SYNTHESIS OF 6,7-DIHYDRO-9,10-DIMETHOXYDIBENZO[af]QUINO-LIZINUM SALT AND ITS D-RING SUBSTITUTED DERIVATIVES

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Abstract – Synthesis of 6,7-dihydro-9,10-dimethoxydibenzo[af]quinolizinium salt (2a) and its derivatives (2b–g) substituted at the D ring has been achieved from 3-(2-bromoaryl)propanoic acid (3) in four steps for future examination of the inhibitory activity of these compounds against topoisomerase. The dihydro-carbostyrils (5a–g), key intermediates in this synthetic scheme, were prepared from the amides (4a–g) via intramolecular aryl amidation reactions.

The dibenzo[af]quinolizinium skeleton (1) has long been known as one of the seven theoretically possible dibenzoquinolizinium compounds. Although the Bischler–Napieralski cyclization of an N-arylethylated carbostyril or dihydrocarbostyril moiety has been mainly employed to form the B ring of this skeleton, several alternative routes have also been reported. The synthesis of 6,7-dihydro-9,10-dimethoxydibenzo[af]quinolizinium iodide (2a), a prototype of this ring system, was performed by Fujii and co-workers via mercuric acetate–edetic acid oxidation of a tetrahydroquinoline and subsequent cyclization of the resulting dihydrocarbostyril. On preliminary examination of the inhibitory activity against topoisomerase I, the quinolizinium iodide (2a) showed a moderate effect (IC$_{50}$ = 13.9 µM). Therefore, the synthesis of 6,7-dihydro-9,10-dimethoxydibenzo[af]quinolizinium salts (2a–g) bearing different substituents on the D ring was undertaken for future structure–activity relationship (SAR) studies.
We envisioned the dihydrocarbostyril (5) as a key intermediate in the synthesis of various dibenzoquinolizinium salts (2), as the lactam structure such as 5 would be available through the intramolecular aryl amidation reaction \(^5\) of the amide (4), and also because conversion of 5 into the iminium salt (7) is feasible via the Bischler–Napieralski reaction described above. Thus, the amides (4a–g) required for the preparation of 5 were obtained from a variety of 3-(2-bromoaryl)propanoic acids (3a–g) in good yields through condensation with homoveratrylamine.

The intramolecular aryl amidation reaction \(^5\) of the amide (4) was first investigated using the method of Buchwald.\(^5\) Thus, treatment of 4a with Pd\(_2\)(dba)\(_3\), P(o-tolyl)\(_3\), and K\(_2\)CO\(_3\) in toluene at 100 °C provided the dihydrocarbostyril (5a)\(^3\) in 50% yield. In contrast, the intramolecular N-arylation of 4a using copper (Cul, N,N'-dimethylethylenediamine, and K\(_2\)CO\(_3\) in toluene at 110 °C) instead of palladium as a transition metal catalyst, an application of intermolecular version,\(^6\) proved less effective. Best results were obtained when the amide (4a) was heated with Pd\(_2\)(dba)\(_3\), t-Bu\(_3\)PHBF\(_4\), and N,N-dicyclohexylmethylamine in DMF at 100 °C;\(^7\) under these conditions, the desired product (5a) was produced in 77% yield. In a similar fashion, other dihydrocarbostyrils (5b–g) were prepared in moderate yields from the amides (4b–g), respectively.

For the conversion of 5 into the dibenzoquinolizinium salts (2a–g), we initially examined the oxidation of
5 followed by the Bischler–Napieralski cyclization of the resulting carbostyril (6), because a few precedents for the cyclization of carbostyrils had been found in the literature. Oxidation of 5b with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), a versatile reagent for the dehydrogenation of carbonyl compounds to give α,β-unsaturated congeners, proceeded smoothly at 80 °C to provide 6b in 79% yield. However, similar treatment of 5c failed to give the desired carbostyril (6c). The mechanism of dehydrogenation by DDQ involves an initial rate-determining transfer of a hydride ion to the quinone oxygen, followed by a rapid proton transfer to the hydroquinone ion. It is likely that the incipient benzylic carbonium ion derived from 5b is stabilized effectively by the 7-methoxy group, whereas such stabilization is unlikely in the carbonium ion arising from 5c. Indeed, oxidation of 5f and 5g bearing electron-donating substituents at the 7-position proceeded as expected, providing 6f and 6g in 81% and 74% yields, respectively. In addition, conversion of 6b into the dibenzoquinolizinium chloride (2b: X = Cl) in 46% yield was achieved in refluxing POCl₃ by means of the Bischler–Napieralski cyclization.

As the oxidation of 5 was found to depend on the substitution pattern of its dihydrocarbostyril ring, we next investigated the cyclization of 5 and subsequent oxidation of the resulting iminium salt (7). The Fujii group previously reported that the cyclization of 5a with POCl₃ followed by treatment of crude 7a with KI afforded 2a (X = I), instead of 7a (X = I), in 38% yield accompanying the tetracyclic base (8) due to the disproportionation of 7a (X = Cl or I). Therefore, to obtain the desired ring system (2) alone, the iminium salt (7a), derived from 5a via cyclization with POCl₃ in refluxing toluene, was treated with 0.5 M aqueous I₂/KI at 0 °C for 30 min to give the 6,7-dihydrodibenzo[a,f]quinolizinium triiodide (2a: X = I₃) in 87% yield from 5a. On similar treatment of the dihydrocarbostyrils (5c–g), the corresponding dibenzoquinolizinium triiodides (2c–g: X = I₃) were prepared in good yields.

In conclusion, 6,7-dihydro-9,10-dimethoxydibenzo[a,f]quinolizinium salt (2a) and its derivatives (2b–g) bearing a range of different substituents on the D ring were successively prepared from the dihydrocarbostyrils (5a–g) through either a cyclization–dehydrogenation route (2a,c–g) or a dehydrogenation–cyclization route (2b). The inhibitory activities of 2a–g against topoisomerase will be reported elsewhere.

EXPERIMENTAL

General Notes. All melting points were taken on a Yamato MP-21 capillary melting point apparatus. Flash chromatography was carried out by using Merck silica gel 60 (No. 9385). The ratios of solvents in mixtures are shown in v/v. Spectra reported herein were recorded on a JEOL JMS-700 mass spectrometer, a Perkin-Elmer Spectrum 100 FT-IR spectrometer, or a JEOL JNM-ECA500 (¹H 500 MHz, ¹³C 125 MHz) NMR spectrometer. Chemical shifts are reported in δ values relative to internal Me₄Si.
2-Bromo-N-[2-(3,4-dimethoxyphenyl)ethyl]benzenepropanamide (4a). A mixture of 2-bromobenzene-
propanoic acid (3a)\(^9\) (4.22 g, 18.4 mmol), homoveratrylamine (3.6 mL, 21 mmol), 1-ethyl-3-(3-dimethyl-
aminopropyl)carbodiimide hydrochloride (4.2 g, 22 mmol), 1-hydroxybenzotriazole (3.0 g, 22 mmol),
and N-ethyldiisopropylamine (6.3 mL, 37 mmol) in DMF (75 mL) was stirred at rt for 19 h. The reaction
mixture was poured into H\(_2\)O (200 mL) and extracted with AcOEt. The AcOEt extracts were washed
successively with 10% aqueous citric acid, H\(_2\)O, and brine, dried over anhydrous Na\(_2\)SO\(_4\), and
concentrated \textit{in vacuo}. Purification of the residual solid by flash chromatography [AcOEt–hexane (1 : 1.2)] gave 4a (6.59 g, 91%) as a slightly yellow solid, mp 94–95 °C; MS (FAB) \(m/z\): 392, 394 (M\(^{+1}\)); IR
(ATR) \(\nu\), cm\(^{-1}\): 3293 (NH), 1637 (CO); 1H-NMR (CDCl\(_3\)) \(\delta\): 2.44 (2H, t, \(J = 7.7\) Hz, COCH\(_2\)CH\(_2\)), 2.70
(2H, t, \(J = 6.9\) Hz, NCH\(_2\)CH\(_2\)), 3.06 (2H, t, \(J = 7.7\) Hz, COCH\(_3\)), 3.47 (2H, dt, \(J = 6.9, 5.9\) Hz, NCH\(_2\)),
3.860 and 3.863 (3H each, s, two MeO’s), 5.39 (1H, br, NH), 6.64 [1H, dd, \(J = 8.1, 2.0\) Hz, C(6)-H], 6.67
[1H, d, \(J = 2.0\) Hz, C(2)-H], 6.78 [1H, d, \(J = 8.1\) Hz, C(5)-H], 7.07 [1H, ddd, \(J = 8.0, 7.0, 2.0\) Hz,
C(4’)-H], 7.22 [1H, ddd, \(J = 7.8, 7.0, 1.2\) Hz, C(5’)-H], 7.26 [1H, dd, \(J = 7.8, 2.0\) Hz, C(6’)-H], 7.52 [1H,
dd, \(J = 8.0, 1.2\) Hz, C(3’)-H)\(^{10}\), 13C-NMR (CDCl\(_3\)) \(\delta\): 32.2 (t), 35.3 (t), 36.5 (t), 40.8 (t), 55.89 (q), 55.95
(q), 111.3 (d), 111.8 (d), 120.7 (d), 124.3 (s), 127.7 (d), 128.1 (d), 130.8 (d), 131.4 (s), 132.8 (d), 140.1 (s),
147.7 (s), 149.0 (s), 171.8 (s).

2-Bromo-N-[2-(3,4-dimethoxyphenyl)ethyl]-4-methoxybenzenepropanamide (4b). Prepared from
2-bromo-4-methoxybenzenepropanoic acid (3b)\(^{11}\) (1.17 g, 4.5 mmol) according to the procedure
described for the preparation of 4a. Purification by flash chromatography [AcOEt–hexane (2 : 1)] provided 4b (1.81 g, 95%) as a pale yellow solid, mp 99–100 °C; MS (EI) \(m/z\): 421, 423 (M\(^{+}\)); IR
(ATR) \(\nu\), cm\(^{-1}\): 3305 (NH), 1638 (CO); 1H-NMR (CDCl\(_3\)) \(\delta\): 2.40 (2H, t, \(J = 7.7\) Hz, COCH\(_2\)CH\(_2\)), 2.70
(2H, t, \(J = 6.9\) Hz, NCH\(_2\)CH\(_2\)), 2.99 (2H, t, \(J = 7.7\) Hz, COCH\(_3\)), 3.46 (2H, dt, \(J = 6.9, 5.9\) Hz, NCH\(_2\)),
3.77, 3.860, and 3.862 (3H each, s, three MeO’s), 5.39 (1H, br, NH), 6.64 [1H, dd, \(J = 8.1, 1.8\) Hz, C(6)-H], 6.68
[1H, d, \(J = 1.8\) Hz, C(2)-H], 6.78 [1H, dd, \(J = 8.5, 2.6\) Hz, C(5’)-H], 6.79 [1H, d, \(J = 8.1\) Hz, C(5)-H], 7.08 [1H,
d, \(J = 2.6\) Hz, C(3’)-H], 7.15 [1H, d, \(J = 8.5\) Hz, C(6’)-H)\(^{10}\), 13C-NMR (CDCl\(_3\)) \(\delta\): 32.2 (t), 35.3 (t), 36.5 (t), 40.8 (t), 55.89 (q), 55.95
(q), 111.3 (d), 111.8 (d), 120.7 (d), 124.3 (s), 127.7 (d), 128.1 (d), 130.8 (d), 131.4 (s), 132.8 (d), 140.1 (s),
147.7 (s), 149.0 (s), 171.8 (s).

2-Bromo-N-[2-(3,4-dimethoxyphenyl)ethyl]-5-methoxybenzenepropanamide (4c). Synthesized from
2-bromo-5-methoxybenzenepropanoic acid (3c)\(^{12}\) (3.32 g, 12.8 mmol) according to the procedure
described for the preparation of 4a. Purification by flash chromatography [AcOEt–hexane (2 : 1)] provided 4c (5.09 g, 94%) as a pale yellow solid, mp 99–100 °C; MS (EI) \(m/z\): 421, 423 (M\(^{+}\)); IR (ATR) \(\nu\), cm\(^{-1}\): 3296
(NH), 1635 (CO); 1H-NMR (CDCl\(_3\)) \(\delta\): 2.43 (2H, t, \(J = 7.8\) Hz, COCH\(_2\)CH\(_3\)), 2.71 (2H, t, \(J = 6.9\) Hz,
NCH\(_2\)CH\(_3\)), 3.02 (2H, t, \(J = 7.8\) Hz, COCH\(_3\)), 3.47 (2H, dt, \(J = 6.9, 5.9\) Hz, NCH\(_2\)), 3.76 (3H, s) and 3.86
(6H, s, three MeO’s), 5.39 (1H, br, NH), 6.64 [1H, dd, \(J = 8.7, 3.1\) Hz, C(4’)-H], 6.65 [1H, dd, \(J = 8.1, 1.9\)
2-Bromo-N-[2-(3,4-dimethoxyphenyl)ethyl]-4-fluorobenzeneopropanamide (4d). Prepared from 2-bromo-4-fluorobenzeneopropanoic acid (3d)\(^{13}\) (4.00 g, 16.2 mmol) according to the method described for the preparation of 4a. Purification by flash chromatography [AcOEt–hexane (1 : 2)] furnished 4d (5.08 g, 76%) as a pale yellow solid, mp 110–111.5 °C; MS (EI) \(m/z\): 409, 411 (M⁺); IR (ATR) \(\nu\), cm⁻¹: 3307 (NH), 1639 (CO); \(^1\)H-NMR (CDCl₃) \(\delta\): 2.41 (2H, t, \(J = 7.6\) Hz, COCH₂CH₂), 2.71 (2H, t, \(J = 6.9\) Hz, NCH₂CH₂), 3.03 (2H, t, \(J = 7.6\) Hz, COCH₂), 3.47 (2H, dt, \(J = 6.9, 6.0\) Hz, NCH₂), 3.86 and 3.87 (3H each, s, two MeO’s), 5.40 (1H, br, NH), 6.64 [1H, dd, \(J = 8.1, 1.9\) Hz, C(6)-H], 6.67 [1H, d, \(J = 1.9\) Hz, C(2)-H], 6.79 [1H, d, \(J = 8.1\) Hz, C(5)-H], 6.95 [1H, ddd, \(J = 8.5, 8.2, 2.6\) Hz, C(5')-H], 7.23 [1H, dd, \(J = 8.5, 6.1\) Hz, C(6')-H], 7.27 [1H, dd, \(J = 8.2, 2.6\) Hz, C(3')-H];\(^{10}\)\(^{13}\)C-NMR (CDCl₃) \(\delta\): 31.3 (t), 35.2 (t), 36.5 (t), 40.7 (t), 55.86 (q), 55.90 (q), 111.2 (d), 111.7 (d), 114.7 (d), 119.9 (d), 120.6 (d), 123.9 (s), 131.2 (d), 131.5 (s), 135.9 (s), 147.7 (s), 149.0 (s), 161.0 (s), 171.5 (s).

2-Bromo-N-[2-(3,4-dimethoxyphenyl)ethyl]-5-chlorobenzeneopropanamide (4e). Synthesized from 2-bromo-5-chlorobenzeneopropanoic acid (3e)\(^{14}\) (5.50 g, 20.9 mmol) according to the procedure described for the preparation of 4a. Purification by flash chromatography [AcOEt–hexane (1 : 1)] gave 4e (8.70 g, 98%) as a colorless solid, mp 107–108 °C; MS (EI) \(m/z\): 425 (M⁺); IR (ATR) \(\nu\), cm⁻¹: 3301 (NH), 1632 (CO); \(^1\)H-NMR (CDCl₃) \(\delta\): 2.42 (2H, t, \(J = 7.7\) Hz, COCH₂CH₂), 2.72 (2H, t, \(J = 7.0\) Hz, NCH₂CH₂), 3.03 (2H, t, \(J = 7.7\) Hz, COCH₂), 3.48 (2H, dt, \(J = 7.0, 5.9\) Hz, NCH₂), 3.86 (6H, s, two MeO’s), 5.40 (1H, br, NH), 6.65 [1H, dd, \(J = 8.0, 2.0\) Hz, C(6)-H], 6.68 [1H, d, \(J = 2.0\) Hz, C(2)-H], 6.79 [1H, d, \(J = 8.0\) Hz, C(5)-H], 7.06 [1H, dd, \(J = 8.5, 2.6\) Hz, C(4')-H], 7.25 [1H, d, \(J = 2.6\) Hz, C(6')-H], 7.44 [1H, d, \(J = 8.5\) Hz, C(3')-H];\(^{10}\)\(^{13}\)C-NMR (CDCl₃) \(\delta\): 32.0 (t), 35.2 (t), 36.1 (t), 40.7 (t), 55.87 (q), 55.92 (q), 111.3 (d), 111.7 (d), 120.6 (d), 122.1 (s), 128.1 (d), 130.6 (d), 131.2 (s), 133.4 (s), 133.8 (d), 141.8 (s), 147.7 (s), 149.1 (s), 171.2 (s).

2-Bromo-N-[2-(3,4-dimethoxyphenyl)ethyl]-4,5-dimethoxybenzeneopropanamide (4f). Obtained from 2-bromo-4,5-dimethoxybenzeneopropanoic acid (3f)\(^{15}\) (6.45 g, 22.3 mmol) according to the method described for the preparation of 4a. Purification by flash chromatography [AcOEt–hexane (2 : 1)] afforded 4b (9.79 g, 97%) as a colorless solid, mp 124–125 °C (lit.\(^{15a,b}\) mp 123–125 °C); MS (FAB) \(m/z\): 452, 454 (M⁺+1); IR (ATR) \(\nu\), cm⁻¹: 3307 (NH), 1641 (CO); \(^1\)H-NMR (CDCl₃) \(\delta\): 2.41 (2H, t, \(J = 7.7\) Hz, COCH₂CH₂), 2.71 (2H, t, \(J = 6.9\) Hz, NCH₂CH₂), 2.99 (2H, t, \(J = 7.7\) Hz, COCH₂), 3.47 (2H, dt, \(J = 6.9, 5.9\) Hz, NCH₂), 3.84 (3H, s), 3.85 (3H, s), and 3.86 (6H, s, four MeO’s), 5.39 (1H, br, NH), 6.65 [1H, dd,
J = 8.0, 1.8 Hz, C(6)-H], 6.67 [1H, d, J = 1.8 Hz, C(2)-H], 6.787 [1H, s, C(6)ʹ-H], 6.788 [1H, d, J = 8.0 Hz, C(5)-H], 6.98 [1H, s, C(3)ʹ-H]; 10 13C-NMR (CDCl₃) δ: 31.9 (t), 35.3 (t), 36.9 (t), 40.8 (t), 55.8 (q), 55.9 (q), 56.0 (q), 56.1 (q), 111.3 (d), 111.8 (d), 113.3 (d), 113.8 (s), 115.5 (d), 120.6 (d), 131.4 (s), 132.1 (s), 147.6 (s), 148.1 (s), 148.4 (s), 149.0 (s), 171.9 (s).

6-Bromo-N-[2-(3,4-dimethoxyphenyl)ethyl]-1,3-benzodioxole-5-propanamide (4g). Synthesized from 6-bromo-1,3-benzodioxole-5-propanoic acid (3g) (7.72 g, 28.3 mmol) according to the method described for the preparation of 4a. Purification by flash chromatography [AcOEt–hexane (2 : 1)] furnished 4g (11.2 g, 91%) as a colorless solid, mp 140–141 °C; MS (EI) m/z: 435, 437 (M⁺); IR (ATR) ν, cm⁻¹: 3268 (NH), 1634 (CO); 1H-NMR (CDCl₃) δ: 2.38 (2H, t, J = 7.7 Hz, COCH2CH2), 2.72 (2H, t, J = 6.9 Hz, NCH2CH2), 3.48 (2H, dt, J = 6.9 Hz, NCH2), 3.87 (6H, s, two MeO’s), 5.39 (1H, br, NH), 6.66 [1H, dd, J = 8.1, 1.9 Hz, C(6)-H], 6.97 [1H, d, J = 1.9 Hz, C(2)-H], 6.79 [1H, d, J = 8.1 Hz, C(5)-H]; 13C-NMR (CDCl₃) δ: 32.1 (t), 35.3 (t), 36.7 (t), 40.8 (t), 55.94 (q), 55.95 (q), 101.7 (t), 110.3 (d), 111.3 (d), 111.8 (d), 112.7 (d), 114.2 (s), 120.7 (d), 131.4 (s), 133.1 (s), 147.0 (s), 147.4 (s), 147.7 (s), 149.1 (s), 171.7 (s).

1-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydro-2(1H)-quinolinone (5a). A stirred solution of 4a (6.01 g, 15.3 mmol), tris(dibenzylideneacetone)dipalladium (1.33 g, 1.5 mmol), tri-t-butylphosphonium tetrafluoroborate (1.05 g, 3.6 mmol), N,N-dicyclohexylmethylamine (4.2 mL, 20 mmol) in DMF (46 mL) was heated in an atmosphere of Ar at 100 °C for 137 h. The reaction mixture was poured into H2O (100 mL) and extracted with AcOEt. The AcOEt extracts were washed successively with 1 M aqueous HCl, H2O and brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to leave a brown oil. Purification by flash chromatography [AcOEt–hexane (2 : 3)] gave 5a (3.66 g, 77%) as a slightly yellow solid, mp 62–63 °C (lit. mp 64.5–65.5 °C). 1H-NMR and IR spectral data for this sample were in agreement with those reported in the literature.³

1-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydro-7-methoxy-2(1H)-quinolinone (5b). A mixture of 4b (3.61 g, 8.5 mmol), tris(dibenzylideneacetone)dipalladium (381 mg, 0.42 mmol), tri-t-butylphosphonium tetrafluoroborate (743 mg, 2.6 mmol), N,N-dicyclohexylmethylamine (2.2 mL, 10 mmol), and DMF (50 mL) was stirred in an atmosphere of Ar at 110 °C for 92 h. The reaction mixture was treated with 1 M aqueous HCl (100 mL) and extracted with AcOEt. The AcOEt extracts were washed successively with H₂O and brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to leave a brown oil. Purification by flash chromatography [AcOEt–hexane (2 : 3)] provided 5b (2.29 g, 78%) as a pale yellow solid, mp 90–91 °C; MS (EI) m/z: 341 (M⁺); IR (ATR) ν: 1662 cm⁻¹ (CO); 1H-NMR (CDCl₃) δ: 2.60 and 2.76 [2H each, t, J = 7.3 Hz, C(3)-H’s, C(4)-H’s], 2.89 (2H, t, J = 7.9 Hz, NCH2CH2), 3.81 (3H, s) and 3.86 (6H, s, three MeO’s), 4.12 (2H, t, J = 7.9 Hz, NCH2), 6.55 [1H, dd, J = 8.2, 2.4 Hz, C(6)-H], 6.61 [1H, d, J = 2.4

10
Hz, C(8)-H], 6.75–6.82 [3H, m, (MeO)2C6H3], 7.07 [1H, d, J = 8.2 Hz, C(5)-H]; 13C-NMR (CDCl3) δ: 24.7 (t), 32.3 (t), 33.0 (t), 43.8 (t), 55.4 (q), 55.87 (q), 55.92 (q), 102.7 (d), 106.5 (d), 111.3 (d), 112.1 (d), 119.0 (s), 120.7 (d), 128.5 (d), 131.2 (s), 140.5 (s), 147.7 (s), 148.9 (s), 159.2 (s), 170.3 (s).

1-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydro-6-methoxy-2(1H)-quinolinone (5c). Prepared from 4c (7.53 g, 17.8 mmol) according to the procedure described for the preparation of 5b. Purification by flash chromatography [AcOEt–hexane (1 : 1)] afforded 5c (3.09 g, 51%) as a pale yellow solid, mp 72–73 °C; MS (EI) m/z: 341 (M+); IR (ATR) ν: 1660 cm–1 (CO); 1H-NMR (CDCl3) δ: 2.60 and 2.78 [2H each, t, J = 7.3 Hz, C(3)-H’s, C(4)-H’s], 2.88 (2H, t, J = 7.8 Hz, NCH2CH2), 3.80 (3H, s) and 3.86 (6H, s, three MeO’s), 4.13 (2H, t, J = 7.8 Hz, NCH2), 6.73–6.81 [5H, m, (MeO)2C6H3, C(5)-H, C(7)-H], 6.95 [1H, d, J = 8.8 Hz, C(8)-H]; 13C-NMR (CDCl3) δ: 25.8 (t), 31.9 (t), 33.0 (t), 43.6 (t), 55.6 (q), 55.89 (q), 55.92 (q), 111.2 (d), 112.0 (d), 112.1 (d), 114.0 (d), 115.2 (d), 120.7 (d), 128.4 (s), 131.2 (s), 133.0 (s), 147.6 (s), 148.9 (s), 155.2 (s), 169.8 (s).

1-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydro-7-fluoro-2(1H)-quinolinone (5d). Synthesized from 4d (4.70 g, 11.5 mmol) according to the method described for the preparation of 5b. Purification by flash chromatography [AcOEt–hexane (1 : 1)] afforded 5d (1.86 g, 49%) as a pale yellow solid, mp 107–108 °C, MS (EI) m/z: 329 (M+); IR (ATR) ν: 1680 cm –1 (CO); 1H-NMR (CDCl3) δ: 2.61 and 2.79 [2H each, t, J = 7.3 Hz, C(3)-H’s, C(4)-H’s], 2.88 (2H, t, J = 7.9 Hz, NCH2CH2), 3.863 and 3.865 (3H each, s, two MeO’s), 4.11 (2H, t, J = 7.9 Hz, NCH2), 6.71 [1H, ddd, J = 8.2, 8.2, 2.4 Hz, C(6)-H], 6.74–6.82 [4H, m, (MeO)2C6H3, C(8)-H], 7.10 [1H, dd, J = 8.2, 6.4 Hz, C(5)-H]; 13C-NMR (CDCl3) δ: 24.9 (t), 31.9 (t), 32.9 (t), 43.7 (t), 55.87 (q), 55.91 (q), 102.9 (d), 109.0 (d), 111.2 (d), 112.0 (d), 120.7 (d), 122.2 (s), 128.9 (d), 130.8 (s), 147.7 (s), 148.9 (s), 162.2 (s), 170.0 (s).

1-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydro-6-chloro-2(1H)-quinolinone (5e). Obtained from 4e (8.50 g, 19.9 mmol) according to the procedure described for the preparation of 5b. Purification by flash chromatography [AcOEt–hexane (1 : 1)] gave 5e (3.98 g, 58%) as a pale yellow solid, mp 96–97 °C, MS (EI) m/z: 345, 347 (M+); IR (ATR) ν: 1669 cm–1 (CO); 1H-NMR (CDCl3) δ: 2.60 and 2.79 [2H each, t, J = 7.3 Hz, C(3)-H’s, C(4)-H’s], 2.87 (2H, t, J = 7.8 Hz, NCH2CH2), 3.855 and 3.859 (3H each, s, two MeO’s), 4.13 (2H, t, J = 7.9 Hz, NCH2), 6.71 [1H, ddd, J = 8.2, 8.2, 2.4 Hz, C(6)-H], 6.74–6.80 [3H, m, (MeO)2C6H3, C(8)-H], 7.14 [1H, d, J = 2.4 Hz, C(5)-H], 7.22 [1H, dd, J = 8.7, 2.4 Hz, C(7)-H]; 13C-NMR (CDCl3) δ: 25.3 (t), 31.6 (t), 32.9 (t), 43.5 (t), 55.88 (q), 55.90 (q), 111.2 (d), 112.0 (d), 116.1 (d), 120.7 (d), 127.3 (d), 127.9 (s), 128.0 (d), 128.6 (s), 130.8 (s), 138.1 (s), 147.7 (s), 148.9 (s), 169.7 (s).

1-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydro-6,7-dimethoxy-2(1H)-quinolinone (5f). Prepared from 4f (4.52 g, 10.0 mmol) according to the procedure described for the preparation of 5b. Purification by flash chromatography [AcOEt–hexane (1 : 1)] afforded 5f (1.37 g, 37%) as a pale yellow solid, mp 132–133 °C, MS (EI) m/z: 371 (M+); IR (ATR) ν: 1642 cm–1 (CO); 1H-NMR (CDCl3) δ: 2.60 and 2.75
[2H each, t, \(J = 7.3\) Hz, C(3)-H’s, C(4)-H’s], 2.91 (2H, t, \(J = 7.6\) Hz, NCH\(_2\)CH\(_3\)), 3.84 (6H, s), 3.85 (3H, s), and 3.87 (3H, s, four MeO’s), 4.13 (2H, t, \(J = 7.6\) Hz, NCH\(_2\)), 2.91 (2H, t, \(J = 7.6\) Hz, NCH\(_2\)CH\(_2\)), 3.84 (6H, s), 3.85 (3H, s), and 3.87 (3H, s, four MeO’s), 4.13 (2H, t, \(J = 7.6\) Hz, NCH\(_2\)), 6.53 and 6.69 [1H each, s, C(5)-H, C(8)-H], 6.73–6.80 [3H, m, (MeO\(_2\))C\(_6\)H\(_3\)]; \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\): 25.2 (t), 32.3 (t), 33.3 (t), 44.0 (t), 55.8 (q), 55.9 (q), 56.29 (q), 56.31 (q), 100.9 (d), 111.3 (d), 111.7 (s), 112.1 (d), 118.7 (s), 120.7 (d), 131.3 (s), 132.9 (s), 144.5 (s), 147.7 (s), 148.0 (s), 169.9 (s).

7.8-Dihydro-5-[2-(3,4-dimethoxyphenyl)ethyl]-1,3-dioxolo[4,5-g]quinolin-6(5H)-one (5g). Prepared from 4g (3.55 g, 8.1 mmol) according to the procedure described for the preparation of 5b. Purification by flash chromatography [AcOEt–hexane (3 : 1)] provided 5g (1.62 g, 56%) as a pale yellow solid, mp 108–109 °C; MS (EI) m/z: 355 (M+) and 295 (M+–1): IR (ATR) \(\nu\): 1663 cm\(^{-1}\) (CO); 1H-NMR (CDCl\(_3\)) \(\delta\): 2.56 and 2.69 [2H each, t, \(J = 7.2\) Hz, C(3)-H’s, C(4)-H’s], 2.87 (2H, t, \(J = 7.9\) Hz, NCH\(_2\)CH\(_2\)), 3.86 and 3.87 (3H each, s, two MeO’s), 4.09 (2H, t, \(J = 7.9\) Hz, NCH\(_2\)), 5.96 (2H, s, OCH\(_2\)O), 6.63 and 6.65 [1H each, s, C(5)-H, C(8)-H], 6.74–6.81 [3H, m, (MeO\(_2\))C\(_6\)H\(_3\)]; \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\): 25.5 (t), 32.2 (t), 33.1 (t), 43.9 (t), 55.89 (q), 55.92 (q), 97.8 (d), 101.3 (t), 108.2 (d), 111.3 (d), 112.1 (d), 119.8 (s), 120.8 (d), 131.0 (s), 133.7 (s), 142.8 (s), 146.9 (s), 147.7 (s), 148.9 (s), 170.0 (s).

1-[2-(3,4-Dimethoxyphenyl)ethyl]-7-methoxy-2(1H)-quinolinone (6b). A solution of 5b (171 mg, 0.5 mmol) and DDQ (136 mg, 0.6 mmol) in dioxane (5 mL) was heated with stirring at 80 °C for 2 h. After the mixture had been concentrated in vacuo, the residue was partitioned between CHCl\(_3\) and 5% aqueous K\(_2\)CO\(_3\). The CHCl\(_3\) extracts were washed successively with H\(_2\)O and brine, dried over anhydrous MgSO\(_4\), and concentrated in vacuo. The residual oil was purified by flash chromatography [AcOEt–hexane (2 : 1)] to give 6b (134 mg, 79%) as a pale yellow solid, mp 125–126 °C; MS (FAB) m/z: 340 (M++1): IR (ATR) \(\nu\): 1646 cm\(^{-1}\) (CO); 1H-NMR (CDCl\(_3\)) \(\delta\): 2.98 (2H, t, \(J = 8.1\) Hz, ArCH\(_2\)), 3.86, 3.87, and 3.89 (3H each, s, three MeO’s), 4.44 (2H, t, \(J = 8.1\) Hz, NCH\(_2\)CH\(_3\)), 6.57 [1H, d, \(J = 9.4\) Hz, C(3)-H], 6.81–6.88 [5H, m, (MeO\(_2\))C\(_6\)H\(_3\), C(6)-H, C(8)-H], 7.48 [1H, d, \(J = 8.4\) Hz, C(5)-H], 7.62 [1H, d, \(J = 9.4\) Hz, C(4)-H]; \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\): 33.1 (t), 44.2 (t), 55.5 (q), 55.9 (q), 56.0 (q), 98.8 (d), 109.4 (d), 111.4 (d), 112.1 (d), 115.2 (s), 118.6 (d), 120.6 (d), 130.3 (d), 131.1 (s), 139.0 (d), 140.9 (s), 147.8 (s), 149.1 (s), 161.8 (s), 162.4 (s).

1-[2-(3,4-Dimethoxyphenyl)ethyl]-6,7-dimethoxy-2(1H)-quinolinone (6f). A mixture of 5f (371 mg, 1.0 mmol), DDQ (318 mg, 1.4 mmol), and dioxane (10 mL) was stirred at 80 °C for 30 min. The reaction mixture was then worked up as described above for the preparation of 6b. Purification by flash chromatography [AcOEt–hexane (10 : 1)] afforded 6f (299 mg, 81%) as a pale brown solid, mp 147–148 °C; MS (FAB) m/z: 370 (M+1): IR (ATR) \(\nu\): 1645 cm\(^{-1}\) (CO); 1H-NMR (CDCl\(_3\)) \(\delta\): 3.02 (2H, t, \(J = 7.8\) Hz, ArCH\(_2\)), 3.82, 3.86, 3.928, and 3.934 (3H each, s, four MeO’s), 4.48 (2H, t, \(J = 7.8\) Hz, NCH\(_2\)), 6.62 [1H, d, \(J = 9.4\) Hz, C(3)-H], 6.72 and 6.95 [1H each, s, C(5)-H, C(8)-H], 6.78–6.84 [3H, m, (MeO\(_2\))C\(_6\)H\(_3\)], 7.59 [1H, d, \(J = 9.4\) Hz, C(4)-H]; \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\): 33.4 (t), 44.5 (t), 55.8 (q), 55.9 (q),
5-[2-(3,4-Dimethoxyphenyl)ethyl]-1,3-dioxolo[4,5-g]quinolin-6(5H)-one (6g). Prepared from 5g (1.13 g, 3.2 mmol) according to the method described for the preparation of 6f. Purification by flash chromatography [AcOEt–hexane (5 : 1)] gave 6g (834 mg, 74%) as a slightly yellow solid, mp 137–139 °C; MS (FAB) m/z: 354 (M++1); IR (ATR) ν: 1650 cm–1 (CO); 1H-NMR (CDCl 3) δ: 2.96 (2H, t, J = 8.2 Hz, ArCH2), 3.877 and 3.879 (3H each, s, two MeO’s), 4.42 (2H, t, J = 8.2 Hz, NCH2), 6.07 (2H, s, OCH2O), 6.60 [1H, d, J = 9.5 Hz, C(3)-H], 6.83–6.89 [3H, m, (MeO)2C6H3], 6.88 and 6.94 [1H each, s, C(5)-H, C(8)-H], 7.55 [1H, d, J = 9.5 Hz, C(4)-H]; 13C-NMR (CDCl 3) δ: 33.2 (t), 44.7 (t), 55.92 (q), 55.94 (q), 95.0 (d), 101.9 (t), 106.5 (d), 111.4 (d), 112.1 (d), 115.4 (s), 119.0 (d), 120.7 (d), 130.9 (s), 136.3 (s), 138.7 (d), 143.3 (s), 147.9 (s), 149.1 (s), 151.0 (s), 161.9 (s).

6,7-Dihydro-9,10-dimethoxydibenzo[a,f]quinolizinium Triiodide (2a: X = I3). A mixture of 5a (311 mg, 1.0 mmol) and POCl 3 (1 mL, 11 mmol) in toluene (5 mL) was heated under reflux with stirring for 6 h. The solvent and excess POCl 3 were distilled off in vacuo to leave an orange solid, which was then triturated with Et2O. The insoluble material was collected by filtration and dissolved in hot H 2O (15 mL). The solution was then cooled and treated with 0.5 M aqueous I2/KI (4 mL) at 0 °C for 30 min. The precipitate that resulted was collected by filtration and dried to afford 2a (549 mg, 87%) as a dark brown solid. Recrystallization from MeOH gave an orange solid, mp 190–191 °C; 1H-NMR (DMSO-d6) δ: 3.33 [2H, t, J = 7.1 Hz, C(7)-H’s], 3.94 and 3.95 (3H each, s, two MeO’s), 5.09 [2H, t, J = 7.1 Hz, C(6)-H’s], 7.26 [1H, s, C(8)-H], 7.82 [1H, s, C(11)-H], 7.94 [1H, dd, J = 8.1, 7.1 Hz, C(2)-H], 8.20 [1H, ddd, J = 9.0, 7.1, 1.5 Hz, C(3)-H], 8.38 [1H, dd, J = 8.1, 1.5 Hz, C(1)-H], 8.64 [1H, d, J = 9.0 Hz, C(4)-H], 8.76 [1H, d, J = 9.0 Hz, C(12)-H], 9.12 [1H, d, J = 9.0 Hz, C(13)-H]; 13C-NMR (DMSO-d6) δ: 24.0 (t), 45.5 (t), 55.0 (q), 55.1 (q), 109.7 (d), 110.2 (d), 117.1 (d), 117.6 (s), 119.0 (d), 126.3 (s), 127.4 (d), 128.9 (d), 130.7 (s), 133.5 (d), 137.3 (s), 143.6 (d), 147.3 (s), 150.2 (s), 153.0 (s). Anal. Calcd for C19H18I3NO2: C, 33.91; H, 2.70; N, 2.08. Found: C, 33.70; H, 2.73; N, 2.04.

6,7-Dihydro-3,9,10-trimethoxydibenzo[a,f]quinolizinium Chloride (2b: X = Cl). A stirred mixture of 6b (170 mg, 0.5 mmol) and POCl 3 (1 mL, 11 mmol) was heated under reflux for 28 h. After cooling, the reaction mixture was treated with cold H 2O, and the insoluble material was collected by filtration and dried to give 2b (82.1 mg, 46%) as a yellow solid, mp 294–295 °C; 1H-NMR (DMSO-d6) δ: 3.31 [2H, t, J = 7.0 Hz, C(7)-H’s], 3.937, 3.943, and 4.11 (3H each, s, three MeO’s), 5.03 [2H, t, J = 7.0 Hz, C(6)-H’s], 7.25 [1H, s, C(8)-H], 7.60 [1H, dd, J = 9.0, 1.9 Hz, C(2)-H], 7.79 [1H, s, C(11)-H], 7.86 [1H, d, J = 1.9 Hz, C(4)-H], 8.31 [1H, d, J = 9.0 Hz, C(1)-H], 8.58 [1H, d, J = 8.8 Hz, C(12)-H], 9.02 [1H, d, J = 8.8 Hz, C(13)-H]; 13C-NMR (DMSO-d6) δ: 25.3 (t), 46.6 (t), 56.1 (q), 56.2 (q), 56.7 (q), 99.1 (d), 110.9 (d), 111.2
6,7-Dihydro-2,9,10-trimethoxydibenzo[af]quinolizinium Triiodide (2c: X = I₃). Cyclization of 5c (341 mg, 1.1 mmol) was carried out as described above for the preparation of 2a, giving the iminium salt (360 mg) as an orange solid. To a solution of the solid in DMSO (1 mL) was added 0.5 M aqueous I₂/KI (2 mL), and the mixture was stirred at 0 °C for 30 min. After addition of H₂O (10 mL), the precipitate that resulted was collected by filtration and dried to afford 2c (620 mg, 88%) as a dark brown solid, mp 274–275 °C; ¹H-NMR (DMSO-d₆) δ: 3.31 [2H, t, J = 7.0 Hz, C(7)-H’s], 3.936, 3.943, and 4.01 (3H each, s, three MeO’s), 5.06 [2H, t, J = 7.0 Hz, C(6)-H’s], 7.22 [1H, s, C(8)-H], 7.79 [1H, s, C(11)-H], 7.81 [1H, dd, J = 9.5, 2.9 Hz, C(3)-H], 7.84 [1H, d, J = 2.9 Hz, C(1)-H], 8.56 [1H, d, J = 9.5 Hz, C(4)-H], 8.70 [1H, d, J = 9.1 Hz, C(12)-H], 8.98 [1H, d, J = 9.1 Hz, C(13)-H]; ¹³C-NMR (DMSO-d₆) δ: 24.0 (t), 45.8 (t), 54.88 (q), 54.92 (q), 55.0 (q), 107.4 (d), 109.8 (d), 110.1 (d), 117.7 (s), 118.9 (d), 119.2 (d), 124.7 (d), 128.3 (s), 130.0 (s), 132.7 (s), 142.2 (d), 147.4 (s), 147.8 (s), 152.7 (s), 157.2 (s).

3-Fluoro-6,7-dihydro-9,10-dimethoxydibenzo[af]quinolizinium Triiodide (2d: X = I₃). Cyclization of 5d (160 mg, 0.49 mmol) and subsequent oxidation were performed as described for the synthesis of 2c to afford 2d (270 mg, 80%) as a dark brown solid, mp 200–201 °C; ¹H-NMR (DMSO-d₆) δ: 3.33 [2H, t, J = 7.1 Hz, C(7)-H’s], 3.95 (6H, s, two MeO’s), 5.01 [2H, t, J = 7.1 Hz, C(6)-H’s], 7.24 [1H, s, C(8)-H], 7.82 [1H, s, C(11)-H], 7.90 [1H, ddd, J = 9.0, 8.2, 2.0 Hz, C(2)-H], 8.49 [1H, dd, J = 9.0 Hz, C(4)-H], 8.73 [1H, d, J = 9.0 Hz, C(12)-H], 9.12 [1H, d, J = 9.0 Hz, C(13)-H]; ¹³C-NMR (DMSO-d₆) δ: 23.9 (t), 46.0 (t), 55.0 (q), 55.1 (q), 103.6 (d), 109.8 (d), 110.5 (d), 117.2 (d), 117.5 (s), 118.4 (d), 123.7 (s), 131.0 (s), 132.1 (d), 139.0 (s), 143.5 (d), 147.5 (s), 151.0 (s), 153.4 (s), 164.0 (s). Anal. Calcd for C₁₉H₁₇F₃I₃NO₂: C, 33.02; H, 2.48; N, 2.03. Found: C, 33.20; H, 2.40; N, 2.08.

2-Chloro-6,7-dihydro-9,10-dimethoxydibenzo[af]quinolizinium Triiodide (2e: X = I₃). Prepared from 5e (170 mg, 0.49 mmol) and subsequent oxidation were performed as described for the preparation of 2c to give 2e (225 mg, 77%) as a dark brown solid, mp 287–288 °C; ¹H-NMR (DMSO-d₆) δ: 3.34 [2H, t, J = 7.1 Hz, C(7)-H’s], 3.951 and 3.954 (3H each, s, two MeO’s), 5.08 [2H, t, J = 7.1 Hz, C(6)-H’s], 7.26 [1H, s, C(8)-H], 7.82 [1H, s, C(11)-H], 8.21 [1H, dd, J = 9.5, 2.5 Hz, C(3)-H], 8.53 [1H, d, J = 2.5 Hz, C(1)-H], 8.66 [1H, d, J = 9.5 Hz, C(4)-H], 8.81 [1H, d, J = 9.1 Hz, C(12)-H], 9.04 [1H, d, J = 9.1 Hz, C(13)-H]; ¹³C-NMR (DMSO-d₆) δ: 23.9 (t), 46.0 (t), 55.0 (q), 55.1 (q), 109.9 (d), 110.5 (d), 117.4 (s), 119.6 (d), 120.3 (d), 127.3 (s), 127.4 (d), 131.0 (s), 131.7 (s), 133.2 (d), 136.1 (s), 142.6 (d), 147.5 (s), 150.6 (s), 153.5 (s). Anal. Calcd for C₁₉H₁₇ClI₃NO₂: C, 32.26; H, 2.42; N, 1.98. Found: C, 32.25; H, 2.61; N, 1.92.

6,7-Dihydro-2,3,9,10-tetramethoxydibenzo[af]quinolizinium Triiodide (2f: X = I₃). Synthesized from 5f (130 mg, 0.35 mmol) according to the method described for the preparation of 2e to furnish 2f (248 mg,
97%) as a brown solid, mp 214–216 °C; 1H-NMR (DMSO-\(d_6\)) \(\delta\): 3.30 [2H, t, \(J = 6.9\) Hz, C(7)-H’s], 3.927, 3.933, 4.01, and 4.14 (3H each, s, four MeO’s), 5.04 [2H, t, \(J = 6.9\) Hz, C(6)-H’s], 7.22 [1H, s, C(8)-H], 7.74, 7.80, and 7.82 [1H each, s, C(1)-H, C(4)-H, C(11)-H], 8.53 [1H, d, \(J = 8.8\) Hz, C(12)-H], 8.87 [1H, d, \(J = 8.8\) Hz, C(13)-H]; 13C-NMR (DMSO-\(d_6\)) \(\delta\): 24.2 (t), 45.8 (t), 54.8 (q), 55.0 (q), 55.1 (q), 55.9 (q), 97.7 (d), 106.7 (d), 109.6 (d), 109.7 (d), 116.4 (d), 118.0 (s), 122.9 (s), 129.3 (s), 134.8 (s), 141.1 (d), 146.7 (s), 147.4 (s), 148.9 (s), 152.2 (s), 154.8 (s). Anal. Calcd for C\(_{21}\)H\(_{22}\)I\(_3\)NO\(_4\): C, 34.41; H, 3.02; N, 1.91. Found: C, 34.71; H, 3.08; N, 2.03.

13,14-Dihydro-2,3-dimethoxybenzo[a][1,3]benzodioxolo[5,6-f]quinolizinum Triiodide (2g: X = I\(_3\)). Prepared from 5g (180 mg, 0.51 mmol) according to the procedure described for the preparation of 2c to provide 2g (350 mg, 96%) as a brown solid, mp 226–227 °C; 1H-NMR (DMSO-\(d_6\)) \(\delta\): 3.27 [2H, t, \(J = 6.9\) Hz, C(7)-H’s], 3.92 and 3.93 (3H each, s, two MeO’s), 4.94 [2H, t, \(J = 6.9\) Hz, C(6)-H’s], 6.44 (2H, s, OCH\(_2\)O), 7.19 [1H, s, C(8)-H], 7.72, 7.74, and 8.16 [1H each, s, C(1)-H, C(4)-H, C(11)-H], 8.52 [1H, d, \(J = 8.9\) Hz, C(12)-H], 8.83 [1H, d, \(J = 8.9\) Hz, C(13)-H]; 13C-NMR (DMSO-\(d_6\)) \(\delta\): 24.1 (t), 46.4 (t), 54.8 (q), 55.0 (q), 95.6 (d), 102.9 (t), 103.5 (d), 109.67 (d), 109.72 (d), 116.7 (d), 117.8 (s), 124.5 (s), 129.4 (s), 136.7 (s), 141.7 (d), 147.2 (s), 147.4 (s), 147.5 (s), 152.3 (s), 153.9 (s). Anal. Calcd for C\(_{20}\)H\(_{18}\)I\(_3\)NO\(_4\): C, 33.50; H, 2.53; N, 1.95. Found: C, 33.69; H, 2.55; N, 1.92.

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REFERENCES AND NOTES


10. For convenience, each skeletal atom in the 3,4-dimethoxyphenyl moiety is indicated by a usual number and each aromatic carbon in the 2-bromophenyl moiety by a primed number.


17. See ref. 3 for 1H-NMR spectral data of the corresponding iodide (2a: X = I).