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Synthesis and antibacterial activity of 5- and 6-hydroxy substituted 4-aminoquinolines and derivatives

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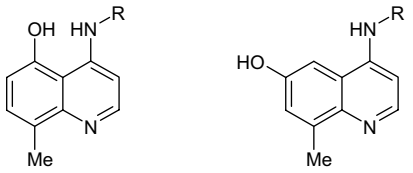
The synthesis and antimicrobial activity of 4-amino-8-methylquinolines **8**, **11** substituted with a hydroxy- or methoxy-group at 5- and at 6-position have been investigated. The title compounds could be prepared by a six-step procedure according to the literature starting from commercially available anilines **1**. The novel 4-aminoquinolines **8,11** exhibited slight antibacterial activity against Gram-positive and Gram-negative bacteria.

1. Introduction

Aminoquinolines and hydroxyquinolines represent essential pharmacophores of antimicrobials, e.g. amodiaquine [1], chloroquine [2], clamoxyquine [3], 8-hydroxyquinoline [4, 5] and quinactol sulfate [6].

As a part of our research interest directed to novel antimicrobial compounds we aimed to explore 4-amino- and 5/6-hydroxy-8-methylquinolines (structures **A** and **B**), the synthesis and antibacterial activities of which are described below.



A **B**

R= alkyl, arylalkyl or aryl

2. Investigations, results and discussion

2.1. Synthesis

5/6-Hydroxy-4-amino-8-methylquinolines (**A** and **B**) were prepared from **1a, b** as starting materials using methods reported previously [7, 8].

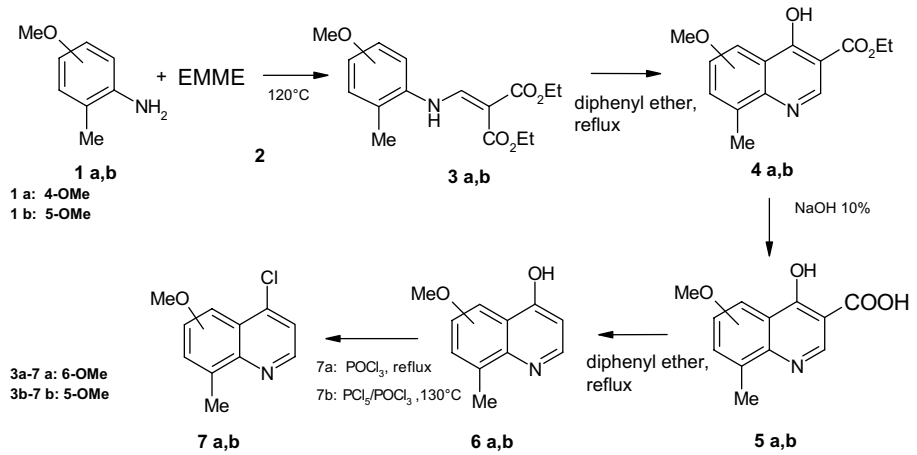
Condensation of equimolar amounts **1a**, **b** with ethoxymethylenemalonic ester **2** yielded the corresponding low-melting crystalline arylaminomethylenemalonates **3**, which underwent cyclization in boiling diphenyl ether to give the quinoline esters **4a**, **b** in 90% yield. Alkaline hydrolysis of **4** afforded the 3-quinolinecarboxylic acids **5**, the decarboxylation of which in refluxing diphenyl ether gave **6** in more than 50% yield as colourless powders (Scheme 2). Subsequent treatment of **6a** with boiling phosphorus oxychloride [7] provided smoothly **7a** in 80% yield. These reaction conditions proved to be not effective for the halogenation of **6b**. However, by reacting **6b** with a mixture of phosphorus pentachloride and oxychloride at 130 °C **7b** could be obtained in good yield of 80% (Scheme 1).

As outlined in Scheme 2 aminolysis of **7** with different amines in phenol as solvent [10] produced the desired 4-aminoquinolines **8a**–**g**. Optimal results were obtained by performing the reactions at temperatures ranging from 50 °C to 150 °C in dependance on the nature of the amine.

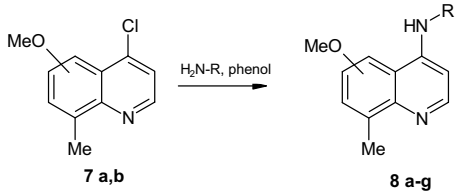
Alternatively **8c** could be synthesized by silylating **6b** (Scheme 3), followed by benzylaminolysis according to a methodology introduced by Vorbrüggen and Krolikiewicz [11].

Chlorination of 4-hydroxy-6-methoxy-8-methylquinoline-3-carboxylate (**4a**) with $PCl_5/POCl_3$ afforded the appropriate chlorinated quinoline **9a** in 60% yield, which in turn could be smoothly converted by n-pentylamine to give **10** (Scheme 4). In contrast to **4a** the corresponding 5-methoxy derivative **4b** resisted chlorination, reflecting significant lower reactivity of the 4-position caused by the carboxylate moiety in ring position 3.

Scheme 1

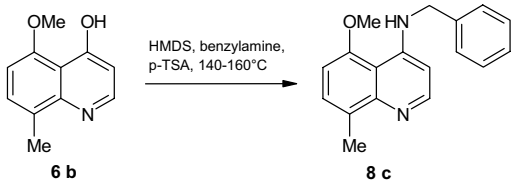


Scheme 2

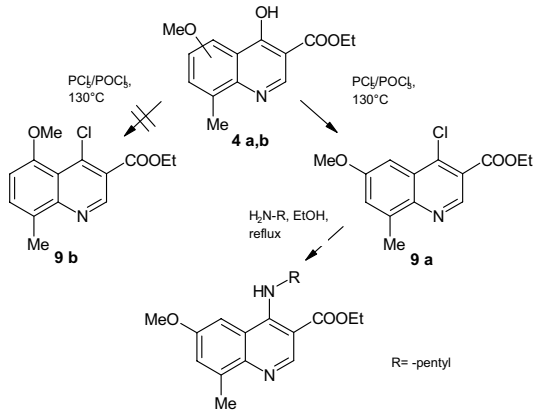


8	OMe	R
a	6-OMe	-4-chlorobenzyl
b	5-OMe	-phenyl
c	5-OMe	-benzyl
d	5-OMe	-4-chlorobenzyl
e	5-OMe	-allyl
f	5-OMe	-phenylethyl
g	5-OMe	-pentyl

Scheme 3

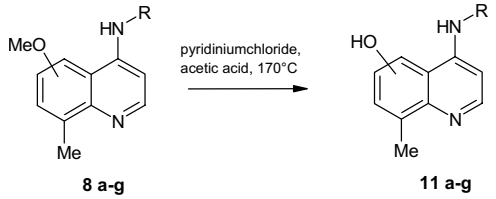


Scheme 4



When subjected to pyridinium chloride **8a**–**g** underwent demethylation at 170 °C as described previously [12] to yield the corresponding 5/6-hydroxyquinolines **11a**–**g** (Scheme 5), identified by a dark green colour reaction with ferric chloride in aqueous methanol.

Scheme 5



All new compounds have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and with the exeption of **11b** and **11g** by elemental analysis.

2.2. Antibacterial results

The 5- and 6-substituted 4-amino-8-methyl-quinolines **8**, **11** prepared in the present study were tested for antibacterial activitiy against Gram-positive and Gram-negative bacteria by the standard serial microdilution method (Table) [13]. The susceptibility of the microorganisms to the compounds was expressed as minimum inhibitory concentration (MIC), additionally in the case of visible growth inhibition the corresponding minimum bactericidal concentration was determined. Most of the synthesized 4-aminoquinolines exhibited antimicrobial activity against *Staphylococcus aureus*. *Escherichia coli* were less sensitive to the 4-amino-5-hydroxyquinolines **11a**–**f** than to 4-amino-5-methoxyquinolines **8a**–**g**. All compounds were inactive against *Pseudomonas aeruginosa*. Compared with modern gyrase inhibitors (ciprofloxacin) the most active compounds 5-methoxy-8-methyl-4-(2-phenyl)ethylamino-quinoline (**8f**) and 4-(4-chloro)benzylamino-6-hydroxy-8-methyl-quinoline (**11a**) showed modest antibacterial efficacy.

3. Experimental

3.1. General methods

Melting points were determined with a Electrothermal IA9000 SERIES-Digital apparatus and are uncorrected. IR spectra were recorded in KBr with a Perkin Elmer 1600 FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Bruker AMX 400 spectrometer. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane. Elemental analyses were run on a Heraeus CHN-O-Rapid, and the values found were within 0.4% of the theoretical values. Mass spectra were scanned on a Finnigan MAT311A spectrometer. Column chromatography was performed on silica gel ICN Silica 100–200 (active).

3.2. General method A

A mixture of equimolar quantities of aniline derivative **1** and diethyl ethoxymethylenemalonate **2** was heated to 120 °C for 1 h. The resulting oil was converted to a grey cristalline solid by cooling to room temperature.

3.3. Diethyl (4-methoxy-2-methyl-anilino)-methylenemalonate (**3a**)

The conditions employed for the preparation of this compound were those described in 3.2. (yield 98%): m.p. 71 °C; IR (KBr): 3266 (NH), 2983

Table: *In vitro* antibacterial activity of synthesized compounds

Compd.	*E. coli* ATCC25922		*S. aureus* ATCC24913		*Ps. aerug.* ATCC27853	
	MIC	MBC	MIC	MBC	MIC	MBC
8a	>512	–	16	32	>512	–
8b	128	256	32	64	>512	–
8c	256	512	32	128	>512	–
8d	64	64	32	32	>512	–
8e	256	>512	>512	–	>512	–
8f	>512	>512	16	32	>512	–
8g	256	256	64	64	>512	–
11a	32	64	16	32	>512	–
11b	–	–	–	–	–	–
11c	>512	–	32	64	>512	–
11d	–	–	–	–	–	–
11f	>512	–	32	64	>512	–
11g	–	–	–	–	–	–
Ciprofloxacin	< 0,1	–	1	–	1	–

MIC: minimal inhibitory concentration (μg/ml); MBC: minimal bactericidal concentration (μg/ml)

(CH, aliphat.), 1681 (C=O), 1636, 1582 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ [ppm] 1.23 (3 H, t, J = 7.1 Hz, CH_2-CH_3), 1.26 (3 H, t, J = 7.1 Hz, CH_2-CH_3), 2.27 (3 H, s, aryl-CH_3), 3.74 (3 H, s, aryl-OCH_3), 4.11 (2 H, q, J = 7.1 Hz, CH_2-CH_3), 4.20 (2 H, q, J = 7.1 Hz, CH_2-CH_3), 6.85 (1 H, d, J = 8.6 Hz, C5-H), 6.89 (1 H, s, C3-H), 7.31 (1 H, d, J = 8.6 Hz, C6-H), 8.33 (1 H, d, J = 13.8 Hz, NH−CH=C), 10.83 (1 H, d, J = 13.8 Hz, NH); ^{13}C NMR (DMSO-d_6): δ [ppm] 14.16 ($-CH_2-CH_3$), 14.21 ($-CH_2-CH_3$), 17.12 (aryl-CH_3), 55.22 (aryl-OCH_3), 59.17 ($-CH_2-CH_3$), 59.49 ($-CH_2-CH_3$), 91.72 (O=C−C−C=O), 112.39 (C6), 116.14 (C5), 118.26 (C3), 129.17 (C2), 131.26 (C1), 152.81 (NH−CH=C), 156.61(C4), 164.78 (C=O), 168.09 (C=O).
$C_{16}H_{21}NO_5$ (307.3)

3.4. Diethyl (5-methoxy-2-methyl-anilino)-methylenmalonate (3b)

The conditions employed for the preparation of this compound were those described in 3.2. (yield 98%): m.p. 79 °C; IR (KBr): 3448 (NH), 2986 (CH, aliphat.), 1681 (C=O), 1637, 1591 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ [ppm] 1.33 (3 H, t, J = 7.1 Hz, CH_2-CH_3), 1.38 (3 H, t, J = 7.1 Hz, CH_2-CH_3), 2.30 (3 H, s, aryl-CH_3), 3.82 (3 H, s, aryl-OCH_3), 4.25 (2 H, q, J = 7.1 Hz, CH_2-CH_3), 4.32 (2 H, q, J = 7.1 Hz, CH_2-CH_3), 6.62 (0,5 H, ABX-d, J = 2.0 Hz, C6-H), 6.64 (0,5 H, ABX-d, J = 2.6 Hz, C6-H), 6.76 (1 H, ABX-d, J = 2.6 Hz, C4-H), 7.11 (1 H, d, J = 8.1 Hz, C3-H), 8.50 (1 H, d, J = 13.7 Hz, NH−CH=C), 11.08 (1 H, d, J= 14.2 Hz, NH); ^{13}C NMR ($CDCl_3$): δ [ppm] 14.35 ($-CH_2-CH_3$), 14.45 ($-CH_2-CH_3$), 16.65 (aryl-CH_3), 55.54 (aryl-OCH_3), 60.10 (O−CH_2-CH_3), 60.41 (O−CH_2-CH_3), 93.83 (O=C−C−C=O), 101.97 (C6), 119.32 (C2), 131.86 (C3), 138.67 (C1), 152.02 (NH−CH=C), 159.13 (C5), 165.83 (C=O), 169.20 (C=O).
$C_{16}H_{21}NO_5$ (307.3)

3.5. General method B

The suspension of diethyl anilino-methylenemalonate **3** (10 mmol) in diphenyl ether (10 ml) was refluxed for 40 min. After dilution with petroleum ether at room temperature the light brown ethyl 4-hydroxy-8-methylquinoline-3-carboxylate **4** was collected by filtration and washed with petroleum ether.

3.6. Ethyl 4-hydroxy-6-methoxy-8-methylquinoline-3-carboxylate or ethyl 6-methoxy-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (4a)

The conditions employed for the preparation of this compound were those described in 3.5. (yield 90%): m.p. 257 °C; IR (KBr): 3223 (OH), 3105 (CH, aromat.), 2987 (CH, aliphat.), 1698 (C=O), 1627, 1586 (C=N, C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ [ppm] 1.28 (3 H, t, J = 7.1 Hz, CH_2-CH_3), 2.49 (3 H, s, C8-CH_3), 3.83 (3 H, s, C5-OCH_3), 4.22 (2 H, q, J = 7.1 Hz, CH_2-CH_3), 7.23 (1 H, d, J = 2.4 Hz, C5-H), 7.46 (1 H, d, J = 2.6 Hz, C7-H), 8.33 (1 H, d, J = 6.6 Hz, C2-H), 11.65 (1 H, d, J = 6.1 Hz, NH); ^{13}C NMR (DMSO-d_6): δ [ppm] 14.21 (CH_2-CH_3), 16.82 (C8-CH_3), 55.22 (C5-OCH_3), 59.44 (CH_2-CH_3), 103.44 (C5), 122.60 (C7), 128.69 (C4a), 129.06 (C3), 132.00 (C4), 143.14 (C2), 156.03 (C6), 164.91 (C8), 172.94 (C=O, ester).
$C_{14}H_{15}NO_4$ (261.3)

3.7. Ethyl 4-hydroxy-5-methoxy-8-methyl-quinoline-3-carboxylate (4b)

The conditions employed for the preparation of this compound were those described in 3.5. (yield 87%): m.p. 181 °C; IR (KBr): 3444 (OH), 3084 (CH, aromat.), 2993 (CH, aliphat.), 1716 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ [ppm] 1.45 (3 H, t, J = 6.6 Hz, CH_2-CH_3), 2.65 (3 H, s, C8-CH_3), 4.01 (3 H, s, C5-OCH_3), 4.48 (2 H, q, J = 6.6 Hz, CH_2-CH_3), 6.82 (1 H, d, J = 7.6 Hz, C6-H), 7.53 (1 H, d, J = 8.6 Hz, C7-H), 9.14 (1 H, s, C2-H), 12.69 (1 H, s, OH); ^{13}C NMR ($CDCl_3$): δ [ppm] 14.21 (CH_2-CH_3), 18.07 (C8-CH_3), 56.40 (C5-OCH_3), 61.81 (CH_2-CH_3), 103.92 (C4a), 106.03 (C6), 132.71 (C7), 137.72 (C3), 140.03 (C8), 149.49 (C2), 156.77 (C8a), 164.01 (C5), 168.41 (C4), 169.69 (C=O).
$C_{14}H_{15}NO_4$ (261.3)

3.8. General method C

A suspension of ethyl 4-hydroxy-8-methylquinoline-3-carboxylate **(4)** (8 mmol) in NaOH 10% was refluxed for 40 min. The solution was allowed to cool to room temperature and was neutralized with conc. HCl. The solid precipitate was filtered, washed with water and dried.

3.9. 4-Hydroxy-6-methoxy-8-methyl-quinoline-3-carboxylic acid (5a)

The conditions employed for the preparation of this compound were those described in 3.8. (yield 97%): m.p. 303 °C; IR (KBr): 3447 (OH), 3062 (CH, aromat.), 2967 (CH, aliphat.), 1700 (C=O, acid), 1653, 1576 (C=N, C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ [ppm] 2.59 (3 H, s, C8-CH_3), 3.89 (3 H, s, C5-OCH_3), 7.39 (1 H, s, C5-H), 7.54 (1 H, s, C7-H), 8.58 (1 H, s, C2-H), 15.55 (1 H, s, COOH), 12.69 (1 H, s, C4-OH); ^{13}C NMR (DMSO-d_6): δ [ppm] 16.68 (C8-CH_3), 55.21 (C5-OCH_3), 103.34 (C5), 121.92 (C7), 128.70 (C4a), 125.60 (C3), 130.43 (C4), 142.84 (C2), 156.08 (C6), 164.90 (C8), 178.94 (C=O, acid).
$C_{12}H_{11}NO_4$ (233.2)

3.10. 4-Hydroxy-5-methoxy-8-methyl-quinoline-3-carboxylic acid (5b)

The conditions employed for the preparation of this compound were those described in 3.8. (yield 61%): m.p. 278 °C; IR (KBr): 3588, 3512 (OH), 3074 (CH, aromat.), 2946 (CH, aliphat.), 1700 (C=O, acid), 1629, 1582 (C=C, C=N,) cm^{-1}; ^1H NMR (DMSO-d_6): δ [ppm] 2.44 (3 H, s, C8-CH_3), 3.86 (3 H, s, C5-OCH_3), 6.95 (1 H, d, J = 8.1 Hz, C7-H), 7.60 (1 H, d, J = 8.1 Hz, C6-H), 8.51 (1 H, s, C2-H), 12.16 (1 H, s, COOH), 15.97 (1 H, s, C4-OH); ^{13}C NMR (DMSO-d_6): δ [ppm] 16.60 (C8-CH_3), 55.91 (C5-OCH_3), 106.82 (C6), 108.40 (C4a), 114.84 (C3), 118.21 (C8), 135.27 (C7), 139.76 (C8a), 143.44 (C2), 158.20 (C5), 166.50 (C4), 179.29 (C=O, acid).
$C_{12}H_{11}NO_4$ (233.2)

3.11. General method D

Decarboxylation of the quinoline-3-carboxylic acid **5** (8 mmol) was effected by heating in refluxing diphenyl ether (20 ml) for a period of up to 60 min. The cooled mixture was diluted with petroleum ether and the white product was removed by filtration.

3.12. 4-Hydroxy-6-methoxy-8-methylquinoline or 6-methoxy-8-methyl-4-oxo-1,4-dihydroquinoline (6a)

The conditions employed for the preparation of this compound were those described in 3.11. (yield 87%): m.p. 174 °C; IR (KBr): 3378 (OH), 3081 (CH, aromat.), 2989 (CH, aliphat.), 1632, 1595, 1559 (C=N, C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ [ppm] 2.46 (3 H, s, C8-CH_3), 3.80 (3 H, s, C5-OCH_3), 6.03 (1 H, d, J = 8.0 Hz, C3-H), 7.17 (1 H, s, C5-H), 7.37 (1 H, s, C7-H), 7.77 (1 H, t, J = 8.0 Hz, C2-H), 11.11 (1 H, d, NH); ^{13}C NMR (DMSO-d_6): δ [ppm] 16.96 (C8-CH_3), 55.48 (C6-OCH_3), 104.02 (C6), 110.92 (C3), 114.23 (C4a), 118.80 (C8), 123.28 (C7),138.82 (C2), 141.12 (C8a), 147.61 (C5), 170.25 (C4). MS: 189.2 (100, M^+), 174.1 (14), 159.2 (18), 146.2 (14), 40.2 (14).
$C_{11}H_{11}NO_2$ (189.2 g/mol)

3.13 4-Hydroxy-5-methoxy-8-methyl-quinoline or 5-methoxy-8-methyl-4-oxo-1,4-dihydroquinoline (6b)

The conditions employed for the preparation of this compound were those described in 3.5. (yield 52%): m.p. 222 °C; IR (KBr): 3388 (OH), 3059 (CH, aromat.), 2990 (CH, aliphat.), 1629, 1595, 1569 (C=N, C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ [ppm] 2.35 (3 H, s, C8-CH_3), 3.46 (1 H, s, NH), 3.76 (3 H, s, C5-OCH_3), 6.00 (1 H, d, J = 7.1 Hz, C3-H), 6.68 (1 H, d, J = 8.2 Hz, C6-H), 7.36 (1 H, d, J = 8.6 Hz, C7-H), 7.70 (1 H, d, J = 7.1 Hz, C2-H); ^{13}C NMR (DMSO-d_6): δ [ppm] 16.96 (C8-CH_3), 55.58 (C5-OCH_3), 103.92 (C6), 110.92 (C3), 115.93 (C4a), 118.82 (C8), 132.28 (C7), 138.82 (C2), 141.12 (C8a), 157.61 (C5), 171.12 (C4).
$C_{11}H_{11}NO_2$ (189.2)

3.14. 4-Chloro-6-methoxy-8-methylquinoline (7a)

4-Hydroxyquinoline **6a** (0.38 g, 2 mmol) was added to $POCl_3$ (3 ml) and heated at 130 °C for 20 min. $POCl_3$ was removed under vacuo, and the residue was stirred in ice-water. After neutralization with NaOH 10% the precipitate was collected on a filter, washed with water and dried (yield 80%): m.p. 114 °C; IR (KBr): 3027 (CH, aromat.), 2924 (CH, aliphat.), 1628, 1584 (C=N, C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ [ppm] !!!2.35 (3 H, s, C8-CH_3), 3.46 (1 H, s, NH), 3.76 (3 H, s, C5-OCH_3), 6.00 (1 H, d, J = 7.1 Hz, C3-H), 6.68 (1 H, d, J = 8.2 Hz, C6-H), 7.36 (1 H, d, J = 8.6 Hz, C7-H), 7.70 (1 H, d, J = 7.1 Hz, C2-H); ^{13}C NMR (DMSO-d_6): δ [ppm] 16.96 (C8-CH_3), 55.58 (C6-OCH_3), 103.92 (C6), 110.92 (C3), 115.93 (C4a), 118.82 (C8), 132.28 (C7), 138.82 (C2), 141.12 (C8a), 157.61 (C5), 171.12 (C4).
$C_{11}H_{10}ClNO$ (207.7 g/mol)

3.15. 4-Chloro-5-methoxy-8-methylquinoline (7b)

A solution of PCl_5 (1.25 g, 6 mmol) and $POCl_3$ (2.76 g, 18 mmol) was heated to 90 °C and the 4-hydroxyquinoline **6b** (1.25 g, 6 mmol) was added. The reaction mixture was stirred at 130 °C for 30 min. After evaporation of the solvent, the residue was taken up in ice-water and the solution was neutralized with NaOH 10%. A crystalline product was obtained by filtration and drying. Sublimation under reduced pressure gave highly purified white product (yield 78%): m.p. 85 °C; IR (KBr): 3004 (CH, aromat.), 2960 (CH, aliphat.), 1628, 1582 (C=N, C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ [ppm] 2.68 (3 H, s, C8-CH_3), 3.94 (3 H, s, C5-OCH_3), 6.86 (1 H, d, J = 8.1 Hz, C3-H), 7.41 (1 H, d, J = 5.1 Hz, C6-H), 7.48 (1 H, d, J = 8.1 Hz, C7-H), 8.70 (1 H, d, J = 5.1 Hz, C2-H); ^{13}C NMR ($CDCl_3$): δ [ppm] 18.52 (C8-CH_3), 56.10 (C5-OCH_3), 107.03 (C6), 118.88 (C4a). 123.11 (C3), 129.53 (C8), 129.85 (C7), 141.05 (C8a), 148.04 (C2), 149.89 (C5), 154.45 (C4).
$C_{11}H_{10}ClNO$ (207.7)

3.16. General method E

A mixture of 4-chloro-quinoline **7** (1.04 g, 5 mmol), amine (5.1 mmol) and phenol (3.76 g, 40 mmol) was heated at constant temperature for up to 70 h. After cooling, CH_2Cl_2 (10 ml) and NaOH 2 mol/l (20 ml) were added. The organic layer was washed with NaOH 2 mol/l, dried over Na_2SO_4 and evaporated. The resulting solid was crystallized from alcohols, affording the 4-aminoquinolines **8**.

3.17. 4-(4-Chloro)benzylamino-6-methoxy-8-methylquinoline (8a)

The conditions employed for the preparation of this compound were those described in 3.16., at 150 °C for 120 min with 4-chlorobenzylamine (yield 90%): m.p. 165 °C; IR (KBr): 3245 (NH), 3078 (CH, aromat.), 2959 (CH, aliphat.), 1589, 1528 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.57 (3 H, s, C8-CH_3), 3.88 (3 H, s, C6-OCH_3), 4.55 (2 H, d, J = 6.1 Hz, $-CH_2-$N), 6.28 (1 H, d, J = 5.6 Hz, C3-H), 7.17 (1 H, d, J = 2.1 Hz, C5-H), 7.37–7.39 (5 H, m, phenyl), 7.47 (1 H, d, J = 2.6 Hz, C7-H), 7.67 (1 H, t, J = 6.1 Hz, NH), 8.20 (1 H, d, J = 5.6 Hz, C2-H); ^{13}C NMR (DMSO-d_6): δ [ppm] 18.32 (C8-$\underline{C}H_3$), 44.83 ($-CH_2-$N), 55.33 (C6-O$\underline{C}H_3$), 98.30 (C3), 99.17 (C5), 119.07 (C4a), 120.35 (C7), 128.26, 128.61 (C2′, C3′, C5′, C6′), 131.17 (C1′), 138.12 (C4′), 142.89 (C8a), 146.97 (C2), 148.85 (C6), 155.35 (C4).
$C_{18}H_{17}ClN_2O$ (312.8)

3.18. 5-Methoxy-8-methyl-4-phenylamino-quinoline (8b)

The conditions employed for the preparation of this compound were those described in 3.16., at 120 °C for 120 min with aniline (yield 50%): m.p. 82 °C; IR (KBr): 3378 (NH), 3055 (CH, aromat.), 2919 (CH, aliphat.), 1585, 1536 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.52 (3 H, s, C8-CH_3), 3.99 (3 H, s, C5-OCH_3), 6.77 (1 H, d, J = 5.1 Hz, C3-H), 6.86 (1 H, d, J = 7.6 Hz, C6-H), 7.19–7.47 (5 H, m, phenyl), 7.38 (1 H, d, J = 7.6 Hz, C7-H), 8.35 (1 H, d, J = 5.1 Hz, C2-H), 9.39 (1 H, s, NH); ^{13}C NMR (DMSO-d_6): δ [ppm] 18.29 (C8-$\underline{C}H_3$), 56.08 (C5-O$\underline{C}H_3$), 100.63 (C3), 103.78 (C6), 110.15 (C4a), 123.86, 124.60, 128.63, (C2′, C3′, C4′, C5′, C6′), 128.21 (C1′), 129.42 (C7), 139.64 (C8a), 149.33 (C2), 149.52 (C5), 155.27 (C4).
$C_{17}H_{16}N_2O$ (264.3)

3.19. 4-Benzylamino-5-methoxy-8-methylquinoline (8c)

The conditions employed for the preparation of this compound were those described in 3.16., at 150 °C for 100 min with benzylamine (yield 80%): m.p. 114 °C.
Alternatively **8c** could be obtained using following procedure: 4-Hydroxy-5-methoxy-8-methylquinoline **6b** (1.5 g, 8 mmol), benzylamine (2.5 g, 24 mmol), 4-toluene sulfonic acid (catalytic) and 1,1,1,3,3,3-hexamethyldisilazane (2.0 g, 13 mmol) were heated at 140 °C for 2 h, the temperature was then increased to 160 °C for 4 h. After removal of the solvent by destillation, the residue was cooled to room temperature. The product was recrystallized from acetone to yield **8c** (yield 68%): m.p. 117 °C; IR (KBr): 3402 (NH), 2998 (CH, aromat.), 2942 (CH, aliphat.), 1595, 1542 (C=N, C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.47 (3 H, s, C8-CH_3), 3.95 (3 H, s, C5-OCH_3), 4.56 (2 H, d, J = 6.1 Hz, $-CH_2-$N), 6.28 (1 H, d, J = 5.6 Hz, C3-H), 6.79 (1 H, d, J = 8.1 Hz, C6-H), 7.32–7.39 (5 H, m, phenyl), 7.34–7.39 (1 H, d in m of phenyl, J = 7.6 Hz, C7-H), 8.24 (1 H, d, J = 5.6 Hz, C2-H), 8.41 (1 H, t, J = 6.1 Hz, NH); ^{13}C NMR (DMSO-d_6): δ [ppm] 18.26 (C8-CH_3), 45.81 ($-CH_2-$N), 55.96 (C5-O$\underline{C}H_3$), 99.30 (C3), 103.39 (C6), 109.82 (C4a), 126.71 C2′, C3′, C5′und C6′), 126.80 (C4′), 127.46 (C8), 128.43 (C1′), 128.61 (C7), 138.56 (C8a), 148.83 (C2), 151.86 (C5), 155.68 (C4).
$C_{18}H_{18}N_2O$ (278.3)

3.20. 4-(4-Chloro)benzylamino-5-methoxy-8-methyl-quinoline (8d)

The conditions employed for the preparation of this compound were those described in 3.17., at 150 °C for 120 min with 4-chlorobenzylamine (yield 57%): m.p. 102 °C; IR (KBr): 3422 (NH), 3023 (CH, aromat.), 2919 (CH, aliphat.), 1586, 1539 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.47 (3 H, s, C8-CH_3), 3.96 (3 H, s, C5-OCH_3), 4.55 (2 H, d, J = 6.1 Hz, $-CH_2-$N), 6.24 (1 H, d, J = 5.6 Hz, C3-H), 6.80 (1 H, d, J = 7.6 Hz, C6-H), 7.36–7.45 (5 H, m, phenyl and C7-H), 8.24 (1 H, d, J = 5.6 Hz, C2-H), 8.49 (1 H, t, J = 6.1 Hz, NH); ^{13}C NMR (DMSO-d_6): δ [ppm] 18.27 (C8-CH_3), 45.08 ($-CH_2-$N), 55.93 (C5-O$\underline{C}H_3$), 99.33 (C3), 103.34 (C6), 109.89 (C4a), 127.65–128.50 (C2′, C3′, C5′, C6′), 127.46 (C8), 128.59 (C7), 131.21 (C1′), 137.79 (C8a), 149.00 (C2), 151.57 (C5), 155.64 (C4).
$C_{18}H_{17}ClN_2O$ (312.8)

3.21. 4-Allylamino-5-methoxy-8-methyl-quinoline (8e)

The conditions employed for the preparation of this compound were those described in 3.16., at 50 °C for 70 h with allylamine (yield 70%): m.p. 86 °C; IR (KBr): 3406 (NH), 3067 (CH, aromat.), 2978 (CH, aliphat.), 1635, 1595, 1537 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.48 (3 H, s, C8-CH_3), 3.93 (5 H, s, C5-OCH_3 and C1′-H_2), 5.19 (1 H, d, J = 10.2 Hz, C3′-H), 5.25 (1 H, d, J = 15.8 Hz, C3′-H), 5.94 (1 H, m, C2′-H), 6.34 (1 H, d, J = 5.6 Hz, C3-H), 6.77 (1 H, d, J = 7.6 Hz, C6-H), 7.34 (1 H, d, J = 7.6 Hz, C7-H), 7.98 (1 H, t, J = 5.6 Hz, NH), 8.31 (1 H, d, J = 5.6 Hz, C2-H); ^{13}C NMR (DMSO-d_6): δ [ppm] 18.36 (C8-CH_3), 44.55 (C1′), 55.86 (C5-OCH_3), 99.08 (C3), 103.12 (C6), 109.86 (C4a), 115.60 (C3′), 127.97 (C8), 128.19 (C7), 134.47 (C2′), 148.92 (C8a), 149.31 (C2), 151.56 (C5), 155.58 (C4).
$C_{14}H_{16}N_2O$ (213.3)

3.22. 5-Methoxy-8-methyl-4-(2-phenyl)ethylamino-quinoline (8f)

The conditions employed for the preparation of this compound were those described in 3.16., at 150 °C for 120 min with 2-phenylethylamine (yield 72%): m.p. 73 °C; IR (KBr): 3412 (NH), 3010 (CH, aromat.), 2925 (CH, aliphat.), 1629, 1577 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.47 (3 H, s, C8-CH_3), 2.99 (2 H, t, J = 6.6 Hz, $-CH_2-$Phenyl), 3.50 (2 H, dt, J = 5.6 Hz and 6.6 Hz, $-CH_2-$N), 3.80 (3 H, s, C5-OCH_3), 6.45 (1 H, d, J = 5.6 Hz, C3-H), 6.72 (1 H, d, J = 8.2 Hz, C6-H), 7.24–7.37 (6 H, m, phenyl and C7-H), 7.72 (1 H, t, NH), 8.34 (1 H, d, J = 5.6 Hz, C2-H); ^{13}C NMR (DMSO-d_6): δ [ppm] 18.32 (C8-$\underline{C}H_3$), 33.81 ($-CH_2-$phenyl), 43.58 ($-CH_2-$N), 55.71 (C5-O$\underline{C}H_3$), 98.58 (C6), 103.26 (C3), 109.66 (C4a), 126.32 (C7), 127.77 (C8a), 128.40, 128.43, 128.72 and 129.27 (C2′, C3′, C4′, C5′, C6′), 139.06 (C1′), 148.56 (C8), 149.38 (C2), 151.61 (C5), 155.47 (C4).
$C_{19}H_{20}N_2O$ (292.4)

3.23. 5-Methoxy-8-methyl-4-pentylamino-quinoline (8g)

The conditions employed for the preparation of this compound were those described in 3.16., at 100 °C for 8 h with 1-pentylamine (yield 30%): m.p. 47 °C; IR (KBr): 3426 (NH), 3065 (CH, aromat.), 2956 (CH, aliphat.), 1589, 1542 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 0.91 (3 H, t, J = 7.1 Hz, C5′-H_3), 1.36–1.39 (4 H, m, C3′-H_2 und C4′-H_2), 1.66 (2 H, m, C2′-H_2), 2.47 (3 H, s, C8-CH_3), 3.21 (2 H, dt, J = 6.6 Hz und 7.1 Hz, $-CH_2-$N), 3.93 (3 H, s, C5-OCH_3), 6.38 (1 H, d, J = 5.6 Hz, C3-H), 6.76 (1 H, d, J = 8.1 Hz, C6-H), 7.34 (1 H, d, J = 8.1 Hz, C7-H), 7.77 (1 H, t, J = 5.1 Hz, NH), 8.32 (1 H, d, J = 5.6 Hz, C2-H); ^{13}C NMR (DMSO-d_6): δ [ppm] 13.86 (C8-$\underline{C}H_3$), 21.79 (C4′), 27.46 (C2′), 28.71 (C5′), 42.13 (C1′), 55.92 (C5-O$\underline{C}H_3$), 98.40 (C3), 103.21 (C6), 109.73 (C4a), 127.83 (C8a), 128.30 (C7), 148.69 (C8), 149.29 (C2), 151.79 (C5), 155.62 (C4).
$C_{16}H_{22}N_2O$ (258.37)

3.24. Ethyl 4-chloro-6-methoxy-8-methylquinoline-3-carboxylate (9a)

A solution of PCl_5 (1.25 g, 6 mmol) and $POCl_3$ (2.76 g, 18 mmol) was heated to 90 °C and the ethyl 4-hydroxy-6-methoxy-8-methylquinoline-3-carboxylate (**4a**) (1.25 g, 6 mmol) was added. The reaction mixture was stirred at 130 °C for 30 min. After evaporation of the solvent, the residue was taken up in ice-water and the solution was neutralized with NaOH 10%. The white crystalline product **9a** was obtained by filtration and drying (yield 55%): m.p. 77 °C; IR (KBr): 3015 (CH, aromat.), 2959 (CH, aliphat.), 1731 (C=O), 1654, 1578 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 1.39 (3 H, t, J = 7.0 Hz, $CH_2-C\underline{H}_3$), 2.68 (3 H, s, C8-CH_3), 3.95 (3 H, s, C6-OCH_3), 4.43 (2 H, q, J = 7.0 Hz, $C\underline{H}_2-CH_3$), 7.40 (1 H, s, C5-H), 7.47 (1 H, s, C7-H), 8.96 (1 H, s, C2-H); ^{13}C NMR ($CDCl_3$): δ [ppm] 14.21 ($CH_2-\underline{C}H_3$), 17.12 (C8-CH_3), 55.26 (C5-OCH_3), 59.56 ($\underline{C}H_2-CH_3$), 103.25 (C5), 108.22 (C8a), 122.83 (C7), 128.29 (C4a), 129.40 (C3), 132.21 (C4), 143.23 (C2), 156.15 (C6), 164.76 (C8), 172.71 (C=O).
$C_{14}H_{14}ClNO_3$ (279.7)

3.25. Ethyl-6-methoxy-8-methyl-4-pentylamino-quinoline-3-carboxylate (10)

A suspension of ethyl 4-chloro-6-methoxy-8-methylquinoline-3-carboxylate (**9**) (0.84 g, 3 mmol) and 1-pentylamine in EtOH (15 ml) was refluxed for 3 h. After evaporation of the solvent, the residue was purified by CC (EtOAc) affording **10** (yield 60%): m.p. 65 °C; IR (KBr): 3156 (NH), 3015 (CH, aromat.), 2936 (CH, aliphat.), 1740 (C=O), 1670, 1570 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 0.86 (3 H, t, J = 7.1 Hz, C5′-H_3), 1.27–1.33 (4 H, m, C3′-H_2 and C4′-H_2), 1.34 (3 H, t, J = 7.1 Hz, ethyl-CH_3), 1.65 (2 H, m, C2′-H_2), 2.59 (3 H, s, C8-CH_3), 3.61 (2 H, dt, J = 6.6 Hz, $-CH_2-$N), 3.87 (3 H, s, C5-OCH_3), 4.32 (2 H, q, J = 7.1 Hz, ethyl-CH_2), 7.29 (1 H, s, C5-H), 7.45 (1 H, s, C7-H), 8.30 (1 H, t, J = 5.1 Hz, NH, secondary amine), 8.75 (1 H, s, C2-H; ^{13}C NMR (DMSO-d_6): δ [ppm] 13.76 (C8-CH_3), 14.05 (ethyl-$\underline{C}H_3$), 18.27 (C5′), 21.68 (C4′), 28.33 (C2′), 29.68 (C3′), 47.65 (C1′), 55.26 (C5-O$\underline{C}H_3$), 60.38 (ethyl-$\underline{C}H_2$), 102.30 (C5), 103.48 (C8a), 119.72 (C4a), 122.00 (C7), 138.29 (C3), 144.25 (C4), 147.51 (C2), 154.24 (C6), 155.19 (C8), 167.92 (C=O).

3.26. General method F

Methoxy-substituted 4-amino-8-methylquinolines **8** (3 mmol) and pryridinium chloride (1.2 g, 10 mmol) were heated with acetic acid (catalytic) at 170 °C for 4 h. After cooling to room temperature, water (30 ml) was

added. The precipitate was collected by filtration and washed with H_2O. From a solution of the solid in MeOH pure product **11** was isolated by adding Et_2O.

3.27. 4-(4-Chloro)benzylamino-6-hydroxy-8-methylquinoline hydrochloride (**11a**)

The conditions employed for the preparation of this compound were those described in 3.26. (yield 81%): m.p. 267 °C; IR (KBr): 3367 (OH), 3222 (NH), 3100 (CH, aromat.), 2978 (CH, aliphat.), 1593, 1560 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.60 (3 H, s, C8-CH_3), 4.77 (2 H, d, J = 6.1 Hz, N−CH_2), 6.66 (1 H, d, J = 7.1 Hz, C3-H), 7.42–7.48 (5 H, m, C5-H and phenyl), 7.69 (1 H, d, J = 2.0 Hz, C7-H), 8.25 (1 H, d, C2-H), 9.61 (1 H, t, J = 6.1 Hz, NH, secondary amine), 10.55 (1 H, s, OH), 13.28 (1 H, s, N1-H); ^{13}C NMR (DMSO-d_6): δ [ppm] 17.58 (C8-$\underline{C}H_3$), 44.83 (N−CH_2), 98.28 (C3), 100.74 (C5), 118.19 (C4a), 125.06 (C8a), 128.51, 128.86, 128.95 (C2′, C3′, C5′, C6′), 130.83 (C4′), 131.69 (C1′), 135.99 (C8), 140.30 (C7), 142.21 (C2), 154.95 (C6), 157.28 (C4).
$C_{17}H_{16}N_2Cl_2$ (335.2)

3.28. 5-Hydroxy-8-methyl-4-phenylamino-quinoline hydrochloride (**11b**)

The conditions employed for the preparation of this compound were those described in 3.26. (yield 90%): m.p. 89 °C; IR (KBr): 3400 (OH), 3311 (NH), 3023 (CH, aromat.), 2933 (CH, aliphat.), 1624, 1534 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.51 (3 H, s, C8-CH_3), 6.60 (1 H, d, J = 7.1 Hz, C3-H), 7.13 (1 H, d, J = 8.2 Hz, C6-H), 7.39–7.63 (6 H, m, C7-H and phenyl), 8.25 (1 H, d, J = 5.1 Hz, C2-H), 11.13 (1 H, s, NH, secondary amine), 12.73 (1 H, s, N1-H), 13.09 (1 H, s, C5-OH); ^{13}C NMR (DMSO-d_6): δ [ppm] 17.11 (C8-$\underline{C}H_3$), 98.95 (C3), 110.54 (C6), 117.45 (C4a), 125.86, 127.77, 129.97 (C2′, C3′, C4′, C5′, C6′), 135.20 (C7), 136.69 (C1′), 138.00 (C8), 142.21 (C2), 152.30 (C8a), 154.96 (C5), 157.27 (C4). MS: m/z (%) = 250.2 (100, M^+), 231.2 (42), 219.1 (69), 173.2 (10).
$C_{16}H_{15}ClN_2O$ (286.8)

3.29. 4-Benzylamino-5-hydroxy-8-methylquinoline hydrochloride (**11c**)

The conditions employed for the preparation of this compound were those described in 3.26. (yield 70%): m.p. 240 °C; IR (KBr): 3421 (OH), 3335 (NH), 3012 (CH, aromat.), 2951 (CH, aliphat.), 1628, 1552 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.45 (3 H, s, C8-CH_3), 4.83 (2 H, d, J = 5.6 Hz, −CH_2−N), 6.64 (1 H, d, J = 7.6 Hz, C3-H), 7.04 (1 H, d, J = 8.6 Hz, C6-H), 7.30–7.42 (5 H, m, phenyl), 7.58 (1 H, d, J = 8.6 Hz, C7-H), 8.25 (1 H, dd, J = 5.6 Hz and 6.1 Hz, C2-H), 10.16 (1 H, t, NH, secondary amine), 12.41 (1 H, s, C5-OH), 12.69 (1 H, d, N1-H); ^{13}C NMR (DMSO-d_6): δ [ppm] 16.92 (C8-$\underline{C}H_3$), 46.28 (−CH_2−N), 98.16 (C3), 110.37 (C6), 118.10 (C4a), 127.00, 127.42, 128.71 (C2′, C3′, C4′, C5′, C6′), 136.80 (C7), 136.94 (C1′), 137.54 (C8), 141.73 (C2), 156.83 (C5), 157.83 (C4).
$C_{17}H_{17}ClN_2O$ (300.8)

3.30. 5-Hydroxy-8-methyl-4-(2-phenyl)ethylamino-quinoline hydrochloride (**11f**)

The conditions employed for the preparation of this compound were those described in 3.26. (yield 85%): m.p. 199 °C; IR (KBr): 3422 (OH), 3300 (NH), 3024 (CH, aromat.), 2939 (CH, aliphat.), 1627, 1550 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 2.43 (3 H, s, C8-CH_3), 3.02 (2 H, t, J = 7.1 Hz, −CH_2−phenyl), 3.76 (2 H, dt, J = 6.6 Hz, −CH_2−N), 6.75 (1 H, d, J = 7.1 Hz, C3-H), 7.03 (1 H, d, J = 8.2 Hz, C6-H), 7.24–7.36 (5 H, m, phenyl), 7.51 (1 H, d, J = 8.2 Hz, C7-H), 8.23 (1 H, d, J = 7.1 Hz, C2-H), 9.68 (1 H, t, J = 5.1, NH, secondary amine), 12.40 (1 H, s, N1-H), 12.79 (1 H, s, OH); ^{13}C NMR (DMSO-d_6): δ [ppm] 17.08 (C8-$\underline{C}H_3$), 33.51 (−CH_2−phenyl), 44.29 (−CH_2−N), 97.60 (C3), 107.15 (C4a), 110.31 (C6), 117.21 (C8a), 126.49, 128.47, 128.76 (C2′, C3′, C4′, C5′, C6′), 134.60 (C7), 137.47 (C1′), 138.14 (C8), 141.61 (C2), 154.89 (C5), 157.56 (C4).
$C_{18}H_{19}ClN_2O$ (314.8)

3.31. 5-Hydroxy-8-methyl-4-pentylamino-quinoline hydrochloride (**11g**)

The conditions employed for the preparation of this compound were those described in 3.26. (yield 65%): m.p. 131 °C; IR (KBr): 3420 (OH), 3338 (NH), 3044 (CH, aromat.), 2954 (CH, aliphat.), 1630, 1560 (C=C, C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ [ppm] 0.90 (3 H, t, J = 6.6 Hz, C5′-H_3), 1.36–1.37 (4 H, m, C3′-H_2 and C4′-H_2), 1.69 (2 H, m, C2′-H_2), 2.46 (3 H, s, C8-CH_3), 3.50 (2 H, m, −CH_2−N), 6.70 (1 H, d, J = 7.1 Hz, C3-H), 7.07 (1 H, d, J = 8.1 Hz, C6-H), 7.52 (1 H, d, J = 8.1 Hz, C7-H), 8.23 (1 H, t, J = 6.1 Hz, C2-H), 9.70 (1 H, t, NH, secondary amine), 12.47 (1 H, s, OH), 12.75 (1 H, d, N1-H); ^{13}C NMR (DMSO-d_6): δ [ppm] 13.79 (C8-$\underline{C}H_3$), 17.10 (C5′), 21.68 (C4′), 27.24 (C2′), 28.38 (C3′), 42.82 (C1′), 97.46 (C3), 107.19 (C4a), 110.35 (C6), 117.23 (C8a), 134.57 (C7), 137.51 (C8), 141.57 (C2), 154.94 (C5), 157.62 (C4). MS: m/z (%) = 227.1 (42, M^+), 192.3 (24), 97.3 (10), 57.3 (10), 40.2 (12).
$C_{15}H_{21}ClN_2O$ (280.8)

3.26. Biological methods

Minimal inhibitory concentration (MIC) values were determined by three fold serial broth microdilution method according to recommendation of WHO-ICS[12]. The microdilution panels were inoculated to give a final organism density of 10^6 CFU/ml in each well, incubated at 36 °C for 18–24 h. The MIC was read as the lowest concentration of the antimicrobial agent at which no visible growth was exhibited.
Aliquots of no visible growth were transferred to 7% sheep blood agar plates. After incubation at 36 °C for 18–24 h and examination for growth, the lowest concentration of compound at which no visible growth occured was considered to be the minimal bactericidal concentration (MBC).

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Received October 10, 2000
Accepted February 20, 2001

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