JOC The Journal of Organic Chemistry

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# Divergent Synthesis of Methylisatoid and Tryptanthrin Derivatives by $Ph_3P-I_2$-Mediated Reaction of Isatins with and without Alcohols

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Cite This: https://dx.doi.org/10.1021/acs.joc.0c02403 Read Online

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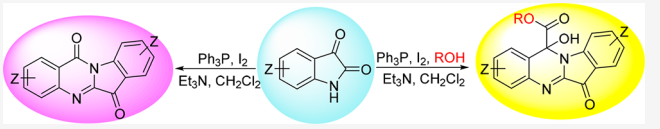
**ABSTRACT:** A novel phosphonium-mediated reaction of isatins is described. In the presence of alcohol, the reaction proceeds to furnish C-12 modified tryptanthrin derivatives. Without alcohol, self-dimerization of isatins gives rise to tryptanthrin and its analogs. This divergent and step-economic approach provides a facile access to diverse indoloquinazoline structures including the natural alkaloids, methylisatoid and cephalanthrin B, in high yields from simple precursors under mild and metal-free reaction conditions.






Tryptanthrin and the related derivatives such as phaitanthrins A–E,[1a] cephalanthrin A,[1b] methylisatoid,[1a–c] and cephalanthrin B[1b] are naturally occurring indolo[2,1-*b*]-quinazoline alkaloids which have been isolated from various plant sources as well as different cell cultures (Figure 1).[1d]

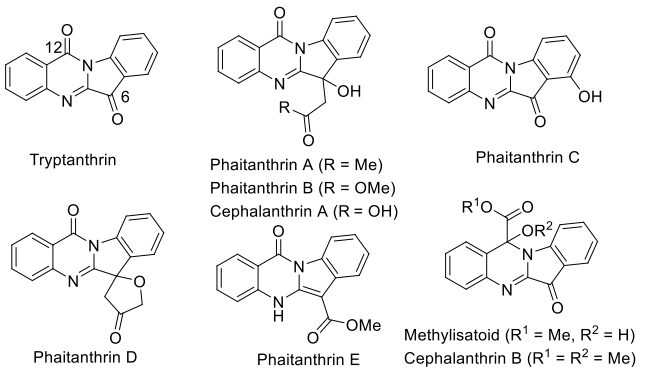



**Figure 1.** Indoloquinazolines isolated from natural sources.

These compounds have attracted considerable interest as potential therapeutic agents mainly due to their broad spectrum of biological and pharmaceutical activities.[2] Some of them include antitumor,[3] antiparasitic,[4] antimicrobial,[5] anti-inflammatory,[6] antimalarial,[7] antiviral,[8] and antitubercular[9] properties.

Owning to their promising benefits, a number of synthetic approaches have been developed to gain access to these core structures.[10] One of the most straightforward methods toward tryptanthrins is through self-dimerization of isatins. Different reaction conditions have been applied including visible-light mediated photoredox catalysis,[11] cathodic reduction,[12] $POCl_3$-mediated reaction,[13] and oxidative cyclization using $I_2$,[14a,b] $KMnO_4$,[14c] or $^tBuO_2H$[14d] as an oxidant. Some recent examples of alternative protocols to install the tryptanthrin framework with different aryl substituents include condensation of isatins with isatoic anhydrides,[15] oxidative cyclization of isatoic anhydrides and 2-aminoacetophenones,[16] photochemical reaction of indoles with anthranilic acids,[17] and copper-catalyzed reaction of isatins with indoles.[18]

Synthesis of other structurally more diverse indoloquinazolines is considered a challenging task which often requires multistep synthesis or the use of complicated substrates. While a number of methods have been introduced for C-6 functionalization of tryptanthrins,[19] modification at the C-12 position remains largely unexplored.[20] Considering these facts and in continuation of our interest in the $Ph_3P-I_2$-mediated reactions,[21] herein, we disclose a novel methodology for the divergent synthesis of methylisatoid and tryptanthrin derivatives (**2** and **3**, respectively) from isatins **1** in the presence and in the absence of alcohols as depicted in Scheme 1.

Our initial investigation involved the reaction between isatin (**1a**) and methanol using the combination of $Ph_3P-I_2$ as an activator in the presence of the triethylamine base. To our surprise, when using a 1:1 mol ratio of **1a** and methanol, instead of the expected *O*-methylisatin **A** (Z = H, R = Me), compound **2a** was isolated in 83% yield. Based on spectroscopic analysis, its structure was identified as 12-hydroxy-12-methoxycarbonyltryptanthrin which is known as methylisatoid.[1] Since *O*-alkylated isatins are highly unstable,[22] *O*-methylated product, if formed, may undergo rapid condensation with another isatin molecule to yield **2**. Due to nucleophilicity of the isatin nitrogen, formation of **2** through

**Received:** October 10, 2020




https://dx.doi.org/10.1021/acs.joc.0c02403
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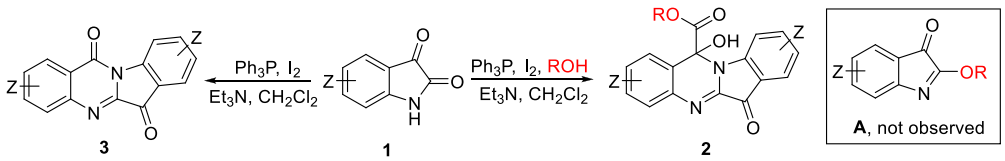
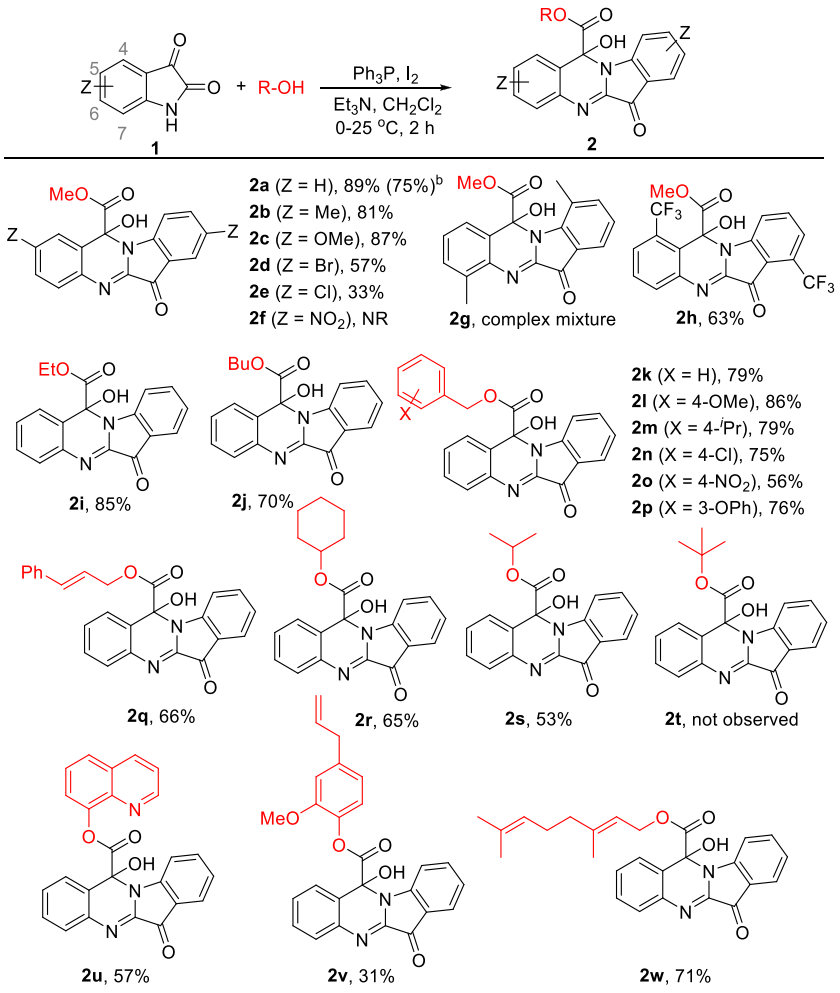
**Scheme 1. Divergent Synthesis of Methylisatoid and Tryptanthrin Derivatives**




**Scheme 2. Synthesis of Methylisatoid Derivatives**[a]




[a]Reaction conditions: **1** (0.68 mmol), $PPh_3$ (0.51 mmol), $I_2$ (0.51 mmol), alcohol (0.51 mmol), $Et_3N$ (1.70 mmol), $CH_2Cl_2$ (5 mL). [b]Reaction performed in gram scale using **1a** (10 mmol).

initial condensation of two molecules of **1a** before reacting with the alcohol is also a possible alternative.

Based on this rationale, we decided to further investigate the reaction toward C-12 modified tryptanthrin derivatives **2**. By adjusting the amounts of the substrates (see Table S1), it was found that using a 2:1.5 mol ratio of **1a** and methanol gave the highest yield of the product **2a** (89%). The reaction in the presence of other organic bases including pyridine, imidazole, and diisopropylethylamine, however, failed to give **2a** as substantial amounts of starting material still remained. Several attempts to increase the yield of **2a** via extending reaction times, increasing the temperature, or changing the order of reagent addition also led to unsatisfactory results, while replacing $I_2$ with other halogenated additives including *N*-chlorosuccinimide, *N*-bromosuccinimide, and *N*-iodosuccinimide led to recovery of unreacted isatin.

Without further optimization of the reaction conditions, the scope and generality of the reaction were then examined with different isatins and alcohols. To determine the scope with regard to the nature of isatin precursors (see Figure S1), methanol was applied as a common nucleophile leading to aryl substituted methylisatoid derivatives. According to Scheme 2, both electronic and steric factors have strong influence on the outcome of the reaction. Isatins with electron-donating group (−Me, −OMe) on the C5, *para* to the nitrogen atom, reacted rapidly to provide the corresponding methyl esters **2b** and **2c** in high yields, whereas those bearing electron-withdrawing groups (−Br and −Cl) at the same position gave lower yields of **2d** and **2e** with some remaining isatin precursors even after


https://dx.doi.org/10.1021/acs.joc.0c02403
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prolonged reaction times (up to 24 h). Owning to the poor nucleophilicity of the aryl amido group, the electron-deficient 5-nitroisatin did not convert to the expected product **2f**. Likewise, the reaction of hindered 7-methylisatin gave rise to a complex mixture in which the expected product **2g** was not isolated. Surprisingly, the presence of $CF_3$ on the C4 of isatin exerts little effect on the yield of **2h**.

With the scope of the reaction with respect to the isatin structure determined, the effect of the type of alcohols on the formation of **2** was further investigated. As shown in Scheme 2, compounds **2i** and **2j** were afforded in high yields from primary alcohols having different carbon chain lengths. Benzyl alcohol and its derivatives also provided the corresponding hydroxy esters **2k**−**2p** in satisfactory yields. Adding an electron-donating −OMe group to the benzene ring of the alcohol led to an increased yield of **2l**, whereas the presence of a strong electron-withdrawing nitro group lowered the yield of **2o**. Cinnamyl alcohol having an $\alpha,\beta$-unsaturated moiety is also a viable substrate giving the product **2q** in moderate yield. Sterically hindered secondary alcohols such as cyclohexanol and 2-propanol are well tolerated providing the corresponding esters **2r** and **2s** in reasonable yields. However, no reaction toward **2t** was observed when using the bulkier *tert*-butanol. In this case, competitive formation of tryptanthrin **3a** was clearly observed.

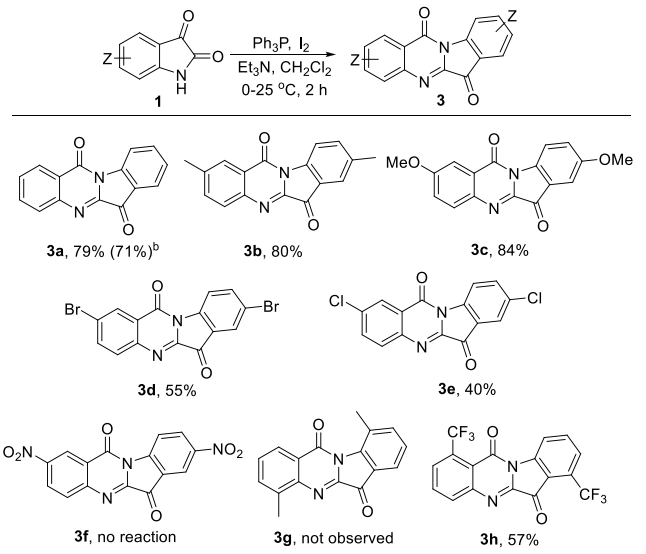
Nevertheless, other more interesting substrates including 8-hydroxyquinoline, a metal chelator with antimicrobial property,[23] eugenol with anticarcinogenic and antitumor actions,[24] and bioactive geraniol[25] gave rise to the corresponding products **2u**, **2v**, and **2w**, respectively, in moderate to good yields. Since drug combination has been proposed as a promising strategy to overcome monotherapy resistance,[26] modification of the tryptanthrin skeleton that would simultaneously provide two bioactive agents would render a great opportunity to achieve new potential drugs having additive and even synergistic properties.

Having successfully prepared methylisatoid derivatives, we then turned our attention to the reaction in the absence of alcohols. Based on the above results, formation of tryptanthrin side product became prominent when poorly nucleophilic alcohols were used. It is thus envisaged that the same reaction conditions without alcohol could be applied to synthesize tryptanthrin derivatives. Indeed, self-dimerization of isatins took place to afford tryptanthrin **3a** and its substituted analogs **3b**−**3h** in various yields (Scheme 3). In accordance with other studies,[13b,14a] the reaction is sensitive to both electronic and steric effects. While the self-condensation process toward **3g** is disfavored due to the presence of sterically hindered methyl group, electron-rich isatins react preferably to those electron-deficient substrates and the reaction toward **3f** failed when using the least reactive 5-nitroisatin.

To demonstrate the synthetic practicality of the reaction, gram-scale syntheses of methylisatoid (**2a**) and tryptanthrin (**3a**) were carried out using 10 mmol of isatin. The reaction proceeded smoothly to afford the desired products **2a** and **3a** in 75% and 71% yield, respectively. Moreover, with **2a** in hand, we then take this opportunity to synthesize the natural alkaloid cephalanthrin B (**4**) which was obtained in high yield through methylation of **2a** with methyl iodide (Scheme 4). Compound **4** showed identical NMR data with the reported literature for cephalanthrin B which was isolated in racemic form.[1b]

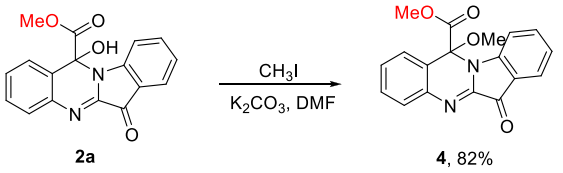
To better understand the reaction mechanism, control experiments were carried out as shown in Scheme 5. Since the

**Scheme 3. Synthesis of Tryptanthrin Derivatives**[a]




[a]Reaction conditions: **1** (0.68 mmol), $PPh_3$ (0.51 mmol), $I_2$ (0.51 mmol), $Et_3N$ (1.70 mmol), $CH_2Cl_2$ (5 mL). [b]Reaction performed in gram scale using **1a** (10 mmol).

**Scheme 4. Synthesis of 4 (Cephalanthrin B)**




ring-opening of isatins by alcohols could give rise to keto ester **5** which is a known precursor toward **2**,[20b,c] the reaction of isatin with methanol was examined in the absence of the $Ph_3P-I_2$ system. Based on Scheme 5a, no reaction was observed suggesting that **5** does not involve in our reaction. It is also well-known that the $Ph_3P-I_2$ reagent is a C−O bond activator, and the reaction should proceed via an initial activation of the tautomerizable amide of isatin. Indeed, using *N*-methylisatin as the substrate led to no reaction (Scheme 5b). When **2a** was subjected to the standard reaction conditions, only trace amount of **3a** was detected (Scheme 5c) indicating that formation of **3a** through hydrolysis and decarboxylation of **2a** did not occur. In addition, replacing methanol with water would theoretically yield the hydrolysate of methylisatoid. However, possibly due to its high reactivity, only the decarboxylated product **3a** was isolated albeit with low yield (Scheme 5d).

It is important to note that, although *O*-methylisatin (**A**) has been applied as a precursor toward methylisatoids,[20b,c] under our conditions, no evidence to support its presence could be found. Moreover, based on the $^{31}P\{^1H\}$ NMR study (Figure S2), triphenylphosphine oxide was the only species observed before adding alcohol, implying a self-dimerized adduct of isatin as the key intermediate. On the basis of the above observation and the previously reported literature,[13b,20b,c] the mechanism for the formation of **2** and **3** was thus proposed as depicted in Scheme 6.

The combination of $Ph_3P$ with $I_2$ provides reactive phosphonium species which react with isatin **1** to yield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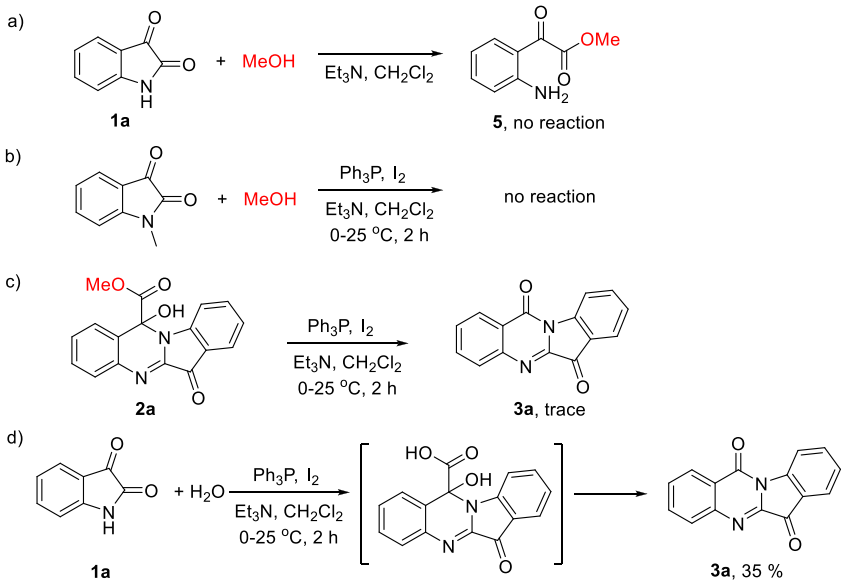
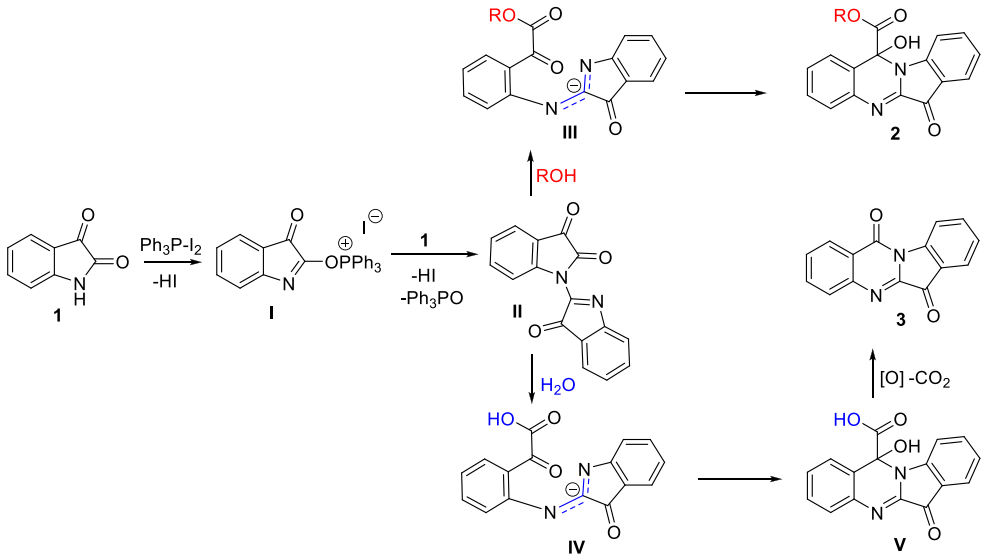
**Scheme 5. Control Experiments**




**Scheme 6. Proposed Mechanism**




intermediate **I**. Substitution with the amide NH of another molecule of isatin provides the dimerized adduct **II**. An alcohol attack at the lactam carbonyl of **II** produces the ring-opening intermediate **III** which upon further cyclization gives rise to the hydroxy ester **2**. In the absence of alcohol, **II** reacts with water, possibly from moist air, to yield **IV**. Oxidative decarboxylation of the cyclized intermediate **V** then furnishes tryptanthrin **3**.

In summary, this work represents the first concise and efficient synthesis of C12-modified tryptanthrin analogs using cheap and readily available isatins as precursors. This divergent approach not only provides an alternative route toward tryptanthrin framework but also enables a facile one-pot synthesis of methylisatoid and the hydroxy ester derivatives in good yields under mild conditions. Its broad substrate scope, operational simplicity, and easy scale-up make the protocol potentially useful for construction of novel indoloquinazoline derivatives inaccessible by the currently available methods.

## EXPERIMENTAL SECTION

**General Information.** All reagents including isatins **1a**-**1f** were purchased from Sigma-Aldrich or TCI and used without further purification. Compounds **1g**[27a] and **1h**[27b] were synthesized according to the reported procedures. All reactions were run in flame- or oven-dried glassware under $N_2$ gas. The reaction was monitored by thin-layer chromatography carried out on silica gel plates ($60F_{254}$, MERCK, Germany) and visualized under UV light (254 nm). Column chromatography was performed over silica gel 60 (70−230 mesh, MERCK, Germany). Melting points were determined using Mettler Toledo DSC equipment at a heating rate of 6 °C/min and are uncorrected. NMR spectra were recorded using a Bruker AVANCE (400 and 500 MHz for $^1$H). Chemical shifts were reported in parts per million (ppm, $\delta$) downfield from tetramethylsilane (TMS). Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qui), sextet (sex), septet (sep), multiplet (m), broad (br), doublet of doublets (dd), triplet of doublets (td), and doublet of doublet of doublets (ddd). High-resolution mass spectra


https://dx.doi.org/10.1021/acs.joc.0c02403
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(HRMS) were recorded using the Agilent 6546 LC/Q-TOF via the electrospray ionization (ESI).

*General Procedure for the Synthesis of Methylisatoid Derivatives* ***2***. To a solution of iodine (129 mg, 0.51 mmol) and triphenylphosphine (134 mg, 0.51 mmol) in freshly distilled dichloromethane (5 mL) were added isatins (0.68 mmol) at 0 °C under $N_2$. After addition of triethylamine (0.24 mL, 1.70 mmol) and stirring for 10 min, alcohol (0.51 mmol) was added, followed by warming up to room temperature with continuous stirring. After completion of the reaction, the crude mixture was concentrated under reduced pressure before purification by column chromatography (CC) using ethyl acetate/hexanes as the eluent.

Gram scale synthesis of **2a** was carried out as described above using **1a** (1.47 g, 10 mmol), iodine (1.9 g, 7.5 mmol), triphenylphosphine (1.97 g, 7.5 mmol), methanol (0.30 mL, 7.5 mmol), and triethylamine (3.5 mL, 25 mmol) in freshly distilled dichloromethane (50 mL) to provide **2a** in 1.16 g (75%).

*Methyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2,* ***2a****).* Orange solid (0.0932 g, 89% yield); mp 240−242 °C; $R_f$ 0.34 (40% EtOAc/hexanes); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.15 (s, 1H), 7.77 (d, $J$ = 7.6 Hz, 1H), 7.74 (t, $J$ = 7.6 Hz, 1H), 7.62 (d, $J$ = 7.6 Hz, 1H), 7.57−7.45 (m, 3H), 7.24 (t, $J$ = 7.6 Hz, 1H), 7.21 (d, $J$ = 7.6 Hz, 1H), 3.68 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ 184.4, 169.5, 149.5, 144.0, 140.0, 138.7, 131.3, 129.5, 128.9, 126.9, 125.9, 125.3, 124.0, 120.1, 113.1, 82.5, 54.1; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{17}H_{13}N_2O_4$ 309.0870, found 309.0870.

*Methyl 12-Hydroxy-2,8-dimethyl-6-oxo-6,12-dihydroindolo[2,1-b]quinazoline-12-carboxylate (Scheme 2,* ***2b****).* Yellow solid (0.093 g, 81% yield); mp 229−230 °C; $R_f$ 0.36 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.51 (s, 1H), 7.37 (d, $J$ = 8.5 Hz, 2H), 7.27 (s, 1H), 7.10 (d, $J$ = 8.5 Hz, 1H), 7.01 (d, $J$ = 8.5 Hz,1H), 5.44 (s, 1H), 3.72 (s, 3H), 2.37 (s, 6H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 183.7, 170.6, 146.9, 143.6, 139.6, 138.2, 137.3, 133.5, 131.9, 129.0, 126.3, 125.5,123.8, 120.6, 111.8, 81.9, 54.4, 21.4, 20.8; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{19}H_{17}N_2O_4$ 337.1183, found 337.1184.

*Methyl 12-Hydroxy-2,8-dimethoxy-6-oxo-6,12-dihydroindolo-[2,1-b]quinazoline-12-carboxylate (Scheme 2,* ***2c****).* Red oil (0.1089 g, 87% yield); $R_f$ 0.31 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.41 (d, $J$ = 8.5 Hz, 1H), 7.21 (s, 1H), 7.14 (d, $J$ = 8.5 Hz, 1H), 7.04 (d, $J$ = 8.5 Hz, 1H), 6.98 (s, 1H), 6.84 (d, $J$ = 8.5 Hz,1H), 5.44 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 183.6, 170.4, 160.3, 156.3, 143.2, 133.3, 130.6, 125.4, 125.0,121.3, 117.0, 113.2, 110.7, 108.3, 82.1, 55.9, 55.8, 54.4; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{19}H_{17}N_2O_6$ 369.1081, found 369.1082.

*Methyl 2,8-Dibromo-12-hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]quinazoline-12-carboxylate (Scheme 2,* ***2d****).* Orange solid (0.0901 g, 57% yield); mp 259−260 °C; $R_f$ 0.32 (40% EtOAc/hexanes); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.43 (s, 1H), 7.94 (d, $J$ = 2.0 Hz, 1H), 7.91 (dd, $J$ = 8.5, 2.0 Hz, 1H), 7.74 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.69 (d, $J$ = 2.5 Hz, 1H), 7.49 (d, $J$ = 8.5 Hz, 1H), 7.19 (d, $J$ = 8.5 Hz, 1H), 3.69 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, DMSO-$d_6$) $\delta$ 182.9, 168.8, 148.1, 144.0, 140.7, 139.3, 134.4, 130.9, 129.5, 127.79, 127.71, 121.93, 121.90, 116.2, 115.4, 82.3, 54.4; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{17}H_{11}{}^{79}Br_2N_2O_4$ 464.9080, found 464.9076, calcd for $C_{17}H_{11}{}^{81}Br_2N_2O_4$ 468.9040, found 468.9039.

*Methyl 2,8-Dichloro-12-hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]quinazoline-12-carboxylate (Scheme 2,* ***2e****).* Orange solid (0.0425 g, 33% yield); mp 257−258 °C; $R_f$ 0.35 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 2.0 Hz, 1H), 7.59 (d, $J$ = 2.5 Hz, 1H), 7.57−7.53 (m, 2H), 7.42 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.30 (s, 1H), 7.21 (d, $J$ = 8.5 Hz, 1H), 3.75 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 169.1, 147.4, 138.2, 137.3, 134.9, 131.3, 130.3, 129.7, 126.3, 125.2, 121.4, 113.9, 54.3; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{17}H_{11}{}^{35}Cl_2N_2O_4$ 377.0090, found 377.0091, calcd for $C_{17}H_{11}{}^{37}Cl_2N_2O_4$ 381.0030, found 381.0034.

*Methyl 12-Hydroxy-6-oxo-3,9-bis(trifluoromethyl)-6,12-dihydroindolo[2,1-b]quinazoline-12-carboxylate (Scheme 2,* ***2h****).* Yellow solid (0.0951 g, 63% yield); mp 230−231 °C; $R_f$ 0.32 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.87 (d, $J$ = 8.0 Hz, 1H), 7.82 (d, $J$ = 8.0 Hz, 1H), 7.76 (d, $J$ = 8.0 Hz, 1H), 7.71 (t, $J$ = 8.0 Hz, 1H), 7.59 (t, $J$ = 8.0 Hz, 1H), 7.47 (d, $J$ = 8.0 Hz, 1H), 5.39 (s, 1H), 3.73 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 179.6, 167.8, 149.8, 142.1, 142.0, 137.2, 134.1, 130.9, 128.7 (q, $^3J_{CF}$ = 6.25 Hz), 128.0 ((q, $^2J_{CF}$ = 36.25 Hz), 123.9 (q, $^1J_{CF}$ = 235.0 Hz), 122.3, 121.1 (q, $^3J_{CF}$ = 6.25 Hz), 118.3, 116.8, 83.0, 54.7; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{19}H_{11}F_6N_2O_4$ 445.0618, found 445.0618.

*Ethyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]quinazoline-12-carboxylate (Scheme 2,* ***2i****).* Orange solid (0.0933 g, 85% yield); mp 240−242 °C; $R_f$ 0.34 (40% EtOAc/hexanes); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.12 (s, 1H), 7.77 (d, $J$ = 7.5 Hz, 1H), 7.74 (t, $J$ = 7.5 Hz, 1H), 7.63 (d, $J$ = 7.5 Hz, 1H), 7.55−7.51 (m, 2H), 7.48−7.44 (m, 1H), 7.24 (d, $J$ = 7.5 Hz, 1H), 7.23 (t, $J$ = 7.5 Hz, 1H), 4.21−4.08 (m, 2H), 1.02 (t, $J$ = 7.0 Hz, 3H); $^{13}$C{$^1$H} NMR (125 MHz, DMSO-$d_6$) $\delta$ 184.5, 168.9, 149.7, 144.1, 140.1, 138.6, 131.2, 129.5, 128.9, 126.9, 126.1, 125.3, 124.0, 120.1, 113.2, 82.6, 62.9, 14.2; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{18}H_{15}N_2O_4$ 323.1026, found 323.1028.

*Butyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]quinazoline-12-carboxylate (Scheme 2,* ***2j****).* Red solid (0.0836 g, 70% yield); mp 171−173 °C; $R_f$ 0.42 (30% EtOAc/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69 (d, $J$ = 7.6 Hz, 1H), 7.58 (t, $J$ = 7.6 Hz, 1H), 7.51 (dd, $J$ = 7.6, 1.6 Hz, 1H), 7.43−7.40 (m, 1H), 7.33−7.21 (m, 2H), 7.18−7.14 (m, 2H), 5.84 (s, 1H), 4.20−4.06 (m, 2H), 1.41−1.34 (m, 2H), 0.99−0.89 (m, 2H), 0.65 (t, $J$ = 7.2 Hz, 4H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 183.5, 169.6, 149.0, 143.9, 139.4, 137.6, 130.9, 129.1, 128.9, 126.0, 125.4, 124.2, 123.7, 120.3, 112.4, 82.0, 67.5, 30.0, 18.5, 13.3; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{20}H_{19}N_2O_4$ 351.1339, found 351.1340.

*Benzyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]quinazoline-12-carboxylate (Scheme 2,* ***2k****).* Orange solid (0.1031 g, 79% yield); mp 175−177 °C; $R_f$ 0.32 (30% EtOAc/hexanes); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.22 (s, 1H), 7.76 (d, $J$ = 7.6 Hz, 1H), 7.65−7.49 (m, 5H), 7.45−7.42 (m, 1H), 7.26−7.17 (m, 5H), 7.05 (d, $J$ = 7.6 Hz, 2H), 5.19 (d, $J$ = 12.4 Hz, 1H), 5.13 (d, $J$ = 12.4 Hz, 1H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ 189.2, 173.4, 154.3, 148.9, 144.9, 143.3, 140.3, 136.1, 134.2, 133.7, 133.5, 133.4, 132.9, 131.7, 130.7, 130.0, 128.8, 128.0, 124.8, 118.1, 117.4, 87.6, 72.7; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{17}N_2O_4$ 385.1183, found 385.1185.

*4-Methoxybenzyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2,* ***2l****).* Orange solid (0.1211 g, 86% yield); mp 178−181 °C $R_f$ 0.37 (30% EtOAc/hexanes); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.16 (s, 1H), 7.75 (d, $J$ = 7.2 Hz, 1H), 7.64−7.53 (m, 4H), 7.45−7.41 (m, 1H), 7.21 (t, $J$ = 7.2 Hz, 1H), 7.12 (d, $J$ = 8.0 Hz, 1H), 7.03 (d, $J$ = 8.4 Hz, 2H), 6.77 (d, $J$ = 8.4 Hz, 2H), 5.14 (d, $J$ = 12.0 Hz, 1H), 5.05 (d, $J$ = 12.0 Hz, 1H), 3.72 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ 184.4, 168.7, 159.7, 149.5, 144.1, 140.1, 138.5, 131.2, 130.3, 129.4, 128.9, 127.4, 126.9, 126.0, 125.2, 123.9, 120.0, 114.1, 113.2, 82.7, 67.9, 55.5; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{24}H_{19}N_2O_5$ 415.1288, found 415.1289.

*4-Isopropylbenzyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2,* ***2m****).* Orange solid (0.1145 g, 79% yield); mp 190−192 °C; $R_f$ 0.36 (30% EtOAc/hexanes); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.19 (s, 1H), 7.75 (d, $J$ = 7.2 Hz, 1H), 7.61 (d, $J$ = 7.6 Hz, 2H), 7.54 (d, $J$ = 2.8 Hz, 2H), 7.46−7.42 (m, 1H), 7.21 (t, $J$ = 7.2 Hz, 1H), 7.15 (d, $J$ = 8.0 Hz, 1H), 7.09 (d, $J$ = 8.0 Hz, 2H), 6.99 (d, $J$ = 8.0 Hz, 2H), 5.17 (d, $J$ = 12.4 Hz, 1H), 5.08 (d, $J$ = 12.4 Hz, 1H), 2.83 (sep, $J$ = 7.2 Hz, 1H), 1.16 (d, $J$ = 7.2 Hz, 6H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ 184.4, 168.7, 149.6, 149.0, 144.1, 140.1, 138.5, 132.9, 131.3, 129.5, 128.9, 128.4, 127.0, 126.7, 126.0, 125.2, 124.0, 120.1, 113.3, 82.8, 68.0, 33.6, 24.3, 24.2; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{26}H_{23}N_2O_4$ 427.1652, found 427.1654.


https://dx.doi.org/10.1021/acs.joc.0c02403
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*4-Chlorobenzyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2, **2n**).* Orange solid (0.0821 g, 75% yield); mp 212−215 °C; $R_f$ 0.34 (30% EtOAc/hexanes); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.23 (s, 1H), 7.75 (dd, $J$ = 8.0, 1.2 Hz, 1H), 7.62 (t, $J$ = 8.0 Hz, 1H), 7.61 (d, $J$ = 7.6 Hz, 1H), 7.54 (d, $J$ = 7.6 Hz, 2H), 7.47−7.42 (m, 1H), 7.27 (d, $J$ = 8.4 Hz, 2H), 7.22 (t, $J$ = 7.6 Hz, 1H), 7.15 (d, $J$ = 8.0 Hz, 1H), 7.09 (d, $J$ = 8.4 Hz, 2H), 5.21 (d, $J$ = 12.4 Hz, 1H), 5.12 (d, $J$ = 12.4 Hz, 1H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ 184.4, 168.6, 149.5, 144.1, 140.1, 138.5, 134.5, 133.4, 131.3, 130.2, 129.5, 128.9, 128.8, 126.9, 125.9, 125.3, 124.0, 120.1, 113.2, 82.8, 67.2; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{16}{}^{35}ClN_2O_4$ 419.0793, found 419.0793, calcd for $C_{23}H_{16}{}^{37}ClN_2O_4$ 421.0763, found 421.0766.

*4-Nitrobenzyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2, **2o**).* Orange solid (0.0817 g, 56% yield); mp 205−207 °C; $R_f$ 0.30 (40% EtOAc/hexanes); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.30 (s, 1H), 8.06 (d, $J$ = 8.0 Hz, 2H), 7.77 (d, $J$ = 7.5 Hz, 1H), 7.64 (t, $J$ = 7.5 Hz, 1H), 7.63 (d, $J$ = 7.5 Hz, 1H), 7.56 (s, 2H), 7.49−7.46 (m, 1H), 7.32 (d, $J$ = 8.0 Hz, 2H), 7.22 (t, $J$ = 7.5 Hz, 1H), 7.18 (d, $J$ = 7.5 Hz, 1H), 5.35 (d, $J$ = 13.5 Hz, 1H), 5.27 (d, $J$ = 13.5 Hz, 1H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ 184.3, 168.5, 149.5, 147.6, 144.2, 143.1, 140.1, 138.5, 131.4, 129.6, 129.1, 129.0, 127.0, 125.8, 125.3, 124.0, 123.8, 120.1, 113.3, 82.8, 66.7; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{16}N_3O_6$ 430.1034, found 430.1034.

*3-Phenoxybenzyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2, **2p**).* Orange oil (0.1228 g, 76% yield); $R_f$ 0.36 (30% EtOAc/hexanes); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.25 (s, 1H), 7.73 (d, $J$ = 7.2 Hz, 1H), 7.64−7.56 (m, 2H), 7.55−7.50 (m, 2H), 7.41−7.35 (m, 3H), 7.24 (t, $J$ = 8.0 Hz, 1H), 7.21−7.13 (m, 3H), 6.93−6.84 (m, 3H), 6.73 (s, 1H), 5.19 (d, $J$ = 12.8 Hz, 1H), 5.12 (d, $J$ = 12.8 Hz, 1H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ 184.4, 168.6, 156.9, 156.8, 149.5, 144.1, 140.1, 138.9, 138.5, 137.7, 131.3, 130, 129.4, 128.9, 126.9, 125.8, 125.3, 124.0, 123.2, 120.1, 119.0, 118.9, 118.4, 113.2, 82.8, 67.5; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{29}H_{21}N_2O_5$ 477.1445, found 477.1446.

*Cinnamyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2, **2q**).* Yellow solid (0.0921 g, 66% yield); mp 197−198 °C; $R_f$ 0.30 (30% EtOAc/hexanes; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.23 (s, 1H), 7.77 (d, $J$ = 7.5 Hz, 1H), 7.68 (t, $J$ = 7.0 Hz, 2H), 7.58−7.53 (m, 2H), 7.49−7.45 (m, 1H), 7.34−7.26 (m, 6H), 7.21 (t, $J$ = 7.5 Hz, 1H), 6.37 (d, $J$ = 16.0 Hz, 1H), 6.18 (dt, $J$ = 16.0, 5.8 Hz, 1H), 4.80 (m, 2H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ 184.5, 168.6, 149.6, 144.1, 140.1, 138.5, 136.0, 133.5, 131.3, 129.5, 129.1, 129.0, 128.6, 127.0, 126.9, 126.0, 125.3, 124.0, 123.0, 120.1, 113.3, 82.7, 66.6; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{25}H_{19}N_2O_4$ 411.1339, found 411.1335.

*Cyclohexyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2, **2r**).* Orange oil (0.0832 g, 65% yield); $R_f$ 0.36 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 7.5 Hz, 1H), 7.59 (dd, $J$ = 7.5, 1.5 Hz, 1H), 7.57 (td, $J$ = 7.5, 1.5 Hz, 1H), 7.46 (dd, $J$ = 7.5, 1.5 Hz, 1H), 7.39 (td, $J$ = 7.5, 1.5 Hz, 1H), 7.34 (td, $J$ = 7.5, 1.5 Hz, 1H), 7.17 (t, $J$ = 7.5 Hz, 1H), 7.15 (d, $J$ = 7.5 Hz, 1H), 4.87−4.82 (m, 1H), 1.60−1.52 (m, 2H), 1.38−1.33 (m, 3H), 1.25−1.09 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 183.9, 169.5, 149.1, 144.0, 139.7, 137.5, 130.9, 129.3, 129.1, 125.52, 125.49, 124.4, 123.8, 120.5, 112.2, 82.0, 76.9, 30.8, 30.6, 24.8, 22.9; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{22}H_{21}N_2O_4$ 377.1496, found 377.1498.

*Isopropyl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2, **2s**).* Orange solid (0.0607 g, 53% yield); mp 205−207 °C; $R_f$ 0.34 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 7.5 Hz, 1H), 7.59−7.54 (m, 2H), 7.49−7.45 (m, 1H), 7.37−7.31 (m, 2H), 7.16 (t, $J$ = 7.5 Hz, 1H), 7.14 (d, $J$ = 7.5 Hz, 1H), 5.06 (sep, $J$ = 6.5 Hz, 1H), 1.06 (d, $J$ = 6.5 Hz, 2H), 1.01 (d, $J$ = 6.5 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 183.8, 169.5, 149.0, 143.9, 139.6, 137.5, 130.9, 129.2, 129.1, 125.6, 125.5, 124.3, 123.7, 120.4, 112.2, 81.9, 72.4, 21.3, 21.1; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{19}H_{17}N_2O_4$ 337.1183, found 337.1184.

*Quinolin-8-yl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]-quinazoline-12-carboxylate (Scheme 2, **2u**).* Orange solid (0.0818 g, 57% yield); mp 236−237 °C; $R_f$ 0.35 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.16 (dd, $J$ = 4.2, 1.5 Hz, 1H), 8.30 (dd, $J$ = 8.5, 1.5 Hz, 1H), 7.80 (ddd, $J$ = 7.5, 1.2, 1.0 Hz, 1H), 7.75 (d, $J$ = 7.5, 1H), 7.74 (d, $J$ = 8.5 Hz, 1H), 7.66 (dd, $J$ = 8.5, 4.5 Hz, 1H), 7.44−7.40 (m, 2H), 7.29−7.25 (m, 2H), 7.18 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.08 (td, $J$ = 7.5, 1.0 Hz, 1H), 6.74 (dd, $J$ = 8.0, 1.5 Hz, 1H), 6.27 (d, $J$ = 8.0 Hz, 1H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 183.2, 172.0, 152.3, 148.7, 148.4, 144.3, 139.0, 137.9, 136.7, 134.9, 131.0, 130.8, 130.6, 129.8, 126.6, 126.4, 125.9, 125.7, 123.8, 123.4, 121.3, 120.7, 110.3, 65.4; HRMS (ESI/QTOF) $m/z$ [M−OH]$^+$ calcd for $C_{25}H_{14}N_3O_3$ 404.1030, found 404.1030.

*4-Allyl-2-methoxyphenyl 12-Hydroxy-6-oxo-6,12-dihydroindolo-[2,1-b]quinazoline-12-carbo-xylate (Scheme 2, **2v**).* Orange solid (0.0466 g, 31% yield); mp 236−237 °C; $R_f$ 0.42 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.32 (s, 1H), 7.84 (td, $J$ = 8.0, 2.0 Hz, 1H), 7.81−7.78 (m, 2H), 7.61−7.54 (m, 3H), 7.44 (d, $J$ = 8.0 Hz, 1H), 7.28 (t, $J$ = 8.0 Hz, 1H), 6.90 (d, $J$ = 2.0 Hz, 1H), 6.79 (d, $J$ = 8.0 Hz, 1H), 6.72 (dd, $J$ = 8.0, 2.0 Hz, 1H), 5.97−5.89 (m, 1H), 5.09−5.03 (m, 2H), 3.52 (s, 3H), 3.33 (d, $J$ = 7.0 Hz, 2H); $^{13}$C{$^1$H} NMR (125 MHz, DMSO-$d_6$) $\delta$ 184.4, 167.1, 150.7, 149.5, 144.0, 140.1, 138.4, 137.7, 137.4, 131.4, 129.5, 129.0, 127.3, 125.7, 125.2, 124.1, 122.1, 120.8, 120.2, 116.6, 113.8, 113.6, 82.7, 55.9, 40.3; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{26}H_{21}N_2O_5$ 441.1445, found 441.1446.

*(E)-3,7-Dimethylocta-2,6-dien-1-yl 12-Hydroxy-6-oxo-6,12-dihydroindolo[2,1-b]quinazoline-12-carboxylate (Scheme 2, **2w**).* Yellow solid (0.1037 g, 71% yield); mp 104−105 °C; $R_f$ 0.32 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.74 (dd, $J$ = 7.5, 1.2 Hz, 1H), 7.57−7.54 (m, 2H), 7.46−7.44 (m, 1H), 7.37−7.31 (m, 2H), 7.16 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.11 (d, $J$ = 8.0 Hz, 1H), 5.39 (s, 1H), 5.09−5.06 (m, 1H), 4.99−4.95 (m, 1H), 4.69 (dd, $J$ = 12.0, 7.2 Hz, 1H), 4.58 (dd, $J$ = 12.0, 7.2 Hz, 1H), 1.94−1.89 (m, 2H), 1.87−1.83 (m, 2H), 1.65 (d, $J$ = 1.0 Hz, 3H), 1.55 (s, 3H), 1.45 (d, $J$ = 1.0 Hz, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 183.7, 170.0, 148.9, 145.3, 143.8, 139.6, 137.4, 132.0, 130.9, 129.2, 129.0, 125.8, 125.4, 124.2, 123.7, 123.4, 120.4, 116.2, 112.3, 81.9, 64.5, 39.3, 26.1, 25.7, 17.7, 16.4; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{26}H_{27}N_2O_4$ 431.1965, found 431.1966.

*General Procedure for the Synthesis of Tryptanthrins **3**.* To a solution of iodine (129 mg, 0.51 mmol) and triphenylphosphine (134 mg, 0.51 mmol) in freshly distilled dichloromethane (5 mL) were added isatins (0.68 mmol), followed by triethylamine (0.24 mL, 1.70 mmol) at 0 °C under $N_2$. The reaction mixture was allowed to warm up to room temperature with continuous stirring. After completion of the reaction, the crude mixture was concentrated under reduced pressure before purification by column chromatography (CC) using ethyl acetate/hexanes as the eluent. Gram scale synthesis of **3a** was carried out as described above using **1a** (1.47 g, 10 mmol), iodine (1.9 g, 7.5 mmol), triphenylphosphine (1.97 g, 7.5 mmol), and triethylamine (3.5 mL, 25 mmol) in freshly distilled dichloromethane (50 mL) to yield **3a** in 0.8815 g (71%).

*Indolo[2,1-b]quinazoline-6,12-dione (Tryptanthrin) (Scheme 3, **3a**).* Yellow solid (0.0667 g, 79% yield); mp 259−260 °C (lit.[14a] mp 260−262 °C); $R_f$ 0.36 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.62 (d, $J$ = 8.5 Hz, 1H), 8.44 (d, $J$ = 8.0 Hz, 1H), 8.03 (d, $J$ = 8.0 Hz, 1H), 7.92 (d, $J$ = 7.5 Hz, 1H), 7.85 (t, $J$ = 7.5 Hz, 1H), 7.79 (t, $J$ = 8.0 Hz, 1H), 7.67 (t, $J$ = 7.5 Hz, 1H), 7.43 (t, $J$ = 7.5 Hz, 1H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 182.6, 158.1, 146.6, 146.4, 144.3, 138.3, 135.2, 130.7, 130.3, 127.6, 127.2, 125.4, 123.8, 121.9, 118.0.

*2,8-Dimethylindolo[2,1-b]quinazoline-6,12-dione (Scheme 3, **3b**).* Yellow solid (0.0752 g, 80% yield); mp 248−250 °C (lit.[11b] mp 249.8−251.6 °C); $R_f$ 0.40 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.48 (d, $J$ = 8.0 Hz, 1H), 8.21 (d, $J$ = 2.0 Hz, 1H), 7.90 (d, $J$ = 8.0 Hz, 1H), 7.69 (d, $J$ = 2.0 Hz, 1H), 7.64 (dd, $J$ = 8.0,


https://dx.doi.org/10.1021/acs.joc.0c02403
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2.0 Hz, 1H), 7.57 (dd, $J$ = 8.0, 2.0 Hz, 1H), 2.55 (s, 3H), 2.45 (s, 3H).

*2,8-Dimethoxyindolo[2,1-b]quinazoline-6,12-dione (Scheme 3, **3c**).* Yellow solid (0.0883 g, 84% yield); mp 284−285 °C (lit.[18] mp 285−288 °C); $R_f$ 0.39 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.51 (d, $J$ = 9.0 Hz, 1H), 7.93 (d, $J$ = 9.0 Hz, 1H), 7.81 (d, $J$ = 3.0 Hz, 1H), 7.38 (dd, $J$ = 9.0, 3.0 Hz, 1H), 7.37 (d, $J$ = 3.0 Hz, 1H), 7.30 (dd, $J$ = 9.0, 3.0 Hz, 1H), 3.99 (s, 3H), 3.89 (s, 3H).

*2,8-Dibromoindolo[2,1-b]quinazoline-6,12-dione (Scheme 3, **3d**).* Yellow solid (0.0762 g, 55% yield); mp 317−319 °C (lit.[13b] mp 319−320 °C); $R_f$ 0.39 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$+$CD_3OD$ 4 drops) $\delta$ 8.50 (d, $J$ = 2.5 Hz, 1H), 8.45 (d, $J$ = 8.5 Hz, 1H), 7.98 (d, $J$ = 2.0 Hz, 1H), 7.91 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.87 (dd, $J$ = 8.5, 2.0 Hz, 1H), 7.83 (d, $J$ = 8.5 Hz, 1H).

*2,8-Dichloroindolo[2,1-b]quinazoline-6,12-dione (Scheme 3, **3e**).* Yellow solid (0.0432 g, 40% yield); mp 288−290 °C (lit.[18] mp 289−291 °C); $R_f$ 0.39 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.53 (d, $J$ = 8.5 Hz, 1H), 8.35 (d, $J$ = 2.5 Hz, 1H), 7.93 (d, $J$ = 8.5 Hz, 1H), 7.84 (d, $J$ = 2.0 Hz, 1H), 7.78 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.73 (dd, $J$ = 8.5, 2.0 Hz, 1H).

*3,9-Bis(trifluoromethyl)indolo[2,1-b]quinazoline-6,12-dione (Scheme 3, **3h**).* Orange solid (0.0744 g, 57% yield); mp 240−242 °C; $R_f$ 0.34 (40% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.03 (d, $J$ = 8.0 Hz, 1H), 8.27 (d, $J$ = 8.0 Hz, 1H), 8.10 (d, $J$ = 8.0 Hz, 1H), 7.96 (t, $J$ = 8.0 Hz, 1H), 7.92 (t, $J$ = 8.0 Hz, 1H), 7.74 (d, $J$ = 8.0 Hz, 1H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 179.6, 167.8, 149.8, 142.08, 142.02, 137.2, 134.1, 130.9, 128.7 (q, $^3J_{CF}$ = 6.25 Hz), 128.0 (q, $^2J_{CF}$ = 33.75 Hz), 122.9 (q, $^1J_{CF}$ = 233.75 Hz), 122.3, 121.1 (q, $^3J_{CF}$ = 6.25 Hz), 118.3, 116.8, 83.0, 54.7; HRMS (ESI/QTOF) $m/z$ [M + H]$^+$ calcd for $C_{17}H_7F_6N_2O_2$ 385.0406, found 385.0407.

*Synthesis of Methyl 12-Methoxy-6-oxo-6,12-dihydroindolo[2,1-b]quinazoline-12-carboxylate (Cephalanthrine B, Scheme 4, **4**).* To a solution of **2a** (105 mg, 0.34 mmol) in anhydrous DMF (3 mL) were added iodomethane (42 μL, 0.68 mmol) and potassium carbonate (94 mg, 0.68 mmol) at 0 °C. After warming up to room temperature, the reaction mixture was stirred for 2 h. The crude mixture was filtered washed with ethyl acetate. The organic layer was concentrated under reduced pressure before purification by column chromatography (CC) using ethyl acetate/hexanes as the eluent to provide compound **4** as a yellow solid (0.0898 g, 82% yield); mp 214−216 °C (lit.[1b] mp 215−217 °C); $R_f$ 0.41 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.83 (d, $J$ = 7.5 Hz, 1H), 7.72 (d, $J$ = 8.0 Hz, 1H), 7.63−7.59 (m, 2H), 7.52 (t, $J$ = 7.5 Hz, 1H), 7.42 (t, $J$ = 7.5 Hz, 1H), 7.24 (d, $J$ = 8.5 Hz, 1H), 7.21 (t, $J$ = 7.5 Hz, 1H), 3.71 (s, 3H), 3.07 (s, 3H); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta$ 184.0, 167.8, 148.9, 144.7, 141.9, 138.0, 131.5, 129.7, 129.4, 126.1, 125.5, 124.0, 120.5, 120.3, 112.3, 87.4, 53.8, 50.6.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02403.

Copies of $^1$H NMR, $^{13}$C{$^1$H} NMR spectra of all new products, optimization data, and $^{31}$P{$^1$H} NMR reaction monitoring study (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work is partially supported by Chiang Mai University, Thailand and The Thailand Research Fund through the Royal Golden Jubilee Ph.D. Program (Grant No. PHD/0072/2559 to N.W.).

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*J. Org. Chem.* XXXX, XXX, XXX−XXX