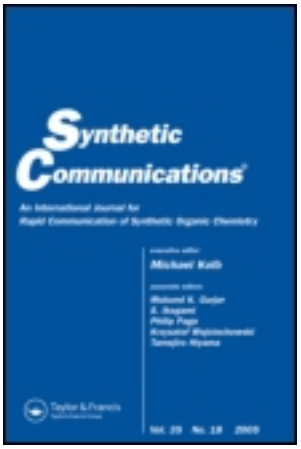

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A GREEN ROUTE FOR SYNTHESIS OF NEW 1,2-NAPHTHOQUINOMETHANE ACETONITRILES IN WATER

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A series of new 2-(3-hydroxy-4-oxo-4H-naphthalen-1-ylidene) acetonitriles was prepared by the cascade Michael addition-elimination reaction of sodium 1,2-naphthoquinone-4-sulfonate with various substituted acetonitriles compounds in ethanol-water in presence of basic catalyst.

Keywords: Antibacterial; cascade reaction; 1,2-naphthoquinomethane; water solvent

INTRODUCTION

Hydroxynaphthoquinones are well known for their chemical and biological properties.[1] The hydroxynaphthoquinones like lawsone[2] and lapachol[3] (Fig. 1) have drawn large interest for being natural products with interesting pharmacological antitumoral, antiprotozoal, anti-inflammatory, antiviral, and antifungal properties.[4–6] Parvaquone, buparvaquone and atovaquone (Fig. 1)[7] represent three synthetic naphthoquinones that were explored for use as antileishmanial and antimalarial drugs during World War II, but this research was temporarily discontinued. Other hydroxynaphthoquinones like conocurvone were shown to inhibit the cytopathogenic efects of HIV-1 in human T-lymphoblastic cells.[8] Some have even reached clinical use level. We are interested in the antimicrobial and antifungal properties of new hydroxynaphthoquinone derivatives.

Although naphthoquinones are relatively well described, 2-hydroxyl-1,4-naphthoquinomethanes remain poorly understood.[9] Naphthoquinomethanes are the equivalent of quinomethanes as the reactive intermediate in benzenic serie.

Recently, organic reactions under green conditions, in water [10,11] or a benign solvent like ethanol have received considerable attention, because of their environmental, acceptability, abundance and low cost.

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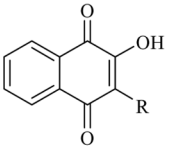


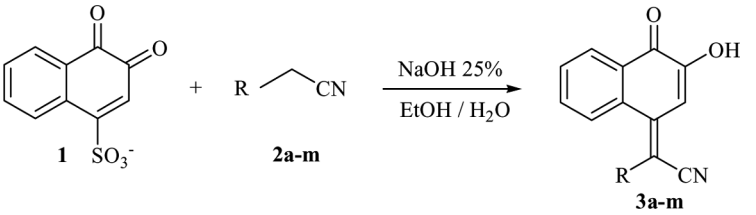
R = H ; lawsone
R = Me ; phthiocol
R = Dimethylally ; lapachol
R = cyclohexyl ; parvaquone
R = 4-(4-chlorophenyl) cyclohexyl ; atovaquone

Figure 1. Natural products.

RESULTS AND DISCUSSION

Based on the Fieser synthesis,[9] we decided to investigate the synthesis of series of new 2-hydroxynaphthoquinomethanes in aqueous from 1,2-naphthoquinone-4-sulfonate **1** and substituted acetonitriles **2a–m**. Synthesis of this type of compounds involves a base catalyzed Michael-type addition, followed by a protonation and elimination of a sulphur dioxide (Scheme 1). Production of 2-hydroxynaphthoquinomethanes **3a–m** is achieved in moderate acceptable to excellent yields (Table 1).

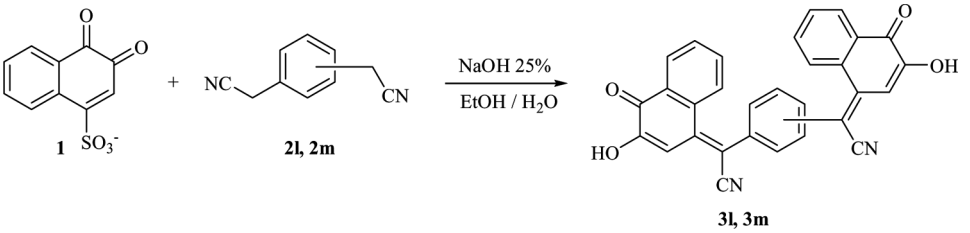
The results are reported in Table 1.



Scheme 1. Synthesis of 2-hydroxynaphthoquinomethanes in aqueous solvent.

Table 1. Synthesis of 2-hydroxynaphthoquinomethanes in aqueous solvent

Entry	R	Product	Yield (%)
1	CN	**3a**	91
2	COOEt	**3b**	37
3	$CONH_2$	**3c**	44
4	SCH_3	**3d**	30
5	thiophen-3-yl	**3e**	60
6	phenyl	**3f**	57
7	2,6-dichlorophenyl	**3g**	60
8	3,4-dimethoxyphenyl	**3h**	74
9	4-methoxyphenyl	**3i**	92
10	4-nitrophenyl	**3j**	67
11	4-chlorophenyl	**3k**	51
12	1,3-phenylene	**3l**	32
13	1,4-phenylene	**3m**	46



Scheme 2. Synthesis of bis-hydroxynaphthoquinones.

The *one-pot* two component condensation-elimination reactions of 1,2-naphthoquinone-4-sulfonate with various active cyanomethylenes compounds, in the presence of sodium hydroxide (25%) as a base, proceeded rapidly by heating (40 °C) the mixture in a water-ethanol mixture for 2 hours.

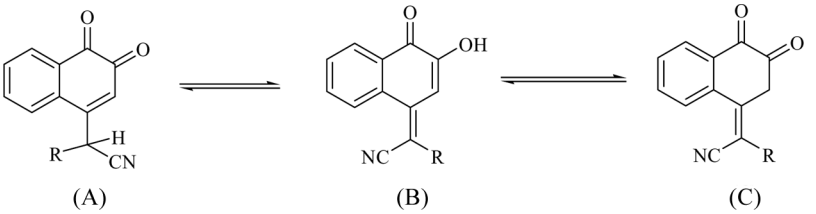
It is noteworthy that different bases (triethylamine, potassium tert-butoxide, sodium ethoxide and potassium carbonate) have been tried to catalyze this reaction, before retaining 25% NaOH in the water-ethanol mixture, for its convenience and in respect to the criteria of "Green Chemistry."

The *meta* and *para*phenylene diacetonitriles afford new bis-hydroxynaphthoquinomethanes (**3l, 3m**) (Scheme 2). These molecules can be of interest, some bisquinones are natural products that possess a diverse array of biological activities.[8,12]

Because of the tautomeric equilibrium (Scheme 3), 2-hydroxynaphthoquinomethane can be obtained in three different forms (A-C). Thus, the exact structures obtained by our method were confirmed as compounds **3a–m** in enolic form (B), by several techniques (^{1}HNMR, ^{13}CNMR, IR, and MS).

The structures of 2-(3-hydroxy-4-oxo-4*H*-naphthalen-1-ylidene) acetonitriles were modelled. Equilibrium geometry were optimized first by molecular mechanic by using the force field MMFF and then by semi-empirical calculation with PM3.[13] The best geometry obtained were calculated with density functional B3LYP (6–31G*). Whereas the Lawsone has a plane structure, the structures of the hydroxynaphthoquinomethanes are concave. The structures obtained with B (R=CN) and Lawsone were presented in Fig. 2.

The *in vitro* antibacterial activity of compounds **3a–m** against four pathogenic bacteria, namely *Pseudomonas aeruginosa* and *Escherichia coli*, which are grams (−), *Enterococcus faecalis* and *Staphylococcus aureus* which are grams (+), was investigated and compared to gentamycin. Compounds **3j** and **3k** showed a very interesting



Scheme 3. Tautomeric equilibrium.

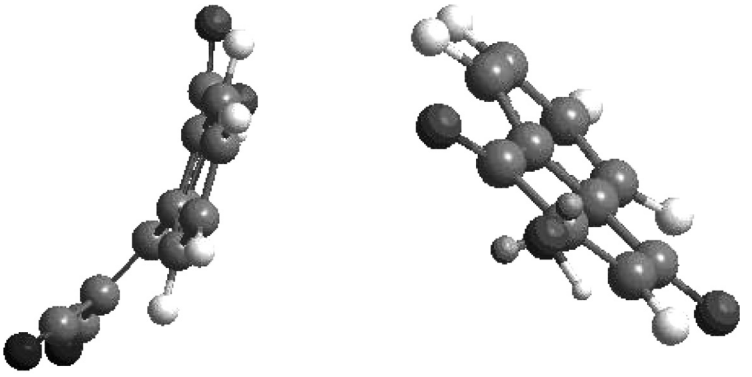


Figure 2. Structures of hydroxynaphthoquinomethanes.

antibacterial effect against *Staphylococcus aureus* and *Enterococcus faecalis*. This research must be sustained for further optimizations.

EXPERIMENTAL

Melting points are determinated and uncorrected. IR spectra were obtained as solids with a Fourier transform Perkin Elmer Spectrum One with ATR accessory. Only significant absorptions are listed. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d6, with a Bruker AC 250 spectrometer. Mass spectra were recorded on a QTOF Micro (Waters), ionisation electrospray positive (ESI), lockspray PEG, infusion introduction (5 μL/min), source temperature 80 °C, desolvatation temperature 120 °C. Optimisation of conformations and theoretical calculations were performed with Spartan software.[13]

General Procedure for the Preparation of 2-Hydroxynaphthoquinomethane

A solution of acidic methylene compounds **2a–m** (1.92 mmol) in ethanol (8 ml) was added at 40 °C to a stirred solution of sodium 1, 2-naphthoquinone-4-sulfonate **1** (0.50 g, 1.92 mmol) in H_2O (22 ml). After 10 minutes, stirring was maintained and a 25% aqueous basic solution of soda (0.50 ml) was added. The mixture is stirred at 40 °C for 2 hours. It cools the mixture and they are acidified by an acid solution of HCl (37%) to give a solid that was collected, dried under vacuum and identified as 2-hydroxynaphthoquinomethanes **3a–m**.

2-(3-Hydroxy-4-oxo-4*H*-naphthalen-1-ylidene) malononitrile (3a). Obtained from malonodinitrile (0.13 g, 1.92 mmol); green solid, 0.38 g (91%), Mp.: 189–190 °C; IR 3387, 2217, 2203, 1659, 1623, 1590, 1402, 1264 cm^{-1}; ^{1}HNMR (DMSO) δ (ppm) 7.56 (s, 1H), 7.72 (s, 1H), 7.77–7.84 (m, 2H), 8.29–8.33 (m, 1H), 8.90 (d, 1H); ^{13}CNMR (DMSO) δ (ppm) 40.8; 113.5; 114.6; 126.8; 128.6; 129.1; 130.1; 133.4;

134.6; 153.5; 155.4; 179.2; MS-ESI m/z $[M+H]^+$ calcd. for $C_{13}H_6N_2O_2$ 223.0508 found 223.0528; 205.1; 196.1; 169.1.

Cyano-(3-hydroxy-4-oxo-4*H*-naphthalen-1-ylidene) acetic acid ethyl ester (3b). Obtained from ethyl cyanoacetate (0.21 g, 1.92 mmol); yellow solid, 0.19 g (37%), Mp.: 130 °C [Lit.[14] 129.9–130.4 °C]; IR 3342, 2205, 1703, 1654, 1629, 1591, 1229 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ (ppm) 1.43 (t, 3H); 4.41 (q, 2H); 7.50 (s, 1H); 7.70–7.81 (m, 2H); 8.09 (s, 1H); 8.26–8.30 (m, 1H); 8.88 (d, 1H); ^{13}CNMR ($CDCl_3$) δ (ppm) 14.1; 63.1; 102.5; 110.5; 127.7; 128.1; 129.5; 132.1; 132.6; 134.0; 150.9; 151.2; 162.5; 179.5; MS-ESI m/z $[M+H]^+$ calcd. for $C_{15}H_{11}NO_4$ 270.0766 found 270.0769; 242.2; 224.1; 214.2; 196.1.

2-Cyano-2-(3-hydoxy-4-oxo-4*H*-naphthalen-1-ylidene) acetamide (3c). Obtained from cyanoacetamide (0.16 g, 1.92 mmol); yellow solid 0.2 g (44%), Mp.: 205–208 °C; IR 3457, 3368, 2194, 1698, 1660, 1630, 1600, 1417, 1228 cm^{-1}; ^{1}HNMR (DMSO) δ (ppm) 7.44 (s, 1H); 7.58–7.72 (m, 2H); 7.92 (s, 1H); 8.18 (d, 1H); 8.76 (d, 1H); 10.26 (s, 2H); ^{13}CNMR (DMSO) δ (ppm) 111.1; 113.1; 117.1; 124.2; 126.3; 128.3; 130.2; 132.4; 140.1; 147.9; 168,1; 179.7; MS-ESI m/z $[M+H]^+$ calcd. for $C_{13}H_8N_2O_3$ 241.0614 found 241.0623; 223.1; 225.1; 214.2; 198.2.

2-(3-Hydroxy-4-oxo-4*H*-naphthalen-1-ylidene)-2-(methylthio) acetonitrile (3d). Obtained from methylthioacetonitrile (0.17 g, 1.92 mmol); orange solid 0.14 g (30%), Mp.: 188–190 °C; IR 3281, 2198, 1620, 1593, 1417, 1225 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ (ppm) 2.71 (s, 3H), 7.10 (s, 1H); 7.49 (s, 1H), 7.58–7.64 (m, 1H), 7.70–7.77 (m, 1H), 8.26–8.30 (m, 1H), 8.96 (d, 1H); ^{13}CNMR ($CDCl_3$) δ (ppm) 17.5; 110.1; 112.9; 115.6; 125.3; 127,.4; 128.3; 130.1; 133.5; 138.1; 148.9; 179.9; MS-ESI m/z $[M+H]^+$ calcd. for $C_{13}H_9NO_2S$: 244.0433 found 244.0444; 226.1; 217.1; 196.1.

2-(3-Hydroxy-4-oxo-4*H*-naphthalen-1-ylidene)-2-(thiophen-3-yl) acetonitrile (3e). Obtained from 2-(thiophen-3-yl) acetonitrile (0.24 g, 1.92 mmol); orange solid 0.32 g (60%), Mp.: 181 °C; IR 3325, 2194, 1634, 1595, 1417, 1239 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ (ppm) 7.15 (s, 1H); 7.20 (s, 1H); 7.28–7.31 (m, 1H); 7.49–7.51 (m, 2H); 7.67 (t, 1H); 7.82 (t, 1H); 8.31–8.34 (m, 1H); 9.06 (d, 1H); ^{13}CNMR ($CDCl_3$) δ (ppm) 108.1; 112.1; 120.1; 125.5; 127.3; 127.6; 128.7; 128.9; 129.2; 130.7; 132.9; 133.6; 135.3; 140.5; 149.3; 179.4; MS-ESI m/z $[M+H]^+$ calcd. for $C_{16}H_9NO_2S$ 280.0432 found 280.0442; 262.1; 253.1; 273.2; 234.1.

2-(3-Hydroxy-4-oxo-4*H*-naphthalen-1-ylidene)-2-phenylacetonitrile (3f). Obtained from phenylacetonitrile (0.23 g, 1.92 mmol); yellow solid 0.30 g (57%), Mp.: 198–200 °C; IR 3321, 2193, 1632, 1595, 1415, 1224 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ (ppm) 6.91 (s, 1H); 6.99 (s, 1H); 7.57 (s, 5H); 7.66–7.72 (t, 1H); 7.78–7.84 (t, 1H); 8.34 (d, 1H); 9.12 (d, 1H); ^{13}CNMR ($CDCl_3$) δ (ppm) 112.1; 118.5; 126.6; 127.6; 129.2; 129.7; 129.9; 130.3; 130.8; 133.7; 141.1; 149.1; 179.4; MS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{11}NO_2$ 274.0868 found 274.0.878; 256.2; 247.2; 228.2.

2-(2,6-Dichlorophenyl)-2-(3-hydroxy-4-oxo-4*H*-naphthalen-1-ylidene) acetonitrile (3g). Obtained from 2,6-dichlorophenylacetonitrile (0.36 g, 1.92 mmol); yellow solid 0.39 g (60%), Mp.: 165–166 °C; IR 3342, 2198, 1640, 1593, 1557, 1407, 1218 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ (ppm) 6.98 (s, 1H); 7.00 (s, 1H); 7.39–7.56 (m, 1H); 7.7–7.75 (t, 1H); 7.85–7.89 (t, 1H); 8.24–8.28 (m, 2H);

8.32–8.36 (m, 1H); 9.20 (d, 1H); ^{13}CNMR ($CDCl_3$) δ (ppm) 111.4; 117.1; 120.2; 126.6; 129.3; 129.4; 130.6; 130.7; 131.6; 132.8; 133.7; 136.3; 141.5; 149.4; 179.4; MS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_9Cl_2NO_2$ 342.0088, found 342.0098; 324; 315; 307; 271.

2-(3-Hydroxy-4-oxo-4*H*-naphthalen-1-ylidene)-2-(3,4-dimethoxyphenyl) acetonitrile (3h). Obtained from (3,4-dimethoxyphenyl) acetonitrile (0.34 g, 1.92 mmol); red solid 0.47 g (74%), Mp.: 208–210 °C; IR 3343, 2193, 1629, 1592, 1520, 1415, 1228 cm^{-1}; ^{1}HNMR (DMSO) δ (ppm) 3.97 (s, 6H); 6.86 (s, 1H); 7.13–7.23 (m, 3H); 7.35 (s, 1H); 7.84 (t, 1H); 7.92 (t, 1H); 8.26 (m, 1H); 8.99 (d, 1H); ^{13}CNMR (DMSO) δ (ppm) 55.7; 55.7; 109.9; 111.7; 112.9; 113.3; 123.2; 125.5; 126.9; 127.1; 130.3; 130.4; 130.8; 131.9; 132.8; 148.8; 149.2; 149.9; 150.9; 178.9; MS-ESI m/z $[M+H]^+$ calcd. for $C_{20}H_{15}NO_4$: 334.1074 found 334.1079; 316.3; 307.3; 288.3.

2-(3-Hydroxy-4-oxo-4*h*-naphthalen-1-ylidene)-2-(4-methoxyphenyl) acetonitrile (3i). Obtained from 4-methoxyphenylacetonitrile (0.28 g, 1.92 mmol); red solid 0.54 g (92%), Mp.: 155–156 °C; IR 3321, 2192, 1634, 1622, 1593, 1411, 1225 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ (ppm) 3.89 (s, 3H); 6.80–6.84 (d, 1H); 6.97 (s, 1H); 7.15–7.19 (d, 2H); 7.36–7.40 (d, 2H); 7.56–7.62 (t, 1H), 7.68–7.75 (t, 1H), 8.24–8.27 (d, 1H), 9.01 (d, 1H); ^{13}CNMR ($CDCl_3$) δ (ppm) 55.5; 109.9; 112.4; 114.6;126.5; 127.5; 130.6; 132.1; 133.5; 141.1; 149.1; 160.0; 177.6; MS-ESI m/z $[M+H]^+$ calcd. for $C_{19}H_{13}NO_3$ 304.0974 found 304.0975; 286.2; 277.1; 258.1.

2-(3-Hydroxy-4-oxo-4*H*-naphthalen-1-ylidene)-2-(4-nitrophenyl) acetonitrile (3j). Obtained from 4-nitrophenylacetonitrile (0.31 g, 1.92 mmol); brown solid 0.41 g (67%), Mp.: 216–217 °C; IR 3294, 2197, 1635, 1592, 1515, 1413, 1212 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ (ppm) 5.30 (s, 1H); 6.71 (s, 1H); 7.81 (t, 2H); 8.24 (d, 1H); 8.30 (d, 2H); 8.38 (d, 2H); 9.08 (d, 1H); ^{13}CNMR ($CDCl_3$) δ (ppm) 109.9; 113.3; 124.4; 126.7; 127.9; 129.4; 131.1; 131.2; 131.4; 132.1; 134.1; 141.3; 149.9; 150.4; 179.3; MS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{10}N_2O_4$ 319.0719 found 319.0721; 301.1; 292.1; 273.1.

2-(4′-Chlorophenyl)-2-(3-hydroxy-4-oxo-4*H*-naphthalen-1-ylidene) acetonitrile (3k). Obtained from 4-chlorophenylacetonitrile (0.29 g, 1.92 mmol); brown solid 0.30 g (51%), Mp.: 180–181 °C; IR 3326, 2186, 1632, 1591, 1413, 1227 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ (ppm) 6.84 (s, 1H); 7.06 (s, 1H); 7.41 (d, 2H); 7.49 (d, 2H); 7.71 (t, 1H); 7.82 (t, 1H); 8.33 (d, 1H); 9.06 (d, 1H); ^{13}CNMR ($CDCl_3$) δ (ppm) 111.4; 117.1; 120.2; 126.6; 127.7; 129.4; 129.5; 131.6; 132.8; 133.8; 136.3; 141.5; 149.4; 179.4; MS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{10}ClNO_2$ 308.0474 found 308.0478; 290.2; 281.2; 273.2; 262.2.

Bis(2-(3-hydroxy-4-oxo-4h-naphthalen-1-ylidene)) *meta*-phenylene diacetonitrile (3l). Obtained from *meta*-Phenylene diacetonitrile (0.30 g, 1.92 mmol); brown solid 0.29 g (32%), Mp.: 210 °C; IR 3289, 2191, 1650, 1638, 1596, 1409, 1222 cm^{-1} ; ^{1}HNMR (DMSO) δ (ppm) 6.67 (s, 2H); 6.74 (s, 2H); 7.31 (d, 1H); 7.68 (d, 2H); 7.78 (t, 4H); 7.91 (d, 1H); 8.24 (d, 2H); 8.99 (d, 2H); ^{13}CNMR (DMSO) δ (ppm) 112.1; 118.9; 120.5; 122.1; 125.7; 127.1; 128.6; 128.9; 129.5; 130.7; 131.7; 133.1; 135.9; 142.3; 152.6; 179.3.

Bis(2-(3-hydroxy-4-oxo-4h-naphthalen-1-ylidene)) *para*-phenylene diacetonitrile (3m). Obtained from *para*-Phenylene diacetonitrile (0.30 g, 1.92 mmol); Orange solid 0.41 g (46%) Mp.: >250 °C; IR 3319, 2192, 1645, 1630, 1584, 1419, 1212 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ (ppm) 6.78 (s, 2H); 7.04 (s, 2H); 7.21 (d, 2H); 7.68 (d, 2H); 7.79 (t, 4H); 8.44 (d, 2H); 8.89 (d, 2H); ^{13}CNMR ($CDCl_3$) δ (ppm) 112.1; 118.6; 120.4; 126.7; 127.3; 128.8; 129.4; 130.2; 131.7; 133.2; 134.9; 142.6; 151.1; 179.2.

CONCLUSIONS

In conclusion, we have synthesized and screened the *in vitro* antibacterial activity of new series of functionalized 1,2-naphthoquinomethane acetonitriles. A mild base in water-ethanol medium, respecting ecological criteria, was used. Our results are very promising since two of the compounds are similar to that of the gentamycin antibiotic.

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