An Environmentally Friendly Electrochemical Method for Synthesis of Benzofuranoquinone Derivatives

Saied Saeed Hosseiny Davarani,*[,a] Mojtaba Shamsipur,[b] Davood Nematollahi,*[,c] Somayyeh Ramyar,[a] and Leila Masoumi[a]

[a] *Department of Chemistry, Faculty of Science, Shahid Beheshti University; Tehran 1983963113, Iran:* [b] *Department of Chemistry, Faculty of Science, Razi University; Kermanshah 67149, Iran: and* [c] *Faculty of Chemistry, Bu-Ali Sina University; Hamadan 65174, Iran.* Received March 28, 2007; accepted May 27, 2007

Electrochemical oxidation of catechols (1a—c) has been studied in the presence of 2-hydroxy-1,4-naphtoquinone (3b) in aqueous solutions, using cyclic voltammetry and controlled-potential coulometry. The results indicated that the electrochemically generated *o*-benzoquinones (2a—c) participate in Michael addition reaction with 3b to the corresponding benzofuranoquinones (8a—c, 10a—c). The electrochemical synthesis of these compounds has been successfully preformed at a carbon rod electrode with good yields using an environmentally friendly method.

Key words Michael addition reaction; electrochemical synthesis; cyclic voltammetry; catechol; 2-hydroxy-1,4-naphtoquinone; benzofuranoquinone

Catechol derivatives are a promising group of compounds worthwhile for further investigation, which may lead to the discovery of selective acting, biodegradable agrochemicals having high human, animal and plant compatibility.[1)] Catechol itself and mono-substituted catechols (–OH, $–CH_3$, $–OCH_3$, –CHO, –COOH) are active in part against *Pseudomonas*, *Bacillus*, but not *Penicillium* species. Caffeic acid is inhibitory to soil bacteria and fungi, but species differences exist, while its methyl ester has more pronounced activity against *Bacillus* and *Pseudomonas* species. Hydroxychavicol inhibits a greater number of microorganisms including *Pseudomonas*, *Cladosporium* and *Pythium* species. Many of flavonoids and catechol derivatives turned out to be as antimicrobial agents.[2)] Also, in recent years, medicinal properties of benzofuran derivatives have been investigated widely and were shown to be effective as antitumor,[3)] antidepressant,[4)] antifungal,[5)] anti-hypertensive, and cytotoxic.[6)] They are also potent and selective oxytocin antagonists,[7)] PDE5 inhibitor for treatment of erectile dysfunction,[8)] and H_3 receptor antagonists.[9)] On the other hand, quinones are of considerable interest because many drugs such as doxorubicin, daunorubicin and mitomycin C in cancer chemotherapy contain quinones,[10)] whereas various other quinones have found use in industry.[11)] Some of them also exhibit antitumor and antimalarial activities[12)] and many of them are also involved in enzyme inhibition and DNA cross-linking.[13)] With due attention to our experiences on electrochemical synthesis of organic compounds,[14—22)] we thought that synthesis of a new organic compounds (**8a**—**c**, **10a**—**c**) with triad structures of catechol, benzofuran and quinone would be useful from the point of view of pharmaceutical properties.

This idea prompted us to investigate the electrochemical oxidation of catechols **1a**—**c** in the presence of 2-hydroxy-1,4-naphtoquinone (**3b**) as a nucleophile and represent a facile and one-pot electrochemical method for the synthesis of some new organic compounds (**8a**—**c**, **10a**—**c**) in high yield using an environmentally friendly method.

Results and Discussion

Electrochemical Study Cyclic voltammetry of 2 mM of catechol (**1a**) in aqueous solution containing 0.2 M acetate buffer (pH=5.0) shows one anodic (A_1) and the corresponding cathodic peak (C_1) which corresponds to the transformation of **1a** to *o*-benzoquinone (**2a**) and *vice-versa* within a quasi-reversible two-electron process (Fig. 1, curve a). Figure 1, curve b, shows cyclic voltammogram of 2 mM of 2-hydroxy-1,4-naphtoquinone (**3b**) in aqueous solution containing 0.2 M acetate buffer (pH=5.0). Cyclic voltammogram ex-

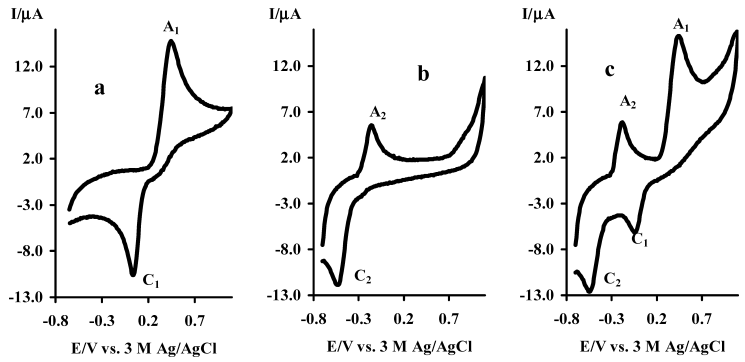


Fig. 1. (a) Cyclic Voltammogram of 2 mM Catechol (**1a**), (b) Cyclic Voltammogram of 2 mM 2-Hydroxy-1,4-naphtoquinone (**3b**), (c) Cyclic Voltammogram of 2 mM **1a** in the Presence of 2 mM **3b**, at a Glassy Carbon Electrode, in Aqueous Solution Containing 0.2 M Acetate Buffer (pH=5.0)

Scan rate: 100 mV s^{-1}. t=25±1 °C.

* To whom correspondence should be addressed. e-mail: nemat@basu.ac.ir

hibits one anodic (A_2) and the corresponding cathodic peak (C_2) which corresponds to the transformation of naphthalene-1,2,4-triol (**3a**) to **3b** (Chart 1).[23]

The oxidation of **1a** in the presence of **3b** as a nucleophile was studied in some detail. Figure 1, (curve c) shows the cyclic voltammogram obtained for a 2 mM solution of **1a** in the presence of 2 mM **3b**. The voltammogram exhibits two anodic (A_1 and A_2) and two corresponding cathodic peaks (C_1 and C_2). Comparison of voltammogram c with a reveals that the peak C_1 which corresponds to the reduction of *o*-benzoquinone (**2a**) decreased. Furthermore, it is seen that proportional to the augmentation of potential sweep rate, the height of the C_1 peak increases (Fig. 2). A similar situation is observed when the **3b** to **1a** concentration ratio is decreased. A plot of peak current ratio (I_{pC1}/I_{pA1}) *versus* scan rate, for a

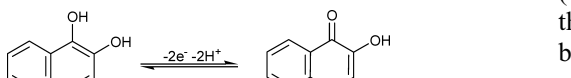


Chart 1

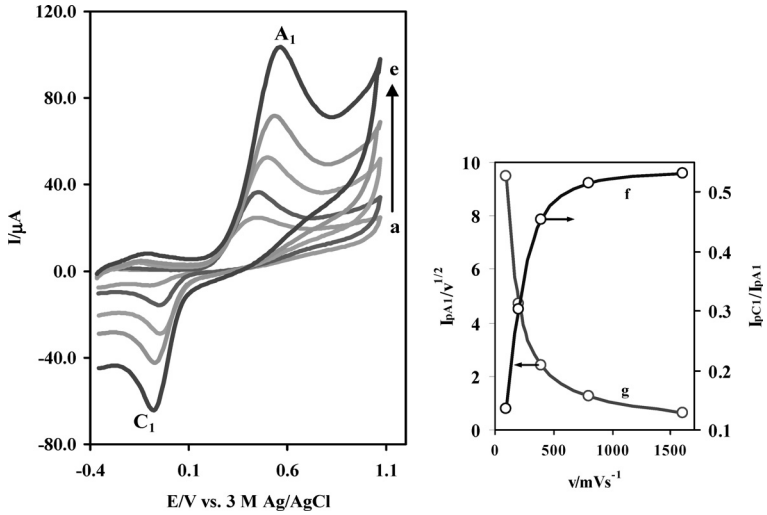
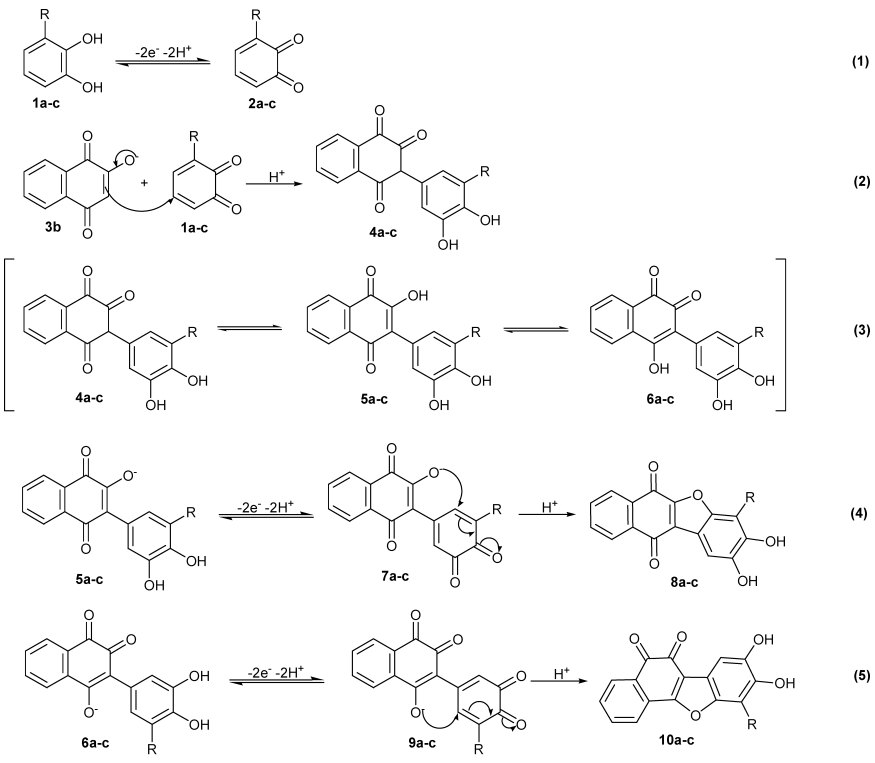


Fig. 2. Typical Cyclic Voltammograms of 2 mM Catechol (**1a**) in the Presence of 2 mM 2-Hydroxy-1,4-naphtoquinone (**3b**), at a Glassy Carbon Electrode, in Aqueous Solution Containing 0.2 M Acetate Buffer (pH=5.0)

Scan rates from (a) to (e) are: 100, 200, 400, 800, 1600 mV s^{-1}, respectively. (f) Variation of peak current ratio (I_{pC1}/I_{pA1}) *versus* scan rate. (g) Variation of peak current function ($I_{pA1}/v^{1/2}$) *versus* scan rate.



R = -H, R = $-CH_3$, R = $-OCH_3$

Chart 2

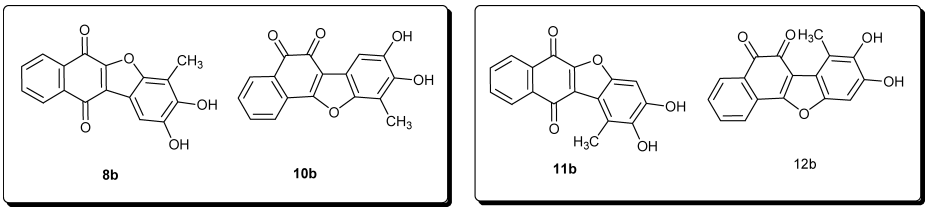


Fig. 3. The Possible Products of Electrochemical Oxidation of 3-Methylcatechol (**1b**) in the Presence of 2-Hydroxy-1,4-naphtoquinone (**3b**)

mixture of **1a** and **3b** confirms the reactivity of *o*-benzoquinone (**2a**) towards **3b**, appearing as an increase in the height of the cathodic peak C_1 at higher scan rates (Fig. 2, curve f). On the other hand, the current function for the A_1 peak, ($I_{pA1}/v^{1/2}$), decreases on increasing the scan rate (Fig. 2, curve g). Controlled-potential coulometry was performed in aqueous solution containing 0.25 mmol of **1a** and 0.25 mmol of **3b** at 0.5 V *versus* 3 M Ag/AgCl. Cyclic voltammetric analysis carried out during the electrolysis shows the progressive disappearance of A_1 peak. All anodic and cathodic peaks disappear when the charge consumption becomes about $4e^-$ per molecule of **1a**. These behavior is adopted as indicative of an ECEC mechanism.[24] According to our results, it seems that the Michael addition reaction of anion **3b** to *o*-benzoquinone (**2a**) (Eq. 2) is faster than other secondary reactions, leading to the intermediates **5a** and **6a**. The oxidation of these compounds (**5a**, **6a**) is easier than the oxidation of the parent-starting molecule (**1a**) by virtue of the presence of an electron-donating group. The intramolecular reaction was performed *via* 1,4-(Michael) addition reaction (Eqs. 4 and 5). The over-oxidation of **8a** and **10a** was circumvented during the preparative reaction because of the more difficult oxidation of formed dihydroxybenzofuranes[14] as well as the insolubility of the products in sodium acetate solution medium.

The electro-oxidation of 3-methylcatechol (**1b**) in the presence of **3b** is considered to involve the Michael acceptor **2b** as an intermediate that could be attacked at positions C-5 or C-4 to yield (**8b**, **10b**) and (**11b**, **12b**) respectively (Fig. 3). The experimental and calculated[25] ^{13}C-NMR results for the methyl carbon in the catechol ring of the products and for the suggested possible structures are shown in Table 1. According to the ^{13}C-NMR results, we suggest that *o*-benzoquinone **2b** is attacked in all possibilities only in the C-5 position by **3b** leading to the formation of the products **8b** and **10b**. The same results obtained for 3-methoxycatechol (**1c**).

The Effect of pH Cyclic voltammogrames of 2 mM solution of **1a** in aqueous solutions in pH 2.0—9.0 have been shown in Fig. 4, curves a. As shown, cyclic voltammograms show one anodic (A_1) and a corresponding cathodic peak (C_1). Furthermore, it is seen that proportional to the increasing of pH, the height of the C_1 peak decreases. On the other hand, in basic solutions, the peak current ratio (I_{pC1}/I_{pA1}) is less than unity and increases with decreasing pH as well as by increasing the potential sweep rate. These observation can be related to the coupling of anionic or dianionic forms of **1a** with *o*-benzoquinone (**2a**) (dimerization reaction).[26,27] The oxidation of **1a** in the presence of **3b** was studied in some detail. Figure 4, (curves b) shows the cyclic voltammogram obtained for a 2 mM solution of **1a** in the presence of 2 mM **3b** in pH 2.0—9.0. As it shown, the peak current ratio (I_{pC1}/I_{pA1}) increases with decreasing pH. This can be related to protonation of anion **3b** and inactivation of it towards Michael addition reaction with **2a** that enhanced by decreasing pH. The ratio of "peak current ratio" in the absence and in the presence of **3b** $[(I_{pA1}/I_{pC1})^{absence}/(I_{pA1}/I_{pC1})^{presence}]$ *versus* pH has been shown in Fig. 4. This curve has a maximum in pH 7.0. Therefore, in this study, solution containing phosphate buffer (pH 7.0, 0.2 M) has been selected as more suitable medium for electrochemical synthesis of compounds **8a**—**c** and **10a**—**c**.

Table 1. Experimental and Calculated ^{13}C-NMR Data for Methyl Carbons

Type	^{13}C-NMR data (ppm)
Experimental	9.2 and 9.3
Calculated for **8b**	8.6
Calculated for **10b**	8.6
Calculated for **11b**	12.6
Calculated for **12b**	12.6

Experimental

Reaction equipments are described in an earlier paper.[15] All chemicals (catechols and 2-hydroxy-1,4-naphtoquinone) were reagent-grade materials. Sodium acetate, phosphate salts and other acids and bases were of pro-analysis grade. These chemicals were used without further purification.

Electrochemical Synthesis of 8a—c and 10a—c In a typical procedure, 100 ml 0.2 M sodium aqueous acetate solution (or phosphate buffer, pH 7.0, 0.2 M) was pre-electrolyzed at the chosen potential (see Table 2), in a two compartment cell. Then, 2.0 mmol of catechols (**1a**—**c**) and 2-hydroxy-1,4-naphtoquinone (**3b**) were added to the cell. The electrolysis was terminated when the decay of the current became more than 95%. Due to the formation of a thin film of product at the surface of the electrode, the process was interrupted during the electrolysis and the graphite anode was washed in acetone in order to reactivate it. At the end of electrolysis, few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solids were collected by filtration and washed with distilled water. After drying, the products were characterized using IR, ^{1}H-NMR, ^{13}C-NMR and MS. The ^{1}H- and ^{13}C-NMR data showed that, in each case two isomers were obtained as final products (Chart 2) and column chromatography attempts for separation of these products were unsuccessful.

Data for **8a** and **10a** ($C_{16}H_8O_5$): IR (KBr) cm^{-1}: 3510, 3439, 3200, 1646, 1584, 1558, 1472, 1322, 1272, 1202, 1070, 1001, 911, 718. ^{1}H-NMR, (300 MHz, DMSO-d_6) δ: 7.10 (1H, s, aromatic in catechol ring), 7.16 (1H, s, aromatic in catechol ring), 7.26 (1H, s, aromatic in catechol ring), and 7.43 (1H, s, aromatic in catechol ring), 7.53—8.05 (8H, m, aromatic), 9.49 (1H, s, hydroxyl), 9.58 (1H, s, hydroxyl), 9.83 (1H, s, hydroxyl), 10.17 (1H, s, hydroxyl) (the peaks 9.49, 9.58, 9.83 and 10.17 will have removed in the presence of a few drops of D_2O). ^{13}C-NMR, (75 MHz, DMSO-d_6) δ: 99.0, 99.3, 105.8, 106.0, 114.2, 115.3, 122.7, 124.4, 126.5, 126.6, 128.4, 129.8, 130.1, 130.8, 132.8, 133.1, 134.4, 134.5, 135.4, 145.5, 146.8, 146.9, 149.7, 150.4, 151.8, 152.2, 160.7, 173.9, 175.2, 179.9, 182.0. MS (EI): *m/z* (relative intensity): 280 (100), 252 (30), 150 (25), 139 (35), 126 (20), 69 (35), 50 (30).

Data for **8b** and **10b** ($C_{17}H_{10}O_5$): IR (KBr) cm^{-1}: 3535, 3224, 1643, 1555, 1481, 1326, 1271, 1070, 999, 867, 794, 671, 471. ^{1}H-NMR, (300 MHz, DMSO-d_6) δ: 2.32 (3H, s, methyl), 2.34 (~3H, s, exact value=2.70, methyl), 7.16 (~1H, s, exact value=0.85, aromatic in catechol ring), 7.34

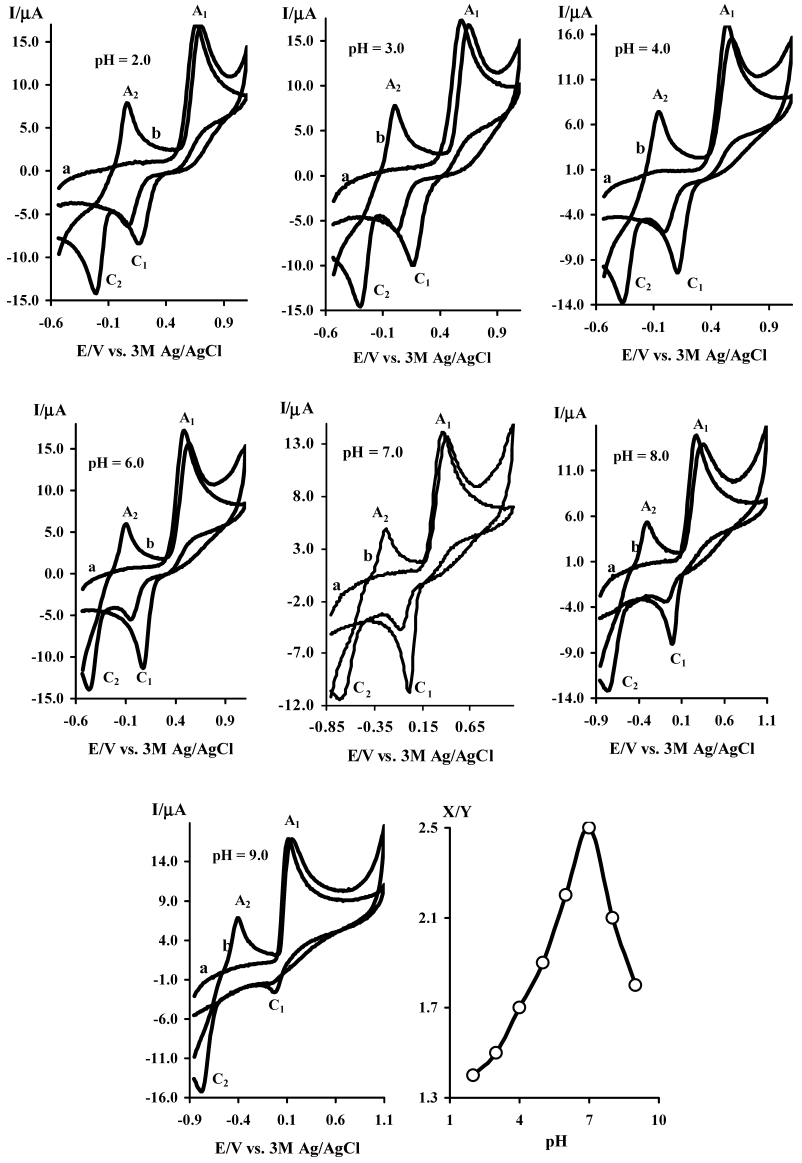


Fig. 4. Cyclic Voltammograms of (a) 2 mM **1a** in the Absence of **3b**, (b) 2 mM **1a** in the Presence of 2 mM **3b** in Various pHs

$X=I_{pA1}/I_{pC1}$ in the absence of **3b**. $Y=I_{pA1}/I_{pC1}$ in the presence of **3b**. Other conditions are the same as reported in Fig. 1.

Table 2. Electroanalytical and Preparative Data

Conversion	Applied potential	Products ratio[a)]	Product yield (%)
1a→**8a** and **10a**	0.40	1 : 1	76
1b→**8b** and **10b**	0.35	1 : 0.85	84
1c→**8c** and **10c**	0.35	1 : 0.75	82

a) Based on the area of the corresponding ^{1}H-NMR peaks.

(1H, s, aromatic in catechol ring), 7.54—8.06 (~8H, m, aromatic), 8.88 (~1H, s, exact value=0.86, hydroxyl), 9.43 (~1H, s, exact value=0.85, hydroxyl), 9.77 (1H, s, hydroxyl), 10.19 (1H, s, hydroxyl). ^{13}C-NMR, (75 MHz, DMSO-d_6) δ: 9.2, 9.3, 102.8, 103.0, 108.5, 108.9, 113.4, 114.4, 117.1, 122.8, 126.4, 126.6, 128.5, 129.7, 130.0, 130.7, 132.8, 133.1, 134.3, 134.5, 135.4, 144.5, 145.0, 146.3, 147.9, 149.4, 151.4, 160.6, 173.8, 175.3, 180.0, 182.1. MS (EI): *m*/*z* (relative intensity): 294 (100), 266 (20), 163 (25), 152.25 (25), 139 (10), 126 (15), 76 (30), 69 (15), 50 (30).

Data for **8c** and **10c** ($C_{18}H_{10}O_6$): IR (KBr) cm^{-1}: 3500, 3319, 3170, 1659, 1463, 1278, 977, 724, 472. ^{1}H-NMR, (300 MHz, DMSO-d_6) δ: 4.02 (3H, s, methoxy), 4.07 (~3H, s, exact value=2.33, methoxy), 7.04 (1H, s, exact value=0.76, aromatic in catechol ring), 7.24 (1H, s, aromatic in catechol ring), 7.54—8.08 (~7H, m, aromatic), 9.08 (~1H, s, exact value=0.76, hydroxyl), 9.62 and 9.66 (~2H, s, s, exact value=1.75, hydroxyl), 10.01 (1H, s, hydroxyl). ^{13}C-NMR, (75 MHz, DMSO-d_6) δ: 61.0, 61.1, 100.2, 100.8, 114.4, 115.7, 123.0, 124.4, 126.6, 126.7, 129.8, 130.1, 130.9, 132.8, 133.2, 133.6, 134.1, 134.5, 134.6, 135.4, 138.3, 141.9, 144.3, 146.6, 147.9, 152.5, 160.8, 174.0, 175.3, 179.9, 182.0. MS (EI): *m*/*z* (relative intensity): 310 (100), 294 (50), 266 (20), 183 (55), 152 (20), 139 (15), 126 (60), 76 (75), 69 (35), 50 (80).

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References

1) AMICBASE-EssOil, Database on Natural Antimicrobials, Review Science, Germany (1999—2002).
2) Pauli A., "Antimicrobial Properties of Catechol Derivatives," 3rd World Congress on Allelopathy, Tsukuba, Japan, August 26—30, 2002.
3) Hayakawa I., Shioya R., Agastuma T., Furokawa H., Sugano Y., *Bioorg. Med. Chem. Lett.*, **14**, 3411—3414 (2004).
4) Gaszner P., Miklya I., *Neuropsychopharmacologia Hungarica: a Magyar Pszichofarmakologiai Egyesulet lapja*, **6**, 210—220 (2004).

5) Masubuchi M., Ebiike H., Kawasaki K., Sogabe S., Morikami K., Shiratori Y., Tsujii S., Fujii T., Sakata K., Hayase M., Shindoh H., Aoki Y., Ohtsuka T., Shimma N., *Bioorg. Med. Chem.*, **11**, 4463—4478 (2003).
6) Banskota A. H., Tezuka Y., Midorikawa K., Matsushige K., Kadota S., *J. Nat. Prod.*, **63**, 1277—1279 (2000).
7) Wyatt P. G., Allen M. J., Chilcott J., Foster A., Livermore D. G., Mordaunt J. E., Scicinski J., Woollard M., *Bioorg. Med. Chem. Lett.*, **12**, 1399—1404 (2002).
8) Jiang W., Sui Z., Macielag M. J., Walsh S. P., Fiordeliso J. J., Lanter J. C., Guan J., Qiu Y., Kraft P., Battacharjee S., Craig E., Haynes-Johnson D., John T. M., Clancy J., *J. Med. Chem.*, **46**, 441—444 (2003).
9) Sun M., Zhao C., Gfesser G. A., Thiffault C., Miller T. R., Marsh K., Wetter J., Curtis M., Faghih R., Esbenshade T. A., Hancock A. A., Cowart M., *J. Med. Chem.*, **48**, 6482—6490 (2005).
10) Blum R. H., Carter S. K., *Ann. Int. Med.*, **80**, 249—259 (1974).
11) Kaleem K., Chertok F., Erhan S., *Prog. Org. Coating*, **15**, 63—71 (1987).
12) Huang Z. D., Chen Y. N., Menon K., Teicher B. A., *J. Med. Chem.*, **36**, 1797—1801 (1993).
13) Bittner S., Meenakshi C., Temtsin G., *Tetrahedron*, **57**, 7423—7429 (2001).
14) Nematollahi D., Rafiee M., *Green Chem.*, **7**, 638—644 (2005).
15) Hosseiny Davarani S. S., Nematollahi D., Mashkouri Najafi N., Masoumi L., Ramyar S., *J. Org. Chem.*, **71**, 2139—2142 (2006).
16) Nematollahi D., Afkhami A., Tammari E., Shariatmanesh T., Hesari M., Shojaeifard M., *Chem. Commun.*, **2007**, 162—164 (2007).
17) Nematollahi D., Workentin M. S., Tammari E., *Chem. Commun.*, **2006**, 1631—1633 (2006).
18) Nematollahi D., Tammari E., *J. Org. Chem.*, **70**, 7769—7772 (2005).
19) Nematollahi D., Habibi D., Rahmati M., Rafiee M., *J. Org. Chem.*, **69**, 2637—2640 (2004).
20) Nematollahi D., Goodarzi H., *J. Org. Chem.*, **67**, 5036—5039 (2002).
21) Nematollahi D., Rahchamani R., *Tetrahedrone Lett.*, **43**, 147—150 (2002).
22) Fotouhi L., Mosavi M., Heravia M. M., Nematollahi D., *Tetrahedron Lett.*, **47**, 8553—8557 (2006).
23) McMillan D. C., Sarvate S. D., Oatis J. E., Jollow D. J., *Toxicol. Sci.*, **82**, 647—655 (2004).
24) Bard A. J., Faulkner L. R., "Electrochemical Methods," 2nd ed., Wiley, New York, 2001, pp. 496—500.
25) CS ChemDraw Ultra 8.0, Cambridge Soft Corporation, 100 Cambridge Park Drive, Cambridge.
26) Nematollahi D., Rafiee M., Samadi-Maybodi A., *Electrochim. Acta*, **49**, 2495—2502 (2004).
27) Ryan M. D., Yueh A., Wen-Yu C., *J. Electrochem. Soc.*, **127**, 1489—1495 (1980).