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Synthesis of isoindolo[1,2-*a*]isoquinoline and isoindolo[2,1-*a*]quinoline derivatives *via* trifluoroacetic acid-mediated cascade reactions

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ABSTRACT

Condensation of methyl 2-acylbenzoates with 2-arylethanamines or 2-acylanilines in the presence of trifluoroacetic acid resulted in the formation of isoindolo[1,2-*a*]isoquinolines or isoindolo[2,1-*a*]quinolines, respectively, in moderate to excellent isolated yields.

1. Introduction

The isoindolo[1,2-*a*]isoquinoline structural motifs are widely distributed in nature (Fig. 1) [1–3]. These natural products and their synthetic analogs have been reported to display a wide spectrum of biological and pharmacological activities [4]. For instance, CRR-271 can act as a poly(ADP-ribose) polymerase-1 inhibitor [5]. Similarly, molecules containing isoindolo[2,1-*a*]quinoline scaffolds have shown protective effects against N_2-induced hypoxia [6], as well as inhibitory activities against DNA gyrase [7] and topoisomerase [8].

A variety of strategies have been developed toward the construction of the isoindolo[1,2-*a*]isoquinoline and isoindolo[2,1-*a*]quinoline frameworks. The most proven method for the synthesis of the former involves a Lewis acid [9] or Brønsted acid [5,10] promoted intramolecular cyclization of *N*-arylethylphthalimide or *N*-arylethyl-3-hydroxyisoindolinone derivatives (Scheme 1a, 1b). Other methods for joining a six-membered piperidine ring onto an existing five-membered pyrrolidine ring to synthesize isoindolo[1,2-*a*]isoquinolines include transition metal-catalyzed coupling reaction [11], Parham type [12] and aryne-mediated [13] cyclization reactions. Synthetic methods concerning assembly of a five-membered pyrrolidine ring onto an existing six-membered piperidine ring are less. These mainly include manipulation of 1-aryltetrahydroisoquinolines [14], amide formation and Diels-Alder reaction of 1-furanyltetrahydroisoquinolines [15], and Parham-type cyclization of 2-(2-halobenzoyl)-dihydroisoquinolinones [16]. Likewise, isoindolo[2,1-*a*]quinolines are mainly synthesized by construction of a six-membered piperidine ring from substrates with an existing 5-membered pyrrolidine ring, including BF_3-mediated [4 + 2] reaction of *N*-acyliminium cation generated from 2-aryl-3-hydroxyisoindolinones with olefins (Scheme 1c) [17], acid or transition metal catalyzed intramolecular ring-closure of 3-substituted 2-arylisoindolinones [6,18,19]. Most of these methods require multiple steps to access the substrates for final ring closure. Therefore, some cascade reactions have been developed. However, the requirement of microwave irradiation for the synthesis of isoindolo[1,2-*a*]isoquinolines by condensation of 2-formylbenzoic acids and 2-phenylethanamine restricts its advancement [20], while the majority of methods for the synthesis of isoindolo[2,1-*a*]quinolines suffer from drawbacks such as limited substrate scope, harsh conditions and/or low product yield [7,8,21]. Herein, we report one-pot synthesis of isoindolo[1,2-*a*]isoquinoline and isoindolo[2,1-*a*]quinoline analogues *via* trifluoroacetic acid-mediated condensation of methyl 2-acylbenzoates with 2-

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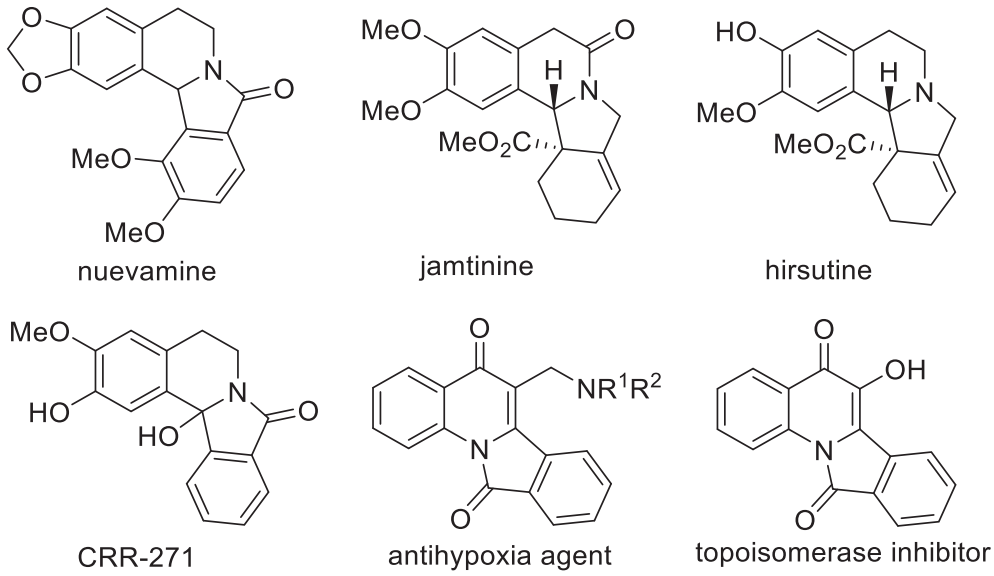


Fig. 1. Representative isoindolo[1,2-*a*]isoquinoline and isoindolo[2,1-*a*]quinoline alkaloids.

arylethanamines or 2-acylanilines, respectively (Scheme 1d, 1e).

2. Results and discussion

3,4-Dimethoxyphenylethanamine **1a** and methyl 2-formylbenzoate **2a** were used as substrates for the optimization of reaction conditions, and the results were summarized in Table 1. Initially, a 1:1 mixture of **1a** and **2a** was treated with an acid in chloroform at 60 °C. Large amount of unidentified polar substances were formed in the presence of a Lewis acid such as $BF_3 \cdot Et_2O$, $TiCl_4$, or $SnCl_4$, and the desired isoindolo[1,2-*a*]isoquinoline **3a** was isolated in low yield (Entries 1–3). Similar outcome was obtained with methanesulfonic acid (Entry 4). Delightfully, **3a** was isolated in 45% yield when trifluoroacetic acid (TFA) was applied, together with tetrahydroisoquinoline **4a** in 21% isolated yield (Entry 5). The isolated yield of **3a** could be increased to 61% when 8 equivalents of TFA was applied (Entry 7). However, further increase of acid loading resulted in reduced product yield due to ammonium salt formation and thus incomplete reaction (Entry 8). **4a** was the sole product obtained when acetic acid was used (Entry 6). With TFA as acid, the solvents and reaction temperatures were screen (Entries 9–15). The best result was obtained when the reaction was carried out in dichloroethane at 70 °C, which provide **3a** in 96% isolated yield (Entry 14).

With the optimal conditions in hand, the substrate scope for the TFA-mediated synthesis of a variety of isoindolo[1,2-*a*]isoquinolines and analogues were investigated (Table 2). While 2-arylethylamines (either substituted or unsubstituted at the aliphatic side chain) with activating methoxy group substituted benzene ring reacted efficiently with methyl 2-formylbenzoates to provide the desired products **3a**-**g** in excellent isolated yields, it is perhaps not surprising that reactions of 2-phenylethanamine and 2-(3-fluorophenyl)ethanamine were less satisfactory in which **3h** and **3i** were obtained in 45% and 18% isolated yields, respectively. The reactions of 2-(3,4-dimethoxyphenyl)ethanamine with methyl 2-acylbenzoates were also successful to give **3j** and **3k** in moderate isolated yields, respectively. Because the efficiency of the reaction is largely dependent on the electronic nature of the aryl group of the ethanamine derivatives, subsequently, we explored the substrate scope of heteroarylethanamines. Under the reaction conditions, a range of indolyl/benzofuranyl/benzothiophenylethanamines reacted with methyl 2-formylbenzoate as expected to give **3l**-**r** in moderate to good isolated yields. To our delight, the reaction of methyl (*R*)-tryptophanate with **2a** gave **3s** in 74% isolated yield as a single diastereoisomer [22].

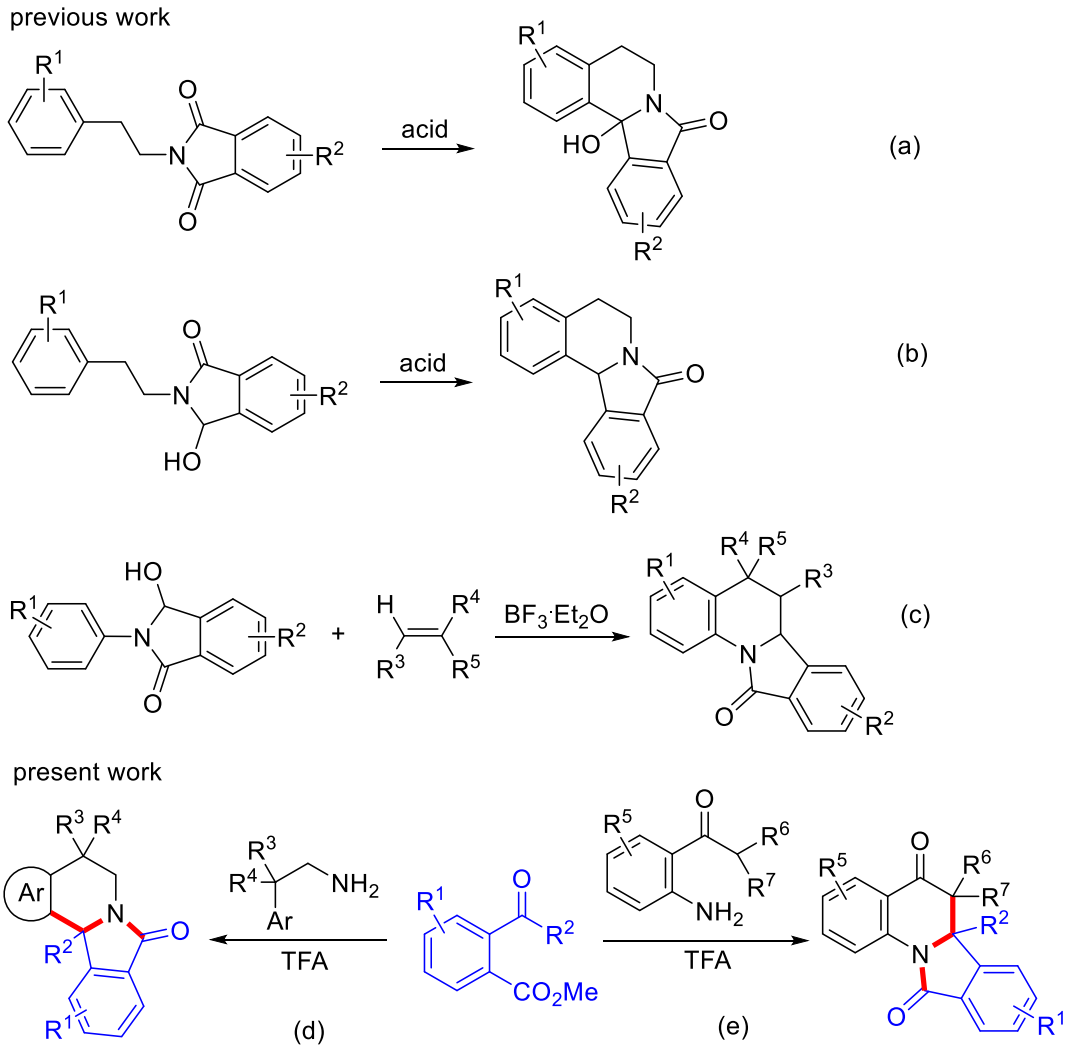
To further demonstrate the application potential of this novel chemistry, we carried out a gram-scale synthesis of **3a**, which was obtained in 91% isolated yield (Scheme 2).

Inspired by the results toward the successful synthesis of isoindolo[1,2-*a*]isoquinoline derivatives, we next turned our attention to the construction of isoindolo[2,1-*a*]quinolines *via* TFA-mediated condensation of 2-acylanilines with methyl 2-formlbenzoate and the results were listed in Table 3. Delightfully, 2-acetylanilines reacted with methyl 2-formylbenzoate to give the desired isoindolo[2,1-*a*]quinolines **6a**-**c** in good to excellent isolated yields. Reactions of the sterically more hindered 2-isobutyrylanilines were less efficient, and the products **6d** and **6e** were obtained in 59% and 54% isolated yields, respectively. Interestingly, 2-propionylaniline reacted with methyl 2-formylbenzoate to provide **6f** in 96% isolated yield, as a mixture of *cis* and *trans* isomers in a ratio of 1:10 (results based on ^{1}H NMR integration). We managed to separate the pure *trans* isomer and confirmed its relative stereochemistry by NOE correlation (SI). The reaction of substrate with a sterically more hindered pyridinyl moiety yielded **6g** in 76% isolate yield, solely as the *trans* isomer.

Having established the method toward the synthesis of isindolo[1,2-*a*]isoquinoline and isoindolo[2,1-*a*]quinoline analogues, further transformations into other useful molecules were explored. First, BBr_3-mediated demethylation of **3a** gave **7** which exhibited anti-inflammatory activity (Scheme 3) [23]. Second, oxidation of **6f** with IBX, followed by bromination of the methyl group and subsequent nucleophilic substitution with diethylamine enabled facile access to compound **10** showing protective effect against N_2-induced hypoxia [6].

3. Conclusion

In summary, we have developed efficient TFA-mediated synthesis of isoindolo[1,2-*a*]isoquinoline and isoindolo[2,1-*a*]quinoline analogues. The former were obtained by cascade Pictet-Spengler–amidation formation reactions between methyl 2-acylbenzoates and 2-arylethanamines, while the latter were



Scheme 1. Literature and present methods for the synthesis of isoindolo[1,2-*a*]isoquinoline and isoindolo[2,1-*a*]quinoline derivatives.

accessed by condensation between methyl 2-formylbenzoate and 1-(2-aminophenyl)ethan-1-ones. Further transformations of isoindolo[1,2-*a*]isoquinoline **3a** and isoindolo[2,1-*a*]quinoline **6f** into biologically active compounds **7** and **10**, respectively, have also been described.

4. Experimental section

4.1. General

Melting points were determined on a XT4A hot-stage apparatus and are uncorrected. IR spectra were obtained using an PerkinElmer FT/IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Agilent AV400 instrument. High-resolution mass spectra were recorded on a Micromass Q-TOF mass spectrometer.

4.2. General procedure for the synthesis of isoindolo[1,2-a] isoquinolines

To a stirred solution of 2-arylethanamine **1** (0.5 mmol) and methyl 2-acyl benzoate **2** (0.5 mmol) in DCE (5 mL) at 0 °C was added TFA (4.0 mmol). The reaction was heated at 70 °C until completion (as monitored by TLC) and cooled. The reaction was quenched with 10% NaOH solution (5 mL). The separated aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel to afford **3a-s**.

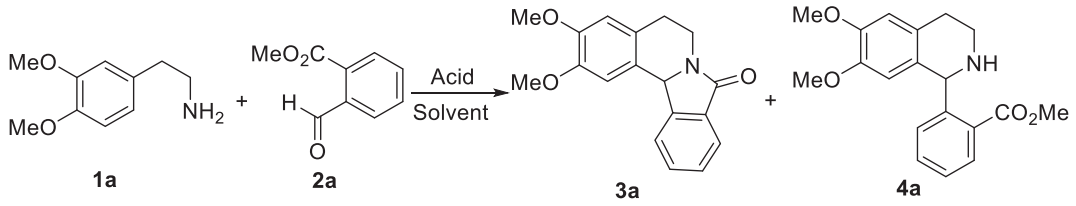
4.3. 2,3-Dimethoxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (3a)

Eluent: 0.7% methanol in dichloromethane; white solid (142 mg, 96%); mp 175–177 °C (lit. [10e], mp 172–173 °C); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.86$ (d, $J = 7.6$ Hz, 1H), 7.82 (dd, $J = 7.7$, 0.9 Hz, 1H), 7.60 (td, $J = 7.6$, 1.2 Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.11 (s, 1H), 6.65 (s, 1H), 5.61 (s, 1H), 4.49 (ddd, $J = 12.9$, 5.9, 3.4 Hz, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.40 (ddd, $J = 12.9$, 10.3, 4.6 Hz, 1H), 3.04–2.95 (m, 1H), 2.76 (dt, $J = 15.8$, 4.0 Hz, 1H) ppm; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{18}NO_3$ 296.1281, found 296.1279.

4.4. 11-Bromo-2,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a] isoquinolin-8(6H)-one (3b)

Eluent: 0.5% methanol in dichloromethane; reddish brown solid (172 mg, 92%); mp 196–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.95$

Table 1
Optimization of reaction conditions for the synthesis of isoindolo[1,2-*a*]isoquinoline **3a**.[a]



Entry	Acid (equiv.)	Solvent	Temp. (°C)	yield 3a (%)[b]	yield 4a (%)[b]
1	$BF_3 \cdot Et_2O$ (4)	$CHCl_3$	60	24	0
2	$TiCl_4$ (4)	$CHCl_3$	60	14	0
3	$SnCl_4$ (4)	$CHCl_3$	60	26	0
4	MsOH (4)	$CHCl_3$	60	11	0
5	TFA (4)	$CHCl_3$	60	45	21
6	AcOH (4)	$CHCl_3$	60	0	82
7	TFA (8)	$CHCl_3$	60	61	9
8[c]	TFA (12)	$CHCl_3$	60	54	0
9[d]	TFA (8)	MeCN	60	22	0
10[e]	TFA (8)	THF	60	45	0
11[f]	TFA (8)	DMF	60	35	0
12[g]	TFA (8)	DMSO	60	29	0
13	TFA (8)	DCE	60	85	0
14	TFA (8)	DCE	70	96	0
15	TFA (8)	DCE	80	67	0

[a] All reactions were carried out using 0.5 mmol **1a** and 0.5 mmol **2a** to react for 5h.
[b] Isolated yield.
[c] 13% 1a recovered.
[d] 23% 1a recovered.
[e] 17% 1a recovered.
[f] 21% 1a recovered.
[g] 24% 1a recovered.

(s, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.62 (dd, J = 8.1, 1.5 Hz, 1H), 7.03 (s, 1H), 6.66 (s, 1H), 5.60 (s, 1H), 4.49 (ddd, J = 13.0, 5.9, 3.2 Hz, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.37 (ddd, J = 13.0, 10.5, 4.5 Hz, 1H), 3.03–2.95 (m, 1H), 2.75 (dt, J = 15.8, 3.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 148.7, 148.1, 146.6, 132.0, 131.8, 127.1, 126.6, 126.4, 125.4, 125.3, 112.2, 108.8, 58.8, 56.5, 56.1, 38.4, 29.1 ppm; IR (neat, cm^{-1}) ν_{max} 1670; HRMS (m/z) $[M + H]^+$ calcd for $C_{18}H_{17}^{79}BrNO_3$ 374.0386, found 374.0384.

4.5. 2,3-Dimethoxy-8-oxo-5,6,8,12b-tetrahydroisoindolo[1,2-a] isoquinoline-11-carbonitrile (3c)

Eluent: 0.5% methanol in dichloromethane; yellow solid (150 mg, 94%); mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.97 (dd, J = 7.8, 0.7 Hz, 1H), 7.82–7.78 (m, 1H), 7.01 (s, 1H), 6.67 (s, 1H), 5.69 (s, 1H), 4.52 (ddd, J = 13.1, 5.9, 3.2 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.43 (ddd, J = 13.1, 10.5, 4.5 Hz, 1H), 3.06–2.96 (m, 1H), 2.79 (dt, J = 15.9, 3.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0, 148.9, 148.3, 145.2, 136.7, 132.7, 127.1, 127.0, 124.9, 124.5, 118.4, 115.2, 112.3, 108.5, 59.1, 56.5, 56.1, 38.5, 29.2 ppm; IR (neat, cm^{-1}) ν_{max} 2331, 1689; HRMS (m/z) $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_3$ 321.1234, found 321.1236.

4.6. 2,3-Dimethoxy-5,5-dimethyl-5,12b-dihydroisoindolo[1,2-a] isoquinolin-8(6H)-one (3d)

Eluent: 40% ethyl acetate in petroleum ether; white solid (149 mg, 92%); mp 181–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.61 (td, J = 7.5, 1.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.17 (s, 1H), 6.81 (s, 1H), 5.69 (s, 1H), 4.37 (d, J = 13.1 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.21 (d, J = 13.1 Hz, 1H), 1.41 (s, 3H), 1.17 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.0, 148.7, 147.8, 144.7, 136.4, 132.6, 131.8, 128.6, 124.8, 124.3, 123.0, 109.1, 108.4, 59.7, 56.2, 56.1, 50.0, 37.1, 30.9, 26.8 ppm; IR (neat, cm^{-1}) ν_{max} 1679; HRMS (m/z) $[M + H]^+$ calcd for $C_{20}H_{22}NO_3$ 324.1594, found 324.1596.

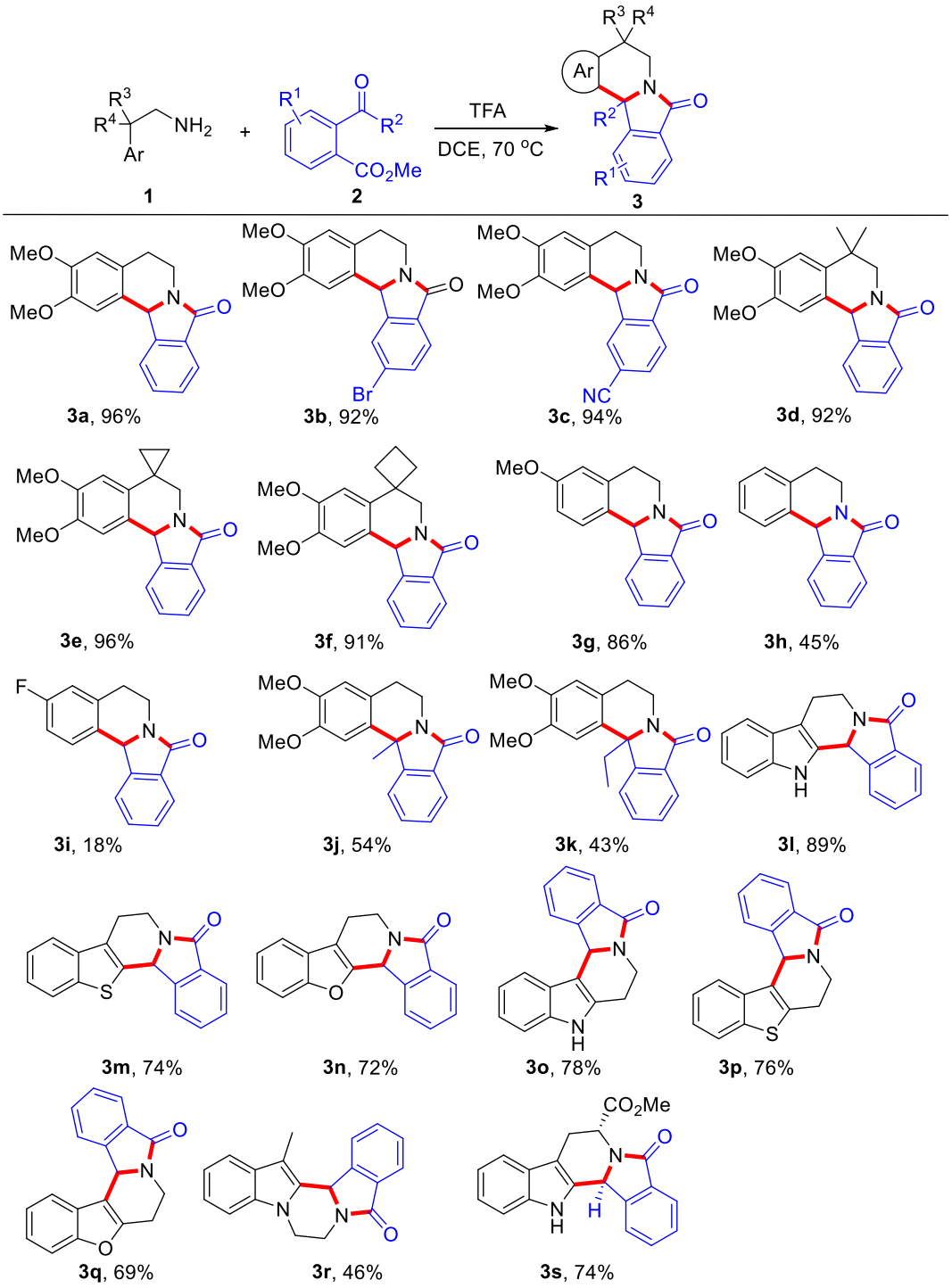
4.7. 2′,3′-Dimethoxy-6′H-spiro[cyclopropane-1,5′-isoindolo[1,2-a] isoquinolin]-8′(12b′H)-one (3e)

Eluent: 0.5% methanol in dichloromethane; white solid (155 mg, 96%); mp 187–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.62 (td, J = 7.6, 1.2 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.16 (s, 1H), 6.31 (s, 1H), 5.78 (s, 1H), 3.94 (d, J = 13.0 Hz, 1H), 3.91 (s, 1H), 3.81 (s, 3H), 3.53 (d, J = 13.0 Hz, 1H), 1.19–1.15 (m, 1H), 1.11–1.58 (m, 1H), 0.98–0.93 (m, 1H), 0.85–0.80 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.0, 148.8, 147.5, 144.4, 133.0, 131.6, 131.5, 128.6, 126.8, 124.2, 123.3, 108.7, 106.0, 60.0, 56.3, 56.0, 47.2, 20.5, 16.7, 12.3 ppm; IR (neat, cm^{-1}) ν_{max} 1693; HRMS (m/z) $[M + H]^+$ calcd for $C_{20}H_{20}NO_3$ 322.1438, found 322.1434.

4.8. 2′,3′-Dimethoxy-6′H-spiro[cyclobutane-1,5′-isoindolo[1,2-a] isoquinolin]-8′(12b′H)-one (3f)

Eluent: 0.5% methanol in dichloromethane; white solid (153 mg, 91%); mp 191–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (dt, J = 7.6, 1.0 Hz, 1H), 7.84 (dq, J = 7.7, 0.9 Hz, 1H), 7.61 (td, J = 7.5, 1.2 Hz, 1H), 7.49 (tt, J = 7.5, 0.8 Hz, 1H), 7.12 (s, 1H), 7.07 (s, 1H), 5.63 (s, 1H), 4.70 (d, J = 13.0 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.40 (d, J = 12.6 Hz, 1H), 2.61–2.49 (m, 1H), 2.37–2.19 (m, 2H), 2.17–1.96 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.1, 148.9, 147.9,

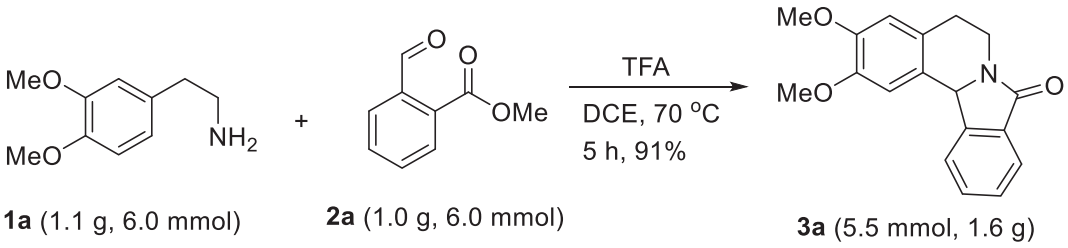
Table 2
Substrate scope for the synthesis of isoindolo[1,2-*a*]isoquinolines and analogues..



144.4, 134.7, 132.9, 131.7, 128.6, 125.2; 124.3, 123.2, 109.3, 108.4, 59.5, 56.3, 56.2, 48.2, 43.3, 34.9, 30.9, 15.3 ppm; IR (neat, cm^{-1}) ν_{max} 1677; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{22}NO_3$ 336.1594, found 336.1596.

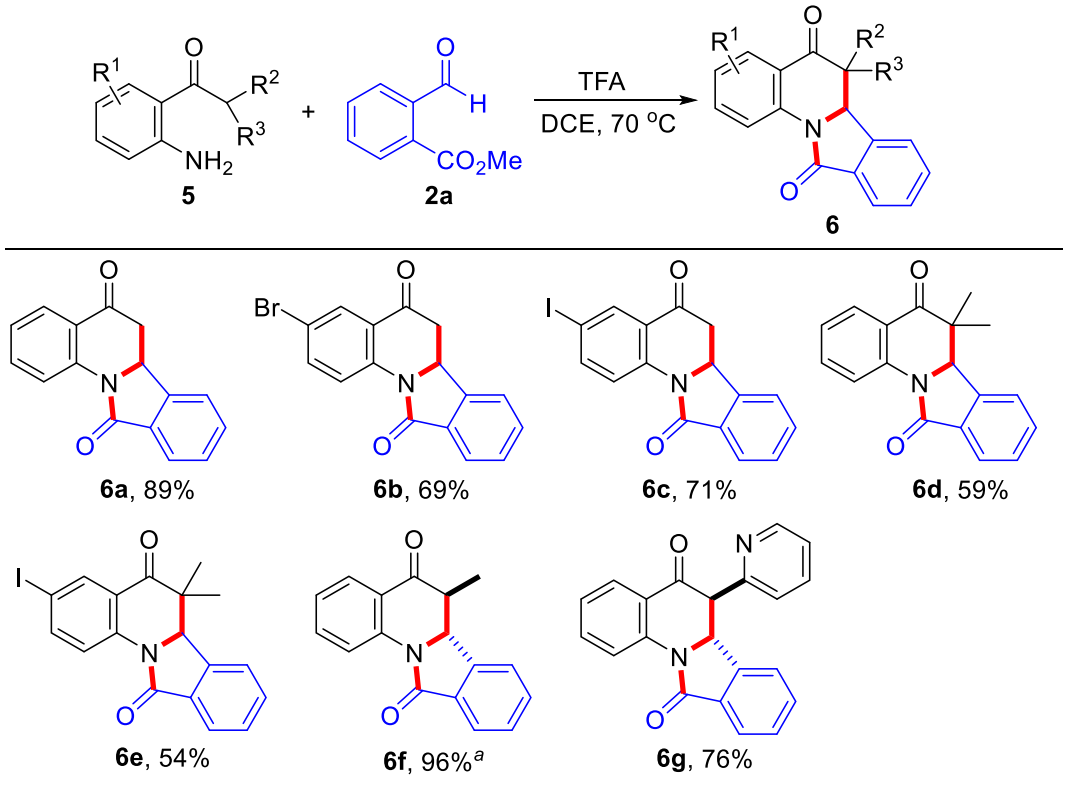
4.9. *3-Methoxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (3g)* [9e,10e]

Eluent: 0.6% methanol in dichloromethane; yellow solid (114 mg, 86%); mp 62–65 °C; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.87$ (d, $J = 7.5$, Hz, 1H), 7.83 (dd, $J = 7.7$, 0.9 Hz, 1H), 7.60 (td, $J = 7.5$, 1.2 Hz, 1H), 7.53 (d, $J = 8.6$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 6.83 (dd, $J = 8.5$,



Scheme 2. Grame-scale synthesis of **3a**.

Table 3
Substrate scope for the synthesis of isoindolo[2,1-*a*]quinolines..



[a] *cis*:*trans* = 1:10

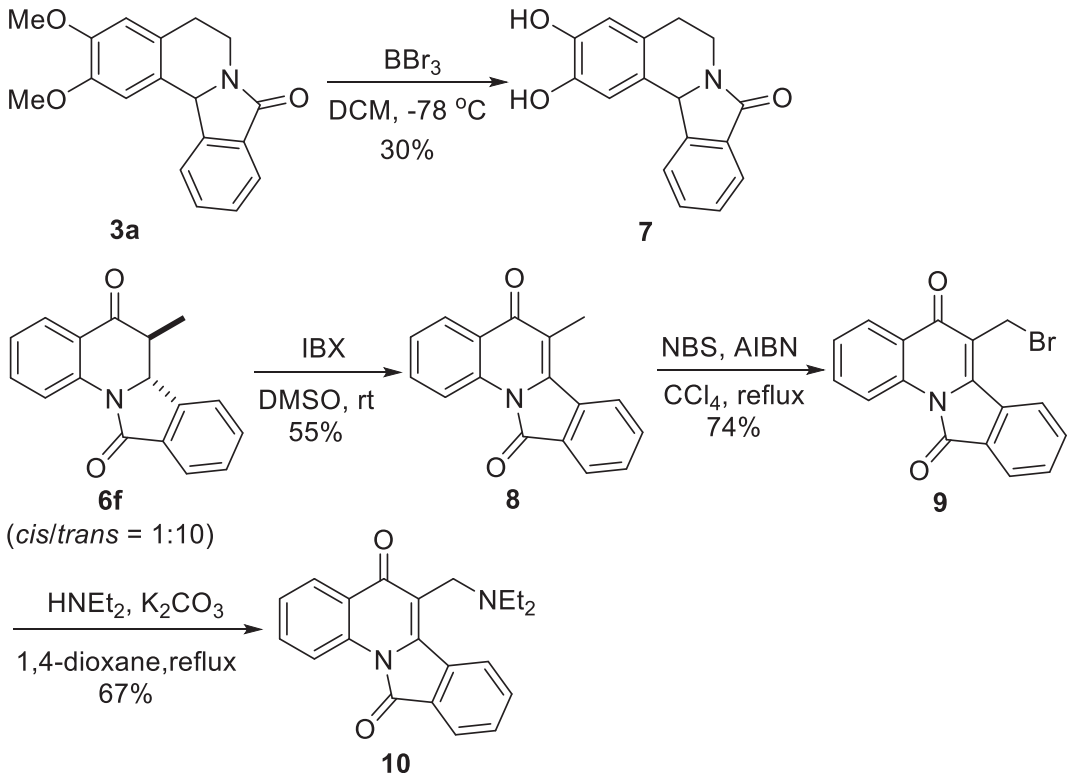
2.7 Hz, 1H), 6.72 (d, J = 2.7 Hz, 1H), 5.62 (s, 1H), 4.43 (ddd, J = 12.9, 6.0, 4.3 Hz, 1H), 3.77 (s, 3H), 3.47 (ddd, J = 12.9, 9.6, 4.8 Hz, 1H), 3.04 (ddd, J = 15.8, 9.6, 6.0 Hz, 1H), 2.85 (dt, J = 15.8, 4.5 Hz, 1H) ppm; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{16}NO_2$ 266.1176, found 266.1178.

4.10. 5,12b-Dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (3h)

Eluent: 0.7% methanol in dichloromethane; white solid (53 mg, 45%); mp 110–112 °C (lit. [10e], mp 114–116 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90–7.88 (m, 1H), 7.87–7.85 (m, 1H), 7.65–7.59 (m, 2H), 7.53–7.47 (m, 1H), 7.29 (td, J = 7.0, 2.0 Hz, 1H), 7.25–7.19 (m, 2H), 5.69 (s, 1H), 4.43 (ddd, J = 12.9, 5.8, 4.6 Hz, 1H), 3.51 (ddd, J = 12.9, 9.4, 4.8 Hz, 1H), 3.13–3.03 (m, 1H), 2.90 (dt, J = 15.9, 4.6 Hz, 1H) ppm; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{14}NO$ 236.1070, found 236.1067.

4.11. 3-Fluoro-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (3i)

Eluent: 0.5% methanol in dichloromethane; white solid (22 mg, 18%); mp 154–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (dt, J = 7.5, 1.0 Hz, 1H), 7.84 (dd, J = 7.7, 1.0 Hz, 1H), 7.65–7.56 (m, 2H), 7.51 (t, J = 7.5 Hz, 1H), 6.98 (td, J = 8.5, 2.8 Hz, 1H), 6.92 (dd, J = 9.2, 2.8 Hz, 1H), 5.64 (s, 1H), 4.43 (ddd, J = 13.0, 6.0, 4.4 Hz, 1H), 3.49 (ddd, J = 13.0, 9.4, 4.9 Hz, 1H), 3.07 (ddd, J = 15.9, 9.4, 6.0 Hz, 1H), 2.89 (dt, J = 15.9, 4.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.0, 161.9 ($J_{F\text{-}C}$ = 245.0 Hz), 144.2, 137.3 ($J_{F\text{-}C}$ = 8.0 Hz), 132.8, 131.8, 130.3 ($J_{F\text{-}C}$ = 3.0 Hz), 128.8, 127.0 ($J_{F\text{-}C}$ = 8.0 Hz), 124.1, 123.5, 116.0 ($J_{F\text{-}C}$ = 21.0 Hz), 114.0 ($J_{F\text{-}C}$ = 21.0 Hz), 58.9, 38.0, 29.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ = 117.7 ppm; IR (neat, cm^{-1}) ν_{max} 1680; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{13}FNO$ 254.0976, found 254.0972.



Scheme 3. Synthesis of compounds **7** and **10**.

4.12. 2,3-Dimethoxy-12b-methyl-5,12b-dihydroisoindolo[1,2-a] isoquinolin-8(6H)-one (3j)

Eluent: 20% ethyl acetate in petroleum ether; white solid (84 mg, 54%); mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85–7.82 (m, 2H), 7.59 (td, J = 7.6, 1.2 Hz, 1H), 7.44 (td, J = 7.5, 0.8 Hz, 1H), 7.16 (s, 1H), 6.56 (s, 1H), 4.61 (ddd, J = 13.3, 6.5, 1.4 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.35 (ddd, J = 13.3, 12.1, 4.4 Hz, 1H), 3.02 (ddd, J = 16.1, 12.1, 6.6 Hz, 1H), 2.70 (ddd, J = 16.1, 4.4, 1.4 Hz, 1H), 1.80 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 150.8, 148.3, 147.8, 132.0, 131.3, 131.1, 128.4, 126.0, 124.0, 122.2, 112.0, 109.4, 63.7, 56.4, 56.0, 35.1, 29.4, 29.0 ppm; IR (neat, cm^{-1}) ν_{max} 1677; HRMS (m/z) [M + H]$^+$ calcd for $C_{19}H_{20}NO_3$ 310.1438, found 310.1439.

4.13. 12b-Ethyl-2,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a] isoquinolin-8(6H)-one (3k)

Eluent: 40% ethyl acetate in petroleum ether; white solid (69 mg, 43%); mp 142–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.60 (td, J = 7.5, 1.2 Hz, 1H), 7.46 (td, J = 7.5, 0.9 Hz, 1H), 7.14 (s, 1H), 6.58 (s, 1H), 4.62 (ddd, J = 13.1, 6.7, 1.4 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.26 (ddd, J = 13.1, 11.9, 4.5 Hz, 1H), 3.05 (ddd, J = 16.2, 12.0, 6.7 Hz, 1H), 2.72 (ddd, J = 16.2, 4.5, 1.4 Hz, 1H), 2.31 (dq, J = 14.5, 7.3 Hz, 1H), 2.20 (dq, J = 14.5, 7.3 Hz, 1H), 0.50 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 148.4, 148.2, 147.7, 132.6, 131.9, 131.4, 128.4, 125.9, 124.0, 122.2, 112.0, 109.4, 67.1, 56.4, 56.0, 35.0, 33.5, 29.2, 7.8 ppm; IR (neat, cm^{-1}) ν_{max} 1676; HRMS (m/z) [M + H]$^+$ calcd for $C_{20}H_{21}NO_3$ 324.1594, found 324.1597.

4.14. 7,8,13,13b-Tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indol-5-one (3l)

Eluent: 0.7% methanol in dichloromethane; pale yellow solid (122 mg, 89%); mp 210–212 °C (lit. [24], mp 212–214 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.37 (s, 1H), 8.30 (dd, J = 7.5, 0.9 Hz, 1H), 7.76–7.69 (m, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43–7.38 (m, 2H), 7.10 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 6.99 (td, J = 7.4, 1.0 Hz, 1H), 6.06 (s, 1H), 4.64–4.55 (m, 1H), 3.41–3.33 (m, 1H), 2.88–2.78 (m, 1H), 2.74–2.65 (m, 1H) ppm; HRMS (m/z) [M + H]$^+$ calcd for $C_{18}H_{15}N_2O$ 275.1179, found 275.1176.

4.15. 8,13b-Dihydrobenzo[4′,5']thieno[2′,3':3,4]pyrido[2,1-a] isoindol-5(7H)-one (3 m)

Eluent: 0.5% methanol in dichloromethane; yellow solid (108 mg, 74%); mp 190–192 °C (lit. [25], mp 193–195 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (dt, J = 7.6, 1.0 Hz, 1H), 7.85–7.78 (m, 2H), 7.68–7.57 (m, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.42–7.29 (m, 2H), 5.85 (s, 1H), 4.89 (ddd, J = 13.4, 5.1, 2.4 Hz, 1H), 3.45 (ddd, J = 13.4, 10.0, 6.3 Hz, 1H), 3.01–2.97 (m, 2H) ppm; HRMS (m/z) [M + H]$^+$ calcd for $C_{18}H_{14}NOS$ 292.0791, found 292.0789.

4.16. 8,13b-Dihydrobenzofuro[2′,3':3,4]pyrido[2,1-a]isoindol-5(7H)-one (3n)

Eluent: 13% ethyl acetate in petroleum ether; yellow solid (99 mg, 72%); mp 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97–7.94 (m, 1H), 7.88 (dt, J = 7.5, 1.0 Hz, 1H), 7.63 (td, J = 7.5, 1.2 Hz, 1H), 7.53–7.48 (m, 2H), 7.46–7.42 (m, 1H), 7.31–7.25 (m, 1H), 7.22 (td, J = 7.4, 1.2 Hz, 1H), 5.78 (s, 1H), 4.88–4.83 (m, 1H), 3.38 (ddd, J = 13.4, 11.2, 4.9 Hz, 1H), 2.96–2.87 (m, 1H), 2.83–2.77 (m,

1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.7, 155.1, 148.9, 141.9, 132.3, 132.1, 129.1, 127.5, 124.5, 124.1, 123, 124.0, 119.5, 112.5, 111.5, 57.0, 37.8, 21.8; IR (neat, cm^{-1}) ν_{max} 1677; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{14}NO_2$ 276.1019, found 276.1018.

4.17. 5,6,7,13b-Tetrahydro-9H-benzo[1,2]indolizino[7,8-b]indol-9-one (3°)

Eluent: 1.4% methanol in dichloromethane; light yellow solid (107 mg, 78%); mp 126–128 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ = 10.25 (s, 1H), 8.21 (dd, *J* = 7.8, 0.9 Hz, 1H), 8.09–8.00 (m, 1H), 7.79–7.76 (m, 1H), 7.63 (td, *J* = 7.6, 1.2 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.40–7.34 (m, 1H), 7.17–7.07 (m, 2H), 6.04 (s, 1H), 4.71 (ddd, *J* = 13.0, 5.9, 1.2 Hz, 1H), 3.34 (ddd, *J* = 13.0, 11.4, 4.5 Hz, 1H), 2.98–2.88 (m, 1H), 2.85–2.78 (m, 1H) ppm; ^{13}C NMR (100 MHz, acetone-d_6) δ = 167.2, 143.7, 136.4, 131.9, 131.7, 130.9, 128.7, 126.2, 123.8, 123.2, 121.6, 118.9, 118.2, 111.3, 107.2, 56.7, 37.7, 21.4 ppm; IR (neat, cm^{-1}) ν_{max} 1668; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$ 275.1179, found 275.1176.

4.18. 6,13b-Dihydrobenzo[4′,5']thieno[3′,2':3,4]pyrido[2,1-a]isoindol-9(7H)-one (3p)

Eluent: 17% ethyl acetate in petroleum ether; yellow solid (111 mg, 76%); mp 132–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.18 (d, *J* = 8.1 Hz, 1H), 8.03 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.93–7.91 (m, 1H), 7.82 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.55–7.45 (m, 3H), 7.38 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 6.09 (s, 1H), 4.87 (ddd, *J* = 12.9, 5.4, 1.3 Hz, 1H), 3.24 (ddd, *J* = 12.9, 11.4, 3.6 Hz, 1H), 3.09–3.00 (m, 1H), 2.90–2.84 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.6, 144.8, 139.0, 137.4, 137.3, 132.5, 132.1, 128.7, 126.9, 124.5, 124.3, 124.1, 124.0, 123.0, 121.6, 59.2, 38.9, 27.1 ppm; IR (neat, cm^{-1}) ν_{max} 1685; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{14}NOS$ 292.0791, found 292.0793.

4.19. 6,13b-Dihydrobenzofuro[3′,2':3,4]pyrido[2,1-a]isoindol-9(7H)-one (3q)

Eluent: 0.5% methanol in dichloromethane; pale yellow solid (95 mg, 69%); mp 187–190 °C (lit. [26], mp 183–185 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.94–7.86 (m, 2H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 7.51–7.44 (m, 2H), 7.34 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29 (td, *J* = 7.7, 1.6 Hz, 1H), 5.88 (s, 1H), 4.90 (dd, *J* = 13.3, 6.1 Hz, 1H), 3.37 (ddd, *J* = 13.2, 11.3, 4.6 Hz, 1H), 3.11–3.02 (m, 1H), 2.84 (dd, *J* = 16.6, 4.7 Hz, 1H) ppm; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{14}NO_2$ 276.1019, found 276.1016.

4.20. 14-Methyl-6,7-dihydroisoindolo[1′,2':3,4]pyrazino[1,2-a]indol-9(13bH)-one (3r)

Eluent: 25% ethyl acetate in petroleum ether; yellow solid (65 mg, 46%); mp 155–157 °C (lit. [27], mp 173 °C decomposition); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94–7.90 (m, 2H), 7.64–7.55 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.24–7.12 (m, 3H), 6.16 (s, 1H), 4.85 (dd, *J* = 13.4, 3.8 Hz, 1H), 4.20 (dd, *J* = 11.7, 3.6 Hz, 1H), 4.03 (td, *J* = 11.7, 4.3 Hz, 1H), 3.45 (ddd, *J* = 13.5, 11.7, 4.1 Hz, 1H), 2.67 (s, 3H) ppm; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$ 289.1335, found 289.1333.

4.21. ***Methyl (7R,13bS)-5-oxo-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole-7-carboxylate*** (***3s***)

Eluent: 25% ethyl acetate in petroleum ether; yellow solid (123 mg, 74%); mp 182–183 °C (lit. [22a], mp 166–168 °C); $[\alpha]_D^{20} = -138°$ (*c* = 1.00 $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3) δ = 9.05 (s, 1H), 7.93 (t, *J* = 8.3 Hz, 2H), 7.59 (td, *J* = 7.5, 1.2 Hz, 1H), 7.51–7.45 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.16 (td, *J* = 8.0, 7.5, 1.4 Hz, 1H), 7.11 (td, *J* = 7.5, 1.2 Hz, 1H), 6.28 (s, 1H), 5.81 (d, *J* = 7.4 Hz, 1H), 3.71 (s, 3H), 3.49 (d, *J* = 16.0 Hz, 1H), 3.25 (ddd, *J* = 16.0, 7.4, 2.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 171.8, 168.6, 143.7, 136.8, 132.5, 131.5, 129.5, 120.0, 126.6, 124.7, 122.8, 122.7, 120.1, 118.7, 111.3, 106.6, 55.5, 52.8, 50.4, 24.6; IR (neat, cm^{-1}) ν_{max} 1721, 1677; HRMS (m/z) [M + H]+ calcd for $C_{19}H_{17}N_2O_3$ 333.1234, found 333.1229.

4.22. General procedure for the synthesis of isoindolo[2,1-a]quinolines

To a stirred solution of 2-acylaniline **5** (0.5 mmol) and methyl 2-formyl benzoate **2a** (0.5 mmol) in DCE (5 mL) at 0 °C was added TFA (8.0 eq). The reaction was heat at 70 °C until completion (as monitored by TLC) and cooled. 10% NaOH solution (5 mL) was added. The separated aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel to afford **6a**-**f**.

4.23. 6,6a-Dihydroisoindolo[2,1-a]quinoline-5,11-dione (6a)

Eluent: 11% ethyl acetate in petroleum ether; white solid (111 mg, 89%); mp 175–177 °C (lit. [6], mp 172–173 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (dd, *J* = 8.4, 0.6 Hz, 1H), 8.06 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.71–7.64 (m, 2H), 7.60–7.55 (m, 1H), 7.53–7.50 (m, 1H), 7.29–7.21 (m, 1H), 5.28 (dd, *J* = 14.2, 3.6 Hz, 1H), 3.32 (dd, *J* = 16.3, 3.6 Hz, 1H), 2.69 (dd, *J* = 16.3, 14.2 Hz, 1H) ppm; HRMS(*m/z*) $[M + H]^+$ calcd for $C_{16}H_{12}NO_2$ 250.0863, found 250.0861.

4.24. 3-Bromo-6,6a-dihydroisoindolo[2,1-a]quinoline-5,11-dione (6b)

Eluent: 14% ethyl acetate in petroleum ether; brown solid (113 mg, 69%); mp 166–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (d, *J* = 8.8 Hz, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 7.97 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.73 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.68 (td, *J* = 7.5, 1.2 Hz, 1H), 7.60–7.55 (m, 1H), 7.52–7.50 (m, 1H), 5.26 (dd, *J* = 14.3, 3.6 Hz, 1H), 3.32 (dd, *J* = 16.4, 3.6 Hz, 1H), 2.68 (dd, *J* = 16.4, 14.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.0, 165.8, 143.6, 140.0, 138.7, 133.3, 131.9, 130.5, 129.6, 125.1, 123.7, 122.2, 122.1, 117.7, 58.6, 42.9 ppm; IR (neat, cm^{-1}) ν_{max} 1705, 1692; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{11}^{79}BrNO_2$ 327.9968, found 327.9967.

4.25. 3-Iodo-6,6a-dihydroisoindolo[2,1-a]quinoline-5,11-dione (6c)

Eluent: 6% ethyl acetate in petroleum ether; reddish brown solid (133 mg, 71%); mp 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (s, 1H), 8.34 (d, *J* = 6.8 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.68 (td, *J* = 7.5, 1.2 Hz, 1H), 7.60–7.56 (m, 1H), 7.52–7.49 (m, 1H), 5.26 (dd, *J* = 14.3, 3.6 Hz, 1H), 3.31 (dd, *J* = 16.3, 3.6 Hz, 1H), 2.67 (dd, *J* = 16.3, 14.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.9, 165.8, 144.1, 143.6, 140.6, 136.6, 133.3, 131.9, 129.6, 125.1, 123.9, 122.3, 122.1, 88.0, 58.6, 42.8 ppm; IR (neat, cm^{-1}) ν_{max} 1703, 1681; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{10}INO_2$ 375.9829, found 375.9820.

4.26. 6,6-Dimethyl-6,6a-dihydroisoindolo[2,1-a]quinoline-5,11-dione (6d)

Eluent: 11% ethyl acetate in petroleum ether; yellow solid (82 mg, 54%); mp 144–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53 (dd, *J* = 8.4, 0.6 Hz, 1H), 8.05 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80–7.97 (m, 1H), 7.67–7.53 (m, 4H), 7.23 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 4.95 (s,

1H), 1.63 (s, 3H), 0.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.8, 166.3, 141.6, 140.4, 135.3, 133.3, 132.5, 129.3, 128.6, 124.9, 124.5, 123.6, 120.5, 120.1, 66.7, 46.7, 19.9, 17.9 ppm; IR (neat, cm^{-1}) ν_{max} 1688, 1671; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{16}NO_2$ 278.1176, found 278.1175.

4.27. 3-Iodo-6,6-dimethyl-6,6a-dihydroisoindolo[2,1-a]quinoline-5,11-dione (6e)

Eluent: 5% ethyl acetate in petroleum ether; brown solid (119 mg, 59%), mp 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39–8.31 (m, 2H), 8.00 (d, *J* = 7.4 Hz, 1H), 7.92 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.66–7.57 (m, 3H), 4.95 (s, 1H), 1.64 (s, 3H), 0.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.6, 166.4, 143.7, 141.4, 139.9, 137.3, 133.1, 132.8, 129.5, 125.1, 123.7, 122.1, 122.1, 88.1, 66.5, 46.7, 19.9, 17.9 ppm; IR (neat, cm^{-1}) ν_{max} 1708, 1671; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{14}INO_2$ 404.0142, found 404.0140.

4.28. 6-Methyl-6,6a-dihydroisoindolo[2,1-a]quinoline-5,11-dione (6f)

Eluent: 3% ethyl acetate in petroleum ether; brown solid (126 mg, 96%, *trans*:*cis* 10:1); the spectroscopic and analytical data for the isolated *trans* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.09 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.07–8.03 (m, 1H), 7.72–7.59 (m, 4H), 7.30–7.25 (m, 1H), 4.93 (d, *J* = 12.8 Hz, 1H), 2.66 (dq, *J* = 12.8, 6.8 Hz 1H), 1.67 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.8, 165.7, 143.5, 141.0, 135.4, 132.6, 132.6, 129.4, 128.0, 125.1, 124.6, 123.9, 122.19, 120.6, 64.1, 47.6, 11.0 ppm; IR (neat, cm^{-1}) ν_{max} 1684, 1667; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{14}NO_2$ 264.1019, found 264.1019.

4.29. trans-6-(Pyridin-2-yl)-6,6a-dihydroisoindolo[2,1-a]quinoline-5,11-dione (6g)

Eluent: 15% ethyl acetate in petroleum ether; yellow solid (124 mg, 76%); mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.76 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 8.57 (d, *J* = 8.3 Hz, 1H), 8.08 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H), 7.70 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.39 (ddd, *J* = 7.7, 4.8, 1.1 Hz, 1H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H), 7.28–7.21 (m, 2H), 6.18 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.06 (d, *J* = 12.8 Hz, 1H), 3.88 (d, *J* = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.6, 166.0, 155.5, 150.2, 143.4, 141.1, 136.9, 135.8, 132.5, 132.3, 129.2, 128.4, 126.7, 124.7, 124.5, 123.3, 123.1, 122.6, 120.6, 62.0, 60.6 ppm; IR (neat, cm^{-1}) ν_{max} 1700, 1670; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{15}N_2O_2$ 327.1128, found 327.1129.

4.30. 2,3-Dihydroxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (7)

To a stirred solution of **3a** (295 mg, 1.0 mmol) in dry DCM (10 mL) at −78 °C was added BBr_3 (1.0 M in DCM, 4.0 mL, 4.0 mmol) dropwise. The resulting mixture was stirred for 1 h at −78 °C before being allowed to warm to room temperature and stirred for a further 1 h. The reaction was quenched with water (3 mL). The separated aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (50% ethyl acetate in petroleum ether) to afford **7** (80 mg, 30%) as red solid; mp 110–112 °C (lit. [10a], mp 114–115 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.98 (s, 1H), 8.89 (s, 1H), 7.96–7.93 (m, 1H), 7.73–7.68 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.09 (S, 1H), 6.56 (s, 1H), 5.69 (s, 1H), 4.17 (ddd, *J* = 12.7, 5.6, 4.1 Hz, 1H), 3.36 (m, 1H, this signal was obscured by the water peak), 2.73–2.63 (m, 2H) ppm; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{13}NO_3$ 268.0968, found 268.0967.

4.31. 6-Methylisoindolo[2,1-a]quinoline-5,11-dione (8)

To a solution of **6f** (1.05 g, 4.0 mmol) in DMSO (5 mL) at room temperature under argon was added dropwise a solution of IBX (1.23 g, 4.4 mmol) in DMSO (5 mL). The reaction was stirred for 2 h before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The separated aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (10% ethyl acetate in petroleum ether) to give **8** (0.58 g, 55%) as yellow solid; mp 249–251 °C (lit. [6], mp 260–261 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.16 (dd, *J* = 8.6, 1.0 Hz, 1H), 8.30 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.03–7.97 (m, 2H), 7.76–7.67 (m, 2H), 7.61 (td, *J* = 7.5, 0.9 Hz, 1H), 7.39 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 2.54 (s, 3H) ppm; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{11}NO_2$ 262.0863, found 262.0861.

4.32. 6-(Bromomethyl)isoindolo[2,1-a]quinoline-5,11-dione (9)

A solution of **8** (522 mg, 2.0 mmol) and AIBN (33 mg, 0.2 mmol) in CCl_4 (10 mL) was cooled to 0 °C. NBS (392 mg, 2.2 mmol) was added in portion. After addition, the mixture was heated at reflux for 6 h and cooled. The bulk of solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (9% ethyl acetate in petroleum ether) to afford **9** (537 mg, 74%) as yellow solid; mp 230–231 °C (lit [6]. 237–241 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.15 (d, *J* = 8.5 Hz, 1H), 8.33 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.13 (dt, *J* = 8.0, 0.9 Hz, 1H), 8.02 (dt, *J* = 7.4, 1.0 Hz, 1H), 7.83 (td, *J* = 7.6, 1.2 Hz, 1H), 7.76–7.68 (m, 2H), 7.43 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 4.93 (s, 2H) ppm; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{10}^{79}BrNO_2$ 339.9968, found 339.9969.

4.33. 6-((Diethylamino)methyl)isoindolo[2,1-a]quinoline-5,11-dione (10)

To a solution of compound **9** (272 mg, 0.8 mmol) in 1,4-dioxane (5 mL) was added potassium carbonate (138 mg, 1.0 mmol) and diethylamine (176 mg, 2.4 mmol). The resulting mixture was heated at reflux for 1 and cooled. The bulk of 1,4-dioxane was removed on a rotary evaporator. The residue was partitioned between ethyl acetate (20 mL) and water (5 mL). The separated organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (9% ethyl acetate in petroleum ether) to afford **10** (178 mg, 67%) as yellow solid; mp 147–149 °C (lit [6]. 153–155 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.17 (d, *J* = 8.6 Hz, 1H), 8.31–8.26 (m, 2H), 7.95 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.75–7.69 (m, 2H), 7.64–7.60 (m, 1H), 7.41 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 3.98 (s, 2H), 2.67 (q, *J* = 7.1 Hz, 4H), 1.07 (t, *J* = 7.1 Hz, 6H) ppm; HRMS (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{20}N_2O_2$ 333.1598, found 333.1597.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2021.132280.

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