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Note

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Synthesis of Tetracyclic Quinazolinones Using a Visible-Light-Promoted Radical Cascade Approach

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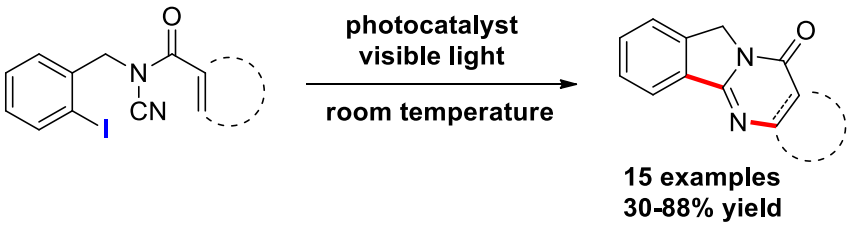
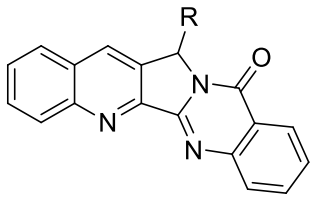


ABSTRACT: A practical approach for the synthesis of tetracyclic pyrroloquinazolines using photoredox strategy has been developed. The visible-light-promoted intramolecular single-electron-transfer (SET) process between photocatalyst and *N*-(2-iodobenzyl)-*N*-acylcyanamides is considered to be involved in this transformation. Targeted pyrroloquinazoline derivatives (15 examples) are presented in good isolated yields (30%-88%).

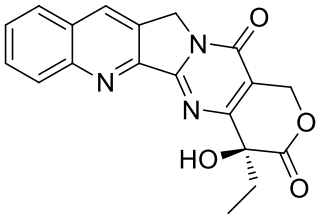
Tetracyclic pyrroloquinazoline occurs as a key structural entity in dozens of natural products, such as luotonins A and E, mackinazolinone, rutaecarpine and deoxyvasicinone (Scheme 1).[1] This type of natural products disclose a wide range of biological activities including the specific cytotoxicity and potent inhibition to proteases, which would be applicable in the discovery of pharmaceutical candidates.[2]

Therefore, the synthesis of heterocyclic compounds bearing the tetracyclic pyrroloquinazoline scaffold has drawn intensive attention to synthetic chemists. Previously, the construction of tetracyclic pyrroloquinazoline scaffold commonly focused on the Pd-catalyzed cyclizations.[3] For example, Li and co-workers reported a Pd-catalyzed approach to prepare tetracyclic pyrroloquinazolines from 2-bromo-*N*-(2-iodobenzyl)benzamides, which underwent cyanation/*N*-addition/*N*-arylation reaction sequence in a two-stage and one-pot manner (Scheme 2a).[3a] The Wu group also reported a decent method to prepare tetracyclic pyrroloquinazolines through palladium-catalyzed carbonylation of 2-bromobenzylamines with 2-bromoanilines (Scheme 2b).[3b] In addition, tetracyclic pyrroloquinazolines could also be prepared through radical approach.[4,5] Malacria and co-workers described the AIBN/*n*-Bu_3SnH-mediated radical cascade cyclization of *N*-(2-iodobenzyl)-*N*-acylcyanamides to prepare pyrroloquinazoline-type polycyclic compounds (Scheme 2c).[4a] A concise total synthesis of luotonin A was achieved using this strategy. The aforementioned methods are normally conducted at elevated temperature or proceed in the presence of toxic reagents (e. g. *n*-Bu_3SnH). These limitations considerably restrict not only the operational simplicity towards the preparation of this pyrroloquinazoline-type tetracyclic compounds, but also the pharmaceutical availability of compounds bearing this characteristic scaffold.

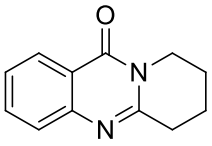
Scheme 1. Quinazolinone-Containing Biologically Active Natural Products



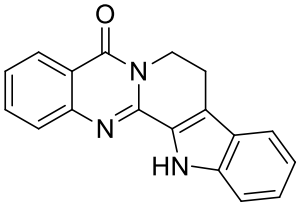
luotonin A, R = H
luotonin B, R = OH
luotonin E, R = OMe



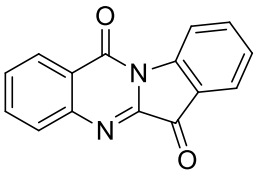
14-azacamptothecin



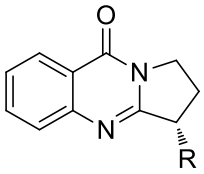
mackinazolinone



rutaecarpine



tryptanthrin

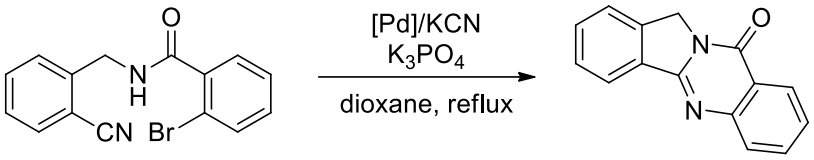


vasicinone, R = OH
deoxyvasicinone, R = H

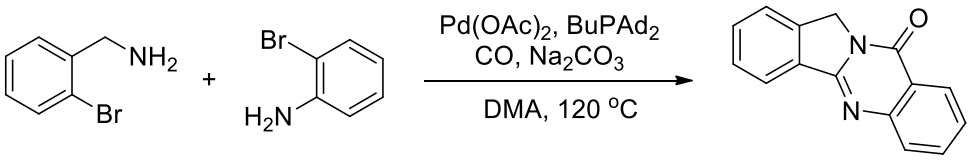
Inspired by these beautiful works, as well as our previous work with respect to the photoredox-catalyzed radical triple bond insertions to construct various heterocycles,[6] we envisioned that the tetracyclic pyrroloquinazolinanes could be prepared by photoredox-catalyzed intramolecular radical cyanide insertion of *N*-(2-iodobenzyl)-*N*-acylcyanamides (Scheme 2d). Several challenges associated with this approach have to be pointed out, including (1) the inertia of aryl iodides[7] for the generation of aryl radical species upon photoredox conditions compared with other active aryl radical precursors such as aryl diazonium salts[8] and diaryliodonium salts,[9] (2) the inertia of the cyano group as the radical acceptor in photoredox catalysis.[10]

Scheme 2. Synthesis of Tetracyclic Quinazolinones

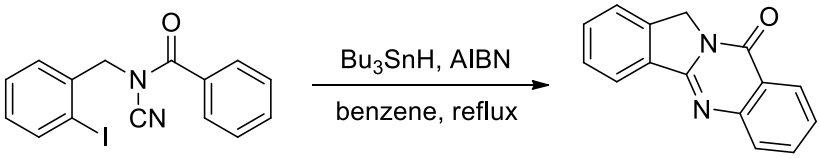
a) Pd-catalyzed sequential cyanation/*N*-addition/*N*-arylation



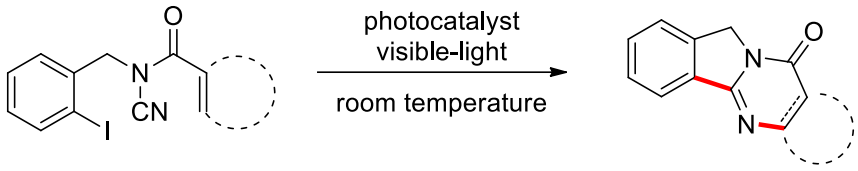
b) Palladium-catalyzed carbonylation



c) AIBN/Bu_3SnH-mediated radical cascade cyclization



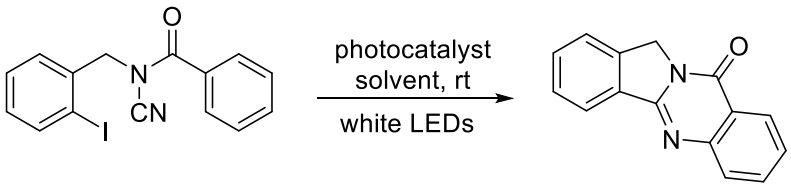
d) Visible-light-promoted radical cascade cyclization: *this work*



With these considerations in mind, we initially used *N*-acyl-*N*-(2-iodobenzyl)-cyanamide (**1a**)[4a] as the model substrate to explore this transformation. To our delight, 30% yield of the desired pyrroloquinazoline **2a** based on ^{1}H NMR analysis was obtained when a solution of **1a**, TEA and *fac*-Ir(ppy)$_3$ (2.0 mol%) in MeCN was irradiated by white LED strips for 12 h at room temperature (Table 1, entry 1). The use of inorganic bases such as Na_2HPO_4 and KO^{t}Bu instead of TEA couldn't give any desired product (entries 2-3). This phenomenon suggests that TEA was not only used as a base, but also played as a quencher of photo-excited catalyst (*fac*-Ir(ppy)$_3$*) in the catalytic cycle. We further screened a range of organic

bases including Ph_3N, DIPEA, DBU, DMAP, NMM and TMEDA (entries 4-9). DIPEA was proved to be the optimal organic base affording **2a** in 69% yield (entry 5). The employment of other commonly used photocatalysts ($Ir(ppy)_2(dtbbpy)PF_6$, $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$, $Ru(bpy)_3Cl_2$ and $Ru(Phen)_3(PF_6)_2$) couldn't give any improvement of the yield (entries 10-13). Other solvents, such as DMF, MeOH, DMSO and CH_2Cl_2, were not superior to MeCN in this transformation (entries 14-17). The use of 3.0 equivalent of DIPEA gave comparable yield of **2a** (entry 18). Satisfactorily, the NMR yield of **2a** could be increased to 87% (83% isolated yield) by diluting the reaction system to 0.02 M (entry 19). The reaction couldn't proceed without photocatalyst or visible light irradiation (entries 20-21).

Table 1. Reaction Condition Optimization[a]



1a **2a**

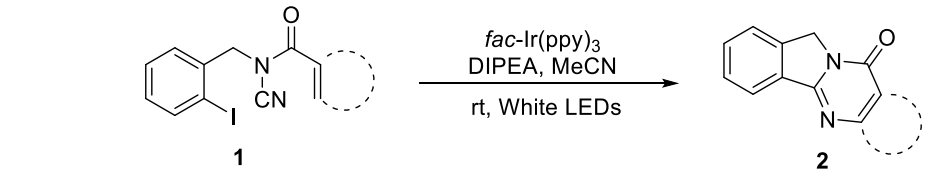
entry	photocatalyst	base	solvent	**2a**/%[b]
1	$Ir(ppy)_3$	TEA	MeCN	30
2	$Ir(ppy)_3$	Na_2HPO_4	MeCN	0
3	$Ir(ppy)_3$	KO^tBu	MeCN	0
4	$Ir(ppy)_3$	Ph_3N	MeCN	0
5	$Ir(ppy)_3$	DIPEA	MeCN	69

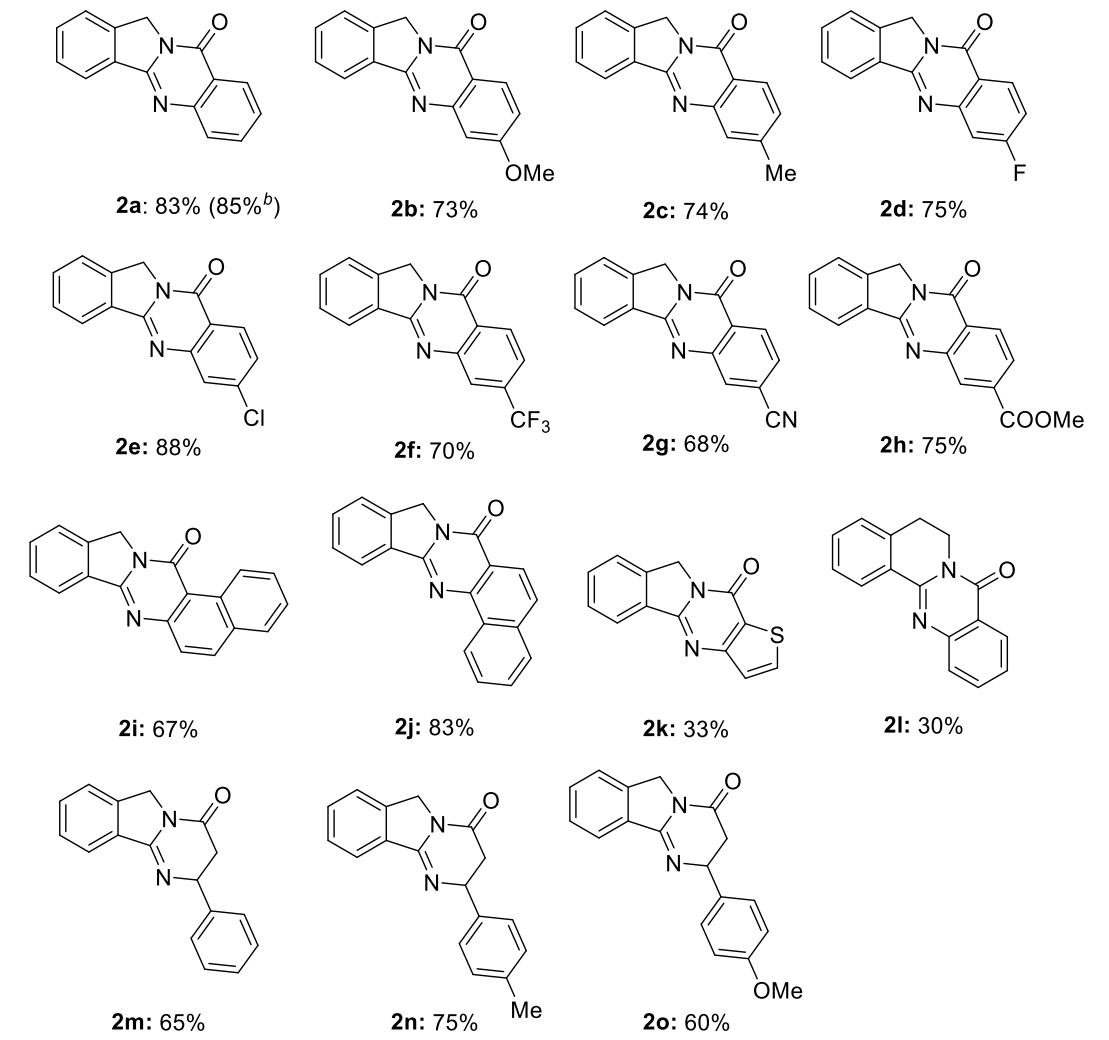
6	$Ir(ppy)_3$	DBU	MeCN	trace
7	$Ir(ppy)_3$	DMAP	MeCN	trace
8	$Ir(ppy)_3$	NMM	MeCN	9
9	$Ir(ppy)_3$	TMEDA	MeCN	38
10	$Ir(ppy)_2(dtbbpy)PF_6$	DIPEA	MeCN	66
11	$Ir(dFCF_3ppy)_2(dtbbpy)PF_6$	DIPEA	MeCN	18
12	$Ru(bpy)_3Cl_2$	DIPEA	MeCN	20
13	$Ru(Phen)(PF_6)_2$	DIPEA	MeCN	17
14	$Ir(ppy)_3$	DIPEA	DMF	29
15	$Ir(ppy)_3$	DIPEA	MeOH	0
16	$Ir(ppy)_3Cl_2$	DIPEA	DMSO	64
17	$Ir(ppy)_3$	DIPEA	CH_2Cl_2	35
18[c]	$Ir(ppy)_3$	DIPEA	MeCN	70
19[d]	**$Ir(ppy)_3$**	**DIPEA**	**MeCN**	**87 (83[e])**
20[f]	$Ir(ppy)_3$	DIPEA	MeCN	0
21	none	DIPEA	MeCN	0

[a]Reaction conditions: a solution of **1a** (0.1 mmol), base (0.2 mmol) and photocatalyst (0.002 mmol, 2.0 mol %) in the indicated solvent (1.0 mL) was irradiated by white LED strips at rt for 12 h. [b]The yields are based on ^{1}HNMR analysis. [c]0.3 mmol of DIPEA was used. [d]5.0 mL of MeCN was used. [e]Isolated yield. [f]Reaction was conducted in the dark.

With the optimized conditions in hand, we then intended to explore the scope of this transformation. In general, the desired cyclization products **2** with 6/5/6/6 ring system were achieved in acceptable to excellent yields (Scheme 3). The substituents on the aryl of benzoyl motif could be a range of electronic donating or withdrawing functional groups (-OMe, -Me, -F, -Cl, -CF_3, -CN, CO_2Me), affording desired products **2a**-**2h** in 68%-88% yields. The aryl of benzoyl motif could also be 1- or 2-naphthalene (**2i**, 67% and **2j**, 83%) and 1-thiophene (**2k**, 33%). In addition, *N*-acylcyanamide derived from 2-iodophenylethanamine was also compatible in this transformation to give **2l** with 6/6/6/6 ring system in 30% yield. Cinnamic acid-derived cyanamides were also be suitable in this transformation to give tricyclic products **2m**-**2o** in 50%-86% yields, which were not achieved in AIBN/*n*-Bu_3SnH-mediated radical cascade cyclization.[4] The reaction could be scaled up to gram scale. When 3 mmol (1.09 g) of **1a** was subjected to standard conditions with 1.0 mol% of photocatalyst, the product **2a** could be isolated in 85% yield.

Scheme 3. Substrate Scope[a]

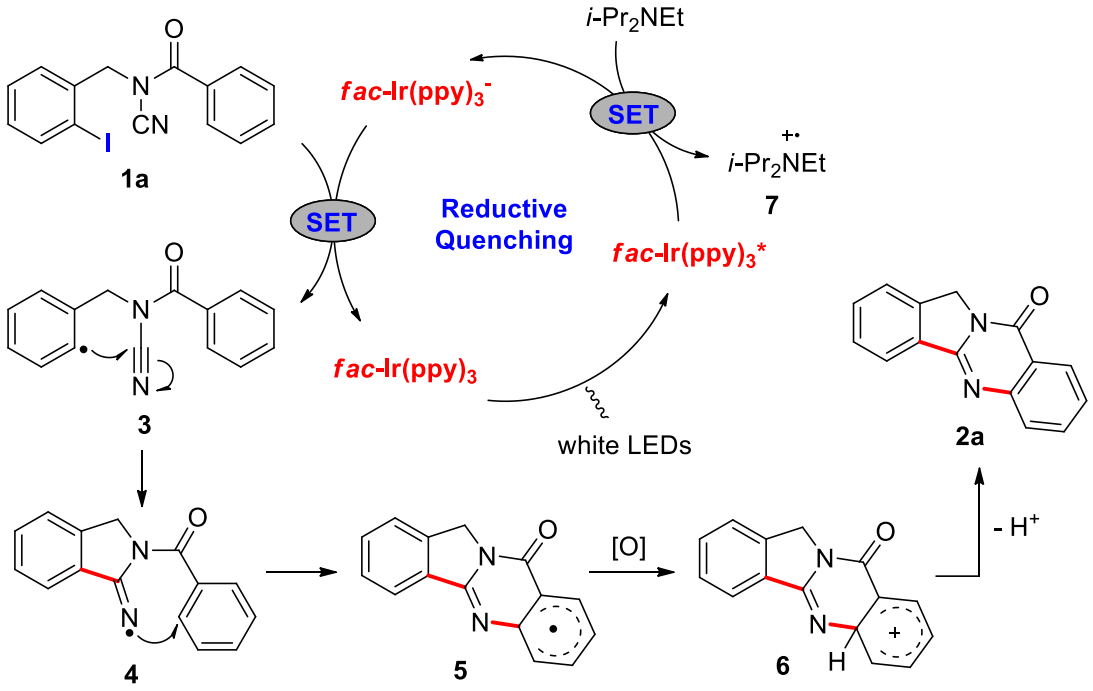




[a]Reaction conditions: a solution of **1a** (0.2 mmol), DIPEA (0.4 mmol) and *fac*-Ir(ppy)$_3$ (0.004 mmol, 2.0 mol %) in MeCN (10.0 mL) was irradiated by white LED strips at rt for 12 h. Yields are for the isolated products. [b]The reaction was running in 5 mmol scale for 24 h, and the loading of *fac*-Ir(ppy)$_3$ was reduced from 2.0 mol % to 1.0 mol %.

To investigate the mechanism of this reaction, a series of emission quenching experiments were performed to acquire further insight into the photoredox catalytic cycle. The experiments revealed that it was DIPEA to quench the excited state of *fac*-Ir(ppy)$_3$ (for details, see the Supporting Information). This result suggests that the reaction might undergo a reductive quenching mechanism. On the basis of the experimental observations, a plausible mechanism is proposed in Scheme 4. The catalytic cycle starts from the photo-excitation of *fac*-Ir(ppy)$_3$ upon visible light irradiation to generate the excited-state photocatalyst (*fac*-Ir(ppy)$_3^*$). The reductive quenching of *fac*-Ir(ppy)$_3^*$ by DIPEA gives *fac*-Ir(ppy)$_3^-$ and *N*-centered radical cation species **7**.[11] Afterwards, single electron transfer (SET) between *N*-acylcyanamide **1a** and *fac*-Ir(ppy)$_3^-$ can afford an aryl radical intermediate **3**,[7] which undergoes intramolecular radical cyclization to give radical intermediate **5**.[12] Subsequently, one electron oxidation of **5** can generate aryl cation intermediate **6**, following the aromatization to give tetracyclic pyrroloquinazoline **2a**.[6]

Scheme 4. Proposed Mechanism



In summary, we have described a practical approach to construct polycyclic pyrroloquinazolines using photoredox-catalyzed intramolecular radical cyanide insertion. This photoredox neutral strategy proceeds under visible light irradiation at room temperature and the experiments are easy to carry out. The hazardous radical initiator AIBN and toxic *n*-Bu_3SnH can be avoided, which renders this protocol particularly valuable in terms of green synthetic chemistry aspect.

Experimental Section

General Information. All reagents and solvents were used without further purification. Thin layer chromatography (TLC) was performed on EMD precoated plates (silica gel 60 F254, Art 5715) and visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid or potassium permanganate, respectively. Column chromatography was performed on EMD Silica Gel 60 (300–

400 Mesh) using a forced flow of 0.5–1.0 bar. ^{1}H NMR (400 MHz), ^{13}C NMR (100MHz) and ^{19}F (376MHz) were measured on a 400 M NMR spectrometer. Chemical shifts are expressed in parts per million (ppm) with respect to the residual solvent peak. Coupling constants are reported as Hertz (Hz), signal shapes and splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a IR spectrophotometer and are reported as wavenumber (cm^{-1}).

General Procedure for Preparation of *N*-acyl-*N*-(2-iodobenzyl)-cyanamides.[4a] KOH (326 mg, 5.8 mmol) was added to a solution of *N*-(2-iodobenzyl)-cyanamide (1.5 g, 5.8 mmol)[4a] in THF/H_2O (15 mL, v:v = 1:1). The mixture was stirred at ambient temperature for 30 min and concentrated under reduced pressure. Toluene (7 mL) was added to the residue. After cooling to 0 °C, acyl chloride (11 mmol) was added slowly. The mixture was then warmed to 25 °C and stirred for another 2 h. After the reaction was complete (as judged by TLC analysis), the reaction mixture was poured into a separatory funnel containing 20 mL of H_2O and 20 mL of CH_2Cl_2. The layers were separated and the organic layers were extracted with H_2O (2 × 20 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The crude product was purified by flash chromatography on silica gel to afford the desired product.

The *N*-acyl-*N*-(2-iodobenzyl)-cyanamides derivatives 1a, 1b, 1f, 1g, 1h and 1k are known compounds and were synthetized according to the literature.[4a]

N-cyano-N-(2-iodobenzyl)-4-methylbenzamide ***(1c)****.* Purification by chromatography (petroleum ether/EtOAc = 15:1) afforded **1c** as a white solid (1.7 g,

79% yield). m.p.: 84—86 ° C; IR (film, cm^{-1}): 2989, 2896, 2230, 1702, 1608, 1567, 1510, 1453, 1435, 835, 756, 742, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.90 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.45–7.37 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.12–7.05 (m, 1H), 4.93 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 144.4, 140.2, 135.9, 130.9, 130.7, 129.3, 129.0, 128.8, 127.8, 110.7, 99.3, 55.3, 21.7; HRMS-DART *m*/*z* calcd for $C_{16}H_{14}ON_2I^+$ [M+H^+] 377.0145, found 377.0143.

N-cyano-4-fluoro-N-(2-iodobenzyl)benzamide ***(1d)****:* Purification by chromatography (petroleum ether/EtOAc = 15:1) afforded **1d** as a white solid (1.5 g, 67% yield). m.p.: 87—89 °C; IR (film, cm^{-1}): 2989, 2895, 2226, 1707, 1603, 1507, 1440, 844, 752, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–7.88 (m, 3H), 7.45–7.37 (m, 2H), 7.21–7.13 (m, 2H), 7.13–7.07 (m, 1H), 4.94 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ167.1, 165.7 (d, *J* = 256.8 Hz) , 140.2, 135.7, 131.7 (d, *J* = 9.4 Hz), 131.1, 130.9, 128.9, 126.8 (d, *J* = 3.3 Hz), 116.1 (d, *J* = 22.3 Hz), 110.4, 99.4, 55.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –103.55; HRMS-DART *m*/*z* calcd for $C_{15}H_{11}ON_2FI^+$ [M+H^+] 380.9895, found 380.9893.

4-chloro-N-cyano-N-(2-iodobenzyl)benzamide ***(1e)****:* Purification by chromatography (petroleum ether/EtOAc = 15:1) afforded **1e** as a white solid (1.7 g, 74% yield). m.p.: 88—89 °C; IR (film, cm^{-1}): 3090, 2975, 2231, 1702, 1590, 1569, 1489, 845, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–7.90 (m, 1H), 7.84–7.79 (m, 2H), 7.49–7.45 (m, 2H), 7.44–7.39 (m, 2H), 7.14–7.06 (m, 1H), 4.93 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ167.2, 140.3, 140.0, 135.6, 131.2, 130.9, 130.3, 129.1, 129.0, 128.9, 110.2, 99.4, 55.4; HRMS-DART *m*/*z* calcd for $C_{15}H_{11}ON_2ClI^+$ [M+H^+]

396.9599, found 396.9599.

*N-cyano-N-(2-iodobenzyl)-1-naphthamide (**1i**):* Purification by chromatography (petroleum ether/EtOAc = 20:1) afforded **1i** as a white solid (1.7 g, 72% yield). m.p.: 132—134 °C; IR (film, cm^{-1}): 2989, 2898, 2231, 1723, 1698, 1688, 1558, 1467, 801, 779, 765, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.95 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.92–7.88 (m, 1H), 7.86 (dd, *J* = 7.1, 0.8 Hz, 1H), 7.64–7.58 (m, 1H), 7.58–7.55 (m, 1H), 7.55–7.50 (m, 1H), 7.49 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.42 (td, *J* = 7.5, 0.9 Hz, 1H), 7.10 (td, *J* = 7.7, 1.7 Hz, 1H), 5.06 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.4, 140.2, 135.8, 133.6, 132.8, 130.84, 130.82, 129.98, 128.9, 128.7, 128.5, 128.0, 127.0, 126.9, 124.4, 124.3, 109.7, 99.4, 54.9; HRMS-DART *m*/*z* calcd for $C_{19}H_{14}ON_2I^+$ [M+H^+] 413.0145, found 413.0141.

*N-cyano-N-(2-iodobenzyl)-2-naphthamide (**1j**):* Purification by chromatography (petroleum ether/EtOAc = 20:1) afforded **1j** as a white solid (1.8 g, 75% yield). m.p.: 82—84 °C; IR (film, cm^{-1}): 3055, 2986, 2901, 2235, 1703, 1684, 1628, 1558, 1466, 833, 752, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.92 (t, *J* =7.4 Hz, 3H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.62–7.50 (m, 2H), 7.45 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 4.98 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.3, 140.2, 135.9, 135.5, 132.1, 131.0, 130.8, 130.4, 129.4, 128.88, 128.89, 128.8, 127.9, 127.8, 127.3, 124.4, 110.6, 99.5, 55.5; HRMS-DART *m*/*z* calcd for $C_{19}H_{14}ON_2I^+$ [M+H^+] 413.0145, found: 413.0145.

*N-cyano-N-(2-iodophenethyl)benzamide (**1l**):* Purification by chromatography (petroleum ether/EtOAc = 20:1) afforded **1l** as a white solid (1.6 g, 76% yield). IR

(film, cm^{-1}): 3085, 3055, 2980, 2230, 1702, 1591, 1568, 1489, 1472, 845, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.76–7.70 (m, 2H) 7.61–7.54 (m, 1H), 7.50–7.42 (m, 2H), 7.36–7.28 (m, 2H), 7.70–6.93 (m, 1H), 4.02 (t, *J* = 7.4 Hz, 2H), 3.24 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.2, 140.0, 139.4, 133.2, 130.9, 130.3, 129.1, 128.7, 128.62, 128.59, 110.9, 100.4, 47.5, 38.6; HRMS-DART *m*/*z* calcd for $C_{16}H_{14}ON_2I^+$ [M+H^+] 377.0145, found: 377.0145.

N-cyano-N-(2-iodobenzyl)cinnamamide ***(1m)****:* Purification by chromatography (petroleum ether/EtOAc = 40:1) afforded **1m** as a white solid (1.2 g, 53% yield). m.p.: 112—114 ℃; IR (film, cm^{-1}): 2975, 2930, 2227, 1680, 1617, 1598, 1570, 1468, 745, 748, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98–7.99 (m, 2H), 7.64–7.58 (m, 2H), 7.47–7.36 (m, 5H), 7.16 (d, *J* = 15.4 Hz, 1H), 7.10–7.05 (m, 1H), 4.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ164.5, 149.1, 140.1, 135.9, 133.5, 131.5, 130.6, 130.2, 129.1, 128.83, 128.79, 113.6, 110.1, 99.2, 54.2; HRMS-DART *m*/*z* calcd for $C_{17}H_{14}ON_2I^+$ [M+H^+] 389.0145, found: 389.0145.

(E)-N-cyano-N-(2-iodobenzyl)-3-(p-tolyl)acrylamide ***(1n)****:* Purification by chromatography (petroleum ether/EtOAc = 40:1) afforded **1n** as a white solid (1.4 g, 60% yield). m.p.: 129—131 °C; IR (film, cm^{-1}): 2968, 2920, 2228, 1695, 1619, 1604, 1568, 1456, 1330, 813, 747, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 11.6, 3.6 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.42 – 7.32 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.15 –7.02 (m, 2H), 4.91 (s, 2H), 2.40 (s, 3H)； ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 149.2, 142.3, 140.1, 136.0, 130.9, 130.6, 130.1, 129.8, 128.9, 128.8, 112.5, 110.2, 99.9, 54.1, 21.6; HRMS-DART *m*/*z* calcd for $C_{18}H_{16}ON_2I^+$ [M+H^+] 403.0302,

found: 403.0302.

*(E)-N-cyano-N-(2-iodobenzyl)-3-(4-methoxyphenyl)acrylamide (**1o**):* Purification by chromatography (petroleum ether/EtOAc = 20:1) afforded **1o** as a white solid (1.6 g, 67% yield). m.p.: 135—137 °C; IR (film, cm^{-1}): 2996, 2928, 2228, 1688, 1616, 1599, 1571, 1508, 1458, 1344, 1289, 821, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93–7.84 (m, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.43–7.31 (m, 2H), 7.09–7.04 (m, 1H), 7.01 (d, *J* = 15.3 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.89 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ164.8, 162.4, 148.8, 140.1, 136.1, 130.7, 130.5, 130.0, 128.8, 126.3, 114.6, 110.9, 110.3, 99.2, 55.5, 54.1; HRMS-DART *m*/*z* calcd for $C_{18}H_{16}O_2N_2I^+$ [M+H^+] 419.0251, found 419.0251.

General Procedure for the Synthesis of Tetracycle Quinazolinones. A 10 mL round bottom flask equipped with a rubber septum and magnetic stir bar was charged with *N*-cyano-*N*-(2-iodobenzyl)benzamide **1a** (0.2 mmol, 1.0 equiv), DIPEA (0.4 mmol, 2.0 equiv) and $Ir(ppy)_3$ (0.004 mmol, 0.02 equiv). The flask was evacuated and backfilled with nitrogen for 3 times. MeCN (10.0 mL) was added with a syringe under nitrogen. The mixture was then irradiated by white LED strips. After the reaction was complete (as judged by TLC analysis), the mixture was concentrated under reduced pressure after filtration. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1).

*Isoindolo[1,2-b]quinazolin-10(12H)-one (**2a**).*[4a] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2a** as a yellow solid (38.8 mg, 83% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 7.5 Hz, 1H),

7.86–7.74 (m, 2H), 7.65–7.54 (m, 3H), 7.49 (t, *J* = 7.4 Hz, 1H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ160.7, 155.0, 149.5, 139.6, 134.3, 132.7, 132.4, 128.9, 127.4, 126.5, 126.4, 123.54, 123.51, 120.6, 49.8.

7-methoxyisoindolo[1,2-b]quinazolin-10(12H)-one ***(2b)***.[4c] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2b** as a yellow solid (38.6 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.8 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 7.66–7.11 (m, 2H), 7.61–7.55 (m, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.13 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ164.6, 160.3, 155.6, 151.8, 139.9, 132.7, 132.3, 128.9, 127.9, 123.5, 123.4, 116.6, 114.2, 108.0, 55.7, 49.7.

7-methylisoindolo[1,2-b]quinazolin-10(12H)-one ***(2c)***.[3b] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2c** as a yellow solid (36.7 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.1 Hz, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 7.66–7.60 (m, 3H), 7.59–7.54 (m, 1H), 7.31 (dd, *J* = 8.1, 0.9 Hz, 1H), 5.13 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ160.5, 155.1, 149.3, 145.4, 139.7, 132.6, 132.4, 128.9, 128.1, 127.0, 126.3, 123.7, 123.5, 118.1, 49.8, 21.9.

7-fluoroisoindolo[1,2-b]quinazolin-10(12H)-one ***(2d)***.[3b] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2d** as a yellow solid (37.8 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (t, *J* = 7.3 Hz, 1H), 8.18 (d, *J* = 7.3 Hz, 1H), 7.73–7.56 (m, 3H), 7.48 (d, *J* = 9.5 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ166.5 (d, *J* = 253.5 Hz), 160.0, 156.2, 151.7 (d, *J* = 13.3 Hz), 139.8, 132.7, 132.4, 129.1 (d, *J* = 11.0 Hz), 129.0, 123.8, 123.6, 117.3,

115.1 (d, J = 23.5 Hz), 112.7 (d, J = 22.2 Hz), 49.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ –103.62;

7-chloroisoindolo[1,2-b]quinazolin-10(12H)-one ***(2e)***. Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2e** as a yellow solid (47.3 mg, 88%). m.p.: 236—238 °C; IR (film, cm^{-1}): 2974, 2920, 1668, 1619, 1597, 1549, 1454, 878, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 1.9 Hz, 1H), 7.69–7.56 (m, 3H), 7.43 (dd, J = 8.5, 1.9 Hz, 1H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ160.1, 156.1, 150.5, 140.5, 139.8, 132.7, 132.4, 129.0, 127.9, 127.0, 126.9, 123.7, 123.5, 119.0, 49.9; HRMS-DART *m*/*z* calcd for $C_{15}H_{10}ON_2Cl^+$ [M+H$^+$] 269.0476, found: 269.0476.

7-(trifluoromethyl)isoindolo[1,2-b]quinazolin-10(12H)-one ***(2f)***.[3b] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2f** as a yellow solid (42.3 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H), 8.11 (s, 1H), 7.74–7.56 (m, 4H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ159.8, 156.2, 149.5, 139.7, 135.8 (q, J = 32.9 Hz), 132.9, 132.2 , 129.2, 127.6, 124.9 (q, J = 4.0 Hz), 123.8, 123.6, 123.5 (q, J = 273.7 Hz), 122.8, 122.3 (q, J = 4.1 Hz), 50.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.11.

10-oxo-10,12-dihydroisoindolo[1,2-b]quinazoline-7-carbonitrile ***(2g)***.[4a] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2g** as a yillow solid (35.3 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 7.5 Hz, 1H), 8.15 (s, 1H), 7.72–7.63 (m, 4H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ159.6, 156.6, 149.6, 139.8, 133.2, 132.3, 132.2, 129.3, 128.1, 127.8,

124.0, 123.6, 123.5, 117.9, 117.6, 50.1.

*Methyl 10-oxo-10,12-dihydroisoindolo[1,2-b]quinazoline-7-carboxylate (**2h**).*[4a] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2h** as a yillow solid (43.8 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.72–7.56 (m, 3H), 5.18 (s, 2H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ166.2, 160.2, 155.7, 149.5, 139.7, 135.4, 132.7, 132.5, 129.3, 129.1, 126.8, 126.4, 123.7, 123.6, 123.5, 52.6, 49.9.

*Benzo[f]isoindolo[1,2-b]quinazolin-14(12H)-one (**2i**).* Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2i** as a yillow solid (38.1 mg, 67%). m.p.: 247—249 °C; IR (film, cm^{-1}): 2989, 2920, 1656, 1621, 1609, 1592, 1552, 1470, 836, 784, 724 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.99 (d, *J* = 8.6 Hz, 1H), 8.34 (d, *J* = 8.9 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.86 (dd, *J* = 8.2, 5.1 Hz, 2H), 7.83–7.74 (m, 2H), 7.71–7.64 (m, 2H), 5.31 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ160.6, 156.1, 152.0, 141.4, 135.9, 132.9, 132.7, 131.8, 131.2, 129.2, 129.01, 128.96, 126.9, 126.8, 126.7, 124.7, 123.3, 113.6, 51.1; HRMS-DART *m*/*z* calcd for $C_{19}H_{13}ON_2^+$ [M+H$^+$] 285.1022, found: 285.1022.

*Benzo[h]isoindolo[1,2-b]quinazolin-7(9H)-one (**2j**).* Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2j** as a yellow solid (47.2 mg, 83%). m.p.: 223—225 °C; IR (film, cm^{-1}): 2919, 2850, 1654, 1651, 1610, 1556, 1469, 763, 735, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51–8.94 (m, 1H), 8.33–8.21 (m, 2H), 7.92–7.86 (m, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.73–7.66 (m, 2H), 7.65–7.53 (m, 3H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ160.7, 154.9, 148.4, 139.7,

136.2, 133.1, 132.2, 130.2, 129.1, 128.8, 127.8, 126.7, 126.6, 125.3, 123.6, 123.4, 121.8, 116.8, 50.0; HRMS-DART *m*/*z* calcd for $C_{19}H_{13}ON_2^+$ [M+H$^+$] 285.1022, found: 285.1023.

Thieno[3',2':4,5]pyrimido[2,1-a]isoindol-11(9H)-one ***(2k)***.[4a] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2k** as a yellow solid (15.8 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 5.3 Hz, 1H), 7.67–7.63 (m, 2H), 7.62–7.56 (m, 1H), 7.48 (d, *J* = 5.3 Hz, 1H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ157.3, 157.0, 156.6, 139.7, 134.6, 132.6, 131.8, 129.1, 124.7, 123.7, 123.6, 121.3, 50.0.

5,6-dihydro-8H-isoquinolino[1,2-b]quinazolin-8-one ***(2l)***.[4b] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2l** as a yellow solid (14.9 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54–8.46 (m, 1H), 8.36–8.27 (m, 1H), 7.94–7.72 (m, 2H), 7.55–7.39 (m, 3H), 7.29 (d, *J* = 7.2 Hz, 1H), 4.42 (t, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ161.7, 149.5, 147.6, 137.1, 134.3, 131.8, 129.4, 128.1, 127.7, 127.53, 127.50, 126.9, 126.6, 120.7, 39.6, 27.4.

2-phenyl-2,6-dihydropyrimido[2,1-a]isoindol-4(3H)-one ***(2m)***.[13] Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2m** as a yellow solid (34.1 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.44–7.35 (m, 3H), 7.35–7.27 (m, 2H), 7.26–7.22 (m, 1H), 7.04–6.92 (m, 2H), 4.92 (s, 2H), 4.18 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.25 (dd, *J* = 18.2, 9.8 Hz, 1H), 2.84 (dd, *J* = 18.2, 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ175.0, 169.6, 139.7, 138.2, 137.3, 129.5, 129.0, 128.3,

128.2, 127.8, 126.4, 97.9, 48.3, 45.1, 38.2.

*2-(p-tolyl)-2,6-dihydropyrimido[2,1-a]isoindol-4(3H)-one (**2n**).* Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2n** as a yellow solid (47.5 mg, 86%). IR (film, cm^{-1}): 3288, 2973, 2920, 1743, 1648, 1514, 1430, 1399, 1346, 818, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.29 (td, *J* = 7.7, 1.0 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.03–6.91 (m, 2H), 4.87 (s, 2H), 4.07 (dd, *J* = 9.8, 6.2 Hz, 1H), 3.20 (dd, *J* = 18.2, 9.9 Hz, 1H), 2.80 (dd, *J* = 18.2, 6.2 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ175.1, 147.1, 139.7, 138.1, 137.5, 130.1, 129.9, 129.0, 128.3, 127.7, 126.3, 97.9, 48.2, 44.9, 38.3, 21.1; HRMS-DART *m/z* calcd for $C_{18}H_{17}ON_2^+$ $[M+H^+]$ 277.1335, found: 277.1335.

*2-(4-methoxyphenyl)-2,6-dihydropyrimido[2,1-a]isoindol-4(3H)-one (**2o**).* Purification by chromatography (petroleum ether/EtOAc = 10:1) afforded **2o** as a yillow solid (29.2 mg, 50%). IR (film, cm^{-1}): 3289, 2966, 2918, 1734, 1648, 1609, 1583, 1512, 1430, 1348, 1249, 832, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.98 (t, *J* = 7.2 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.87 (s, 2H), 4.07 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.82 (s, 3H), 3.20 (dd, *J* = 18.2, 9.9 Hz, 1H), 2.79 (dd, *J* = 18.2, 6.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.9, 170.6, 159.5, 139.7, 137.1, 129.8, 129.1, 129.0, 128.4, 126.6, 114.8, 97.9, 55.4, 48.6, 44.1, 38.2. HRMS-DART *m/z* calcd for $C_{18}H_{17}O_2N_2^+$ $[M+H^+]$ 293.1285, found: 293.1284.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publication website at DOI:

Characterization of products (copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra)

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