Supplementary Information

Molecular Hybridization as a powerful tool towards Multitarget Quinoidal Systems: Synthesis, Trypanocidal and Antitumor activities of Naphthoquinone-based 5-iodo-1,4-disubstituted-, 1,4- and 1,5-disubstituted-1,2,3-triazoles


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**General experimental details**

All chemicals were obtained from commercial sources and used without further purification. Solvents were distilled and when required were dried by distillation according to standard procedure.\(^1\) Melting points were obtained on a Thomas Hoover apparatus and are uncorrected. Column chromatography was performed on silica gel (SilicaFlash G60 UltraPure 60-200 µm, 60 Å). Infrared spectra were recorded on a Shimadzu FTIR Spectrometer IR Prestige-21.\(^1\)\(^\text{H}\) and \(^{13}\text{C}\) NMR were recorded at room temperature using a Bruker AVANCE DRX200 and DRX400 MHz, in the solvents indicated, with tetramethylsilane (TMS) as internal reference. Chemical shifts (\(\delta\)) are given in parts per million (ppm) and coupling constants (\(J\)) in Hertz (Hz). The mass spectrometer was operated in the positive ion mode. A standard atmospheric pressure photoionization (APPI) source was used to generate the ions. The sample was injected using a constant flow (3 µL/min). The solvent was an acetonitrile/methanol mixture. The APPI-Q-TOF MS instrument was calibrated in the mass range of 50-3000 m/z using an internal calibration standard (low concentration tuning mix solution) supplied by Agilent Technologies. Data were processed employing Bruker Data Analysis software version 4.0. Compounds were named following IUPAC rules as applied by ChemBioDraw Ultra (version 12.0).
Synthesis of known substrates

Lawsone was acquired from Sigma-Aldrich (St. Louis, MO, USA). C-allyl lawsone (26) was prepared from lawsone as previously reported. Lapachol (1) (2-hydroxy-3-(3’-methyl-2’-butenyl)-1,4-naphthoquinone) was extracted from the heartwood of *Tabebuia* sp. (Tecoma). Initially, a saturated aqueous sodium carbonate solution was added to the sawdust of ipe. After the formation of the lapachol sodium salt, hydrochloric acid was added, allowing the precipitation of lapachol. After filtration, a yellow solid was obtained. This solid was purified by a series of recrystallizations with appropriate solvents. Nor-lapachol (3) was prepared by Hooker oxidation reaction. Azide derivatives 5, 10, 16, 22 and 29 were prepared according previous reports and their data are consistent with the literature. Quinone-based 1,2,3-triazoles 8, 11, 25, 34-38 were already reported in the literature and prepared as previously published procedures. Cp*RuCl(PPh₃)₂ was prepared and purified as described in the literature.

General procedures for novel compounds

2-(azidomethyl)-2,3-dihydronaphtho[2,3-b]furan-4,9-dione (30)

![Reaction Scheme](image)

Compound 28 (0.5 mmol) was dissolved in dimethyl formamide (DMF) (3 mL) in a 25 mL round-bottom flask equipped with a magnetic stirring bar. To this solution were added NaN₃ (1.5 mmol). The stirring was continued at room temperature for 24 h. The reaction mixture was extracted with ethyl acetate/water 1:1 (100 mL) and washed sequentially with water (3 x 50 mL). The organic layer was separated and dried over Na₂SO₄. The solvent was removed under reduced pressure to afford the crude product, which was purified on a silica column using a gradient mixture of hexane/ethyl acetate as eluent with increasing polarity. Compound 30 was obtained as a yellow solid (90% yield); m.p. 116-117 ºC. ¹H NMR (200 MHz, CDCl₃) δ 8.06-7.94 (m, 2H), 7.71-7.57 (m, 2H), 5.23-5.09 (m, 1H), 3.75 (dd, J = 3.7 and 13.3 Hz, 1H), 3.56 (dd, J = 5.0 and
13.3 Hz, 1H), 3.26 (dd, \( J = 10.8 \) and 17.4 Hz, 1H), 3.02 (dd, \( J = 7.5 \) and 17.4 Hz, 1H).

\(^{13}\text{C} \text{ NMR (CDCl}_3, 50 \text{ MHz)} \delta \): 181.8, 177.1, 159.4, 134.1, 133.0, 132.6, 131.2, 126.1, 125.8, 124.0, 83.6, 53.5, 30.0. ESI/HRMS (\( m/\text{z} \)) [M+H]^+: 256.0716. Calcd for [C\(_{13}\)H\(_{10}\)N\(_3\)O\(_3\)]: 256.0722.

**General procedure for the synthesis of quinone-based 1,5-disubstituted-1,2,3-triazoles**

Previous procedure as described by Zhang and co-workers\(^{11}\) was used to perform the synthesis of quinone-based 1,5-disubstituted 1,2,3-triazoles. The reactions were carried out under nitrogen atmosphere using standard Schlenk techniques. A mixture of the respective azide quinone (0.1 mmol), phenylacetylene (0.2 mmol) and 10 mol% of the catalyst [Cp*RuCl(PPh\(_3\))\(_2\)] in 4 mL of dry dichloromethane was stirred at room temperature or 50 °C during 24 h. After this period, the reaction medium was poured into water, layers were separated and the aqueous layer was extracted with ethyl acetate and dried with Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure to afford the crude product, which was purified on a silica column using a gradient mixture of hexane/ethyl acetate as eluent with increasing polarity.

**General procedure for the synthesis of quinone-based 5-iodo-1,4-disubstituted-1,2,3-triazoles\(^{12}\)**

The respective quinone (0.55 mmol) was dissolved in CH\(_3\)CN (10 mL) in a 50 mL round-bottom flask equipped with a magnetic stirring bar. To this solution were added NaI (2.0 mmol) and Cu(ClO\(_4\))\(_2\).6H\(_2\)O (2.0 mmol). The reaction was stirred for ~10 min, and then TEA (0.55 mmol) and phenylacetylene (0.7 mmol) were added. The stirring was continued at room temperature for 24 h. The reaction mixture was extracted with ethyl acetate/water 1:1 (100 mL) and washed sequentially with a saturated solution of NH\(_4\)Cl (50 mL). The organic layer was separated and dried over Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure to afford the crude product, which was purified on a silica column using a gradient mixture of hexane/ethyl acetate as eluent with increasing polarity.
General procedure for the synthesis of quinone-based 1,4-disubstituted-1,2,3-
triazoles\textsuperscript{13}

To a mixture of 1 mmol of the respective quinone-azide with CuSO\textsubscript{4}.5H\textsubscript{2}O (5 mol %) and sodium ascorbate (5 mol %) in 8 mL CH\textsubscript{2}Cl\textsubscript{2}/H\textsubscript{2}O (1:1 v/v), the corresponding alkyne (1.1 equivalents) was added. The mixture was stirred overnight at room temperature. The organic phase was extracted with dichloromethane, dried with NaSO\textsubscript{4} and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using a gradient mixture of hexane/ethyl acetate as eluent with increasing polarity.

2,2-Dimethyl-3-(5-phenyl-1\texttextsuperscript{H}-1,2,3-triazol-1-yl)-2,3-dihydronaphtho[1,2-\texttextit{b}]furan-4,5-dione (6).

\[
\text{\begin{align*}
\text{\textit{C}p^*\text{RuCl(PPPh}_3)_2} & \text{ } \text{\textit{Ph}} \\
\text{CH}_2\text{Cl}_2, 50 ^\circ \text{C} & \text{ } 24 \text{h}
\end{align*}}
\]

Compound 6 was obtained as a yellow solid (45% yield); m.p. 170-172 °C. IR (KBr, cm\textsuperscript{-1}) \textit{v}: 2930 (w), 1662 (s), 1628 (s), 1224 (m). \textsuperscript{1}\textsuperscript{H} NMR (400 MHz, CDCl\textsubscript{3}) \textit{\delta}: 8.14 (d, \textit{J} = 7.6 Hz, 1H), 7.78 (d, \textit{J} = 6.8 Hz, 1H), 7.72 (s, 1H), 7.70-7.47 (m, 7H), 5.68 (s, 1H), 1.42 (s, 3H), 1.21 (s, 3H). \textsuperscript{13}\textsuperscript{C} NMR (100 MHz, CDCl\textsubscript{3}) \textit{\delta}: 180.4, 174.8, 171.1, 139.2, 134.7, 133.0, 131.6, 130.0, 129.9, 129.6, 129.5, 127.1, 126.6, 125.5, 113.4, 95.2, 64.2, 27.7, 21.3. \textit{EI/HRMS (m/z) [M+H]^+}: 372.1295. \textsuperscript{C}ald. for [C\textsubscript{22}H\textsubscript{18}N\textsubscript{3}O\textsubscript{3}]\textsuperscript{+}: 372.1343.

3-(5-Iodo-4-phenyl-1\texttextsuperscript{H}-1,2,3-triazol-1-yl)-2,2-dimethyl-2,3-dihydronaphtho[1,2-\texttextit{b}]furan-4,5-dione (7).

\[
\text{\begin{align*}
\text{Cu(ClO}_4)_2, \text{NaI} & \text{ } \text{\textit{Ph}} \\
\text{N(\text{Et})}_3, \text{CH}_3\text{CN} & \text{ } \text{24h}
\end{align*}}
\]
Compound 7 was obtained as a yellow solid (90% yield); m.p. 238-240 °C. IR (KBr, cm⁻¹) ν: 1596 (m), 1567 (m). ¹H NMR (400 MHz, DMSO-d₆) δ 8.04 (d, J = 7.4 Hz, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.82-7.72 (m, 3H), 7.44 (t, J = 7.5 Hz, 2H), 7.37 (d, J = 7.4 Hz, 1H), 5.96 (s, 1H), 1.79 (s, 3H), 1.12 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆, CDCl₃) δ 180.0, 174.1, 170.0, 149.0, 135.0, 133.1, 131.3, 130.2, 129.3, 128.7, 128.5, 128.4, 127.1, 126.6, 125.1, 94.9, 66.78, 27.4, 21.7. EI/HRMS (m/z) [M+H]⁺: 498.0298. Cald. for [C₂₂H₁₇IN₃O₃]⁺: 498.0309.

3-Bromo-2,2-dimethyl-4-(5-phenyl-1H-1,2,3-triazol-1-yl)-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (12).

Compound 12 was obtained as a green solid (30% yield); m.p. 137-138 °C. IR (KBr, cm⁻¹) ν: 2927 (w), 1615 (s), 1578 (m). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 8.2 Hz, 1H), 7.92-7.85 (m, 3H), 7.72 (t, J = 7.8 Hz, 1H), 7.68 (s, 1H), 7.62 (t, J = 7.0 Hz, 1H), 7.54-7.47 (m, 3H), 5.58 (d, J = 9.9 Hz, 1H), 4.91 (d, J = 9.9 Hz, 1H), 1.81 (s, 3H), 1.53 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆, CDCl₃) δ 177.80, 176.16, 162.75, 135.22, 132.29, 130.80, 130.48, 129.68, 129.24, 128.81, 126.91, 125.29, 111.31, 83.64, 55.98, 28.36, 19.80. EI/HRMS (m/z) [M+H]⁺: 498.0298. Cald. for [C₂₂H₁₇IN₃O₃]⁺: 498.0309.

3-Bromo-4-(5-iodo-4-phenyl-1H-1,2,3-triazol-1-yl)-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (13).

Compound 13 was obtained as a yellow solid (65% yield); m.p. 160-162 °C. IR (KBr, cm⁻¹) ν: 1650 (m), 1596 (m), 1398 (m). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 7.0 Hz, 1H), 7.37 (d, J = 7.0 Hz, 1H), 5.96 (s, 1H), 1.79 (s, 3H), 1.12 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆, CDCl₃) δ 180.0, 174.1, 170.0, 149.0, 135.0, 133.1, 130.2, 129.3, 128.7, 128.5, 128.4, 127.1, 126.6, 125.1, 94.9, 66.78, 27.4, 21.7. EI/HRMS (m/z) [M+H]⁺: 498.0298. Cald. for [C₂₂H₁₇IN₃O₃]⁺: 498.0309.
Hz, 1H), 7.99-7.90 (m, 2H), 7.74 (t, J = 7.7 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.51-7.41 (m, 2H), 7.44-7.34 (m, 2H), 5.90 (d, J = 9.7 Hz, 1H), 4.98 (d, J = 9.7 Hz, 1H), 1.87 (s, 3H), 1.72 (s, 3H). 13C NMR (100 MHz, CDCl₃) δ 177.8, 176.2, 162.6, 135.3, 132.4, 131.8, 130.8, 130.6, 130.3, 129.3, 128.7, 128.5, 128.0, 126.5, 125.4, 111.3, 83.9, 58.6, 55.4, 27.9, 20.1. EI/HRMS (m/z) [M+H]+: 589.9590. Cald. for [C₂₃H₁₈BrN₃O₃]⁺: 589.9571.

2,2-Dimethyl-4-(5-phenyl-1H-1,2,3-triazol-1-yl)-3,4-dihydro-2H-benzo[g]chromene-5,10-dione (17).

Compound 17 was obtained as a yellow solid (35% yield); m.p.: 125-127 °C. IR (KBr, cm⁻¹) ν: 1732 (s), 1643 (s), 1389 (m). ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, J = 8.6 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.73 (s, 1H), 7.71-7.66 (m, 4H), 7.59-7.52 (m, 3H), 5.83-5.51 (m, 1H), 2.54 (dd, J = 13.9, 6.7 Hz, 1H), 2.24 (dd, J = 14.1, 6.9 Hz, 1H), 1.59 (s, 3H), 1.37 (s, 3H). EI/HRMS (m/z) [M+H]^+: 498.0298. Cald. for [C₂₂H₁₇IN₃O₃]⁺: 498.0309.

4-(5-Iodo-4-phenyl-1H-1,2,3-triazol-1-yl)-2,2-dimethyl-3,4-dihydro-2H-benzo[g]chromene-5,10-dione (18).

Compound 18 was obtained as a yellow solid (65% yield); m.p. 215-217 °C. IR (KBr, cm⁻¹) ν: 1596 (m), 1550 (m), 1402 (m). ¹H NMR (200 MHz, DMSO-d₆) δ 8.08-8.03 (m, 1H), 7.92 (d, J = 7.4 Hz, 2H), 7.90-7.81 (m, 3H), 7.53 (t, J = 7.5 Hz, 2H), 7.45 (t, J
= 7.4 Hz, 1H), 5.88 (t, J = 6.7 Hz, 1H), 2.53-2.49 (m, 2H), 1.50 (s, 3H), 1.46 (s, 3H).  
$^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 181.9, 179.0, 155.5, 148.2, 134.9, 134.6, 133.9, 133.4, 131.4, 130.7, 130.5, 128.7, 128.4, 127.0, 126.2, 125.8, 116.5, 79.5, 50.8, 27.1, 25.4. Ei/HRMS (m/z) [M+H]$^+$: 512.0453. Cald. for [C$_{23}$H$_{19}$IN$_3$O$_3$]$^+$: 512.0471.

2,2-Dimethyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-3,4-dihydro-2H-benzo[g]chromene-5,10-dione (19).

Compound 19 was obtained as a light orange solid (40% yield); m.p. 125-126 °C. IR (KBr, cm$^{-1}$) v: 3125 (w), 1650 (s), 1605 (s). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.17 (d, J = 6.5 Hz, 1H), 8.05 (d, J = 6.4 Hz, 1H), 7.96-7.82 (m, 3H), 7.79-7.72 (m, 2H), 7.48-7.34 (m, 2H), 7.36 (d, J = 7.15, 1H), 5.94-5.83 (m, 1H), 2.91 (dd, J = 14.6, 5.9 Hz, 1H), 2.43 (dd, J = 14.5, 5.8 Hz, 1H), 1.58 (s, 3H), 1.38 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 182.8, 179.4, 156.3, 155.8, 134.6, 133.5, 131.8, 131.1, 128.8, 128.2, 126.7, 126.6, 126.5, 125.8, 125.7, 115.2, 100.0, 79.4, 50.0, 39.1, 26.7. EI/HRMS (m/z) [M+H]$^+$: 498.0298. Cald. for [C$_{22}$H$_{17}$IN$_3$O$_3$]$^+$: 498.0309.

2,2-Dimethyl-3-(5-phenyl-1H-1,2,3-triazol-1-yl)-2,3-dihydronaphtho[2,3-b]furan-4,9-dione (23).

Compound 23 was obtained as a yellow solid (60% yield); m.p. 207-209 °C. IR (KBr, cm$^{-1}$) v: 3134 (w), 1700 (s), 1664 (s), 1400 (m). $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 8.16 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.76-7.72 (m, 3H), 7.67-7.55 (m, 5H), 5.78 (s,
3-(5-Iodo-4-phenyl-1H-1,2,3-triazol-1-yl)-2,2-dimethyl-2,3-dihyronaphtho[2,3-b]furan-4,9-dione (24).

\[
\begin{align*}
\text{Cu}(	ext{ClO}_4)_2, \text{NaI} &\quad \text{Ph} \\
&\quad \text{N(Et)}_3, \text{CH}_3\text{CN}
\end{align*}
\]

Compound 24 was obtained as a yellow solid (60% yield); m.p. 239-240 °C. IR (KBr, cm\(^{-1}\)) \(\nu\): 1596 (m), 1550 (m) 1402 (m). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.17 (dd, \(J = 7.1, 1.8\) Hz, 1H), 8.04 (dd, \(J = 6.5, 2.4\) Hz, 1H), 7.95 (d, \(J = 7.1\) Hz, 2H), 7.74 (ddd, \(J = 6.6, 4.3, 1.8\) Hz, 2H), 7.47 (t, \(J = 7.3\) Hz, 2H), 7.41 (t, \(J = 7.3\) Hz, 1H), 6.01 (s, 1H), 1.80 (s, 3H), 1.23 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 180.8, 177.9, 160.92, 149.9, 134.6, 133.3, 132.8, 131.8, 129.7, 128.8, 128.5, 127.5, 126.7, 126.4, 119.2, 93.7, 67.8, 27.5, 21.8. EI/HRMS (m/z) [M+H]\(^+\): 498.0285. Cald. for [C\(_{22}\)H\(_{17}\)IN\(_3\)O\(_3\)]\(^+\): 498.0314.

2-((5-Phenyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihyronaphtho[1,2-b]furan-4,5-dione (31).

\[
\begin{align*}
\text{Cp}^*\text{RuCl(PPh}_3\text{)}_2 &\quad \text{Ph} \\
&\quad \text{CH}_2\text{Cl}_2, \text{rt}
\end{align*}
\]

Compound 31 was obtained as an orange solid (45% yield); m.p. 198-199 °C. IR (KBr, cm\(^{-1}\)) \(\nu\): 3135 (w), 1651 (m), 1625 (s), 1404 (m). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.06 (d, \(J = 7.1\) Hz, 1H), 7.76 (s, 1H), 7.39 (t, \(J = 4.9\) Hz, 2H), 7.46-7.37 (m, 6H), 5.59 (dt, \(J = 11.0, 7.6\) Hz, 1H).
= 12.4, 6.2 Hz, 1H), 4.73 (d, J = 5.7 Hz, 2H), 3.29 (dd, J = 15.7, 10.2 Hz, 1H), 2.89 (dd, J = 15.8, 6.8 Hz, 1H). \(^{13}\text{C NMR (100 MHz, CDCl}_3\) \(\delta\) 180.5, 175.3, 168.8, 138.7, 134.5, 133.3, 132.2, 130.5, 129.8, 129.7, 129.3, 128.8, 128.6, 128.5, 126.8, 126.6, 124.6, 114.5, 84.7, 51.3, 29.9. \(\text{EI/HRMS (m/z) [M+H]}^+\): 358.1150. \textbf{Cald. for [C}_{21}\text{H}_{16}\text{N}_3\text{O}_3]^+: 358.1186.}

2-((5-Iodo-4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihyronaphtho[1,2-b]furan-4,5-dione (32).

\[
\begin{align*}
\text{Cu(ClO}_4)_2, \text{Nal} & \quad \text{N(Et)}_3, \text{CH}_3\text{CN} \\
\text{Cu(ClO}_4)_2, \text{Nal} & \quad \text{N(Et)}_3, \text{CH}_3\text{CN}
\end{align*}
\]

Compound 32 was obtained as an orange solid (35% yield); \(\text{m.p. 238-240 °C. IR (KBr, cm}^{-1}) v: 1596 (m), 1527 (m), 1402 (m). \text{H NMR (200 MHz, CDCl}_3\) \(\delta\) 8.25 (d, J = 8.7 Hz, 1H), 7.96-7.94 (m, 2H), 7.77 (d, J = 6.8 Hz, 1H), 7.65-7.57 (m, 1H), 7.50-7.34 (m, 4H), 5.87-5.44 (m, 1H), 4.95-4.64 (m, 2H), 3.58 (dd, J = 15.7, 10.0 Hz, 1H), 3.21 (dd, J = 15.7, 6.9 Hz, 1H). \(^{13}\text{C NMR (100 MHz, CDCl}_3, \text{DMSO-d}_6\) \(\delta\): 180.5, 175.2, 168.9, 148.0, 134.8, 132.3, 130.5, 130.2, 129.6, 128.8, 128.3, 126.9, 125.7, 124.5, 120.8, 114.7, 84.5, 53.3, 30.8, 29.5. \(\text{EI/MS (m/z) [M+H]}^+\): 484. \textbf{Cald. for [C}_{21}\text{H}_{15}\text{IN}_3\text{O}_3]^+: 484.}

2-((4,5-Diphenyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihyronaphtho[1,2-b]furan-4,5-dione (33).

\[
\begin{align*}
\text{Cp*RuCl(PPh}_3)_2 & \quad \text{CH}_2\text{Cl}_2, 50 ^\circ\text{C} \quad \text{24 h} \\
\text{Cp*RuCl(PPh}_3)_2 & \quad \text{CH}_2\text{Cl}_2, 50 ^\circ\text{C} \quad \text{24 h}
\end{align*}
\]
Compound 33 was obtained as an orange solid (35% yield); m.p. 138-140 ºC. IR (KBr, cm⁻¹) v: 3092 (w), 1652 (s), 1625 (s), 1414 (m). ¹H NMR (200 MHz, CDCl₃) δ 8.07 (d, J = 8.4 Hz, 2H), 7.83-7.29 (m, 12H), 5.69-5.57 (m, 1H), 4.56 (d, J = 6.6 Hz, 2H), 3.30 (dd, J = 15.7, 10.2 Hz, 1H), 2.89 (dd, J = 15.9, 6.9 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 168.9, 156.1, 134.5, 132.2, 132.1, 130.7, 130.6, 130.1, 129.7, 129.6, 128.6, 128.0, 127.4, 126.9, 126.9, 124.6, 114.6, 100.0, 84.5, 51.2, 30.0. EI/MS (m/z) [M+Na]⁺: 456. Cald. for [C₂₇H₁₉N₃O₃Na]⁺: 456. After 12 hours of acquisition, it was not possible to detect the resonances related to the carbonyl carbons, possible due to high relaxation times associated to these nuclei.

2-((4-Phenyl-1H,1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho[2,3-b]furan-4,9-dione (39).

![Chemical structure of Compound 39]

Compound 39 was obtained as an yellow solid (85% yield); m.p. 214-216 ºC. IR (KBr, cm⁻¹) v: 2924 (w), 1677 (s), 1661 (s), 1595 (m). ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 3.0 Hz, 2H), 7.98 (s, 1H), 7.82 (d, J = 7.1 Hz, 2H), 7.78-7.67 (m, 2H), 7.43 (t, J = 7.0 Hz, 2H), 7.35 (d, J = 7.0 Hz, 1H), 5.58-5.40 (m, 1H), 4.85 (d, J = 7.9 Hz, 2H), 3.44 (dd, J = 9.4, 7.1 Hz, 1H), 3.17 (dd, J = 9.6, 7.1 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 181.6, 177.3, 160.2, 159.1, 155.9, 134.4, 133.2, 132.8, 128.8, 128.4, 126.4, 126.3, 125.8, 124.2, 100.0, 83.1, 53.1, 30.3. EI/MS (m/z) [M+Na]⁺: 380. Cald. for [C₂₁H₁₅N₃O₃Na]⁺: 380.

2-((5-Phenyl-1H,1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho[2,3-b]furan-4,9-dione (40).

![Chemical structure of Compound 40]
Compound 40 was obtained as a yellow solid (40% yield); m.p. 218-220 °C. IR (KBr, cm⁻¹) v: 2927 (w), 1680 (s), 1654 (s), 1203 (s). ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 7.3 Hz, 2H), 7.76-7.74 (m, 3H), 7.53-7.40 (m, 5H), 5.53 (dt, J = 12.5, 6.4 Hz, 1H), 4.66 (d, J = 5.7 Hz, 2H), 3.37 (dd, J = 17.4, 10.6 Hz, 1H), 3.13 (dd, J = 17.6, 7.3 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 181.8, 177.1, 159.0, 139.0, 134.3, 133.2, 133.2, 132.8, 131.4, 129.8, 129.3, 129.2, 126.4, 126.3, 126.2, 83.0, 50.8, 30.9. EI/HRMS (m/z) [M+H]+: 358.1117. Cald. for [C₂₁H₁₆N₃O₃]⁺: 358.1186.

2-((5-Iodo-4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihyronaphtho[2,3-b]furan-4,9-dione (41).

![Reaction Scheme](image)

Compound 41 was obtained as a yellow solid (80% yield); m.p. 230-231 °C. IR (KBr, cm⁻¹) v: 1654 (m), 1596 (m), 1402 (m). ¹H NMR (400 MHz, CDCl₃) δ 8.08 (t, J = 6.7 Hz, 2H), 7.93 (d, J = 10.5 Hz, 2H), 7.81-7.78 (m, 3H), 7.51-7.37 (m, 3H), 5.73-5.36 (m, 1H), 4.83 (d, J = 4.2 Hz, 1H), 3.35 (dd, J = 17.1, 8.6 Hz, 1H), 3.14 (dd, J = 17.3, 8.1 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, DMSO-ｄ₆) δ 177.57, 177.40, 149.88, 137.32, 134.30, 133.17, 130.16, 128.75, 128.62, 128.48, 128.20, 127.46, 126.29, 126.23, 126.07, 125.67, 83.05, 82.75, 52.90, 30.72, 30.15. EI/MS (m/z) [M+Na]⁺: 506. Cald. for [C₂₁H₁₄IN₃O₃Na]⁺: 506. After 12 hours of acquisition, it was not possible to detect the resonances related to the carbonyl carbons and some quaternary carbons, possible due to high relaxation times associated to these nuclei.

**Biological**

**Trypanocidal activity**

Stock solutions of the compounds were prepared in dimethyl sulfoxide (DMSO), with the final concentration of the latter in the experiments never exceeding 0.1%. Preliminary experiments showed that concentrations of up to 0.5%, DMSO have no deleterious effect on the parasites. Bloodstream trypomastigotes of the Y strain were
obtained at the peak of parasitaemia from infected albino mice, isolated by differential centrifugation and resuspended in Dulbecco's modified Eagle medium (DME) to a parasite concentration of $10^7$ cells/mL in the presence of 10% of mouse blood. This suspension (100 µL) was added in the same volume of each compound previously prepared at twice the desired final concentrations. Cell counts were performed in Neubauer chamber and the trypanocidal activity was expressed as IC$_{50}$, corresponding to the concentration that leads to lysis of 50% of the parasites.

**Antitumor activity**

Compounds were tested for cytotoxic activity against several human cancer cell lines obtained from the National Cancer Institute, NCI (Bethesda, MD, US). Peripheral blood mononuclear cells (PBMC) were isolated from the heparinized blood of healthy, non-smoker donors who had not taken any medication at least 15 days prior to sampling, using a standard method of density-gradient centrifugation on Histopaque-1077 (Sigma Aldrich Co. - St. Louis, MO/USA). All cancer cell lines and PBMC were maintained in RPMI 1640 medium. All culture media were supplemented with 20% (PBMC) or 10% (cancer cells) fetal bovine serum, 2 mM L-glutamine, 100 IU/mL penicillin and 100 µg/mL streptomycin at 37 ºC with 5% CO$_2$. PBMC cultures were also supplemented with 2% phytohaemagglutinin. In the cytotoxicity experiments, cells were plated in 96-well plates (0.7 x $10^5$ to 0.1 x $10^6$ cells/well for cancer cells and 1 x $10^6$ cells/well for PBMC). All tested compounds were dissolved in DMSO. The final concentration of DMSO in the culture medium was kept constant (0.1%, v/v). Doxorubicin (0.001-1.10 µM) was used as the positive control, and negative control groups received the same amount of vehicle (DMSO). The cell viability was determined through the reduction of the yellow dye 3-(4,5-dimethyl-2-thiazol)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to a blue formazan product, as described by Mosmann.$^{14}$ At the end of the incubation time (72 h), the plates were centrifuged and the medium was replaced with fresh medium (200 µL) containing 0.5 mg/mL MTT. Three hours later, the MTT formazan product was dissolved in DMSO (150 µL) and the absorbance was measured using a multiplate reader (Spectra Count, Packard, Ontario, Canada). The drug effect was quantified as the percentage of control absorbance of the reduced dye at 550 nm. All cell treatments were carried out with three replicates.
X-Ray analysis

Diffraction data for compounds 6 and 30 were collected on a Bruker CCD SMART APEX II single crystal diffractometer with Mo Kα radiation (0.71073 Å) at 296K. The data were processed with SAINT\textsuperscript{15} and were corrected for absorption using SADABS.\textsuperscript{16} X-ray diffraction data of compound 24 was obtained on an Enraf-Nonius Kappa-CCD diffractometer (95 mm CCD camera on k-goniostat) using graphite monochromated MoKa radiation (0.71073 Å), at room temperature. Data collections were carried out using the COLLECT software\textsuperscript{17} up to 50° in 2θ. Integration and scaling of the reflections, correction for Lorentz and polarization effects were performed with the HKL DENZO-SCALEPACK system of programs.\textsuperscript{18} The structure of the compounds 12 and 31 has been determined from X-ray diffraction on a Rigaku XtaLAB Mini diffractometer (75 mm CCD camera) using graphite monochromated MoKα radiation (0.71073 Å), at room temperature. Data collections were carried out using the CrystalClear (Rigaku) software\textsuperscript{19,20} up to 50° in 2θ. Final unit cell parameters were based on 4524 reflections for 12 compound and 12162 reflections for 31 respectively. Integration and scaling of the reflections, correction for Lorentz and polarization effects were performed with the CrystalStructure system of programs. The structures were solved by direct methods using SHELXS-97\textsuperscript{21} and subsequent Fourier-difference map analyses yielded the positions of the nonhydrogen atoms, the refinement was performed using SHELXL-97.\textsuperscript{22} Molecular graphics were generated with ORTEP-3\textsuperscript{23}; software used to prepare material for publication, WinGX-Routine.\textsuperscript{24} All H atoms were located by geometric considerations placed (C-H = 0.93-0.96 Å) and refined as riding with \(U_{iso}(H) = 1.5U_{eq} \) (C-methyl) or 1.2\( U_{eq} \) (other). The reference numbers for the compounds are CCDC 1063676 for 6, 1451944 for 12, 1451739 for 24, 1044480 for 30 and 1451945 for 31. Copies of the available material can be obtained, free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CH21EZ, UK (fax: +44-1223-336-033 or e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Data for compound 6

\( \text{C}_{22}\text{H}_{17}\text{N}_{3}\text{O}_{3} \); M = 371.39; monoclinic, space group \( P2_1/c \); \( a = 6.869(5) \) Å, \( b = 9.080(8) \) Å, \( c = 29.959(2) \) Å; \( \alpha = \gamma = 90^\circ \), \( \beta = 95.405(5)^\circ \); \( V = 1860.3(2) \) Å\(^3\); \( Z = 4 \); \( D_c = 1.326 \) g.cm\(^{-1}\); \( F(000) = 776 \); \( T = 296(2) \) K; orange block, size 0.29 x 0.20 x 0.08 mm; 3821
independent measured reflections, refinement based on $F^2$ to give $R_1 [F^2 > 4\sigma(F^2)] = 0.047; w_2 = 0.104$ for 16801 observed reflections, and 300 parameters.

**Data for compound 12**

C$_{23}$H$_{19}$BrN$_3$O$_3$; $M = 463.3$; monoclinic, space group $P2_1/n$; $a = 7.088(2)$ Å, $b = 18.229(4)$ Å, $c = 15.373(3)$ Å; $\alpha = \gamma = 90^\circ$, $\beta = 90.77^\circ$; $V = 1986.2(7)$ Å$^3$; $Z = 4$; D$_c$ = 1.55 g.cm$^{-1}$; $F(000) = 940$; $T = 293(2)$ K; orange block, size 0.22 x 0.19 x 0.18 mm; 4456 independent measured reflections, refinement based on $F^2$ to give $R_1 [F^2 > 4\sigma(F^2)] = 0.043; w_2 = 0.123$ for 3384 observed reflections, and 271 parameters.

**Data for compound 24**

C$_{22}$H$_{16}$IN$_3$O$_3$; $M = 496.27$; monoclinic, space group $P2_1/c$; $a = 8.4787(3)$ Å, $b = 28.5968(6)$ Å, $c = 8.8356(2)$ Å; $\alpha = \gamma = 90^\circ$, $\beta = 115.3^\circ$; $V = 1936.4(2)$ Å$^3$; $Z = 4$; D$_c$ = 1.7 g.cm$^{-1}$; $F(000) = 980$; $T = 293(2)$ K; orange block, size 0.271 x 0.215 x 0.170 mm; 3586 independent measured reflections, refinement based on $F^2$ to give $R_1 [F^2 > 4\sigma(F^2)] = 0.047; w_2 = 0.13$ for 2990 observed reflections, and 262 parameters.

**Data for compound 30**

C$_{13}$H$_9$N$_3$O$_3$; $M = 255.23$; monoclinic, space group $P2_1/n$; $a = 9.368(5)$ Å, $b = 8.486(5)$ Å, $c = 14.910(7)$ Å; $\alpha = \gamma = 90^\circ$, $\beta = 102.189(4)^\circ$; $V = 1158.61(11)$ Å$^3$; $Z = 4$; D$_c$ = 1.463 g.cm$^{-1}$; $F(000) = 528$; $T = 296(2)$ K; yellow block, size 0.65 x 0.34 x 0.14 mm; 2512 independent measured reflections, refinement based on $F^2$ to give $R_1 [F^2 > 4\sigma(F^2)] = 0.048; w_2 = 0.117$ for 9716 observed reflections, and 173 parameters.

**Data for compound 31**

C$_{21}$H$_{18}$N$_3$O$_3$; $M = 357.36$; monoclinic, space group $P2_1/c$; $a = 7.530(2)$ Å, $b = 24.791(6)$ Å, $c = 9.241(2)$ Å; $\alpha = \gamma = 90^\circ$, $\beta = 110.7^\circ$; $V = 1613.9(7)$ Å$^3$; $Z = 4$; D$_c$ = 1.471 g.cm$^{-1}$; $F(000) = 744$; $T = 293(2)$ K; orange block, size 0.37 x 0.30 x 0.23 mm; 3650 independent measured reflections, refinement based on $F^2$ to give $R_1 [F^2 > 4\sigma(F^2)] = 0.063; w_2 = 0.15$ for 2466 observed reflections, and 244 parameters.
Figure S1: $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 6.

Figure S2: $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 6.
**Figure S3:** $^1$H NMR spectrum (400 MHz, DMSO-$d_6$) of compound 7.

**Figure S4:** $^{13}$C NMR spectrum (100 MHz, DMSO-$d_6$, CDCl$_3$) of compound 7.
Compound 12

Figure S5: $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 12.

Figure S6: $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 12.
Figure S7: $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 13.

Figure S8: $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 13.
Figure S9: $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 17.
Compound 18

Figure S10: $^1$H NMR spectrum (200 MHz, DMSO-$d_6$) of compound 18.

Figure S11: $^{13}$C NMR spectrum (100 MHz, DMSO-$d_6$) of compound 18.
Compound 19

Figure S12: $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 19.

Figure S13: $^{13}$C NMR (100 MHz, DMSO-$d_6$) spectra of compound 19.
Compound 23

Figure S14: $^1$H NMR spectrum (200 MHz, CDCl$_3$) of compound 23.

Figure S15: $^{13}$C NMR spectrum (50 MHz, CDCl$_3$) of compound 23.
Figure S16: $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 24.

Figure S17: $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 24.
Figure S18: $^1$H NMR spectrum (200 MHz, CDCl$_3$) of compound 30.

Figure S19: $^{13}$C NMR spectrum (50 MHz, CDCl$_3$) of compound 30.
Figure S20: $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 31.

Figure S21: $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 31.
Figure S22: $^1$H NMR spectrum (200 MHz, CDCl$_3$) of compound 32.

Figure S23: $^{13}$C NMR spectrum (100 MHz, CDCl$_3$, DMSO-$d_6$) of compound 32.
Figure S24: $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 33.

Figure S25: $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 33.
**Figure S26:** $^1$H NMR spectrum (200 MHz, CDCl$_3$) of compound 39.

**Figure S27:** $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 39.
Figure S28: $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 40.

Figure S29: $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 40.
Figure S30: $^1$H NMR spectrum (200 MHz, CDCl$_3$) of compound 41.

Figure S31: $^{13}$C NMR (100 MHz, CDCl$_3$, DMSO-$d_6$) spectra of compound 41.


