New oxirane derivatives of 1,4-naphthoquinones and their evaluation against *T. cruzi* epimastigote forms

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**A B S T R A C T**

New oxirane derivatives were synthesized using six naphthoquinones as the starting materials. Our biological results showed that these oxiranes acted as trypanocidal agents against *Trypanosoma cruzi* with minimal cytotoxicity in the VERO cell line compared to naphthoquinones. In particular, oxirane derivative 14 showed low cytotoxicity in a mammalian cell line and exhibited better activity against epimastigote forms of *T. cruzi* than the current drug used to treat Chagas disease, benznidazole.

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**1. Introduction**

Chagas disease is an important endemic disease caused by the protozoan parasite *Trypanosoma cruzi*. According to the World Health Organization approximately 16–18 million people worldwide are infected and approximately 50,000 individuals die each year from this disease. Due to migration, the incidence of infection is also growing in non-endemic areas, further increasing the risk of transmission by blood transfusion and organ transplantation.1

The disease has two clinical phases: the acute stage and the chronic stage. The acute phase is usually asymptomatic, but 10–50% of asymptomatic patients die during this phase, especially children younger than two years.2 In the chronic phase, 20% of cases develops heart disease, digestive problems, or irreversible neurological damage. Two drugs have been on the market since the 70s for the treatment of it: nifurtimox and benznidazole (Fig. 1). In some countries, benznidazole is the only drug approved for clinical use. However, besides being very toxic with severe side effects, its use is limited to the acute phase of the disease. Moreover, there are currently no formulations for pediatric use. Benznidazole is the most commonly used drug to treat this disease; however, there are strains of *T. cruzi* that are resistant to benznidazole. Thus, the search for trypanocidal compounds is extremely necessary and should be encouraged.

Chagas disease occurs mainly in the tropical countries of North and South America, and is concentrated in the poorest countries therein, as the vector is restricted to this continent. Chagas disease is considered to be a neglected disease3 by the WHO due to the lack of interest by large pharmaceutical companies that seek highly profitable products. In Latin America, approximately ten million individuals are infected with Chagas disease, with a predominant number of cases being chronic cases of the disease.4,5 The main problem is that this disease leads to heart disease, which causes disability and mortality in individuals during their productive phase of life. This disease is a serious public health problem in poorer areas of countries where this disease is endemic.

Researchers are still trying to find new biochemical targets and new chemical entities with minimal toxicity toward normal cells...
that may have potential activity against the *T. cruzi* parasite. In this regard, several synthetic substances continue to be reported in the literature, most of them inspired by bioactive natural products. To date, none have gone on to become a new drug for the treatment of Chagas disease. A few natural and synthetic substances that have a good level of activity against *T. cruzi* are shown in Figure 2.

Among the substances shown in Figure 2, some are naphthoquinones derivatives, recognized as privileged structures in the search of new trypanocidal compounds. The 2-lapachone (1) is a natural substance present in Brazilian trees of the genus *Tabebuia*, which, together with lapachol, has been used by indigenous people for the treatment of many parasitic infections. Although, it has not yet become a drug, its structure has been widely exploited in medicinal chemistry as a prototype for new candidates against *T. cruzi*, such as compounds 2a, b and 3. The 1,4-naphthoquinone isomer has served as inspiration for compounds 4 and 5, which showed excellent trypanocidal activities. The combination of molecular cores of [1,2,3]-triazoles and the naphthoquinone were used to synthesize compound 6, which exhibited good trypanocidal activity. Based on the fact that complexes of platinum (II) are used in 50% of all cancer therapies, these complexes were also synthesized and evaluated against *T. cruzi*. The gold complex with the ligand N-oxide pyridine-2-thiol (7) showed potent anti-*T. cruzi* activity in vitro with specific action on the fumarate reductase enzyme. The E-64 (8) is a natural product quite active against trypomastigotes of *T. cruzi*.

Compound 4, obtained from x-lapachone (9), was the only oxirane that showed high trypanocidal activity with excellent minimal cytotoxicity in VERO cells. Comparatively, 4 showed trypanocidal activity similar to 2-lapachone (1), which is a natural product with potent trypanocidal activity. Importantly, the substitution of one carbonyl of naphthoquinone generated a new class of trypanocidal compounds with low cytotoxicity against mammalian cells. Because the oxirane derivatives have different molecular properties, their pharmacological mechanisms of action are different.

The main mechanism of action of the naphthoquinones, such as compound 1, operates by inducing apoptosis in *T. cruzi* through damage caused by oxidative stress. However, other mechanisms occur, such as inhibitory activities on cysteine and serine proteinases of *T. cruzi*, similar to the effect of the natural product E-64 (8). Compound 4 specifically inhibited the serine proteinase of *T. cruzi*, interfering with the establishment of infection.

The data in the literature for compound 4 show its potential as a prototype of inhibitor of the serine proteinase and is potential compound for the development of new trypanocidal agents. Therefore, the objective of this work is to synthesize new oxirane derivatives obtained from 1,4-naphthoquinones (Fig. 3 and Table 1) and to evaluate them against epimastigotes forms of *T. cruzi*.

2. Chemistry

2.1. General procedures

Melting points were obtained on a Thomas Hoover apparatus and are reported uncorrected values. Analytical grade solvents were used. Column chromatography was performed on silica gel (Acros Organics 0.035–0.070 mm, pore diameter of approximately 6 nm). Infrared spectra were recorded on a FTIR Spectrometer IR Prestige-21 e Shimadzu. 1H and 13C NMR spectra were recorded at room temperature using a VNMRSYS-500 or a Varian MR 400 instrument in the solvents indicated in their monographs, with TMS as the internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) are reported in Hertz. Low resolution mass spectra were obtained using a gas chromatograph mass spectrometer GCMSQP2010 PLUS Shimadzu with column DB-5MS and GCMS-QPS000 (EI MS, 70 eV). High resolution mass spectra (electrospray ionization) were obtained using a QTOF Micro (Waters, Manchester, UK) mass spectrometer (HRESIMS). The ions in mass spectra were described as mass-to-charge ratio (m/z) and the relative abundance in percentage of the base peak intensity. All the compounds were named using the program CS ChemDraw Ultra version 10.0. 2,3-Dichloronaphthoquinone 19 is commercially available while naphthoquinones 9, 11, 15 and 17 were prepared by standard procedures as described in the literature. Oxiranes 14 and 20 were previously synthesized. The structure of oxirane 16 was previously determined by our group. However, the chemical shifts and the presence of two carbonyl groups clearly show that the position of methylene group (CH2) is placed in the double bond, as in compound 10. Therefore, the correct structure for compound 16 is the one reported herein, which was confirmed by X-ray crystallography (Fig. 4). In our previous work, from the reaction of 9 with diazomethane (entry 1) it was only isolate the naphthoquinone 4. However, it was now
possible isolate the compound 10, as minor component along with 4, in another reactive π-bond for cyclopropanation in the 1,4-naphthoquinone system. In other reactions was not possible to isolate the cyclopropanation product in the double bonds. Due to two reactive double bonds the cyclopropanation of 17 (entry 5) led to a mixture of compounds.

### Table 1
Yields of cyclopropane (10) and oxirane derivatives obtained from naphthoquinones

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,4-Naphthoquinone</th>
<th>Oxirane derivative</th>
<th>Yield (%), t (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>23 (5)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>70 (2)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>80 (2)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>60 (3)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>35 (4)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>52 (3)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2. Synthesis

A solution of diazomethane in ethyl ether (10 mL) was added to a solution of naphthoquinone (1 mmol) in 3:1 diethyl ether/ethanol (20 mL). The reaction was carried out at room temperature for 2–5 days (see Table 1). The solvent was evaporated under reduced pressure, and the crude product was purified by silica gel column chromatography using hexane-ethyl acetate as eluent (Fig. 3 and Table 1).

#### 2.2.1. 2,2-Dimethyl-3,4,4a,10a-tetrahydro-4a,10a-cyclopropyl-2H-benzog[10]chromene-5,10-dione (10)

White solid; Yield 23%; mp 116–119 °C; IR (KBr) 2976, 2931, 1680, 1593, 1298, 1255, 972, 954 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm 8.04 (dd, J = 8.20, 4.76 Hz, 1H), 7.99 (dd, J = 8.22, 4.73 Hz, 1H), 7.80–7.64 (m, 2H), 2.65 (ddd, J = 14.39, 12.29, 7.00 Hz, 1H), 2.29–2.13 (m, 1H), 1.95 (d, J = 5.64 Hz, 1H), 1.73 (d, J = 5.67 Hz, 1H), 1.66–1.47 (m, 2H), 1.34 (s, 3H), 1.14 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 194.5, 193.2, 134.0, 133.9, 132.0, 131.9, 127.0, 126.9, 73.1, 65.6, 37.3, 32.1, 31.6, 29.6, 22.6, 17.6; EIMS m/z (rel int): 256 (56, M+), 241 (39), 227 (24), 213 (54), 198 (52), 188 (23), 173 (18), 159 (20), 142 (46), 132 (30), 115 (71), 104 (97), 95 (30), 76 (100), 69 (19), 43 (69). HRESIMS m/z 257.1171 [M+H]+ (Calcd for C₁₆H₁₇O₃+: 257.1172).

#### 2.2.2. 2,2-Dimethyl-3,4,6,7,8,9-hexahydrospiro[benzo[g]chromene-10,2'-oxirane]-5(2'H)-one (12)

White solid; Yield 70%; mp 75–78 °C; IR (KBr) 2974, 2939, 2868, 1662, 1614, 1454, 1417, 1363, 1336, 1307, 1273, 1269, 73.1, 65.6, 37.3, 32.1, 31.6, 29.6, 22.6, 16.7; EIMS m/z (rel int): 260 (63, M+), 245 (16), 227 (15), 215 (3), 204 (100), 189 (19), 174 (19), 157 (6), 146 (12), 131 (10), 115 (11), 105 (10), 91 (30), 77 (28), 65 (14), 55 (12), HRESIMS m/z 261.1476 [M+H]+. (Calcd for C₁₆H₂₁O₃+: 261.1485).

#### 2.2.3. 2-Methoxy-4H-spiro[naphthalene-1,2'-oxirane]-4-one (14)

White solid; Yield 80%; mp 140–143 °C; IR (KBr) 3072, 2995, 2953, 2900, 2850, 1647, 1608, 1570, 1462, 1382, 1237, 1269, 1234, 1213, 1149, 1122, 1085, 1062, 1031, 972, 898, 835, 781, 754 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ ppm 8.17 (d, J = 7.78 Hz, 1H), 7.58 (t, J = 8.07 Hz, 1H), 7.49 (t, J = 7.46 Hz, 1H), 7.23 (d, J = 7.79 Hz 1H), 6.01 (s, 1H), 3.85 (s, 3H), 3.70 (d, J = 6.75 Hz, 1H),

![Figure 4. ORTEP representations (30% probability displacement ellipsoids) of compounds 10 (a) and 16 (b).](http://dx.doi.org/10.1016/j.bmc.2012.06.027)
3.2.4. 2,2-Dimethyl-2C(1) and relevant distances are presented in Table 2 and Table 3. These

1141, 904, 866, 840, 810, 756 cm
3045, 2924, 1664, 1595, 1568, 1456, 1325, 1282, 1238, 1165, 128 (24), 115 (29), 102 (6), 89 (12), 77 (14), 63 (12), 51 (10). HRESIMS m/z 203.0713 [M+H]+ (Calcd for C12H11O3; 203.0703).

2.2.4. 2,3-Dimethyl-2H-spiro[naphthalene-2,3-b][furan-9,2-
oxirane]-4(3H)-one (16)

White solid; Yield 60%; mp 123–126 °C; IR (KBr) 3066, 2966, 2926, 2858, 1660, 1600, 1568, 1460, 1417, 1375, 1271, 1211, 1165, 1122, 1090, 861, 896, 754 cm–1; 1H NMR (400 MHz, CDCl3) δ ppm 8.18 (d, J = 7.64 Hz, 1H), 7.52 (m, 2H), 7.20 (d, J = 6.71 Hz, 1H), 3.70 (d, J = 6.52 Hz, 1H), 3.44 (d, J = 6.53 Hz, 1H), 2.93 (s, 2H), 1.52 (s, 3H), 1.51 (s, 3H); 13C NMR (125 MHz, CDCl3) δ ppm 181.5, 168.1, 136.2, 134.2, 131.8, 128.6, 126.4, 122.6, 117.4, 92.2, 57.3, 50.8, 40.2, 28.3, 28.2; EIMS m/z (rel int): 242 (100 %), 227 (20), 211 (5), 200 (19), 183 (9), 171 (15), 116 (14), 128 (24), 115 (35), 105 (13), 89 (12), 77 (19), 63 (12), 43 (45). HRESIMS m/z 243.1028 [M+H]+ (Calcd for C12H11O3; 243.1016).

2.2.5. 2-(Allyloxy)-4H-spiro[naphthalene-1,2-oxirane]-4-one (18)

White solid; Yield 35%; mp 92–94 °C; IR (KBr) 3028, 2924, 1656, 1610, 1570, 1460, 1408, 1365, 1325, 1269, 1236, 1203, 1145, 1103, 1060, 1028, 966, 983, 873, 831, 781, 750 cm–1; 1H NMR (400 MHz, CDCl3) δ ppm 8.17 (d, J = 7.79 Hz, 1H), 7.57 (t, J = 7.58 Hz, 2H), 7.24 (d, J = 7.79 Hz, 1H), 6.05–5.94 (m, 1H), 6.00 (s, 1H), 5.39 (dd, J = 26.73, 13.93 Hz, 2H), 4.55 (t, J = 5.41 Hz, 2H), 3.72 (d, J = 6.81 Hz, 1H), 3.31 (d, J = 6.80 Hz, 1H); 13C NMR (125 MHz, CDCl3) δ ppm 184.6, 168.0, 137.1, 132.6, 132.0, 128.5, 126.4, 122.8, 119.4, 118.2, 106.9, 69.7, 57.9 EIMS m/z (rel int): 228 (100 %), 213 (61), 199 (12), 185 (15), 181 (9), 152 (16), 128 (24), 115 (29), 102 (6), 89 (12), 77 (14), 63 (12), 51 (10). HRESIMS m/z 229.0863 [M+H]+ (Calcd for C12H11O3; 229.0859).

2.2.6. 2,3-Dichloro-4H-spiro[naphthalene-1,2-oxirane]-4-one (20)

White solid; Yield 52%; mp 149–150 °C; IR (KBr) 3103, 3074, 3045, 2924, 1664, 1595, 1568, 1456, 1328, 1288, 1218, 1165, 1141, 904, 866, 840, 810, 756 cm–1; 1H NMR (400 MHz, CDCl3) δ ppm 8.23 (d, J = 7.83 Hz, 1H), 7.66 (t, J = 8.21 Hz, 1H), 7.55 (t, J = 7.58 Hz, 1H), 7.31 (d, J = 7.91 Hz, 1H), 3.77 (d, J = 6.09 Hz, 1H), 3.37 (d, J = 6.08 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ ppm 176.1, 148.4, 137.7, 135.3, 133.8, 131.0, 129.4, 127.9, 123.4, 58.2, 55.2; EIMS m/z (rel int): 239 (16 %), 212 (41), 205 (12), 184 (33), 182 (52), 177 (83), 147 (100), 135 (7), 113 (34), 99 (15), 97 (19), 74 (22), 63 (24), 50 (13). HRESIMS m/z 240.9817 [M+H]+ (Calcd for C11H11Cl2O2; 240.9818).

2.3. Crystal structure of compounds 10 and 16

The position of the oxirane ring in the compounds of 10 and 16 was determined unequivocally by X-ray diffraction analysis. The crystal structures are shown in Figure 4. The crystallographic data and relevant distances are presented in Table 2 and Table 3. These results demonstrate the maintenance of carbonyl groups in C(1)=O(1) and C(4)=O(3) in the compound 10 and the cyclopropyl between the C(2) and C(3). For compound 16, the oxirane moiety was observed between the atoms of C(1) and O(1), possibly due to influences of the oxygen atom O(2) in the furan ring. The modifications in compound 16 maintain the characteristic planar rings. However, the cyclohex-2-ene-1,4-dione in compound 10 adopts a boat conformation. The crystal packing of these structures is stabilized by weak interactions of the type C–H · · · O and π–π stacking.

2.4. Crystallographic data for the structure of compounds 10 and 16

have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 864803 and 864804. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

3. Biology studies

3.1. Cell viability assay

T. cruzi Y epimastigote forms (5 × 10^5 cell/mL) were treated with 50 μM of each compound for 72 h. The cells were centrifuged (1500 g), washed in PBS, and then incubated with 30 μg/mL of propidium iodide for 15 min. Data were analyzed using a C6 flow cytometer (Accuri). A total of 10,000 events were acquired in the region previously described as corresponding epimastigote forms.
3.2. Trypanocidal activity

Stock solutions of each compound (5 mM) were prepared in dimethylsulfoxide (DMSO). Epimastigote forms of T. cruzi Y (10⁶ cells/mL) were incubated with compounds diluted in DMSO in 50 μM concentration, during 72 h in BHI medium supplemented with 10% fetal bovine serum (Sigma) at 28 °C. Trypanocidal effects were quantitatively monitored by direct counting in a Neubauer chamber using Optical Microscopy (Olympus B×41). Non-treated cultures and cultures treated with 1% DMSO (v/v) were also included as negative controls. Benznidazole, the current drug used to treat Chagas disease, was also evaluated to compare its activity to the other compounds synthesized in this study. The activities of the compounds were expressed as IC₅₀, corresponding to the concentration that leads to 50% parasite growth inhibition. The IC₅₀ was calculated using the statistical program Probits.

3.3. Cytotoxicity assay in mammalian cell

The cytotoxic effects of the oxiranes and naphthoquinones were evaluated using VERO cells (ATCC, CRL-1586), a fibroblast cell line established from the kidney of African green monkeys (Cercopithecus aethiops). Cytotoxic effects on cells were analyzed after 72 h of VERO cell treatment with compounds (at the same concentrations used in the experiment for trypanocidal activity). Cells were maintained in Dulbecco’s modified minimum essential medium (Sigma), supplemented with 5% fetal bovine serum and HEPES buffer (Sigma). Cells were then plated in multiwell dishes (24 wells, Nuclon) at densities of 10⁵ cells per well. Culture medium final volume was then adjusted to 1 mL per well and cells were incubated at 37 °C for 24 h to promote adhesion. Afterward, the cells were exposed to the drugs, diluted to different concentrations (50 μM), at a final 1-mL volume of culture medium over 72 h. The cells were then washed twice with phosphate-buffered saline (PBS) and fixed for 15 min with 0.2% formaldehyde in PBS. The cells were then stained with 0.25 mL of 0.2% CBBR-250 prepared in 10% (v/v) acetic acid and 40% (v/v) methanol in distilled water for 1 h at room temperature. CBBR-250 stain was eluted from the cells with 1.0 mL of 1% sodium dodecyl sulfate for 1 h. Cell quantification was performed correlating cell number and CBBR-250 absorbance, through spectrophotometry at 595 nm.

4. Results

4.1. Rationale

The absence of effective drugs for the treatment of Chagas disease drives the search for new compounds that have activities against T. cruzi and that also have low toxicity to mammalian cells.

4.2. Drug screening

Screening tests were performed to analyze cell viability by flow cytometry. We used the fluorescent dye propidium iodide, which binds to DNA, but can only penetrate into cells that don’t have intact plasma membrane. Several compounds exhibited high trypanocidal activity. Two compounds, 10 and 12, showed a mortality rate lower than benznidazole. Apparently, changes in the aromatic ring of 9 or replacing the ring with oxirane cause profound changes in the trypanocidal effect. Compound 15 (% of dead cells at 50 μM = 91.4 ± 8.3) had an activity profile similar to β-lapachone (1) (% of dead cells at 50 μM = 91.3 ± 6.3), a naphthoquinone known to have interesting biological activities, including trypanocidal and anti-neoplastic activities. We did not find any significant solvent effects on the drugs at the higher concentrations used in this assay (Table 4).

Most of the results of the drug screening test match up with the IC₅₀ (50% inhibitory concentration) (Table 5) quantified by direct counting in a Neubauer chamber. Compound 10 showed no activity against T. cruzi or Vero cells and was the least cytotoxic compound. The other compounds had extremely low IC₅₀ values; in addition, the CC₅₀ values (cytotoxicity concentration that kills 50% of the cells) were as low as the IC₅₀ values. All oxirane ring-containing compounds showed lower cytotoxicity than the naphthoquinones from which they were derived. This finding may suggest a mechanism of suppression of ROS (reactive oxygen species) mediated by oxiranes. Two drugs showed promise for further studies: compounds 14 and 12 both showed a high CC₅₀ and an IC₅₀ similar to benznidazole (Table 5). Compound 14 showed a better trypanocidal activity in the assay using the Neubauer chamber (IC₅₀ = 1.13 μM) than in the screening test using a flow cytometer (% of dead cells at 50 μM = 74.2 ± 3.8). The differing results from these two techniques may be due to the mechanism of action of the compound. Propidium iodide only stains cells that have a disrupted membrane, so it is possible that the mechanism of action of this compound does not involve the attack of the plasmatic membrane or other mechanisms that evolves to its disruption, such as, apoptosis and production of oxygen reactive species. These compounds may delay cell division, and therefore, these substances may not be adequately screened by the cytometer technique. Thus, the Neubauer chamber may be the more appropriate technique because this assay does not analyze cell viability, but compares the

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀ (μM)</th>
<th>CC₅₀ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoxy-α-Lapachone (4)</td>
<td>0.05</td>
<td>&gt;50</td>
</tr>
<tr>
<td>17</td>
<td>0.02</td>
<td>&lt;1</td>
</tr>
<tr>
<td>18</td>
<td>0.2</td>
<td>&lt;1</td>
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<tr>
<td>β-Lapachone (1)</td>
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<td>&lt;3.1</td>
</tr>
<tr>
<td>19</td>
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<td>Benznidazole</td>
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</tr>
<tr>
<td>10</td>
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Mean and standard deviation of at least two independent experiments in duplicates.

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growth of the control group with the treated group. Therefore, the use of two techniques is essential for evaluating trypanocidal and trypanostatic substances.

Compound **14** appears to be the best candidate for use as a trypanocidal agent among the compounds tested because it showed activity comparable to epoxy-lapachone (4). Compound **4**, described previously in the literature, demonstrated activity against both the tripomastigote and amastigote forms, while exhibiting no toxicity in macrophages. These results reinforce the safety and effectiveness of this compound for its future design as a new substance for use in the treatment of Chagas disease.

The mechanism of action of compound **4** remains to be elucidated; however, when the quinone moiety is replaced by an oxirane ring, it appears that there is no cell damage associated with oxidative stress. Several authors have described different oxirane mechanisms of action in *T. cruzi*, such as the inhibition of some specific proteases. 18,19

This pioneering study demonstrated the potent inhibition of the growth of *T. cruzi* epimastigote forms by the oxirane derivatives of -lapachone. These derivatives show great potential as promising compounds in the search for new drugs to treat Chagas disease.

5. Conclusion

This paper showed that oxirane derivatives exhibited reduced cytotoxicity in mammalian cells compared to their corresponding naphthoquinones. Moreover, these oxirane derivatives maintained similar trypanocidal activities as their naphthoquinone counterparts. Compound **14** showed high trypanocidal activity and low cytotoxicity, comparable to benznidazole. Thus, compound **14** emerges as a promising candidate for the development of a new drug for the treatment of this disease. Studies to evaluate the effects of compound **14** in amastigotes and trypanomastigotes, as well as investigations into its mechanism of action, are currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.06.027.

References and notes