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Synthesis of Fused Pyrimido[1,6-*a*]indolones via Rhodium(III)-Catalyzed Cascade Annulations

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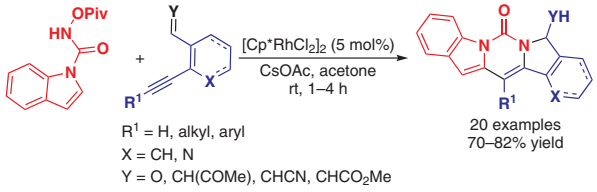
This work is dedicated to Dr. J. S. Yadav on the occasion of his 70th birthday for his contributions to organic synthesis



Received: 07.08.2020
Accepted after revision: 04.09.2020
Published online: 12.10.2020
DOI: 10.1055/s-0040-1707312; Art ID: ss-2020-n0280-op

Abstract A novel method for the synthesis of fused pyrimido[1,6-*a*]-indolone derivatives by annulation of 2-alkynylaryl aldehydes/2-alkynyl-arylidene ketones with *N*-(pivaloyloxy)-1*H*-indole-1-carboxamide catalyzed by rhodium has been accomplished. The reaction proceeds through C–H activation based annulation with alkyne moiety followed by addition of nitrogen on to aldehyde/activated alkene to give the products in moderate to good yields. Highly fluorescent dipyrrinone analogues could be synthesized from the derived products.

Key words *N*-(pivaloyloxy)-1*H*-indole-1-carboxamide, C–H activation, *aza*-Michael addition, cascade annulation, pyrimido[1,6-*a*]indolone

Indole-based polycyclic structures are of immense importance due to their widespread presence in various alkaloids and have attracted significant attention in both organic and medicinal chemistry.[1,2] In particular, the pyrimido[1,6-*a*]indolone is found in various biologically active natural products and in pharmaceuticals, acting as 5-HT3 receptor antagonist, topoisomerase II inhibitors, etc. (Figure 1).[3] Due to their promising fluorescent properties they are also widely applied in material chemistry. A series of new analogues of this motif have been prepared and studied for their photophysical properties.[4] In view of the importance of these scaffolds, there have been significant efforts in developing rapid and efficient methods towards the construction of pyrimido[1,6-*a*]indolones.[5,6] Among them, [4+2] annulation of indole-1-carboxamides with various two-carbon coupling partners such as alkynes,[5a] alkenes,[5a,b] α-halo ketones,[5c] diazo compounds[5d] was found to be an attractive strategy. However, despite significant advancement, all these reactions are usually limited to the mono-annulation through the insertion of two carbon agent. To the best of our knowledge, there is only one literature report available for the cascade annulation of indole-1-carboxamides with 1,6-enynes to polycyclic-indole motif.[7] Hence, the development of cascade annulations of indole-1-carboxamides still remains inspiring to explore towards the synthesis of polycyclic fused pyrimido[1,6-*a*]indolones.

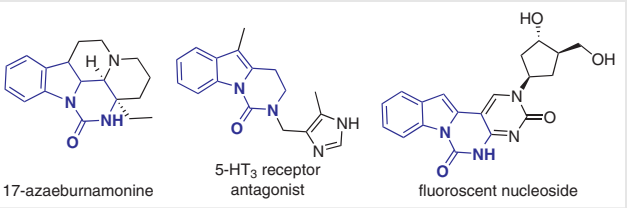


Figure 1 Representative compounds containing pyrimido[1,6-*a*]indolone motif

On the other hand, [Rh^{III}Cp*]-catalyzed C–H activation and oxidative annulation reactions is an emerging strategy to access diverse heterocyclic compounds.[8] Since, the discovery of *N*-pivaloyloxy group as an internal oxidant that plays dual role as both directing and oxidizing group by Fagnou and co-workers,[9] it was extensively used to construct a wide variety of nitrogen containing heterocycles.[10] Inspired by these findings, we reported a cascade annulation of *N*-(pivaloyloxy)benzamides with 2-alkynyl aldehydes catalyzed by rhodium.[11a] The reaction proceeds via alkyne insertion followed by addition of N–H on to aldehyde furnishing the products with aminal functionality. The synthetic utility of the reaction was successfully demonstrated by the synthesis of Rosettacin. In 2014, Cui research group reported the *N*-carboxamides as directing groups for C-2 functionalization of indoles.[5a] Recently, we have studied the reaction of *N*-(pivaloyloxy)benzamides with 1,5-enynes via C–H activation to access functionalized aromathecins involving Rh(III)-catalyzed domino [4+2] annulation/*aza*-Michael Addition.[11b] These results prompted us to explore the reactivity of *N*-(pivaloyloxy)-1*H*-indole-1-

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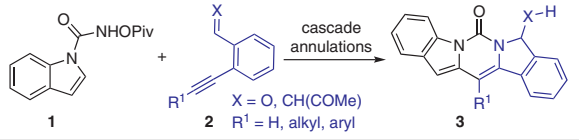
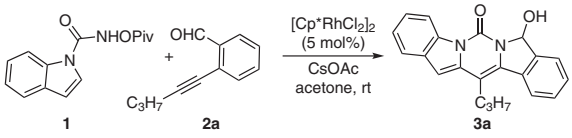
carboxamides with 2-alkynyl aldehydes/activated alkenes. In continuation of our interest towards construction of fused-indole derivatives,[12] herein we report a cascade annulation approach for the synthesis of polycyclic-fused pyrimido[1,6-*a*]indolones (Scheme 1).



Scheme 1 Cascade annulations of *N*-(pivaloyloxy)-1*H*-indole-1-carboxamides with 2-alkynyl aldehydes/activated alkenes

Initially, the reaction of *N*-(pivaloyloxy)-1*H*-indole-1-carboxamide (**1**) with 2-(pent-1-yn-1-yl)benzaldehyde (**2a**) subjected to the reaction conditions used in our earlier work: 5 mol% $[RhCp^*Cl_2]_2$ and CsOAc in acetone at room temperature. To our delight, the reaction progressed smoothly to afford the product **3a** in 79% yield (Table 1, entry 1). The reactions in other solvents like MeCN, *t*-AmOH, DMF, and MeOH proved that acetone is the best choice of solvent (entries 2–5). The reaction in the presence of $Pd(OAc)_2$ found to be futile (entry 6). Use of various bases such as NaOAc, Cs_2CO_3, and K_2CO_3 resulted in the formation of product **3a** in low yields (entries 7 to 9).

Table 1 Optimization of Reaction Conditions[a]

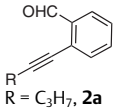
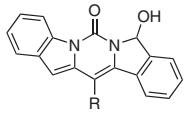
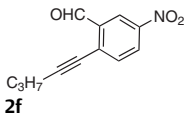
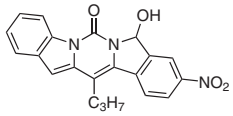
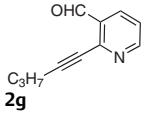
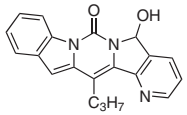
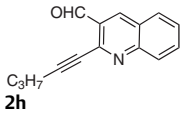
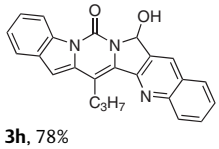


Entry	Catalyst	Solvent	Base	Time (h)	Yield (%)[b] of **3a**
1	**$[RhCp^*Cl_2]_2$**	**acetone**	**CsOAc**	**2**	**79**
2	$[RhCp^*Cl_2]_2$	MeCN	CsOAc	6	76
3	$[RhCp^*Cl_2]_2$	*t*-AmOH	CsOAc	6	78
4	$[RhCp^*Cl_2]_2$	DMF	CsOAc	6	22
5	$[RhCp^*Cl_2]_2$	MeOH	CsOAc	6	5
6	$Pd(OAc)_2$	acetone	CsOAc	24	0
7	$[RhCp^*Cl_2]_2$	acetone	NaOAc	6	39
8	$[RhCp^*Cl_2]_2$	acetone	Cs_2CO_3	6	45
9	$[RhCp^*Cl_2]_2$	acetone	K_2CO_3	6	40

[a] Reaction conditions: **1** (1.0 equiv), alkynyl aldehyde **2a** (1.2 equiv), catalyst (5 mol%), and base (2 equiv) in solvent (2 mL).
[b] Isolated yield.

We next investigated the scope of the reaction (Table 2). The reactions of alkynyl aldehydes with varying alkyl chains on alkyne **2b** ($R^1 = C_4H_9$) and **2c** ($R^1 = C_5H_{11}$) afforded the desired products **3b** and **3c** in 73 and 72% yield, respectively (Table 2, entries 2, 3). In the same way, the alkynes bearing substituents like hydroxymethyl (**2d**) gave the corresponding product **3d** in 78% yield (entry 4). In all reactions, the regioselective insertion of internal alkyne was observed to provide pyrimido-indolones. Notably, the reaction of *N*-(pivaloyloxy)-1*H*-indole-1-carboxamide with terminal alkynyl enone, 2-ethynylbenzaldehyde (**2e**), ensued well to afford the product **3e** in 72% yield (entry 5) under the present reaction conditions. The alkynyl aldehyde **2f** bearing nitro group on the phenyl ring was also participated in the cascade annulations to give **3f** in 76% yield (entry 6). Pleasingly, the replacement of a phenyl ring of alkynyl aldehyde with heteroaromatic rings like pyridine- and quinoline-based alkynyl aldehydes underwent the annulations smoothly under the reaction conditions to give the corresponding products **3g** and **3h** in 70 and 78%, respectively (entries 7, 8).

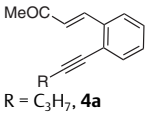
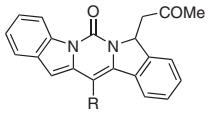
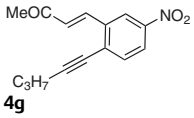
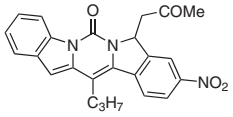
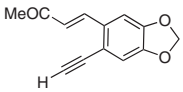
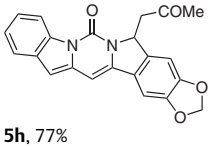
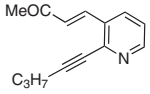
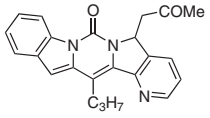
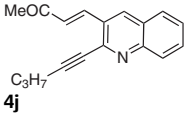
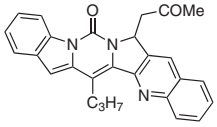
Table 2 Reaction of **1** with Diverse *o*-Alkynyl Aldehydes **2**[a]

Entry	Alkynyl aldehyde **2**	Time (h)	Product **3**, yield[b]
1	 R = C_3H_7, **2a**	2	 R = C_3H_7, **3a**, 79%
2	R = C_4H_9, **2b**	2	R = C_4H_9, **3b**, 73%
3	R = C_5H_{11}, **2c**	2	R = C_5H_{11}, **3c**, 72%
4	R = CH_2OH, **2d**	3	R = CH_2OH, **3d**, 78%
5	R = H, **2e**	2	R = H, **3e**, 72%
6	 **2f**	3	 **3f**, 76%
7	 **2g**	2.5	 **3g**, 70%
8	 **2h**	4	 **3h**, 78%

[a] Reaction conditions: **1** (1.0 equiv), alkynyl aldehyde **2** (1.2 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), and CsOAc (2 equiv) in acetone (2 mL).
[b] Isolated yield.

With these successful results in hand, we envisioned to expand the method to *o*-alkynylbenzylidene ketones, wherein alkyne insertion with subsequent *aza*-Michael addition of nitrogen on to α,β-unsaturated carbonyl moiety would lead to the annulated products (Table 3). We initiated our studies with the reaction of (*Z*)-4-[2-(pent-1-yn-1-

Table 3 Reaction of **1** with *o*-Alkynylbenzylidene Ketones[a]

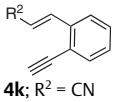
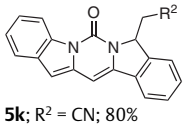
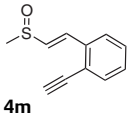
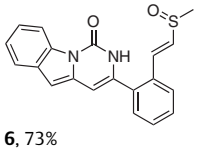
Entry	*o*-Alkynylbezylidene ketone **4**	Time (h)	Pyrimido[1,6-*a*]indolone **5**, Yield[b]
1	 R = C_3H_7, **4a**	5	 R = C_3H_7, **5a**, 81%
2	R = C_4H_9, **4b**	4	R = C_4H_9, **5b**, 79%
3	R = C_5H_{11}, **4c**	5	R = C_5H_{11}, **5c**, 78%
4	R = CH_2OH, **4d**	4	R = CH_2OH, **5d**, 82%
5	R = *c*-Pr, **4e**	4	R = *c*-Pr, **5e**, 74%
6	R = H, **4f**	4	R = H, **5f**, 78%
7	 **4g**	5	 **5g**, 82%
8	 **4h**	4	 **5h**, 77%
9	 **4i**	4	 **5i**, 78%
10	 **4j**	5	 **5j**, 64%

[a] Reaction conditions: **1** (1.0 equiv), alkynylbenzylidene ketone **4** (1.2 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), and CsOAc (2 equiv) in acetone (2 mL).
[b] Isolated yield.

yl)phenyl]but-3-en-2-one (**4a**) with *N*-(pivaloyloxy)-1*H*-indole-1-carboxamide (**1**) under the above optimized conditions. Gratifyingly, the reaction produced the desired product **5a** in 81% yield (Table 3, entry 1). Next, the scope of the reaction with variable substituents on alkyne such as *n*-butyl (**4b**), *n*-pentyl (**4c**), CH_2OH (**4d**), and cyclopropyl (**4e**) were studied. All the substrates were well tolerated in the annulation with **1** to furnish the corresponding fused pyrimido[1,6-*a*]indolones **5b–e** in good yields (entries 2–5). The (*Z*)-4-(2-ethynylphenyl)but-3-en-2-one (**4f**) having terminal alkyne successfully delivered **5f** in 78% yield (entry 6). The 1,5-enynones bearing electronically different groups on the phenyl ring like nitro (**5g**), methylenedioxy (**5h**) were compatible in the present cascade annulations to offer the products **5g** to **5h** in good yields (entries 7, 8). The reaction of *N*-(pivaloyloxy)-1*H*-indole-1-carboxamide with heterocyclic based enynones, pyridyl-enynone **4i** and quinolinyl-enynone **4j**, furnished the corresponding annulated proucts **5i** and **5j** in 78 and 64% yield, respectively (entries 9, 10).

Further, to expand the scope of the electron-withdrawing group, a few alkynyl substrates were examined (Table 4). Delightfully, the reaction of **1a** with (*E*)-3-(2-ethynylphenyl)acrylonitrile (**4k**) provided the fused pyrimido[1,6-*a*]indolone **5k** in 80% yield (Table 4, entry 1). Likewise, the substrate having conjugated ester group (CO_2Me, **4l**) is also found to be suitable for the present cascade-annulation to offer the corresponding product **5l** in 55% yield (entry 2). However, the reaction (*E*)-1-ethynyl-2-[2-(methylsulfinyl)vinyl]benzene (**4m**) with **1** with **5m** failed to provide the desired product, instead alkyne insertion product **6** was isolated in 73% yield (entry 3).

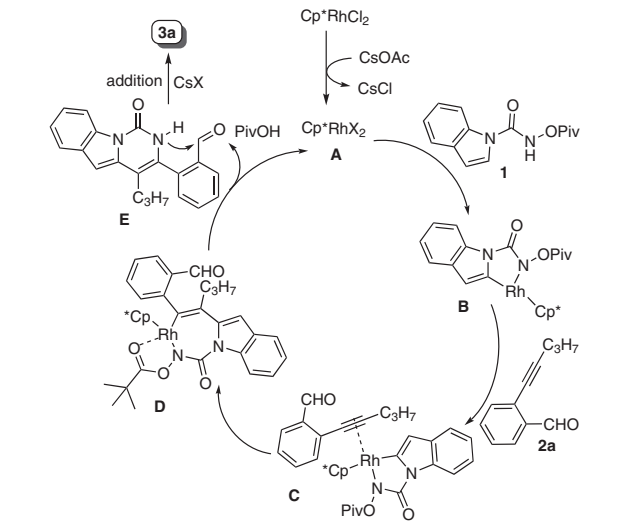
Table 4 Scope of Alkynylenones with Different Electron-Withdrawing Groups (EWGs)[a]

Entry	Enynes with different EWGs	Time (h)	Product; yield[b]
1	 **4k**; R^2 = CN	4	 **5k**; R^2 = CN; 80%
2	**4l**; R^2 = CO_2Me	4	**5l**; R^2 = CO_2Me; 55%
3	 **4m**	**4**	 **6**, 73%

[a] Reaction conditions: 1 (1.0 equiv), alkynylbenzylidene ketone 4 (1.2 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), and CsOAc (2 equiv) in acetone (2 mL).
[b] Isolated yield.

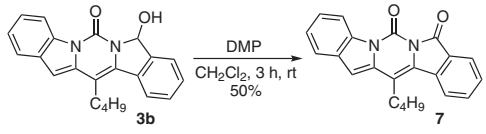
Based on the above outcomes, a feasible mechanism is proposed as shown in Scheme 2. The reaction involves insertion of alkyne into the five-membered rhodacycle **B** via C–H activation based C–C bond formation. Subsequent reductive elimination and oxidative addition of N–O bond (**C** and **D**) leads to pyrimido[1,6-*a*]indolone **E**. Next, base-promoted addition of amide NH on to aldehyde takes place, similar to the reported cascade reactions.[10c,f] In the case of alkynyl enones (Tables 2 and 3), *aza*-Michael addition of NH to the conjugated olefin provides the desired product **5**.

To demonstrate the additional transformations of the obtained products, fused pyrimido[1,6-*a*]indolone **3b** was synthesized in gram scale and subjected to further oxidation in the presence of Dess–Martin periodinane (DMP), which led to the formation of pyrimido[1,6-*a*]indole-6,8-dione **7** in 50% yield (Scheme 3). This compound holds bridg-



Scheme 2 Possible reaction mechanism

ing of the two nitrogens with a carbonyl group, which might results in a dramatic increase in fluorescence like in dipyrrinones.[13] Therefore, the developed method paves the way for expeditious synthesis of *N*,*N*′-carbonyl derivatives.



Scheme 3 Synthesis of pyrimido[1,6-*a*]indole-6,8-dione **7**

In conclusion, an efficient method has been developed for the construction of fused pyrimido[1,6-*a*]indolones from the annulation of *N*-(pivaloyloxy)-1*H*-indole-1-carboxamide with 1,5-enynones. The reaction involves cascade Rh(III)-catalyzed C–H activation, alkyne insertion and addition of amide nitrogen to aldehyde to provide the products with aminal functionality, which can be further oxidized. The reaction was also found to be effective with substrates bearing activated alkenes, wherein alkyne insertion/*aza*-Michael addition sequence provides the annulated products in good yields.

All the reactions were performed in oven-dried glass apparatus. Air and moisture sensitive reactions were carried out under inert atmosphere (N_2) using freshly distilled anhydrous solvents. Commercially available reagents were used as received without any purification. All reactions were monitored by TLC carried out on silica plates using UV light and anisaldehyde for visualization. Column chromatography was performed on silica gel (100–200 mesh) using hexanes and EtOAc as eluent. ^{1}H NMR was recorded in $CDCl_3$ and DMSO-d_6 on 500 MHz, 400 MHz and 300 MHz. ^{13}C NMR was recorded on 125 MHz, 100 MHz and 75 MHz, using TMS as an internal standard. Chemical shifts are given in ppm and *J* values are given in hertz (Hz). δ = 7.26 and 77 are the residual peaks of $CDCl_3$ in ^{1}H NMR and ^{13}C NMR, respectively; δ = 2.50 and 39.52 are the residual peaks of DMSO-d_6 in ^{1}H NMR and ^{13}C NMR, respectively. FTIR spectra were recorded on alpha (Bruker) IR spectrophotometer. High-resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

Starting Materials

N-(Pivaloyloxy)-1*H*-indole-1-carboxamide (1)[5a]

N-(Pivaloyloxy)-1*H*-indole-1-carboxamide (**1**) was prepared using the literature procedure, and the data were compared with the reported data.

2-Alkynyl Aldehydes 2a–h; General Procedure

To a solution of 2-bromoaryl aldehyde (1.0 equiv) and 1-alkyne (1.2 equiv) in NEt_3 was added $PdCl_2(PPh_3)_2$ (2 mol%). The mixture was stirred for 5 min and CuI (1 mol%) was added. The resulting mixture was then heated under N_2 atmosphere at 50 °C until completion of the reaction. After cooling, the solution was filtered, and the solid was washed several times with Et_2O. After evaporation of the solvent, the product was purified by column chromatography on silica gel (eluent: 5% EtOAc in hexanes) to afford compound **2**.

2-Alkynyl aldehydes **2a**,[14a] **2b**,[14b] **2c**,[14c] **2d**,[14d] **2e**,[14b] **2g**,[14e] **2h**[14e] are known compounds. They were characterized by spectral data, which were in agreement with literature values.

5-Nitro-2-(pent-1-yn-1-yl)benzaldehyde (2f)

To a solution of 2-bromo-5-nitrobenzaldehyde (200 mg, 0.87 mmol) and 1-pentyne (71 mg, 1.04 mmol) in NEt_3 (5 mL) was added $PdCl_2(PPh_3)_2$ (12.2 mg, 0.0174 mmol, 2 mol%). The mixture was stirred for 5 min and CuI (1.7 mg, 0.0087 mmol, 1 mol%) was added. The resulting mixture was then heated under N_2 atmosphere at 50 °C for 4 h. After cooling, the solution was filtered, and the solid was washed several times with Et_2O. After evaporation of the solvent, the product was purified by column chromatography on silica gel (eluent: 5% EtOAc in hexanes) to afford the compound **2f** as a yellow oil; yield: 152 mg (80%).

IR (KBr): 3094, 2965, 2228, 1704, 1528, 1350, 749 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.54 (s, 1 H), 8.71 (d, *J* = 2.4 Hz, 1 H), 8.35 (dd, *J* = 8.5, 2.4 Hz, 1 H), 7.68 (d, *J* = 8.5 Hz, 1 H), 2.54 (t, *J* = 7.0 Hz, 2 H), 1.78–1.63 (m, 2 H), 1.09 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 146.9, 136.7, 134.6, 133.5, 127.6, 122.3, 104.3, 75.7, 21.8, 21.8, 13.7.

HRMS-ESI: *m*/*z* calcd for $C_{12}H_{12}NO_3$ [M + H]$^+$: 218.0817; found: 218.0823.

Rh(III)-Catalyzed Cascade Annulation; General Procedure

To a solution of *N*-(pivaloyloxy)-1*H*-indole-1-carboxamide **1** (0.38 mmol, 1 equiv) and 2-alkynyl aldehyde **2** or alkynyl enone **4** (0.46 mmol, 1.2 equiv) in anhyd acetone (2.0 mL) were added $[RhCp^*Cl_2]_2$ (0.019 mmol, 0.05 equiv) and CsOAc (0.76 mmol, 2 equiv) under N_2 atmosphere and the reaction mixture was stirred for the given time (Tables 1 and 2) at rt. After completion of the reaction (monitored by TLC), the mixture was filtered through Celite and washed with CH_2Cl_2 (3 × 10 mL). The combined filtrates were concentrated under reduced pressure and the resultant residue was purified by column chromatography over silica gel (eluent: 7% EtOAc in hexanes) to obtain the corresponding pyrimido[1,6-*a*]indolone **3** or **5**.

8-Hydroxy-13-propylisoindolo[2′,1′:3,4]pyrimido[1,6-*a*]indol-(8*H*)-one (3a)

White solid; yield: 100 mg (79%); mp 185–187 °C.

IR (KBr): 3690, 3311, 2937, 1678, 1463, 1397, 1062, 756 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.60–8.53 (m, 1 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 7.74–7.68 (m, 1 H), 7.66–7.58 (m, 2 H), 7.54 (t, *J* = 7.4 Hz, 1 H), 7.37–7.31 (m, 2 H), 7.29 (d, *J* = 7.8 Hz, 1 H), 6.92 (s, 1 H), 6.77 (d, *J* = 7.7 Hz, 1 H), 3.06–2.94 (m, 2 H), 1.73 (dt, *J* = 14.9, 7.5 Hz, 2 H), 1.09 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.1, 141.0, 138.1, 132.9, 132.9, 131.3, 130.4, 130.2, 129.6, 124.8, 123.6, 123.3, 122.6, 120.0, 115.2, 107.6, 98.2, 82.7, 27.7, 22.0, 13.9.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{19}N_2O_2$ $[M + H]^+$: 331.1447; found: 331.1456.

13-Butyl-8-hydroxyisoindolo[2′,1′:3,4]pyrimido[1,6-*a*]indol-6(8*H*)-one (3b)

Yellow solid; yield: 96 mg (73%); mp 190–192 °C.

IR (KBr): 3633, 3319, 2955, 2860, 1669, 1394, 1044, 752 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.55 (dd, *J* = 6.0, 2.8 Hz, 1 H), 7.85 (d, *J* = 7.8 Hz, 1 H), 7.70 (dd, *J* = 5.7, 2.9 Hz, 1 H), 7.60 (dd, *J* = 17.6, 7.5 Hz, 2 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.37–7.26 (m, 3 H), 6.87 (s, 1 H), 6.75 (d, *J* = 7.7 Hz, 1 H), 3.06–2.92 (m, 2 H), 1.74–1.61 (m, 2 H), 1.58–1.47 (m, 2 H), 0.95 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.1, 140.9, 137.9, 132.9, 132.7, 131.3, 130.4, 130.1, 129.5, 124.8, 123.5, 123.2, 122.5, 119.9, 115.1, 107.7, 98.0, 82.6, 30.9, 25.7, 22.2, 13.9.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}N_2O_2$ $[M + H]^+$: 345.1603; found: 345.1614.

8-Hydroxy-13-pentylisoindolo[2′,1′:3,4]pyrimido[1,6-*a*]indol-(8*H*)-one (3c)

Yellow solid; yield: 97 mg (72%); mp 193–194 °C.

IR (KBr): 3751, 3621, 3380, 2924, 1698, 1465, 1380, 755 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.67–8.59 (dd, *J* = 6.0, 3.3 Hz, 1 H), 7.78 (d, *J* = 7.7 Hz, 1 H), 7.68 (dd, *J* = 11.2, 5.3 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.2 Hz, 1 H), 7.41–7.33 (m, 2 H), 6.94 (d, *J* = 3.3 Hz, 1 H), 6.71 (s, 1 H), 4.71 (s, 1 H), 3.07–2.87 (m, 2 H), 1.83–1.74 (m, *J* = 15.7, 7.9 Hz, 2 H), 1.56–1.49 (m, 2 H), 1.48–1.38 (m, *J* = 14.3, 7.1 Hz, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 138.7, 138.3, 133.6, 132.7, 132.4, 130.8, 130.6, 129.6, 125.3, 124.1, 123.4, 123.3, 120.0, 115.9, 109.5, 98.9, 83.4, 32.3, 28.7, 26.9, 22.8, 14.2.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{23}N_2O_2$ $[M + H]^+$: 359.1760; found: 359.1752.

8-Hydroxy-13-(hydroxymethyl)isoindolo[2′,1′:3,4]pyrimido-[1,6-*a*]indol-6(8*H*)-one (3d)

Brown solid; yield: 95 mg (78%); mp 215–217 °C.

IR (KBr): 3755, 3631, 3311, 2926, 1686, 1546, 1047, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.59–8.53 (m, 1 H), 8.05 (d, *J* = 7.5 Hz, 1 H), 7.72 (dd, *J* = 5.8, 2.7 Hz, 1 H), 7.65–7.53 (m, 3 H), 7.40–7.31 (m, 3 H), 6.95 (s, 1 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 5.40 (t, *J* = 5.2 Hz, 1 H), 4.89 (d, *J* = 5.2 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 146.1, 141.1, 137.5, 135.3, 132.8, 130.9, 130.4, 129.9, 129.8, 124.5 (2 C), 123.6, 122.4, 119.9, 115.1, 106.9, 97.9, 82.9, 55.1.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{15}N_2O_3$ $[M + H]^+$: 319.1083; found: 319.1095.

8-Hydroxyisoindolo[2′,1′:3,4]pyrimido[1,6-*a*]indol-6(8*H*)-one (3e)

White solid; yield: 80 mg (72%); mp 205–207 °C.

IR (KBr): 3570, 3625, 2926, 2453, 1693, 1549, 748 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.59–8.52 (m, 1 H), 7.98–7.92 (m, 1 H), 7.72–7.65 (m, 1 H), 7.65–7.60 (m, 1 H), 7.59–7.51 (m, 2 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.37–7.30 (m, 2 H), 7.26 (s, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.74 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.4, 140.5, 137.8, 136.3, 132.6, 131.1, 130.6, 130.3, 129.9, 124.6, 123.6, 122.4, 121.3, 119.8, 115.1, 98.6, 91.2, 83.6.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{13}N_2O_2$ $[M + H]^+$: 289.0977; found: 289.0984.

8-Hydroxy-10-nitro-13-propylisoindolo[2′,1′:3,4]pyrimido-[1,6-*a*]indol-6(8*H*)-one (3f)

Red solid; yield: 109 mg (76%); mp 200–202 °C.

IR (KBr): 3406, 2255, 2130, 1656, 997, 762 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.57–8.47 (m, 1 H), 8.38–8.28 (m, 2 H), 8.04 (d, *J* = 8.6 Hz, 1 H), 7.75–7.67 (m, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.39–7.29 (m, 2 H), 7.05 (s, 1 H), 6.83 (d, *J* = 7.5 Hz, 1 H), 3.10–2.92 (m, 2 H), 1.78–1.65 (m, 2 H), 1.09 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ = 147.1, 145.6, 141.8, 137.1, 136.9, 133.0, 130.7, 129.9, 125.1, 123.7, 123.4, 122.9, 119.9, 119.8, 115.1, 111.3, 99.8, 81.9, 27.8, 21.9, 13.8.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{16}N_3O_4$ $[M - H]^+$: 374.1141; found: 374.1145.

5-Hydroxy-14-propylpyrido[2″,3″:3′,4′]pyrrolo[1′,2′:3,4]-pyrimido[1,6-*a*]indol-7(5*H*)-one (3g)

Yellow solid; yield: 89 mg (70%); mp 173–175 °C.

IR (KBr): 3746, 3594, 2959, 1692, 1400, 786 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.77 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.63–8.53 (m, 1 H), 8.04 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.78–7.68 (m, 1 H), 7.49 (dd, *J* = 7.7, 4.9 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.39–7.34 (m, 2 H), 6.98 (s, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 3.46–3.27 (m, 2 H), 1.82–1.70 (m, 2 H), 1.02 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.9, 146.6, 138.0, 135.7, 133.4, 133.3, 132.3, 131.6, 130.8, 124.2, 124.1, 123.4, 120.7, 115.7, 110.1, 99.8, 81.8, 26.8, 22.9, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{18}N_3O_2$ $[M + H]^+$: 332.1399; found: 332.1388.

8-Hydroxy-15-propylindolo[1″,2″:3′,4′]pyrimido[1′,6′:1,2]-pyrrolo[3,4-*b*]quinolin-6(8*H*)-one (3h)

Green solid; yield: 114 mg (78%); mp 198–200 °C.

IR (KBr): 3748, 3608, 2923, 2321, 1669, 747 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.57–8.53 (m, 1 H), 8.52 (s, 1 H), 8.03 (t, *J* = 7.7 Hz, 2 H), 7.77 (t, *J* = 7.7 Hz, 1 H), 7.69 (dd, *J* = 6.3, 2.6 Hz, 1 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.34–7.28 (m, 2 H), 6.98 (s, 1 H), 6.87 (d, *J* = 8.1 Hz, 1 H), 3.54–3.38 (m, 2 H), 1.81–1.70 (m, 2 H), 1.04 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.6, 148.8, 146.1, 137.4, 133.1, 132.9, 132.8, 132.3, 132.2, 130.6, 130.3, 129.2, 128.7, 127.2, 123.7, 123.1, 120.3, 115.3, 111.2, 99.8, 80.9, 26.7, 22.6, 14.0.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{20}N_3O_2$ [M + H]$^+$: 382.1556; found: 382.1550.

2-Alkynyl Enones 4a–h; General Procedure

A solution of the respective aldehyde (1 equiv) and 1-(triphenylphosphoranylidene)propan-2-one (1.2 equiv) in toluene (0.5 M) was stirred at 90 °C for 4 h. After completion of the reaction (confirmed by TLC), the reaction mixture was allowed to attain rt and concentrated under reduced pressure. The obtained crude product was purified by column chromatography over silica gel using hexane/EtOAc as eluent.

2-Alkynyl enones **4a**,[15a] **4b**,[15b] **4f**,[15c] **4i**,[15d] **4k**,[15e] and **4l**[15f] are known compounds. They were characterized by spectral data, which were in agreement with literature values.

(*E*)-4-[2-(Hept-1-yn-1-yl)phenyl]but-3-en-2-one (4c)

Following the general procedure, a solution of 2-(hept-1-yn-1-yl)benzaldehyde (200 mg, 1.0 mmol) and 1-(triphenylphosphoranylidene)propan-2-one (381 mg, 1.2 mmol) in toluene (0.5 M) was stirred at 90 °C for 4 h. The obtained crude product was purified by column chromatography over silica gel (7% EtOAc in PE) to afford **4c** as a brown oil; yield: 228 mg (95%).

IR (KBr): 2937, 2228, 1674, 1470, 1256, 983, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 16.5 Hz, 1 H), 7.65–7.59 (m, 1 H), 7.49–7.42 (m, 1 H), 7.33–7.27 (m, 2 H), 6.71 (d, *J* = 16.5 Hz, 1 H), 2.50 (t, *J* = 7.1 Hz, 2 H), 2.41 (s, 3 H), 1.70–1.62 (m, 2 H), 1.52–1.44 (m, 2 H), 1.42–1.31 (m, 2 H), 0.95–0.89 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.84, 142.03, 135.60, 132.95, 129.95, 128.45, 127.94, 125.90, 125.29, 97.28, 78.29, 31.21, 28.47, 26.94, 22.29, 19.66, 14.03.

HRMS-ESI: *m*/*z* calcd for $C_{17}H_{21}O$ [M + H]$^+$: 241.1592; found: 241.1577.

(*E*)-4-[2-(3-Hydroxyprop-1-yn-1-yl)phenyl]but-3-en-2-one (4d)

Following the general procedure, a solution of 2-(3-hydroxyprop-1-yn-1-yl)benzaldehyde (200 mg, 1.25 mmol) and 1-(triphenylphosphoranylidene)propan-2-one (477 mg,1.5 mmol) in toluene (0.5 M) was stirred at 90 °C for 4 h. After completion of the reaction (confirmed by TLC), the reaction mixture was allowed to attain rt and concentrated under reduced pressure. The obtained crude product was purified by column chromatography over silica gel (7% EtOAc in PE) to afford **4d** as a brown oil; yield: 240 g (96%).

IR (KBr): 3929, 3644, 3411, 2924, 1668, 1363, 1261, 1031, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 16.4 Hz, 1 H), 7.63–7.58 (m, 1 H), 7.49–7.44 (m, 1 H), 7.35–7.28 (m, 2 H), 6.75 (d, *J* = 16.4 Hz, 1 H), 4.57 (s, 2 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1, 141.4, 135.7, 133.1, 130.0, 128.8, 128.3, 126.1, 123.9, 93.9, 82.9, 51.5, 27.7.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{12}O_2Na$ [M + Na]$^+$: 223.0735; found: 223.0721.

(*E*)-4-[2-(Cyclopropylethynyl)phenyl]but-3-en-2-one (4e)

Following general procedure, a solution of 2-(cyclopropylethynyl)benzaldehyde (200 mg, 1.17 mmol) and 1-(triphenylphosphoranylidene)propan-2-one (381 mg,1.2 mmol) in toluene (0.5 M) was stirred at 90 °C for 4 h. After completion of the reaction (confirmed by TLC), the reaction mixture was allowed to attain rt and concentrated under reduced pressure. The obtained crude product was purified by column chromatography over silica gel (7% EtOAc in PE) to afford **4e** (220 mg, 92%) as a pale yellow oil.

IR (KBr): 3843, 3644, 3447, 3046, 2747, 1727, 1255, 760, 647 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 16.5 Hz, 1 H), 7.59 (dd, *J* = 5.1, 4.2 Hz, 1 H), 7.46–7.40 (m, 1 H), 7.32–7.24 (m, 2 H), 6.71 (d, *J* = 16.5 Hz, 1 H), 2.41 (s, 3 H), 1.58–1.49 (m, 1 H), 0.95 (ddd, *J* = 8.1, 5.5, 3.4 Hz, 2 H), 0.86 (ddd, *J* = 7.6, 5.5, 3.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.87, 142.06, 135.83, 133.03, 130.02, 128.46, 127.97, 126.09, 125.23, 100.49, 73.50, 27.15, 9.12 (2 C), 0.53.

HRMS-ESI: *m*/*z* calcd for $C_{15}H_{15}O$ [M + H]$^+$: 211.1123; found: 211.1110.

(*E*)-4-[5-Nitro-2-(pent-1-yn-1-yl)phenyl]but-3-en-2-one (4g)

Following the general procedure, a solution of 5-nitro-2-(pent-1-yn-1-yl)benzaldehyde (200 mg, 0.92 mmol) and 1-(triphenylphosphoranylidene)propan-2-one (351.7 mg, 1.20 mmol) in toluene (0.5 M) was stirred at 90 °C for 4 h. The crude product was purified by column chromatography over silica gel (7% EtOAc in PE) to afford **4g** (213 mg, 90%) as a white solid; mp 170–172 °C.

IR (KBr): 3839, 3403, 2968, 2226, 1682, 1522, 1350, 1082, 984 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 2.3 Hz, 1 H), 8.14 (dd, *J* = 8.6, 2.3 Hz, 1 H), 8.00 (d, *J* = 16.4 Hz, 1 H), 7.60 (d, *J* = 8.6 Hz, 1 H), 6.86 (d, *J* = 16.3 Hz, 1 H), 2.54 (t, *J* = 7.0 Hz, 2 H), 2.43 (s, 3 H), 1.76–1.68 (m, 2 H), 1.11 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 146.9, 139.1, 137.2, 133.9, 131.4, 130.2, 124.1, 121.0, 103.1, 77.7, 28.0, 22.0, 21.9, 13.7.

HRMS-ESI: *m*/*z* calcd for $C_{15}H_{16}NO_3$ [M + H]$^+$: 258.1130; found: 258.1118.

(*E*)-4-[2-(Pent-1-yn-1-yl)pyridin-3-yl]but-3-en-2-one (4h)

A solution of 2-(pent-1-yn-1-yl)nicotinaldehyde (200 mg, 1.15 mmol) and 1-(triphenylphosphoranylidene)propan-2-one (441 mg,1.38 mmol) in toluene (0.5 M) was stirred at 90 °C for 4 h. After completion of the reaction (confirmed by TLC), the reaction mixture was allowed to attain rt and concentrated under reduced pressure. The obtained crude product was purified by column chromatography over silica gel (7% EtOAc in PE) to afford **4h** as a pale-yellow oil, yield: 236 mg (96%).

IR (KBr): 3850, 3457, 2967, 2227, 1678, 1427, 1260, 985, 804 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.55 (dd, *J* = 4.7, 1.6 Hz, 1 H), 7.99 (d, *J* = 16.5 Hz, 1 H), 7.90 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.31–7.22 (m, 1 H), 6.73 (d, *J* = 16.5 Hz, 1 H), 2.53 (t, *J* = 7.0 Hz, 2 H), 2.42 (s, 3 H), 1.80–1.67 (m, 2 H), 1.11 (t, *J* = 7.4 Hz. 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 151.1, 143.9, 139.6, 133.2, 131.6, 130.0, 122.6, 97.4, 78.5, 27.2, 21.8, 21.6, 13.7.

HRMS-ESI: *m*/*z* calcd for $C_{14}H_{16}NO$ [M + H]$^+$: 214.1232; found: 214.1220.

(*E*)-4-[2-(Pent-1-yn-1-yl)quinolin-3-yl]but-3-en-2-one (4j)

A solution of 2-(pent-1-yn-1-yl)quinoline-3-carbaldehyde (400 mg, 1.73 mmol) and 1-(triphenylphosphoranylidene)propan-2-one (855 mg, 2.69 mmol) in toluene (0.5 M) was stirred at 90 °C for 4 h. After completion of the reaction (confirmed by TLC), the reaction mixture was allowed to attain rt and concentrated under reduced pressure. The obtained crude product was purified by column chromatography over silica gel (10% EtOAc in PE) to afford **4j** as a brown solid; yield: 424 mg (90%); mp 100–102 °C.

IR (KBr): 3055, 2963, 2230, 1674, 1256, 1177, 980, 761 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (s, 1 H), 8.14 (d, *J* = 16.4 Hz, 1 H), 8.06 (d, *J* = 8.5 Hz, 1 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 7.76–7.71 (m, 1 H), 7.55 (dd, *J* = 8.0, 7.1 Hz, 1 H), 6.87 (d, *J* = 16.4 Hz, 1 H), 2.58 (t, *J* = 7.1 Hz, 2 H), 2.46 (s, 3 H), 1.77 (dd, *J* = 14.5, 7.3 Hz, 2 H), 1.14 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.0, 148.5, 143.8, 139.8, 133.4, 131.1, 129.9, 129.3, 128.9, 128.1, 127.6, 126.7, 97.0, 79.1, 27.2, 21.9, 21.7, 13.8.

HRMS-ESI: *m*/*z* calcd for $C_{18}H_{18}NO$ [M + H]$^+$: 264.1388; found: 264.1382.

(*E*)-1-Ethynyl-2-[2-(methylsulfinyl)vinyl]benzene (4m)

To a stirred solution of (*E*)-trimethyl({2-[2-(methylsulfinyl)vinyl]phenyl}ethynyl)silane (800 mg, 3.00 mmol) was added K_2CO_3 (1.20 g, 9.1 mmol) in MeOH at 0 °C and the mixture was stirred for 30 min to complete the reaction at rt. The obtained crude product was purified by column chromatography over silica gel (7% EtOAc in PE) to afford **4m** as a pale yellow oil; yield: 464 mg (80%).

IR (KBr): 3292, 2923, 1733, 1592, 1446, 1242, 944, 761, 654 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.42 (m, 2 H), 7.28 (td, *J* = 7.4, 3.9 Hz, 1 H), 7.13 (td, *J* = 7.5, 1.2 Hz, 1 H), 6.94 (d, *J* = 15.5 Hz, 1 H), 6.79 (d, *J* = 15.5 Hz, 1 H), 3.32 (s, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.11, 133.35, 129.13, 128.47, 126.30, 124.10, 122.15, 119.43, 82.30, 81.80, 14.80.

HRMS-ESI: *m*/*z* calcd for $C_{11}H_{11}OS$ [M + H]$^+$: 191.0531; found: 191.0525.

8-(2-Oxopropyl)-13-propylisoindolo[2′,1′:3,4]pyrimido[1,6-*a*]-indol-6(8*H*)-one (5a)

Yellow solid; yield: 115 mg (81%); mp 180–182 °C.

IR (KBr): 3515, 3379, 2963, 1682, 1381, 1170, 762 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ = 8.54 (d, *J* = 7.7 Hz, 1 H), 7.85 (d, *J* = 7.8 Hz, 1 H), 7.67 (d, *J* = 7.1 Hz, 1 H), 7.56–7.42 (m, 3 H), 7.36–7.23 (m, 2 H), 6.80 (s, 1 H), 5.82 (dd, *J* = 6.9, 3.0 Hz, 1 H), 3.65 (dd, *J* = 17.5, 3.2 Hz, 1 H), 3.13 (dd, *J* = 17.5, 7.3 Hz, 1 H), 3.05–2.94 (m, 2 H), 2.13 (s, 3 H), 1.84–1.67 (m, 2 H), 1.11 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ = 205.5, 145.9, 142.1, 138.0, 134.4, 132.4, 131.8, 130.2, 129.3, 128.7, 123.3, 123.2, 123.1, 121.9, 119.5, 115.2, 106.8, 96.8, 58.5, 45.8, 30.3, 27.8, 21.7, 13.8.

HRMS-ESI: *m*/*z* calcd for $C_{24}H_{23}N_2O_2$ [M + H]$^+$: 371.1760; found: 371.1760.

13-Butyl-8-(2-oxopropyl)isoindolo[2′,1′:3,4]pyrimido[1,6-*a*]indol-6(8*H*)-one (5b)

Yellow solid; yield: 117 mg (79%); mp 190–192 °C.

IR (KBr): 3563, 3334, 2955, 1693, 1382, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70–8.63 (m, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.70–7.64 (m, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.3 Hz, 1 H), 7.44–7.37 (m, 1 H), 7.37–7.30 (m, 2 H), 6.68 (s, 1 H), 5.98 (dd, *J* = 8.2, 2.5 Hz, 1 H), 3.86 (dd, *J* = 17.7, 3.1 Hz, 1 H), 3.09–2.97 (m, 2 H), 2.91 (dd, *J* = 17.7, 8.4 Hz, 1 H), 2.22 (s, 3 H), 1.83–1.71 (m, *J* = 12.2, 7.6 Hz, 2 H), 1.63–1.52 (m, 2 H), 1.03 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.8, 146.9, 142.5, 138.4, 134.2, 133.3, 132.6, 130.7, 129.4, 128.9, 123.8 (2 C), 123.4, 122.6, 119.6, 116.1, 108.3, 97.4, 58.9, 47.2, 31.1, 30.7, 26.7, 23.2, 14.2.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{25}N_2O_2$ [M + H]$^+$: 385.1916; found: 385.1917.

8-(2-Oxopropyl)-13-pentylisoindolo[2′,1′:3,4]pyrimido[1,6-*a*]-indol-6(8*H*)-one (5c)

Yellow solid; yield: 119 mg (78%); mp 178–180 °C.

IR (KBr): 3710, 3523, 3425, 3141, 2925, 1691, 1377, 760 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69–8.64 (m, 1 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 7.70–7.64 (m, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.4 Hz, 1 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 7.38–7.32 (m, 2 H), 6.68 (s, 1 H), 5.98 (dd, *J* = 8.3, 3.0 Hz, 1 H), 3.86 (dd, *J* = 17.7, 3.1 Hz, 1 H), 3.04–2.97 (m, 2 H), 2.91 (dd, *J* = 17.7, 8.4 Hz, 1 H), 2.22 (s, 3 H), 1.81–1.74 (m, 2 H), 1.59–1.50 (m, 2 H), 1.47–1.40 (m, 2 H), 0.95 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 147.1, 142.6, 138.4, 134.2, 133.3, 132.7, 130.8, 129.9, 129.0, 123.8, 123.8, 123.5, 122.7, 119.7, 116.1, 108.4, 97.4, 58.9, 47.3, 32.3, 30.7, 28.7, 27.0, 22.8, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{27}N_2O_2$ [M + H]$^+$: 399.2073; found: 399.2057.

13-(Hydroxymethyl)-8-(2-oxopropyl)isoindolo[2′,1′:3,4]-pyrimido[1,6-*a*]indol-6(8*H*)-one (5d)

Yellow solid; yield: 113 mg (82%); mp 181–183 °C.

IR (KBr): 3513, 3023, 1694, 1387, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 7.0 Hz, 1 H), 8.02 (d, *J* = 7.9 Hz, 1 H), 7.54 (d, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 6.6 Hz, 1 H), 7.42–7.35 (m, 2 H), 7.26 (d, *J* = 23.1 Hz, 3 H), 6.71 (s, 1 H), 5.77 (d, *J* = 7.9 Hz, 1 H), 5.12–4.99 (m, 2 H), 3.75 (d, *J* = 17.6 Hz, 1 H), 2.85 (dd, *J* = 17.7, 8.3 Hz, 1 H), 2.18 (s, 3 H), 1.71 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.7, 146.8, 142.6, 137.5, 137.1, 133.0, 131.5, 130.6, 130.2, 129.2, 124.6, 123.9, 123.4, 122.8, 119.7, 115.8, 105.7, 97.2, 59.1, 57.3, 46.8, 30.7.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{19}N_2O_3$ [M + H]$^+$: 359.1394; found: 359.1396.

13-Cyclopropyl-8-(2-oxopropyl)isoindolo[2′,1′:3,4]pyrimido-[1,6-*a*]indol-6(8*H*)-one (5e)

Yellow solid; yield: 105 mg (74%); mp 180–182 °C.

IR (KBr): 3893, 3015, 1694, 1467, 1379, 760 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 7.8 Hz, 1 H), 8.29 (d, *J* = 7.8 Hz, 1 H), 7.67 (dd, *J* = 6.8, 1.4 Hz, 1 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.3 Hz, 1 H), 7.44–7.39 (m, *J* = 7.4, 0.9 Hz, 1 H), 7.37–7.30 (m, 2 H), 6.90 (s, 1 H), 5.96 (dd, *J* = 8.4, 2.9 Hz, 1 H), 3.85 (dd, *J* = 17.7, 3.1 Hz, 1 H), 2.90 (dd, *J* = 17.7, 8.4 Hz, 1 H), 2.21 (s, 3 H), 2.07–1.95 (m, 1 H), 1.32–1.19 (m, 2 H), 0.92–0.78 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.8, 147.0, 142.7, 138.5, 137.6, 133.1, 132.4, 130.8, 129.7, 128.6, 125.2, 123.8, 123.5, 122.6, 119.7, 116.0, 107.7, 98.8, 59.1, 47.2, 30.7, 9.1, 8.0.

HRMS-ESI: *m*/*z* calcd for $C_{24}H_{21}N_2O_2$ [M]$^+$: 369.1603; found: 369.1603.

8-(2-Oxopropyl)isoindolo[2′,1′:3,4]pyrimido[1,6-*a*]indol-6(8*H*)-one (5f)

Yellow solid; yield: 98 mg (78%); mp 175–177 °C.

IR (KBr): 3830, 3520, 3025, 1693, 1380, 759 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68–8.60 (m, 1 H), 7.69–7.60 (m, 2 H), 7.50 (d, *J* = 6.9 Hz, 1 H), 7.47–7.38 (m, 2 H), 7.37–7.29 (m, 2 H), 6.81 (s, 1 H), 6.58 (s, 1 H), 5.96 (dd, *J* = 8.5, 2.7 Hz, 1 H), 3.90 (dd, *J* = 17.8, 3.1 Hz, 1 H), 2.91 (dd, *J* = 17.8, 8.6 Hz, 1 H), 2.22 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.7, 147.4, 142.0, 139.3, 136.3, 133.1, 132.0, 131.1, 130.4, 128.9, 123.9 (2C), 122.6, 120.9, 119.7, 115.9, 98.4, 90.9, 59.6, 46.7, 30.7.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{17}N_2O_2$ [M + H]$^+$: 329.1290; found: 329.1280.

10-Nitro-8-(2-oxopropyl)-13-propylisoindolo[2′,1′:3,4]pyrimido-[1,6-*a*]indol-6(8*H*)-one (5g)

Brown solid; yield: 131 mg (82%); mp 200–202 °C.

IR (KBr): 3797, 3531, 3372, 2923, 1696, 1342, 758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.67–8.61 (m, 1 H), 8.38–8.30 (m, 2 H), 7.86 (d, *J* = 8.6 Hz, 1 H), 7.72–7.64 (m, 1 H), 7.41–7.34 (m, 2 H), 6.81 (s, 1 H), 5.98 (dd, *J* = 8.0, 2.5 Hz, 1 H), 3.86 (dd, *J* = 18.2, 2.9 Hz, 1 H), 3.10 (dd, *J* = 18.2, 8.0 Hz, 1 H), 3.05–2.99 (m, 2 H), 2.23 (s, 3 H), 1.88–1.77 (m, 2 H), 1.16 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.3, 147.9, 146.6, 143.6, 138.7, 137.5, 133.5, 132.5, 130.6, 124.7, 124.2, 123.7, 123.6, 120.2, 119.4, 116.1, 111.9, 99.7, 58.7, 46.5, 30.6, 29.0, 22.4, 14.5.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}N_3O_4$ [M + H]$^+$: 416.1610; found: 416.1613.

5-(2-Oxopropyl)[1,3]dioxolo[4″,5″:5′,6′]isoindolo[2′,1′:3,4]-pyrimido[1,6-*a*]indol-7(5*H*)-one (5h)

Yellow solid: yield: 110 mg (77%); mp 235–247 °C.

IR (KBr): 3921, 3521, 3341, 2918, 1695, 1475, 1318, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 7.3 Hz, 1 H), 7.61 (d, *J* = 6.9 Hz, 1 H), 7.40–7.28 (m, 2 H), 6.98 (d, *J* = 26.9 Hz, 2 H), 6.57 (d, *J* = 31.6 Hz, 2 H), 6.04 (s, 2 H), 5.83 (d, *J* = 7.2 Hz, 1 H), 3.91 (d, *J* = 17.7 Hz, 1 H), 2.83 (dd, *J* = 17.8, 8.8 Hz, 1 H), 2.22 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.9, 150.3, 148.9, 147.2, 139.4, 136.8, 136.4, 132.9, 131.2, 125.5, 123.8, 122.4, 119.5, 115.9, 104.5, 102.2, 100.6, 97.8, 89.3, 59.3, 46.8, 30.3.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{17}N_2O_4$ [M + H]$^+$: 373.1188; found: 373.1180.

5-(2-Oxopropyl)-14-propylpyrido[2″,3″:3′,4′]pyrrolo[1′,2′:3,4]py-rimido[1,6-*a*]indol-7(5*H*)-one (5i)

Brown solid; yield: 111 mg (78%); mp 195–197 °C.

IR (KBr): 3712, 3524, 2967, 1686, 1406, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71–8.64 (m, 2 H), 7.85 (d, *J* = 7.8 Hz, 1 H), 7.71–7.66 (m, 1 H), 7.41–7.34 (m, 2 H), 7.23 (dd, *J* = 7.8, 4.8 Hz, 1 H), 6.78 (s, 1 H), 5.96 (dd, *J* = 9.2, 2.7 Hz,), 4.05 (dd, *J* = 18.1, 3.0 Hz, 1 H), 3.44–3.35 (m, 2 H), 2.82 (dd, *J* = 18.1, 9.3 Hz, 1 H), 2.23 (s, 3 H), 1.86–1.76 (m, 2 H), 1.07 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 152.8, 150.6 147.0, 138.0, 136.4, 133.3, 132.1, 131.7, 130.7, 123.9, 123.0, 122.9, 119.9, 116.1, 111.2, 99.0, 57.1, 46.8, 30.6, 27.1, 22.9, 14.2.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{22}N_3O_2$ [M + H]$^+$: 372.1712; found: 372.1715.

8-(2-Oxopropyl)-15-propylindolo[1″,2″:3′,4′]pyrimido-[1′,6′:1,2]pyrrolo[3,4-*b*]quinolin-6(8*H*)-one (5j)

Green solid; yield: 58 mg (64%); mp 240–242 °C.

IR (KBr): 3745, 3700, 3083, 2925, 2855, 1732, 1518, 1217, 1027, 773, 734 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.70 (dd, *J* = 6.1, 3.3 Hz, 1 H), 8.24 (s, 1 H), 8.13 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 7.9 Hz, 1 H), 7.77–7.68 (m, 2 H), 7.58–7.52 (m, 1 H), 7.41–7.36 (m, 2 H), 6.86 (s, 1 H), 6.09 (dd, *J* = 9.3, 1.8 Hz, 1 H), 4.10 (dd, *J* = 18.2, 2.8 Hz, 1 H), 3.57 (dd, *J* = 8.6, 7.0 Hz, 2 H), 2.92 (dd, *J* = 18.2, 9.3 Hz, 1 H), 2.25 (s, 3 H), 1.93–1.83 (m, 2 H), 1.16 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.1, 153.4, 149.2, 147.1, 137.9, 133.9, 133.5, 131.6, 130.9, 130.8, 130.1, 129.9, 128.3, 127.4, 127.2, 123.9, 123.2, 120.1, 116.2, 113.0, 99.5, 56.6, 47.5, 30.6, 27.5, 23.0, 14.4.

HRMS-ESI: *m*/*z* calcd for $C_{27}H_{24}N_3O_2$ [M + H]$^+$: 422.1869; found: 422.1863.

2-(6-Oxo-6,8-dihydroisoindolo[2′,1′:3,4]pyrimido[1,6-*a*]indol-8-yl)acetonitrile (5k)

Yellow solid; yield: 96 mg (80%); mp 243–245 °C.

IR (KBr): 3896, 3522, 3314, 3021, 2687, 2251, 1695, 1385, 757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66–8.58 (m, 1 H), 7.73 (dd, *J* = 5.4, 3.0 Hz, 1 H), 7.65 (dd, *J* = 5.8, 3.1 Hz, 2 H), 7.54 (pent, *J* = 7.4 Hz, 2 H), 7.40–7.34 (m, 2 H), 6.86 (s, 1 H), 6.64 (s, 1 H), 5.71 (dd, *J* = 6.1, 3.7 Hz, 1 H), 3.57–3.42 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.4, 138.5, 138.4, 135.8, 133.2, 132.5, 131.1, 130.7, 130.1, 124.2, 123.3, 123.2, 121.5, 119.9, 115.9, 115.8, 99.6, 91.9, 59.0, 22.3.

HRMS-ESI: *m*/*z* calcd for $C_{20}H_{14}N_3O$ [M + H]$^+$: 312.1137; found: 312.1141.

Methyl 2-(6-Oxo-6,8-dihydroisoindolo[2′,1′:3,4]pyrimido-[1,6-*a*]indol-8-yl)acetate (5l)

Pink solid; yield: 72 mg (55%); mp 113–115 °C.

IR (KBr): 3866, 3698, 3068, 1739, 1696, 1464, 1381, 1222, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69–8.60 (m, 1 H), 7.70–7.59 (m, 2 H), 7.53–7.41 (m, 3 H), 7.38–7.30 (m, 2 H), 6.81 (s, 1 H), 6.59 (s, 1 H), 5.89 (dd, *J* = 7.7, 3.5 Hz, 1 H), 3.67 (s, 3 H), 3.62 (dd, *J* = 16.3, 3.7 Hz, 1 H), 3.02 (dd, *J* = 16.3, 7.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.73, 147.39, 141.04, 139.22, 136.23, 133.13, 132.27, 131.07, 130.31, 129.15, 123.87, 123.40, 122.66, 121.06, 119.66, 116.03, 98.51, 90.94, 60.12, 52.03, 37.47.

HRMS-ESI: *m*/*z* calcd for $C_{21}H_{16}N_2O_3Na$ [M + Na]$^+$: 367.1059; found: 367.1053.

(*E*)-3-{2-[2-(Methylsulfinyl)vinyl]phenyl}pyrimido[1,6-*a*]indol-1(2*H*)-one (6)

Off-white solid; yield: 97 mg (73%); mp 198–200 °C.

IR (KBr): 3843, 3644, 3447, 3046, 2747, 1727, 1255, 760, 647 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.05 (s, 1 H), 8.54 (dd, *J* = 8.0, 0.7 Hz, 1 H), 7.73–7.64 (m, 2 H), 7.46–7.39 (m, 2 H), 7.38–7.26 (m, 3 H), 7.13 (d, *J* = 15.4 Hz, 1 H), 6.65 (s, 1 H), 6.45 (d, *J* = 1.6 Hz, 1 H), 6.40 (d, *J* = 15.5 Hz, 1 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.5, 137.3, 136.3, 135.8, 132.6, 131.9, 130.9, 130.3, 129.9, 129.1, 126.9, 125.6, 124.0, 122.3, 121.6, 120.1, 115.8, 99.5, 97.7, 14.5.

HRMS-ESI: *m*/*z* calcd for $C_{20}H_{17}N_2O_2S$ [M + H]$^+$: 349.1011; found: 349.1024.

13-Butylisoindolo[2′,1′:3,4]pyrimido[1,6-*a*]indole-6,8-dione (7)

To a stirred solution of compound **3b** (50 mg, 0.145 mmol) in anhydrous CH_2Cl_2 Dess–Martin periodinane (73.9 mg, 0.174 mmol) was added at 0 °C under N_2 atmosphere and the reaction mixture stirred at room temperature for 2 h. It was quenched with a 1:1 mixture of saturated solutions of hypo and $NaHCO_3$ (4 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over (Na_2SO_4), concentrated and the residue was purified by column chromatography on silica gel (15% EtOAc in hexanes) to afford the compound **7**.

Yellow solid; yield: 25 mg (50%); mp 190–192 °C.

IR (KBr): 3872, 3728, 3516, 3435, 3021, 1777, 1368, 751 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.64 (dd, *J* = 8.2, 0.5 Hz, 1 H), 8.02 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 7.9 Hz, 1 H), 7.77–7.68 (m, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.54–7.49 (m, 1 H), 7.45–7.35 (m, 1 H), 7.35–7.28 (m, 1 H), 6.81 (s, 1 H), 3.02 (t, *J* = 8 Hz, 2 H), 1.82–1.74 (m, 2 H), 1.60–1.51 (m, 2 H), 1.04 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 143.7, 135.7, 135.5, 134.6, 133.9, 130.4, 129.5, 128.4, 127.6, 125.7, 125.4, 124.6, 123.1, 120.9, 116.5, 115.4, 104.2, 31.2, 27.0, 23.1, 13.9.

HRMS-ESI: *m*/*z* calcd for $C_{22}H_{19}N_2O_2$ $[M + H]^+$: 343.1449; found: 343.1447.

Funding Information

C.R.R. thanks the Science and Engineering Research Board (SERB), New Delhi, for funding the project (EMR/2016/006253). Y.L.P. thanks Department of Science and Technology (DST) for a financial grant under Women Scientists Scheme-A [WOS-A, Grant No. SR/WOS-A/CS-1034/2014 (G)]. S.B. and K.M. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for research fellowships.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707312. Copies of ^1H and ^{13}C NMR spectra for all new compounds are provided.

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