3H), 1.32 (s, 3H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 177.1, 146.1, 143.2, 136.2, 131.6, 129.5, 129.3, 123.5, 122.9, 116.3, 115.6, 109.2, 108.1, 64.3, 38.5, 26.5, 26.1, 18.1. HRMS (ESI) m/z calcd for $C_{20}H_{20}BrN_2O$ $[M - H]^-$ 383.0759; found 383.0753.

**3-((4-Methoxyphenyl)amino)-1,3-bis(3-methylbut-2-en-1-yl)indolin-2-one (2x).** White solid (160 mg, 82% yield); mp 99-101 ºC. IR (KBr, ν, $cm^{-1}$) 3319, 1698. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.32 (d, $J$ = 7.3 Hz, 1H), 7.29-7.25 (m, 2H), 7.04 (t, $J$ = 7.5 Hz, 1H), 6.79 (d, $J$ = 7.8 Hz, 1H), 6.52 (d, $J$ = 8.8 Hz, 2H), 6.23 (d, $J$ = 8.8 Hz, 2H), 5.00 (t, $J$ = 7.5 Hz, 2H), 4.35-4.21 (m, 2H), 4.09 (s, 1H), 3.63 (s, 3H), 2.68-2.56 (m, 2H), 1.79 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 1.54 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 177.6, 153.4, 139.0, 137.2, 136.5, 130.3, 128.7, 123.9, 122.5, 118.4, 117.9, 115.9, 114.3, 108.9, 65.4, 55.5, 38.7, 38.0, 26.0, 25.6, 18.1, 18.0. HRMS (ESI) m/z calcd for $C_{25}H_{30}N_2NaO_2$ $[M + Na]^+$ 413.2205; found 413.2235.

**1-Benzyl-3-(3-methylbut-2-en-1-yl)-3-(phenylamino)indolin-2-one (2y).** White solid (170 mg, 89% yield); mp 96-98 ºC. IR (KBr, ν, $cm^{-1}$) 3360, 1715. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.32-7.23 (m, 6H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.93 (t, *J* = 7.2 Hz, 2H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.65 (t, *J* = 7.3 Hz, 1H), 6.20 (d, *J* = 7.7 Hz, 2H), 5.07 (t, *J* = 7.6 Hz, 1H), 4.96 (d, *J* = 15.5 Hz, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.40 (s, 1H), 2.75-2.64 (m, 2H), 1.67 (s, 3H), 1.57 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 177.9, 145.3, 142.0, 137.8, 135.8, 130.1, 129.0, 128.8, 128.7, 127.6, 123.8, 122.9, 119.1, 115.7, 115.3, 109.5, 64.5, 44.1, 39.2, 26.1, 18.1. HRMS (ESI) m/z calcd for $C_{26}H_{26}N_2NaO$ $[M + Na]^+$ 405.1943; found 405.1940.

**Procedure for the Synthesis of Compounds 4k and 4u.** Sodium bicarbonate (1.5 mmol) and iodine (1.5 mmol) were added to compounds **2k** or **2u** (0.5 mmol) in anhydrous acetonitrile (15 ml). After the mixture was stirred at room temperature for 6 h under nitrogen, the solvent was removed under reduced pressure. To the residue was added a solution of sodium sulfite. The mixture was extracted with dichloromethane for three times and dried over anhydrous magnesium sulfate. The residue was purified by column chromatography (5/1 petroleum ether/ethyl acetate) to afford the products **4k** or **4u**.

**1'-(4-Bromophenyl)-4'-iodo-5',5'-dimethylspiro[indoline-3,2'-pyrrolidin]-2-one (4k).** White solid (223 mg, 90% yield); mp 223-225 ºC. IR (KBr, ν, $cm^{-1}$) 1712. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 10.77 (s, 1H), 7.22-7.13 (m, 3H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.89 (dd, *J* = 17.6, 7.7 Hz, 2H), 6.39 (d, *J* = 9.0 Hz, 2H), 4.72 (dd, *J* = 12.7, 6.2 Hz, 1H), 2.68-2.55 (m, 2H), 1.75 (s, 3H), 1.49 (s, 3H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 179.7, 142.4, 141.6, 131.5, 129.6, 129.4, 123.4, 123.0, 119.3, 110.7, 110.3, 71.7, 64.4, 46.8, 33.0, 26.4, 25.2. HRMS (ESI) m/z calcd for $C_{19}H_{17}BrIN_2O$ $[M - H]^-$ 494.9569; found 494.9548.

**4'-Iodo-1,5',5'-trimethyl-1'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (4u).** White solid (199 mg, 92% yield); mp 95-97 ºC. IR (KBr, ν, $cm^{-1}$) 1715. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 4H), 7.06 (d, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.23 (d, *J* = 8.8 Hz, 2H), 4.95 (dd, *J* = 12.9, 6.2 Hz, 1H), 3.27 (s, 3H), 2.69-2.54 (m, 2H), 1.79 (s, 3H), 1.57 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 178.4, 142.7, 142.4, 137.5, 137.3, 129.2, 129.1, 123.5, 122.8, 121.2, 108.5, 82.2, 71.6, 64.6, 47.5, 32.7, 27.3, 26.6, 25.3. HRMS (ESI) m/z calcd for $C_{20}H_{21}IN_2NaO$ $[M + Na]^+$ 455.0596; found 455.0583.

**Procedure for the Synthesis of Alcohol 5.** Compound **2a** (146 mg, 0.5 mmol), selenium dioxide (28 mg, 0.25 mmol), pivalic acid (102 mg, 1.0 mmol), and dichloromethane (5 mL) were added to a 25 mL flask. After 12 h of stirring at room temperature, the reaction mixture was diluted with dichloromethane, washed with sat. sodium bicarbonate and brine, and purified by column chromatography (1/1 petroleum ether/ethyl acetate) to afford alcohol **5**.

**3-(4-Hydroxy-3-methylbut-2-en-1-yl)-3-(phenylamino)indolin-2-one (5).** White solid (116 mg, 75% yield); mp 101-103 ºC. IR (KBr, ν, $cm^{-1}$) 3335, 1716. $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 10.63 (s, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 6.96-6.87 (m, 4H), 6.46 (t, *J* = 7.2 Hz, 1H), 6.28 (s, 1H), 6.16 (d, *J* = 8.0 Hz, 2H), 4.97 (t, *J* = 7.4 Hz, 1H), 4.61 (t, *J* = 5.3 Hz, 1H), 3.69 (d, *J* = 5.1 Hz, 2H), 2.68-2.53 (m, 2H), 1.62 (s, 3H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ 179.3, 146.9, 141.6, 140.4, 130.6, 129.1, 129.0, 123.9, 122.2, 118.3, 117.0, 113.5, 110.3, 64.3, 59.7, 37.9, 22.1. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O_2$ $[M - H]^-$ 307.1447; found 307.1467.

**General Procedure for the Synthesis of α-Adduct 6.** Cinnamyl bromide (1.0 mmol) was added to a suspension of activated zinc powder (1.5 mmol) in dry THF (5 mL); the reaction

mixture was refluxed for 1 h. The solution was filtered through a Schlenk filter and kept under $N_2$ for the following reaction. Isatin-derived Imines **1** (0.5 mmol) and cinnamylzinc bromide prepared above were added to a 15 mL sealed tube. The resulting mixture was sealed and submerged into a 120 °C silicon oil bath. After 8 h, the solution was cooled to room temperature and the product was purified by column chromatography (3/1 petroleum ether/ethyl acetate) to afford α-product **6**.

**3-Cinnamyl-3-(phenylamino)indolin-2-one (6a).** White solid (153 mg, 90% yield); mp 194-196 ºC. IR (KBr, ν, $cm^{-1}$) 3360, 1717. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.56 (s, 1H), 7.22-7.18 (m, 2H), 7.17-7.12 (m, 4H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.84-6.79 (m, 3H), 6.40 (t, *J* = 7.2 Hz, 1H), 6.27 (s, 1H), 6.25 (d, *J* = 16.6 Hz, 1H), 6.14 (d, *J* = 8.2 Hz, 2H), 5.86 (dt, *J* = 15.3, 7.4 Hz, 1H), 2.77 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.58 (dd, *J* = 13.1, 8.4 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 179.0, 146.9, 141.5, 137.2, 134.3, 130.6, 129.2, 129.1, 127.9, 126.4, 124.0, 123.0, 122.3, 117.2, 113.7, 110.4, 64.7, 43.2. HRMS (ESI) m/z calcd for $C_{23}H_{20}N_2NaO$ $[M + Na]^+$ 363.1473; found 363.1491.

**5-Bromo-3-cinnamyl-3-(phenylamino)indolin-2-one (6e).** White solid (184 mg, 88% yield); mp 201-203 ºC. IR (KBr, ν, $cm^{-1}$) 3137, 1722. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.76 (s, 1H), 7.36 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.26-7.21 (m, 3H), 7.20-7.15 (m, 3H), 6.89 (t, *J* = 7.2 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.46 (t, *J* = 7.3 Hz, 1H), 6.39 (s, 1H), 6.29 (d, *J* = 15.8 Hz, 1H), 6.16 (d, *J* = 7.7 Hz, 2H), 5.89-5.82 (m, 1H), 2.83 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.64 (dd, *J* = 13.3, 8.5 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 178.5, 146.6, 140.9, 137.1, 134.7, 133.2, 132.0, 129.2, 129.1, 128.0, 126.8, 126.4, 122.5, 117.5, 114.2, 113.6, 112.3, 64.9, 43.0. HRMS (ESI) m/z calcd for $C_{23}H_{18}BrN_2O$ $[M - H]^-$ 417.0603; found 417.0625.

**3-Cinnamyl-3-((4-methoxyphenyl)amino)indolin-2-one (6j).** White solid (133 mg, 72% yield); mp 167-169 ºC. IR (KBr, ν, $cm^{-1}$) 3304, 1710. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.52 (s, 1H), 7.24-7.19 (m, 2H), 7.17-7.12 (m, 5H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.48 (d, *J* = 9.2 Hz, 2H), 6.26 (d, *J* = 15.8 Hz, 1H), 6.14 (d, *J* = 8.9 Hz, 2H), 5.92-5.84 (m, 1H), 5.89 (s, 1H), 3.48 (s, 3H), 2.77 (dd, *J* = 13.3, 6.4 Hz, 1H), 2.58 (dd, *J* = 13.2, 8.3 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 179.3, 151.9, 141.6, 140.9, 137.2, 134.2, 130.9, 129.1, 129.1, 127.8, 126.4, 124.2, 123.2, 122.2, 115.4, 114.6, 110.3, 65.3, 55.6, 43.2. HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_2$ [M − H]$^-$ 369.1603; found 369.1588.

**3-((4-Bromophenyl)amino)-3-cinnamylindolin-2-one (6k).** White solid (180 mg, 86% yield); mp 191-194 ºC. IR (KBr, ν, $cm^{-1}$) 3308, 1713. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.71 (s, 1H), 7.31-7.20 (m, 6H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.97 (t, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.64 (s, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 6.18 (d, *J* = 8.9 Hz, 2H), 5.97-5.86 (m, 1H), 2.86 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.67 (dd, *J* = 13.3, 8.4 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 178.6, 146.2, 141.5, 137.1, 134.5, 131.6, 130.0, 129.4, 129.1, 127.9, 126.4, 124.1, 122.8, 122.4, 115.6, 110.5, 108.2, 64.7, 43.1. HRMS (ESI) m/z calcd for $C_{23}H_{18}BrN_2O$ [M − H]$^-$ 417.0603; found 417.0626.

**3-Cinnamyl-3-((4-(trifluoromethyl)phenyl)amino)indolin-2-one (6l).** White solid (177 mg, 87% yield); mp 164-166 ºC. IR (KBr, ν, $cm^{-1}$) 3313, 1715. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.78 (s, 1H), 7.30-7.17 (m, 9H), 7.13 (s, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.39-6.26 (m, 3H), 5.92 (dt, *J* = 15.1, 7.2 Hz, 1H), 2.90 (dd, *J* = 13.0, 6.4 Hz, 1H), 2.71 (dd, *J* = 12.7, 8.6 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 178.2, 149.9, 141.5, 137.1, 134.6, 129.6, 129.5, 129.1, 127.9, 126.5, 126.4, 125.6 (*J* = 268.5 Hz), 124.1, 124.0, 122.5,

122.5, 117.0 ($J$ = 31.8 Hz), 113.0, 110.6, 64.5. HRMS (ESI) m/z calcd for $C_{24}H_{18}F_3N_2O$ [M − H]$^-$ 407.1371; found 407.1381.

**3-Cinnamyl-5-fluoro-3-(o-tolylamino)indolin-2-one (6q).** White solid (164 mg, 88% yield); mp 187-189 ºC. IR (KBr, ν, cm$^{-1}$) 3368, 1724. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.68 (s, 1H), 7.26-7.21 (m, 4H), 7.19-7.15 (m, 1H), 7.02-7.00 (m, 2H), 6.91 (d, $J$ = 7.0 Hz, 1H), 6.84 (dd, $J$ = 9.2, 4.3 Hz, 1H), 6.64 (t, $J$ = 7.7 Hz, 1H), 6.46-6.39 (m, 2H), 5.97 (dt, $J$ = 15.5, 7.5 Hz, 1H), 5.60 (d, $J$ = 7.9 Hz, 1H), 4.96 (s, 1H), 2.86 (dd, $J$ = 13.5, 6.5 Hz, 1H), 2.73 (dd, $J$ = 13.3, 8.2 Hz, 1H), 2.14 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 178.8, 159.7 ($J$ = 236.3 Hz), 143.9, 137.6, 137.6, 137.1, 135.0, 132.8 ($J$ = 7.6 Hz), 130.5, 129.1, 128.0, 126.8, 123.6, 122.8, 117.9, 115.6 ($J$ = 23.3 Hz), 111.7 ($J$ = 24.4 Hz), 111.5, 111.3, 111.2, 64.7 ($J$ = 1.5 Hz), 43.3, 18.1. HRMS (ESI) m/z calcd for $C_{24}H_{20}FN_2O$[M − H]$^-$ 371.1560; found 371.1566.

**3-Cinnamyl-3-((4-fluorophenyl)amino)-1-methylindolin-2-one (6v).** White solid (151 mg, 81% yield); mp 133-135 ºC. IR (KBr, ν, cm$^{-1}$) 3321, 1701. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.28 (t, $J$ = 7.6 Hz, 1H), 7.25-7.19 (m, 2H), 7.18-7.12 (m, 4H), 7.06 (d, $J$ = 7.6 Hz, 1H), 7.00 (t, $J$ = 7.6 Hz, 1H), 6.69 (t, $J$ = 8.9 Hz, 2H), 6.35 (s, 1H), 6.24 (d, $J$ = 15.8 Hz, 1H), 6.09-6.60 (m, 2H), 5.86-5.80 (m, 1H), 3.10 (s, 3H), 2.80 (dd, $J$ = 13.5, 7.1 Hz, 1H), 2.61 (dd, $J$ = 13.4, 8.2 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 177.2, 155.3 ($J$ = 231.2 Hz), 143.4, 143.4 ($J$ = 1.7 Hz), 137.1, 134.4, 129.7, 129.4, 129.1, 127.9, 126.3, 123.8, 123.0, 122.8, 115.5 ($J$ = 21.9 Hz), 114.8 ($J$ = 7.3 Hz), 109.3, 64.8, 43.2, 26.6. HRMS (ESI) m/z calcd for $C_{24}H_{20}FN_2O$ [M − H]$^-$ 371.1560; found 371.1550.

**1-Benzyl-3-cinnamyl-3-(phenylamino)indolin-2-one (6y).** White solid (176 mg, 82% yield); mp 122-124 ºC. IR (KBr, ν, cm$^{-1}$) 3354, 1712. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.33 (d, $J$ =

7.1 Hz, 2H), 7.29-7.20 (m, 6H), 7.16-7.12 (m, 4H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.85 (t, *J* = 7.9 Hz, 2H), 6.51-6.47 (m, 2H), 6.35 (d, *J* = 15.8 Hz, 1H), 6.17 (d, *J* = 7.8 Hz, 2H), 5.82 (dt, *J* = 15.4, 7.4 Hz, 1H), 4.97 (d, *J* = 15.6 Hz, 1H), 4.89 (d, *J* = 15.6 Hz, 1H), 2.96 (dd, *J* = 13.3, 6.2 Hz, 1H), 2.82 (dd, *J* = 13.2, 8.3 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 177.5, 146.7, 142.3, 137.0, 136.7, 134.6, 130.0, 129.3, 129.1, 129.0, 128.9, 128.0, 127.9, 127.8, 126.4, 123.9, 123.1, 122.6, 117.5, 114.0, 109.9, 64.5, 43.6, 43.5. HRMS (ESI) m/z calcd for $C_{30}H_{25}N_2O$ $[M - H]^-$ 429.1967; found 429.1987.

**5-Bromo-3-cinnamyl-3-(p-tolylamino)indolin-2-one (6z).** White solid (173 mg, 80% yield); mp 196-198 ºC. IR (KBr, ν, cm$^{-1}$) 3334, 1715. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.80 (s, 1H), 7.41 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.41 (s, 1H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.25-7.19 (m, 3H), 6.94 (t, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.51 (t, *J* = 7.3 Hz, 1H), 6.43 (s, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 6.22 (d, *J* = 8.1 Hz, 2H), 5.91 (dt, *J* = 15.3, 7.3 Hz, 1H), 3.33 (s, 3H), 2.88 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.69 (dd, *J* = 12.9, 8.5 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 177.9, 146.0, 140.3, 136.5, 134.1, 132.7, 131.4, 128.6, 128.6, 127.4, 126.2, 125.8, 122.0, 116.9, 113.6, 113.0, 111.8, 64.3, 42.4. HRMS (ESI) m/z calcd for $C_{24}H_{21}BrN_2NaO$ $[M + Na]^+$ 455.0735; found 455.0717.

**Procedure for the Synthesis of α-Adduct 7.** Geranyl bromide (1.0 mmol) and lithium chloride (2.0 mmol) was added to a suspension of activated zinc powder (1.5 mmol) in dry THF (5 mL); the reaction mixture was stirred for 1 h at room temperature. The solution was filtered through a Schlenk filter and kept under $N_2$ for the following reaction. Imine **1t** (157 mg, 0.5 mmol) and geranylzinc bromide prepared above were added to a 15 mL sealed tube. The resulting mixture was sealed and submerged into a 120 °C silicon oil bath. After 8 h, the

solution was cooled to room temperature and the product was purified by column chromatography (3/1 petroleum ether/ethyl acetate) to afford α-product **7**.

**(E)-5-Bromo-3-(3,7-dimethylocta-2,6-dien-1-yl)-1-methyl-3-(phenylamino)indolin-2-one (7).** White solid (176 mg, 78% yield); mp 113-115 ºC. IR (KBr, ν, $cm^{-1}$) 3348, 1704. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.5, 7.4 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.66 (t, *J* = 7.4 Hz, 1H), 6.17-6.13 (m, 2H), 5.04 (t, *J* = 7.4 Hz, 2H), 4.37 (s, 1H), 3.24 (s, 3H), 2.70-2.64 (m, 1H), 2.89-2.53 (m, 1H), 2.02-1.96 (m, 4H), 1.67 (s, 3H), 1.59 (s, 3H), 1.55 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.3, 144.9, 142.2, 141.7, 132.3, 131.9, 131.7, 129.1, 126.9, 123.8, 119.1, 119.0, 115.8, 114.9, 114.4, 114.4, 109.7, 64.4, 40.0, 39.0, 26.7, 26.4, 25.7, 17.8, 16.4. HRMS (ESI) m/z calcd for $C_{25}H_{29}BrN_2NaO$ $[M + Na]^+$ 475.1361; found 475.1337.

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