Supporting Information

Synthesis and Structure–Activity Analysis of New Phosphonium Salts with Potent Activity against African Trypanosomes

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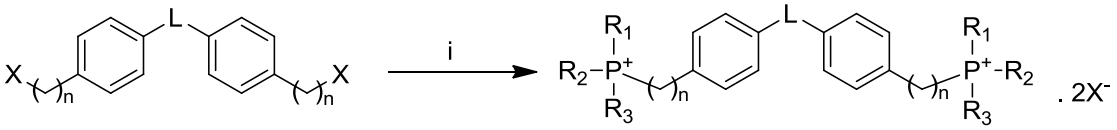
Chemistry. All dry solvents were purchased from Aldrich or Fluka in Sure/Seal bottles. All reactions requiring anhydrous conditions or an inert atmosphere were performed under argon atmosphere. All reactions were monitored by Thin Layer Chromatography (TLC) using silica gel 60 F_{254} plates (Merck) or HPLC–MS. Chromatography was performed with Isolute SI prepacked columns. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 300 or Varian Inova 400 spectromether. Chemical shifts of the ^{1}H NMR spectra were internally referenced to the residual proton resonance of the deuterated solvents: $CDCl_3$ (δ 7.26 ppm), D_2O (δ 4.6 ppm), CD_3OD (δ 3.49 ppm) and DMSO (δ 2.49 ppm). *J* values are given in Hz. Melting points were determined in open capillary tubes with a SMP3–Stuart Scientific apparatus or Mettler Toledo MP70 melting point system, and are uncorrected. All compounds are >95% pure by HPLC or combustion analysis otherwise noted. Elemental analysis was performed on a Heraeus CHN–O Rapid analyser. Analytical results were within ± 0.4 % of the theoretical values unless otherwise noted. Analytical HPLC–MS was run with an Xbridge C18–3.5 μm (2.1×100mm) column on a Waters 2695 separation module coupled with a Waters Micromass ZQ spectromether using electrospray ionization (ESI^+). The following HPLC conditions were used: column temperature = 30 ºC, gradient time = 5 min, H_2O/CH_3CN (10:90 → 90:10) (HCO_2H 0.1 %), flow rate = 0.25 mL/min, UV detection: diode array (λ = 190−400 nm). Semi-preparative HPLC-MS was run with a SunFire Prep C18 – 5 μm (19 × 150 mm) column on a Waters separation module (Waters 2545/SFO/2767) coupled to a Waters 3100 Mass Detector using ESI^+. The fractions were collected with a Waters 2767 Sampler Manager.

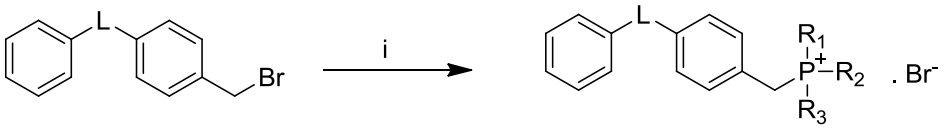
Scheme 1.[a] Synthesis of the Phosphonium Salt Derivatives[b]



n = 1, X = Br: **1a**, **1b**, **1c**, **1d**, **1e, 10f, 11g**
n = 1, X = Cl: **3a, 12f, 13g**
n = 2, X = Cl: **16f**, **17g**

18a-32a, **35a-45a**, **47a-50a**, **53a**, **19b-c**, **23b-e**, **25b-c**, **28b-c**, **28f-g**, **33b-c**, **34b-c**, **38b-c**, **43b-c**, **44b-c**, **45b-g**, **46b-c**, **51b-c**, **52b-c**, **53b-c**

L = CO (**a**), CH_2 (**b**), O (**c**), SO_2 (**d**), NAc (**e**), $(CH_2)_2$ (**f**), $(CH_2)_3$ (**g**)



2a, **2c**

56a, 56c, 57a, 57c, 58a-63a

[a] Reagents and conditions. (i) $R_1R_2R_3P$ (excess), DMF or toluene, Δ. [b] See Tables 1–4 for substituents pattern.

1. General procedure for the synthesis of the bisphosphonium salts. A Kimax tube was charged with the appropriate bis-halogenated precursor (100 mg, ~0.28 mmol) and flushed with argon. Anhydrous DMF (3 mL) was added followed by the phosphine (1.12 mmol, 4 equiv). The tube was flushed with argon, stopped, and the reaction mixture was stirred at 100 °C for 20 h. A higher temperature (150 ºC) and longer reaction time were necessary with the 4,4'-bischloroethyl linkers **16f** and **17g**. Different workup procedures were used depending on whether the product precipitated from the reaction mixture or not. Workup I: the reaction was allowed to cool to room temperature and the precipitated product was collected by filtration, rinsed successively with toluene and Et_2O, and dried under vacuum. Workup II: the reaction mixture was transferred to a flask. Then, toluene (10–20 mL) was added to precipitate the product. The flask was

stored in the fridge overnight. The supernatant was removed and the precipitate was rinsed with toluene. Et_2O (10 mL) was added and the precipitate was triturated with a spatula. The solid was collected, rinsed with Et_2O and dried under vacuum.

4,4'-bis((triethylphosphonio)methyl)diphenylether dibromide (19c). The reaction was carried out toluene following the general procedure with triethylphosphine and **1c**. The product was obtained as a white hygroscopic solid (105 mg, 61%) following workup I procedure and recrystallization in DMF/Toluene. HPLC = 94% pure; mp 221–224 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.7, 4H, Ar*H*), 6.89 (d, *J* = 7.7, 4H, Ar*H*), 4.04 (d, *J* = 14.8, 4H, P*CH*$_2$), 2.35 (dq, *J* = 14.7, 7.4, 12H, *CH*$_2$CH$_3$), 1.21 (dt, *J* = 17.6, 7.4, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8 (d, *J* = 3.6), 131.9 (d, *J* = 4.9), 123.2 (d, *J* = 8.7), 119.9 (d, *J* = 2.8), 25.3 (d, *J* = 45.4), 12.0 (d, *J* = 48.3), 5.9 (d, *J* = 5.5). LRMS (ES$^+$) m/z = 431.44 [(M-H)]$^+$, 215.92 [M^{2+}, 100%]. Anal. ($C_{26}H_{44}Br_2P_2O$) Calc: C, 52.72; H, 7.15; Br, 26.98. Found: C, 52.53; H, 7.18; Br, 26.40.

4,4'-bis((triisobutylphosphonio)methyl)diphenylmethane dibromide (23b). The reaction was carried out following the general procedure with triisobutylphosphine and **1b**. The product was obtained as a white solid (146 mg, 69%) following workup II procedure; mp 224 ºC with previous softening (DMF/toluene); HPLC > 95% pure; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 8.1, 2.3, 4H, Ar*H*), 7.07 (d, *J* = 7.0, 4H, Ar*H*), 4.28 (d, *J* = 14.7, 4H, P*CH*$_2$), 3.88 (s, 2H, Ph*CH*$_2$Ph), 2.35 (dd, *J* = 13.0, 6.4, 12H, *CH*$_2$), 2.20 – 2.04 (m, 6H, *CH*), 1.09 (dd, *J* = 6.6, 0.5, 36H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0 (dd, *J* = 3.7, 1.1), 130.9 (d, *J* = 5.1), 129.9 (d, *J* = 3.0), 126.5 (d, *J* = 8.8), 41.1 (s), 29.1 (d, *J* = 42.7), 28.3 (d, *J* = 44.3), 25.1 (d, *J* = 8.5), 23.8 (d, *J* = 4.7). LRMS (ES$^+$) *m/z* 597.58 [(M-H)$^+$], 298.98 [M^{2+}, 100%].

4,4'-bis((triisobutylphosphonio)methyl)diphenylether dibromide (23c). The reaction was carried out following the general procedure with triisobutylphosphine and **1c**. The product was obtained as a white solid (156 mg, 64%) following workup II procedure; mp 222–223 ºC with previous softening (DMF/toluene); HPLC > 94% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.3, 2.0, 4H, Ar*H*), 6.85 (d, *J* = 8.3, 4H, Ar*H*), 4.42 (d, *J* = 14.7, 4H, P*CH*$_2$), 2.35 (dt, *J* = 29.4, 14.7, 12H, *CH*$_2$), 2.19 (qd, *J* = 12.6, 6.4, 6H, *CH*), 1.11 (d, *J* = 6.4, 36H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7 (d, *J* = 3.7), 132.5 (d, *J* = 4.9), 123.8 (d, *J* = 8.8), 119.5 (d, *J* = 2.6), 29.4, 28.9, 27.9 (d, *J* = 44.5) 25.2 (d, *J* = 8.5), 23.8 (d, *J* = 4.7). LRMS (ES^+) *m/z* 599.61 [$(M-H)^+$], 299.89 [M^{2+}, 100%].

4,4'-bis((triisobutylphosphonio)methyl)diphenylsulphone dibromide (23d). The reaction was carried out following the general procedure at 100 °C with triisobutylphosphine and **1d**. The product was obtained as a white solid (50.9 mg, 85%) following workup II procedure; mp 74–75 ºC; HPLC = 94% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 – 7.60 (m, 8H, Ar*H*), 4.64 (d, *J* = 11.1, 4H, P*CH*$_2$), 2.46 – 2.29 (m, 12H, *CH*$_2$), 2.26 – 2.11 (m, 6H, *CH*), 1.11 (br s, 36H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1 (d , *J* = 3.1), 135.6 (d, *J* = 8.8), 132.7 – 132.5 (m), 128.7, 29.7 (d, *J* = 42.3), 25.5 (d, *J* = 8.4), 24.9 (d, *J* = 8.6), 23.9 (d, *J* = 4.3). LRMS (ES^+) *m/z* 647.63 [$(M-H)^+$], 324.04 [M^{2+}, 100%].

4,4'-bis((triisobutylphosphonio)methyl)diphenylacetamide dibromide (23e). The reaction was carried out following the general procedure at 100 °C with triisobutylphosphine and **1e**. The product was obtained as a yellow/white oily solid (30.3 mg, 30%) following workup II procedure; HPLC > 80% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.47 (m, 4H, Ar*H*), 7.24 – 7.11 (m, 4H, Ar*H*), 4.41 (br s, 4H, P*CH*$_2$), 2.36 (br s, 12H, *CH*$_2$), 2.19 (br s, 6H, *CH*), 2.00 (s, 3H, CO*CH*$_3$), 1.10 (br s,

36H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 142.8 (d, *J* = 2.1), 132.7 – 131.9 (m), 128.7 (d, *J* = 61.1), 125.4, 29.5 (d, *J* = 42.8), 28.5 (d, *J* = 43.6), 25.3 (d, *J* = 8.5), 24.2, 23.9 (d, *J* = 4.5). LRMS (ES^+) *m/z* 640.70 [$(M-H)^+$], 320.47 [M^{2+}, 100%].

4,4'-bis((trihexylphosphonio)methyl)diphenylether dibromide (25c). The reaction was carried out following the general procedure with trihexylphosphine and **1c**. The reaction was concentrated to ca. 1 mL to give a yellowish oil that was diluted with toluene (5 mL). Addition of Et_2O (10 mL) caused precipitation of an oily residue. The flask was stored in the fridge overnight. The supernatant was removed and the oily precipitate was rinsed with toluene. Et_2O (10 mL) was added to the oily precipitate, which was triturated with a spatula to give the product as a yellowish solid. Recrystallization from EtOH/Et_2O yielded **25c** as an off-white solid (73.7 mg, 32%); mp 137 ºC with previous softening (DMF/EtOH); HPLC > 95% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7, 4H, Ar*H*), 6.87 (d, *J* = 7.7, 4H, Ar*H*), 4.37 (d, *J* = 15.0, 4H, P*CH*$_2$), 2.37 (br s, 12H, P*CH*$_2$$CH_2$), 1.49 – 1.23 (m, 48H, *CH*$_2$), 0.87 (br s, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7 (d, *J* = 3.7) , 132.0 (d, *J* = 4.8), 123.7 (d, *J* = 8.8), 119.6 (d, *J* = 2.4), 31.2, 30.6 (d, *J* = 14.6), 26.4 (d, *J* = 45.4), 22.5, 22.0 (d, *J* = 4.7), 19.2 (d, *J* = 46.3), 14.0. LRMS (ES^+) *m/z* 767.83 [$(M-H)^+$], 384.09 [M^{2+}, 100%].

4,4'-bis((dimethylphenylphosphonio)methyl)diphenylmethane dibromide (28b). The reaction was carried out following the generalprocedure with dimethylphenylphosphine and **1b**. The product was obtained as a white hygroscopic solid (185 mg, 95%) following workup II procedure; mp >300 ºC with previous softening (DMF/toluene); HPLC > 95% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.47 (m, 10 H, Ar*H*), 6.97 (dd, *J* = 10.8, 8.2, 4H, Ar*H*), 6.89 (d, *J* = 8.2, 4H, Ar*H*), 4.18 (d, *J* = 15.4, 4H, P*CH*$_2$), 3.73 (s, 2H, Ph*CH*$_2$Ph), 2.26 (d, *J* = 13.8, 12H, *CH*$_3$). ^{13}C NMR

(75 MHz, $CDCl_3$) δ 140.9 (d, *J* = 4.1), 134.6 (d, *J* = 2.9), 131.6 (d, *J* = 9.7), 130.4 (d, *J* = 5.4), 129.9 (d, *J* = 12.3), 129.6 (d, *J* = 3.5), 125.7 (d, *J* = 9.1), 119.6 (d, *J* = 83.8), 40.9, 30.9, 7.2 (d, *J* = 55.7). LRMS (ES^+) *m/z* 469.41 [$(M-H)^+$], 234.81 [M^{2+}, 100%].

4,4'-bis((dimethylphenylphosphonio)methyl)diphenylether dibromide (28c). The reaction was carried out following the general procedure with dimethylphenylphosphine and **1c**. The product was obtained as a hygroscopic oily solid after workup II. Recrystallization from EtOH/Et_2O yielded a hygroscopic off-white solid (71.7 mg, 41%); mp 112–114 ºC (decomp) with previous softening (DMF/EtOH); HPLC > 95% pure; ^1H NMR (300 MHz, CD_3OD) δ 7.93 – 7.79 (m, 6H, Ar*H*), 7.77 – 7.53 (m, 4H, Ar*H*), 7.15 (dd, *J* = 8.5, 2.7, 4H, Ar*H*), 6.96 (d, *J* = 8.5, 4H, Ar*H*), 4.05 (d, *J* = 15.3, 4H, P*CH*$_2$), 2.27 (d, *J* = 14.1, 12H, *CH*$_3$). ^{13}C NMR (75 MHz, CD_3OD) δ 158.4 (d, *J* = 3.9), 135.7 (d, *J* = 2.9), 133.0 – 132.8 (m), 131.0 (d, *J* = 12.4), 124.5 (dd, *J* = 8.9, 2.7), 121.7, 120.6 (d, *J* = 3.3), 31.9 (d, *J* = 48.8), 6.80 (d, *J* = 56.0), 6.78 (d, *J* = 56). LRMS (ES^+) *m/z* 471.37 [$(M-H)^+$], 235.93 [M^{2+}, 100%].

4,4'-bis((diphenyl-n-propylphosphonio)methyl)diphenylmethane dibromide (33b). The reaction was carried out following the general procedure with diphenyl-n-propylphosphine and **1b**. The product was obtained as a white solid following workup II procedure (207.5 mg, 80%). HPLC > 95% pure; mp 124–125 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.55 (m, 20H, Ar*H*), 6.90 (dd, *J* = 8.2, 2.4, 4H, Ar*H*), 6.80 (d, *J* = 8.2, 4H, Ar*H*), 4.68 (d, *J* = 14.4, 4H, P*CH*$_2$), 3.70 (s, 2H, Ph*CH*$_2$Ph), 2.98 – 2.85 (m, 4H, *CH*$_2$), 1.55 – 1.39 (m, 4H, *CH*$_2$), 1.01 (td, *J* = 7.2, 1.6, 6H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9 (dd, *J* = 4.1, 1.1), 135.0 (d, *J* = 3.0), 133.6 (d, *J* = 9.2), 130.8 (d, *J* = 5.5), 130.2 (d, *J* = 12.1), 129.4 (d, *J* = 3.4), 125.2 (d, *J* = 8.5), 117.1 (d, *J* = 82.2), 41.3 – 40.2 (m), 30.0 (d, *J* = 46.1), 22.1 (d, *J* = 49.6), 15.9 (d, *J* = 4.2), 15.3 (d, *J* = 17.0). LRMS (ES^+) m/z = 649.50 $[(M-H)]^+$, 325.25 [M^{2+}, 100%].

4,4'-bis((*n*-propyldiphenylphosphonio)methyl)diphenylether dibromide (33c). The reaction was carried out following the general procedure with diphenyl-n-propylphosphine and **1c**. The product was obtained as a beige solid following workup II procedure (179.6 mg, 81%). HPLC = 91% pure; mp 170–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 11.8, 7.6, 10H, Ar*H*), 7.67 (dd, *J* = 27.6, 6.0, 10H, Ar*H*), 7.04 – 6.99 (m, 4H, Ar*H*), 6.51 (d, *J* = 8.2, 4H, Ar*H*), 4.97 (d, *J* = 14.5, 4H, P*CH*$_2$), 3.08 (dd, *J* = 15.8, 12.3, 4H, *CH*$_2$), 1.57 – 1.41 (m, 4H, *CH*$_2$), 1.03 (t, *J* = 6.8, 6H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4 (d, *J* = 4.1), 134.9 (d, *J* = 2.5), 133.9 (d, *J* = 9.2), 132.3 (d, *J* = 5.3), 130.2 (d, *J* = 12.1), 128.7 (d, *J* = 61.0), 122.6 (d, *J* = 8.6), 118.9 (d, *J* = 3.0), 117.1 (d, *J* = 82.0), 22.4 (d, *J* = 49.3), 15.9 (d, *J* = 4.1), 15.3 (d, *J* = 17.0). LRMS (ES^+) m/z = 651.48 $[(M-H)]^+$, 326.31 $[M^{2+}$, 100%]. Anal. ($C_{44}H_{46}Br_2OP_2$) Calc: C, 65.04; H, 5.71; Br, 19.67. Found: C, 64.98; H, 5.90; Br, 19.11.

4,4'-bis((diphenylisopropylphosphonio)methyl)diphenylmethane dibromide (34b). The reaction was carried out following the general procedure with diphenylisopropylphosphine and **1b**. The product was obtained as a white solid following workup I procedure and recrystallization in DMF/toluene (215 mg, 95%). HPLC > 95% pure; mp >300 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.48 (m, 20H, Ar*H*), 6.76 (dd, *J* = 8.2, 2.5, 4H, Ar*H*), 6.58 (d, *J* = 8.2, 4H, Ar*H*), 4.92 (d, *J* = 13.5, 4H, P*CH*$_2$), 4.07 (qd, *J* = 14.6, 6.9, 2H, *CH*), 3.53 (s, 2H, Ph*CH*$_2$Ph), 1.27 (dd, *J* = 18.4, 6.9, 12H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4 (dd, *J* = 3.7, 1.0), 134.9 (d, *J* = 2.6), 134.7 (d, *J* = 8.3), 130.8 (d, *J* = 5.2), 130.0 (d, *J* = 11.7), 129.1 (d, *J* = 3.1), 125.7 (d, *J* = 8.8), 115.0 (d, *J* = 80.1), 40.8 (s), 27.9 (d, *J* = 44.0), 22.3 (d, *J* = 45.9), 16.1 (d, *J* = 2.3). LRMS (ES^+) m/z = 649.50 $[(M-H)]^+$, 324.99 $[M^{2+}$, 100%]. Anal. ($C_{45}H_{48}Br_2P_2$) Calc: C, 66.68; H, 5.97; Br, 19.71. Found: C, 66.50; H, 6.04; Br, 19.28.

4,4'-bis((isopropyldiphenylphosphonio)methyl)diphenylether dibromide (34c). The reaction was carried out following the general procedure with diphenylisopropilphosphine and **1c**. The product was obtained as a white solid following workup I procedure (171.4 mg, 72%). HPLC > 95% pure; mp > 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 10.5, 8.2, 8H, Ar*H*), 7.72 (dd, *J* = 8.1, 6.4, 4H, Ar*H*), 7.61 (dd, *J* = 7.4, 2.7, 8H, Ar*H*), 6.63 (dd, *J* = 8.3, 2.1, 4H, Ar*H*), 6.14 (d, *J* = 8.2, 4H), 5.21 (d, *J* = 13.9, 4H, P*CH*$_2$), 4.36 (qd, *J* = 12.5, 6.0, 2H, *CH*), 1.31 (dd, *J* = 18.3, 6.5, 12H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4 (d, *J* = 3.9), 135.0 (d, *J* = 8.4), 134.6, 132.1 (d, *J* = 5.1), 129.8 (d, *J* = 11.8), 123.0 (d, *J* = 9.3), 118.0, 115.0 (d, *J* = 80.0), 27.3 (d, *J* = 43.5), 22.8 (d, *J* = 45.3), 16.2 (d, *J* = 2.2). LRMS (ES$^+$) m/z = 651.48 [(M-H)]$^+$, 326.18 [M^{2+}, 100%]. Anal. ($C_{44}H_{46}Br_2OP_2$) Calc: C, 65.04; H, 5.71; Br, 19.67. Found: C, 65.04; H, 5.69; Br, 19.07.

4,4'-bis((cyclohexyldiphenylphosphonio)methyl)benzophenone dibromide (35a). The reaction was carried out following the general procedure with cyclohexyldiphenylphosphine and **1a**. The reaction was stirred for 3 days. The product was obtained as a white hygroscopic solid (195.8 mg, 80%) following workup I procedure; mp 213.6 – 213.9 ºC; HPLC = 99% pure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 10.7, 8.9, 8H, Ar*H*), 7.72 (t, *J* = 6.9, 4H, Ar*H*), 7.61 – 7.55 (m, 8H, Ar*H*), 6.72 – 6.54 (m, 8H, Ar*H*), 5.59 (d, *J* = 15.3, 4H, P*CH*$_2$), 4.41 (dd, *J* = 23.0, 11.3, 2H, *CH*), 2.34 (br, 4H, *CH*$_2$), 1.89 – 1.65 (m, 10H, *CH*$_2$), 1.13 – 0.98 (m, 6H, *CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 135.1 (d, *J* = 8.5), 134.8 (d, *J* = 3.7), 134.6 (d, *J* = 2.3), 133.8 (d, *J* = 9.6), 131.0 (d, *J* = 5.4), 130.7 (d, *J* = 4.9), 129.8 (d, *J* = 11.8), 129.2 (d, *J* = 2.6), 114.9 (d, *J* = 79.9), 27.4 (d, *J* = 42.5), 25.9, 25.7, 25.6. LRMS (ES$^+$) *m/z* 743.53 [(M-H)$^+$], 372.05 [M^{2+}, 100%].

4,4'-bis((diphenyl-p-tolylphosphonio)methyl)diphenylmethane dibromide (38b). The reaction was carried out following the general procedure with diphenyl-p-tolylphosphine and **1b**. The product was obtained as a white solid (204 mg, 80%) following workup I procedure; mp 234 ºC with previous softening (DMF/toluene); HPLC > 95% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.50 (m, 24H, Ar*H*), 7.42 (dd, *J* = 7.9, 2.9, 4H, Ar*H*), 6.97 (dd, *J* = 14.0, 11.8, 4H, Ar*H*), 6.84 (d, *J* = 7.8, 4H, Ar*H*), 5.23 (d, *J* = 14.1, 4H, P*CH*$_2$), 3.75 (s, 2H, Ph*CH*$_2$Ph), 2.45 (s, 6H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6 (d, *J* = 3.0), 141.2 (dd, *J* = 4.1, 1.2), 135.1 (d, *J* = 2.9), 134.4 (d, *J* = 9.9), 131.7 (d, *J* = 5.4), 131.1 (d, *J* = 13.0), 130.3 (d, *J* = 12.5), 129.4 (d, *J* = 3.1), 125.2 (d, *J* = 8.6), 118.2 (d, *J* = 85.9), 114.1 (d, *J* = 88.1), 41.2, 30.7 (d, *J* = 47.4), 22.0. LRMS (ES$^+$) *m/z* 745.56 [(M-H)$^+$], 373.03 [M^{2+}, 100%].

4,4'-bis((tri-4-chlorophenylphosphonio)methyl)benzophenone dibromide (39a). The reaction was carried out following the general procedure with tris(4-chlorophenyl)phosphine and **1a**. The reaction was stirred for 3 days. The product was obtained as a white solid (207.6 mg, 63%) following workup II procedure; mp 285.9 ºC; HPLC > 95% pure. ^{1}H NMR (400 MHz, DMSO) δ 7.86 (dd, *J* = 8.7, 2.7, 12H, Ar*H*), 7.77 (dd, *J* = 12.2, 8.7, 12H, Ar*H*), 7.56 (d, *J* = 8.1, 4H, Ar*H*), 7.19 (dd, *J* = 8.1, 2.2, 4H, Ar*H*), 5.43 (d, *J* = 16.4, 4H, P*CH*$_2$). ^{13}C NMR (101 MHz, DMSO) δ 194.6, 141.0 (d, *J* = 3.6), 136.5 (d, *J* = 3.8), 136.1 (d, *J* = 11.4), 132.6 (d, *J* = 8.8), 131.0 (d, *J* = 5.4), 130.4 (d, *J* = 13.4), 130.1 (d, *J* = 2.3), 115.9 (d, *J* = 88.7), 28.0 (d, *J* = 46.2). LRMS (ES$^+$) *m/z* 937.22 [(M-H)$^+$], 468.99 [M^{2+}, 100%].

4,4'-bis((tri-4-fluorophenylphosphonio)methyl)benzophenone dibromide (40a). The reaction was carried out following the general procedure with tris(4-fluorophenyl)phosphine and **1a** for 17 h. The product was obtained as a white solid (179.7 mg, 65%) following workup II procedure; mp 297–297.8 ºC; HPLC > 95% pure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (ddd, *J* = 12.1, 8.8, 5.0, 12H, Ar*H*), 7.34 – 7.27 (m, 12H, Ar*H*), 7.08 (s, 8H, Ar*H*), 6.15 (d, *J* = 16.5, 4H, P*CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 137.9 (dd, *J* = 9.9, 11.6), 135.6 (d, *J* = 3.6), 131.9 – 131.8 (m), 129.8 (d, *J* = 4.0), 129.2, 128.4, 118.1 (dd, *J* = 14.1, 22.2), 113.5 (dd, *J* = 3.2, 90.6). LRMS (ES^+) *m/z* 839.29 [$(M-H)^+$], 420.20 [M^{2+},100 %].

4,4'-bis((di-2-methoxyphenylphenylphosphonio)methyl)benzophenone dibromide (42a). The reaction was carried out following the general procedure with bis(2-methoxyphenylphenyl)phosphine and **1a** for one day. The product was obtained as a grey hygroscopic solid (111.5 mg, 37%) following workup II procedure and recrystallization from EtOH/Et_2O; mp 291.4 ºC (decomp.); HPLC = 90 % pure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.29 (m, 34H, Ar*H*), 5.08 (d, *J* = 16.2, 4H, P*CH*$_2$), 3.75 (s, 12H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 161.8 (d, *J* = 2.2), 138.0, 136.8 (d, *J* = 3.5), 135.8 (d, *J* = 8.0), 134.7 (d, *J* = 2.9), 134.4 (d, *J* = 8.5), 133.5 (d, *J* = 10.0), 130.9 (d, *J* = 6.2), 130.4 (d, *J* = 2.9), 129.9 (d, *J* = 12.9), 122.7 (d, *J* = 12.9), 118.0 (d, *J* = 89.4), 113.0 (d, *J* = 6.8), 105.3 (d, *J* = 90.6), 56.7, 30.8. LRMS (ES^+) m/z 851.33 [$(M-H)^+$], 426.22 [M^{+2}, 94 %].

4,4'-bis((tri-2-methoxyphenylphosphonio)methyl)benzophenone dibromide (43a). The reaction was carried out following the general procedure at 50ºC with tris(2-methoxyphenyl)phosphine and **1a** for 17 h. The product was obtained as a white hygroscopic solid (264.1 mg, 89%) following workup II procedure; mp 219.5–225.2 ºC (decomp.), HPLC = 95% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 21.6, 13.4, 8H, Ar*H*), 7.47 – 7.25 (m, 12H, Ar*H*), 7.23 – 7.13 (m, 12H, Ar*H*), 4.85 (dd, *J* = 26.4, 16.5, 4H, P*CH*$_2$), 3.64 (s, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 161.4 (d, *J* = 2.4), 137.5 (d, *J* = 1.7), 136.4 (d, *J* = 3.1), 135.8 (d, *J* = 8.0), 135.3 (d, *J* = 8.4),130.2

(broad), 130.1, 122.3 (d, J = 13.0), 112.9 (d, J = 6.8), 105.5 (d, J = 92.4), 56.5, 30.8. LRMS (ES^+) *m/z* 911.53 [$(M-H)^+$], 455.97 [M^{2+}, 100%].

4,4'-bis((tri-4-trifluoromethylphenylphosphonio)methyl)benzophenone dibromide (44a). The reaction was carried out following the general procedure with tris(4-trifluoromethyl)phenyl)phosphine and **1a**. The reaction was concentrated under vacuum until the formation of an oily solid which was diluted with EtOH. Toluene was added to produce precipitation of the product as a white solid (120 mg, 40%). HPLC > 97% pure; mp 237.1°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, J = 11.4, 8.6, 12H, Ar*H*), 7.97 – 7.80 (m, 12H, Ar*H*), 7.10 (s, 8H, Ar*H*), 4.08 (s, 4H, P*CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 137.3 (d, J = 31.0), 135.7 (d, J = 10.6), 131.8 (d, J = 3.1), 130.1, 127.3 (d, J = 12.0), 124.6, 121.2 (d, J = 84.9), 121.0, 40.8, 29. LRMS (ES^+) m/z = 1139.49 $[(M-H)]^+$, 570.04 [M^{2+}, 100%].

4,4'-bis((tris(4-trifluoromethylphenyl)phosphoniomethyl)diphenylmethane dibromide (44b). The reaction was carried out following the general procedure with tris(4-trifluoromethylphenyl)phosphine and **1b**. The product was obtained as a white solid following workup II procedure (283.7 mg, 71%). HPLC > 95% pure; mp > 300 °C. ^{1}H NMR (300 MHz, DMSO) δ 8.12 (dd, J = 8.1, 2.6, 12H, Ar*H*), 8.04 (dd, J = 11.8, 8.5, 12H, Ar*H*), 7.02 (d, J = 8.0, 4H, Ar*H*), 6.93 (d, J = 8.0, 4H, Ar*H*), 5.46 (d, J = 16.4, 4H, P*CH*$_2$), 3.83 (s, 2H, *CH*$_2$). ^{13}C NMR (75 MHz, DMSO) δ 142.2 (dd, J = 4.2, 1.6), 136.5 (d, J = 10.7), 135.7 (d, J = 3.3), 135.3 (d, J = 3.2), 131.8 (d, J = 5.7), 130.3, 127.7 (dd, J = 13.1, 3.7), 125.9 (d, J = 1.3), 125.4 (d, J = 8.8), 122.8 (d, J = 85.6), 27.9. LRMS (ES^+) m/z = 1125.83 $[(M-H)]^+$, 563.14 [M^{2+}, 100%]. Anal. ($C_{57}H_{38}Br_2F_{18}P_2$) Calc: C, 53.21; H, 2.98; Br, 12.42. Found: C, 53.13; H, 3.15; Br, 11.48.

4,4'-bis((tris(4-trifluoromethylphenyl)phosphoniomethyl)diphenylether dibromide (44c). The reaction was carried out following the general procedure with

tris(4-trifluoromethylphenyl)phosphine and **1c**. The product was obtained as a white solid following workup II procedure (285.2 mg, 72%). HPLC > 95% pure; mp > 300 °C. ^{1}H NMR (300 MHz, DMSO) δ 8.15 (dd, *J* = 8.4, 2.6, 12H, Ar*H*), 8.03 (dd, *J* = 12.3, 8.4, 12H, Ar*H*), 6.99 (dd, *J* = 8.3, 2.6, 4H, Ar*H*), 6.86 (d, *J* = 8.3, 4H, Ar*H*), 5.39 (d, *J* = 15.5, 4H, P*CH*$_2$). LRMS (ES$^+$) m/z = 1127.79 [(M-H)]$^+$, 564.12 [M^{2+}, 100%]. Anal. ($C_{56}H_{36}Br_2F_{18}OP_2$) Calc: C, 52.20; H, 2.82; Br, 12.40. Found: C, 52.12; H, 3.01; Br, 11.58.

4,4'-bis((tri-p-tolylphosphonio)methyl)diphenylmethane dibromide (45b). The reaction was carried out following the general procedure with tri-p-tolylphosphine and **1b**. The product was obtained as a white solid (228.7 mg, 80%) following workup II procedure; mp 198 ºC with previous softening (DMF/toluene); HPLC > 95% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 12.2, 8.3, 12H, Ar*H*), 7.42 – 7.35 (m 12H, Ar*H*), 6.97 (dd, *J* = 8.0, 2.2, 4H, Ar*H*), 6.86 (d, *J* = 8.0, 4H, Ar*H*), 5.07 (d, *J* = 14.2, 4H, P*CH*$_2$), 3.76 (s, 2H, Ph*CH*$_2$Ph), 2.44 (s, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3 (d, *J* = 3.0), 141.2 – 140.9 (m,), 134.3 (d, *J* = 10.1), 131.6 (d, *J* = 5.4), 131.0 (d, *J* = 12.9), 129.4 (d, *J* = 3.1), 125.4 (d, *J* = 8.5), 114.7 (d, *J* = 88.4), 41.2, 31.0 (d, *J* = 48.3), 22.0. LRMS (ES$^+$) *m/z* 801.70 [(M-H)$^+$], 401.02 [M^{2+}, 100%].

4,4'-bis((tri(p-tolyl)phosphonio)methyl)diphenylsulphone dibromide (45d). The reaction was carried out following the general procedure at 100 °C with tri-p-tolylphosphine and **1d**. The product was obtained as a white solid (144.2, 89%) following workup I procedure; mp 280–281°C with previous softening (DMF/toluene); HPLC > 94% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.47 (m, 18H, Ar*H*), 7.37 (m, 14H, Ar*H*), 5.41 (d, *J* = 15.2, 4H, *CH*$_2$), 2.45 (s, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7 (d, *J* = 3.0), 141.0 (d, *J* = 3.8), 134.5 (d, *J* = 8.3), 134.3 (d, *J* = 10.3),

132.8 (d, *J* = 5.1), 131.2 (d, *J* = 13.1), 128.0 (d, *J* = 2.6), 114.1 (d, *J* = 88.9), 31.0 (d, *J* = 48.7), 22.0. LRMS (ES^+) *m/z* 851.61 [$(M-H)^+$], 426.01 [M^{2+}, 100%].

4,4'-bis((tri-*p*-tolylphosphonio)methyl)diphenylethane dichloride (45f). The reaction was carried out following the general procedure with tri-p-tolylphosphine and **12f**. The product was obtained as a white solid following workup II procedure (58 mg, 45%). HPLC > 99% pure; mp > 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 12.1, 8.1, 12H, Ar*H*), 7.40 (dd, *J* = 8.1, 3.0, 12H, Ar*H*), 6.93 – 6.88 (m, 4H, Ar*H*), 6.79 (d, *J* = 7.7, 4H, Ar*H*), 5.12 (d, *J* = 14.0, 4H, P*CH*$_2$), 2.74 (s, 4H, *CH*$_2$*CH*$_2$), 2.46 (s, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) 146.4 (d, *J* = 2.8), 141.6 (d, *J* = 3.9), 134.3 (d, *J* = 10.0), 131.4 (d, *J* = 5.4), 131.0 (d, *J* = 12.9), 129.2 (d, *J* = 2.9), 124.9 (d, *J* = 8.5), 114.7 (d, *J* = 88.5), 37.2, 31.1 (d, *J* = 49.1), 22.0. LRMS (ES^+) m/z = 815.62 [$(M-H)]^+$, 408.15 [M^{2+}, 100%].

4,4'-bis((tri-*p*-tolylphosphonio)methyl)diphenylethane dibromide (45f). The reaction was carried out following the general procedure with tri-p-tolylphosphine (146.3 mg, 0.48 mmol) and **10f** (70.8 mg, 0.192 mmol) . The product was obtained as a white hygrocopic solid following workup II procedure (178.4 mg, 95%). HPLC = 94 % pure; mp 276.4 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.32 (m, 24H, Ar*H*), 6.91 (d, *J* = 7.6, 4H, Ar*H*), 6.79 (d, *J* = 7.6, 4H, Ar*H*), 5.12 (d, *J* = 14.1, 4H, P*CH*$_2$), 2.74 (s, 4H, *CH*$_2$*CH*$_2$), 2.46 (s, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5 (d, *J* = 4.0), 140.5 (d, *J* = 12.5), 135.9 (d, *J* = 2.7), 134.4 (d, *J* = 9.6), 131.7 – 130.9 (m), 130.1 (d, *J* = 13.2), 129.0 (d, *J* = 2.9), 124.9 (d, *J* = 8.5), 117.8 (d, *J* = 85.0), 37.1, 30.8 (d, *J* = 47.4), 21.6. LRMS (ES^+) m/z = 815.98 [$(M-H)]^+$, 408.23 [M^{2+}, 100%].

4,4'-bis((tri-*p*-tolylphosphonio)methyl)diphenylpropane dichloride (45g). The reaction was carried out following the general procedure with tri-p-tolylphosphine and **13g** for 6 days. The product was obtained as a white solid following workup II

procedure (66.9 mg, 54%). HPLC > 99% pure; mp 194.9 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 11.9, 8.2, 12H, Ar*H*), 7.45 − 7.35 (m, 12H, Ar*H*), 6.94 (d, *J* = 7.6, 4H, Ar*H*), 6.88 (d, *J* = 7.6, 4H, Ar*H*), 5.18 (d, *J* = 14.7, 4H, P*CH*$_2$), 2.73 − 2.20 (m, 22H, Ph*CH*$_2$, *CH*$_3$), 1.94 − 1.70 (m, 2H, *CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3 (d, *J* = 3.0), 142.4 (d, *J* = 4.1), 134.3 (d, *J* = 10.1), 131.5 (d, *J* = 5.4), 131.0 (d, *J* = 12.9), 129.1 (d, *J* = 3.3), 124.8 (d, *J* = 8.5), 114.8 (d, *J* = 88.4), 34.8, 32.5, 31.0 (d, *J* = 48.1), 22.0 (d, *J* =1.3). LRMS (ES^+) m/z = 829.68 $[(M-H)]^+$, 415.08 $[M^{2+}$, 100%]. Anal. ($C_{59}H_{60}Cl_2P_2$. 8 H_2O) Calc: C, 67.50; H, 7.23; Cl, 6.87. Found: C, 67.79; H, 6.62; Cl, 6.95.

4,4'-bis((tri-*p*-tolylphosphonio)methyl)diphenylpropane dibromide (45g). The reaction was carried out following the general procedure with tri-p-tolylphosphine (141.4 mg, 0.464 mmol) and **11g** (71 mg, 0.186 mmol). The reaction was concentrated under vacuum until the formation of an oily solid which was diluted with hot EtOH. Cold Et_2O was added to produce precipitation of the product as a white hygroscopic solid. The flask was allowed to stand in the freezer overnight. The solid was collected, rinsed with Et_2O and dried under vacuum (156.4 mg, 85%). HPLC > 95% pure; mp 203.1 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 − 7.32 (m, 24H, Ar*H*), 6.95 – 6.79 (m, 8H, Ar*H*), 5.14 (d, *J* = 13.9, 4H, P*CH*$_2$), 2.55 – 2.29 (m, 22H, Ph*CH*$_2$, *CH*$_3$), 1.84 −1.75 (m, 2H, *CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3 (d, *J* = 3.9), 140.5 (d, *J* = 12.4), 135.9 (d, *J* = 2.8), 134.5 (d, *J* = 9.6), 131.8 – 131.1 (m), 130.0 (d, *J* = 13.2), 128.9 (d, *J* = 3.0), 124.7 (d, *J* = 8.6), 117.9 (d, *J* = 84.9), 34.8, 32.4, 30.8 (d, *J* = 47.2), 21.7. LRMS (ES^+) m/z = 829.98 $[(M-H)]^+$, 415.44 $[M^{2+}$, 100%].

4,4'-bis((tri-*m*-tolylphosphonio)methyl)diphenylmethane dibromide (46b). The reaction was carried out in toluene following the general procedure with tri-*m*-tolylphosphine and **1b**. The product was obtained as a white solid following workup I

procedure and recrystallization in DMF/toluene (185.6 mg, 66%). HPLC > 95% pure; mp 294 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.32 (m, 24H, Ar*H*), 6.97 (d, *J* = 8.0, 4H, Ar*H*), 6.88 (d, *J* = 8.0, 4H, Ar*H*), 5.17 (d, *J* = 14.0, 4H, P*CH*$_2$), 3.77 (s, 2H, *CH*$_2$), 2.37 (s, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1 (dd, *J* = 4.0, 1.4), 140.6 (d, *J* = 12.4), 136.0 (d, *J* = 2.8), 134.5 (d, *J* = 9.6), 131.8 (d, *J* = 5.4), 131.6 (d, *J* = 9.7), 130.2 (d, *J* = 13.3), 129.3 (d, *J* = 3.0), 125.4 (d, *J* = 8.6), 117.8 (d, *J* = 85.0), 41.1 (d, *J* = 21.6), 21.7. LRMS (ES^+) m/z = 801.63 $[(M-H)]^+$, 401.01 $[M^{2+}$, 100%]. Anal. ($C_{57}H_{56}Br_2P_2$) Calc: C, 71.11; H, 5.86; Br, 16.60. Found: C, 70.97; H, 5.93; Br, 15.98.

4,4'-bis((tri-*m*-tolylphosphonio)methyl)diphenylether dibromide (46c). The reaction was carried out following the general procedure with tri-*m*-tolylphosphine and **1c**. The product was obtained as a greyish solid following workup II procedure (230.6 mg, 82%). HPLC > 95% pure; mp 283 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.39 (m, 24H, Ar*H*), 7.05 (brd, 4H, Ar*H*), 6.65 (d, *J* = 7.8, 4H, Ar*H*), 5.25 (d, *J* = 14.3, 4H, P*CH*$_2$), 2.40 (s, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8 (d, *J* = 3.9), 140.6 (d, *J* = 12.5), 136.0 (d, *J* = 2.8), 134.5 (d, *J* = 9.7), 133.2 (d, *J* = 5.4), 131.6 (d, *J* = 9.6), 130.1 (d, *J* = 13.2), 122.6 (d, *J* = 8.6), 119.0 (d, *J* = 3.0), 117.8 (d, *J* = 84.9), 21.7. LRMS (ES^+) m/z = 803.61 $[(M-H)]^+$, 402.33 $[M^{2+}$, 100%].

4,4'-bis((benzyldiphenylphosphonio)methyl)benzophenone dibromide (50a). The reaction was carried out following general procedure with benzyldiphenylphosphine and **1a** for 62 h. The product obtained was a grey solid (241.5 mg, 94%) following workup II procedure; mp 297–300.5 ºC; HPLC > 95% pure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.41 (m, 12H, Ar*H*), 7.00 – 6.67 (m, 26H, Ar*H*), 5.12 (d, *J* = 15.3, 4H, P*CH*$_2$), 4.74 (d, *J* = 14.2, 4H, *CH*$_{2Bn}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 136.1 (d, *J* = 2.9), 135.0, 134.6 (d, *J* = 8.8), 133.3 (d, *J* = 8.9), 130.8, 129.9,

129.8, 128.8, 128.2, 127.6 (d, *J* = 8.6), 115.9 (d, *J* = 82.9), 30.2 (d, *J* = 45.2), 29.7 (d, *J* = 44.3). LRMS (ES^+) *m/z* 759.35 [$(M-H)^+$], 379.89 [M^{2+}, 100%].

4,4'-bis((diphenylpentafluorophenylphosphonio)methyl)diphenylmethane dibromide (51b). The reaction was carried out in toluene following the general procedure with pentafluorophenyldiphenylphosphine and **1b**. The product was obtained as a yellowish solid following workup I procedure (198.7 mg, 70%). HPLC > 95% pure; mp 235 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.39 (m, 20H, Ar*H*), 7.10 (d, *J* = 7.6, 4H, Ar*H*), 6.69 (d, *J* = 7.6, 4H, Ar*H*), 5.54 (d, *J* = 15.2, 4H, P*CH*$_2$), 3.85 – 3.44 (m, 2H, *CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 135.9, 134.3 (d, *J* = 10.4), 132.3 (d, *J* = 41.0), 131.8, 131.2 (d, *J* = 9.7), 130.4 (d, *J* = 13.1), 129.5 (d, *J* = 13.8), 128.8 (d, *J* = 11.2), 128.7 (d, *J* = 61.1), 125.4, 115.4 (dd, *J* = 87.6, 6.0), 41.1, 21.6. LRMS (ES^+) m/z = 898.2 $[M]^+$, 449.1[M^{2+}].

4,4'-bis((diphenylpentafluorophenylphosphonio)methyl)diphenylether dibromide (51c). The reaction was carried out following the general procedure with diphenylpentafluorophenylphosphine and **1c**. The product was obtained as a white solid following workup II procedure (230.6 mg, 82%). mp 245–248 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 – 7.89 (m, 8H, Ar*H*), 7.84 – 7.51 (m, 12H, Ar*H*), 6.84 (dd, *J* = 8.0, 2.8, 4H, Ar*H*), 6.25 (d, *J* = 8.0, 4H, Ar*H*), 5.87 (d, *J* = 14.9, 4H, P*CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1 (d, *J* = 121.7), 149.6 (d, *J* = 64.9), 146.1, 140.1 (d, *J* = 50.0), 137.0, 135.6, 134.3 (d, *J* = 10.6), 133.3 (d, *J* = 6.0), 130.4 (d, *J* = 13.4), 120.7 (d, *J* = 66.9), 118.2, 115.7 (d, *J* = 88.4). LRMS (ES^+) m/z = 899.49 $[(M-H)]^+$, 449.88 [M^{2+}, 100%]. Anal. ($C_{50}H_{30}Br_2F_{10}OP_2$) Calc: C, 56.63; H, 3.04; Br, 15.07. Found: C, 56.50; H, 3.06; Br, 15.17.

4,4'-bis((diphenylphosphinobenzen-3-sodiumsulfonate)methyl)diphenylmethane dibromide (52b). The reaction was

carried out in toluene following the general procedure with sodium diphenylphosphinobenzen-3-sulfonate and **1b**. The product was obtained as a white solid following workup I procedure (293.4 mg, 96%). HPLC = 92% pure; mp 129 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 – 8.20 (m, 4H, Ar*H*), 7.87 – 7.80 (m, 2H, Ar*H*), 7.77 – 7.66 (m, 4H, Ar*H*), 7.25 – 7.19 (m, 18H, Ar*H*), 6.82 (d, *J* = 8.1, 4H, Ar*H*), 6.74 (dd, *J* = 8.1, 2.0, 4H, Ar*H*), 4.68 (d, *J* = 14.2, 4H, P*CH*$_2$), 3.73 (s, 2H, *CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (d, *J* = 8.1), 141.6 – 141.4 (m), 137.9 (d, *J* = 13.2), 136.4 (d, *J* = 10.1), 135.4 (d, *J* = 1.9), 135.3 (d, *J* = 13.4), 134.0 (d, *J* = 9.7), 133.7 (d, *J* = 19.7), 131.9 (d, *J* = 10.5), 131.2 – 131.1 (m), 131.1 (d, *J* = 26.9), 130.3 (d, *J* = 12.6), 129.7 (d, *J* = 2.7), 129.0, 128.6 (d, *J* = 7.0), 126.6 (s), 125.2 – 122.8 (m), 117.1 (d, *J* = 85.7). LRMS (ES^+) m/z = 877.46 $[(M-H)]^+$, 439.09 $[M^{2+}$, 100%].

4,4'-bis((diphenylphosphinobenzen-3-sodiumsulfonate)methyl)diphenyl ether dibromide (52c). The reaction was carried out following the general procedure with diphenylphosphinobenzen-3-sodiumsulfonate and **1c**. The product was obtained as a white solid following workup II procedure (178.6 mg, 58%). HPLC > 95% pure; mp 268 °C. ^{1}H NMR (300 MHz, DMSO) δ 8.12 – 7.49 (m, 28H, Ar*H*), 6.98 (dd, *J* = 8.1, 2.4, 4H, Ar*H*), 6.84 (d, *J* = 8.1, 4H, Ar*H*), 5.17 (d, *J* = 15.3, 4H, P*CH*$_2$).. ^{13}C NMR (75 MHz, DMSO) δ 156.3 (d, *J* = 3.7), 149.9 (d, *J* = 11.5), 135.2, 134.1 (d, *J* = 9.7), 132.5 (d, *J* = 5.0), 132.1, 130.6 (d, *J* = 10.8), 130.1 (d, *J* = 12.4), 129.9 (d, *J* = 12.5), 122.7 (d, *J* = 8.5), 119.1 (d, *J* = 2.6), 117.7 (d, *J* = 85.3). LRMS (ES^+) m/z = 879.40 $[(M-H)]^+$, 440.01 $[M^{2+}$, 100%]. Anal. ($C_{50}H_{40}Br_2Na_2O_7P_2S_2$) Calc: C, 55.36; H, 3.72; S, 5.91; Br, 14.37. Found: C, 55.16; H, 3.98; S, 5.63; Br, 13.81.

4,4'-bis((tri-1-naphthylphosphonio)methyl)benzophenone dibromide (53a). The reaction was carried out following gerenal procedure with tri(naphthalen-2-yl)phosphine and **1a** for 17 h. The product obtained as a white hygroscopic solid (145.2

mg, 42%) following workup I procedure and recrystallization from EtOH/Et_2O. ; mp 267.2–270 ºC (decomp.); HPLC = 93 % pure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (br s, 6H, Ar*H*), 8.23 (d, *J* = 6.4, 6H, Ar*H*), 7.92 (br s, 12H, Ar*H*), 7.69 (s, 6H, Ar*H*), 7.45 (dd, *J* = 17.5, 6.9, 12H, Ar*H*), 7.08 – 6.52 (m, 8H, Ar*H*), 5.87 (d, *J* = 10.3, 4H, P*CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 138.6 (d, *J* = 11.0), 137.2 (d, *J* = 2.6), 136.2, 134.4 – 134.1 (m), 132.6 (d, *J* = 8.6), 130.8 – 130.4 (m), 129.7, 129.2, 127.7, 125.9 – 125.4 (m), 114.4 (d, *J* = 81.3), 33.4 (d, *J* = 47.7). LRMS (ES^+) *m/z* 1031.56 [$(M-H)^+$], 516.10 [M^{2+}, 100%].

4,4'-bis((tri(1-naphthyl)phosphonio)methyl)diphenylether dibromide (53c). The reaction was carried out following the general procedure with tri-1-naphthylphosphine and **1c**. The product was obtained as a white solid (83.6 mg, 26%) following workup I procedure and recrystallization from DCM/Et_2O; mp 239 ºC (decomp); HPLC > 98% pure; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 11.4, 6H, Ar*H*), 8.27 (d, *J* = 7.7, 6H, Ar*H*), 7.94 (dd, *J* = 19.7, 8.0, 12H, Ar*H*), 7.72 (br s, 6H, Ar*H*), 7.47 (dt, *J* = 14.5, 6.9, 12H, Ar*H*), 6.83 (d, *J* = 7.5, 4H, Ar*H*), 6.02 (d, *J* = 7.5, 4H, Ar*H*), 5.71 (d, *J* = 10.7, 4H, *CH*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5 (d, *J* = 3.3), 138.5 (d, *J* = 10.8), 137.1 (d, *J* = 2.9), 134.3 (d, *J* = 9.6), 132.6 (d, *J* = 8.4), 132.2 (d, *J* = 6.5), 130.5, 129.1, 127.6, 126.0 - 125.6 (m), 124.0 (d, *J* = 7.5), 118.7 (d, *J* = 1.9), 114.6 (d, *J* = 80.9), 32.7 (d, *J* = 47.4). LRMS (ES^+) *m/z* 1019.80 [$(M-H)^+$], 510.01 [M^{2+}, 100%].

2. General procedure for the synthesis of the monophosphonium salts. The appropriate halogenated precursor (100 mg, ~0.36 mmol) was added to a Kimax tube and dissolved in anhydrous DMF (3 mL) under argon atmosphere. The phosphine was then added (0.72 mmol, 2 equiv.), the tube was stopped, and the reaction mixture was

stirred at 100 °C for 20 h. Next, the reaction mixture was transferred to a flask and DMF was evaporated under vacuum. Subsequently, toluene (10–20 mL) was added to precipitate the product and the flask was stored in the fridge overnight. The supernatant was removed and the precipitate was rinsed with toluene. Et_2O (10 mL) was added and the precipitate was triturated with a spatula. The solid was collected, rinsed with Et_2O and dried under vacuum.

(4-benzoylbenzyl)tri-*m*-tolylphosphonium bromide (57a). The reaction was carried out following the general procedure with **2a** and tri-m-tolylphosphine. The product was obtained as an off-white solid following workup II procedure (139.6 mg, 65%). HPLC > 95% pure; mp 198 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 21H, Ar*H*), 5.52 (d, *J* = 12.8, 2H, P*CH*$_2$), 2.39 (s, 9H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 140.7 (d, *J* = 12.6), 137.4 (d, *J* = 3.5), 137.0, 136.0 (d, *J* = 3.24), 134.6 (d, *J* = 9.8), 132.9, 132.8, 132.7, 131.56 (d, *J* = 9.72), 130.16 (d, *J* = 3.42), 130.0, 128.46, 117.61 (d, *J* = 85.12), 31.14 (d, *J* = 47.1), 21.64. LRMS (ES^+) m/z = 500.21 $[(M+H)]^+$. Anal. ($C_{35}H_{32}BrOP$) Calc: C, 72.54; H, 5.57; Br, 13.79. Found: C, 72.36; H, 5.61; Br, 13.67.

(4-benzoylbenzyl)triisobutylphosphonium bromide (58a). The reaction was carried out following the general procedure with **2a** and triisobutylphosphine. The product was obtained as an off-white solid following workup II procedure (121.5 mg, 60%). HPLC > 95% pure; mp 114.7 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.34 (m, 9H, Ar*H*), 4.61 (d, *J* = 15.4, 2H, P*CH*$_2$Ph), 2.40 (dd, *J* = 12.9, 6.2, 6H, P*CH*$_2$CH), 2.27 – 2.02 (m, 3H, *CH*), 1.10 (d, *J* = 6.4, 18H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 137.6 (d, *J* = 3.6), 137.0, 133.7 (d, *J* = 8.8), 133.0, 130.9, 130.9, 130.1, 128.5, 29.2 (d, *J* = 42.4), 28.7 (d, *J* = 44.2), 25.1 (d, *J* = 8.5), 23.9 (d, *J* = 4.7).. LRMS (ES^+) m/z =

398.27 $[(M+H)]^+$. Anal. ($C_{26}H_{38}BrOP$) Calc: C, 65.40; H, 8.08; Br, 16.74. Found: C, 65.70; H, 8.00; Br, 16.86.

(4-benzoylbenzyl)diphenyl-*p*-tolylphosphonium bromide (59a). The reaction was carried out following the general procedure with **2a** and diphenyl-p-tolylphosphine. The product was obtained as an off-white solid following workup II procedure (117.6 mg, 63%). HPLC > 95% pure; mp 213.7 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.20 (m, 23H, Ar*H*), 5.60 (d, *J* = 14.8, 2H, P*CH*$_2$), 2.44 (s, 3H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 146.7 (d, *J* = 3.0), 137.4 (d, *J* = 3.8), 137.0, 135.1 (d, *J* = 2.8), 134.5 (d, *J* = 10.0), 132.9, 132.5 (d, *J* = 8.6), 131.8 (d, *J* = 5.4), 131.1 (d, *J* = 13.1), 130.4, 130.3 (d, *J* = 3.2), 130.2 (d, *J* = 2.1), 128.5, 118.0 (d, *J* = 86.0), 113.8 (d, *J* = 88.4), 22.0. LRMS (ES^+) m/z = 472.24 $[(M+H)]^+$. Anal. ($C_{33}H_{28}BrOP$) Calc: C, 71.87; H, 5.12; Br, 14.49. Found: C, 70.40; H, 4.87; Br, 14.22.

(4-benzoylbenzyl)triethylphosphonium bromide (60a). The reaction was carried out following the general procedure with **2a** and triethylphosphine. The product was obtained as a white solid following workup II procedure (142.0 mg, 90%). mp 169.3 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.51 (m, 7H, Ar*H*), 7.46 (t, *J* = 7.4, 2H, Ar*H*), 4.53 (d, *J* = 15.9, 2H, P*CH*$_2$Ph), 2.53 (dq, *J* = 15.2, 7.6, 6H, *CH*$_2$CH$_3$), 1.24 (dt, *J* = 18.0, 7.6, 9H, *CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 137.6 (d, *J* = 3.5), 136.9, 133.4 (d, *J* = 8.7), 132.9, 131.0 (d, *J* = 2.9), 130.4 (d, *J* = 4.9), 130.1, 128.5, 12.6, 6.2 (d, *J* = 5.6). LRMS (ES^+) m/z = 314.10 $[(M+H)]^+$. Anal. ($C_{20}H_{26}BrOP$) Calc: C, 61.08; H, 6.66; Br, 20.32. Found: C, 60.99; H, 6.65; Br, 19.99.

(4-benzoylbenzyl)tri-*o*-methoxyphenylphosphonium bromide (61a). The reaction was carried out following the general procedure with **2a** and tri(2-methoxyphenyl)phosphine. The product was obtained as a white solid following workup II procedure (187.2 mg, 85%). HPLC > 95% pure; mp 109 ºC. ^{1}H NMR (300 MHz,

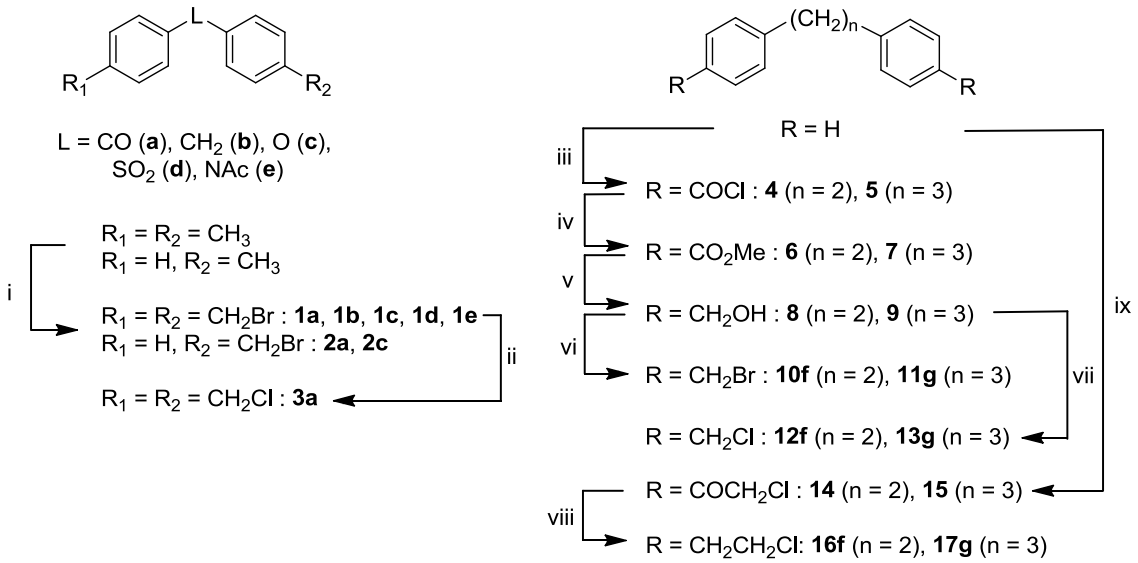
$CDCl_3$) δ 7.74 (t, *J* = 7.8, 3H, Ar*H*), 7.66 – 7.49 (m, 6H, Ar*H*), 7.44 (d, *J* = 7.7, 2H, Ar*H*), 7.33 (dd, *J* = 14.1, 7.7, 4H, Ar*H*), 7.19 – 7.11 (m, 6H, Ar*H*), 4.82 (d, *J* = 16.4, 2H, P*CH*$_2$), 3.67 (s, 9H, O*CH*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 137.5 (d, *J* = 1.9), 137.1, 136.8, 135.6 (d, *J* = 8.1), 135.3 (d, *J* = 8.4), 134.5 (d, *J* = 8.8), 132.8, 130.2 (d, *J* = 2.1), 130.0, 129.9, 128.5, 122.3 (d, *J* = 13.0), 112.8 (d, *J* = 6.8), 105.4 (d, *J* = 92.3), 56.5. LRMS (ES^+) m/z = 548.30 $[(M+H)]^+$. Anal. ($C_{35}H_{32}BrO_4P$) Calc: C, 66.99; H, 5.14; Br, 12.73. Found: C, 66.87; H, 5.12; Br, 11.80.

(4-benzoylbenzyl)dimethylphenylphosphonium bromide (63a). The reaction was carried out following the general procedure with **2a** and dimethylphenylphosphine. The product was obtained as a white solid (95 mg, 76 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 12.6, 7.3, 2H, Ar*H*), 7.75 – 7.54 (m, 8H, Ar*H*), 7.46 (t, *J* = 7.5, 2H, Ar*H*), 7.32 (dd, *J* = 8.2, 2.6, 2H, Ar*H*), 4.90 (d, *J* = 16.4, 2H, P*CH*$_2$), 2.62 (s, 3H, *CH*$_3$), 2.57 (s, 3H, *CH*$_3$). ^{13}C NMR (75 MHz, DMSO) δ 195.0, 136.7, 136.4 (d, *J* = 3.9), 134.0 (d, *J* = 2.7), 133.6 (d, *J* = 8.9), 132.5, 131.6 (d, *J* = 9.9), 129.9 (d, *J* = 5.4), 129.7 (d, *J* = 3.2), 129.2, 129.1, 128.3, 120.1 (d, *J* = 84.3), 30.4 (d, *J* = 47.3), 6.11 (d, *J* = 54.7). LRMS (ES^+) m/z = 333.0. Anal. ($C_{22}H_{22}BrOP$) Calc: C, 62.94; H, 5.37; Br, 19.33. Found: C, 62.81; H, 5.36; Br, 19.29.

3. Synthesis of the linkers 2a, 3a, 10f, 11g, 12f, 13g

The 4,4'-bisbromomethyl linkers **1a**,[1] **1b**,[2] **1d**,[3] and **1e**[4] were synthesized by *N*-bromosuccinimide (NBS) bromination of the 4,4'-dimethylphenyl precursors as previously reported. The linkers **1c** and **2c** were commercially available.

Scheme 2.[a] Synthesis of the Linkers.



[a] Reagents and conditions. (i) NBS, ^{t}BuOOH $_{cat.}$, CCl_4, reflux, 20–52%; (ii) $BiCl_3$, 1,2-dichloroethane, Δ, 60–72%; (iii) 1) oxalyl chloride, $AlCl_3$, CH_2Cl_2, -15 ºC, 5h; 2) chlorobenzene, reflux, 5h, 80–84%; (iv) MeOH, rt, quantitative; (v) $LiAlH_4$, THF, reflux, 18h, 90–94%; (vi) thionyl bromide, CH_2Cl_2, rt, 2h, 82–95%; (vii) thionyl chloride, CH_2Cl_2, rt, 2h, 68–97%; (viii) $ClCOCH_2Cl$, $AlCl_3$, CH_2Cl_2, reflux, 3h, 94%; (ix) Et_3SiH, CF_3CO_2H, 0 ºC → 45 ºC→ rt, 61–90%.

4-bromomethylphenylbenzophenone (2a). A mixture of 4-methylbenzophenone (3g, 15.3 mmol), *N*-bromosuccinimide (2.72g, 15.3 mmol), and benzoyl peroxide (200mg) in CCl_4 (100 mL) was flushed with argon and refluxed overnight. The reaction was

filtered hot on a fritted glass funnel. The succinimide precipitate was rinsed with a small amount of CCl_4. The filtrate was washed successively with 5% $NaHCO_3$ (40 mL) and brine (30 mL), dried over anhydrous $MgSO_4$ and evaporated under vacuum to yield 3.98 g of crude product. Successive recrystallizations in CCl_4, toluene and CH_2Cl_2 were necessary to obtain analitically pure **2a** as colorless solid (986 mg, 23%); mp 98–100 °C. HPLC ≥ 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.74 (m, 5H), 7.50 (dd, *J* = 8.0, 1.6, 4H), 6.69 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 142.2, 137.5, 132.6, 130.7, 130.1, 129.1, 128.5, 126.7, 32.4. LRMS (ES^+) *m/z* = 275.19 $[M+H]^+$.

4,4'-bis(chloromethyl)benzophenone (3a). In a Kimax tube was added bismuth trichloride (87.4 mg, 0.277 mmol) and 1,2-dichloroethane (1.26 g, 12.69 mmol) under argon atmosphere and continuous stirring. Next, compound **1a** (51 mg, 0.138 mmol) was added all and the reaction was stirred at 45–50 °C for 5 days. Dichloromethane was added (ca. 25 mL) and the reaction mixture was filtered. The precipitate was washed with CH_2Cl_2 and the combined filtrates were evaporated under vacuum. The product was obtained as a hygroscopic white solid (23.1 mg, 60%). HPLC > 85% pure, mp 94.1 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1, 4H), 7.52 (d, *J* = 8.1, 4H), 4.65 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 142.0, 137.4, 130.6, 128.6, 45.5. LRMS (ES^+) m/z = 279.19 $[M+H]^+$.

1,2-Bis(4-chloroformylphenyl)ethane (4). A solution of oxalyl chloride (5.01 g, 39.50 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise to a solution of $AlCl_3$ (5.27 g, 39.50 mmol) in CH_2Cl_2 (50 mL), at -15°C under argon atmosphere. After 30 min stirring at -15 ºC, a solution of 1,2-diphenylethane (2 g, 10.97 mmol) was added dropwise over a 30 min period. The reaction was stirred 5 h at -15 °C and poured onto crushed ice (500 g). The organic layer was decanted and the aqueous phase extracted 3 times with a mixture of CH_2Cl_2/Et_2O (1:1). The combined organic layers were washed

with brine, dried (Na_2SO_4), and evaporated under vacuum. The crude product was suspended in chlorobenzene and refluxed for 5 h. The solvent was removed under vacuum to give an off-white solid (2.83 g, 84%). mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1, 4H), 7.20 (d, *J* = 8.1, 4H), 2.98 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 149.2, 131.9, 131.0, 129.3, 37.2. Anal. ($C_{16}H_{12}Cl_2O_2$) Calc: C, 65.54; H, 4.39; Cl, 14.81. Found: C, 65.61; H, 4.37; Cl, 14.99.

1,3-Bis(4-chloroformylphenyl)propane (5).[5] The same procedure was used starting from 1,3-diphenylpropane (2.04 g, 10.19 mmol). Compound **5** was obtained as a pale yellow solid (2.61 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 12.3, 8.2, 4H), 7.32 (dd, *J* = 8.2, 2.4, 4H), 3.08 – 2.43 (m, 4H), 2.25 – 1.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 145.1, 133.6, 129.2, 128.9, 35.4, 31.3.

1,2-Bis(4-methoxycarbonylphenyl)ethane (6).[6] A solution of **4** (540 mg, 1.75 mmol) in MeOH (25 mL) was stirred at room temperature overnight. The solvent was removed under vacuum to yield **6** as an off-white solid (510 mg, quantitative). HPLC = 90% pure; mp 106–109 °C (Lit.[6] 160–164 ºC, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1, 4H), 7.19 (d, *J* = 8.1, 4H), 3.90 (s, 6H), 2.98 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 146.6, 129.8, 129.2, 128.6, 52.2, 37.5. LRMS (ES^+) m/z = 299.32 $[M+H]^+$. Anal. ($C_{18}H_{18}O_4$) Calc: C, 72.47; H, 6.08. Found: C, 72.41; H, 5.91.

1,3-Bis(4-methoxycarbonylphenyl)propane (7). A solution of **5** (2.51 g, 7.84 mmol) in MeOH (100 mL) was stirred at room temperature overnight. The solvent was removed under vacuum and the crude product was purified by silica chromatography with hexane/EtOAc (9:1) to yield **7** as an off-white solid (2.43 g, 99.5%). HPLC > 95% pure; mp 92–93 °C (Lit.[6] 85–86.5 ºC, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2, 4H), 7.24 (d, *J* = 8.2, 4H), 3.90 (s, 6H), 2.69 (t, *J* = 7.6, 4H), 2.05 – 1.93 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 147.6, 129.9, 128.6, 128.1, 52.1, 35.5, 32.4.

LRMS (ES^+) m/z = 313.33 $[M+1]^+$. Anal. ($C_{19}H_{20}O_4$) Calc: C, 73.03; H, 6.45. Found: C, 73.26; H, 6.52.

1,2-Bis(4-hydroxymethylphenyl)ethane (8). A solution of **6** (250 mg, 0.84 mmol) in dry THF (10 mL) was added dropwise, under argon, to a suspension of $LiAlH_4$ (302 mg, 7.96 mmol) in dry THF (10 mL). The reaction mixture was refluxed overnight. The cooled reaction was hydrolyzed by dropwise addition of water followed by acidification with 0.1 M HCl. The organic layer separated and the aqueous phase extracted with CH_2Cl_2 (3×). The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated under vacuum to yield **8** as a yellowish solid (183 mg, 90%). HPLC = 94% pure; mp 135–134 °C (Lit.[6] 157–159 ºC, xylene). ^{1}H NMR (300 MHz, DMSO) δ 7.21 (d, *J* = 8.1, 4H), 7.17 (d, *J* = 8.1, 4H), 5.09 (t, *J* = 5.7, 2H), 4.44 (d, *J* = 5.7, 4H), 2.84 (s, 4H). ^{13}C NMR (75 MHz, DMSO) δ 139.9, 139.8, 128.1, 126.5, 62.8, 36.8. LRMS (ES^+) *m/z* = 260.4 $[(M+H_2O)]^+$. Anal. ($C_{16}H_{18}O_2$) Calc: C, 79.31; H, 7.49. Found: C, 79.14; H, 7.53.

1,3-Bis(4-hydroxymethylphenyl)propane (9). The same procedure was used starting from **7** (500 mg, 1.60 mmol). Compound **9** was obtained as a yellow solid (403 mg, 94%). HPLC > 95% pure; mp 122.7 ºC. ^{1}H NMR (400 MHz, DMSO) δ 7.19 (d, *J* = 8.1, 4H), 7.16 (d, *J* = 8.1, 4H), 5.10 (t, *J* = 5.7, 2H), 4.45 (d, *J* = 5.7, 4H), 2.56 (t, 4H), 1.90 – 1.79 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 140.3, 139.9, 128.0, 126.6, 62.8, 34.4, 32.9. LRMS (ES^+) *m/z* = 274.4 $[(M+H_2O)]^+$.

1,2-Bis(4-bromomethylphenyl)ethane (10f). Thionyl bromide (237.5 mg, 1.14 mmol) was added to a solution of **8** (138.4 mg, 0.57 mmol) in dry CH_2Cl_2 (5 mL). The reaction was stirred 1 h at room temperature. The solvent was removed under vacuum to give a dark orange solid. The solid was redissolved in toluene and the solvent was evaporated under vacuum. This operation was repeated once to dry the solid completely

(180.4 mg, 86%); mp 117–118 °C (Lit.[6] 126–129 ºC, petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0, 4H), 7.15 (d, *J* = 8.0, 4H), 4.49 (s, 4H), 2.90 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 136.9, 131.3, 129.2, 35.6, 30.8. Anal. ($C_{16}H_{16}Br_2$) Calc: C, 52.21; H, 4.38; Br, 43.41. Found: C, 51.95; H, 4.19; Br, 43.11.

1,3-Bis(4-bromomethylphenyl)propane (11g). The same procedure was used starting from **9** (400 mg, 1.56 mmol). Compound **11g** was obtained as a brown solid (566.3 mg, 95%); mp 122–125 °C (Lit.[6] 131–132 ºC, petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0, 4H), 7.16 (d, *J* = 8.0, 4H), 4.50 (s, 4H), 2.65 (t, *J* = 7.7 4H), 2.02 – 1.83 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 143.0, 135.7, 129.5, 129.3, 35.5, 34.1, 33.0. Anal. ($C_{16}H_{16}Br_2$) Calc: C, 53.43; H, 4.75; Br, 41.82. Found: C, 53.22; H, 4.71; Br, 39.67.

1,2-Bis(4-chloromethylphenyl)ethane (12f). Thionyl chloride (248 mg, 2.08 mmol) was added to a solution of **8** (201.9 mg, 0.834 mmol) in dry CH_2Cl_2 (5 mL). The reaction was stirred 4h at room temperature. The solvent was removed under vacuum to give a light brown solid. The solid was recrystallized with hexane (226.4 mg, 97%); HPLC > 94% pure; mp 92.5–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0, 4H), 7.17 (d, *J* = 8.0, 4H), 4.58 (s, 4H), 2.91 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 135.4, 129.0, 128.8, 46.3, 37.5. LRMS (ES^+) m/z = 302.33 $[(M+Na)]^+$. Anal. ($C_{16}H_{16}Cl_2$) Calc: C, 68.83; H, 5.78; Cl, 25.40. Found:C, 68.59; H, 5.53; Cl, 25.11.

1,3-Bis(4-chloromethylphenyl)propane (13g). The same procedure was used starting from **9** (174.8 mg, 0.682 mmol). Compound **13g** was obtained as a light yellow solid (136.6 mg, 68%). HPLC > 92% pure; mp 107.8–108.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0, 4H), 7.17 (d, *J* = 8.0, 4H), 4.58 (s, 4H), 2.65 (t, *J* = 7.6, 4H), 1.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 135.1, 128.9, 128.8, 46.4, 35.2, 32.8. LRMS (ES^+) m/z = 316.32 $[(M+Na)]^+$.

4. Synthesis of the 4,4'-bis(2-chloroethylphenyl) linkers 16f and 17g.

1,2-Bis(4-(chlorophenylethanone))ethane (14). A two-neck round bottomed flask equipped with a reflux condenser was charged with aluminum trichloride (21.94 g, 164.54 mmol), chloroacetyl chloride (4.83 g, 42.78 mmol), CH_2Cl_2 (150 mL) and 1,2-diphenylethane (3g, 16.45 mmol) all in continuous stirring and under argon atmosphere. The reaction mixture was stirred at room temperature for 20 min, then refluxed for 3h, and finally left stirring overnight at room temperature. The supernatant was poured into ice-water with stirring. The white emulsion that formed was decanted and the organic layer was dried ($MgSO_4$) and filtered. The solvent was evaporated yielding an off-white solid (5.48 g, 99%). HPLC > 99% pure; mp 133.9–140.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.8, 4H), 7.19 (d, *J* = 7.8, 4H), 4.36 (s, 4H), 2.95 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 147.8, 132.5, 129.2, 129.0, 46.1, 37.4. LRMS (ES^+) m/z = 335.20 $[(M+H)]^+$. Anal. ($C_{18}H_{16}Cl_2O_2$) Calc: C, 64.49; H, 4.81; Cl, 21.15. Found: C, 64.71; H, 4.99; Cl, 21.33.

1,3-Bis(4-(chlorophenylethanone))propane (15). The same procedure was used starting from aluminum trichloride (20.37 g, 152.83 mmol), chloroacetyl chloride (4.31g, 38.21mmol), dichloromethane (150 mL) and 1,3-diphenylpropane (3g, 15.28 mmol). Compound **15** was obtained as a light yellow solid (5.19 g, 97%). HPLC > 98% pure; mp 81.7–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.3, 4H), 7.30 (d, *J* = 8.3, 4H), 4.69 (s, 4H), 2.76–2.69 (m, 4H), 2.06–1.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 148.8, 132.4, 129.1, 129.0, 46.0, 35.5, 32.1. LRMS (ES^+) m/z = 349.19 $[(M+H)]^+$. Anal. ($C_{19}H_{18}Cl_2O_2$) Calc: C, 65.35; H, 5.19; Cl, 20.30. Found: C, 65.47; H, 5.24; Cl, 20.55.

1,2-bis(4-(2-chloroethyl)phenyl)ethane (16f)[7]**.** Trifluoroacetic acid (13.21 g, 115.9 mmol) was added to a flask containing **14** (1 g, 2.9 mmol) under Ar atmosphere. The stirred solution was cooled to 0 °C and triethylsilane (1.69 g, 14.5 mmol) was added dropwise. After the addition finished, the ice-bath was removed and the reaction mixture was heated to 45 ºC for 20 min. The reaction was stirred at room temperature for 68 h and poured into ice/water. The emulsion was extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under vaccum. The light brown oily solid was recrystallized with CH_2Cl_2/hexane several times to yield a light yellow hygroscopic solid (803.4 mg, 90%). HPLC > 95% pure; mp 85.6–88.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 8H), 3.62 (t, *J* = 7.5, 4H), 2.97 (d, *J* = 7.5, 4H), 2.81 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 135.8, 128.9, 128.8, 45.2, 39.0, 37.6. LRMS (ES^+) m/z = 305.27 $[(M–H)]^+$. Anal. ($C_{18}H_{20}Cl_2$) Calc: C, 70.36; H, 6.56; Cl, 23.08. Found: C, 70.39; H, 6.82; Br, 22.85.

1,3-bis(4-(2-chloroethyl)phenyl)propane (17g). The same procedure was used starting from compound **15** (1 g, 2.86 mmol), trifluoroacetic acid (13.06 g, 114.59 mmol) and triethylsilane (1.67 g, 14.32 mmol). Compound **17g** was obtained as a light yellow hygroscopic semi-solid (560.9 mg, 61%). HPLC > 95% pure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 8H), 3.70 (t, *J* = 7.5, 4H), 3.04 (t, *J* = 7.5, 4H), 2.67 – 2.59 (m, 4H), 2.00 – 1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 135.6, 128.9, 128.8, 45.2, 39.0, 35.2, 33.0. LRMS (ES^+) m/z = 285.38 $[(M\text{-}Cl)]^+$. Anal. ($C_{19}H_{22}Cl_2$) Calc: C, 71.03; H, 6.09; Cl, 22.07. Found: C, 70.78; H, 7.19; Cl, 21.78.

5. CoMFA Models

Figure S1. Molecular Alignment of the Phosphonium Salts.

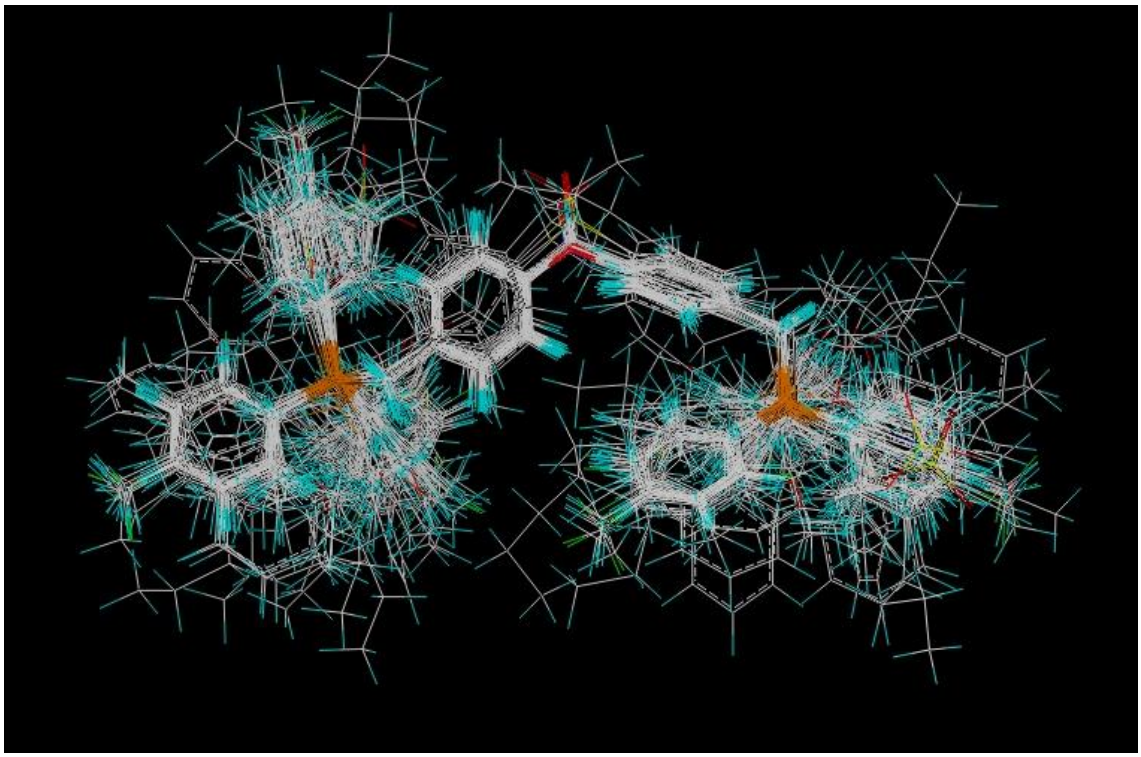


Table S1. QSAR Model for *T. b. rhodesiense.*

Compd	pEC_{50}[a] *T. b. rhodesiense*	Sets	Predicted *T. b. rhod*	Error
28b	-0.4126	test	-0.813	0.4004
44b	-0.2355	test	0.207	0.4425
52b	<-1.963	test	0.879	ND
53a	0.3979	test	0.88	0.4821
34c	0.2328	test	0.153	0.0798
25c	0.8827	test	0.404	0.4787
63a	-1.2289	test	-0.197	1.0319
41a	0.5376	test	0.511	0.0266
52c	<-1.963	test	0.95	ND
36a	0.585	test	0.403	0.182
19a	-1.891	test	-1.167	0.724
43c	0.8153	test	0.922	0.1067
40a	0.3468	test	-0.005	0.3518
48a	-1.1402	test	-0.57	0.5702
60a	<-2.404	test	-0.495	ND
23e	-1.0584	test	-0.065	0.9934

49a	0.2168	test	0.541	0.3242
19b	-1.2718	test	-1.398	0.1262
28c	-0.5829	test	-1.002	0.4191
56c	2.698	test	0.582	2.116
43a	0.699	test	0.989	0.29
46b	0.6364	test	0.701	0.0646
57c	1.853	test	0.339	1.514
23b	0.4868	training	0.25	0.2368
38c	0.8477	training	0.592	0.2557
38b	0.699	training	0.683	0.016
25b	0.7447	training	0.783	0.0383
45c	0.7696	training	0.668	0.1016
45b	1.0044	training	0.945	0.0594
53c	0.4157	training	0.239	0.1767
53b	0.5243	training	0.719	0.1947
43b	0.6799	training	0.8	0.1201
45d	0.762	training	0.946	0.184
23d	-0.7998	training	-0.734	0.0658
45e	0.7986	training	0.927	0.1284
19c	-1.5038	training	-1.253	0.2508
55	0.4389	training	0.427	0.0119
33b	0.0975	training	0.02	0.0775
34b	0.2725	training	0.319	0.0465
51b	-1.2041	training	-1.097	0.1071
54	0.6655	training	0.626	0.0395
33c	0.2464	training	-0.053	0.2994
46c	0.3116	training	0.418	0.1064
51c	-1.1072	training	-1.241	0.1338
56a	1.0915	training	0.858	0.2335
57a	0.5622	training	0.53	0.0322
58a	-0.6513	training	-0.251	0.4003
59a	0.5735	training	0.551	0.0225
61a	0.4248	training	0.5	0.0752
23c	-0.2087	training	-0.382	0.1733
62a	0.9872	training	0.835	0.1522
28f	-0.0803	training	-0.137	0.0567
29a	-0.4624	training	-0.54	0.0776
31a	0.1831	training	0.073	0.1101
28a	-0.9445	training	-0.8	0.1445
18a	-2.1038	training	-1.99	0.1138
26a	0.7055	training	0.605	0.1005
32a	0.2565	training	0.077	0.1795
22a	0.4498	training	0.757	0.3072
27a	0.6576	training	0.545	0.1126
23a	-0.1644	training	-0.146	0.0184
37a	0.7959	training	0.646	0.1499

38a	0.585	training	0.676	0.091
30a	0.4949	training	0.613	0.1181
47a	0.5376	training	0.365	0.1726
25a	0.9508	training	0.765	0.1858
35a	0.3665	training	0.267	0.0995
39a	0.3872	training	0.329	0.0582
21a	-0.9823	training	-0.985	0.0027
20a	-0.9294	training	-1.009	0.0796
42a	0.6383	training	0.825	0.1867
45a	0.6576	training	0.99	0.3324
50a	0.3188	training	0.39	0.0712
24a	0.5391	training	0.659	0.1199
44c	-0.721	training	-0.738	0.017
45g	1.0915	training	1.224	0.1325
45f	1.0757	training	1.1	0.0243
28g	-0.0856	training	-0.041	0.0446

[a] $pEC_{50} = -\log_{10}[EC_{50}\,(\mu M)]$

Table S2. Validation Results for *T. b. rhodesiense* Model

	q^2	r^2	Error	F
LOO	0.463	-	-	-
LSO	0.422	-	-	-
Bootstrapping	-	0.941	0.14	-
No Validation	-	0.955	-	209

Figure S2. CoMFA Model for *T. b. rhodesiense*. Plot of $-\log_{10}[EC_{50}\,(\mu M)]_{experimental}$ vs. $-\log_{10}[EC_{50}(\mu M)]_{predicted}$ for *T. b. rhodesiense*. Outliers are not shown; see tables S1 and S2.

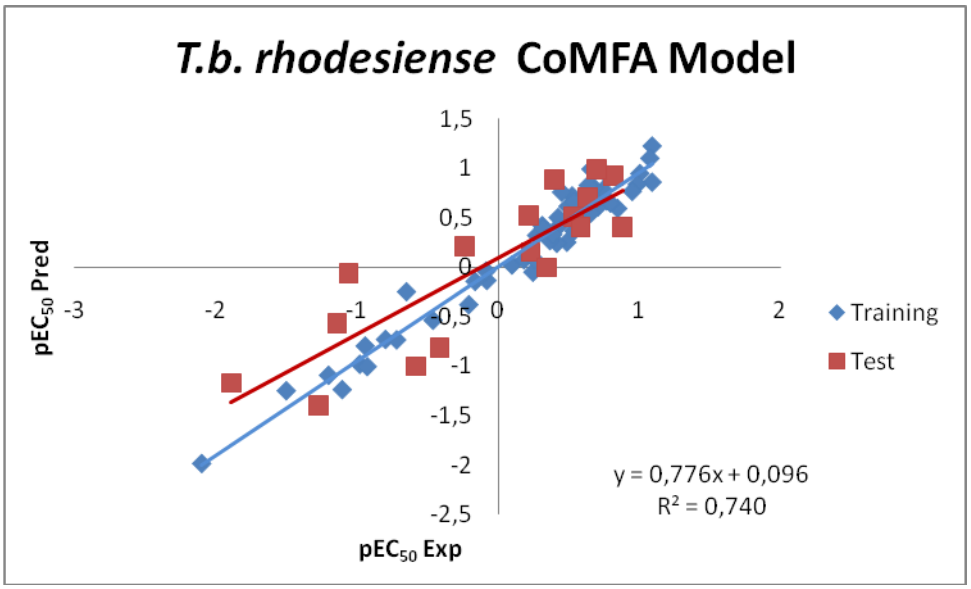


Table S3. QSAR Model for *T. b. brucei*.

Compound	pEC_{50}[a] *T. b. brucei*	Sets	Predicted *T. b. brucei*	Error
28b	-0.7364	test	-0.716	0.0204
44b	0.6383	test	1.125	0.4867
52b	<-2	test	1.474	ND
53a	0.8239	test	1.013	0.1891
34c	0.4776	test	-0.233	0.7106
25c	1.4318	test	0.733	0.6988
63a	-1.6243	test	-0.118	1.5063
41a	0.5686	test	0.536	0.0326
52c	<-2	test	1.685	ND
36a	0.6198	test	0.165	0.4548
19a	<-2	test	-1.422	ND
43c	1.2518	test	0.933	0.3188
40a	0.1549	test	0.334	0.1791
48a	-1.567	test	-0.423	1.144
60a	<-2	test	-0.421	ND
23e	ND	test	-0.461	ND
19b	-1.3328	test	-1.257	0.0758
49a	0.1549	test	0.296	0.1411
28c	-0.8573	test	-0.696	0.1613
56c	1.82391	test	0.862	0.96190874
43a	1	test	1.059	0.059
46b	0.857	test	1.413	0.556
57c	1.55284	test	0.968	0.58484197
23b	0.1549	training	-0.318	0.4729
38c	1.0862	training	1.004	0.0822
38b	0.6198	training	0.82	0.2002
25b	1.4815	training	1.544	0.0625
45c	1.6198	training	1.436	0.1838
45b	1.0969	training	1.186	0.0891
53c	0.8013	training	0.905	0.1037
53b	0.8601	training	1.077	0.2169
43b	1.0969	training	1.417	0.3201
45d	0.6421	training	0.338	0.3041
23d	-1.2227	training	-1.024	0.1987
45e	0.4921	training	0.609	0.1169
19c	-1.5627	training	-1.396	0.1667
55	1.3665	training	1.233	0.1335
33b	0.4283	training	0.385	0.0433
34b	0.3565	training	0.459	0.1025
51b	-0.4286	training	-0.314	0.1146
54	1.6198	training	1.471	0.1488
33c	0.5901	training	0.492	0.0981

46c	1.2441	training	1.528	0.2839
51c	-1.365	training	-0.646	0.719
56a	1.6198	training	1.338	0.2818
57a	0.767	training	0.768	0.001
58a	-0.7709	training	-0.195	0.5759
59a	0.8182	training	0.928	0.1098
61a	0.684	training	1.01	0.326
23c	0.2291	training	-0.738	0.9671
62a	1.9586	training	1.41	0.5486
28f	-0.4133	training	-0.542	0.1287
29a	-0.934	training	-0.769	0.165
31a	-0.1847	training	-0.147	0.0377
28a	-1.2826	training	-0.738	0.5446
26a	0.8539	training	0.701	0.1529
32a	0.0132	training	0.041	0.0278
22a	0.3188	training	0.119	0.1998
27a	1.3768	training	1.664	0.2872
23a	-0.4183	training	-0.51	0.0917
37a	0.699	training	0.545	0.154
38a	0.7447	training	0.72	0.0247
30a	0.6198	training	0.824	0.2042
47a	0.5376	training	-0.053	0.5906
25a	1.4202	training	1.835	0.4148
35a	0.5528	training	0.283	0.2698
39a	0.0809	training	-0.135	0.2159
21a	-1.3128	training	-1.093	0.2198
20a	-1.2951	training	-1.315	0.0199
42a	0.6576	training	0.638	0.0196
45a	1.0315	training	1.024	0.0075
50a	0.0757	training	0.012	0.0637
24a	0.699	training	0.752	0.053
44c	0.585	training	0.403	0.182
45g	1.5376	training	1.205	0.3326
45f	0.8153	training	0.852	0.0367
28g	-0.1038	training	-0.083	0.0208

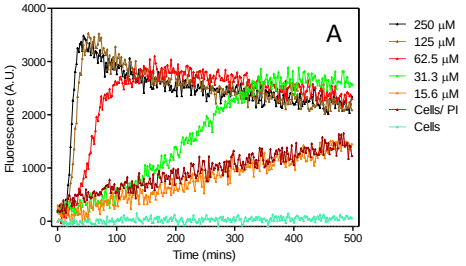
[a] $pEC_{50} = -\log_{10}[EC_{50}\,(\mu M)]$

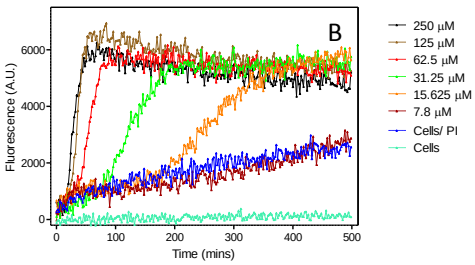
6. Effect of Compounds on Parasite Viability as Determined with the Propidium Iodide Assay.

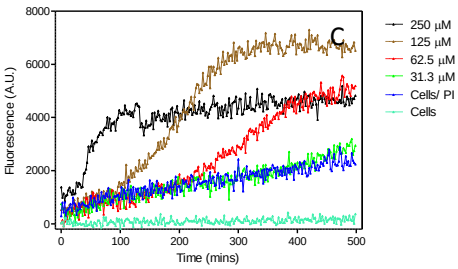
Real time monitoring of cell survival after treatment with phosphonium compounds. The experiment was performed exactly as described in the legend to Figure 1 in the main manuscript.

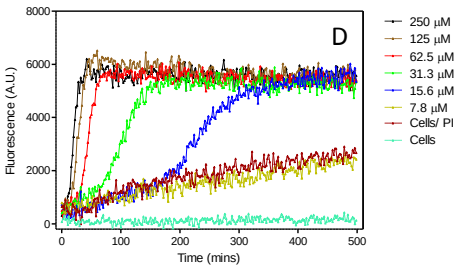
A. Compound **45e**
B. Compound **26a**
C. Compound **47a**
D. Compound **38a**
E. Compound **25b**
F. Compound **35a**
G. Compound **55**
H. Compound **36a**
I. Compound **25c**
J. Compound **43c**
K. Compound **43a**
L. Compound **45d**

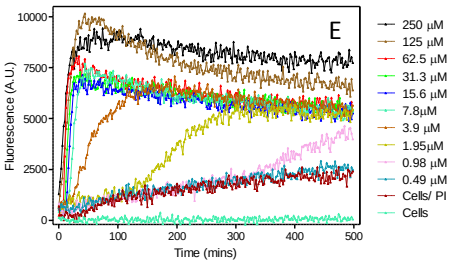
In all cases, doubling dilutions of 250 µM – 0.49 µM were used. Only traces up to the first concentration to have no effect on cell viability over the duration of the experiment (250 2-min cycles) were shown.

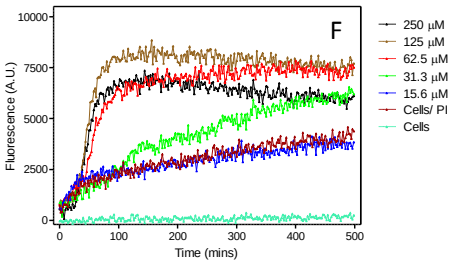

A
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
Cells/ PI
Cells

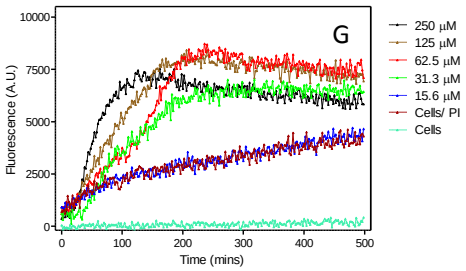

B
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.25 µM
15.625 µM
7.8 µM
Cells/ PI
Cells

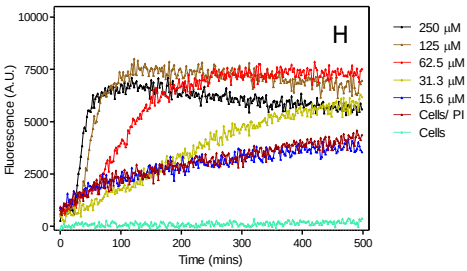

C
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
Cells/ PI
Cells

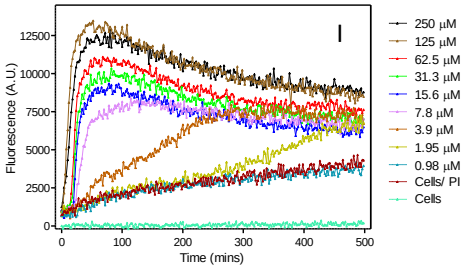

D
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
7.8 µM
Cells/ PI
Cells

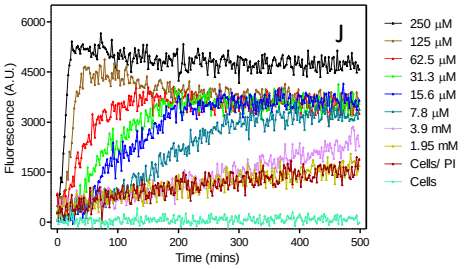

E
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
7.8µM
3.9 µM
1.95µM
0.98 µM
0.49 µM
Cells/ PI
Cells

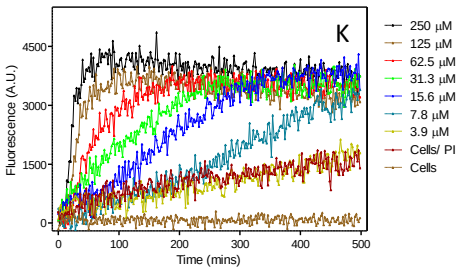

F
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
Cells/ PI
Cells

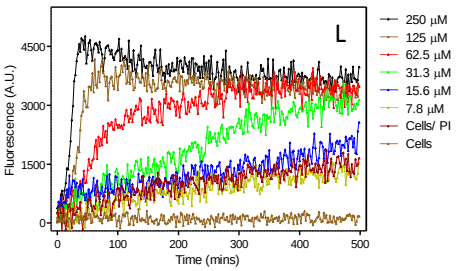

G
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
Cells/ PI
Cells


H
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
Cells/ PI
Cells


I
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
7.8 µM
3.9 µM
1.95 µM
0.98 µM
Cells/ PI
Cells


J
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
7.8 µM
3.9 mM
1.95 mM
Cells/ PI
Cells


K
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
7.8 µM
3.9 µM
Cells/ PI
Cells


L
Fluorescence (A.U.)
Time (mins)
250 µM
125 µM
62.5 µM
31.3 µM
15.6 µM
7.8 µM
Cells/ PI
Cells

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