# Sequential Alcohol Oxidation/ Putative Homo Claisen-Tishchenko-Type Reaction to give esters: A Key process in accessing Novel Biologically active Lactone Macrocycles

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## Supporting information

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# NMR Spectra ($^{1}$H 400MHz; $^{13}$C 100MHz) of the alcohols substrates (1a)-(1j):

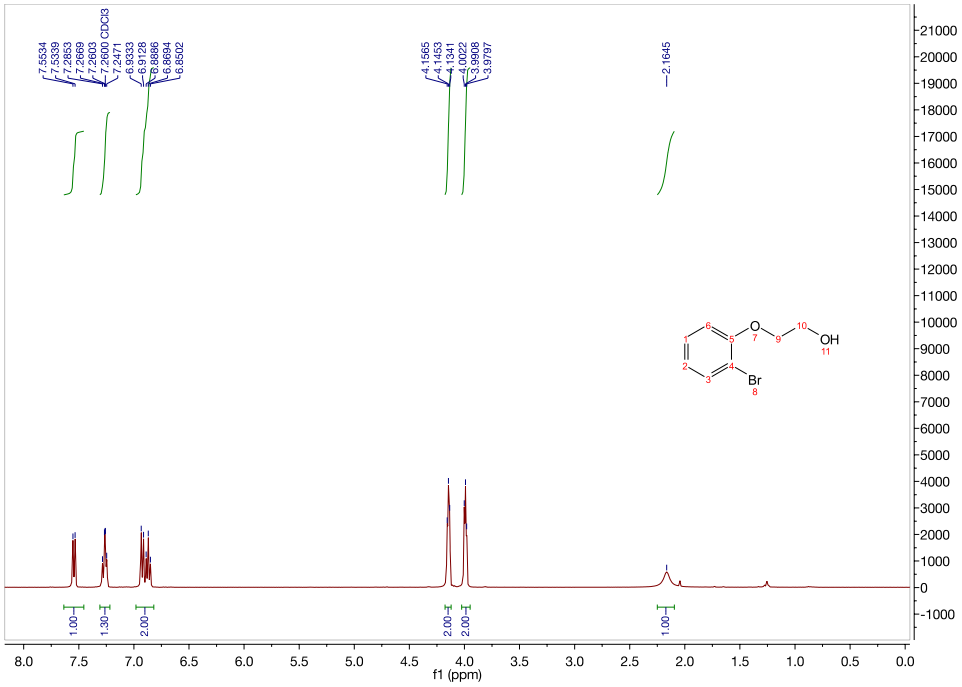


Figure S1. $^{1}$H NMR spectrum of (2-bromophenoxy)ethanol (**1a**) in $CDCl_3$.

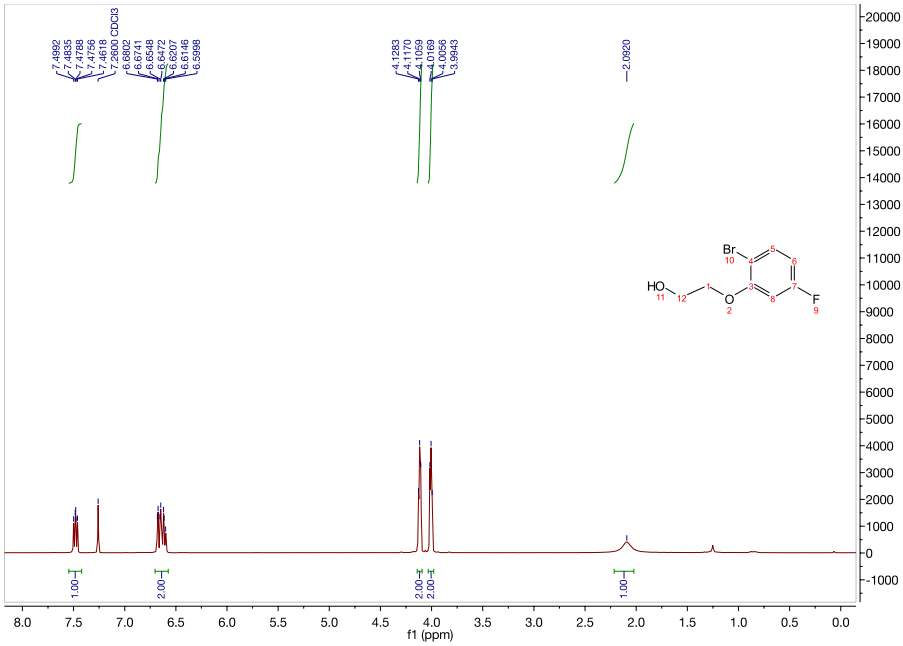

Figure S2. $^{1}$H NMR spectrum of 2-(2-bromo-5-fluorophenoxy)ethanol (**1b**) in $CDCl_3$.

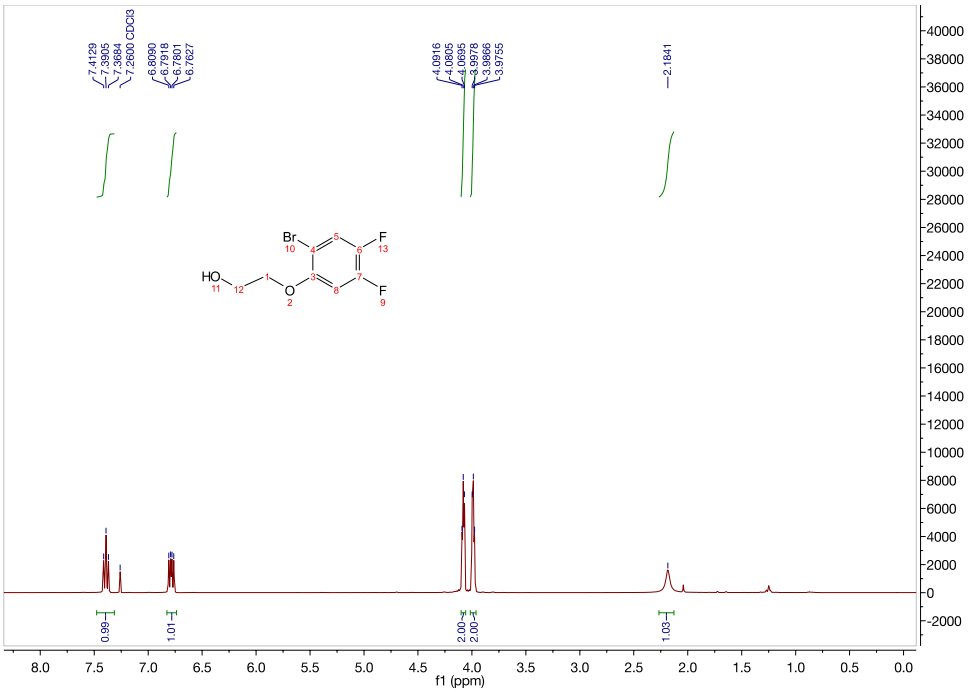


Figure S3. $^{1}$H NMR spectrum of 2-(2-bromo-4,5-difluorophenoxy)ethanol (**1c**) in $CDCl_3$.

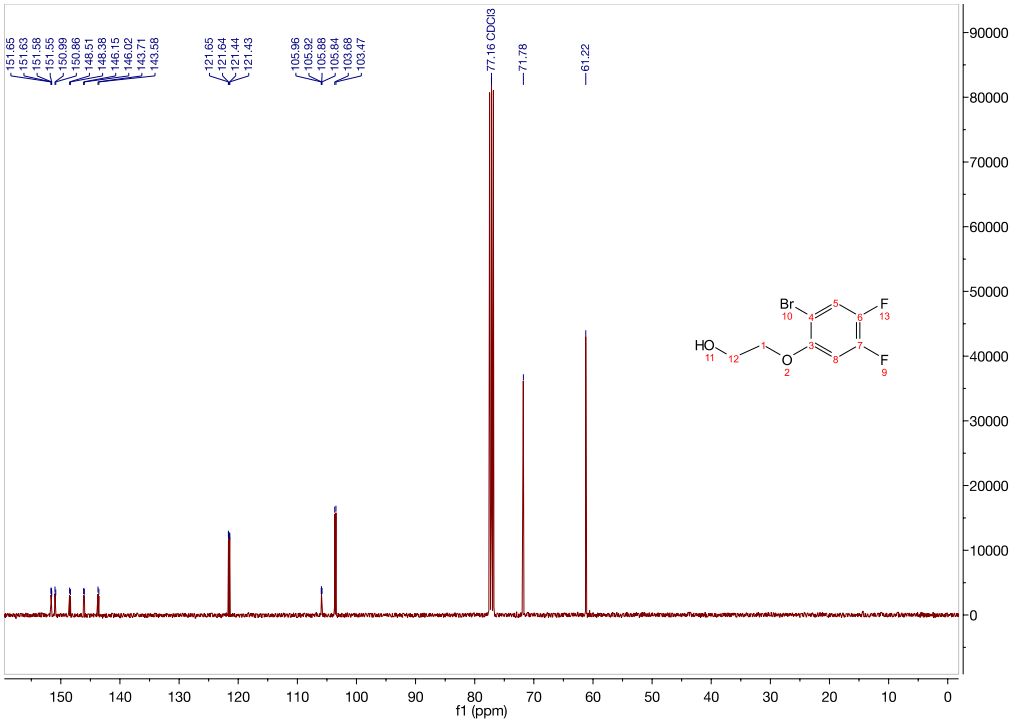


Figure S4. $^{13}$C NMR spectrum of 2-(2-bromo-4,5-difluorophenoxy)ethanol (**1c**) in $CDCl_3$.

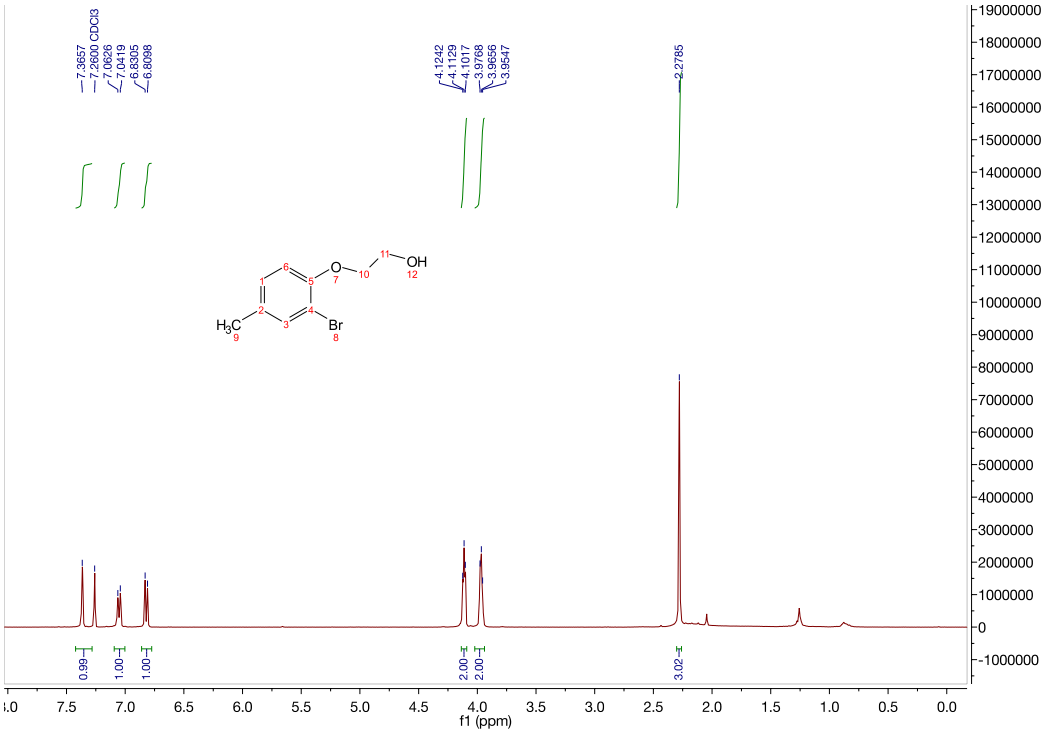


Figure S5. $^{1}$H NMR spectrum of 2-(2-bromo-4-methylphenoxy)ethanol (**1d**) in $CDCl_3$.

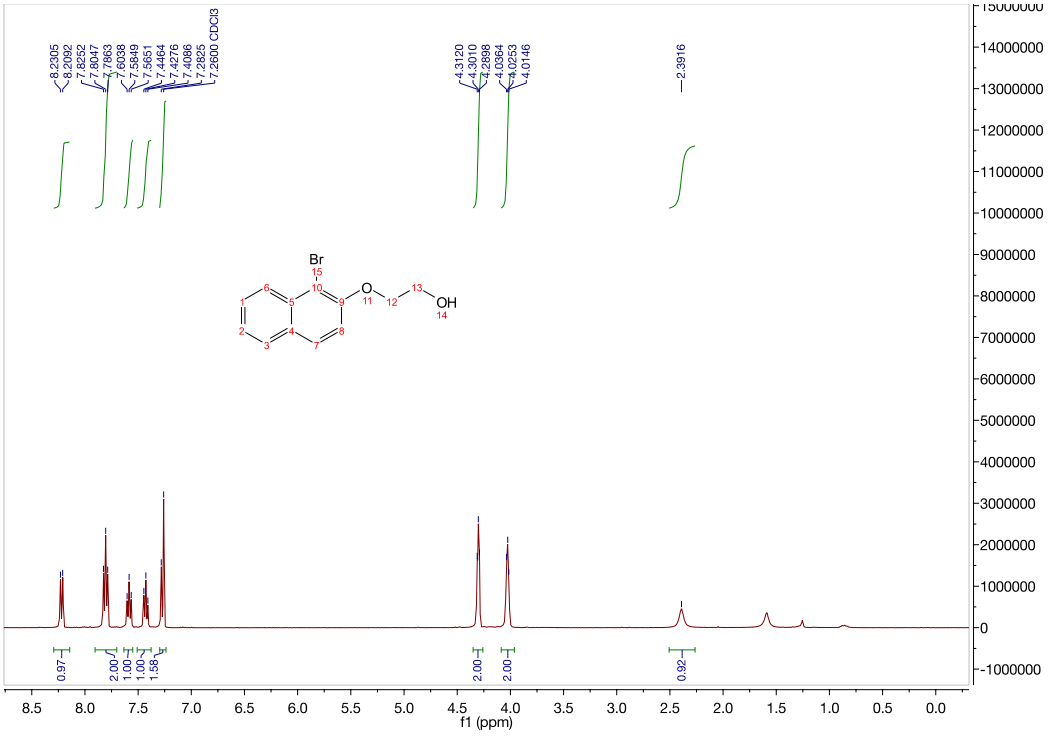


Figure S6. $^{1}$H NMR spectrum of 2-(1-bromonaphth-2-yloxy)ethanol (**1e**) in $CDCl_3$.

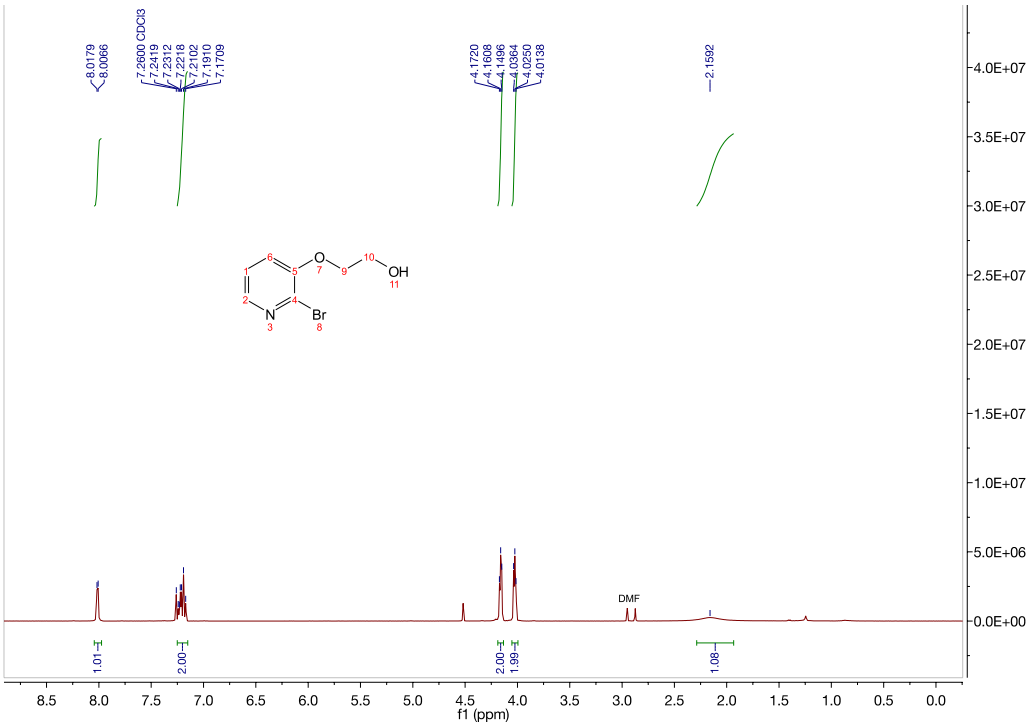


Figure S7. $^{1}$H NMR spectrum of 2-((2-bromopyridin-3-yl)oxy)ethanol (**1f**) in $CDCl_3$.

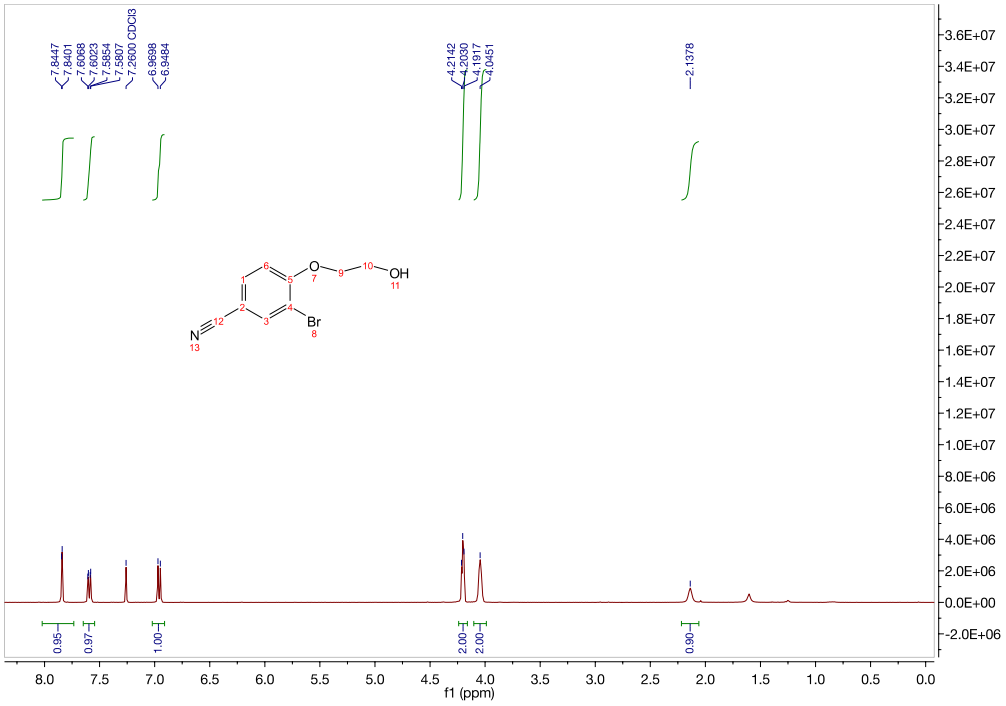


Figure S8. $^{1}$H NMR spectrum of 2-(2-bromo-4-cyanophenoxy)ethanol (**1g**) in $CDCl_3$.

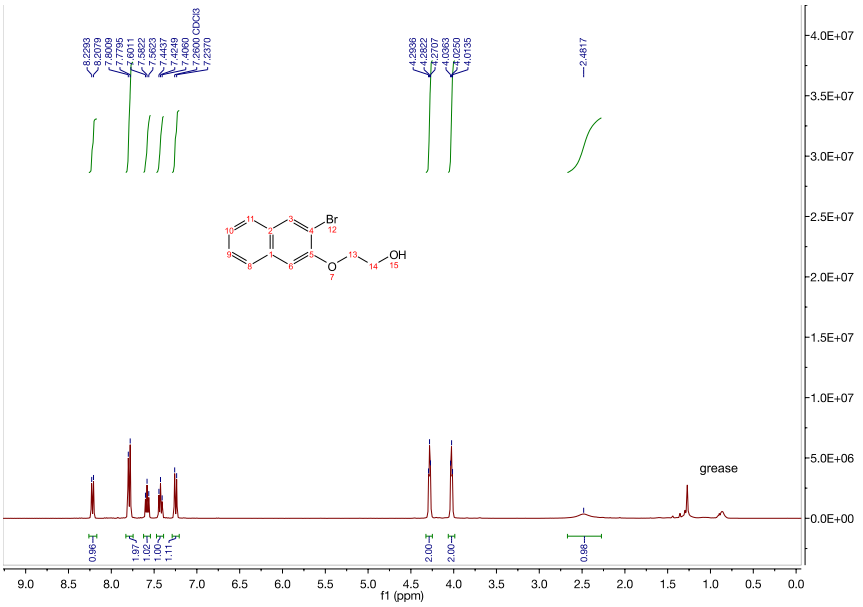


Figure S9. $^{1}$H NMR spectrum of 2-(3-bromonaphthalenoxy)ethanol (**1h**) in $CDCl_3$.

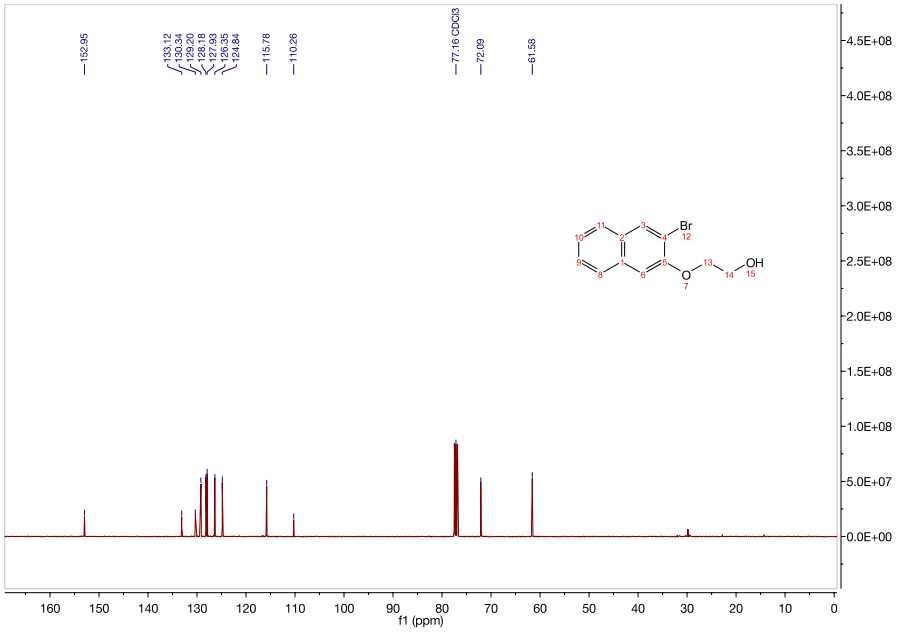


Figure S10. $^{13}$C NMR spectrum of 2-(3-bromonaphthalenoxy)ethanol (**1h**) in $CDCl_3$.

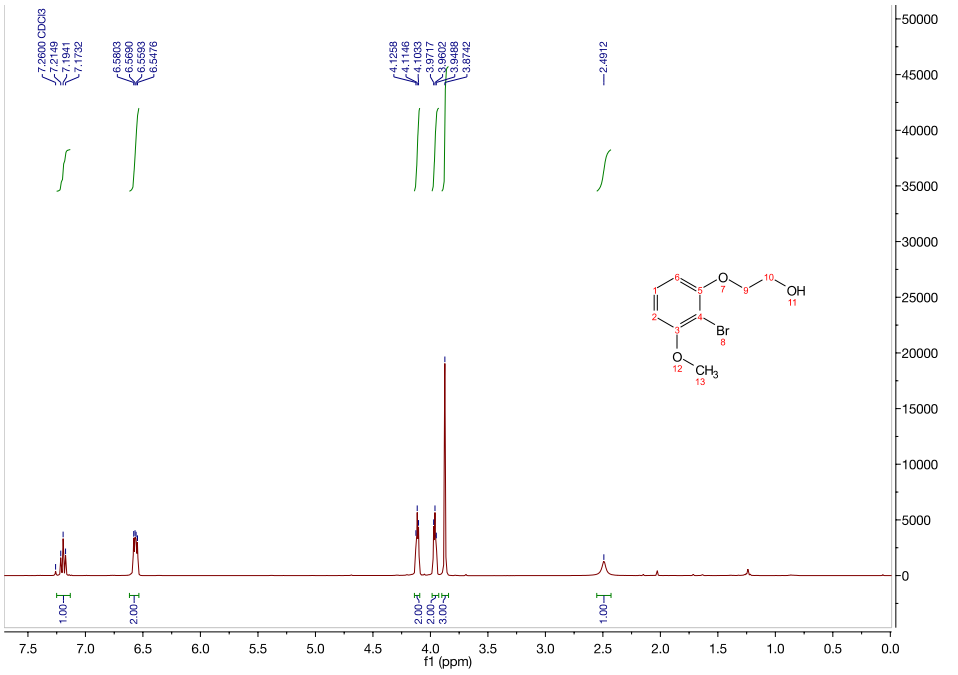


Figure S11. $^{1}$H NMR spectrum of 2-(2-bromo-3-methoxyphenoxy)ethanol (**1i**) in $CDCl_3$.

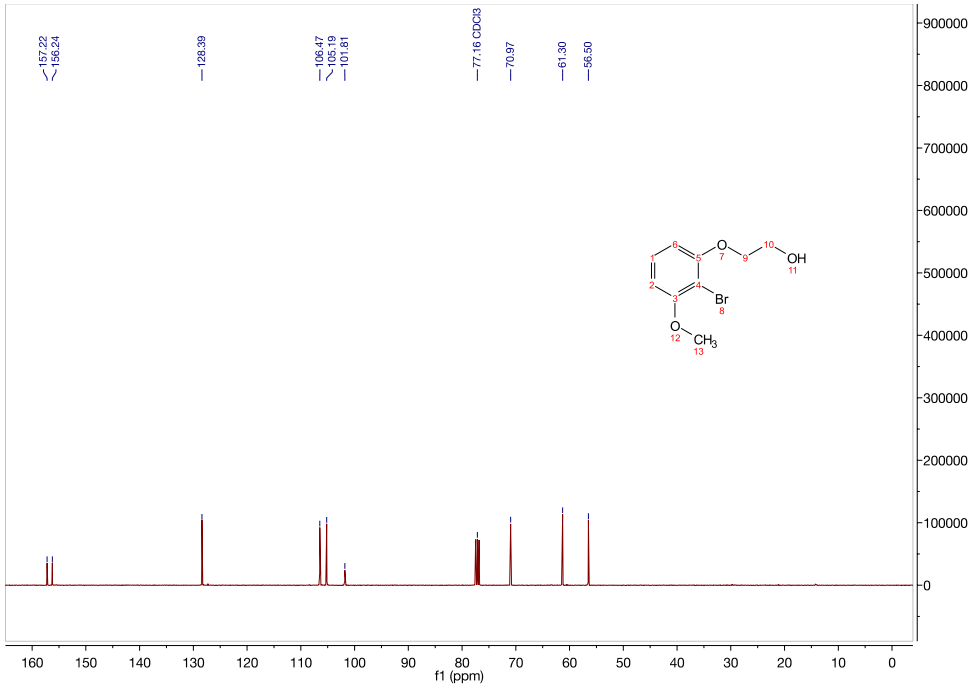


Figure S12. $^{13}$C NMR spectrum of 2-(2-bromo-3-methoxyphenoxy)ethanol (**1i**) in $CDCl_3$.

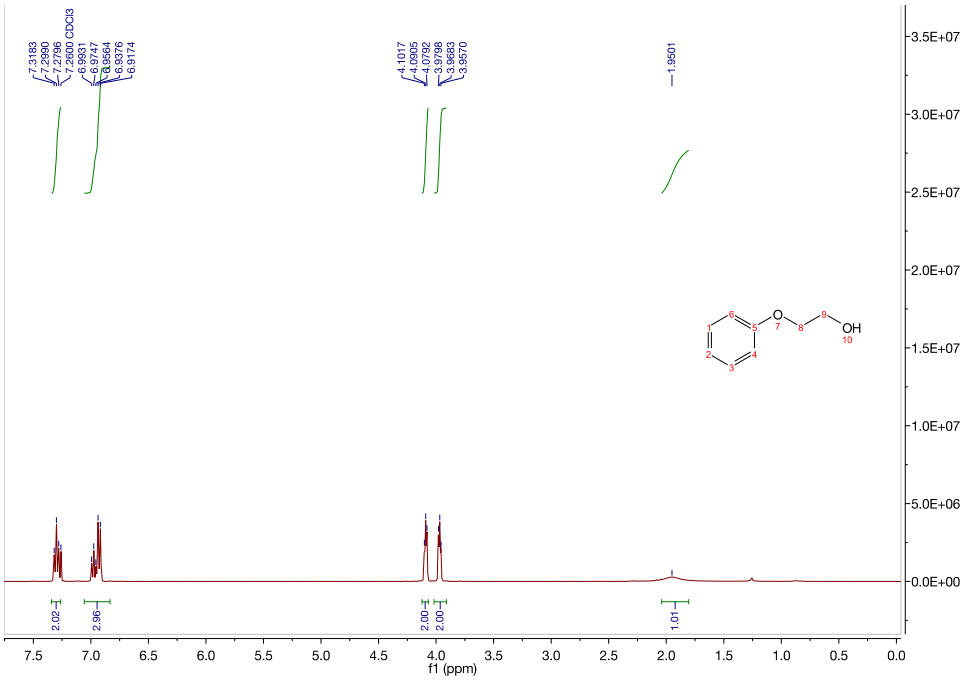


Figure S13. $^{1}H$ NMR spectrum of 2-(phenoxy)ethanol (**1j**) in $CDCl_3$. (http://dx.doi.org/10.1016/j.molcatb.2015.03.010 )

## NMR Spectra ($^{1}$H 400MHz; $^{13}$C 100MHz) of the ester products (2a)-(2j):

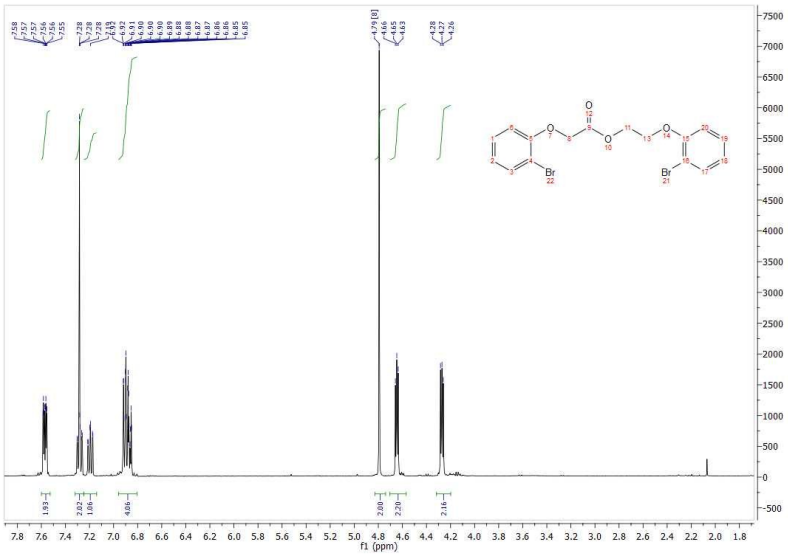

Figure S14. $^{1}$H NMR spectrum of 2-(2-bromophenoxy)ethyl 2-(2-bromophenoxy)acetate (**2a**) in $CDCl_3$.

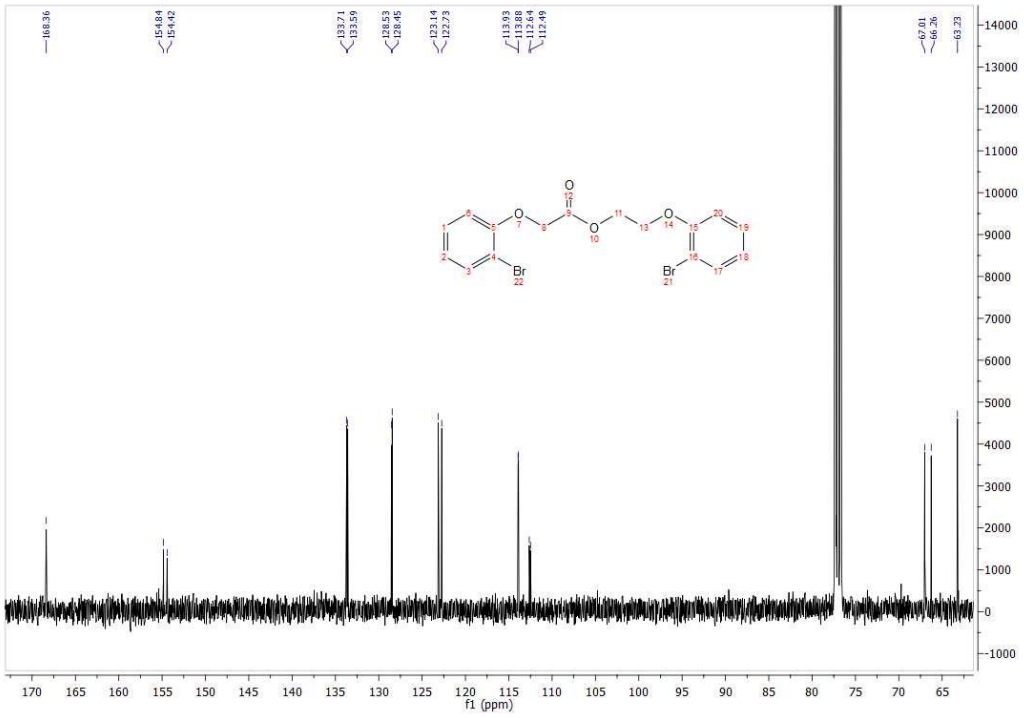

Figure S15. $^{13}$C NMR spectrum of 2-(2-bromophenoxy)ethyl 2-(2-bromophenoxy)acetate (**2a**) in $CDCl_3$**.**

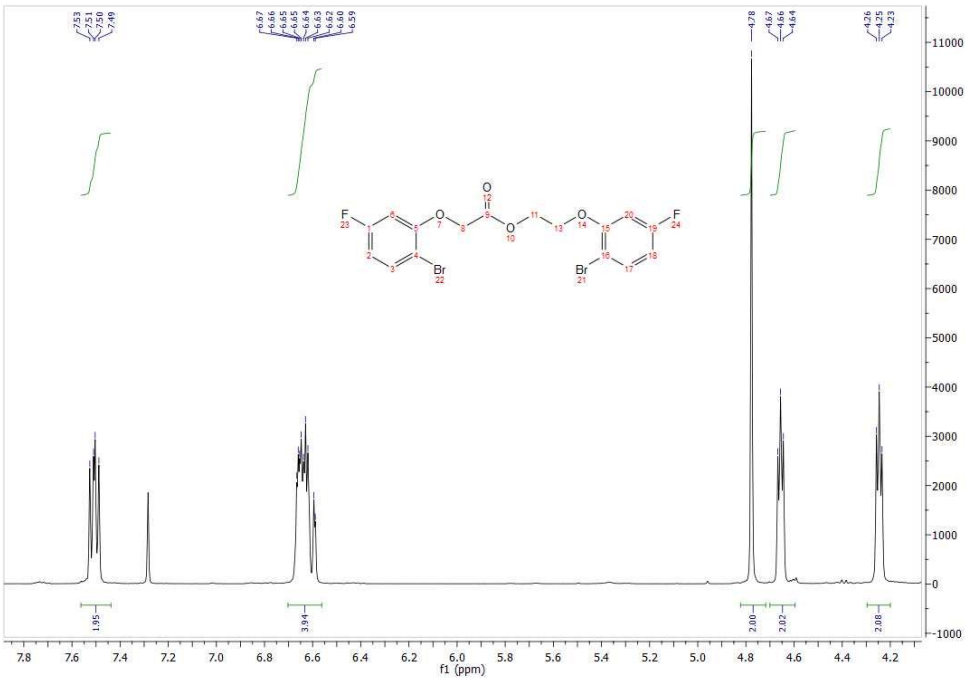

Figure S16. $^{1}$H NMR spectrum of 2-(2-bromo-5-fluorophenoxy)ethyl 2-(2-bromo-5-fluorophenoxy)acetate (**2b**) in $CDCl_3$.

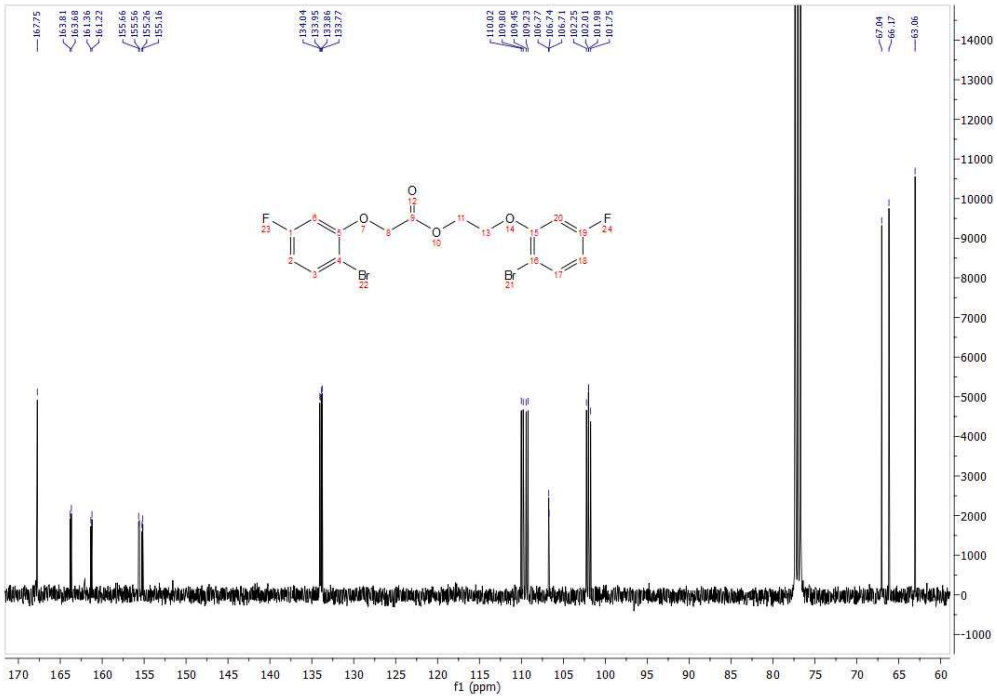

Figure S17. $^{13}$C NMR spectrum of 2-(2-bromo-5-fluorophenoxy)ethyl 2-(2-bromo-5-fluorophenoxy)acetate (**2b**) in $CDCl_3$.

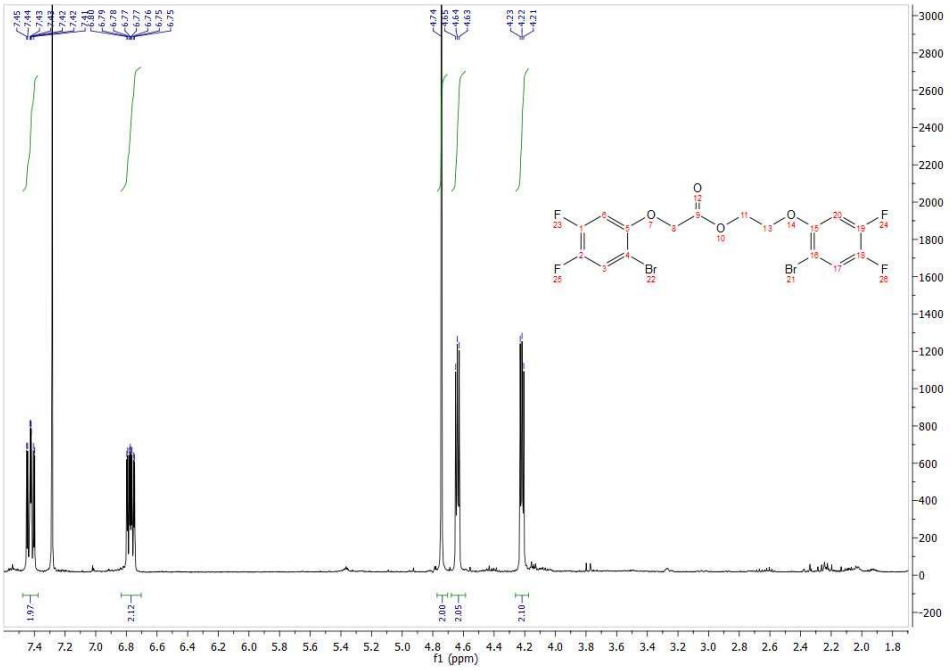

Figure S18. $^{1}$H NMR spectrum of 2-(2-bromo-4,5-difluorophenoxy)ethyl 2-(2-bromo-4,5-difluorophenoxy)acetate (**2c**) in $CDCl_3$.

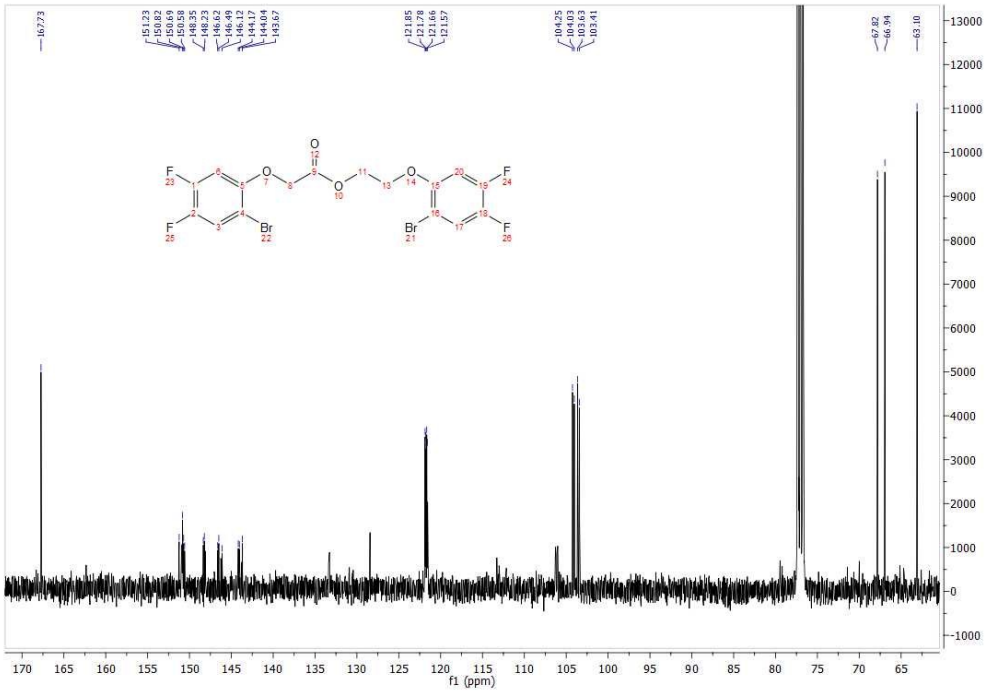

Figure S19. $^{13}$C NMR spectrum of 2-(2-bromo-4,5-difluorophenoxy)ethyl 2-(2-bromo-4,5-difluorophenoxy)acetate (**2c**) in $CDCl_3$.

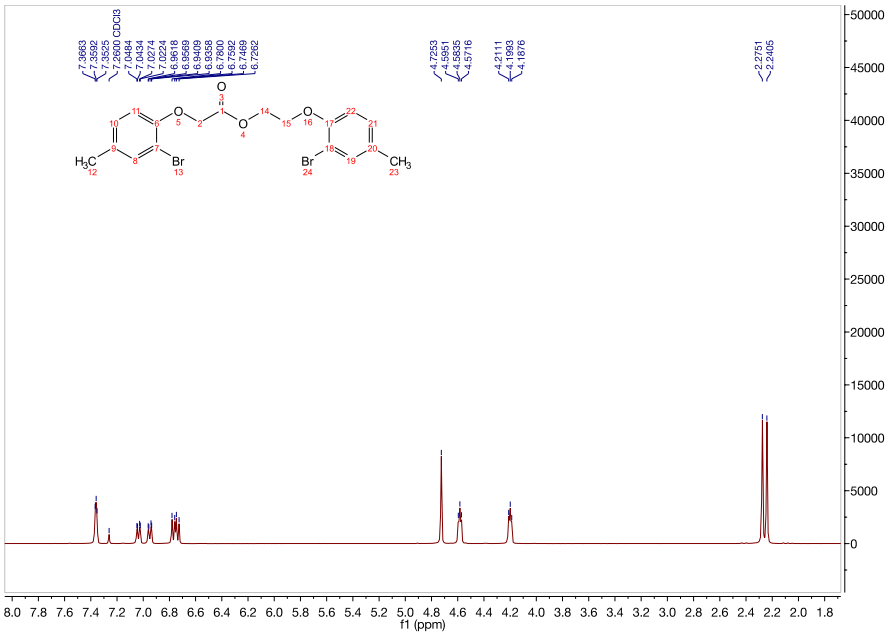

Figure S20. $^{1}$H NMR spectrum of 2-(2-bromo-4-methylphenoxy)ethyl 2-(2-bromo-4-methylphenoxy)acetate (**2d**) in $CDCl_3$.

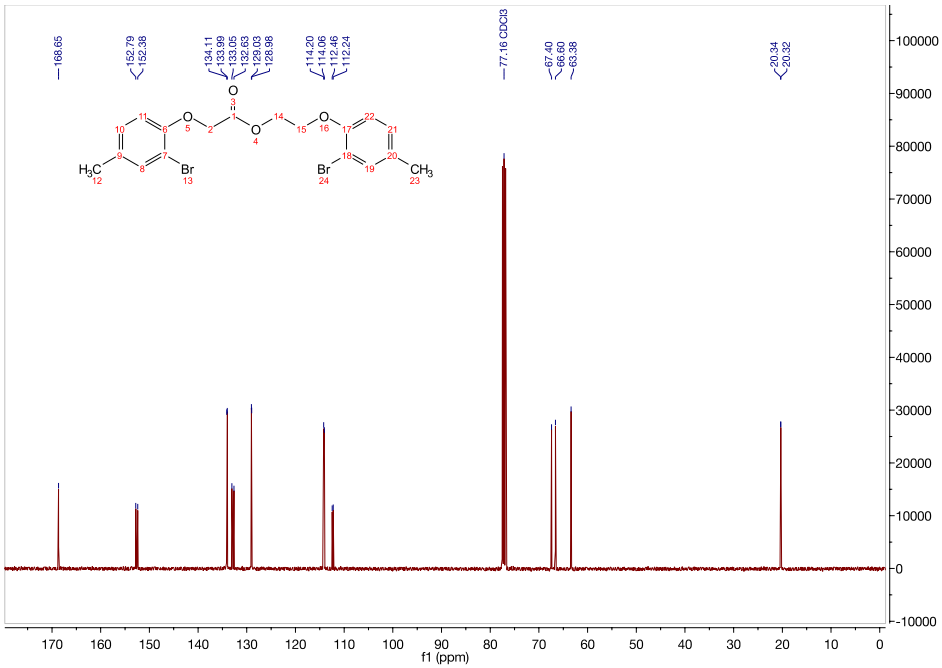

Figure S21. $^{13}$C NMR spectrum of 2-(2-bromo-4-methylphenoxy)ethyl 2-(2-bromo-4-methylphenoxy)acetate (**2d**) in $CDCl_3$.

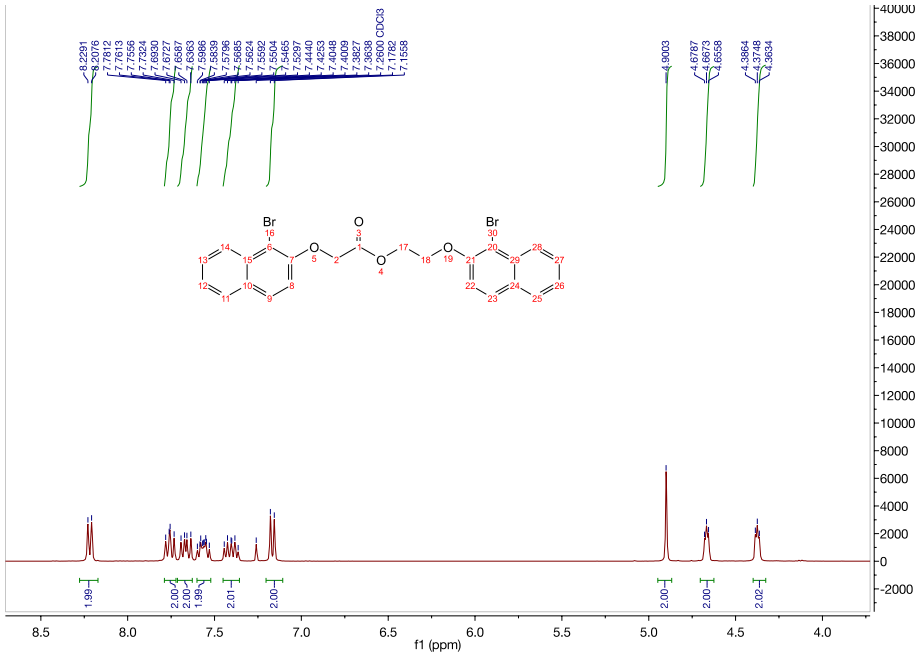

Figure S22. $^{1}$H NMR spectrum of 2-((1-bromonaphthalen-2-yl)oxy)ethyl 2-((1-bromonaphthalen-2-yl)oxy)acetate (**2e**) in $CDCl_3$.

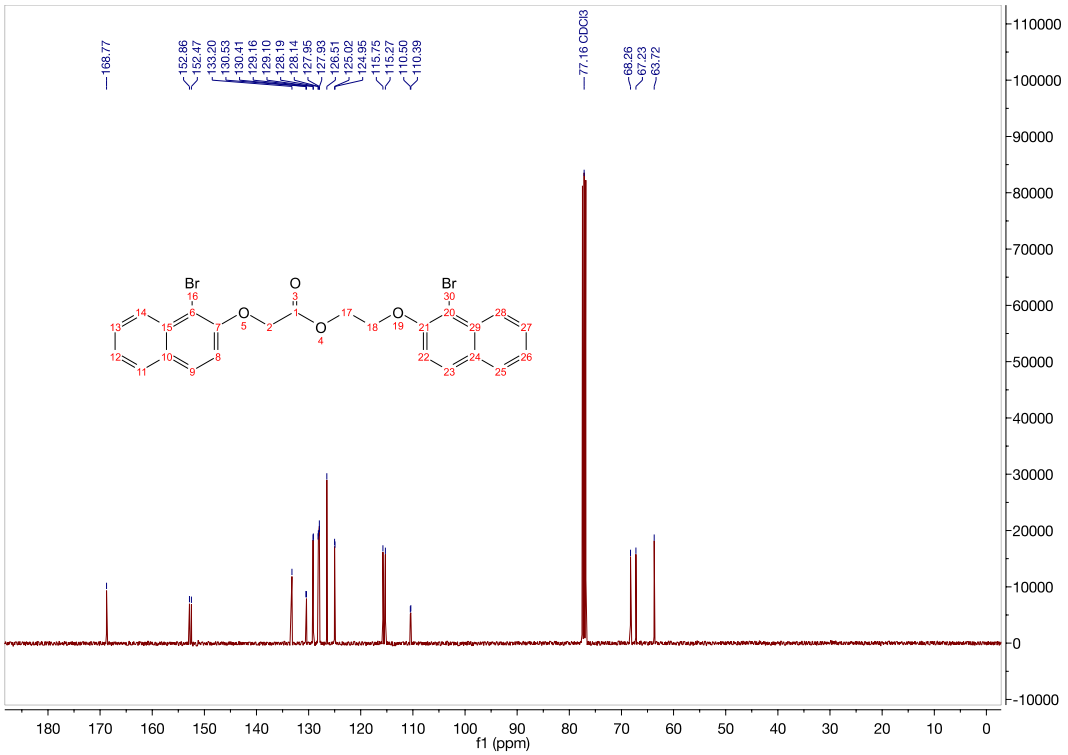

Figure S23. $^{13}$C NMR spectrum of 2-((1-bromonaphthalen-2-yl)oxy)ethyl 2-((1-bromonaphthalen-2-yl)oxy)acetate (**2e**) in $CDCl_3$.

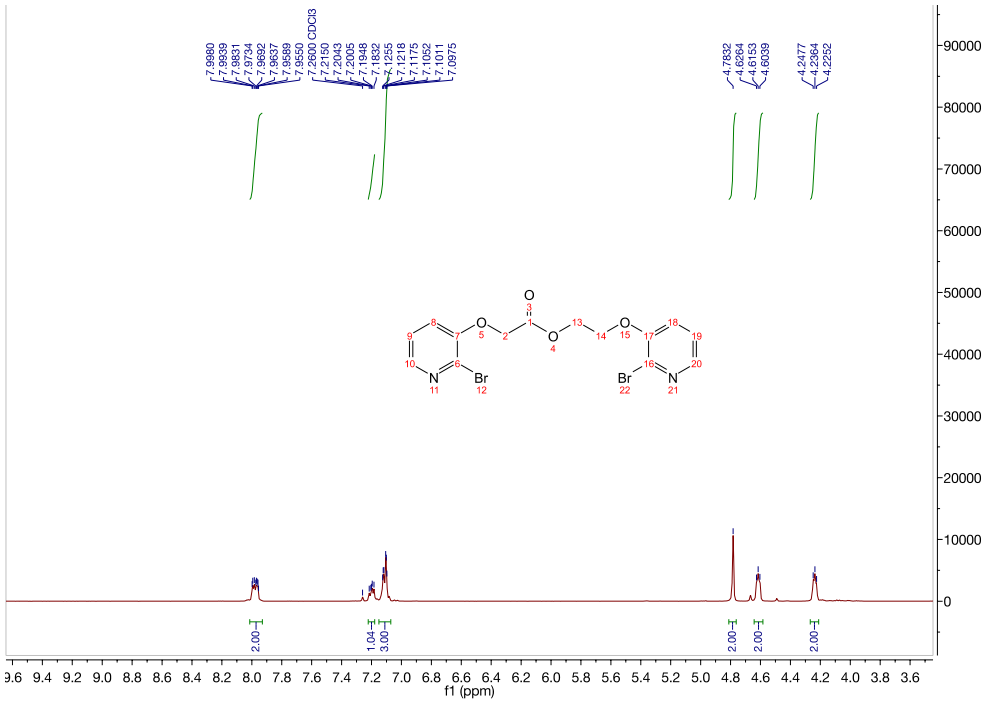

Figure S24. $^{1}$H NMR spectrum of 2-((2-bromopyridin-3-yl)oxy)ethyl 2-((2-bromopyridin-3-yl)oxy)acetate (**2f**) in $CDCl_3$.

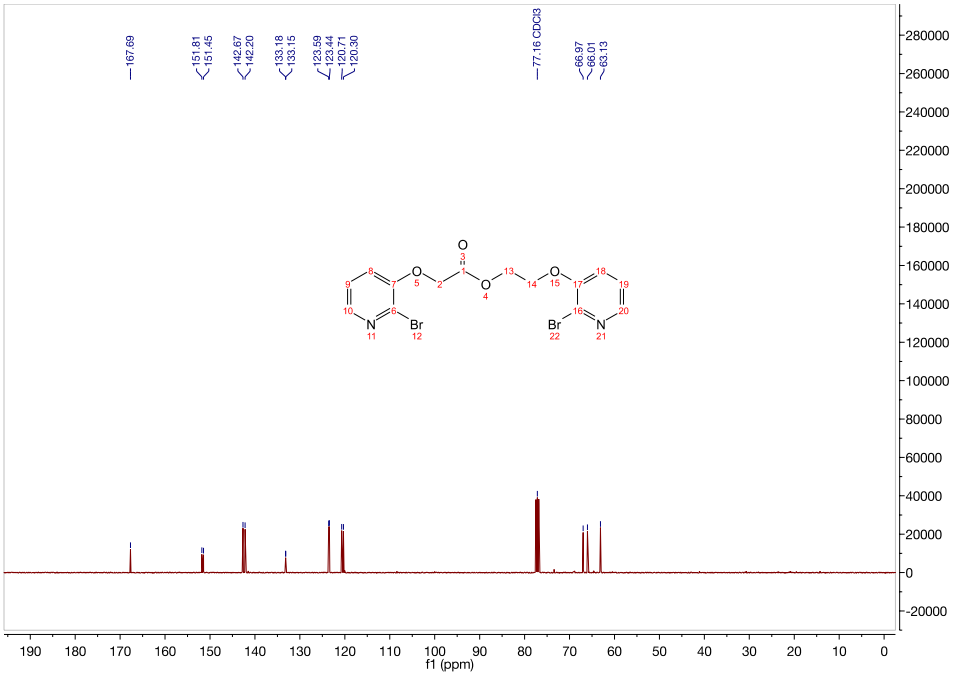

Figure S25. $^{13}$C NMR spectrum of 2-((2-bromopyridin-3-yl)oxy)ethyl 2-((2-bromopyridin-3-yl)oxy)acetate (**2f**) in $CDCl_3$.

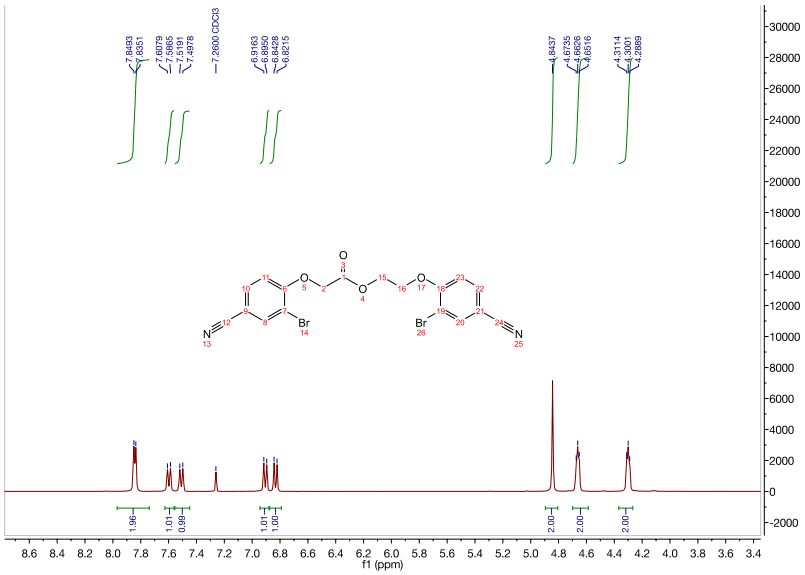

Figure S26. $^{1}$H NMR spectrum of 2-(2-bromo-4-cyanophenoxy)ethyl 2-(2-bromo-4-cyanophenoxy)acetate (**2g**) in $CDCl_3$.

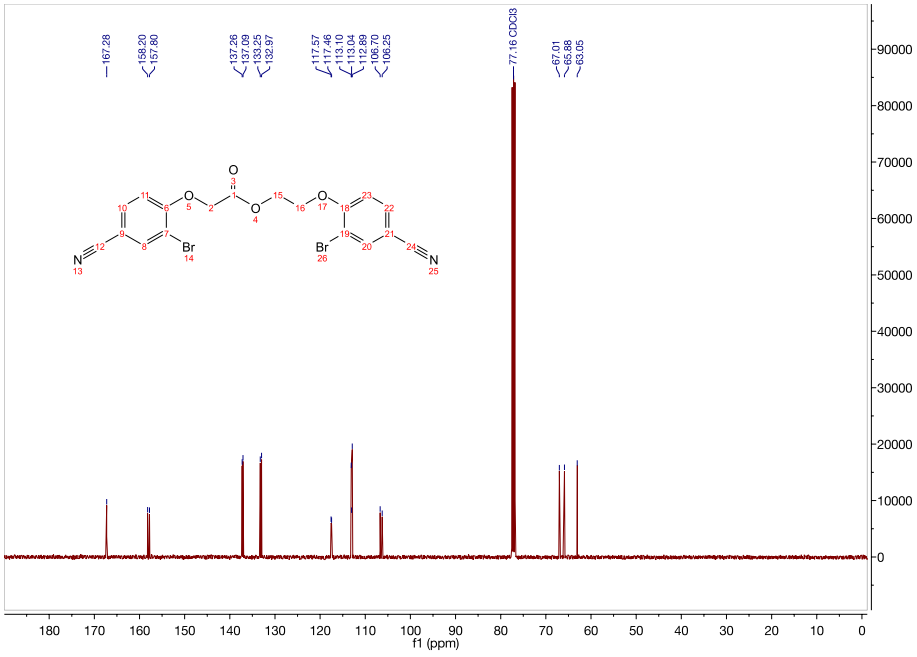

Figure S27. $^{13}$C NMR spectrum of 2-(2-bromo-4-cyanophenoxy)ethyl 2-(2-bromo-4-cyanophenoxy)acetate (**2g**) in $CDCl_3$.

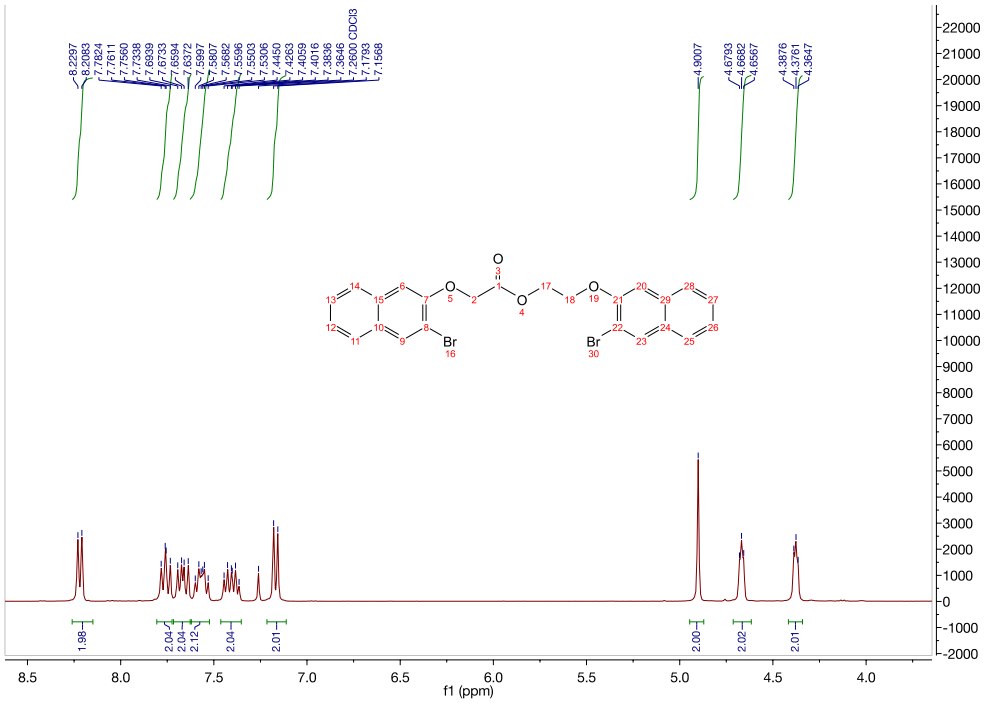


Figure S28. $^{1}$H NMR spectrum of 2-((3-bromonaphthalen-2-yl)oxy)ethyl 2-((3-bromonaphthalen-2-yl)oxy)acetate (**2h**) in $CDCl_3$.

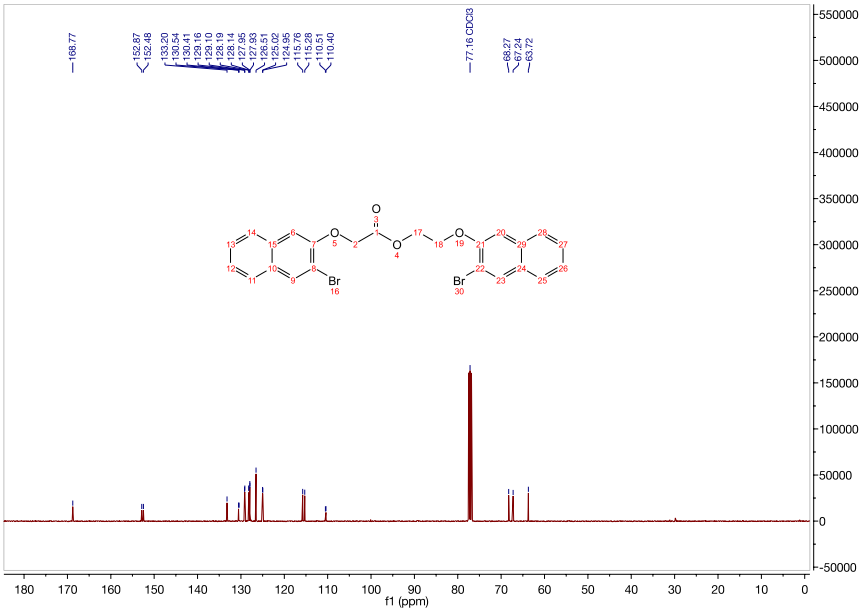


Figure S29. $^{13}$C NMR spectrum of 2-((3-bromonaphthalen-2-yl)oxy)ethyl 2-((3-bromonaphthalen-2-yl)oxy)acetate (**2h**) in $CDCl_3$.

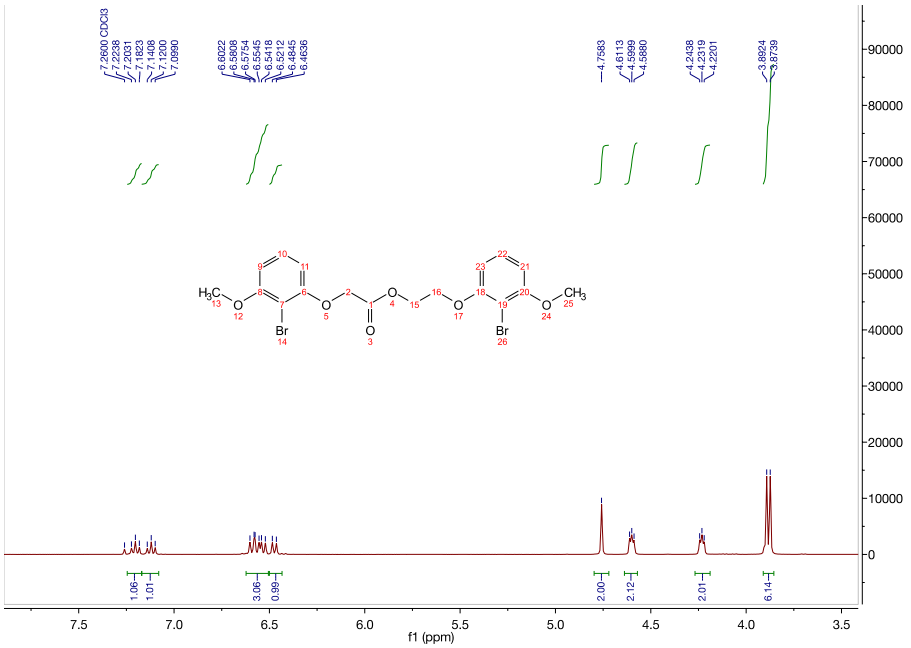


Figure S30. $^{1}$H NMR spectrum of 2-(2-bromo-3-methoxyphenoxy)ethyl 2-(2-bromo-3-methoxyphenoxy)acetate (**2i**) in $CDCl_3$.

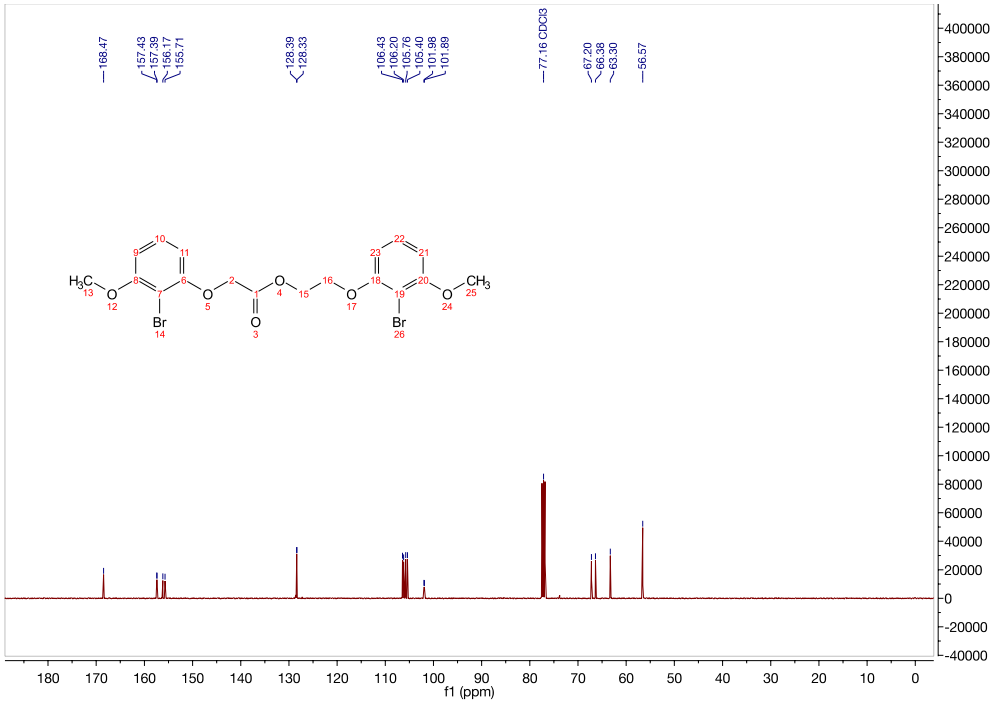


Figure S31. $^{13}$C NMR spectrum of 2-(2-bromo-3-methoxyphenoxy)ethyl 2-(2-bromo-3-methoxyphenoxy)acetate (**2i**) in $CDCl_3$.

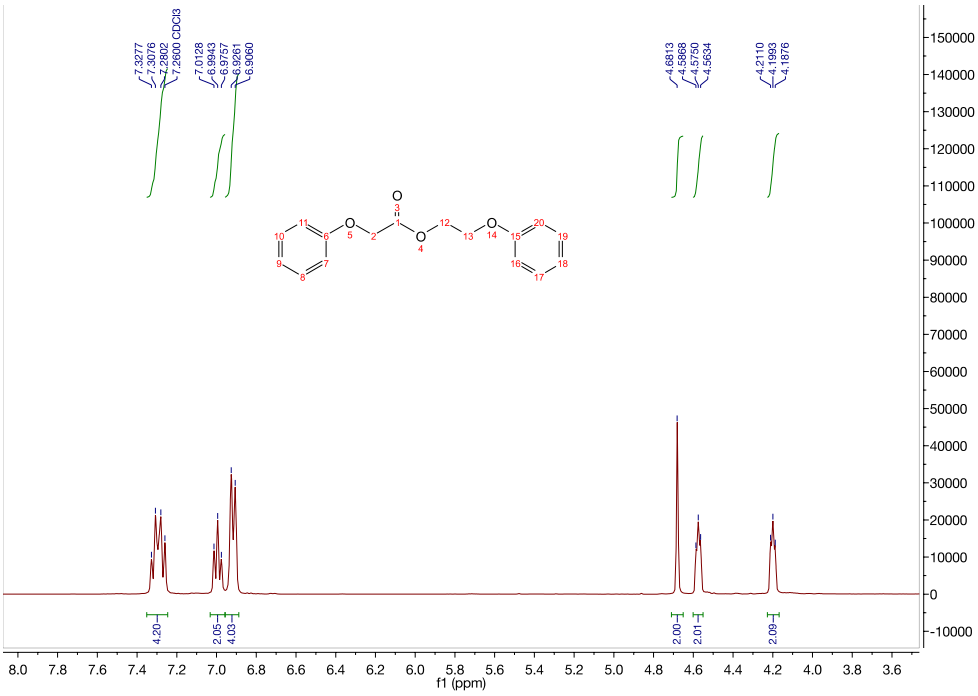


Figure S32. $^{1}$H NMR spectrum of 2-(phenoxy)ethyl 2-(phenoxy)acetate (**2j**) in $CDCl_3$.

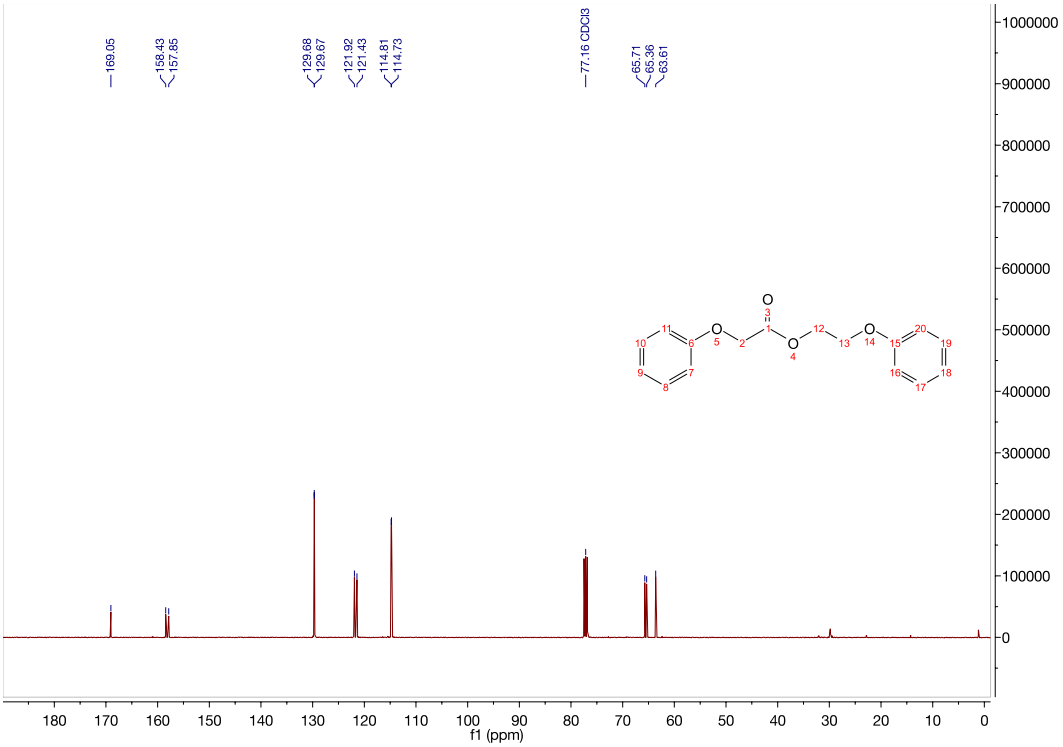


Figure S33. $^{13}$C NMR spectrum of 2-(phenoxy)ethyl 2-(phenoxy)acetate (**2j**) in $CDCl_3$.

**Monitoring the reaction by $^1$H NMR**

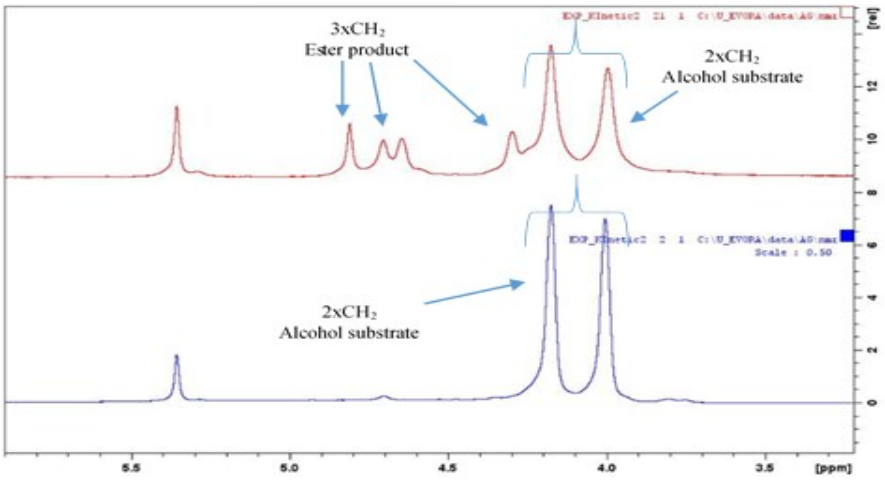


**Figure S34.** Monitoring the formation of 2-(2-bromophenoxy)ethyl 2-(2-bromophenoxy)acetate (**2a**) by $^1$H NMR.

The blue spectrum shows the situation at the beginning of the experiment (time = 0). At this point, we see the peaks corresponding to the two $CH_2$ units present (due to poor resolution as broad singlets) in the alcohol substrate. The red spectrum describes the situation at the end of the experiment (time = 20h). At this point, the peaks corresponding to the three $CH_2$ units present in the ester product are already visible (as again three broad singlets).

## NMR based Kinetics Studies

The samples were prepared as follows: 0.5 mL of deuterated chloroform was added to an NMR tube under $N_2$. After this, the alcohol and PCC were also added to the tube. The tube was closed and placed inside the NMR machine for analysis. Several $^1$H spectra were taken (at hourly intervals) during the 20 hours.

**Kinetic Experiments via $^1$H NMR spectroscopy** [1,2]

[1] Mathew, J. S.; Klussmann, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, E. A. C.; Blackmond, D. G. *J. Org. Chem.* **2006**, *71*, 4711 – 4722.

[2] Blackmond, D. G. *Angew. Chem. Int. Ed*. **2005**, *44*, 4302 – 4320.

The study was conducted using a Bruker Avance III 400 MHz with a broad-band-observe (BBO) probe. For this study, a new **au** was created by writing EDAU in the command editor, following the methodology described below by Professor Glenn Facey, Department of Chemistry, University of Ottawa.

***Kinetic_t***

In this program, the user should set up the appropriate parameters and then run the program (by typing ***xau kinetic_t***).

```
/* kinetic */
/* written by Glenn Facey, August 24, 2005 */
/* This program sets up and runs a kinetic experiment */
/* The user is asked to input the number of spectra, */
/* the number of scans for each spectrum and the time in */
/* seconds between the end of an acquisition and the */
/* beginning of the next. The program will measure the */
/* receiver gain and start the acquisitions. */
GETCURDATA
GETINT("Enter total number of spectra",i1)
GETINT("Enter the number of scans for each spectrum",i2)
GETINT("Enter the time interval (in seconds)", i3)
STOREPAR("ns",i2)
Proc_err(0,"Kinetic Run in Progress");
RGA
ZG
TIMES(i1-1)
IEXPNO
SETCURDATA
STOREPAR("ns",i2)
ssleep(i3);
ZG
END
QUITMSG("Data Collection Finished")
```

In this experiment was used the pulse program described below:

Pulse program ***zg30kin.gf***

```
;zg30kin.gf
;avance-version (12/01/11)
;1D sequence
;using 30 degree flip angle
;
;$CLASS=HighRes
;$DIM=1D
;$TYPE=
;$SUBTYPE=
;$COMMENT=
;$RECOMMEND=y
#include <Avance.incl>
"acqt0=-p1*0.66/3.1416"
1 ze
2 30m
  d1
  p1*0.33 ph1
  go=2 ph31
  30m mc #0 to 2 F0(zd)
exit
ph1=0 2 2 0 1 3 3 1
ph31=0 2 2 0 1 3 3 1
;pl1 : f1 channel - power level for pulse (default)
;p1 : f1 channel -  90 degree high power pulse
```

;d1 : relaxation delay; 1-5 * T1

;ns: 1 * n, total number of scans: NS * TD0

;$Id: zg30,v 1.11.6.1 2012/01/31 17:56:41 ber Exp $

The procedure used by Dr. Michael Bernstein, is described below, for a better comprehension of the results.[3]

**C ∝ AI/NN**

Where **C** is the concentration of a chemical species, **AI** is the absolute integral for a multiplet attributable to that species, and **NN** is the number of nuclides (Hs, usually) for that multiplet.

From this we derive:

**C = CCF * AI/NN**

This says that a proportionality constant – which we call the Concentration Conversion Factor (**CCF**) – allows us to convert a measured **AI/NN** into a concentration. Fundamentally, the **CCF** only needs to be determined once for an experiment, and then it is applicable to all chemical species in the reaction!

**Determining the CCF[8,4]**

It therefore follows that the sensible way to proceed with quantified, reaction kinetics data extraction hinges on the determination of the **CCF** for that particular experiment. Once that has been performed, then all other species concentrations can be determined by applying the equation where the **AI** is determined by the software, and **NN** is provided by the user.

## Biological Assays

[3] - http://mestrelab.com/blog/determining-concentrations-when-using-nmr-to-model-chemical-reactions/

[4] Garrido, B.C.; de Carvalho, L.J. *Magn. Reson. Chem.* **2015**, *53*, 135 – 141.

The biological assays to access the anti-cholinesterases potential were performed by determination of the concentration of synthetized compounds that inhibits 50% of activity (IC50) followed a modified Ellman[5] method developed by Bacalhau *et al.*[6] Dose-response curves for AChE and BChE are presented in **Figure S35**. All the compounds have higher inhibition to AChE than BChE, thus being more selective to this enzyme. The incubation time was studied for the compounds with both enzymes, and was found to be crucial to the inhibition process (**Figure S19**), except for compound (4), that showed no significant improvement on the IC50 value (**table 4, entry 4**). Compounds **(2c), (2d), (2f)** and **(4)** present a dose-response curve that, not only is compatible with the incubation period, but also with the corresponding $IC_{50}$ value and show potential to be target drugs for AChE (**Figure S35**).

[5] Ellman, G.; Courtney, K.; Andres, V.; Featherstone, R. Biochemical Pharmacology. **1961**, 7, 88.

[6] Bacalhau, P.; San Juan, A.; Marques, C. S.; Peixoto, D.; Burke, A. J.; Caldeira, A. T.; Martins, M. R. Neurodegener Dis. **2015**, 15(suppl 1), 741.

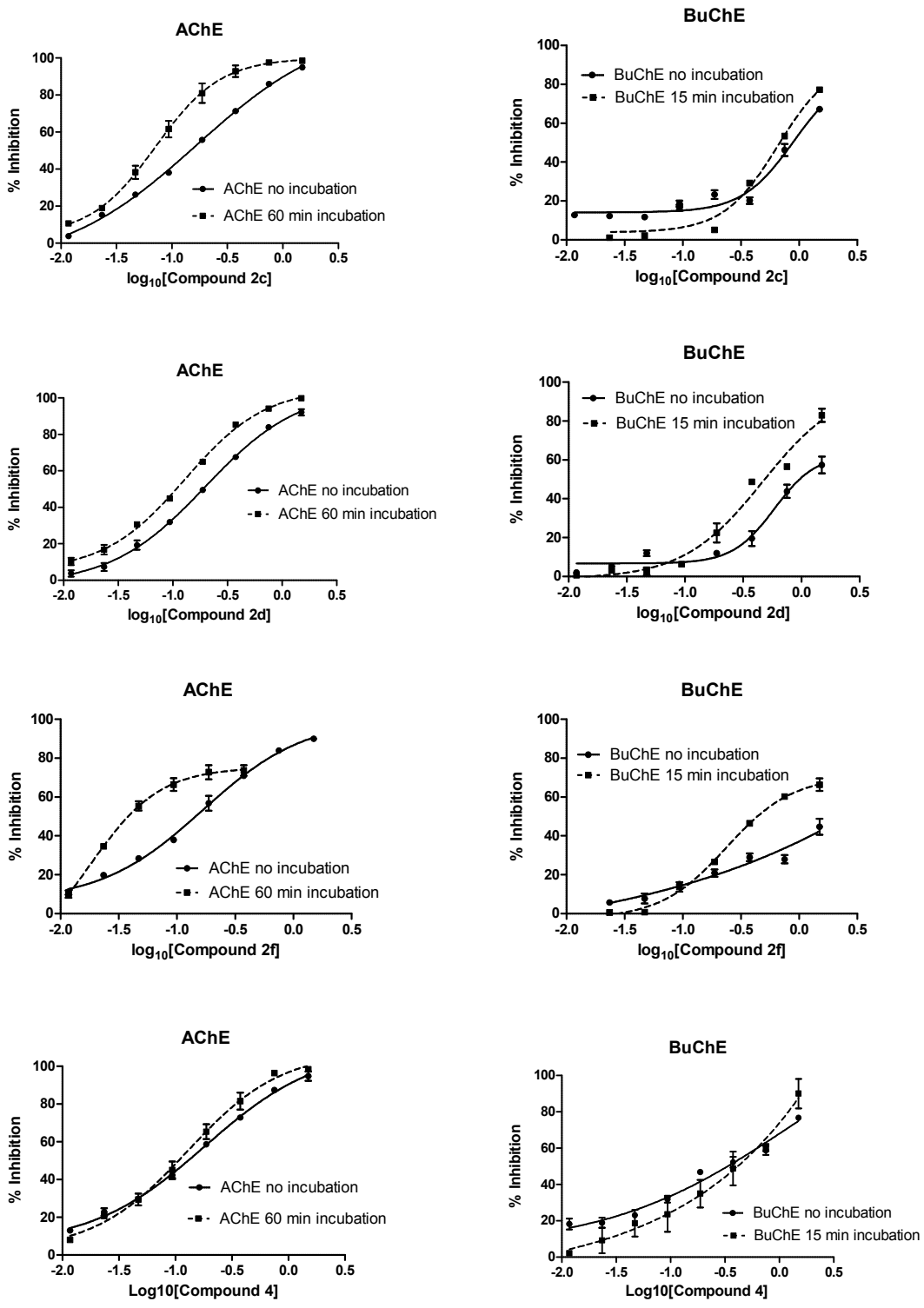


Figure S35. Dose-response curves with and without incubation, for eeAChE and eqBuChE.