Design, Synthesis and Conformational Analysis of Oligobenzanilides as Multi-Facial α-helix Mimetics

Theo Flack, Charles Romain, Andrew J. P. White, Peter R. Haycock, and Anna Barnard*

Department of Chemistry, Molecular Sciences Research Hub, Imperial College London, London, W12 0BZ, UK.

E-mail: a.barnard@imperial.ac.uk

Contents

Supplementary Figures and Tables

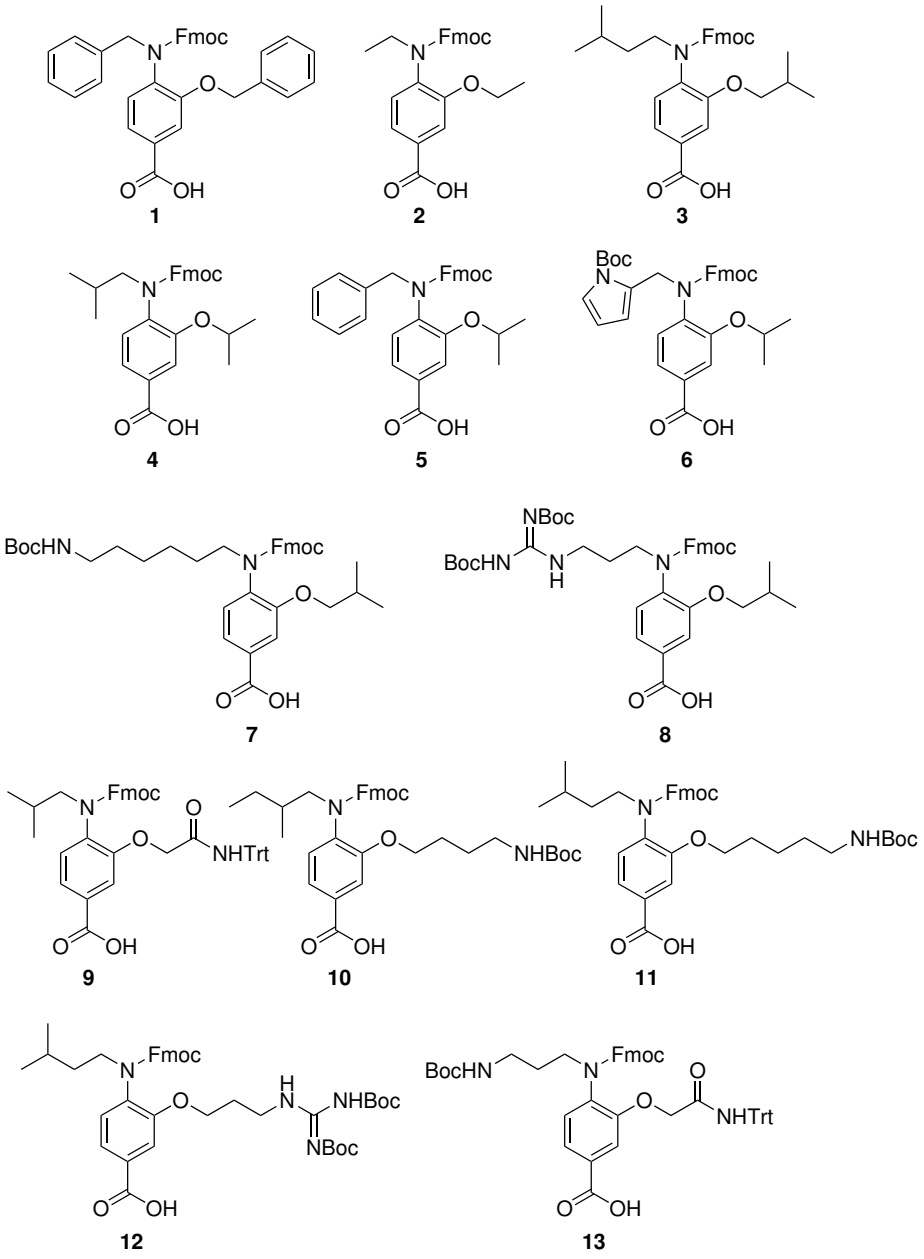


Figure S1: Chemical space explored using the synthetic route developed.

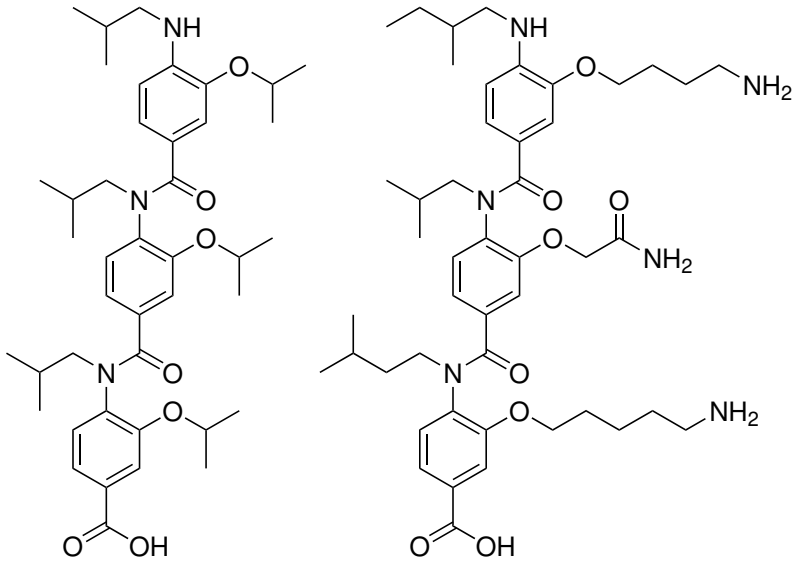


Figure S2: Trimers synthesised using the solid-phase methodology developed.

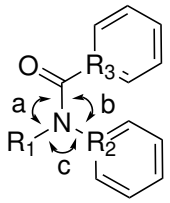


Table S1: Geometrical properties of the two crystallographically independent form of **16** calculated from the X-ray crystal structure.

Compound	ω_1 (°)[a]	ω_2 (°)[b]	ω_3 (°)[c]	ω_4 (°)[d]	τ(°)[e]	χ_c (°)[f]	χ_N (°)[g]	a+b+c (°)
3-S$_a$	-19.4	-4.4	173.7	163.6	11.9	2.9	12.1	359.0
3-R$_a$	25.9	7.0	-170.3	-156.7	16.5	2.7	16.3	358.2

[a] ω_1 (°) = $\angle R_3CNR_2$ [b] ω_2 (°) = $\angle OCNR_1$ [c] ω_3 (°) = $\angle R_3CNR_1$ [d] ω_4 (°) = $\angle OCNR_2$
[e] τ (°) = (ω_1 + ω_2)/2 [f] χ_c (°) = (ω_1 + ω_4)-180 [g] χ_N (°) = (ω_1 + ω_3) - 180

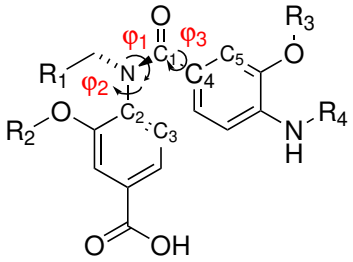


Table S2: Deviation of aromatic rings from planarity of the amide bond. Values of 90° for Φ_2 and Φ_3 represents absolute perpendicularity between the plane of the amide and the aromatic ring.

Compound	Φ_1 (°) [a]	Φ_2 (°) [b]	Φ_3 (°) [c]
3-S$_a$	163.6	52.9	40.6
3-R$_a$	-156.7	-48.2	-38.9

[a] Φ_1 (°) = $\angle C_2NC_1O$
[b] Φ_2 (°) = $\angle C_3C_2NC_1$
[c] Φ_3 (°) = $\angle C_5C_4C_1N$

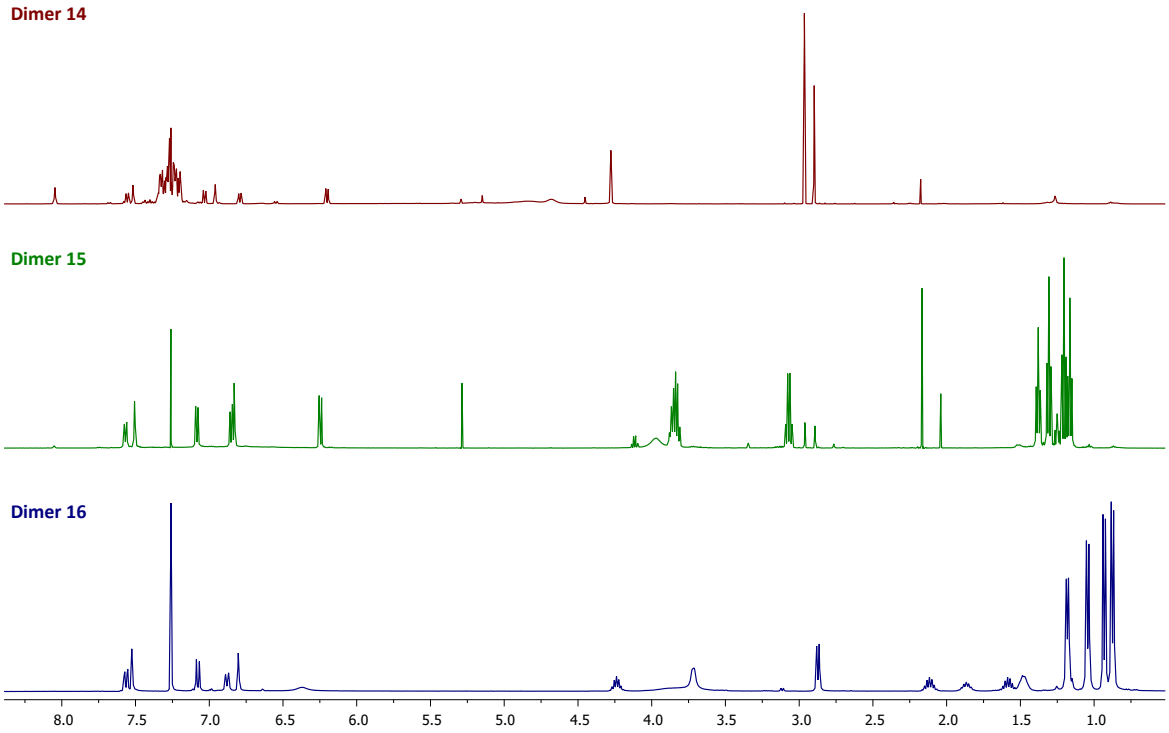


Figure S3: ^{1}H NMR spectra of dimers **14-16** at 298K. DOIs: 10.14469/hpc/5163, 10.14469/hpc/5164, 10.14469/hpc/5165

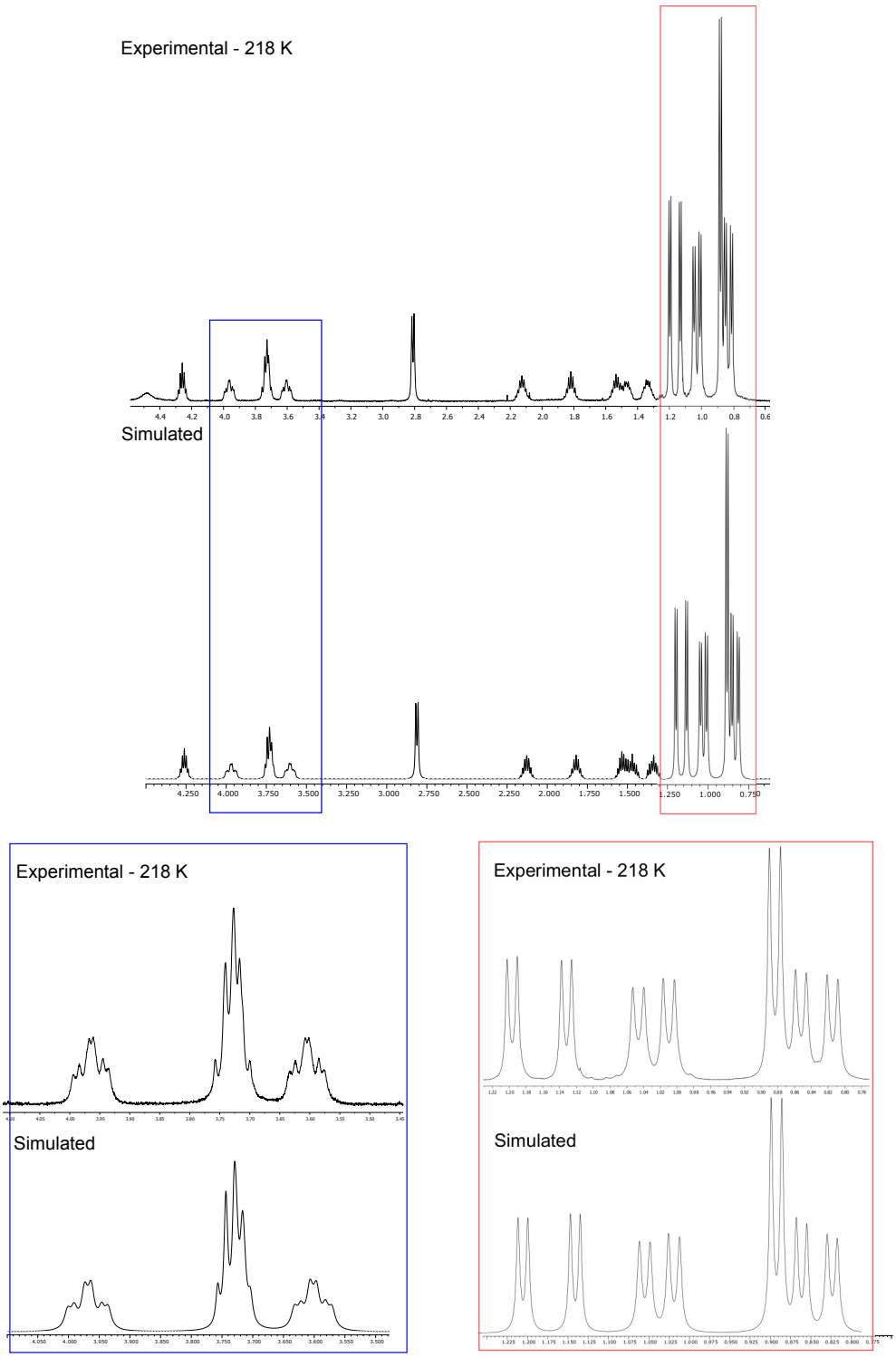


Figure S4: Experimental and simulated ^{1}H NMR spectra of dimer **16** at the slow exchange limit. Inlets show anisochronicity observed for methylene protons 2-Hα and 2-Hα' (blue) and methyl doublets 2-Hγ', 2-Hδ' and 1-Hβ' (red). DOI: 10.14469/hpc/5165

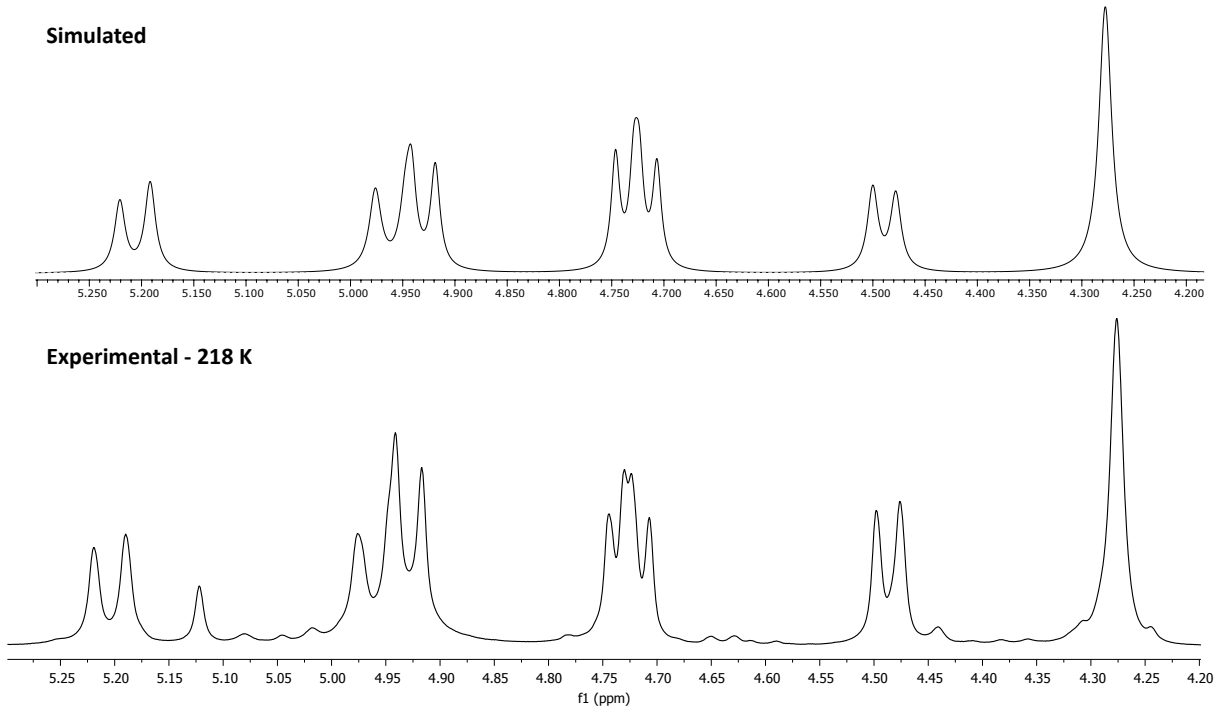


Figure S5: Experimental and simulated ^{1}H NMR spectra of dimer **14** at the slow exchange limit. Anisochronicity is observed for methylene protons 2-Hα, 2-Hα' and 1-Hα'. DOI: 10.14469/hpc/5163

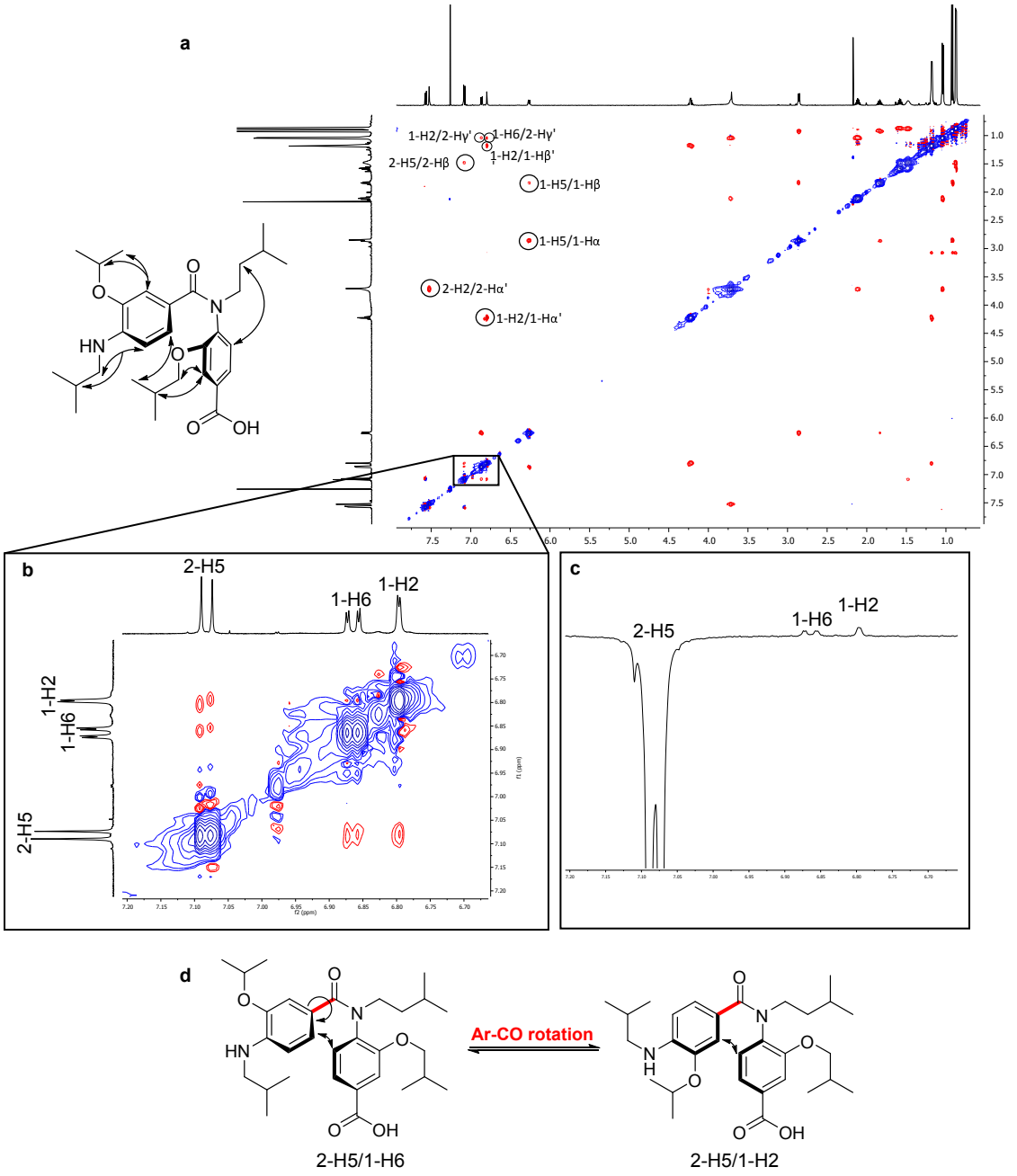


Figure S6: ^{1}H-^{1}H NOESY analysis of dimer **16** at room temperature. **a** ^{1}H-^{1}H NOESY spectra. True nOe correlations are circled in black. COSY artefacts are left uncircled. nOe correlations observed are shown as double-headed arrows. **b** Partial 2D ^{1}H-^{1}H NOESY spectra (7.20 - 6.20 ppm) showing *inter*-monomer correlations between 2-H5 and 1-H6/1-H2. **c** Selective NOE spectra confirming the through-space correlation between protons 2-H5 and 1-H6/1-H2. **d** Rotation about the Ar-CO bond in solution leads to simultaneous proximity between protons 2-H5 and 1-H6/1-H2. DOI: 10.14469/hpc/5165

Computational Supporting Information

Computational details:

DFT calculations were performed using Gaussian 09 (revision D01). Unless otherwise stated, calculations used the ωB97xD density functional (which includes a second-generation dispersion correction) and the 6-31G(d,p) basis set for all atoms. A self-consistent reaction cavity continuum solvation model was used with DMSO as the solvent [scrf=(cpcm,solvent=DMSO)]. All calculations were performed with ultrafine grid (integral=grid=ultrafine) and without restriction on symmetry (No Symm). All transition states were characterized by normal coordinate analysis revealing precisely one imaginary mode corresponding to the intended reaction. Vibrational frequency calculations only were performed using 6-311++G(d,p) basis set for selected transition states as per Table S9.

The geometry of the molecular structure determined by X-Ray diffraction was used as a starting point to build a molecular structure where all alkyl groups have been replaced by methyl groups. Geometry optimisation of this molecule model led to compound $\mathbf{I}_{\text{anti/cis}}$ (S7) which will be the reference (ΔG_{298} = 0 kcal/mol) and the starting point of the following calculations. Full coordinates for all the stationary points are available on the data repository at DOI: 10.14469/hpc/5171.

To distinguish the different possible conformations, the following notations will be used (as defined in Figure 2 and Figure S8):

cis / trans

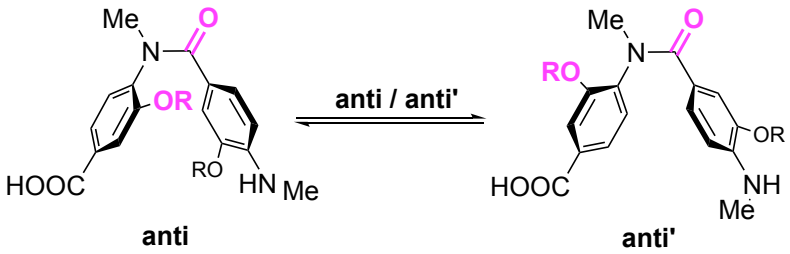
for folded and extended conformations, respectively.

anti / sym

with regards to the position of the O-alkoxy substituent of the aryl moieties.

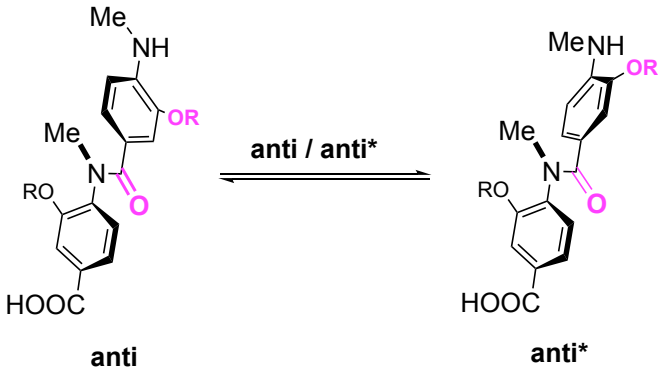
anti/ syn

prime (') is used in cis conformations (when relevant) to indicate that the O-alkoxy substituent of the Aryl-N group is pointing away from the carbonyl (in the absence of the O-alkoxy substituent of the Aryl-N is pointing toward the carbonyl)



anti* / syn*

star (*) is used in trans conformations (when relevant) to indicate that the O-alkoxy substituent of the Aryl-C(O) group is pointing in opposite direction of the carbonyl group.



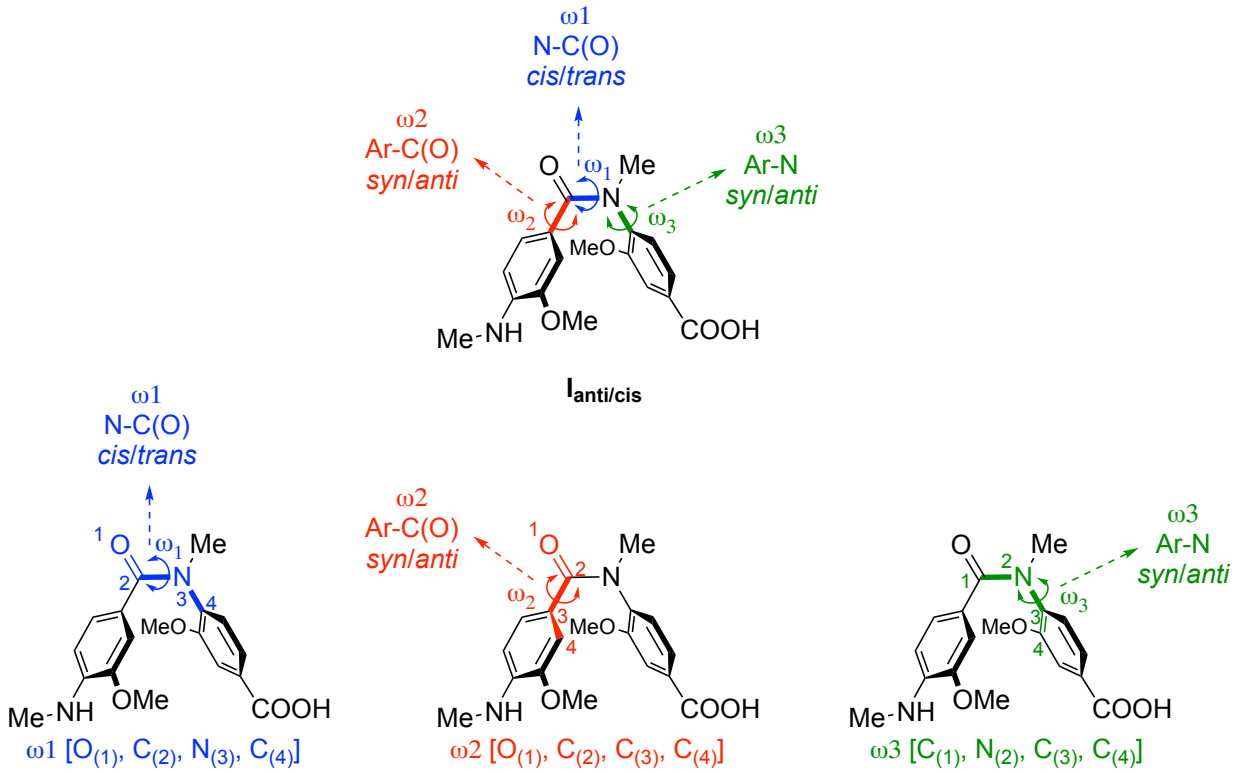


Figure S7: Selected dihedral angles $\omega 1$, $\omega 2$ *and* $\omega 3$ corresponding to amide bond rotation (blue), aryl-C(O) bond rotation (red) and aryl-N bond rotation (green), respectively.

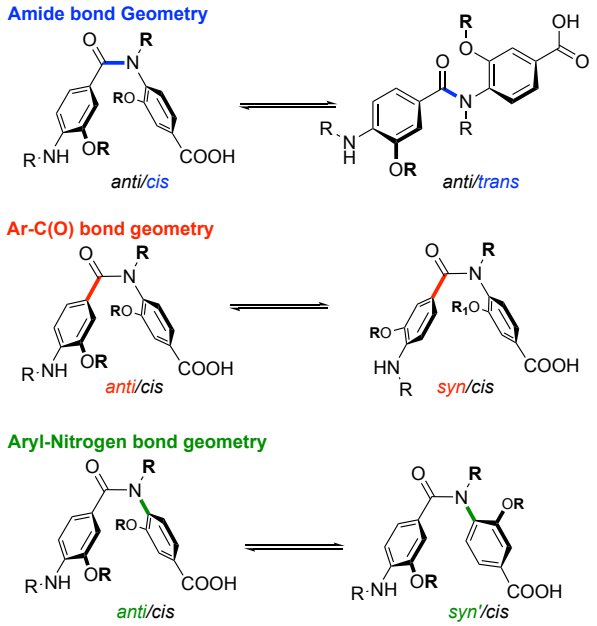


Figure S8: Example of conformational exchanges (as per Figure 2 in manuscript).

Amide bond rotation (dihedral angle $\omega 1$ rotation):

A relaxed scan of the amide dihedral angle $\omega 1$(36 x 10°) was performed using $\mathbf{I}_{\text{anti/cis}}$ as starting point. The total energy (kcal/mol) was plotted against the dihedral angle $\omega 1$ and show a series of minima and maxima as per Figure S9. Maxima were subjected to transition state optimisation. Minima were deduced from the corresponding TS (either using IRC calculations or by moving atoms along the negative frequency of the TS).

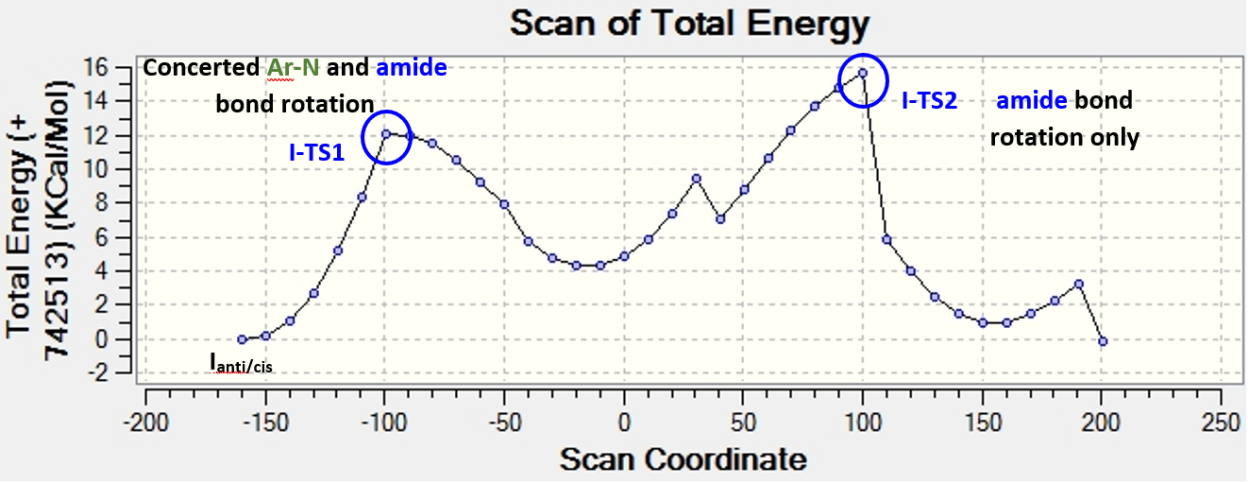


Figure S9: Relaxed potential energy scan of the amide dihedral angle $\omega 1$ rotation.

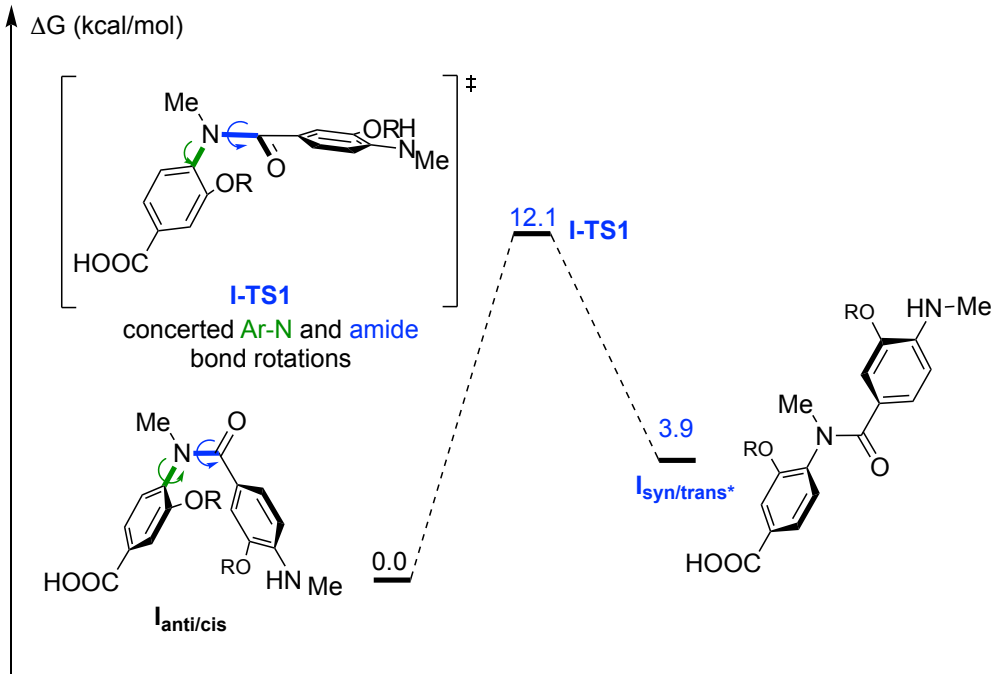


Figure S10: Concerted rotations of the amide bond and Ar-N bond leading to an anti/cis ↔ syn/trans conformational exchange via transition state **I-TS1** (ΔG_{298} = 12.1 kcal/mol) obtained from relaxed scan (Figure S9).

Table S3: Data for Figure S10 (all data at DOI: 10.14469/hpc/5272.

Name	ΔG_{298} (kcal/mol)	Job ID	DOI:
$\mathbf{I_{anti/cis}}$	0 (reference)	10050139	10.14469/hpc/5267
I-TS1	12.1	10051682	10.14469/hpc/5273
$\mathbf{I_{syn/trans*}}$	3.9	10050358	10.14469/hpc/5274
IRC I-TS1	***	10050319	10.14469/hpc/5275

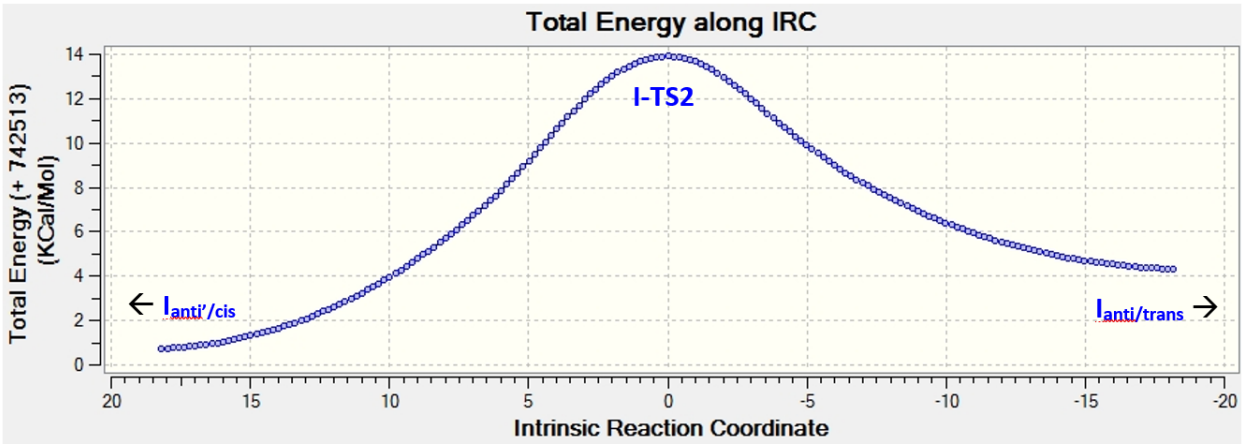


Figure S11: Total energy along IRC from **I-TS1**.

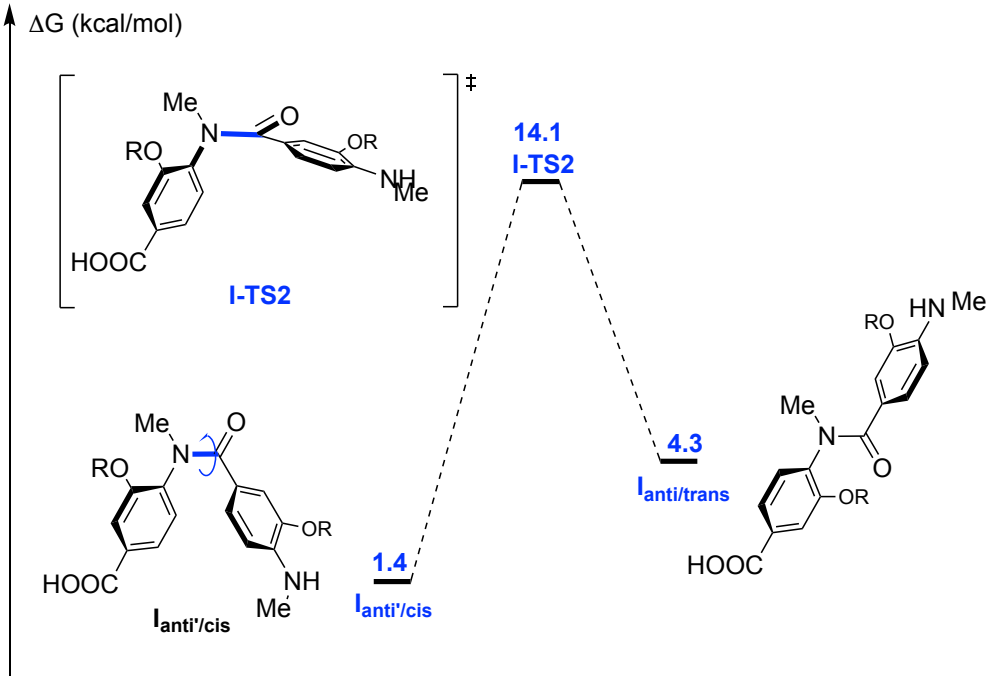


Figure S12: Rotation of the amide bond only leading to a cis/trans conformational exchange from an anti conformation via transition state **I-TS2** (ΔG_{298} = 14.1 kcal/mol) obtained from relaxed scan (Figure S9).

Table S4: Data for S12 (all data at DOI: 10.14469/hpc/5272).

Name	ΔG_{298} (kcal/mol)	Job ID	DOI:
$\mathbf{I_{anti/cis}}$	0 (reference)	10050139	10.14469/hpc/5267
$\mathbf{I_{anti'/cis}}$	1.4	10052065	10.14469/hpc/5276
I-TS2	14.1	10051683	10.14469/hpc/5277
$\mathbf{I_{anti/trans}}$	4.3	10051924	10.14469/hpc/5278
IRC I-TS2	***	10051760	10.14469/hpc/5279

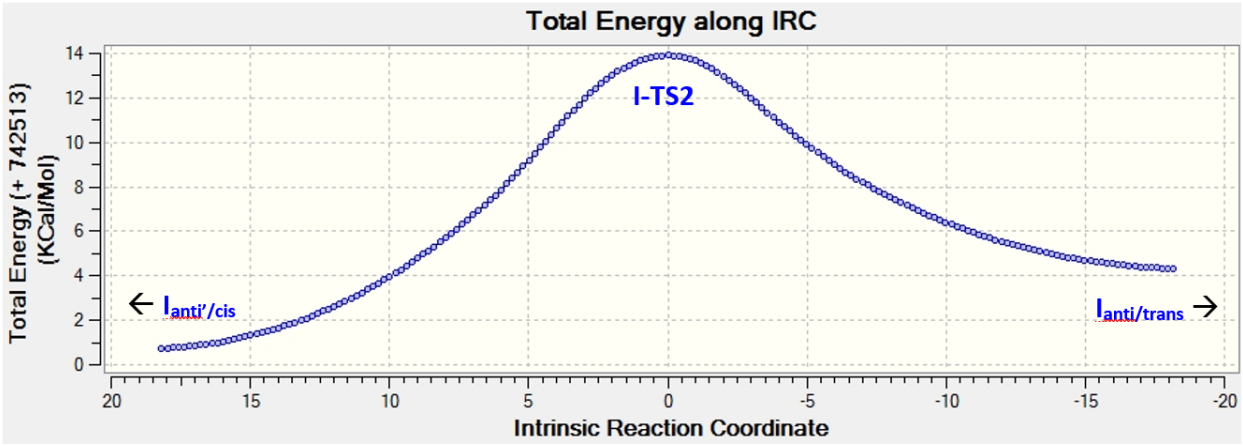


Figure S13: Total energy along IRC from **I-TS2**.

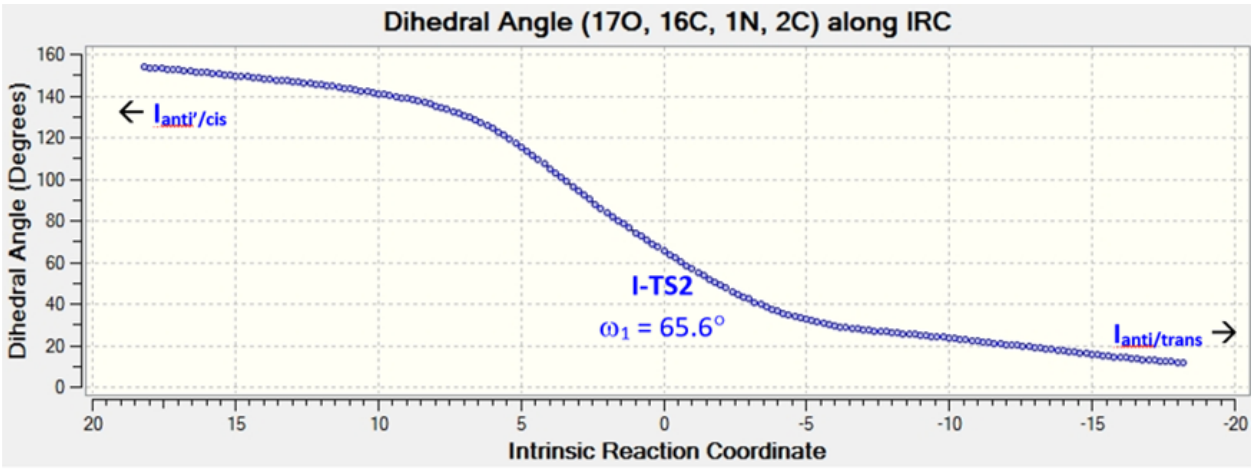


Figure S14: $\omega 1$ along IRC from **I-TS2**.

Based on the geometry of **I-TS2**, a transition state **I-TS3** corresponding to *syn'/cis* ↔ *syn/trans* conformational exchange involving an amide bond rotation only was found.

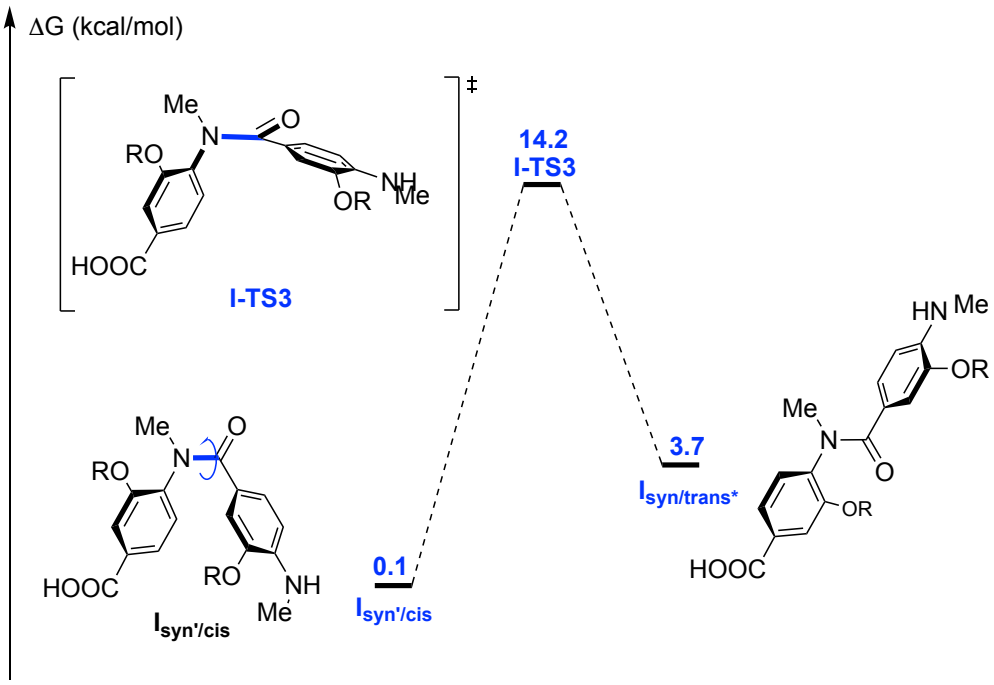


Figure S15: Rotation of the amide bond only leading to a cis/trans conformational exchange from a syn' conformation via transition state **I-TS3** (ΔG_{298} = 14.4 kcal/mol) from a syn' conformation.

Table S5: Data for S15 (all data at DOI: 10.14469/hpc/5272)

Name	**ΔG_{298} (kcal/mol)**	**Job ID**	**DOI:**
$\mathbf{I}_{\text{anti/cis}}$	0 (reference)	10050139	10.14469/hpc/5267
$\mathbf{I}_{\text{syn'/cis}}$	0.1	10052297	10.14469/hpc/5280
I-TS3	14.2	10051689	10.14469/hpc/5281
$\mathbf{I}_{\text{syn/trans*}}$	3.7	10052296	10.14469/hpc/5282
IRC I-TS3	***	10052168	10.14469/hpc/5283

Transition states **I-TS4** and **I-TS5** were found with the O-methoxy of the benzamide not 'passing' underneath the amide moiety and thus not leading to a syn/anti interconversion, contrary to **I-TS1** and **I-TS6** (described in Figure S10 and Figure S19). It appears that the O-methoxy 'moves away' to allow the carbonyl rotation.

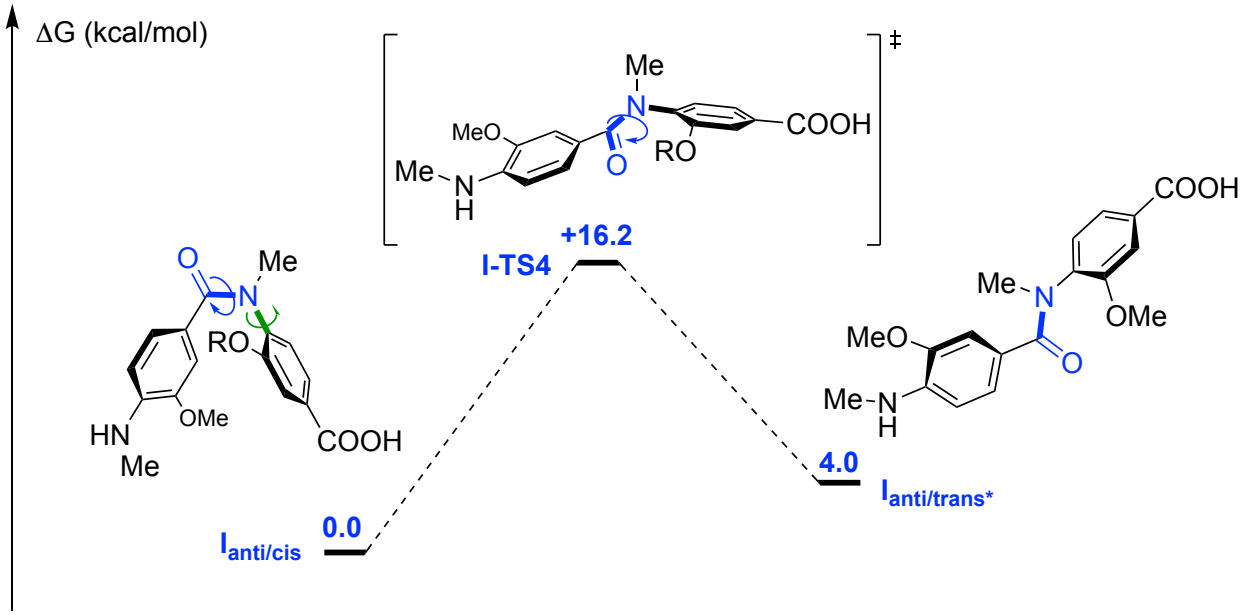


Figure S16: Rotation of the amide bond only leading to a cis/trans conformational exchange from an anti conformation via transition state **I-TS4** (ΔG_{298} = 16.2 kcal/mol).

Table S6: Data for Figure S16 (all data at DOI: 10.14469/hpc/5272).

Name	ΔG_{298} (kcal/mol)	Job ID	DOI:
$\mathbf{I}_{\text{anti/cis}}$	0 (reference)	10050139	10.14469/hpc/5267
I-TS4	16.2	10053641	10.14469/hpc/5284
$\mathbf{I}_{\text{anti/trans*}}$	4.0	10053925	0.14469/hpc/5285
IRC I-TS4	***	10053911	10.14469/hpc/5286

Table S7: Data for Figure S18 (all data at DOI: 10.14469/hpc/5272)

Name	ΔG_{298} (kcal/mol)	Job ID	DOI:
$\mathbf{I}_{\text{anti/cis}}$	0 (reference)	10050139	10.14469/hpc/5267
$\mathbf{I}_{\text{syn/cis}}$	0.3	10050255	10.14469/hpc/5288
I-TS5	16.2	10050255	10.14469/hpc/5288
$\mathbf{I}_{\text{syn/trans}}$	4.1	10053933	10.14469/hpc/5287
IRC I-TS5	***	10053642	10.14469/hpc/5290

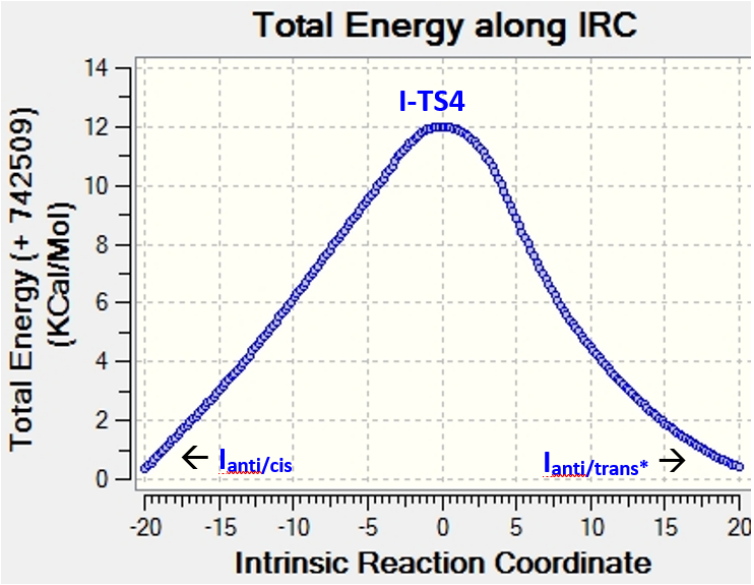


Figure S17: Total energy along IRC from **I-TS4**.

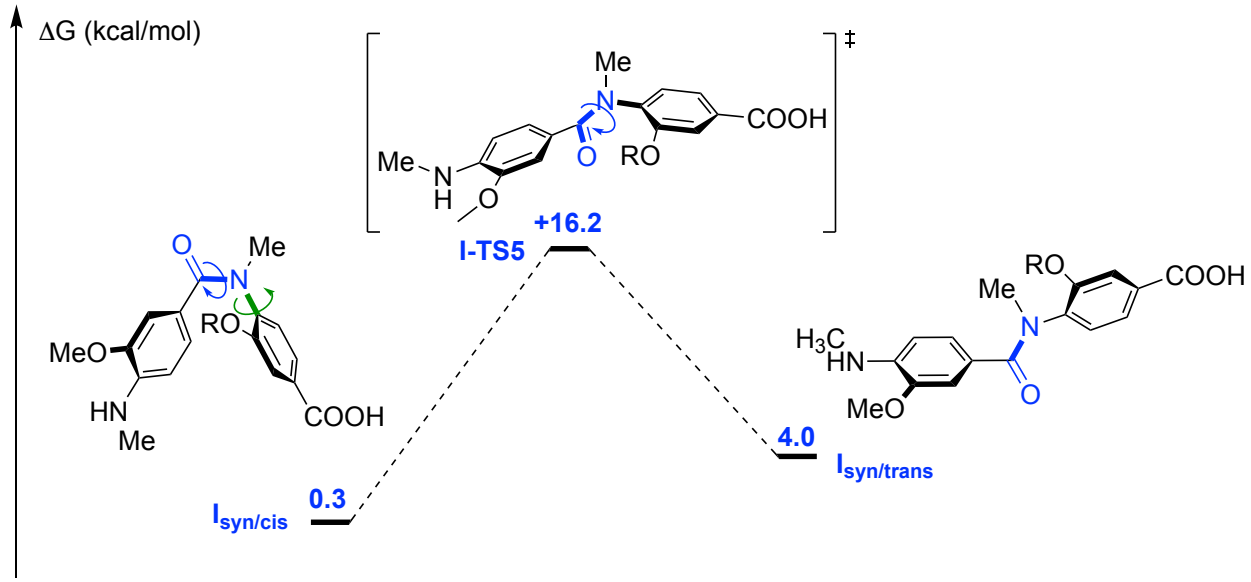


Figure S18: Rotation of the amide bond only leading to a cis/trans conformational exchange from a syn conformation via transition state **I-TS5** (ΔG_{298} = 16.2 kcal/mol).

To cover every possibility, from the geometry of **I-TS1** corresponding to an anti/cis ↔ syn/trans conformational exchange, **I-TS6** corresponding to a syn/cis ↔ anti/trans conformational exchange was calculated and found to be ΔG_{298} = 12.4 kcal/mol.

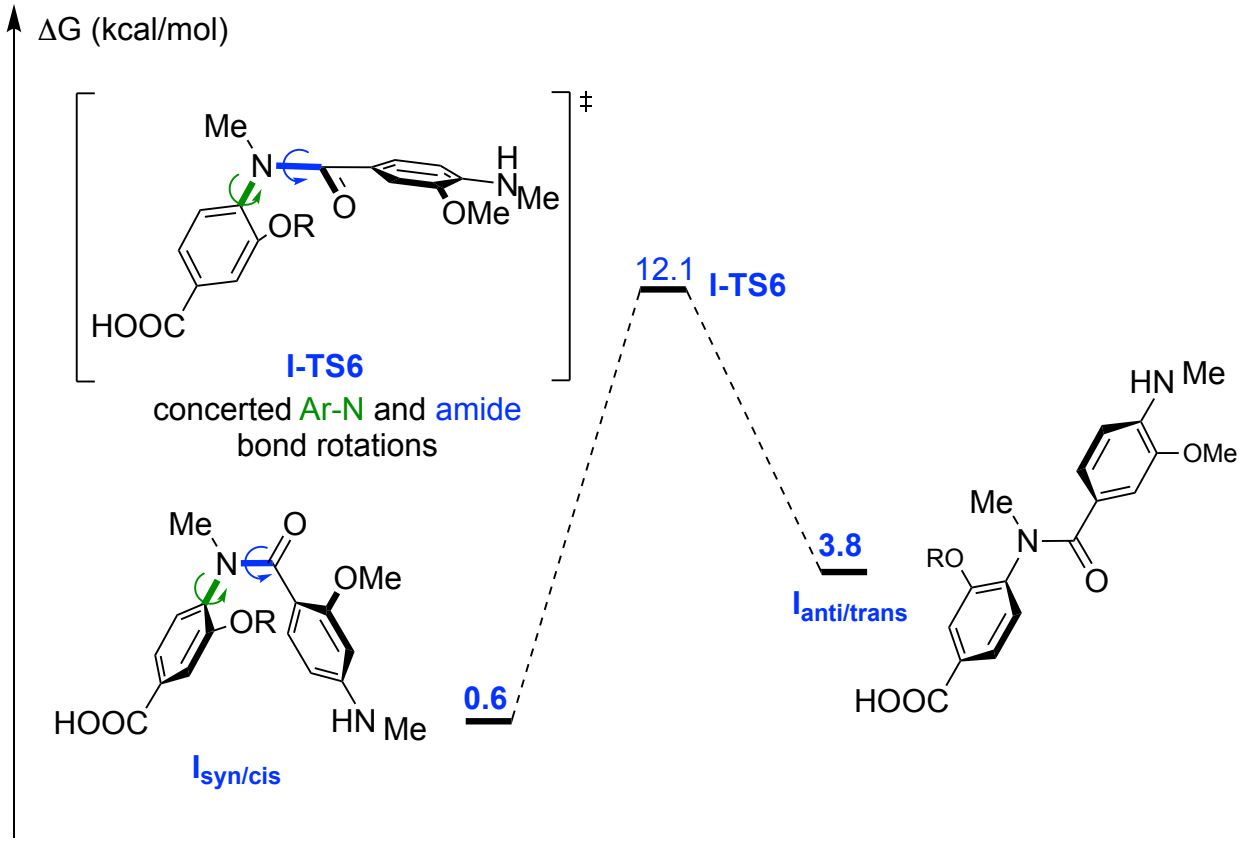


Figure S19: Concerted rotations of the amide bond and Ar-N bond leading to a syn/cis ↔ anti/trans conformational exchange via transition state **I-TS6** (ΔG_{298} = 12.4 kcal/mol) deduced from I-TS1 (Figure S10).

Table S8: Data for Figure S19 (all data at DOI: 10.14469/hpc/5272).

Name	**ΔG_{298} (kcal/mol)**	**Job ID**	**DOI:**
$\mathbf{I}_{syn/cis}$	0.6	10053931	10.14469/hpc/5293
I-TS6	12.1	10053991	10.14469/hpc/5291
$\mathbf{I}_{anti/trans}$	3.8	10053941	10.14469/hpc/5292

Structure	Conformation exchange	ΔG_{298} (kcal/mol)	Bond rotation(s)
I-TS1	anti/cis ↔ syn/trans*	12.1	Concerted Ar-N and Ar-N
I-TS2	anti'/cis ↔ anti/trans	14.1	Amide only
I-TS2	anti/cis ↔ anti/trans*	16.2	Amide only
I-TS2	syn/cis ↔ anti/trans	12.1	Concerted Ar-N and amide
I-TS3	syn'/cis ↔ syn/trans*	14.4	Amide only
I-TS5	syn/cis ↔ syn/trans	16.2	Amide only

Overall, it appears that concerted Ar-N and amide bond rotations have slightly lower energy barrier (δG_{298} = 12.1 kcal/mol and 12.1 kcal/mol for **I-TS1** and **III-TS6**, respectively) than amide bond rotation only (e.g. ΔG_{298} = 14.1 kcal/mol and 16.2 kcal/mol for **I-TS2** and **I-TS4**, respectively). Depending on the orientation of the Ar-N moiety regarding the carbonyl of the amide group, rotation of the amide bond will allow the carbonyl group to push the O-methoxy substituent of the Ar-N and induce concerted rotations (as per I-TS1 and III-TS6).

Table S9: Comparison of selected TS at different DFT levels (all data at DOI: 10.14469/hpc/5320)

Structure	wB97xD		M06-2X	
	6-31G(d,p)a	**6-311++G(d,p)b** (DOI)	**6-31G(d,p)a** (DOI)	**6-311++G(d,p)b** (DOI)
$\mathbf{I}_{anti/cis}$	0.00	0.00 (10.14469/hpc/5321)	0.00 (10.14469/hpc/5326)	0.00 (10.14469/hpc/5331)
I-TS1	12.13	10.11 (10.14469/hpc/5322)	10.89 (10.14469/hpc/5322)	10.87 (10.14469/hpc/5332)
I-TS2	14.08	14.93 (10.14460/hpc/5323)	12.4 (10.14469/hpc/5328)	13.45 (10.14469/hpc/5333)
I-TS4	16.2	16.57 (10.14469/hpc/5324)	15.08 (0.14469/hpc/5329)	15.88 (10.14469/hpc/5334)
I-TS4	16.68	16.63 (10.14469/hpc/5325)	15.48 (10.14469/hpc/5330)	15.74 (10.14469/hpc/5335)

a) geometry optimisation and vibrational frequency calculations performed using density functional and basis set (for all atoms) as notified in the table; b) vibrational frequency calculations only using geometry optimized using 6-31G(d,p) basis set (for all atoms) and density functional as indicated in the table.

Ar-C(O) rotation (dihedral angle $\omega 2$ rotation)

A relaxed scan of the Ar-C(O) dihedral angle $\omega 2$ (36 x 10°) was performed using an extended conformation (II) as starting point. The total energy (kcal/mol) was plotted against the dihedral angle $\omega 2$ and show a series of minima and maxima as per Figure S20. Maxima were subjected to transition state optimisation. Minima were deduced from the corresponding TS by moving atoms along the negative frequency.

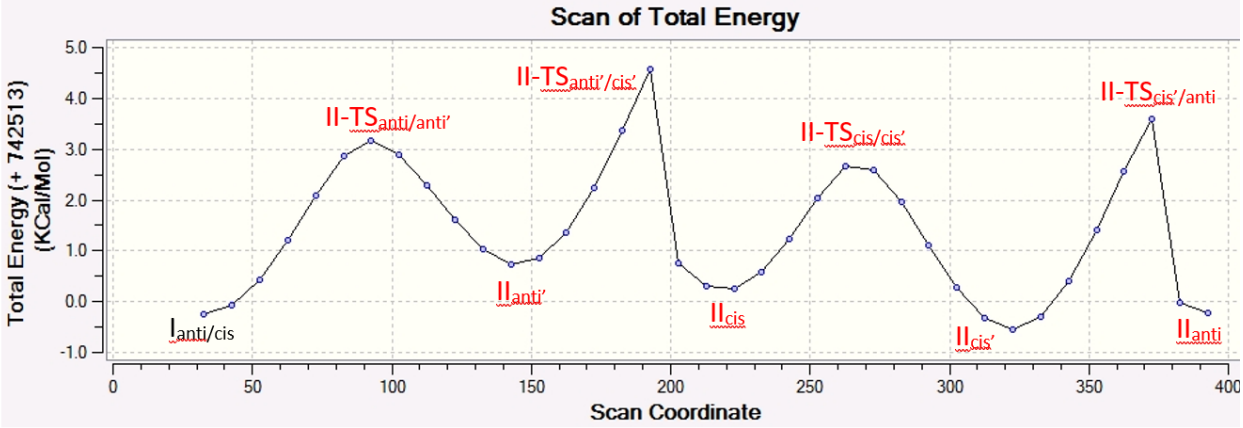


Figure S20: Relaxed potential energy scan of the Ar-C(O) dihedral angle $\omega 2$ rotation in cis conformation.

Figure S20 shows independent rotations about the Ar-C(O) bond in cis-conformations with energy barriers below 6 kcal/mol on the potential energy surface, in line with a free rotation in solution at room temperature. During rotations about the Ar-C(O) bond, the molecule can keep adopting cis-conformations, i.e. rotation of the Ar-C(O) bond can occur without inducing amide bond rotations (without cis/trans conformational exchange).

A relaxed scan of the Ar-C(O) dihedral angle $\omega 2$ (36 x 10°) was performed using $\mathbf{I}_{syn/trans}$ as starting point. The total energy (kcal/mol) was plotted against the dihedral angle $\omega 2$ and shows a series of minima and maxima as per Figure S22. Maxima were subjected to transition state optimisation. Minima were deduced from the corresponding TS by moving atoms along the negative frequency.

Figure S22 shows that Ar-C(O) bond rotations in trans conformations occur with energy barriers below 10 kcal/mol on the PES ($\mathbf{I}_{\text{anti/cis}}$ as reference with $\Delta G_{298} = 0$ kcal/mol).

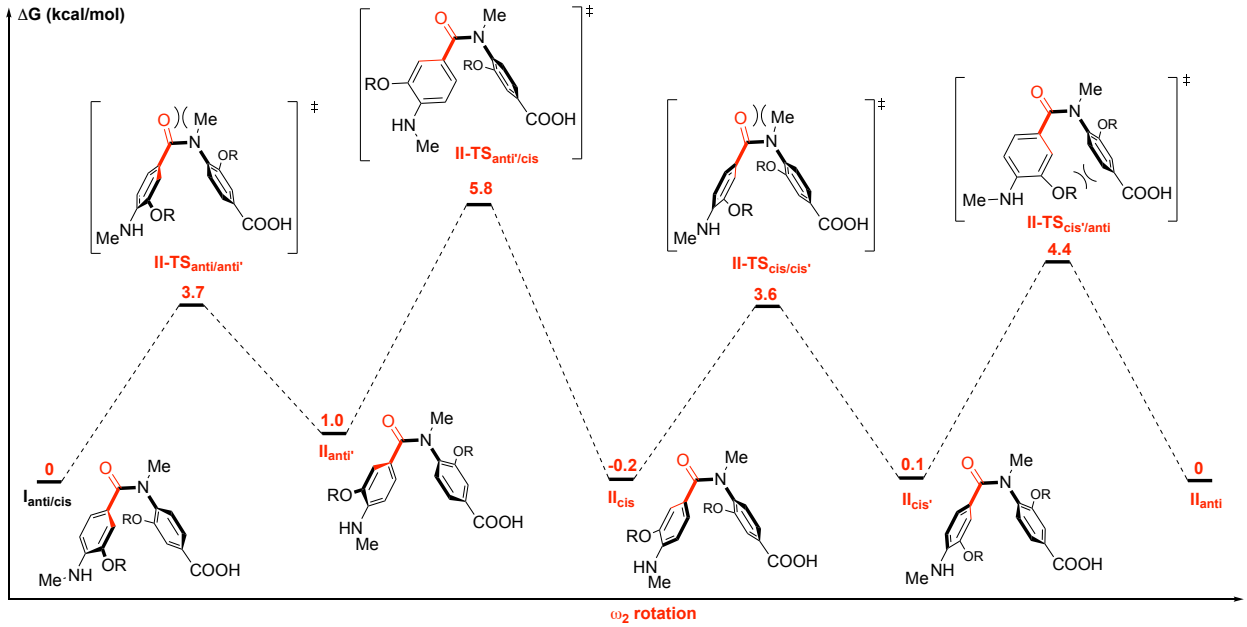


Figure S21: Ar-C(O) dihedral rotation energy profile in cis-conformation (from relaxed scan as per Figure S20.)

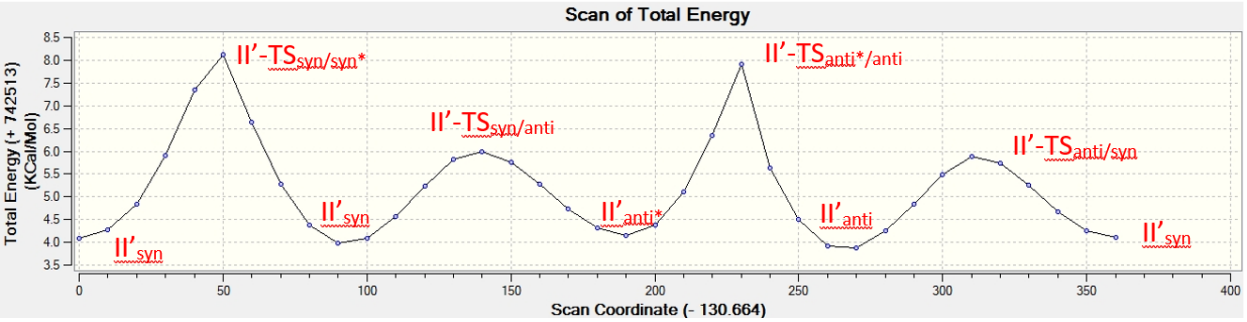


Figure S22: Relaxed potential energy scan of the Ar-C(O) dihedral angle $\omega 2$ rotation in trans conformation.

Does not induce *cis/trans* conformational exchange (no concerted amide bond rotations).

Table S10: Data for Figure S21 (all data at DOI: 10.14469/hpc/5294).

Name	ΔG_{298} (kcal/mol)	Job ID	DOI:
$\mathbf{I_{anti/cis}}$	0.0	10050139	10.14469/hpc/5267
$\mathbf{II\text{-}TS_{anti/anti'}}$	3.7	10050943	10.14469/hpc/5295
$\mathbf{II_{anti'}}$	1.0	10052008	10.14469/hpc/5296
$\mathbf{II\text{-}TS_{anti'/cis}}$	5.8	10050994	10.14469/hpc/5297
$\mathbf{II_{cis}}$	-0.2	10052006	10.14469/hpc/5298
$\mathbf{II\text{-}TS_{anti'/cis}}$	3.6	10050944	10.14469/hpc/5299
$\mathbf{II_{cis'}}$	0.1	10052007	10.14469/hpc/5300
$\mathbf{II\text{-}TS_{cis'/anti}}$	4.4	10050953	10.14469/hpc/5301

Table S11: Data for Figure S23 (all data at DOI: 10.14469/hpc/5294)

Name	ΔG_{298} (kcal/mol)	Job ID	DOI:
$\mathbf{II_{syn}}$ $(= \mathbf{I_{syn/trans}})$	3.9	10053635	10.14469/hpc/5302
$\mathbf{II'\text{-}TS_{anti/anti'}}$	9.6	10053603	10.14469/hpc/5303
$\mathbf{II'_{syn}}$	4.2	10053627	10.14469/hpc/5304
$\mathbf{II'\text{-}TS_{syn'/anti}}$	6.4	10053604	10.14469/hpc/5305
$\mathbf{II'S_{anti}}$	4.0	10053628	10.14469/hpc/5306
$\mathbf{II'TS_{anti'/anti}}$	9.0	10053605	10.14469/hpc/5307
$\mathbf{II'\text{-}TS_{anti/syn}}$	4.2	10053643	10.14469/hpc/5308
$\mathbf{II'\text{-}TS_{anti/syn}}$	6.0	10053606	10.14469/hpc/5309
$\mathbf{II'_{syn}}$	3.9	10053629	10.14469/hpc/5310

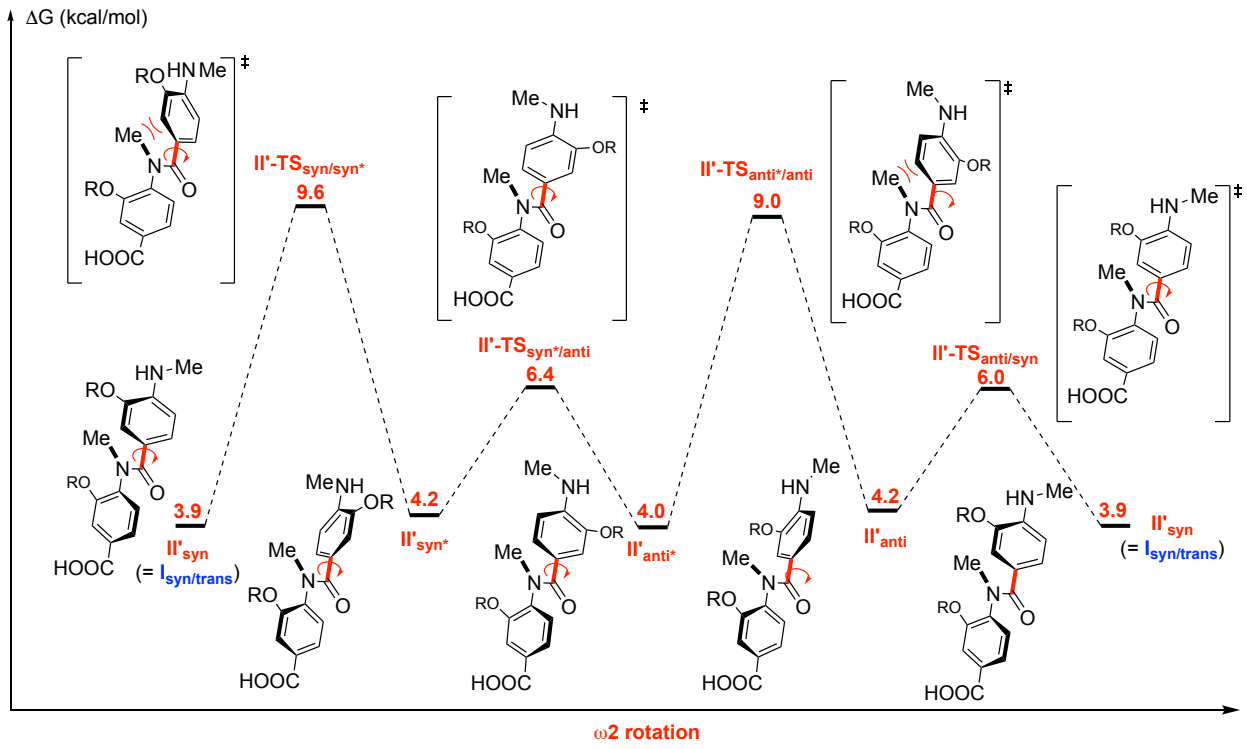


Figure S23: Ar-C(O) dihedral rotation energy profile in trans-conformation (from relaxed scan as per Figure S22).

Ar-N roation (dihedral angle ω3 rotation)

From $\mathbf{I}_{\text{anti/cis}}$, a relaxed scan of the Ar-N dihedral angle (72 x 10°) was performed. The total energy (kcal/mol) was plotted against the dihedral ω3 and show a series of minima and maxima as per Figure S24. Maxima were subjected to transition state optimisation followed by IRC calculations to confirm the identity of the TS. Both ends of the IRC were subjected to optimisation and the output geometries were found in good accordance with the minima found in the scan (excepted when notified). As deduced form IRC, III-TS5 was found to directly lead to $\mathbf{III}_{\text{anti/cis}}$. $\mathbf{III}_{\text{anti/cis}}$ and the corresponding III-TS6 (as noted in Figure S24) were calculated but were not included in the reaction profile.

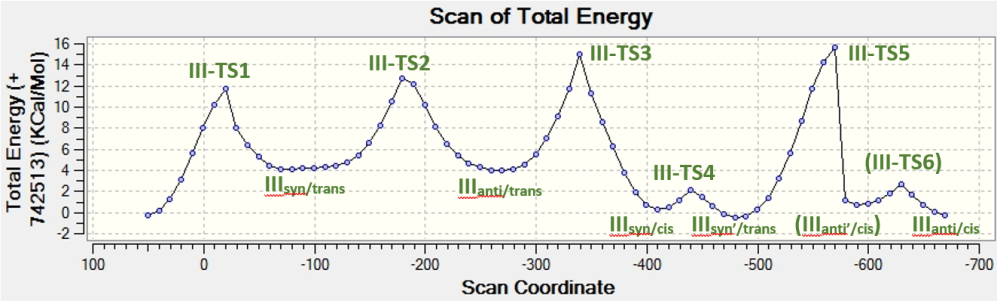


Figure S24: Relaxed potential energy scan of the Ar-N dihedral angle $\omega 3$ rotation.

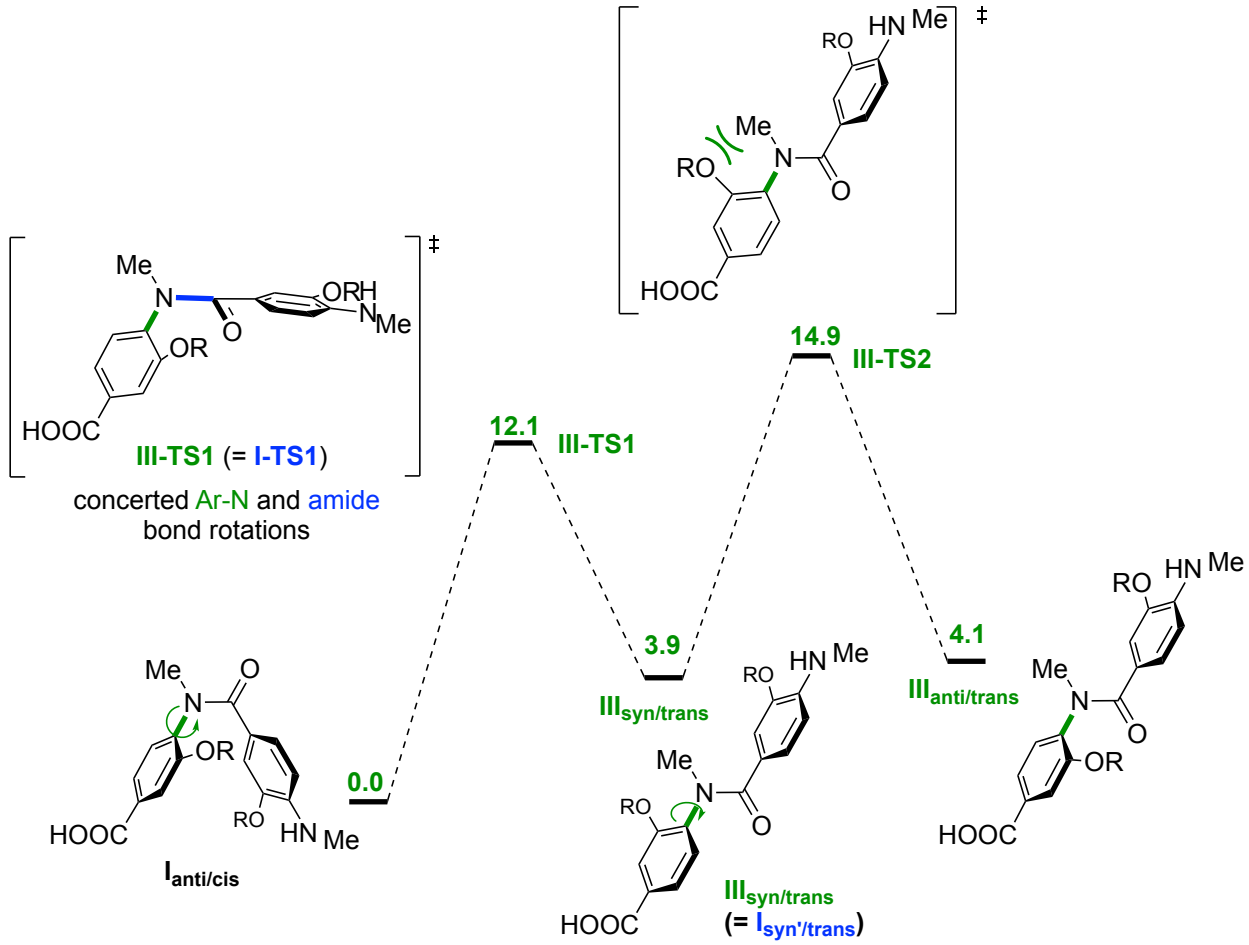


Figure S25: Ar-N dihedral angle $\omega 3$ rotation energy profile (as per Figure S24).

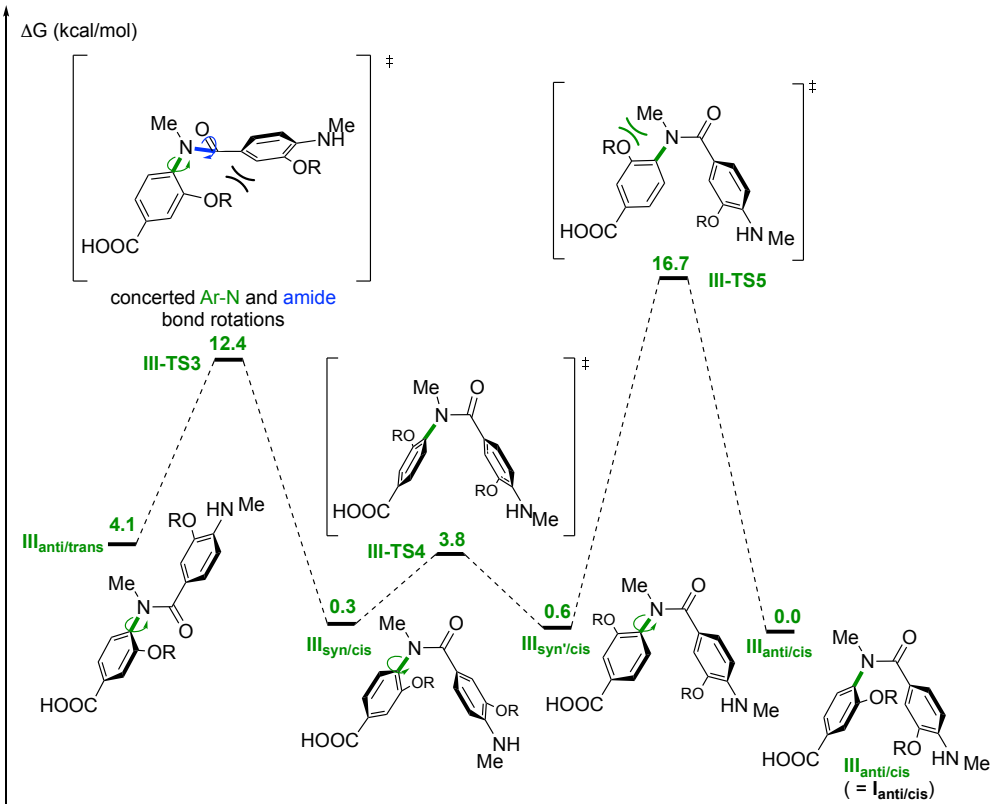


Figure S26: Ar-N dihedral angle $\omega 3$ rotation energy profile (as per Figure S24.)

Table S12: Data for Figure S25 and Figure S26 (all data at DOI: 10.14469/hpc/5311).

Name	ΔG_{298} (kcal/mol)	Job ID	DOI:
III-TS1)	12.1	10050284	10.14469/hpc/5312
$III_{syn/trans}$	3.9	10050358	10.14469/hpc/5274
III-TS2	14.9	10050297	10.14469/hpc/5313
$III_{anti/trans}$	4.1	10051635	10.14469/hpc/5314
III-TS3	12.4	10050417	10.14469/hpc/5315
$III_{syn/cis}$	0.3	10050461	10.14469/hpc/5318
III-TS4	3.8	10051078	10.14469/hpc/5317
$III_{syn/cis}$	0.6	10051052	10.14469/hpc/5316
III-TS5	16.7	10050464	10.14469/hpc/5319

Ar-N rotation (dihedral angle ω3 rotation) with restricted *cis* conformation (restricted dihedral angle ω1).

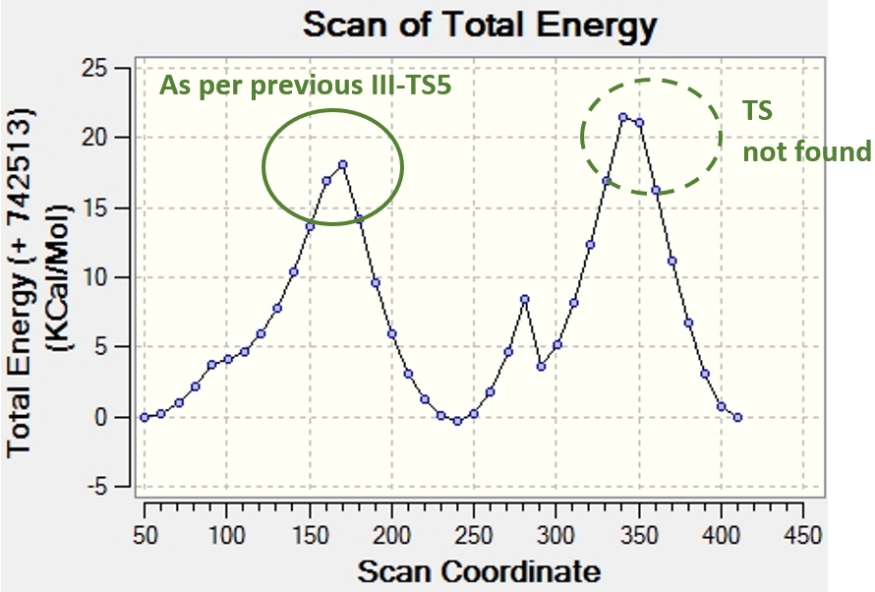


Figure S27: Restricted potential energy scan of Ar-N dihedral angle ω3 rotation with amide bond blocked in cis conformation.

The transition state corresponding to a solely dihedral rotation of the Ar-N bond in constrained cis conformation has not been found upon explicit optimization of the geometries of the maxima from the above restricted scan. This is likely due to the steric bulk induced by the ortho substituent of the Ar-N. Thus, rotation about the Ar-N bond either trigger the amide bond rotation and lead to a trans conformation (as per **I-TS1** G298=12.1 kcal/mol) or lead a steric clash with the N-Me group (as per **III-TS5** ΔG_{298} = 16.7 kcal/mol).

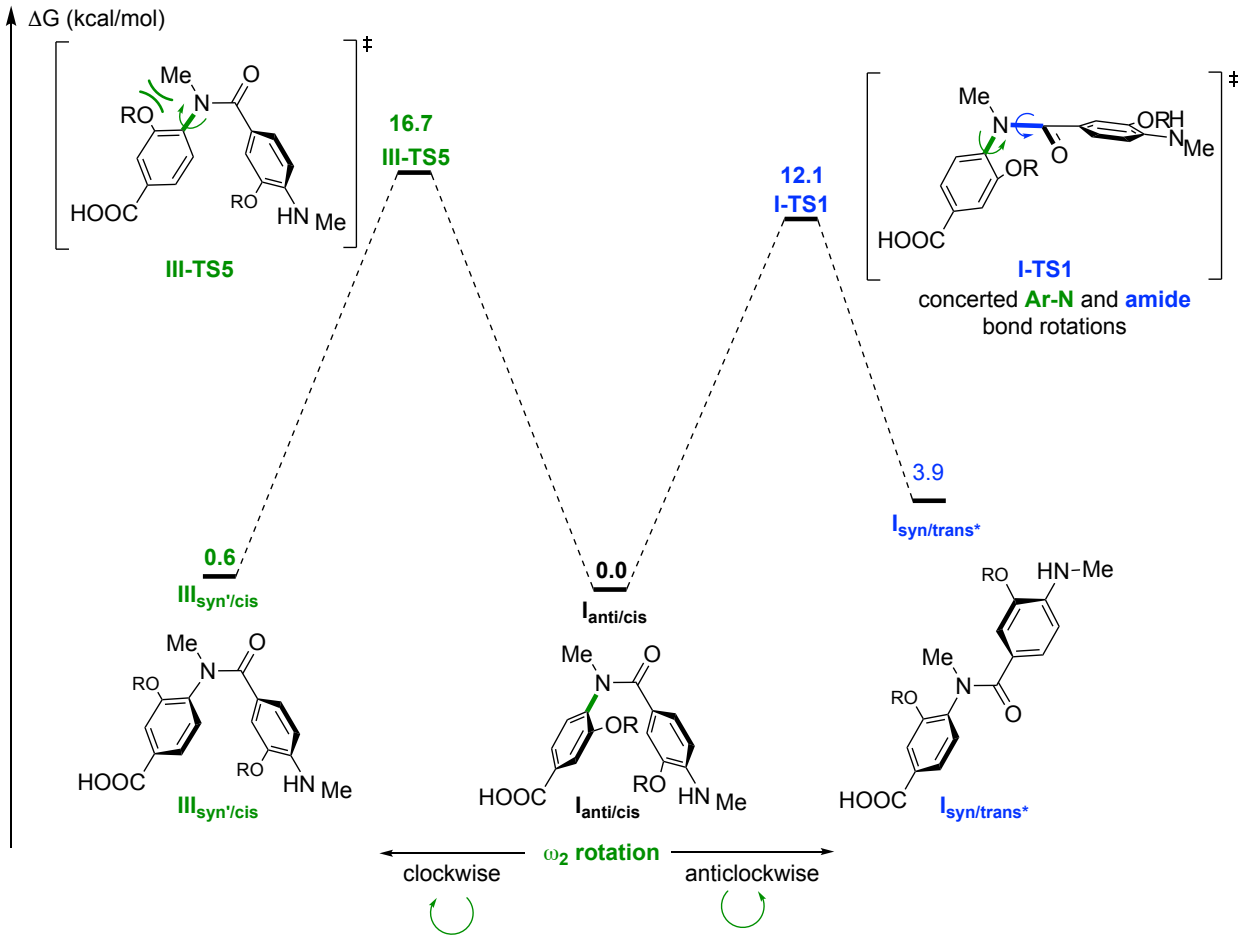


Figure S28: Independent (left) and concerted rotations (right) about Ar-N bond.

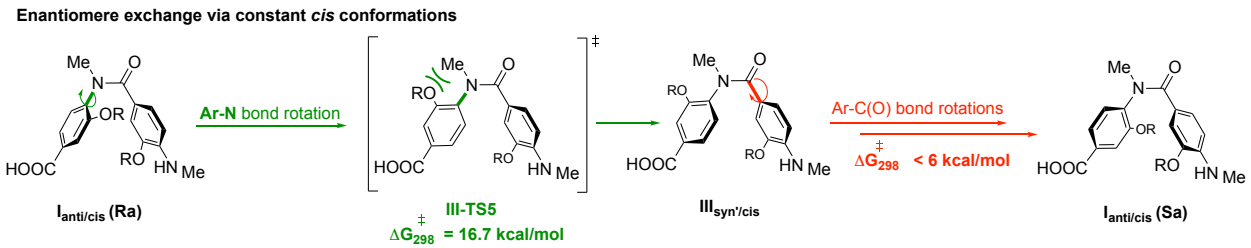


Figure S29: Enantiomer exchange via bond rotations in constant cis conformations (lowest maximum energy barrier at 16.7 kcal/mol).

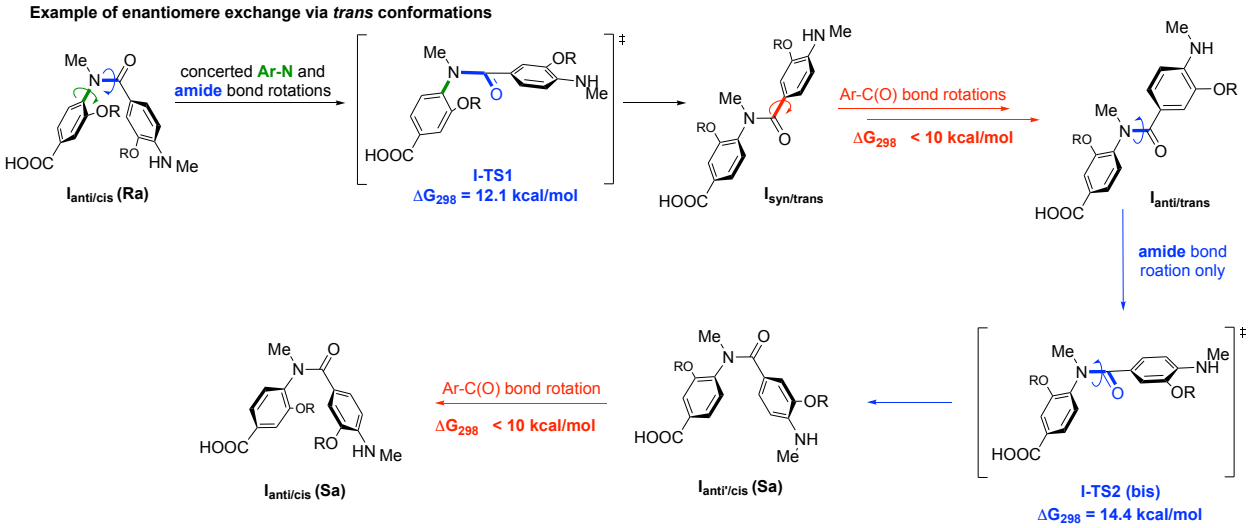


Figure S30: Possible enantiomer exchange pathway via bond rotations leading to trans conformations (lowest maximum energy barrier at 14.4 kcal/mol).

Boltzmann Distributions:

The population distributions of the extended vs folded conformations were calculated based on their relative energy via amide, Ar-N or concerted rotations using the following assumptions:

- The population difference is a function of two dihedral angles (Ar-N and amide).
- Take X-ray crystal structure as minimum energy conformation.
- Entropies of the conformers are similar.

Calculations were performed as follows: The probability that state Ei is occupied is;

$$P_i = Ce^{\frac{-E_i}{kT}}$$

The constant C can be found by summing over all P_i, which should give unity–the probability that *some* state is occupied. Thus, $1 = C\sum P_i$, or $C = \frac{1}{z}$, where $Z = \sum P_i$ is called the *partition function*. Each state of the system is represented in Z by its Boltzmann factor. Boltzmann factor at 298 K and at standard state (1 M) is;

$$N_i = e^{\frac{-\varepsilon_i}{k_b T}}$$

The resulting population distribution is;

$$\frac{N_J}{N} = \frac{e^{\frac{-\varepsilon_J}{k_b T}}}{\sum_i e^{\frac{-\varepsilon_i}{k_b T}}}$$

$N_{total} = 1.000000001383280000$

Table S13: Boltzmann populations of conformers at 298K

Energy Level No.	**Conformation**	**Relative Energy (kcal/mol)**	**Relative Energy (cal/mol)**	**Boltzmann Factor (N_i)**	**Population (N_i/N_{total})**
1	X-ray	0.0	0.0	1.00	1.00
2	Concerted	12.1	12100	$1.34x10^{-9}$	$1.34x10^{-9}$
3	Amide	14.1	14100	$4.56x10^{-11}$	$4.56x10^{-11}$
4	Ar-N	16.7	16700	$5.66x10^{-13}$	$5.66x10^{-13}$

Chemical Synthesis

General Methods

General Information

All non-aqueous reactions were performed in oven dried flasks, under a nitrogen atmosphere via a Schlenk line unless stated otherwise. Solvents were removed under reduced pressure at 40 °C. Analytical thin layer chromatography was performed on Merck Si60, F254 aluminium chromatography plates. Spots were visualized by UV light (operating at 254 and 365 nm), and using the appropriate stain (potassium permanganate, ninhydrin or bromocresol green). Flash column chromatography was carried out manually on Merck 60 silica gel, eluting with solvents as supplied, under a positive air pressure, or run on a Biotage Isolera One flash purification system using a Biotage SNAP KP-Sil cartridge. Where stated, SPE ion exchange was performed using Biotage ISOLUTE SCX-II cartridges eluting with methanolic ammonia (2 N).

Crystal structure images produced using CYLview, 1.0b; Legault, C. Y., Universit de Sherbrooke, 2009. (http://www.cylview.org)

NMR Spectra files are available at the DOI links for each compound in the methods section.

Materials

All solvents and reagents were purchased from Sigma-Aldrich Ltd (Gillingham, UK), Apollo Scientific (Stockport, UK), Acros Organics (Geel, Belgium), Alfa Aesar (Heysham, UK), Fluorochem (Hadfield, UK) and VWR (Radnor, US) unless otherwise stated, and were used without further purification. Anhydrous solvents were dispensed using Pure SolvTM solvent drying towers (Innovative Technology Inc.). Brine refers to a saturated solution of sodium chloride.

Instrumentation

^{1}H NMR spectra were recorded on Bruker AV-400 instrument at 400 MHz using deuterated solvents as a reference for internal deuterium lock unless stated otherwise. Chemical shift data is given as δ_H in units of parts per million (ppm) relative to tetramethylsilane (TMS), where δ_H(TMS) = 0.00 ppm. Coupling constants (J), calculated using MestReNova™ NMR software, are quoted in Hz and recorded to the nearest 0.1 Hz. Data are presented as follows: δ, integration, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sep = septet, m = multiplet), coupling constant (J) and assignment. The following internal references were used: $\delta_H(CDCl_3)$ = 7.26 ppm; $\delta_H(C_6D_6)$ = 7.16 ppm; $\delta_H((CD_3)_2SO)$ = 2.50 ppm; $\delta_C(CD_3OD)$ = 3.31 ppm.

^{13}C NMR spectra were recorded on Bruker AV-400 instrument at 101 MHz using deuterated solvents as a reference for internal deuterium lock unless stated otherwise. Chemical shift data is given as δ_C in units of parts per million (ppm) relative to tetramethylsilane (TMS), where δ(TMS) = 0.00 ppm. Data are presented as follows: δ and assignment. The following internal references were used: δ_C $CDCl_3$ = 77.16; δ_C C_6D_6 = 128.06; $\delta_C(CD_3)_2SO$ = 39.52; $\delta_C(CD_3OD)$ = 49.00.

High resolution mass spectrometry (HRMS) data were acquired by the Imperial College Mass Spectrometry service and m/z values are reported in Daltons. HRMS analyses were performed on a Waters LCT Premier Electrospray Time of Flight mass spectrometer operating in both ES+ and ES- mode. Samples were references against; Leucine-enkephalin $[M+H]^+$ = 556.2771, Sulfadimethoxine $[M+H]^+$ = 311.0814. MassLynx v4.1 software was used to analyse spectra. This version of the software does not account for the electron and all the calibrations/references are calculated accordingly.

Analytical and preparative LC-MS experiments were performed on a Waters LC-MS platform consisting of a Waters 2767 sample manager, Waters 515 HPLC pump, XBridge™ C_{18} columns (Analytical - 4.6 mm x 100 mm, Preparative - 19 mm x 100 mm) coupled to a Waters 2998 Photodiode Array detector (200-700 nm) and a Waters 3100 mass spectrometer

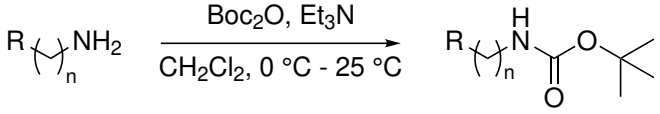
(ESI+ and ESI-). For analytical runs, a linear gradient of 1.2 mL/min from 5% solvent A (H_2O/FA 0.1%) to 98% solvent B (CH_3CN/FA 0.1%) over 10 mins was used unless stated otherwise. For preparative runs, a linear gradient of 20 mL/min from 5% solvent A to 98% solvent B over 10 min was used unless stated otherwise. MassLynx v4.1 software was used to analyse spectra and chromatograms obtained.

Infra-red spectra were recorded as solids or neat liquids on an Agilent Cary 630 FT-IR spectrometer. Selected absorbances (υ_{max}) are recorded as frequency of absorption (cm^{-1}).

X-ray crystallography was performed by the Imperial College X-ray Crystallography Service . Single crystal X-ray data were collected on an Agilent Xcalibur PX Ultra A diffractometer with graphite monochromatized (Cu-K = 0.615 mm^{-1}) radiation at 173 K.

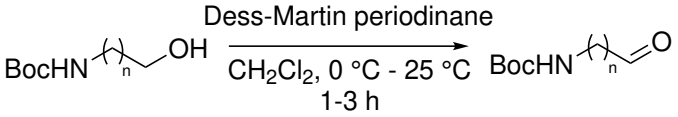
General Procedures for Monomer Synthesis

Procedure A (*N*-Boc protection of amines)



To a stirring solution of amine (1 eq.) in anhydrous dichloromethane (10 mL/g) was added anhydrous triethylamine (1.2 eq.) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate (1 eq.) was added portion-wise over 10 min. The reaction mixture was warmed to room temperature and stirred for 16 h under a nitrogen atmosphere. The reaction was followed by TLC (ninhydrin). The reaction mixture was diluted with dichloromethane (50 mL/g). The organic layer was washed with 0.1 M hydrochloric acid (10 mL/g x2), water (10 mL/g) and brine (10 mL/g), dried ($MgSO_4$) and concentrated *in vacuo*.

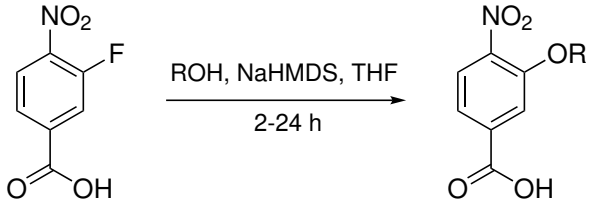
Procedure B (Oxidation of alcohol)



A stirring solution of alcohol (1 eq.) in anhydrous dichloromethane (10 mL/g) was cooled to 0 °C under a nitrogen atmosphere. DessMartin periodinane (1.2 eq.) was added portion-wise over 5 min. The reaction mixture was stirred at 0 °for 15 min, then warmed to room temperature slowly. The reaction was followed by TLC (dinitrophenylhydrazine). Upon completion, the reaction mixture was diluted with diethyl ether (100 mL/g) and 10% sodium thiosulphate solution (25 mL/g) and saturated sodium bicarbonate solution (25 ml/g) were added. The resulting suspension was stirred rapidly until the precipitate was fully dissolved. The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL/g). The organic layers were combined and washed with 10% sodium thiosulphate solution (2 x 20 mL/g), saturated sodium bicarbonate solution (2 x 20 mL/g)

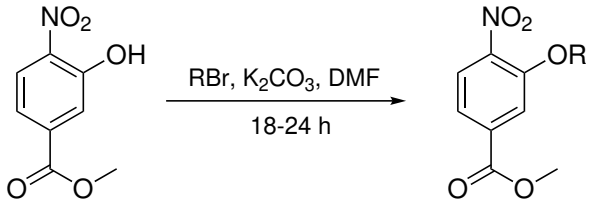
and brine (20 mL/g), dried ($MgSO_4$) and concentrated *in vacuo*. The product was verified by ^{1}H NMR and carried forward without further purification.

Procedure C (S_NAr)



Procedure adapted from Shaginian *et al.*[1] Sodium hydride (60 % dispersion in mineral oil) (2.5 eq.) was suspended in anhydrous tetrahydrofuran (20 mL/g) and the alcohol (1.1 eq.) was added dropwise at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 15 min. 3-fluoro-4-nitrobenzoic acid (1 eq.) was added portion-wise over 10 min at 0 °C with rapid stirring. The reaction mixture was stirred at 0°C for 15 min, then warmed to room temperature slowly. The reaction was followed by TLC (bromocresol green) and LC-MS. Upon completion, saturated NH_4Cl (10 mL/g) was added and the reaction mixture was poured into ethyl acetate (50 mL/g). The organic layer was washed with 1 M hydrochloric acid (20 mL/g x 3), water (20 ml/g) and brine (20 ml/g). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*.

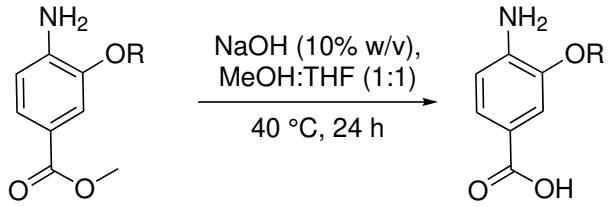
Procedure D (Phenol Alkylation)



Procedure adapted from Murphy *et al.*[2] To a stirred solution of methyl-3-hydroxy-4-nitrobenzoate in (1 eq.) and potassium carbonate (5 eq.) in dimethylformamide (10 mL/g) was added bromide (1.5 eq.). The reaction mixture was warmed to 50 °C under a nitrogen atmosphere. The reaction was followed by TLC (potassium permanganate) and LC-MS. Upon completion, the reaction mixture was cooled to room temperature, poured into water

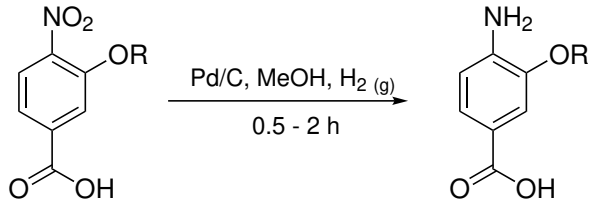
(20 mL/g) and extracted with ethyl acetate (3 x 100 mL/g). The combined organic fractions were washed with 5% lithium chloride (20 mL/g x 2), water (20 mL/g x 2) and brine (20 mL/g), dried ($MgSO_4$) and concentrated *in vacuo*.

Procedure E (Ester Hydrolysis)



Procedure adapted from Murphy *et al.*[2] To a stirring solution of amino ester in methanol: tetrahydrofuran (20 mL/g, 1:1, v/v) was added 10 % sodium hydroxide solution (10 mL/g) and the reaction mixture heated to 40 °C. The reaction mixture was stirred for 16 h and followed by TLC (ninhydrin and bromocresol green) and LC-MS. Further equivalents of alcohol and sodium hydride were added if required. Upon completion, the organic solvents were removed *in vacuo*, the residue dissolved in water (20 mL/g) and acidified to pH 4 with conc. hydrochloric acid. The precipitate was extracted with dichloromethane (50 mL/g x 3), the combined organic extracts washed with water (20 mL/g x 2) and brine (20 mL/g x 1), dried ($MgSO_4$ and concentrated *in vacuo*.

Procedure F (Hydrogenation - Pd/C)



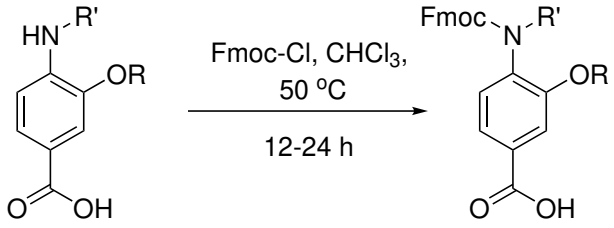
A flame-dried, two-necked round-bottom flask equipped with a stirrer bar was evacuated and backfilled with argon (x 3). The flask was charged with palladium on carbon (10 wt.%) and a solution of nitro-acid/nitro-ester in methanol (20 mL/g) was added to the flask under inert atmosphere. The flask was evacuated with care and backfilled with hydrogen (x3). The reaction mixture was stirred gently and followed by TLC (ninhydrin) and LC-MS.

Upon completion, the reaction was filtered through a celite plug and concentrated *in vacuo*. The residue was taken up in dichloromethane and washed with water (20 mL/g x2) and brine (20 mL/g x 1), dried ($MgSO_4$ and concentrated *in vacuo*. In the majority of cases, the product was of sufficient purity to take forward without further purification.

Procedure G (Reductive Amination)

Procedure adapted from Long *et al.*[3] To a solution of primary aniline (1 eq.) in anhydrous methanol (20 mL/g) was added aldehyde (1.1 eq.) and 2-methylpyridine borane complex (1.2 eq) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature and followed by TLC (ninhydrin) and LC-MS. Upon completion, the solvent was removed *in vacuo*. The crude reaction mixture was dissolved in dichloromethane (50 mL/g) and washed with 1M hydrochloric acid (20 mL/g x 3), water (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography or trituration afforded the desired product.

Procedure H (Fmoc protection of anilines)



Procedure adapted Long *et al.*[3] A solution of fluorenylmethyloxycarbonyl chloride (1.2 eq) in anhydrous chloroform (10 mL/g) was added dropwise to a solution of secondary aniline (1 eq) and sodium hydrogen carbonate (1.2 eq) in anhydrous chloroform (20 mL/g). The reaction mixture was stirred at 50 °C under a nitrogen atmosphere and followed by

TLC (ninhydrin). Upon completion, the reaction was concentrated and the crude reaction mixture was dissolved in dichloromethane (50 mL/g). The organic layer was washed with 1 M hydrochloric acid (20 mL/g x3) and brine (20 mL), dried ($MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography afforded the desired product.

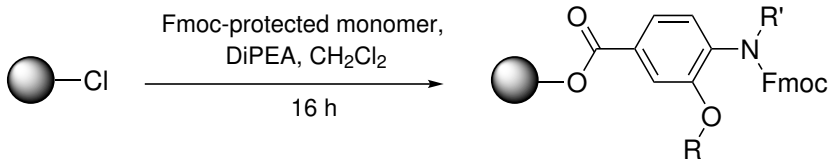
Solid-phase Synthesis of Oligomers

General Methods

2-chlorotrityl chloride resin (1.15 mmol/g, 100-200 mesh; carrier: polystyrene, crosslinked with 1 % DVB) was purchased from Merck (Kenilworth, US). TentaGel S Rink-amide Fmoc resin (0.21 mmol/g, 100-200 mesh; carrier: polystyrene mesh, crosslinked with 1 % DVB) was purchased from Rapp Polymere (Tübingen, DE). 1-Chloro-*N,N*,2-trimethyl-1-propenylamine (Ghosez's reagent) and anhydrous *N*-methyl-2-pyrrolidone were purchased from Sigma-Aldrich Ltd (Gillingham, UK). Ghosez's reagent was aliquoted into flame-dried 1 mL amber vials under an argon atmosphere and stored at -20 °C. Couplings were performed under microwave irradiation using a Biotage Initiator Classic. Biotage microwave reaction vials (2-5 mL, cat. # 351521) were equipped with a Biotage microwave stirrer (2-5 mL, cat. # 355543) and sealed with a Biotage septa cap (cat. # 352598). All other reactions were performed on an orbital shaker in a 5 mL polypropylene syringe fitted with a frit and Luer plug. Resin washes (*vide infra*) consisted of; *N*-methyl-2-pyrrolidone (5 mL x3), *N,N*-dimethylformamide (5 mL x3) and dichloromethane (5 ml x3). All washes were left to stand for 10 sec and then filtered under water vacuum.

General Procedures for SPS

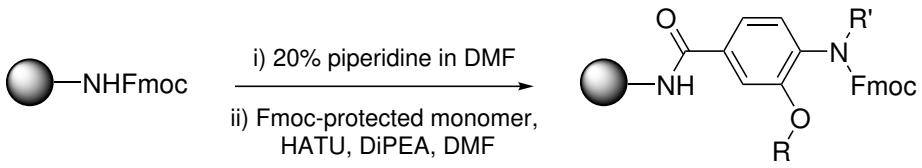
Resin Loading (2-Cl Trt)



In a flame-dried, two-necked round-bottom flask, 2-Chlorotrityl chloride resin (0.3 mmol/g) was swelled in anhydrous dichloromethane (10 mL/g) for 30 min under a nitrogen atmosphere. A solution of Fmoc protected monomer (1.5 eq) in anhydrous dicholoromethane

(2 mL/g) and anhydrous *N,N*-diisopropylethylamine (5 eq.) were added and the reaction mixture was stirred gently at room temperature for 16 h under a nitrogen atmosphere. The reaction mixture was transferred to a syringe and filtered under water vacuum. The resin was washed (Section) and dried under a flow of nitrogen. Remaining reactive sites on the resin were "capped" with dichloromethane:*N,N*-diisopropylethylamine:methanol (17:2:1, 10 mL/g, 30 min). The resin was washed and stored under reduced pressure in a desiccator. Exact resin loading was calculated via UV-Vis spectroscopy (*vide infra*).

Resin Loading (Rink Amide)



In a flame-dried, two-necked round-bottom flask, rink amide resin (0.22 mmol/g) was swelled in anhydrous DMF (10 mL/g) for 30 min under a nitrogen atmosphere. Fmoc protected monomer (2 eq.) was pre-activated with HATU (1.95 eq.) and anhydrous *N,N*-diisopropylethylamine (5 eq.) in anhydrous dimethylformamide (1 mL/g) for 15 min under a nitrogen atmosphere. The pre-activated monomer solution was added to the resin and stirred gently at room temperature for 16h under a nitrogen atmosphere. The reaction mixture was transferred to a syringe and filtered under water vacuum. The resin was washed (Section) and dried under a flow of nitrogen. Remaining reactive sites on the resin were acetylated with acetic anhydride (5% in DMF, v/v, 10 mL/g, 45 min). The resin was washed and stored under reduced pressure in a desiccator. Exact resin loading was calculated via UV-Vis spectroscopy (*vide infra*).

Determination of Resin Loading

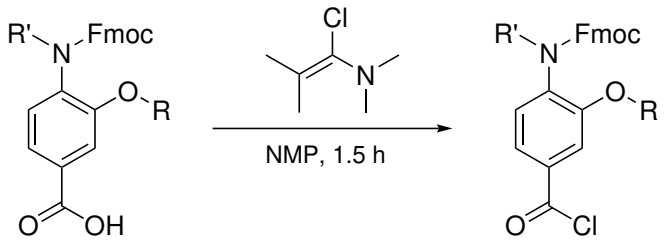
Before Fmoc deprotection, the level of resin substiution was determined using UV-Vis spectrosccopy. The dibenzofulvene-piperidine adduct has UV absorption maxima at 290 nm (ε= 5,280-5,800 M^{-1}) and 301 nm (ε= 6,200-7,800 M^{-1}). The absorption maxima at 290 nm (A_{290}) was recorded and resin loading calculated using Equation 1;

$$Loading(mmol/g) = (A_{290})/(w(mg) \times 1.75) \quad (1)$$

where *w (mg)* = weight of resin in mg

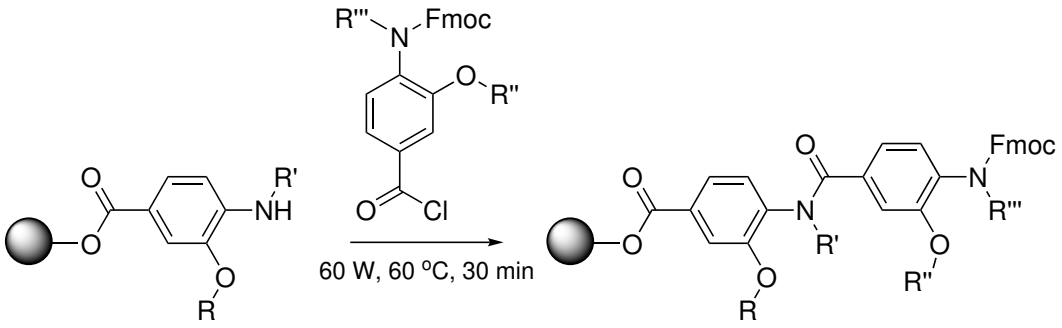
Procedure - *ca.*1 mg of resin was weighed and the mass recorded to 2 d.p. The resin was suspended in 20% piperidine in DMF (3 mL) (20% piperidine) in a quartz cuvette and left for 10 min with occasional agitation. A_{290} was measured in comparison to a 20% piperidine blank. Recordings were performed in triplicate. Molar equivalents for subsequent couplings were calculated with respect to (w.r.t) the determined resin loading.

General Procedure for Acyl Chloride Preactivation



A flame-dried, two-necked round bottom flask was evacuated and backflushed with nitrogen (x3). A solution of Fmoc protected monomer (2 eq. w.r.t resin loading) in anhydrous *N*-methyl-2-pyrrolidone (1 mL) and Ghosez's reagent (1.9 eq. w.r.t resin loading) were added under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 h. Acid chloride formation was followed by LC-MS. An aliquot of reaction mixture (10 µL) was removed, quenched with anhydrous methanol (100 uL) and left for 15 min. Reaction progress was determined by the ratio of methyl carboxylate/carboxylic acid peak areas in the HPLC trace (50% MeCN to 98% MeCN (0.1% FA) over 10 min).

General Procedure for Oligomer Formation - Double Coupling



Procedure adapted from Long *et al* for a Biotage Initiator microwave reactor (*cf.* CEM Liberty™ microwave assisted peptide synthesiser).[3] Fmoc protected pre-loaded resin (0.2-0.3 mmol/g, 1 eq.) was swelled in *N*-methyl-2-pyrrolidone (5 mL, 5 min) and washed (Section). A solution of 20% piperidine in NMP (5 mL, 20 min x2) was added to the resin. The resin was washed, dried under a flow of nitrogen, transferred to a flame-dried microwave reaction vial and dried further under high vacuum (30 min). The vial was evacuated and backfilled with nitrogen (x3). A solution of Fmoc protected acyl chloride obtained by pre-activation (*vide supra*) in *N*-methyl-2-pyrrolidone was added to the reaction vial and heated via microwave irradiation (60 W, 60 °C, 30 min, stirring = 300 RPM). The reaction mixture was transferred to a 5 mL syringe, filtered under water vacuum and the resin washed and dried under a flow of nitrogen. The resin was transferred to a flame-dried microwave vial, dried under high vacuum and a second solution of acyl chloride (2 eq. w.r.t resin loading) was added under a nitrogen atmosphere. The reaction mixture was subjected to microwave irradiation (60 W, 60 °C, 20 min, stirring = 300 RPM). The reaction mixture was transferred to a syringe, filtered under water vacuum and dried under a flow of nitrogen. The coupling efficiency was determined by UV-Vis spectroscopy (*vide supra).*

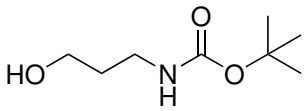
General Procedure for Cleavage from Solid Support

A final Fmoc deprotection was performed (20% piperidine, 5 mL, 20 min x 2) and the resin washed thoroughly with dichloromethane (10 x 5 mL). The resin was dried under a nitrogen atmosphere. A solution of 30% hexafluoro-2-propanol in dichloromethane (5 mL,

1 h) was added and shaken rapidly. The reaction mixture was filtered and the filtrate was concentrated under a flow of nitrogen (*ca.* 1 mL). The crude product was precipitated by addition of ice-cold ether and isolated via centrifugation. The crude solid was dissolved in acetonitrile:water (1:1, 5 mL) and lyophilised to afford an off-white solid. The helix mimetics were analysed and purified (if necessary) by LC-MS. Purity and identity of the helix mimetics was determined via LC-MS.

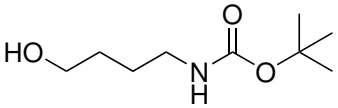
Sidechains

***tert*-butyl (3-hydroxypropyl)carbamate (SC1)**



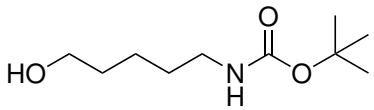
SC1 was synthesised from 3-amino propan-1-ol (5.00 g, 66.56 mmol) using general procedure A to yield the title compound as a colourless oil (12.64 g, 100%). Rf (n-hex:EtOAc, 1:1) = 0.3; ν_{max}/cm^{-1} : 3339 (O-H), 2976 (N-H), 2875, 1685 (C=O), 1511, 1366, 1249, 1165, 1042; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.99 (s, 1H, O**H**), 3.63 (q, J = 5.6 Hz, 2H, HOC$\mathbf{H}_2$), 3.42 (t, J = 4.7 Hz, 1H, N**H**), 3.25 (q, J = 6.3 Hz, 2H, HNC$\mathbf{H}_2$), 1.65 (p, J = 6.0 Hz, 2H, $HOCH_2C\mathbf{H}_2$), 1.42 (s, 9H, $(C\mathbf{H}_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) : δ_C = 157.1 (**C**=O), 79.5 ($\mathbf{C}(CH_3)_3$), 59.2 (HO$\mathbf{C}H_2$), 37.0 (NH$\mathbf{C}H_2$), 32.8 ($HOCH_2\mathbf{C}H_2$), 28.4 ($(\mathbf{C}H_3)_3$); HRMS-ESI (m/z); Calcd. for $[C_8H_{17}NO_3Na\text{-}H]^-$: 198.1106. Found: 198.1105. DOI: 10.14469/hpc/5181

***tert*-Butyl (4-hydroxybutyl)carbamate (SC2)**



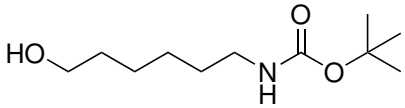
SC2 was synthesised from 4-amino butan-1-ol (5.00 g, 56.09 mmol) using general procedure A to yield the title compound as a colourless oil (11.20 g, 98%). Rf (n-hex:EtOAc, 1:1) = 0.3; ν_{max}/cm^{-1} : 3345 (O-H), 2932 (N-H), 2870, 1685 (C=O), 1523, 1366, 1249, 1165, 1036; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.68 (t, J = 5.8 Hz, 2H, HOC$\mathbf{H}_2$), 3.17 (t, J = 7.4 Hz, 2H, HNC$\mathbf{H}_2$), 1.65 1.54 (m, 4H, $HOCH_2C\mathbf{H}_2C\mathbf{H}_2CH_2$), 1.46 (s, 9H, $(C\mathbf{H}_3)_3$) (**H**O and **H**N protons not observed); ^{13}C NMR (101 MHz, $CDCl_3$) : δ_C 156.2 (**C**=O), 79.3 ($\mathbf{C}(CH_3)_3$), 62.5 (HO$\mathbf{C}H_2$), 40.5 (HN$\mathbf{C}H_2$), 29.72 ($HOCH_2\mathbf{C}H_2$), 28.42 ($(\mathbf{C}H_3)_3$), 26.6 ($HNCH_2\mathbf{C}H_2$); HRMS-ESI (m/z); Calcd. for $[C_9H_{19}NO_3+H]^+$: 190.1445. Found: 190.1443. DOI: 10.14469/hpc/5183

***tert*-Butyl (5-hydroxypentyl)carbamate (SC3)**



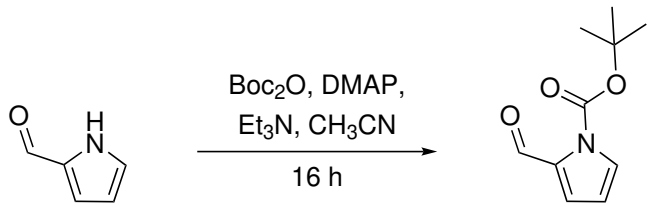
SC3 was synthesised from 5-amino pentan-1-ol (3.00 g, 29.08 mmol) using general procedure A to yield the title compound as a colourless oil (5.81 g, 98%). R*f* (*n*-hex:EtOAc, 1:1) = 0.35; ν_{max}/cm^{-1} : 3340 (O-H), 2932 (N-H), 2864, 1685 (C=O), 1523, 1366, 1249, 1165, 1053; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.64 (br, 1H, O**H**), 3.61 (t, J = 6.5 Hz, 2H, HOC$\mathbf{H}_2$), 3.10 (t, J = 7.0 Hz, 2H, HNC$\mathbf{H}_2$), 2.42 (br, 1H, N**H**), 1.61 1.33 (m, 15H, $HOCH_2C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2CH_2NH$ & $(C\mathbf{H}_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 156.1 (**C**=O), 79.1 ($\mathbf{C}(CH_3)_3$), 62.5 ($HO\mathbf{C}H_2$), 40.5 ($HN\mathbf{C}H_2$), 32.2 ($HOCH_2\mathbf{C}H_2$), 29.8 ($HNCH_2\mathbf{C}H_2$), 28.4 (($\mathbf{C}H_3)_3$), 22.9 ($HOCH_2CH_2\mathbf{C}H_2$); HRMS-ESI (*m/z*): Calcd. for $[C_{10}H_{22}NO_3+H]^+$: 204.1597. Found: 204.1600. DOI: 10.14469/hpc/5184

***tert*-Butyl (6-hydroxyhexyl)carbamate (SC4)**



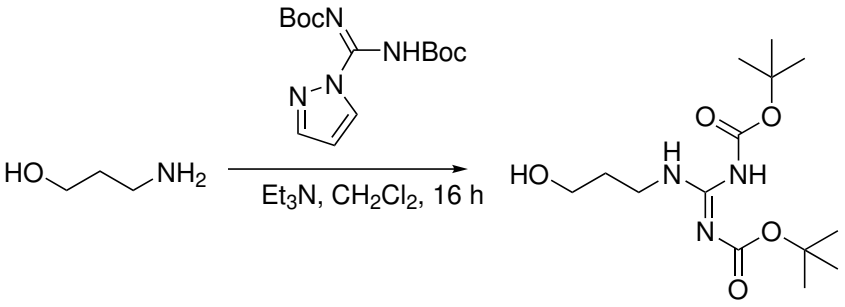
SC4 was synthesised from 6-amino hexan-1-ol (1.00 g, 8.50 mmol) using general procedure A to yield the title compound as an amorphous white solid (1.73 g, 100%). ν_{max}/cm^{-1} : 3368 (O-H), 2932 (N-H), 2859, 1685 (C=O), 1517, 1366, 1243, 1165, 1059; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.27 (s, 1H, O**H**), 3.60 (t, J = 6.5 Hz, 2H, HOC$\mathbf{H}_2$), 3.08 (t, J = 7.0 Hz, 2H, HNC$\mathbf{H}_2$), 1.59 1.50 (m, 2H, $HOCH_2C\mathbf{H}_2$), 1.49 1.27 (m, 15H, $HOCH_2CH_2C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2$ & $(C\mathbf{H}_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 156.1 (**C**=O), 79.1 ($\mathbf{C}(CH_3)_3$), 62.6 ($HO\mathbf{C}H_2$), 40.5 ($HN\mathbf{C}H_2$), 32.58 ($HOCH_2\mathbf{C}H_2$), 30.06 ($HNCH_2\mathbf{C}H_2$), 28.4 (($\mathbf{C}H_3)_3$), 26.4 ($HOCH_2CH_2\mathbf{C}H_2$), 25.3 ($HOCH_2CH_2CH_2\mathbf{C}H_2$).; HRMS-ESI (*m/z*): Calcd. for $[C_{11}H_{24}NO_3+H]^+$:218.1756. Found: 218.1760. DOI: 10.14469/hpc/5185

***N*-*tert*-Butoxycarbonylpyrrole-2-carboxaldehyde (SC5)**



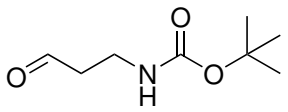
To a stirring solution of pyrrole-2-carboxaldehyde (3.00 g, 31.54 mmol, 1.00 eq.) in anhydrous acetonitrile (20 mL) under a nitrogen atmosphere were added di-*tert*-butyl dicarbonate (6.90 g, 31.54 mmol, 1.00 eq.), anhydrous triethylamine (5.10 mL, 37.85 mmol, 1.2 eq.) and 4-(dimethylamino)pyridine (0.38 g, 3.15 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 16h. The solvent was removed *in vacuo* and purification by column chromatography [SiO_2, EtOAc/hexanes, 0:1 to 1:9] afforded the title product as a colourless oil (5.81 g, 95%). R*f* (EtOAc/Hexanes, 1:9) = 0.3; ν_{max}/cm^{-1} : 3138 (N-H), 1746 (HC=O), 1668 (NC=O), 1439, 1332, 1293, 1249; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.33 (d, J = 0.7 Hz, 1H, **H**C=O), 7.45 (dd, J = 3.1, 1.8 Hz, 1H, ArC**H**), 7.19 (dd, J = 3.7, 1.8 Hz, 1H, ArC**H**), 6.29 (ddd, J = 3.7, 3.0, 0.7 Hz, 1H, ArC**H**), 1.65 (s, 9H, (C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 182.3 (**C**=O), 148.4 (N**C**=O), 134.7 (Ar**C**), 127.4 (Ar**C**H), 121.2 (Ar**C**H), 111.7 (Ar**C**H), 85.8 (**C**(CH$_3$)$_3$), 27.9 ((**C**H$_3$)$_3$); HRMS-ESI (*m/z*): Calcd. for $[C_{10}H_{13}NO_3+H]^+$: 196.0974. Found: 196.0980. DOI: 10.14469/hpc/5186

3-(*N,N*'-di-*tert*-butoxycarbonylguanidino)-propan-1-ol (SC6)



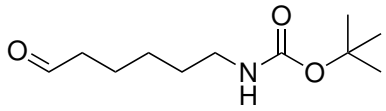
To a stirring solution of 3-amino propan-1-ol (0.20 mL, 2.66 mmol, 1.00 eq.) in anhydrous dichloromethane (15 mL) was added anhydrous triethylamine (0.35 mL, 2.66 mmol, 1.00 eq.) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and *N,N*-di-Boc-1*H*-pyrazole-1-carboxamidine (0.85 g, 2.73 mmol, 1.50 eq.) was added in one portion. The reaction was followed by TLC (ninhydrin). After 5h, the reaction was diluted with dichloromethane (50 mL), washed with 0.1 M hydrochloric acid (2 x 20 mL), water (1 x 20 mL) and brine (1 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography [SiO_2, CH_2Cl_2:EtOAc, 1:1] afforded the title compound as a white solid (0.75 g, 89%). R*f* (CH_2Cl_2/MeOH 95:5) = 0.5; ν_{max}/cm^{-1} : 3278 (O-H), 2977, 1729 (C=O), 1634 (C=N), 1556, 1131; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 11.47 (s, 1H, N**H**), 8.48 (s, 1H, N**H**), 4.71 (s, 1H, O**H**), 3.65 3.54 (m, 4H, HOC$\mathbf{H}_2$CH_2C$\mathbf{H}_2$), 1.77 1.63 (m, 2H, HOCH_2C$\mathbf{H}_2$), 1.52 (s, 9H, (C$\mathbf{H}_3$)$_3$), 1.50 (s, 9H, (C$\mathbf{H}_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$); δ_C = 162.8 (**C**=N), 157.2 (**C**=O), 153.2 (**C**=O), 83.5 (**C**(CH$_3$)$_3$), 79.5 (**C**(CH$_3$)$_3$), 57.7 (HO**C**H$_2$), 36.8 (HN**C**H$_2$), 32.9 (HOCH$_2$**C**H$_2$), 28.2 ((**C**H$_3$)$_3$), 28.1 ((**C**H$_3$)$_3$); HRMS-ESI (*m/z*): Calcd. for [$C_{14}H_{27}N_3O_5$+H]$^+$: 318.2029. Found: 318.2029. DOI: 10.14469/hpc/5187

***tert*-Butyl (3-oxopropyl)carbamate** (**SC7**)



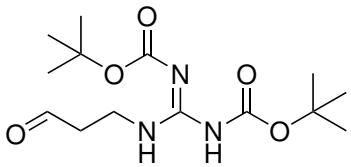
SC7 was synthesised from **SC1** (1.00 g, 5.78 mmol) using general procedure B to yield the title compound as a yellow oil (0.90 g, 91% (crude)). Product carried forward without further purification. R_f (CH_2Cl_2:MeOH, 9:1) = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 9.80 (d, J = 1.0 Hz, **H**C=O), 4.90 (s, 1H, N**H**), 3.42 (q, J = 6.0 Hz, 2H, O=CHC$\mathbf{H}_2$), 2.76 2.61 (m, 2H, NHC$\mathbf{H}_2$), 1.54 1.50 (m, 2H, NHCH_2C$\mathbf{H}_2$), 1.42 (s, 9H, (C$\mathbf{H}_3$)$_3$). NMR data consistent with literature.[4] DOI: 10.14469/hpc/5188

***tert*-Butyl (6-oxohexyl)carbamate** (**SC8**)



SC8 was synthesised from **SC4** (0.44 g, 2.03 mmol) using general procedure B to yield the title compound as a colourless oil (0.25 g, 57%). Product carried forward without further purification. R_f (EtOAc:n-hex, 1:1) = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.77 (s, 1H), 4.57 (s, 1H, **N**H), 3.13 (q, J = 6.7 Hz, 2H, O=CHC$\mathbf{H}_2$), 2.45 (td, J = 7.3, 1.7 Hz, 2H, NHC$\mathbf{H}_2$), 1.66 (dt, J = 15.0, 7.3 Hz, 2H, O=CHCH_2C$\mathbf{H}_2$), 1.57 1.31 (m, 13H, (C**H**)$_3$) & 2 x C$\mathbf{H}_2$). NMR data consistent with literature.[5] DOI: 10.14469/hpc/5189

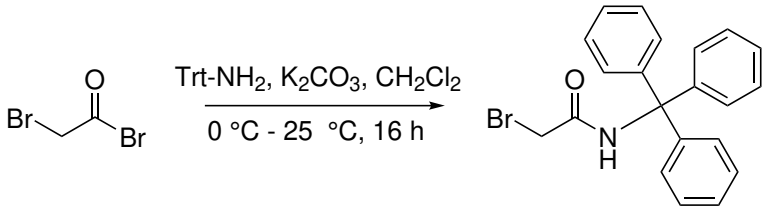
***tert*-Butyl (3-oxopropyl)carbamate** (**SC9**)



SC9 was synthesised from **SC6** (1.00 g, 3.15 mmol) using general procedure B to yield the title compound as a colourless oil (0.64 g, 65%). Product carried forward without further purification. R_f (CH_2Cl_2:MeOH, 95:5) = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 9.85 (t, J

= 1.0 Hz, 1H, **H**C=O), 3.76 (t, J = 6.1 Hz, 2H, HC=OC**H**$_2$), 2.81 (td, J = 6.1, 1.0 Hz, 2H, HC=OCH$_2$C**H**$_2$), 1.53 (s, 9H, (C**H**$_3$)$_3$), 1.51 (s, 9H, (C**H**$_3$)$_3$). NMR data consistent with literature.[6] DOI: 10.14469/hpc/5190

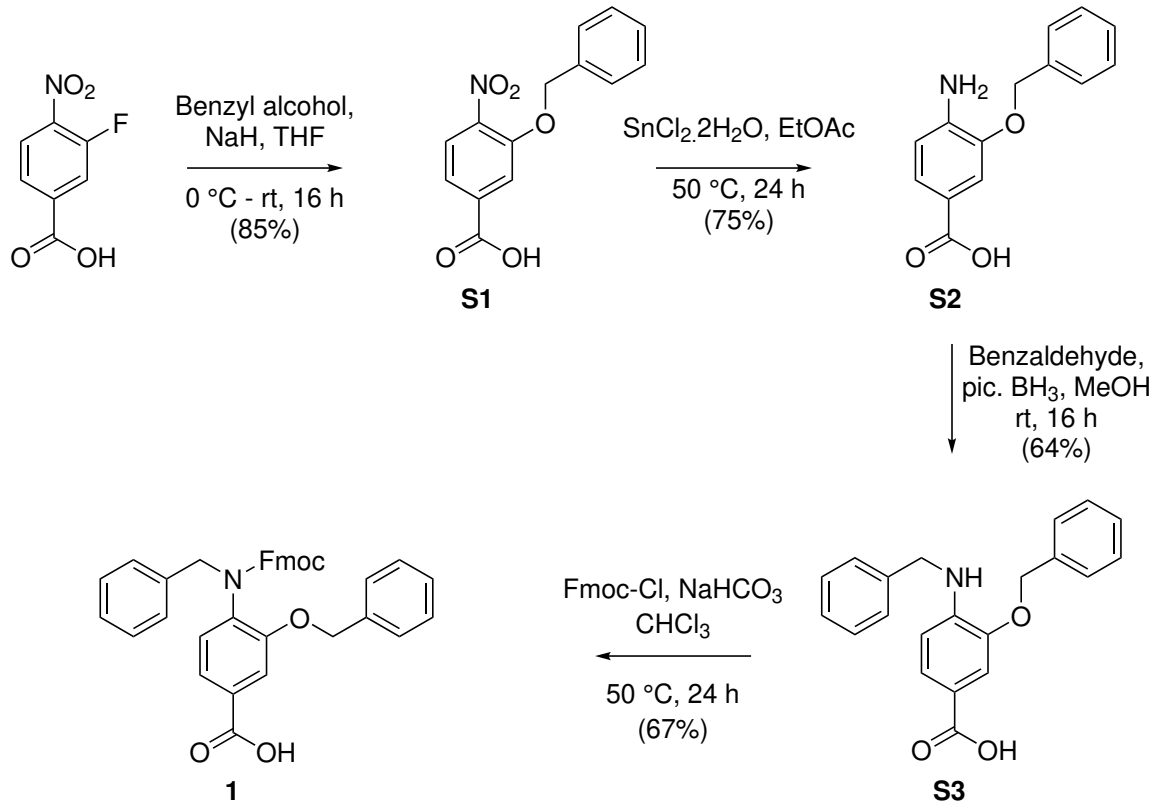
2-Bromo-*N*-tritylacetamide (**SC10**)



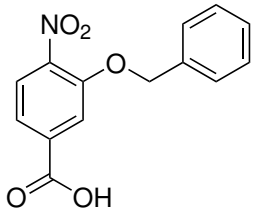
A stirring solution of tritylamine (3.00 g, 11.57 mmol, 1.00 eq.) and potassium carbonate (1.90 g, 13.90 mmol, 1.20 eq.) in anhydrous dichloromethane (50 mL) was cooled to 0 °C and bromoacetyl bromide (1.01 mL, 11.57 mmol, 1.00 eq.) was added dropwise under a nitrogen atmosphere. The reaction mixture was warmed to room temperature over 1h and stirred at room temperature for 16 h. The reaction mixture was diluted with dichloromethane (50 mL), washed with water (20 mL x 2) and brine (20 mL x 2), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography [SiO_2, CH_2Cl_2] afforded the title compound as a white solid (4.28 g, 97%). R_f (CH_2Cl_2) = 0.6; ν_{max}/cm^{-1} : 3261, 3053, 3027 (N-H), 1657 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (s, 1H, N**H**), 7.38 7.18 (m, 15H, trityl), 3.92 (s, 2H, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$); δ_C 164.3 (**C**=O), 144.0 (Ar**C**), 128.5 (Ar**C**), 128.1 (Ar**C**), 127.3 (Ar**C**), 70.9 (**C**−(C$_6$H$_5$)$_3$), 30.0 (Br**C**H2); HRMS-ESI (*m/z*): Calcd. for [$C_{21}H_{18}BrNO$+Br]$^-$ 457.9755; Found; 457.9747. DOI: 10.14469/hpc/5191

Monomer Synthesis

Synthesis of 1



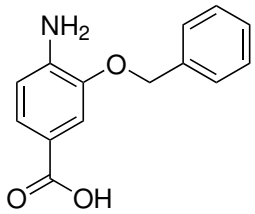
3-(benzyloxy)-4-nitrobenzoic acid (S1)



S1 was synthesised from 3-fluoro-4-nitrobenzoic acid (2.00 g, 10.80 mmol) using general Procedure C. Crude product triturated with diethylether to afford the title compound as a yellow solid (2.32 g, 85%). R_f (n:hex:EtOAc, 1:1, 0.1% AcOH) = 0.45; $\nu_{max}/\mathrm{cm}^{-1}$: 3060 (O-H), 2831, 1690 (C=O), 1606, 1523 (NO_2), 1293, 1249; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 13.61 (s, 1H, O**H**), 7.99 (d, J = 8.3 Hz, 1H, ArC**H**), 7.87 (d, J = 1.5 Hz, 1H, ArC**H**), 7.66 (dd, J = 8.3, 1.6 Hz, 1H, ArC**H**), 7.50 7.28 (m, 5H, phenyl), 5.39 (s, 2H, OC$\mathbf{H}_2$); ^{13}C NMR

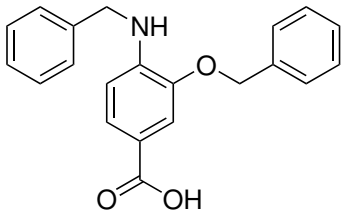
(101 MHz, DMSO-d_6): δ_C 165.7 (**C**=O), 150.5 (Ar**C**$-NO_2$), 142.3 (Ar**C**-O), 135.8 (Ar**C**H), 135.6 (Ar**C**), 128.5 (Ar**C**H), 128.1 (Ar**C**H), 127.3 (Ar**C**H), 125.03 (Ar**C**H), 121.6 (Ar**C**H), 115.8 (Ar**C**H), 70.6 (O**C**H_2); HRMS-ESI (*m/z*): Calcd. for $[C_{14}H_{11}NO_5+H]^+$: 272.0559. Found: 272.0567. DOI: 10.14469/hpc/5109

4-amino-3-(benzyloxy)benzoic acid (**S2**)



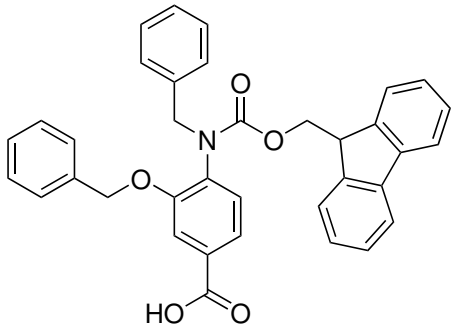
To a stirring solution of **S1** (2.00 g, 7.20 mmol, 1.00 eq.) in anhydrous ethyl acetate (50 mL) was added tin(II) chloride dihydrate (8.10 g, 36.00 mmol, 5.00 eq.). The reaction mixture was heated to 50 °C under a nitrogen atmosphere for 24 h with a calcium chloride drying tube attached. Upon completion, saturated sodium hydrogen carbontate (50 mL) was added dropwise with rapid stirring. The resulting precipitate was removed *via* filtration through celite and the filtrate was transferred to a separating funnel. The aqueous mixture was extracted with ethyl acetate (50 mL x 3) and the combined organic fractions washed with saturated sodium bicarbonate (20 mL x 2), water (20 mL x 2) and brine (20 mL), dried ($MgSO_4$). The solvent was removed *in vaccuo* to afford the title compound as a pale yellow solid (1.35 g, 75 %). R_f (*n*:hex:EtOAc, 1:1) = 0.70; ν_{max}/cm^{-1} : 1690 (C=O), 1623 (N-H), 1523, 1439; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 12.14 (s, 1H, O**H**), 7.68 7.29 (m, 7H, 2 x ArC**H** & phenyl), 6.72 (d, J = 8.0 Hz, 1H, ArC**H**), 6.10 5.30 (br, 2H, N$\mathbf{H}_2$), 5.16 (s, 2H, OC$\mathbf{H}_2(C_6H_5)$); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 168.1 (**C**=O), 144.5 (Ar**C**O), 143.5 (Ar**C**N), 137.7 (Ar**C**), 128.8 (Ar**C**H phenyl), 128.2 (Ar**C**H phenyl), 127.8 (Ar**C**H phenyl), 124.7 (Ar**C**H), 117.9 (Ar**C**H), 113.1 (Ar**C**H), 112.9 (Ar**C**H), 69.8 (O**C**$H_2(C_6H_5)$); HRMS-ESI (*m/z*): Calcd. for $[C_{14}H_{13}NO_3-H]^-$: 242.0817. Found: 242.0823. DOI: 10.14469/hpc/5110

4-(benzylamino)-3-(benzyloxy)benzoic acid (S3)



S3 was synthesised from **S2** (1.30 g, 5.30 mmol) using general procedure C. Precipitate isolated via vacuum filtration. The resulting solid was recrystallised from hot methanol to afford the product as a white solid (1.11g, 64%). R_f (EtOAc:n-hex, 1:2) = 0.45. ν_{max}/cm^{-1} : 2864 (O-H), 1668 (C=O), 1601, 1455, 1277; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 12.08 (s, 1H, O**H**), 7.57 7.53 (m, 2H, 2 x ArC**H**), 7.44 7.29 (m, 9H, ArC**H** x 9), 7.25 7.19 (m, 1H, ArC**H**), 6.45 (d, J = 8.4 Hz, 1H, ArC**H**), 6.39 (t, J = 6.4 Hz, 1H, N**H**), 5.22 (s, 2H, C$\mathbf{H}_2$), 4.45 (d, J = 6.3 Hz, 2H, C$\mathbf{H}_2$); ^{13}C NMR (101 MHz, DMSO-d_6): δ167.9 (**C**=O), 144.8 (Ar**C**O), 142.8 (Ar**C**N), 140.2 (Ar**C**), 137.5 (Ar**C**), 128.9 (Ar**C**), 128.8 (Ar**C**), 128.2 (Ar**C**), 127.9 (Ar**C**), 127.3 (Ar**C**), 127.1 (Ar**C**), 124.8 (Ar**C**), 117.5 (Ar**C**), 112.2 (Ar**C**), 108.9 (Ar**C**), 70.1 (**C**H_2), 46.1 (**C**H_2). HRMS-ESI (*m/z*): Calcd. for $[C_{21}H_{19}NO_3+H]^+$: 334.1443. Found: 334.1453. DOI: 10.14469/hpc/5111

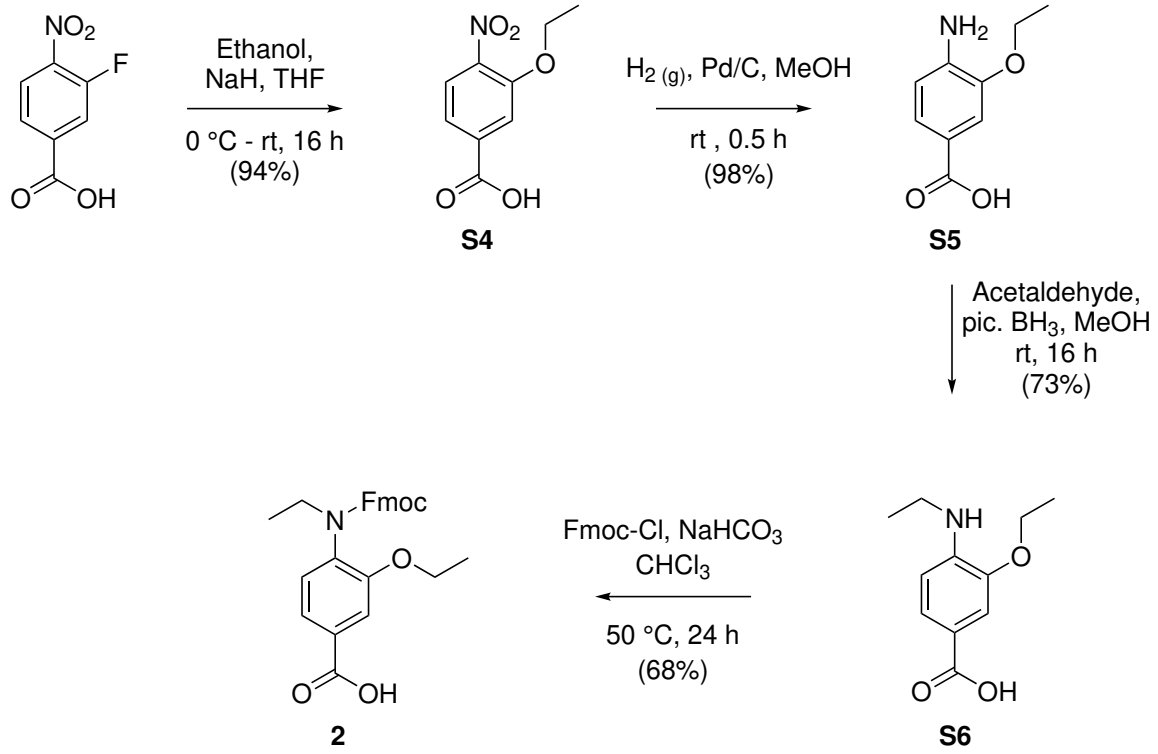
4-((((9H-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)-3-(benzyloxy)benzoic acid (1)



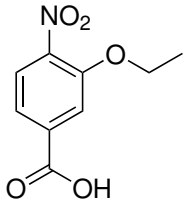
1 was synthesised from **S3** (1.00 g, 3.00 mmol) using general procedure D. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 95:5 over 15 CV] to afford the title compound as an amorphous white solid (1.12 g, 67%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.2;

ν_{max}/cm^{-1}: 2937, 1713, 1612, 1562, 1255; ^{1}H NMR (500 MHz, DMSO-d$_6$, 373K) δ_H 12.48 (s, 1H, O**H**), 7.76 (d, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.61 (d, J = 1.8 Hz, 1H, ArC**H**), 7.44 (dd, J = 8.1, 1.8 Hz, 1H, ArC**H**), 7.36 7.24 (m, 9H), 7.21 7.10 (m, 7H), 6.98 (d, J = 8.1 Hz, 1H, ArC**H**), 5.03 (s, 2H, OC**H**$_2$), 4.70 (s, 2H, NC**H**$_2$), 4.34 (d, J = 6.6 Hz, 2H, OC**H**$_2$CH), 4.07 (t, J = 6.6 Hz, 1H, OCH$_2$C**H**); ^{13}C NMR (126 MHz, DMSO-d$_6$, 373 K) δ_C: 166.0 (**C**=O), 154.4 (**C**=O), 153.5, 143.1, 140.3, 136.8, 136.1, 133.8, 130.6, 128.8 (Ar**C**H), 127.7, 127.5, 127.5, 127.1, 126.9, 126.5, 126.2, 124.2, 121.3 (Ar**C**H), 119.3 (Ar**C**H Fmoc), 113.8 (Ar**C**H), 69.6 (O**C**H$_2$), 66.5 (O**C**H$_2$CH), 52.3 (N**C**H$_2$), 46.2 (OCH**C**H$_2$)(one aromatic carbon not observed); HRMS-ESI (m/z): Calcd. for [C$_{36}$H$_{29}$NO$_5$+H]$^+$: 556.2124. Found: 556.2125. DOI: 10.14469/hpc/5112

Synthesis of 2



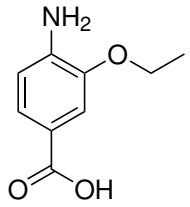
3-ethoxy-4-nitrobenzoic acid (**S4**)



S4 was synthesised from 3-fluoro-4-nitrobenzoic acid (2.00 g, 10.80 mmol) using general Procedure C to afford the title compound as a brown solid (2.47 g, 94%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.5; ν_{max}/cm^{-1} : 1657 (C=O), 1528 (NO_2), 1287, 1237; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 13.57 (s, 1H, O**H**), 7.95 (d, J = 8.3 Hz, 1H, ArC**H**), 7.74 (d, J = 1.6 Hz, 1H, ArC**H**), 7.63 (dd, J = 8.3, 1.6 Hz, 1H, ArC**H**), 4.28 (q, J = 6.9 Hz, 2H, O−C$\mathbf{H}_2$), 1.35 (t, J = 6.9 Hz, 3H, O−CH_2C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 166.2 (**C**=O), 151.2 (Ar**C**NO_2), 142.7 (Ar**C**O), 136.1 (Ar**C**), 125.3 (Ar**C**H), 121.7 (Ar**C**H), 115.8 (Ar**C**H), 65.8 (O**C**H_2), 14.7 (OCH_2**C**H_3); HRMS-ESI (m/z): Calcd. for $[C_9H_9NO_5$-H]$^-$: 210.0402. Found:

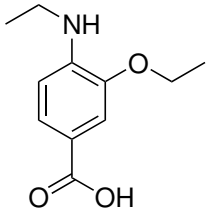
210.0398. DOI: 10.14469/hpc/5113

4-amino-3-ethoxybenzoic acid (S5)



S5 was synthesised from **S4** (2.50 g, 11.42 mmol) using general Procedure B to afford the title compound as a brown solid (2.03 g, 98%). (R_f EtOAC:n-hex, 1:1) = 0.50; ν_{max}/cm^{-1} : 1690 (C=O), 1623 (N-H), 1522, 1254; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 12.08 (s, 1H, O**H**), 7.36 (dd, J = 8.1, 1.8 Hz, 1H, ArC**H**), 7.29 (d, J = 1.8 Hz, 1H, ArC**H**), 6.64 (d, J = 8.2 Hz, 1H, ArC**H**), 5.48 (s, 2H, N$\mathbf{H}_2$), 4.03 (q, J = 6.9 Hz, 2H, OC$\mathbf{H}_2$), 1.36 (t, J = 6.9 Hz, 3H, $OCH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 168.0 (**C**=O), 144.7 (Ar**C**O), 143.4 (Ar**C**N), 124.4 (Ar**C**), 117.8 (Ar**C**H), 112.6 (Ar**C**H), 112.5 (Ar**C**H), 63.9 ($O\mathbf{C}H_2CH_3$), 15.2 ($OCH_2\mathbf{C}H_3$); HRMS-ESI (m/z): Calcd. for $[C_9H_{11}NO_3+H]^+$: 182.0817. Found: 182.0824. DOI: 10.14469/hpc/5114

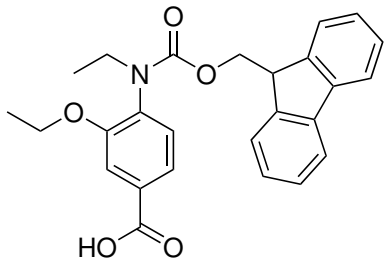
3-ethoxy-4-(ethylamino)benzoic acid (**S6**)



S6 was synthesised from **S5** (2.03 g, 11.21 mmol) using general procedure C. Trituration from dichloromethane afforded the title product as a white solid (1.78 g, 73%). R_f (n-hex:EtOAc, 1:1) = 0.3; ν_{max}/cm^{-1} : 2970 (O-H), 1712 (C=O), 1612, 1562; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 12.07 (s, 1H, O**H**), 7.46 (dd, J = 8.3, 1.9 Hz, 1H, ArC**H**), 7.27 (d, J = 1.6 Hz, 1H, ArC**H**), 6.54 (d, J = 8.3 Hz, 1H, ArC**H**), 5.44 (t, J = 5.8 Hz, 1H, N**H**), 4.06 (q, J = 6.9 Hz, 2H, OC$\mathbf{H}_2CH_3$), 3.25 3.12 (m, 2H, NHC$\mathbf{H}_2$), 1.37 (t, J = 6.9 Hz, 3H, $OCH_2C\mathbf{H}_3$), 1.17 (t, J = 7.1 Hz, 3H, $NHCH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, DMSO-d_6): δ_C 168.1 (**C**=O), 144.8

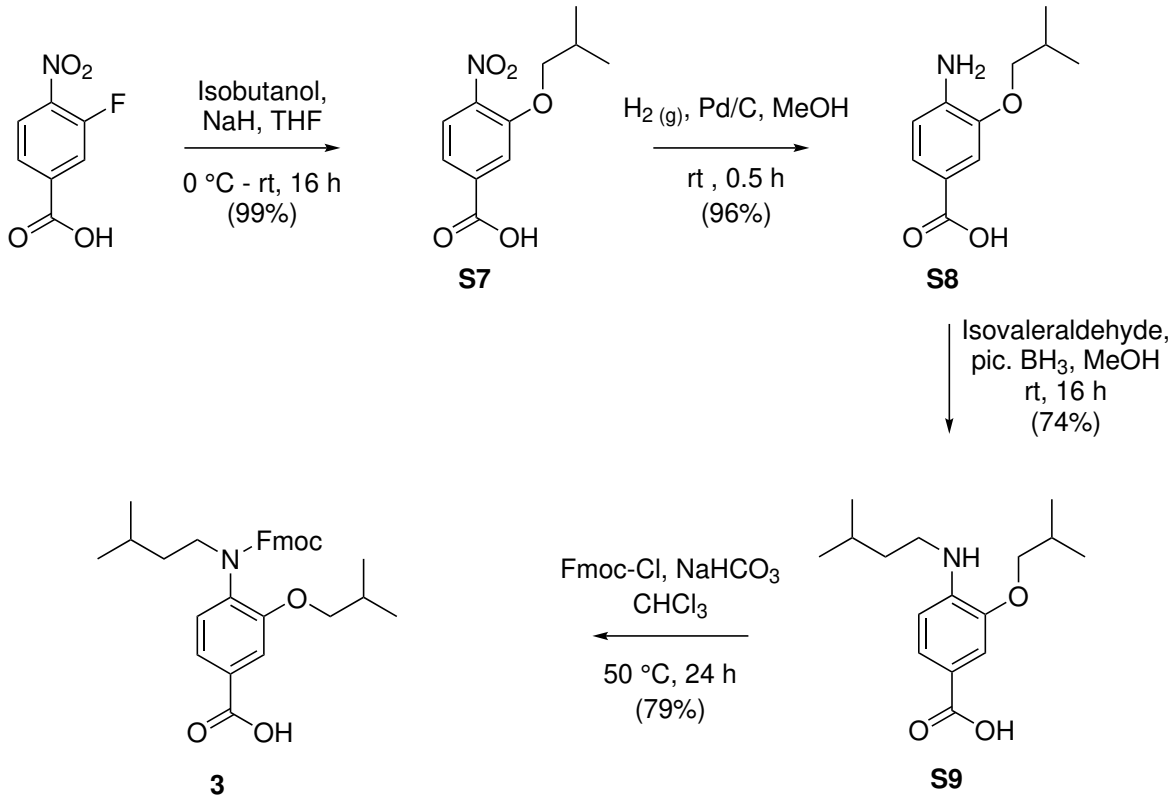
(Ar**C**O), 142.8 (Ar**C**N), 124.8 (Ar**C**H), 117.0 (Ar**C**), 111.2 (Ar**C**H), 107.8 (Ar**C**H), 64.0 (O**C**H_2), 37.2 (NH**C**H_2), 15.1 (O**C**H_2CH_3), 14.7 (NH**C**H_2CH_3); HRMS-ESI (*m/z*): Calcd. for [$C_{11}H_{15}NO_3$+H]$^+$: 210.1130. Found: 210.1128. DOI: 10.14469/hpc/5115

4-((((9H-fluoren-9-yl)methoxy)carbonyl)(ethyl)amino)-3-ethoxybenzoic acid (2)

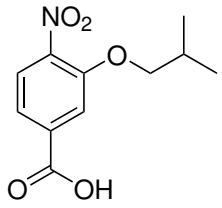


2 was synthesised from **S6** (1.50 g, 7.10 mmol) using general procedure D. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 20 CV] to afford the title compound as an amorphous white solid (2.08 g, 68%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.35; ν_{max}/cm^{-1}: 2971, 2742, 1713, 1562, 1444, 1192; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): δ_H 12.55 (s, 1H, O**H**), 7.75 (d, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.56 7.51 (m, 2H, 2 x ArC**H**), 7.34 (t, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.30 (d, J = 7.7 Hz, 2H, 2 x ArC**H** Fmoc), 7.19 (t, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.14 (d, J = 7.9 Hz, 1H, ArC**H**), 4.31 (d, J = 6.7 Hz, 2H, OC**H**$_2$Fmoc), 4.08 (t, J = 6.7 Hz, 1H, OCH$_2$C**H**Fmoc), 4.02 (q, J = 6.9 Hz, 2H, OC**H**$_2$), 3.52 (q, J = 7.1 Hz, 2H, NC**H**$_2$), 1.24 (t, J = 6.9 Hz, 3H, OCH$_2$C**H**$_3$), 1.00 (t, J = 7.1 Hz, 3H, NCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K): δ_C 166.2 (**C**=O), 153.9 (**C**=O), 143.3 (Ar**C**), 140.3 (Ar**C**), 133.8, 130.7, 129.0 (Ar**C**H), 126.9 (Ar**C**H), 126.2 (Ar**C**H), 124.2 (Ar**C**H), 121.2 (Ar**C**H), 119.3 (Ar**C**H), 113.4 (Ar**C**H), 66.2 (O**C**H$_2$ Fmoc), 63.5 (O**C**H$_2$), 46.3 (OCH$_2$**C**H Fmoc), 43.4 (N**C**H$_2$), 13.9 (OCH$_2$**C**H$_3$), 12.5 (NCH$_2$**C**H$_3$)(one aromatic carbon not observed); HRMS-ESI (*m/z*): Calcd. for [$C_{26}H_{27}NO_5$-H]: 432.1827. Found: 432.1811. DOI: 10.14469/hpc/5116

Synthesis of 3



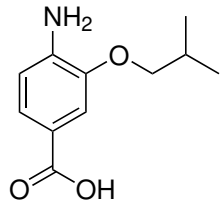
3-isobutoxy-4-nitrobenzoic acid (**S7**)



S7 was synthesised from 3-fluoro-4-nitrobenzoic acid (5.00 g, 27.01 mmol) using general procedure C to afford the title compound as a yellow solid (6.21 g, 99%). R_f (CH_2Cl_2:MeOH, 95:5) = 0.50; ν_{max}/cm^{-1} : 2960 (O-H), 1690 (C=O), 1606, 1517 (NO_2), 1243; ^{1}H NMR (400 MHz, MeOD): δ_H 7.84 (d, J = 8.3 Hz, 1H, ArC**H**), 7.82 (d, J = 1.5 Hz, 1H, ArC**H**), 7.70 (dd, J = 8.3, 1.6 Hz, 1H, ArC**H**), 3.98 (d, J = 6.3 Hz, 2H, OC$\mathbf{H}_2$), 2.12 (sep, J = 6.6 Hz, 1H, OCH_2C**H**), 1.07 (d, J = 6.7 Hz, 6H, $CH(C\mathbf{H}_3)_2$); ^{13}C NMR (101 MHz, MeOD): δ_C 166.3 (**C**=O), 151.5 (Ar**C**NO_2), 142.7 (Ar**C**O), 135.4 (Ar**C**), 124.5 (Ar**C**H), 121.1 (Ar**C**H), 115.1

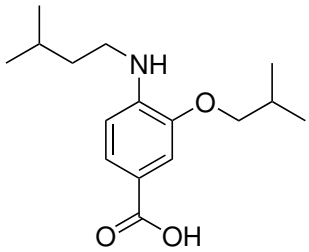
(Ar**C**H), 75.5 (O**C**H_2, 28.1 (O−CH_2**C**H), 17.9 (CH(**C**H_3)$_2$); HRMS-ESI (*m/z*): Calcd. for [$C_{11}H_{13}NO_5$-H]$^-$: 238.0715. Found: 238.0721. DOI: 10.14469/hpc/5117

4-amino-3-isobutoxybenzoic acid (**S8**)



S8 was synthesised from **S7** (6.20 g, 26.66 mmol) using general procedure B. Purification by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 - 95:5 over 10 CV] afforded the title product as a pale brown solid (5.50 g, 96%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.45; ν_{max}/cm^{-1} : 2920 (O-H), 1679 (C=O), 1612, 1517, 1287, 1030; ^{1}H NMR (400 MHz, MeOD): δ_H 7.49 (dd, J = 8.2, 1.8 Hz, 1H, ArC**H**), 7.42 (d, J = 1.8 Hz, 1H, ArC**H**), 6.71 (d, J = 8.2 Hz, 1H, ArC**H**), 3.82 (d, J = 6.4 Hz, 2H, OC$\mathbf{H}_2$), 2.14 (sep, J = 6.6 Hz, 1H, OCH_2C**H**), 1.09 (d, J = 6.7 Hz, 6H, $OCH_2CH(C\mathbf{H}_3)_2$); ^{13}C NMR (101 MHz, MeOD): δ_C 169.3 (**C**=O), 145.4 (Ar**C**O), 142.7 (Ar**C**N), 124.1 (Ar**C**H), 118.2 (Ar**C**), 112.5 (Ar**C**H), 111.9 (Ar**C**H), 74.4 (O**C**H_2CH), 28.1 (OCH_2**C**H), 18.2 ($OCH_2CH(\mathbf{C}H_3)_3$); HRMS-ESI (*m/z*): Calcd. for [$C_{11}H_{15}NO_3$+H]$^+$: 210.1130. Found : 210.1134. DOI: 10.14469/hpc/5118

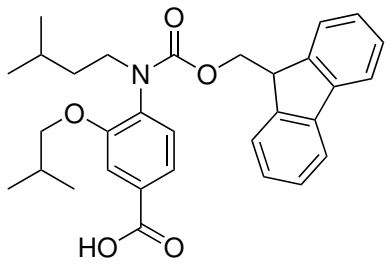
3-isobutoxy-4-(isopentylamino)benzoic acid (S9)



S9 was synthesised from **S8** (0.83 g, 4.25 mmol) using general procedure C. Precipitate isolated via vacuum filtration and washed with ice-cold methanol (3 x 20 mL) to afford the title product as a white solid (0.88g, 74 %). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.72 (dd, J = 8.3, 1.8 Hz, 1H, Ar**C**H), 7.42 (d, J = 1.8 Hz, 1H,

Ar**C**H), 6.55 (d, J = 8.5 Hz, 1H, Ar**C**H), 3.82 (d, J = 6.5 Hz, 2H, OC**H**), 3.22 (t, J = 7.5 Hz, 2H, NHC$\mathbf{H}_2$), 2.14 (sep, J = 6.6 Hz, 1H, OHCH_2C$\mathbf{H}_2$), 1.73 (sep, J = 6.7 Hz, 1H, NHCH_2CH_2C**H**), 1.57 (td, J = 7.0, 1.9 Hz, 2H, NHCH_2CH_2C$\mathbf{H}_2$CH), 1.05 (d, J = 6.7 Hz, 6H, OCH_2CH(C$\mathbf{H}_3$)$_2$, 0.97 (d, J = 6.6 Hz, 6H, NCH_2CH_2CH(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (101 MHz, MeOD): δ_C 172.6 (**C**=O), 144.8 (Ar**C**O), 143.5 (Ar**C**N), 125.6 (Ar**C**H), 115.7 (Ar**C**), 111.0 (Ar**C**H), 107.6 (Ar**C**H), 74.7 (O**C**H_2), 41.2 (NH**C**H_2), 38.2 (OCH_2**C**H), 28.2 (NCH_2**C**H_2), 26.1 (OCH_2**C**H), 22.6 (OCH_2CH(**C**H_3)$_2$), 19.4 (NHCH_2CH_2CH(**C**H_3)$_2$); HRMS-ESI (*m/z*): Calcd. for [$C_{16}H_{25}NO_3$+H]$^+$: 280.1913. Found: 280.1908. DOI: 10.14469/hpc/5119

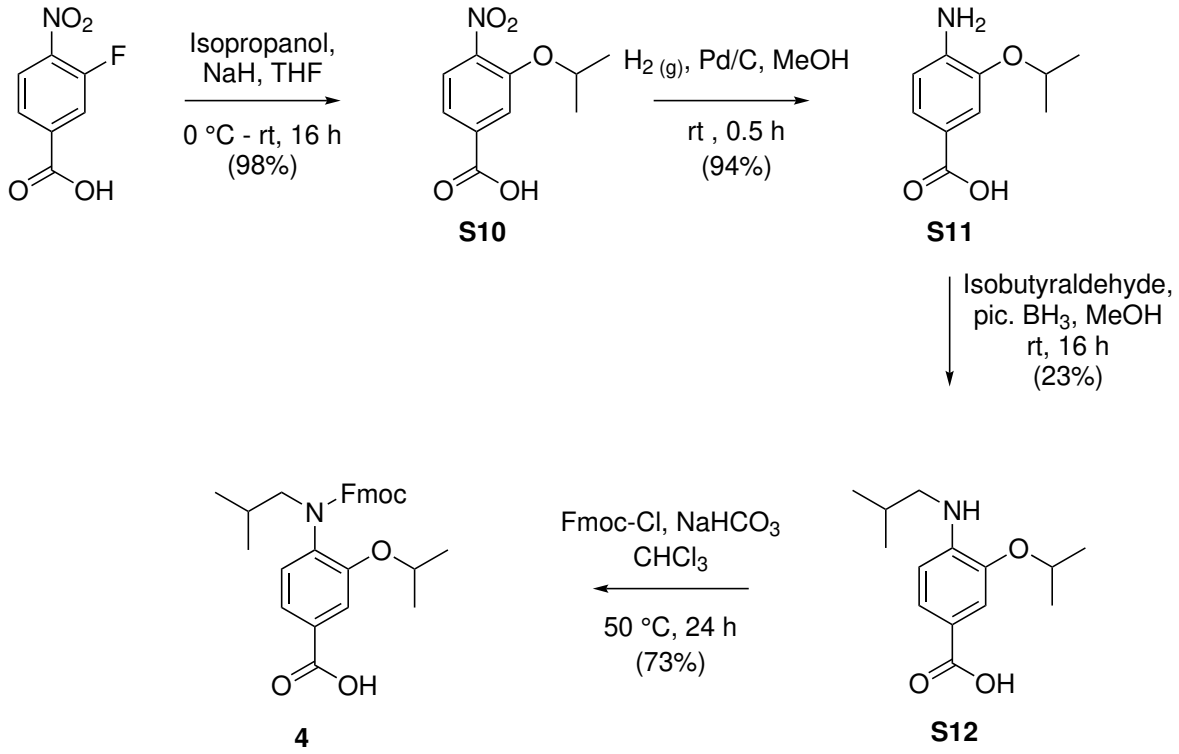
4-((((9H-fluoren-9-yl)methoxy)carbonyl)(isopentyl)amino)-3-isobutoxybenzoic acid (**3**)



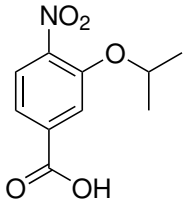
3 was synthesised from **S9** (0.50 g, 2.00 mmol) using general procedure D. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 95:5 over 10 CV] to afford the title compound as a white solid (0.72 g, 79%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.3; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): δ_H 12.50 (s, 1H, O**H**) 7.74 (d, J = 7.7 Hz, 2H, 2 x ArC**H** Fmoc), 7.55 7.50 (m, 2H, 2 x ArC**H**), 7.35 (d, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.28 (br, 2H, 2 x ArC**H** Fmoc), 7.19 (t, J = 7.4 Hz, 2H, 2 x ArC**H** Fmoc), 7.14 (d, J = 8.4 Hz, 1H, ArC**H**), 4.30 (br s, 2H, OC$\mathbf{H}_2$CH Fmoc), 4.07 (br s, J = 7.1 Hz, 1H, OCH_2C**H** Fmoc), 3.72 (d, J = 6.1 Hz, 2H, OC$\mathbf{H}_2$), 3.49 (br s, 2H, ArNC$\mathbf{H}_2$), 1.93 (sep, J = 6.7 Hz ,1H, OCH_2C**H**), 1.51 (sep, J = 6.6 Hz, 1H, ArNCH_2CH_2C**H**), 1.30 (q, J = 7.3 Hz, 2H, ArNCH_2C$\mathbf{H}_2$CH), 0.91 (d, J = 6.7 Hz, 6H, OCH_2CH(C$\mathbf{H}_3$)$_2$), 0.80 (d, J = 6.6 Hz, 6H, ArNCH_2CH_2CH(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K): δ_C = 166.1 (**C**=O), 154.1 (**C**=O), 143.2 (Ar**C**O), 140.3 (Ar**C**N), 133.9, 130.6, 128.8 (Ar**C**H), 126.8 (Ar**C**H Fmoc), 126.2 (Ar**C**H Fmoc), 124.5, 124.2

(Ar**C**H Fmoc), 121.1, 119.2 (Ar**C**H Fmoc), 113.1 (Ar**C**H), 73.9 (O**C**H_2), 66.2 (O**C**H_2CH Fmoc), 47.0 (ArN**C**H_2), 46.2 (OCH_2**C**H Fmoc), 36.3 (ArNCH_2**C**H_2), 27.3 (OCH_2**C**H), 24.6 (ArNCH_2CH_2**C**H), 21.6 (OCH_2CH(**C**H_3)$_2$), 18.2 (ArNCH_2CH_2CH(**C**H_3)$_2$); HRMS-ESI (*m/z*): Calcd. for $[C_{31}H_{35}NO_5+H]^+$: 502.2593. Found: 502.2592. DOI: 10.14469/hpc/5120

Synthesis of 4

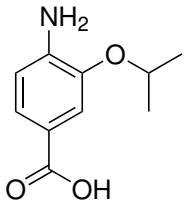


3-isopropoxy-4-nitrobenzoic acid (**S10**)



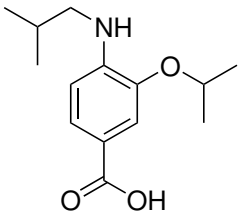
S10 was synthesised from 3-fluoro-4-nitrobenzoic acid (5 g, 27.01 mmol) using general procedure C to afford the title compound as a yellow solid (6.03 g, 98%). R_f (n-hex:EtOAc, 1:4, 0.1% AcOH) = 0.3; $\nu_{max}/\mathrm{cm}^{-1}$: 2954 (O-H), 1657 (C=O), 1533 (NO_2), 1277, 1209; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83 7.80 (m, 2H, 2 x ArC**H**), 7.76 (dd, J = 8.3, 1.6 Hz, 1H, ArC**H**), 4.82 (sep, J = 6.1 Hz, 1H, C**H**$(CH_3)_2$, 1.46 (d, J = 6.1 Hz, 6H, CH(C**H**$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 169.9 (**C**=O), 150.8 (Ar**C**NO_2), 144.4 (Ar**C**O), 133.3 (Ar**C**), 125.1 (Ar**C**H), 121.8 (Ar**C**H), 117.4 (Ar**C**H), 73.2 (O**C**H$(CH_3)_2$), 21.8 (CH(**C**$H_3)_2$); HRMS-ESI (m/z): Calcd. for $[C_{10}H_{11}NO_5\text{-H}]^-$: 224.0559. Found: 224.0568. DOI: 10.14469/hpc/5121

3-isopropoxy-4-nitrobenzoic acid (S11)



S11 was synthesised from **S10** (6.00 g, 26.66 mmol) using general procedure B. Purification by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 - 97.5:2.5 over 10 CV] afforded the title product as an off white solid (4.91 g, 94%). R_f (CH_2Cl_2:MeOH, 95:5) = 0.5; ν_{max}/cm^{-1} : 3429 (N-H), 2953 (O-H), 2864, 1657 (C=O), 1595, 1533, 1277, 1210; ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.49 (dd, J = 8.2, 1.8 Hz, 1H, ArC**H**), 7.46 (d, J = 1.8 Hz, 1H, ArC**H**), 6.72 (d, J = 8.2 Hz, 1H, ArC**H**), 4.61 (sep, J = 6.2 Hz, 1H, OC**H**$(CH_3)_2$), 1.36 (d, J = 6.0 Hz, 6H, OCH(C**H**$_3)_2$); ^{13}C NMR (101 MHz, CD_3OD): δ_C 169.1 (C=O), 144.3 (Ar**C**O), 142.4 (Ar**C**N), 124.0 (Ar**C**H), 119.1 (Ar**C**) 114.2 (Ar**C**H), 113.6 (Ar**C**H), 70.7 (O**C**H, 21.0 (OCH(**C**$H_3)_2$); HRMS-ESI (m/z): Calcd. for $[C_{10}H_{13}NO_3+H]^+$: 196.0974. Found : 196.0967. DOI: 10.14469/hpc/5122

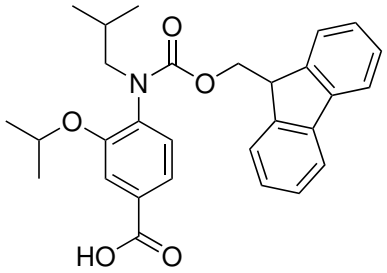
4-(isobutylamino)-3-isopropoxybenzoic acid (**S12**)



S12 was synthesised from **S11** (2.00 g, 6.06 mmol) using general procedure C. Recrystallised from hot ethanol to afford product as a white solid (0.56 g, 23%). R_f (n-hex:EtOAc, 7:3) = 0.3; ν_{max}/cm^{-1} : 3418 (O-H), 1657 (C=O), 1595, 1444, 1366, 1276; ^{1}H NMR (400 MHz, $CDCl_3$); δ_H 7.68 (dd, J = 8.4, 1.8 Hz, 1H, ArC**H**), 7.46 (d, J = 1.8 Hz, 1H, ArC**H**), 6.54 (d, J = 8.4 Hz, 1H, ArC**H**), 5.13 (br, 1H, N**H**), 4.64 (sep, J = 6.1 Hz, 1H, OC**H**$(CH_3)_2$), 3.02 (d, J = 6.9 Hz, 2H, NHC**H**$_2$), 1.95 (sep, J = 6.7 Hz, 1H, $NHCH_2$C**H**), 1.37 (d, J =

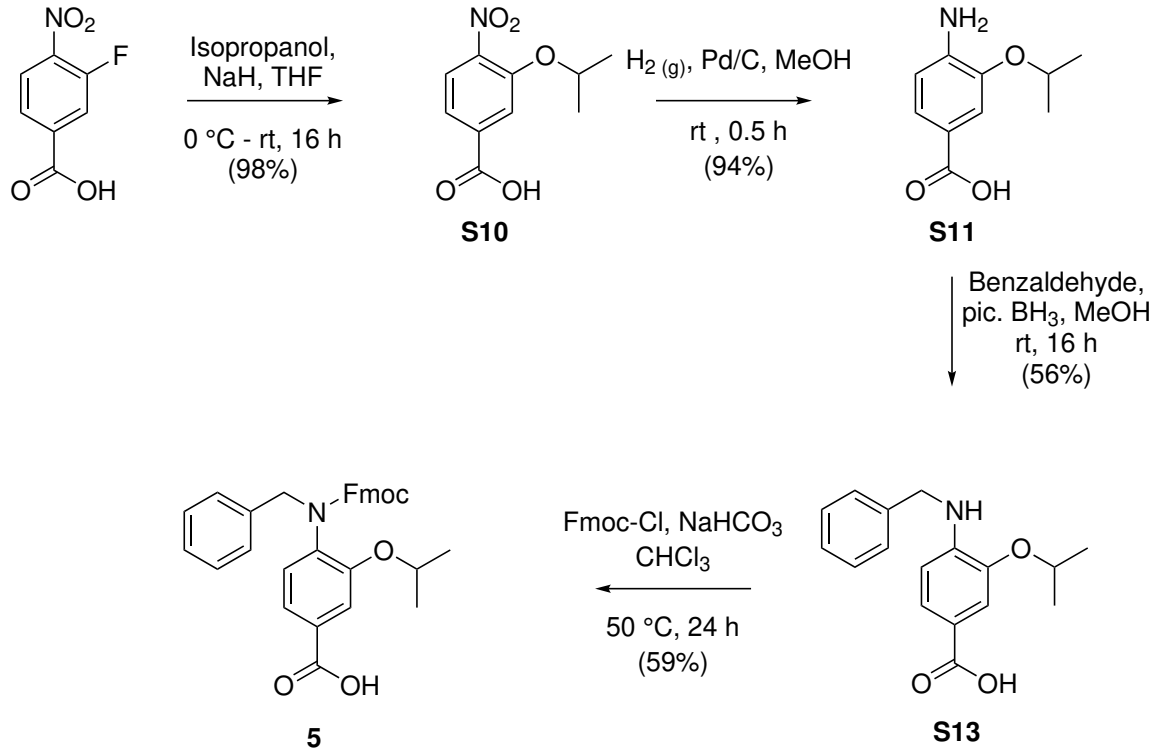
6.0 Hz, 6H, OCH(C**H**$_3$)$_2$), 0.99 (d, J = 6.6 Hz, 6H, NHCH$_2$CH(C**H**$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 172.4 (**C**=O), 144.4 (Ar**C**O), 143.4 (Ar**C**N), 125.6 (ArC**H**), 115.6 (Ar**C**), 113.1 (Ar**C**H), 107.9 (Ar**C**H), 70.1 (O**C**H(CH$_3$)$_2$), 50.7 (NH**C**H$_2$), 28.0 (NHCH$_2$**C**H$_2$), 22.2 (OCH(**C**H$_3$)$_2$), 20.4 (NHCH$_2$CH$_2$(**C**H$_3$)$_2$); HRMS-ESI (*m/z*): Calcd. for [$C_{14}H_{21}NO_3$+H]$^+$ 252.1600. Found: 252.1608. DOI: 10.14469/hpc/5123

4-((((9H-fluoren-9-yl)methoxy)carbonyl)(isobutyl)amino)-3-isopropoxybenzoic acid (4)

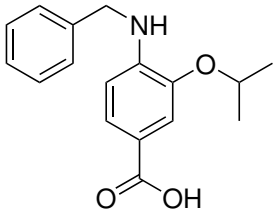


4 was synthesised from **S12** (0.50 g, 1.80 mmol) using general procedure D. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 95:5 over 10 CV] to afford the title compound as a colourless oil (0.62 g, 73%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.3; ^{1}H NMR (400 MHz, DMSO-d$_6$, 373 K): δ_H 7.76 (d, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.52 (d, J = 1.8 Hz, 1H, ArC**H**), 7.49 (dd, J = 8.1, 1.8 Hz, 1H, ArC**H**), 7.35 (t, 2H, 2 x ArC**H** Fmoc), 7.29 (br, 2H, 2 x ArC**H** Fmoc), 7.19 (t, 2H, 2 x ArC**H** Fmoc), 7.13 (d, J = 8.0 Hz, 1H, ArC**H**), 4.56 (sep, J = 6.0 Hz, 1H, OC**H**(CH$_3$)$_2$), 4.32 (d, J = 6.4 Hz, 2H, OC**H**$_2$ Fmoc), 4.07 (t, J = 6.5 Hz, 1H, OCH$_2$C**H** Fmoc), 3.30 (br, 2H, ArNC**H**$_2$), 1.64 (sep, 7.2 Hz, 1H, ArNCH$_2$C**H**), 1.20 (d, J = 6.0 Hz, 6H, OCH(C**H**$_3$)$_2$), 0.80 (d, J = 6.6 Hz, 6H, ArNCH(C**H**$_3$)$_2$); ^{13}C NMR (101 MHz, DMSO-d$_6$, 373 K): δ_C 166.6 (**C**=O), 154.9 (**C**=O), 153.1, 143.7, 140.7, 135.4, 130.9, 129.5 (Ar**C**H), 127.3 (Ar**C**H Fmoc), 126.6 (Ar**C**H Fmoc), 124.7 (Ar**C**H Fmoc), 121.3 (Ar**C**H), 119.7 (Ar**C**H Fmoc), 114.7 (Ar**C**H), 70.3 (O**C**H), 66.6 (O**C**H$_2$CH Fmoc), 56.5, 46.8, 26.9, 21.6, 19.9; HRMS-ESI (*m/z*): Calcd. for [$C_{29}H_{31}NO_5$+H]$^+$: 474.2280. Found: 474.2296. DOI: 10.14469/hpc/5124

Synthesis of 5



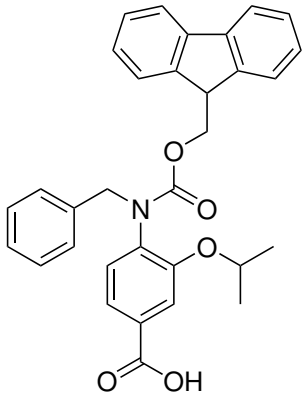
4-(benzylamino)-3-isopropoxybenzoic acid (**S13**)



S13 was synthesised from **S11** (1.00 g, 7.29 mmol) using general procedure G. Precipitate isolated by vacuum filtration to afford the title compound as a white solid (0.93 g, 56%). R_f (n-hex:EtOAc, 1:1) = 0.7; $\nu_{max}/\mathrm{cm}^{-1}$: 3301 (N-H), 2971 (O-H), 1668 (C=O), 1595, 1522, 1410, 1277, 1203, 1115; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (dd, J = 8.4, 1.8 Hz, ArC**H**), 7.52 (d, J = 1.8 Hz, 1H, ArC**H**), 7.44 7.29 (m, 5H, benzyl), 6.57 (d, J = 8.4 Hz, 1H, ArC**H**), 4.71 (sep, J = 6.2 Hz, 1H, O**C**H$(CH_3)_2$), 4.48 (s, 2H, NHC$\mathbf{H}_2(C_6H_5)$), 1.41 (d, J = 6.0 Hz, 6H, $(OCHC\mathbf{H}_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) : δ_C 172.5 (**C**=O), 143.9 (Ar**C**O), 143.7 (Ar**C**N), 138.6 (Ar**C** phenyl), 128.8 (Ar**C** phenyl), 127.4 (Ar**C**H phenyl), 127.2 (Ar**C**H

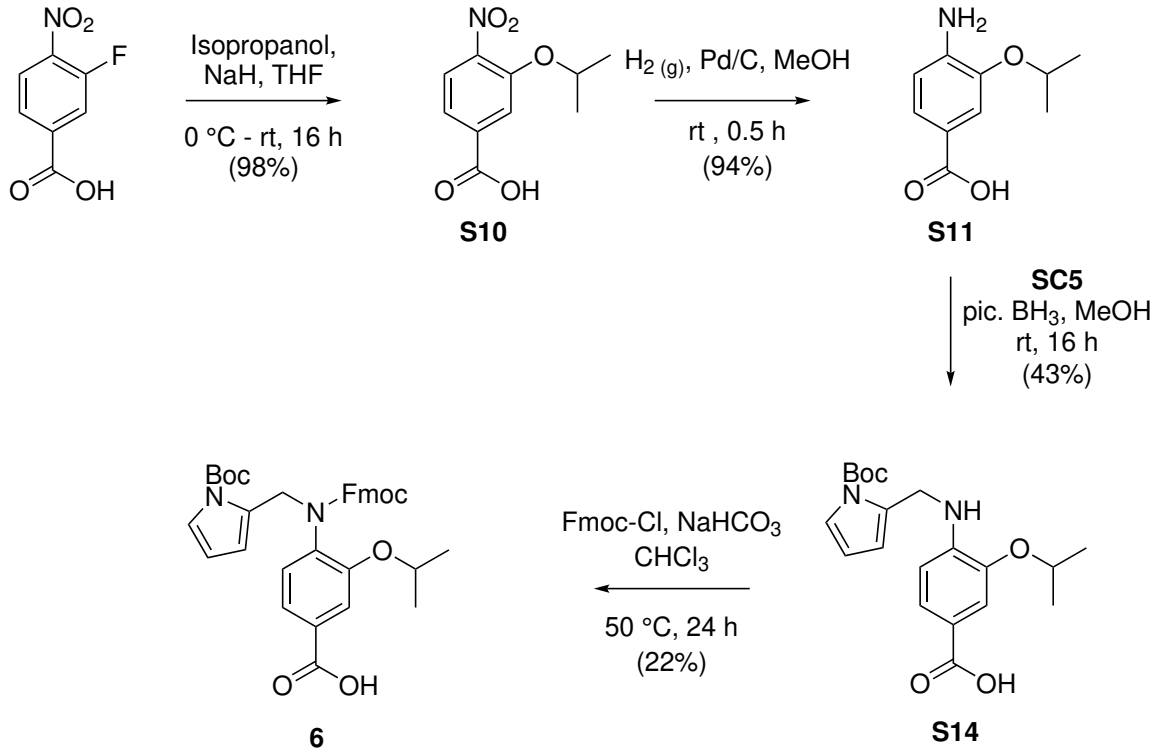
phenyl), 125.4 (Ar**C**H), 116.5 (Ar**C**), 112.9 (Ar**C**H), 108.5 (Ar**C**H), 71.0 (O**C**H$(CH_3)_2$), 47.2 (N**C**H$_2$(C_6H_5)), 22.2 (OCH(**C**H$_3$)$_2$); HRMS-ESI (*m/z*); Calcd. for [$C_{17}H_{19}NO_3$+H]: 286.1456 Found: 286.1443. DOI: 10.14469/hpc/5134

4-((((9H-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)-3-isopropoxybenzoic acid (5)

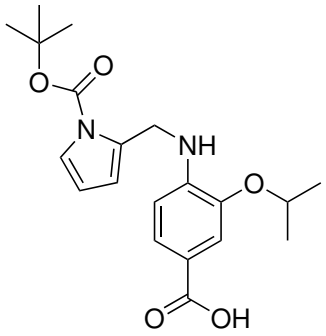


5 was synthesised from **S13** (0.50 g, 2.20 mmol) using general procedure H. Purified by column chromatography [SiO_2, EtOAc:n-hex, 2:8 to 1:1 over 10 CV] to afford the title compound as a white solid (0.62 g, 59%). R_f (EtOAc:n-hex, 1:1) = 0.3; ν_{max}/cm^{-1}: 2976, 1702, 1595, 1449, 1405; ^{1}H NMR (500 MHz, DMSO-d$_6$, 373 K) δ_H 12.46 (s, 1H, O**H**), 7.76 (d, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.48 (d, J = 1.9 Hz, 1H, ArC**H**), 7.38 (dd, J = 8.1, 1.8 Hz, 1H, ArC**H**), 7.36 – 7.33 (m, 2H, 2 x ArC**H** Fmoc), 7.29 (br, 2H, 2 x ArC**H** Fmoc), 7.25 – 7.11 (m, 7H, 2 x ArC**H** Fmoc & C_6**H**$_5$), 6.94 (d, J = 8.1 Hz, 1H, ArC**H**), 4.67 (s, 2H, ArNC**H**$_2$(C_6H_5)), 4.52 (sep, J = 5.9 Hz, 1H, OC**H**), 4.38 (d, J = 6.6 Hz, 2H, OC**H**$_2$CH Fmoc), 4.10 (t, J = 6.6 Hz, 1H, OCH$_2$C**H** Fmoc), 1.17 (d, J = 6.0 Hz, 6H, OCH(C**H**$_3$)$_2$); ^{13}C NMR (101 MHz, DMSO-d$_6$): δ_C 168.1 (**C**=O), 153.3 (**C**=O), 145.7 , 143.7, 143.7, 141.2, 140.2, 128.8, 128.6, 127.6, 127.2, 125.7, 125.2, 124.6, 120.3, 117.5, 113.6, 108.9 (Ar**C**H), 71.1 (O**C**H$_2$), 64.3 (OCH$_2$Fmoc), 50.6 (ArN**C**H$_2$), 46.1 (OCH$_2$**C**H Fmoc), 22.3 (CH(**C**H$_3$)$_2$); HRMS-ESI (*m/z*): Calcd. for [$C_{32}H_{29}NO_5$+H]$^+$: 508.2124. Found: 508.2136. DOI: 10.14469/hpc/5135

Synthesis of 6



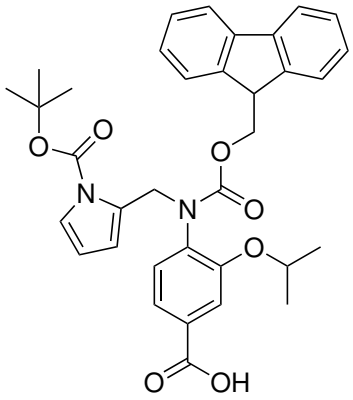
4-(((1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl)methyl)amino)-3-isopropoxybenzoic acid (S14)



S14 was synthesised from **S11** (0.96 g, 4.90 mmol) using general procedure G. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as a white solid (0.80 g, 43%). R_f (CH_2Cl_2:MeOH, 95:5) = 0.3; ν_{max}/cm^{-1} : 3468 (N-H), 2976 (O-H), 1735 (C=O), 1662 (C=O), 1590, 1539, 1444, 1276, 1126; ^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 7.65 (dd, J = 8.3, 1.8 Hz, 1H, ArC**H**), 7.44 (d, J = 1.9 Hz, 1H,

ArC**H**), 7.21 (dd, J = 3.4, 1.8 Hz, 1H, ArC**H** pyrrole), 6.64 (d, J = 8.5 Hz, 1H, ArC**H**), 6.16 (dd, J = 3.3, 1.8 Hz, 1H, ArC**H** pyrrole), 6.08 (t, J = 3.3 Hz, 1H, ArC**H** pyrrole), 5.59 (s, 1H, N**H**), 4.69 4.57 (m, 3H, OC**H** & NHC$\mathbf{H}_2$), 1.60 (s, 9H, (C$\mathbf{H}_3$)$_3$), 1.36 (d, J = 6.0 Hz, 6H, (C$\mathbf{H}_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) : δ_C 172.1 (**C**=O), 149.3 (N**C**=O), 143.7 (Ar**C**O), 143.6 (Ar**C**N), 131.7 (Ar**C** pyrrole), 125.3 (Ar**C**H), 121.8 (Ar**C**H pyrrole), 116.0 (Ar**C**), 113.3 (Ar**C**H pyrrole), 113.0 (Ar**C**H), 110.1 (Ar**C**H pyrrole), 108.4 (Ar**C**H), 84.0 (**C**(CH$_3$)$_3$), 70.7 (O**C**H), 40.7 (NH**C**H$_2$), 28.0 (C(**C**H$_3$)$_3$), 22.1 (**C**H$_3$)$_2$; HRMS-ESI (*m/z*); Calcd. for [$C_{20}H_{26}N_2O_5$+H]$^+$: 375.1920 Found: 375.1907. DOI: 10.14469/hpc/5136

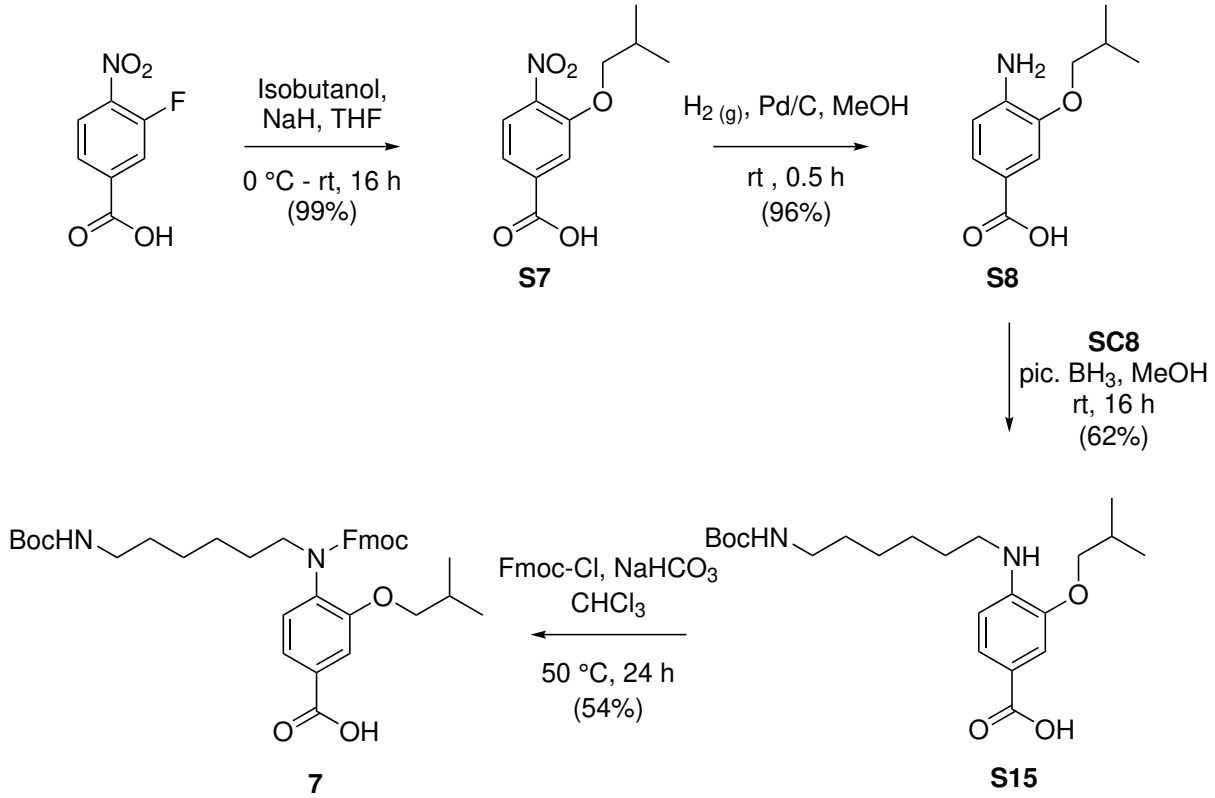
4-((((9H-fluoren-9-yl)methoxy)carbonyl)((1-(*tert*-butoxycarbonyl)-1H-pyrrol-2-yl)methyl)amino)-3-isopropoxybenzoic acid (6)



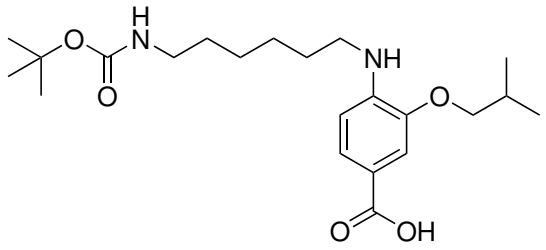
6 was synthesised from **S14** (173 mg, 0.46 mmol) using general procedure H. Purified by column chromatography [SiO_2, EtOAc:n-hex] to afford the title compound as a colourless oil (62.7 mg, 22%). R_f (EtOAc:n-hex, 1:1) = 0.5; ν_{max}/cm^{-1} : 2976 (O-H), 1685 (C=O), 1422, 1310; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): δ_H 12.49 (s, 1H, O**H**), 7.75 (d, J = 7.6 Hz, 2H,2 x ArC**H** Fmoc), 7.49 (d, J = 1.9 Hz, 1H, ArC**H**), 7.39 (dd, J = 8.1, 1.8 Hz, 1H, ArC**H**), 7.34 (t, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.28 (d, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.17 (t, J = 7.4 Hz, 2H, 2 x ArC**H** Fmoc), 7.11 (dd, J = 3.4, 1.8 Hz, 1H, ArC**H** pyrolle), 6.99 (d, J = 8.0 Hz, 1H, ArC**H**), 6.11 (ddt, J = 2.9, 1.9, 1.0 Hz, 1H, ArC**H** pyrolle), 6.05 (t, J = 3.3 Hz, 1H, ArC**H** pyrolle), 4.93 (s, 2H, ArNC$\mathbf{H}_2$), 4.55 (sep, J = 6.0 Hz, 1H, OC**H**(CH$_3$)$_2$), 4.33 (d, J = 6.7 Hz, 2H, OC$\mathbf{H}_2$CH Fmoc), 4.09 (t, J = 6.7 Hz, 1H, OCH$_2$C**H**

Fmoc), 1.50 (s, 9H, ($C\mathbf{H}_3$)$_3$), 1.21 (d, J = 6.0 Hz, 6H, OCH($C\mathbf{H}_3$)$_2$); ^{13}C NMR (101 MHz, DMSO-d_6: δ_c 167.3 (**C**=O), 153.4 (**C**=O), 149.1 (**C**=O), 144.1 (**ArC**), 144.0, 141.2, 131.4, 130.3, 128.2, 128.0, 127.6, 127.3, 125.7, 125.5, 122.0, 121.6, 120.6, 120.5, 110.7 (**ArCH**), 84.4 (C($\mathbf{C}H_3$)$_3$), 70.6 (OCH), 67.3 (OCH_2CHFmoc), 46.9 (OCH_2CHFmoc), 27.9 (C($\mathbf{C}H_3$)$_3$), 22.1 (OCH($\mathbf{C}H_3$)$_2$); HRMS-ESI (*m/z*): Calcd. for $[C_{35}H_{36}N_2O_7+H]^+$: 597.2601. Found: 597.2617. DOI: 10.14469/hpc/5137

Synthesis of 7



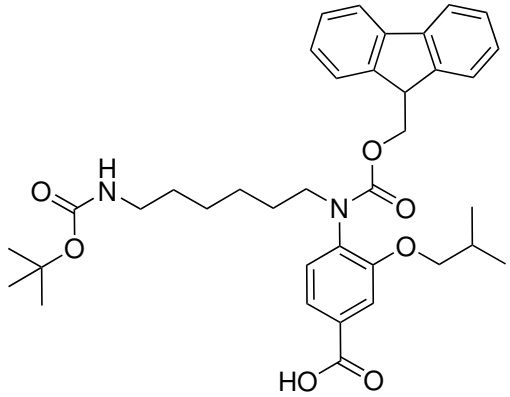
4-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-3-isobutoxybenzoic acid (S15)



S15 was synthesised from **S8** (271 mg, 1.39 mmol) using general procedure G. Purified by column chromatography [SiO_2, CH_2Cl_2:AcOH, 100:0.1] to afford the title compound as a white solid (352 mg, 62%). R_f (*n*-hex:EtOAc, 1:1) = 0.5; ν_{max}/cm^{-1} : 3384 (N-H), 2965 (O-H), 2920, 1668 (C=O), 1601 (NC=O), 1523, 1444, 1249, 1170; ^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 7.69 (dd, J = 8.3, 1.8 Hz, 1H, ArC**H**), 7.41 (d, J = 1.8 Hz, 1H, ArC**H**), 6.56 (d, J = 8.4 Hz, 1H, ArC**H**), 4.52 (s, 1H, **H**NC=O), 3.82 (d, J = 6.6 Hz, 2H, OC$\mathbf{H}_2$CH),

3.20 (t, J = 7.2 Hz, 2H, ArNHC**H**$_2$), 3.12 (q, J = 6.1 Hz, 2H, HNC=OC**H**$_2$), 2.15 (sep, J = 6.7 Hz, 1H, OCH$_2$C**H**), 1.67 (p, J = 7.1 Hz, 2H), 1.56 1.31 (m, 15H, 3 x C**H** & (C**H**$_3$)$_3$), 1.04 (d, J = 6.7 Hz, 6H, OCH$_2$CH(C**H**$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) : δ_C 171.9 (**C**=O), 156.0 (N**C**=O), 145.0 (Ar**C**O), 143.0 (Ar**C**N), 125.5 (Ar**C**H), 116.0 (Ar**C**), 111.1 (Ar**C**H), 108.0 (Ar**C**H), 79.1 (O**C**(CH$_3$)$_3$), 74.7 (O**C**H$_2$CH(CH$_3$)$_2$), 43.0 (NC=O**C**H$_2$), 40.5, 30.0, 29.1, 28.4 (OC(**C**H$_3$)$_3$), 28.2, 26.7, 26.5, 19.4 (OCH$_2$CH(**C**H$_3$)$_2$); HRMS-ESI (*m/z*); Calcd. for [$C_{22}H_{36}N_2O_5$+H]: 409.2702. Found: 409.2704. DOI: 10.14469/hpc/5138

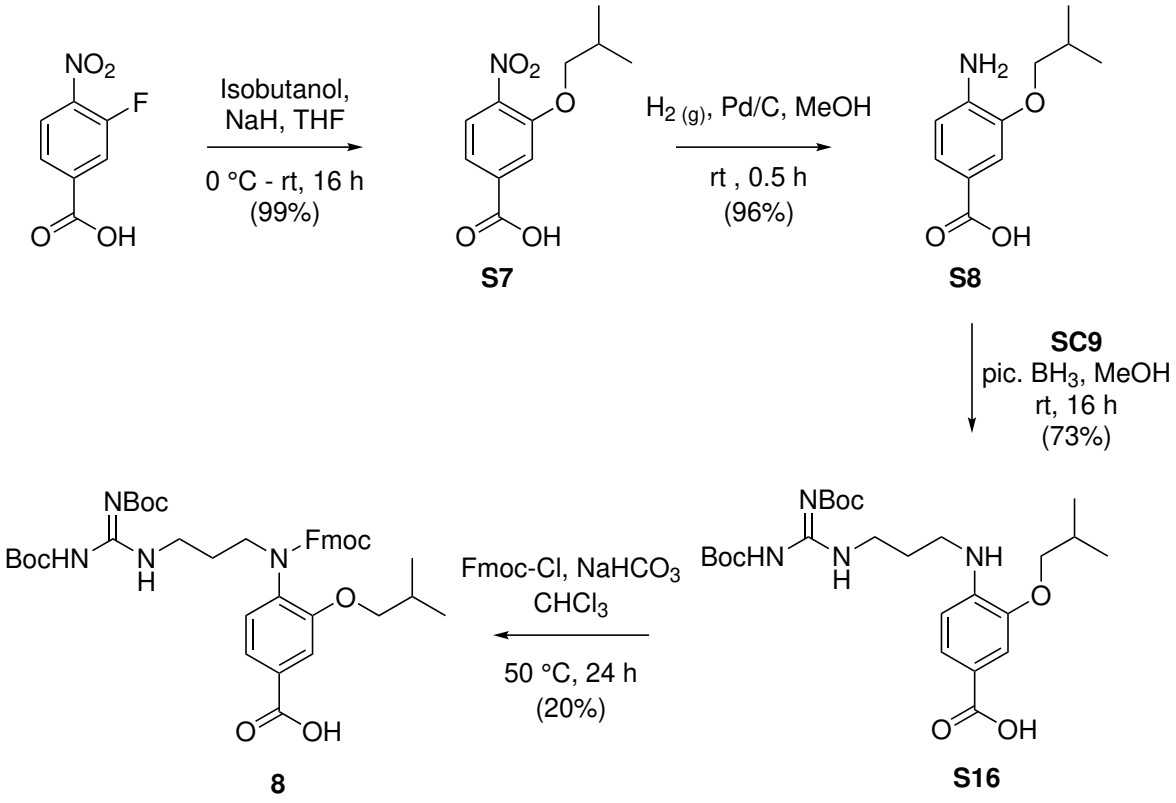
4-((((9H-fluoren-9-yl)methoxy)carbonyl)(6-((*tert*-butoxycarbonyl)amino)hexyl) amino)-3-isobutoxybenzoic acid (**7**)



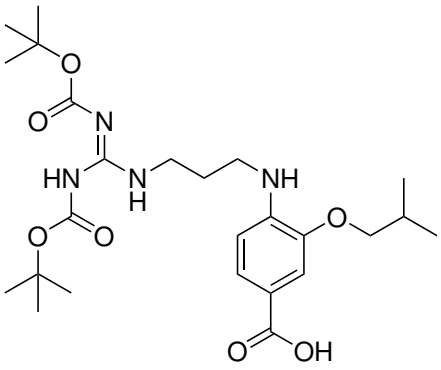
7 was synthesised from **S15** (270 mg, 0.66 mmol) using general procedure H. Purified by column chromatography [SiO_2, CH_2Cl_2:AcOH, 100:0.1] to afford the title compound as a colourless oil (224 mg, 54%). R_f (CH_2Cl_2:AcOH, 100:0.1) = 0.15; ν_{max}/cm^{-1}: 2953, 1696, 1506, 1405, 1254, 1154; ^{1}H NMR (400 MHz, DMSO-d$_6$, 373 K): δ_H 11.82 (s, 1H, O**H**), 7.76 (d, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.55 7.48 (m, 2H, 2 x ArC**H**), 7.34 (t, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.28 (d, J = 16.3 Hz, 2H, 2 x ArC**H** Fmoc), 7.19 (t, J = 7.4 Hz, 2H, 2 x ArC**H** Fmoc), 7.14 (d, J = 8.5 Hz, 1H, ArC**H**), 6.21 (s, 1H, N**H**), 4.29 (br s, 2H, OC**H**$_2$CH Fmoc), 4.07 (br s, J = 6.8 Hz, 1H, OCH$_2$C**H** Fmoc), 3.72 (d, J = 6.1 Hz, 2H, OC**H**$_2$CH), 3.45 (br, 2H, ArNC**H**$_2$), 3.12-2.82 (m, 6H, 3 x C**H**$_2$), 2.02 1.85 (br m, 1H, OCH$_2$C**H**), 1.37 (s, 9H, (C**H**$_3$)$_3$)), 1.25 1.15 (m, 4H, 2 x C**H**$_2$), 0.91 (d, J = 6.7 Hz, 6H, OCH$_2$CH(C**H**$_3$)$_2$); ^{13}C NMR (101 MHz, DMSO-d$_6$, 373 K): δ_C 170.8 (**C**=O), 166.2 (**C**=O), 155.0 (**C**=O), 154.1,

143.2, 140.3, 134.0, 130.7, 128.8, 126.9, 126.2, 124.2, 121.1, 119.3, 113.1, 76.8 (O**C**$(CH_3)_3$), 73.9 (OC**H**$_2$), 66.2 (OC**H**$_2$CH Fmoc), 48.7, 46.2 (OCH_2**C**HFmoc), 28.9, 27.8 (OC(**C**$H_3)_3$), 27.3, 25.4, 25.4, 20.2, 18.5, 18.2; HRMS-ESI (*m/z*): Calcd. for $[C_{37}H_{46}N_2O_7+H]^+$: 631.3396. Found: 631.3383. DOI: 10.14469/hpc/5139

Synthesis of 8



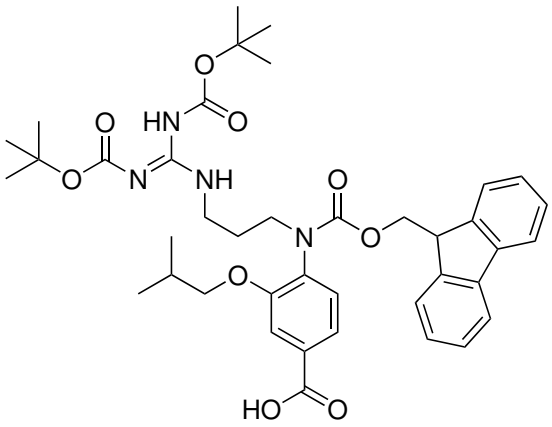
(Z)-4-((3-(2,3-bis(*tert*-butoxycarbonyl)guanidino)propyl)amino)-3-isobutoxy benzoic acid (S16)



S16 was synthesised from **S8** (280 mg, 1.44 mmol) using general procedure G. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as a white solid (537 mg, 73%). R_f (CH_2Cl_2:MeOH, 95:5) = 0.75; ν_{max}/cm^{-1} : 1H NMR (400 MHz, $CDCl_3$) δ_H 11.48 (s, 1H, N**H**), 8.41 (t, J = 5.4 Hz, 1H, N**H**), 7.69

(dd, J = 8.3, 1.8 Hz, 1H, ArC**H**), 7.42 (d, J = 1.8 Hz, 1H, ArC**H**), 6.55 (d, J = 8.4 Hz, 1H, ArC**H**), 4.85 (s, 1H, N**H**), 3.81 (d, J = 6.6 Hz, 2H, OC$\mathbf{H}_2$(CH_3)$_2$), 3.54 (td, J = 7.0, 5.3 Hz, 2H, NHC$\mathbf{H}_2$), 3.31 (t, J = 7.0 Hz, 2H, NHC$\mathbf{H}_2$), 2.14 (sep, J = 6.7 Hz, 1H, OCH_2C**H**(CH_3)$_2$), 1.95 (p, J = 7.0 Hz, 2H $NHCH_2$C$\mathbf{H}_2$), 1.50 (s, 9H, C$\mathbf{H}_3$)$_3$), 1.49 (s, 9H, C$\mathbf{H}_3$)$_3$), 1.04 (d, J = 6.7 Hz, 6H, OCH_2CH(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.0 (**C**=O), 163.5 (**C**=N), 156.3 (**C**=O), 153.3 (**C**=O), 145.0 (Ar**C**O), 142.9 (Ar**C**N), 125.4 (Ar**C**H), 116.4 (Ar**C**), 111.2 (Ar**C**H), 107.7 (Ar**C**H), 83.2 (O**C**(CH_3)$_3$), 79.3 (O**C**(CH_3)$_3$), 74.8 (O**C**H_2CH(CH_3)$_2$), 40.5 (NH**C**H_2), 38.6 (NH**C**H_2), 28.9 ($NHCH_2$**C**H_2CH_2NH), 28.3 (OC(**C**H_3)$_3$), 28.2 (OCH_2**C**H(CH_3)$_2$, 28.1 (OC(**C**H_3)$_3$), 19.4 (OCH_2CH(**C**H_3)$_2$); HRMS-ESI (*m/z*); Calcd. for $[C_{25}H_{40}N_4O_7+H]^+$: 509.2975. Found: 509.2978. DOI: 10.14469/hpc/5140

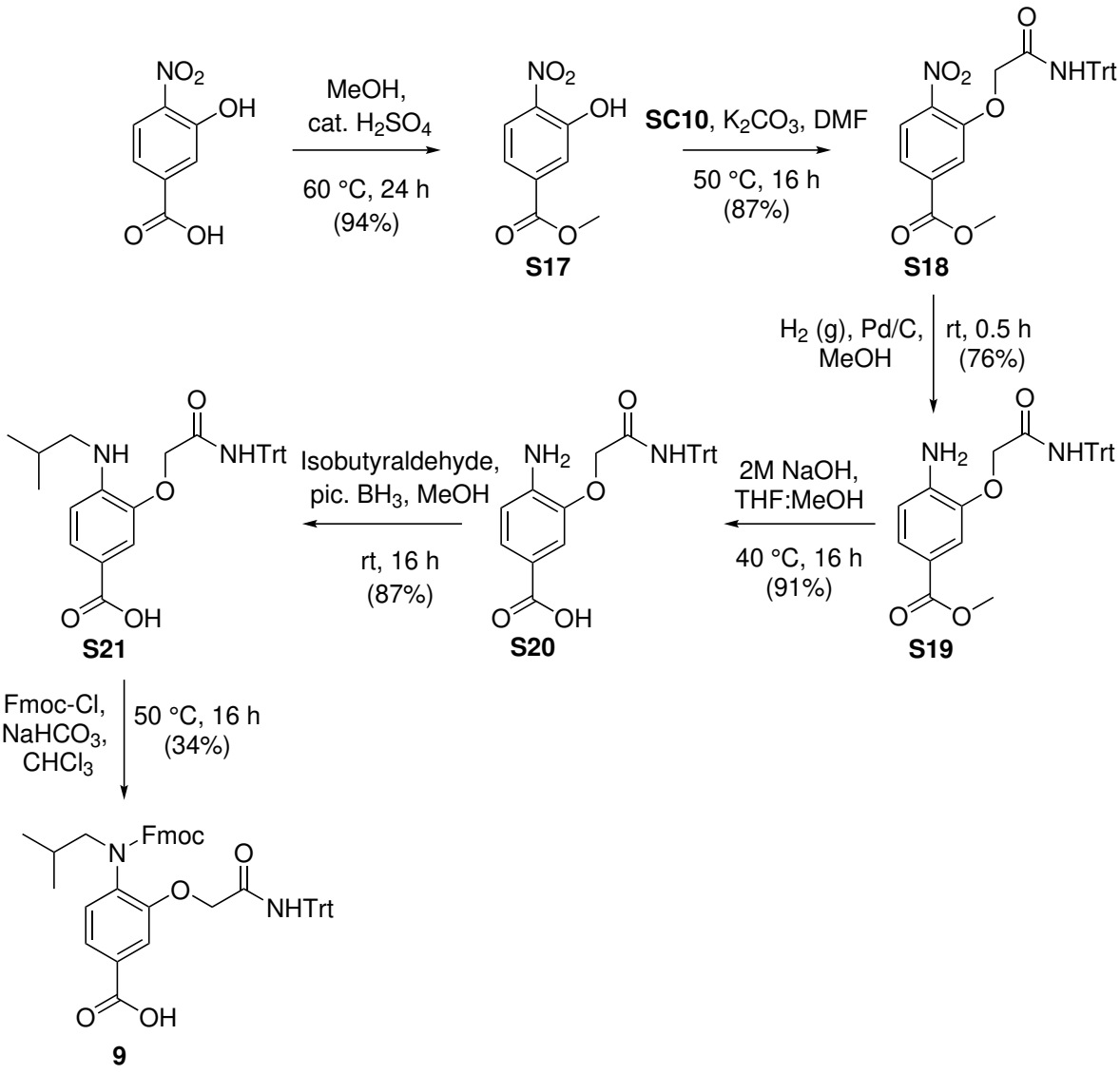
(Z)-4-((((9H-fluoren-9-yl)methoxy)carbonyl)(3-(2,3-bis(*tert*-butoxycarbonyl) guanidino) propyl)amino)-3-isobutoxybenzoic acid (8)



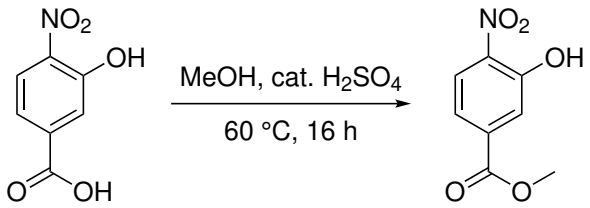
8 was synthesised from **S16** (100 mg, 0.19 mmol) using general procedure H. Purified by column chromatography [SiO_2, EtOAc:n-hex, 1:9 to 2:8 over 10 CV] to afford the title compound as an amorphous, white solid (28 mg, 20%); R_f (CH_2Cl_2) = 0.25; ν_{max}/cm^{-1}: 3043, 1802, 1772, 1743, 1710, 1137; ^{1}H NMR (400 MHz, $CDCl_3$, 323 K): δ_H 11.51 (s, 1H, O**H**), 8.48 (t, J = 5.4 Hz, 1H, N**H**), 8.11 (s, 1H, N**H**), 7.78 (d, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.67 (d, J = 8.0 Hz, 1H, ArC**H**), 7.62 (d, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.54 7.49 (m, 2H, 2 x ArC**H**), 7.41 (t, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.32 (t, J = 7.5 Hz, 2H, ArC**H**), 4.50 (d, J = 7.2 Hz, 2H, OC$\mathbf{H}_2$CH Fmoc), 4.38 (t, J

= 6.2 Hz, 2H, OC$\mathbf{H}_2$CH), 4.32 (t, J = 7.1 Hz, 1H, $OCH_2C\mathbf{H}$ Fmoc), 3.89 (d, J = 6.5 Hz, 2H, ArNC$\mathbf{H}_2$), 3.60 (td, J = 6.9, 5.3 Hz, 2H, $ArNCH_2CH_2C\mathbf{H}_2$), 2.20 (sep, J = 6.7 Hz, 1H, $OCH_2C\mathbf{H}$), 2.08 (q, J = 6.5 Hz, 2H, $ArNCH_2C\mathbf{H}_2CH_2$), 1.50 (s, 9H, $(C\mathbf{H}_3)_3$)), 1.47 (s, 9H, $(C\mathbf{H}_3)_3$)), 1.10 (d, J = 6.7 Hz, 6H, $OCH_2CH(C\mathbf{H}_3)_2$; ^{13}C NMR (101 MHz, $CDCl_3$, 323 K) : δ_C: 166.3 (**C**=O), 163.6, 156.3, 153.3, 152.9, 146.5, 143.7, 141.34, 132.1, 127.9, 127.1, 125.0, 124.3, 123.4, 120.1, 117.0, 111.9, 83.2 ($\mathbf{C}(CH_3)_3$), 79.3 ($\mathbf{C}(CH_3)_3$), 75.3 (O**C**H_2CH), 67.4 (O**C**H_2CH_2 Fmoc), 62.6 ($ArNCH_2CH_2\mathbf{C}H_2$), 47.0 ($OCH_2\mathbf{C}$H Fmoc), 38.1 (ArN**C**$H_2CH_2CH_2$), 28.5 ($ArNCH_2\mathbf{C}H_2CH_2$), 28.3 $(\mathbf{C}H_3)_3$, 28.2 ($OCH_2\mathbf{C}$H), 28.1 $(\mathbf{C}H_3)_3$, 19.3 ($OCH_2CH\mathbf{C}H_3)_2$); HRMS-ESI (m/z): Calcd. for $[C_{40}H_{50}N_4O_9+H]^+$: 731.3656. Found: 731.3657. DOI: 10.14469/hpc/5141

Synthesis of 9



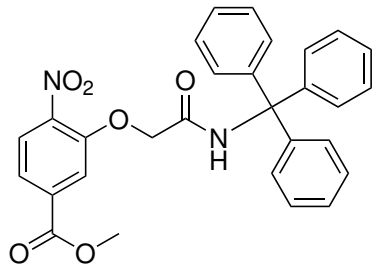
Methyl 3-hydroxy-4-nitrobenzoate (**S17**)



To a stirring solution of 3-hydroxy-4-nitrobenzoic acid (2.00 g, 2.00 mmol, 1.00 eq.) in methanol (40 mL) was added $\geq$ 98% sulphuric acid (0.10 mL, cat.). The mixture was heated

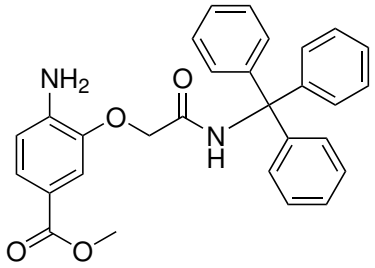
at reflux for 24 h and the solvent removed *in vacuo*. The residue was taken up in ethyl acetate (100 mL), washed with saturated sodium bicarbonate (20 mL x 2), water (20 mL x 1) and brine (1 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as an orange solid (2.04 g, 94%). R*f* (*n*-hex:EtOAc, 1:1) = 0.9; ν_{max}/cm^{-1} : 1724 (C=O), 1674, 1607, 1517 (ArC−NO_2), 1433, 1277; ^{1}H NMR (400 MHz, MeOD): δ_H 8.11 (d, J = 8.7 Hz, 1H, ArC**H**), 7.73 (d, J = 1.6 Hz, 1H, ArC**H**), 7.60 (dd, J = 8.6, 1.7 Hz, 1H, ArC**H**), 3.95 (s, 3H, OC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, MeOD) δ_C 165.1 (**C**=O), 153.1 (Ar**C**-NO_2), 137.8 (Ar**C**), 136.6 (Ar**C**), 125.1 (Ar**C**H), 120.5 (Ar**C**H), 119.8 (Ar**C**H), 51.9 (O**C**H_3; HRMS-ESI (*m/z*): Calcd. for [$C_8H_7NO_5$-H]$^-$: 196.0246 Found: 196.0255. DOI: 10.14469/hpc/5142

Methyl 4-nitro-3-(2-oxo-2-(tritylamino)ethoxy)benzoate (**S18**)



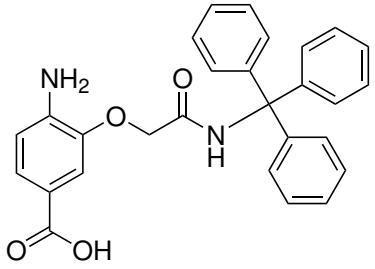
S18 was synthesised from **S17** (1.18 g, 5.98 mmol) using general procedure D. Purification by column chromatography [SiO_2, *n*-hex:EtOAc, 10:0 - 95:5 over 10 CV] afforded the title product as a yellow solid (2.82 g, 95 %). R_f (*n*-hex:EtOAc, 1:1) = 0.45; ν_{max}/cm^{-1} : 3407 (N-H), 1730 (C=O), 1690 (C=O), 1590, 1523 (NO_2), 1300, 1232; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.14 (s, 1H, N**H**), 8.02 (d, J = 8.4 Hz, 1H, ArC**H**), 7.80 (dd, J = 8.4, 1.5 Hz, 1H, ArC**H**), 7.73 (d, J = 1.6 Hz, 1H, ArC**H**), 7.37 7.22 (m, 15H, trityl), 4.68 (s, 2H, OC$\mathbf{H}_2$), 3.98 (s, 3H, OC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 165.1 (**C**=O), 164.8 (**C**=O), 150.4 (Ar**C**NO_2), 144.4 (Ar**C**O), 128.8 (Ar**C**H trityl), 128.2 (Ar**C**H trityl), 127.4 (Ar**C**H trityl), 126.6, 123.0, 115.7 (ArC**H**), 70.8 (**C**(C_6H_5)$_3$), 68.5 (O**C**H_2), 53.2 (O**C**H_3) (trityl quaternary carbon not observed); HRMS-ESI (*m/z*): Calcd. for [$C_{29}H_{24}N_2O_6$-H]$^-$: 495.1550. Found: 495.1556. DOI: 10.14469/hpc/5143

Methyl 4-amino-3-(2-oxo-2-(tritylamino)ethoxy)benzoate (S19)



S19 was synthesised from **S18** (4.24 g, 8.56 mmol) using Procedure F but ethyl acetate used as solvent due to poor solubility in methanol. Purified by column chromatography [SiO_2, *n*-hex:EtOAc, 10:0 to 1:1 over 20 CV] to afford the title compound as a white solid (3.34 g, 83%). R_f (*n*-hex:EtOAc, 1:1) = 0.20; ν_{max}/cm^{-1} : 3356 (N-H), 1668 (C=O), 1612, 1522; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.67 7.63 (m, 2H, ArC**H** & N**H**), 7.56 (d, J = 1.7 Hz, 1H, ArC**H**), 7.34 7.26 (m, 10H, trityl), 7.23 7.17 (m, 5H, trityl), 6.76 (d, J = 8.2 Hz, 1H, ArC**H**), 4.65 (s, 2H, OC**H**$_2$), 3.90 (s, 3H, OC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 166.9 (**C**=O), 166.8 (**C**=O), 144.4 (Ar**C**O), 144.1 (Ar**C**N), 128.8 (Ar**C**), 128.7 (Ar**C**H trityl), 128.2 (Ar**C**H trityl), 127.4 (Ar**C**H trityl), 125.7 (Ar**C**H), 114.8 (Ar**C**H), 113.7 (Ar**C**H), 70.5 (**C**$(C_6H_5)_3$), 68.8 (O**C**H_2), 52.0 (O**C**H_3) (quarternary carbon not observed); HRMS-ESI (*m/z*): Calcd. for $[C_{29}H_{26}N_2O_4+H]^+$: 467.1965. Found: 467.1971. DOI: 10.14469/hpc/5144

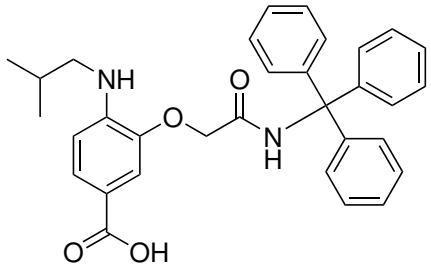
4-amino-3-(2-oxo-2-(tritylamino)ethoxy)benzoic acid (**S20**)



S20 was synthesised from **S19** (2.80 g, 6.06 mmol) using general procedure E. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as a white solid (2.10 g, 76 %). R_f (CH_2Cl2:MeOH, 97.5:2.5) = 0.45; ν_{max}/cm^{-1} : 3396 (N-H), 2920 (O-H), 2848, 1697 (C=O), 1618 (C=O), 1523, 1238 (C-O); ^{1}H NMR

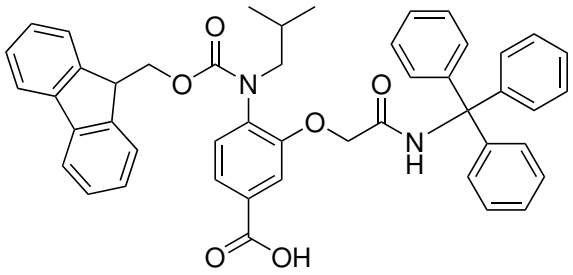
(400 MHz, $CDCl_3$): δ_H 12.18 (s, 1H, O**H**), 8.73 (s, 1H, N**H**), 7.41 7.35 (m, 2H, 2 x ArC**H**), 7.32 7.14 (m, 15H, trityl), 6.64 (d, J = 8.1 Hz, 1H, ArC**H**), 5.60 (s, 2H, N$\mathbf{H}_2$), 4.74 (s, 2H, C$\mathbf{H}^2$); $_{13}$C NMR (101 MHz, $CDCl_3$): δ_C 170.0 (**C**=O), 167.7 (**C**=O), 145.0 (Ar**C**O), 144.0 (Ar**C**N), 143.4 (Ar**C**), 128.9 (Ar**C**H trityl), 128.0 (Ar**C**H trityl), 127.0 (Ar**C**H trityl), 125.0 (Ar**C**H), 113.2 (Ar**C**H trityl), 113.0 (Ar**C**H), 69.7 (**C**$(C_6H_5)_3$), 67.7 (O**C**H_2) (quarternary carbon not observed). HRMS-ESI (*m/z*): Calcd. for $[C_{28}H_{24}N_2O_4+H]^+$: 453.1805. Found: 453.1814. DOI: 10.14469/hpc/5145

4-(isobutylamino)-3-(2-oxo-2-(tritylamino)ethoxy)benzoic acid (**S21**)



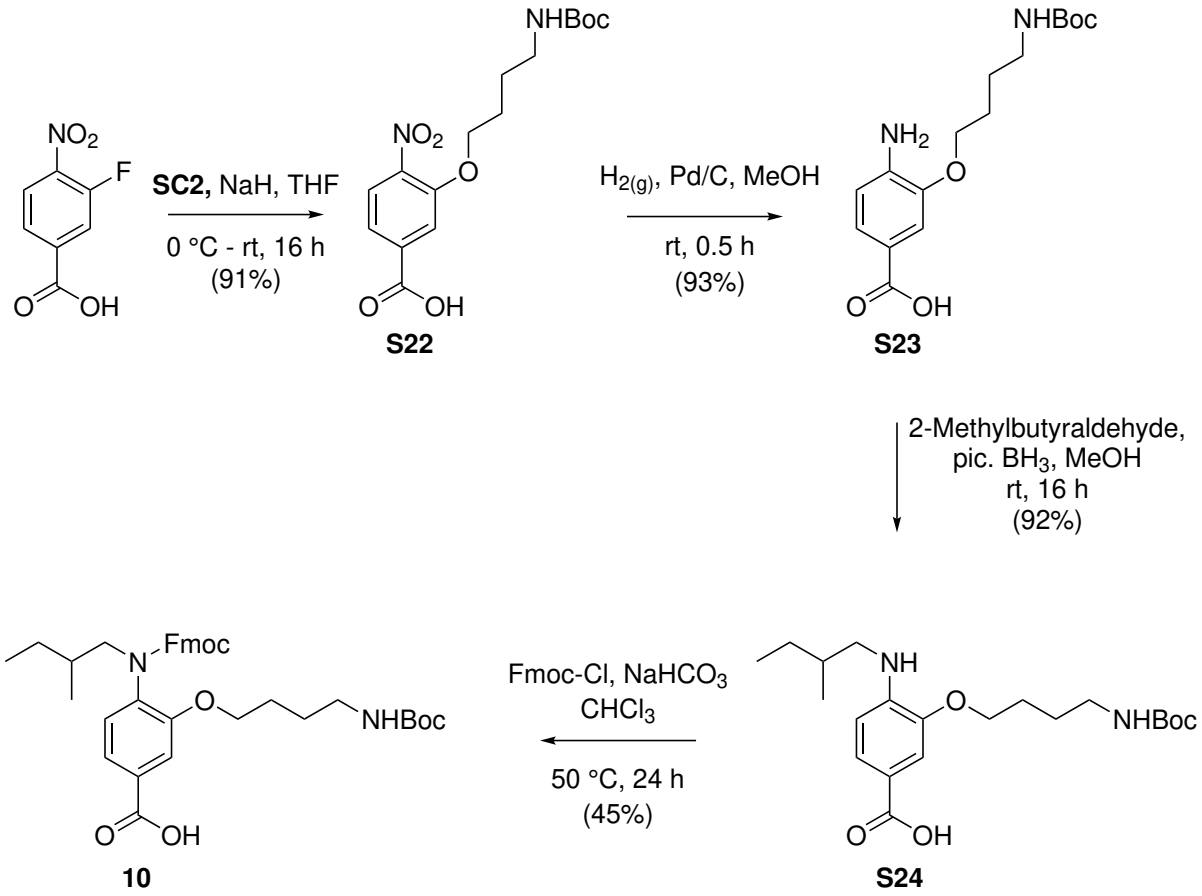
S21 was synthesised from **S20** (1.00 g, 2.21 mmol) using general procedure G. Purified by recrystallisation from hot methanol to afford the title compound as a white solid (1.01 g, 87%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (dd, J = 8.4, 1.7 Hz, 1H, ArC**H**), 7.58 (d, J = 1.8 Hz, 1H, ArC**H**), 7.52 (s, 1H, N**H**), 7.34 7.25 (m, 10H, trityl), 7.22 7.17 (m, 5H, trityl), 6.63 (d, J = 8.5 Hz, 1H, ArC**H**), 4.67 (s, 2H, OC$\mathbf{H}_2$), 3.02 (d, J = 6.9 Hz, 2H, NHC$\mathbf{H}_2$), 1.88 (sep, J = 6.7 Hz, 1H, NHCH_2C**H**), 0.97 (d, J = 6.7 Hz, 6H, NHCH_2CH(C$\mathbf{H}_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 171.1 (**C**=O), 166.7 (N**C**=O), 144.3 (Ar**C**O), 143.2 (Ar**C**N), 143.1 (Ar**C** trityl), 128.5 (Ar**C**H trityl), 128.1 (Ar**C**H trityl), 127.2 (Ar**C**H trityl), 127.1 (Ar**C**H), 116.2 (Ar**C**) (Ar**C**), 112.7 (Ar**C**H), 108.8 (Ar**C**H), 70.4 (**C**$(C_6H_5)_3$), 68.6 (**O**CH_2), 50.8 (ArNH**C**H_2), 28.0 (ArNHCH_2**C**H), 20.4 (ArNHCH_2**C**H(**C**$H_3)_2$); HRMS-ESI (*m/z*): Calcd. for $[C_{32}H_{32}N_2O_4+H]^+$: 523.2593. Found: 523.2597. DOI: 10.14469/hpc/5146

4-((((9H-fluoren-9-yl)methoxy)carbonyl)(isobutyl)amino)-3-(2-oxo-2-(tritylamino) ethoxy)benzoic acid (9)

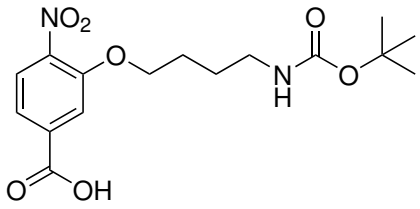


9 was synthesised from **S21** (1.00 g, 1.96 mmol) using general procedure H. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as an amorphous, pale yellow solid (0.89 g, 61%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.5; ν_{max}/cm^{-1}: 2595, 1696, 1511, 1405, 1154; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): δ_H 12.50 (s, 1H, O**H**), 8.09 (s, 1H, N**H**), 7.77 (d, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.59 (d, J = 1.8 Hz, 1H, ArC**H**), 7.56 (dd, J = 8.0, 1.8 Hz, 1H, ArC**H**), 7.35 (t, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.31 – 7.12 (m, 20H, trityl, 2 x ArC**H** Fmoc, ArC**H**), 4.61 (s, 2H, OC$\mathbf{H}_2$), 4.29 (d, J = 6.4 Hz, 2H, OC$\mathbf{H}_2$CH), 4.06 (t, J = 6.5 Hz, 1H, OCH_2C**H**), 3.31 (s, 2H, ArNC$\mathbf{H}_2$), 1.67 – 1.57 (m, 1H, $ArNCH_2$C**H**), 0.74 (d, J = 6.6 Hz, 6H, (C$\mathbf{H}_3$)$_2$); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K): δ_C 165.9 (**C**=O), 165.6 (**C**=O), 154.3 (**C**=O), 152.7, 143.9, 143.2, 140.3, 134.1, 130.5, 128.8, 127.9, 127.0, 126.8, 126.2, 126.0, 124.2, 121.9 (Ar**C**H), 119.3 (Ar**C**H Fmoc), 113.7 (Ar**C**H), 69.2 (**C**-(C_6H_6)$_3$), 67.6 (O**C**H), 66.2 (O**C**H_2CH Fmoc), 55.9 (ArN**C**H_2), 46.3 (OCH_2**C**H Fmoc), 26.5 ($ArNCH_2$**C**H_2), 19.3 ($ArNCH_2CH$(C$\mathbf{H}_3$)$_2$); HRMS-ESI (m/z): Calcd. for $[C_{47}H_{42}N_2O_6+H]^+$: 731.3140. Found: 731.3121. DOI: 10.14469/hpc/5147

Synthesis of 10



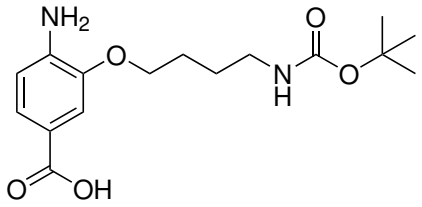
3-(4-((*tert*-butoxycarbonyl)amino)butoxy)-4-nitrobenzoic acid (S22)



S22 was synthesised from 3-fluoro-4-nitrobenzoic acid (2.00 g, 10.80 mmol) using general procedure C to afford the title compound as a yellow solid (3.14 g, 82%). Rf (EtOAc/AcOH 100:0.1) = 0.6; $\nu_{max}/\mathrm{cm}^{-1}$: 3362 (N-H), 2976 (O-H), 2926, 1690 (C=O), 1522 (NO_2), 1249, 1165; ^{1}H NMR (400 MHz, MeOD): δ_H 7.86 7.81 (m, 2H, 2 x ArC**H**), 7.69 (dd, J = 8.3, 1.5 Hz, 1H, ArC**H**), 4.23 (t, J = 6.2 Hz, 2H, OC$\mathbf{H}_2$), 3.14 (t, J = 6.8 Hz, 2H, NHC$\mathbf{H}_2$), 1.86 (p, J = 8.5 Hz, 2H, $OCH_2C\mathbf{H}_2$), 1.69 (p, J = 7.0 Hz, 2H, $NHCH_2C\mathbf{H}_2$), 1.45 (s, 9H,

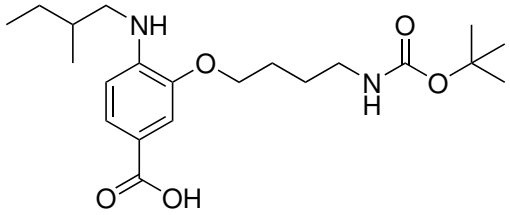
($C\mathbf{H}_3)_3$); ^{13}C NMR (101 MHz, MeOD): δ_C 166.2 (**C**=O), 157.2 (N**C**=O), 151.4 (Ar**C**NO_2), 142.6 (Ar**C**O), 135.4 (Ar**C**), 124.6 (Ar**C**H), 121.2 (Ar**C**H), 115.2 (Ar**C**H), 78.5 (**C**$(CH_3)_3$), 69.1 (O**C**H_2), 61.2 (N**C**H_2), 39.5 ($OCH_2\mathbf{C}H_2$), 27.4 (C(**C**$H_3)_3$, 25.9 ($NCH_2\mathbf{C}H_2$); HRMS-ESI (*m/z*): Calcd. for $[C_{16}H_{22}N_2O_7$-H]$^-$: 353.1356. Found : 353.1349. DOI: 10.14469/hpc/5148

(Z)-3-(3-(2,3-bis(4-amino-3-(4-((*tert*-butoxycarbonyl)amino)butoxy)benzoic acid (S23)



S23 was synthesised from **S22** (3.14 g, 8.90 mmol) using general procedure F. Residue triturated with dichloromethane to afford the title product as a white solid (2.06 g, 70%). R*f* (CH_2Cl_2:MeOH 97.5:2.5) = 0.25; ν_{max}/cm^{-1} : 3468 (N-H), 2942 (O-H), 1668 (C=O), 1612, 1271; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 12.07 (s, 1H, O**H**), 7.35 (dd, J = 8.2, 1.7 Hz, 1H, ArC**H**), 7.27 (d, J = 1.8 Hz, 1H, ArC**H**), 6.85 (t, J = 5.7 Hz, 1H, N**H**), 6.63 (d, J = 8.2 Hz, 1H, ArC**H**), 5.50 (s, 2H, ArN$\mathbf{H}_2$), 3.97 (t, J = 6.3 Hz, 2H, OC$\mathbf{H}_2CH_2$), 3.00 (q, J = 6.6 Hz, 2H, NHC$\mathbf{H}_2$), 1.80 1.68 (m, 2H, $OCH_2C\mathbf{H}_2CH_2$), 1.66 1.51 (m, 2H, $NHCH_2C\mathbf{H}_2$), 1.39 (s, 9H, (C$\mathbf{H}_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6) : δ_C 168.0 (**C**=O), 156.1 (N**C**=O), 144.8 (Ar**C**O), 143.3 Ar(**C**N), 124.4 (ArC**H**), 117.7 (Ar**C**), 112.5 (ArC**H**), 112.3 (ArC**H**), 77.8 (**C**$(CH_3)_3$), 67.9 (O**C**H_2CH_2), 40.0 (N**C**H_2CH_2 HSQC), 28.7 ((**C**$H_3)_3$, 26.7 ($OCH_2\mathbf{C}H_2CH_2$), 26.6 ($OCH_2CH_2\mathbf{C}H_2CH_2NH$); ^{1}H-^{13}C NMR ((400, 101) MHz, DMSO-d6) $\delta_{H/C}$ (7.35 124.36), (7.28 112.30), (6.63 112.48), (3.97 67.92), **(3.00 39.96)**, (1.74 26.67, (1.57 26.61), (1.39 28.73); HRMS-ESI (*m/z*): Calcd. for $[C_{16}H_{25}N_2O_5$-H]$^-$: 325.1775. Found : 325.1763. DOI: 10.14469/hpc/5149

3-(4-((*tert*-butoxycarbonyl)amino)butoxy)-4-((2-methylbutyl)amino)benzoic acid (S24)



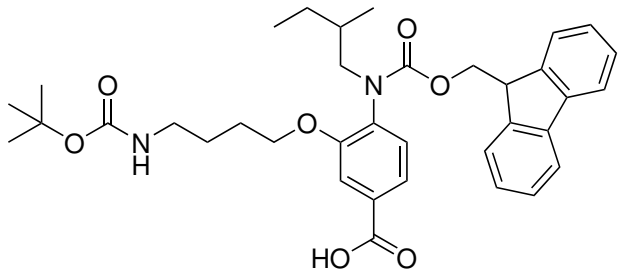
S24 was synthesised from **S23** (1.00 g, 1.27 mmol) using general procedure G. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as a white solid (0.88 g, 88%). R_f (*n*-hex:EtOAc:AcOH, 1:1:0.01) = 0.45; ν_{max}/cm^{-1}: 3367 (N-H), 2954 (O-H), 1680 (C=O), 1601, 1523, 1277; ^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 7.68 (dd, J = 8.4, 1.8 Hz, 1H, Ar**C**H), 7.40 (d, J = 1.8 Hz, 1H, Ar**C**H), 6.53 (d, J = 8.4 Hz, 1H, Ar**C**H), 4.64 (s, 1H, N**H**), 4.06 (t, J = 6.3 Hz, 2H, OC**H**$_2$), 3.21 (q, J = 6.8 Hz, 2H, C**H**$_2$NHC=O), 3.13 (dd, J = 12.7, 6.1 Hz, ArNC**H**$_2$), 2.98 (dd, J = 12.7, 7.3 Hz, 1H, ArNC**H'**$_2$), 1.85 (dq, J = 12.1, 6.5 Hz, 2H, OCH_2C**H**$_2$), 1.79 1.60 (m, 3H, $ArNHCH_2C$**H** & OCH_2C**H**$_2$), 1.44 (s, 10H, (C**H**$_3$)$_3$ & $ArNHCH_2CH(CH_3)C$**H**$_2$), 1.30 1.14 (m, 1H, $ArNHCH_2CH(CH_3)C$**H'**$_2$), 0.99 0.90 (m, 6H, $ArNHCH_2CH(C$**H**$_3)CH_2C$**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) : δ_C 171.7 (**C**=O), 156.0 (**C**=O), 144.6 (Ar**C**O), 143.5 (Ar**C**N), 125.7 (Ar**C**H), 115.7 (Ar**C**), 111.1 (Ar**C**H), 107.7 (Ar**C**H), 79.3 (O**C**$(CH_3)_3$), 68.0 O**C**H_2CH_2), 48.9 (ArNH**C**H_2), 40.3 (**C**H_2NHC=O), 34.4 ($ArNHCH_2$**C**H), 28.4 (OC(**C**$H_3)_3$), 27.3 ($ArNCH_2CHC$**H**$_2$), 27.0 (CH_2**C**H_2NHC=O), 26.5 (OCH_2**C**H_2), 17.5 ($ArNHCH_2CH(CH_3)CH_2$**C**H_3), 11.3 ($ArNHCH_2CH($**C**H_3)

CH_2CH_3); HRMS-ESI (m/z); Calcd. for [$C_{21}H_{34}N_2O_5$+H] : 395.2546. Found : 395.2553.

DOI: 10.14469/hpc/5150

4-((((9H-fluoren-9-yl)methoxy)carbonyl)(2-methylbutyl)amino)-

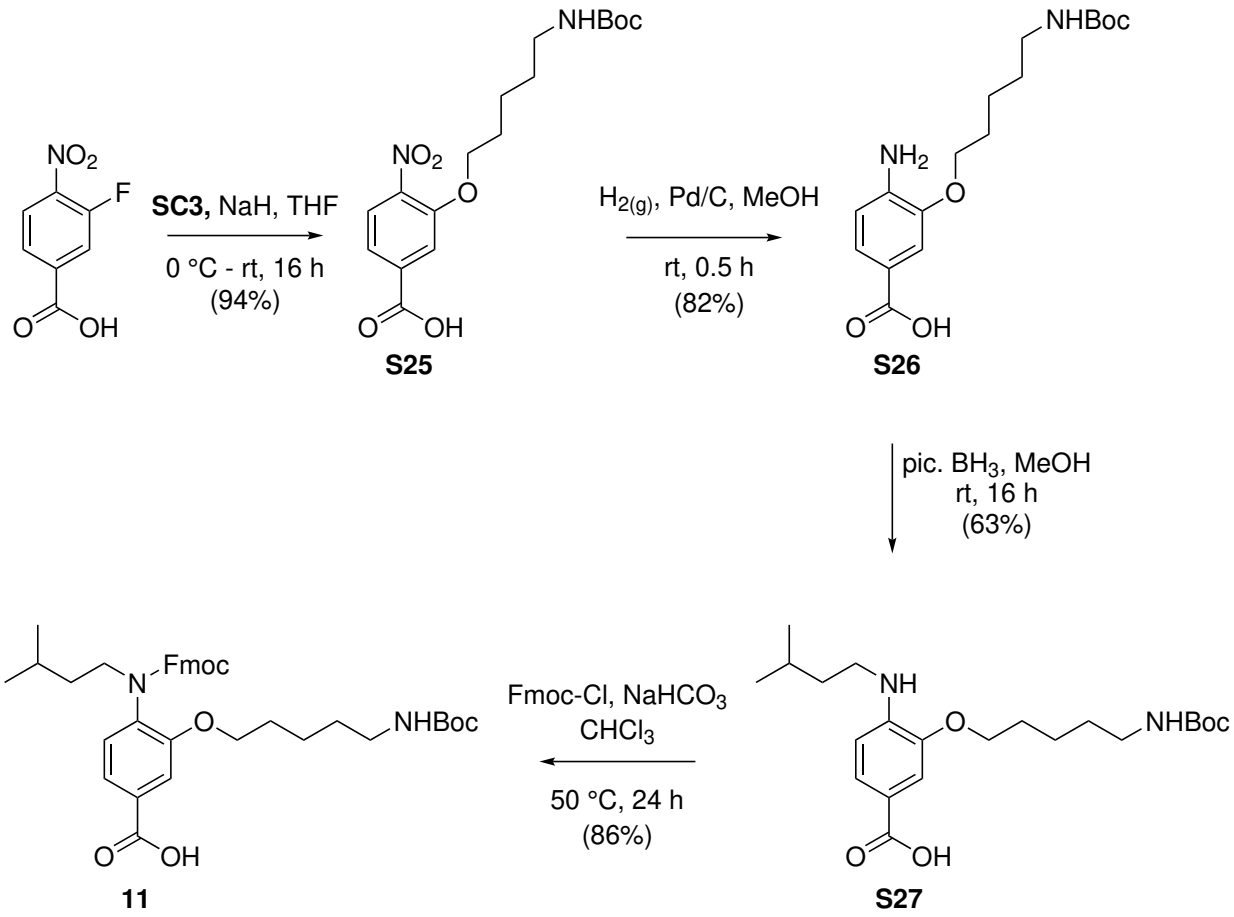
3- (4-((*tert*-butoxycarbonyl)amino)butoxy)benzoic acid (10)



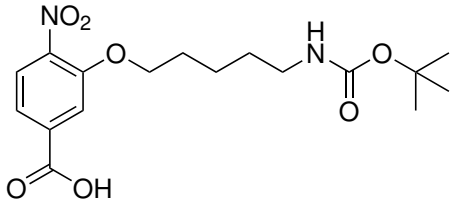
10 was synthesised from **S24** (0.90 g, 2.29 mmol) using general procedure H. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as an amorphous, white solid (0.48 g, 34%); R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.25; ν_{max}/cm^{-1}: 2959, 1696, 1405, 1160; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 12.43 (s, 1H, O**H**), 7.76 (d, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.53 (d, J = 1.8 Hz, 1H, ArC**H**), 7.51 (dd, J = 8.0, 1.8 Hz, 1H, ArC**H**), 7.35 (t, J = 7.5 Hz, 2H, 2 x ArC**H** Fmoc), 7.31 (br, 2H, 2 x ArC**H** Fmoc), 7.20 (t, J = 7.4 Hz, 2H, 2 x ArC**H** Fmoc), 7.13 (d, J = 8.0 Hz, 1H, ArC**H**), 6.27 (s, 1H, N**H**), 4.34 (br, 2H, OC$\mathbf{H}_2$CH Fmoc), 4.08 (br, 1H, OCH_2C**H** Fmoc), 3.96 (t, J = 6.4 Hz, 2H, OC$\mathbf{H}_2CH_2$), 3.40 (br, 1H, ArNC**H**), 3.32 (s, 1H, ArNC**H'**), 2.96 (td, J = 6.8, 5.8 Hz, 2H, $OCH_2CH_2CH_2C\mathbf{H}_2$), 1.66 (p, J = 7.1 Hz, 2H, $OCH_2C\mathbf{H}_2$), 1.55 1.47 (m, 2H, $OCH_2CH_2C\mathbf{H}_2$), 1.47 1.39 (m, 1H, $ArNCH_2C\mathbf{H}$), 1.37 (s, 9H, $(C\mathbf{H}_3)_3$), 1.36 1.26 (m, 1H, $ArNCH_2CH(CH_3)C\mathbf{H}_2$), 1.04 (m, 1H, $ArNCH_2CH(CH_3)C\mathbf{H'}_2$), 0.81 0.74 (m, 6H, $ArNCH_2CH(C\mathbf{H}_3)CH_2C\mathbf{H}_3$); ^{13}C NMR (126 MHz, DMSO-d_6): δ_C 166.6 (**C**=O), 155.5 (**C**=O), 154.9 (**C**=O), 154.2, 143.7, 140.8, 134.8, 131.0, 129.2 (Ar**C**H), 127.3 (Ar**C**H Fmoc), 126.6 (Ar**C**H Fmoc), 124.6 (Ar**C**H Fmoc), 121.5 (Ar**C**H), 119.7 (Ar**C**H Fmoc), 113.7 (Ar**C**H), 77.4 ($\mathbf{C}(CH_3)_3$), 68.1 ($O\mathbf{C}H_2$), 66.6 ($O\mathbf{C}H_2$CH Fmoc), 54.8 ($ArN\mathbf{C}H_2$), 46.8 (OC$\mathbf{H}_2$CH Fmoc), 39.7 ($OCH_2CH_2CH_2\mathbf{C}H_2$), 33.3 ($OCH_2CH_2\mathbf{C}H_2$), 28.2 ($(\mathbf{C}H_3)_3$), 26.3 ($ArNCH_2\mathbf{C}H$), 26.2 ($OCH_2\mathbf{C}H_2$), 26.0 ($OCH_2CH_2C\mathbf{H}_2$), 16.7 ($ArNCH_2CH(CH_3)CH_2\mathbf{C}H_3$), 10.5 ($ArNCH_2CH(\mathbf{C}H_3)CH_2CH_3$); HRMS-ESI ($m/z$): Calcd. for $[C_{36}H_{44}N_2O_7+H]^+$: 617.3257.

Found: 617.3227. DOI: 10.14469/hpc/5151

Synthesis of 11



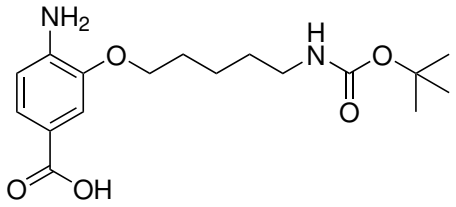
3-((5-((-butoxycarbonyl)amino)pentyl)oxy)-4-nitrobenzoic acid (**S25**)



S25 was synthesised from 3-fluoro-4-nitrobenzoic acid (4.00 g, 21.60 mmol) using general procedure C to afford the title compound as a yellow solid (7.51 g, 94%). Rf (EtOAc/AcOH 100:0.1) = 0.6. $\nu_{max}/\mathrm{cm}^{-1}$: 3378 (N-H) 2937 (O-H), 2865, 1695 (C=O), 1528 (NO_2), 1254, 1170; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 13.56 (s, 1H, O**H**), 7.95 (d, J = 8.3 Hz, 1H, ArC**H**), 7.74 (d, J = 1.6 Hz, 1H, ArC**H**), 7.62 (dd, J = 8.3, 1.6 Hz, 1H, ArC**H**), 6.78 (t, J = 5.7 Hz, 1H, N**H**), 4.20 (t, J = 6.3 Hz, 2H, OC$\mathbf{H}_2$), 2.98 2.82 (m, 2H, NC$\mathbf{H}_2$), 1.78 1.66

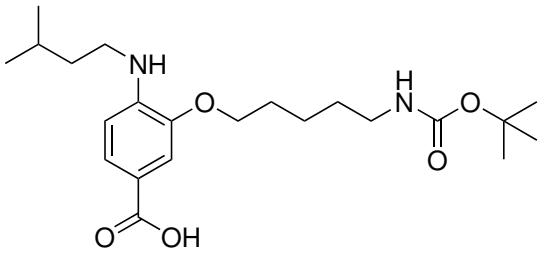
(m, 2H, H_8, $OCH_2C\mathbf{H}_2$), 1.44 1.34 (m, 13H, $OCH_2CH_2C\mathbf{H}_2C\mathbf{H}_2$ & $(C\mathbf{H}_3)_3$); ^{13}C NMR (400 MHz, DMSO-d_6): δ_C 165.8 (**C**=O), 155.6 (N**C**=O), 150.9 (Ar**C**NO_2), 142.1 (Ar**C**O), 135.7 (Ar**C**O), 124.9 (Ar**C**H), 121.2 (Ar**C**H), 115.3 (Ar**C**H), 77.3 (**C**$(CH_3)_3$), 69.3 (O**C**H_2), 39.5 (N**C**H_2, HSQC), 29.0 ($OCH_2\mathbf{C}H_2$), 28.3 ($OCH_2\mathbf{C}H_2$), 28.0 (C(**C**$H_3)_3$), 22.5 ($OCH_2CH_2\mathbf{C}H_2$); ^{1}H-^{13}C NMR ((400, 101) MHz, DMSO-d_6) $\delta_{H/C}$ (7.96 124.74), (7.77 115.04), (7.64 120.97), (4.22 69.06), (2.93 39.51), (2.52 39.52), (1.73 27.77), (1.43 22.29), (1.38 28.04). HRMS-ESI (m/z): Calcd. for $[C_{17}H_{24}N_2O_7+H]^+$: 367.1512. Found : 367.1505. DOI: 10.14469/hpc/5152

(4-Amino-3-((5-((*tert*-butoxycarbonyl)amino)pentyl)oxy)benzoic acid (**S26**)



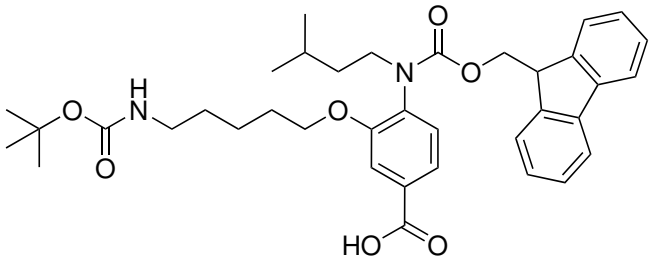
S26 was synthesised from **S25** (7.51 g, 20.40 mmol) using general procedure F. Residue triturated with dichloromethane to afford the title product as a white solid (5.67 g, 82%). Rf (CH_2Cl_2:MeOH 97.5:2.5) = 0.30; ^{1}H NMR (400 MHz, DMSO-d_6): ν_{max}/cm^{-1} : 3468 (N-H), 2942 (O-H), 1668 (C=O), 1612, 1271; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 12.07 (s, 1H, O**H**), 7.34 (dd, J = 8.2, 1.8 Hz, 1H, ArC**H**), 7.26 (d, J = 1.8 Hz, 1H, Ar**C**H), 6.80 (t, J = 5.7 Hz, 1H, N**H**), 6.62 (d, J = 8.2 Hz, 1H, ArC**H**), 5.47 (s, 2H, N$\mathbf{H}_2$), 3.94 (t, J = 6.4 Hz, 2H, OC$\mathbf{H}_2CH_2$), 2.93 (td, J = 6.8, 6.3 Hz, 2H, NC$\mathbf{H}_2CH_2$), 1.72 (tt, J = 10.3, 6.4 Hz, 2H, $OCH_2C\mathbf{H}_2CH_2$), 1.45 1.40 (m, 4H, $OCH_2CH_2C\mathbf{H}_2CH_2$), 1.36 (s, 9H, $(C\mathbf{H}_3)_3$; ^{13}C NMR (400 MHz, DMSO-d_6): δ_C 168.0 (**C**=O), 156.0 (N**C**=O), 144.8 (Ar**C**O), 143.3 (Ar**C**N), 124.4 (Ar**C**H), 117.7 (Ar**C**), 112.5 (Ar**C**H), 112.2 (Ar**C**H), 77.8 (**C**$(CH_3)_3$)), 68.1 (OC$\mathbf{H}_2CH_2$), 40.0 (NHC$\mathbf{H}_2CH_2$, HSQC), 29.7 ($OCH_2C\mathbf{H}_2$), 28.9 ($NHCH_2C\mathbf{H}_2$), 28.7 (($C\mathbf{H}_3)_3$), 23.3 (($OCH_2CH_2C\mathbf{H}_2$); ^{1}H-^{13}C NMR ((400, 101) MHz, DMSO-d_6) $\delta_{H/C}$ (7.35 124.19), (7.27 112.27), (6.64 112.49), (3.95 68.13), (2.95 39.97), (1.75 29.06), (1.38 28.61); HRMS-ESI (m/z): Calcd. for $[C_{17}H_{27}N_2O_5$-H]$^-$: 339.1912. Found : 339.1920. DOI: 10.14469/hpc/5153

3-((5-((*tert*-Butoxycarbonyl)amino)pentyl)oxy)-4-(isopentylamino)benzoic acid (S27)



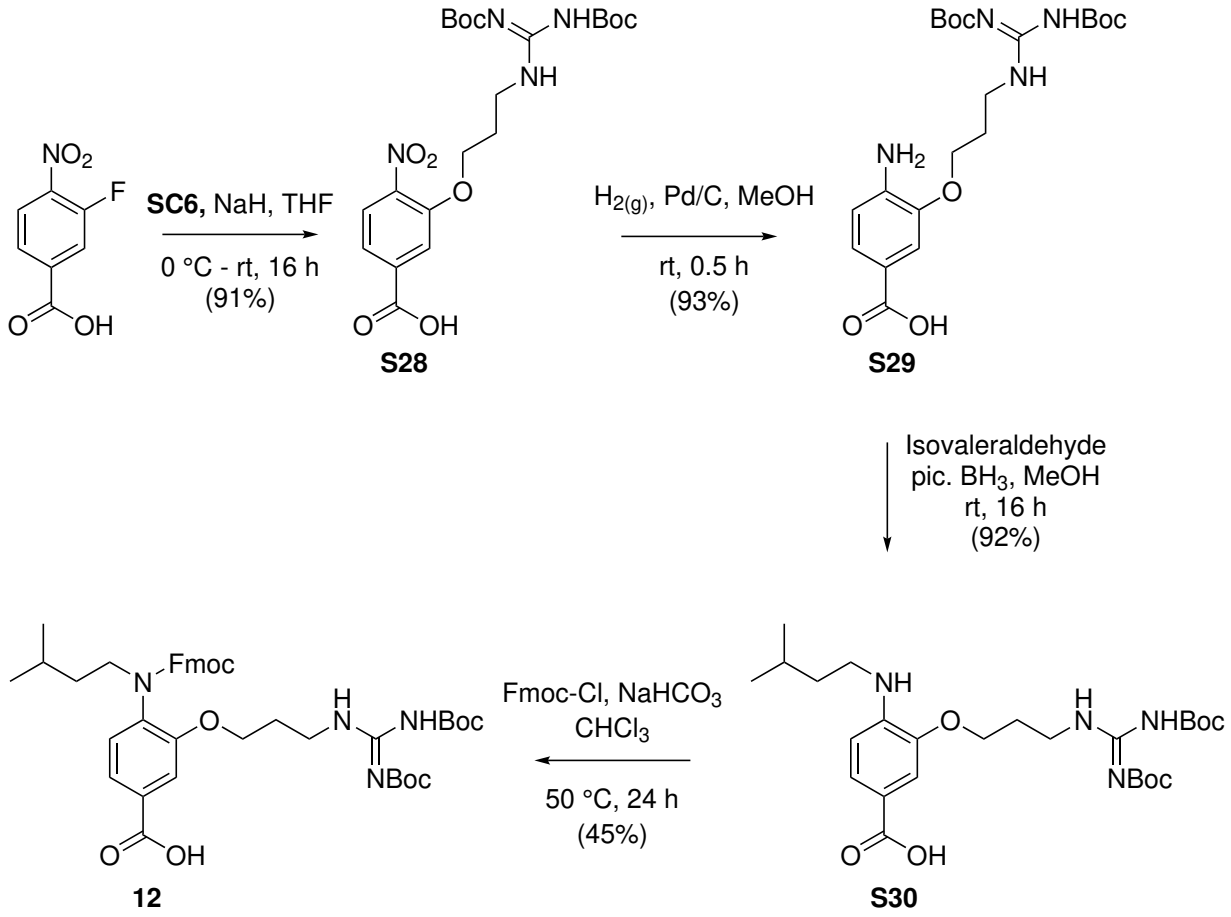
S27 was synthesised from **S26** (3.00 g, 8.90 mmol) using general procedure G. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as a white solid (2.29 g, 63%). R_f (CH_2Cl2:MeOH, 97.5, 2.5 = 0.4; ν_{max}/cm^{-1} : 3440 (N-H), 1662 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.70 (dd, J = 8.4, 1.8 Hz, 1H, ArC**H**), 7.41 (d, J = 1.8 Hz, 1H, ArC**H**), 6.54 (d, J = 8.5 Hz, 1H, ArC**H**), 4.56 (s, 1H, N**H**), 4.04 (t, J = 6.5 Hz, 2H, OC$\mathbf{H}_2$), 3.27 3.10 (m, 4H, C$\mathbf{H}_2$NHC=O & NHC$\mathbf{H}_2$), 1.84 (dt, J = 6.7 Hz, 2H, $OCH_2\mathbf{C}H_2CH_2$), 1.72 (sep, J = 6.7 Hz, 1H, $OCH_2C\mathbf{H}(CH_3)_2$), 1.62 1.38 (m, 13H, $(C\mathbf{H}_3)_3$ & 2 x CH_2), 0.97 (d, J = 6.6 Hz, 6H, $OCH_2CH(C\mathbf{H}_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 172.0 (**C**=O), 156.0 (N**C**=O), 144.7 (Ar**C**O), 143.4 (Ar**C**N), 125.7 (Ar**C**H), 115.8 (Ar**C**), 111.0 (Ar**C**H), 107.6 (Ar**C**H), 79.2 (O**C**$(CH_3)_3$), 68.2 ($O\mathbf{C}H_2CH_2$), 41.3 (NC=O$\mathbf{C}H_2$), 40.5 (NH$\mathbf{C}H_2CH_2$), 38.2, 29.9, 28.9, 28.4 (OC($\mathbf{C}H_3)_3$), 26.1, 23.4 ($NHCH_2CH_2\mathbf{C}H(CH_3)_2$), 22.6 ($NHCH_2CH_2CH(\mathbf{C}H_3)_2$); HRMS-ESI ($m/z$): Calcd. for $[C_{22}H_{36}N_2O_5+H]^+$: 409.2710. Found : 409.2702. DOI: 10.14469/hpc/5154

4-((((9H-Fluoren-9-yl)methoxy)carbonyl)(isopentyl)amino)-3-((5-((*tert*-butoxycarbonyl)amino)pentyl)oxy)benzoic acid (11)

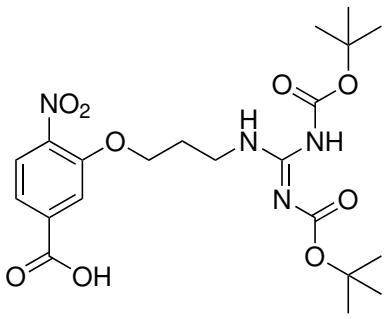


11 was synthesised from **S27** (1.57 g, 2.50 mmol) using general procedure H. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 15 CV] to afford the title compound as an amorphous pale yellow solid (1.35 g, 86%); R_f (CH_2Cl_2) = 0.25; ν_{max}/cm^{-1}: 2932, 1702, 1277, 1171, 1512; ^{1}H NMR (400 MHz, DMSO-d6, 373 K): δ_H 7.74 (d, J = 7.7 Hz, 2H, 2 x ArC**H** Fmoc), 7.56 7.50 (m, 2H, 2 x ArC**H**), 7.35 (d, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.28 (br, 2H, 2 x ArC**H** Fmoc), 7.20 (t, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.12 (d, J = 7.2 Hz, 1H, ArC**H**), 4.32 (d, J = 6.5 Hz, 2H, OC**H**$_2$CH Fmoc), 4.07 (t, J = 6.3 Hz, 1H, OCH$_2$C**H** Fmoc), 3.94 (t, J = 6.4 Hz, 2H, O**C**H$_2$CH$_2$), 3.48 (d, J = 8.0 Hz, 2H, ArNC**H**$_2$), 2.98 (q, J = 6.6 Hz, 1H), 2.94 2.87 (m, 3H), 1.70 1.60 (m, 2H), 1.56 1.41 (m, 3H), 1.37 (d, J = 0.4 Hz, 9H, (C**H**$_3$)$_3$), 1.35 1.23 (m, 2H), 0.80 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d6, 373 K): δ_C 166.2 (**C**=O), 155.0 (**C**=O), 154.1 (**C**=O), 143.2 (Ar**C**), 140.3 (Ar**C**), 133.9, 130.6, 128.9, 126.9, 126.2, 124.2, 121.1, 119.3, 119.1, 113.2, 76.9 (**C**(CH$_3$)$_3$)), 67.8 (O**C**H$_2$CH$_2$), 66.2 (O**C**H$_2$CH Fmoc), 63.5, 49.9, 46.9, 46.3, 36.2, 28.5, 27.8 ((**C**H$_3$)$_3$), 24.6, 22.2, 21.6 (ArNCH$_2$CH$_2$CH(**C**H$_3$)$_2$). HRMS-ESI (m/z): Calcd. for [$C_{37}H_{46}N_2O_7$+H]$^+$: 631.3383. Found: 631.3372. DOI: 10.14469/hpc/5155

Synthesis of 12



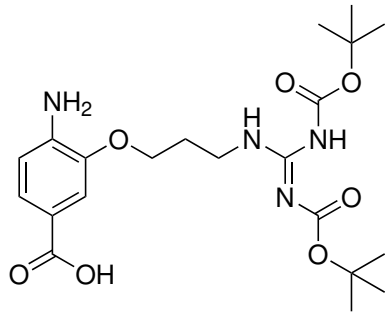
(Z)-3-(3-(2,3-Bis(*tert*-butoxycarbonyl)guanidino)propoxy)-4-nitrobenzoic acid (S28)



S28 was synthesised from 3-fluoro-4-nitrobenzoic acid (1.00 g, 5.30 mmol) using general procedure C. Purification by column chromatography [SiO_2, EtOAc:AcOH, 100:0.1] afforded the title product as a pale yellow solid (2.38 g, 91%). R*f* (EtOAc:AcOH, 100:0.1) = 0.3;

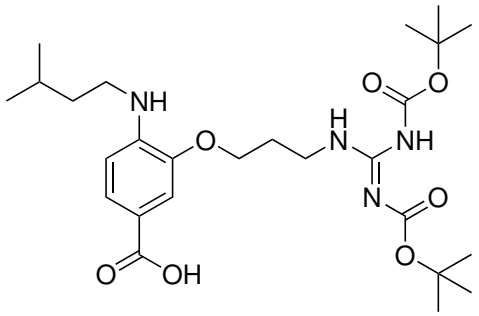
ν_{max}/cm^{-1} : 3289 (O-H), 2976, 1723 (C=N), 1684 (C=O), 1606, 1522 (NO_2), 1282, 1343, 1131; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.44 (s, 1H, N**H**), 8.64 (s, 1H, N**H**), 7.77 (d, J = 8.3 Hz, 1H, ArC**H**), 7.70 (d, J = 1.4 Hz, 1H, ArC**H**), 7.67 (dd, J = 5.1, 1.5 Hz, 1H, ArC**H**), 4.18 (t, J = 5.9 Hz, 2H, OC$\mathbf{H}_2$), 3.68 - 3.63 (m, 4.9 Hz, 2H, NC$\mathbf{H}_2$), 2.17 (p, J = 5.9 Hz, 2H, $OCH_2C\mathbf{H}_2$), 1.49 (s, 9H, $(C\mathbf{H}_3)_3$), 1.46 (d, J = 1.2 Hz, 9H, $(C\mathbf{H}_3)_3$); HRMS-ESI (*m/z*): Calcd. for $[C_{21}H_{30}N_4O_9+H]^+$: 483.2091. Found : 483.2079. DOI: 10.14469/hpc/5156

(Z)-4-Amino-3-(3-(2,3-bis(*tert*-butoxycarbonyl)guanidino)propoxy)benzoic acid (S29)



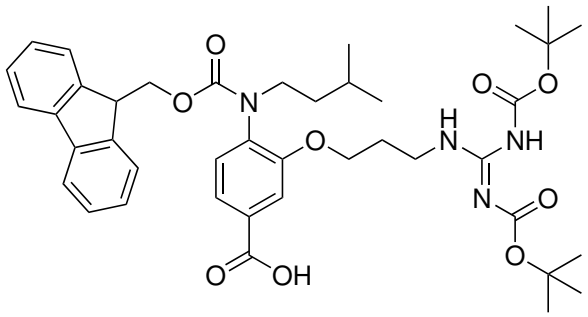
S29 was synthesised from **S28** (2.38 g, 4.91 mmol) using general procedure F. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as a white solid (2.07 g, 93%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.4; ν_{max}/cm^{-1} : 3334 (N-H), 2982 (O-H), 1724 (C=N), 1618 (C=O), 1131; ^{1}H NMR (400 MHz, $CDCl_3$): δ11.51 (s, 1H, N**H**), 8.52 (t, J = 5.7 Hz, 1H, N**H**), 7.64 (dd, J = 8.2, 1.7 Hz, 1H, ArC**H**), 7.50 (d, J = 1.7 Hz, 1H, ArC**H**), 6.69 (d, J = 8.2 Hz, 1H, ArC**H**), 4.18 (t, J = 5.7 Hz, 2H, $OC\mathbf{H}_2CH_2$), 3.69 (q, J = 6.6 Hz, 2H, $NC\mathbf{H}_2CH_2$), 3.65 3.56 (br m, 1H, $N\mathbf{H}CH_2$), 2.12 (p, J = 6.5 Hz, 2H, $OCH_2C\mathbf{H}_2$), 1.52 (s, 9H, $(C\mathbf{H}_3)_3$), 1.51 (s, 9H, $(C\mathbf{H}_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 171.5 (**C**=N), 163.4 (**C**=O), 156.2 (N**C**=O), 153.3 (N**C**=O), 145.0 (Ar**C**O), 142.2 (Ar**C**N), 125.3 (Ar**C**H), 118.2 (Ar**C**), 113.2 (Ar**C**H), 112.6 (Ar**C**H), 83.3 ($\mathbf{C}(CH_3)_3$), 79.4 ($\mathbf{C}(CH_3)_3$), 66.4 ($O\mathbf{C}(CH_3)_3$), 38.6 ($NH\mathbf{C}H_2$), 28.8 ($(C\mathbf{H}_3)_3$), 28.3 ($OCH_2C\mathbf{H}_2CH_2$), 28.1 ($(C\mathbf{H}_3)_3$), 28.1 ($NCH_2CH_2C\mathbf{H}_2CH_2$); HRMS-ESI (*m/z*): Calcd. for $[C_{21}H_{33}N_4O_7+H]^-$: 453.2349. Found: 453.2355. DOI: 10.14469/hpc/5157

(Z)-3-(3-(2,3-Bis(*tert*-butoxycarbonyl)guanidino)propoxy)-4-(isopentylamino) benzoic acid (S30)



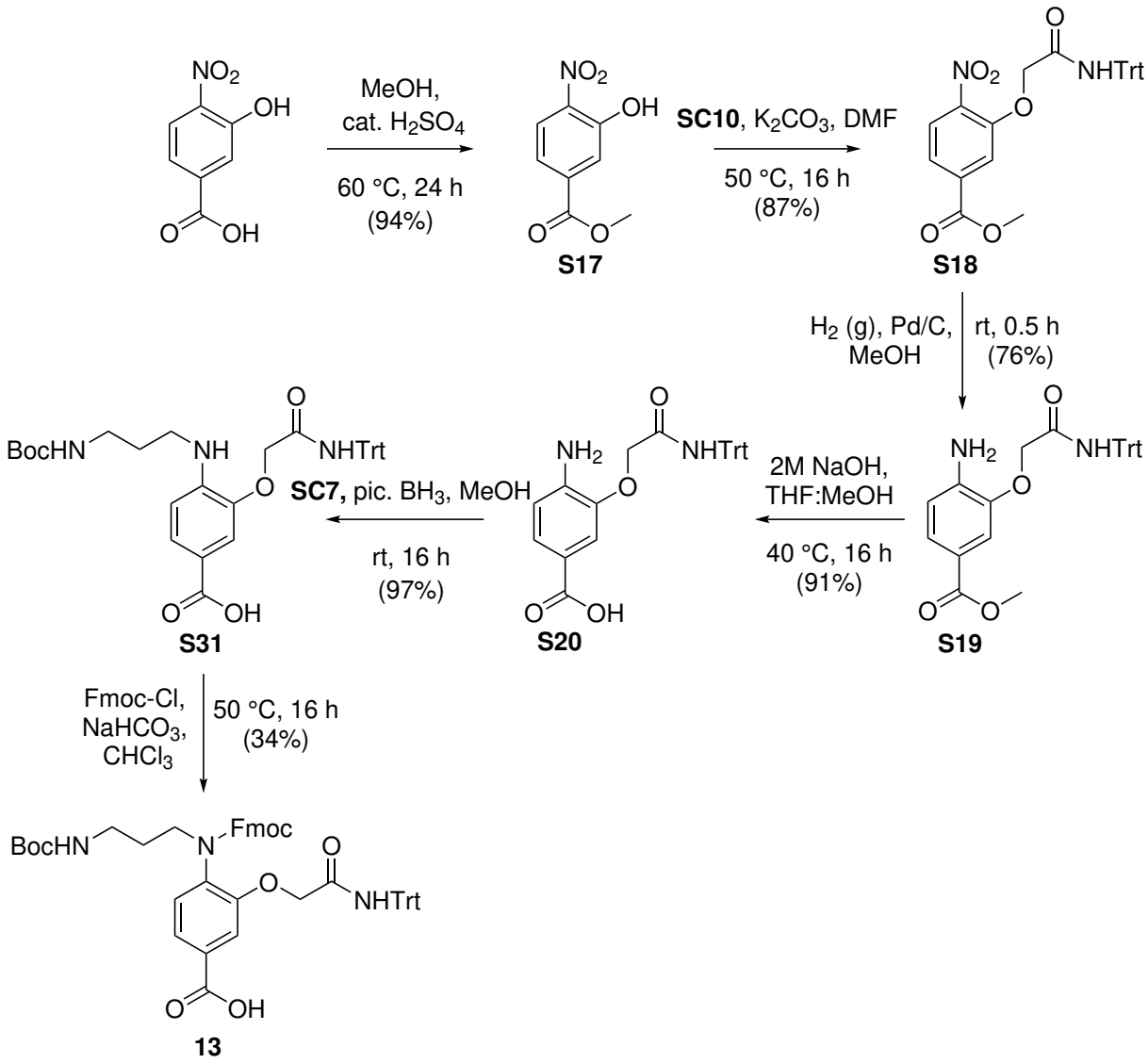
S30 was synthesised from **S29** (0.56 g, 1.23 mmol) using general procedure G. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as a white solid (0.59g, 92%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 11.46 (s, 1H, N**H**), 8.46 (t, J = 5.3 Hz, 1H, N**H**), 7.71 (dd, J = 8.3, 1.8 Hz, 1H, ArC**H**), 7.43 (d, J = 1.8 Hz, 1H, ArC**H**), 6.54 (d, J = 8.4 Hz, 1H, ArC**H**), 4.14 (t, J = 6.0 Hz, 2H, OC$\mathbf{H}_2$), 3.64 (dt, J = 6.7, 5.5 Hz, 2H, $OCH_2CH_2C\mathbf{H}_2NH$), 3.21 (t, J = 7.5 Hz, 2H, $ArNHC\mathbf{H}_2$), 2.15 2.09 (m, 2H, $OCH_2C\mathbf{H}_2CH_2NH$), 1.78 1.65 (m, 1H, $NHCH_2C\mathbf{H}_2C\mathbf{H}(CH_3)_2$), 1.62 1.45 (m, 20H, 2 x $(C\mathbf{H}_3)_3$ & $ArNHCH_2C\mathbf{H}_2$), 1.01 0.93 (m, 6H, $ArNHCH_2CH_2CH(C\mathbf{H}_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 172.2 (**C**=O), 163.5 (**C**=N), 156.3 (**C**=O), 153.3 (**C**=O), 144.5 (Ar**C**O), 143.3 (Ar**C**N), 125.9 (Ar**C**H), 115.8 (Ar**C**), 111.2 (Ar**C**H), 107.7 (Ar**C**H), 83.2 ($O\mathbf{C}(CH_3)_3$), 79.3 ($O\mathbf{C}(CH_3)_3$), 66.0 ($O\mathbf{C}H_2CH_2$), 41.3, 38.2, 38.1, 28.8 ($OC(\mathbf{C}H_3)_3$), 28.3, 28.1 ($OC(\mathbf{C}H_3)_3$), 26.1, 22.6 ($NHCH_2CH_2CH(\mathbf{C}H_3)_2$); LRMS ($m/z$): Calcd. for $[C_{26}H_{42}N_4O_7+H]^+$: 523.313. Found : 523.381. DOI: 10.14469/hpc/5158

(Z)-4-((((9H-Fluoren-9-yl)methoxy)carbonyl)(isopentyl)amino)-3-(3-(2,3-bis (*tert*-butoxycarbonyl)guanidino)propoxy)benzoic acid (12)

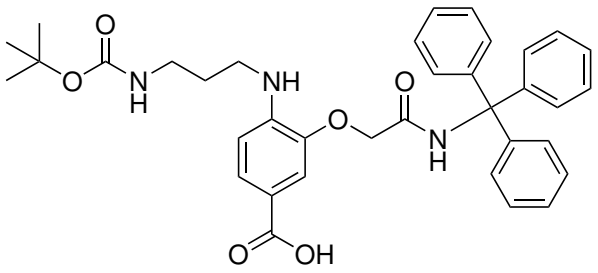


12 was synthesised from **S30** (0.40 g, 0.76 mmol) using general procedure H. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 100:0 to 95:5 over 15 CV] to afford the title compound as an amorphous, pale pink solid (0.26 g, 45%). Compound unstable at temperature required to resolve the NMR spectrum. R_f (CH_2Cl_2:MeOH, 97.2:2.5) = 0.35; ν_{max}/cm^{-1} : 2954, 1707, 1612, 1282, 1131; ^{1}H NMR (500 MHz, DMSO-d_6, 353 K): δ_H 11.34 (s, 1H, N**H**), 8.20 (s, 1H, N**H**), 7.75 (d, J = 7.6 Hz, 2H, 2 x ArC**H** Fmoc), 7.57 7.48 (m, 2H, 2 x ArC**H**), 7.37 7.24 (m, 4H, 4 x ArC**H**), 7.19 (t, J = 7.3 Hz, 2H, 2 x ArC**H** Fmoc), 7.11 (d, J = 8.0 Hz, 1H, ArC**H**), 4.33 (br, 2H, OC$\mathbf{H}_2$CH Fmoc), 4.05 (br, 1H, OCH_2C**H** Fmoc), 4.00 (t, J = 6.3 Hz, 2H, OC$\mathbf{H}_2CH_2$), 3.47 (br, 2H, ArNC$\mathbf{H}_2$), 3.40 (t, J = 6.8 Hz, 2H, OCH_2CH_2C$\mathbf{H}_2$), 1.91 (p, J = 6.6 Hz, 2H, OCH_2C$\mathbf{H}_2CH_2$), , 1.39 (br, J = 12.3 Hz, 19H, 2 x C(C$\mathbf{H}_3$)$_3$ & $ArNCH_2CH_2$C**H**), 1.26 (br, J = 6.0 Hz, 2H, $ArNCH_2$C$\mathbf{H}_2$CH), 0.79 (d, J = 6.5 Hz, 6H, (C$\mathbf{H}_3$)$_2$); ^{13}C NMR (126 MHz, DMSO-d_6, 323 K): δ167.3 (**C**=O), 163.5 (**C**=N), 155.8 (**C**=O), 154.9, 154.6, 152.4, 144.0, 141.1, 134.2, 131.4, 129.9 (Ar**C**H), 127.9, 127.2, 125.4, 122.2 (Ar**C**H), 120.4 (Ar**C**H Fmoc), 113.6 (Ar**C**H), 83.2 (**C**CH_3), 78.4 (**C**CH_3), 67.1 (O**C**H_2CH_2), 66.2 (O**C**H_2CHFmoc), 47.6 (ArN**C**H_2CH_2), 46.9 (OCH_2**C**H Fmoc), 37.7 (OCH_2CH_2**C**H_2), 37.0 (OCH_2**C**H_2CH_2), 28.9 ($ArNCH_2CH_2$**C**H), 28.4 (C(**C**H_3)$_3$), 28.0 (C(**C**H_3)$_3$), 25.5 ($ArNCH_2$**C**H_2CH), 22.8 ((**C**H_3)$_2$); HRMS-ESI (*m/z*): Calcd. for $[C_{41}H_{52}N_4O_9+H]^+$: 745.3813. Found: 745.3820. DOI: 10.14469/hpc/5159

Synthesis of 13

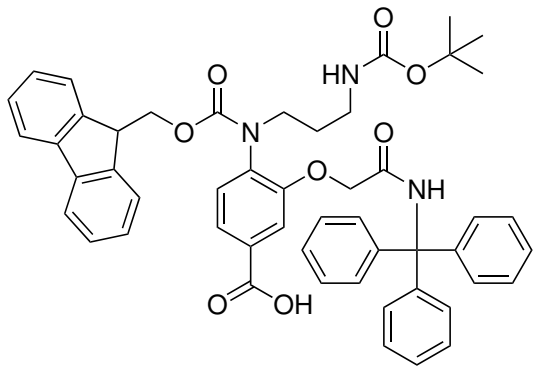


4-((3-((*Tert*-butoxycarbonyl)amino) propyl)amino)-3-(2-oxo-2-(tritylamino)ethoxy) benzoic acid (S31)



S31 was synthesised from **S20** (0.50g, 1.12 mmol) using general procedure G. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the title compound as a colourless oil (0.66 g, 97%). R_f (CH_2Cl_2:MeOH, 97.5:2.5) = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.77 (d, J = 8.5 Hz, 1H, ArC**H**), 7.56 (d, J = 2.4 Hz, 1H, ArC**H**), 7.35 – 7.16 (m, 15H, trityl), 6.62 (d, J = 8.5 Hz, 1H, ArC**H**), 4.82 (br, 1H, N**H**), 4.64 (s, 2H, OC$\mathbf{H}_2$), 3.68 (t, J = 5.7 Hz, 2H, NC$\mathbf{H}_2$), 3.31 (q, J = 6.3 Hz, 2H, ArNCH_2CH_2C$\mathbf{H}_2$NH), 1.73 – 1.64 (m, 2H, ArNCH_2C$\mathbf{H}_2$CH_2), 1.47 (s, 9H, (C$\mathbf{H}_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 170.6 (**C**=O), 166.9 (**C**=O), 144.3 (Ar**C**), 143.4 (Ar**C**), 128.7, 128.7, 128.6 (Ar**C** trityl), 128.1 (Ar**C** trityl), 128.0, 127.2, 126.9, 113.0 (Ar**C**H), 108.8 (Ar**C**H), 70.4 (**C**(C_6H_5)$_3$), 68.7 (O**C**H_2), 59.2 (ArN**C**H_2), 36.9 (ArNCH_2CH_2**C**H_2), 32.9 (ArNCH_2**C**H_2CH_2), 28.4 (C(**C**H_3)$_3$); LRMS-ESI (*m/z*); Calcd. for $[C_{36}H_{39}N_3O_6+H]^+$: 610.291. Found: 610.389. DOI: 10.14469/hpc/5160

4-((((9H-Fluoren-9-yl)methoxy)carbonyl)(3-((*tert*-butoxycarbonyl)amino) propyl)amino)-3-(2-oxo-2-(tritylamino)ethoxy)benzoic acid (13)

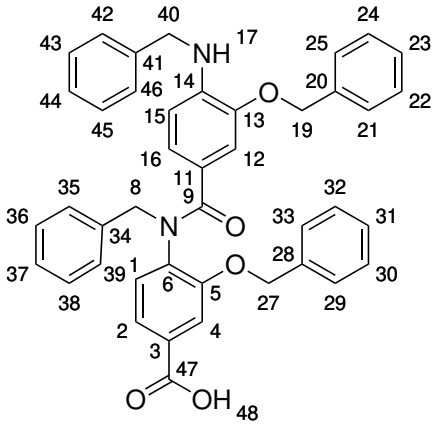


13 was synthesised from **S31** (0.50 g, 0.82 mmol) using general procedure H. Purified by column chromatography [SiO2, CH_2Cl_2:MeOH, 100:0 to 95:5 over 10 CV] to afford the title compound as a pale yellow oil. An alcohol by-product could not be separated from the title compound. R_f (CH_2Cl_2) = 0.45; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 8.10 (s, 1H, N**H**), 7.76 (dt, J = 7.5, 0.9 Hz, 2H, ArC**H** Fmoc), 7.60 – 7.55 (m, 2H, A x ArC**H**), 7.37 – 7.31 (m, 2H, ArC**H** Fmoc), 7.27 – 7.13 (m, 20H, trityl & 5 x ArC**H**), 6.12 (s, 1H, N**H**), 4.61 (s, 2H, OC$\mathbf{H}_2$), 4.23 (d, J = 6.7 Hz, 2H, OC$\mathbf{H}_2$CH), 4.03 (t, J = 6.9 Hz, 1H, OCH_2C**H**), 3.50 (q, J = 7.3,

5.2 Hz, 2H, ArNC$\mathbf{H}_2$), 2.88 (qd, J = 7.1, 5.8 Hz, 2H, ArNCH$_2$CH$_2$C$\mathbf{H}_2$), 1.55 1.51 (m, 2H, ArNCH$_2$C$\mathbf{H}_2$CH$_2$), 1.35 (s, 9H, (C$\mathbf{H}_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d$_6$, 373 K): δ_C 166.2 (**C**=O), 155.5 (**C**=O), 155.4 (**C**=O), 154.5 (**C**=O), 153.3, 144.3, 143.6, 140.7, 133.9, 131.2, 129.5, 128.4, 128.3, 127.5, 127.4, 127.3 (Ar**C**H Fmoc), 126.7, 126.5, 124.7, 122.3 (Ar**C**H), 119.8 (Ar**C**H Fmoc), 113.9 (Ar**C**H), 77.3 (**C**(CH$_3$)$_3$), 69.5 (**C**(C$_6$H$_5$)$_3$), 67.8 (O**C**H$_2$), 66.8 (O**C**H$_2$CHFmoc), 46.9 (OCH$_2$**C**HFmoc), 46.6 (ArN**C**H$_2$), 37.5 (ArNCH$_2$CH$_2$**C**H$_2$), 32.8 (ArNCH$_2$**C**H$_2$CH$_2$), 28.2 (C(**C**H$_3$)$_3$); HRMS-ESI (*m/z*): Calcd. for [C$_{51}$H$_{49}$N$_3$O$_8$+H]$^+$: 832.3598. Found: 832.3593. DOI: 10.14469/hpc/5161

Oligomer Synthesis

4-(*N*-benzyl-4-(benzylamino)-3-(benzyloxy)benzamido)-3-(benzyloxy)benzoic acid (**14**)



Synthesised on a 30 µmol scale using the general procedure for oligomer formation using double couplings as standard. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the product as a colourless oil (8.2 mg, 42%). R_f (CH_2Cl_2) = 0.65; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.57 7.52 (m, 2H, $\mathbf{H_{2/4}}$), 7.34 7.17 (m, 20H, ArC**H**), 7.02 (d, J = 8.0 Hz, 1H, $\mathbf{H_1}$), 6.97 (d, J = 1.8 Hz, 1H, $\mathbf{H_{12}}$), 6.83 (dd, J = 8.3, 1.9 Hz, 1H, $\mathbf{H_{16}}$), 6.24 (d, J = 8.3 Hz, 1H, $\mathbf{H_{14}}$), 5.06 (br, 2H, H_{27}), 4.84 (s, 2H, $\mathbf{H_{19}}$), 4.71 (s, 2H, $\mathbf{H_8}$), 4.28 (s, 2H, $\mathbf{H_{40}}$); HRMS-ESI (*m/z*): Calcd. for $[C_{22}H_{28}N_2O_5+H]^+$ 649.2702. Found: 649.2721. DOI: 10.14469/hpc/5163

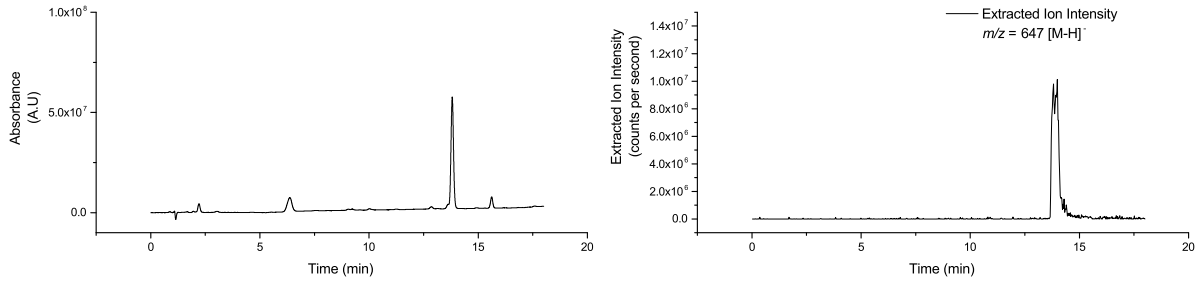
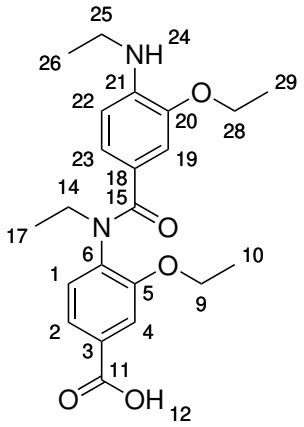


Figure S31: UV chromatogram and extracted ion chromatogram of **14**

3-ethoxy-4-(3-ethoxy-*N*-ethyl-4-(ethylamino)benzamido)benzoic acid (15)



Synthesised on a 30 µmol scale using using the general procedure for oligomer formation using double couplings as standard. R_f (CH_2Cl_2) = 0.50; Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 10 CV] to afford the product as a colourless oil (2.8 mg, 23%).; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.58 (dd, J = 8.0, 1.7 Hz, 1H, $\mathbf{H_2}$), 7.52 (d, J = 1.7 Hz, 1H, $\mathbf{H_4}$), 7.10 (d, J = 8.0 Hz, 1H, $\mathbf{H_1}$), 6.88 (dd, J = 8.2, 1.9 Hz, 1H, $\mathbf{H_{23}}$), 6.84 (d, J = 1.8 Hz, 1H, $\mathbf{H_{19}}$), 6.26 (d, J = 8.3 Hz, 1H, $\mathbf{H_{22}}$), 3.99 (q, J = 6.8 Hz, 2H, $\mathbf{H_9}$), 3.89 3.82 (m, 4H, $\mathbf{H_{14/28}}$), 3.09 (q, J = 7.2 Hz, 2H, $\mathbf{H_{25}}$), 1.38 (t, J = 6.9 Hz, 3H, H_{10}), 1.30 (t, J = 7.0 Hz, 3H, $\mathbf{H_{29}}$), 1.21 (t, J = 7.2 Hz, 3H, $\mathbf{H_{17}}$), 1.18 (t, J = 7.1 Hz, 3H, $\mathbf{H_{26}}$); HRMS-ESI (*m/z*): Calcd. for $[C_{42}H_{36}N_2O_5+H]^+$: 401.2076. Found: 401.2093. DOI: 10.14469/hpc/5164

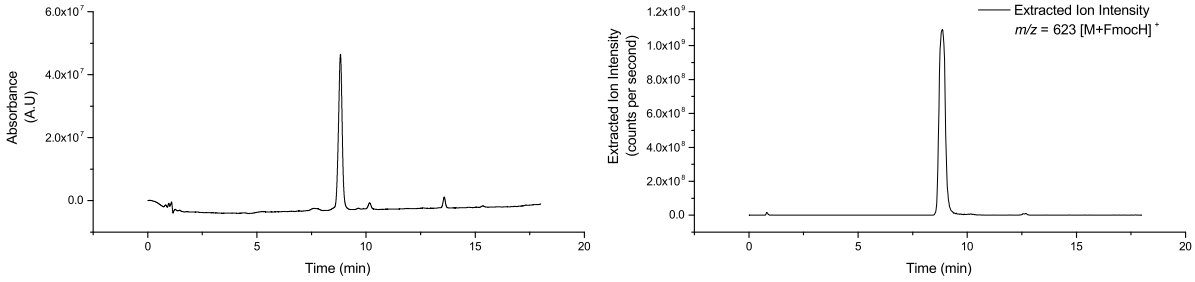
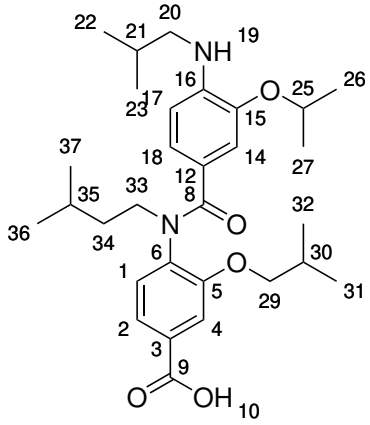


Figure S32: UV chromatogram and extracted ion chromatogram of **15**

3-isobutoxy-4-(4-(isobutylamino)-*N*-isopentyl-3-isopropoxybenzamido)benzoic acid (16)



Synthesised on a 30 µmol scale using the general procedure for oligomer formation using double couplings as standard. Purified by column chromatography [SiO_2, CH_2Cl_2:MeOH, 10:0 to 9:1 over 20 CV] to afford the title compound as a white solid (6.2 mg, 40%). R_f (CH_2Cl_2) = 0.60. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.56 (dd, J = 8.2, 1.7 Hz, 1H, $\mathbf{H_2}$), 7.52 (d, J = 1.8 Hz, 1H, $\mathbf{H_4}$), 7.08 (d, J = 8.0 Hz, 1H, $\mathbf{H_1}$), 6.88 (dd, J = 8.3, 1.8 Hz, 1H, $\mathbf{H_{18}}$), 6.80 (d, J = 1.8 Hz, 1H, H_{14}), 6.37 (br, 1H, $\mathbf{H_{17}}$), 4.24 (hept, J = 6.3 Hz, 1H, $\mathbf{H_{25}}$), 4.02 3.51 (m, 4H, $\mathbf{H_{29\ \&\ 33}}$), 2.87 (d, J = 6.8 Hz, 2H, $\mathbf{H_{20}}$), 2.12 (hept, J = 6.7 Hz, 1H, $\mathbf{H_{30}}$), 1.87 (dt, J = 13.4, 6.7 Hz, 1H, $\mathbf{H_{21}}$), 1.73 1.38 (m, 3H, $H_{\mathbf{34\ \&\ 35}}$), 1.18 (d, J = 6.0 Hz, 6H, $\mathbf{H_{26\ \&\ 27}}$), 1.04 (d, J = 6.7 Hz, 6H, $\mathbf{H_{31\ \&\ 32}}$), 0.93 (d, J = 6.7 Hz, 6H, $\mathbf{H_{22\ \&\ 23}}$), 0.88 (d, J = 6.4 Hz, 6H, $\mathbf{H_{36\ \&\ 37}}$); HRMS-ESI (*m/z*): Calcd. for $[C_{30}H_{44}N_2O_5+H]^+$: 513.3328. Found: 513.3336. DOI: 10.14469/hpc/5165

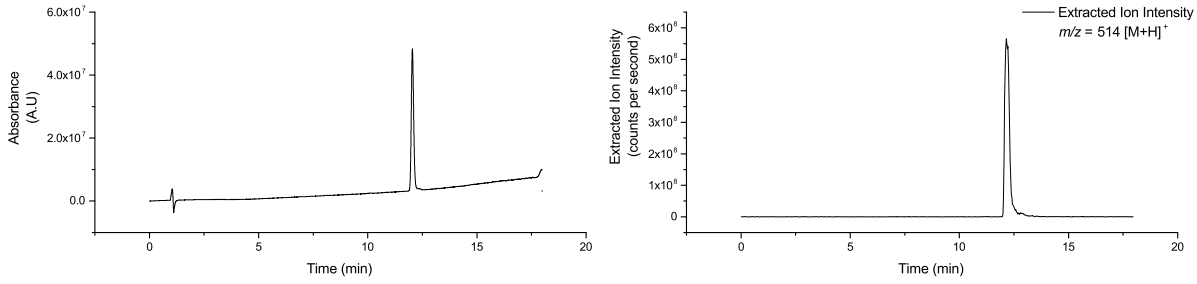
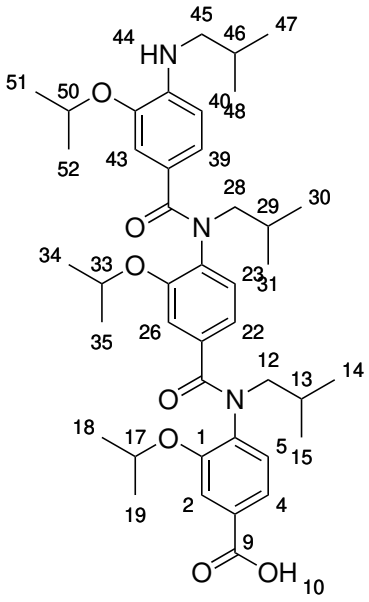


Figure S33: UV chromatogram and extracted ion chromatogram of **16**

Trimers

4-(*N*-Isobutyl-4-(*N*-isobutyl-4-(isobutylamino)-3-isopropoxybenzamido)-3-isopropoxybenzamido)-3-isopropoxybenzoic acid (**17**)



Synthesised on a 30 µmol scale using the general procedure for oligomer formation using double couplings as standard. Purified by column chromatography to afford the title compound as a white solid (2.14 mg, 10%). ^{1}H NMR (500 MHz, DMSO-d6, 398 K): $_{H}$ 7.42 (dd, J = 8.0, 1.7 Hz, 1H), 7.38 (d, J = 1.7 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.82 (dd, J = 8.1, 1.8 Hz, 1H), 6.71 6.67 (m, 3H), 6.28 (d, J = 8.1 Hz, 1H), 4.53 (hept, 1H), 4.22 (hept, J = 6.1 Hz, 1H), 4.15 (hept, J = 6.0 Hz, 1H), 3.60 (d, J = 7.0 Hz, 2H), 3.45 (d, J = 6.9 Hz, 2H), 2.90 (d, J = 6.7 Hz, 2H), 1.92 1.74 (m, 2H), 1.66 (d, J = 6.8 Hz, 1H), 1.19 (d, J = 6.0 Hz, 6H), 1.17 (d, J = 6.0 Hz, 6H), 1.05 (d, J = 6.0 Hz, 6H), 0.92 0.88 (m, 12H), 0.79 (d, J = 6.7 Hz, 6H); HRMS-ESI (*m/z*): Calcd. for $[C_{42}H_{59}N_3O_7+H]^+$ 718.4431. Found: 718.4445. DOI: 10.14469/hpc/5162

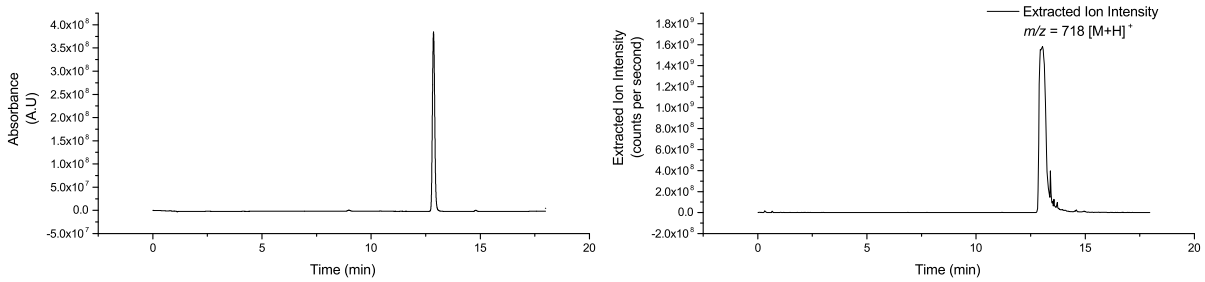
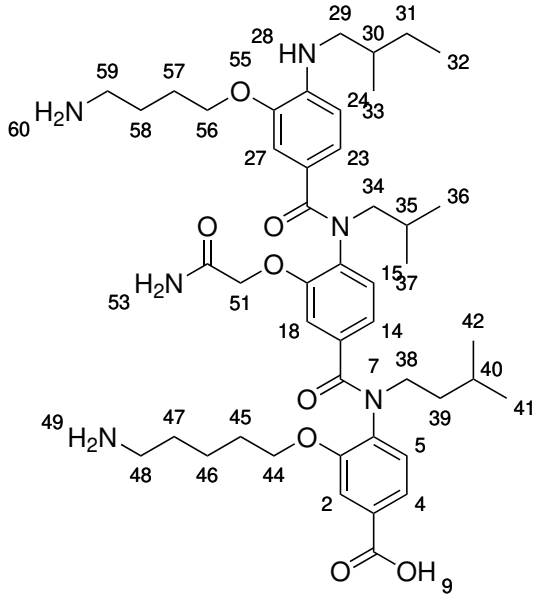


Figure S34: UV chromatogram and extracted ion chromatogram of **17**

4-(3-(2-Amino-2-oxoethoxy)-4-(3-(4-aminobutoxy)-*N*-isobutyl-4-((2-methylbutyl) amino)benzamido)-*N*-isopentylbenzamido)-3-((5-aminopentyl)oxy)benzoic acid (**18**)



Synthesised on a 20 µmol scale using the general procedure for oligomer formation using double couplings as standard. Cleavage and global deprotection was performed using Reagent K (TFA/TIPS/H_2O/thiosanisole/phenol/EDT, 82.5/5/5/5/2.5, 5 mL). After 1 h, the reaction column was evacuated and the TFA solution was concentrated to *ca.* 1 mL under a steady flow of nitrogen. The crude oligomer was precipitated via addition of ice-cold ether and subsequently isolated via centrifugation. Mass directed purification by RP LC-MS afforded the title compound as a white solid (0.42 mg, 2.5%). Not enough sample was recovered after mass directed purification to obtain a ^{1}H NMR spectrum. HRMS-ESI

(m/z): Calcd. for $[C_{46}H_{68}N_6O_8\text{-}H]^-$ 831.5020. Found: 831.5031.

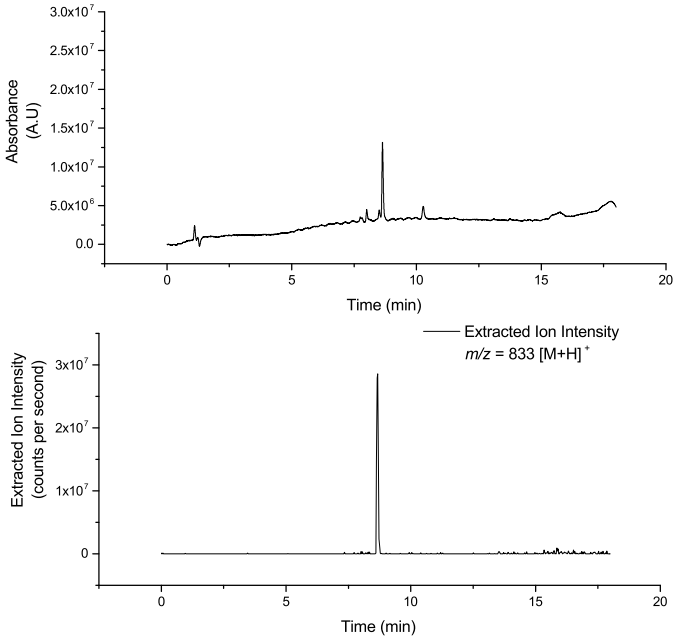


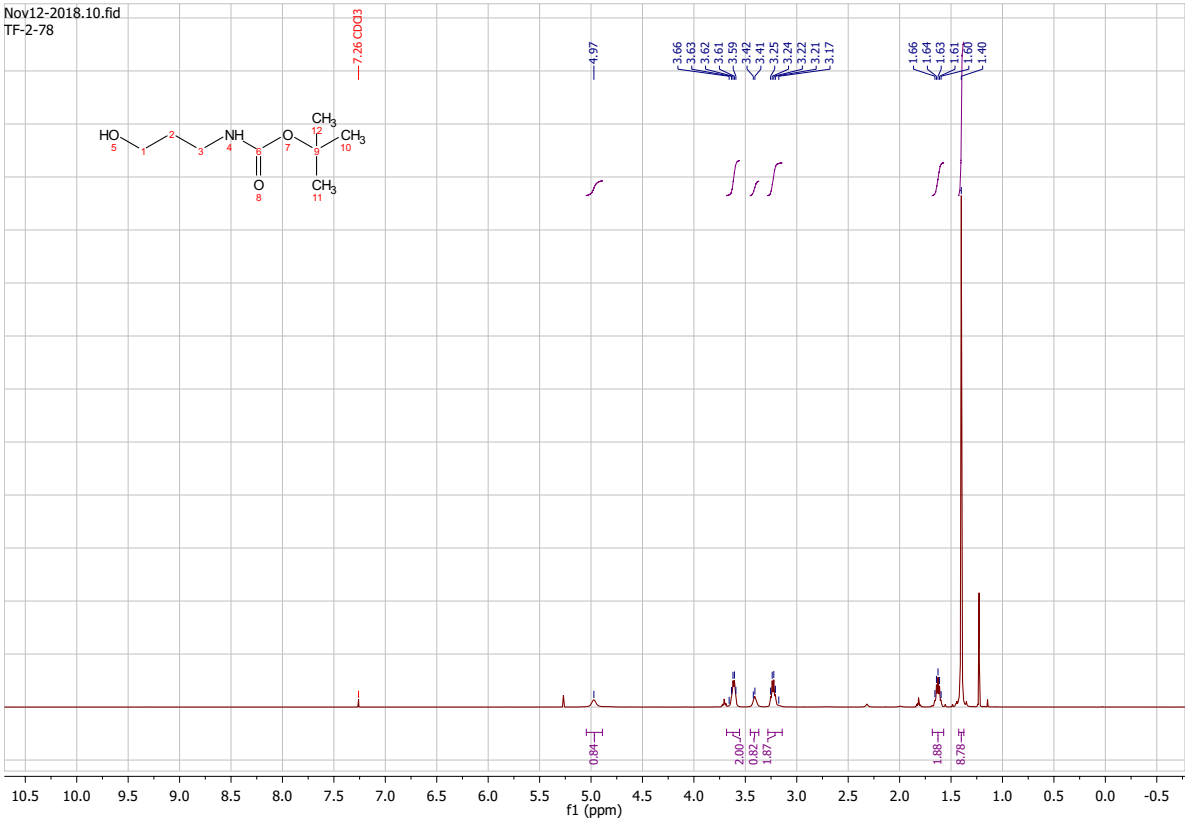
Figure S35: UV chromatogram and extracted ion chromatogram of **18**

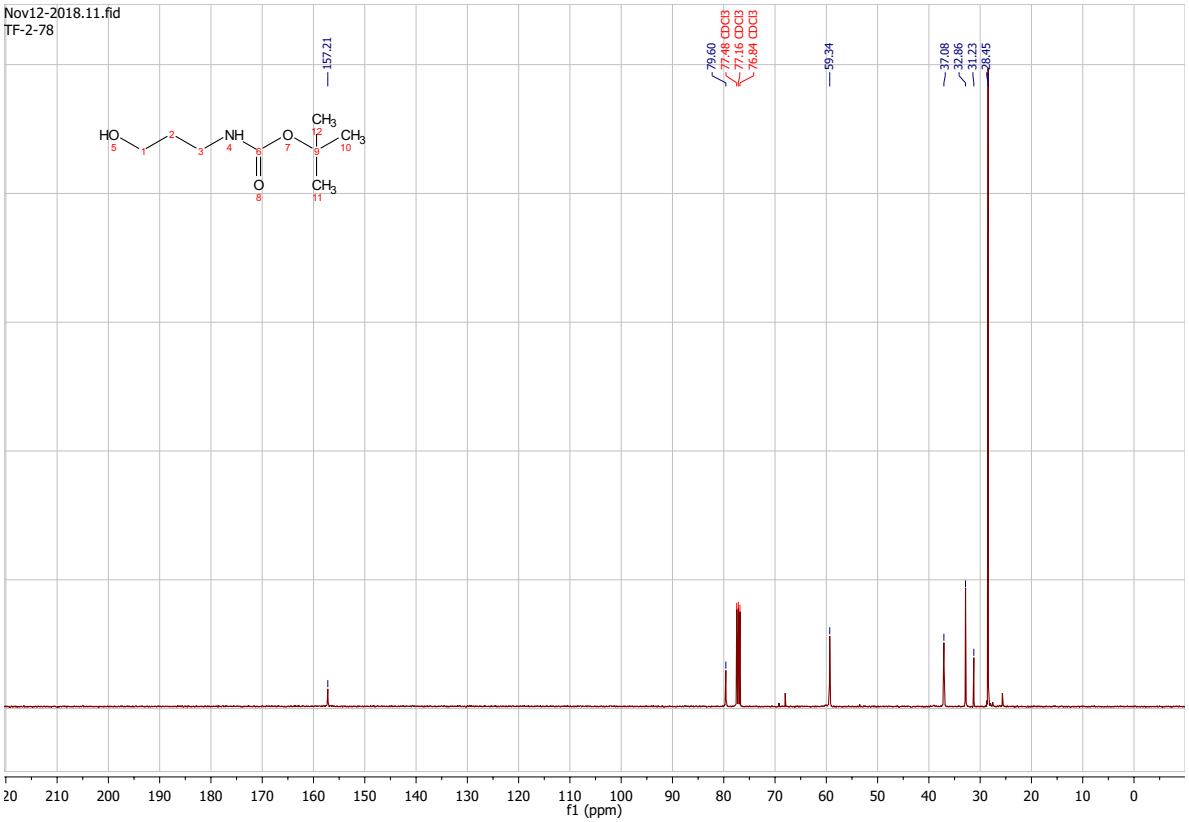
NMR Spectra

NMR Spectra files are available at the DOI links for each compound in the methods section above

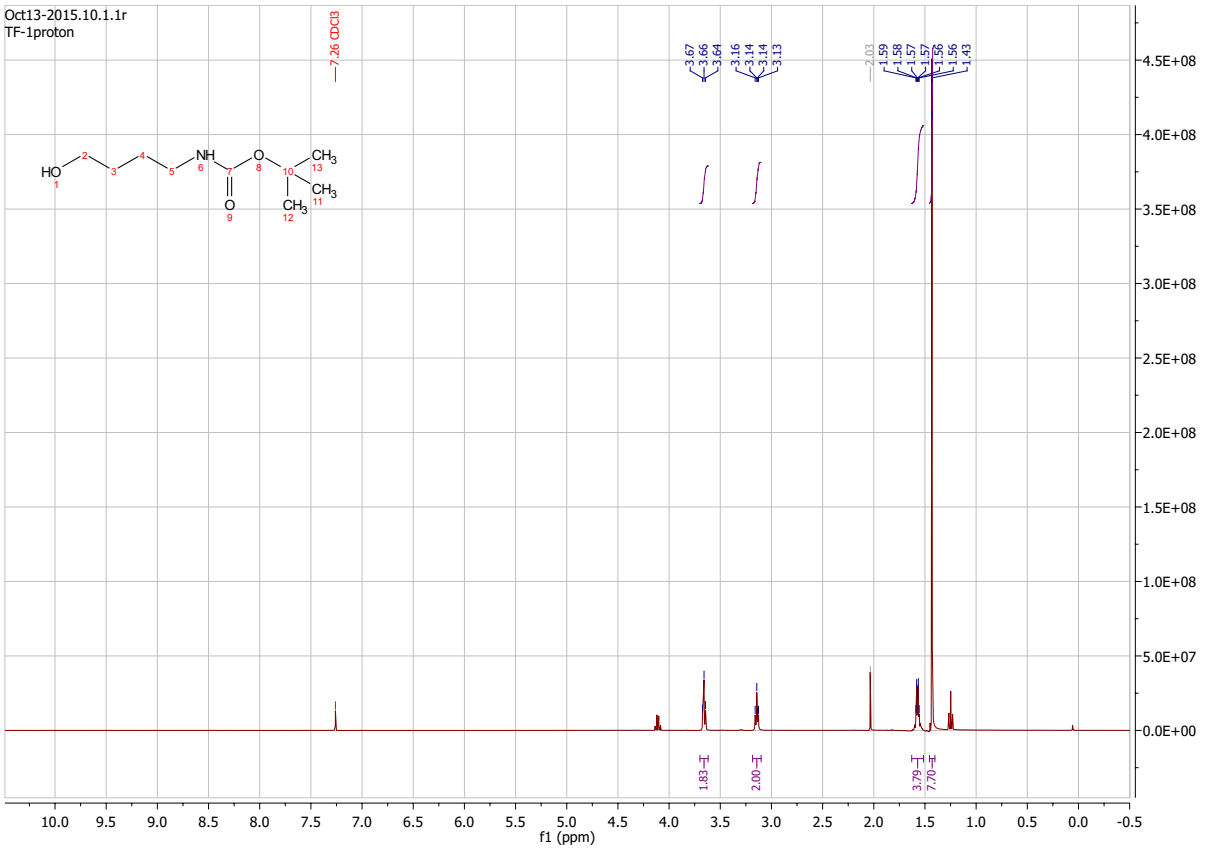
NMR Spectra for Sidechains (SC1-SC10)

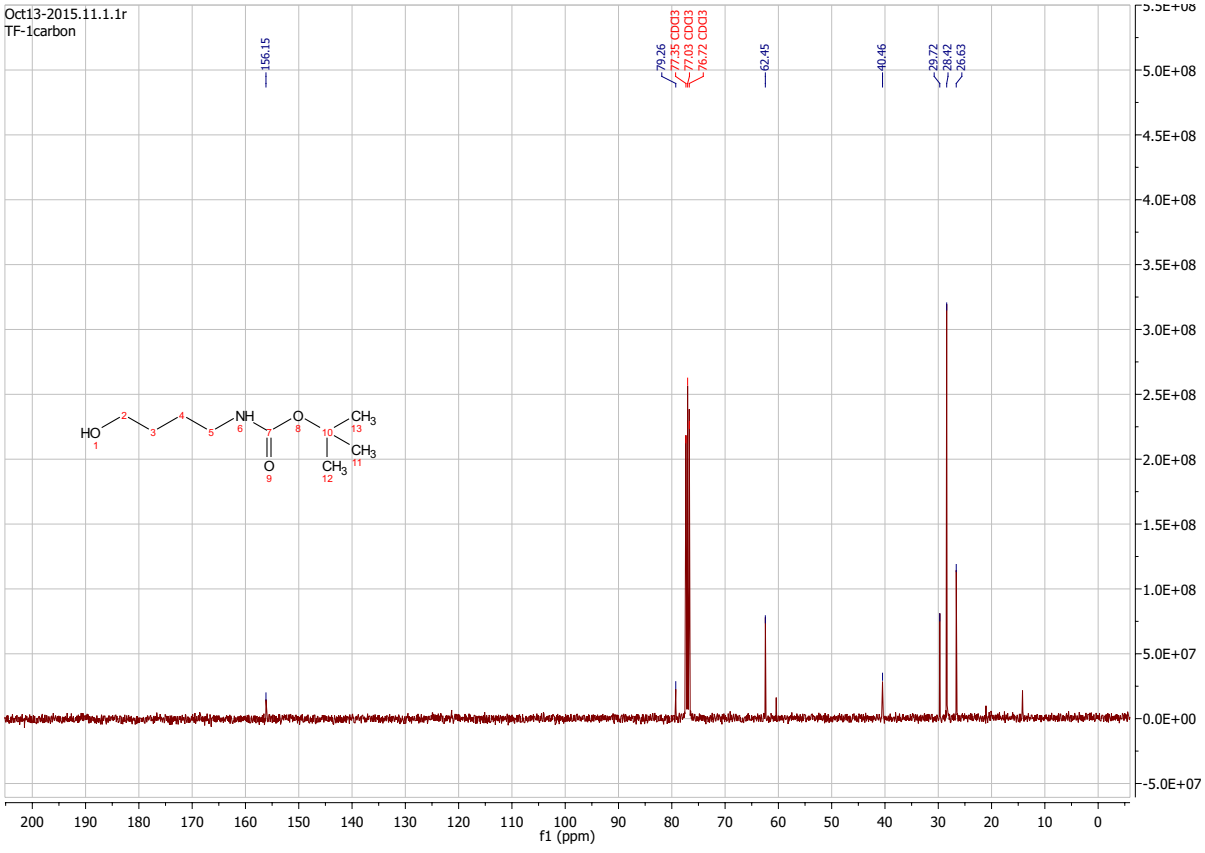
SC1


Nov12-2018.10.fid
TF-2-78
7.26 CDCl3
4.97
3.66
3.63
3.62
3.61
3.59
3.42
3.41
3.25
3.24
3.22
3.21
3.17
1.66
1.64
1.63
1.61
1.60
1.40
HO
NH
O
CH3
0.84
2.00
0.82
1.87
1.88
8.78
f1 (ppm)

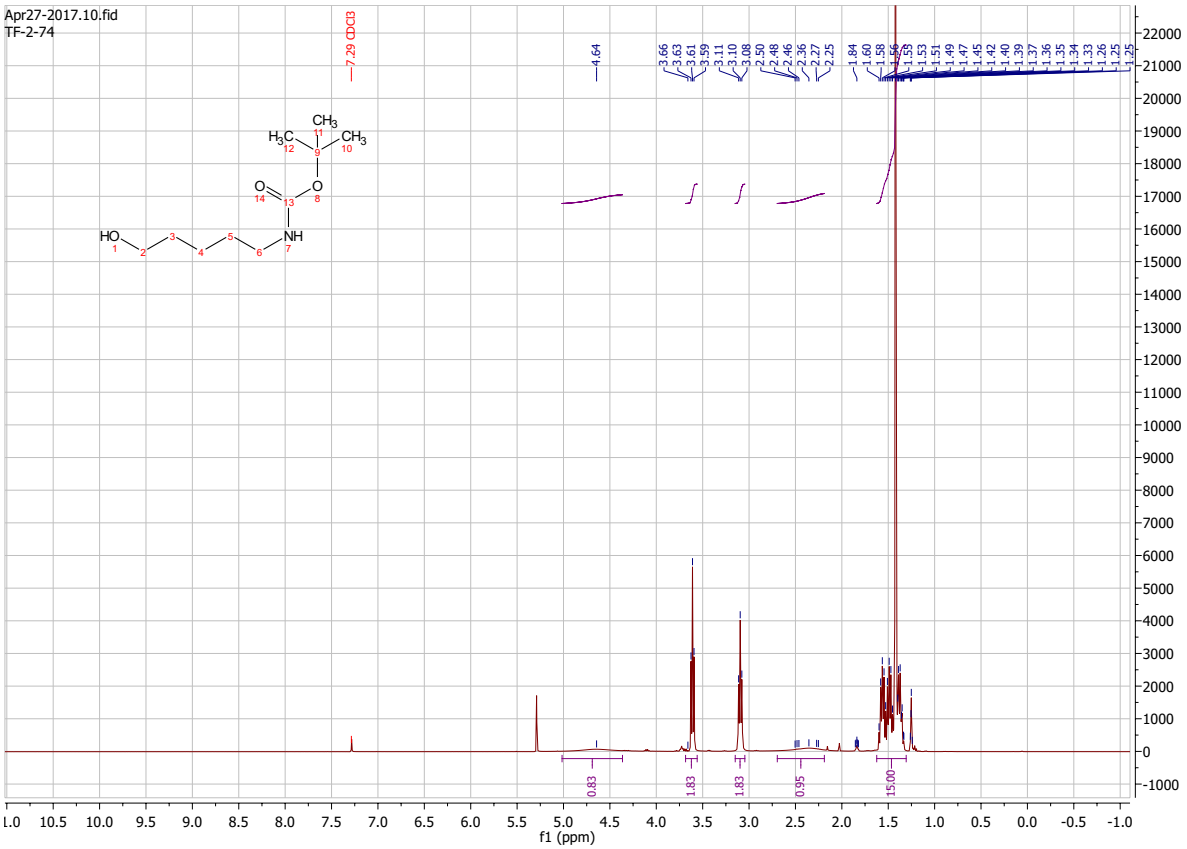

Nov12-2018.11.fid
TF-2-78
157.21
79.60
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
59.34
37.08
32.86
31.23
28.45
HO
NH
O
CH3
f1 (ppm)

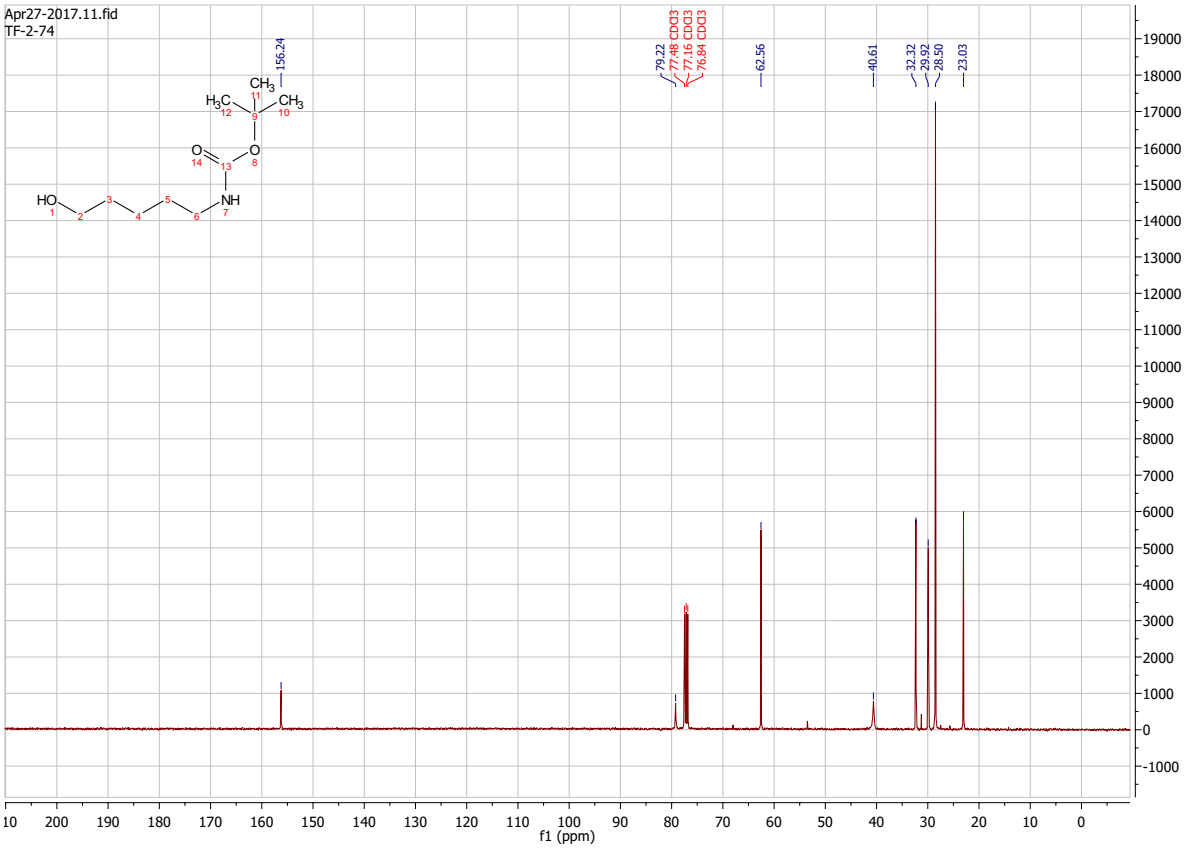
SC2


Oct13-2015.10.1.1r
TF-1proton
7.26 CDCl3
3.67
3.66
3.64
3.16
3.14
3.14
3.13
2.03
1.59
1.58
1.57
1.57
1.56
1.56
1.43
1.83
2.00
3.79
7.70
f1 (ppm)

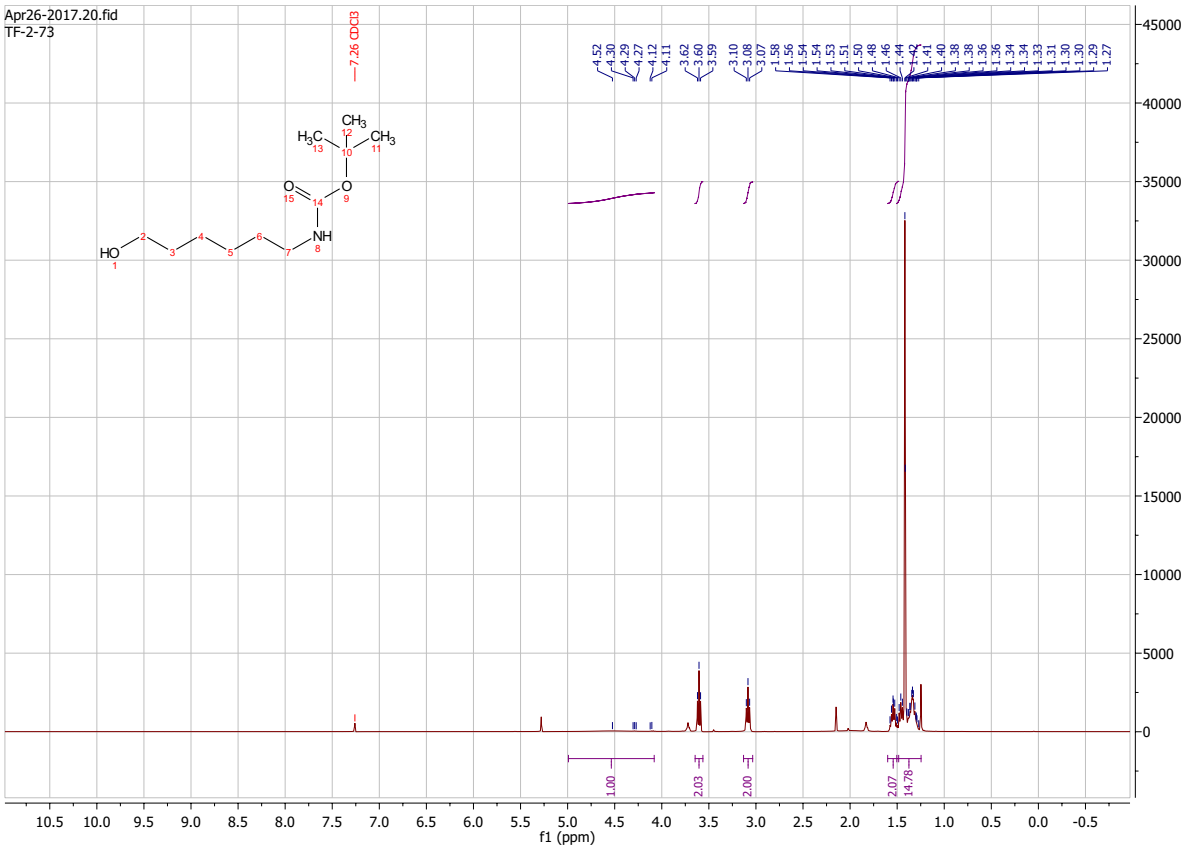

Oct13-2015.11.1.1r
TF-1carbon
156.15
79.26
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
62.45
40.46
29.72
28.42
26.63
f1 (ppm)

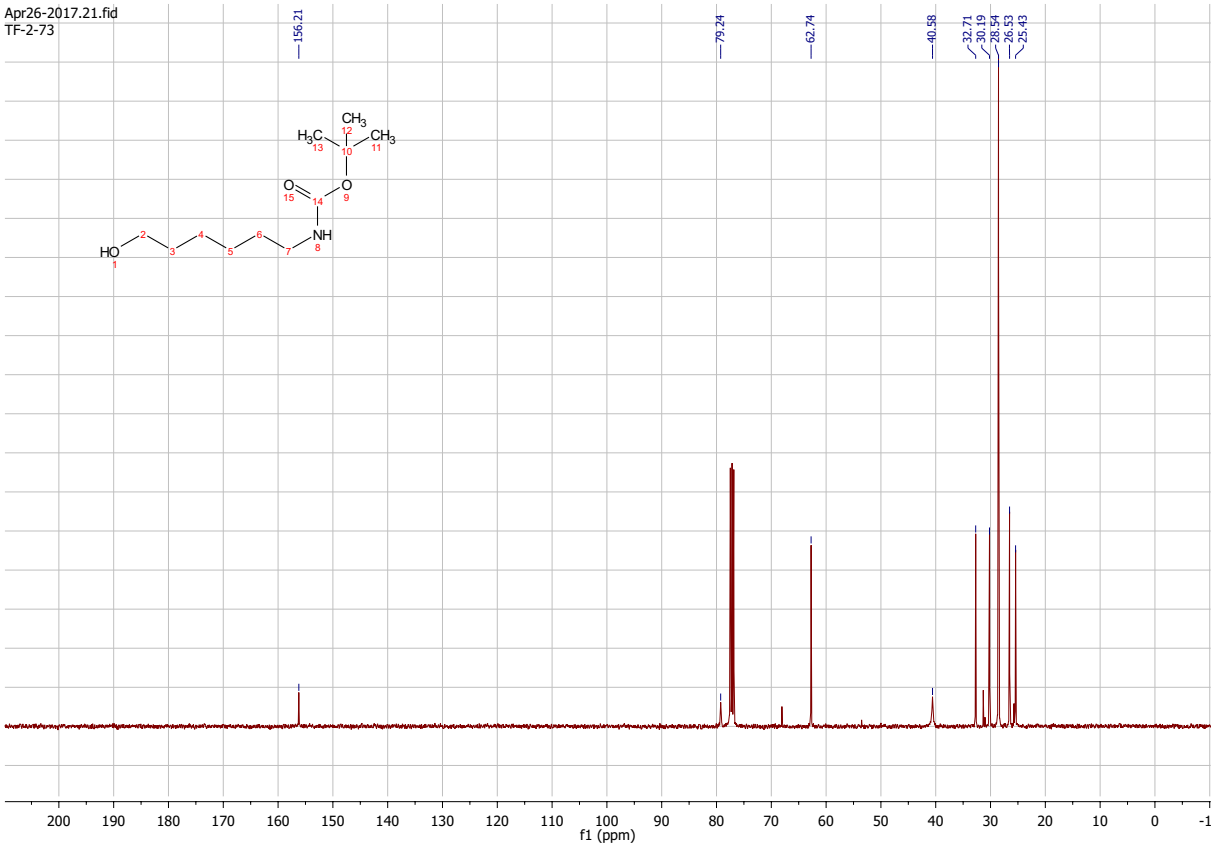
SC3



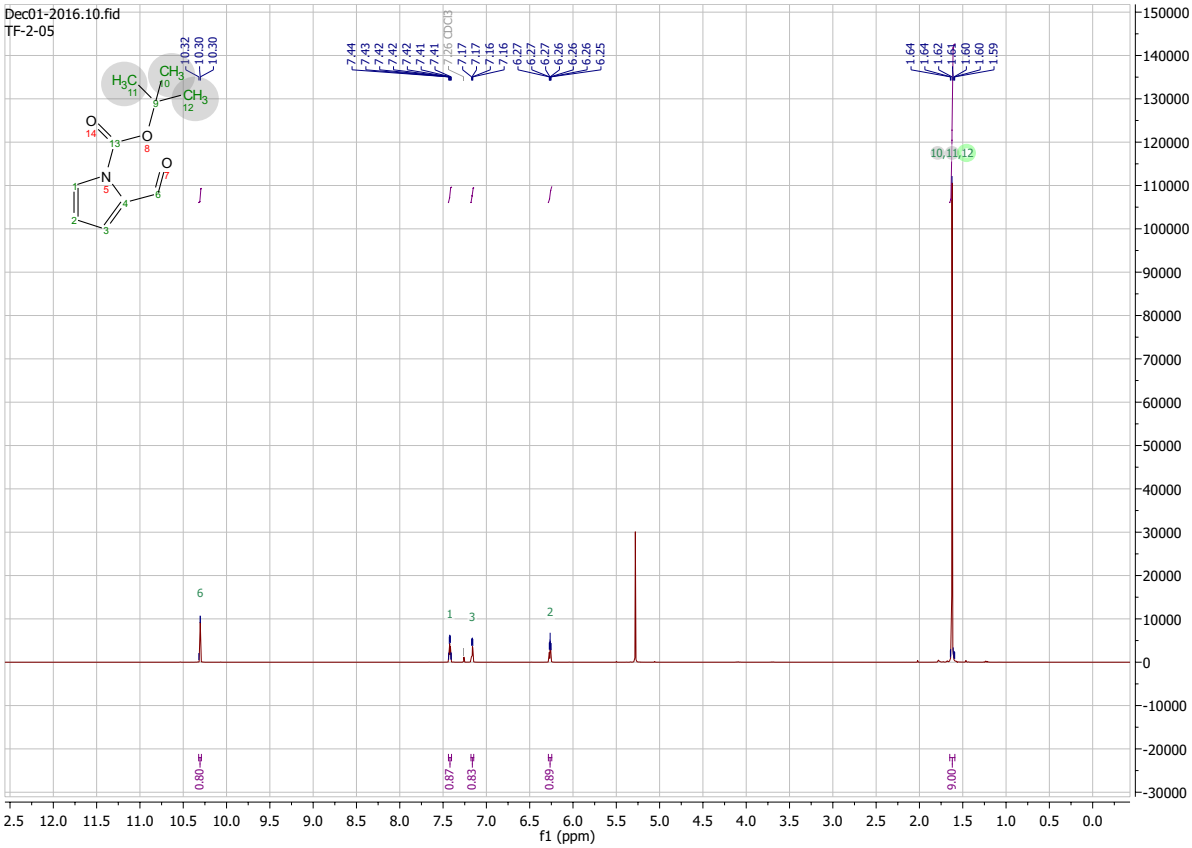


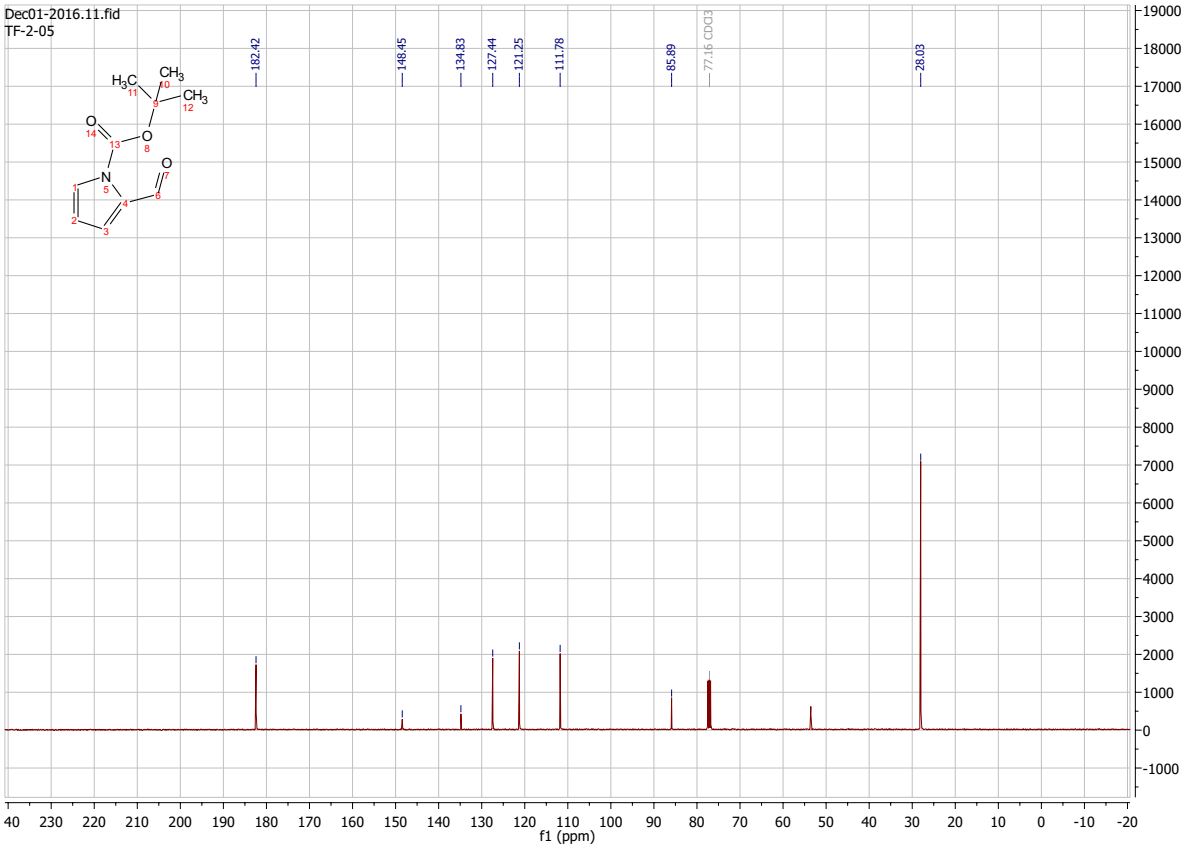
SC4


Apr26-2017.20.fid
TF-2-73
7.26 CDCl3
4.52
4.30
4.29
4.27
4.12
4.11
3.62
3.60
3.59
3.10
3.08
3.07
1.58
1.56
1.54
1.54
1.53
1.51
1.50
1.48
1.46
1.44
1.42
1.41
1.40
1.38
1.38
1.36
1.36
1.34
1.34
1.33
1.31
1.30
1.30
1.29
1.27
1.00
2.03
2.00
2.07
14.78
f1 (ppm)

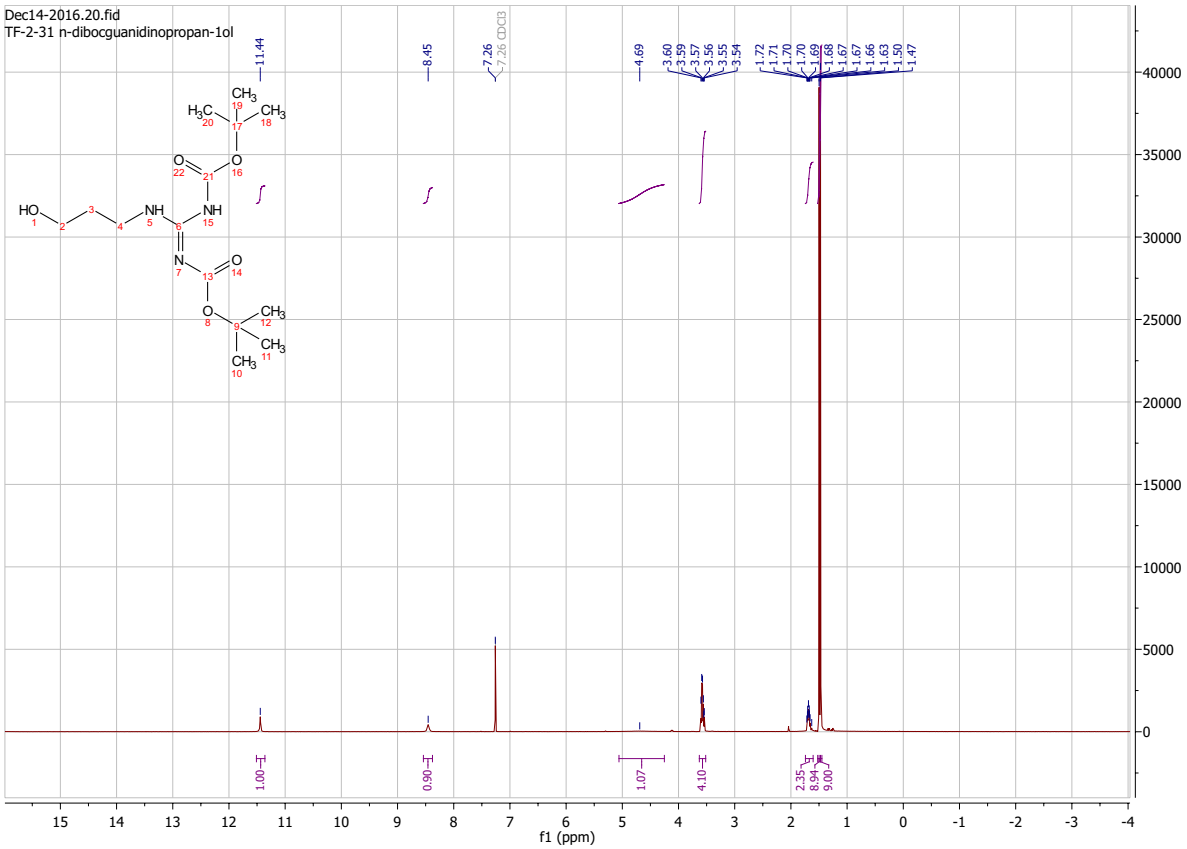

Apr26-2017.21.fid
TF-2-73
156.21
79.24
62.74
40.58
32.71
30.19
28.54
26.53
25.43
f1 (ppm)

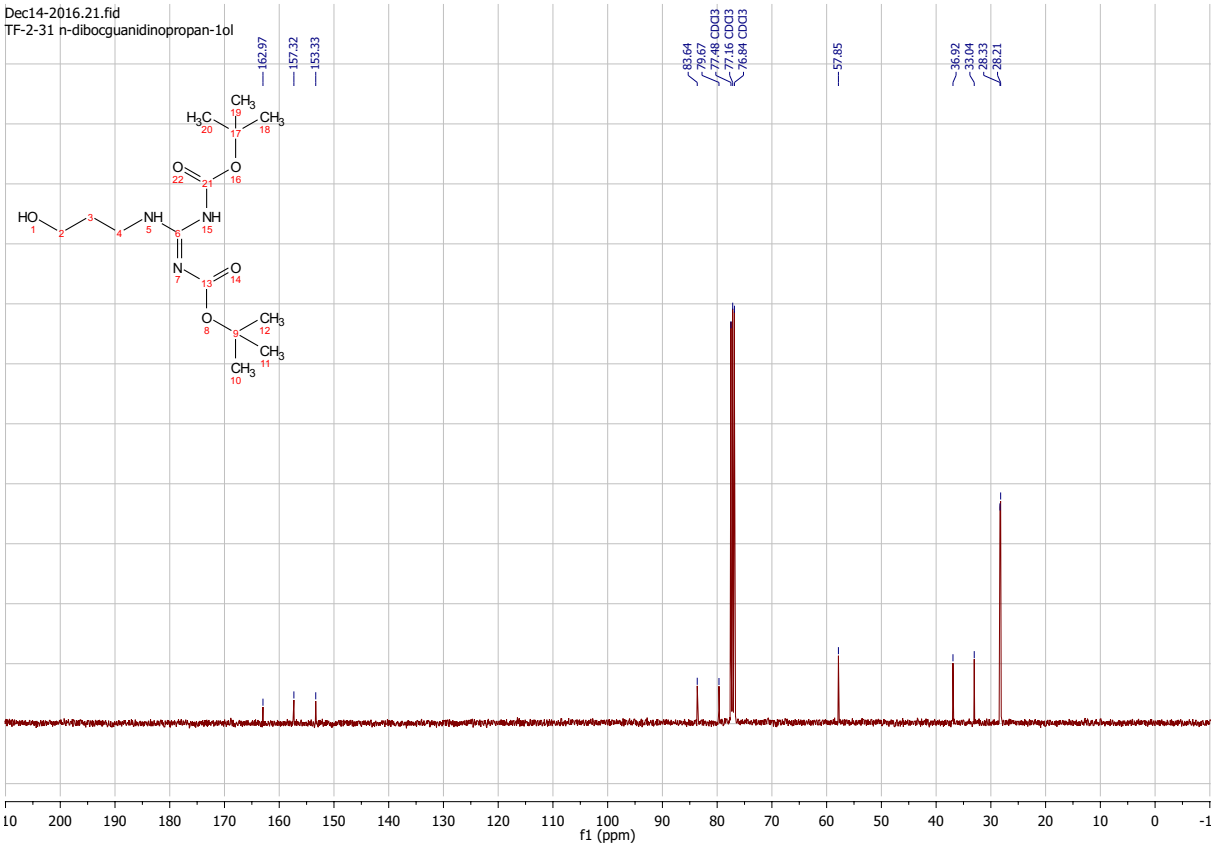
SC5


Dec01-2016.10.fid
TF-2-05
7.44
7.43
7.42
7.42
7.42
7.41
7.41
7.41
7.25 CDCl3
7.17
7.17
7.16
7.16
6.27
6.27
6.27
6.26
6.26
6.26
6.25
1.64
1.64
1.62
1.61
1.60
1.60
1.59
1.32
1.30
1.30
10,11,12
6
1
3
2
0.80
0.87
0.83
0.89
9.00
f1 (ppm)

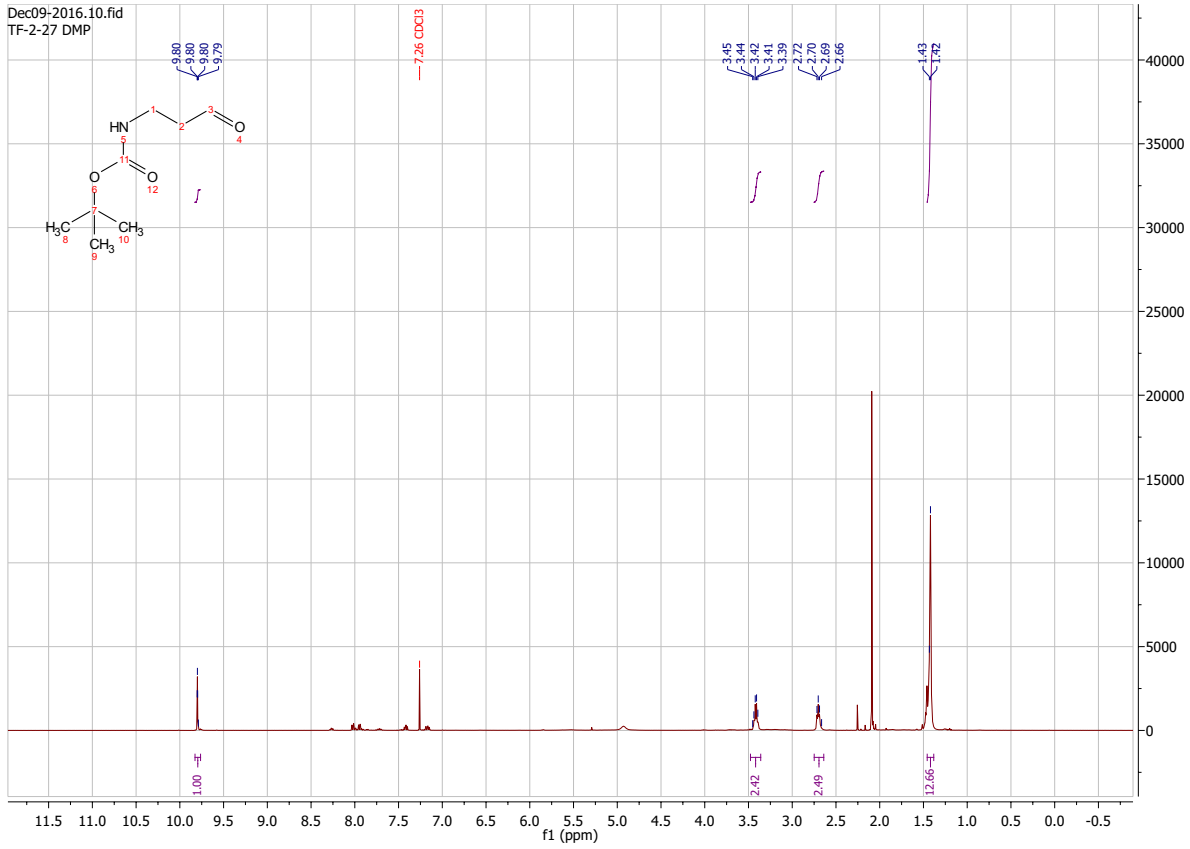

Dec01-2016.11.fid
TF-2-05
182.42
148.45
134.83
127.44
121.25
111.78
85.89
77.16 CDCl3
28.03
f1 (ppm)

SC6

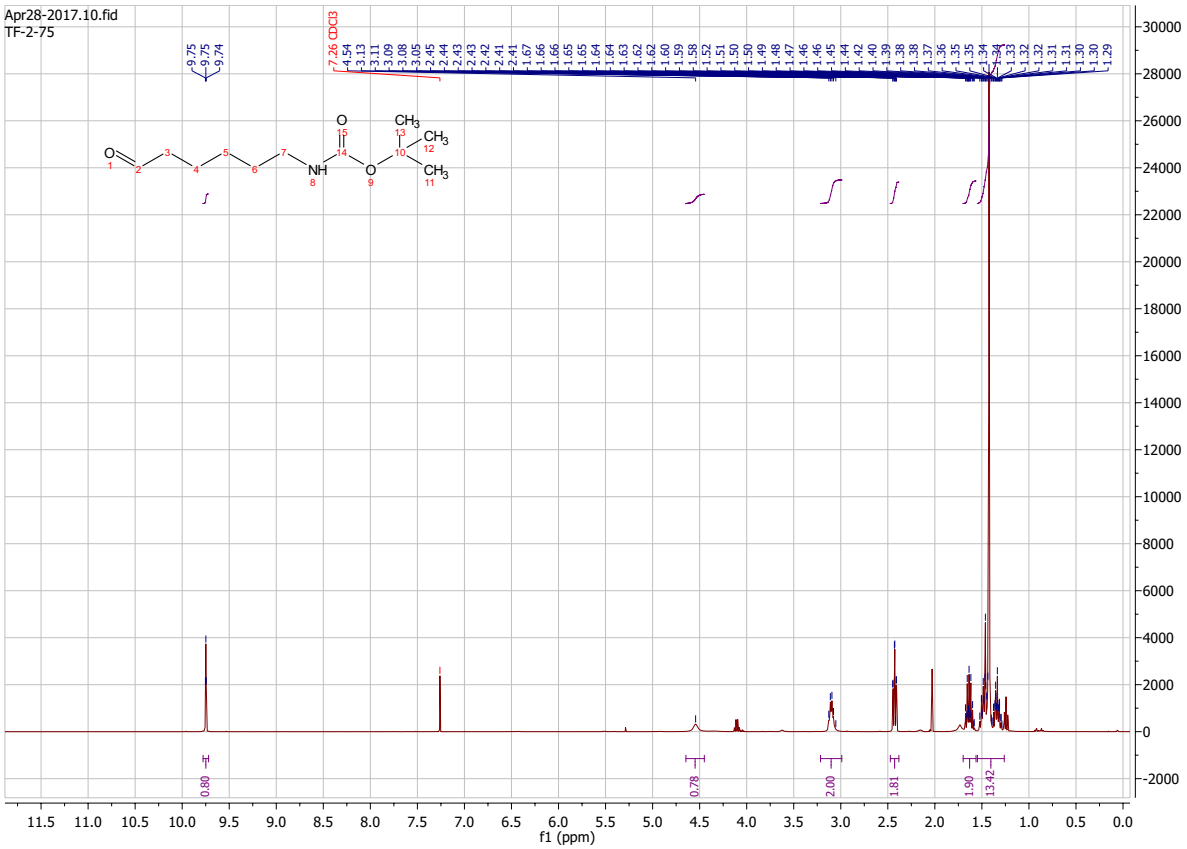

Dec14-2016.20.fid
TF-2-31 n-dibocguanidinopropan-1ol
11.44
8.45
7.26
7.26 CDCl3
4.69
3.60
3.59
3.57
3.56
3.55
3.54
1.72
1.71
1.70
1.70
1.69
1.68
1.67
1.67
1.66
1.63
1.50
1.47
1.00
0.90
1.07
4.10
2.35
8.94
9.00
f1 (ppm)


Dec14-2016.21.fid
TF-2-31 n-dibocguanidinopropan-1ol
162.97
157.32
153.33
83.64
79.67
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
57.85
36.92
33.04
28.33
28.21
f1 (ppm)

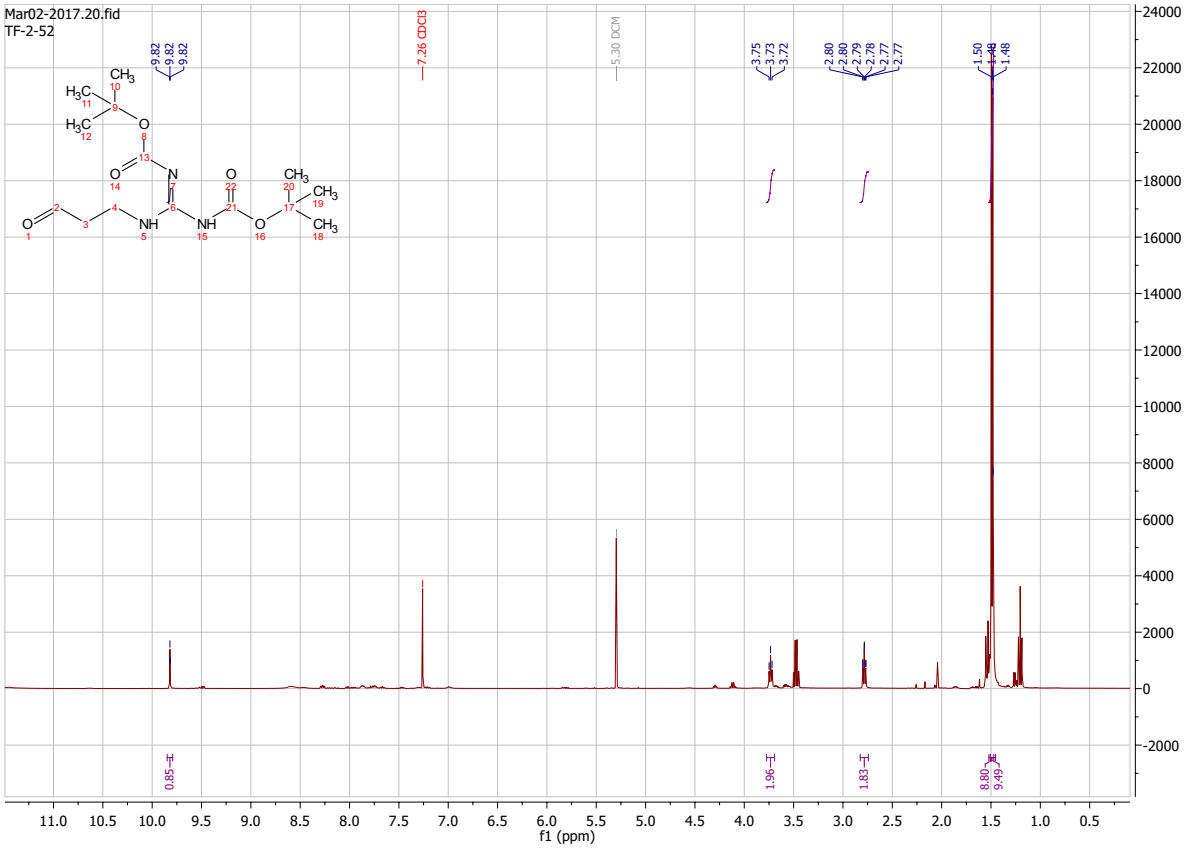
SC7


Dec09-2016.10.fid
TF-2-27 DMP
9.80
9.80
9.80
9.79
7.26 CDCl3
3.45
3.44
3.42
3.41
3.39
2.72
2.70
2.69
2.66
1.43
1.42
HN
O
O
O
H3C
CH3
CH3
1.00
2.42
2.49
12.66
f1 (ppm)

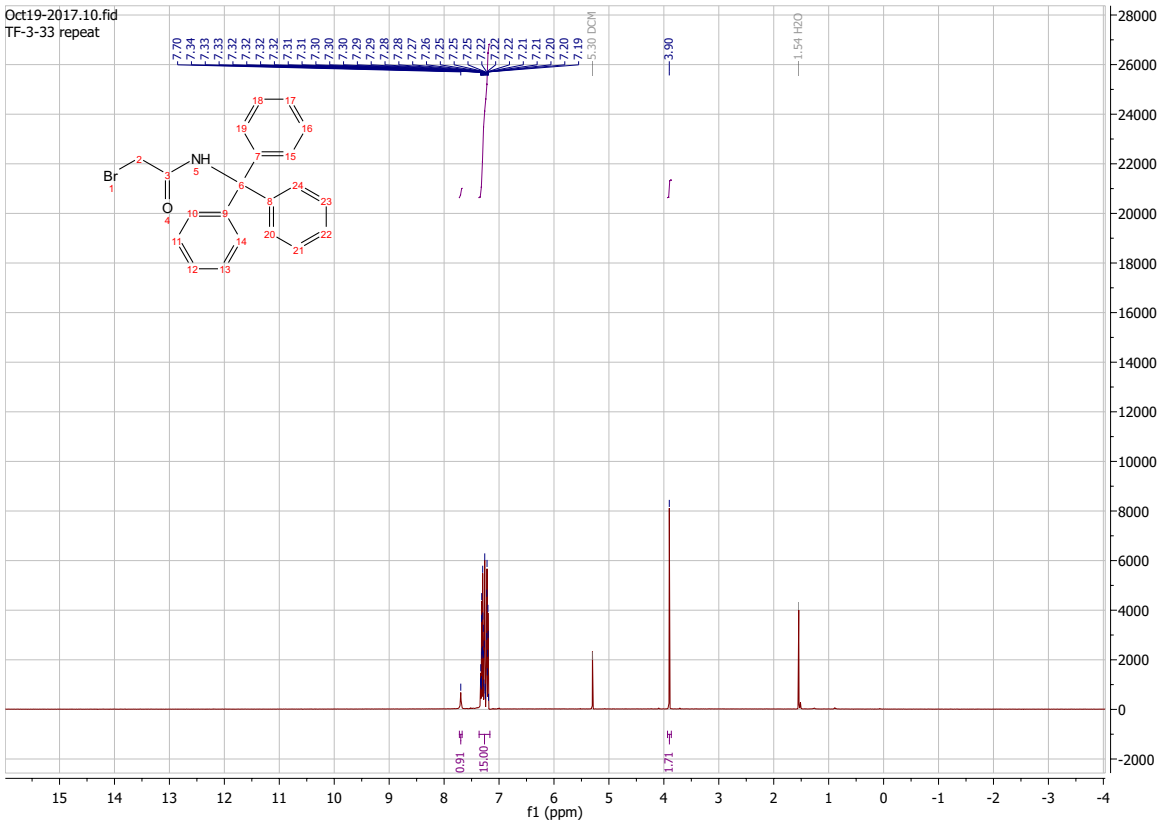
SC8

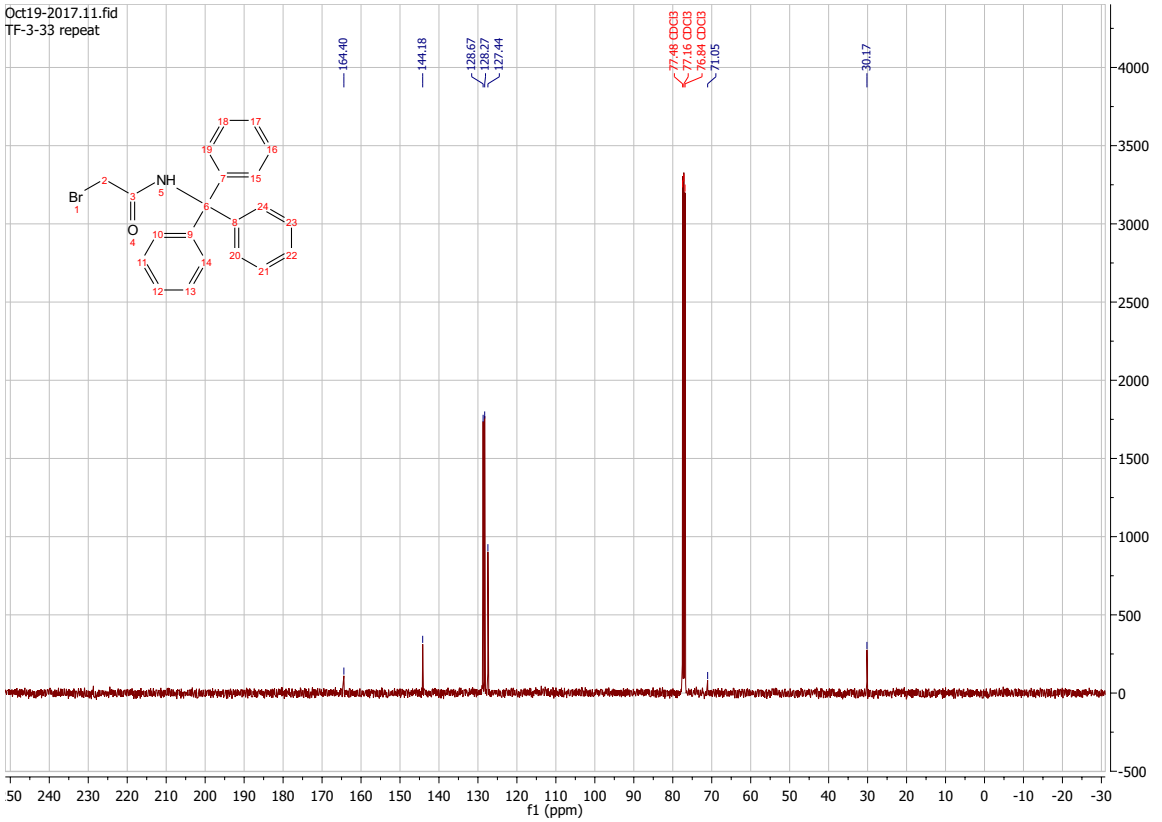


SC9

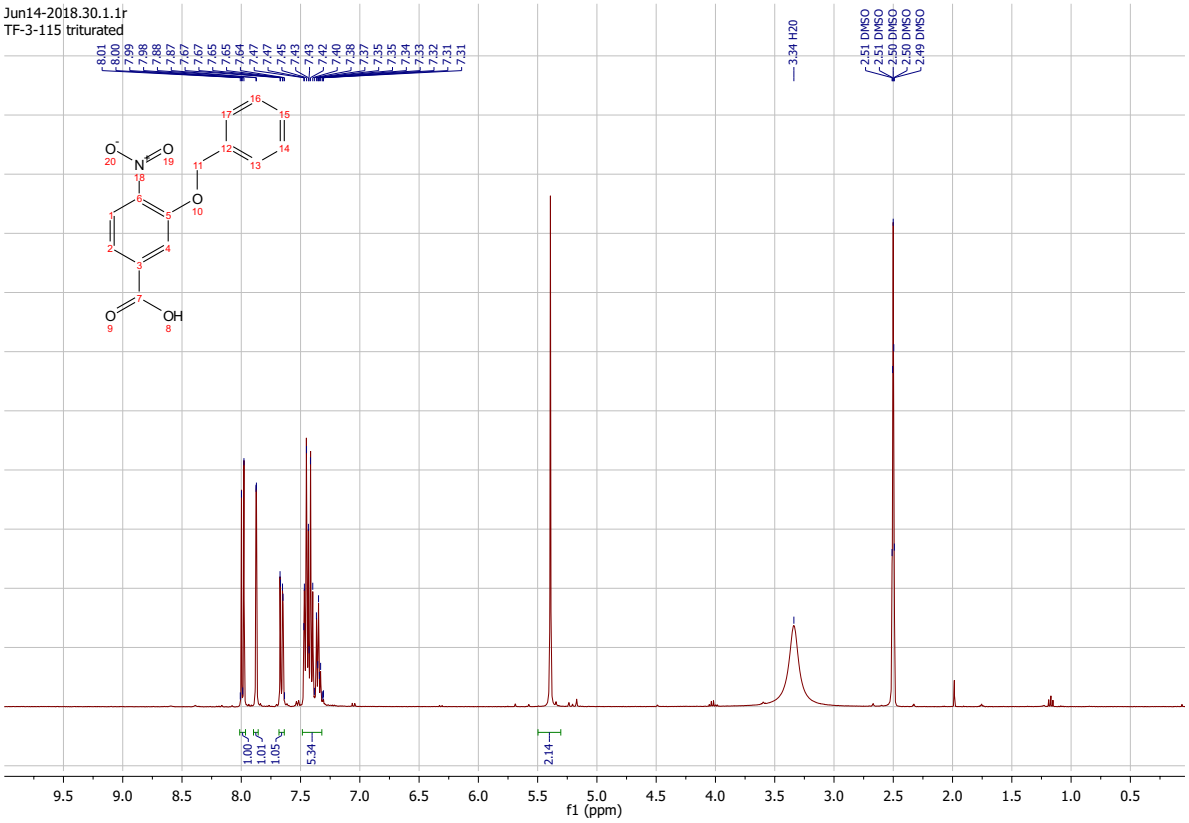

Mar02-2017.20.fid
TF-2-52
7.26 CDCl3
5.30 DCM
9.82
3.75
3.73
3.72
2.80
2.79
2.78
2.77
1.50
1.48
0.85
1.96
1.83
8.80
9.49
f1 (ppm)

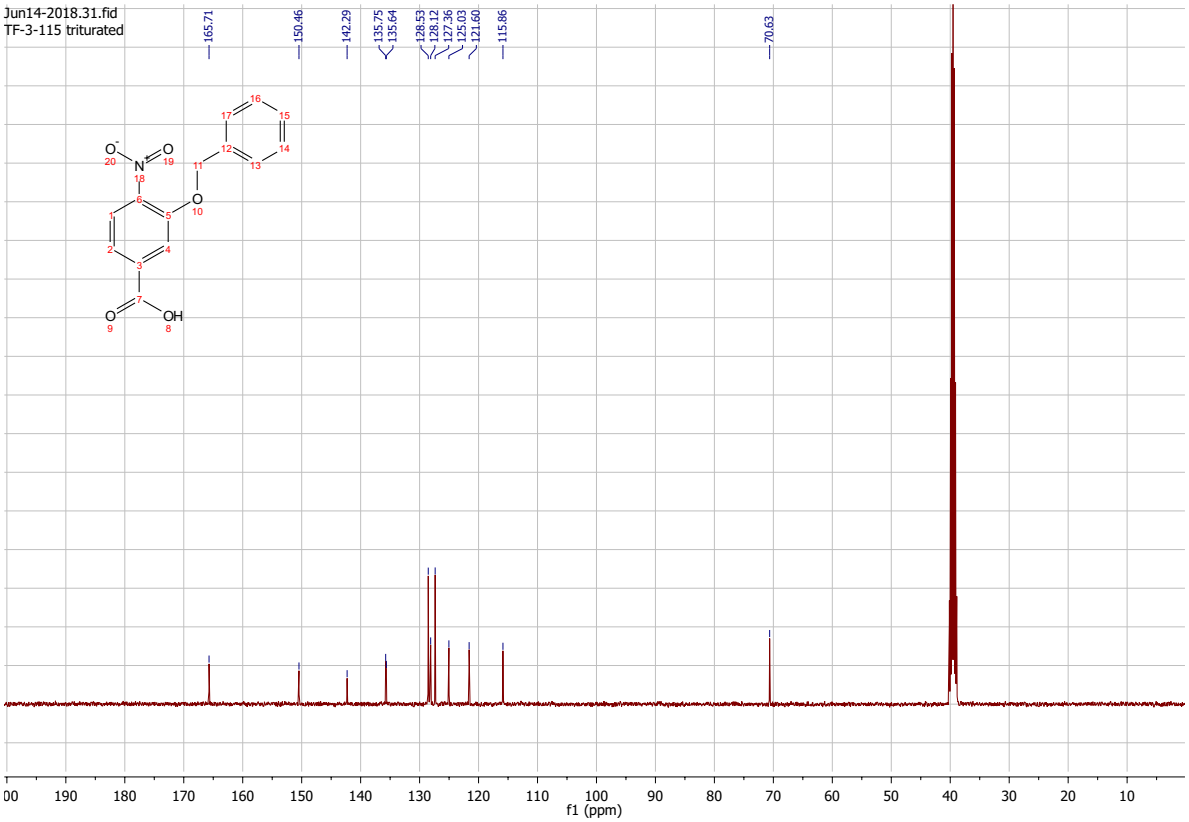
SC10

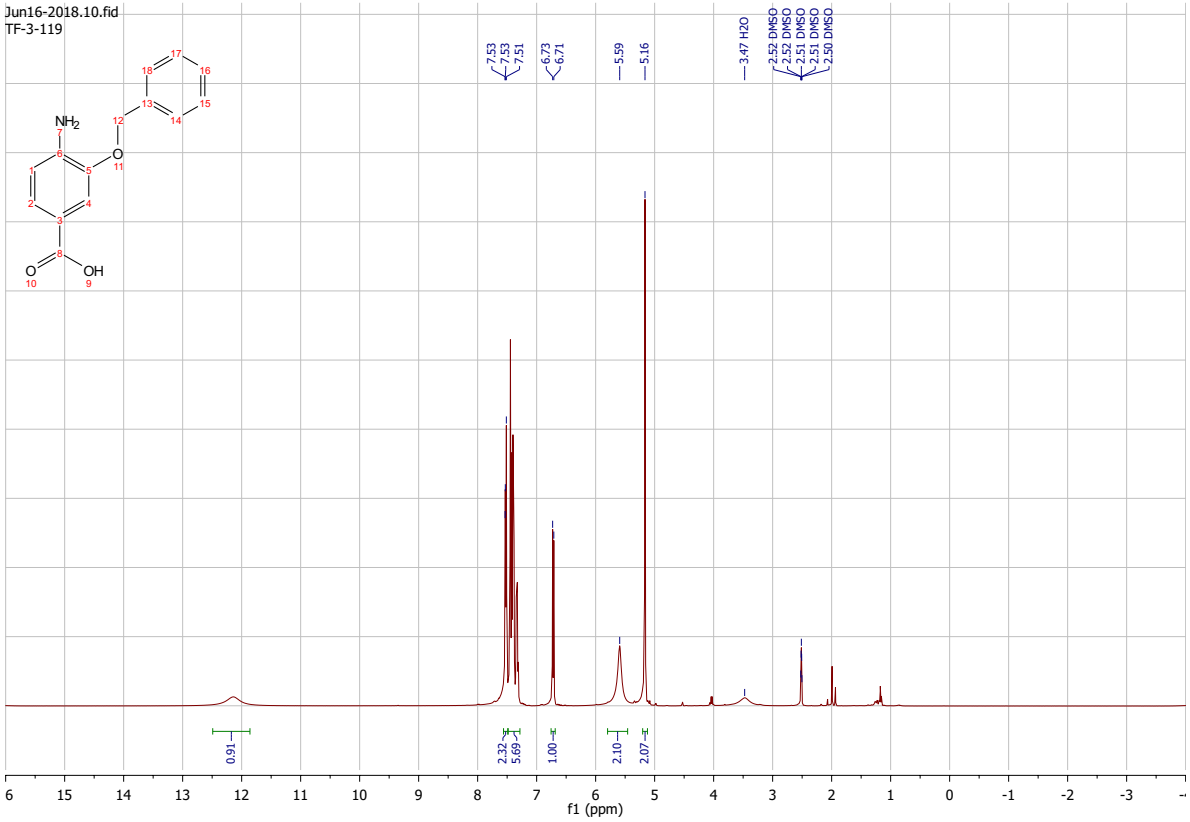

Oct19-2017.10.fid
TF-3-33 repeat
7.70
7.34
7.33
7.33
7.32
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.30
7.29
7.29
7.28
7.28
7.27
7.26
7.25
7.25
7.25
7.22
7.22
7.22
7.21
7.21
7.21
7.20
7.20
7.19
5.30 DCM
3.90
1.54 H2O
0.91
15.00
1.71
f1 (ppm)

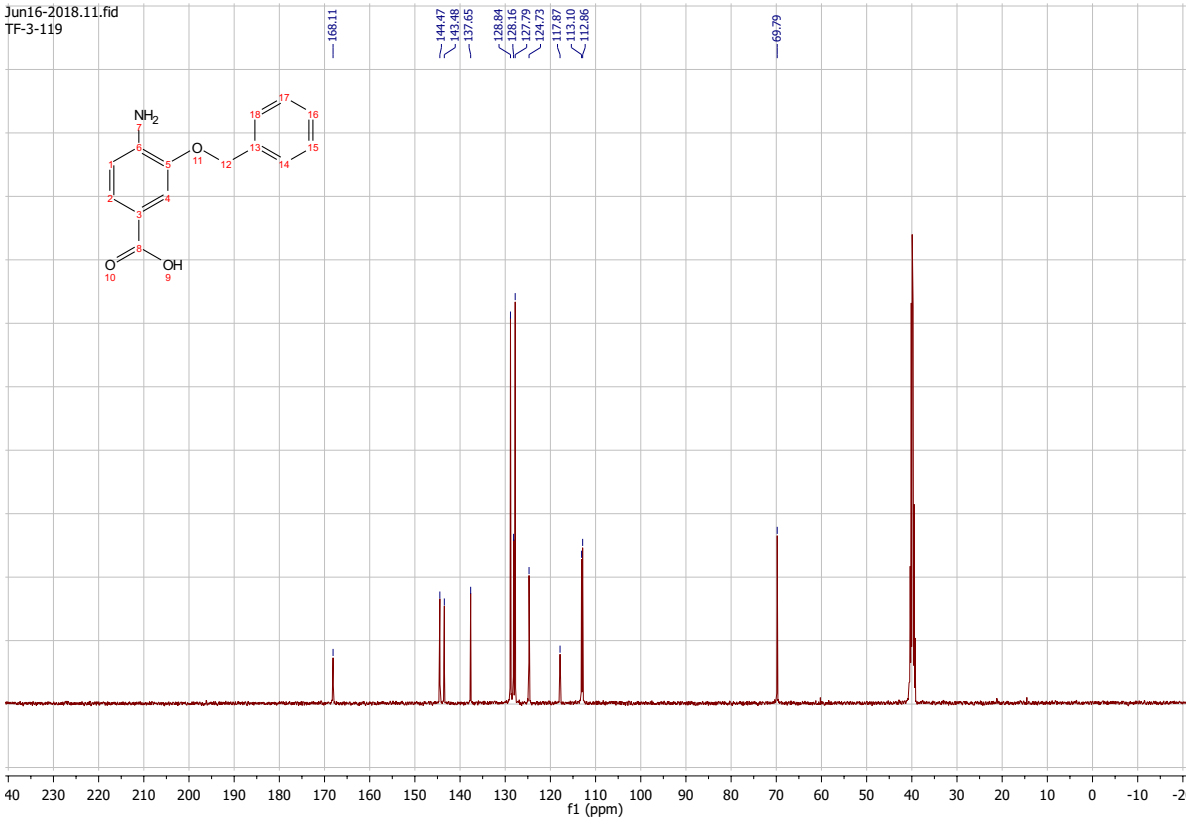

Oct19-2017.11.fid
TF-3-33 repeat
164.40
144.18
128.67
128.27
127.44
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.05
30.17
f1 (ppm)

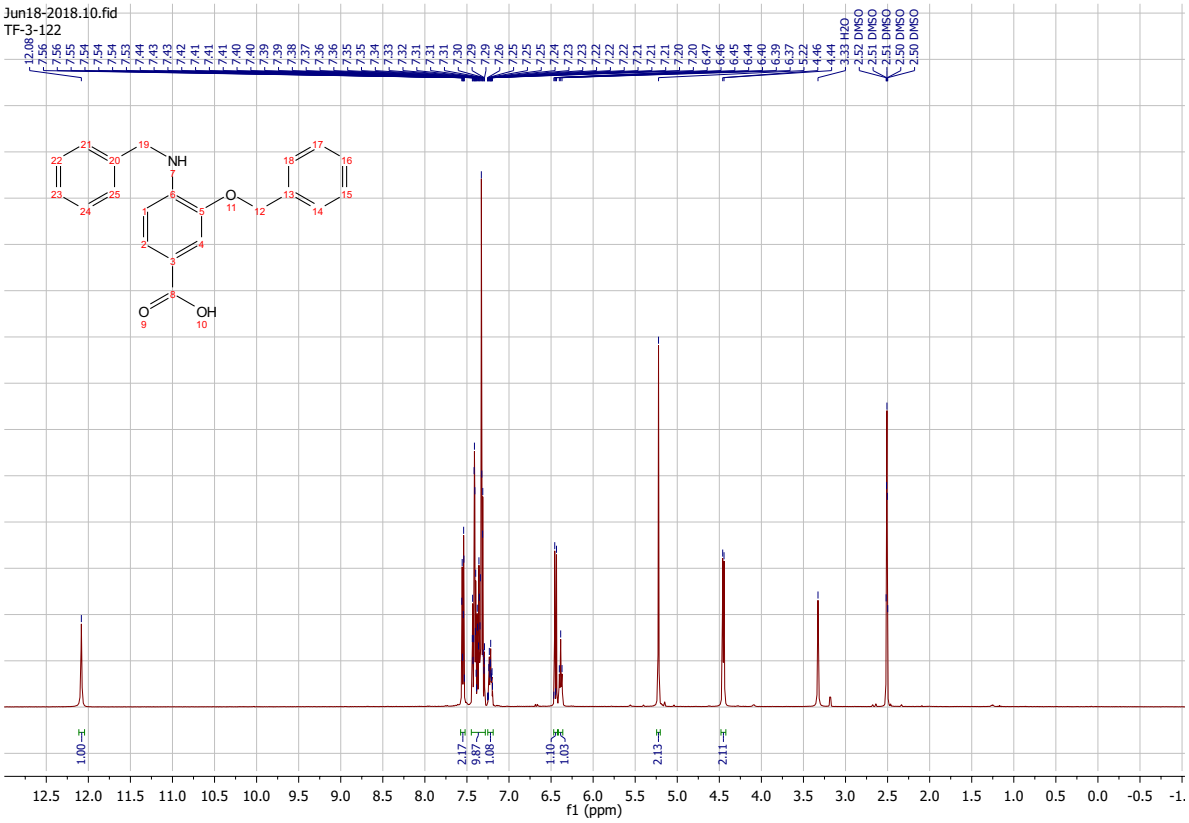
Spectra for Monomers 1-13 and Intermediates S1-S31

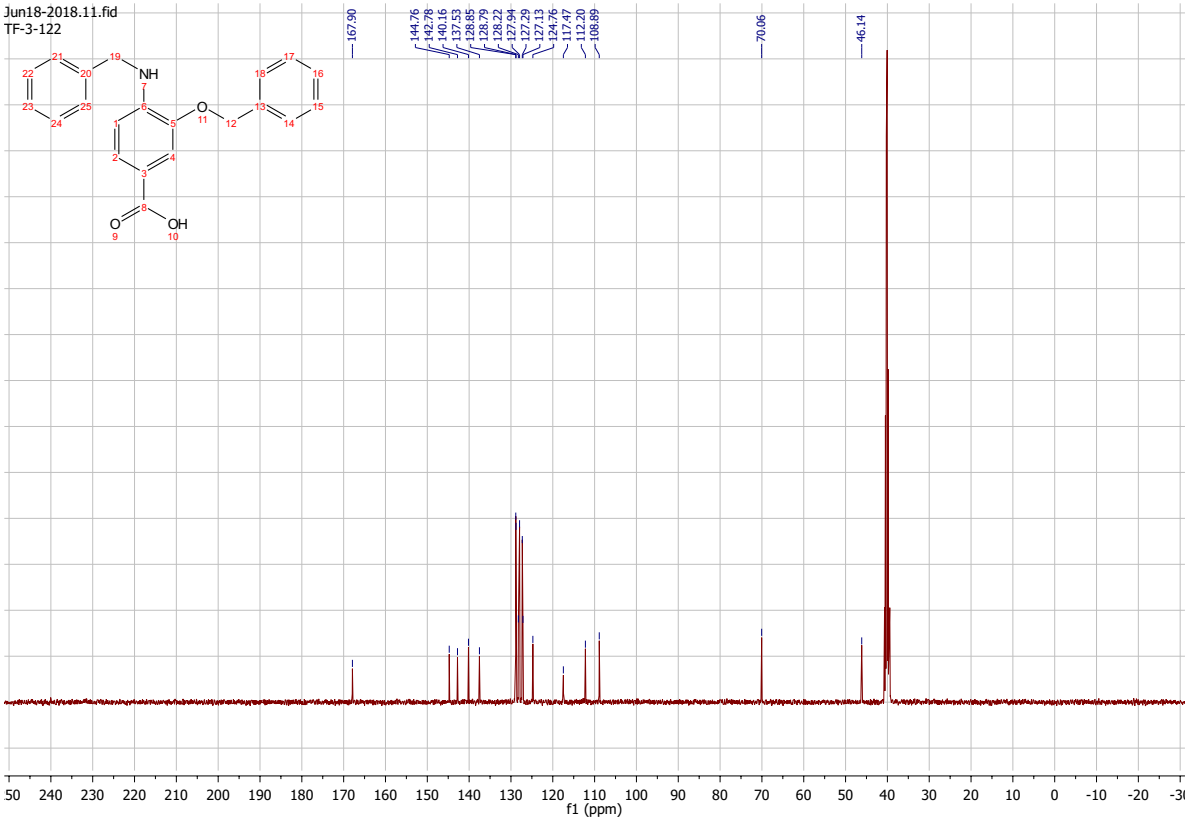

Jun14-2018.30.1.1r
TF-3-115 triturated
8.01
8.00
7.99
7.98
7.88
7.87
7.67
7.67
7.65
7.65
7.64
7.47
7.47
7.45
7.43
7.43
7.42
7.40
7.38
7.37
7.35
7.35
7.34
7.33
7.32
7.31
7.31
3.34 H2O
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
1.00
1.01
1.05
5.34
2.14
f1 (ppm)

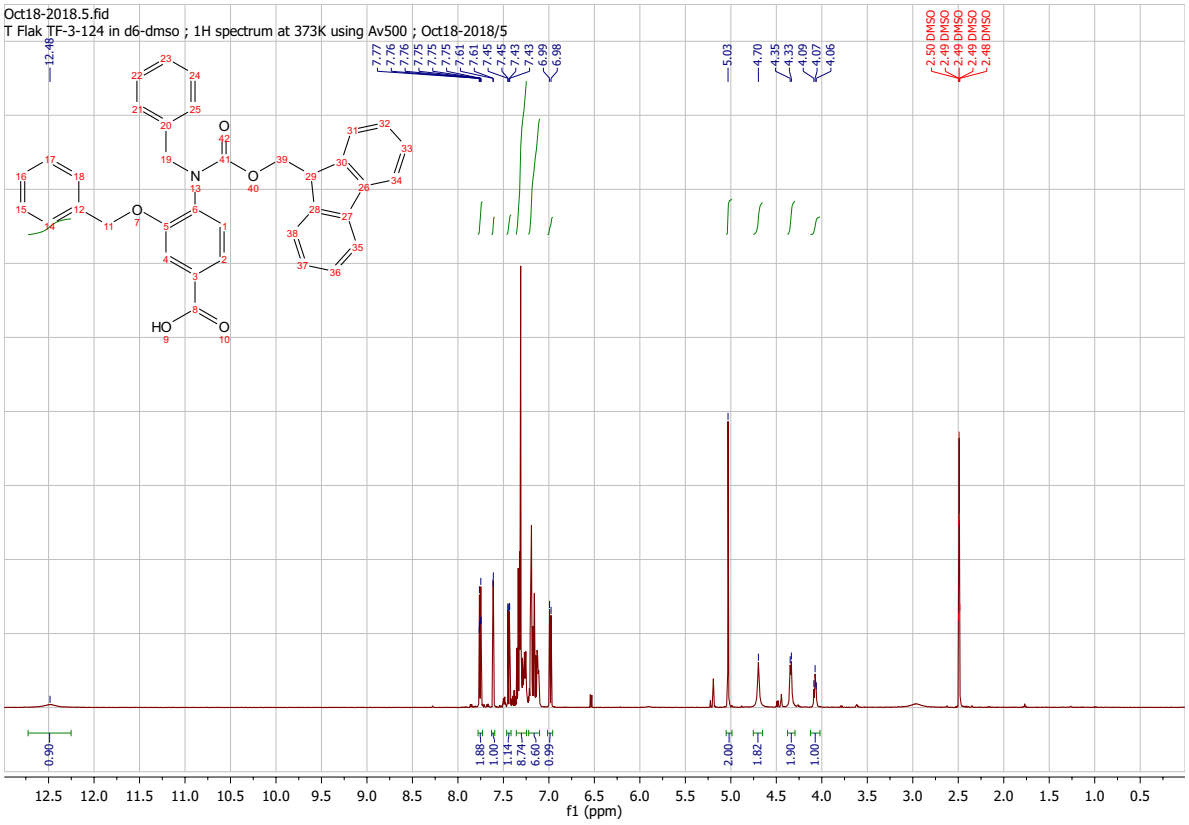

Jun14-2018.31.fid
TF-3-115 triturated
165.71
150.46
142.29
135.75
135.64
128.53
128.12
127.36
125.03
121.60
115.86
70.63
f1 (ppm)

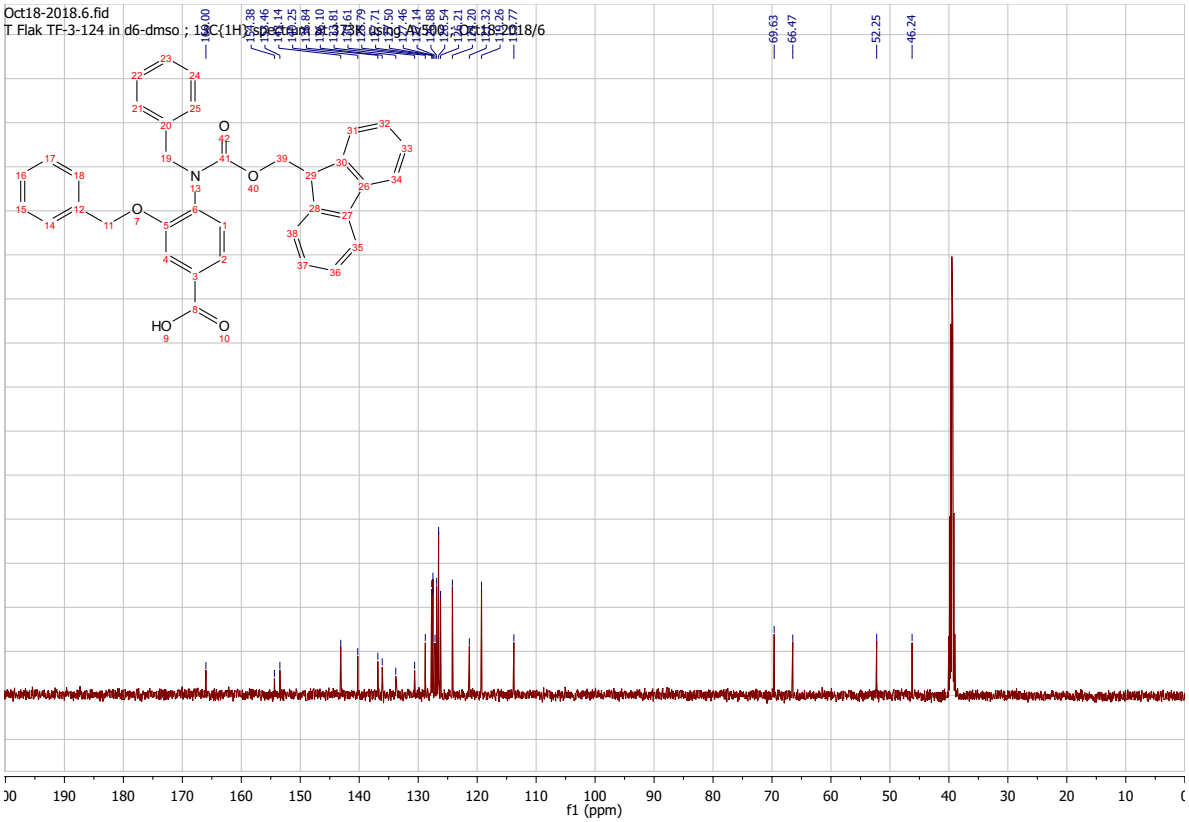

Jun16-2018.10.fid
TF-3-119
7.53
7.53
7.51
6.73
6.71
5.59
5.16
3.47 H2O
2.53 DMSO
2.52 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
0.91
2.32
5.69
1.00
2.10
2.07
f1 (ppm)

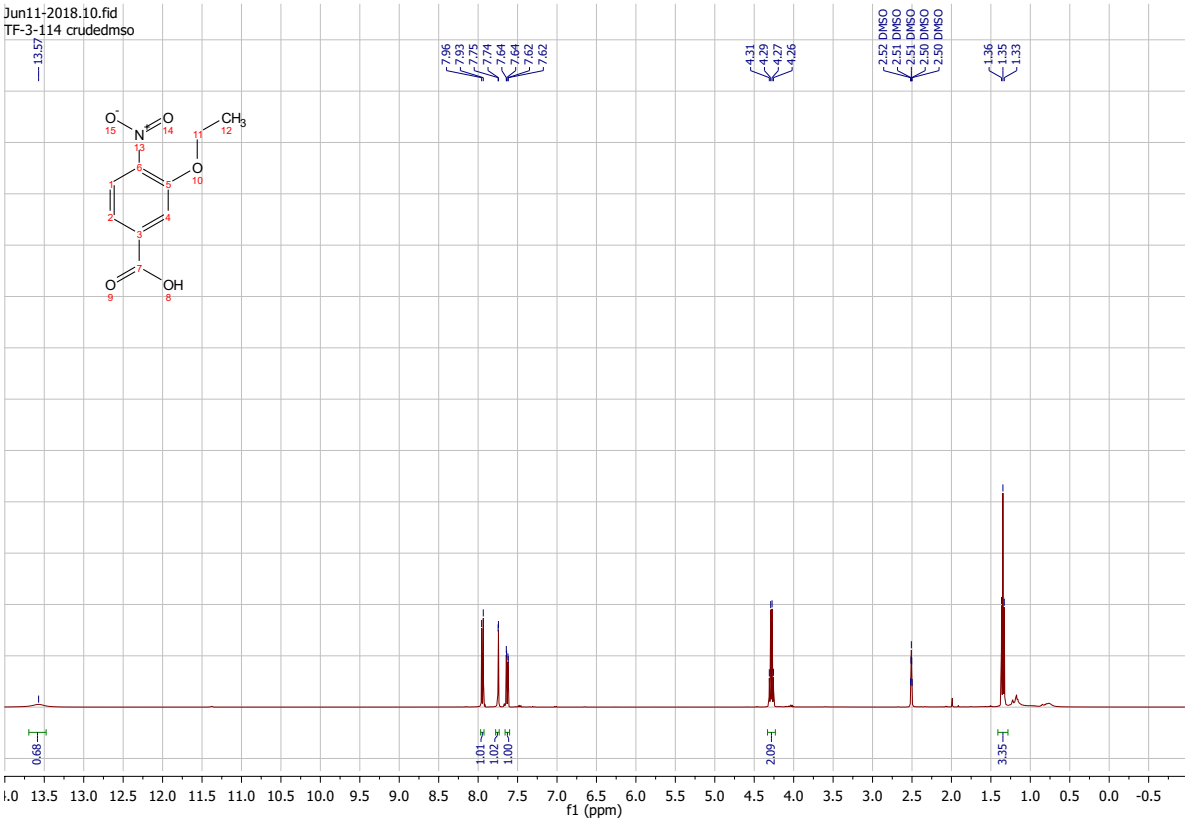

Jun16-2018.11.fid
TF-3-119
168.11
144.47
143.48
137.65
128.84
128.16
127.79
124.73
117.87
113.10
112.86
69.79
f1 (ppm)

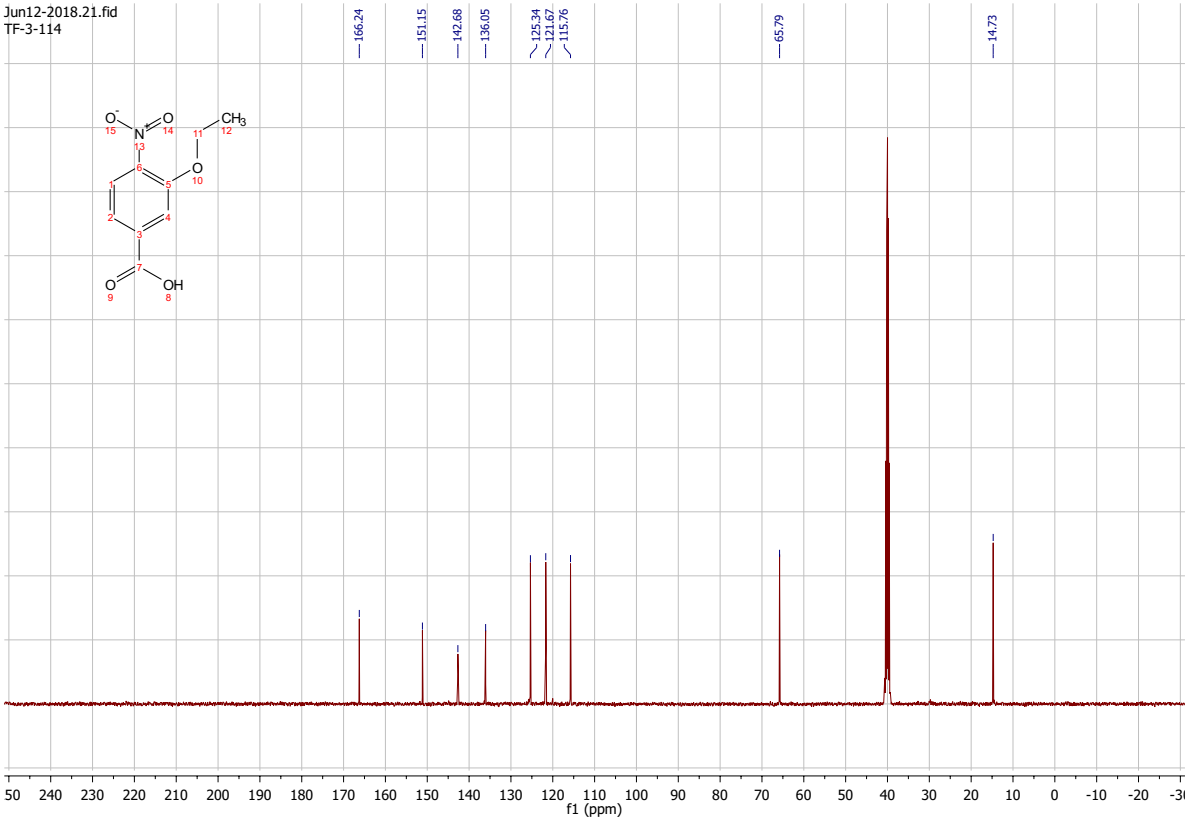

Jun18-2018.10.fid
TF-3-122
f1 (ppm)

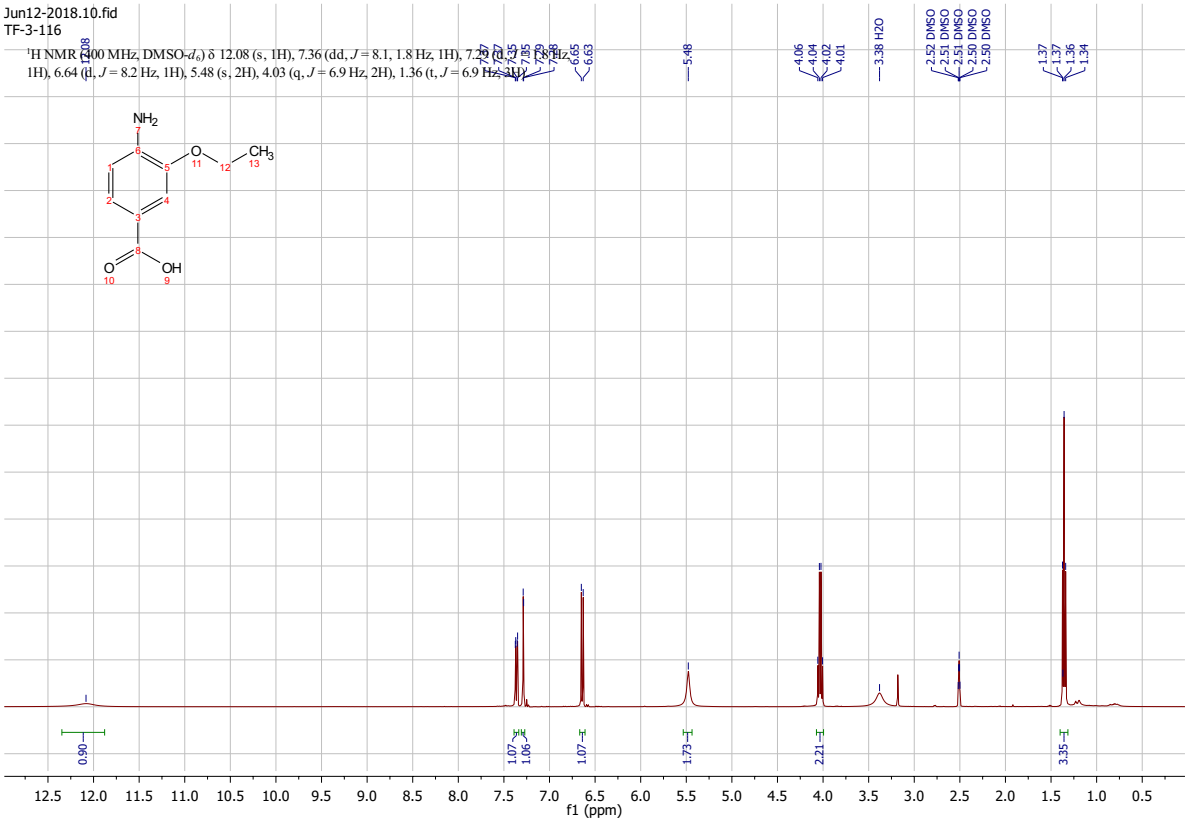

Jun18-2018.11.fid
TF-3-122
f1 (ppm)

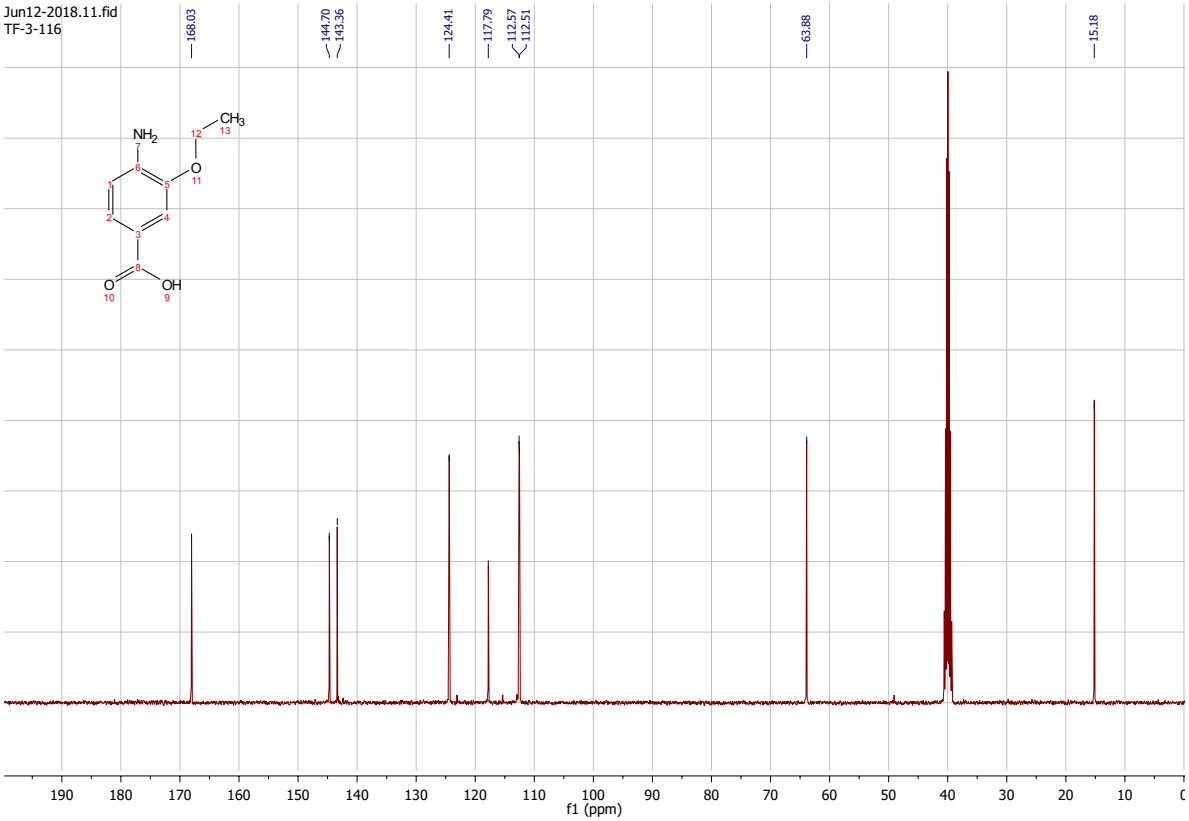

Oct18-2018.5.fid
T Flak TF-3-124 in d6-dmso ; 1H spectrum at 373K using Av500 ; Oct18-2018/5
f1 (ppm)

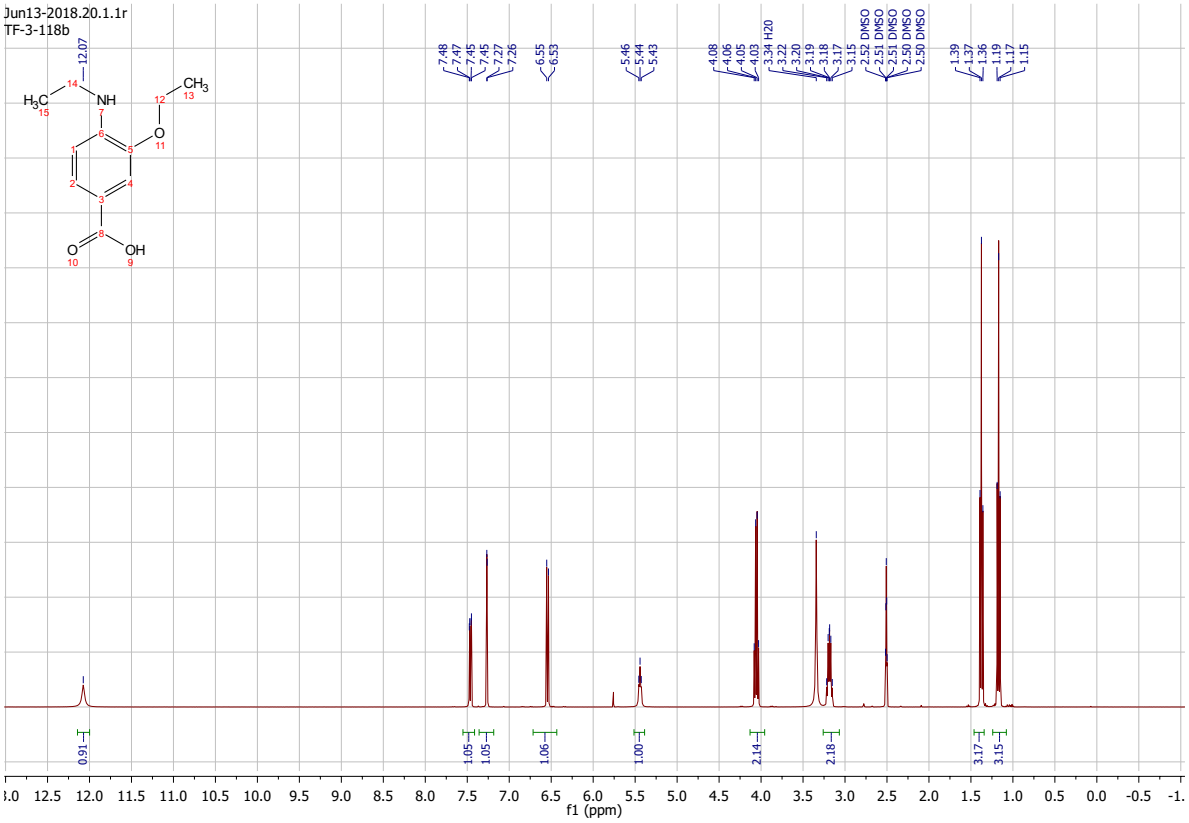

Oct18-2018.6.fid
T Flak TF-3-124 in d6-dmso ; 13C{1H} spectrum at 373K using Av500 ; Oct18-2018/6
f1 (ppm)

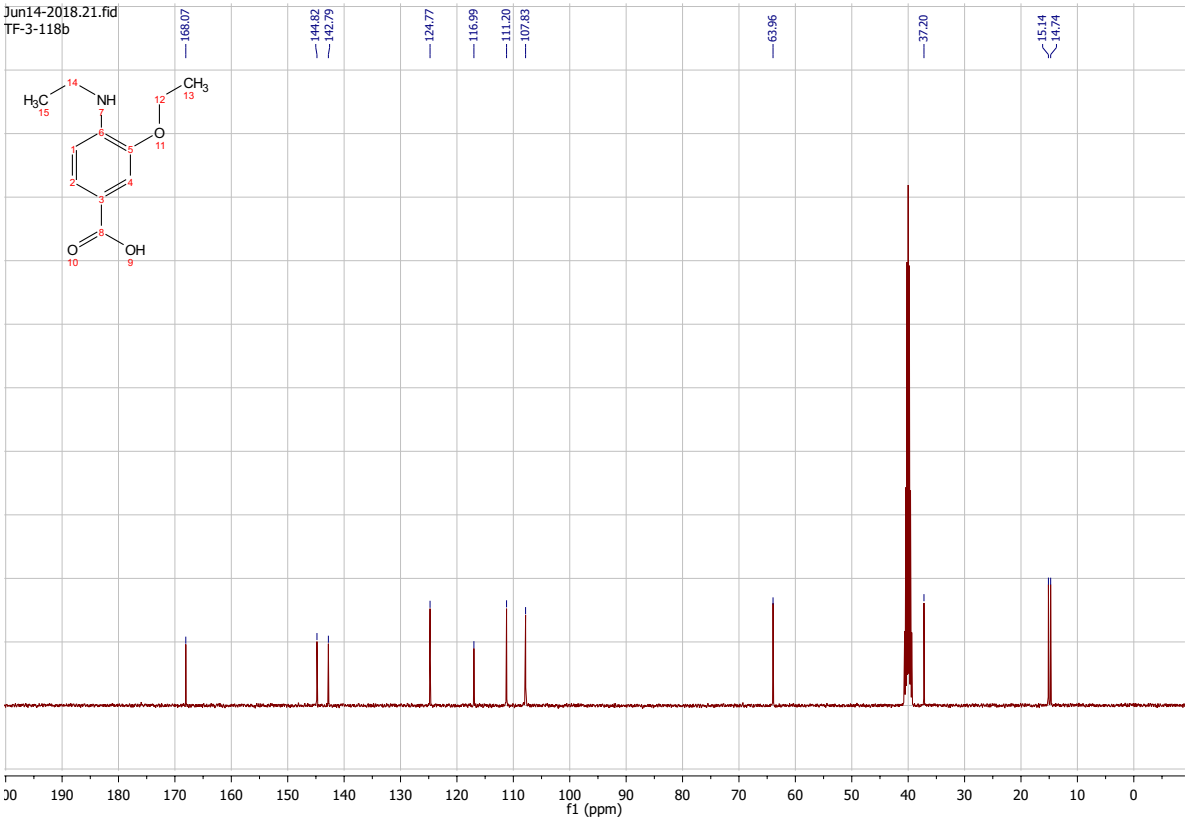

Jun11-2018.10.fid
TF-3-114 crudedmso
13.57
7.96
7.93
7.75
7.74
7.64
7.64
7.62
7.62
4.31
4.29
4.27
4.26
2.52 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
1.36
1.35
1.33
0.68
1.01
1.02
1.00
2.09
3.35
f1 (ppm)


Jun12-2018.21.fid
TF-3-114
166.24
151.15
142.68
136.05
125.34
121.67
115.76
65.79
14.73
f1 (ppm)

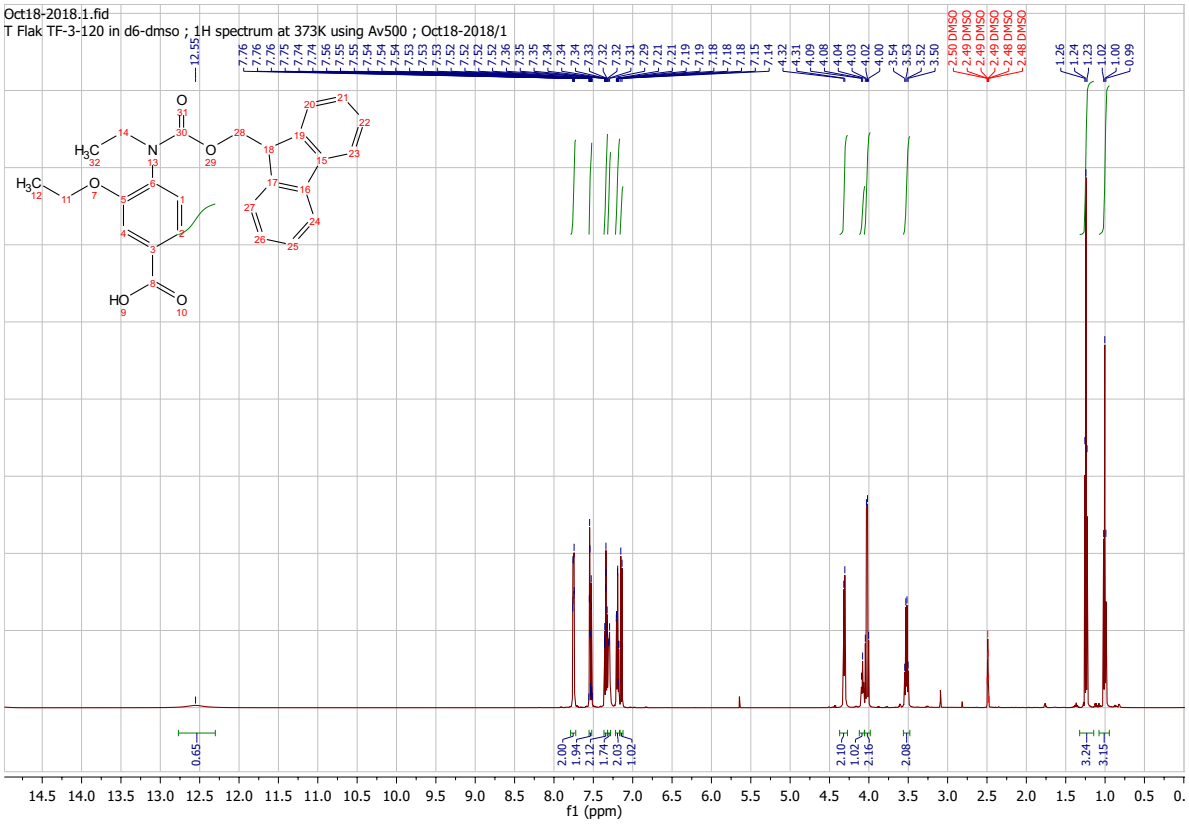

Jun12-2018.10.fid
TF-3-116
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.08 (s, 1H), 7.36 (dd, J = 8.1, 1.8 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.48 (s, 2H), 4.03 (q, J = 6.9 Hz, 2H), 1.36 (t, J = 6.9 Hz, 3H)
12.08
7.37
7.35
7.29
7.28
6.65
6.63
5.48
4.06
4.04
4.02
4.01
3.38 H2O
2.52 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
1.37
1.37
1.36
1.34
NH2
O
CH3
OH
0.90
1.07
1.06
1.07
1.73
2.21
3.35
f1 (ppm)

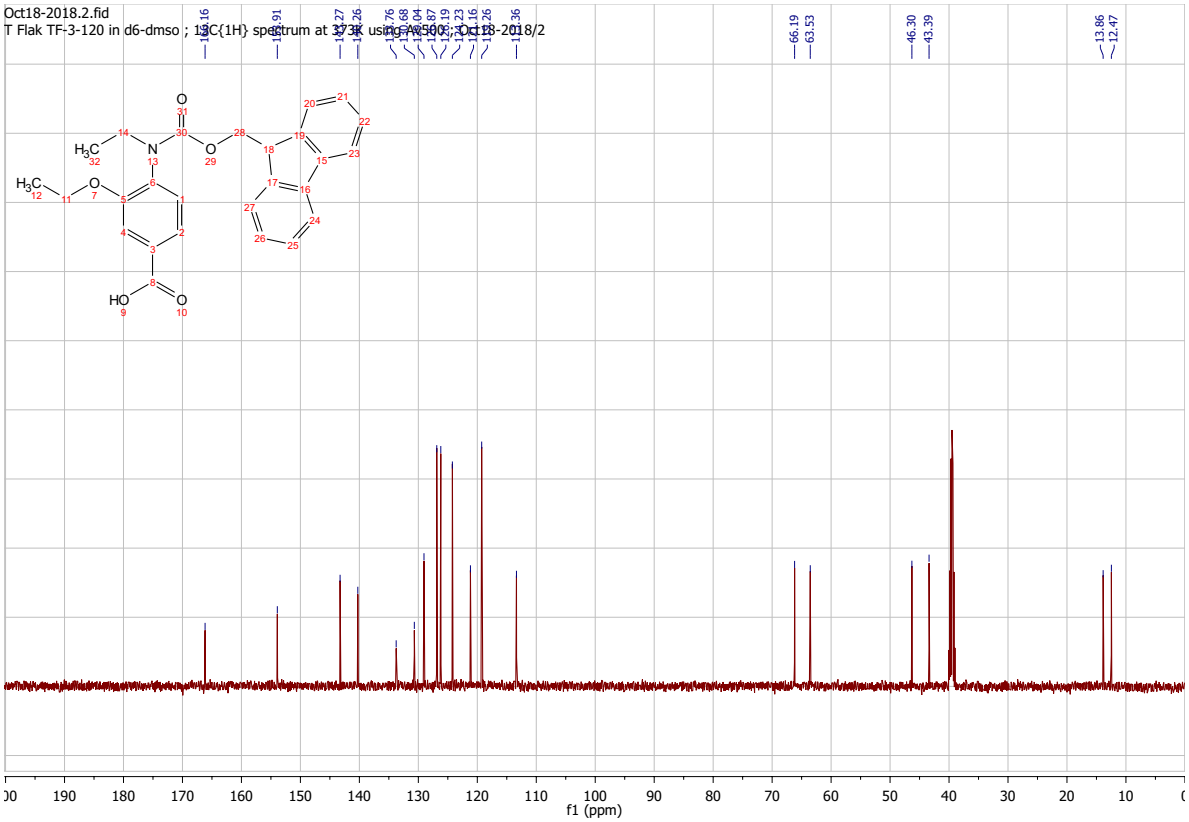

Jun12-2018.11.fid
TF-3-116
168.03
144.70
143.36
124.41
117.79
112.57
112.51
63.88
15.18
NH2
CH3
O
OH
f1 (ppm)

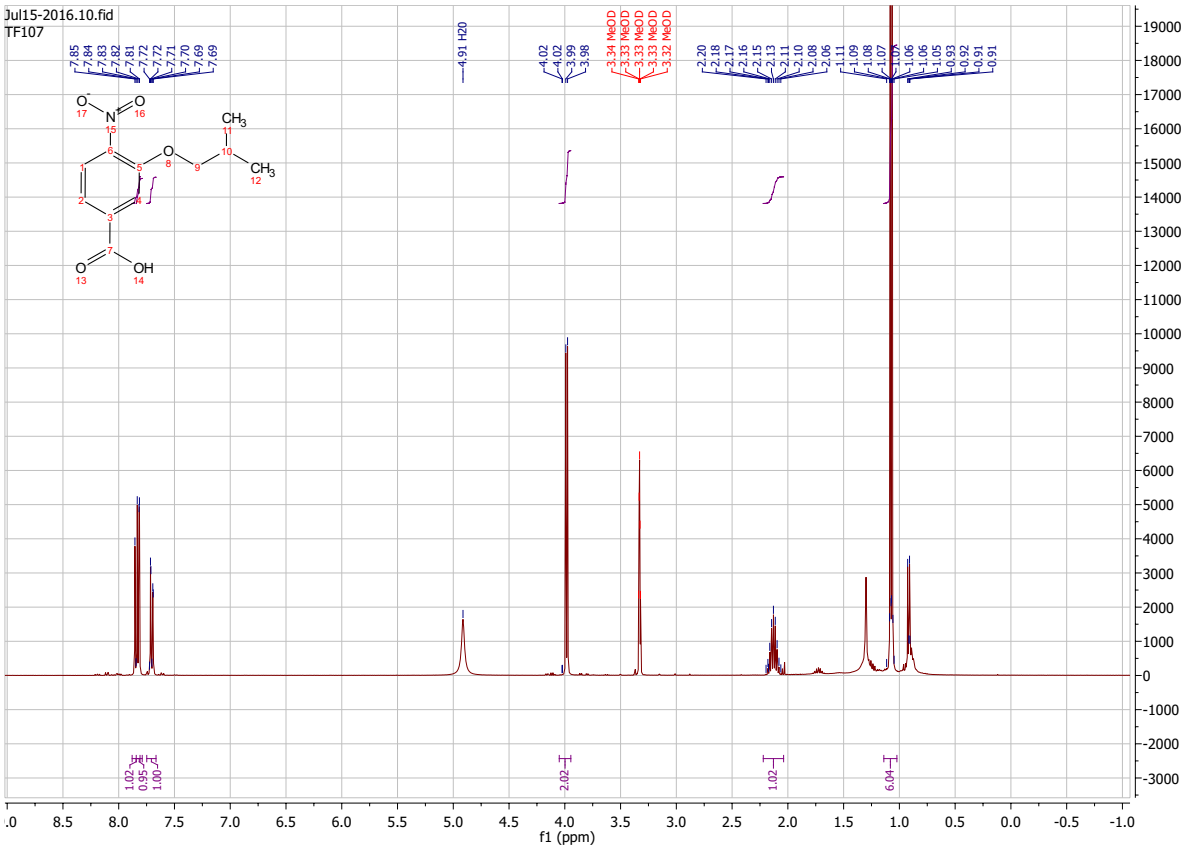

Jun13-2018.20.1.1r
TF-3-118b
f1 (ppm)

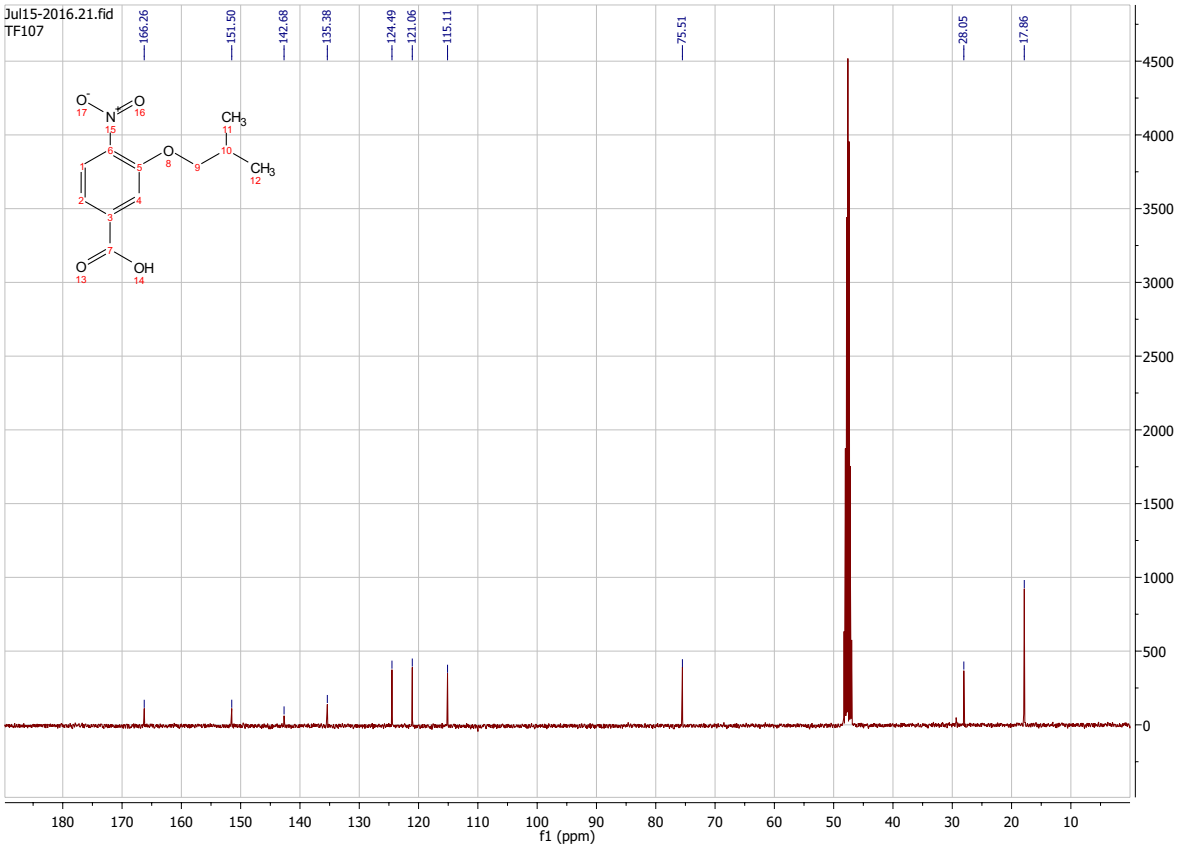

Jun14-2018.21.fid
TF-3-118b
f1 (ppm)

2

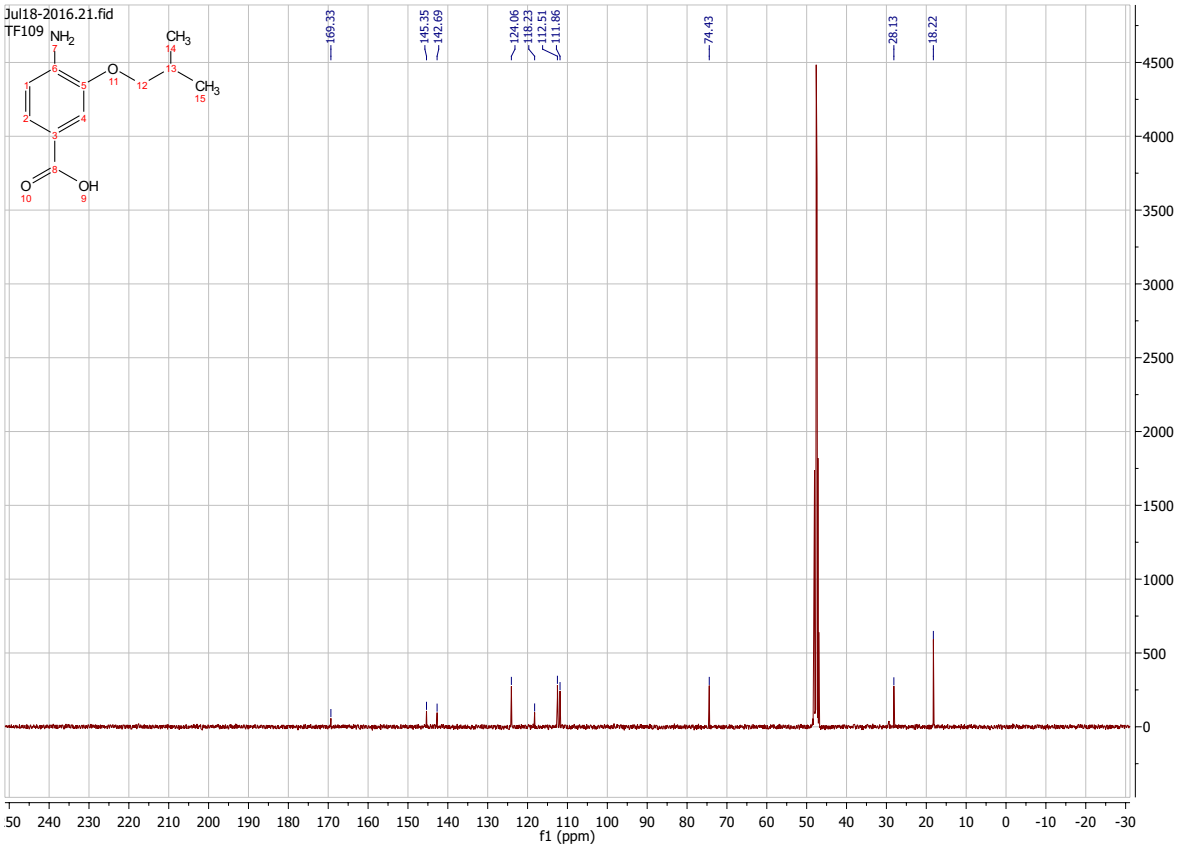

Oct18-2018.1.fid
T Flak TF-3-120 in d6-dmso ; 1H spectrum at 373K using Av500 ; Oct18-2018/1
f1 (ppm)

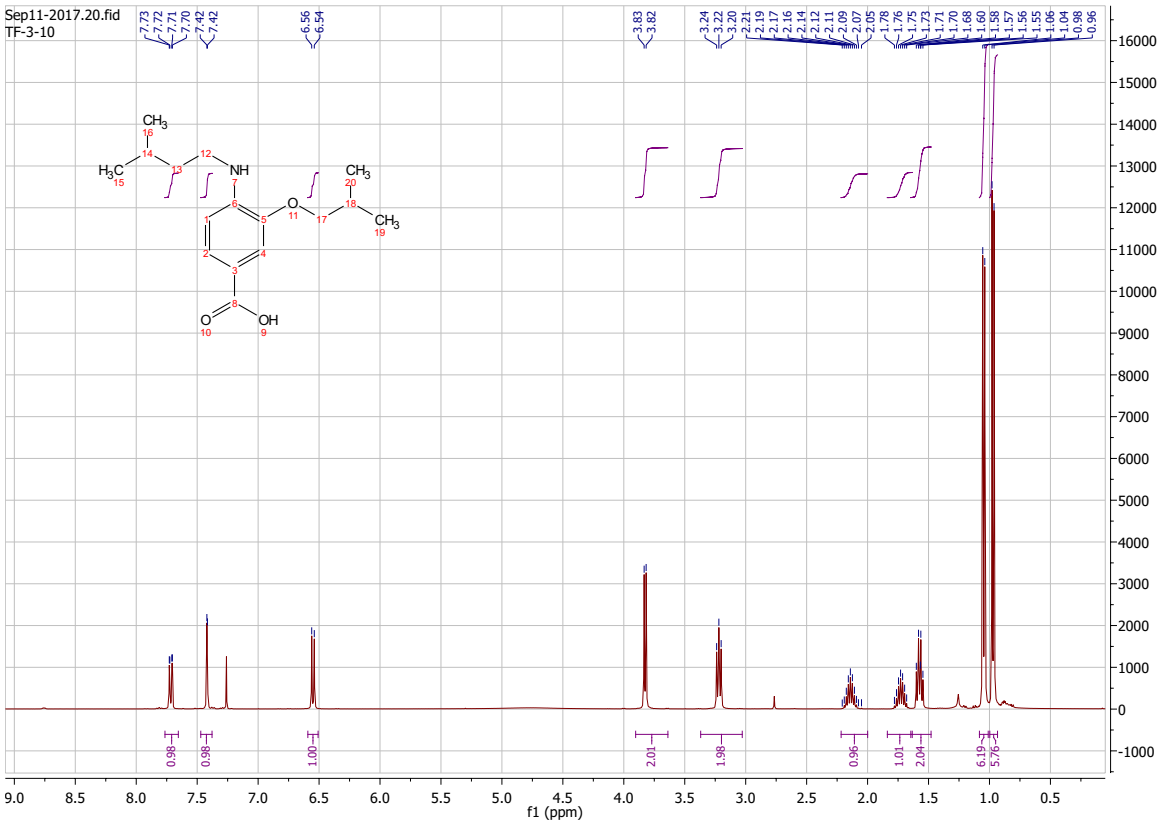

Oct18-2018.2.fid
T Flak TF-3-120 in d6-dmso ; 13C{1H} spectrum at 373K using Av500 ; Oct18-2018/2
f1 (ppm)

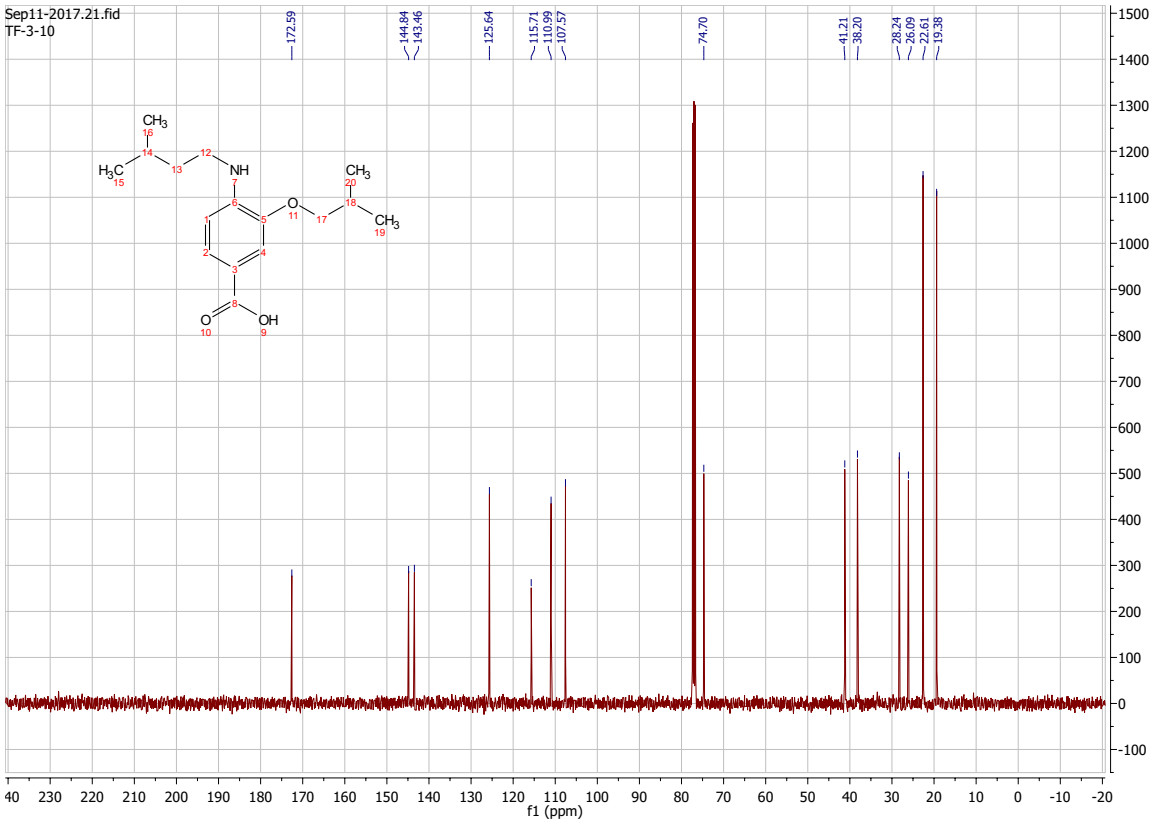

Jul15-2016.10.fid
TF107
7.85
7.84
7.83
7.82
7.81
7.72
7.71
7.70
7.69
7.69
4.91 H20
4.02
4.02
3.99
3.98
3.34 MeOD
3.33 MeOD
3.33 MeOD
3.33 MeOD
3.32 MeOD
2.20
2.18
2.17
2.16
2.15
2.13
2.11
2.10
2.08
2.06
1.11
1.09
1.08
1.07
1.06
1.06
1.06
1.05
0.93
0.92
0.91
0.91
1.02
0.95
1.00
2.02
1.02
6.04
f1 (ppm)


Jul15-2016.21.fid
TF107
166.26
151.50
142.68
135.38
124.49
121.06
115.11
75.51
28.05
17.86
f1 (ppm)

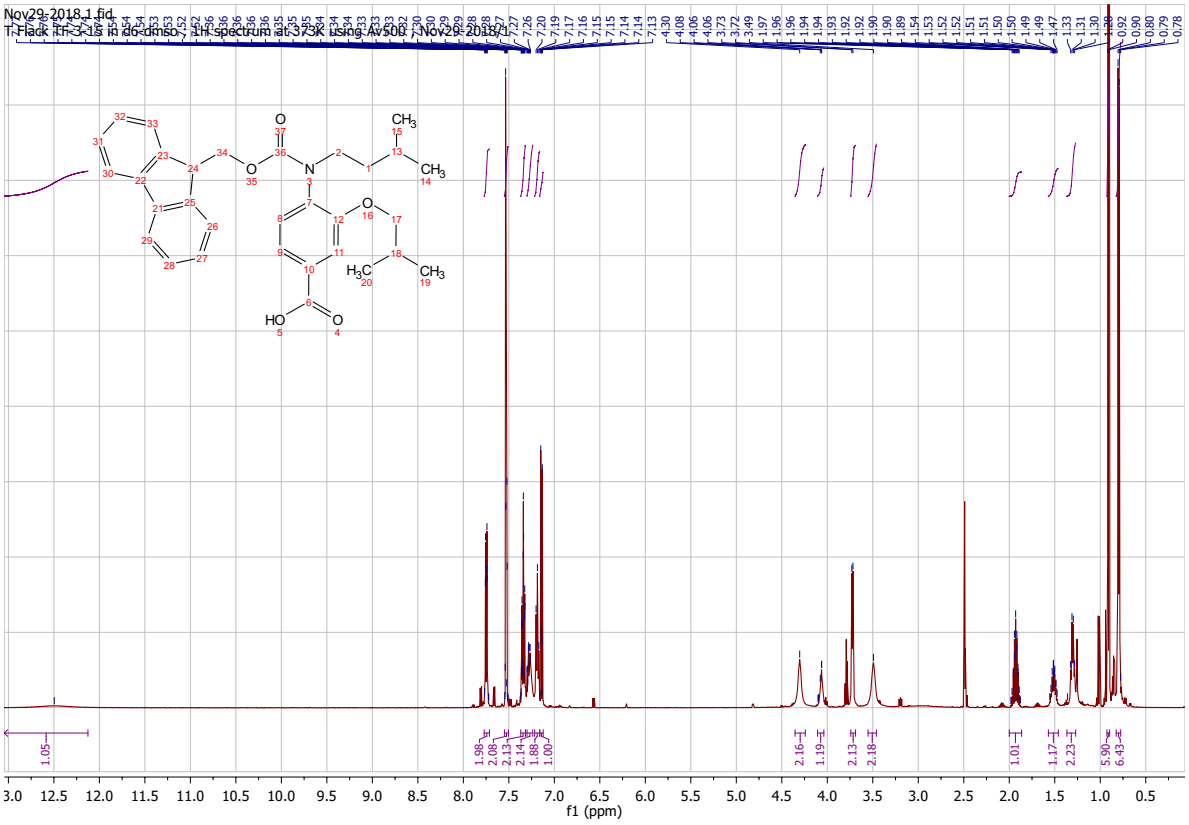

Jul18-2016.20.fid
TF109
A (d) 7.42
C (dd) 7.49
E (d) 6.71
F (d) 3.82
D (hept) 2.14
B (d) 1.09
f1 (ppm)

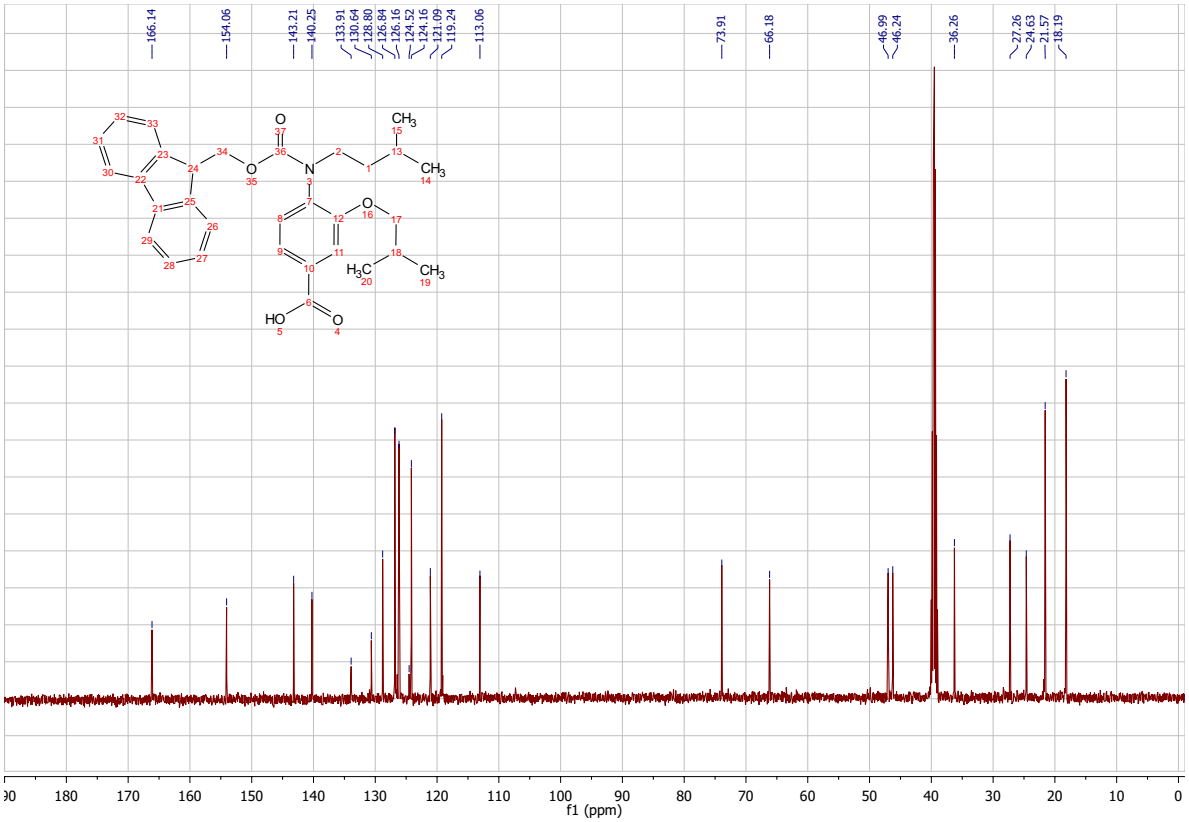

Jul18-2016.21.fid
TF109
f1 (ppm)

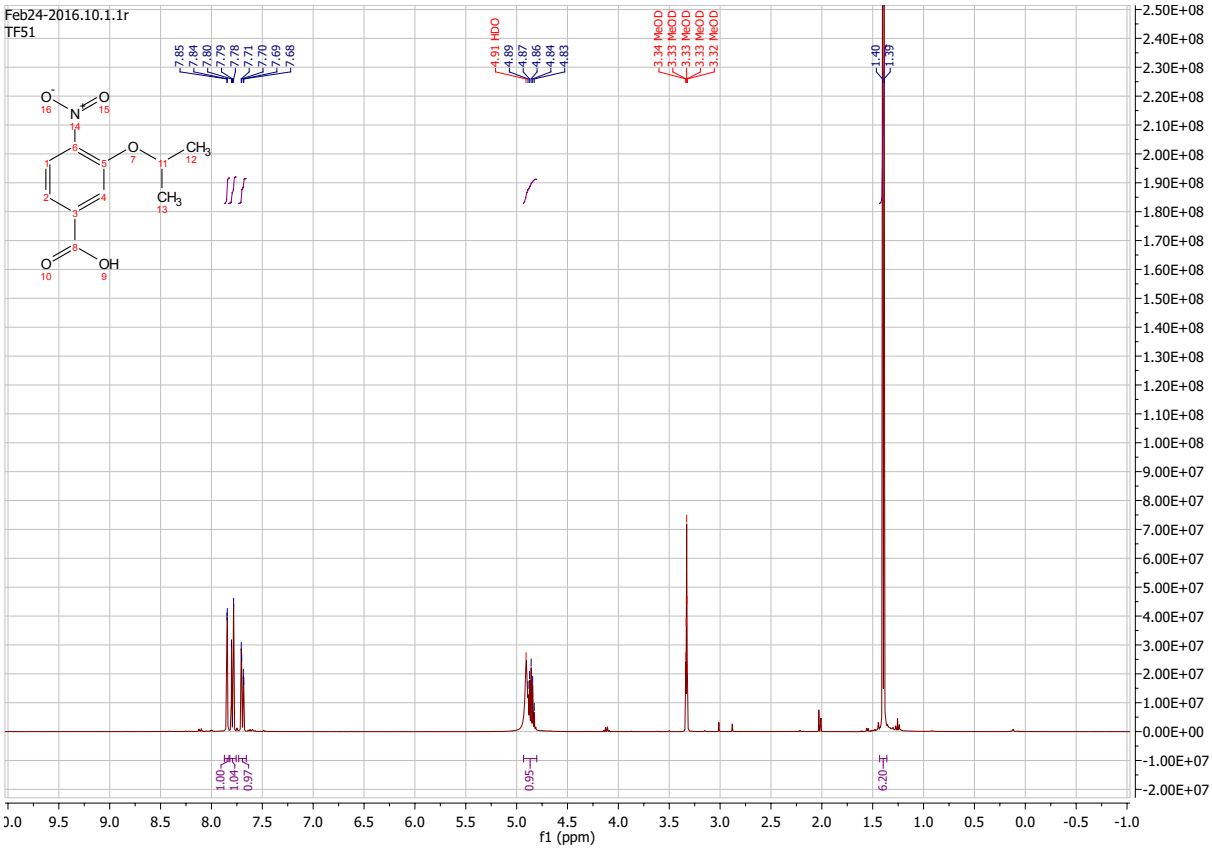

Sep11-2017.20.fid
TF-3-10
f1 (ppm)

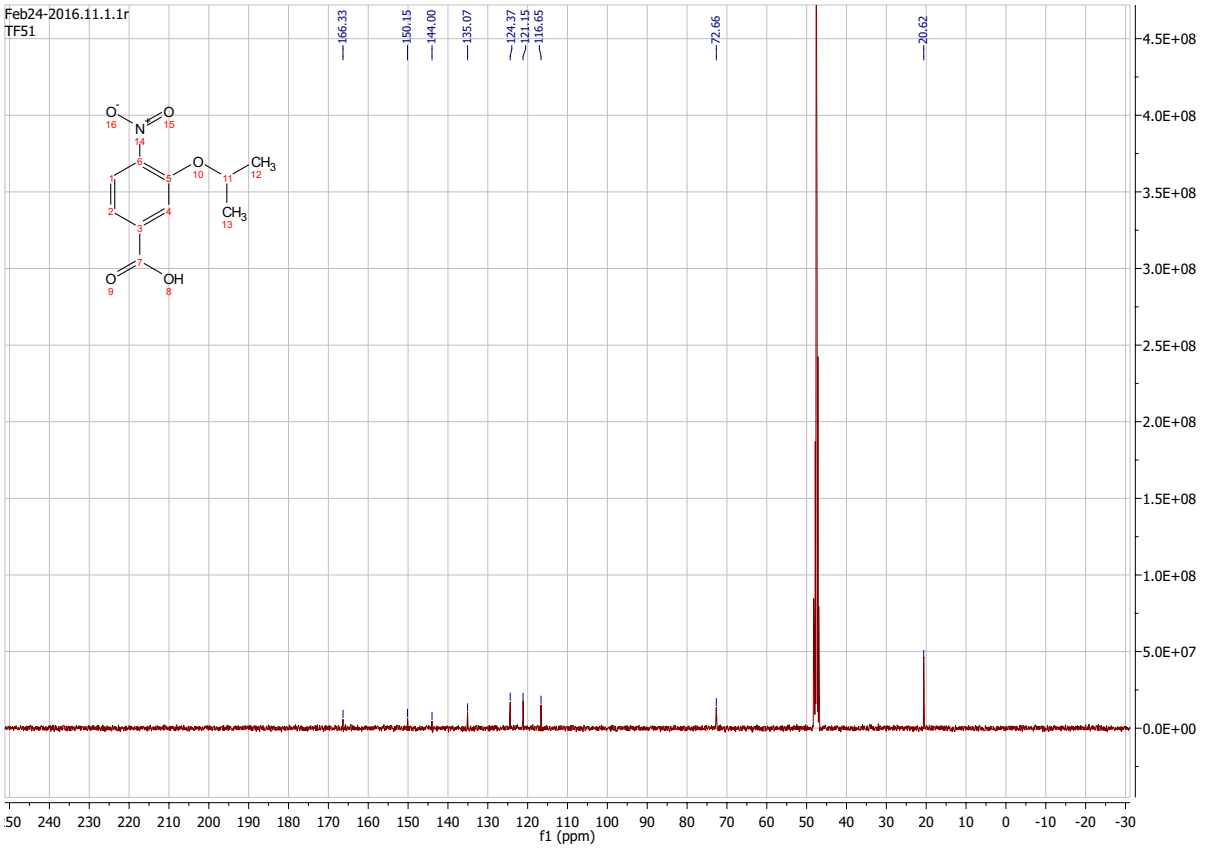

Sep11-2017.21.fid
TF-3-10
f1 (ppm)

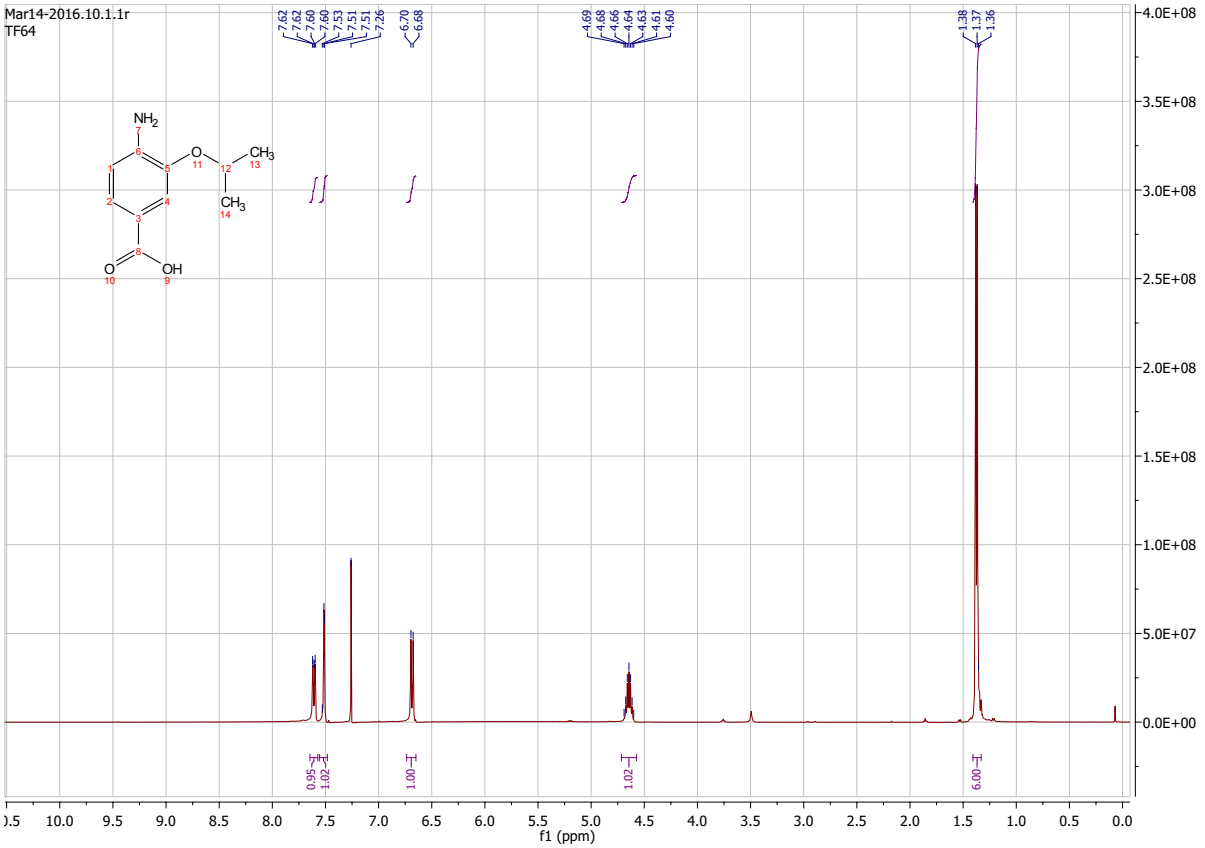
3

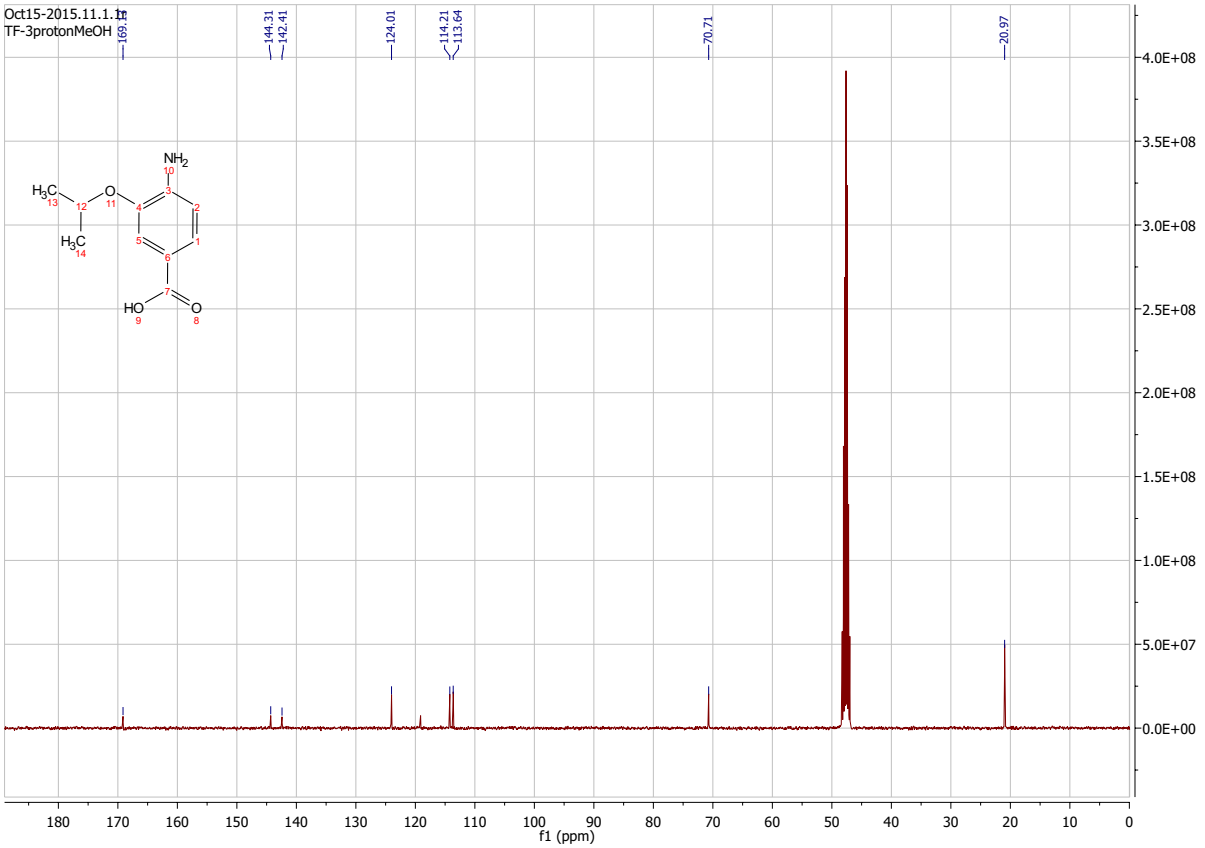

Nov29-2018-1.fid
1-Flack rh-2-15 in dcl-dmso ; 1H spectrum at 373K using Av500 ; Nov29-2018/1
f1 (ppm)

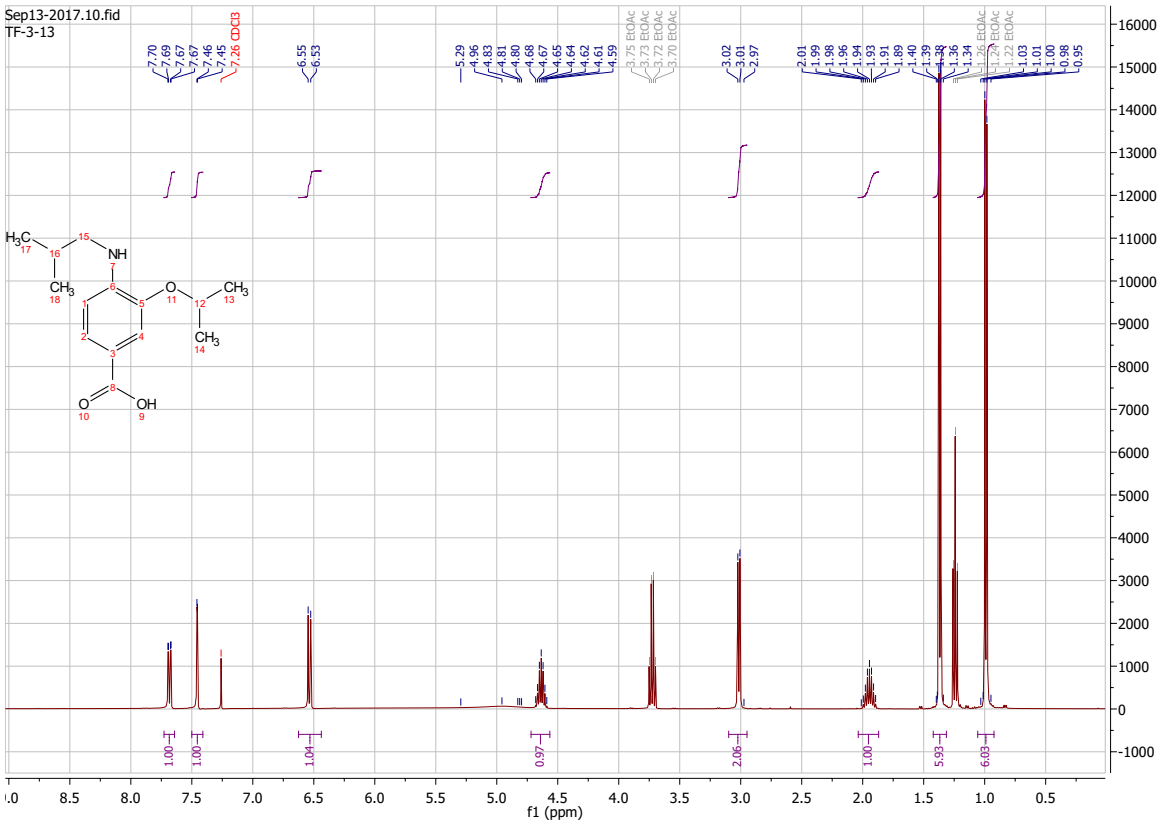

166.14
154.06
143.21
140.25
133.91
130.64
128.80
126.84
126.16
124.52
124.16
121.09
119.24
113.06
73.91
66.18
46.99
46.24
36.26
27.26
24.63
21.57
18.19
f1 (ppm)

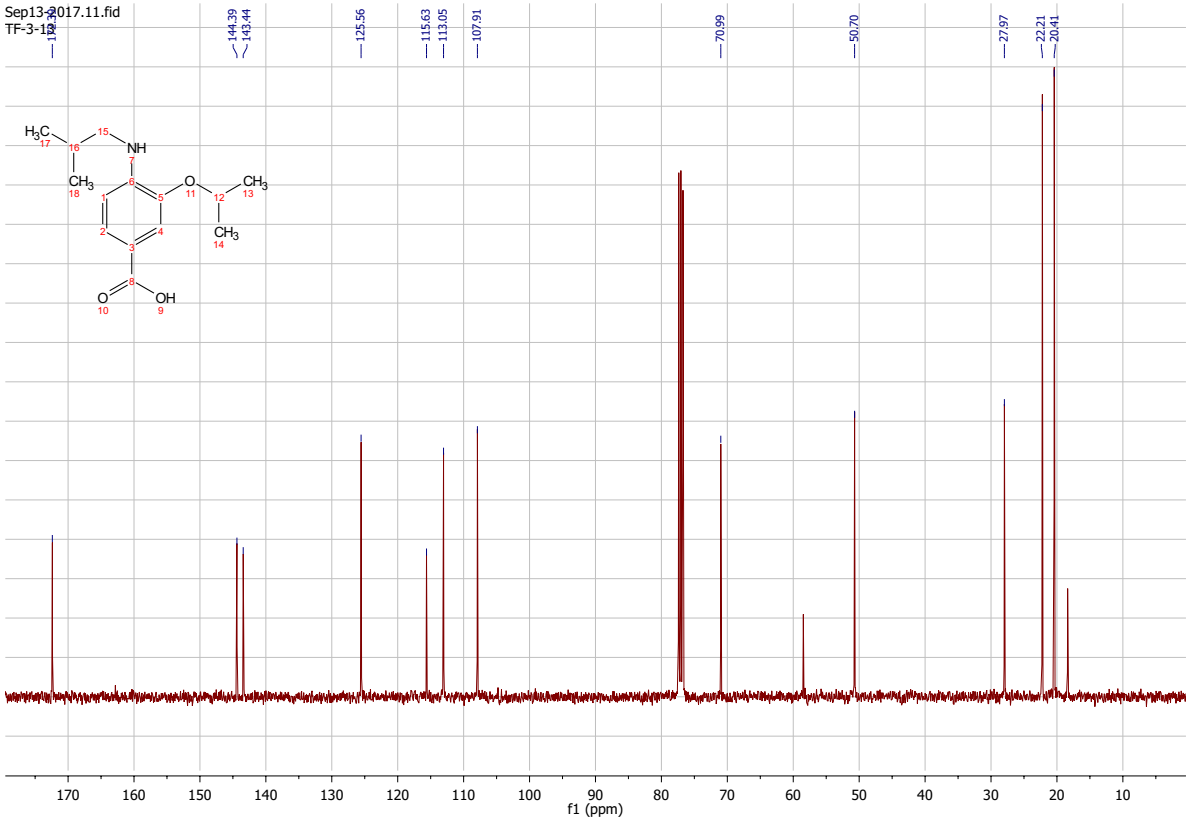

Feb24-2016.10.1.1r
TF51
7.85
7.84
7.80
7.79
7.78
7.71
7.70
7.69
7.68
4.91 HDO
4.89
4.87
4.86
4.84
4.83
3.34 MeOD
3.33 MeOD
3.33 MeOD
3.33 MeOD
3.32 MeOD
1.40
1.39
1.00
1.04
0.97
0.95
6.20
f1 (ppm)

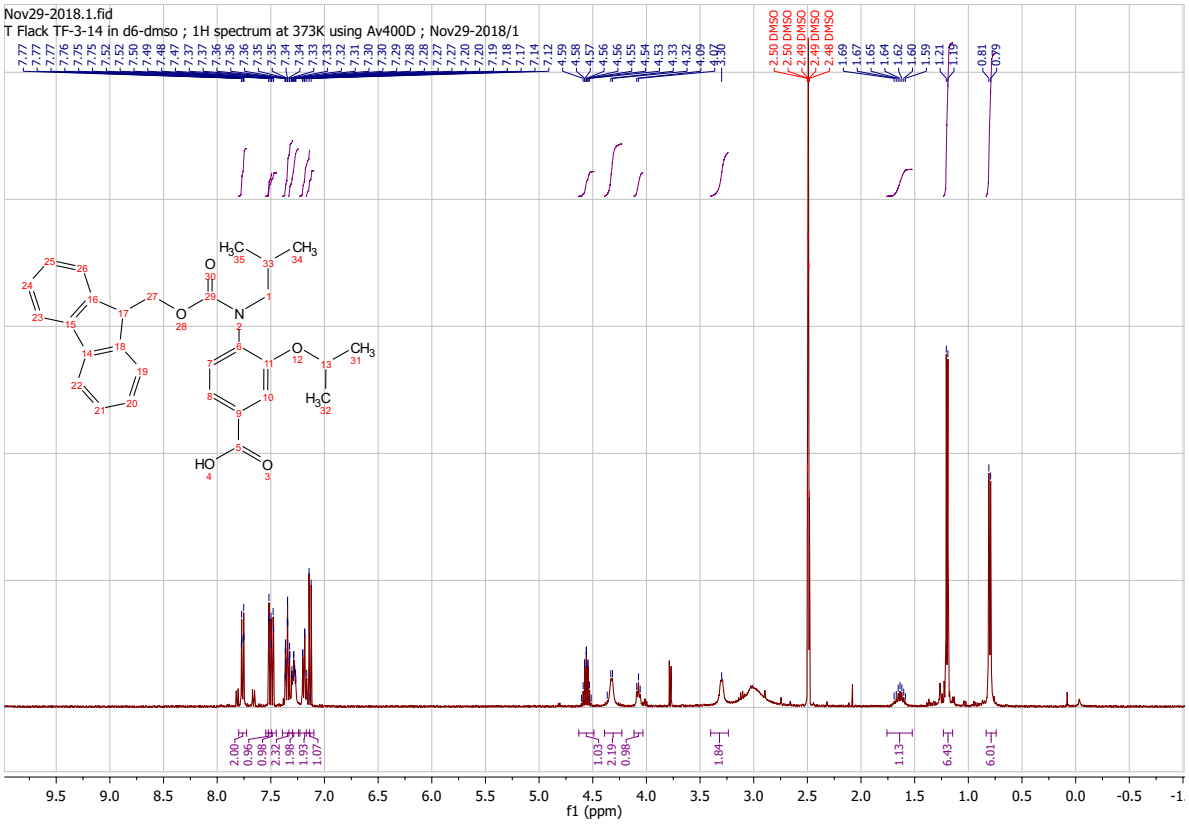

Feb24-2016.11.1.1r
TF51
166.33
150.15
144.00
135.07
124.37
121.15
116.65
72.66
20.62
f1 (ppm)

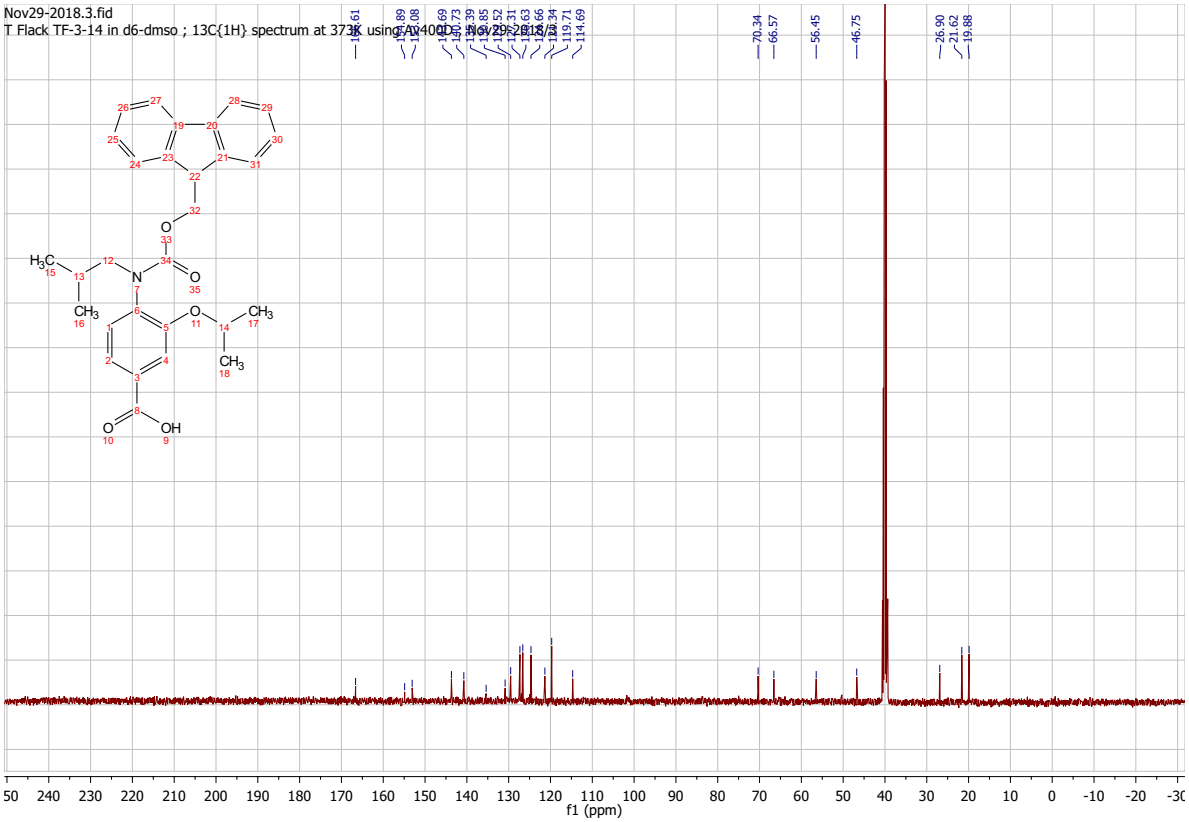

Mar14-2016.10.1.1r
TF64
7.62
7.62
7.60
7.60
7.53
7.51
7.51
7.26
6.70
6.68
4.69
4.68
4.66
4.64
4.63
4.61
4.60
1.38
1.37
1.36
NH2
CH3
CH3
OH
0.95
1.02
1.00
1.02
6.00
f1 (ppm)

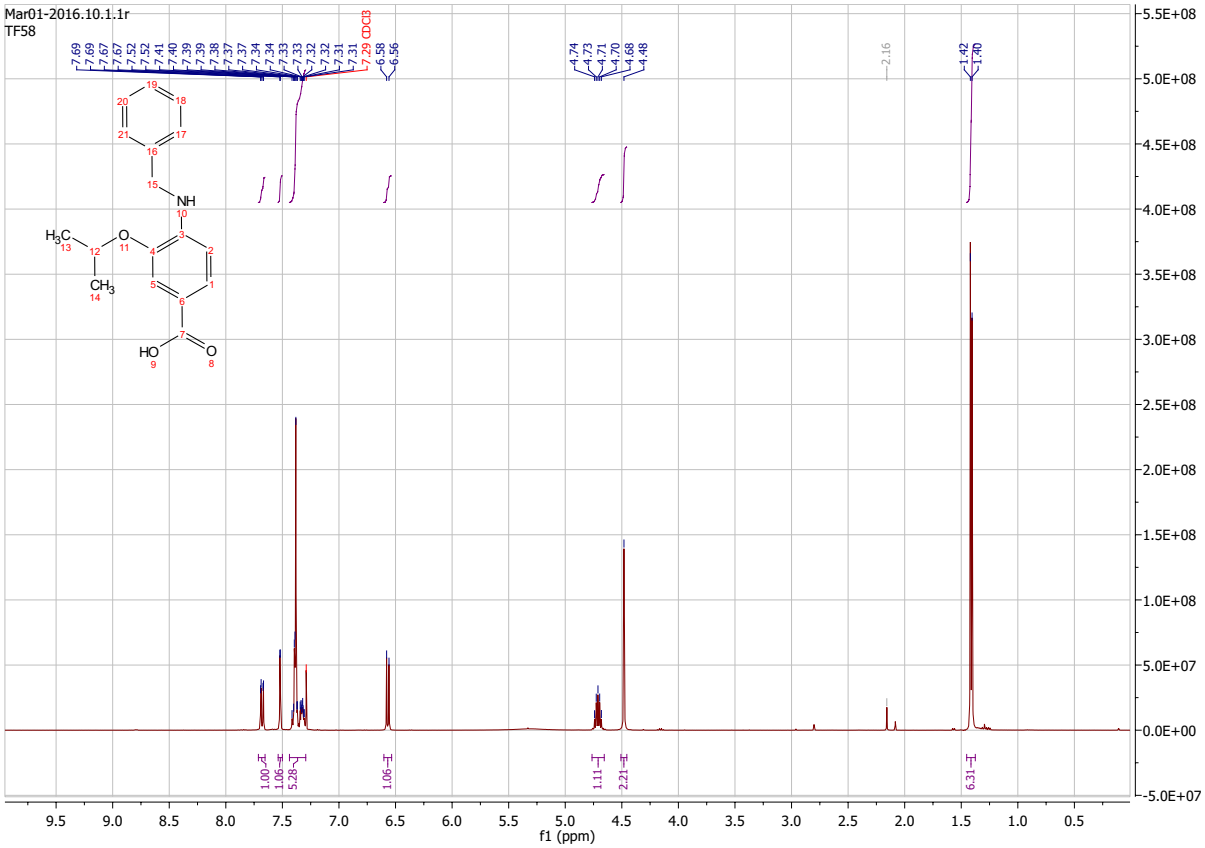

Oct15-2015.11.1.1r
TF-3protonMeOH
169.12
144.31
142.41
124.01
114.21
113.64
70.71
20.97
NH2
H3C
H3C
HO
O
f1 (ppm)

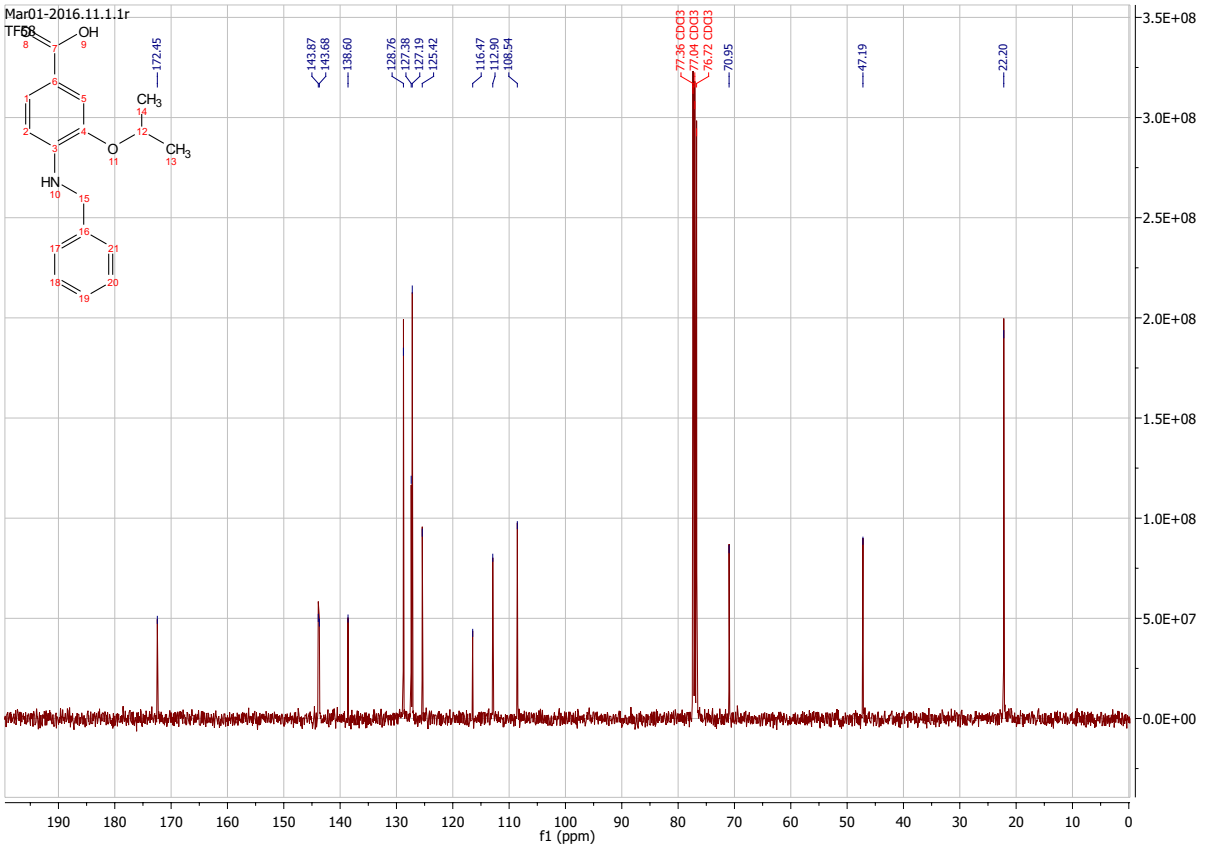

Sep13-2017.10.fid
TF-3-13
f1 (ppm)

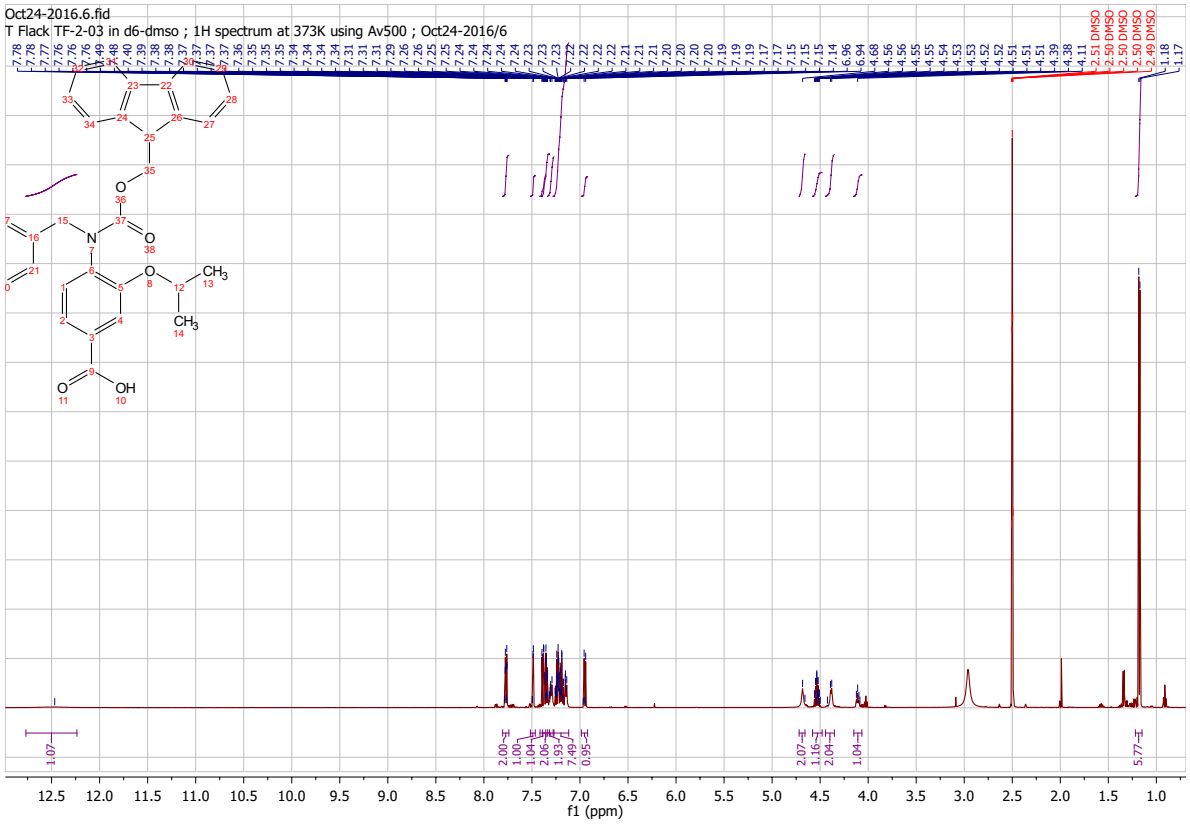

Sep13-2017.11.fid
f1 (ppm)

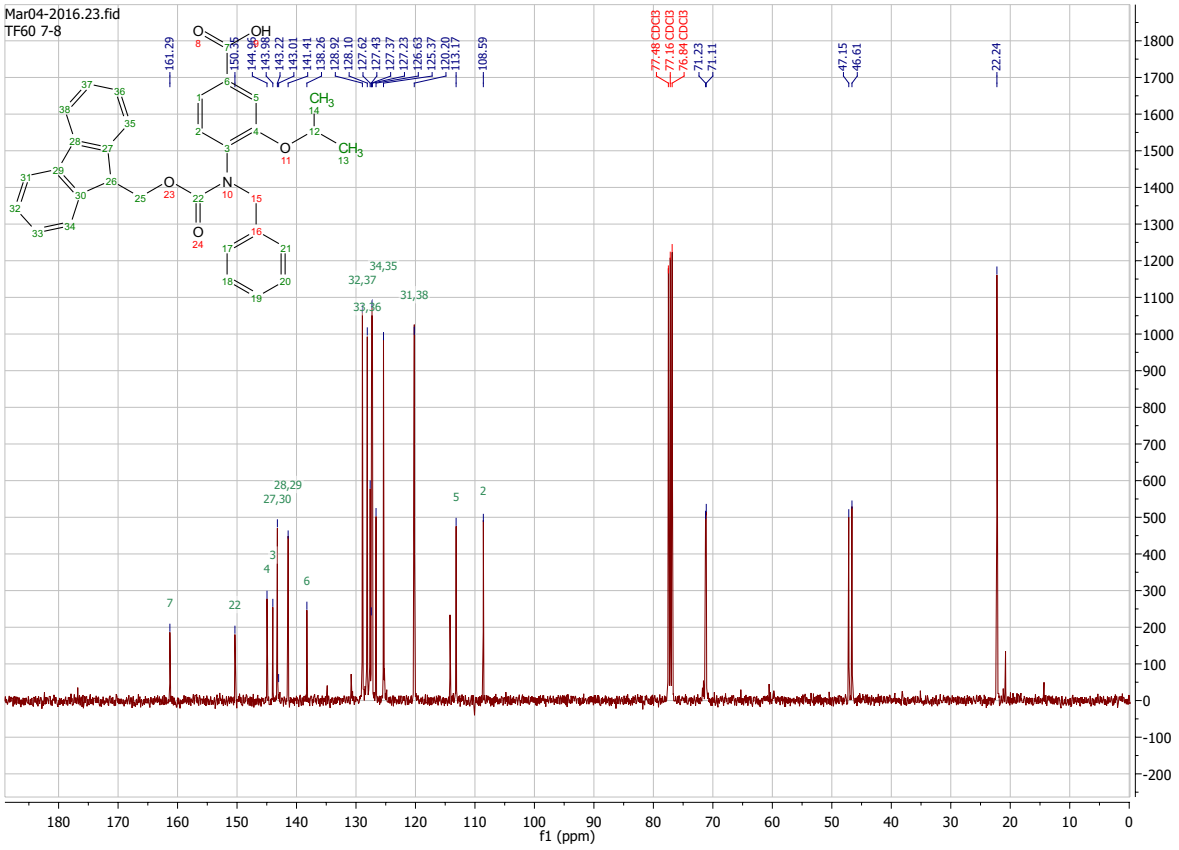

Nov29-2018.1.fid
T Flack TF-3-14 in d6-dmso ; 1H spectrum at 373K using Av400D ; Nov29-2018/1
f1 (ppm)

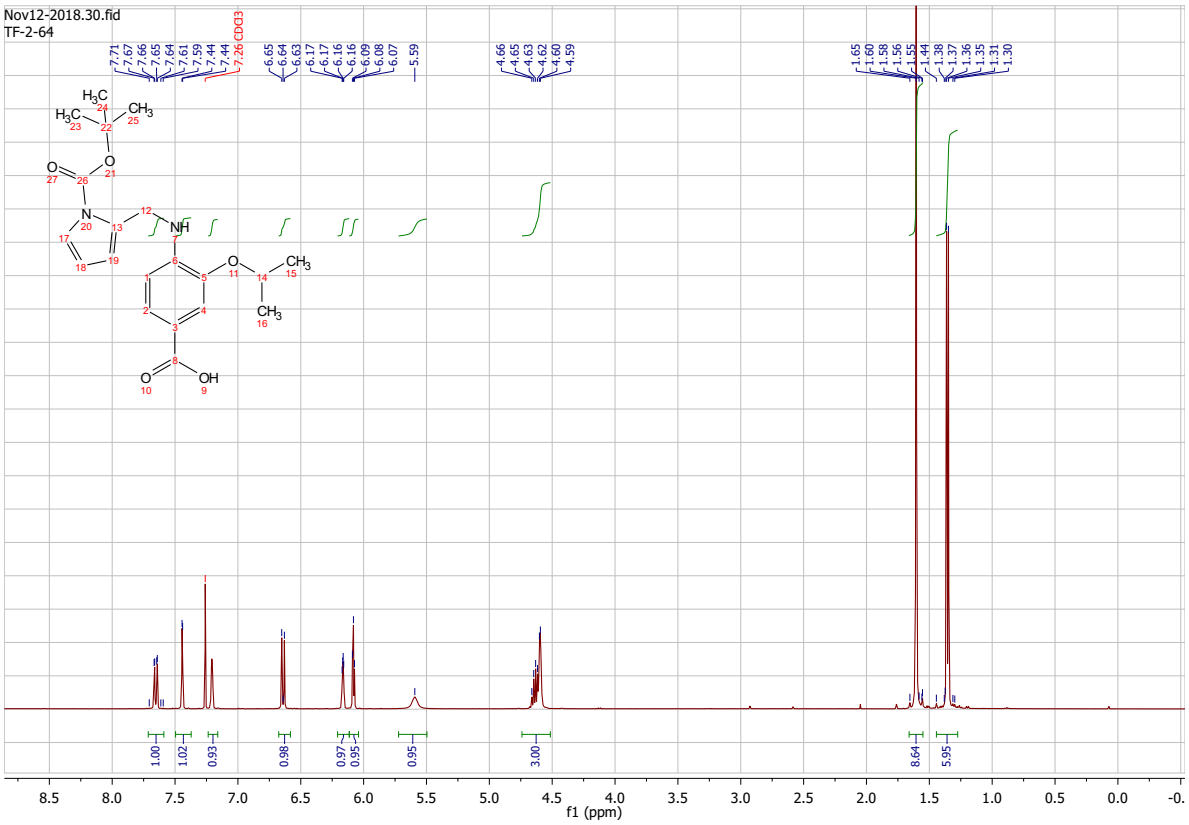

Nov29-2018.3.fid
T Flack TF-3-14 in d6-dmso ; 13C{1H} spectrum at 373K using Av400D ; Nov29-2018/3
f1 (ppm)

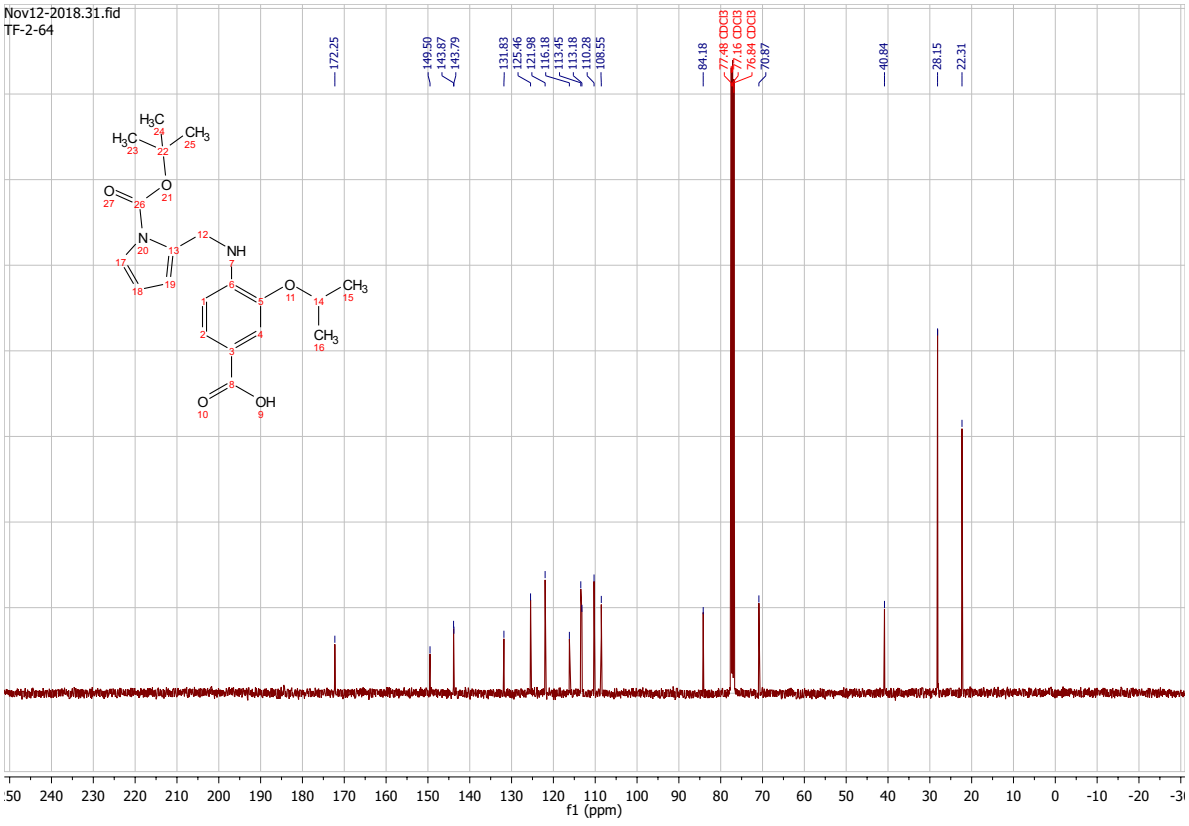

Mar01-2016.10.1.1r
TF58
f1 (ppm)


Mar01-2016.11.1.1r
TF58
f1 (ppm)

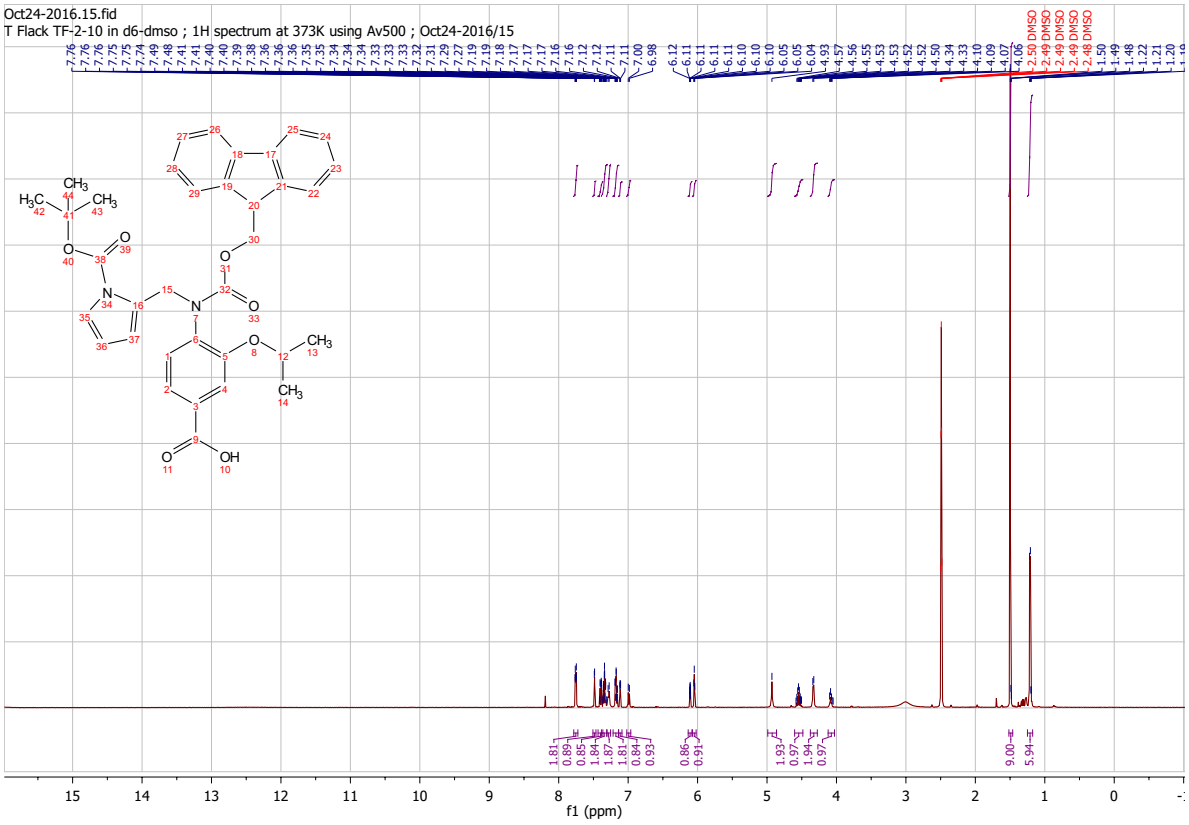

Oct24-2016.6.fid
T Flack TF-2-03 in d6-dmso ; 1H spectrum at 373K using Av500 ; Oct24-2016/6
f1 (ppm)

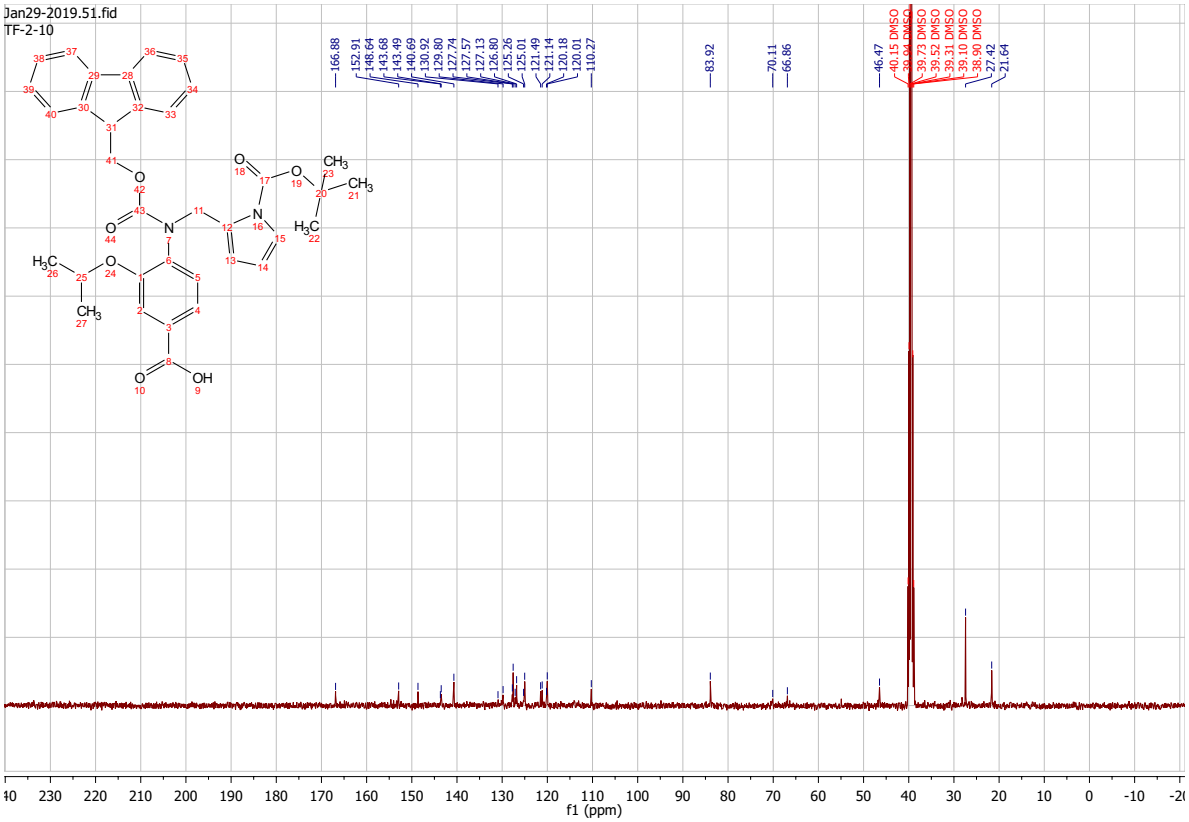

Mar04-2016.23.fid
TF60 7-8
f1 (ppm)

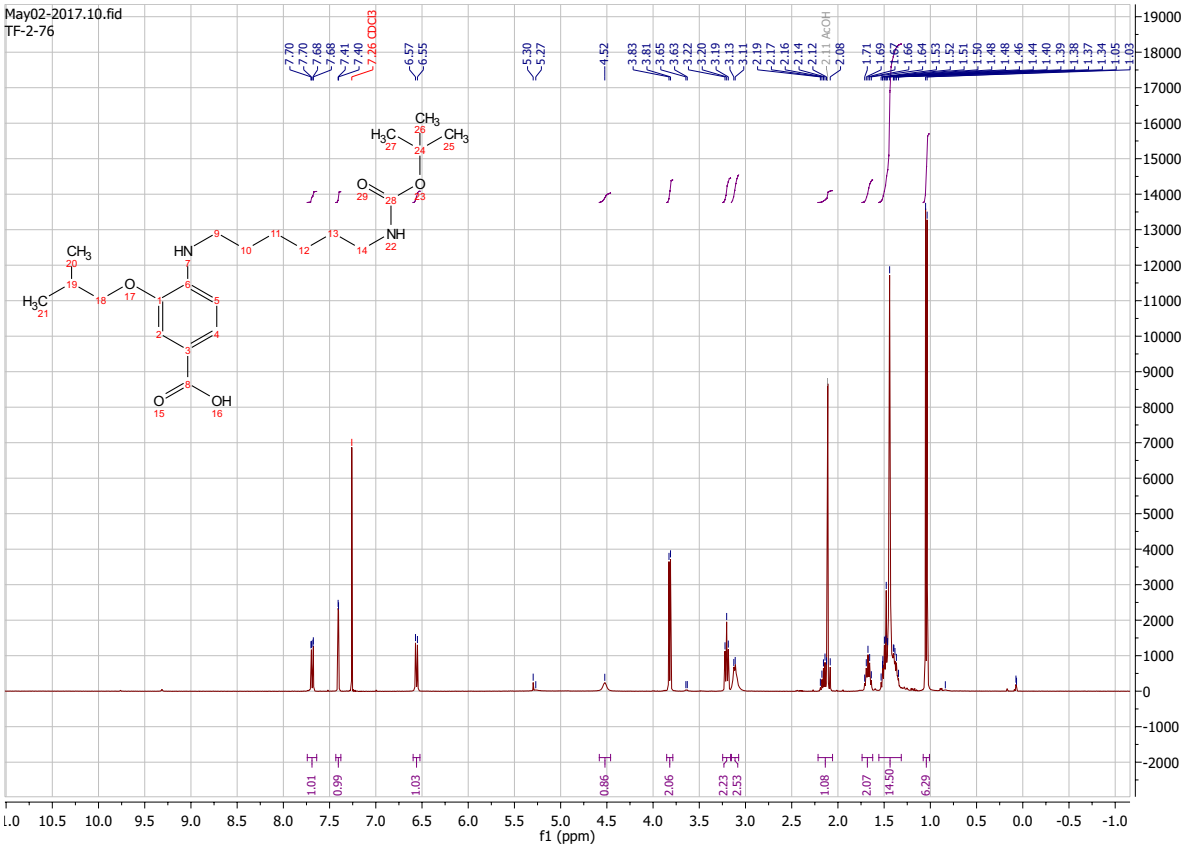

Nov12-2018.30.fid
TF-2-64
f1 (ppm)

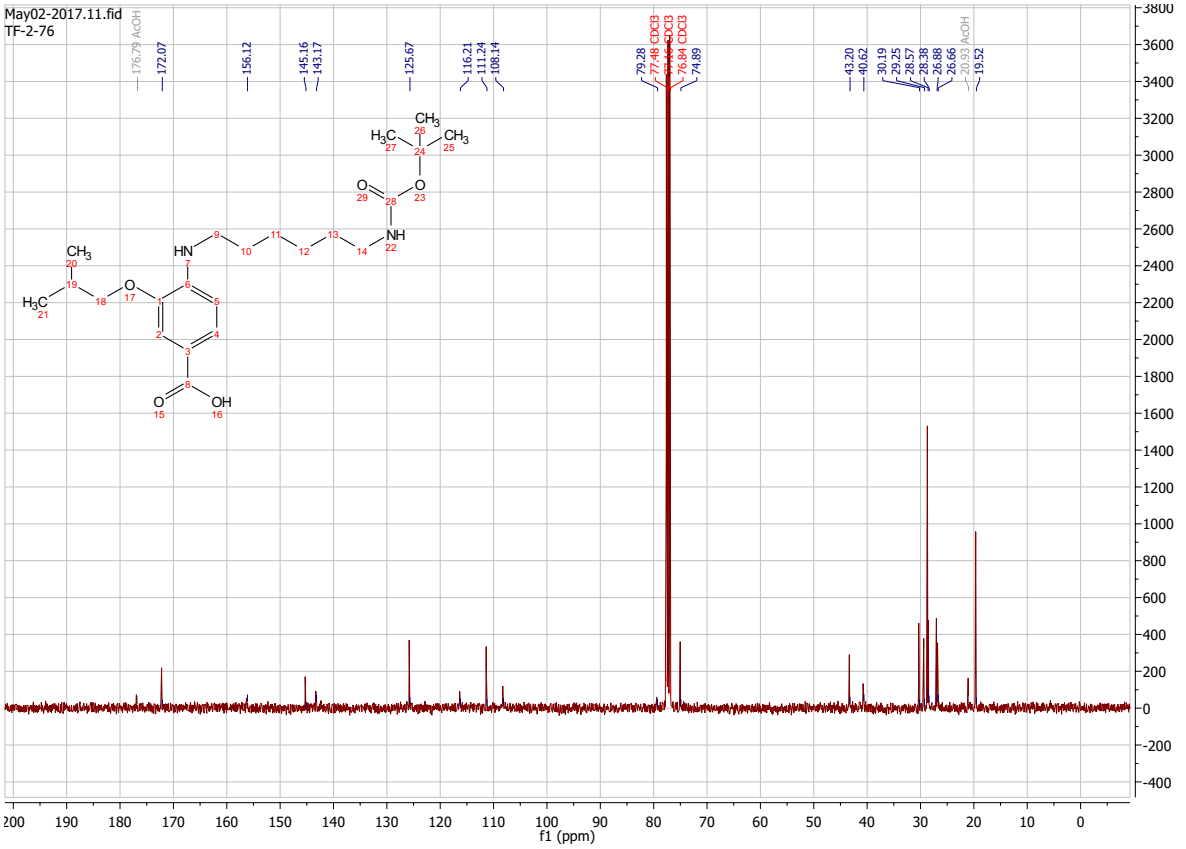

Nov12-2018.31.fid
TF-2-64
f1 (ppm)

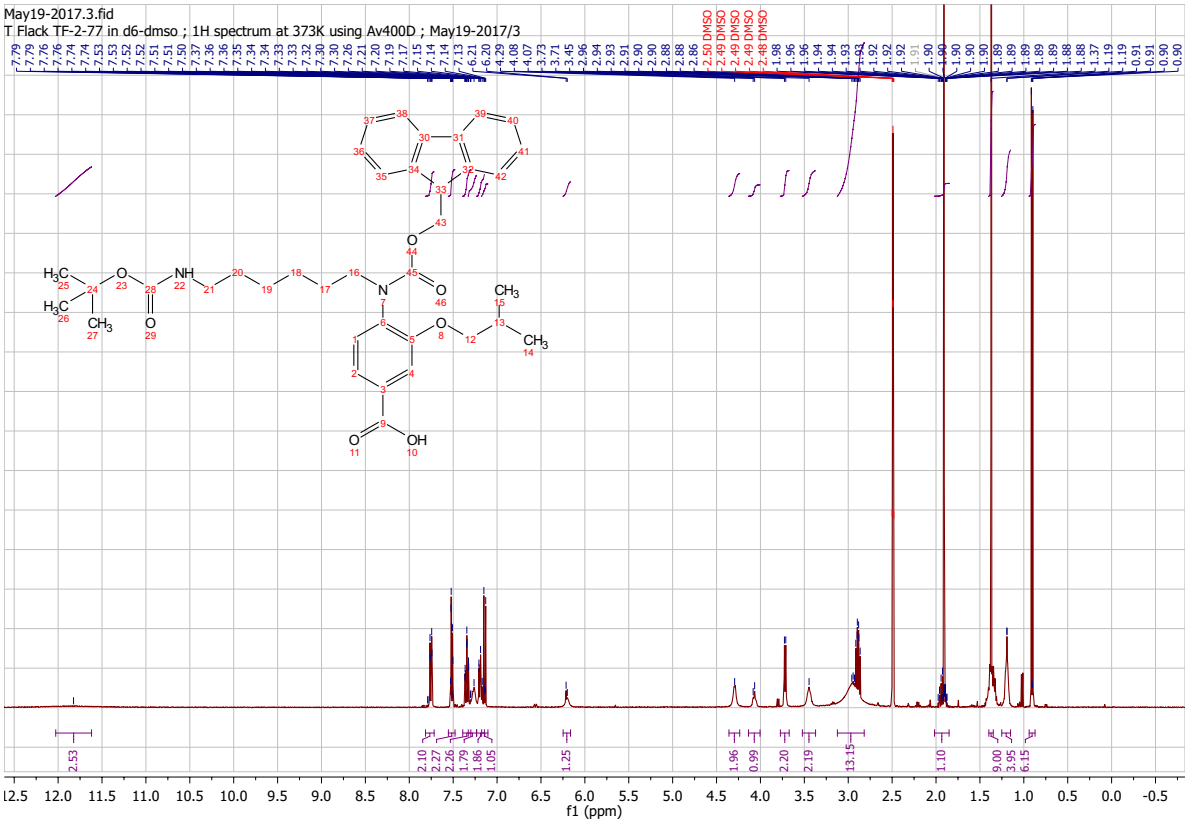
6

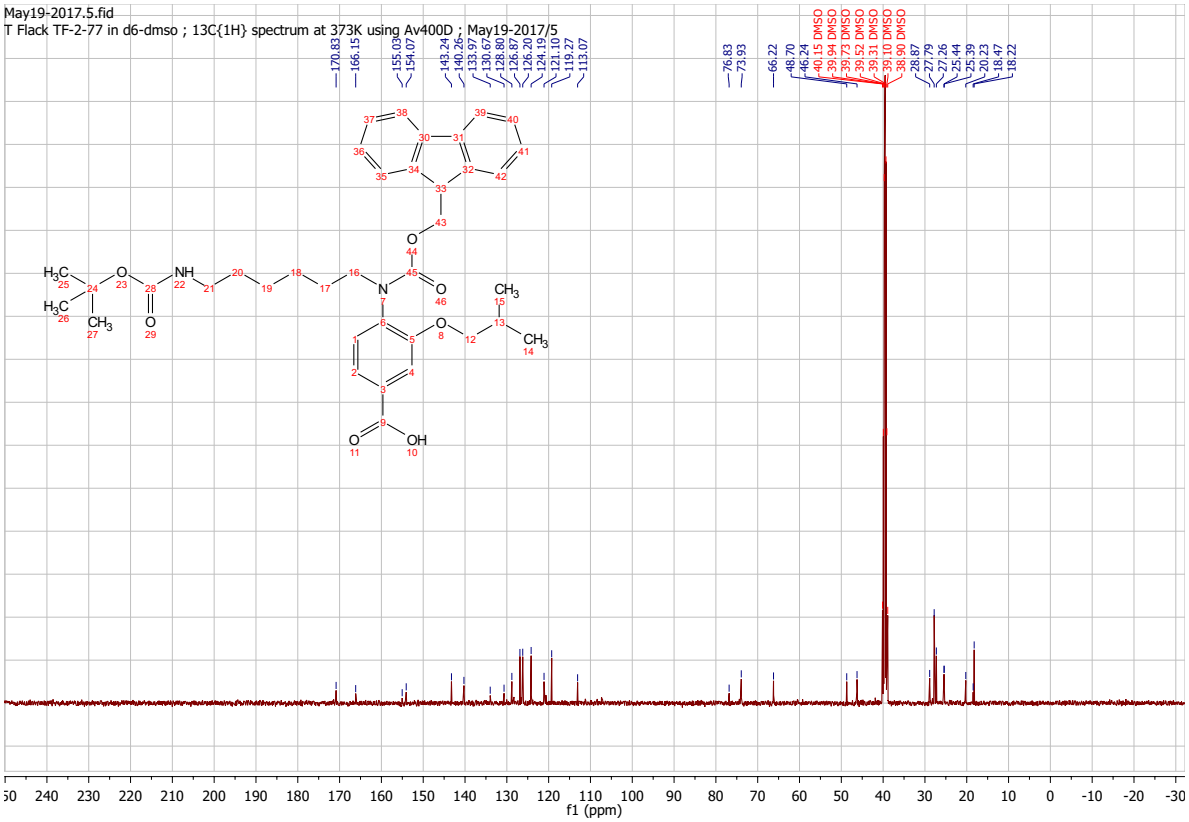

Oct24-2016.15.fid
T Flack TF-2-10 in d6-dmso ; 1H spectrum at 373K using Av500 ; Oct24-2016/15
f1 (ppm)

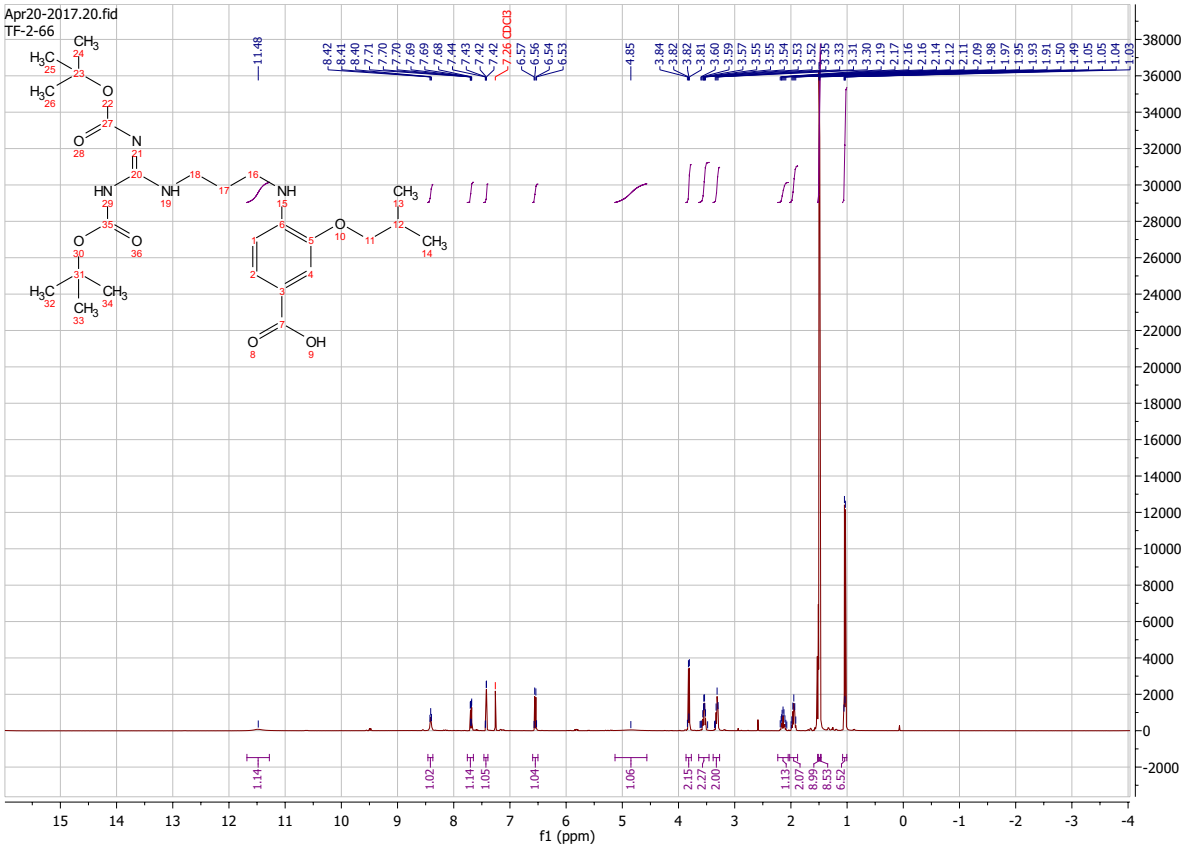

Jan29-2019.51.fid
TF-2-10
f1 (ppm)

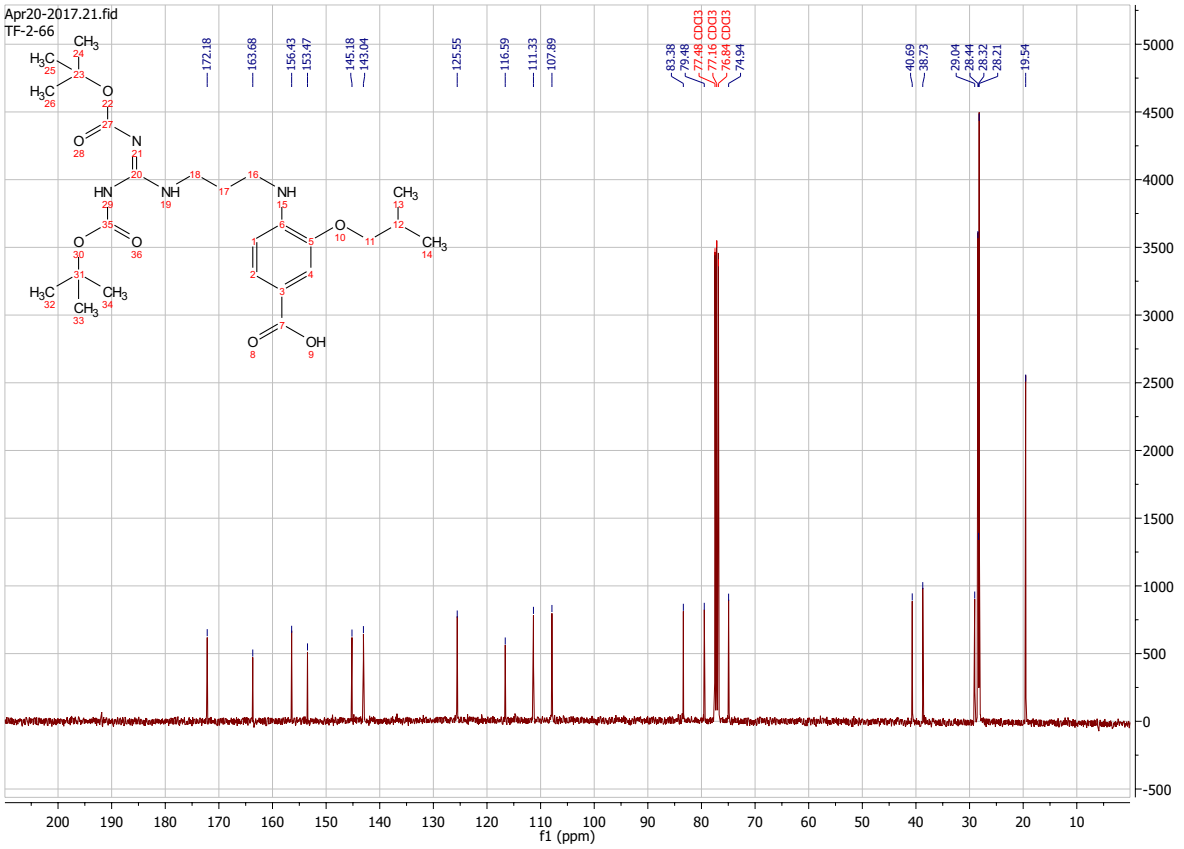

May02-2017.10.fid
TF-2-76
f1 (ppm)

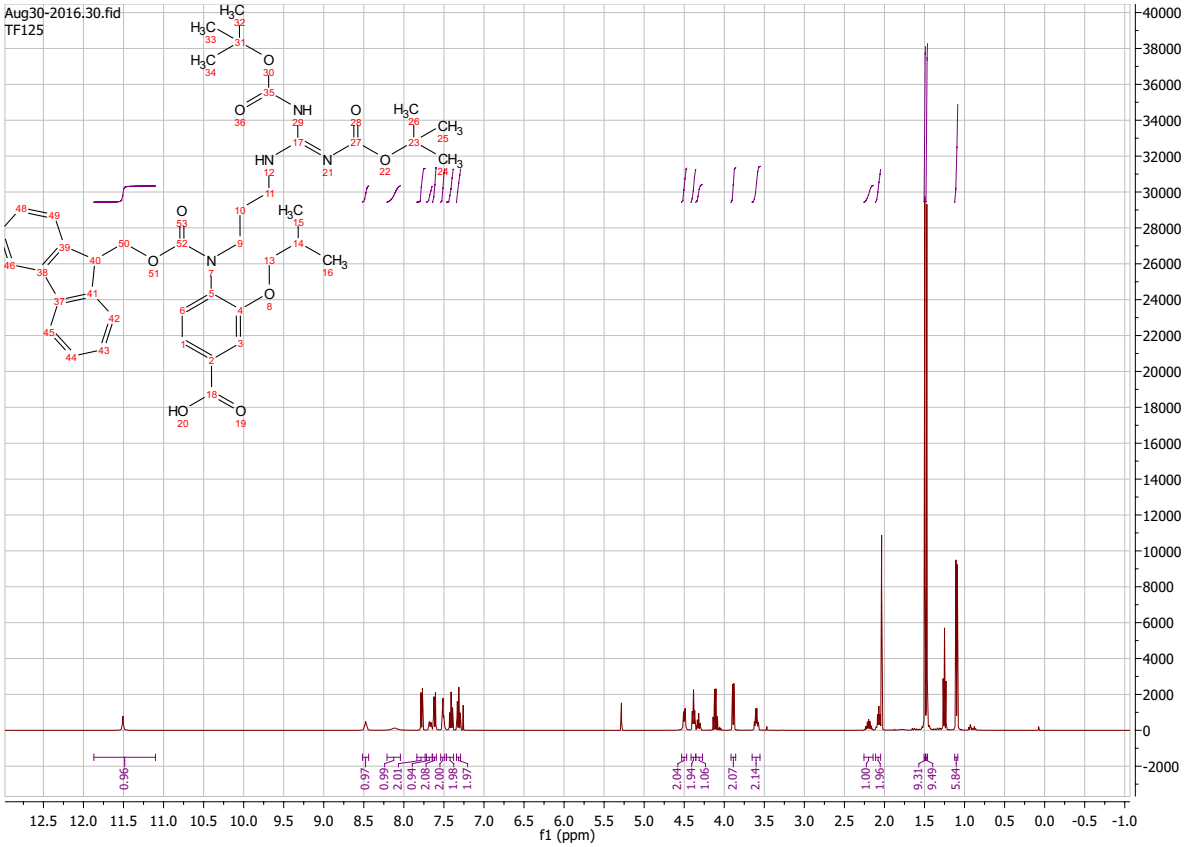

May02-2017.11.fid
TF-2-76
f1 (ppm)

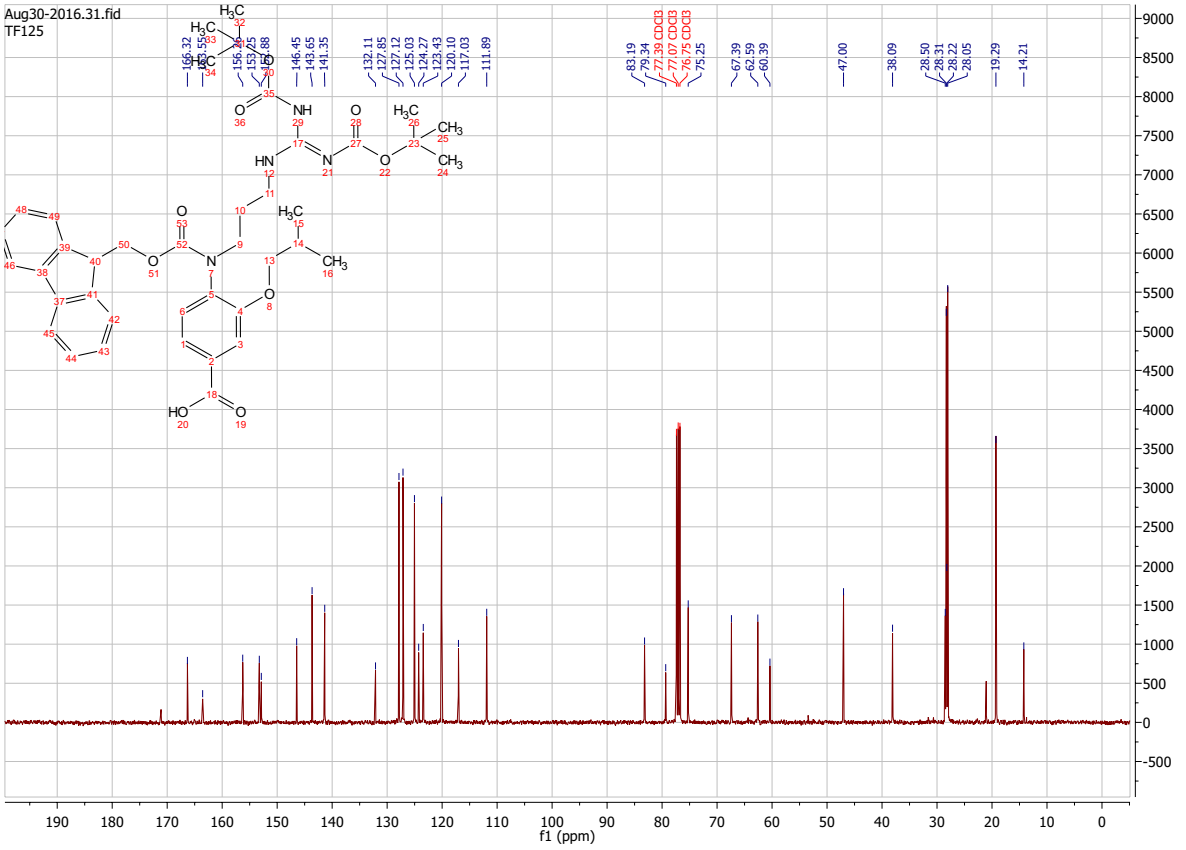

May19-2017.3.fid
T Flack TF-2-77 in d6-dmso ; 1H spectrum at 373K using Av400D ; May19-2017/3
f1 (ppm)

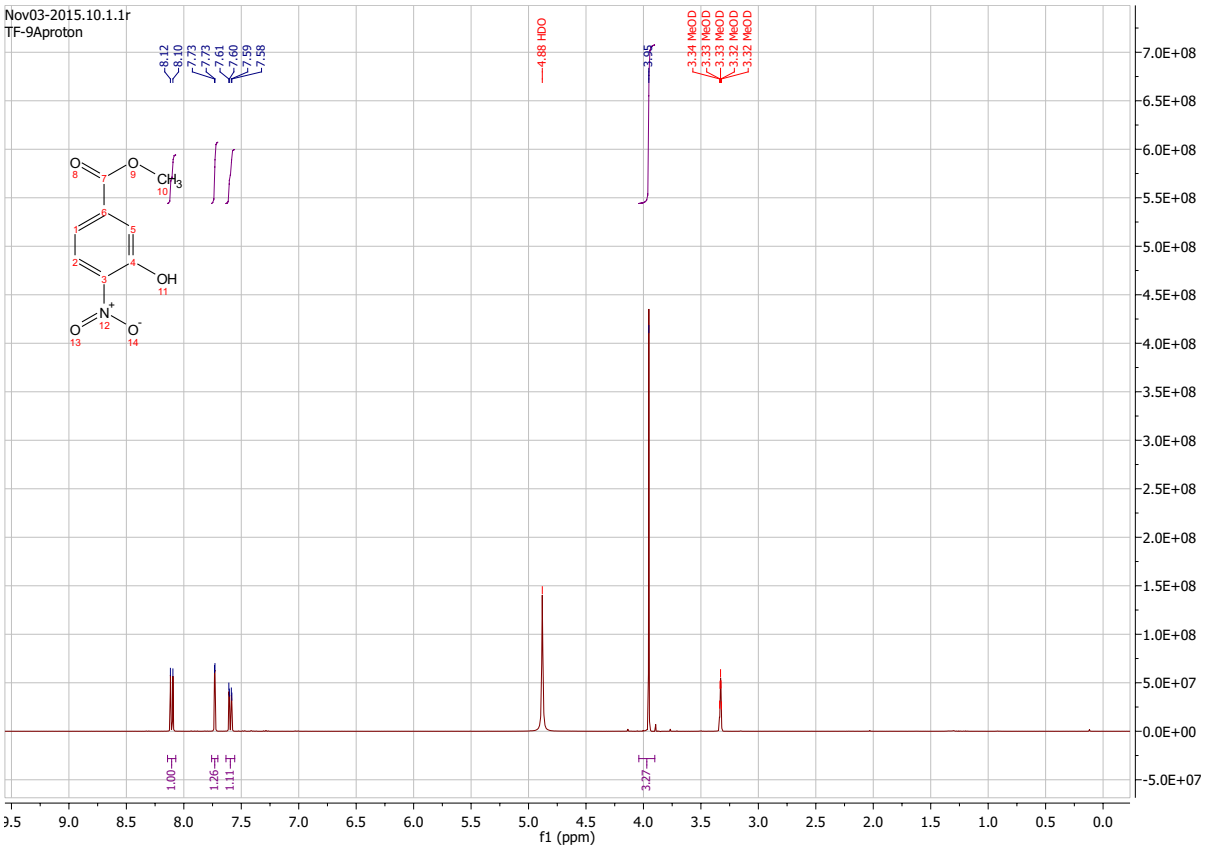

May19-2017.5.fid
T Flack TF-2-77 in d6-dmso ; 13C{1H} spectrum at 373K using Av400D ; May19-2017/5
f1 (ppm)

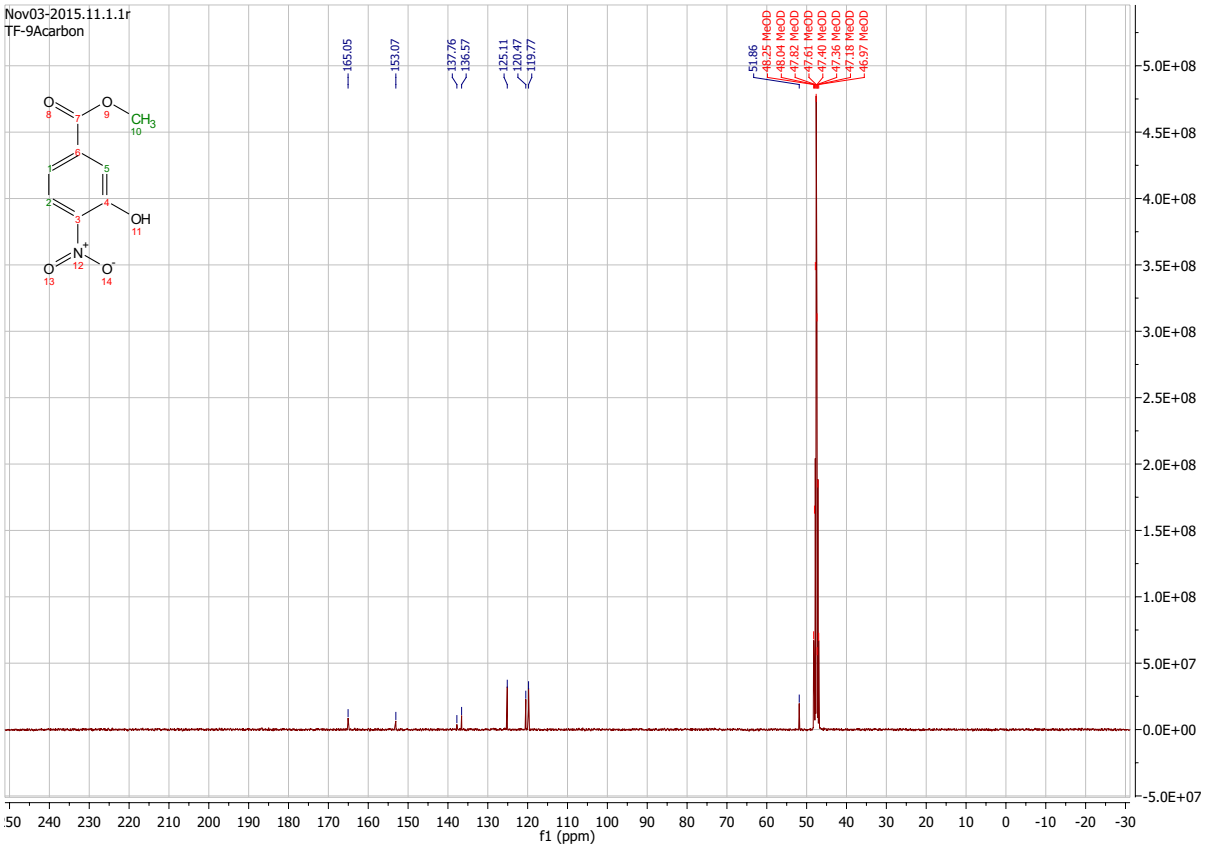

Apr20-2017.20.fid
TF-2-66
f1 (ppm)

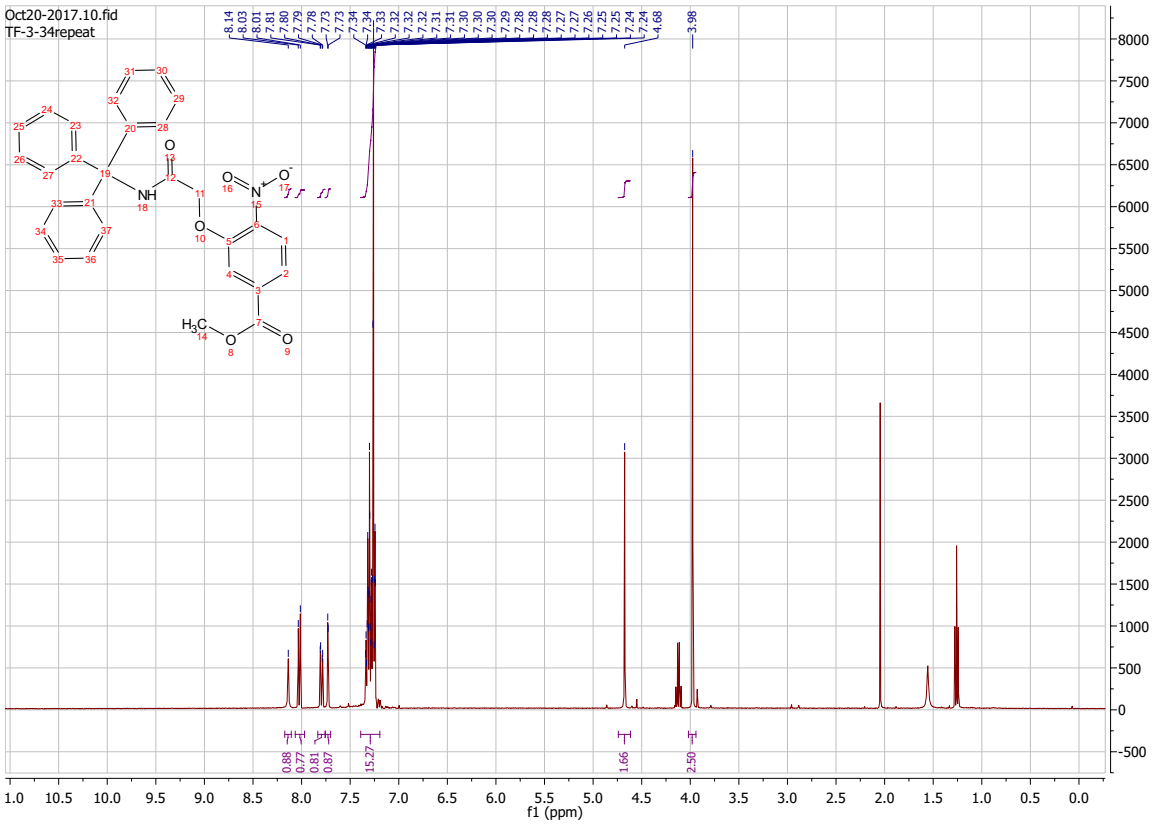

Apr20-2017.21.fid
TF-2-66
f1 (ppm)

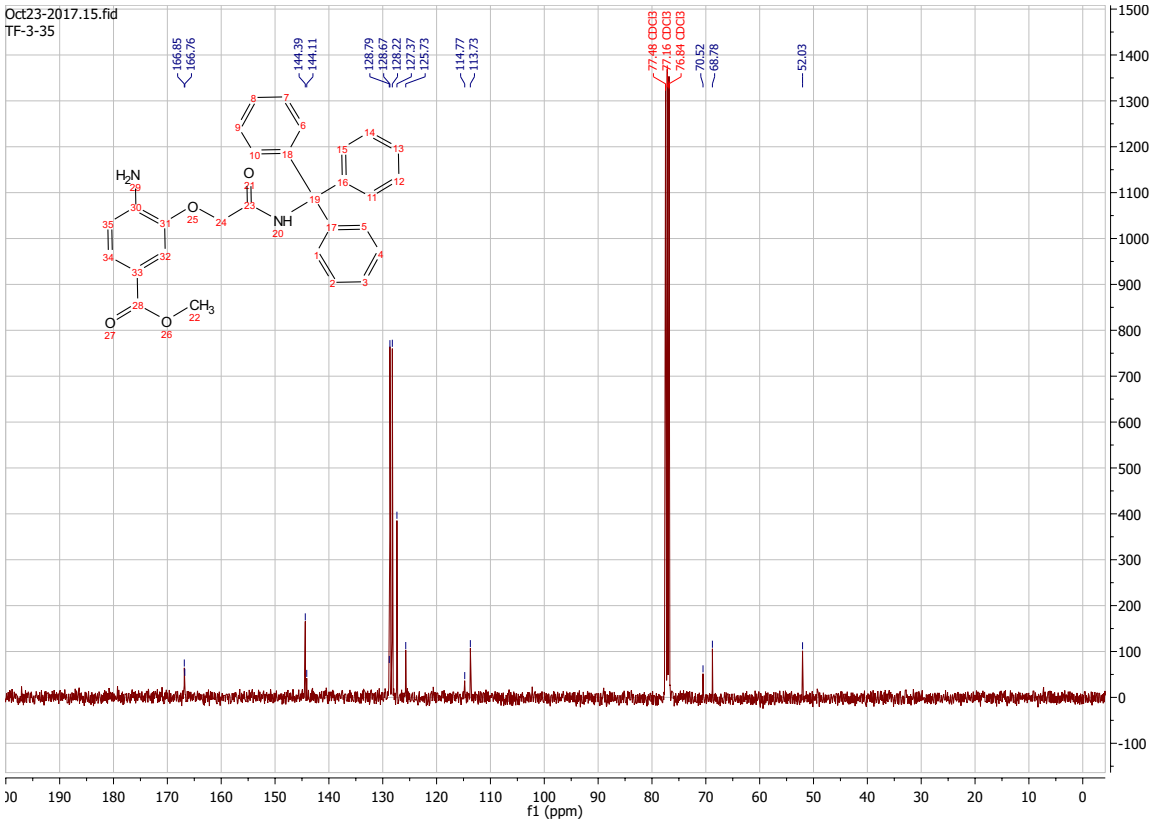

Aug30-2016.30.fid
TF125
f1 (ppm)

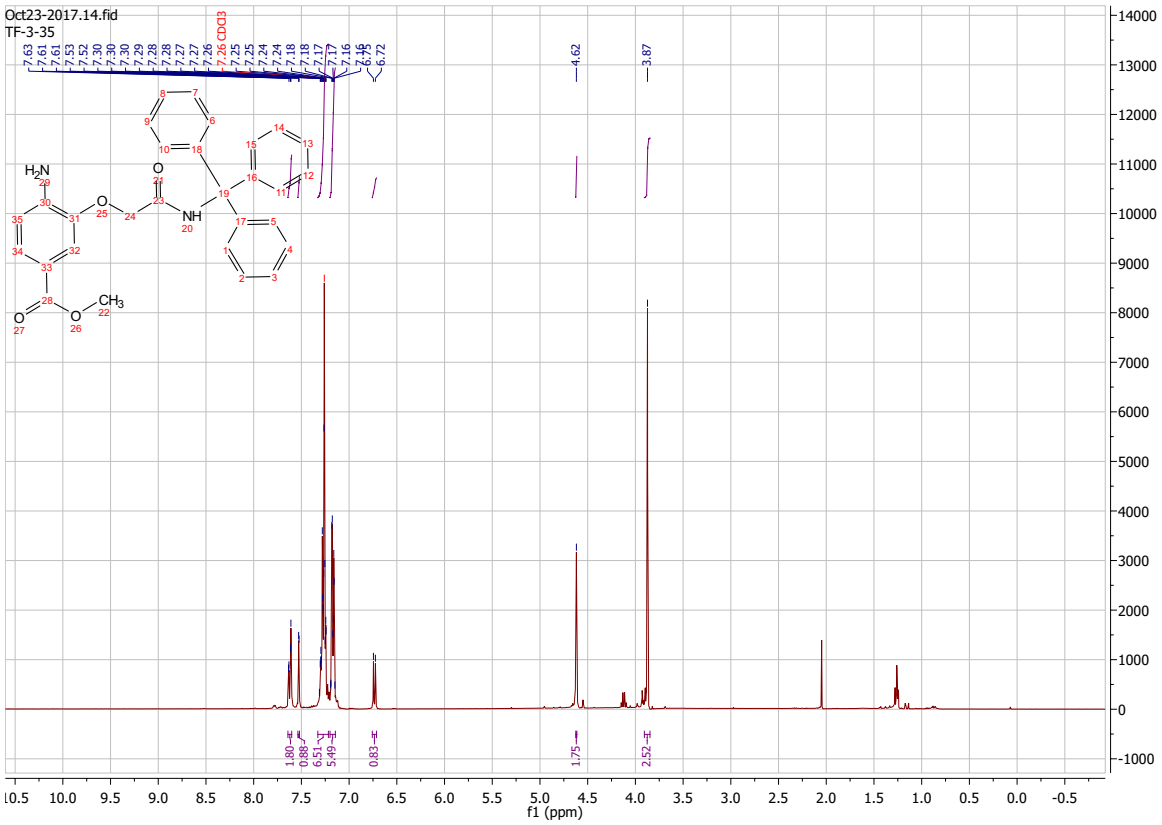

Aug30-2016.31.fid
TF125
f1 (ppm)

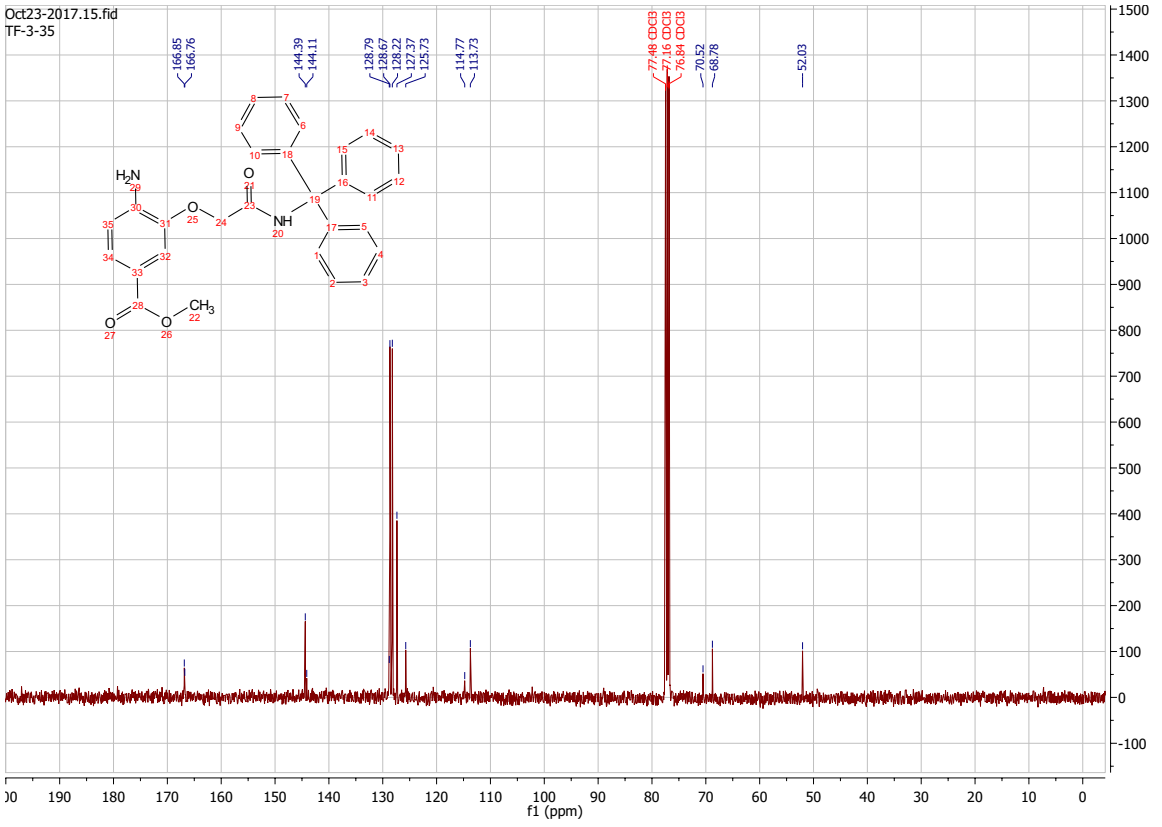

Nov03-2015.10.1.1r
TF-9Aproton
8.12
8.10
7.73
7.73
7.61
7.60
7.59
7.58
4.88 HDO
3.95
3.34 MeOD
3.33 MeOD
3.33 MeOD
3.32 MeOD
3.32 MeOD
1.00
1.26
1.11
3.27
f1 (ppm)

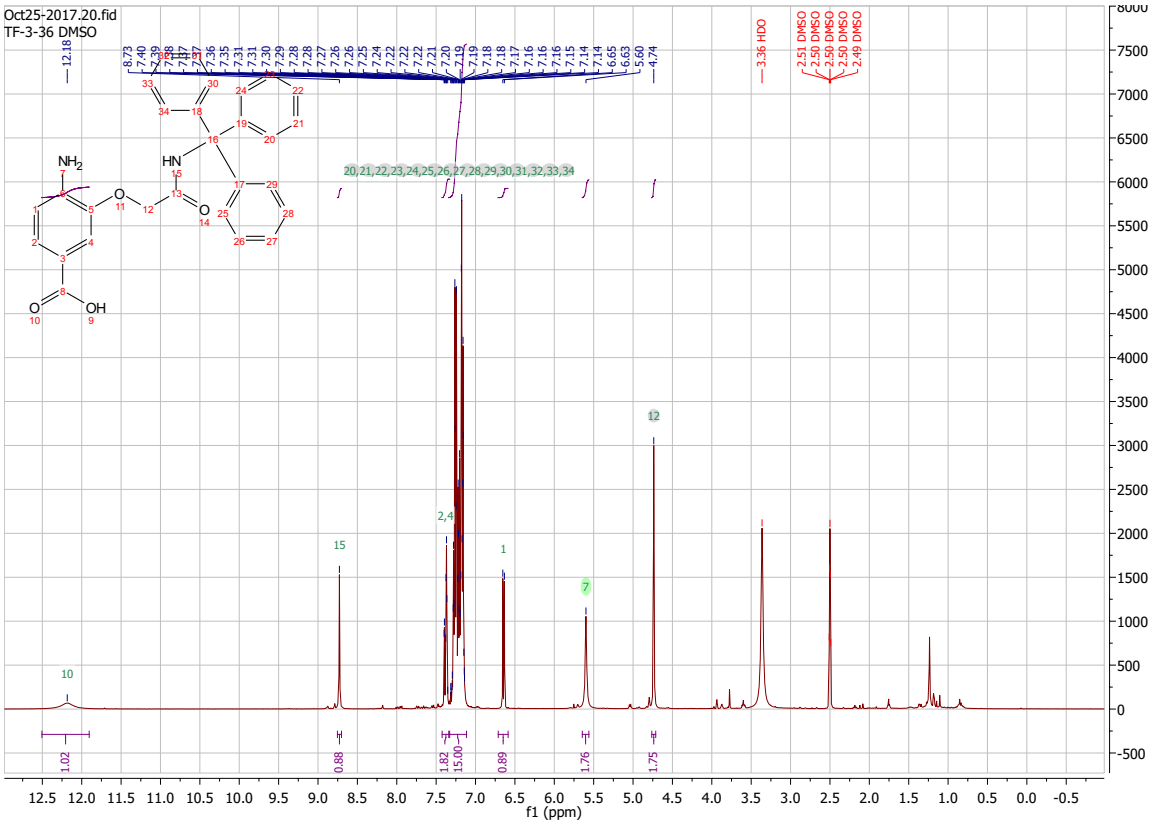

Nov03-2015.11.1.1r
TF-9Acarbon
165.05
153.07
137.76
136.57
125.11
120.47
119.77
51.86
48.25 MeOD
48.04 MeOD
47.82 MeOD
47.61 MeOD
47.40 MeOD
47.36 MeOD
47.18 MeOD
46.97 MeOD
f1 (ppm)

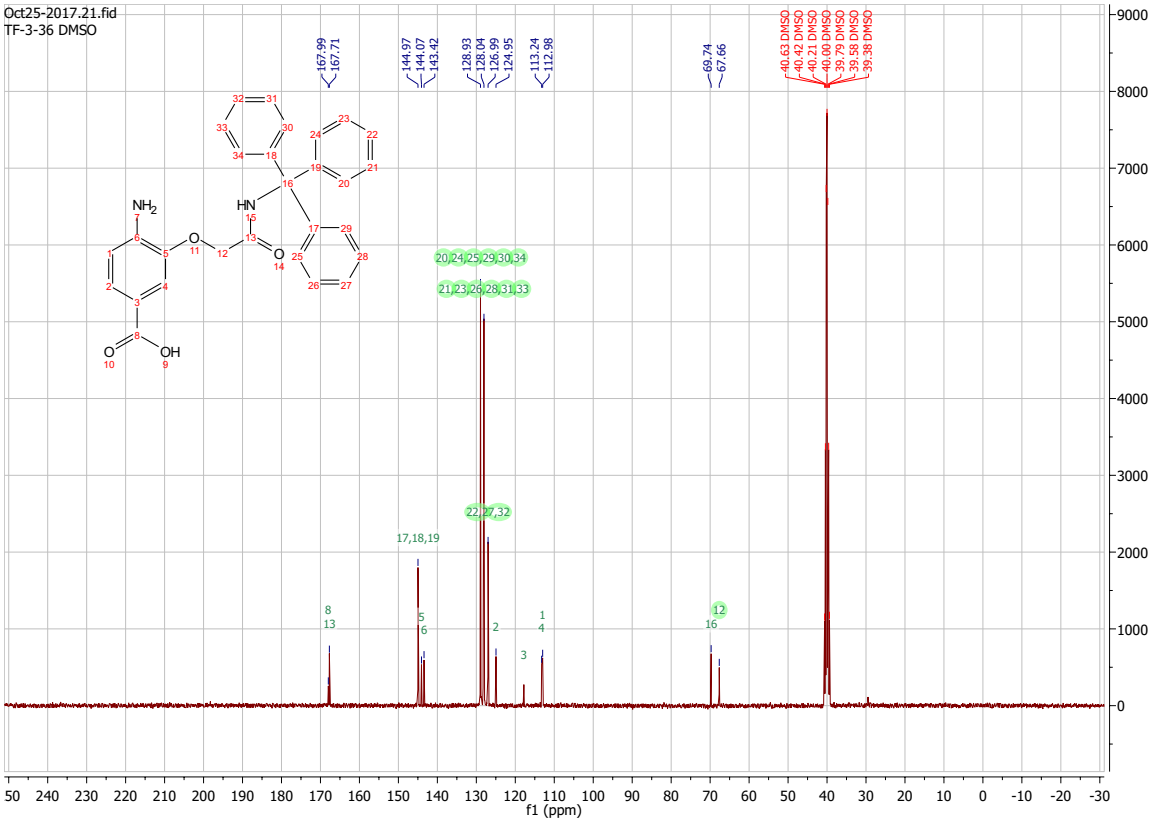

Oct20-2017.10.fid
TF-3-34repeat
f1 (ppm)

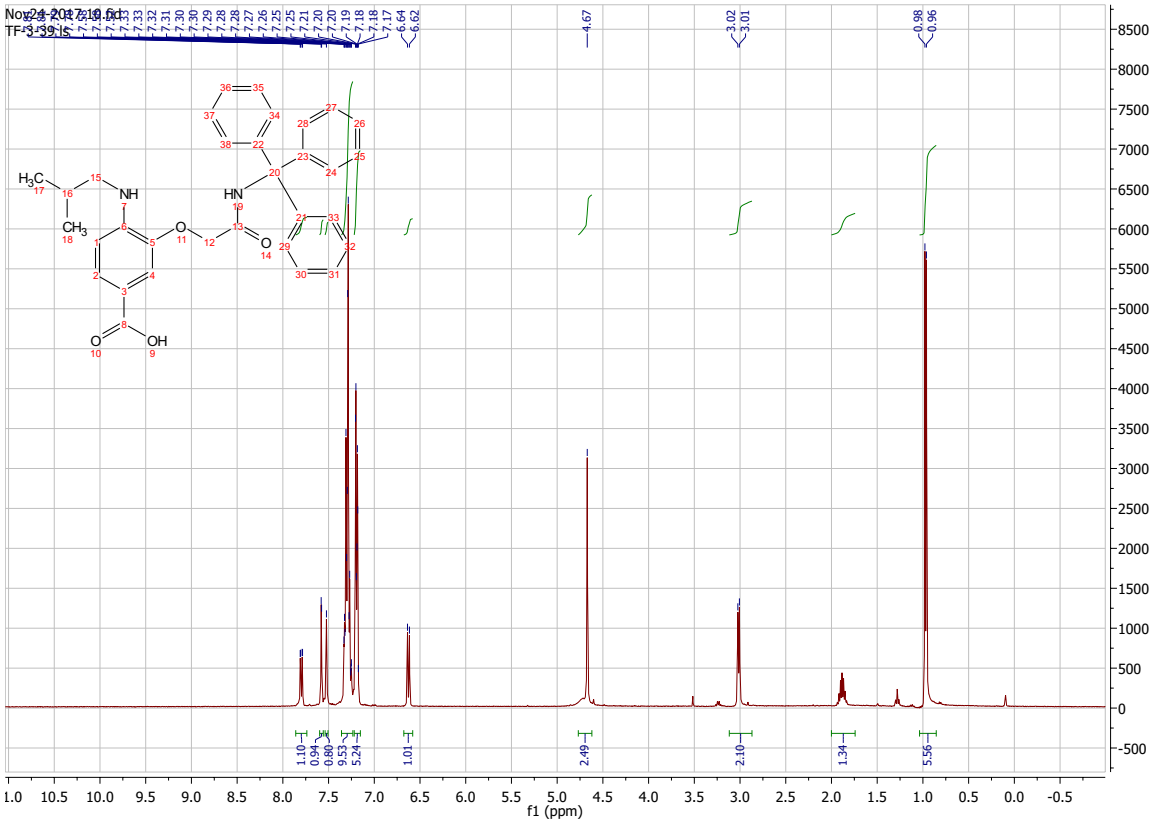

Oct23-2017.15.fid
TF-3-35
f1 (ppm)

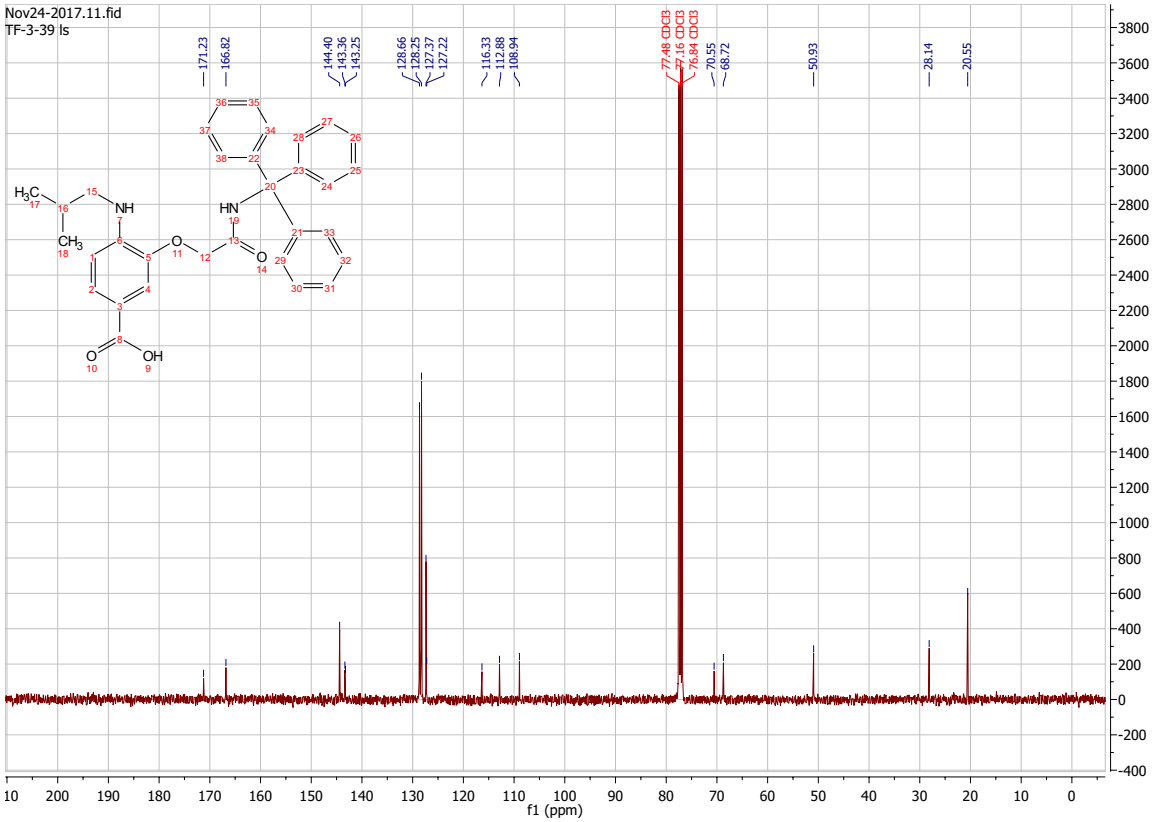

Oct23-2017.14.fid
TF-3-35
f1 (ppm)

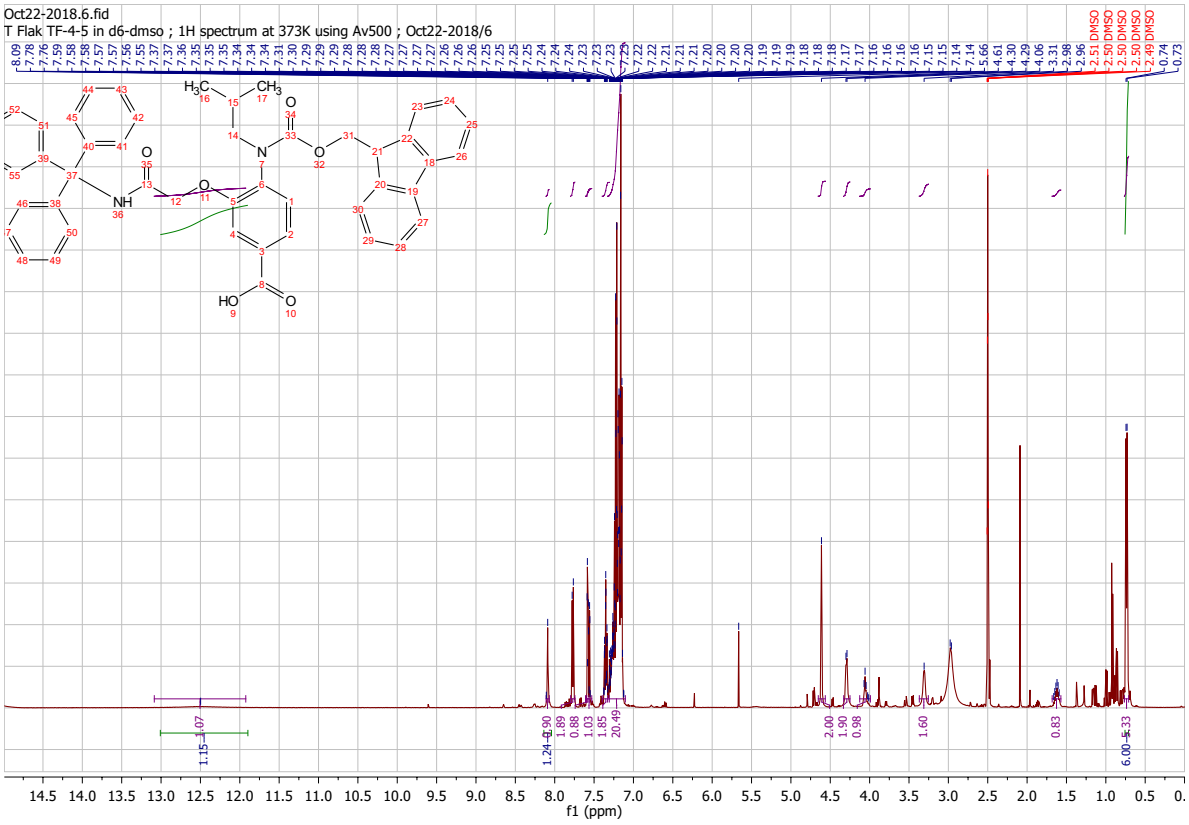

Oct23-2017.15.fid
TF-3-35
f1 (ppm)

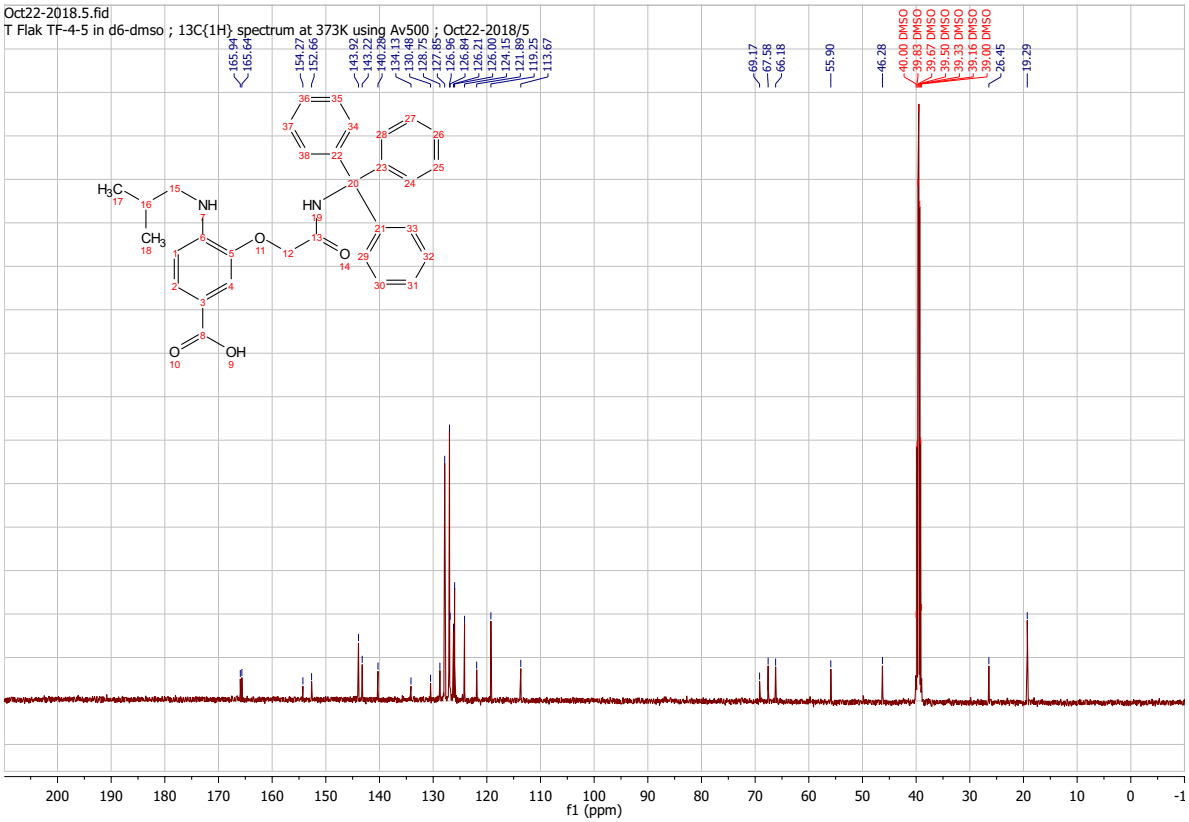

Oct25-2017.20.fid
TF-3-36 DMSO
f1 (ppm)


Oct25-2017.21.fid
TF-3-36 DMSO
f1 (ppm)

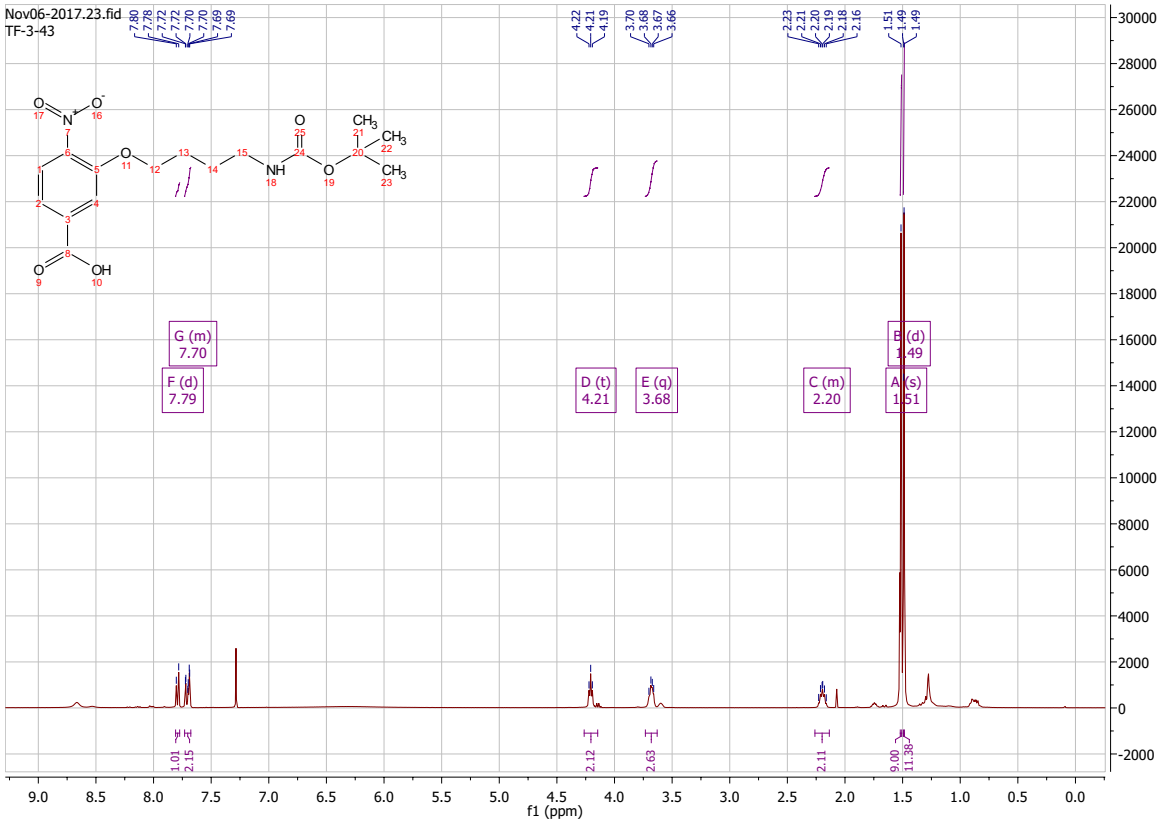

Nov24-2017.10.fid
TF-3-39 ls
4.67
3.02
3.01
0.98
0.96
6.64
6.62
1.10
0.94
0.80
9.53
5.24
1.01
2.49
2.10
1.34
5.56
f1 (ppm)

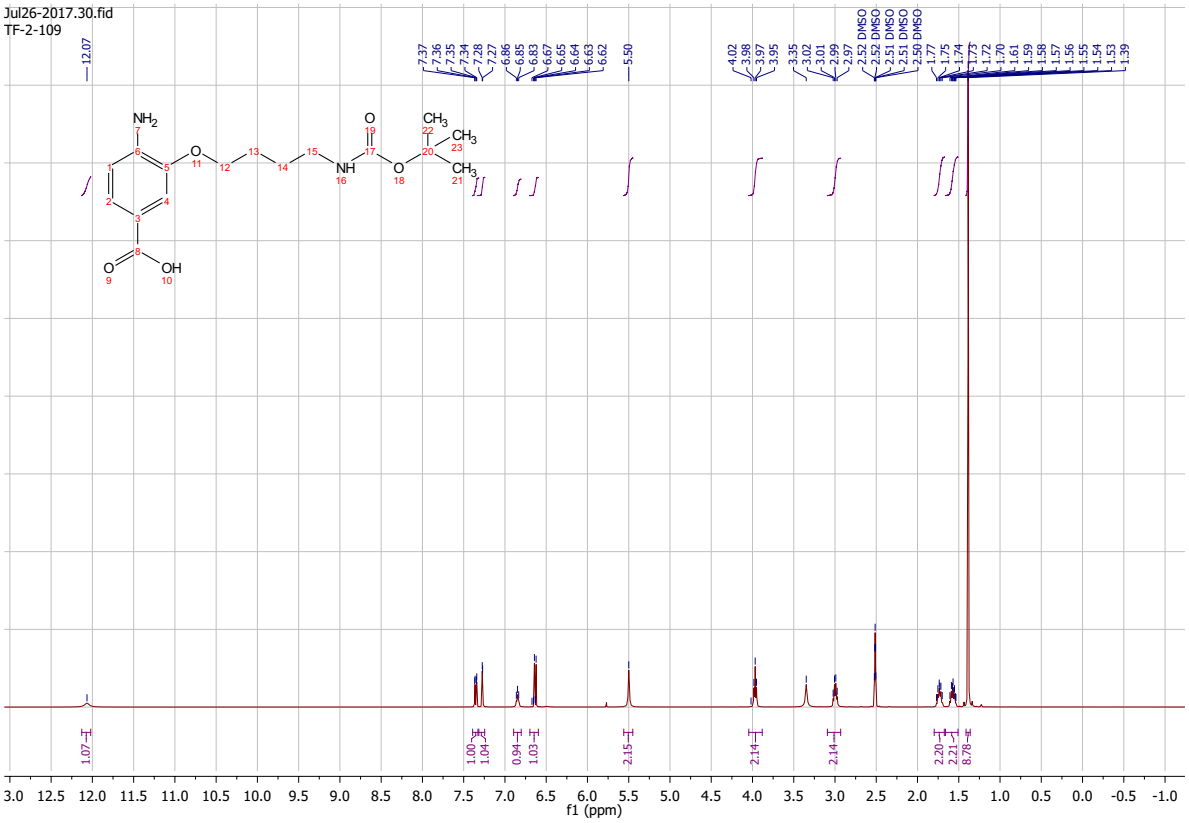

Nov24-2017.11.fid
TF-3-39 ls
171.23
166.82
144.40
143.36
143.25
128.66
128.25
127.37
127.22
116.33
112.88
108.94
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
70.55
68.72
50.93
28.14
20.55
f1 (ppm)

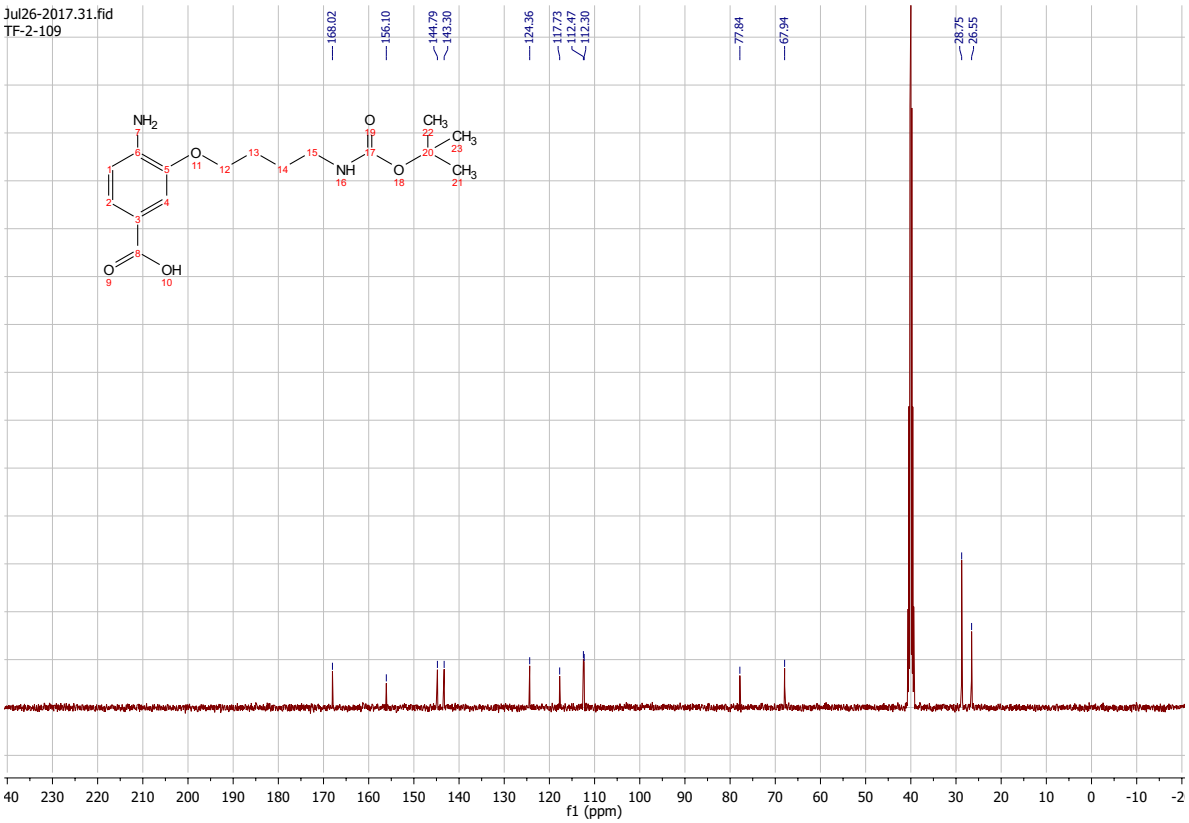

Oct22-2018.6.fid
T Flak TF-4-5 in d6-dmso ; 1H spectrum at 373K using Av500 ; Oct22-2018/6
f1 (ppm)

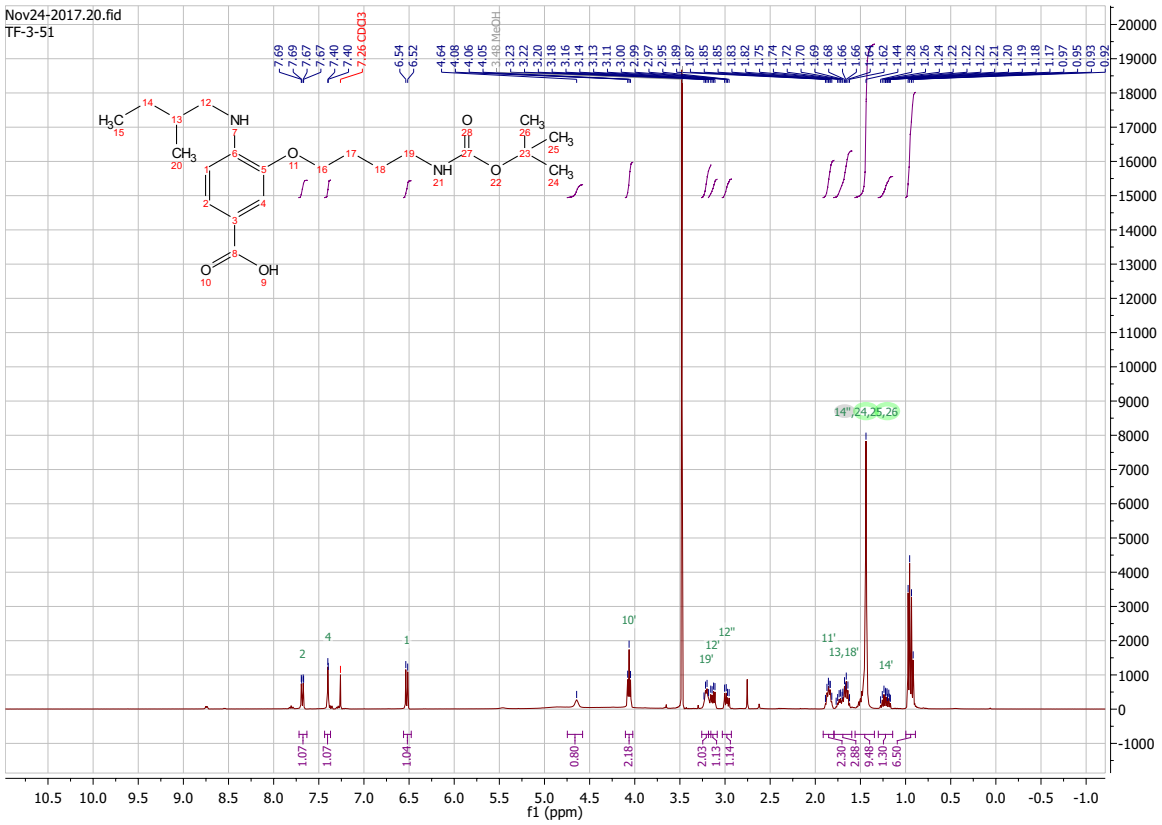

Oct22-2018.5.fid
T Flak TF-4-5 in d6-dmso ; 13C{1H} spectrum at 373K using Av500 ; Oct22-2018/5
f1 (ppm)

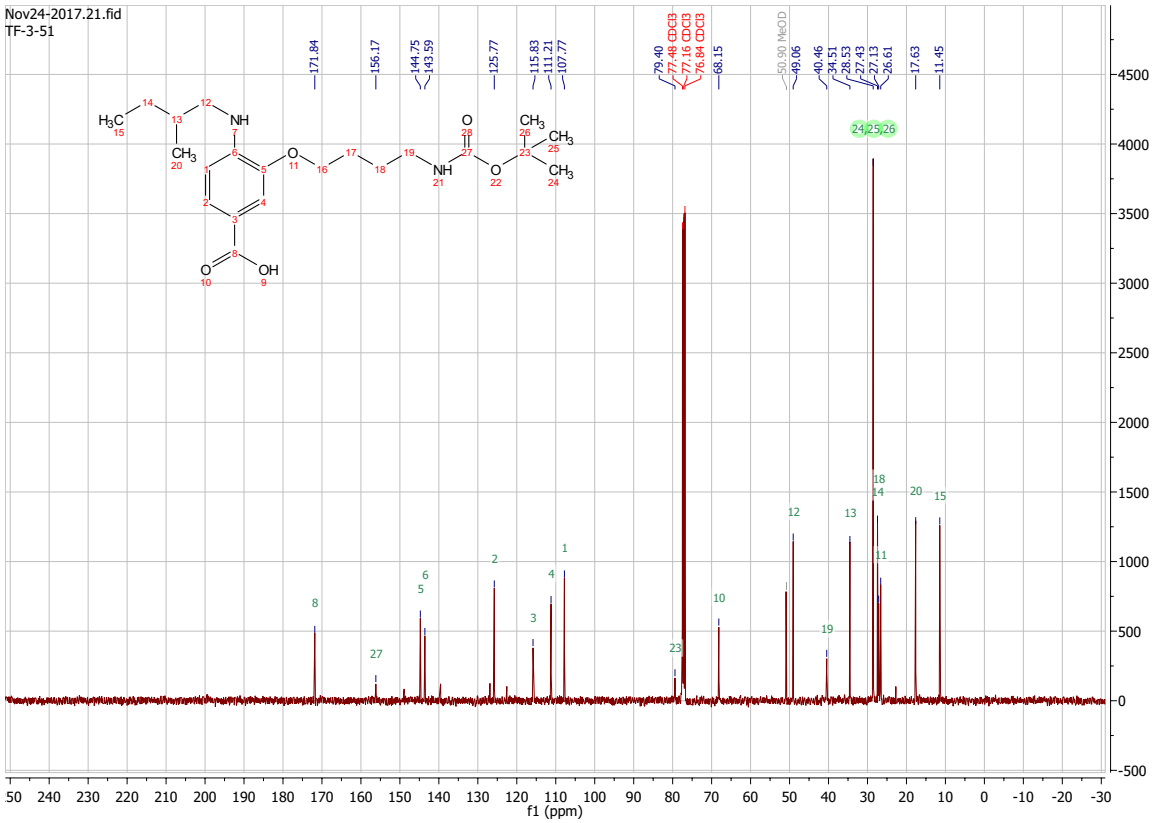
S22

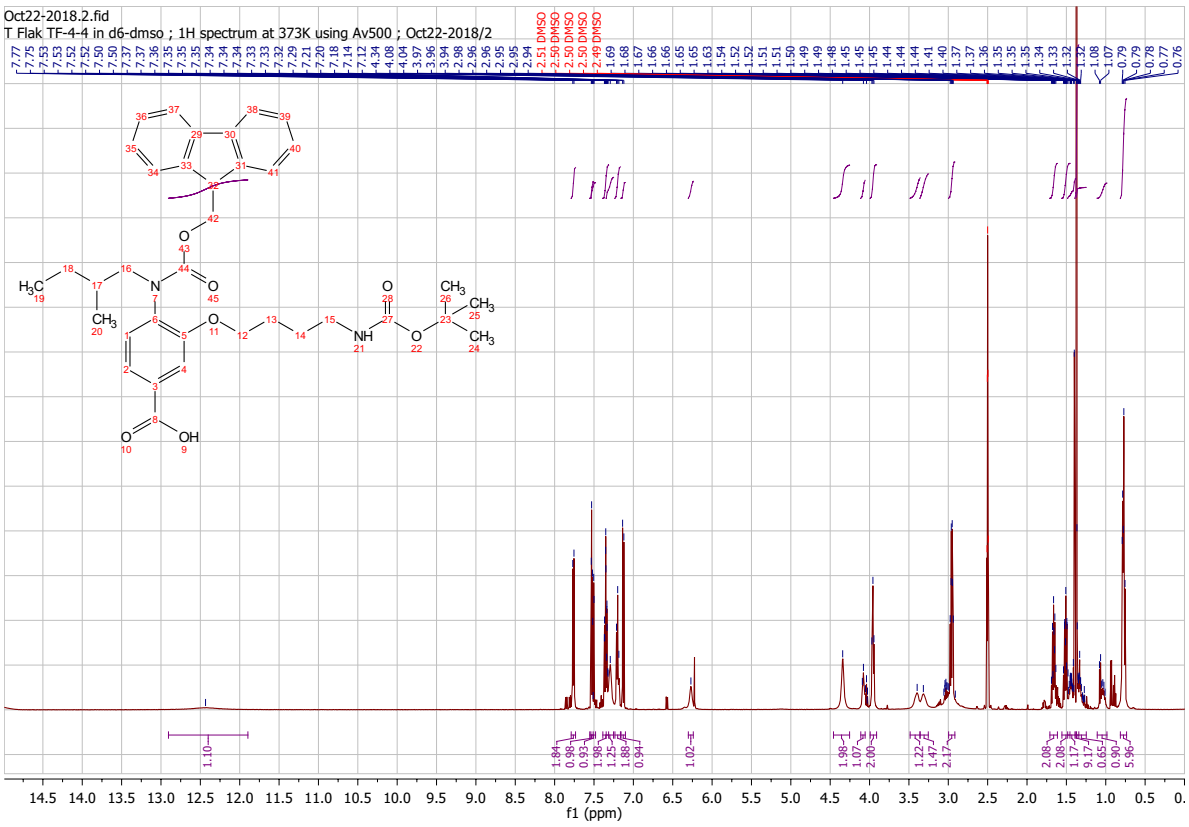

Nov06-2017.23.fid
TF-3-43
G (m)
7.70
F (d)
7.79
D (t)
4.21
E (q)
3.68
C (m)
2.20
B (d)
1.49
A (s)
1.51
f1 (ppm)

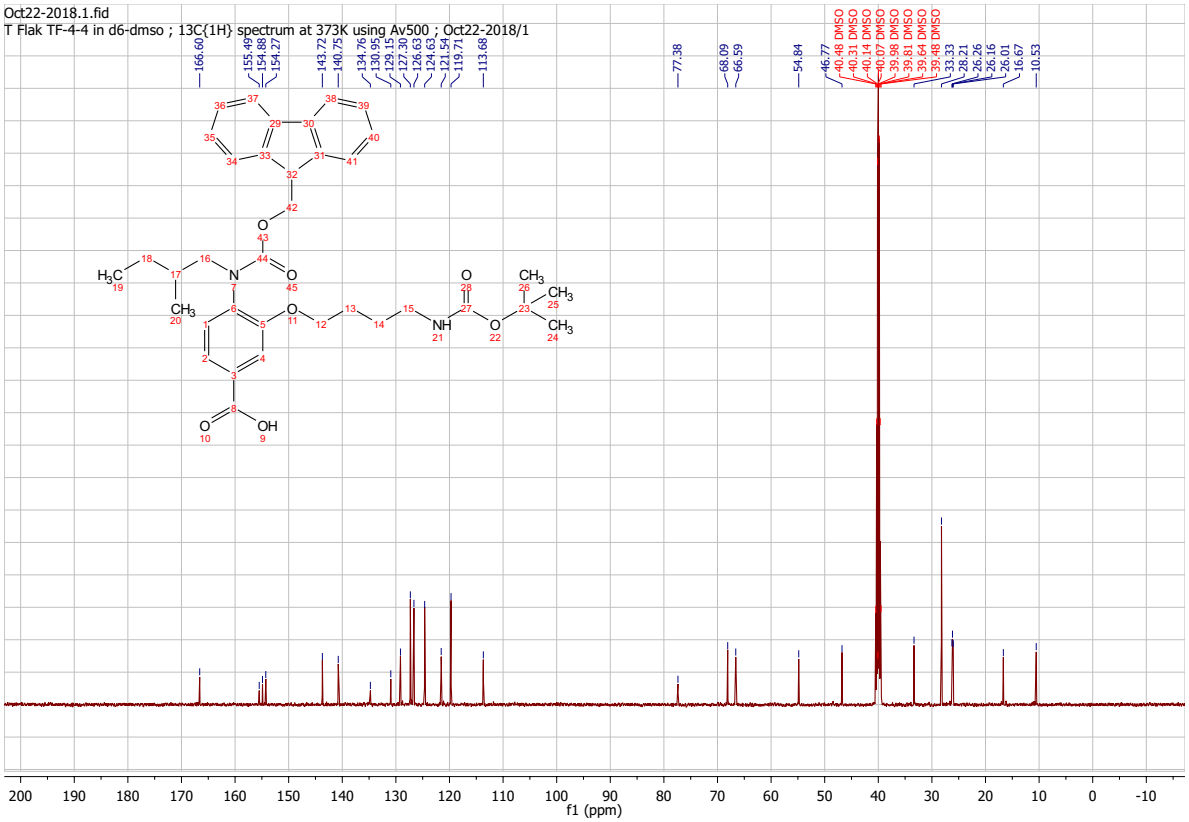

Jul26-2017.30.fid
TF-2-109
f1 (ppm)

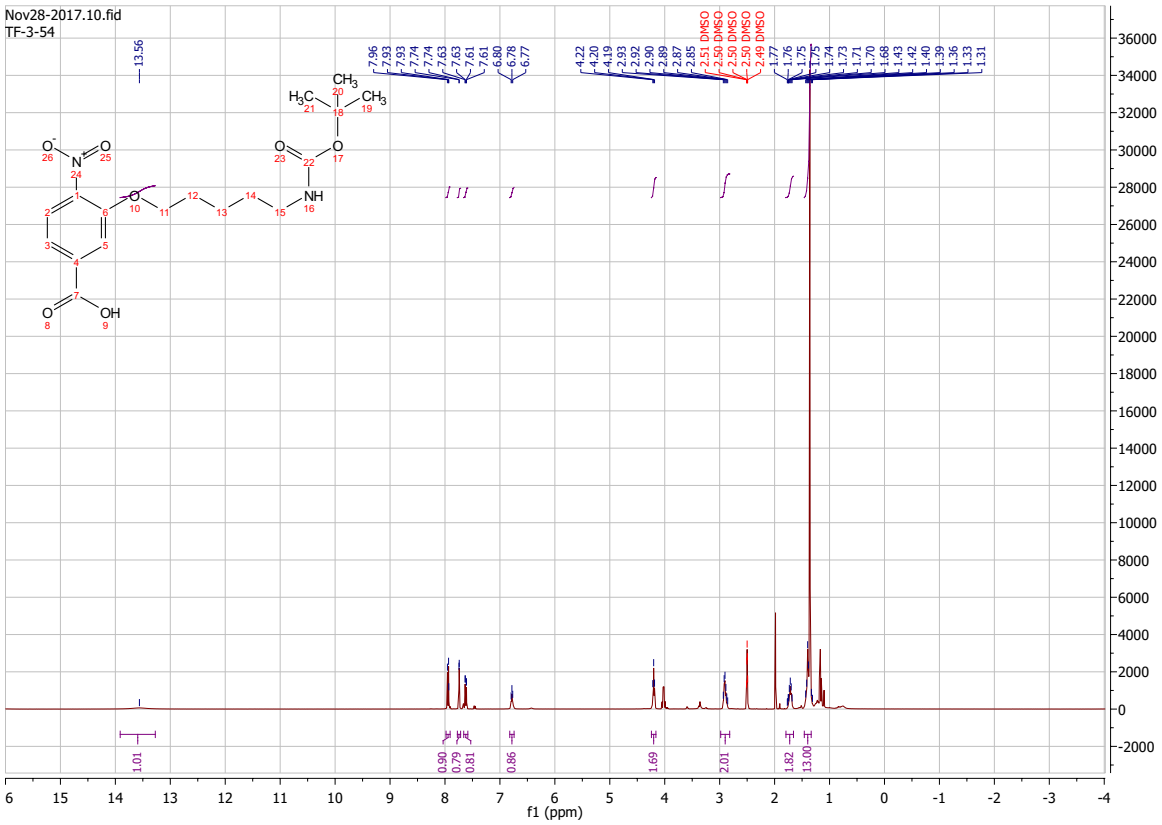

Jul26-2017.31.fid
TF-2-109
f1 (ppm)

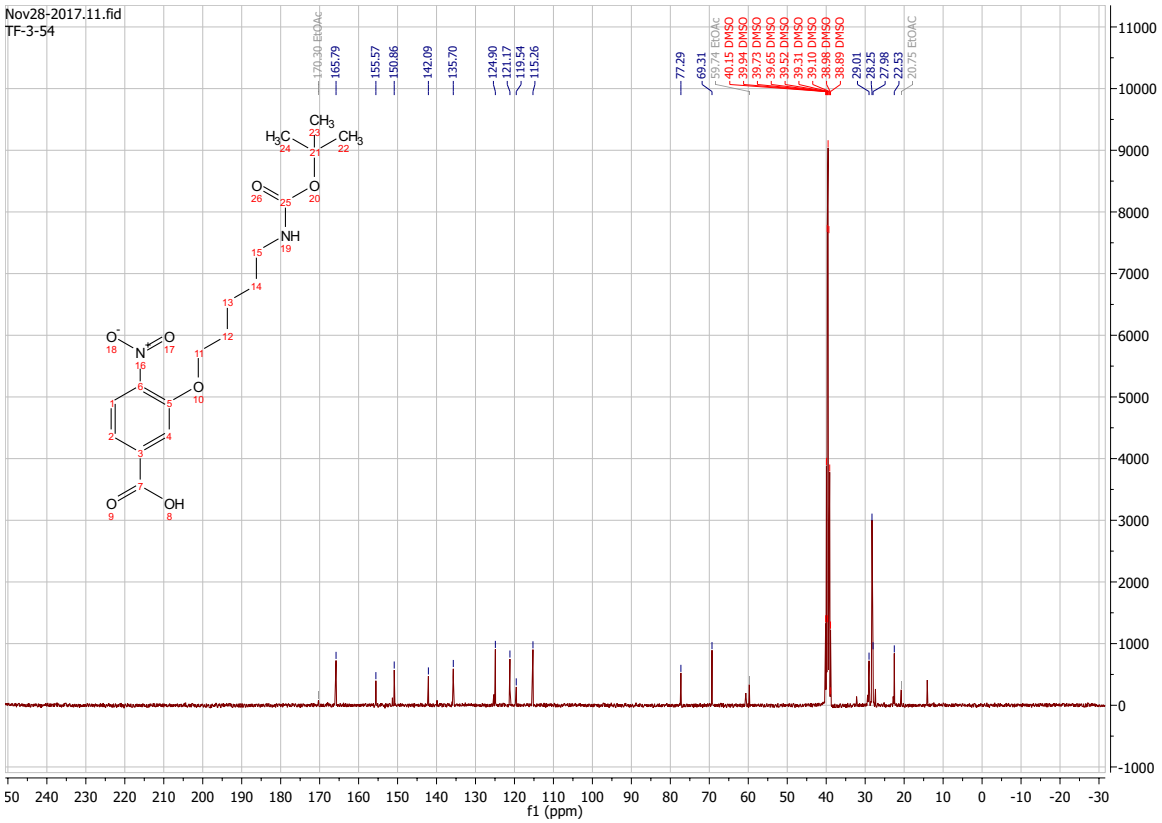

Nov24-2017.20.fid
TF-3-51
f1 (ppm)

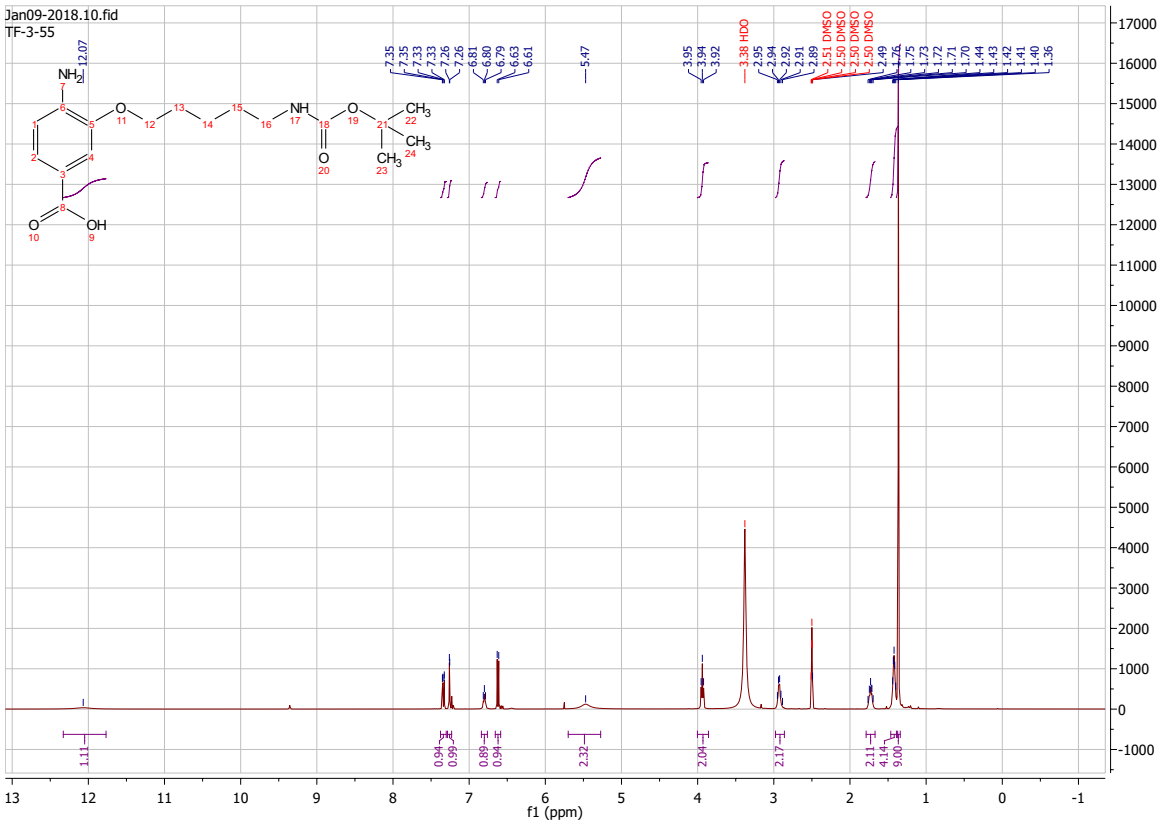

Nov24-2017.21.fid
TF-3-51
f1 (ppm)

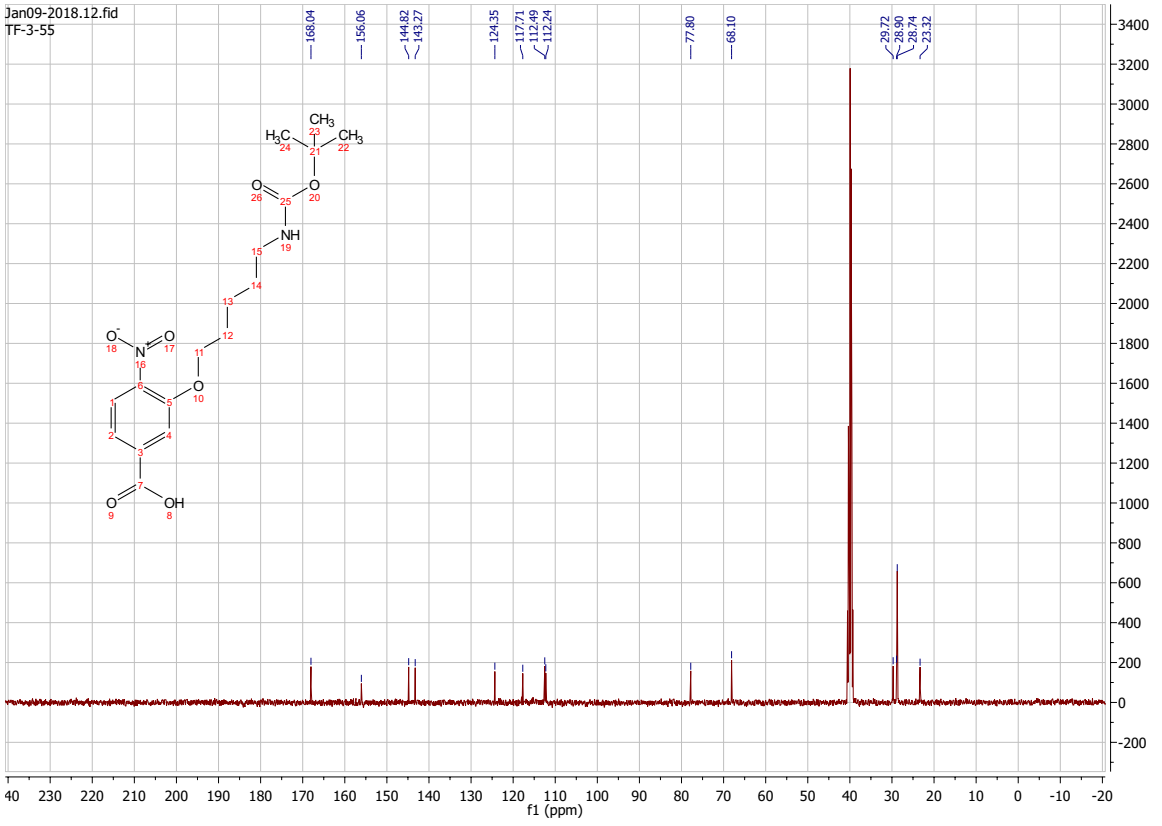

Oct22-2018.2.fid
T Flak TF-4-4 in d6-dmso ; 1H spectrum at 373K using Av500 ; Oct22-2018/2
f1 (ppm)

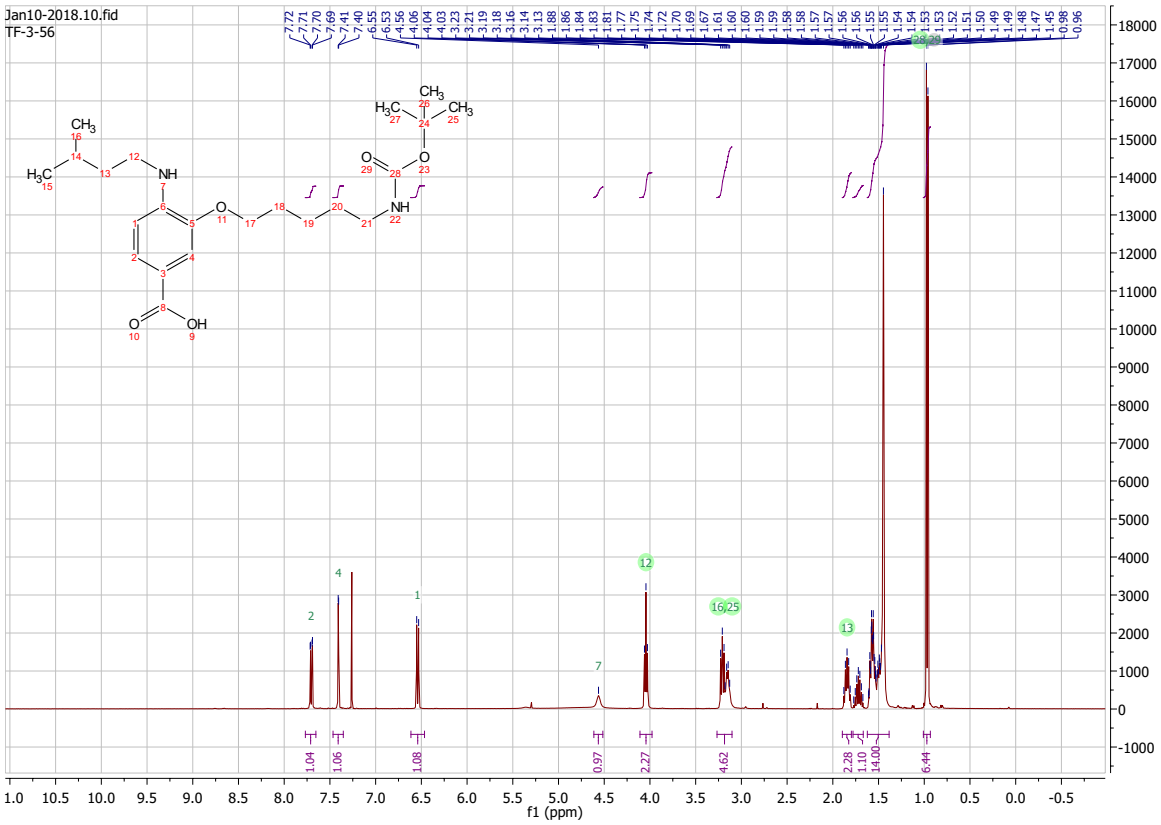

Oct22-2018.1.fid
T Flak TF-4-4 in d6-dmso ; 13C{1H} spectrum at 373K using Av500 ; Oct22-2018/1
f1 (ppm)

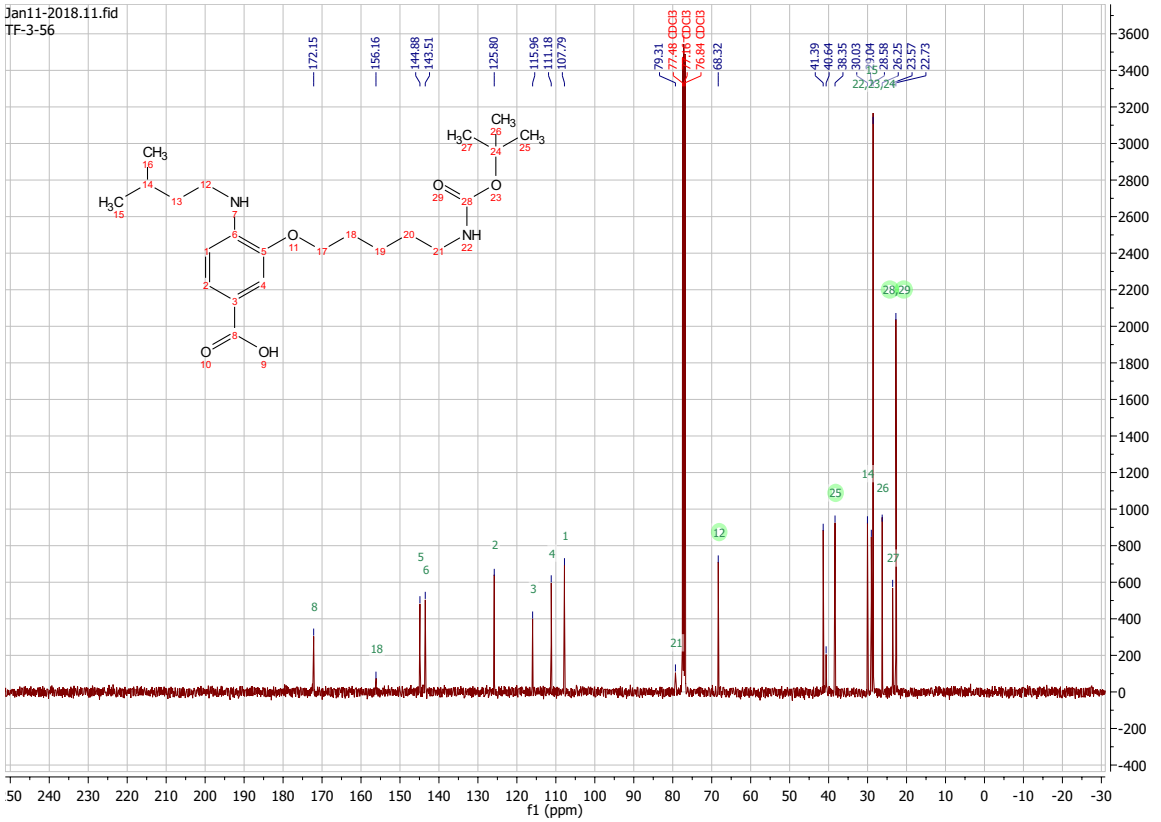

Nov28-2017.10.fid
TF-3-54
f1 (ppm)

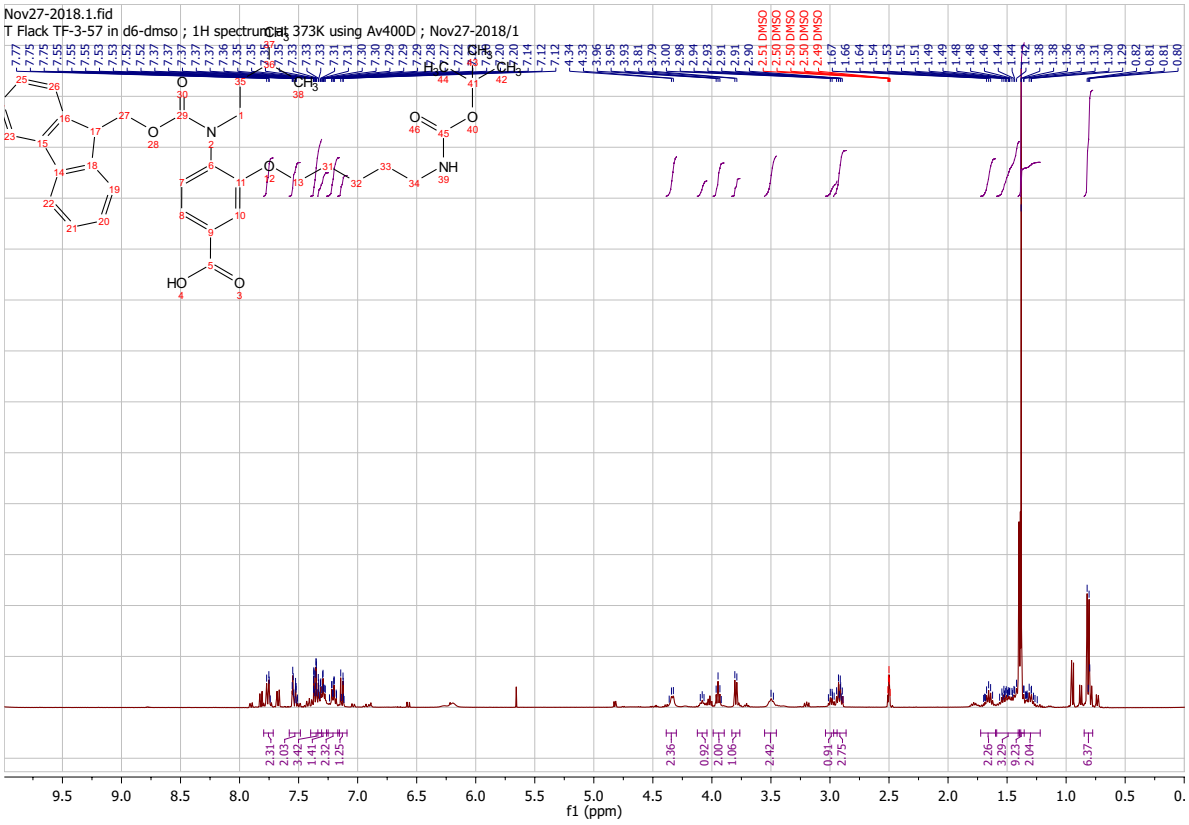

Nov28-2017.11.fid
TF-3-54
f1 (ppm)

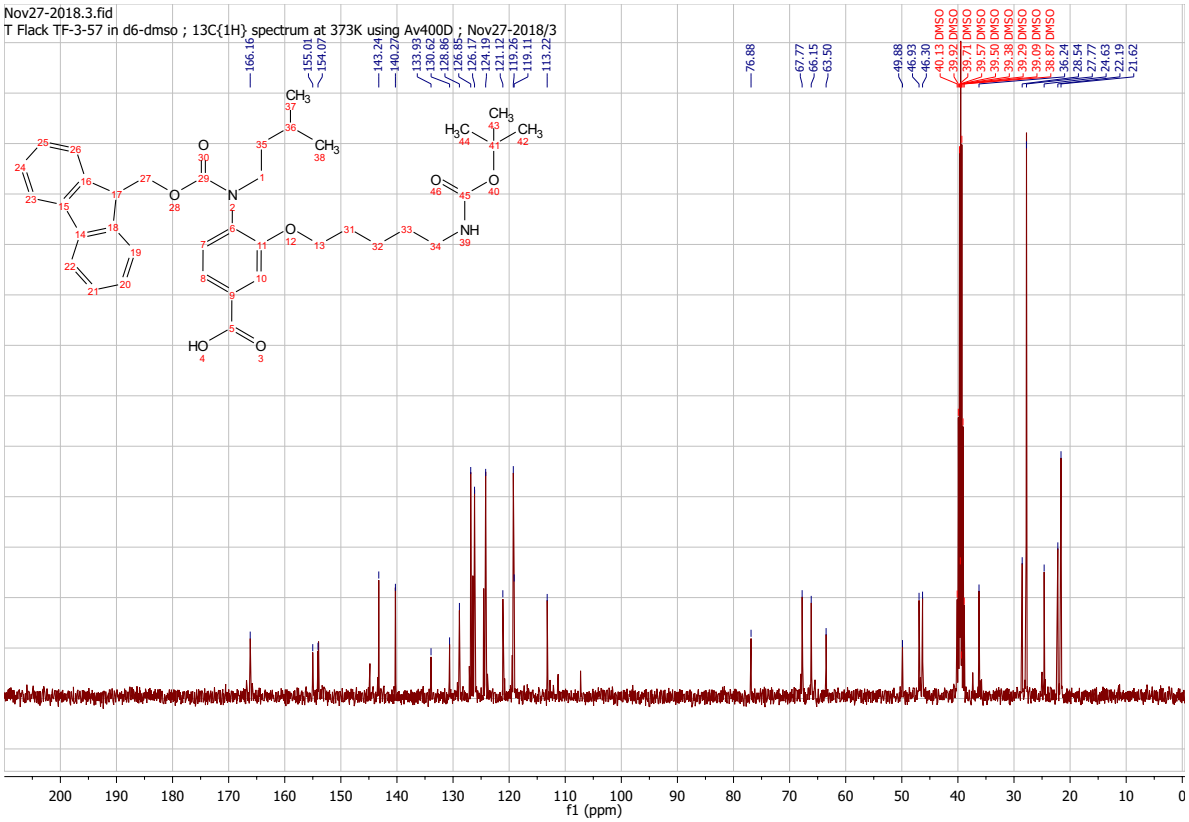

Jan09-2018.10.fid
TF-3-55
f1 (ppm)

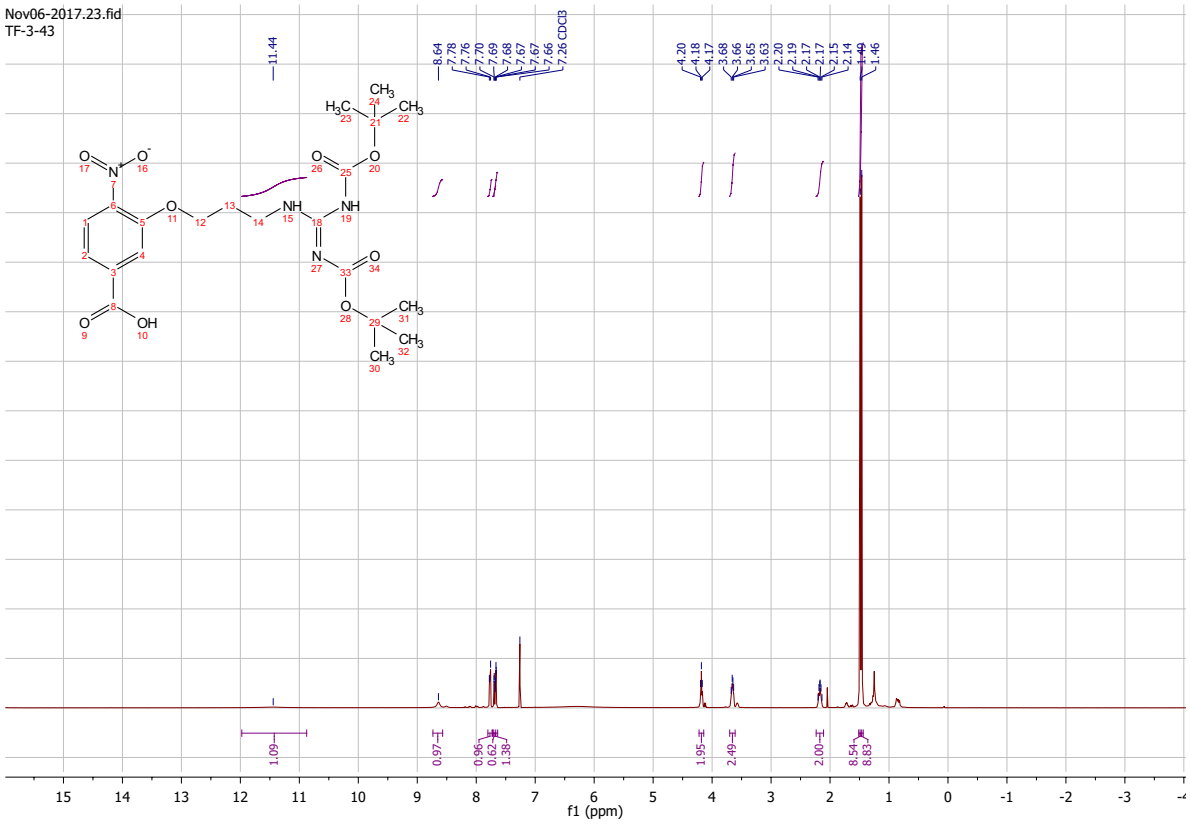

Jan09-2018.12.fid
TF-3-55
f1 (ppm)

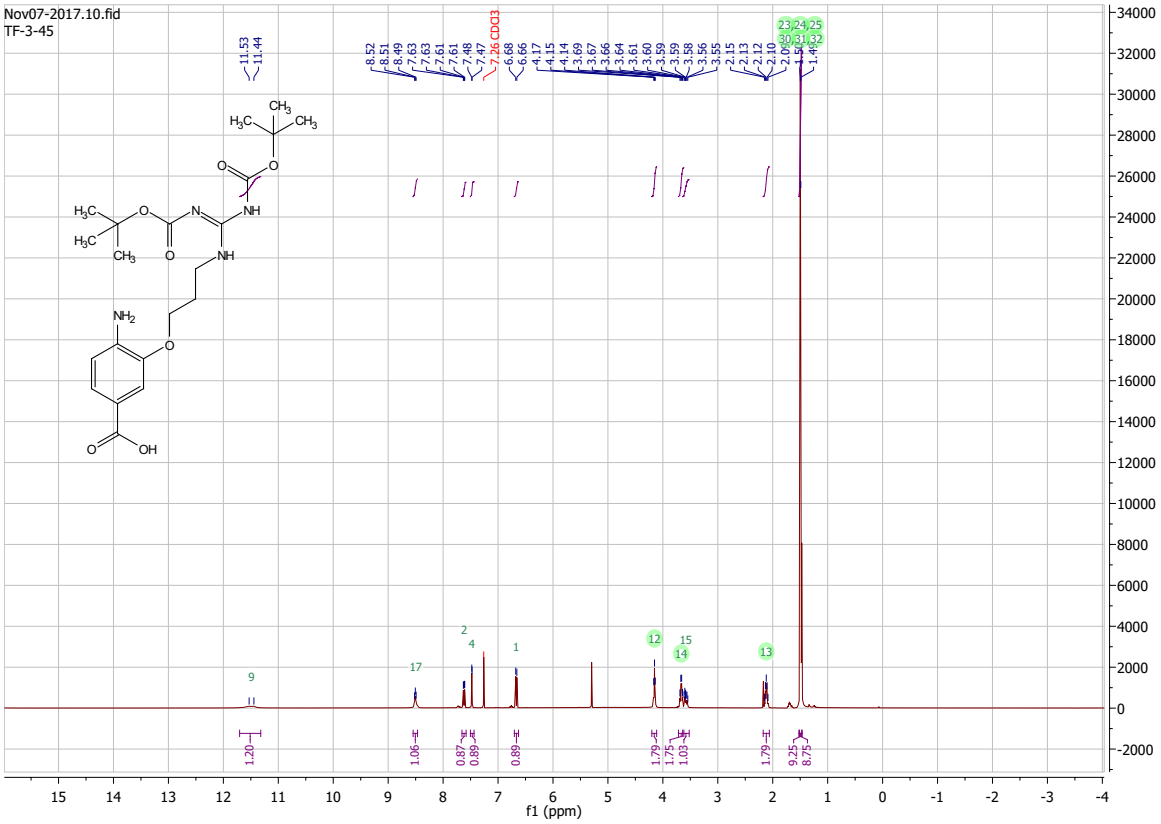

Jan10-2018.10.fid
TF-3-56
f1 (ppm)

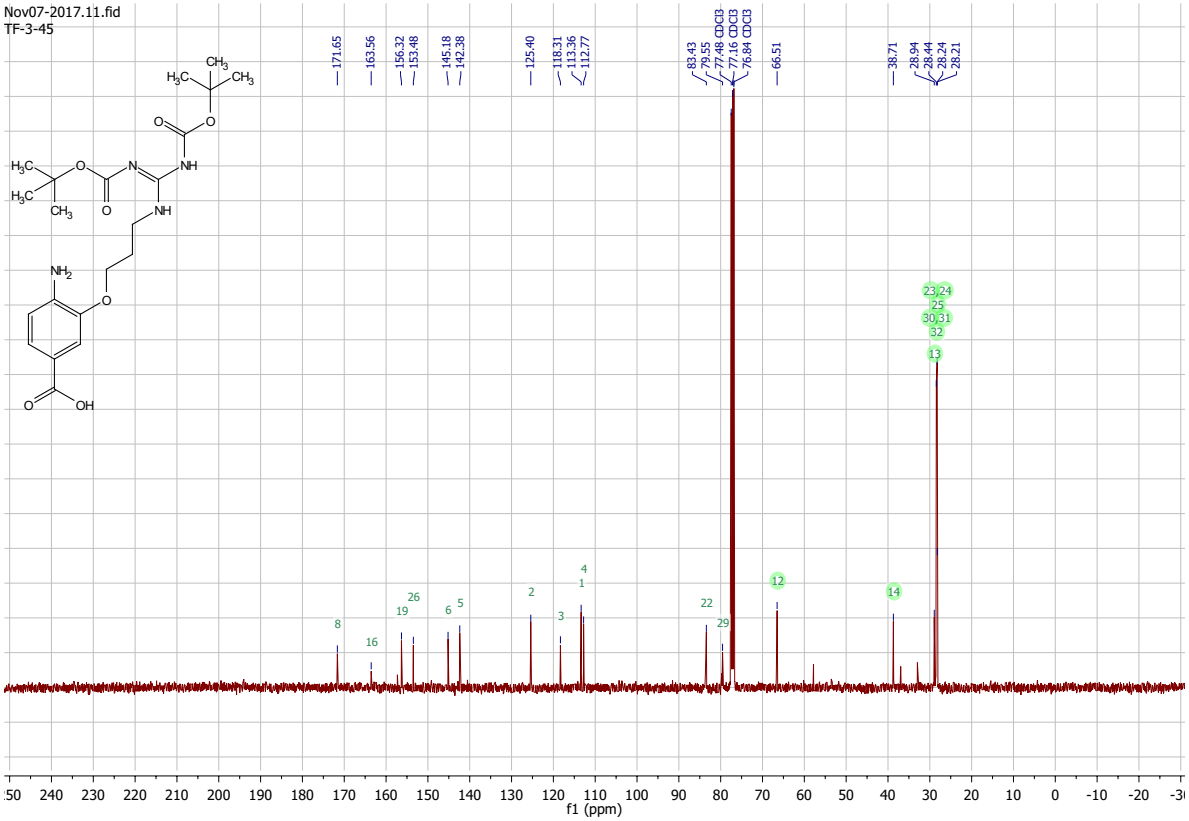

Jan11-2018.11.fid
TF-3-56
f1 (ppm)

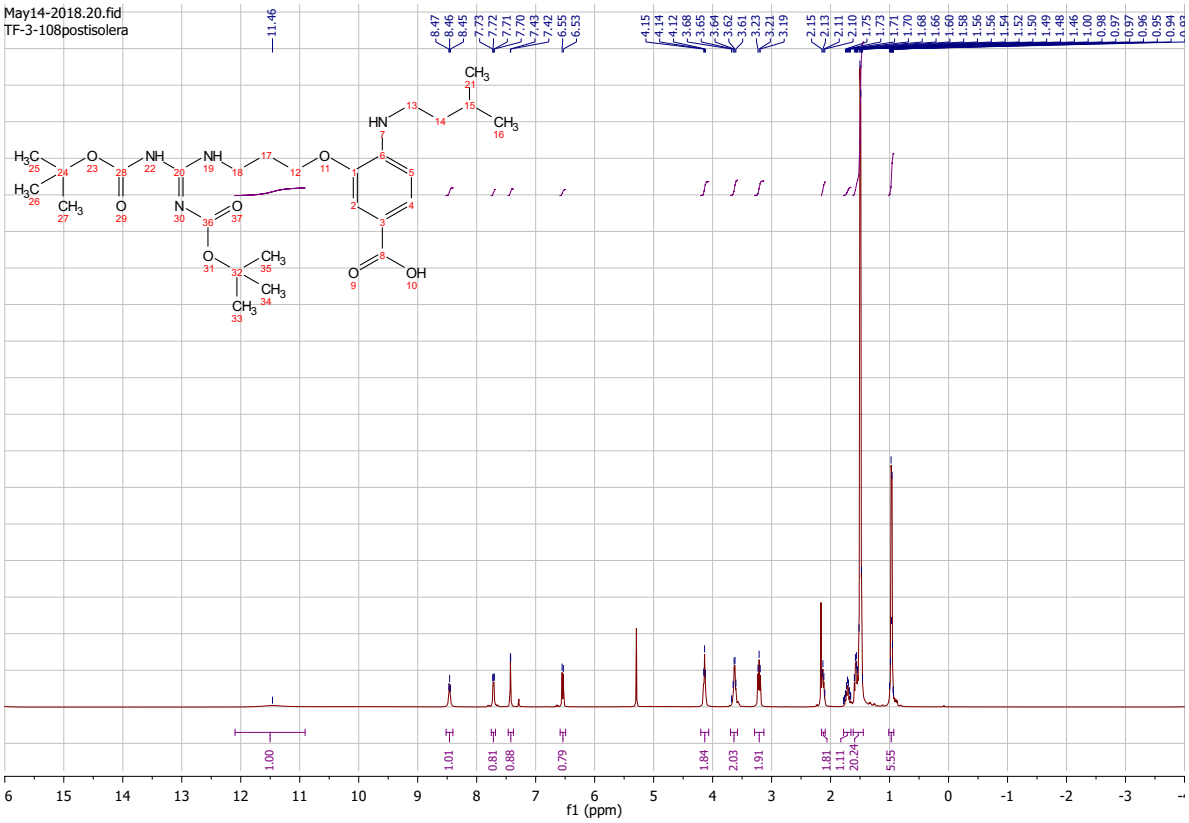

Nov27-2018.1.fid
T Flack TF-3-57 in d6-dmso ; 1H spectrum at 373K using Av400D ; Nov27-2018/1
f1 (ppm)

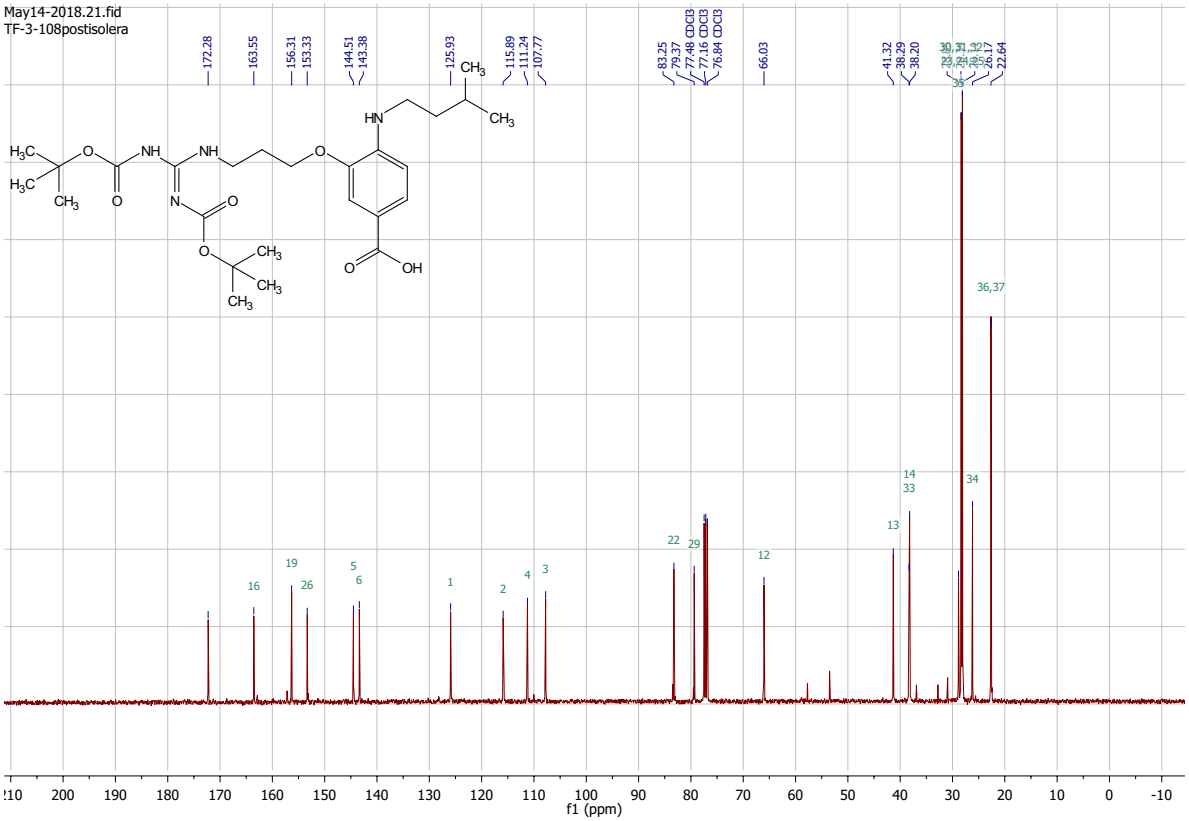

Nov27-2018.3.fid
T Flack TF-3-57 in d6-dmso ; 13C{1H} spectrum at 373K using Av400D ; Nov27-2018/3
f1 (ppm)

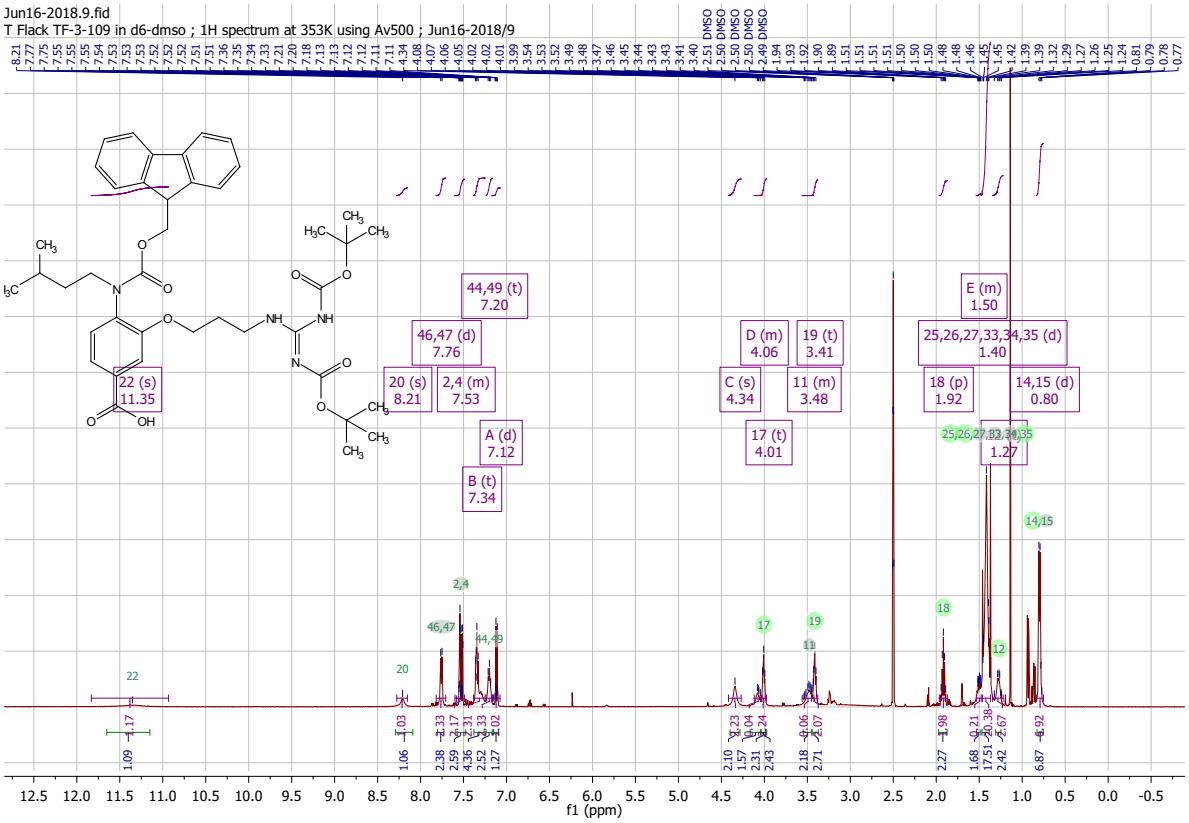

Nov06-2017.23.fid
TF-3-43
11.44
8.64
8.78
7.76
7.70
7.69
7.68
7.67
7.67
7.66
7.26 CDCl3
4.20
4.18
4.17
3.68
3.66
3.65
3.63
2.20
2.19
2.17
2.17
2.15
2.14
1.49
1.46
1.09
0.97
0.96
0.62
1.38
1.95
2.49
2.00
8.54
8.83
f1 (ppm)

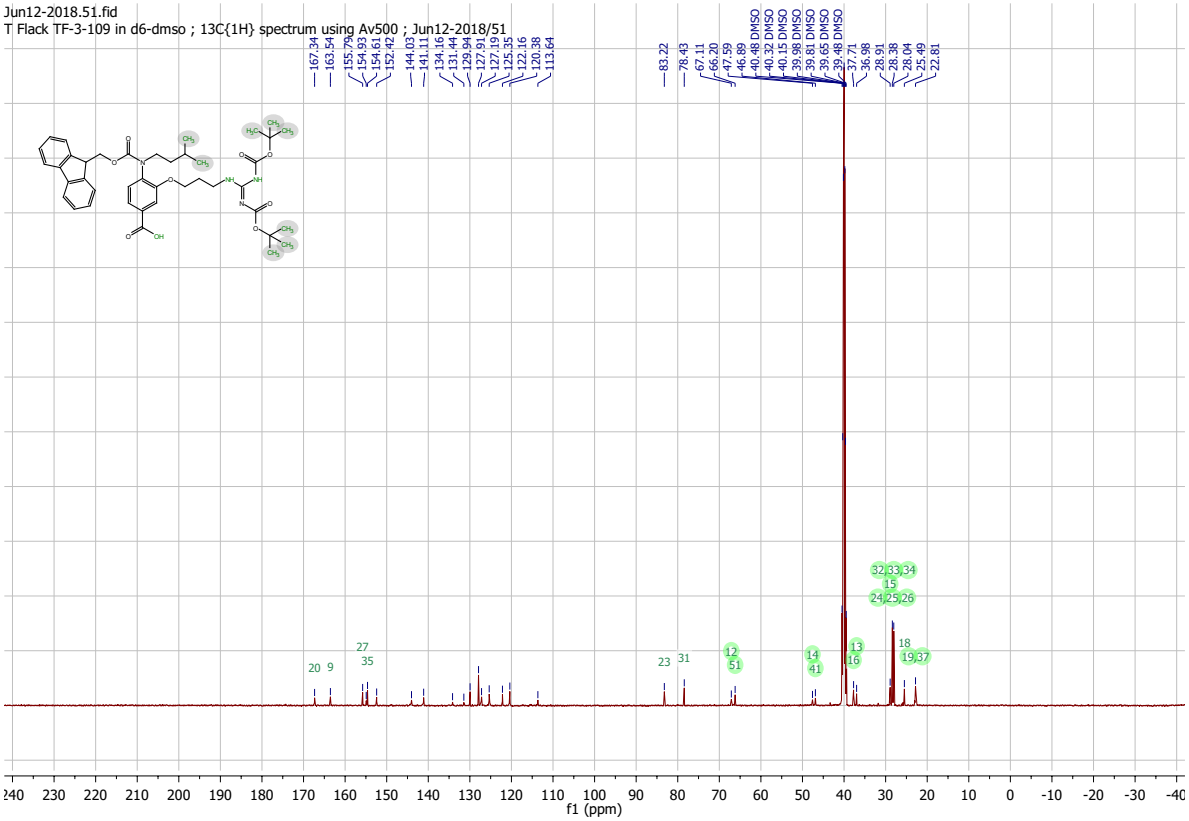

Nov07-2017.10.fid
TF-3-45
f1 (ppm)

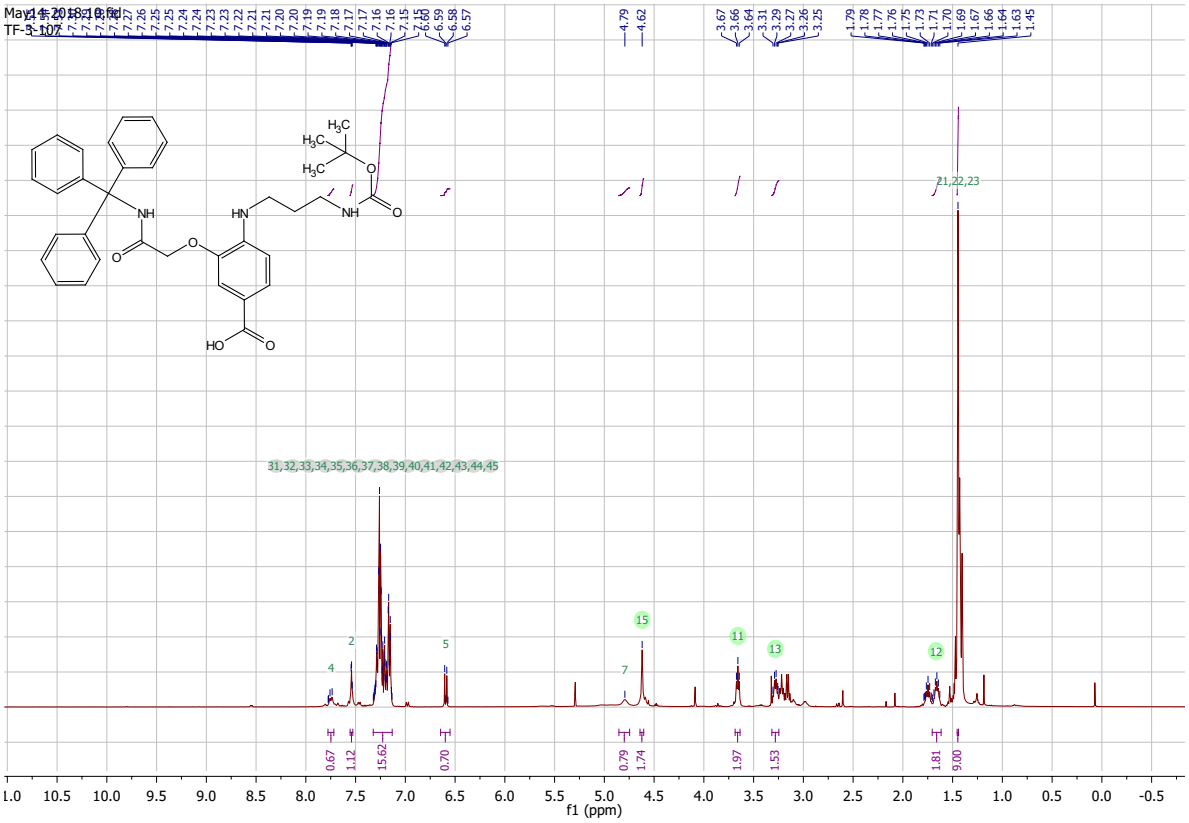

Nov07-2017.11.fid
TF-3-45
f1 (ppm)

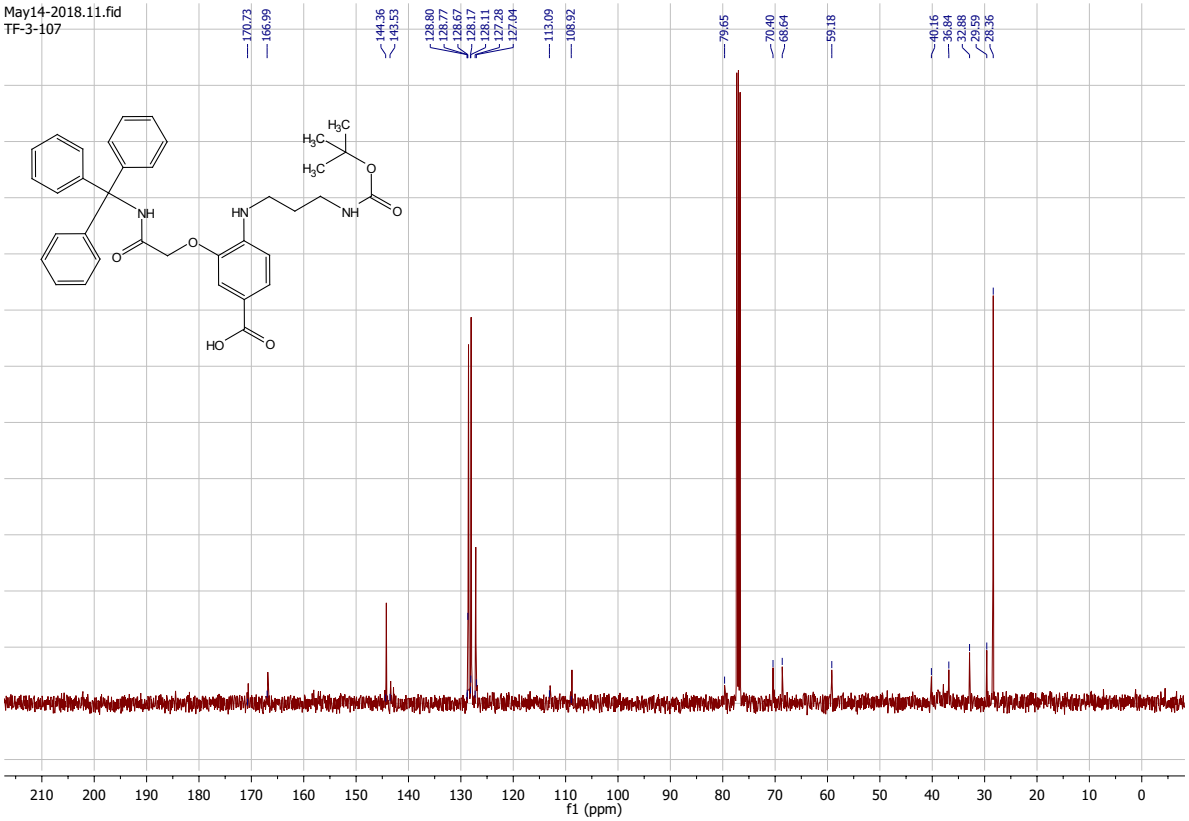

May14-2018.20.fid
TF-3-108postisolera
f1 (ppm)

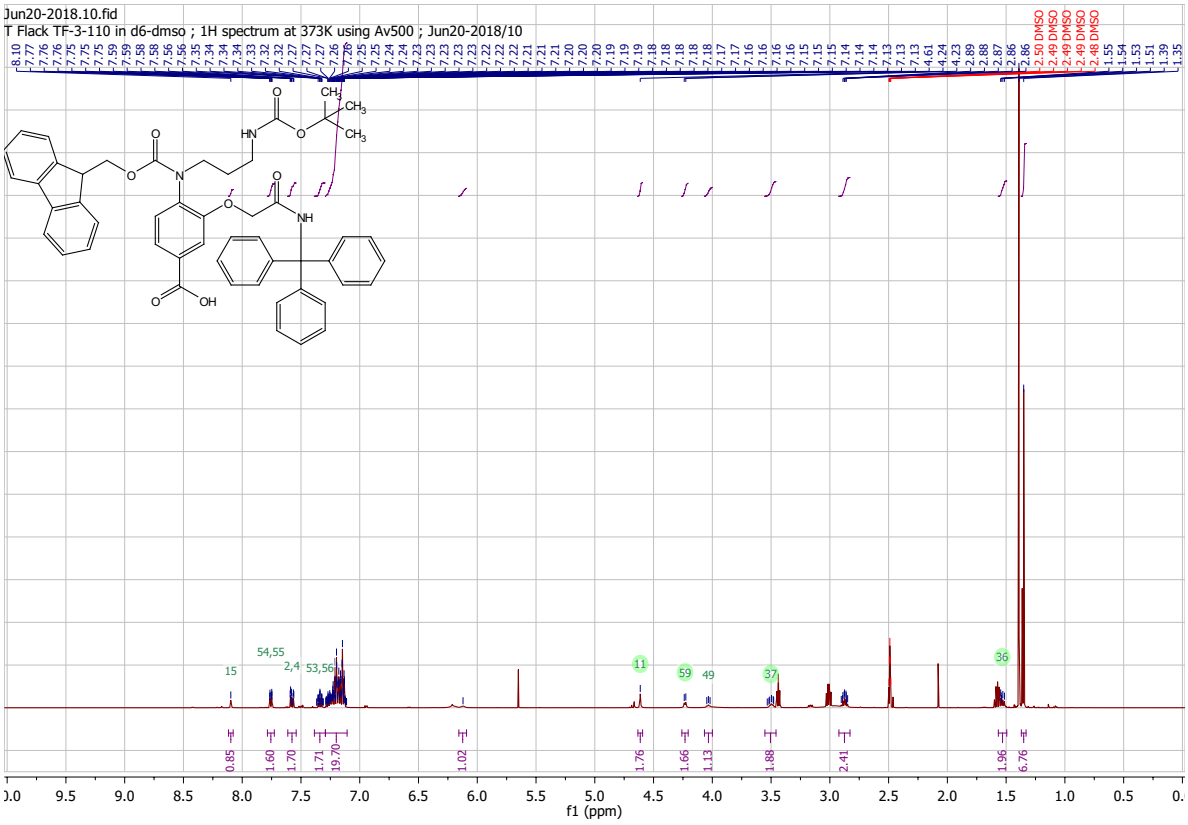

May14-2018.21.fid
TF-3-108postisolera
f1 (ppm)

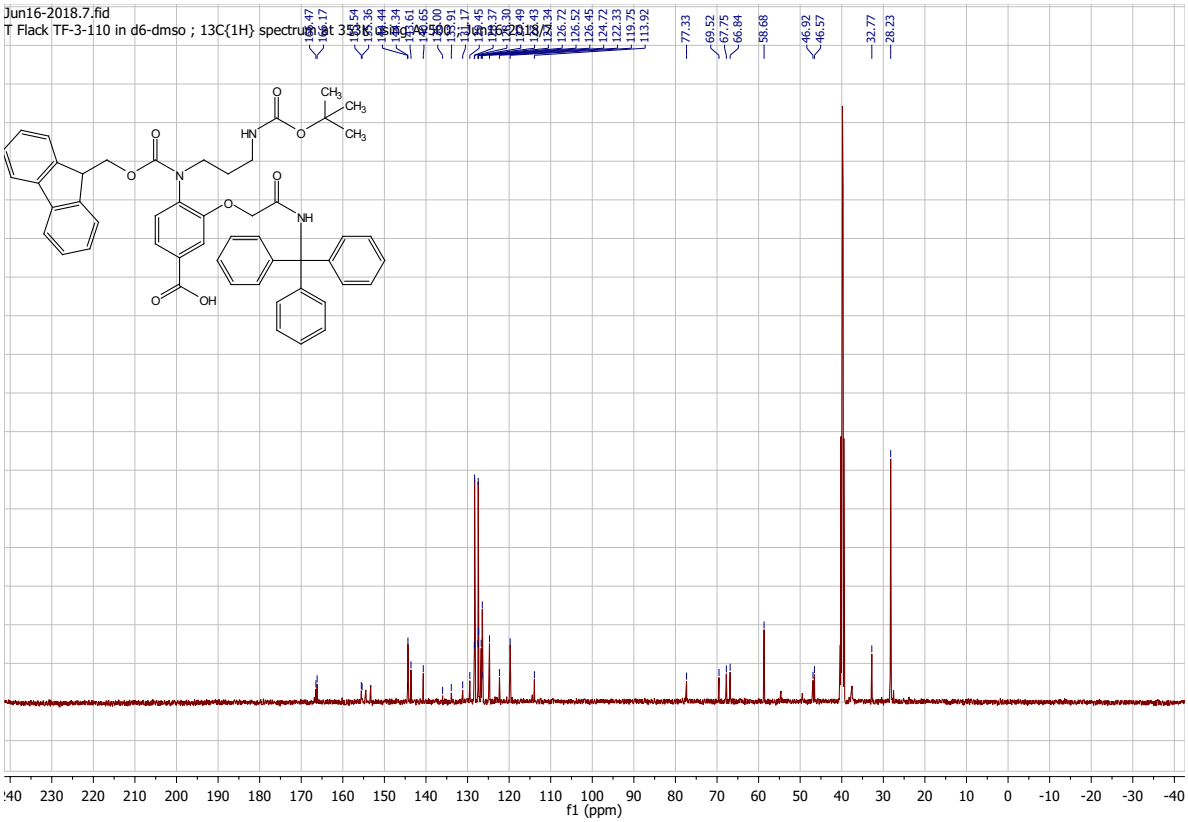

Jun16-2018.9.fid
T Flack TF-3-109 in d6-dmso ; 1H spectrum at 353K using Av500 ; Jun16-2018/9
44,49 (t) 7.20
46,47 (d) 7.76
20 (s) 8.21
2,4 (m) 7.53
A (d) 7.12
B (t) 7.34
22 (s) 11.35
D (m) 4.06
19 (t) 3.41
C (s) 4.34
11 (m) 3.48
17 (t) 4.01
E (m) 1.50
25,26,27,33,34,35 (d) 1.40
18 (p) 1.92
14,15 (d) 0.80
1.27
f1 (ppm)


Jun12-2018.51.fid
T Flack TF-3-109 in d6-dmso ; 13C{1H} spectrum using Av500 ; Jun12-2018/51
f1 (ppm)


May14-2018.10.fid
TF-3-107
4.79
4.62
3.67
3.66
3.64
3.31
3.29
3.27
3.26
3.25
1.79
1.78
1.77
1.76
1.75
1.73
1.71
1.70
1.69
1.67
1.66
1.64
1.63
1.45
21,22,23
31,32,33,34,35,36,37,38,39,40,41,42,43,44,45
0.67
1.12
15.62
0.70
0.79
1.74
1.97
1.53
1.81
9.00
f1 (ppm)

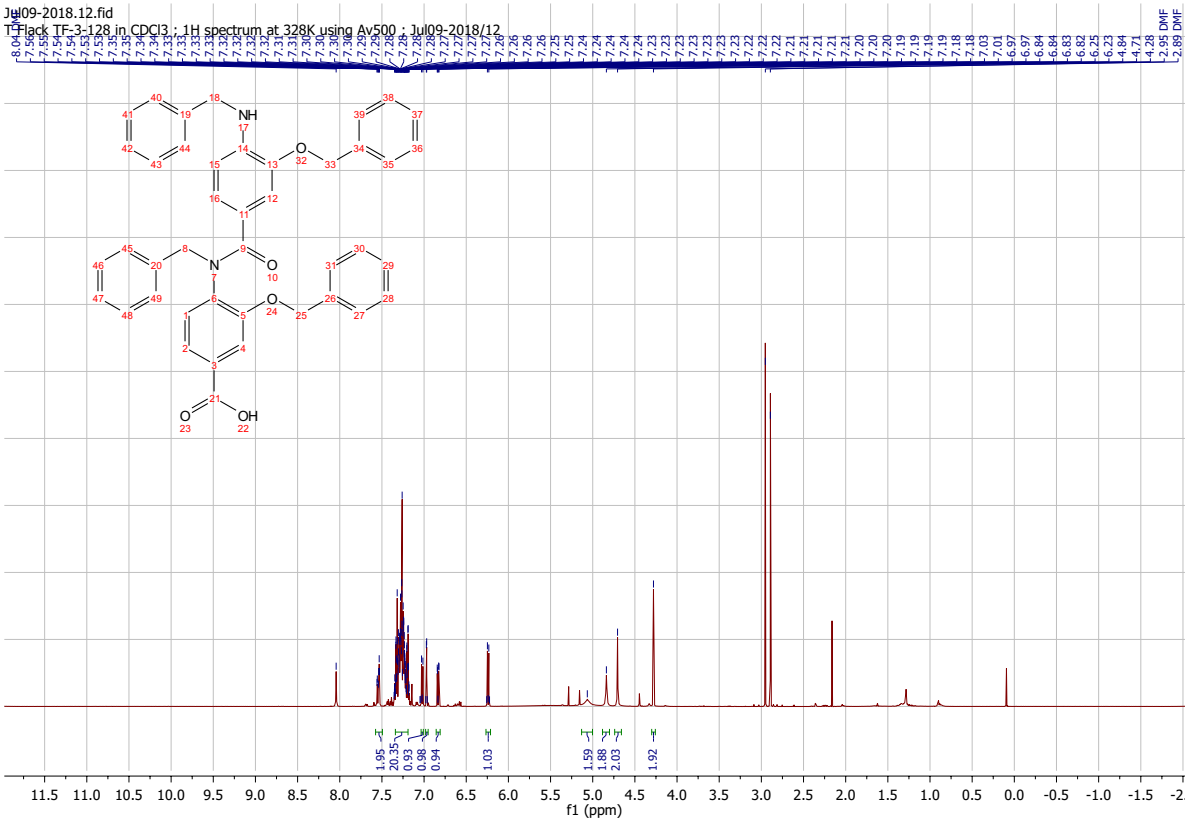

May14-2018.11.fid
TF-3-107
170.73
166.99
144.36
143.53
128.80
128.77
128.67
128.17
128.11
127.28
127.04
113.09
108.92
79.65
70.40
68.64
59.18
40.16
36.84
32.88
29.59
28.36
f1 (ppm)


Jun20-2018.10.fid
T Flack TF-3-110 in d6-dmso ; 1H spectrum at 373K using Av500 ; Jun20-2018/10
f1 (ppm)

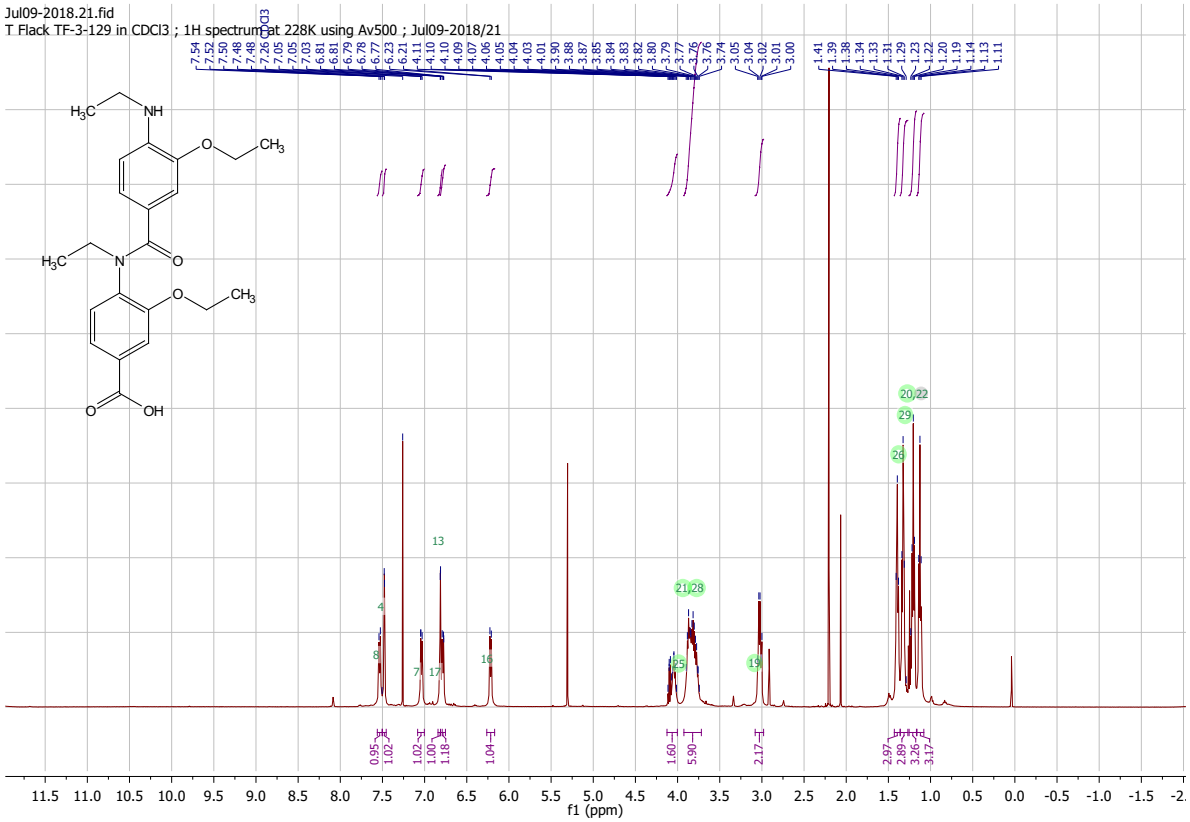

Jun16-2018.7.fid
T Flack TF-3-110 in d6-dmso ; 13C{1H} spectrum at 353K using Av500 ; Jun16-2018/7
f1 (ppm)

NMR Spectra for Oligomers (Dimers 14-16 and Trimer 17)

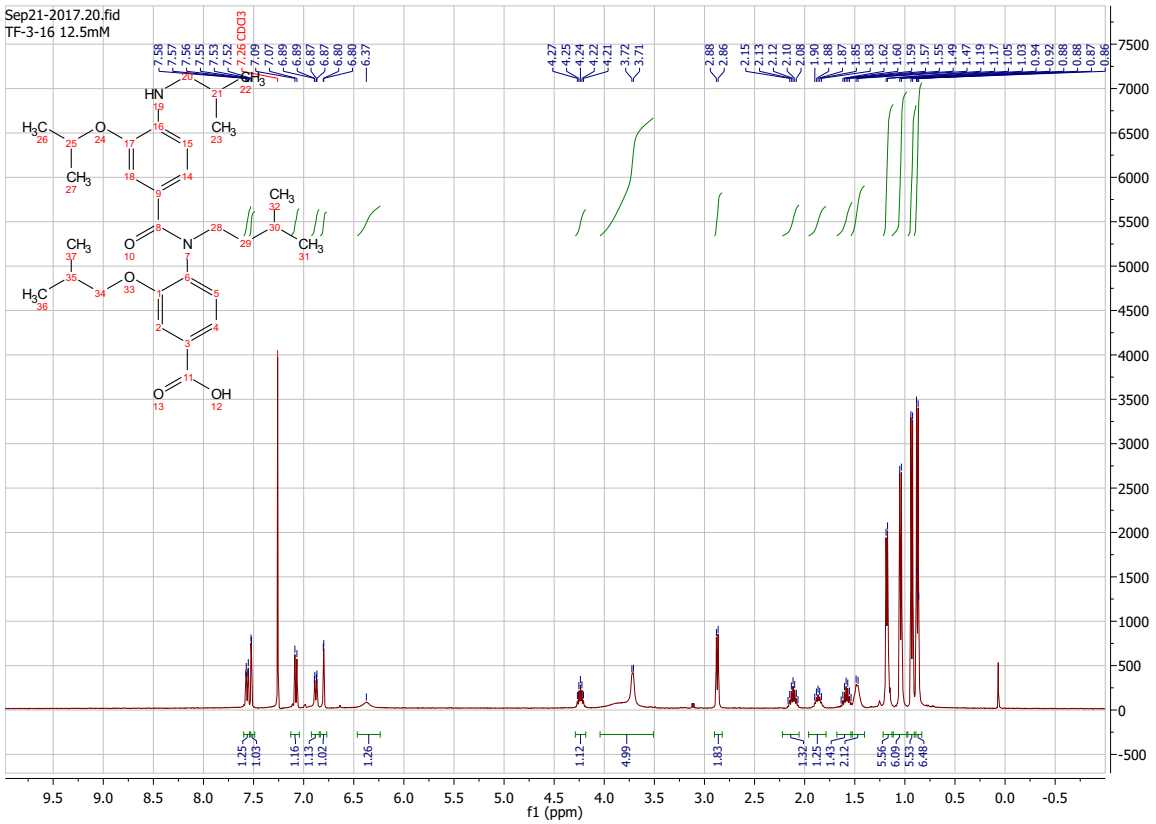
14



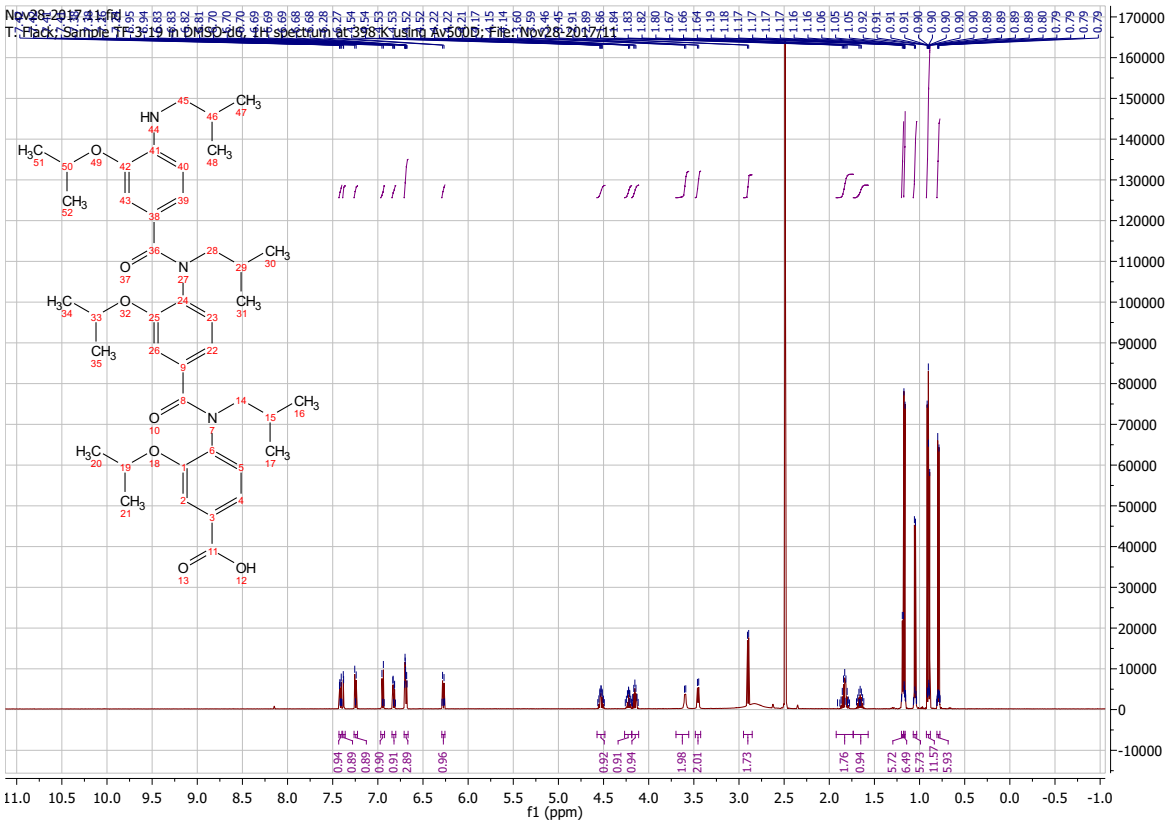
15


Jul09-2018.21.fid
T Flack TF-3-129 in CDCl3 ; 1H spectrum at 228K using Av500 ; Jul09-2018/21
f1 (ppm)

16



17


Nov28-2017-1.fid
T: Flack; Sample TF-3-19 in DMSO-d6; 1H spectrum at 398 K using Av500D; File: Nov28-2017-11
f1 (ppm)

Variable Temperature NMR Spectroscopy

The barrier to rotation about the Ar-N axis (ΔG), the rate of *enantiomerisation* (k) and the half-life of *racemisation* ($t_{1/2}$) were calaculated using the equations presented by Sandstrom.[7] If two chemically equivalent nuclei are exchanged by an intermolecular process (e.g. A $\rightleftharpoons$ B), the observed NMR spectrum is a function of the difference in resonance frequencies ($\Delta\nu_A$ - $\Delta\nu_B$) and the rate of exchange (k) (Figure S36).

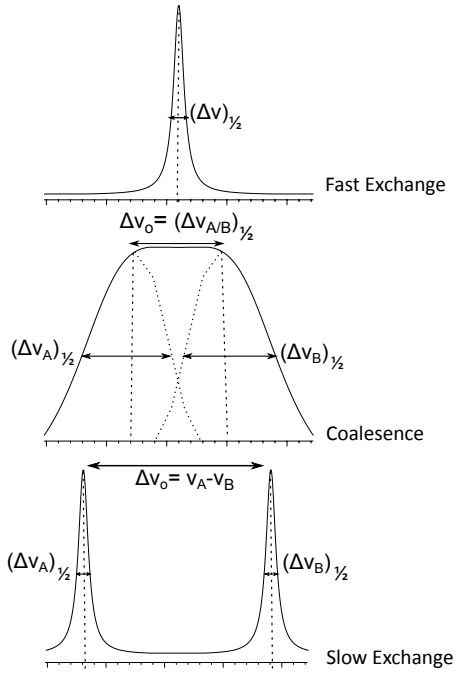


Figure S36: The exchange regimes observed in a reversible, unimolecular process . At the slow exchange limit, the rate of chemical exchange is much slower than the NMR timescale and so the NMR spectrum consists of two resonances. At the coalesence temperature, the rate of chemical exchange is approximately equal to the NMR timescale and so a single broad resonance is observed in the NMR spectrum. When the rate of chemical exchange is fast compared to the NMR timescale, the NMR spectrum appears as a single resonance at the mean of the chemical shifts observed in the slow exchange regime. This is known as the fast exchange limit.

At the coalesence temperature, assuming an equal population of conformers, the lifetime of a conformation is equal to:

$$\tau = \frac{\sqrt{2}}{\pi\Delta\nu_{1/2}} \tag{2}$$

Assuming first-order kinetics, the rate constant (k) is inversely proportional to the lifetime

τ:

$$k = \frac{1}{\tau} \tag{3}$$

Therefore, at the coalesence temperature, the rate of exchange between the two species is equal to:

$$k = \frac{\pi \Delta \nu_o}{\sqrt{2}} \quad \text{(for uncoupled signals)} \tag{4}$$

$$k = \pi \sqrt{\frac{(\Delta \nu_o)^2 + 6(J_{AB})^2}{2}} \quad \text{(for coupled signals)} \tag{5}$$

These approximate values of k were refined using gNMR v5.0 (`https://home.cc.umanitoba.ca`). The Gibbs Free Energy of Activation ($\Delta G^{\ddagger}$) is related to the rate constant by the Eyring equation;

$$k = \kappa(\frac{k_b T}{h}) e^{\frac{\Delta G^{\ddagger}}{RT}} \tag{6}$$

where $\varkappa$ is the transmision coefficient (assumed to be equal to 1 in most cases), k_b is the Boltzmann constant, T is the temperature, h is the Planck constant and R is the gas constant. Therefore, substituting the value for k into the following formula gives the value of $\Delta G^{\ddagger}$ in kJ/mol;

$$\Delta G^{\ddagger} = 0.01914 \times T_c \times (10.319 + log_{10}(\frac{T_c}{k})) \tag{7}$$

Table S14: Barriers to bond rotation in amides **14,15** and **16** via VT ^{1}H NMR analysis

Amide	Solvent	Coalescing Signals	$\Delta\nu$/ Hz	J_{AB} / Hz	T_c / K	k_{approx} / s^{-1}	k /s^{-1}	$\Delta G^{\ddagger}_{\text{Ar-N}}$[a] / kJ mol^{-1}	$t_{1/2}$[b] / s
1	$CDCl_3$	1-Hα	113.40	10.98	298.00	258.90	264.02	59.16	0.0013
1	$CDCl_3$	2-Hα'	123.18	14.06	328.00	284.31	287.13	65.14	0.0012
1	$CDCl_3$	2-Hα	180.61	14.02	318.00	402.24	401.59	62.19	0.0009
3	$CDCl_3$	1-Hβ'	32.44	-	278.00	72.06	67.44	58.18	0.0051
3	$CDCl_3$	2-Hγ'	18.13	-	273.00	40.27	38.76	58.35	0.0089
3	$CDCl_3$	2-Hδ	18.66	-	268.00	41.45	39.12	57.22	0.0089
3	$CDCl_3$	2-Hβ	67.35		288.00	149.60	129.21	58.80	0.0027
2[c]	$CDCl_3$	2-Hα'	-	-	-	-	-	-	-
2	$CDCl_3$	1-Hα'	-	-	-	-	-	-	-
2	$CDCl_3$	2-Hα	-	-	-	-	-	-	-

[a] Barrier to bond rotation at coalescence temperature.
[b] $t_{1/2} = \ln 2/2k$ - corresponds to the rate of racemisation. k is the rate constant for enantiomerisation of the amide. [c] Thermodynamic parameters for **2** could not be determined due to spectral crowding.

X-ray Crystallography

The X-ray crystal structure of 16

Crystal data for **16**: $C_{30}H_{44}N_2O_5$, M = 512.67, triclinic, P-1 (no. 2), a = 10.9267(3), b = 13.0725(6), c = 21.6323(9) Å, α = 75.589(4), β = 87.706(3), γ = 85.942(3)°, V = 2984.4(2) Å^3, Z = 4 [two independent molecules], Dc = 1.141 g cm^3, υ(Cu-Kα) = 0.615 mm^1, T = 173 K, colourless platy needles, Agilent Xcalibur PX Ultra A diffractometer; 11411 independent measured reflections (R_{int} = 0.0348), F2 refinement,[8,9] R1(obs) = 0.0461, wR2(all) = 0.1285, 8414 independent observed absorption-corrected reflections [|Fo| > 4σ(|Fo|), completeness to $\Theta_{full}(67.7°)$ = 98.9%], 699 parameters. CCDC 1902316.

The structure of **16** was found to contain two crystallographically independent molecules (**3-A** and **3-B**) in the asymmetric unit. The OH and NH hydrogen atoms on O14A, N26A, O14B and N26B were all located from ΔF maps and refined freely subject to OH and NH distance constraints of 0.90 Å.

References

(1) Shaginian, A.; Whitby, L. R.; Hong, S.; Hwang, I.; Farooqi, B.; Searcey, M.; Chen, J.; Vogt, P. K.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 5564–5572.

(2) Murphy, N. S.; Prabhakaran, P.; Azzarito, V.; Plante, J. P.; Hardie, M. J.; Kilner, C. A.; Warriner, S. L.; Wilson, A. J. *Chem. Eur. J.* **2013**, *19*, 5546–5550.

(3) Long, K.; Edwards, T. A.; Wilson, A. J. *Bioorg. Med. Chem.* **2013**, *21*, 4034–4040.

(4) Skerlj, R. T. et al. *J. Med. Chem.* **2010**, *53*, 3376–3388.

(5) Grünenfelder, C. E.; Kisunzu, J. K.; Wennemers, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 8571–8574.

(6) Sarciaux, M.; Pantel, L.; Midrier, C.; Serri, M.; Gerber, C.; Marcia De Figueiredo, R.; Campagne, J. M.; Villain-Guillot, P.; Gualtieri, M.; Racine, E. *J. Med. Chem.* **2018**, *61*, 7814–7826.

(7) Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic Pr, 1983.

(8) Bruker AXS, *SHELXTL v5.1*; 1998.

(9) Sheldrick, G. M. *Acta Cryst.* **2015**, *C71*, 3–8.