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Full Paper

Friedel–Crafts Chemistry. Part 48. Concise Synthesis of Condensed Azaheterocyclic [1,8]naphthyridinones, Azepino-, Azocino-, and Azoninoquinoline Systems via Friedel–Crafts Ring Closures

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Unprecedented construction of a novel series of quinoline heteropolycycles (tetracyclic keto-analogues of [1,8] naphthyridinones, azepino-, azocino- and azonino[2,3-*b*]quinolinones systems) **10a–i** by Friedel–Crafts cycliacylation reactions is described. Starting heterocyclic acids precursors **3a–i** were prepared from easily accessible 2-chloroquinoline-3-carbaldehyde **1** via a three different synthetic pathways. Acid-catalyzed ring closures of the resulting tosylated acids were achieved under the influence of both Brønsted and Lewis acid catalysts. The present strategy enables a straightforward synthesis to fused tetracyclic quinolinone skeletons as demonstrated by concise and atom-economical syntheses.

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Introduction

Condensed aza-heterocycles containing the quinoline moiety are widely found in many biologically active natural alkaloids[1] as well as in synthetic pharmaceuticals[2] and often incorporated into drugs[3] (Fig. 1) such as quinine, quinidine, glaucine, dictamnine, camptothecin, and mefloquine. Many quinoline-containing compounds exhibit a wide diversity of pharmacological anti-tumoural, anti-inflammatory, antimalarial, antituberculosis, and antiplasmodial activities.[4] Moreover, fused-quinoline scaffolds are reported as important intermediates in the manufacture of dyestuffs,[5] polymers,[6] agrochemicals,[7] electroluminescent devices,[8] semiconductors, and biosensors.[9]

Although considerable attention has been directed towards the synthesis of heterocycles containing the quinoline nucleus owing to the chemical importance and potential biological activities of this class of compounds, the search for new versatile, simple, and efficient procedures for construction of *N*-medium-sized rings fused to quinoline still remains an academic challenge.[10]

Literature surveys reveal that various condensed quinolines have been synthesized and numerous synthetic routes to five- or six-membered heteroaromatic rings fused to quinoline have been reported.[11] Among the most efficient procedures for fused quinoline system synthesis are the Doebner–von Miller reaction,[12] Skraup synthesis,[13] Combes synthesis,[14] Friedlander synthesis,[15] Knorr synthesis,[16] Conrad–Limpach synthesis,[17] Fitzinger reaction,[18] microwave irradiation,[19] Diels–Alder reaction,[20] Friedel–Crafts reaction,[21] alkynes cycloaddition reactions,[22] Mukaiyama aldol synthesis,[23] Sakurai–Hosomi allylation reactions,[24] transition metal-catalyzed heteroannulation reactions,[25] and other specific reactions.[26]

However, syntheses of seven-, eight- and nine-membered *N*-containing rings fused to quinoline are extremely rare. A few methods based on cycloaddition reactions of acyclic intermediates have been described in the literature for the synthesis of azepino [1,2-*a*], [2,3-*b*], [3,2-*b*], [4,3-*b*], and [4,5-*b*]quinolines.[27]

Furthermore, numerous natural products and medicinally important molecules contain *N*-heterocyclic rings (e.g. azepines, azocines, and azonines).[28] In addition to their industrial applications,[29] several azepines and azocines (Fig. 2) are often found in pharmaceuticals[30] and drugs[31] (e.g. antidepressant drugs (tetracyclic antidepressant, TCA)). Because of entropic and transannular penalties in the ring-forming transition states, medium-sized *N*-containing systems are difficult to obtain by traditional ring-closure procedures.[32]

Nevertheless, the last four decades have provided strong incentives in the construction of seven- and eight-membered *N*-heterocyclic rings based on cyclization reactions.[33–41] However, synthesis of larger-ring members (e.g. azonines and azecines) remains unknown, with the exception of some examples isolated from naturally occurring alkaloids, in particular erythrina, laurifonine, vincristine, and cephalotaxus.[42]

In recent years, our research has been focussed on the development of an efficient and concise synthesis of medium-sized *N*-heterocycles. In our previous work,[43,44] we reported a straightforward synthetic protocol for the construction of a novel series of *N*-carbocycles of various ring sizes via classical Friedel–Crafts[45] ring-closure procedures. In light of the above findings, herein we describe a concise and efficient protocol for the construction of novel fused aza-tetracyclic quinoline scaffolds incorporating six-, seven-, eight-, and nine-membered ring amine systems via a Friedel–Crafts ring-closure approach.

Results and Discussion

The heteroaryl acid precursors **3a–i** required for the present work were obtained from an easily accessible 2-chloro-3-quinolinecarboxaldehyde (**1**)[46] intermediate via three different

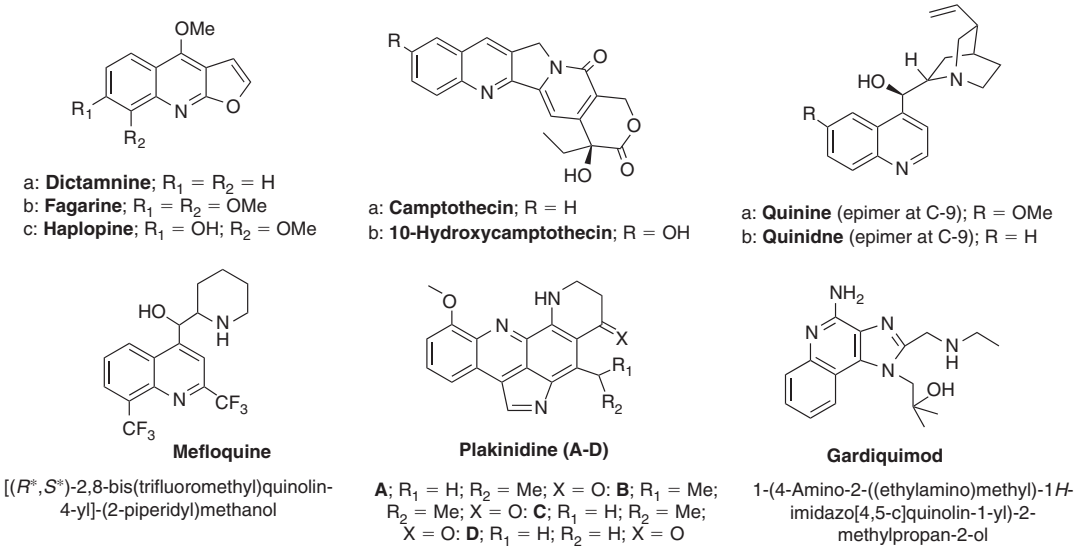


Fig. 1. Structural motifs of quinoline-based natural products and drugs.

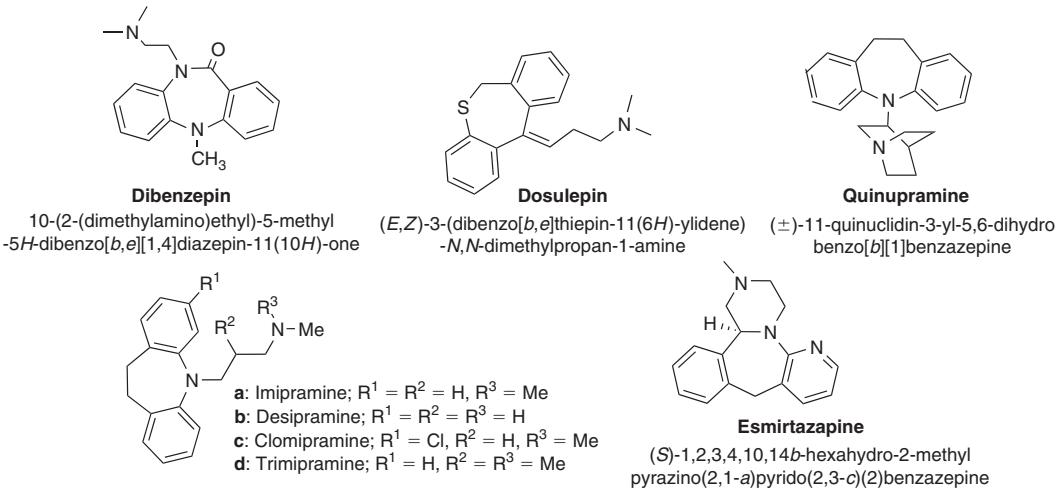


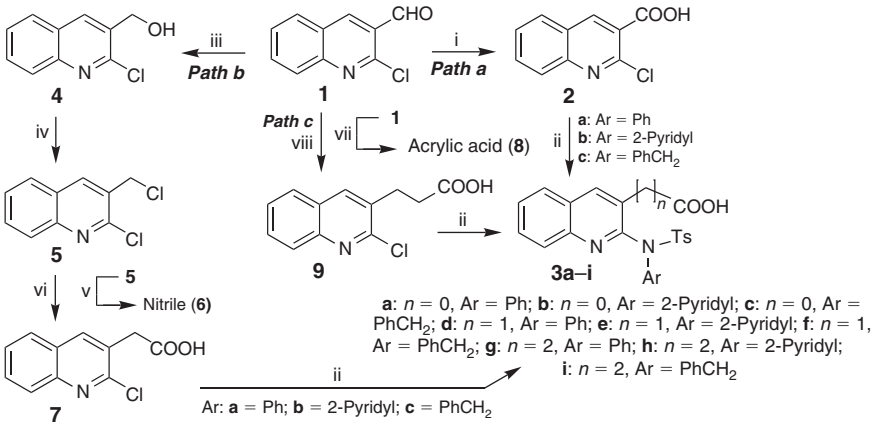
Fig. 2. Medium-sized heterocyclic ring template-containing pharmaceuticals.

synthetic routes as depicted in Scheme 1. *Path a* involved the production of heterocyclic acids **3a–c**. The first step involved the oxidation of aldehyde **1** with alkaline $KMnO_4$ following literature procedures to give 2-chloroquinoline-3-carboxylic acid (**2**).[47] In the next step, the resulting halo-acid **2** was allowed to react with various aromatic tosylated amines (PhNHTs, *N*-tosylpyridin-2-amine or $TsNHCH_2Ph$) in the presence of K_2CO_3/Cu in anhydrous DMSO to afford substituted quinoline carboxylic acids **3a–c**.

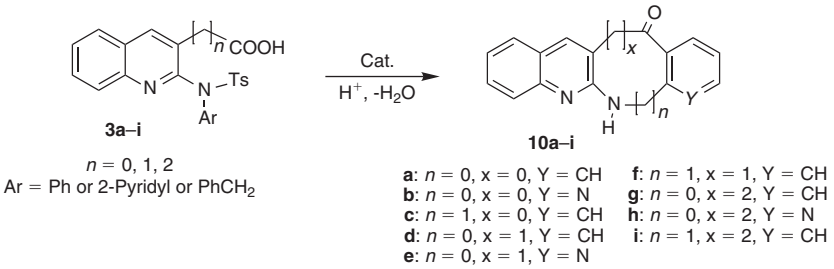
The second route (*Path b*) included the conversion of aldehyde **1** to another set of precursors acids **3d–f** through three consecutive reaction steps: (i) reduction of aldehyde **1** to (2-chloroquinolin-3-yl)methanol (**4**)[48] following the literature procedure with $NaBH_4$ in methanol, which was converted to the corresponding chloride **5** with $SOCl_2$ in pyridine and then into 2-(2-chloroquinolin-3-yl)acetonitrile (**6**) by reaction with KCN in ethanol; (ii) hydrolysis of the resulting acetonitrile **6** by refluxing with NaOH in EtOH solution to afford 2-(2-chloroquinolin-3-yl)acetic acid (**7**); and finally (iii) coupling of the latter acid **7** with different aromatic tosylated amines to give acids **3d–f** in high yields.

Alternatively, in *Path c*, the versatile starting aldehyde **1** was converted to 3-(2-chloroquinolin-3-yl)acrylic acid (**8**) by reaction with acetic anhydride and sodium acetate. Reduction of acid **8** with sodium amalgam (Na/Hg) in NaOH solution afforded 3-(2-chloroquinolin-3-yl)propanoic acid (**9**). Finally, acid **9** was reacted under Ullmann *N*-coupling conditions with aromatic tosylated amines to give the corresponding substituted 3-(quinolin-3-yl)propanoic acids **3g–i** in good yields.

Our synthetic protocol allows access to functionalized keto-tetracyclic quinoline derivatives **10a–i** ([1,8]naphthyridinones, pyrido[2,3-*b*][1,8]naphthyridinones, azepino[2,3-*b*]quinolinones, pyrido[3′,2′:6,7]azepino[2,3-*b*]quinolinones, azocino[2,3-*b*]quinolinones, pyrido[3′,2′:7,8]azocino[2,3-*b*]quinolinones, and azonino[2,3-*b*]quinolinones) by acid-catalyzed Friedel–Crafts cycliacylations of tosylated acids precursors **3a–i**. Ring closures of quinoline carboxylic acids **3a–i** were induced by heating with $AlCl_3/CH_3NO_2$ or polyphosphoric acid (PPA) or P_2O_5 catalysts under different reaction conditions (Scheme 2 and Tables 1 and 2). The removal of the Ts-group takes place concurrently with the closure step of the heterocyclic acids, as shown in different examples in the literature.[49]

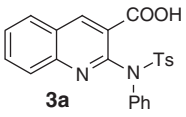
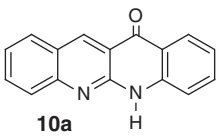
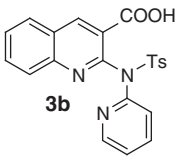
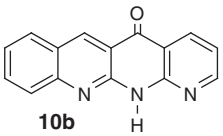
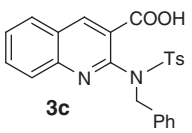
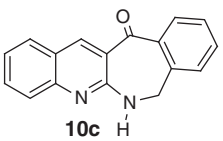


Scheme 1. Reagents and conditions: (i) $KMnO_4/H_2O$/*t*-butanol, 70–80°C, NaOH, 4 h; (ii) aromatic tosylated amines (PhNHTs, *N*-tosylpyridin-2-amine or $TsNHCH_2Ph$), K_2CO_3/pyridine/Cu/DMSO, 110–120°C, 6 h, reflux; (iii) $NaBH_4$/MeOH, 2 h, HCl, room temperature (rt); (iv) $SOCl_2$/pyridine, 3 h; (v) KCN/EtOH, 3 h, reflux; (vi) NaOH, 8 h, reflux, HCl; (vii) $(Ac_2O/AcONa)/Na_2CO_3$, 120–130°C, 8 h; (viii) Na/Hg (2.5 %), NaOH, 2 h, rt.



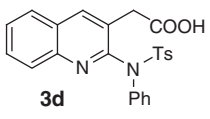
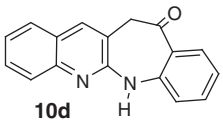
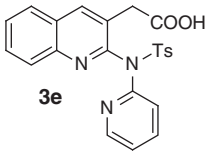
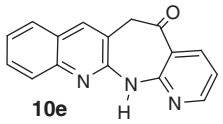
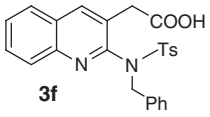
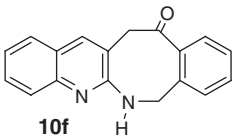
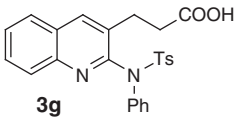
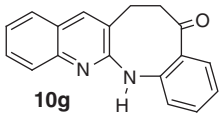
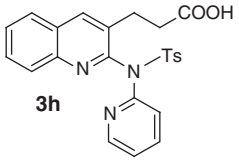
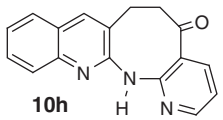
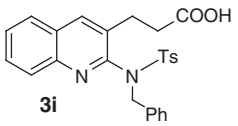
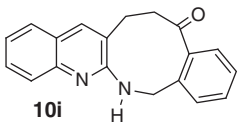
Scheme 2. Cycliacylations of acids **3a–i** under Friedel–Crafts conditions (Tables 1 and 2).

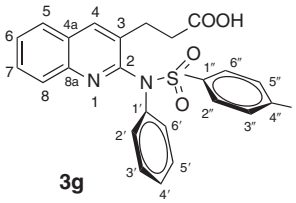
Table 1. Friedel–Crafts cycliacylations of quinoline carboxylic acids 3a–c

Entry	Substrate	Product	Conditions	Product [%][A]
1	 **3a**	 **10a**	$AlCl_3/CH_3NO_2$[B], DCM[C], 2 h, rt P_2O_5[D], toluene, 9 h, rt PPA[E], 2 h, 220°C	**10a** (88) **10a** (92) **10a** (75)
2	 **3b**	 **10b**	$AlCl_3/CH_3NO_2$, DCM, 2 h, rt P_2O_5, toluene, 8 h, rt PPA, 2 h, 220°C	**10b** (90) **10b** (88) **10b** (80)
3	 **3c**	 **10c**	$AlCl_3/CH_3NO_2$, DCM, 2 h, rt P_2O_5, toluene, 5 h, rt PPA, 2 h, 220°C	**10c** (89) **10c** (85) **10c** (80)

[A]Isolated yield relative to substrate.
[B]With $AlCl_3/CH_3NO_2$ catalyst, reactant proportions were: acid, 0.002 mol; $AlCl_3$, 0.0024 mol; CH_3NO_2, 0.024 mol; solvent, 10 mL.
[C]Dichloromethane.
[D]With P_2O_5 catalyst, reactant proportions were: acid, 0.5 g, and P_2O_5, 5 g in anhydrous toluene (15 mL).
[E]With PPA catalyst, reactant proportions were: acid, 0.5 g, and PPA, 5 g.

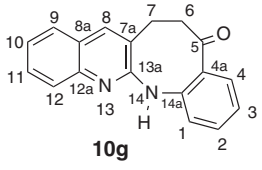
Table 2. Friedel–Crafts cycliacylations of quinoline carboxylic acids 3d–i

Entry	Substrate	Product	Conditions	Product [%]
1	 **3d**	 **10d**	$AlCl_3/CH_3NO_2$, DCM, 2 h, rt P_2O_5, toluene, 5 h, rt PPA, 3 h, 220°C	**10d** (85) **10d** (90) **10d** (81)
2	 **3e**	 **10e**	$AlCl_3/CH_3NO_2$, DCM, 2 h, rt P_2O_5, toluene, 4 h, rt PPA, 1 h, 230°C	**10e** (92) **10e** (86) **10e** (80)
3	 **3f**	 **10f**	$AlCl_3/CH_3NO_2$, DCM, 2 h, rt P_2O_5, toluene, 5 h, rt PPA, 2 h, 210°C	**10f** (92) **10f** (90) **10f** (82)
4	 **3g**	 **10g**	$AlCl_3/CH_3NO_2$, DCM, 2 h, rt P_2O_5, toluene, 5 h, rt PPA, 2 h, 210°C	**10g** (93) **10g** (84) **10g** (78)
5	 **3h**	 **10h**	$AlCl_3/CH_3NO_2$, DCM, 2 h, rt P_2O_5, toluene, 4 h, rt PPA, 1 h, 220°C	**10h** (92) **10h** (82) **10h** (76)
6	 **3i**	 **10i**	$AlCl_3/CH_3NO_2$, DCM, 2 h, rt P_2O_5, toluene, 3 h, rt PPA, 2 h, 230°C	**10i** (91) **10i** (80) **10i** (83)



3g

3-(2-(*N*-phenyl-*N*-tosylamino)quinolin-3-yl)propanoic acid



10g

5,6,7,14-tetrahydro-14*H*-benzo[7,8]azocino[2,3-*b*]quinoline-5-one

Fig. 3. Structures of tetracyclic product **10g** and its precursor heterocyclic acid **3g**.

The identity of the products was supported by elemental analysis, IR, ^{1}H NMR, and mass spectral studies. Thus, the ^{1}H NMR data proved the formation of condensed heterocycles **10a–i**. For example, the ^{1}H NMR spectrum for heterocyclic acid **3g** (Fig. 3) displayed five signals in which aromatic protons appeared at δ 6.7–8.3 ppm and the methyl group appeared as a singlet at δ 2.5 ppm respectively. The two adjacent CH_2 groups exhibits two triplet signals near δ 2.3 and 2.5 ppm, and a broad singlet at δ 11.2 ppm was assigned to the –COOH proton. In comparison with acid **3g**, the ^{1}H NMR spectrum of tetracyclic quinoline **10g** showed an apparent singlet near δ 2.96 for the two adjacent CH_2 protons, while the aromatic protons appear as three sets of complex overlapping signals in the range of δ 7.33–7.73 ppm and the NH proton appears as a singlet at δ 9.74 ppm. Moreover, the IR spectrum of **10g** showed strong absorptions at 1740 (C=O) and 3380 (N–H) cm^{-1} characteristic for an eight-membered amine ring.

Conclusions

A variety of new keto-tetracyclic quinoline skeletons **10a–i**, [1,8] naphthyridines, azepino-, azocino-, and azonino-fused quinoline systems, were obtained from easily prepared 2-chloro-3-quinolinecarboxaldehyde **1** accessible by short synthetic pathways in good yields by Friedel–Crafts cycliacylations. The method allows incorporation of the two bioactive medium-sized *N*-containing heterocycles and quinoline scaffolds in molecular fused forms and in one collective protocol. The results provide concise and facile routes to quinoline fused *N*-medium-ring heteropolycycles.

Experimental

General

All melting points were determined with a digital Gallenkamp capillary melting point apparatus and are uncorrected. Infrared

spectra were measured on a Mattson 5000 Fourier-transform (FT)IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol LA 400 MHz FT-NMR (400 MHz for ^{1}H, 100 MHz for ^{13}C) and on Varian NMR (90 MHz) spectrometers. Chemical shifts (δ) are reported in parts per million downfield from TMS as internal standard and coupling constants are expressed as *J* values in Hertz. Elemental analyses were performed with a PerkinElmer 2400 Series II instrument. Mass spectra were measured on a Jeol JMS 600 spectrometer at an ionizing potential of 70 eV using the direct inlet system. Reactions were monitored by TLC using precoated silica plates (0.2 mm, Kiesel 60, F254, E. Merck) and visualized with UV light. Flash column chromatography was performed on silica gel (230–400 mesh, E. Merck).

Path a describes the synthesis of quinoline carboxylic acid **3a–c** starting from 2-chloroquinoline-3-carbaldehyde (**1**) via two reaction steps.

*Synthesis of 2-Chloroquinoline-3-Carboxylic Acid (**2**)*

To a solution of aldehyde **1**[46] (3.8 g, 20 mmol) in a mixture of H_2O/*t*-butanol (1 : 1, 30 mL) was added a solution of $KMnO_4$ (4.0 g, 25 mmol) in H_2O (30 mL) at 70–80°C over 30 min. Then, a solution of NaOH (10 %, 30 mL) was added with stirring until the solution turned alkaline. The reaction mixture was stirred at the same temperature for 4 h. The reaction mixture was filtered and the resulting clear filtrate was acidified with HCl solution (40 mL, 30 %). The resulting acid was purified by dissolving in $NaHCO_3$ solution (50 mL, 10 %) and the whole solution was filtered on hot and then neutralized with dilute HCl. The resulting precipitate was filtered, washed with water, and dried to give (3.6 g, 88 %) of crude acid. Crystallization from methanol gave 3.4 g (84 %) of pure 2-chloroquinoline-3-carboxylic acid (**2**) as white crystals, mp 178–180°C (lit. 181–182°C[47]). ν_{max} (KBr)/cm^{-1} 3090, 2980, 2950, 1720, 1605, 1585, 1460, 1435, 1395, 1225, 745. δ_H (90 MHz, $CDCl_3$) 6.8–8.0 (m, 5H, Ar–H), 10.5 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 126.6 (1C, Ar, C-4a), 127.1 (1C, Ar, C-6), 127.2 (1C, Ar, C-5), 128.0 (1C, Ar, C-8), 128.8 (1C, Ar, C-3), 129.0 (1C, Ar, C-7), 129.6 (1C, Ar, C-4), 149.4 (1C, Ar, C-8a), 151.0 (1C, Ar, C-2), 165.5 (1C, COOH). *m/z* (EI, 70 eV) (%) 209 ($M^+ + 2$, 18), 207 (45), 190 (100), 172 (30), 162 (64), 127 (32), 104 (16), 91 (50), 76 (18). Anal. Calc. for $C_{10}H_6ClNO_2$ (207.5): C 57.83, H 2.89, N 6.74, Cl, 17.10. Found: C 57.73, H 2.91, N 6.80 Cl, 17.28 %.

Path b includes the synthesis of quinoline carboxylic acids **3d–f** starting from 2-chloroquinoline-3-carbaldehyde (**1**) via five reaction steps.

*Synthesis of 2-(2-Chloroquinolin-3-yl)acetic Acid (**7**)*

The title acid was obtained in a series of four consecutive steps starting with 2-chloroquinoline-3-carbaldehyde. A summary of the steps is given in the following.

*(2-Chloroquinolin-3-yl)methanol (**4**)*

To an ice-cold stirred mixture of 2-chloroquinoline-3-carbaldehyde **1** (5.7 g, 30 mmol) in methanol (25 mL), $NaBH_4$ (2.3 g, 60 mmol) was added portionwise over 20 min. After complete addition, the reaction mixture was stirred for 30 min, quenched with ice-cold water (50 mL), and finally acidified with aqueous HCl solution (30 mL, 20 %). Separation and purification of the product following literature procedures gave 5.1 g (90 %) of crude product. Crystallization from methanol gave 4.7 g (84 %) of pure (2-chloroquinolin-3-yl)methanol (**4**) as white crystals; mp 159–161°C (lit. 162–163°C[48]). ν_{max} (KBr)/cm^{-1} 3410, 3065, 2930, 1615, 1610, 1489, 1360, 1189, 1102, 1027, 716, 703, 660. δ_H (90 MHz, $CDCl_3$) 2.3 (s, 1H, OH), 5.2 (s, 2H, CH_2), 6.7–8.3 (m, 5H, Ar–H). δ_C (100 MHz, $CDCl_3$) 62.523 (1C, –CH_2OH), 126.6 (1C, Ar, C-4a), 127.1 (1C, Ar, C-6), 128.0 (1C, Ar, C-5), 128.8 (1C, Ar, C-8), 129.0 (C, Ar, C-3), 129.6 (1C, Ar, C-7), 130.6 (1C, Ar, C-4), 149.4 (1C, Ar, C-8a), 151.0 (1C, Ar, C-2). *m/z* (EI, 70 eV) (%) 195 ($M^+ + 2$, 5), 193 (M^+, 22), 192 (20), 176 (100), 162 (32), 107 (24), 104 (9), 90 (16), 76 (8). Anal. Calc. for $C_{10}H_8ClNO$ (193.5): C 62.01, H 4.13, N 7.23, Cl 18.34. Found: C 62.14, H 4.18, N 7.05, Cl 18.55 %.

*2-Chloro-3-(chloromethyl)quinoline (**5**)*

To an ice-cold stirred solution of (2-chloroquinolin-3-yl) methanol **4** (5.8 g, 30 mmol) in dry pyridine (4.7 g, 60 mmol) was added freshly distilled $SOCl_2$ (9.5 g, 80 mmol) over a period of 10 min, while the temperature was kept below 15°C. The reaction mixture was then heated on a steam bath for 3 h and then poured with efficient stirring into cold water (70 mL). The product was extracted with diethyl ether (3 × 40 mL) and the combined organic layers were washed with $NaHCO_3$ solution (3 × 30 mL) and finally with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed under vacuum to afford a crude residue (5.8 g, 92 %). Crystallization from *n*-hexane gave 5.4 g (86 %) of pure 2-chloro-3-(chloromethyl)quinoline (**5**) as white crystals; mp 74–76°C. ν_{max} (KBr)/cm^{-1} 3070, 2920, 2890, 1595, 1550, 1490, 1350, 1080, 765, 697. δ_H (90 MHz, $CDCl_3$) 4.7 (s, 2H, CH_2), 7.4–8.5 (m, 5H, Ar–H). δ_C (100 MHz, $CDCl_3$) 40.3 (1C, –CH_2), 126.5 (1C, Ar, C-4a), 127.2 (1C, Ar, C-6), 127.5 (2C, Ar, C-5, C-8), 129.9 (2C, Ar, C-3, C-7), 136.0 (1C, Ar, C-4), 145.6 (1C, Ar, C-8a), 153.4 (1C, Ar, C-2). *m/z* (EI, 70 eV) (%) 214 (11), 212 (M^+, 27), 177 (100), 163 (58), 142 (35), 128 (82), 105 (14), 91 (8), 76 (6). Anal. Calc. for $C_{10}H_7Cl_2N$ (212): C 56.60, H 3.30, N 6.60, Cl 33.49. Found: C 56.72, H 3.24, N 6.40, Cl 33.63 %.

*2-(2-Chloroquinolin-3-yl)acetonitrile (**6**)*

To a warm solution of 2-chloro-3-(chloromethyl)quinoline **5** (4.2 g, 20 mmol) in ethanol (30 mL) was added a solution of potassium cyanide (4.0 g, 60 mmol) in water (15 mL) over a period of 30 min. The reaction mixture was then refluxed for 3 h, and the most of the solvent was removed by simple distillation. The resulting residue was diluted with water (50 mL) and the product was extracted with diethyl ether (2 × 30 mL). The combined ether extracts were treated as described before to yield 3.4 g (85 %) of crude product. Crystallization from aqueous acetone gave 3.1 g (78 %) of pure 2-(2-chloroquinolin-3-yl) acetonitrile (**6**) as white needles; mp 115–117°C. ν_{max} (KBr)/cm^{-1} 3050, 2920, 2350, 1595, 1510, 1410, 1360, 1160, 1085, 785. δ_H (90 MHz, $CDCl_3$) 5.3 (s, 2H, CH_2), 7.4–8.5 (m, 5H, Ar–H). δ_C (100 MHz, $CDCl_3$) 16.5 (1C, –CH_2), 119.0 (1C, –CN), 126.5 (1C, Ar, C-4a), 127.0 (1C, Ar, C-6), 127.5 (2C, Ar, C-5, C-8), 130.4 (1C, Ar, C-7), 131.5 (1C, Ar, C-3), 137.5 (1C, Ar, C-4), 146.2 (1C, Ar, C-8a), 153.5 (1C, Ar, C-2). *m/z* (EI, 70 eV) (%) 204 ($M^+ + 2$, 7), 202 (M^+, 30), 180 (74), 176 (72), 167 (100), 160 (48), 90 (13), 76 (4). Anal. Calc. for $C_{11}H_7ClN_2$ (202.5): C 65.18, H 3.45, N 13.82, Cl 17.53. Found: C 65.04, H 3.62, N 13.64, Cl 17.68 %.

*2-(2-Chloroquinolin-3-yl)acetic acid (**7**)*

A mixture of nitrile **6** (4.0 g, 20 mmol), sodium hydroxide (2.4 g, 60 mmol), water (10 mL), and ethanol (30 mL) was

refluxed for 8 h. The solution was cooled to room temperature, diluted with water (70 mL), and extracted with diethyl ether (2 × 20 mL). The ether extracts were discarded and the aqueous layer was heated to boiling, cooled, and adjusted to pH 5–6 with acetic acid. After standing overnight, the resulting precipitate was filtered off, washed with water, and dried to give 3.6 g (82 %) of crude product. Crystallization from ethanol gave 3.3 g (75 %) of pure 2-(2-chloroquinolin-3-yl)acetic acid **7** as white needles; mp 158–160°C. ν_{max} (KBr)/cm^{-1} 3060, 2900, 2370–2700, 1690, 1595, 1510, 1410, 1215, 785. δ_H (90 MHz, $CDCl_3$) 3.9 (s, 2H, CH_2) 7.2–8.0 (m, 5H, Ar–H), 10.4 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 42.5 (1C, –CH_2), 126.5 (1C, Ar, C-4a), 127.0 (1C, Ar, C-6), 127.5 (2C, Ar, C-5, C-8), 130.4 (1C, Ar, C-7), 131.5 (1C, Ar, C-3), 137.5 (1C, Ar, C-4), 146.5 (1C, Ar, C-8a), 154.2 (1C, Ar, C-2), 176.5 (1C, COOH). *m/z* (EI, 70 eV) (%) 223 ($M^+ + 2$, 8), 221 (26), 186 (55), 176 (100), 162 (20), 127 (48), 90 (13), 77 (8). Anal. Calc. for $C_{10}H_6ClNO_2$ (221.5): C 59.59, H 3.61, N 6.32, Cl 16.02. Found: C 59.52, H 3.75, N 6.19, Cl 16.12 %.

Path c includes the synthesis of quinoline carboxylic acids **3g–i** starting from 2-chloroquinoline-3-carbaldehyde (**1**) through three reaction steps.

*Synthesis of 3-(2-Chloroquinolin-3-yl)propanoic acid (**9**)*

This acid was obtained in a series of two consecutive steps starting with commercially available *o*-toluidine. A summary of the steps is given in the following.

*3-(2-Chloroquinolin-3-yl)acrylic acid (**8**)*

A mixture of aldehyde **1** (2.8 g, 15 mmol), acetic anhydride (2.0 g, 20 mmol), and sodium acetate (1.6 g, 20 mmol) was heated in an oil bath at 120–130°C with occasionally stirring for 8 h. The warm mixture was poured with stirring into water (30 mL), basified with Na_2CO_3 solution (20 mL, 30 %), and extracted with ether (3 × 20 mL). The ether extracts were discarded and the resulting solution was heated with decolourizing carbon (1 g), filtered while hot, and then poured with stirring into ice-cold HCl solution (50 mL, 20 %). After standing overnight, the white precipitate was collected, washed with water, and dried to give 2.8 g (84 %) of crude acid. Crystallization from ethanol gave 2.7 g (80 %) of pure 3-(2-chloroquinolin-3-yl) acrylic acid **8** as white crystals; mp 165–167°C. ν_{max} (KBr)/cm^{-1} 3250–2500, 1690, 1663, 1610, 1489, 1262, 1189, 1102, 1027, 980, 716, 703, 658. δ_H (90 MHz, $CDCl_3$) 6.2 (d, 1H, 9, CH), 6.5 (d, 1H, 9, CH), 6.8–8.2 (m, 5H, Ar–H), 11.2 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 121.5 (1C, Ar, =C^{α}H), 126.5 (1C, Ar, C-4a), 129.4 (1C, Ar, C-5), 127.5 (2C, Ar, C-6, C-8), 130.5 (2C, Ar, C-3, C-7), 135.4 (1C, Ar, C-4), 147.4 (1C, Ar, C-8a), 150.5 (1C, Ar, =C^{β}H), 152.2 (1C, Ar, C-2), 170.5 (1C, COOH). *m/z* (EI, 70 eV) (%) 235 ($M^+ + 2$, 15), 233 (49), 216 (64), 189 (100), 168 (18), 155 (30), 91 (22), 90 (6), 77 (5). Anal. Calc. for $C_{12}H_8ClNO_2$ (233.5): C 61.67, H 3.42, N 5.99, Cl 15.20. Found: C 61.52, H 3.50, N 5.95, Cl 15.37 %.

*3-(2-Chloroquinolin-3-yl)propanoic acid (**9**)*

To a solution of acrylic acid **8** (3.5 g, 15 mmol) in sodium hydroxide (20 mL, 1 M) was treated with sodium amalgam (Na/Hg; 40 g, 2.5 %) in small portions over a period of 10 min with vigorous stirring. The reaction mixture was stirred for additional 2 h at room temperature and then the mercury was separated, washed with water, and washings were added to the main solution. The solution was filtered and the resulting clear filtrate was acidified using HCl solution (10 mL). The resultant crude acid was filtered off, washed excessively with water, and dried to give 3.2 g (93 %) of the crude acid. Crystallization from aqueous ethanol gave 3.0 g (87 %) of pure 3-(2-chloroquinolin-3-yl)propanoic acid **9** as white crystals; mp 120–122°C. ν_{max} (KBr)/cm^{-1} 3370, 3090, 2988, 2540, 1720, 1605, 1580, 1460, 1445, 1335, 1180, 745. δ_H (90 MHz, $CDCl_3$) 2.6 (t, 2H, 7.5, CH_2), 2.9 (t, 2H, 7.5, CH_2), 6.8–8.2 (m, 5H, Ar–H), 10.5 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 26.5 (1C, –C^{β}H), 37.0 (1C, –$C^{\alpha}H_2$), 126.5 (1C, Ar, C-4a), 127.8 (1C, Ar, C-6), 127.4 (2C, Ar, C-5, C-8), 129.8 (1C, Ar, C-7), 136.5 (1C, Ar, C-4), 137.2 (1C, Ar, C-3), 145.4 (1C, Ar, C-8a), 153.5 (1C, Ar, C-2), 179.0 (1C, COOH). *m/z* (EI, 70 eV) (%) 237 ($M^+ + 2$, 8), 235 (30), 218 (40), 191 (100), 190 (84), 169 (25), 91 (12), 90 (6), 77 (7). Anal. Calc. for $C_{12}H_{10}ClNO_2$ (235.5): C 61.14, H 4.24, N 5.94, Cl 15.07. Found: C 61.22, H 4.14, N 5.79, Cl 15.20 %.

*General Procedure for Arylation of 3-(2-Chloroquinolin-3-yl) Carboxylic Acids (**3a–i**)*

A mixture of 2-chloroquinoline carboxylic acids **2**, **7** or **9** (16 mmol), K_2CO_3 (4.1 g, 30 mmol), tosylated aryl amine (PhNHTs, *N*-tosylpyridin-2-amine or $TsNHCH_2Ph$) (20 mmol), and Cu (0.3 g) in anhydrous DMSO (20 mL) was heated with continuous stirring for 6 h at 110–20°C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled and treated with NaOH solution (50 mL, 10 %) and decolourizing carbon (2 g). The reaction mixture was heated with continuous stirring for 20 min, then filtered by suction. The resulting cold filtrate was acidified with aqueous HCl solution (40 mL, 10 %) and the resulting precipitate was filtered, washed with water, dried, and recrystallized to give the pure acids **3a–i**. The yields and spectral data of acids **3a–i** are given in the following.

*2-(N-Phenyl-N-tosylamino)quinoline-3-Carboxylic Acid (**3a**)*

White plates; 83 %; mp 152–154°C (ethanol). ν_{max} (KBr)/cm^{-1} 3080, 2980, 2730, 1690, 1600, 1580, 1455, 1430, 1355, 1143, 760. δ_H (90 MHz, $CDCl_3$) 2.4 (s, 3H, CH_3), 6.7–8.4 (m, 14H, Ar–H), 11.2 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 25.2 (1C, –CH_3), 110.8 (1C, Ar, C-3), 116.3 (2C, Ar, C-2′, C-6′), 118.8 (1C, Ar, C-4′), 120.2 (1C, Ar, C-4a), 123.1 (1C, Ar, C-6), 125.5 (1C, Ar, C-8), 127.2 (2C, Ar, C-2″, C-6″), 128.2 (1C, Ar, C-5), 129.4 (4C, Ar, C-3′, C-5′, C-3″, C-5″), 131.4 (1C, Ar, C-7), 136.7 (1C, Ar, C-1″), 138.3 (1C, Ar, C-4), 141.4 (1C, Ar, C-4″), 146.7 (1C, Ar, C-1′), 148.1 (1C, Ar, C-8a), 166.8 (1C, Ar, C-2), 169.7 (1C, COOH). *m/z* (EI, 70 eV) (%) 418 (M^+, 18), 417 ($M^+ - 1$, 11), 401 (2), 387 (10), 373 (2), 360 (7), 298 (5), 286 (9), 281 (17), 268 (100), 252 (67), 226 (11), 216 (2), 207 (27), 202 (10), 191 (98), 189 (81), 181 (35), 178 (52), 167 (36), 165 (72), 105 (19), 91 (56), 77 (13). Anal. Calc. for $C_{23}H_{18}N_2O_4S$ (418): C 66.02, H 4.30, N 6.69, S 7.65. Found: C 66.15, H 4.32, N 6.55, S 7.61 %.

*2-(N-(Pyridin-2-yl)-N-tosylamino)quinoline-3-Carboxylic Acid (**3b**)*

Yellow crystals; 79 %; mp 168–170°C (benzene). ν_{max} (KBr)/cm^{-1} 3075, 2969, 2740, 1695, 1605, 1570, 1455, 1420, 1330, 1245, 1180, 760. δ_H (90 MHz, $CDCl_3$) 2.4 (s, 3H, CH_3), 6.8–8.6 (m, 13H, Ar–H), 10.5 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 25.3 (1C, –CH_3), 109.9 (1C, Ar, C-1″), 110.8 (1C, Ar, C-3), 113.3 (1C, Ar, C-4′), 120.2 (1C, Ar, C-4a), 123.1(1C, Ar, C-6), 125.2 (1C, Ar, C-8), 127.2 (2C, Ar, C-2″, C-6″), 128.5 (1C, Ar,

C-5), 129.4 (2C, Ar, C-3″, C-5″), 131.4 (1C, Ar, C-7), 136.5 (1C, Ar, C-6′), 138.8 (2C, Ar, C-4, C-5′), 141.6 (1C, Ar, C-4″), 148.2 (2C, Ar, C-8a, C-3′), 161.1 (1C, Ar, C-4′), 166.5 (1C, Ar, C-2), 169.4 (1C, COOH). *m/z* (EI, 70 eV) (%) 419 (M^+, 4), 401 (1), 387 (10), 374 (2), 360 (13), 298 (4), 284 (11), 282 (18), 265 (100), 252 (74), 226 (11), 207 (26), 202 (12), 191 (99), 189 (92), 178 (56), 167 (33), 165 (77), 152 (17), 105 (20), 91 (56), 77 (15). Anal. Calc. for $C_{22}H_{17}N_3O_4S$ (419): C 63.00, H 4.05, N 10.02, S 7.63. Found: C 63.14, H 4.10, N 9.89, S 7.52 %.

*2-(*N*-Benzyl-N-tosylamino)quinoline-3-Carboxylic Acid (**3c**)*

White crystals; 82 %; mp 140–142°C (ethanol). ν_{max} (KBr)/cm^{-1} 3065, 2973, 2550, 1690, 1610, 1570, 1465, 1440, 1335, 1250, 760. δ_H (90 MHz, $CDCl_3$) 2.4 (s, 3H, CH_3), 4.5 (s, 2H, CH_2), 6.7–8.3 (m, 14H, Ar–H), 10.8 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 25.4 (1C, –CH_3), 47.7 (1C, N–CH_2), 110.8 (1C, Ar, C-3), 120.2 (1C, Ar, C-4a), 123.1 (1C, Ar, C-6), 125.2 (1C, Ar, C-8), 126.8 (1C, Ar, C-4′), 127.2 (4C, Ar, C-2′, C-6′, C-2″, C-6″), 128.6 (3C, Ar, C-5, C-3′, C-5′), 129.4 (2C, Ar, C-3″, C-5″), 131.6 (1C, Ar, C-7), 136.7 (1C, Ar, C-1″), 138.3 (1C, Ar, C-4), 141.6 (2C, Ar, C-1′, C-4″), 148.3 (1C, Ar, C-8a), 167.2 (1C, Ar, C-2), 169.4 (1C, COOH). *m/z* (EI, 70 eV) (%) 432 (M^+, 17), 387 (6), 360 (14), 298 (2), 286 (2), 282 (8), 268 (100), 265 (50), 252 (43), 227 (6), 215 (7), 207 (7), 202 (10), 191 (95), 189 (67), 179 (21), 165 (54), 152 (13), 105 (5), 91 (97), 77 (9). Anal. Calc. for $C_{24}H_{20}N_2O_4S$ (432): C 66.66, H 4.62, N 6.48, S 7.40. Found: C 66.74, H 4.68, N 6.37, S 7.52 %.

*2-(2-(*N*-Phenyl-N-tosylamino)quinolin-3-yl)acetic Acid (**3d**)*

White needles; 77 %; mp 164–166°C (ethanol). ν_{max} (KBr)/cm^{-1} 3065, 2975, 2568, 1715, 1590, 1575, 1450, 1430, 1380, 1130, 765. δ_H (90 MHz, $CDCl_3$) 2.4 (s, 3H, CH_3), 3.5 (s, 2H, CH_2), 6.3–8.2 (m, 14H, Ar–H), 11.5 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 25.5 (1C, –CH_3), 39.8 (1C, –CH_2), 116.3 (2C, Ar, C-2′, C-6′), 118.8 (1C, Ar, C-4′), 121.4 (2C, Ar, C-3, C-4a), 122.0 (1C, Ar, C-6), 125.0 (1C, Ar, C-8), 126.1 (1C, Ar, C-5), 127.2 (2C, Ar, C-2″, C-6″), 127.9 (1C, Ar, C-7), 129.4 (4C, Ar, C-3′, C-5′, C-3′, C-5′), 134.5 (1C, Ar, C-4), 136.7 (1C, Ar, C-1″), 141.6 (1C, Ar, C-4″), 144.8 (1C, Ar, C-8a), 146.7 (1C, Ar, C-1′), 168.7 (1C, Ar, C-2), 175.3 (1C, COOH). *m/z* (EI, 70 eV) (%), 432 (M^+, 22), 387 (5), 360 (13), 345 (2), 297 (2), 282 (7), 268 (100), 253 (38), 226 (8), 207 (4), 202 (11), 191 (97), 178 (50), 167 (18), 165 (58), 152 (14), 105 (4), 91 (96), 77 (8). Anal. Calc. for $C_{24}H_{20}N_2O_4S$ (432): C 66.66, H 4.62, N 6.48, S 7.40. Found: C 66.64; H 4.60; N 6.54; S 7.37 %.

*2-(2-(*N*-(Pyridin-2-yl)-N-tosylamino)quinolin-3-yl)acetic Acid (**3e**)*

Yellowish crystals; 75 %; mp 146–148°C (acetone). ν_{max} (KBr)/cm^{-1} 3110, 2978, 2765, 1715, 1600, 1590, 1460, 1430, 1330, 1120, 765. δ_H (90 MHz, [D6]DMSO) 2.4 (s, 3H, CH_3), 3.5 (s, 2H, CH_2), 6.7–8.2 (m, 13H, Ar–H), 11.4 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 25.2 (1C, –CH_3), 39.8 (1C, –CH_2), 109.9 (1C, Ar, C-6′), 113.3 (1C, Ar, C-4′), 121.4 (2C, Ar, C-3, C-4a), 122.0 (1C, Ar, C-6), 125.0 (1C, Ar, C-8), 126.1 (1C, Ar, C-5), 127.2 (2C, Ar, C-2″, C-6″), 127.9 (1C, Ar, C-7), 129.4 (2C, Ar, C-3″, C-5″), 134.5 (1C, Ar, C-4), 136.7 (1C, Ar, C-1′), 138.3 (1C, Ar, C-5′), 141.6 (1C, Ar, C-4″), 144.8 (1C, Ar, C-8a), 148.2 (1C, Ar, C-3′), 161.1 (1C, Ar, C-1′), 168.7 (1C, Ar, C-2), 176.3 (1C, COOH). *m/z* (EI, 70 eV) (%) 433 (M^+, 14), 387 (5), 360 (12), 297 (2), 282 (7), 269 (100), 252 (47), 226 (9), 207 (4), 202 (12), 191 (99), 178 (53), 167 (17), 165 (61), 152 (15), 105 (3), 91 (98), 77 (8). Anal. Calc. for $C_{23}H_{19}N_3O_4S$ (433): C 63.74, H 4.38, N 9.69, S 7.39. Found: C 63.68, H 4.43, N 9.75, S 7.30 %.

*2-(2-(*N*-Benzyl-N-tosylamino)quinolin-3-yl)acetic Acid (**3f**)*

White crystals; 78 %; mp 150–152°C (benzene). ν_{max} (KBr)/cm^{-1} 3095, 2980, 2780, 1720, 1600, 1590, 1480, 1430, 1360, 1130, 760. δ_H (90 MHz, $CDCl_3$) 2.4 (s, 3H, CH_3), 3.5 (s, 2H, CH_2), 4.5 (s, 2H, CH_2), 6.8–8.5 (m, 13H, Ar–H), 10.8 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 25.3 (1C, –CH_3), 39.8 (1C, –CH_2), 48.0 (1C, N–CH_2), 122.0 (1C, Ar, C-6), 121.4 (1C, Ar, C-4a), 121.2 (1C, Ar, C-3), 125.0 (1C, Ar, C-8), 126.1 (1C, Ar, C-5), 126.8 (1C, Ar, C-4′), 127.2 (4C, Ar, C-2′, C-6′, C-2′, C-6′), 127.9 (1C, Ar, C-8), 128.6 (2C, Ar, C-3′, C-5′), 129.4 (2C, Ar, C-3′, C-5′), 134.5 (1C, Ar, C-4), 136.7 (1C, Ar, C-1″), 141.6 (2C, Ar, C-1′, C-4″), 144.8 (1C, Ar, C-8a), 168.7(1C, Ar, C-2), 175.3 (1C, COOH). *m/z* (EI, 70 eV) (%) 446 (M^+, 24), 401 (25), 387 (12), 360 (10), 297 (2), 282 (7), 268 (100), 252 (40), 226 (9), 207 (4), 202 (11), 191 (92), 178 (53), 167 (15), 165 (42), 152 (15), 105 (3), 91 (97), 77 (12). Anal. Calc. for $C_{25}H_{22}N_2O_4S$ (446): C 67.26, H 4.93, N 6.27, S 7.17. Found: C 67.18, H 4.91, N 6.29, S 7.24 %.

*3-(2-(*N*-Phenyl-N-tosylamino)quinolin-3-yl)propanoic Acid (**3g**)*

White crystals; 85 %; mp 155–157°C (ethanol). ν_{max} (KBr)/cm^{-1} 3060, 2979, 2520, 1725, 1605, 1585, 1475, 1435, 1365, 1280, 1083, 765. δ_H (90 MHz, $CDCl_3$) 2.3 (t, 2H, 6, CH_2), 2.5 (s, 3H, CH_3), 2.8 (t, 2H, 6, CH_2), 6.7–8.3 (m, 14H, Ar–H), 11.2 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 25.4 (1C, –CH_3), 25.1 (1C, –CH_2), 36.4 (1C, –*C*H_2–COOH), 116.3 (2C, Ar, C-2′, C-6′), 118.8 (1C, Ar, C-4′), 121.2 (2C, Ar, C-3, C-4a), 122.0 (1C, Ar, C-6), 125.0 (1C, Ar, C-8), 126.1 (1C, Ar, C-5), 127.2 (2C, Ar, C-2″, C-6″), 127.9 (1C, Ar, C-7), 129.6 (4C, Ar, C-3′, C-5′, C-3′, C-5′), 134.5 (1C, Ar, C-4), 136.7 (1C, Ar, C-1″), 141.6 (1C, Ar, C-4″), 144.8 (1C, Ar, C-8a), 146.7 (1C, Ar, C-1′), 168.7 (1C, Ar, C-2), 177.6 (1C, COOH). *m/z* (EI, 70 eV) (%) 446 (M^+, 12), 386 (18), 360 (12), 297 (8), 282 (13), 269 (100), 252 (62), 226 (9), 207 (12), 202 (10), 191 (97), 178 (56), 167 (18), 165 (52), 152 (15), 105 (4), 91 (92), 77 (7). Anal. Calc. for $C_{25}H_{22}N_2O_4S$ (446): C 67.26, H 4.93, N 6.27, S 7.17. Found: C 67.25, H 5.07, N 6.15, S 7.20 %.

*3-(2-(*N*-(Pyridin-2-yl)-N-tosylamino)quinolin-3-yl) propanoic Acid (**3h**)*

White crystals; 80 %; mp 152–154°C (ethanol). ν_{max} (KBr)/cm^{-1} 3035, 2965, 2610, 1724, 1600, 1575, 1450, 1430, 1375, 1035, 759. δ_H (90 MHz, $CDCl_3$) 2.3 (s, 3H, CH_3), 2.5 (t, 2H, 7.5, CH_2), 2.9 (t, 2H, 7.5, CH_2), 6.7–8.2 (m, 13H, Ar–H), 10.8 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 25.1 (1C, –CH_3), 27.3 (1C, –CH_2), 36.4 (1C, –*C*H_2–COOH), 109.9 (1C, Ar, C-6′), 113.3 (1C, Ar, C-4′), 121.2 (2C, Ar, C-3, C-4a), 122.0 (1C, Ar, C-6), 125.0 (1C, Ar, C-8), 126.1 (1C, Ar, C-5), 127.2 (2C, Ar, C-2″, C-6″), 127.9 (1C, Ar, C-7), 129.4 (2C, Ar, C-3″, C-5″), 134.5 (1C, Ar, C-4), 136.7 (1C, Ar, C-1′), 138.3 (1C, Ar, C-5′), 141.6 (1C, Ar, C-4″), 144.8 (1C, Ar, C-8a), 148.2 (1C, Ar, C-3′), 161.1 (1C, Ar, C-1′), 168.7 (1C, Ar, C-2), 177.5 (1C, COOH). *m/z* (EI, 70 eV) (%) 447 (M^+, 32), 402 (8), 387 (9), 362 (11), 297 (8), 282 (10), 268 (100), 253 (60), 225 (11), 207 (10), 205 (15), 191 (98), 178 (62), 167 (20), 152 (10), 91 (90), 77 (6). Anal. Calc. for $C_{24}H_{21}N_3O_4S$ (447): C 64.42, H 4.69, N 9.39, S 7.15. Found: C 64.59, H 4.64, N 9.25, S 7.22 %.

*3-(2-(N-Benzyl-N-tosylamino)quinolin-3-yl)propanoic Acid (**3i**)*

White plates; 85 %, mp 137–139°C (methanol). ν_{max} (KBr)/cm^{-1} 3077, 2984, 2668, 1718, 1600, 1570, 1435, 1410, 1374, 1230, 1080, 760. δ_H (90 MHz, $CDCl_3$) 2.3 (s, 3H, CH_3), 2.6 (t, 2H, 7.5, CH_2), 2.9 (t, 2H, 7.5, CH_2), 4.5 (s, 2H, CH_2), 6.7–8.3 (m, 14H, Ar–H), 11.3 (s, 1H, COOH). δ_C (100 MHz, $CDCl_3$) 25.3 (1C, –CH_3), 27.1 (1C, –CH_2), 36.4 (1C, –CH_2–COOH), 48.0 (1C, N–CH_2), 121.2 (2C, Ar, C-3, C-4a), 122.0 (1C, Ar, C-6), 125.0 (1C, Ar, C-8), 126.1 (1C, Ar, C-5), 126.8 (1C, Ar, C-4′), 127.0 (4C, Ar, C-2′, C-6′, C-2′, C-6′), 127.9 (1C, Ar, C-8), 128.6 (2C, Ar, C-3′, C-5′), 129.4 (2C, Ar, C-3′, C-5′), 134.5 (1C, Ar, C-4), 136.7 (1C, Ar, C-1″), 141.6 (2C, Ar, C-1′, C-4″), 144.8 (1C, Ar, C-8a), 168.7 (1C, Ar, C-2), 177.2 (1C, COOH). *m/z* (EI, 70 eV) (%) 460 (M^+, 17), 415 (8), 388 (20), 360 (11), 282 (9), 268 (100), 252 (40), 225 (9), 207 (4), 202 (10), 191 (95), 178 (51), 167 (15), 165 (40), 152 (14), 105 (4), 91 (98), 77 (10). Anal. Calc. for $C_{26}H_{24}N_2O_4S$ (460): C 67.82, H 5.21, N 6.08, S 6.95. Found: C 67.85, H 5.36, N 6.12, S 6.81 %.

Friedel–Crafts Procedures

Acid-catalyzed ring closures of carboxylic acids **3a–i** were carried out in the presence of $AlCl_3/CH_3NO_2$ or P_2O_5 or PPA and are reported below. In general, the crude oily products were purified by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 3 : 1) or by crystallization from a suitable solvent for the solid products. The conditions and yields for products **10a–i** are shown in Tables 1 and 2. The physical and spectral data of the products are given in the following.

Procedure A: Cycliacylations Using $AlCl_3/CH_3NO_2$ Catalyst

To a solution of $AlCl_3$ (2.4 mmol) in CH_3NO_2 (24 mmol) was added a solution of required acid precursor **3a–i** (2.0 mmol) in dichloromethane (DCM) (10 mL) dropwise with efficient stirring over 10–15 min. The reaction mixture was further stirred for a certain time at room temperature (Tables 1 and 2) and decomposed by careful addition of ice-cold HCl solution (20 mL, 10 %). The residue was extracted with ether (3 × 20 mL) and the combined organic phases were washed with Na_2CO_3 (20 mL, 10 %), then water, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude products **10a–i**.

Procedure B: Cycliacylations Using P_2O_5 Catalyst

A solution of acid **3a–i** (0.5 g) and P_2O_5 (5 g) in dry benzene (10 mL) was refluxed for the required time (Tables 1 and 2) and after cooling to room temperature, the reaction mixture was diluted with ether (40 mL). The organic layer was separated, washed successively with a saturated solution of $NaHCO_3$, then water, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude products **10a–i**.

Procedure C: Cycliacylations Using PPA Catalyst

A stirred mixture of acid **3a–i** (0.5 g) and PPA (5.0 g) was heated on an oil bath and kept at the required temperature for the time shown in Tables 1 and 2. Afterwards, the flask was cooled to room temperature and basified by addition of $NaHCO_3$ solution (40 mL, 30 %). The residue was extracted with ether (3 × 20 mL) and the combined organic phases were washed with water, dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum to give the crude products **10a–i**.

*5,12-Dihydro-5H-dibenzo[b,g][1,8]naphthyridin-12-one (**10a**)*

Yellow needles, 89 %, mp 148–150°C (benzene). ν_{max} (KBr)/cm^{-1} 3390, 3085, 2984, 1685, 1600, 1585, 1480, 1450, 1385, 1280, 1075, 740. δ_H (400 MHz, $CDCl_3$) 7.33–7.38 (m, 3H), 7.51 (quin, 1H, 2.4), 7.62 (dq, 2H, 2.0, 3.2, 2.4 and 2.0), 7.86 (dt, 1H, 1.6 and 2.0), 7.93 (dd, 1H, 1.6 and 2.0), 8.49 (d, 1H, 1.6), 9.53 (s, 1H, NH). δ_C (100 MHz, $CDCl_3$) 117.6 (1C, Ar, C-12a), 118.1 (1C, Ar,C-4), 119.2 (1C, Ar,C-2), 122.2 (1C, Ar, C-11a), 125.9 (1C, Ar, C-9), 126.6 (1C, Ar, C-10a), 127.1 (1C, Ar, C-7), 128.0 (1C, Ar, C-10), 128.5 (1C, Ar, C-1), 128.8 (1C, Ar, C-8), 129.0 (1C, Ar, C-3), 131.5 (1C, Ar, C-11), 141.1 (1C, Ar, C-6a), 146.4 (1C, Ar, C-4a), 157.0 (1C, Ar, C-5a), 185.0 (1C, C=O, C-12). *m/z* (EI, 70 eV) (%) 247 ($M^+ + 1$, 7), 246 (M^+, 34), 245 ($M^+ - 1$, 100), 232 (9), 231 (26), 217 (57), 216 (78), 205 (18), 203 (33), 192 (49), 177 (6), 166 (5), 150 (7), 104 (19), 91 (2), 77 (6), 56 (15). Anal. Calc. for $C_{16}H_{10}N_2O$ (246): C 78.04, H 4.06, N 11.38. Found: C 78.16, H 4.11, N 11.20 %.

*5,12-Dihydro-12H-benzo[g]pyrido[2,3-b][1,8]naphthyridin-5-one (**10b**)*

Pear-shaped crystals; 85 %; mp 184–186°C (acetone). ν_{max} (KBr)/cm^{-1} 3420, 3065, 2960, 1693, 1610, 1590, 1475, 1440, 1380, 1270, 1130, 760. δ_H (400 MHz, $CDCl_3$) 6.94 (q, 1H, 5.6, 2.4 and 5.2), 7.42 (septet (sp), 1H, 0.4, 1.6, 5.6 and 2.0), 7.62 (q, 1H, 2.0, 5.6 and 2.0), 7.85 (dq, 2H, 2.0, 2.0, 1.6 and 2.4), 7.93 (dd, 1H, 2.0 and 2.0), 8.50 (d, 1H, 2.0), 9.55 (s, 1H, NH). δ_C (100 MHz, $CDCl_3$) 118.1 (2C, Ar, C-3, C-4a), 123.3 (1C, Ar, C-5a), 126.6 (1C, Ar, C-8), 127.1 (1C, Ar, C-6a), 127.8 (1C, Ar, C-10), 128.0 (1C, Ar, C-7), 128.5 (1C, Ar, C-9), 128.9 (1C, Ar, C-6), 129.0 (1C, Ar, C-10a), 146.4 (1C, Ar, C-4), 150.6 (1C, Ar, C-11a), 157.0 (2C, Ar, C-2, C-12a), 185.0 (1C, C=O, C-5). *m/z* (EI, 70 eV) (%) 248 ($M^+ + 1$, 20), 247 (M^+, 20), 245 ($M^+ - 2$, 68.5), 232 (3), 217 (39), 203 (49), 191 (100), 189 (9), 178 (23), 166 (18), 151 (9), 91 (15), 90 (11), 77 (2), 66 (2), 57 (18). Anal. Calc. for $C_{15}H_9N_3O$ (247): C 72.87, H 3.64, N 17.00. Found: C 72.84, H 3.58, N 17.14 %.

*6,7,12-Trihydro-6H-benzo[5,6]azepino[2,3-b]quinoline-12-one (**10c**)*

White plates; 86 %; mp 154–156°C (cyclohexane). ν_{max} (KBr)/cm^{-1} 3362, 3082, 2945, 1692, 1600, 1590, 1475, 1440, 1380, 1275, 1172, 769. δ_H (400 MHz, $CDCl_3$) 4.94 (s, 2H, CH_2), 7.35 (sp, 2H, 7.6, 1.6, 4.4, 1.6 and 7.6), 7.62 (quin, 2H, 2.0, 0.8, 2.8, 4.0 and 1.6), 7.72–7.75 (m, 2H), 7.83 (d, 1H, 8.0), 7.86 (dd, 1H, 1.6 and 1.6), 8.30 (d, 1H, 1.6), 10.24 (s, 1H, NH). δ_C (100 MHz, $CDCl_3$) 48.7 (1C, –CH_2, C-7), 118.1 (1C, Ar, C-12a), 125.8 (1C, Ar, C-2), 126.6 (1C, Ar, C-4, C-13a), 127.0 (1C, Ar, C-11a), 127.1 (1C, Ar, C-10), 128.0 (1C, Ar, C-8), 128.5 (1C, Ar, C-1), 128.8 (1C, Ar, C-11), 129.0 (1C, Ar, C-3), 131.4 (1C, Ar, C-9), 132.4 (1C, Ar, C-7a), 133.1 (1C, Ar, C-13), 146.5 (1C, Ar, C-4a), 157.0 (1C, Ar, C-5a), 185.1 (1C, C=O, C-12). *m/z* (EI, 70 eV) (%) 261 ($M^+ + 1$, 58), 259 ($M^+ - 2$, 6.6), 244 (3), 232 (94), 230 (62), 228 (6), 215 (11), 202 (82), 201 (65), 190 (85), 177 (100), 166 (7), 164 (20), 94 (7), 90 (0.1), 77 (1). Anal. Calc. for $C_{17}H_{12}N_2O$ (260): C 78.46, H 4.61, N 10.76. Found: C 78.55, H 4.48, N 10.84 %.

*12,13-Dihydro-5H-benzo[6,7]azepino[2,3-b]quinoline-13-one (**10d**)*

White needles; 90 %; mp 142–144°C (benzene). ν_{max} (KBr)/cm^{-1} 3465, 3090, 2975, 1729, 1600, 1480, 1460, 1440, 1365,

1230, 745. δ_H (400 MHz, $CDCl_3$) 4.05 (s, 2H, CH_2), 7.33 – 7.39 (m, 3H), 7.47 (quin, 1H, 6.4, 2.0, 2.8 and 2.0), 7.55 (dt, 1H, 2.0, 4.4, 2.4 and 0.8), 7.68 (dq, 3H, 1.2, 1.6, 2.0 and 1.6), 6.88 (dt, 1H, 2.0, 1.6 and 1.2), 9.52 (s, 1H, NH). δ_C (100 MHz, $CDCl_3$) 45.5 (1C, –CH_2, C-12), 117.6 (1C, Ar, C-4), 122.2 (1C, Ar, C-2), 122.5 (1C, Ar, C-13a), 126.6 (1C, Ar, C-10a), 126.8 (1C, Ar, C-11a), 127.1 (1C, Ar, C-9), 128.0 (1C, Ar, C-7), 128.5 (1C, Ar, C-10), 128.8 (1C, Ar, C-8), 129.0 (1C, Ar, C-1), 130.6 (1C, Ar, C-11), 131.5 (1C, Ar, C-3), 141.1 (1C, Ar, C-6a), 146.4 (1C, Ar, C-4a), 157.0 (1C, Ar, C-5a), 199.22 (1C, C=O, C-13). *m/z* (EI, 70 eV) (%) 261 ($M^+ + 1$, 54), 260 (M^+, 6), 258 ($M^+ - 2$, 5), 233 (12), 232 (87), 230 (65), 218 (7), 216 (11), 201 (70), 191 (15), 190 (82), 177 (100), 164 (34), 152 (2), 94 (8), 77 (2). Anal. Calc. for $C_{17}H_{12}N_2O$ (260): C 78.46, H 4.61, N 10.76. Found: C 78.42, H 4.71, N 10.74 %.

*5,6-Dihydro-13*H*-pyrido[3′,2′:6,7]azepino[2,3-*b*]quinolin-5-one (**10e**)*

Yellowish crystals; 88 %; mp 138–140°C (acetone). ν_{max} (KBr)/cm^{-1} 3394, 3070, 2970, 1735, 1580, 1474, 1450, 1385, 1270, 1130, 1075, 765. δ_H (400 MHz, $CDCl_3$) 4.10 (s, 2H, CH_2), 6.93 (q, 1H, 5.6, 2.0 and 4.8), 7.47 (q, 1H, 1.2 and 1.6), 7.62 (d, 1H, 1.6), 7.62–7.82 (m, 4H), 8.13 (dd, 1H, 1.6, 3.2 and 1.6), 9.70 (s, 1H, NH). δ_C (100 MHz, $CDCl_3$) 45.5 (1C, –CH_2, C-6), 118.1 (1C, Ar, C-3), 123.3 (1C, Ar, C-4a), 126.6 (1C, Ar, C-6a), 127.1 (1C, Ar, C-7a), 127.8 (1C, Ar, C-9), 128.0 (1C, Ar, C-11), 128.5 (1C, Ar, C-8), 128.8 (1C, Ar, C-10), 129.0 (1C, Ar, C-7), 130.6 (1C, Ar, C-4), 146.4 (1C, Ar, C-11a), 150.6 (1C, Ar, C-2), 157.0 (2C, Ar, C-12a, C-13a), 199.2 (1C, C=O, C-5). *m/z* (EI, 70 eV) (%) 262 ($M^+ + 1$, 23), 261 (M^+, 87), 260 ($M^+ - 1$, 14), 246 (100), 231 (10), 229 (31), 217 (11), 192 (84), 177 (6), 167 (6), 164 (21), 90 (6), 77 (74), 56 (7). Anal. Calc. for $C_{16}H_{11}N_3O$ (261): C 73.56, H 4.21, N 16.09. Found: C 73.41, H 4.37, N 16.11 %.

*7,12,13-Trihydro-6*H*-benzo[6,7]azocino[2,3-*b*]quinoline-12-one (**10f**)*

White plates; 85 %; mp 162–164°C (methanol). ν_{max} (KBr)/cm^{-1} 3410, 3070, 2970, 1745, 1610, 1574, 1465, 1440, 1380, 1270, 1137, 755. δ_H (400 MHz, $CDCl_3$) 3.99 (s, 2H, CH_2), 4.67 (s, 2H, CH_2), 7.11 (dt, 1H, 1.2 and 1.2), 7.33–7.42 (m, 3H), 7.51 (d, 1H, 7.6), 7.63 (sp, 3H, 1.2, and 2.0), 7.92 (dt, 1H, 1.6, 0.8 and 1.6), 10.25 (s, 1H, NH). δ_C (100 MHz, $CDCl_3$) 45.5 (1C, –CH_2–, C-13), 48.69 (1C, –CH_2–, C-7), 125.87 (1C, Ar, C-13a), 126.63 (1C, Ar, C-2, C-14a), 127.02 (1C, Ar, C-4), 127.16 (1C, Ar, C-1), 128.09 (1C, Ar, C-8), 128.52 (1C, Ar, C-10), 128.88 (1C, Ar, C-3), 129.02 (1C, Ar, C-11), 130.67 (1C, Ar, C-9), 131.42 (1C, Ar, C-11a), 132.39 (1C, Ar, C-14), 133.15 (1C, Ar, C-7a), 146.48 (1C, Ar, C-4a), 157.00 (1C, Ar, C-5a), 193.00 (1C, C=O, C-12). *m/z* (EI, 70 eV) (%) 274 (M^+, 19), 271 ($M^+ - 3$, 2), 270 (76), 269 (29), 255 (26), 178 (100), 164 (47), 114 (50), 91 (71), 77 (23). Anal. Calc. for $C_{18}H_{14}N_2O$ (274): C 78.83, H 5.10, N 10.21. Found: C 78.85, H 5.27, N 10.09 %.

*5,6,7,14-Tetrahydro-14*H*-benzo[7,8]azocino[2,3-*b*]quinoline-5-one (**10g**)*

White crystals; 92 %; mp 188–190°C (ethanol). ν_{max} (film)/cm^{-1} 3380, 3066, 2950, 1740, 1595, 1494, 1475, 1450, 1355, 768. δ_H (400 MHz, $CDCl_3$) 2. 96 (app s, 4H, CH_2–CH_2), 7.33–7.37 (m, 2H), 7.44–7.49 (m, 2H), 7.62–7.73 (m, 5H), 9.74 (s, 1H, NH). δ_C (100 MHz, $CDCl_3$) 30.0 (1C, –CH_2–, C-7), 44.4 (1C, –CH_2–, C-6), 117.6 (1C, Ar, C-1), 122.2 (1C, Ar, C-3), 124.5 (1C, Ar, C-4a), 126.6 (1C, Ar, C-7a), 127.1 (1C, Ar, C-8a), 128.1 (1C, Ar, C-10), 128.5 (1C, Ar, C-9), 128.8 (1C, Ar, C-12), 129.0 (1C, Ar, C-11), 130.5 (1C, Ar, C-4), 130.6 (1C, Ar, C-2), 131.5 (1C, Ar, C-8), 141.1 (1C, Ar, C-12a), 146.4 (1C, Ar, C-14a), 157.0 (1C, Ar, C-13a), 204.3 (1C, C=O, C-5). *m/z* (EI, 70 eV) (%) 274 (M^+, 3), 272 ($M^+ - 2$, 3), 271 (3), 270 (23), 269 (100), 192 (21), 191 (69), 178 (33), 166 (13), 114 (19), 91 (2), 90 (19), 77 (7), 56 (2). Anal. Calc. for $C_{18}H_{14}N_2O$ (274): C 78.83, H 5.10, N 10.21. Found: C 78.69, H 5.04, N 10.27 %.

*5,6,7,14-Tetrahydro-14*H*-pyrido[3′,2′:7,8]azocino[2,3-*b*]quinolin-5-one (**10h**)*

Pale yellow crystals; 84 %; mp 118–120°C (acetone). ν_{max} (KBr)/cm^{-1} 3420, 3084, 2975, 1745, 1580, 1490, 1465, 1450, 1355, 765. δ_H (400 MHz, $CDCl_3$) 2.62 (t, 2H, 6, CH_2), 2.97 (t, 2H, 6, CH_2), 6.93 (q, 1H, 5.2), 7.47 (q, 1H, 6.0), 7.62–7.81 (m, 5H), 8.14 (q, 1H, 2.0 and 3.2), 9.65 (s, 1H, NH). δ_C 30.0 (1C, –CH_2–, C-7), 44.4 (1C, –CH_2–, C-6), 118.1 (1C, Ar, C-3), 123.3 (1C, Ar, C-4a), 126.6 (1C, Ar, C-7a), 127.1 (1C, Ar, C-8a), 127.8 (1C, Ar, C-10), 128.0 (1C, Ar, C-9), 128.5 (1C, Ar, C-12), 128.8 (1C, Ar, C-11), 129.0 (1C, Ar, C-8), 130.6 (1C, Ar, C-4), 146.4 (1C, Ar, C-12a), 150.6 (1C, Ar, C-2), 157.0 (2C, Ar, C-13a, C-14a), 199.2 (1C, C=O, C-5). *m/z* (EI, 70 eV) (%) 275 (M^+, 4), 269 (100), 206 (83), 192 (35), 190 (98), 178 (35), 165 (29), 104 (6), 91 (35), 77 (8), 65 (3). Anal. Calc. for $C_{17}H_{13}N_3O$ (275): C 74.18, H 4.72, N 15.27. Found: C 74.25, H 4.78, N 15.16 %.

*7,12,13,14-Tetrahydro-6*H*-benzo[7,8]azonino[2,3-*b*]quinoline-12-one (**10i**)*

White crystals; 86 %; mp 122–24°C (ethanol). ν_{max} (KBr)/cm^{-1} 3420, 3035, 2960, 1742, 1605, 1582, 1490, 1460, 1345, 759. δ_H (400 MHz, $CDCl_3$) 2.79 (t, 2H, 5.6, CH_2), 2.94 (t, 2H, 5.6, CH_2), 4.69 (s, 2H, CH_2), 7.20 (ddd, 1H, 1.6, 2.4 and 1.2), 7.32–7.39 (m, 2H), 7.45–7.53 (m, 2H), 7.60–7.64 (m, 3H), 7.89–7.92 (ddd, 1H, 1.2, 2.8, and 1.6), 9.92 (s, 1H, NH). δ_C 30.0 (1C, –CH_2–, C-14), 44.4 (1C, –CH_2–, C-13), 48.7 (1C, –CH_2–, C-7), 125.8 (1C, Ar, C-15a,), 126.6 (2C, Ar, C-2, C-14a), 127.0 (1C, Ar, C-4), 127.1 (1C, Ar, C-1), 128.0 (1C, Ar, C-8), 128.5 (1C, Ar, C-10), 128.8 (1C, Ar, C-3), 129.0 (1C, Ar, C-11), 130.6 (1C, Ar, C-9), 131.4 (1C, Ar, C-11a), 132.3 (1C, Ar, C-15), 133.1 (1C, Ar, C-7a), 146.4 (1C, Ar, C-4a), 157.0 (1C, Ar, C-5a), 206.8 (1C, C=O, C-12). *m/z* (EI, 70 eV) (%) 288 (M^+, 7), 286 (3), 283 (100), 254 (78), 207 (11), 206 (60), 190 (15), 177 (61), 166 (5), 164 (22), 128 (16), 113 (10), 83 (41), 90 (0.3). Anal. Calc. for $C_{19}H_{16}N_2O$ (288): C 79.16, H 5.55, N 9.72. Found: C 79.12, H 5.60, N 9.84 %.

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