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 *Dutaillyea 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.

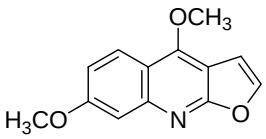


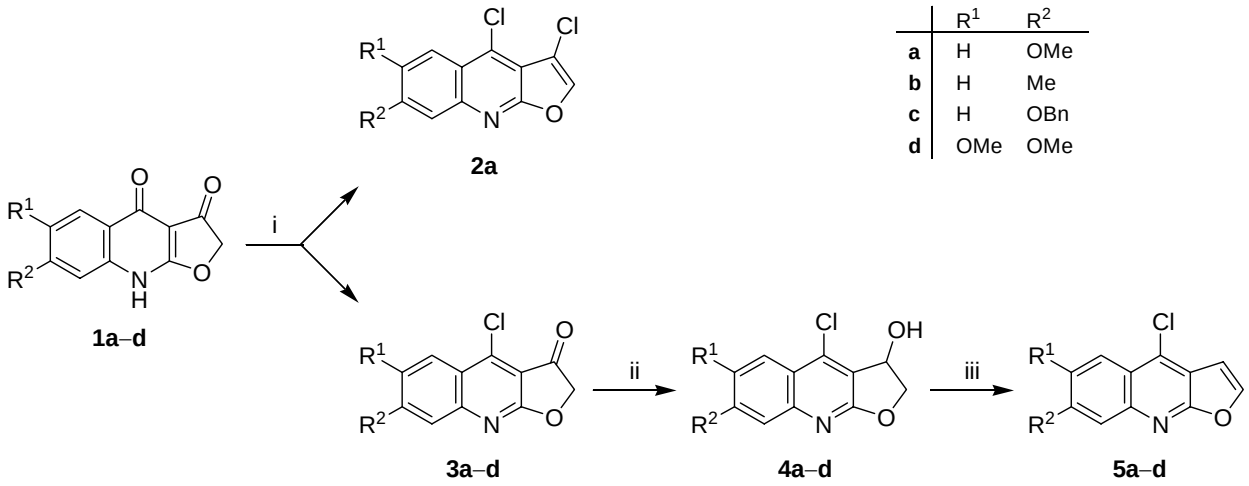
Figure 1. Evolitrine **6a**.

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.[11–13] This paper describes the isolation of Evolitrine from twigs extracts of Rutaceae plant *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 *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. ^{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.

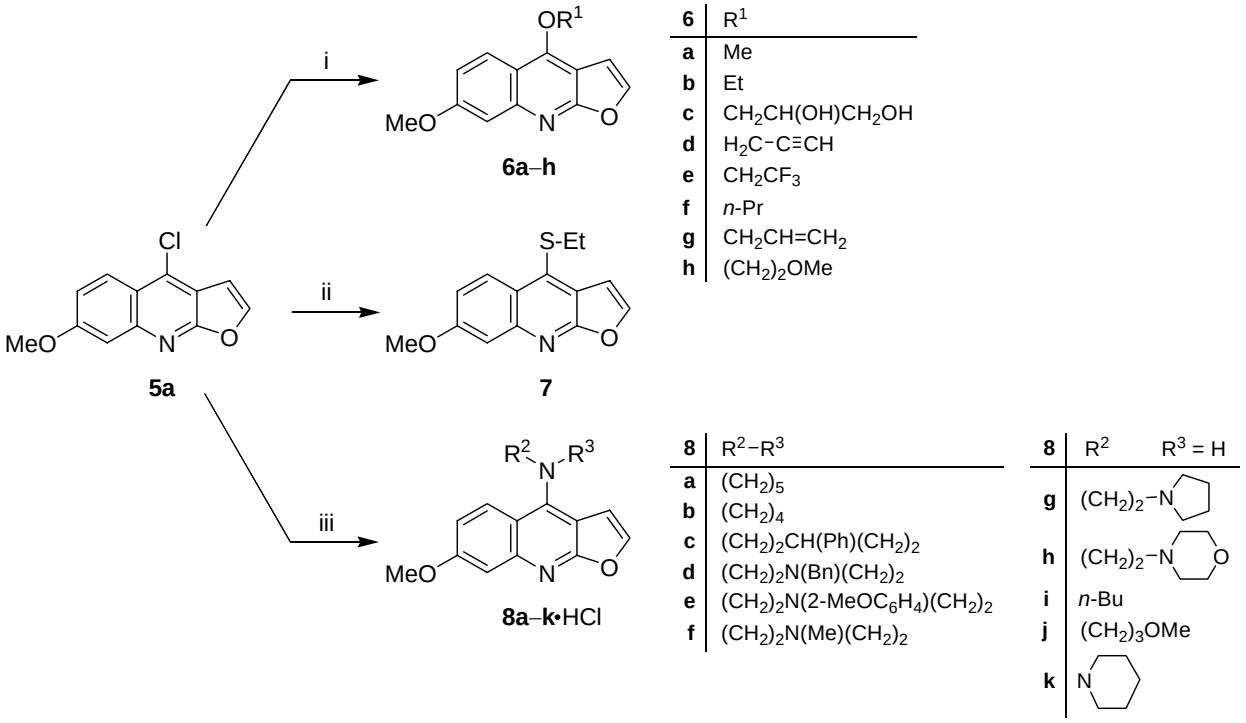
The synthesis of furo[2,3-*b*]quinoline-3,4(2*H*,9*H*)-diones **1a**–**d** has been described in the literature: Condensation of appropriately substituted anilines with diethyl malonate, followed by treatment with NaH, reaction of the resulting sodium salt with chloroacetyl chloride and work-up with triethylamine in THF afforded the corresponding ethyl 2-anilino-4-oxo-4,5-dihydrofuran-3-carboxylates,[14–16] which upon thermolysis at 240 °C for 20 min yielded furo[2,3-*b*]quinoline-3,4(2*H*,9*H*)-diones **1a**–**d**.[17,18] By conventional method, diketo compounds **1a–d** were treated with phosphorus oxytrichloride[17] to give 4-chlorofuro[2,3-*b*]quinolin-3(2*H*)-ones **3a–d** in moderate yields; the formation of **3a** was accompanied by some 3,4-dichlorofuro[2,3-*b*]quinoline **2a** (Scheme 1).[19] The conversion of quinolindiones **1a–d** into chloro compound **3a–d** was erratic due to solubility problems. From the reaction of **1a** with trifluoroacetic acid, pyridine, and phosphorus oxytrichloride **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 oxytrichloride 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**.[3,7] These alcohols were dehydrated with potassium hydrogen sulfate and dioxane to provide 4-chlorofuro[2,3-*b*]quinolines as the main intermediates **5a–d**.[15,20]



	R^1	R^2
a	H	OMe
b	H	Me
c	H	OBn
d	OMe	OMe

Scheme 1. Reagents and conditions: i. $POCl_3$, CH_2Cl_2, reflux, 3h; or CF_3CO_2H, CH_2Cl_2, reflux, 3h, pyridine, $POCl_3$, reflux, 2h; or Aliquat 336, $POCl_3$, CH_2Cl_2, r.t., 48 h. ii. $NaBH_4$, MeOH, 0 °C; r.t., 1 h; 2 N HCl. iii. $KHSO_4$, 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.



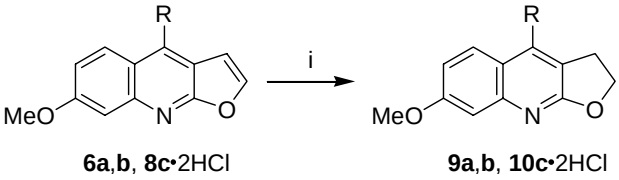
6	R^1
a	Me
b	Et
c	$CH_2CH(OH)CH_2OH$
d	$H_2C{-}C{\equiv}CH$
e	CH_2CF_3
f	*n*-Pr
g	$CH_2CH{=}CH_2$
h	$(CH_2)_2OMe$

8	$R^2{-}R^3$
a	$(CH_2)_5$
b	$(CH_2)_4$
c	$(CH_2)_2CH(Ph)(CH_2)_2$
d	$(CH_2)_2N(Bn)(CH_2)_2$
e	$(CH_2)_2N(2\text{-}MeOC_6H_4)(CH_2)_2$
f	$(CH_2)_2N(Me)(CH_2)_2$

8	R^2 R^3 = H
g	$(CH_2)_2$–N
h	$(CH_2)_2$–N O
i	*n*-Bu
j	$(CH_2)_3OMe$
k	N

Scheme 2. Reagents and conditions: i. R^1OH, Na, N_2, reflux, 3 h; or R^1OH, NaH, N_2, dioxane, DMSO, 90 °C; or R^1OH, K_2CO_3, acetone, r.t., 10 min. ii. EtSH, NaH, DMF. iii. R^2R^3NH, MeCN; HCl/Et_2O.

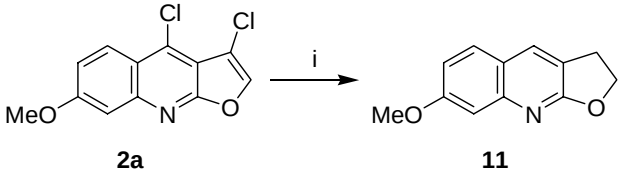
Hydrogenation of compounds **6a**,**b** and **8c**·2HCl with 10% Pd/C catalyst yielded products **9a**,**b** and **10c**·HCl, respectively (Scheme 3).[21] Hydrogenolysis of **2a** in the presence of 10% Pd/C and anhydrous sodium acetate gave product **11**[22] (Scheme 4). Treatment of compound **3a** with dry methanol gave product **12** (Scheme 5).



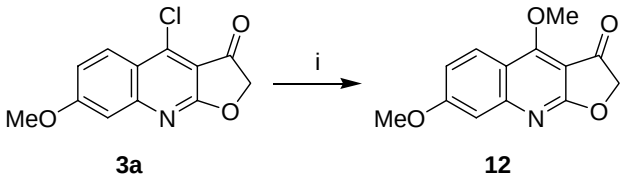
6, 9	R
a	OMe
b	OEt

8c, **10c** R = N Ph

Scheme 3. Reagents and conditions: i. MeOH, 10% Pd/C, H_2, 25 psi, 1–5h; for **10c**·2HCl: HCl/Et_2O.



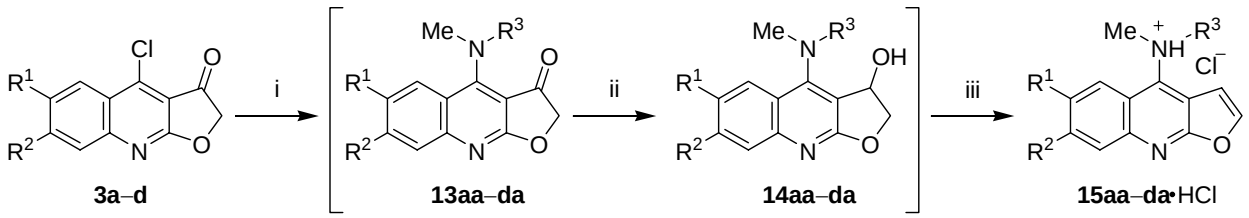
Scheme 4. Reagents and conditions: i. DMF/MeOH, NaOAc, 10% Pd/C, H_2, 30 psi, 30 min.



3a **12**

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.



3a–**d** **13aa**–**da** **14aa**–**da** **15aa**–**da**•HCl

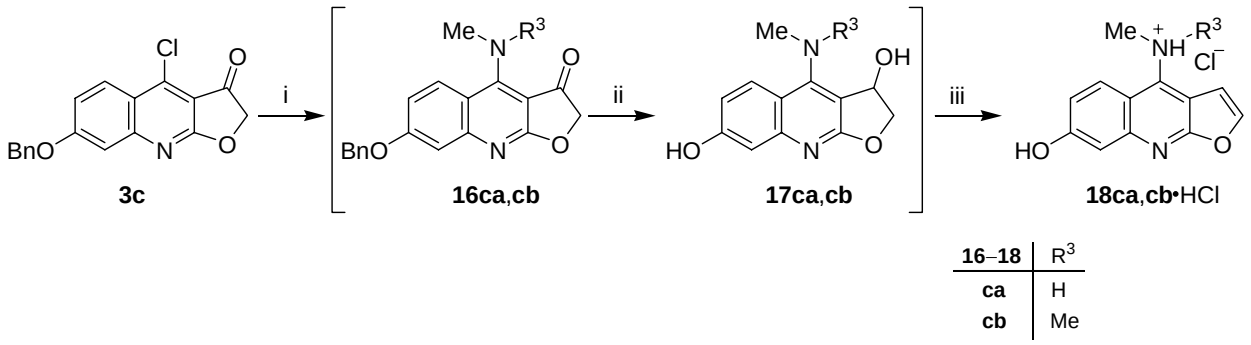
3	R^1	R^2
a	H	OMe
b	H	Me
c	H	OBn
d	OMe	OMe

13–**15**	R^1	R^2	R^3
aa	H	OMe	H
ab	H	OMe	Me
ba	H	Me	H
bb	H	Me	Me
ca	H	OBn	H
cb	H	OBn	Me
da	OMe	OMe	H

Scheme 6. Reagents and conditions: i. CH_2Cl_2, $MeNH_2$ or Me_2NH in toluene, r.t., 1 h; ii. $NaBH_4$, MeOH, 0 °C → r.t., 1 h. iii. $KHSO_4$, dioxane, 110 °C, 3 h; HCl/Et_2O.

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_2Cl_2, $MeNH_2$ or Me_2NH 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_2O.

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**

Treatment	Dose mg/kg p.o.	% Inhibition of carrageenan edema
Evolitrine **6a**	10	12
	20	57
	40	65
	60	78
Indomethacin	05	55

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, adrenaloctomised (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-ankenda* 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

Compd.	AI activity at 100 mg/kg [%]	Compd.	AI activity at 100 mg/kg [%]	Compd.	AI activity at 100 mg/kg [%]
2a	not active	**8b**·HCl	54	**10c**·HCl	16
4a	10	**8c**·2HCl	11	**11**	not active
5a	8	**8d**·2HCl	38	**12**	not active
6a	83	**8e**·2HCl	not active	**15aa**·HCl	44
6b	51	**8f**·2HCl	16	**15ab**·HCl	65
6c	24	**8g**·2HCl	04	**15ba**·HCl	16
6d	37	**8h**·HCl	not active	**15bb**·HCl	28
6e	24	**8i**·HCl	28	**15ca**·HCl	13
6f	33	**8j**·HCl	13	**15cb**·HCl	36
6g	52	**8k**·2HCl	25	**15da**·HCl	34
6h	60	**9a**	50	**18ca**·HCl	not active
8a·HCl	24	**9b**	36	**18cb**·HCl	not active

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(2*H*)-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_2SO_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

(1.88 g, 35%).

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 refluxed 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. ^{1}H NMR (90 MHz, $CDCl_3$, drop of TFA): δ 4.00 (3H, s, OCH_3), 7.22–7.40 (1H, dd, J = 2.4, 8.8 Hz, H_{Ar}), 7.56 (1H, d, J = 2.45 Hz, H_{Ar}), 7.78 (1H, s, H_{Ar}), 8.25 (1H, d, J = 8.8 Hz, H_{Ar}). IR. (KBr): $\tilde{\nu}$ 3150, 2900, 1610, 1560, 1420, 1250, 1130, 1000, 900 cm^{-1}. Anal. calcd for $C_{12}H_7Cl_2NO_2$ (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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.98 (3H, s, OCH_3), 4.76 (2H, s, CH_2), 7.0–7.23 (2H, m, H_{Ar}), 8.1 (1H, d, J = 8.78 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 2400, 1710, 1600, 1490, 1150 cm^{-1} Anal. calcd for $C_{12}H_8ClNO_3$ (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(2*H*)-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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.6 (3H, s, CH_3), 4.8 (2H, s), 7.21 (1H, d, J = 2.5 Hz, H_{Ar}), 7.3–7.42 (1H, dd, J = 2.5, 8.9 Hz, H_{Ar}), 8.18 (1H, d, J = 8.9 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 2350, 1700, 1620, 1520, 1300, 1200, 1050 cm^{-1}.

7-(Benzyloxy)-4-chlorofuro[2,3-*b*]quinolin-3(2*H*)-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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 4.8 (2H, s, CH_2), 4.99 (2H, s, CH_2), 7.20 (1H, d, J = 2.5 Hz, H_{Ar}), 7.3-7.6 (5H, m, H_{Ar}), 7.42 (1H, dd, J = 2.5, 8.9 Hz, H_{Ar}), 8.15 (1H, d, J = 8.9 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 2420, 1710, 1610, 1510, 1320, 1200, 1100, 900 cm^{-1}. Anal. calcd for $C_{18}H_{12}ClNO_3$ (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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 4.1 (6H, 2s, 2x OCH_3), 5.1 (2H, s), 7.6 (2H, 2s, H_{Ar}). IR (KBr): $\tilde{\nu}$ 1700, 1610, 1510, 1440, 1250, 1050 cm^{-1}. Anal. calcd for $C_{13}H_{10}ClNO_4$ (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 $NaBH_4$ (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 Na_2SO_4 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. ^{1}H NMR (90 MHz, $CDCl_3$, drop of TFA): δ 3.98 (3H, s, OCH_3), 5.10 (2H, m, CH_2), 5.80 (1H, m, CH), 7.20 (1H, d, J = 2.46 Hz, H_{Ar}), 7.20–7.40 (1H, dd, J = 2.46, 8.78 Hz, H_{Ar}), 8.15 (1H, d, J = 8.78 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 3150, 2900, 1620, 1500, 1410, 1310, 1220, 1020 cm^{-1}. Anal. calcd for $C_{12}H_{10}ClNO_3$ (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. ^{1}H NMR: δ 2.56 (3H, s, CH_3), 4.46 (2H, m, CH_2), 5.56 (1H, m, CH), 7.00–7.20 (2H, m, H_{Ar}), 7.70 (1H, d, J = 8.9 Hz, H_{Ar}); IR (KBr): $\tilde{\nu}$ 3300, 2400, 1700, 1600, 1420, 1240, 1100, 820 cm^{-1}.

7-Benzyloxy-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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 4.46 (2H, m, CH_2), 5.10 (2H, s, CH_2), 5.50 (1H, m, CH), 6.90–7.10 (1H, dd, J = 2.5, 8.9 Hz, H_{Ar}), 7.20 (1H, d, J = 2.5 Hz, H_{Ar}), 7.22–7.58 (5H, m, H_{Ar}), 7.80 (1H, d, J = 8.9 Hz, H_{Ar}). 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 addidion 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 Na_2SO_4 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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.98 (3H, s, OCH_3), 6.9 (1H, d, J = 2.35 Hz, H_{Ar}), 7.12–7.30 (1H, dd, J = 2.35, 8.89 Hz, H_{Ar}), 7.4 (1H, d, J = 2.35 Hz, H_{Ar}), 7.7 (1H, d, J = 2.35 Hz, H_{Ar}), 8.15 (1H, d, J = 8.89 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 3100, 1610, 1500, 1410, 1220, 1130, 1020, 900, 850 cm^{-1}. Anal. calcd for $C_{12}H_8ClNO_2$ (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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.6 (3H, s, CH_3), 6.85 (1H, d, J = 2.5 Hz, H_{Ar}), 7.20–7.40 (1H, dd, J = 2.5,8.9 Hz, H_{Ar}), 7.75 (1H, d, J = 2.5 Hz, H_{Ar}), 7.80 (1H, d, J = 2.5 Hz, H_{Ar}), 8.1 (1H, d, J = 8.9 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 2900, 2350, 1610, 1580, 1390, 1150, 900, 810 cm^{-1}. Anal. calcd for $C_{12}H_8ClNO$ (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-Benzyloxy-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, $CDCl_3$): δ 5.19 (2H, s, CH_2), 6.85 (1H, d, J = 2.5 Hz, H_{Ar}), 7.18–7.6 (7H, m, H_{Ar}), 7.67(1H, d, J = 2.5 Hz, H_{Ar}), 8.1 (d, 1H , J = 8.9 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 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-dimethoxy-furo[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): δ 4.05 (6H, 2s, 2 OCH_3), 6.90 (1H, d, J = 2.5 Hz, H_{Ar}), 7.38-7.43 (2H, 2s, H_{Ar}), 7.78 (1H, d, J = 2.5 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 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_2SO_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, $CDCl_3$): δ 3.98 (3H, s, OCH_3), 4.20 (3H, s, OCH_3), 6.95 (1H, d, J = 2.5 Hz, H_{Ar}), 7.05 (1H, dd, J = 2.52, 8.91 Hz, H_{Ar}), 7.22 (1H, d, J = 8.9 Hz, H_{Ar}), 7.50 (1H, d, J = 2.52 Hz, H_{Ar}), 8.10 (1H, d, J = 8.91 Hz, H_{Ar}). IR (KBr): 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_2SO_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, $CDCl_3$): δ 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, H_{Ar}), 7.1 (1H, dd, J = 2.51, 8.57 Hz, H_{Ar}), 7.3 (1H, d, J = 2.51 Hz, H_{Ar}), 7.56 (1H, d, J = 2.51 Hz, H_{Ar}), 8.15 (1H, d, J = 8.57 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 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-yloxy)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[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_2SO_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 togive **6c** (0.6 g, 49%) as a pale yellow solid; mp 174–175 °C. ^{1}H NMR: (90 MHz, $CDCl_3$/DMSO-d_6): δ 3.85 (2H, m, C$\underline{H}_2$OH), 3.98 (3H, s, OCH_3), 4.10–4.40 (1H, m, C$\underline{H}$OH), 4.75 (2H, d, J = 5.25 Hz, OCH_2), 7.1 (1H, dd, J = 2.5, 8.9 Hz, H_{Ar}), 7.6 (2H, m, H_{Ar}), 8.2 (1H, d, J = 8.9 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 3400 (br), 3100, 2900, 1690, 1590, 1420, 1350, 1220, 1090, 950 cm^{-1}. Anal. calcd for $C_{15}H_{15}NO_5$ (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-ynyloxy)furo[2,3-*b*]quinoline (6d). To the solution of propargyl alcohol (0.5 mL, 8.60 mmol) in dry acetone (20 mL) was added anhydrous K_2CO_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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.6 (1H, t, J = 2.51 Hz, ≡CH), 3.92 (3H, s, OCH_3), 5.2 (2H, d, J = 2.51 Hz, OCH_2), 7.00–7.18 (2H, m, H_{Ar}), 7.3 (1H, d, J = 2.47 Hz, H_{Ar}), 7.58 (1H, d, J = 2.47 Hz, H_{Ar}), 8.1 (1H, d, J = 8.79 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 3240, 3100, 2100, 1610, 1590, 1420, 1220, 1100, 1010, 910, 850 cm^{-1}. Anal. calcd for $C_{15}H_{11}NO_3$ (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-trifluroethanol (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_2SO_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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.96 (3H, s, OCH_3), 4.90 (2H, q, J = 8.4 Hz, OCH_2CF_3), 6.82 (1H, d, J = 2.75 Hz, H_{Ar}), 7.15 (1H, dd, J = 2.75, 8.75 Hz, H_{Ar}), 7.35 (1H, d, J = 2.5 Hz, H_{Ar}), 7.60 (1H, d, J = 2.75 Hz, H_{Ar}), 8.10 (1H, d, J = 8.75 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 3100, 2950, 1610, 1590, 1410, 1280, 1150, 1020, 960, 825 cm^{-1}.

Anal. calcd for $C_{14}H_{10}F_3NO_3$ (297.23): C, 56.57; H, 3.39; F, 19.18; N, 4.71. Found: C, 56.29; H, 3.48; F, 19.28; N, 4.41.

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_2SO_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, $OCH_2C\underline{H}_2CH_3$), 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): $\tilde{\nu}$ 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): $\tilde{\nu}$ 3100, 2900, 1610, 1580, 1410, 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 sodiumhydride (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 hydride 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_3OCH_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): $\tilde{\nu}$ 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 ethylmercaptan (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 Na_2SO_4 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. ^{1}H NMR (90 MHz, DMSO-d_6): δ 1.10 (3H, t, J = 7.5 Hz, SCH_2CH_3), 3.10 (2H, q, J = 7.5 Hz, SCH_2), 3.92 (3H, s, OCH_3), 7.20 (1H, d, J = 2.54 Hz, H_{Ar}), 7.3-7.4 (2H, m, H_{Ar}), 8.18 (1H, d, J = 2.54 Hz, H_{Ar}), 8.35 (1H, d, J = 8.91 Hz, H_{Ar}). IR (KBr): $\tilde{\nu}$ 3400, 3100, 1610, 1410, 1220, 1000, 900 cm^{-1}. Anal. calcd for $C_{14}H_{13}NO_2S$ (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**. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.80 (6H, m), 3.40 (4H, m), 3.90 (3H, s, OCH_3), 6.90 (1H, d, J = 2.45 Hz, H_{Ar}), 6.92-7.10 (1H, dd, J = 2.45, 8.9 Hz, H_{Ar}), 7.28 (1H, d, J = 2.45 Hz, H_{Ar}), 7.50 (1H, d, J = 2.45 Hz, H_{Ar}), 7.90 (1H, d, J = 8.9 Hz, H_{Ar}).

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): $\tilde{\nu}$ 3100, 2900, 2810, 1600, 1420, 1230, 1050, 950, 850 cm^{-1}. Anal. calcd for $C_{17}H_{19}ClN_2O_2$ (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 (0.61g, 8.6 mmol) were converted into **8b**·HCl (0.40g, 61%) as a white solid; mp 197–199 °C. IR (KBr): $\tilde{\nu}$ 3450, 1610, 1500, 1220, 1000, 850 cm^{-1}. Anal. calcd for $C_{16}H_{17}ClN_2O_2$ (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**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.90–2.20 (4H, m), 3.8 (3H, s, OCH_3), 3.80–4.00 (4H, m), 6.80–6.95 (1H, dd, J = 2.5, 8.9 Hz, H_{Ar}), 7.00 (1H, d, J = 2.5 Hz, H_{Ar}), 7.25 (1H, d, J = 2.5 Hz, H_{Ar}), 7.38 (1H, d, J = 2.5 Hz, H_{Ar}), 8.10 (1H, d, J = 8.9 Hz, H_{Ar}).

7-Methoxy-4-(4-phenylpiperidin-1-yl)furo[2,3-*b*]quinoline dihydrochloride hydrate (8c·2HCl·H$_2$O). As described for **8a**·HCl, **5a** and 4-phenylpiperidine (1.39 g, 8.6 mmol) were converted into **8c**·2HCl·H_2O (0.45 g, 48%) as a white solid; mp 193–194 °C. IR (KBr): $\tilde{\nu}$ 3400,

3100, 2900, 2500, 1620, 1580, 1450, 1250, 1020, 850 cm^{-1}. Anal. calcd for $C_{22}H_{26}Cl_2N_2O_3$ (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, $CDCl_3$): δ 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 $C_{23}H_{25}Cl_2N_3O_2$·(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, $CDCl_3$): δ 2.7–2.9 (4H, m), 3.65 (2H, s, CH_2Ph), 3.6–3.8 (4H, m), 3.98 (3H, s, OCH_3), 6.96 (1H, d, J = 2.35 Hz, H_{Ar}), 7.12 (1H, dd, J = 2.35, 8.9 Hz, H_{Ar}), 7.25–7.41 (6H, m, H_{Ar}), 7.58 (1H, d, J = 2.35 Hz, H_{Ar}), 7.95 (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_2O). As described for **8a**·HCl, **5a** and 4-(2-methoxyphenyl)-1,4-piperazine (1.62 g, 8.6 mmol) gave **8e**·2HCl·H_2O (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 $C_{23}H_{27}Cl_2N_3O_4$ (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, $CDCl_3$): δ 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 $C_{17}H_{19}Cl_2N_3O_2$ (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, $CDCl_3$): δ 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_2O). As described for **8a**·HCl, **5a** and 1-(2-aminoethyl)pyrrolidine (0.98 g, 8.6 mmol) gave **8g**·2HCl·H_2O (0.30 g, 35%) as a white solid; mp 205–207 °C. IR (KBr): $\tilde{\nu}$ 3300, 2950, 2550, 1650, 1590, 1300, 1150, 1000, 850 cm^{-1}. Anal. calcd for $C_{18}H_{25}Cl_2N_3O_3$ (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_2O): δ 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, 1250, 1020, 850 cm^{-1}. Anal. calcd for $C_{18}H_{22}ClN_3O_3$ (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, $CDCl_3$): δ 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, 1020, 880 cm^{-1}. Anal. calcd for $C_{16}H_{19}ClN_2O_2$ (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, $CDCl_3$): δ 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, 8.88 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_2O). As described for **8a**·HCl, **5a** and 3-methoxypropylamine (0.77 g, 8.6 mmol) gave **8j**·HCl·H_2O (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 $C_{16}H_{21}ClN_2O_4$ (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, $CDCl_3$): δ 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, 1420, 1250, 1100, 850 cm^{-1}. Anal. calcd for $C_{17}H_{21}Cl_2N_3O_2$ (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, $CDCl_3$): δ 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): δ 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. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.50 (3H, t, *J* = 7.4 Hz, OCH_2CH_3), 3.50 (2H, t, *J* = 7.5 Hz, CH_2), 3.62-3.70 (6H, 2s, 2 x OCH_3), 4.56 (2H, t, *J* = 7.5 Hz, CH_2), 4.40 (2H, q, *J* = 7.4 Hz, $OC\underline{H}_2CH_3$), 6.90 (1H, m, H_{Ar}), 7.82-8.00 (2H, m, H_{Ar}). IR (KBr): $\tilde{\nu}$ 3000, 1620, 1500, 1400, 1240, 1130, 1210, 1010, 950 cm^{-1}. Anal. calcd for $C_{14}H_{15}NO_3$ (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.H_2O (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 % $NaHCO_3$ (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 Na_2SO_4 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**. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.8–2.18 (4H, m, 2 CH_2), 2.5–2.9 (1H, m, CH), 3.0–3.5 (6H, m, 3 CH_2), 3.8 (3H, s, OCH_3), 4.56 (2H, t, *J* = 8.13 Hz, CH_2), 6.9 (1H, dd, *J* = 2.5, 8.89 Hz, H_{Ar}), 7.18 (1H, d, *J* = 8.89 Hz, H_{Ar}), 7.3 (5H, m, H_{Ar}), 7.9 (1H, d, *J* = 2.5 Hz, H_{Ar}).

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 recrystalized from acetone/petroleum ether to yield **10c**·2HCl. (0.47 g, 75%) as a white solid; mp 267–268 °C. IR (KBr): $\tilde{\nu}$ 3500, 2950, 1610, 1590, 1420, 1220, 1090, 1020, 950 cm^{-1}. Anal. calcd for $C_{23}H_{26}Cl_2N_2O_2$ (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 $CHCl_3$ layer was separated, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was passed through a silica gel column with 2% acetonitrile in chloroform as eluent. Recrystallizion from ethyl acetate/petroleum ether furnished the pure product **11** (0.237 g, 86.5%) as a white solid; mp 130–131 °C. ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.30 (2H, t, *J* = 8.13 Hz, CH_2), 3.82 (3H, s, OCH_3), 4.60 (2H, t, *J* = 8.13 Hz, CH_2), 6.82–7.00 (1H, dd, *J* = 2.41, 8.9 Hz, H_{Ar}), 7.18 (1H, d, *J* = 2.41 Hz, H_{Ar}), 7.50 (1H, d, *J* = 8.9 Hz, H_{Ar}). 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(2*H*)-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): δ 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_2O)
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_2SO_4 and concentrated in vaccuo. 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_2SO_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, $CDCl_3$): δ 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}).

To the solution of the free base **15aa** in dry ether (10 mL) was added 5% HCl in ether (5 mL); the mixture was stirred at room temperature for 30 min and concentrated to give a yellow residue, which was recrystallized from methanol/ether to yield **15aa**·HCl·H_2O (0.62 g, 54.9%) as a white solid; mp 234–236 °C. IR (KBr): $\tilde{\nu}$ 3350, 2300, 1600, 1500, 1300, 1000, 840 cm^{-1}. Anal. calcd for $C_{13}H_{15}ClN_2O_3$ (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 $C_{14}H_{15}ClN_2O_2$ (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, $CDCl_3$): δ 3.22 (6H, 2 s, 2 NCH_3), 3.96 (3H, s, OCH_3), 7.10 (1H, d, J = 2.5 Hz, H_{Ar}), 7.15 (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 methylamine (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 $C_{13}H_{13}ClN_2O$ (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, $CDCl_3$): δ 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 $C_{14}H_{15}ClN_2O$ (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, $CDCl_3$): δ 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 methylamine (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 $C_{19}H_{17}ClN_2O_2$ (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, $CDCl_3$): δ 3.45 (3H, s, NCH_3), 5.15 (2H, s, OCH_2Ph), 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 (1.13 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 $C_{20}H_{19}ClN_2O_2$ (354.83): C, 67.70; H, 5.40; Cl, 9.99; N, 7.89. Found: C, 67.47; H, 5.46; Cl, 10.06; N, 7.54.

Free base **15cb**: ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.80 (6H, 2 s, 2 NCH_3), 5.20 (2H, s, OCH_2Ph), 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_2O). As described for **15aa**·HCl, **3a** and methylamine (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): $\tilde{\nu}$ 3450, 3200, 2400, 1640, 1600, 1500, 1260, 1020, 850 cm^{-1}. Anal. calcd for $C_{14}H_{17}ClN_2O_3$·(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, $CDCl_3$): δ 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_2O). 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 Na_2SO_4 and concentrated in vacuo to furnish **17ca**.

To the solution of **17ca** in MeOH (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 1h. 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 Na_2SO_4 and concentrated in vaccuo. The residual solid was dissolved in 1,4-dioxane (25 mL), and to the solution was added anhydrous $KHSO_4$ (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 Na_2SO_4 and concentrated in vacuo. The solid residue was recrystallized from acetone/ petroleum ether to afford the free base **18ca**. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.56 (3H, s, CH_3), 7.10 (1H, d, J = 2.5 Hz, H_{Ar}), 7.12–7.28 (2H, m, H_{Ar}), 7.50 (1H, d, J = 2.5 Hz, H_{Ar}), 7.85 (1H, d, J = 8.9 Hz, H_{Ar}).

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·0.5H_2O (0.45 g, 68%) as a white solid; mp 242–244 °C. IR (KBr): $\tilde{\nu}$ 3350, 2500, 1620, 1550, 1390, 1250, 980, 840 cm^{-1}. Anal. calcd for $C_{12}H_{12}ClN_2O_{2.5}$·(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·H_2O). As described for **18ca**·HCl·0.5H_2O, dimethylamine (0.68 g, 15 mmol) in toluene (10 mL) and **3c** (1.0 g, 3 mmol) gave **18cb**·HCl·H_2O (0.62 g, 71%) as a white solid; mp 254–256 °C. IR (KBr): $\tilde{\nu}$ 2900, 2350, 1620, 1580, 1400, 1220, 1080, 850 cm^{-1}. Anal. calcd for $C_{13}H_{15}ClN_2O_2$·(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**: ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.60 (6H, 2 s, 2 CH_3), 7.00 (1H, d, J = 2.5 Hz, H_{Ar}), 7.05–7.15 (2H, m, H_{Ar}), 7.50 (1H, d, J = 2.5 Hz, H_{Ar}), 8.00 (1H, d, J = 8.9 Hz, H_{Ar}).

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