Isolation, synthesis and biological activity of Evolitrine and analogs

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Dedicated to Dr. Nitya Anand on the occasion of his 80th birthday
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Abstract
Evolitrine (4,7-dimethoxyfuro[2,3-b]quinoline, 6a) was isolated from the dichloromethane extract of Evodia lunu-ankeda twigs. For the total synthesis the key chloro intermediate 3a was prepared in a novel way. The alkoxy, amino, dihydro derivatives of 6a were prepared. Evolitrine and some of its derivatives show anti-inflammatory activity.

Keywords: Evolitrine, Evodia lunu-ankenda, furo[2,3-b]quinoline, antiinflammatory activity, Aliquat 336

Introduction
We have been working in the area of inflammation to search for potential anti-inflammatory (AI) agents from plant sources. A number of plant extracts has been routinely tested for AI indication.

Evolitrine 6a (Figure 1) was already known in the literature both from plants and synthetic sources. Evolitrine was isolated from bark and leaves of E. Litoris,1 bark of E. Belahe Ballion,2 petrol extract of the timber of Acronychia Pedunculata,3 wood of Esenbeckia species,4 stem barks of Dutaillya Drepacea,5 leaves of Melicope Indica,6 root bark of E. lunu-ankenda,7, 8 aerial parts of E. Lunu-ankenda,9 etc. Recently, Evolitrine was isolated from stem wood of E. lunu-ankenda, and its antifeedant activity has been reported.10 However, any anti-inflammatory activity of Evolitrine has not been reported.

Figure 1. Evolitrine 6a.
The goal of the project was to take advantage of the lead, to synthesize the natural product and derivatives. There are some reports on the synthesis of Evolitrine.\textsuperscript{11–13} This paper describes the isolation of Evolitrine from twigs extracts of Rutaceae plant \textit{Evodia lunu-ankenda} Merill, the syntheses of Evolitrine and some derivatives; finally, structure activity relationship (SAR) of the derivatives are considered.

**Results and Discussion**

The dichloromethane extract of \textit{Evodia lunu-ankeda} twigs showed inhibition (67\% at 400 mg/kg) of carrageenan induced edema. The crude extract was subjected to flash chromatography on silica gel, and some of the fractions had enriched activity. After repeated chromatography of this fraction, one fraction showed 57\% inhibition at 20 mg/kg. \textsuperscript{1}H NMR, IR, CHN analysis and mass spectra proved the extract as the known alkaloid Evolitrine. This compound has no ulcerogenic effect up to 300 mg/kg p.o. (per os); it showed significant inhibition of adjuvant arthritis at 100 and 200 mg/kg p.o. of the original extract.

The synthesis of furo[2,3-\textit{b}]quinoline-3,4(2\textit{H},9\textit{H})-diones 1a–d has been described in the literature: Condensation of appropriately substituted anilines with diethyl malonate, followed by treatment with NaH, reaction of the resulting sodium salt with chloroacetyl chloride and work-up with triethylamine in THF afforded the corresponding ethyl 2-anilino-4-oxo-4,5-dihydrofuran-3-carboxylates,\textsuperscript{14–16} which upon thermolysis at 240 °C for 20 min yielded furo[2,3-\textit{b}]quinoline-3,4(2\textit{H},9\textit{H})-diones 1a–d.\textsuperscript{17,18} By conventional method, diketo compounds 1a–d were treated with phosphorus oxychloride\textsuperscript{17} to give 4-chlorofuro[2,3-\textit{b}]quinolin-3(2\textit{H})-ones 3a–d in moderate yields; the formation of 3a was accompanied by some 3,4-dichlorofuro[2,3-\textit{b}]quinoline 2a (Scheme 1).\textsuperscript{19} The conversion of quinolinindiones 1a–d into chloro compound 3a–d was erratic due to solubility problems. From the reaction of 1a with trifluoroacetic acid, pyridine, and phosphorus oxychloride 5a and 4a were obtained in 50\% and 10\%, respectively. However, upon prolonged reaction time most of 1a was converted into the corresponding dichloro compound 2a. The key monochloro compounds 3a–d were prepared in a novel way: Solid dicarbonyl compounds 1a–d were treated without solvent with 2 molar equivalents of phosphorus oxychloride and 10\% phase transfer catalyst Aliquat 336 (tricaprylmethyl-ammonium chloride) to afford compounds 3a–d in 70–80\% yield. This reaction was repeated several times, scaled to 50–60 g batches and gave consistent results. The monochloro keto compounds 3a–d were reduced with sodiumborohydride in methanol to the corresponding alcohols 4a–d.\textsuperscript{3,7} These alcohols were dehydrated with potassium hydrogen sulfate and dioxane to provide 4-chlorofuro[2,3-\textit{b}]quinolines as the main intermediates 5a–d.\textsuperscript{15,20}
Scheme 1. Reagents and conditions: i. POCl₃, CH₂Cl₂, reflux, 3h; or CF₃CO₂H, CH₂Cl₂, reflux, 3h, pyridine, POCl₃, reflux, 2h; or Aliquat 336, POCl₃, CH₂Cl₂, r.t., 48 h. ii. NaBH₄, MeOH, 0 °C; r.t., 1 h; 2 N HCl. iii. KHSO₄, 1,4-dioxane, reflux, 3 h.

Reaction of compound 5a with sodium methoxide in methanol provided an efficient synthesis of Evolitrine 6a (Scheme 2); the synthetic product was identical with the isolated natural product Evolitrine both with respect to structure and biological activity. Analogously, 4-alkoxy-substituted 7-methoxyfuro[2,3-b]quinolines 6b–h were prepared (Scheme 2): In a nitrogen atmosphere sodium metal was added to the dry alcohol and followed by chloro compound 5a, and the resulting reaction mixture was heated at reflux. Similarly, some modifications were carried out by substituting the 4-chloro substituent of 5a with the ethyl-sulfanyl group under basic conditions to give product 7, and by replacing the 4-chloro substituent of 5a with various amines (primary, secondary) and a hydrazine derivative in acetonitrile solution amines 8a–k were obtained (Scheme 2). For testing these amines were converted into their salts 8a–k·HCl.
Scheme 2. Reagents and conditions: i. R¹OH, Na, N₂, reflux, 3 h; or R¹OH, NaH, N₂, dioxane, DMSO, 90 °C; or R¹OH, K₂CO₃, acetone, r.t., 10 min. ii. EtSH, NaH, DMF. iii. R²R³NH, MeCN; HCl/Et₂O.

Hydrogenation of compounds 6a,b and 8c·2HCl with 10% Pd/C catalyst yielded products 9a,b and 10c·HCl, respectively (Scheme 3).²¹ Hydrogenolysis of 2a in the presence of 10% Pd/C and anhydrous sodium acetate gave product 11²² (Scheme 4). Treatment of compound 3a with dry methanol gave product 12 (Scheme 5).

Scheme 3. Reagents and conditions: i. MeOH, 10% Pd/C, H₂, 25 psi, 1–5h; for 10c·2HCl: HCl/Et₂O.

Scheme 4. Reagents and conditions: i. DMF/MeOH, NaOAc, 10% Pd/C, H₂, 30 psi, 30 min.
Scheme 5. Reagents and conditions: i. MeOH, reflux, 30 h.

Displacement of the chloro substituent in 5a–d with methyl- and dimethylamine gave only poor yields of the corresponding amines 15. Higher yields of 15aa–da·HCl were obtained when chloro ketones 3a–d were treated with methylamine or dimethylamine to give 13aa–da (Scheme 6). Reduction of the carbonyl group of 13aa–da to the corresponding hydroxy derivatives 14aa–da was followed by dehydration and treatment with HCl/ether to yield 15aa–da·HCl.

Scheme 6. Reagents and conditions: i. CH2Cl2, MeNH2 or Me2NH in toluene, r.t., 1 h; ii. NaBH4, MeOH, 0 °C → r.t., 1 h. iii. KHSO4, dioxane, 110 °C, 3 h; HCl/Et2O.

Using the chloro ketone 3c as starting material the 7-hydroxy compounds 18a,b·HCl were prepared by displacement of the 4-chloro substituent with methyl- and dimethylamine, respectively; subsequent hydrogenation effected debenzylation and reduction of the carbonyl group; finally, dehydration followed by treatment with HCl/ether gave 18a,b·HCl (Scheme 7).

We have also synthesized other derivatives such as 4-arylamino derivatives; they will be reported later.
Scheme 7. i. CH$_2$Cl$_2$, MeNH$_2$ or Me$_2$NH in toluene, r.t., 1 h; ii. MeOH, 10% Pd/C, H$_2$, 50 psi, 3 h; MeOH, NaBH$_4$, 0 °C → r.t., 1 h. iii. KHSO$_4$, dioxane, 110 °C, 3 h; HCl/Et$_2$O.

Biological activity

Dichloromethane extract of *Evodia lunu-ankeda* twigs exhibited 43% inhibition of carrageenan-induced rat paw edema in rats. Since the activity was found to be independent of adrenal pituitary axis and cyclooxygenase inhibition (Table 1) and without any cardiovascular effect (300 mg/kg) the extract was further examined in adjuvant arthritis in rats. Significant inhibition was observed at 100 and 200 mg/kg p.o. administered through a period of 21 days, without any toxic symptoms or loss in weight.

Table 1. Antiinflammatory activity of Evolitrine 6a

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose mg/kg p.o.</th>
<th>% Inhibition of carrageenan edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evolitrine 6a</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>78</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>05</td>
<td>55</td>
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</table>

Carrageenan-induced rat-paw model and adjuvant induced arthritis in rats$^{23,24}$ have remained the most relevant and widely used animal models predicting AI potentials of a drug in acute and chronic inflammatory conditions respectively. Therefore, the plant extract was tested in these two models along with few other biological models. In carrageenan-induced rat paw edema model, the rats in a group of six were fasted 24 h prior to the initiation of an experiment. The aqueous suspension of dichloromethane extract of *Evodia lunu-ankeda* twigs was orally administered to the rats. After 1 h, 0.05 mL of 0.5% w/v carrageenan suspension in saline was intrapedally injected into the left hind paw of all the rats under study. The contralateral paw received equivalent amount of saline. The paw volumes were determined immediately and 3 h
after carrageenan injection, on a water plethysmometer. At the dose of 300 mg/kg p.o., dichloromethane extract of *Evodia lunu-ankeda* twigs exhibited 43% inhibition of carrageenan-induced rat paw edema, whereas Indomethacin brought about 57% inhibition at the dose of 10 mg/kg p.o. To rule out the involvement of endogenous steroids, which may get released after drug treatment exerting antiinflammatory effect, adrenalecotomised (ADX) rats were used for the above study. In ADX animals at the above mentioned doses of dichloromethane extract of *Evodia lunu-ankeda* twigs and Indomethacin inhibition of edema was 53% and 62%, respectively, without any unwanted cardiovascular effects. At the dose of 300 mg/kg p.o., the test extract did not have any ulcerogenic effects as against 82% ulceration seen with Indomethacin at 10 mg/kg p.o. In the model of chronic inflammation, i.e. adjuvant induced arthritis in rats, which bears similarity to human rheumatoid arthritis, significant inhibition of paw edema was seen at 100 mg and 200 mg/kg p.o. given for the first 21 days post-induction of arthritis. No toxic symptoms or loss in weight were observed in animals under study.

Evolitrine 6a isolated from *Evodia lunu-ankeda* merill was found to be an effective antiinflammatory/immunomodulatory agent. It showed 57% inhibition of carrageenan induced rat paw edema at 20 mg/kg (Table 1). Evolitrine 6a effectively inhibited the formation of edema provoked by the sub-plantar injection of carrageenan. The high degree of dose responses suggested that evolitrine possessed very interesting activity in the acute model of inflammation. Although, Evolitrine 6a was found to be as potent as indomethacin, the absence of gastric irritation produced by the former compound, makes it a more desirable anti-inflammatory agent. The activities of Evolitrine 6a and of most derivatives are listed in Table 2.

### Table 2. Antiinflammatory (AI) activity of Evolitrine derivatives

<table>
<thead>
<tr>
<th>Compd.</th>
<th>AI activity at 100 mg/kg [%]</th>
<th>Compd.</th>
<th>AI activity at 100 mg/kg [%]</th>
<th>Compd.</th>
<th>AI activity at 100 mg/kg [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>not active</td>
<td>8b·HCl</td>
<td>54</td>
<td>10c·HCl</td>
<td>16</td>
</tr>
<tr>
<td>4a</td>
<td>10</td>
<td>8c·2HCl</td>
<td>11</td>
<td>11</td>
<td>not active</td>
</tr>
<tr>
<td>5a</td>
<td>8</td>
<td>8d·2HCl</td>
<td>38</td>
<td>12</td>
<td>not active</td>
</tr>
<tr>
<td>6a</td>
<td>83</td>
<td>8e·2HCl</td>
<td>not active</td>
<td>15aa·HCl</td>
<td>44</td>
</tr>
<tr>
<td>6b</td>
<td>51</td>
<td>8f·2HCl</td>
<td>16</td>
<td>15ab·HCl</td>
<td>65</td>
</tr>
<tr>
<td>6c</td>
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<td>8g·2HCl</td>
<td>04</td>
<td>15ba·HCl</td>
<td>16</td>
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<tr>
<td>6d</td>
<td>37</td>
<td>8h·HCl</td>
<td>not active</td>
<td>15bb·HCl</td>
<td>28</td>
</tr>
<tr>
<td>6e</td>
<td>24</td>
<td>8i·HCl</td>
<td>28</td>
<td>15ca·HCl</td>
<td>13</td>
</tr>
<tr>
<td>6f</td>
<td>33</td>
<td>8j·HCl</td>
<td>13</td>
<td>15cb·HCl</td>
<td>36</td>
</tr>
<tr>
<td>6g</td>
<td>52</td>
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<td>25</td>
<td>15da·HCl</td>
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<tr>
<td>6h</td>
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<td>9a</td>
<td>50</td>
<td>18ca·HCl</td>
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</tr>
<tr>
<td>8a·HCl</td>
<td>24</td>
<td>9b</td>
<td>36</td>
<td>18cb·HCl</td>
<td>not active</td>
</tr>
</tbody>
</table>
Conclusions

Evolitrine 6a was isolated from *Evodia lunu-ankenda* Merill, synthesized more efficiently and found to be an effective antiinflammatory/immunomodulatory agent. It showed 57% inhibition of carrageenan-induced rat paw edema at 20 mg/kg. Evolitrine 6a effectively inhibited the formation of edema provoked by the sub-plantar injection of carrageenan. Changes made at 4-position in Evolitrine skeleton, did not give better active compounds. For instance, the derivatives 6b–6h with 7-OCH$_3$ and 4-alkoxy groups were found to be active in carrageenan-induced rat paw edema model. Some of the derivatives 8a–8k, 15aa–15da·HCl and 18a–18b·HCl having 7-alkoxy or alkyl with 4-amino groups and 2,3-dihydro derivatives 9a,b and 10c·HCl were found to retain activity. However, compounds 11 and 12 had no activity as compared to Evolitrine 6a. A new and better method to synthesize 4-chloro compounds 3 was found.

Experimental Section

**General Procedures.** Melting points were determined with a Kofler hot stage apparatus (benzoic acid was used as melting point standard). IR spectra were measured as KBr pellets using a Perkin-Elmer 157 Spectrometer. $^1$H NMR spectra were recorded on a JEOL FT-90 MHz. Petroleum ether refers to the fraction of boiling range 60–80 °C.

**Isolation of Evolitrine from *Evodia lunu-ankenda* Merill.** The air-dried plant material (1 kg) was pulverized, extracted with petroleum ether (5 L) to remove fatty material: this extract was discarded. The residue was extracted with dichloromethane (3 x 2 L), concentrated and gave the dichloromethane extract (60 g). This dichloromethane extract was subjected to silica gel chromatography using 0–10% methanol in chloroform as eluent: 62 fractions (each fraction 230–250 mL) were collected; fractions 37–43 had enriched activity. These active fractions were further purified on silica gel column with 0–10% methanol in chloroform as eluent. The final purification was carried out on a silica gel column with 5% acetonitrile in chloroform as eluent to give pure Evolitrine 6a.

**3,4-Dichloro-7-methoxyfuro[2,3-b]quinoline (2a) and 4-chloro-7-methoxyfuro[2,3-b]quinolin-3(2H)-one (3a). Typical procedures**

**Method A.** To the solution of the dicarbonyl compound 1a (5 g, 21.64 mmol) in dichloromethane (5 mL) at 0 °C was added dropwise phosphorus oxytrichloride (7.95 mL, 86.56 mmol) over a period of 30 min. The reaction mixture was heated at reflux for 3 h, cooled and slowly poured into ice water. The dichloromethane layer was separated, dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was passed through a silica gel column with 0.5–2% acetonitrile in chloroform as eluent. Two pure compounds were obtained, the dichloro compound 2a (0.58 g, 10%) as a white solid and the monochloro compound 3a as a white solid.
Method B. To the solution of the dicarbonyl compound 1a (5 g, 21.64 mmol) in dichloromethane (25 mL) was added a solution of TFA (5 mL, 64.93 mmol) in dichloromethane (5 mL), and the reaction mixture was heated at reflux for 3 h. Then, solutions of pyridine (3.64 g, 43.28 mmol) in dichloromethane (10 mL) and of phosphorus oxytrichloride (7.95 mL, 86.56 mmol) in dichloromethane (10 mL) were added simultaneously. The reaction mixture was heated at reflux for 2 h and subsequently poured in ice water. Work-up as described before gave 2a (0.58 g, 10%) and 3a (2.68 g, 50%).

Method C. A mixture of the dicarbonyl compound 1a (10 g, 43.28 mmol), Aliquat 336 (1.74 g, 4.328 mmol) and phosphorus oxytrichloride (7.95 mL, 86.56 mmol) was kept for 48 h at room temperature in a nitrogen atmosphere. The reaction mixture was poured into ice water and extracted with dichloromethane (100 mL). Work-up as described before gave pure 3a (8.64 g, 80%) as a white solid.

2a. mp 212–213 °C. 1H NMR (90 MHz, CDCl3, drop of TFA): δ 4.00 (3H, s, OCH3), 7.22–7.40 (1H, dd, J = 2.4, 8.8 Hz, HAr), 7.56 (1H, d, J = 2.45 Hz, HAr), 7.78 (1H, s, HAr), 8.25 (1H, d, J = 8.8 Hz, HAr). IR (KBr): ν 3150, 2900, 1610, 1560, 1420, 1250, 1130, 1000, 900 cm–1. Anal. calcd for C12H7Cl2NO2 (268.10): C, 53.76; H, 2.63; Cl, 26.45; N, 5.22. Found: C, 53.93; H, 2.69; Cl, 26.28; N, 5.06.

3a. mp 245–247°C. 1H NMR (90 MHz, CDCl3): δ 3.98 (3H, s, OCH3), 4.76 (2H, s, CH2), 7.0–7.23 (2H, m, HAr), 8.1 (1H, d, J = 8.78 Hz, HAr). IR (KBr): ν 2400, 1710, 1600, 1490, 1150 cm–1. Anal. calcd for C12H8ClNO3 (249.65): C, 57.73; H, 3.23; Cl, 14.20; N, 5.61. Found: C, 57.45; H, 3.01; Cl, 13.95; N, 5.46.

4-Chloro-7-methylfuro[2,3-b]quinolin-3(2H)-one (3b). As described for 3a, Method c, 1b (5 g, 23.23 mmol), Aliquat 336 and phosphorus oxytrichloride provided 3b (3.26 g, 60%) as a white solid; mp 195–197 °C. 1H NMR (90 MHz, CDCl3): δ 2.6 (3H, s, CH3), 4.8 (2H, s, CH2), 7.21 (1H, d, J = 2.5 Hz, HAr), 7.3–7.42 (1H, dd, J = 2.5, 8.9 Hz, HAr), 8.18 (1H, d, J = 8.9 Hz, HAr). IR (KBr): ν 2350, 1700, 1620, 1520, 1300, 1200, 1050 cm–1.

7-(Benzyloxy)-4-chlorofuro[2,3-b]quinolin-3(2H)-one (3c). As described for 3a, Method c, 1c (5.0 g, 16.27 mmol) Aliquat 336 and phosphorus oxytrichloride provided 3c (3.65 g, 69%) as a white solid; mp 235 °C. 1H NMR (90 MHz, CDCl3): δ 4.8 (2H, s, CH2), 4.99 (2H, s, CH2), 7.20 (1H, d, J = 2.5 Hz, HAr), 7.3-7.6 (5H, m, HAr), 7.42 (1H, dd, J = 2.5, 8.9 Hz, HAr), 8.15 (1H, d, J = 8.9 Hz, HAr). IR (KBr): ν 2420, 1710, 1610, 1510, 1320, 1200, 1100, 900 cm–1. Anal. calcd for C18H12ClNO3 (325.75): C, 66.37; H, 3.71; Cl, 10.88; N, 4.3%. Found: C, 66.26; H, 3.5; Cl, 10.60; N, 4.16.

4-Chloro-6,7-dimethoxyfuro[2,3-b]quinolin-3-one (3d). As described for 3a, Method c, 1d (5.0 g, 18.99 mmol), Aliquat 336 and phosphorus oxytrichloride provided 3c (3.18 g, 60%) as off white solid; mp 205–207 °C. 1H NMR (90 MHz, CDCl3): δ 4.1 (6H, 2s, 2x OCH3), 5.1 (2H, s), 7.6 (2H, 2s, HAr). IR (KBr): ν 2420, 1710, 1610, 1510, 1440, 1250, 1100, 1050 cm–1. Anal. calcd for C13H10ClNO4 (279.68): C, 55.83; H, 3.6; Cl, 12.68; N, 5.01%. Found: C, 56.02; H, 3.8; Cl, 12.82; N, 4.73.
4-Chloro-7-methoxy-2,3-dihydro-furo[2,3-b]quinolin-3-ol (4a). To the stirred solution of the monochloro carbonyl compound 3a (5 g, 20.08 mmol) in methanol (50 mL) was added portion-wise at 0 °C NaBH₄ (1.14 g, 30.12 mmol). Stirring of the reaction mixture was continued at room temperature for 1 h. The solvent was evaporated; the residue after addition of water (50 mL) was acidified with 2 N HCl and extracted with chloroform. The chloroform layer was separated, dried over Na₂SO₄ and concentrated in vacuo. The crude product was recrystallized from methanol/ether to give 4a (4.53 g, 90%) as a white solid; mp 192–195 °C. ¹H NMR (90 MHz, CDCl₃, drop of TFA): δ 3.98 (3H, s, OCH₃), 5.10 (2H, m, CH₂), 5.80 (1H, m, CH), 7.20 (1H, d, J = 2.46 Hz, Hₐ), 7.20–7.40 (1H, dd, J = 2.46, 8.78 Hz, Hₐ), 8.15 (1H, d, J = 8.78 Hz, Hₐ). IR (KBr): ν ~ 3150, 2900, 1620, 1500, 1410, 1310, 1220, 1020 cm⁻¹. Anal. calcd for C₁₂H₁₀ClNO₃ (251.67): C, 57.27; H, 4.00; Cl, 14.09; N, 5.57. Found: C, 56.84; H, 4.02; Cl, 14.34; N, 5.95.

4-Chloro-7-methyl-2,3-dihydrofuro[2,3-b]quinolin-3-ol (4b). As described for 4a, 3b (5.0 g, 21.40 mmol) was converted into 4b (4.03 g, 80%) as a white solid; mp 154 °C. ¹H NMR: δ 2.56 (3H, s, CH₃), 4.46 (2H, m, CH₂), 5.56 (1H, m, CH), 7.00–7.20 (2H, m, Hₐ), 7.70 (1H, d, J = 8.9 Hz, Hₐ). IR (KBr): ν ~ 3300, 2400, 1700, 1600, 1420, 1240, 1100, 820 cm⁻¹.

7-Benzylxylo-4-chloro-2,3-dihydrofuro[2,3-b]quinolin-3-ol (4c). As described for 4a, 3c (5.0 g, 16.27 mmol) was converted into 4c (4.12 g, 82%) as a white solid; mp 145 °C. ¹H NMR (90 MHz, CDCl₃): δ 4.46 (2H, m, CH₂), 5.10 (2H, s, CH₂), 5.50 (1H, m, CH), 6.90–7.10 (1H, dd, J = 2.5, 8.9 Hz, Hₐ), 7.20 (1H, d, J = 2.5 Hz, Hₐ), 7.22–7.58 (5H, m, Hₐ), 7.80 (1H, d, J = 8.9 Hz, Hₐ). IR (KBr): 3200, 2350, 1680, 1510, 1380, 980 cm⁻¹.

4-Chloro-7-methoxyfuro[2,3-b]quinoline (5a). A mixture of anhydrous potassium hydrogen sulfate (12.2 g, 89.6 mmol) and 4a (4.5 g, 17.92 mmol) in dry dioxane (50 mL) was heated at refluxed for 3 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue after addition of water (50 mL) was basified with sodium hydroxide solution (20%) and extracted with chloroform (2 x 50 mL). The chloroform layer was separated, dried over Na₂SO₄ and concentrated in vacuo. The crude product was passed through a silica gel column with 0.5–2% acetonitrile in chloroform as eluent affording pure 5a (2.8 g, 68%) as a white solid; mp 179–180 °C. ¹H NMR (90 MHz, CDCl₃): δ 3.98 (3H, s, OCH₃), 6.9 (1H, d, J = 2.35 Hz, Hₐ), 7.12–7.30 (1H, dd, J = 2.35, 8.9 Hz, Hₐ), 7.4 (1H, d, J = 2.35 Hz, Hₐ), 7.7 (1H, d, J = 2.35 Hz, Hₐ), 8.15 (1H, d, J = 8.9 Hz, Hₐ). IR (KBr): ν ~ 3100, 1610, 1500, 1410, 1220, 1130, 1020, 900, 850 cm⁻¹. Anal. calcd for C₁₂H₈ClNO₂ (233.65) C, 61.69; H, 3.45; Cl, 15.17; N, 5.99. Found: C, 61.43; H, 3.28; Cl, 15.18; N, 5.84.

Chloro-7-methylfuro[2,3-b]quinoline (5b). As described for 5a, 4b (4.0 g, 16.97 mmol) gave 5b (2.21 g, 60%) as a white solid; mp 179–180 °C. ¹H NMR (90 MHz, CDCl₃): δ 2.6 (3H, s, CH₃), 6.85 (1H, d, J = 2.5 Hz, Hₐ), 7.20–7.40 (1H, dd, J = 2.5, 8.9 Hz, Hₐ), 7.7 (1H, d, J = 2.5 Hz, Hₐ), 8.1 (1H, d, J = 8.9 Hz, Hₐ). IR (KBr): ν ~ 2900, 2350, 1610, 1580, 1390, 900, 810 cm⁻¹. Anal. calcd for C₁₂H₈ClNO (217.65): C, 66.20; H, 3.7; Cl, 16.29; N, 6.44. Found: C, 66.35; H, 3.79; Cl, 15.96; N, 6.43.
7-Benzyl@d2oxy-4-chlorofuro[2,3-b]quinoline\(^{11}\) (5c). As described for 5a, 4c (4.0 g, 12.13 mmol) gave 5b (2.50 g, 65%) as a white solid; mp 120–122 °C. \(^1\)H NMR (90 MHz, CDCl\(_3\)): \(\delta\) 5.19 (2H, s, CH\(_2\)), 6.85 (1H, d, \(J = 2.5\) Hz, HA\(_{\text{Ar}}\)), 7.18–7.6 (7H, m, HA\(_{\text{Ar}}\)), 7.67 (1H, d, \(J = 2.5\) Hz, HA\(_{\text{Ar}}\)), 8.1 (d, 1H, \(J = 8.9\) Hz, HA\(_{\text{Ar}}\)). IR (KBr): \(\bar{\nu}\) 2900, 1620, 1580, 1540, 1500, 1460, 1150 cm\(^{-1}\). Anal. calcd for C\(_{18}\)H\(_{12}\)ClNO\(_2\) (309.75): C, 69.8; H, 3.90; Cl, 11.45; N, 4.52. Found: C, 69.85; H, 3.79; Cl, 11.36; N, 4.43.

4-Chloro-6,7-dimethoxy-2,3-dihydrofuro[2,3-b]quinolin-3-ol (4d), 4-Chloro-6,7-dimethoxyfuro[2,3-b]quinoline (5d). As described for 4a, 3d (5.0 g, 17.88 mmol) was converted into 4d (4.28 g, 85%), which was used without characterization for the next step according to the procedure for 5a furnishing 5d (2.24 g, 60%) as a white solid; \(^1\)H NMR (90 MHz, CDCl\(_3\)/DMSO-\(d_6\)): \(\delta\) 4.05 (6H, 2s, 2 OCH\(_3\)), 6.90 (1H, d, \(J = 2.5\) Hz, HA\(_{\text{Ar}}\)), 7.38–7.43 (2H, 2s, HA\(_{\text{Ar}}\)), 7.78 (1H, d, \(J = 2.5\) Hz, HA\(_{\text{Ar}}\)). IR (KBr): \(\bar{\nu}\) 1600, 1510, 1450, 1280, 1140 cm\(^{-1}\). Anal. calcd for C\(_{13}\)H\(_{10}\)ClNO\(_3\) (263.68): C, 59.22; H, 3.82; Cl, 13.45; N, 5.31. Found: C, 59.43; H, 3.72; Cl, 13.30; N, 5.19.

4,7-Dimethoxyfuro[2,3-b]quinoline, Evolitrine (6a). To the solution of sodium metal (0.5 g, 21.74 mmol) in absolute methanol (25 mL) in a nitrogen atmosphere was added 4-chloro-7-methoxyfuro[2,3-b]quinoline (5a) (1 g, 4.29 mmol), and the reaction mixture was heated at reflux for 3 h. The solvent was evaporated in vacuo, the residue was dissolved in chloroform and the extract was washed with water until neutral reaction, dried over anhydrous Na\(_2\)SO\(_4\), and concentrated in vacuo. The crude compound was passed through a silica gel column with 5–20% acetonitrile in chloroform as eluent. Recrystallization from ethyl acetate/petroleum ether furnished the pure product 8a (0.72 g, 74%) as a white solid; mp 120–121 °C (lit.\(^{12}\) mp 114–115 °C). \(^1\)H NMR (90 MHz, CDCl\(_3\)): \(\delta\) 3.98 (3H, s, OCH\(_3\)), 4.20 (3H, s, OCH\(_3\)), 6.95 (1H, d, \(J = 2.5\) Hz, HA\(_{\text{Ar}}\)), 7.05 (1H, dd, \(J = 2.52, 8.91\) Hz, HA\(_{\text{Ar}}\)), 7.22 (1H, d, \(J = 8.9\) Hz, HA\(_{\text{Ar}}\)), 7.50 (1H, d, \(J = 2.52\) Hz, HA\(_{\text{Ar}}\)), 8.10 (1H, d, \(J = 8.91\) Hz, HA\(_{\text{Ar}}\)). IR (KBr): \(\bar{\nu}\) 2900, 1640, 1600, 1470, 1380, 1280, 960 cm\(^{-1}\). Anal. calcd for C\(_{13}\)H\(_{11}\)NO\(_3\) (229.23): C, 68.12; H, 4.84; N, 6.11. Found: C, 68.09; H, 5.09; N, 6.38.

4-Ethoxy-7-methoxyfuro[2,3-b]quinoline (6b). To the solution of sodium metal (0.5 g, 21.74 mmol) in absol. ethanol (30 mL) in nitrogen atmosphere was added 5a (1 g, 4.29 mmol), and the reaction mixture was heated at reflux for 3 h. The solvent was evaporated in vacuo, the residue was dissolved in chloroform, and the extract was washed with water until neutral reaction, dried over anhydrous Na\(_2\)SO\(_4\), and concentrated in vacuo. The crude product was passed through a silica gel column with 5–20% acetonitrile in chloroform as eluent. Recrystallization from ethyl acetate/petroleum ether furnished pure 6b (0.76 g, 75%) as a white solid; mp 108–109 °C. \(^1\)H NMR (90 MHz, CDCl\(_3\)): \(\delta\) 1.6 (3H, t, \(J = 6.25\) Hz, CCH\(_3\)), 3.98 (3H, s, OCH\(_3\)), 4.7 (2H, q, \(J = 6.25\) Hz, OCH\(_2\)), 6.95 (1H, d, \(J = 2.51\) Hz, HA\(_{\text{Ar}}\)), 7.1 (1H, dd, \(J = 2.51, 8.57\) Hz, HA\(_{\text{Ar}}\)), 7.3 (1H, d, \(J = 2.51\) Hz, HA\(_{\text{Ar}}\)), 7.56 (1H, d, \(J = 2.51\) Hz, HA\(_{\text{Ar}}\)), 8.15 (1H, d, \(J = 8.57\) Hz, HA\(_{\text{Ar}}\)). IR (KBr): \(\bar{\nu}\) 3000, 2300, 1610, 1590, 1415, 1220, 1020, 970, 880 cm\(^{-1}\). Anal. calcd for C\(_{14}\)H\(_{13}\)NO\(_3\) (243.26): C, 69.13; H, 5.39; N, 5.76. Found: C, 69.34; H, 5.51; N, 5.57.
3-(7-Methoxyfuro[2,3-b]quinolin-4-yl)propane-1,2-diol (6c). 50% Sodium hydride (0.4 g, 8.69 mmol) was washed with dry dioxane in a nitrogen atmosphere, and dry dioxane (30 mL), (S)-(−)-glycerol 1,2-acetonide\textsuperscript{25} (0.6 g, 4.6 mmol) and 5a (1.05 g, 4.55 mmol) were added. The reaction mixture was heated at 90 °C for 23 h. The solvent was concentrated in vacuo, the residue was taken up in chloroform (50 mL), and the solution was washed with water (100 mL). The chloroform layer was separated, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude solid residue was recrystallized from ethyl acetate/petroleum ether to furnish the pure solid product. This product was dissolved in dry methanol (20 mL), anhydrous p-toluenesulphonic acid (0.2 g, 1.09 mmol) was added, and the reaction mixture was stirred at room temperature for 23 h. Triethylamine (1 mL) was added, and the solvent was removed in vacuo. The crude product was passed through a silica gel column with 2–5% methanol in chloroform as eluent to give 6c (0.6 g, 49%) as a pale yellow solid; mp 174–175 °C. \textsuperscript{1}H NMR: (90 MHz, CDCl\textsubscript{3}/DMSO-\textsubscript{d}\textsubscript{6}): \( \delta \) 3.85 (2H, m, CH\textsubscript{2}OH), 3.98 (3H, s, OCH\textsubscript{3}), 4.10–4.40 (1H, m, CH\textsubscript{OH}), 4.75 (2H, d, \( J = 5.25 \) Hz, OCH\textsubscript{2}), 7.1 (1H, dd, \( J = 2.5, 8.9 \) Hz, H\textsubscript{Ar}), 7.6 (2H, m, H\textsubscript{Ar}), 8.2 (1H, d, \( J = 8.9 \) Hz, H\textsubscript{Ar}). IR (KBr): \( \tilde{\nu} \) 3400 (br), 3100, 2900, 1690, 1590, 1420, 1350, 1220, 1090, 950 cm\textsuperscript{−1}. Anal. calcd for C\textsubscript{15}H\textsubscript{15}NO\textsubscript{5} (289.28): C, 62.28; H, 5.23; N, 4.84. Found: C, 62.32; H, 5.15; N, 4.94.

7-Methoxy-4-(prop-2-ynyl)quinoline (6d). To the solution of propargyl alcohol (0.5 mL, 8.60 mmol) in dry acetone (20 mL) was added anhydrous K\textsubscript{2}CO\textsubscript{3} (1.38 g, 10 mmol), and the reaction mixture was stirred at room temperature for 10 min. Then 5a (0.5 g, 2.15 mmol) was added with a trace of 18-crown-6, and the reaction mixture was heated at 65 °C for 48 h. Upon filtration, the filtrate was concentrated, and the crude product was passed through a silica gel column with 2% acetonitrile in chloroform as eluent. Pure 6d was obtained. (0.21 g, 40%) as a off white solid; mp 176–177 °C. \textsuperscript{1}H NMR (90 MHz, CDCl\textsubscript{3}): \( \delta \) 2.6 (1H, t, \( J = 2.51 \) Hz, \( \equiv \text{CH} \)), 3.92 (3H, s, OCH\textsubscript{3}), 5.2 (2H, d, \( J = 2.51 \) Hz, OCH\textsubscript{2}), 7.00–7.18 (2H, m, H\textsubscript{Ar}), 7.58 (1H, d, \( J = 2.47 \) Hz, H\textsubscript{Ar}), 8.1 (1H, d, \( J = 8.79 \) Hz, H\textsubscript{Ar}). IR (KBr): \( \tilde{\nu} \) 3240, 3100, 2100, 1610, 1590, 1420, 1220, 1100, 1010, 910, 850 cm\textsuperscript{−1}. Anal. calcd for C\textsubscript{15}H\textsubscript{11}NO\textsubscript{3} (253.27): C, 71.14; H, 4.38; N, 5.53. Found: C, 71.37; H, 4.56; N, 5.38.

7-Methoxy-4-(2,2,2-trifluoroethoxy)furo[2,3-b]quinoline (6e). To sodiumhydride (0.4 g, 8.60 mmol), washed with dry dioxane, was added dry DMSO (10 mL) in a nitrogen atmosphere. The reaction mixture was heated at 70 °C for 30 min until sodium hydride was completely dissolved. The solution was allowed to attain room temperature and 2,2,2-trifluoroethanol (0.47 mL, 6.44 mmol) and a solution of 5a (0.75 g, 3.22 mmol) in DMSO (3 mL) was added. The reaction mixture was stirred at room temperature for 16 h, diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The crude product was passed through a silica gel column with 2% acetonitrile in chloroform as eluent. Pure 6e was obtained after recrystallized from ethyl acetate/petroleum ether (0.61 g, 64%) as a pale yellow solid; mp 157–158 °C. \textsuperscript{1}H NMR (90 MHz, CDCl\textsubscript{3}): \( \delta \) 3.96 (3H, s, OCH\textsubscript{3}), 4.90 (2H, q, \( J = 8.4 \) Hz, OCH\textsubscript{2}CF\textsubscript{3}), 6.82 (1H, d, \( J = 2.75 \) Hz, H\textsubscript{Ar}), 7.15 (1H, dd, \( J = 2.75, 8.75 \) Hz, H\textsubscript{Ar}), 7.35 (1H, d, \( J = 2.5 \) Hz, H\textsubscript{Ar}), 7.60 (1H, d, \( J = 2.75 \) Hz, H\textsubscript{Ar}), 8.10 (1H, d, \( J = 8.75 \) Hz, H\textsubscript{Ar}). IR (KBr): \( \tilde{\nu} \) 3100, 2950, 1610, 1590, 1410, 1280, 1150, 1020, 960, 825 cm\textsuperscript{−1}.
7-Methoxy-4-propoxyfuro[2,3-b]quinoline (6f). To the solution of sodium metal (0.5 g, 21.74 mmol) in dry 1-propanol (25 mL) in a nitrogen atmosphere was added 4-chloro-7-methoxyfuro[2,3-b]quinoline (5a) (1 g, 4.29 mmol). The reaction mixture was heated under reflux for 3 h. The solvent was evaporated in vacuo, the residue was dissolved in chloroform, and the extract was washed with water until neutral reaction, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude product was passed through a silica gel column with 5–20% acetonitrile in chloroform as eluent. Recrystallization from ethyl acetate/petroleum ether furnished the pure product 6f (0.77 g, 70%) as off white solid; mp 117–118 °C. $^1$H NMR (90 MHz, CDCl$_3$): δ 1.10 (3H, t, $J$ = 5.02 Hz, CH$_3$), 1.80–2.20 (2H, m, OCH$_2$CH$_2$CH$_3$), 3.90 (3H, s, OCH$_3$), 4.65 (2H, t, $J$ = 6.27 Hz, OCH$_2$), 6.90 (1H, d, $J$ = 2.39 Hz, H$_{Ar}$), 7.05 (1H, dd, $J$ = 2.39, 8.82 Hz, H$_{Ar}$), 7.30 (1H, d, $J$ = 2.39 Hz, H$_{Ar}$), 7.50 (1H, d, $J$ = 2.39 Hz, H$_{Ar}$), 8.10 (1H, d, J = 8.82 Hz, H$_{Ar}$), IR (KBr): $\nu$ ~ 3100, 2900, 1610, 1590, 1410, 1250, 1100, 1020, 950, 850 cm$^{-1}$. Anal. calcd for C$_{15}$H$_{15}$NO$_3$ (257.29): C, 70.02; H, 5.88; N, 5.44. Found: C, 69.78; H, 5.95; N, 5.24.

4-(Allyloxy)-7-methoxyfuro[2,3-b]quinoline (6g). To the solution of sodium metal (0.5 g, 21.74 mmol) in dry allyl alcohol (25 mL) in a nitrogen atmosphere was added 4-chloro-7-methoxyfuro[2,3-b]quinoline (5a) (1 g, 4.29 mmol), and the reaction mixture was heated under refluxed for 3 h. Work-up as described before furnished the pure product 6a (0.84 g, 73.5%) as an off white solid; mp 104–105 °C. $^1$H NMR (90 MHz, CDCl$_3$): δ 3.97 (3H, s, OCH$_3$), 5.18 (2H, m, OCH$_2$), 5.30–5.60 (2H, m, =CH$_2$), 6.00–6.40 (1H, m, =CH), 6.90 (1H, d, $J$ = 2.51 Hz, H$_{Ar}$), 7.10 (1H, dd, $J$ = 2.50, 8.89 Hz, H$_{Ar}$), 7.35 (1H, d, $J$ = 2.51 Hz, H$_{Ar}$), 7.60 (1H, d, $J$ = 2.51 Hz, H$_{Ar}$), 8.20 (1H, d, J = 8.89 Hz, H$_{Ar}$), IR (KBr): $\nu$ ~ 3100, 2900, 1610, 1580, 1410, 1410, 1250, 1350, 1220, 1060, 940, 900 cm$^{-1}$. Anal. calcd for C$_{15}$H$_{13}$NO$_3$ (255.27): C, 70.58; H, 5.13; N, 5.49. Found: C, 70.91; H, 5.04; N, 5.60.

7-Methoxy-4-(2-methoxyethoxy)furo[2,3-b]quinoline (6h). To sodium hydroxide (0.4 g, 8.33–10 mmol), washed with dry dioxane, was added dry DMSO (10 mL) in a nitrogen atmosphere. The reaction mixture was heated at 70 °C for 30 min until sodium hydroxide was completely dissolved. To the solution at room temperature was added a solution of 2-methoxyethanol (0.34 mL, 4.30 mmol) and 5a (0.5 g, 2.15 mmol) in DMSO (3 mL). The reaction mixture was stirred at room temperature for 16 h, diluted with water and extracted with ethyl acetate. Work-up as described before by chromatography on silica gel with 2% acetonitrile in chloroform as eluent followed by recrystallization from ethyl acetate/petroleum ether gave pure 6h (0.75 g, 64 %) as an off white solid; mp 157–159 °C. $^1$H NMR (90 MHz, CDCl$_3$): δ 3.50 (3H, s, CH$_3$OCH$_2$), 3.84 (2H, t, $J$ = 5.02 Hz, O CH$_2$), 3.98 (3H, s, OCH$_3$), 4.78 (2H, t, $J$ = 5.02 Hz, OCH$_2$), 6.94 (1H, d, $J$ = 2.5 Hz, H$_{Ar}$), 7.07 (1H, dd, $J$ = 2.5, 8.9 Hz, H$_{Ar}$), 7.32 (1H, d, $J$ = 2.5 Hz, H$_{Ar}$), 7.54 (1H, d, $J$ = 2.5 Hz, H$_{Ar}$), 8.10 (1H, d, J = 8.9 Hz, H$_{Ar}$), IR (KBr): $\nu$ ~ 3150, 1620, 1420, 1310, 1250, 1000, 860, 840 cm$^{-1}$. Anal. calcd for C$_{15}$H$_{15}$NO$_4$ (273.29): C, 65.93; H, 5.53; N, 5.13. Found: C, 65.79; H, 5.27; N, 4.91.
4-Ethylsulfanyl-7-methoxyfuro[2,3-b]quinoline (7). Sodium hydride (55-65%, 1.2 g, 25–30 mmol) was washed with petroleum ether (2x10 mL) in a nitrogen atmosphere, and dry dimethylformamide (15 mL) was added. The reaction flask was cooled in an ice-bath to 0°C, and ethyl mercaptan (1.3 mL, 17.5 mmol) was added. After 5 min, 5a (1.0 g, 4.3 mmol) was added, and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over Na₂SO₄ and solvent was concentrated in vacuo. The crude product was passed through a silica gel column with 10% ethyl acetate in petroleum ether as eluent to yield 7 (0.33 g, 33%) as a pale yellow solid, mp 107–108 °C. ¹H NMR (90 MHz, DMSO-d₆): δ 1.10 (3H, t, J = 7.5 Hz, SCH₂CH₃), 3.10 (2H, q, J = 7.5 Hz, SCH₂), 3.92 (3H, s, OCH₃), 7.20 (1H, d, J = 2.54 Hz, Hₐ), 7.3-7.4 (2H, m, Hₐ), 8.18 (1H, d, J = 2.54 Hz, Hₐ), 8.35 (1H, d, J = 8.91 Hz, Hₐ). IR (KBr): ν 3400, 3100, 1610, 1410, 1220, 1000, 900 cm⁻¹. Anal. calcd for C₁₄H₁₃NO₂S (259.32): C, 64.84; H, 5.05; N, 5.40; S, 12.36. Found: C, 64.66; H, 5.23; N, 5.33; S, 12.22.

7-Methoxy-4-(piperidin-1-yl)furo[2,3-b]quinoline hydrochloride (8a·HCl) To the solution of 5a (0.5 g, 2.15 mmol) in dry acetonitrile (20 mL) was added piperidine (0.85 g, 8.60 mmol). The reaction mixture was stirred at 90–95 °C for 24 h. The solvent was removed in vacuo, the residue was taken up in chloroform (50 mL), and the solution was washed with water (100 mL). The chloroform layer was separated and concentrated in vacuo. The crude product was passed through a silica gel column with 15% acetonitrile in chloroform as eluent to yield the free base 8a. ¹H NMR (90 MHz, CDCL₃): δ 1.80 (6H, m), 3.40 (4H, m), 3.90 (3H, s, OCH₃), 6.90 (1H, d, J = 2.45 Hz, Hₐ), 6.92-7.10 (1H, dd, J = 2.45, 8.9 Hz, Hₐ), 7.28 (1H, d, J = 2.45 Hz, Hₐ), 7.50 (1H, d, J = 2.45 Hz, Hₐ), 7.90 (1H, d, J = 8.9 Hz, Hₐ).

To the solution of 8a in dry ether (10 mL) was added 5% HCl in ether (5 mL). After stirring at room temperature for 30 min, the mixture was concentrated to give a yellow residue, which was recrystallized from acetone/petroleum ether to afford 8a·HCl (0.4 g, 67.9%) as a white solid; mp 130–131 °C. IR (KBr): ν 3100, 2900, 2810, 1600, 1420, 1230, 1050, 950, 850 cm⁻¹. Anal. calcd for C₁₇H₁₉ClN₂O₂ (318.81): C, 64.05; H, 6.01; Cl, 11.20; N, 9.92. Found, C, 63.89; H, 5.83; Cl, 11.10; N, 8.56.

7-Methoxy-4-(pyrrolidin-1-yl)furo[2,3-b]quinoline hydrochloride (8b·HCl). As described for 8a·HCl, 5a and pyrrolidine (0.61 g, 8.6 mmol) were converted into 8b·HCl (0.40 g, 61%) as a white solid; mp 197–199 °C. IR (KBr): ν 3450, 1610, 1500, 1220, 1000, 850 cm⁻¹. Anal. calcd for C₁₆H₁₇ClN₂O₂ (304.77): C, 63.06; H, 5.62; Cl, 11.63; N, 9.19; Found: C, 63.16; H, 5.42; Cl, 11.49, N, 8.98.

Free base 8b: ¹H NMR (90 MHz, CDCl₃) δ 1.90–2.20 (4H, m), 3.8 (3H, s, OCH₃), 3.80–4.00 (4H, m), 6.80–6.95 (1H, dd, J = 2.5, 8.9 Hz, Hₐ), 7.00 (1H, d, J = 2.5 Hz, Hₐ), 7.25 (1H, d, J = 2.5 Hz, Hₐ), 7.38 (1H, d, J = 2.5 Hz, Hₐ), 8.10 (1H, d, J = 8.9 Hz, Hₐ).

7-Methoxy-4-(4-phenylpiperidin-1-yl)furo[2,3-b]quinoline dihydrochloride hydrate (8c·2HCl·H₂O). As described for 8a·HCl, 5a and 4-phenylpiperidine (1.39 g, 8.6 mmol) were converted into 8c·2HCl·H₂O (0.45 g, 48%) as a white solid; mp 193–194 °C. IR (KBr): ν 3400,
3100, 2900, 2500, 1620, 1580, 1450, 1250, 1020, 850 cm\(^{-1}\). Anal. calcd for C\(_{22}\)H\(_{26}\)Cl\(_2\)N\(_2\)O\(_3\) (449.37): C, 61.47; H, 5.83; Cl, 15.78; N, 6.23. Found: C, 61.24; H, 5.46; Cl, 15.69; N, 6.54.

Free base 8c: \(^{1}\)H NMR (90 MHz, CDCl\(_3\)): \(\delta\) 2.00–2.30 (4H, m), 2.70–3.00 (1H, m, CH), 3.20–3.60 (4H, m), 4.00 (3H, s, OCH\(_3\)), 7.05, (2H, m, H\(_{Ar}\)), 7.30–7.50 (6H, m, H\(_{Ar}\)), 7.60 (1H, d, \(J = 2.47\) Hz, H\(_{Ar}\)), 8.05 (1H, d, \(J = 8.96\) Hz, H\(_{Ar}\)).

4-(4-Benzylpiperazin-1-yl)-7-methoxyfuro[2,3-b]quinoline dihydrochloride (8d·2HCl). As described for 8a·HCl, 5a and 4-benzylpiperazine (1.50 g, 8.6 mmol) gave 8d·2HCl (0.29 g, 31%) as a white solid; mp 180–181 °C. IR (KBr): \(\tilde{\nu}\) 3400, 2600, 1620, 1590, 1480, 1240, 1000, 950, 840 cm\(^{-1}\). Anal. calcd for C\(_{23}\)H\(_{25}\)Cl\(_2\)N\(_3\)O\(_2\)·(446.38): C, 61.89; H, 5.64; Cl, 15.88; N, 9.41; Found: C, 61.61; H, 5.55; Cl, 15.68; N, 9.39.

Free base 8d: \(^{1}\)H NMR (90 MHz, CDCl\(_3\)): \(\delta\) 2.7–2.9 (4H, m), 3.65 (2H, s, CH\(_2\)Ph), 3.6–3.8 (4H, m), 3.98 (3H, s, OCH\(_3\)), 6.96 (1H, d, \(J = 2.35\) Hz, H\(_{Ar}\)), 7.05 (1H, dd, \(J = 2.35, 8.9\) Hz, H\(_{Ar}\)), 7.25–7.41 (6H, m, H\(_{Ar}\)), 7.58 (1H, d, \(J = 8.9\) Hz, H\(_{Ar}\)).

7-Methoxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)furo[2,3-b]quinoline dihydrochloride hydrate (8e·2HCl·H\(_2\)O). As described for 8a·HCl, 5a and 4-benzylpiperazine (1.62 g, 8.6 mmol) gave 8e·2HCl·H\(_2\)O (0.43 g, 42%) as a white solid; mp 200–202 °C. IR (KBr): \(\tilde{\nu}\) ~ 3450, 2600, 1610, 1590, 1490, 1250, 1100, 1000 cm\(^{-1}\). Anal. calcd for C\(_{23}\)H\(_{27}\)Cl\(_2\)N\(_3\)O\(_4\) (480.39): C, 57.51; H, 5.66; Cl, 14.76; N, 8.75. Found: C, 57.66; H, 5.63; Cl, 14.82; N, 8.79.

Free base 8e: \(^{1}\)H NMR (90 MHz, CDCl\(_3\)): \(\delta\) 3.2–3.4 (4H, m), 3.5–3.75 (4H, m), 3.82 (6H, 2 s, 2 OCH\(_3\)), 6.84–7.16 (6H, m, H\(_{Ar}\)), 7.3 (1H, d, \(J = 2.5\) Hz, H\(_{Ar}\)), 7.56 (1H, d, \(J = 2.5\) Hz, H\(_{Ar}\)), 8.0 (1H, d, \(J = 8.78\) Hz, H\(_{Ar}\)).

7-Methoxy-4-(4-methylpiperazin-1-yl)furo[2,3-b]quinoline dihydrochloride (8f·2HCl). As described for 8a·HCl, 5a and 1-methyl-piperazine (0.86 g, 8.6 mmol) gave 8f·2HCl (0.42 g, 66%) as a white solid; mp 267–268 °C. IR (KBr): \(\tilde{\nu}\) ~ 3400, 2150, 2600, 1620, 1500, 1225, 1030, 830 cm\(^{-1}\). Anal. calcd for C\(_{17}\)H\(_{19}\)Cl\(_2\)N\(_3\)O\(_2\) (370.28): C, 55.14; H, 5.72; Cl, 19.15; N, 11.35. Found: C, 54.98; H, 5.63; Cl, 19.24; N, 11.29.

Free base 8f: \(^{1}\)H NMR (90 MHz, CDCl\(_3\)): \(\delta\) 2.45 (3H, s, N-CH\(_3\)), 2.7 (4H, 2 t, \(J = 3.31\) Hz, NCH\(_2\)), 3.78 (4H, 2 t, \(J = 3.31\) Hz, CH\(_2\)), 3.99 (3H, s, OCH\(_3\)), 7.0 (1H, d, \(J = 2.52\) Hz, H\(_{Ar}\)), 7.05 (1H, dd, \(J = 2.52, 8.9\) Hz, H\(_{Ar}\)), 7.38 (1H, d, \(J = 2.52\) Hz, H\(_{Ar}\)), 7.6 (1H, d, \(J = 2.52\) Hz, H\(_{Ar}\)), 8.0 (1H, d, \(J = 8.9\) Hz, H\(_{Ar}\)).

7-Methoxy-N-(2-(pyrrolidin-1-yl)ethyl)furo[2,3-b]quinolin-4-amine dihydrochloride hydrate (8g·2HCl·H\(_2\)O). As described for 8a·HCl, 5a and 1-(2-aminoethyl)pyrrolidine (0.98 g, 8.6 mmol) gave 8g·2HCl·H\(_2\)O (0.30 g, 35%) as a white solid; mp 222–223 °C. IR (KBr): \(\tilde{\nu}\) 3350, 2950, 2550, 1590, 1300, 1150, 1000, 850 cm\(^{-1}\). Anal. calcd for C\(_{18}\)H\(_{25}\)Cl\(_2\)N\(_3\)O\(_3\) (402.32): C, 53.74; H, 6.26; Cl, 17.62; N, 10.44. Found: C, 53.80; H, 6.48; Cl, 17.43; N, 10.58.

Free base 8g: \(^{1}\)H NMR (90 MHz, D\(_2\)O): \(\delta\) 1.6–2.1 (6H, m), 3.0–3.4 (4H, m), 3.7 (2H, m), 4.0 (3H, s, OCH\(_3\)), 4.2 (2H, m), 6.75 (1H, d, \(J = 2.49\) Hz, H\(_{Ar}\)), 7.1–7.3 (2H, m, H\(_{Ar}\)), 7.3 (1H, d, \(J = 2.49\) Hz, H\(_{Ar}\)), 7.8 (1H, d, \(J = 2.49\) Hz, H\(_{Ar}\)), 8.0 (1H, d, \(J = 8.79\) Hz, H\(_{Ar}\)).

7-Methoxy-N-(2-morpholinoethyl)furo[2,3-b]quinolin-4-amine hydrochloride (8h·HCl). As described for 8a·HCl, 5a and 2-morpholin-4-ylethylamine (1.12 g, 8.6 mmol) gave 8h·HCl (0.27 g, 34%) as a white solid; mp 222–223 °C. IR (KBr): \(\tilde{\nu}\) 3350, 2950, 2550, 1640, 1600, 1500, 1225, 1030, 830 cm\(^{-1}\). Anal. calcd for C\(_{18}\)H\(_{25}\)Cl\(_2\)N\(_3\)O\(_3\) (402.32): C, 53.74; H, 6.26; Cl, 17.62; N, 10.44. Found: C, 53.80; H, 6.48; Cl, 17.43; N, 10.58.
1500, 1250, 1020, 850 cm$^{-1}$. Anal. calcd for C$_{18}$H$_{22}$ClN$_3$O$_3$ (363.84): C, 59.42; H, 6.09; Cl, 9.74; N, 11.55. Found: C, 59.52; H, 6.18; Cl, 9.99; N, 11.41.

Free base 8h: $^1$H NMR (90 MHz, CDC$_{13}$): $\delta$ 2.56 (4H, m), 2.8 (2H, m), 3.66–3.82 (6H, m), 3.9 (3H, s, OCH$_3$), 6.9 (1H, d, $J = 2.55$ Hz, H$_{Ar}$), 7.05 (1H, dd, $J = 2.5$, 8.92 Hz, H$_{Ar}$), 7.4 (1H, d, $J = 2.55$ Hz, H$_{Ar}$), 7.42 (1H, d, $J = 2.55$ Hz, H$_{Ar}$), 7.7 (1H, d, $J = 8.92$ Hz, H$_{Ar}$).

N-Butyl-7-methoxyfuro[2,3-b]quinolin-4-amine hydrochloride (8i·HCl). As described for 8a·HCl, 5a and n-butylamine (0.63 g, 8.6 mmol) gave 8i·HCl (0.32 g, 49%) as a white solid; mp 202–203 °C. IR (KBr): $\tilde{\nu}$ 3400, 3200, 2900, 2600, 1640, 1590, 1290, 1150, 1150, 1020, 880 cm$^{-1}$. Anal. calcd for C$_{16}$H$_{19}$ClN$_2$O$_2$ (306.79): C, 62.64; H, 6.24; N, 9.13; Cl, 11.56. Found: C, 62.44; H, 6.20; N, 9.17; Cl, 11.63.

Free base 8i: $^1$H NMR (90 MHz, CDC$_{13}$): $\delta$ 1.0 (3H, s, CH$_3$), 1.3-1.9 (4H, m), 3.65, (2H, m), 3.9 (3H, s, OCH$_3$), 6.82 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.00 (1H, dd, $J = 2.5$, 8.88 Hz, H$_{Ar}$), 7.3 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.4 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.6 (1H, d, $J = 8.88$ Hz, H$_{Ar}$) 7.00 (1H, dd, $J = 2.5$, 8.9 Hz, H$_{Ar}$), 7.3 (1H, d, $J = 2.5$ Hz, H$_{Ar}$).

7-Methoxy-N-(3-methoxypropyl)furo[2,3-b]quinolin-4-amine hydrochloride hydrate (8j·HCl·H$_2$O). As described for 8a·HCl, 5a and 3-methoxypropylamine (0.77 g, 8.6 mmol) gave 8j·HCl·H$_2$O (0.58 g, 79%) as a white solid; mp 201–203 °C. IR (KBr): $\tilde{\nu}$ 3300, 3100, 2900, 2500, 1640, 1590, 1250, 1100, 1020, 850 cm$^{-1}$. Anal. calcd for C$_{16}$H$_{21}$ClN$_2$O$_4$ (340.80): C, 56.39; H, 6.21; Cl, 10.40; N, 8.22. Found: C, 56.16; H, 6.17; Cl, 10.60; N, 8.36.

Free base 8j: $^1$H NMR for the free base (90 MHz, CDCl$_3$): $\delta$ 1.90, (2H, m, CH$_2$), 2.10 (2H, m, CH$_2$), 3.40 (3H, s, OCH$_3$), 3.64 (2H, t, $J = 3.75$ Hz, CH$_2$), 3.90 (3H, s, OCH$_3$), 6.95 (2H, m, H$_{Ar}$), 7.3 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.40 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.6 (1H, d, $J = 8.9$ Hz, H$_{Ar}$).

7-Methoxy-N-(piperidin-1-yl)furo[2,3-b]quinolin-4-amine dihydrochloride (8k·2HCl). As described for 8a·HCl, 5a and piperidine-1-ylamine (0.86 g, 8.6 mmol) gave 8k·2HCl (0.62 g, 78 %) as a white solid; mp 173–175 °C. IR (KBr): $\tilde{\nu}$ 3450, 2900, 2600, 1610, 1590, 1250, 1100, 850 cm$^{-1}$. Anal. calcd for C$_{17}$H$_{21}$Cl$_2$N$_3$O$_2$ (370.28): C, 55.14; H, 5.72; Cl, 19.15; N, 11.35. Found, C, 55.26; H, 5.63; Cl, 19.43; N, 11.38.

Free base 8k: $^1$H NMR (90 MHz, CDCl$_3$): $\delta$ 1.8 (6H, m), 2.40 (4H, m), 3.90 (3H, s, OCH$_3$), 6.9 (1H, d, $J = 2.45$ Hz, H$_{Ar}$), 7.00 (1H, dd, $J = 2.45$, 8.9 Hz, H$_{Ar}$), 7.3 (1H, d, $J = 2.45$ Hz, H$_{Ar}$), 7.42 (1H, d, $J = 2.45$ Hz, H$_{Ar}$), 7.9 (1H, d, $J = 8.9$ Hz, H$_{Ar}$).

4,7-Dimethoxy-2,3-dihydrofuro[2,3-b]quinoline (9a). To the solution of 6a (0.4 g, 1.75 mmol) in methanol (15 mL) was added Pd/C (10%, 0.08 g). The reaction mixture was hydrogenated at 25 psi for 5 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The crude product was passed through a silica gel column with 2–5% acetonitrile in chloroform as eluent. Recrystallization from ethyl acetate/petroleum ether furnished the pure product 9a (0.42 g, 60%) as a white solid; mp 145–146 °C. $^1$H NMR (90 MHz, CDCl$_3$/DMSO-$d_6$): $\delta$ 3.62-3.7 (2H, t, $J = 8.4$ Hz, CH$_2$), 3.8 (6H, 2s, 2 OCH$_3$), 4.2 (2H, t, $J = 8.4$ Hz, CH$_2$), 6.8–6.9 (1H, dd, $J = 2.48$, 8.9 Hz, H$_{Ar}$), 7.15 (1H, d, $J = 8.9$ Hz, H$_{Ar}$), 7.9 (1H, d, $J = 8.9$ Hz, H$_{Ar}$). IR (KBr): $\tilde{\nu}$ 3100, 2300, 1620, 1560, 1400, 1230, 1010, 980 cm$^{-1}$. Anal. calcd for C$_{13}$H$_{13}$NO$_3$ (231.25): C, 67.52; H,5.67; N, 6.06. Found: C, 67.55; H, 5.76; N, 6.21.
4-Ethoxy-7-methoxy-2,3-dihydrofuro[2,3-b]quinoline (9b). To the solution of 6b (0.14 g, 0.58 mmol) in methanol (15 mL) was added Pd/C (10%, 0.07 g). The reaction mixture was hydrogenated at 25 psi for 1 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The crude product was passed through a silica gel column with 4% acetonitrile in chloroform as eluent. Recrystallization from ethyl acetate/petroleum ether furnished the pure product 9b (0.13 g, 80%) as a pale yellow solid; mp 147–148 °C. 1H NMR (90 MHz, CDCl3): δ 1.50 (3H, t, J = 7.4 Hz, OCH2CH3), 3.50 (2H, t, J = 7.5 Hz, CH2), 3.62-3.70 (6H, 2s, 2 x OCH3), 4.56 (2H, t, J = 7.5 Hz, CH2), 4.40 (2H, q, J = 7.4 Hz, OCH2CH3), 6.90 (1H, m, HAr), 7.82-8.00 (2H, m, HAr). IR (KBr): ν ~ 3000, 1620, 1500, 1400, 1240, 1130, 1210, 1010, 950 cm⁻¹. Anal. calcd for C14H15NO3 (245.28): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.39; H, 6.03; N, 5.63.

7-Methoxy-4-(4-phenylpiperidin-1-yl)-2,3-dihydrofuro[2,3-b]quinoline dihydrochloride (10c·2HCl). To the solution of 8c·2HCl.H2O (0.65 g, 1.5 mmol) in methanol (50 mL) was added Pd/C (10%, 0.2 g). The reaction mixture was hydrogenated at 25 psi for 2 h. The catalyst was filtered off, washed with 50% chloroform in methanol (25 mL). The filtrate was basified with 2% NaHCO3 (50 mL) and extracted with chloroform (2 x 25 mL). The organic layer was separated, washed with water (2 x 25 mL), dried over anhydrous Na2SO4 and concentrated to give a yellow residue. The crude product was passed through a silica gel column with 4% acetonitrile in chloroform as eluent to yield the free base 10c. 1H NMR (90 MHz, CDCl3): δ 1.8–2.18 (4H, m, 2 CH2), 2.5–2.9 (1H, m, CH), 3.0–3.5 (6H, m, 3 CH2), 3.8 (3H, s, OCH3), 4.56 (2H, t, J = 8.13 Hz, CH2), 6.9 (1H, dd, J = 2.5, 8.89 Hz, HAr), 7.18 (1H, d, J = 8.89 Hz, HAr), 7.3 (5H, m, HAr), 7.9 (1H, d, J = 2.5 Hz, HAr).

To the solution of 10c in dry ether (10 mL) was added 5% HCl in ether (5 mL). After stirring at room temperature for 30 min the mixture was concentrated to give a yellow residue, which was recrystallized from acetone/petroleum ether to yield 10c·2HCl. (0.47 g, 75%) as a white solid; mp 267–268 °C. IR (KBr): ν ~ 3500, 2950, 1610, 1590, 1420, 1220, 1090, 1020, 950 cm⁻¹. Anal. calcd for C23H26Cl2N2O2 (433.38): C, 63.74; H, 6.05; Cl, 16.36; N, 6.46. Found: C, 63.59; H, 5.93; Cl, 16.21; N, 6.66.

7-Methoxy-2,3-dihydrofuro[2,3-b]quinoline (11). To the solution of 2a (0.37 g, 1.38 mmol) in dimethylformamide/methanol (10/10 mL) was added sodium acetate (2.0 g, 24 mmol) and Pd/C (10%, 0.14 g). The reaction mixture was hydrogenated at 30 psi for 30 min. The catalyst was filtered off and washed with methanol (10 mL). The filtrate was concentrated in vacuo. The residue was dissolved in chloroform (50 mL) and the extract was washed with water (2 x 50 mL). The CHCl3 layer was separated, dried over anhydrous Na2SO4 and concentrated in vacuo. The crude product was passed through a silica gel column with 2% acetonitrile in chloroform as eluent. Recrystallization from ethyl acetate/petroleum ether furnished the pure product 11 (0.237 g, 86.5%) as a white solid; mp 130–131 °C. 1H NMR (90 MHz, CDCl3): δ 3.30 (2H, t, J = 8.13 Hz, CH2), 3.82 (3H, s, OCH3), 4.60 (2H, t, J = 8.13 Hz, CH2), 6.82–7.00 (1H, dd, J = 2.41, 8.9 Hz, HAr), 7.18 (1H, d, J = 2.41 Hz, HAr), 7.50 (1H, d, J = 8.9 Hz, HAr). IR
(KBr): $\tilde{\nu}$ 3400, 3100, 1610, 1500, 1400, 1240, 1020, 940 cm$^{-1}$. Anal. calcd for C$_{12}$H$_{11}$NO$_2$ (201.22): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.89; H, 5.42; N, 6.69.

4,7-Dimethoxyfuro[2,3-b]quinolin-3(2H)-one (12). The solution of 3a (1.0 g, 4 mmol) in dry methanol (25 mL) was heated at reflux for 30 h. The solvent was concentrated in vacuo, and the crude compound was recrystallized from ethyl acetate/petroleum ether to furnish the pure product 12 (0.723 g, 73.5%) as a white solid; mp 208–209 °C. $^1$H NMR (90 MHz, CDCl$_3$/DMSO-d$_6$): $\delta$ 3.98 (3H, s, OCH$_3$), 4.60 (3H, s, OCH$_3$), 4.70 (3H, s, CH$_2$), 6.90–7.05 (1H, dd, $J = 2.52, 8.91$ Hz, H$_{Ar}$), 7.10 (1H, d, $J = 8.91$ Hz, H$_{Ar}$), 8.10 (1H, d, $J = 8.91$ Hz, H$_{Ar}$). IR (KBr): $\tilde{\nu}$ 2900, 2800, 1700, 1620, 1590, 1425, 1250, 850 cm$^{-1}$. Anal. calcd for C$_{13}$H$_{11}$NO$_4$ (245.23). C, 63.67; H, 4.52; N, 5.71. Found: C, 63.60; H, 4.9; N, 5.46.

7-Methoxy-N-methylfuro[2,3-b]quinolin-4-amine hydrochloride hydrate (15aa·HCl·H$_2$O)

To the solution of 3a (1.0 g, 4 mmol) in dichloromethane (20 mL) was added a saturated solution of methylamine (0.78 g, 25 mmol) in toluene (10 mL). The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was triturated with ethyl acetate/petroleum ether to furnish 13aa.

To the solution of compound 13aa in methanol (15 mL) was added portion-wise NaBH$_4$ (0.17 g, 4.5 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, and concentrated in vacuo. Addition of water (50 mL) was followed by extraction with chloroform (2 x 25 mL). The chloroform layer was separated, dried over Na$_2$SO$_4$ and concentrated in vacuo. The residual solid was triturated with ethyl acetate/petroleum ether to furnish 14aa.

A mixture of 14aa and anhydrous KHSO$_4$ (2.48 g, 18.25 mmol) in 1,4-dioxane (25 mL) was stirred at 110 °C for 3 h, filtered, and the filtrate was concentrated. The solid residue was taken up in chloroform (50 mL), the solution was washed with aq. NaOH (10%, 50 mL) followed by water (50 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was passed through a silica gel column with 2% methanol in chloroform as eluent to yield the free base 15aa. $^1$H NMR (90 MHz, CDCl$_3$): $\delta$ 3.38 (3H, s, NCH$_3$), 3.86 (3H, s, OCH$_3$), 6.76 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.00 (1H, dd, $J = 2.5, 8.9$ Hz, H$_{Ar}$), 7.22 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.40 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.90 (1H, d, $J = 8.9$ Hz, H$_{Ar}$). IR (KBr): $\tilde{\nu}$ 3350, 2300, 1600, 1500, 1300, 1000, 840 cm$^{-1}$. Anal. calcd for C$_{13}$H$_{15}$ClN$_2$O$_3$ (282.73): C, 55.23; H, 5.35; Cl, 12.54; N, 9.91. Found, C, 55.40; H, 5.32; Cl, 12.43; N, 10.08.

7-Methoxy-N,N-dimethylfuro[2,3-b]quinolin-4-amine hydrochloride (15ab·HCl).

As described for 15aa·HCl, 3a and dimethylamine (1.13 g, 25 mmol) in toluene (10 mL) gave 15ab·HCl (0.69 g, 61.80%) as a white solid; mp 218–219 °C.; IR (KBr): 3480, 2600, 2300, 1640, 1400, 1170, 1020, 860 cm$^{-1}$. Anal. calcd for C$_{14}$H$_{15}$ClN$_2$O$_2$ (278.74): C, 60.33; H, 5.42; Cl, 12.72; N, 10.05. Found: C, 60.43; H, 5.28; Cl, 12.45; N, 10.09.
Free base 15ab: $^1$H NMR (90 MHz, CDCl$_3$): $\delta$ 3.22 (6H, 2 s, 2 NCH$_3$), 3.96 (3H, s, OCH$_3$), 7.10 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.75 (1H, dd, $J = 2.5$, 8.9 Hz, H$_{Ar}$), 7.36 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.56 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 8.00 (1H, d, $J = 8.9$ Hz, H$_{Ar}$).

N,7-Dimethylfuro[2,3-b]quinolin-4-amine hydrochloride (15ba·HCl). As described for 15aa·HCl, 3a and methyamine (0.78 g, 25 mmol) in toluene (10 mL) gave 15ba·HCl (0.53 g, 50%) as a white solid; mp 258–260 °C. IR (KBr): $\tilde{\nu}$ 3400, 3200, 2350, 1650, 1600, 1310, 1050, 850 cm$^{-1}$. Anal. calcd for C$_{13}$H$_{13}$ClN$_2$O (248.71): C, 62.78; H, 5.27; Cl, 14.25; N, 11.26. Found, C, 62.49; H, 5.37; Cl, 14.35; N, 11.49.

Free base 15ba: $^1$H NMR (90 MHz, CDCl$_3$): $\delta$ 2.60 (3H, s, CH$_3$), 3.58 (6H, 2 s, 2 NCH$_3$), 7.20 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.40–7.60 (3H, m, H$_{Ar}$), 7.90 (1H, d, $J = 8.9$ Hz, H$_{Ar}$).

$N,N$-7-Trimethylfuro[2,3-b]quinolin-4-amine hydrochloride (15bb·HCl). As described for 15aa·HCl, 3a and dimethylamine (1.13 g, 25 mmol) in toluene (10 mL) gave 15bb·HCl (1.12 g, 49%) as a white solid; mp 208–209 °C. IR (KBr): $\tilde{\nu}$ 3500, 3100, 2500, 1650, 1600, 1410, 1300, 1100, 850 cm$^{-1}$. Anal. calcd for C$_{14}$H$_{15}$ClN$_2$O (262.74): C, 64.00; H, 5.75; Cl, 13.49; N, 10.66. Found: C, 63.86; H, 5.78; Cl, 13.60; N, 10.52.

Free base 15bb: $^1$H NMR (90 MHz, CDCl$_3$): $\delta$ 2.60 (3H, s, CH$_3$), 3.60 (6H, 2 s, 2 NCH$_3$), 7.18 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.20 (1H, m, H$_{Ar}$), 7.60 (2H, m, H$_{Ar}$), 8.10 (1H, d, $J = 8.9$ Hz, H$_{Ar}$).

7-(Benzyloxy)-$N$-methylfuro[2,3-b]quinolin-4-amine hydrochloride (15ca·HCl). As described for 15aa·HCl, 3a and methyamine (0.78 g, 25 mmol) in toluene (10 mL) gave 15ca·HCl (0.59 g, 57%) as a white solid; mp 234–236 °C. IR (KBr): $\tilde{\nu}$ 3350, 2800, 2350, 1650, 1610, 1250, 1050, 850 cm$^{-1}$. Anal. calcd for C$_{19}$H$_{17}$ClN$_2$O$_2$ (340.08): C, 66.96; H, 5.03; Cl, 10.40; N, 8.22. Found: C, 66.75; H, 5.04; Cl, 10.28; N, 8.38.

Free base 15ca: $^1$H NMR (90 MHz, CDCl$_3$): $\delta$ 3.45 (3H, s, NCH$_3$), 5.15 (2H, s, OCH$_2$Ph), 7.00–7.50 (9H, m, H$_{Ar}$), 8.00 (1H, d, $J = 8.9$ Hz, H$_{Ar}$).

7-(Benzyloxy)-$N,N$-dimethylfuro[2,3-b]quinolin-4-amine hydrochloride (15cb·HCl). As described for 15aa·HCl, 3a and dimethylamine (0.78 g, 25 mmol) in toluene (10 mL) gave 15cb·HCl (0.65 g, 60%) as a white solid; mp 190–192 °C. IR (KBr): $\tilde{\nu}$ 3200, 2350, 1650, 1610, 1250, 1050, 850 cm$^{-1}$. Anal. calcd for C$_{20}$H$_{19}$ClN$_2$O$_2$ (354.83): C, 67.70; H, 5.40; Cl, 9.99; N, 7.89. Found: C, 67.47; H, 5.46; Cl, 10.28; N, 7.54.

Free base 15cb: $^1$H NMR (90 MHz, CDCl$_3$): $\delta$ 3.80 (6H, 2 s, 2 NCH$_3$), 5.20 (2H, s, OCH$_3$Ph), 7.20–7.50 (9H, m, H$_{Ar}$), 8.00 (1H, d, $J = 8.9$ Hz, H$_{Ar}$).

6,7-Dimethoxy-$N$-methylfuro[2,3-b]quinolin-4-amine hydrochloride hydrate (15da·HCl·H$_2$O). As described for 15aa·HCl, 3a and methyamine (0.78 g, 25 mmol) in toluene (10 mL) gave 15da·HCl (0.67 g, 60%) as a white solid; mp 239–241 °C. IR (KBr): $\tilde{\nu}$ 3500, 3200, 2400, 1640, 1600, 1500, 1260, 1020, 850 cm$^{-1}$. Anal. calcd for C$_{14}$H$_{17}$ClN$_2$O$_3$ (312.75): C, 53.77; H, 5.48; Cl, 11.34; N, 8.96. Found: C, 53.68; H, 5.45; Cl, 11.46; N, 8.77.

Free base 15da: $^1$H NMR (90 MHz, CDCl$_3$): $\delta$ 3.50 (3H, s, NCH$_3$), 4.00 (6H, 2 s, 2 OCH$_3$), 7.20, (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.42 (1H, s, H$_{Ar}$), 7.58 (1H, d, $J = 2.5$ Hz, H$_{Ar}$), 7.70 (1H, s, H$_{Ar}$).

4-(Methylamino)furo[2,3-b]quinolin-7-ol hydrochloride hemihydrate (18ca·HCl·0.5 H$_2$O). To the solution of 3c (1.0 g, 3 mmol) in dichloromethane (20 mL) was added a saturated solution
of methylamine (0.47 g, 15 mmol) in toluene (10 mL). The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residual solid was triturated with ethyl acetate/petroleum ether to furnish 16ca.

To the solution of 16ca (0.37 g, 1.38 mmol) in methanol (15 mL) was added Pd/C (10%, 0.05 g). The reaction mixture was hydrogenated at 50 psi for 3 h. The catalyst was filtered off and washed with 50% chloroform in methanol (25 mL) because the product was found to be adsorbed on the catalyst; the filtrate was concentrated in vacuo. The residue was dissolved in chloroform (50 mL), and the solution was washed with water (2 x 50 mL). The chloroform layer was separated, dried over anhydrous Na2SO4 and concentrated in vacuo to furnish 17ca.

To the solution of 17ca in MeOH (15 mL) was added portion wise NaBH4 (0.17 g, 4.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The solvent was concentrated in vacuo. Addition of water (50 mL) was followed by extraction with chloroform (2 x 25 mL). The chloroform layer was separated, dried over Na2SO4 and concentrated in vacuo. The residual solid was dissolved in 1,4-dioxane (25 mL), and to the solution was added anhydrous KHSO4 (2.48 g, 18.25 mmol). The reaction mixture was stirred at 110 °C for 3 h, filtered and the filtrate was concentrated. The solid residue was taken up in chloroform (50 mL), the solution was washed with aq NaOH (10% 50 mL) and water (50 mL). The organic layer was separated, dried over Na2SO4 and concentrated in vacuo. The solid residue was recrystallized from acetone/ petroleum ether to afford the free base 18ca. 1H NMR (90 MHz, CDCl3): δ 2.56 (3H, s, CH3), 7.10 (1H, d, J = 2.5 Hz, HAr), 7.12–7.28 (2H, m, HAr), 7.50 (1H, d, J = 2.5 Hz, HAr), 7.85 (1H, d, J = 8.9 Hz, HAr).

To the solution of the pure base 18ca in dry ether (10 mL) was added 5% HCl in ether (5 mL). After stirring at room temperature for 30 min the mixture was concentrated, and the yellow residue was recrystallized from methanol/ether to yield 18ca·HCl·0.5H2O (0.45 g, 68%) as a white solid; mp 242–244 °C. IR (KBr): ν̃ 3350, 2500, 1620, 1550, 1390, 1250, 980, 840 cm–1. Anal. calcd for C12H12ClN2O2·(259.69): C, 55.50; H, 4.66; Cl, 13.65; N, 10.79. Found: C, 55.67; H, 4.72; Cl, 13.42; N, 10.93.

4-(Dimethylamino)furo[2,3-b]quinolin-7-ol hydrochloride hydrate (18cb·HCl·H2O). As described for 18ca·HCl·0.5H2O, dimethylamine (0.68 g, 15 mmol) in toluene (10 mL) and 3c (1.0 g, 3 mmol) gave 18cb·HCl·H2O (0.62 g, 71%) as a white solid; mp 254–256 °C. IR (KBr): ν̃ 2900, 2350, 1620, 1580, 1400, 1220, 1080, 850 cm–1. Anal. calcd for C13H15ClN2O2·(282.73): C, 55.23; H, 5.35; Cl, 12.54; N, 9.91. Found: C, 55.39; H, 5.48; Cl, 12.31; N, 10.08.

Free base 18cb: 1H NMR (90 MHz, CDCl3): δ 2.60 (6H, 2 s, 2 CH3), 7.00 (1H, d, J = 2.5 Hz, HAr), 7.05–7.15 (2H, m, HAr), 7.50 (1H, d, J = 2.5 Hz, HAr), 8.00 (1H, d, J = 8.9 Hz, HAr).

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References