Bioorg. Med. Chem. 40 (2021) 116164

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

# Ruthenium(II)- and Palladium(II)-catalyzed position-divergent C—H oxygenations of arylated quinones: Identification of hydroxylated quinonoid compounds with potent trypanocidal activity

Talita B. Gontijo [a,b,1], Renato L. de Carvalho [a,b,1], Luiza Dantas-Pereira [c], Rubem F. S. Menna-Barreto [c], Torben Rogge [a], Lutz Ackermann [a,d,*], Eufrânio N. da Silva Júnior [b,*]

[a] Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstraße 2, 37077 Göttingen, Germany
[b] Institute of Exact Sciences, Department of Chemistry, Federal University of Minas Gerais, CEP 31270-901, Belo Horizonte, MG, Brazil
[c] Laboratory of Cellular Biology, IOC, FIOCRUZ, Rio de Janeiro, RJ 21045-900, Brazil
[d] DZHK (German Center for Cardiovascular Research), Potsdamer Strasse 58, 10785 Berlin, Germany

ARTICLE INFO

*Keywords:*
Quinones
Chagas disease
Ruthenium
Palladium
C—H Oxygenation

ABSTRACT

A diversity-oriented synthesis of hydroxylated aryl-quinones *via* C—H oxygenation reactions and their evaluation against *Trypanosoma cruzi*, the etiological agent of Chagas disease, was accomplished. With the use of ruthenium (II)- or palladium(II)-based catalysts, complementary regioselectivities were observed in the hydroxylation reactions and we have identified 9 compounds more potent than benznidazole (Bz) among these novel arylated and hydroxylated quinones. For instance, 5-hydroxy-2-[4-(trifluoromethyl)phenyl]-1,4-naphthoquinone (**4h**) with an $IC_{50}$/24 h value of 22.8 μM is 4.5-fold more active than the state-of-the-art drug Bz. This article provides the first example of the application of C—H activation for the position-selective hydroxylation of arylated quinones and the identification of these compounds as trypanocidal drug candidates.

## 1. Introduction

With almost 8 million infected people worldwide and 10,000 deaths every year, Chagas disease represents a serious health problem, especially for people living in low-income rural areas of endemic countries in Latin America, and is considered a neglected tropical illness.[1-3] This disease is caused by the hemoflagellate protozoan named *Trypanosoma cruzi*, that is classically transmitted by the feces of triatomine bugs, by the ingestion of contaminated food and beverages, or even by infected blood (congenitally, organ transplants or during blood transfusion). With the decline in new cases derived from the classical route (by the vector) or blood transfusion, congenital and especially oral transmissions became more relevant epidemiologically.[4,5] As a result of the migratory flux, the process of globalization to well-developed areas was intensified and many infected individuals are living on all continents, allowing for the incidence of this disease in non-endemic countries.[6,7]

The clinical course of Chagas disease shows two very distinct phases. In the acute phase the parasitemia is high and the patients are frequently asymptomatic or oligosymptomatic while in the chronic phase the parasitemia is sub patent. The chronic phase can be classified by clinical manifestations into indeterminate (asymptomatic) or symptomatic that can present digestive (characterized by megacolon or mega esophagus), and cardiac (with progressive fibrotic cardiomyopathy) forms.[8-10] The most recurrent cause of death in chronic individuals is heart failure due to cardiac dysfunction such as cardioembolism, bradyarrhythmia and apical aneurysm.[11-13] Furthermore, current etiological treatment is based on 2-nitroimidazole benznidazole and the 5-nitrofuran nifurtimox, developed in the late 1960s. Even after half a century, the chemotherapy for Chagas disease has remained unchanged, being efficient for acute cases, but showing strong limitations in the chronic phase.[14,15] The active search for alternative drugs/combinations for this neglected disease is easily justified by the limited activity in chronic patients together with the observed side effects.[16] The absence of an adequate treatment for symptomatic chronic cases also results in a global economic burden of billions of dollars and a reduction in work productivity.[17,18]

Motivated by the urgent demand to identify new compounds with outstanding trypanocidal activity, our research group has in recent years

* Corresponding authors.
*E-mail addresses:* Lutz.Ackermann@chemie.uni-goettingen.de (L. Ackermann), eufranio@ufmg.br (E.N. da Silva Júnior).
[1] These authors contributed equally.

https://doi.org/10.1016/j.bmc.2021.116164
Received 18 March 2021; Received in revised form 11 April 2021; Accepted 13 April 2021
Available online 20 April 2021

investigated the potential of quinones for the treatment of Chagas disease.[19,20] In this context, approaches involving modern and elegant synthetic strategies were employed to access novel trypanocidal quinones, such as rhodium-catalyzed C—H bond halogenations,[21] sequential C—H iodination/organoyl thiolation reactions,[22] ruthenium(II)-catalyzed C—H alkenylation,[23] selenation of quinones with copper complexes and carbon nanotube–copper ferrite as catalysts,[24] and more recently rhodium-catalyzed [2 + 2 + 2] cycloadditions[25] (Scheme 1). In 2018, we developed a straightforward approach for the synthesis of a variety of hydroxylated quinones *via* catalysis with ruthenium(II),[26] which allowed us to test the bioactivity of these compounds and demonstrate their outstanding activity against *T. cruzi* (Scheme 1).

In the present report, we describe our efforts towards the synthesis and trypanocidal evaluation of arylated quinones and their subsequent selective A-ring or aryl hydroxylation catalyzed by ruthenium or palladium complexes. This study represents the first example of ruthenium- and palladium-catalyzed position-complementary C—H hydroxylation[27] of arylated quinoidal compounds and the preparation of novel molecules with potent trypanocidal activity *via* formation of 5-membered ruthenacycles or 6-membered palladacycles[28–33] (Scheme 2).

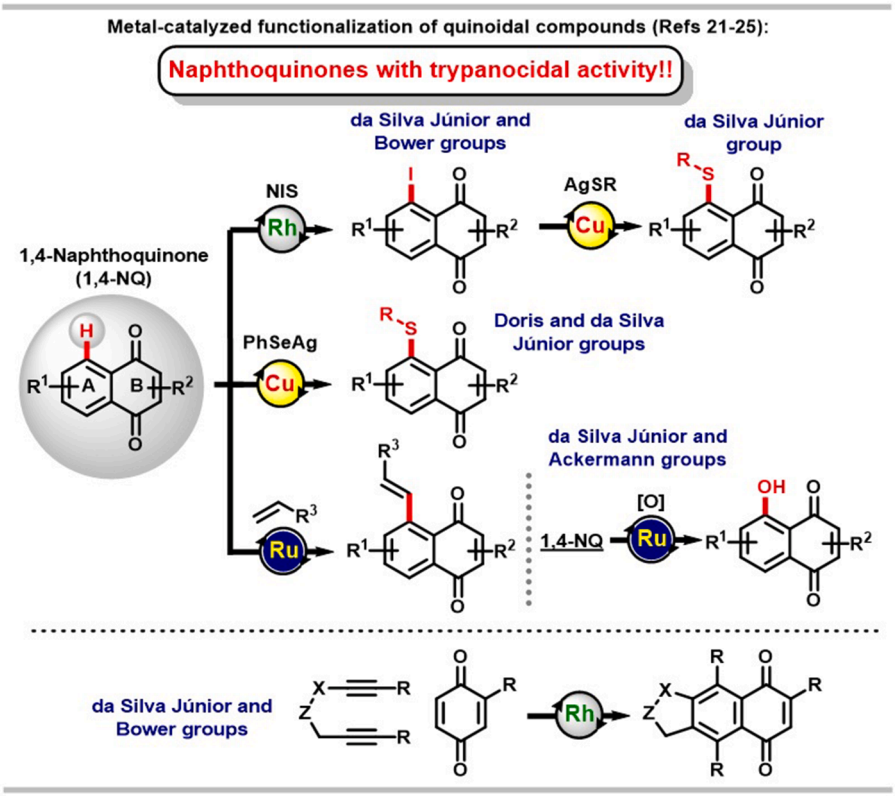
## 2. Results and discussion

### 2.1. Chemistry

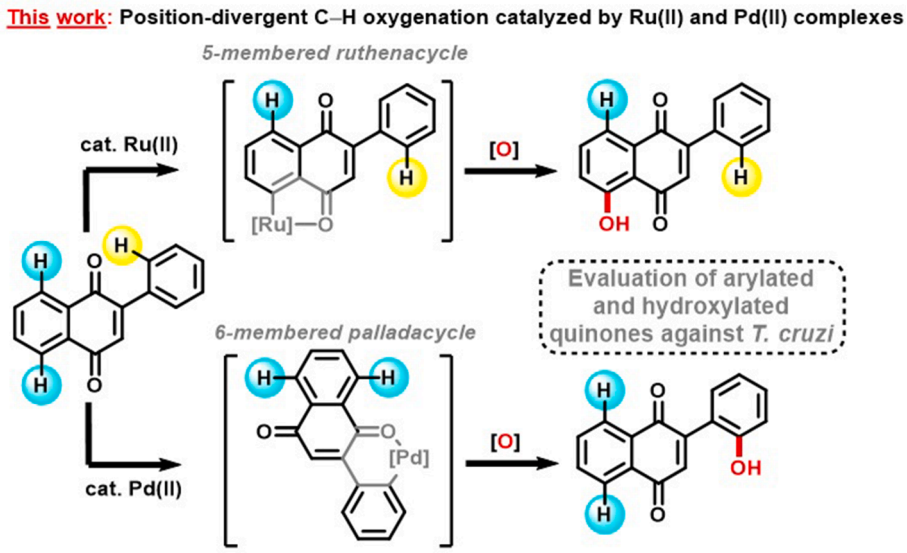
Aware of the ability of 1,4-naphthoquinones (1,4-NQs) to act as trypanocidal agents, we set out to investigate C-2 arylated 1,4-NQs **3**, accessed *via* C—H arylation of 1,4-NQs. Subsequent structural modification *via* C—H oxygenation under ruthenium and palladium catalysis was also accomplished. In general, there are several methods reported in the literature for the preparation of this class of compounds, with important contributions by Itahara,[34] Molina,[35] Baran,[36] and Akagi.[37] However, it is worth noting that the trypanocidal activity of these substances has thus far not been explored. These novel insights will be discussed in the biological section (*vide infra*). To this end, we chose the protocol described by Baran and co-workers[36] to prepare a variety of 2-aryl-1,4-naphthoquinones (**3a-m**) through the reaction of 1,4-naphthoquinone (**1**) with differently substituted aryl boronic acids (**2a-m**) in the presence of catalytic amounts of silver(I) nitrate and ammonium persulfate as the oxidant in a mixture of trifluorotoluene/water as the solvent. The applicability to a diverse range of boronic acids and the user-friendly work-up of the reaction was an important factor for the choice of this method, which allowed us to obtain the desired compounds in moderate yield (Scheme 3). Furthermore, the novel compounds **3h**, **3i** and **3j** are described here for the first time.

With the arylated compounds in hand, we initiated our studies for the introduction of a hydroxyl group at the A-ring of the quinoidal system of aryl 1,4-NQ **3a** using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and PIFA as the mild oxidizing agent. This methodology was recently reported by us and employed for the synthesis of a variety of hydroxylated quinones,[26] but proved to be susceptible to the substituents present on the B-ring of the quinonoid precursor. In general, the presence of electron-donating groups favors the weak *O*-coordination of the metal *via* the carbonyl group, leading to the formation of the desired product. In this context, we applied the previously described method to obtain a series of hydroxylated aryl-quinone derivatives. As expected, a transformation of deactivated arylated derivatives proved particularly challenging due to a significantly reduced reactivity. In contrast, product **4a** was obtained in 30% yield from 2-phenyl-1,4-naphthoquinone (**3a**) (Scheme 4).

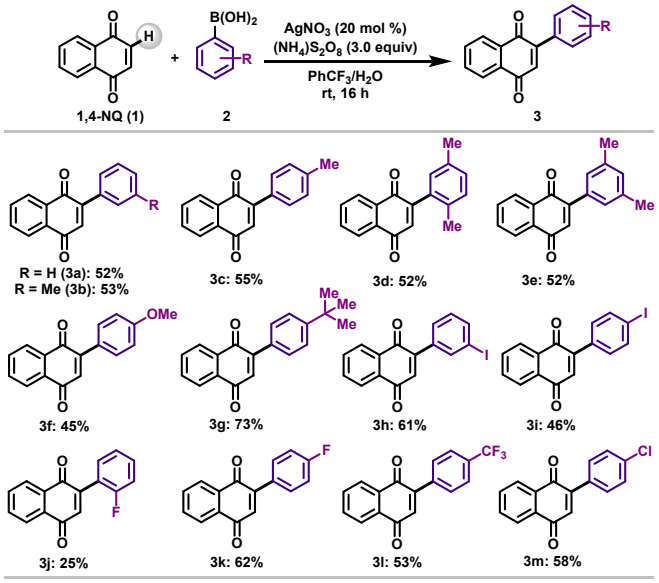
Using compound **3a** as a model substrate, we also evaluated the use of different oxidants, *e.g.* $K_2S_2O_8$, PIDA, $(NH_4)_2S_2O_8$, OXONE®, *m*CPBA, $KIO_3$, and PIFA/$K_2S_2O_8$ in the presence of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, but unfortunately, in all cases the yield of the desired product **4a** was lower. We also tested alternative catalysts in the presence of PIFA as an oxidizing agent. However, $RuBr_3$, $Ru_3(CO)_{12}$, $Ru(O_2CMes)_2(p$-



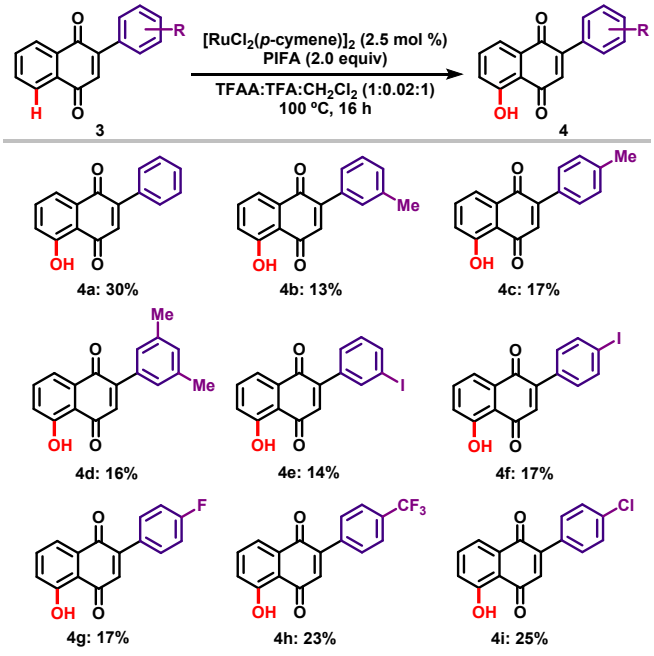

**Scheme 1.** Overview of trypanocidal 1,4-naphthoquinones recently developed by our group.[21-26.]




**Scheme 2.** Strategies for C—H oxygenation of arylated quinones.




**Scheme 3.** Synthesis of monoarylated 1,4-naphthoquinone derivatives **3a-m**.




**Scheme 4.** Synthesis of C—H oxygenated compounds **4a-i**.

cymene), $Ru(OAc)_2(PPh_3)_2$ and $Ru(OPiv)_2(PPh_3)_2$ fell short in delivering the desired product **4a**.

All compounds shown in Scheme 3 were subjected to the C—H oxygenation reaction using PIFA as the oxidizing agent and $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and the obtained products are depicted in Scheme 4. Unfortunately, even after considerable experimentation, some derivatives could not be obtained and most compounds were isolated in somewhat improvable yields. Considering the tremendous biological potential of the target compounds, we evaluated the obtained hydroxylated quinones against *T. cruzi*. Further studies will be carried out in our laboratories aiming at the identification of reaction conditions that allow for the preparation of compounds **4** in improved yields and will be published in due course. Structural assignments were based on detailed NMR spectroscopy analysis and X-ray diffraction measurement of product **4a** (Figure 1).

A plausible mechanism can be proposed for the ruthenium-catalyzed C—H hydroxylation based on previous reports described in the literature (Scheme 5).[38-41] The mechanism usually starts with the formation of the active ruthenium(II) species **A** from the pre-catalyst $[RuCl_2(p\text{-cymene})]$ in the presence of PIFA. The active species can then facilitate the C—H activation of the substrate, releasing one of the trifluoroacetate ligands bearing the hydrogen removed from the activated site. This process generates the intermediate **B** with the phenyl-group oriented to the opposite site of the coordination sphere due to steric effects, as ruthenium catalysts are known to suffer directly from steric effects of the substituents.[42] The intermediate **B** can then undergo an oxidative addition in the presence of the oxidant PIFA. During this process, not only an additional trifluoroacetate ligand is introduced to the coordination sphere of the catalyst, but also the *p*-cymene ligand is substituted by another trifluoroacetate ligand. Thus, the ruthenium metallocentre is oxidized from ruthenium(II) to ruthenium(IV) and the coordination number of the catalyst also increases from four to six, thereby forming intermediate **C**. A subsequent re-organization of the ligands enables the

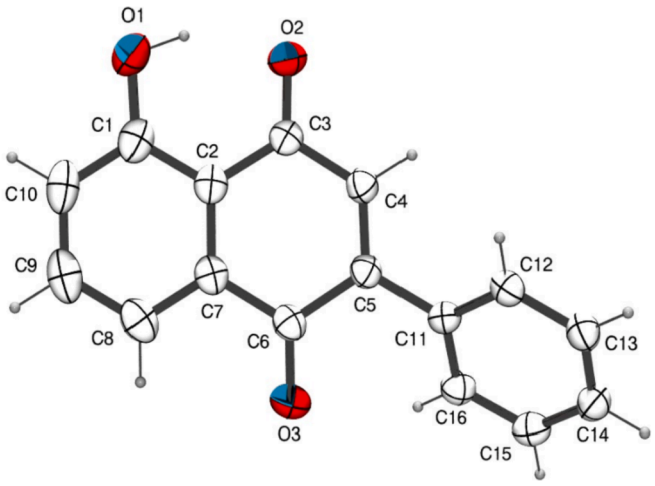



**Figure 1.** ORTEP-3 projection of **4a**, showing the atom numbering and displacement ellipsoids at the 50% probability level.

transfer of one of the coordinated trifluoroacetate ligands to the active site of the substrate, consequently resulting in a C-5 functionalization *via* a reductive elimination (intermediate **D**) and reducing the ruthenium metallocentre to its original oxidation state. A ligand-substitution with *p*-cymene releases the C-5 acetylated product (intermediate **E**) and regenerates the catalytically-active ruthenium-species **A**. The desired product **F** is finally obtained after work-up under acidic conditions.

In addition, the novel oxygenated derivatives **5a-c** were prepared through palladium-catalyzed C—H oxygenation, in which the substrates **3a**, **3d** and **3k** were submitted to a reaction with PIFA as the oxidant and $Pd(OAc)_2$ as the catalyst at 100 °C to afford **5a-c** in moderate yields (44 to 60%). In contrast to the ruthenium-catalyzed C—H oxygenation (*vide supra*), the reaction selectively occurred at the aryl ring previously installed at the B-ring of the 1,4-naphthoquinones (Scheme 6). Structural assignments were based on detailed NMR spectroscopy analysis and X-ray diffraction of product **5a** (Figure 2).

In contrast to ruthenium catalysis, the position-selectivity in palladium catalysis is known to be mainly controlled by electronic effects, thus preferentially interacting with regions of higher electron densities.[43] A resonance analysis of the substrate structure indicates that the phenyl ring located at the C-2 position of the substrate is influenced by an indirect and weak electron-withdrawing effect of the quinoidal carbonyl groups, compared to the direct and more pronounced electron-withdrawing effect on the naphthoquinoidal aromatic ring exhibited by both quinoidal carbonyl groups. This information, combined with previously published materials,[44,45] provides a mechanistic rationale for the observed regioselectivity of this transformation and the facile formation of the 6-membered metallocycle present in intermediate **B** (Scheme 7). Afterwards, a sequential oxidative addition leads to the formation of the palladium(IV) intermediate **C.** The coordinated acetate ligands present in this intermediate undergo reorganization and one of them is transferred to the activated site of the substrate *via* a reductive elimination. In this process, the palladium is reduced to palladium(II) and intermediate **D** is obtained. A decoordination of the acetylated intermediate **E** regenerates the catalytically-active palladium species **A**. A final work-up step in acidic media enables the formation of the desired *ortho*-hydroxylated product **F**.

### 2.2. Biological studies

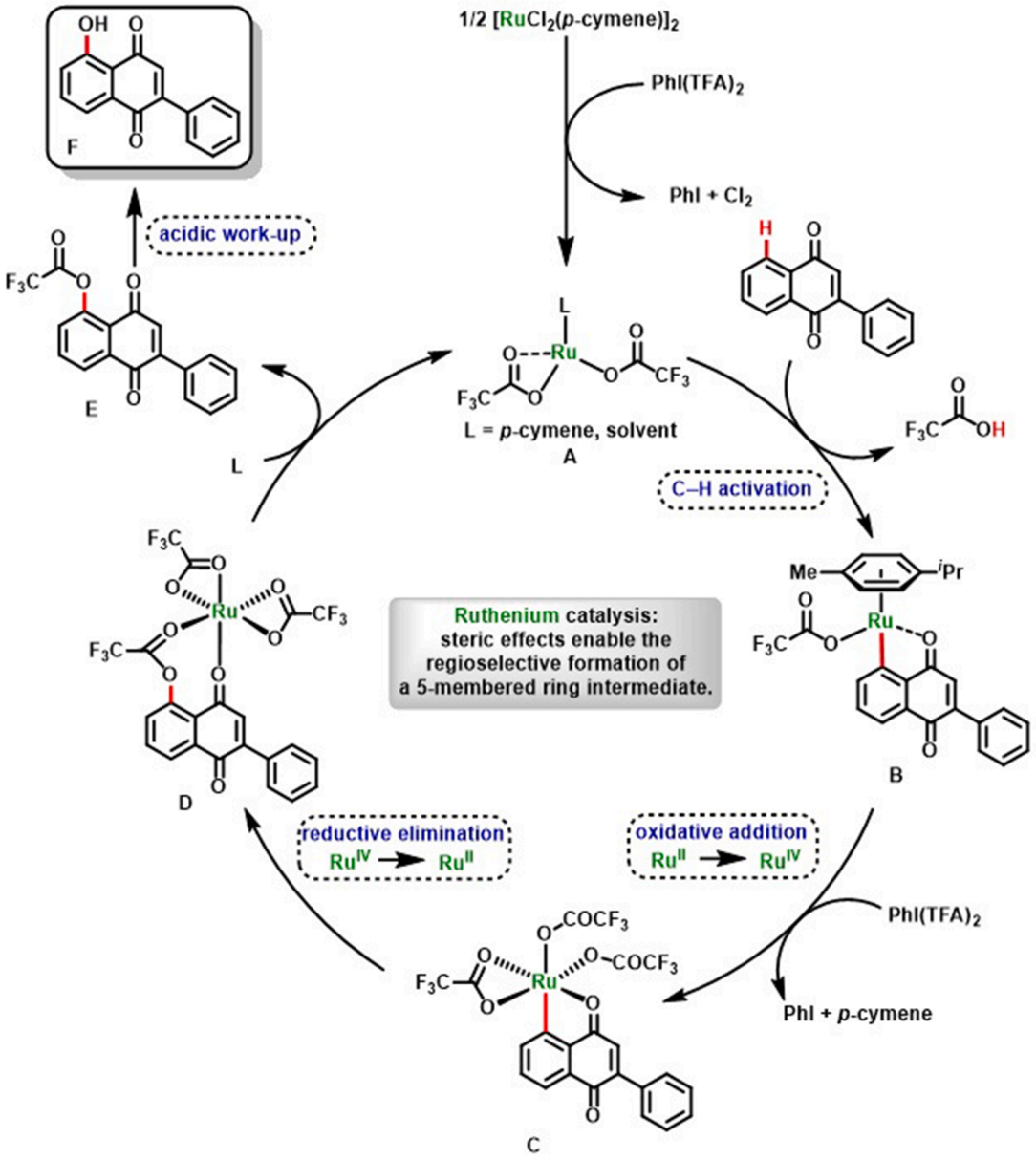
In recent years, the intensification of efforts aimed at identifying new trypanocidal compounds based on naphthoquinoidal structures has gained considerable momentum due to the outstanding trypanocidal potential of these compounds.[46-48] Although quinones are molecules with a simple basic framework, their structural modification involves highly challenging synthetic strategies.[49,50] The control of the chemical reactivity of these compounds requires an ability to control electrophilic or nucleophilic sites in order to achieve selective functionalizations.[51] In this context, 1,4-NQ has been used as a prototype to explore new synthetic routes and consequently access new trypanocidal agent candidates. Hence, we employed 1,4-NQ as the starting material of choice for B-ring modifications and aryl group introductions and screened the thus obtained compounds against *T. cruzi* in its infective trypomastigote form (Table 1).

Initially, we observed that the installation of an aryl group in the B-ring of 1,4-NQ resulted in no pronounced trypanocidal effect and both compounds, 1,4-NQ and **3a**, exhibited a similar activity against the parasite. Subsequent studies were then carried out with electron-donating as well as electron-withdrawing groups on the aryl ring in order to modulate the electronic properties of the arene and study their trypanocidal activity. When only one methyl group was installed on the aryl ring (**3b** and **3c**) no pronounced effect was observed and the compounds exhibited a moderate activity against *T. cruzi* with $IC_{50}$/24 h values = 104.7 and 185.0 μM, respectively. To our delight, the introduction of two methyl groups strongly enhanced the trypanocidal activity and compounds **3d** ($IC_{50}$/24 h = 56.5 μM) and **3 g** ($IC_{50}$/24 h = 25.7 μM) were approximately 2 and 4 times more active than benznidazole, the positive control used in our study. Compounds containing electron-withdrawing groups did not show any prominent trypanocidal activity (Scheme 8).

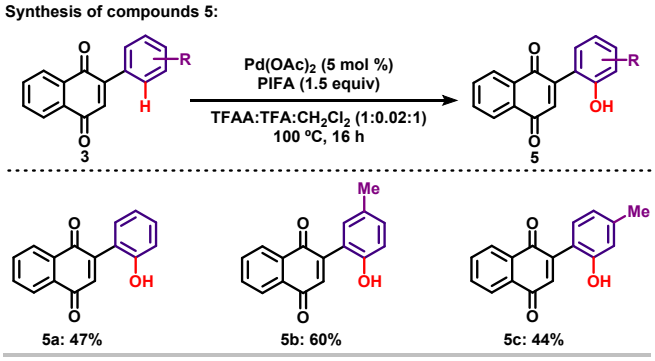
Following our strategy, we evaluated the trypanocidal activity of the hydroxylated compounds obtained *via* C—H activation. As expected, the trypanocidal activity of the compounds was enhanced and in some cases the results obtained were very promising. The hydroxylated compounds **5b** and **5c**, substituted with a methyl-group, displayed an increased trypanocidal activity compared to their respective synthetic precursors, naphthoquinones **3b** and **3c** (Scheme 9). In the case of compound **5c** the trypanocidal activity was enhanced 2.5-fold, which renders **5c** more active than Bz. The potent trypanocidal activity of this derivative demonstrates the efficiency of the strategy applied here and showcases the ability of palladium-catalyzed C—H oxygenations to considerably enhance the antiparasitic activity of a compound in only one synthetic step. To our pleasant surprise, the results were even more promising when compounds containing electron-withdrawing groups were used as precursors for the preparation of hydroxylated derivatives. While compounds **3k** and **3l** containing fluorine and $CF_3$-groups were inactive against *T. cruzi* with $IC_{50}$/24 h values > 500 μM for **3k** and 335.2 μM for **3l**, compounds **4g** and **4h** obtained *via* ruthenium(II)-catalyzed hydroxylations showed an impressive increase in their trypanocidal activity. In particular, **4h** was 4.5 times more active than Bz and can be considered an important lead structure for further studies (Scheme 9).

## 3. Conclusions

The development of new efficient drugs against the parasite that causes Chagas disease is a difficult objective to achieve. As a neglected disease that typically affects low-income populations, investment in the development of new drugs against *T. cruzi* is limited and often discontinued. In this context, basic research carried out in public health institutions and universities is a fundamental part in advancing the search for new treatments in order to obtain a cure or to improve the quality of life of patients contaminated with the parasite. In the present manuscript, we described a series of novel arylated quinones and hydroxylated aryl-quinones with prominent trypanocidal activity. Our strategy for the preparation of these compounds was based on just two synthetic steps with the use of easily accessible catalysts allowing for the synthesis of these compounds in a quick and user-friendly fashion. It should be noted that potential trypanocidal drugs can thus be prepared in only a few synthetic operations and with the use of readily accessible starting materials, considering that the target population in general does not have strong financial resources. Finally, our study revealed 9 novel




**Scheme 5.** Proposed mechanism for the ruthenium-catalyzed C—H hydroxylation.




**Scheme 6.** Synthesis of hydroxylated quinones **5a-d**.

compounds more active than benznidazole, the drug currently used in the therapeutics of Chagas disease, of which 2 compounds are approximately 4-fold more active than Bz. This work represents an important contribution to the search of potential trypanocidal drugs for further studies and optimization.

## 4. Experimental section

### 4.1. Chemistry

All catalytic reactions were carried out in 25 mL Schlenk- or pressure tubes. 1,4-Naphthoquinone was purified *via* reduced pressure sublimation using a cold finger sublimation apparatus (50 °C, 0.9 mbar) and stored in a glovebox to prevent contact with moisture. Other chemicals were obtained from commercial sources and used without further purification. Yields refer to isolated compounds, estimated to be > 95% pure as determined by $^{1}$H NMR. TLC: Merck, TLC Silica gel 60 $F_{254}$, detection at 254 nm. Chromatographic separations were carried out on

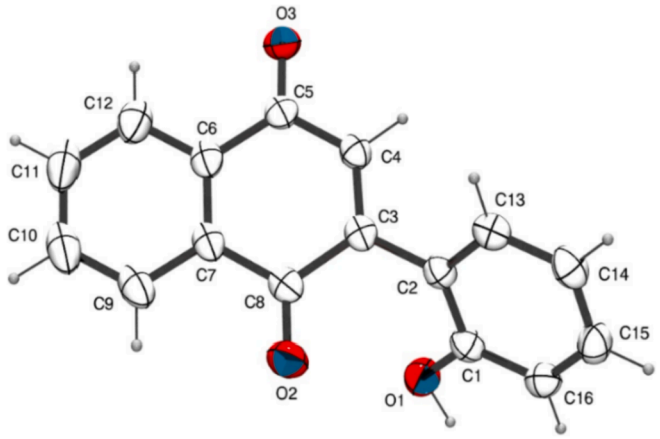
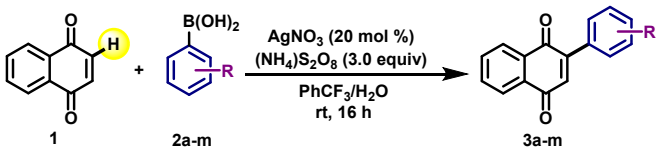


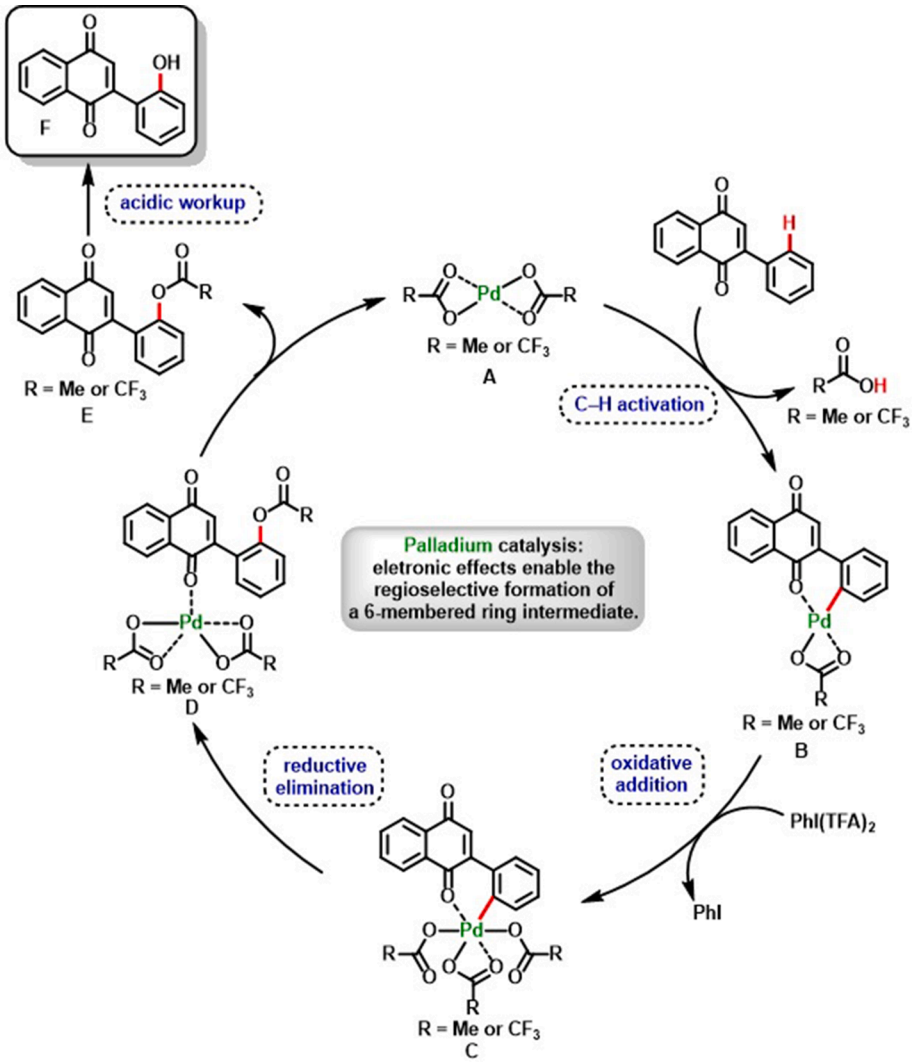

**Figure 2.** ORTEP-3 projection of **5a**, showing the atom numbering and displacement ellipsoids at the 50% probability level.

Merck Geduran SI-60 (0.040–0.063 mm). IR spectra were recorded on a Bruker ATR FT-IR Alpha device. MS: EI-MS: Jeol AccuTOF at 70 eV; ESI-MS: Bruker maXis and MicrOTOF. High resolution mass spectrometry (HRMS): Bruker maXis, Bruker MicrOTOF and Jeol AccuTOF. Melting points (M.p.): Büchi 540 capillary melting point apparatus, values are uncorrected. NMR spectra were recorded on Bruker Avance 300, Avance III 300, instruments. If not otherwise specified, chemical shifts ($\delta$) are provided in ppm.

### 4.2. General procedure for the synthesis of arylated quinones **3a-m**




To a solution of naphthoquinone (**1**) (3.16 mmol, 1.0 equiv, 500 mg) in trifluorotoluene (8 mL) was added the corresponding boronic acid (**2**) (4.75 mmol, 1.5 equiv), water (8 mL), silver(I) nitrate (0.1 M solution in water, 0.63 mmol, 20 mol %, 6 mL) and ammonium persulfate (2.15 g, 9.5 mmol, 3.0 equiv). The solution was stirred vigorously at room temperature for 16 h. After 16 h, the reaction was diluted with dichloromethane (20 mL) and washed with an aq. sodium bicarbonate solution (5%). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL), dried over sodium sulfate and evaporated *in vacuo*. Purification was performed by silica gel chromatography (hexane/dichloromethane 50:50) to yield the chromatographically and spectroscopically pure product **3**.[36]




**Scheme 7.** Proposed mechanism for the palladium-catalyzed C—H hydroxylation.

**Table 1**
$IC_{50}$/24 h (μM) of quinones against the trypomastigote form of *T. cruzi*.[a]

| Compound | $IC_{50}$/24 h |
|---|---|
| **3a** | 96.8 (±6.1) |
| **3b** | 104.7 (±15.5) |
| **3c** | 185.0 (±20.2) |
| **3d** | 56.5 (±2.2) |
| **3e** | >500 |
| **3f** | 303.2 (±12.5) |
| **3g** | 25.7 (±7.0) |
| **3h** | 303.6 (±39.0) |
| **3i** | >500 |
| **3j** | 157.2 (±11.2) |
| **3k** | >500 |
| **3l** | 335.2 (±31.1) |
| **3m** | >1000 |
| **4a** | 114.9 (±7.6) |
| **4b** | 95.4 (±17.2) |
| **4c** | 156.4 (±20.2) |
| **4d** | >500 |
| **4e** | 35.1 (±7.2) |
| **4f** | >500 |
| **4g** | 71.5 (±8.7) |
| **4h** | 22.8 (±3.8) |
| **4i** | >1000 |
| **5a** | 162.8 (±21.6) |
| **5b** | 99.2 (±11.2) |
| **5c** | 72.6 (±1.0) |

[a] Mean ± SD of at least three independent experiments, 5% of blood at 4 °C. $IC_{50}$/24 h for benznidazole = 103.6 (±0.6).[19]

#### 4.2.1. 2-Phenyl-1,4-naphthoquinone (*3a*)

The general procedure for the synthesis of arylated quinones was followed using phenylboronic acid (**2a**) (579 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3a** (382 mg, 1.64 mmol, 52% yield) as a yellow solid. m. p. (°C) = 95.7–98.6; IR (solid, $cm^{-1}$) $\nu$ = 3034, 1662, 1651, 1588, 1245; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.19–8.16 (m, 1H), 8.12–8.09 (m, 1H), 7.78–7.75 (m, 2H), 7.59–7.56 (m, 2H), 7.48–7.46 (m, 3H), 7.07 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 185.2 ($C_q$), 184.5 ($C_q$), 148.2 ($C_q$), 135.3 (CH), 134.0 (CH), 133.9 (CH), 133.5 ($C_q$), 132.5 ($C_q$), 132.2 ($C_q$), 130.1 (CH), 129.5 (CH), 128.6 (CH), 127.1 (CH), 126.1 (CH); HRMS ($ESI^+$): 235.0754 $[M + H]^+$. Cald. for $[C_{16}H_{11}O_2]^+$: 235.0759. The data are consistent with those reported in the literature.[35]

#### 4.2.2. 2-(m-Tolyl)-1,4-naphthoquinone (*3b*)

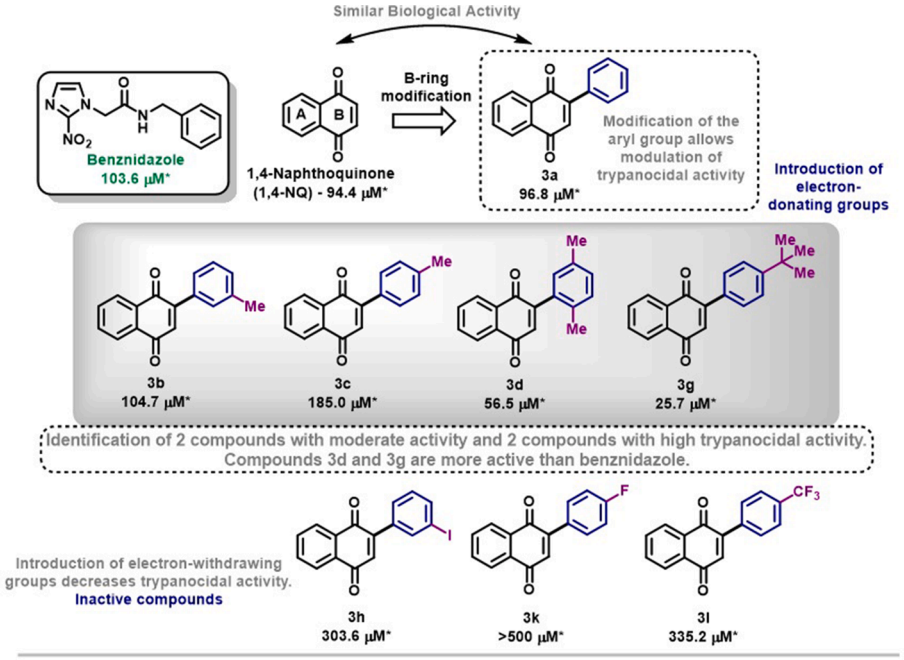
The general procedure for the synthesis of arylated quinones was followed using *m*-tolylboronic acid (**2b**) (646 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3b** (419 mg, 1.68 mmol, 53% yield) as a yellow solid. m. p. (°C) = 118.1–121.8; IR (solid, $cm^{-1}$) $\nu$ = 2918, 1664, 1652, 1590, 1261; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.20–8.17 (m, 1H), 8.13–8.10 (m, 1H), 7.79–7.76 (m, 2H),7.38–7.36 (m, 3H), 7.33–7.28 (m, 1H), 7.06 (s, 1H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 185.3 ($C_q$), 184.6 ($C_q$), 148.5 ($C_q$), 138.3 ($C_q$), 135.3 (CH), 134.0 (CH), 133.9 (CH), 133.5 ($C_q$), 132.6 ($C_q$), 132.2 ($C_q$), 131.0 (CH), 130.2 (CH), 128.5 (CH), 127.2 (CH), 126.7 (CH), 126.1 (CH), 21.6 ($CH_3$); HRMS ($ESI^+$): 249.0910 $[M + H]^+$, Cald. for $[C_{17}H_{13}O_2]^+$: 249.0916. The data are consistent with those reported in the literature.[52]

#### 4.2.3. 2-(p-Tolyl)-1,4-naphthoquinone (*3c*)

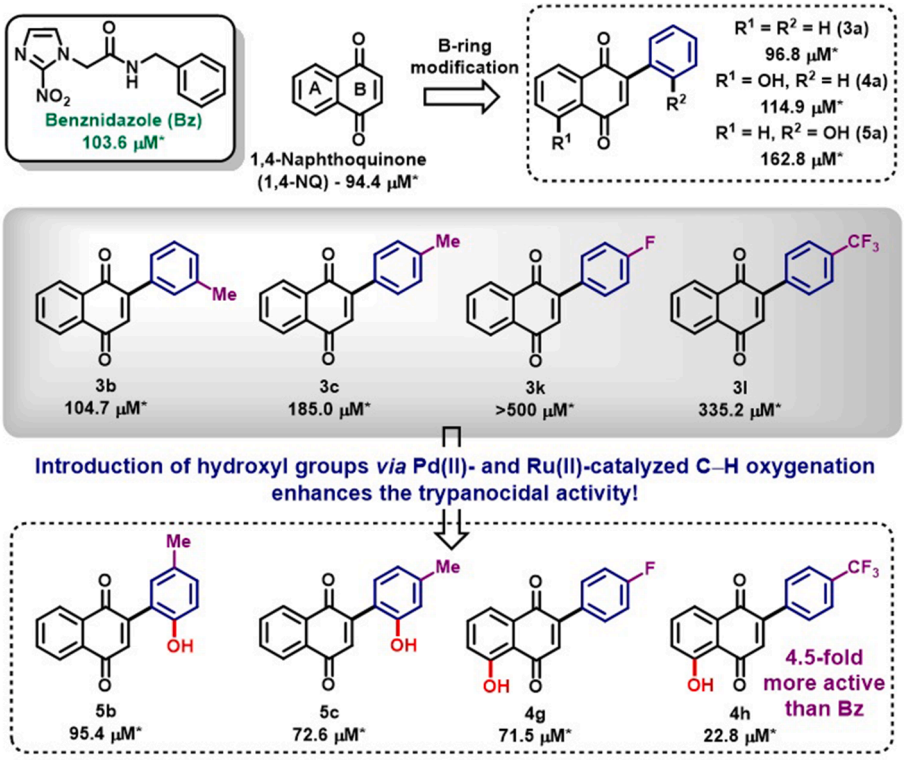
The general procedure for the synthesis of arylated quinones was followed using *m*-tolylboronic acid (**2c**) (646 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3c** (434 mg, 1.75 mmol, 55% yield) as a yellow solid. m. p. (°C) = 102.9–105.6; IR (solid, $cm^{-1}$) $\nu$ = 2921, 1664, 1650, 1577, 1223; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.20–8.17 (m, 1H), 8.14–8.10 (m, 1H), 7.79–7.76 (m, 2H), 7.50 (d, $J$ = 8.2 Hz, 2H), 7.29 (d, $J$ = 8.2 Hz, 2H), 7.07 (s, 1H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 185.3 ($C_q$), 184.7 ($C_q$), 148.2 ($C_q$), 140.6 ($C_q$), 134.7 (CH), 133.9 (CH), 133.9 (CH), 132.7 ($C_q$), 132.2 ($C_q$), 130.6 ($C_q$), 129.5 (CH), 129.4 (CH), 127.2 (CH), 126.1 (CH), 21.5 ($CH_3$); HRMS ($ESI^+$): 249.0910 $[M + H]^+$, Cald. for $[C_{17}H_{13}O_2]^+$: 249.0916. The data are consistent with those reported in the literature.[52]

#### 4.2.4. 2-(2,5-Dimethylphenyl)-1,4-naphthoquinone (*3d*)

The general procedure for the synthesis of arylated quinones was followed using (2,4-dimethylphenyl)boronic acid (**2d**) (712 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3d** (430 mg, 1.64 mmol, 52% yield) as a




**Scheme 8.** Trypanocidal B-ring substituted quinones. *$IC_{50}$/24 h values for the lytic activity on bloodstream trypomastigotes.




**Scheme 9.** Trypanocidal hydroxylated quinones. *$IC_{50}$/24 h values for the lytic activity on bloodstream trypomastigotes.

yellow solid. m.p. (°C) = 89.5–91.8; IR (solid, $cm^{-1}$) $\nu$ = 2923, 1660, 1589, 1124; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ = 8.18–8.13 (m, 2H), 7.78 (dd, $J$ = 5.6, 3.2 Hz, 2H), 7.17 (s, 2H), 7.00 (s, 1H), 6.92, (s, 1H), 2.35 (s, 3H), 2.18 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ = 185.4 ($C_q$), 184.2 ($C_q$), 150.9 ($C_q$), 136.9 (CH), 135.4 ($C_q$), 134.0 (CH), 134.0 (CH), 133.7 ($C_q$), 133.2 ($C_q$), 132.4 ($C_q$), 132.3 ($C_q$), 130.4 (CH), 130.3 (CH), 129.9 (CH), 127.2 (CH), 126.2 (CH), 21.0 ($CH_3$), 20.0 ($CH_3$); HRMS ($ESI^+$): 263.1067 $[M + H]^+$. Cald. for $[C_{18}H_{15}O_2]^+$: 263.1072. The data are consistent with those reported in the literature.[53]

#### 4.2.5. 2-(3,5-Dimethylphenyl)-1,4-naphthoquinone (3e)

The general procedure for the synthesis of arylated quinones was followed using (3,5-dimethylphenyl)boronic acid (**2e**) (712 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3e** (480 mg, 1.83 mmol, 58% yield) as a yellow solid. m.p. (°C) = 149.3–152.9; IR (solid, $cm^{-1}$) $\nu$ = 2916, 1663, 1650, 1589, 1292; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ = 8.19–8.16 (m, 1H), 8.13–8.10 (m, 1H), 7.79–7.76 (m, 2H), 7.18 (s, 2H), 7.12 (bs, 1H), 7.05 (s, 1H), 2.38 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ = 185.4 ($C_q$), 184.7 ($C_q$), 148.7 ($C_q$), 138.2 ($C_q$), 135.2 (CH), 134.0 (CH), 133.9 (CH), 133.5 ($C_q$), 132.7 ($C_q$), 132.2 ($C_q$), 131.9 (CH), 127.3 (CH), 127.2 (CH), 126.1 (CH), 21.5 ($CH_3$); HRMS ($ESI^+$): 263.1067 $[M + H]^+$. Cald. for $[C_{18}H_{15}O_2]^+$: 263.1072. The data are consistent with those reported in the literature.[52]

#### 4.2.6. 2-(4-Methoxyphenyl)-1,4-naphthoquinone (3f)

The general procedure for the synthesis of arylated quinones was followed using (4-methoxyphenyl)boronic acid (**2f**) (722 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3f** (376 mg, 1.42 mmol, 45% yield) as a red solid. m.p. (°C) = 124.9–126.8; IR (solid, $cm^{-1}$) $\nu$ = 2916, 1650, 1589, 1292; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ = 8.20–8.16 (m, 1H), 8.12–8.08 (m, 1H), 7.79–7.73 (m, 2H), 7.58 (d, $J$ = 8.7 Hz, 2H), 7.04 (s, 1H), 6.99 (d, $J$ = 8.7 Hz, 2H), 3.87 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ = 185.3 ($C_q$), 185.0 ($C_q$), 161.5 ($C_q$), 147.5 ($C_q$), 133.9 (CH), 133.9 (CH), 132.7 ($C_q$), 132.3 ($C_q$), 131.2 (CH), 127.2 (CH), 126.0 (CH), 125.8 ($C_q$), 114.2 (2 × CH), 55.5 ($CH_3$); HRMS ($ESI^+$): 265.0859 $[M + H]^+$, Cald. for $[C_{17}H_{13}O_3]^+$: 265.0865. The data are consistent with those reported in the literature.[52]

#### 4.2.7. 2-[4-(tert-Butyl)phenyl]-1,4-naphthoquinone (3g)

The general procedure for the synthesis of arylated quinones was followed using (4-(*tert*-butyl)phenyl)boronic acid (**2g**) (846 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3g** (674 mg, 2.32 mmol, 73% yield) as yellow solid. m.p. (°C) = 103.1–104.6; IR (solid, $cm^{-1}$) $\nu$ = 2949, 1665, 1661, 1555, 1242; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ = 8.22–8.17 (m, 1H), 8.15–8.09 (m, 1H), 7.80–7.74 (m, 2H), 7.56–7.48 (m, 4H), 7.08 (s, 1H), 1.37 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ = 185.4 ($C_q$), 184.8 ($C_q$), 153.7 ($C_q$), 148.1 ($C_q$), 134.8 (CH), 133.9 (CH), 133.9 (CH), 132.7 ($C_q$), 132.3 ($C_q$), 130.6 ($C_q$), 129.4 (CH), 127.2 (CH), 126.1 (CH), 125.7 (CH), 35.0 ($C_q$), 31.3 ($CH_3$); HRMS ($ESI^+$): 291.1380 $[M + H]^+$, Cald. for $[C_{20}H_{19}O_2]^+$: 291.1385. The data are consistent with those reported in the literature.[52]

#### 4.2.8. 2-(3-Iodophenyl)-1,4-naphthoquinone (3h)

The general procedure for the synthesis of arylated quinones was followed using (2-iodophenyl)boronic acid (**2h**) (1.18 g, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3h** (709 mg, 1.95 mmol, 61% yield) as a yellow solid. m.p. (°C) = 127.6–128.5; IR (solid, $cm^{-1}$) $\nu$ = 1684, 1658, 1588, 1296, 769; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ = 8.20–8.15 (m, 1H), 8.14–8.09 (m, 1H), 7.91 (t, $J$ = 1.6 Hz, 1H), 7.82–7.77 (m, 3H), 7.53 (dt, $J$ = 8.1, 1.2 Hz, 1H), 7.21 (t, $J$ = 7.8 Hz, 1H), 7.05 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ = 184.9 ($C_q$), 184.0 ($C_q$), 146.7 ($C_q$), 139.0 (CH), 138.2 (CH), 135.8 (CH), 135.5 ($C_q$), 134.2 (CH), 134.1 (CH), 132.4 ($C_q$), 132.1 ($C_q$), 130.2 (CH), 128.8 (CH), 127.2 (CH), 126.2 (CH), 94.2 ($C_q$); HRMS ($ESI^+$): 360.9720 $[M + H]^+$, Cald. for $[C_{16}H_{10}IO_2]^+$: 360.9725.

#### 4.2.9. 2-(4-Iodophenyl)-1,4-naphthoquinone (3i)

The general procedure for the synthesis of arylated quinones was followed using (4-iodophenyl)boronic acid (**2i**) (1.18 g, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3i** (523 mg, 1.46 mmol, 46% yield) as an orange solid. m.p. (°C) = 142.5–144.1; IR (solid, $cm^{-1}$) $\nu$ = 1654, 1591, 1297, 771; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.21–8.15 (m, 1H), 8.15–8.09 (m, 1H), 7.84–7.83 (m, 1H), 7.81–7.77 (m, 3H), 7.33–7.29 (m, 2H), 7.07 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 185.0 ($C_q$), 184.2 ($C_q$), 147.3 ($C_q$), 137.9 (CH), 135.3 (CH), 134.2 (CH), 134.1 (CH), 132.9 ($C_q$), 132.5 ($C_q$), 132.2 ($C_q$), 131.2 (CH), 127.3 (CH), 126.2 (CH), 97.0 ($C_q$); HRMS ($ESI^+$): 360.9720 $[M + H]^+$, Cald. for $[C_{16}H_{10}IO_2]^+$: 360.9725.

#### 4.2.10. 2-(2-Fluorophenyl)-1,4-naphthoquinone (3j)

The general procedure for the synthesis of arylated quinones was followed using (2-fluorophenyl)boronic acid (**2j**) (664 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3j** (200 mg, 0.8 mmol, 25% yield) as a yellow solid. m.p. (°C) = 90.8–93.5; IR (solid, $cm^{-1}$) $\nu$ = 1660, 1615, 1451, 1219, 751; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.19–8.16 (m, 1H), 8.15–8.10 (m, 1H), 7.81–7.76 (m, 2H), 7.50–7.42 (m, 1H), 7.38 (td, $J$ = 7.4, 1.7 Hz, 1H), 7.27–7.22 (m, 1H), 7.18–7.15 (m, 1H), 7.09 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 184.9 ($C_q$), 183.2 ($C_q$), 160.2 (d, $^1J_{C-F}$ = 248.8 Hz, $C_q$), 144.9 ($C_q$), 137.6 (d, $^4J_{C-F}$ = 2.2 Hz, CH), 134.1 (d, $^3J_{C-F}$ = 6.9 Hz, CH), 132.3 ($C_q$), 132.2 ($C_q$), 131.8 (d, $^3J_{C-F}$ = 8.4 Hz, CH), 131.3 (d, $^4J_{C-F}$ = 2.9 Hz, CH), 127.2 (CH), 126.3 (CH), 124.3 (CH), 124.3 (CH), 121.7 (d, $^2J_{C-F}$ = 14.6 Hz, $C_q$), 116.2 (d, $^2J_{C-F}$ = 21.8 Hz, CH); HRMS ($ESI^+$): 253.0659 $[M + H]^+$, Cald. for $[C_{16}H_{10}FO_2]^+$: 253.0665.

#### 4.2.11. 2-(4-Fluorophenyl)-1,4-naphthoquinone (3k)

The general procedure for the synthesis of arylated quinones was followed using (4-fluorophenyl)boronic acid (**2k**) (664 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3k** (434 mg, 1.98 mmol, 62% yield) as a yellow solid. m.p. (°C) = 133.1–135.3; IR (solid, $cm^{-1}$) $\nu$ = 1660, 1592, 1503, 1223; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.21–8.15 (m, 1H), 8.14–8.09 (m, 1H), 7.81–7.75 (m, 2H), 7.62–7.55 (m, 2H), 7.20–7.13 (m, 2H), 7.05 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 185.1 ($C_q$), 184.5 ($C_q$), 164.1 (d, $^1J_{C-F}$ = 249.5 Hz, $C_q$), 147.1 ($C_q$), 135.2 (CH), 134.1 (CH), 134.1 (CH), 132.5 ($C_q$), 132.2 ($C_q$), 131.6 (d, $^3J_{C-F}$ = 8.4 Hz, CH), 129.5 (d, $^4J_{C-F}$ = 3.4 Hz, $C_q$), 127.2 (CH), 126.2 (CH), 115.8 (d, $^2J_{C-F}$ = 21.6 Hz, CH); HRMS ($ESI^+$): 253.0659 $[M + H]^+$, Cald. for $[C_{16}H_{10}FO_2]^+$: 253.0665. The data are consistent with those reported in the literature.[35]

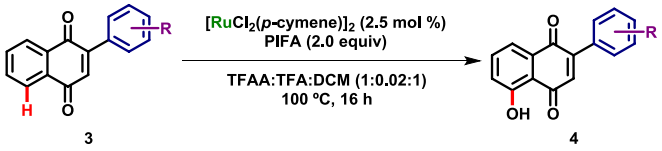
#### 4.2.12. 2-[4-(Trifluoromethyl)phenyl]-1,4-naphthoquinone (3l)

The general procedure for the synthesis of arylated quinones was followed using [4-(trifluoromethyl)phenyl]boronic acid (**2l**) (902 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3l** (512 mg, 1.68 mmol, 53% yield) as a yellow solid. m.p. (°C) = 123.1–126.2; IR (solid, $cm^{-1}$) $\nu$ = 1656, 1592, 1248, 913, 846; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.22–8.17 (m, 1H), 8.16–8.11 (m, 1H), 7.84–7.77 (m, 2H), 7.74 (d, $J$ = 8.4 Hz, 2H), 7.68 (d, $J$ = 8.5 Hz, 2H), 7.10 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 184.9 ($C_q$), 184.0 ($C_q$), 147.0 ($C_q$), 137.0 ($C_q$), 136.3 (CH), 134.3 (CH), 134.3 (CH), 132.3 ($C_q$), 132.2 ($C_q$), 131.7 ($C_q$), 130.0 (CH), 127.3 (CH), 126.3 (CH), 125.5 (q, $^4J_{C-F}$ = 3.7 Hz, CH), 122.2 ($C_q$); HRMS ($ESI^+$): 303.0627 $[M + H]^+$, Cald. for $[C_{17}H_{10}F_3O_2]^+$: 303.0633. The data are consistent with those reported in the literature.[35,54]

#### 4.2.13. 2-(4-Chlorophenyl)-1,4-naphthoquinone (3m)

The general procedure for the synthesis of arylated quinones was followed using (4-chlorophenyl)boronic acid (**2m**) (743 mg, 4.75 mmol). Purification by column chromatography (hexane/dichloromethane 50:50) yielded product **3m** (454 mg, 1.83 mmol, 58% yield) as a yellow solid; m.p. (°C) = 162.3–164.6; IR (solid, $cm^{-1}$) $\nu$ = 1666, 1654, 1589, 1249, 777; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.21–8.15 (m, 1H), 8.15–8.09 (m, 1H), 7.80–7.76 (m, 2H), 7.55–7.51 (m, 2H), 7.47–7.43 (m, 2H), 7.07 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 185.1 ($C_q$), 184.3 ($C_q$), 147.1 ($C_q$), 136.6 ($C_q$), 135.4 (CH), 134.2 (CH), 134.1 (CH), 132.5 ($C_q$), 132.2 ($C_q$), 131.9 ($C_q$), 130.9 (CH), 128.9 (CH), 127.3 (CH), 126.2 (CH); HRMS ($ESI^+$): 269.0364 $[M + H]^+$, Cald. for $[C_{16}H^{35}_{10}ClO_2]^+$: 269.0369. The data are consistent with those reported in the literature.[54]

### 4.3. General procedure A: Reactions with ruthenium(II) as catalyst




The corresponding naphthoquinone **3** (0.4 mmol), [bis(trifluoroacetoxy)iodo]benzene (PIFA) (344 mg, 0.8 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (5.6 mg, 2.5 mol %) were added to a pressure tube. Trifluoroacetic anhydride (TFAA) (1 mL), trifluoroacetic acid (0.02 mL) and dichloromethane (1 mL) were subsequently added. The tube was sealed and the mixture was stirred at 100 °C for 16 h and then cooled to 25 °C. The mixture was transferred to a 25 mL flask and under vigorous magnetic stirring dichloromethane (1 mL), $H_2O$ (1 mL) and an aq. solution of HCl (1 M, 0.2 mL) were added dropwise. After 5 min, the solution was extracted with dichloromethane (3 × 10 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

#### 4.3.1. 5-Hydroxy-2-phenyl-1,4-naphthoquinone (4a)

The general procedure A was followed using 2-phenyl-1,4-naphthoquinone (**3a**) (94 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielded **4a** (30 mg, 30%) as an orange solid. m.p. (°C) = 120.1–121.2; IR (solid, $cm^{-1}$) $\nu$ = 3052, 1633, 1589, 1251; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 12.01 (s, 1H), 7.71–7.62 (m, 2H), 7.58–7.55 (m, 2H), 7.49–7.47 (m, 3H), 7.29 (d, $J$ = 8.2 Hz, 1H), 7.03 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 190.3 ($C_q$), 183.8 ($C_q$), 161.2 ($C_q$), 149.3 ($C_q$), 136.5 (CH), 135.1 (CH), 133.2 ($C_q$), 132.5 ($C_q$), 130.4 (CH), 129.6 (CH), 128.6 (CH), 124.3 (CH), 119.9 (CH), 115.3 ($C_q$); HRMS ($ESI^+$): 251.0703 $[M + H]^+$, Cald. for $[C_{16}H_{11}O_3]^+$: 251.0708. The data are consistent with those reported in the literature.[35] *The structure of the product was also confirmed by X-ray diffraction* (CCDC number = 2070027).

#### 4.3.2. 5-Hydroxy-2-(m-tolyl)-1,4-naphthoquinone (4b)

The general procedure A was followed using 2-(*m*-tolyl)-1,4-naphthoquinone (**3b**) (99 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielded **4b** (13.5 mg, 13%) as an orange solid. m.p. (°C) = 130.9–131.7; IR (solid, $cm^{-1}$) $\nu$ = 3040, 2921, 1632, 1582, 1292; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 12.02 (s, 1H), 7.71 (dd, $J$ = 7.5, 1.4 Hz, 1H), 7.65 (t, $J$ = 8.0, 1H), 7.36 (d, $J$ = 5.1 Hz, 3H), 7.33–7.28 (m, 2H), 7.02 (s, 1H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 190.4 ($C_q$), 183.9 ($C_q$), 161.2 ($C_q$), 149.6 ($C_q$), 138.4 ($C_q$), 136.5 (CH), 135.0 (CH), 133.2 ($C_q$), 132.6 ($C_q$), 131.3 (CH), 130.2 (CH), 128.6 (CH), 126.7 (CH), 124.3 (CH), 119.9 (CH), 115.3 ($C_q$), 21.6 ($CH_3$); HRMS ($ESI^+$): 265.0859 $[M + H]^+$, Cald. for $[C_{17}H_{13}O_3]^+$: 265.0865.

#### 4.3.3. 5-Hydroxy-2-(p-tolyl)-1,4-naphthoquinone (4c)

The general procedure A was followed using 2-(*p*-tolyl)-1,4-naphthoquinone (**3c**) (99 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielded **4c** (18 mg, 17%) as an orange solid. m.p. (°C) = 171.7–172.6; IR (solid, $cm^{-1}$) $\nu$ = 2920, 2852, 1633, 1587, 1248; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 12.04 (s, 1H), 7.70 (dd, $J$ = 7.5, 1.3 Hz, 1H), 7.64 (t, $J$ = 8.0 Hz, 1H), 7.48 (d, $J$ = 8.2

Hz, 2H), 7.28 (d, $J$ = 8.1 Hz, 3H), 7.02 (s, 1H), 2.42 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 190.4 ($C_q$), 184.0 ($C_q$), 161.2 ($C_q$), 149.3 ($C_q$), 141.0 ($C_q$), 136.4 (CH), 134.4 (CH), 132.6 ($C_q$), 130.4 ($C_q$), 129.6 (CH), 129.4 (CH), 124.3 (CH), 119.8 (CH), 115.3 ($C_q$), 21.6 ($CH_3$); HRMS (ESI$^+$): 265.0859 [M + H]$^+$, Cald. for $[C_{17}H_{13}O_3]^+$: 265.0865. The data are consistent with those reported in the literature.[36]

#### 4.3.4. 2-(3,5-Dimethylphenyl)-5-hydroxy-1,4-naphthoquinone (4d)

The general procedure A was followed using 2-(3,5-dimethylphenyl)-1,4-naphthoquinone (**3e**) (105 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielded **4d** (17.5 mg, 16%) as an orange solid. m.p. (°C) = 154.6–156.8; IR (solid, cm$^{-1}$) $\nu$ = 2918, 2853, 1631, 1597, 1228; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 12.03 (s, 1H), 7.70 (dd, $J$ = 7.3, 0.9 Hz, 1H), 7.64 (t, $J$ = 7.28 (dd, $J$ = 8.1, 1.0 Hz, 1H), 7.17 (s, 2H), 7.13 (s, 1H), 7.00 (s, 1H), 2.38 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 190.4 ($C_q$), 184.0 ($C_q$), 161.2 ($C_q$), 149.8 ($C_q$), 138.3 ($C_q$), 136.4 (CH), 134.9 (CH), 133.2 ($C_q$), 132.6 ($C_q$), 132.2 (CH), 127.3 (CH), 124.2 (CH), 119.8 (CH), 115.3 ($C_q$), 21.5 ($CH_3$); HRMS (ESI$^+$): 279.1016 [M + H]$^+$, Cald. for $[C_{18}H_{15}O_3]^+$: 279.1021.

#### 4.3.5. 5-Hydroxy-2-(3-iodophenyl)-1,4-naphthoquinone (4e)

The general procedure A was followed using 2-(3-iodophenyl)-1,4-naphthoquinone (**3 h**) (144 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielded **4e** (21 mg, 14%) as an orange solid. m.p. (°C) = 155.9–157.8; IR (solid, cm$^{-1}$) $\nu$ = 3051, 1665, 1632, 1591, 1240; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 11.95 (s, 1H), 7.91 (t, $J$ = 1.6 Hz, 1H), 7.82 (dt, $J$ = 7.9, 1.0 Hz, 1H), 7.72–7.63 (m, 2H), 7.53 (dt, $J$ = 8.0, 1.1 Hz, 1H), 7.30 (dd, $J$ = 7.8, 1.7 Hz, 1H), 7.21 (t, $J$ = 7.8 Hz, 1H), 7.02 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 190.0 ($C_q$), 183.3 ($C_q$), 161.3 ($C_q$), 147.8 ($C_q$), 139.2 (CH), 138.1 (CH), 136.7 (CH), 135.6 (CH), 135.2 ($C_q$), 132.3 ($C_q$), 130.2 (CH), 128.8 (CH), 124.6 (CH), 120.0 (CH), 115.2 ($C_q$), 94.2 ($C_q$); HRMS (ESI$^+$): 376.9669 [M + H]$^+$, Cald. for $[C_{16}H_{10}IO_3]^+$: 376.9675.

#### 4.3.6. 5-Hydroxy-2-(4-iodophenyl)-1,4-naphthoquinone (4f)

The general procedure A was followed using 2-(4-iodophenyl)-1,4-naphthoquinone (**3i**) (144 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielded **4f** (25 mg, 17%) as an orange solid. m.p. (°C) = 176.2–178.1; IR (solid, cm$^{-1}$) $\nu$ = 3045, 2920, 1631, 1568, 1229, 763; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 11.96 (s, 1H), 7.81 (dt, $J$ = 8.5, 2.2 Hz, 2H), 7.71–7.62 (m, 2H), 7.32–7.28 (m, 3H), 7.02 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 190.0 ($C_q$), 183.4 ($C_q$), 161.3 ($C_q$), 148.3 ($C_q$), 137.9 (CH), 136.6 (CH), 135.1 (CH), 132.6 ($C_q$), 132.3 ($C_q$), 131.1 (CH), 124.5 (CH), 120.0 (CH), 115.2 ($C_q$), 97.4 ($C_q$); HRMS (ESI$^+$): 398.9489 [M + Na]$^+$, Cald. for $[C_{16}H_9IO_3Na]^+$: 398.9494.

#### 4.3.7. 2-(4-Fluorophenyl)-5-hydroxy-1,4-naphthoquinone (4g)

The general procedure A was followed using 2-(4-fluorophenyl)-1,4-naphthoquinone (**3 k**) (101 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielded **4g** (19 mg, 17%) as an orange solid. m.p. (°C) = 171.7–172.6; IR (solid, cm$^{-1}$) $\nu$ = 3042, 1636, 1598, 1231, 1159; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 11.98 (s, 1H), 7.70 (dd, $J$ = 7.5, 1.6 Hz, 1H), 7.65 (t, $J$ = 7.9 Hz, 1H), 7.60–7.56 (m, 2H), 7.29 (dd, $J$ = 8.0, 1.6 Hz, 1H), 7.19–7.13 (m, 2H), 7.01 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 190.2 ($C_q$), 183.7 ($C_q$), 164.2 (d, $^1J_{C-F}$ = 250.0 Hz, $C_q$), 161.3 ($C_q$), 148.2 ($C_q$), 136.6 (CH), 134.9 (CH), 132.4 ($C_q$), 131.7 (d, $^3J_{C-F}$ = 8.4 Hz, CH), 129.2 (d, $^4J_{C-F}$ = 3.4 Hz, $C_q$), 124.5 (CH), 119.9 (CH), 115.9 (d, $^2J_{C-F}$ = 21.6 Hz, CH), 115.2 ($C_q$); HRMS (ESI$^+$): 291.0428 [M + Na]$^+$, Cald. for $[C_{16}H_9FO_3Na]^+$: 291.0433. The data are consistent with those reported in the literature.[35]

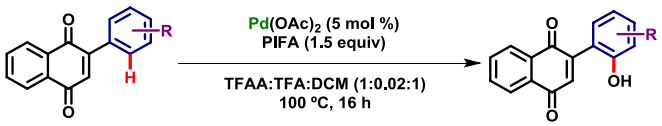
#### 4.3.8. 5-Hydroxy-2-[4-(trifluoromethyl)phenyl]-1,4-naphthoquinone (4h)

The general procedure A was followed using 2-[4-(trifluoromethyl) phenyl]-1,4-naphthoquinone (**3l**) (121 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielded **4h** (30 mg, 23%) as an orange solid. m.p. (°C) = 159.8–161.4; IR (solid, cm$^{-1}$) $\nu$ = 1645, 1610, 1452, 1320, 847; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 11.94 (s, 1H), 7.76–7.66 (m, 6H), 7.32 (dd, $J$ = 7.9, 1.6 Hz, 1H), 7.07 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 189.9 ($C_q$), 183.3 ($C_q$), 161.5 ($C_q$), 148.1 ($C_q$), 136.8 (CH), 136.6 ($C_q$), 136.2 (CH), 132.2 ($C_q$), 132,0 ($C_q$), 130.0 (CH), 125.6 (q, $^4J_{C-F}$ = 3.7 Hz, CH), 124.7 (CH), 120.1 (CH), 115.3 ($C_q$); HRMS (EI$^+$): 318.0501 [M$^+$], Cald. For $[C_{17}H_9F_3O_3]^+$: 318.0504. The data are consistent with those reported in the literature.[35]

#### 4.3.9. 2-(4-Chlorophenyl)-5-hydroxy-1,4-naphthoquinone (4i)

The general procedure A was followed using 2-(4-chlorophenyl)-1,4-naphthoquinone (**3 m**) (107 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 95:5) yielded **4i** (28,1 mg, 25%) as an orange solid. m.p. (°C) = 205.0–206.1; IR (solid, cm$^{-1}$) $\nu$ = 3046, 2920, 1633, 1584, 1254; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 11.97 (s, 1H), 7.71 (dd, $J$ = 7.5, 1.6 Hz, 1H), 7.66 (t, $J$ = 7.9 Hz, 1H), 7.54–7.51 (m, 2H), 7.47–7.44 (m, 2H), 7.30 (dd, $J$ = 7.9, 1.6 Hz, 1H), 7.03 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 190.1 ($C_q$), 183.6 ($C_q$), 161.3 ($C_q$), 148.1 ($C_q$), 136.9 ($C_q$), 136.7 (CH), 135.1 (CH), 132.4 ($C_q$), 131.6 ($C_q$), 130.9 (CH), 129.0 (CH), 124.5 (CH), 120.0 (CH), 115.3 ($C_q$); HRMS (ESI$^+$): 285.0313 [M + H]$^+$, Cald. for $[C_{16}H^{35}_{10}ClO_3]^+$: 285.0318.

### 4.4. General procedure B: Reactions with palladium(II) as catalyst




3 5

The corresponding naphthoquinone **3** (0.4 mmol), [bis(trifluoroacetoxy)iodo]benzene (PIFA) (258 mg, 0.6 mmol) and $Pd(OAc)_2$ (4.5 mg, 5 mol %) were added to a pressure tube. Trifluoroacetic anhydride (TFAA) (1 mL), trifluoroacetic acid (0.02 mL) and dichloromethane (1 mL) were subsequently added. The tube was sealed and the mixture was stirred at 100 °C for 16 h and then cooled to 25 °C. The mixture was transferred to a 25 mL flask and under vigorous magnetic stirring dichloromethane (1 mL), $H_2O$ (1 mL) and an aq. solution of HCl (1 M, 0.2 mL) were added dropwise. After 5 min, the solution was extracted with dichloromethane (3 × 10 mL) and dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

#### 4.4.1. 2-(2-Hydroxyphenyl)-1,4-naphthoquinone (5a)

The general procedure B was followed using 2-phenyl-1,4-naphthoquinone (**3a**) (94 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 85:15) yielded **5a** (47 mg, 47%) as an orange solid. m.p. (°C) = 161.8–163.9; IR (solid, cm$^{-1}$) $\nu$ = 3241, 1663, 1640, 1587, 1262; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.22–8.17 (m, 1H), 8.15–8.10 (m, 1H), 7.83–7.76 (m, 2H), 7.41–7.35 (m, 1H), 7.28–7.25 (m, 1H), 7.11 (bs, 1H), 7.07 (s, 1H), 7.06–7.00 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 187.2 ($C_q$), 185.0 ($C_q$), 154.2 ($C_q$), 148.7 ($C_q$), 138.3 (CH), 134.6 (CH), 134.2 (CH), 132.5 ($C_q$), 132.3 (CH), 132.0 ($C_q$), 131.2 (CH), 127.6 (CH), 126.4 (CH), 122.5 ($C_q$), 121.5 (CH), 118.7 (CH); HRMS (ESI$^+$): 251.0703 [M + H]$^+$, Cald. for $[C_{16}H_{11}O_3]^+$: 251.0708. The data are consistent with those reported in the literature.[35] *The structure of the product was also confirmed by X-ray diffraction* (CCDC number = 2070026).

#### 4.4.2. 2-(2-Hydroxy-5-methylphenyl)-1,4-naphthoquinone (5b)

The general procedure B was followed using 2-(*m*-tolyl)-1,4-naphthoquinone (**3b**) (99 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 85:15) yielded **5b** (64 mg, 60%) as a dark red solid. m.p. (°C) = 199.5–200.6; IR (solid, cm$^{-1}$) $\nu$ = 3273,

2914, 1663, 1589, 1247; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta = 8.22–8.16$ (m, 1H), 8.15–8.09 (m, 1H), 7.83–7.76 (m, 2H), 7.18 (dd, $J = 8.2$, 1.9 Hz, 1H), 7.06 (s, 2H), 6.92 (d, $J = 8.2$ Hz, 1H), 6.87 (bs, 1H), 2.32 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta = 187.2$ ($C_q$), 185.0 ($C_q$), 152.0 ($C_q$), 148.9 ($C_q$), 138.2 (CH), 134.6 (CH), 134.1 (CH), 133.0 (CH), 132.5 ($C_q$), 132.0 ($C_q$), 131.4 (CH), 130.9 ($C_q$), 127.6 (CH), 126.4 (CH), 122.3 ($C_q$), 118.7 (CH), 20.6 ($CH_3$); HRMS ($ESI^+$): 265.0859 $[M + H]^+$, Cald. for $[C_{17}H_{13}O_3]^+$: 265.0865.

#### 4.4.3. 2-(2-Hydroxy-4-methylphenyl)-1,4-naphthoquinone (5c)

The general procedure B was followed using 2-(*p*-tolyl)-1,4-naphthoquinone (**3c**) (99 mg, 0.40 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 85:15) yielded **5c** (47 mg, 44%) as a red solid. m.p. (°C) = 155.0–158.1; IR (solid, $cm^{-1}$) $\nu = 3252$, 1662, 1642, 1575, 1244; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta = 8.21–8.16$ (m, 1H), 8.14–8.08 (m, 1H), 7.82–7.75 (m, 2H), 7.30 (bs, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.05 (s, 1H), 6.85–6.82 (m, 2H), 2.35 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta = 187.6$ ($C_q$), 185.0 ($C_q$), 154.2 ($C_q$), 148.8 ($C_q$), 143.2 ($C_q$), 137.8 (CH), 134.6 (CH), 134.1 (CH), 132.6 ($C_q$), 132.0 ($C_q$), 131.1 (CH), 127.6 (CH), 126.4 (CH), 122.5 (CH), 119.6 ($C_q$), 119.4 (CH), 21.4 ($CH_3$); HRMS ($ESI^+$): 265.0859 $[M + H]^+$, Cald. for $[C_{17}H_{13}O_3]^+$: 265.0865.

## 5. Animals

Albino Swiss mice were employed for the trypanocidal and cytotoxicity assays, in accordance with the guidelines of the Colégio Brasileiro de Experimentação Animal (COBEA), and these were performed under biosafety conditions. All animal experimentation procedures were approved by the Comissão de Ética em Experimentação Animal (CEUA/Fiocruz), license LW 16/13.

## 6. Trypanocidal assay

The experiments were performed with the Y strain of *T. cruzi*.[55] Stock solutions of the compounds were prepared in dimethylsulfoxide (DMSO), with the final concentration of the latter in the experiments never exceeding 0.1%. Preliminary experiments showed that at concentrations of up to 0.5%, DMSO has no deleterious effect on the parasites.[56] Bloodstream trypomastigotes were obtained from infected Albino Swiss mice at the peak of parasitemia by differential centrifugation. The parasites were resuspended to a concentration of $10 \times 10^6$ cells/mL in DMES medium. This suspension (100 µL) was added to the same volume of each of the compounds, which had been previously prepared at twice the desired final concentrations. The incubation was performed in 96-well microplates (Nunc Inc., Rochester, USA) at 37 °C for 24 h. Benznidazole (Lafepe, Brazil), the standard drug for treatment of chagasic patients, was used as control. Cell counts were performed in a Neubauer chamber, and the activity of the compounds corresponding to the concentration that led to 50% lysis of the parasites was expressed as the $IC_{50}$/24 h.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

E. N. da Silva Júnior acknowledges funding from CNPq (PQ 309774/2020-9), FAPEMIG (PPM-00638-16 and PPM-00635-18), INCT-Catálise/CNPq/FAPESC, Return Fellowship of the Alexander von Humboldt Foundation (AvH) and the Royal Society of Chemistry for the research fund grant (R19-9781). A special thanks to CAPES and DAAD for research cooperation project under the PROBRAL programme (Proc. No. 99999.008126/2015-01) and Capes-Humboldt Research Fellowship for experienced researchers (Proc. No. 88881.145517/2017-01). L.A. acknowledges funding from the DFG (Gottfried-Wilhelm-Leibniz prize) and SPP 1807. We thank Dr. Christopher Golz (Georg-August-Universität Göttingen) for assistance with the X-ray diffraction analysis.

## Appendix A. Supplementary material

Supplementary data ($^{1}$H and $^{13}$NMR spectra) related to this article can be found online at https://doi.org/10.1016/j.bmc.2021.116164.

## References

1 WHO. Chagas disease – Epidemiology, 2017. http://www.who.int/chagas/epidemiology/en/. Accessed March 2021.
2 Antinori S, Galimberti L, Bianco R, Grande R, Galli M, Corbellino M. *Eur J Intern Med*. 2017;43:6.
3 Padilla JA, Cortés-Serra N, Pinazo MJ, et al. *Expert Ver Anti Infect Ther*. 2019;17:673.
4 Messenger LA, Bern C. *Curr Opin, Infect Dis*. 2018;31:415.
5 Santana RAG, Guerra MGVB, Sousa DR, et al. *Emerg Infect Dis*. 2019;25:132.
6 Rassi Júnior A, Rassi A, Marin-Neto JA. *Lancet*. 2010;375:1388.
7 Liu Q, Zhou XN. *Infect Dis Poverty*. 2015;4:1.
8 Bern C. *N Engl J Med*. 2015;373:456.
9 Dias JC, Ramos Junior AN, Gontijo ED, et al. *Epidemiol Serv Saude*. 2016;25:7.
10 Vieira JL, Távora FRF, Sobral MGV, et al. *Curr Cardiol Rep*. 2019;21:1.
11 Higuchi ML, Benvenuti LA, Reis MM. *Cardiovasc Res*. 2003;60:96.
12 Marin-Neto JA, Cunha-Neto E, Maciel BC, Simões MV. *Circulation*. 2007;115:1109.
13 Rassi Júnior A, Rassi A, Rezende JM. *Infect Dis Clin North Am*. 2012;26:275.
14 Coura JR, Borges-Pereira J. *Mem Inst Oswaldo Cruz*. 2011;106:641.
15 Morillo CA, Marin-Neto JA, Avezum A, et al. *N Engl J Med*. 2015;373:1295.
16 Chatelain E, Ioset JR. *Expert Opin Drug Discov*. 2018;13:141.
17 Lee BY, Bacon KM, Bottazzi ME, Hotez PJ. *Lancet Infect Dis*. 2013;13:342.
18 Abuhab A, Trindade E, Aulicino GB, Fujii S, Bocchi EA, Bacal F. *Int J Cardiol*. 2013;168:2375.
19 Jardim GAM, Reis WJ, Ribeiro MF, et al. *RSC Adv*. 2015;5:78047.
20 Bahia SBBB, Reis WJ, Jardim GAM, et al. *Med Chem Commun*. 2016;7:1555.
21 Jardim GAM, Silva TL, Goulart MOF, et al. *Eur J Med Chem*. 2017;136:406.
22 Jardim GAM, Oliveira WXC, de Freitas RP, et al. *Org Biomol Chem*. 2018;16:1686.
23 Dias GG, Nascimento TA, Almeida AKA, et al. *Eur J Org Chem*. 2019:2344.
24 Jardim GAM, Bozzi IAO, Oliveira WXC, et al. *New J Chem*. 2019;43:13751.
25 Wood JM, Satam NS, Almeida RG, et al. *Bioorg Med Chem*. 2020;28, 115565.
26 Dias GG, Rogge T, Kuniyil R, et al. *Chem Commun*. 2018;54:12840.
27 Thirunavukkarasu VS, Kozhushkov SI, Ackermann L. *Chem Commun*. 2014;50:29.
28 Sun Y-H, Sun T-Y, Wu Y-D, Zhang X, Rao Y. *Chem Sci*. 2016;7:2229.
29 Yuan Y-C, Bruneau C, Dorcet V, Roisnel T, Gramage-Doria R. *J Org Chem*. 2019;84:1898.
30 Gramage-Doria R. *Chem Eur J*. 2020;26:9688.
31 Ackermann L, Vicente R, Althammer A. *Org Lett*. 2008;10:2299.
32 Ackermann L, Vicente R, Born R. *Adv Synth Catal*. 2008;350:741.
33 Ackermann L, Althammer A, Fenner S. *Angew Chem Int Ed*. 2008;48:2001.
34 Itahara T. *J Org Chem*. 1985;50:5546.
35 Molina MT, Navarro C, Moreno A, Csákÿ AG. *Org Lett*. 2009;11:4938.
36 Fujiwara Y, Domingo V, Seiple IB, Gianatassio R, Del Bel M, . PS, Baran. *J Am Chem Soc*. 2011;133:3292–3293.
37 Akagi Y, Komatsu T. *Tetrahedron Lett*. 2020;61, 152446.
38 Yang F, Rauch K, Kettelhoit K, Ackermann L. *Angew Chem Int Ed*. 2014;53:11285.
39 Bu Q, Kuniyil R, Shen Z, Gońka E, Ackermann L. *Chem Eur J*. 2020;26:16450.
40 Massignan L, Tan X, Meyer TH, Kuniyil R, Messinis AM, Ackermann L. *Angew Chem Int Ed*. 2020;59:3184.
41 Raghuvanshi K, Zell D, Ackermann L. *Org Lett*. 2017;19:1278.
42 Sun YS, Sun TY, Wu YD, Zhang X, Rao Y. *Chem Sci*. 2016;7:2229.
43 Lyons TW, Sanford MS. *Chem Rev*. 2010;110:1147.
44 Dai C, Han Y, Liu L, Huang ZB, Shi DQ, Zhao Y. *Org Chem Front*. 2020;7:1703.
45 Ackermann L, Potukuchi HK. *Org Biomol Chem*. 2018;8:4503.
46 Lara LS, Moreira CS, Calvet CM, et al. *Eur J Med Chem*. 2018;144:572.
47 Lara LS, Lechuga GC, Moreira CS, et al. *Molecules*. 2021;26:423.
48 Salmon-Chemin L, Buisine E, Yardley V, et al. *J Med Chem*. 2001;44:548.
49 Dennis DG, Okumura M, Sarlah D. *J Am Chem Soc*. 2019;141(26):10193.
50 Bian J, Qian X, Wang N, et al. *Org Lett*. 2015;17:3410.
51 Jardim GAM, Bower JF, da Silva Júnior EN. *Org Lett*. 2016;18:4454.
52 Wang D, Ge B, Li L, Shan J, Ding Y. *J Org Chem*. 2014;79:8607.
53 Hwu JR, Wetzel JM. *J Org Chem*. 1985;50:3946.
54 Zhou B, Liu Q, Wang H, Jin H, Liu Y. *Tetrahedron*. 2019;75:3815.
55 Silva LHP, Nussenszweig V. *Folia Clin Biol*. 1953;20:191.
56 de Castro SL, Pinto MCFR, Pinto AV. *Microbios*. 1994;78:83.