

Supplementary Material

Pyrimidine-2,4-diamines as antiplasmodial antifolates

Tswene D. Seanego,^a Hanna F. Klein,^a Natasha C. Jansen van Vuuren,^{b,c} Robyn L. van Zyl,^{b,c} and Amanda L. Rousseau^{*a,c}

^aMolecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Private Bag 3, PO WITS, 2050, South Africa

^bPharmacology Division, Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road, Parktown 2193, South Africa

^cWITS Research Institute for Malaria (WRIM), University of the Witwatersrand, 7 York Road, Parktown 2193, South Africa

Email: Amanda.Rousseau@wits.ac.za

Table of Contents

S1. ¹ H and ¹³ C NMR spectra of 1-(4-bromobutoxy)-4-chlorobenzene (9a).....	S3
S2. ¹ H and ¹³ C NMR spectra of 1-(4-bromobutoxy)-3,4-dichlorobenzene (9b).....	S4
S3. ¹ H and ¹³ C NMR spectra of 1-(4-bromobutoxy)-3,5-dichlorobenzene (9c).....	S5
S4. ¹ H and ¹³ C NMR spectra of 1-(4-bromobutoxy)-3-fluorobenzene (9d).....	S6
S5. ¹ H and ¹³ C NMR spectra of 1-(4-bromobutoxy)-4-fluorobenzene (9e).....	S7
S6. ¹ H and ¹³ C NMR spectra of 1-(4-bromobutoxy)-3-(trifluoromethyl)benzene (9f).....	S8
S7. ¹ H and ¹³ C NMR spectra of 2,4-dibromo-1-(4-bromobutoxy)benzene (9g).....	S9
S8. ¹ H and ¹³ C NMR spectra of 5-(4-chlorophenoxy)pentanenitrile (10a).....	S10
S9. ¹ H and ¹³ C NMR spectra of 5-(3,4-dichlorophenoxy)pentanenitrile (10b).....	S11
S10. ¹ H and ¹³ C NMR spectra of 5-(3,5-dichlorophenoxy)pentanenitrile (10c).....	S12
S11. ¹ H and ¹³ C NMR spectra of 5-(3-fluorophenoxy)pentanenitrile (10d).....	S13
S12. ¹ H and ¹³ C NMR spectra of 5-(4-fluorophenoxy)pentanenitrile (10e).....	S14
S13. ¹ H and ¹³ C NMR spectra of 5-(3-(trifluoromethyl)phenoxy)pentanenitrile (10f).....	S15
S14. ¹ H and ¹³ C NMR spectra of 5-(2,4-dibromophenoxy)pentanenitrile (10g).....	S16
S15. ¹ H and ¹³ C NMR spectra of 2-benzoyl-5-(4-chlorophenoxy)pentanenitrile (11a).....	S17
S16. ¹ H and ¹³ C NMR spectra of 2-benzoyl-5-(3,4-dichlorophenoxy)pentanenitrile (11b).....	S18
S17. ¹ H and ¹³ C NMR spectra of 2-benzoyl-5-(3,5-dichlorophenoxy)pentanenitrile (11c).....	S19
S18. ¹ H and ¹³ C NMR spectra of 2-benzoyl-5-(3-fluorophenoxy)pentanenitrile (11d).....	S20
S19. ¹ H and ¹³ C NMR spectra of 2-benzoyl-5-(4-fluorophenoxy)pentanenitrile (11e).....	S21
S20. ¹ H and ¹³ C NMR spectra of 2-benzoyl-5-(3-(trifluoromethyl)phenoxy)pentanenitrile (11f).....	S22
S21. ¹ H and ¹³ C NMR spectra of 2-benzoyl-5-(2,4-dibromophenoxy)pentanenitrile (11g).....	S23
S22. ¹ H and ¹³ C NMR spectra of 5-(3-(4-chlorophenoxy)propyl)-6-phenylpyrimidine-2,4-diamine (6a).....	S24
S23. ¹ H and ¹³ C NMR spectra of 5-(3-(3,4-dichlorophenoxy)propyl)-6-phenylpyrimidine-2,4-diamine (6b).....	S25
S24. ¹ H and ¹³ C NMR spectra of 5-(3-(3,5-dichlorophenoxy)propyl)-6-phenylpyrimidine-2,4-diamine (6c).....	S26
S25. ¹ H and ¹³ C NMR spectra of 5-(3-(3-fluorophenoxy)propyl)-6-phenylpyrimidine-2,4-diamine (6d).....	S27
S26. ¹ H and ¹³ C NMR spectra of 6-(4-(4-chlorophenoxy)butoxy)pyrimidine-2,4-diamine (7a).....	S28
S27. ¹ H and ¹³ C NMR spectra of 6-(4-(3,4-dichlorophenoxy)butoxy)pyrimidine-2,4-diamine (7b).....	S29
S28. ¹ H and ¹³ C NMR spectra of 6-(4-(3,5-dichlorophenoxy)butoxy)pyrimidine-2,4-diamine (7c).....	S30

S29. ^1H and ^{13}C NMR spectra of 6-(4-(3-fluorophenoxy)butoxy)pyrimidine-2,4-diamine (7d)	S31
S30. ^1H and ^{13}C NMR spectra of 6-(4-(4-fluorophenoxy)butoxy)pyrimidine-2,4-diamine (7e)	S32
S31. ^1H and ^{13}C NMR spectra of 6-(4-(3-(trifluoromethyl)phenoxy)butoxy)pyrimidine-2,4-diamine (7f).....	S33
S32. ^1H and ^{13}C NMR spectra of 6-(3-(4-chlorophenoxy)propoxy)pyrimidine-2,4-diamine (7g).....	S34
S33. ^1H and ^{13}C NMR spectra of 6-(3-(3,4-dichlorophenoxy)propoxy)pyrimidine-2,4-diamine (7h)	S35
S34. ^1H and ^{13}C NMR spectra of 6-(3-(3,5-dichlorophenoxy)propoxy)pyrimidine-2,4-diamine (7i).....	S36
S35. ^1H and ^{13}C NMR spectra of 6-(3-(4-fluorophenoxy)propoxy)pyrimidine-2,4-diamine (7j)	S37

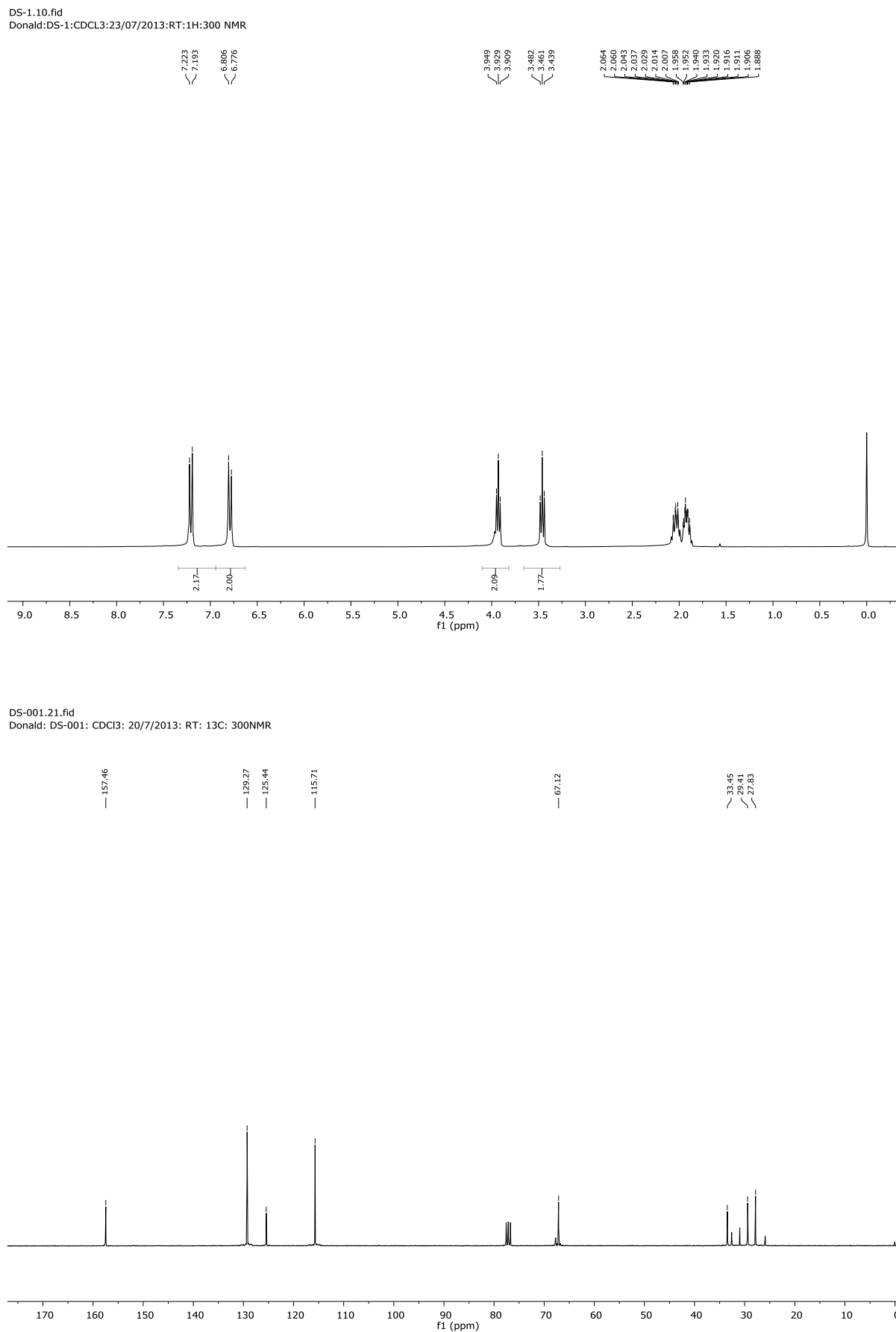
Figure S1. ^1H and ^{13}C NMR spectra of 1-(4-bromobutoxy)-4-chlorobenzene (**9a**).

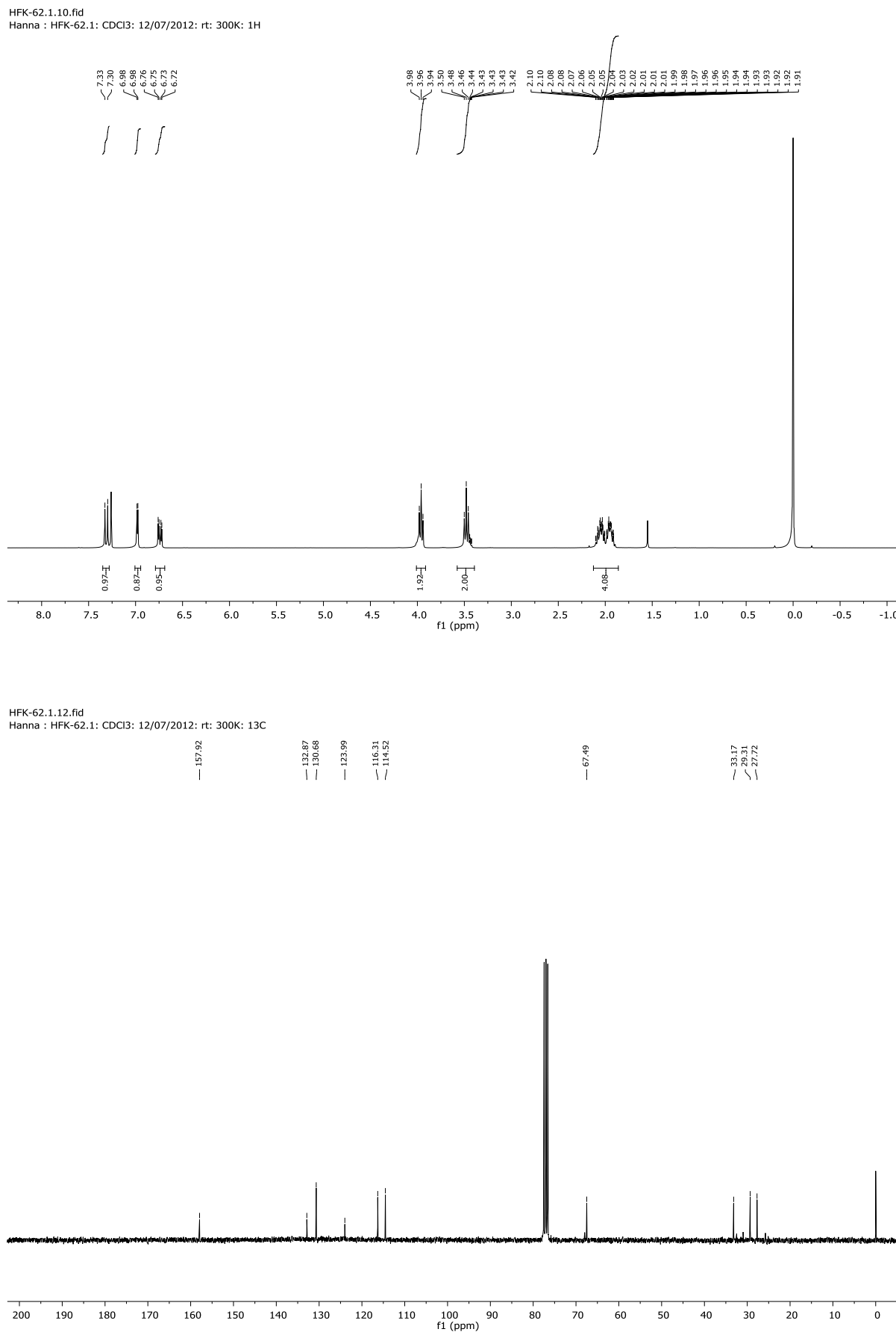
Figure S2. ^1H and ^{13}C NMR spectra of 1-(4-bromobutoxy)-3,4-dichlorobenzene (**9b**).

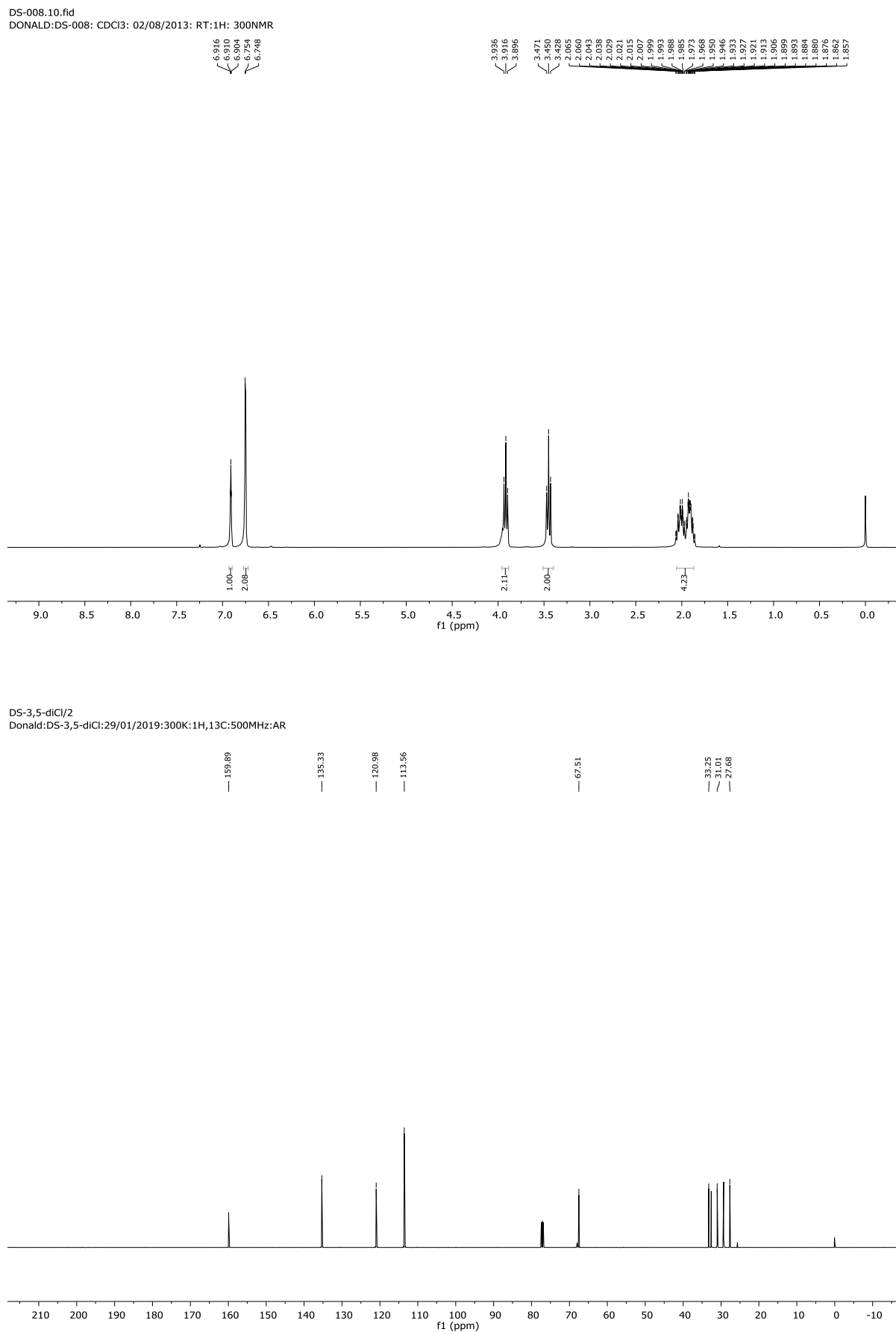
Figure S3. ^1H and ^{13}C NMR spectra of 1-(4-bromobutoxy)-3,5-dichlorobenzene (**9c**).

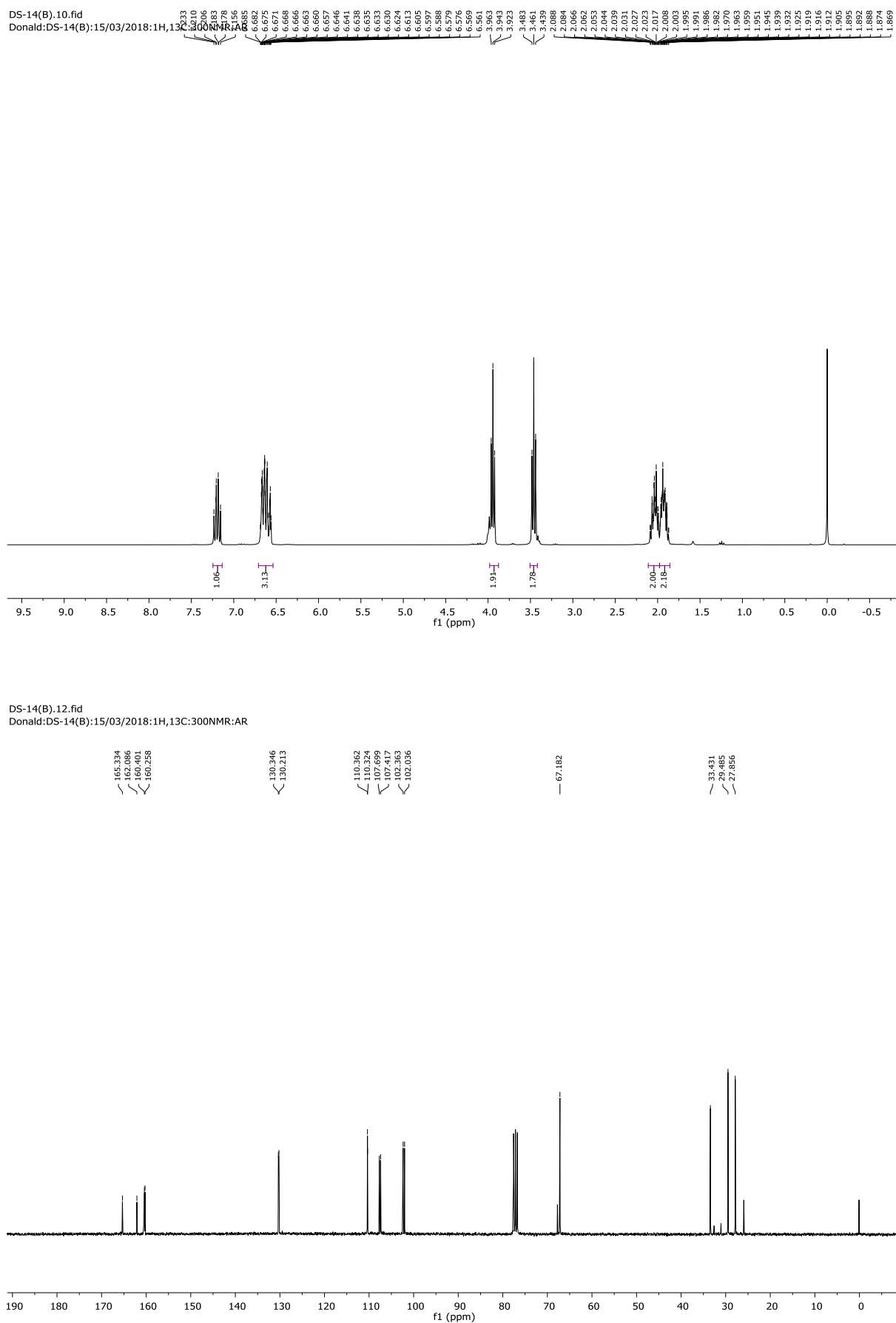
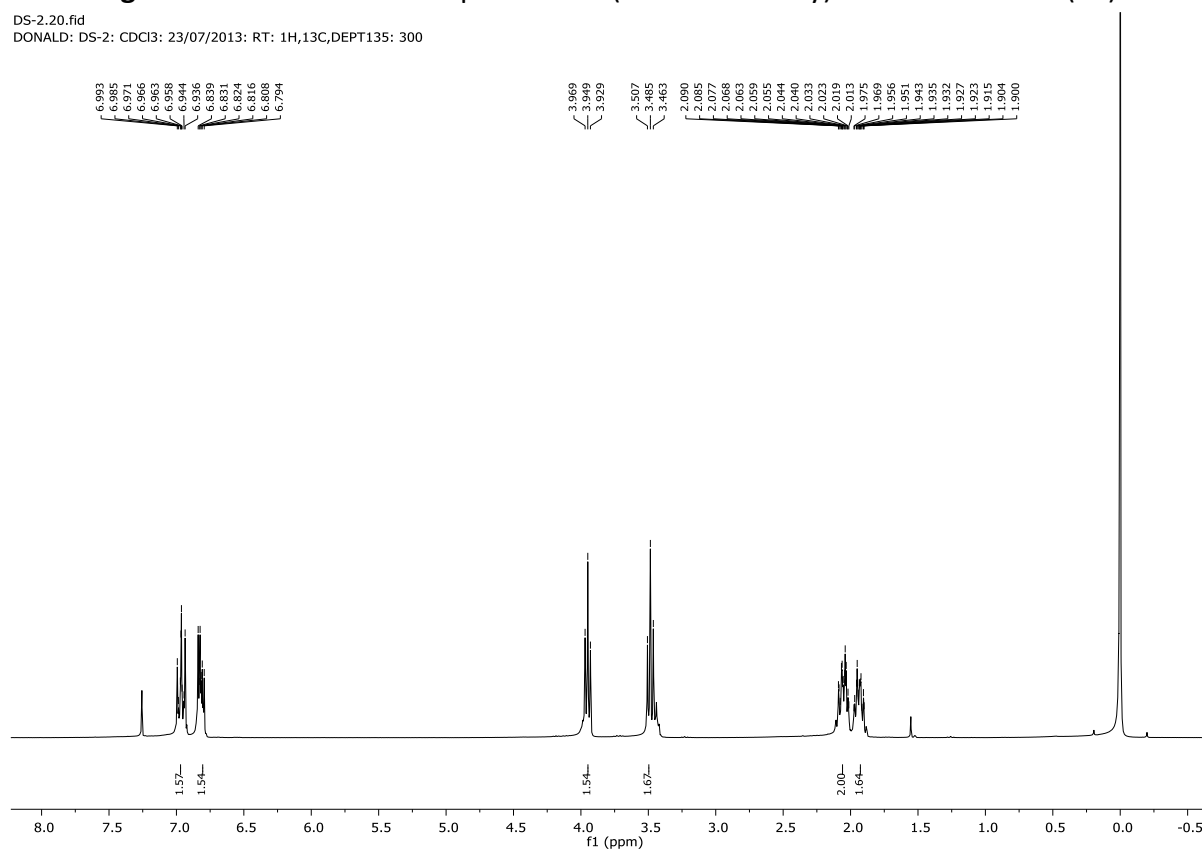
Figure S4. ^1H and ^{13}C NMR spectra of 1-(4-bromobutoxy)-3-fluorobenzene (**9d**).

Figure S5. ^1H and ^{13}C NMR spectra of 1-(4-bromobutoxy)-4-fluorobenzene (**9e**).

DS-2.20.fid

DONALD: DS-2: CDCl₃: 23/07/2013: RT: ^1H , ^{13}C ,DEPT135: 300

DS-2.21.fid

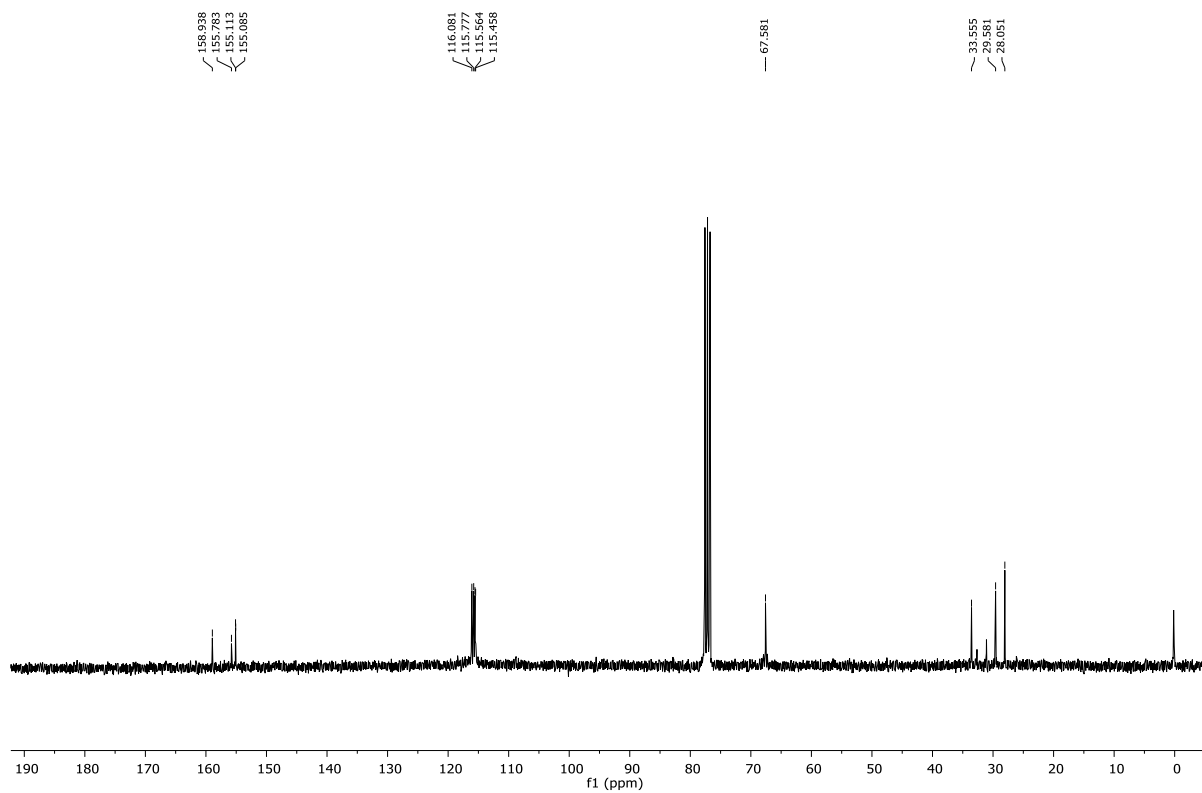
DONALD: DS-2: CDCl₃: 23/07/2013: RT: ^1H , ^{13}C ,DEPT135: 300

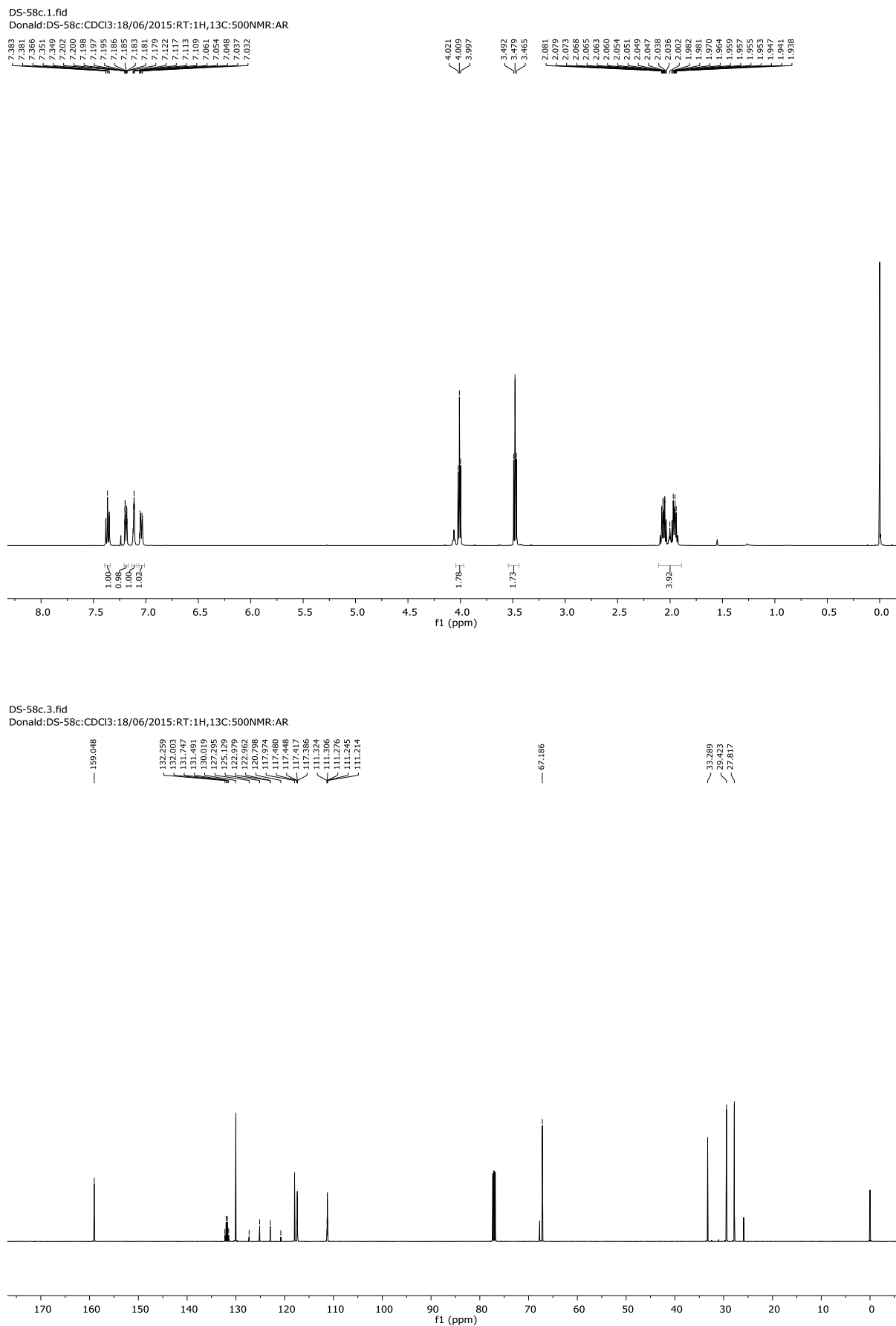
Figure S6. ^1H and ^{13}C NMR spectra of 1-(4-bromobutoxy)-3-(trifluoromethyl)benzene (**9f**).

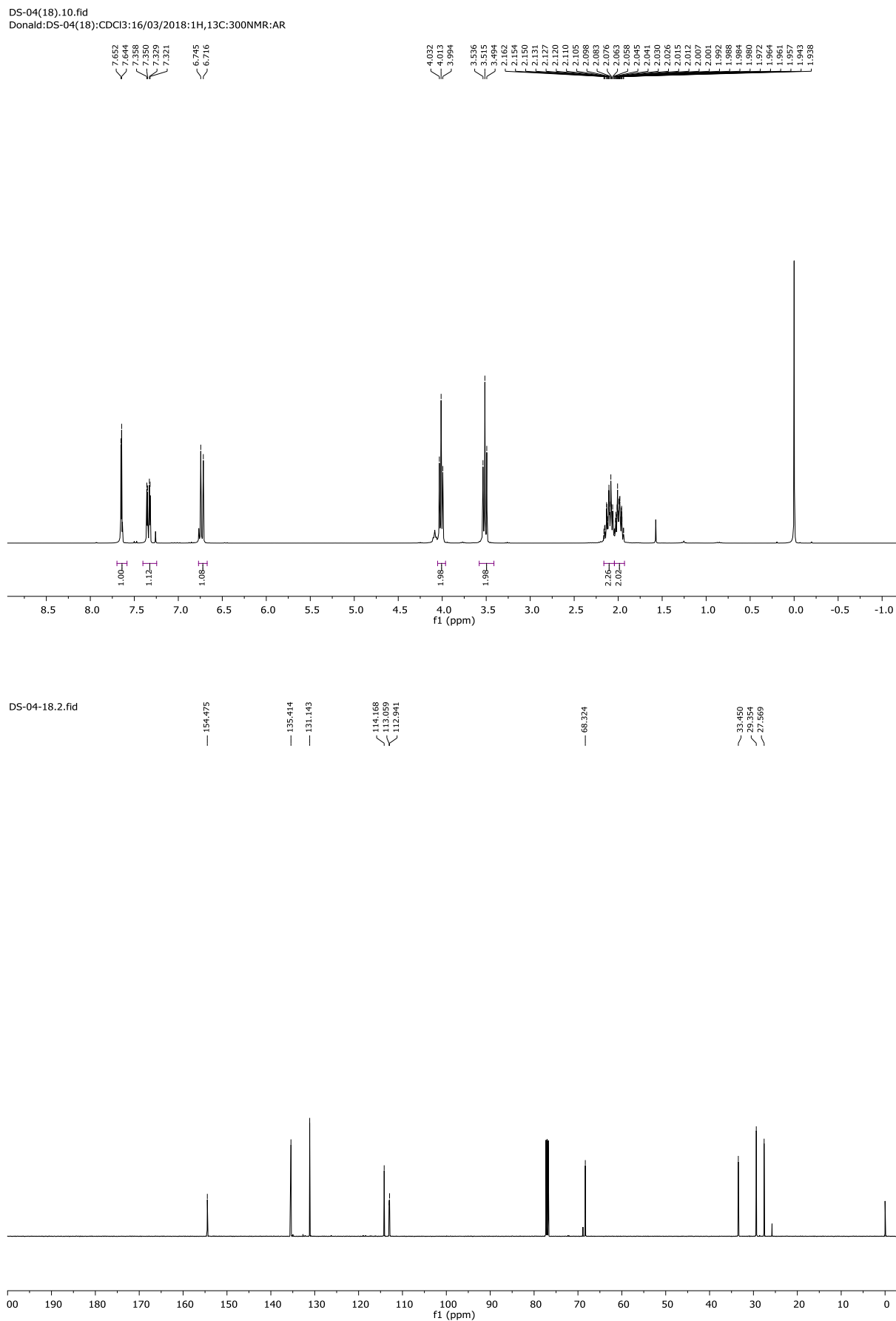
Figure S7. ^1H and ^{13}C NMR spectra of 2,4-dibromo-1-(4-bromobutoxy)benzene (**9g**).

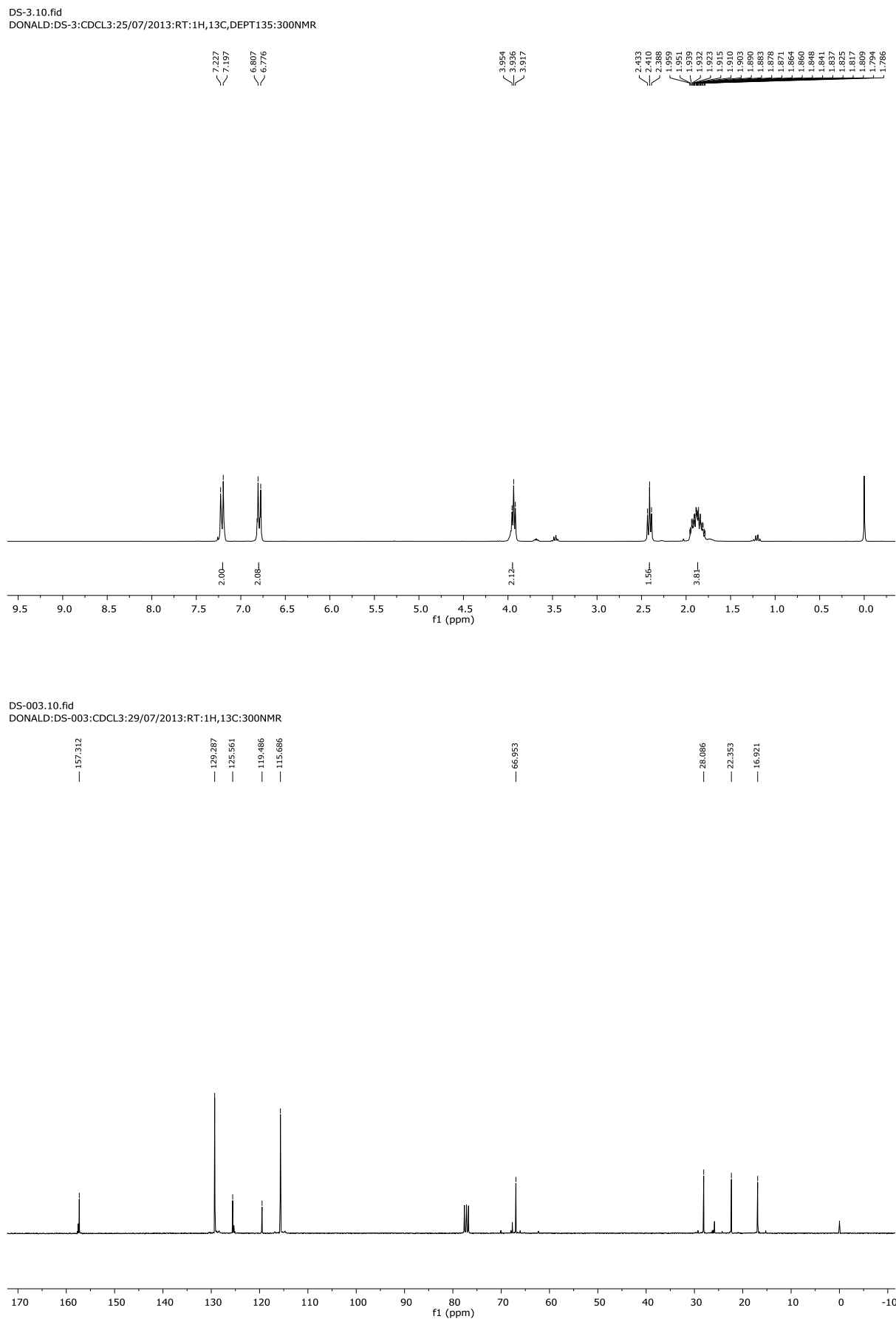
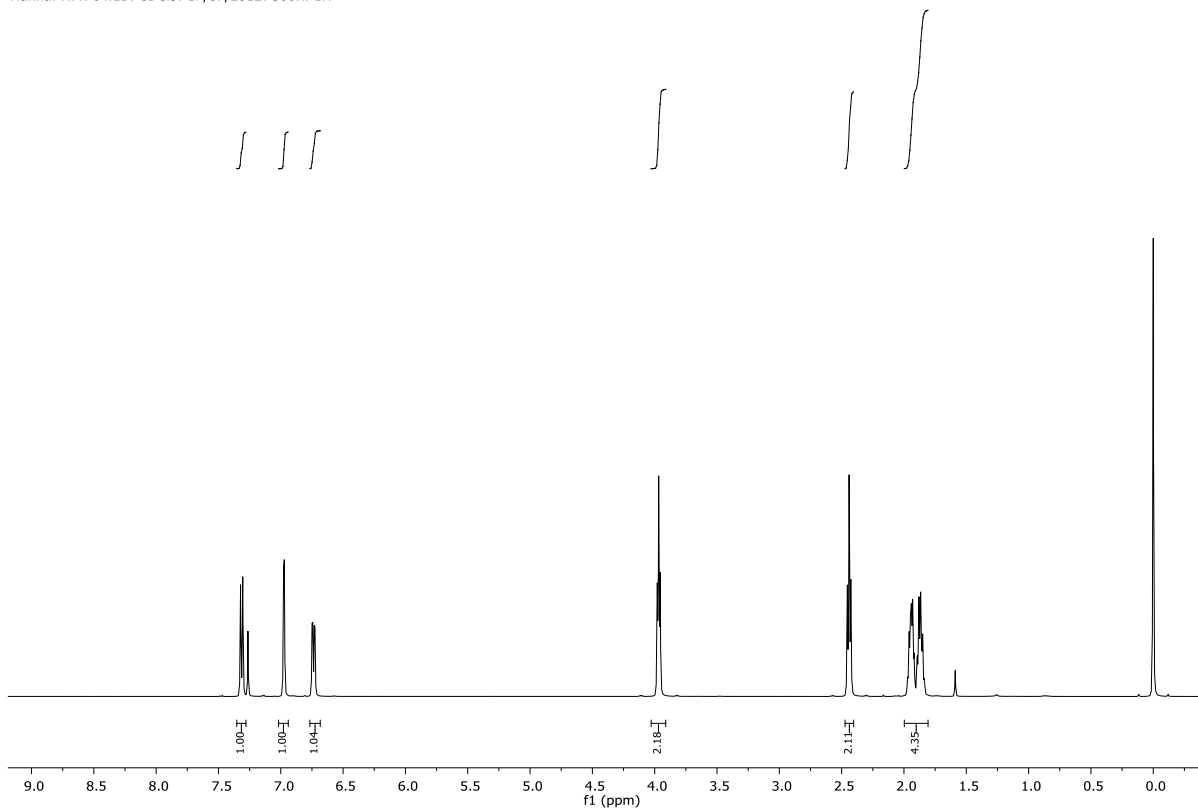
Figure S8. ^1H and ^{13}C NMR spectra of 5-(4-chlorophenoxy)pentanenitrile (**10a**).

Figure S9. ^1H and ^{13}C NMR spectra of 5-(3,4-dichlorophenoxy)pentanenitrile (**10b**).

HFK-64.1B.1.fid
Hanna: HFK-64.1B: CDCl₃: 17/07/2012: 500K: ^1H



HFK-64.1B.2.fid
Hanna: HFK-64.1B: CDCl₃: 17/07/2012: 500K: ^{13}C

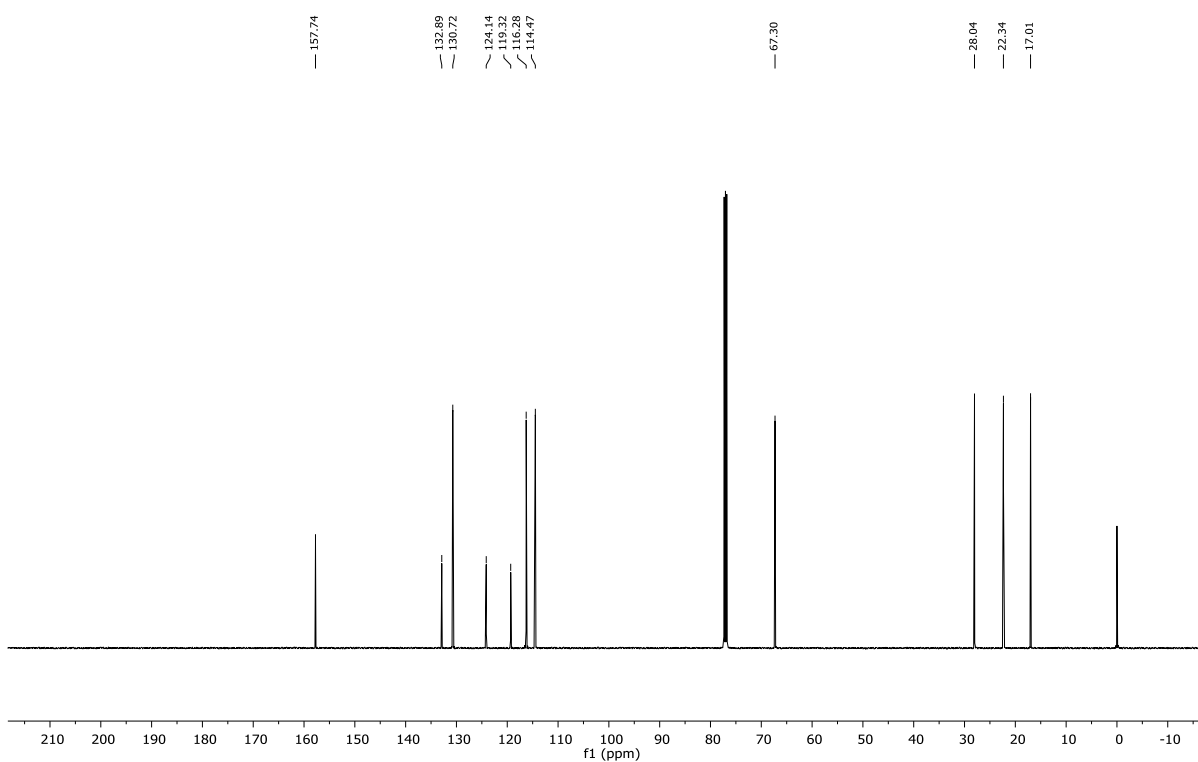


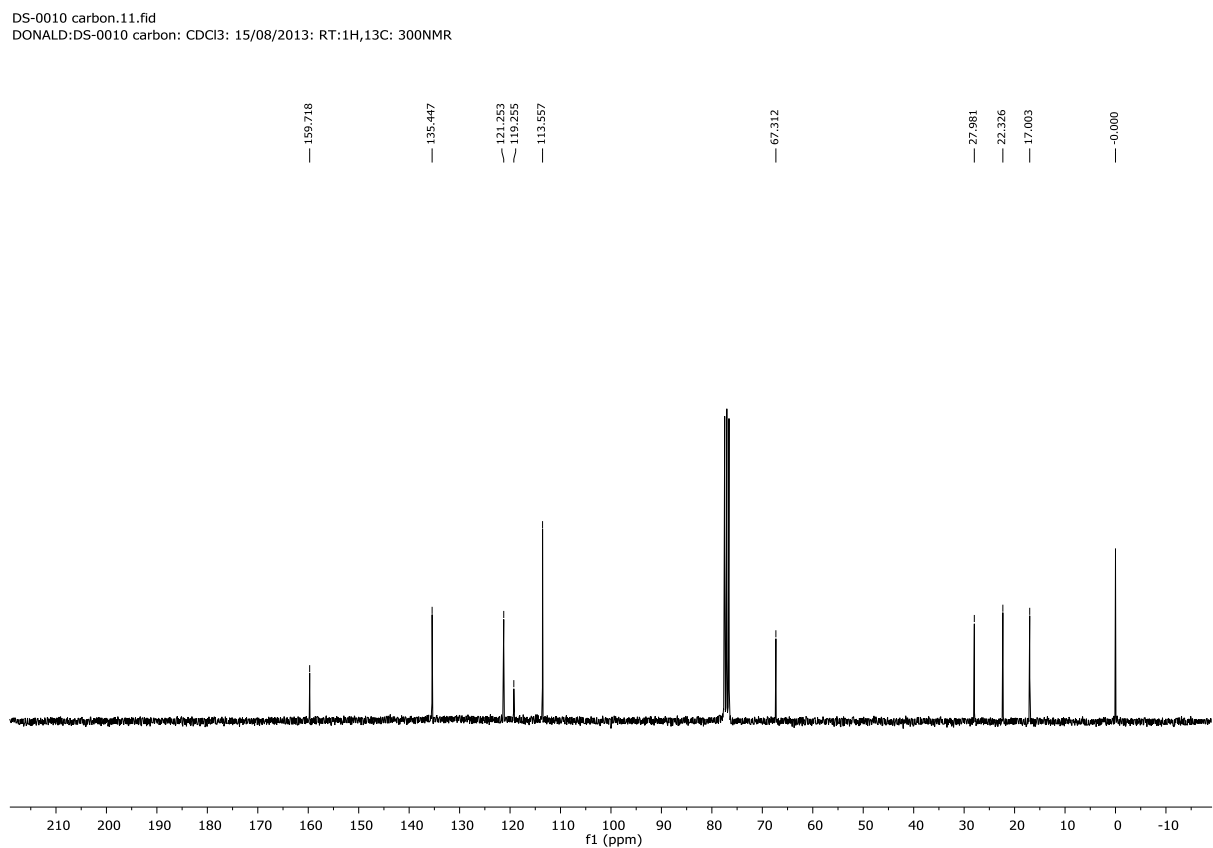
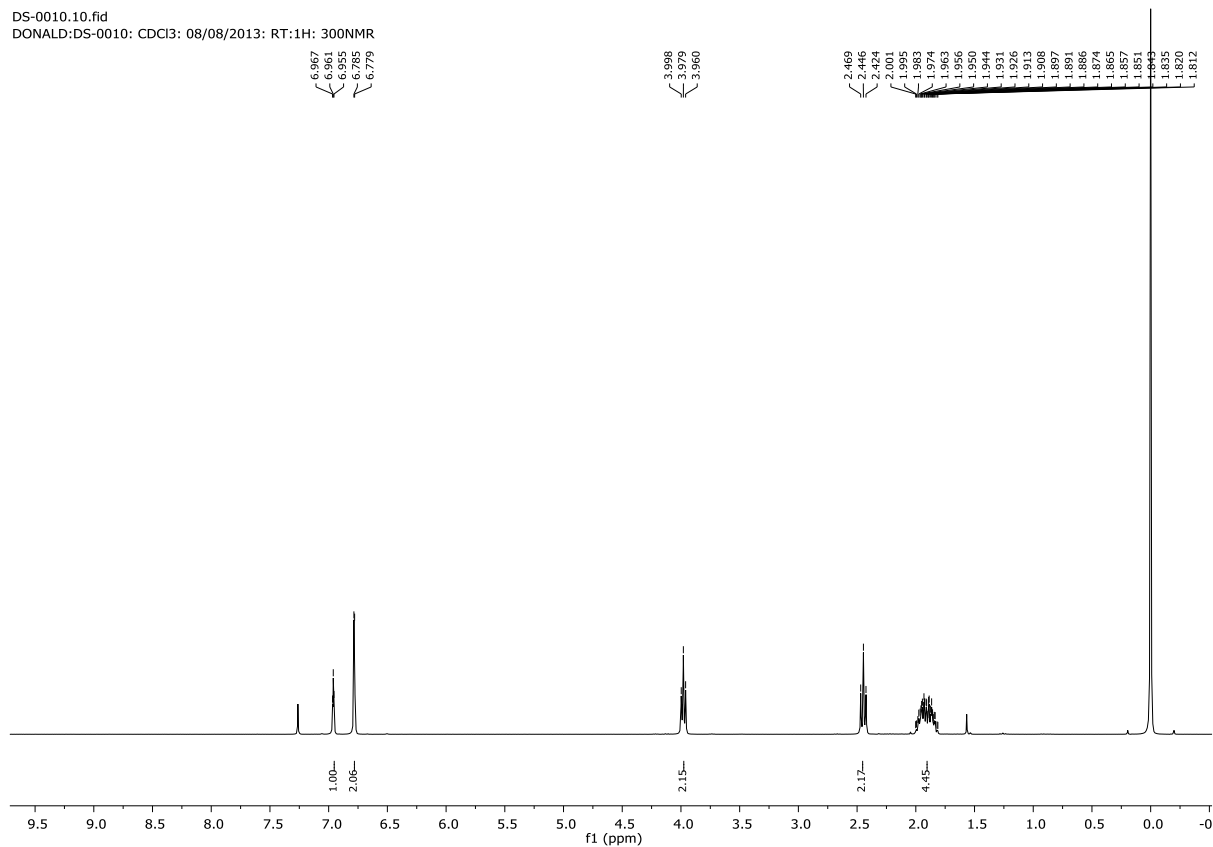
Figure S10. ^1H and ^{13}C NMR spectra of (5-(3,5-dichlorophenoxy)pentanenitrile (**10c**).

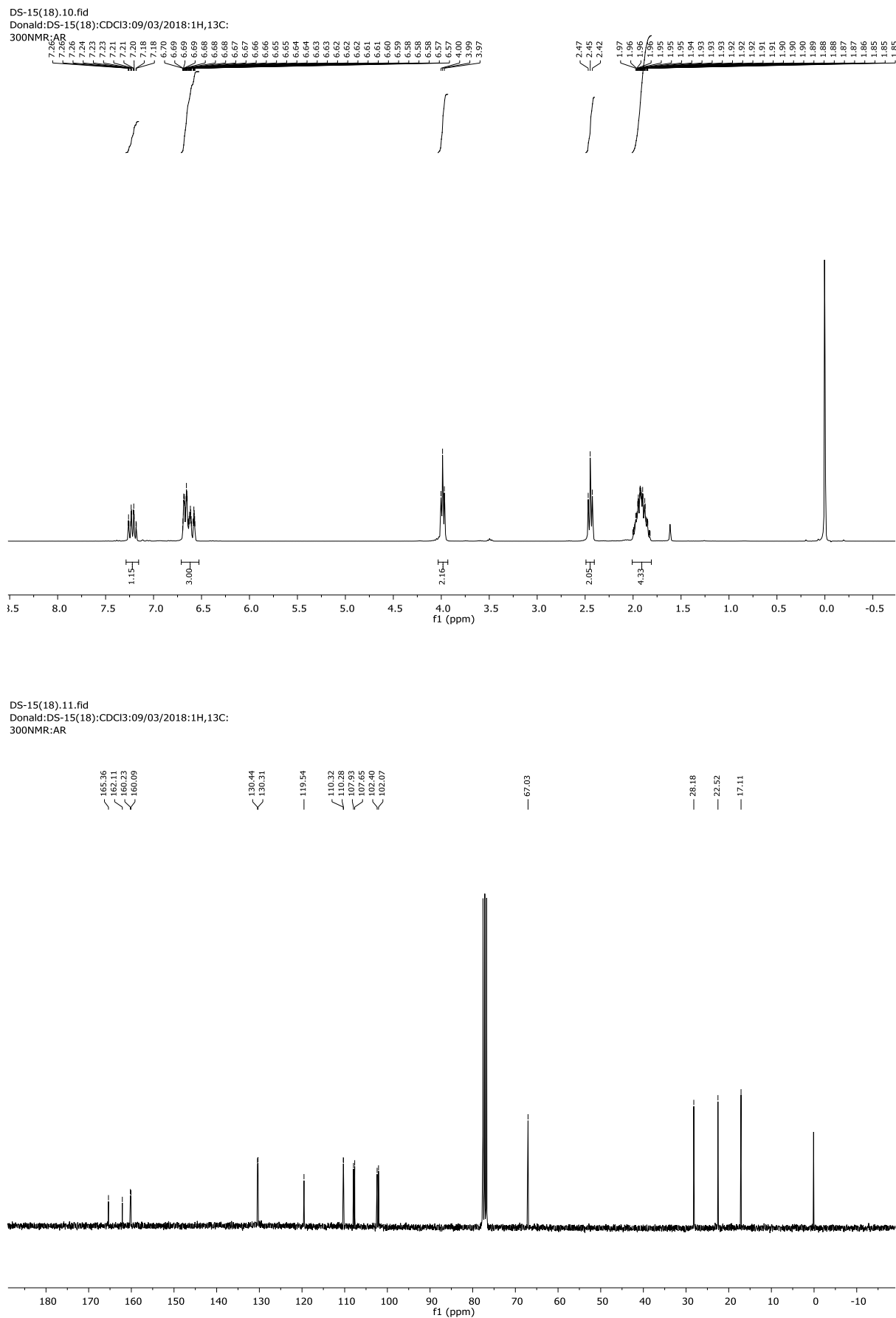
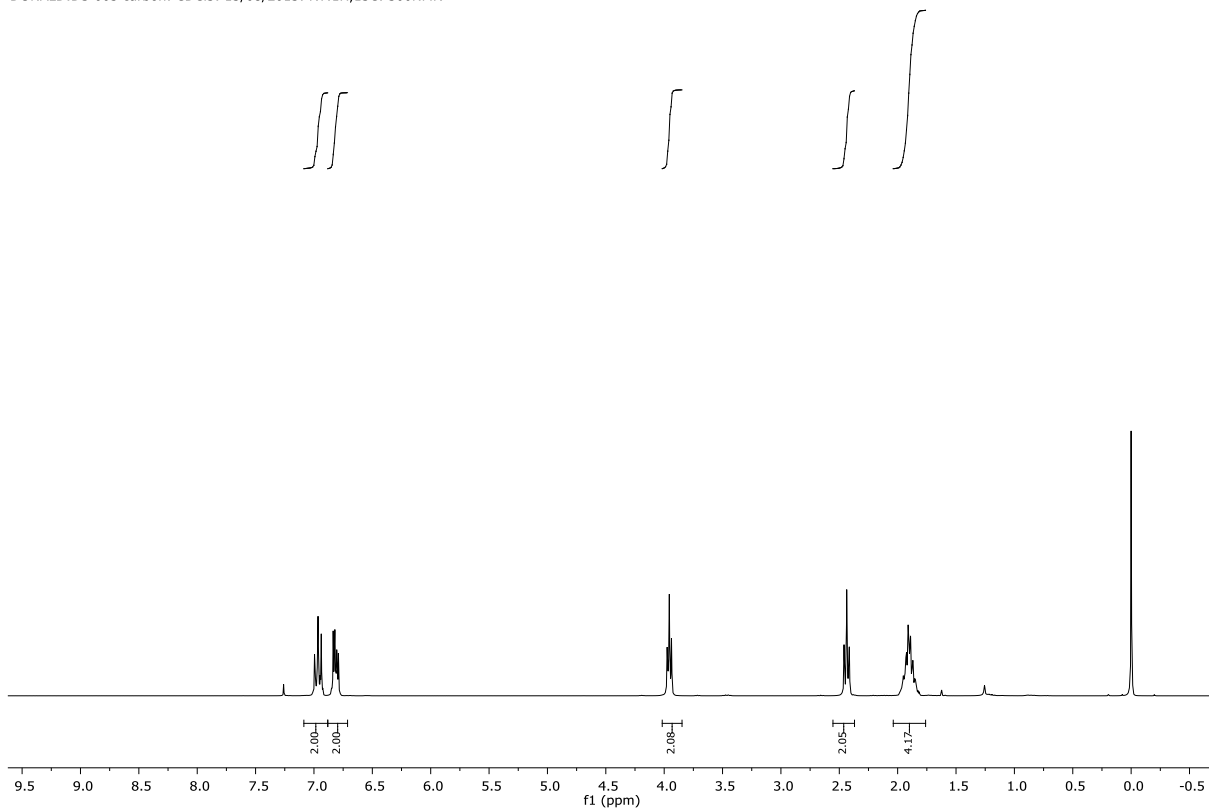
Figure S11. ^1H and ^{13}C NMR spectra of 5-(3-fluorophenoxy)pentanenitrile (**10d**).

Figure S12. ^1H and ^{13}C NMR spectra of 5-(4-fluorophenoxy)pentanenitrile (**10e**).

DS-005 carbon.10.fid

DONALD:DS-005 carbon: CDCl₃: 15/08/2013: RT:1H,13C: 300NMR

DS-005 carbon.11.fid

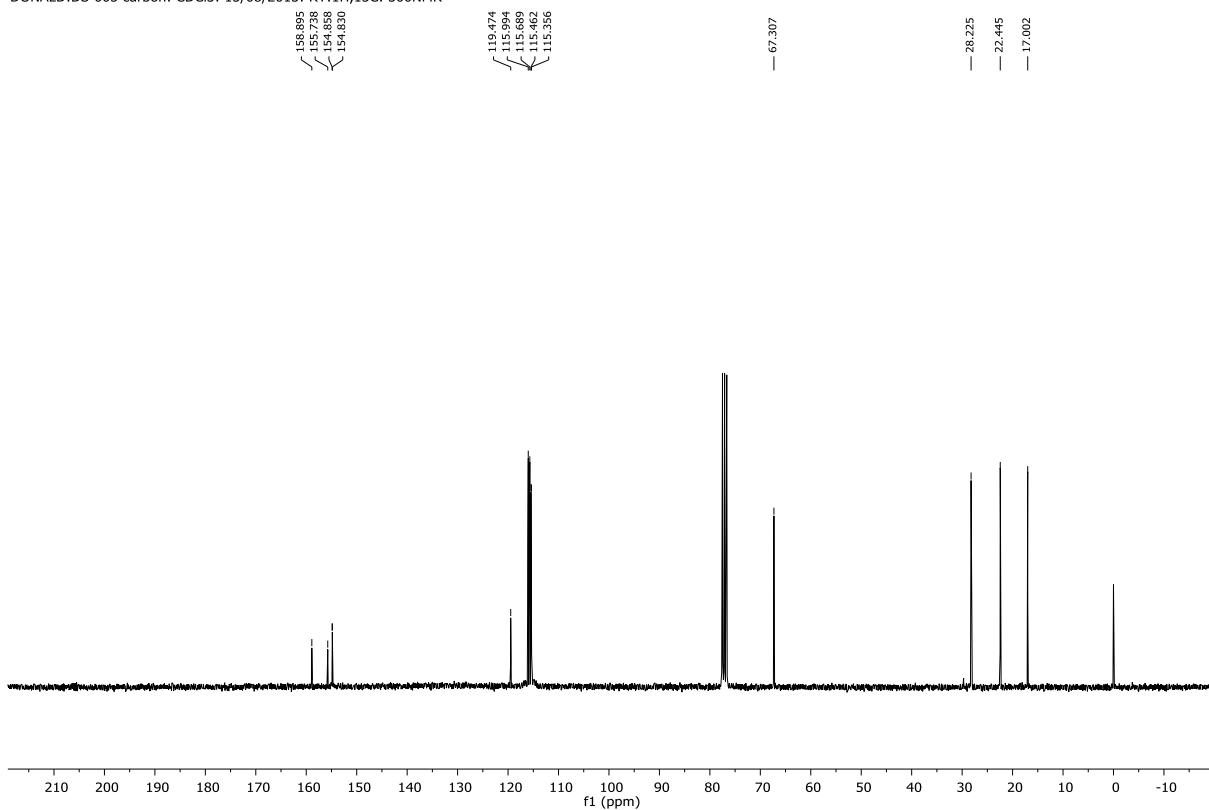
DONALD:DS-005 carbon: CDCl₃: 15/08/2013: RT:1H,13C: 300NMR

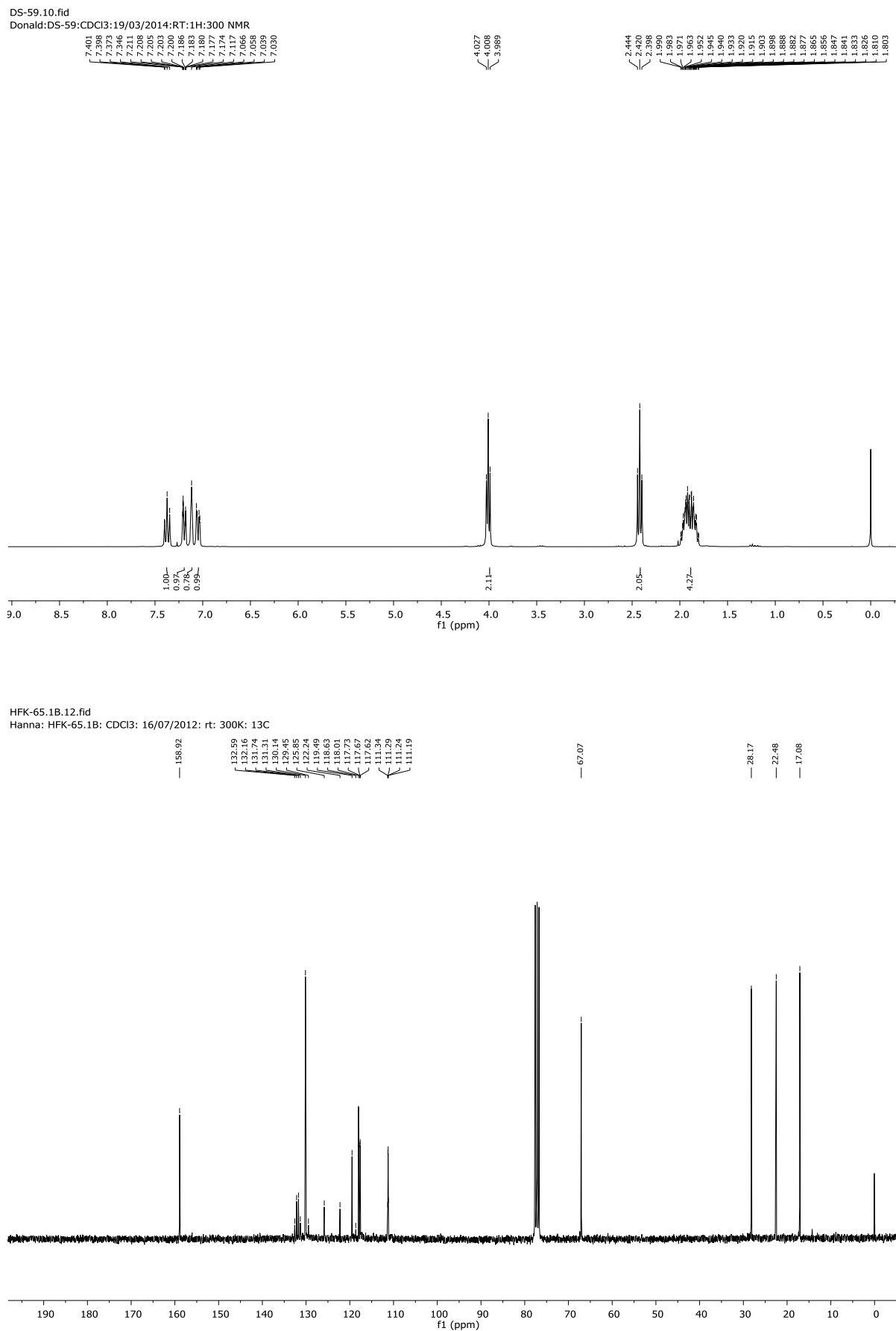
Figure S13. ^1H and ^{13}C NMR spectra of 5-(3-(trifluoromethyl)phenoxy)pentanenitrile (**10f**).

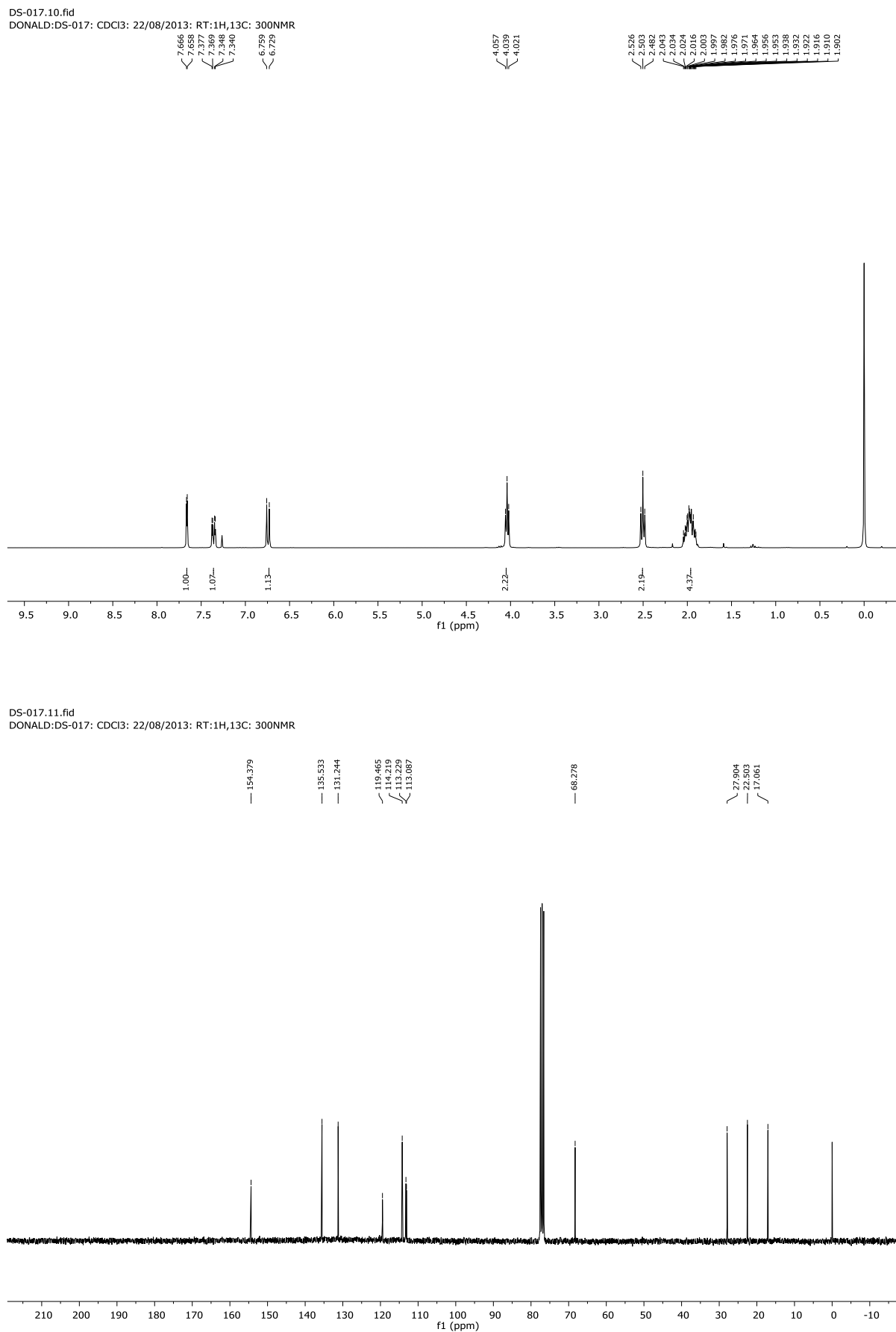
Figure S14. ^1H and ^{13}C NMR spectra of 5-(2,4-dibromophenoxy)pentanenitrile (**10g**).

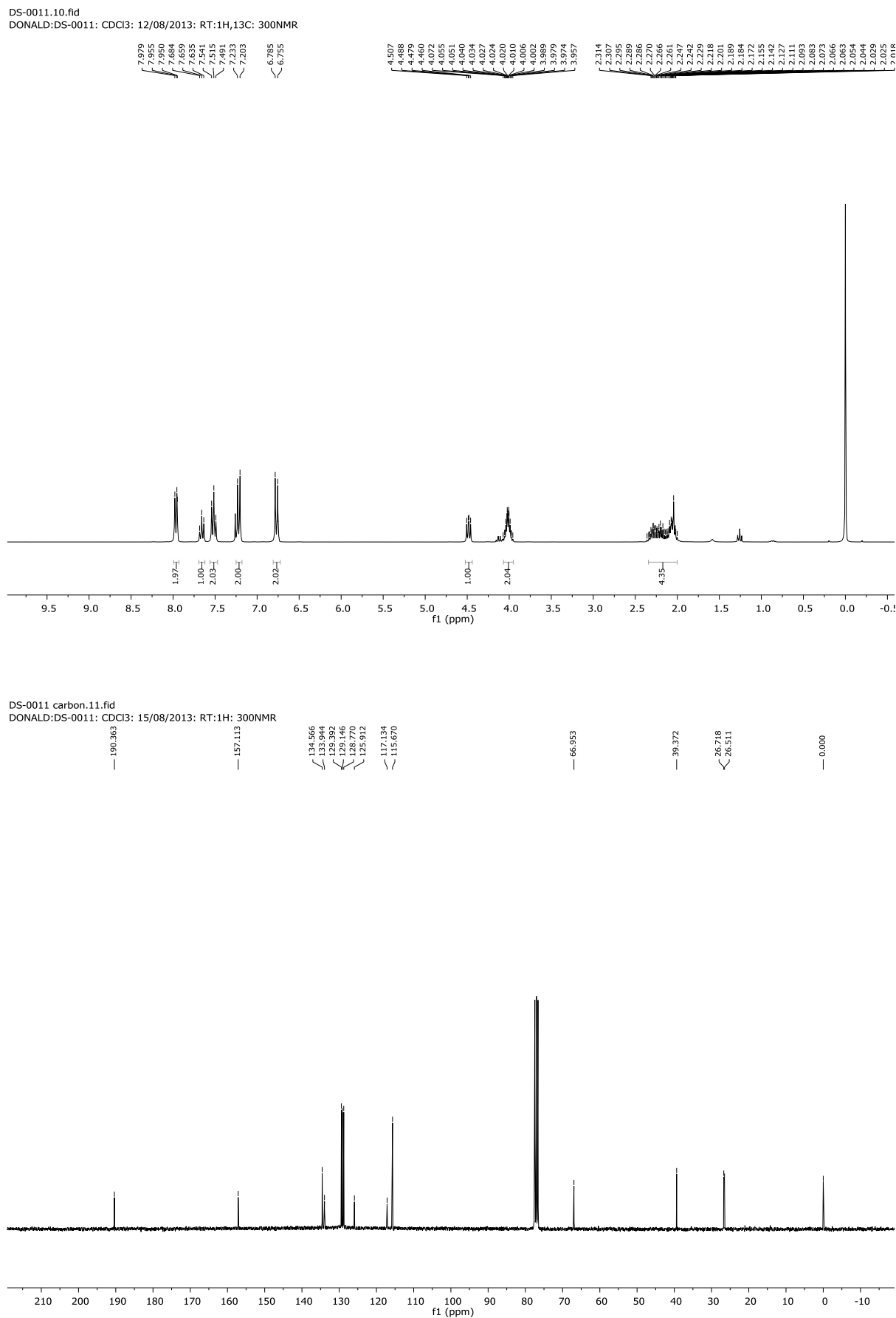
Figure S15. ^1H and ^{13}C NMR spectra of 2-benzoyl-5-(4-chlorophenoxy)pentanenitrile (**11a**).

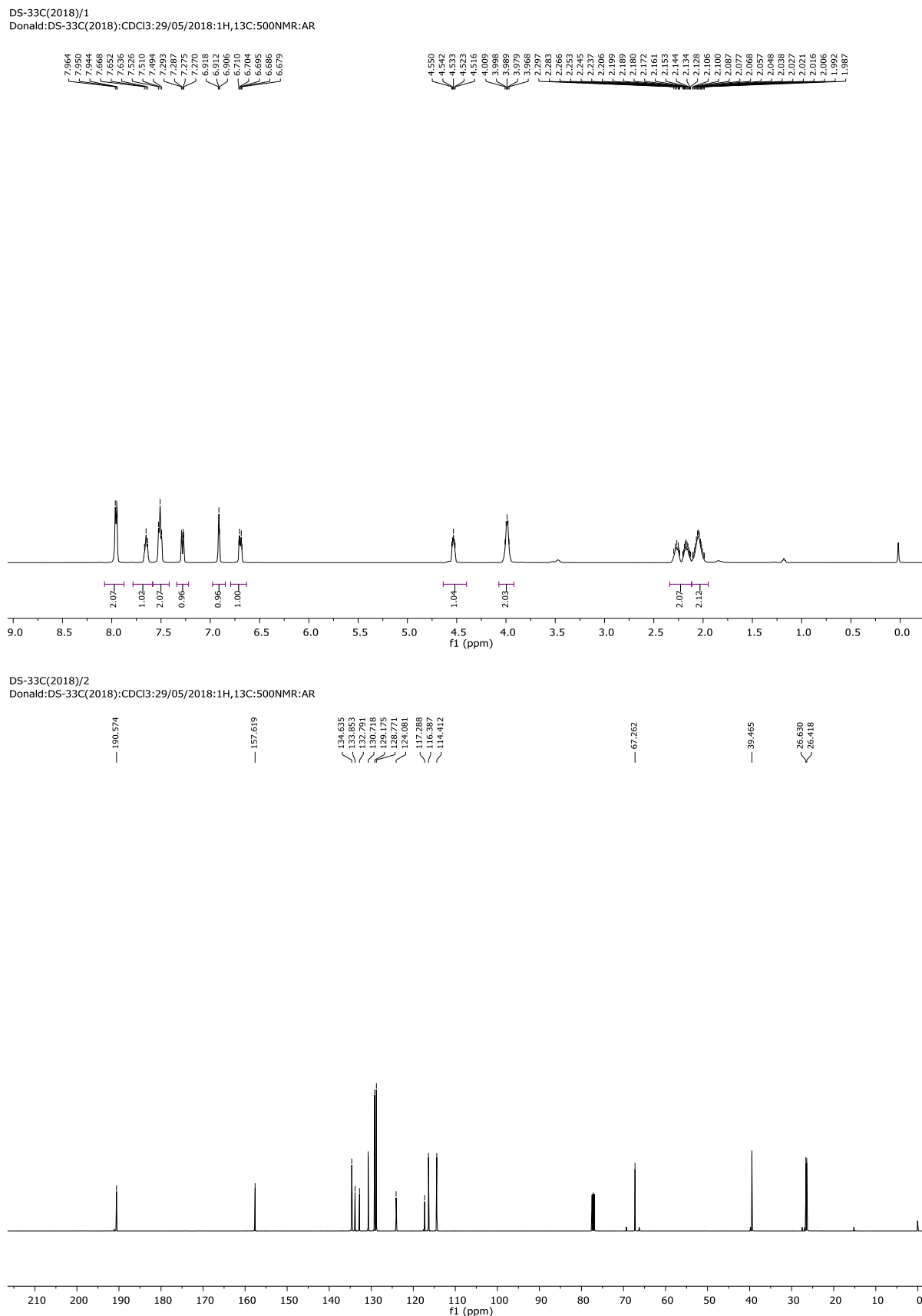
Figure S16. ^1H and ^{13}C NMR spectra of 2-benzoyl-5-(3,4-dichlorophenoxy)pentanenitrile (**11b**).

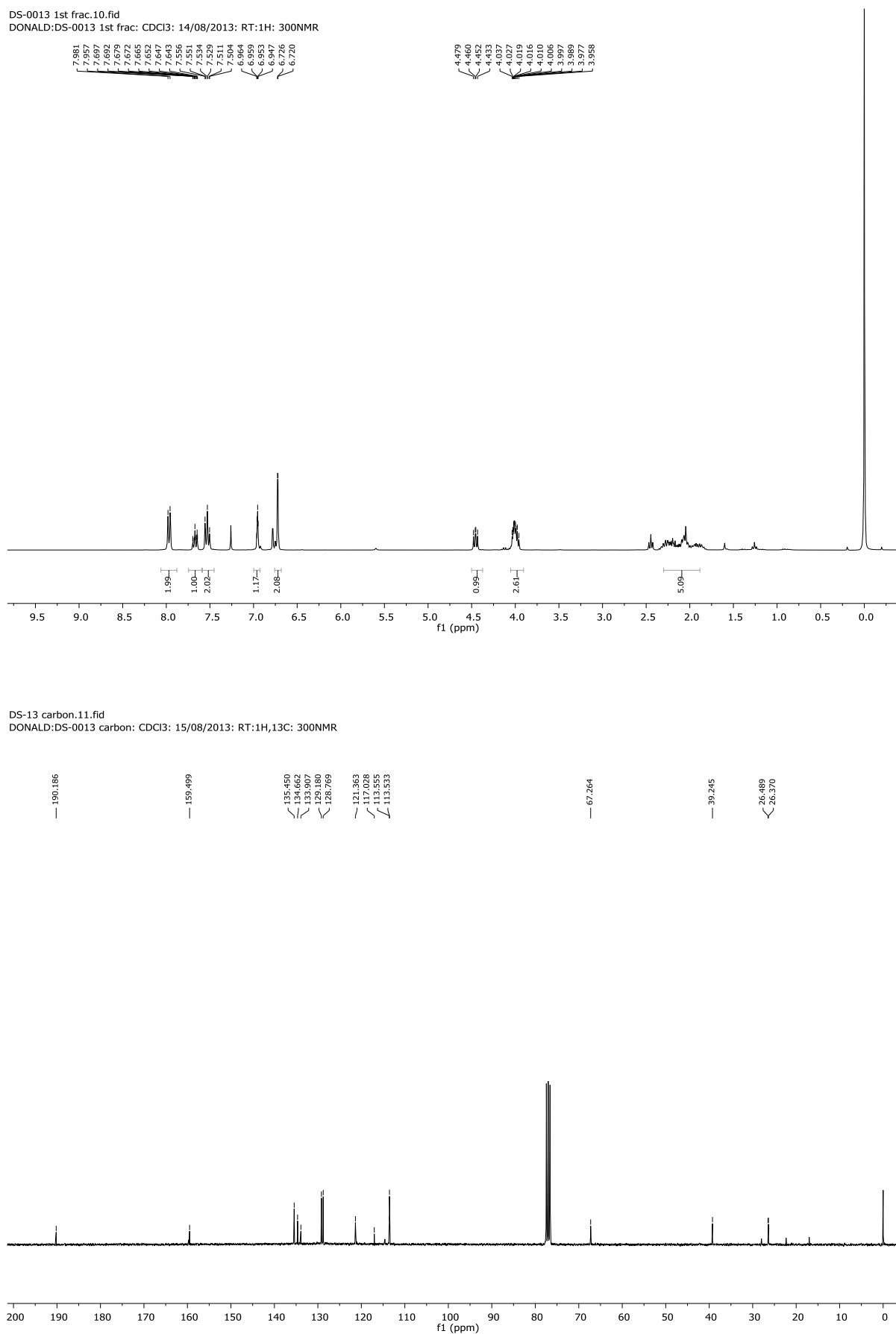
Figure S17. ^1H and ^{13}C NMR spectra of 2-benzoyl-5-(3,5-dichlorophenoxy)pentanenitrile (**11c**).

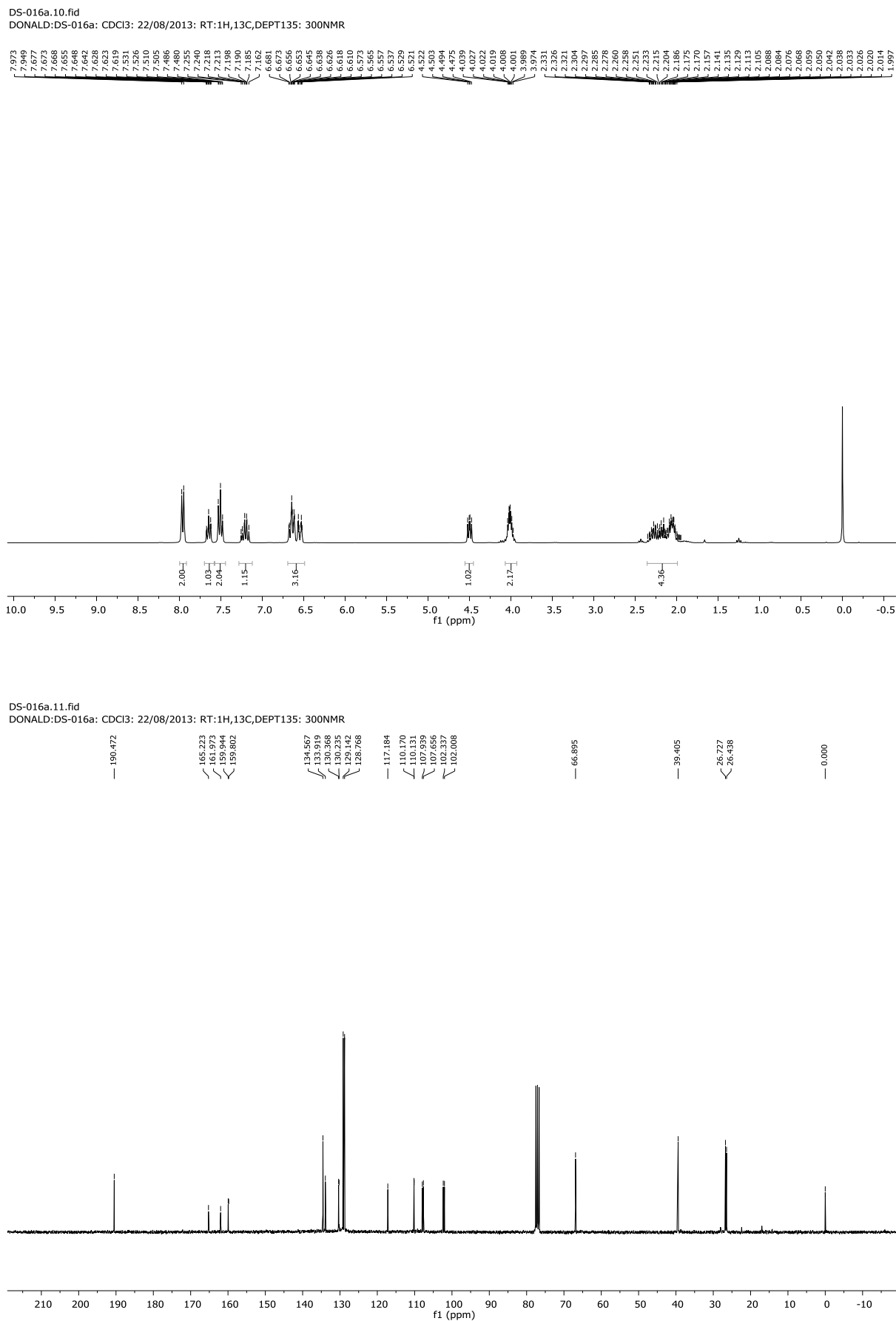
Figure S18. ^1H and ^{13}C NMR spectra of 2-benzoyl-5-(3-fluorophenoxy)pentanenitrile (**11d**).

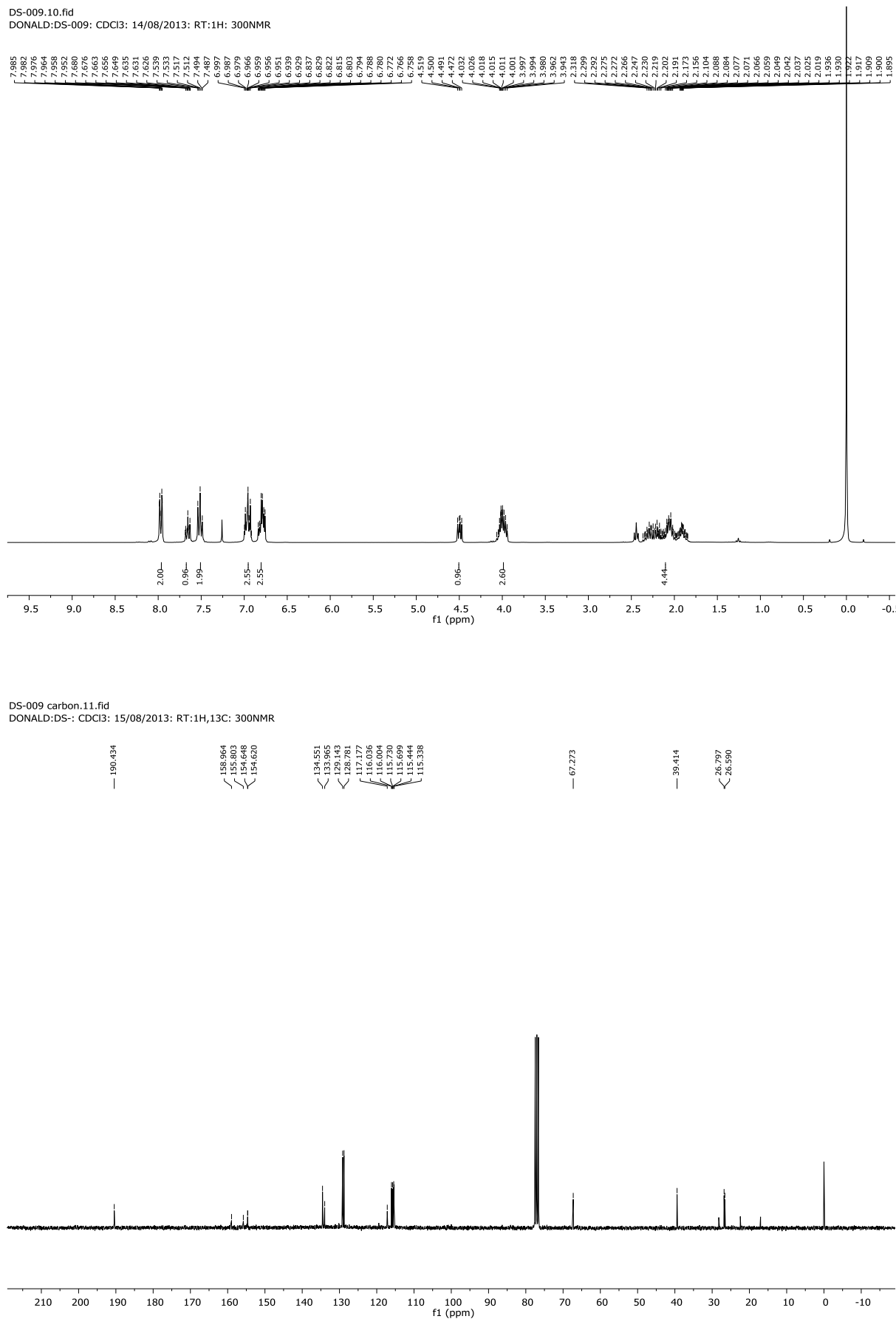
Figure S19. ^1H and ^{13}C NMR spectra of 2-benzoyl-5-(4-fluorophenoxy)pentanenitrile (**11e**).

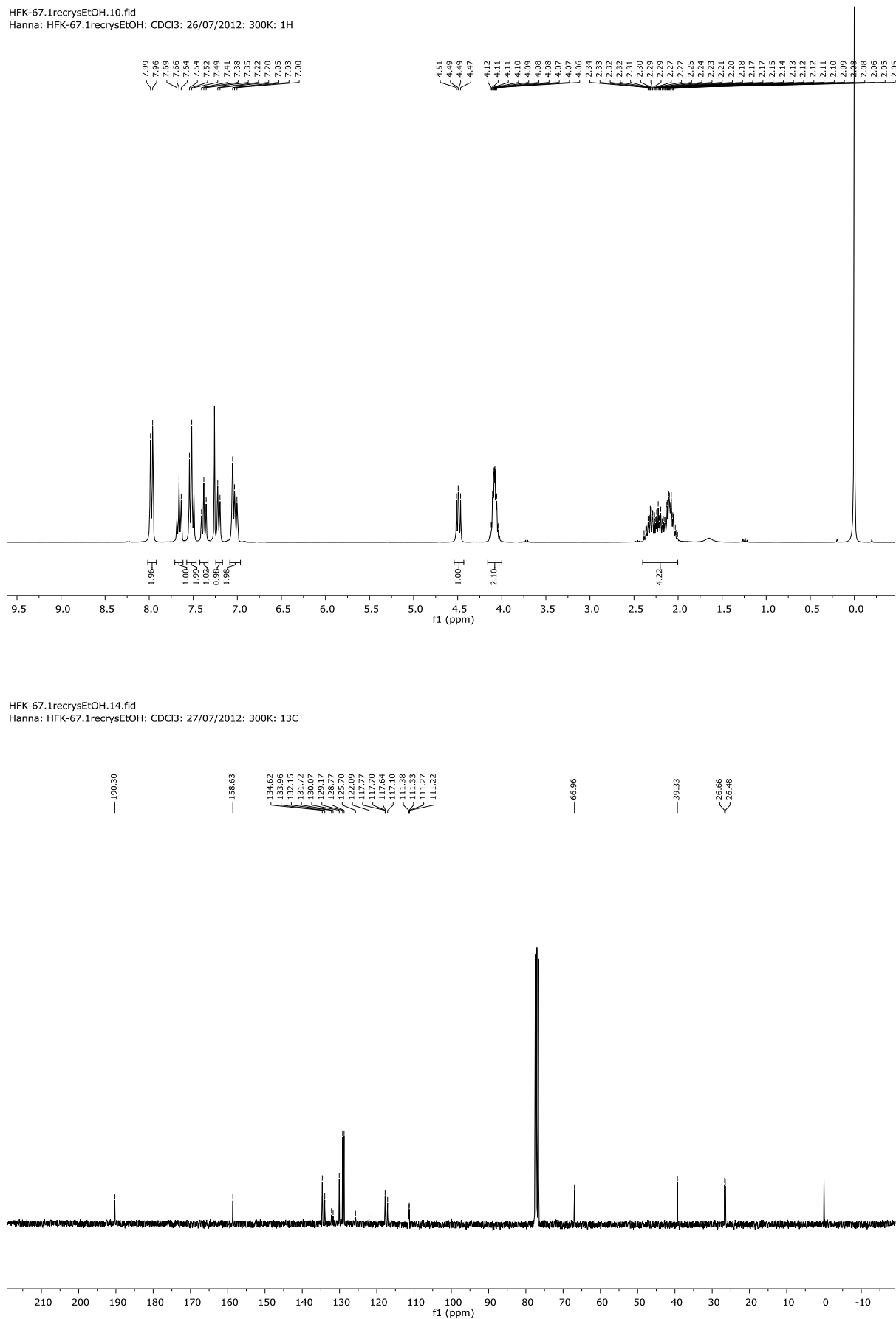
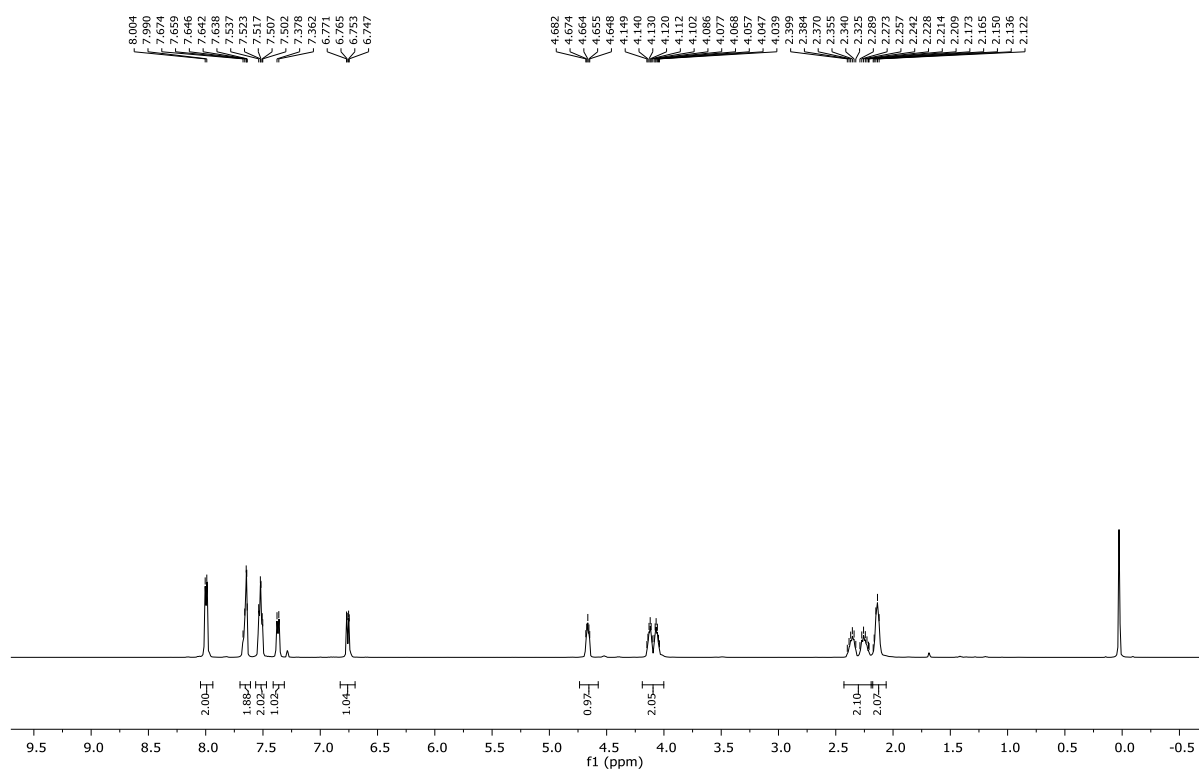
Figure S20. ^1H and ^{13}C NMR spectra of 2-benzoyl-5-(3-(trifluoromethyl)phenoxy)pentanenitrile (**11f**).

Figure S21. ^1H and ^{13}C NMR spectra of 2-benzoyl-5-(2,4-dibromophenoxy)pentanenitrile (**11g**).

DS-18C(2018)/1
Donald:DS-18C(2018):CDCl₃:29/05/2018:1H,13C:500NMR:AR



DS-18C(2018)/2
Donald:DS-18C(2018):CDCl₃:29/05/2018:1H,13C:500NMR:AR

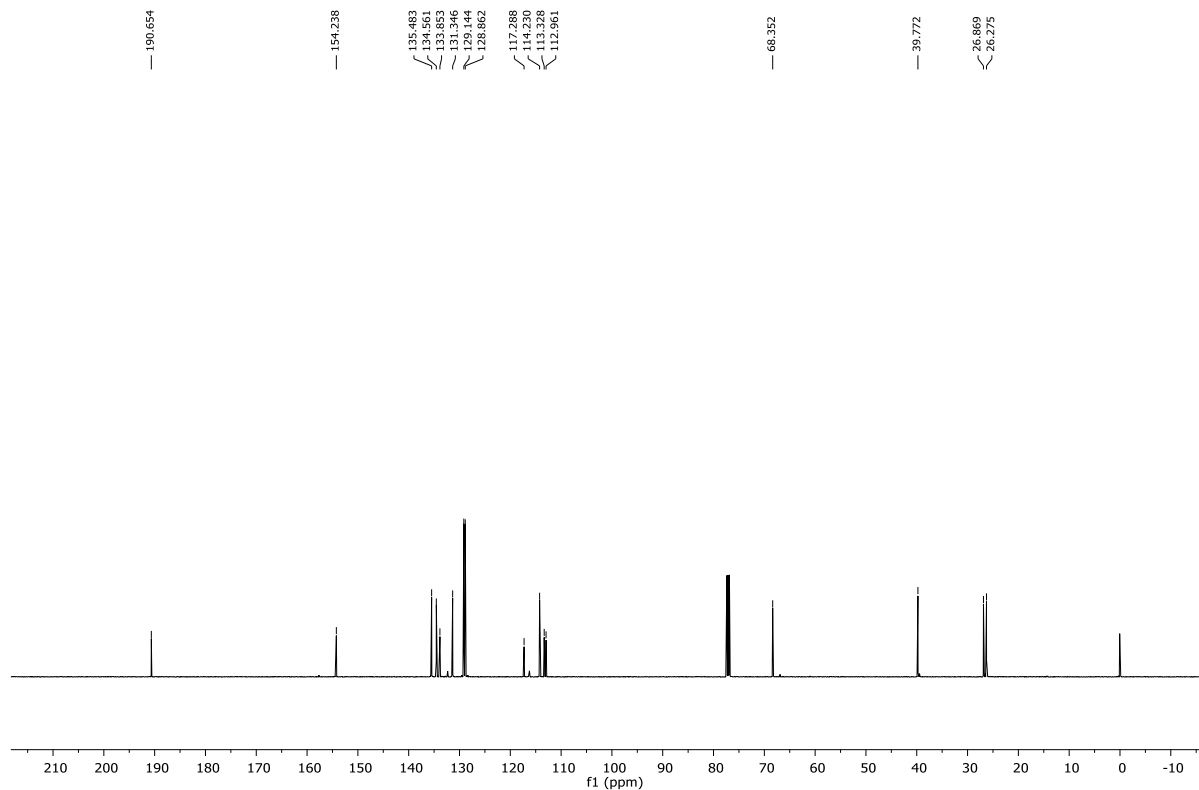
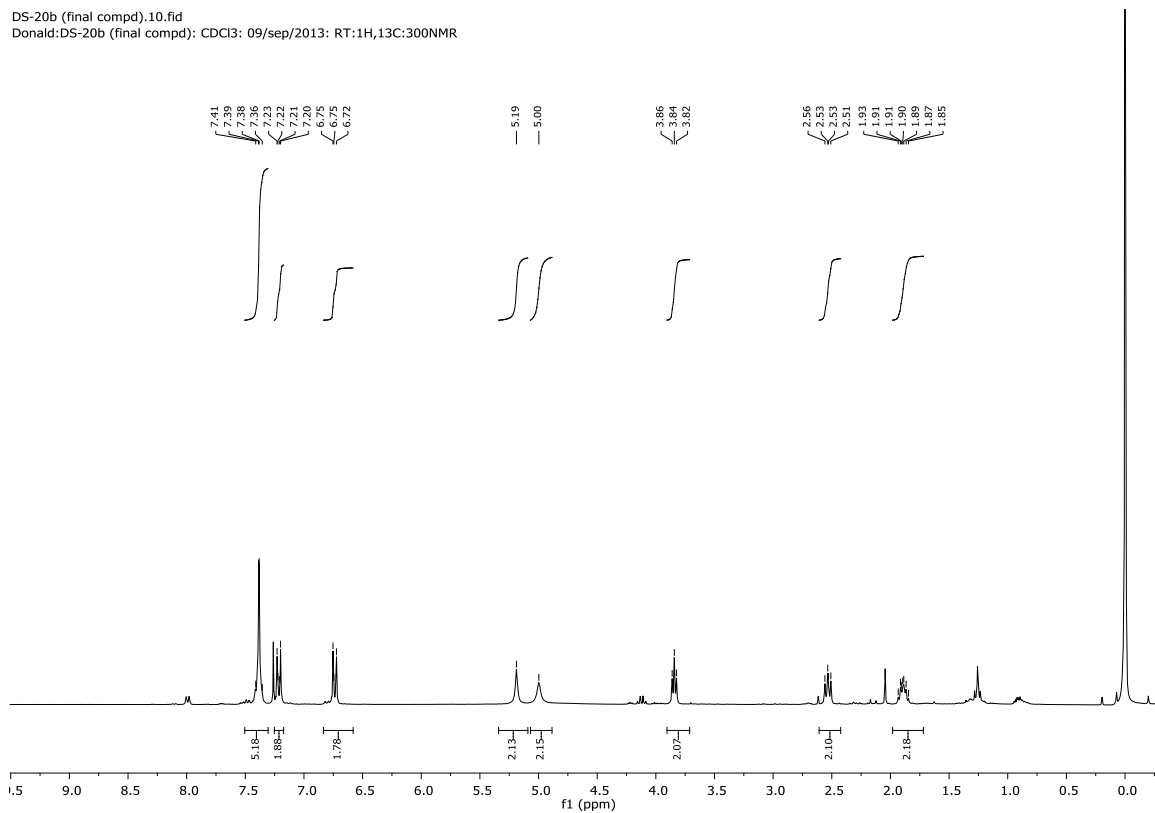


Figure S22. ^1H and ^{13}C NMR spectra of 5-(3-(4-chlorophenoxy)propyl)-6-phenylpyrimidine-2,4-diamine (**6a**).

DS-20b (final compd).10.fid

Donald:DS-20b (final compd): CDCl₃: 09/sep/2013: RT:1H,13C:300NMR

DS-20b (final compd).11.fid

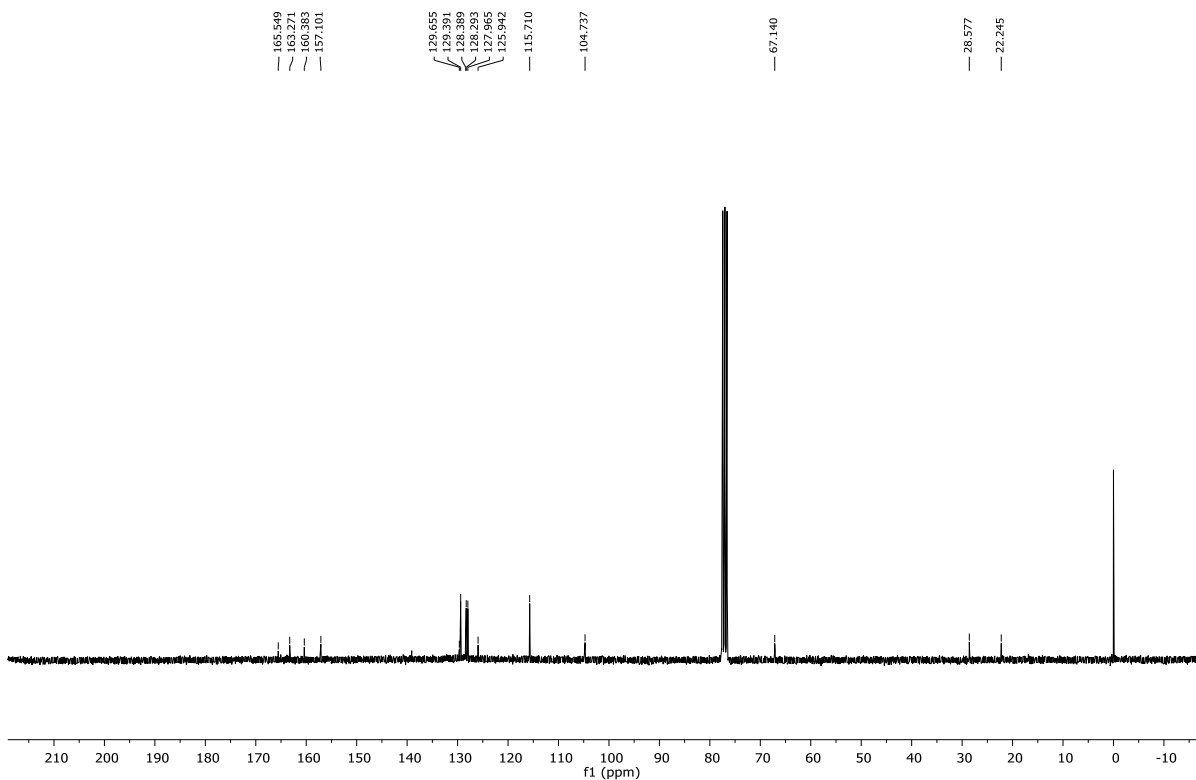
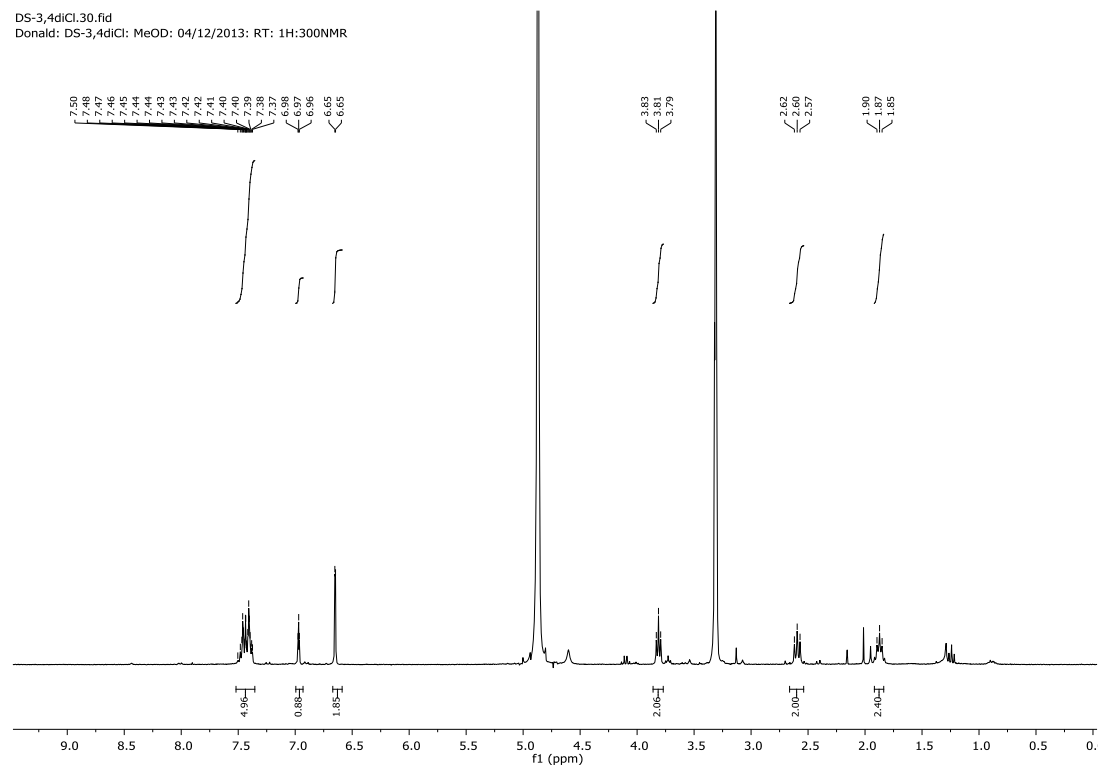
Donald:DS-20b (final compd): CDCl₃: 09/sep/2013: RT:1H,13C:300NMR

Figure S23. ^1H and ^{13}C NMR spectra of 5-(3-(3,4-dichlorophenoxy)propyl)-6-phenylpyrimidine-2,4-diamine (**6b**).

DS-026.4.fid
Donald: DS 026: MeOD: 10/03/2014: 300K: 1H, 13C: 500NMR

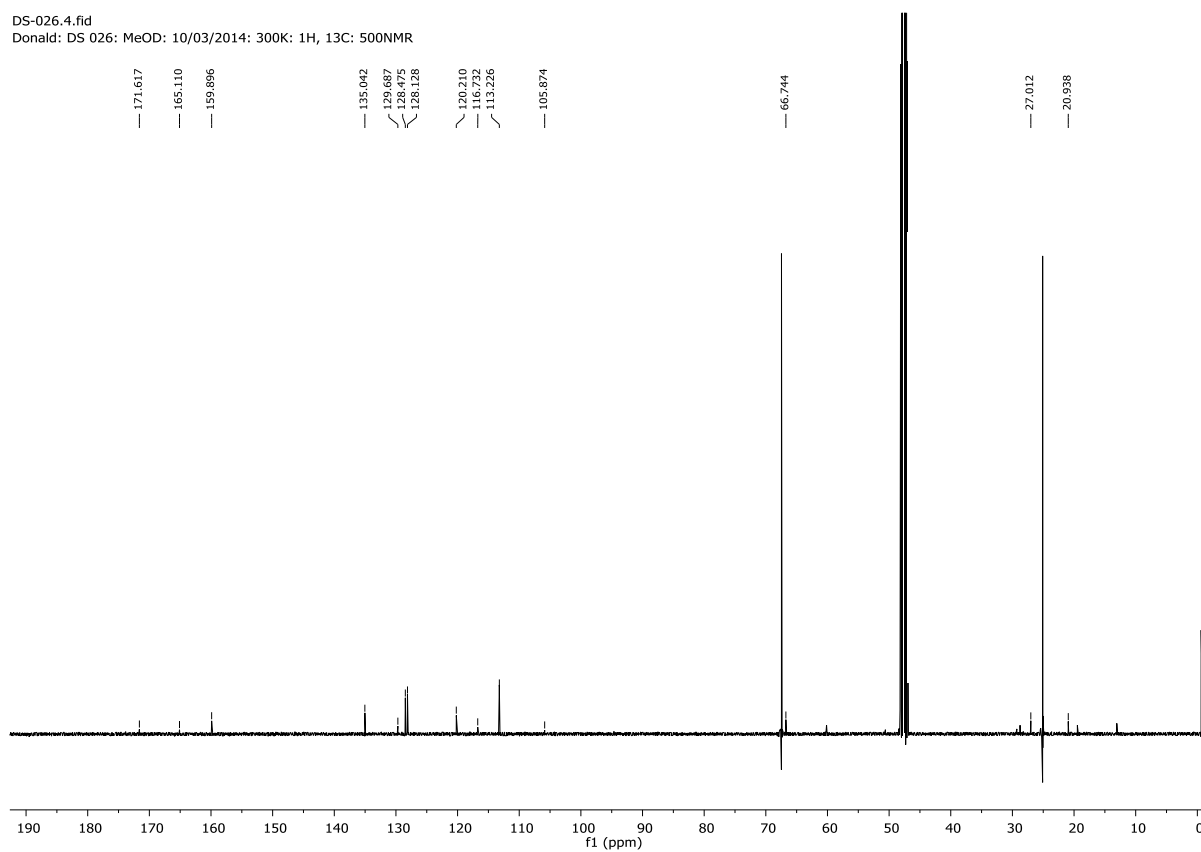
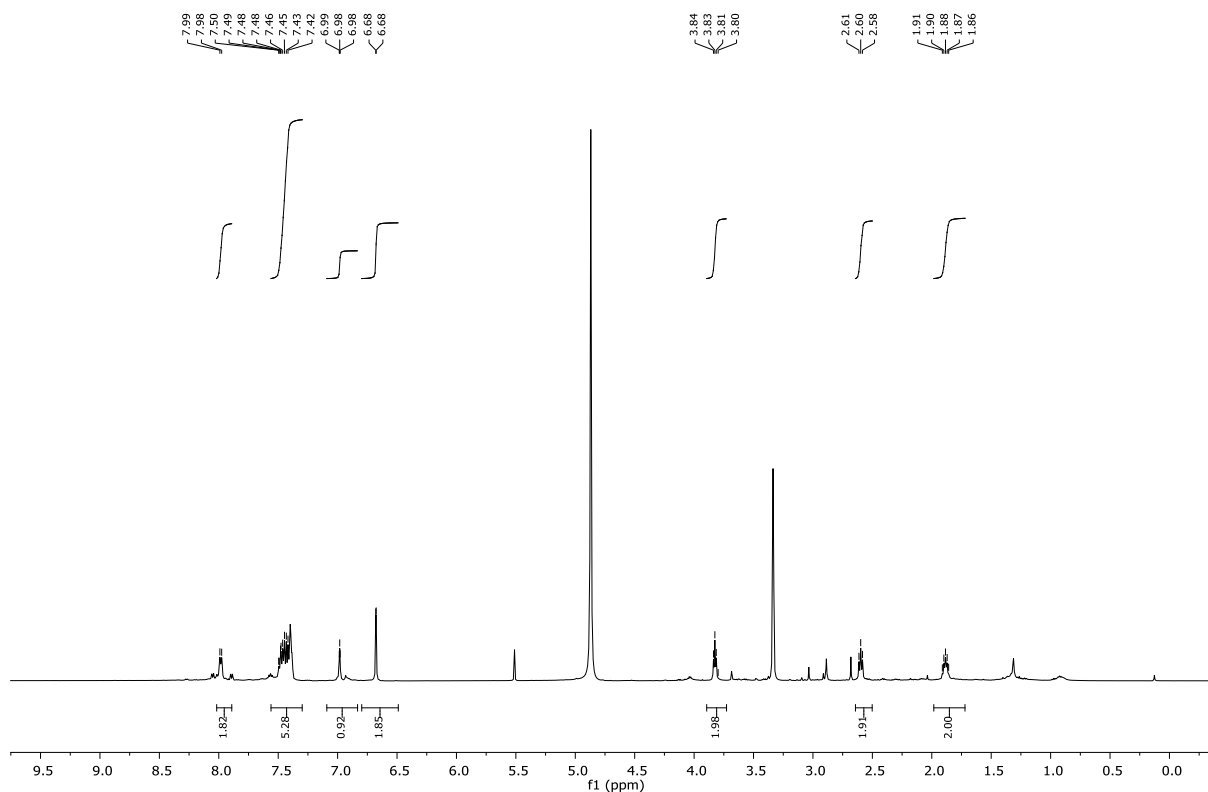


Figure S24. ^1H and ^{13}C NMR spectra of 5-(3-(3,5-dichlorophenoxy)propyl)-6-phenylpyrimidine-2,4-diamine (**6c**).

DS-24(FP).1.fid

Donald-24(FP): MeOD:30/09/2013:RT:1H,13C:500NMR



DS-24(FP).2.fid

Donald-24(FP): MeOD:30/09/2013:RT:1H,13C:500NMR

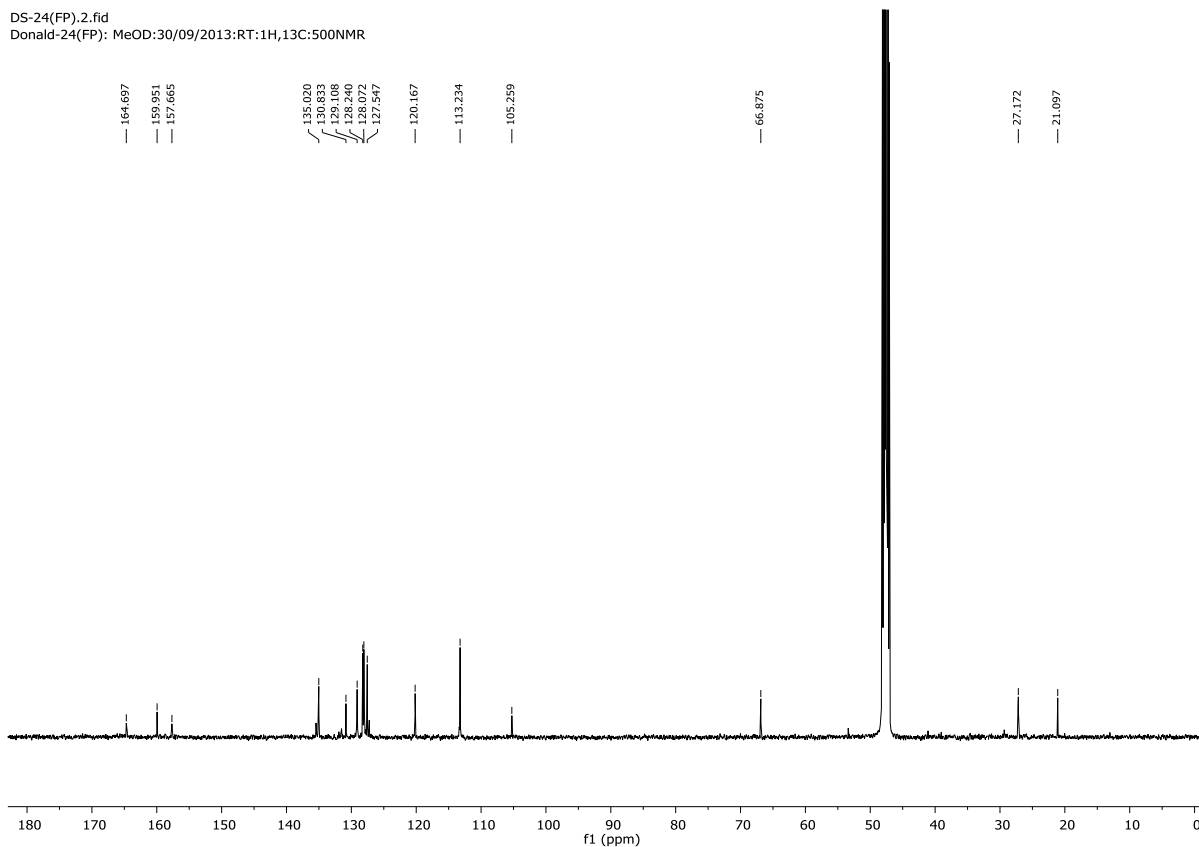


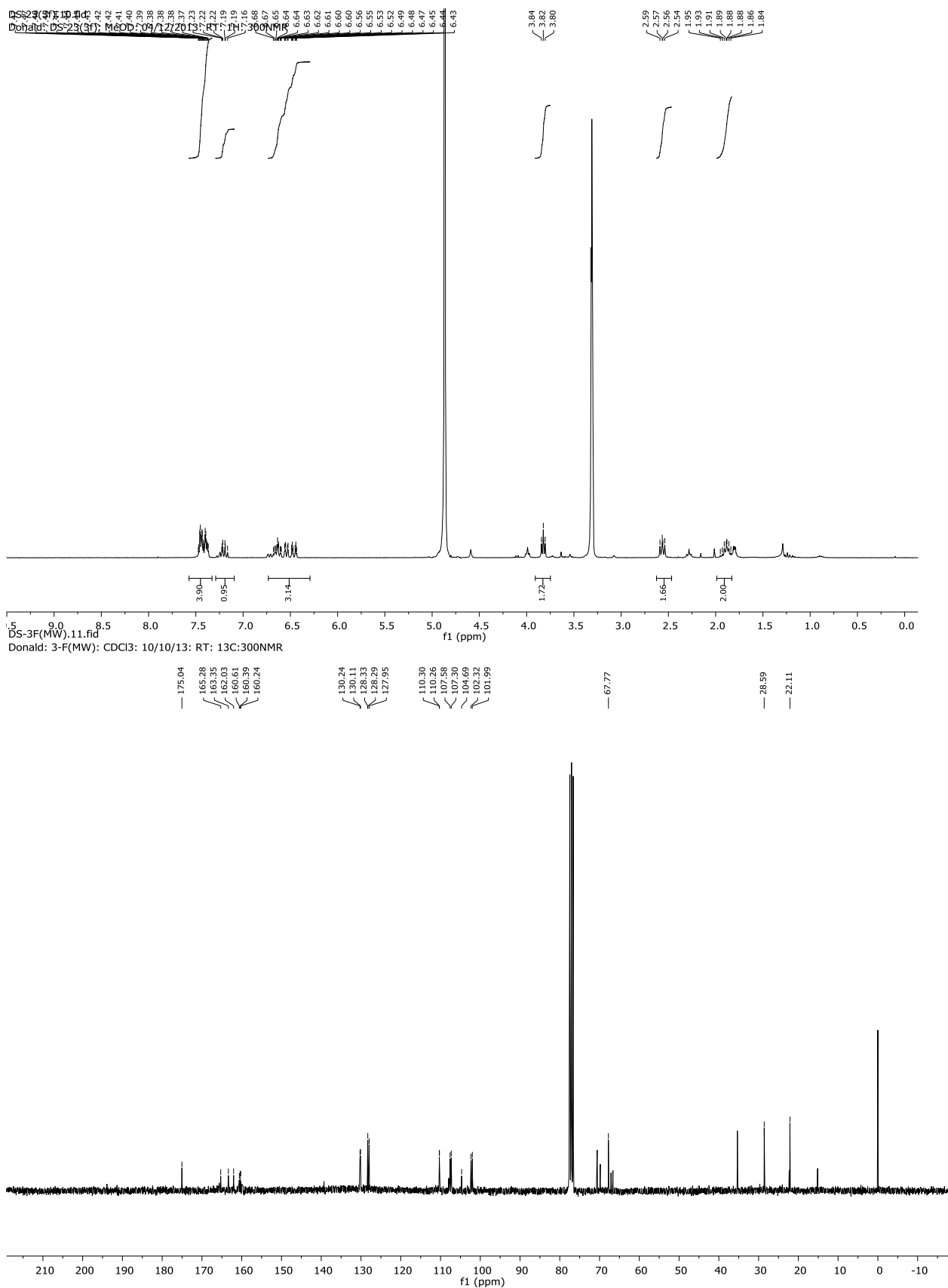
Figure S25. ^1H and ^{13}C NMR spectra of 5-(3-(3-fluorophenoxy)propyl)-6-phenylpyrimidine-2,4-diamine (**6d**).

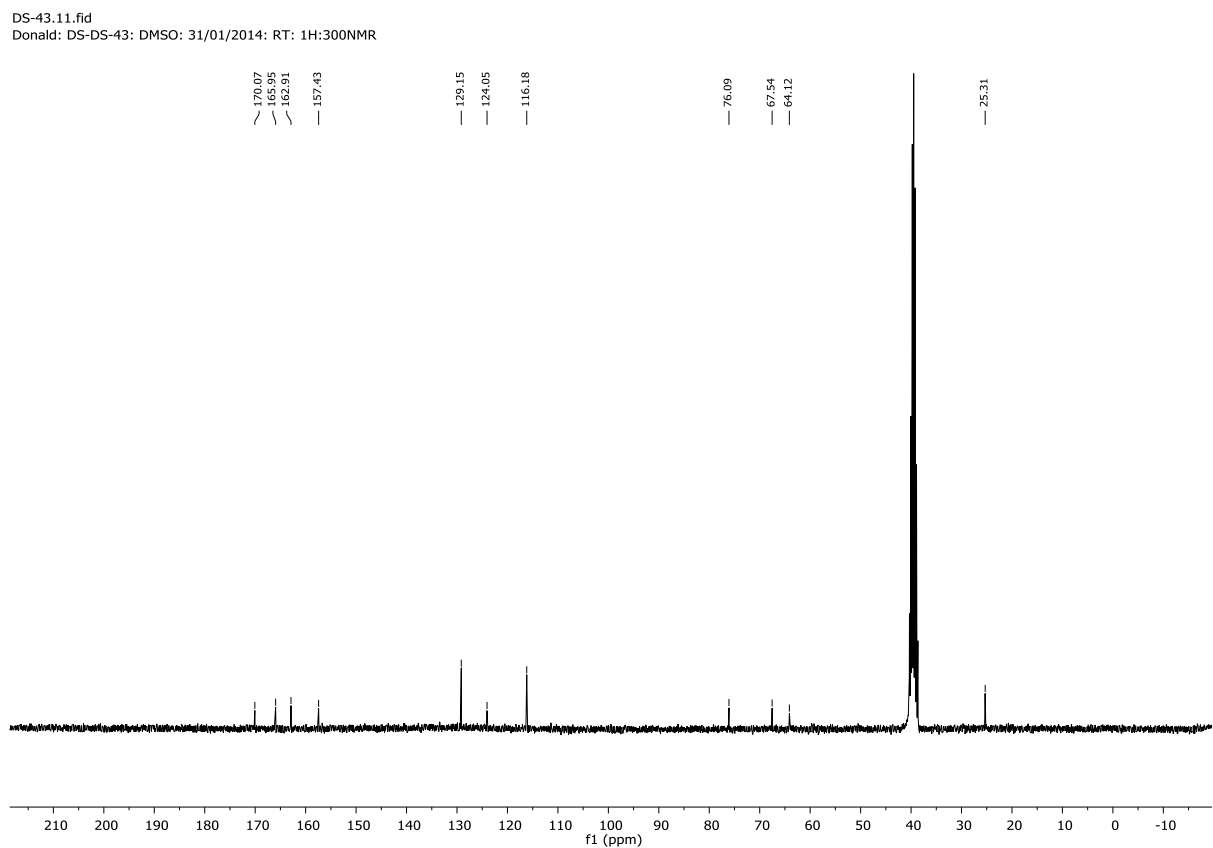
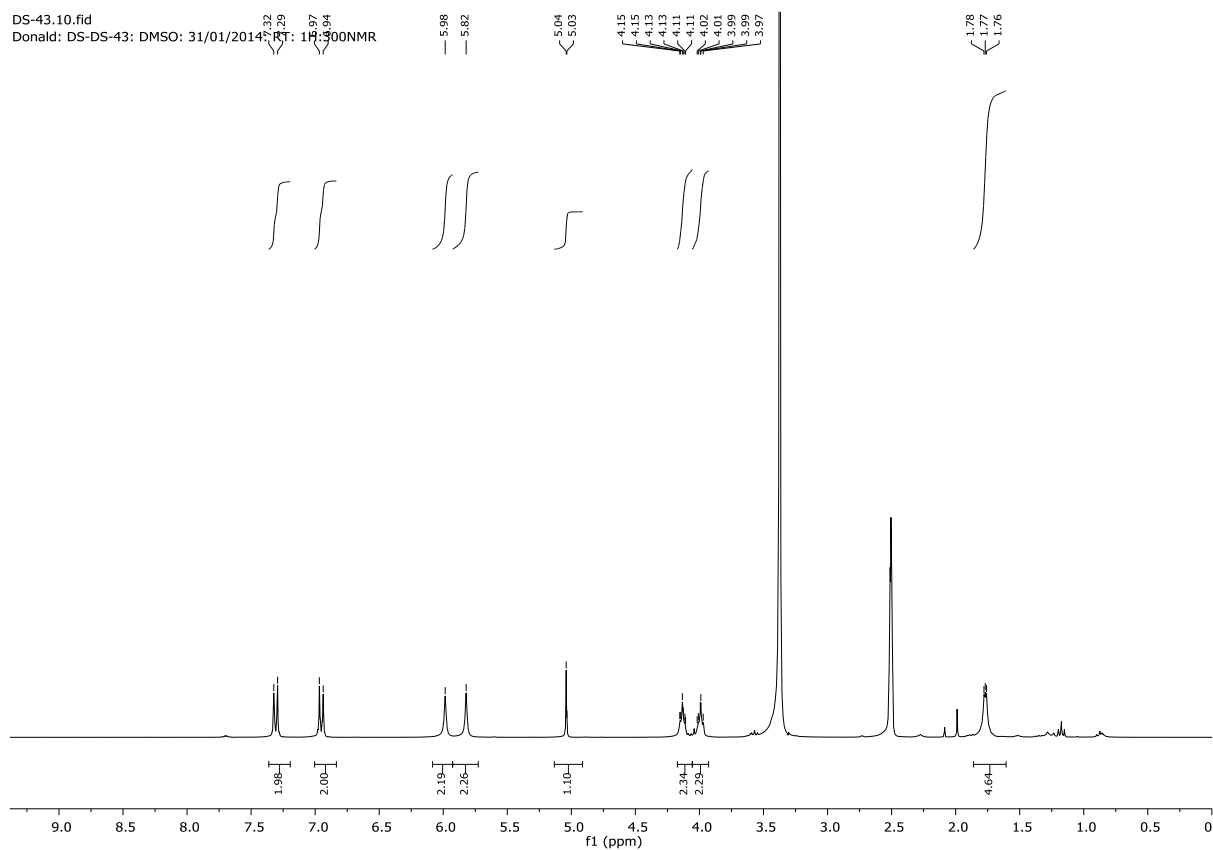
Figure S26. ^1H and ^{13}C NMR spectra of 6-(4-(4-chlorophenoxy)butoxy)pyrimidine-2,4-diamine (**7a**).

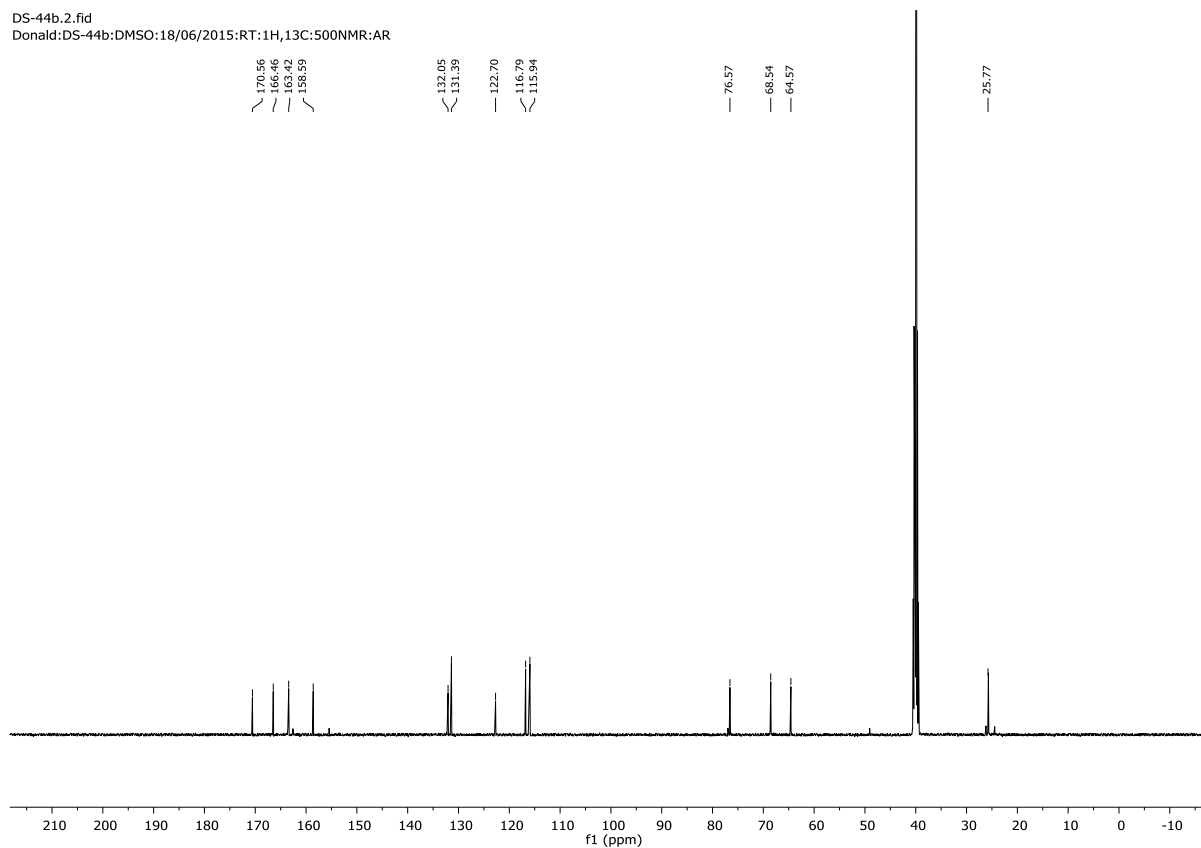
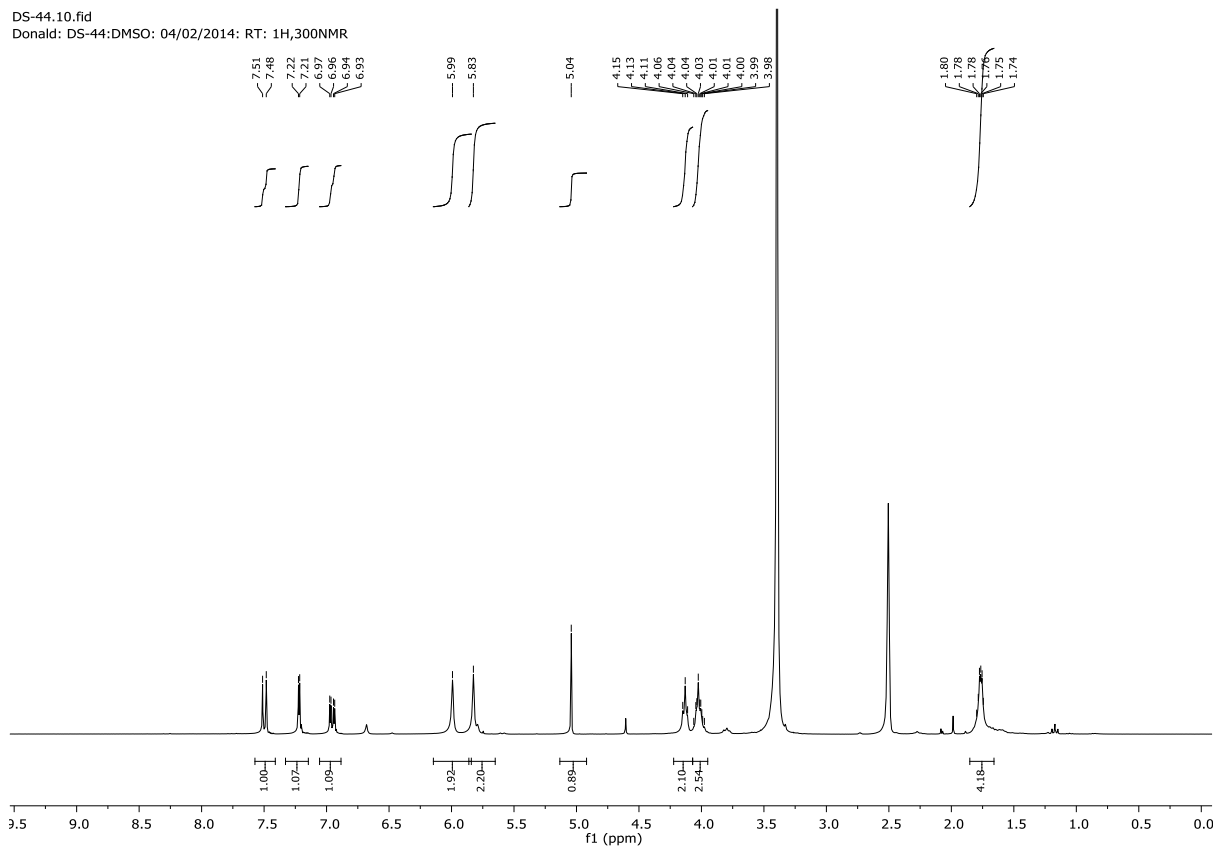
Figure S27. ^1H and ^{13}C NMR spectra of 6-(4-(3,4-dichlorophenoxy)butoxy)pyrimidine-2,4-diamine (**7b**).

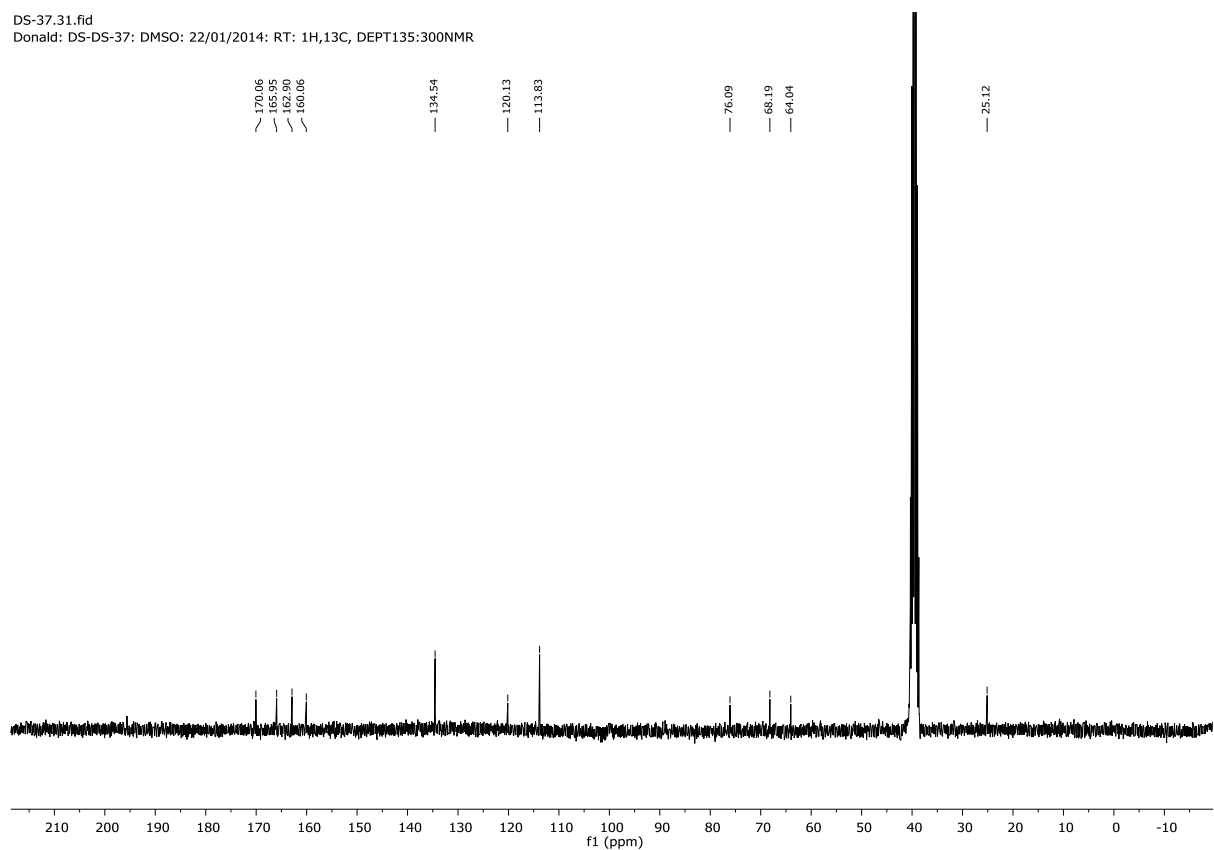
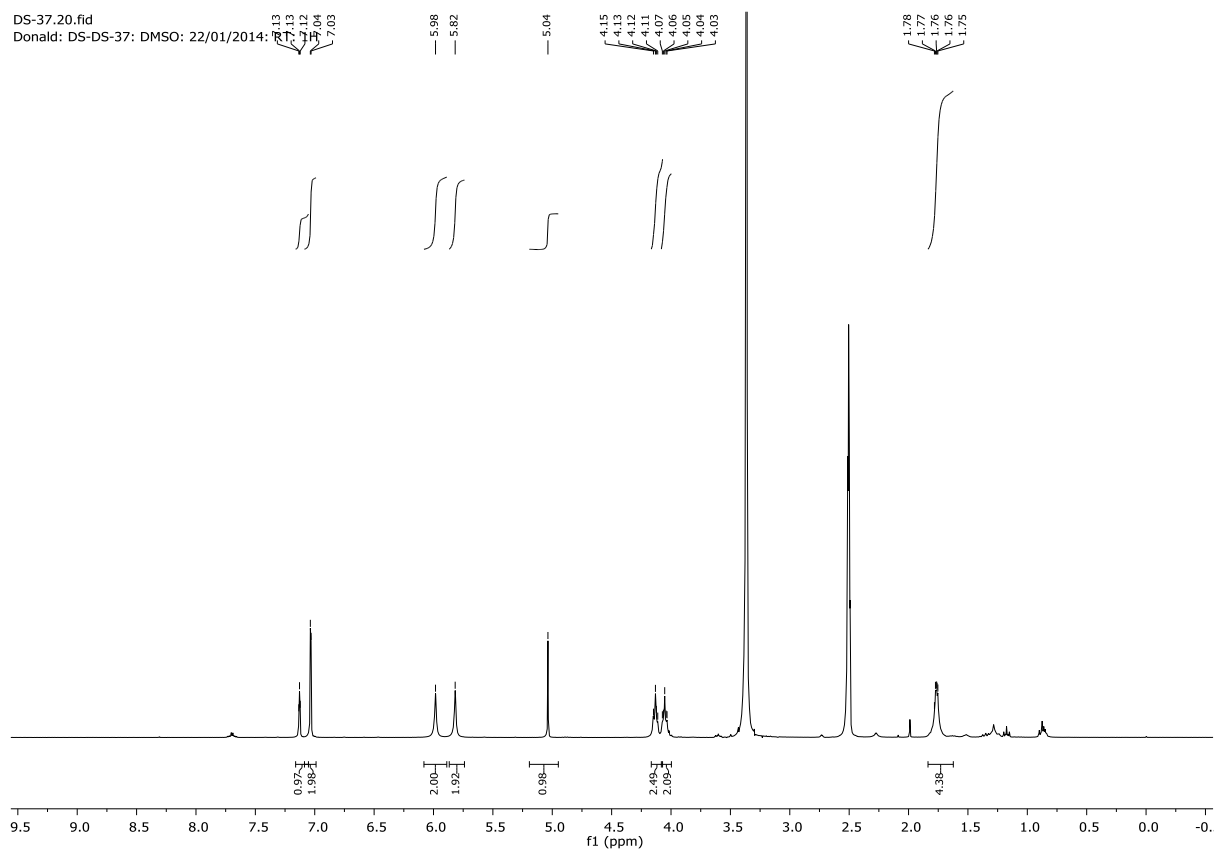
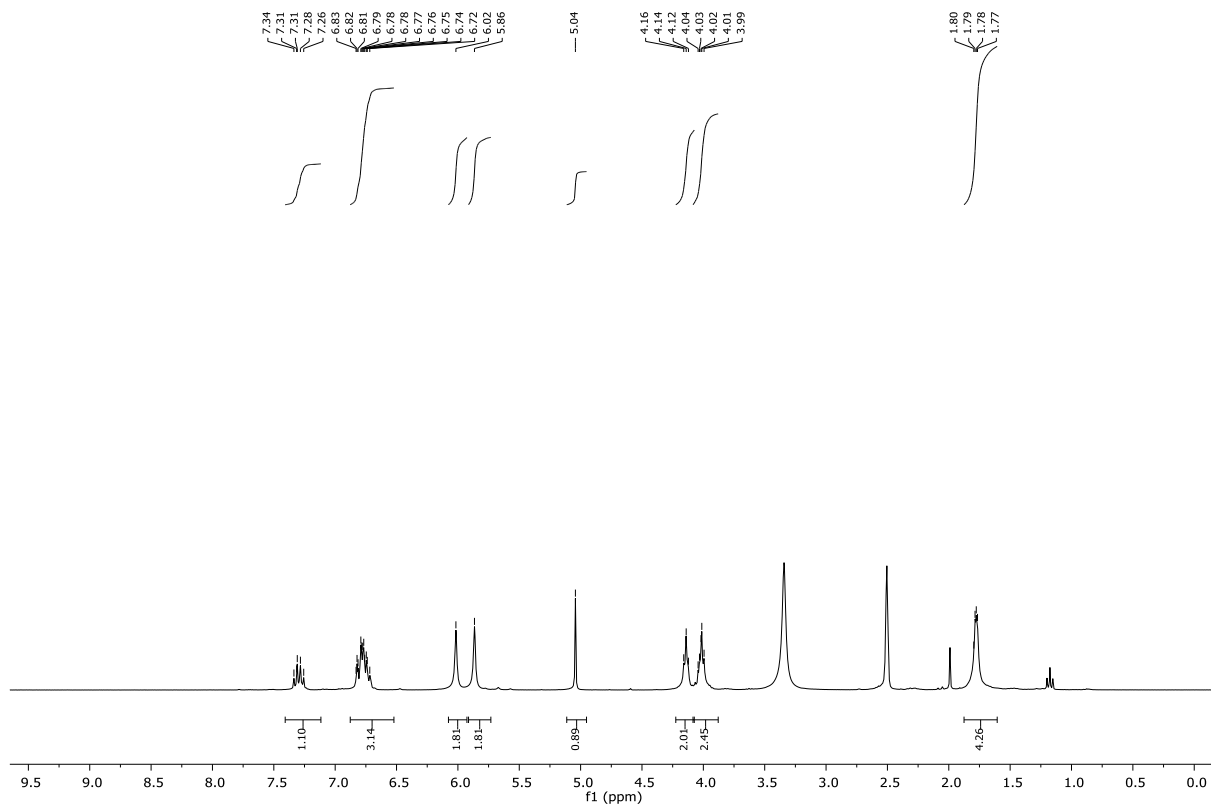
Figure S28. ^1H and ^{13}C NMR spectra of 6-(4-(3,5-dichlorophenoxy)butoxy)pyrimidine-2,4-diamine (**7c**).

Figure S29. ^1H and ^{13}C NMR spectra of 6-(4-(3-fluorophenoxy)butoxy)pyrimidine-2,4-diamine (**7d**).

DS-45.10.fid

Donald:DS-45:DMSO:26/04/2014:RT:1H,13C:300NMR



DS-45.11.fid

Donald:DS-45:DMSO:26/04/2014:RT:1H,13C:300NMR

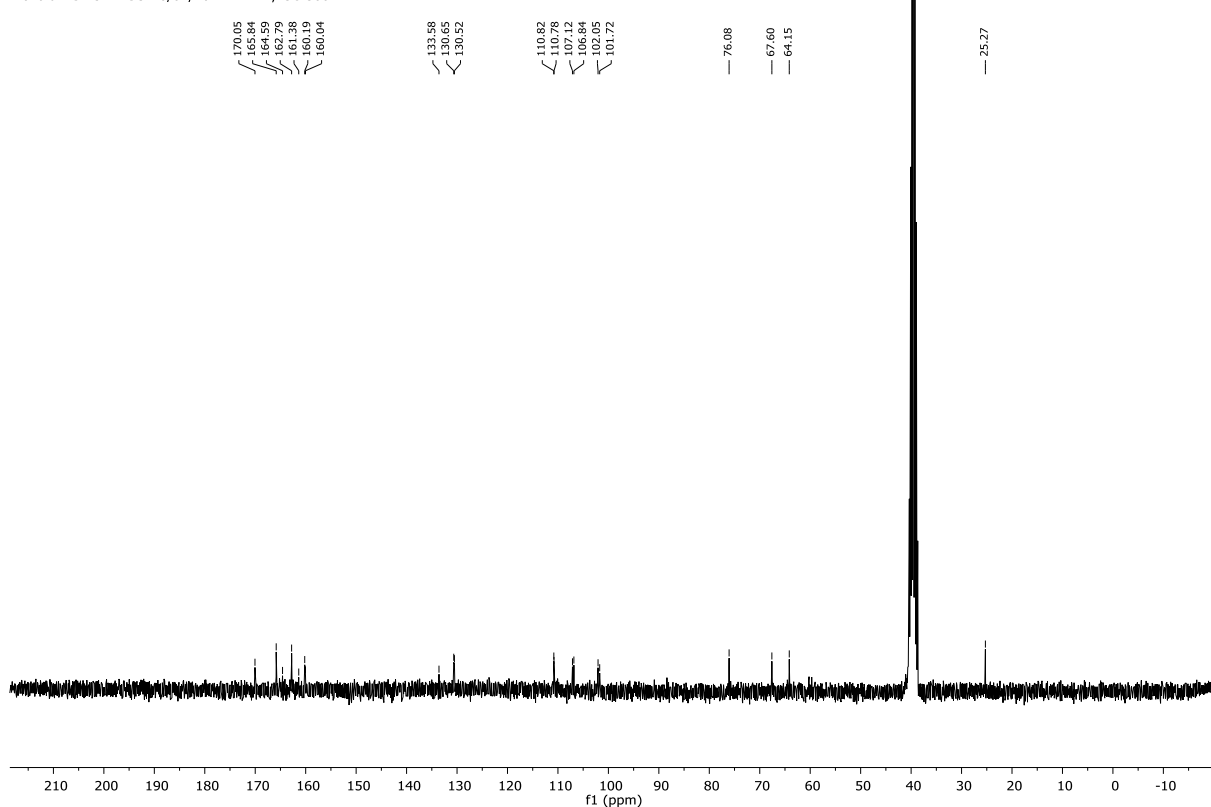


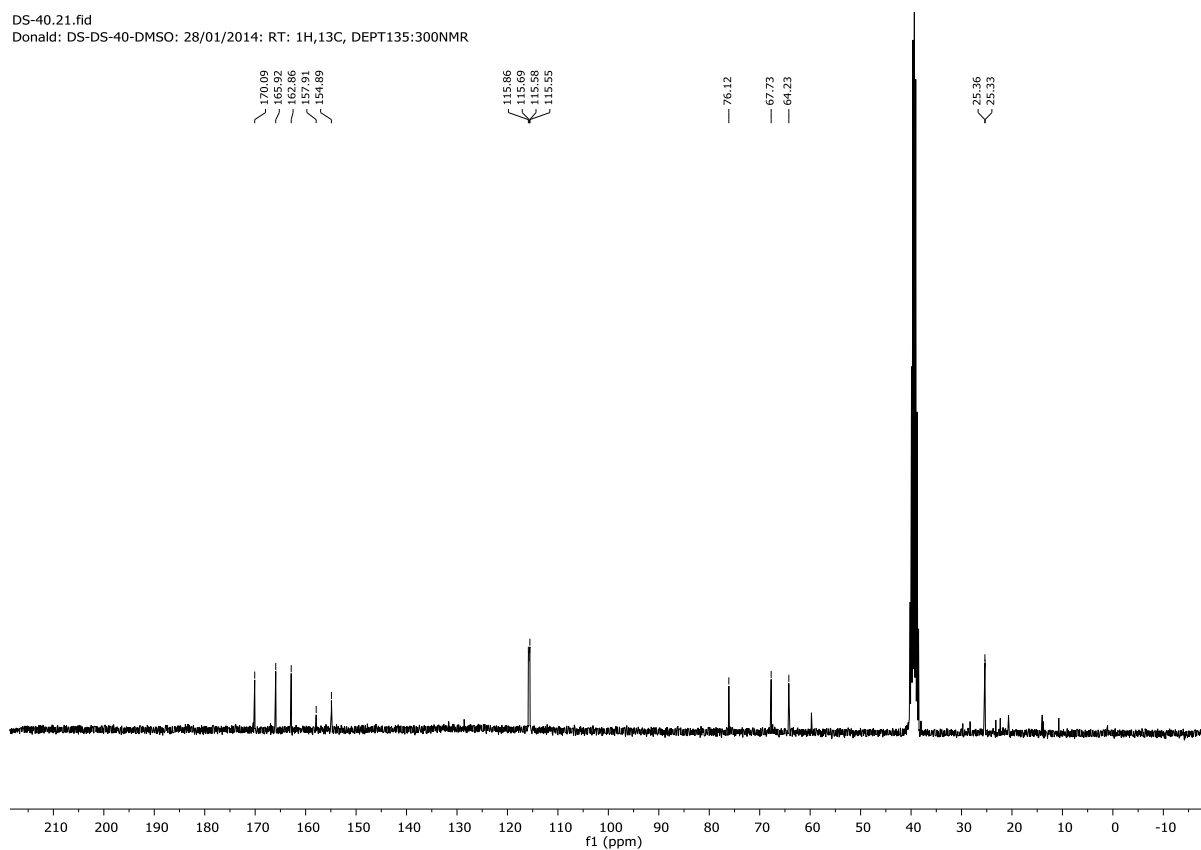
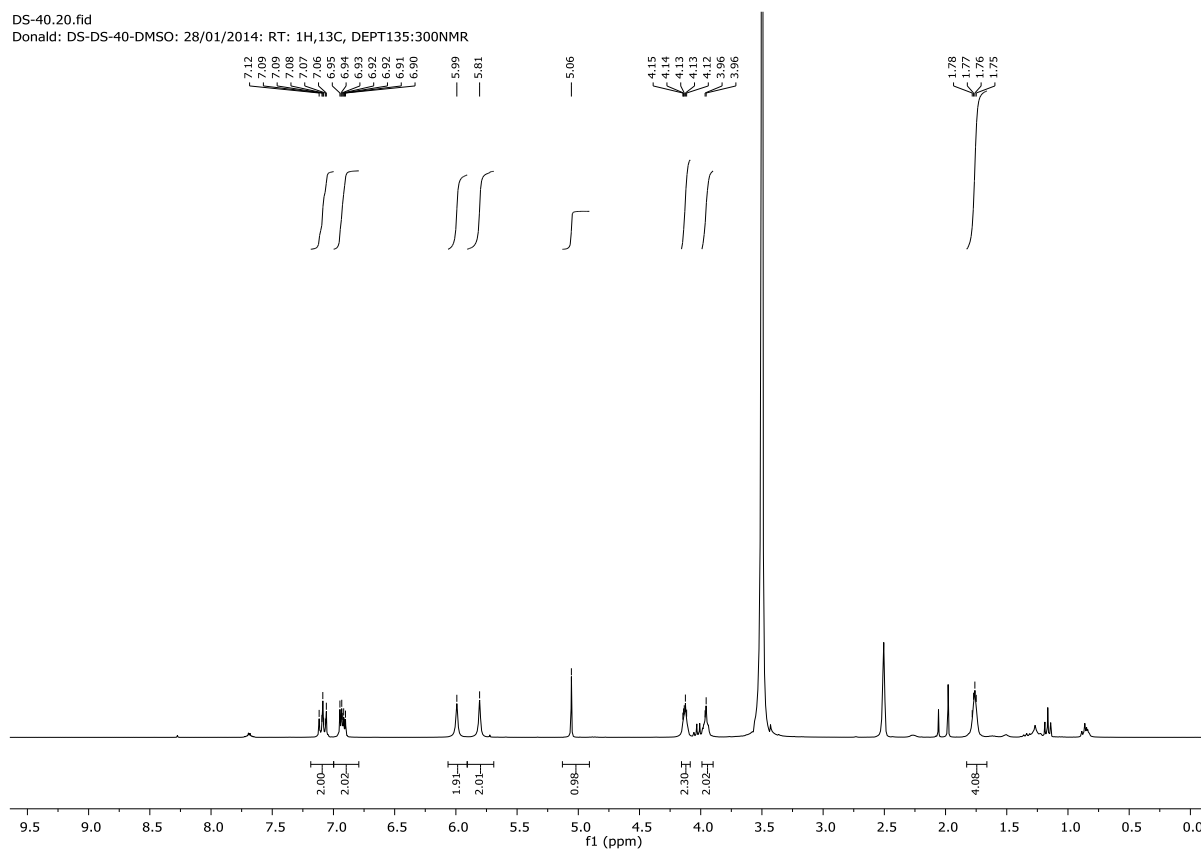
Figure S30. ^1H and ^{13}C NMR spectra of 6-(4-(4-fluorophenoxy)butoxy)pyrimidine-2,4-diamine (**7e**).

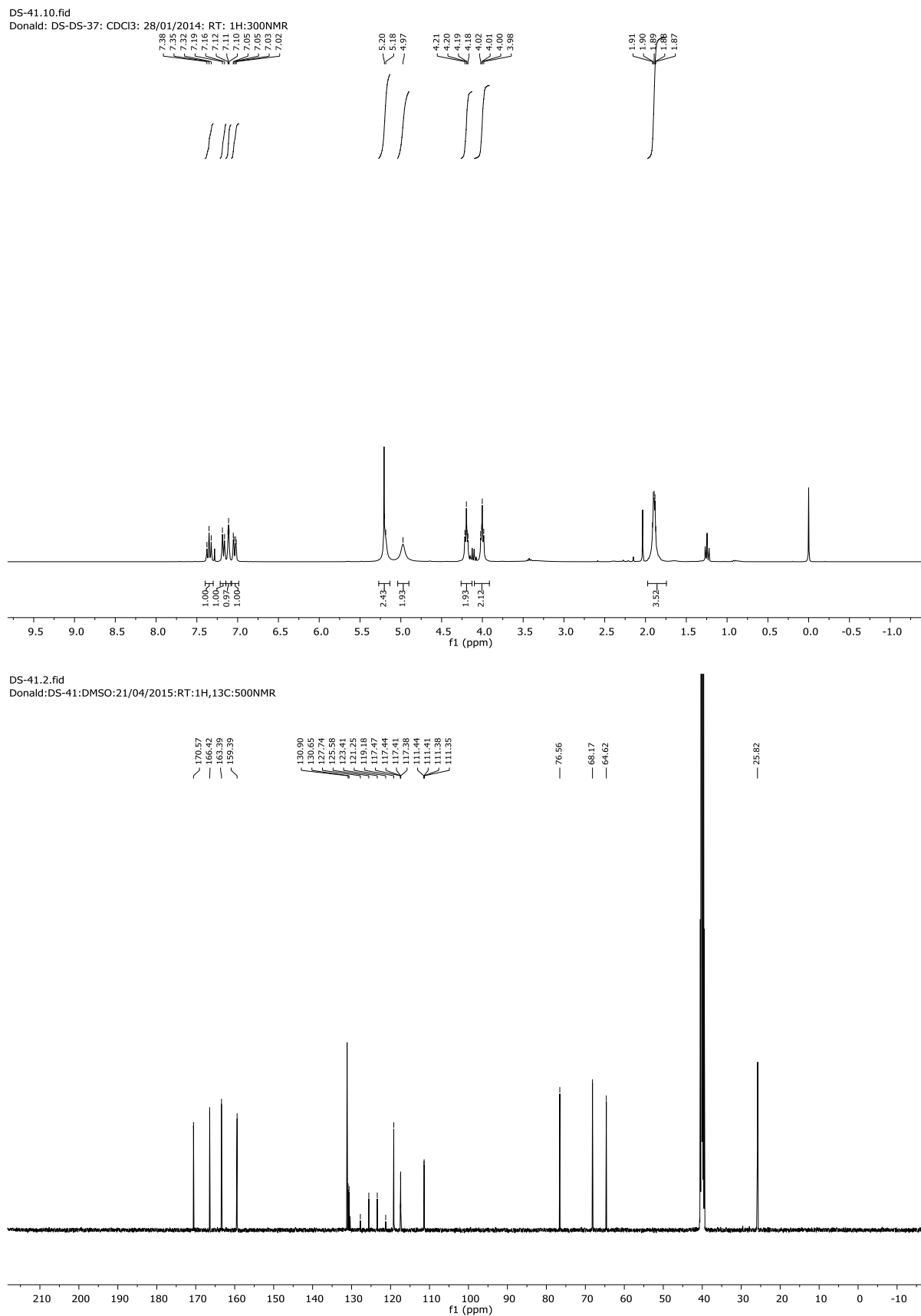
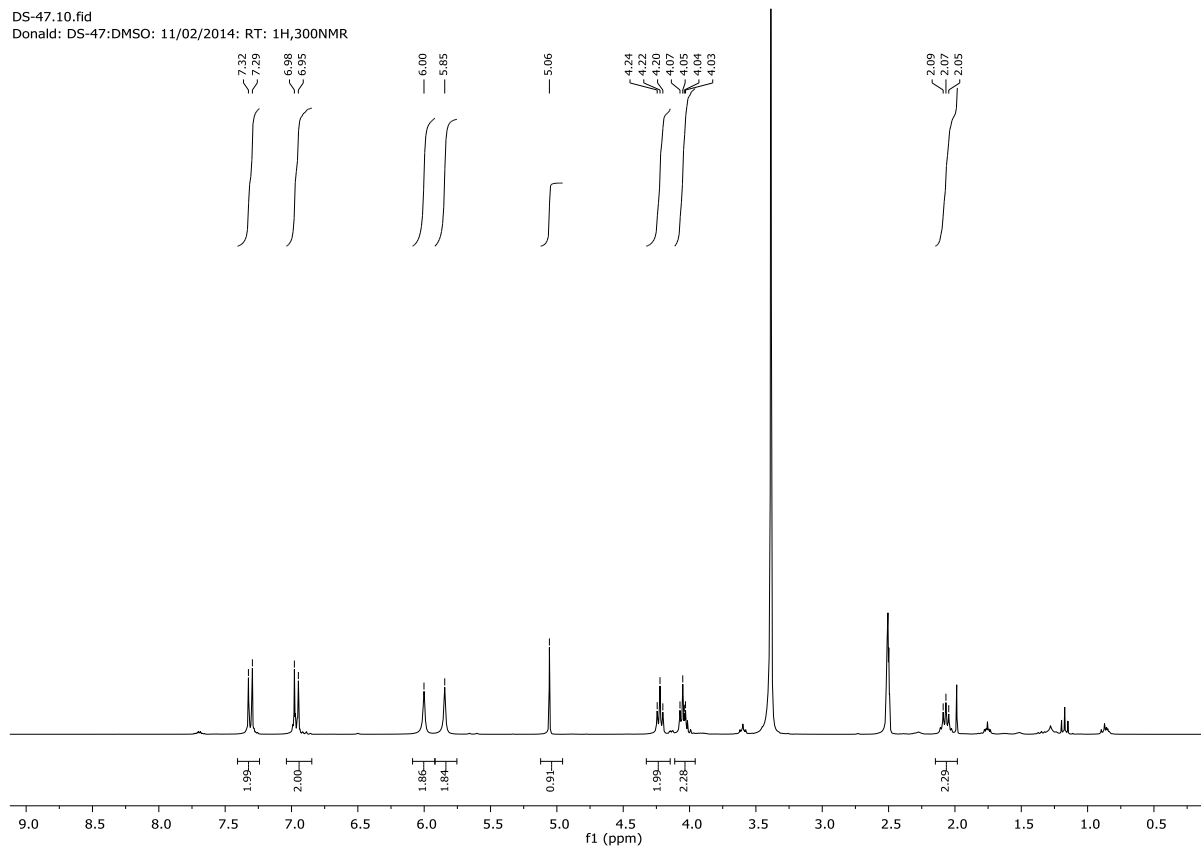
Figure S31. ^1H and ^{13}C NMR spectra of 6-(4-(3-(trifluoromethyl)phenoxy)butoxy)pyrimidine-2,4-diamine (**7f**).

Figure S32. ^1H and ^{13}C NMR spectra of 6-(3-(chlorophenoxy)propoxy)pyrimidine-2,4-diamine (**7g**).

DS-47.11.fid
Kamogelo (Donald): DS-47: DMSO: 23/07/2020: 1H, 13C: 300K, 200MNR

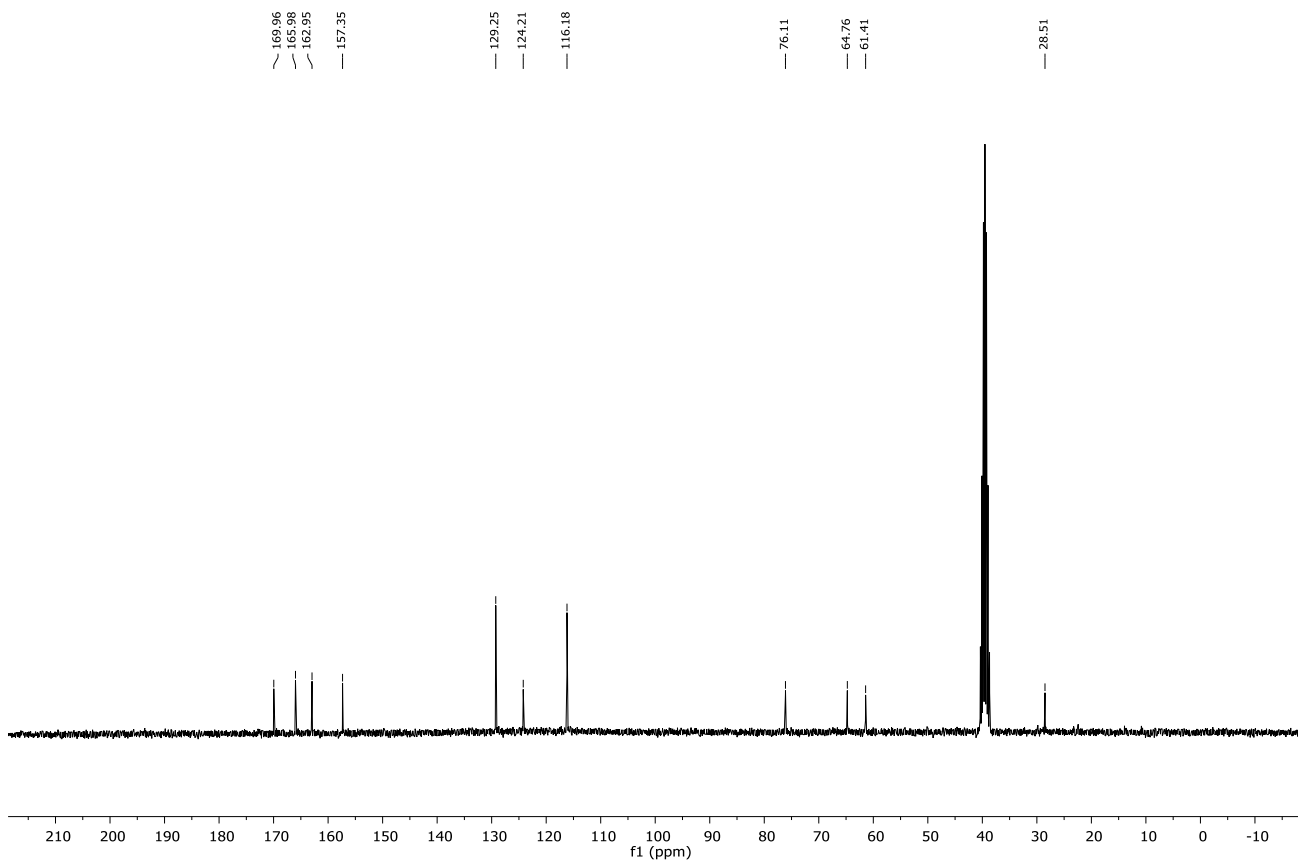


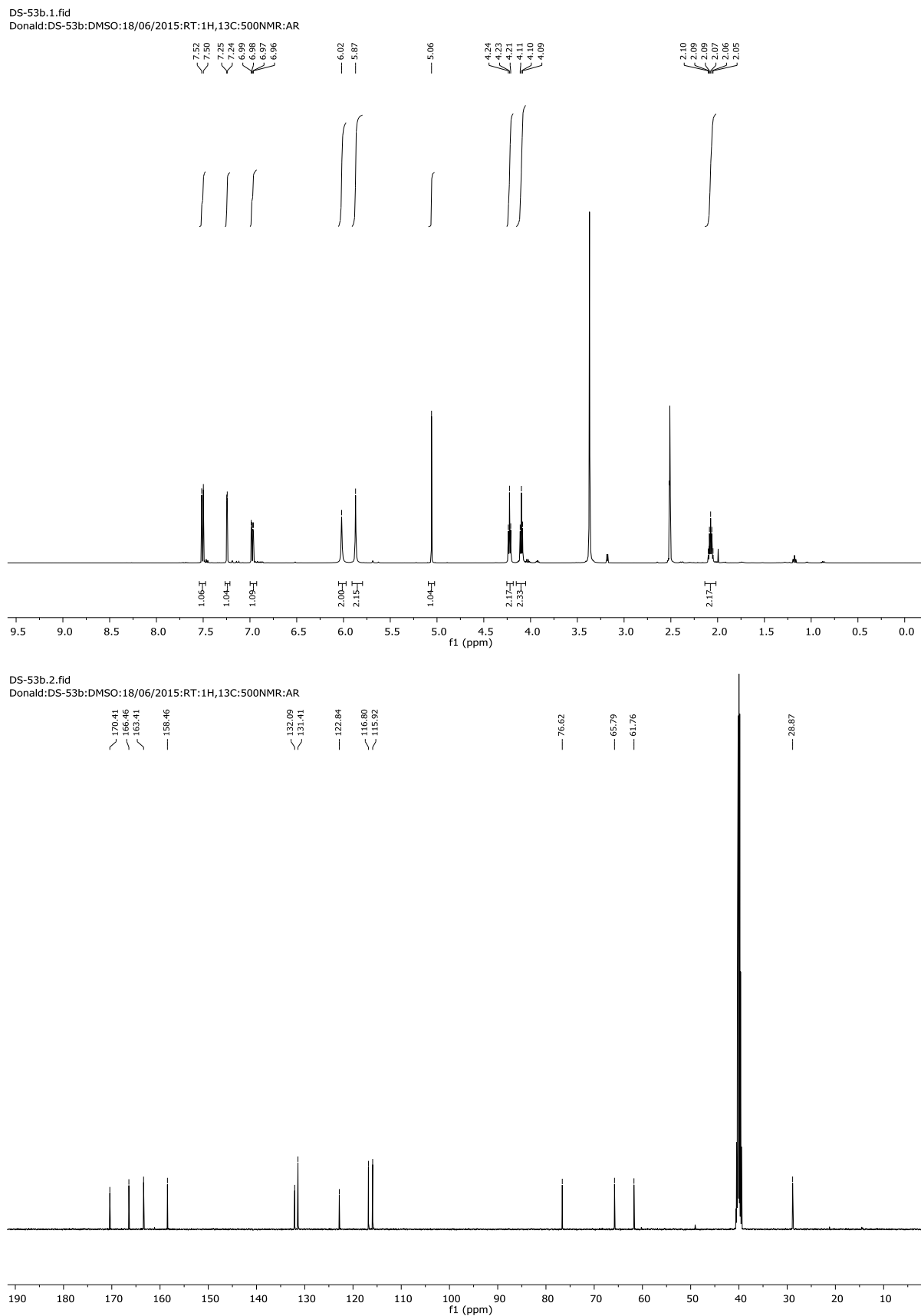
Figure S33. ^1H and ^{13}C NMR spectra of 6-(3-(3,4-dichlorophenoxy)propoxy)pyrimidine-2,4-diamine (**7h**).

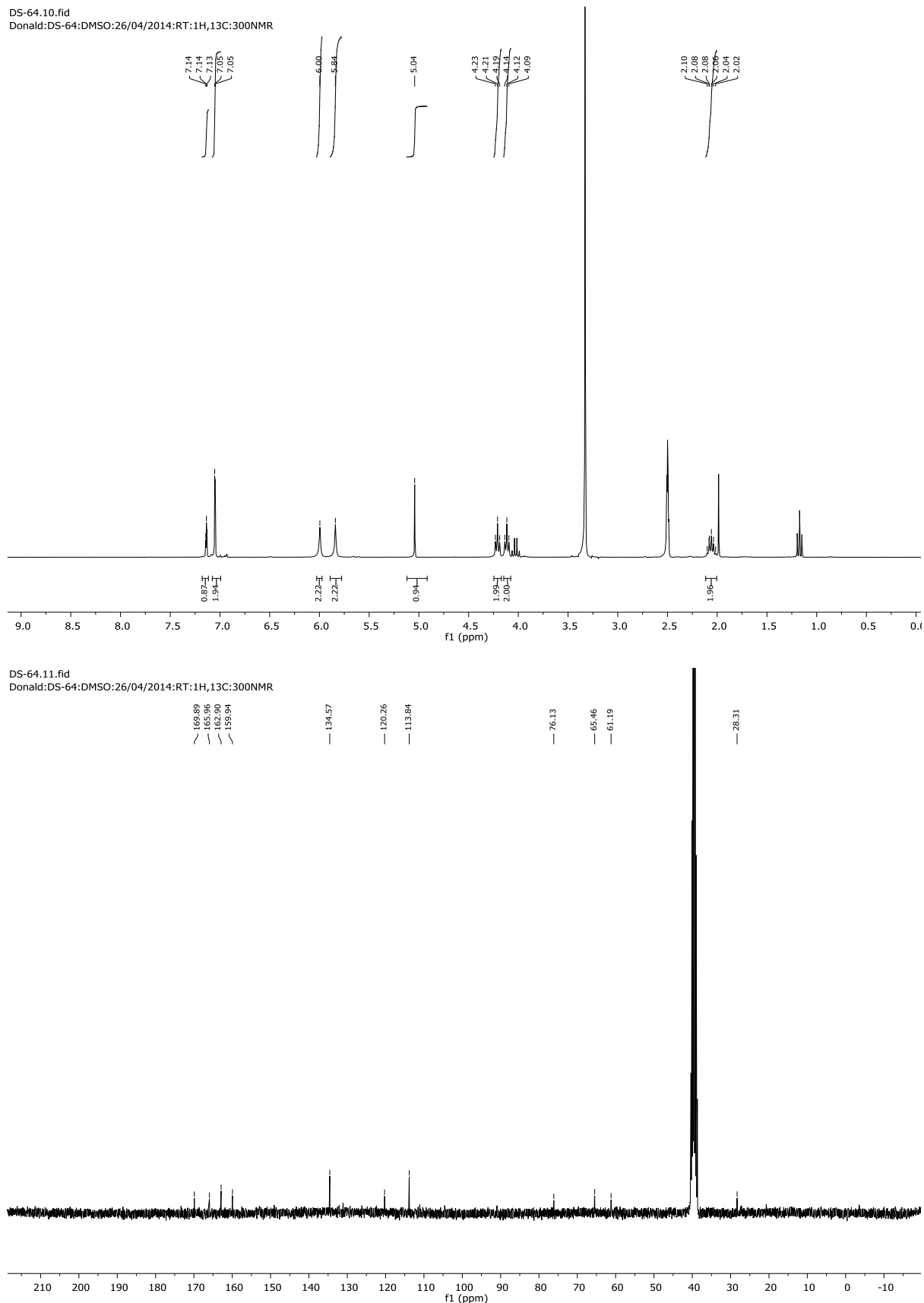
Figure S34. ^1H and ^{13}C NMR spectra of 6-(3-(3,5-dichlorophenoxy)propoxy)pyrimidine-2,4-diamine (**7i**).

Figure S35. ^1H and ^{13}C NMR spectra of 6-(3-(4-fluorophenoxy)propoxy)pyrimidine-2,4-diamine (**7j**).