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Preparation and Fungitoxicity of Some Dichloro-8-Quinolinols

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Summary. 2,5-, 3,5-, 3,7-, 4,5-, 5,6-, und 6,7-Dichloro-8-quinolinols were prepared and tested along with their 3,6- and 5,7-analogues against six fungi (*Aspergillus niger*, *A. oryzae*, *Myrothecium verrucaria*, *Trichoderma viride*, *Mucor cirinelloides*, and *Trichophyton mentagrophytes*) in *Sabouraud* dextrose broth. Most of the compounds were strongly antifungal, inhibiting five of the fungi below 1 μg/ml. This activity is attributed to intramolecular synergism. *M. cirinelloides* was inhibited less by these compounds.

Keywords. Dichloro-8-quinolinols; Antifungal activity; Intramolecular synergism.

Darstellung und Fungitoxizität einiger Dichlor-8-chinolinole

Zusammenfassung. 2,5-, 3,5-, 3,7-, 4,5-, 5,6-, und 6,7-Dichlor-8-chinolinole wurden dargestellt und zusammen mit ihren 3,6- und 5,7-Analoga gegenüber sechs Pilzen (*Aspergillus niger*, *A. oryzae*, *Myrothecium verrucaria*, *Trichoderma viride*, *Mucor cirinelloides*, and *Trichophyton mentagrophytes*) auf *Sabouraud*-Dextrose-Nährboden getestet. Die meisten Verbindungen zeigten starke fungistatische Wirkung mit einer Hemmkonzentration unterhalb 1 μg/ml. Diese Aktivität wird einer intramolekularen Synergie zugeschrieben. *M. cirinelloides* wurde durch diese Verbindungen weniger stark gehemmt.

Introduction

In the course of our studies of structure to antifungal activity relationships of 8-quinolinol and its substituted analogues, it has been observed that 8-quinolinols with substituents in positions 5, 6, and 7 attack different sites from each other and from 8-quinolinol and its 2-, 3-, and 4-, substituted analogues. This was determined by the presence or absence of synergism between pairs of compounds and by the protection of the fungi by cysteine when the substituent was located on the pyridine ring but not when the phenol ring was substituted [1, 2].

The enhanced activity of the disubstituted 8-quinolinols was explained on the basis of intramolecular synergism, *i.e.*, a mixture of minimal inhibitory concentrations (MICs) of 5- and 7-chloro-8-quinolinols were synergistic, but when

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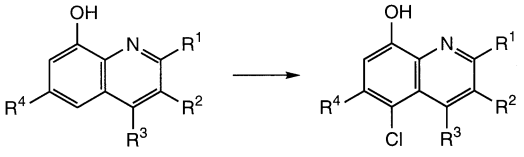
the MIC of this synergistic mixture was admixed with a MIC of 5,7-dichloro-8-quinolinol the result was additive. The same was true for combinations of 8-quinolinol and 5-, 6-, or 7-substituted analogues, thus allowing for the extension of the concept of intramolecular synergism to explain the enhanced activity of the 5-, 6-, or 7-monosubstituted 8-quinolinols over 8-quinolinol [3].

It has been reported that 3,6-dichloro-8-quinolinol is the most fungitoxic member of this class of compounds and that the dibromo analogue is less active [4]. When combinations of analogous bromo chloro compounds were studied, 6-bromo-3-chloro-8-quinolinol was found to be more active than its reverse analogue [5], but less fungitoxic than 3,6-dichloro-8-quinolinol. To determine if compounds of still greater fungitoxicity could be found, the preparation of additional dichloro-8-quinolinols was undertaken.

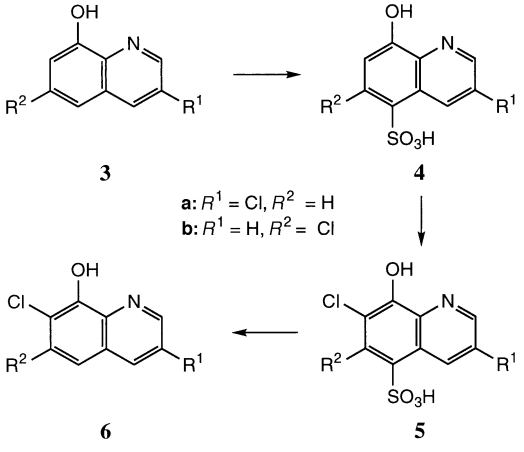
Results and Discussion

The 2,5-, 3,5-, 4,5-, and 5,6-dichloro-8-quinolinols were prepared from the respective monochloro-8-quinolinols [6] by reaction with N-chlorosuccinimide (*NCS*) in 93% sulfuric acid at ambient temperatures as shown in Scheme 1. The preparation of 3,7- and 6,7-dichloro-8-quinolinols was carried out by sulfonation of the 3- and 6-chloro-8-quinolinols in position 5 with 18% oleum, followed by chlorination of position 7 with *NCS* and desulfonation in 15% sulfuric acid in acetic acid (Scheme 2). It should be mentioned that a side reaction took place



1 **a:** R^1 = Cl, R^2 = R^3 = R^4 = H **2**
b: R^2 = Cl, R^1 = R^3 = R^4 = H
c: R^3 = Cl, R^1 = R^2 = R^4 = H
d: R^4 = Cl, R^1 = R^2 = R^3 = H

Scheme 1



3 **4**

a: R^1 = Cl, R^2 = H
b: R^1 = H, R^2 = Cl

6 **5**

Scheme 2

Table 1. Antifungal activity of dichloro-8-quinolinols in *Sabouraud* dextrose broth at 28°C in shake cultures after six days

	Minimal Inhibitory Concentrations (mmol/l (μg/ml))					
	A. niger	*A. oryzae*	*M. verrucaria*	*T. viride*	*M. cirinelloides*	*T. mentagrophytes*
2a	>0.47 (>100)[a]	0.093 (20)	0.042 (9)	>0.47 (>100)	>0.47 (>100)	0.093 (20)
2b	<0.0047 (<1)[b]	<0.0047 (<1)	<0.0047 (<1)	<0.0047 (<1)	0.14 (30)	<0.0047 (<1)
8[c]	<0.0047 (<1)	<0.0047 (<1)	<0.0047 (<1)	<0.0047 (<1)	0.033 (7)	<0.0047 (<1)
6a	<0.0047 (<1)	<0.0047 (<1)	<0.0047 (<1)	<0.0047 (<1)	0.28 (60)	<0.0047 (<1)
2c[d]	0.0093 (2)	0.0093 (2)	<0.0047 (<1)	0.019 (4)	0.028 (6)	<0.0047 (<1)
2d	<0.0047 (<1)	<0.0047 (<1)	<0.0047 (<1)	<0.0047 (<1)	0.093 (20)	<0.0047 (<1)
9[e]	<0.0047 (<1)	<0.0047 (<1)	<0.0047 (<1)	0.0093 (>.2)	>0.47 (>100)	<0.0047 (<1)
6b	<0.0047 (<1)	<0.0047 (<1)	<0.0047 (<1)	0.014 (3)	0.23 (50)	<0.0047 (<1)

[a] The symbol > indicates above 100 μg/ml (the highest level tested); [b] < indicates below 1 μg/ml (the lowest level tested); MICs from 1–10 were obtained in increments of 1 and from 10–100 in increments if 10; [c] compound **8** is 3,6-dichloro-8-quinolinol; data taken from Ref [5] except the result for *T. mentagrophytes* which is new; [d] for reproducible results, fresh solutions had to be prepared for each test because this compound hydrolyzes on standing in *DMSO*; [e] compound **9** is 5,7-dichloro-8-quinolinol; it was purchased from Aldrich Chemical Co.

during the chlorination of the monochloro-8-quinolinol-5-sulfonic acids. The sulfonyl group in position 5 was replaced in part by chlorine, yielding 3,5,7-trichloro-8-quinolinol (**7**) from **4a** along with **5a** and 5,6,7-trichloro-8-quinolinol from **4b** and **5b**. These trichloro-8-quinolinols were obtained in significant yield.

^{1}H and ^{13}C NMR data characterizing these compounds are shown in the experimental section. As reported previously, 5-sulfonic acids cause a shift of the proton at C-4 to higher δ values than that at C-2 which generally has the highest δ value in quinolines [7]. A similar effect of a 5-sulfonyl substituent can also be seen in the ^{13}C NMR spectra where C-4 is shifted some 10 ppm higher than in most nonsulfonic acids; however, it does not move to higher δ values than C-2 as it does in the ^{1}H NMR spectra. One exception to this rule is shown by 3-chloro-8-quinolinol-5-sulfonic acid where the 3-chloro substituent counteracts the effect of the 5-sulfonyl substituent in the ^{13}C NMR spectrum.

Table 1 contains a summary of the antifungal data obtained for the six compounds in addition to the results of 3,6- and 5,7-dichloro-8-quinolinols. The 2,5-dichloro analogue was the least active of the eight compounds: not inhibiting *A. niger*, *T. viride*, and *M. cirinelloides* below 100 μg/ml, but inhibiting *A. oryzae* (20 μg/ml), *M. verrucaria* (9 μg/ml), and *T. mentagrophytes* (20 μg/ml). The last three results were close to those obtained with 8-quinolinol [1]. The relatively poor toxicity of this analogue compared with the other members of the table can be rationalized on the basis of chlorine in position 2 yielding a compound with poor fungitoxicity even though 5-chloro-8-quinolinol is quite fungitoxic [1]. 4,5-Dichloro-8-quinolinol was the next least active compound, but it was at least or more fungitoxic than any monochloro-8-quinolinol except 6-chloro-8-quinolinol against *A. niger*, and 5-, 6-, and 7-chloro-8-quinolinols against *T. viride*. The remaining dichloro-8-quinolinols were much more active than any monochloro-8-quinolinol and in most cases caused complete inhibition of the fungus below 1 μg/ml. *M. cirinelloides* was the most resistant organism to these compounds [1].

Since all binary combinations of monochloro-8-quinolinols formed synergistic mixtures except for those containing 2-chloro-8-quinolinol which could not be tested because of the inactivity of the compound, and because binary mixtures containing 3- and 6-chloro and 5- and 7-chloro-8-quinolinols in combination with MICs of the respective 3,6- and 5,7-dichloro-8-quinolinols showed additive antifungal activity [3], we believe that the enhanced activity of the dichloro-8-quinolinols tested herein is due to intramolecular synergism. The significance of intramolecular synergism is that it takes smaller amounts of xenobiotics to affect a target cell or organism. It may also be more difficult for these cells to develop resistance to a compound which attacks two sites simultaneously compared to a material which affects only one site.

Experimental

Antifungal testing

The dichloro-8-quinolinols were tested for antifungal activity in *Sabouraud* dextrose broth (Difco) according to published methods [8–11]. The six fungi employed included *Aspergillus niger* (ATCC 1004), *A. oryzae* (ATCC 1011), *Myrothecium verrucaria* (ATCC 9095), *Trichoderma viride* (ATCC 8678), *Mucor cirinelloides* (ATCC 7941), and *Trichophyton mentagrophytes* (ATCC 9129).

Compounds

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The purity of samples was established by ^{1}H and ^{13}C NMR spectroscopy at 300 MHz and 75 MHz with a Bruker DPX-300 spectrometer using *DMSO*-d_6 as solvent and *TMS* as internal standard. Elemental analyses matched the calculated values satisfactorily for **2a–d** (C,H,Cl,N), **4a**,**b** (C,H,Cl,N,S), **5a**,**b** (C,H,Cl,N,S), and **6a**, **b** (C,H,Cl,N).

2,5-Dichloro-8-quinolinol (**2a**; $C_9H_5Cl_2NO$)

To a solution of **1a** [6] (2.0 g, 0.011 mol) in 40 ml of 93% sulfuric acid, *NCS* (1.5 g, 0.011 mol) was added at ambient temperatures with stirring overnight. The solution was poured into 400 ml of deionized water stirred for 10 min. The product was obtained by filtration, washing with deionized water, and drying at 50°C. The yield was 2.0 g (85%), m.p.: 118–120°C. Steam distillation raised the m.p. to 121–122°C. The analytical sample was crystallized from acetonitrile, m.p.: 121–121.5°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.48 (d, H-4), 7.72 (d, $J_{34} = 8.89$ Hz, H-3), 7.64 (d, H-6), 7.19 (d, $J_{67} = 8.37$ Hz, H-7), 10.4 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 152.3 (C-8), 148.9 (C-2), 138.7 (C-8a), 136.3 (C-4), 128.0 (C-6), 125.1 (C-4a), 123.8 (C-3), 118.8 (C-5), 113.7 (C-7) ppm.

3,5-Dichloro-8-quinolinol (**2b**; $C_9H_5Cl_2NO$)

2b was prepared from **1b** [6] in the same manner as **2a** was prepared from **1a**. The yield of product was 98% from a 0.011 mol run, m.p.: 152–153°C. The analytical sample was crystallized from acetonitrile, m.p.: 154–155°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.71 (d, $J_{24} = 2.26$ Hz, H-2), 8.24 (d, H-4), 7.46 (d, $J_{67} = 8.43$ Hz, H-6), 6.94 (d, H-7), 10.5 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 153.1 (C-8), 147.6 (C-2), 137.1 (C-8a), 130.4 (C-4), 129.5 (C-6), 129.0 (C-3), 126.4 (C-4a), 117.6 (C-5), 112.4 (C-7) ppm.

4,5-Dichloro-8-quinolinol (**2c**; $C_9H_5Cl_2NO$)

2c was prepared from **1c** [6] as was **2a** from **1a**. The product was obtained in 100% yield based on a 0.011 mol run, m.p.: 148–149°C. After steam distillation the melting point was 152–154°C; the analytical sample was crystallized from acetonitrile, m.p.: 155–156°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.79 (d, $J_{23} = 4.62$ Hz, H-2), 7.83 (d, H-3), 7.67 (d, $J_{67} = 8.47$ Hz, H-6), 7.16 (d, H-7), 10.3 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 153.3 (C-8), 148.0 (C-2), 140.7 (C-4), 139.9 (C-8a), 131.9 (C-6), 125.8 (C-3), 122.9 (C-4a), 116.5 (C-5), 112.2 (C-7) ppm.

5,6-Dichloro-8-quinolinol (**2d**; $C_9H_5Cl_2NO$)

2d was prepared from **1d** [6] by the same procedure as for **2a** and obtained in 92% yield from a 0.011 mol run, m.p.: 149–150°C. The analytical sample was crystallized from acetonitrile, m.p.: 153–154°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 9.02 (dd, $J_{23} = 4.17$ Hz, $J_{24} = 1.41$ Hz H-2), 8.54 (dd, $J_{34} = 8.59$ Hz, H-4), 7.81 (dd, H-3), 7.32 (s, H-7), 10.8 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 153.5 (C-8), 149.1 (C-2), 137.9 (C-8a), 132.8 (C-4), 130.3 (C-6), 126.7 (C-4a), 123.9 (C-3), 116.5 (C-5), 112.5 (C-7) ppm.

3-Chloro-8-quinolinol-5-sulfonic acid (**4a**; $C_9H_6ClNO_4S$)

To 14 ml of 18% oleum cooled to < 10°C, 2.0 g (0.011 mol) of **3a** [6] were added with stirring. When the solution was complete, it was refrigerated overnight and then poured into a mixture of water and ice with stirring. The crystalline precipitate was filtered, washed with water and acetone, and dried on air. The yield of product was 2.76 g, (94.7%), m.p.: < 360°C. An analytical sample crystallized from aqueous *DMSO* melted > 360°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 9.25 (d, $J_{24} = 2.20$ Hz, H-2), 10.6 (d, H-4), 7.97 (d, $J_{67} = 8.25$ Hz, H-6), 7.10 (d, H-7), 5.0 (s, SO_3H) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 153.6 (C-8), 146.1 (C-2), 135.1 (C-8a), 135.0 (C-4), 133.3 (C-5), 128.2 (C-3), 127.9 (C-6), 125.5 (C-4a), 110.5 (C-7) ppm.

6-Chloro-8-quinolinol-5-sulfonic acid (**4b**; $C_9H_6ClNO_4S \cdot 0.5H_2O$)

4b was prepared from **3b** [6] by the same manner as **4a** in 84.1% yield from a 0.018 mol run, m.p.: 230–235°C. The analytical sample prepared by crystallization from aqueous *DMSO* melted at 232–235°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 9.08 (dd, $J_{23} = 5.11$ Hz, $J_{24} = 1.11$ Hz H-2), 10.3 (dd, H-4), 8.13 (dd, $J_{34} = 9.03$ Hz, H-3), 7.30 (s, H-7), 7.0 (s, SO_3H) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 149.0 (C-8), 145.6 (C-2), 143.8 (C-4), 132.8 (C-8a), 132.3 (C-5), 129.2 (C-6), 128.1 (C-4a), 122.9 (C-3), 116.9 (C-7) ppm.

3,7-Dichloro-8-quinolinol-5-sulfonic acid (**5a**; $C_9H_5Cl_2NO_4S$)

A stirred mixture of **4a** (4.0 g, 0.016 mol) and *NCS* (2.1 g, 0.016 mol) in 89 ml H_2O was adjusted to *pH* 7.0 with KOH. Stirring was continued for about 0.5 h until a negative starch iodide test was obtained, and the solution was acidified with concentrated sulfuric acid and cooled in an ice bath. The product was obtained by filtration, washed with water followed by hot acetone, and dried on air. The process may have to be repeated until the starting material is nearly completely chlorinated as monitored by ^{1}H NMR. The yield of product was 2.2 g (47%), m.p.: 322–325°C. The analytical sample was crystallized from water, m.p.: 323–325°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 9.14 (d, $J_{24} = 2.38$ Hz, H-4), 8.94 (d, H-2), 7.93 (s, H-6), 9.63 (s, SO_3H) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 150.3 (C-8), 147.5 (C-2), 136.9 (C-8a), 134.0 (C-4), 133.9 (C-5), 128.5 (C-3), 127.8 (C-6), 124.0 (C-4a), 114.6 (C-7) ppm. The acetone soluble product was 3,5,7-trichloro-8-quinolinol (40%) as characterized by ^{1}H and ^{13}C NMR, m.p.: 155–159°C. An independent synthesis is described below.

6,7-Dichloro-8-quinolinol-5-sulfonic acid (**5b**, $C_9H_5Cl_2NO_4S$)

5b was prepared in the same manner from **4b** [6] as **5a** in 65.7% yield of from a 0.012 mol run, m.p.: 182–183°C. The analytical sample was prepared by crystallization from water, m.p.: 182–183°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 9.00 (dd, $J_{23} = 4.55$ Hz, $J_{24} = 1.10$ Hz, H-2), 10.05 (dd, H-4), 7.88 (dd, $J_{34} = 8.2$ Hz, H-3), 5.0 (s, SO_3H) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 148.2 (C-8), 146.3 (C-2), 142.0 (C-4), 134.1 (C-8a), 132.8 (C-5), 130.6 (C-6), 125.6 (C-4a), 122.5 (C-3), 119.1 (C-7) ppm.

The acetone soluble product was 5,6,7-trichloro-8-quinolinol (20%) as characterized by ^{1}H and ^{13}C NMR, m.p.: 210–214°C (Ref. [12]: m.p.: 213–214°C, Ref. [13]: 220–225°C); ^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 9.02 (dd, $J_{23} = 4.15$ Hz, $J_{24} = 1.15$ Hz, H-2), 8.55 (dd, H-4), 7.81 (dd, $J_{34} = 8.66$ Hz, H-3), 11.4 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 150.5 (C-8), 150.0 (C-2), 137.1 (C-8a), 133.1 (C-4), 129.6 (C-6), 124.7 (C-4a), 124.1 (C-3), 118.0 (C-5), 115.4 (C-7) ppm.

3,7-Dichloro-8-quinolinol (**6a**; $C_9H_5Cl_2NO$)

5a (2.5 g, 0.012 mol) was heated under reflux with stirring in 25 ml of 15% H_2SO_4 in acetic acid overnight. The solution was poured into 250 ml of water and adjusted to *pH* 7 with NH_3. After cooling in an ice bath with stirring the product was obtained by filtration, washed with deionized water, and dried at 50°C overnight. The yield of **6a** was 1.6 g (88.9%), m.p.: 162–165°C. An analytical sample was crystallized from acetonitrile, m.p.: 170–171°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.88 (d, $J_{24} = 2.31$ Hz, H-2), 8.55 (d, H-4), 7.64 (d, $J_{56} = 8.85$ Hz, H-6), 7.43 (d, H-5), 11.0 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 149.5 (C-8), 147.6 (C-2), 136.9 (C-8a), 134.5 (C-4), 129.8 (C-6), 128.2 (C-3), 127.8 (C-4a), 117.6 (C-5) 116.8 (C-7) ppm.

6,7-Dichloro-8-quinolinol (**6b**; $C_9H_5Cl_2NO$)

6b was prepared from **5b** in the same manner as **6a** in 98.6% yield from a 0.01 mol run, m.p.: 185–188°C. The analytical sample was crystallized from acetonitrile, m.p.: 191–192°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.94 (dd, $J_{23} = 4.12$ Hz, $J_{24} = 1.41$ Hz, H-2), 8.36 (dd, H-4), 7.74 (dd, $J_{34} = 8.7$ Hz, H-3), 10.8 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 151.3 (C-8), 149.3 (C-2), 137.1 (C-8a), 135.6 (C-4), 130.2 (C-6), 126.9 (C-4a), 123.0 (C-3), 117.5 (C-5), 114.9 (C-7) ppm.

3,5,7-Trichloro-8-quinolinol (**7**; $C_9H_4Cl_3NO$)

7 was prepared from **1b** [6] by the same method as **2b** except that two equivalents of *NCS* were employed in the chlorination. A 0.011 mol run yielded 99% of product, m.p.: 146–149°C, and the analytical sample crystallized from acetonitrile melted at 159–160°C.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.92 (d, $J_{24} = 1.87$ Hz, H-2), 8.42 (d, H-4), 7.81 (s, H-6), 11.2 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 149.3 (C-8), 148.5 (C-2), 137.0 (C-8a), 130.9 (C-4), 129.7 (C-3), 129.1 (C-6), 125.2 (C-4a), 117.9 (C-5), 116.4 (C-7) ppm.

3,6-dichloro-8-quinolinol (**8**; $C_9H_5Cl_2NO$)

8 was prepared as described previously [5].

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.82 (d, $J_{24} = 2.20$ Hz, H-2), 8.46 (d, H-4), 7.48 (d, $J_{57} = 2.2$ Hz, H-5), 7.18 (d, H-7), 10.7 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 154.9 (C-8), 147.1 (C-2), 135.6 (C-8a), 133.5 (C-4), 132.9 (C-6), 129.1 (C-4a), 129.7 (C-3), 115.8 (C-5), 112.7 (C-7) ppm.

5,7-Dichloro-8-quinolinol (**9**; $C_9H_5Cl_2NO$)

9 was obtained from Aldrich Chemical Co.

^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.98 (dd, $J_{23} = 4.12$ Hz, $J_{24} = 1.41$ Hz, H-2), 8.46 (dd, H-4), 7.72 (dd, $J_{34} = 8.7$ Hz, H-3), 7.75 (s, H-6), 10.8 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 149.2 (C-8), 149.8 (C-2), 138.9 (C-8a), 132.8 (C-4), 127.7 (C-6), 124.7 (C-4a), 123.1 (C-3), 118.9 (C-5), 115.5 (C-7) ppm.

For comparison with all of the above, the NMR spectra of 8-quinolinol obtained from Aldrich were recorded. ^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 8.91 (dd, $J_{23} = 4.0$ Hz, $J_{24} = 1.5$ Hz, H-2), 8.36 (dd, H-4), 7.57 (dd, $J_{34} = 8.5$ Hz, H-3), 7.48 (dd, $J_{56} = 8.1$ Hz, $J_{57} = 1.1$ Hz, H-6), 7.46 (dd, H-5), 7.22 (dd, $J_{67} = 7.8$ Hz, H-7), 9.90 (s, OH) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 153.2 (C-8), 148.2 (C-2), 138.7 (C-8a), 136.0 (C-4), 127.5 (C-6), 128.8 (C-4a), 121.8 (C-3), 117.8 (C-5), 111.3 (C-7) ppm.

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