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One-Pot Synthesis of *N*-Fused Quinolone-4 Tetracyclic Scaffolds from 2,2-Disubstituted Indolin-3-ones

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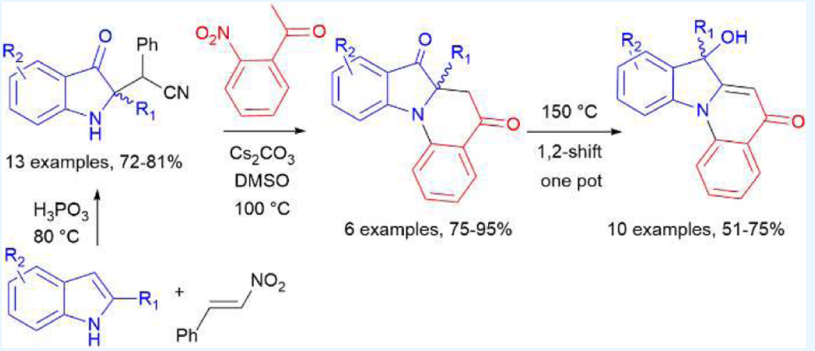

ABSTRACT: A cascade transformation of C2-quaternary indoxyls leading to an efficient assembly of complex (dihydro)indolo[1,2-*a*]quinolin-5-one ring systems is reported. The method involves the gram-scale preparation of 2-(2-aryl-3-oxoindolin-2-yl)-2-phenylacetonitriles which are then converted with methyl ketones to the corresponding 2-(2-oxo-2-aryl(alkyl)ethyl)-2-phenylindolin-3-ones. The latter can either be isolated with good yields (75−96%) or, in the case of *o*-nitroacetophenone, used *in situ* for further base-assisted intramolecular S_NAr cyclization resulting in indoxyl-fused quinolone-4 hybrids (up to 95%).

1. INTRODUCTION

While primarily known for its antibacterial properties,[1−3] the quinolone-4 core has long been recognized as an omnipotent pharmacological motif demonstrating a wide range of biological activities including anticancer, antimalarial, antifungal, anti-inflammatory, and antiviral effects.[4,5] In this view, the exploration[6,7] of new structurally diverse quinolone derivatives remains highly valuable for the development of novel drugs across various therapeutic areas. Apart from structure−activity relationship (SAR)-driven[8] selective functionalization[9] of the quinolone skeleton at specific positions, another approach to achieving diversity lies in combining the quinolone moiety with other pharmacophores, including ring-fused ones. In recent years, these hybrid molecules[10,11] have attracted particular interest due to their potential ability to act on different drug targets (dual mode of action) and to overcome some of the drawbacks (toxicity, drug resistance, side effects, etc.) associated with each of the substructural domains.

Herein, we would like to present an effective, one-pot synthesis of previously unknown tetracyclic quinolones **1** and **2** (Figure 1) in which the potent indoxyl entity (shaded blue) found in many natural alkaloids[12] is embedded within the quinolinone framework (highlighted in black).

It should be noted that there are numerous examples (Figure 2) of ring-fused 4-quinolones,[7,13] both naturally occurring[14−16] and synthetic.[17−19] For instance, the tricyclic alkaloid **3**, a member of the *Penicillium*-derived quinolactacin family,[15] has been shown to inhibit acetylcholinesterase (AChE), whereas

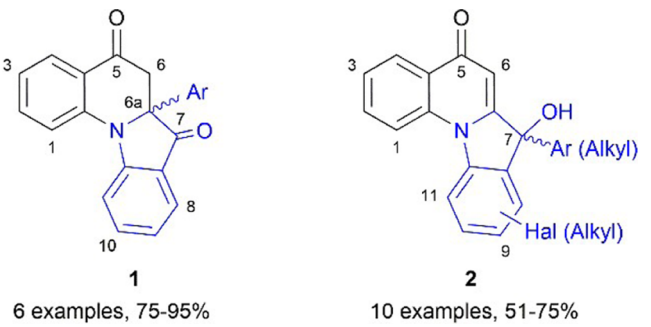

Figure 1. Indolo[1,2-*a*]quinolinones **1** and **2** prepared by a single-step, cascade annulation reaction as described here.

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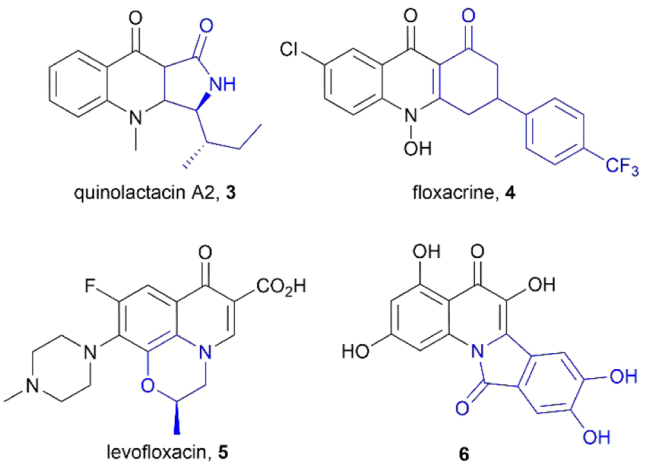


Figure 2. Selected examples of ring-fused biologically active 4-quinolones.

floxacrine **4** displays antimalarial activity.[20] Third-generation fluoroquinolone **5** is one of the most commonly prescribed antibiotics[2] and the compound **6**[21] exhibits potential antitumor effects.

In contrast, only a small number[21−25] of the polycyclic quinolone derivatives annulated at face *a* (as in isoindolo[2,1-*a*]quinolinone **6**) have been described so far, making such templates generally underrepresented in drug discovery. Therefore, unlike the much more common indolo[1,2-*a*]quinolines,[26,27] to our knowledge, no examples of indolo-[1,2-*a*]quinolinone-**2**-like structures have been reported in the literature, and to date, only one representative of quinolone **1** is known.[28]

2. RESULTS AND DISCUSSION

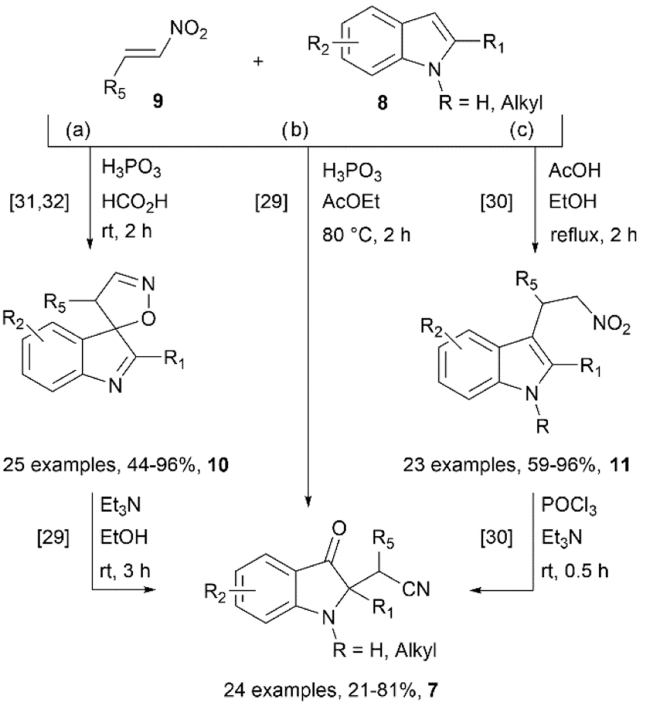
Some years ago, we developed several convenient protocols[29,30] for the gram-scale synthesis of 2-(3-oxoindolin-2-yl)-2-arylacetonitriles **7** (Scheme 1) starting from 2-substituted indoles **8** and nitroalkenes **9**. One of these methods[29] involves a direct, single-step, acid-catalyzed preparation of acetonitriles **7** (Scheme 1b) while the other two proceed through chromatographically isolated intermediates—spirocyclic indolines **10**[31,32] or nitroethylindoles **11**[30] (Scheme 1a,c, respectively).

It is worth noting that target compounds **7** belong to a subclass of 2,2-disubstituted indolin-3-ones (also referred to as pseudoindoxyls) which is both interesting from the synthetic[33,34] (as a versatile building block to related heterocycles) and the medicinal chemistry viewpoint as they are structural parts of many biologically active natural products.[12] For us, subsequent studies of such C2-quaternary indolin-3-ones **7** indeed turned out to be a fruitful area of research, leading to the discovery of several unexpected rearrangements[35−37] (Scheme 2).

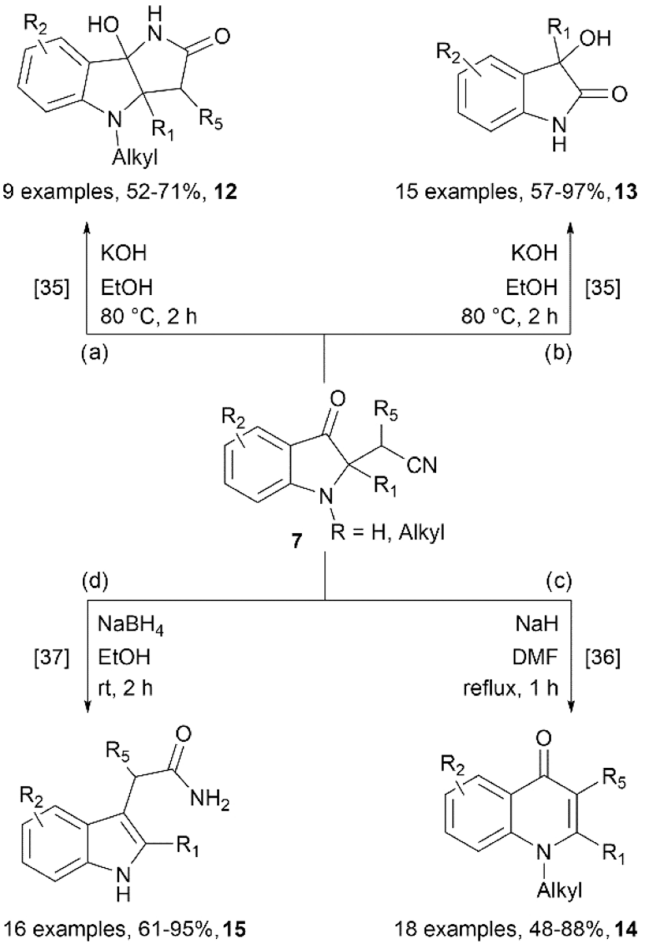
We speculated back then that the KOH-assisted transformation[35] of *N*-unsubstituted 2-(3-oxoindolin-2-yl)-acetonitriles **7** to 3-hydroxyindolin-2-ones **13** (Scheme 2b) likely occurs through intermediates **17** (Scheme 3), which are essentially activated C-acylimines known[38] for their diverse reactivity and ambiphilic properties.

Hence, for example, chemoselective nucleophilic addition at the imine carbon of such preformed indolin-3-ones **17**[39,40] is one of the two most common synthetic approaches to 2,2-

Scheme 1. Synthetic Pathways for Preparation of Acetonitriles 7 from Indoles 8 and Nitroalkenes 9



Scheme 2. Cascade Rearrangements Involving Acetonitriles 7



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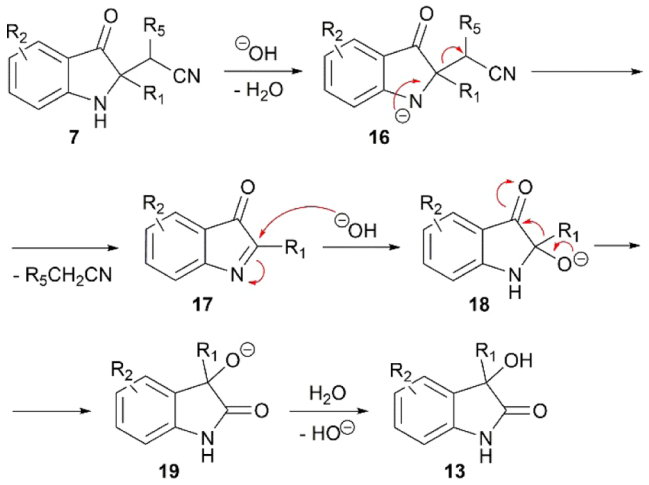
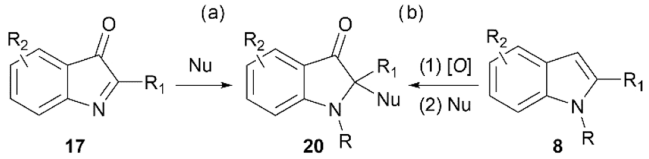
Scheme 3. Plausible Mechanism of the Acetonitriles 7 to Indolin-2-Ones 13 Conversion



disubstituted indoxyls **20** (Scheme 4a) followed by direct oxidative dearomatization on 2-substituted indoles **8** with various nucleophiles[41,42] (Scheme 4b).

Scheme 4. General Approaches to 2,2-Disubstituted Indoxyls 20



Based on the preceding considerations, it was hypothesized that under specific base/reagent conditions, iminium intermediates **17** generated *in situ* from acetonitriles **7** (Scheme 3) could be trapped with a suitable nucleophilic reagent leading to the target C2-quaternary indolin-3-ones **20** (Scheme 4). We selected simple ketones **21** as model coupling substrates because, upon a reaction with acetonitriles **22**, they are expected to form the corresponding indolin-3-ones **23** featuring a *β*-carbonyl functional group at the C2 position (Scheme 5l). This kind of functionalized pseudoindoxyls has been shown[28,43] to be useful in the synthesis of other *N*-heterocyclic derivatives. However, only a few number of efficient, practical approaches[28,43−52] to such derivatives is known (Scheme 5a−k).

The results of the screening experiments are presented in Table 1. They were very encouraging, confirming the validity of our initial concept while the identified reaction conditions—1.5 equiv of cesium carbonate in 1,4-dioxane at 100 °C (entry 8)—consistently delivered an excellent yield (up to 95%) of the target indolinone **23aa**.

Having these at hand, synthesizing a set of 16 indolinone **23** samples (Scheme 6) to assess the substrate scope of the method (five indolinones **22** vs 11 ketones **21**) was straightforward.

The presented data highlights excellent yields (75−96%) across a wide range of starting reagents. That, coupled with the fact that nitriles **22** are readily available in one step[29] on a gram scale from the corresponding 2-substituted indoles **8** and nitroalkenes **9** (Scheme 1), makes the given procedure a valuable addition to already existing methods for the preparation of such C2-quaternary indoxyls **23** (Scheme 5a−k). As expected, the latter in our case were formed as racemates except for the compound **23al** which gave a diastereomeric mixture of about 1:1. The structure and purity of all new compounds were unambiguously established using NMR and high-resolution mass spectrometry, and the identity of the known indolinones **23** was confirmed by comparison of their physical and spectral data with those previously described.

The plausible mechanism for this transformation appears relatively straightforward (Scheme 7). It likely proceeds, as in case[35] of hydroxyl ion in the role of a nucleophile (Scheme 3), through the ejection of a stabilized benzyl cyanide ion **25** as a good leaving group.

As previously noted, C2-disubstituted indolin-3-ones **23** containing *β*-carbonyl functions can undergo further useful synthetic transformations[28,43] (Scheme 8).

We were particularly intrigued by the sequence (h−i) in Scheme 5 because it offers access not only to virtually unknown indoxyl-fused 4-quinolinones **31** but also, upon further carbonyl group reduction, to tetracyclic tetrahydroindolo[1,2-*a*]quinolines **32**. The structural core of these compounds is found in a large family[53] of plant-derived monoterpene indole alkaloids (Figure 3).

The literature review revealed that dihydroindolo[1,2-*a*]quinoline-5,7-dione **31** is apparently the only reported representative of its class, so the development of practical approaches to the latter is imperative for the search for novel therapeutic candidates among such *N*-condensed 4-quinolones. It should be noted that around the same time, we were also working on a separate project[54] focused on the intramolecular cyclization of 2′-nitrochalcone derivatives via *ipso*-substitution of the $-NO_2$ group. This experience led us to hypothesize that the *ortho*-nitro group might be more effective compared to the bromine one in the desired annulation reaction of *o*-substituted indolinone **30** (Scheme 8h). Furthermore, *o*-nitroacetophenones **21** needed to afford the corresponding indolinones **23** are generally more readily available than their Br-substituted counterparts. And, since we already knew that *o*-nitroindoxyl **23af** (Scheme 6) could be obtained with near-quantitative yield, it was decided from the very beginning to pursue the development of a one-pot, tandem transformation leading to the target tetracyclic quinolones **1** (Scheme 9).

As previously discussed, the optimal conditions for S_NAr intramolecular cyclization involving *ipso*-substitution of the $-NO_2$ group which proved successful in our prior project[54] was a combination of DBU (2 equiv) at 80 °C in dimethyl sulfoxide (DMSO) as the solvent. So, we first tried to carry out the intended annulation reaction in the presence of DBU and Cs_2CO_3 but in a dioxane medium for convenience. This did not work, yielding only the expected indolinone **23af** and not the target quinolone **1af**. However, replacing dioxane with DMSO and running the reaction sequentially, first with 1.5 equiv of Cs_2CO_3 at 100 °C for 1 h and then adding 2 equiv of DBU and heating at 100 °C for another hour, the desired product **1af** was obtained with an excellent yield of 95%. At this point, we decided to focus on creating a small library of these *N*-bridged heterocycles **1** (Scheme 10), as we did not see much potential in searching for alternative options. In a process, we accidentally made another interesting discovery when a laboratory hot plate malfunctioned, causing the oil bath temperature to exceed 150 °C. This resulted in the formation of a previously unknown compound **2af** via, supposedly, 1,2-

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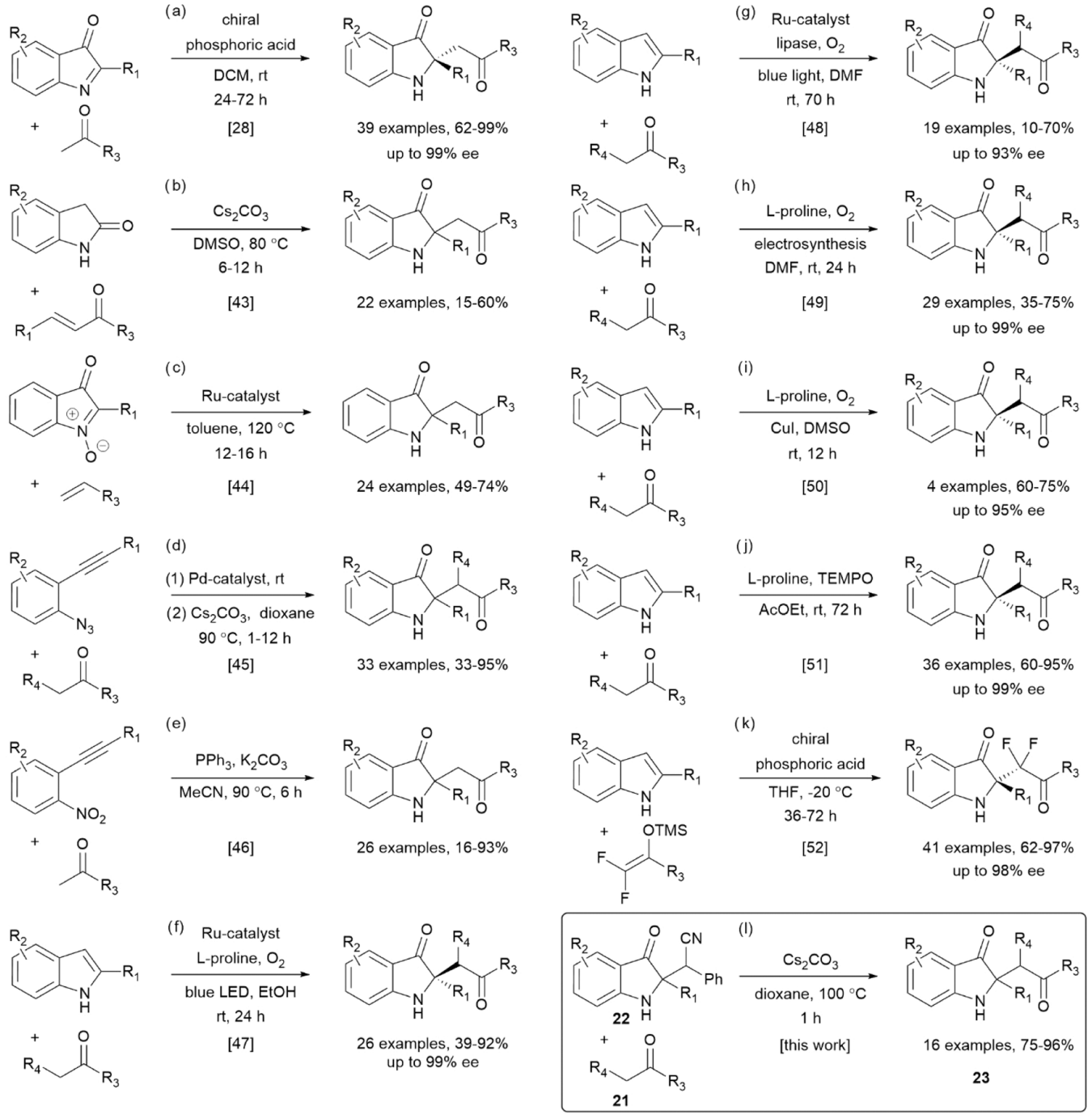
Scheme 5. Synthetic Pathways to 2,2-Disubstituted Indoxyls 23: Previous and Present Work



aryl shift. We took advantage of this unexpected finding and prepared another set of such indolo[1,2-*a*]quinolinones **2** (Scheme 10). Interestingly, the 1,2-shift in the *tert*-butyl derivative **2lf** occurred at a temperature as low as 100 °C which can be attributed to the high mobility of the *t*-Bu group.

As can be seen, the yields of both tetracyclic heterocycles **1** and **2** are quite good (51−95%), which makes the described approach to these compounds practical. A complete set of NMR and high-resolution mass spectrometry (HRMS) data confirms their identity and, additionally, the lattice parameters and crystal structure of the compounds **1gf** and **2df** were obtained by X-ray diffraction analysis (Figures 4 and 5, respectively).

The mechanism of this reaction is believed to be a S_NAr intramolecular cyclization, as outlined below (Scheme 11).

The reaction begins with *NH*-deprotonation to produce anion **33**, followed by nucleophilic attack at the *ipso* position of the $-NO_2$ group. Our limited study indicates that the solvent-base combination may influence the stability of the sigma complex **34** since the DMSO−DBU pair provided the best results. Elimination of NO_2 anion then triggers rearomatization leading to the formation of product **1af**. An increase in temperature accompanied by a 4-fold excess of bases, leads to initially an anion **35** which is then rearranged through a 1,2-aryl shift into the more stable intermediate **36** and then into the product **2af**. The above-mentioned 1,2-shift in indolin-3-

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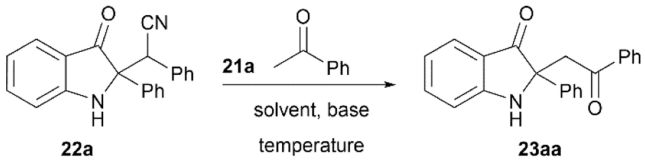
Table 1. Results of Screening Experiments to Afford 2,2-Disubstituted Indolin-3-one 23aa[a]



entry	solvent	base (equiv)	T (°C)	yield (%)[b]
1	xylene	MeONa (1)	reflux	30
2	DMF	NaH (1)	100	49
3	DMSO	Cs_2CO_3 (1)	100	57
4	DMSO	DBU (1)	100	15
5	DMSO	KOH (1)	100	0
6	THF	Cs_2CO_3 (1)	reflux	71
7	dioxane	Cs_2CO_3 (1)	reflux	89
8	dioxane	Cs_2CO_3 (1.5)	reflux	95
9	dioxane	Cs_2CO_3 (3)	reflux	95
10	dioxane	K_2CO_3 (1.5)	reflux	82

[a]Reaction conditions: **22a** (1.0 mmol), **21a** (1.0 mmol), base (× equiv) in solvent (2.0 mL) at the given temperature for 1 h. [b]Isolated yield.

one systems has already been observed[35] by us (Scheme 3) where it resulted in the formation of a more stable cyclic amide **19**. The main driving force behind this rearrangement is the aromatization of the quinolone moiety.

3. CONCLUSIONS

This paper presents a new, efficient Cs_2CO_3-assisted reaction for preparing 2-(2-oxo-(aryl/alkyl)ethyl)-2-(aryl/alkyl)indolin-3-ones. Although many approaches to the latter have been proposed, the given procedure starts with readily available on a gram scale in a single step 2-(2-aryl-3-oxoindolin-2-yl)-2-phenylacetonitriles and can therefore be considered a practical and valuable alternative to the existing pathways. With this discovery, we developed a robust, one-pot synthetic protocol that led to previously largely unknown classes of tetracyclic *N*-fused indoloquinolines that combine two of the most potent pharmacophores within a single molecule.

4. EXPERIMENTAL PART

4.1. General Information. NMR spectra, ^{1}H, ^{13}C, and ^{19}F were measured in solutions of $CDCl_3$ or DMSO-d_6 on Bruker AVANCE-III HD instrument (at 400, 101, and 376 MHz, respectively). Residual solvent signals were used as internal standards, in DMSO-d_6 (2.50 ppm for ^{1}H, and 40.45 ppm for ^{13}C nuclei) or $CDCl_3$ (7.26 ppm for ^{1}H, and 77.16 ppm for ^{13}C nuclei). HRMS spectra were measured on Bruker maXis impact (electrospray ionization, in MeCN solutions, employing HCO_2Na−HCO_2H for calibration). IR spectra were measured on FT-IR spectrometer Shimadzu IRAffinity-1S equipped with an ATR sampling module. Reaction progress, purity of isolated compounds, and R_f values were monitored with thin-layer chromatography (TLC) on Silufol UV-254 plates. Column chromatography was performed on silica gel (32−63 μm, 60 Å pore size). Melting points were measured with the Stuart SMP30 apparatus. All acetonitriles **22** except novel **22l,e,i,n** were synthesized according to the previously reported procedure[29] and were identical to those described. All reagents and solvents were purchased from commercial vendors.

4.2. Preparation of Novel Acetonitriles 22l,e,i,n (General Procedure).[29] Wheaton microreactor equipped with magnetic spin-vane and Mininert valve was charged with a mixture of (2-nitrovinyl)benzene (2.0 mmol), corresponding 2-substituted indole (2.0 mmol), phosphorus acid (2.0 g), and formic acid (2.0 g). The mixture was vigorously stirred for 2 h at room temperature, while it turned dark red and homogenized. Then, the mixture was poured into water (50 mL) and the formed crude spirane precipitate was collected and washed with water (4 × 20 mL), dried, and dissolved in ethanol (4 mL). Triethylamine (204 mg, 2.0 mmol) was added, and the resulting solution was stirred at room temperature for 3 h. The crystalline precipitate of crude product was formed, which was collected and purified by preparative column chromatography on silica gel, eluting with ethyl acetate/hexane mixture (v/v).

*4.2.1. 2-(2-(tert-Butyl)-3-oxoindolin-2-yl)-2-phenylacetonitrile (**22l**).* This compound was prepared by general procedure employing 2-(*tert*-butyl)-1*H*-indole (346 mg, 2.0 mmol) (346 mg, 2.0 mmol) and (2-nitro vinyl)benzene (298 mg, 2.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:8, v/v). The titled compound was obtained as a yellowish solid, mp 206−207 °C, R_f 0.22 (EtOAc/hexane, 1:6, v/v). Yield 444 mg (1.46 mmol, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (s, 1H), 7.53−7.46 (m, 2H), 7.41−7.35 (m, 2H), 7.33−7.27 (m, 3H), 6.86 (d, J = 8.1 Hz, 1H), 6.64 (t, J = 7.3 Hz, 1H), 4.66 (s, 1H), 0.85 (s, 9H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 201.5, 161.8, 137.4, 133.5, 129.6 (2C), 128.4, 128.3 (2C), 123.3, 120.4, 119.6, 117.5, 111.5, 73.5, 40.1, 38.0, 25.3 (3C); FTIR, ν_{max}: 3256, 2978, 2249, 1658, 1615, 1471, 1329, 1258, 1165, 1056 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{20}H_{20}N_2NaO$ [M + Na]$^+$: 327.1468, found: 327.1469 (−0.3 ppm).

*4.2.2. 2-(5,6-Dimethoxy-3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile (**22e**).* This compound was prepared by general procedure employing 5,6-dimethoxy-2-phenyl-1*H*-indole (506 mg, 2.0 mmol) and (*E*)-(2-nitrovinyl)benzene (298 mg, 2.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:2, v/v). The titled compound was obtained as a brown solid, mp 271−274 °C, R_f 0.11 (EtOAc/hexane, 1:2, v/v). Yield 614 mg (1.6 mmol, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.54 (d, J = 7.3 Hz, 2H), 7.32−7.19 (m, 8H), 6.87 (s, 1H), 6.68 (s, 1H), 5.21 (s, 1H), 3.90 (s, 3H), 3.69 (s, 3H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 196.1, 159.6, 158.8, 143.8, 135.4, 132.0, 129.4 (2C), 128.3 (2C), 128.2 (3C), 128.0, 126.1 (2C), 119.1, 108.6, 104.3, 94.6, 73.5, 55.9, 55.7, 43.5. FTIR, ν_{max}: 3226, 2311, 2286, 1703, 1665, 1558, 1487, 1464, 1339, 1279, 1159 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{24}H_{20}N_2NaO_3$ [M + Na]$^+$: 407.1336, found: 407.1338 (−0.5 ppm).

*4.2.3. 2-(6-Methoxy-3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile (**22i**).* This compound was prepared by general procedure employing 6-methoxy-2-phenyl-1*H*-indole (446 mg, 2.0 mmol) and (*E*)-(2-nitrovinyl)benzene (298 mg, 2.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:2, v/v). The titled compound was obtained as a yellow solid, mp 256−258 °C, R_f 0.22 (EtOAc/hexane, 1:2, v/v). Yield 552 mg (1.56 mmol, 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.55 (d, J = 7.1 Hz, 2H), 7.37 (d, J = 8.6 Hz, 1H), 7.28−7.23 (m, 8H), 6.58 (d, J = 1.9 Hz, 1H), 6.37 (dd, J = 8.6, 2.0 Hz, 1H), 5.23 (s, 1H), 3.86 (s, 3H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 196.4, 168.2, 164.4, 135.7, 132.2, 129.8 (2C), 128.76 (2C), 128.74 (3C), 128.5,

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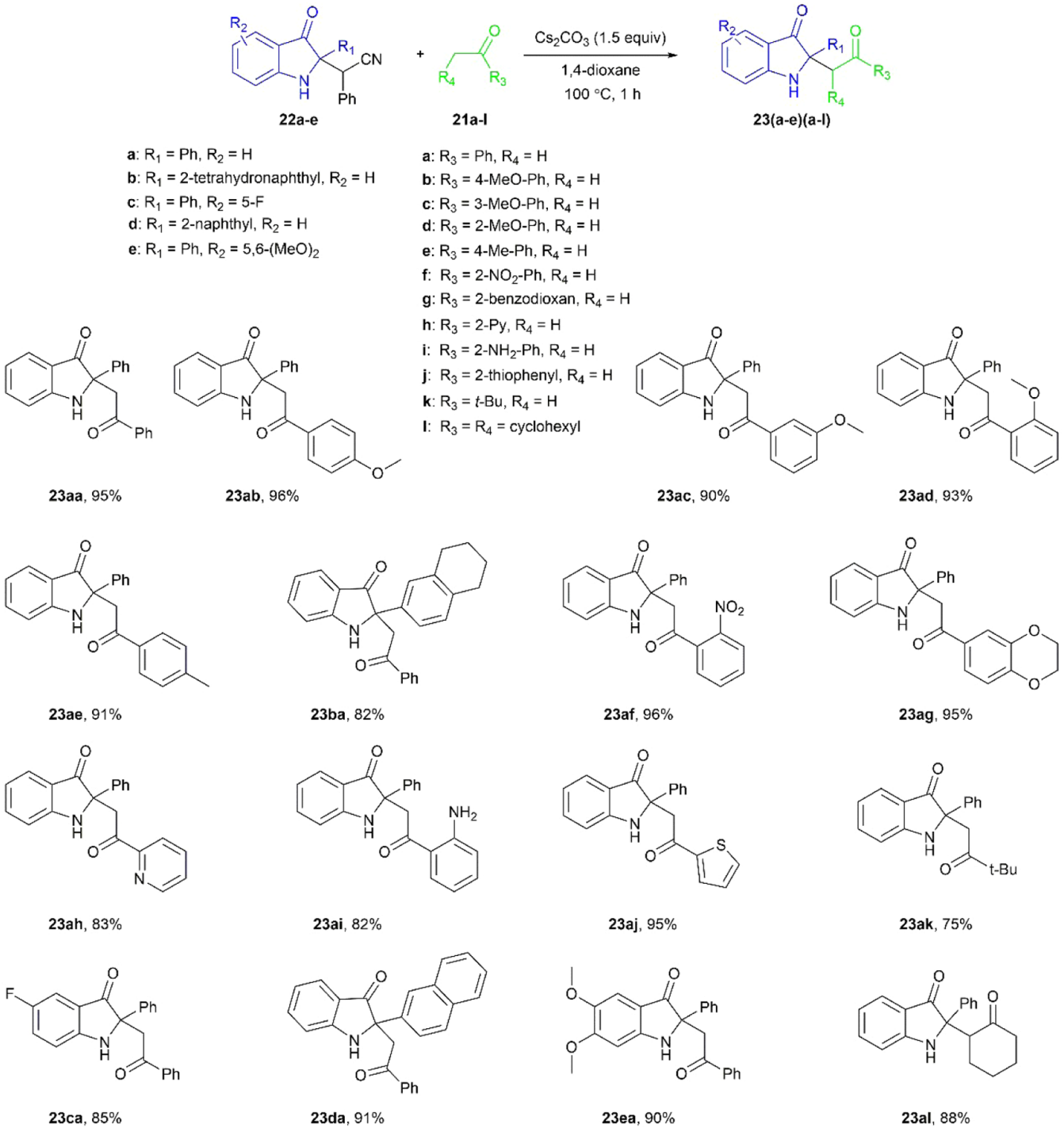
Scheme 6. Substrate Scope in Cs_2CO_3-Assisted Reaction of Acetonitriles 22 with Various Ketones 21



126.6 (3C), 119.4, 111.5, 109.3, 94.8, 73.9, 56.1, 43.9. FTIR, ν_{max}: 3226, 2331, 1711, 1649, 1575, 1481, 1450, 1339, 1253, 1147 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{18}N_2NaO_2$ $[M + Na]^+$: 377.1260, found: 377.1261 (−0.3 ppm).

*4.2.4. 2-(5-Fluoro-2-(naphthalen-2-yl)-3-oxoindolin-2-yl)-2-phenylacetonitrile (**22n**).* This compound was prepared by general procedure employing 5-fluoro-2-(naphthalen-2-yl)-1*H*-indole (522 mg, 2.0 mmol), (*E*)-(2-nitrovinyl)benzene (298 mg, 2.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a yellow solid, mp 238−239 °C, R_f 0.21 (EtOAc/hexane, 1:4, v/v). Yield 564 mg (1.44 mmol, 72%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.97 (s, 1H), 7.93−7.82 (m, 3H), 7.77 (d, J = 8.4 Hz, 1H), 7.53−7.45 (m, 3H), 7.32−7.25 (m, 3H), 7.25−7.17 (m, 4H), 5.48 (s, 1H). ^{13}C {^1H} NMR (101 MHz, DMSO-d_6) δ 198.5, 158.7, 155.6 (d, J = 236.9 Hz), 132.4, 132.3, 132.0, 131.5, 129.4 (2C), 128.4 (3C), 128.2, 127.9, 127.5, 126.7, 126.6, 126.5 (d, J = 27.5 Hz), 125.2, 124.1, 118.8, 117.7 (d, J = 7.6 Hz), 114.1 (d, J = 7.7 Hz), 109.3 (d, J = 22.5 Hz), 74.4, 43.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ −125.27. FTIR, ν_{max}: 3349, 2273, 1711, 1647, 1511, 1476, 1337, 1251, 1209 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{26}H_{17}FN_2NaO$ $[M + Na]^+$: 415.1217, found: 415.1214 (0.7 ppm).

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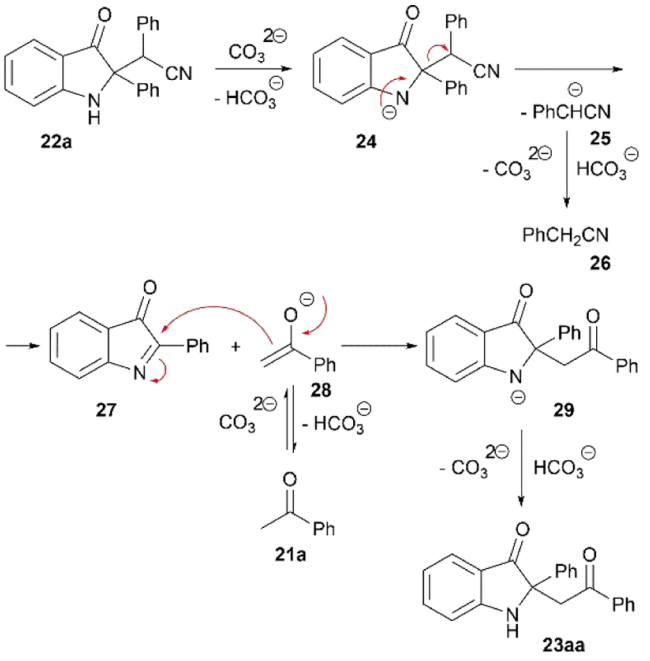
Scheme 7. Proposed Mechanism to Product 23aa



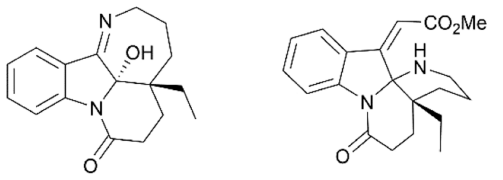
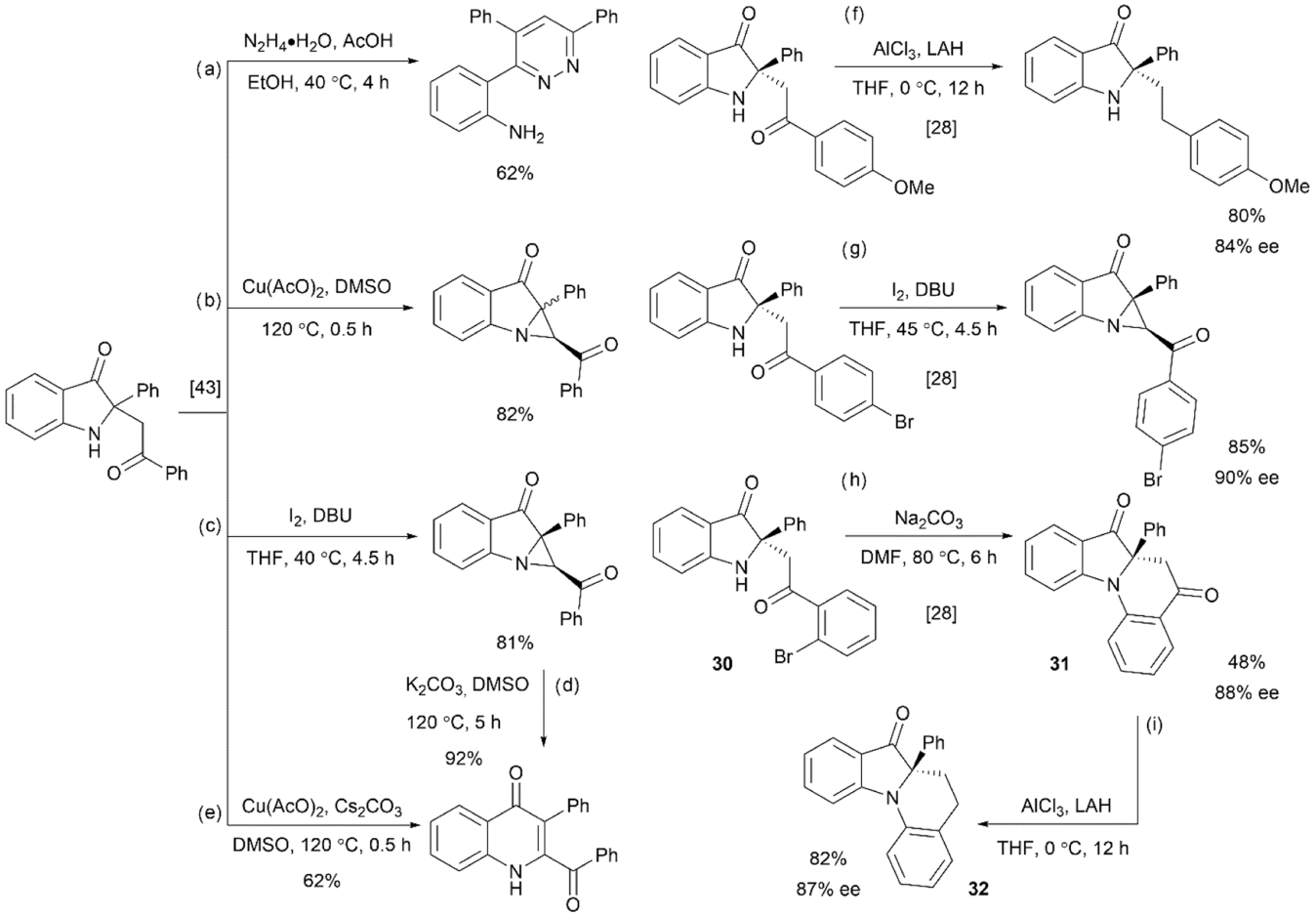


Figure 3. Some polycyclic indole-based alkaloids isolated from *Kopsia* plants.

4.3. Preparation of Indolinones 23 (Typical Procedure A). Starting acetonitrile **22** (1.0 mmol), corresponding methylketone (**21**) (1.0 mmol), and 2 mL of 1,4-dioxane were charged in a 10 mL round-bottom flask. Then, Cs_2CO_3 (489 mg, 1.5 mmol) was added and the resulting mixture was stirred at 100 °C for 1 h. The reaction progress was monitored by TLC. After completion reaction mixture was poured into water and extracted with EtOAc (4 × 25 mL). The combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by preparative column chromatography on silica gel, eluting with ethyl acetate/hexane mixture (v/v).

*4.3.1. 2-(2-Oxo-2-phenylethyl)-2-phenylindolin-3-one (**23aa**).*[28,55] This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), acetophenone **21a** (120 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as a pale-yellow solid, mp 186−187 °C, (lit.[55] mp 147−149 °C), R_f 0.38 (EtOAc/hexane, 1:4, v/v). Yield 311 mg

Scheme 8. Known Synthetic Applications Involving Indolinones 23



https://doi.org/10.1021/acsomega.4c07691
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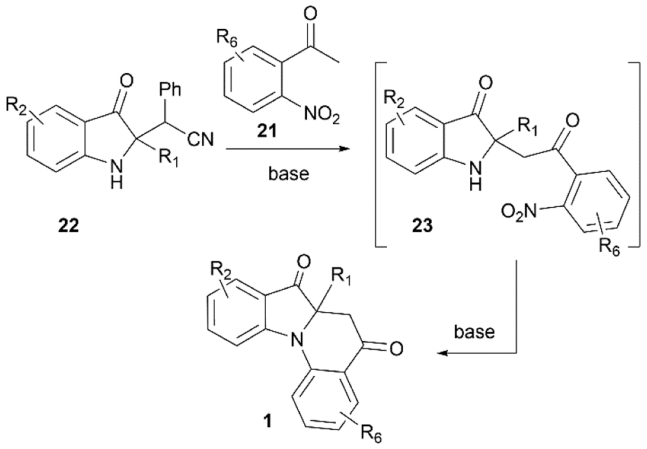
Scheme 9. Proposed Single-Step, Cascade Pathway for Preparation of Fused 4-quinolones 1 from Acetonitriles 22



(0.95 mmol, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00−7.91 (m, 3H), 7.63 (t, J = 7.3 Hz, 1H), 7.56 (d, J = 7.5 Hz, 2H), 7.53−7.44 (m, 3H), 7.41 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.28−7.21 (m, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.72 (t, J = 7.3 Hz, 1H), 4.22 (d, J = 18.1 Hz, 1H), 3.75 (d, J = 18.1 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.7, 196.3, 161.2, 139.3, 137.0, 136.4, 133.5, 128.8 (2C), 128.4 (2C), 128.1 (2C), 127.3, 125.5 (2C), 124.4, 118.3, 117.4, 111.9, 68.8, 45.7. FTIR, ν_{max}: 3246, 1682, 1617, 1483, 1221, 1059, 756, 691 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{22}H_{17}NNaO_2$ [M + Na]$^+$: 350.1151, found: 350.1154 (−0.9 ppm).

*4.3.2. 2-(2-(4-Methoxyphenyl)-2-oxoethyl)-2-phenylindolin-3-one (**23ab**).*[28,55] This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(4-methoxyphenyl)ethanone **21b** (150 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v, EtOAc). The titled compound was obtained as a pale-yellow solid, mp 208−210 °C (lit.[55] mp 205−206 °C), R_f 0.27 (EtOAc/hexane, 1:4, v/v). Yield 343 mg (0.96 mmol, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 8.6 Hz, 3H), 7.54 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.02 (dd, J = 8.5, 3.2 Hz, 3H), 6.71 (t, J = 7.3 Hz, 1H), 4.16 (d, J = 17.9 Hz, 1H), 3.82 (s, 3H), 3.66 (d, J = 17.9 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.7, 194.6, 163.3, 161.1, 139.4, 137.0, 130.5 (2C), 129.4, 128.4 (2C), 127.2, 125.5 (2C), 124.3, 118.2, 117.3, 113.9 (2C), 111.9, 68.9, 55.6, 45.3. FTIR, ν_{max}: 3327, 1684, 1557, 1487, 1249, 1171, 821, 754, 702 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{19}NNaO_3$ [M + Na]$^+$: 380.1257, found: 380.1252 (1.3 ppm).

*4.3.3. 2-(2-(3-Methoxyphenyl)-2-oxoethyl)-2-phenylindolin-3-one (**23ac**).*[28] This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(3-methoxyphenyl)ethanone **21c** (150 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as a pale-yellow solid, mp 138−140 °C (lit.[28] mp 97−99 °C), R_f 0.32 (EtOAc/hexane, 1:4, v/v). Yield 321 mg (0.90 mmol, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.59−7.51 (m, 3H), 7.49−7.38 (m, 4H), 7.32 (t, J = 7.4 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.20 (dd, J = 8.1, 2.0 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.71 (t, J = 7.3 Hz, 1H), 4.18 (d, J = 18.2 Hz, 1H), 3.79 (s, 3H), 3.76 (d, J = 18.2 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.6, 196.1, 161.2, 159.4, 139.3, 137.7, 137.0, 129.9, 128.4 (2C), 127.2, 125.5 (2C), 124.3, 120.7, 119.7, 118.3, 117.4, 112.3, 111.9, 68.8, 55.3, 45.8. FTIR, ν_{max}: 3373, 1701, 1682, 1613, 1494, 1322, 1008, 750 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{19}NNaO_3$ [M + Na]$^+$: 380.1257, found: 380.1259 (−0.5 ppm).

*4.3.4. 2-(2-(2-Methoxyphenyl)-2-oxoethyl)-2-phenylindolin-3-one (**23ad**).* This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(2-methoxyphenyl)ethanone **21d** (150 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as a pale-yellow solid, mp 131−133 °C, R_f 0.27 (EtOAc/hexane, 1:4, v/v). Yield 321 mg (0.93 mmol, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.53 (t, J = 7.9 Hz, 1H), 7.47 (dd, J = 13.1, 7.8 Hz, 4H), 7.37 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.70 (t, J = 7.3 Hz, 1H), 4.09 (d, J = 18.1 Hz, 1H), 3.88 (s, 3H), 3.57 (d, J = 18.1 Hz, 1H).^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.4, 197.4, 161.1, 158.4, 139.3 (2C), 137.0, 134.1, 129.5, 128.4 (2C), 127.1, 125.3 (2C), 124.3, 120.5, 118.0, 117.3, 112.5, 111.8, 69.0, 55.8, 50.6. FTIR, ν_{max}: 3231, 1682, 1556, 1489, 1322, 1242, 1177, 1012, 763 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{19}NNaO_3$ [M + Na]$^+$: 380.1257, found: 380.1259 (−0.5 ppm).

*4.3.5. 2-(2-Oxo-2-(p-tolyl)ethyl)-2-phenylindolin-3-one (**23ae**).*[28,55] This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(*p*-tolyl)ethanone **21e** (134 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as a pale-yellow solid, mp 190−191 °C (lit.[55] mp 177−179 °C), R_f 0.43 (EtOAc/hexane, 1:4, v/v). Yield 310 mg (0.91 mmol, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.85 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.31 (t, J = 7.6 Hz, 4H), 7.24 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.71 (t, J = 7.4 Hz, 1H), 4.17 (d, J = 18.1 Hz, 1H), 3.69 (d, J = 18.0 Hz, 1H), 2.36 (s, 3H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.7, 195.8, 161.2, 143.9, 139.3, 137.0, 133.9, 129.3 (2C), 128.4 (2C), 128.2 (2C), 127.2, 125.5 (2C), 124.4, 118.2, 117.4, 111.9, 68.8, 45.6, 21.2. FTIR, ν_{max}: 3399, 1686, 1621, 1561, 1490, 1326, 1180, 1048, 895, 756 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{19}NNaO_2$ [M + Na]$^+$: 364.1308, found: 364.1311 (−0.8 ppm).

*4.3.6. 2-(2-(2-Nitrophenyl)-2-oxoethyl)-2-phenylindolin-3-one (**23af**).* This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(2-nitrophenyl)ethanone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as an orange solid, mp 160−161 °C, R_f 0.19 (EtOAc/hexane, 1:4, v/v). Yield 357 mg (0.96 mmol, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 7.6 Hz, 2H), 7.84−7.77 (m, 1H), 7.77−7.69 (m, 2H), 7.56−7.45 (m, 3H), 7.39−7.29 (m, 3H), 7.26 (t, J = 7.2 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.72 (t, J = 7.3 Hz, 1H), 3.96 (d, J = 17.8 Hz, 1H), 3.75 (d, J = 17.8 Hz, 1H).^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 199.9, 197.9, 161.3, 146.3, 138.6, 137.3, 134.7, 133.9, 132.0, 128.7,

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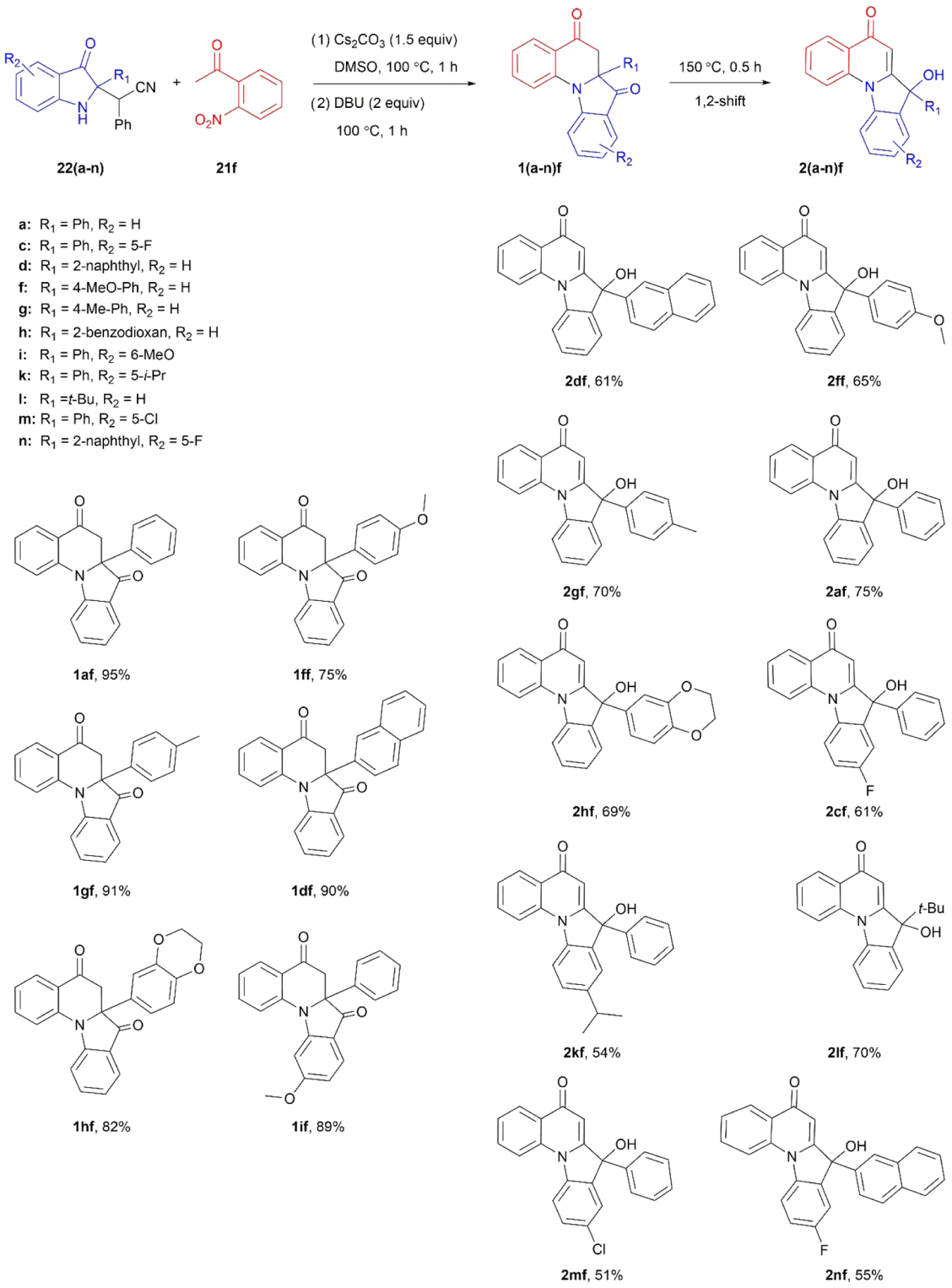
Scheme 10. Preparation of (Dihydro)indolo[1,2-*a*]quinolinones 1 and 2



128.5 (2C), 127.4, 125.4 (2C), 124.5, 124.2, 117.8, 117.6, 112.0, 68.7, 48.4. FTIR, ν_{max}: 3396, 1686, 1523, 1490, 1345, 1221, 1045, 903, 742 cm^{-1}; HRMS (ESI TOF) *m*/*z* calcd. for $C_{22}H_{16}N_2NaO_4$ $[M + Na]^+$: 395.1002, found: 395.1001 (0.3 ppm).

*4.3.7. 2-(2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-oxoethyl)-2-phenylindolin-3-one (**23ag**).* This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)ethanone **21g** (178 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as a pale-yellow solid, mp 160−162 °C, R_f 0.16 (EtOAc/hexane, 1:4, v/v). Yield 366 mg (0.95 mmol, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.53 (d, J = 7.7 Hz, 2H), 7.51−7.41 (m, 3H), 7.39 (d, J = 7.6 Hz, 1H), 7.31 (t, J =

https://doi.org/10.1021/acsomega.4c07691
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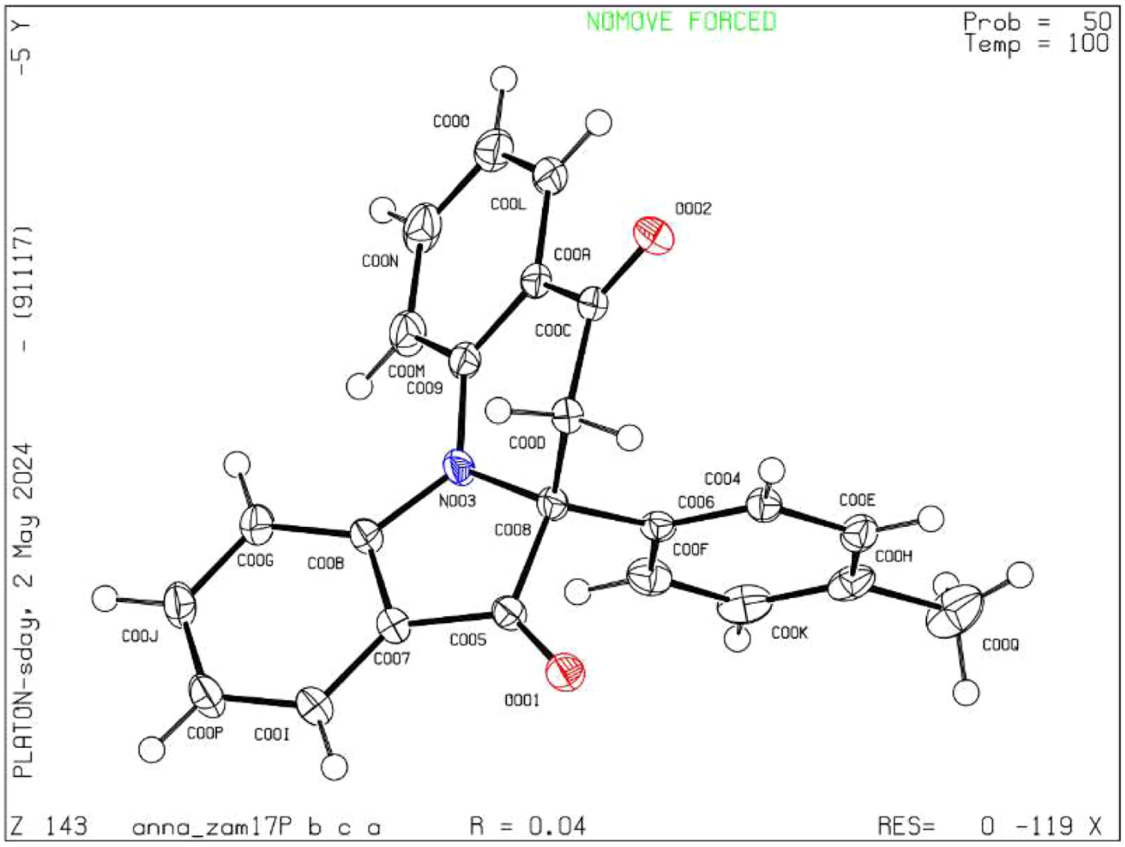

Figure 4. ORTEP plot of **1gf** (CCDC #2352893) showing atom numbering schemes and 50% probability ellipsoids.

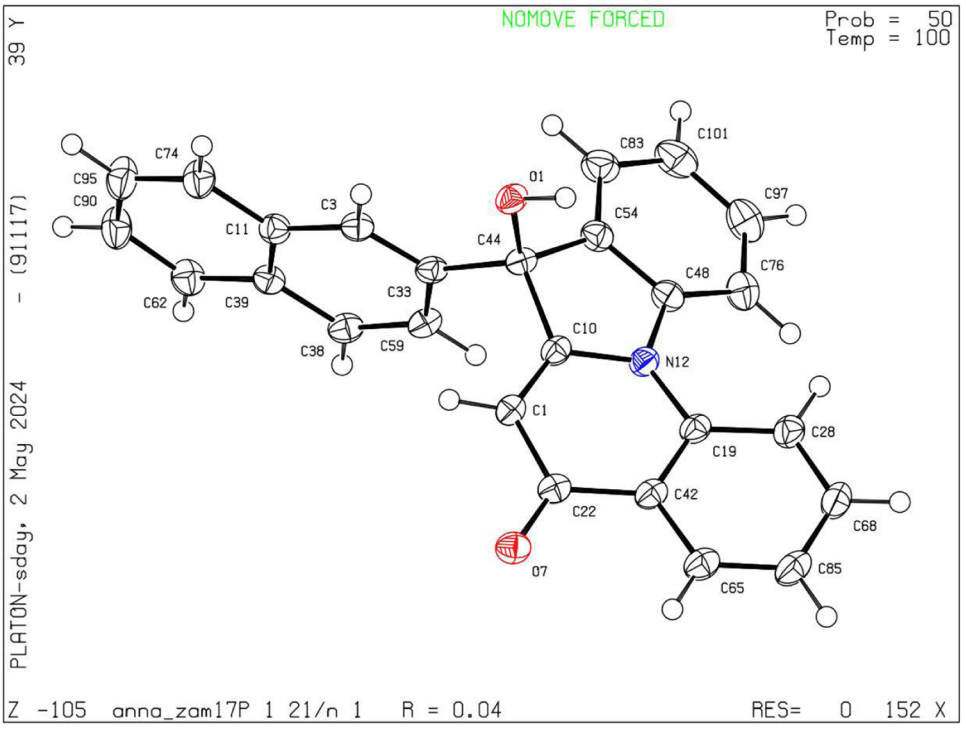

Figure 5. ORTEP plot of **2df** (CCDC #2352894) showing atom numbering schemes and 50% probability ellipsoids.

7.5 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 6.71 (t, J = 7.4 Hz, 1H), 4.35−4.23 (m, 4H), 4.12 (d, J = 18.0 Hz, 1H), 3.64 (d, J = 18.0 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.6, 194.6, 161.2, 148.1, 143.2, 139.3, 137.0, 130.1, 128.4 (2C), 127.2, 125.5 (2C), 124.4, 122.2, 118.2, 117.4, 117.12, 117.07, 111.9, 68.9, 64.6, 63.9, 45.3. FTIR, ν_{max}: 3269, 1684, 1619, 1494, 1329, 1295, 1069, 750 cm^{-1}; HRMS (ESI TOF) m/z calcd. for

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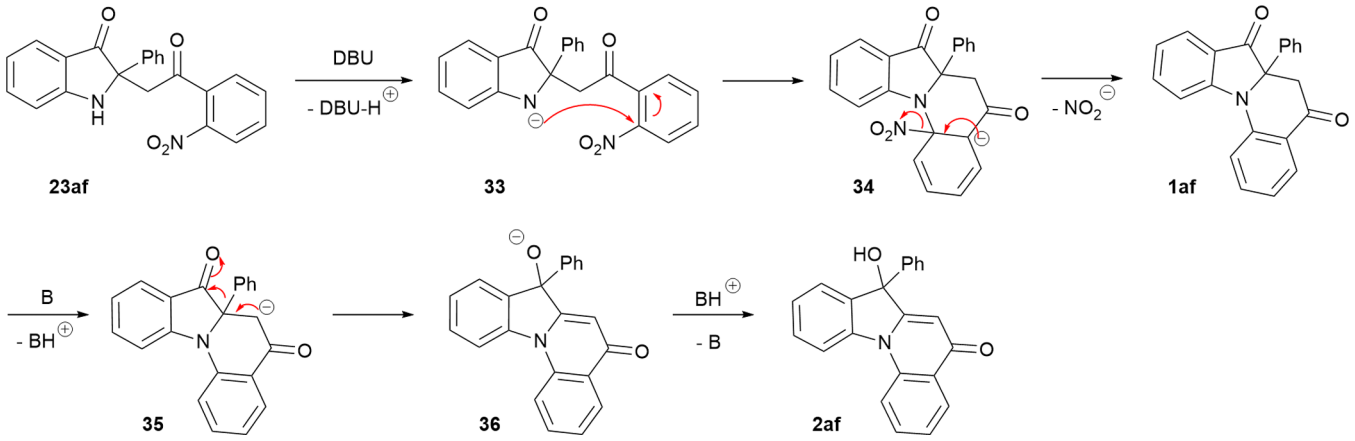
Scheme 11. Mechanistic Rationale for the Formation of Products 1af and 2af



$C_{24}H_{19}NNaO_4$ [M + Na]$^+$: 408.1206, found: 408.1201 (1.2 ppm).

*4.3.8. 2-(2-Oxo-2-(pyridin-2-yl)ethyl)-2-phenylindolin-3-one (**23ah**).* This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(pyridin-2-yl)ethanone **21h** (121 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as a pale-yellow solid, mp 150−151 °C, R_f 0.16 (EtOAc/hexane, 1:4, v/v). Yield 272 mg (0.83 mmol, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 4.1 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.86 (d, J = 7.8 Hz, 1H), 7.71−7.64 (m, 1H), 7.50 (dd, J = 13.5, 7.9 Hz, 3H), 7.41 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.72 (t, J = 7.3 Hz, 1H), 4.60 (d, J = 18.1 Hz, 1H), 3.64 (d, J = 18.1 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.7, 197.6, 161.2, 152.5, 149.3, 139.2, 137.7, 137.1, 128.5 (2C), 128.1, 127.3, 125.4 (2C), 124.4, 121.3, 118.2, 117.5, 111.9, 68.7, 44.6. FTIR, ν_{max}: 3373, 1697, 1682, 1617, 1557, 1490, 1328, 1001, 765 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{21}H_{16}N_2NaO_2$ [M + Na]$^+$: 351.1104, found: 351.1106 (−0.6 ppm).

*4.3.9. 2-(2-Oxo-2-(thiophen-2-yl)ethyl)-2-phenylindolin-3-one (**23aj**).*[28] This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(thiophen-3-yl)ethanone **21j** (121 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as a pale-yellow solid, mp 206−207 °C (lit.[28] mp 115−117 °C), R_f 0.35 (EtOAc/hexane, 1:4, v/v). Yield 317 mg (0.95 mmol, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 3.7 Hz, 1H), 7.99 (d, J = 4.9 Hz, 1H), 7.96 (s, 1H), 7.54 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.28−7.21 (m, 2H), 7.01 (d, J = 8.2 Hz, 1H), 6.71 (t, J = 7.4 Hz, 1H), 4.13 (d, J = 17.5 Hz, 1H), 3.69 (d, J = 17.5 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.3, 189.3, 161.2, 143.5, 139.1, 137.1, 135.3, 134.1, 128.9, 128.5 (2C), 127.3, 125.5 (2C), 124.4, 118.2, 117.5, 111.9, 68.8, 45.9. FTIR, ν_{max}: 3317, 1680, 1490, 1251, 1048, 953, 863, 752 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{20}H_{15}NNaO_2S$ [M + Na]$^+$: 356.0716, found: 356.0717 (−0.3 ppm).

*4.3.10. 2-(2-(2-Aminophenyl)-2-oxoethyl)-2-phenylindolin-3-one (**23ai**).* This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(2-aminophenyl)ethanone **21i** (135 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as a yellow solid, mp 155−157 °C, R_f 0.45 (EtOAc/hexane, 1:4, v/v). Yield 280 mg (0.82 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.4 Hz, 2H), 7.45 (t, J = 8.1 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.9 Hz, 2H), 7.04 (s, 2H), 7.02 (d, J = 8.3 Hz, 1H), 6.70 (t, J = 8.0 Hz, 2H), 6.52 (t, J = 7.3 Hz, 1H), 4.12 (d, J = 17.8 Hz, 1H), 3.62 (d, J = 17.7 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.8, 197.8, 161.1, 151.1, 139.5, 136.9, 134.3, 131.5, 128.4 (2C), 127.1, 125.5 (2C), 124.4, 118.3, 117.3, 116.9, 116.3, 114.5, 111.9, 69.0, 46.0. FTIR, ν_{max}: 3327, 1671, 1568 1424, 1249, 1127, 1019, 924, 851 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{22}H_{18}N_2NaO_2$ [M + Na]$^+$: 365.1260, found: 365.1257 (0.8 ppm).

*4.3.11. 2-(3,3-Dimethyl-2-oxobutyl)-2-phenylindolin-3-one (**23ak**).* This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 3,3-dimethylbutan-2-one **21k** (100 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:7, v/v). The titled compound was obtained as a pale-yellow solid, mp 136−137 °C, R_f 0.54 (EtOAc/hexane, 1:4, v/v). Yield 230 mg (0.75 mmol, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.48−7.42 (m, 3H), 7.35 (d, J = 7.7 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.68 (t, J = 7.4 Hz, 1H), 3.69 (d, J = 18.1 Hz, 1H), 3.17 (d, J = 18.1 Hz, 1H), 1.05 (s, 9H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 211.5, 200.5, 161.1, 139.2, 136.9, 128.3 (2C), 127.2, 125.4 (2C), 124.3, 118.0, 117.3, 111.8, 68.7, 44.2, 43.5, 25.9 (3C). FTIR, ν_{max}: 3396, 1701, 1684, 1557, 1492, 1328, 1251, 1068, 750 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{20}H_{21}NNaO_2$ [M + Na]$^+$: 330.1465, found: 330.1466 (−0.3 ppm).

*4.3.12. 2-(2-Oxocyclohexyl)-2-phenylindolin-3-one (**23al**).*[44] This compound was prepared by typical procedure A employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), cyclohexanone **21l** (98 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:6, v/v). The titled compound was obtained as a pale-yellow solid, mp 204−205 °C, R_f 0.37 (EtOAc/hexane, 1:4, v/v). Yield 268 mg (0.88 mmol, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (s, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.41 (t, J =

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7.3 Hz, 1H), 7.31 (d, J = 7.0 Hz, 3H), 7.26 (d, J = 6.7 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.1 Hz, 1H), 3.60 (d, J = 7.7 Hz, 1H), 2.39 (dt, J = 13.1, 6.6 Hz, 1H), 2.14 (d, J = 14.1 Hz, 1H), 1.95 (s, 1H), 1.73 (s, 1H), 1.54 (dd, J = 35.2, 8.5 Hz, 4H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 207.4, 200.4, 160.4, 138.3, 135.9, 128.5 (2C), 127.4, 125.7 (2C), 123.9, 119.9, 117.1, 111.5, 71.7, 57.8, 41.4, 27.9, 26.1, 24.1. FTIR, ν_{max}: 3361, 1699, 1682, 1617, 1489, 1322, 954, 750 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{20}H_{19}NNaO_2$ [M + Na]$^+$: 328.1308, found: 328.1311 (−0.9 ppm).

*4.3.13. 2-(Naphthalen-2-yl)-2-(2-oxo-2-phenylethyl)-indolin-3-one (**23da**).* This compound was prepared by typical procedure A employing 2-(3-oxo-2-(2-(naphthalen-2-yl)-3-oxoindolin-2-yl)-2-phenylacetonitrile **22d** (374 mg, 1.0 mmol), acetophenone **21a** (120 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:6, v/v). The titled compound was obtained as a pale-yellow solid, mp 214−216 °C, R_f 0.34 (EtOAc/hexane, 1:4, v/v). Yield 343 mg (0.91 mmol, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 2H), 7.98 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 8.6 Hz, 3H), 7.73−7.66 (m, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.56−7.44 (m, 5H), 7.42 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.74 (t, J = 7.3 Hz, 1H), 4.34 (d, J = 18.2 Hz, 1H), 3.87 (d, J = 18.2 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.6, 196.4, 161.3, 137.1, 136.9, 136.4, 133.5, 132.8, 132.2, 128.8 (2C), 128.1 (2C), 128.0, 127.9, 127.4, 126.3, 126.0, 124.4, 124.1, 123.9, 118.3, 117.5, 112.1, 68.9, 45.7. FTIR, ν_{max}: 3386, 1701, 1680, 1619, 1489, 1324, 1102, 1056, 756 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{26}H_{19}NNaO_2$ [M + Na]$^+$: 400.1308, found: 400.1306 (0.5 ppm).

*4.3.14. 2-(2-Oxo-2-phenylethyl)-2-(5,6,7,8-tetrahydronaphthalen-2-yl)indolin-3-one (**23ba**).* This compound was prepared by typical procedure A employing 2-(3-oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)indolin-2-yl)-2-phenylacetonitrile **22b** (378 mg, 1.0 mmol), acetophenone **21a** (120 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:6, v/v). The titled compound was obtained as a pale-yellow solid, mp 152−153 °C, R_f 0.49 (EtOAc/hexane, 1:4, v/v). Yield 312 mg (0.82 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 7.6 Hz, 2H), 7.86 (s, 1H), 7.62 (t, J = 7.1 Hz, 1H), 7.53−7.42 (m, 3H), 7.39 (d, J = 7.6 Hz, 1H), 7.26−7.20 (m, 2H), 7.03−6.94 (m, 2H), 6.70 (t, J = 7.3 Hz, 1H), 4.15 (d, J = 18.1 Hz, 1H), 3.69 (d, J = 18.0 Hz, 1H), 2.64 (s, 4H), 1.67 (s, 4H).^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.8, 196.3, 161.1, 136.9, 136.5, 136.4, 136.2, 135.3, 133.4, 129.0, 128.7 (2C), 128.1 (2C), 125.8, 124.3, 122.7, 118.4, 117.3, 111.9, 68.6, 45.8, 29.1, 28.4, 22.8, 22.7. FTIR, ν_{max}: 3331, 3070, 1772, 1699, 1684, 1559, 1510, 1054, 828 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{26}H_{23}NNaO_2$ [M + Na]$^+$: 404.1621, found: 404.1624 (−0.7 ppm).

*4.3.15. 5-Fluoro-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one (**23ca**).*[55] This compound was prepared by typical procedure A employing 2-(5-fluoro-3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22c** (342 mg, 1.0 mmol), acetophenone **21a** (120 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:6, v/v). The titled compound was obtained as a pale-yellow solid, mp 154−155 °C (lit.[55] mp 151−153 °C), R_f 0.37 (EtOAc/hexane, 1:4, v/v). Yield 293 mg (0.85 mmol, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 7.4 Hz, 2H), 7.87 (s, 1H), 7.64 (t, J = 7.3 Hz, 1H), 7.52 (dt, J = 15.4, 7.6 Hz, 4H), 7.38 (td, J = 9.1, 2.7 Hz, 1H), 7.33 (t, J = 7.4 Hz, 2H), 7.26 (t, J = 7.1 Hz, 1H), 7.18 (dd, J = 7.6, 2.4 Hz, 1H), 7.04 (dd, J = 8.9, 3.9 Hz, 1H), 4.21 (d, J = 18.1 Hz, 1H), 3.81 (d, J = 18.1 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 200.5, 196.2, 158.1, 155.1 (d, J = 235.1 Hz), 138.9, 136.2, 133.4, 124.9 (d, J = 25.4 Hz), 128.7 (2C), 128.4 (2C), 128.1 (2C), 127.3, 125.5 (2C), 118.4 (d, J = 7.4 Hz), 113.2 (d, J = 7.6 Hz), 108.9 (d, J = 22.2 Hz), 69.8, 45.9. ^{19}F NMR (376 MHz, DMSO-d_6) δ −127.07. FTIR, ν_{max}: 3399, 1684, 1563, 1489, 1247, 1196, 1048, 878, 823 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{22}H_{16}FNNaO_2$ [M + Na]$^+$: 368.1057, found: 368.1058 (−0.3 ppm).

*4.3.16. 5,6-Dimethoxy-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one (**23ea**).* This compound was prepared by typical procedure A employing 2-(5,6-dimethoxy-3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22e** (384 mg, 1.0 mmol), acetophenone **21a** (120 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:6, v/v). The titled compound was obtained as a pale-yellow solid, mp 218−219 °C, R_f 0.12 (EtOAc/hexane, 1:3, v/v). Yield 348 mg (0.90 mmol, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 7.6 Hz, 2H), 7.69 (s, 1H), 7.62 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.8 Hz, 4H), 7.29 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.1 Hz, 1H), 6.82 (s, 1H), 6.62 (s, 1H), 4.21 (d, J = 18.0 Hz, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.57 (d, J = 18.0 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 198.2, 196.6, 159.0, 158.2, 143.1, 139.9, 136.6, 133.4, 128.8 (2C), 128.3 (2C), 128.0 (2C), 127.0, 125.4 (2C), 108.7, 104.7, 94.4, 69.4, 55.8, 55.8, 45.1. FTIR, ν_{max}: 3346, 1667, 1623, 1559, 1492, 1246, 1217, 1048, 851 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{24}H_{21}NNaO_4$ [M + Na]$^+$: 410.1363, found: 410.1360 (0.7 ppm).

4.4. Preparation of Quinolones 1 (Typical Procedure B). Starting acetonitrile **22** (1.0 mmol), corresponding acetophenone **21f** (1.0 mmol), and 2 mL of DMSO were charged in a 10 mL round-bottom flask. Then, Cs_2CO_3 (489 mg, 1.5 mmol) was added and the resulting mixture was stirred at 100 °C for 1 h. After this, DBU (2.0 mmol, 304 mg) was added and the reaction mixture was stirred for another hour. The reaction progress was monitored by TLC. After completion reaction mixture was poured into water and extracted with EtOAc (4 × 25 mL). The combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by preparative column chromatography on silica gel, eluting with ethyl acetate/hexane mixture.

*4.4.1. 6a-Phenyl-6,6a-dihydroindolo[1,2-a]quinoline-5,7-dione (**1af**).*[28] This compound was prepared by typical procedure B employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(2-nitrophenyl)-ethanone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:6, v/v). The titled compound was obtained as a yellow solid, mp 246−247 °C (lit.[28] mp 204−206 °C), R_f 0.32 (EtOAc/hexane, 1:4, v/v). Yield 309 mg (0.95 mmol, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.85−7.78 (m, 1H), 7.78−7.70 (m, 3H), 7.35 (d, J = 7.0 Hz, 2H), 7.33−7.25 (m, 3H), 7.13 (q, J = 7.6 Hz, 2H), 3.55 (d, J = 16.5 Hz, 1H), 3.43 (d, J = 16.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.4, 191.1, 154.3, 141.7, 138.5, 136.1, 134.8, 129.1 (2C), 128.4, 127.3, 126.3 (2C), 125.8, 122.8, 122.7, 121.5, 120.3, 120.2, 111.0, 72.5, 43.2. FTIR, ν_{max}: 3300, 2952, 1657, 1598, 1513, 1402, 1261, 1133, 1025 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{22}H_{15}NNaO_2$ [M + Na]$^+$: 348.0995, found: 348.0997 (−0.6 ppm).

*4.4.2. 6a-(Naphthalen-2-yl)-6,6a-dihydroindolo[1,2-a]-quinoline-5,7-dione (**1df**).* This compound was prepared by

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typical procedure B employing 2-(2-(naphthalen-2-yl)-3-oxoindolin-2-yl)-2-phenylacetonitrile **22d** (374 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:6, v/v). The titled compound was obtained as a yellow solid, mp 258−261 °C, R_f 0.29 (EtOAc/hexane, 1:4, v/v). Yield 337 mg (0.90 mmol, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 8.1 Hz, 1H), 8.01−7.94 (m, 2H), 7.91−7.78 (m, 4H), 7.74 (t, J = 9.3 Hz, 3H), 7.52−7.44 (m, 2H), 7.42−7.35 (m, 1H), 7.16 (t, J = 7.4 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 3.73 (d, J = 16.6 Hz, 1H), 3.51 (d, J = 16.7 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 197.5, 191.2, 154.5, 141.6, 138.6, 136.0, 132.8, 132.5, 132.4, 129.0, 128.0, 127.4, 127.3, 126.8, 126.7, 126.2, 125.8, 123.3, 122.9, 122.8, 121.5, 120.5, 120.3, 111.1, 72.8, 43.0. FTIR, ν_{max}: 3229, 1699, 1686, 1617, 1490, 1318, 1288, 1244, 811, 748 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{26}H_{17}NNaO_2$ [M + Na]$^+$: 398.1151, found: 398.1147 (1.0 ppm).

*4.4.3. 6a-(4-Methoxyphenyl)-6,6a-dihydroindolo[1,2-a]-quinoline-5,7-dione (**1ff**).* This compound was prepared by typical procedure B employing 2-(2-(4-methoxyphenyl)-3-oxoindolin-2-yl)-2-phenylacetonitrile **22f** (324 mg, 1.0 mmol), 1-(2-nitrophenyl)ethanone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:6, v/v). The titled compound was obtained as a yellow solid, mp 231−234 °C, R_f 0.27 (EtOAc/hexane, 1:4, v/v). Yield 266 mg (0.75 mmol, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.80 (t, J = 7.7 Hz, 1H), 7.74 (t, J = 9.2 Hz, 3H), 7.23 (d, J = 8.7 Hz, 2H), 7.13 (q, J = 7.0 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.65 (s, 3H), 3.48 (d, J = 16.5 Hz, 1H), 3.39 (d, J = 16.5 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 197.8, 191.2, 159.3, 154.2, 141.6, 138.5, 136.0, 127.6 (2C), 127.3, 126.3, 125.8, 122.9, 122.6, 121.4, 120.3, 120.3, 114.5 (2C), 111.0, 72.2, 55.1, 43.1. FTIR, ν_{max}: 3316, 2909, 1696, 1558, 1479, 1431, 1349, 1298, 971, 799 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{17}NNaO_3$ [M + Na]$^+$: 378.1101, found: 378.1104 (0.8 ppm).

*4.4.4. 6a-(p-Tolyl)-6,6a-dihydroindolo[1,2-a]quinoline-5,7-dione (**1gf**).* This compound was prepared by typical procedure B employing 2-(3-Oxo-2-(*p*-tolyl)indolin-2-yl)-2-phenylacetonitrile **22g** (338 mg, 1.0 mmol), 1-(2-nitrophenyl)-ethanone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:6, v/v). The titled compound was obtained as a yellow solid, mp 224−226 °C, R_f 0.38 (EtOAc/hexane, 1:4, v/v). Yield 308 mg (0.91 mmol, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.81 (t, J = 7.7 Hz, 1H), 7.77−7.68 (m, 3H), 7.21 (d, J = 8.2 Hz, 2H), 7.16−7.06 (m, 4H), 3.50 (d, J = 16.5 Hz, 1H), 3.39 (d, J = 16.6 Hz, 1H), 2.18 (s, 3H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 197.6, 191.2, 154.2, 141.7, 138.5, 137.9, 136.0, 131.8, 129.7 (2C), 127.3, 126.2 (2C), 125.8, 122.9, 122.6, 121.4, 120.3, 120.3, 111.0, 72.4, 43.1, 20.5. FTIR, ν_{max}: 3396, 1699, 1563, 1475, 1460, 1362, 1246, 928, 744 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{17}NNaO_2$ [M + Na]$^+$: 362.1151, found: 362.1149 (0.6 ppm).

*4.4.5. 6a-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-6,6a-dihydroindolo[1,2-a]quinoline-5,7-dione (**1hf**).* This compound was prepared by typical procedure B employing 2-(2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-oxoindolin-2-yl)-2-phenylacetonitrile **22h** (382 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:4, v/v). The titled compound was obtained as a yellow solid, mp 266−269 °C, R_f 0.19 (EtOAc/hexane, 1:4, v/v). Yield 314 mg (0.82 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.83−7.69 (m, 4H), 7.13 (t, J = 7.4 Hz, 2H), 6.77 (s, 3H), 4.15 (s, 4H), 3.45 (d, J = 16.6 Hz, 1H), 3.35 (d, J = 16.4 Hz, 1H).^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 197.5, 191.2, 154.1, 143.7, 141.7, 138.5, 136.1, 127.4, 127.4, 125.8, 122.9 (2C), 122.7, 121.4, 120.3, 120.3, 119.1, 117.7, 115.0, 111.0, 72.0, 64.0, 64.0, 43.0. FTIR, ν_{max}: 3354, 17724, 1701, 1686, 1561, 1506, 1469, 1364, 1244, 1069, 759 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{24}H_{17}NNaO_4$ [M + Na]$^+$: 406.1050, found: 406.1047 (0.7 ppm).

*4.4.6. 10-Methoxy-6a-phenyl-6,6a-dihydroindolo[1,2-a]-quinoline-5,7-dione (**1if**).* This compound was prepared by typical procedure B employing 2-(6-methoxy-3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22i** (354 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:5, v/v). The titled compound was obtained as a yellow solid, mp 118−120 °C, R_f 0.21 (EtOAc/hexane, 1:4, v/v). Yield 316 mg (0.89 mmol, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 8.4 Hz, 1H), 7.75 (t, J = 7.3 Hz, 2H), 7.64 (d, J = 8.6 Hz, 1H), 7.33−7.24 (m, 6H), 7.13 (t, J = 7.5 Hz, 1H), 6.76−6.70 (m, 1H), 3.98 (s, 3H), 3.52 (d, J = 16.6 Hz, 1H), 3.40 (d, J = 16.6 Hz, 1H).^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 195.0, 191.3, 168.0, 156.3, 141.5, 136.2, 135.2, 129.0 (2C), 128.3, 127.4, 127.3, 126.2 (2C), 123.0, 122.9, 120.5, 113.4, 110.3, 94.4, 73.2, 56.1, 43.4. FTIR, ν_{max}: 3365, 1774, 1701, 1686, 1561, 1508, 1358, 1249, 1115, 730 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{17}NNaO_3$ [M + Na]$^+$: 378.1101, found: 378.1102 (−0.3 ppm).

4.5. Preparation of Quinolones 2 (Typical Procedure C). Starting acetonitrile **22** (1.0 mmol), corresponding acetophenone **21f** (1.0 mmol), and 2 mL of DMSO were charged in a 10 mL round-bottom flask. Then, Cs_2CO_3 (489 mg, 1.5 mmol) was added and the resulting mixture was stirred at 100 °C for 1 h. After this, DBU (2.0 mmol, 304 mg) was added and the reaction mixture was stirred for another hour. The reaction temperature was increased to 150 °C and the reaction mixture was stirred for 30 min more. The reaction progress was monitored by TLC. After completion reaction mixture was poured into water and extracted with EtOAc (4 × 25 mL). The combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by preparative column chromatography on silica gel, eluting with ethyl acetate/hexane mixture.

*4.5.1. 7-Hydroxy-7-(naphthalen-2-yl)indolo[1,2-a]-quinolin-5(7H)-one (**2df**).* This compound was prepared by typical procedure C employing 2-(2-(naphthalen-2-yl)-3-oxoindolin-2-yl)-2-phenylacetonitrile **22d** (374 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a gray solid, mp 276−278 °C, R_f 0.51 (EtOAc/hexane, 1:1, v/v). Yield 229 mg (0.61 mmol, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 8.6 Hz, 1H), 8.35 (d, J = 8.3 Hz, 1H), 8.28 (d, J = 6.9 Hz, 1H), 8.10 (s, 1H), 7.98−7.89 (m, 2H), 7.88−7.84 (m, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.60−7.49 (m, 4H), 7.42 (d, J = 7.2 Hz, 1H), 7.32−7.25 (m, 3H), 6.20 (s, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 176.8, 162.0, 141.4, 140.5, 137.9, 137.7, 133.1, 132.6, 132.4, 130.2, 128.2 (2C), 127.5, 126.47,

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126.46, 126.4, 126.1, 125.7, 125.5, 124.5, 123.6, 123.6, 117.1, 114.3, 107.3, 79.6. FTIR, ν_{max}: 3105, 1867, 1735, 1686, 1557, 1506, 1244, 1186, 863 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{26}H_{17}NNaO_2$ $[M + Na]^+$: 398.1151, found: 398.1153 (−0.5 ppm).

*4.5.2. 7-Hydroxy-7-(4-methoxyphenyl)indolo[1,2-a]quinolin-5(7H)-one (**2ff**).* This compound was prepared by typical procedure C employing 2-(2-(4-methoxyphenyl)-3-oxoindolin-2-yl)-2-phenylacetonitrile **22f** (354 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a gray solid, mp 295−297 °C, R_f 0.46 (EtOAc/hexane, 1:1, v/v). Yield 231 mg (0.65 mmol, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 8.6 Hz, 1H), 8.27 (t, J = 8.0 Hz, 2H), 7.88 (t, J = 7.6 Hz, 1H), 7.58−7.49 (m, 2H), 7.40 (d, J = 7.2 Hz, 1H), 7.33−7.24 (m, 3H), 7.06 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.17 (s, 1H), 3.71 (s, 3H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 176.7, 162.4, 158.8, 141.2, 138.2, 137.6, 135.2, 133.1, 130.0, 126.5 (3C), 126.1, 125.6, 125.4, 124.4, 117.0, 114.1, 113.8 (2C), 107.0, 79.2, 55.1. FTIR, ν_{max}: 3269, 1739, 1685, 1534, 1498, 1329, 1224, 1039, 861 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{17}NNaO_3$ $[M + Na]^+$: 378.1101, found: 378.1104 (−0.8 ppm).

*4.5.3. 7-Hydroxy-7-(p-tolyl)indolo[1,2-a]quinolin-5(7H)-one (**2gf**).* This compound was prepared by typical procedure C employing 2-(3-oxo-2-(*p*-tolyl)indolin-2-yl)-2-phenylacetonitrile **22g** (338 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a gray solid, mp 268−272 °C, R_f 0.25 (EtOAc/hexane, 1:1, v/v). Yield 237 mg (0.70 mmol, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 8.6 Hz, 1H), 8.28 (dd, J = 11.4, 8.4 Hz, 2H), 7.89 (t, J = 7.3 Hz, 1H), 7.53 (q, J = 8.0 Hz, 2H), 7.38 (d, J = 7.1 Hz, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 7.07 (s, 1H), 6.14 (s, 1H), 2.25 (s, 3H). ^{13}C {^{1}H} NMR (101 MHz, DMSO) δ 176.7, 162.3, 141.2, 140.4, 138.2, 137.6, 137.0, 133.1, 130.0, 129.0 (2C), 126.4, 126.1, 125.6, 125.4, 125.1 (2C), 124.4, 117.0, 114.1, 107.1, 79.4, 20.6. FTIR, ν_{max}: 3392, 1680, 1636, 1556, 1490, 1468, 1301, 1102, 1069, 748 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{23}H_{17}NNaO_2$ $[M + Na]^+$: 362.1151, found: 362.1148 (0.8 ppm).

*4.5.4. 7-Hydroxy-7-phenylindolo[1,2-a]quinolin-5(7H)-one (**2af**).* This compound was prepared by typical procedure C employing 2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22a** (324 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a gray solid, mp 276−277 °C, R_f 0.51 (EtOAc/hexane, 1:1, v/v). Yield 244 mg (0.75 mmol, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 8.7 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 7.2 Hz, 1H), 7.59−7.49 (m, 2H), 7.40 (d, J = 7.2 Hz, 1H), 7.37−7.26 (m, 6H), 7.14 (s, 1H), 6.15 (s, 1H).^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 176.7, 162.2, 143.2, 141.2, 138.0, 137.6, 133.1, 130.1, 128.5 (2C), 127.8, 126.4, 126.0, 125.6, 125.4, 125.1 (2C), 124.4, 117.1, 114.1, 107.1, 79.5. FTIR, ν_{max}: 3396, 1701, 1636, 1573, 1559, 1466, 1293, 1102, 1068, 752 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{22}H_{15}NNaO_2$ $[M + Na]^+$: 348.0995, found: 348.0991 (1.2 ppm).

*4.5.5. 7-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-7-hydroxyindolo[1,2-a]quinolin-5(7H)-one (**2hf**).* This compound was prepared by typical procedure C employing 2-(2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-oxoindolin-2-yl)-2-phenylacetonitrile **22h** (382 mg, 1.0 mmol), 1-(2-nitrophenyl)ethanone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a gray solid, mp 270−271 °C, R_f 0.17 (EtOAc/hexane, 1:1, v/v). Yield 264 mg (0.69 mmol, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 8.6 Hz, 1H), 8.26 (t, J = 7.4 Hz, 2H), 7.88 (t, J = 7.3 Hz, 1H), 7.58−7.49 (m, 2H), 7.41 (d, J = 7.2 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.05 (s, 1H), 6.86 (d, J = 1.9 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.70 (dd, J = 8.5, 2.0 Hz, 1H), 6.16 (s, 1H), 4.20 (s, 4H).^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 176.7, 162.2, 143.1, 143.0, 141.2, 138.0, 137.6, 136.3, 133.1, 130.1, 126.4, 126.1, 125.5, 125.4, 124.4, 118.1, 117.1, 117.0, 114.1, 113.9, 107.0, 79.1, 64.08, 64.05. FTIR, ν_{max}: 3388, 1682, 1638, 1559, 1506, 1284, 1108, 1062, 893 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{24}H_{17}NNaO_4$ $[M + Na]^+$: 406.1050, found: 406.1046 (1.0 ppm).

*4.5.6. 9-Fluoro-7-hydroxy-7-phenylindolo[1,2-a]quinolin-5(7H)-one (**2cf**).* This compound was prepared by typical procedure C employing 2-(5-fluoro-3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22c** (342 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a gray solid, mp 302−303 °C, R_f 0.52 (EtOAc/hexane, 1:1, v/v). Yield 209 mg (0.61 mmol, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, J = 8.6 Hz, 1H), 8.33 (dd, J = 8.7, 3.2 Hz, 1H), 8.26 (d, J = 7.8 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.40−7.25 (m, 8H), 6.17 (s, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 176.6, 162.2, 159.6 (d, J = 243.6 Hz), 142.7, 140.5 (d, J = 7.8 Hz), 137.5, 137.3, 133.1, 128.6 (2C), 128.0, 126.4, 126.0, 125.1 (2C), 124.5, 116.8, 116.4 (d, J = 23.5 Hz), 115.6 (d, J = 8.2 Hz), 112.78 (d, J = 24.4 Hz), 107.3, 79.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ −117.03. FTIR, ν_{max}: 3346, 1873, 1732, 1699, 1684, 1556, 1471, 1184, 876 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{22}H_{14}FNNaO_2$ $[M + Na]^+$: 366.0901, found: 366.0902 (−0.3 ppm).

*4.5.7. 7-Hydroxy-9-isopropyl-7-phenylindolo[1,2-a]quinolin-5(7H)-one (**2kf**).* This compound was prepared by typical procedure C employing 2-(5-isopropyl-3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22k** (366 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a gray solid, mp 148−151 °C, R_f 0.37 (EtOAc/hexane, 1:1, v/v). Yield 198 mg (0.54 mmol, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 8.6 Hz, 1H), 8.28−8.24 (m, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.91−7.86 (m, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.43−7.40 (m, 1H), 7.38−7.30 (m, 5H), 7.27 (s, 1H), 7.14 (s, 1H), 6.15 (s, 1H), 2.98−2.89 (m, 1H), 1.17 (dd, J = 9.0, 7.0 Hz, 6H).^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 176.7, 162.4, 145.9, 143.4, 139.4, 138.2, 137.5, 133.0, 128.5 (2C), 127.8, 127.7, 126.4, 126.0, 125.1 (2C), 124.3, 123.3, 117.0, 114.0, 107.0, 79.6, 32.9, 24.0, 23.7. FTIR, ν_{max}: 3350, 1734, 1697, 1607, 1559, 1477, 1374, 1142, 1121, 934 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{25}H_{21}NNaO_2$ $[M + Na]^+$: 390.1465, found: 390.1463 (0.5 ppm).

*4.5.8. 9-Chloro-7-hydroxy-7-phenylindolo[1,2-a]quinolin-5(7H)-one (**2mf**).* This compound was prepared by typical procedure C employing 2-(5-chloro-3-oxo-2-phenylindolin-2-yl)-2-phenylacetonitrile **22m** (359 mg, 1.0 mmol), 1-(2-

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nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a gray solid, mp 302−304 °C, R_f 0.28 (EtOAc/hexane, 1:1, v/v). Yield 183 mg (0.51 mmol, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 7.5 Hz, 1H), 8.29 (dd, J = 22.0, 7.1 Hz, 2H), 7.89 (s, 1H), 7.61−7.52 (m, 2H), 7.41−7.26 (m, 7H), 6.17 (s, 1H).^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 176.7, 161.9, 142.6, 140.3, 140.0, 137.3, 133.2, 129.8, 129.3, 128.6 (2C), 128.0, 126.5, 126.0, 125.3, 125.1 (2C), 124.6, 117.0, 115.7, 107.3, 79.3. FTIR, ν_{max}: 3403, 3120, 1699, 1684, 1636, 1512, 1469, 1248, 1182, 746 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{22}H_{14}ClNNaO_2$ [M + Na]$^+$: 382.0605, found: 382.0609 (−1.0 ppm).

*4.5.9. 9-Fluoro-7-hydroxy-7-(naphthalen-2-yl)indolo[1,2-a]quinolin-5(7H)-one (**2nf**).* This compound was prepared by typical procedure C employing 2-(5-fluoro-2-(naphthalen-2-yl)-3-oxoindolin-2-yl)-2-phenylacetonitrile **22n** (392 mg, 1.0 mmol), 1-(2-nitrophenyl)ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a gray solid, mp 305−308 °C, R_f 0.51 (EtOAc/hexane, 1:1, v/v). Yield 216 mg (0.55 mmol, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 8.6 Hz, 1H), 8.37 (dd, J = 8.9, 3.6 Hz, 1H), 8.27 (d, J = 7.3 Hz, 1H), 8.10 (s, 1H), 7.98−7.81 (m, 4H), 7.57−7.48 (m, 3H), 7.46−7.36 (m, 2H), 7.34−7.26 (m, 2H), 6.21 (s, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 176.6, 162.1, 159.6 (d, J = 243.7 Hz), 140.5 (d, J = 7.7 Hz), 139.9, 137.6 (d, J = 1.8 Hz) 137.4, 133.2, 132.6, 132.5, 128.4, 128.3, 127.5, 126.5, 126.5 (2C), 126.0, 124.5, 123.7, 123.5, 116.9, 116.5 (d, J = 23.2 Hz), 115.7 (d, J = 8.3 Hz), 112.9 (d, J = 24.5 Hz), 107.5, 79.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ −117.00. IR, ν_{max}: 3281, 11696, 1665, 1515, 1268, 1139, 1025, 838 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{26}H_{16}FNNaO_2$ [M + Na]$^+$: 416.1057, found: 416.1055 (0.5 ppm).

*4.5.10. 7-(tert-Butyl)-7-hydroxyindolo[1,2-a]quinolin-5(7H)-one (**2lf**).* This compound was prepared by typical procedure C employing 2-(2-(*tert*-butyl)-3-oxoindolin-2-yl)-2-phenylacetonitrile **22l** (304 mg, 1.0 mmol), 1-(2-nitrophenyl)-ethenone **21f** (165 mg, 1.0 mmol). Purification by column chromatography (EtOAc/hexane, 1:3, v/v). The titled compound was obtained as a white solid, mp 244−245 °C, R_f 0.28 (EtOAc/hexane, 1:1, v/v). Yield 213 mg (0.70 mmol, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (d, J = 8.6 Hz, 1H), 8.25 (d, J = 7.9 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 7.4 Hz, 1H), 7.53−7.45 (m, 2H), 7.28 (t, J = 7.5 Hz, 1H), 6.37 (s, 1H), 6.35 (s, 1H), 0.92 (s, 9H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 176.0, 162.5, 141.8, 137.1, 135.8, 132.8, 129.5, 126.4, 126.3, 126.0, 124.3, 123.9, 117.5, 112.3, 108.5, 83.5, 38.7, 24.0 (3C). FTIR, ν_{max}: 3388, 1871, 1735, 1699, 1636, 1515, 1456, 1295, 1240, 851 cm^{-1}; HRMS (ESI TOF) m/z calcd. for $C_{20}H_{19}NNaO_2$ [M + Na]$^+$: 328.1308, found: 328.1312 (−1.2 ppm).

■ ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c07691.

Copies of the NMR spectra of all products and starting compounds **22**; X-ray crystallographic structure determination for compounds **1fg** and **2df** (PDF)

Accession Codes

CCDC 2352893 and 2352894 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, 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

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