Studies on quinones. Part 42: Synthesis of furylquinone and hydroquinones with antiproliferative activity against human tumor cell lines

Julio Benites, Jaime A. Valderrama, Felipe Rivera, Leonel Rojo, Nair Campos, Madalena Pedro and Maria Sao Jose Nascimento

Abstract—The preparation of furyl-1,4-quinone and hydroquinones by reaction of 2-furaldehyde N,N-dimethylhydrazone with benzo- and naphthoquinones is reported. Access to furylnaphthoquinones from unactivated quinones requires acid-induced conditions, however oxidative coupling reactions of activated quinones proceed under neutral conditions. The in vitro cytotoxic activity of the prepared compounds against a panel of three human cancer cell lines has been studied. Most of the furyl-1,4-quinones exhibited good antiproliferative activity (GI50 = 6.5–33.5 μm) against the MCF-7, NCI-H460, and SF-268 (CNS cancer) cell lines chosen for testing.

1. Introduction

Natural and synthetic quinonoid compounds are well-known substances which possess a variety of biological properties such as antibacterial, antifungal, antiprotozoal, inhibition of HIV-1 reverse transcriptase, and antitumor activity. Some of these pharmacological effects have been attributed to the formation of DNA-damaging anion-radical intermediates formed by bioreduction of the quinone nucleus. Biological redox activity is recognized as playing a key role in a number of processes, including the triggering of cellular events that can be exploited for therapeutic uses.

Previous work on the synthesis and antiprotozoan activity of euryfuryl-1,4-quinones and hydroquinones indicates that quinone and hydroquinone groups are essential for the cytotoxic effects. The evaluation also showed that the lipophilic fragment, derived from the antitumoral sesquiterpene euryfuran, seems to attenuate the cytotoxicity.

Our reported procedures for the synthesis of euryfurylquinone and hydroquinones were developed by furylation of quinones through oxidative coupling and Michael addition reactions. The arylation reaction proceeds under mild conditions for benzoquinones containing an electron-withdrawing substituent (activated quinones) to give the corresponding euryfurylhydroquinone (i.e., compound 1, Fig. 1). Depending on the quinone substituents, the Michael adducts undergo in situ redox reactions to give the respective euryfurylquinones.

Keywords: Quinones; Michael addition; Oxidative coupling; Cytotoxicity.

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In the case of the preparation of euryfurynaphthoquinones (compound 2, Fig. 1), the oxidative coupling reaction with quinones not bearing electron-withdrawing groups requires acetic acid to induce the Michael addition of the euryfuran to the quinone double bond.

In this communication, we disclose the design and chemical synthesis of furylquinone and hydroquinones, and their activity to inhibit the in vitro growth of three human tumor cell lines. The choice of a furyl substituent like 2-dialkylfur-5-yl was justified by the following reasons: (a) its occurrence in antitumor and antitrypanosomal drugs of the nifurtimox series, (b) a probable synergistic effect in the biological activity by combination with a quinone system in one molecule, and (c) precedents on the preparation of dimethylhydrazofuryl-1,4-quinones by oxidative coupling of furfural N,N-dimethylhydrazone with 1,4-quinones.

2. Results and discussion

2.1. Chemistry

We initiated the synthesis of furylquinone and hydroquinones by attempting the preparation of furylquinone 5 from commercially available furfural dimethylhydrazone 3 and 1,4-naphthoquinone 4 by the procedure reported by Potts and col. The treatment was conducted by refluxing compounds 3 and 4 in toluene (Scheme 1). Analysis (TLC) of the reaction mixture after 2 h showed the presence of 3 and 4 and no reaction was detected even after 10 h of reflux. Similar results were found in the treatment of hydrazone 3 with 1,4-benzoquinone 6, which were heated in boiling toluene for 24 h (Scheme 1). The presence of the starting compounds 3 and 6 together with trace amounts of a red polar substance was detected (TLC) in the resulting deep red reaction mixture.

We assumed that the lack of formation of furyl-1,4-quinones 5 and 7 is due to a non favorable equilibrium displacement from the substrates toward the Michael adduct intermediates. Based on this assumption, the reactions of nucleophile 3 with quinones 4 and 6 were studied in the presence of silver(I) oxide. We expected that this oxidant would induce an irreversible conversion of the addition products to the corresponding furylquinones 5 and 7, thus preventing a retro-Michael reaction. However, TLC analysis of the reaction mixture after 24 h showed the presence of the substrates together with trace amounts of polar products.

Based on our previous results on the reaction of euryfuran with unactivated quinones, we attempted to prepare furylquinones by using acetic acid to induce the oxidative coupling reaction. Treatment of nucleophile 3 with quinones 4 and 6 was carried out in acetic acid solutions at room temperature. This yielded the expected furylquinones 5 and 7 in 63 and 42% yield, respectively (Scheme 2). Under similar conditions furylquinones 9 and 11 (Scheme 2) were prepared in 77 and 69% yield by reaction of hydrazone 3 with 2-chloro-1,4-naphthoquinone 8 and 2-methoxy-1,4-benzoquinone 10 (Scheme 2).

The results indicate that oxidative coupling reactions of hydrazone 3 with quinones 4, 6, 8, and 10 are induced by
the acetic acid, which probably acts by decreasing the LUMO energies of electrophiles 4, 6, 8, and 10, thus improving the HOMO–LUMO interactions with nucleophile 3.

Next we studied the reaction of compound 3 with activated benzoquinones. A preliminary trial with 3 and acetylbenzoquinone 12a (1.1 equiv) in dichloromethane at room temperature was studied. The reaction proceeds rapidly (TLC) to give a mixture of compounds 13–15 as evidenced by 1H NMR analysis of the crude. This result indicates that 12a acts as a Michael acceptor and as an oxidant in the oxidative coupling reaction. In the first step, a conjugate addition of 3 to quinone 12a proceeds to give the Michael adduct 13 which, by a further redox reaction with 12a, yielded furyl-1,4-benzoquinone 14 and 2,5-dihydroxyacetophenone 15 (Scheme 3).

In order to control the reaction between 3 and 12a toward the formation of furylquinone 14, the oxidative coupling reaction of 3 with quinone 12a was attempted in the presence of silver(I) oxide as a co-oxidant. Quinone 12a, generated by oxidation from 2,5-dihydroxyacetophenone 15 with Ag₂O, was reacted in situ with 3. The treatment, performed with 4 equivalents of silver(I) oxide, provides furylquinone 14 as a blue syrupy product in nearly quantitative yield (Scheme 4).

We have found (TLC and 1H NMR) that furylquinone 14 undergoes partial conversion to hydroquinone 13 on exposure to air. Moreover, attempts to obtain 13 by catalytic hydrogenation of quinone 14 showed that 13 undergoes partial aerobic oxidation to 14.

Furylquinone 16 was prepared by oxidative coupling of formylbenzoquinone 12b with hydrazone 3 using the procedure for preparing quinone 14. The treatment yielded 16 (94%) as a deep green solid unstable upon exposure to air. Furylhydroquinone 17, a quite stable yellow solid compound, was prepared in 74% yield by reduction of quinone 16 with Zn–AcOH.

The different stabilities of acylhydroquinones 13 and 17 under aerobic conditions are probably related to the steric hindrance between the substituents on the aromatic ring. These interactions are clearly seen in molecular models of compounds 13 and 17 (Fig. 2).

It is interesting to point out that the optimized conformation of 13 and 17 performed with the CSChem3D software, reveals differences for the distances between the oxygen of the acyl group and the hydrogen atom of the \( \sigma \)-hydroxyl group, suggesting a more favorable intramolecular hydrogen bonding stabilization for compound 17 than 13.

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In order to acquire information on the influence of the dimethyldrazonofuryl substituent on the biological activity of furylhydroquinone 17, compounds 18, 19, and 20 were prepared to be included in the biological study.

Dialdehyde 18 was obtained in 68% yield by acid-induced hydrolysis of hydrazone 17. Acylhydroquinones 19 and 20 were prepared by conjugate addition of 1-butanol and hydrogen chloride to the respective quinones 12 and 15 (Scheme 5), according to previously reported procedures. 15,16

![Scheme 5. Preparation of 6-substituted dihydroxybenzaldehydes 18–20.](image)

2.2. Biology

Compounds 5, 7, 9, 11, and 17–20 were evaluated for their capacities to inhibit the in vitro growth of MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer) cell lines, after 48-h continuous exposure. The results, expressed as the concentration causing 50% of cell growth inhibition (GI50), are summarized in Table 1.

All the compounds exhibited a growth inhibiting effect (GI50 ≤ 33.5 μM) against the MCF-7 breast adenocarcinoma cell line. Furfuryl-1,4-quinones 5, 9, and 11 exhibited growth inhibitory effect levels (GI50 ≤ 27.2 μM) lower than furylhydroquinones 17–20 against non-small cell lung cancer (NCI-H460) and CNS cancer cell (SF-268).

Although, in most cases the growth inhibiting effects were moderate, more potent effects were found with quinones 5, 7, 9, and 11 (entries 1–4) than with hydroquinones 17–20 (entries 5–8). This could be explained assuming that the cytotoxic activity of these compounds depends on their abilities to accept electrons. In the case of quinone compounds the inductive effects of the fused aromatic ring, Cl and OMe substituents on the 1,4-benzoquinone moiety of 5, 9, and 11 probably determine their greater cytotoxicities with respect to that of 7. The electron affinities of quinones 5, 7, 9, and 11, evaluated through the LUMO energies, 17 support this assumption. In fact, calculation of the LUMO energies of quinones 5 (−0.7220 eV), 7 (−0.6883 eV), 9 (−0.9992 eV), and 11 (−0.7629)17 indicates that the less cytotoxic quinone 7 possesses the lowest affinity with the highest value of the LUMO energy. In spite of no correlation of cytotoxic activities and LUMO energies for quinones 5, 9, and 11, the above observations can be explained by the argument that the quinones inhibit the cell proliferation through an oxidative stress mechanism which arises from the capacity of the quinone compounds to enter redox cycles. 9,18

Comparison of the inhibitory activity of compounds 17–20 (entries 5–8) indicates moderate inhibition (GI50 ≤ 38.3 μM) against the MCF-7 and SF-268 cell lines. Since no significant differences were found by changing the substituents located in the 6-position of the acylhydroquinone systems, except for compound 20, apparently the acylhydroquinone core seems to be essential for the cytotoxic activity.

It is noteworthy that while compounds 5, 9, and 11 showed to be equally potent for the three cell lines, compounds 17–20 displayed slight inhibition on the NCI-H460 cell line. This different cell line response may reflect a tumor type-specific sensitivity to these compounds.

3. Conclusions

In summary, a number of furyl-1,4-quinone and hydroquinones were synthesized through oxidative coupling reactions from 1,4-quinones and furfural dimethylhydrazone. These compounds were tested in an in vitro cytotoxic assay against three cancer cell lines: MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer). Some compounds showed good inhibition of the growth of the tested cancer cells, with GI50 in the low-middle micromolar range. The biological evaluation indicates that furyl-1,4-quinones 5, 7, and 11 were more active than hydroquinones 17–20. These results, together with the values of the LUMO energies of 5, 7, and 11, suggest that cell growth inhibition by quinones is related to the generation of active oxygen species (ROS) after redox cycling. The described oxidative coupling chemistry and biological evaluation provided significant information about the molecular design of new cytotoxic agents based on quinonoid compounds.

4. Experimental

4.1. Chemical synthesis

All reagents were of commercial quality, reagent grade, and were used without further purification. Melting points (mp) were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Bruker vector 22-FT spectrophotometer using KBr discs, and wavenumbers are given in cm−1. Proton nuclear magnetic resonance (1H NMR) spectra were measured at 200 and 400 MHz on Bruker AM-200 and AM-400 spectrometers. Chemical shifts are expressed in ppm downfield relative to TMS (δ scale), and coupling constants (J) are reported in Hz. Carbon nuclear magnetic resonance (13C NMR) spectra were
measured at 50 and 100 MHz on Bruker AM-200 and AM-400 spectrometers. High resolution mass spectra were run at the Universidad de Granada, Spain. Silica gel 60 (70–230 mesh) and TLC aluminum foil 60 F254 (Merck, Darmstadt) were used for preparative column and analytical TLC, respectively.

4.1.1. 2-(5-N,N-Dimethylhydrazonofur-2-yl)-1,4-naphthoquinone (5). A suspension of hydrazone 3 (66 mg, 0.5 mmol) and 4 (150 mg, 0.9 mmol) in glacial acetic acid (15 mL) was vigorously stirred for 12 h at room temperature. The reaction mixture was poured into water (100 mL), neutralized with sodium hydrogencarbonate, and extracted with dichloromethane (2× 30 mL). The organic extract was washed with water and dried over MgSO4. The solvent was evaporated under reduced pressure and the residue was submitted to successive purification by column chromatography (1:1 hexane/ethyl acetate) to yield pure 5 as a blue solid (175 mg, 63%); mp 172–173 °C (lit.,14 175–176 °C); IR (KBr): ν 1674 and 1642 (C=O), 1541 (C=N); 1H NMR (200 MHz, CDCl3): δ 8.11–8.03 (m, 2H, 5- and 8-H), 7.76–7.68 (m, 2H, 6- and 7-H), 7.64 (d, 1H, J = 3.7 Hz, 30- or 40-H), 7.29 (s, 1H, 3-H), 6.99 (s, 1H, CH=N), 6.57 (d, 1H, J = 3.7 Hz, 40- or 30-H), 3.06 (s, 6H, 2× Me); 13C NMR (50 MHz, CDCl3): δ 184.6, 183.5, 156.1, 145.6, 134.6, 133.8, 133.3, 132.4, 132.3, 126.6, 126.1, 125.8, 121.9, 119.7, 109.7, 42.5 (2C). HRFABMS calcd for C17H14N2O3Na [M+Na]+ 317.0902, found 317.0917.

4.1.2. 2-(5-N,N-Dimethylhydrazonofur-2-yl)-1,4-benzoquinone (7). A suspension of 6 (312 mg, 2.9 mmol) and hydrazone 3 (200 mg, 1.4 mmol) in glacial acetic acid (15 mL) was vigorously stirred for 24 h at room temperature. The reaction mixture was poured into water (100 mL), neutralized with sodium hydrogencarbonate, and extracted with dichloromethane (2× 30 mL). The organic extract was washed with water and dried over MgSO4. The solvent was evaporated under reduced pressure and the residue was submitted to successive purification by column chromatography (1:1 hexane/ethyl acetate) to yield pure 7 as a blue solid (175 mg, 63%); mp 172–173 °C (lit.,14 175–176 °C); IR (KBr): ν 1674 and 1642 (C=O), 1541 (C=N); 1H NMR (200 MHz, CDCl3): δ 8.11–8.03 (m, 2H, 5- and 8-H), 7.76–7.68 (m, 2H, 6- and 7-H), 7.64 (d, 1H, J = 3.7 Hz, 30- or 40-H), 7.29 (s, 1H, 3-H), 6.99 (s, 1H, CH=N), 6.57 (d, 1H, J = 3.7 Hz, 40- or 30-H), 3.06 (s, 6H, 2× Me); 13C NMR (50 MHz, CDCl3): δ 184.6, 183.5, 156.1, 145.6, 134.6, 133.8, 133.3, 132.4, 132.3, 126.6, 126.1, 125.8, 121.9, 119.7, 109.7, 42.5 (2C). HRFABMS calcd for C17H14N2O3Na [M+Na]+ 317.0902, found 317.0917.

### Table 1. Effect of furylquinones and hydroquinones on the growth of three human tumor cell lines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>GI50 (μM)</th>
<th>MCF-7</th>
<th>NCI-H460</th>
<th>SF-268</th>
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<td>1</td>
<td><img src="image1" alt="Furylquinone Structure" /></td>
<td>7.7 ± 1.2</td>
<td>6.8 ± 1.9</td>
<td>6.5 ± 0.9</td>
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<tr>
<td>2</td>
<td><img src="image2" alt="Furylquinone Structure" /></td>
<td>33.5 ± 0.8</td>
<td>148.2 ± 13.3</td>
<td>100.3 ± 5.1</td>
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</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Furylquinone Structure" /></td>
<td>8.1 ± 1.4</td>
<td>10.9 ± 1.6</td>
<td>9.3 ± 1.4</td>
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</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Furylquinone Structure" /></td>
<td>8.2 ± 0.7</td>
<td>27.2 ± 1.5</td>
<td>9.1 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Furylquinone Structure" /></td>
<td>29.4 ± 0.9</td>
<td>93.0 ± 3.9</td>
<td>38.3 ± 3.4</td>
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<tr>
<td>6</td>
<td><img src="image6" alt="Furylquinone Structure" /></td>
<td>20.3 ± 0.2</td>
<td>80.2 ± 4.4</td>
<td>35.8 ± 1.5</td>
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</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Furylquinone Structure" /></td>
<td>29.2 ± 1.5</td>
<td>63.3 ± 1.7</td>
<td>27.5 ± 2.4</td>
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</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Furylquinone Structure" /></td>
<td>15.6 ± 0.6</td>
<td>121.5 ± 2.0</td>
<td>18.8 ± 0.5</td>
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</tr>
<tr>
<td>9</td>
<td>Doxorubicin⁴</td>
<td>42.8 ± 8.2</td>
<td>94.0 ± 8.7</td>
<td>93.0 ± 7.0</td>
<td></td>
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</table>

Results are means ± SEM of 6–9 independent experiments performed in duplicate. Data from the positive control doxorubicin are expressed as nM.
temperature. The reaction mixture was poured into water (100 mL), neutralized with sodium hydrogencarbonate, and extracted with dichloromethane (2 × 30 mL). The organic extract was washed with water and dried over MgSO4. The solvent was evaporated under reduced pressure and the residue was column chromatographed (1:1 hexane/ethyl acetate) to give pure 7 as a blue solid (297 mg, 42%); mp 126–127 °C (lit.14 mp 126–127 °C); IR (KBr): v 1660 and 1640 (C=O); 1H NMR (200 MHz, CDCl3): δ 7.48 (d, 1H, J = 3.7 Hz, 3'- or 4'-H), 7.0 (s, 1H, 3-H), 6.77 (s, 2H, 5- and 6-H), 6.68 (s, 1H, CH=N), 6.59 (d, 1H, J = 3.7 Hz, 4'- or 3'-H), 3.60 (s, 6H, 2x Me); 13C NMR (50 MHz, CDCl3): δ 189.2, 188.4, 151.9, 151.3, 151.1, 142.0, 124.1, 123.9, 110.4, 109.5, 108.6, 42.8, 42.7. HRFABMS calcd for C13H12N2O3Na [M+Na]+ 367.0745, found 367.0756.

4.1.5. 3-Acetyl-2-(5-N,N-dimethylhydrazonofur-2-yl)-1,4-benzoquinone (14). A suspension of hydrazone 3 (152 mg, 1.1 mmol), 12a (150 mg, 1.0 mmol), silver(I) oxide (928 mg, 4 mmol), and magnesium sulfate (500 mg) in benzene (25 mL) was vigorously stirred for 1 h at room temperature. The deep blue solution was filtered and the solids were washed with benzene. The filtrate was evaporated under vacuum and the residue was purified by column chromatography (dichloromethane) to give quinone 14 (280 mg, 98%) as a blue viscous oil: IR (KBr) v 1700 (C=O acetyl), 1660 and 1630 (C=O quinone); 1H NMR (200 MHz): δ 7.62 (d, 1H, J = 4 Hz, 4'-H), 6.93 (s, 1H, N=CH), 6.77 (s, 2H, 5- and 6-H), 6.60 (d, 1H, J = 4 Hz, 3'-H), 3.10 (s, 6H, NMe2), 2.60 (s, 3H, COMe). Anal. calcd for C14H14N2O4Na: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.52; H, 5.05; N, 9.85.

4.1.4. 2-(5-N,N-Dimethylhydrazonofur-2-yl)-5-methoxy-1,4-benzoquinone (11). A suspension of hydrazone 3 (72 mg, 0.52 mmol) and 8 (192.0 mg, 1.0 mmol) in glacial acetic acid (15 mL) was vigorously stirred for 8 h at room temperature. The reaction mixture was poured into water (100 mL), neutralized with sodium hydrogencarbonate, and extracted with dichloromethane (2 × 30 mL). The organic extract was washed with water and dried over MgSO4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (1:1 hexane/ethyl acetate) to yield pure 9 as a blue solid (254 mg, 77%); mp 139–140 °C; IR (KBr): v 1673 and 1652 (C=O); 1H NMR (200 MHz, CDCl3); δ 8.18–8.07 (m, 2H, 5- and 8-H), 7.75–7.71 (m, 2H, 6- and 7-H), 7.65 (d, 1H, J = 3.8 Hz, 3'- or 4'-H), 7.08 (s, 1H, CH=N), 6.69 (d, 1H, J = 3.8 Hz, 4'- or 3'-H), 3.08 (s, 6H, 2x Me); 13C NMR (50 MHz, CDCl3): δ 181.9, 178.0, 157.0, 144.3, 134.9, 134.0, 133.8, 132.3, 132.2, 131.4, 127.1, 126.8, 124.8, 119.9, 108.3, 42.5 (2C) HRFABMS calced for C17H13Cl2N2O4 [M+H]+ 329.0692, found 329.0682.

4.1.7. 2,5-Dihydroxy-6-(5-N,N-dimethylhydrazonofur-2-yl)-benzaldehyde (17). A suspension of hydrazone 3 (284 mg, 2.05 mmol), 2,5-dihydroxybenzaldehyde (276 mg, 2 mmol), and silver(I) oxide (1.86 g, 8 mmol) in benzene (25 mL) was vigorously stirred for 1 h at room temperature. The resulting deep blue mixture was filtered, the solids were washed with benzene, and the filtrate was evaporated under reduced pressure to give crude quinone 16 (511 mg, 94%) as an unstable green solid. Crude quinone 16 (300 mg, 1.1 mmol), zinc dust (1 g, 15.4 mmol), and glacial acetic acid (1 mL) in dichloromethane (10 mL) were stirred for 5 min at room temperature. The mixture was filtered and the solid washed with dichloromethane. The filtrate was washed with water and the organic phase was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (chloroform) to afford furylhydroquinone 17 as orange crystals (233 mg, 78%); mp 127–128 °C; IR (KBr): v 3180 (OH), 1649 (C=O), 1556 (C=N); 1H NMR (200 MHz, CDCl3): δ 10.51 (s, 1H, OH), 9.89 (s, 1H, CHO), 7.18 (d, 1H, J = 9.1 Hz 6-H), 7.03 (s, 1H, N=CH), 6.89 (d, 1H, J = 9.1 Hz, 3- or 4-H), 6.58 (d, 1H, J = 3.4 Hz, 3'- or 4'-H), 6.49 (d, 1H, J = 3.4 Hz, 4'- or 3'-H), 3.01 (s, 6H, 2x Me); 13C NMR (50 MHz, CDCl3): δ 161.2, 156.9, 153.9, 146.8, 144.4, 126.6, 120.8, 119.3, 117.9, 117.1, 115.7, 108.1, 42.6 (2C). HRFABMS calded for C14H14N2O4Na [M+Na]+ 297.0841, found 297.0854.

4.1.8. 2,5-Dihydroxy-6-chlorobenzaldehyde (20). A suspension of 2,5-dihydroxybenzaldehyde (170 mg, 1.23 mmol), silver (II) oxide (510 mg, 2.2 mmol), magnesium sulfate (500 mg), and dichloromethane (35 mL) was vigorously stirred for 2 h. The mixture was filtered and the solids were washed with dichloromethane (15 mL). Dry hydrogen chloride was bubbled through the filtrate for 5 min and the resulting solution was left overnight at room temperature. The solvent was removed and the residue was purified by column chromatography (dichloromethane) to give pure 20 as a gold yellow solid (146 mg, 69%); mp 155–157°C.

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Acknowledgments

References and notes

17. The LUMO energies were performed using the semiempirical MM2 method implemented in the CSChem 3D software.