Supporting information

Flow synthesis of nature-inspired mitochondria-targeted phenolic derivatives as potential neuroprotective agents

Desirée Pecora,[1] Francesca Annunziata,[1] Sergio Pegurri,[1] Pasquale Picone,[2] Andrea Pinto,[3] Domenico Nuzzo,[2,*] Lucia Tamborini[1,*]

[1]Department of Pharmaceutical Sciences, University of Milan, via Mangiagalli 25, 20133 Milan, Italy.

[2]Istituto per la Ricerca e l'Innovazione Biomedica (IRIB), CNR, Via Ugo La Malfa 153, 90146 Palermo, Italy.

[3]Department of Food, Environmental and Nutritional Sciences, University of Milan, via Celoria 2, 20133 Milan, Italy.

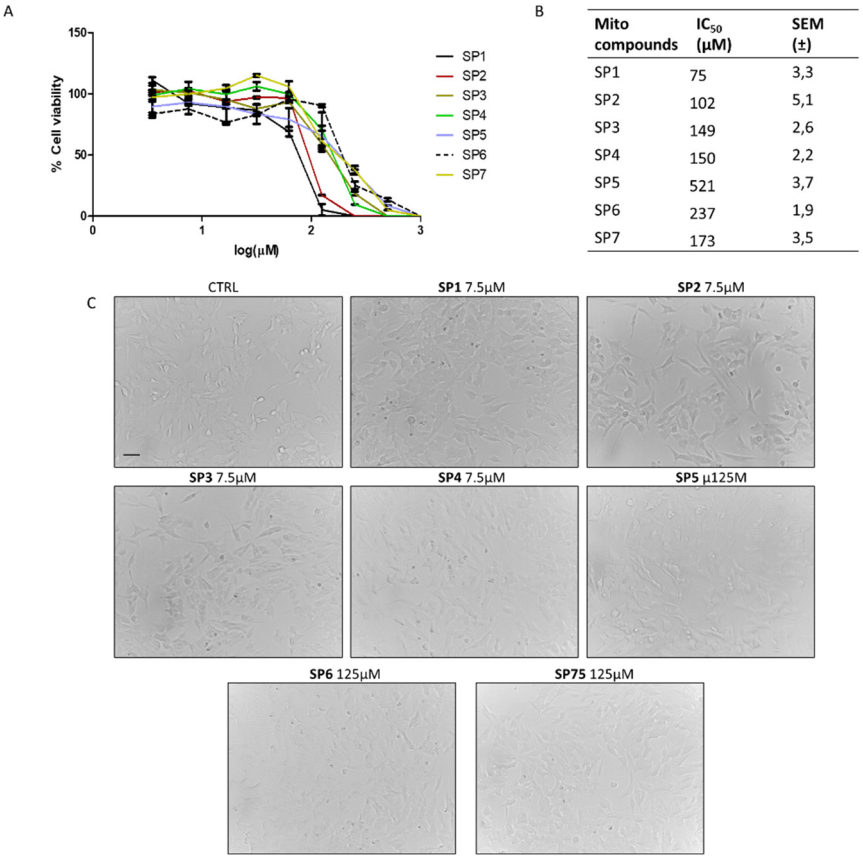
*Correspondence: lucia.tamborini@unimi.it; Tel.: + 39 0250319367; domenico.nuzzo@irib.cnr.it; Tel: +39 0916809518

Contents

- Table S1 page 2
- Figure S1 page 3
- NMR spectra page 4

Table S1. Overall yields obtained exploiting the two-step flow procedure reported in Paragraph 2.1

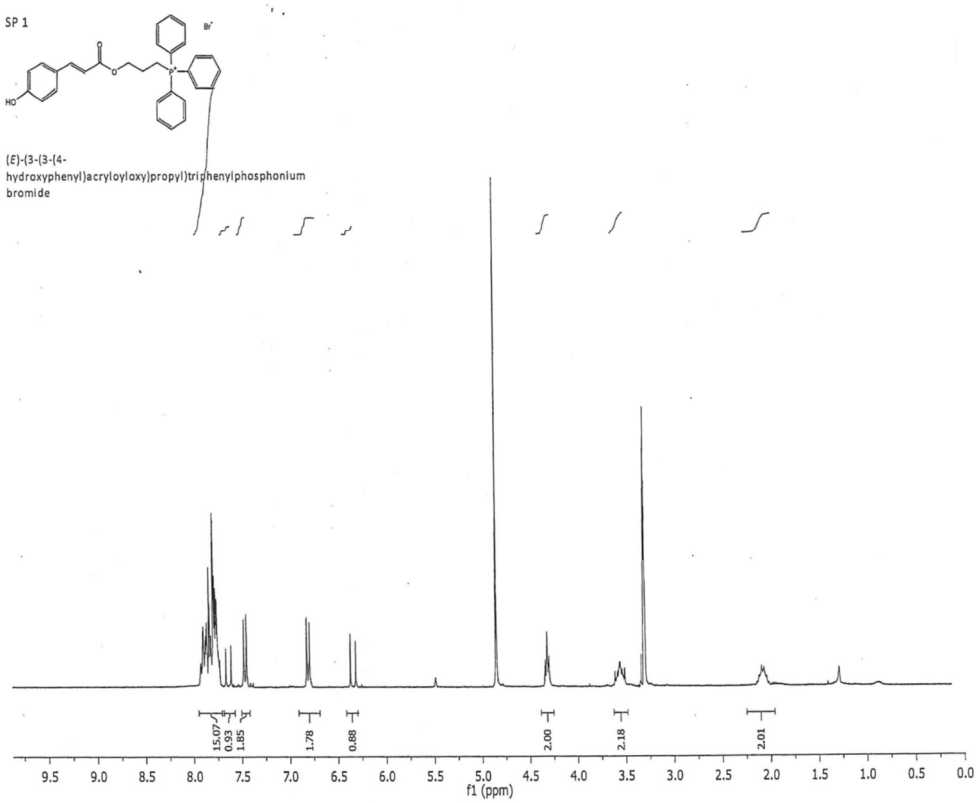
Compound	Yield (%)
SP1	37
SP2	29
SP3	49
SP4	40
SP5	50
SP6	21
SP7	18

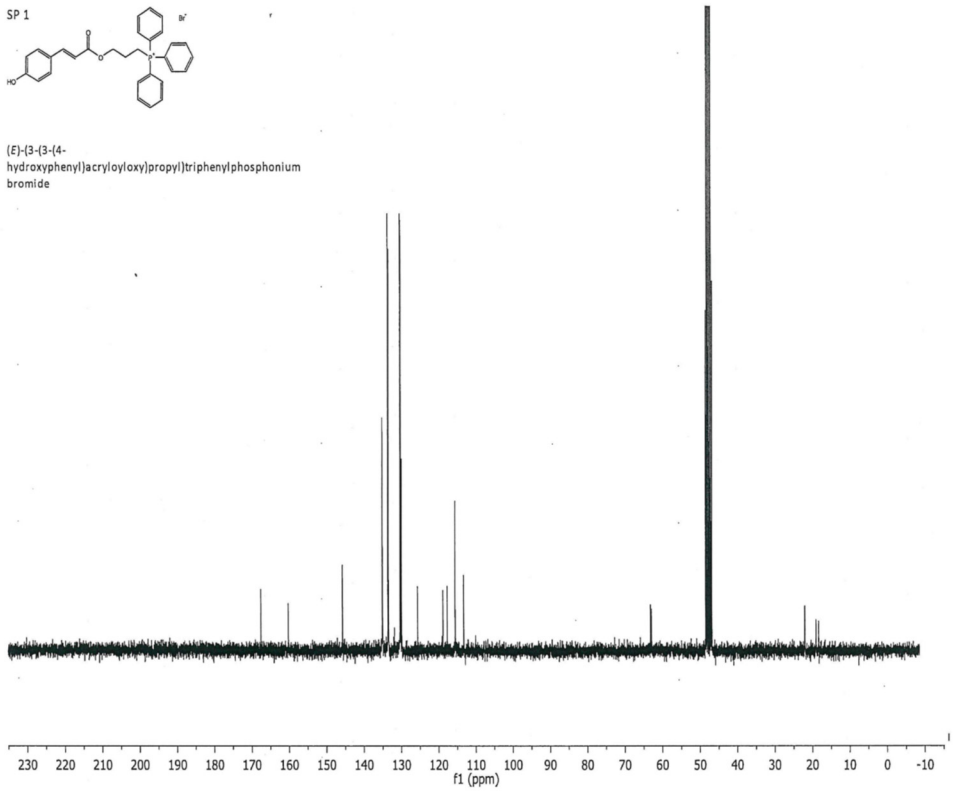


Mito compounds	IC_{50} (μM)	SEM (±)
SP1	75	3,3
SP2	102	5,1
SP3	149	2,6
SP4	150	2,2
SP5	521	3,7
SP6	237	1,9
SP7	173	3,5

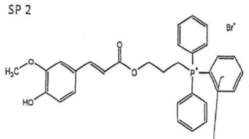
Figure S1. Effects of the MITO compounds **SP1-7** on cell viability and morphology of SH-SY5Y cells for 72 hours. A) MTS cell viability assay at 3.5, 7.5, 16.6, 31.5, 62.5,125, 250, 500 μM and 1 mM for 72 hours. B) IC_{50} concentrations calculated in GraphPad Prisma 8.4.3 software, fraction of alive cells (%) is provided on vertical axis and log concentration (μM) on horizontal axis. The IC_{50} is the concentration at which the curve passes through the 50% inhibition level. C) Representative morphological images of untreated cells (CTRL) and cells treated with the MITO compounds.

^{1}H and ^{13}C NMR spectra of compounds SP1-7

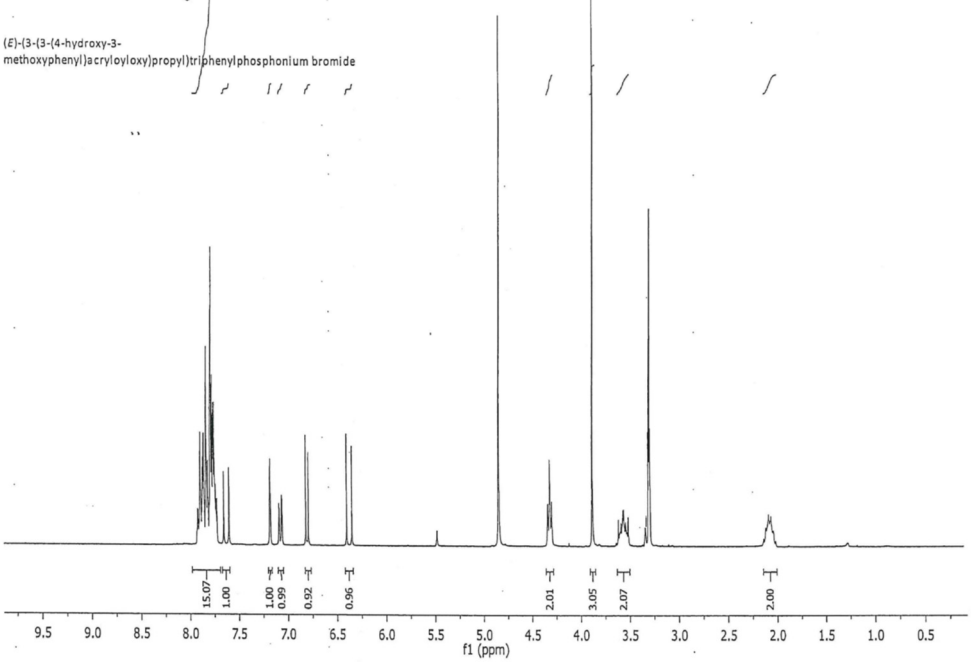




SP 2

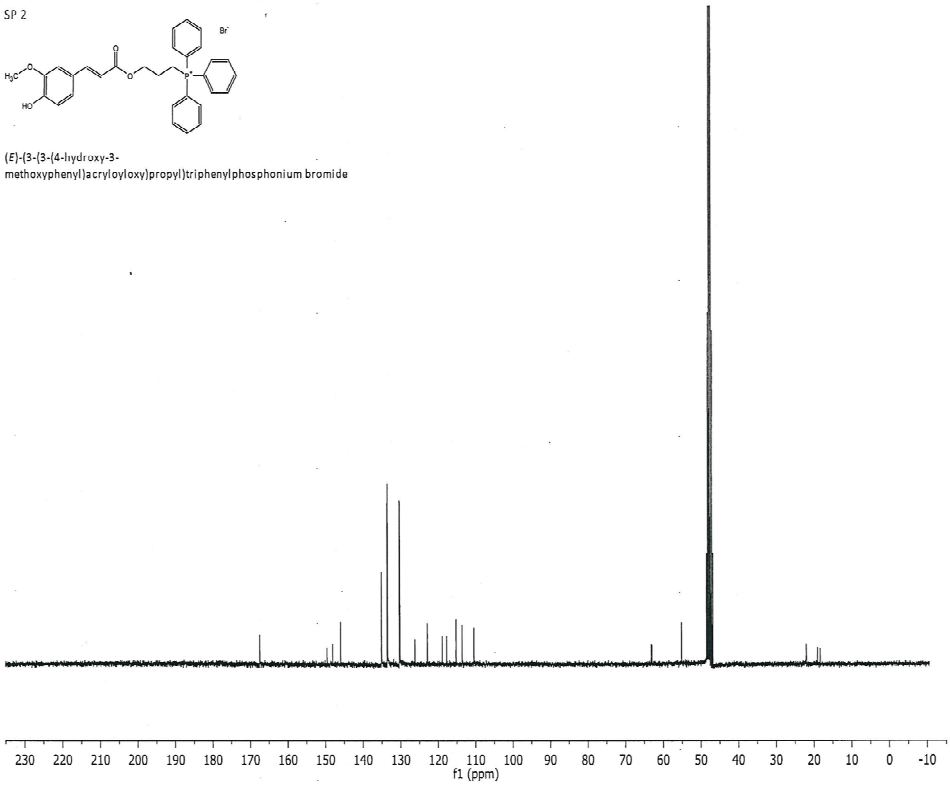


(*E*)-(3-(3-(4-hydroxy-3-methoxyphenyl)acryloyloxy)propyl)triphenylphosphonium bromide

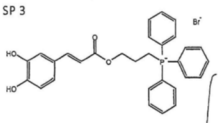


SP 2

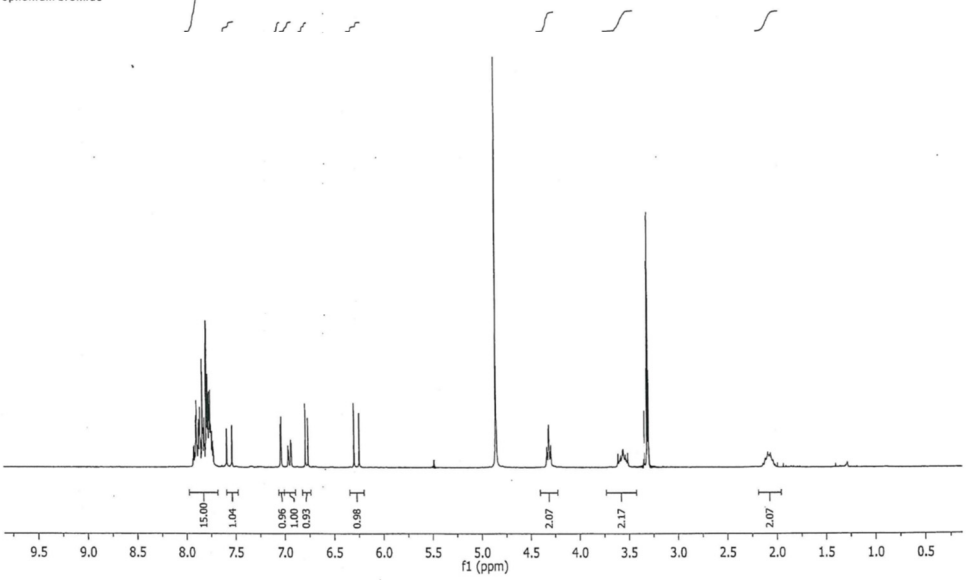
(*E*)-(3-(3-(4-hydroxy-3-methoxyphenyl)acryloyloxy)propyl)triphenylphosphonium bromide



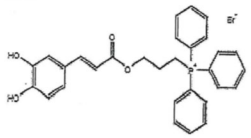
SP 3



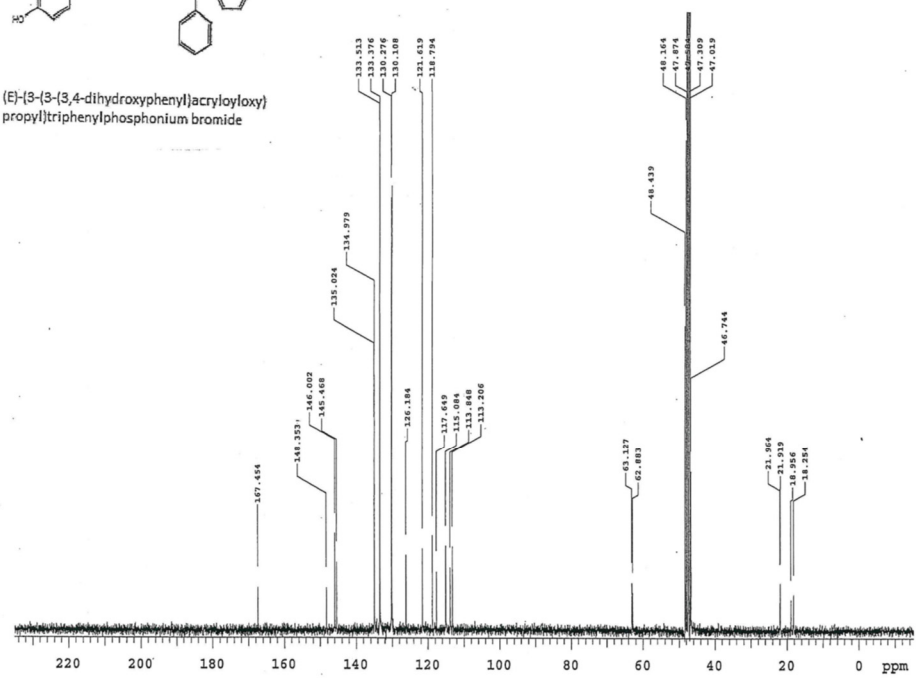
(*E*)-(3-(3-(3,4-dihydroxyphenyl)acryloyloxy)propyl)triphenylphosphonium bromide



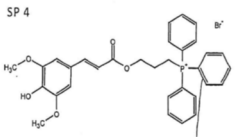
SP 3



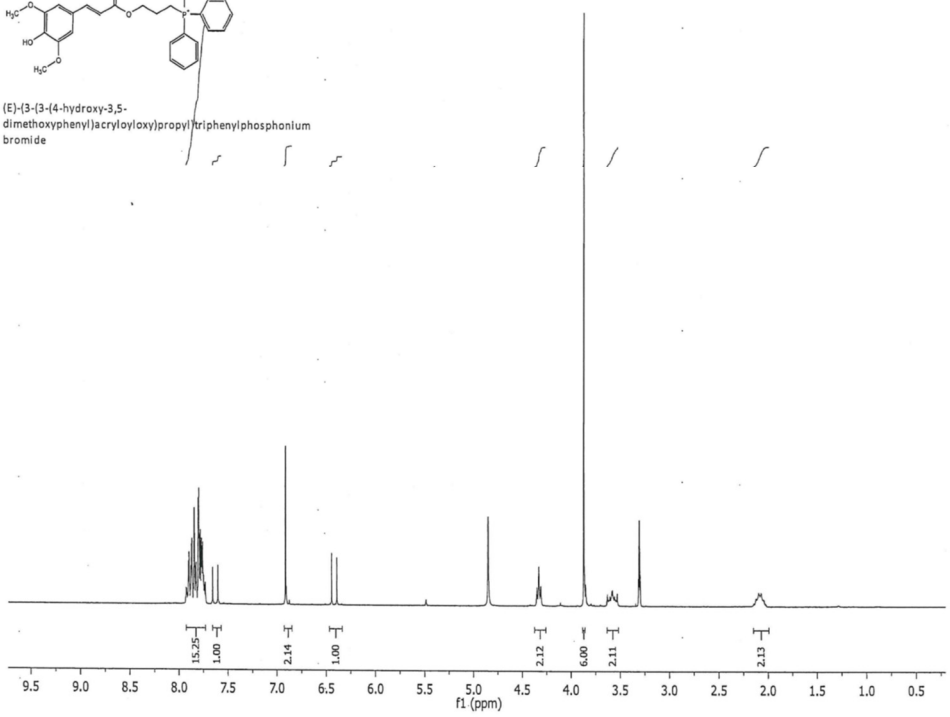
(E)-(3-(3-(3,4-dihydroxyphenyl)acryloyloxy)propyl)triphenylphosphonium bromide



SP 4

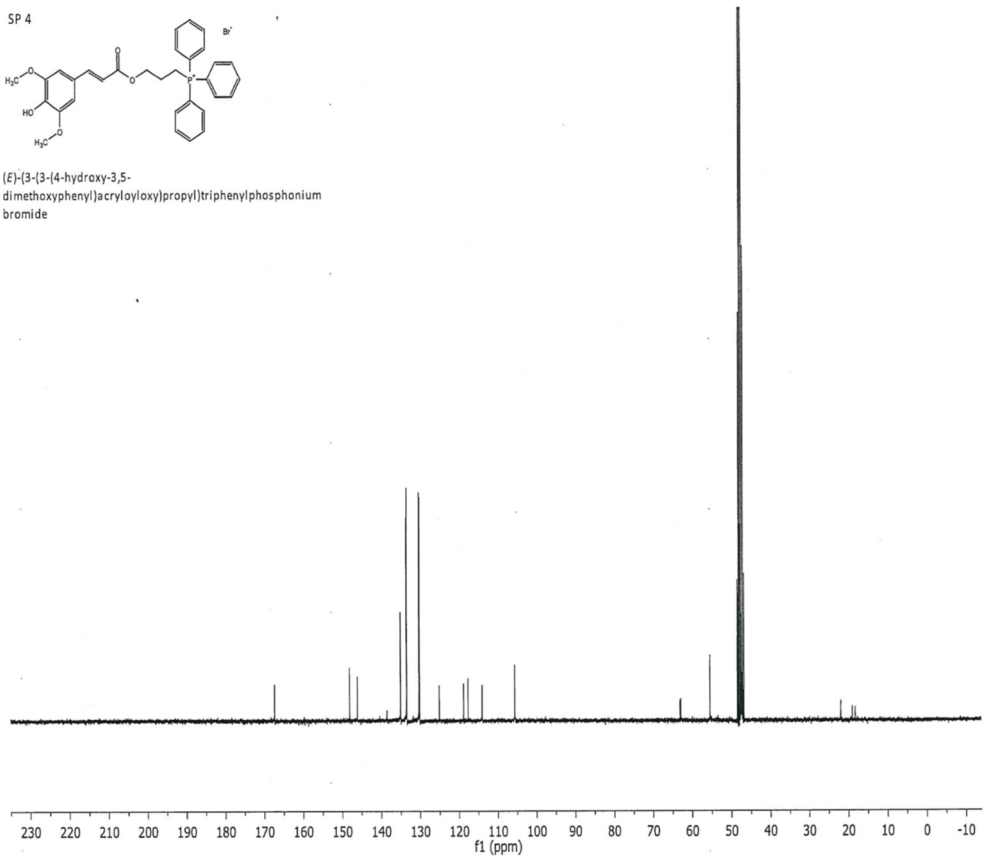


(E)-(3-(3-(4-hydroxy-3,5-dimethoxyphenyl)acryloyloxy)propyl)triphenylphosphonium bromide



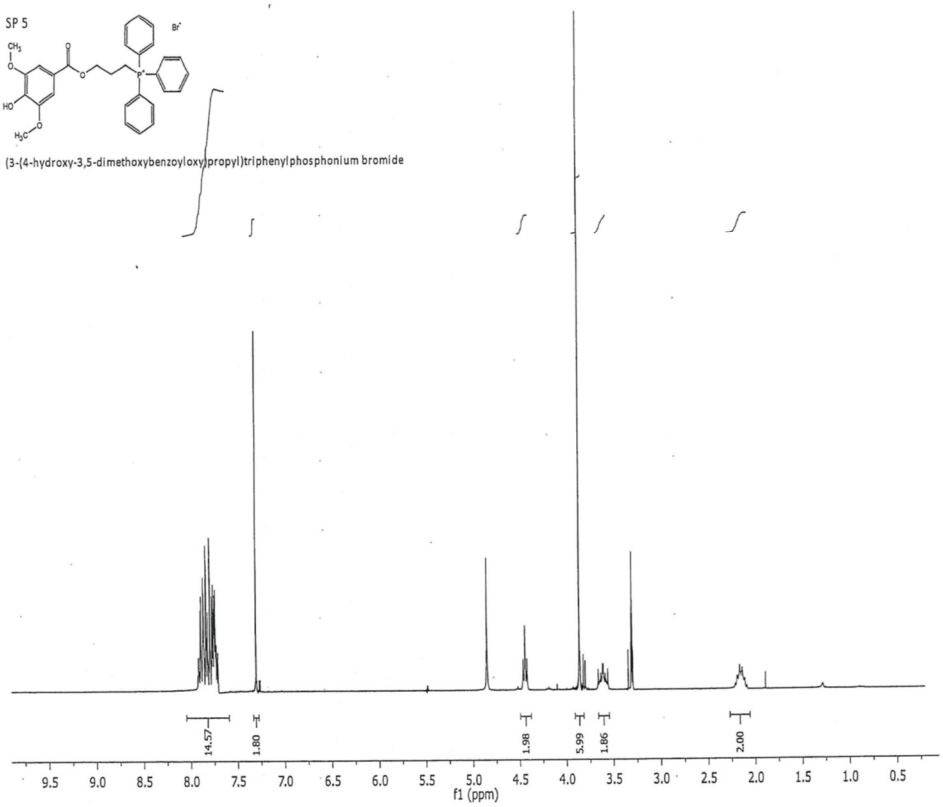
SP 4

(*E*)-(3-(3-(4-hydroxy-3,5-dimethoxyphenyl)acryloyloxy)propyl)triphenylphosphonium bromide



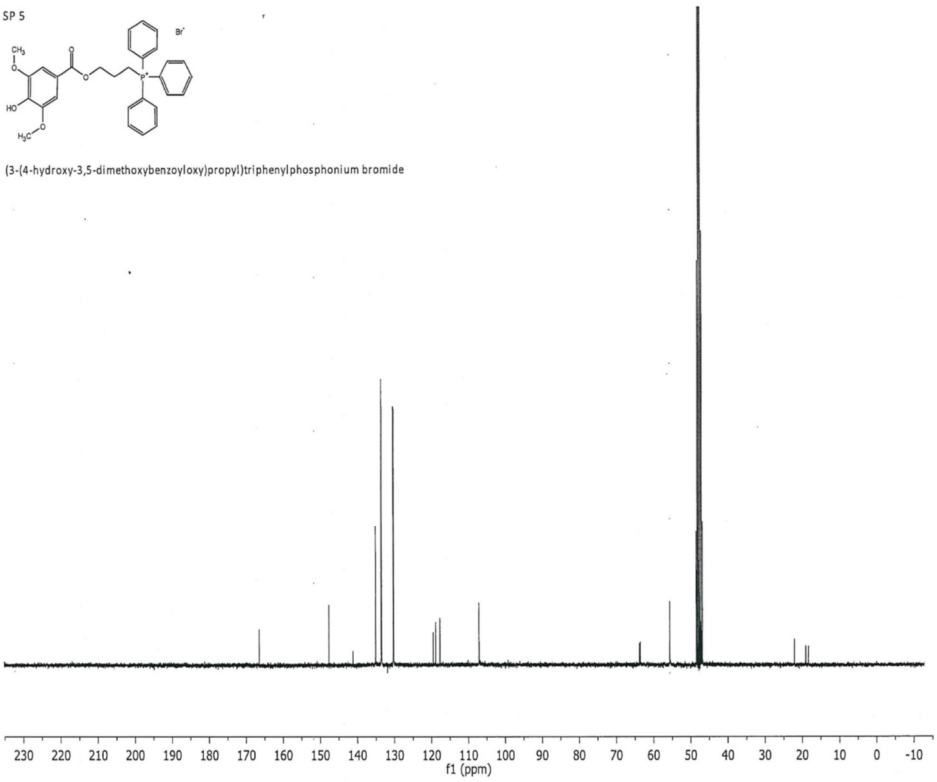
SP 5

(3-(4-hydroxy-3,5-dimethoxybenzoyloxy)propyl)triphenylphosphonium bromide

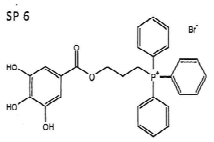


SP 5

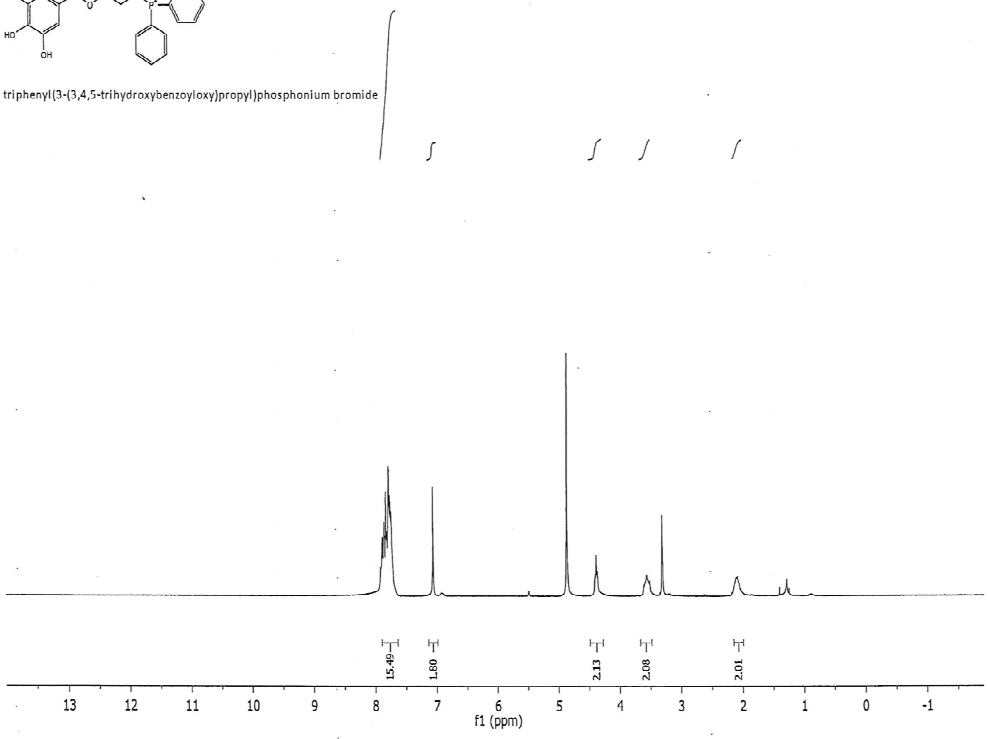
(3-(4-hydroxy-3,5-dimethoxybenzoyloxy)propyl)triphenylphosphonium bromide



SP 6

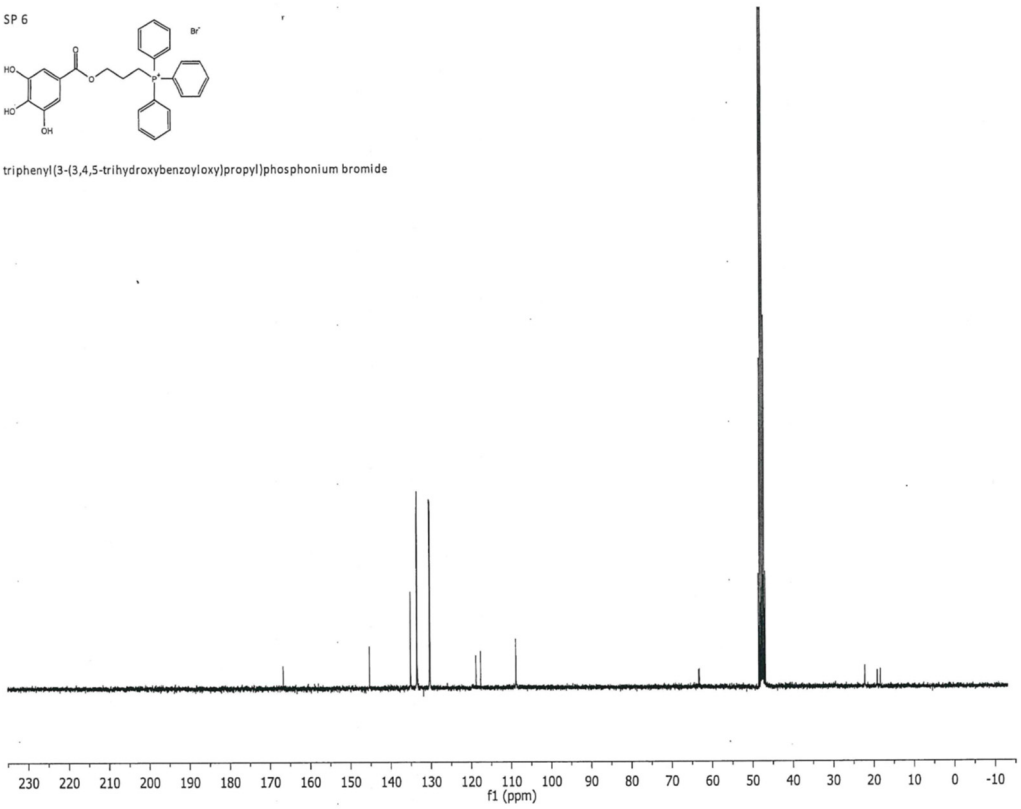


triphenyl(3-(3,4,5-trihydroxybenzoyloxy)propyl)phosphonium bromide

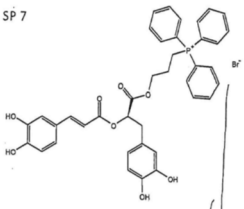


SP 6

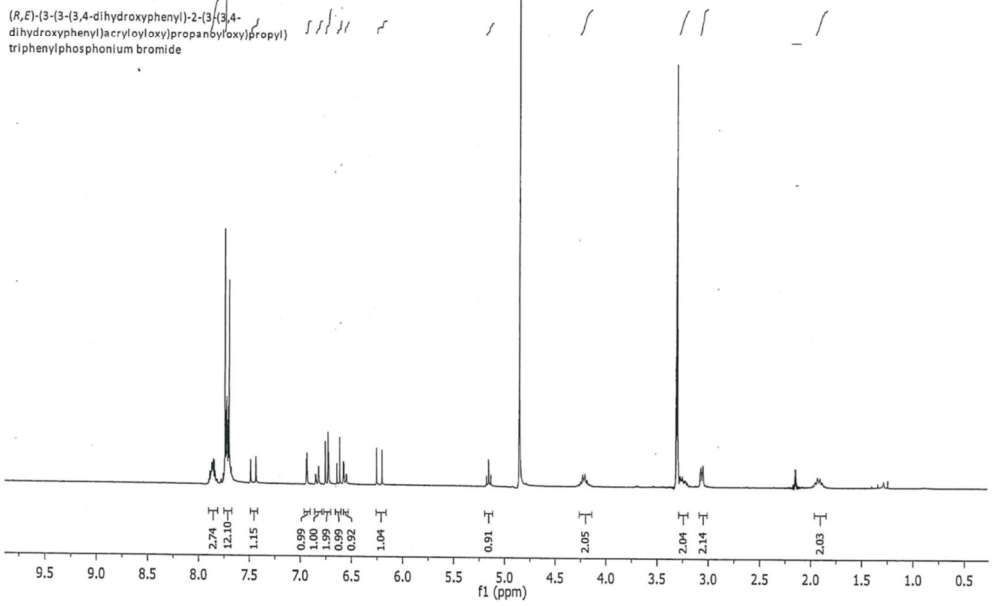
triphenyl(3-(3,4,5-trihydroxybenzoyloxy)propyl)phosphonium bromide

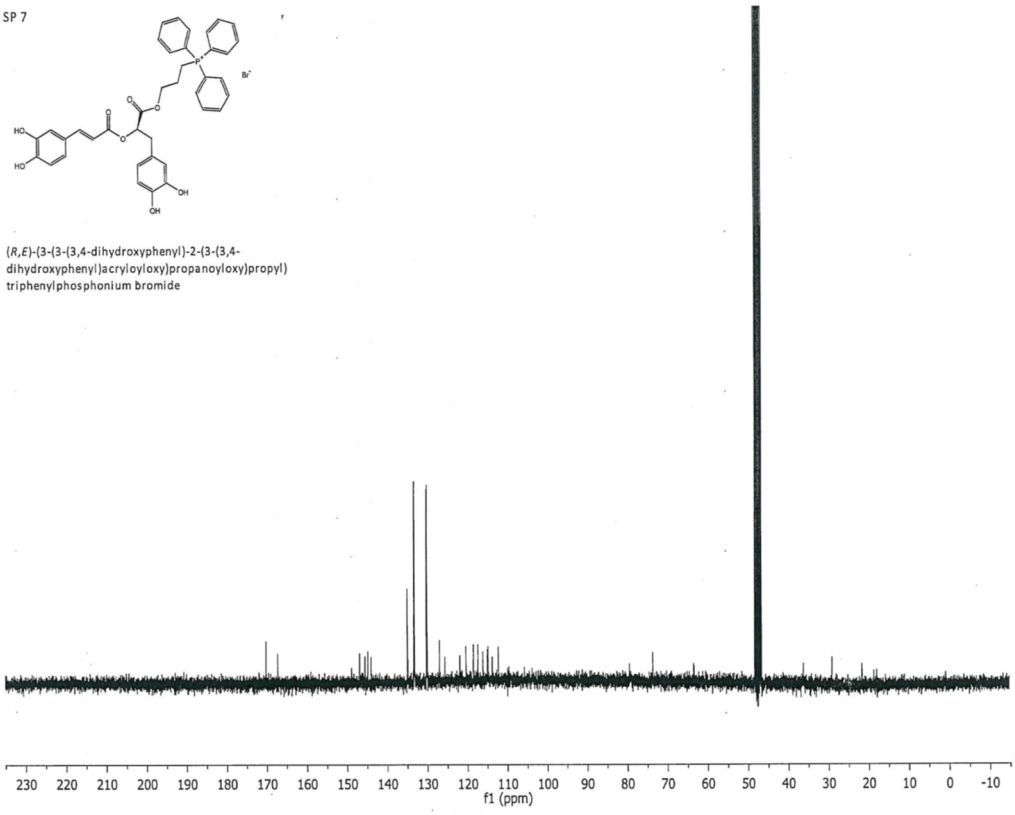


SP 7



(*R*,*E*)-(3-(3-(3,4-dihydroxyphenyl)-2-(3-(3,4-dihydroxyphenyl)acryloyloxy)propanoyloxy)propyl) triphenylphosphonium bromide



SP 7

(*R*,*E*)-(3-(3-(3,4-dihydroxyphenyl)-2-(3-(3,4-dihydroxyphenyl)acryloyloxy)propanoyloxy)propyl) triphenylphosphonium bromide