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# Synthesis of Phaitanthrin E and Tryptanthrin through Amination/Cyclization Cascade

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Phaitanthrin E was biomimetically synthesized from methyl indole-3-carboxylate and methyl anthranilate or anthranilic acid using the ester group as an activating group. The reaction proceeds through NCS-mediated dearomatization/TFA-catalyzed protonation of indolenine/C-2 amination/$Et_3N$-promoted aromatization and cyclization in one-pot procedure. This method is capable of converting simple biomass materials to phaitanthrin E. The synthesis not only allows assessment of antiproliferative activity, but also affords experimental support for the hypothetical biosynthetic pathway of phaitanthrin E. The resulting phaitanthrin E derivatives were evaluated for in-vitro antiproliferative activity against human colorectal cancer cells (DLD-1). The biogenetic intermediate of phaitanthrin E showed higher antiproliferative activity than the natural product, phaitanthrin E. Furthermore, a concise synthesis of tryptanthrin is also accomplished from indole-3-carbaldehyde and methyl anthranilate using the aldehyde group as an activating group.

Keywords: Biomimetic · Synthesis · Alkaloids · Cascade reaction· Indoles

## Introduction

Alkaloids with an indolo[2,1-*b*]quinazoline have attracted considerable interest because of their intriguing tetracyclic core and wide range of promising biological activities.[1-3] Phaitanthrins A (**1**), B (**2**), C (**3**), D (**4**), and E (**5aa**) were isolated from the Taiwanese orchid *Phaius mishmensi* by Wu and co-workers

(Figure 1a). [4] In these alkaloids, biological activity of **5aa** have not been systematically evaluated because only a limited amount of sample has been obtained from the natural source (2.0 mg of **5aa** was isolated from 3.5 kg of dried *P. mishmensis* plants). In 2015, Argade and co-workers reported the first pioneering synthesis of **5aa** through unusual rearrangement of **4** to **5aa**.[5] This synthesis is a milestone and useful, but the multi-step synthesis is not adequate for supply of sample materials with various substituents for biological assessments.

Recently, aromatic hydrocarbons, methyl indole-3-carboxylate (**6a**), methyl anthranilate (**7a**), and anthranilic acid (**8**), were also isolated from the *P. mishmensis* with phaitanthrins (Figure 1b).[6-7] These reports suggested that naturally occurring **5aa** is biogenetically derived from methyl indole-3-carboxylate and anthranilic acid. The biosynthesis of indoloquinazoline alkaloids, tryptanthrin (**10**), phaitanthrin A (**1**), B (**2**), and C (**3**), starting from tryptophan and anthranilic acid have been proposed (Scheme 1a).[4,8] In addition, the biogenetic pathway of phaitanthrin D (**4**) starting from anthranilic acid (**8**), *o*-aminophenylacetic acid (**9**), and glycolic acid was proposed by Argade and co-workers (Scheme 1b).[4, 9-10] However, the biosynthesis of **5aa** was not proposed to date among the phaitanthrins. On the basis of earlier studies[5, 9-10] and our previous work on the synthesis of tryptanthrin from simple biomass materials,[11-13] we next set out to synthesize phaitanthrin E (**5aa**) from simple biomass materials on the basis of the hypothetical biosynthetic pathway. In this paper, we report the full details of our approach to phaitanthrin E (**5aa**), as well as the biogenetic precursor of naturally occurring phaitanthrin E (**5aa**) (Scheme 1c).[14-15] Furthermore, the synthesized phaitanthrin E derivatives were evaluated for antiproliferative effects against human colorectal cancer cells (DLD-1), and were found to have promising anticancer properties competitive with the natural phaitanthrin E.

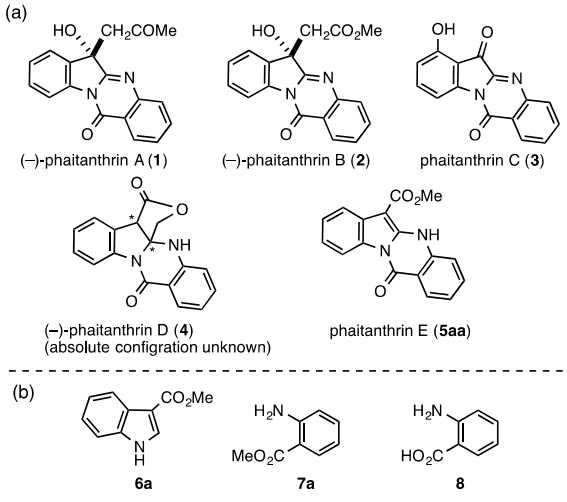
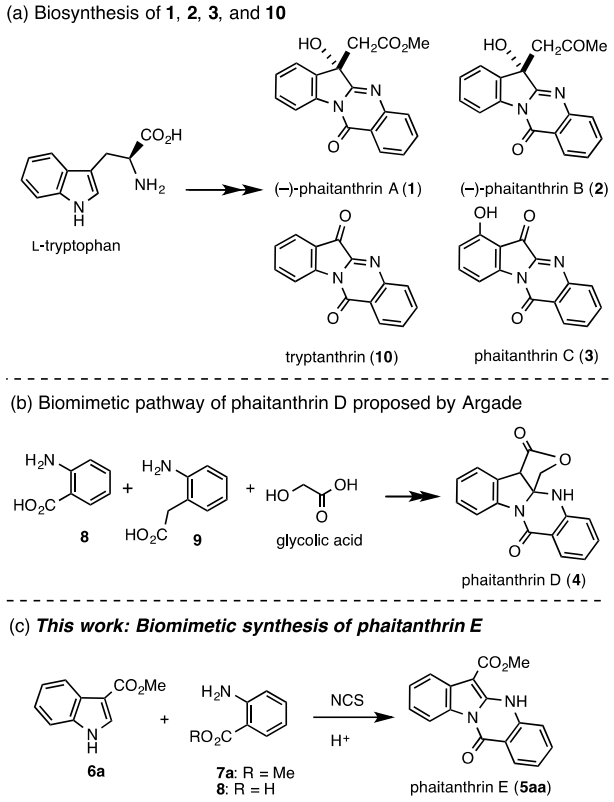



**Figure 1.** Phaitanthrins A-E and aromatic hydrocarbons.

## Results and Discussion

*Synthesis of Phaitanthrin E Derivatives via Acid-catalyzed Amination/Cyclization Cascade*

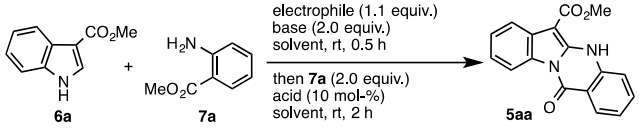
Anthranilate, renewable resource and simple biomass, is frequently used as biomimetic synthesis precursors. [16-18] Previous endeavors using anthranilates to obtain indoloquinazolines are a few and only limited to tryptanthrin (**10**). [19] Furthermore, the synthesis of phaitanthrin E through the reaction of renewable resources has yet to be developed. On the basis of evidence that methyl indole-3-carboxylate, methyl anthranilate, and phaitanthrin E were isolated from nature, we envisioned that these compounds would be possible precursors of phaitanthrin E.




**Scheme 1.** Plausible biogenetic pathway of indoloquinazoline alkaloids.

The cascade reaction play an important role in total synthesis and biogenesis. [20] Amination/cyclization on indole nitrogen could be the most rapid formation of polyheterocycles. However, the transformation remains challenging and the precedents is rare. In addition, the electrophilic C-2 selective reactions of indole have been limited to intramolecular reaction because of the high nucleophilicity at C-3 position of indole, which undergo C-2/C-3 dimerization. [21-

[24] In 2004, Herranz reported the the synthesis of tetracyclic heterocycle initiated by nitrile protonation of tryptophan-derived α-amino nitrile, which cascade sequence proceeded through intramolecular C-2 selective amination of indole ring, followed by intramolecular cyclization at nitrogen atom of indole ring. [25] Roche developed a double annulative cascade reaction of tryptophan-containing peptide triggered by the fluorine-mediated dearomatization of indoles (Scheme 1b). [26] This elegant cascade sequence is efficient to build the stereochemically dense tetracyclic α-carboline.



**Scheme 2.** Cascade reaction with **6a** and **7a**.

**Table 1.** Optimization of the reaction conditions.[a]

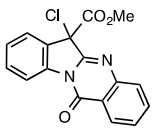
| Entry | Acid | $E^+$ | Base | Solvent | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | AcOH | NCS | $Et_3N$ | $CH_2Cl_2$ | 5 |
| 2 | $Et_3N$•HCl | NCS | $Et_3N$ | $CH_2Cl_2$ | 12 |
| 3 | HCl | NCS | $Et_3N$ | $CH_2Cl_2$ | 84 |
| 4 | $H_2SO_4$ | NCS | $Et_3N$ | $CH_2Cl_2$ | 82 |
| 5 | $HNO_3$ | NCS | $Et_3N$ | $CH_2Cl_2$ | 60 |
| 6 | $H_3PO_4$ | NCS | $Et_3N$ | $CH_2Cl_2$ | 46 |
| 7 | $HClO_4$ | NCS | $Et_3N$ | $CH_2Cl_2$ | 70 |
| 8 | $MeSO_3H$ | NCS | $Et_3N$ | $CH_2Cl_2$ | 55 |
| 9 | $CCl_3CO_2H$ | NCS | $Et_3N$ | $CH_2Cl_2$ | 52 |
| ***10*** | ***TFA*** | ***NCS*** | ***$Et_3N$*** | ***$CH_2Cl_2$*** | ***90*** |
| 11 | TFA | NFSI | $Et_3N$ | $CH_2Cl_2$ | 0 |
| 12 | TFA | NBS | $Et_3N$ | $CH_2Cl_2$ | 0 |
| 13 | TFA | NIS | $Et_3N$ | $CH_2Cl_2$ | 0 |
| 14 | TFA | NCS | pyridine | $CH_2Cl_2$ | 0 |
| 15 | TFA | NCS | DMAP | $CH_2Cl_2$ | 0 |
| 16 | TFA | NCS | $iPr_2NEt$ | $CH_2Cl_2$ | 8 |
| 17 | TFA | NCS | $Et_2NH$ | $CH_2Cl_2$ | 0 |
| 18 | TFA | NCS | DABCO | $CH_2Cl_2$ | 74 |
| 19 | TFA | NCS | DBU | $CH_2Cl_2$ | 45 |
| 20 | TFA | NCS | NaOH | $CH_2Cl_2$ | 0 |
| 21 | TFA | NCS | $K_2CO_3$ | $CH_2Cl_2$ | 5 |
| 22 | TFA | NCS | $Et_3N$ | $CHCl_3$ | 84 |
| 23 | TFA | NCS | $Et_3N$ | DMF | 6 |
| 24 | TFA | NCS | $Et_3N$ | MeCN | 70 |
| 25 | TFA | NCS | $Et_3N$ | THF | 0 |
| 26 | ----- | NCS | $Et_3N$ | $CH_2Cl_2$ | 0[c] |
| 27 | TFA | ---- | $Et_3N$ | $CH_2Cl_2$ | 0 |
| 28 | TFA | NCS | ------ | $CH_2Cl_2$ | 0[d] |

[a] Reaction conditions: **6a** (1 mmol), **7a** (2 mmol), acid (10 mol-%), electrophile (1.1 mmol), and base (2 mmol) in solvent (10 mL). [b] Isolated yield. [c] Compound **11** was obtained in 45% yield. [d] Compound **11** was obtained in 24% yield.

For our initial investigation, we chose indole-3-carboxylate (**6a**) and methyl anthranilate (**7a**) (Scheme 2 and Table 1). We were pleased to find that a combination of NCS (1.1 equiv.) and $Et_3N$ (2.0 equiv.) in $CH_2Cl_2$ in the presence of AcOH (10 mol-%) could be used to form phaitanthrin E (**5aa**) in 5% yield (Table 1, Entry 1). An acid catalyst screening showed that TFA is better than other catalysts such as AcOH, $Et_3N$·HCl, conc.HCl, conc.$H_2SO_4$, $HNO_3$, $H_3PO_4$, $HClO_4$, $MeSO_3H$, and $CCl_3CO_2H$ (Table 1, Entries 2-10).

Interestingly, replacing NCS with *N*-fluorobenzenesulfonamide (NFSI), NBS, or NIS resulted in no product (Table 1, Entries 11-13). In the case of NBS, indole-3-carboxylate acts as an efficient bromine source in the combination of NBS.[27] Therefore, substrate **6a** acts as a bromine source, resulting no reaction. After screening of bases such as $Et_3N$, pyridine, DMAP, $iPr_2NEt$, DABCO, DBU, NaOH and $K_2CO_3$, $Et_3N$ was found to show the highest reactivity (Table 1, Entries 14-21). Because the acid catalyst was neutralized, this cascade reaction did not proceed in the presence of inorganic bases such as NaOH or $K_2CO_3$. In contrast, organic bases would form the ammonium salts, which might act as a catalyst releasing acid. Changing the solvent to $CHCl_3$, DMF, MeCN, and THF failed to improve the yields (Table 1, Entries 22-25).

Next, some control experiments were conducted. In the absence of NCS, no product was obtained (Table 1, Entry 27). However, the byproduct **11** (Figure 2) was obtained as the sole product without the use of TFA or $Et_3N$ (Table 1, Entries 26 and 28). These results strongly suggest that the combined use of TFA, NCS, and $Et_3N$ is necessary to operate this cascade (Table 1, Entries 26-28). Finally, the optimal reaction conditions were TFA (10 mol-%), NCS (1.1 equiv.), $Et_3N$ (2.0 equiv.) in $CH_2Cl_2$; this afforded phaitanthrin E (**5aa**) in 90% yield (Table 1, Entry 10).



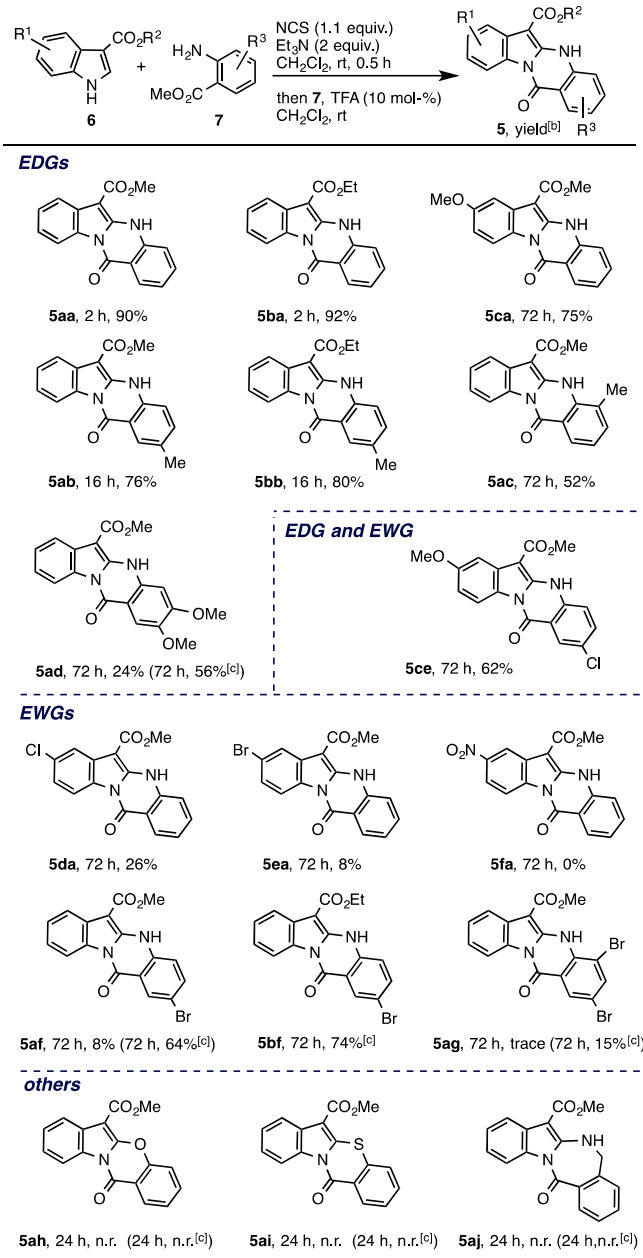

**11**

**Figure 2.** Structure of undesired product **11**.

We investigated the scope of the new cascade reaction using the optimized reaction conditions (Scheme 3). The reaction worked well with electron-donating groups (EDG) such as methoxy (**5ca**), methyl (**5ab**, **5bb**, and **5ac**), and dimethoxy (**5ad**) including ethyl ester (**5ba** and **5bb**). In case of methyl 4,5-

dimethoxyanthranilate, byproduct **12ad** (Figure 3) was obtained in 43% yield along with **5ad** in 24% yield. A combination of EDG and electron-withdrawing group (EWG) afforded the corresponding compound **5ce** in 62% yield.

The cascade reaction of electron-deficient substrates afforded the corresponding products in low yields. For example, **5af** was isolated in 8% yield along with byproduct **12af** (Figure 3) in 70% yield. We detected no product (**5fa**) or a trace amount of product (**5ag**) using methyl 5-nitroindole-3-carboxylate or methyl 3,5-dibromoanthranilate, respectively. In these cases, the corresponding 2-aminated products were observed by $^1$H-NMR analysis of the crude products. These directly demonstrate that EWGs at indole ring or anthranilate inhibit the cyclization step. Hence, the lower yields obtained for electron-deficient substrates can be attributed to the low nucleophilicity at the cyclization step. To promote the cyclization step, an additional base was also investigated. When we used $K_2CO_3$ as an additional base, the yield of **5af** increased to 64%. Additionally, this method could improve the yield for methyl 4,5-dimethoxyanthranilate (**5ad**: 56%) and methyl 3,5-dibromoanthranilate (**5ag**: 15% yield). For both electron-rich and -deficient subatrates, the cyclization step can be considered the rate-limiting step for this cascade reaction.




**Scheme 3.** Substrate scope and limitation.[a] [a] Reaction conditions: **6** (3 mmol), **7** (6 mmol), TFA (10 mol-%), NCS (3.3 mmol), and $Et_3N$ (6 mmol) in $CH_2Cl_2$ (25 mL). [b] Isolated yield. [c] $K_2CO_3$ was added to the mixture at rt, and the mixture was stirred for 16 h.

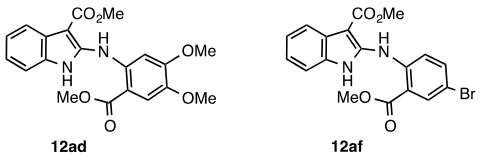
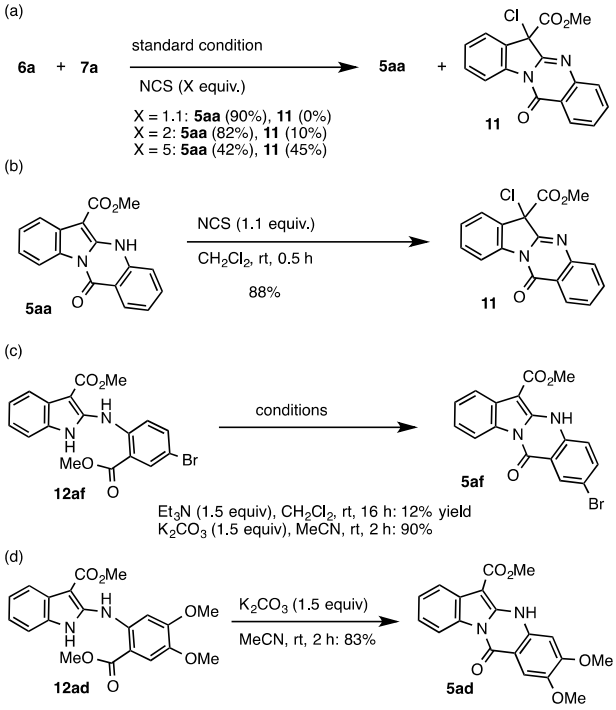



**Figure 3.** Major byproducts.

To broaden the scope of nucleophile, other nucleophiles such as methyl salicylate, methyl thiosalicylate, and methyl 2-aminomethylbenzoate were also attempted (**5ah**, **5ai**, and **5aj**). However, no desired product was observed. Aniline is important in the bond-forming processes of the initial nucleophilic attack at C-2 position of the indole ring in this cascade reaction.

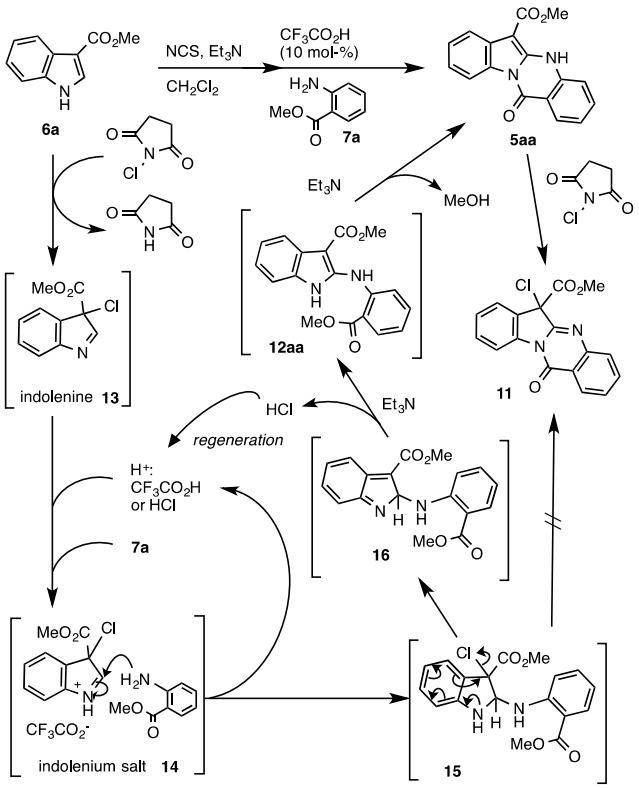
To gain mechanistic insight, we first investigated the effects of an amount of NCS (Scheme 4). Increasing NCS resulted in lower yields due to chlorination side product **11** (Scheme 4a). Considering that byproduct **11** was possibly derived from **5aa**, we then examined the reaction between **5aa** and NCS (Scheme 4b); only **11** could be isolated in 88% yield. These results suggest that **11** is not involved in the catalytic cycle of this cascade reaction but is derived from the final compound **5aa**.

In Scheme 3, we found that an additional base could promote the cascade reaction. To access the reaction mechanism, we performed the cyclization of isolated intermediates **12af** (Scheme 4c). When $Et_3N$ and $K_2CO_3$ was used as a base, **12af** was cyclized in 12% and 92% yield, respectively. This method could also be applicable to the cyclization of **12ad** (Scheme 4d). These examples suggest that a very delicate balance of electronic and steric factors is important in the cyclization step involved in the cascade reaction.




**Scheme 4.** Mechanistic studies.

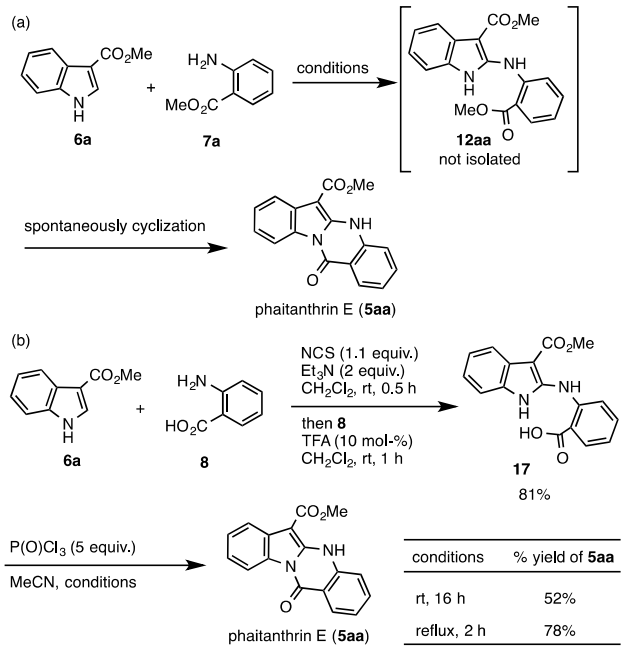
On the basis of the mechanistic investigations and literature precedents,[28-41] a plausible reaction mechanism is outlined in Scheme 5. A 3-chloroindolenine**13** is generated in situ through dearomatization of **6a** by NCS.[28-35] This then protonated by acid catalyst, affording indolenium salt **14**,[36-39] which could increase the electrophilicity of C-2 of the indole ring.[40] Mannich-type reaction of methyl anthranilate lead to the formation of C-2 aminated intermediate **15**. The intermediate **15** undergoes aromatization with the release of HCl assisted by $Et_3N$ to give one of a biogenetic precursor **12aa** and regenerate the acid catalyst.[41] Finally, cyclization gives **5aa** with the release of MeOH. At this stage, the presence of excess NCS promotes the formation of the undesired product **11**. Additionally, **6a**[27] and anthranilate[42] possibly can act as a catalyst to enhance the electrophilicity of NCS thus accelerate the dearomatization of **6a**. Thus, **6a** is both a substrate and a catalyst in this cascade reaction; this is in sharp contrast with previously reported reactions with indoles between indoles and anthranilates.




**Scheme 5.** Plausible mechanism

*Synthesis of Biogenetic Intermediate of Phaitanthrin E*

With the aim to confirm the biogenetic synthesis of phaitanthrin E, synthesis of biogenetic intermediate **12aa** was conducted (Scheme 6). In contrast to isolation of **12ad** and **12af**, the intermediate **12aa** could not be isolated under various conditions (Scheme 6a). These indicate that the cyclization of **12aa** spontaneously proceeds. In order to delay the cyclization, we selected anthranilic acid (**8**) as a substrate and performed the reaction instead of **7a** under the standard condition (Scheme 6b). Expectedly, the reaction stopped at the cyclization step and a possible biogenetic intermediate **17** could be obtained in 81% yield. Besides, **17** could be cyclized to provide **5aa** in 78% yield via dehydration using $P(O)Cl_3$.

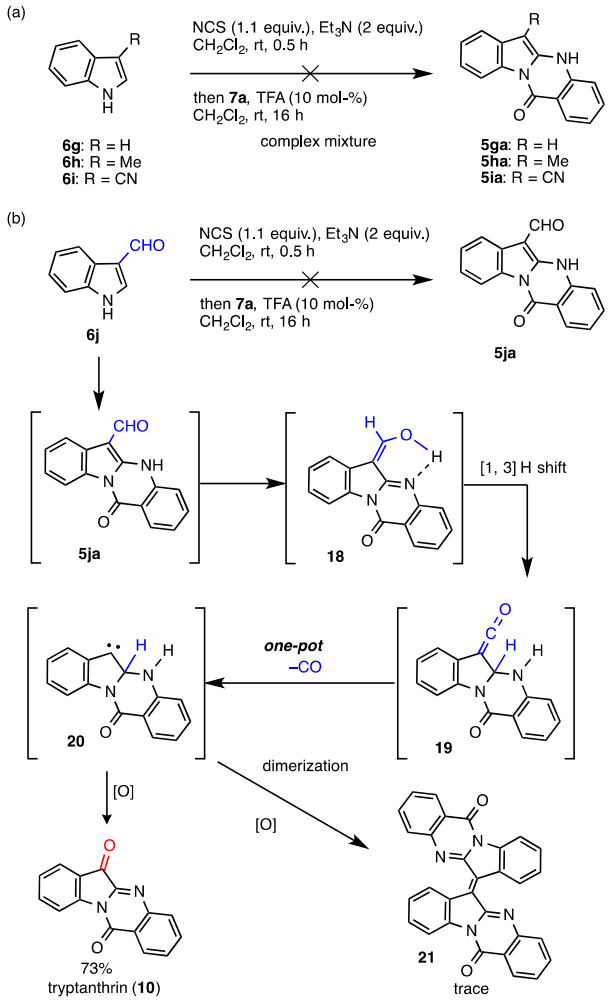



**Scheme 6.** Isolation of plausible biogenetic intermediate **17**.

*Synthesis of Tryptanthrin via Amination/Cyclization Cascade*

Following success with indole-3-carboxylate, we sought to expand the cascade reaction to include alternative heterocyclic cores (Scheme 7). The reactions with **6g**, **6h**, and **6i** produced neither **5** nor 2-aminated products, while only complex mixtures were afforded (Scheme 7a). These experiments mean that the ester acts as an activating group against this cascade sequence. Surprisingly, indole-3-carbaldehyde (**6j**) was amenable to the reaction conditions, and without further optimization afforded tryptanthrin (**10**) in 73% yield and a trace amount of violet dimer **21**, although the expected **5ja** could not be obtained (Scheme 7b). On the basis of previous investigations,[43-44, 48] we propose a mechanism for this transformation. First, **6j** reacts with **7a** to produce **5ja**. Then, intermediate **18** forms through keto-enol tautomerization.[10] Subsequently, 1,3-hydrogen shift of

formyl hydrogen to iminic carbon in **18** occurred to produce a ketene intermediate **19**.[43] An ejection of carbon monoxide and subsequent oxidation of **20** could afford the deformylative product **10**.[44] Although the aldehyde group is removable under mild reaction conditions,[45-47] the aldehyde group herein could act as an activating group to promote 2-amination/cyclization.[48] The violet dimer **21**[49] would be formed via dimerization of the carbene intermediate **20**. This result suggests that the removal of aldehyde group proceeds through 1,3-hydrogen shift mechanism. The details are not clear and are under investigations.




**Scheme 7.** Unexpected synthesis of **10** using the aldehyde group as an activating group.

## *Antiproliferative Activity*

Finally, the synthesized phaitanthrin E derivatives were tested for antiproliferative activity against human colorectal cancer (CRC) cells (DLD-1) by an WST-1 assay.[50] Due to their solubility issue, four compounds, **5aa**, **17**, **5ab** and **5af**, were selected for the biological experiments. Four compounds were tested at a

range of 0.1 to 100 μmol/L with regard to their antiproliferative effects in human CRC DLD-1 cells.

Significant suppression of the proliferation rates by both compound **17** and **5af** after 20 h was observed (Figure 4). The vehicle (DMSO, control) alone showed no effect on the cell proliferation. $IC_{50}$ values of **5aa**, **17**, **5ab** and **5af** were >100, 34.0, 85.5, and 32.5 μmol/L, respectively (Table 2, Entries 1-4). Thus, the biogenetic intermediate **17** showed higher antiproliferative activity than the natural product, phaitanthrin E (**5aa**) (Table 2, Entries 1-2). Furthermore, compounds with electro-withdrawing substituent was found to show promising inhibitory activity against human CRC DLD-1 cells (Table 2, Entries 3-4). These results suggest that phaitanthrin E derivatives represent a new class of powerful inhibitors against human cancer cells.

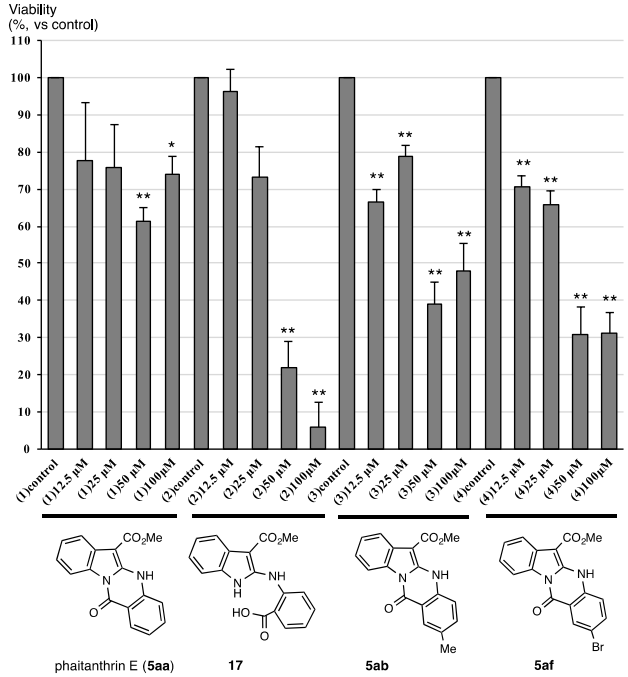



**Figure 4.** Antiproliferative effects by 4 compounds in human colorectal cancer cells (DLD-1).[a] [a] DLD-1 cells cultured in 24-well plastic plates were tested with two compounds for 20 h. The cell proliferation was evaluated by water-soluble tetrazolium salt (WST)-1 assay. Means ± standard error (SE), n = 3. **P*<0.05 and ***P*<0.01 vs control cells.

**Table 2.** $IC_{50}$ value of phaitanthrin E derivatives.[a]

| Entry | Compound | $IC_{50}$ [μM] |
|---|---|---|
| 1 | **5aa** | >100 |
| 2 | **17** | 34.0 |
| 3 | **5ab** | 85.5 |
| 4 | **5af** | 32.5 |

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

## Conclusion

In conclusion, we have developed a novel cascade reaction of indole-3-carboxylates via the ester group as an activating group, where simple biomass materials undergo 2-amination/cyclization cascade to afford phaitanthrin E derivatives. This method is reliable and broadly applicable to large variety of substrates. To elucidate

the usefulness of the cascade reaction developed herein, a concise synthesis of tryptanthrin is also accomplished via the aldehyde group as an activating group. In addition, four compounds were tested for in vitro antiproliferative activity against human colorectal cancer (CRC) cells (DLD-1). A possible biogenetic intermediate **17** and bromo-substituted phaitanthrin E **5af** were found to show better suppression of the proliferation rates than phaitanthrin E.

## Experimental Section

*Typical procedure A for the synthesis of **5aa**, **5ba**, **5ca**, **5ab**, **5bb**, **5ac**, **5ad**, **5ce**, **5da**, **5ea**, and **5af***

NCS (441 mg, 3.3 mmol) was added to a solution of **6a** (526 mg, 3 mmol) and $Et_3N$ (0.84 mL, 6 mmol) in $CH_2Cl_2$ (25 mL) at room temperature, and the mixture was stirred at room temperature. After 0.5 h, anthranilic acid methyl ester **7a** (907 mg, 6 mmol) and trifluoroacetic acid (22 μL, 0.3 mmol) in $CH_2Cl_2$ (5 mL) was dropwise added to the reaction mixtures and the mixture was stirred at room temperature. After 2 h, the mixture was added to 10% NaOH solution at 0 °C, extracted with AcOEt (150 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (3/1) to give **5aa** (791 mg, 90% yield).

*Typical procedure B for the synthesis of **5ad**, **5af**, **5bf** and **5ag***

NCS (3.3 mmol) was added to a solution of **6a** (3 mmol) and $Et_3N$ (0.84 mL, 6 mmol) in $CH_2Cl_2$ (25 mL) at room temperature, and the mixture was stirred at room temperature. After 0.5 h, 5-bromoanthranilic acid methyl ester **11c** (1.38 g, 6 mmol) and trifluoroacetic acid (22 μL, 0.3 mmol) in $CH_2Cl_2$ (10 mL) was dropwise added to the reaction mixtures and the mixture was stirred at room temperature. After 72 h, $K_2CO_3$ (829 mg, 6 mmol) was portionwise added to the mixture at room temperature, and stirred at room temperature. After 16 h, the mixture was added to $H_2O$ at 0 °C, extracted with AcOEt (150 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (3/1) to give **5ac** (715 mg, 64% yield).

**Phaitanthrin E (5aa).** An amorphous white powder (791 mg, 90% yield). M.p. 214 – 216 °C. FT-IR ($CHCl_3$): 3329, 1697, 1665, 1626, 1579. $^1$H-NMR (500 MHz, $CDCl_3$): 10.29 (br s, 1H); 8.70 (d, *J* = 8.0 Hz, 1H); 8.39 (d, *J* = 8.0 Hz, 1H); 7.94 (d, *J* = 8.0 Hz, 1H); 7.71 (td, *J* = 1.7, 7.7 Hz, 1H); 7.43 (td, *J* = 1.2, 8.0 Hz, 1H); 7.30-7.34 (m, 2H); 7.28 (d, *J* = 8.6 Hz, 1H); 4.01 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 167.3; 158.5; 144.1; 138.2; 135.3; 130.4; 128.7; 126.3; 125.7; 123.2; 122.4; 119.4; 116.3; 115.7; 114.4; 86.7; 51.4. ESI-HR-MS (pos.): 293.0926 ($C_{17}H_{13}N_2O_3^+$, [*M* + H]$^+$; calc. 293.0926).

**Ethyl 12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5ba).** An amorphous white powder **(**845 mg, 92% yield). M.p. 182 – 183 °C. FT-IR ($CHCl_3$): 3327, 1697, 1660, 1625, 1579. $^1$H-NMR (500 MHz, $CDCl_3$): 10.32 (br s, 1H); 8.71 (d, *J* = 8.0 Hz, 1H); 8.39 (d, *J* = 8.0 Hz, 1H); 7.96 (d, *J* = 8.0 Hz, 1H); 7.71 (t, *J* = 8.6 Hz, 1H); 7.44 (t, *J* = 7.5 Hz, 1H); 7.32 (t, *J* = 7.5 Hz, 2H); 7.27 (d, *J* = 8.0 Hz, 1H); 4.47 (dd, *J* = 6.9, 14.3 Hz, 2H);1.51 (t, *J* = 6.9 Hz, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 167.1; 158.6; 144.1; 138.2; 135.3; 130.4; 128.7; 126.4; 125.7; 123.1; 122.4; 119.5; 116.3; 115.7; 114.3; 86.9; 60.3; 14.7. ESI-HR-MS (pos.): 329.0898 ($C_{18}H_{14}N_2NaO_3^+$, [*M* + Na]$^+$; calcd. 329.0902).

**Methyl 8-methoxy-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5ca).** An amorphous white powder (724 mg, 75% yield). M.p. 234 – 235 °C. FT-IR ($CHCl_3$): 3325, 1689, 1625, 1579, 1529. $^1$H-NMR (500 MHz, [$D_6$]DMSO): 11.26 (br s, 1H); 8.49 (d, *J* = 8.6 Hz, 1H); 8.20 (d, *J* = 8.0 Hz, 1H); 7.95 (d, *J* = 8.6 Hz, 1H); 7.77 (t, *J* = 8.0 Hz, 1H); 7.46 (s, 1H); 7.33 (t, *J* = 7.5 Hz, 1H); 6.84 (d, *J* = 9.2 Hz, 1H); 3.91 (s, 3H); 3.82 (s, 3H). $^{13}$C -NMR (125 MHz, [$D_6$]DMSO): 165.2; 158.5; 158.0; 144.0; 139.7; 135.3; 128.8; 127.5; 124.6; 123.2; 118.0; 116.9; 113.9; 109.5; 103.4; 86.4; 55.9; 51.3. ESI-HR-MS (pos.): 345.0851 ($C_{18}H_{14}N_2NaO_3^+$, [*M* + Na]$^+$; calcd. 345.0851).

**Methyl 2-methyl-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5ab).** An amorphous white powder (698 mg, 76% yield). M.p. 216 – 218 °C. FT-IR ($CHCl_3$): 3332, 1697, 1662, 1620, 1577. $^1$H-NMR (500 MHz, $CDCl_3$): 10.25 (br s, 1H); 8.69 (d, *J* = 8.6 Hz, 1H); 8.19 (s, 1H); 7.95 (d, *J* = 7.5 Hz, 1H); 7.53 (dd, *J* = 1.2, 8.0 Hz, 1H); 7.43 (t, *J* = 7.5 Hz, 1H); 7.31 (td, *J* = 1.2, 8.1 Hz, 1H); 7.19 (d, *J* = 8.0 Hz, 1H); 4.01 (s, 3H); 2.47 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 167.4; 158.6; 144.3; 136.6; 136.1; 133.1; 130.4; 128.1; 126.4; 125.7; 122.3; 119.4; 116.3; 115.6; 114.2; 86.3; 51.3; 20.9. ESI-HR-MS (pos.): 306.1005 ($C_{18}H_{14}N_2O_3^+$, [*M*]$^+$; calcd. 306.1004).

**Ethyl 2-methyl-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5bb).** Pale yellow solids (768 mg, 80% yield). M.p. 194 – 195 °C. FT-IR ($CHCl_3$): 3329, 1691, 1658, 1620, 1577. $^1$H-NMR (500 MHz, $CDCl_3$): 10.25 (br s, 1H); 8.70 (d, *J* = 8.6 Hz, 1H); 8.16 (s, 1H); 7.94 (d, *J* = 8.0 Hz, 1H); 7.51 (dd, *J* = 1.8, 8.0 Hz, 1H); 7.42 (td, *J* = 1.1, 6.9 Hz, 1H); 7.30 (td, *J* = 1.2, 6.9 Hz, 1H); 7.16 (d, *J* = 8.6 Hz, 1H); 4.46 (dd, *J* = 7.4, 14.4 Hz, 2H); 2.46 (s, 3H); 1.50 (t, *J* = 6.9 Hz, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 167.1; 158.6; 144.2; 136.5; 136.1; 133.0; 130.4; 128.1; 126.5; 125.6; 122.2; 119.4; 116.3; 115.6; 114.1; 86.5; 60.2; 20.9; 14.7. ESI-HR-MS (pos.): 343.1062 ($C_{19}H_{16}N_2NaO_3^+$, [*M* + Na]$^+$; calcd. 343.1059).

**Methyl 4-methyl-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5ac).** An amorphous pale yellow powder (476 mg, 52% yield). M.p. 220 – 222 °C. FT-IR ($CHCl_3$): 3446, 3334, 1697, 1624. $^1$H-NMR (500 MHz, $CDCl_3$): 10.41 (br s, 1H); 8.70 (d, *J* = 8.1 Hz, 1H); 8.25 (d, *J* = 8.0 Hz, 1H); 7.93 (d, *J* = 6.3 Hz, 1H); 7.56 (d, *J* = 7.4 Hz, 1H); 7.42 (t, *J* = 8.0 Hz, 1H); 7.32 (t, *J* = 8.1 Hz, 1H); 7.23 (t, *J* = 8.0 Hz, 1H); 4.02 (s, 3H); 2.55 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 167.7; 158.8; 144.2; 136.9; 135.9; 130.3; 126.5; 125.7; 123.3; 122.7; 122.4; 119.4; 116.3; 114.2; 86.8; 51.4;16.4. ESI-HR-MS (pos.): 307.1077 ($C_{18}H_{15}N_2O_3^+$, [*M* + H]$^+$; calcd. 307.1083).

**Methyl 2,3-dimethoxy-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5ad).** An amorphous white powder **(**255 mg, 24% yield). M.p. 210 – 212 °C. FT-IR ($CHCl_3$): 3332, 1681, 1658, 1629, 1616. $^1$H-NMR (500 MHz, $CDCl_3$): 10.23 (br s, 1H); 8.69 (d, *J* = 8.0 Hz, 1H); 7.93 (d, *J* = 7.5 Hz, 1H); 7.69 (s, 1H); 7.42 (t, *J* = 8.0 Hz, 1H); 7.30 (t, *J* = 8.1 Hz, 1H); 6.66 (s, 1H); 4.00 (s, 3H); 3.99 (s, 3H); 3.97 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 167.4; 158.2; 155.9; 146.3; 144.2; 134.2; 130.2; 126.2; 125.5; 122.1; 119.3; 116.2; 107.9; 106.7; 97.5; 86.1; 56.5; 56.4; 51.3. ESI-HR-MS (pos.): 353.1141 ($C_{19}H_{17}N_2O_5^+$, [*M* + H]$^+$; calcd. 353.1137).

**Methyl 2-((4,5-dimethoxy-2-(methoxycarbonyl)phenyl)amino)-1*H*-indole-3-carboxylate (12ad).** An amorphous white powder (496 mg, 43% yield). M.p. 224 – 226 °C. FT-IR ($CHCl_3$): 3446, 1670, 1593, 1566. $^1$H-NMR (500 MHz, [$D_6$]DMSO): 11.65 (br s, 1H); 10.73 (br s, 1H); 7.67 (d, *J* = 8.0 Hz, 1H); 7.42 (s, 1H); 7.22 (d, *J* = 8.0 Hz, 1H); 7.17 (s, H); 7.03 (td, *J* = 1.2, 8.0 Hz, 1H); 6.98 (td, *J* = 1.2, 7.5 Hz, 1H); 3.88 (s, 3H); 3.83 (s, 3H); 3.81 (s, 3H); 3.78 (s, 3H). $^{13}$C-NMR (125 MHz, [$D_6$]DMSO): 166.9; 166.2; 154.3; 146.8; 143.9; 136.9; 133.3; 126.3; 121.7; 121.1; 119.2; 113.5; 111.5; 108.6; 103.2; 88.3; 56.4; 56.1; 52.6; 50.9. ESI-HR-MS (pos.): 407.1220 ($C_{20}H_{20}N_2NaO_6^+$, [*M* + Na]$^+$; calcd. 407.1219).

**Methyl 2-chloro-8-methoxy-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5ce).** An amorphous white powder (666 mg, 62% yield). M.p. 234 – 235 °C. FT-IR ($CHCl_3$): 3325, 1689, 1625, 1579, 1529. $^1$H-NMR (500 MHz, [$D_6$]DMSO): 11.39 (br s, 1H); 8.40 (d, *J* = 9.2 Hz, 1H); 8.05 (s, 1H); 7.93 (d, *J* = 9.2 Hz, 1H); 7.75 (d, *J* = 9.2 Hz, 1H); 7.39 (s, 1H); 6.78 (d, *J* = 8.6 Hz, 1H); 3.87 (s, 3H); 3.78 (s, 3H). $^{13}$C-NMR (125 MHz, [$D_6$]DMSO): 165.1; 158.1; 157.6; 144.4; 139.6; 134.8; 129.2; 126.6; 126.2; 124.4; 121.0; 116.8; 115.2; 109.3; 103.4; 86.7; 55.9; 51.2. ESI-HR-MS (pos.): 359.0613 ($C_{18}H_{14}ClN_2O_4^+$, [*M* + H]$^+$; calcd. 357.0642).

**Methyl 8-chloro-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5da)**. An amorphous white powder (258 mg, 26% yield). M.p. 286 – 289 °C. FT-IR ($CHCl_3$): 3332, 1697, 1662, 1620, 1577. $^1$H-NMR (500 MHz, [$D_6$]DMSO): 11.47 (br s, 1H); 8.58 (d, *J* = 8.6 Hz, 1H); 8.20 (dd, *J* = 1.2, 8.0 Hz, 1H); 8.00 (d, *J* = 8.6 Hz, 1H); 7.89 (d, *J* = 2.3 Hz, 1H); 7.79 (td, *J* = 1.8, 7.7 Hz, 1H); 7.35 (t, *J* = 8.0 Hz, 1H); 7.28 (dd, *J* = 2.3, 8.6 Hz, 1H); 3.91 (s, 3H). $^{13}$C-NMR(125 MHz, [$D_6$]DMSO): 164.9; 158.8; 144.7; 140.0; 135.7; 130.4; 129.2; 128.7; 127.7; 123.5; 121.7; 118.6; 118.3; 117.5; 114.1; 86.1; 51.4. ESI-HR-MS (pos.): 327.0545, 329.0516 ($C_{17}H_{12}ClN_2O_3^+$, [*M* + H]$^+$; calcd. 3270536, 329.0507).

**Methyl 8-bromo-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5ea).** An amorphous pale yellow powder (89 mg, 8% yield). M.p. 303 – 306 °C. FT-IR ($CHCl_3$): 3462, 1689. $^1$H-NMR (500 MHz, [$D_6$]DMSO): 11.47 (br s, 1H); 8.53 (d, *J* = 8.6 Hz, 1H); 8.20 (d, *J* = 8.0 Hz, 1H); 8.03 (d, *J* = 1.7 Hz, 1H); 8.00 (d, *J* = 8.6 Hz, 1H); 7.97 (t, *J* = 7.4 Hz, 1H); 7.79 (t, *J* = 9.2 Hz, 1H); 7.41 (dd, *J* = 2.3, 9.2 Hz, 1H); 7.34 (t, *J* = 7.5 Hz, 1H); 3.91 (s, 3H). $^{13}$C-NMR (125 MHz, [$D_6$]DMSO): 164.9; 158.9; 144.7; 135.6; 134.6; 129.6; 129.1; 127.5; 124.3; 123.4; 121.5; 118.6; 118.4; 117.8; 114.1; 85.9; 51.4. ESI-HR-MS (pos.): 369.9951, 371.9937 ($C_{17}H_{11}BrN_2O_3^+$, [*M*]$^+$; calcd. 369.9953, 371.9933).

**Methyl 2-bromo-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5af).** Yellow solids (92 mg, 8% yield). M.p. 240 – 242 °C. FT-IR ($CHCl_3$): 3325, 1730, 1697, 1625. $^1$H-NMR ([$D_6$]DMSO): 11.50 (br s, 1H); 8.59 (d, *J* = 8.1 Hz, 1H); 8.25 (d, *J* = 1.7 Hz, 1H); 7.97 (t, *J* = 9.2 Hz, 2H); 7.93 (dd, *J* = 2.3, 9.2 Hz, 1H); 7.41 (t, *J* = 8.0 Hz, 1H); 7.28 (t, *J* = 6.9 Hz, 1H); 3.91 (s, 3H). $^{13}$C-NMR ([$D_6$]DMSO): 165.2; 157.9; 143.4; 138.9; 138.0; 130.1; 129.4; 127.2; 125.9; 122.3; 120.4; 119.6; 116.1; 115.8; 114.7; 86.8; 51.5. ESI-HR-MS (pos.): 369.9949, 371.9935 ($C_{17}H_{11}BrN_2O_3^+$, [*M*]$^+$ calcd. 369.9953, 371.9933).

**Methyl 2-((4-bromo-2-(methoxycarbonyl)phenyl)amino)-1*H*-indole-3-carboxylate (12af).** An amorphous pale yellow powder (849 mg, 70% yield). M.p. 234 – 236 °C. FT-IR ($CHCl_3$): 3446, 1668, 1583. $^1$H-NMR (500 MHz, $CDCl_3$): 11.27 (br s, 1H); 8.38 (br s, 1H); 8.18 (d, *J* = 2.3 Hz, 1H); 7.90 (d, *J* = 7.5 Hz, 1H); 7.63 (dd, *J* = 1.7, 8.6 Hz, 1H); 7.49 (d, *J* = 8.6 Hz, 1H); 7.22 (d, *J* = 7.5 Hz, 1H); 7.19 (t, *J* = 7.5 Hz, 1H); 7.12 (t, *J* = 7.5 Hz, 1H); 3.98 (s, 3H); 3.96 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 166.8; 166.2; 145.1; 141.0; 137.3; 135.2; 131.6; 126.1; 122.4; 121.7; 120.1; 118.6; 118.0; 113.3; 110.2; 90.7; 52.8; 51.1. ESI-HR-MS (pos.): 425.0111, 427.0098 ($C_{18}H_{15}BrN_2NaO_4^+$, [*M* + Na]$^+$; calcd. 425.0113, 427.0092).

**Ethyl 2-bromo-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5bf)**. Yellow solids (858 mg, 74% yield). M.p. 320 – 323 °C. IR ($CHCl_3$): 3365, 1670, 1625. $^1$H-NMR (500 MHz, $CDCl_3$): 10.36 (br s, 1H); 8.69 (d, *J* = 8.0 Hz, 1H); 8.51 (d, *J* = 2.3 Hz, 1H); 7.97 (d, *J* = 8.0 Hz, 1H); 7.79 (dd, *J* = 2.3, 8.6 Hz, 1H); 7.45 (td, *J* = 1.2, 7.5 Hz, 1H); 7.34 (td, *J* = 1.2, 8.6 Hz, 1H); 7.18 (d, *J* = 9.2 Hz, 1H); 4.48 (dd, *J* = 6.9, 14.3 Hz, 2H); 1.50 (t, *J* = 6.9 Hz, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 167.0; 157.3; 143.6; 138.2; 137.1; 131.2; 130.3; 126.4; 125.9; 122.7; 119.6; 117.4; 116.3; 115.7; 115.6; 87.4; 60.5; 14.7. ESI-HR-MS (pos.): 385.0190, 387.0171 ($C_{18}H_{13}BrN_2NaO_3^+$, [*M* + Na]$^+$; calcd. 385.0188, 387.0167).

**Methyl 2,4-dibromo-12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (5ag).** Yellow solids (208 mg, 15% yield). M.p. 235 – 238 °C. IR ($CHCl_3$): 3367, 1697, 1604, 1570, 1535. $^1$H-NMR (500 MHz, $CDCl_3$): 10.81 (br s, 1H); 8.66 (d, *J* = 8.0 Hz, 1H); 8.49 (s, 1H); 8.05 (s, 1H); 7.99 (m, 1H); 7.47 (t, *J* = 8.0 Hz, 1H); 7.36 (t, *J* = 8.0 Hz, 1H); 4.05 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 167.1; 156.5; 142.7; 140.0; 135.5; 130.7; 130.2; 126.2; 123.1; 119.8; 116.3; 116.2; 114.9; 110.3; 88.3; 51.7 (one $sp^2$ signal was not observed because of overlapping). ESI-HR-MS (pos.): 470.8953, 472.8953, 474.8930 ($C_{17}H_{10}Br_2N_2NaO_3^+$, [*M* + Na]$^+$; calcd. 470.8956, 472.8935, 474.8915).

**Methyl 6-chloro-12-oxo-6,12-dihydroindolo[2,1-*b*]quinazoline-6-carboxylate (11).** NCS (134 mg, 1.1 mmol) was added to a solution of **5aa** (292 mg, 1 mmol) in $CH_2Cl_2$ (10 mL) at room temperature, and the mixture was stirred at room temperature. After 0.5 h, the mixture was added to 10% NaOH solution at 0 °C, extracted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (3/1) to give **11** (287 mg, 88% yield) as white solids. M.p. 188 – 191 °C. FT-IR ($CHCl_3$): 1764, 1689, 1647, 1600. $^1$H-NMR (500 MHz, [$D_6$]acetone): 8.52 (dd, *J* = 1.2, 8.0 Hz, 1H); 8.35 (dd, *J* = 1.2, 8.0 Hz, 1H); 7.88 (dt, *J* = 1.7, 7.5 Hz, 1H); 7.75 (d, *J* = 7.4 Hz, 1H); 7.63 (dt, *J* = 1.7, 7.8 Hz, 1H); 7.61 (dd, *J* = 1.2, 7.5 Hz, 1H); 7.59 (dd, *J* = 1.2, 8.0 Hz, 1H); 7.24 (dt, *J* = 1.1, 7.4 Hz, 1H); 6.36 (br s, 1H); 3.65 (s, 3H). $^{13}$C-NMR (125 MHz, [$D_6$]acetone): 169.7; 158.9; 157.9; 147.3; 140.2; 134.8; 131.0; 130.6; 128.0; 127.9; 127.0; 126.8; 124.1; 122.1; 116.8; 79.4; 52.9. ESI-HR-MS (pos.): 327.0536, 329.0515 ($C_{17}H_{12}ClN_2O_3^+$, [*M* + H]$^+$; calcd. 327.0536, 329.0507).

*Cyclization of **12af** (Scheme 4d)*

$K_2CO_3$ (138 mg, 1 mmol) was added to a solution of **12af** (202 mg, 0.5 mmol) in MeCN (10 mL) at room temperature, and the mixture was stirred at room temperature. After 2 h, the mixture was added to $H_2O$ at 0 °C, extracted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (3/1) to give **5af** (167 mg, 90% yield).

*Cyclization of **12ad** (Scheme 4d)*

$K_2CO_3$ (138 mg, 1 mmol) was added to a solution of **12ad** (192 mg, 0.5 mmol) in MeCN (10 mL) at room temperature, and the mixture was stirred at room temperature. After 2 h, the mixture was added to $H_2O$ at 0 °C, extracted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (3/1) to give **5ad** (147 mg, 83% yield).

**2-((3-((Methylperoxy)-λ$^2$-methyl)-1*H*-indol-2-yl)amino)benzoic acid (17).** NCS (441 mg, 3.3 mmol) was added to a solution of **6a** (526 mg, 3 mmol) and $Et_3N$ (0.84 mL, 6 mmol) in $CH_2Cl_2$ (25 mL) at room temperature, and the mixture was stirred at room temperature. After 0.5 h, anthranilic acid **8** (823 mg, 6 mmol) and trifluoroacetic acid (22 μL, 0.3 mmol) in $CH_2Cl_2$ (5 mL) was dropwise added to the reaction mixtures and the mixture was stirred at room temperature. After 2 h, the mixture was added to 10% NaOH solution at 0 °C, extracted with AcOEt (150 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (2/1) to give **17** (757 mg, 81% yield) as white solids. M.p. 210 – 213 °C. FT-IR ($CHCl_3$): 3446, 1668, 1600. $^1$H-NMR (500 MHz, $CDCl_3$): 9.92 (br s, 1H); 8.58 (br s, 1H); 8.20 (dd, *J* = 1.2, 8.0 Hz, 1H); 8.10 (dd, *J* = 1.7, 6.9 Hz, 1H); 7.33-7.41 (m, 2H); 7.23-7.29 (m, 2H); 6.75 (t, *J* = 8.0 Hz, 1H); 6.72 (d, *J* = 8.6 Hz, 1H); 3.92 (s, 3H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 165.2; 164.7; 151.5; 147.9; 136.1; 132.6; 130.3; 124.2; 122.9; 122.5; 121.5; 117.2; 117.0; 111.2; 108.1; 92.6; 51.2. ESI-HR-MS (pos.): 333.0856 ($C_{17}H_{14}N_2NaO_4^+$, [*M*+Na]$^+$; calcd. 333.0851).

*Cyclization of **17** at room temperature*

$POCl_3$ (383 mg, 2.5 mmol) was added to a solution of **17** (155 mg, 0.5 mmol) in MeCN (10 mL) at room temperature, and the mixture was stirred at room temperature. After 16 h, the mixture was added to $H_2O$ at 0 °C and stirred for 0.5 h at 0 °C. Then, the mixture was extracted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (3/1) to give **5aa** (76 mg, 52% yield).

*Cyclization of **17** under reflux*

$POCl_3$ (383 mg, 2.5 mmol) was added to a solution of **17** (155 mg, 0.5 mmol) in MeCN (10 mL) at room temperature, and the mixture was stirred under reflux. After 2 h, the mixture was added to $H_2O$ at 0 °C and stirred for 0.5 h at 0 °C. Then, the mixture was extracted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (3/1) to give **5aa** (114 mg, 78% yield).

**Tryptanthrin (10).** NCS (441 mg, 3.3 mmol) was added to a solution of **6j** (436 mg, 3 mmol) and $Et_3N$ (0.84 mL, 6 mmol) in $CH_2Cl_2$ (25 mL) at room temperature, and the mixture was stirred at room temperature. After 0.5 h, anthranilic acid **8** (907 mg, 6 mmol) and trifluoroacetic acid (22 μL, 0.3 mmol) in $CH_2Cl_2$ (5 mL) was dropwise added to the reaction mixtures and the mixture was stirred at room temperature. After 2 h, the mixture was added to 10% NaOH solution at 0 °C, extracted with AcOEt (150 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with hexane/AcOEt (5/1) to give **10** (545 mg, 73% yield) as a yellow solid. M.p. 266 – 268 °C. FT-IR: ($CHCl_3$): 1728, 1694. $^1$H-NMR (500 MHz, $CDCl_3$): 8.60 (d, *J* = 8.0 Hz, 1H); 8.41 (dd, *J* = 1.2, 8.0 Hz, 1H); 8.01 (d, *J* = 8.0 Hz, 1H); 7.90 (d, *J* = 7.5 Hz, 1H); 7.84 (td, *J* = 1.2, 8.0 Hz, 1H); 7.78 (td, *J* = 1.2, 7.5 Hz, 1H); 7.66 (t, *J* = 7.5 Hz, 1H); 7.42 (t, *J* = 8.0 Hz, 1H). $^{13}$C-NMR (125 MHz, $CDCl_3$): 182.7; 158.2; 146.7; 146.4; 144.4; 138.4; 135.2; 130.8; 130.3; 127.6; 127.3; 125.5; 123.8; 122.0; 118.1. ESI-HR-MS (pos.): 249.0669 ($C_{15}H_9N_2O_2^+$, [*M* + H]$^+$; calcd. 249.0664).

*Cell proliferation assay (WST-1 assay)*

Human colorectal cancer DLD-1 cells were obtained from the American Type Culture Collection (Manassas, VA, USA), and were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS), 4mM L-glutamine, 40,000 U/L penicillin, and 40 mg/L streptomycin. Cells were cultured at 37 °C in a humidified atmosphere of 95% air and 5% $CO_2$. Cells were seeded at a density of 5 x 104 cells/mL into 24-well plates in growth medium containing 10% FBS. After adherence for 4 h, cells were reintroduced to the medium containing compounds or vehicle (DMSO) in 1% FBS/DMEM and incubated for 20 h. WST-1

reagent added to each well for measurement of cell viability. The value of cell viability was monitored at 450 nm using an ELISA reader (TECAN Japan, Tokyo, Japan). The $IC_{50}$ is defined as the compound concentration required for the inhibition of cell proliferation by 50% in comparison with cells treated with DMSO, considered as 100% viability.

*Statistical analysis*

All experiments were carried out at least two times, and are presented with representative data. Significant differences between the means of two groups were analysed by t test, and differences were taken as statiscally significant, $*P<0.05$ and $**P<0.01$.

## Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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## Author Contribution Statement

*T. Abe* conceived and designed the project and prepared the manuscript. *T. Abe* conducted the experiments and analyzed the data. *M. Terasaki* conducted experiments on antiproliferative activity and analyzed the data.

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