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ORIGINAL PAPER

Synthesis of 8-oxoprotoberberines using acid-mediated cyclization or the Heck reaction

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Abstract A facile method of synthesizing 8-oxoprotoberberines is described from 6-benzoyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline-5-carbaldehyde via acid-mediated cyclization or from 2-(2-iodophenethyl)isoquinolin-1(2*H*)-one via the Heck reaction. The present method offers several advantages, such as good yields and a simple procedure.

Keywords 8-Oxoprotoberberines · Acid-mediated · Cyclization · Heck reaction

Introduction

Protoberberine alkaloids (Fig. 1) constitute an important class of natural products that are typically characterized by a tetracyclic ring skeleton with an isoquinoline core [1, 2]. Due to their diverse biological properties, such as antitumor, antiviral, and antimicrobial activities [3–11], considerable attention has been focused on the efficient synthesis of these alkaloids [12–21]. However, previously reported methods require the use of harsh conditions [13, 14], involve lengthy sequences with low overall yields [18], need complicated starting materials [18, 19, 21], and various substituted protoberberine derivatives are in short supply [12–14]. Thus, the development of a simple and efficient method for the synthesis of protoberberines is demanded.

Our group has been researching the synthesis and pharmacological properties of natural products [22–27]. Recently, we have focused on the synthesis of protoberberines because of their diverse biological properties [28, 29]. We noted that Wakchaure et al. reported the synthesis of dehydrogusanlung D and dehydroisogusanlung D using a similar synthetic route involving the Heck reaction. However, the reaction time of their synthesis was long, and two different reaction conditions were used to synthesize two compounds. Hence, we wish to report an efficient and general protocol for the synthesis of 8-oxoprotoberberines from 6-benzoyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline-5-carbaldehyde (**3**) via acid-mediated cyclization or 2-(2-iodophenethyl)isoquinolin-1(2*H*)-one (**5**) via the Heck reaction (Scheme 1).

Results and discussion

Our strategy commenced with the preparation of compound **3d**. To achieve this, a condensation reaction between (5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)methanol (**1**) [30, 31] and 3,4-dimethoxybenzoic

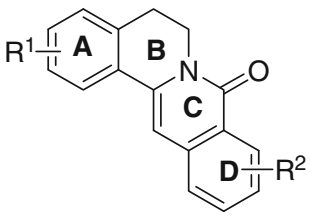

Fig. 1 Structure of protoberberines

A. Chen and K. Zhao contributed equally to this work.

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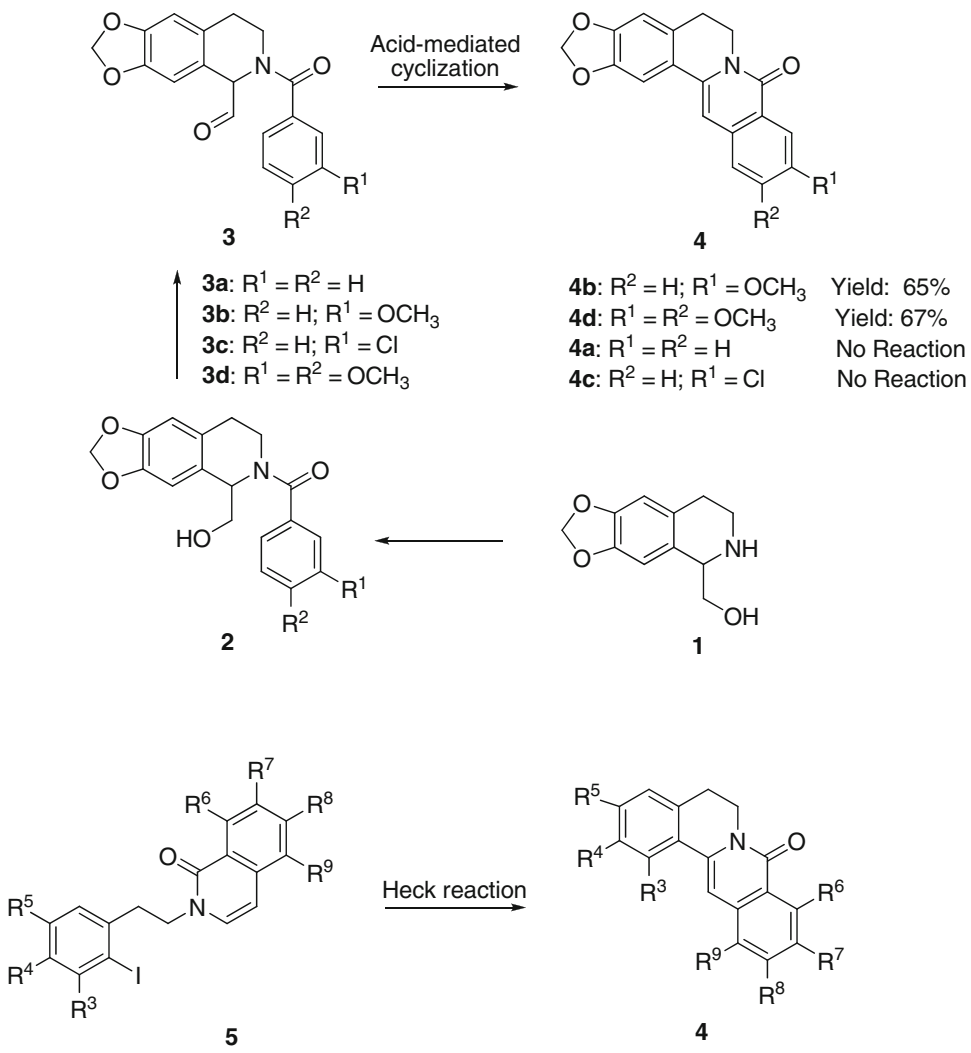
Scheme 1

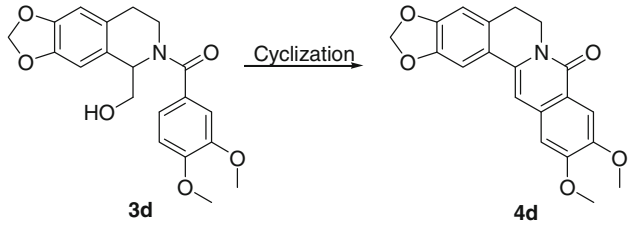


5e: $R^3 = R^6 = R^7 = R^8 = R^9 = H$; $R^4, R^5 = -OCH_2O-$
5f: $R^3 = R^6 = R^9 = H$; $R^4, R^5 = -OCH_2O-$; $R^7, R^8 = -OCH_2O-$
5g: $R^3 = R^6 = R^9 = H$; $R^4, R^5 = -OCH_2O-$; $R^7 = R^8 = OCH_3$
5h: $R^3 = R^6 = R^7 = R^8 = H$; $R^4, R^5 = -OCH_2O-$; $R^9 = NO_2$
5i: $R^3 = R^6 = R^7 = R^8 = R^9 = H$; $R^4 = R^5 = OCH_3$
5j: $R^3 = R^6 = R^9 = H$; $R^4 = R^5 = OCH_3$; $R^7, R^8 = -OCH_2O-$
5k: $R^3 = R^6 = R^9 = H$; $R^4 = R^5 = R^7 = R^8 = OCH_3$
5l: $R^3 = R^6 = R^7 = R^8 = H$; $R^4 = R^5 = OCH_3$; $R^9 = NO_2$
5m: $R^6 = R^7 = R^8 = R^9 = H$; $R^3 = R^4 = R^5 = OCH_3$
5n: $R^6 = R^9 = H$; $R^3 = R^4 = R^5 = OCH_3$; R^7 , $R^8 = -OCH_2O-$
5o: $R^6 = R^9 = H$; $R^3 = R^4 = R^5 = R^7 = R^8 = OCH_3$
5p: $R^6 = R^7 = R^8 = H$; $R^3 = R^4 = R^5 = OCH_3$; $R^9 = NO_2$

acid was carried out to yield the compound **2d**, which furnished compound **3d** via subsequent oxidation by *o*-iodoxybenzoic acid (IBX) in a mixture of toluene and DMSO. After **3d** had been obtained, acid-mediated cyclization to convert **3d** to **4d** was explored, and the results are summarized in Table 1.

As shown in Table 1, Lewis acids such as $BF_3{\cdot}Et_2O$ and $TiCl_4$ were unsuitable for the cyclization (Table 1, entries 1

Table 1 Effects of different reaction conditions on the cyclization of **3d**



Entry	Acid	Temperature/°C	Time/h	Yield/%[a]
1	$BF_3{\cdot}Et_2O$	RT	12	NR[d]
2	$BF_3{\cdot}Et_2O$	50	24	NR[d]
3	$TiCl_4$	RT	12	NR[d]
4	$TiCl_4$	50	24	NR[d]
5	CF_3COOH	RT	12	5
6	CF_3COOH	50	8	13
7	H_2SO_4/AcOH[b]	RT	12	17
8	H_2SO_4/AcOH[b]	60	16	48
9	HCl/AcOH[c]	RT	12	23
10	HCl/AcOH[c]	60	8	55
11	HCl/AcOH[c]	60	16	67
12	HCl/AcOH[c]	60	24	56
13	HCl/AcOH[c]	80	16	43

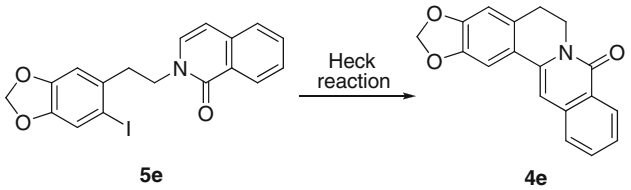
[a] Isolated yields after chromatography on silica gel

[b] All reactions were performed with H_2SO_4/AcOH (1:5)

[c] All reactions were performed with HCl/AcOH (1:1)

[d] No reaction was observed

Table 2 Optimizing the conditions of the Heck reaction for the cyclization of **5e**



Entry	Palladium	Ligands	Bases	Additives	Solvent	Yield/%[a]
1[b]	$Pd_2(dba)_3$	P(*o*-tol)$_3$	Et_3N	None	CH_3CN	Trace
2[c]	$Pd(OAc)_2$	PPh_3	Et_3N	Ag_2CO_3	DMF	18
3[c]	$Pd(OAc)_2$	PPh_3	K_2CO_3	Ag_2CO_3	DMF	20
4[c]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Ag_2CO_3	DMF	10
5[d]	$Pd(OAc)_2$	None	K_2CO_3	*n*-Bu_4NBr	DMF	70
6[d]	$Pd(PPh_3)_4$	None	K_2CO_3	*n*-Bu_4NBr	DMF	20
7[d]	$Pd(PPh_3)_2Cl_2$	None	K_2CO_3	*n*-Bu_4NBr	DMF	55
8[d]	$Pd(OAc)_2$	None	Cs_2CO_3	*n*-Bu_4NBr	DMF	52
9[d]	$Pd(OAc)_2$	PPh_3	K_2CO_3	*n*-Bu_4NBr	DMF	58

[a] Isolated yields after chromatography on silica gel

[b] Reaction conditions: palladium (5 mol%), ligand (10 mol%), base (2 equiv), 85 °C

[c] Reaction conditions: palladium (13 mol%), ligand (26 mol%), base (2.2 equiv), additive (2 eq), 150 °C

[d] Reaction conditions: palladium (10 mol%), bases (2 eq), additive (1 equiv), 110 °C

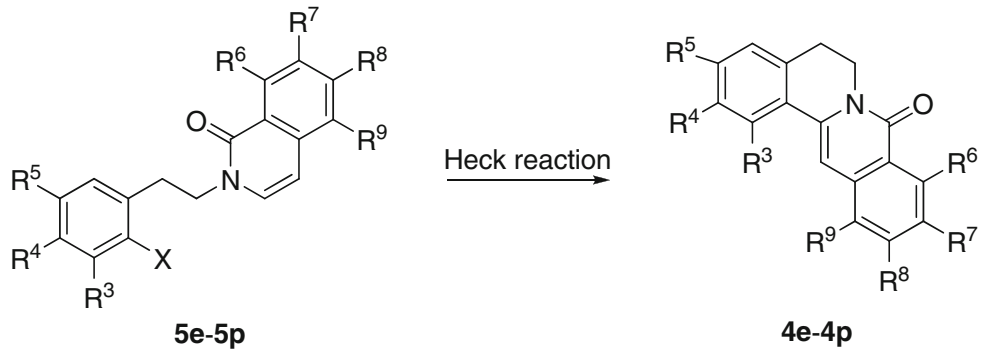
and 3). Moreover, raising the reaction temperature and extending the reaction time did not lead to any of the target product **4d** in the presence of $BF_3{\cdot}Et_2O$ or $TiCl_4$ (Table 1, entries 2 and 4). A trace amount of the desired product **4d** was observed when the reaction was stirred in CF_3CO_2H (Table 1, entries 5 and 6). We then carried out the cyclization reaction in different mixed acid systems (Table 1, entries 7–11). The target product **4d** [19] was obtained in 67% yield at 60 °C for 16 h in HCl/AcOH (Table 1, entry 11). Using a higher temperature or a longer reaction time reduced the yield of compound **4d** (Table 1, entries 12 and 13) due to the decomposition of **4d** under strongly acidic conditions.

Subsequently, the optimized conditions were used to synthesize **4a**–**4c**. However, **3a** and **3c** could not be cyclized successfully to afford the corresponding products **4a** and **4c**, while **4b** was obtained in 65% yield. This indicated that the strong electron-donating substituents (e.g., OMe) on aromatic ring D are indispensable to the cyclization. When aromatic ring D carried weak electron-donating substituents (e.g., Cl), or even no substituent, the reaction could not proceed smoothly. Therefore, we turned our attention towards the synthesis of **4** from **5** [20] via the Heck reaction to obtain various 8-oxoprotoberberine derivatives.

We took the Heck reaction of **5e** as a model reaction to search for suitable reaction conditions. As shown in Table 2, the conditions employed by Fukuyama for the Heck reaction of **5e** using $Pd_2(dba)_3$ as the catalyst and Et_3N as base in CH_3CN at 85 °C for 18 h [32] were examined initially (Table 2, entry 1). Unfortunately, only a trace amount of the target product **4e** was observed. Continuing our investigation into the conditions of the Heck reaction, we optimized the reaction conditions of compound **5e** in terms of the catalyst [$Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, or $Pd(OAc)_2$], ligand [PPh_3 or P(*o*-tol)$_3$], additive [Ag_2CO_3 or *n*-Bu_4NBr], and base [Et_3N, K_2CO_3, or Cs_2CO_3] (Table 2, entries 2–9) [33], among the catalyzed conditions, the presence of *n*-Bu_4NBr as additive, 10 mol% $Pd(OAc)_2$, and 2 equiv of K_2CO_3 in DMF at 110 °C for 5 h (Table 2, entries 5) proved to be the best.

With the optimal reaction conditions identified, compounds **5f**–**5p** were transformed into the corresponding

Table 3 Synthesis of 8-oxoprotoberberines **4e–4p**



Entry	Product	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Yield/%[a] [refs.][b]
1	**4e**	H	$-OCH_2O-$		H	H	H	H	70 [15]
2	**4f**	H	$-OCH_2O-$		H	$-OCH_2O-$		H	74 [34]
3	**4g**	H	$-OCH_2O-$		H	OCH_3	OCH_3	H	65 [34]
4	**4h**	H	$-OCH_2O-$		H	H	H	NO_2	62
5	**4i**	H	OCH_3	OCH_3	H	H	H	H	69 [15]
6	**4j**	H	OCH_3	OCH_3	H	$-OCH_2O-$		H	76 [35]
7	**4k**	H	OCH_3	OCH_3	H	OCH_3	OCH_3	H	67 [36]
8	**4l**	H	OCH_3	OCH_3	H	H	H	NO_2	64 [37]
9	**4m**	OCH_3	OCH_3	OCH_3	H	H	H	H	60
10	**4n**	OCH_3	OCH_3	OCH_3	H	$-OCH_2O-$		H	62
11	**4o**	OCH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	H	44
12	**4p**	OCH_3	OCH_3	OCH_3	H	H	H	NO_2	42

[a] Isolated yields after chromatography on silica gel

[b] References in which the compounds have been reported

8-oxoprotoberberine derivatives in moderate to good yields ranging from 42 to 76%. As illustrated in Table 3, the steric hindrance seemed to have an effect on the results. For example, compounds **5e–5l** gave the desired products with 64–76% yields (Table 3, entries 1–8), while 42–62% yields were obtained when **5m–5p** were used as substrates (Table 3, entries 9–12) because of the *ortho*-methoxy group at the position R^3 on ring A of compounds **4m–4p**, or the *ortho*-nitro group at the position R^9 on ring D of the compound **4p**. In summary, the palladium-catalyzed Heck reaction of compounds **5e–5p** has been carried out in moderate to good yields (42–76%). In particular, we successfully synthesized the compounds **4h**, **4l**, and **4p**, which have an electron-withdrawing group (NO_2) on aromatic ring D. To the best of our knowledge, this is the first report of the synthesis of these compounds.

In conclusion, the 8-oxoprotoberberines were successfully synthesized using acid-mediated cyclization or the Heck reaction. Our synthesis provides a simple and versatile method for synthesizing diverse substituted protoberberines. Therefore, this protocol is a good addition to the existing methods.

Experimental

NMR spectra were recorded on a Varian Mercury VX300 Fourier transform spectrometer. The chemical shifts are reported in ppm using the signals of $CDCl_3$ as internal standards for the ^1H and ^{13}C spectra. EI–MS were obtained on a Shimadzu GCMS-QP5050A spectrometer. ESI–MS were run on a Bruker Esquire 3000 plus spectrometer in MeOH. Melting points were determined with a WRS-1B apparatus. Thin-layer chromatographic (TLC) plates (silica gel 60 GF, with glass support) from Yantai Jiangyou Company were used to monitor the progress of the reaction and were visualized with 254 nm UV light. Unless otherwise mentioned, all chemicals and materials were used as received from commercial suppliers without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone under nitrogen. Dichloromethane (DCM) was distilled from calcium hydride.

General procedure for the synthesis of compounds ***2a–2d***

To a solution of 208 mg (5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)methanol (**1**, 1 mmol) in 10 cm^3 CH_2Cl_2 at room temperature, 210 mg 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 1.1 mmol), 30 mg 1-hydroxybenzotriazole (HOBt, 0.2 mmol), 111 mg Et_3N (1.1 mmol), and different benzoic acids (1.1 mmol) were added. The resulting mixture was stirred for 5 h and then diluted with 20 cm^3 CH_2Cl_2. The organic phase was washed with 2 N HCl and brine. The organic solvent was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by gel silica column chromatography, eluting with $CHCl_3$:MeOH = 120:1 to provide the pure products **2a–2d**.

[7,8-Dihydro-5-(hydroxymethyl)-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl]phenylmethanone (**2a**, $C_{18}H_{17}NO_4$)
White solid; m.p.: 53–55 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (m, 5H), 6.72 (s, 1H), 6.60 (s, 1H), 5.92 (s, 2H), 5.74 (m, 1H), 4.08–3.47 (m, 4H), 2.97–2.61 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 146.8, 146.5, 135.7, 130.0, 128.6, 127.2, 126.8, 125.6, 108.5, 107.3, 101.0, 66.9, 55.6, 42.1, 29.2 ppm; ESI–MS: *m/z* = 311.2 ($[M + 1]^+$).

[7,8-Dihydro-5-(hydroxymethyl)-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl](3-methoxyphenyl)methanone
(**2b**, $C_{19}H_{19}NO_5$)
White solid; m.p.: 50–52 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (m, 1H), 7.02 (m, 3H), 6.72 (s, 1H), 6.60 (s, 1H), 5.94 (s, 2H), 5.73 (m, 1H), 4.09-3.79 (m, 3H), 3.86 (s, 3H), 3.53 (m, 1H), 2.92–2.62 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 159.6, 146.9, 146.5, 137.0, 129.7, 127.3, 125.5, 118.7, 116.1, 112.1, 108.5, 107.3, 101.0, 67.1, 55.6, 55.4, 42.1, 29.2 ppm; ESI–MS: *m/z* = 341.2 ($[M + 1]^+$).

(3-Chlorophenyl)[7,8-dihydro-5-(hydroxymethyl)-[1,3]-dioxolo[4,5-g]isoquinolin-6(5H)-yl]methanone
(**2c**, $C_{18}H_{16}ClNO_4$)
White solid; m.p.: 128–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.27 (m, 4H), 6.71 (s, 1H), 6.63 (s, 1H), 5.95 (s, 2H), 5.72 (m, 1H), 4.08–3.50 (m, 4H), 2.96–2.63 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 146.9, 146.6, 137.3, 134.7, 130.1, 130.0, 129.7, 127.0, 125.4, 124.9, 108.6, 107.3, 101.2, 66.8, 55.5, 42.2, 29.2 ppm; ESI–MS: *m/z* = 345.1 ($[M + 1]^+$).

[7,8-Dihydro-5-(hydroxymethyl)-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl](3,4-dimethoxyphenyl)methanone
(**2d**, $C_{20}H_{21}NO_6$)
White solid; m.p.: 75–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (m, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.72 (s, 1H), 6.62 (s, 1H), 5.95 (s, 2H), 5.69 (m, 1H), 4.03–3.91 (m, 3H), 3.94 (s, 6H), 3.53 (m, 1H), 2.98–2.67 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 150.7, 149.0, 146.9, 146.5, 127.8, 127.1, 125.7, 120.0, 110.8, 110.4, 108.5, 107.5, 101.0, 67.1, 56.1, 56.0, 55.9, 42.2, 29.3 ppm; ESI–MS: *m/z* = 371.2 ($[M + 1]^+$).

General procedure for the synthesis of compounds ***4b, 4d***

To a mixture of **2a–2d** (1 mmol) and 420 mg IBX (1.5 mmol), 1 cm^3 toluene and 1 cm^3 DMSO were added. After stirring at room temperature for 5 h, the reaction mixture was diluted with 20 cm^3 H_2O and extracted with ethyl acetate (2 × 20 cm^3). The organic phase was washed with a saturated solution of $NaHCO_3$ and brine. The organic solvent was dried over anhydrous sodium sulfate. Concentration gave a residue to which was added 1 cm^3 concentrated HCl and 1 cm^3 AcOH at room temperature. After stirring the reaction mixture for 16 h, ammonia solution and EtOAc were added and the organic phase was washed with H_2O and brine. The organic solvent was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by gel silica column chromatography eluting with $CHCl_3$:MeOH = 120:1 to provide the pure products **4b**, **4d**.

5,6-Dihydro-10-methoxy-8H-benzo[g]-1,3-benzodioxolo[5,6-a]quinolizin-8-one (**4b**, $C_{19}H_{15}NO_4$)
White solid; m.p.: 198–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.24 (s, 1H), 6.83 (s, 1H), 6.72 (s, 1H), 6.01 (s, 2H), 4.36 (t, *J* = 6.0 Hz, 2H), 3.94 (s, 3H), 2.91 (t, *J* = 6.0 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.8, 158.6, 148.5, 147.5, 135.4, 130.9, 129.9, 127.9, 125.8, 124.1, 123.3, 108.1, 107.7, 104.9, 101.9, 101.6, 55.8, 40.0, 28.7 ppm; HR-ESI–MS: *m/z* = 321.1007 (calcd for $C_{19}H_{15}NO_4$ 321.1001).

General procedure for the synthesis of compounds ***4e–4p***

A mixture of the appropriate 2-(2-iodophenethyl)isoquinolin-1(2*H*)-one **5** (0.119 mmol), 2.69 mg $Pd(OAc)_2$ (0.012 mmol), 33 mg K_2CO_3 (0.239 mmol), and 38.36 mg *n*-Bu_4NBr (0.119 mmol) in 3 cm^3 dry DMF was heated to 110 °C for 5 h. The reaction mixture was quenched with a saturated solution of NH_4Cl. The organic phase was washed with H_2O and brine. The organic solvent was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by gel silica column chromatography, eluting with petroleum:EtOAc = 5:1 to provide the pure products **4e–4p**.

5,6-Dihydro-12-nitro-8H-benzo[g]-1,3-benzodioxolo-[5,6-a]quinolizin-8-one (**4h**, $C_{18}H_{12}N_2O_5$)
Orange solid; m.p.: 247–250 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.75$ (d, $J = 7.8$ Hz, 1H), 8.43 (d, $J = 7.8$ Hz, 1H), 7.72 (s, 1H), 7.48 (t, $J = 7.8$ Hz, 1H), 7.33 (s, 1H), 6.73 (s, 1H), 6.05 (s, 2H), 4.33 (t, $J = 6$ Hz, 2H), 2.94 (t, $J = 6$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.0$, 150.0, 148.0, 144.5, 141.4, 134.8, 131.2, 131.0, 130.1, 126.6, 124.8, 123.2, 108.2, 106.0, 102.0, 96.5, 40.0, 28.4 ppm; HR-ESI–MS: $m/z = 336.0750$ (calcd for $C_{18}H_{12}N_2O_5$ 336.0746).

5,6-Dihydro-1,2,3-trimethoxy-8H-dibenzo[a,g]quinolizin-8-one (**4m**, $C_{20}H_{19}NO_4$)
White solid; m.p.: 128–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.43$ (d, $J = 8.1$ Hz, 1H), 7.61 (d, $J = 8.1$ Hz, 1H), 7.60 (s, 1H), 7.57 (t, $J = 8.1$ Hz, 1H), 7.45 (t, $J = 8.1$ Hz, 1H), 6.59 (s, 1H), 4.33 (t, $J = 6$ Hz, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.85 (s, 3H), 2.89 (t, $J = 6$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.4$, 154.1, 153.0, 137.1, 133.9, 133.6, 132.3, 132.1, 127.9, 126.7, 126.6, 124.8, 116.8, 107.0, 106.7, 61.4, 61.1, 56.2, 40.0, 30.1 ppm; HR-ESI–MS: $m/z = 337.1320$ (calcd for $C_{20}H_{19}NO_4$ 337.1314).

5,6-Dihydro-1,2,3-trimethoxy-8H-benzo[a][1,3]benzodioxolo[5,6-g]quinolizin-8-one (**4n**, $C_{21}H_{19}NO_6$)
White solid; m.p.: 169–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$ (s, 1H), 7.52 (s, 1H), 6.90 (s, 1H), 6.57 (s, 1H), 6.57 (s, 2H), 4.30 (t, $J = 6$ Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H), 2.87 (t, $J = 6$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.5$, 153.9, 152.8, 152.0, 147.8, 142.1, 134.3, 133.4, 132.8, 120.4, 116.7, 107.0, 106.6, 105.8, 104.2, 101.7, 61.4, 61.1, 56.2, 39.9, 30.1 ppm; HR-ESI–MS: $m/z = 381.1219$ (calcd for $C_{21}H_{19}NO_6$ 381.1212).

5,6-Dihydro-1,2,3,10,11-pentamethoxy-8H-dibenzo[a,g]quinolizin-8-one (**4o**, $C_{22}H_{23}NO_6$)
White solid; m.p.: 127–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (s, 1H), 7.56 (s, 1H), 6.92 (s, 1H), 6.58 (s, 1H), 4.33 (t, $J = 6$ Hz, 2H), 4.01 (s, 3H), 4.00 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 2.88 (t, $J = 6$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.6$, 153.8, 153.6, 152.7, 149.3, 133.3, 132.7, 132.6, 118.9, 116.9, 107.8, 107.0, 106.5, 106.3, 106.0, 61.3, 61.1, 56.4, 56.3, 56.2, 39.9, 30.1 ppm; HR-ESI–MS: $m/z = 397.1530$ (calcd for $C_{22}H_{23}NO_6$ 397.1525).

5,6-Dihydro-1,2,3-trimethoxy-12-nitro-8H-dibenzo[a,g]quinolizin-8-one (**4p**, $C_{20}H_{18}N_2O_6$)
Orange solid; m.p.: 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.75$ (d, $J = 8.1$ Hz, 1H), 8.41 (s, 1H), 8.38 (d, $J = 8.1$ Hz, 1H), 7.49 (t, $J = 8.1$ Hz, 1H), 6.59 (s, 1H), 4.32 (t, $J = 6$ Hz, 2H), 4.00 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 2.92 (t, $J = 6$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.1$, 155.1, 153.7, 145.1, 142.3, 138.0, 134.4, 133.8, 131.0, 129.7, 126.6, 124.9, 116.0, 106.8, 100.5, 61.3, 61.2, 56.3, 40.1 ppm; HR-ESI–MS: $m/z = 382.1172$ (calcd for $C_{20}H_{18}N_2O_6$ 382.1165).

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