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Synthesis of Novel Isoquinolino[5,4-*ab*]phenanthridine Derivatives via Pictet–Spengler Reaction

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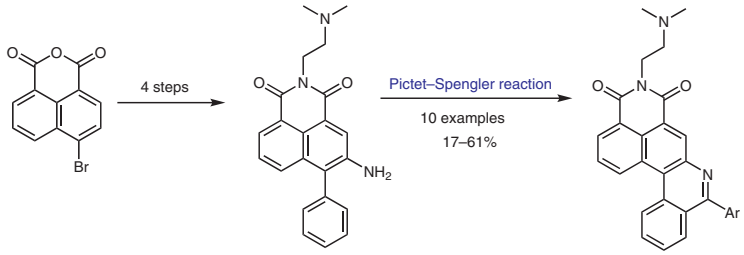

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Abstract The reaction of 5-amino-2-[2-(dimethylamino)ethyl]-6-phenyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione with a series of aldehydes in acidic media (phosphoric acid, trifluoromethanesulfonic acid, and trifluoroacetic acid) is described. This key step is based on the Pictet–Spengler reaction to synthesize ten novel isoquinolino[5,4-*ab*]phenanthridine derivatives. The most effective acid is phosphoric acid and optimized yields were obtained. The frameworks of target compounds are unique and have never been reported.

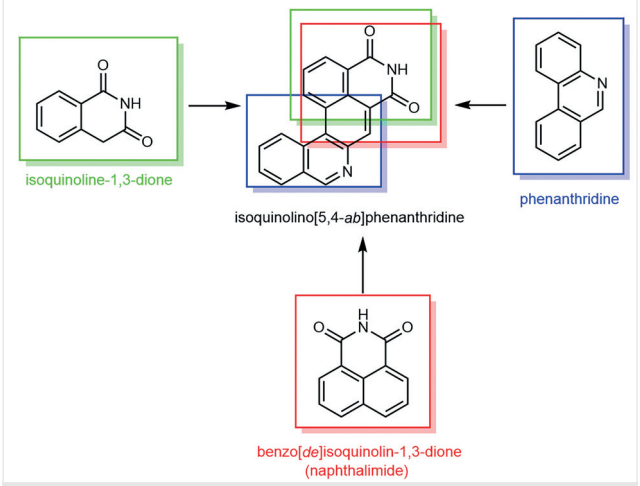
Key words homophthalimide, isoquinoline-1,3-dione, naphthalimide, phenanthridine, Pictet–Spengler reaction, Suzuki–Miyaura cross-coupling reaction

Compounds possessing isoquinoline-1,3-dione (also known as homophthalimide) framework present a wide variety of biological activities.[1] They have been reported as selective inhibitors of tyrosyl DNA phosphodiesterase II (TDP2)[2] and cyclin-dependent kinase.[3] The extensive studies of inhibiting TDP2 are needed because TDP2 retarded the efficacy of DNA-damage of anticancer drugs.

Phenanthridine-based derivatives were discovered in natural products and chemists were interested in their broad spectrum of biological activities.[4] Owing to the importance of phenanthridine derivatives, numerous syntheses have been reported.[5] The most common and key strategy employed for their syntheses was the Pictet–Spengler reaction.[6]

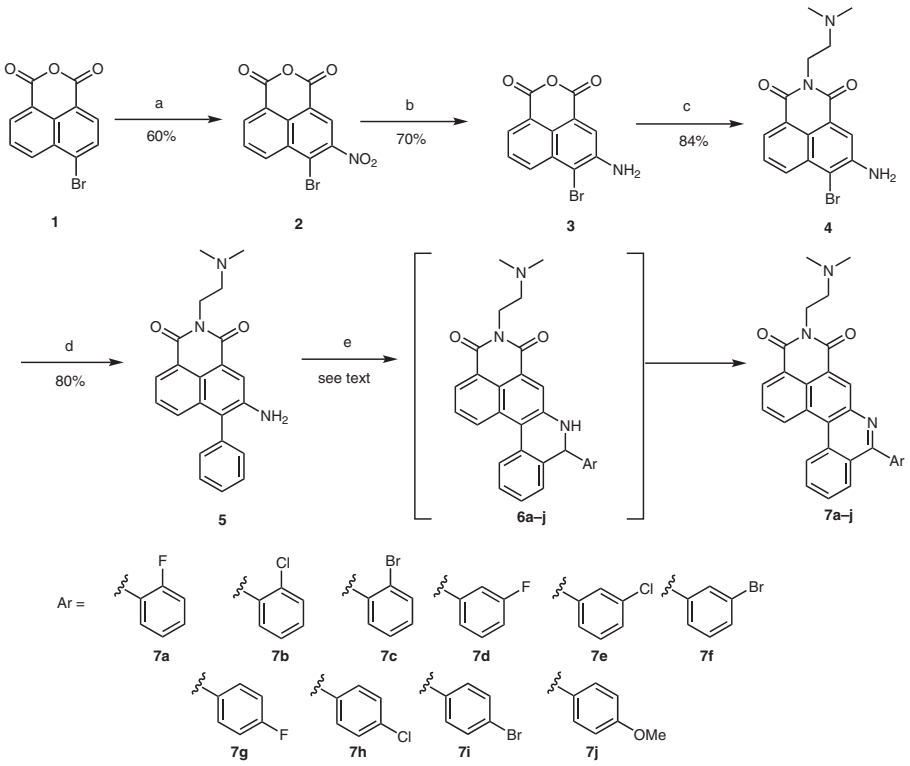
1*H*-Benz[*de*]isoquinoline-1,3-dione (naphthalimide) derivatives show anticancer properties.[7] The most prominent drugs are mitonafide[8] and amonafide.[8a,9] Furthermore, naphthalimide derivatives were synthesized as dyes due to their photostability.[10] Their derivatives were also used as sensors due to the intensive fluorescent properties.[11] On the other hand, we have recently reported the use of naphthalimide derivatives against murine melanoma.[12]

We are interested in incorporating the above-mentioned compounds frameworks into a novel isoquinolino[5,4-*ab*]phenanthridine-based motif (Scheme 1) in five steps using 6-bromobenzo[*de*]isochromene-1,3-dione (**1**) as starting material. The key steps involved a Suzuki–Miyaura cross-coupling reaction between **4** and phenylboronic acid as well as Pictet–Spengler reaction (Scheme 2, vide infra).



Scheme 1 Representative structures of isoquinoline-1,3-dione, naphthalimide, phenanthridine, and isoquinolino[5,4-*ab*]phenanthridine

The synthesis of target molecules **7a–j** is straightforward as described in Scheme 2. Nitration of the commercially available **1** afforded **2**. The nitro group of **2** was reduced by $SnCl_2$ dihydrate and the resulting **3** was converted into imide **4**. Compound **4** was coupled with phenylboronic acid to afford amino compound **5**[13] via Suzuki–Miyaura re-



Scheme 2 Synthesis of isoquinolino[5,4-*ab*]phenanthridine derivatives **7a–j**. *Reagents and conditions*: a) HNO_3, H_2SO_4, 60%; b) $SnCl_2{\cdot}2H_2O$/HCl, 70%; c) $NH_2CH_2CH_2N(Me)_2$, EtOH, 84%; d) phenylboronic acid, $PdCl_2/PPh_3$, 80%; e) aldehydes, air oxygen, acid (see text).

action. Pictet–Spengler reaction (PSR) was a powerful tool in the syntheses of a variety of alkaloids.[6] In order to study whether the electron-withdrawing property will influence the yields or not, the corresponding *o*-, *m*- and *p*-halo-substituted benzaldehydes were selected to react with amino compound **5** via Pictet–Spengler reaction to afford **7a–i**. In addition, *p*-anisaldehyde, which has an electron-donating group was used for comparison purpose (→ **7j**). Three common acids, phosphoric acid (PA),[6b] trifluoromethanesulfonic acid (TfOH),[6e] and trifluoroacetic acid (TFA)[6c,d,g] were used as solvents and surveyed, respectively.[14] It is noteworthy to mention that the formation of imines from **5** and aldehydes followed by intramolecular electrophilic aromatic substitution afforded **6a–j**, which were not isolated throughout the reaction courses. The subsequent oxidation of **6a–j** by air oxygen led to target molecules **7a–j**.

When compound **5** and two equivalents of the corresponding aldehydes were heated at 140–150 °C in phosphoric acid (PA) as solvent, the resulting target molecules **7a–j** were obtained in moderate to lower yields (Table 1). However, when six equivalents of aldehydes were used (see experimental), all target molecules were formed in satisfactory yields, except **7j** (entry 10). The low yield of **7j** was consistent with the results of the less reactive aldehydes in PA reaction in the literature.[6c] When trifluormethanesulfonic acid (TfOH) was used as solvent and catalyst instead, the yields were all lower than those in phosphoric acid. On the other hand, much longer reaction times (up to days) were required and lower yields were obtained when trifluoroacetic acid (TFA) was used instead of PA.

Among the three selected acids in this study, phosphoric acid is the best choice not only in yields but also in the reaction time for Pictet–Spengler reaction. The electron-withdrawing property on corresponding aldehydes did not influence too much the yields of **7a–i** in PA. These results were quite consistent with the conclusion of report.[6g] However, the contrast result was while *p*-anisaldehyde was used (→ **7j**). The electron-donating group in aromatic ring might retard the intermediate (an imine) to undergo intramolecular electrophilic substitution reaction even when phosphoric acid was employed. The acids of TfOH and TFA conditions afforded no reaction or very low yield in the synthesis of **7j** (Table 1, entry 10).

In conclusion, we have accomplished an efficient synthesis of a series of novel isoquinolino[5,4-*ab*]phenanthridine derivatives **7a–j** in five steps from the commercially available **1**. This protocol provides a substrate scope that electron-withdrawing property in benzaldehydes to provide higher yields. It is important to mention that more equivalents of aldehydes (up to six equivalents) and using phosphoric acid were essential to obtain the optimized yields of target molecules.

Table 1 Optimized Yields of Pictet–Spengler Reaction with Respective to PA, TfOH, and TFA

Entry	PA		TfOH		TFA		Product
	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (d)	Yield (%)	
1	10	51	10	18	3.5	11 (12)[a]	**7a**
2	9.5	47	10	29	4	42	**7b**
3	10	49	10	39	4	32	**7c**
4	8.5	57	22	20 (61)[a]	4.5	37	**7d**
5	8.5	51	8	38	3.5	28 (31)[a]	**7e**
6	8.5	49	10	43	3.5	33 (39)[a]	**7f**
7	10	61	8.5	32 (38)[a]	4.5	28 (38)[a]	**7g**
8	9.5	58	10	41	4.5	34 (36)[a]	**7h**
9	8.5	61	22	24 (54)[a]	4.5	14 (16)[a]	**7i**
10	8.5	17	22	NR	4	4 (7)[a]	**7j**

[a] Yield in parentheses is for the recovery of **5**.

All chemicals were commercially available and used without further purification, unless otherwise stated. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 600 MHz instrument. Chemical shifts were reported in ppm and referenced to the residue of solvent: ($CDCl_3$: 7.26 ppm for ^{1}H; 77.0 ppm for ^{13}C; DMSO: 2.49 ppm for ^{1}H; 39.5 ppm for ^{13}C). ^{19}F NMR (376.3 MHz) spectra were recorded on a Bruker AVIII 400 instrument. Melting points were determined on Fargo MP-2D and are not corrected. IR spectra were recorded on a Thermo Scientific Nicolet *i*S5 spectrophotometer. HRMS data were collected on a JMS-700 instrument.

6-Bromo-5-nitrobenzo[*de*]isochromene-1,3-dione (2)

Compound **1** (0.50 g, 1.804 mmol) was dissolved in concd H_2SO_4 (10 mL) and followed by the dropwise addition of concd HNO_3 (0.15 mL, 3.609 mmol) at 0 °C and the mixture was stirred for 1 h. At the end of the reaction time, the mixture was diluted with ice water and filtered by suction. The resulting pale yellow solid was purified by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/hexane 1:6) to afford **2** as a white solid; yield: 0.351 g (60%); mp 233–236 °C.

IR (KBr): 1785.8, 1754.9, 1594.8, 1546.3, 1330.6, 1282.4, 1149.4, 1035.6 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.92 (d, *J* = 8.6 Hz, 1 H), 8.84 (d, *J* = 7.3 Hz, 1 H), 8.82 (s, 1 H), 8.10 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.7, 158.2, 149.6, 136.4, 136.2, 131.8, 130.8, 130.6, 127.2, 123.9, 119.7, 119.6.

HRMS (EI): *m*/*z* calcd for $C_{12}H_5BrNO_5$ [M + H]$^+$: 321.9351; found: 321.9273.

5-Amino-6-bromobenzo[*de*]isochromene-1,3-dione (3)

Compound **2** (0.351 g, 1.089 mmol) was dissolved in AcOH (10 mL) and followed by the addition of $SnCl_2{\cdot}2H_2O$ (1.114 g, 4.359 mmol) in concd HCl (0.5 mL) dropwise at 0 °C and stirred for 6 h. At the end of reaction time, the mixture was filtered by suction and the resulting solid was washed with ice water to afford **3** as a yellow solid; yield: 0.225 g (70%); mp 276.1–276.5 °C; R_f = 0.38 (CH_2Cl_2/hexane 6:1).

IR (KBr): 3475.1, 3372.9, 1772.3, 1731.8, 1618.0, 1563.0, 1423.2, 1284.4, 1153.2, 1027.9 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.31 (d, *J* = 8.6 Hz, 1 H), 8.19 (d, *J* = 7.1 Hz, 1 H), 8.12 (s, 1 H), 7.83 (t, *J* = 8.5 Hz, 1 H), 6.42 (s, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.6, 160.4, 145.6, 131.8, 130.9, 128.9, 127.5, 123.4, 123.1, 119.3, 119.0, 107.4.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_7BrNO_3$ [M + H]$^+$: 291.9609; found: 291.9613.

5-Amino-6-bromo-2-[2-(dimethylamino)ethyl]-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4)

Compound **3** (0.629 g, 2.153 mmol) and *N*,*N*-dimethylenediamine (0.282 mL, 2.584 mmol) in anhyd EtOH (13 mL) were refluxed under N_2 for 3 h. The mixture was filtered by suction and the resulting solid was washed with cold EtOH to afford **4** as a yellow solid; yield: 0.668 g (84%); mp 194–196 °C; R_f = 0.32 (CH_2Cl_2/MeOH 7:3)

IR (KBr): 3425.0, 1699.0, 1654.6, 1616.1, 1427.1, 1340.3, 1160.9 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 7.1 Hz, 1 H), 8.25 (d, *J* = 8.3 Hz, 1 H), 8.00 (s, 1 H), 7.69 (t, *J* = 7.5 Hz, 1 H), 4.76 (s, 2 H), 4.30 (t, *J* = 6.7 Hz, 2 H), 2.67 (t, *J* = 6.7 Hz, 2 H), 2.36 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.1, 163.7, 143.3, 131.8, 130.9, 128.3, 127.7, 122.8, 122.7, 122.6, 121.3, 110.0, 57.1, 45.7 (2 ×), 38.2.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}BrN_3O_2$ [M + H]$^+$: 362.0504; found: 362.0502.

5-Amino-2-[2-(dimethylamino)ethyl]-6-phenyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (5)

To a solution of compound **4** (0.6608 g, 1.82 mmol), $PdCl_2$ (0.0194 g, 0.109 mmol), and PPh_3 (0.0576 g, 0.219 mmol) in MeOH (15 mL) were added KOH (0.205 g, 3.60 mmol) and phenylboronic acid (0.448 g, 3.60 mmol) in MeOH (5 mL) under N_2, and the reaction mixture was stirred for 9 h. At the end of reaction time, the mixture was filtered by suction and the resulting solid was washed with cold MeOH. The solid was purified by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 7:5) to afford **5** as a yellow solid; yield: 0.526 g (80%); mp 174–175 °C; R_f = 0.3 (CH_2Cl_2/MeOH 7:5).

IR (KBr): 3452.0, 3363.2, 1699.0, 1650.8, 1610.3, 1415.5, 1384.6, 1151.5 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 6.8 Hz, 1 H), 8.13 (s, 1 H), 7.61 (d, *J* = 8.3 Hz, 1 H), 7.59 (t, *J* = 7.5 Hz, 2 H), 7.52 (t, *J* = 7.3 Hz, 1 H), 7.48 (t, *J* = 7.9 Hz, 1 H), 7.35 (d, *J* = 7.1 Hz, 2 H), 4.34 (d, *J* = 6.6 Hz, 2 H), 4.00 (s, 2 H), 2.66 (d, *J* = 6.6 Hz, 2 H), 2.36 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.6, 164.2, 142.4, 135.2, 130.6, 130.3, 129.6, 128.5, 127.2, 127.0, 125.8, 122.7, 122.4, 122.0, 57.0, 45.8 (2 ×), 38.2.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}N_3O_2$ [M + H]$^+$: 360.1712; found: 360.1707.

Pictet–Spengler Reactions To Form 7a; Typical Reactions

Reaction in Phosphoric Acid (PA): To a stirred solution of compound **5** (0.0506 g, 0.1407 mmol) in phosphoric acid (0.9 mL) was added 2-fluorobenzaldehyde (0.0299 mL, 0.2821mmol). The mixture was heated at 140–150 °C for 2 h and the remaining 4 equiv of the corresponding aldehyde were added in intervals of 2 equiv every 2 h. At the end of the reaction, the mixture was poured into ice water and aq 14.2 N KOH was added until pH 10. The mixture was filtered by suction and the solid was washed with H_2O to afford a yellow-green solid.

Reaction in Trifluoromethanesulfonic Acid (TfOH): To a solution of compound **5** (0.0307 g, 0.0854 mmol) in TfOH (1 mL) was added 2-fluorobenzaldehyde (0.0181 mL, 0.1708 mmol) in a sealed tube. The mixture was heated at 140–150 °C and the remaining 4 equiv of the corresponding aldehyde were added in 2 equiv in every 2 h interval. After the addition was completed, the mixture was heated for further 4 h. At the end of reaction time, the mixture was cooled in an ice bath and aq KOH was added to the mixture until basic. The mixture was filtered by suction and the solid was washed with water to afford a black solid. The solid was purified by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 23:0.3 to 15:0.3) to afford **7a** as a pale-yellow solid; yield: 0.0073 g (18%).

Reaction in Trifluoroacetic Acid (TFA): To a solution of compound **5** (0.0507 g, 0.1410 mmol) in TFA (1 mL) was added 2-fluorobenzaldehyde (0.0299 mL, 0.2821 mmol) in a sealed tube. The mixture was heated at 140–150 °C and the remaining 4 equiv of the corresponding aldehyde were added in two equiv in every 2 h interval. After the addition was completed, the mixture was heated for further 3.5 d. At the end of reaction time, the mixture was cooled in in ice bath and aq KOH was added to the mixture until basic. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$). The resulting mixture was purified by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 23:0.3 to 15:0.3) to afford **7a** as a pale-yellow solid; yield: 0.0075 g (11%) (12% based on the recovery of **5**).

Yields for products **7a–j** are reported in Table 1 for the three typical procedures.

9-(2-Fluorophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7a)

The solid was purified by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 23:0.1 to 10:0.1) to afford **7a** as a pale-yellow solid; mp 215–216 °C; R_f = 0.37 (CH_2Cl_2/MeOH 1:0.1).

IR (KBr): 1700.9, 1658.5, 1616.1, 1384.6, 1357.6, 1241.9 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.37 (d, *J* = 8.2 Hz, 1 H), 9.30 (s, 1 H), 9.07 (d, *J* = 8.5 Hz, 1 H), 8.75 (d, *J* = 7.1 Hz, 1 H), 8.08 (d, *J* = 5.5 Hz, 1 H), 8.00–7.96 (m, 2 H), 7.80 (t, *J* = 7.4 Hz, 2 H), 7.60–7.58 (m, 1 H), 7.44 (t, *J* = 7.1 Hz, 1 H), 7.30 (t, *J* = 9.0 Hz, 1 H), 4.40 (t, *J* = 6.6 Hz, 2 H), 2.73 (t, *J* = 6.6 Hz, 2 H), 2.38 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.5, 163.6, 160.1 ($^1J_{C,F}$ = 247.0 Hz), 157.7, 142.6, 135.1, 133.4, 132.2, 131.9, 131.4 ($^3J_{C,F}$ = 7.9 Hz), 131.3, 130.2, 128.8, 128.6 ($^2J_{C,F}$ = 20.0 Hz), 127.9, 127.8, 127.4 ($^3J_{C,F}$ = 7.3 Hz), 126.6, 126.5, 126.5, 124.8 ($^3J_{C,F}$ = 8.0 Hz), 123.4, 123.0, 57.0, 45.8 (2 ×), 38.4.

^{19}F NMR (376.3 MHz, $CDCl_3$): δ = –113.2.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}FN_3O_2$ [M + H]$^+$: 464.1774; found: 464.1775.

9-(2-Chlorophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7b)

Prepared following the Typical Procedure 1 (PA). Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 23:0.1 to 15:0.1) afforded **7b** as a pale-yellow solid; mp 144–146 °C; R_f = 0.37 (CH_2Cl_2/MeOH 1:0.1).

IR (KBr): 1702.8, 1660.4, 1600.6, 1436.7, 1384.6, 1357.6, 1241.9, 1056.8 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.37 (d, *J* = 8.4 Hz, 1 H), 9.30 (s, 1 H), 9.06 (d, *J* = 8.4 Hz, 1 H), 8.74 (d, *J* = 7.3 Hz, 1 H), 7.99 (d, *J* = 6.8 Hz, 1 H), 7.97 (d, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.77 (t, *J* = 7.7 Hz, 1 H), 7.66 (t, *J* = 4.9 Hz, 1 H), 7.60 (t, *J* = 4.2 Hz, 1 H), 7.54–7.52 (m, 2 H), 4.41 (t, *J* = 6.6 Hz, 2 H), 2.76 (t, *J* = 6.6 Hz, 2 H), 2.40 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.4, 163.6, 160.4, 142.5, 137.7, 135.1, 133.4, 133.3, 132.2, 131.3, 129.9, 128.7, 128.5, 127.9, 127.7, 127.5, 127.4, 127.3, 124.8, 123.3, 123.0, 56.8, 45.7 (2 ×), 38.2.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}ClN_3O_2$ [M + H]$^+$: 480.1479; found: 480.1481.

9-(2-Bromophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7c)

Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 26:0.1 to 15:0.1) afforded **7c** as a pale-yellow solid; mp 183–184 °C; R_f = 0.37 (CH_2Cl_2/MeOH 1:0.1).

IR (KBr): 1702.8, 1656.6, 1600.6, 1384.6, 1348.0, 1243.9, 1025.9 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.32 (d, *J* = 8.5 Hz, 1 H), 9.23 (s, 1 H), 9.04 (d, *J* = 8.3 Hz, 1 H), 8.73 (dd, *J* = 7.1 Hz, 1 H), 8.28 (d, *J* = 8.3 Hz, 1 H), 7.99 (d, *J* = 7.3 Hz, 1 H), 7.96 (d, *J* = 8.7 Hz, 1 H), 7.81–7.76 (m, 5 H), 4.39 (d, *J* = 6.6 Hz, 2 H), 2.72 (d, *J* = 6.6 Hz, 2 H), 2.38 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.4, 163.6, 160.6, 142.3, 137.5, 135.0, 133.2, 132.9, 131.9, 131.7, 131.2, 130.1, 128.7, 128.4, 127.8, 127.7, 127.4, 127.0, 124.2, 124.0, 123.3, 123.1, 57.0, 45.8 (2 ×), 38.4.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}BrN_3O_2$ [M + H]$^+$: 524.0974; found: 524.0974.

9-(3-Fluorophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7d)

Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 20:0.5) afforded **7d** as a pale-yellow solid; R_f = 0.45 (CH_2Cl_2/MeOH 1:0.1); mp 236–238 °C.

IR (KBr): 1699.0, 1656.6, 1616.1, 1440.6, 1384.6, 1357.6, 1025.9 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.34 (d, *J* = 8.3 Hz, 1 H), 9.26 (s, 1 H), 9.06 (d, *J* = 8.5 Hz, 1 H), 8.74 (d, *J* = 7.2 Hz, 1 H), 8.32 (d, *J* = 8.3 Hz, 1 H), 8.00 (d, *J* = 7.5 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 7.81 (d, *J* = 7.3 Hz, 1 H), 7.66 (d, *J* = 7.4 Hz, 1 H), 7.62–7.57 (m, 2 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 4.40 (t, *J* = 6.6 Hz, 2 H), 2.73 (t, *J* = 6.6 Hz, 2 H), 2.38 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.4, 163.6, 162.8 ($^1J_{C,F}$ = 246.0 Hz), 160.4, 142.3, 140.7 ($^3J_{C,F}$ = 7.4 Hz), 140.7 ($^3J_{C,F}$ = 7.4 Hz), 135.0, 133.2, 132.9, 131.2, 130.2 ($^3J_{C,F}$ = 8.1 Hz), 13.1, 128.7, 128.6, 128.4, 127.8, 127.7, 127.4, 127.0, 125.8, 124.3, 123.4, 123.1, 117.1 ($^2J_{C,F}$ = 22.0 Hz), 116.3 ($^2J_{C,F}$ = 22.0 Hz), 57.0, 45.8 (2 ×), 38.4.

^{19}F NMR (376.3 MHz, $CDCl_3$): δ = –112.3.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}FN_3O_2$ [M + H]$^+$: 464.1774; found: 464.1775.

9-(3-Chlorophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7e)

Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 22:0.3) afforded **7e** as a pale-yellow solid; mp 236–238 °C; R_f = 0.45 (CH_2Cl_2/MeOH 1:0.1).

IR (KBr): 1699.0, 1654.6, 1598.7, 1432.9, 1357.6, 1079.9, 1025.0 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.33 (d, *J* = 8.4 Hz, 1 H), 9.25 (s, 1 H), 9.05 (d, *J* = 8.4 Hz, 1 H), 8.74 (d, *J* = 7.3 Hz, 1 H), 8.29 (d, *J* = 8.2 Hz, 1 H), 8.01–7.96 (m, 2 H), 7.88 (s, 1 H), 7.81 (t, *J* = 7.4 Hz, 1 H), 7.76 (d, *J* = 6.4 Hz, 1 H), 7.57–7.55 (m, 2 H), 4.39 (t, *J* = 6.6 Hz, 2 H), 2.72 (t, *J* = 6.6 Hz, 2 H), 2.38 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 164.4, 163.6, 160.3, 142.3, 140.4, 134.9, 134.7, 133.2, 132.9, 131.3, 130.2, 130.1, 129.9, 129.5, 128.8, 128.7, 128.4, 128.2, 127.7, 127.4, 127.0, 124.3, 123.4, 123.1, 57.0, 45.8, 38.4.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}ClN_3O_2$ [M + H]$^+$: 480.1479; found: 480.1476.

9-(3-Bromophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7f)

Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 25:0.3 to 20:0.3) afforded **7f** as a pale-yellow solid; mp 238–242 °C; R_f = 0.45 (CH_2Cl_2/MeOH 1:0.1).

IR (KBr): 1700.9, 1658.5, 1600.6, 1434.8, 1355.7, 1241.9, 1155.0 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.33 (d, *J* = 8.3 Hz, 1 H), 9.25 (s, 1 H), 9.06 (d, *J* = 8.5 Hz, 1 H), 8.74 (dd, *J* = 7.4, 1.4 Hz, 1 H), 8.29 (d, *J* = 8.3 Hz, 1 H), 8.03 (t, *J* =1.7 Hz, 1 H), 8.02–7.97 (m, 2 H), 7.84–7.80 (m, 2 H), 7.74–7.70 (m, 1 H), 7.50 (t, *J* = 7.9 Hz, 1 H), 4.40 (t, *J* = 7.2 Hz, 2 H), 2.72 (t, *J* = 7.2 Hz, 2 H), 2.38 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 164.4, 163.6, 160.2, 142.3, 140.7, 134.9, 133.2, 132.9, 132.8, 132.4, 131.3, 130.2, 130.0, 128.8, 128.7, 128.4, 127.8, 127.7, 127.5, 127.0, 124.3, 123.1, 122.8, 57.0, 45.8 (2 ×), 38.4.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}BrN_3O_2$ [M + H]$^+$: 524.0974; found: 524.0974.

9-(4-Fluorophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7g)

Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 16:0.5) afforded **7g** as a pale-yellow solid; mp 241–245 °C; R_f = 0.37 (CH_2Cl_2/MeOH 1:0.1).

IR (KBr): 1702.8, 1658.5, 1602.6, 1384.6, 1355.7, 1240.0, 1159.0, 1024.0 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.31 (d, *J* = 8.3 Hz, 1 H), 9.23 (s, 1 H), 9.03 (d, *J* = 8.3 Hz, 1 H), 8.72 (d, *J* = 7.3 Hz, 1 H), 8.29 (d, *J* = 8.2 Hz, 1 H), 7.99 (d, *J* = 8.3 Hz, 1 H), 7.97 (d, *J* = 7.5 Hz, 1 H), 7.89 (d, *J* = 5.5 Hz, 1 H), 7.88 (d, *J* = 5.5 Hz, 1 H), 7.80 (t, *J* = 7.7 Hz, 1 H), 7.31 (t, *J* = 8.5 Hz, 2 H), 4.39 (t, *J* = 6.6 Hz, 2 H), 2.72 (t, *J* = 6.6 Hz, 2 H), 2.38 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.4, 163.6, 163.5 ($^1J_{C,F}$ = 246.0 Hz), 160.7, 142.3, 134.9, 134.7, 133.2, 132.9, 132.0 ($^3J_{C,F}$ = 8.0 Hz, 2 ×), 131.2, 130.1, 128.8, 128.6, 128.4, 127.7, 127.6, 127.4, 127.1, 124.1, 123.3, 123.0, 115.8 ($^2J_{C,F}$ = 21.0 Hz, 2 ×), 56.9, 45.8 (2 ×), 38.3.

^{19}F NMR (376.3 MHz, $CDCl_3$): δ = –111.7.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}FN_3O_2$ [M + H]$^+$: 464.1774; found: 464.1773.

9-(4-Chlorophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7h)

Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 20:0.5) afforded **7h** as a pale-yellow solid; mp 236–239 °C; R_f = 0.37 (CH_2Cl_2/MeOH 1:0.1).

IR (KBr): 1702.8, 1660.4, 1600.6, 1384.6, 1357.6, 1241.0, 1091.0, 1016.0 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.37 (d, *J* = 8.4 Hz, 1 H), 9.30 (s, 1 H), 9.06 (d, *J* = 8.5 Hz, 1 H), 8.74 (d, *J* = 7.3 Hz, 1 H), 7.99 (d, *J* = 6.8 Hz, 1 H), 7.97 (d, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.77 (t, *J* = 7.7 Hz, 1 H), 7.66 (t, *J* = 4.9 Hz, 1 H), 7.60 (t, *J* = 4.2 Hz, 1 H), 7.54–7.52 (m, 2 H), 4.41 (t, *J* = 6.6 Hz, 2 H), 2.76 (t, *J* = 6.6 Hz, 2 H), 2.40 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.4, 163.6, 160.4, 142.5, 137.7, 135.1, 133.4, 133.3, 132.2, 131.3, 129.9, 128.7, 128.5, 127.9, 127.7, 127.5, 127.4, 127.3, 124.8, 123.3, 123.0, 56.8, 45.6 (2 ×), 38.2.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}ClN_3O_2$ [M + H]$^+$: 480.1479; found: 480.1478.

9-(4-Bromophenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7i)

Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 25:0.5) afforded **7i** as a pale-yellow solid; mp 251–252 °C; R_f = 0.37 (CH_2Cl_2/MeOH 1:0.1).

IR (KBr): 1702.8, 1658.5, 1618.0, 1436.7, 1384.6, 1346.1, 1241.9, 1089.0, 1024.0 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.37 (d, *J* = 8.5 Hz, 1 H), 9.29 (s, 1 H), 9.07 (d, *J* = 8.5 Hz, 1 H), 8.74 (d, *J* = 7.4 Hz, 1 H), 8.07–7.96 (m, 2 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 7.79 (d, *J* = 7.2 Hz, 1 H), 7.76 (d, *J* = 7.7 Hz, 1 H), 7.63 (dd, *J* = 7.4, 1.7 Hz, 1 H), 7.57 (td, *J* = 7.5, 0.9 Hz, 1 H), 7.45 (td, *J* = 7.7, 1.7 Hz, 1 H), 4.39 (t, *J* = 7.2 Hz, 2 H), 2.71 (t, *J* = 7.2 Hz, 2 H), 2.37 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.4, 163.6, 161.5, 142.4, 139.6, 135.0, 133.4, 133.1, 132.2, 131.3, 131.2, 130.6, 130.2, 128.7, 128.5, 127.8, 127.7, 127.5, 127.4, 124.8, 123.3, 123.0, 122.8, 56.9, 45.8 (2 ×), 38.3.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}BrN_3O_2$ [M + H]$^+$: 524.0974; found: 524.0969.

9-(4-Methoxyphenyl)-5-[2-(dimethylamino)ethyl]-4*H*-isoquinolino[5,4-*ab*]phenanthridine-4,6(5*H*)-dione (7j)

Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2/MeOH 21.5:0.5) afforded **7j** as a yellow solid; mp 170–172 °C; R_f = 0.5 (CH_2Cl_2/MeOH 1:0.1).

IR (KBr): 1700.9, 1658.5, 1602.6, 1384.6, 1357.6, 1243.0, 1025.0 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.31 (d, *J* = 8.5 Hz, 1 H), 9.25 (s, 1 H), 9.01 (d, *J* = 8.4 Hz, 1 H), 8.71 (dd, *J* = 7.3, 0.8 Hz, 1 H), 8.38 (d, *J* = 8.2 Hz, 1 H), 7.97–7.94 (m, 2 H), 7.87 (dd, *J* = 6.7, 1.9 Hz, 2 H), 7.78 (t, *J* = 7.1 Hz, 1 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 4.40 (t, *J* = 7.2 Hz, 2 H), 3.94 (s, 3 H), 2.73 (t, *J* = 7.2 Hz, 2 H), 2.39 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.5, 163.7, 161.5, 160.8, 142.4, 135.1, 133.1, 133.0, 131.6, 131.0, 129.9, 129.2, 128.5, 127.6, 127.3, 127.2, 123.9, 123.3, 122.8, 114.2, 56.9, 55.0, 45.7 (2 ×), 38.3.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{26}N_3O_3$ $[M + H]^+$: 476.1974; found: 476.1972.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610670. Spectra of the new compounds are included.

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