Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.
This journal is © The Royal Society of Chemistry 2024

# Supporting Information for

# "Clemastine/Tamoxifen Hybrids as Easily Accessible Antileishmanial Drug Leads"

Agostino, V. S. [1,4]; Buerdsell, M. B.[1]; Uliana, S. R. B. [2]; Denny, P. W. [3]; Coelho, A. C.[4]; Steel, P. G. [1];

[1] Department of Chemistry, Durham University, United Kingdom;

[2] Department of Parasitology, Biomedical Sciences Institute, University of Sao Paulo, Brazil

[3] Department of Biosciences, Durham University, United Kingdom

[4] Department of Animal Biology, Institute of Biology, University of Campinas, Brazil

p.g.steel@durham.ac.uk

# 1. Synthetic procedures and compound characterisation

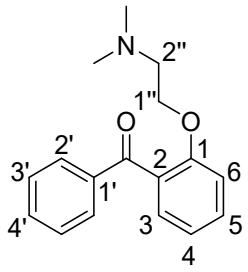
## General procedure A

$Cs_2CO_3$ (4.7 equiv.) was added to a solution of hydroxybenzophenone (1 equiv.) in anhydrous DMF or MeCN (0.03 M), and the resulting suspension stirred at RT for 30 min. Dibromoalkyl (5 equiv.) was then added and the solution stirred overnight at RT. The reaction mixture was diluted in water (X mL) and extracted with EtOAc (3 x X mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure.

## General procedure B

To a solution of hydroxybenzophenone (1 equiv.) in anhydrous DMF (0.3 M), caesium carbonate (3.5 equiv.) and TBAI (0.1 equiv.) were added. The mixture was heated to 60ºC and stirred for 15 min. Alkyl chloride (2 equiv.) was then added and the resultant solution heated under reflux overnight. After cooling to room temperature, sat. $Na_2CO_{3(aq)}$ was added (X mL) and the products were extracted with EtOAc (3 x X mL). The combined organic layers were washed with sat. $NaCO_{3(aq)}$ (4 x 2X mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

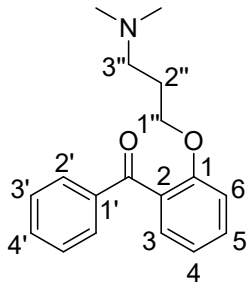
**[2''-(2-benzoylphenoxy)ethyl]dimethylamine 1**




A solution of 2-hydroxybenzophenone (100 mg, 0.5 mmol) in anhydrous acetone (2 mL) was stirred with potassium carbonate (209 mg, 1.5 mmol) and potassium iodide (92 mg, 0.5 mmol) for 20 min when 2-dimethylamine ethylchloride hydrochloride (106 mg, 0.74 mmol) in anhydrous acetone (2 mL) was slowly added to the mixture. The reaction was then heated to 40ºC and stirred for 72 hours. After cooling, the reaction mixture was diluted with water and the products extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (10% MeOH in DCM) to afford the title compound **47** (43 mg, 32%) as a yellow oil.

$\delta_H$ (700 MHz, $CDCl_3$) 7.77 (dd, *J* = 7.1, 1.2 Hz, 2H, 2'-***H***), 7.55 – 7.51 (m, 1H, 4'-***H***), 7.47 – 7.44 (m, 1H, 5-***H***), 7.43 – 7.39 (m, 3H, 3'-***H***, 3-***H***), 7.05 (dt, *J* = 7.4, 0.9 Hz, 1H, 4-***H***), 6.97 (dd, *J* = 8.4, 0.9 Hz, 1H, 6-***H***), 4.00 (t, *J* = 5.8 Hz, 2H, 1''-C***H₂***), 2.37 (t, *J* = 5.8 Hz, 2H, 2''-C***H₂***), 2.10 (s, 6H, C***H₃*** x2); $\delta_C$ (176 MHz, $CDCl_3$) 196.7 ($Ar_2$***C***O), 156.7 (***C***-1), 138.3 (***C***-1'), 132.7 (***C***-4'), 132.0 (***C***-5), 129.7 (***C***-3), 129.6 (***C***-2'), 129.2 (***C***-2), 128.1 (***C***-3'), 120.8 (***C***-4), 112.6 (***C***-6), 67.3 (***C***-1''), 57.6 (***C***-2''), 45.8 (***C***$H_3$); Accurate mass: found [M+H] 270.1507, $C_{17}H_{20}NO_2$ requires *M,* 270.1494.

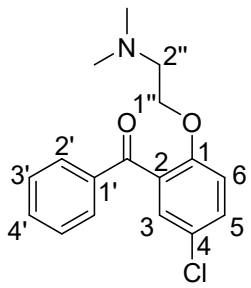
**[3''-(2-benzoylphenoxy)propyl]dimethylamine 2**




2-hydroxybenzophenone (70 mg, 0.35 mmol) was reacted with 3-dimethylaminopropylchloride hydrochloride (84 mg, 0.53 mmol) following general procedure B. Purification by column chromatography (10% MeOH in DCM) afforded the title compound **49** (71 mg, 71%) as a yellow oil.

$\delta_H$ (700 MHz, $CDCl_3$) 7.79 – 7.75 (m, 2H, 2'-***H***), 7.55 – 7.50 (m, 1H, 4'-***H***), 7.46 – 7.39 (m, 4H, 3-***H***, 5-***H***, 3'-***H***), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H, 4-***H***), 6.97 – 6.93 (m, 1H, 6-***H***), 3.92 (t, *J* = 6.1 Hz, 2H, 1''-$\boldsymbol{H_2}$), 2.05 (s, 6H, C$\boldsymbol{H_3}$ x2), 1.96 (t, *J* = 7.4 Hz, 2H, 3'' $\boldsymbol{H_2}$), 1.59 (m, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (176 MHz, $CDCl_3$), 196.9 ($Ar_2$***C***O), 156.7 (***C***-1), 138.5 (***C***-1'), 132.7 (***C***-4'), 132.0 (***C***-5), 129.7 (***C***-3), 129.5 (***C***-2'), 129.05 (***C***-2), 128.1 (***C***-3'), 120.6 (***C***-4), 112.1 (***C***-6), 66.4 (***C***-1''), 55.9 (***C***-3''), 45.3 (***C***$H_3$), 27.1 (***C***-2''); Accurate mass: found [M+H] 284.1658, $C_{18}H_{22}NO_2$ requires M, 284.1651.

**[2''-(2-benzoyl-4-chlorophenoxy)ethyl]dimethylamine 3**

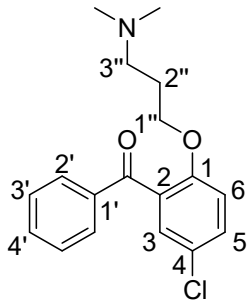



5-chloro-2-hydroxybenzophenone (100 mg, 0.43 mmol) was reacted with 2-dimethylamino-ethylchloride hydrochloride (490 mg, 1.5 mmol) following general

procedure B. The product was purified by column chromatography (10% MeOH in DCM with 1% $NEt_3$) to afford the title compound **49** (63 mg, 48%) as a yellow oil.

$\delta_H$ (700 MHz, $CDCl_3$) 7.78 – 7.75 (m, 2H, 2'-***H***), 7.58 – 7.55 (m, 1H, 4'-***H***), 7.45 – 7.42 (m, 2H, 3'-***H***), 7.41 (dd, *J* = 8.8, 2.6 Hz, 1H, 5-***H***), 7.37 (d, *J* = 2.6 Hz, 1H, 3-***H***), 6.91 (d, *J* = 8.8 Hz, 1H, 6-***H***), 3.97 (t, *J* = 5.8 Hz, 2H, 1''-$\boldsymbol{H_2}$), 2.35 (t, *J* = 5.8 Hz, 2H, 2''-$\boldsymbol{H_2}$), 2.08 (s, 6H, C$\boldsymbol{H_3}$); $\delta_C$ (176 MHz, $CDCl_3$) 195.0 ($Ar_2\boldsymbol{C}O$), 155.2 (***C***-1), 137.6 (***C***-1'), 133.0 (***C***-4'), 131.6 (***C***-5), 130.5 (***C***-4), 129.6 (***C***-2'), 129.3 (***C***-3), 128.3 (***C***-3'), 126.0 (***C***-2), 113.9 (***C***-6), 67.9 (***C***-1''), 57.5 (***C***-2''), 45.8 (***C***$H_3$); Accurate mass: found [M+H] 304.1119, $C_{17}H_{19}N^{35}ClO_2$ requires *M*, 304.1104.

**[3''-(2-benzoyl-4-chlorophenoxy)propyl]dimethylamine 4**

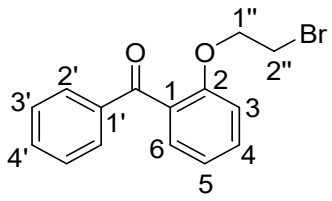



5-chloro-2-hydroxybenzophenone (100 mg, 0.43 mmol) was reacted with 3-dimethylaminepropylchloride hydrochloride (136 mg, 0.86 mmol) following general procedure B. The product was purified by column chromatography (10% MeOH in DCM with 1% $NEt_3$) to afford the title compound **49** (53 mg, 39%) as a yellow oil.

$\delta_H$ (700 MHz, $CDCl_3$) 7.79 – 7.76 (m, 2H, 2'-***H***), 7.60 – 7.56 (m, 1H, 4'-***H***), 7.48 – 7.45 (m, 2H, 3'-***H***), 7.41 (dd, 1H, *J* = 8.8, 2.6 Hz, 5-***H***), 7.37 (d, 1H, *J* = 2.6, 3-***H***), 6.90 (d, 1H, *J* = 8.8, 6-***H***), 3.97 (t, 2H, *J* = 5.7, 1''-$\boldsymbol{H_2}$), 2.39 – 2.33 (m, 6H, C$\boldsymbol{H_3}$ x2), 2.32 – 2.24 (m, 2H, 3''-$\boldsymbol{H_2}$), 1.88 (m, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (176 MHz, $CDCl_3$) 194.8 ($Ar_2\boldsymbol{C}O$), 154.8 (***C***-1), 137.8 (***C***-1'), 133.2 (***C***-4'), 131.8 (***C***-5), 130.1 (***C***-4), 129.6 (***C***-2'), 129.5 (***C***-3), 128.5

(***C***-3'), 126.3 (***C***-2), 113.6 (***C***-6), 66.0 (***C***-1''), 55.4 (***C***-3''), 43.9 (***C***$H_3$), 25.5 (***C***-2''); Accurate mass: found [M+H] 318.1261, $C_{18}H_{21}N^{35}ClO_2$ requires *M*, 318.1261.

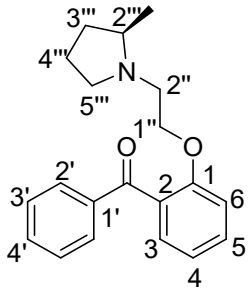
**2-(2''-bromoethoxy)phenyl](phenyl)methanone 5a**




1,2-dibromoethane (0.262 mL, 3.027 mmol) was reacted with 2-hydroxybenzophenone (150 mg, 0.757 mmol) in anhydrous DMF (3 mL) following general procedure A. Purification by column chromatography (0 to 100% Chloroform) afforded the title compound (82 mg, 36%) as a colourless oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.83 – 7.79 (m, 2H, 2'-***H***), 7.61 – 7.56 (m, 1H, 4'-***H***), 7.51 – 7.43 (m, 4H, 4-***H***, 6-***H***, 3'-***H***), 7.10 – 7.06 (m, 1H, 5-***H***), 7.02 – 6.99 (m, 1H, 3-***H***), 4.09 – 4.05 (m, 2H, 1''-***H₂***), 3.68 – 3.64 (m, 2H, 2''-***H₂***); $\delta_C$ (151 MHz, $CDCl_3$) 196.5 ($Ar_2$***C***O), 156.9 (***C***-2), 138.4 (***C***-1'), 132.9 (***C***-4'), 132.5 (***C***-4), 130.3 (***C***-6), 129.5 (***C***-2'), 128.8 (***C***-1), 128.4 (***C***-3'), 121.1 (***C***-5), 113.4 (***C***-3), 70.5 (***C***-1''), 61.1 (***C***-2''). Accurate mass: found [M+H] 305.0193, $C_{15}H_{14}{}^{79}BrO_2$ requires *M*, 305.0177.

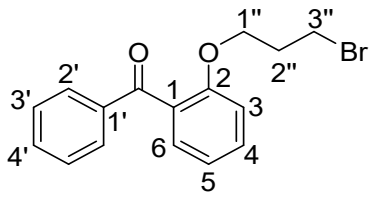
**(2’’’*R*)-*N*-[2’’-(2-benzoylphenoxy)ethyl]-2’’’-methylpyrrolidine 5**




2-(2’’-Bromoethoxy)phenyl](phenyl)methanone (82 mg, 0.27 mmol) was reacted with (2R)-methylpyrrolidine hydrochloride (37 mg, 0.303 mmol) in anhydrous DMF following general procedure B. Product was purified by column chromatography (10% MeOH in DCM) to afford the title compound (45 mg, 53%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.80 – 7.75 (m, 2H, 2’-***H***), 7.56 – 7.52 (m, 1H, 4’-***H***), 7.48 – 7.44 (m, 1H, 5-***H***), 7.44 – 7.38 (m, 3H, 3’-***H***, 3-***H***), 7.05 (td, *J* = 7.5, 0.9 Hz, 1H, 4-***H***), 6.98 (dd, *J* = 8.4, 0.9 Hz, 1H, 6-***H***), 4.24 – 3.97 (m, 2H, 1’’-***H₂***), 3.01 – 2.92 (m, 1H, 5’’’-***H***), 2.92 – 2.81 (m, 1H, 2’’-***H***), 2.37 – 2.29 (m, 1H, 2’’-***H***), 2.30 – 2.22 (m, 1H, 2’’’-***H***), 2.06 – 1.05 (m, 1H, 5’’’-***H***), 1.88 – 1.78 (m, 1H, 3’’’-***H***), 1.73 – 1.62 (m, 1H, 4’’’-***H***), 1.61 – 1.51 (m, 1H, 4’’’-***H***), 1.42 – 1.31 (m, 1H, 3’’’-***H***), 1.01 (d, *J* = 6.1 Hz, 3H, C***H₃***); $\delta_C$ (151 MHz, $CDCl_3$) 196.7 ($Ar_2$***C***O), 156.5 (***C***-1), 138.2 (***C***-1’), 132.7 (***C***-4’), 132.0 (***C***-5), 129.6 (***C***-2’, ***C***-3), 129.0 (***C***-2), 128.1 (***C***-3’), 120.8 (***C***-4), 112.4 (***C***-6), 67.5 (***C***-1’’), 60.4 (***C***-2’’’) 54.4 (***C***-5’’’), 51.9 (***C***-2’’), 32.1 (***C***-3’’’), 21.7 (***C***-4’’’), 18.5 (***C***$H_3$). Accurate mass: found [M+H] 310.1820, $C_{20}H_{24}NO_2$ requires *M*, 310.1807.

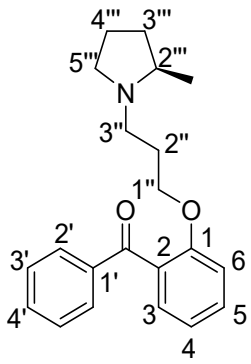
**[2-(3''-bromopropoxy)phenyl](phenyl)methanone 6a**




2-hydroxybenzophenone (70 mg, 0.35 mmol) was reacted with 1,3-dibromopropane (0.12 mL, 1.41 mmol) in anhydrous DMF (1.2 mL) following general procedure A. Purification by column chromatography (10% MeOH in DCM) afforded the title compound (45 mg, 42%) as a colourless oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.79 – 7.76 (m, 2H, 2'-***H***), 7.57 – 7.53 (m, 1H, 4'-***H***), 7.50 – 7.43 (m, 4H, 4-***H***, 6-***H***, 3'-***H***), 7.10 – 7.06 (m, 1H, 5-***H***), 6.99 – 6.96 (m, 1H, 3-***H***), 4.02 (t, *J* = 5.6 Hz, 2H, 1''-$\boldsymbol{H_2}$), 2.97 (t, *J* = 6.3 Hz, 2H, 3''-$\boldsymbol{H_2}$), 1.97 (tt, *J* = 6.3, 5.6 Hz, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (151 MHz, $CDCl_3$) 196.7 ($Ar_2$***C***O), 156.4 (***C***-2), 138.4 (***C***-1'), 132.7 (***C***-4'), 132.1 (***C***-4), 129.9 (***C***-6), 129.3 (***C***-2'), 128.9 (***C***-1), 128.3 (***C***-3'), 120.9 (***C***-5), 111.9 (***C***-3), 65.2 (***C***-1''), 31.9 (***C***-3''), 29.7 (***C***-2''). Accurate mass: found [M+H] 319.0324, $C_{16}H_{15}{}^{79}BrO_2$ requires *M*, 319.0334.

**(2'''*R*)-*N* -[3''-(2-benzoylphenoxy)propyl]-2'''-methylpyrrolidine 6**

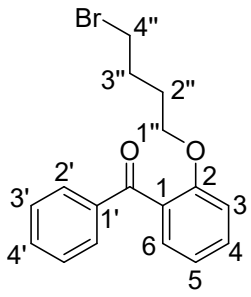



[2-(3''-bromopropoxy)phenyl](phenyl)methanone (106 mg, 0.332 mmol) was reacted with (2*R*)-Methylpyrrolidine hydrochloride (44 mg, 0.362 mmol) following general

procedure B. Product was purified by column chromatography (10% MeOH in DCM with 1% $NEt_3$) to afford the title compound (40 mg, 66%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.81 – 7.76 (m, 2H, 2'-***H***), 7.55 – 7.51 (m, 1H, 4'-***H***), 7.45 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 1H, 5-***H***), 7.43 – 7.39 (m, 3H, 3'-***H***, 3-***H***), 7.05 (td, *J* = 7.5, 0.9 Hz, 1H, 4-***H***), 6.96 (dd, *J* = 8.4, 0.9 Hz, 1H, 6-***H***), 4.02 – 3.89 (m, 2H, 1''-$\boldsymbol{H_2}$), 3.06 (s, 1H, 5'''-***H***), 2.64 – 2.54 (m, 1H, 3''-***H***), 2.33 – 2.17 (m, 1H, 2'''-***H***), 2.05 – 1.95 (m, 1H, 5'''-***H***), 1.93 – 1.81 (m, 2H, 3''-***H***, 3'''-***H***), 1.80 – 1.60 (m, 4H, 2''-$\boldsymbol{H_2}$, 4'''-$\boldsymbol{H_2}$), 1.44 (s, 1H, 3'''-***H***), 1.08 – 0.94 (m, 3H, C$\boldsymbol{H_3}$); $\delta_C$ (151 MHz, $CDCl_3$) 196.8 ($Ar_2$***C***O), 156.6 (***C***-1), 138.3 (***C***-1'), 132.7 (***C***-4'), 132.1 (***C***-5), 129.7 (***C***-3), 129.6 (***C***-2'), 129.0 (***C***-2), 128.2, 120.7 (***C***-4), 112.1 (***C***-6), 66.6 (***C***-1''), 60.5 (***C***-2'''), 53.6 (***C***-5'''), 50.5 (***C***-3''), 32.4 (***C***-3'''), 27.7 (***C***-2''), 21.5 (***C***-4'''), 18.3 (***C***$H_3$). Accurate mass: found [M+H] 324.1963, $C_{21}H_{26}NO_2$ requires *M*, 324.1964.

**[2-(4''-bromobutoxy)phenyl](phenyl)methanone 7a**

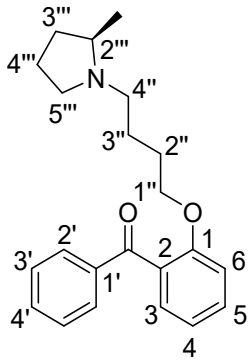



1,4-dibromobutane (0.36 mL, 3.023 mmol) was reacted with 2-hydroxybenzophenone (156 mg, 0.79 mmol) in anhydrous DMF (8 mL) following general procedure B. Product was purified by column chromatography (0-100% DCM in Hexane) to afford title product (203 mg, 78%) as a white solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.76 (d, *J* = 7.4 Hz, 2H, 2'-***H***), 7.54 (t, *J* = 7.6 Hz, 1H, 4'-***H***), 7.50 – 7.36 (m, 4H, 4- ***H***, 6- ***H***, 3'-***H***), 7.06 (t, *J* = 7.4 Hz, 1H, 5-***H***), 6.94 (d, *J* = 8.3 Hz, 1H, 3-

***H***), 3.90 (t, *J* = 5.8 Hz, 2H, 1''-***H*$_2$**), 3.17 (t, *J* = 6.5 Hz, 2H, 4''- ***H*$_2$**), 1.69 – 1.56 (m, 2H, 2''-***H*$_2$**), 1.52 (m, 2H, 3''-***H*$_2$**); $\delta_C$ (151 MHz, $CDCl_3$) 196.8 ($Ar_2$***C***O), 156.6 (***C***-2), 138.5 (***C***-1'), 132.7 (***C***-4'), 132.1 (***C***-4), 129.8 (***C***-6), 129.4 (***C***-2'), 129.0 (***C***-1), 128.2 (***C***-3'), 120.8 (***C***-5), 112.0 (***C***-3), 66.9 (***C***-1''), 33.3 (***C***-4''), 28.7 (***C***-2''), 27.4 (***C***-3''). Accurate mass: found [M+H] 333.0476, $C_{17}H_{18}{}^{79}BrO_2$ requires *M*, 333.0490.

**(2'''*R*)- *N* -[4''-(2-benzoylphenoxy)butyl]-2'''-methylpyrrolidine 7**

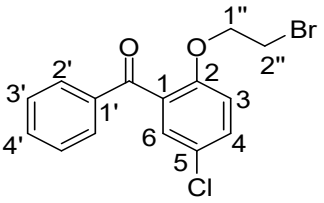



[2-(4''-bromobutoxy)phenyl](phenyl)methanone (150 mg, 0.45 mmol) was reacted with (2*R*)-methylpyrrolidine hydrochloride (57.5 mg, 0.47 mmol) in anhydrous DMF (2.5 mL) following general procedure B. Product was purified by column chromatography (10% MeOH in DCM) to afford the title compound (70 mg, 46%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.80 – 7.76 (m, 2H, 2'-***H***), 7.55 – 7.51 (m, 1H, 4'-***H***), 7.45 (td, *J* = 8.5, 7.5 Hz, 1H, 5-***H***), 7.43 – 7.37 (m, 3H, 3-***H***, 3'-***H***), 7.03 (td, *J* = 7.5, 0.9 Hz, 1H, 4-***H***), 6.95 (d, *J* = 8.5 Hz, 1H, 6-***H***), 3.98 – 3.84 (m, 2H, 1''-***H*$_2$**), 3.11 – 2.99 (m, 1H, 5'''-***H***), 2.72 – 2.61 (m, 1H, 4''-***H***), 2.42 – 2.22 (m, 1H, 2'''-***H***), 2.14 – 1.95 (m, 2H, 4''-***H***, 5'''-***H***), 1.96 – 1.85 (m, 1H, 3'''-***H***), 1.85 – 1.72 (m, 1H, 4'''-***H***), 1.72 – 1.62 (m, 1H, 4'''-***H***), 1.61 – 1.50 (m, 1H, 2''-***H***), 1.52 – 1.31 (m, 4H, 2''-***H***, 3''-***H*$_2$**, 3'''-***H***), 1.10 (d, *J* = 6.2 Hz, 3H, C***H*$_3$**); $\delta_C$ (151 MHz, $CDCl_3$) 196.7 ($Ar_2$***C***O), 156.7 (***C***-1), 138.2 (***C***-1'), 132.7 (***C***-4'), 131.9 (***C***-5), 129.6 (***C***-3), 129.6 (***C***-2'), 129.0 (***C***-2), 128.1 (***C***-3'), 120.5 (***C***-4), 112.2 (***C***-6), 68.1 (***C***-1''), 60.6 (***C***-2'''), 53.4 (***C***-5'''), 53.3 (***C***-4''), 32.4 (***C***-3'''), 26.9 (***C***-2''),

24.4 (***C***-3''), 21.5 (***C***-4'''), 18.2 (***C***$H_3$). Accurate mass: found [M+H] 338.2133, $C_{22}H_{28}NO_2$ requires *M*, 338.2120.

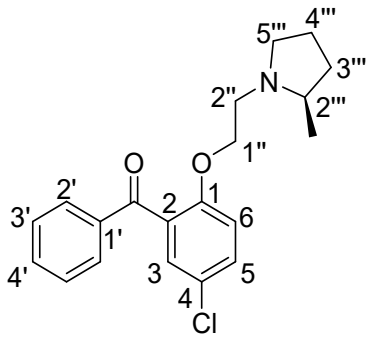
**[2-(2''-bromopropoxy)-5-chlorophenyl](phenyl)methanone 8a**




5-chloro-2-hydroxybenzophenone (100 mg, 0.43 mmol) was reacted with 2-bromoethane (0.15 mL, 1.72 mmol) in anhydrous DMF (1.4 mL) following general procedure A. Purification by column chromatography (100% Chloroform) afforded the title compound (78 mg, 54%) as a colourless oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.79 – 7.75 (m, 2H, 2'-***H***), 7.60 – 7.55 (m, 1H, 4'-***H***), 7.47 – 7.43 (m, 2H, 3'-***H***), 7.43 – 7.40 (m, 1H, 4-***H***), 7.40 – 7.38 (m, 1H, 3-***H***), 6.93 – 6.89 (m, 1H, 6-***H***), 4.20 – 4.15 (m, 2H, 1''-***H₂***), 3.28 – 3.23 (m, 2H, 2''-***H₂***); $\delta_C$ (151 MHz, $CDCl_3$) 194.7 ($Ar_2$***C***O) 154.3 (***C***-1), 137.5 (***C***-1'), 133.2 (***C***-4'), 131.5 (***C***-5), 130.9 (***C***-4), 129.6 (***C***-2'), 129.5 (***C***-3), 128.3 (***C***-3'), 126.8 (***C***-2), 114.4 (***C***-6), 68.8 (***C***-1''), 27.8 (***C***-2''); Accurate mass: found [M+H] 338.9784, $C_{15}H_{13}{}^{35}Cl^{79}BrO_2$ requires *M*, 338.9787.

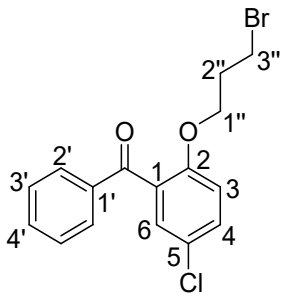
**(2'''*R*)-*N* -[2-(2''-benzoyl-4-chlorophenoxy)ethyl]-2'''-methylpyrrolidine 8**




(2*R*)-methylpyrrolidine hydrochloride (22.6 mg, 0.18 mmol) was reacted with [2-(2-bromoethoxy)-5-chlorophenyl](phenyl)methanone (60 mg, 0.18 mmol) in dry DMF (2 mL) following general procedure B. Product was purified by column chromatography (0 to 10% MeOH in DCM) to afford the title product (18 mg, 31%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.78 – 7.74 (m, 2H, 2'-***H***), 7.57 – 7.53 (m, 1H, 4'-***H***), 7.44 – 7.41 (m, 2H, 3'-***H***), 7.39 (dd, *J* = 8.8, 2.6 Hz, 1H, 5-***H***), 7.35 (d, *J* = 2.6 Hz, 1H, 3-***H***), 6.91 (d, *J* = 8.8 Hz, 1H, 6-***H***), 4.07 – 3.95 (m, 2H, 1''-$\boldsymbol{H_2}$), 2.87 (ddd, *J* = 9.3, 8.2, 2.9 Hz, 1H, 5'''-***H***), 2.84 – 2.78 (m, 1H, 2''-***H***), 2.25 – 2.15 (m, 2H, 2''-***H***, 2'''-***H***), 1.91 (q, *J* = 8.9 Hz, 1H, 5'''-***H***), 1.84 – 1.76 (m, 1H, 3'''-***H***), 1.68 – 1.59 (m, 1H, 4'''-***H***), 1.59 – 1.49 (m, 1H, 4'''-***H***), 1.35 – 1.26 (m, 1H, 3'''-***H***), 0.95 (d, *J* = 6.0 Hz, 3H, C$\boldsymbol{H_3}$); $\delta_C$ (151 MHz, $CDCl_3$) 195.1 ($Ar_2$***C***O), 155.2 (***C***-1), 137.6 (***C***-1'), 133.1 (***C***-4'), 131.5 (***C***-5), 130.4 (***C***-2), 129.63 (***C***-2'), 129.2 (***C***-3), 128.3 (***C***-3'), 125.9 (***C***-4), 113.7 (***C***-6), 68.4 (***C***-1''), 60.1 (***C***-2'''), 54.6 (***C***-5'''), 51.9 (***C***-2''), 32.2 (***C***-3'''), 21.7 (***C***-4'''), 18.8 (***C***$H_3$). Accurate mass: found [M+H] 344.1430, $C_{20}H2_3{}^{35}ClNO_2$ requires *M*, 344.1417.

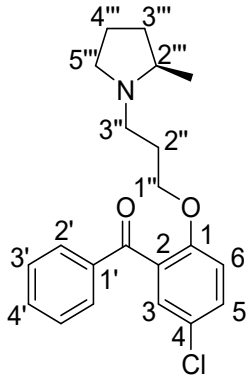
**[2-(3''-bromopropoxy)-5-chlorophenyl](phenyl)methanone 9a**




5-chloro-2-hydroxybenzophenone (100 mg, 0.43 mmol) was reacted with 1,3-dibromopropane (0.220 mL, 2.15 mmol) in anhydrous DMF (1.4 mL) following general procedure A. Purification by column chromatography (75% EtOAc in Hexane) afforded the title compound **56b** (70 mg, 46%) as a white solid.

$\delta_H$ (700 MHz, $CDCl_3$) 7.78 – 7.75 (m, 2H, 2'-***H***), 7.59 – 7.56 (m, 1H, 4'-***H***), 7.48 – 7.44 (m, 2H, 3'-***H***), 7.43 – 7.41 (m, 1H, 4-***H***), 7.40 (d, *J* = 2.6 Hz, 1H, 6-***H***), 6.92 (d, *J* = 8.8 Hz, 1H, 3-***H***), 4.00 (t, *J* = 5.6 Hz, 2H, 1''-$\boldsymbol{H_2}$), 2.96 (t, *J* = 6.3 Hz, 2H, 3''-$\boldsymbol{H_2}$), 1.99 – 1.94 (m, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (176 MHz, $CDCl_3$) 195.0 ($Ar_2\boldsymbol{C}O$), 154.9 (***C***-2), 137.7 (***C***-1'), 133.1 (***C***-4'), 131.7 (***C***-4), 130.3 (***C***-1), 129.5 (***C***-6), 129.3 (***C***-2'), 128.4 (***C***-3'), 126.2 (***C***-5), 113.4 (***C***-3), 65.7 (***C***-1''), 31.8 (***C***-2''), 29.5 (***C***-3''); Accurate mass: found [M+H] 352.9937, $C_{16}H_{16}N^{35}Cl^{79}BrO_2$ requires *M*, 352.9944.

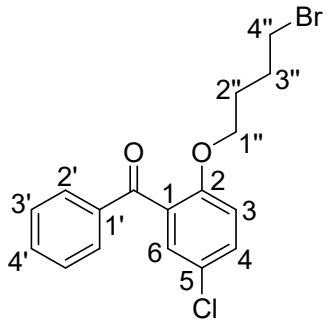
**(2'''*R*)-*N*-[3''-(2-benzoyl-4-chlorophenoxy)propyl]-2'''-methylpyrrolidine 9**




**56b** (60 mg, 0.17 mmol) was reacted with (2*R*)-Methylpyrrolidine hydrochloride (21.7 mg, 0.178 mmol) following general procedure B. The product was purified by column chromatography (10% MeOH in DCM with 1% $NEt_3$) to afford the title compound **59** (40 mg, 66%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.80 – 7.74 (m, 2H, 2'-***H***), 7.59 – 7.54 (m, 1H, 4'-***H***), 7.47 – 7.43 (m, 2H, 3'-***H***), 7.41 (dd, *J* = 8.8, 2.6 Hz, 1H, 5-***H***), 7.36 (d, *J* = 2.6 Hz, 1H, 3-***H***), 6.91 (d, *J* = 8.8 Hz, 1H, 6-***H***), 4.01 – 3.91 (m, 2H, 1''-***H₂***), 3.29 – 3.10 (m, 1H, 5'''-***H***), 2.74 – 2.63 (m, 1H, 3''-***H***), 2.57 – 2.40 (m, 1H, 2'''-***H***), 2.26 – 2.10 (m, 1H, 5'''-***H***), 2.06 – 1.92 (m, 3H, 2''-***H***, 3''-***H***, 3'''-***H***), 1.92 – 1.83 (m, 1H, 4'''-***H***), 1.83 – 1.69 (m, 2H, 2''-***H***, 4'''-***H***), 1.65 – 1.51 (m, 1H, 3'''-***H***), 1.18 – 1.09 (m, 3H, C***H₃***); $\delta_C$ (151 MHz, $CDCl_3$) 194.9 ($Ar_2$***C***O), 154.9 (***C***-1), 137.7 (***C***-1'), 133.2 (***C***-4'), 131.7 (***C***-5), 130.2 (***C***-4), 129.6 (***C***-2'), 129.4 (***C***-3), 128.4 (***C***-3'), 126.1 (***C***-2), 113.6 (***C***-6), 66.6 (***C***-1''), 61.7 (***C***-2'''), 53.3 (***C***-5''') 50.2 (***C***-3''), 31.9 (***C***-3'''), 26.8 (***C***-2''), 21.4 (***C***-4'''), 17.3 (***C***$H_3$); Accurate mass: found [M+H] 358.1582, $C_{21}H_{25}N^{35}ClO_2$ requires 358.1574.

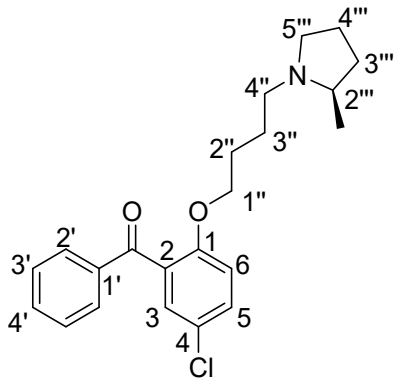
**[2-(4''-bromobutoxy)-5-chlorophenyl](phenyl)methanone 10a**




$Na_2CO_3$ (2.3 g, 21.7 mmol) was added to a solution of 1,4-dibromobutane (0.1.3 mL, 10.74 mmol) in anhydrous acetonitrile (20 mL). A solution 5-chloro-2-hydroxybenzophenone (500 mg, 2.15 mmol) in anhydrous acetonitrile (23 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and product was purified by column chromatography (0-100% DCM in Hexane) to afford the title compound (269 mg, 34%) as a colourless oil.

$\delta_H$ (400 MHz, $CDCl_3$) 7.78 – 7.73 (m, 2H, 2'-***H***), 7.60 – 7.54 (m, 1H, 4'-***H***), 7.47 – 7.37 (m, 4H, 3'-***H***, 4-***H***, 6-***H***), 6.90 – 6.85 (m, 1H, 3-***H***), 3.88 (t, *J* = 5.7 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.16 (t, *J* = 6.4 Hz, 2H, 4''-$\boldsymbol{H_2}$), 1.65 – 1.55 (m, 2H, 2''-$\boldsymbol{H_2}$), 1.55 – 1.43 (m, 2H, 3''- $\boldsymbol{H_2}$); $\delta_C$ (101 MHz, $CDCl_3$) 195.2 ($Ar_2\boldsymbol{C}O$), 155.2 (***C***-2), 137.8 (***C***-1'), 133.2 (***C***-4'), 131.7 (***C***-4), 130.3 (***C***-1), 129.4 (***C***-6), 129.4 (***C***-2'), 128.4 (***C***-3'), 125.9 (***C***-5'), 113.4 (***C***-3), 67.4 (***C***-1''), 33.2 (***C***-4''), 28.6 (***C***-2''), 27.4 (***C***-3''). Accurate mass: found [M+H] 367.0094, $C_{17}H_{17}{}^{79}Br^{35}ClO_2$ requires *M*, 367.0100.

**(2'''*R*)-*N*-[4''-(2-benzoyl-4-chlorophenoxy)butyl]-2'''-methylpyrrolidine 10**

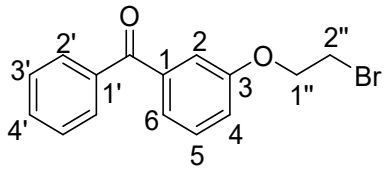



To a solution of (2*R*)-Methylpyrrolidine hydrochloride (50 mg, 0.41 mmol), KI (4.5 mg, 0.027 mmol) and $Na_2CO_3$ (132.6 mg, 1.25 mmol) in dry acetonitrile (7 mL) at 70ºC, [2-(4-bromobutoxy)-5-chlorophenyl](phenyl)methanone (100 mg, 0.27 mmol) in dry acetonitrile (7 mL) was slowly added. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT, filtered and concentrated under reduced pressure. Crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (22 mg, 22%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) δ 7.80 – 7.73 (m, 2H, 2'-***H***), 7.58 – 7.52 (m, 1H, 4'-***H***), 7.45 – 7.40 (m, 2H, 3'-***H***), 7.39 (dd, *J* = 8.8, 2.6 Hz, 1H, 5-***H***), 7.34 (d, *J* = 2.6 Hz, 1H, 3-***H***), 6.88 (d, *J* = 8.8 Hz, 1H, 6-***H***), 3.94 – 3.84 (m, 2H, 1''-$\boldsymbol{H_2}$), 3.10 – 2.98 (m, 1H, 5'''-***H***), 2.72 – 2.60 (m, 1H, 4''-***H***), 2.40 – 2.24 (m, 1H, 2'''-***H***), 2.09 – 1.95 (m, 2H, 4''-***H***, 5'''-***H***), 1.95 – 1.87 (m, 1H, 3'''-***H***), 1.84 – 1.72 (m, 1H, 4'''-***H***), 1.71 – 1.63 (m, 1H, 4'''-***H***), 1.59 – 1.51 (m, 1H, 2''-***H***), 1.51 – 1.43 (m, 2H, 2''-***H***, 3'''-***H***), 1.43 – 1.38 (m, 1H, 3''-***H***), 1.38 – 1.30 (m, 1H, 3''-***H***), 1.09 (d, *J* = 6.1 Hz, 3H, C$\boldsymbol{H_3}$); $\delta_C$ (151 MHz, $CDCl_3$) 195.1 ($Ar_2$***C***O), 155.3 (***C***-1), 137.5 (***C***-1'), 133.1 (***C***-4'), 131.5 (***C***-5), 130.3 (***C***-2), 129.6 (***C***-2'), 129.2 (***C***-3), 128.3 (***C***-3'), 125.7 (***C***-4), 113.6 (***C***-6), 68.6 (***C***-1''), 60.7 (***C***-2'''), 53.5

(***C***-5’’’), 53.3 (***C***-4’’), 32.4 (***C***-3’’’), 26.9 (***C***-2’’), 24.4 (***C***-3’’), 21.5 (***C***-4’’’), 18.3 (***C***$H_3$). Accurate mass: found [M+H] 372.1738, $C_{22}H_{27}{}^{35}ClNO_2$ requires *M*, 372.1730.

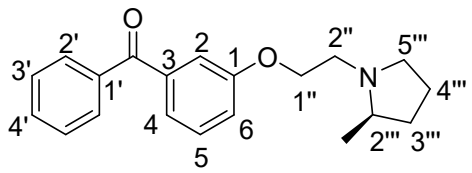
**[3-(2’’-bromoethoxy)phenyl](phenyl)methanone 11a**




$Cs_2CO_3$ (986 g, 3.03 mmol) was added to a solution of 1,2-dibromoethane (0.35 mL, 4.04 mmol) in anhydrous acetonitrile (5 mL). A solution of 3-hydroxybenzophenone (200 mg, 1.01 mmol) in anhydrous acetonitrile (5 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and product was purified by column chromatography (0-100% Chloroform in Hexane) to afford the title compound (116 mg, 38%) as a colourless oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.82 – 7.78 (m, 2H, 2’-***H***), 7.61 – 7.57 (m, 1H, 4’-***H***), 7.52 – 7.46 (m, 2H, 3’-***H***), 7.42 – 7.35 (m, 3H, 2-***H***, 5-***H***, 6-***H***), 7.18 – 7.14 (m, 1H, 4-***H***), 4.35 (t, *J* = 6.1 Hz, 2H, 1’’-***H₂***), 3.66 (t, *J* = 6.1 Hz, 2H, 2’’-***H₂***); $\delta_C$ (151 MHz, $CDCl_3$) 196.2 ($Ar_2$***C***O), 158.1 (***C***-3), 139.0 (***C***-1), 137.5 (***C***-1’), 132.5 (***C***-4’), 130.0 (***C***-2’), 129.4 (***C***-5), 128.3 (***C***-3’), 123.5 (***C***-6), 119.5 (***C***-4), 115.1 (***C***-2), 68.0 (***C***-1’’), 28.9 (***C***-2’’). Accurate mass: found [M+H] 305.0184, $C_{15}H_{14}{}^{79}BrO_2$ requires *M*, 305.0177.

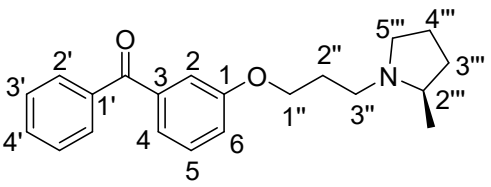
**(2’’’*R*)- *N* -[2’’-(3-benzoylphenoxy)ethyl]-2’’’-methylpyrrolidine 11**



To a solution of (2*R*)-methylpyrrolidine hydrochloride (48 mg, 0.39 mmol), KI (5.4 mg, 0.033 mmol) and $Na_2CO_3$ (105 mg, 1.64 mmol) in dry acetonitrile (10 mL) at 70ºC, [3-(2-bromoethoxy)phenyl](phenyl)methanone (100 mg, 0.33 mmol) in dry acetonitrile (6 mL) was slowly added. Mixture stirred overnight under nitrogen atmosphere. The solution was cooled down to RT, filtered and concentrated under reduced pressure. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (69 mg, 68%) as a yellow solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.80 – 7.75 (m, 2H, 2'-***H***), 7.58 – 7.54 (m, 1H, 4'-***H***), 7.48 – 7.43 (m, 2H, 3'-***H***), 7.37 – 7.30 (m, 3H, 2-***H***, 4-***H***, 5-***H***), 7.15 – 7.10 (m, 1H, 6-***H***), 4.19 (t, *J* = 6.0 Hz, 2H, 1''-***H*****$_2$**), 3.30 (ddd, *J* = 9.5, 8.9, 3.1 Hz, 1H, 5'''-***H***), 3.25 (dt, *J* = 12.5, 6.0 Hz, 1H, 2''-***H***), 2.64 (dt, *J* = 12.5, 6.0 Hz, 1H, 2''-***H***), 2.60 – 2.51 (m, 1H, 2'''-***H***), 2.38 (q, *J* = 8.9 Hz, 1H, 5'''-***H***), 2.00 – 1.90 (m, 1H, 3'''-***H***), 1.90 – 1.79 (m, 1H, 4'''-***H***), 1.79 – 1.69 (m, 1H, 4'''-***H***), 1.55 – 1.43 (m, 1H, 3'''-***H***), 1.18 (d, *J* = 6.1 Hz, 3H, C***H*****$_3$**); $\delta_C$ (151 MHz, $CDCl_3$) 196.4 ($Ar_2$***C***O), 158.6 (***C***-1), 138.9 (***C***-3), 137.5 (***C***-1'), 132.4 (***C***-4'), 129.9 (***C***-2'), 129.2 (***C***-5), 128.2 (***C***-3'), 122.9 (***C***-4), 119.2 (***C***-6), 115.2 (***C***-2), 66.9 (***C***-1''), 60.9 (***C***-2'''), 54.7 (***C***-5'''), 52.5 (***C***-2''), 32.2 (***C***-3'''), 21.8 (***C***-4'''), 18.6 (***C***$H_3$). Accurate mass: found [M+H] 310.1819, $C_{20}H_{24}NO_2$ requires *M*, 310.1807.

**(2'''*R*)-*N* -[3''-(3-benzoylphenoxy)propyl]-2'''-methylpyrrolidine 12**

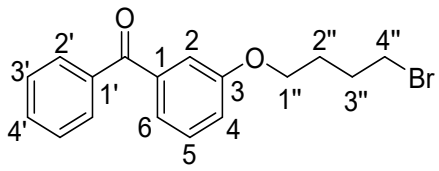



To a solution of (2*R*)-methylpyrrolidine hydrochloride (45.7 mg, 0.37 mmol), KI (0.5 mg, 0.003 mmol) and $Na_2CO_3$ (152.7 mg, 1.44 mmol) in dry acetonitrile (10 mL) at 70ºC, [3-(3-bromopropoxy)phenyl](phenyl)methanone (100 mg, 0.31 mmol) in dry

acetonitrile (6 mL) was slowly added. Mixture stirred overnight under nitrogen atmosphere. The solution was cooled down to RT, filtered and concentrated under reduced pressure. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (77 mg, 77%) as a yellow solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.82 – 7.78 (m, 2H, 2'-***H***), 7.59 (ddt, *J* = 8.7, 7.0, 1.3 Hz, 1H, 4'-***H***), 7.51 – 7.46 (m, 2H, 3'-***H***), 7.39 – 7.31 (m, 3H, 2-***H***, 4-***H***, 5-***H***), 7.13 (ddd, *J* = 8.1, 2.6, 1.2 Hz, 1H, 6-***H***), 4.13 – 4.04 (m, 2H, 1''-$\boldsymbol{H_2}$), 3.32 – 3.18 (m, 1H, 5'''-***H***), 3.04 (q, *J* = 8.8 Hz, 1H, 3''-***H***), 2.50 – 2.37 (m, 1H, 2'''-***H***), 2.37 – 2.26 (m, 1H, 3''-***H***), 2.26 – 2.14 (m, 1H, 5'''-***H***), 2.13 – 2.01 (m, 2H, 2''-$\boldsymbol{H_2}$), 2.01 – 1.90 (m, 1H, 3'''-***H***), 1.90 – 1.79 (m, 1H, 4'''-***H***), 1.79 – 1.68 (m, 1H, 4'''-***H***), 1.56 – 1.42 (m, 1H, 3'''-***H***), 1.15 (d, *J* = 6.0 Hz, 3H, C$\boldsymbol{H_3}$); $\delta_C$ (151 MHz, $CDCl_3$) 196.5 ($Ar_2$***C***O), 158.9 (***C***-1), 138.8 (***C***-3), 137.6 (***C***-1'), 132.4 (***C***-4'), 130.0 (***C***-2'), 129.2 (***C***-5), 128.2 (***C***-3'), 122.8 (***C***-4), 119.2 (***C***-6), 115.1 (***C***-2), 66.5 (***C***-1''), 60.6 (***C***-2'''), 53.9 (***C***-5'''), 50.7 (***C***-3''), 32.6 (***C***-3'''), 28.1 (***C***-2''), 21.6 (***C***-4'''), 18.6 (***C***$H_3$). Accurate mass: found [M+H] 324.1971, $C_{21}H_{26}NO_2$ requires *M*, 324.1964.

**[3-(4''-bromobutoxy)phenyl](phenyl)methanone 13a**

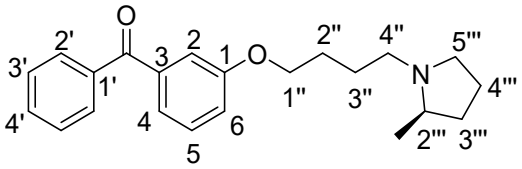



$Cs_2CO_3$ (986 g, 3.03 mmol) was added to a solution of 1,4-dibromobutane (0.48 mL, 4.04 mmol) in anhydrous acetonitrile (5 mL). A solution of 3-hydroxybenzophenone (200 mg, 1.01 mmol) in anhydrous acetonitrile (5 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and product was purified by column

chromatography (0-100% DCM in Hexane) to afford the title compound (201 mg, 60%) as a colourless oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.82 – 7.79 (m, 2H, 2'-***H***), 7.61 – 7.57 (m, 1H, 4'-***H***), 7.51 – 7.46 (m, 2H, 3'-***H***), 7.37 (t, *J* = 7.7 Hz, 1H, 5-***H***), 7.35 – 7.32 (m, 2H, 2-***H***, 6-***H***), 7.13 – 7.10 (m, 1H, 4-***H***), 4.05 (t, *J* = 6.1 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.49 (t, *J* = 6.1 Hz, 2H, 4''-$\boldsymbol{H_2}$), 2.11 – 2.04 (m, 2H, 2''-$\boldsymbol{H_2}$), 2.01 – 1.93 (m, 2H, 3''-$\boldsymbol{H_2}$); $\delta_C$ (151 MHz, $CDCl_3$) 196.5 ($Ar_2$***C***O), 158.8 (***C***-3), 138.9 (***C***-1), 137.6 (***C***-1'), 132.4 (***C***-4'), 130.0 (***C***-2'), 129.2 (***C***-5), 128.2 (***C***-3'), 122.9 (***C***-6), 119.2 (***C***-4), 114.9 (***C***-2), 67.1 (***C***-1''), 33.3 (***C***-4''), 29.4 (***C***-2''), 27.8 (***C***-3''). Accurate mass: found [M+H] 333.0490, $C_{17}H_{18}{}^{79}BrO_2$ requires *M*, 333.0490.

**(2'''*R*)-*N*-[4''-(3-benzoylphenoxy)butyl]-2'''-methylpyrrolidine 13**

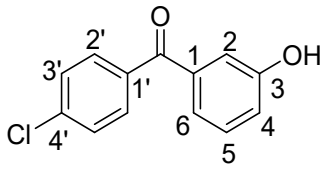



To a solution of (2*R*)-methylpyrrolidine hydrochloride (73 mg, 0.6 mmol), KI (5 mg, 0.03 mmol) and $Na_2CO_3$ (159 mg, 1.5 mmol) in dry acetonitrile (7 mL) at 70ºC, [3-(4-bromobutoxy)phenyl](phenyl)methanone (100 mg, 0.3 mmol) in dry acetonitrile (8 mL) was slowly added. Mixture stirred overnight under nitrogen atmosphere. The solution was cooled down to RT, filtered and concentrated under reduced pressure. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (48 mg, 48%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.83 – 7.77 (m, 2H, 2'-***H***), 7.61 – 7.55 (m, 1H, 4'-***H***), 7.48 (t, *J* = 7.7 Hz, 2H, 3'-***H***), 7.36 (t, *J* = 8.0 Hz, 1H, 5-***H***), 7.34 – 7.30 (m, 2H, 2-***H***, 4-***H***), 7.13 – 7.07 (m, 1H, 6-***H***), 4.09 – 3.98 (m, 2H, 1''-$\boldsymbol{H_2}$), 3.49 – 3.26 (m, 1H, 5'''-***H***), 3.07 – 2.90 (m, 1H, 4''-***H***), 2.71 – 2.51 (m, 1H, 2'''-***H***), 2.47 – 2.24 (m, 2H, 1''-***H***, 5'''-***H***), 2.08 – 1.98

(m, 1H, 3'''-***H***), 1.98 – 1.73 (m, 6H, 2''-***H₂***, 3''-***H₂***, 4'''-***H₂***), 1.68 – 1.56 (m, 1H, 3'''-***H***), 1.35 – 1.14 (m, 3H, C***H₃***); $\delta_C$ (151 MHz, $CDCl_3$) 196.5 ($Ar_2$***C***O), 158.8 (***C***-1), 138.9 (***C***-3), 137.6 (***C***-1'), 132.4 (***C***-4'), 130.0 (***C***-2'), 129.2 (***C***-5), 128.2 (***C***-3'), 122.8 (***C***-4), 119.2 (***C***-6), 115.0 (***C***-2), 67.7 (***C***-1''), 61.4 (***C***-2'''), 53.5 (***C***-5'''), 53.4 (***C***-4''), 32.2 (***C***-3'''), 24.3 (***C***-3''), 21.5 (***C***-4'''), 17.7 (***C***$H_3$). Accurate mass: found [M+H] 338.2130, $C_{22}H_{28}NO_2$ requires *M*, 338.2120.

**3-(4'-chlorobenzoyl)phenol H** [1]

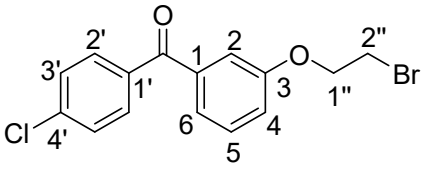



3-methoxybenzoic acid (500 mg, 3.28 mmol) was dissolved in thionyl chloride (3 mL) and heated under reflux for 2h. After cooling to RT, the volatiles were removed under reduced pressure and the products redissolved in anhydrous chlorobenzene (10 mL). $AlCl_3$ (1.31 g, 9.86 mmol) was added in portions over 20 minutes and the mixture stirred for 24h at 70ºC. After cooling to room temperature, the reaction mixture was added to 3M HCl (aq.) (10 mL) in a separating funnel and extracted with DCM (3x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced solid. The crude product was submitted to column chromatography (0-100% DCM in Hexane) to afford the title product (670 mg, 87%) as a brown solid.

$\delta_H$ (400 MHz, $CDCl_3$) 7.79 – 7.73 (m, 2H, 2'-***H***), 7.48 – 7.43 (m, 2H, 3'-***H***), 7.39 – 7.33 (m, 1H, 5-***H***), 7.33 – 7.26 (m, 2H, 2-***H***, 6-***H***), 7.12 – 7.07 (m, 1H, 4-***H***), 5.76 (s, 1H, O***H***); $\delta_C$ (101 MHz, $CDCl_3$) 195.6 ($Ar_2$***C***O), 155.9 (***C***-3), 139.2 (***C***-4'), 138.6 (***C***-1), 135.6 (***C***-1'), 131.5 (***C***-2'), 129.7 (***C***-5), 128.7 (***C***-3'), 122.7 (***C***-6), 120.1 (***C***-4), 116.4 (***C***-2);

*m/z* (LC-MS, $ESI^+$) 233 [M($^{35}Cl$)+H] and 235 [M($^{37}Cl$)+H]) in a 3:1 ratio. All data agrees with literature.

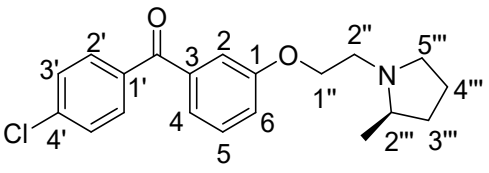
**[3-(2''-bromoethoxy)phenyl](4'-chlorophenyl)methanone 14a**




$Cs_2CO_3$ (420 mg, 1.28 mmol) was added to a solution of 1,2-dibromoethane (0.15 mL, 1.72 mmol) in anhydrous acetonitrile (5 mL). A solution of 4'-chloro-3-hydroxybenzophenone (100 mg, 0.43 mmol) in anhydrous acetonitrile (5 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and product purified by column chromatography (0-100% DCM in Hexane) to afford the title compound (94 mg, 65%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.75 (d, *J* = 8.4 Hz, 2H, 2'-***H***), 7.46 (d, *J* = 8.4 Hz, 2H, 3'-***H***), 7.42 – 7.38 (m, 1H, 5-***H***), 7.35 – 7.32 (m, 2H, 2-***H***, 6-***H***), 7.18 – 7.15 (m, 1H, 4-***H***), 4.35 (t, *J* = 6.1 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.66 (t, *J* = 6.1 Hz, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (151 MHz, $CDCl_3$) 195.0 ($Ar_2$***C***O), 158.2 (***C***-3), 138.9 (***C***-4'), 138.6 (***C***-1), 135.7 (***C***-1'), 131.4 (***C***-2'), 129.5 (***C***-5), 128.6 (***C***-3'), 123.3 (***C***-6), 119.6 (***C***-4), 115.1 (***C***-2), 68.0 (***C***-1''), 28.9 (***C***-2''). Accurate mass: found [M+H] 338.9789, $C_{15}H_{13}N^{35}Cl^{79}BrO_2$ requires *M*, 338.9787.

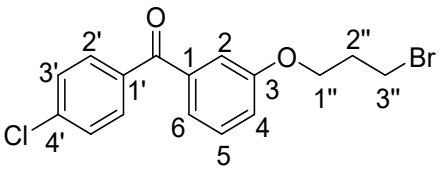
**(2'''*R*)-*N*-{2''-[3-(4'-chlorobenzoyl)phenoxy]ethyl}-2'''-methylpyrrolidine 14**



To a solution of (2*R*)-Methylpyrrolidine hydrochloride (50.1 mg, 0.41 mmol), KI (3.4 mg, 0.021 mmol) and $Na_2CO_3$ (110 mg, 1.038 mmol) in dry acetonitrile (5 mL) at 70ºC, [3-(2-bromoethoxy)phenyl](4-chlorophenyl)methanone (70 mg, 0.41 mmol) in dry acetonitrile (5 mL) was slowly added. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT, filtered and concentrated under reduced pressure. Crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (56 mg, 80%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.76 – 7.71 (m, 2H, 2'-***H*****$_2$**), 7.46 – 7.42 (m, 2H, 3'-***H*****$_2$**), 7.39 – 7.35 (m, 1H, 5-***H***), 7.32 – 7.28 (m, 2H, 2-***H***, 4-***H***), 7.18 – 7.12 (m, 1H, 6-***H***), 4.38 – 4.30 (m, 1H, 1''-***H***), 4.30 – 4.21 (m, 1H, 1''-***H***), 3.49 – 3.41 (m, 1H, 5'''-***H***), 3.41 – 3.32 (m, 1H, 2''-***H***), 2.88 – 2.76 (m, 2H, 2''-***H***, 2'''-***H***), 2.64 – 2.52 (m, 1H, 5'''-***H***), 2.09 – 2.00 (m, 1H, 3'''-***H***), 2.00 – 1.89 (m, 1H, 4'''-***H***), 1.89 – 1.78 (m, 1H, 4'''-***H***), 1.66 – 1.57 (m, 1H, 3'''-***H***), 1.29 (d, *J* = 6.2 Hz, 3H, C***H*****$_3$**); $\delta_C$ (151 MHz, $CDCl_3$) 195.1 ($Ar_2$***C***O), 158.3 (***C***-1), 138.9 (***C***-4'), 138.6 (***C***-3), 135.7 (***C***-1'), 131.4 (***C***-2'), 129.5 (***C***-5), 128.63 (***C***-3'), 122.9 (***C***-4), 119.3 (***C***-6), 115.2 (***C***-2), 66.0 (***C***-1''), 61.8 (***C***-2'''), 54.6 (***C***-5'''), 52.3 (***C***-2''), 31.9 (***C***-3'''), 21.7 (***C***-4'''), 17.9 (***C***$H_3$). Accurate mass: found [M+H] 344.1427, $C_{20}H_{23}N^{35}ClO_2$ requires *M*, 344.1417.

**[3-(3''-bromopropoxy)phenyl](4'-chlorophenyl)methanone 15a**

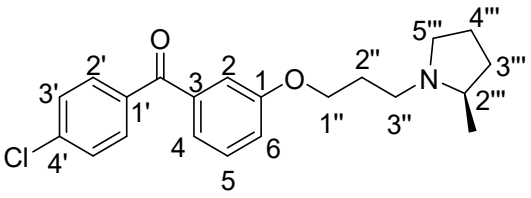



$Cs_2CO_3$ (630 mg, 1.93 mmol) was added to a solution of 1,3-dibromopropane (0.33 mL, 3.22 mmol) in anhydrous acetonitrile (6 mL). A solution of 4'-chloro-3-hydroxybenzophenone (150 mg, 0.64 mmol) in anhydrous acetonitrile (7 mL) was

slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and product submitted to column chromatography (0-100% DCM in Hexane) to afford the title compound contaminated with 32% (4-chlorophenyl) [3-(prop-2-en-1-yloxy)phenyl] methanone (166 mg, 73%) as a white solid.

$\delta_H$ (400 MHz, $CDCl_3$) 7.79 – 7.73 (m, 2H, 2'-***H***), 7.49 – 7.43 (m, 2H, 3'-***H***), 7.42 – 7.36 (m, 1H, 5-***H***), 7.34 – 7.29 (m, 2H, 2-***H***, 6-***H***), 7.16 – 7.11 (m, 1H, 4-***H***), 4.16 (t, *J* = 5.8 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.61 (t, *J* = 6.4 Hz, 2H, 3''-$\boldsymbol{H_2}$), 2.38 – 2.29 (m, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (101 MHz, $CDCl_3$) 195.2 ($Ar_2\boldsymbol{C}O$), 158.8 (***C***-3), 138.9 (***C***-4'), 138.6 (***C***-1), 135.8 (***C***-1'), 131.5 (***C***-2'), 129.4 (***C***-5), 128.7 (***C***-3'), 122.9 (***C***-6), 119.4 (***C***-4), 115.0 (***C***-4), 65.5 (***C***-1''), 32.2 (***C***-3''), 29.8 (***C***-2''). Accurate mass: found [M+H] 352.9951, $C_{16}H_{15}N^{35}Cl^{79}BrO_2$ requires *M*, 352.9944.

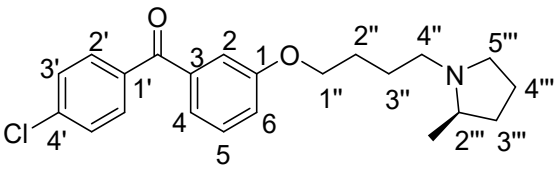
**(2'''R)-*N*-{3''-[3-(4'-chlorobenzoyl)phenoxy]propyl}-2'''-methylpyrrolidine 15**




To a solution of (2*R*)-Methylpyrrolidine hydrochloride (68.8 mg, 0.56 mmol), KI (4.7 mg, 0.028 mmol) and $Na_2CO_3$ (150 mg, 1.41 mmol) in dry acetonitrile (5 mL) at 70ºC, [3-(3-bromopropoxy)phenyl](4-chlorophenyl)methanone (100 mg, 0.28 mmol) in dry acetonitrile (5 mL) was slowly added. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT, filtered and concentrated under reduced pressure. Crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (41 mg, 41%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.76 – 7.72 (m, 2H, 2-***H*****$_2$**), 7.46 – 7.43 (m, 2H, 3'-***H***), 7.36 (t, *J* = 8.0 Hz, 1H, 5-***H***), 7.31 – 7.26 (m, 2H, 2-***H***, 4-***H***), 7.15 – 7.10 (m, 1H, 6-***H***), 4.12 – 4.03 (m, 2H, 1''-***H*****$_2$**), 3.30 – 3.21 (m, 1H, 5'''-***H***), 3.09 – 2.99 (m, 1H, 3''-***H***), 2.50 – 2.41 (m, 1H, 2'''-***H***), 2.37 – 2.28 (m, 1H, 3''-***H***), 2.28 – 2.19 (m, 1H, 5'''-***H***), 2.13 – 2.02 (m, 2H, 2''-***H*****$_2$**), 2.02 – 1.93 (m, 1H, 3'''-***H***), 1.89 – 1.79 (m, 1H, 4'''-***H***), 1.79 – 1.69 (m, 1H, 4'''-***H***), 1.55 – 1.46 (m, 1H, 3'''-***H***), 1.16 (d, *J* = 6.2 Hz, 3H, C***H*****$_3$**); $\delta_C$ (151 MHz, $CDCl_3$) 195.2 ($Ar_2$***C***O), 158.9 (***C***-1), 138.8 (***C***-4'), 138.5 (***C***-3), 135.8 (***C***-1'), 131.4 (***C***-2'), 129.3 (***C***-5), 128.6 (***C***-3'), 122.5 (***C***-4), 119.3 (***C***-6), 115.0 (***C***-2), 66.5 (***C***-1''), 60.8 (***C***-2'''), 53.8 (***C***-5'''), 50.7 (***C***-3''), 32.5 (***C***-3'''), 28.0 (***C***-2''), 21.6 (***C***-4'''), 18.4 (***C***$H_3$). Accurate mass: found [M+H] 358.1579, $C_{21}H_{25}N^{35}ClO_2$ requires *M*, 358.1574.

**(2'''*R*)-*N*-{4''-[3-(4'-chlorobenzoyl)phenoxy]butyl}-2'''-methylpyrrolidine 16**

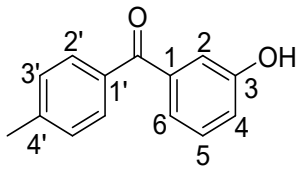



$Cs_2CO_3$ (630 mg, 1.93 mmol) was added to a solution of 1,4-dibromobutane (0.385 mL, 3.22 mmol) in anhydrous acetonitrile (16 mL). A solution 4'-chloro-3-hydroxybenzophenone (150 mg, 0.64 mmol) in anhydrous acetonitrile (16 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and crude product was submitted to column chromatography (0-100% DCM in Hexane) to remove inorganic salts. Resultant product (130 mg) in dry acetonitrile (10 mL) was slowly added to a stirring solution of (2*R*)-methylpyrrolidine hydrochloride (86 mg, 0.71 mmol), KI (6 mg, 0.035 mmol) and $Na_2CO_3$ (187.4 mg, 1.77 mmol) in dry acetonitrile (8 mL) at 70ºC. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT,

filtered and concentrated under reduced pressure. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (35 mg, 27%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.77 – 7.73 (m, 2H, 2'-***H₂***), 7.47 – 7.43 (m, 2H, 3'-***H₂***), 7.39 – 7.35 (m, 1H, 5), 7.30 – 7.27 (m, 2H, 2-***H***, 4-***H***), 7.13 – 7.10 (m, 1H, 6-***H***), 4.09 – 3.97 (m, 2H, 1''-***H₂***), 3.35 – 3.23 (m, 1H, 5'''-***H***), 3.00 – 2.88 (m, 1H, 4''-***H***), 2.61 – 2.40 (m, 1H, 2'''-***H***), 2.37 – 2.20 (m, 2H, 4''-***H***, 5'''-***H***), 2.07 – 1.94 (m, 1H, 3'''-***H***), 1.92 – 1.84 (m, 2H, 2''-***H***, 4'''-***H***), 1.83 – 1.71 (m, 4H, 2''-***H***, 3''-***H₂***, 4'''-***H***), 1.62 – 1.48 (m, 1H, 3'''-***H***), 1.20 (d, *J* = 6.2 Hz, 3H, ***C***$H_3$); $\delta_C$ (151 MHz, $CDCl_3$) 195.3 ($Ar_2$***C***O), 159.0 (***C***-1), 138.9 (***C***-4'), 138.5 (***C***-3), 135.9 (***C***-1'), 131.4 (***C***-2'), 129.3 (***C***-5), 128.6 (***C***-3'), 122.5 (***C***-4), 119.4 (***C***-6), 114.9 (***C***-2), 67.8 (***C***-1''), 61.0 (***C***-2'''), 53.6 (***C***-4''), 53.5 (***C***-5'''), 32.3 (***C***-3'''), 27.2 (***C***-2''), 24.6 (***C***-3''), 21.5 (***C***-4'''), 18.1 (***C***$H_3$). Accurate mass: found [M+H] 372.1716, $C_{22}H_{27}N^{35}ClO_2$ requires *M*, 372.1730.

**3-(4'-methylbenzoyl)phenol I** [2]

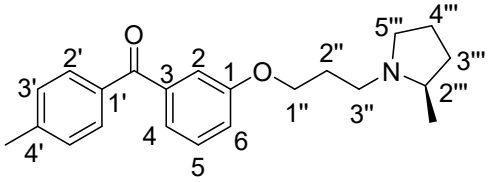



3-methoxybenzoic acid (1 g, 6.57 mmol) was dissolved in thionyl chloride (3 mL) and heated under reflux for 2h. After cooling down to RT, the volatiles were removed under reduced pressure and the products redissolved in anhydrous toluene (10 mL). $AlCl_3$ (2.63 g, 19.72 mmol) was added in portions over 20 minutes and the mixture stirred for 24h at 70ºC. After cooling to room temperature, the reaction mixture was added to 3M HCl (aq.) (10 mL) in a separating funnel and extracted with DCM (3x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and

concentrated under reduced solid. The crude product was submitted to column chromatography (0-100% EtOAc in Hexane) to afford the title product (1.16 g, 83%) as a brown solid.

$\delta_H$ (400 MHz, $CDCl_3$) 7.73 (d, *J* = 8.2 Hz, 2H, 2'-***H₂***), 7.37 – 7.26 (m, 5H, 2-***H***, 5-***H***, 6-***H***, 3'-***H₂***), 7.09 – 7.06 (m, 1H, 4-***H***), 2.44 (s, 3H, -C***H₃***); $\delta_C$ (101 MHz, $CDCl_3$) 196.5 ($Ar_2$***C***O), 155.7 (***C***-3), 143.5 (***C***-4'), 139.3 (***C***-1), 134.7 (***C***-1'), 130.4 (***C***-2'), 129.5 (***C***-5), 129.0 (***C***-3'), 122.7 (***C***-6), 119.5 (***C***-4), 116.4 (***C***-2), 21.7 (-***C***$H_3$). *m/z* (LC-MS, $ESI^+$) 213.25 [M+H]. All data agrees with literature.

**(2'''*R*)-*N*-{3''-[3-(4'-methylbenzoyl)phenoxy]propyl}2'''-methylpyrrolidine 17**

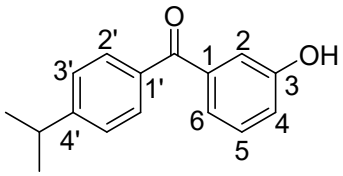



$Cs_2CO_3$ (2.2 g, 6.75 mmol) was added to a solution of 1,3-dibromopropane (0.72 mL, 7.07 mmol) in anhydrous acetonitrile (20 mL). A solution of 3-(4-methylbenzoyl)phenol (300 mg, 1.41 mmol) in anhydrous acetonitrile (27 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and crude product was submitted to column chromatography (0-100% DCM in Hexane) to remove inorganic salts. Resultant product (200 mg) in dry acetonitrile (15 mL) was then slowly added to a stirring solution of (2*R*)-Methylpyrrolidine hydrochloride (87.6 mg, 0.72 mmol), KI (10 mg, 0.06 mmol) and $Na_2CO_3$ (292.6 mg, 2.76 mmol) in dry acetonitrile (15 mL) at 70ºC. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT, filtered and concentrated under reduced pressure. Crude mixture was submitted to

column chromatography (10% MeOH in DCM) to afford the title compound (119 mg, 59%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.74 – 7.70 (m, 2H, 2'-***H₂***), 7.38 – 7.34 (m, 1H, 5-***H***), 7.33 – 7.30 (m, 2H, 2-***H***, 4-***H***), 7.29 – 7.27 (m, 2H, 3'-***H₂***), 7.12 – 7.09 (m, 1H, 6-***H***), 4.15 – 4.02 (m, 2H, 1''-***H₂***), 3.46 – 3.30 (m, 1H, 5'''-***H***), 3.19 – 3.06 (m, 1H, 3''-***H***), 2.75 – 2.55 (m, 1H, 2'''-***H***), 2.53 – 2.45 (m, 1H, 3''-***H***), 2.44 (s, 3H, ArC***H₃***), 2.43 – 2.36 (m, 1H, 5'''-***H***), 2.27 – 2.16 (m, 1H, 2''-***H***), 2.16 – 2.08 (m, 1H, 2''-***H***), 2.08 – 1.99 (m, 1H, 3'''-***H***), 1.98 – 1.87 (m, 1H, 4'''-***H***), 1.87 – 1.76 (m, 1H, 4'''-***H***), 1.66 – 1.59 (m, 1H, 3-***H***), 1.32 – 1.20 (m, 3H, C***H₃***); $\delta_C$ (151 MHz, $CDCl_3$) 196.2 ($Ar_2$***C***O), 158.7 (***C***-1), 143.3 (***C***-4'), 139.3 (***C***-3), 134.8 (***C***-1'), 130.3 (***C***-2'), 129.2 (***C***-5), 128.9 (***C***-3'), 122.7 (***C***-4), 118.8 (***C***-6), 115.1 (***C***-2), 66.2 (***C***-1''), 61.4 (***C***-2'''), 53.6 (***C***-5'''), 50.7 (***C***-3''), 32.3 (***C***-3'''), 27.5 (***C***-2''), 21.6 (Ar***C***$H_3$), 21.5 (***C***-4'''), 17.8 (***C***$H_3$). Accurate mass: found [M+H] 338.2116, $C_{22}H_{28}NO_2$ requires *M*, 338.2120

**3-[4'-(isopropanyl)benzoyl]phenol J**

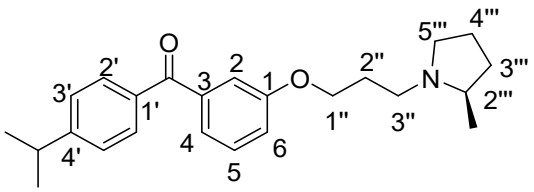



3-methoxybenzoic acid (1 g, 6.57 mmol) was dissolved in thionyl chloride (3 mL) and refluxed for 2h. After cooling down to RT, volatiles were removed under reduced pressure and products redissolved in anhydrous cumene (10 mL). $AlCl_3$ (2.63 g, 19.72 mmol) was added in portions over 20 minutes and mixture stirred for 24h at 70ºC. After cooling down to room temperature, reaction mixture was added to 3M HCl (aq.) (10 mL) in a separating funnel and extracted with DCM (3x10 mL). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under

reduced solid. Crude was submitted to column chromatography (0-100% EtOAc in Hexane) to afford de title product (1.58 g, 100%) as a light brown solid.

$\delta_H$ (400 MHz, $CDCl_3$) 7.80 – 7.71 (m, 2H, 2'-***H***), 7.38 – 7.29 (m, 5H, 2-***H***, 5-***H***, 6-***H***, 3'-***H*****$_2$**), 7.11 – 7.05 (m, 1H, ), (h, *J* = 7.0 Hz, 1H, C***H***), 1.29 (d, *J* = 7.0 Hz, 6H, 2xC***H*****$_3$**); $\delta_C$ (151 MHz, $CDCl_3$) 196.0 ($Ar_2$***C***O), 155.5 (***C***-3), 154.1 (***C***-4'), 139.5 (***C***-1), 135.1 (***C***-1'), 130.4 (***C***-2'), 129.5 (***C***-5), 126.4 (***C***-3'), 122.7 (***C***-6), 119.3 (***C***-4), 116.4 (***C***-2), 34.3 (***C***H), 23.7 (2x***C***$H_3$). Accurate mass: found [M+H] 241.1236, $C_{16}H_{17}O_2$ requires *M*, 241.1229

**(2'''*R*)-*N*-(3''-{3-[4'-(propan-2''''-yl)benzoyl]phenoxy}propyl)-2'''-methylpyrrolidine 18**

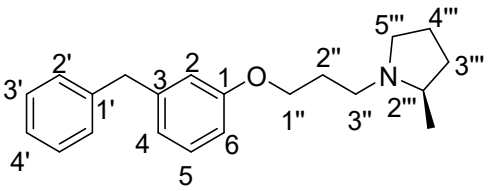



$Cs_2CO_3$ (1.25 g, 3.83 mmol) was added to a solution of 1,3-dibromopropane (0.42 mL, 4.16 mmol) in anhydrous acetonitrile (10 mL). A solution 3-[4-(propan-2-yl)benzoyl]phenol (200 mg, 0.83 mmol) in anhydrous acetonitrile (17 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and crude product was submitted to column chromatography (0-100% DCM in Hexane) to to remove inorganic salts. Resultant product (150 mg) in dry acetonitrile (15 mL) was then slowly added to a stirring solution of (2*R*)-Methylpyrrolidine hydrochloride (60.6 mg, 0.49 mmol), KI (7 mg, 0.042 mmol) and $Na_2CO_3$ (202.4 mg, 1.91 mmol) in dry acetonitrile (11 mL) at 70ºC. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT, filtered and concentrated under reduced pressure.

Crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (76 mg, 50%) as a brown oil.

$\delta_H$ (400 MHz, $CDCl_3$) 7.78 – 7.70 (m, 2H, 2'-***H₂***), 7.38 – 7.28 (m, 5H, 2-***H***, 4-***H***, 5-***H***, 3'-***H₂***), 7.13 – 7.08 (m, 1H, 6-***H***), 4.12 – 4.02 (m, 2H, 1''-***H₂***), 3.26 – 3.18 (m, 1H, 3''-***H***), 3.07 – 2.93 (m, 2H, C***H***, 5'''-***H***), 2.42 – 2.32 (m, 1H, 2'''-***H***), 2.30 – 2.21 (m, 1H, 3''-***H***), 2.21 – 2.13 (m, 1H, 5'''-***H***), 2.08 – 1.99 (m, 2H, 2''-***H₂***), 1.99 – 1.88 (m, 1H, 3'''-***H***), 1.88 – 1.65 (m, 2H, 4'''-***H₂***), 1.51 – 1.40 (m, 1H, 3'''-***H***), 1.26 (d, *J* = 7.0 Hz, 6H, 2xC***H₃***), 1.10 (d, *J* = 6.0 Hz, 3H, C***H₃***); $\delta_C$ (101 MHz, $CDCl_3$) 196.3 ($Ar_2$***C***O), 158.9 (***C***-3), 153.9 (***C***-4'), 139.2 (***C***-1), 135.2 (***C***-1'), 130.4 (***C***-2'), 129.1 (***C***-5), 126.4 (***C***-3'), 122.7 (***C***-6), 118.9 (***C***-4), 115.1 (***C***-2), 66.6 (***C***-1''), 60.5 (***C***-2'''), 53.9 (***C***-5'''), 50.8 (***C***-3''), 34.3 (***C***H), 32.6 (***C***-3'''), 28.3 (***C***-2''), 23.7 (2x***C***$H_3$), 21.6 (***C***-4'''), 18.7 (***C***$H_3$). Accurate mass: found [M+H] 366.2446, $C_{24}H_{34}NO_2$ requires *M*, 366.2433.

**(2'''*R*)-*N*-[3''-(3-benzylphenoxy)propyl]-2'''-methylpyrrolidine 19**

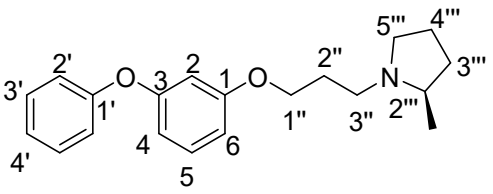



$Cs_2CO_3$ (1.061 g, 3.26 mmol) was added to a solution of 1,3-dibromopropane (0.44 mL, 4.34 mmol) in anhydrous acetonitrile (26 mL). A solution of 3-benzylphenol (200 mg, 1.086 mmol) in anhydrous acetonitrile (26 mL) was slowly added and stirred overnight at RT. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and crude product was submitted to column chromatography (0-80% EtOAc in Hexane). Resultant product (127 mg, 0.42 mmol) in dry acetonitrile (10 mL) was slowly added to a stirring solution of (2*R*)-methylpyrrolidine hydrochloride (61 mg, 0.50 mmol), KI (1 mg, 0.004 mmol) and

$Na_2CO_3$ (203 mg, 1.92 mmol) in dry acetonitrile (10 mL) at 60ºC. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT, filtered and concentrated under reduced pressure. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (50 mg, 39%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.31 – 7.27 (m, 2H, 3'-***H***), 7.23 – 7.16 (m, 4H, 4-***H***, 2'-***H***, 4'-***H***), 6.84 – 6.80 (m, 1H, 6-***H***), 6.72 – 6.66 (m, 2H, 2-***H***, 4-***H***), 4.08 – 4.03 (m, 1H, 1''-***H***), 4.03 – 3.98 (m, 1H, 1''-***H***), 3.94 (s, 2H, C***H₂***), 3.53 – 3.38 (m, 1H, 3''-***H***), 3.38 – 3.21 (m, 1H, 5'''-***H***), 3.10 – 2.98 (m, 1H, 2'''-***H***), 2.97 – 2.71 (m, 1H, 5'''-***H***), 2.71 – 2.50 (m, 1H, 3''-***H***), 2.40 – 2.17 (m, 3H, 2''-***H₂***, 3'''-***H***), 2.13 – 1.91 (m, 2H, 4'''-***H₂***), 1.79 – 1.49 (m, 3H, C***H₃***), 1.28 – 1.21 (m, 1H, 3'''-***H***); $\delta_C$ (151 MHz, $CDCl_3$) 158.3 (***C***-1), 142.9 (***C***-3), 140.7 (***C***-1'), 129.6 (***C***-5), 128.9 (***C***-3'), 128.5 (***C***-4'), 126.2 (***C***-2'), 122.0 (***C***-2), 115.2 (***C***-6), 111.7 (***C***-4), 82.2 (***C***-1''), 64.7 (***C***-2'''), 41.9 (***C***$H_2$), 31.4 (***C***-3''), 29.7 (***C***-5'''), 25.4 (***C***-3'''), 25.1 (***C***-2''), 21.2 (***C***-4'''), 15.5 (***C***$H_3$). Accurate mass: found [M+H] 310.2203, $C_{21}H_{27}NO$ requires *M*, 310.2197.

**(2'''*R*)-2'''-methyl-*N*-[3''-(3-phenoxyphenoxy)propyl]pyrrolidine 20**

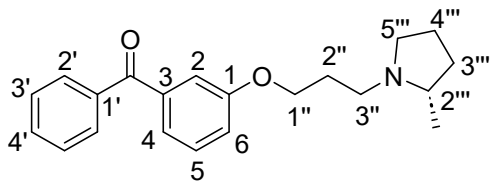



$Cs_2CO_3$ (1.05 g, 3.22 mmol) was added to a solution of 1,3-dibromopropane (0.44 mL, 4.29 mmol) in anhydrous acetonitrile (27 mL). A solution of 3-phenoxyphenol (200 mg, 1.074 mmol) in anhydrous acetonitrile (27 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and crude product was submitted to column chromatography

(0-100% EtOAc in Hexane) to remove inorganic salts. The resultant product (320 mg, 1.042 mmol) in dry acetonitrile (25 mL) was slowly added to a stirring solution of (2*R*)-methylpyrrolidine hydrochloride (0.152 mg, 1.25 mmol), KI (2 mg, 0.010 mmol) and $Na_2CO_3$ (508 mg, 4.79 mmol) in dry acetonitrile (25 mL) at 60ºC. The mixture stirred overnight under nitrogen atmosphere. The solution was cooled down to RT, filtered and concentrated under reduced pressure. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (127 mg, 39%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.34 – 7.30 (m, 2H, 3'-***H***), 7.22 – 7.17 (m, 1H, 5-***H***), 7.11 – 7.07 (m, 1H, 4'-***H***), 7.03 – 6.99 (m, 2H, 2'-***H***), 6.66 – 6.62 (m, 1H, 6-***H***), 6.59 – 6.55 (m, 2H, 2-***H***, 4-***H***), 4.04 – 3.93 (m, 2H, 1''-***H₂***), 3.27 – 3.19 (m, 1H, 3''-***H***), 3.05 – 2.96 (m, 1H, 5'''), 2.46 – 2.37 (m, 1H, 2'''-***H***), 2.33 – 2.25 (m, 1H, 5'''-***H***), 2.25 – 2.17 (m, 1H, 3'''-***H***), 2.09 – 1.99 (m, 2H, 2''-***H₂***), 1.99 – 1.91 (m, 1H, 3'''-***H***), 1.88 – 1.77 (m, 1H, 4'''-***H***), 1.77 – 1.68 (m, 1H, 4'''-***H***), 1.53 – 1.43 (m, 1H, 3'''-***H***), 1.15 (d, *J* = 6.2 Hz, 3H, C***H₃***); $\delta_C$ (151 MHz, $CDCl_3$) 160.3 (***C***-1), 158.4 (***C***-3), 156.9 (***C***-1'), 130.1 (***C***-5), 129.7 (***C***-3'), 123.3 (***C***-4'), 119.0 (***C***-2'), 110.9 (***C***-2), 109.4 (***C***-6), 105.4 (***C***-4), 66.4 (***C***-1''), 60.7 (***C***-2'''), 53.8 (***C***-3''), 50.7 (***C***-5'''), 32.5 (***C***-3'''), 28.1 (***C***-2''), 21.6 (***C***-4'''), 18.5 (***C***$H_3$). Accurate mass: found [M+H] 315.4259, $C_{20}H_{25}NO_2$ requires *M*, 315.4251.

**(2'''*S*)-1-[3''-(3-benzoylphenoxy)propyl]-2'''-methylpyrrolidine 21**

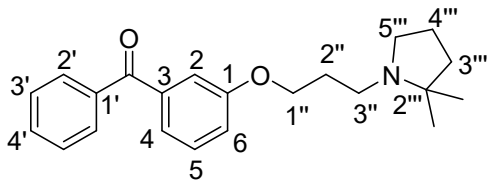



3-hydroxybenzophenone (135 mg, 0.68 mmol) was added to a suspension of KI (17 mg, 0.102 mmol) and $Na_2CO_3$ (579 mg, 5.46 mmol) in dry acetonitrile (3 mL). The

resultant mixture stirred at 70ºC for 15 min. (*S*)-2-chlorophenyl(phenyl)methanol (148 mg, 0.75 mmol), in dry acetonitrile (3 mL), was then added to the suspension and the reaction mixture then stirred at 70ºC. Once full conversion was achieved, the reaction mixture was cooled down to RT, filtered and concentrated under reduced pressure. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (150 mg, 68%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.84 – 7.77 (m, 2H, 2'-***H***), 7.63 – 7.55 (m, 1H, 4'-***H***), 7.52 – 7.44 (m, 2H, 3'-***H***), 7.42 – 7.29 (m, 3H, 2-***H***, 4-***H***,5-***H***), 7.16 – 7.09 (m, 1H, 6-***H***), 4.16 – 4.00 (m, 2H, 1''-***H₂***), 3.33 – 3.18 (m, 1H, 5'''-***H***), 3.10 – 2.95 (m, 1H, 3''-***H***), 2.60 – 2.36 (m, 1H, 2'''-***H***), 2.35 – 2.25 (m, 1H, 3''-***H***), 2.25 – 2.11 (m, 1H, 5'''-***H***), 2.10 – 2.01 (m, 2H, 2''-***H₂***), 2.01 – 1.90 (m, 1H, 3'''-***H***), 1.90 – 1.79 (m, 1H, 4'''-***H***), 1.78 – 1.69 (m, 1H, 4'''-***H***), 1.57 – 1.38 (m, 1H, 3'''-***H***), 1.15 (d, *J* = 6.1 Hz, 3H, C***H₃***); $\delta_C$ (151 MHz, $CDCl_3$) 196.5 ($Ar_2$***C***O), 159.0 (***C***-1), 138.9 (***C***-3), 137.6 (***C***-1'), 132.4 (***C***-4'), 130.0 (***C***-2'), 129.2 (***C***-5), 128.2 (***C***-3'), 122.8 (***C***-4), 119.2 (***C***-6), 115.1 (***C***-2), 66.5 (***C***-1''), 60.6 (***C***-2'''), 53.9 (***C***-5'''), 50.7 (***C***-3''), 32.6 (***C***-3'''), 28.2 (***C***-2''), 21.6 (***C***-4'''), 18.6 (***C***$H_3$). Accurate mass: found [M+H] 338.2114, $C_{22}H_{27}NO_2$ requires *M*, 338.2120.

**_N_-[3''-(3-benzoylphenoxy)propyl]-2''',2'''-dimethylpyrrolidine 22**

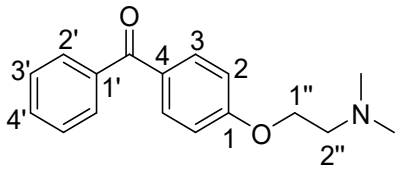



3-hydroxybenzophenone (104 mg, 0.52 mmol) was added to a suspension of KI (13 mg, 0.079 mmol) and $Na_2CO_3$ (446 mg, 4.21 mmol) in dry acetonitrile (2.5 mL). The resultant mixture stirred at 70ºC for 15 min. 1-(3-chloropropyl)-2,2-dimethylpyrrolidine (95.6 mg, 0.54 mmol), in dry acetonitrile (2.5 mL), was then added to the suspension

and the reaction mixture then stirred at 70ºC. Once full conversion was achieved, the reaction mixture was cooled down to RT, filtered and concentrated under reduced pressure. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (43 mg, 25%) as a clear oil.

$\delta_H$ (599 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 2H, 2'-***H***), 7.62 – 7.54 (m, 1H, 4'-***H***), 7.51 – 7.42 (m, 2H, 3'-***H***), 7.39 – 7.33 (m, 2H, 5-***H,*** 2-***H***), 7.33 – 7.29 (m, 1H, 4-***H***), 7.14 – 7.10 (m, 1H, 6-***H***), 4.08 (t, *J* = 6.3 Hz, 2H, 1''-$\boldsymbol{H_2}$), 2.79 – 2.71 (m, 2H, 5'''-$\boldsymbol{H_2}$), 2.54 (t, *J* = 7.1 Hz, 2H, 3''-$\boldsymbol{H_2}$), 1.97 – 1.89 (m , 2H, 2''-$\boldsymbol{H_2}$), 1.78 – 1.71 (m, 2H, 4'''-$\boldsymbol{H_2}$), 1.65 – 1.59 (m, 2H, 3'''-$\boldsymbol{H_2}$), 0.97 (s, 6H, 2xC$\boldsymbol{H_3}$); $\delta_C$ (151 MHz, $CDCl_3$) 196.7 ($Ar_2$**C**O), 159.3 (**C**-1, 139.0 (**C**-3), 137.8 (**C**-1'), 132.5 (**C**-4'), 130.2 (**C**-2'), 129.3 (**C**-5), 128.4 (**C**-3'), 122.7 (**C**-4), 119.4 (**C**-6), 115.3 (**C**-2), 66.7 (**C**-1''), 60.3 (**C**-2'''), 51.1 (**C**-5'''), 45.4 (**C**-3''),40.0 (**C**-3'''), 29.1 (**C**-2''), 22.9 (***C***$H_3$), 20.6 (**C**-4'''). Accurate mass: found [M+H] 338.2114, $C_{22}H_{28}NO_2$ requires *M*, 338.2120.

**[2''-(4-benzoylphenoxy)ethyl]dimethylamine 23**

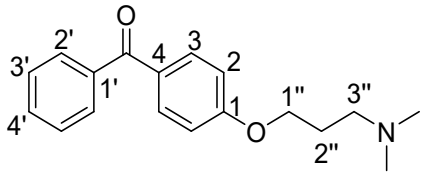



4-hydroxybenzophenone (70 mg, 0.35 mmol) was reacted with 2-dimethylamino-ethylchloride hydrochloride (76 mg, 0.53 mmol) following general procedure B. The product was purified by column chromatography (10% MeOH in DCM with 1% $NEt_3$) to afford the title compound **61** (59 mg, 62%) as a yellow oil.

$\delta_H$ (700 MHz, $CDCl_3$) 7.83 – 7.80 (m, 2H, 3-***H***), 7.76 – 7.73 (m, 2H, 2'-***H***), 7.58 – 7.54 (m, 1H, 4'-***H***), 7.49 – 7.45 (m, 2H, 3'-***H***), 7.00 – 6.96 (m, 2H, 2-***H***), 4.21 (t, *J* = 5.6 Hz, 2H, 1''-$\boldsymbol{H_2}$), 2.87 (t, *J* = 5.6 Hz, 2H, 2''-$\boldsymbol{H_2}$), 2.43 (s, 6H, C$\boldsymbol{H_3}$); $\delta_C$ (176 MHz, $CDCl_3$)

195.5 ($Ar_2$***C***O), 162.2 (***C***-1), 138.2 (***C***-1'), 132.5 (***C***-3), 131.9 (***C***-4'), 130.3 (***C***-4), 129.7 (***C***-2'), 128.2 (***C***-3'), 114.1 (***C***-2), 65.8 (***C***-1''), 57.9 (***C***-2''), 45.6 (***C***$H_3$); Accurate mass: found [M+H] 270.1481, $C_{17}H_{20}NO_2$ requires *M*, 270.1494.

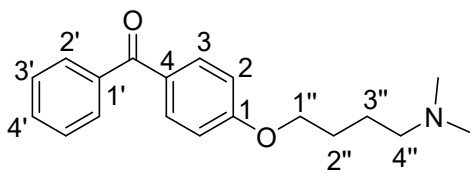
**[3''-(4-benzoylphenoxy)propyl]dimethylamine 24**




4-hydroxybenzophenone (100 mg, 0.50 mmol) was reacted with 3-dimethylamino-propylchloride hydrochloride (159.5 mg, 1 mmol) following general procedure B. The product was purified by column chromatography (10% MeOH in DCM) to afford the title compound (84 mg, 59%) as a colourless oil.

$\delta_H$ (700 MHz, $CDCl_3$) 7.83 – 7.80 (m, 2H, 3-***H***), 7.76 – 7.74 (m, 2H, 2'-***H***), 7.58 – 7.54 (m, 1H, 4'-***H***), 7.49 – 7.45 (m, 2H, 3'-***H***), 6.97 – 6.94 (m, 2H, 2-***H***), 4.12 (t, *J* = 6.3 Hz, 2H, 1''-***H₂***), 2.62 – 2.54 (m, 2H, 3''-***H₂***), 2.35 (s, 6H, C***H₃***), 2.09 – 2.03 (m, 2H, 2''-***H₂***); $\delta_C$ (176 MHz, $CDCl_3$) 195.5 ($Ar_2$***C***O), 162.6 (***C***-1), 138.3 (***C***-1'), 132.5 (***C***-3), 131.8 (***C***-4'), 130.1 (***C***-4), 129.7 (***C***-2'), 128.1 (***C***-3'), 114.0 (***C***-2), 66.3 (***C***-1''), 56.1 (***C***-3''), 45.2 (***C***$H_3$), 27.1 (***C***-2''). Accurate mass: found [M+H] 284.1644, $C_{18}H_{22}NO_2$ requires *M*, 284.1651.

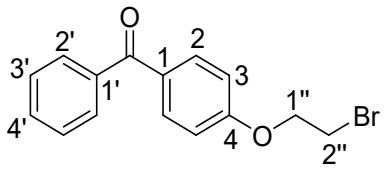
**[4''-(4-benzoylphenoxy)butyl]dimethylamine 25**



[4-(4''-bromobutoxy)phenyl](phenyl)methanone **28a** (128 mg, 0.38 mmol) was reacted with dimethylamine hydrochloride (38 mg, 0.46 mmol) in anhydrous acetonitrile (19 mL) following general procedure B. Product was purified by column chromatography (10% MeOH in DCM) to afford the title compound (60 mg, 52%) as a clear oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.83 – 7.78 (m, 2H, 3-***H***), 7.76 – 7.71 (m, 2H, 2'-***H***), 7.58 – 7.53 (m, 1H, 4'-***H***), 7.50 – 7.42 (m, 2H, 3'-***H***), 6.96 – 6.89 (m, 2H, 2-***H***), 4.09 (t, *J* = 5.9 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.04 – 2.96 (m, 2H, 4''-$\boldsymbol{H_2}$), 2.73 (s, 6H, 2xC$\boldsymbol{H_3}$), 2.08 – 1.99 (m, 2H, 3''-$\boldsymbol{H_2}$), 1.97 – 1.89 (m, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (151 MHz, $CDCl_3$) 195.5 ($Ar_2$***C***O), 162.2 (***C***-1), 138.1 (***C***-4), 132.6 (***C***-3), 131.9 (***C***-4'), 130.4 (***C***-1'), 129.7 (***C***-2'), 128.2 (***C***-3'), 113.9 (***C***-2), 67.1 (***C***-1''), 57.9 (***C***-4''), 43.3 (***C***$H_3$), 26.4 (***C***-2''), 21.9 (***C***-3''). Accurate mass: found [M+H] 298.1807, $C_{19}H_{23}NO_2$ requires *M*, 298.1815.

**[4-(2''-bromoethoxy)phenyl](phenyl)methanone 26a**

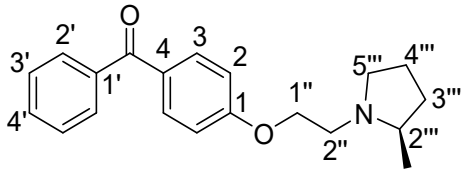



1,2-Dibromoethane (0.175 mL, 2.02 mmol) was reacted with 4-Hydroxybenzophenone (100 mg, 0.50 mmol) in anhydrous acetonitrile (5 mL) following general procedure A. Purification by column chromatography (100% Chloroform) afforded the title compound (90 mg, 58.7%) as a white solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.85 – 7.82 (m, 2H, 2-***H***), 7.78 – 7.74 (m, 2H, 2'-***H***), 7.59 – 7.55 (m, 1H, 4'-***H***), 7.50 – 7.46 (m, 2H, 3'-***H***), 7.00 – 6.96 (m, 2H, 3-***H***), 4.38 (t, *J* = 6.2 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.68 (t, *J* = 6.2 Hz, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (176 MHz, $CDCl_3$) 195.4 ($Ar_2$***C***O), 161.6 (***C***-4), 138.1 (***C***-1'), 132.6 (***C***-2), 131.9 (***C***-4'), 130.8 (***C***-1), 129.7 (***C***-2'), 128.2 (***C***-3'),

114.1 (***C***-3), 67.8 (***C***-1''), 28.5 (***C***-2''). Accurate mass: found [M+H] 305.0175, $C_{15}H_{14}{}^{79}BrO_2$ requires *M*, 305.0177.

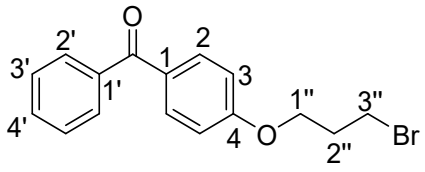
**(2'''*R*)-1'''-[2''-(4-benzoylphenoxy)ethyl]-2'''-methylpyrrolidine 26**




To a solution of (2*R*)-methylpyrrolidine hydrochloride (43 mg, 0.35 mmol), KI (5 mg, 0.033 mmol) and $K_2CO_3$ (208 mg, 1.51 mmol) in dry acetonitrile (30.5 mL) at 70ºC, [4-(2''-Bromoethoxy)phenyl](phenyl)methanone (100 mg, 0.33 mmol) in dry acetonitrile (30 mL) was slowly added. The mixture was then stirred overnight under a nitrogen atmosphere. The solution was then cooled to RT, filtered and concentrated. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (29 mg, 28%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.83 – 7.78 (m, 2H, 3-***H***), 7.76 – 7.72 (m, 2H, 2'-***H***), 7.57 – 7.53 (m, 1H, 4'-***H***), 7.49 – 7.44 (m, 2H, 3'-***H***), 6.98 – 6.93 (m, 2H, 2-***H***), 4.20 (td, *J* = 6.1, 2.0 Hz, 2H, 1''-***H*****$_2$**), 3.32 – 3.20 (m, 2H, 2''-***H***, 5'''-***H***), 2.65 – 2.58 (m, 1H, 2''-***H***), 2.53 – 2.43 (m, 1H, 2'''-***H***), 2.38 – 2.30 (m, 1H, 5'''-***H***), 1.99 – 1.91 (m, 1H, 3'''-***H***), 1.89 – 1.78 (m, 1H, 4'''-***H***), 1.78 – 1.70 (m, 1H, 4'''-***H***), 1.52 – 1.41 (m, 1H, 3'''-***H***), 1.16 (d, *J* = 6.2 Hz, 3H, C***H*****$_3$**); $\delta_C$ (151 MHz, $CDCl_3$) 195.5 ($Ar_2$***C***O), 162.4 (***C***-1), 138.3 (***C***-1'), 132.5 (***C***-3), 131.8 (***C***-4'), 130.1 (***C***-4), 129.7 (***C***-2'), 128.1 (***C***-3'), 114.1 (***C***-2), 67.3 (***C***-1''), 60.6 (***C***-2'''), 54.8 (***C***-5'''), 52.5 (***C***-2''), 32.3 (***C***-3'''), 21.9 (***C***-4'''), 18.9 (***C***$H_3$). Accurate mass: found [M+H] 324.1976, $C_{21}H_{24}NO_2$ requires *M*, 324.1964.

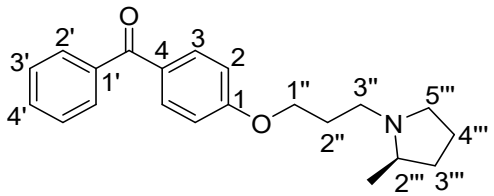
**[4-(3''-bromopropoxy)phenyl](phenyl)methanone 27a**




4-Hydroxybenzophenone (100 mg, 0.50 mmol) was reacted with 1,3-Dibromopropane (0.3 mL, 3.03 mmol) in anhydrous DMF (5 mL) following general procedure A. Purification by column chromatography (100% Chloroform) afforded the title compound (128 mg, 79%) as a colourless oil.

$\delta_H$ (700 MHz, $CDCl_3$) 7.85 – 7.81 (m, 2H, 2-***H***), 7.77 – 7.74 (m, 2H, 2'-***H***), 7.58 (t, *J* = 7.5 Hz, 1H, 4'-***H***), 7.50 – 7.45 (m, 2H, 3'-***H***), 6.99 – 6.96 (m, 2H, 3-***H***), 4.20 (t, *J* = 5.8 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.62 (t, *J* = 6.4 Hz, 2H, 3''-$\boldsymbol{H_2}$), 2.36 (p, *J* = 6.1 Hz, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (176 MHz, $CDCl_3$) 195.5 ($Ar_2\boldsymbol{C}O$), 162.3 (***C***-4), 138.2 (***C***-1'), 132.5 (***C***-2), 131.90 (***C***-4'), 130.4 (***C***-1), 129.7 (***C***-2'), 128.2 (***C***-3'), 114.0 (***C***-3), 65.5 (***C***-1''), 32.1 (***C***-3''), 29.7 (***C***-2''). Accurate mass: found [M+H] 319.0332, $C_{16}H_{16}{}^{79}BrO_2$ requires *M*, 319.0334.

**(2'''*R*)-1'''-[3''-(4-benzoylphenoxy)propyl]-2'''-methylpyrrolidine 27**

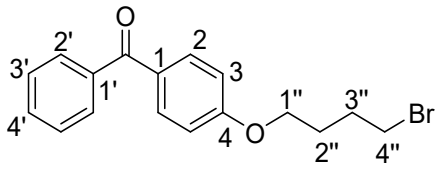



[4-(3''-Bromopropoxy)phenyl](phenyl)methanone (70 mg, 0.22 mmol) was reacted with (2*R*)-methylpyrrolidine hydrochloride (28 mg, 0.23 mmol) following general

procedure B. The product was purified by column chromatography (10% MeOH in DCM) to afford the title compound (17 mg, 25%) as a brown solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.83 – 7.79 (m, 2H, 3-***H***), 7.76 – 7.73 (m, 2H, 2'-***H***), 7.58 – 7.54 (m, 1H, 4'-***H***), 7.49 – 7.44 (m, 2H, 3'-***H***), 6.96 – 6.93 (m, 2H, 2-***H***), 4.18 – 4.09 (m, 2H, 1''-$\boldsymbol{H_2}$), 3.43 – 3.32 (m, 1H, 5'''-***H***), 3.19 – 3.09 (m, 1H, 3''-***H***), 2.71 – 2.58 (m, 1H, 2'''-***H***), 2.54 – 2.45 (m, 1H, 3''-***H***), 2.45 – 2.35 (m, 1H, 5'''-***H***), 2.27 – 2.18 (m, 1H, 2''-***H***), 2.18 – 2.09 (m, 1H, 2''-***H***), 2.08 – 1.99 (m, 1H, 3'''-***H***), 1.98 – 1.88 (m, 1H, 4'''-***H***), 1.86 – 1.76 (m, 1H, 4'''-***H***), 1.67 – 1.57 (m, 1H, 3'''-***H***), 1.34 – 1.24 (m, 3H, C$\boldsymbol{H_3}$); $\delta_C$ (151 MHz, $CDCl_3$) 195.5 ($Ar_2$***C***O), 162.4 (***C***-1), 138.2 (***C***-1'), 132.5 (***C***-3), 131.9 (***C***-4'), 130.2 (***C***-4), 129.7 (***C***-2'), 128.1 (***C***-3'), 113.9 (***C***-2), 66.2 (***C***-1''), 61.4 (***C***-2'''), 53.6 (***C***-5'''), 50.5 (***C***-3''), 32.2 (***C***-3'''), 27.4 (***C***-2''), 21.5 (***C***-4'''), 17.8 (***C***$H_3$). Accurate mass: found [M+H] 324.1959, $C_{21}H_{26}NO_2$ requires *M*, 324.1964.

**[4-(4''-bromobutoxy)phenyl](phenyl)methanone 28a**

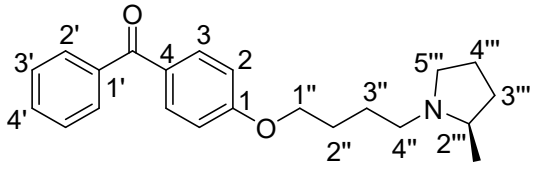



1,4-Dibromobutane (0.602 mL, 5.045 mmol) was reacted with 4-Hydroxybenzophenone (200 mg, 1.009 mmol) in anhydrous DMF (5 mL) following general procedure A. Purification by column chromatography (0 to 100% DCM in Hexane) afforded the title compound (159 mg, 47%) as a white solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.84 – 7.80 (m, 2H, 2-***H***), 7.78 – 7.73 (m, 2H, 2'-***H***), 7.59 – 7.54 (m, 1H, 4'-***H***), 7.50 – 7.45 (m, 2H, 3'-***H***), 6.97 – 6.92 (m, 2H, 3-***H***), 4.09 (t, *J* = 6.1 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.50 (t, *J* = 6.6 Hz, 2H, 4''-$\boldsymbol{H_2}$), 2.13 – 2.06 (m, 2H, 2''-$\boldsymbol{H_2}$), 2.04 – 1.95 (m, 2H, 3''-$\boldsymbol{H_2}$); $\delta_C$ (151 MHz, $CDCl_3$) 195.5 ($Ar_2$***C***O), 162.5 (***C***-4), 138.3 (***C***-1'), 132.6 (***C***-

2), 131.9 (***C***-4'), 130.2 (***C***-1), 129.7 (***C***-2'), 128.2 (***C***-3'), 113.9 (***C***-3), 67.1 (***C***-1''), 33.2 (***C***-4''), 29.3 (***C***-2''), 27.7 (***C***-3''). Accurate mass: found [M+H] 333.0493, $C_{17}H_{18}{}^{79}BrO_2$ requires *M*, 333.0490.

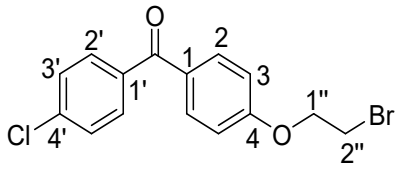
**(2'''*R*)-1'''-[4''-(4-benzoylphenoxy)butyl]-2'''-methylpyrrolidine 28**




[4-(4''-Bromobutoxy)phenyl](phenyl)methanone (100 mg, 0.300 mmol) was reacted with (2*R*)-methylpyrrolidine hydrochloride (38 mg, 0.312 mmol) in DMF following general procedure B. Product was purified by column chromatography (10% MeOH in DCM) to afford the title compound (31 mg, 31%) as a light brown solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.84 – 7.77 (m, 2H, 3-***H***), 7.77 – 7.70 (m, 2H, 2'-***H***), 7.58 – 7.52 (m, 1H, 4'-***H***), 7.49 – 7.43 (m, 2H, 3'-***H***), 6.97 – 6.90 (m, 2H, 2-***H***), 4.06 (t, *J* = 6.4 Hz, 2H, 1''-***H*****$_2$**), 3.28 – 3.18 (m, 1H, 5'''-***H***), 2.93 – 2.84 (m, 1H, 4''-***H***), 2.42 – 2.34 (m, 1H, 2'''-***H***), 2.23 – 2.10 (m, 2H, 4''-***H***, 5'''-***H***), 1.99 – 1.91 (m, 1H, 3'''-***H***), 1.91 – 1.85 (m, 1H, 2''-***H***), 1.85 – 1.79 (m, 2H, 2''-***H***, 4'''-***H***), 1.78 – 1.66 (m, 3H, 3''-***H*****$_2$**, 4'''-***H***), 1.54 – 1.41 (m, 1H, 3'''-***H***), 1.15 (d, *J* = 6.1 Hz, 3H, C***H*****$_3$**); $\delta_C$ (151 MHz, $CDCl_3$) 195.6 ($Ar_2$***C***O), 162.7 (***C***-1), 138.3 (***C***-1'), 132.5 (***C***-3), 131.8 (***C***-4'), 129.9 (***C***-4), 129.7 (***C***-2'), 128.1 (***C***-3'), 114.0 (***C***-2), 67.9 (***C***-1''), 60.6 (***C***-2'''), 53.7 (***C***-5'''), 53.6 (***C***-4''), 32.5 (***C***-3'''), 27.2 (***C***-2''), 24.9 (***C***-3''), 21.6 (***C***-4'''), 18.5 (***C***$H_3$). Accurate mass: found [M+H] 338.2139, $C_{22}H_{28}NO_2$ requires *M*, 338.2120.

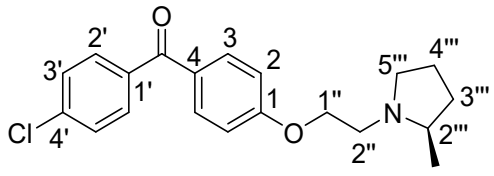
**[4-(2''-bromoethoxy)phenyl](4'-chlorophenyl)methanone 29a**




1,2-Dibromoethane (0.15 mL, 1.72 mmol) was reacted with 4-Chloro-4'-hydroxybenzophenone (100 mg, 0.43 mmol) in anhydrous DMF (4.5 mL) following general procedure A. Purification by column chromatography (100% DCM) afforded the title compound (32 mg, 22.3%) as a white solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.82 – 7.78 (m, 2H, 2-***H***), 7.73 – 7.69 (m, 2H, 2'-***H***), 7.47 – 7.44 (m, 2H, 3'-***H***), 7.00 – 6.96 (m, 2H, 3-***H***), 4.38 (t, *J* = 6.2 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.68 (t, *J* = 6.2 Hz, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (151 MHz, $CDCl_3$) 194.2 ($Ar_2\boldsymbol{C}O$), 161.8 (***C***-4), 138.4 (***C***-1'), 136.4 (***C***-4'), 132.5 (***C***-2), 131.2 (***C***-2'), 130.5 (***C***-1), 128.6 (***C***-3'), 114.3 (***C***-3), 67.9 (***C***-1''), 28.5 (***C***-2''). Accurate mass: found [M+H] 338.9796, $C_{15}H_{13}N^{35}Cl^{79}BrO_2$ requires *M*, 338.9807.

**(2'''*R*)-1'''-{2''-[4-(4'-chlorobenzoyl)phenoxy]ethyl}-2'''-methylpyrrolidine 29**

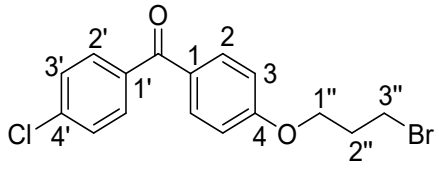



[4-(2''-Bromoethoxy)phenyl](4'-chlorophenyl)methanone (30 mg, 0.088 mmol) was reacted with (2*R*)-methylpyrrolidine hydrochloride (11.3 mg, 0.093 mmol) in anhydrous MeCN following general procedure B. Product was purified by column

chromatography (10% MeOH in DCM) to afford the title compound (7 mg, 23%) as a brown solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.81 – 7.76 (m, 2H, 3-***H***), 7.72 – 7.68 (m, 2H, 2'-***H***), 7.47 – 7.43 (m, 2H, 3'-***H***), 6.99 – 6.95 (m, 2H, 2-***H***), 4.50 – 4.20 (m, 2H, 1''-$\boldsymbol{H_2}$), 3.51 – 3.22 (m, 2H, 2''-***H***, 5'''-***H***), 2.87 – 2.61 (m, 2H, 2''-***H***, 2'''-***H***), 2.61 – 2.41 (m, 1H, 5'''-***H***), 2.10 – 1.98 (m, 1H, 3'''-***H***), 1.98 – 1.88 (m, 1H, 4'''-***H***), 1.88 – 1.77 (m, 1H, 4'''-***H***), 1.68 – 1.50 (m, 1H, 3'''-***H***), 1.34 – 1.25 (m, 3H, C$\boldsymbol{H_3}$); $\delta_C$ (151 MHz, $CDCl_3$) 194.2 ($Ar_2$***C***O), 162.2 (***C***-1) 138.3 (***C***-1'), 136.5 (***C***-4'), 132.4 (***C***-3), 131.1 (***C***-2'), 130.1 (***C***-4), 128.5 (***C***-3'), 114.2 (***C***-2), 66.4 (***C***-1''), 61.4 (***C***-2'''), 54.4 (***C***-5'''), 52.2 (***C***-2''), 33.9 (***C***-3'''), 21.7 (***C***-4'''), 18.0 (***C***$H_3$). Accurate mass: found [M+H] 344.1425, $C_{20}H_{23}N^{35}ClO_2$ requires *M*, 344.1417.

**[4-(3''-bromopropoxy)phenyl](4'-chlorophenyl)methanone 30a**

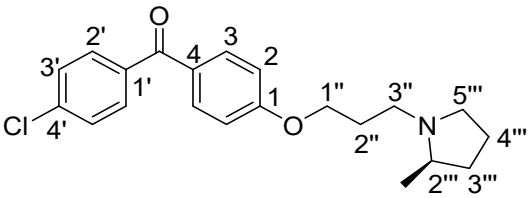



1,3-Dibromoproane (0.349 mL, 3.438 mmol) was reacted with 4-Hydroxybenzophenone (200 mg, 0.860 mmol) in anhydrous acetonitrile (4.5 mL) following general procedure A. Purification by column chromatography (50% Hexane in DCM) afforded the title compound (193 mg, 64%) as a white solid.

$\delta_H$ (599 MHz, $CDCl_3$) 7.81 – 7.77 (m, 2H, 2-***H***), 7.73 – 7.69 (m, 2H, 2'-***H***), 7.47 – 7.44 (m, 2H, 3'-***H***), 7.00 – 6.95 (m, 2H, 3-***H***), 4.20 (d, *J* = 5.9 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.62 (t, *J* = 5.9 Hz, 2H, 3''-$\boldsymbol{H_2}$), 2.36 (p, *J* = 5.9 Hz, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (151 MHz, $CDCl_3$) 194.2 ($Ar_2$***C***O), 162.5 (***C***-4), 138.3 (***C***-1'), 136.5 (***C***-4'), 132.5 (***C***-2), 131.1 (***C***-2'), 130.0 (***C***-1), 128.5

(***C***-3'), 114.1 (***C***-3), 65.5 (***C***-1''), 32.1 (***C***-2''), 29.6 (***C***-3''). Accurate mass: found [M+H] 352.9944, $C_{16}H_{15}N^{35}Cl^{79}BrO_2$ requires *M*, 352.9944.

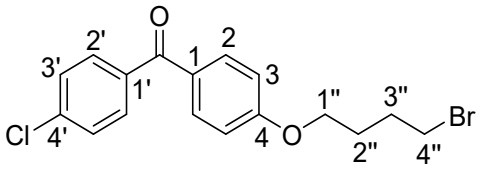
**(2'''*R*)-*N*-{3''-[4-(4'-chlorobenzoyl)phenoxy]propyl}-2'''-methylpyrrolidine 30**




[4-(3-bromopropoxy)phenyl](4-chlorophenyl)methanone (106 mg, 0.300 mmol) was reacted with (2*R*)-Methylpyrrolidine hydrochloride (44 mg, 0.384 mmol) following general procedure B. Product was purified by column chromatography (10% MeOH in DCM) to afford the title compound (49 mg, 46%) as a brown solid.

$\delta_H$ (400 MHz, $CDCl_3$) 7.87 – 7.77 (m, 2H, 3-***H₂***), 7.77 – 7.65 (m, 2H, 2'-***H₂***), 7.51 – 7.42 (m, 2H, 3'-***H₂***), 7.07 – 6.91 (m, 2H, 2-***H₂***), 4.24 – 4.05 (m, 2H, 1''-***H₂***), 3.34 – 3.18 (m, 1H, 5'''-***H***), 3.12 – 2.96 (m, 1H, 3''-***H***), 2.50 – 2.34 (m, 1H, 2'''-***H***), 2.34 – 2.25 (m, 1H, 3''-***H***), 2.25 – 2.15 (m, 1H, 5'''-***H***), 2.15 – 2.03 (m, 2H, 2''-***H₂***), 2.03 – 1.92 (m, 1H, 3'''-***H***), 1.92 – 1.68 (m, 2H, 4'''-***H₂***), 1.55 – 1.42 (m, 1H, 3'''-***H***), 1.22 – 1.08 (m, 3H, C***H₃***). $\delta_C$ (151 MHz, $CDCl_3$) 194.2 ($Ar_2$***C***O), 162.3 (***C***-1), 138.4 (***C***-1'), 136.4 (***C***-4'), 132.5 (***C***-3), 131.1 (***C***-2'), 130.1 (***C***-4), 128.5 (***C***-3'), 114.1 (***C***-2), 65.9 (***C***-1''), 64.3 (***C***-2'''), 53.3 (***C***-5'''), 50.5 (***C***-3''), 31.9 (***C***-3'''), 26.6 (***C***-2''') 21.4 (***C***-4'''), 17.9 (***C***$H_3$). Accurate mass: found [M+H] 358.1575, $C_{21}H_{25}N^{35}ClO_2$ requires *M*, 358.1574.

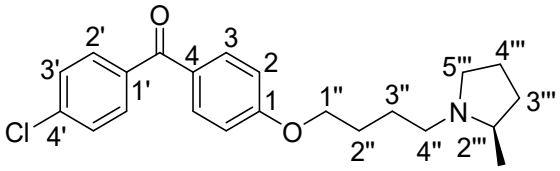
**[4-(4''-bromobutoxy)phenyl](4'-chlorophenyl)methanone 31a**




1,4-dibromobutane (0.411 mL, 3.428 mmol) was reacted with 4'-Chloro-4-hydroxybenzophenone (150 mg, 0.757 mmol) in anhydrous DMF (8.6 mL) following general procedure A. The product was precipitated overnight at -20ºC. Solvent was removed using a glass pipette and white solid left was washed with cold EtOAc to afford the title product (135 mg, 41%).

$\delta_H$ (599 MHz, $CDCl_3$) 7.80 – 7.77 (m, 2H, 2-***H***), 7.72 – 7.69 (m, 2H, 2'-***H***), 7.47 – 7.44 (m, 2H, 3'-***H***), 6.97 – 6.93 (m, 2H, 3-***H***), 4.09 (t, *J* = 6.0 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.50 (t, *J* = 6.6 Hz, 2H, 4''-$\boldsymbol{H_2}$), 2.13 – 2.06 (m, 2H, 3''-$\boldsymbol{H_2}$), 2.03 – 1.96 (m, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (151 MHz, $CDCl_3$) 194.2 ($Ar_2\boldsymbol{C}O$), 162.7 (***C***-4), 138.3 (***C***-1'), 136.5 (***C***-4'), 132.5 (***C***-2), 131.1 (***C***-2'), 129.83 (***C***-1), 128.5 (***C***-3'), 114.09 (***C***-3), 67.16 (***C***-1''), 33.21 (***C***-4''), 29.32 (***C***-3''), 27.73 (***C***-2''). Accurate mass: found [M+H] 367.0097, $C_{17}H_{17}N^{35}Cl^{79}BrO_2$ requires *M*, 367.367.0100.

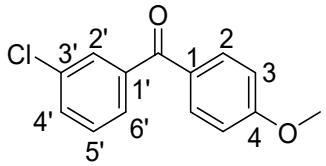
**(2'''*R*)-*N*-{4''-[4-(4'-chlorobenzoyl)phenoxy]butyl}-2'''-methylpyrrolidine 31**




[4-(4-bromobutoxy)phenyl](4-chlorophenyl)methanone (92 mg, 0.25 mmol) was reacted with (2*R*)-Methylpyrrolidine hydrochloride (35 mg, 0.29 mmol) in dry DMF (2.5 mL) following general procedure B. Product was purified by column chromatography (10% MeOH in DCM) to afford the title compound (48 mg, 52%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.80 – 7.74 (m, 2H, 3-***H₂***), 7.72 – 7.66 (m, 2H, 2-***H₂***), 7.46 – 7.40 (m, 2H, 2'-***H₂***), 6.97 – 6.90 (m, 2H, 3'-***H₂***), 4.11 – 4.01 (m, 2H, 1''-***H₂***), 3.40 – 3.26 (m, 1H, 5'''-***H***), 3.03 – 2.91 (m, 1H, 4''-***H***), 2.67 – 2.47 (m, 1H, 2'''-***H***), 2.42 – 2.24 (m, 2H, 4''-***H***, 5'''-***H***), 2.06 – 1.96 (m, 1H, 3'''-***H***), 1.96 – 1.73 (m, 6H, 2''-***H₂***, 3''-***H₂***, 4'''-***H₂***), 1.64 – 1.55 (m, 1H, 3'''-***H₂***), 1.24 (d, *J* = 6.3 Hz, 3H, C***H₃***); $\delta_C$ (151 MHz, $CDCl_3$) 194.2 ($Ar_2$***C***O), 162.8 (***C***-1), 138.2 (***C***-1'), 136.5 (***C***-4'), 132.4 (***C***-3), 131.1 (***C***-2'), 129.7 (***C***-4), 128.5 (***C***-3'), 114.1 (***C***-2), 67.8 (***C***-1''), 61.2 (***C***-2'''), 53.5 (***C***-5'''), 53.4 (***C***-4''), 32.2 (***C***-3'''), 27.1 (***C***-2''), 24.4 (***C***-3''), 21.5 (***C***-4'''), 17.9 (***C***$H_3$). Accurate mass: found [M+H] 372.1736, $C_{22}H_{27}N^{35}ClO_2$ requires *M*, 372.1730.

**(3'-chlorophenyl)(4-methoxyphenyl)methanone Ea** [3]

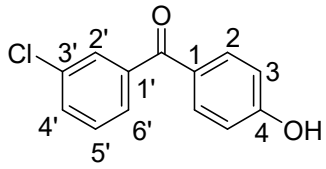



3-chlorobenzoate (1g, 6.39 mmol) was dissolved in thionyl chloride (3 mL) and refluxed for 3hours. After cooling down to RT, volatiles were removed under reduced pressure. 3-benzoyl chloride was then added to a solution of anisole (0.85 mL, 7.78 mmol) in anhydrous DCE (31 mL). $AlCl_3$ (1.04 g, 7.78 mmol) was added in portions over 20 minutes and mixture stirred for 24h at RT. In a separating funnel, the reaction mixture was added to 3M HCl (aq.) (30 mL) and extracted with DCM (3x20 mL). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced solid. Crude was submitted to column chromatography (0-100% EtOAc in Hexane) to afford de title product (1.19 g, 77%) as a white solid.

$\delta_H$ (400 MHz, $CDCl_3$) 7.84 – 7.79 (m, 2H, 2-***H₂***), 7.75 – 7.71 (m, 1H, 2'-***H***), 7.64 – 7.60 (m, 1H, 6'-***H***), 7.56 – 7.52 (m, 1H, 4'-***H***), 7.44 – 7.39 (m, 1H, 5'-***H***), 7.00 – 6.96 (m, 2H,

3-***H₂***), 3.90 (s, 3H, C***H₃***); $\delta_C$ (101 MHz, $CDCl_3$) 194.1 ($Ar_2$***C***O), 163.5 (***C***-4), 139.9 (***C***-5), 134.4 (***C***-1'), 132.6 (***C***-2), 131.9 (***C***-3'), 129.6 (***C***-5'), 129.6 (***C***-6'), 129.5 (***C***-4'), 127.8 (***C***-2'), 113.8 (***C***-3), 55.6 (***C***$H_3$). *m/z* (LC-MS, $ESI^+$) 247 [M($^{35}$Cl)+H] and 249 [M($^{37}$Cl)+H]) in a 3:1 ratio. All data agrees with literature.

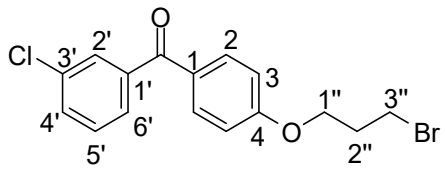
**4-(3'-chlorobenzoyl)phenol Eb** [3]




$AlCl_3$ (421.2 mg, 3.16 mmol) was added to a solution of (3-chlorophenyl)(4-methoxyphenyl)methanone (208 mg, 0.843 mmol) in dry toluene (5.6 mL) and mixture was heated under reflux for 2h. The mixture was cooled then poured into 3M HCl (aq.) (10 mL) in a separating funnel and extracted with EtOAc (3x15 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title product (196 mg, 99%) as a brown solid.

$\delta_H$ (400 MHz, $CDCl_3$) 7.81 – 7.75 (m, 2H, 2-***H***), 7.75 – 7.70 (m, 1H, 2'-***H***), 7.62 (dt, *J* = 7.8, 1.4 Hz, 1H, 6'-***H***), 7.57 – 7.52 (m, 1H, 4'-***H***), 7.42 (t, *J* = 7.8 Hz, 1H, 5'-***H***), 6.96 – 6.89 (m, 2H, 3-***H***); $\delta_C$ (101 MHz, $CDCl_3$) 194.2 ($Ar_2$***C***O), 160.0 (***C***-4), 139.9 (***C***-3'), 134.5 (***C***-1'), 132.9 (***C***-2), 131.9 (***C***-4'), 129.7 (***C***-1'), 129.6 (***C***-2'), 129.6 (***C***-5'), 127.8 (***C***-6'), 115.3 (***C***-3). *m/z* (LC-MS, $ESI^+$) 233 [M($^{35}$Cl)+H] and 235 [M($^{37}$Cl)+H]) in a 3:1 ratio. All data agrees with literature.

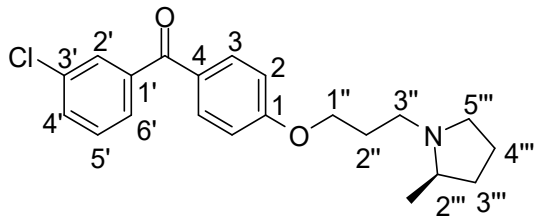
**[4-(3''-bromopropoxy)phenyl](3'-chlorophenyl)methanone 32a**




$Na_2CO_3$ (683.3 mg, 6.45 mmol) was added to a solution of 1,3-dibromopropane (0.327 mL, 3.22 mmol) in anhydrous acetonitrile (15.2 mL). A solution of 4-(3-chlorobenzoyl)phenol (150 mg, 0.645 mmol) in anhydrous acetonitrile (17 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and product was purified by column chromatography (0 to 100% Chloroform) to afford the title compound (90 mg, 59%) as a yellow oil.

$\delta_H$ (400 MHz, $CDCl_3$) 7.84 – 7.78 (m, 2H, 2-***H***), 7.73 (t, *J* = 1.8 Hz, 1H, 2'-***H***), 7.62 (dt, *J* = 7.8, 1.4 Hz, 1H, 6'-***H***), 7.56 – 7.51 (m, 1H, 4'-***H***), 7.42 (t, *J* = 7.8 Hz, 1H, 5'-***H***), 7.01 – 6.95 (m, 2H, 3-***H***), 4.21 (t, *J* = 5.8 Hz, 2H, 1''-$\boldsymbol{H_2}$), 3.62 (t, *J* = 6.3 Hz, 2H, 3''-$\boldsymbol{H_2}$), 2.41 – 2.32 (m, 2H, 2''-$\boldsymbol{H_2}$); $\delta_C$ (101 MHz, $CDCl_3$) 194.0 ($Ar_2\boldsymbol{C}O$), 162.6 (***C***-4), 139.9 (***C***-3'), 134.4 (***C***-1'), 132.6 (***C***-2), 131.9 (***C***-4'), 129.7 (***C***-1), 129.6 (***C***-2'), 129.6 (***C***-5'), 127.8 (***C***-6'), 114.2 (***C***-3), 65.6 (***C***-1''), 32.1 (***C***-2''), 29.7 (***C***-3''). *m/z* (LC-MS, $ESI^+$) 353 [M($^{35}Cl^{79}Br$)+H], 355 [M($^{37}Cl^{79}Br$)+H]) and 357 [M($^{37}Cl^{81}Br$)+H]) in a 3:4:1 ratio.

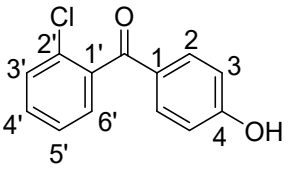
**(2'''*R*)-*N*-{3''-[4-(3'-chlorobenzoyl)phenoxy]propyl}-2'''-methylpyrrolidine 32**



To a solution of (2*R*)-methylpyrrolidine hydrochloride (37.1 mg, 0.305 mmol), KI (4.2 mg, 0.025 mmol) and $Na_2CO_3$ (124 mg, 1.71 mmol) in dry acetonitrile (7 mL) at 70ºC, [4-(3-Bromopropoxy)phenyl](3-chlorophenyl)methanone (96 mg, 0.27 mmol) in dry acetonitrile (5 mL) was slowly added. The mixture stirred overnight under nitrogen atmosphere. The solution was then cooled to RT, filtered, and concentrated under reduced pressure. The crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (51 mg, 53%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.82 – 7.78 (m, 2H, 3-***H***), 7.72 (t, *J* = 1.9 Hz, 1H, 2'-***H***), 7.61 (dt, *J* = 7.8, 1.3 Hz, 1H, 6'-***H***), 7.55 – 7.52 (m, 1H, 4'-***H***), 7.41 (t, *J* = 7.8 Hz, 1H, 5'-***H***), 6.99 – 6.95 (m, 2H, 2-***H***), 4.18 – 4.09 (m, 2H, 1''-***H₂***), 3.35 – 3.21 (m, 1H, 5'''-***H***), 3.12 – 3.00 (m, 1H, 3''-***H***), 2.59 – 2.41 (m, 1H, 2'''-***H***), 2.42 – 2.30 (m, 1H, 3''-***H***), 2.30 – 2.19 (m, 1H, 5'''-***H***), 2.19 – 2.04 (m, 2H, 2''-***H₂***), 2.04 – 1.92 (m, 1H, 3'''-***H***), 1.92 – 1.81 (m, 1H, 4'''-***H***), 1.81 – 1.71 (m, 1H, 4'''-***H***), 1.60 – 1.44 (m, 1H, 3'''-***H***), 1.18 (d, *J* = 6.0 Hz, 3H, C***H₃***); $\delta_C$ (151 MHz, $CDCl_3$) 193.9 ($Ar_2$***C***O), 162.9 (***C***-1), 139.9 (***C***-3'), 134.4 (***C***-1'), 132.5 (***C***-3), 131.8 (***C***-4'), 129.6 (***C***-2'), 129.5 (***C***-5'), 129.4 (***C***-4), 127.7 (***C***-6'), 114.2 (***C***-2), 66.5 (***C***-1''), 60.6 (***C***-2'''), 53.8 (***C***-5'''), 50.6 (***C***-3''), 32.5 (***C***-3'''), 27.9 (***C***-2''), 21.6 (***C***-4'''), 18.4 (***C***$H_3$). Accurate mass: found [M+H] 358.1584, $C_{21}H_{25}N^{35}ClO_2$ requires *M*, 358.1574.

**4-(2'-chlorobenzoyl)phenol D** [4]

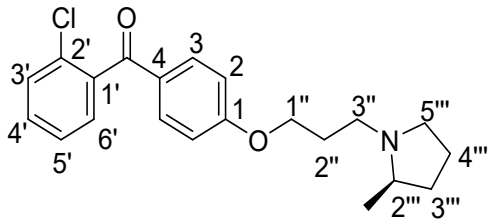



2-chlorobenzoic acid (1g, 6.39 mmol) was dissolved in thionyl chloride (3 mL) and refluxed for 3hours. After cooling down to RT, volatiles were removed under reduced

pressure and a solution of anisole (0.85 mL, 7.78 mmol) in anhydrous DCE (31 mL) was added. $AlCl_3$ (1.04 g, 7.78 mmol) was added in portions over 20 minutes and mixture stirred for 2h at RT and 2h at 80ºC. After cooling down to room temperature, reaction mixture was added to 3M HCl (aq.) (30 mL) in a separating funnel and extracted with DCM (3x20 mL). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced solid. Crude was submitted to column chromatography (0-100% EtOAc in Hexane) to afford de title product (1.04 g, 70%) as a white solid.

$\delta_H$ (400 MHz, $CDCl_3$) 7.78 – 7.72 (m, 2H, 2-***H₂***), 7.48 – 7.39 (m, 2H, 3'-***H***, 6'-***H***), 7.37 – 7.33 (m, 2H, 4'-***H***, 5'-***H***), 6.91 – 6.84 (m, 2H, 3-***H₂***), 5.79 (s, 1H, OH); $\delta_C$ (101 MHz, $CDCl_3$) 194.1 ($Ar_2$***C***O), 160.7 (***C***-4), 138.8 (***C***-1), 132.9 (***C***-2), 131.1 (***C***-1'), 130.9 (***C***-2'), 130.0 (***C***-5'), 129.6 (***C***-4'), 128.9 (***C***-3'), 126.7 (***C***-6'), 115.5 (***C***-3). *m/z* (LC-MS, $ESI^+$) 233 [M($^{35}$Cl)+H] and 235 [M($^{37}$Cl)+H]) in a 3:1 ratio. All data agrees with literature.

**(2'''*R*)-*N*-{3''-[4-(2'-chlorobenzoyl)phenoxy]propyl}-2''-methylpyrrolidine 33**

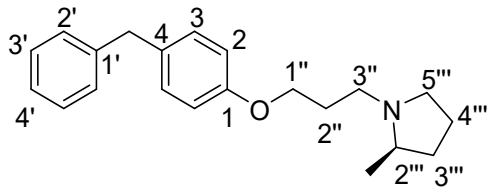



$Cs_2CO_3$ (1.93 g, 5.93 mmol) was added to a solution of 1,3-dibromopropane (0.65 mL, 6.45 mmol) in anhydrous acetonitrile (20 mL). A solution of 4-(2-chlorobenzoyl)phenol (300 mg, 1.29 mmol) in anhydrous acetonitrile (23 mL) was slowly added and stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was concentrated under reduced pressure and product was submitted to column

chromatography (0-100% DCM in Hexane) remove inorganic salts. Resultant product (100 mg) in dry acetonitrile (7 mL) was slowly added to a stirring solution of (2*R*)-Methylpyrrolidine hydrochloride (41.3 mg, 0.34 mmol), KI (4.7 mg, 0.028 mmol) and $Na_2CO_3$ (138 mg, 1.30 mmol) in dry acetonitrile (7 mL) at 70ºC. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT, filtered and concentrated under reduced pressure. Crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (20 mg, 20%) as a yellow solid.

$\delta_H$ (400 MHz, $CDCl_3$) 7.81 – 7.74 (m, 2H, 3'-***H*****$_2$**), 7.47 – 7.37 (m, 2H, 3'-***H***, 6'-***H***), 7.37 – 7.32 (m, 2H, 4'-***H***, 5'-***H***), 6.96 – 6.89 (m, 2H, 2-***H*****$_2$**), 4.19 – 4.01 (m, 2H, 1''-***H*****$_2$**), 3.36 – 3.12 (m, 1H, 5'''-***H***), 3.12 – 2.92 (m, 1H, 3''-***H***), 2.51 – 2.33 (m, 1H, 2''-***H***), 2.33 – 2.22 (m, 1H, 3''-***H***), 2.22 – 2.13 (m, 1H, 5'''-***H***), 2.13 – 2.00 (m, 2H, 2''-***H*****$_2$**), 2.00 – 1.90 (m, 1H, 3'''-***H***), 1.90 – 1.76 (m, 1H, 4'''-***H***), 1.77 – 1.66 (m, 1H, 4'''-***H***), 1.58 – 1.38 (m, 1H, 3'''-***H***), 1.22 – 1.01 (m, 3H, C***H*****$_3$**); $\delta_C$ (101 MHz, $CDCl_3$) 193.9 ($Ar_2$***C***O), 163.6 (***C***-1), 139.0 (***C***-2'), 132.5 (***C***-3), 131.1 (***C***-4), 130.8 (***C***-1'), 129.9 (***C***-5'), 129.3 (***C***-4'), 128.9 (***C***-6'), 126.7 (***C***-3'), 114.3 (***C***-2), 66.7 (***C***-1''), 60.7 (***C***-2'''), 53.9 (***C***-5'''), 50.6 (***C***-3''), 32.6 (***C***-3'''), 28.2 (***C***-2''), 21.6 (***C***-3'''), 18.7 (***C***$H_3$). Accurate mass: found [M+H] 344.1427, $C_{20}H_{23}N^{35}ClO_2$ requires *M*, 344.1417.

**(2'''*R*)-N-[3''-(4-benzylphenoxy)propyl]-2'''-methylpyrrolidine 34**

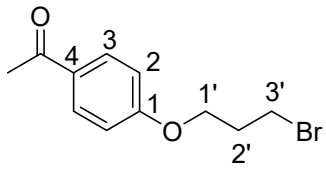



(*R*)-2-chlorophenyl(phenyl)methanol (80 mg, 0.49 mmol) was dissolved in anhydrous DMF (2 mL), to which tBuOK (107 mg, 0.95 mmol), TBAI (32 mg, 0.087 mmol) and 4-

benzylphenol (80 mg, 0.434 mmol) were added. The solution stirred overnight at 70ºC. Once full conversion was achieved, the reaction mixture was diluted with water and extracted with EtOAc. Once concentrated under reduced pressure, the crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (73 mg, 54%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.30 – 7.26 (m, 2H, 3'-***H***), 7.21 – 7.15 (m, 3H, 2'-***H***, 4'-***H***), 7.11 – 7.07 (m, 2H, 3-***H***), 6.85 – 6.81 (m, 2H, 2-***H***), 4.04 – 3.96 (m, 2H, 1''-$\boldsymbol{H_2}$), 3.93 (s, 2H, C$\boldsymbol{H_2}$), 3.23 – 3.15 (m, 1H, 3''-***H***), 3.02 – 2.94 (m, 1H, 5'''-***H***), 2.36 – 2.28 (m, 1H, 2'''-***H***), 2.26 – 2.18 (m, 1H, 5'''-***H***), 2.18 – 2.10 (m, 1H, 3''-***H***), 2.04 – 1.96 (m, 2H, 2''-***H***), 1.96 – 1.88 (m, 1H, 3'''-***H***), 1.84 – 1.75 (m, 1H, 4'''-***H***), 1.74 – 1.66 (m, 1H, 4'''-***H***), 1.49 – 1.40 (m, 1H, 3'''-***H***), 1.11 (d, J = 6.1 Hz, 3H, C$\boldsymbol{H_3}$); $\delta_C$ (151 MHz, $CDCl_3$) 157.4 (***C***-1), 141.6 (***C***-4), 133.1 (***C***-1'), 129.8 (***C***-3), 128.8 (***C***-2'), 128.4 (***C***-3'), 125.9 (***C***-4'), 114.5 (***C***-2), 66.5 (***C***-1''), 60.3 2'''), 53.9 (***C***-3''), 50.9 (***C***-5'''), 41.0 (***C***$H_2$), 32.7 (***C***-3'''), 28.6 (***C***-2''), 21.6 (***C***-4'''), 18.9 (***C***$H_3$). Accurate mass: found [M+H] 310.2197, $C_{21}H_{27}NO$ requires *M*, 310.2203.

**4-[1-(3'-bromopropoxy)phenyl]ethenone 35a**

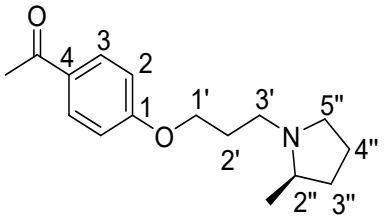



A solution of 4'-hydroxyacetophenone (200 mg, 1.47 mmol) in EtOAc (2.1 mL) was slowly added to a solution of 1,3-dibromopropane (1.1 mL, 11.018 mmol), potassium carbonate (710 mg, 5.14 mmol) and triethylbenzylammonium chloride (33 mg, 0.148 mmol) in EtOAc (2.1 mL). After refluxing overnight, reaction was cooled to room temperature, filtered, diluted with water (5 mL) and extracted with EtOAc (10 mL).

Combined organic layers were washed with 1M NaOH (aq), brine and dried over $MgSO_4$. After filtration, volatiles were removed and crude mixture was submitted to column chromatography (0-100% EtOAc in Hexane) to afford title product (201 mg, 53%) as a colourless oil.

$\delta_H$ (400 MHz, $CDCl_3$) 7.96 – 7.90 (m, 2H, 3-***H₂***), 6.97 – 6.90 (m, 2H, 2-***H₂***), 4.17 (t, *J* = 6.0 Hz, 2H, 1'-***H₂***), 3.61 (t, *J* = 6.0 Hz, 2H, 3'-***H₂***), 2.56 (s, 3H, C***H₃***), 2.34 (p, *J* = 6.0 Hz, 2H, 2'-***H₂***); $\delta_C$ (101 MHz, $CDCl_3$) 196.8 ($Ar_2$***C***O), 162.6 (***C***-1), 130.6 (***C***-3), 130.5 (***C***-4), 114.2 (***C***-2), 65.5 (***C***-1'), 32.1 (***C***-3'), 29.7 (***C***-2'), 26.4 (***C***$H_3$). Accurate mass: found [M+H] 257.0193, $C_{11}H_{14}N^{79}BrO_2$ requires *M*, 257.0177.

**4-(1-{3'-[(2''*R*)-2''-methylpyrrolidine]propoxy}phenyl)ethenone 35**

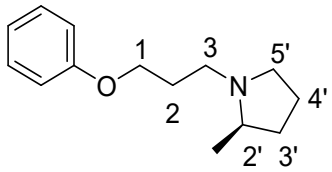



To a solution of (2*R*)-Methylpyrrolidine hydrochloride (56.8 mg, 0.46 mmol), KI (6.5 mg, 0.039 mmol) and $Na_2CO_3$ (189.6 mg, 1.79 mmol) in dry acetonitrile (10 mL) at 70ºC, 1-[4-(3-bromopropoxy)phenyl]ethan-1-one (100 mg, 0.39 mmol) in dry acetonitrile (10 mL) was slowly added. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT, filtered and concentrated under reduced pressure. Crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (69 mg, 69%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.94 – 7.90 (m, 2H, 3-***H₂***), 6.95 – 6.90 (m, 2H, 2-***H₂***), 4.14 – 4.05 (m, 2H, 1'-***H₂***), 3.28 – 3.17 (m, 1H, 5''-***H***), 3.06 – 2.97 (m, 1H, 3'-***H***), 2.55 (s, 3H, COC***H₃***), 2.44 – 2.33 (m, 1H, 2''-***H***), 2.32 – 2.24 (m, 1H, 3'-***H***), 2.24 – 2.14 (m, 1H, 5''-

***H***), 2.10 – 2.01 (m, 2H, 2'-***H*****$_2$**), 2.00 – 1.91 (m, 1H, 3''-***H***), 1.87 – 1.77 (m, 1H, 4''-***H***), 1.77 – 1.68 (m, 1H, 4''-***H***), 1.53 – 1.41 (m, 1H, 3''-***H***), 1.13 (d, *J* = 6.1 Hz, 3H, C***H*****$_3$**); $\delta_C$ (151 MHz, $CDCl_3$) 196.8 ($Ar_2$***C***O), 162.9 (***C***-1), 130.5 (***C***-3), 130.2 (***C***-4), 114.1 (***C***-2), 66.6 (***C***-1'), 60.5 (***C***-2''), 53.9 (***C***-5''), 50.6 (***C***-3'), 32.6 (***C***-3''), 28.2 (***C***-2'), 26.3 (CO***C***$H_3$), 21.6 (***C***-4''), 18.7 (***C***$H_3$). Accurate mass: found [M+H] 262.1809, $C_{16}H_{24}NO_2$ requires *M*, 262.1807.

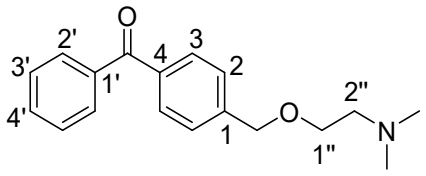
**(2'*R*)-2'-methyl-*N*-(3-phenoxypropyl)pyrrolidine 36**




A solution of phenol (200 mg, 2.12 mmol) in acetonitrile (4 mL) was slowly added to a mixture of potassium carbonate (1.46 g, 10.63 mmol) and 1,3- dibromopropane (1.1 mL, 10.63 mmol) in dry acetonitrile (3 mL) at 70ºC. After stirring overnight, reaction mixture was cooled to room temperature and filtered. Volatiles were removed and crude mixture was submitted to column chromatography (0-100% EtOAc in Hexane) to remove inorganic salts. Resultant product (100 mg) in dry acetonitrile (13 mL) was slowly added to a stirring solution of (2*R*)-Methylpyrrolidine hydrochloride (67.8 mg, 0.56 mmol), KI (7.7 mg, 0.046 mmol) and $Na_2CO_3$ (226.7 mg, 2.14 mmol) in dry acetonitrile (10 mL) at 70ºC. Mixture stirred overnight under nitrogen atmosphere. Solution was cooled down to RT, filtered and concentrated under reduced pressure. Crude mixture was submitted to column chromatography (10% MeOH in DCM) to afford the title compound (35 mg, 35%) as a brown oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.30 – 7.26 (m, 2H, 2xAr***H***), 6.95 – 6.92 (m, 1H, Ar***H***), 6.92 – 6.88 (m, 2H, 2xAr***H***), 4.10 – 3.97 (m, 2H, 1-***H₂***), 3.28 – 3.20 (m, 1H, 5'-***H***), 3.08 – 2.98 (m, 1H, 3-***H₂***), 2.47 – 2.34 (m, 1H, 2'-***H***), 2.34 – 2.25 (m, 1H, 3-***H***), 2.25 – 2.15 (m, 1H, 5'-***H***), 2.11 – 2.01 (m, 2H, 2-***H₂***), 2.01 – 1.91 (m, 1H, 3'-***H***), 1.87 – 1.78 (m, 1H, 4'-***H***), 1.78 – 1.68 (m, 1H, 4'-***H***), 1.53 – 1.44 (m, 1H, 3'-***H***), 1.15 (d, *J* = 6.1 Hz, 3H, C***H₃***). $\delta_C$ (151 MHz, $CDCl_3$) 158.9 (***C***-Ar), 129.4 (***C***-Ar), 120.6 (***C***-Ar), 114.5 (***C***-Ar), 66.2 (***C***-1), 60.6 (***C***-2'), 53.9 (***C***-5'), 50.8 (***C***-3), 32.6 (***C***-3'), 28.3 (***C***-2), 21.6 (***C***-4'), 18.7 (***C***$H_3$). Accurate mass: found [M+H] 220.1711, $C_{14}H_{22}NO_2$ requires *M*, 220.1701.

**{2''-[(4-benzoylphenyl)methoxy]ethyl}dimethylamine 37**

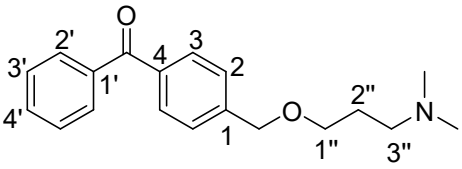



To a suspension of NaH (60% in mineral oil) (40 mg, 1 mmol) in anhydrous THF (1 mL), 2-dimethylaminoethanol **34** (0.05 mL, 0.48 mmol) was slowly added. After heating under reflux for 1h, a solution of 4-bromomethyl benzophenone (50 mg, 0.18 mmol) and TBAI (6 mg, 0.02 mmol) in anhydrous THF (1 mL) was added dropwise, and mixture then heated under reflux overnight. The reaction was then diluted with sat. $NaCO_{3(aq)}$ (15 mL) and products extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with sat. $Na_2CO_{3(aq)}$ (3 x 30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title ether (20 mg, 39%) as a yellow oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.81 – 7.77 (m, 4H, 3-***H***, 2'-***H***), 7.60 – 7.56 (m, 1H, 4'-***H***), 7.50 – 7.44 (m, 4H, 2-***H***, 3'-***H***), 4.63 (s, 2H, ArC***H₂***), 3.66 (t, 2H, *J* = 5.6 Hz, 1''-***H₂***), 2.67 (t, 2H, *J* = 5.6 Hz, 2''-***H₂***), 2.37 (s, 6H, C***H₃***); $\delta_C$ (151 MHz, $CDCl_3$) 196.4 ($Ar_2$***C***O), 142.9

(***C***-1), 137.6 (***C***-1'), 136.8 (***C***-4), 132.3 (***C***-4'), 130.2 (***C***-3), 129.9 (***C***-2'), 128.2 (***C***-3'), 127.2 (***C***-2), 72.6 (Ar***C***$H_2$), 68.1 (***C***-1''), 58.6 (***C***-2''), 45.6 (***C***$H_3$). Accurate mass: found [M+H] 284.1646, $C_{18}H_{22}NO_2$ requires *M*, 284.1651.

**{3''-[(4-benzoylphenyl)methoxy]propyl}dimethylamine 38**




To a suspension of NaH (60% in mineral oil) (22 mg, 0.545 mmol) in anhydrous DMF (1.5 mL), 2-dimethylaminoethanol **34** (0.073 mL, 0.612 mmol) was slowly added and let stir for 1 hour at RT. After, a solution of 4-bromomethyl benzophenone (100 mg, 0.363 mmol) and TBAI (13 mg, 0.036 mmol) in anhydrous DMF (2 mL) was added dropwise, and the mixture stirred overnight at RT. The reaction was then diluted with sat. $Na_2CO_{3(aq)}$ (15 mL) and products extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with sat. $Na_2CO_{3(aq)}$ (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography (20% MeOH in DCM) to afford the title compound (16 mg, 15%) as a colourless oil.

$\delta_H$ (599 MHz, $CDCl_3$) 7.80 – 7.77 (m, 4H, 2'-***H***, 3-***H***), 7.60 – 7.57 (m, 1H, 4'-***H***), 7.50 – 7.46 (m, 2H, 3'-***H***), 7.45 – 7.42 (m, 2H, 2-***H***), 4.59 (s, 2H, ArC***H₂***), 3.59 (t, *J* = 6.3 Hz,

2H, 1''-***H*****$_2$**), 2.61 – 2.54 (m, 2H, 3''-***H*****$_2$**), 2.41 – 2.34 (m, 6H, C***H*****$_3$**), 1.95 – 1.88 (m, 2H, 2''-***H*****$_2$**); $\delta_C$ (151 MHz, $CDCl_3$) 196.4 ($Ar_2$***C***O), 143.2 (***C***-1), 137.6 (***C***-1'), 136.8 (***C***-4), 132.3 (***C***-4'), 130.2 (***C***-4), 129.9 (***C***-2'), 128.2 (***C***-3'), 127.1 (***C***-2), 72.4 (Ar***C***$H_2$), 68.6 (***C***-1''), 56.4 (***C***-3''), 44.8 (***C***$H_3$), 27.2 (***C***-2''). Accurate mass: found [M+H] 298.1800, $C_{19}H_{24}NO_2$ requires *M*, 298.1807.

## References


1 J. Debnath, S. Siricilla, B. Wan, D. C. Crick, A. J. Lenaerts, S. G. Franzblau and M. Kurosu, *J. Med. Chem.*, 2012, **55**, 3739–3755.

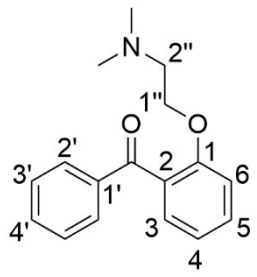
2 Z. Zhang, M. G. Lindale and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2011, **133**, 6403–6410.

3 S. Sultan, M. U. S. Bhat, M. A. Rizvi and B. A. Shah, *J. Org. Chem.*, 2019, **84**, 8948–8958.

4 W. Liu, J. Guo, S. Xing and Z. Lu, *Org. Lett.*, 2020, **22**, 2532–2536.

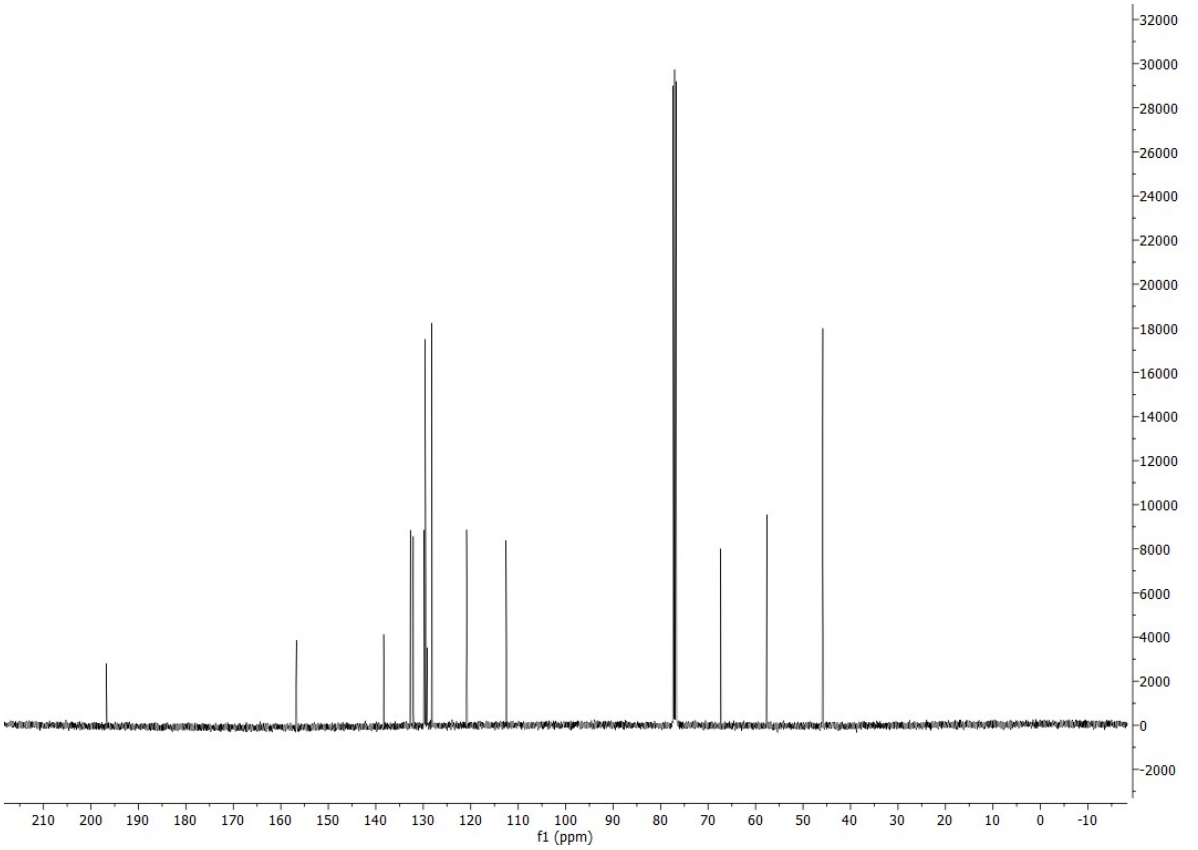
## 2. $^{1}H$ and $^{13}C$ NMR spectra of all compounds

**[2’’-(2-benzoylphenoxy)ethyl]dimethylamine 1**

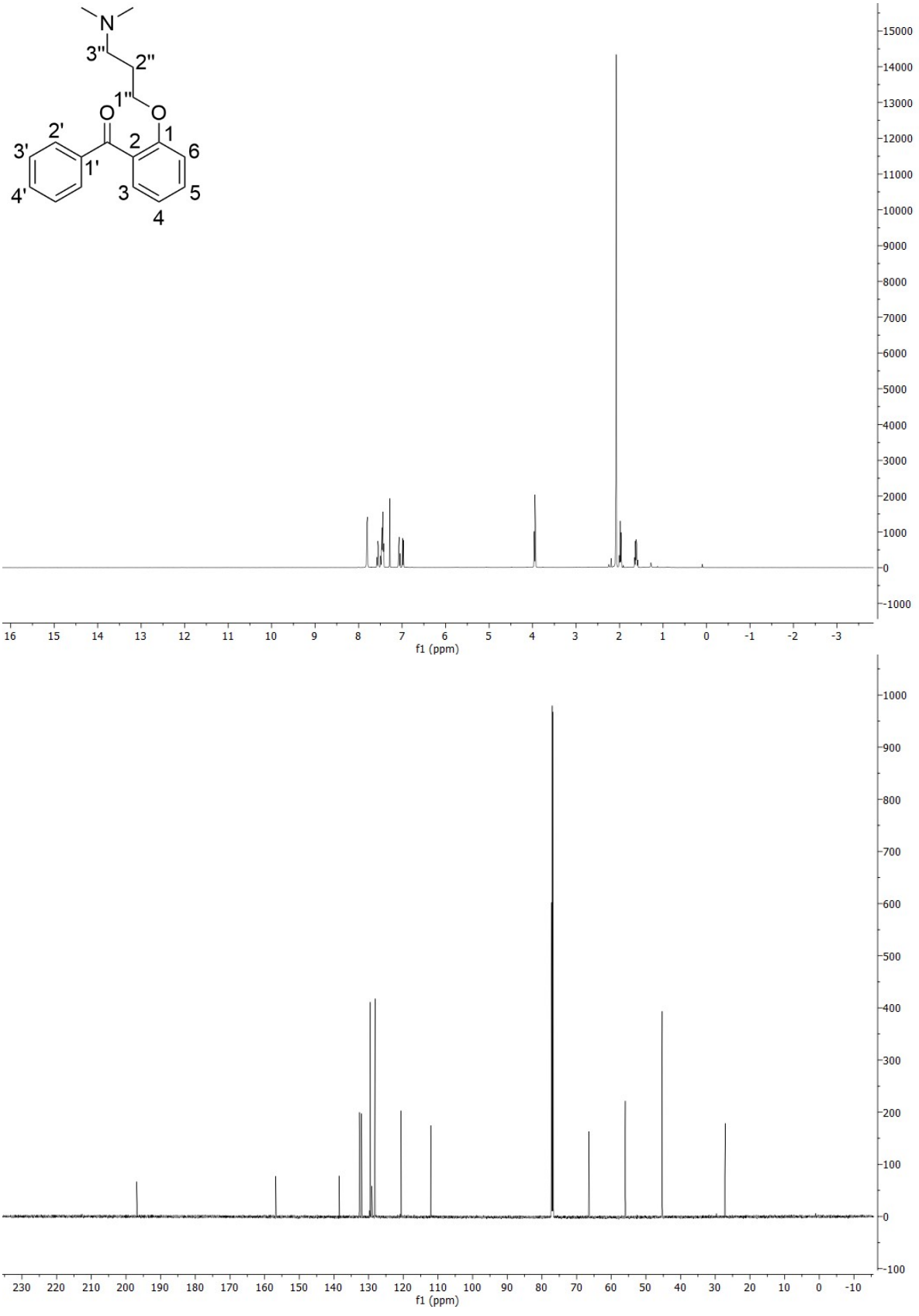




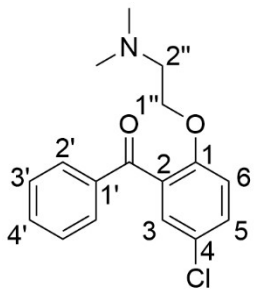




## [3’’-(2-benzoylphenoxy)propyl]dimethylamine 2

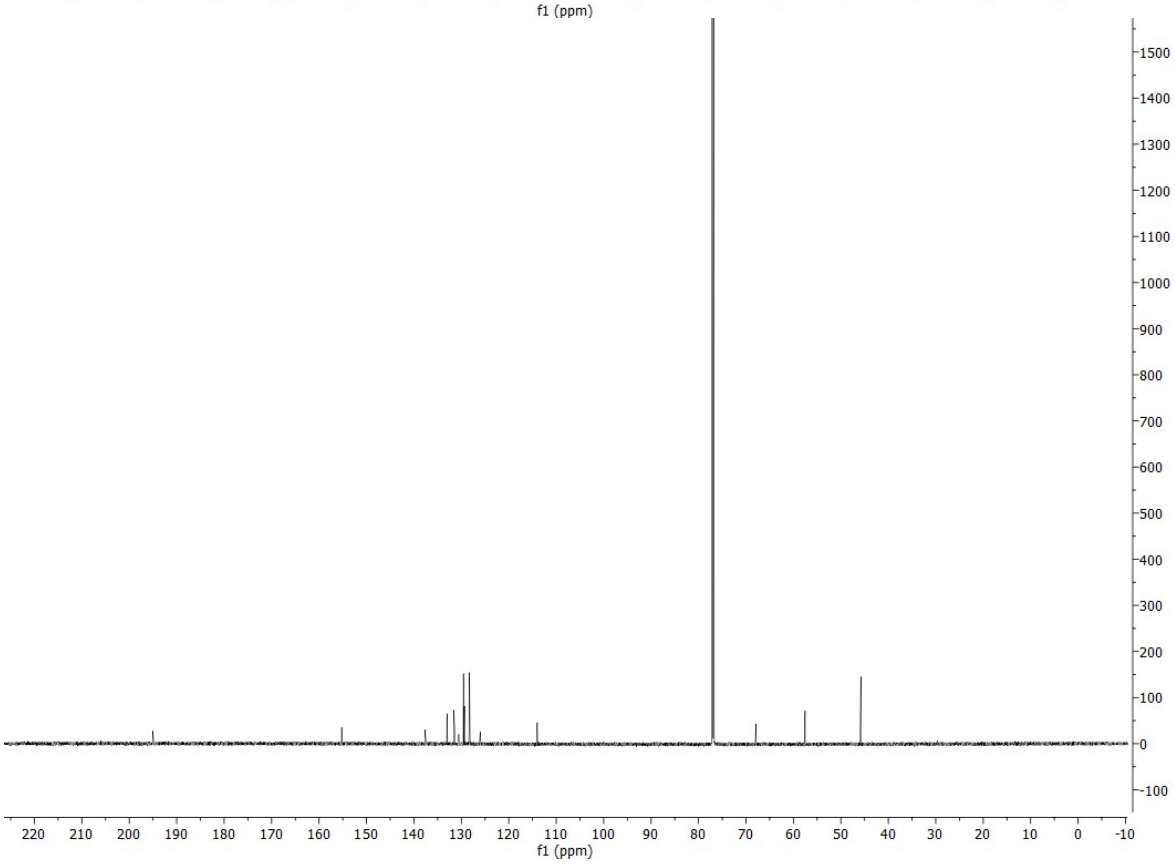


## [2’’-(2-benzoyl-4-chlorophenoxy)ethyl]dimethylamine 3

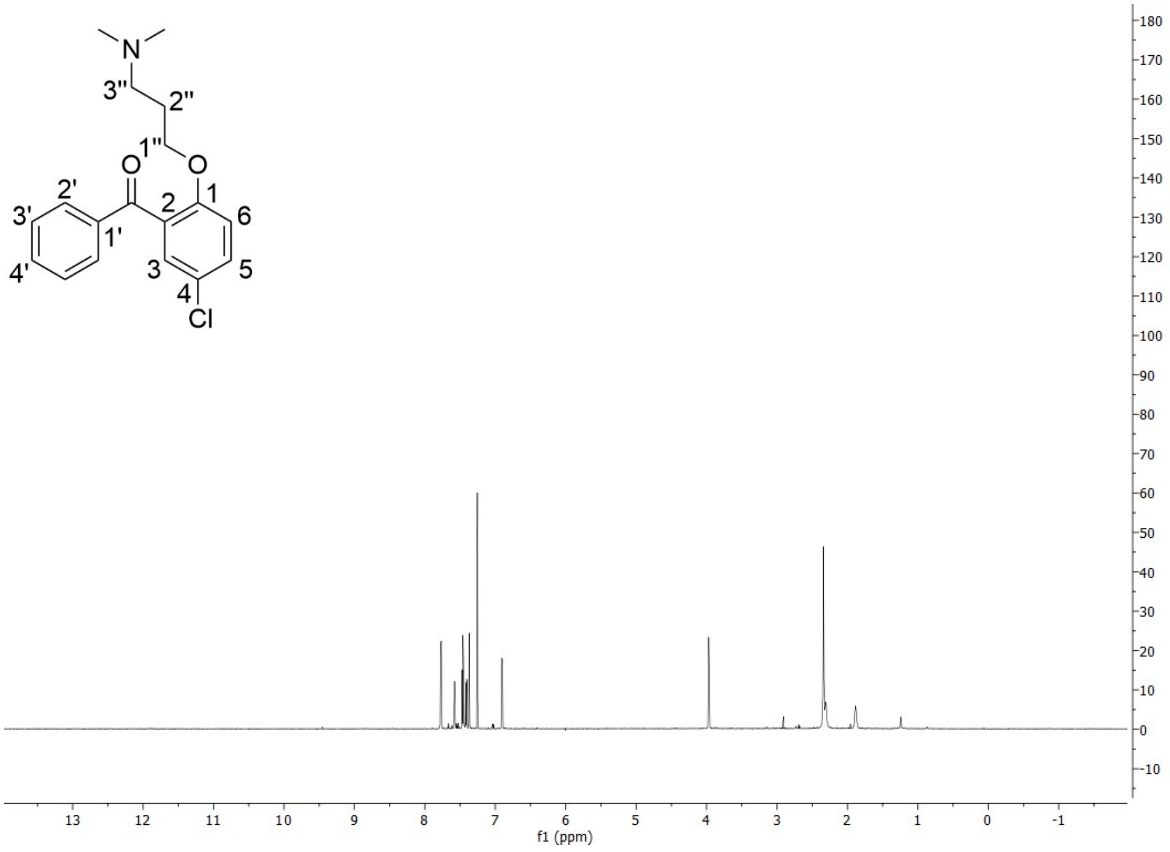


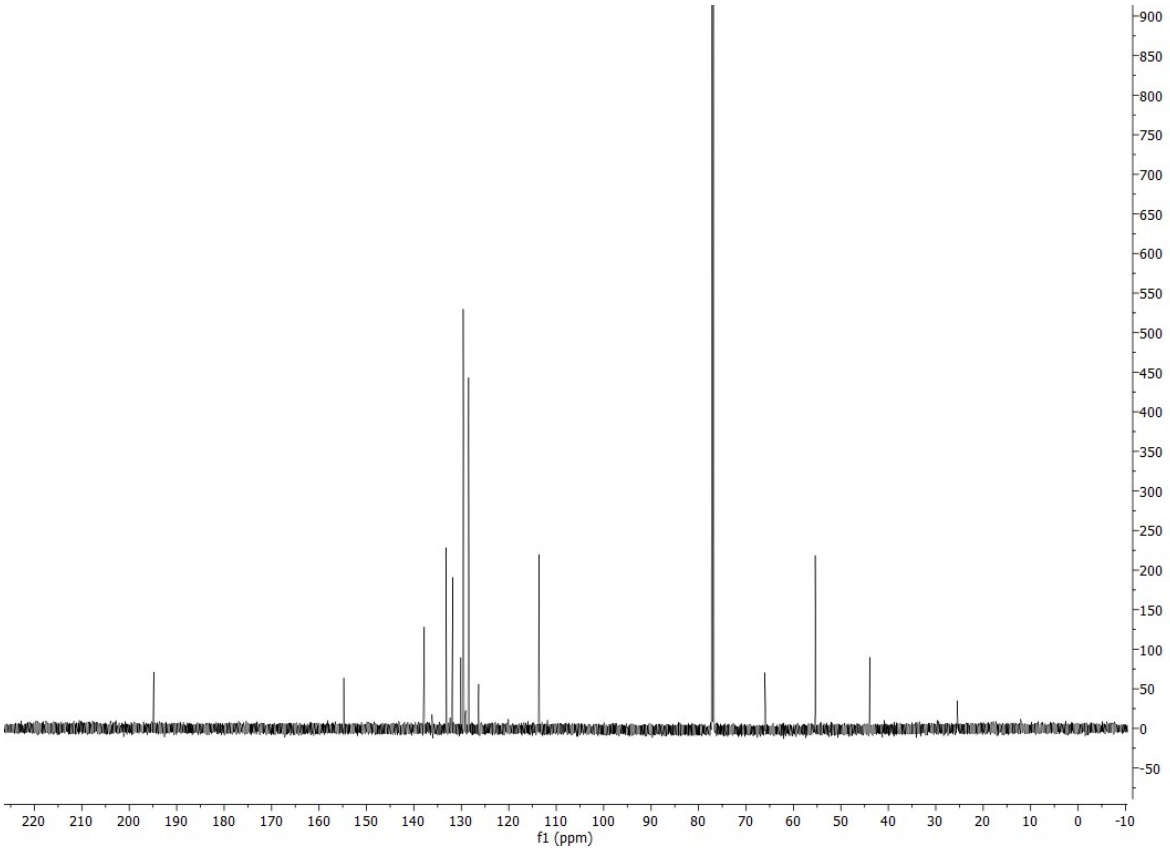




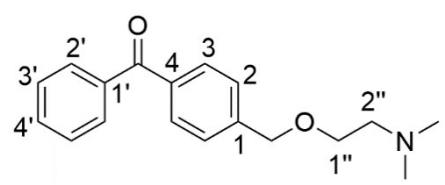


## [3’’-(2-benzoyl-4-chlorophenoxy)propyl]dimethylamine 4



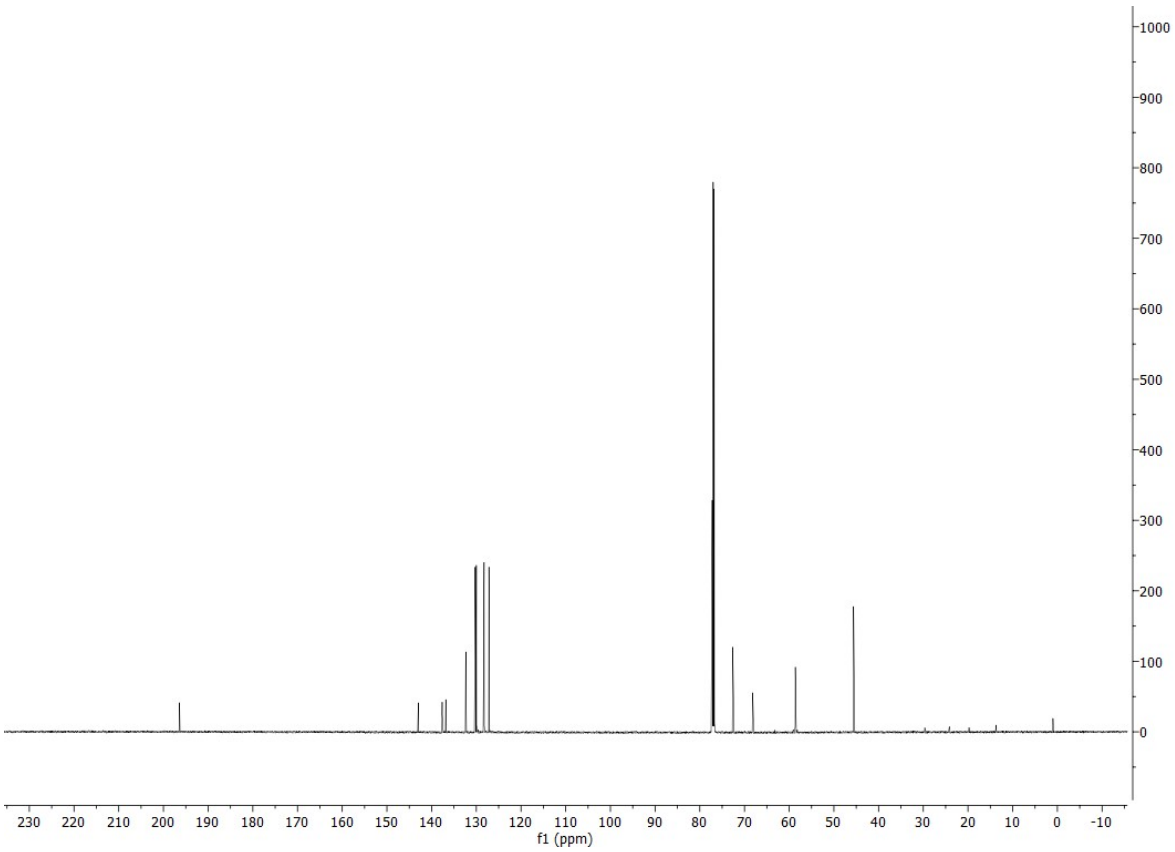



**{2’’-[(4-benzoylphenyl)methoxy]ethyl}dimethylamine 118**

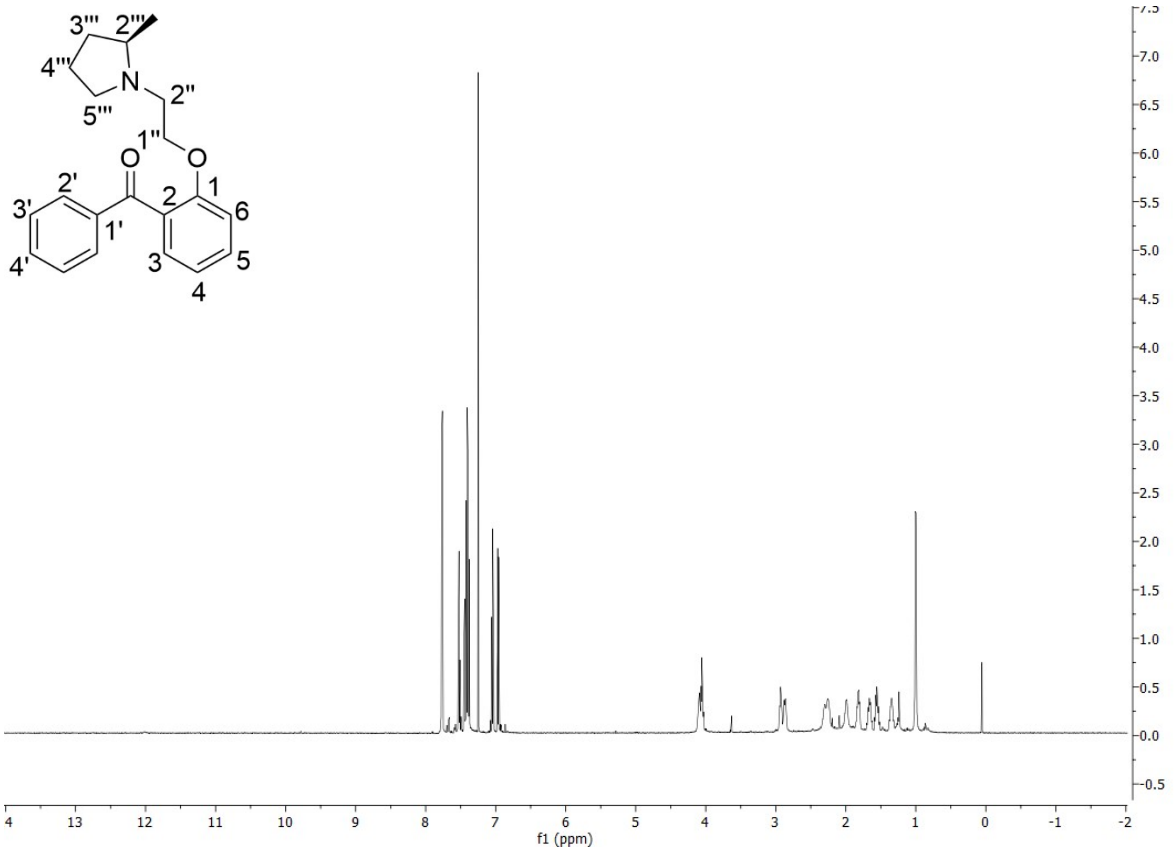


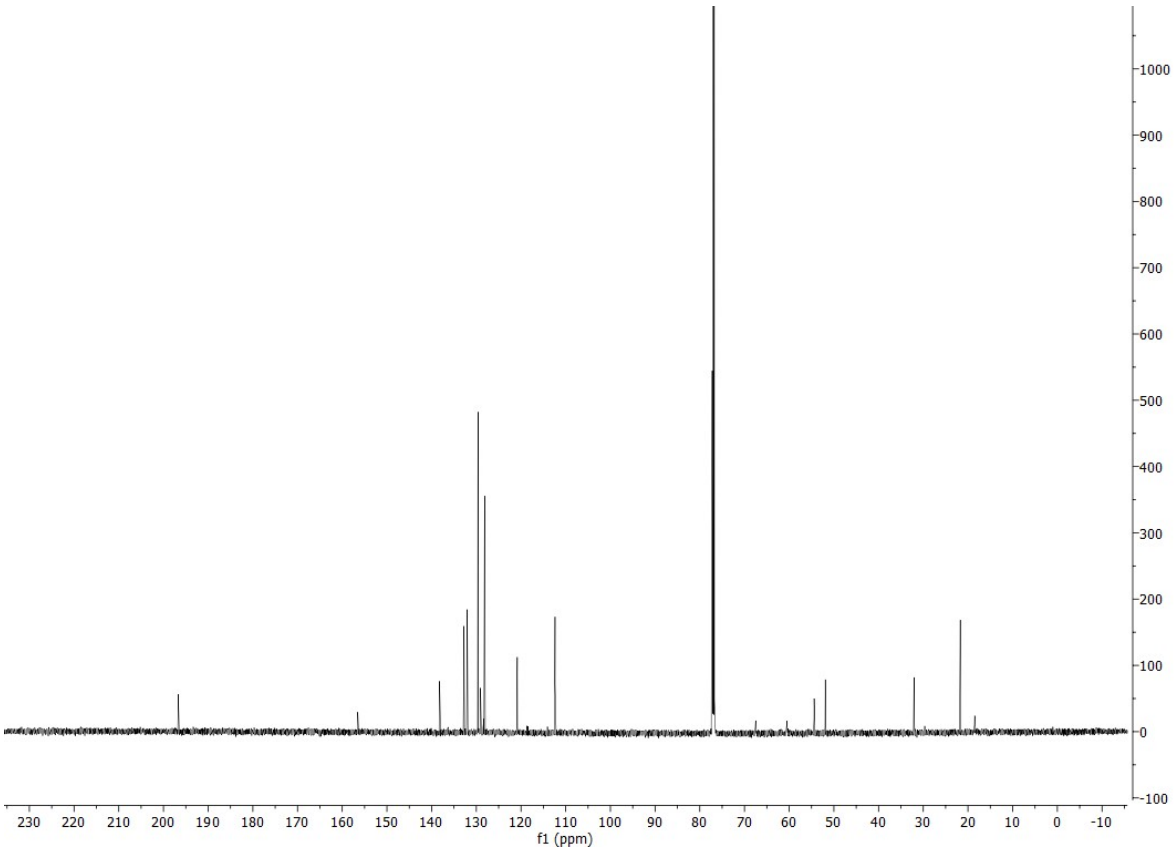




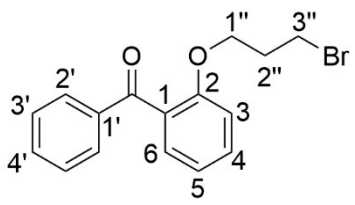


**(2*R*)-*N*-[2’’-(2-benzoylphenoxy)ethyl]-2’’’-methylpyrrolidine 5**



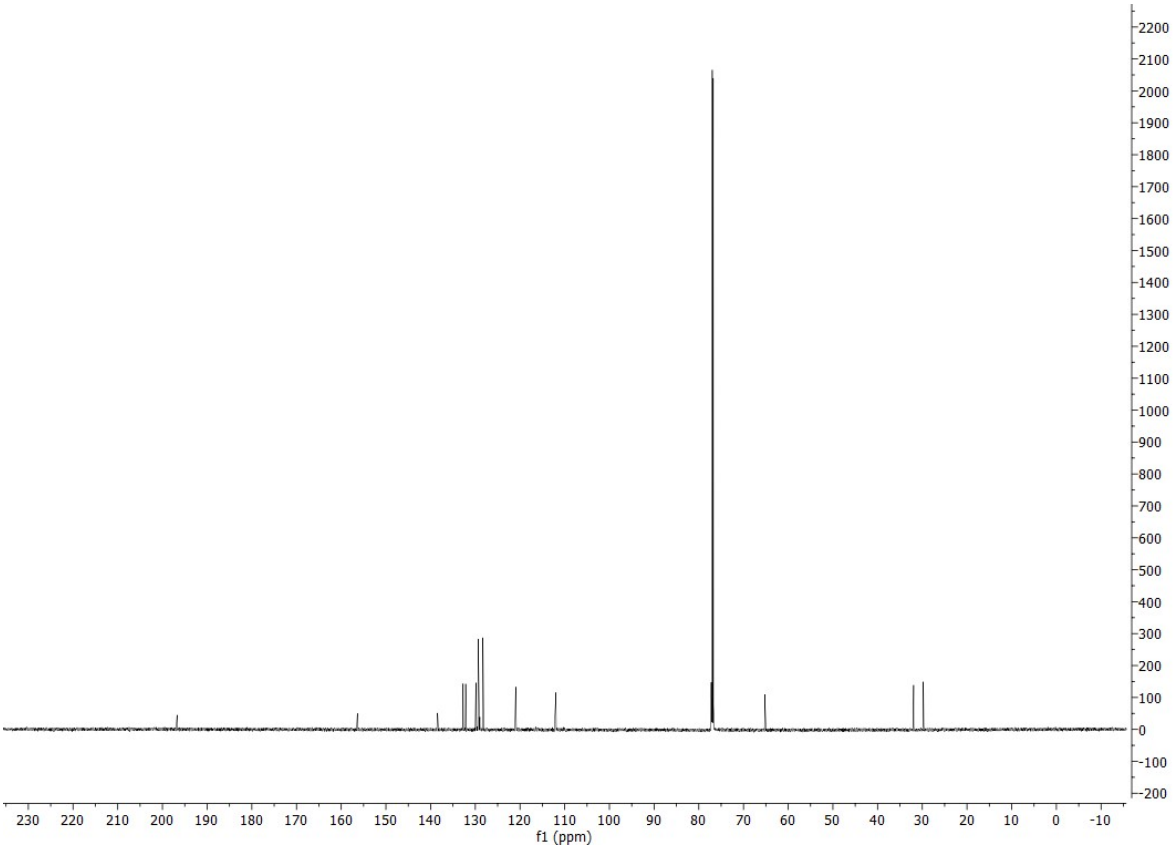



## [2-(3’’-bromopropoxy)phenyl](phenyl)methanone 6a

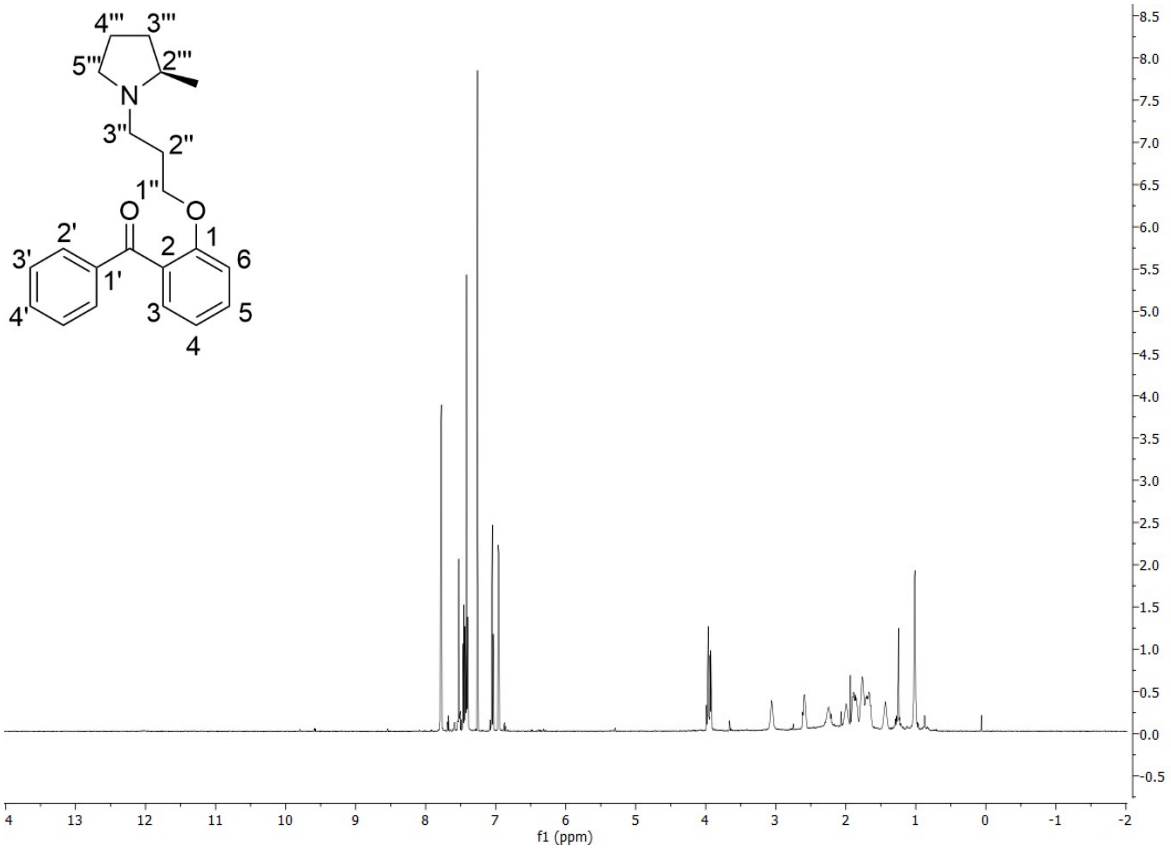


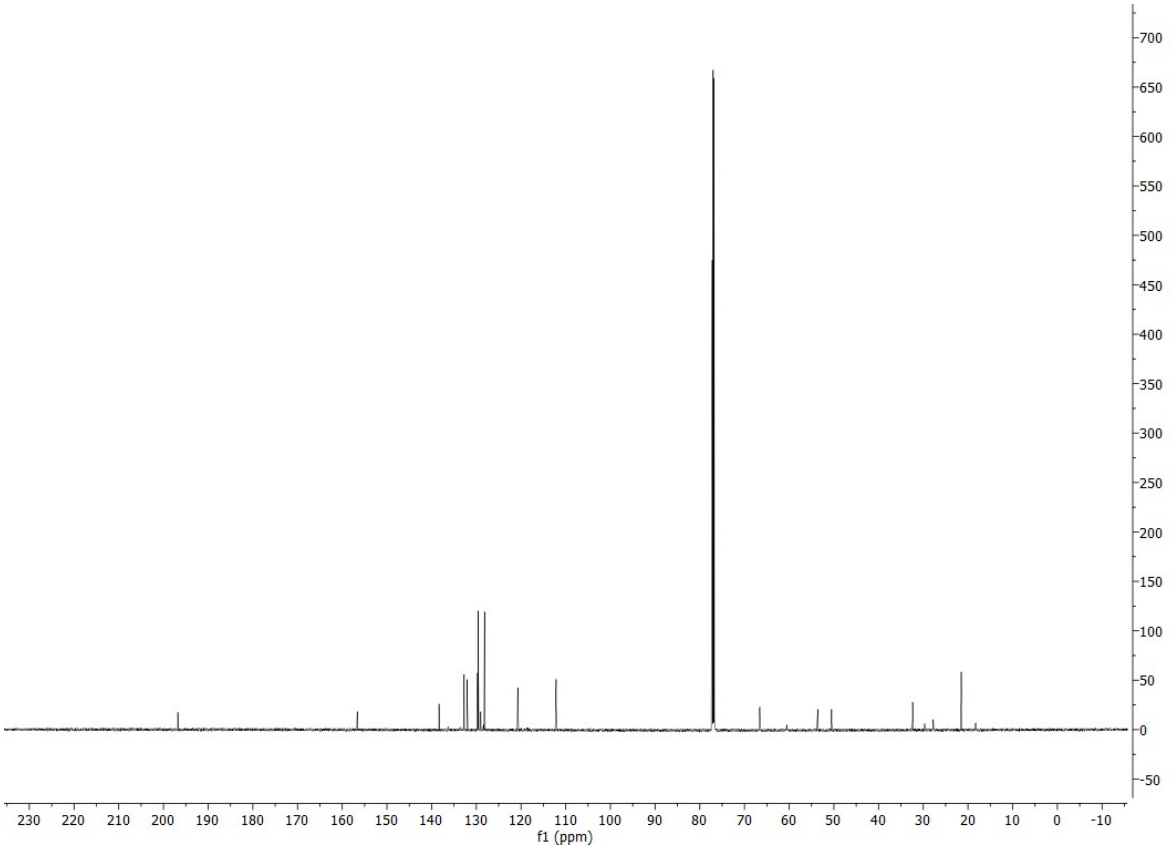




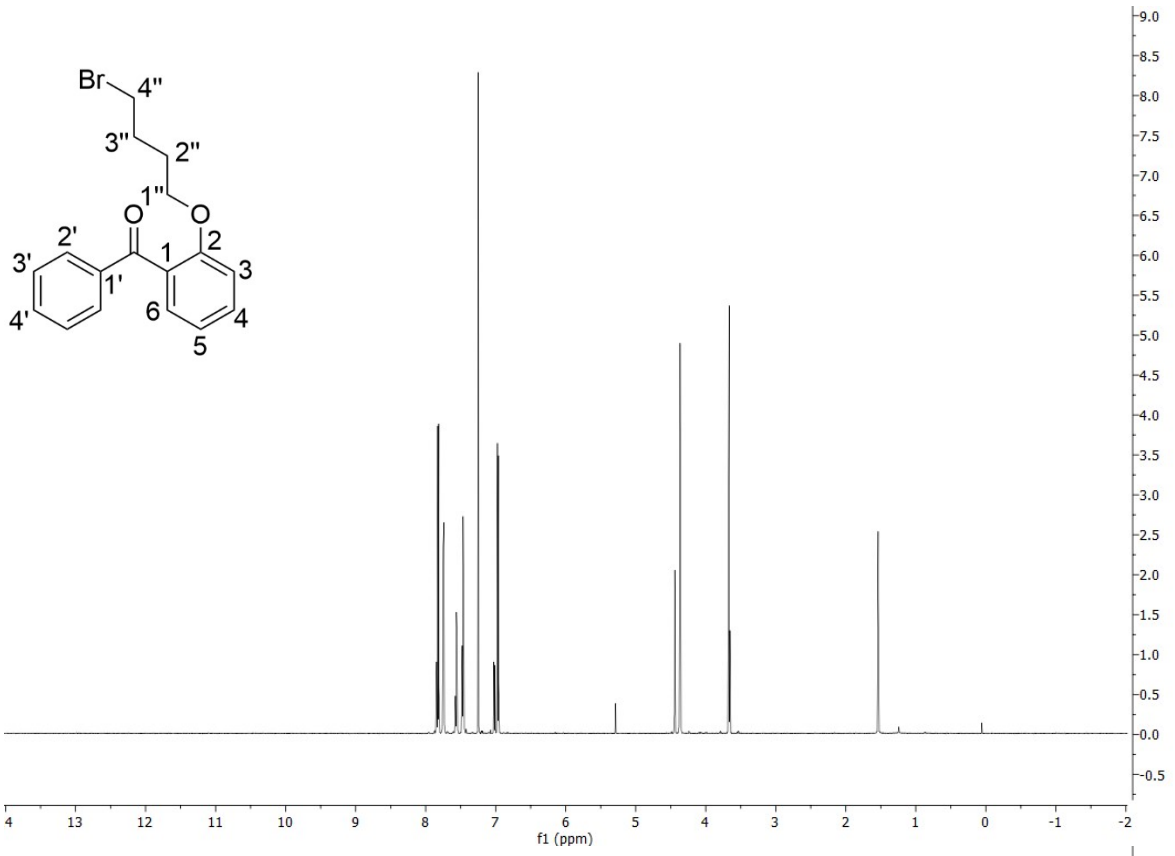


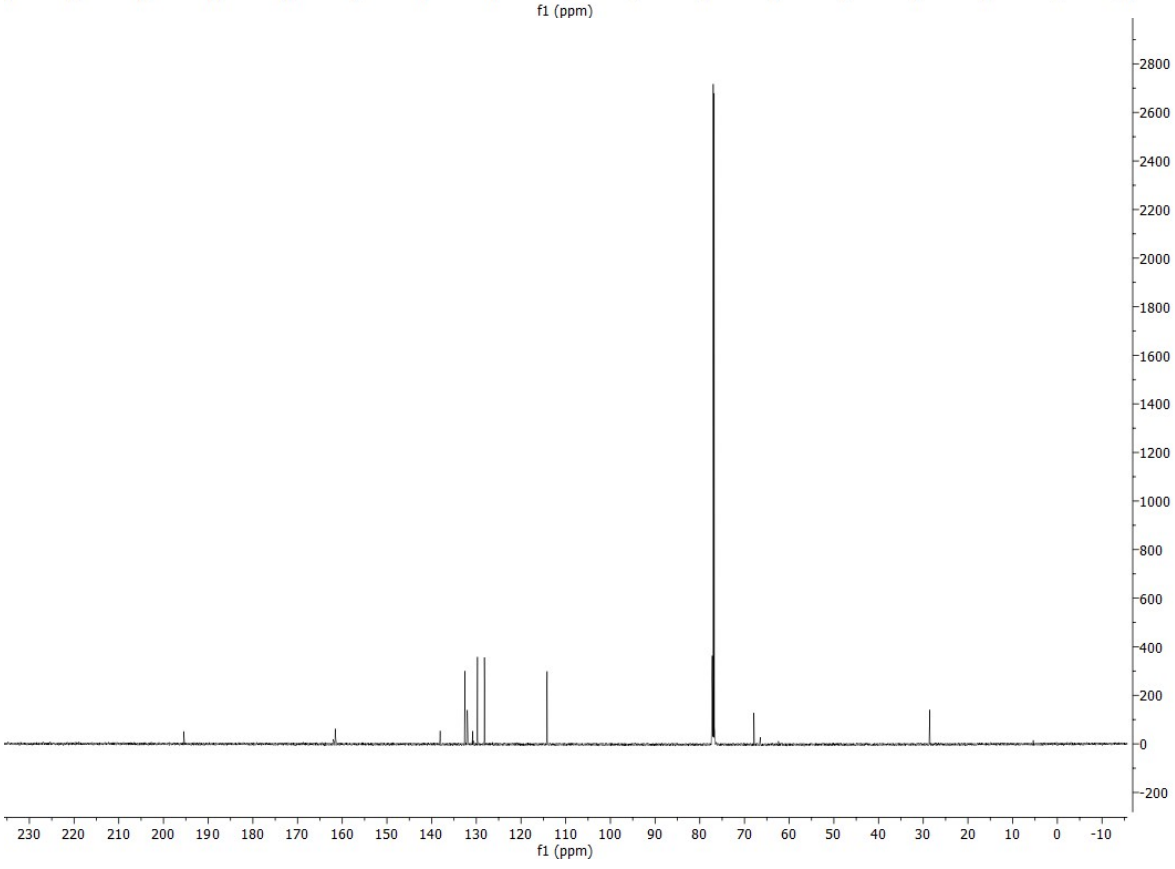
**(2’’’*R*)-*N* -[3’’-(2-benzoylphenoxy)propyl]-2’’’-methylpyrrolidine 6**



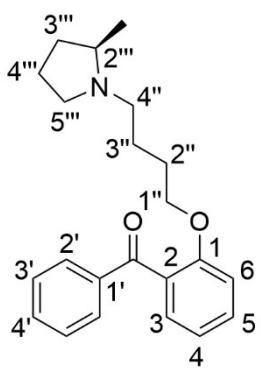



## [2-(4’’-bromobutoxy)phenyl](phenyl)methanone 7a



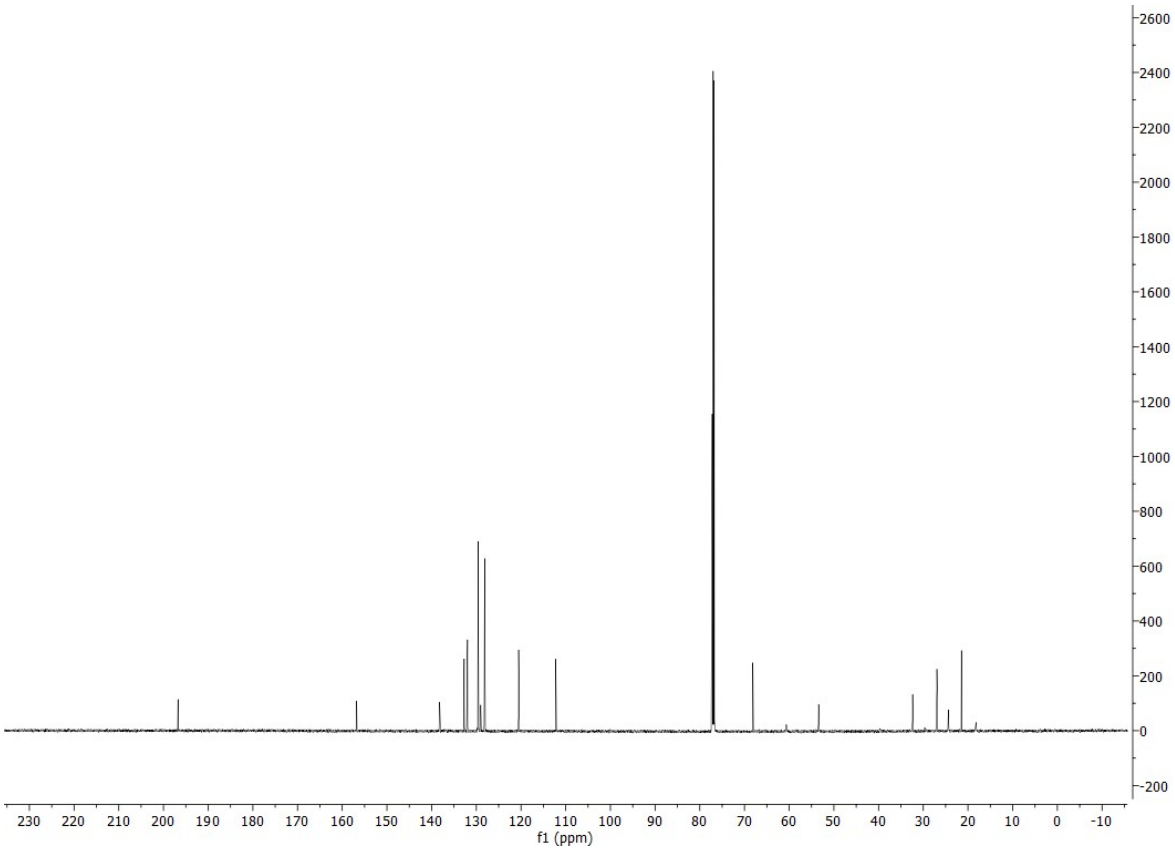



**(2’’’*R*)- *N* -[4’’-(2-benzoylphenoxy)butyl]-2’’’-methylpyrrolidine 7**

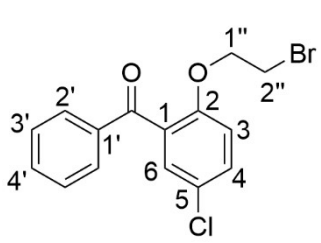






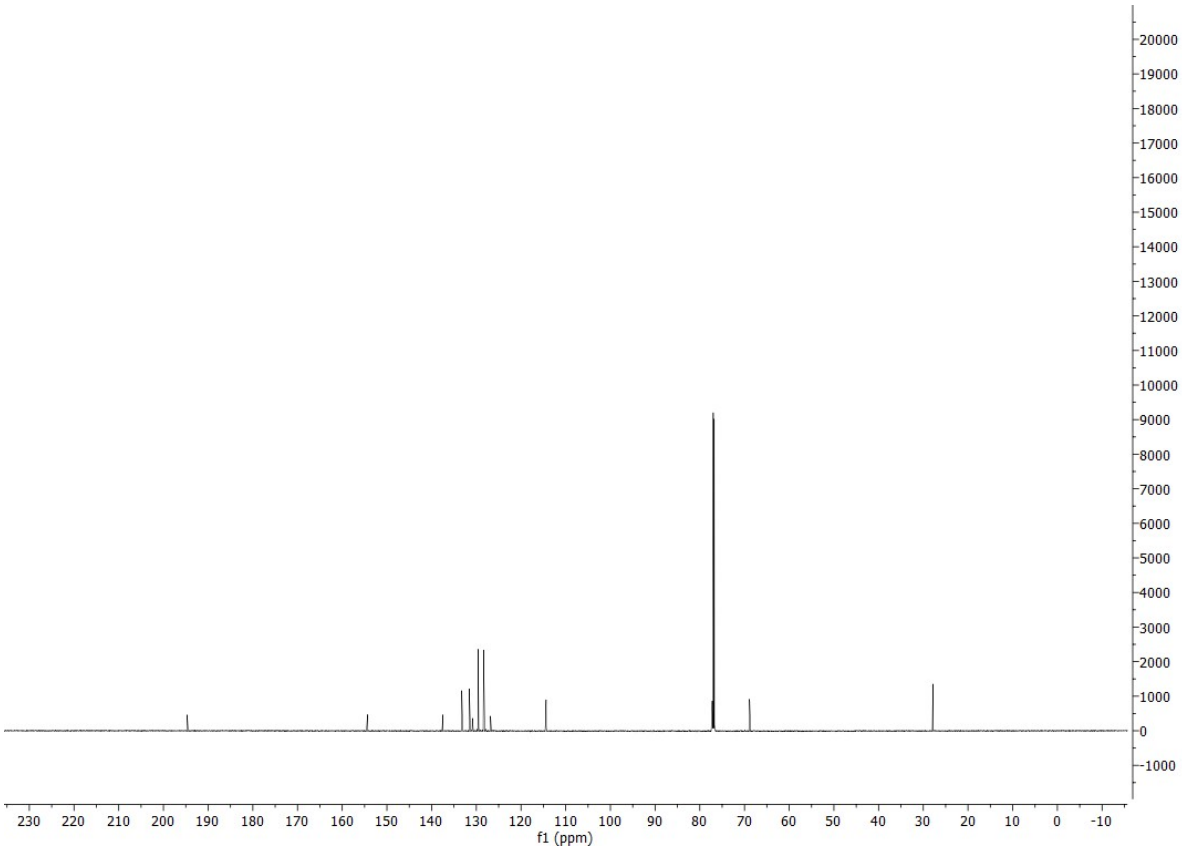


## [2-(2’’-bromopropoxy)-5-chlorophenyl](phenyl)methanone 8a

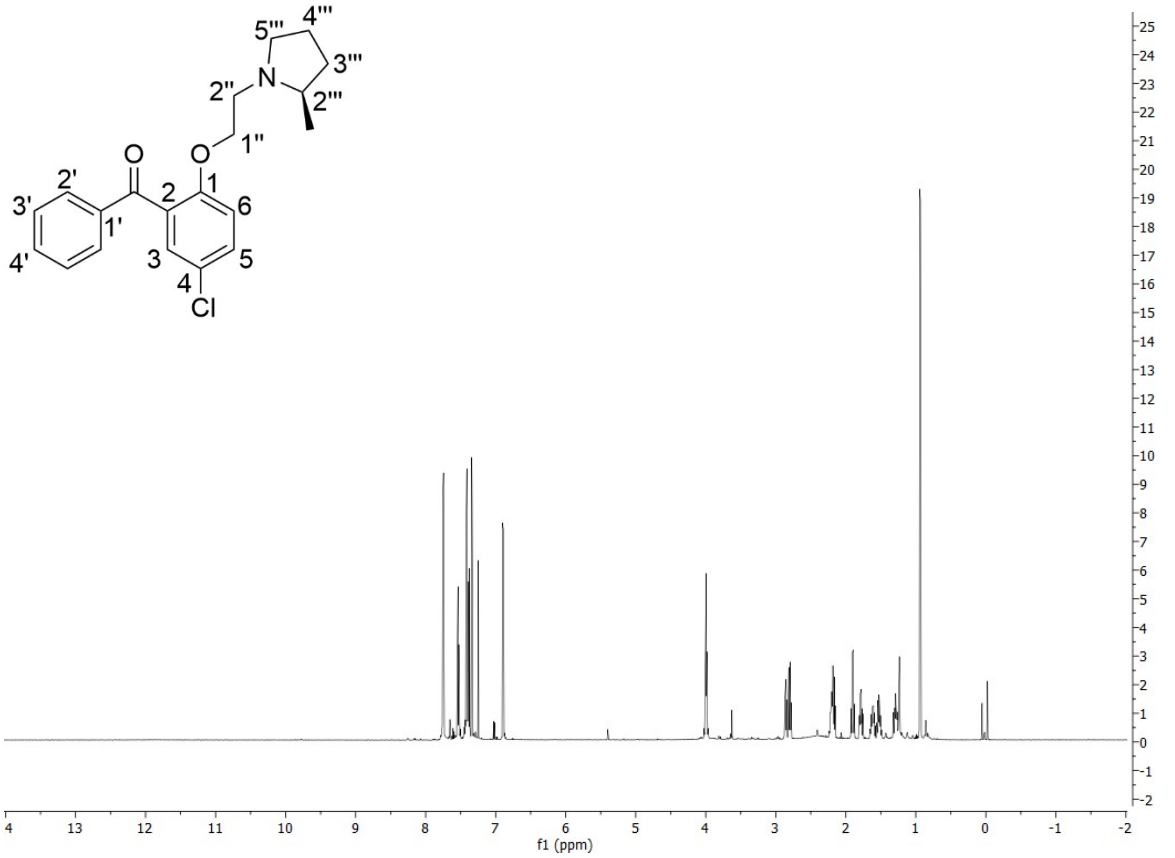


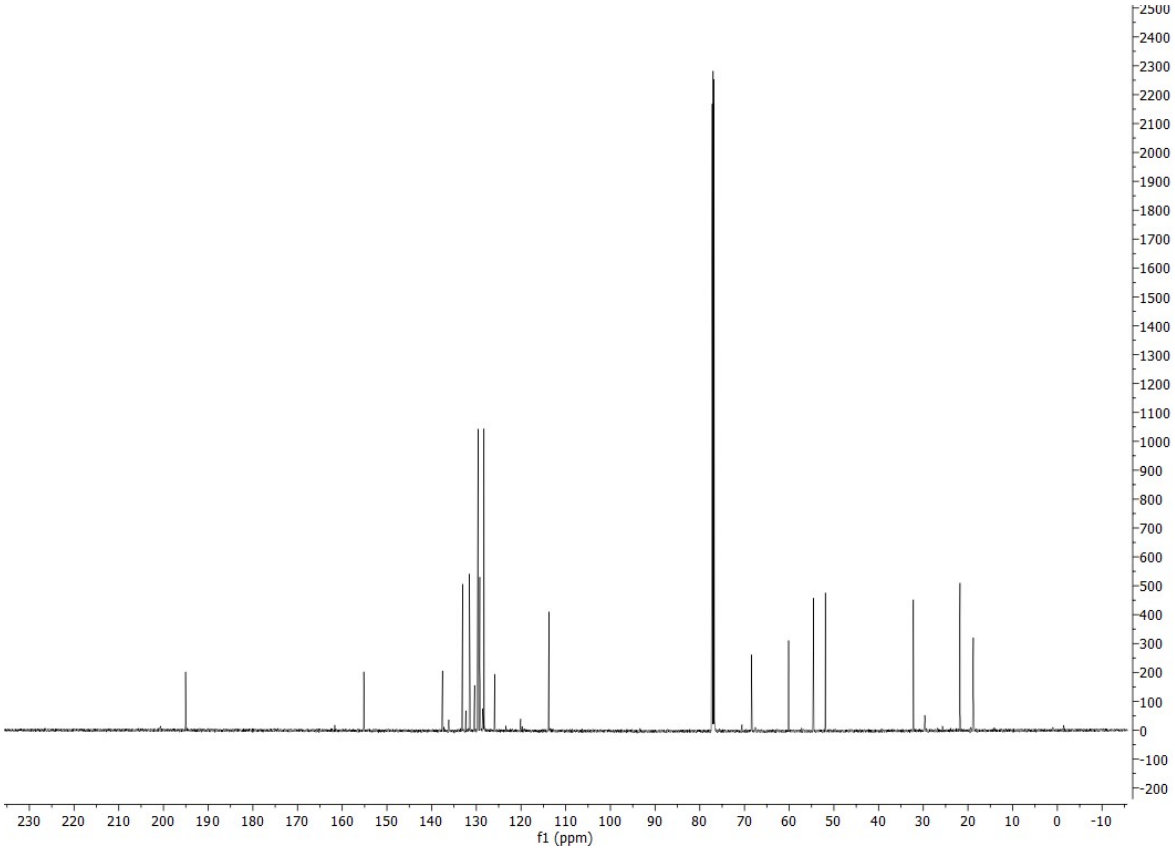




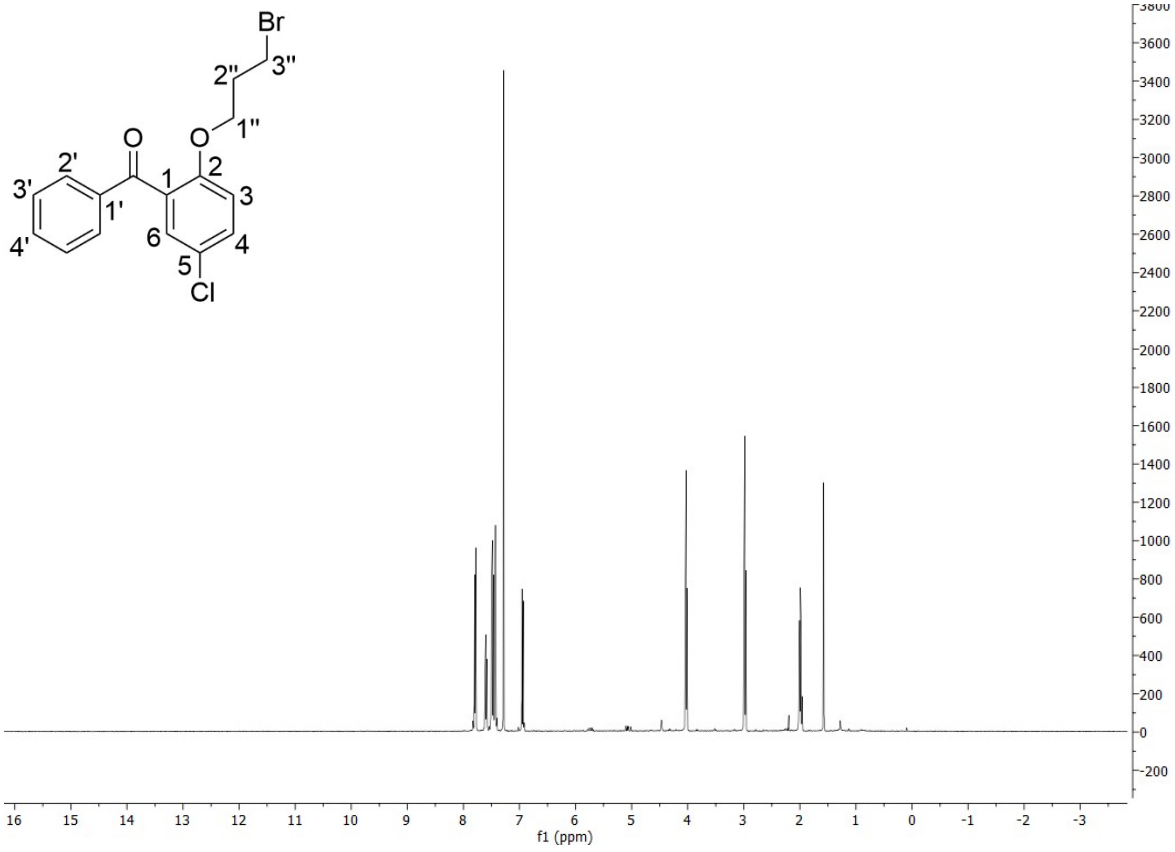


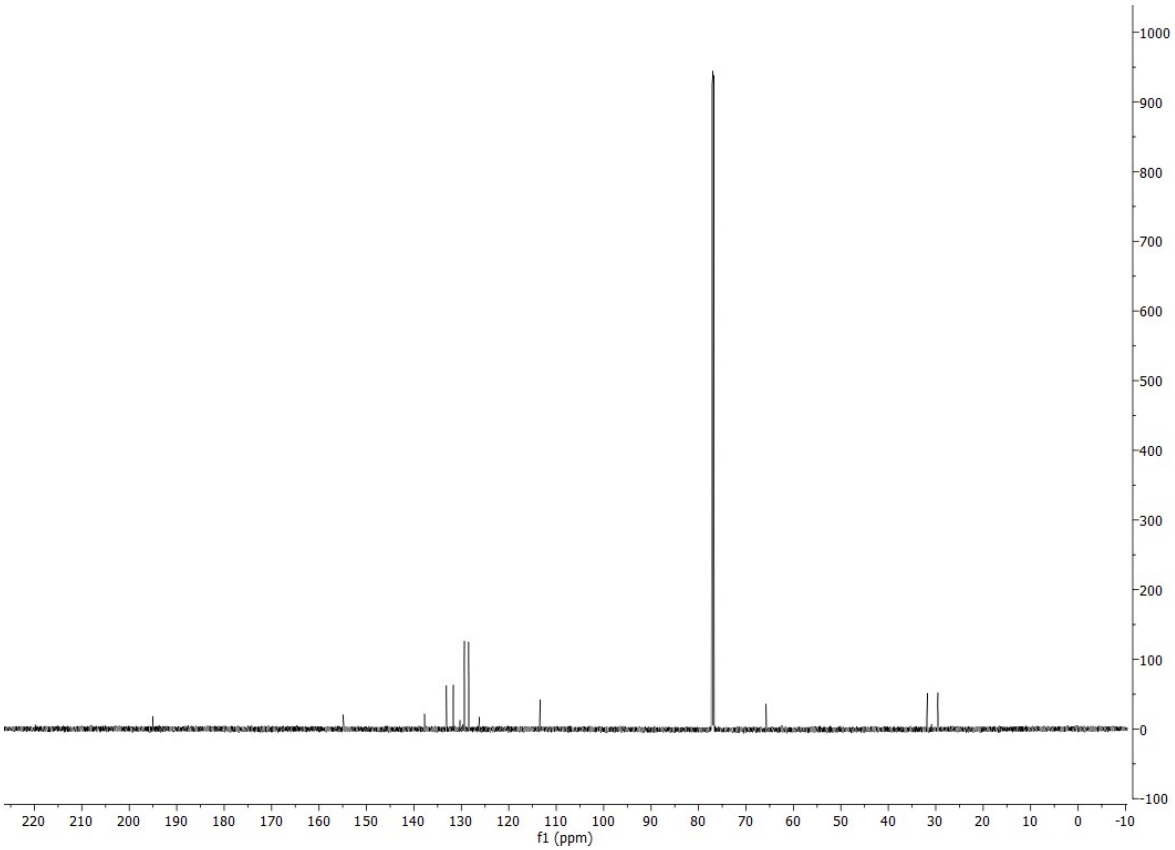
**(2’’’*R*)-*N* -[2-(2’’-benzoyl-4-chlorophenoxy)ethyl]-2’’’-methylpyrrolidine 8**



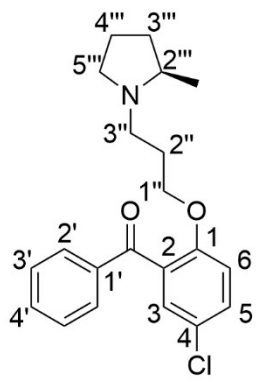



## [2-(3’’-bromopropoxy)-5-chlorophenyl](phenyl)methanone 9a



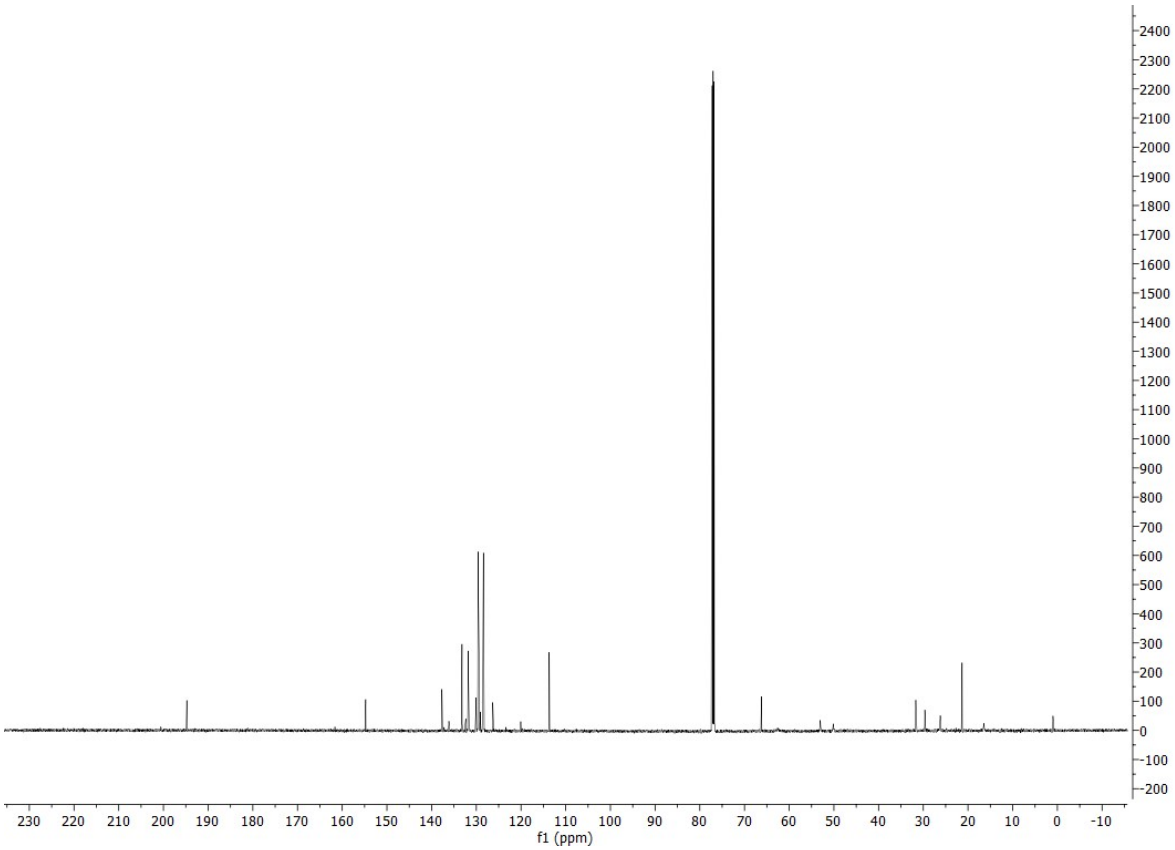



**(2*R*)-*N*-[3’’-(2-benzoyl-4-chlorophenoxy)propyl]-2’’’-methylpyrrolidine 9**

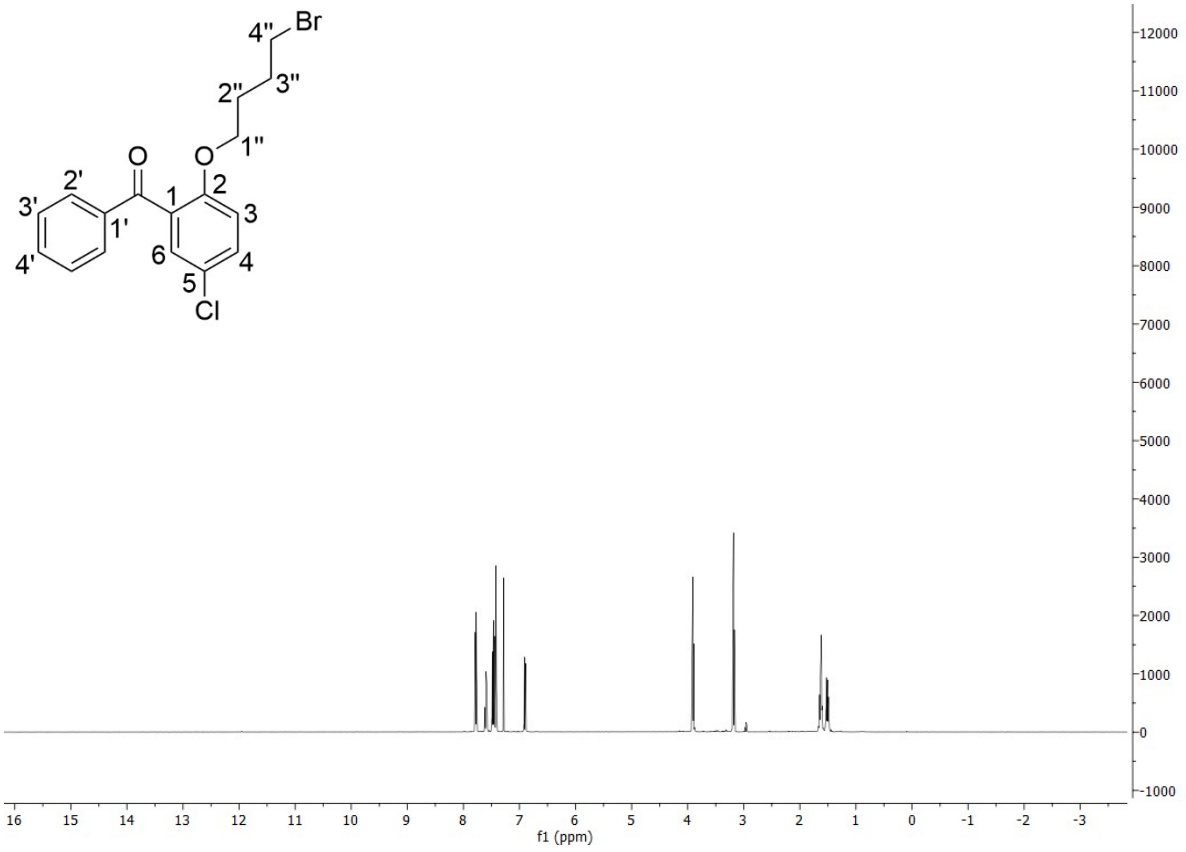


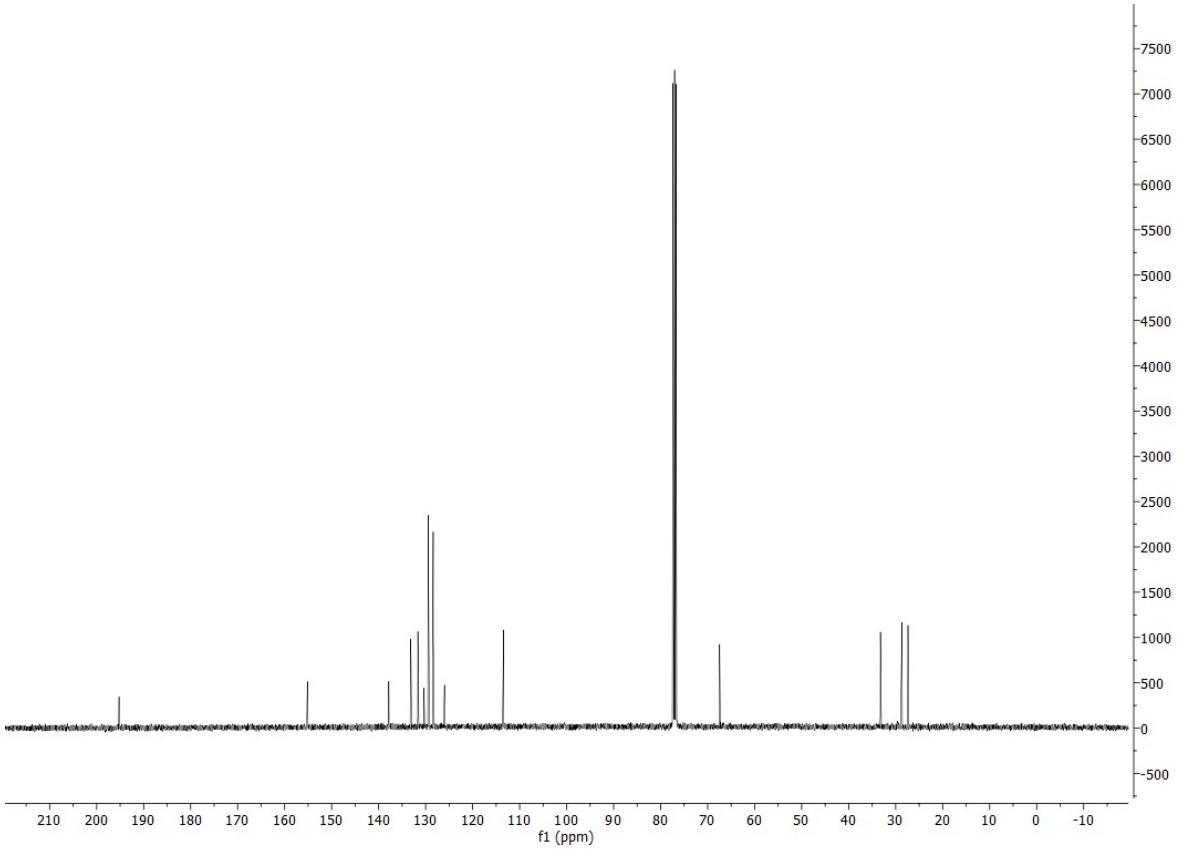




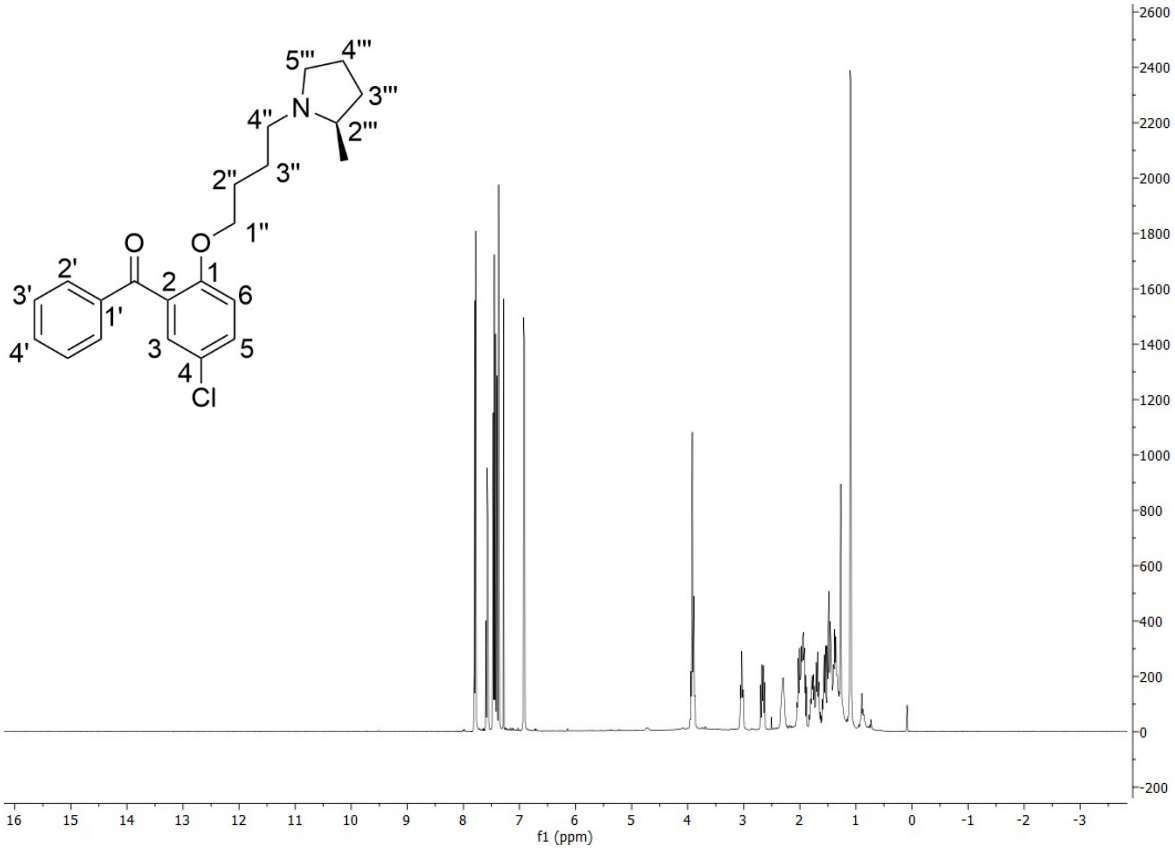


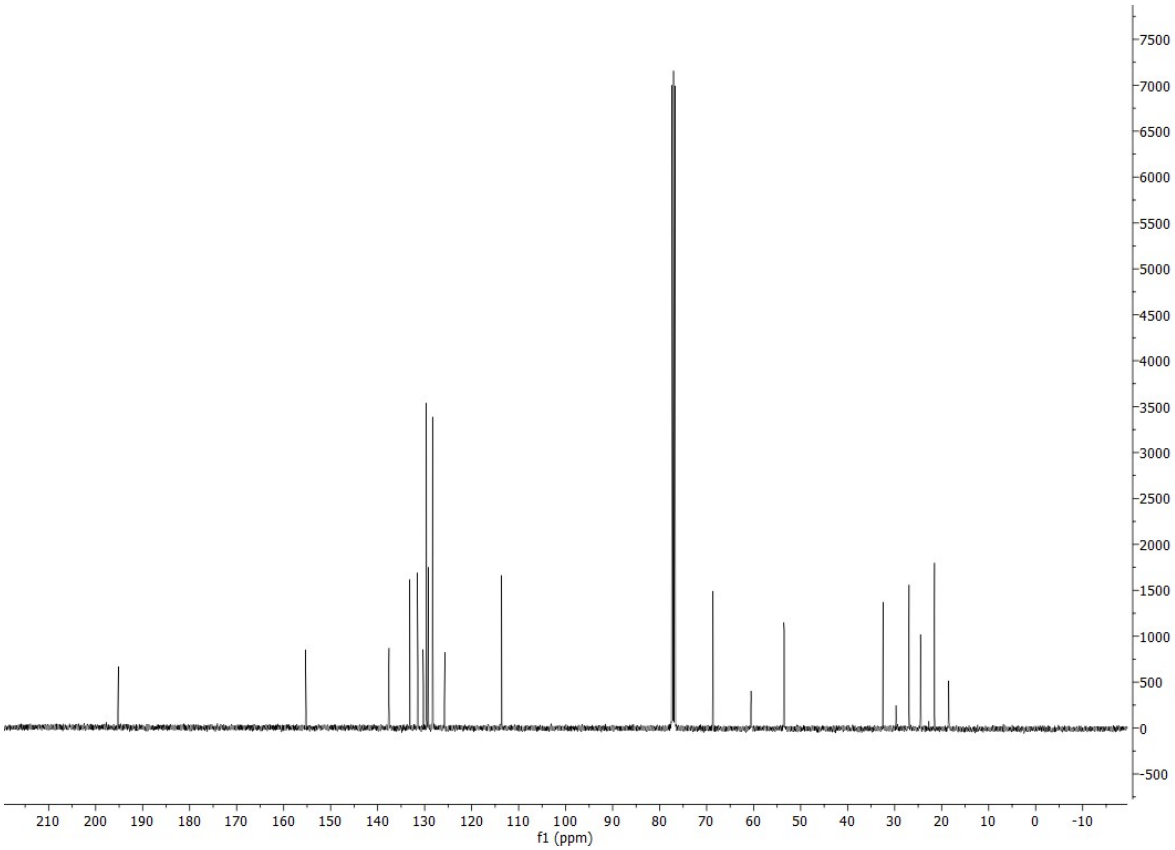
## [2-(4’’-bromobutoxy)-5-chlorophenyl](phenyl)methanone 10a



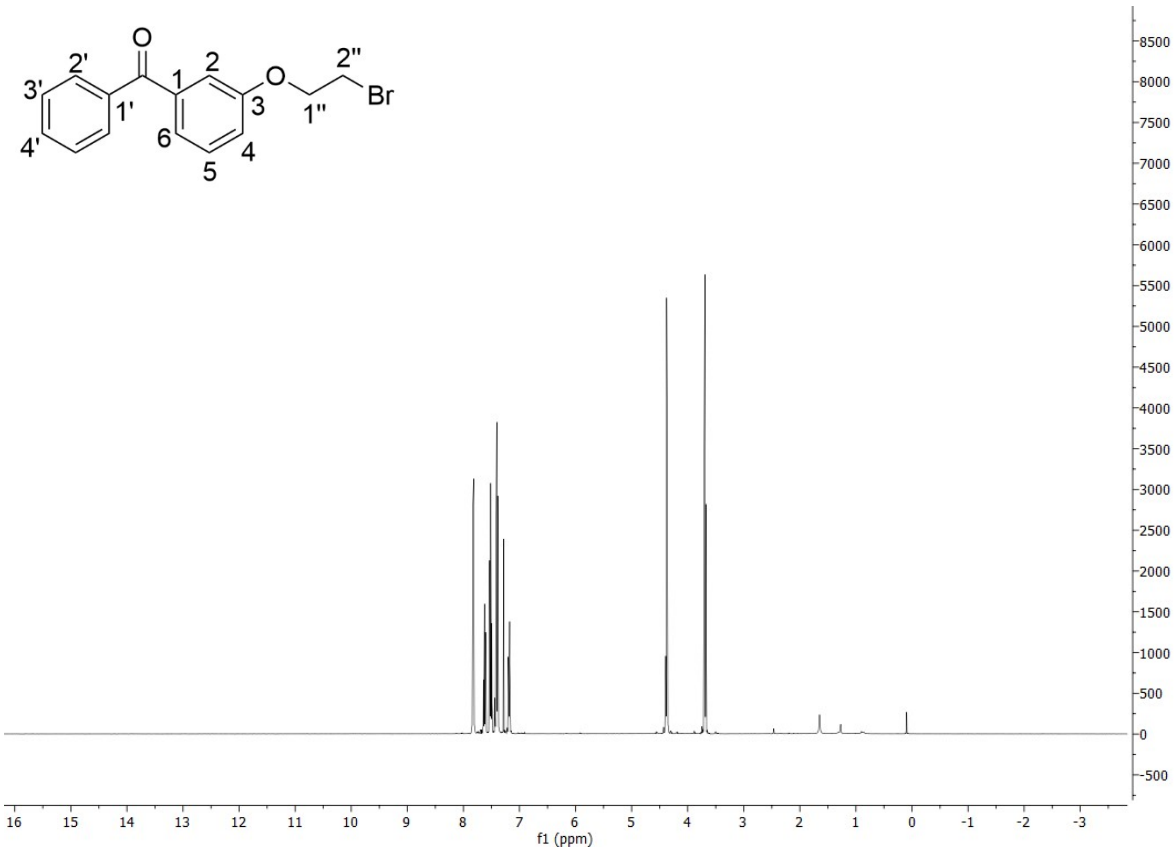

7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

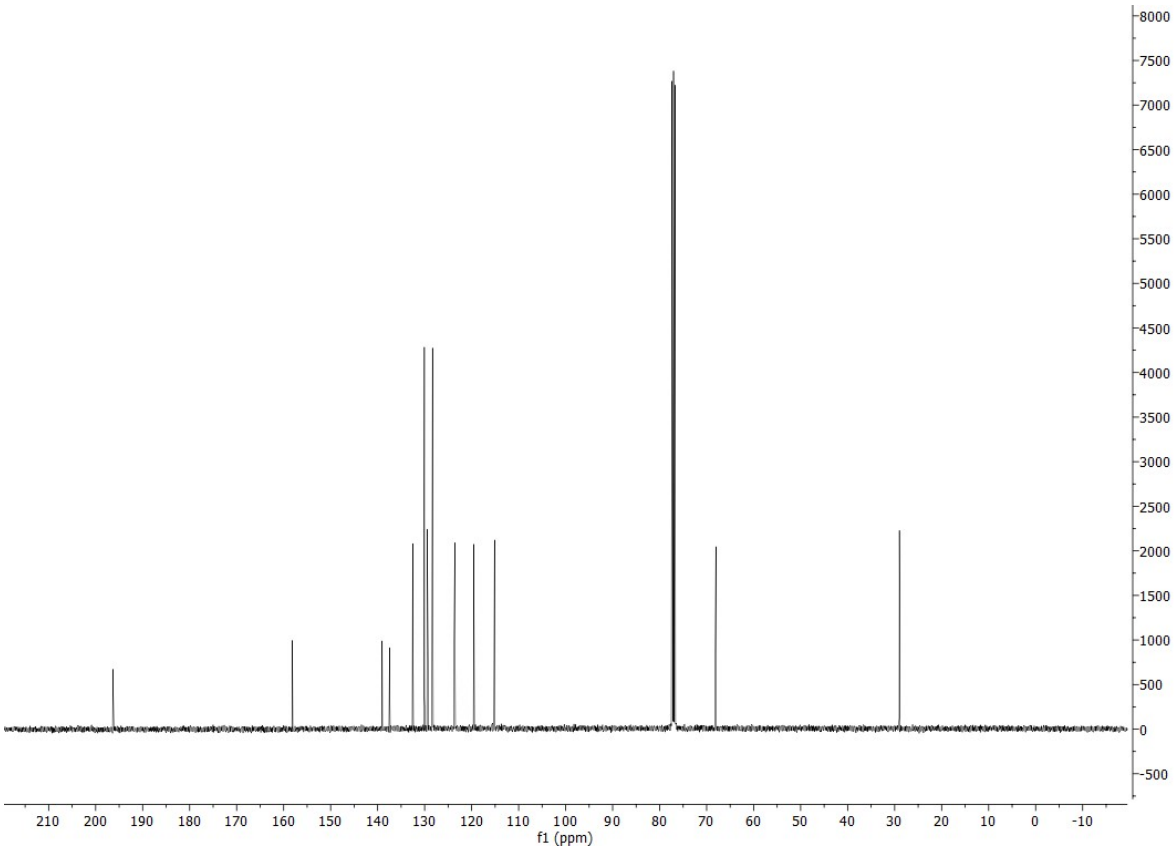
**(2*R*)-*N*-[4’’-(2-benzoyl-4-chlorophenoxy)butyl]-2’’’-methylpyrrolidine 10**



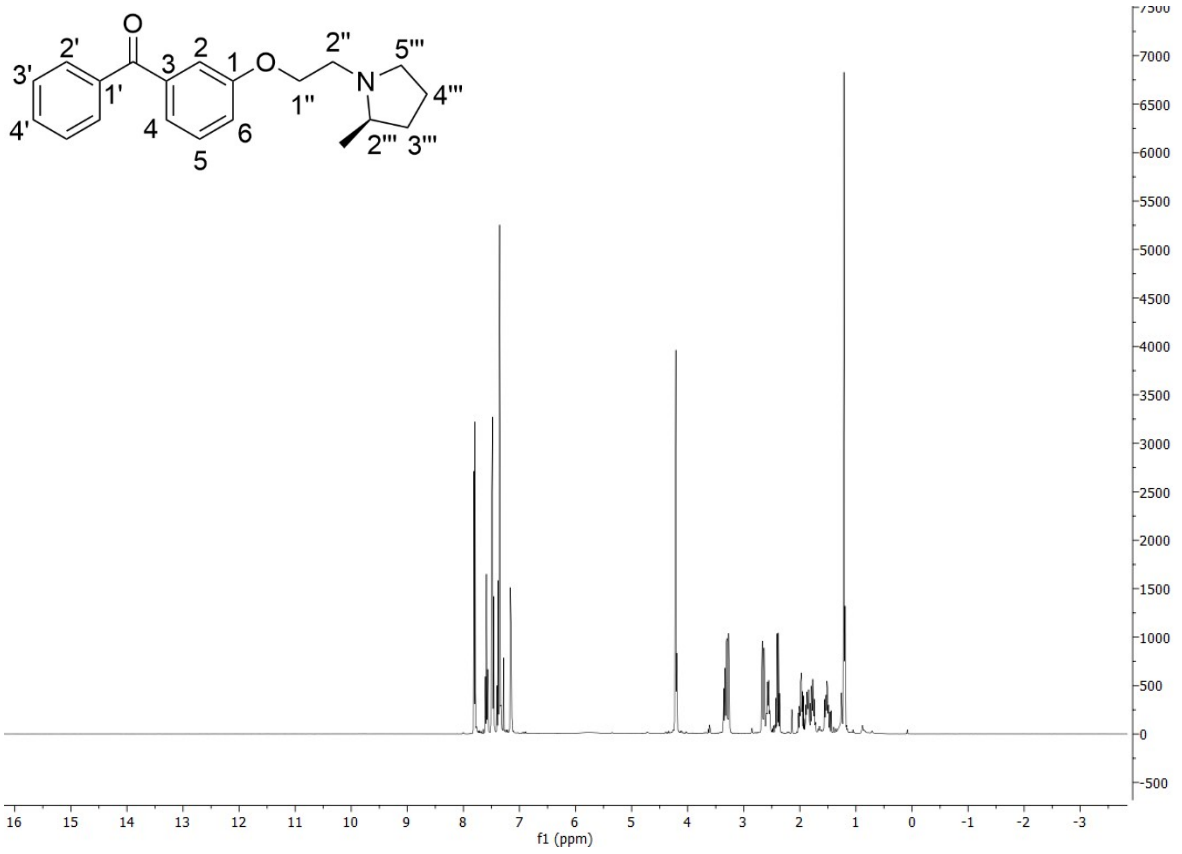



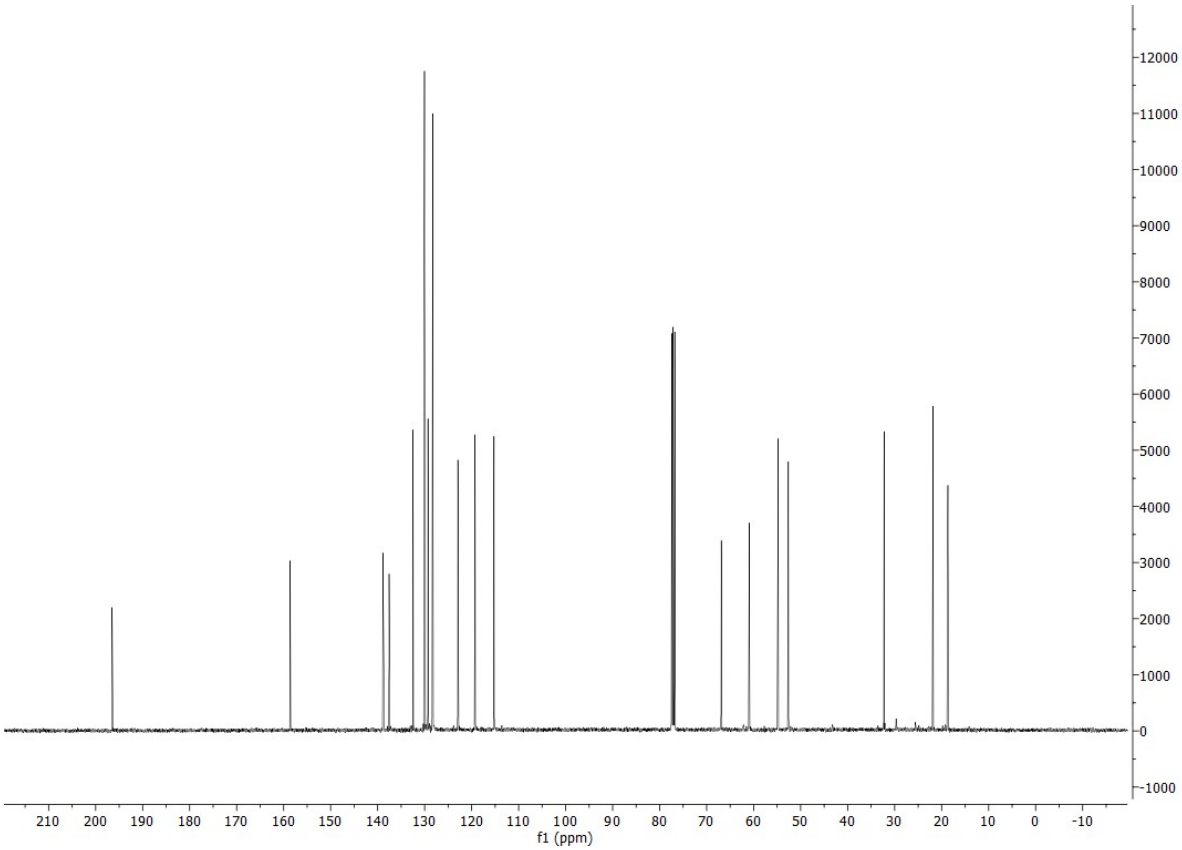
## [3-(2’’-bromoethoxy)phenyl](phenyl)methanone 11a



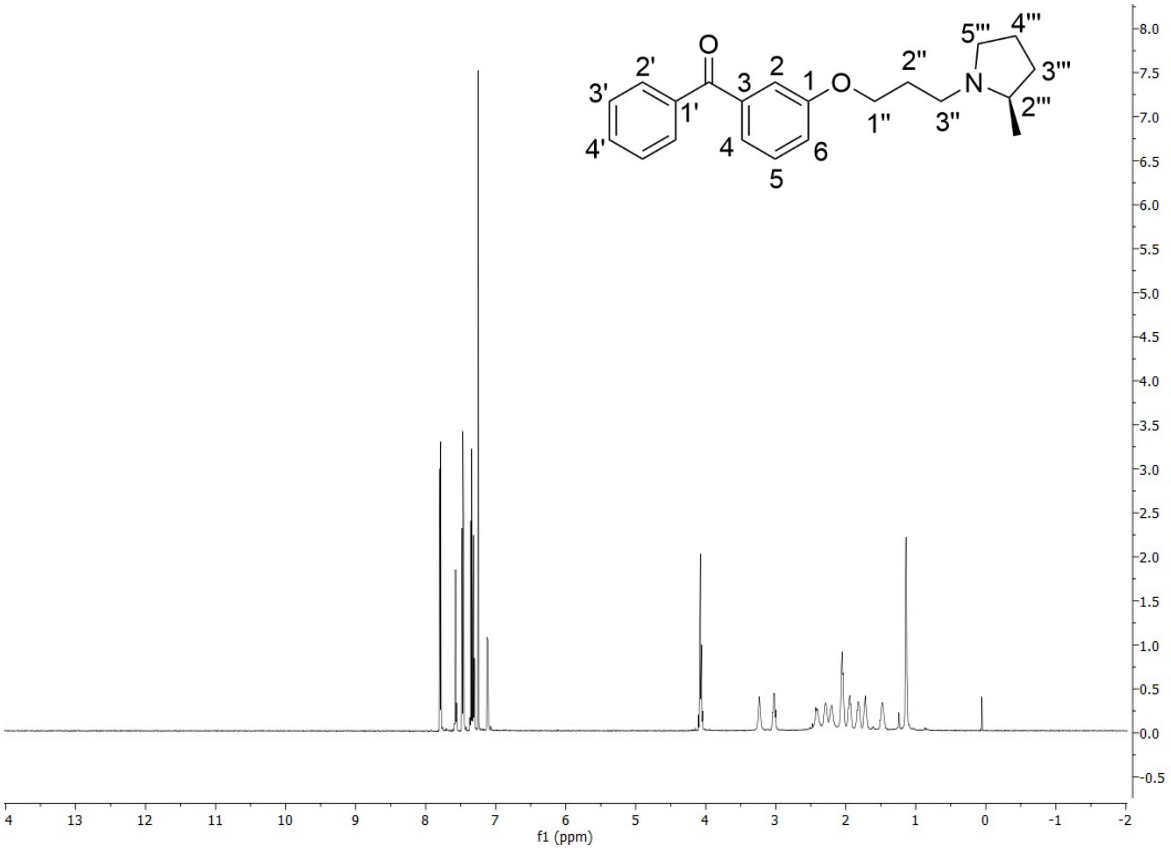



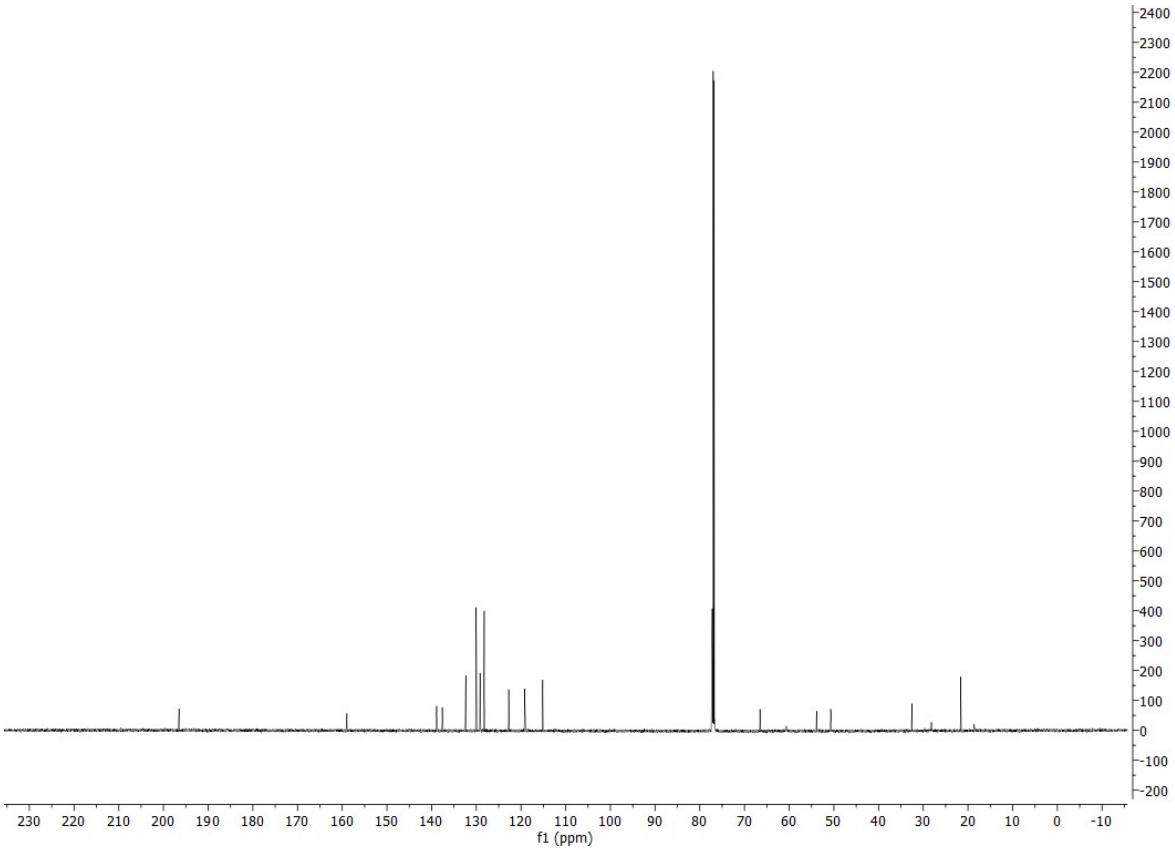
**(2’’’*R*)- *N* -[2’’-(3-benzoylphenoxy)ethyl]-2’’’-methylpyrrolidine 11**



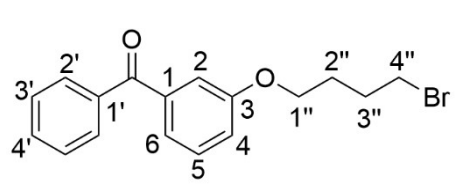



**(2’’’*R*)-*N* -[3’’-(3-benzoylphenoxy)propyl]-2’’’-methylpyrrolidine 12**



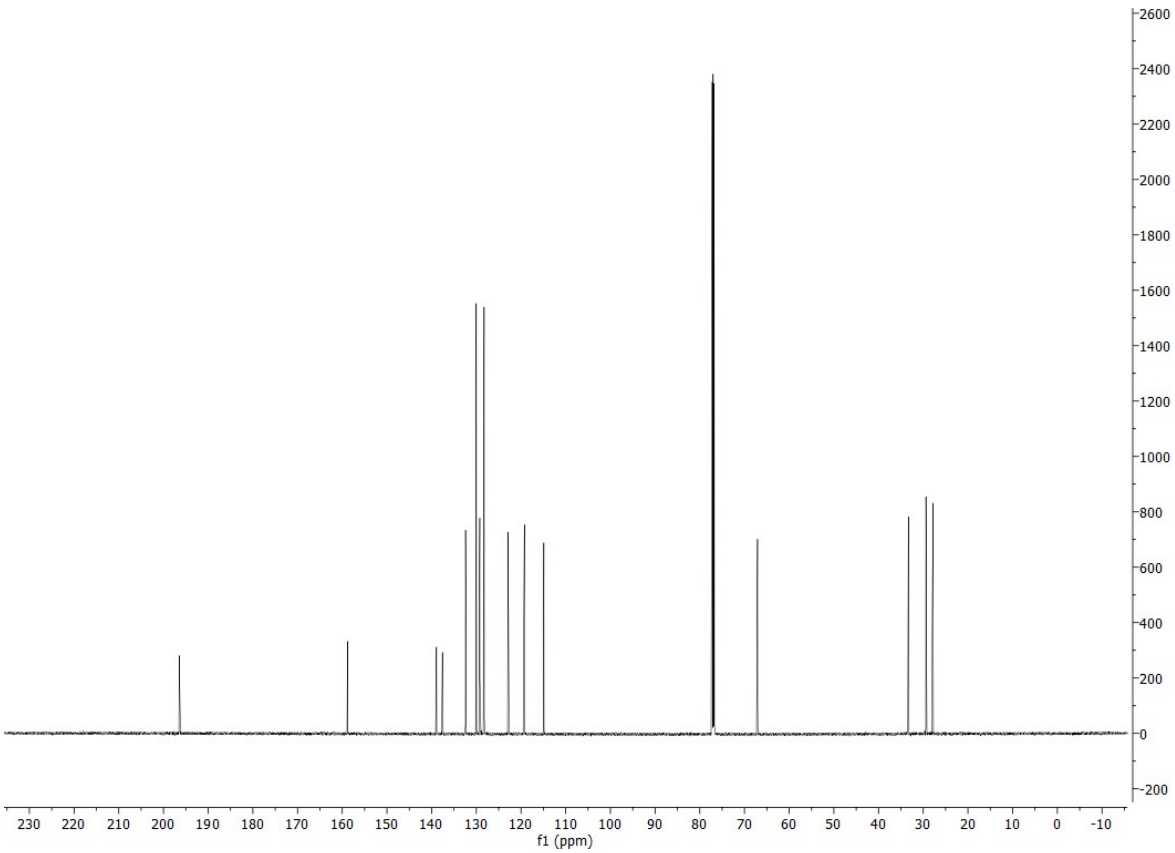



## [3-(4’’-bromobutoxy)phenyl](phenyl)methanone 13a

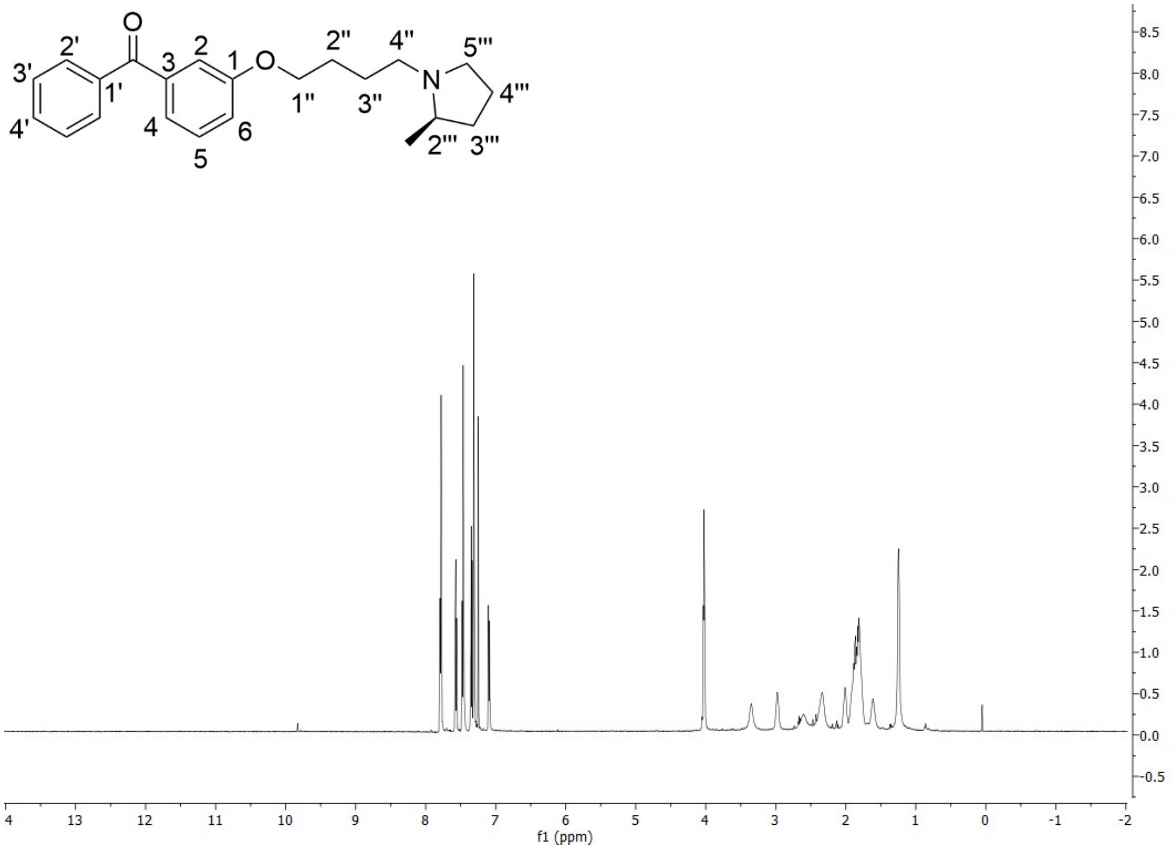


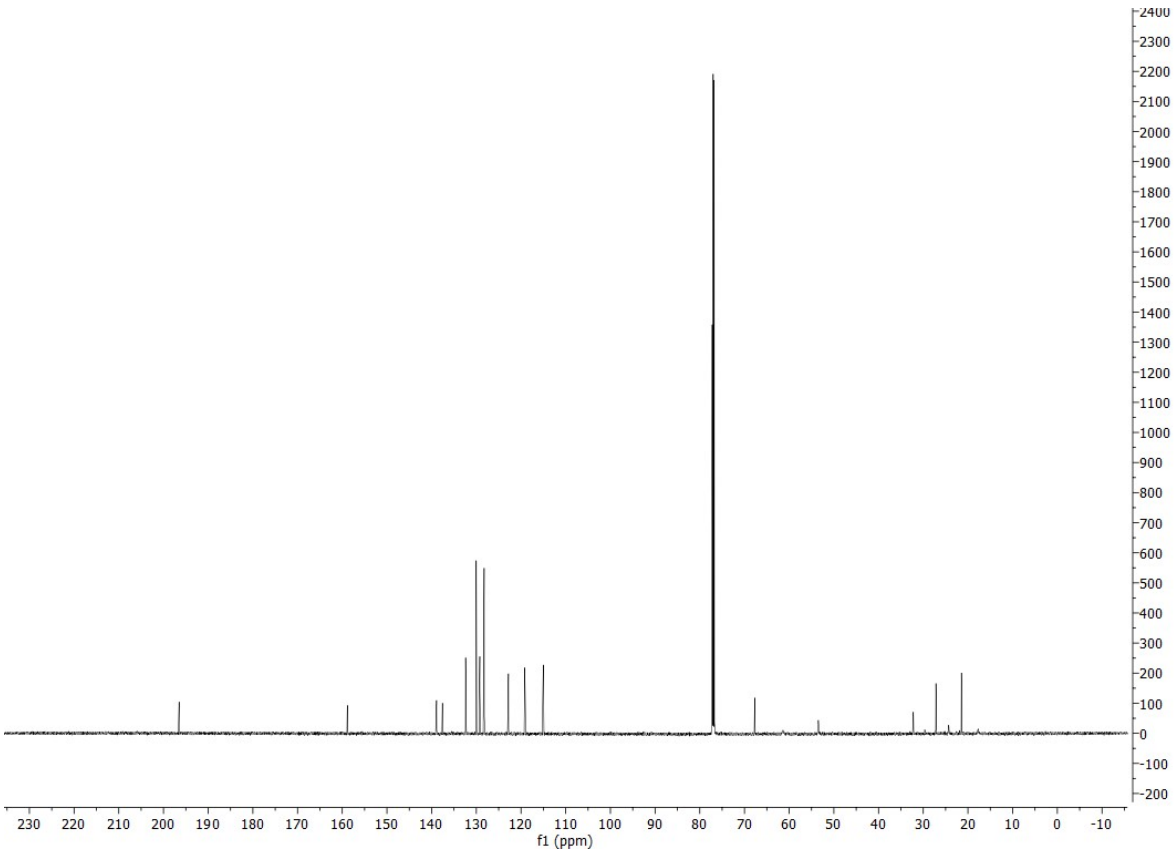




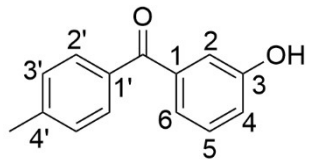


**(2’’’*R*)-*N*-[4’’-(3-benzoylphenoxy)butyl]-2’’’-methylpyrrolidine 13**



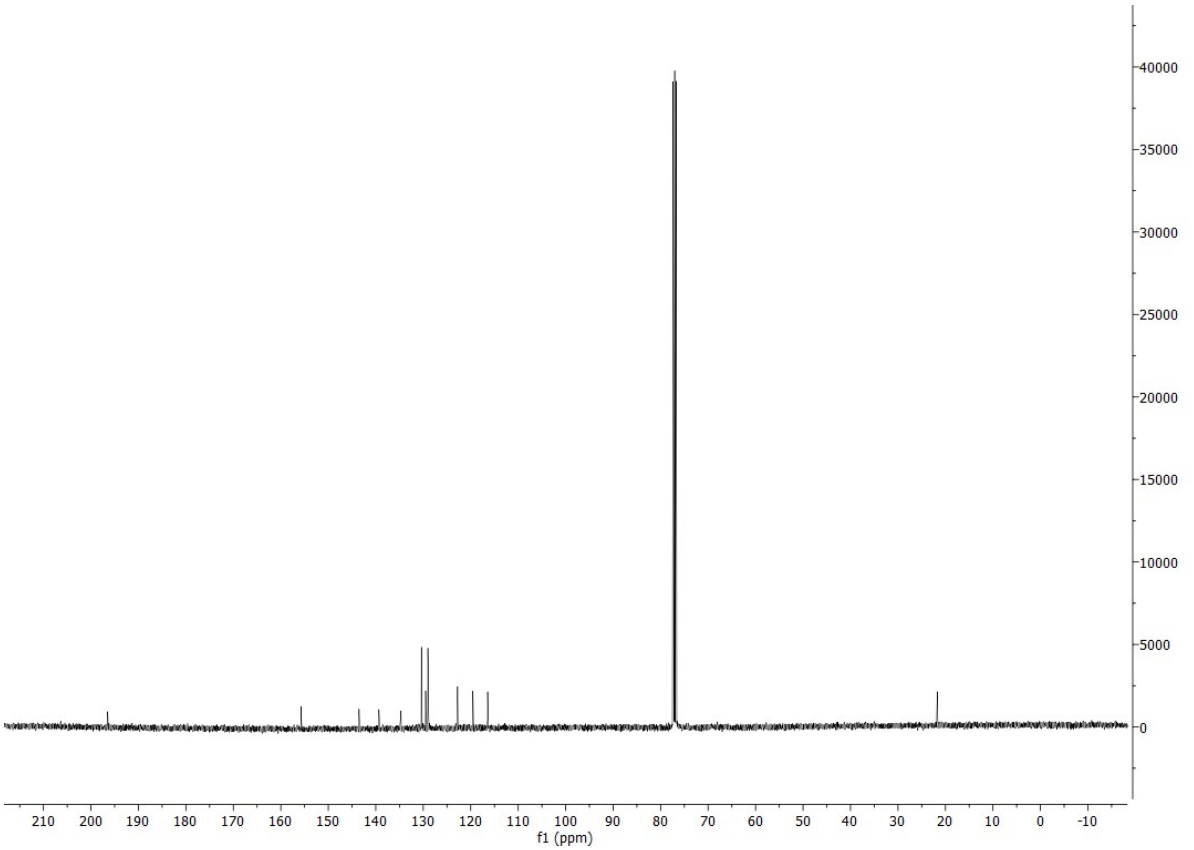



## 3-(4’-methylbenzoyl)phenol I

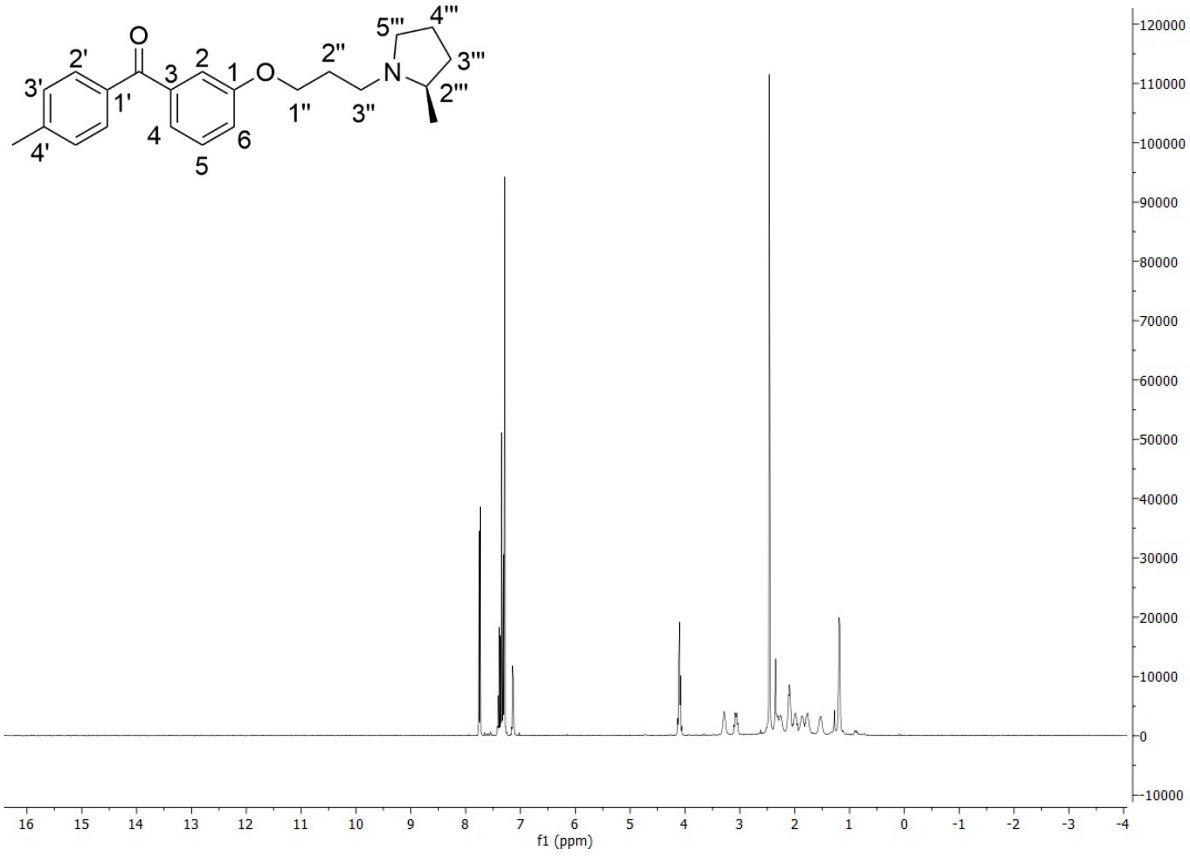


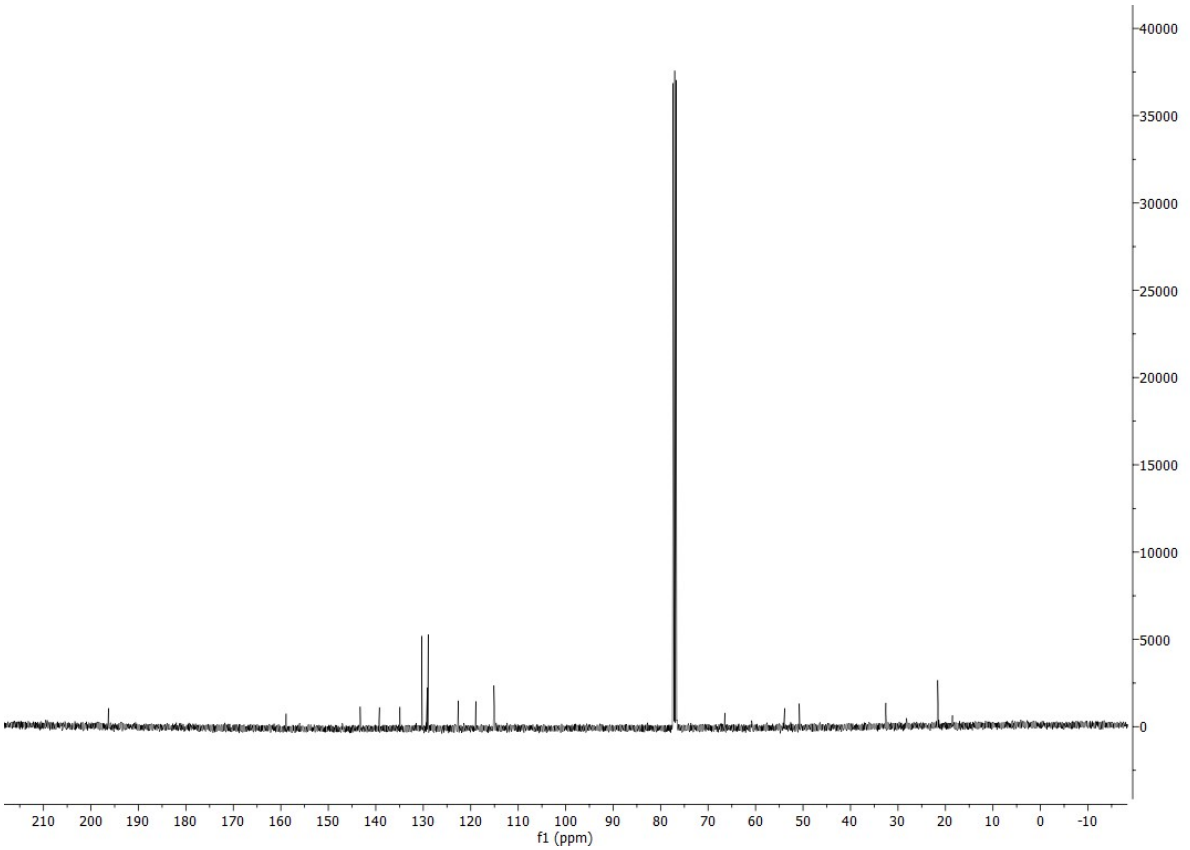




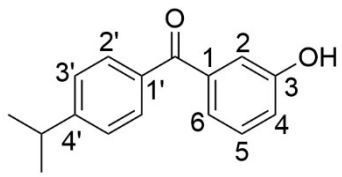


**(2’’’*R*)-*N*-{3’’-[3-(4’-methylbenzoyl)phenoxy]propyl}2’’’-methylpyrrolidine 17**



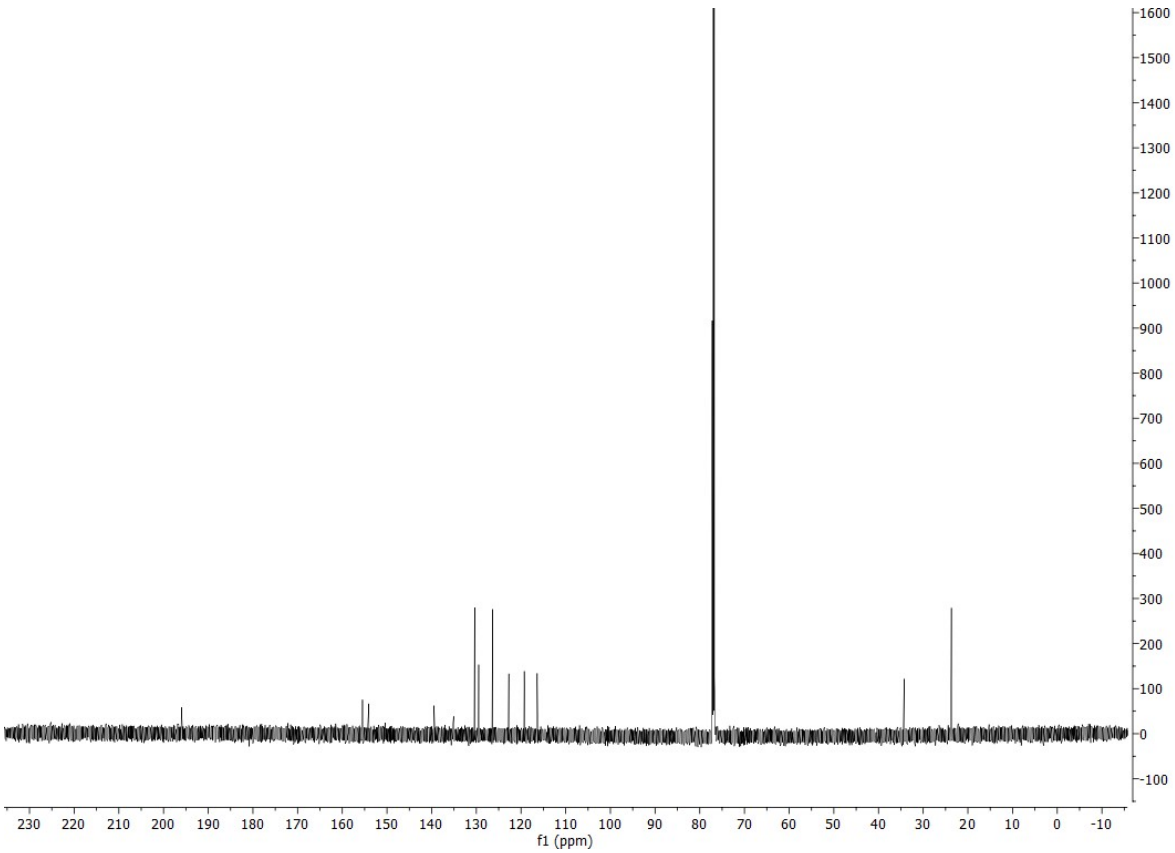



## 3-[4’-(isopropanyl)benzoyl]phenol J

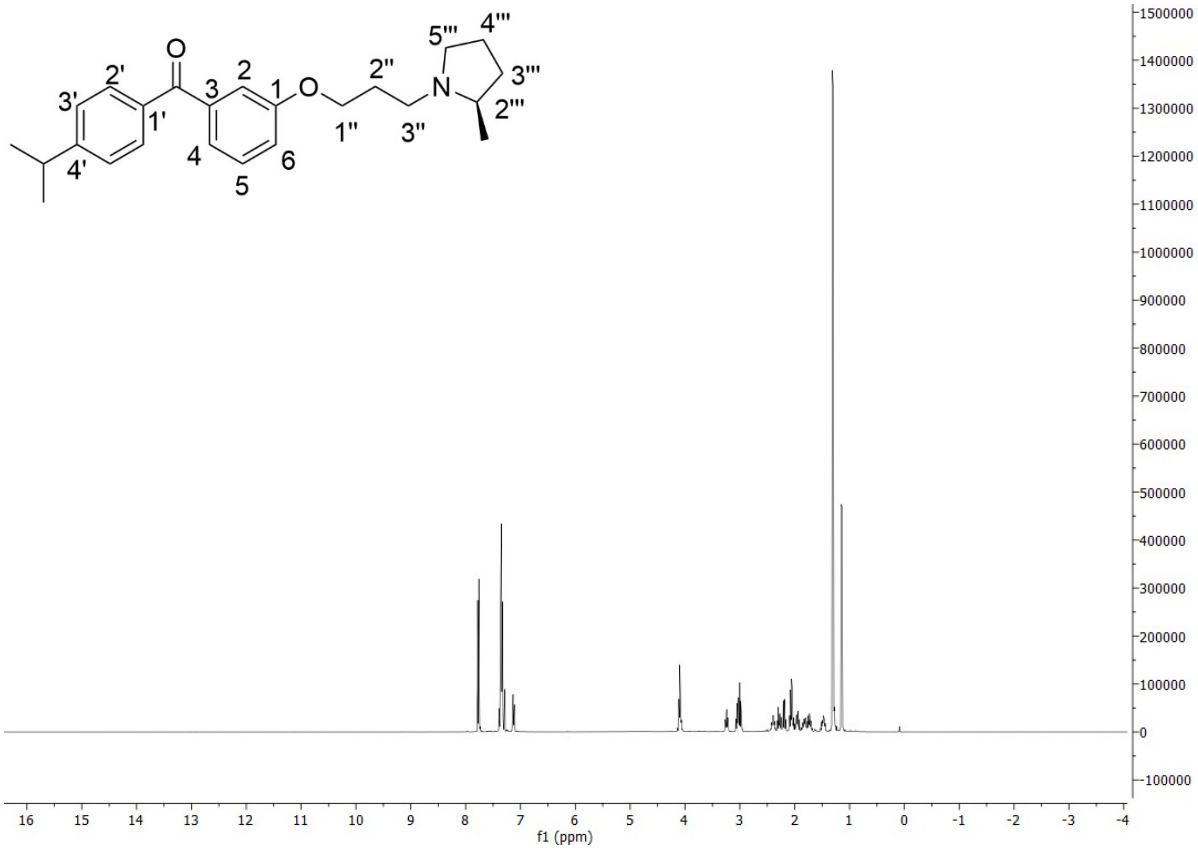


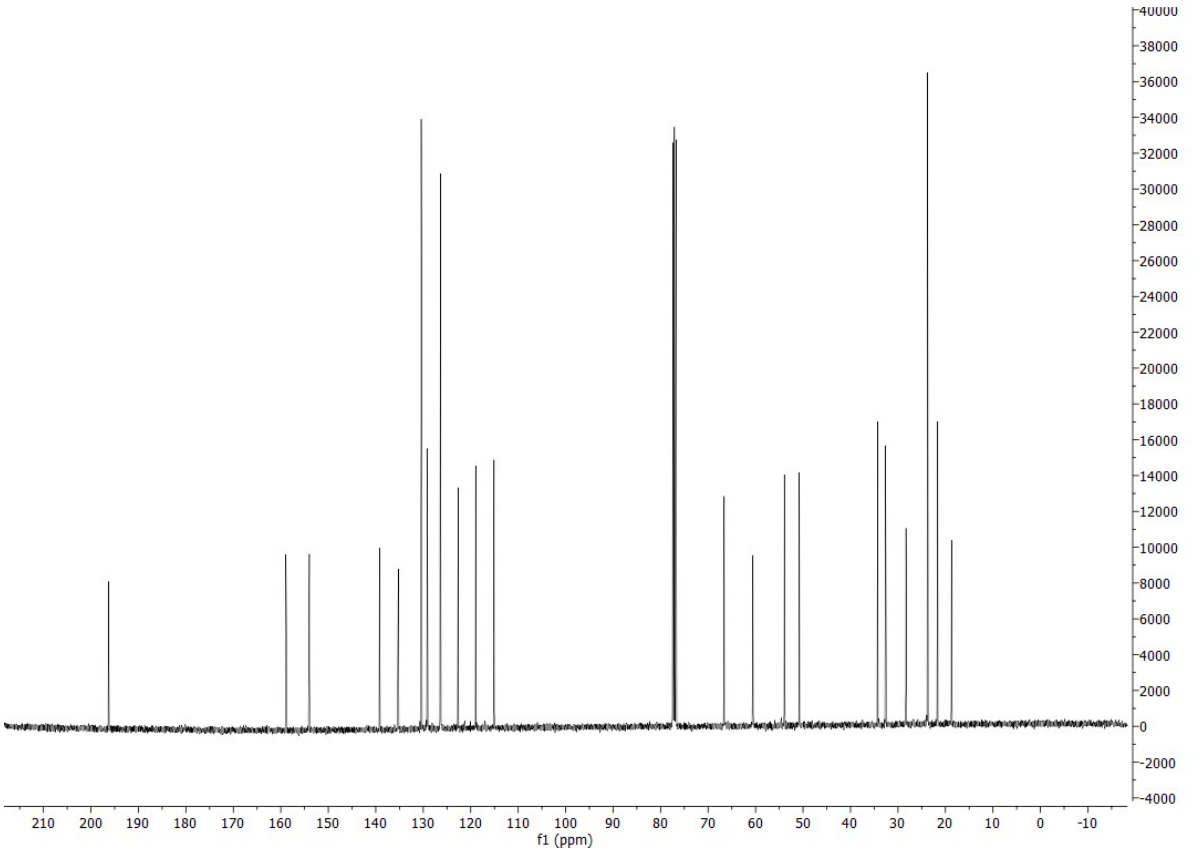




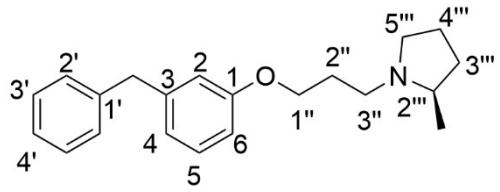


**(2*R*)-*N*-(3’’-{3-[4’-(propan-2’’’’-yl)benzoyl]phenoxy}propyl)-2’’’-methylpyrrolidine 18**



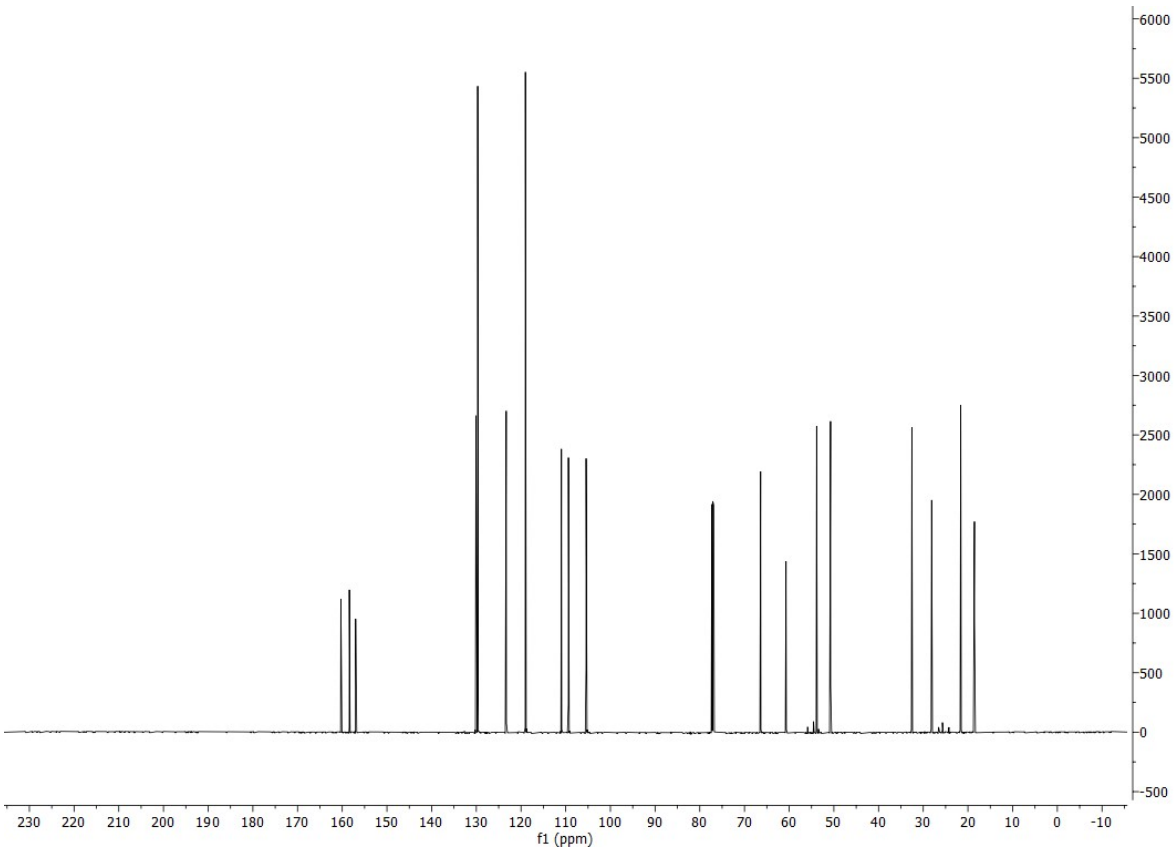



**(2’’’*R*)-*N*-[3’’-(3-benzylphenoxy)propyl]-2’’’-methylpyrrolidine 19**

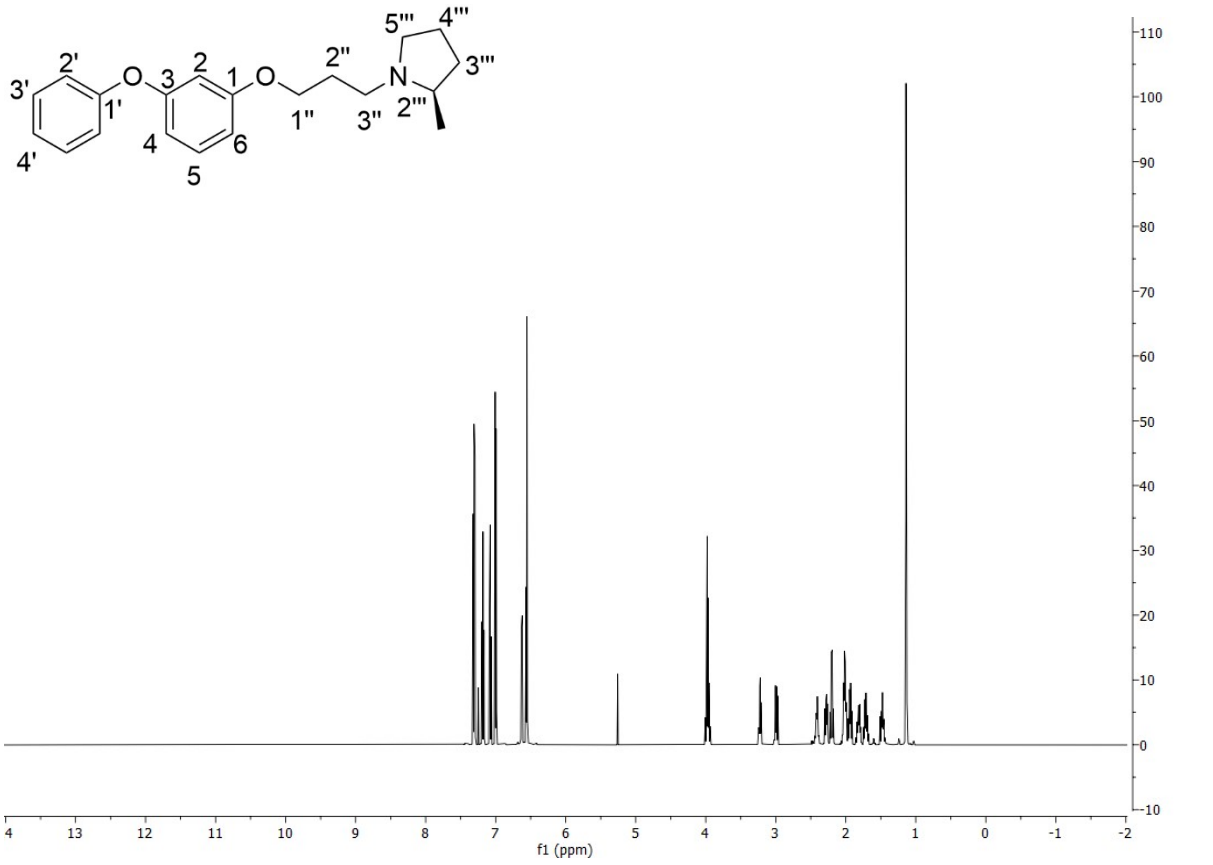




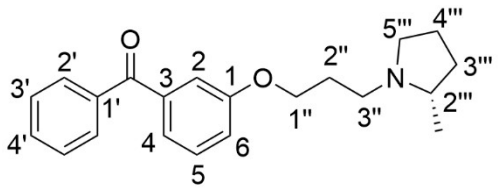


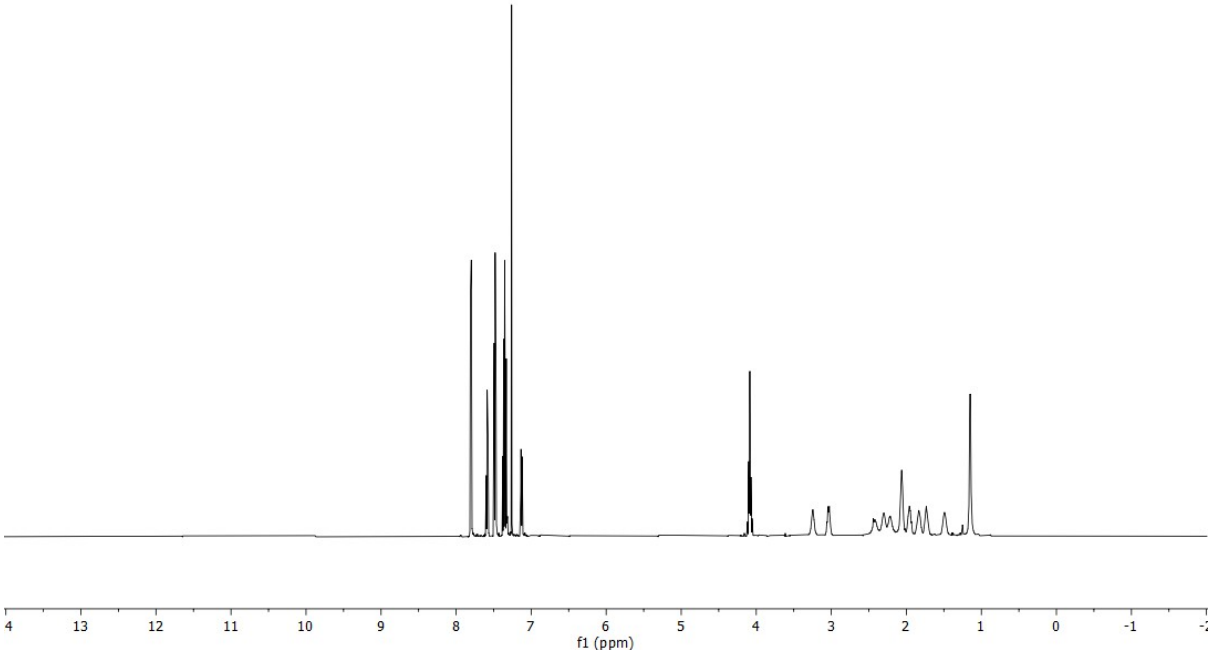


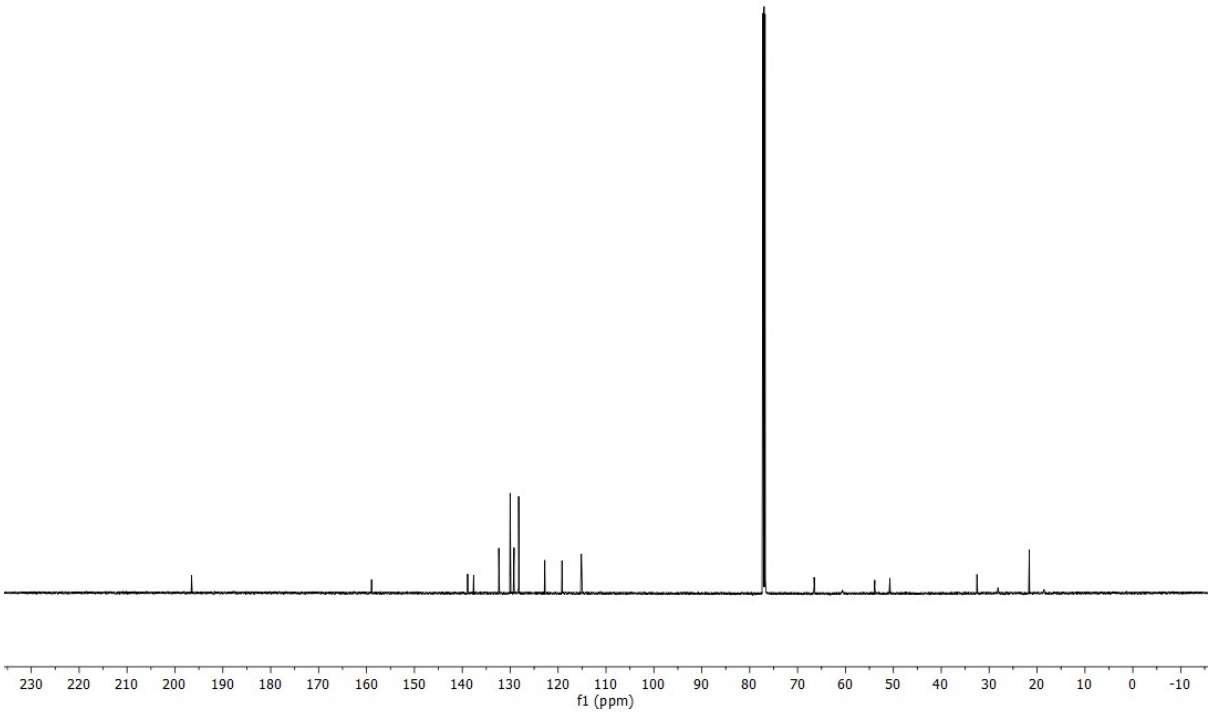
**(2’’’*R*)-2’’’-methyl-*N*-[3’’-(3-phenoxyphenoxy)propyl]pyrrolidine 20**



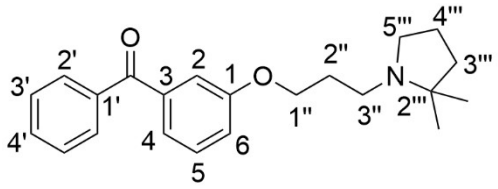
**(2’’’*S*)-1-[3’’-(3-benzoylphenoxy)propyl]-2’’’-methylpyrrolidine 21**



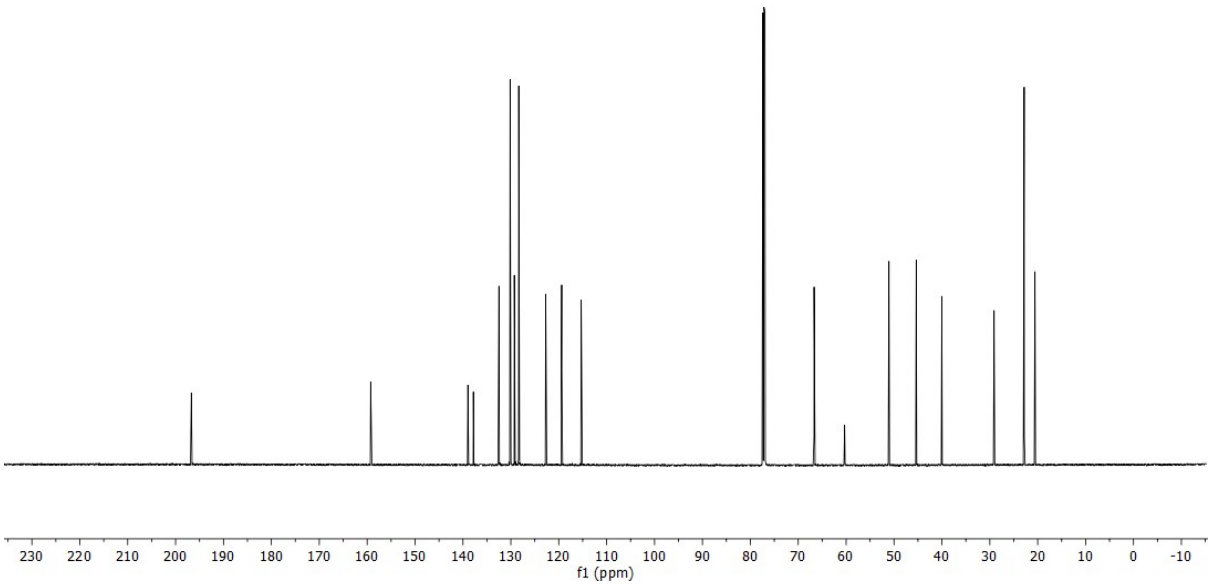



**_N_-[3’’-(3-benzoylphenoxy)propyl]-2’’’,2’’’-dimethylpyrrolidine 22**

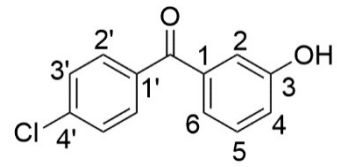






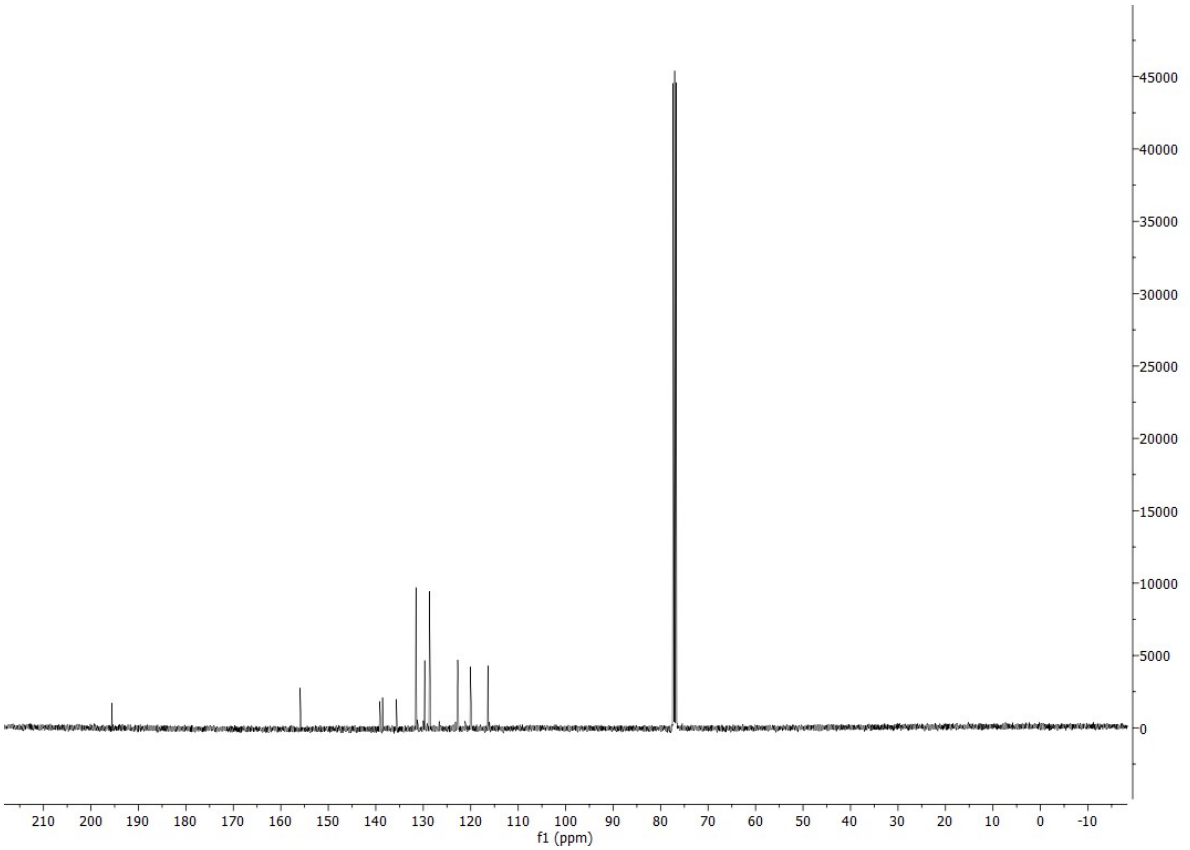


## 3-(4’-chlorobenzoyl)phenol H

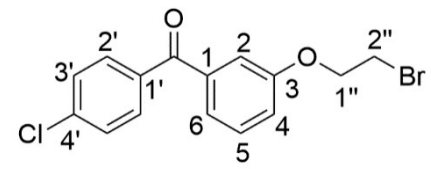






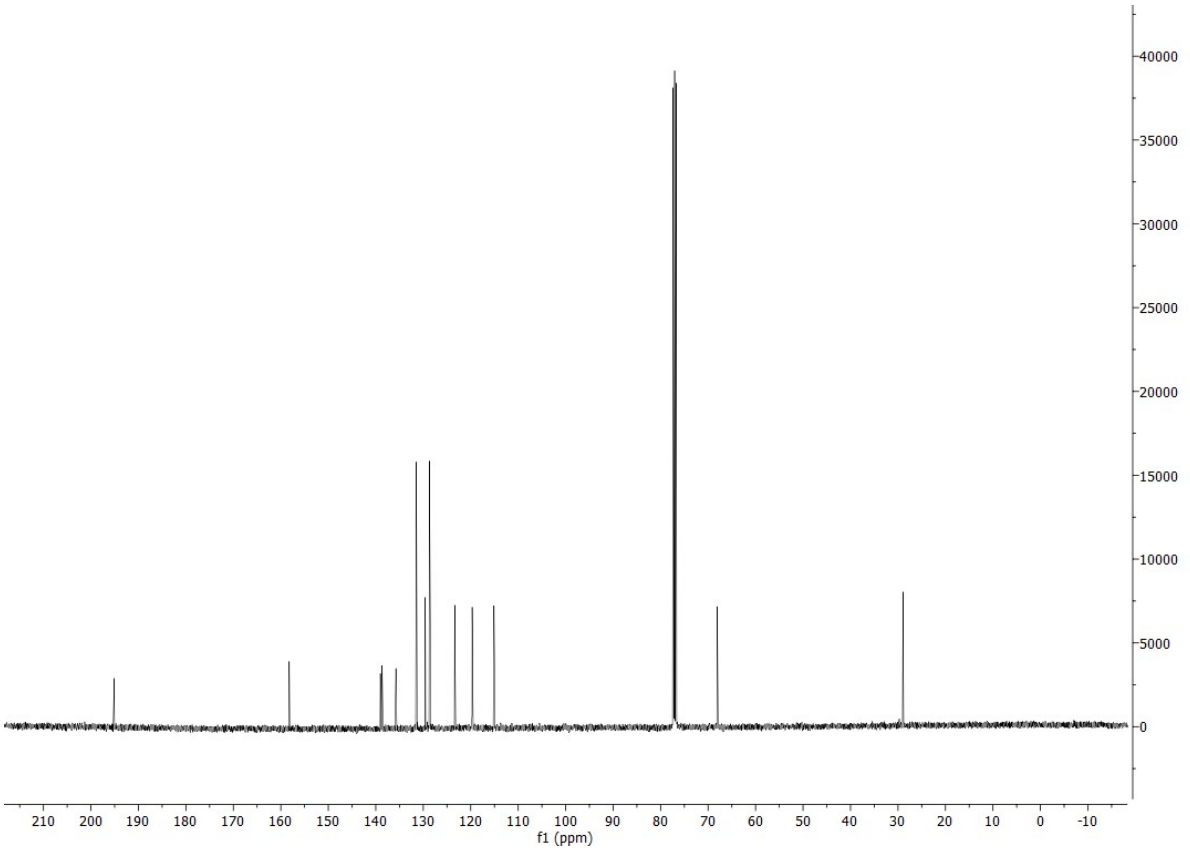


## [3-(2’’-bromoethoxy)phenyl](4’-chlorophenyl)methanone 14a

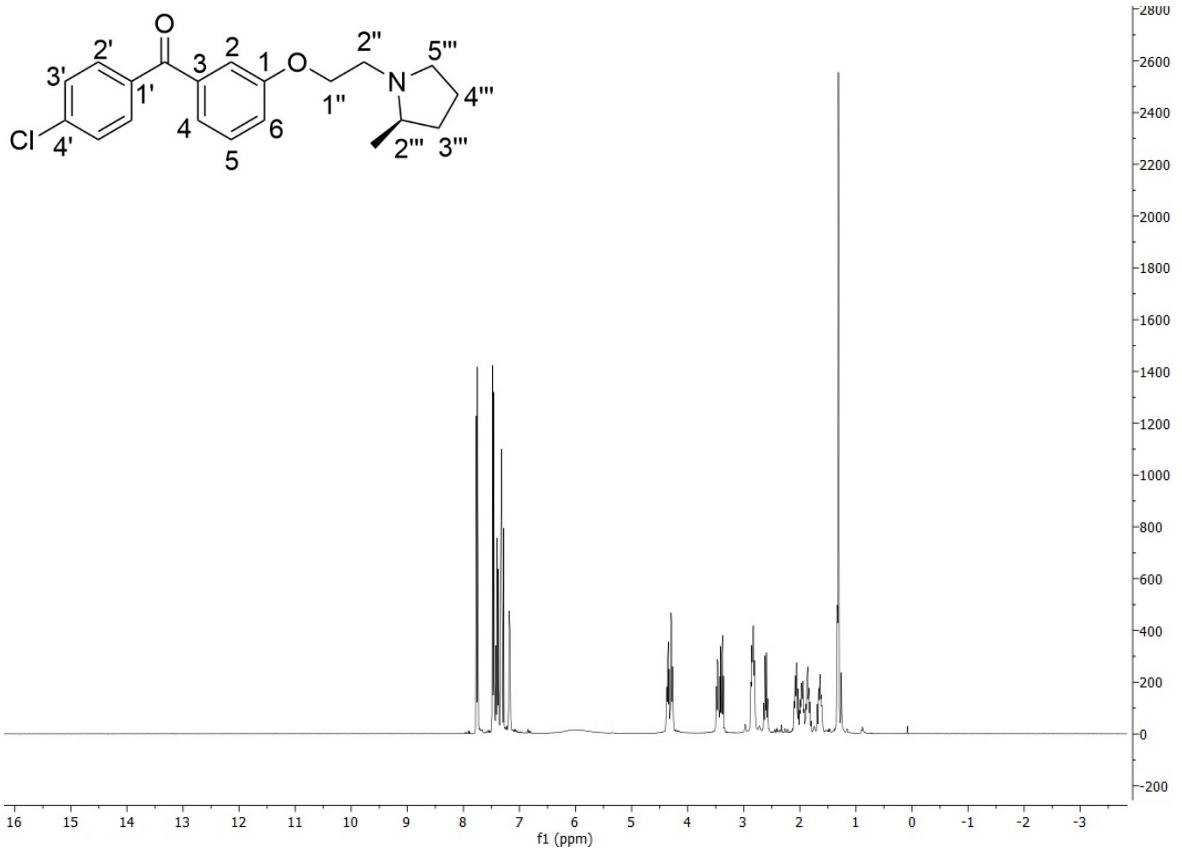


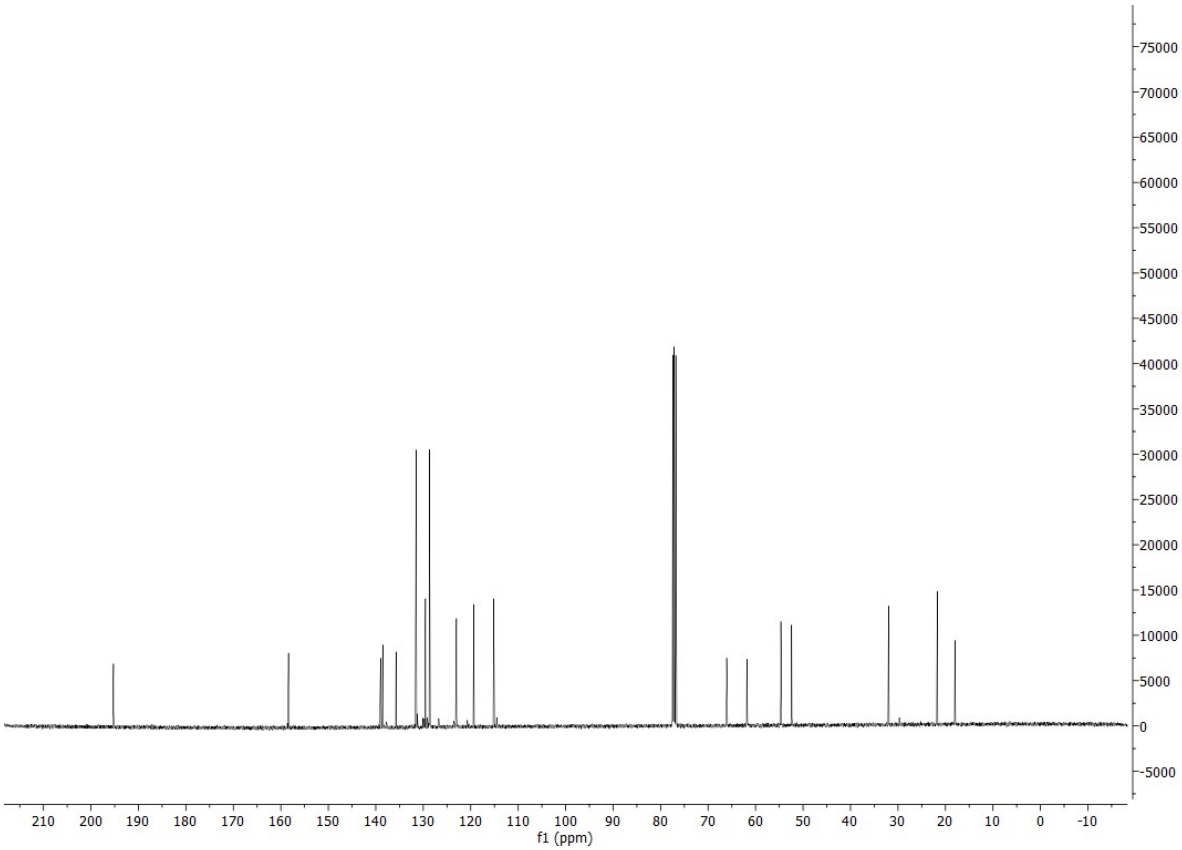




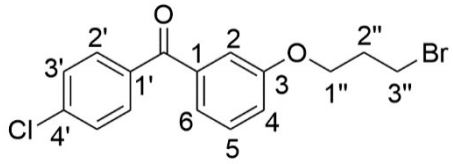


**(2’’’*R*)-*N*-{2’’-[3-(4’-chlorobenzoyl)phenoxy]ethyl}-2’’’-methylpyrrolidine 14**



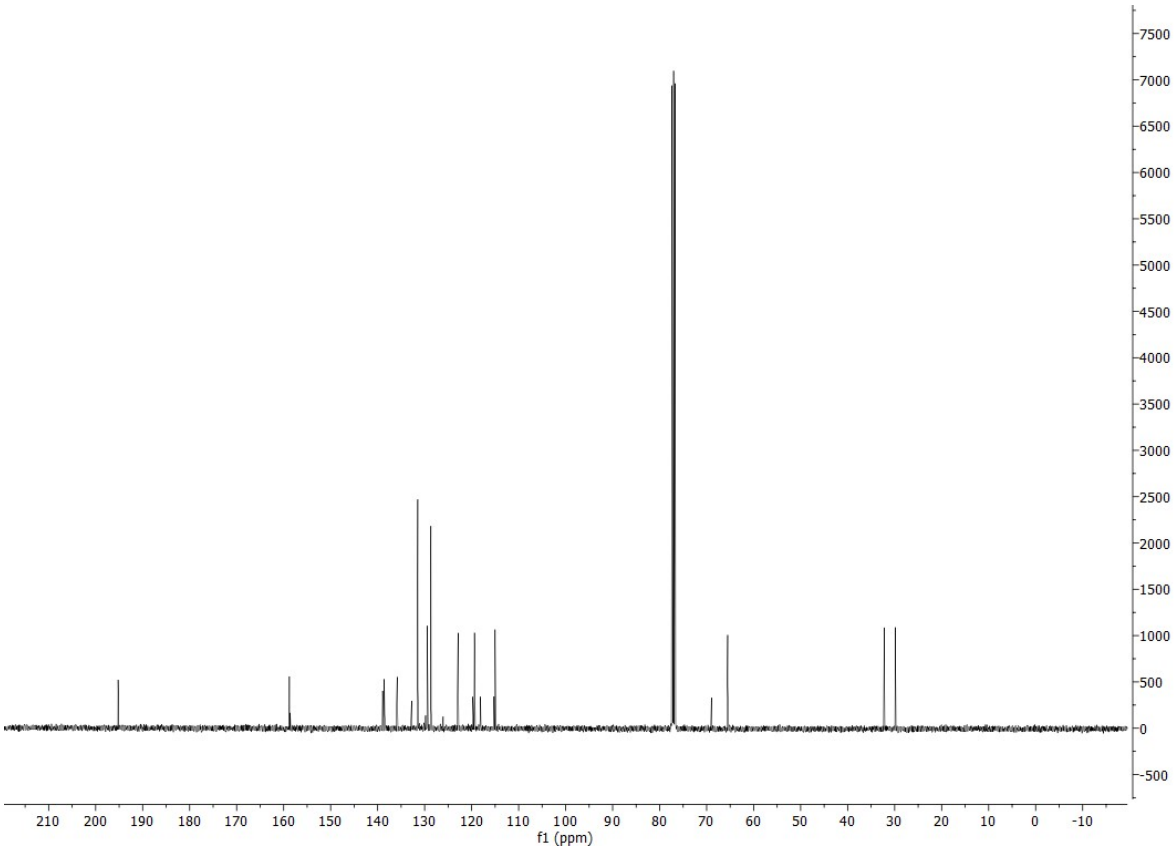



## [3-(3’’-bromopropoxy)phenyl](4’-chlorophenyl)methanone 15a

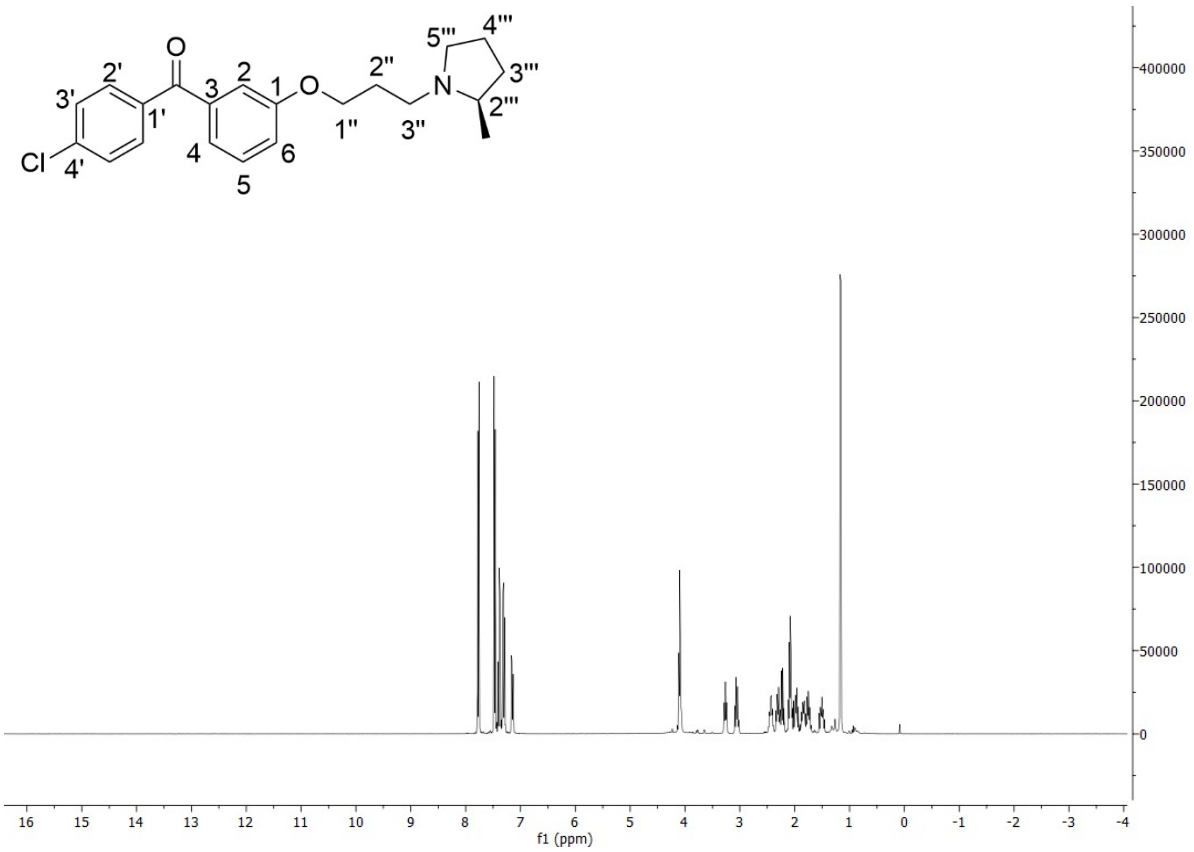


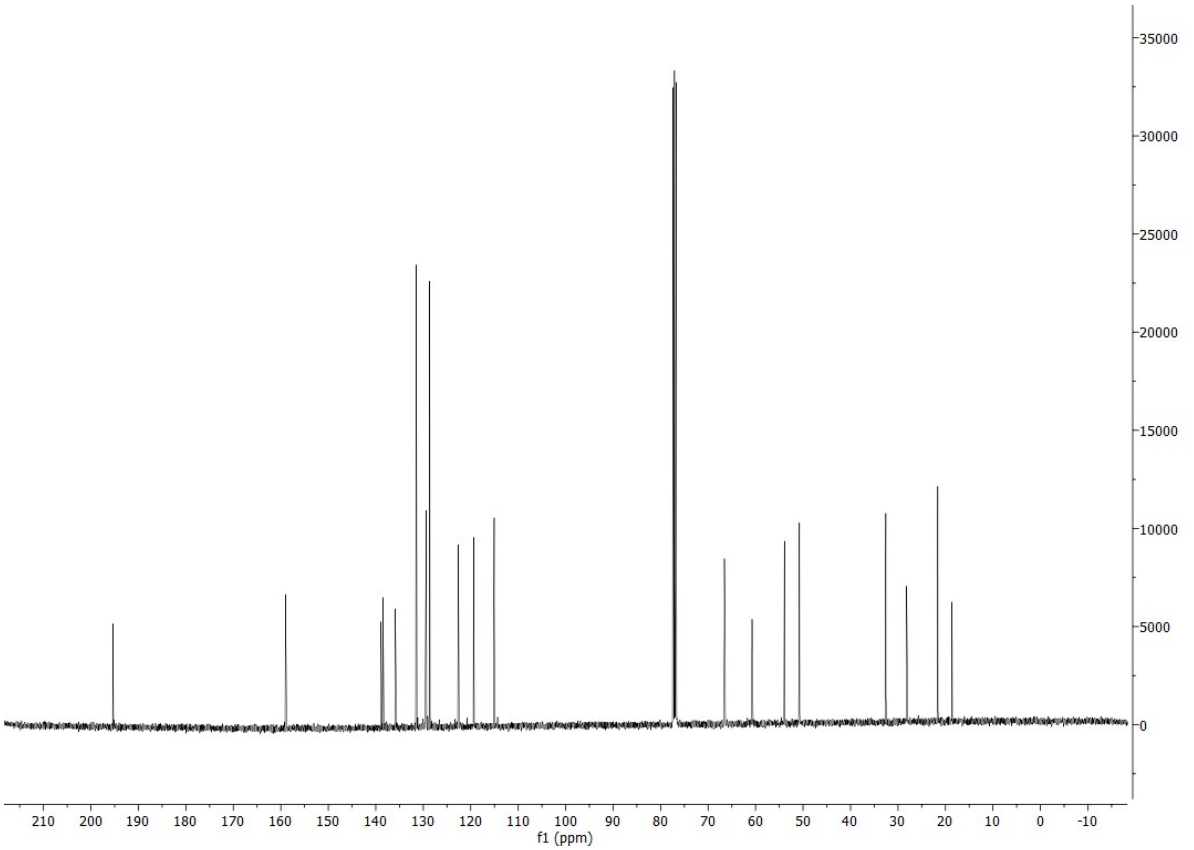




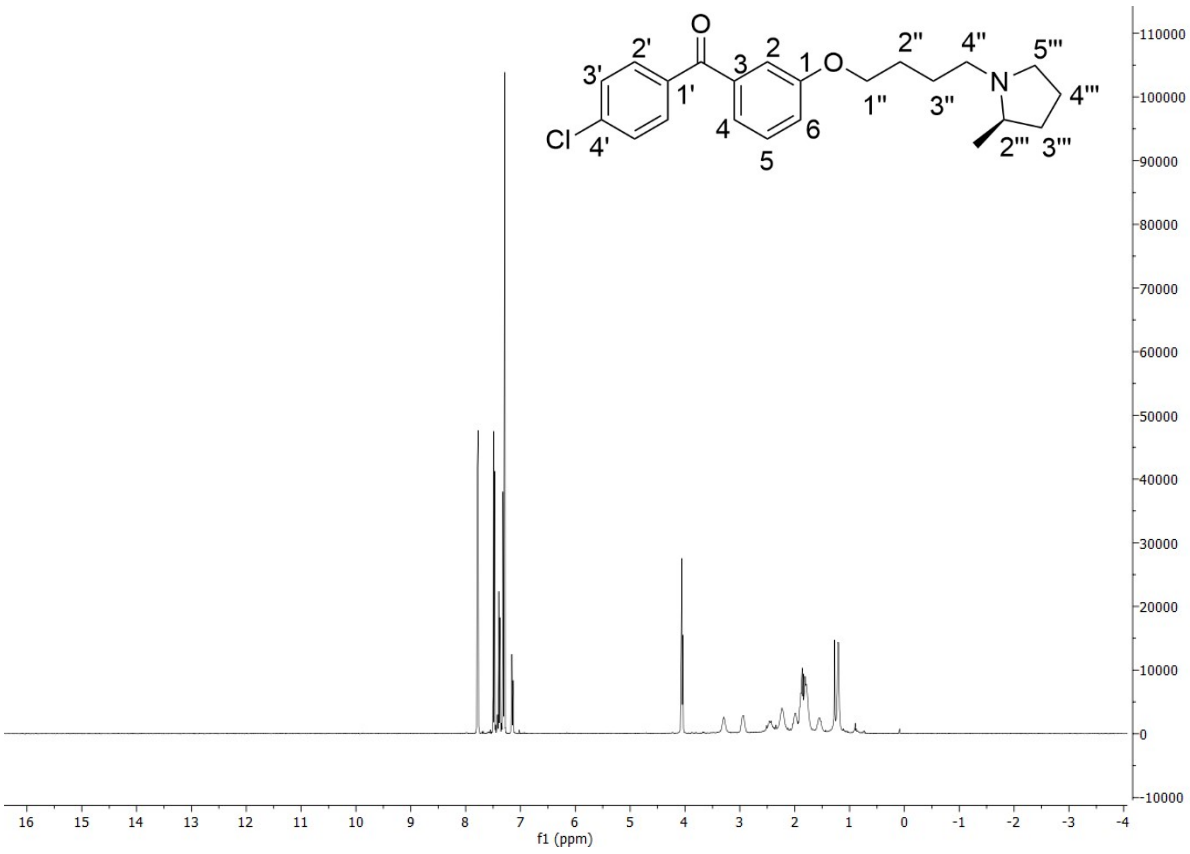


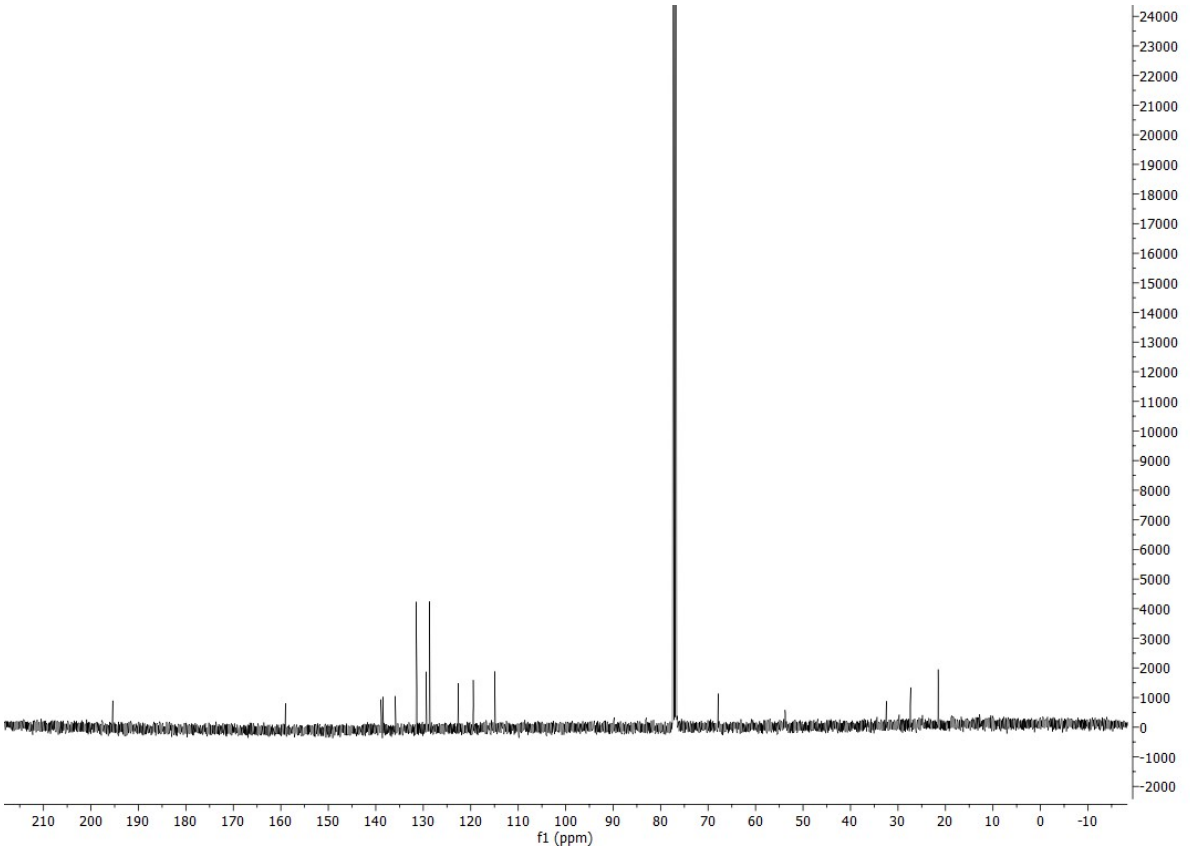
**(2’’’R)-*N*-{3’’-[3-(4’-chlorobenzoyl)phenoxy]propyl}-2’’’-methylpyrrolidine 15**



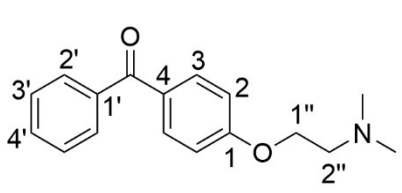



**(2’’’*R*)-*N*-{4’’-[3-(4’-chlorobenzoyl)phenoxy]butyl}-2’’’-methylpyrrolidine 16**



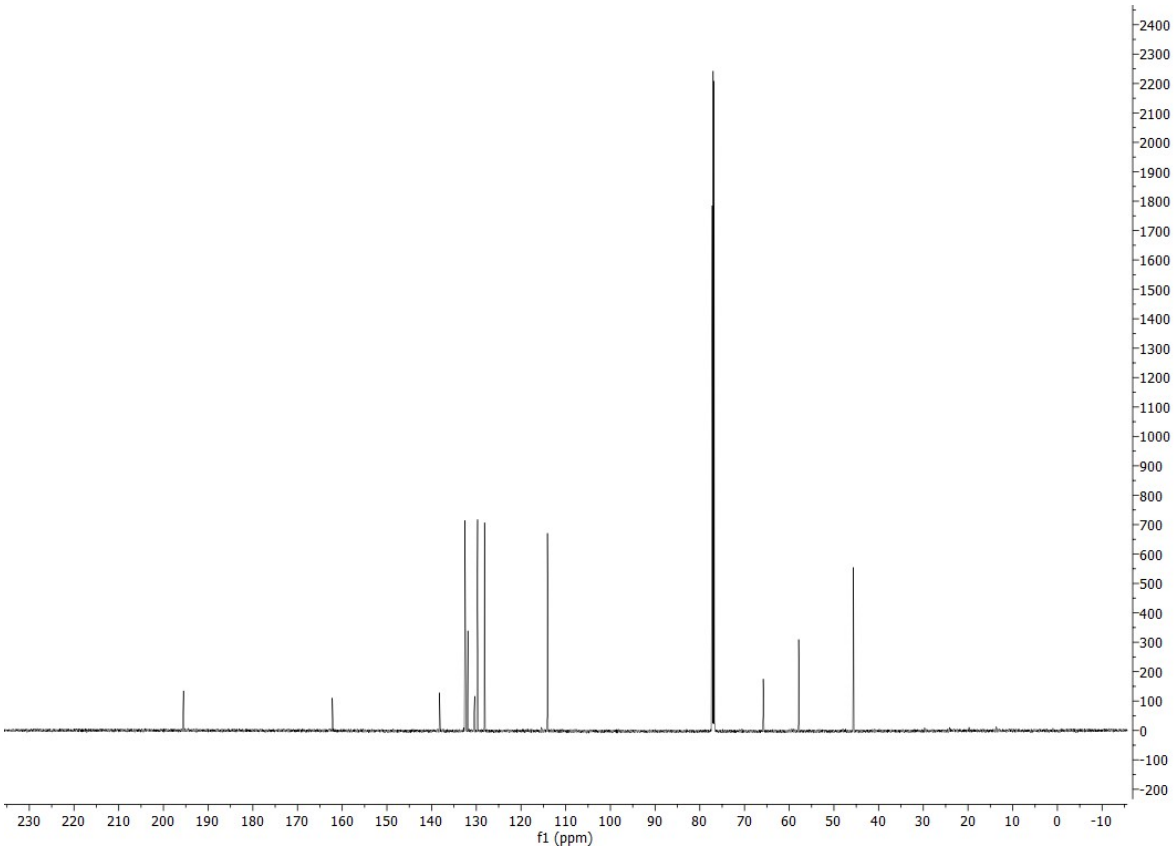



## [2’’-(4-benzoylphenoxy)ethyl]dimethylamine 23

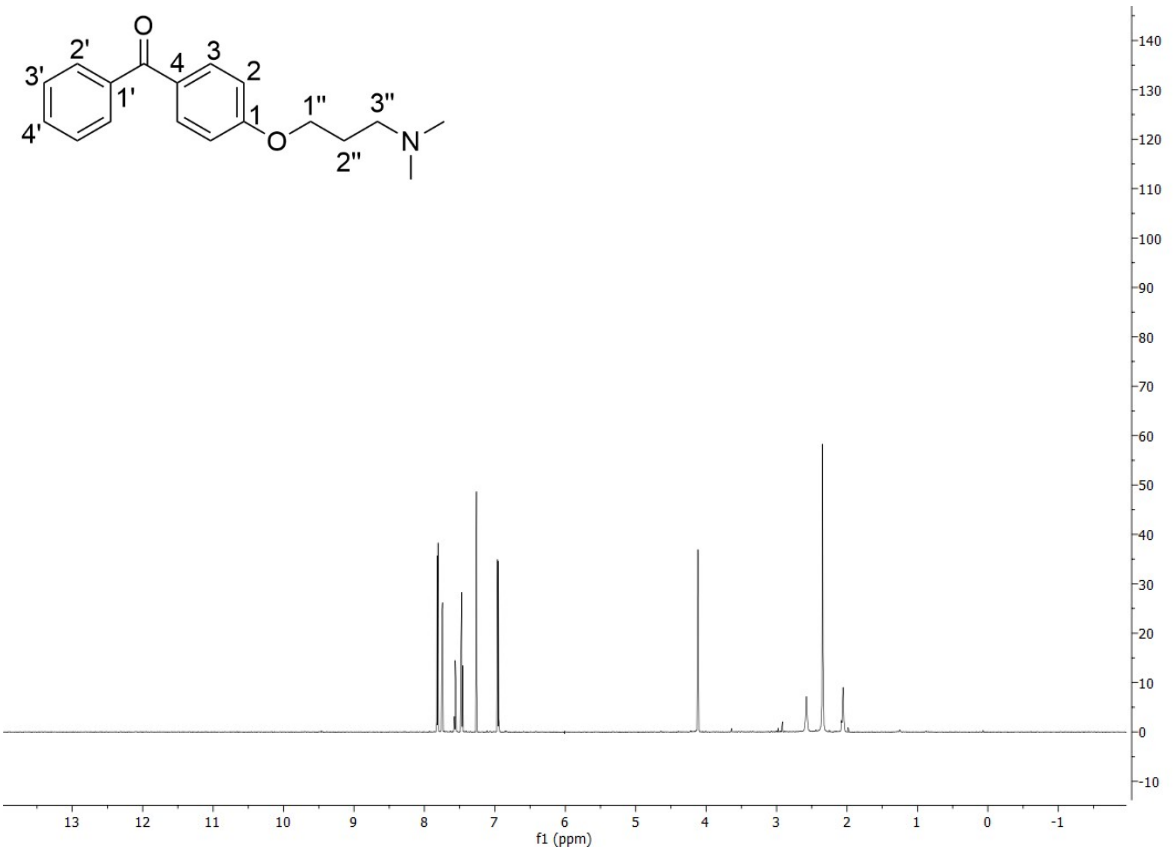


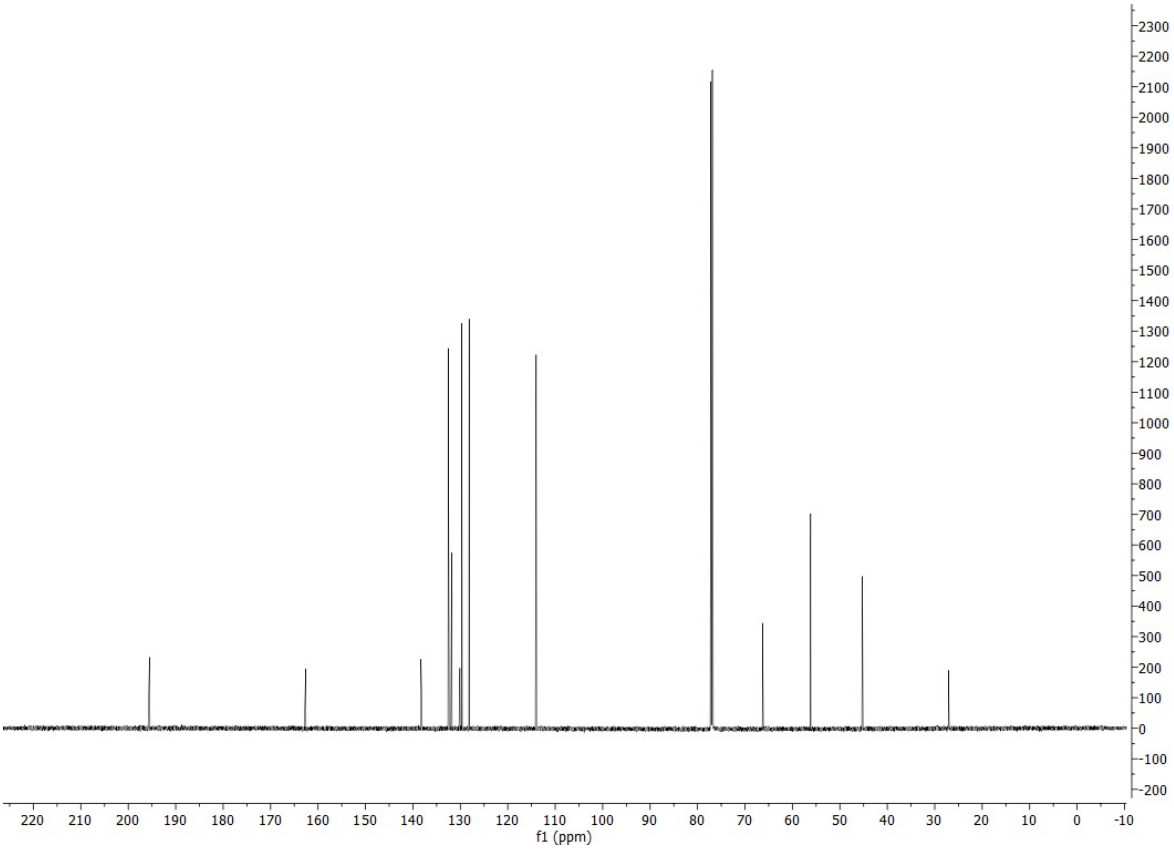




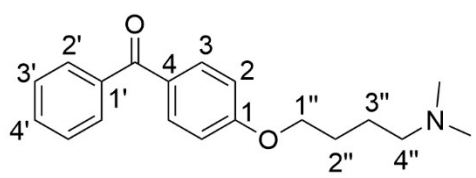


## [3’’-(4-benzoylphenoxy)propyl]dimethylamine 24



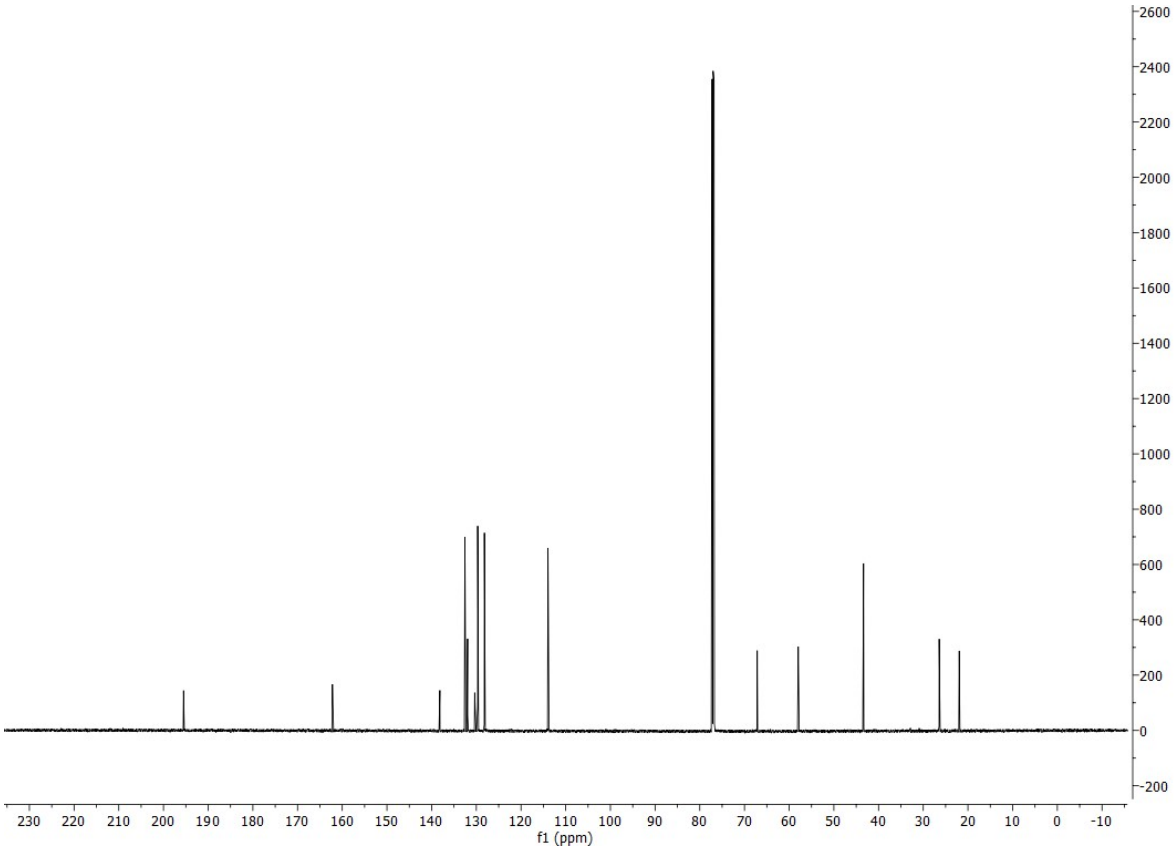



## [4’’-(4-benzoylphenoxy)butyl]dimethylamine 25

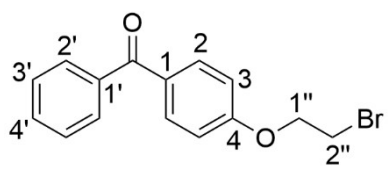




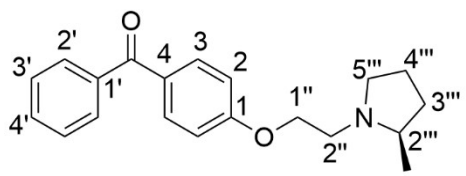




## [4-(2’’-bromoethoxy)phenyl](phenyl)methanone 26a

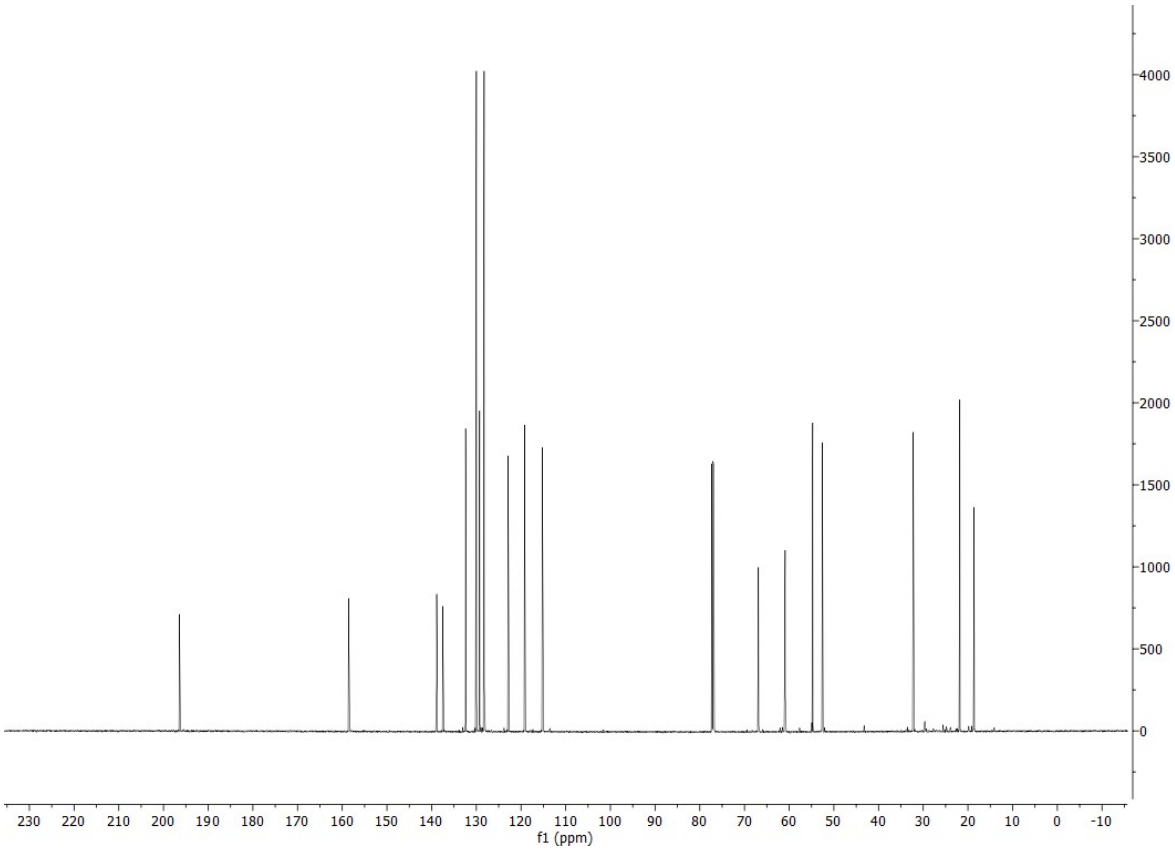


**(2’’’*R*)-1’’’-[2’’-(4-benzoylphenoxy)ethyl]-2’’’-methylpyrrolidine 26**

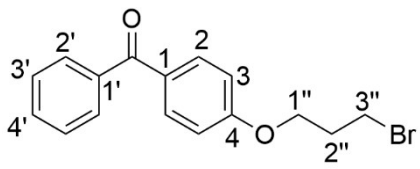






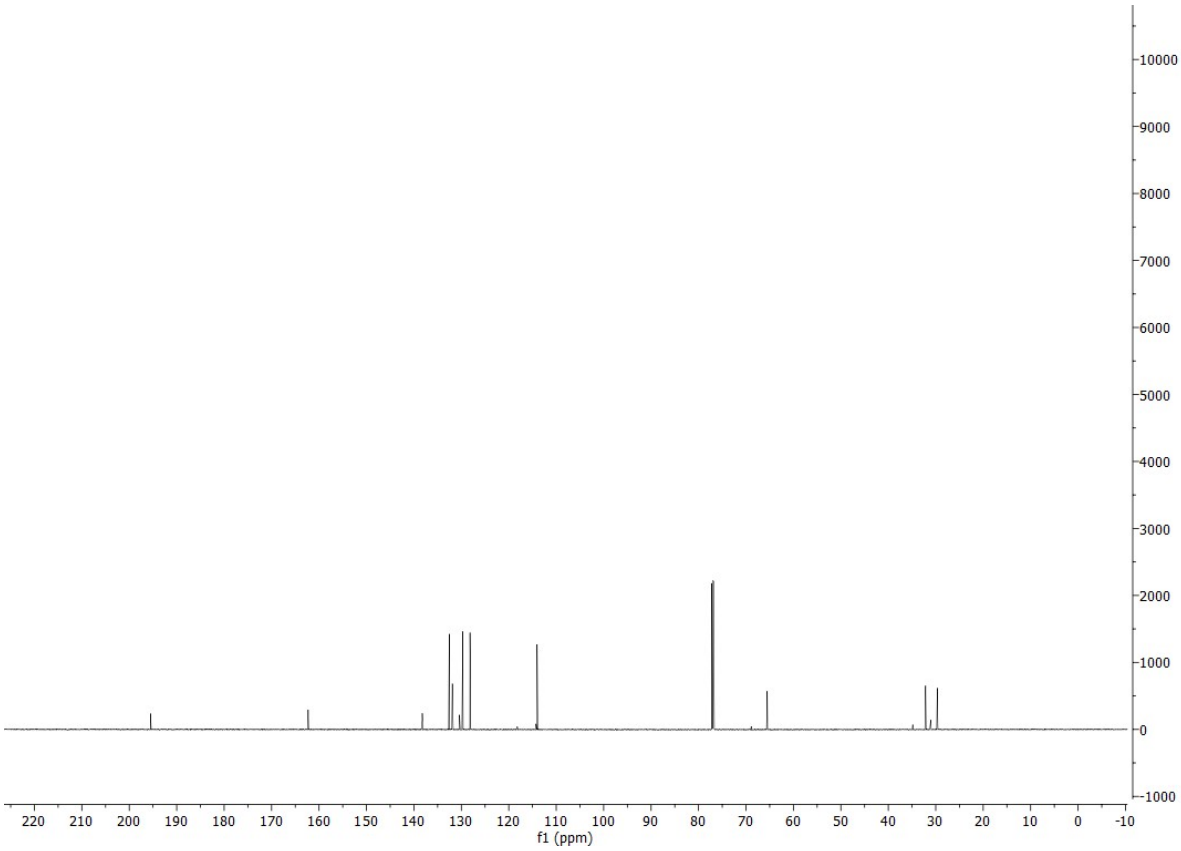


## [4-(3’’-bromopropoxy)phenyl](phenyl)methanone 27a

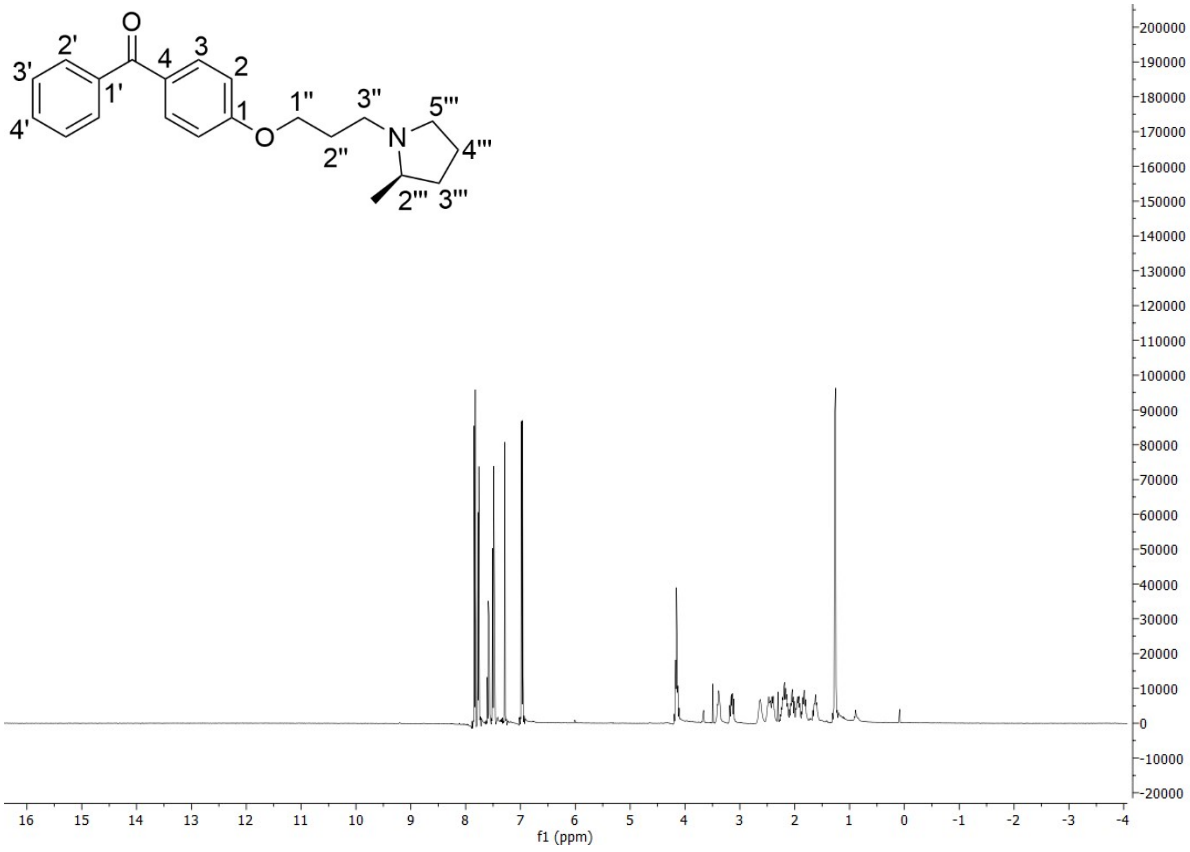


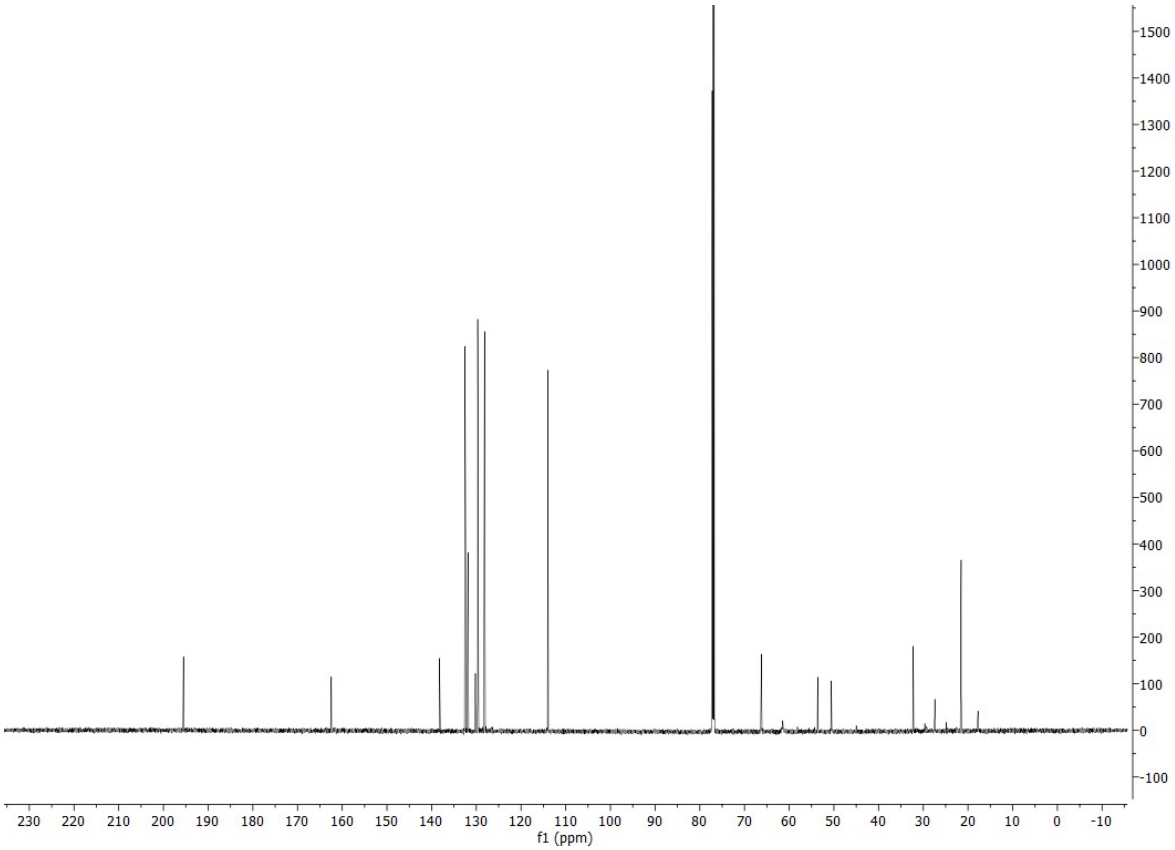




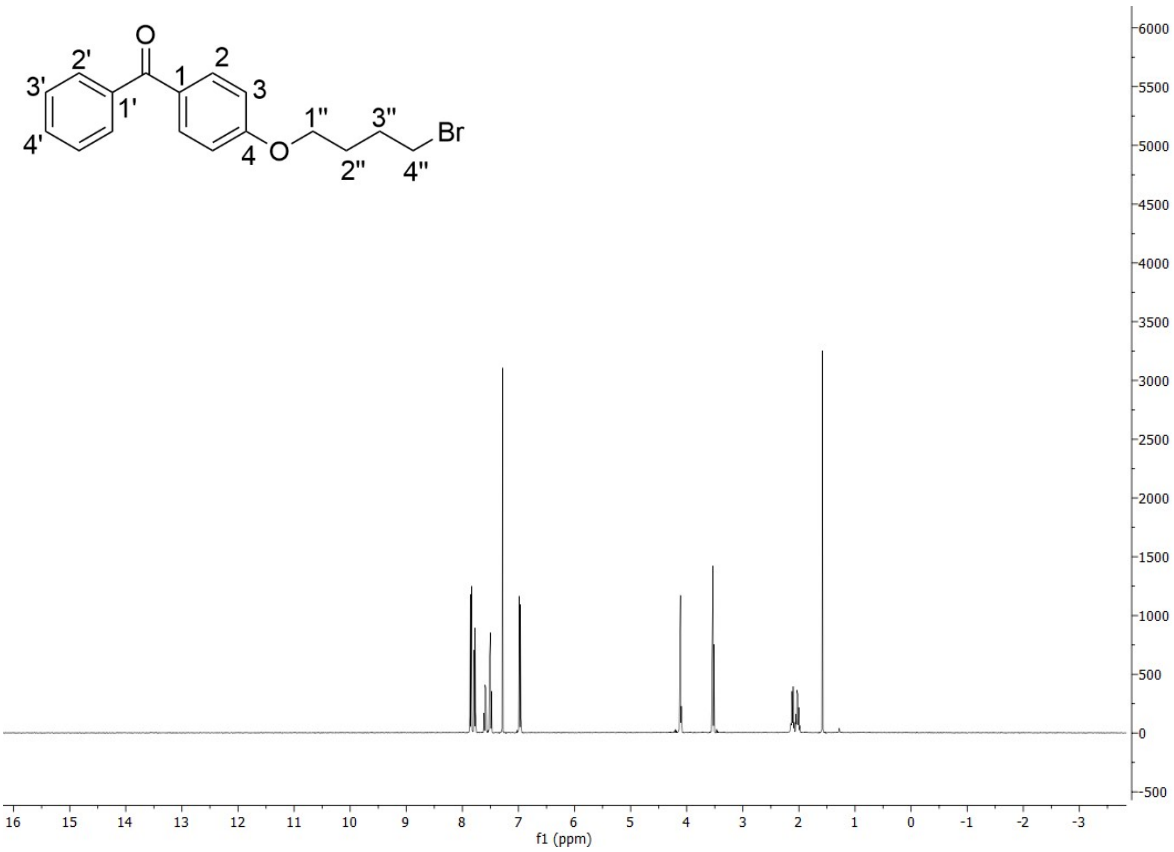


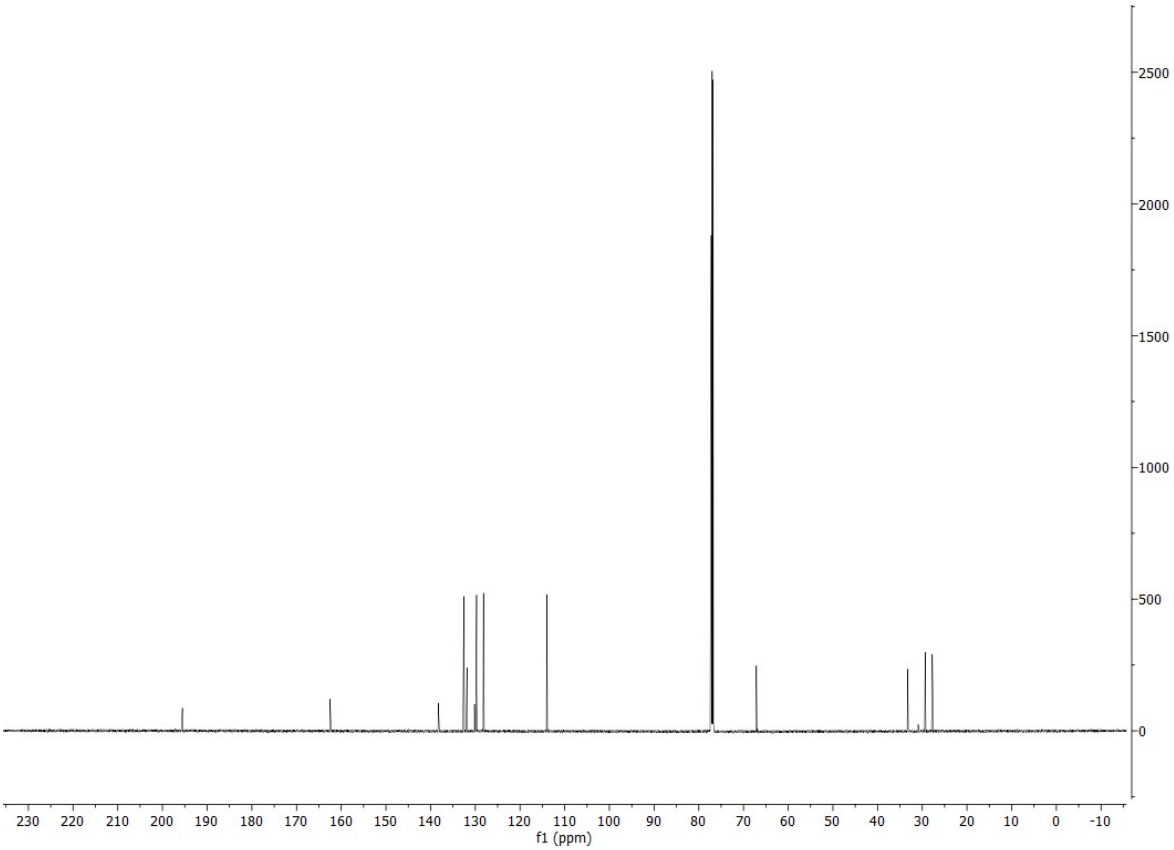
**(2’’’*R*)-1’’’-[3’’-(4-benzoylphenoxy)propyl]-2’’’-methylpyrrolidine 27**



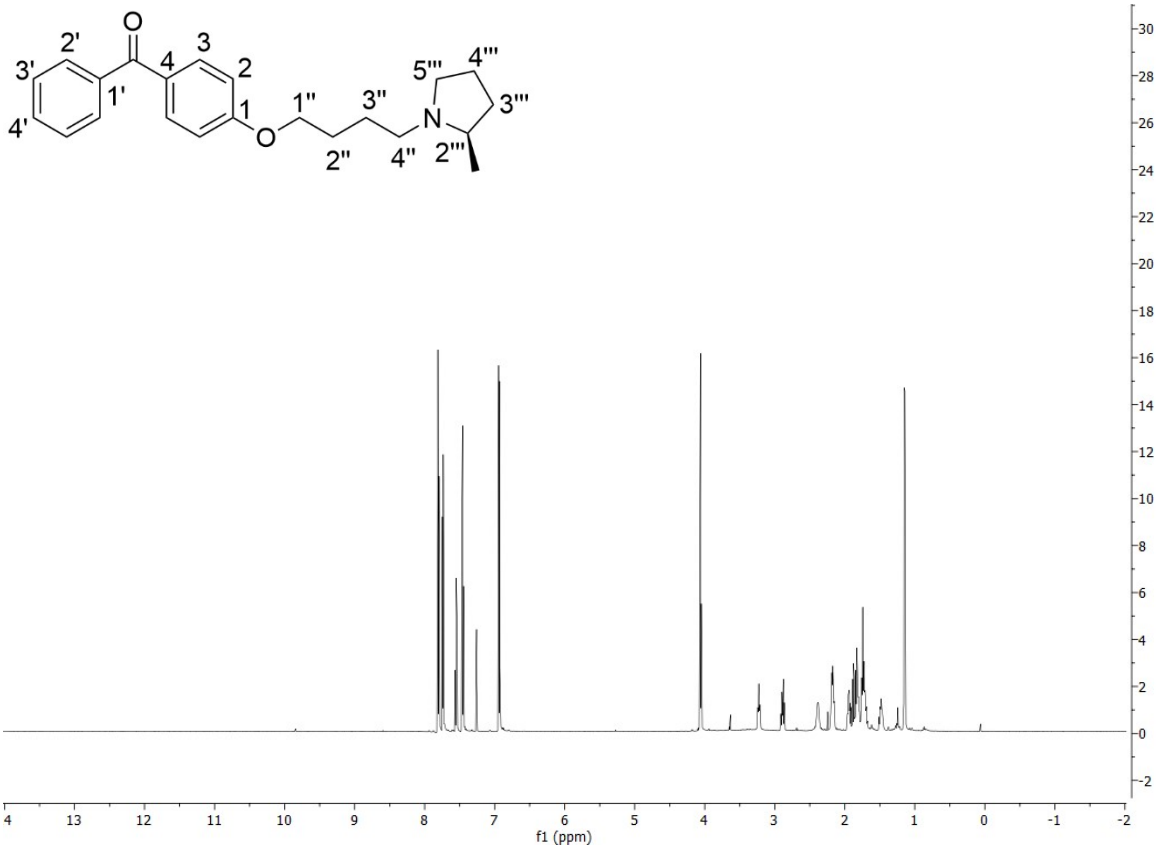



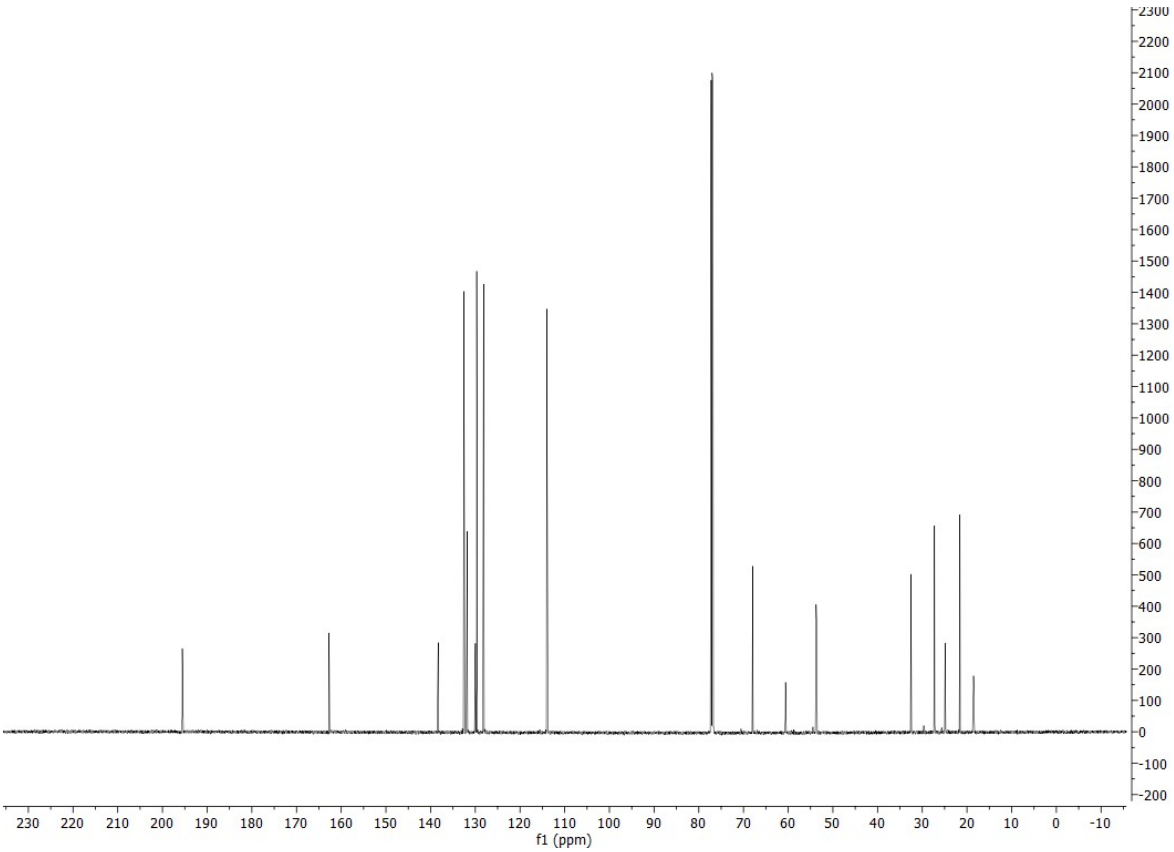
## [4-(4’’-bromobutoxy)phenyl](phenyl)methanone 28a



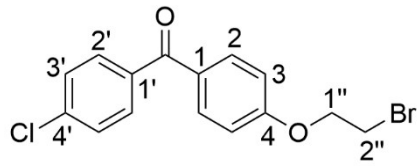



**(2’’’*R*)-1’’’-[4’’-(4-benzoylphenoxy)butyl]-2’’’-methylpyrrolidine 28**



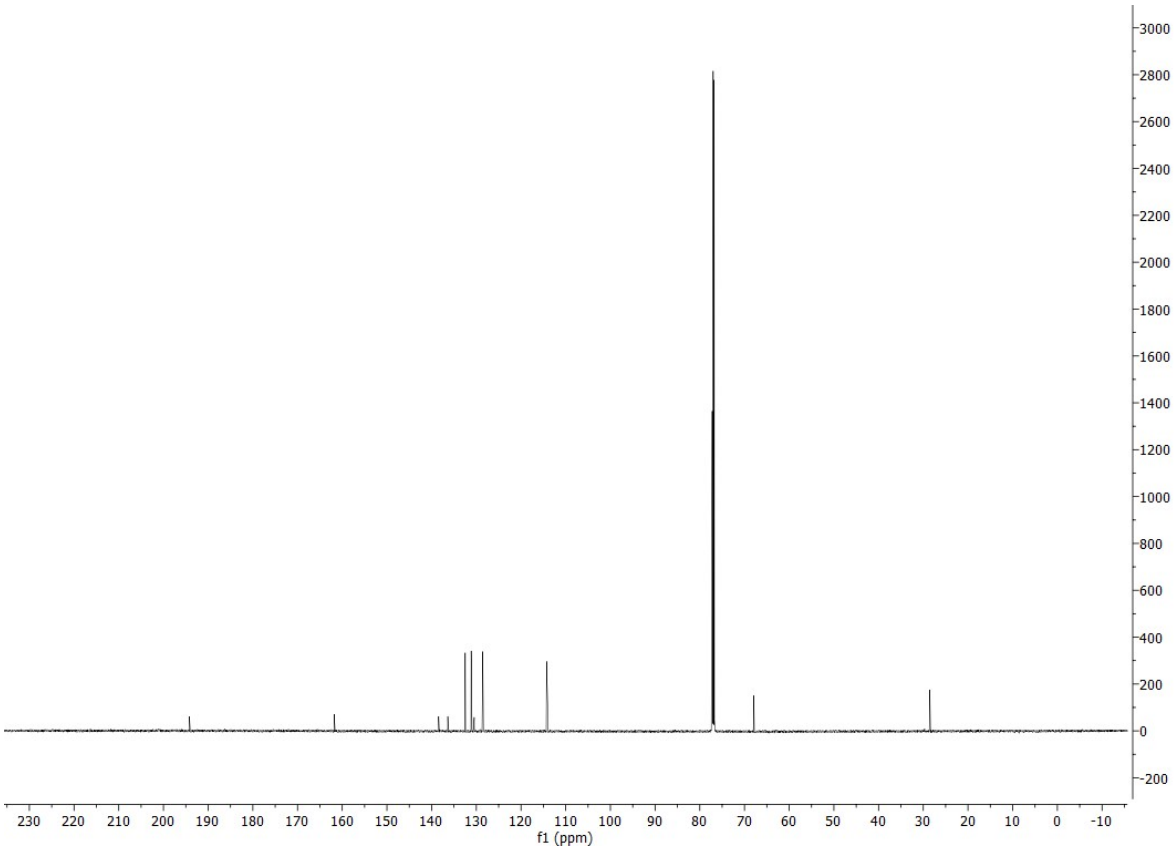



## [4-(2’’-bromoethoxy)phenyl](4’-chlorophenyl)methanone 29a

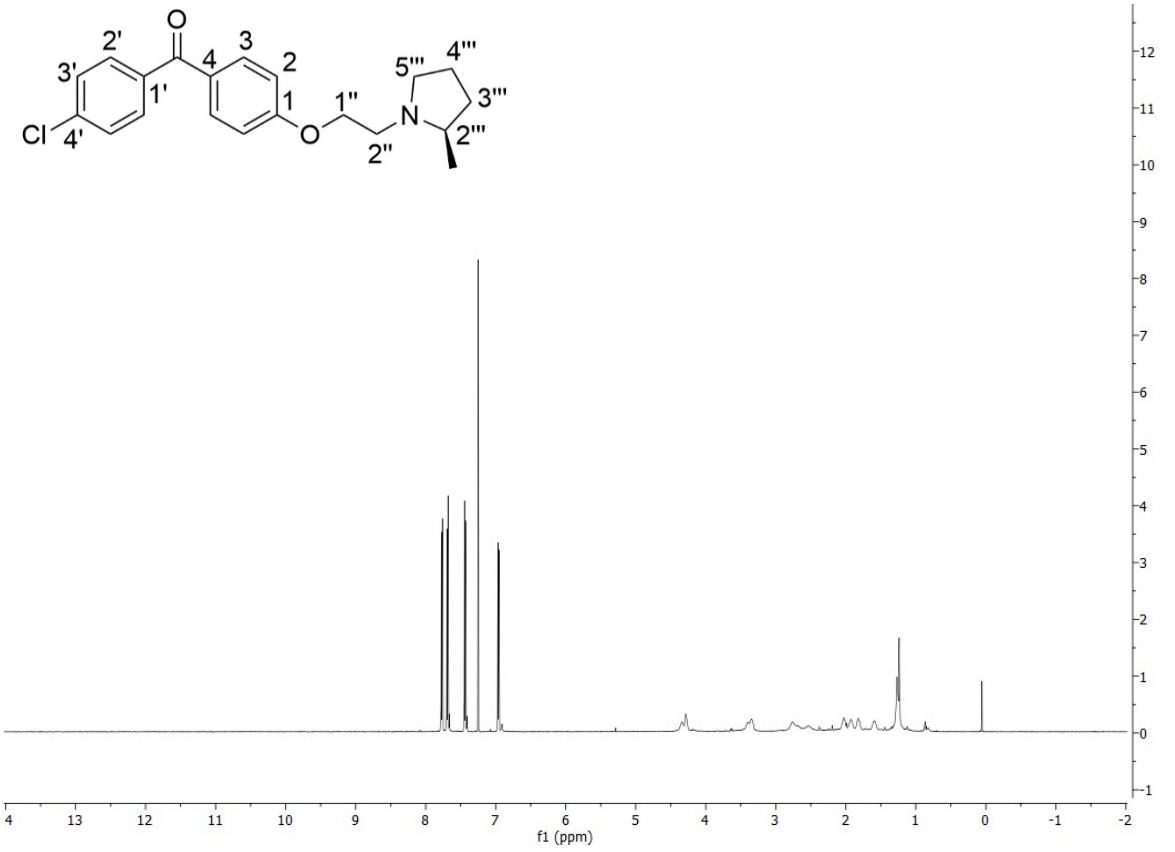


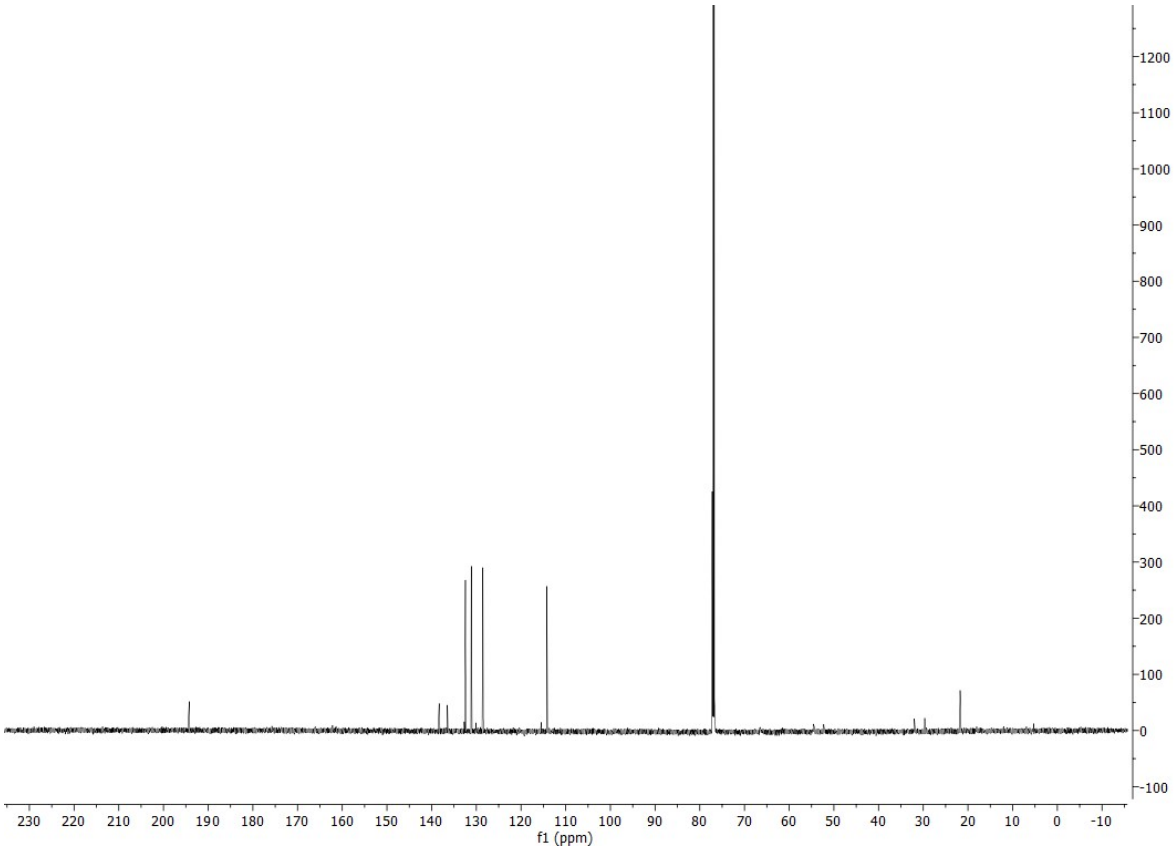




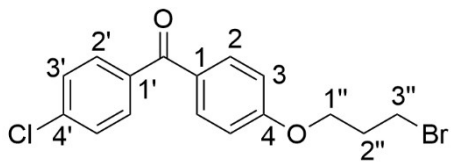


**(2’’’*R*)-1’’’-{2’’-[4-(4’-chlorobenzoyl)phenoxy]ethyl}-2’’’-methylpyrrolidine 29**



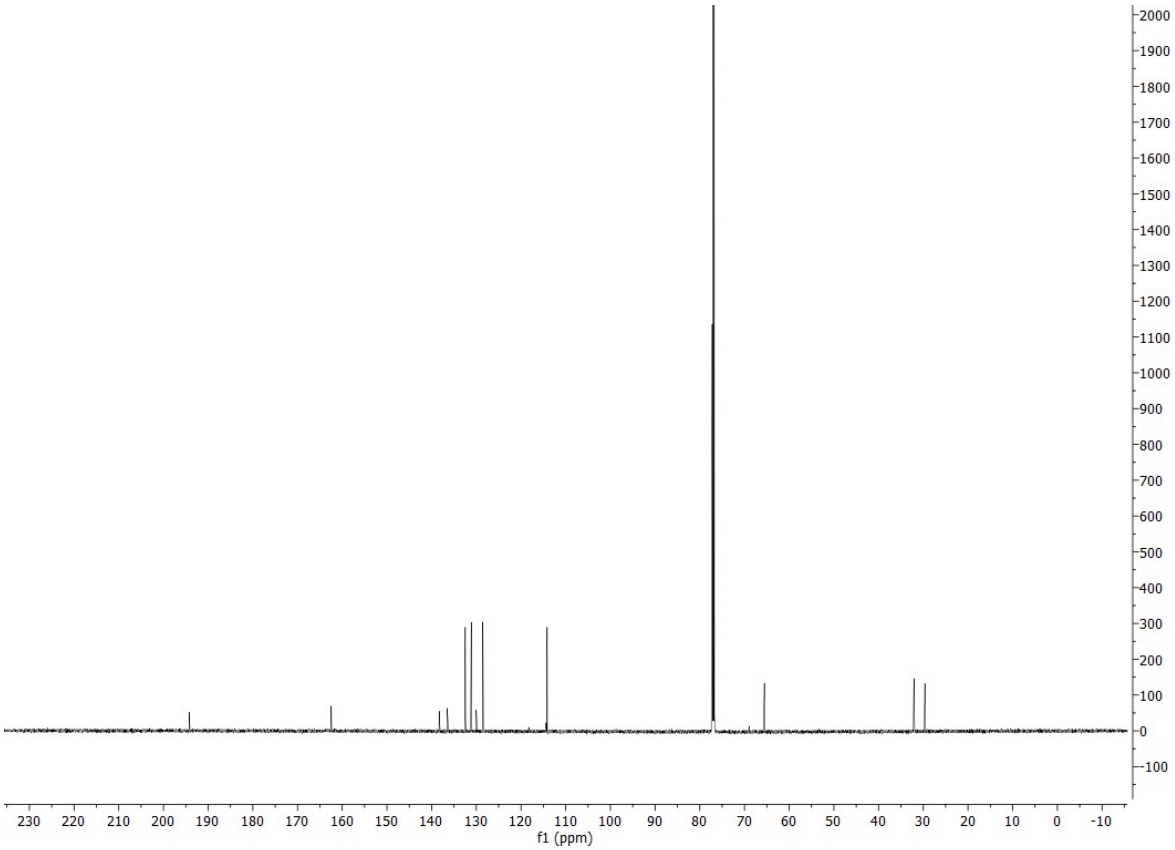



## [4-(3’’-bromopropoxy)phenyl](4’-chlorophenyl)methanone 30a

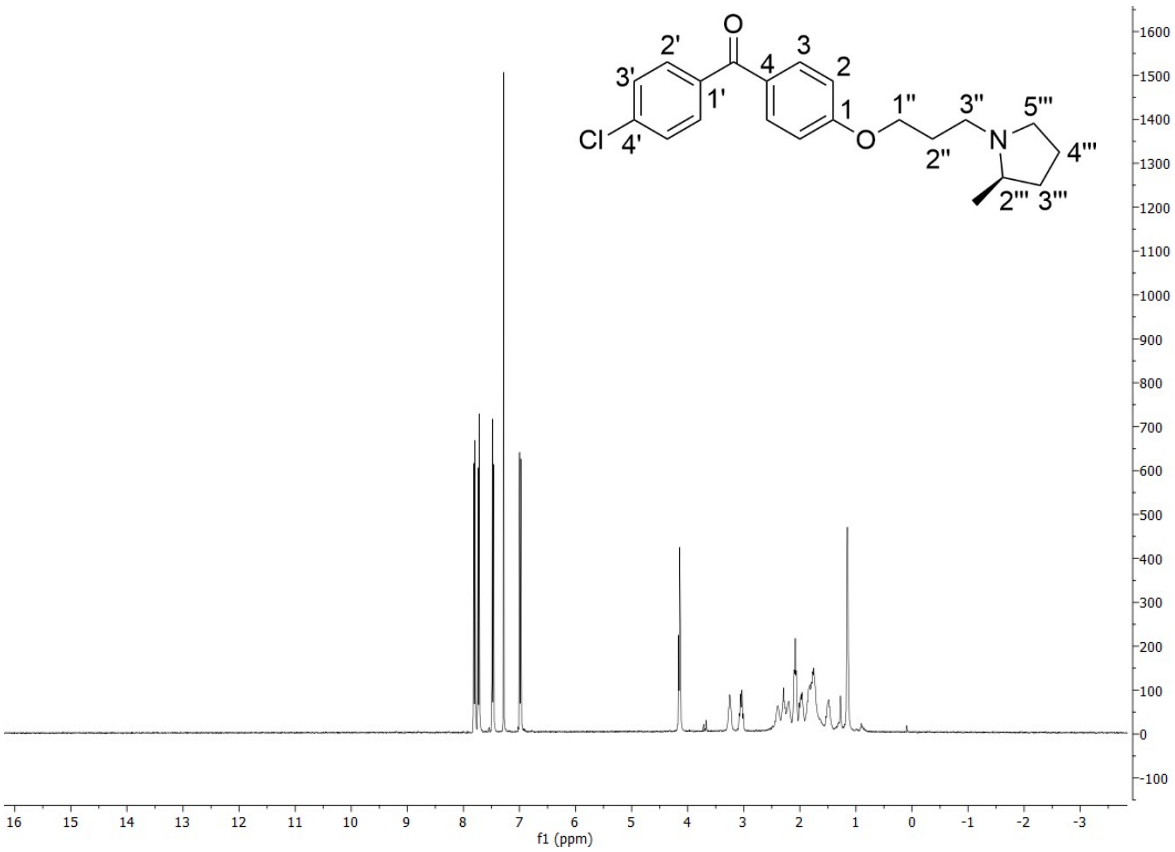


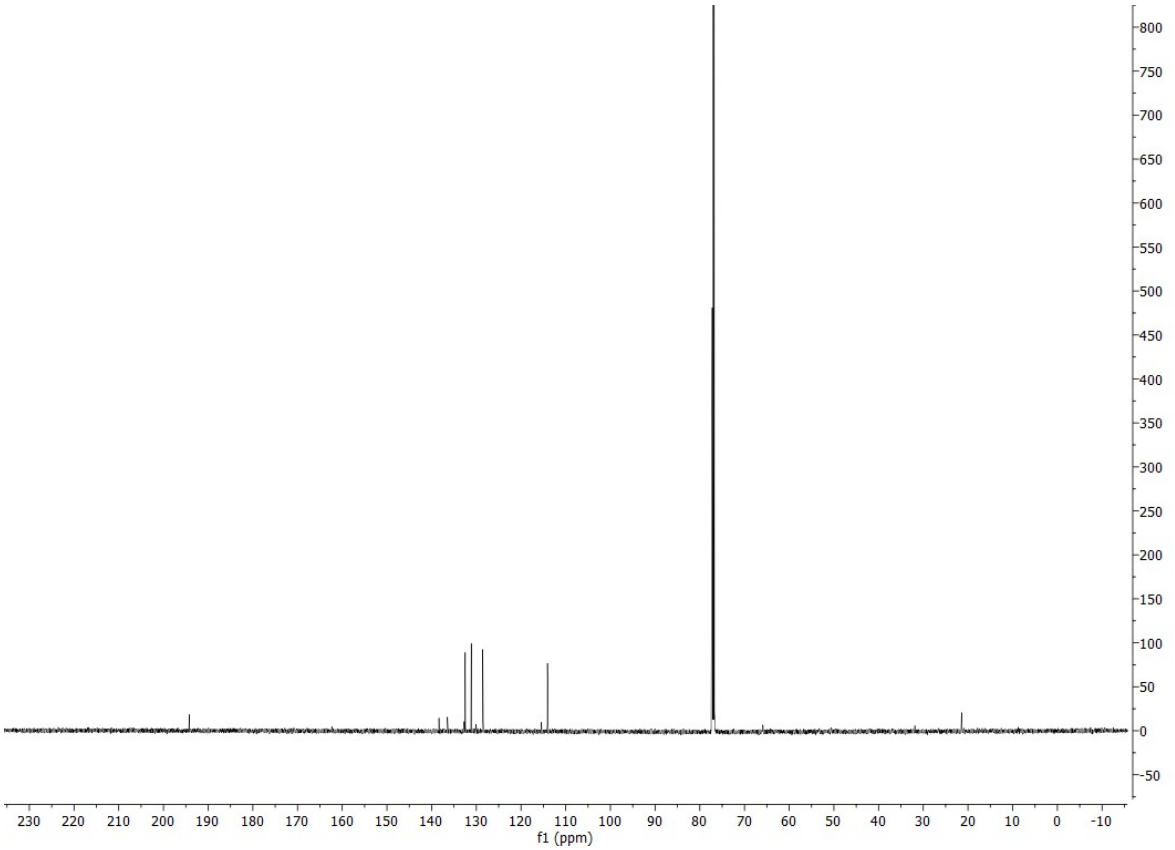




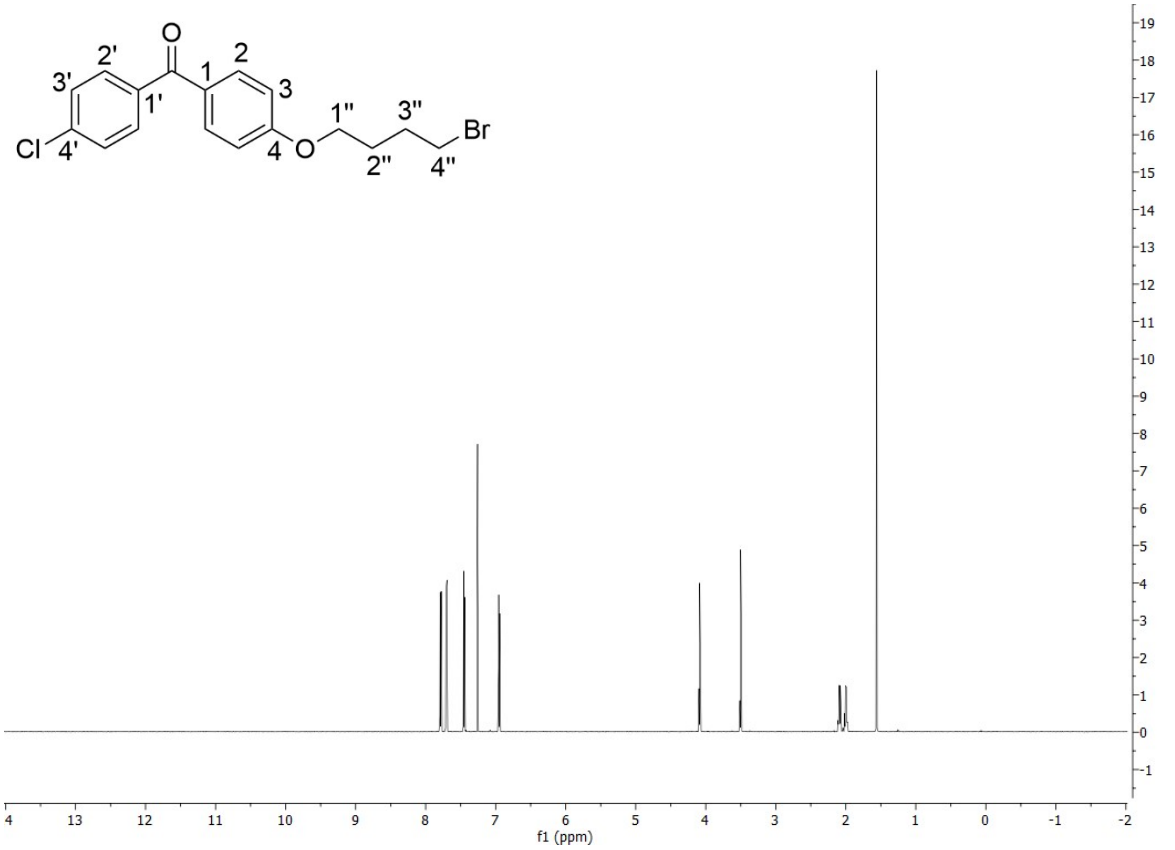


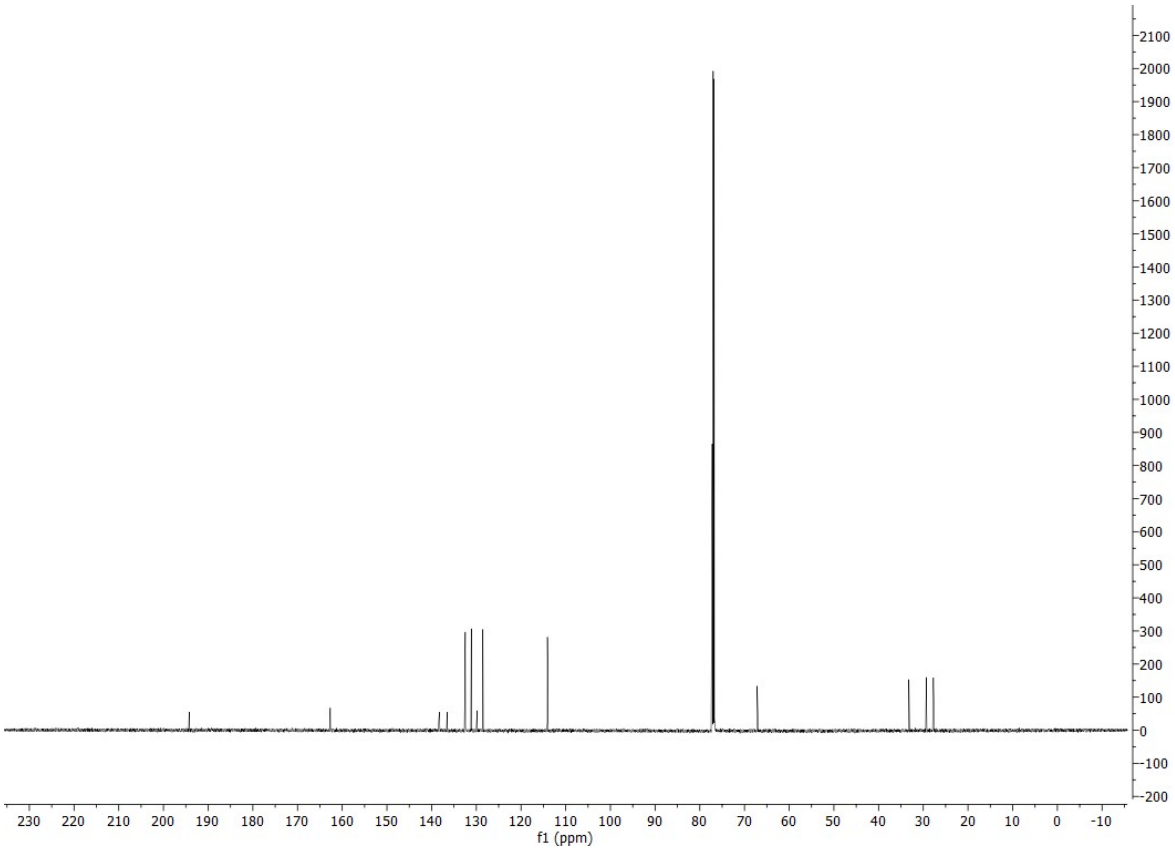
**(2’’’*R*)-*N*-{3’’-[4-(4’-chlorobenzoyl)phenoxy]propyl}-2’’’-methylpyrrolidine 30**



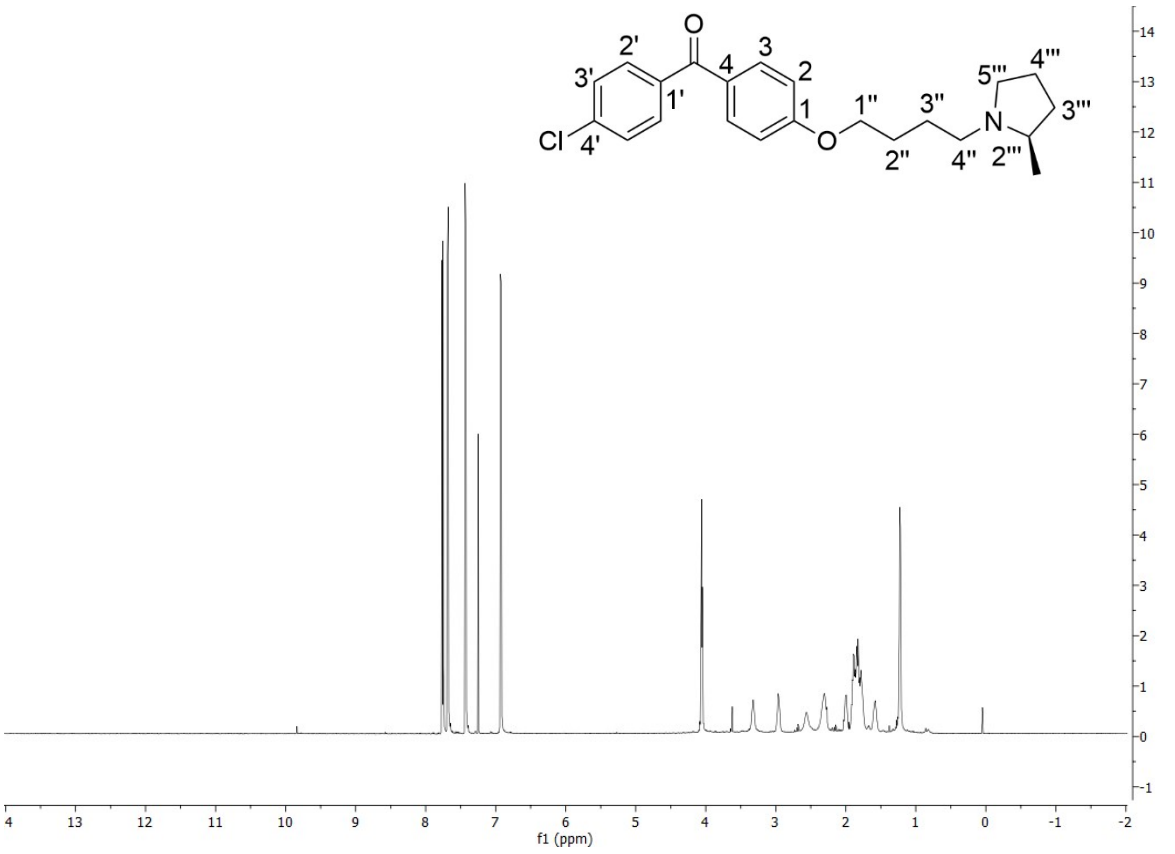



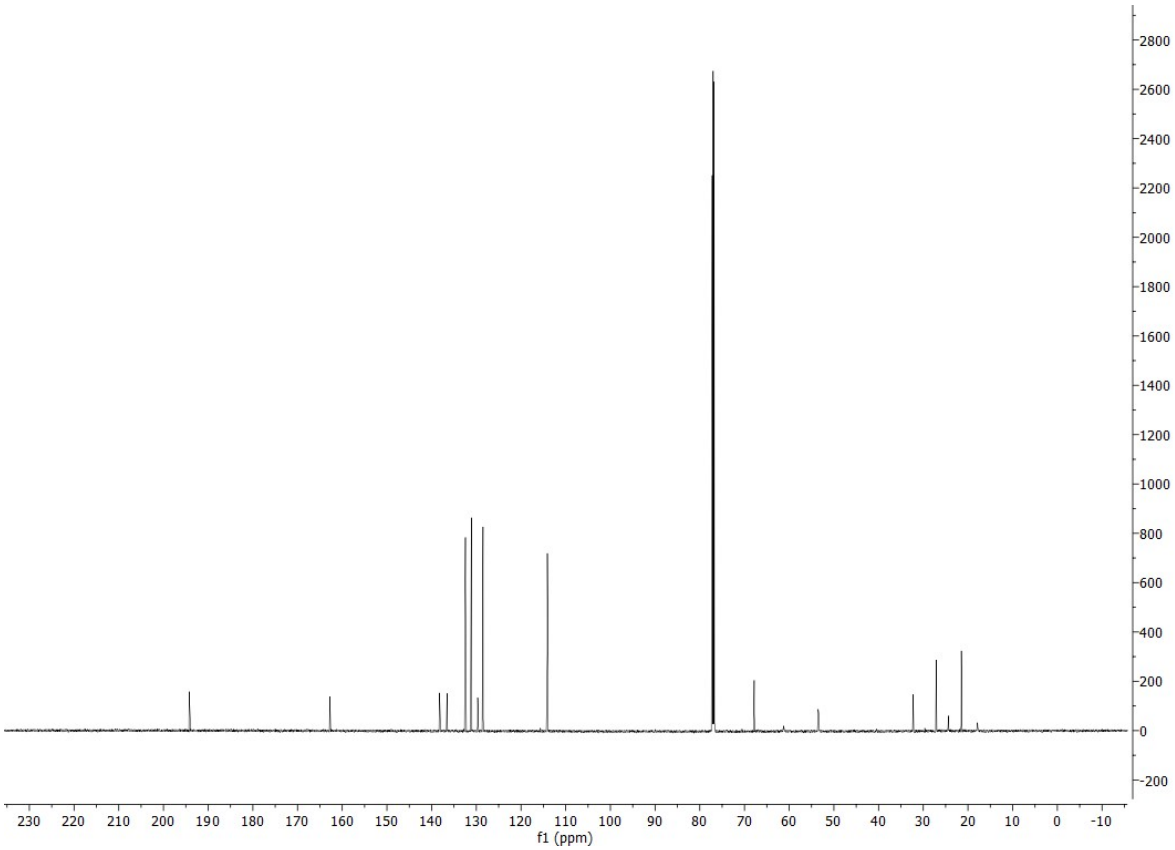
## [4-(4’’-bromobutoxy)phenyl](4’-chlorophenyl)methanone 31a



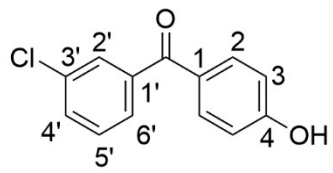



**(2’’’*R*)-*N*-{4’’-[4-(4’-chlorobenzoyl)phenoxy]butyl}-2’’’-methylpyrrolidine 31**



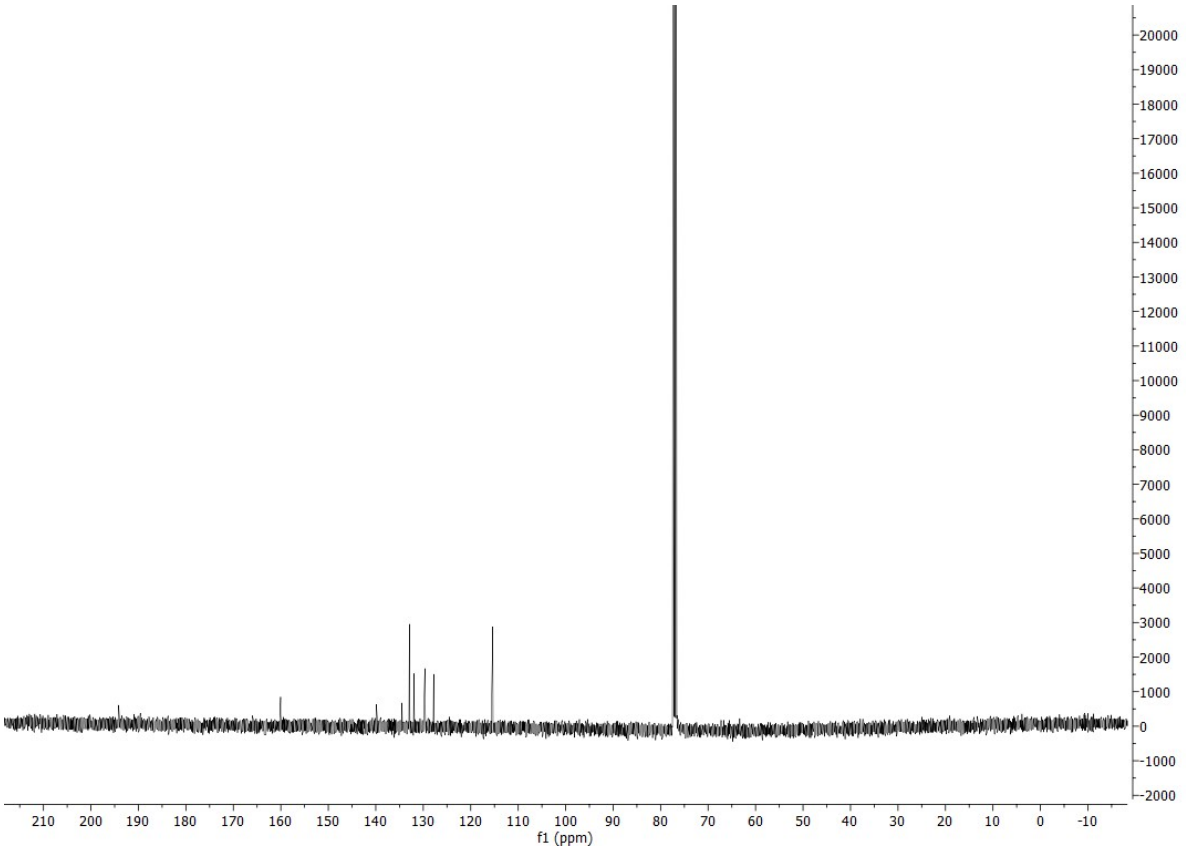



## 4-(3’-chlorobenzoyl)phenol E

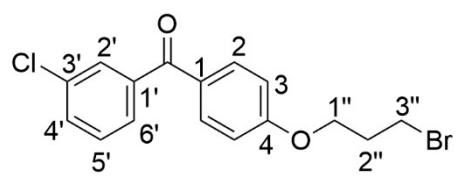






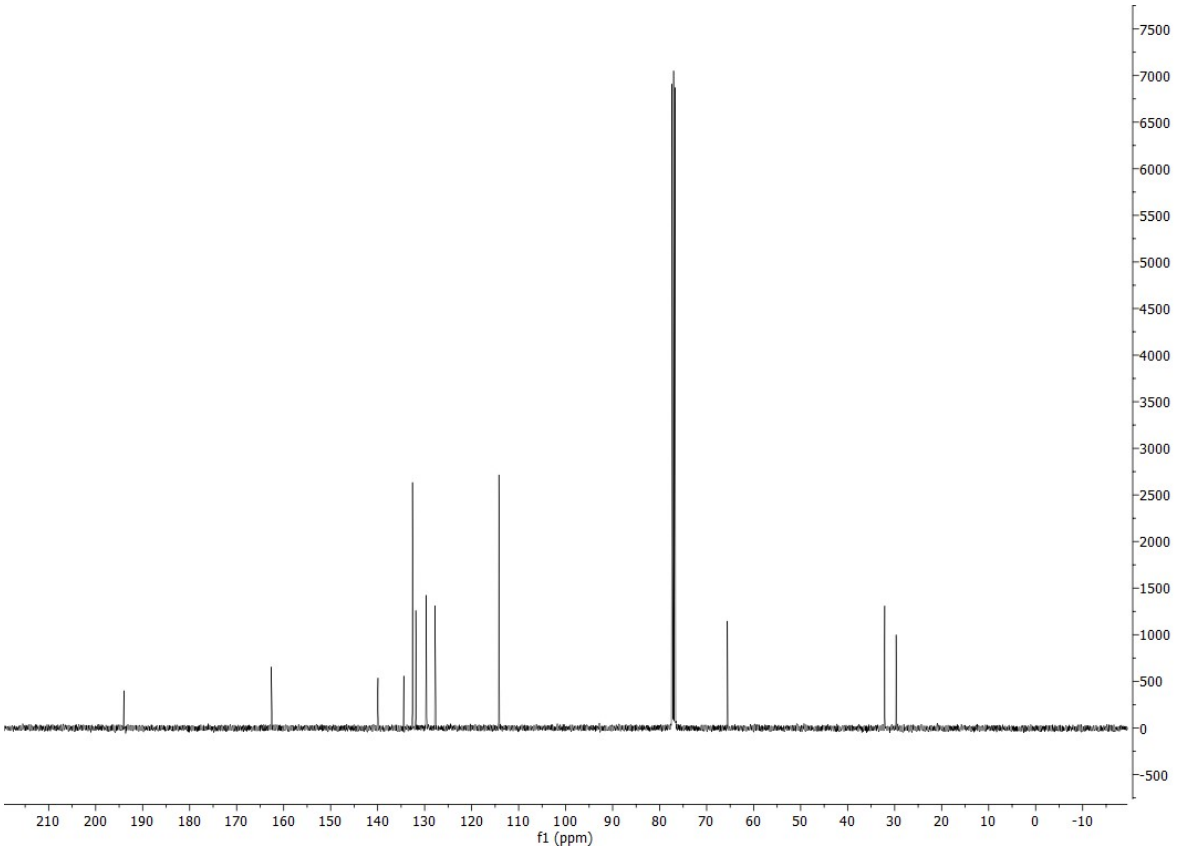


## [4-(3’’-bromopropoxy)phenyl](3’-chlorophenyl)methanone 32a

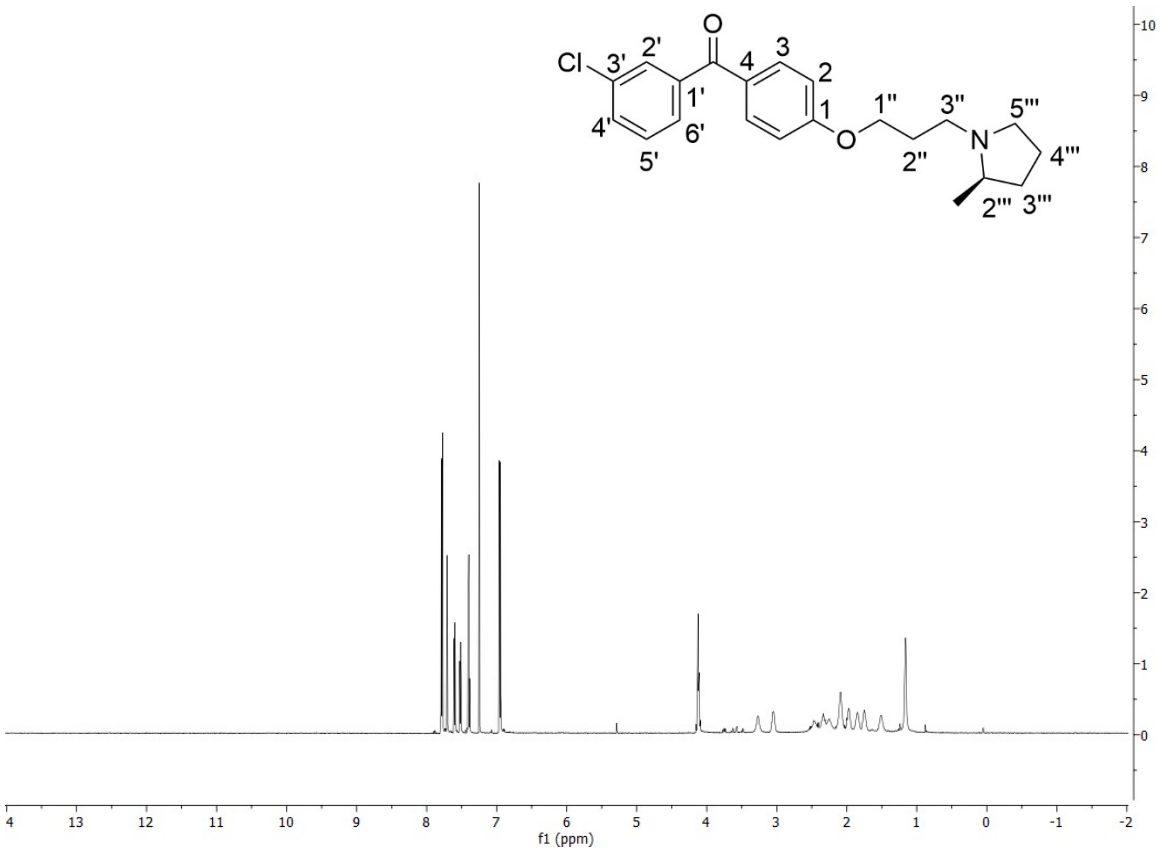


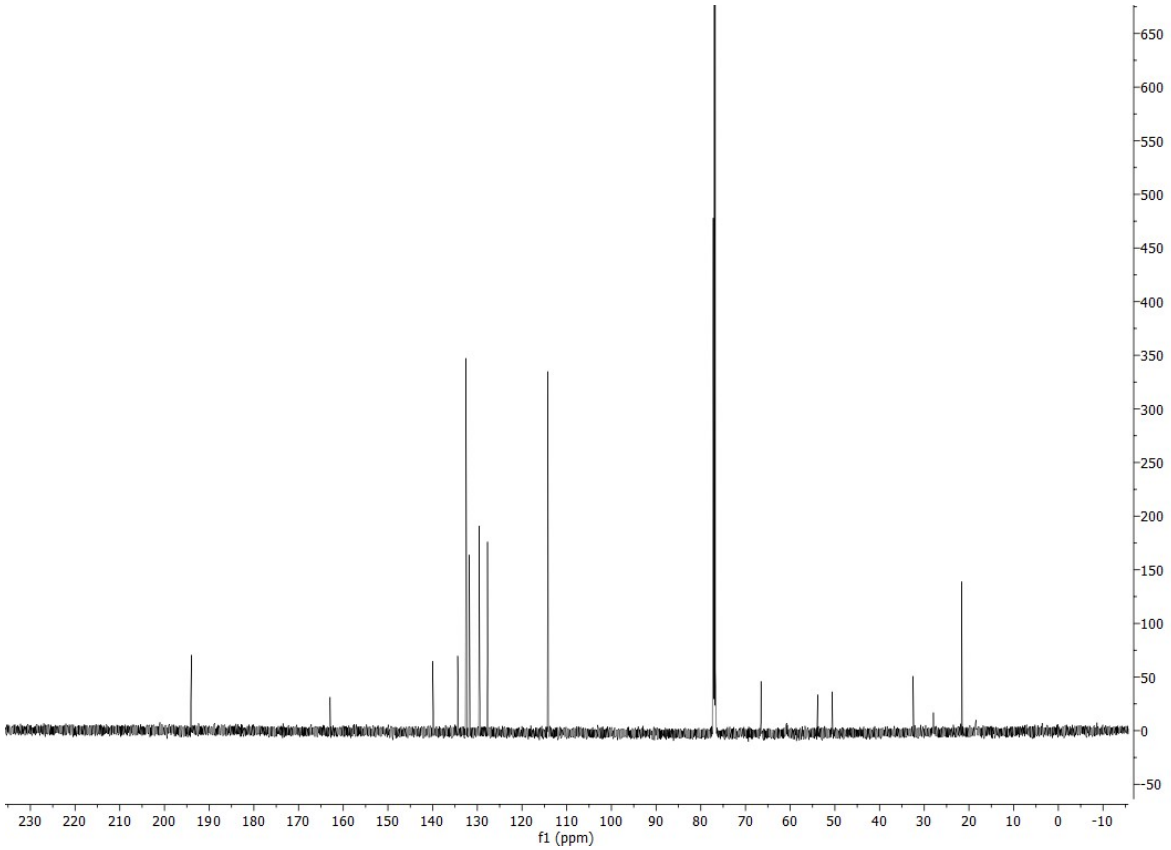




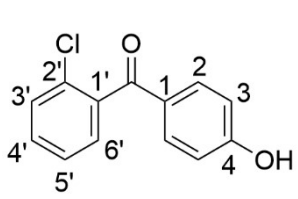


**(2’’’*R*)-*N*-{3’’-[4-(3’-chlorobenzoyl)phenoxy]propyl}-2’’’-methylpyrrolidine 32**



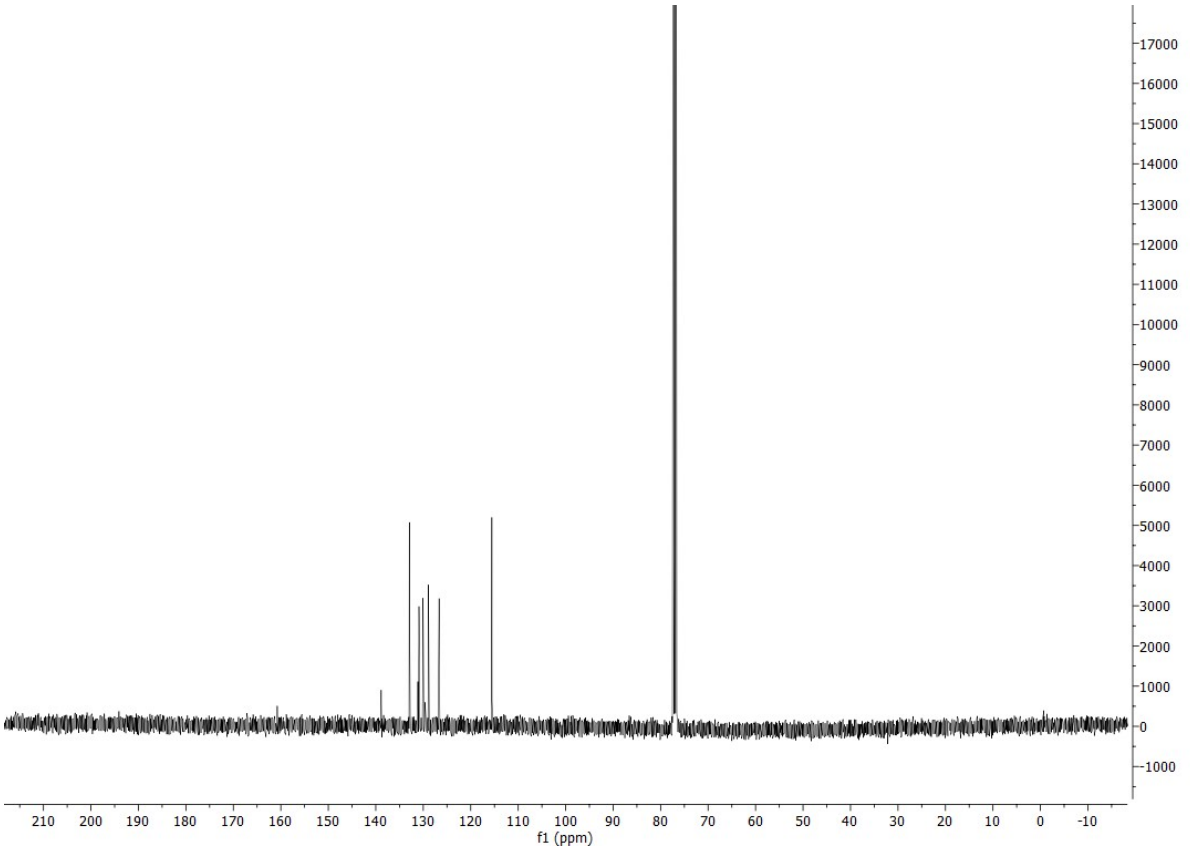



## 4-(2’-chlorobenzoyl)phenol D

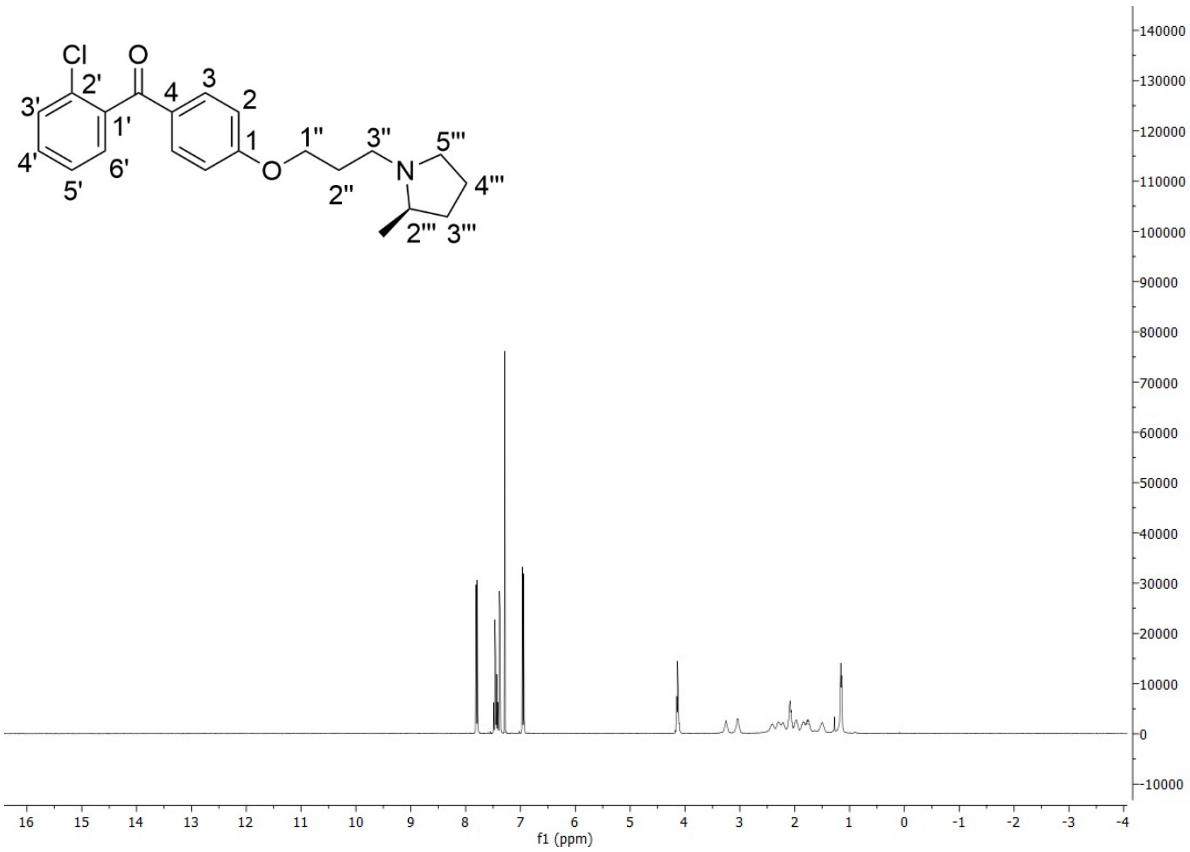


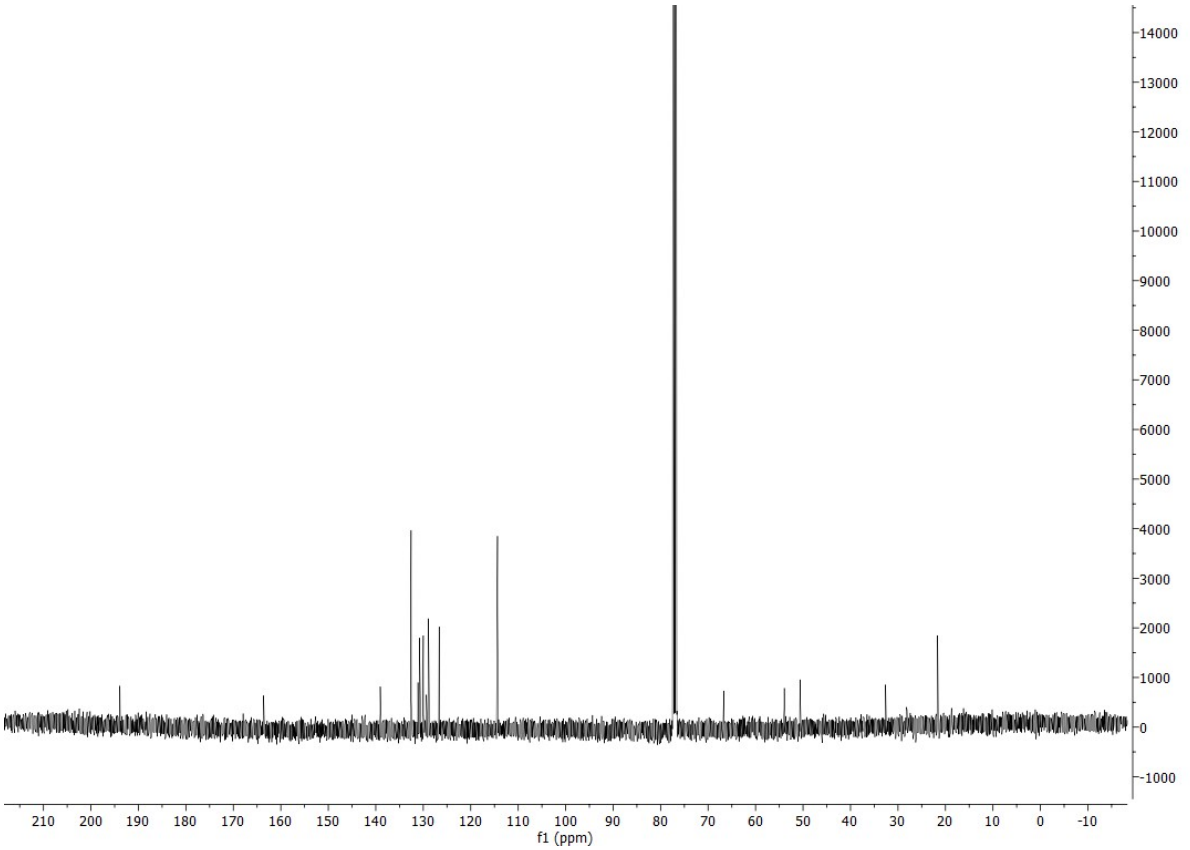




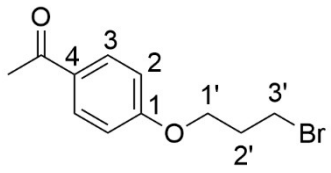


**(2’’’*R*)-*N*-{3’’-[4-(2’-chlorobenzoyl)phenoxy]propyl}-2’’-methylpyrrolidine 33**



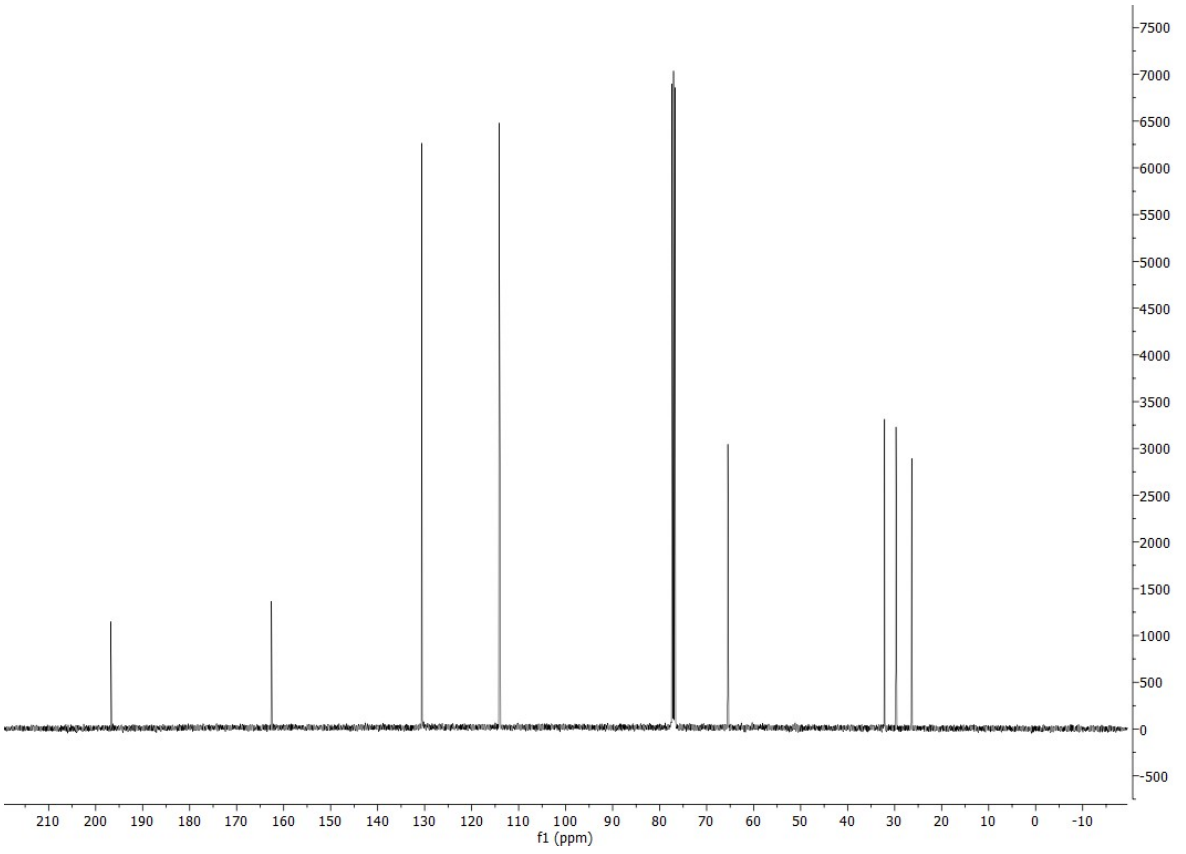



## 4-[1-(3’-bromopropoxy)phenyl]ethenone 35a

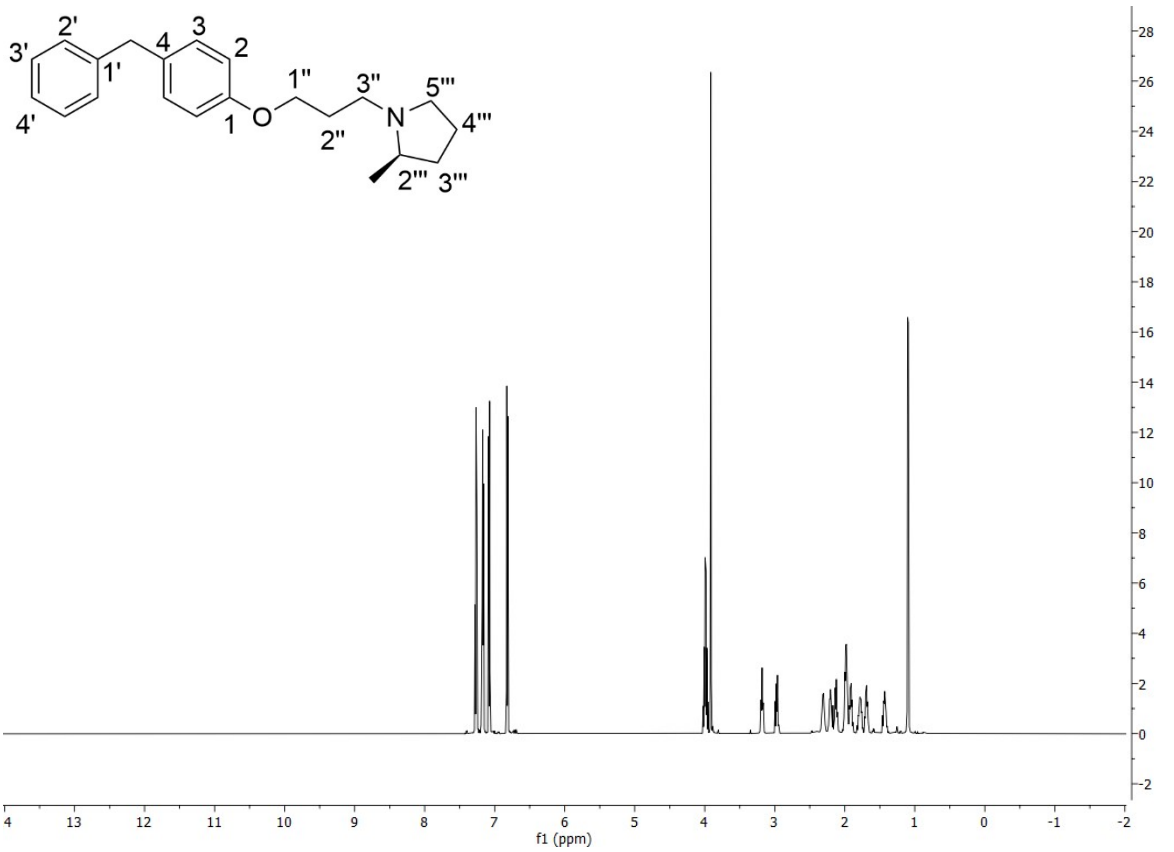


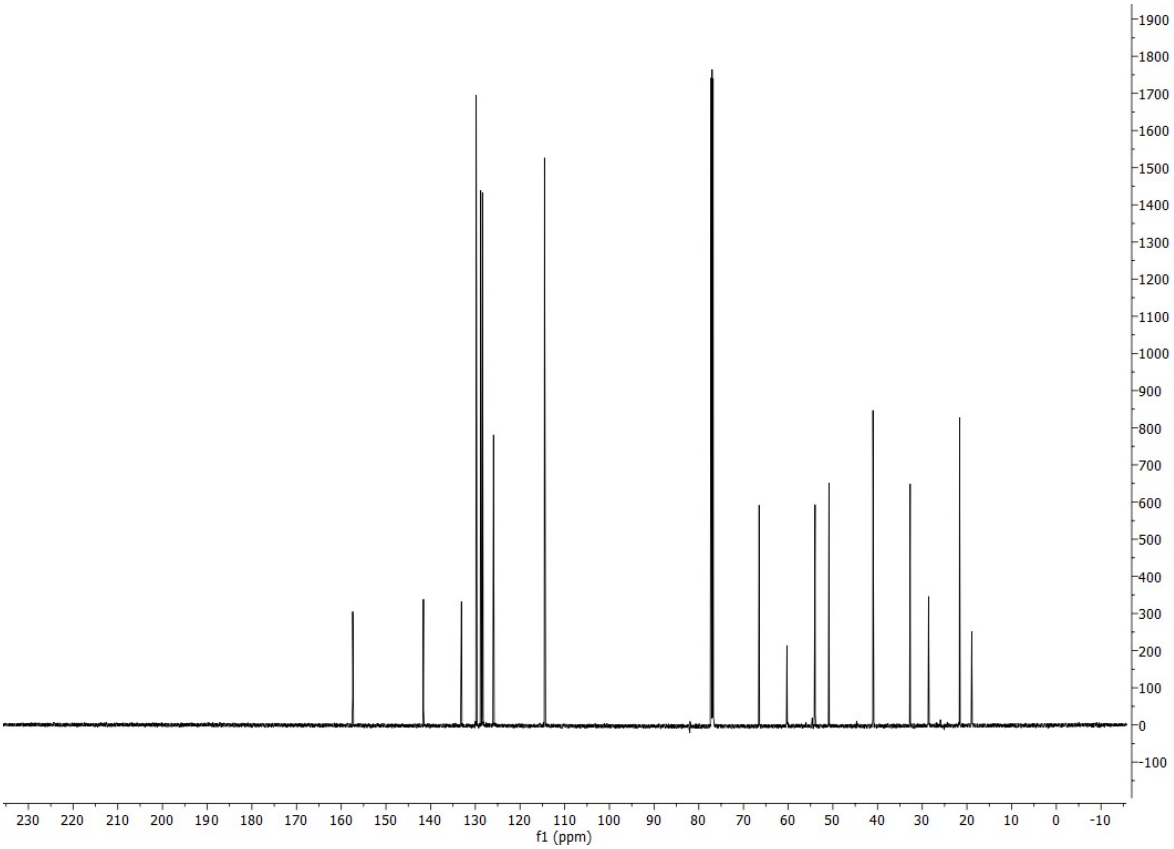




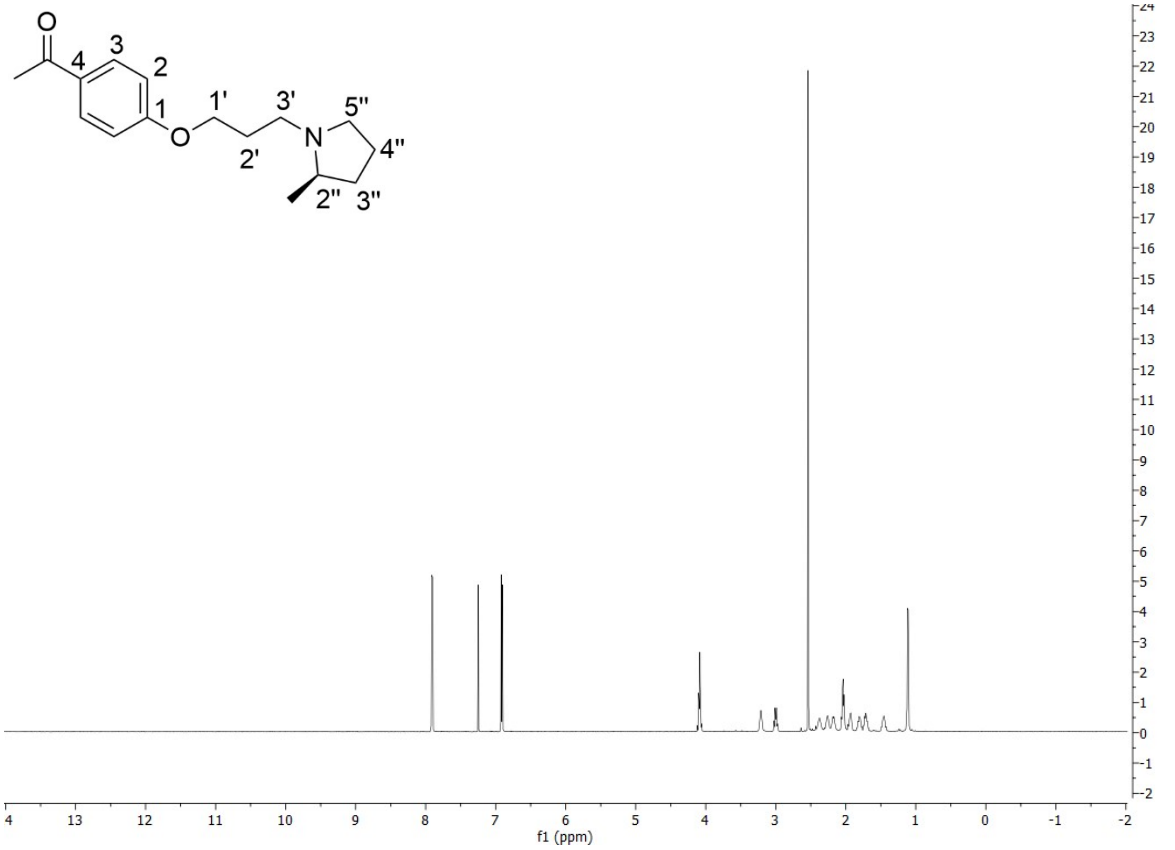


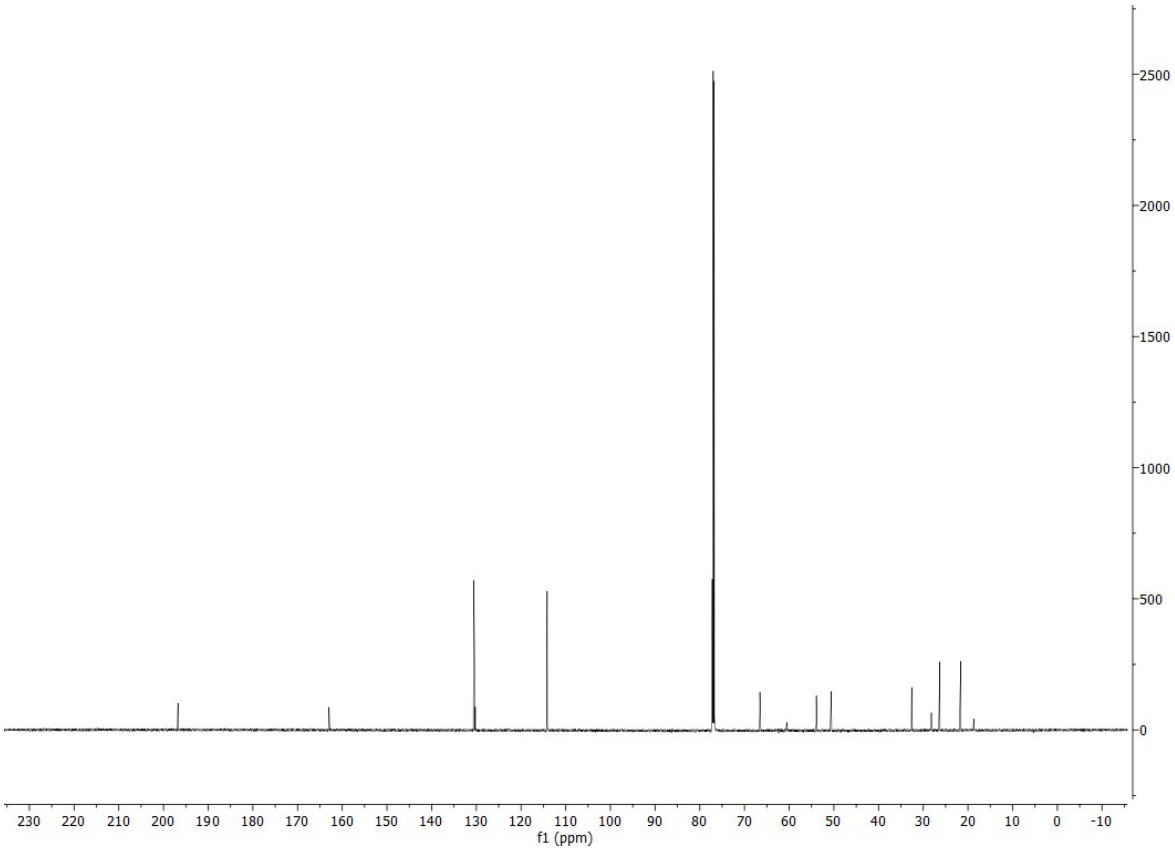
**(2’’’*R*)-N-[3’’-(4-benzylphenoxy)propyl]-2’’’-methylpyrrolidine 34**



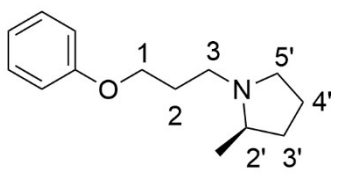



## 4-(1-{3’-[(2’’*R*)-2’’-methylpyrrolidine]propoxy}phenyl)ethenone 35



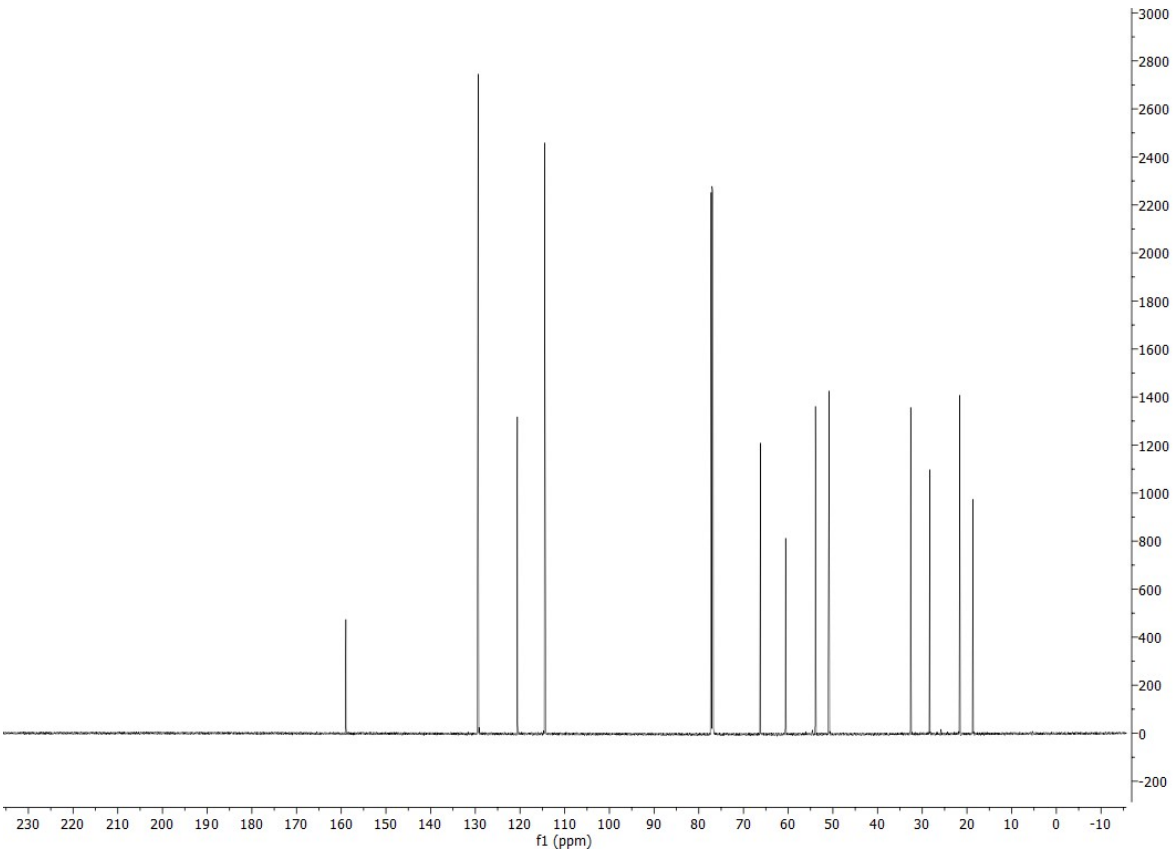



**(2'*R*)-2'-methyl-*N*-(3-phenoxypropyl)pyrrolidine 36**

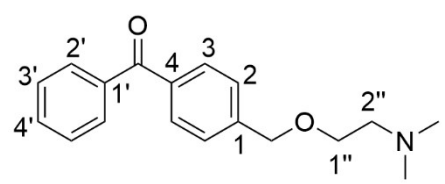






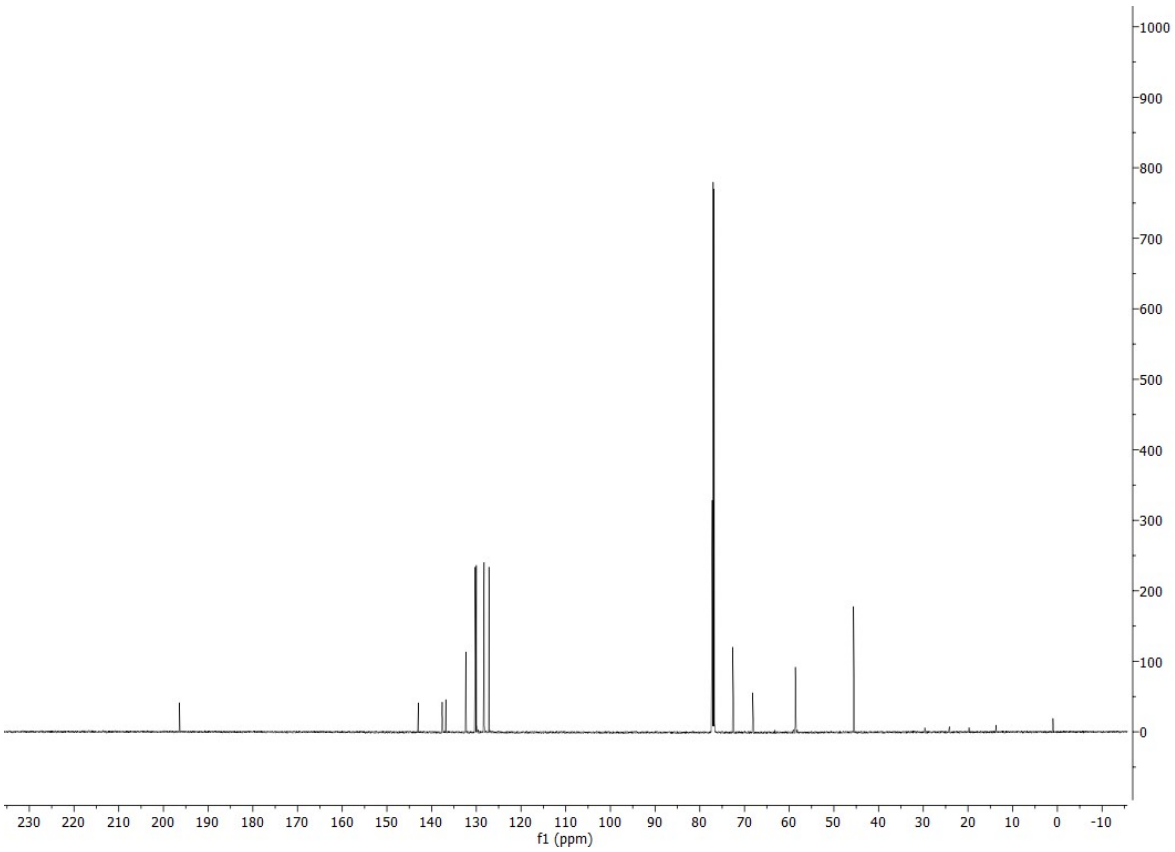


**{2’’-[(4-benzoylphenyl)methoxy]ethyl}dimethylamine 37**









**{3’’-[(4-benzoylphenyl)methoxy]propyl}dimethylamine 38**