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

Samara Ben B. B. Bahia,[a] Wallace J. Reis,[a] Guilherme A. M. Jardim,[a] Francielly T. Souto,[a] Carlos A. de Simone,[b] Claudia C. Gatto,[c] Rubem F. S. Menna-Barreto,[d] Solange L. de Castro,[d] Bruno C. Cavalcanti,[e] Claudia Pessoa,[e] Maria H. Araújo[a] and Eufrânio N. da Silva Júnior[a]*

[a]Institute of Exact Sciences, Department of Chemistry, Federal University of Minas Gerais, Belo Horizonte, 31270-901, MG, Brazil;
[b]Institute of Physics, Department of Physics and Informatics, University of São Paulo, São Carlos, 13560-160, SP, Brazil;
[c]Institute of Chemistry, University of Brasilia, Brasilia, 70904-970, DF, Brazil;
[d]Oswaldo Cruz Institute, FIOCRUZ, Rio de Janeiro, 21045-900, RJ, Brazil;
[e]Department of Physiology and Pharmacology, Federal University of Ceará, Fortaleza, CE, 60430-270, Brazil.

Corresponding author: Tel.: 55 31 34095720; fax: 55 31 34095700.
E-mail address: eufranio@ufmg.br (E.N. da Silva Júnior).

Contents

General experimental details

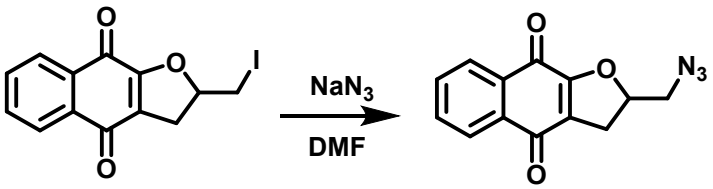
All chemicals were obtained from commercial sources and used without further purification. Solvents were distilled and when required were dried by distillation according to standard procedure.[1] Melting points were obtained on a Thomas Hoover apparatus and are uncorrected. Column chromatography was 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}H and ^{13}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 (δ) 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.[2] 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.[3] *Nor*-lapachol (**3**) was prepared by Hooker oxidation reaction.[4] Azide derivatives **5**, **10**, **16**, **22** and **29** were prepared according previous reports and their data are consistent with the literature.[5,6,7,8] Quinone-based 1,2,3-triazoles **8**, **11**, **25**, **34-38** were already reported in the literature and prepared as previously published procedures.[5,6,7,8,9] Cp*RuCl(PPh_3)$_2$ was prepared and purified as described in the literature.[10]

General procedures for novel compounds

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



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 NaN_3 (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 Na_2SO_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. Compound **30** was obtained as a yellow solid (90% yield); **m.p.** 116-117 ºC. **^{1}H NMR (200 MHz, $CDCl_3$)** 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}C NMR ($CDCl_3$, 50 MHz) δ** 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. **EI/HRMS (*m/z*) $[M+H]^+$:** 256.0716. **Cald for $[C_{13}H_{10}N_3O_3]^+$:** 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 ºC 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_2SO_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.

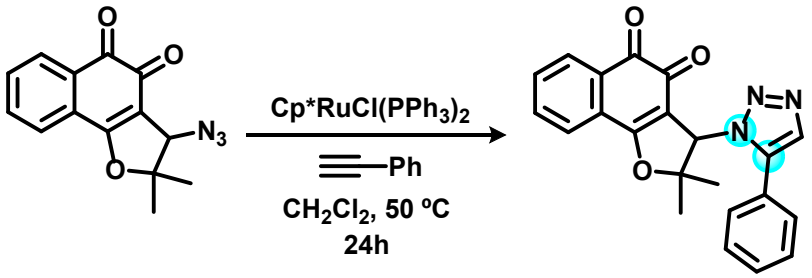
General procedure for the synthesis of quinone-based 5-iodo-1,4-disubstituted-1,2,3-triazoles[12]

The respective quinone (0.55 mmol) was dissolved in CH_3CN (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 $Cu(ClO_4)_2 \cdot 6H_2O$ (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 satured solution of NH_4Cl (50 mL). The organic layer was separated and dried over Na_2SO_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[13]

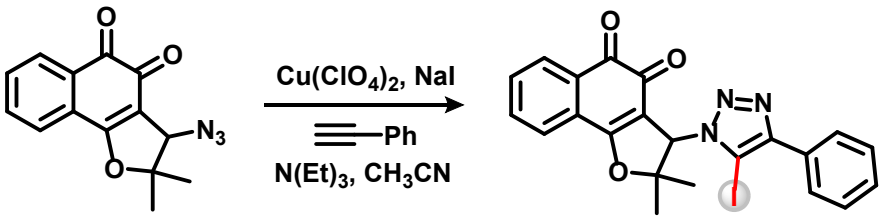
To a mixture of 1 mmol of the respective quinone-azide with $CuSO_4 \cdot 5H_2O$ (5 mol %) and sodium ascorbate (5 mol %) in 8 mL CH_2Cl_2/H_2O (1:1 v/v), the corresponding alkyne (1.1 equivalents) was added. The mixture was stirred overnight at room temperature. The organic phase was extracted with dichloromethane, dried with $NaSO_4$ 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*H*-1,2,3-triazol-1-yl)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (6).



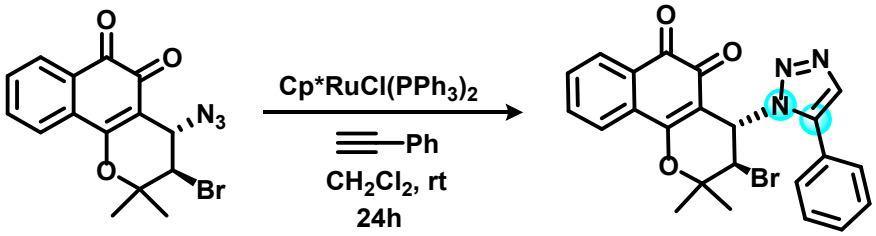
Compound **6** was obtained as a yellow solid (45% yield); **m.p.** 170-172 ºC. **IR (KBr, cm^{-1}) ν:** 2930 (w), 1662 (s), 1628 (s), 1224 (m). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.14 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 6.8 Hz, 1H), 7.72 (s, 1H), 7.70-7.47 (m, 7H), 5.68 (s, 1H), 1.42 (s, 3H), 1.21 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 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. **EI/HRMS (*m/z*) [M+H]$^+$:** 372.1295. **Cald. for [$C_{22}H_{18}N_3O_3$]$^+$:** 372.1343.

3-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (7).



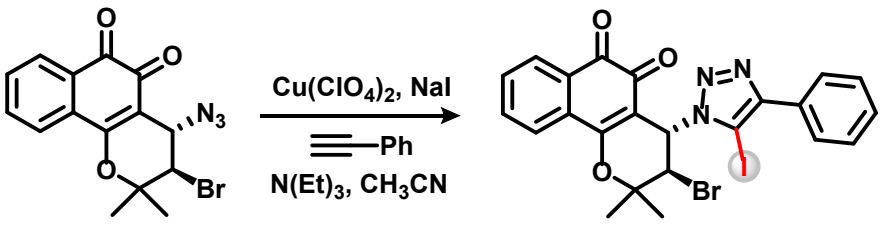
Compound **7** was obtained as a yellow solid (90% yield); **m.p.** 238-240 ºC. **IR (KBr, cm^{-1}) ν:** 1596 (m), 1567 (m). **^{1}H NMR (400 MHz, DMSO-d_6) δ** 8.04 (d, *J* = 7.4 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.82-7.72 (m, 3H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 7.4 Hz, 1H), 5.96 (s, 1H), 1.79 (s, 3H), 1.12 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6, $CDCl_3$) 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 [$C_{22}H_{17}IN_3O_3$]$^+$:** 498.0309.

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



Compound **12** was obtained as a green solid (30% yield); **m.p.** 137-138 ºC. **IR (KBr, cm^{-1}) ν:** 2927 (w), 1615 (s), 1578 (m). **^{1}H NMR (400 MHz, $CDCl_3$) 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). **^{13}C NMR (100 MHz, DMSO-d_6, $CDCl_3$) 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 [$C_{22}H_{17}IN_3O_3$]$^+$:** 498.0309.

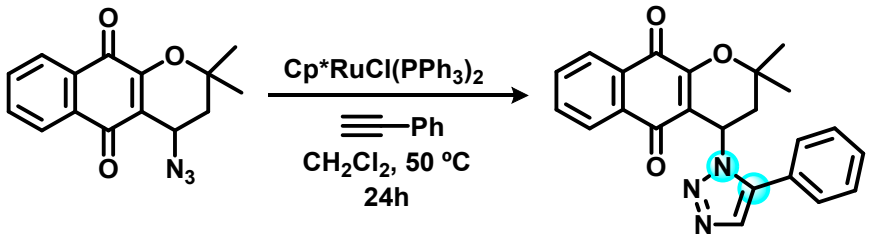
3-Bromo-4-(5-iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5,6-dione (13).



Compound **13** was obtained as a yellow solid (65% yield); **m.p.** 160-162 ºC. **IR (KBr, cm^{-1}) ν:** 1650 (m), 1596 (m), 1398 (m). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.10 (d, *J* = 7.6

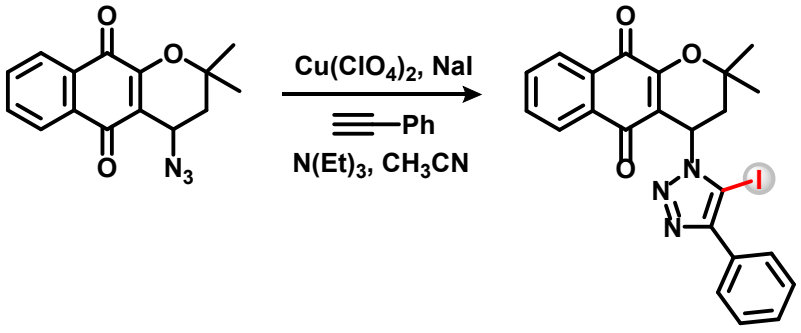
Hz, 1H), 7.99-7.90 (m, 2H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.51-7.41 (m, 2H), 7.44-7.34 (m, 2H), 5.90 (d, *J* = 9.7 Hz, 1H), 4.98 (d, *J* = 9.7 Hz, 1H), 1.87 (s, 3H), 1.72 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 177.8, 176.2, 162.6, 135.3, 132.4, 131.8, 130.8, 130.6, 130.3, 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 $[C_{23}H_{18}BrIN_3O_3]^+$:** 589.9571.

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



Compound **17** was obtained as a yellow solid (35% yield); **m.p.:** 125-127 ºC. **IR (KBr, cm^{-1}) v:** 1732 (s), 1643 (s), 1389 (m). **^{1}H NMR (400 MHz, $CDCl_3$) 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 $[C_{22}H_{17}IN_3O_3]^+$:** 498.0309.

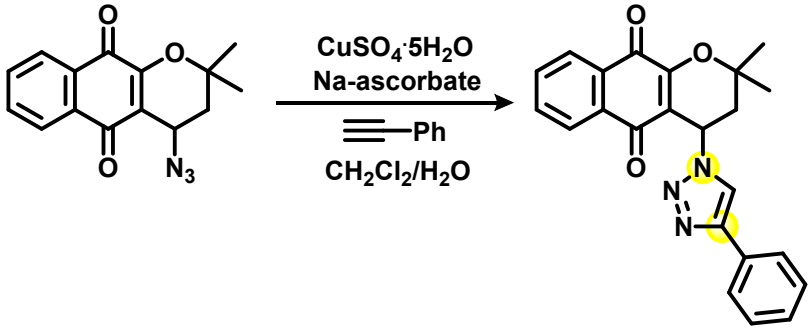
4-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (18).



Compound **18** was obtained as a yellow solid (65% yield); **m.p.** 215-217 ºC. **IR (KBr, cm^{-1}) v:** 1596 (m), 1550 (m), 1402 (m). **^{1}H NMR (200 MHz, DMSO-d_6) 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*

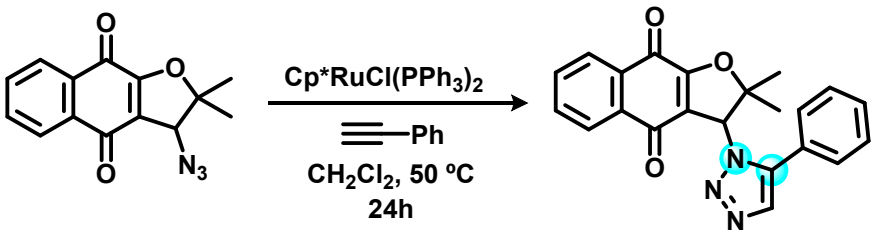
= 7.4 Hz, 1H), 5.88 (t, *J* = 6.7 Hz, 1H), 2.53-2.49 (m, 2H), 1.50 (s, 3H), 1.46 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 181.9, 179.0, 155.5, 148.2, 134.9, 134.6, 133.9, 133.4, 131.4, 130.7, 130.5, 128.7, 128.4, 127.0, 126.2, 125.8, 116.5, 79.5, 50.8, 27.1, 25.4. **EI/HRMS (*m/z*) [M+H]$^+$:** 512.0453. **Cald. for [$C_{23}H_{19}IN_3O_3$]$^+$:** 512.0471.

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



Compound **19** was obtained as a light orange solid (40% yield); **m.p.** 125-126 ºC. **IR (KBr, cm^{-1}) ν:** 3125 (w), 1650 (s), 1605 (s). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 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, $CDCl_3$) δ** 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 [$C_{22}H_{17}IN_3O_3$]$^+$:** 498.0309.

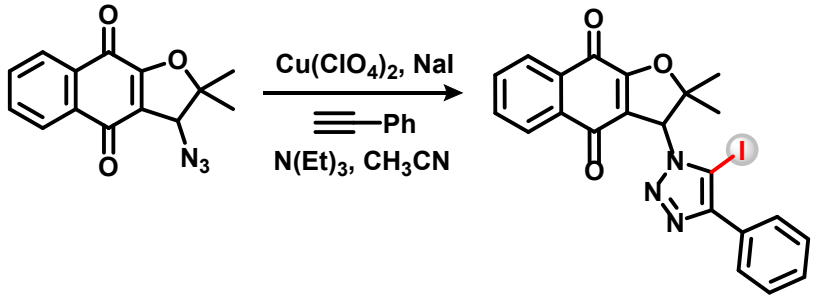
2,2-Dimethyl-3-(5-phenyl-1*H*-1,2,3-triazol-1-yl)-2,3-dihydronaphtho[2,3-*b*]furan-4,9-dione (23).



Compound **23** was obtained as a yellow solid (60% yield); **m.p.** 207-209 ºC. **IR (KBr, cm^{-1}) ν:** 3134 (w), 1700 (s), 1664 (s), 1400 (m). **^{1}H NMR (200 MHz, $CDCl_3$) δ** 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,

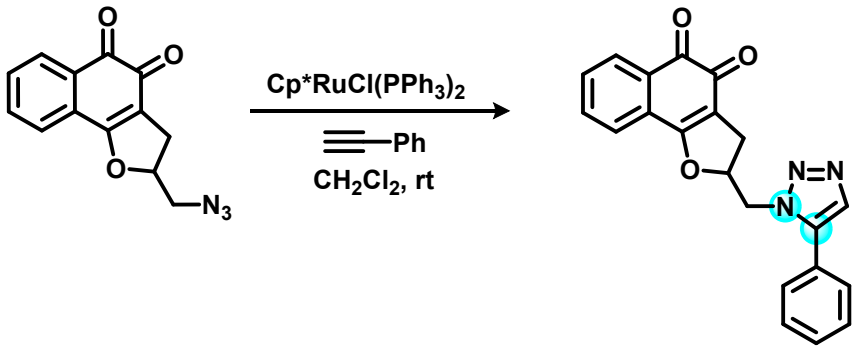
1H), 1.40 (s, 3H), 1.18 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$)** δ 181.29, 178.03, 161.07, 134.67, 133.45, 132.92, 132.00, 130.16, 129.47, 129.40, 126.88, 126.53, 126.16, 120.14, 93.75, 65.03, 27.50, 21.12. **EI/HRMS (*m/z*) $[M+H]^+$:** 372.1270. **Cald. for $[C_{22}H_{18}N_3O_3]^+$:** 372.1343.

3-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)-2,2-dimethyl-2,3-dihydronaphtho[2,3-*b*]furan-4,9-dione (24).



Compound **24** was obtained as a yellow solid (60% yield); **m.p.** 239-240 ºC. **IR (KBr, cm^{-1}) v:** 1596 (m), 1550 (m) 1402 (m). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 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, $CDCl_3$)** δ 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 $[C_{22}H_{17}IN_3O_3]^+$:** 498.0314.

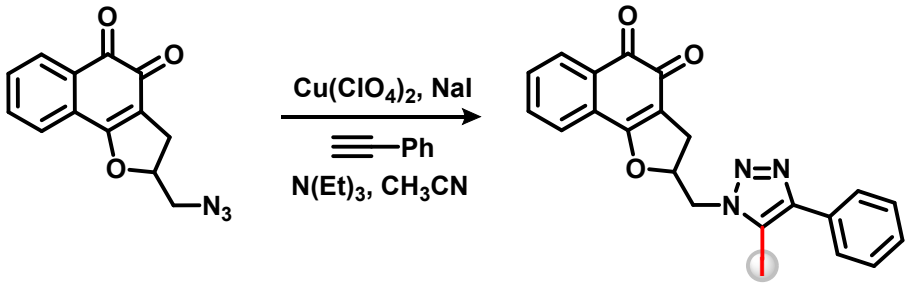
2-((5-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (31).



Compound **31** was obtained as an orange solid (45% yield); **m.p.** 198-199 ºC. **IR (KBr, cm^{-1}) v:** 3135 (w), 1651 (m), 1625 (s), 1404 (m). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (d, J = 7.1 Hz, 1H), 7.76 (s, 1H), 7.59 (t, J = 4.9 Hz, 2H), 7.46-7.37 (m, 6H), 5.59 (dt, J

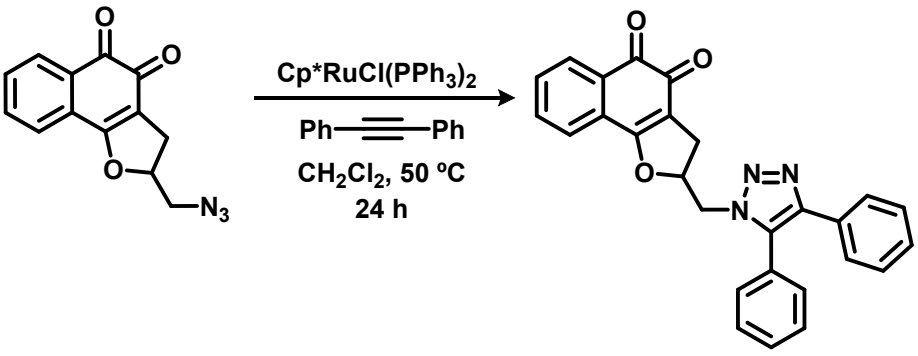
= 12.4, 6.2 Hz, 1H), 4.73 (d, *J* = 5.7 Hz, 2H), 3.29 (dd, *J* = 15.7, 10.2 Hz, 1H), 2.89 (dd, *J* = 15.8, 6.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 180.5, 175.3, 168.8, 138.7, 134.5, 133.3, 132.2, 130.5, 129.8, 129.7, 129.3, 128.8, 128.6, 128.5, 126.8, 126.6, 124.6, 114.5, 84.7, 51.3, 29.9. **EI/HRMS (*m/z*) $[M+H]^+$:** 358.1150. **Cald. for $[C_{21}H_{16}N_3O_3]^+$:** 358.1186.

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



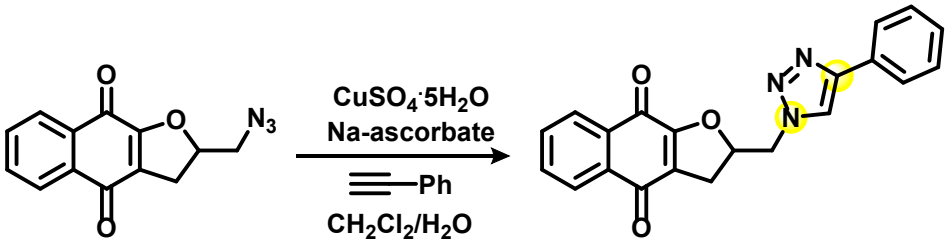
Compound **32** was obtained as an orange solid (35% yield); **m.p.** 238-240 °C. **IR (KBr, cm^{-1}) v:** 1596 (m), 1527 (m), 1402 (m). **^{1}H NMR (200 MHz, $CDCl_3$) δ** 8.25 (d, *J* = 8.7 Hz, 1H), 7.96-7.94 (m, 2H), 7.77 (d, *J* = 6.8 Hz, 1H), 7.65-75.7 (m, 1H), 7.50-7.34 (m, 4H), 5.87-5.44 (m, 1H), 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}C NMR (100 MHz, $CDCl_3$, DMSO-d_6) δ:** 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. **EI/MS (*m/z*) $[M+H]^+$:** 484. **Cald. for $[C_{21}H_{15}IN_3O_3]^+$:** 484.

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



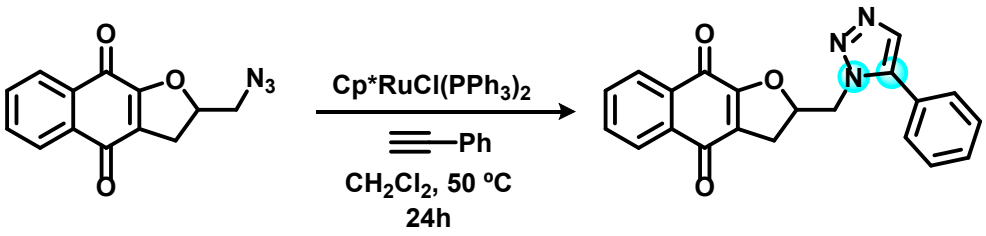
Compound **33** was obtained as an orange solid (35% yield); **m.p.** 138-140 ºC. **IR (KBr, cm^{-1}) ν:** 3092 (w), 1652(s), 1625 (s), 1414 (m). **^{1}H NMR (200 MHz, $CDCl_3$)** δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.83-7.29 (m, 12H), 5.69-5.57 (m, 1H), 4.56 (d, *J* = 6.6 Hz, 2H), 3.30 (dd, *J* = 15.7, 10.2 Hz, 1H), 2.89 (dd, *J* = 15.9, 6.9 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** 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 [$C_{27}H_{19}N_3O_3Na$]$^+$:** 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-1*H*-1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho[2,3-*b*]furan-4,9-dione (39).



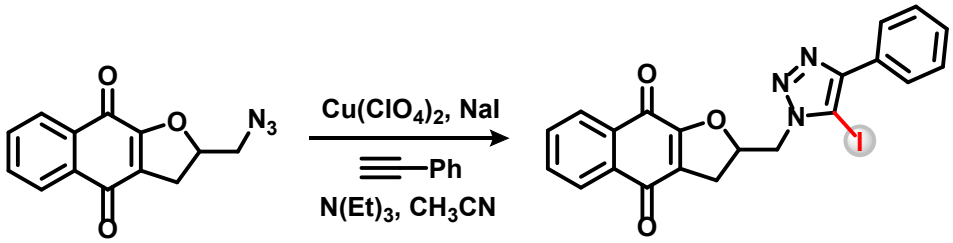
Compound **39** was obtained as an yellow solid (85% yield); **m.p.** 214-216 ºC. **IR (KBr, cm^{-1}) ν:** 2924 (w), 1677(s), 1661 (s), 1595 (m). **^{1}H NMR (400 MHz, CDCl3)** δ 8.07 (d, *J* = 3.0 Hz, 2H), 7.98 (s, 1H), 7.82 (d, *J* = 7.1 Hz, 2H), 7.78-7.67 (m, 2H), 7.43 (t, *J* = 7.0 Hz, 2H), 7.35 (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). **^{13}C NMR (100 MHz, $CDCl_3$)** 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 [$C_{21}H_{15}N_3O_3Na$]$^+$:** 380.

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



Compound **40** was obtained as a yellow solid (40% yield); **m.p.** 218-220 ºC. **IR (KBr, cm^{-1}) v:** 2927 (w), 1680 (s), 1654 (s), 1203 (s). **^{1}H NMR (400 MHz, $CDCl_3$) 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). **^{13}C NMR (100 MHz, $CDCl_3$) 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 $[C_{21}H_{16}N_3O_3]^+$:** 358.1186.

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



Compound **41** was obtained as a yellow solid (80% yield); **m.p.** 230-231 ºC. **IR (KBr, cm^{-1}) v:** 1654 (m), 1596 (m), 1402 (m). **^{1}H NMR (400 MHz, $CDCl_3$) 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). **^{13}C NMR (100 MHz, $CDCl_3$, DMSO-d_6) 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 $[C_{21}H_{14}IN_3O_3Na]^+$:** 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 (0.7×10^5 to 0.1×10^6 cells/well for cancer cells and 1×10^6 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-2*H*-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[15] and were corrected for absorption using SADABS.[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[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.[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[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[21] and subsequent Fourier-difference map analyses yielded the positions of the nonhydrogen atoms, the refinement was performed using SHELXL-97.[22] Molecular graphics were generated with ORTEP-3[23]; software used to prepare material for publication, WinGX-Routine.[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 $1.2U_{eq}$(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

$C_{22}H_{17}N_3O_3$; M = 371.39; monoclinic, space group $P2_1/c$; a = 6.869(5) Å, b = 9.080(8) Å, c = 29.959(2) Å; $\alpha = \gamma = 90°$, $\beta = 95.405(5)°$; V = 1860.3(2) Å^3; Z = 4; Dc = 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

$C_{23}H_{17}BrN_3O_3$; M = 463.3; monoclinic, space group $P2_1/n$; a = 7.088(2) Å, b = 18.229(4) Å, c = 15.373(3) Å; $\alpha = \gamma = 90^o$, $\beta = 90.77^o$; V = 1986.2(7) Å^3; Z = 4; Dc = 1.55 g.cm^{-1}; F(000) = 940; T = 293(2) 6 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

$C_{22}H_{16}IN_3O_3$; M = 496.27; monoclinic, space group $P2_1/c$; a = 8.4787(3) Å, b = 28.5968(6) Å, c = 8.8356(2) Å; $\alpha = \gamma = 90^o$, $\beta = 115.3^o$; V = 1936.4(2) Å^3; Z = 4; Dc = 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

$C_{13}H_9N_3O_3$; M = 255.23; monoclinic, space group $P2_1/n$; a = 9.368(5) Å, b = 8.486(5) Å, c = 14.910(7) Å; $\alpha = \gamma = 90^o$, $\beta = 102.189(4)^o$; V = 1158.61(11) Å^3; Z = 4; Dc = 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

$C_{21}H_{15}N_3O_3$; M = 357.36; monoclinic, space group $P2_1/c$; a = 7.530(2) Å, b = 24.791(6) Å, c = 9.241(2) Å; $\alpha = \gamma = 90^o$, $\beta = 110.7^o$; V = 1613.9(7) Å^3; Z = 4; Dc = 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.

Compound **6**

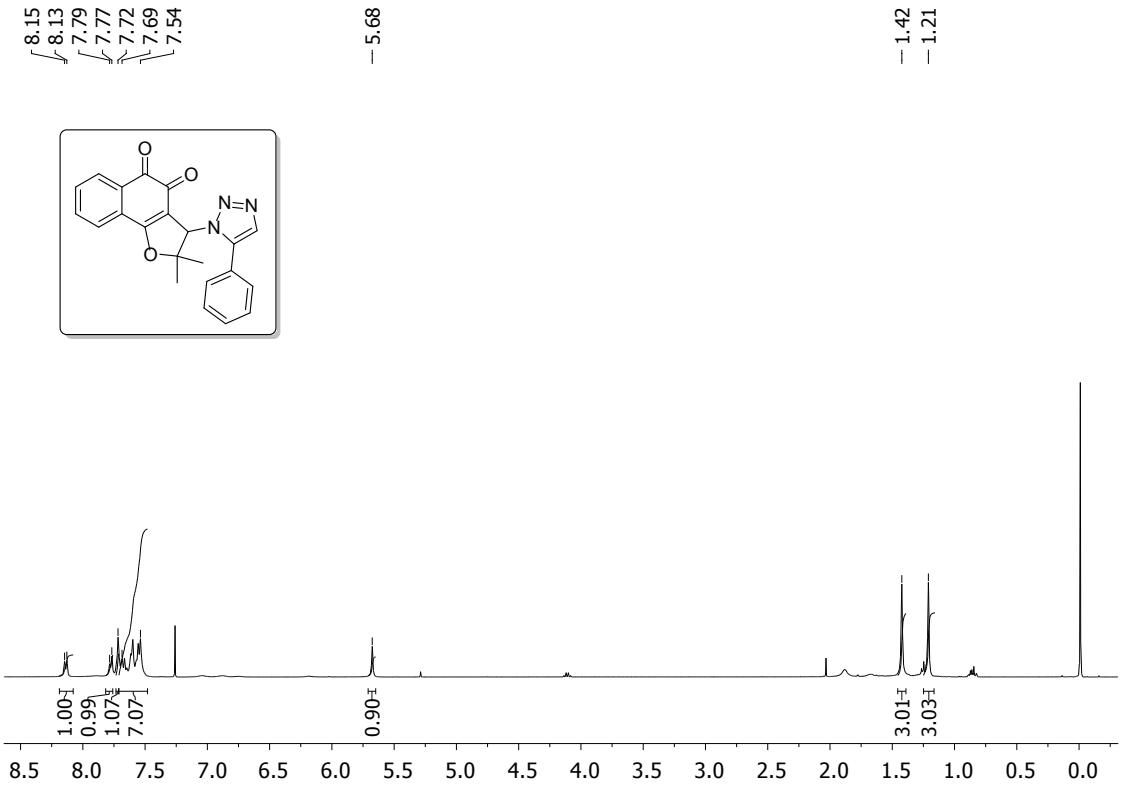


Figure S1: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **6**.

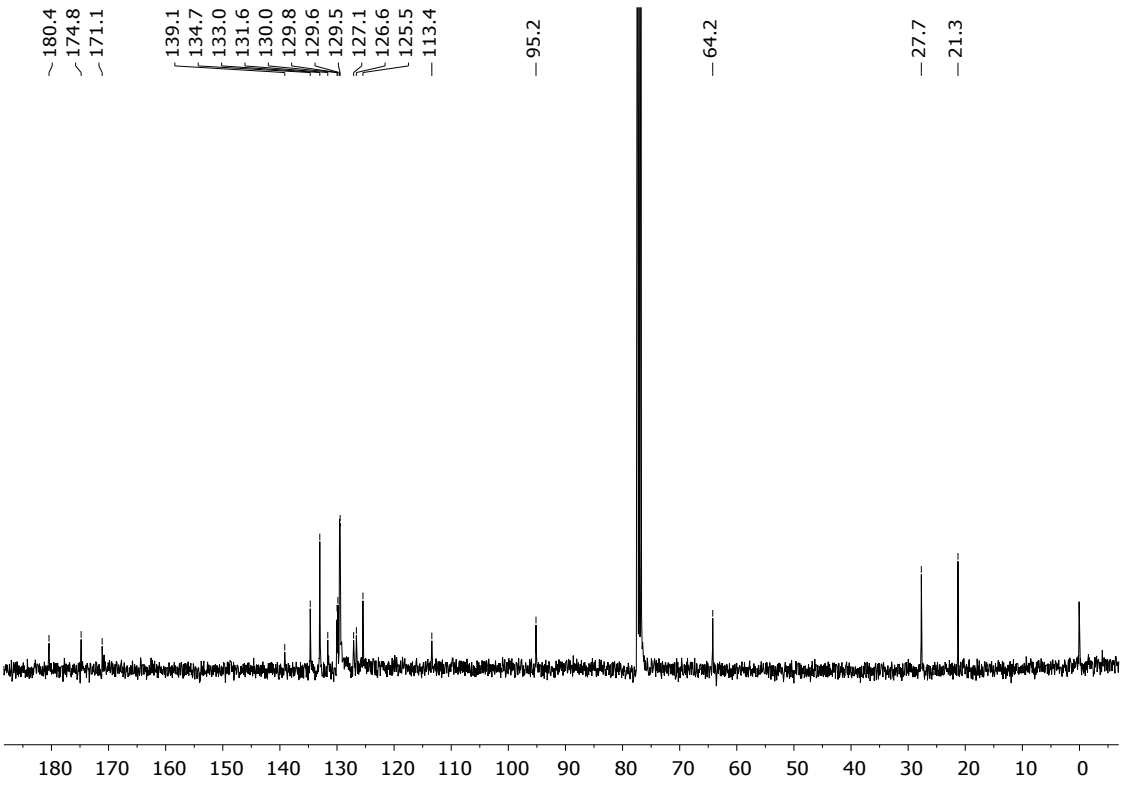


Figure S2: ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **6**.

Compound **7**

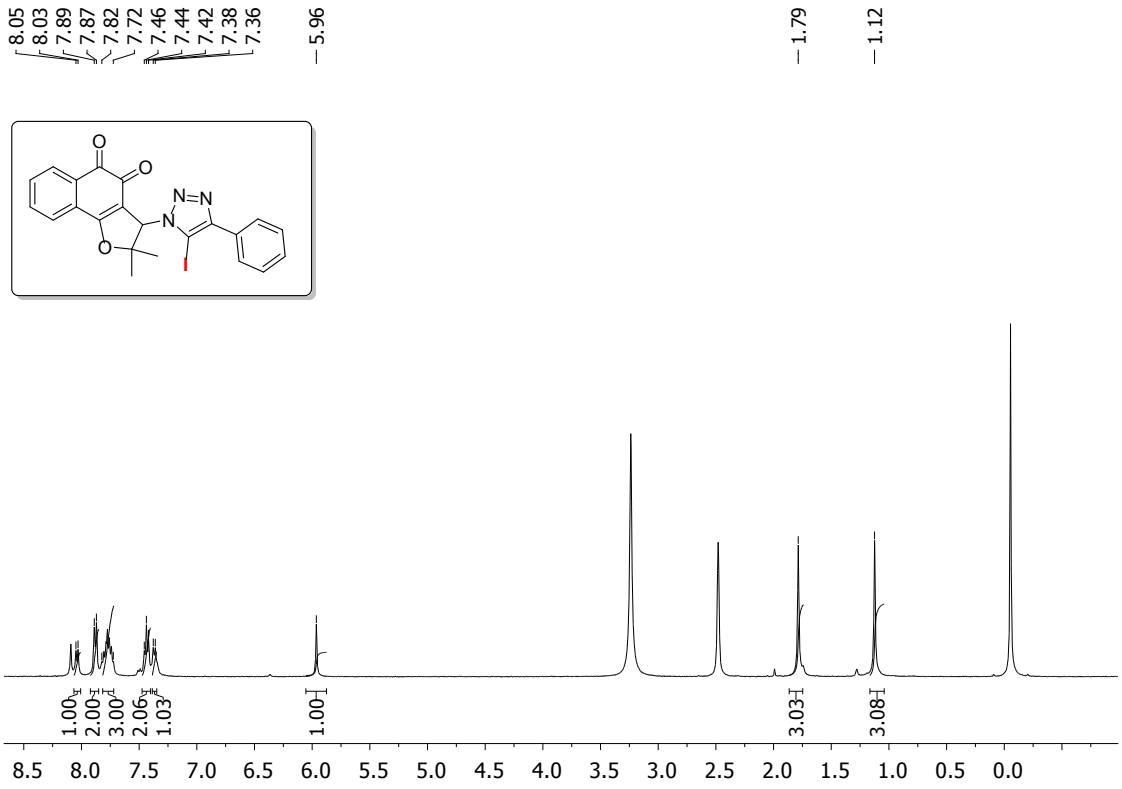


Figure S3: ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of compound **7**.

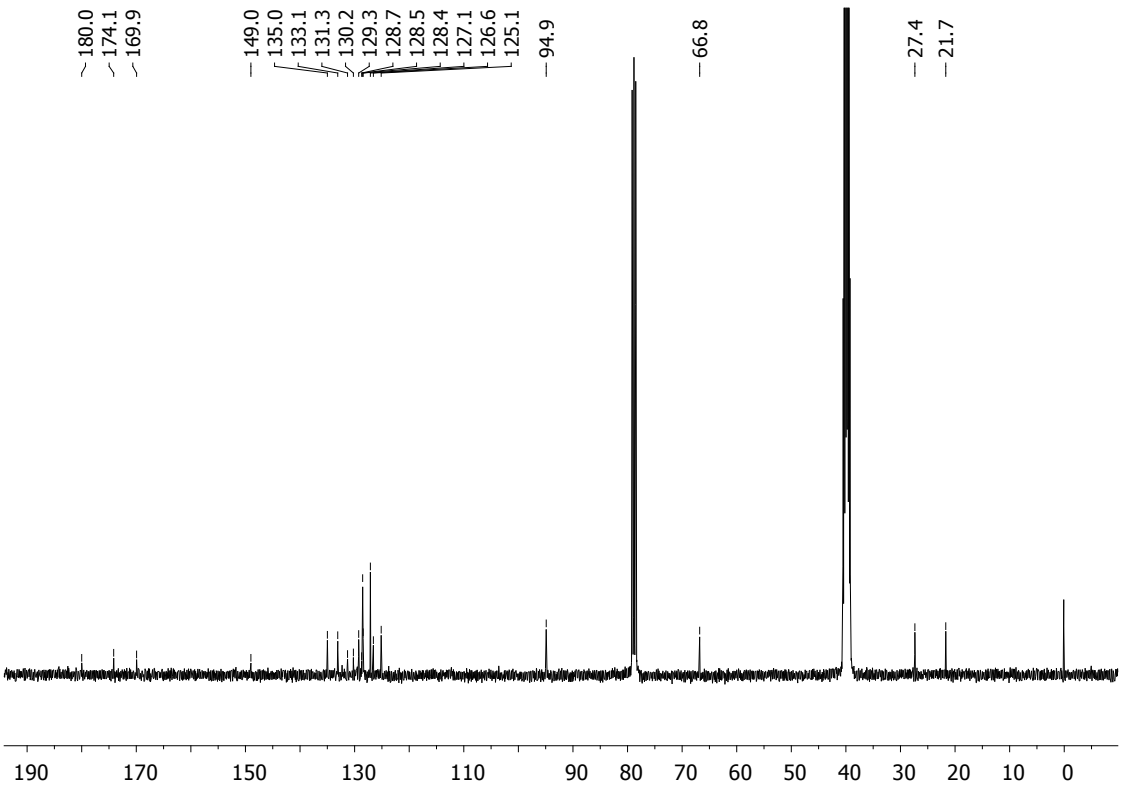


Figure S4: ^{13}C NMR spectrum (100 MHz, DMSO-d_6, $CDCl_3$) of compound **7**.

Compound **12**

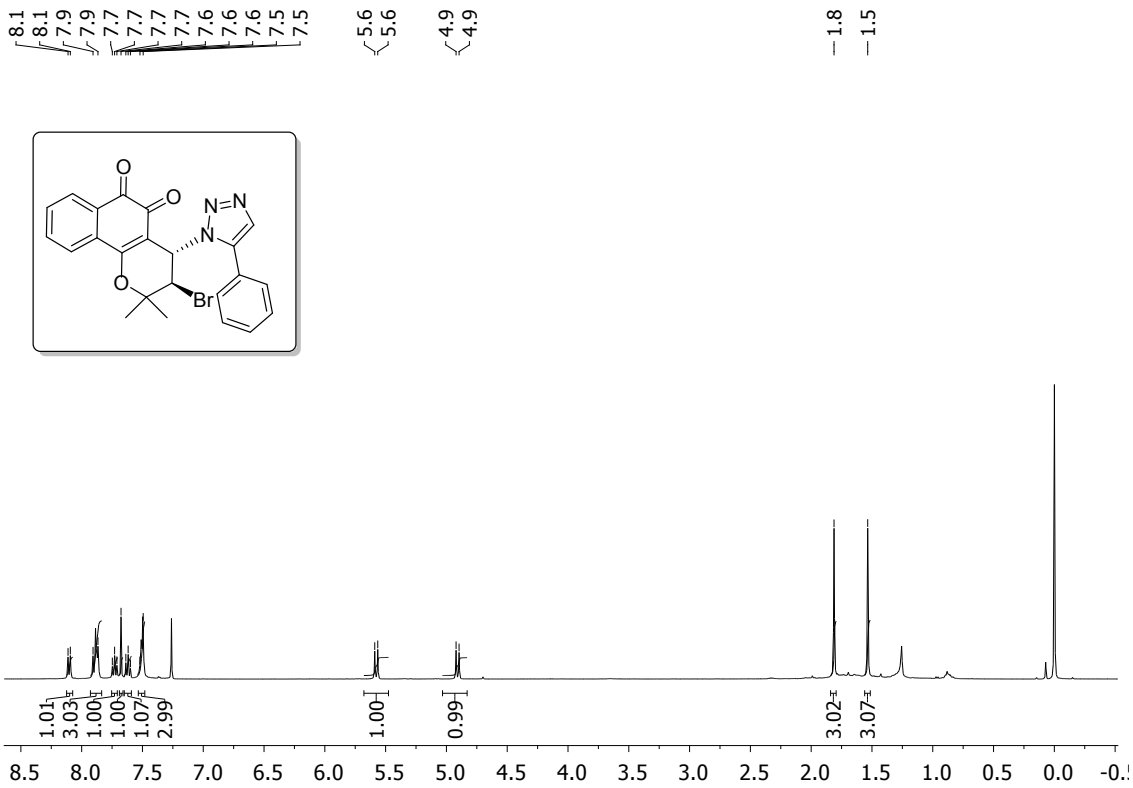


Figure S5: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **12**.

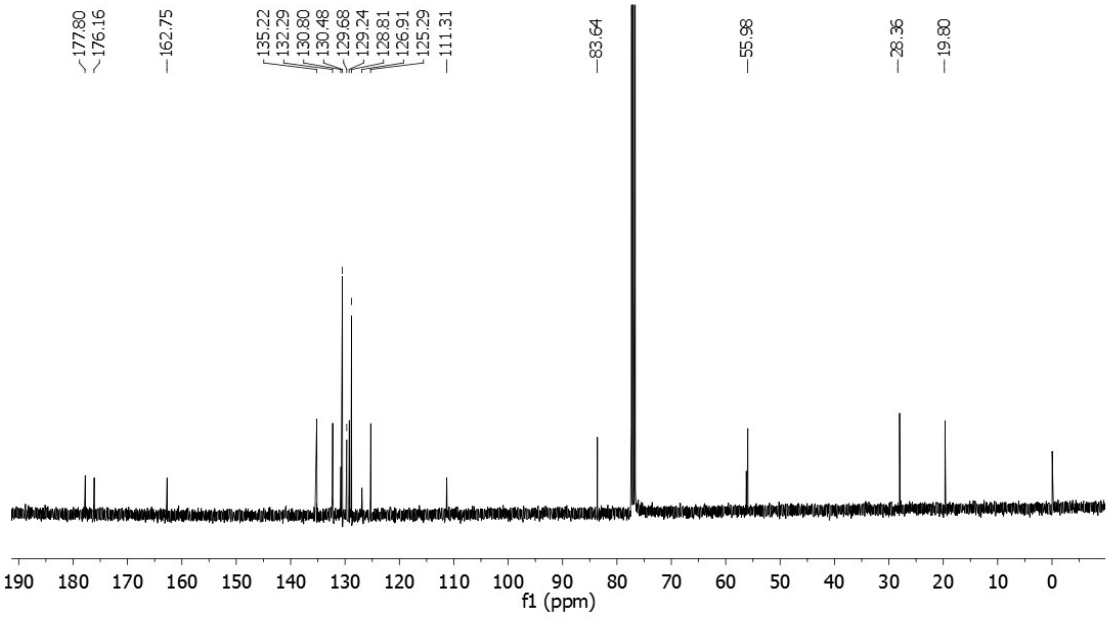


Figure S6: ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **12**.

Compound **13**

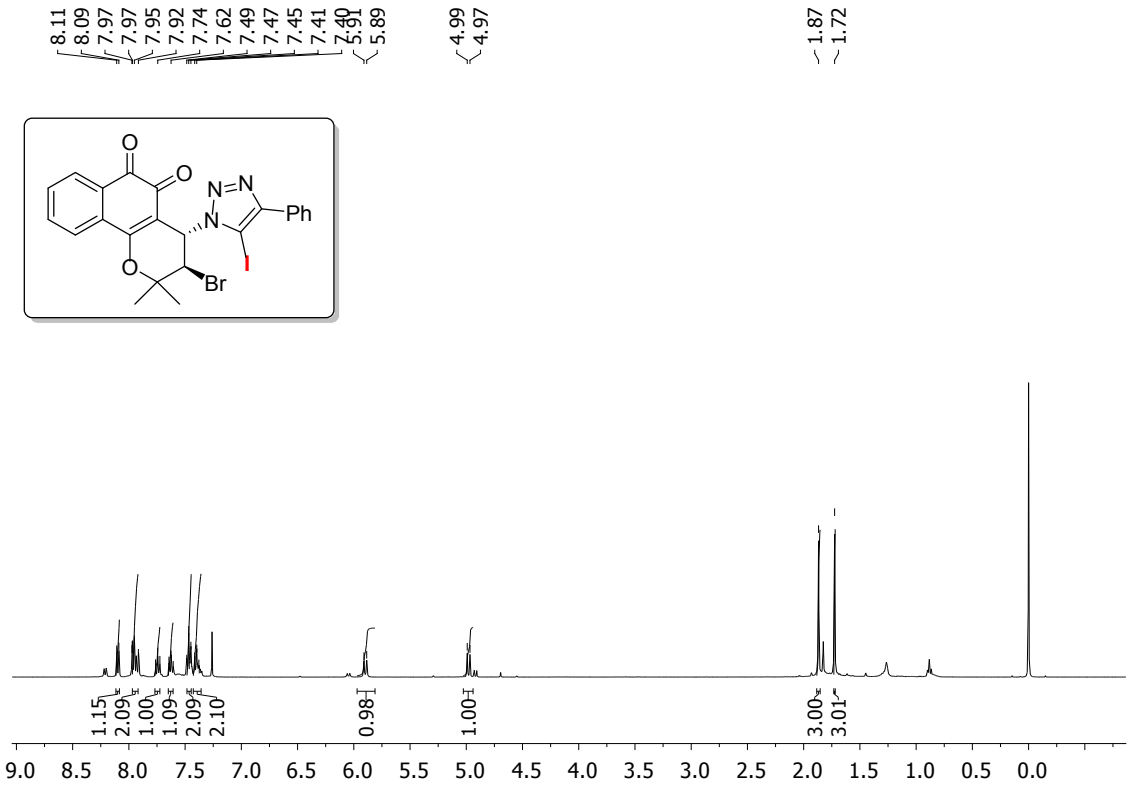


Figure S7: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **13**.

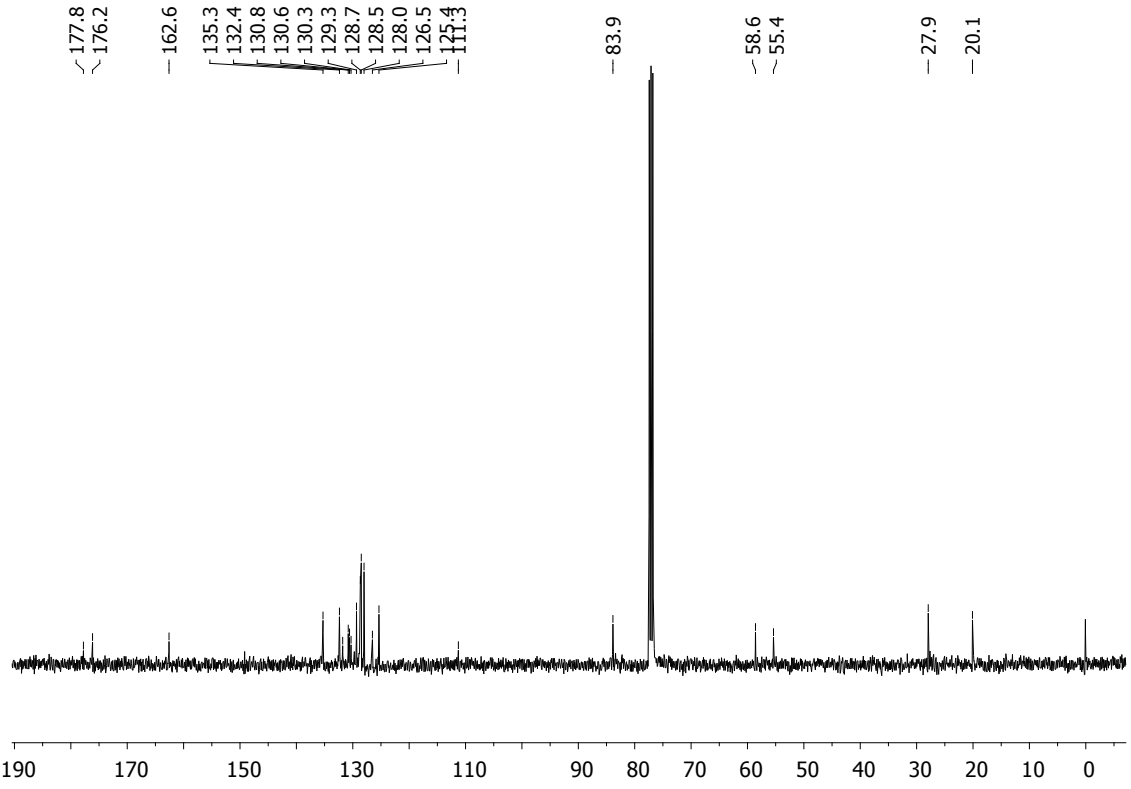


Figure S8: ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **13**.

Compound **17**

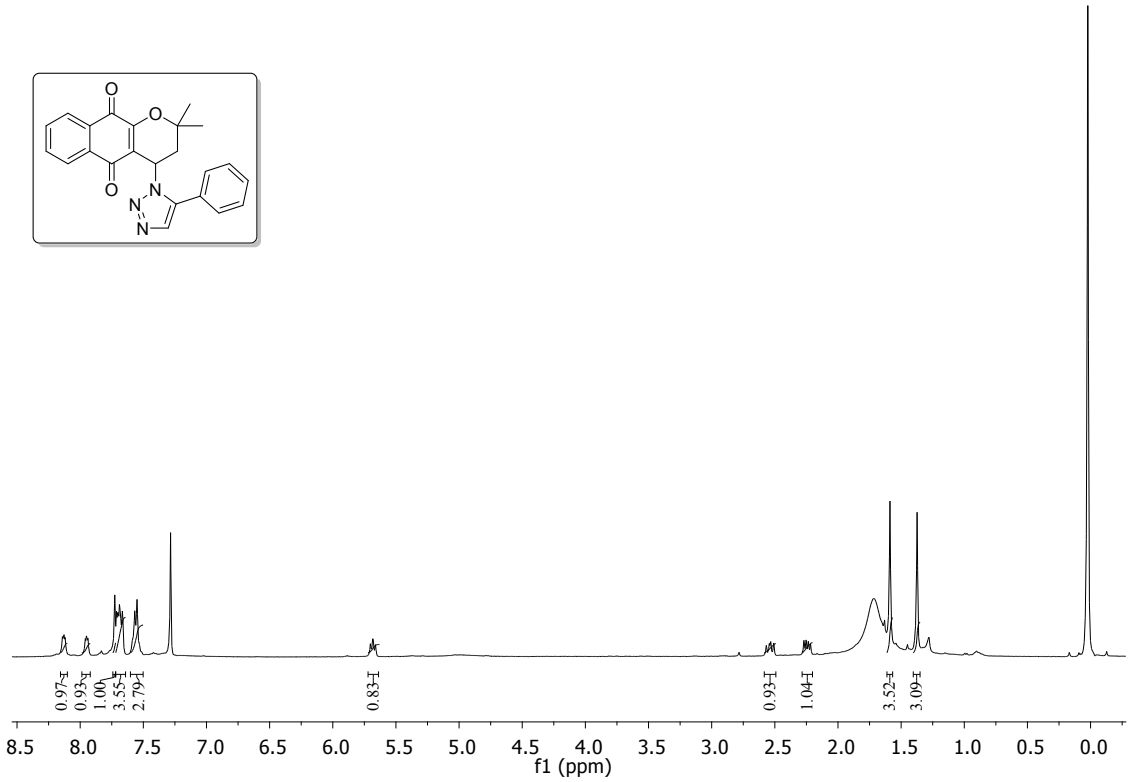


Figure S9: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **17**.

Compound **18**

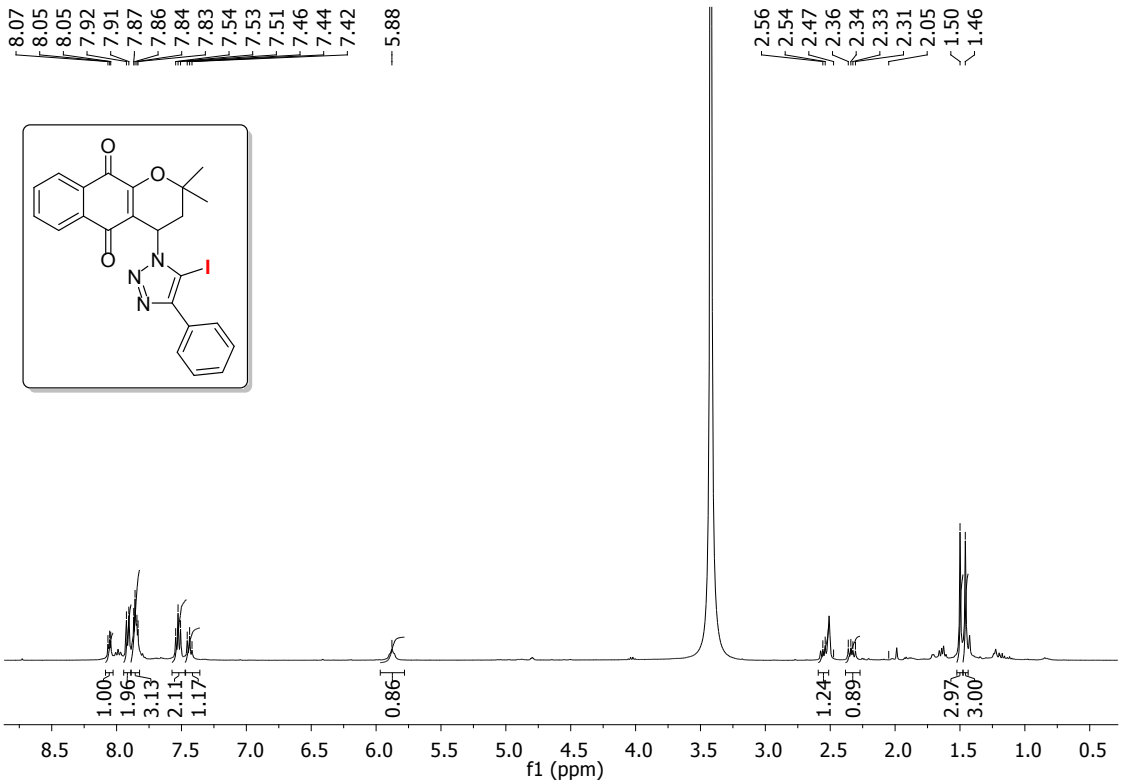


Figure S10: ^{1}H NMR spectrum (200 MHz, DMSO-d_6) of compound **18**.

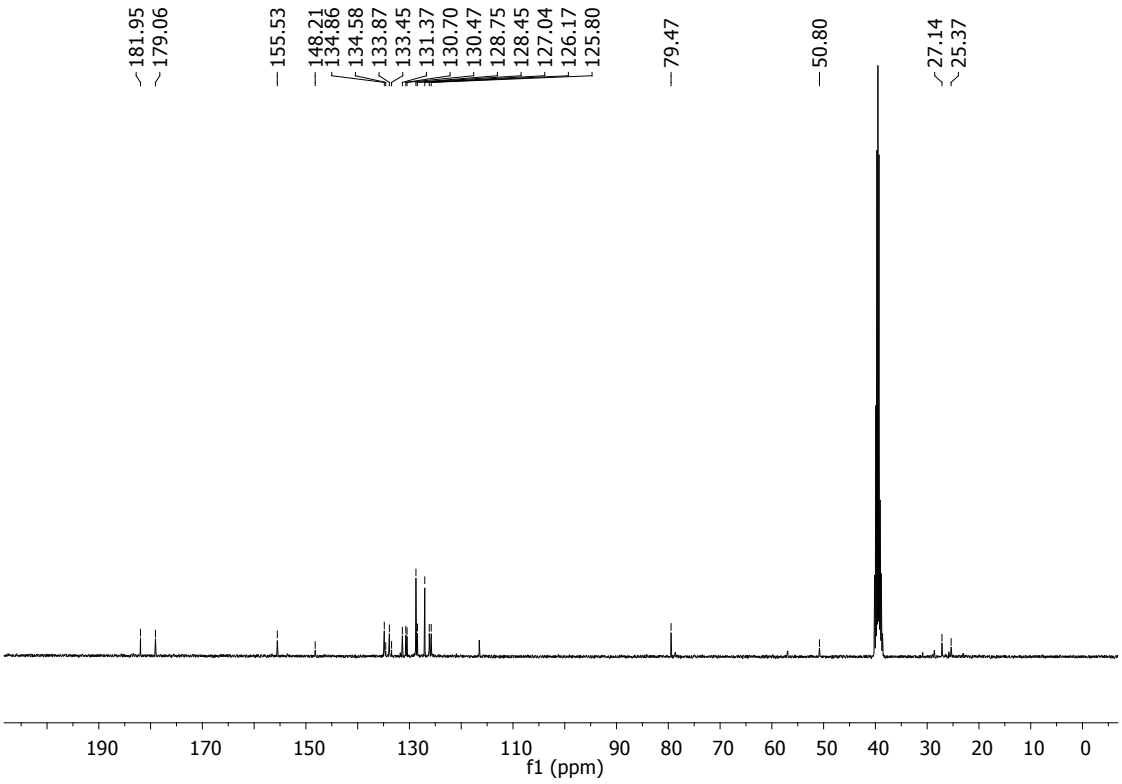


Figure S11: ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of compound **18**.

Compound **19**

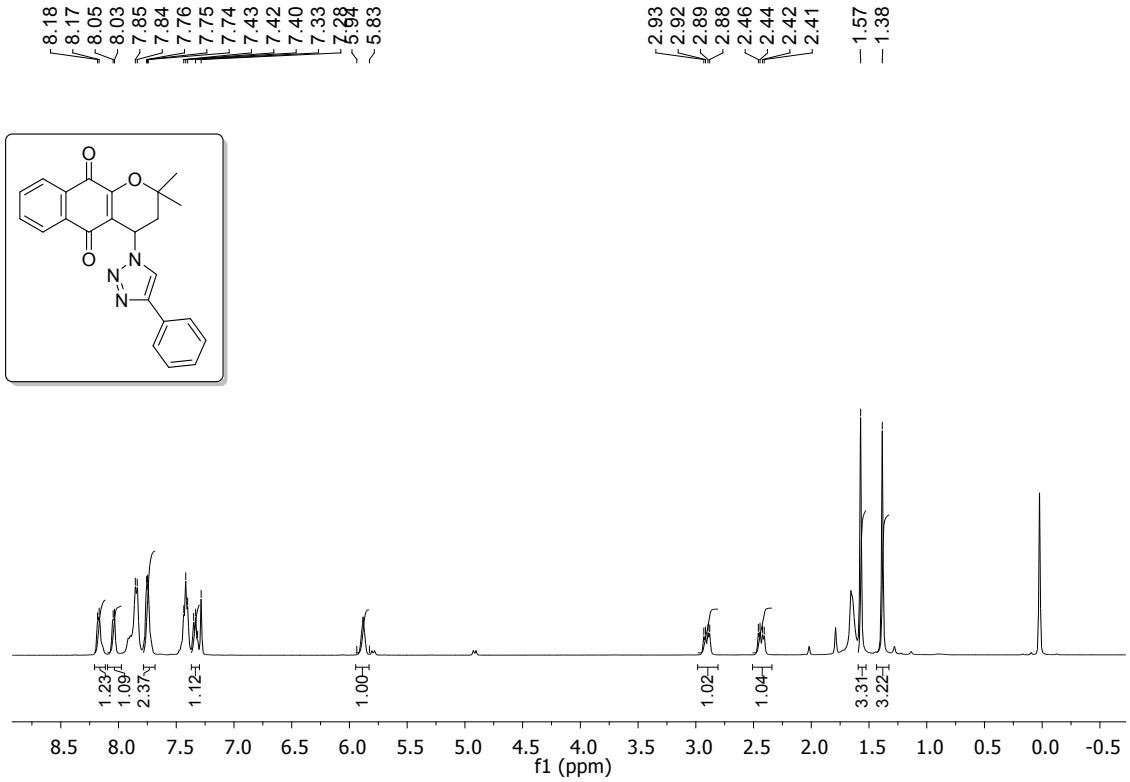


Figure S12: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **19**.

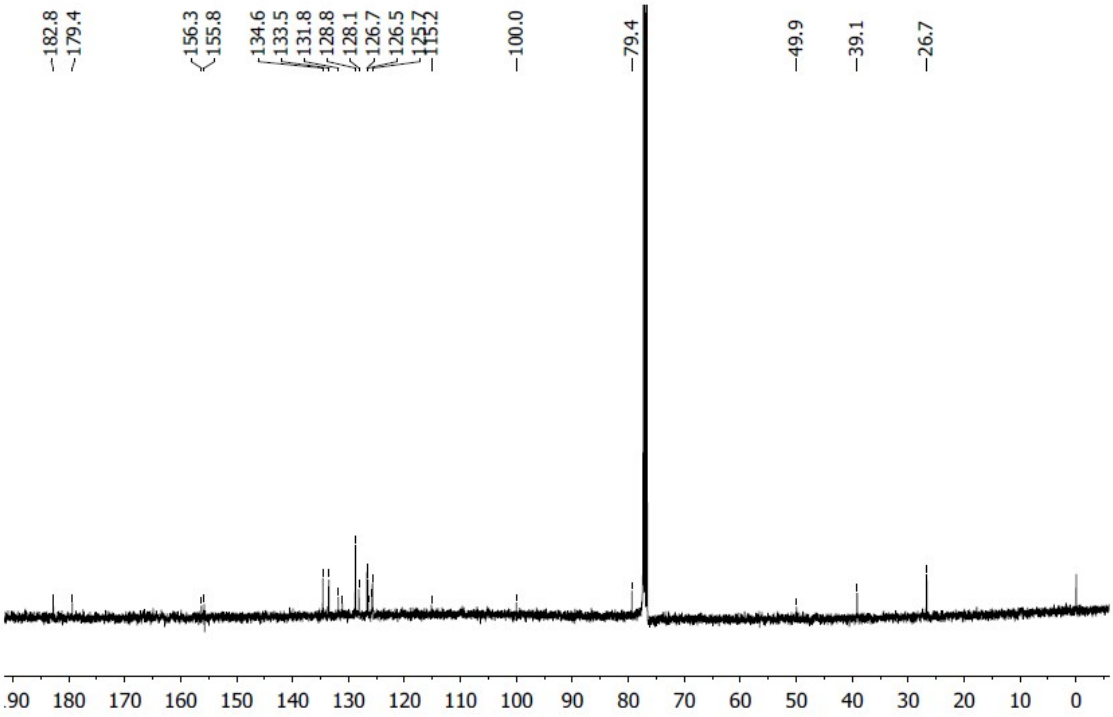


Figure S13: ^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **19**.

Compound **23**

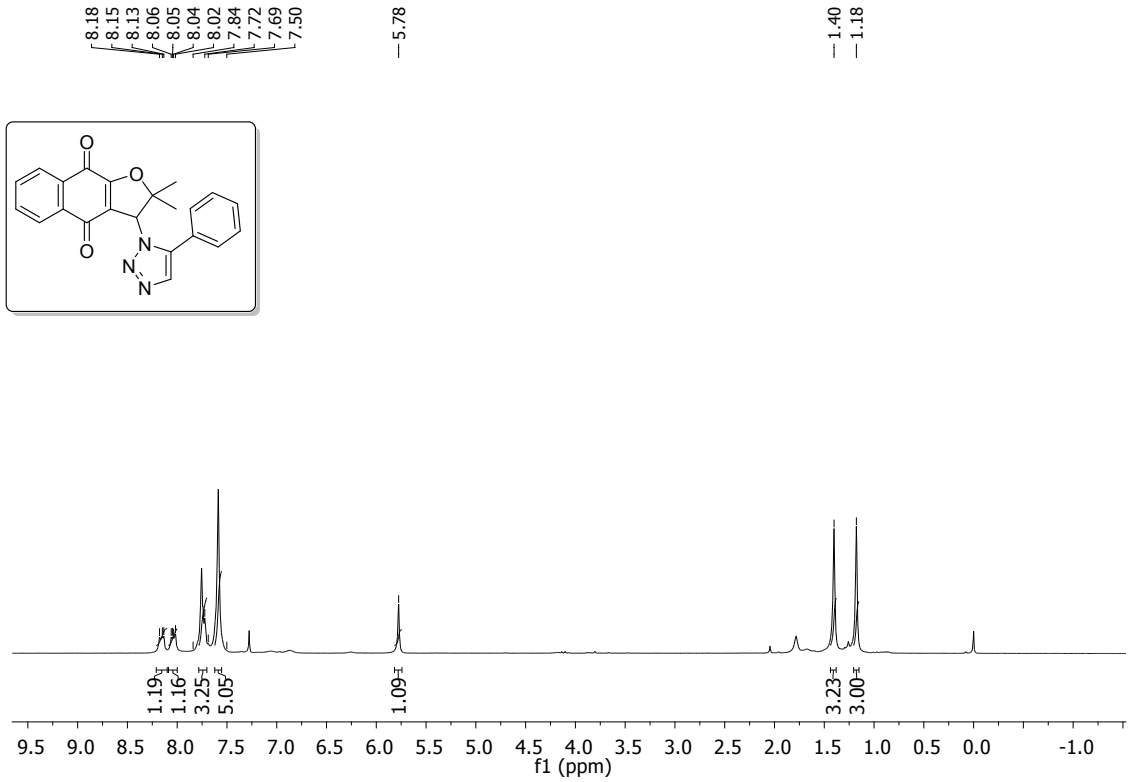


Figure S14: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **23**.

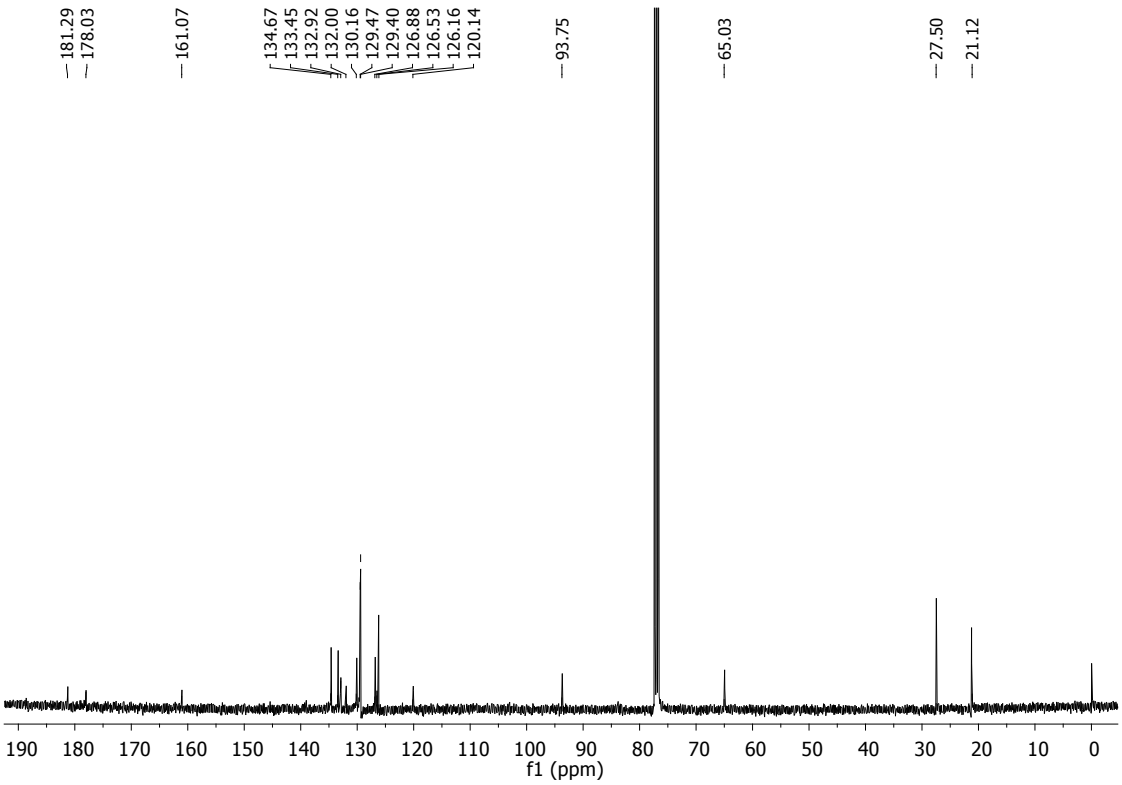


Figure S15: ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **23**.

Compound **24**

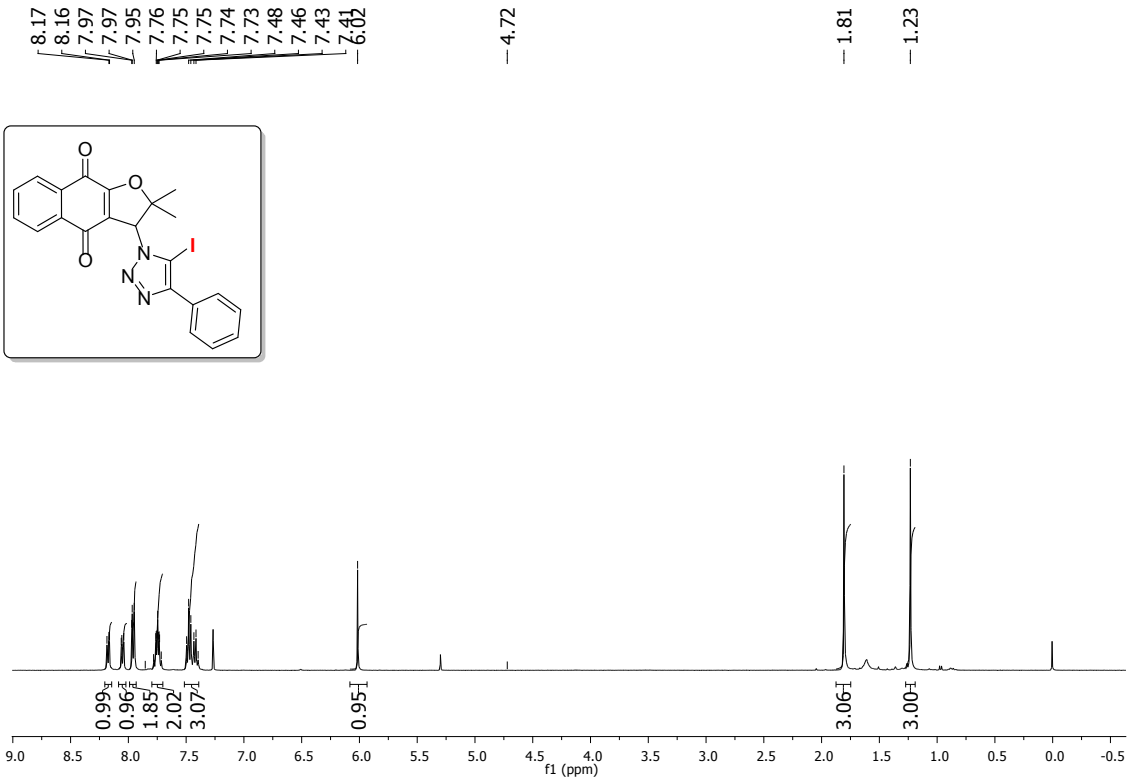


Figure S16: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **24**.

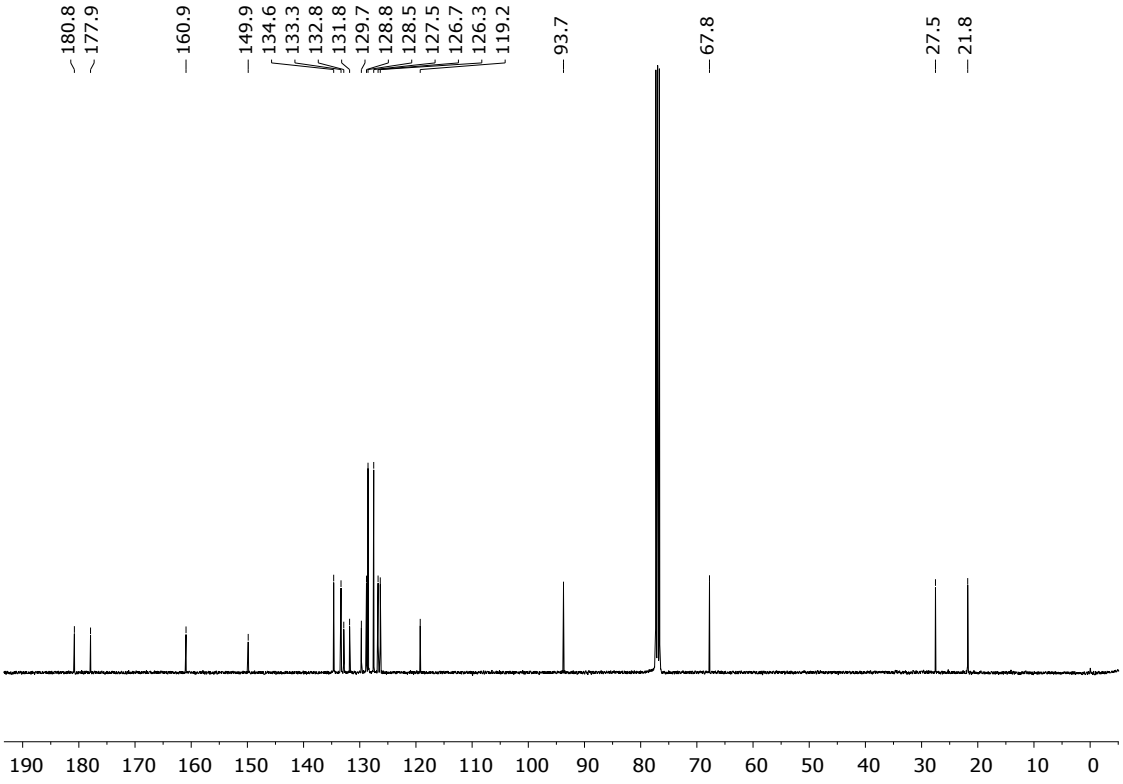


Figure S17: ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **24**.

Compound **30**

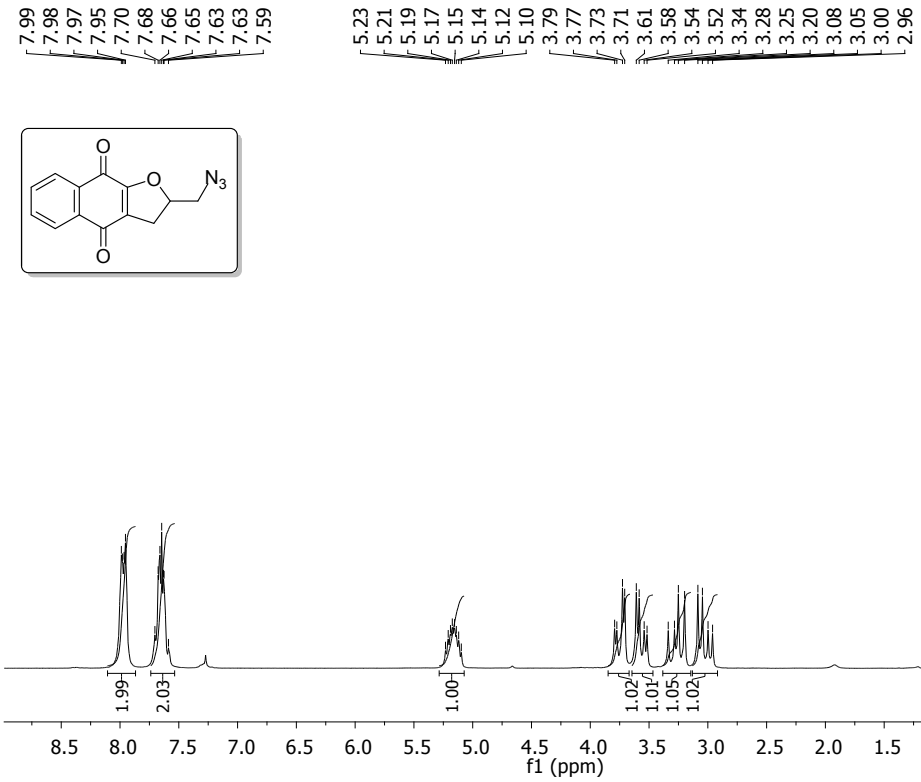


Figure S18: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **30**.

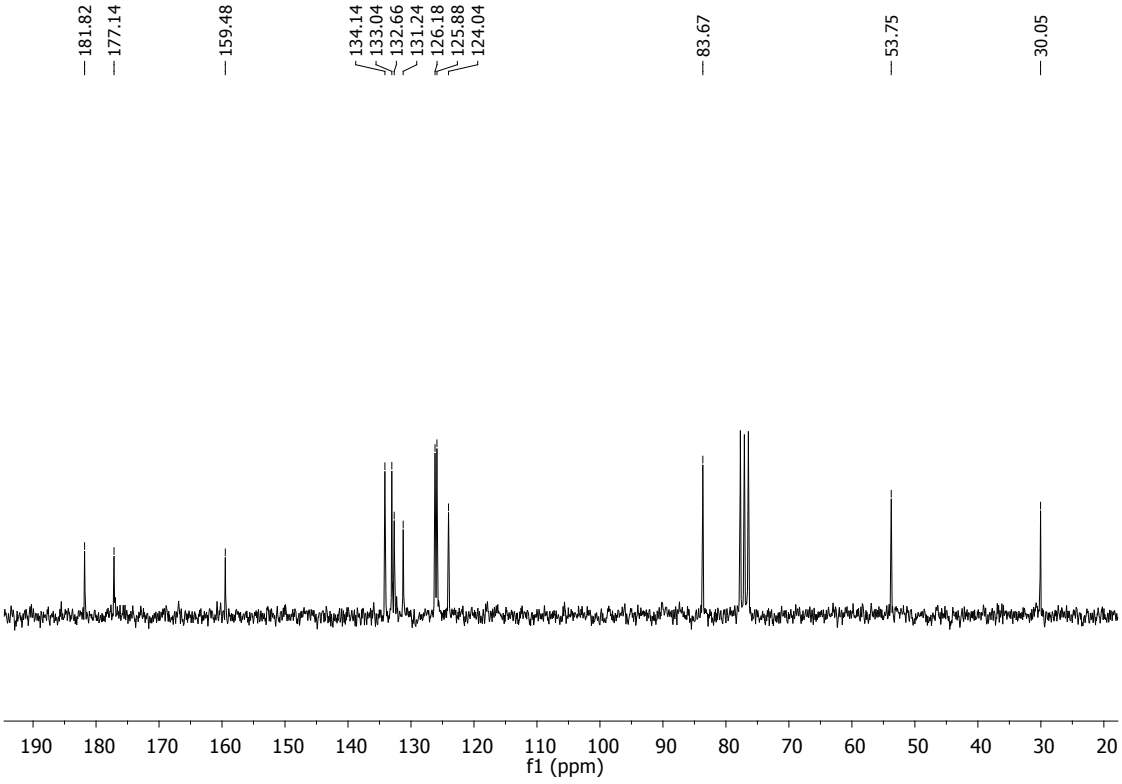


Figure S19: ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **30**.

Compound **31**

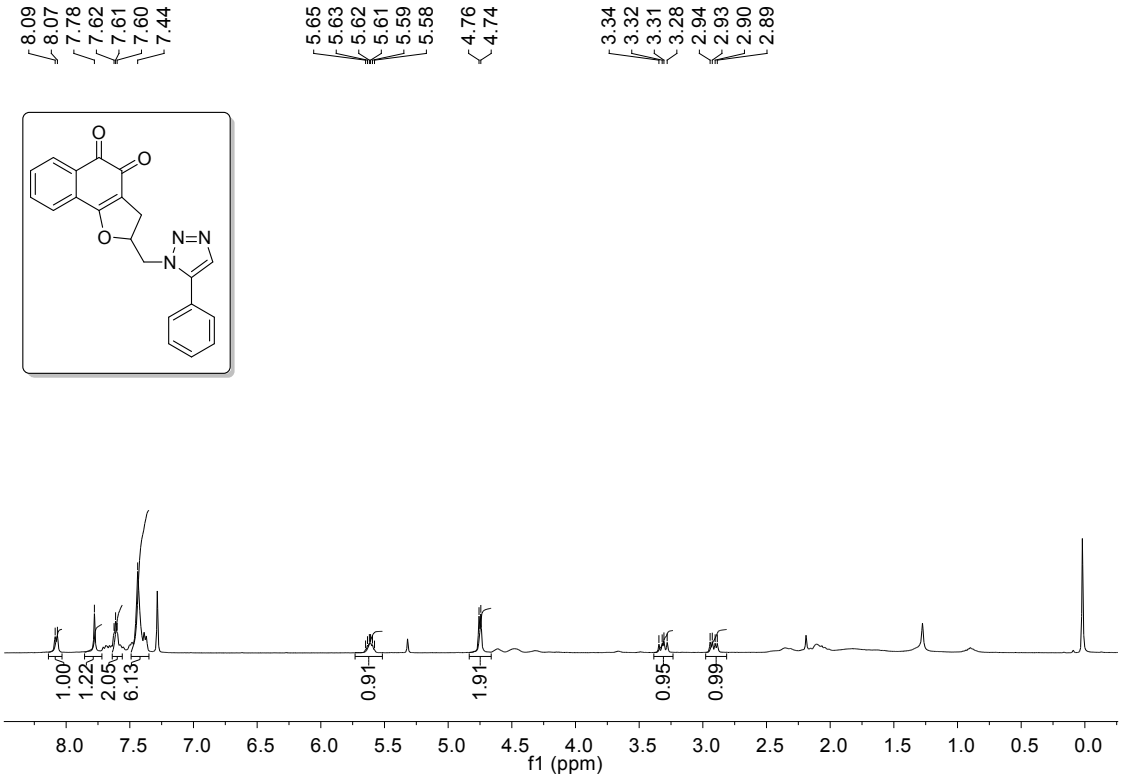


Figure S20: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **31**.

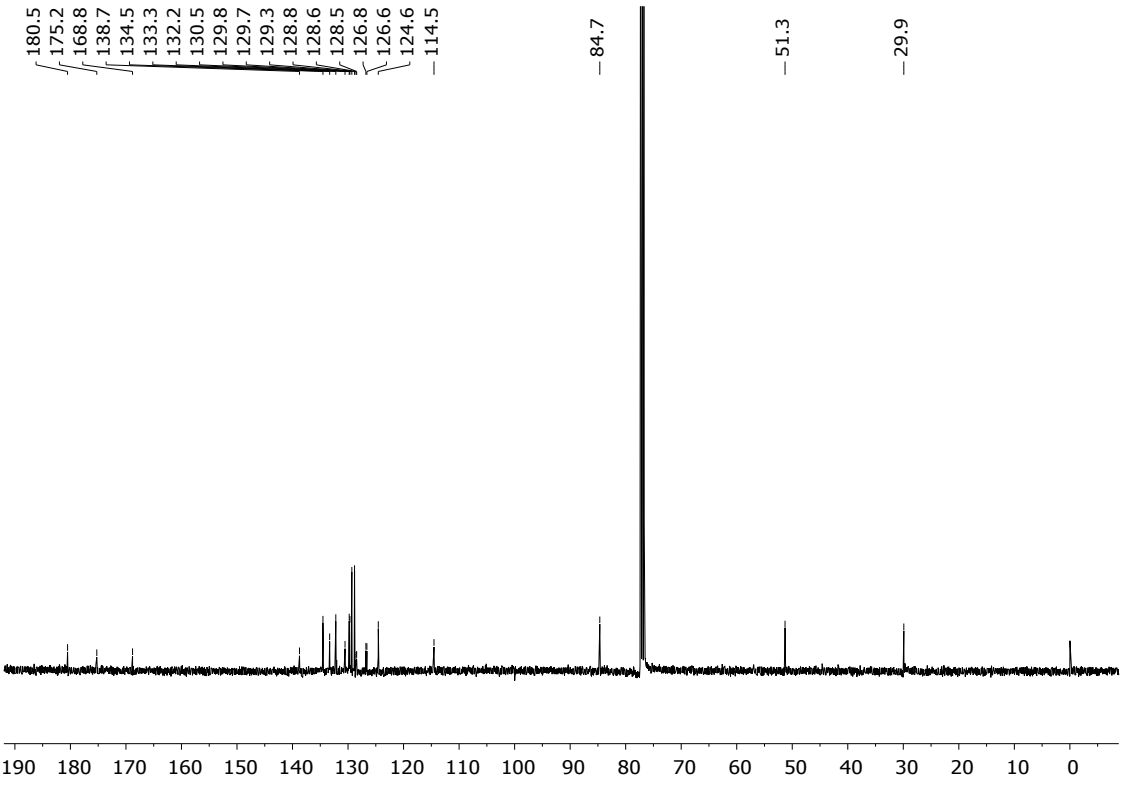


Figure S21: ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **31**.

Compound **32**

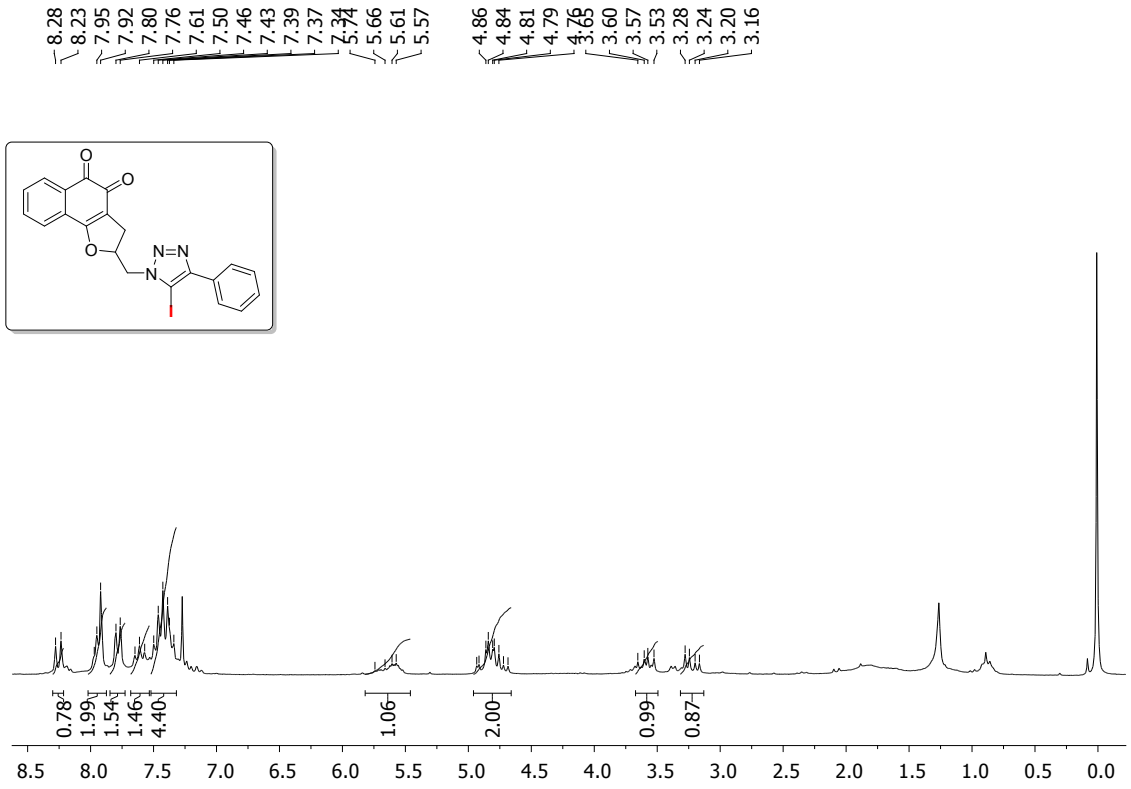


Figure S22: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **32**.

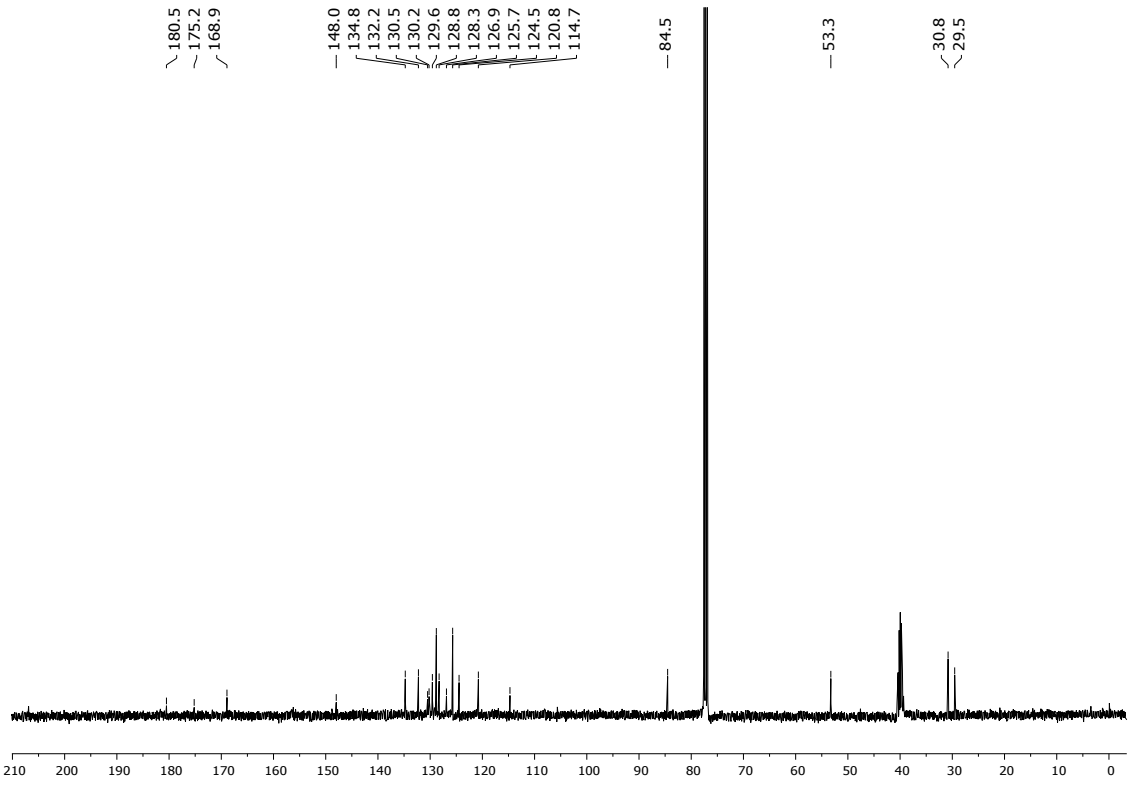


Figure S23: ^{13}C NMR spectrum (100 MHz, $CDCl_3$, DMSO-d_6) of compound **32**.

Compound **33**

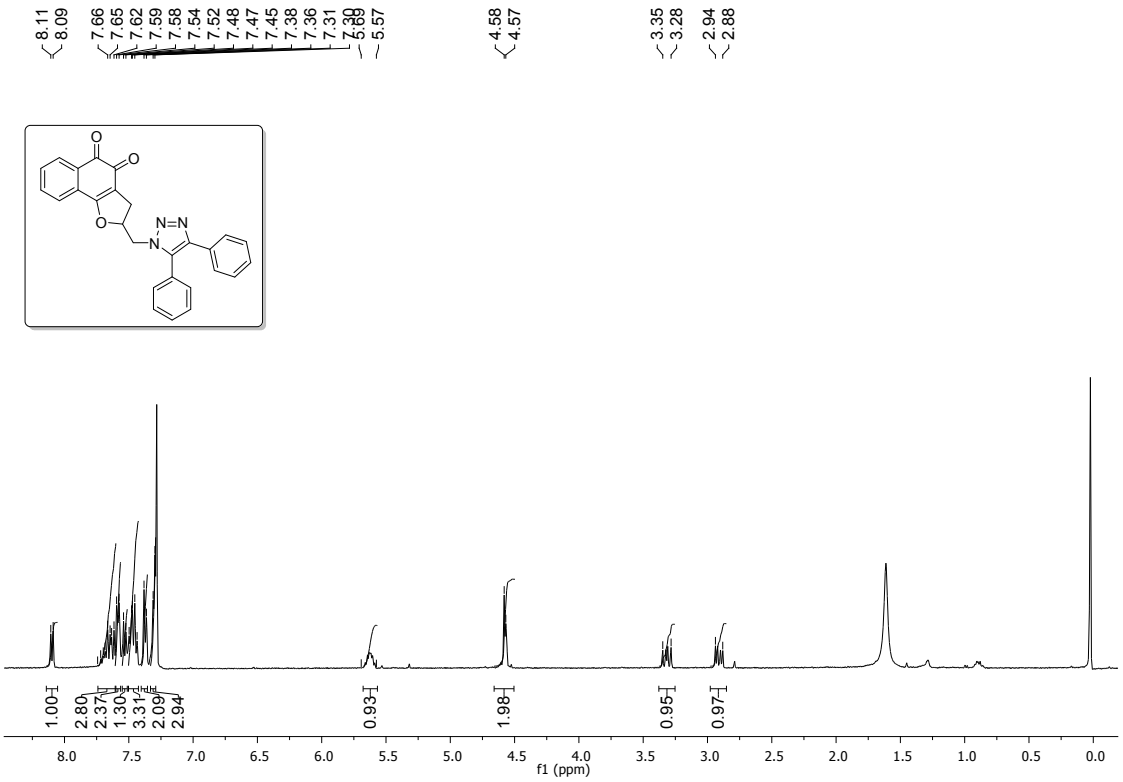


Figure S24: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **33**.

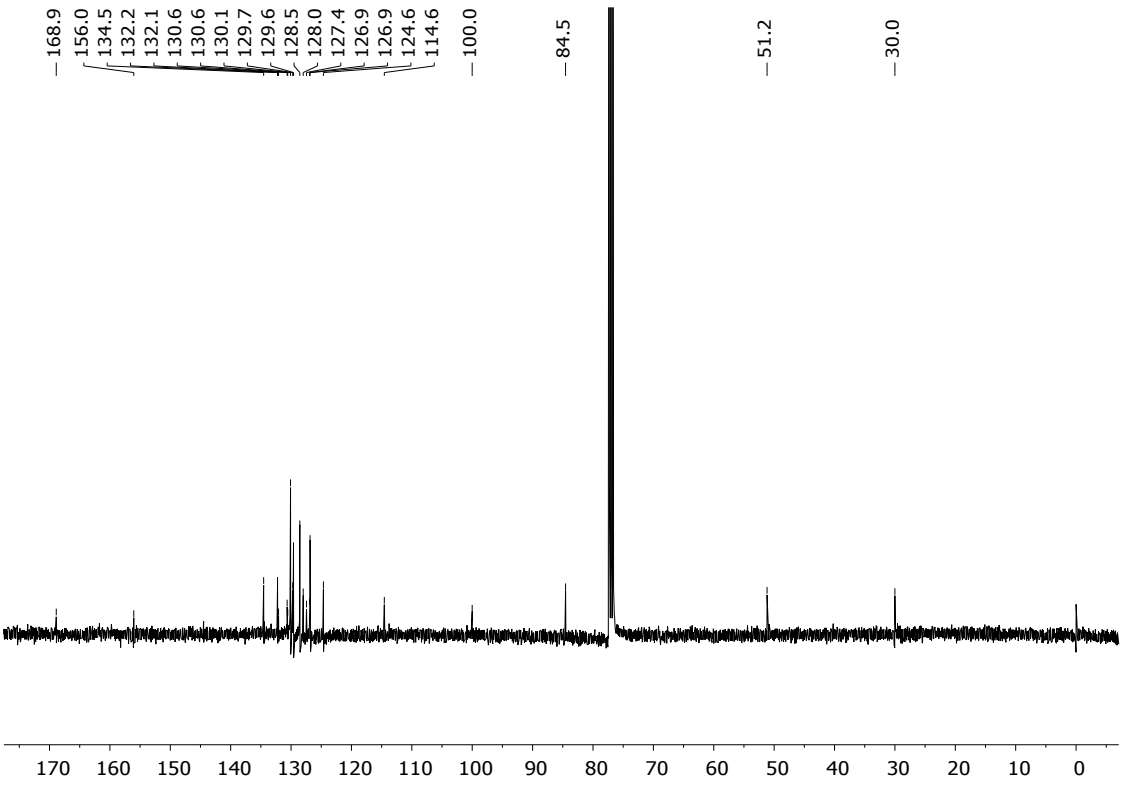


Figure S25: ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **33**.

Compound **39**

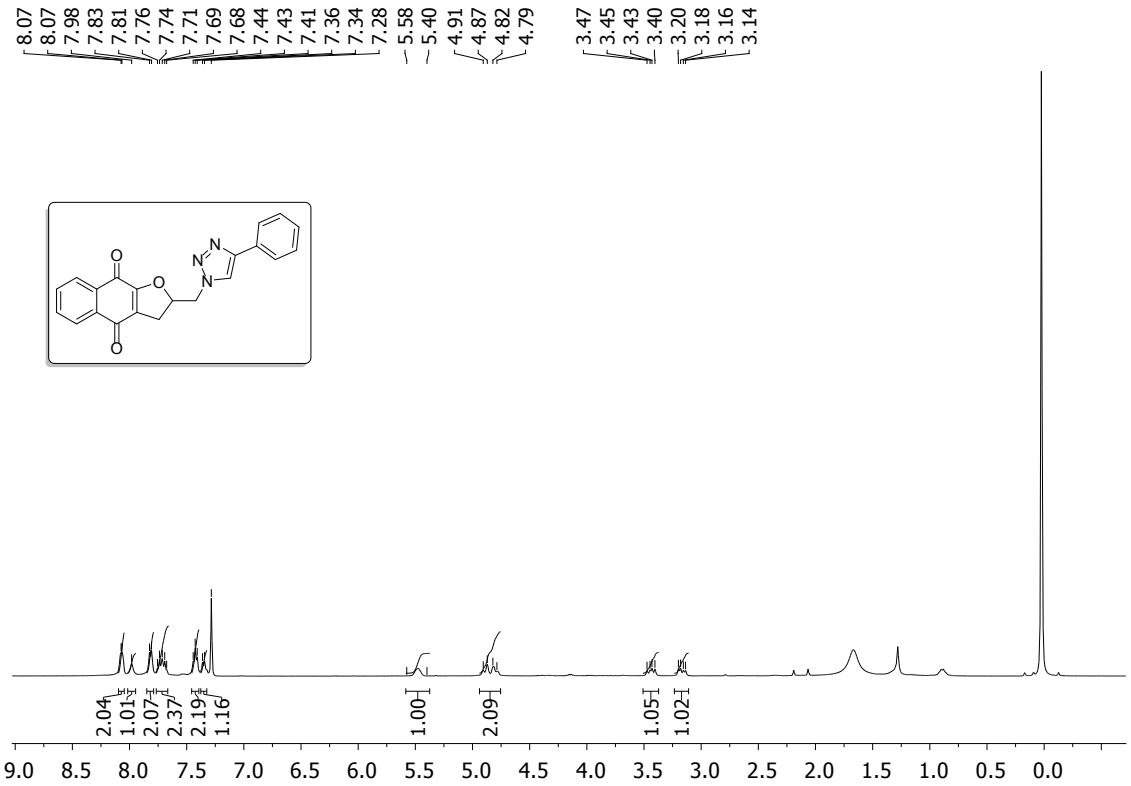


Figure S26: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **39**.

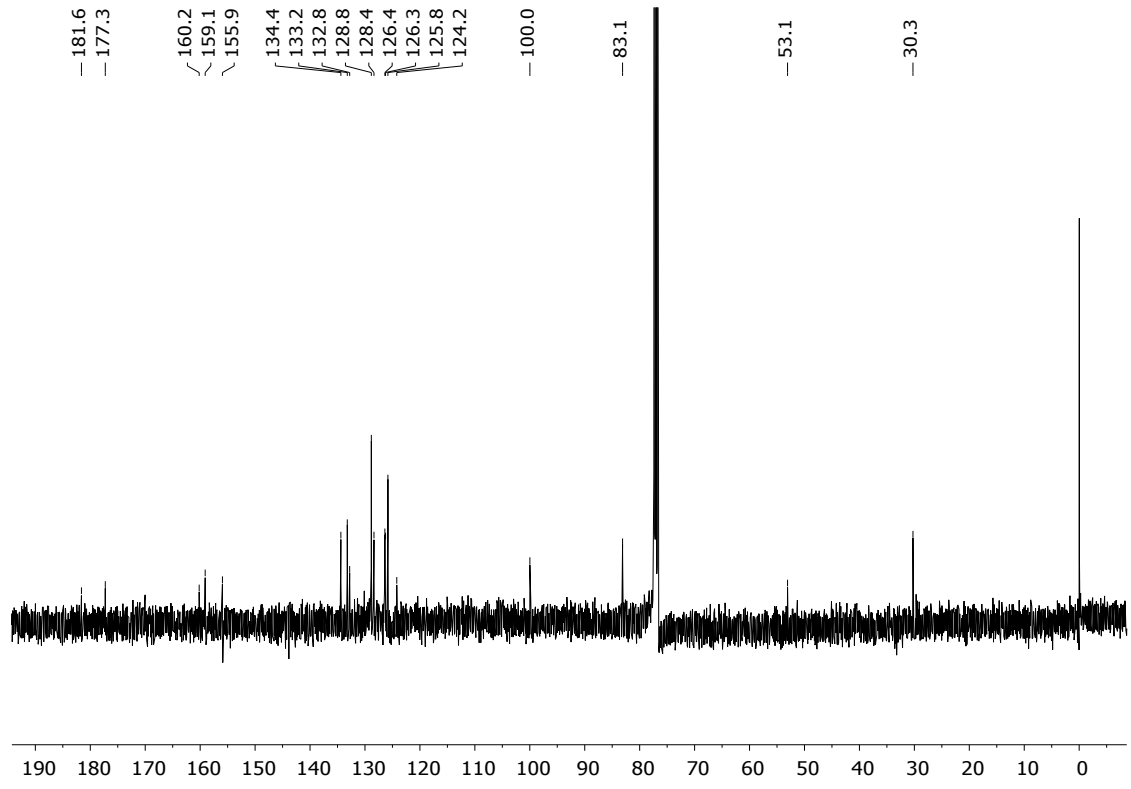


Figure S27: ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **39**.

Compound **40**

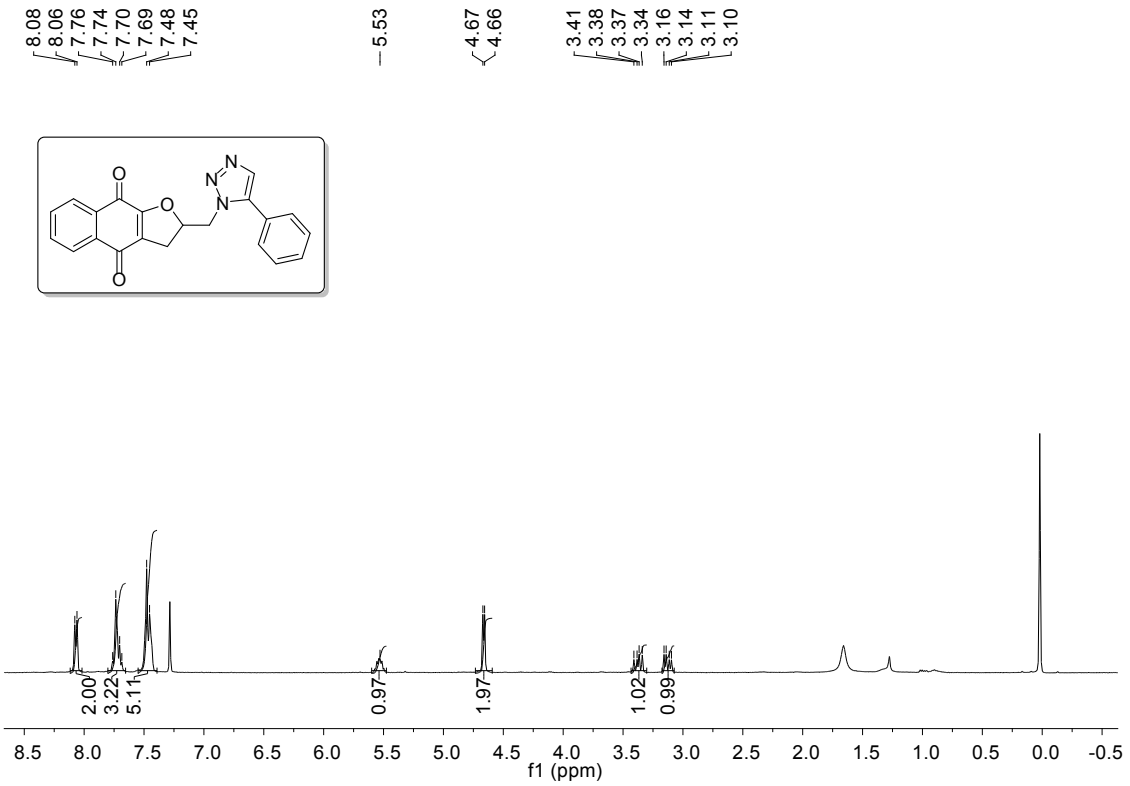


Figure S28: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **40**.

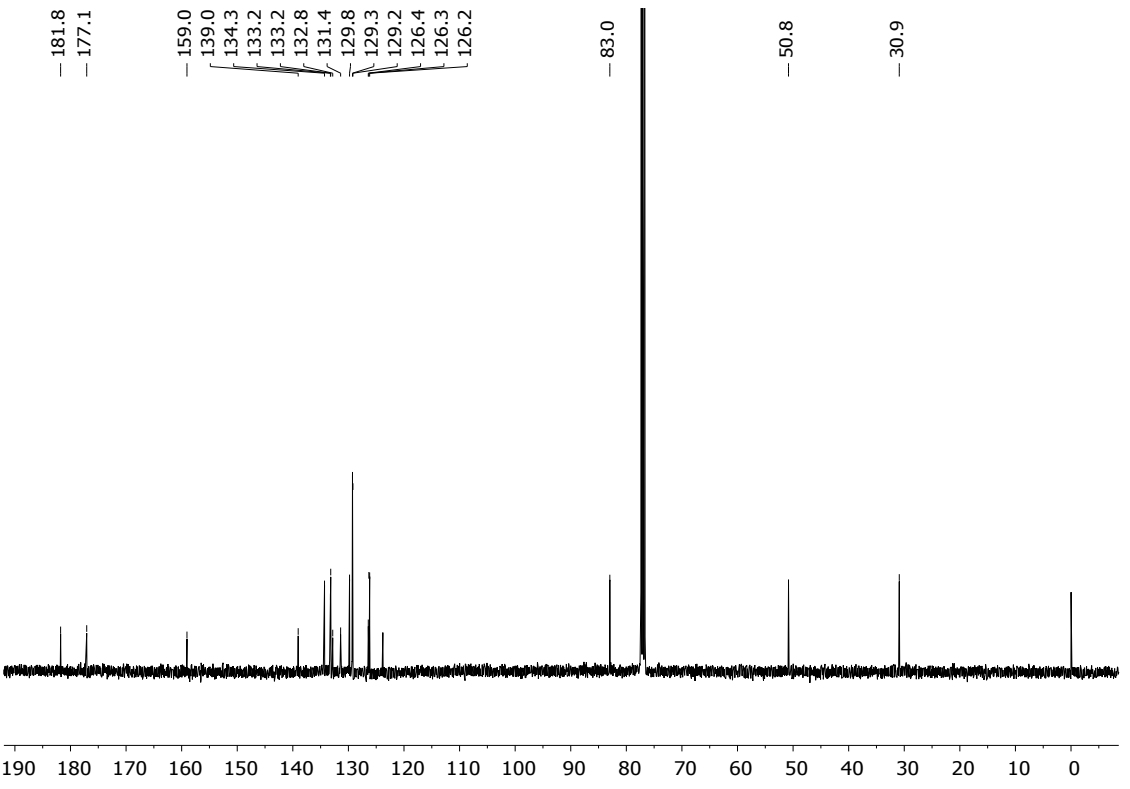


Figure S29: ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **40**.

Compound **41**

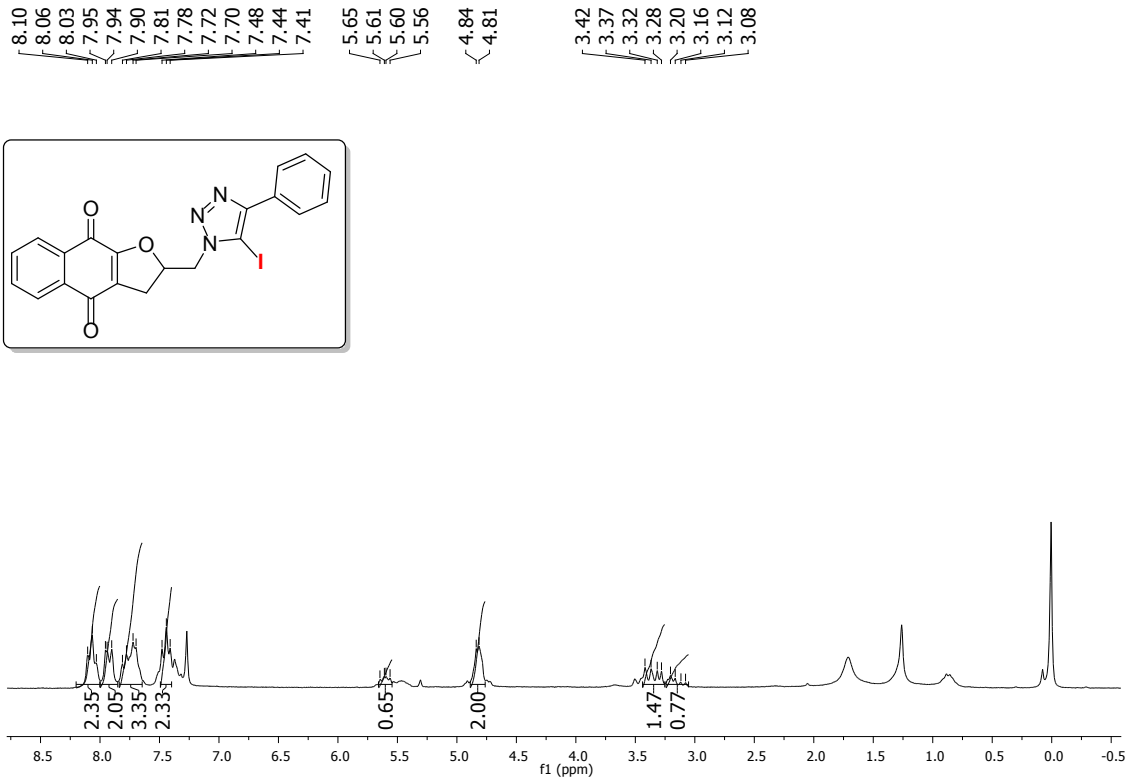


Figure S30: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **41**.

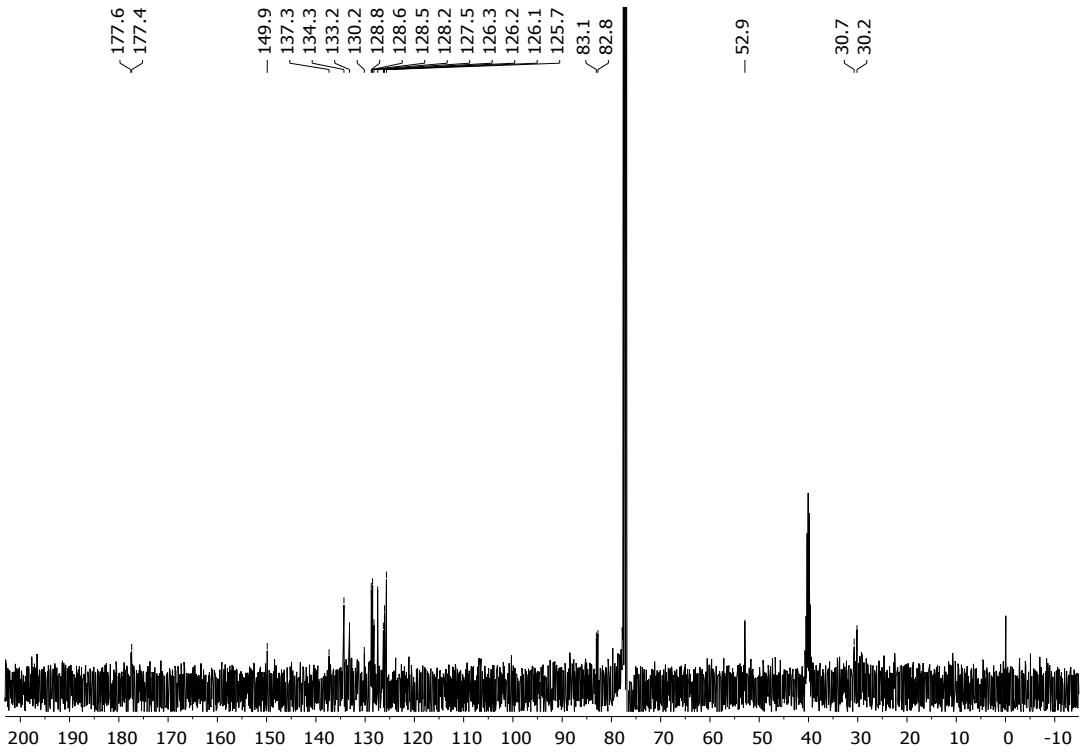


Figure S31: ^{13}C NMR (100 MHz, $CDCl_3$, DMSO-d_6) spectra of compound **41**.

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