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Rh(III)-Catalyzed C−H Functionalization of Indolines with Readily Accessible Amidating Reagent: Synthesis and Anticancer Evaluation

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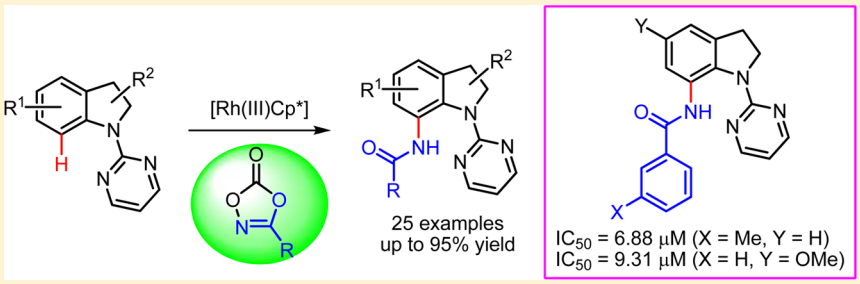
Supporting Information



ABSTRACT: The rhodium(III)-catalyzed direct C−H functionalization of various indolines with 1,4,2-dioxazol-5-ones as new amidating agents is described. This transformation provides efficient preparation of C7-amidated indolines known to display potent anticancer activity. The synthetic compounds were evaluated for in vitro anticancer activity against human prostate adenocarcinoma cells (LNCaP), human endometrial adenocarcinoma cells (Ishikawa), and human ovarian carcinoma cells (SKOV3). Compound **4f** was found to be highly cytotoxic, with activity competitive with that of anticancer agent doxorubicin.

INTRODUCTION

Indolic scaffolds are recognized as ubiquitous structures found in a large number of natural products and pharmaceuticals.[1] Particularly, C7-amidated indolines and indoles have attracted considerable attention by virtue of the discovery of interesting biological properties.[2] In fact, this class of compounds is known to display diverse biological profiles, such as tubulin polymerization inhibition,[2a−c] histone deacetylase (HDAC) inhibitory activity,[2d] acyl CoA-monoacylglycerol acyltransferase-2 (MGAT2) inhibition for hypocholesterolemic action,[2e,f] and antiproliferative activity (Figure 1).[2g] The biological activities of these compounds are closely associated with C7-amino functionality but vary depending on the nature and/or position of the substituents on indolic scaffolds.

The past decade witnessed transition-metal-catalyzed C−H functionalization as a powerful method for the efficient construction of structurally diverse molecules in organic and medicinal chemistry.[3] In this context, a great deal of effort has been devoted to the C−H functionalization of indolic scaffolds with various coupling partners.[4] In particular, the directing group-assisted C-7 functionalizations of indolines have been an area of intensive research due to their prevalence in many pharmaceutical agents.[5] For example, acylation, arylation, alkylation, alkynylation, and olefination of indolines at the C-7 position have been described with the use of various transition-metal catalysts.[6] Additionally, the C7-amidations of indolines with organic azides were also reported by Zhu, Chang, and Zhou/Li under Ru(II) and Ir(III) catalysis.[7] Moreover, the C-7 functionalization of indolines could be readily transformed to the corresponding C7-functionalized indoles, which are difficult to synthesize due to the inherent C2- and C3-selectivity of indoles under metal catalysis.

Recently, dioxazolones have been used as new amidating sources for the direct C−H amidation reactions by Chang and Li under Rh(III) and Co(III) catalysis.[8] Subsequently, various research groups have demonstrated the synthetic utility of dioxazolones via the C−H activation protocol.[9] In continuation of our recent works on the catalytic C-7 functionalizations of indolines,[10] we herein disclose the Rh(III)-catalyzed direct C−H amidation of indolines with dioxazolones under mild reaction conditions. Also, our synthetic compounds have been evaluated for the cytotoxic effect against human prostate adenocarcinoma cells (LNCaP), human endometrial adenocarcinoma cells (Ishikawa), and human ovarian carcinoma cells (SKOV3) and were found to have promising anticancer properties competitive with anticancer agent doxorubicin.

RESULTS AND DISCUSSION

Our study was initiated by examining the coupling of 1-(pyrimidin-2-yl)indoline (**1a**) and 3-phenyl-1,4,2-dioxazol-5-one (**2a**) in the presence of 2.5 mol % of $[RhCp^*Cl_2]_2$, 10 mol % of $AgNTf_2$, and 10 mol % of NaOAc in DCE at 60 °C for 24 h (Table 1). Gratifyingly, C7-amidated indoline **3a** was formed in 96% yield (Table 1, entry 1). Moreover, the exclusion of NaOAc did not alter the catalytic reactivity to afford our desired

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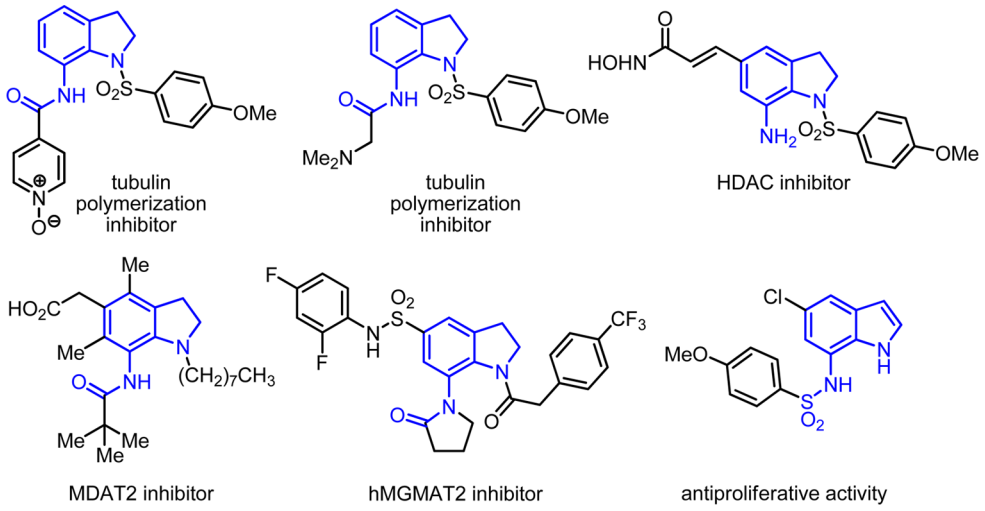
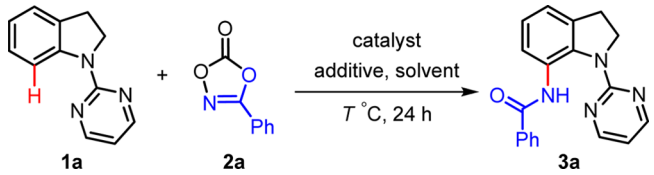


Figure 1. Biologically relevant C7-amidated indolinic and indolic compounds.

Table 1. Selected Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	additive (mol %)	solvent	T (°C)	yield (%)[b]
1	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10), NaOAc (10)	DCE	60	96
2	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	DCE	60	97
3	$[RhCp^*Cl_2]_2$ (2.5)	NaOAc (10)	DCE	60	N.R.
4	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	DCE	40	99
5	**$[RhCp^*Cl_2]_2$ (2.5)**	**$AgNTf_2$ (10)**	**DCE**	**rt**	**95**
6	$[RhCp^*Cl_2]_2$ (2.5)	$AgSbF_6$ (10)	DCE	rt	70
7	$[RhCp^*Cl_2]_2$ (2.5)	$AgBF_4$ (10)	DCE	rt	41
8	$[RhCp^*Cl_2]_2$ (2.5)	$AgPF_6$ (10)	DCE	rt	21
9	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	THF	rt	60
10	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	CH_2Cl_2	rt	56
11	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	1,4-dioxane	rt	45
12	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	MeCN	rt	5
13	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	MeOH	rt	32
14	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	C_6H_5Cl	rt	50
15	$[RhCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	toluene	rt	44
16	$[RhCp^*Cl_2]_2$ (1)	$AgNTf_2$ (5)	DCE	rt	52
17	$[CoCp^*(CO)I_2]$ (5)	$AgNTf_2$ (10)	DCE	rt	10
18	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	DCE	rt	5
19	$[IrCp^*Cl_2]_2$ (2.5)	$AgNTf_2$ (10)	DCE	rt	10

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (2.5 mol %), additive (quantity noted), solvent (1 mL) under air at indicated temperature for 24 h in pressure tubes. [b]Isolated yield by flash column chromatography.

product (Table 1, entry 2). However, the $AgNTf_2$ additive was found to be essential for this transformation (Table 1, entry 3). Notably, this reaction can smoothly proceed at room temperature to give **3a** in comparable yield (Table 1, entry 5). Further screening of silver additives and solvents revealed that the combination of $AgNTf_2$ additive in DCE solvent was found to be most effective (Table 1, entries 6−15). In addition, a lower amount of Rh catalyst resulted in a decreased yield (Table 1, entry 16). Other catalysts such as $[CoCp^*(CO)I_2]$, $[Ru(p\text{-cymene})Cl_2]_2$, and $[IrCp^*Cl_2]_2$ were found to be less effective (Table 1, entries 17−19).

With the optimized reaction conditions in hand, the efficacy of various directing groups on indolines **1b−1f** was examined (Table 2). The 2-pyridinyl directing group was found to be compatible for this coupling reaction to afford **3b** in 90% yield. However, other directing groups such as carbamoyl, acetyl, pivaloyl, and benzoyl directing groups did not deliver the corresponding products **3c−3f** under the present reaction conditions. Next, to explore the substrate scope and limitation of this reaction, a broad range of 2-pyrimidinyl indolines **1g−1p** were screened. Indolines containing OMe and Me groups at the C4-position underwent the cross-coupling in low to moderate yields at room temperature. Interestingly, an elevated temper-

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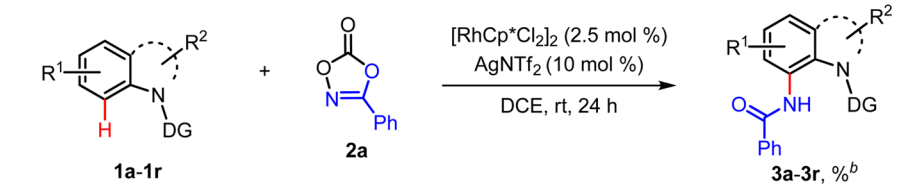
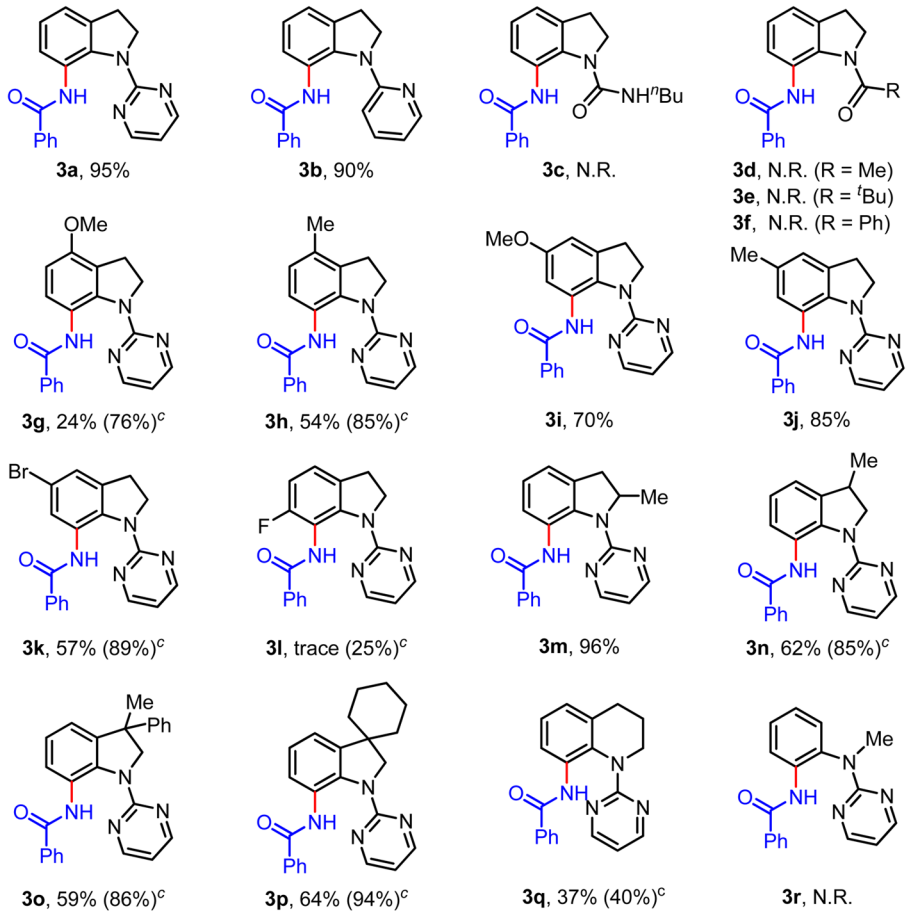
Table 2. Scope of Indolines[a]





[a]Reaction conditions: **1a−1r** (0.2 mmol), **2a** (0.3 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgNTf_2$ (10 mol %), DCE (1 mL) under air at room temperature for 24 h in pressure tubes. [b]Isolated yield by flash column chromatography. [c]The reaction was carried out at 80 °C.

ature (80 °C) provided the corresponding products **3g** and **3h** in high yields. In addition, C5-substituted indolines smoothly underwent the amidation reaction to give **3i−3k** in moderate to high yields at room temperature. However, C6-substituted indoline **1l** was found to be less reactive, even though the reaction was carried out at elevated temperature. To our pleasure, C2- and C3-substituted indolines **1m−1p** proved to be good substrates for this coupling reaction affording the corresponding products **3m−3p** in good to high yields at room temperature. In addition, increasing the reaction temperature could afford the higher yields in C3-substituted cases. Furthermore, tetrahydroquinoline **1q** was also coupled with **2a** to give **3q**, albeit in low yield. However, *N*-methyl aniline **1r** failed to deliver the coupling product **1r** under the present reaction conditions.

To further investigate the substrate scope of this reaction, a range of dioxazolones was screened to be coupled with indoline **1a**, as shown in Table 3. Dioxazolones **2b−2i** containing either electron-donating or -withdrawing groups at the *para*- and *meta*-positions of aromatic ring were found to afford the amidated products **4b−4i** in good to excellent yields. It should be mentioned that nitro or chloro groups were tolerated and could act as versatile functionalities for further elaboration. In addition, this transformation was compatible with heterocycle-containing dioxazolone **2j** to give **4j** in 59% yield. Finally, we were delighted to see the amidation reaction of 3-alkyl-substituted dioxazolones **2k** and **2l** in 97% and 94% yields, respectively.

To demonstrate the utility of C7-amidated indolines, we performed the oxidation of **3a** using DDQ in 1,4-dioxane to deliver C7-amidated indole **5a** in 66% yield (Scheme 1).[10d,e] In addition, deprotection of amide group on **3a** under basic hydrolysis furnished C7-amino indoline **5b** in 60% yield.

A plausible reaction mechanism is depicted in Scheme 2. A cationic [Cp*Rh(III)] complex is generated in the presence of $AgNTf_2$ in situ as an active catalyst, which then coordinates to the N atom of the pyrimidinyl group of 1-(pyrimidin-2-yl)indolines (**1a**) and subsequently undergoes C−H activation to deliver rhodacyclic intermediate **I**.[11] Coordination of **2a** and migratory insertion results in the formation of a seven-

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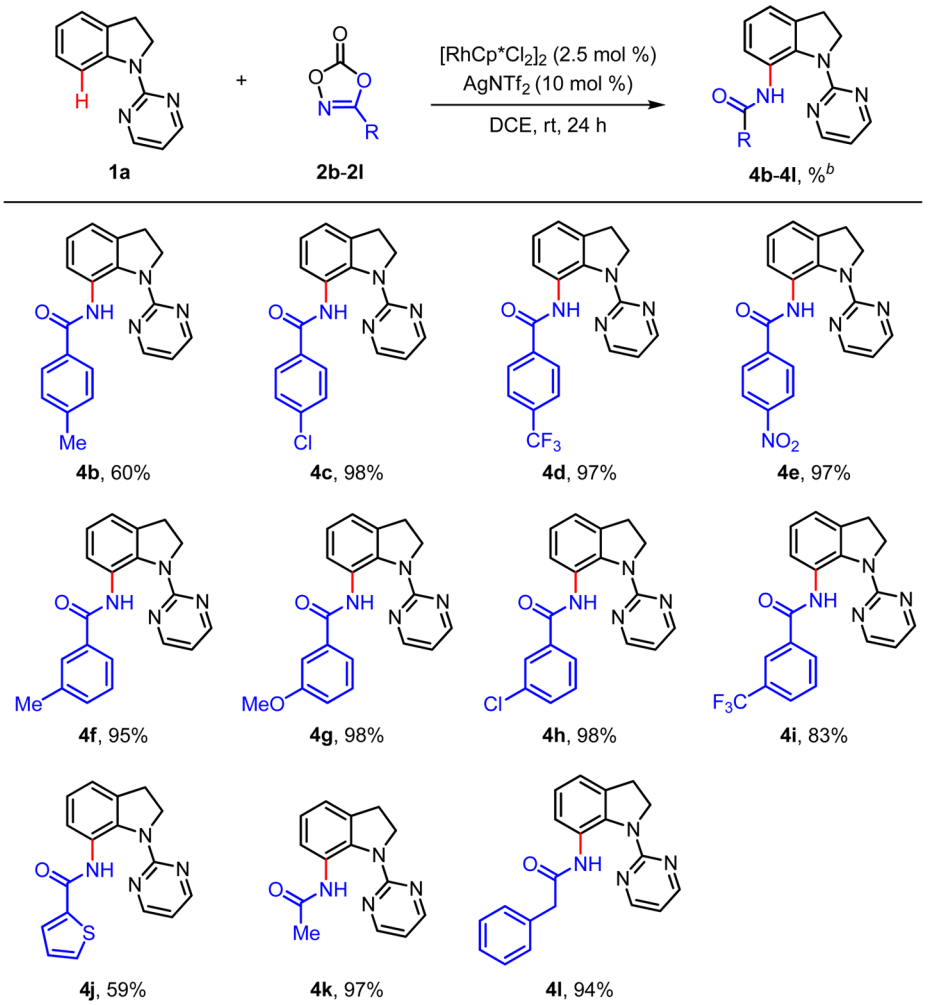
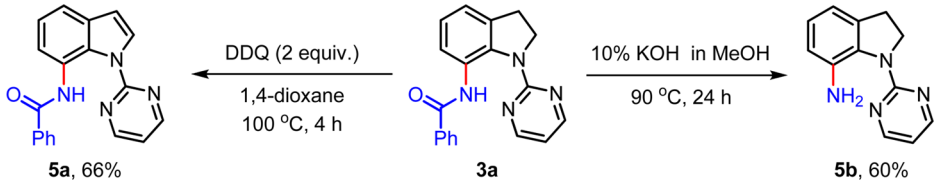
Table 3. Scope of Dioxazolones[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2b–2l** (0.3 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgNTf_2$ (10 mol %), DCE (1 mL) under air at room temperature for 24 h in pressure tubes. [b]Isolated yield by flash column chromatography. [c]The reaction was carried out at 80 °C.

Scheme 1. Synthetic Transformation of C7-Amidated Indoline



membered Rh(III)-amido species **III** with subsequent release of CO_2. Finally, protonation can take place to generate our desired product **3a** and regenerate the active Rh(III) species.

All the synthesized C7-amidated indolines were tested for growth inhibition activity against human prostate adenocarcinoma cells (LNCaP), human endometrial adenocarcinoma cells (Ishikawa), and human ovarian carcinoma cells (SKOV3), respectively. The results of inhibitory activity are summarized in Table 4. All cancer cells were exposed for 24 h to increasing concentrations of compounds **3a**, **3b**, **3g–3q**, **4b–4l**, **5a**, and **5b**, and their survival was determined using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay.[12] Several of C7-amidated indolines such as **3i**, **3m**, **3n**, and **4f** displayed promising growth inhibition in LNCaP, Ishikawa, and SKOV3 cells. In particular, compound **4f** showed the most potent activities (IC_{50} = 6.88 μM against LNCaP cells, IC_{50} = 8.87 μM against SKOV3 cells) among the tested compounds. The antiproliferative activities of **4f** were similar to that of the well-known anticancer agent doxorubicin (IC_{50} = 7.41 μM against LNCaP cells, IC_{50} = 10.31 μM against SKOV3 cells) as a positive control.[13] The results show that C7-amidated indoline derivatives represent a new class of strong inhibitors against human prostate and ovarian cancer cells.

CONCLUSION

In conclusion, we described the rhodium(III)-catalyzed direct C–H amidation reaction of a range of indolines with 1,4,2-dioxazol-5-ones to afford biologically important C7-amidated indolines. These transformations have been applied to a wide range of substrates and typically proceed with excellent levels of

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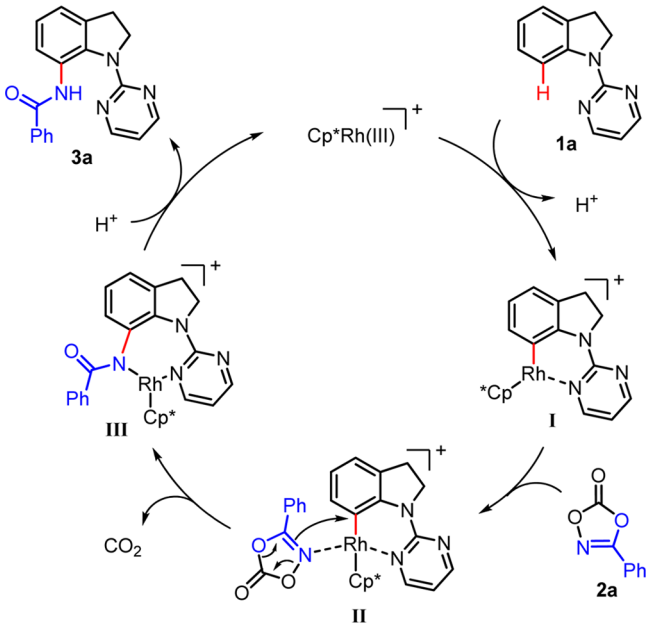
Scheme 2. Proposed Reaction Pathway



chemoselectivity as well as with high functional group tolerance. In addition, all synthesized compounds were tested for in vitro anticancer activity against human prostate adenocarcinoma cells (LNCaP), human endometrial adenocarcinoma cells (Ishikawa), and human ovarian carcinoma cells (SKOV3). Compound **4f** was found to exhibit a cytotoxic effect competitive with that of the well-known anticancer agent doxorubicin. Further studies to determine the biological action of C7-amidated indolines are underway.

EXPERIMENTAL SECTION

Typical Procedure for the Reaction of Indolines with Dioxazolones (3a−3q and 4b−4l). To an oven-dried sealed tube charged with 1-(pyrimidin-2-yl)indoline (**1a**) (39.4 mg, 0.2 mmol, 100 mol %), $[RhCp^*Cl_2]_2$ (3.1 mg, 0.005 mmol, 2.5 mol %), and $AgNTf_2$ (7.8 mg, 0.02 mmol, 10 mol %) were added 3-phenyl-1,4,2-dioxazol-5-one (**2a**) (48.9 mg, 0.3 mmol, 150 mol %) and DCE (1 mL). The reaction mixture was allowed to stir for 24 h at room temperature. The reaction mixture was diluted with EtOAc (3 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 3:1) to afford **3a** (60.3 mg) in 95% yield.

*N-(1-(Pyrimidin-2-yl)indolin-7-yl)benzamide (**3a**).* 60.3 mg (95%); yellow solid; mp = 151.2−151.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (br s, 1H), 8.41 (d, J = 4.8 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.47 (tt, J = 7.2, 1.2 Hz, 1H), 7.43−7.93 (m, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 6.68 (t, J = 4.8 Hz, 1H), 4.44 (t, J = 8.0 Hz, 2H), 3.08 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 159.1, 157.6, 135.9, 135.8, 134.4, 131.2, 128.3, 127.1, 126.9, 124.3, 123.6, 121.1, 111.3, 51.7, 28.5; IR (KBr) υ 3081, 2921, 1665, 1584, 1552, 1455, 1420, 1323, 1280, 996, 780, 705 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{17}N_4O$ $[M + H]^+$ 317.1402, found 317.1391.

*N-(1-(Pyridin-2-yl)indolin-7-yl)benzamide (**3b**).* 56.9 mg (90%); yellow solid; mp = 132.2−134.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (br s, 1H), 8.19 (d, J = 4.8 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 8.0, 1.2 Hz, 1H), 7.47−7.36 (m, 3H), 7.08 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 6.75 (t, J = 6.0 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.06 (t, J = 8.4 Hz, 2H), 3.14 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 155.5, 146.4, 138.5, 135.8, 135.7, 134.1, 131.1, 128.2, 127.1, 125.8, 123.9, 123.1, 121.0, 114.3, 111.1, 53.0, 28.7; IR (KBr) υ 3057, 2922, 1660, 1592, 1560, 1512, 1466, 1434, 1420, 1376, 1300, 1270, 1255, 1159, 1064, 988, 904, 768, 703 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{18}N_3O$ $[M + H]^+$ 316.1449, found 316.1440.

*N-(4-Methoxy-1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3g**).* 52.7 mg (76%); yellow solid; mp = 193.2−195.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (br s, 1H), 8.41 (d, J = 4.8 Hz, 2H), 7.87−7.81 (m, 3H), 7.46 (tt, J = 7.6, 1.2 Hz, 1H), 7.42−7.38 (m, 2H), 6.74 (d, J = 9.2 Hz, 1H), 6.69 (t, J = 4.8 Hz, 1H), 4.44 (t, J = 8.4 Hz, 2H), 3.85 (s, 3H), 3.02 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.2, 157.6, 152.7, 136.1, 136.0, 131.1, 128.3, 127.1, 124.9, 122.4, 120.2, 111.4, 106.9, 55.6, 52.1, 25.2; IR (KBr) υ 3015, 2924, 1730, 1657, 1582, 1550, 1504, 1457, 1342, 1267, 1222, 1099, 792, 735 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{19}N_4O_2$ $[M + H]^+$ 347.1508, found 347.1498.

*N-(4-Methyl-1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3h**).* 56.2 mg (85%); white solid; mp = 114.0−120.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (br s, 1H), 8.43 (d, J = 4.8 Hz, 2H), 7.84−7.79 (m, 3H), 7.47 (tt, J = 8.8, 1.2 Hz, 1H), 7.42−7.38 (m, 2H), 6.99 (d, J = 8.0 Hz, 1H), 6.69 (t, J = 4.8 Hz, 1H), 4.46 (t, J = 8.0 Hz, 2H), 3.02 (t, J = 8.0 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 159.2, 157.7, 136.1, 134.3, 134.1, 131.2, 130.4, 128.3, 127.2, 125.6, 124.6, 123.9, 111.4, 51.6, 27.4, 18.4; IR (KBr) υ 3007, 2971, 1664, 1584, 1551, 1506, 1455, 1320, 1301, 1222, 801, 706 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{19}N_4O$ $[M + H]^+$ 331.1558, found 331.1549.

Table 4. Cytotoxicity of Synthetic Compounds in Human Cancer Cells[a]

	IC_{50} (μM)				IC_{50} (μM)		
compds	LNCaP	Ishikawa	SKOV3	compds	LNCaP	Ishikawa	SKOV3
3a	>50	>50	>50	**4c**	>50	>50	>50
3b	>50	>50	>50	**4d**	>50	>50	>50
3g	>50	>50	>50	**4e**	>50	>50	>50
3h	>50	>50	>50	**4f**	6.88	7.16	8.87
3i	9.31	10.17	10.14	**4g**	>50	>50	>50
3j	>50	>50	>50	**4h**	>50	>50	>50
3k	>50	>50	>50	**4i**	>50	>50	>50
3l	32.62	35.51	>50	**4j**	>50	>50	>50
3m	13.93	14.20	28.61	**4k**	>50	>50	>50
3n	11.65	12.07	20.05	**4l**	>50	>50	>50
3o	>50	>50	>50	**5a**	>50	>50	>50
3p	>50	>50	>50	**5b**	>50	>50	>50
3q	>50	>50	>50	doxorubicin	7.41	5.02	10.31
4b	>50	>50	>50				

[a] IC_{50} value: substance concentration necessary for 50% inhibition of cell viability.

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*N-(5-Methoxy-1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3i**).* 48.6 mg (70%); yellow sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.64 (br s, 1H), 8.38 (d, J = 4.8 Hz, 2H), 7.86−7.83 (m, 2H), 7.62 (s, 1H), 7.49 (tt, J = 8.4, 1.2 Hz, 1H), 7.44−7.40 (m, 2H), 6.66−6.64 (m, 2H), 4.44 (t, J = 8.0 Hz, 2H), 3.84 (s, 3H), 3.05 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 159.1, 157.7, 156.9, 137.2, 136.0, 131.4, 128.4, 127.9, 127.8, 127.3, 110.9, 108.7, 106.9, 55.7, 51.7, 29.0; IR (KBr) υ 3055, 2901, 1665, 1585, 1549, 1458, 1418, 1378, 1304, 1267, 1159, 1044, 995, 791, 706 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{20}H_{18}N_4O_2$ $[M]^+$ 346.1430, found 346.1434.

*N-(5-Methyl-1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3j**).* 56.4 mg (85%); orange solid; mp = 165.3−169.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.44 (br s, 1H), 8.41 (d, J = 4.8 Hz, 2H), 7.86−7.83 (m, 2H), 7.76 (s, 1H), 7.48 (tt, J = 8.4, 1.2 Hz, 1H), 7.43−7.39 (m, 2H), 6.88 (s, 1H), 6.67 (t, J = 4.8 Hz, 1H), 4.44 (t, J = 8.0 Hz, 2H), 3.05 (t, J = 8.0 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 159.2, 157.7, 136.0, 135.9, 134.5, 132.1, 131.2, 128.3, 127.2, 126.7, 123.8, 122.0, 111.1, 51.8, 28.7, 21.0; IR (KBr) υ 3053, 2906, 1665, 1584, 1549, 1457, 1416, 1367, 1305, 1266, 1221, 995, 848, 792 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{20}H_{18}N_4O$ $[M]^+$ 330.1481, found 330.1480.

*N-(5-Bromo-1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3k**).* 70.5 mg (89%); yellow solid; mp = 181.6−184.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (br s, 1H), 8.42 (d, J = 4.8 Hz, 2H), 8.15 (s, 1H), 7.82−7.80 (m, 2H), 7.49 (tt, J = 8.4, 1.2 Hz, 1H), 7.44−7.40 (m, 2H), 7.16 (s, 1H), 6.73 (t, J = 4.8 Hz, 1H), 4.45 (t, J = 8.0 Hz, 2H), 3.07 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 159.1, 157.8, 137.7, 135.6, 133.7, 131.6, 129.1, 128.4, 128.0, 127.2, 126.0, 124.0, 116.8, 111.7, 51.8, 28.5; IR (KBr) υ 3058, 2898, 1666, 1586, 1552, 1455, 1408, 1375, 1295, 1178, 996, 850, 792, 705 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{16}BrN_4O$ $[M + H]^+$ 395.0507, found 395.0499.

*N-(6-Fluoro-1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3l**).* 16.9 mg (25%); yellow sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (br s, 1H), 8.46 (d, J = 4.8 Hz, 2H), 7.89 (d, J = 7.2 Hz, 2H), 7.49 (tt, J = 8.4, 1.2 Hz, 1H), 7.44−7.40 (m, 2H), 7.06−7.03 (m, 1H), 6.93 (t, J = 8.0 Hz, 1H), 6.73 (t, J = 4.8 Hz, 1H), 4.48 (t, J = 8.0 Hz, 2H), 3.08 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 159.1, 157.7, 157.1 (d, J_{C-F} = 246.3 Hz), 138.2 (d, J_{C-F} = 5.4 Hz), 134.5, 131.6, 130.5 (d, J_{C-F} = 2.8 Hz), 128.4, 127.5, 121.8 (d, J_{C-F} = 9.6 Hz), 115.5 (d, J_{C-F} = 17.9 Hz), 112.0, 111.4 (d, J_{C-F} = 21.9 Hz), 52.7, 28.0; IR (KBr) υ 3011, 2924, 1672, 1582, 1552, 1455, 1309, 1281, 1222, 1027, 794, 703 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{16}FN_4O$ $[M + H]^+$ 335.1308, found 335.1296.

*N-(2-Methyl-1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3m**).* 63.6 mg (96%); orange solid; mp = 147.7−151.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.43 (br s, 1H), 8.43 (d, J = 4.8 Hz, 2H), 7.98 (d, J = 8.0 Hz, 1H), 7.86−7.84 (m, 2H), 7.47 (tt, J = 7.2, 1.6 Hz, 1H), 7.44−7.40 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 6.70 (t, J = 4.8 Hz, 1H), 5.25−5.18 (m, 1H), 3.47−3.41 (m, 1H), 2.58 (d, J = 15.6 Hz, 1H), 1.32 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 158.8, 157.7, 136.0, 134.6, 132.9, 131.3, 128.3, 127.5, 127.2, 124.5, 123.4, 121.6, 118.9, 111.4, 59.0, 35.9, 20.2; IR (KBr) υ 3051, 2922, 2852, 1663, 1580, 1548, 1455, 1419, 1378, 1302, 1279, 1185, 1054, 984, 904, 792, 768, 733 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{20}H_{18}N_4O$ $[M]^+$ 330.1481, found 330.1479.

*N-(3-Methyl-1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3n**).* 56.2 mg (85%); yellow sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (br s, 1H), 8.42 (d, J = 4.8 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.85−7.83 (m, 2H), 7.48 (tt, J = 8.8, 1.2 Hz, 1H), 7.43−7.39 (m, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.69 (t, J = 4.8 Hz, 1H), 4.72 (dd, J = 11.2, 8.4 Hz, 1H), 3.90 (dd, J = 11.2, 7.6 Hz, 1H), 3.45−3.36 (m, 1H), 1.32 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 159.3, 157.7, 141.0, 136.0, 134.2, 131.3, 128.4, 127.2, 126.9, 124.6, 123.7, 119.8, 111.4, 59.4, 34.9, 18.6; IR (KBr) υ 3002, 2852, 1664, 1582, 1380, 1305, 1252, 794, 746, 704 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{19}N_4O$ $[M + H]^+$ 331.1558, found 331.1549.

*N-(3-Methyl-3-phenyl-1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3o**).* 70.1 mg (86%); light yellow solid; mp = 157.4−159.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (br s, 1H), 8.37 (d, J = 4.8 Hz, 2H), 7.99 (d, J = 8.0 Hz, 1H), 7.86−7.84 (m, 2H), 7.48 (tt, J = 8.8, 1.6 Hz, 1H), 7.43−7.39 (m, 2H), 7.26−7.14 (m, 6H), 6.90 (dd, J = 7.2, 1.2 Hz, 1H), 6.65 (t, J = 4.8 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 159.4, 157.8, 145.9, 143.7, 135.9, 134.4, 131.4, 128.4, 128.3, 127.2, 127.1, 126.6, 126.4, 125.1, 123.9, 120.5, 111.5, 66.9, 47.8, 25.9; IR (KBr) υ 3011, 2923, 1666, 1583, 1551, 1451, 1302, 1222, 1069, 792 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{19}N_4O$ $[M + H]^+$ 331.1558, found 331.1549.

*N-(1′-(Pyrimidin-2-yl)spiro[cyclohexane-1,3′-indolin]-7′-yl)-benzamide (**3p**).* 72.4 mg (94%); yellow sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (br s, 1H), 8.44 (d, J = 4.8 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.84−7.82 (m, 2H), 7.49 (tt, J = 8.4, 1.2 Hz, 1H), 7.44−7.40 (m, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.01 (dd, J = 7.2, 1.2 Hz, 1H), 6.71 (t, J = 4.8 Hz, 1H), 4.32 (s, 2H), 1.78−1.71 (m, 3H), 1.64−1.59 (m, 5H), 1.52−1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 159.7, 157.9, 145.1, 136.1, 133.8, 131.3, 128.4, 127.3, 127.1, 124.8, 123.9, 118.8, 111.4, 61.2, 44.2, 35.9, 25.6, 23.1; IR (KBr) υ 3052, 2924, 2852, 1665, 1582, 1549, 1442, 1416, 1376, 1301, 1265, 1222, 1178, 1066, 980, 897, 791, 733 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{24}H_{25}N_4O$ $[M + H]^+$ 385.2016, found 385.2028.

*N-(1-(Pyrimidin-2-yl)-1,2,3,4-tetrahydroquinolin-8-yl)benzamide (**3q**).* 26.5 mg (40%); white solid; mp = 142.5−145.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 8.45 (d, J = 4.8 Hz, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.61−7.59 (m, 2H), 7.44 (tt, J = 8.4, 1.2 Hz, 1H), 7.36−7.32 (m, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 6.72 (t, J = 4.8 Hz, 1H), 4.06 (br s, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.11−2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 160.8, 158.3, 135.1, 134.4, 134.3, 133.0, 131.4, 128.5, 126.9, 125.9, 125.5, 122.4, 111.9, 45.0, 26.3, 23.1; IR (KBr) υ 3045, 2909, 1669, 1579, 1551, 1450, 1421, 1310, 1265, 1245, 1122, 1074, 800, 740 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{24}H_{25}N_4O$ $[M + H]^+$ 385.2016, found 385.2028.

*4-Methyl-N-(1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**4b**).* 39.6 mg (60%); yellow solid; mp = 192.7−194.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (br s, 1H), 8.43 (d, J = 4.8 Hz, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.14 (t, J = 7.2 Hz, 1H), 7.04 (dd, J = 7.6, 1.2 Hz, 1H), 6.70 (t, J = 4.8 Hz, 1H), 4.45 (t, J = 8.0 Hz, 2H), 3.09 (t, J = 8.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 159.2, 157.7, 141.7, 135.8, 134.5, 133.1, 129.1, 127.2, 127.1, 124.5, 123.7, 121.0, 111.4, 51.8, 28.7, 21.4; IR (KBr) υ 3081, 2972, 1725, 1666, 1582, 1457, 1362, 1314, 1280, 845, 794 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{20}H_{18}N_4O$ $[M]^+$ 330.1481, found 330.1480.

*4-Chloro-N-(1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**4c**).* 68.9 mg (98%); yellow solid; mp = 156.1−164.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (br s, 1H), 8.42 (d, J = 4.8 Hz, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.79−7.75 (m, 2H), 7.40−7.37 (m, 2H), 7.15 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.72 (t, J = 4.8 Hz, 1H), 4.46 (t, J = 8.0 Hz, 2H), 3.10 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 159.2, 157.7, 137.5, 135.9, 134.5, 134.4, 128.7, 128.6, 126.8, 124.5, 123.6, 121.3, 111.4, 51.8, 28.6; IR (KBr) υ 3009, 2971, 1732, 1584, 1458, 1335, 1266, 1222, 847, 735 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{19}H_{15}ClN_4O$ $[M]^+$ 350.0934, found 350.0932.

*N-(1-(Pyrimidin-2-yl)indolin-7-yl)-4-(trifluoromethyl)benzamide (**4d**).* 74.6 mg (97%); yellow solid; mp = 149.5−157.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.67 (br s, 1H), 8.42 (d, J = 4.8 Hz, 2H), 7.95−7.90 (m, 3H), 7.68 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.73 (d, J = 4.8 Hz, 1H), 4.47 (t, J = 8.0 Hz, 2H), 3.11 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 159.2, 157.7, 139.4, 136.1, 134.5, 133.1 (q, J_{C-F} = 32.6 Hz), 127.7, 126.6, 125.4 (q, J_{C-F} = 3.6 Hz), 124.6, 123.7 (q, J_{C-F} = 270.5 Hz), 123.6, 121.5, 111.5, 51.8, 28.6; IR (KBr) υ 3053, 2930, 1721, 1585, 1552, 1458, 1342, 1322, 1280, 1126, 1065, 738 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{20}H_{15}F_3N_4O$ $[M]^+$ 384.1198, found 384.1201.

*4-Nitro-N-(1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**4e**).* 70.2 mg (97%); yellow solid; mp = 206.3−208.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (br s, 1H), 8.42 (d, J = 4.8 Hz, 2H), 8.27 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 6.74 (t, J = 4.8 Hz, 1H), 4.47

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(t, J = 8.0 Hz, 2H), 3.12 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 159.1, 157.7, 149.4, 141.8, 136.1, 134.5, 128.3, 126.3, 124.6, 123.6, 123.5, 121.7, 111.6, 51.8, 28.5; IR (KBr) υ 3046, 2960, 1664, 1583, 1521, 1457, 1360, 1240, 1061, 992, 794, 711 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{19}H_{15}N_5O_3$ $[M]^+$ 361.1175, found 361.1175.

3-Methyl-N-(1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**4f**). 62.9 mg (95%); orange solid; mp = 125.2−126.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.34 (br s, 1H), 8.42 (d, J = 4.8 Hz, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.64−7.62 (m, 2H), 7.32−7.28 (m, 2H), 7.15 (t, J = 7.2 Hz, 1H), 7.04 (dd, J = 7.2, 1.2 Hz, 1H), 6.70 (t, J = 4.8 Hz, 1H), 4.46 (t, J = 8.0 Hz, 2H), 3.09 (t, J = 8.0 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 159.2, 157.7, 138.1, 135.9, 135.8, 134.5, 132.0, 128.2, 127.9, 127.1, 124.5, 124.2, 123.6, 121.0, 111.3, 51.8, 28.6, 21.3; IR (KBr) υ 3045, 2917, 1664, 1582, 1550, 1447, 1417, 1376, 1308, 1222, 1188, 1068, 994, 925, 793, 772, 727 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{20}H_{18}N_4O$ $[M]^+$ 330.1481, found 330.1480.

3-Methoxy-N-(1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**4g**). 67.9 mg (98%); orange sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.43 (br s, 1H), 8.43 (d, J = 4.8 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.70 (t, J = 4.8 Hz, 1H), 4.46 (t, J = 8.0 Hz, 2H), 3.82 (s, 3H), 3.10 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.7, 159.2, 157.7, 137.5, 135.9, 134.5, 129.2, 127.1, 124.5, 123.6, 121.1, 119.1, 117.3, 112.8, 111.4, 55.4, 51.8, 28.6; IR (KBr) υ 3069, 2960, 1666, 1583, 1551, 1457, 1334, 1240, 1163, 1122, 1042, 996, 794, 771 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{20}H_{18}N_4O_2$ $[M]^+$ 346.1430, found 346.1430.

3-Chloro-N-(1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**4h**). 68.6 mg (98%); orange solid; mp = 137.1−139.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (br s, 1H), 8.45 (d, J = 4.8 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.06 (dd, J = 7.6, 1.2 Hz, 1H), 6.73 (t, J = 4.8 Hz, 1H), 4.46 (t, J = 8.0 Hz, 2H), 3.10 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 159.1, 157.7, 137.8, 135.9, 134.4, 134.3, 131.2, 129.8, 127.3, 126.6, 125.7, 124.5, 123.5, 121.3, 111.5, 51.8, 28.6; IR (KBr) υ 3037, 2942, 1664, 1584, 1456, 1361, 1311, 1223, 996, 792, 735 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{19}H_{15}ClN_4O$ $[M]^+$ 350.0934, found 350.0935.

N-(1-(Pyrimidin-2-yl)indolin-7-yl)-3-(trifluoromethyl)benzamide (**4i**). 63.9 mg (83%); orange solid; mp = 133.1−135.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.62 (br s, 1H), 8.44 (d, J = 4.8 Hz, 2H), 8.11 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.72 (t, J = 4.8 Hz, 1H), 4.47 (t, J = 8.0 Hz, 2H), 3.11 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 159.2, 157.8, 136.7, 136.0, 134.6, 131.2, 130.7 (q, J_{C-F} = 32.6 Hz), 129.2, 127.8 (q, J_{C-F} = 3.5 Hz), 126.6, 124.5, 123.7, 123.6 (q, J_{C-F} = 3.7 Hz), 122.4 (q, J_{C-F} = 271.1 Hz), 121.5, 111.5, 51.8, 28.6; IR (KBr) υ 3055, 2932, 1670, 1585, 1552, 1457, 1421, 1361, 1201, 1166, 1125, 1072, 774, 740 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{20}H_{15}F_3N_4O$ $[M]^+$ 384.1198, found 384.1195.

N-(1-(Pyrimidin-2-yl)indolin-7-yl)thiophene-2-carboxamide (**4j**). 38.1 mg (59%); brown solid; mp = 144.5−146.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (br s, 1H), 8.52 (d, J = 4.8 Hz, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 3.6, 1.2 Hz, 1H), 7.44 (dd, J = 4.8, 1.2 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.07−7.05 (m, 2H), 6.76 (t, J = 4.8 Hz, 1H), 4.47 (t, J = 8.0 Hz, 2H), 3.10 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 159.4, 157.9, 140.1, 135.9, 134.7, 129.7, 128.7, 127.5, 126.7, 124.6, 124.0, 121.3, 111.4, 51.7, 28.7; IR (KBr) υ 3061, 2921, 1652, 1584, 1551, 1455, 1424, 1368, 1303, 1210, 1067, 994, 855, 734 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{17}H_{14}N_4OS$ $[M]^+$ 322.0888, found 322.0887.

N-(1-(Pyrimidin-2-yl)indolin-7-yl)acetamide (**4k**). 49.5 mg (97%); yellow solid; mp = 125.5−126.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (br s, 1H), 8.46 (d, J = 4.8 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.73 (t, J = 4.8 Hz, 1H), 4.43 (t, J = 8.4 Hz, 2H), 3.07 (t, J = 8.0 Hz, 2H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 159.2, 157.6, 135.8, 134.1, 126.9, 124.5, 123.4, 120.9, 111.4, 51.9, 28.6, 24.5; IR (KBr) υ 3050, 2920, 1681, 1582, 1550, 1451, 1420, 1377, 1306, 1240, 1186, 1063, 994, 791, 764, 746, 719 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{14}H_{14}N_4O$ $[M]^+$ 254.1168, found 254.1169.

2-Phenyl-N-(1-(pyrimidin-2-yl)indolin-7-yl)acetamide (**4l**). 62.2 mg (94%); white solid; mp = 129.9−133.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (br s, 1H), 8.10 (d, J = 4.4 Hz, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.30−7.23 (m, 5H), 7.13 (d, J = 7.2 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.59 (t, J = 4.8 Hz, 1H), 4.45 (t, J = 8.0 Hz, 2H), 3.71 (s, 2H), 3.07 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 159.3, 157.5, 135.7, 134.8, 134.7, 129.5, 128.7, 128.5, 127.2, 124.4, 124.1, 121.2, 111.4, 51.7, 45.0, 28.8; IR (KBr) υ 3071, 3011, 1745, 1583, 1360, 1241, 940, 738 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{20}H_{18}N_4O$ $[M]^+$ 330.1481, found 330.1482.

General Procedure and Characterization Data for Oxidation of 3a. To a stirred solution of *N*-(1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3a**) (63.3 mg, 0.2 mmol, 100 mol %) in 1,4-dioxane (1 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (90.8 mg, 0.4 mmol, 200 mol %) at room temperature. The reaction mixture was allowed to stir for 4 h at 100 °C. The reaction mixture was diluted with EtOAc (1 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc/CH_2Cl_2 = 3:1:1) to afford 41.5 mg of **5a** in 66% yield.

N-(1-(Pyrimidin-2-yl)-1H-indol-7-yl)benzamide (**5a**). 41.5 mg (66%); light brown solid; mp = 171.6−173.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.97 (br s, 1H), 8.42 (d, J = 4.8 Hz, 2H), 8.34 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 3.6 Hz, 1H), 7.91 (d, J = 7.2 Hz, 2H), 7.56−7.46 (m, 3H), 7.36 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 4.8 Hz, 1H), 6.67 (t, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 158.1, 156.8, 137.1, 134.2, 131.3, 128.7, 128.5, 127.4, 126.3, 125.9, 123.4, 118.3, 117.3, 116.2, 108.3; IR (KBr) υ 3074, 3013, 1728, 1571, 1365, 1221, 1065, 790 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{19}H_{14}N_4O$ $[M]^+$ 314.1168, found 314.1166.

General Procedure and Characterization Data of Deprotection of Benzoyl Group (5b). To an oven-dried sealed tube charged with *N*-(1-(pyrimidin-2-yl)indolin-7-yl)benzamide (**3a**) (63.3 mg, 0.2 mmol, 100 mol %) was added 10% KOH in MeOH (2.5 mL) solution. The mixture was stirred for 24 h at 90 °C. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (*n*-hexanes/EtOAc/CH_2Cl_2 = 3:1:2) to afford **5b** (25.6 mg) in 60% yield.

1-(Pyrimidin-2-yl)indolin-7-amine (**5b**). 25.6 mg (60%); dark brown sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 4.8 Hz, 2H), 6.92 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 7.2 Hz, 1H), 6.67−6.61 (m, 2H), 4.42 (t, J = 7.6 Hz, 2H), 4.31 (br s, 2H), 3.05 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 157.7, 136.2, 135.9, 130.7, 125.1, 117.3, 115.4, 110.7, 52.0, 29.3; IR (KBr) υ 3396, 3264, 2887, 1577, 1545, 1469, 1444, 1379, 1284, 1243, 1184, 1159, 1058, 988, 791, 755, 722 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{12}H_{12}N_4$ $[M]^+$ 212.1062, found 212.1064.

Cancer Cell Growth Inhibition Assay (MTT Assay). Human prostate adenocarcinoma cells (LNCaP), human endometrial adenocarcinoma cells (Ishikawa), and human ovarian carcinoma cells (SKOV3) were grown in DMEM medium supplemented with 1% of penicillin/streptomycin, and 10% fetal bovine serum (all from Life Technologies, Grand Island, NY). Cells were seeded in 96-well plates (3×10^3 cells/well) containing 100 μL of growth medium for 24 h. After medium removal, 100 μL of fresh medium containing individual analogue compounds at different concentrations were added to each well and incubated at 37 °C for 48 h. After 24 h of culture, the cells were supplemented with 1 μL of test compounds dissolved in DMSO (less than 0.025% in each preparation). After 24 h of incubation, 100 μL of the MTT reagent were added to each well. After 4 h of incubation at 37 °C, the supernatant was aspirated, and the formazan crystals were dissolved in 100 μL of DMSO at 37 °C for 10 min with gentle agitation. The absorbance per well was measured at 540 nm using a VERSA max Microplate Reader (Molecular Devices Corp., USA). The IC_{50} was defined as the compound concentration required

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inhibiting cell proliferation by 50% in comparison with cells treated with the maximum amount of DMSO (0.025%) and considered as 100% viability.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02020.

^{1}H and ^{13}C NMR copies of all products (PDF)

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Notes

The authors declare no competing financial interest.

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