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Synthesis of Fused Tetracyclic Compounds *via* Oxidative Annulation: Access to Copper-Catalyzed Indolo[1,2-*a*]Quinolines and to Ruthenium-Catalyzed Isoquinolin-1[2H]-ones

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ABSTRACT: A facile double oxidative annulation of (en-3-yn-1-yl)phenylbenzamides was developed allowing us to synthetize fused tetracyclic compounds. Under copper catalysis, the reaction proceeds with high efficiency and leads to new indolo[1,2a]quinolines *via* a decarbonylative double oxidative annulation. On the other hand, under ruthenium catalysis, new isoquinolin-1[2H]-ones were obtained *via* a double oxidative annulation.

INTRODUCTION

Polycyclic heteroaromatic compounds often exhibit interesting biological and physical properties, as in pharmaceuticals, biologically active products, fluorescent bioimaging probes and optoelectronic materials.¹ Therefore, particular attention has been devoted to design efficient catalytic routes to synthesize these compounds.² Among them, indolo[1,2-*a*]quinoline unit is an important scaffold found in many organic compounds such as functional materials (Figure 1).³ For instance, compound **A** is suitable for applications of one-photon/two-photon targeted imaging in live cell.⁴ compound **B** is an organic semiconductor⁵ and compound **C** a solar cell photosensitizer⁶.

Figure 1. Examples of Indolo[1,2-a]quinolines with Application in the Field of Organic Functional Materials.



On the other hand, isoquinolin-1(2H)-ones have attracted considerable attention as a privileged structure present in various biologically active and/or natural products (Figure 2).⁷⁻⁸ For instance, compound **D** is a potent enhancer of antifungal activity of fluconazole against Candida Albicans.⁹ Compound **E** exhibits neuroprotective activity.¹⁰ While compound **F** shows anti-breast cancer activity.¹¹

Figure 2. Examples of Bioactive Compounds Containing Isoquinolin-1(2H)-one Scaffolds.



To synthetize such molecules, oxidative addition of benzamides with alkynes has drawn lot of attention as it does not require prefunctionalization of the substrates while affording multi-substituted adducts.¹² In particular, alkynyl-tethered amides, are well-recognized as versatile building blocks towards *N*-containing cyclic architectures, proved to be efficient in intramolecular oxidative annulations, leading to isoquinolinone fused tricyclic compounds.¹³ However, only few examples of access to tetracyclic adducts have been described.¹⁴⁻¹⁶ The group of Song developed a rhodium(III)-catalyzed intramolecular annulation triggered by C-H activation (Scheme 1a).¹⁴ The group of Reddy also used rhodium catalyst to successfully annulate propargyl amino phenyl benzamides to access isoquinolino quinoxalinones (Scheme 1b).¹⁵ More recently, the group of Zhou reported an efficient copper-catalyzed preparation of benzo[3,4]indolo[1,2- *b*]isoquinoline-8ones (Scheme 1c).¹⁶

Scheme 1. Intramolecular Oxidative Annulation of Alkynyl-tethered Amides



In connection with our research interest focused on the use of organo bis-boranes as versatile intermediates in heterocyclic chemistry,¹⁷ we herein report the synthesis of (en-3-yn-1-yl)phenylbenzamides and their conversion to fused tetra-, and pentacyclic compounds through intramolecular double oxidative annulation (Scheme 1d). Surprisingly, copper catalysis allowed us to obtained new indolo[1,2-*a*]quinolines **5** *via* a decarbonylative double oxidative annulation. A simple change of the catalytic system to ruthenium opened the way to hitherto unreported isoquinolin-1[2H]-ones **6** *via* a double oxidative annulation.

RESULTS AND DISCUSSION

Initially, benzamide 1a and bispinacol boronate 2a selected as model substrates and were the alkenylbenzamide 3a, was obtained in 70% yield, in presence of [1,1'-bis(diphenylphosphino) ferrocene]dichloro palladium(II) and potassium phosphate tribasic monohydrate in THF/H₂O at reflux for 1 hour, via a Suzuki-Miyaura cross-coupling reaction.¹⁸ As previously reported, this reaction occurred regioselectively at the terminal C-B bond with the formation of a single (E)-stereomer (Scheme 2a).^{17d,e} Compound **3a** was then engaged in a second Suzuki-Miyaura cross-coupling reaction with 5-(bromoethynyl)-1,2,3-trimethoxybenzene, using the same conditions, heating at reflux 12 hours. The desired alkynyltethered benzamide **4a** could be obtained in good yield (Scheme 2b). In order to perform the oxidative annulation

on compound **4a**, we used the conditions described by Zhou,¹⁶ *i.e.* catalysis with CuCN in dimethylformamide (DMF) at 110 °C for one day under air. Surprisingly, it did not result in the expected adduct **6a**, but instead the indolo[1,2-*a*]quinoline **5a**, without carbonyl function, was formed (Scheme 2c, Table 1, entry 1). The structure of this adduct was later confirmed by X-Ray diffraction crystallography (Scheme 4). This interesting result could be a new method to synthetize substituted indolo[1,2-*a*]quinolines.

However, changing the conditions, isoquinolin-1(2H)one **6a** could be obtained using 2.2 equivalents of copper acetate monohydrate and dichloro(*p*cymene)ruthenium(II) dimer as catalyst, at reflux of dichloroethane (DCE) for 16h under air (Scheme 2c).¹⁵

Scheme 2. Synthesis of Indolo[1,2-*a*]quinoline 5a and Isoquinolin-1(2H)-one 6a



Some other conditions were tested to optimize the yields of **5a**. Changing the solvent to toluene, dichloroethane or tert-amyl alcohol did not improve the yields (Table 1, entries 2-4). By changing the catalyst to copper, compound **5a** was obtained in very low yield (Table 1, entry 6).19 The effect of radical scavengers such as butylated hydroxytoluene (BHT) or 2,2,6,6tetramethylpiperidine 1-oxyl (TEMPO) was also investigated. The desired compound 5a was obtained in around 50% yield adding 2 equivalents of BHT or TEMPO (Table 1, entries 5 and 6). This result may help us to discard the idea of a radical pathway for its formation.

Table 1. Synthesis of Indolo[1,2-*a*]quinolines. Optimization of the Reaction Conditions^a

Entry	Cat.	Additive	Solvent	Yield 5a ^b
1	CuCN		DMF	68
2	CuCN		Tol	12
3	CuCN		<i>t</i> AmOH	29
4	CuCN		DCEc	0
5	CuCN	BHTc	DMF	49
6	CuCN	TEMPOd	DMF	51

7 Cu DMSO ^e 21	
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 $^{\rm a}$ Reaction conditions: **4a** (0.1 mmol), CuCN (0.02 mmol), solvent (2 mL), under air, 110 °C, 24 h. $^{\rm b}$ Yields of isolated products. $^{\rm c}$ Radical scavenger butylated hydroxytoluene (44 mg, 0.2 mmol). $^{\rm d}$ $^{\rm c}$ Radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (31 mg, 0.2 mmol). $^{\rm e}$ **4a** (0.1 mmol), Cu (0.01 mmol), DMSO (1 mL), under air, 100 °C, 24 h.

Based on these experimental results and literature,^{16,19} the proposed mechanism for transformation of 4 to 5 is shown in Scheme 3. The formation of the intermediate A probably occurred by an oxidative addition under air atmosphere, through a sequential DMF-aided Cu insertion into the amide C-N bond. Decarbonylation assisted by solvent would, then, proceed with the formation of the intermediate B.19 Further support for the proposed mechanism is derived from the fact that replacing of DMF with dichloroethane inhibits the reaction (Table 1, entry 4). The next step would afford the seven-membered ring intermediate **C** with coordination of the alkyne to the metal after elimination of CO. Copper-catalyzed C-H activation would then afford the intermediate D. An intramolecular Nattacked cis-addition would then occur leading to polycyclic copper species E. Finally, this intermediate E would undergo a reductive elimination to provide final product 5 with regeneration of Cu^{1,16}

Scheme 3. Proposed Reaction Mechanism of Formation of 5.



order to explore the generality of the In decarbonylative double oxidative annulation into indolo[1,2-*a*]quinolines **5** as well as the potential of these three steps sequences, we extended these results to various benzamides 1^{20} and bispinacol boronates 2^{21} . New (Z)-N-(2-(2-(pinacolylvinyl)phenyl benzamides 3 with methyl or chlorine on aromatic rings could be obtained via a Suzuki-Miyaura cross-coupling reaction, in good yields (61-70%) (See SI). Compounds 3 were further engaged in a Suzuki-Miyaura cross-coupling reaction with different (bromoethynyl)benzene derivatives to lead to various (en-3-yn-1-yl)phenylbenzamides 4 in 60% to 72% yields (See SI).

With diversified alkyne-amides in hand, we decided to investigate the scope of the decarbonylative double oxidative annulation with copper cyanide as catalyst.¹⁶ A large variety of indolo[1,2-*a*]quinolines **5** could be prepared by this protocole in good yields (58-70%) (Scheme 4). The indolo[1,2-*a*]quinolines **5** were then fully characterized by ¹H, ¹³C, ¹⁹F NMR and mass spectrometry (see SI). As previously stated, a single crystal of compound **5I** was grown by slow evaporation of a methylene chloride solution and the structure was further ascertained by X-ray diffraction crystallography (Scheme 4).²² It proved that this double oxidative annulation occurred with loss of the carbonyl group.

Exploring the effect of substituents on amide unit, we found that electron-donating methyl substituent (4f) was tolerated in *para* to the carbonyl with no loss of reactivity. Incorporation of halogen such as Cl at the same position was also successful giving products 5m and 5n in comparable yields. Similarly, annulation reaction tolerated both electron-donating and electron-with-drawing groups in the phenyl substituent of the alkyne like methyl, trimethoxy, cyano and trifluoromethyl groups. It is noteworthy that the reaction of compound **4e** having a pyridine afforded product 5e in a 58% yield. Moreover, the reaction was proven to be scalable (3.2 mmol) with (E)cyclohexylethenyl-1,2-bis(boronate) 2c as model substrate, delivering the desired product 5l in 27% isolated yield over three steps by obtention of intermediates 3h and 41 with respectively 62% and 67% yields (see SI for more details). When we extended the study of these oxidative annulation to naphtyl amide, compound 4g gave access to the indolo[1,2-*a*]quinoline **5g** with fused pentacycles. Unfortunately, under the same conditions, no reaction occurred with compound **4h**, having a thiophenyl group, and the expected product could not be synthetized.

Scheme 4. Scope of Indolo[1,2-a]Quinolines 5^{a,b}



We, then, explored the scope of the double oxidative annulation, this time, with $[Ru(p-cymene)Cl_2]_2$ as catalyst in presence of copper acetate monohydrate.^{15,23} This pro-

vided us a large variety of isoquinolin-1(2H)-ones 6 with good yields (58-77%) (Scheme 5). As observed, for the synthesis of compounds 5, no significant influence was noticed on changing substituents. The indolo[1,2*a*]quinolines **6** were, likewise, fully characterized by 1 H, ¹³C, ¹⁹F NMR and mass spectrometry (see SI). ¹³C NMR spectra display a signal in the 160-165 ppm region that confirms the presence of the carbonyl group of the amide function. The structure of compound **6m** was ascertained by X-ray diffraction crystallography (Scheme 5).²⁴ The synthesis of **6l** could be performed on 1 mmole scale from **3h** without a significant loss of yield (see SI). Isoquinolin-1(2H)-ones 6g and 6h, with naphtyl and thiophenyl group respectively, could be obtained in 65% and 58%, giving a fused pentacyclic compound in the case of naphtyl derivative.

Scheme 5. Scope of Isoquinolin-1(2H)-ones 6^{a,b}



CONCLUSION

In this article, we have developed a simple and effi-cient route to a large range of fused tetra- and pentacyclic indolo[1,2-*a*]quinoline and isoquinolin-1(2H)-one derivatives through a double oxidative annulation starting from the same enynylphenylbenzamides. It is noticed that the formation of the indolo[1,2-*a*]quinolines occurred with a decarbonylation. A detailed investigation is undertaken on the scope of the reaction to show an excellent functionalgroup tolerance. These fused compounds may find important applications in the area of biology, as well as in material science and research in these directions is ongoing in our groups.

EXPERIMENTAL SECTION

General Information All solvents and all commercially available chemicals were used without further purification. ¹H

NMR (400 or 500 MHz), ¹³C NMR (101 or 126 MHz) and ¹⁹F (376 MHz) spectra were recorded on Bruker AC 400 and AC 500 spectrometers. Chemical shifts δ are given in ppm, and coupling constants J in hertz. Multiplicities are presented as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hex = hexuplet, m = multiplet, ttd = triplet of triplet of doublets. High-resolution mass spectrometry (HRMS) (ESI+) was performed using Xevo G2-XS QTof double-focusing mass spectrometer. Purifications by silica gel chromatography were carried out on silica 0.060-0.200 mm, 60 Å. Analytical thinlayer chromatography was performed on Merck silica gel 60 F254 plates. Melting points were measured on a melting-point apparatus Stuart SMP10 and are uncorrected. For the synthesis of compounds **3** and **4** see SI.

Synthesis of Indolo[1,2-a]Quinolines 5. In a round bottom flask, were placed compound **4** (0.10 mmol) and CuCN (2 mg, 0.02 mmol) in DMF (2 mL). The resulting suspension was stirred at 110 $^{\circ}$ C using an oil bath, under air, for 24 h. The reaction mixture was then cooled to room temperature, diluted with water and extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and evaporated under vacuum. The residue was purified by column chromatography (230-400 mesh Silica gel, EtOAc in Hexane) to give the corresponding cyclized products **5**. The reaction was also carried out on a 0.66 mmol scale for **5**.

6-Butyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2-a]quinolone **5a**. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 30 mg (68%). White solid, mp = 190-193 °C. $R_f = 0.60$ (Hexane/EtOAc: 80/20). ¹H NMR (500 MHz, CDCl₃) δ 8.61 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.57 (ddd, J = 8.5, 7.2, 1.6 Hz, 1H), 7.45 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.36 (ddd, J = 7.8, 7.0, 0.7 Hz, 1H), 7.32 (td, J = 7.5, 0.9 Hz, 1H), 6.96 (s, 1H), 6.73 (s, 2H), 3.96 (s, 3H), 3.86 (s, 6H), 2.56-2.52 (m, 2H), 1.46-1.39 (m, 2H), 1.04 (hex, J = 7.4 Hz, 2H), 0.74 (t, J = 7.4 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.9, 138.8, 137.5, 135.2, 132.8, 131.8, 131.4, 129.8, 128.2, 127.9, 127.8, 124.5, 123.3, 122.5, 120.7, 120.3, 115.2, 113.9, 111.3, 108.7, 61.1, 56.2 (2C), 38.0, 33.7, 26.8, 26.0. HRMS (ESI+) calculated for [M+H]+ (C₂₉H₃₀NO₃): 440.2226, found 440.2220. 6-Butyl-7-(p-tolyl)indolo[1,2-a]quinolone **5b**. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 24 mg (67%). White solid, mp = 183-187 °C. R_f = 0.60 (Hexane/EtOAc: 90/10). ¹H NMR (400 MHz, CDCl₃) δ 8.60 (d, J = 8.4 Hz, 1H), 8.50 (d, J = 8.6 Hz, 1H), 7.60 (dd, J = 7.6, 1.5 Hz, 1H), 7.58-7.53 (m, 2H), 7.43 (ddd, J = 8.5, 7.0, 1.3 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.34-7.27 (m, 4H), 6.92 (s, 1H), 2.51-2.46 (m, 2H), 2.47 (s, 3H), 1.38-1.29 (m, 2H), 0.97 (hex, J = 7.5 Hz, 2H), 0.69 (t, J = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 136.6, 135.9, 133.7, 132.8, 132.4, 132.0, 131.6, 131.5, 128.5, 127.8, 127.6, 124.4, 122.7, 122.4, 122.1, 121.6, 120.0, 115.3, 114.0, 111.8, 33.0, 31.7, 22.3, 21.3, 13.6. HRMS (ESI+) calculated for [M+H]⁺ (C₂₇H₂₆N): 364.2065, found 364.2035. 4-(6-Butylindolo[1,2-a]quinolin-7-yl)benzonitrile 5c. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 23 mg (62%). Yellow solid, mp = 192-197 °C. R_f = 0.50 (Hexane/EtOAc: 90/10). ¹H NMR (400 MHz, CDCl₃) δ 8.63 (d, J = 8.5 Hz, 1H), 8.53 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.68-7.55 (m, 4H), 7.49-7.45 (m, 2H), 7.39-7.32 (m, 2H), 7.02 (s, 1H), 2.44 (dd, J = 8.0, 7.3 Hz, 2H), 1.36-1.29 (m, 2H), 0.97 (hex, J = 7.2 Hz, 2H), 0.70 (t, J = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 141.8, 135.6, 132.7, 132.6, 132.5, 132.2, 131.6, 130.6, 128.1, 124.3, 123.6, 123.2, 122.6, 122.3, 119.3, 119.2, 115.5, 114.3, 110.7, 109.7, 33.2, 31.4, 22.3, 13.7. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₇H₂₃N₂): 375.1861, found 375.1838. *6-Butyl-7-(2-(trifluoromethyl)phenyl)indolo[1,2-a]quinolone*

5d. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 27 mg (65%). Yellow solid, mp = 197-199 °C. R_f = 0.60 (Hexane/EtOAc: 90/10). ¹H NMR (500 MHz, CDCl₃) δ 8.65 (d, *J* = 8.4 Hz, 1H), 8.54 (d, *J* = 8.7 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.67-7.52 (m, 5H), 7.46 (ddd, *J* = 8.5, 6.1, 2.2 Hz, 1H), 7.38-7.29 (m, 3H), 6.97 (s, 1H), 2.42-2.14 (m, 2H), 1.57-1.39 (m, 2H), 1.07 (hex, *J* = 7.4 Hz, 1H), 0.96 (hex, *J* = 7.4 Hz, 1H), 0.75 (t, *J* = 7.4 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 135.9, 135.4, 134.5, 133.5, 133.2, 132.0, 131.5 (q, *J* = 29.3 Hz), 131.1, 128.1, 128.0, 127.9, 126.2 (q, *J* = 5.2 Hz), 124.5, 124.2 (q, *J* = 274.2 Hz), 123.0, 122.7, 122.2, 122.0, 120.1, 115.5, 114.2, 107.6, 32.1, 31.5, 22.6, 13.8. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ - 59.0. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₇H₂₃F₃N): 418.1783, found 418.1772.

6-Butyl-7-(pyridin-3-yl)indolo[1,2-a]quinolone **5e.** Purified by flash column chromatography (EtOAc/Hexane = 1/9); 20 mg (58%). Yellow solid, mp = 201-203 °C. R_f = 0.50 (Hexane/EtOAc: 90/10). ¹H NMR (400 MHz, CDCl₃) δ 8.79 (s, 1H), 8.70 (d, *J* = 4.1 Hz, 1H), 8.61 (d, *J* = 8.5 Hz, 1H), 8.52 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.99 (s, 1H), 2.44 (dd, *J* = 7.9, 7.9 Hz, 2H), 1.40-1.29 (m, 2H), 1.03-0.93 (m, 2H), 0.71 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 151.7, 147.7, 139.4, 135.7, 133.2, 132.6, 132.3, 131.1, 128.15, 128.09, 124.3, 123.4, 123.1, 123, 122.6, 122.3, 119.3, 115.4, 114.3, 107.2, 33.2, 31.4, 22.4, 13.7. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₅H₂₃N₂): 351.1861, found 351.1854.

6-Butyl-9-methyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2-

a]quinoline **5***f*. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 32 mg (70%). White solid, mp = 187-191 °C. $R_f = 0.60$ (Hexane/EtOAc: 90/10). ¹H NMR (400 MHz, CDCl₃) δ 8.59 (d, *J* = 8.4 Hz, 1H), 8.36-8.25 (m, 1H), 7.61-7.53 (m, 2H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.30 (td, *J* = 7.4, 1.0 Hz, 1H), 7.20 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.90 (s, 1H), 6.72 (s, 2H), 3.95 (s, 3H), 3.86 (s, 6H), 2.67 (s, 3H), 2.57-2.49 (m, 2H), 1.49-1.37 (m, 2H), 1.04 (hex, *J* = 7.4 Hz, 2H), 0.73 (t, *J* = 7.4 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.8, 137.3, 135.9, 133.8, 132.5, 132.4, 132.1, 131.8, 129.4, 127.9, 127.7, 124.6, 123.8, 122.8, 122.3, 119.8, 115.5, 114.2, 111.7, 109.1, 61.1, 56.3 (2C), 33.1, 32.4, 22.7, 22.6, 13.9. HRMS (ESI*) calculated for [M+H]⁺ (C₃₀H₃₂NO₃): 454.2382, found 454.2381.

6-Butyl-7-(2-(trifluoromethyl)phenyl)benzo[5,6]indolo[1,2-

a]quinoline **5***g.* Purified by flash column chromatography (EtOAc/Hexane = 2/8); 32 mg (68%). White solid, mp = 205-208 °C. $R_f = 0.60$ (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.74 (d, *J* = 8.5 Hz, 1H), 8.68 (d, *J* = 9.3 Hz, 1H), 8.04-7.91 (m, 2H), 7.78 (d, *J* = 9.3 Hz, 1H), 7.74-7.65 (m, 4H), 7.60 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.44-7.36 (m, 2H), 7.23-7.15 (m, 2H), 6.98 (s, 1H), 2.31-2.13 (m, 2H), 1.46 (quint, *J* = 7.6 Hz, 2H), 1.07 (hex, *J* = 7.4 Hz, 1H), 0.96 (hex, *J* = 7.2 Hz, 1H), 0.75 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 137.8, 134.9, 134.4, 133.4, 132.3, 131.8, 131.5 (q, *J* = 29.3 Hz), 130.6, 129.3, 128.5, 128.43, 128.37, 128.1, 127.5, 126.6 (q, *J* = 5.3 Hz), 125.6, 125.1, 124.9, 124.3, 124.2 (q, *J* = 277.5 Hz), 123.9, 123.6, 123.3, 121.6, 116.4, 114.8, 109.4, 31.8, 31.8, 22.7, 13.9. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -60.6. HRMS (ESI+) calculated for [M+H]+ (C₃₁H₂5F₃N): 468.1939, found 468.1918.

3-Methyl-6-propyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2-

a]quinolone **5***j*. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 30 mg (69%). White solid, mp = 186-189 °C. $R_f = 0.60$ (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz,

CDCl₃) δ 8.53 (d, *J* = 8.5 Hz, 1H), 8.44 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 6.93 (s, 1H), 6.74 (s, 2H), 3.98 (s, 3H), 3.87 (s, 6H), 2.62 (s, 3H), 2.52-2.44 (m, 2H), 1.47 (hex, *J* = 7.3 Hz, 2H), 0.68 (t, *J* = 7.3 Hz, 3H). ¹³C{1H} NMR (101 MHz, CDCl₃) δ 152.7, 138.1, 137.3, 135.9, 132.8, 132.2, 132.0, 131.7, 131.4, 127.8, 124.0, 123.0, 122.12, 122.08, 121.9, 120.0, 115.8, 114.2, 111.5, 109.1, 61.2, 56.3 (2C), 35.2, 23.6, 22.4, 13.9. HRMS (ESI+) calculated for [M+H]⁺ (C₂₉H₃₀NO₃): 440.2226, found 440.2220.

3-Chloro-6-propyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2-

a]quinolone **5***k*. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 29 mg (67%). White solid, mp = 193-197 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (500 MHz, CDCl₃) δ 8.49 (d, *J* = 8.9 Hz, 1H), 8.41 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.46 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 6.85 (s, 1H), 6.72 (s, 2H), 3.97 (s, 3H), 3.87 (s, 6H), 2.51-2.47 (m, 2H), 1.48 (hex, *J* = 7.5 Hz, 2H), 0.68 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.8, 137.4, 134.9, 134.2, 132.1, 131.9, 131.3, 131.2, 127.9, 127.5, 127.1, 125.9, 122.8, 122.2, 121.7, 120.3, 116.5, 113.9, 112.4, 109.1, 61.1, 56.3 (2C), 35.1, 23.5, 13.9. HRMS (ESI+) calculated for [M+H]⁺ (C₂₈H₂₇ClNO₃): 460.1679, found 460.1674.

10-Chloro-6-cyclohexyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2*alquinolone* **51.** Purified by flash column chromatography (EtOAc/Hexane = 2/8); 33 mg (66%), 211 mg (64%) on a 0.66 mmol scale. White solid, mp = 194-198 °C. $R_f = 0.60$ (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.49 (d, I =1.6 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 7.62 (dd, J = 7.7, 1.4 Hz, 1H), 7.58 (ddd, J = 8.7, 7.4, 1.6 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.33 (td, J = 7.5, 0.8 Hz, 1H), 7.31 (dd, J = 8.5, 1.7 Hz, 1H), 7.00 (s, 1H), 6.69 (s, 2H), 3.96 (s, 3H), 3.85 (s, 6H), 2.72 (tt, J = 11.6, 2.7 Hz, 1H), 1.82 (d, J = 12.4 Hz, 1H), 1.75-1.51 (m, 4H), 1.34 (tdd, J = 12.8, 12.8, 3.3 Hz, 2H), 1.14 (ttd, J = 13.1, 13.1, 3.7 Hz, 1H), 0.98-0.72 (m, 2H). $^{13}\mathrm{C}\{^{1}\mathrm{H}\}$ NMR (101 MHz, CDCl3) δ 153.0, 139.0, 137.7, 135.3, 133.0, 132.0, 131.5, 129.9, 128.3, 128.1, 128.0, 124.7, 123.4, 122.6, 120.9, 120.4, 115.3, 114.1, 111.4, 108.9, 61.2, 56.4 (2C), 38.2, 33.9, 26.9, 26.2. HRMS (ESI⁺) calculated for [M+H]⁺ (C₃₁H₃₁ClNO₃): 500.1992, found 500.1987.

9-Chloro-6-cyclohexyl-7-(2-(trifluoromethyl)phenyl)indolo[1,2alquinoline 5m. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 31 mg (65%). White solid, mp =190-195 °C. Rf = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, J = 1.4 Hz, 1H), 8.49 (s, 1H), 7.92-7.85 (m, 1H), 7.72-7.55 (m, 4H), 7.48 (dd, J = 6.9, 1.6 Hz, 1H), 7.34 (td, J = 7.5, 0.8 Hz, 1H), 7.28 (dd, J = 8.6, 1.7 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.01 (s, 1H), 2.26 (tt, J = 11.8, 2.7 Hz, 1H), 1.81-1.65 (m, 3H), 1.55-1.46 (m, 3H), 1.20-1.01 (m, 2H), 0.80 (ttd, J = 13.3, 13.3, 3.8 Hz, 1H), 0.36 (ttd, J = 13.1, 12.8, 3.4 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 138.7, 135.3, 135.1, 133.9, 133.8, 132.1, 131.5, 131.4 (q, J = 29.3 Hz), 130.3, 128.4, 128.2, 128.1, 127.9, 126.3 (q, J = 5.3 Hz), 124.7, 124.2 (q, J = 274.2 Hz), 123.4, 122.7, 121.1, 120.8, 115.4, 114.1, 107.1, 38.2, 35.2, 31.7, 26.9, 26.6, 26.1. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -59.9. HRMS (ESI+) calculated for [M+H]+ (C₂₉H₂₄ClF₃N): 478.1549, found 478.1532.

6-Benzyl-9-chloro-7-(3,4,5-trimethoxyphenyl)indolo[1,2-

a]quinolone **5n.** Purified by flash column chromatography (EtOAc/Hexane = 2/8); 33 mg (65%). White solid, mp = 201-204 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (500 MHz, CDCl₃) δ 8.51 (d, *J* = 1.5 Hz, 1H), 8.51 (d, *J* = 8.3 Hz, 1H), 7.68-7.58 (m, 2H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.16-7.11 (m, 3H), 6.91 (s, 1H),

6.83-6.80 (m, 2H), 6.38 (s, 2H), 3.97 (s, 2H), 3.95 (s, 3H), 3.68 (s, 6H). $^{13}C{^{1}H}$ NMR (101 MHz, CDCl₃) δ 152.5, 139.2, 137.2, 135.6, 132.7, 131.9, 130.3, 130.2, 129.7, 128.5, 128.3, 128.2, 128.1, 125.9, 125.7, 124.1, 123.3, 122.5, 120.8, 115.2, 113.9, 112.3, 108.7, 60.9, 55.9, 39.0. HRMS (ESI+) calculated for [M+H]+ (C₃₂H₂₇ClNO₃): 508.1679, found 508.1674.

Synthesis of Isoquinolones 6. In a round bottom flask, were placed compound **4** (0.10 mmol) in DCE (2 mL), $[Ru(p-cymene)Cl_2]_2$ (1.5 mg, 0.0025 mmol) and $Cu(OAc)_2$ ·H₂O (44 mg, 0.22 mmol) were then added. The resulting suspension was stirred at reflux, using an oil bath, under air, for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (230-400 mesh Silica gel, EtOAc in Hexane) to give the corresponding cyclized products **6**. The reaction was also carried out on a 0.66 mmol scale for **6**l.

6-Butyl-7-(3,4,5-trimethoxyphenyl)-12H-isoquinolino[2,3-

a]quinolin-12-one **6a.** Purified by flash column chromatography (EtOAc/Hexane = 2/8); 35 mg (75%). White solid, mp = 168-172 °C. R_f = 0.50 (Hexane/EtOAc: 80/20). ¹H NMR (500 MHz, CDCl₃) δ 8.56 (d, *J* = 8.9 Hz, 1H), 7.91 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.36-7.31 (m, 2H), 7.27-7.23 (m, 2H), 6.85 (s, 1H), 4.06 (s, 3H), 3.91 (s, 3H), 3.11 (s, 3H), 1.55-1.50 (m, 2H), 1.12-1.05 (m, 2H), 0.90 (hex, *J* = 7.4 Hz, 2H), 0.69 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 163.7, 153.5, 138.2, 136.6, 135.8, 135.1, 134.0, 133.5, 132.6, 128.5, 128.3, 127.2, 126.7, 126.4, 125.5, 125.4, 125.3, 125.1, 120.4, 117.6, 109.2, 61.3, 56.4 (2C), 35.2, 32.7, 22.5, 13.9. HRMS (ESI+) calculated for [M+H]+ (C₃₀H₃₀NO₄): 468.2175, found 468.2169.

6-Butyl-7-(p-tolyl)-12H-isoquinolino[2,3-a]quinolin-12-one **6b**. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 28 mg (72%). White solid, mp =175-178 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.76 (s, 1H), 8.74-8.73 (m, 1H), 8.65-8.58 (m, 1H), 7.62-7.48 (m, 2H), 7.36-7.31 (m, 2H), 7.31-7.20 (m, 5H), 6.85 (d, *J* = 0.9 Hz, 1H), 2.47 (s, 3H), 1.81-1.74 (m, 2H), 1.21-1.13 (m, 2H), 0.94 (hex, *J* = 7.3 Hz, 2H), 0.70 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 163.7, 138.1, 136.8, 136.0, 135.2, 135.0, 134.1, 132.5, 132.0, 129.4, 128.2, 127.1, 126.6, 126.3, 125.5, 125.3, 125.2, 120.4, 117.9, 35.4, 31.9, 22.3, 21.5, 13.9. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₈H₂₆NO): 392.2014, found 392.1998. 4-(6-Butyl-12-oxo-12H-isoquinolino[2,3-a]quinolin-7-

yl)benzonitrile **6c**. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 27 mg (68%). Yellow solid, mp = 178-182 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, *J* = 8.1 Hz, 1H), 7.93 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.63-7.59 (m, 1H), 7.59-7.56 (m, 1H), 7.51 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 1H), 7.39-7.32 (m, 3H), 7.20 (td, *J* = 7.6, 1.1 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.74 (s, 1H), 2.51-2.45 (m, 2H), 1.76-1.67 (m, 2H), 1.44 (hex, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ¹³C{1H} NMR (101 MHz, CDCl₃) δ 163.4, 143.6, 135.5, 134.8, 134.2, 133.0, 132.8, 132.3, 131.0, 129.3, 128.4, 127.5, 126.9, 126.4, 125.5, 125.0, 124.8, 124.4, 120.2, 118.6, 115.4, 112.0, 35.5, 31.6, 22.1, 13.7. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₈H₂₃N₂O): 403.1810, found 403.1799.

6-Butyl-7-(2-(trifluoromethyl)phenyl)-12H-isoquinolino[2,3a]quinolin-12-one **6d.** Purified by flash column chromatography (EtOAc/Hexane = 2/8); 31 mg (70%). Yellow solid, mp = 179-182 °C. R_f = 0.70 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.65-8.63 (m, 1H), 8.52-8.50 (m, 1H), 7.75 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.58-7.51 (m, 2H), 7.46-7.39 (m, 2H), 7.37-7.35 (m, 1H), 7.29-7.25 (m, 1H), 7.24 (s, 1H), 7.19-7.15 (m, 1H), 6.79 (s, 1H), 6.69-6.66 (m, 1H), 1.78-1.70 (m, 1H), 1.56-1.48 (m, 1H), 1.21-1.13 (m, 2H), 0.95-0.79 (m, 2H), 0.64 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 164.3, 137.5, 137.1, 135.0, 134.9, 134.8, 134.4, 132.5, 131.7, 131.4 (q, *J* = 29.8 Hz), 128.7, 128.2, 127.9, 127.1, 126.8 (q, *J* = 4.9 Hz), 126.6, 126.4, 125.4, 125.3, 124.95, 124.89, 123.9 (q, *J* = 274.4 Hz), 120.6, 113.0, 34.7, 31.8, 22.3, 13.8. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -60.0. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₈H₂₃F₃NO): 446.1732, found 446.1713.

6-Butyl-7-(pyridin-3-yl)-12H-isoquinolino[2,3-a]quinolin-12one **6e.** Purified by flash column chromatography (EtOAc/Hexane = 2/8); 23 mg (60%). Yellow solid, mp = 186-189 °C. R_f = 0.40 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H), 8.77-8.70 (m, 1H), 8.68-8.61 (m, 1H), 8.01 (d, *J* = 7.1 Hz, 1H), 7.69 (s, 1H), 7.63 (t, *J* = 6.9 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.42-7.37 (m, 2H), 7.30 (td, *J* = 7.6, 1.1 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 7.00 (s, 1H), 1.80-1.73 (m, 1H), 1.65-1.58 (m, 1H), 1.24-1.15 (m, 2H), 0.96 (hex, *J* = 7.2 Hz, 2H), 0.71 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 163.5, 150.7, 147.5, 141.4, 135.9, 135.6, 135.0, 133.9, 133.1, 129.9, 128.7, 127.7, 127.1, 126.7, 125.7, 125.2, 124.9, 124.3, 120.3, 112.6, 36.0, 31.4, 22.2, 13.9. HRMS (ESI+) calculated for [M+H]+ (C₂₆H₂₃N₂O): 379.1805, found 379.1788.

6-Butyl-9-methyl-7-(3,4,5-trimethoxyphenyl)-12H-

isoquinolino[*2*,*3*-*a*]*quinolin-12-one* **6***f*. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 37 mg (77%). White solid, mp = 165-169 °C. $R_f = 0.50$ (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.73 (d, *J* = 8.8 Hz, 1H), 8.51 (d, *J* = 8.2 Hz, 1H), 7.39-7.31 (m, 3H), 7.27-7.23 (m, 1H), 7.08 (s, 1H), 6.86 (s, 1H), 6.58 (s, 2H), 3.97 (s, 3H), 3.83 (s, 6H), 2.42 (s, 3H), 1.86-1.82 (m, 2H), 1.23-1.18 (m, 2H), 0.99 (hex, *J* = 7.4 Hz, 2H), 0.73 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 163.5, 153.4, 143.2, 138.1, 136.6, 135.8, 135.1, 134.1, 133.4, 128.3, 128.2, 127, 126.2, 125.2, 125.1, 124.9, 122.9, 120.4, 117.4, 109.1, 61.2, 56.3 (2C), 35.1, 32.6, 22.4, 22.3, 13.8. HRMS (ESI+) calculated for [M+H]+ (C₃₁H₃2NO₄): 482.2331, found 482.2307. *6-Butyl-7-(2-(trifluoromethyl)phenyl)-14H-*

benzo[6,7]isoquinolino[2,3-a]quinolin-14-one 6g. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 32 mg (65%). Yellow solid, mp = 177-180 °C. Rf = 0.50 (Hexane/EtOAc: 90/10). ¹H NMR (400 MHz, CDCl₃) δ 10.19 (d, J = 8.6 Hz, 1H), 8.78 (d, J = 8.4 Hz, 1H), 7.91-7.84 (m, 3H), 7.84 (d, J = 9.0 Hz, 1H), 7.82-7.78 (m, 1H), 7.70-7.65 (m, 2H), 7.63 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.53-7.44 (m, 1H), 7.44-7.37 (m, 2H), 7.30 (td, J = 7.4, 1.0 Hz, 1H), 7.26 (s, 1H), 7.02 (s, 1H), 6.78 (d, J = 9.0 Hz, 1H), 1.94-1.84 (m, 1H), 1.71-1.60 (m, 1H), 1.37-1.26 (m, 2H), 1.00 (hex, J = 7.4 Hz, 1H), 0.93 (hex, J = 7.2 Hz, 1H), 0.73 (t, I = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 165.3, 138.3, 138.1, 135.9, 135.0, 134.7, 134.6, 133.6, 132.0, 131.9, 131.7 (q, J = 29.7 Hz), 131.4, 128.9, 128.8, 128.7, 128.5, 127.3, 127.1, 126.9 (q, J = 5.0 Hz), 126.6, 126.5, 125.5, 124.9, 124.3 (q, J = 274.5 Hz), 123.4, 120.4, 118.0, 112.5, 34.5, 32.0, 22.4, 13.9. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -59.6. HRMS (ESI+) calculated for [M+H]⁺ (C₃₂H₂₅F₃NO): 496.1883, found 496.1862.

6-Butyl-7-(2-(trifluoromethyl)phenyl)-11H-

thieno[3',2':4,5]*pyrido*[1,2-*a*]*quino*l*in*-11-*one* **6h**. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 26 mg (58%). Yellow solid, mp = 186-189 °C. R_f = 0.60 (Hexane/EtOAc: 90/10).¹H NMR (400 MHz, CDCl₃) δ 9.11 (d, *J* = 9.1 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.65 (dtd, *J* = 7.4, 7.5, 1.4 Hz, 1H), 7.64-7.57 (m, 2H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.43-7.39

(m, 2H), 7.33 (ddd, J = 7.3, 7.3, 1.0 Hz, 1H), 6.99 (s, 1H), 6.48 (d, J = 5.3 Hz, 1H), 2.04-1.88 (m, 1H), 1.80-1.72 (m, 1H), 1.34-1.26 (m, 2H), 0.99 (hex, J = 7.7 Hz, 1H), 0.90 (hex, J = 6.7 Hz, 1H), 0.72 (t, J = 7.3 Hz, 3H). ¹³C{1H} NMR (126 MHz, CDCl₃) δ 160.2, 145.6, 138.1, 136.7, 135.0, 134.7, 133.7, 133.4, 131.7, 130.5 (q, J = 29.6 Hz), 128.7, 128.2, 127.7, 126.8 (q, J = 4.9 Hz), 126.4, 125.8, 125.3, 124.9, 123.5 (q, J = 275.1 Hz), 121.4, 111.7, 34.8, 31.9, 22.3, 13.8. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -59.9. HRMS (ESI+) calculated for [M+H]+ (C₂₆H₂₁F₃NOS): 452.1296, found 452.1282.

6-Propyl-7-(3,4,5-trimethoxyphenyl)-12H-isoquinolino[2,3-

a]quinolin-12-one **6i.** Purified by flash column chromatography (EtOAc/Hexane = 2/8); 36 mg (76%). White solid, mp =161-164 °C. R_f = 0.50 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.74 (d, *J* = 8.6 Hz, 1H), 8.61 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.62 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H), 7.54 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.39-7.28 (m, 3H), 7.31-7.22 (m, 1H), 6.88 (s, 1H), 6.59 (s, 2H), 3.96 (s, 3H), 3.83 (s, 6H), 1.94-1.78 (m, 2H), 1.27 (hex, *J* = 7.3 Hz, 2H), 0.62 (t, *J* = 7.3 Hz, 3H). ¹³C{1H} NMR (126 MHz, CDCl₃) δ 163.7, 153.5, 138.3, 136.6, 135.7, 135.2, 133.9, 133.4, 132.6, 128.7, 128.3, 127.2, 126.7, 126.4, 125.5, 125.4, 125.2, 125.1, 120.5, 117.6, 109.1, 61.4, 56.4 (2C), 37.5, 23.7, 13.7. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₉H₂₈NO₄): 454.2013, found 454.1996.

3-Chloro-6-propyl-7-(3,4,5-trimethoxyphenyl)-12H-

isoquinolino[*2*,*3*-*a*]*quinolin-12-one* **6k**. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 33 mg (67%). White solid, mp = 172-175 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.70 (d, *J* = 9.1 Hz, 1H), 8.59 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.63 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 2.5 Hz, 1H), 7.27 (dd, *J* = 9.5, 2.5 Hz, 1H), 6.79 (s, 1H), 6.58 (s, 2H), 3.96 (s, 3H), 3.83 (s, 6H), 1.86-1.78 (m, 2H), 1.26 (hex, *J* = 7.3 Hz, 2H), 0.62 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 163.5, 153.6, 138.4, 137.2, 136.5, 133.5, 133.3, 133.1, 132.8, 130.4, 128.2, 127.5, 127.0, 126.9, 126.8, 125.6, 125.5, 125.0, 122.0, 118.3, 109.0, 61.3, 56.4 (2C), 37.5, 23.6, 13.7. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₉H₂₇ClNO₄): 488.1629, found 488.1607.

9-Chloro-6-cyclohexyl-7-(3,4,5-trimethoxyphenyl)-12H-

isoquinolino[*2*,*3*-*a*]*quinolin-12-one* **61**. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 37 mg (71%), 240 mg (69%) on a 0.66 mmol scale. White solid, mp =178-181 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (500 MHz, CDCl₃) δ 8.69 (d, *J* = 8.5 Hz, 1H), 8.53 (d, *J* = 8.6 Hz, 1H), 7.47 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.38 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.37-7.33 (m, 2H), 7.28 (td, *J* = 7.4, 1.0 Hz, 1H), 6.99 (s, 1H), 6.57 (s, 1H), 3.97 (s, 3H), 3.84 (s, 6H), 1.86 (tt, *J* = 11.5, 2.9 Hz, 1H), 1.66-1.50 (m, 4H), 1.13 (tdd, *J* = 12.7, 12.7, 2.8 Hz, 2H), 1.09-0.97 (m, 2H), 0.76 (ttd, *J* = 12.4, 12.4, 3.4 Hz, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 163.1, 153.9, 140.7, 139.3, 138.5, 137.8, 135.3, 134.7, 133.2, 130.1, 127.4, 127.1, 126.74, 126.66, 125.5, 125.1, 124.7, 123.4, 120.0, 116.4, 108.8, 61.4, 56.5 (2C), 39.4, 34.1, 27.0, 26.2. HRMS (ESI⁺) calculated for [M+H]⁺ (C₃₂H₃₁ClO₄N): 528.1942, found 528.1918.

9-Chloro-6-cyclohexyl-7-(2-(trifluoromethyl)phenyl)-12H-

isoquinolino[*2*,3-*a*]*quinolin-12-one* **6m.** Purified by flash column chromatography EtOAc/Hexane = 1/9); 36 mg (71%). Yellow solid, mp = 170-173 °C. $R_f = 0.60$ (Hexane/EtOAc: 90/10). ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, *J* = 8.3 Hz, 1H), 8.51 (d, *J* = 8.6 Hz, 1H), 7.89 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.78-7.63 (m, 2H), 7.44 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.39-7.32 (m, 2H), 7.30-7.24 (m, 1H), 7.01 (s, 1H), 6.71 (d, *J* = 1.9 Hz, 1H), 1.75 (tt, *J* = 11.4, 2.7 Hz, 1H), 1.66-1.47 (m, 5H), 1.32 (tdd, *J* = 12.0, 11.9, 2.8 Hz, 1H), 1.11-0.91 (m, 2H), 0.64

(ttd, J = 12.5, 12.5, 3.9 Hz, 1H), 0.50 (ttd, J = 12.9, 12.7, 3.9 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 163.8, 140.2, 139.1, 138.3, 137.0, 135.9, 134.6, 133.9, 132.6, 131.2 (q, J = 29.8 Hz), 129.8, 129.0, 127.4, 127.4 (q, J = 4.4 Hz), 127.3, 127.0, 126.7, 125.6, 124.9, 124.6, 123.9 (q, J = 274.4 Hz), 123.1, 120.2, 111.8, 39.1, 34.8, 32.9, 26.8, 26.4, 25.9. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -60.6. HRMS (ESI+) calculated for [M+H]+ (C₃₀H₂₄ClF₃NO): 506.1499, found 506.1492.

6-Benzyl-9-chloro-7-(3,4,5-trimethoxyphenyl)-12H-

isoquinolino[2,3-*a*]*quinolin-12-one* **6n**. Purified by flash column chromatography EtOAc/Hexane = 2/8); 37 mg (69%). White solid, mp = 182-186 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.56 (d, *J* = 8.5 Hz, 1H), 7.66-7.57 (m, 4H), 7.38 (td, *J* = 7.4, 7.2, 0.9 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.12 (s, 1H), 7.05-7.01 (m, 3H), 6.95 (dd, *J* = 7.1, 2.4 Hz, 2H), 6.49 (s, 1H), 4.06 (s, 2H), 4.02 (s, 3H), 3.67 (s, 3H), 3.60 (s, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 192.4, 151.3, 141.7, 139.9, 139.1, 138.3, 138.2, 137.9, 134.1, 131.5, 130.4, 129.4, 128.7, 128.4, 128.1, 127.9, 127.4, 127.2, 126.4, 124.3, 123.8, 120.6, 120.5, 110.9, 97.0, 62.2, 61.8, 56.1, 39.8. HRMS (ESI+) calculated for [M+H]+ (C₃₃H₂₇ClNO₄): 536.1629, found 536.1616.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data of compounds **3** and **4**, ¹H, ¹³C, ¹¹B and ¹⁹F NMR spectra for new compounds **3-6**, X-ray crystallography data of compounds **51** and **6m** (file type, i.e., PDF)

Accession Codes

CCDC 2205942 and **2205943** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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