

Supporting Information

Spiroligozymes for Transesterifications: Design and Relationship of Structure to Activity

Mahboubeh Kheirabadi,[†] Nihan Çelebi-Ölçüm,[‡] Matthew F. L. Parker,[†] Qingquan Zhao,[†] Gert
Kiss,[‡] K. N. Houk,[‡] and Christian. E. Schafmeister*[†]

[†]Department of Chemistry, Temple University, 1901 N. 13th Street, Philadelphia, PA

[‡]Department of Chemistry and Biochemistry, University of California, Los Angeles, California
90095-1569

*To whom correspondence should be addressed: meister@temple.edu

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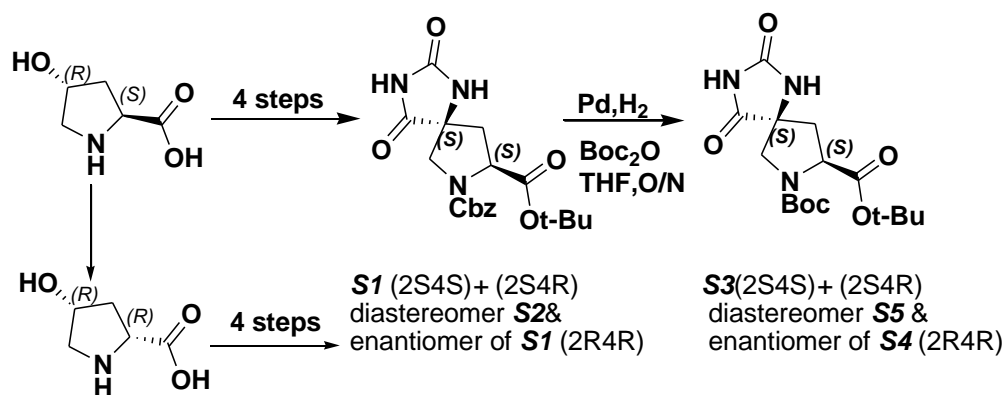
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General Methods

- All reagents were used as received unless otherwise noted. Anhydrous solvents were shown below: Anhydrous dichloromethane (CH₂Cl₂, 99.8%, extra dry over molecular sieves, <0.005% Water), anhydrous *N,N*-dimethylformamide (DMF, 99.8%, extra dry over molecular sieves), anhydrous tetrahydrofuran (THF, 99.9%, Stabilized with Approx. 25ppm BHT), anhydrous ethyl ether (Et₂O, 99.0%, <0.03% water, 1 ppm peroxide inhibitor).
- *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'* tetramethyluroniumhexafluorophosphate (HATU), 1-hydroxyl-7-azabenzotriazole (HOAt) were obtained from Genscript.

- HPLC-MS analysis was performed on a C18 column (3.5 μ m packing, 4.6 mm x 150 mm) with a solvent system of H₂O/Acetonitrile with 0.1 % formic acid at a flow rate of 0.8 mL/min.¹
- ¹H-NMR and ¹³C-NMR experiments were performed on a Bruker 500 MHz. ¹⁹F-NMR was performed on a Bruker 400 MHz. Deuterated solvents were purchased from Acros chemicals or Sigma Aldrich. Analysis of 2D NMR data was performed using Sparky 3, T. D. Goddard and D. G. Kneller, University of California, San Francisco.
- Reverse-Phase Purifications were performed on an automated flash chromatography system with a 40 gm Reverse Phase Column using water/acetonitrile with 0.1% formic acid at a flow rate of 40mL/min.
- High-Resolution MS was performed on a Time-Of-Flight (TOF) analyzer instrument.

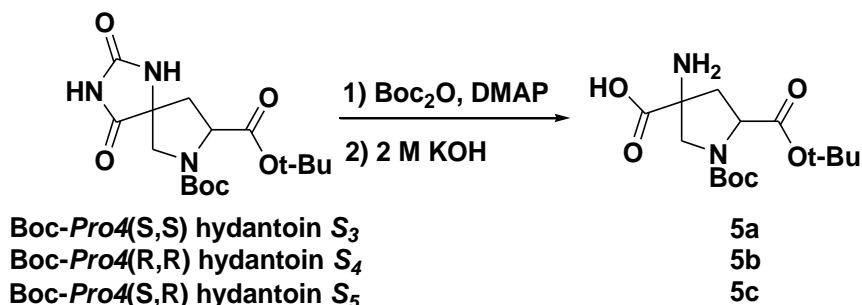
General procedure for the synthesis of *N*-Boc protected *Pro4* hydantoins (A).



The synthesis of the Cbz- protected hydantoins, compound **S1**, **S2**, and enantiomer of **S1** from *trans*-4- hydroxyproline has been published.¹ The mixture of *N*-Cbz protected *Pro4*(*S,S*) **S1**, *Pro4*(*S,R*) **S2** hydantoins or *Pro4*(*R,R*), *Pro4*(*R,S*) (3.00 g, 7.7mmole), Boc₂O (3.4 g, 15.4 mmol), and Pd/C (150 mg) was dissolved in tetrahydrofuran (77 ml, conc. 100 mM) in a 250 ml flask to which a hydrogen balloon was fitted. The vessel was aspirated using house vacuum and backfilled with hydrogen 5 times. The mixture was stirred at room temperature overnight. After 12-16 hours, the Pd/C was filtered away and the filtrate was combined with 5-10 grams of celite and the solvent was evaporated under vacuum. The product was then purified by silica gel

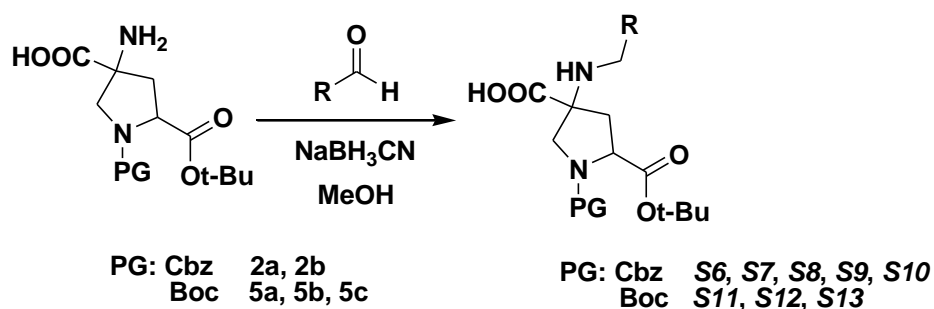
chromatography with a gradient of 0% MeOH in DCM to 5% MeOH in DCM to obtain pure Boc-hydantoin diastereomers **S3** and **S5** or **S4** and the diastereomer of **S4** as white solids.

General procedure for the synthesis of *N*-Boc protected *Pro4* amino acids (**B**).



Pure *N*-Boc protected hydantoin **S3** or **S4** or **S5** (5.0 g, 14.1mmol), DMAP (dimethylaminopyridine, 86 mg, 0.7 mmol), Boc₂O (9.2 g, 42.3 mmol) and HPLC grade THF (60 ml) were added to a 500 ml round bottom flask and allowed to stir for 1.5 hrs at room temperature. A solution of 2 M potassium hydroxide (60 ml) was then added to the reaction mixture with vigorous stirring and the homogenous mixture was stirred at room temperature for 30 minutes. The reaction mixture was then transferred to a 500 ml separatory funnel and 150 ml of diethyl ether was added. The aqueous layer was then transferred to a beaker and cooled to 0 °C in an ice bath. 2M HCl was then added drop wise while stirring until the pH reached 7 as measured using pH paper. As the pH approaches 7 the amino acid product rapidly precipitates out as a white solid. The solid product was then filtered through a Buchner funnel and dried under high vacuum to yield a white solid as *N*-Boc protected bis-amino acids **5a** or **5b** or **5c**.

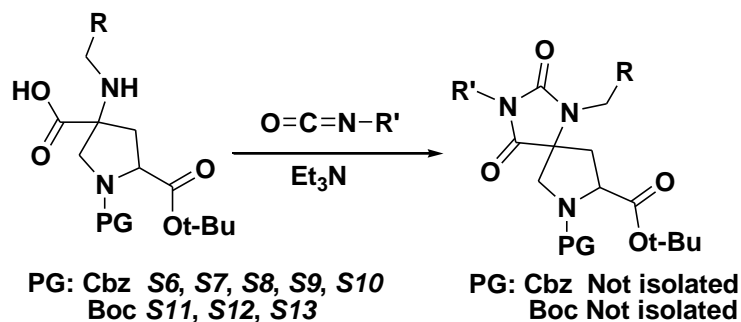
General procedure for the reductive alkylation of the *Pro4* monomers (**C**).



The starting material, *pro4* amino acid **2a-b** or **5a-c** (3.0 mmol) was dissolved in methanol (20 ml, concentration of 151 mM) and the aldehyde **3a-c** or **6** (3.0 mmol) was added in a single portion. The solution was stirred at room temperature for 30 minutes and then NaBH₃CN (188 mg, 3.0 mmol) was added in a single portion as a solid. The homogenous mixture was allowed to stir for 12 hours at room temperature. The progress of the reaction was evaluated at 12 hours by diluting 10 µl of the reaction with 500 µl acetonitrile and injecting 30 µl of this solution into a C18 reverse phase HPLC-MS. Typically after 12 hours no remaining starting material is seen by LCMS. The reaction mixture was combined with 5-10 g of celite and the solvent was removed

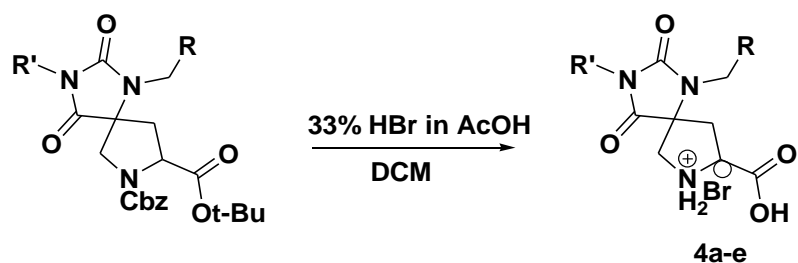
using vacuum. The celite bound product was reverse phase purified using a C₁₈ column with a gradient of 30-100% H₂O/ACN with 0.1% formic acid. The desired fractions were pooled and lyophilized.

General procedure for isocyanate capping of functionalized *Pro4*-amino acids (D).



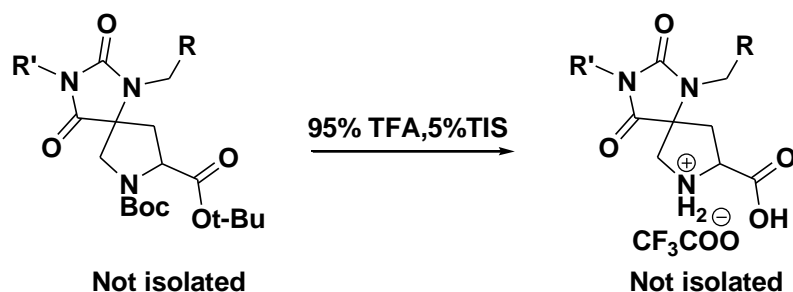
The starting material, the reductively alkylated *Pro4* amino acid *S6-S13* (2 mmol) and triethylamine (4 mmol) were combined in dry THF (5 ml/ mmol of starting material) and then the isocyanate (2 mmol) was added in a single portion. The mixture was stirred at room temperature for 24h. At this point 20 ml saturated NH₄Cl was added and the reaction mixture was extracted with EtOAc (2×100 ml). The combined organic layers were washed with saturated NaHCO₃ (2× 50 ml) and brine (2×50 ml), dried over sodium sulfate and concentrated.

General procedure for HBr deprotection of *N*-Cbz and *tert*-butyl ester groups (E).



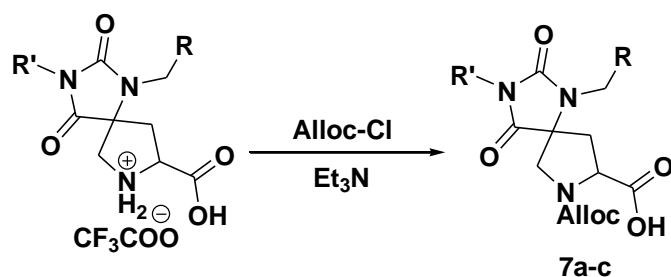
The crude *N*-Cbz protected material was dissolved in DCM (approximately 2 ml/100 mg product) and 33% HBr in AcOH (1 ml/100 mg product) was added and the mixture was allowed to stir for 1.5 hour at room temperature. The solvent was removed *in vacuo*, residue was resuspended in DCM and solvent removed under reduced pressure twice to remove excess HBr. The product was resuspended in DCM (approximately 2 ml/50 mg crude product). The resulting solids were filtered and washed several times with DCM and dried under vacuum. The product was crystallized from methanol by dissolving the crude solids in 15 ml MeOH / 1g of crude solid and then placing the methanol solution at -40°C for one hour.

General procedure for TFA deprotection of *N*-Boc and *tert*-butyl ester groups (F).



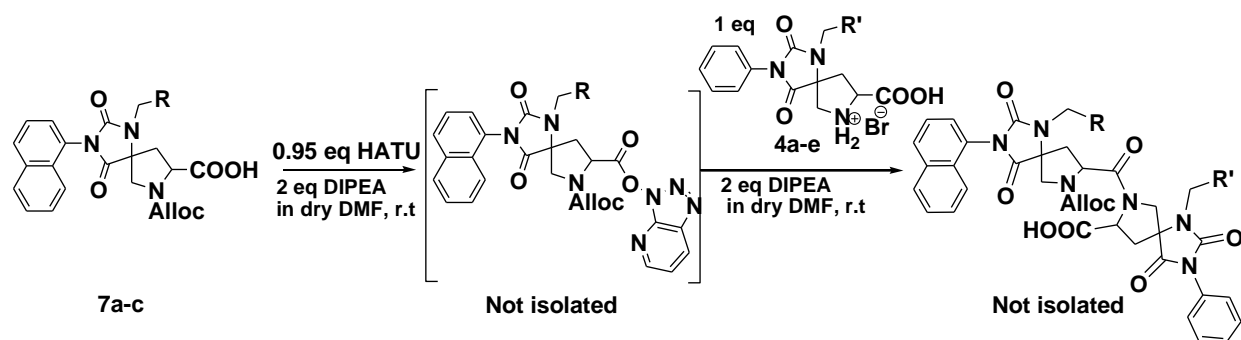
The crude *N*-Boc protected material was dissolved in trifluoroacetic acid (approximately 1 ml/ 50 mg product) and triisopropylsilane (TIS) (53 μ l/50 mg product) was added as a scavenger. The mixture was allowed to stir for 4h at room temperature. The solvent was removed using vacuum, and the residue was resuspended in DCM (10 ml) and toluene (2 ml) and the solvent was removed under reduced pressure to remove excess TFA. Residue was dried under vacuum overnight.

General procedure for Alloc protection of amino acids (G).



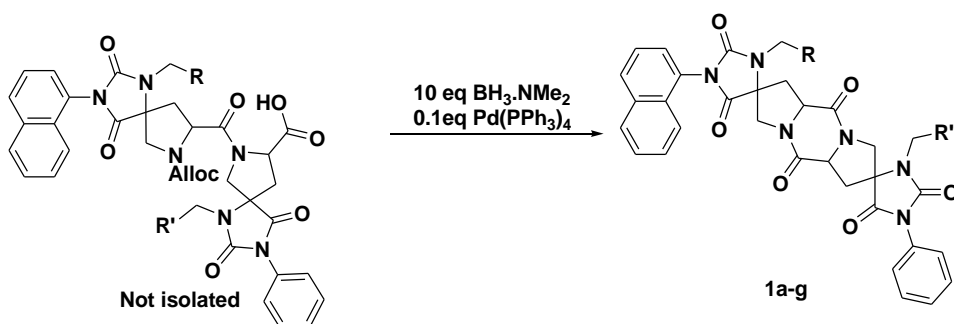
Pro4 functionalized trifluorocarboxylate in the scheme above (2 mmol) was dissolved in THF (50 mM). The solution was cooled to 0⁰C with an ice bath. Et₃N (20 mmol) was added to the solution followed by drop-wise addition of allyl chloroformate (20 mmol) over 10 minutes. The reaction mixture was stirred at 0⁰C for 0.5 h; after which the ice bath was removed and the mixture was allowed to stir overnight at room temperature. At this point saturated ammonium chloride (20 ml) was added and the product was extracted with EtOAc (100 ml). The organic layer was washed with brine and dried over sodium sulfate and loaded onto celite (combined with 5 g celite and the solvent was evaporated). The product was then purified using silica-gel flash chromatography with a gradient of 0% MeOH in DCM to 5% MeOH in DCM.

General procedure for *Bis*-amino acid activation and coupling (H).



In a flame dried vial, the *N*-Alloc protected *bis*-amino acids **7a-c** and **4a** to be activated (0.3 mmol) and HATU (0.29 mmol) were suspended in DMF (final concentration of bis-amino acid is 50 mM) under argon. With stirring, DIPEA (0.6 mmol) was then added in one portion and the mixture was stirred for 1.5 hours at room temperature. The other *Pro4*-amino acids **4a-4e** (0.3 mmol) was then suspended in a minimal volume of DMF (~200 μ L), and DIPEA (0.6 mmol). Resulting solution was then added to the preactivated amino acid drop wise and allowed to react overnight at room temperature.

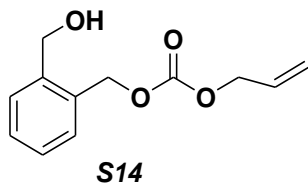
General procedure for diketopiperazine closure (I).



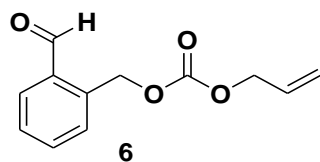
To the crude coupling solution from step **H**, was added borane dimethylamine complex (1.8 mmol) as a scavenger and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0) (30 μ mol). Simultaneous deprotection of the alloc protecting groups and partial diketopiperazine (DKP) closure were observed using C18 reverse phase HPLC-MS after 24 hour stirring at room temperature. To ensure complete diketopiperazine formation in the next step a quick workup is needed to remove excess borane dimethylamine scavenger. The reaction mixture was diluted by adding 50 ml ethyl acetate and the organic layer was washed with brine (3 \times 10 ml) after which the organic layer was dried with NaSO_4 and the solvent was removed under reduced pressure. The resulting residue was dissolved in 1:2 DMF/DCM (final concentration 100 mM respect to *N*-Alloc protected starting material), followed by addition of HOAt (2 mmol) and DIC (2 mmol). The mixture was allowed to stir for 3 hours at room temperature. Workup of the reaction was carried out by diluting the crude mixture by adding 100 ml ethyl acetate and the organic layer was washed using a sequence of saturated ammonium chloride (3 \times 20 ml), brine (3 \times 20 ml), saturated sodium bicarbonate (3 \times 20 ml), and then brine again (3 \times 20 ml). The product was loaded onto celite by adding 5 g celite and removing the solvent in vacuum and purified by silica-gel chromatography with a gradient of 0% MeOH in DCM to 5% MeOH in DCM. A second

purification was then carried out using C₁₈ reverse phase with a gradient of 0-100% H₂O/ACN with 0.1% formic acid.

Synthesis of aldehydes :

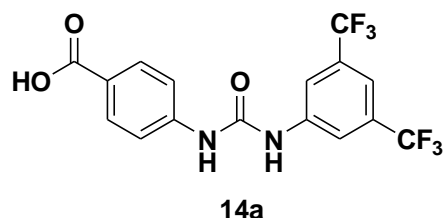


2-(hydroxymethyl)benzyl allyl carbonate S14: To a 1 L round bottom flask equipped with a magnetic stir bar, 1,2-benzenedimethanol (5 g, 36 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (4.3 ml, 29 mmol) was dissolved in 450 ml HPLC-grade THF. The solution was cooled to 0^oC (ice/water) followed by drop-wise addition over 30 minutes of Alloc-Cl (3.8 ml, 36 mmol) in 50 ml THF using a separatory funnel. The reaction allowed to stir for 2 hours at room temperature. At this point the reaction was quenched with 50 ml saturated ammonium chloride. Then the solvent was reduced to 50 ml under reduced pressure. The resulting residue was dissolved in 500 ml ethyl acetate and transferred to a separatory funnel. The organic layer was washed sequentially with 50 ml saturated ammonium chloride, and then with 50 ml saturated sodium bicarbonate followed by 50 ml brine. The organic layer was dried over anhydrous sodium sulfate and filtered and the product was combined with 10 g celite and the solvent was removed using vacuum. The product was then purified by silica gel chromatography using a gradient of 0% MeOH in DCM to 5% methanol in DCM. (6.0 g, 75% yield, 20% recovered starting material). ¹H NMR (500 MHz, CDCl₃, 293 K, δ) 7.43-7.42 (d, 1H, *J* = 1.50), 7.413-7.41(d, 1H, *J* = 1.50), 7.38-7.34 (td, 1H, *J* = 1.5, 7.5), 7.34-7.31 (td, 1H, *J* = 1.5, 7.0), 5.96-5.88 (m, 1H), 5.37-5.33 (dq, 1H, *J* = 1.5, 17), 5.29 (s, 2H), 5.28-5.25 (dq, 1H, *J* = 1.0, 10.5), 4.74 (s, 2H), 4.63-4.62 (dt, 2H, *J* = 1.35, 6), 2.46 (s, 1H). ¹³C NMR (125 MHz, CDCl₃, 293 K, δ) 155.02, 139.52, 133.32, 131.55, 129.99, 129.28, 129.02, 128.28, 119.21, 68.83, 67.42, 62.97. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 15.80 min; HRMS-ESI: *m/z* calcd for C₁₂H₁₄O₄ (M+H)⁺ 223.0965, found 223.0963.

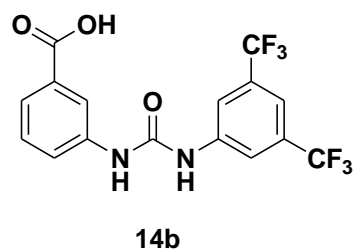


2-formylbenzyl allyl carbonate 6: In a 250 ml round bottom flask, mono O-Alloc protected benzyl alcohol *S14* (4g, 18 mmol) was dissolved in 150 ml chloroform followed by addition of activated MnO₂ (20 g, 180 mmol). The reaction mixture was stirred at room temperature for 48 hours. The manganese dioxide was filtered off with a plug of cotton covered by celite and washed with chloroform and the combined chloroform filtrate was washed with water and dried over anhydrous sodium sulfate. The product was combined with 10 g celite and the solvent was removed using vacuum. The product was then purified by silica gel chromatography using a gradient of 0% MeOH in DCM to 5% MeOH in DCM (3.5 g, yield 88%). ¹H NMR (500 MHz, CDCl₃, 293 K, δ) 10.16 (s, 1H), 7.87-7.86 (dd, 1H, *J* = 1.0, 7.5), 7.62-7.58 (m, 2H), 7.55-7.52 (dt,

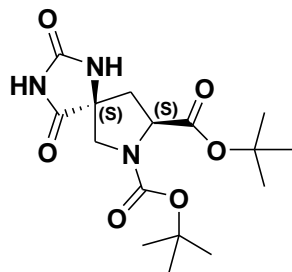
1H, $J=1.5$, 8), 5.99-5.91 (m, 1H), 5.63 (s, 2H), 5.39-5.35 (dq, 1H, $J=1.5$, 17), 5.29-5.27 (d, 1H, $J=1.0$), 4.67-4.65 (dt, 2H, $J=1.5$, 5.5). ^{13}C NMR (125 MHz, CDCl_3 , 293 K, δ) 192.75, 154.87, 137.38, 134.14, 133.96, 133.50, 131.61, 128.67, 128.29, 119.21, 68.86, 66.97. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R = 18.97$ min; HRMS-ESI: m/z calcd for $\text{C}_{12}\text{H}_{12}\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 221.0808, found: 221.0817.



4-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)benzoic acid 14a : 3-Aminobenzoic acid (1 g, 7.3 mmol) was dissolved in 30 ml dry THF. Followed by addition of DIPEA (1.3 ml, 7.3 mmol) and 3,5-Bis(trifluoromethyl)phenyl isocyanate (1.3 ml, 7.3 mmol). The reaction mixture was stirred for 12 hours at room temperature. After which the solvent was removed and product was purified by C_{18} reverse phase with a gradient of 0-100% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid (2.6 g, 91% yield). ^1H NMR (500 MHz, $\text{MeOD}-d_4$, 293 K, δ). 8.06 (s, 2H), 7.95-7.93 (d, 2H, $J=9$), 7.56-7.52 (m, 3H). ^{13}C NMR (125 MHz, $\text{MeOD}-d_4$, 293 K, δ) 169.79, 154.25, 144.93, 142.90, 133.37 (q), 132.11, 126.08, 123.86, 119.65, 119.35, 116.40. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R = 22.64$ min; HRMS-ESI: m/z calcd for $\text{C}_{16}\text{H}_{10}\text{F}_6\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 393.0668, found 393.0670.



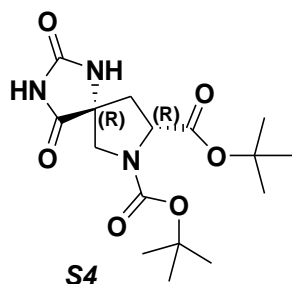
3-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)benzoic acid 14b : The same procedure as compound **14a** was used (2.5 g, 87% yield). ^1H NMR (500 MHz, $\text{MeOD}-d_4$, 293 K, δ) 8.064-8.057 (t, 1H, $J=2$), 8.05 (s, 2H), 7.73-7.71 (dq, 1H, $J=1$, 8), 7.68-7.66 (dt, 1H, $J=1.5$, 8), 7.50 (s, 1H), 7.39-7.36 (t, 1H, $J=8$). ^{13}C NMR (125 MHz, $\text{MeOD}-d_4$, 293 K, δ) 169.82, 154.69, 143.06, 140.55, 133.05 (q), 130.18, 126.04, 125.53, 125.00, 123.87, 121.72, 119.59, 116.24. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R = 22.35$ min; HRMS-ESI: m/z calcd for $\text{C}_{16}\text{H}_{10}\text{F}_6\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 393.0668, found 393.0665.



S3

7,8-di-tert-butyl (5S,8S)-2,4-dioxo-1,3,7-triazaspiro[4.4]nonane-7,8-dicarboxylate S3:

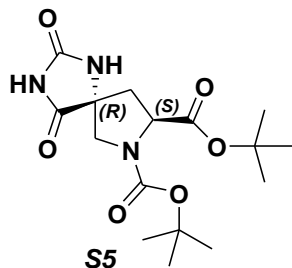
General procedure **A**, starting from trans-hydroxy proline has been used. (Overall 60% yield in 5 steps). ^1H NMR (500 MHz, MeOD- d_4 , 345 K, δ), 4.40-4.37 (dd, 1H, $J = 5.5, 9$), 3.85-3.83 (d, 1H, $J = 11.5$), 3.60-3.57 (d, 1H, $J = 11.5$), 2.73-2.69 (dd, 1H, $J = 9, 13.5$), 2.15-2.11 (dd, 1H, $J = 5.5, 13.5$), 1.50 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, MeOD- d_4 , 345K, δ) 177.46, 173.44, 158.17, 155.33, 83.60, 82.27, 66.87, 60.55, 55.11, 40.16, 28.83, 28.48. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R = 17.24$ min; HRMS-ESI: m/z calcd for $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_6$ ($\text{M}+\text{Na}$) $^+$ 378.1636, found 378.1636.



S4

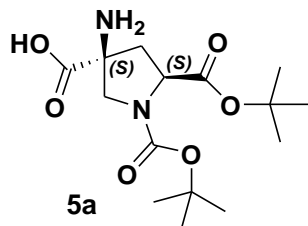
7,8-di-tert-butyl (5R,8R)-2,4-dioxo-1,3,7-triazaspiro[4.4]nonane-7,8-dicarboxylate S4:

Synthesis of *N*-Cbz protected *pro4* (2R, 4R) and (2R, 4S) hydantoins has been published.¹ General procedure **A**, starting from cis-hydroxy proline has been used. (Overall 60% yield in 5 steps). ^1H NMR (500 MHz, MeOD- d_4 , 345 K, δ) 4.40-4.37 (dd, 1H, $J = 5.5, 8.5$), 3.85-3.82 (d, 1H, $J = 11.5$), 3.59-3.56 (d, 1H, $J = 11.5$), 2.73-2.68 (dd, 1H, $J = 9, 13$), 2.15-2.11 (dd, 1H, $J = 5.5, 13.5$), 1.50 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, MeOD- d_4 , 345K, δ) 177.61, 173.51, 158.30, 155.45, 83.68, 82.37, 66.81, 60.59, 55.12, 40.15, 28.82, 28.47. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R = 17.27$ min; HRMS-ESI: m/z calcd for $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_6$ ($\text{M}+\text{Na}$) $^+$ 378.1636, found 378.1635.

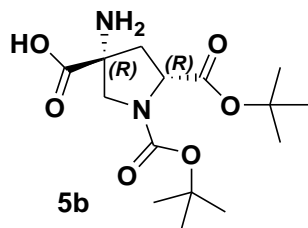


7,8-di-*tert*-butyl (5R,8S)-2,4-dioxo-1,3,7-triazaspiro[4.4]nonane-7,8-dicarboxylate S5:

General procedure **A**, starting from *trans*-hydroxy proline has been used. (with 1:5 diastereomeric ratio of *S5* to *S3*, overall 52% yield in 5 steps). ^1H NMR (500 MHz, $\text{DMSO-}d_6$, 1% TFA, 345 K, rotamers were observed for 3 to 1 ratio, major rotamer was reported, δ). 8.30 (s, 1H), 4.33-4.29 (t, 1H, $J = 8.5$), 3.62-3.60 (d, 1H, $J = 11.5$), 3.53-3.51 (d, 1H, $J = 11$), 2.96 (broad singlet, H_2O), 2.41-2.37 (dd, 1H, $J = 9, 13$), 2.26-2.21 (dd, 1H, $J = 9, 13.5$), 1.45-1.42 (m, 18 H). ^{13}C NMR (125 MHz, $\text{MeOD-}d_4$, 345 K, rotamers were observed with 3 to 1 ratio, major rotamer was reported, δ) 176.05, 172.47, 158.59, 155.54, 83.42, 82.35, 68.17, 60.48, 57.13, 41.86, 28.84, 28.47. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R = 16.65$ min; HRMS-ESI: m/z calcd for $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_6$ ($\text{M}+\text{Na}$) $^+$ 378.1636, found 378.1635.

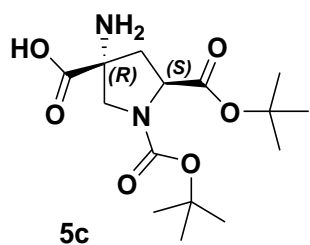


(3S,5S)-1,5-di(*tert*-butoxycarbonyl)-3-aminopyrrolidine-3-carboxylic acid 5a: General procedure **B** starting from *N*-Boc *Pro4* (2*S*, 4*S*) hydantoin **S3** has been used. (80% yield from **S3**). ^1H -NMR (500 MHz, $\text{DMSO-}d_6$, 1% TFA, 345 K, δ) 4.25- 4.22 (t, 1H, $J = 8.5$), 3.99-3.97 (d, 1H, $J = 11.5$), 3.61-3.59 (d, 1H, $J = 11.5$), 2.82-2.78 (dd, 1H, $J = 8.5, 13$), 2.33-2.29 (dd, 1H, $J = 8, 13.5$), 1.46 (s, 9H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $\text{MeOD-}d_4$, 345K, δ) 180.22, 174.51, 156.15, 82.82, 81.44, 61.64, 61.55, 60.19, 43.63, 28.97, 28.57. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R = 12.58$ min; HRMS-ESI: m/z calcd for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$ 331.1864, found 331.1867.

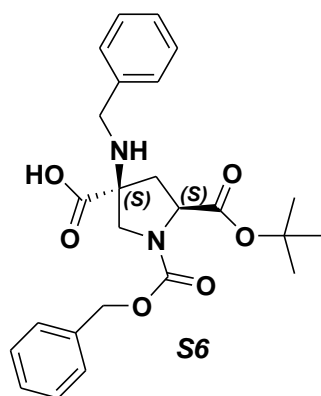


(3R,5R)-1,5-di(*tert*-butoxycarbonyl)-3-aminopyrrolidine-3-carboxylic acid 5b: General procedure **B** starting from *N*-Boc *Pro4* (2*R*, 4*R*) hydantoin **S4** has been used. (80% yield from

S4). ^1H -NMR (500 MHz, $\text{DMSO-}d_6$, 1% TFA, 330 K, δ) 4.25-4.22 (t, 1H, $J=8.0$), 3.99-3.96 (d, 1H, $J=11.5$), 3.57-3.55 (d, 1H, $J=11.5$), 2.83-2.79 (dd, 1H, $J=9, 13.5$), 2.28-2.23 (dd, 1H, $J=8, 13.5$), 1.49-1.42 (m, 18H). ^{13}C NMR (125 MHz, $\text{MeOD-}d_4$, 330K, δ) 175.23, 175.16, 155.67, 83.91, 82.16, 65.35, 61.13, 57.49, 40.80, 28.84, 28.47. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R=12.56$ min; HRMS-ESI: m/z calcd for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$ 331.1864, found 331.1861.

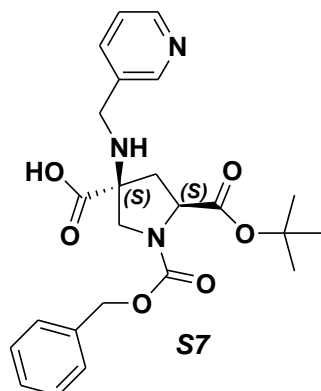


(3R,5S)-1,5-di(tert-butoxycarbonyl)-3-aminopyrrolidine-3-carboxylic acid 5c: General procedure **B** starting from Boc-*Pro4* (2S, 4R) hydantoin **S5** has been used. (72% yield from **S5**). ^1H -NMR (500 MHz, $\text{DMSO-}d_6$, 0.1% TFA added, 350 K, δ) 4.39-3.35 (dd, 1H, $J=7.5, 8.5$), 3.90-3.87 (d, 1H, $J=12$), 3.72-3.70 (d, 1H, $J=12$), 2.70-2.66 (t, 1H, $J=13.5$), 2.47-2.44 (m, 1H), 1.43-1.42 (m, 18H). ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$, 0.1% TFA added, 350 K, δ) 171.01, 170.13, 152.70, 79.99, 78.47, 63.10, 58.30, 55.65, 39.01, 27.72, 27.35. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R=12.13$ min; HRMS-ESI: m/z calcd for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$ 331.1864, found 331.1864.

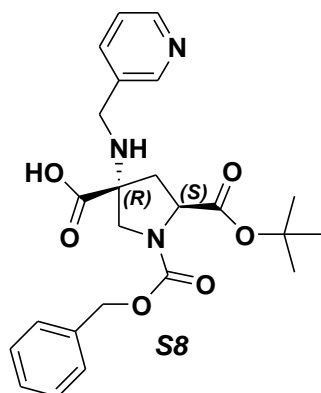


(3S,5S)-1-((benzyloxy)carbonyl)-5-(tert-butoxycarbonyl)-3-(benzylamino)pyrrolidine-3-carboxylic acid S6: The reaction was carried out via the general procedure **C** of the reductive alkylation of bis-amino acids starting from *N*-Cbz *pro4* (2S, 4S) amino acid **2a** and benzaldehyde. (1.2 g, 86% yield from **2a**). ^1H -NMR (500 MHz, $\text{DMSO-}d_6$, 350K, δ) 7.48-7.31 (m, 10 H), 5.11 (s, 2H), 4.36-4.33 (t, 1H, $J=8.2$), 4.23-4.15 (m, 3H), 3.72-3.70 (d, 1H, $J=11.4$), 2.96-2.92 (dd, 1H, $J=8.4, 13.3$), 2.38-2.34 (dd, 1H, $J=8.5, 13.3$), 1.38 (s, 9H). ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$, 350K, δ) 174.42, 170.90, 154.23, 140.40, 137.29, 128.70, 128.46, 128.14, 127.76, 127.20, 81.20, 66.67, 59.44, 54.97, 49.03, 30.92, 28.15, 28.06. HPLC analysis (C_{18} reverse phase, 30 min,

5-95% H₂O/ACN with 0.1% formic acid) $t_R = 17.3$ min; HRMS-ESI: m/z calcd for C₂₅H₃₀N₂O₆ (M+H)⁺ 455.2177, found 455.2182.

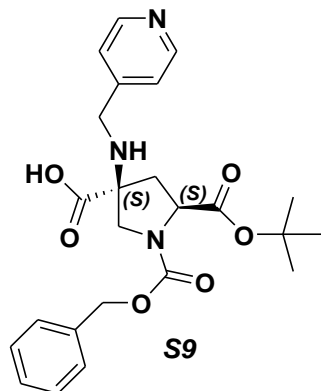


(3S,5S)-1-((benzyloxy)carbonyl)-5-(tert-butoxycarbonyl)-3-((pyridin-3-yl)methylamino)pyrrolidine-3-carboxylic acid S7: The reaction was carried out via the general procedure C of the reductive alkylation of bis-amino acids starting from the *N*-Cbz *pro4* (2S, 4S) amino acid **2a** and 3-pyridine carboxaldehyde (1.0 g, 73% yield from **2a**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA, 365 K, δ) 8.66 (s, 1H), 8.60-8.59 (d, 1H, $J = 4.7$), 8.05-8.04 (d, 1H, $J = 7.8$), 7.59-7.56 (t, 1H, $J = 6.6$), 7.37-7.31 (m, 5H), 5.11 (s, 2H), 4.32-4.29 (dd, 1H, $J = 6.5, 8.4$), 4.03-4.01 (d, 1H, $J = 11.1$), 3.96-3.94 (d, 1H, $J = 14$), 3.90-3.87 (d, 1H, $J = 13.95$), 3.52-3.50 (d, 1H, $J = 11.1$), 2.80-2.76 (dd, 1H, $J = 8.75, 13.05$), 2.18-2.14 (dd, 1H, $J = 6.20, 13.15$), 1.36 (s, 9H). ¹³C NMR (125 MHz, DMSO-*d*₆, 365K, δ) 173.65, 169.41, 153.40, 148.98, 147.61, 136.33, 135.25, 135.19, 127.90, 127.34, 126.94, 122.71, 80.40, 65.84, 58.46, 54.28, 53.86, 45.57, 38.44, 27.25. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) $t_R = 13.37$ min; HRMS-ESI: m/z calcd for C₂₄H₂₉N₃O₆ (M+H)⁺ 456.2129, found 456.2129.

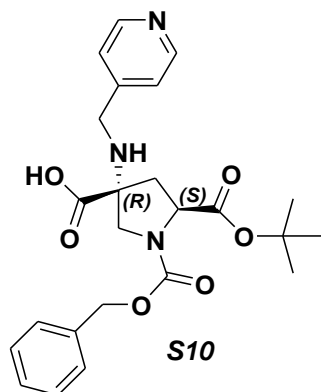


(3R,5S)-1-((benzyloxy)carbonyl)-5-(tert-butoxycarbonyl)-3-((pyridin-3-yl)methylamino)pyrrolidine-3-carboxylic acid S8: The reaction was carried out using the general procedure C of the reductive alkylation of bis-amino acids starting from the *N*-Cbz *pro4* (2S, 4R) amino acid **2b** and 3-pyridine carboxaldehyde (894 mg, 65% yield starting from **2b**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA, 365 K, δ) 8.64 (s, 1H), 8.59-8.58 (d, 1H, $J = 4.7$), 8.01-8.00 (d, 1H, $J = 7.8$),

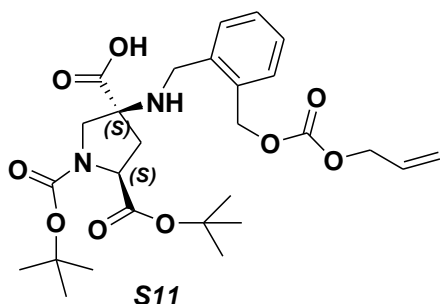
7.56-7.54 (dd, 1H, $J = 5.1, 7.7$), 7.37-7.30 (m, 5H), 5.08 (d, 2H, $J = 4.55$), 4.39-4.36 (t, 1H, $J = 7.8$), 3.98-3.95 (d, 1H, $J = 14.15$), 3.90-3.87 (d, 1H, $J = 14.15$), 3.82-3.79 (d, 1H, $J = 11.6$), 3.75-3.73 (d, 1H, $J = 11.65$), 2.58-2.55 (dd, 1H, $J = 5.05, 13.15$), 2.39-2.35 (dd, 1H, $J = 7.3, 14.05$), 1.38(s, 9H). ^{13}C NMR (125 MHz, DMSO- d_6 , 365K, δ) 173.66, 170.43, 153.59, 148.89, 147.55, 136.37, 135.52, 135.03, 127.86, 127.31, 126.91, 122.72, 80.38, 65.81, 58.91, 58.42, 53.98, 44.92, 37.31, 27.22. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R = 13.16$ min; HRMS-ESI: m/z calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_6$ ($\text{M}+\text{H}$) $^+$ 456.2129, found 456.2126.



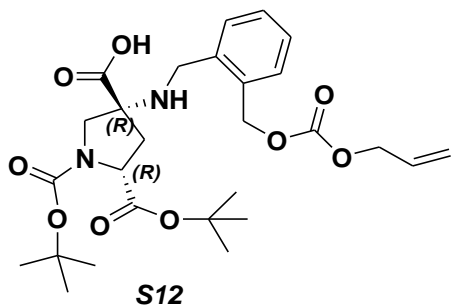
(3S,5S)-1-((benzyloxy)carbonyl)-5-(tert-butoxycarbonyl)-3-((pyridin-4-yl)methylamino)pyrrolidine-3-carboxylic acid S9: The reaction was carried out via the general procedure C of the reductive alkylation of bis-amino acids starting from the *N*-Cbz pro4(2S, 4S) amino acid **2a** and 4-pyridine carboxaldehyde (963.0 g, 70% yield from **2a**). ^1H NMR (500 MHz, DMSO- d_6 , 345K, δ) 8.46-8.45 (d, 2H, $J = 5.5$), 7.37-7.29 (m, 7H), 5.08 (s, 2H), 4.29-4.26 (dd, 1H, $J = 6, 8.5$), 3.98-3.96 (d, 1H, $J = 11$), 3.76-3.73 (d, 1H, $J = 14.5$), 3.69-3.66 (d, 1H, $J = 14.5$), 3.44-3.42 (d, 1H, $J = 11$), 2.74-2.69 (dd, 1H, $J = 9, 13$), 2.10-2.06 (dd, 1H, $J = 5.5, 13$), 1.39-1.36 (m, 9H). ^{13}C NMR (125 MHz, DMSO- d_6 , 365K, δ) 173.47, 169.79, 153.23, 148.74, 148.62, 136.27, 127.65, 127.08, 126.72, 122.27, 80.22, 66.54, 65.68, 58.35, 54.16, 46.83, 38.01, 27.20. HPLC analysis (C_{18} reverse phase, 30 min, 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid) $t_R = 13.025$ min; HRMS-ESI: m/z calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_6$ ($\text{M}+\text{H}$) $^+$ 456.2129, found 456.2129.



(3R,5S)-1-((benzyloxy)carbonyl)-5-(tert-butoxycarbonyl)-3-((pyridin-4-yl) methylamino) pyrrolidine-3-carboxylic acid S10: The reaction was carried out via the general procedure C of the reductive alkylation of bis-amino acids starting from the *N*-Cbz *pro4* (2S, 4R) amino acid **2b** and 4-pyridine carboxaldehyde (853.0 g, 62% yield from **2b**). ¹H NMR (500 MHz, DMSO-*d*₆, 345K, δ) 8.45-8.44 (d, 2H, *J* = 5), 7.32 (s, 4H), 7.30-7.29 (d, 3H, *J* = 5.5), 5.1-5.03 (m, 2H), 4.31 (s, 1H), 3.79-3.76 (d, 1H, *J* = 15 Hz), 3.69-3.67 (d, 3H, *J* = 8), 2.45-2.41 (t, 1H, *J* = 12.5), 2.24 (s, 1H), 1.36 (s, 9H). ¹³C NMR (125 MHz, DMSO-*d*₆, 345K, δ) rotamers observed. 172.82, 170.40, 153.56, 149.52, 148.86, 136.38, 127.83, 127.28, 126.90, 122.28, 80.36, 67.20, 66.48, 65.79, 58.55, 53.88, 46.30, 38.39, 27.26. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 12.94 min. HRMS-ESI: *m/z* calcd for C₂₄H₂₉N₃O₆ (M+H)⁺ 456.2129, found 456.2130.

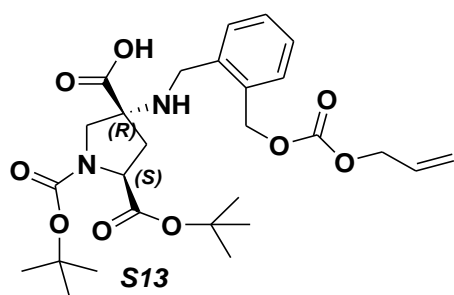


(3S,5S)-1,5-bis[(tert-butoxy)carbonyl]-3-([2-([[(prop-2-en-1-yloxy)carbonyl]oxy)methyl]phenyl] methyl)amino)pyrrolidine-3-carboxylic acid S11: The reaction was carried out via the general procedure C of the reductive alkylation of bis-amino acids with the *N*-Boc *pro4* (2S, 4S) amino acid **5a** and the aldehyde **6** (1.2g, 75% yield from **5a**). ¹H NMR (500 MHz, DMSO-*d*₆, 345K, δ) 7.40-7.39 (d, 1H, *J* = 7), 7.35-7.27 (m, 3H), 5.95-5.91 (m, 1H), 5.35-5.31 (dq, 1H, *J* = 1.5, 17.5), 5.28 (s, 2H), 5.26-5.23 (dd, 1H, *J* = 1, 9.5), 4.63-4.61 (dt, 2H, *J* = 1.5, 5.5), 4.19-4.11 (dd, 1H, *J* = 7, 8.5), 3.89-3.87 (d, 1H, *J* = 10.5), 3.74-3.71 (d, 1H, *J* = 12.5), 3.69-3.66 (d, 1H, *J* = 13), 3.31-3.29 (d, 1H, *J* = 10.5), 2.70 broad triplet (t, 1H), 2.00-1.96 (dd, 1H, *J* = 7, 13), 1.39 (s, 18 H). ¹³C NMR (125 MHz DMSO-*d*₆, 345K, δ) 174.09, 170.88, 154.15, 152.83, 137.93, 133.72, 132.13, 129.60, 129.08, 128.41, 127.27, 118.38, 80.49, 78.97, 66.89, 66.72, 66.42, 58.69, 54.10, 45.64, 38.35, 27.88, 27.56. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 19.03 min; HRMS-ESI: *m/z* calcd for C₂₇H₃₈N₂O₉ (M+H)⁺ 535.265, found 535.2649.

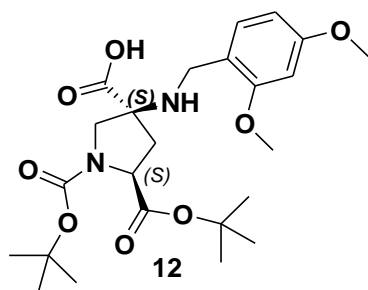


(3R,5R)-1,5-bis[(tert-butoxy)carbonyl]-3-([2-([[(prop-2-en-1-yloxy)carbonyl]oxy)methyl]phenyl] methyl)amino)pyrrolidine-3-carboxylic acid S12: The

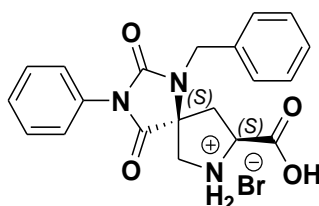
reaction was carried out via the general procedure **C** of the reductive alkylation of bis-amino acids with the *N*-Boc *pro4* (2*R*, 4*R*) amino acid **5b** and the aldehyde **6** (1.2g, 75% yield starting from **5b**). ¹H NMR (500 MHz, DMSO-*d*₆, 345 K, δ) 7.40-7.39 (d, 1H, *J* = 7), 7.35-7.27 (m, 3H), 5.97-5.91 (m, 1H), 5.35-5.34 (dq, 1H, *J* = 1.5, 17), 5.28 (s, 2H), 5.26-5.23 (dd, 1H, *J* = 1.5, 10.5), 4.63 (dt, 2H, *J* = 1.5, 5.5), 4.14-4.11 (dd, 1H, *J* = 7, 8.5), 3.89-3.87 (d, 1H, *J* = 11), 3.74-3.71 (d, 1H, *J* = 13), 3.69-3.66 (d, 1H, *J* = 13), 3.31-3.29 (d, 1H, *J* = 10.5), 2.70 (s, 1H), 2.00-1.96 (dd, 1H, *J* = 6.5, 13). 1.39 (s, 18 H). ¹³C NMR (125 MHz DMSO-*d*₆, 345K, δ) 173.73, 170.37, 152.66, 152.59, 137.82, 133.42, 131.79, 129.12, 128.60, 127.97, 126.79, 117.88, 80.12, 78.68, 67.52, 66.41, 61.54, 58.45, 53.89, 45.38, 38.22, 27.66, 27.29. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 19.29 min. HRMS-ESI: *m/z* calcd for C₂₇H₃₈N₂O₉ (M+H)⁺ 535.265, found 535.2648.



(3*R*,5*S*)-1,5-bis[(*tert*-butoxy)carbonyl]-3-([2-((prop-2-en-1-yloxy)carbonyl)oxy)methyl]phenyl)methylamino)pyrrolidine-3-carboxylic acid **S13**: The reaction was carried out via the general procedure **C** of the reductive alkylation of bis-amino acids with the *N*-Boc *pro4* (2*S*, 4*R*) amino acid **5c** and the aldehyde **6** (1.1g, 70% yield from **5c**). ¹H NMR (500 MHz, DMSO-*d*₆, 345K, δ) 7.38-7.27 (m, 4H), 5.97-5.92 (m, 1H), 5.35-5.30 (dq, 1H, *J* = 1.5, 17), 5.28 (s, 1H), 5.27 (s, 1H), 5.26-5.23 (dq, 1H, *J* = 1, 10.5), 4.63-4.62 (dt, 2 H, *J* = 1.5, 5.5), 3.78-3.76 (d, 1H, *J* = 13), 3.71-3.68 (d, 1H, *J* = 13.5), 3.64-3.62 (d, 1H, *J* = 11), 3.62-3.57 (m, 2H), 2.42-2.37 (dd, 1H, *J* = 8, 13), 2.24-2.20 (dd, 1H, *J* = 8, 13). 1.43-1.39 (m, 18H). ¹³C NMR (125 MHz DMSO-*d*₆, 345K, δ) 172.85, 170.77, 153.78 (2C, overlap), 138.49, 133.47, 131.78, 128.96, 127.92, 126.67, 126.22, 117.87, 80.19, 78.76, 67.51, 66.25, 61.50, 58.48, 52.96, 44.84, 36.84, 27.63, 27.30. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 19.41 min; HRMS-ESI: *m/z* calcd for C₂₇H₃₈N₂O₉ (M+H)⁺ 535.265, found: 535.2649.

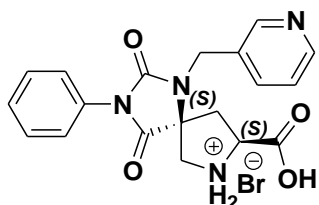


(3S,5S)-1,5-di(*tert*-butoxycarbonyl)-3-(2,4-dimethoxybenzylamino)pyrrolidine-3-carboxylic acid 12: The reaction was carried out via the general procedure **C** of the reductive alkylation of bis-amino acids starting from *N*-Boc *pro4* (2S, 4S) amino acid **5a** and 2,4-dimethoxybenzaldehyde (1.1g, 76% yield starting from **5a**). ¹H NMR (500 MHz, DMSO-*d*₆, 345 K, δ) 7.21-7.19 (d, 1H, *J* = 8), 6.53-6.52 (d, 1H, *J* = 2.5), 6.48-6.45 (dd, 1H, *J* = 2.5, 8.5), 4.15-4.12 (dd, 1H, *J* = 6, 8.5), 3.86-3.84 (d, 1H, *J* = 11), 3.78 (s, 3H), 3.76 (s, 3H), 3.64-3.61 (d, 1H, *J* = 13), 3.58-3.56 (d, 1H, *J* = 13), 3.34-3.32 (d, 1H, *J* = 10.5), 2.68 (broad triplet, 1H), 2.01-1.98 (dd, 1H, *J* = 6.5, 13), 1.40 (s, 18 H). ¹³C NMR (125 MHz DMSO-*d*₆, 345K, from HMBC, δ) 172.87, 170.52, 159.65, 158.62, 157.49, 129.35, 119.03, 103.96, 97.67, 80.04, 79.31, 78.51, 66.25, 58.37, 54.94, 53.56, 42.23, 37.85, 27.29 (2C). HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 17.65 min. HRMS-ESI: *m/z* calcd for C₂₄H₃₆N₂O₈ (M+H)⁺ 481.2544, found 481.2546.



4a

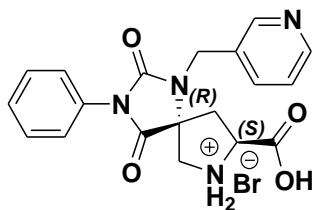
(5S,8S)-1-benzyl-2,4-dioxo-3-phenyl-1,3,7-triazaspiro[4.4]nonane-8-carboxylic acid 4a: The reaction was carried out via the general procedure **D** of hydantoin formation starting from **S6** and phenyl isocyanate; following by deprotection of Cbz, and *tert*-butyl protecting groups by 33% HBr/AcOH in DCM using the general procedure **E** (875 mg, 98% yield from **S6**). ¹H NMR (500 MHz, DMSO-*d*₆, 350 K, δ). 7.52-7.30 (m, 10 H), 4.72 (s, 2H), 4.58-4.54 (dd, 1H, *J* = 6.8, 12.3), 3.76-3.73 (d, 1H, *J* = 13.4), 3.60-3.57 (d, 1H, *J* = 13.4), 2.87-2.83 (dd, 1H, *J* = 6.8, 13.7), 2.52-2.45 (m, 1H). ¹³C NMR (125 MHz, DMSO-*d*₆, 350K, δ) 174.23, 169.64, 154.85, 138.03, 132.20, 129.13, 128.93, 128.56, 127.61, 127.28, 127.22, 68.37, 59.69, 49.01, 42.78, 35.30. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 26.3 min; HRMS-ESI: *m/z* calcd for C₂₀H₁₉N₃O₄ (M+H)⁺ 366.1448, found: 366.1450.



4b

(5S,8S)-2,4-dioxo-3-phenyl-1-(pyridin-3-ylmethyl)-1,3,7-triazaspiro[4.4]nonane-8-carboxylic acid 4b: The reaction was carried out via the general procedure **D** of hydantoin formation starting from **S7** and phenyl isocyanate; following by deprotection of Cbz, and *tert*-butyl protecting groups by 33% HBr/AcOH in DCM using the general procedure **E** (823 mg, 92% yield from **S7**). ¹H NMR (500 MHz, DMSO-*d*₆, 292.4 K, δ) 9.01 (s, 1H), 8.90-8.89 (d, 1H, *J* = 5.45), 8.62-8.60 (d, 1H, *J* = 8.2), 8.10-8.07 (dd, 1H, *J* = 5.65, 8.1), 7.54-7.49 (m, 4H), 7.45-7.41

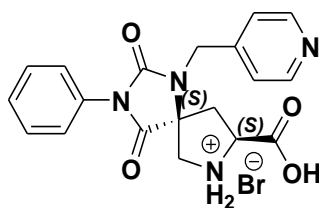
(m, 1H), 4.93 (s, 2H), 4.56-4.52 (dd, 1H, $J = 6.55, 12.55$), 3.72-3.69 (d, 1H, $J = 13.55$), 3.54-3.51 (d, 1H, $J = 13.6$), 2.97-2.93 (dd, 1H, $J = 6.65, 13.7$), 2.47-2.45 (d, 1H, $J = 13.25$). ^{13}C NMR (125 MHz, DMSO- d_6 , 292.4 K, from HMBC, δ) 173.09, 167.69, 154.39, 143.51, 142.38, 140.92, 140.52, 137.11, 131.2, 128.29, 127.56, 126.34, 66.91, 58.01, 47.72, 40.53, 33.73. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) $t_R = 5.69$ min; HRMS-ESI: m/z calcd for C₁₉H₁₈N₄O₄ (M+H)⁺ 367.1401, found 367.1402.



4c

(5R,8S)-2,4-dioxo-3-phenyl-1-(pyridin-3-ylmethyl)-1,3,7-triazaspiro[4.4]nonane-8-carboxylic acid 4c:

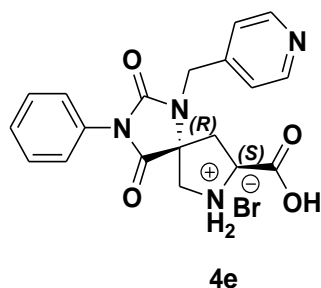
The reaction was carried out via the general procedure **D** of hydantoin formation starting from **S8** and phenyl isocyanate; following by deprotection of Cbz, and *tert*-butyl protecting groups by 33% HBr/AcOH in DCM using the general procedure **E** (760 mg, 85% yield from **S8**). ^1H NMR (500 MHz, DMSO- d_6 , 292.4 K, δ) 9.11 (s, 1H), 8.94-8.93 (d, 1H, $J = 5.55$), 8.73-8.72 (d, 1H, $J = 8.2$), 8.15-8.12 (dd, 1H, $J = 5.80, 8.1$), 7.52-7.48 (m, 4H), 7.42-7.41 (m, 1H), 5.03 (s, 2H), 4.77-4.74 (dd, 1H, $J = 4.8, 9.75$), 3.83-3.80 (d, 1H, $J = 13.25$), 3.64-3.61 (d, 1H, $J = 13.3$), 2.85-2.80 (dd, 1H, $J = 4.85, 14.65$), 2.72-2.67 (dd, 1H, $J = 9.95, 14.65$). ^{13}C NMR (125 MHz, DMSO- d_6 , 292.4 K, from HMBC, δ) 172.82, 168.81, 154.72, 144.68, 140.66, 140.07, 137.65, 131.45, 128.56, 128.33, 127.55, 126.40, 67.50, 58.24, 49.3, 40.41, 34.60. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) $t_R = 5.75$ min; HRMS-ESI: m/z calcd for C₁₉H₁₈N₄O₄ (M+H)⁺ 367.1401, found 367.1404.



4d

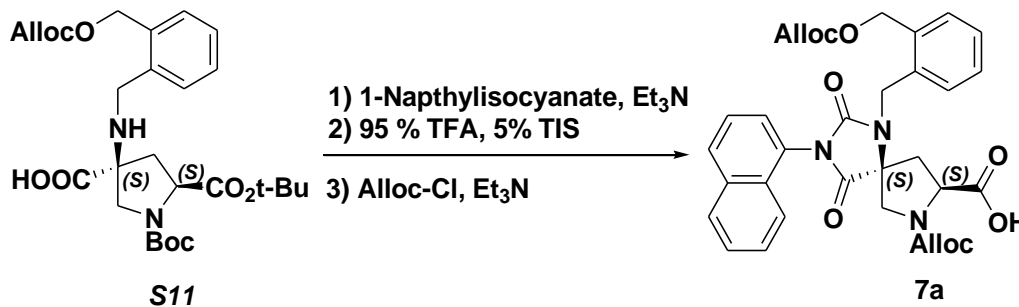
(5S,8S)-2,4-dioxo-3-phenyl-1-(pyridin-4-ylmethyl)-1,3,7-triazaspiro[4.4]nonane-8-

carboxylic acid 4d: The reaction was carried out via the general procedure **D** of hydantoin formation starting from **S9** and phenyl isocyanate; following by deprotection of Cbz, and *tert*-butyl protecting groups by 33% HBr/AcOH in DCM using the general procedure **E** (850 mg, 95% yield from **S9**). ^1H NMR (500 MHz, DMSO- d_6 , 292.4 K, δ) 8.96-8.94 (d, 2H, $J = 6$), 8.17 (s, 2H), 7.54-7.49 (m, 4H), 7.43-7.41 (m, 1H), 5.14 (s, 2H), 4.54-4.51 (dd, 1H, $J = 6, 12.5$), 3.79-3.76 (d, 1H, $J = 14$), 3.61-3.58 (d, 1H, $J = 13.5$), 3.04-3.00 (dd, 1H, $J = 6.5, 14$), 2.47-2.42 (t, 1H, $J = 13$). ^{13}C NMR (125 MHz, DMSO- d_6 , 292.4 K, δ) 173.40, 167.78, 157.92, 154.54, 141.93, 131.49, 128.66, 128.23, 126.75, 124.42, 66.98, 58.29, 48.04, 42.74, 33.90. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) $t_R = 5.12$ min; HRMS-ESI: m/z calcd for C₁₉H₁₈N₄O₄ (M+H)⁺ 367.1401, found 367.1402.



(5R,8S)-2,4-dioxo-3-phenyl-1-(pyridin-4-ylmethyl)-1,3,7-triazaspiro[4.4]nonane-8-

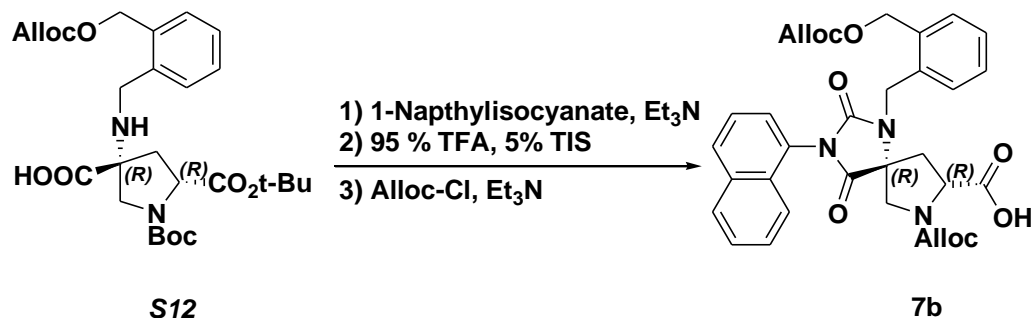
carboxylic acid 4e: The reaction was carried out via the general procedure **D** of hydantoin formation starting from **S10** and phenyl isocyanate; following by deprotection of Cbz, and *tert*-butyl protecting groups by 33% HBr/AcOH in DCM using the General procedure **E** (698 mg, 78% yield from **S10**). ¹H NMR (500 MHz, DMSO-*d*₆, 298K, δ) 8.95-8.94 (d, 2H, *J* = 6.5), 8.18-8.17 (d, 2H, *J* = 6.5), 7.53-7.47 (m, 4H), 7.44-7.41 (m, 1H), 5.09 (s, 2H), 4.72-4.69 (dd, 1H, *J* = 5, 10), 3.87-3.84 (d, 1H, *J* = 13.5), 3.61-3.59 (d, 1H, *J* = 13.5), 2.90-2.86 (dd, 1H, *J* = 5, 14.5), 2.66-2.62 (dd, 1H, *J* = 10, 15). ¹³C NMR (125 MHz, DMSO-*d*₆, 298 K, from HMBC, δ) 172.71, 168.80, 158.02, 154.42, 141.41, 131.20, 128.42, 127.72, 126.15, 124.10, 67.42, 58.01, 49.03, 42.61, 34.12. HPLC analysis (C₁₈ reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 5.27 min. HRMS-ESI: *m/z* calcd for C₁₉H₁₈N₄O₄ (M+H)⁺ 367.1401, found 367.1403.



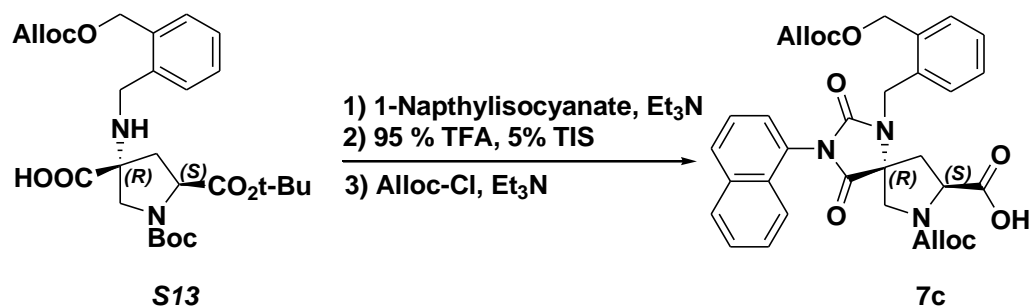
(5S,8S)-3-(naphthalen-1-yl)-2,4-dioxo-7-[(prop-2-en-1-yloxy)carbonyl]-1-[[2-((prop-2-en-1-yloxy)carbonyloxy)methyl]phenyl]methyl)-1,3,7-triazaspiro[4.4]nonane-8-carboxylic acid 7a:

The reaction was carried out via the general procedure **D** of hydantoin formation starting from **S11** and 1-Naphthyl isocyanate; following by deprotection of Boc and *tert*-butyl protecting groups using the general procedure **F**. The crude material was carried out to the next step, Alloc protection of secondary nitrogen, using standard procedure **G** (1.1g, 90% yield from **S11**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 365K, Atropisomers were observed in 50:50 population due to the high barrier of 1-Naphthyl rotation, δ) 8.12-8.03 (m, 2H), 7.82-7.78 (m, 1H), 7.65-7.60 (m, 4H), 7.48-7.41 (m, 3H), 7.38-7.35 (m, 1H), 5.97-5.82 (m, 2H), 5.35 (s, 2H), 5.31-5.22 (m, 3H), 5.16-5.13 (d, 1H, *J* = 10.55), 4.91-4.80 (m, 2H), 4.65-4.63 (dd, 2H, *J* = 1.1, 5.55), 4.52-4.51 (d, 2H, *J* = 4.05), 4.48-4.45 (dd, 1H, *J* = 8.45, 13.3), 4.11-4.08 (dd, 1H, *J* = 3.85, 11.65), 3.68-3.56 (2d, 1H, *J* = 11.8), 2.92-2.82 (m, 1H), 2.47-2.28 (m, 1H). ¹³C NMR (125 MHz, DMSO-*d*₆, 365 K, δ) 173.57, 171.82, 154.41, 153.77, 153.20, 135.32, 133.45, 132.78, 132.72, 131.72, 129.43, 129.19, 127.87, 127.72, 127.31, 127.28, 127.15, 127.04, 126.90, 126.75, 126.10, 124.97, 122.09, 117.97, 116.32, 67.66, 66.35, 64.93, 57.24, 49.03 (2C), 34.82 (2C).

HPLC analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) t_R = 22.11 min; HRMS-ESI: m/z calcd for C₃₃H₃₁N₃O₉ (M+H)⁺ 614.2133, found 614.2129.

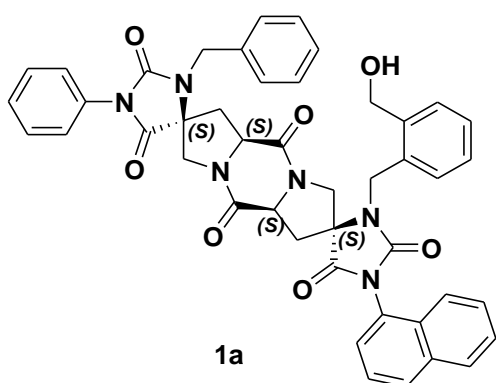


(5R,8R)-3-(naphthalen-1-yl)-2,4-dioxo-7-[(prop-2-en-1-yloxy)carbonyl]-1-[[2-([(prop-2-en-1-yloxy)carbonyl]oxy)methyl]phenyl)methyl]-1,3,7-triazaspiro[4.4]nonane-8-carboxylic acid 7b: The reaction was carried out via the general procedure **D** of hydantoin formation starting from **S12** and 1-Naphthyl isocyanate; following by deprotection of Boc and *tert*-butyl protecting group using general procedure **F**. The crude material was subjected to Alloc protection using standard procedure **G** (1.1g, 90% yield from **S12**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 365 K, Atropisomers were observed in 50:50 population due to the high barrier of 1-Naphthyl rotation, δ) 8.12-8.03 (m, 2H), 7.82-7.78 (m, 1H), 7.67-7.59 (m, 4H), 7.48-7.35 (m, 4H), 5.98-5.82 (m, 2H), 5.35 (s, 2H), 5.31-5.13 (m, 4H), 4.92-4.80 (m, 2H), 4.65-4.63 (dt, 2H, *J* = 1.35, 5.6), 4.52-4.51 (d, 2H, *J* = 5), 4.48-4.43 (m, 1H), 4.11-4.08 (dd, 1H, *J* = 4.38, 11.8), 3.68-3.56 (Two doublets, 1H, *J* = 11.85), 2.92-2.82 (m, 1H), 2.46-2.36 (m, 1H). ¹³C NMR (125 MHz DMSO-*d*₆, 365 K, δ) 173.58, 171.86, 154.44, 153.80, 153.23, 135.34, 133.48, 132.80, 132.56, 131.72, 129.53, 129.20, 128.61, 127.74, 127.32, 127.20, 127.09, 126.92, 126.84, 126.77, 126.12, 124.99, 122.11, 117.99, 116.36, 67.69, 66.37, 64.97, 57.24, 49.05 (2C), 34.77 (2C). HPLC Analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) t_R = 22.096 min; HRMS-ESI: m/z calcd for C₃₃H₃₁N₃O₉ (M+H)⁺ 614.2133, found 614.2128.

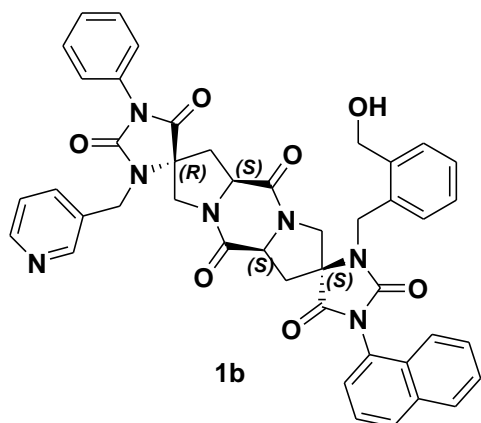


(5R,8S)-3-(naphthalen-1-yl)-2,4-dioxo-7-[(prop-2-en-1-yloxy)carbonyl]-1-[[2-([(prop-2-en-1-yloxy)carbonyl]oxy)methyl]phenyl)methyl]-1,3,7-triazaspiro[4.4]nonane-8-carboxylic acid 7c: The reaction was carried out via the general procedure **D** of hydantoin formation starting from **S13** and 1-Naphthyl isocyanate; following by deprotection of Boc and *tert*-butyl protecting group using general procedure **F**. The crude material was carried out to the next step using standard procedure **G** (1.05g, 86% yield from **S13**). ¹H NMR (500 MHz, DMSO-*d*₆, 1%

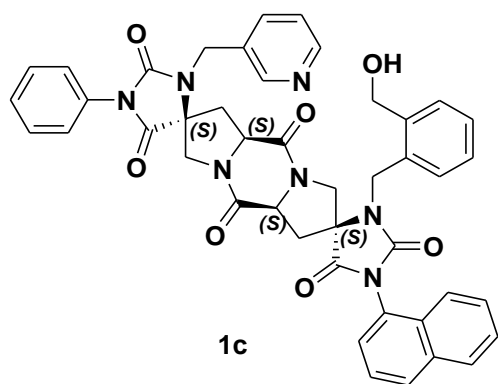
TFA added, 365 K, Atropisomers were observed in 50:50 population due to the high barrier of 1-Naphthyl rotation, δ 8.07-8.03 (m, 2H), 7.82-7.73 (m, 1H), 7.65-7.60 (m, 4H), 7.48-7.36 (m, 4H), 5.97-5.83 (m, 2H), 5.36-5.17 (m, 6H), 4.81 (s, 2H), 4.64-4.63 (d, 2H, $J = 5.5$), 4.46-4.32 (m, 3H), 4.18-4.00 (Two doublets, 1H, $J = 12$ Hz), 3.77-3.70 (m, 1H), 3.10-2.88 (m, 1H), 2.60-2.55 (m, 1H). ^{13}C NMR (125 MHz DMSO- d_6 , 365 K, δ) 171.73 (2C, overlapped), 154.53, 153.77, 152.56, 135.19, 133.49, 132.62, 132.52, 131.73, 129.53, 129.21, 128.50, 128.09, 127.84, 127.64, 127.44, 126.93, 126.76, 126.14, 125.04, 122.45, 122.09, 117.99, 116.66, 69.49, 67.70, 66.46, 65.02, 57.82 (2C, overlapped), 53.24, 41.15. HPLC analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) $t_R = 21.97$ min; HRMS-ESI: m/z calcd for C₃₃H₃₁N₃O₉ (M+H)⁺ 614.2133, found 614.2135.



(3'S,4S,9'S,11'S)-3-benzyl-3'-{[2-(hydroxymethyl)phenyl]methyl}-1''-(naphthalen-1-yl)-1-phenyldispiro[imidazolidine-4,5'-[1,7]diazatricyclo[7.3.0.0^{3,7}]dodecane-11',4''-imidazolidine]-2,2',2'',5,5'',8'-hexone 1a: Synthesis of bi-functional spiroligomer **1a** has been done using the general procedure **H** and **I** respectively starting from **7a** and **4a** (93 mg, 40% overall yield in two steps starting from **7a**). ^1H NMR (500 MHz, DMSO- d_6 , 1% TFA added, 360 K, δ) 8.07-8.06 (d, 1H, $J = 8$), 8.04-8.03 (d, 1H, $J = 7$), 7.84-7.83 (d, 1H, $J = 8.5$), 7.69-7.68 (d, 1H, $J = 7$), 7.65-7.59 (m, 3H), 7.52-7.47 (m, 4H), 7.42-7.24 (m, 10H), 4.81-4.73 (m, 4H), 4.69-4.66 (d, 1H, $J = 16.5$), 4.64 (s, 2H), 4.62-4.59 (d, 1H, $J = 16.5$), 3.95-3.70 (m, 4H), 2.79-2.74 (m, 1H), 2.67-2.53 (m, 2H), 2.49-2.46 (m, 1H). ^{13}C NMR (From HMBC, 125 MHz DMSO- d_6 , 1% TFA added, 360 K, δ) 173.80, 173.01, 164.50, 164.32, 154.41, 154.10, 138.63, 136.72, 134.30, 133.50, 129.82, 129.50, 129.3, 129.12, 129.0, 128.0, 127.92, 127.63, 127.0, 126.84, 126.62, 126.53, 126.40, 126.22, 125.94, 125.83, 125.60, 124.95, 122.01, 66.63, 66.11, 60.63, 57.82, 57.74, 48.32, 42.34, 42.25, 39.80, 33.41, 33.24. HPLC Analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) $t_R = 22.096$ min; HRMS-ESI: m/z calcd for C₄₅H₃₈N₆O₇ (M+H)⁺ 775.2875, found 775.2868.

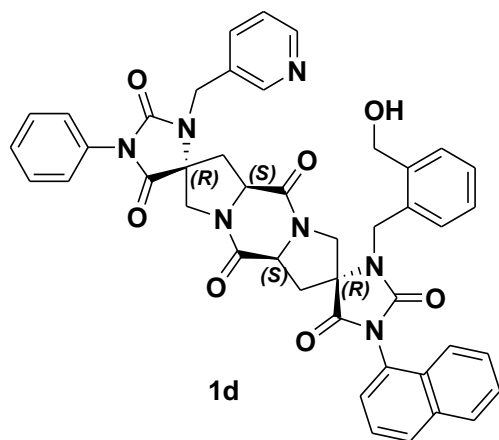


(3'S,4S,5'R,9'S)-3-[[2-(hydroxymethyl)phenyl]methyl]-1-(naphthalen-1-yl)-1''-phenyl-3''-(pyridin-3-ylmethyl)dispiro[imidazolidine-4,11'-[1,7]diazatricyclo[7.3.0.0^{3,7}]dodecane-5',4''-imidazolidine]-2,2',2'',5,5'',8'-hexone 1b: Synthesis of bi-functional spiroligomer **1b** has been done using general procedure **H** and **I** respectively starting from **7a** and **4c** (58mg, 25% overall yield in two steps starting from **7a**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 360 K, δ) 8.87 (s, 1H), 8.71-8.70 (d, 1H, *J* = 5.5), 8.38-8.34 (m, 1H), 8.08-8.03 (m, 2H), 7.84 -7.77 (m, 2H), 7.70-7.56 (m, 4H), 7.51-7.50 (m, 4H), 7.45-7.39 (m, 2H), 7.33-7.24 (m, 3H), 4.90-4.72 (m, 6H), 4.61 (s, 2H), 4.07-4.05 (d, 1H, *J* = 13), 3.92-3.76 (m, 2H), 3.62-3.60 (d, 1H, *J* = 13), 2.77-2.54 (m, 4H). ¹³C NMR (From HMBC, 125 MHz DMSO-*d*₆, 1% TFA added, 360 K, δ) 173.72, 171.80, 164.32, 164.25, 154.12 (2C), 143.50, 143.43, 140.23, 138.82, 135.43, 135.15, 133.92, 133.31, 131.32, 130.40, 129.44, 129.05, 128.02, 127.92, 127.74, 127.43, 126.72, 126.53, 126.44, 126.15, 125.92, 125.83, 125.50, 124.82, 124.66, 66.45, 66.29, 60.42, 58.11, 57.93, 50.84, 48.02, 40.55, 39.66, 35.04, 34.91. HPLC Analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 16.0 min; HRMS-ESI: *m/z* calcd for C₄₄H₃₇N₇O₇ (M+H)⁺ 776.2827, found 776.2821.

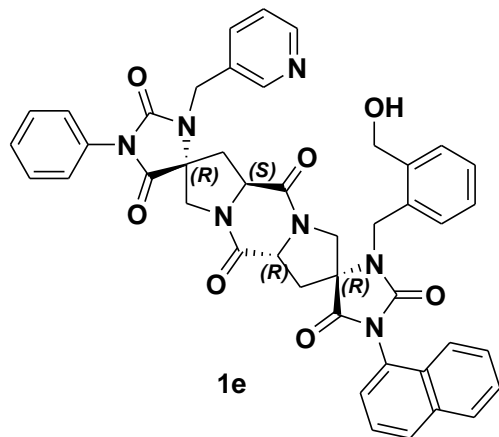


(3'S,4S,5'S,9'S)-3-[[2-(hydroxymethyl)phenyl]methyl]-1-(naphthalen-1-yl)-1''-phenyl-3''-(pyridin-3-ylmethyl)dispiro[imidazolidine-4,11'-[1,7]diazatricyclo[7.3.0.0^{3,7}]dodecane-5',4''-imidazolidine]-2,2',2'',5,5'',8'-hexone 1c: Synthesis of bi-functional spiroligomer **1c** has been done using general procedure **H** and **I** respectively starting from **7a** and **4b** (63 mg, 27% yield in two steps starting from **7a**). ¹H NMR (500 MHz, DMSO-*d*₆, 293K, δ) 8.50 (s, 1H), 8.49-8.48 (dd, 1H, *J* = 2.5, 3.5), 8.11-8.09 (d, 1H, *J* = 8.5), 8.07-8.05 (dt, 1H, *J* = 1.5, 10), 7.93-7.92 (m, 1H),

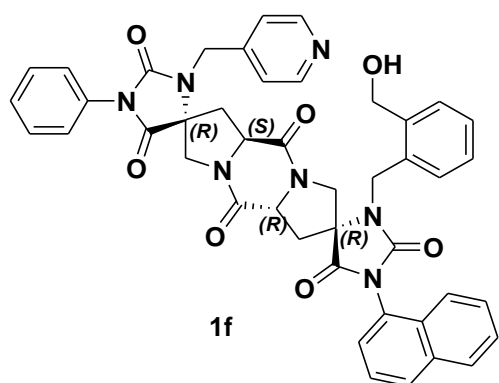
7.79-7.76 (m, 2H), 7.69-7.62 (m, 3H), 7.50-7.49 (m, 4H), 7.43-7.38 (m, 3H), 7.34-7.25 (m, 3H), 5.27-5.25 (t, 1H, $J = 5.5$), 4.87-4.53 (m, 8H), 4.06-4.03 (dd, 1H, $J = 5, 13$), 3.86-3.67 (m, 3H), 3.33 (H₂O), 2.85-2.36 (m, 4H). ¹³C NMR (From HMBC, 125 MHz, DMSO-*d*₆, 293K, δ) 174.0, 172.92, 164.80, 164.52, 154.73, 154.45, 148.20, 147.72, 138.66, 134.75, 134.35, 134.26, 134.05, 133.42, 133.35, 133.02, 131.74, 129.66, 128.53, 128.13, 128.04, 127.35, 127.24, 127.03, 126.84, 126.68, 126.4, 125.45, 124.83, 123.64, 123.35, 66.53, 66.24, 60.48, 58.12, 57.92, 49.14, 48.07, 40.11, 39.73, 33.26, 32.92. HPLC Analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) $t_R = 17.2$ min; HRMS-ESI: m/z calcd for C₄₄H₃₇N₇O₇ (M+H)⁺ 776.2827, found 776.2821.



(3'S,4R,5'R,9'S)-3-[[2-(hydroxymethyl)phenyl]methyl]-1-(naphthalen-1-yl)-1''-phenyl-3''-(pyridin-3-ylmethyl)dispiro[imidazolidine-4,11'-[1,7]diazatriacyclo[7.3.0.0^{3,7}]dodecane-5',4''-imidazolidine]-2,2',2'',5,5'',8'-hexone 1d: Synthesis of bi-functional spirologomer **1d** has been done using general procedure **H** and **I** respectively starting from **7c** and **4c** (58 mg, 25% yield in two steps starting from **7c**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 360 K, δ) 8.84 (s, 1H), 8.69 (s, 1H), 8.23-8.22 (d, 1H, $J = 8$), 8.12-8.03 (m, 2H), 7.78-7.59 (m, 6H), 7.50-7.43 (m, 6H), 7.40-7.30 (m, 3H), 4.95-4.78 (m, 4H), 4.71-4.64 (m, 2H), 4.59-4.56 (t, 1H, $J = 8$), 4.48-4.43 (dd, 1H, $J = 8.5, 18.5$), 4.096-4.070 (d, 1H, $J = 13$), 4.02-3.98 (dd, 1H, $J = 10, 11$), 3.88-3.71 (two doublets, 1H, $J = 13$), 3.59-3.56 (d, 1H, $J = 13$), 2.80-2.69 (m, 3H), 2.63-2.58 (dd, 1H, $J = 8.5, 14$). ¹³C NMR (From HMBC, 125 MHz, DMSO-*d*₆, 1% TFA added, 360 K, δ) 172.39, 171.62, 164.28, 164.15, 154.20, 153.85, 144.62, 144.40, 138.89, 138.62, 134.74, 134.35, 133.28, 131.50, 130.15, 129.32, 128.05, 127.56, 126.88, 126.74, 126.52, 126.28, 126.14, 125.73, 125.52, 124.85, 124.51, 124.12, 123.56, 123.02, 121.76, 66.87, 66.06, 60.63, 57.95, 57.75, 50.56, 49.84, 40.44, 40.26, 34.92, 34.34. HPLC Analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) $t_R = 16.25$ min; HRMS-ESI: m/z calcd for C₄₄H₃₇N₇O₇ (M+H)⁺ 776.2827, found 776.2822.

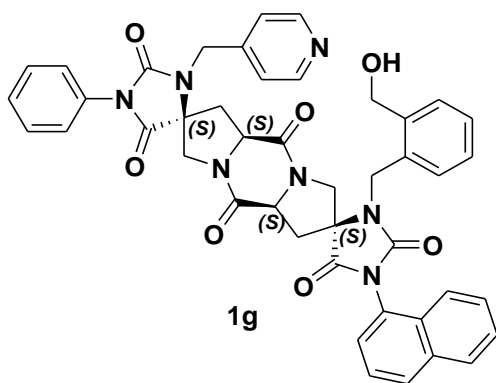


(3'S,4R,5'R,9'R)-3-[[2-(hydroxymethyl)phenyl]methyl]-1-(naphthalen-1-yl)-1''-phenyl-3''-(pyridin-3-ylmethyl)dispiro[imidazolidine-4,11'-[1,7]diazatricyclo[7.3.0.0^{3,7}]dodecane-5',4''-imidazolidine]-2,2',2'',5,5'',8'-hexone 1e: Synthesis of bi-functional spiroligomer **1e** has been done using general procedure **H** and **I** respectively starting from **7b** and **4c** (47mg, 20% yield in two steps starting from **7b**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 360 K, δ) 8.89 (s, 1H), 8.76-8.75 (d, 1H, *J* = 5.5), 8.38-8.37 (d, 1H, *J* = 7.5), 8.08-8.04 (m, 2H), 7.85-7.81 (m, 2H), 7.70-7.60 (m, 5H), 7.47-7.27 (m, 8H), 4.92 (s, 2H), 4.85-4.69 (m, 4H), 4.67-4.52 (m, 3H), 4.23-4.04 (Two doublets, 1H, *J* = 13.5), 3.80-3.71 (t, 1H, *J* = 14), 3.35-3.33 (d, 1H, *J* = 13), 2.78-2.51 (m, 3H), 2.48-2.36 (m, 1H). ¹³C NMR (From HMBC, 125 MHz DMSO-*d*₆, 1% TFA added, 360 K, δ) 174.23, 173.28, 162.21, 161.82, 154.15, 154.02, 143.45, 143.42, 140.40, 138.78, 135.45, 134.12, 133.37, 133.22, 131.28, 129.32, 129.02, 128.05, 127.72, 127.51, 127.28, 126.98, 126.72, 126.60, 126.25, 126.03, 125.92, 125.62, 125.01, 124.89, 121.78, 66.48, 65.67, 60.42, 58.57, 58.41, 49.78, 49.45, 40.50, 39.71, 36.63, 36.32. HPLC Analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 16.30 min; HRMS-ESI: *m/z* calcd for C₄₄H₃₇N₇O₇ (M+H)⁺ 776.2827, found 776.2821.

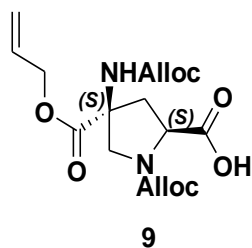


(3'S,4R,5'R,9'R)-3-[[2-(hydroxymethyl)phenyl]methyl]-1-(naphthalen-1-yl)-1''-phenyl-3''-(pyridin-4-ylmethyl)dispiro[imidazolidine-4,11'-[1,7]diazatricyclo[7.3.0.0^{3,7}]dodecane-5',4''-imidazolidine]-2,2',2'',5,5'',8'-hexone 1f: Synthesis of bi-functional spiroligomer **1f** has been done using general procedure **H** and **I** respectively starting from **7b** and **4e** (42mg, 18% yield in two steps starting from **7b**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 360 K, δ) 8.88 (s,

2H), 8.11-8.03 (m, 4H), 7.83-7.82 (d, 1H, $J = 8.5$), 7.72-7.60 (m, 4H), 7.49-7.45 (m, 4H), 7.44-7.35 (m, 3H), 7.31-7.26 (m, 2H), 5.06 (s, 2H), 4.85-4.82 (d, 1H, $J = 16.5$), 4.72-4.68 (d, 1H, $J = 16.5$), 4.65-4.54 (m, 5H), 4.22-4.10 (Two doublets, 1H, $J = 13.5$), 3.77-3.71 (t, 1H, $J = 13.5$), 3.45-3.32 (d, 1H, $J = 13$), 2.79-2.73 (m, 1H), 2.66-2.58 (m, 2H), 2.58-2.39 (m, 1H). ^{13}C NMR (From HMBC, 125 MHz DMSO- d_6 , 1% TFA added, 360 K, δ) 174.45, 173.78, 162.66, 162.21, 157.18, 154.42, 142.28, 139.30, 134.43, 133.65, 131.40, 130.56, 129.58, 129.41, 129.02, 128.27, 128.22, 127.78, 127.13, 127.0, 126.56, 126.45, 126.23, 125.88, 125.42, 125.20, 124.76, 122.28, 66.78, 65.86, 60.72, 58.56, 58.43, 50.07, 49.58, 43.02, 40.12, 36.67, 36.58. HPLC Analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) $t_R = 15.96$ min; HRMS-ESI: m/z calcd for C₄₄H₃₇N₇O₇ (M+H)⁺ 776.2827, found 776.2822.

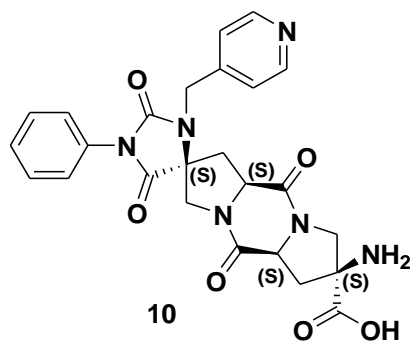


(3'S,4S,5'S,9'S)-3-{[2-(hydroxymethyl)phenyl]methyl}-1-(naphthalen-1-yl)-1''-phenyl-3'''-(pyridin-4-ylmethyl)dispiro[imidazolidine-4,11'-[1,7]diazatricyclo[7.3.0.0^{3,7}]dodecane-5',4''-imidazolidine]-2,2',2'',5,5'',8'-hexone 1g: Synthesis of bi-functional spirologomer **1g** has been done using general procedure **H** and **I** respectively starting from **7a** and **4d** (65mg, 28% yield in two steps starting from **7a**). ^1H NMR (500 MHz, DMSO- d_6 , 1% TFA added, 360 K, δ) 8.77-8.76 (d, 2H, $J = 3.5$), 8.08-8.06 (d, 1H, $J = 8$), 8.05-8.03 (d, 1H, $J = 7$), 7.95 (s, 2H), 7.85-7.83 (d, 1H, $J = 7.5$), 7.70-7.69 (d, 1H, $J = 7$), 7.66-7.61 (m, 3H), 7.54-7.48 (m, 4H), 7.42-7.38 (m, 3H), 7.33-7.25 (m, 2H), 4.88 (s, 2H), 4.84-4.74 (m, 4H), 4.63 (s, 2H), 3.96-3.86 (m, 2H), 3.79-3.73 (m, 2H), 2.83-2.54 (m, 3H), 2.48-2.44 (m, 1H). ^{13}C NMR (From HMBC, 125 MHz, DMSO- d_6 , 1% TFA added, 360 K, δ) 173.56, 172.67, 164.42, 164.21, 155.72, 154.29, 154.22, 142.58, 138.45, 134.42, 134.20, 133.55, 131.11, 129.58, 129.31, 128.10, 127.62, 127.12, 126.89, 126.67, 126.58, 126.32, 126.01, 125.92, 125.25, 124.88, 124.76, 123.81, 122.13, 66.62, 66.05, 60.62, 57.88, 57.59, 48.68, 48.13, 42.05, 39.53, 33.42, 33.23. HPLC analysis (5-95% H₂O/ACN with 0.1% formic acid) $t_R = 15.72$ min; HRMS-ESI: m/z calcd for C₄₄H₃₇N₇O₇ (M+H)⁺ 776.2827, found 776.2825.



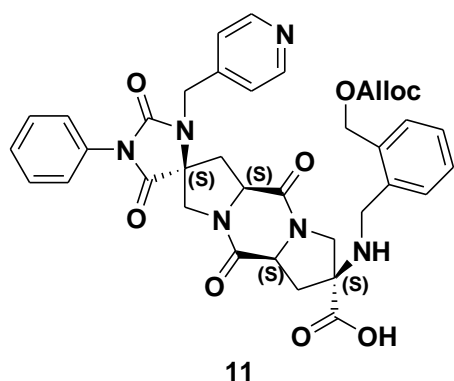
(2S,4S)-1,4-bis[(prop-2-en-1-yloxy)carbonyl]-4-[[prop-2-en-1-yloxy]carbonyl]amino} pyrrolidine-2-carboxylic acid **9:**

To a solution of *N*-Boc *Pro4* (2S,4S) amino acid **5a** (2g, 6 mmol) in 50 ml dry THF was added DIPEA (3.2ml, 18 mmol) and DMAP (367 mg, 3 mmol), following by drop-wise addition of Alloc-Cl (1.9 ml, 18 mmol). The reaction mixture was allowed to stir for 24 hours at room temperature. At this point, 10 ml saturated ammonium chloride was added to the reaction mixture and product extracted to the organic layer with 200 ml ethyl acetate. The organic layer was washed with saturated sodium bicarbonate (3 × 30 ml) and then brine (30 ml). Combined organic layer was dried over sodium sulfate and solvent was removed using vacuum. Boc and *tert*-butyl protecting groups were removed according to the general procedure **F**. The crude material was subjected to Alloc protection using general procedure **G**. The product was then purified using silica-gel flash chromatography with a gradient of 0% MeOH in DCM to 5% MeOH in DCM. The product can be stained on TLC plate using iodine-silica stain powder (2.1g, 95% yield from **5a**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 345 K, δ) 7.93 (s, 1H), 5.92-5.83 (m, 3H), 5.32-5.17 (m, 6H), 4.60-4.59 (dt, 2H, *J* = 1.5, 5.5), 4.54-4.51 (t, 2H, *J* = 6), 4.49-4.47 (dt, 2H, *J* = 1.5, 5), 4.31 (broad triplet, 1H), 4.20-4.00 (d, 1H, *J* = 11.5), 3.55-3.53 (d, 1H, *J* = 11.5), 2.89 (broad singlet, 1H), 2.31-2.27 (dd, 1H, *J* = 6.5, 13.5). ¹³C NMR (From HMBC, 125 MHz, DMSO-*d*₆, 1% TFA added, 360 K, δ) 170.96, 170.34, 154.56, 154.33, 132.38, 132.14, 131.33, 116.93, 116.57, 116.17, 64.67, 64.49, 63.87, 61.35, 57.27, 54.27, 51.13, 38.42. HPLC analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 15.96 min; HRMS-ESI: *m/z* calcd for C₁₇H₂₂N₂O₈ (M+H)⁺ 383.1449, found 383.1452.

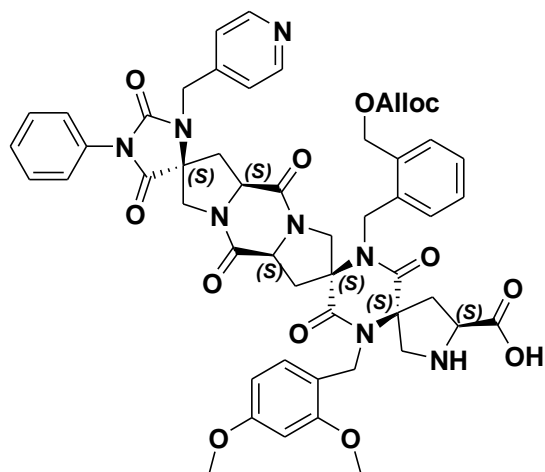


(3'S,4S,9'S,11'S)-11'-amino-2,2',5,8'-tetraoxo-1-phenyl-3-(pyridin-4-ylmethyl)-1',7'-diazaspiro[imidazolidine-4,5'-tricyclo[7.3.0.0^{3,7}]dodecane]-11'-carboxylic acid **10:** The functionalized spirolygomer **10** has been synthesized using standard procedure **H** for coupling of amino acids starting from amino acid **9** and compound **4d**. In a flame dried vial, the *N*-Alloc protected amino amino acid **9** (2g, 5.2 mmol) and HATU (1.8g, 4.94 mmol) were dissolved in 20 ml dry DMF under argon. DIPEA (1.8 ml, 10.4 mmol) was then added and reaction mixture was stirred for 3 hours at room temperature. Then a solution of amino acid **4d** (2.3g, 5.2 mmol) and DIPEA (1.8 ml, 10.4 mmol) in 10 ml dry DMF was added drop-wise to the reaction mixture. Quantitative coupling was observed within 24 hours stirring at room temperature; monitored by HPLC-MS. At this point, a solution of tetrakis(triphenylphosphine)-palladium (0) (601 mg, 0.52

mmol) in 5 ml dry DCM and a solution of Phenylsilane (1.3 ml, 10.4 mmol) in 5 ml DCM was added sequentially to the reaction mixture. Simultaneous deprotection of alloc group and DKP closure were observed by HPLC-MS after stirring for 24 hours at room temperature. After which, the reaction mixture was diluted up with EtOAc (400 ml). Product extracted into the aqueous layer by 2M HCl (3 × 50 ml). Combined aqueous layer was rotavaped off at 60⁰C up to about 5 ml. The resulting solution was reverse phase purified using C₁₈ column with a gradient of 0-100% H₂O/ACN with 0.1% formic acid. ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 345 K, δ) 8.80 (s, 2H), 7.88 (d, 2H, *J* = 5.5), 7.54-7.49 (m, 4H), 7.44-7.40 (m, 1H), 4.88-4.87 (d, 2H, *J* = 2.5), 4.83-4.79 (t, 1H, *J* = 8.5), 4.71-4.68 (t, 1H, *J* = 8.5), 3.92-3.89 (d, 1H, *J* = 12.5), 3.87-3.84 (d, 1H, *J* = 12.5), 3.81-3.79 (d, 1H, *J* = 12.5), 3.71-3.69 (d, 1H, *J* = 12.5), 2.77-2.74 (dd, 2H, *J* = 8, 13.5), 2.73-2.55 (m, 2H). ¹³C NMR (From HMBC, 125 MHz, DMSO-*d*₆, 1% TFA added, 360 K, δ) 172.56, 172.43, 169.98, 169.67, 163.95, 153.95, 143.52, 131.04, 127.94, 127.07, 126.02, 123.15, 65.89, 65.80, 59.63, 57.78, 51.18, 48.18, 41.58, 35.42, 32.89. HPLC analysis (5 reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 6.60 min; HRMS-ESI: *m/z* calcd for C₂₅H₂₄N₆O₆ (M+H)⁺ 505.183, found 505.1829.



(3'S,4S,9'S,11'S)-2,2',5,8'-tetraoxo-1-phenyl-11'-([2-((prop-2-en-1-yloxy) carbonyl)oxy]methyl)phenyl]methyl}amino)-3-(pyridin-4-ylmethyl)-1',7'-diazaspiro[imidazolidine-4,5'-tricyclo[7.3.0.0^{3,7}]dodecane]-11'-carboxylic acid 11: Starting from dimer **10**, reductive alkylation has been done as procedure **C** using aldehyde **6** (1.9g, 52% yield from **9**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 345 K, δ) 8.52 (s, 2H), 7.54-7.49 (m, 5H), 7.43-7.40 (m, 2H), 7.36-7.32 (m, 2H), 7.30-7.29 (d, 2H, *J* = 5), 7.26-7.20 (m, 2H), 5.35-5.23 (m, 4H), 4.74-4.71 (t, 1H, *J* = 8.5), 4.66-4.54 (m, 4H), 4.52-4.49 (t, 1H, *J* = 7), 3.85-3.83 (d, 1H, *J* = 13), 3.77-3.75 (d, 1H, *J* = 12), 3.68-3.67 (m, 3H), 3.62-3.59 (d, 1H, *J* = 11), 2.70-2.66 (dd, 1H, *J* = 7.5, 13.5), 2.59-2.54 (m, 2H), 2.35-2.33 (m, 1H). ¹³C NMR (From HMBC, 125 MHz DMSO-*d*₆, 1% TFA added, 360 K, δ) 172.52, 172.34, 164.58, 164.38, 153.83, 153.74, 148.85, 145.48, 145.39, 138.34, 132.15, 131.23, 127.93, 127.27, 127.07, 126.33, 126.05, 121.33, 121.09, 117.61, 112.66, 66.39, 66.19, 66.07, 61.28, 57.38, 57.24, 48.78, 48.67, 41.33, 41.25, 35.16, 33.21. HPLC analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) *t*_R = 11.16 min; HRMS-ESI: *m/z* calcd for C₃₇H₃₆N₆O₉ (M+H)⁺ 709.2617, found 709.2608.

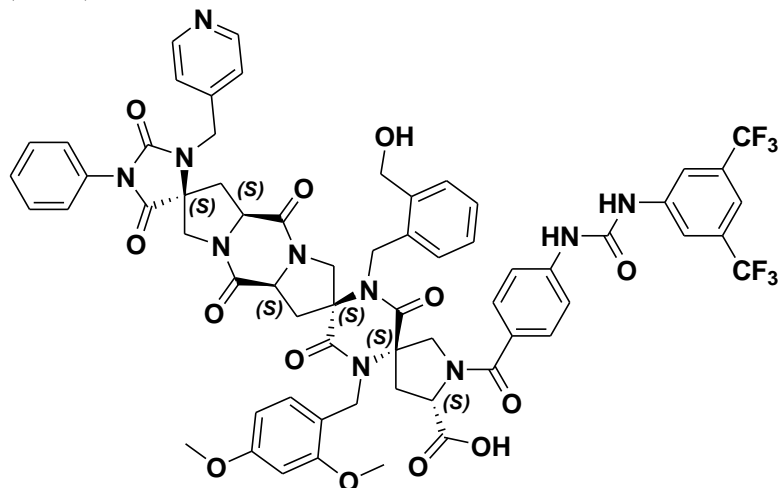


13

(3'S,4S,5''S,5'''S,9'S,11'S)-4''-[(2,4-dimethoxyphenyl)methyl]-2,2',3'',5,6'',8'-hexaexo-1-phenyl-1''-{[2-({[(prop-2-en-1-yloxy)carbonyloxy]methyl)phenyl]methyl}-3-(pyridin-4-ylmethyl)trisp[ro[imidazolidine-4,5'-[1,7]diazatriacyclo[7.3.0.0^{3,7}]dodecane-11',2''-piperazine-5'',3'''-pyrrolidine]-5'''-carboxylic acid 13:

Dimer **11** was activated using the following procedure: In a 100 ml flame dried round bottom flask equipped with argon, dimer **11** (709 mg, 1 mmol) and HOAt (817 mg, 6 mmol) were dissolved in 12 ml (2:1 dry DCM/DMF), Then DIC (155 μ l, 1 mmol) was added. The reaction mixture was allowed to stir for 1 hour. After which another equivalent of DIC was added and solution was stirred for another 1 hour to complete activation of dimer amino acid. Then a solution of amino acid **12** (481 mg, 1 mmol) and DIPEA (349 μ l, 2 mmol) in 2 ml dry DMF was added to the reaction mixture drop-wise while stirring at room temperature. After 12 hours, 10 μ l of the solution was taken and diluted up with 500 μ l acetonitrile and injected to HPLC-MS. Two major peaks were observed which were attributed to the product **13** and the open diketopiperazine product. To close DKP, additional HOAt (272 mg, 2 mmol) and DIC (310 μ L, 2 mmol) were added to the reaction mixture and solution was allowed to stir for 4 hour at room temperature. Workup has been done using the following procedure: The solution was transferred to a separatory funnel and diluted with ethyl acetate (100 ml). The organic layer was washed sequentially with saturated NH_4Cl , (3 \times 10 ml), Brine (3 \times 10 ml), saturated sodium bicarbonate (3 \times 10 ml) then brine only. The combined organic layer was dried over sodium sulfate and solvent was removed under high vacuum. To the crude product was added 50 ml solution of 95% TFA, 5 % TIS. After 1.5 hours, Solvent was removed and again the crude product was subjected to the acidic solution for another 1.5 hours. At this point solvent was removed and the crude product was dissolved in minimum amount of acetonitrile and purified with reverse phase C_{18} column with a gradient of 5-95% $\text{H}_2\text{O}/\text{ACN}$ with 0.1% formic acid (290 mg, 29% overall yield from **11**). ^1H NMR (500 MHz, $\text{DMSO}-d_6$, 1% TFA added, 345 K, δ) 8.75 (s, 2H), 7.91-7.90 (d, 2H, $J = 8$), 7.52-7.48 (m, 4H), 7.43-7.41 (m, 3H), 7.34-7.31 (t, 1H, $J = 7.5$), 7.21-7.20 (d, 1H, $J = 7.5$), 7.02-7.00 (d, 1H, $J = 8.5$), 6.61 (s, 1H), 6.54-6.52 (m, 1H), 5.96-5.88 (m, 1H), 5.34-5.23 (m, 4H), 4.86-4.84 (d, 2H, $J = 11$), 4.80-4.71 (m, 3H), 4.62-4.61 (m, 5H), 4.47-4.43 (m, 1H), 3.90-3.88 (d, 2H, $J = 13$), 3.85 (s, 3H), 3.78 (s, 3H), 3.74-3.58 (4H), 2.89-2.85 (dd, 1H, $J = 7.5, 14$), 2.76-2.71 (m, 2H), 2.64-53 (m, 3H). ^{13}C NMR (From HMBC, 125 MHz $\text{DMSO}-d_6$, 1% TFA added, 345 K, δ) 172.32, 172.25, 167.49, 167.25, 159.23, 156.43, 155.93, 154.12, 142.05, 135.21, 135.07, 131.22, 131.02, 130.98, 128.56, 127.94,

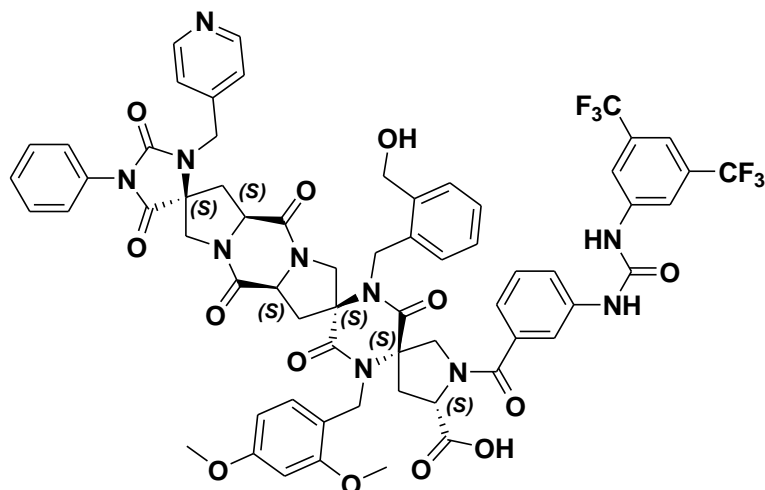
127.61, 126.28, 126.05, 125.94, 124.12, 124.04, 123.63, 123.51, 117.75, 116.28, 104.46, 98.12, 84.94, 67.58, 66.25, 65.86, 58.29, 57.53, 57.14, 54.83, 53.82, 51.76, 51.45, 50.56, 50.36, 48.38, 48.12, 43.16, 41.78, 37.21, 37.08, 33.17. HPLC analysis (5 reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) t_R = 14.34 min; HRMS-ESI: m/z calcd for C₅₂H₅₂N₈O₁₃ (M+H)⁺ 997.3727, found 997.3721.



15a

(3'S,4S,5''S,9'S,11'S)-1'''-[4-({[3,5-bis(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]carbonyl]-4''-[(2,4-dimethoxyphenyl)methyl]-1''-[2-(hydroxymethyl)phenyl]methyl]-2,2',3'',5,6'',8'-hexaexo-1-phenyl-3-(pyridin-4-ylmethyl)trisp[ir]o[imidazolidine-4,5'-[1,7]diazatricyclo[7.3.0.0]^{3,7}]dodecane-11',2''-piperazine-5'',3'''-pyrrolidine]-5'''-carboxylic acid 15a: Activation of carboxylic acid **14a** has been done using the following procedure: In a flame dried vial, 4-urea benzoic acid **14a** (98 mg, 250 μ mol) and HATU (90 mg, 237 μ mol) were dissolved in 4 ml dry DMF under argon, then DIPEA (87 μ l, 500 μ mol) was added. The reaction mixture was allowed to stir for 5 min at room temperature. The resulting solution was combined with the solution of trimer **13** (249 mg, 250 μ mol) in 1 ml dry DMF. The reaction mixture was allowed to stir for 8 hours at room temperature. At this point to remove Alloc protecting group, a solution of Pd(PPh₃)₄ (29 mg, 25 μ mmol) and BH₃.NMe₂ (35 mg, 1.5 mmmol) in 1 ml dry DCM was added and The deprotection was allowed to continue for 8 hours at room temperature. To quench the reaction and get free hydroxyl, 4mL 1M HCl was added and the solution was stirred for two hours. After which the product was reverse phase purified using C₁₈ column with a gradient of 5-95% H₂O/ACN with 0.1% formic acid (80 mg, 25% yield from **13**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 345 K, δ) 9.57 (s, 1H), 9.23 (s, 1H), 8.79-8.78 (d, 2H, J = 5), 8.14 (s, 2H), 8.01-8.00 (d, 2H, J = 5.5), 7.57 (s, 1H), 7.52-7.48 (m, 6H), 7.42-7.39 (t, 1H, J = 7), 7.36-7.35 (d, 1H, J = 7.5), 7.32-7.31 (d, 2H, J = 8.5), 7.23-7.18 (m, 2H), 7.04-7.03 (d, 1H, J = 8.5), 6.95-6.94 (d, 1H, J = 7), 6.62 (s, 1H), 6.55-6.53 (dd, 1H, J = 2, 8.5), 4.89 (s, 2H), 4.73-4.56 (m, 7H), 4.53 (s, 2H), 3.99-3.92 (m, 2H), 3.88-3.84 (m, 5H), 3.79 (s, 3H), 3.73-3.70 (d, 1H, J = 13), 3.68-3.65 (d, 1H, J = 13.5), 2.84 (dd, 1H, J = 9, 13.5), 2.72-2.70 (dd, 1H, J = 6, 13), 2.68-2.63 (dd, 1H, J = 7.5, 14), 2.55-2.53 (d, 1H, J = 12.5), 2.46-2.44 (m, 2H). ¹³C NMR (From HMBC,125 MHz, DMSO-*d*₆, 1% TFA added, 345 K, δ) 172.38, 171.71, 168.0, 167.67, 167.42, 159.2, 157.78, 156.82, 156.45, 155.52, 154.21, 141.79, 141.29, 140.58, 137.90, 134.31, 131.19, 128.79, 128.11, 128.0, 127.67, 127.56, 126.28, 125.78, 123.80, 123.29, 122.70,

121.78, 121.57, 117.60, 117.38, 116.89, 113.90, 113.59, 104.82, 98.15, 66.22, 65.78, 60.73, 58.67, 58.37, 57.81, 55.15, 52.18, 48.37, 48.20, 43.0, 41.92, 40.63, 37.35, 33.41, 33.20. HPLC analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) t_R = 20.05 min; HRMS-ESI: m/z calcd for C₆₄H₅₆F₆N₁₀O₁₃ (M+H)⁺ 1287.4005, found 1287.3996.



15b

(3'S,4S,5''S,9'S,11'S)-1'''-[3-([3,5-bis(trifluoromethyl)phenyl]carbamoyl)amino)phenyl]carbonyl]-4''-(2,4-dimethoxyphenyl)methyl]-1''-[2-(hydroxymethyl)phenyl]methyl]-2,2',3'',5,6'',8'-hexaoxo-1-phenyl-3-(pyridin-4-ylmethyl)trisp[irrolidone-4,5'-[1,7]diazatricyclo[7.3.0.0^{3,7}]dodecane-11',2''-piperazine-5'',3'''-pyrrolidine]-5'''-carboxylic acid 15b:

The same procedure has been used for spirogozyme **15a** using 3-urea benzoic acid (74mg, 23% yield from **13**). ¹H NMR (500 MHz, DMSO-*d*₆, 1% TFA added, 345 K, δ) 9.48 (s, 1H), 9.09 (s, 1H), 8.77 (s, 2H), 8.13 (s, 2H), 7.97-7.96 (d, 2H, $J = 5.5$), 7.56-7.48 (m, 7H), 7.42-7.79 (m, 1H), 7.35-7.33 (d, 1H, $J = 7.5$), 7.32-7.29 (t, 1H, $J = 8$), 7.22-7.19 (m, 2H), 7.04-7.02 (d, 1H, $J = 8.5$), 6.97-6.95 (t, 2H, $J = 7.5$), 6.59 (d, 1H, $J = 2.5$), 6.53-6.51 (dd, 1H, $J = 1.5, 8.5$), 4.87 (s, 2H), 4.73-4.57 (m, 7H), 4.53 (s, 2H), 4.00-3.65 (m, 12H), 2.86-2.82 (dd, 1H, $J = 9.5, 14$), 2.73-2.69 (dd, 1H, $J = 7.5, 13.5$), 2.67-2.62 (dd, 1H, $J = 7.5, 13.5$), 2.56-2.54 (m, 1H), 2.46-2.42 (dd, 2H, $J = 8.5, 13.5$). ¹³C NMR (From HMBC, 125 MHz, DMSO-*d*₆, 1% TFA added, 345 K, δ) 172.56, 171.72, 168.11, 167.89, 167.45, 164.78, 164.12, 159.30, 156.62, 156.18, 155.11, 154.28, 142.21, 141.39, 138.67, 137.89, 137.56, 136.0, 134.32, 131.23, 127.89, 127.51, 126.78, 126.43, 126.05, 123.81, 121.79, 120.82, 120.32, 120.01, 119.05, 117.56, 117.18, 117.0, 116.68, 116.41, 113.82, 104.88, 98.22, 66.18, 65.89 (2C), 60.72, 58.78, 57.67, 55.1 (2CH₃), 52.16, 48.57, 48.38, 48.31, 43.12, 41.87, 40.05, 37.88, 37.67, 33.42. HPLC analysis (reverse phase, 30 min, 5-95% H₂O/ACN with 0.1% formic acid) t_R = 20.05 min; HRMS-ESI: m/z calcd for C₆₄H₅₆F₆N₁₀O₁₃ (M+H)⁺ 1287.3919, found 1287.3914.

References:

- 1.) Schafmeister, C.E.; Brown, Z.Z.; Gupta, S. Shape-Programmable Macromolecules. *Acc. Chem. Res.* **2008**, 41, 1387-1398.

Kinetics supporting info: Kinetic experiments were carried out by combining the spiroligomers **1a-g** with an excess of vinyl trifluoroacetate in CDCl_3 at 22°C . The progress of the reaction was monitored by ^{19}F -NMR.

Sample preparation

CDCl_3 was passed through a short column of basic alumina just before each kinetic experiment. The following stock solutions of vinyl trifluoroacetate in CDCl_3 , trifluorotoluene in CDCl_3 as internal standard, and spiroligomer in CDCl_3 were prepared. To a dried NMR tube was added sequentially spiroligomer solution, CDCl_3 , trifluorotoluene solution, and finally vinyl trifluoroacetate solution. The progress of reaction was monitored by ^{19}F -NMR at 22°C . Initial concentrations were obtained by recording the weight of NMR Tube before and after each addition. The product concentration was obtained by the ratio of integration of the internal standard and the product peak. Due to slow reaction of spiroligomer **1a**, J. Young NMR tube was used to avoid evaporization of the solvent over the course of reaction.

Determination of the kinetic order of spiroligomer in acylation:

In order to determine the order of reaction with respect to concentration of spiroligomer, three experiments were set under pseudo first order condition with three different concentration of each spiroligomer and excess of vinyl trifluoroacetate. The following are the time dependent acylation of spiroligomers **1a-g**. The data fitted to the first order rate equation.

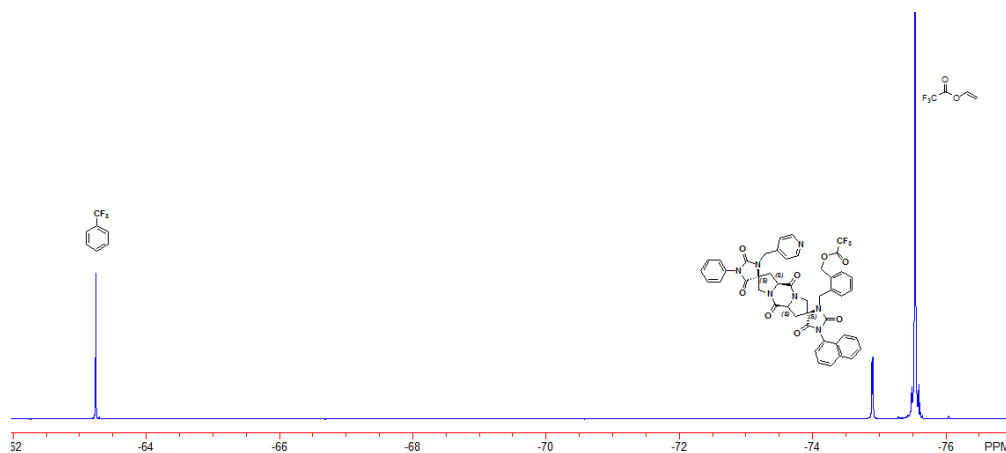
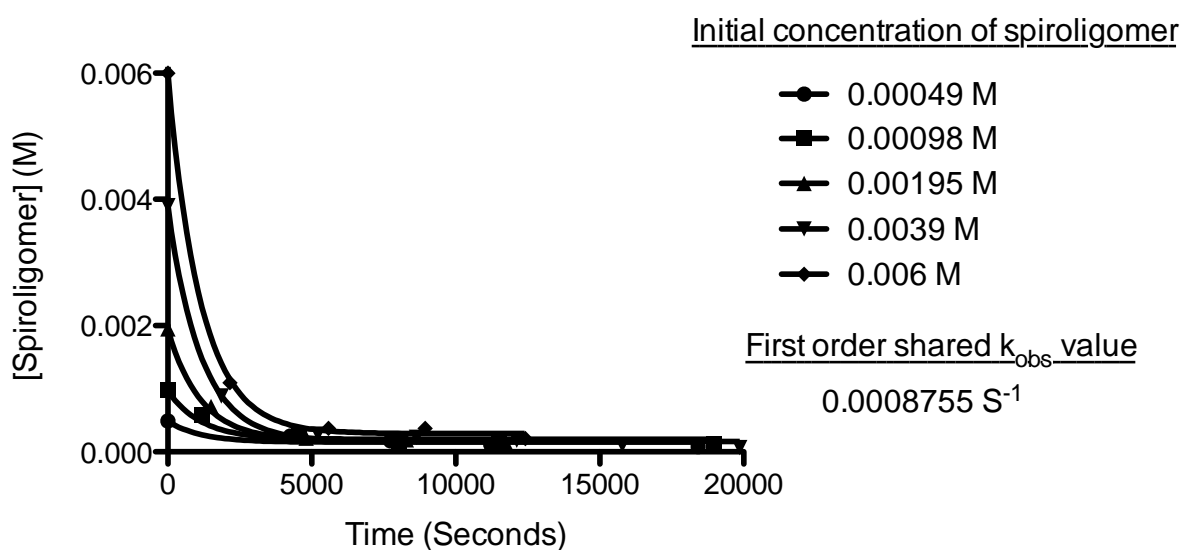
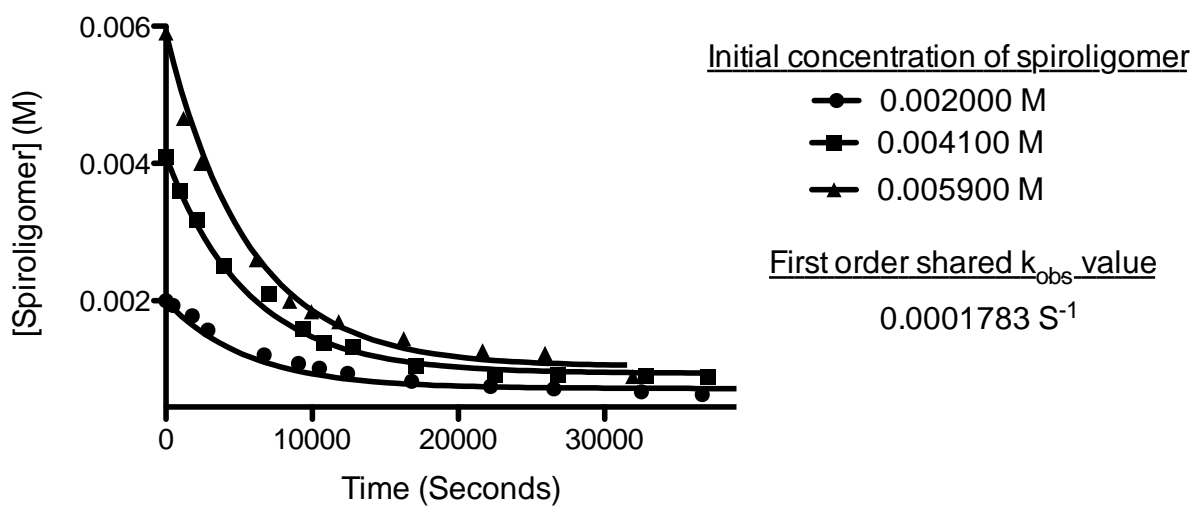


Figure S1. Progress of acylation reaction of spiroligomer **1g** (starting concentration 6 mM) with excess of vinyl trifluoroacetate (100 mM) in presence of trifluorotoluene (5.2 mM) at time 93 min.

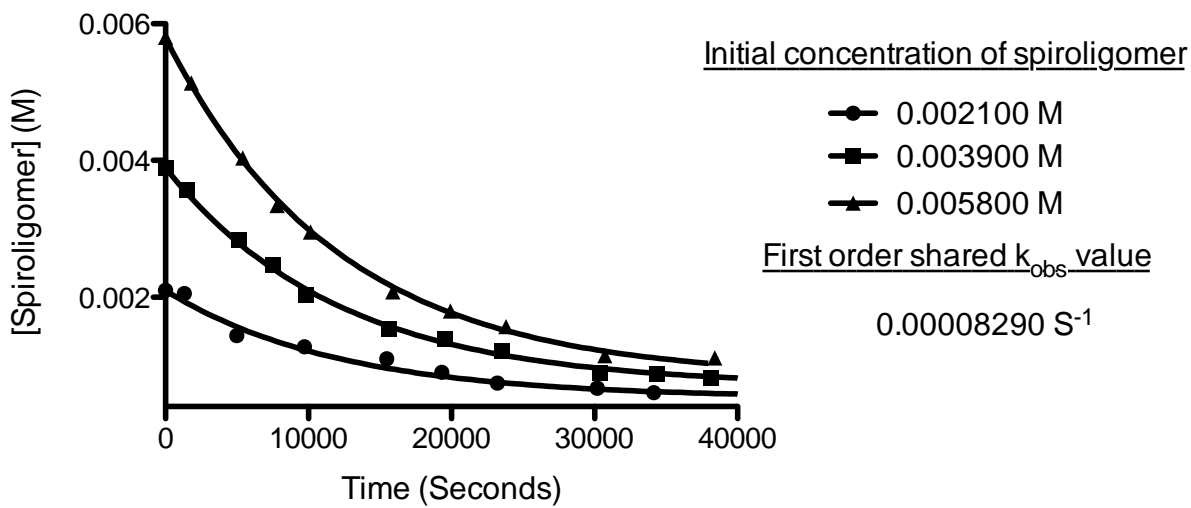
Kintetic of acylation of Spiroligomer 1g



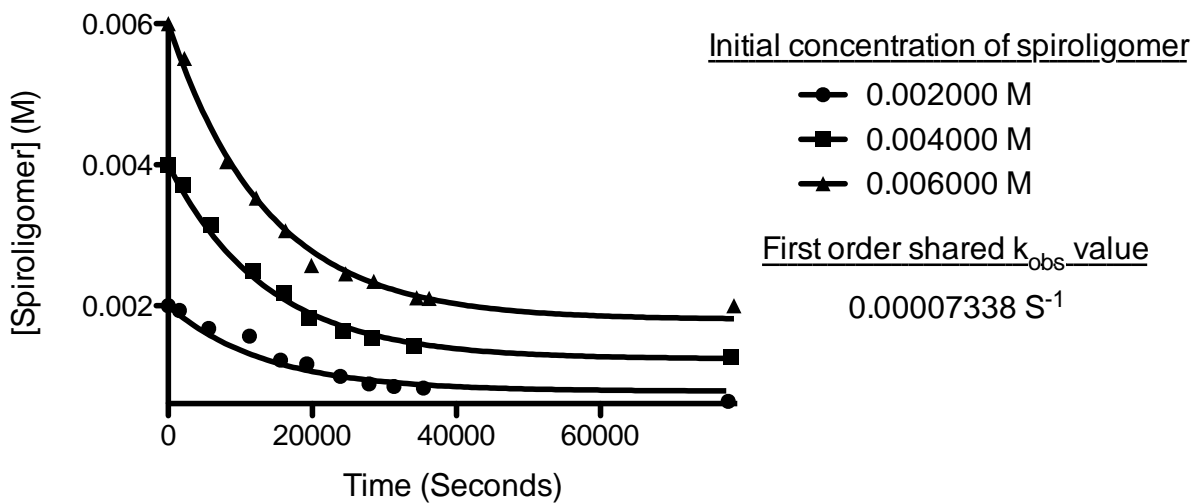
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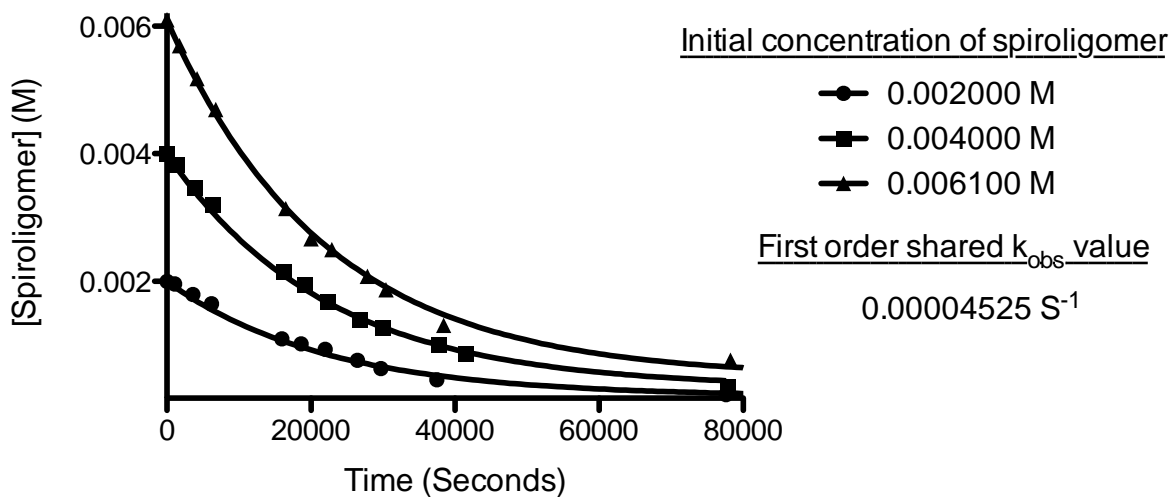
Kintetic of acylation of Spiroligomer 1c



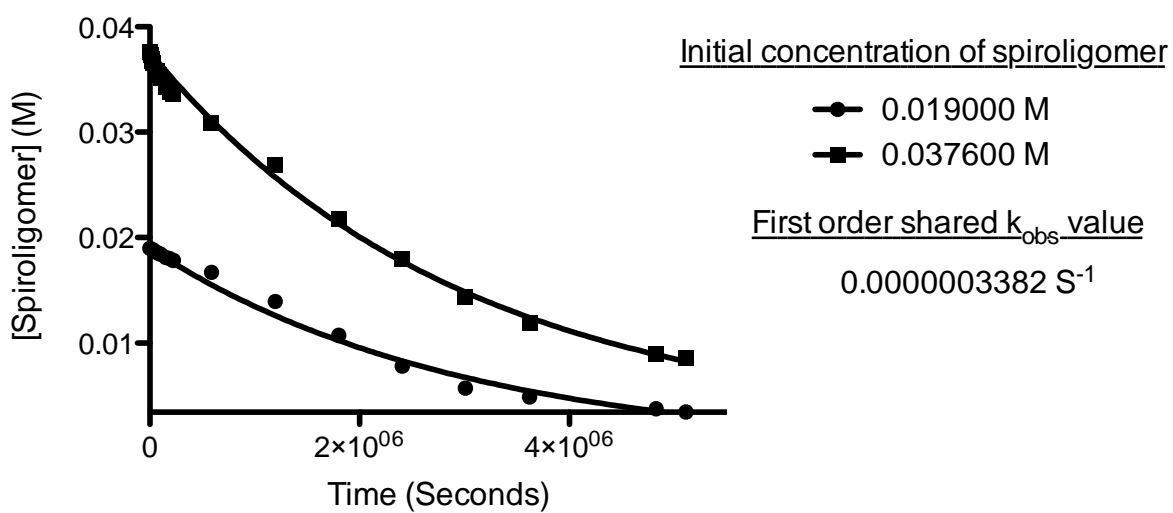
Kintetic of acylation of Spiroligomer 1d



Kintetic of acylation of Spiroligomer 1e



Kintetic of acylation of Spiroligomer 1a



Transesterification :

Stock solutions in dry CDCl_3 were prepared as above with the only difference that spiroligozymes were dissolved in a mixture of 1:1 CDCl_3 and dry MeOH. NMR samples were prepared with sequential addition of trifluorotoluene as internal standard, CDCl_3 , vinyl trifluoroacetate, and stock solution of spiroligozymes in CDCl_3 and MeOH. The reaction was immediately monitored by ^{19}F -NMR at 22°C . The initial concentrations were obtained using the weight of NMR tube before and after each addition. The progress of the initial conversions was measured at appropriate time intervals to get k_{obs} value. In order to extract k_1 and k_2 , The k_{obs} values were determined at several concentrations of vinyl trifluoroacetate. The $k_{\text{uncatalyzed}}$ was determined in the same way but in absence of catalyst.

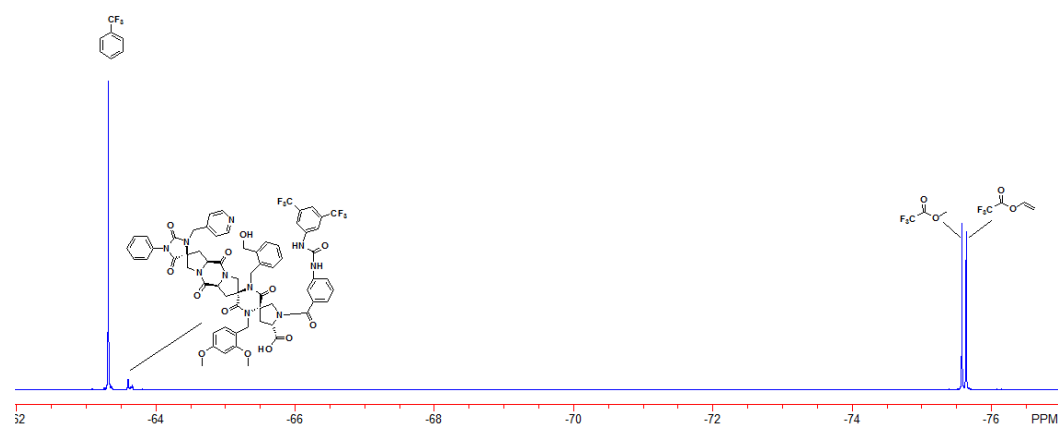


Figure S2. ^{19}F -NMR spectra at time 62 min of acyl-transfer reaction from vinyl trifluoroacetate (initial concentration 10.5 mM) to MeOH (1M), in presence of spiroligozyme **15b** (6.0 mM).

Table S4. Determination of rate constants for **15b**-catalyzed transesterification of vinyl trifluoroacetate with MeOH^a

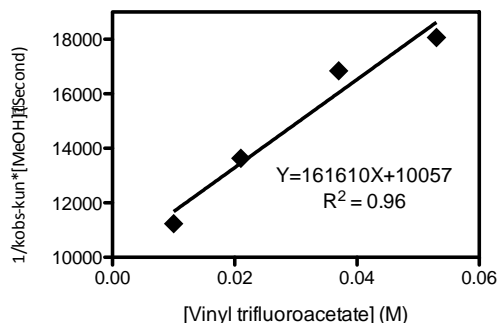
	Concentration of spiroligozyme 15b (M) ^a			
	0.01	0.021	0.037	0.053
<i>k</i>_{obs} (s ⁻¹)	0.000168766	0.000153086	0.000139127	0.000135102
1/(<i>k</i>_{obs} – <i>k</i>_{un}[S]) (s)	11234.87449	13637.2513	16843.6485	18068.62319

^a The reaction was carried with 6 mole % catalyst under pseudo first order conditions using 0.6 mM **15b**, and different concentration of vinyl trifluoroacetate ranging from 10 mM to 53 mM and 1 M methanol.

Kinetic equation:²

$$\frac{1}{k_{obs} - k_{un} [MeOH]} = \frac{[vinyl\ trifluoroacetate]}{k_2 [Spiroligozyme]_0 [MeOH]} + \frac{1}{k_1 [Spiroligozyme]_0}$$

Plotting $1/(k_{obs} - k_{un}[S])$ against concentration of vinyl trifluoroacetate gave a straight line, from which k_1 and k_2 can be obtained. $k_{un} = 0.000076 \text{ (M}^{-1}\text{S}^{-1}\text{)}$



$k_1 \text{ (M}^{-1}\text{S}^{-1}\text{)}$	$k_2 \text{ (M}^{-1}\text{S}^{-1}\text{)}$	k_1/k_{un}	k_2/k_{un}
0.17	0.01	2200	130

$\Delta G^\ddagger = RT \left[\ln \left(\frac{k_B}{h} \right) - \ln \left(\frac{k}{T} \right) \right]$; Where k_B is the Boltzmann constant and h is the Planck constant, $\left(\frac{k_B}{h} \right) = 2.08358 \times 10^{10} \text{ K}^{-1}\text{s}^{-1}$, $T = 295.15 \text{ K}$, $R = 1.986 \times 10^{-3} \text{ kcal K}^{-1}\text{mol}^{-1}$. Applying the experimental rate constants k_1 and k_2 into the equation, gives $\Delta G_1^\ddagger = 18.3 \text{ kcal mol}^{-1}$, $\Delta G_2^\ddagger = 20.0 \text{ kcal mol}^{-1}$.

References:

Tadashi Ema.; Daisuke Tanida.; Tatsuya Matsukawa.; Takashi Sakai, Biomimetic trifunctional organocatalyst showing a great acceleration for the transesterification between vinyl ester and alcohol. *Chem. Commun.* **2008**, 957-959.

Computational Details

Theozyme Calculations

We used Gaussian 09¹ to locate the transition states for the nucleophilic activation of vinyl trifluoroacetate in the presence of catalytic side chain mimics of enzymes and spirologozymes. Methanol, 4-methylimidazole, and acetate were used to mimic the nucleophilic triad of serine hydrolases and proteases, serine, histidine, and aspartate/glutamate respectively. The nucleophilic dyad of spirologozymes was represented by methanol and 3- or 4-methylpyridine depending on the attachment position of the pyridine to the spirologozyme backbone. Geometry optimizations were carried out using the B3LYP/6-31G(d) level of theory.² Solvent and medium effects were taken into account in the optimizations using the Integral-Equation-Formalism Polarizable Continuum Model (IEF-PCM).³ A dielectric constant of 4 was used to represent the electrostatic environment of an enzyme active site for calculations with the catalytic triad, whereas a dielectric continuum representing chloroform was employed to solvate the spirologozymes. Energies were refined by single point calculations with the M06-2X/6-31++G(2d,p)⁴ using IEF-PCM with radii and non-electrostatic terms for the SMD solvation model⁵ as implemented in Gaussian 09. M06-2X density functional method was chosen to include nonlocal effects of electronic dispersion and for its good performance for thermochemical kinetics. Single point energies in solution including all computed corrections were augmented with the correction to Gibbs free energy from unscaled B3LYP frequencies computed for 1 mol/L solute at 298 K. The free energies are reported in the text with respect the separated substrate and pre-organized catalyst complex.

Optimized transition structures are given in Figure S3. The absolute energies (in Hartrees) of all stationary points in theozyme calculations are listed in Table S1. DFT calculations with the model catalysts predict the facile formation of the tetrahedral intermediate when the ideal alignment of the base is achieved.

¹ Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery Jr JA, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2010) Gaussian 09, Revision C.01. Gaussian, Inc., Wallingford CT.: (2004) Gaussian 03, Revision C.02. Gaussian, Inc., Wallingford CT.

² (a) Becke ADJ (1993) Chem. Phys. 98: 5648– 5652. (b) Lee C, Yang W, Parr RG (1998) Phys. Rev. B 37: 785– 789 (c) Vosko SH, Wilk L, Nusair M (1980) Can. J. Phys. 58: 1200– 1211 (d) Stephens PJ, Devlin FJ, Chabalowski CF, Frisch MJ (1994) J. Phys. Chem. 98: 11623– 11627.

³ (a) Cossi M, Barone V, Cammi R, Tomasi J (1996) Chem. Phys. Lett. 255: 327-335; (b) Cancès E, Mennucci B, Tomasi J (1997) J. Chem. Phys. 107: 3032-3041; (c) Tomasi J, Mennucci B, Cammi R (2005) Chem. Rev. 105: 2999-3093.

⁴ Zhao Y, Truhlar DG (2008) Theor. Chem. Acc. 120: 215– 241.

⁵ Marenich AV, Cramer CJ, Truhlar DG (2009) J. Phys. Chem. B 113: 6378-6396.

Figure S3. Transition structures for the nucleophilic addition of model Ser-His-Asp/Glu triad and pyridine-alcohol dyad to vinyl trifluoroacetate. Activation free energies (ΔG^\ddagger) are given in kcal/mol with respect to separated substrate and catalytic triad/dyad complex and distances are given in Å.

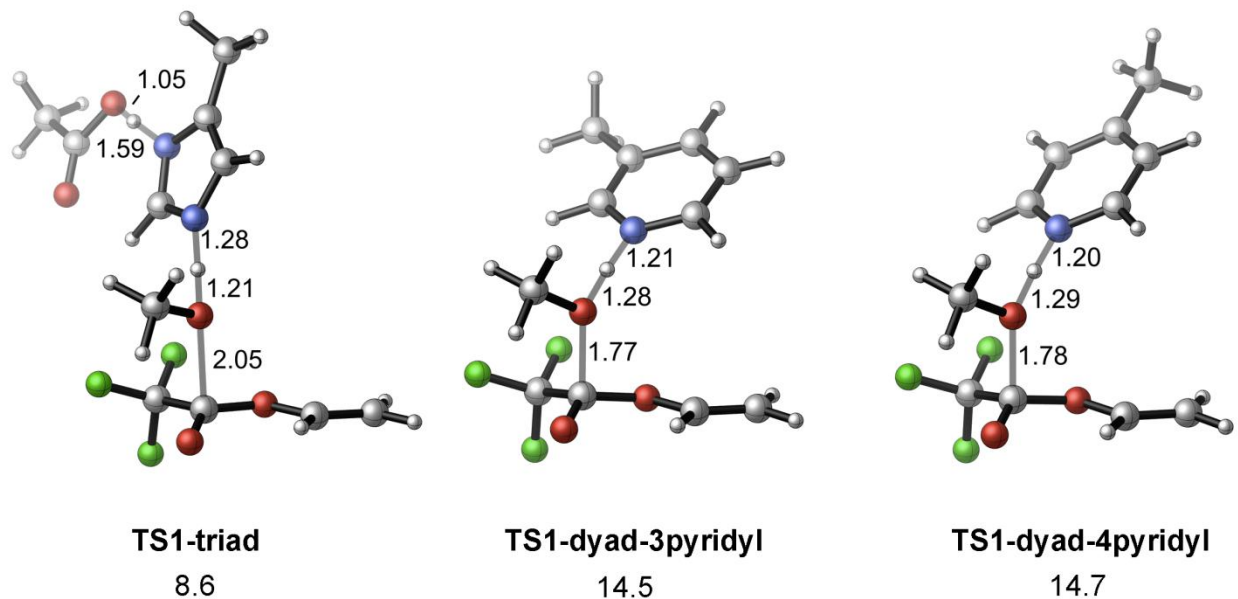


Table S1. Absolute energies (in Hartrees) of the stationary points in theozyme calculations.

M06-2X/6-31++G(d,p) in solvent (IEF-PCM, SMD)//		B3LYP/6-31G(d) in solvent (IEF-PCM, SMD)				
		SCF (w/ PCM corrections)	SCF (w/ PCM corrections)	ZPE	Hcorr	Gcorr
triad	Vinyl trifluoroacetate	-604.018856	-604.175338	0.071404	0.081051	0.037771
	Model catalyst complex	-609.701670	-609.884604	0.200738	0.217017	0.157856
	TS1-triad	-1213.725145	-1214.063509	0.270351	0.295973	0.213903
dyad	Vinyl trifluoroacetate	-604.173732	-604.174826	0.071401	0.080980	0.039570
	Model catalyst complex (4-pyridyl)	-403.344470	-403.345738	0.170079	0.181591	0.134712
	Model catalyst complex (3-pyridyl)	-403.343517	-403.344769	0.170166	0.181634	0.135013
	TS1-dyad (4-pyridyl)	-1007.507338	-1007.510546	0.239190	0.259496	0.191427
	TS1-dyad (3-pyridyl)	-1007.506001	-1007.519594	0.241567	0.262614	0.174583

Molecular Dynamics Simulations

We performed molecular dynamics (MD) simulations using AMBER11⁶ to investigate the dynamical behavior of spiroligozymes in the presence of explicit solvent molecules. The spiroligozyme parameters were generated with the antechamber module of AMBER 11.6 using the general AMBER force field (GAFF)⁷, with partial charges set to fit the electrostatic potential generated at HF/6-31G(d) by RESP.⁸ The charges were calculated according to the Merz-Singh-Kollman scheme^{9,10} using Gaussian 03.1. The spiroligozymes were immersed in a chloroform box¹¹ ensuring a solvent layer of at least 10 Å around the spiroligozymes. This resulted in the addition of up to 244 solvent molecules. Simulations were performed using the general Amber force field. A two-stage minimization approach was used. Initially, the positions of solvent molecules were minimized followed by an unrestrained minimization of all atoms. The systems were then heated in six 50 K, 50 ps steps from 0 to 300 K at constant volume periodic boundary conditions. Harmonic restraints of 10 kcal/mol were applied to the spiroligozyme, and the Langevin equilibration scheme was used to control and equalize the temperature. A 1 fs time step was used during the heating stages to allow potential inhomogeneities to self-adjust. Each system was then equilibrated initially for 2 ns with a 2 fs time step at constant volume, followed by a 2 ns equilibration with a 2 fs time step at a constant pressure of 1 atm. A 20 ns production molecular dynamics simulation was carried out for each system using pmemd¹² using the isothermal-isobaric ensemble (NPT). Long-range electrostatic effects were modeled using the particle-mesh-Ewald method.¹³ Trajectories were saved every 100 steps (0.2 ps). This resulted in a total of 100,000 frames from the production MD run. Post-MD data analysis was performed using the ptraj module of AMBER 11.6. In order to investigate the effect solvent on the pre-organization of the catalytic functional groups, simulations were also carried out in a box of dichloromethane molecules.¹⁴

An overlay of representative snapshots from the MD simulations and reactive spiroligozyme conformer optimized with density functional theory (M06-2X/6-31G(d) in chloroform) is shown in Figure S4. None of the spiroligozymes showed strong H-bonding patterns between the catalytic dyad in the MD simulations (< 1 % occupancy). An alternative favorable interaction of benzyl alcohol with the spiroligozyme backbone competes strongly with the H-bonding between pyridine and alcohol. The catalytic functional groups are highly flexible; no stable conformational state is observed during the simulation. Simulations in chloroform and dichloromethane gave similar results.

⁶ Case DA, Darden TA, Cheatham III TE, Simmerling CL, Wang J, Duke RE, Luo R, Walker RC, Zhang W, Merz KM, Roberts B, Wang B, Hayik S, Roitberg A, Seabra G, Kolossváry I, Wong KF, Paesani F, Vanicek J, Liu J, Wu X, Brozell SR, Steinbrecher T, Gohlke H, Cai Q, Ye X, Wang J, Hsieh MJ, Cui G, Roe DR, Mathews DH, Seetin MG, Sagui C, Babin V, Luchko T, Gusarov S, Kocalenko A, Kollman PA (2010), AMBER 11, University of California, San Francisco.

⁷ Wang J, Wolf RM, Caldwell JW, Kollman PA, Case DA (2004) *J. Comput. Chem.* 25: 1157-1174; (2005) *J. Comput. Chem.* 26: 114.

⁸ (a) Bayly CI, Cieplak P, Cornell WD, Kollman PA (1993) *J. Phys. Chem.* 97:10269-10280; (b) Wang JM, Cieplak P, Kollman PA (2000) *J. Comput. Chem.* 21:1049-1074.

⁹ Besler BH, Merz KM, Kollman PA (1990) *J. Comput. Chem.* 11:431-439.

¹⁰ Singh UC, Kollman PA (1984) *J. Comput. Chem.* 5:129-145.

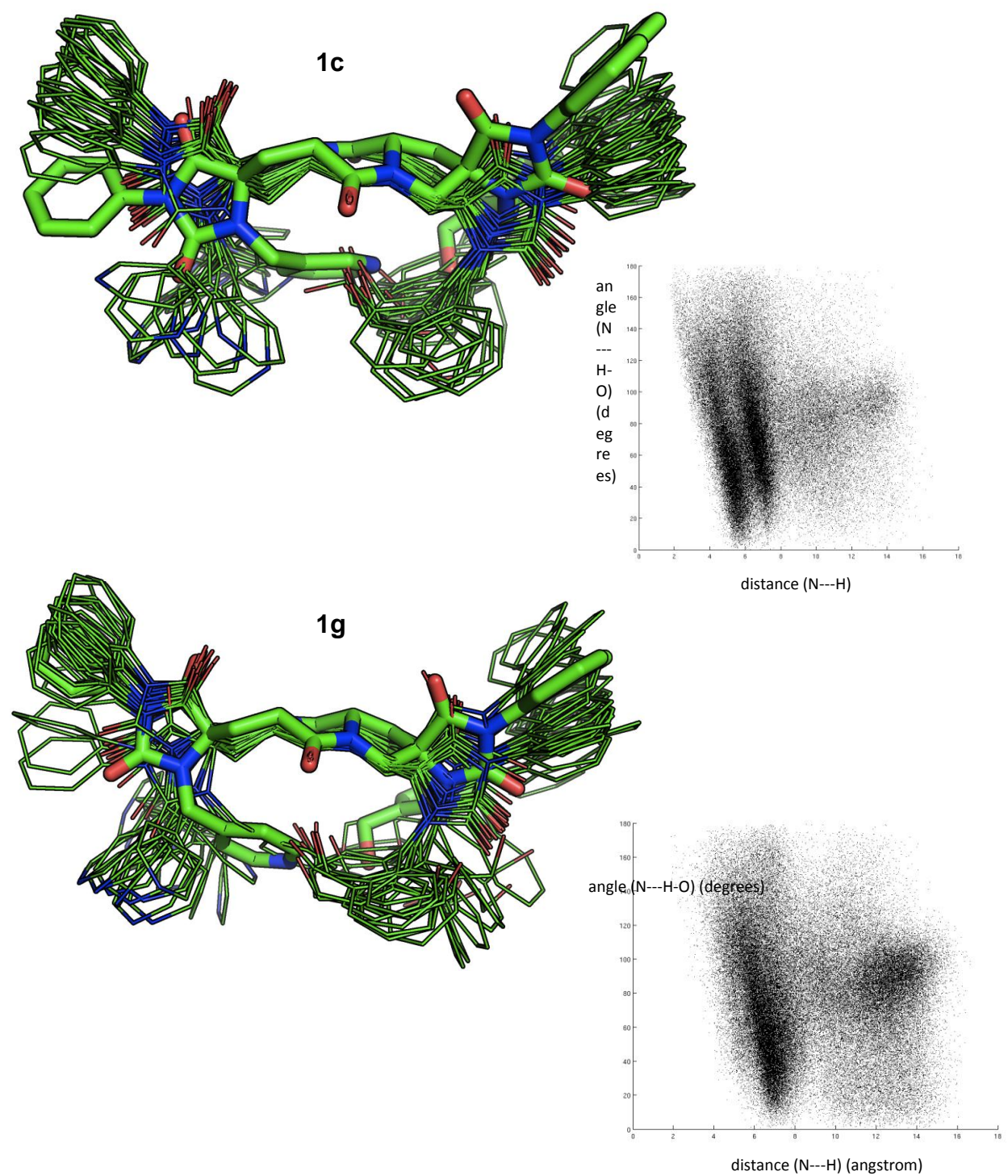
¹¹ Cieplak P, Caldwell JW, Kollman PA (2001) *J. Comp. Chem.* 22: 1048-1057.

¹² Duke RE, Pedersen LG (2003) PMEMD. University of North Carolina, Chapel Hill.

¹³ Darden T, York D, Pedersen L (1993) *J. Chem. Phys.* 98:10089-10092.

¹⁴ Blas JR, Marquez M, Sessler JL, Luque FJ, Orozco M (2002) *J. Am. Chem. Soc.* 124:12796.

Figure S4. Overlay of the QM optimized geometry (in sticks) with the representative snapshots (in lines) from 20 ns production MD, and distance versus angle scatter plots for the pyridine-alcohol H-bond from 20 ns MD.



Conformational Analysis

We carried out an extensive conformational search for the designed spiroligozymes using MacroModel¹⁵ to explore their structural preferences. The conformational search was carried out with the OPLS-2005 force field¹⁶ using a mixed torsional and low mode sampling procedure as implemented in MacroModel. Polak-Ribiere Conjugate Gradient minimization method¹⁷ was used with convergence criterion for energy set to <0.001 kJ/mol. The solvent effects were taken into account using the GB/SA solution model,¹⁸ which treats the solvents as a fully equilibrated analytical continuum starting near the van der Waals surface of the solute, with parameters for chloroform. The conformational search produced 1557 conformers in the range of 5 kcal/mol. The resulting structures were clustered and a total of 25 lowest energy conformers were selected for further optimization using density functional theory. A set of 20 representative snapshots was also selected from the 20 ns MD production run for additional analysis with density functional theory. The selected structures were subjected to full geometry optimization with M06-2X/6-31G(d)4 in a dielectric continuum treated with IEF-PCM solvation model3 representing chloroform as the solvent. Single point energies including radii and non-electrostatic terms for the SMD solvation model5 were calculated at the same level of theory. All 45 conformers for each spiroligozyme were sorted with respect to their energies in solution including all computed corrections. All density functional theory calculations were performed using Gaussian09.1

The structures of low energy conformers of spiroligozymes **1c**, **1g** and **15b** optimized with M06-2X/6-31G(d) in chloroform (ONIOM(B3LYP/6-31G(d):PM6) for **15b**) are shown in Figures S5 – S7. Their absolute energies in Hartrees are given in Table S2. Only the lowest energy conformers that differ in the orientation of catalytic dyad in the 3 kcal/mol energy range are listed. Rotomers of these structures with respect to the non-catalytic spiroligozyme substituents are not displayed.

In **1c**, pyridine and alcohol can form a H-bond in three different orientations (**1c-1**, **1c-2** and **1c-3**). Only one of these conformers (**1c-2**) allows the attack of the substrate from the unhindered face of the spiroligozyme. The other low energy conformer (**1c-4**) shows an alternative favorable interaction between the alcohol and amide oxygen of the spiroligozyme backbone. The relative positioning of pyridine and alcohol in **1g**, however, permits only a single H-bonding conformation (**1g-2**). Other stable conformers of **1g** display favorable interactions between the alcohol and spiroligozyme backbone together with a highly flexible pyridine (**1g-1**, **1g-3** and **1g-4**).

Because of the excessively large size of **15b** to perform an extensive conformational analysis using high-level quantum mechanical calculations, only two conformers were evaluated to estimate the energy difference between the pre-organized (**15b-2**) and non-pre-organized (**15b-1**) states. The starting structure of **15b-1** is selected from the MD snapshots based on the occupancies of H-bonds from the 20 ns simulation.

¹⁵ MacroModel, version 9.9, Schrödinger, LLC, New York, NY, 2011.

¹⁶ Banks JL, Beard HS, Cao Y, Cho AE, Damm W, Farid R, Felts AK, Halgren TA, Mainz DT, Maple JR, Murphy R, Philipp DM, Repasky MP, Zhang LY, Berne BJ, Friesner RA, Gallicchio E, Levy RM. (2005) *J. Comp. Chem.* 26: 1752.

¹⁷ Polak E, Ribiere G (1969) *Recherche Operationelle, Serie Rouge* 16: 35.

¹⁸ Still WC, Tempczyk A, Hawley RC; Hendrickson T (1990) *J. Am. Chem. Soc.* 112: 6127.

Figure S5. Optimized conformers of spiroligozyme **1c** with different catalytic dyad orientations within 3 kcal/mol energy range. Relative energies including all computed PCM corrections (ΔE) are given in kcal/mol and distances are given in Å.

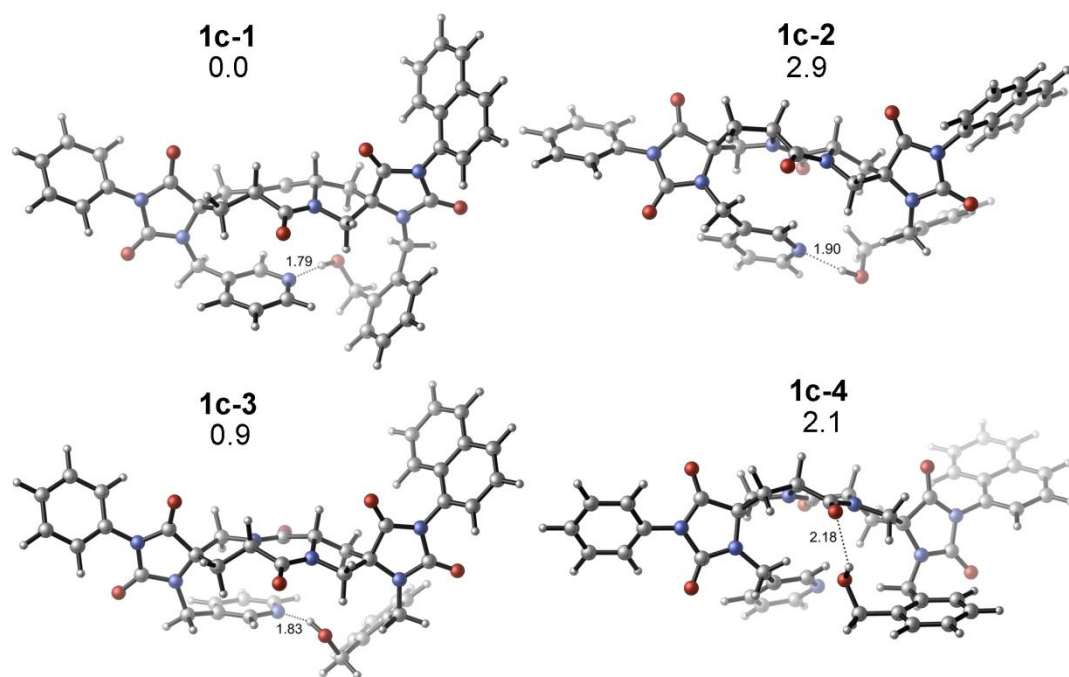


Figure S6. Optimized conformers of spiroligozyme **1g** with different catalytic dyad orientations within 3 kcal/mol energy range. Relative energies including all computed PCM corrections (ΔE) are given in kcal/mol and distances are given in Å.

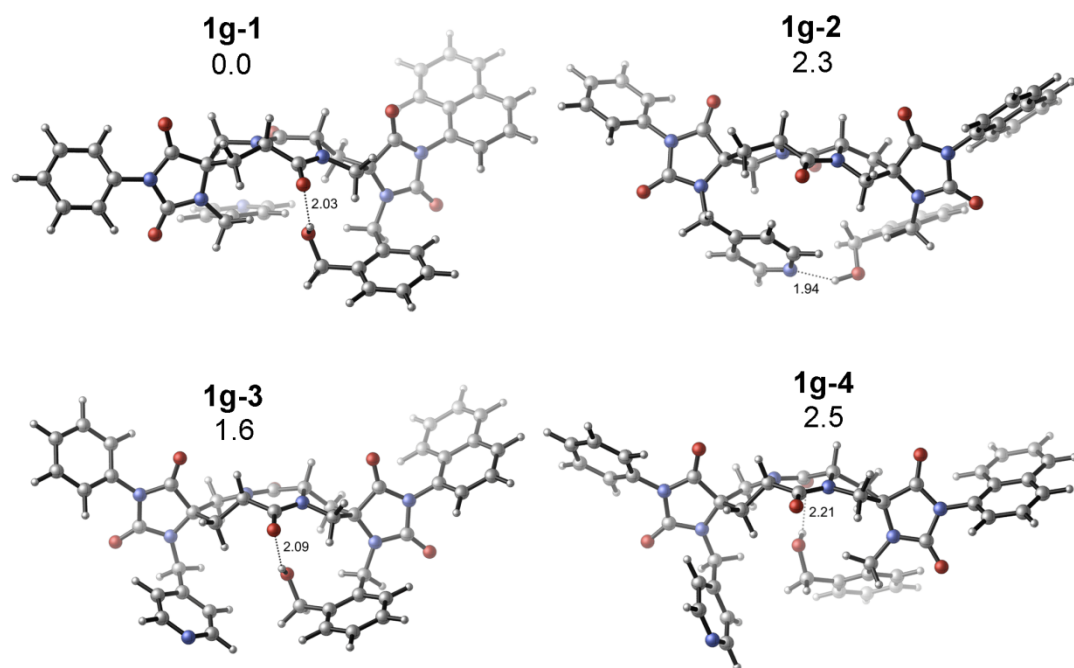


Figure S7. Optimized conformers of spiroligozyme **15b**. Relative energies including all computed PCM corrections (ΔE) are given in kcal/mol and distances are given in Å.

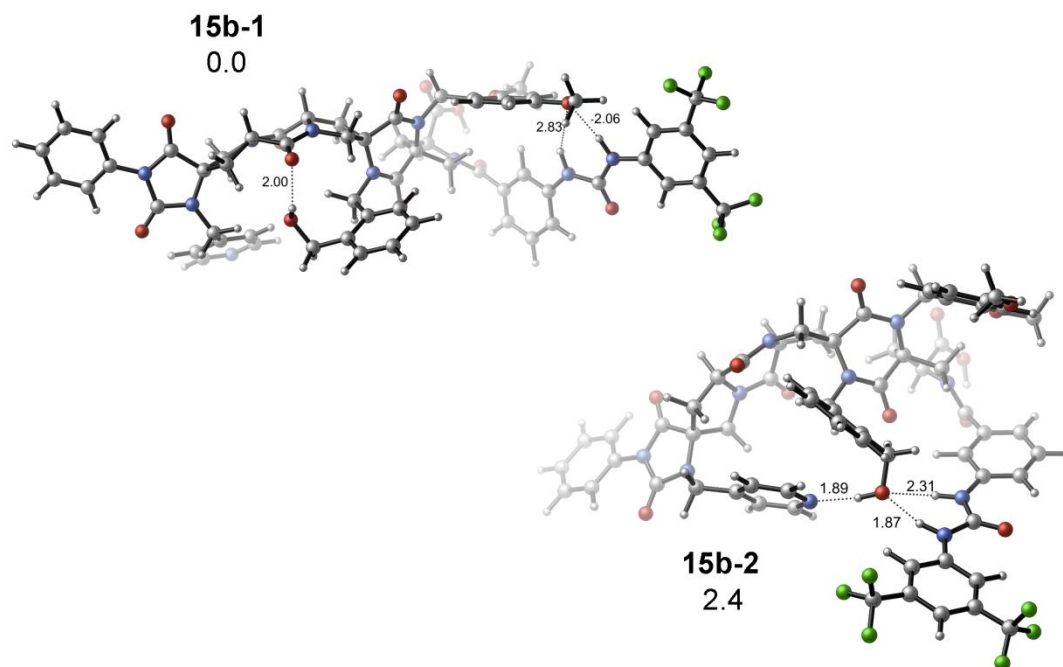


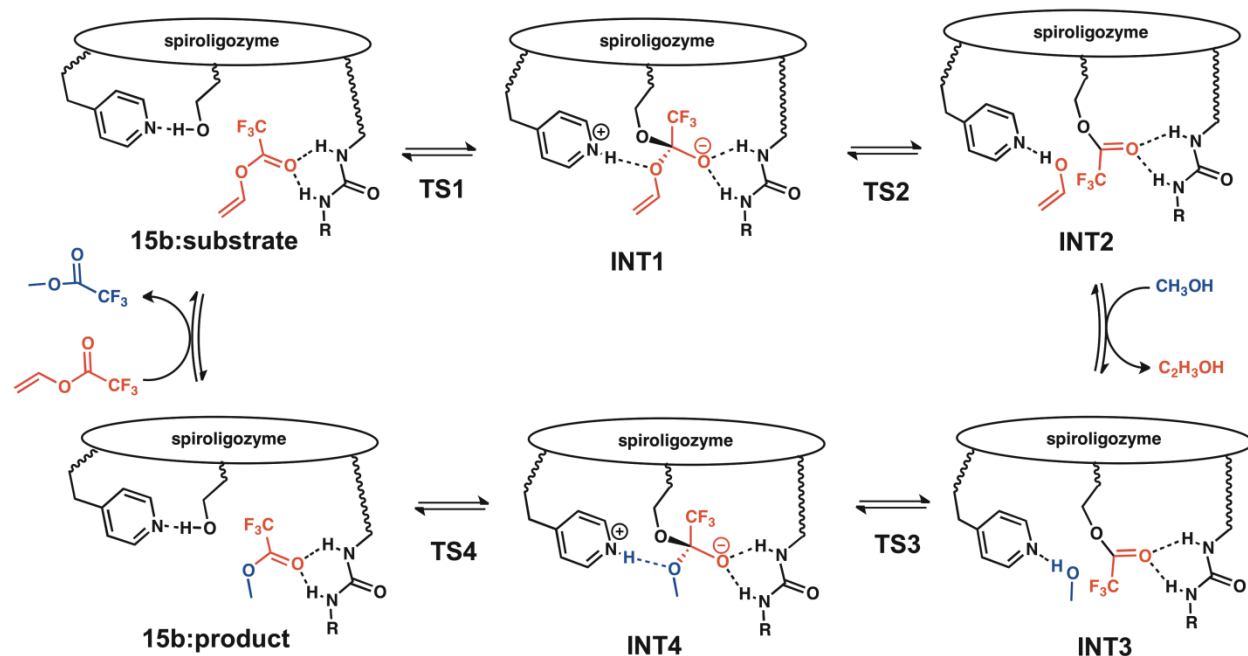
Table S2. Absolute energies (in Hartrees) of the spiroligozyme conformers within 3 kcal/mol energy range.

	M06-2X/6-31G(d) in chloroform (IEF-PCM, SMD)//M06-2X/6-31G(d) in chloroform (IEF-PCM, UFF)			
	1c-1	1c-2	1c-3	1c-4
SCF (w/ PCM corrections)	-2607.985067	-2607.980437	-2607.983621	-2607.981667
	1g-1	1g-2	1g-3	1g-4
SCF (w/ PCM corrections)	-2607.980039	-2607.976300	-2607.977467	-2607.976063
	M06-2X/6-31G(d) in CH ₂ Cl ₂ (IEF-PCM, SMD)//ONIOM(B3LYP/6-31G(d):PM6)			
	15b-1	15b-2		
SCF (w/ PCM corrections)	-4595.48990355	-4595.48614287		

Energy Profile

All stationary points for the spiroligozyme-catalyzed acyl transfer reaction from vinyl trifluoroacetate to methanol (see Scheme S1) were located using Gaussian 09.1 ONIOM MO:MO type calculations^{19,20,21} were used for the geometry optimizations, as high accuracy model chemistries scale unfavorably with the size of the molecule. Two layers were defined within the structure that were treated at different levels of theory. The high level was composed of 4-methylpyridine, *o*-tolylmethanol, 1-(3,5-bis(trifluoromethyl)phenyl)-3-phenylurea groups of the spiroligozyme and the substrates (vinyl trifluoroacetate and methanol), and was treated with density functional B3LYP/6-31G(d).² The low level included the atoms of the spiroligozyme backbone and was treated at the semiempirical PM6²² level of theory. The transition states were characterized using the harmonic vibrational frequencies. Due to a convergence failure in the ONIOM optimization of **TS3**, this transition state was located using a relaxed potential energy surface scan for the formation of the C–O bond with 0.01 Å increments between $d_{(C-O)} = 1.93$ and $d_{(C-O)} = 1.71$ (see Chart S1). The 3D representations of all stationary points are shown in Figures S8 – S10. The energies of all located stationary points were refined with single point calculations on the complete system at the M06-2X/6-31G(d) level of theory⁴ in a dielectric continuum representing chloroform using the IEF-PCM3 with radii and non-electrostatic terms for SMD solvation model.⁵ Single point energies in solution including all computed corrections (in Hartrees) are listed in the Table S3.

Scheme S1. 15b-catalyzed acyl transfer reaction from vinyl trifluoroacetate to methanol.



¹⁹ Svensson M, Humbel S, Morokuma K (1996) *J. Chem. Phys.* 105: 3654-3661.

²⁰ Vreven T, Morokuma K (2000) *J. Comput. Chem.* 21: 1419-1432.

²¹ Dapprich S, Komaromi I, Byun KS, Morokuma K, Frisch M (1999) *J. Mol. Struct. THEOCHEM* 462: 1-21.

²² Stewart JJP (2007) Optimization of parameters for semiempirical methods. V. Modification of NDDO approximations and application to 70 elements. *J. Mol. Model.* 13: 1173-1213.

Figure S8. Transition structures for the acyl transfer reaction from vinyl trifluoroacetate to methanol catalyzed by spiroligozyme **15b**. Relative energies including all computed PCM corrections (ΔE) are given in kcal/mol with respect to the substrate-catalyst complex (**15b:substrate**) and distances are given in Å.

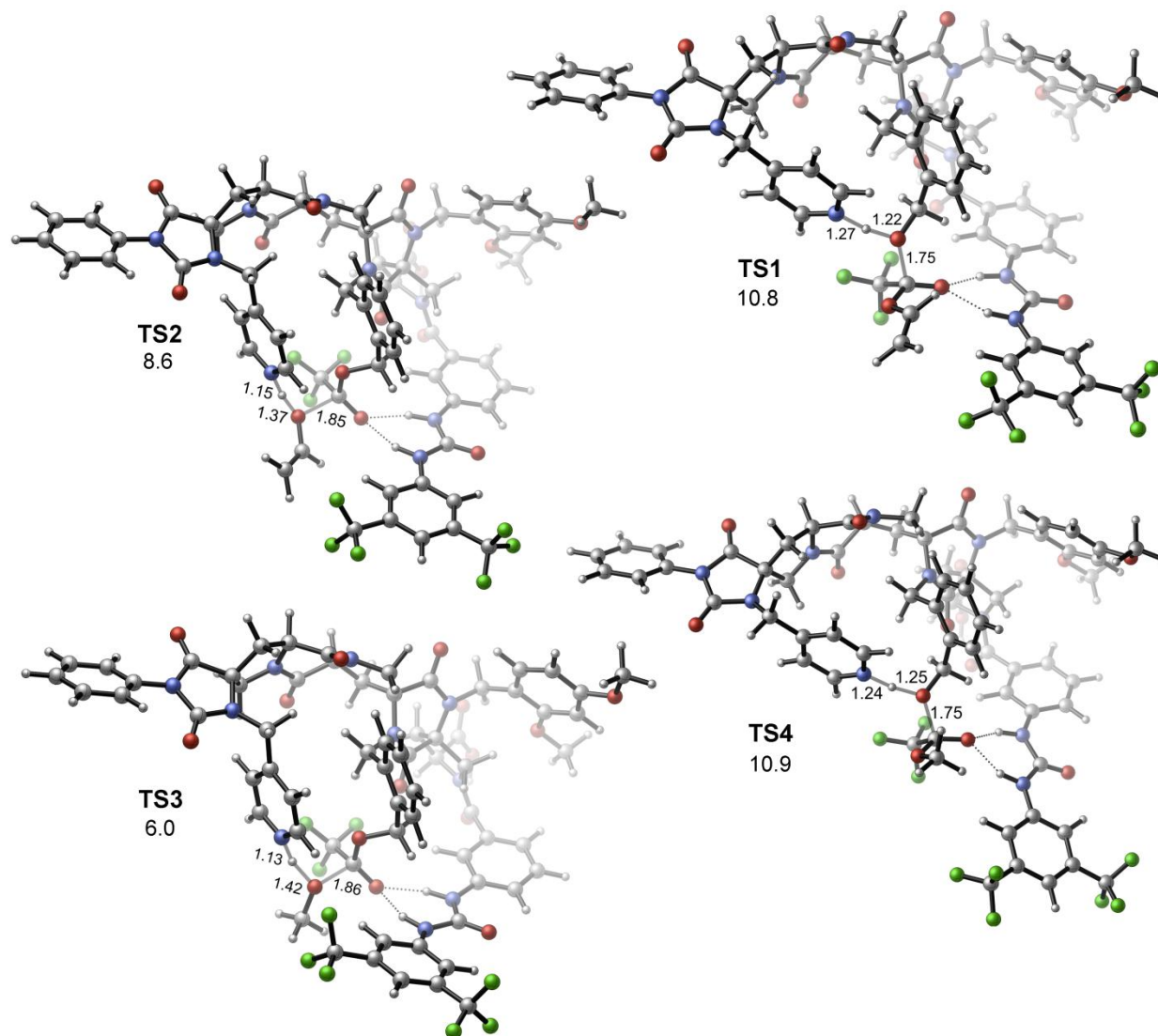


Figure S9. Intermediate structures for the acyl transfer reaction from vinyl trifluoroacetate to methanol catalyzed by spiroligozyme **15b**. Relative energies including all computed PCM corrections (ΔE) are given in kcal/mol with respect to the substrate-catalyst complex (**15b:substrate**) and distances are given in Å.

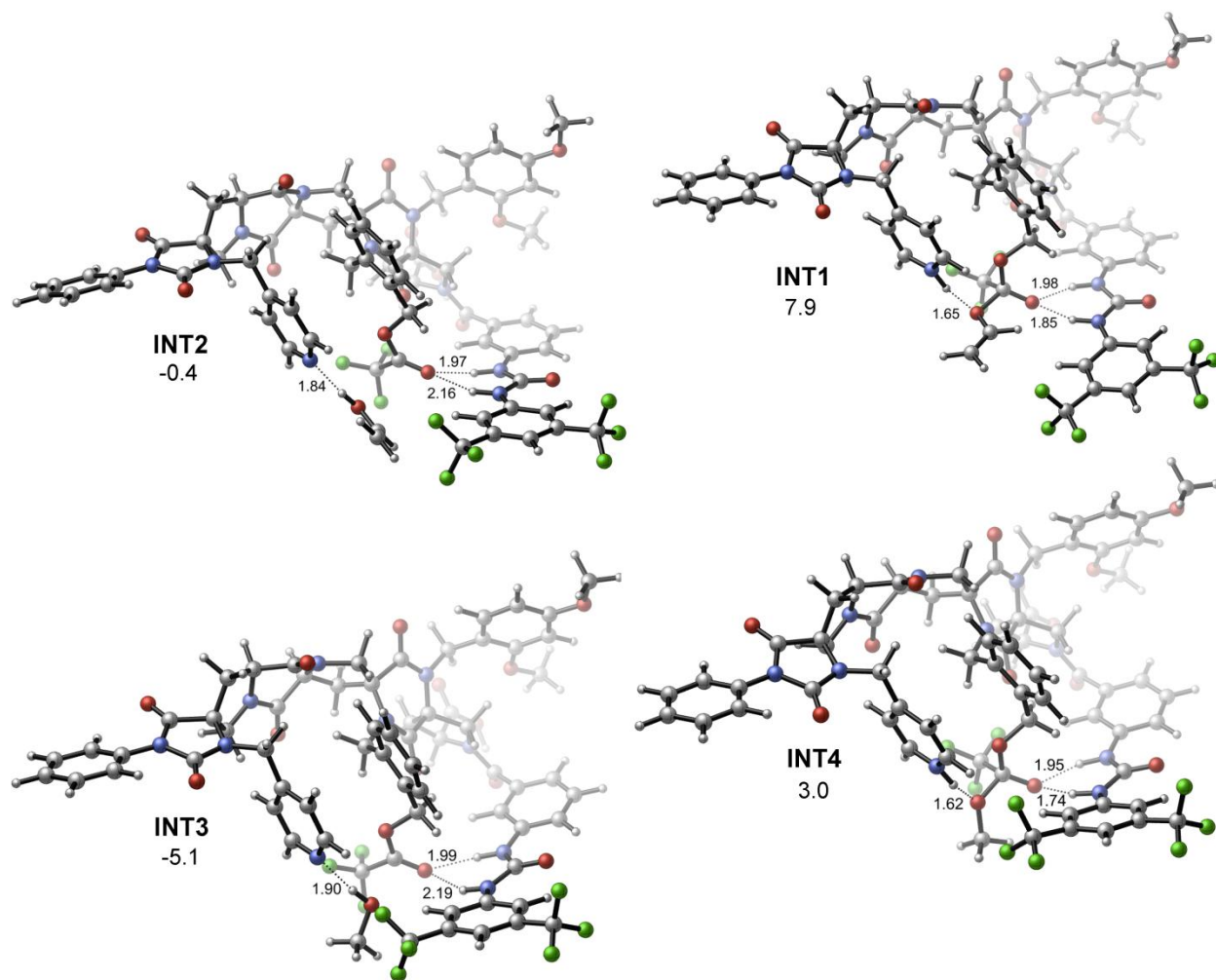


Figure S10. Complexes of spiroligozyme **15b** with the substrate and product for the acyl transfer reaction from vinyl trifluoroacetate to methanol. Relative energies including all computed PCM corrections (ΔE) are given in kcal/mol with respect to the substrate-catalyst complex (**15b:substrate**) and distances are given in Å.

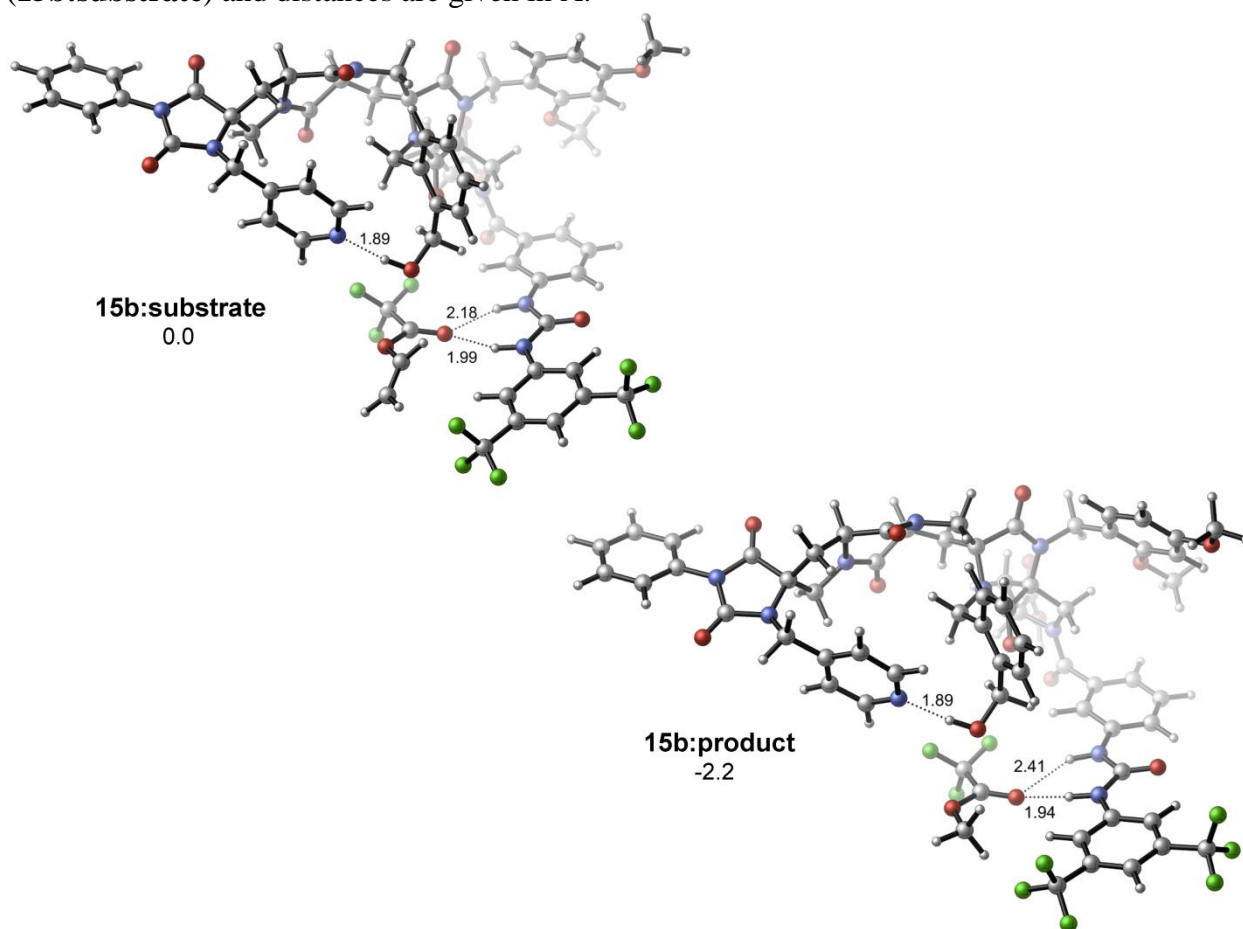


Chart S1. Relaxed potential energy surface scan for the formation C–O bond in the addition of methanol to acylated spiroligozyme.

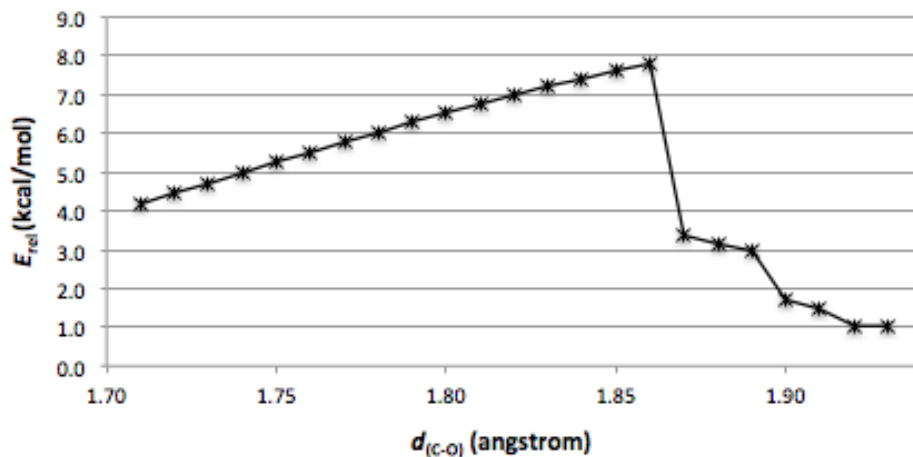
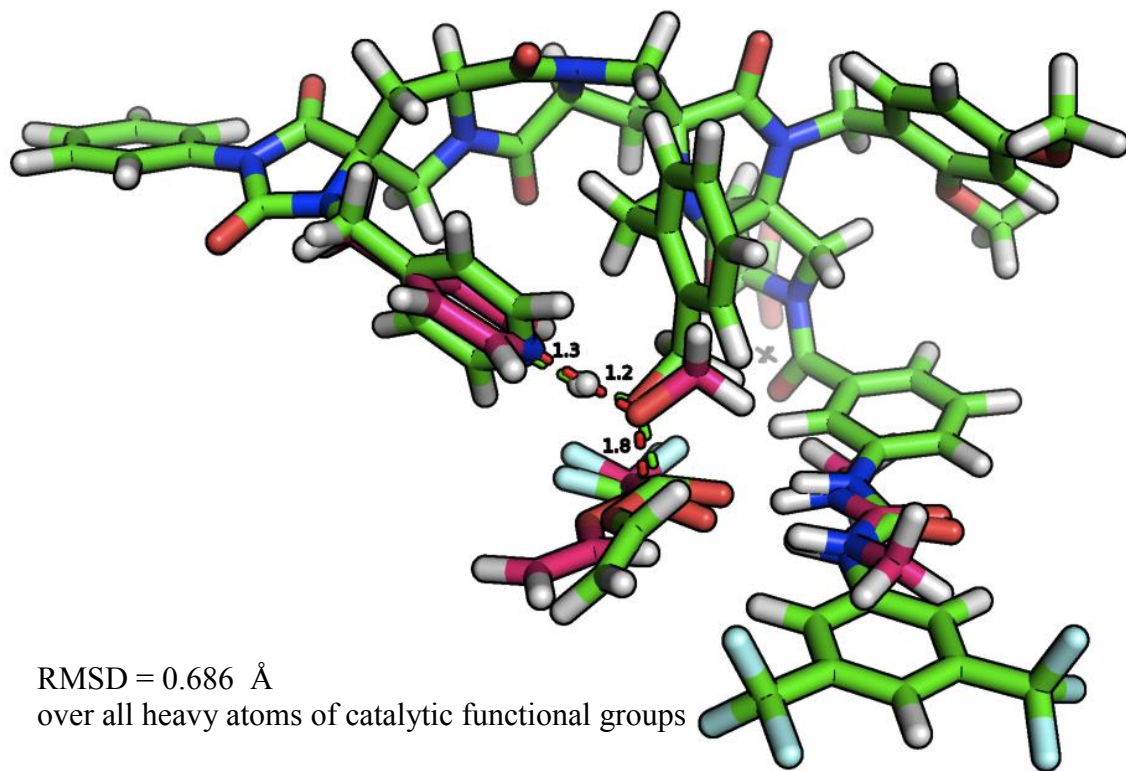


Table S3. Absolute energies (in Hartrees) of the stationary points along the **15b**-catalyzed acyl transfer reaction from vinyl trifluoroacetate to methanol.

M06-2X/6-31G(d) in chloroform (IEF-PCM, SMD)//ONIOM(B3LYP/6-31G(d):PM6)					
	15b:substrate	TS1	INT1	TS2	INT2
SCF (w/ PCM corrections)	-5199.464151	-5199.450413	-5199.451512	-5199.446993	-5199.464777
	INT3	TS3	INT4	TS4	15b:product
SCF (w/ PCM corrections)	-5161.396989	-5161.371452	-5161.384004	-5161.379315	-5161.392319
M06-2X/6-31G(d) in chloroform (IEF-PCM, SMD)//B3LYP/6-31G(d)					
	methanol	vinyl alcohol	vinyl trifluoroacetate		
SCF (w/ PCM corrections)	-115.659353	-153.734672	-603.959194		

Figure S11. Overlay of trifunctional theozyme model (magenta) with **TS1** of the acyl transfer reaction from vinyl trifluoroacetate to methanol catalyzed by **15b**.



Cartesian Coordinates

TS1-triad

B3LYP/6-31G(d) in diethylether (IEF-PCM, SMD)

O	1.95899	0.84738	0.91338
C	-4.82652	-1.47024	-0.30323
O	-3.79102	-2.07939	-0.06853
O	-4.92982	-0.15190	-0.37851
C	-2.33377	2.42334	0.10784
C	-0.97497	2.54708	0.31169
N	-2.63316	1.07783	0.03927
C	-1.46675	0.44384	0.19800
N	-0.43079	1.28353	0.36599
H	-0.36345	3.43421	0.41883
H	-4.00346	0.30811	-0.20643
H	0.80110	1.01770	0.59624
H	-1.37115	-0.63312	0.18663
C	-6.15675	-2.16140	-0.53892
H	-6.88020	-1.85265	0.22468
H	-6.56787	-1.86783	-1.51141
H	-6.03228	-3.24561	-0.50548
C	-3.38385	3.48239	-0.03339
H	-3.90626	3.41282	-0.99726
H	-4.15117	3.40755	0.74963
H	-2.93985	4.48202	0.03246
C	3.23032	-0.57153	0.14711
C	2.06174	0.95302	2.30735
H	1.20560	0.49900	2.83618
H	2.97695	0.44918	2.64978
H	2.12684	2.00765	2.63076
O	4.16603	-0.62995	0.92304
C	2.15502	-1.66885	0.13291
F	1.06898	-1.37213	-0.59997
F	1.75862	-1.97405	1.37846
F	2.69299	-2.79947	-0.40070
O	3.28893	-0.00847	-1.11153
C	4.25295	0.94805	-1.30966
H	4.86191	1.16469	-0.43879
C	4.40209	1.53697	-2.49361
H	5.16980	2.29241	-2.62288
H	3.77208	1.29097	-3.34347

TS1-dyad (4-pyridyl)

B3LYP/6-31G(d) in chloroform (IEF-PCM, SMD)

C	1.13799	-0.67077	2.51723
H	0.57741	-0.16182	3.31422
H	0.86203	-1.73604	2.51874

H	2.20783	-0.58342	2.74079
O	0.88381	-0.04805	1.27423
H	-0.31810	-0.12734	0.82493
C	-2.06991	-1.14364	-0.10074
C	-3.40098	-1.08868	-0.48782
C	-4.13776	0.08748	-0.29099
C	-3.47575	1.17667	0.29893
C	-2.14589	1.05662	0.66534
N	-1.46785	-0.08715	0.46664
H	-1.45738	-2.02700	-0.24256
H	-3.86085	-1.95918	-0.94410
H	-3.99541	2.11413	0.47067
H	-1.58615	1.86758	1.11945
C	2.28962	0.10611	0.19319
O	3.31465	0.27304	0.84963
O	1.74301	1.11810	-0.64041
C	2.11893	-1.21361	-0.58957
C	1.97559	2.40461	-0.24036
H	2.65288	2.50072	0.60298
C	1.41476	3.44064	-0.86445
H	0.75044	3.31044	-1.71436
H	1.63513	4.45036	-0.53433
F	0.90355	-1.36332	-1.16811
F	2.31483	-2.27388	0.21809
F	3.03574	-1.28788	-1.58061
C	-5.58376	0.18771	-0.69022
H	-5.92878	-0.72375	-1.18581
H	-6.21530	0.36155	0.18962
H	-5.74226	1.03319	-1.36999

TS1-dyad (3-pyridyl)

B3LYP/6-31G(d) in chloroform (IEF-PCM, SMD)

C	1.12338	-0.43470	2.54551
H	0.64497	0.16984	3.32884
H	0.76906	-1.47247	2.63665
H	2.20701	-0.41564	2.71077
O	0.84938	0.12076	1.27474
H	-0.36892	0.14562	0.88545
C	-2.26076	-0.80165	0.22378
C	-3.59463	-0.69120	-0.16340
C	-4.13665	0.60247	-0.20874
C	-3.35686	1.70996	0.11833
C	-2.03457	1.51040	0.49521
N	-1.52110	0.27287	0.54237
H	-1.75375	-1.75939	0.27849

H	-3.76413	2.71443	0.08157
H	-1.36091	2.32007	0.75505
C	2.18230	0.09573	0.10761
O	3.25830	0.23764	0.68352
O	1.64779	1.08318	-0.76621
C	1.87462	-1.25920	-0.56733
C	1.97318	2.37596	-0.46593
H	2.70865	2.48518	0.32557
C	1.42904	3.40254	-1.12060
H	0.70605	3.25858	-1.91893
H	1.72487	4.41626	-0.87174
F	0.61687	-1.36378	-1.05680
F	2.05500	-2.27352	0.30127
F	2.71802	-1.46296	-1.60452
C	-4.40470	-1.90734	-0.52514
H	-5.31538	-1.96965	0.08188
H	-4.71621	-1.87050	-1.57596
H	-3.83181	-2.82702	-0.37544
H	-5.17364	0.73869	-0.50496

Model catalyst (triad)

B3LYP/6-31G(d) in diethylether (IEF-PCM, SMD)

O	2.28888	-0.00755	-0.95353
C	9.62327	-1.07834	0.06896
O	8.69263	-1.87498	-0.01015
O	9.50780	0.23271	0.06000
C	6.59948	2.34987	-0.18622
C	5.22329	2.26803	-0.29989
N	7.08504	1.06139	-0.14309
C	5.99507	0.27470	-0.23037
N	4.83921	0.94576	-0.32714
H	4.49728	3.07190	-0.36239
H	8.46602	0.55161	-0.02779
H	3.17797	0.33035	-0.65075
H	6.07379	-0.80575	-0.22233
C	11.07039	-1.53262	0.18779
H	11.65268	-1.16129	-0.66379
H	11.52482	-1.11659	1.09442
H	11.12744	-2.62302	0.21839
C	7.49572	3.54924	-0.11596
H	8.08146	3.57485	0.81410
H	8.21876	3.57530	-0.94377
H	6.90977	4.47469	-0.16139
C	2.45301	-0.38217	-2.29767
H	3.20342	-1.18126	-2.43936
H	1.49316	-0.76377	-2.67177
H	2.75097	0.45846	-2.95060

Model catalyst (4-pyridyl)

B3LYP/6-31G(d) in chloroform (IEF-PCM, SMD)

C	-3.94552	0.03428	0.69057
H	-3.51522	-0.68171	1.41125
H	-3.79176	1.04891	1.09710
H	-5.02621	-0.14587	0.64781
O	-3.42659	-0.12067	-0.61474
H	-2.45048	0.00072	-0.54827
C	0.14571	1.19548	-0.18544
C	1.52712	1.19765	-0.02484
C	2.21537	-0.02060	0.06984
C	1.44679	-1.18804	0.00115
C	0.06595	-1.09462	-0.16100
N	-0.58699	0.07220	-0.25498
H	-0.40286	2.13156	-0.26401
H	2.06298	2.14194	0.02312
H	1.91729	-2.16488	0.06980
H	-0.54606	-1.99214	-0.22056
C	3.71185	-0.06129	0.23672
H	4.21376	0.42609	-0.60824
H	4.02096	0.47287	1.14353
H	4.08030	-1.08916	0.30420

Model catalyst (3-pyridyl)

B3LYP/6-31G(d) in chloroform (IEF-PCM, SMD)

C	3.66154	-0.54590	0.65258
H	3.48487	0.23083	1.41610
H	3.16288	-1.46875	0.99537
H	4.73963	-0.74287	0.62170
O	3.25394	-0.14842	-0.64092
H	2.28724	0.03648	-0.58715
C	-0.40831	-0.70321	-0.23896
C	-1.78138	-0.58260	-0.00157
C	-2.27478	0.71321	0.20147
C	-1.40430	1.79957	0.15956
C	-0.05188	1.56352	-0.08403
N	0.44142	0.33366	-0.28034
H	0.03144	-1.68528	-0.40400
H	-1.76292	2.81283	0.31363
H	0.66284	2.38239	-0.12386
C	-2.67873	-1.79286	0.03706
H	-3.18761	-1.87988	1.00495
H	-3.45825	-1.73610	-0.73278
H	-2.11121	-2.71413	-0.12842
H	-3.33479	0.86655	0.39134

Vinyl trifluoroacetate

B3LYP/6-31G(d) in diethylether (IEF-PCM, SMD)

C	0.02332	0.59843	-0.00269
O	0.07135	1.80111	0.00538
O	1.05127	-0.26207	-0.00661
C	-1.29670	-0.20197	-0.00094
C	2.35195	0.24905	0.00271
H	2.41322	1.33027	0.01298
C	3.37555	-0.59321	-0.00118
H	3.23727	-1.67013	-0.01173
H	4.38685	-0.20162	0.00657
F	-1.35810	-1.01844	-1.06753
F	-2.33970	0.63100	-0.03778
F	-1.38589	-0.95522	1.11006

B3LYP/6-31G(d) in chloroform (IEF-PCM, SMD)

C	0.02378	0.59723	-0.00659
O	0.07114	1.80031	-0.00361
O	1.05138	-0.26271	-0.00654
C	-1.29605	-0.20195	-0.00057
C	2.35247	0.24970	0.00727
H	2.41161	1.33082	0.02825
C	3.37558	-0.59284	-0.00385
H	3.23540	-1.66929	-0.02533
H	4.38722	-0.20233	0.00931
F	-1.35825	-1.02467	-1.06224
F	-2.33861	0.63147	-0.04176
F	-1.38530	-0.94854	1.11490

1c-1

M06-2X/6-31G(d) in chloroform (IEF-PCM)

C	-0.57115	-0.00542	-1.15354
N	0.52543	0.01332	-0.37124
O	-0.68585	0.62135	-2.19670
C	-1.68026	-0.89891	-0.58533
N	-1.74985	-0.74140	0.86672
O	-0.70269	-0.53755	2.87421
C	-0.65535	-0.66598	1.66060
N	4.78221	-0.75382	-0.25428
O	-4.68668	-2.85747	-0.12340
C	0.63525	-0.77954	0.85849
N	3.87028	1.08305	0.63585
O	-7.19319	0.96215	0.28142
C	2.74281	0.22819	0.33093
N	-6.26408	-1.15518	-0.04861
O	0.92279	2.75988	2.17270
C	1.70539	0.81317	-0.65259

N	-4.90907	0.60371	0.26729
O	6.17210	0.99964	0.40939
C	1.88386	-0.22114	1.53398
N	-0.96664	2.88127	0.16331
O	2.87522	-1.96520	-0.75063
C	-3.07130	-0.50273	-1.08030
C	-3.10076	-0.77242	1.39240
C	-4.01209	-0.53848	0.16193
C	3.42667	-0.98509	-0.30310
C	5.06482	0.52292	0.29112
C	3.80869	2.36052	1.33342
C	-4.99814	-1.69496	-0.01092
C	-6.22553	0.24219	0.18111
C	-4.55024	1.91209	0.80285
C	-1.04394	3.41721	-1.05394
C	-2.24931	3.54543	-1.74290
C	-3.40888	3.07745	-1.14267
C	-3.33650	2.49416	0.12510
C	-2.08880	2.43188	0.73526
C	-9.80673	-3.31208	-0.72145
C	-8.82132	-3.83311	0.11347
C	-7.64991	-3.12040	0.35139
C	-7.46824	-1.88499	-0.26819
C	-8.44430	-1.35626	-1.11185
C	-9.61623	-2.07250	-1.32873
C	2.47318	5.55535	-1.24262
C	1.82413	5.32690	-0.03171
C	2.23378	4.30535	0.82815
C	1.47892	4.05988	2.11928
C	3.31560	3.49492	0.45247
C	3.96725	3.73051	-0.75919
C	3.55153	4.75287	-1.60739
C	7.76322	-3.35884	-1.69848
C	6.94329	-3.78981	-0.62238
C	5.93910	-2.91952	-0.11179
C	5.78628	-1.64527	-0.73221
C	6.59633	-1.24804	-1.76501
C	7.60185	-2.11450	-2.25029
C	5.15379	-3.34822	0.99080
C	5.34896	-4.58645	1.54639
C	6.33420	-5.46169	1.02859
C	7.11320	-5.06929	-0.02856
H	-1.44978	-1.94217	-0.84573
H	0.78099	-1.83804	0.59936
H	-4.37568	1.84694	1.88433
H	-0.10819	3.76173	-1.48794

H	-2.26798	3.99689	-2.72821	O	-6.70447	0.46081	-1.62371
H	-4.36721	3.14913	-1.65158	C	2.35088	-0.18746	-0.57762
H	-1.97675	2.00691	1.73373	N	-6.53428	-0.92680	0.25209
H	-10.72043	-3.86992	-0.89969	O	1.25295	4.32561	-1.23038
H	-8.96362	-4.79789	0.58957	C	1.20511	-0.54904	-1.55184
H	-6.88070	-3.51697	1.00354	N	-4.67627	-0.29292	-0.81947
H	-8.28662	-0.39283	-1.58235	O	5.57976	0.42850	-1.80624
H	-10.37901	-1.66128	-1.98200	C	1.60546	0.36408	0.64808
H	2.13787	6.35376	-1.89750	N	-1.11520	2.81213	-1.32339
H	0.97554	5.94499	0.25264	O	2.70429	-2.43650	0.32276
H	0.32060	2.70360	1.39308	C	-3.30951	-2.28390	-0.09723
H	4.81511	3.10590	-1.03340	C	-3.34201	-0.29905	1.32658
H	4.06753	4.92280	-2.54719	C	-4.19603	-1.08063	0.29942
H	8.52714	-4.03450	-2.07317	C	3.13085	-1.46273	-0.25387
H	6.45779	-0.26525	-2.20334	C	4.55334	0.00994	-1.31803
H	8.23604	-1.78805	-3.06758	C	3.22477	2.10621	-1.32952
H	4.40086	-2.68505	1.40260	C	-5.50884	-1.52321	0.95092
H	4.74500	-4.89889	2.39234	C	-6.03339	-0.17061	-0.83664
H	6.47279	-6.44033	1.47689	C	-3.84945	0.26947	-1.87026
H	7.87822	-5.72943	-0.42832	C	-1.80383	3.80969	-0.76188
H	2.00537	0.71569	-1.69976	C	-3.17240	3.74765	-0.51375
H	1.62328	0.65055	2.14078	C	-3.85574	2.59389	-0.86941
H	-3.42145	-1.18418	-1.85705	C	-3.14933	1.54043	-1.45131
H	-3.22638	-0.00415	2.15995	C	-1.78259	1.70220	-1.65365
H	1.51906	1.86984	-0.43032	C	-10.61069	-1.26951	1.21090
H	2.39013	-0.96154	2.15693	C	-9.66688	-1.08708	2.21912
H	-3.04179	0.50107	-1.50385	C	-8.31749	-0.96458	1.90433
H	-3.31230	-1.74483	1.85134	C	-7.91895	-1.04168	0.57081
H	4.83324	2.56406	1.65790	C	-8.85261	-1.23240	-0.44670
H	-5.42601	2.54649	0.64860	C	-10.20071	-1.33810	-0.11853
H	0.69841	4.82598	2.22755	C	4.58639	4.22963	2.19309
H	3.18343	2.24421	2.21924	C	3.30074	4.45001	1.71481
H	2.14521	4.15370	2.98368	C	2.81465	3.80010	0.57507
				C	1.38758	4.09721	0.15921
				C	3.65507	2.89926	-0.09945
				C	4.96268	2.71227	0.36743
				C	5.42795	3.35954	1.50646
				C	7.54394	-4.05253	-0.38688
				C	7.55429	-2.88151	0.41749
				C	6.49167	-1.94291	0.30005
				C	5.46485	-2.21787	-0.64862
				C	5.47170	-3.35689	-1.40933
				C	6.52550	-4.29015	-1.27321
				C	6.49190	-0.78934	1.12763
				C	7.51004	-0.57650	2.02177
				C	8.57638	-1.50168	2.13238
1c-2							
M06-2X/6-31G(d) in chloroform (IEF-PCM)							
C	-0.96791	-1.62308	-1.00473				
N	0.15383	-0.96801	-0.64355				
O	-1.24470	-1.93939	-2.15381				
C	-1.86367	-1.88587	0.21508				
N	-1.97566	-0.63529	0.97296				
O	-0.92979	1.20868	1.82559				
C	-0.89336	0.13156	1.25423				
N	4.38957	-1.29079	-0.78126				
O	-5.59657	-2.24498	1.91640				
C	0.38259	-0.53744	0.74448				
N	3.36774	0.66294	-1.15228				

C	8.59475	-2.62753	1.35024	C	-0.51404	-0.23290	0.89039
H	-1.37264	-2.66189	0.81860	N	4.82486	-0.87000	-0.79569
H	0.59777	-1.41423	1.36987	O	-4.61353	-2.72096	-0.09669
H	-4.52095	0.47331	-2.70968	C	0.70822	-0.53040	0.04352
H	-1.23350	4.70109	-0.51027	N	3.83015	1.09028	-1.20746
H	-3.68293	4.58963	-0.06040	O	-7.23113	1.04808	-0.01716
H	-4.92814	2.50576	-0.70917	C	2.73723	0.16237	-0.99444
H	-1.21001	0.90343	-2.12395	N	-6.24366	-1.06952	-0.00495
H	-11.66313	-1.35868	1.46039	O	0.71984	3.02253	-1.64040
H	-9.97976	-1.03300	3.25684	C	1.67191	0.08904	-2.10960
H	-7.57712	-0.81895	2.68229	N	-4.93967	0.75184	-0.09692
H	-8.52382	-1.28638	-1.47775	O	6.14018	1.03895	-1.06248
H	-10.93164	-1.48103	-0.90775	C	1.90739	0.37480	0.29734
H	4.93312	4.74890	3.08125	N	-1.03520	2.90089	0.49737
H	2.64900	5.14911	2.23317	O	2.98345	-2.26913	-0.82615
H	0.53726	3.73238	-1.53830	C	-3.20352	-0.44533	-1.50453
H	5.63158	2.05731	-0.18335	C	-2.96185	-0.45148	0.96006
H	6.44664	3.19373	1.84433	C	-4.01443	-0.36745	-0.18368
H	8.35988	-4.76244	-0.28244	C	3.48384	-1.16820	-0.87482
H	4.66791	-3.53054	-2.11752	C	5.05126	0.50860	-1.02783
H	6.52252	-5.18896	-1.88035	C	3.70947	2.52373	-1.43637
H	5.67350	-0.07785	1.06235	C	-4.96136	-1.56254	-0.09062
H	7.49776	0.30714	2.65231	C	-6.24454	0.34689	-0.03848
H	9.37504	-1.31777	2.84384	C	-4.61298	2.14280	-0.39621
H	9.40434	-3.34738	1.43445	C	-1.13373	3.17752	1.79775
H	1.46292	-1.35022	-2.24941	C	-2.35800	3.23531	2.46172
H	1.28417	1.38930	0.44496	C	-3.51444	2.94084	1.75150
H	-3.59822	-3.14260	0.51221	C	-3.41935	2.60907	0.39817
H	-3.49625	0.78113	1.27369	C	-2.15532	2.63700	-0.18088
H	0.91757	0.34072	-2.12857	C	-9.70729	-3.44048	0.20740
H	2.21215	0.36161	1.55523	C	-8.58645	-3.76956	0.96630
H	-3.42853	-2.54448	-1.15158	C	-7.44176	-2.98068	0.90885
H	-3.57629	-0.65192	2.33818	C	-7.42392	-1.86582	0.07204
H	2.18840	2.31251	-1.59380	C	-8.53621	-1.53121	-0.69925
H	-3.12172	-0.48048	-2.20060	C	-9.67932	-2.31986	-0.61986
H	1.05612	4.98782	0.71097	C	2.78578	4.72868	2.15641
H	3.83976	2.38360	-2.19036	C	1.97154	4.86089	1.03459
H	0.72110	3.28055	0.47718	C	2.24555	4.16294	-0.14336

1c-3

M06-2X/6-31G(d) in chloroform (IEF-PCM)

C	-0.70906	-0.51498	-2.00701	C	4.18000	3.18980	0.93630
N	0.47344	-0.33509	-1.38878	C	3.89593	3.88907	2.10616
O	-0.88879	-0.32951	-3.20239	C	7.88290	-3.72807	-0.30448
C	-1.83408	-0.99123	-1.09360	C	6.90204	-3.59321	0.71317
N	-1.68526	-0.50177	0.27287	C	5.87760	-2.61440	0.57588
O	-0.42824	0.15769	2.04546	C	5.86360	-1.82819	-0.61363

C	4.40675	3.01944	2.83681	H	4.36761	2.87320	-1.25485
C	7.94073	-3.67355	-0.94629	H	0.24513	4.28374	0.86469
C	7.72605	-2.81801	0.16702				
C	6.62729	-1.91419	0.15273				
C	5.80332	-1.88575	-1.01057	1g-1			
C	6.02357	-2.72788	-2.06879	M06-2X/6-31G(d) in chloroform (IEF-PCM)			
C	7.10403	-3.64013	-2.03146	C	-0.60839	0.30862	-1.93278
C	6.39337	-1.09458	1.28843	N	0.54459	-0.10238	-1.37944
C	7.22503	-1.16009	2.37669	O	-0.75741	1.41298	-2.45217
C	8.33321	-2.04155	2.38487	C	-1.71325	-0.73999	-1.89518
C	8.57357	-2.85298	1.30646	N	-1.71451	-1.43091	-0.60888
H	-1.96314	-2.01972	-0.71194	O	-0.59454	-2.52792	1.03919
H	0.64164	-1.82953	0.37702	C	-0.59696	-1.82404	0.04277
H	-4.45314	2.48297	1.29637	N	4.91637	-0.20975	-0.12833
H	-1.56618	3.45043	-3.63040	O	-5.49344	-2.11974	-2.05206
H	-4.01261	3.37958	-4.12470	C	0.70477	-1.30293	-0.55474
H	-5.59790	2.84367	-2.25629	N	3.27207	1.12351	0.59417
H	-2.18560	2.65280	0.35647	O	-6.22999	1.11258	1.12668
H	-10.32958	-4.46565	1.11192	C	2.61202	0.14200	-0.24072
H	-10.28838	-2.34983	2.40925	N	-6.25544	-0.55538	-0.51504
H	-8.38467	-0.77649	2.16356	O	-0.37223	2.42672	0.16405
H	-6.57634	-3.41309	-0.69960	C	1.74338	0.72833	-1.37638
H	-8.46645	-4.99706	-0.44173	N	-4.30113	0.30291	0.15261
H	3.20990	3.91369	4.38945	O	5.42098	1.53866	1.33927
H	1.27916	4.32939	2.89846	C	1.67650	-0.82326	0.52246
H	-0.18886	2.72385	-0.86861	N	-1.76102	-0.89360	4.37296
H	5.35049	2.18772	1.08716	O	3.72682	-1.53539	-1.61529
H	5.25994	2.83114	3.48154	C	-3.13837	-0.17927	-2.02949
H	8.78067	-4.36231	-0.91824	C	-3.05503	-1.84925	-0.24346
H	5.36853	-2.68270	-2.93269	C	-3.93792	-0.71666	-0.81255
H	7.26977	-4.30321	-2.87394	C	3.79343	-0.65640	-0.78707
H	5.54017	-0.42339	1.30381	C	4.61337	0.90760	0.69391
H	7.03118	-0.53268	3.24114	C	2.60429	2.21907	1.28511
H	8.98520	-2.07604	3.25181	C	-5.30786	-1.24925	-1.23379
H	9.41498	-3.54065	1.30670	C	-5.64435	0.38478	0.35389
H	1.67247	-0.48016	-2.73652	C	-3.36366	1.12013	0.90095
H	1.70390	0.94761	0.94134	C	-3.07871	-0.82337	4.15070
H	-3.92672	-1.16394	-1.75938	C	-3.64725	-0.18515	3.05427
H	-2.99209	0.94265	1.70765	C	-2.80344	0.41992	2.12119
H	1.30952	1.15263	-2.12406	C	-1.43291	0.36042	2.34639
H	2.47386	-0.60945	1.31993	C	-10.41028	-1.07628	-0.86920
H	-3.33335	0.49310	-1.68410	C	-9.56598	-2.18399	-0.85549
H	-3.15450	-0.76554	2.12958	C	-8.19030	-2.01956	-0.72652
H	2.60664	2.73435	-1.37708	C	-7.66498	-0.73209	-0.62606
H	-5.88613	2.70812	0.28510	C	-8.49941	0.38506	-0.64651
H	1.28426	4.41439	-0.55997	C	-9.87379	0.20488	-0.76048
				C	2.50340	5.87650	-1.02266
				C	1.32407	5.36487	-0.49027

C	1.31642	4.18317	0.25470	H	9.87768	-1.81934	-1.07878
C	-0.00391	3.65733	0.77513	H	6.87283	1.25608	-1.04760
C	2.52527	3.49895	0.46404	H	9.21495	0.52949	-1.49256
C	3.70634	4.02072	-0.06862	H	4.66437	-2.65536	0.67256
C	3.70010	5.19946	-0.80902	H	5.36661	-4.96353	1.09820
C	8.86220	-1.48761	-0.88031	H	7.69002	-5.69498	0.58696
C	7.92734	-2.42776	-0.37301	H	9.31967	-4.08011	-0.33655
C	6.59172	-2.01696	-0.09743				
C	6.24739	-0.66169	-0.37260				
C	7.16993	0.22975	-0.85890				
C	8.49603	-0.18677	-1.10952				
C	5.67906	-2.96132	0.44228				
C	6.07338	-4.25253	0.68246				
C	7.39609	-4.66811	0.39426				
C	8.29974	-3.77491	-0.11857				
C	-0.96660	-0.30718	3.47730				
H	0.10314	-0.37753	3.66765				
H	-1.50956	-1.45190	-2.70779				
H	1.16141	-2.10807	-1.14603				
H	2.25190	0.67146	-2.34368				
H	1.48028	1.76623	-1.17352				
H	1.12664	-0.26610	1.28690				
H	2.20925	-1.64113	1.01077				
H	-3.59715	-0.52895	-2.95565				
H	-3.12985	0.91300	-2.04164				
H	-3.13997	-1.96245	0.83854				
H	-3.31569	-2.79441	-0.73741				
H	3.17653	2.40449	2.19921				
H	1.61004	1.87286	1.57688				
H	-3.91162	2.01649	1.20771				
H	-2.54786	1.43783	0.24252				
H	-3.71479	-1.30214	4.89189				
H	-4.72660	-0.15317	2.93305				
H	-0.75039	0.82102	1.63658				
H	-11.48296	-1.21108	-0.96467				
H	-9.97744	-3.18465	-0.93961				
H	-7.52750	-2.87678	-0.71214				
H	-8.07339	1.37787	-0.56398				
H	-10.52529	1.07265	-0.77094				
H	2.48692	6.79573	-1.59947				
H	0.38513	5.88733	-0.65584				
H	-0.48530	2.55654	-0.79572				
H	-0.78280	4.41403	0.62284				
H	0.04127	3.44960	1.84899				
H	4.64442	3.50474	0.11793				
H	4.62978	5.58877	-1.21216				
				1g-2			
				M06-2X/6-31G(d) in chloroform (IEF-PCM)			
				C	-0.89752	-1.11926	-1.70437
				N	0.27159	-0.86824	-1.08429
				O	-1.06455	-1.01366	-2.91229
				C	-2.01044	-1.49569	-0.71596
				N	-1.96860	-0.55373	0.40547
				O	-0.73721	0.67774	1.86186
				C	-0.81012	-0.16953	0.98471
				N	4.63899	-1.11287	-0.92617
				O	-4.74800	-2.42517	1.16456
				C	0.40693	-0.87660	0.37935
				N	3.48337	0.80149	-0.91062
				O	-7.50280	0.61391	-0.89130
				C	2.49595	-0.23053	-0.68246
				N	-6.43406	-1.04877	0.35265
				O	1.05516	4.39331	-0.58449
				C	1.41454	-0.30645	-1.77859
				N	-5.20125	0.38503	-0.85534
				O	5.77064	0.89685	-1.26365
				C	1.71396	-0.13438	0.64373
				N	-1.67940	3.94983	-1.13863
				O	2.92503	-2.62614	-0.52404
				C	-3.40606	-1.33924	-1.31495
				C	-3.22479	0.11146	0.69418
				C	-4.23809	-0.54032	-0.28315
				C	3.34025	-1.50346	-0.69460
				C	4.73907	0.29463	-1.06280
				C	3.22581	2.23590	-0.82438
				C	-5.13706	-1.48480	0.51242
				C	-6.49127	0.06417	-0.52032
				C	-4.94054	1.26402	-1.98910
				C	-1.49529	2.85817	-1.88374
				C	-2.51677	1.96995	-2.20912
				C	-3.79863	2.21844	-1.72113
				C	-3.99394	3.35677	-0.93892
				C	-9.78322	-2.82586	2.16289
				C	-8.61831	-2.61678	2.89725
				C	-7.51156	-2.01922	2.30308

C	-7.57719	-1.64582	0.96163	H	0.13730	4.56780	-0.87965
C	-8.73346	-1.85787	0.21328	H	0.21043	4.01782	1.28027
C	-9.83830	-2.44242	0.82473	H	0.48872	2.59655	0.28330
C	3.62334	3.67568	3.22814	H	5.38719	2.16410	0.75544
C	2.41765	3.83956	2.55371	H	5.64660	2.94306	3.08904
C	2.25253	3.39498	1.23954	H	8.87025	-4.29558	-0.76938
C	0.91442	3.57611	0.56252	H	5.26662	-2.94817	-2.69717
C	3.33291	2.77385	0.59340	H	7.24395	-4.47491	-2.62243
C	4.54698	2.62426	1.27002	H	5.58153	-0.31613	1.30838
C	4.69503	3.06699	2.58080	H	7.19990	-0.17604	3.14039
C	7.99795	-3.64860	-0.80221	H	9.22392	-1.62743	3.15725
C	7.81046	-2.70626	0.24405	H	9.60074	-3.24658	1.32896
C	6.67010	-1.85605	0.22382				
C	5.77726	-1.96878	-0.88116				
C	5.97408	-2.88943	-1.87639				
C	7.09760	-3.74738	-1.83135				
C	6.46577	-0.94687	1.29519				
C	7.36784	-0.87361	2.32571				
C	8.51638	-1.70212	2.33768				
C	8.72785	-2.59956	1.32306				
C	-2.91203	4.18971	-0.67865				
H	-3.03503	5.08659	-0.07783				
H	-1.83811	-2.51884	-0.35705				
H	0.45060	-1.91168	0.74183				
H	1.70936	-0.93627	-2.62201				
H	1.18493	0.69527	-2.16321				
H	1.49930	0.90826	0.88277				
H	2.27281	-0.55755	1.48093				
H	-3.86338	-2.30624	-1.52998				
H	-3.32966	-0.79753	-2.25955				
H	-3.13780	1.18765	0.52503				
H	-3.51013	-0.04779	1.73844				
H	2.24380	2.44781	-1.25321				
H	3.96677	2.72191	-1.46539				
H	-5.86902	1.81437	-2.15662				
H	-4.73338	0.67687	-2.89150				
H	-0.48031	2.69316	-2.24213				
H	-2.29762	1.10551	-2.83038				
H	-4.97416	3.58920	-0.53316				
H	-10.64602	-3.28764	2.63201				
H	-8.56933	-2.91321	3.94003				
H	-6.60157	-1.84811	2.86692				
H	-8.76448	-1.55971	-0.82782				
H	-10.74309	-2.60521	0.24793				
H	3.72645	4.02844	4.24958				
H	1.58102	4.31972	3.05418				
				1g-3			
				M06-2X/6-31G(d) in chloroform (IEF-PCM)			
				C	-0.48964	-0.02008	-1.19871
				N	0.71259	-0.43376	-0.76554
				O	-0.63913	0.97200	-1.91075
				C	-1.68041	-0.84671	-0.75466
				N	-1.48643	-1.43999	0.56890
				O	-0.19121	-2.12594	2.28823
				C	-0.29776	-1.69806	1.14734
				N	5.17711	-0.32639	-0.07674
				O	-4.12287	-2.73884	-1.01920
				C	0.93679	-1.40572	0.30926
				N	3.63842	1.13272	0.63354
				O	-7.09649	-0.11028	1.29172
				C	2.87365	0.01814	0.11281
				N	-5.90583	-1.65164	-0.00452
				O	-0.14126	2.11688	0.74225
				C	1.89483	0.38047	-1.02809
				N	-4.79193	-0.09200	1.14925
				O	5.86881	1.69570	0.86860
				C	2.00854	-0.71580	1.15450
				N	-4.46699	4.72324	-0.46010
				O	3.79753	-1.96514	-0.96432
				C	-2.92503	0.01230	-0.55169
				C	-2.71497	-1.50161	1.34841
				C	-3.76326	-0.81977	0.43823
				C	3.97286	-0.91177	-0.39607
				C	4.98330	0.94244	0.52807
				C	3.07255	2.31401	1.26950
				C	-4.57954	-1.87510	-0.30580
				C	-6.04718	-0.55111	0.87608
				C	-4.56974	1.11612	1.92403
				C	-5.46744	3.84258	-0.56252
				C	-5.54696	2.66988	0.18093

C	-4.52569	2.37802	1.08469	H	-6.01546	-4.29398	-0.17841
C	-3.47623	3.28686	1.19763	H	-8.19196	-0.67455	-0.94134
C	-9.12053	-3.89814	-1.51140	H	-10.09270	-2.00189	-1.82544
C	-7.97322	-4.54081	-1.05224	H	1.86319	6.22029	-2.26299
C	-6.91034	-3.80217	-0.54218	H	0.10928	5.36263	-0.74272
C	-7.00150	-2.41184	-0.50963	H	-0.38547	2.14215	-0.20113
C	-8.14017	-1.75643	-0.97482	H	-0.57192	4.12950	1.05644
C	-9.20177	-2.50804	-1.46784	H	0.57259	3.36709	2.15940
C	2.09978	5.43690	-1.54993	H	4.68145	3.49592	-0.50255
C	1.11602	4.95434	-0.69233	H	4.16413	5.28064	-2.14477
C	1.39333	3.94664	0.23503	H	9.92363	-2.13834	-1.58950
C	0.27176	3.42905	1.10991	H	6.86484	0.88323	-1.65542
C	2.68977	3.41024	0.28992	H	9.10700	0.06186	-2.37458
C	3.67508	3.90305	-0.56813	H	5.19327	-2.50632	1.31314
C	3.38614	4.90881	-1.48534	H	6.05167	-4.66301	2.10145
C	8.95493	-1.76264	-1.27181	H	8.25315	-5.51401	1.30967
C	8.17330	-2.55577	-0.39132	H	9.60560	-4.16941	-0.26303
C	6.90317	-2.08216	0.04530				
C	6.45791	-0.82547	-0.45740				
C	7.23439	-0.07389	-1.30262				
C	8.50271	-0.54444	-1.70835				
C	6.15209	-2.86828	0.95844				
C	6.63452	-4.07306	1.40125				
C	7.88821	-4.55605	0.95340				
C	8.63855	-3.81239	0.08060				
C	-3.49807	4.43755	0.41162				
H	-2.69493	5.16816	0.48895				
H	-1.86707	-1.63077	-1.49951				
H	1.31900	-2.34546	-0.10725				
H	2.31343	0.15594	-2.01350				
H	1.62552	1.43805	-0.99600				
H	1.52189	0.01890	1.80247				
H	2.57717	-1.41212	1.77252				
H	-3.45333	0.23970	-1.47883				
H	-2.63089	0.95293	-0.07389				
H	-2.58577	-0.95534	2.28855				
H	-2.98434	-2.53390	1.58949				
H	3.83863	2.68575	1.95645				
H	2.21542	1.99905	1.86662				
H	-3.63800	1.00451	2.48728				
H	-5.38836	1.18082	2.64688				
H	-6.25162	4.08945	-1.27466				
H	-6.39837	2.00540	0.06776				
H	-2.64727	3.09855	1.87499				
H	-9.94958	-4.47904	-1.90272				
H	-7.90375	-5.62330	-1.08384				
				1g-4			
				M06-2X/6-31G(d) in chloroform (IEF-PCM)			
				C	0.53628	-1.35669	1.44836
				N	-0.64355	-1.43022	0.80200
				O	0.63958	-1.10606	2.64073
				C	1.77147	-1.61946	0.60742
				N	1.57092	-1.46300	-0.83685
				O	0.25278	-0.92032	-2.59048
				C	0.37380	-1.33523	-1.44091
				N	-5.12116	-0.40972	0.77227
				O	4.54823	-2.93068	-0.06053
				C	-0.83801	-1.72681	-0.61004
				N	-3.21674	0.73400	0.54854
				O	6.83068	1.00842	-0.69044
				C	-2.83698	-0.65296	0.35120
				N	6.03429	-1.17077	-0.36089
				O	0.64933	1.32786	-0.70688
				C	-1.90739	-1.19886	1.46971
				N	4.58144	0.51657	-0.56835
				O	-5.11152	1.88944	1.19497
				C	-2.09085	-0.91854	-0.98048
				N	4.12149	4.18931	2.99920
				O	-4.37281	-2.54443	0.26444
				C	2.86874	-0.59994	0.91126
				C	2.76298	-0.94611	-1.50030
				C	3.75160	-0.64845	-0.34864
				C	-4.18699	-1.36287	0.43626
				C	-4.52832	0.87534	0.87955
				C	-2.27111	1.83973	0.57275

C	4.79358	-1.75823	-0.23234	H	3.22738	5.67962	1.88870
C	5.91486	0.22926	-0.55999	H	3.20142	4.40806	-0.23836
C	4.09780	1.87568	-0.66041	H	5.07336	1.15615	1.87634
C	3.62832	4.66927	1.85254	H	10.63717	-3.76015	-0.11963
C	3.60842	3.95427	0.66128	H	10.28870	-2.00431	-1.83952
C	4.12462	2.65759	0.63936	H	8.12735	-0.79192	-1.95886
C	4.64897	2.15388	1.82473	H	6.66875	-3.06244	1.37906
C	9.69346	-3.22650	-0.16910	H	8.82018	-4.29075	1.48748
C	9.49850	-2.24075	-1.13419	H	-2.11153	4.66917	-4.03941
C	8.28858	-1.55768	-1.20930	H	-0.00873	4.12823	-2.84688
C	7.27947	-1.86115	-0.29710	H	0.49249	1.05649	-1.62927
C	7.46532	-2.83987	0.67842	H	0.34811	2.94393	0.46821
C	8.67456	-3.52528	0.73225	H	1.13877	3.31822	-1.06506
C	-2.14125	4.09657	-3.11797	H	-4.33361	2.61269	-0.99984
C	-0.96185	3.79261	-2.44534	H	-4.28506	3.89488	-3.10445
C	-0.97418	3.05831	-1.25736	H	-10.19257	-1.36970	1.97671
C	0.34408	2.71801	-0.60207	H	-6.26598	0.00083	3.07548
C	-2.20054	2.61285	-0.73654	H	-8.65112	-0.43061	3.67070
C	-3.38037	2.92806	-1.41256	H	-5.90205	-1.20599	-1.55838
C	-3.35486	3.66143	-2.59598	H	-7.47005	-2.09471	-3.22391
C	-9.15459	-1.16613	1.72811	H	-9.82873	-2.59263	-2.60065
C	-8.70585	-1.44201	0.40989	H	-10.61594	-2.16548	-0.29787
C	-7.35110	-1.17927	0.05638				
C	-6.49156	-0.66701	1.07051				
C	-6.95039	-0.40045	2.33534				
C	-8.30140	-0.64698	2.66690				
C	-6.92711	-1.42257	-1.27663				
C	-7.80516	-1.91665	-2.20696				
C	-9.14794	-2.19675	-1.85387				
C	-9.58551	-1.96206	-0.57671				
C	4.62117	2.95357	2.96654				
H	5.02401	2.57313	3.90239				
H	2.12502	-2.63466	0.82584				
H	-1.02089	-2.80155	-0.75062				
H	-2.30618	-2.13812	1.87110				
H	-1.77564	-0.48862	2.28842				
H	-1.79697	0.03691	-1.42270				
H	-2.71542	-1.44867	-1.70111				
H	3.41271	-0.82757	1.82954				
H	2.41938	0.39513	0.99481				
H	2.51114	-0.03202	-2.04532				
H	3.16544	-1.67015	-2.21429				
H	-1.29227	1.42281	0.82717				
H	-2.57423	2.51233	1.38261				
H	3.06668	1.83772	-1.03034				
H	4.70225	2.39960	-1.40779				
				15b-1			
				ONIOM(B3LYP/6-31G(d):PM6)			
				C	4.98068	-2.17065	-1.07658
				N	3.95273	-1.39394	-1.60047
				O	4.75624	-3.19086	-0.44470
				C	6.40081	-1.70019	-1.43999
				N	6.51935	-0.21636	-1.40315
				O	5.49111	1.82060	-1.28466
				C	5.42548	0.63463	-1.54426
				N	10.88025	-1.25734	-0.29773
				O	11.18721	-0.90983	2.04336
				C	4.17497	-0.03202	-2.15549
				N	9.05803	-1.01479	1.08191
				O	9.76263	-1.57472	-2.34093
				C	7.45129	-2.22102	-0.44379
				N	7.96936	3.48528	3.28629
				O	0.32519	-1.01139	-2.79109
				C	7.77818	0.22163	-0.74352
				N	1.64044	0.23515	0.25121
				O	0.61829	1.66092	1.69161
				C	8.47881	-1.08230	-0.28036
				N	-0.33035	0.87667	-1.70773
				O	-2.87348	5.56144	0.18270
				C	1.89549	-0.19213	-1.14141

N	-1.76935	3.61736	-0.15120	C	-11.05901	-2.39532	-0.64614
O	-8.12004	0.83053	2.35242	C	-11.45659	-3.22029	-1.84228
C	2.52548	-1.60918	-1.25401	C	-1.15653	4.72622	-2.30066
N	-6.42344	1.10123	0.81602	C	-5.19404	-0.71261	-2.21873
O	-2.07645	5.71716	-2.32552	C	-6.69333	-2.61096	-2.05698
C	2.89755	0.76838	-1.84981	C	-5.14154	0.68388	-2.39325
N	-8.21202	-0.26770	0.32449	C	-3.87775	1.26009	-2.53930
O	-0.74842	4.29127	-3.35147	C	-4.73876	3.49808	-2.97923
C	9.74641	-1.34477	-1.16266	C	-2.68513	0.48334	-2.51762
O	-6.48394	-1.17381	-2.03980	C	-2.80135	-0.89760	-2.36283
C	10.47088	-1.03140	1.08015	C	-4.05011	-1.51214	-2.19443
O	-3.64326	2.60145	-2.65962	C	0.94009	-3.90608	3.24313
C	8.27155	-0.75659	2.29932	C	2.25355	-3.48683	3.45934
O	5.02684	-1.95612	1.96267	C	2.75920	-2.33105	2.85305
C	6.90663	2.78008	2.88619	C	4.19501	-1.93438	3.13063
C	6.95307	1.42312	2.55177	C	1.92767	-1.57445	1.99791
C	8.17066	0.74541	2.63314	C	0.61441	-2.00501	1.79076
C	14.92218	-1.68816	-1.50974	C	0.11828	-3.15846	2.40460
C	14.61621	-1.05445	-0.30118	C	9.28480	1.47637	3.05171
C	13.28990	-0.90732	0.10906	F	-12.14869	-2.23647	3.63099
C	9.13406	2.82856	3.36243	F	-13.75630	-1.50563	2.36413
C	12.26115	-1.40878	-0.70683	F	-12.36253	-0.10347	3.28023
C	12.55705	-2.04992	-1.92205	F	-11.95824	-2.45008	-2.83381
C	13.89092	-2.18174	-2.31429	F	-12.39509	-4.13765	-1.53504
C	2.48318	-0.28258	1.35821	F	-10.39535	-3.88175	-2.36365
C	0.72024	1.24071	0.55204	H	6.63517	-2.05453	-2.48427
C	-0.17680	1.82567	-0.58030	H	4.33648	-0.11449	-3.26673
C	-1.35791	1.14270	-2.76669	H	7.91404	-3.16135	-0.79776
C	0.56088	-0.17070	-1.93966	H	6.98235	-2.47703	0.53423
C	-1.55223	2.16495	0.06786	H	8.38926	0.79419	-1.47926
C	-0.66444	4.25445	-0.90942	H	7.56687	0.92035	0.09978
C	0.43158	3.18216	-1.03697	H	2.04044	-2.18628	-2.08673
C	-2.79776	4.35466	0.42296	H	2.41897	-2.23715	-0.34100
C	-5.69276	2.32765	2.84881	H	2.47421	1.18342	-2.78500
C	-5.60711	2.04225	1.47353	H	3.13088	1.65485	-1.21944
C	-4.64448	2.70304	0.69829	H	7.25868	-1.19446	2.18236
C	-3.78093	3.62788	1.28380	H	8.77698	-1.27788	3.14808
C	-3.86407	3.92367	2.64386	H	5.96410	3.32568	2.82661
C	-4.82703	3.26291	3.41186	H	6.04979	0.90787	2.23486
C	-7.62869	0.57878	1.26157	H	15.95881	-1.79647	-1.82242
C	-11.93630	-2.25012	0.42644	H	15.41737	-0.66937	0.33024
C	-11.55695	-1.42999	1.48901	H	13.06796	-0.41834	1.06112
C	-12.45978	-1.31334	2.69252	H	9.99298	3.41373	3.69235
C	-10.33635	-0.75721	1.49855	H	11.76275	-2.43384	-2.56617
C	-9.45696	-0.90846	0.41310	H	14.12448	-2.67541	-3.25792
C	-9.83198	-1.73625	-0.65529	H	3.51670	-0.45406	1.00203

H	2.54102	0.50621	2.15267	H	6.80117	0.87265	2.38452
H	-1.47402	2.24989	-2.89006	H	5.14499	1.36717	2.02483
H	-0.95072	0.76717	-3.74283	C	5.58171	0.18921	-0.72420
H	-1.54792	1.94763	1.16678	H	6.17246	-0.17454	-1.59466
H	-2.38577	1.57568	-0.37369	H	4.68292	0.70075	-1.13744
H	-0.28782	5.15647	-0.35193	C	6.39501	1.11957	0.21898
H	1.30676	3.45902	-0.41692	C	1.55685	-3.10241	1.36118
H	0.80728	3.12452	-2.08298	C	2.33949	-2.61423	2.60879
H	-6.43935	1.82909	3.45268	H	2.40786	-3.44392	3.36212
H	-6.14384	0.89423	-0.13748	H	1.87582	-1.75293	3.14344
H	-4.58255	2.50043	-0.37289	C	2.68066	-3.71877	0.47541
H	-3.20229	4.66106	3.09407	H	2.78038	-4.80431	0.67594
H	-4.90980	3.47817	4.47484	H	2.46439	-3.62819	-0.61613
H	-7.69308	-0.45494	-0.53104	O	3.95245	-0.38208	3.37193
H	-12.89026	-2.76201	0.43403	O	4.04912	-2.13234	-1.44891
H	-10.05993	-0.12082	2.32610	C	7.92096	0.83961	-0.00227
H	-9.15643	-1.86916	-1.50150	N	8.48901	2.03873	-0.53517
H	-2.39367	6.05453	-1.40344	C	7.50888	3.10026	-0.58627
H	-6.22397	-3.07039	-1.18220	N	6.24836	2.54366	-0.18235
H	-6.32082	-3.03820	-2.99383	C	5.28246	3.46415	0.45191
H	-7.79259	-2.67990	-2.00785	H	5.37693	3.45016	1.55807
H	-6.05691	1.25760	-2.48015	H	5.52890	4.50430	0.11796
H	-4.19660	4.45381	-3.09856	N	1.10936	2.78617	-0.57539
H	-5.44890	3.54625	-2.15066	C	2.06579	2.69488	-1.51158
H	-5.21369	3.19892	-3.91746	H	1.73126	2.45098	-2.51924
H	-1.89330	-1.51511	-2.38314	O	7.67994	4.24270	-0.92557
H	-4.10276	-2.58781	-2.06626	C	3.42058	2.89091	-1.24328
H	0.56761	-4.80727	3.72424	H	4.15063	2.81911	-2.04855
H	2.90266	-4.06687	4.11321	O	8.50483	-0.18440	0.22092
H	4.61096	-2.59328	3.90707	C	3.82348	3.18134	0.06362
H	4.26352	-0.90865	3.50835	C	12.51051	2.46800	-1.81513
H	4.88371	-2.81490	1.51570	H	13.54267	2.57647	-2.14381
H	-0.04371	-1.42784	1.14417	C	11.93494	1.19740	-1.71833
H	-0.90860	-3.46635	2.22397	H	12.52068	0.31281	-1.97084
H	10.26220	0.99606	3.14002	C	10.61092	1.04643	-1.30048

15b-2

ONIOM(B3LYP/6-31G(d):PM6)

N	3.71245	-2.29204	2.12858	H	0.70033	3.17339	1.41185
C	4.33007	-1.07316	2.44554	C	9.86319	2.19047	-0.97362
C	5.54984	-0.73956	1.56529	C	10.43111	3.47202	-1.06465
H	6.40487	-1.41734	1.84568	H	9.85223	4.36718	-0.82335
N	5.18942	-0.95464	0.13727	C	11.75558	3.59891	-1.48900
C	4.38219	-2.00295	-0.28716	H	12.20024	4.59185	-1.56510
C	3.98354	-2.98798	0.83523	N	0.79756	-2.05297	0.63675
H	4.83008	-3.71179	0.98426	C	1.11278	-0.60597	0.77979
C	5.98167	0.73623	1.65422	H	2.18532	-0.48063	1.02457

H	0.96461	-0.12028	-0.21205	C	-4.78012	4.16597	-0.79079
C	-0.07768	-2.44455	-0.38242	C	-6.08066	4.60278	-1.09254
C	-0.51940	-3.93765	-0.46916	H	-6.73399	3.97175	-1.67735
N	-0.43834	-4.57338	0.86555	C	-6.50840	5.84904	-0.63459
C	-1.35384	-5.70458	1.23554	C	-7.92441	6.28396	-0.91506
H	-1.64732	-6.25309	0.30718	F	-8.02765	7.63025	-0.99619
H	-0.76541	-6.42619	1.85984	F	-8.76783	5.88553	0.06603
C	0.55031	-4.21487	1.77919	F	-8.39441	5.77052	-2.07078
O	0.65204	-4.76791	2.86136	C	-0.61866	-6.22891	-3.27700
O	-0.51192	-1.62799	-1.18113	O	-1.18558	-6.38985	-4.49798
C	-1.94813	-3.94775	-1.09695	H	-1.47783	-5.52269	-4.95873
H	-2.51015	-3.01325	-0.88372	O	-0.28833	-7.20715	-2.65358
H	-2.56979	-4.80019	-0.71830	C	-4.81055	-4.44398	3.47189
N	-1.73337	-4.14681	-2.55142	O	-5.99260	-4.09380	4.07129
C	-0.40870	-4.76817	-2.81763	C	-5.93877	-3.49845	5.39264
H	0.12330	-4.21441	-3.64172	H	-7.00344	-3.33189	5.60487
C	0.37349	-4.68715	-1.49939	H	-5.39188	-2.55189	5.35999
H	1.34972	-4.18061	-1.65180	H	-5.50098	-4.20138	6.10726
H	0.61503	-5.71236	-1.13132	C	-5.00255	-5.01765	2.19910
C	-2.41113	-3.51556	-3.59926	H	-6.01129	-5.13755	1.81911
O	-2.06724	-3.80415	-4.74527	C	-3.86880	-5.40927	1.49163
C	-5.67441	-0.83103	-2.92474	O	-3.89459	-5.98648	0.24203
H	-6.49144	-0.13512	-2.78993	C	-5.18278	-6.26072	-0.36673
C	-4.36179	-0.41590	-2.63018	H	-4.88520	-6.74368	-1.30764
N	-4.04165	0.86005	-2.13739	H	-5.72015	-5.32574	-0.54900
H	-3.05649	1.03192	-1.96293	H	-5.75805	-6.94805	0.26120
C	-3.30301	-1.32189	-2.81995	C	-2.55600	-5.24144	2.00582
H	-2.27426	-1.01547	-2.59979	C	-2.42394	-4.68286	3.28197
C	-3.55703	-2.60609	-3.29789	H	-1.42011	-4.56975	3.71121
C	-4.85612	-3.02274	-3.59506	C	-3.53371	-4.27208	4.02436
H	-5.04211	-4.01700	-3.99578	H	-3.39273	-3.83848	5.00731
C	-5.90355	-2.12189	-3.39751	C	-1.05495	1.62699	3.86292
H	-6.92402	-2.41949	-3.62791	H	-1.57501	2.19695	4.62882
C	-4.90961	1.90636	-1.84218	C	-1.60445	1.49467	2.59178
N	-4.24069	2.95043	-1.22016	H	-2.55431	1.97195	2.36133
H	-3.27121	2.77886	-0.94526	C	-0.95828	0.76463	1.58070
O	-6.10843	1.90106	-2.09160	C	-1.63574	0.73979	0.22634
C	-5.67835	6.67954	0.11805	H	-2.68785	0.46892	0.35066
H	-6.02106	7.65140	0.45155	H	-1.18774	-0.01102	-0.43961
C	-4.38960	6.23658	0.41675	O	-1.64628	2.01876	-0.42694
C	-3.49174	7.08016	1.28127	H	-0.71262	2.29167	-0.61801
F	-3.74162	8.39869	1.13403	C	0.27646	0.14253	1.85207
F	-2.18311	6.88065	0.99911	C	0.81809	0.29607	3.13762
F	-3.65222	6.79461	2.59590	H	1.79002	-0.15590	3.36676
C	-3.94121	4.99655	-0.02822	C	0.17152	1.01951	4.13621
H	-2.93381	4.66737	0.20716	H	0.62880	1.11122	5.11858

C	2.82387	3.28906	1.03293
H	3.06612	3.52240	2.06669

15b-substrate complex

ONIOM(B3LYP/6-31G(d):PM6)

N	-4.35821	2.23397	1.73613
C	-4.92898	1.08971	2.30745
C	-6.17492	0.58908	1.55191
H	-7.01986	1.31679	1.71521
N	-5.86156	0.51034	0.09826
C	-5.05458	1.43969	-0.54832
C	-4.65344	2.64496	0.33267
H	-5.51438	3.36862	0.34280
C	-6.60921	-0.83282	1.95012
H	-7.39649	-0.81295	2.72629
H	-5.75875	-1.38800	2.40146
C	-6.28674	-0.78066	-0.49979
H	-6.89669	-0.59489	-1.41175
H	-5.40507	-1.38147	-0.81916
C	-7.08469	-1.48297	0.63511
C	-2.25903	3.09599	0.87004
C	-3.03172	2.74459	2.16920
H	-3.19299	3.66947	2.78683
H	-2.50447	2.01488	2.83333
C	-3.37570	3.31933	-0.19484
H	-3.55587	4.40017	-0.35917
H	-3.09338	2.90948	-1.18848
O	-4.50006	0.59740	3.33252
O	-4.73372	1.31539	-1.71402
C	-8.61232	-1.21338	0.41479
N	-9.22569	-2.48182	0.16719
C	-8.26727	-3.55682	0.29839
N	-6.98230	-2.96152	0.52561
C	-5.99521	-3.75754	1.28479
H	-6.08968	-3.58206	2.37702
H	-6.22092	-4.83925	1.10624
N	-1.86152	-3.09421	0.11810
C	-2.80046	-3.34452	-0.80568
H	-2.45782	-3.37626	-1.83860
O	-8.47345	-4.74000	0.20907
C	-4.14266	-3.55397	-0.49078
H	-4.86163	-3.76774	-1.28083
O	-9.16820	-0.15047	0.43935
C	-4.54859	-3.48969	0.84574
C	-13.30749	-3.06019	-0.83260
H	-14.35510	-3.20693	-1.08934
C	-12.70676	-1.81195	-1.02256

H	-13.28831	-0.98291	-1.42721
C	-11.36286	-1.61285	-0.69912
H	-10.91101	-0.62936	-0.84488
C	-2.24448	-3.05265	1.40034
H	-1.46307	-2.85432	2.12984
C	-10.62013	-2.68449	-0.17481
C	-11.21339	-3.94252	0.02257
H	-10.63920	-4.78386	0.41897
C	-12.55760	-4.11944	-0.31215
H	-13.02183	-5.09509	-0.16422
N	-1.30040	2.05558	0.43123
C	-1.56139	0.61100	0.69139
H	-2.61558	0.47076	1.00158
H	-1.44119	0.05441	-0.26321
C	-0.29605	2.37443	-0.48484
C	-0.00230	3.86434	-0.82728
N	-0.47808	4.78497	0.22708
C	0.00870	6.20837	0.24613
H	0.31050	6.50198	-0.79279
H	-0.86245	6.85999	0.51513
C	-1.51304	4.44615	1.08973
O	-1.88366	5.21021	1.96715
O	0.35601	1.49627	-1.02632
C	1.53712	3.96239	-1.06060
H	2.07785	3.08105	-0.64318
H	1.98868	4.86870	-0.59185
N	1.70847	4.04403	-2.53151
C	0.44944	4.42704	-3.21441
H	0.30272	3.80513	-4.14060
C	-0.67507	4.18869	-2.19564
H	-1.33260	3.36615	-2.53384
H	-1.32698	5.08735	-2.11649
C	2.81334	3.60554	-3.25888
O	2.81262	3.78760	-4.47506
C	6.09703	1.90614	-1.10166
H	6.92779	1.47324	-0.56151
C	5.04696	1.07528	-1.53551
N	5.01389	-0.31560	-1.32509
H	4.24784	-0.80675	-1.77615
C	3.96621	1.64721	-2.23065
H	3.14288	1.01411	-2.56730
C	3.95162	3.01631	-2.48937
C	4.99284	3.84548	-2.06873
H	4.97730	4.91053	-2.28789
C	6.05793	3.27239	-1.37349
H	6.88293	3.89545	-1.03516

H	3.45465	3.64866	-3.13705	O	1.99682	5.19004	-2.47169
H	2.75136	2.00643	-3.04863	O	0.01997	1.76340	0.94831
C	3.71212	3.57737	-0.17758	C	-1.00914	4.28555	1.14924
H	3.93983	4.66493	-0.19701	H	-1.70966	3.55704	0.68420
H	3.44717	3.35346	0.88294	H	-1.41666	5.31142	0.95743
O	4.81344	0.60271	-3.54110	N	-0.90623	4.09683	2.62186
O	4.88290	1.56835	1.49888	C	0.49402	4.29740	3.09233
C	8.59560	-1.45284	-0.26309	H	0.85615	3.38549	3.64975
N	9.01044	-2.79137	0.01612	C	1.33418	4.53658	1.82906
C	7.93778	-3.73103	-0.21428	H	2.29094	3.97365	1.87345
N	6.77055	-2.97652	-0.54957	H	1.62990	5.60759	1.74135
C	5.74789	-3.62722	-1.38972	C	-1.81436	3.38203	3.40067
H	5.81008	-3.28791	-2.44588	O	-1.53710	3.17944	4.58735
H	5.92814	-4.73014	-1.39262	C	-5.60471	2.27607	1.75440
N	1.69713	-2.98532	-0.03099	H	-6.56818	1.99210	1.35289
C	2.67714	-3.13555	0.87506	C	-4.61070	1.29196	1.92580
H	2.38340	-3.07010	1.91719	N	-4.77667	-0.05945	1.58708
O	7.98935	-4.93191	-0.10047	H	-3.95187	-0.65202	1.69011
C	3.99633	-3.34946	0.49033	C	-3.36242	1.67389	2.45635
H	4.76221	-3.47315	1.25209	H	-2.58959	0.92034	2.60905
O	9.29087	-0.47545	-0.19787	C	-3.12672	3.00541	2.79385
C	4.31972	-3.39119	-0.87057	C	-4.10931	3.98485	2.62805
C	12.86168	-3.91278	1.37683	H	-3.92173	5.01890	2.90962
H	13.85314	-4.20000	1.72756	C	-5.34572	3.59983	2.10667
C	12.33668	-2.66043	1.71155	H	-6.13065	4.34118	1.96968
H	12.92024	-1.97003	2.32370	C	-5.92671	-0.67790	1.12615
C	11.06632	-2.28295	1.27037	N	-5.71220	-2.01930	0.84451
H	10.66537	-1.30256	1.53288	H	-4.76026	-2.36654	0.96650
C	1.98062	-3.06349	-1.34104	O	-7.00920	-0.11198	0.98083
H	1.14390	-2.94346	-2.02149	C	-8.37025	-4.93458	-0.66249
C	10.32648	-3.17864	0.48072	H	-9.03636	-5.69708	-1.04530
C	10.84321	-4.43780	0.13504	C	-7.03754	-5.22688	-0.37616
H	10.26416	-5.13545	-0.47285	C	-6.48271	-6.60356	-0.62473
C	12.11343	-4.79636	0.59237	F	-7.43877	-7.49496	-0.95819
H	12.52211	-5.77468	0.33200	F	-5.83773	-7.08981	0.46089
N	1.63580	2.22048	-0.59126	F	-5.57488	-6.59997	-1.63632
C	1.81690	0.76511	-0.84546	C	-6.17947	-4.25143	0.12699
H	2.82539	0.57385	-1.26157	H	-5.14861	-4.50782	0.35410
H	1.77589	0.23223	0.12838	C	-6.63771	-2.94188	0.35033
C	0.67254	2.60025	0.34468	C	-7.98255	-2.64072	0.06908
C	0.44833	4.11819	0.62246	H	-8.35146	-1.64199	0.24750
N	0.74850	4.91074	-0.58788	C	-8.82315	-3.63553	-0.42912
C	0.00496	6.18132	-0.87664	C	-10.24217	-3.27557	-0.78104
H	-0.24658	6.68133	0.09014	F	-10.73750	-2.30735	0.02083
H	0.70475	6.87196	-1.41447	F	-11.07273	-4.33896	-0.68890
C	1.74451	4.52306	-1.47854	F	-10.34089	-2.81509	-2.05301

C	4.33792	1.88510	0.41581	C	-6.16330	-2.75090	-1.81361
C	12.57363	3.54943	-0.26299	H	-6.51074	-3.75853	-2.03102
H	13.50920	4.08840	-0.40551	C	-6.97420	-1.84454	-1.12797
C	12.38827	2.29735	-0.85702	H	-7.96270	-2.15021	-0.79096
H	13.18198	1.85813	-1.46287	C	-5.41697	2.24334	-0.48189
C	11.19161	1.59803	-0.68329	N	-4.64546	3.39746	-0.54517
H	11.06621	0.61688	-1.14597	H	-3.74663	3.31947	-1.02689
C	2.29235	3.13896	0.18079	O	-6.51395	2.18081	0.06363
H	1.45733	3.72059	0.54846	C	-5.41248	7.25692	0.97829
C	10.17658	2.16943	0.10184	H	-5.58808	8.25243	1.36599
C	10.35098	3.42518	0.70620	C	-4.35628	7.00601	0.10488
H	9.56102	3.87953	1.30918	C	-3.40253	8.09957	-0.29179
C	11.55429	4.10781	0.51466	F	-3.79392	9.31286	0.14648
H	11.69524	5.08509	0.97835	F	-3.25228	8.17810	-1.63241
N	0.61587	-2.23320	0.26900	F	-2.15849	7.87756	0.21705
C	1.17421	-0.85222	0.35794	C	-4.14107	5.72849	-0.40759
H	2.28407	-0.90922	0.36450	H	-3.33722	5.56397	-1.11869
H	0.88387	-0.28844	-0.55598	C	-4.96656	4.65503	-0.03463
C	-0.49516	-2.41565	-0.57204	C	-6.04272	4.90432	0.83730
C	-1.04796	-3.84452	-0.84118	H	-6.70408	4.09454	1.10867
N	-0.60927	-4.81561	0.18352	C	-6.24947	6.19375	1.32444
C	-1.31305	-6.14081	0.30928	C	-7.36457	6.43136	2.30989
H	-1.79780	-6.38955	-0.67017	F	-7.85416	7.68948	2.22039
H	-0.53096	-6.92560	0.47693	F	-6.93943	6.27017	3.58706
C	0.56724	-4.64468	0.89539	F	-8.39541	5.58094	2.12943
O	0.93922	-5.46968	1.71713	C	-2.17869	-5.92359	-3.41046
O	-1.04454	-1.45847	-1.08651	O	-3.22049	-6.13778	-4.25133
C	-2.59972	-3.70098	-0.91933	H	-3.70520	-5.28799	-4.56476
H	-2.95005	-2.72393	-0.51169	O	-1.58232	-6.87323	-2.96365
H	-3.13537	-4.49613	-0.34764	C	-4.14521	-6.37394	3.54055
N	-2.93953	-3.83170	-2.35625	O	-5.15150	-6.48668	4.46585
C	-1.83406	-4.44339	-3.13036	C	-4.80324	-6.38230	5.86943
H	-1.71133	-3.91720	-4.11808	H	-5.78214	-6.50597	6.35154
C	-0.57755	-4.29355	-2.25881	H	-4.38212	-5.39573	6.08299
H	0.11340	-3.55816	-2.71075	H	-4.12131	-7.18955	6.15159
H	-0.02157	-5.25549	-2.21122	C	-4.61710	-6.49005	2.21778
C	-4.02714	-3.24828	-3.01206	H	-5.67483	-6.65341	2.04345
O	-4.21739	-3.56930	-4.18404	C	-3.68260	-6.38664	1.19055
C	-6.55321	-0.54165	-0.86859	O	-3.98579	-6.45054	-0.14871
H	-7.19323	0.15405	-0.34237	C	-5.34243	-6.78489	-0.53818
C	-5.28319	-0.11283	-1.30405	H	-5.24911	-6.83941	-1.63263
N	-4.78248	1.18062	-1.10724	H	-6.02762	-5.99038	-0.23117
H	-3.86200	1.37763	-1.50731	H	-5.62820	-7.75625	-0.12348
C	-4.45633	-1.02572	-1.98552	C	-2.29890	-6.17653	1.43921
H	-3.46867	-0.70758	-2.32532	C	-1.88421	-6.08054	2.77090
C	-4.90250	-2.32322	-2.23234	H	-0.81733	-5.93910	2.98597

C	-2.79007	-6.16758	3.83196	H	5.71932	-0.92623	-1.39321
H	-2.43376	-6.08296	4.85126	C	7.00741	-1.07613	0.42761
C	0.04033	1.46152	3.89806	C	0.91753	-3.53456	0.66309
H	-0.23526	2.03956	4.77677	C	1.84719	-3.41018	1.89974
C	-0.69088	1.58689	2.71833	H	1.69410	-4.27987	2.59784
H	-1.53435	2.27233	2.68074	H	1.67507	-2.49226	2.51017
C	-0.36937	0.85295	1.56686	C	1.82963	-4.04664	-0.49564
C	-1.18544	1.10711	0.31874	H	1.56189	-5.08124	-0.78801
H	-2.07364	1.69592	0.55939	H	1.70092	-3.43929	-1.41852
H	-1.52782	0.16842	-0.14126	O	4.19182	-2.07777	2.93552
O	-0.35717	1.83293	-0.60432	O	3.88338	-2.67724	-1.98868
H	1.41182	3.13412	-1.67421	C	8.54328	-0.95096	0.14780
C	0.71938	-0.04595	1.60262	N	8.89073	0.42379	0.30453
C	1.45845	-0.13862	2.78951	C	7.73760	1.21852	0.67554
H	2.32292	-0.81302	2.83281	N	6.61329	0.33967	0.66121
C	1.13150	0.59492	3.93001	C	5.36985	0.73553	1.33183
H	1.72583	0.48336	4.83423	H	4.83136	-0.15443	1.73477
C	3.32065	2.66656	0.97816	H	5.58990	1.39862	2.19743
H	3.31071	2.89545	2.03837	N	2.54104	2.74555	-1.21968
C	-1.02121	2.26901	-1.81947	C	3.40396	1.87993	-1.77052
O	-2.26042	2.50808	-1.76761	H	3.28555	1.69917	-2.83312
C	-0.59318	1.30246	-2.95790	O	7.70067	2.39472	0.92736
F	-1.11170	0.07554	-2.74061	C	4.35633	1.23524	-0.99399
F	0.76559	1.13782	-3.02909	H	5.03871	0.52557	-1.46300
F	-1.00380	1.72358	-4.15798	O	9.28162	-1.84909	-0.14939
O	-0.12019	3.50384	-2.16398	C	4.41474	1.48593	0.38175
C	-0.52141	4.65590	-1.55045	C	12.77151	2.03583	-0.27206
H	-1.44531	4.55569	-0.99188	H	13.76820	2.44862	-0.42009
C	0.16032	5.80180	-1.61664	C	12.42522	0.81294	-0.85471
H	1.06570	5.90798	-2.20824	H	13.15441	0.26998	-1.45732
H	-0.22778	6.67937	-1.11270	C	11.14886	0.27513	-0.67388

TS2

ONIOM(B3LYP/6-31G(d):PM6)

N	3.23627	-3.46999	1.38441
C	4.30136	-2.77212	1.93968
C	5.62847	-2.99173	1.17599
H	5.95249	-4.05913	1.32301
N	5.39546	-2.74440	-0.27408
C	4.16945	-3.06573	-0.87605
C	3.28606	-3.99412	-0.00949
H	3.74223	-5.02222	-0.00855
C	6.74029	-2.02697	1.61242
H	7.65891	-2.59584	1.87309
H	6.46347	-1.48554	2.54375
C	6.29176	-1.68721	-0.80509
H	7.02167	-2.16068	-1.50642

H	10.89712	-0.68550	-1.12820
C	2.57834	3.01902	0.09255
H	1.82952	3.71288	0.45726
C	10.21673	0.97894	0.10680
C	10.55306	2.20717	0.69957
H	9.82901	2.76504	1.29872
C	11.83377	2.72750	0.50112
H	12.09992	3.68262	0.95573
N	0.23922	-2.26803	0.29623
C	1.00564	-0.98771	0.31989
H	2.09277	-1.21397	0.33376
H	0.80366	-0.43166	-0.62019
C	-0.90198	-2.31137	-0.51955
C	-1.63970	-3.65968	-0.76558
N	-1.33530	-4.65664	0.28287

C	-2.20927	-5.87280	0.43903	C	-6.16376	7.43264	2.10568
H	-2.72075	-6.08193	-0.53561	F	-5.95896	7.21317	3.42709
H	-1.53889	-6.75038	0.63069	F	-7.33544	6.84725	1.78575
C	-0.14213	-4.63421	0.98836	F	-6.32132	8.76801	1.95489
O	0.11336	-5.48314	1.82960	C	-3.00953	-5.68522	-3.24950
O	-1.33453	-1.29384	-1.03393	O	-4.07939	-5.81810	-4.07078
C	-3.15934	-3.31982	-0.85526	H	-4.47342	-4.93445	-4.41710
H	-3.37646	-2.28746	-0.49412	O	-2.51387	-6.67563	-2.76940
H	-3.79217	-4.00960	-0.24713	C	-5.05212	-5.64915	3.66119
N	-3.52025	-3.47182	-2.28551	O	-6.06591	-5.60623	4.58403
C	-2.49948	-4.24198	-3.03372	C	-5.70929	-5.51445	5.98646
H	-2.32370	-3.77756	-4.04400	H	-6.69674	-5.49916	6.46676
C	-1.22836	-4.19638	-2.17112	H	-5.16442	-4.58585	6.17889
H	-0.46864	-3.54919	-2.64778	H	-5.13799	-6.39621	6.29060
H	-0.77325	-5.20837	-2.09699	C	-5.53307	-5.73939	2.33956
C	-4.55095	-2.81038	-2.95728	H	-6.60273	-5.77088	2.16443
O	-4.80663	-3.17190	-4.10470	C	-4.59144	-5.78481	1.31473
C	-6.62484	0.33903	-0.93042	O	-4.89861	-5.84277	-0.02417
H	-7.14266	1.14608	-0.42850	C	-6.28381	-6.03166	-0.41055
C	-5.30177	0.53707	-1.36966	H	-6.19565	-6.12933	-1.50243
N	-4.58777	1.73222	-1.21008	H	-6.87432	-5.15568	-0.13008
H	-3.68022	1.76543	-1.67207	H	-6.67949	-6.95142	0.03087
C	-4.63375	-0.51741	-2.01740	C	-3.19271	-5.74769	1.56461
H	-3.60355	-0.37640	-2.35412	C	-2.77091	-5.66967	2.89525
C	-5.28205	-1.73372	-2.22483	H	-1.69500	-5.66175	3.11157
C	-6.59608	-1.93581	-1.80072	C	-3.68212	-5.61031	3.95363
H	-7.10181	-2.88098	-1.98504	H	-3.31942	-5.54493	4.97217
C	-7.25080	-0.88692	-1.15095	C	0.28830	1.65593	3.73967
H	-8.27650	-1.01762	-0.81224	H	0.12019	2.31663	4.58647
C	-4.96012	2.85880	-0.49484	C	-0.42418	1.83865	2.55553
N	-3.96042	3.82696	-0.52726	H	-1.14457	2.65030	2.48471
H	-3.11710	3.59130	-1.05057	C	-0.23894	1.00120	1.44566
O	-6.02375	2.98585	0.10094	C	-1.05420	1.29993	0.20909
C	-3.89058	7.71692	1.10454	H	-1.75262	2.11479	0.40675
H	-3.85872	8.72131	1.50761	H	-1.64078	0.42563	-0.11328
C	-2.80980	7.19739	0.39520	O	-0.15372	1.67440	-0.86052
C	-1.57812	8.02804	0.15310	H	1.64153	3.11149	-1.83930
F	-1.59220	9.18567	0.84600	C	0.68939	-0.06019	1.52320
F	-1.44060	8.35050	-1.15728	C	1.41313	-0.21037	2.71289
F	-0.45099	7.36257	0.50313	H	2.15490	-1.01417	2.79193
C	-2.85154	5.90738	-0.13104	C	1.22058	0.62360	3.81490
H	-1.99450	5.52425	-0.67978	H	1.79699	0.46074	4.72284
C	-3.99147	5.10448	0.03879	C	3.51158	2.41175	0.91853
C	-5.08502	5.61968	0.75833	H	3.51229	2.64544	1.97819
H	-5.96631	5.01019	0.89369	C	-0.76665	2.02998	-2.05768
C	-5.01736	6.91093	1.27810	O	-1.91159	2.50163	-2.09644

C	-0.36491	1.03737	-3.16725	O	7.89578	0.20866	1.18520
F	-1.03712	-0.12278	-2.96183	C	4.43471	0.36797	-0.77739
F	0.95488	0.72625	-3.14834	H	4.75436	-0.53944	-1.29350
F	-0.67299	1.48778	-4.38400	O	8.03506	-4.22159	-0.23945
O	0.48291	3.30953	-2.54589	C	4.58305	0.49577	0.60551
C	-0.04681	4.54789	-2.63630	C	12.56518	-1.61884	-0.25351
H	-1.07855	4.54637	-2.98791	H	13.63741	-1.52678	-0.41623
C	0.59179	5.68961	-2.34817	C	11.84438	-2.63710	-0.88455
H	1.62494	5.71290	-2.01030	H	12.35660	-3.34203	-1.54004
H	0.08794	6.64039	-2.47331	C	10.46782	-2.76296	-0.68511

INT2

ONIOM(B3LYP/6-31G(d):PM6)

N	1.85536	-4.20237	1.35243	H	3.25752	3.62378	0.81033
C	3.06182	-3.81168	1.93091	C	9.81385	-1.85343	0.16354
C	4.28968	-4.33901	1.15246	C	10.52835	-0.82764	0.80505
H	4.32008	-5.45983	1.23928	H	10.02470	-0.10924	1.45751
N	4.13000	-3.95746	-0.27874	C	11.90321	-0.71846	0.58717
C	2.87298	-4.00040	-0.89530	H	12.46122	0.07853	1.07978
C	1.80035	-4.72505	-0.04214	N	-0.63196	-2.25676	0.09666
H	2.02763	-5.82578	-0.04064	C	0.51550	-1.30311	-0.00498
C	5.61305	-3.72713	1.62605	H	1.46853	-1.86752	0.03930
H	6.34622	-4.52847	1.85794	H	0.48546	-0.81122	-1.00172
H	5.48125	-3.17003	2.58044	C	-1.74571	-1.98900	-0.70842
C	5.23422	-3.08342	-0.74997	C	-2.92831	-2.99464	-0.80731
H	5.78991	-3.61790	-1.55776	N	-2.86922	-4.04986	0.22480
H	4.84108	-2.13337	-1.19687	C	-4.05307	-4.95876	0.42660
C	6.13209	-2.82294	0.48715	H	-4.61615	-5.04161	-0.53837
C	-0.37301	-3.64412	0.55717	H	-3.65782	-5.98491	0.64492
C	0.53225	-3.72051	1.81733	C	-1.70747	-4.36691	0.91159
H	0.12688	-4.46923	2.55276	O	-1.70399	-5.24377	1.76304
H	0.61854	-2.75608	2.37192	O	-1.82248	-0.93563	-1.32393
C	0.36994	-4.46782	-0.53964	C	-4.23139	-2.14054	-0.70700
H	-0.14567	-5.43009	-0.73054	H	-4.02061	-1.09573	-0.38240
H	0.38213	-3.93982	-1.51822	H	-4.96022	-2.56199	0.02450
O	3.11792	-3.14061	2.94464	N	-4.83252	-2.16188	-2.06298
O	2.67708	-3.54223	-2.00110	C	-4.24804	-3.22302	-2.91630
C	7.62400	-3.16120	0.14723	H	-4.06972	-2.82680	-3.95497
N	8.38647	-1.98144	0.38010	C	-2.92417	-3.61564	-2.23761
C	7.54268	-0.89361	0.85633	H	-2.06756	-3.24929	-2.83456
N	6.21326	-1.38600	0.85210	H	-2.81770	-4.72249	-2.19782
C	5.12171	-0.63906	1.49658	C	-5.71195	-1.21291	-2.58249
H	4.28589	-1.33186	1.75290	O	-6.27384	-1.46557	-3.64808
H	5.48125	-0.20015	2.45405	C	-6.21480	2.47483	-0.46054
N	3.44286	2.55360	-0.94416	H	-6.32951	3.41330	0.06657
C	3.87012	1.41359	-1.50425	C	-5.02762	2.22216	-1.17190
H	3.74646	1.33037	-2.57952	N	-3.95375	3.12112	-1.26631

H	-3.20347	2.82594	-1.88475	H	-8.58635	-4.88496	-0.03763
C	-4.88518	0.99853	-1.84674	C	-4.95535	-4.53222	1.54575
H	-3.96552	0.79406	-2.40041	C	-4.52881	-4.53702	2.87623
C	-5.90661	0.05145	-1.81062	H	-3.49052	-4.81237	3.09965
C	-7.08945	0.29472	-1.11189	C	-5.39435	-4.21017	3.92453
H	-7.89109	-0.43997	-1.09933	H	-5.02970	-4.21822	4.94455
C	-7.22409	1.51278	-0.44014	C	0.76046	1.74667	3.12861
H	-8.13779	1.72639	0.11033	H	0.83066	2.50482	3.90438
C	-3.70778	4.23192	-0.47756	C	0.16697	2.05061	1.90491
N	-2.47017	4.80308	-0.77572	H	-0.21871	3.05261	1.73260
H	-1.91632	4.35394	-1.49817	C	0.04776	1.09174	0.88849
O	-4.46840	4.65967	0.38041	C	-0.69823	1.51620	-0.34889
C	-0.33256	7.75926	1.34377	H	-1.04684	2.54204	-0.24590
H	0.22971	8.51497	1.87772	H	-1.57061	0.87659	-0.54904
C	0.29632	6.91040	0.43445	O	0.15271	1.44473	-1.54262
C	1.76923	7.04620	0.15665	H	2.12556	3.58164	-1.84008
F	2.39645	7.81621	1.06844	C	0.54400	-0.21254	1.09529
F	2.00551	7.59378	-1.05923	C	1.16176	-0.48744	2.32065
F	2.39175	5.83793	0.15489	H	1.57045	-1.48684	2.50423
C	-0.42279	5.93507	-0.25591	C	1.26236	0.46481	3.33543
H	0.09484	5.27219	-0.94892	H	1.73372	0.19864	4.27876
C	-1.80435	5.79951	-0.04485	C	4.16496	1.69645	1.18352
C	-2.44953	6.65126	0.86676	H	4.26857	1.86798	2.25169
H	-3.51170	6.54896	1.03475	C	-0.36132	1.99341	-2.63104
C	-1.70507	7.61251	1.54946	O	-1.40438	2.61198	-2.71646
C	-2.39067	8.47068	2.58178	C	0.41920	1.61654	-3.90533
F	-2.36819	7.88500	3.80251	F	-0.13775	0.49455	-4.41016
F	-3.68509	8.69593	2.27647	F	1.71619	1.36286	-3.68155
F	-1.78757	9.67362	2.71455	F	0.31838	2.58268	-4.82030
C	-5.22041	-4.42025	-3.03168	O	1.36544	3.97435	-2.33506
O	-6.42408	-4.16794	-3.60131	C	1.89129	4.85798	-3.32059
H	-6.57005	-3.19525	-3.90621	H	2.39576	5.71816	-2.86321
O	-4.96666	-5.54865	-2.68549	H	2.59278	4.34595	-3.99406
C	-6.72571	-3.89331	3.62186	H	1.05014	5.22165	-3.91697
O	-7.69311	-3.56197	4.53569				
C	-7.32948	-3.54304	5.93933				
H	-8.27905	-3.25784	6.41152	INT3			
H	-6.55821	-2.78915	6.12083	ONIOM(B3LYP/6-31G(d):PM6)			
H	-7.01380	-4.53926	6.26246	N	3.91068	-3.12659	1.42279
C	-7.21164	-3.88193	2.29858	C	4.91749	-2.31238	1.93797
H	-8.25111	-3.63529	2.11345	C	6.20128	-2.31739	1.07564
C	-6.31290	-4.19764	1.28355	H	6.67776	-3.33375	1.14668
O	-6.60899	-4.18392	-0.05657	N	5.82653	-2.04637	-0.34022
C	-7.99331	-4.07571	-0.47330	C	4.63292	-2.54034	-0.87909
H	-7.89804	-4.20322	-1.56522	C	3.95073	-3.60639	0.01260
H	-8.38905	-3.09169	-0.21305	H	4.54925	-4.55626	-0.04339
				C	7.20002	-1.22403	1.47903
				H	8.20331	-1.66744	1.65484

H	6.91708	-0.75468	2.44723	C	-0.31015	-2.22842	-0.39008
C	6.50805	-0.84154	-0.87728	C	-0.92499	-3.63244	-0.68388
H	7.21809	-1.16082	-1.67793	N	-0.63019	-4.56947	0.42356
H	5.77369	-0.13803	-1.35106	C	-1.48141	-5.79073	0.64308
C	7.25159	-0.20199	0.32262	H	-1.98626	-6.06481	-0.31579
C	1.57988	-3.36581	0.77187	H	-0.79543	-6.64583	0.88057
C	2.53686	-3.18787	1.98225	C	0.56099	-4.49068	1.13397
H	2.47454	-4.08140	2.66382	O	0.83306	-5.29400	2.01207
H	2.31111	-2.30027	2.61683	O	-0.83294	-1.22645	-0.85626
C	2.49092	-3.85568	-0.39419	C	-2.45005	-3.43809	-0.92950
H	2.33221	-4.93451	-0.59433	H	-2.75026	-2.37348	-0.77682
H	2.25984	-3.33427	-1.34906	H	-3.08501	-4.04732	-0.24194
O	4.78831	-1.68560	2.97399	N	-2.70035	-3.85677	-2.33259
O	4.21713	-2.18409	-1.96199	C	-1.51961	-4.51259	-2.94192
C	8.73345	0.11749	-0.07295	H	-1.36095	-4.12913	-3.98792
N	8.92972	1.51412	0.12259	C	-0.33676	-4.15663	-2.02979
C	7.72100	2.15070	0.62605	H	0.30182	-3.39563	-2.51771
N	6.72441	1.14162	0.67292	H	0.30414	-5.05070	-1.86564
C	5.45690	1.36359	1.38501	C	-3.83756	-3.58019	-3.08884
H	5.02264	0.38802	1.70467	O	-3.94311	-4.11405	-4.19362
H	5.64326	1.95189	2.31088	C	-6.77759	-0.89997	-1.49881
N	2.40639	3.42773	-0.93453	H	-7.51521	-0.21244	-1.10524
C	3.18086	2.49387	-1.50445	C	-5.47454	-0.43722	-1.76306
H	2.97076	2.27021	-2.54767	N	-5.04237	0.87779	-1.54526
O	7.58199	3.30464	0.93752	H	-4.08645	1.06292	-1.83226
C	4.18949	1.81927	-0.81933	C	-4.52222	-1.33254	-2.27773
H	4.78625	1.06650	-1.33913	H	-3.51206	-0.97811	-2.49628
O	9.54237	-0.67722	-0.46916	C	-4.86494	-2.66291	-2.51059
C	4.42355	2.11740	0.52586	C	-6.15583	-3.12916	-2.25862
C	12.53157	3.60313	-0.68807	H	-6.42518	-4.16064	-2.47489
H	13.45621	4.13835	-0.89630	C	-7.09970	-2.23208	-1.75190
C	12.29010	2.36143	-1.28348	H	-8.11468	-2.57016	-1.55432
H	13.02949	1.92656	-1.95675	C	-5.70810	1.89823	-0.88787
C	11.10594	1.66721	-1.02577	N	-4.89360	3.01721	-0.73378
H	10.93656	0.69448	-1.49251	H	-3.92940	2.92943	-1.03674
C	2.63808	3.72660	0.34916	O	-6.86421	1.82900	-0.49054
H	2.00222	4.49263	0.78864	C	-5.75812	6.77354	0.98168
C	10.15846	2.23157	-0.15471	H	-5.96407	7.74474	1.41399
C	10.39122	3.47760	0.45138	C	-4.49205	6.46783	0.48689
H	9.65371	3.92840	1.12081	C	-3.39635	7.50001	0.51245
C	11.58031	4.15555	0.17538	F	-3.69104	8.53998	1.31879
H	11.76372	5.12490	0.64014	F	-3.16007	8.00999	-0.72282
N	0.83949	-2.13205	0.40170	F	-2.22415	6.97505	0.94130
C	1.53809	-0.81513	0.45054	C	-4.22426	5.22023	-0.07547
H	2.63310	-0.98625	0.47143	H	-3.22995	5.00891	-0.46362
H	1.31784	-0.26484	-0.48602	C	-5.23186	4.24585	-0.15287

N	2.92348	2.46824	-1.39410	H	-6.76221	2.79108	-0.32405
C	3.68155	1.49490	-1.92085	C	-5.22412	1.74453	-1.41672
H	3.62646	1.36654	-2.99508	N	-4.24839	2.74736	-1.42458
O	7.81787	1.09514	0.86793	H	-3.39888	2.51208	-1.93771
C	4.45661	0.68222	-1.10711	C	-4.88422	0.53999	-2.05882
H	5.04947	-0.11160	-1.55916	H	-3.89916	0.43893	-2.51802
O	8.53154	-3.38837	-0.14090	C	-5.79624	-0.51309	-2.10080
C	4.44010	0.87210	0.27878	C	-7.05964	-0.40008	-1.51757
C	12.70027	-0.26808	-0.23727	H	-7.77379	-1.21942	-1.56164
H	13.76120	-0.05875	-0.37541	C	-7.39040	0.79972	-0.87898
C	12.08766	-1.29050	-0.96887	H	-8.36957	0.91191	-0.41724
H	12.67214	-1.87949	-1.67832	C	-4.18720	3.90517	-0.66731
C	10.72840	-1.56571	-0.80209	N	-2.96289	4.53526	-0.85150
H	10.25862	-2.36779	-1.37377	H	-2.29550	4.03430	-1.44673
C	2.91418	2.70276	-0.07196	O	-5.08262	4.31730	0.06629
H	2.27796	3.51338	0.26445	C	-1.15309	7.70233	1.25914
C	9.98790	-0.80266	0.11563	H	-0.66916	8.51273	1.78865
C	10.59157	0.22473	0.85894	C	-0.41956	6.84287	0.44046
H	10.01261	0.82081	1.56698	C	1.07070	6.98924	0.30321
C	11.95078	0.48587	0.67163	F	1.53886	8.11293	0.88099
H	12.42833	1.28456	1.24250	F	1.45972	7.00770	-0.99344
N	-0.37735	-2.25852	0.10145	F	1.72799	5.94560	0.88108
C	0.63009	-1.15449	0.13085	C	-1.03812	5.80200	-0.24575
H	1.65107	-1.58277	0.19733	H	-0.44705	5.13495	-0.86958
H	0.57775	-0.59288	-0.82670	C	-2.42396	5.59646	-0.12515
C	-1.45599	-2.10848	-0.78033	C	-3.17330	6.45889	0.69102
C	-2.55298	-3.20981	-0.86720	H	-4.23992	6.31059	0.78456
N	-2.44141	-4.20067	0.22613	C	-2.52846	7.49367	1.37058
C	-3.58804	-5.14049	0.49128	C	-3.34394	8.36856	2.28534
H	-4.25343	-5.17248	-0.40640	F	-3.54252	7.78217	3.49164
H	-3.16730	-6.17320	0.60034	F	-4.56928	8.62854	1.77680
C	-1.22745	-4.49014	0.83198	F	-2.74594	9.55715	2.52318
O	-1.12906	-5.42771	1.61496	C	-4.65093	-4.88719	-3.12117
O	-1.58462	-1.09475	-1.45029	O	-5.75718	-4.76342	-3.89695
C	-3.92134	-2.46127	-0.85552	H	-5.92494	-3.81308	-4.26983
H	-3.80592	-1.38787	-0.57667	O	-4.44847	-5.96077	-2.59981
H	-4.64810	-2.89780	-0.12720	C	-5.81850	-4.19902	4.05448
N	-4.46766	-2.59786	-2.23016	O	-6.64282	-3.87976	5.10094
C	-3.75470	-3.63835	-3.01199	C	-6.11304	-3.98470	6.45047
H	-3.54257	-3.26815	-4.05659	H	-6.97617	-3.67627	7.05563
C	-2.44819	-3.91116	-2.25406	H	-5.27397	-3.29540	6.58369
H	-1.58276	-3.53698	-2.83764	H	-5.83007	-5.01900	6.66788
H	-2.27090	-5.00430	-2.14715	C	-6.45283	-4.06188	2.80405
C	-5.39678	-1.75482	-2.82774	H	-7.48801	-3.73738	2.76213
O	-5.85025	-2.07450	-3.93229	C	-5.70731	-4.35534	1.66373
C	-6.49441	1.86724	-0.82242	O	-6.18752	-4.25749	0.38000

C	0.53920	-1.15012	0.10459	C	-0.31574	5.78465	-0.34698
H	1.51179	-1.68120	0.17912	H	0.15207	5.09993	-1.04828
H	0.51033	-0.67685	-0.90251	C	-1.71204	5.74271	-0.17638
C	-1.65081	-1.96996	-0.68000	C	-2.30934	6.62235	0.74401
C	-2.83228	-2.97952	-0.70201	H	-3.38075	6.59469	0.88447
N	-2.77869	-3.95776	0.40501	C	-1.50931	7.51210	1.46200
C	-3.96288	-4.85226	0.66011	C	-2.15169	8.40616	2.49172
H	-4.51387	-5.00554	-0.30426	F	-2.18304	7.81253	3.70891
H	-3.56780	-5.85757	0.95819	F	-3.42358	8.71963	2.17308
C	-1.63060	-4.19920	1.14088	F	-1.47179	9.56659	2.64276
O	-1.62859	-5.00336	2.06231	C	-5.12522	-4.50956	-2.86236
O	-1.69590	-0.99849	-1.41304	O	-6.31389	-4.26887	-3.46856
C	-4.13034	-2.11054	-0.66844	H	-6.42906	-3.31335	-3.83886
H	-3.91677	-1.04961	-0.40251	O	-4.90253	-5.61924	-2.44095
H	-4.87129	-2.48421	0.07602	C	-6.67709	-3.55001	3.73074
N	-4.71488	-2.20772	-2.02780	O	-7.65615	-3.14936	4.60421
C	-4.13166	-3.32675	-2.80518	C	-7.30750	-3.01269	6.00486
H	-3.92869	-2.99635	-3.86273	H	-8.26158	-2.68871	6.44141
C	-2.82705	-3.70326	-2.08236	H	-6.53756	-2.24607	6.13058
H	-1.95541	-3.39868	-2.69317	H	-6.99583	-3.97814	6.41362
H	-2.74849	-4.80603	-1.96303	C	-7.14544	-3.63755	2.40423
C	-5.54972	-1.26768	-2.63446	H	-8.18113	-3.40180	2.18666
O	-6.08073	-1.58008	-3.70080	C	-6.23424	-4.03052	1.42777
C	-6.15161	2.51740	-0.72503	O	-6.51189	-4.12191	0.08786
H	-6.29419	3.47984	-0.24987	C	-7.88426	-3.99517	-0.36185
C	-4.93588	2.24801	-1.38197	H	-7.77343	-4.19571	-1.44160
N	-3.87551	3.15723	-1.47244	H	-8.25067	-2.98347	-0.17435
H	-3.08324	2.86129	-2.04993	H	-8.51144	-4.75446	0.11349
C	-4.75326	0.99273	-1.99133	C	-4.88084	-4.34711	1.73315
H	-3.81082	0.77534	-2.49852	C	-4.47262	-4.25260	3.06569
C	-5.76641	0.03685	-1.93971	H	-3.43777	-4.51044	3.32339
C	-6.97616	0.29761	-1.29381	C	-5.35138	-3.84669	4.07497
H	-7.76884	-0.44709	-1.27256	H	-5.00019	-3.77773	5.09713
C	-7.14983	1.54495	-0.68914	C	0.60941	1.97316	3.17162
H	-8.08490	1.77324	-0.18133	H	0.63597	2.75124	3.93067
C	-3.66481	4.28981	-0.69879	C	-0.02938	2.20258	1.95467
N	-2.40147	4.81725	-0.94998	H	-0.49281	3.16801	1.76579
H	-1.81765	4.27624	-1.60858	C	-0.09143	1.21924	0.95565
O	-4.46421	4.75646	0.10534	C	-0.76414	1.58703	-0.34851
C	-0.12366	7.55818	1.29609	H	-1.38662	2.47096	-0.20146
H	0.47906	8.26370	1.85484	H	-1.41827	0.78209	-0.71207
C	0.46065	6.67904	0.38269	O	0.26575	1.86223	-1.30656
C	1.95221	6.61761	0.23364	H	2.33136	2.66486	-2.05321
F	2.56399	7.76397	0.57905	C	0.50746	-0.03728	1.18377
F	2.33443	6.31014	-1.02965	C	1.15960	-0.24378	2.40675
F	2.49243	5.63656	1.02646	H	1.63764	-1.21040	2.60599

C	1.21277	0.73702	3.39712
H	1.71843	0.52859	4.33764
C	4.00843	1.74383	0.66383
H	4.22413	2.10216	1.66475
C	-0.18749	2.31556	-2.60777
O	-1.24746	3.02538	-2.67187
C	-0.24796	1.06629	-3.53463
F	-1.30266	0.28284	-3.23083
F	0.86220	0.27327	-3.44096
F	-0.35994	1.42262	-4.82909
O	1.08164	3.02951	-3.01695
C	0.95653	3.99635	-4.06095
H	-0.07862	4.34229	-4.10759
H	1.61414	4.83754	-3.82044
H	1.24595	3.56506	-5.02651

TS4

ONIOM(B3LYP/6-31G(d):PM6) (DCM, IEF-PCM)

N	-4.99479	2.22138	1.50885
C	-5.53164	1.07241	2.09983
C	-6.57445	0.35602	1.22046
H	-7.51307	0.98207	1.19304
N	-6.02659	0.21784	-0.15944
C	-5.29502	1.22392	-0.77348
C	-5.18514	2.52071	0.05796
H	-6.14102	3.10382	-0.07446
C	-6.89844	-1.07627	1.67649
H	-7.83023	-1.10764	2.27742
H	-6.10851	-1.46603	2.35511
C	-6.13322	-1.17096	-0.67454
H	-6.58706	-1.17019	-1.69149
H	-5.12629	-1.63554	-0.77706
C	-7.00390	-1.90631	0.38201
C	-2.91307	3.23015	0.77944
C	-3.77004	2.88507	2.02875
H	-4.06825	3.82580	2.56237
H	-3.24552	2.25424	2.78937
C	-3.96751	3.35865	-0.35735
H	-4.26834	4.41882	-0.49854
H	-3.56983	3.03286	-1.34733
O	-5.22169	0.72889	3.22649
O	-4.81429	1.08748	-1.88611
C	-8.48273	-1.94549	-0.13251
N	-8.81623	-3.32228	-0.32058
C	-7.73512	-4.18511	0.09308
N	-6.63435	-3.34883	0.46490
C	-5.69518	-3.87118	1.47624

H	-5.93498	-3.49675	2.49340
H	-5.78599	-4.98456	1.50920
N	-1.55851	-2.96978	0.64187
C	-2.35992	-3.35787	-0.36363
H	-1.90288	-3.41893	-1.34573
O	-7.72743	-5.39222	0.08284
C	-3.70013	-3.65525	-0.14529
H	-4.32053	-3.97385	-0.97923
O	-9.20821	-1.01345	-0.35073
C	-4.23195	-3.53524	1.14433
C	-12.47863	-4.74477	-1.90102
H	-13.42160	-5.10978	-2.30864
C	-11.96177	-3.51644	-2.32563
H	-12.50316	-2.92289	-3.06492
C	-10.75291	-3.04033	-1.81277
H	-10.35755	-2.07935	-2.14570
C	-2.03986	-2.87541	1.89095
H	-1.33567	-2.55942	2.65379
C	-10.06777	-3.81241	-0.86026
C	-10.57698	-5.04573	-0.42285
H	-10.03891	-5.64662	0.31247
C	-11.78478	-5.50466	-0.95380
H	-12.18745	-6.46408	-0.62320
N	-1.87217	2.22572	0.44645
C	-1.95696	0.81669	0.91702
H	-2.98506	0.59161	1.26207
H	-1.76415	0.14709	0.05178
C	-0.84958	2.54979	-0.44670
C	-0.67833	4.03587	-0.88755
N	-1.14877	4.94535	0.17861
C	-0.52496	6.29733	0.36250
H	-0.18987	6.68070	-0.63179
H	-1.32518	6.99816	0.71531
C	-2.21842	4.60560	1.00097
O	-2.62202	5.37481	1.86145
O	-0.10216	1.68886	-0.88305
C	0.81836	4.23195	-1.27818
H	1.49932	3.59815	-0.66793
H	1.15527	5.29377	-1.15868
N	0.88353	3.88517	-2.72332
C	-0.46440	3.95842	-3.35583
H	-0.71517	2.98048	-3.86074
C	-1.45118	4.25628	-2.21794
H	-2.35529	3.61540	-2.29697
H	-1.82914	5.30305	-2.28009
C	1.89649	3.14345	-3.32734

C	4.96003	1.62499	0.31461	H	13.10941	-4.67715	0.36457
C	4.53056	2.74793	-0.65811	N	1.21803	2.04228	-0.56457
H	5.38514	3.47322	-0.74937	C	1.48503	0.58974	-0.75861
C	6.55897	-0.78791	-2.02489	H	2.52792	0.44516	-1.10396
H	7.34633	-0.79529	-2.80120	H	1.41258	0.08829	0.23055
H	5.72896	-1.40288	-2.43519	C	0.22960	2.40814	0.35499
C	6.23339	-0.57438	0.41607	C	-0.01989	3.92474	0.62545
H	6.83364	-0.31090	1.31521	N	0.25473	4.71427	-0.59514
H	5.36791	-1.17844	0.77172	C	-0.48161	5.99292	-0.87574
C	7.05554	-1.32737	-0.66812	H	-0.79014	6.45384	0.09404
C	2.10804	3.07534	-1.14767	H	0.24366	6.70332	-1.35119
C	2.85069	2.63868	-2.43944	C	1.26657	4.34587	-1.47501
H	2.95701	3.51286	-3.13771	O	1.52181	5.01441	-2.46427
H	2.32978	1.83946	-3.02296	O	-0.41402	1.56245	0.95245
C	3.25814	3.45713	-0.16895	C	-1.47567	4.07049	1.15553
H	3.41487	4.55427	-0.15669	H	-2.12803	3.23689	0.80759
H	3.02227	3.17405	0.88398	H	-1.95900	5.02644	0.82899
O	4.36561	0.44752	-3.46723	N	-1.35859	4.09248	2.63595
O	4.65311	1.58929	1.48968	C	0.02755	4.39786	3.07454
C	8.57331	-0.99296	-0.46996	H	0.37792	3.62951	3.81854
N	9.22826	-2.22074	-0.13751	C	0.89006	4.37858	1.80390
C	8.30623	-3.33332	-0.19314	H	1.77011	3.71685	1.93243
N	7.00255	-2.79738	-0.45718	H	1.30309	5.39609	1.60444
C	6.03870	-3.67404	-1.15450	C	-2.28125	3.54752	3.52998
H	6.11758	-3.56462	-2.25652	O	-2.02683	3.59211	4.73209
H	6.30338	-4.73374	-0.91029	C	-5.94003	1.98646	1.94868
N	1.89835	-3.07179	0.02061	H	-6.86152	1.58308	1.55110
C	2.85197	-3.25536	0.94507	C	-4.82776	1.13946	2.10725
H	2.51908	-3.25198	1.98153	N	-4.84263	-0.23286	1.79866
O	8.55118	-4.50040	-0.02459	H	-4.04105	-0.76242	2.12701
C	4.19656	-3.44087	0.62593	C	-3.63121	1.67231	2.61600
H	4.92879	-3.59805	1.41711	H	-2.75863	1.02826	2.73783
O	9.09413	0.08323	-0.56884	C	-3.55977	3.01870	2.96336
C	4.58824	-3.42624	-0.71627	C	-4.65978	3.86546	2.81559
C	13.32564	-2.59375	0.89540	H	-4.59855	4.91116	3.10811
H	14.37719	-2.68779	1.16065	C	-5.84312	3.33084	2.30434
C	12.68313	-1.35646	1.00212	H	-6.71818	3.96555	2.18561
H	13.23594	-0.48324	1.35021	C	-5.81104	-0.92060	1.07994
C	11.33379	-1.22459	0.66713	N	-5.48991	-2.26365	0.94464
H	10.84893	-0.24933	0.74739	H	-4.63452	-2.58793	1.38468
C	2.26858	-3.07431	-1.26595	O	-6.82164	-0.40847	0.61550
H	1.47577	-2.92655	-1.99531	C	-7.54092	-5.39966	-0.98766
C	10.62826	-2.35318	0.21607	H	-8.05774	-6.22379	-1.46395
C	11.26359	-3.60097	0.10259	C	-6.30509	-5.59303	-0.36577
H	10.71844	-4.48562	-0.23627	C	-5.64331	-6.94292	-0.42184
C	12.61249	-3.70994	0.44736	F	-4.97618	-7.12647	-1.58499

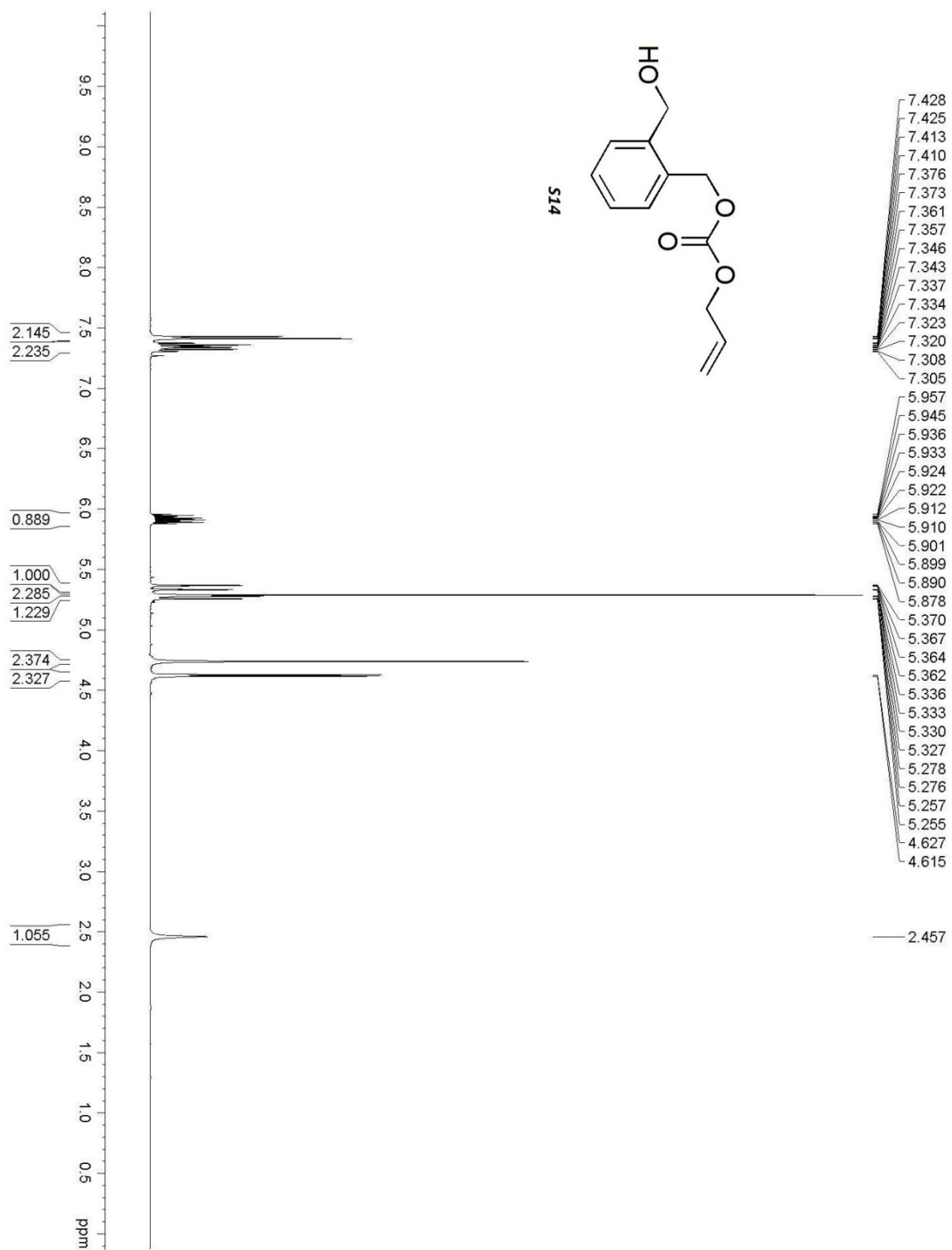
F	-6.53652	-7.94829	-0.31938	C	0.83925	-0.01366	-3.13629
F	-4.73427	-7.10559	0.57446	H	1.73214	0.53961	-3.44855
C	-5.65342	-4.53753	0.25874	C	0.06449	-0.63880	-4.10840
H	-4.69885	-4.70216	0.74463	H	0.33751	-0.55404	-5.15747
C	-6.22121	-3.25236	0.28155	C	3.59152	-3.23892	-1.67545
C	-7.46141	-3.04787	-0.34148	H	3.82775	-3.22302	-2.73700
H	-7.91305	-2.06638	-0.32407	C	-1.87959	-3.22680	2.68108
C	-8.09918	-4.12318	-0.96552	O	-3.02743	-2.92746	2.42133
C	-9.40669	-3.86471	-1.67113	C	-0.94946	-2.26670	3.44984
F	-9.20885	-3.29494	-2.88256	F	-1.30131	-0.99404	3.21352
F	-10.19843	-3.02665	-0.96901	F	0.34209	-2.42126	3.12470
F	-10.10363	-5.00377	-1.87916	F	-1.07997	-2.50078	4.76934
C	0.05815	5.78373	3.76112	O	-1.30661	-4.40448	2.52072
O	-0.56773	5.87209	4.95928	C	-2.05898	-5.39129	1.78034
H	-1.07052	5.02890	5.25546	H	-3.00836	-5.60033	2.27724
O	0.62401	6.75687	3.32734	H	-2.22603	-5.02035	0.76761
C	-3.84828	5.47357	-3.51057	H	-1.43102	-6.28073	1.76776
O	-5.00474	5.35424	-4.23678				
C	-4.90499	4.90087	-5.61074				
H	-5.95882	4.89567	-5.92002	methanol			
H	-4.48036	3.89349	-5.64746	B3LYP/6-31G(d)			
H	-4.32446	5.61351	-6.20344	O	0.74915	0.12249	0.00000
C	-4.08478	5.90767	-2.19082	H	1.13410	-0.76641	0.00001
H	-5.10288	6.10490	-1.87351	C	-0.66233	-0.01953	0.00000
C	-2.98086	6.06156	-1.35620	H	-1.07969	0.99110	-0.00030
O	-3.05129	6.48514	-0.04718	H	-1.03680	-0.54400	-0.89302
C	-4.35274	6.81582	0.50150	H	-1.03685	-0.54349	0.89330
H	-4.08760	7.16448	1.50866				
H	-4.98171	5.92108	0.53794	vinyl alcohol			
H	-4.81635	7.61892	-0.07987	B3LYP/6-31G(d)			
C	-1.65600	5.79167	-1.78894	O	1.13611	-0.29762	-0.00003
C	-1.47679	5.38243	-3.11517	C	-0.03531	0.41249	-0.00001
H	-0.45875	5.19566	-3.48045	H	0.06853	1.49748	-0.00004
C	-2.55577	5.21122	-3.98566	C	-1.22846	-0.17876	0.00001
H	-2.37916	4.88664	-5.00419	H	-1.32466	-1.25969	0.00005
C	-1.05571	-1.37885	-3.72244	H	-2.13057	0.42121	-0.00002
H	-1.67471	-1.87410	-4.46679	H	1.88043	0.31961	0.00022
C	-1.36772	-1.48081	-2.37150				
H	-2.22469	-2.07148	-2.05658	vinyl trifluoroacetate			
C	-0.59457	-0.84829	-1.38239	B3LYP/6-31G(d)			
C	-1.00968	-1.09628	0.05852	C	0.02282	0.59375	-0.00047
H	-2.07094	-0.85433	0.17880	O	0.08352	1.79438	-0.00043
H	-0.46281	-0.45437	0.76309	O	1.05251	-0.27350	-0.00029
O	-0.88309	-2.47367	0.42263	C	-1.30100	-0.20041	-0.00004
H	0.07269	-2.71478	0.35598	C	2.34652	0.24527	0.00035
C	0.53011	-0.09204	-1.76857	H	2.39408	1.32721	0.00125
				C	3.37998	-0.58579	-0.00011
				H	3.24878	-1.66263	-0.00107

H	4.38783	-0.18747	0.00049
F	-1.37447	-0.98731	-1.08765
F	-2.33794	0.63831	-0.00426
F	-1.37746	-0.98000	1.09267

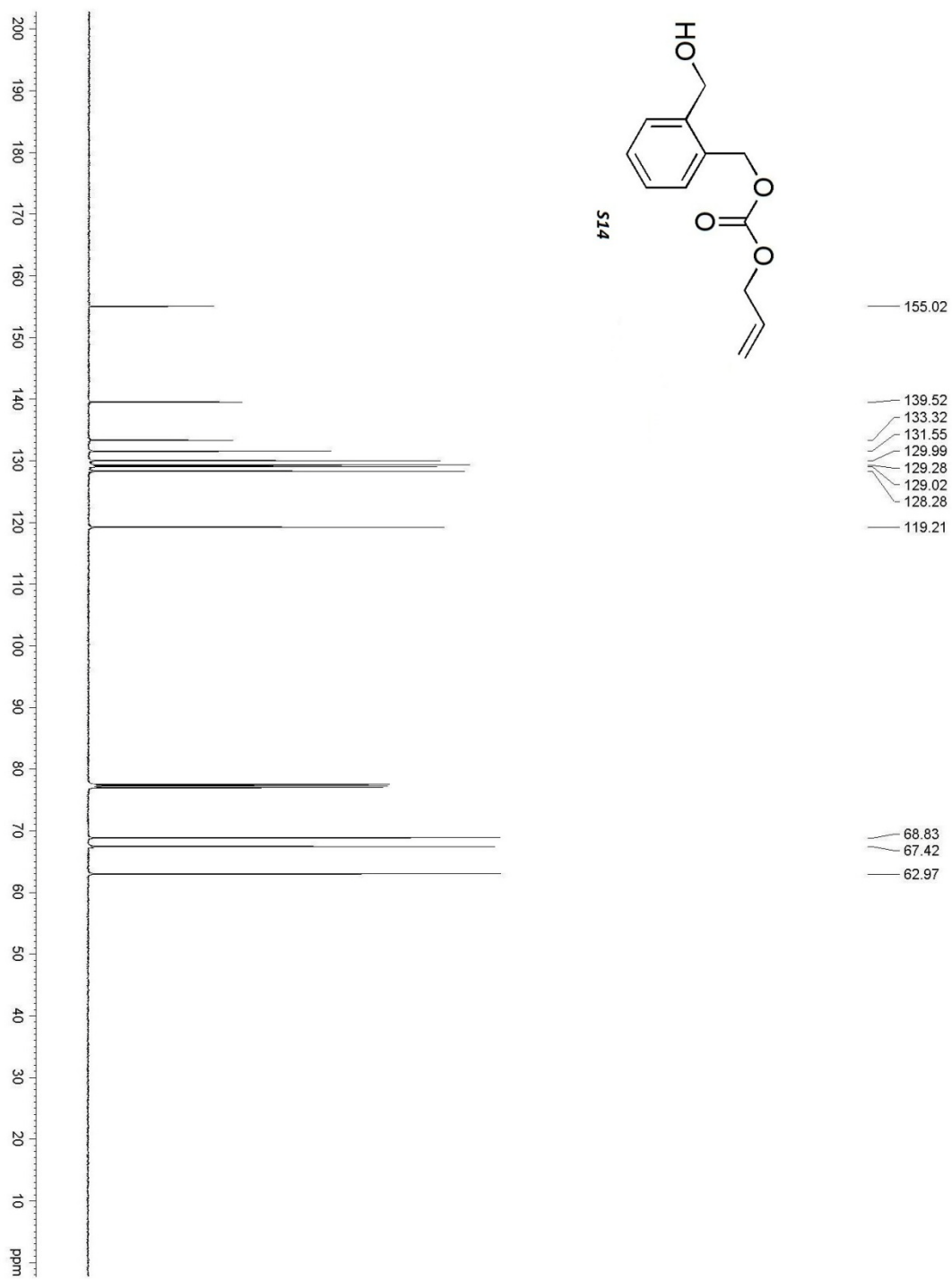
Full citation for manuscript reference **26**.

Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery Jr JA, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2010) Gaussian 09, Revision C.01. Gaussian, Inc., Wallingford CT.: (2004) Gaussian 03, Revision C.02. Gaussian, Inc., Wallingford CT.

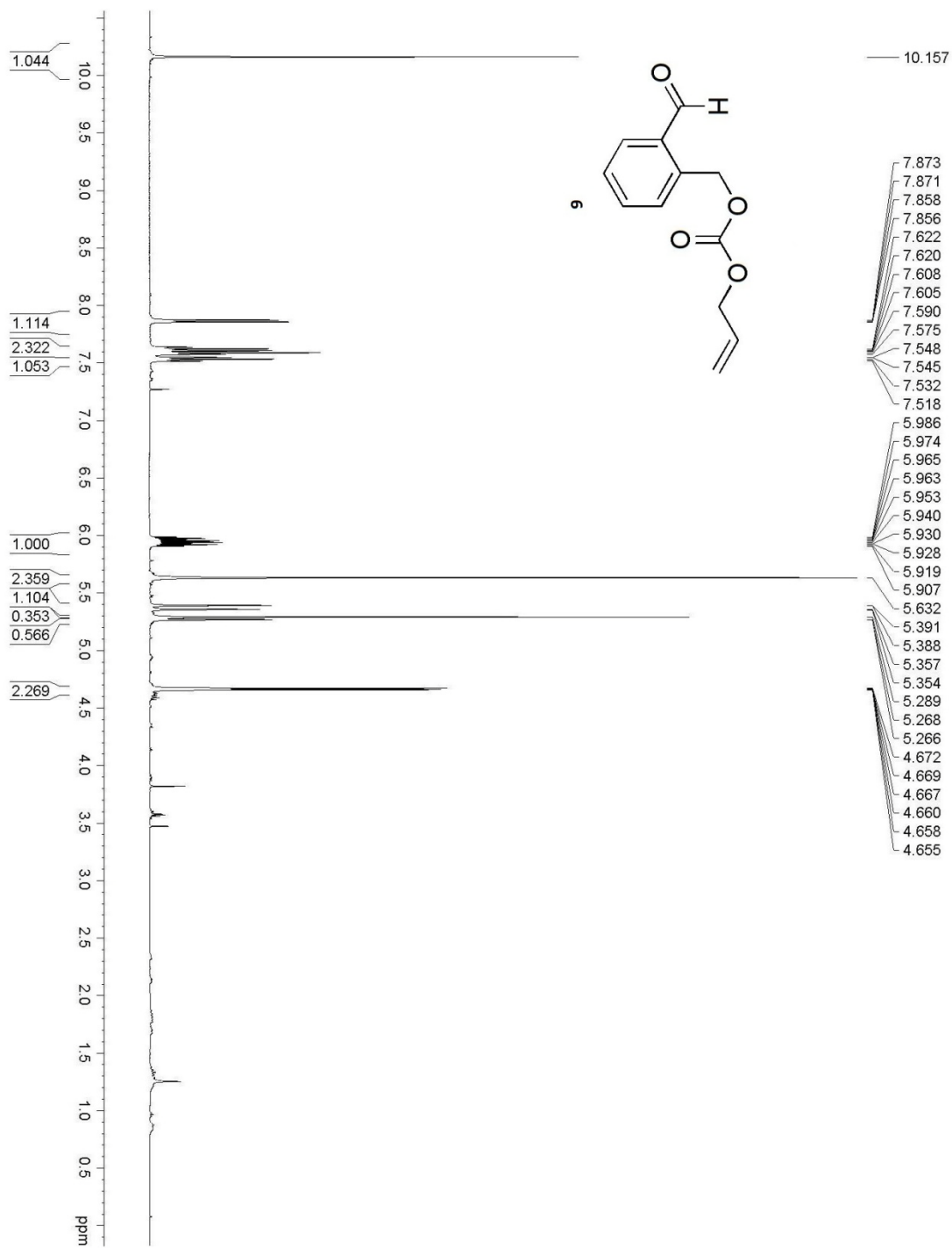
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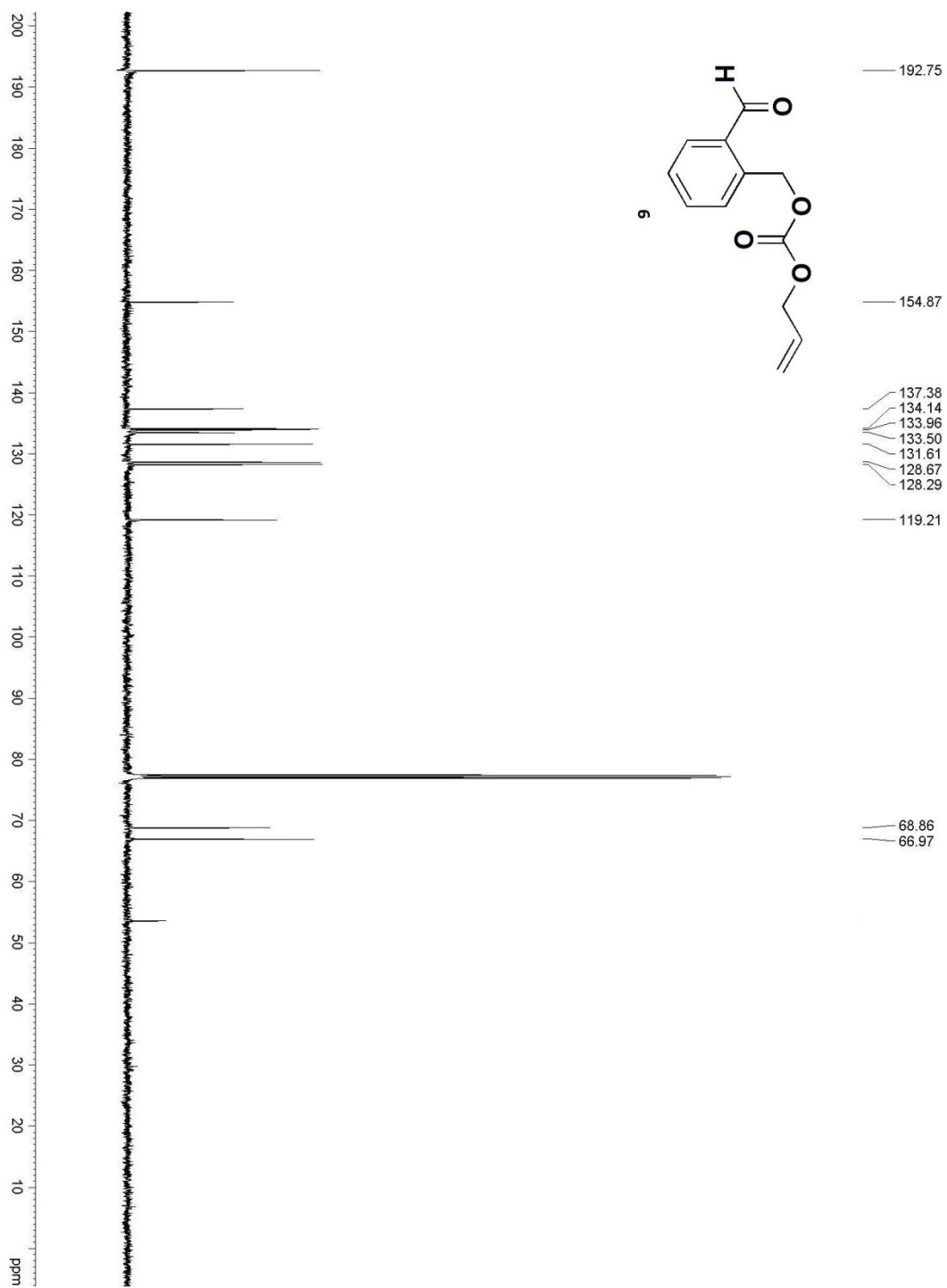
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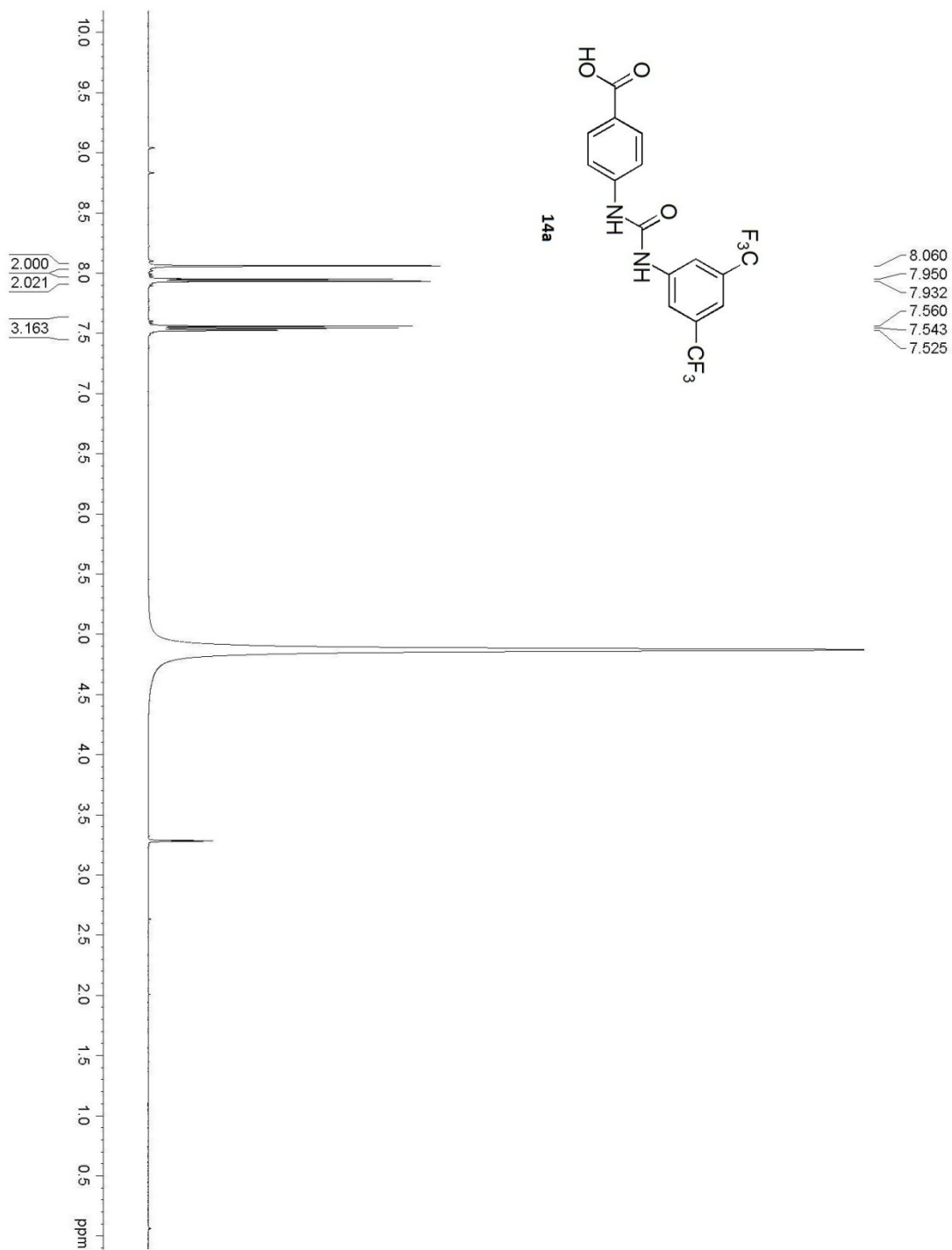
¹H-NMR of Compound 6



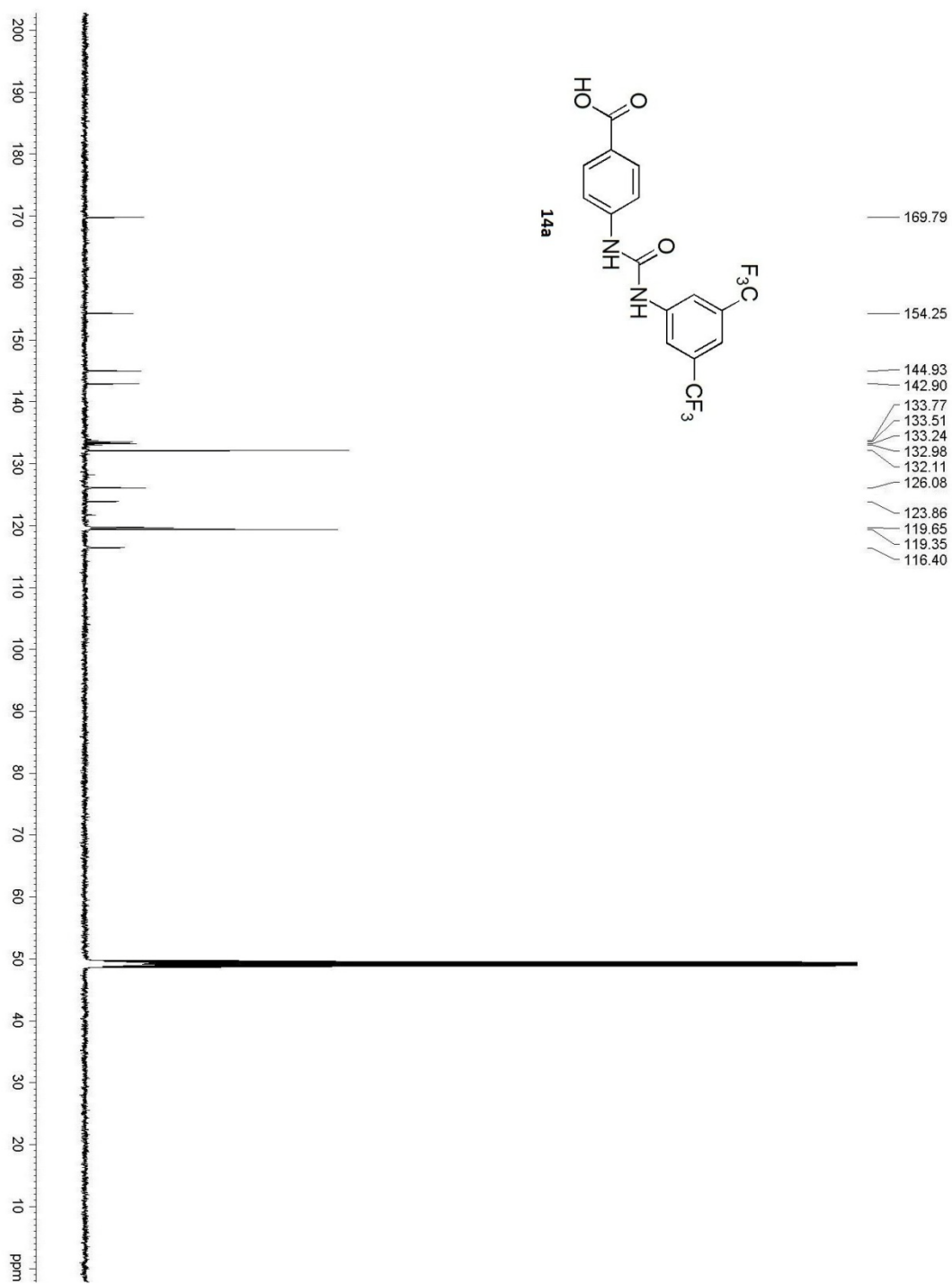
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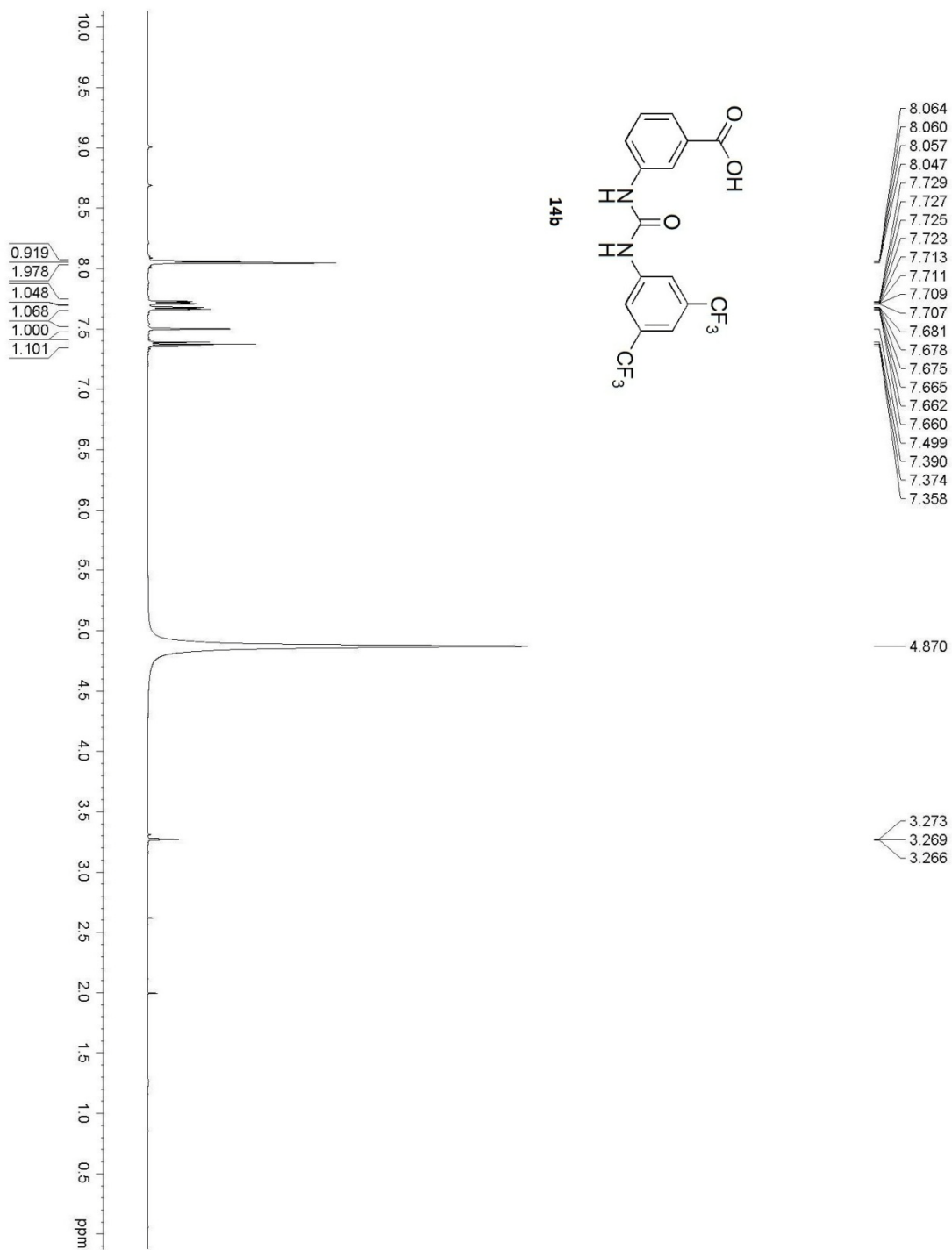
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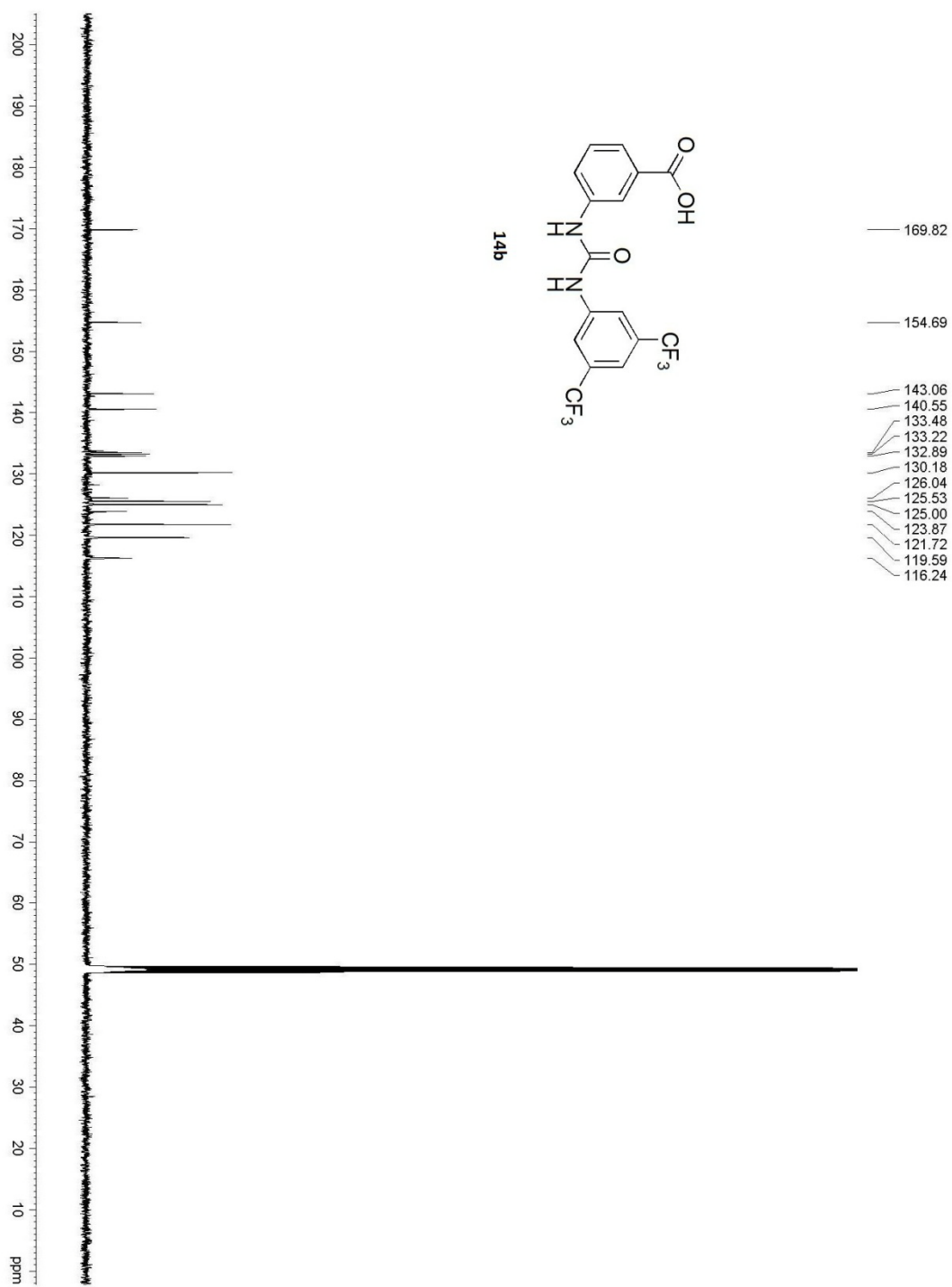
^{13}C -NMR of Compound



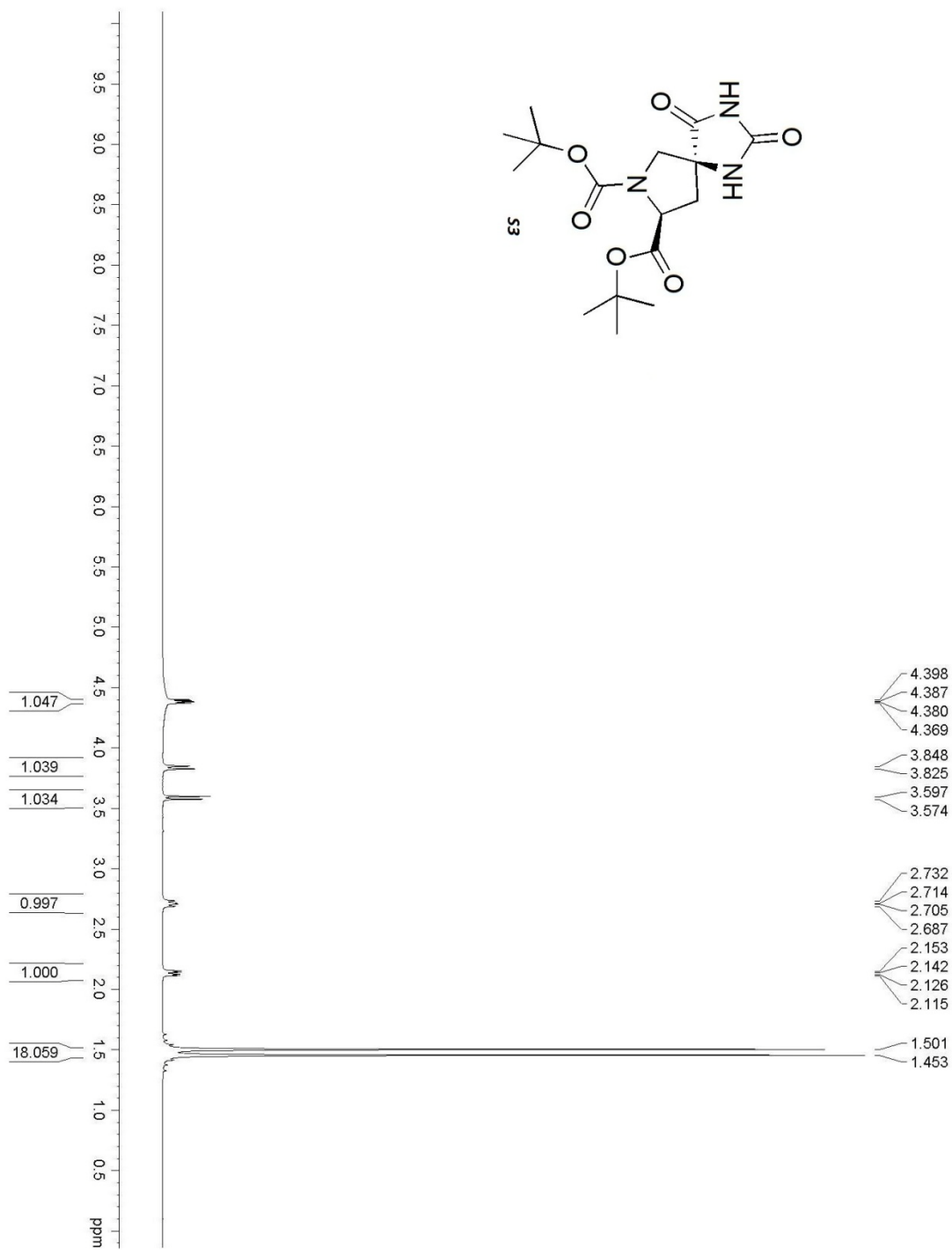
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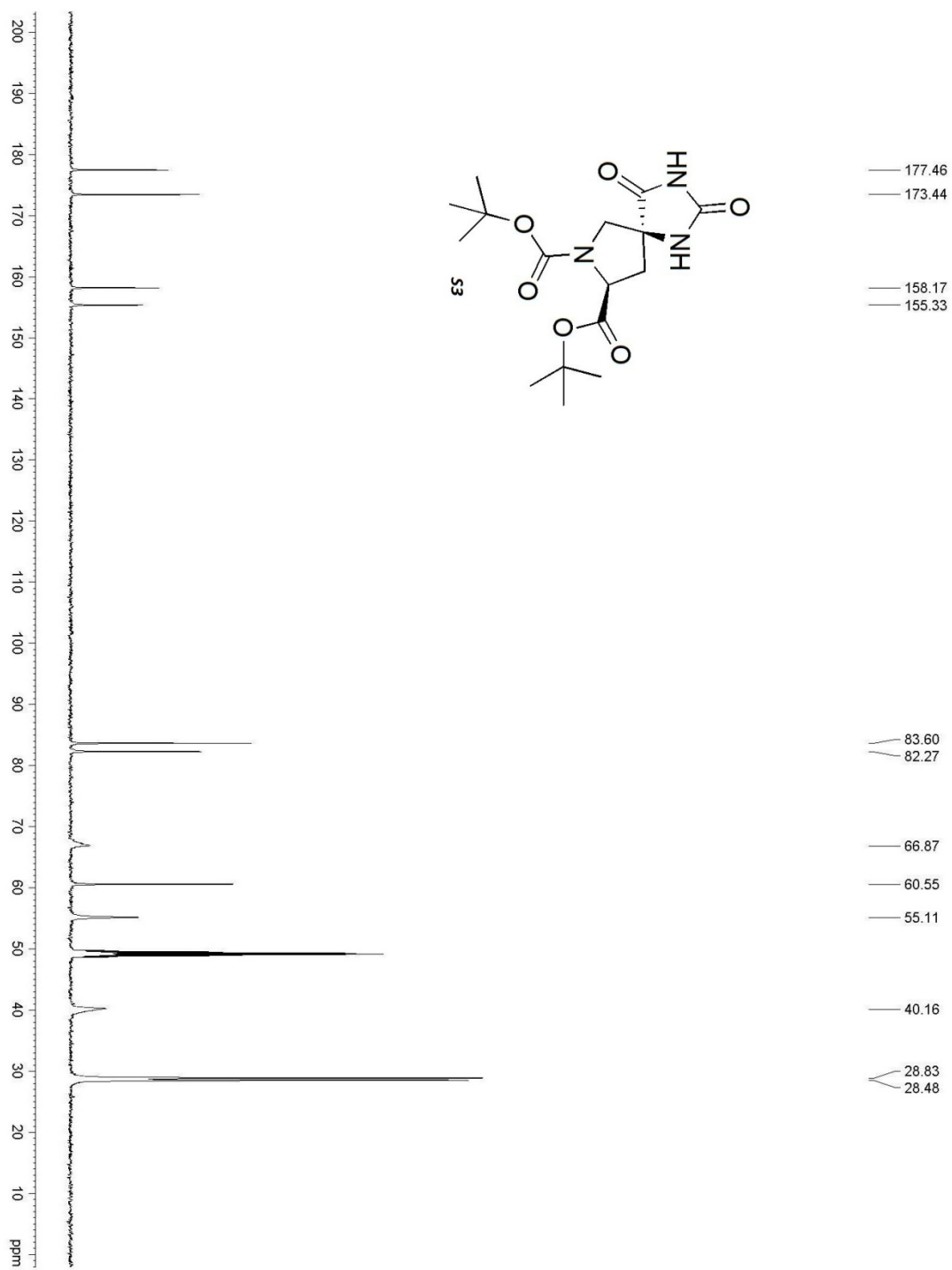
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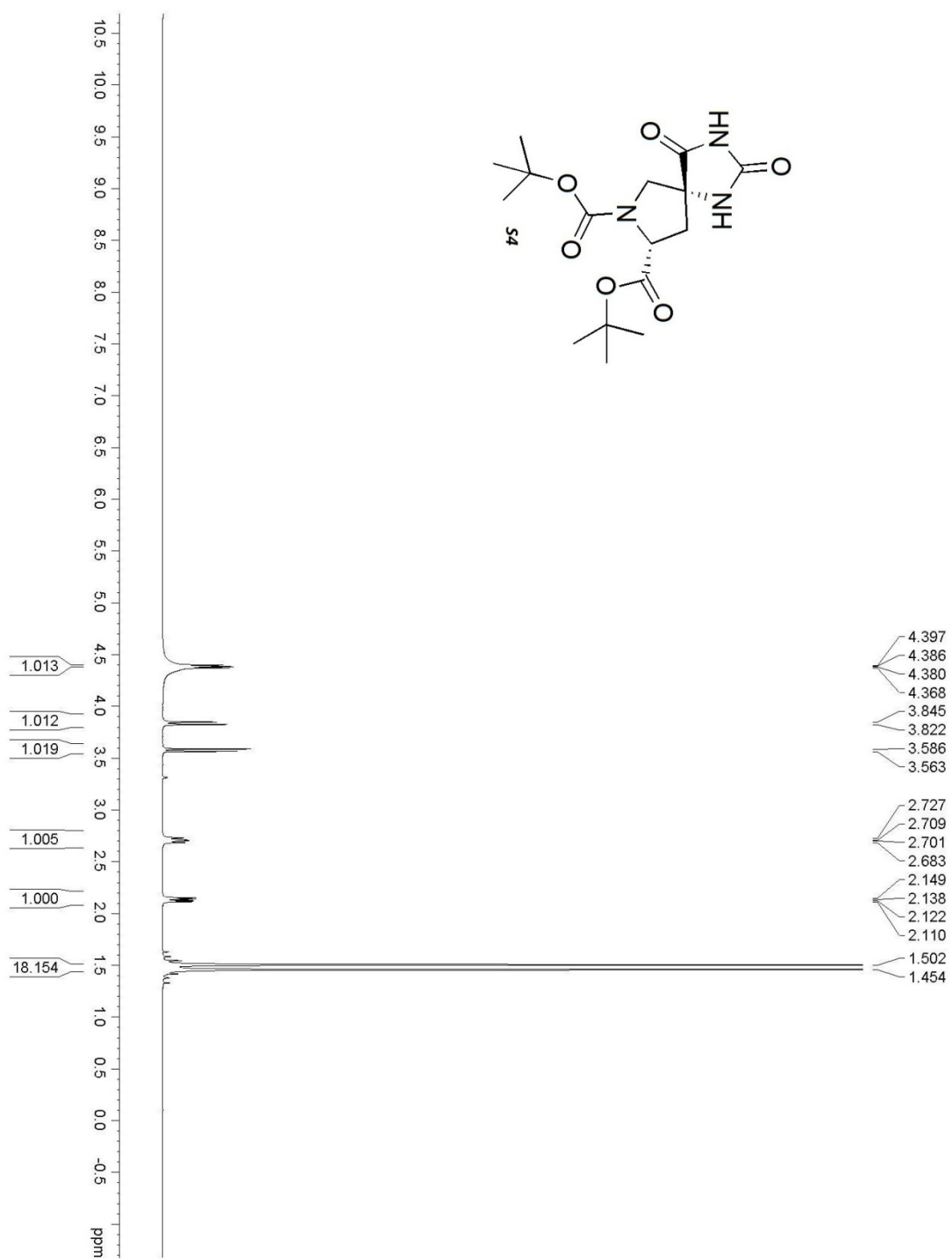
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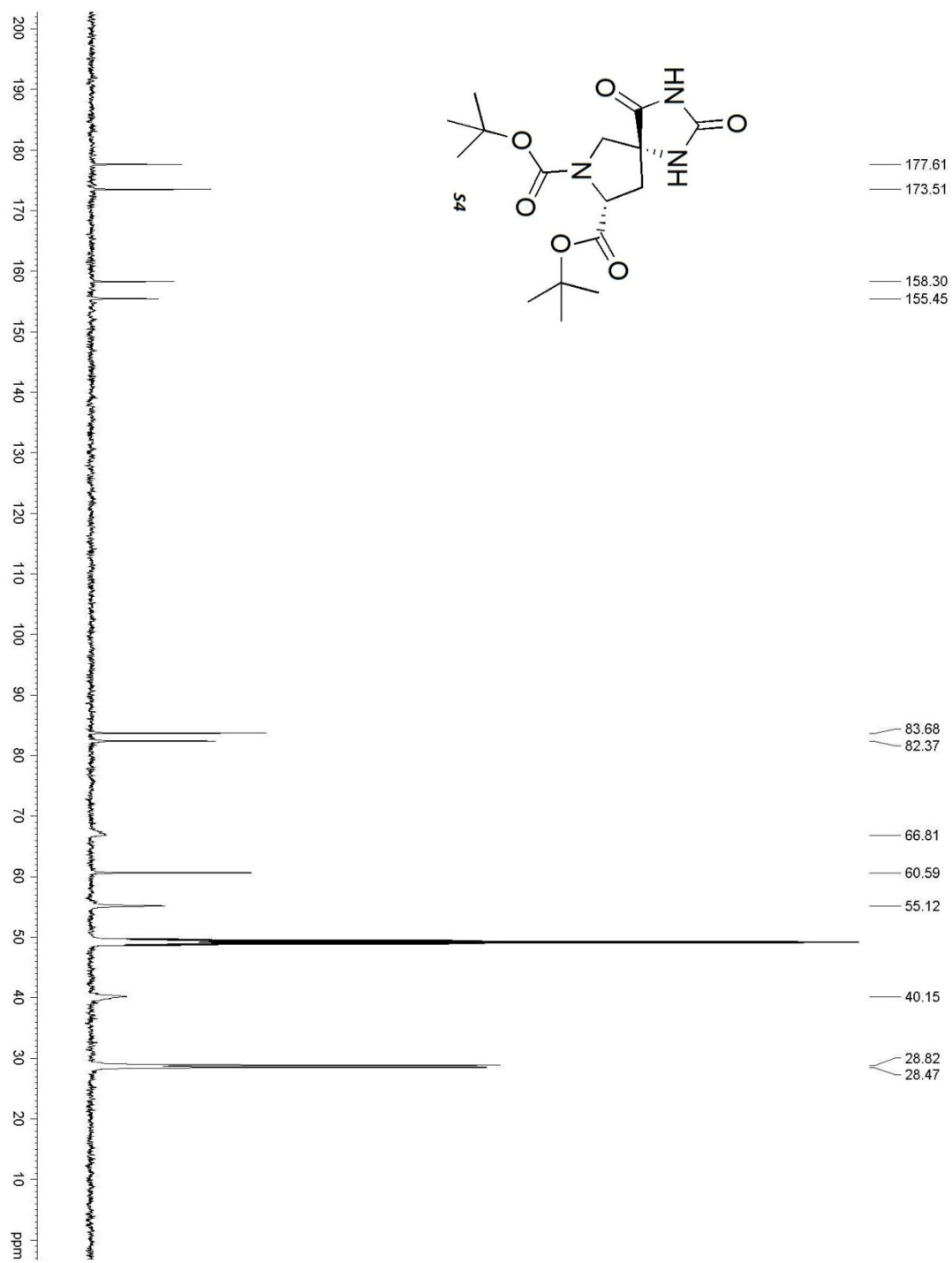
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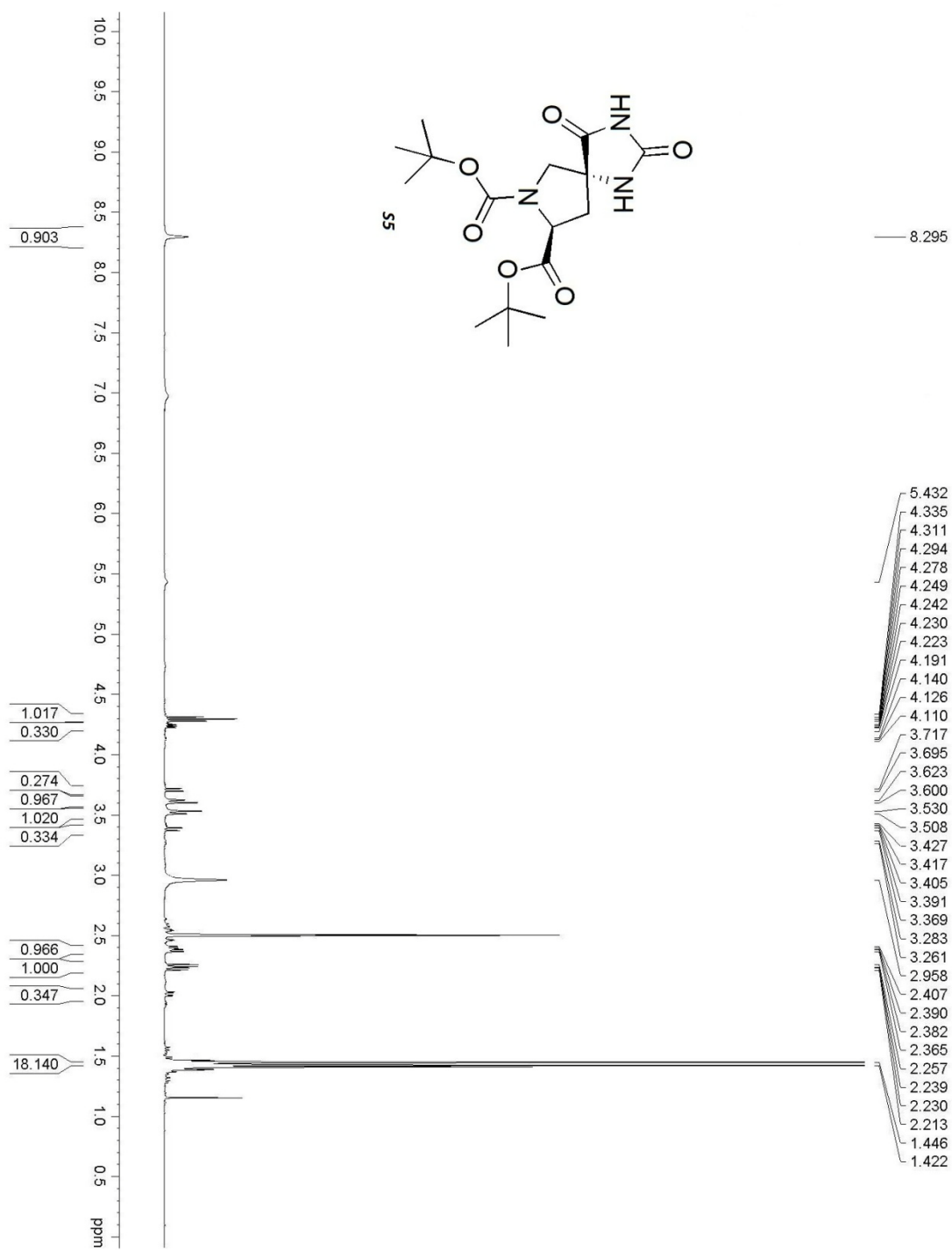
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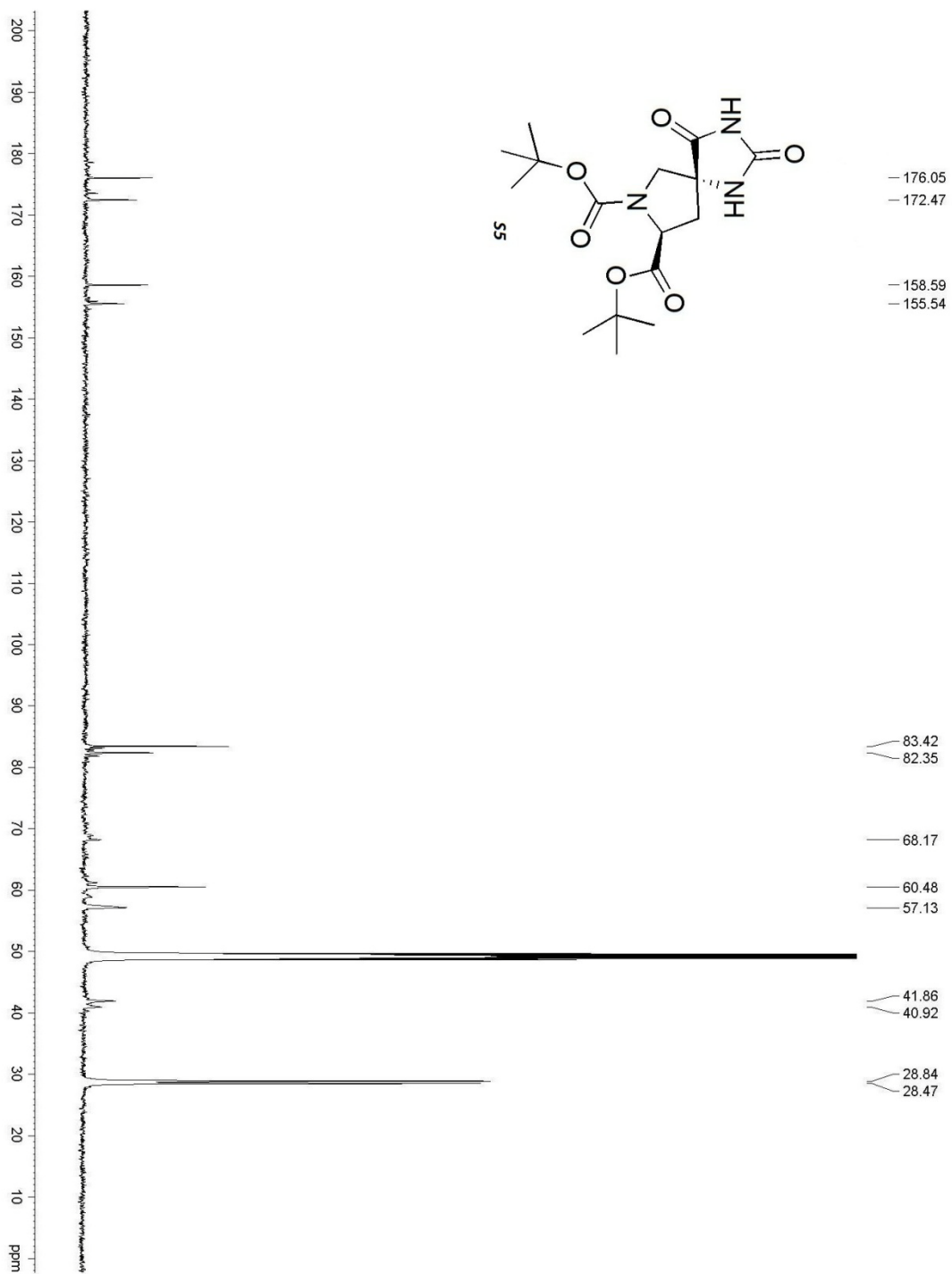
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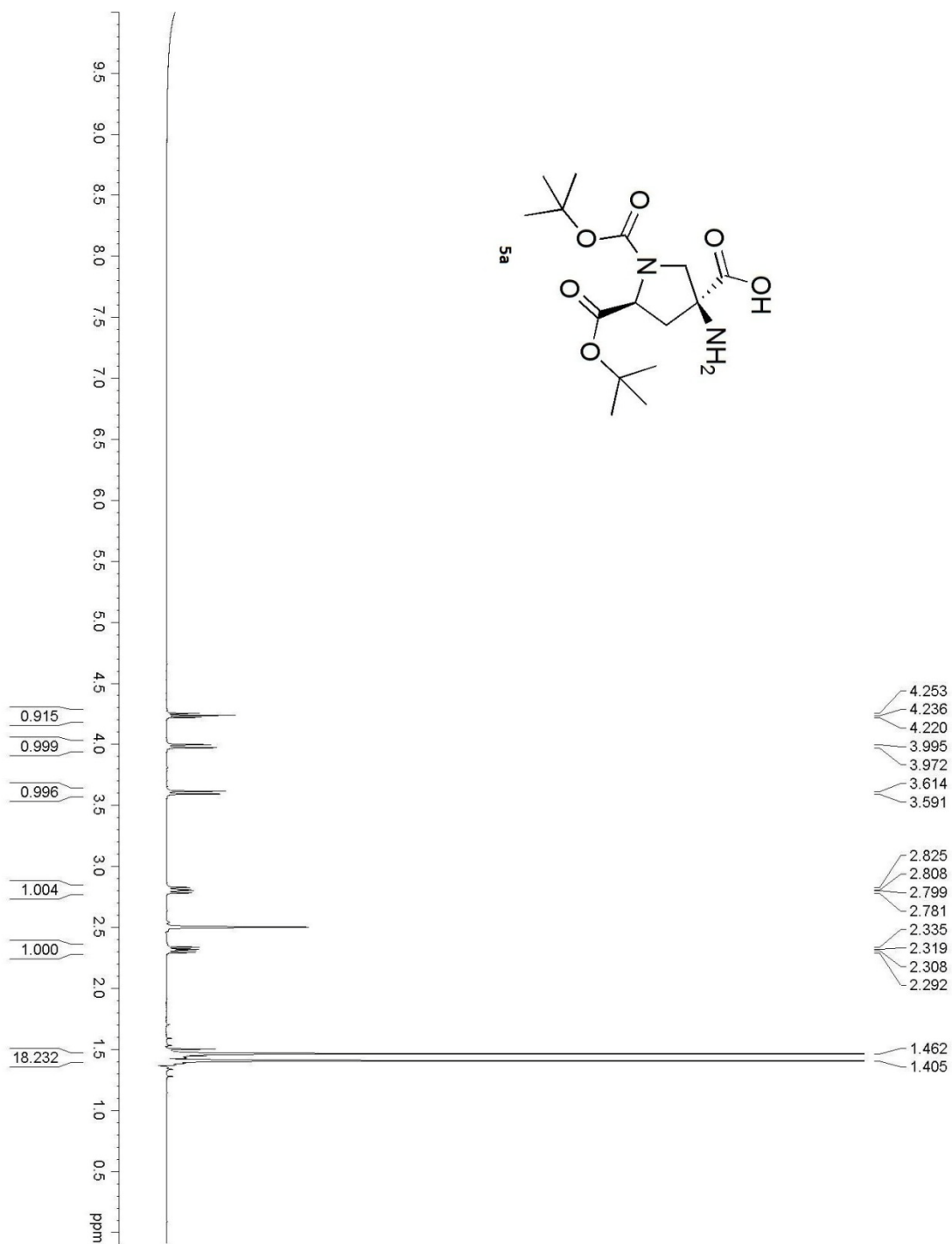
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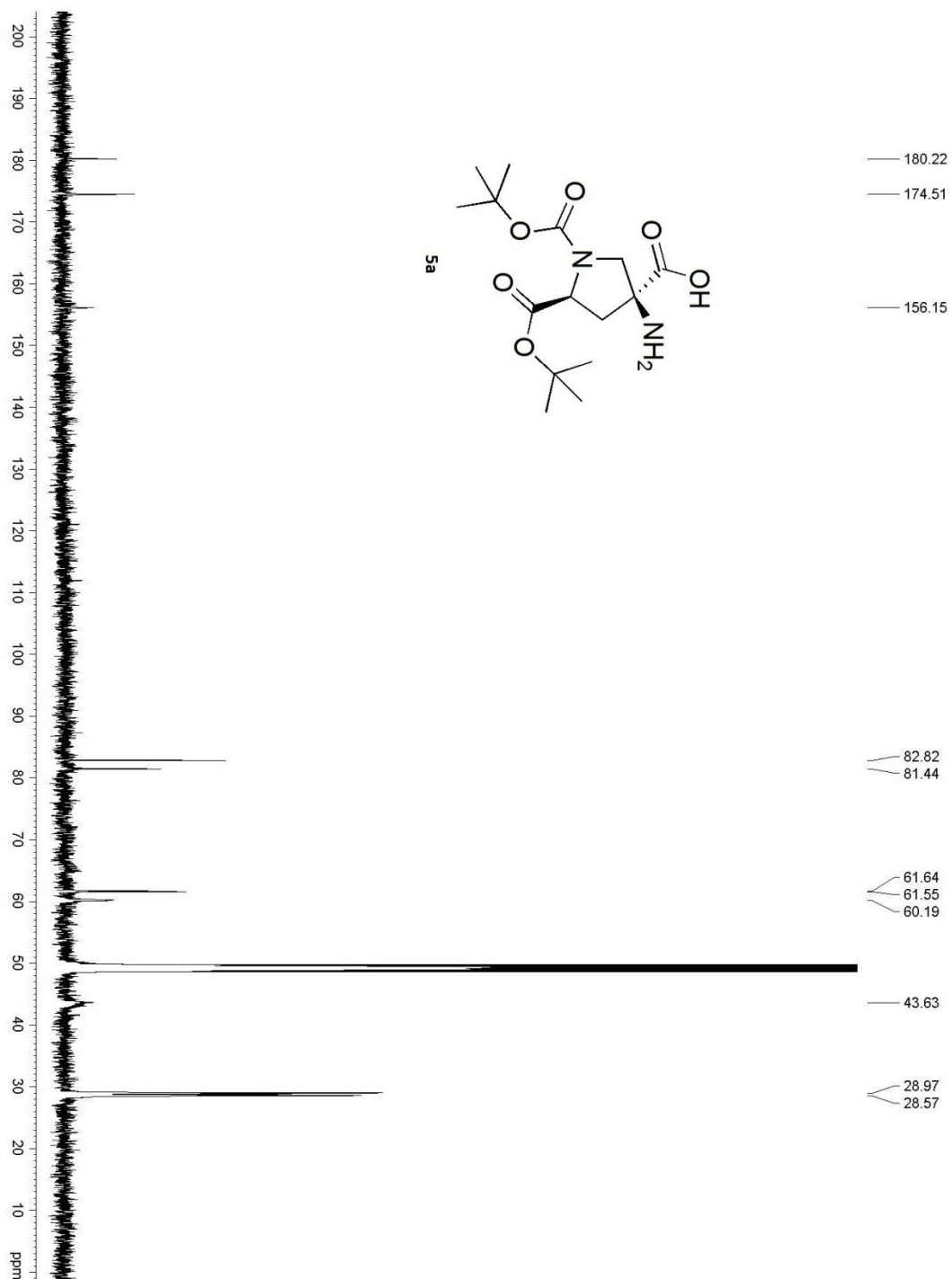
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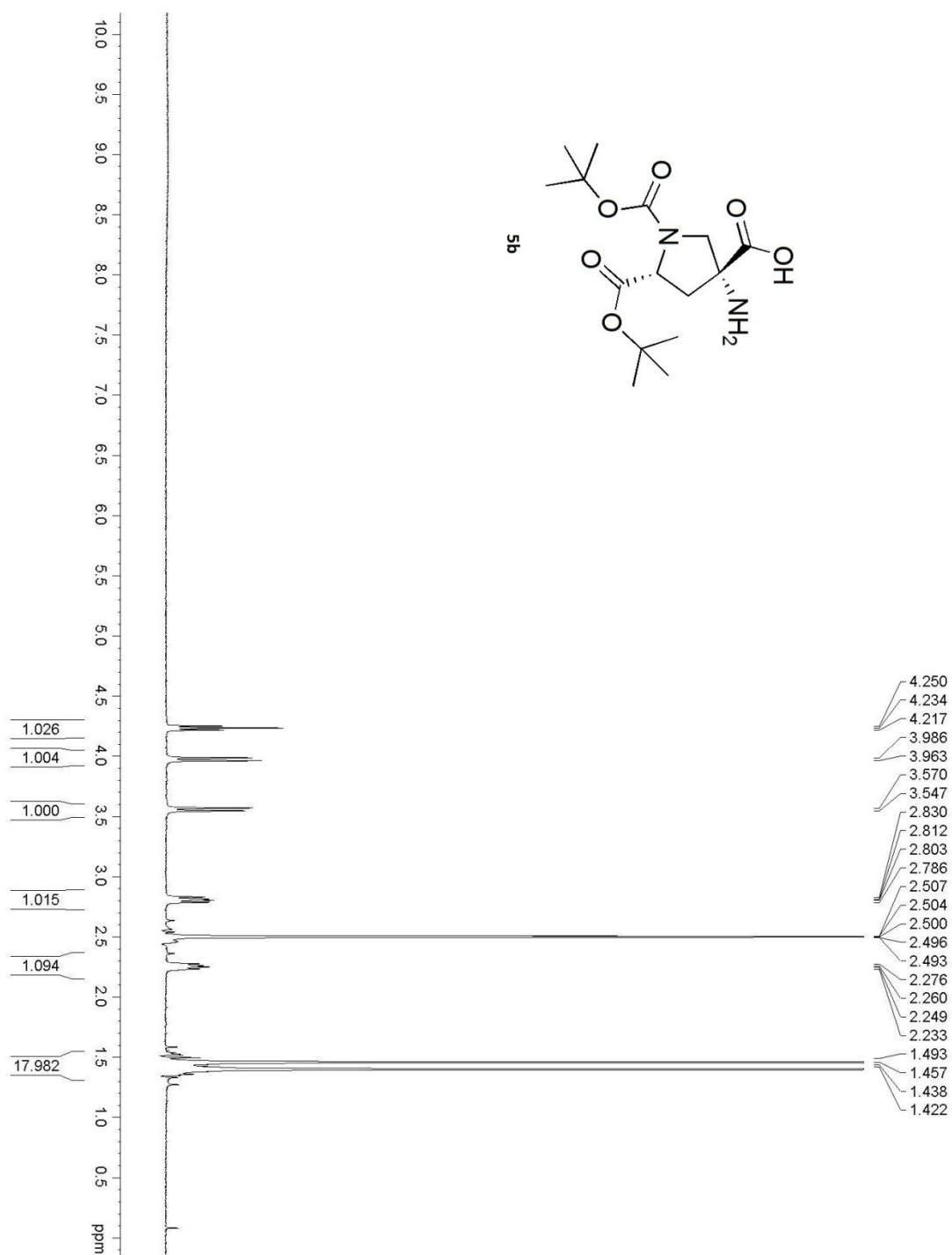
¹H-NMR of Compound 5a



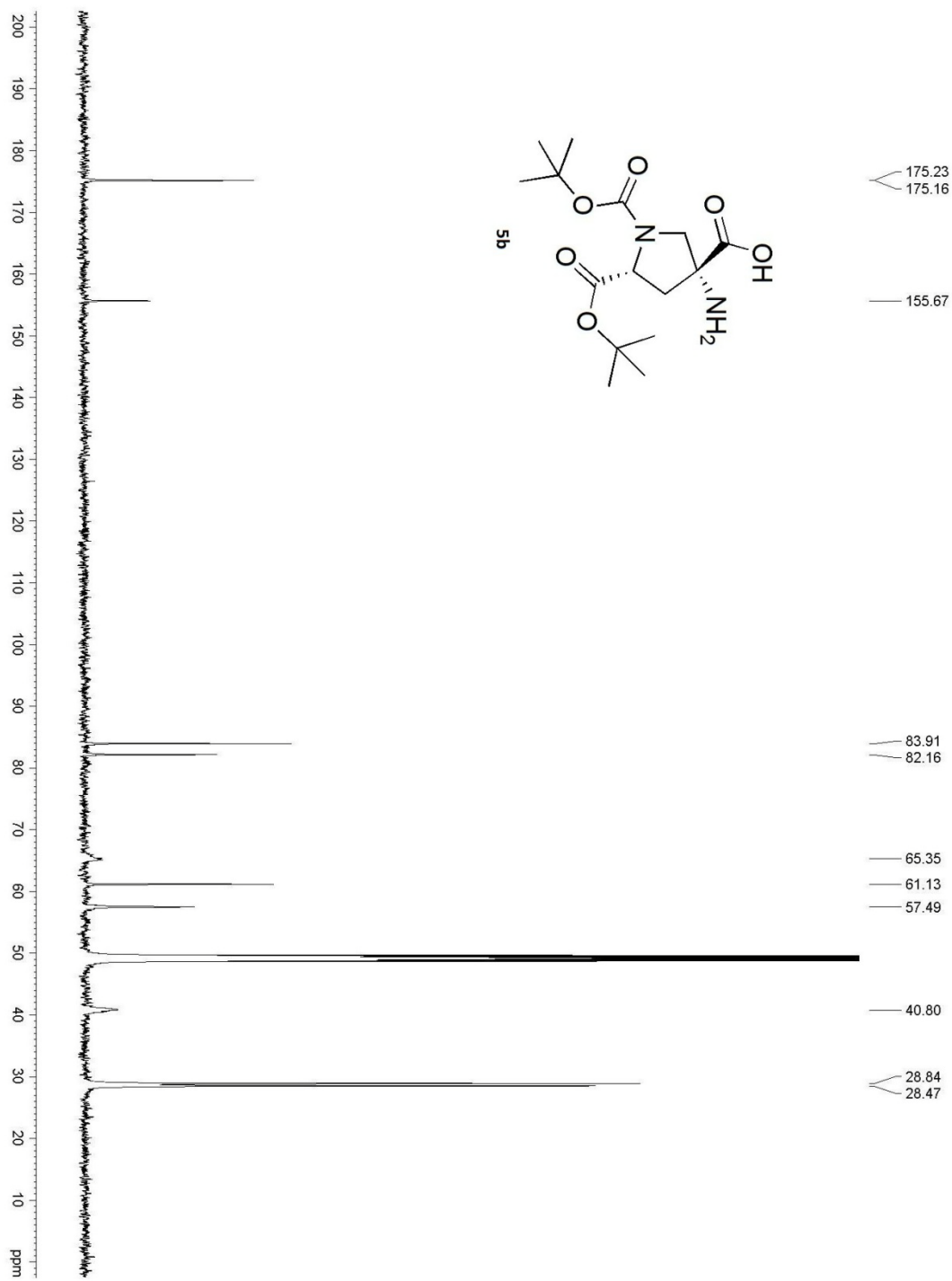
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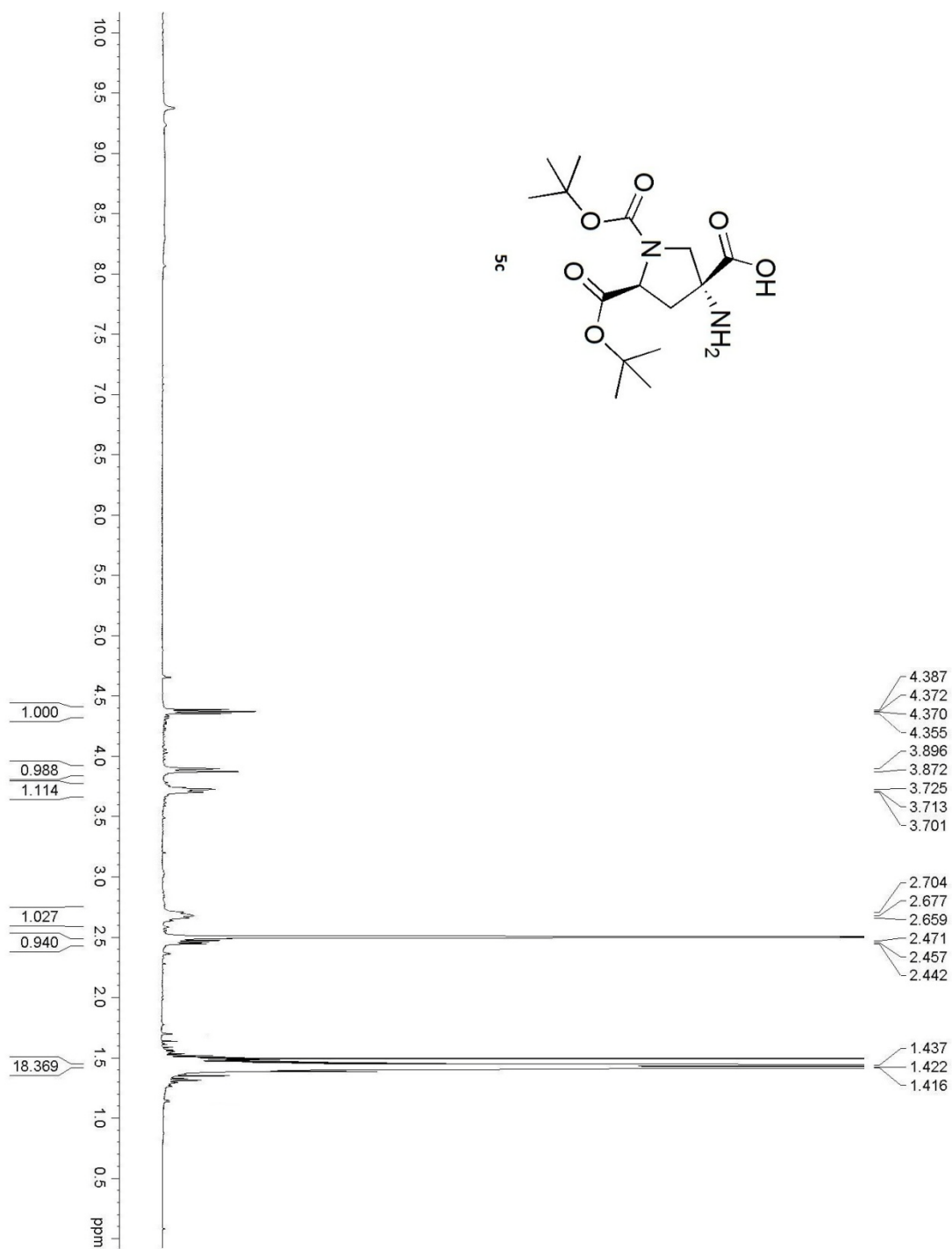
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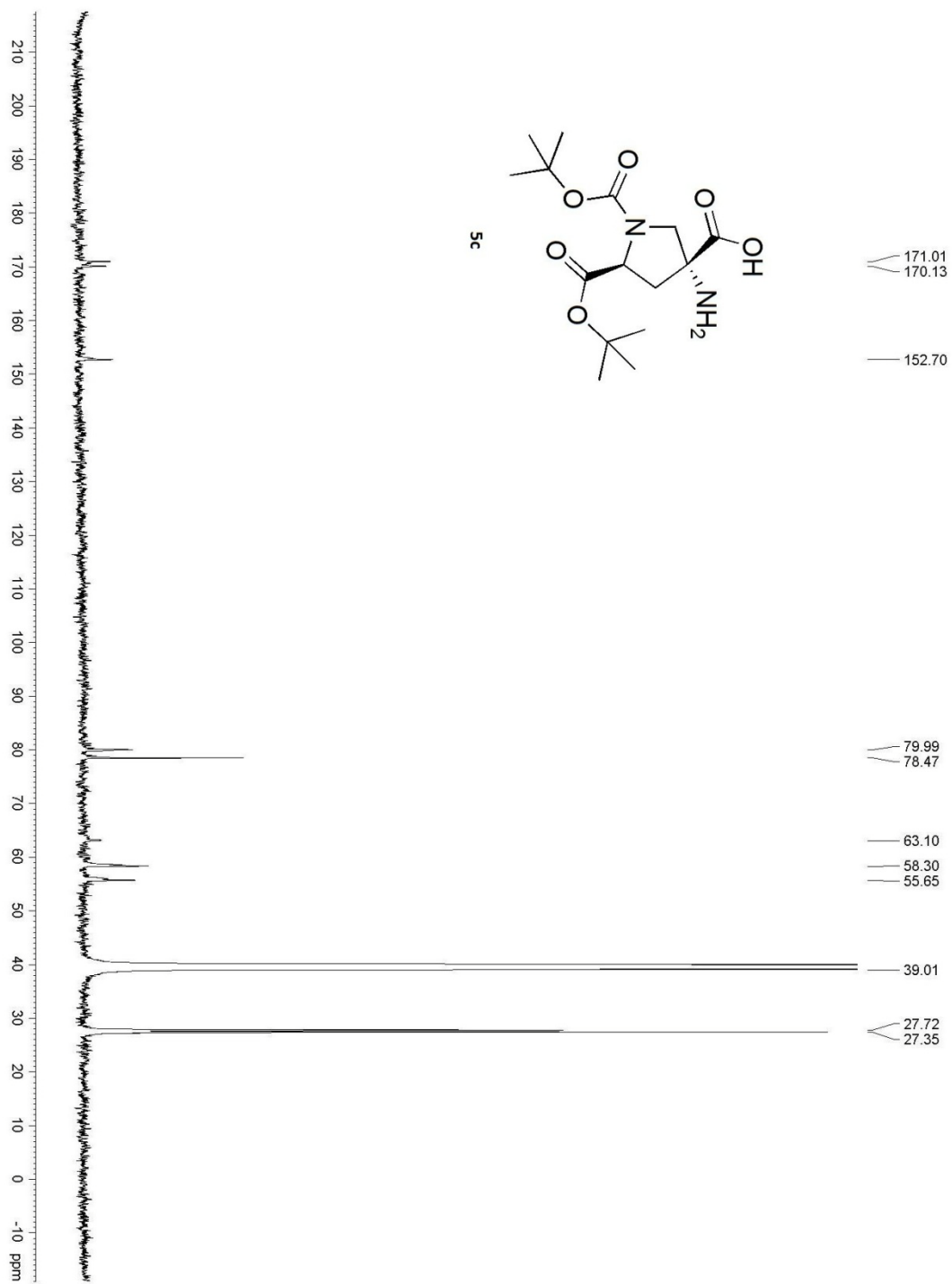
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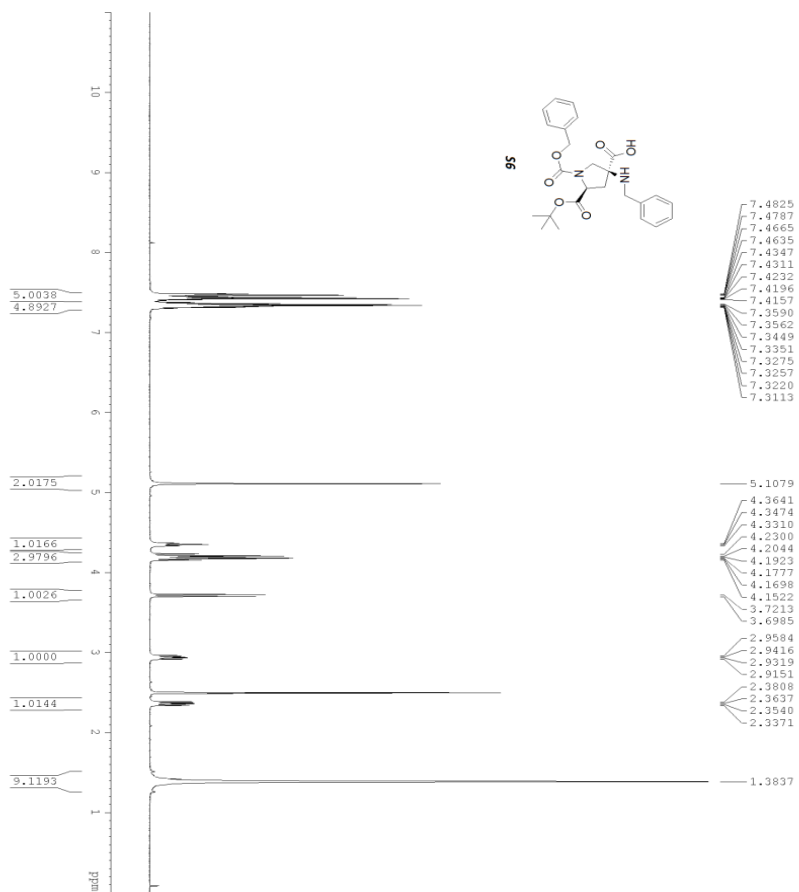
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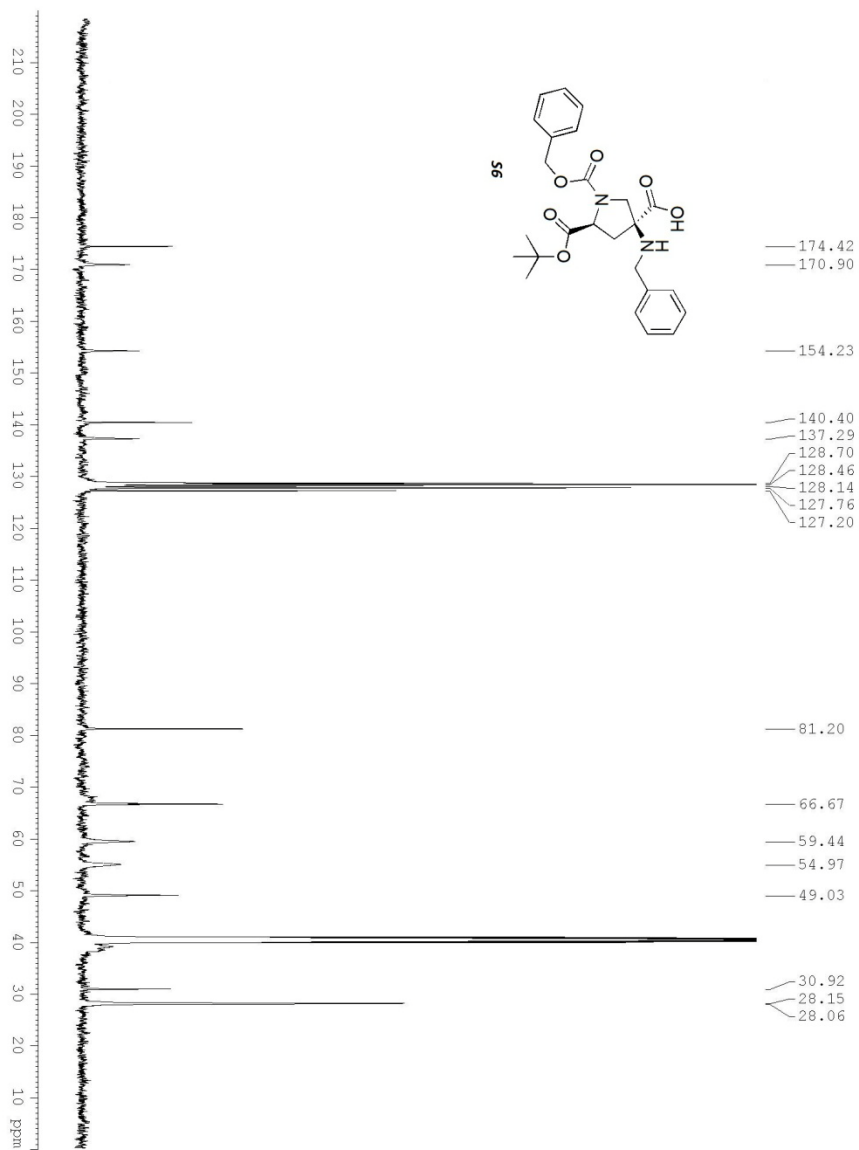
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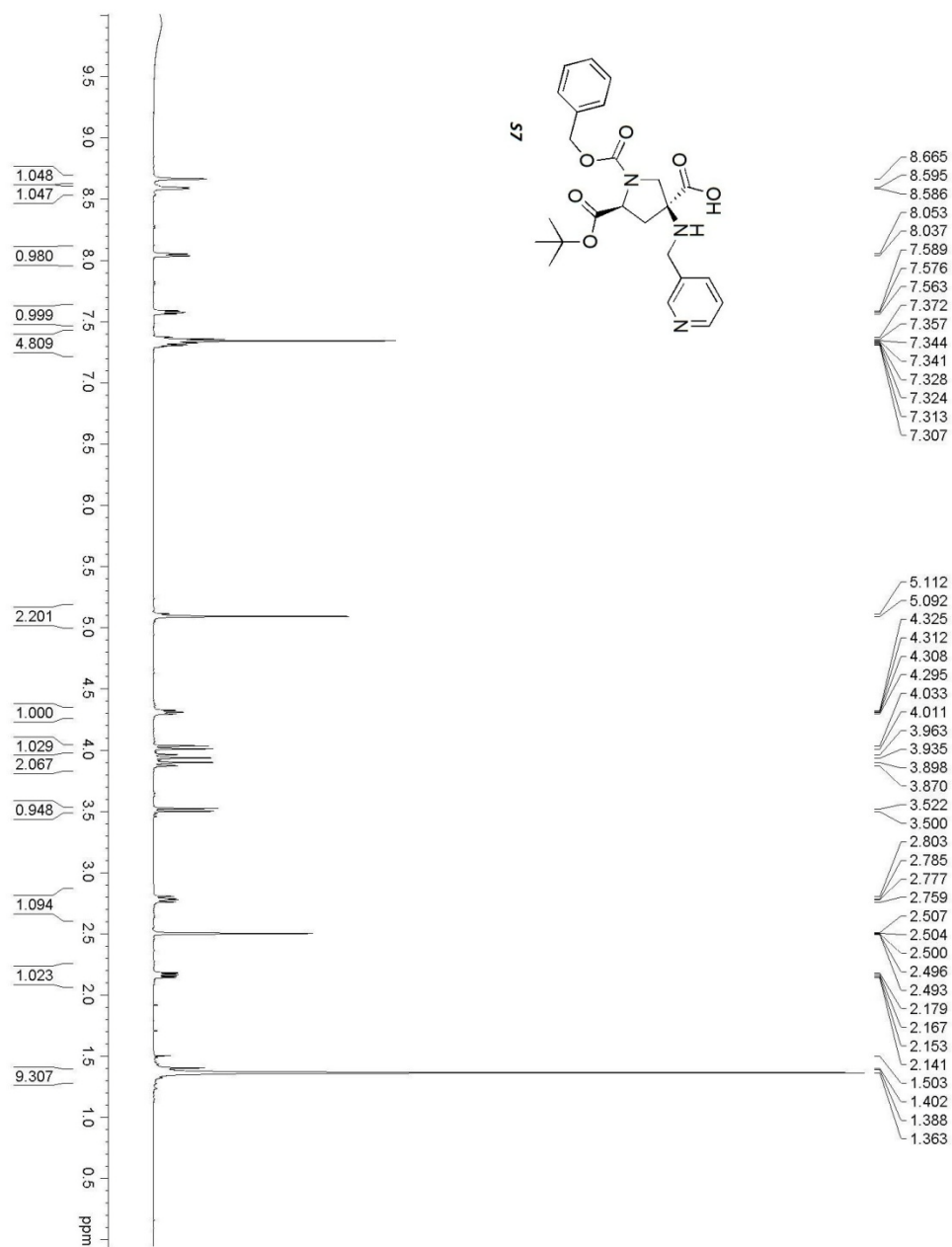
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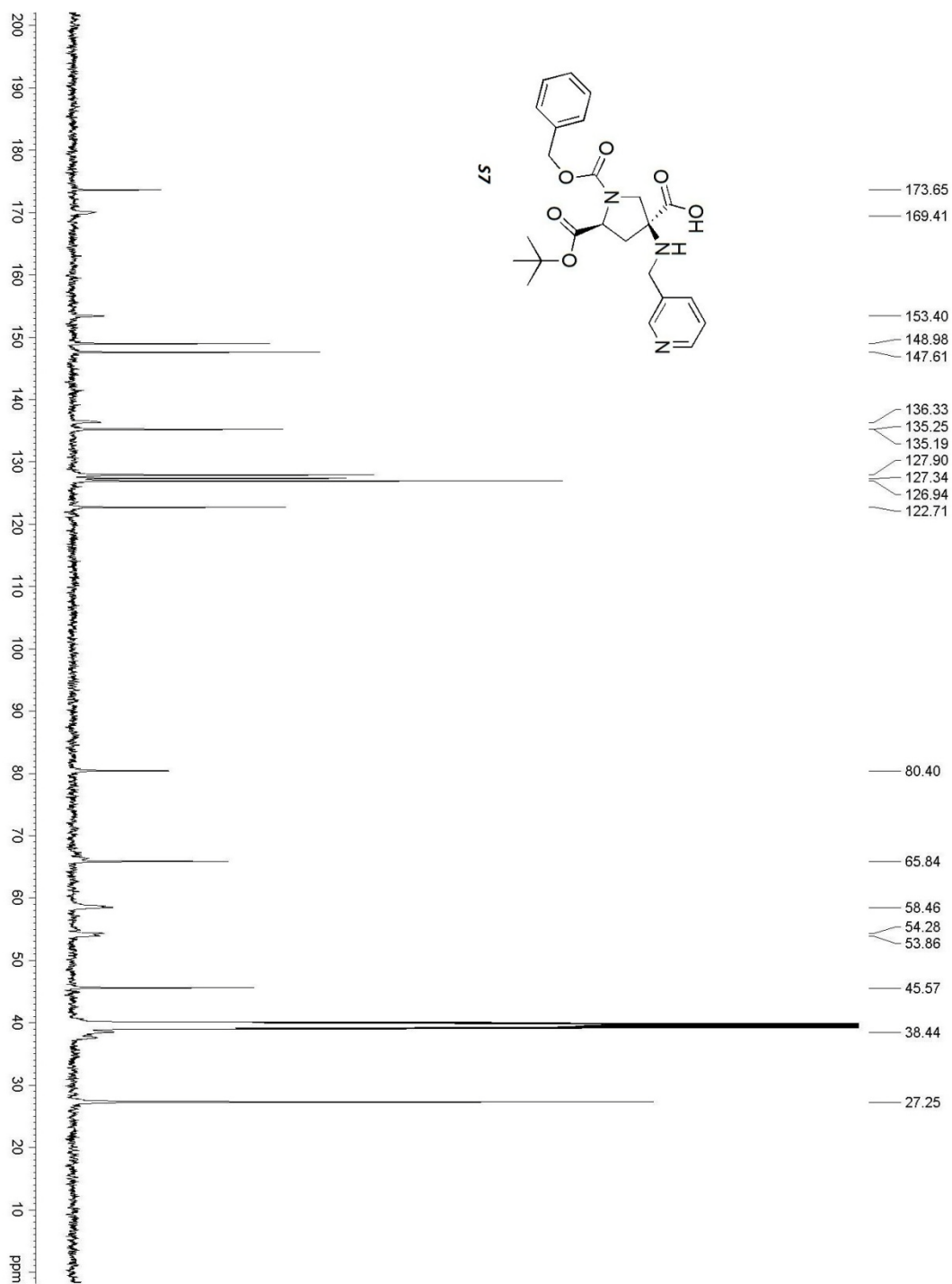
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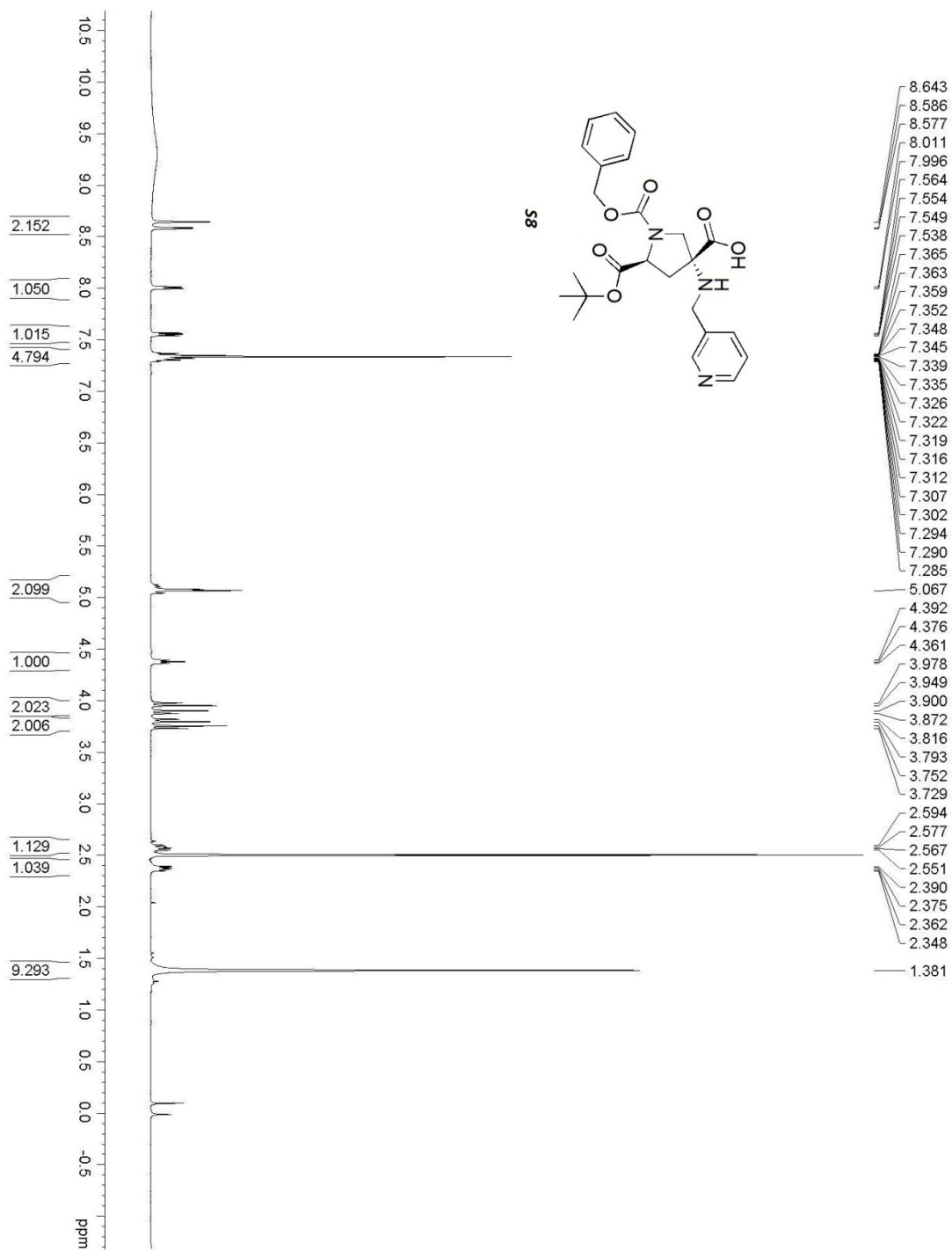
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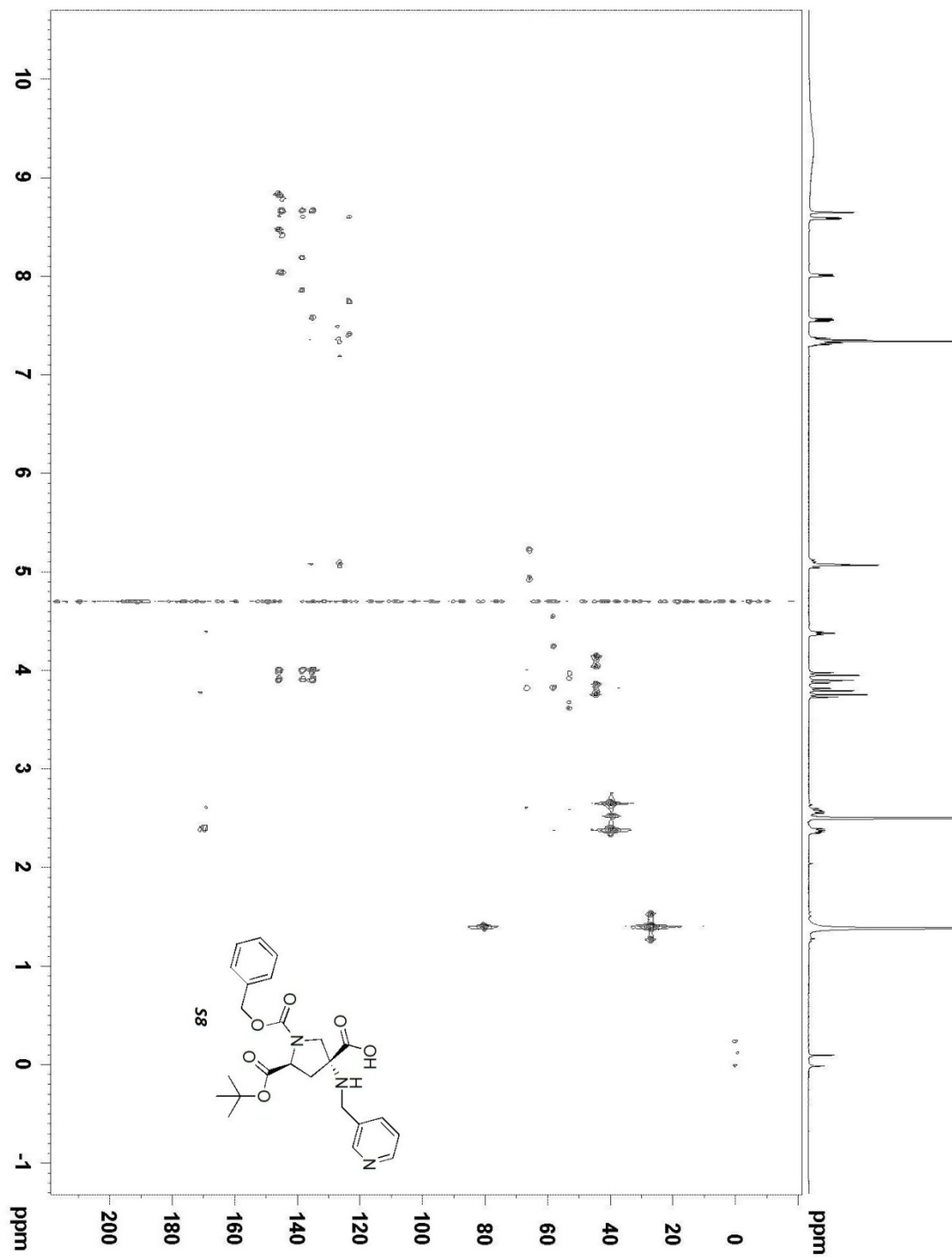
^{13}C -NMR of Compound S7



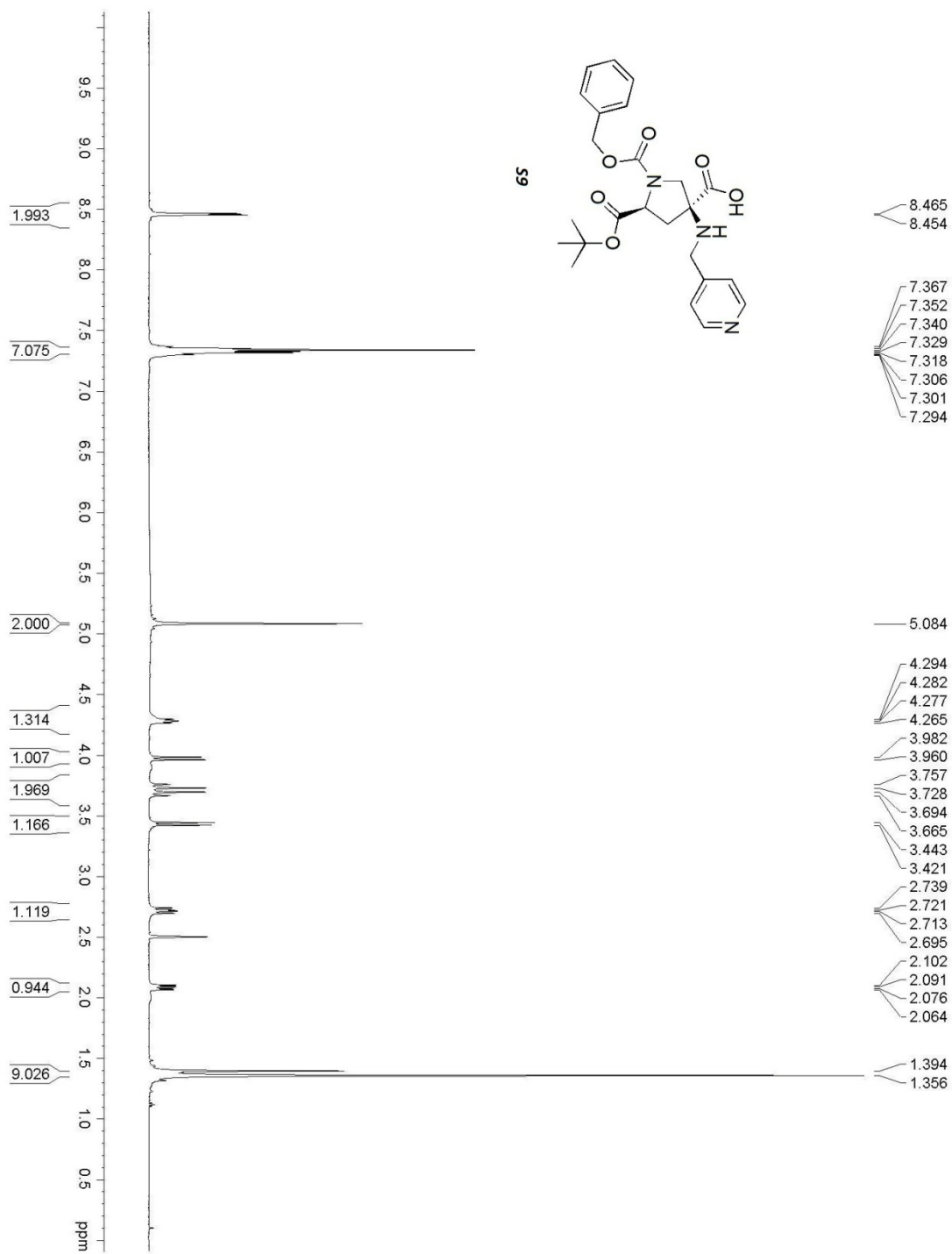
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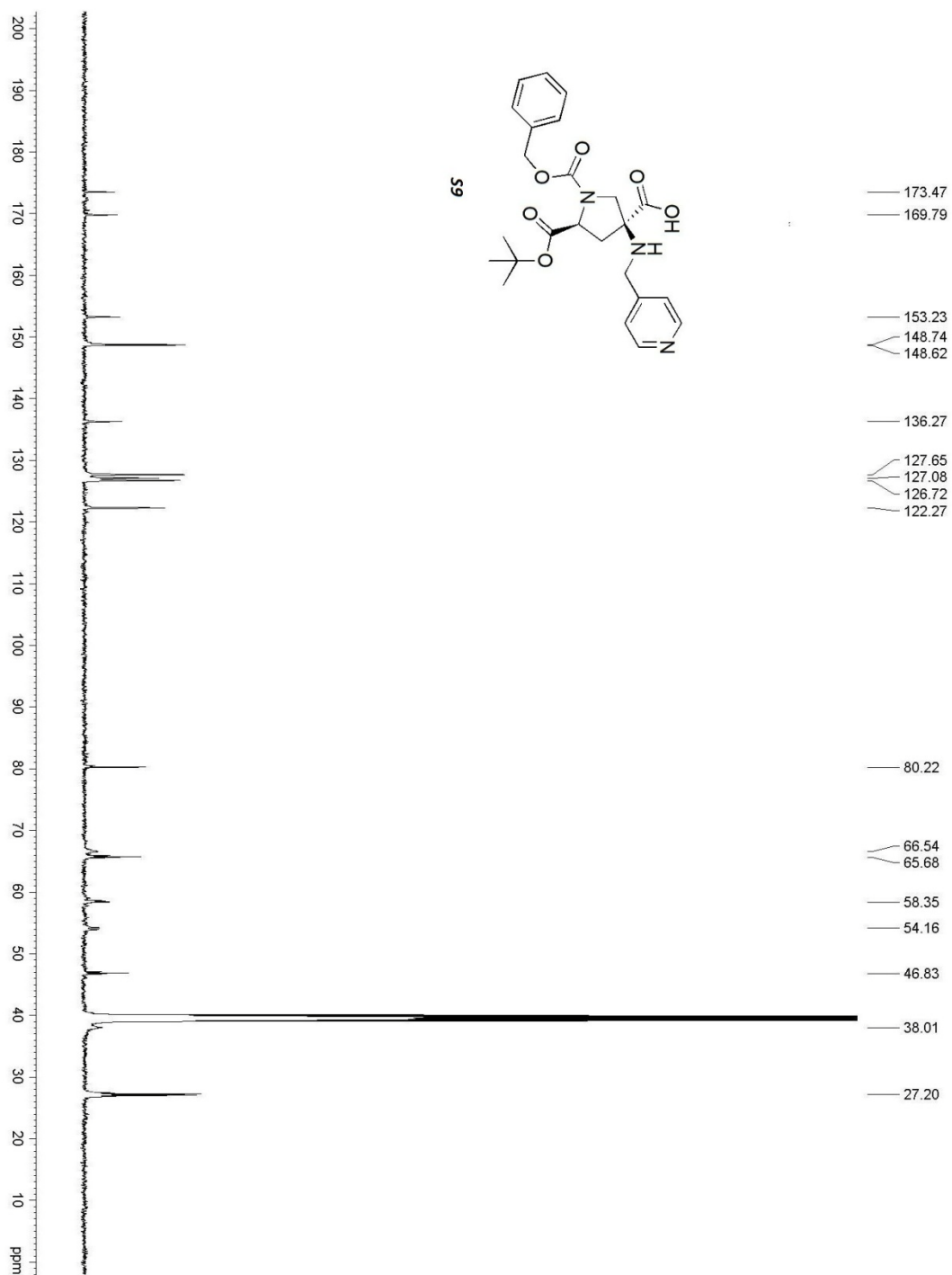
HMBC of Compound S8



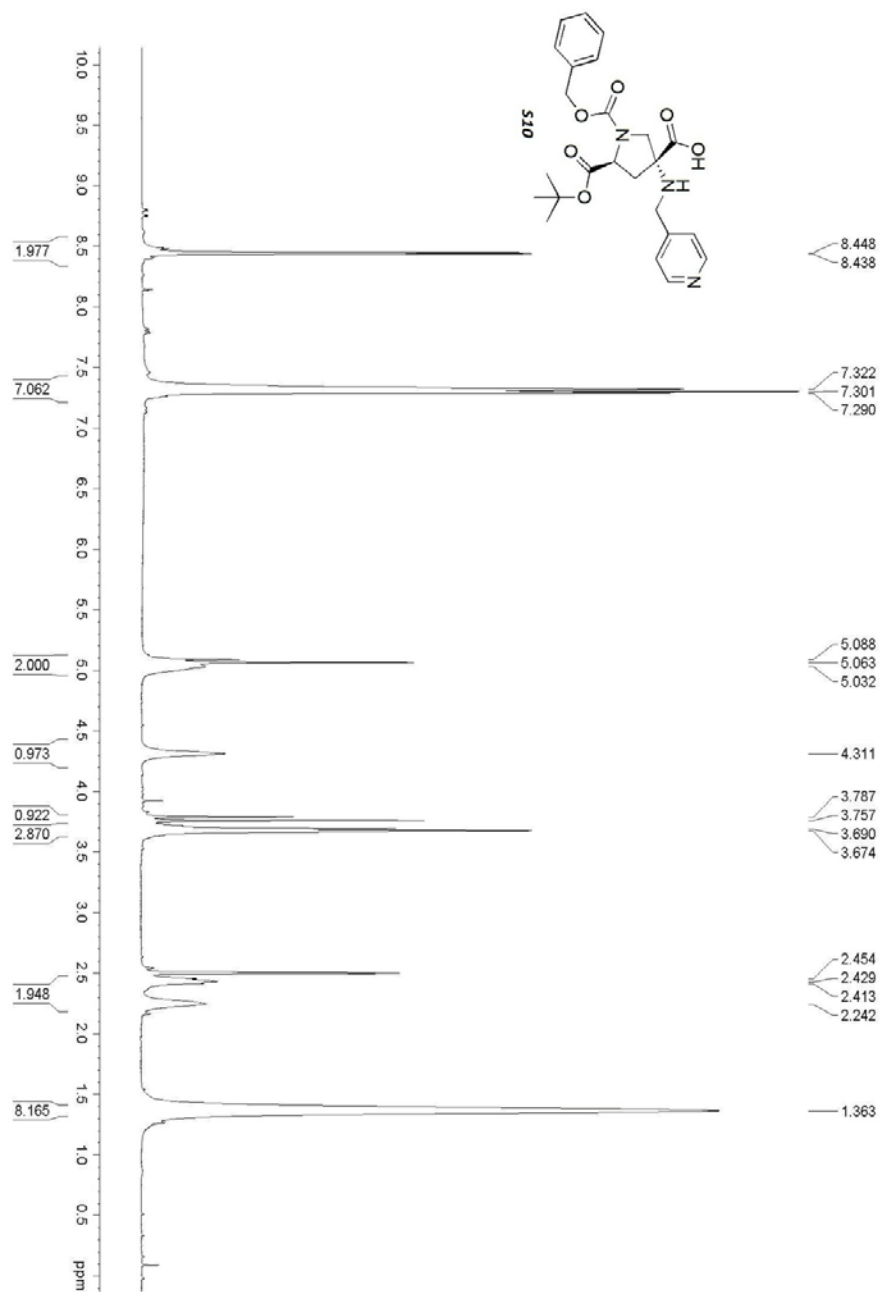
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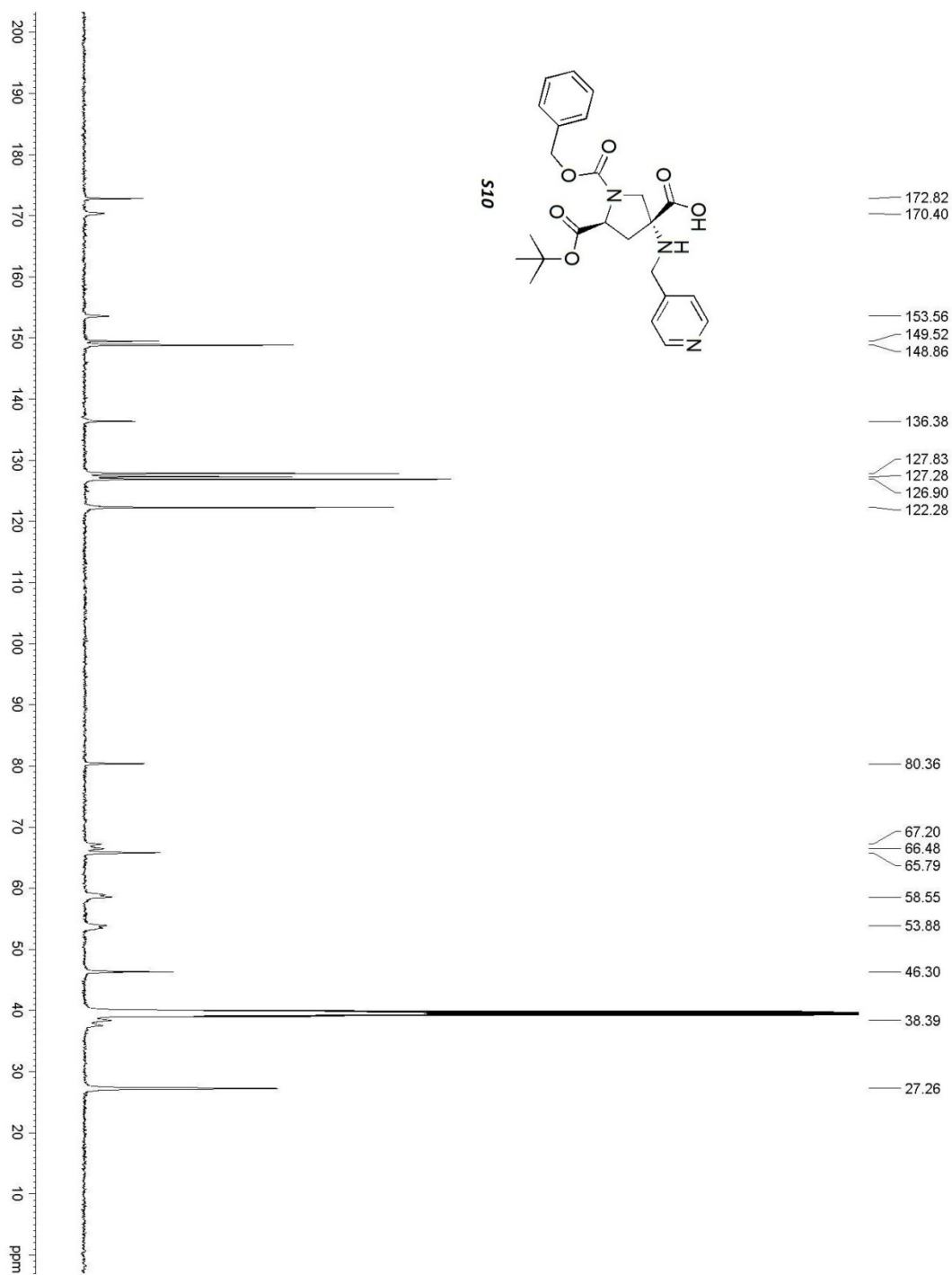
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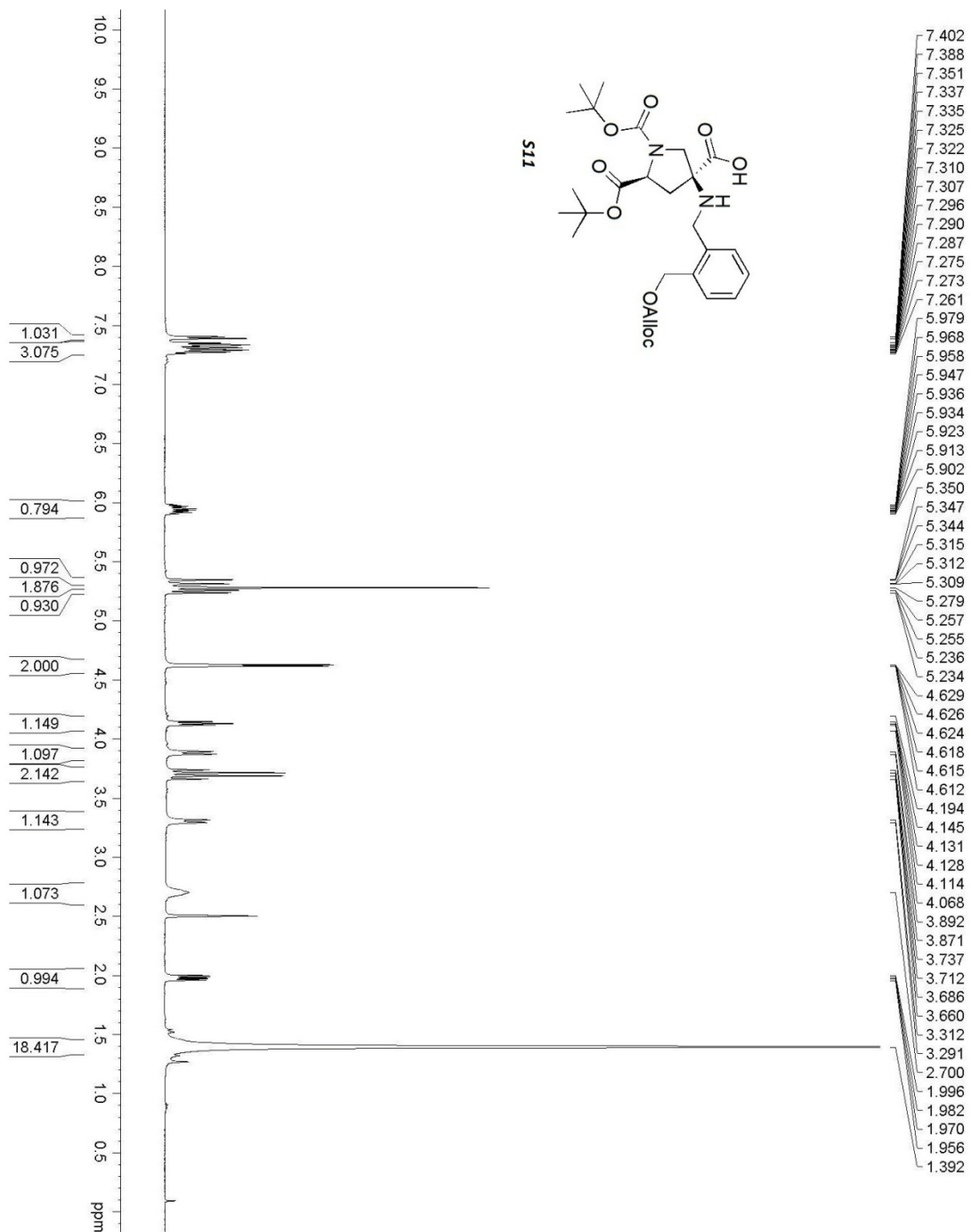
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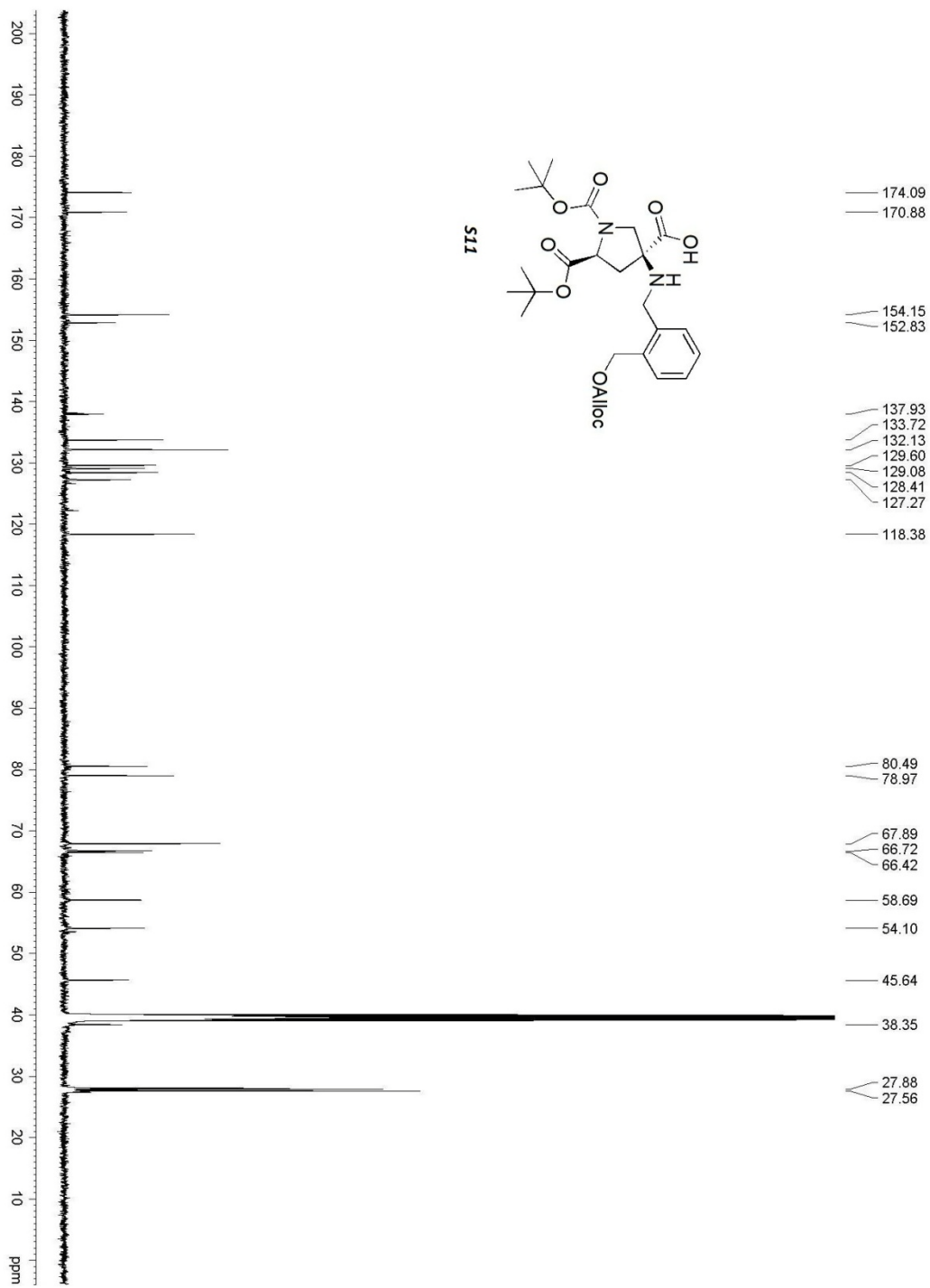
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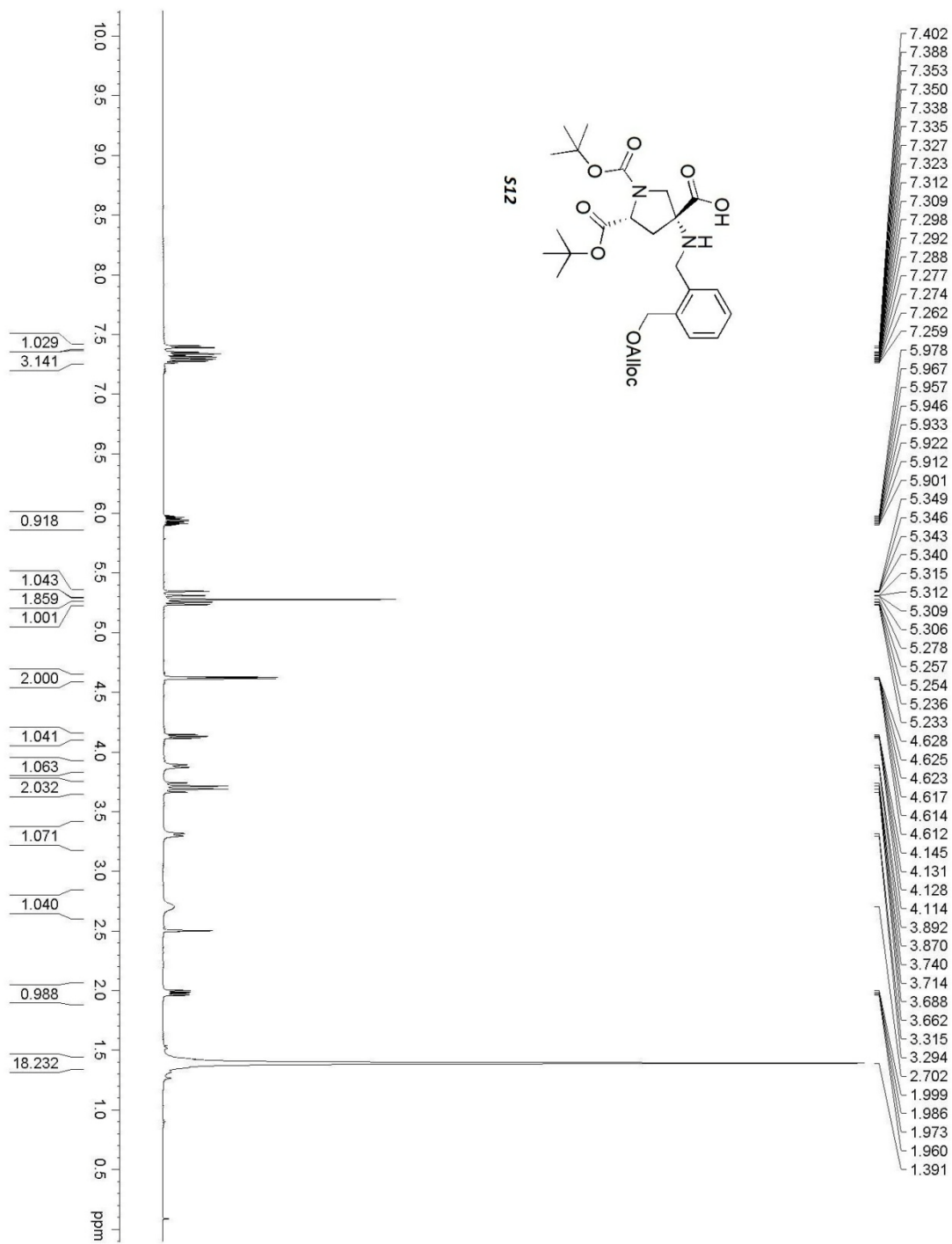
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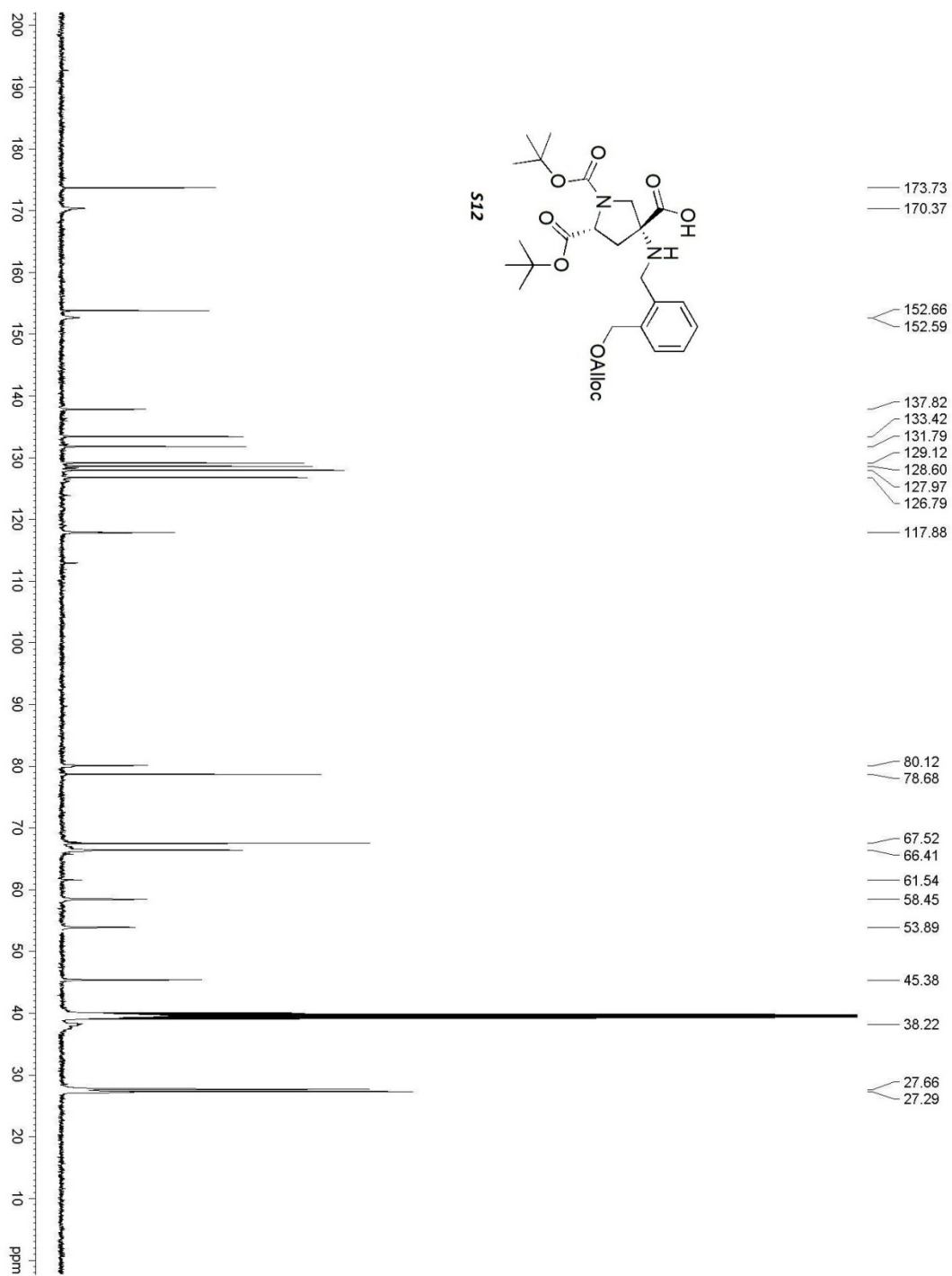
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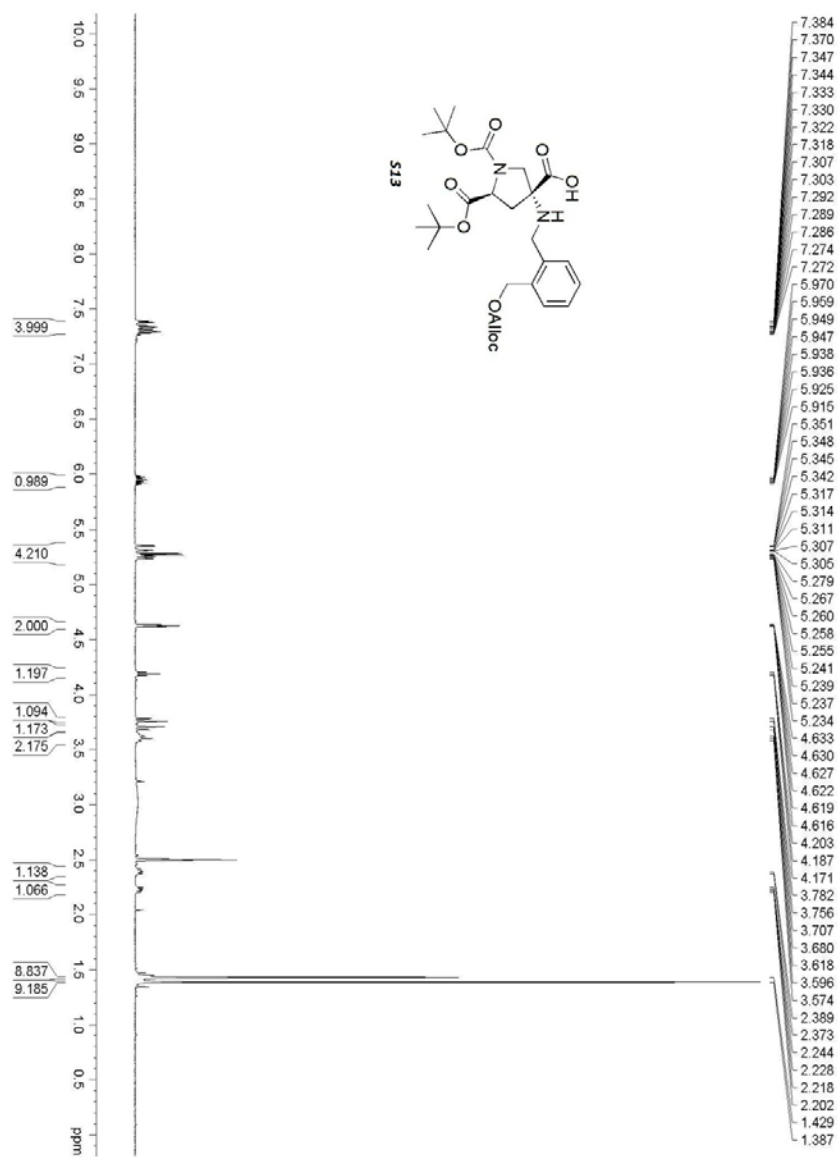
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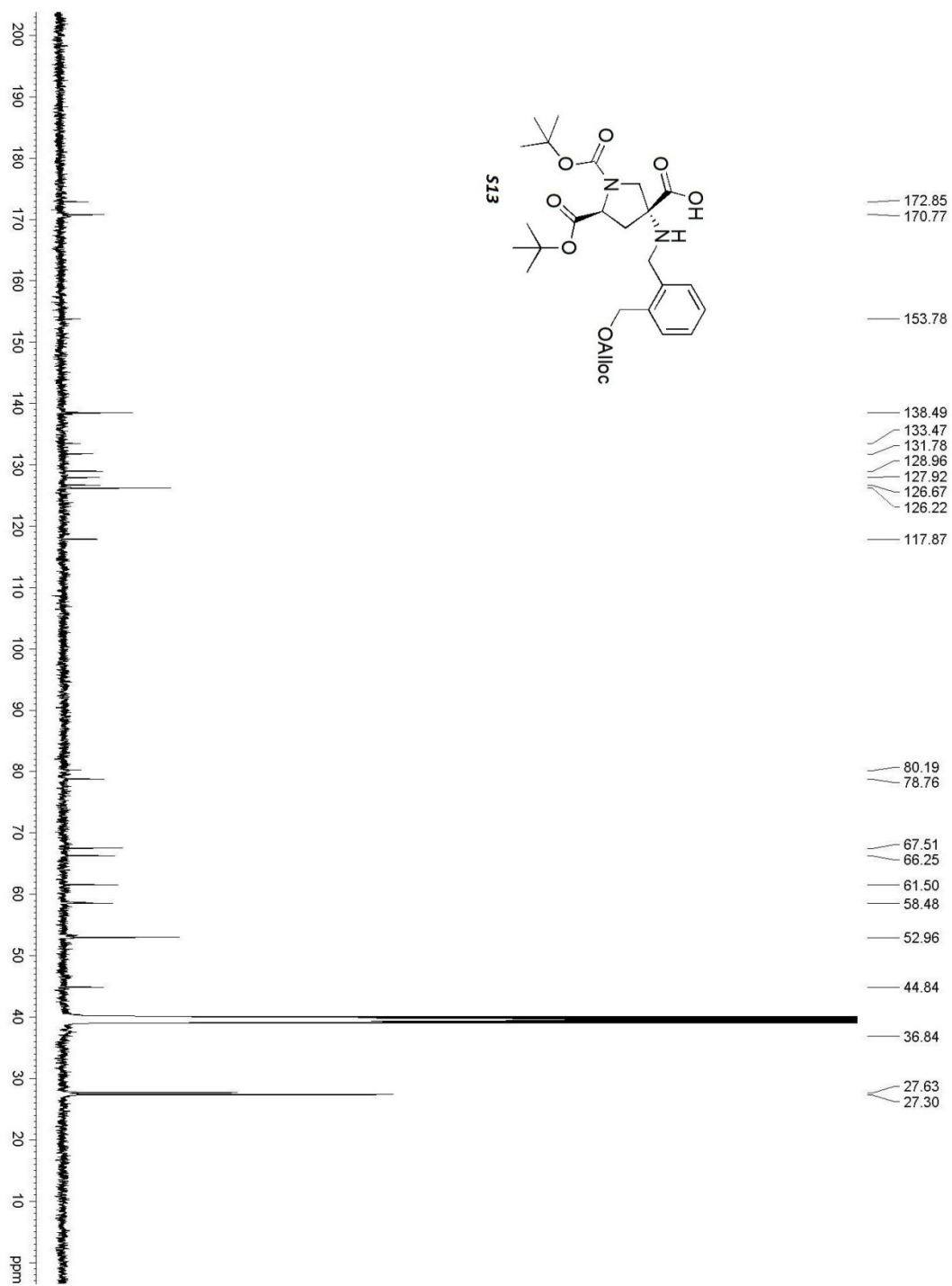
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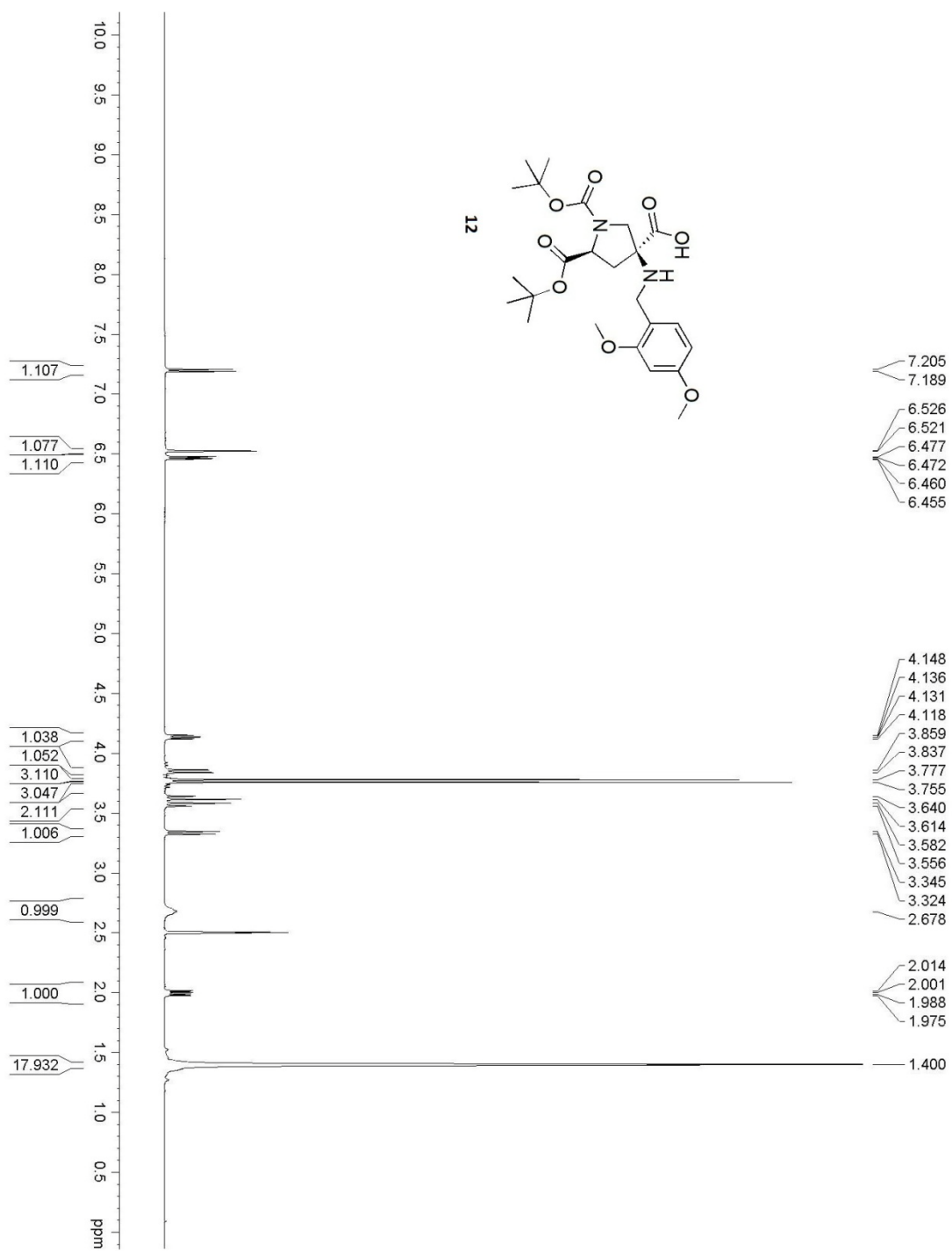
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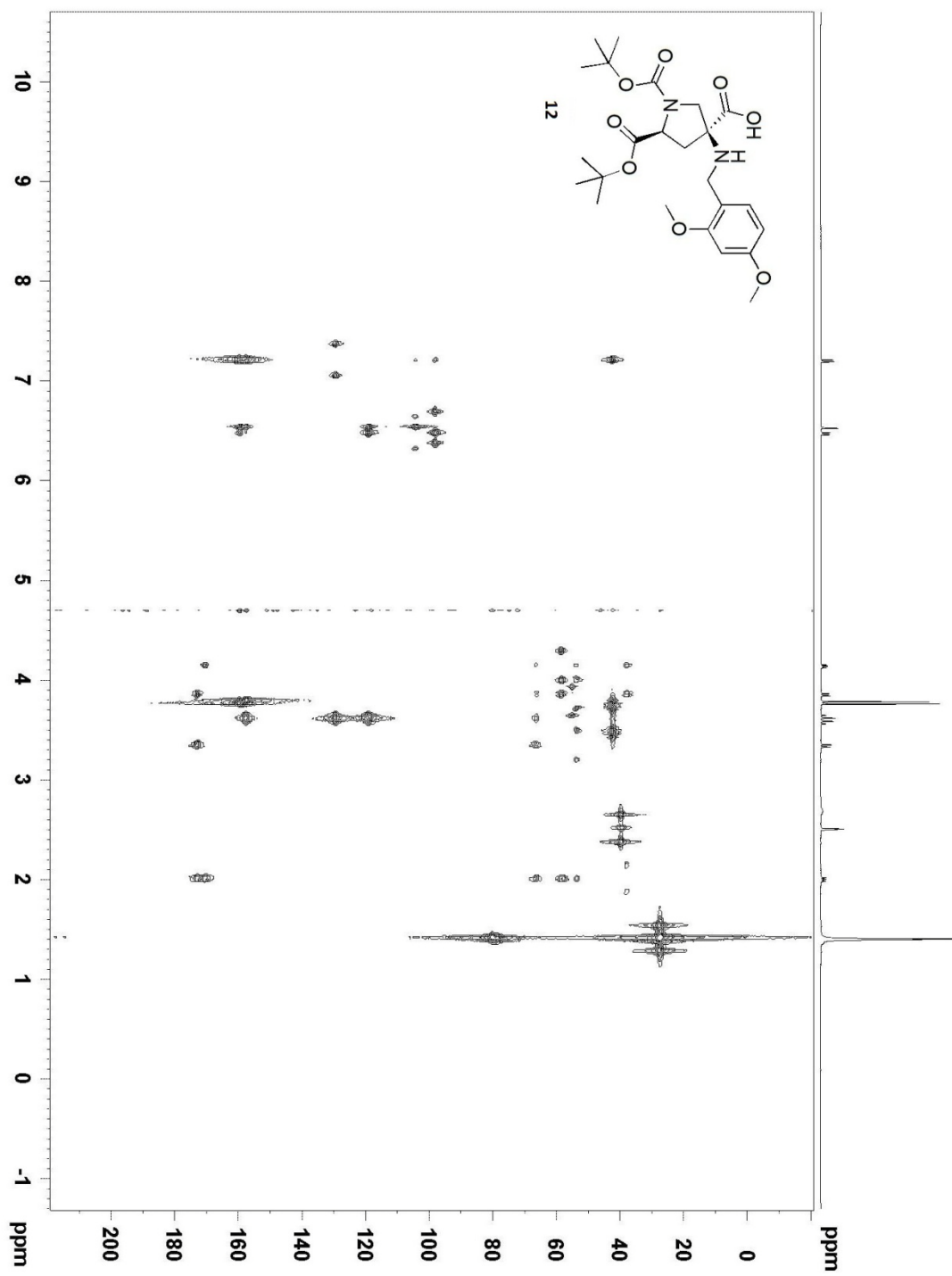
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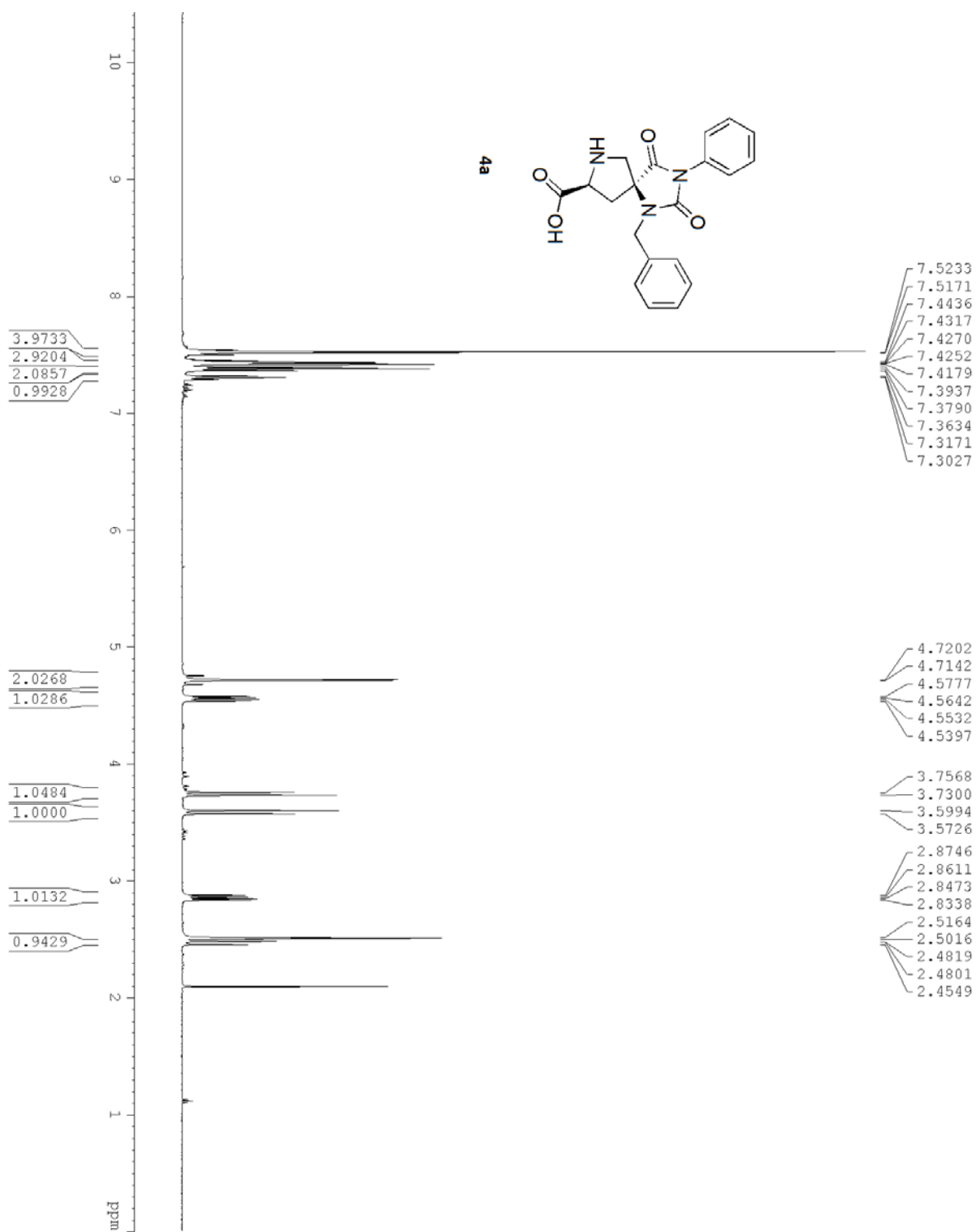
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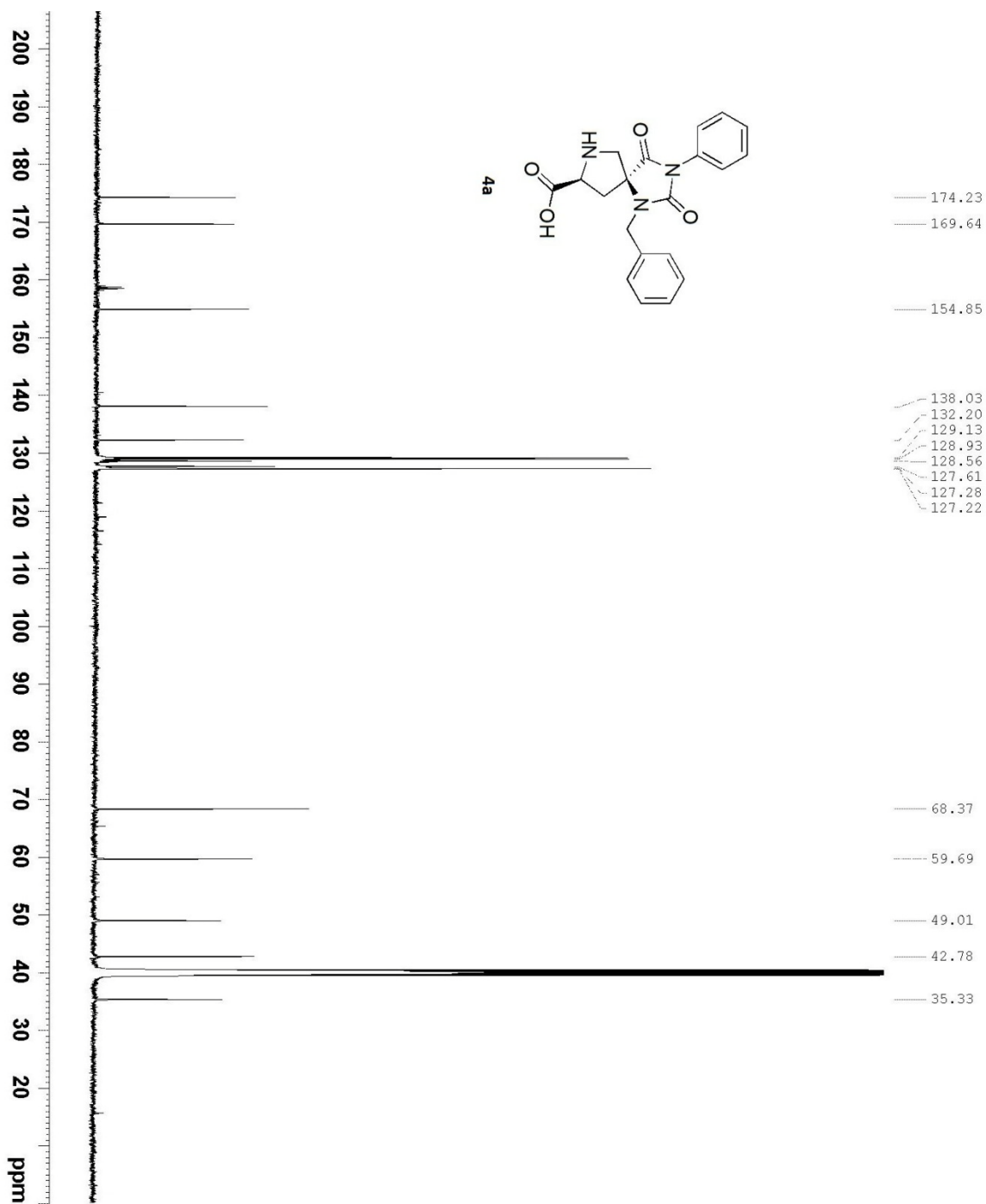
HMBC of Compound 12



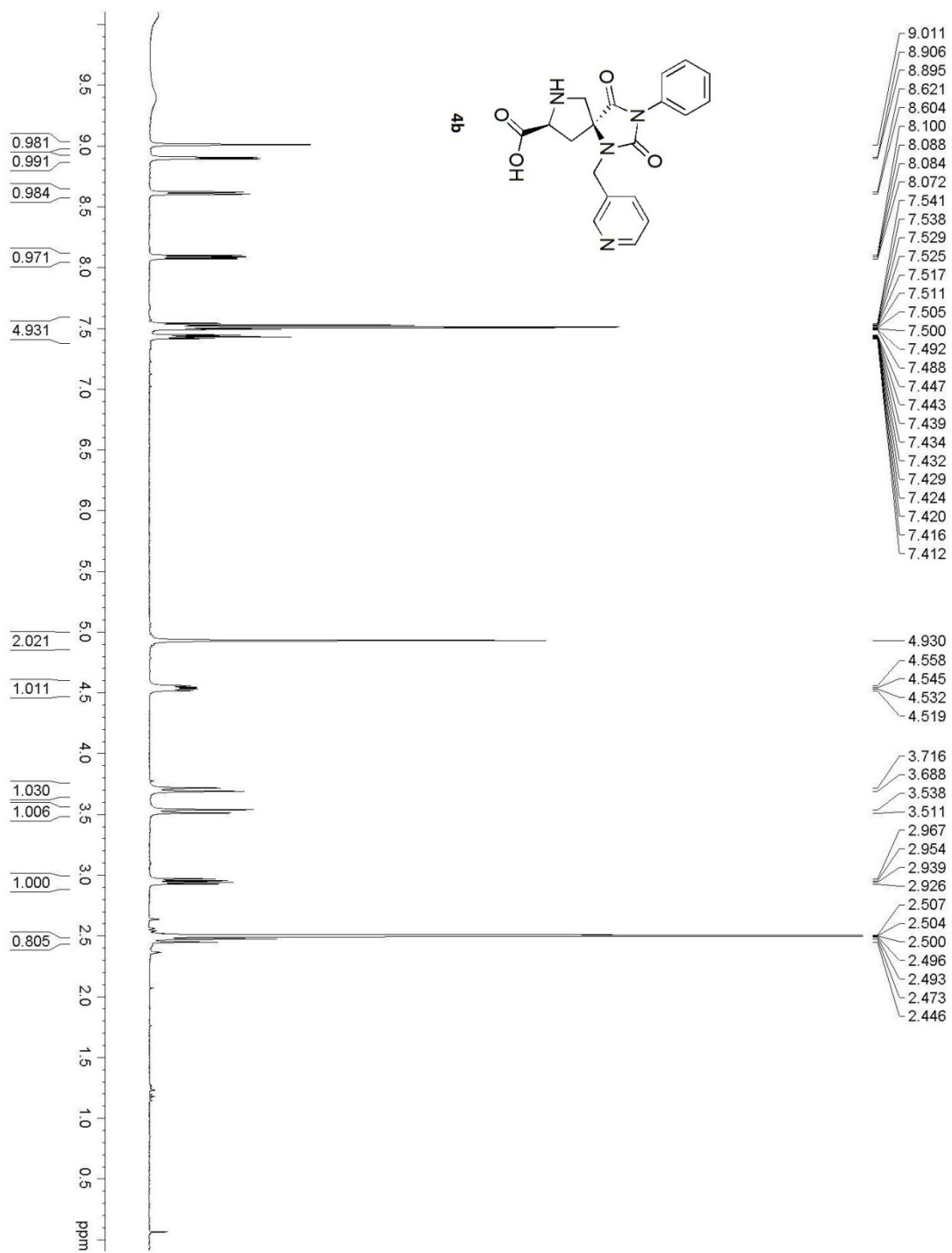
¹H-NMR of Compound 4a



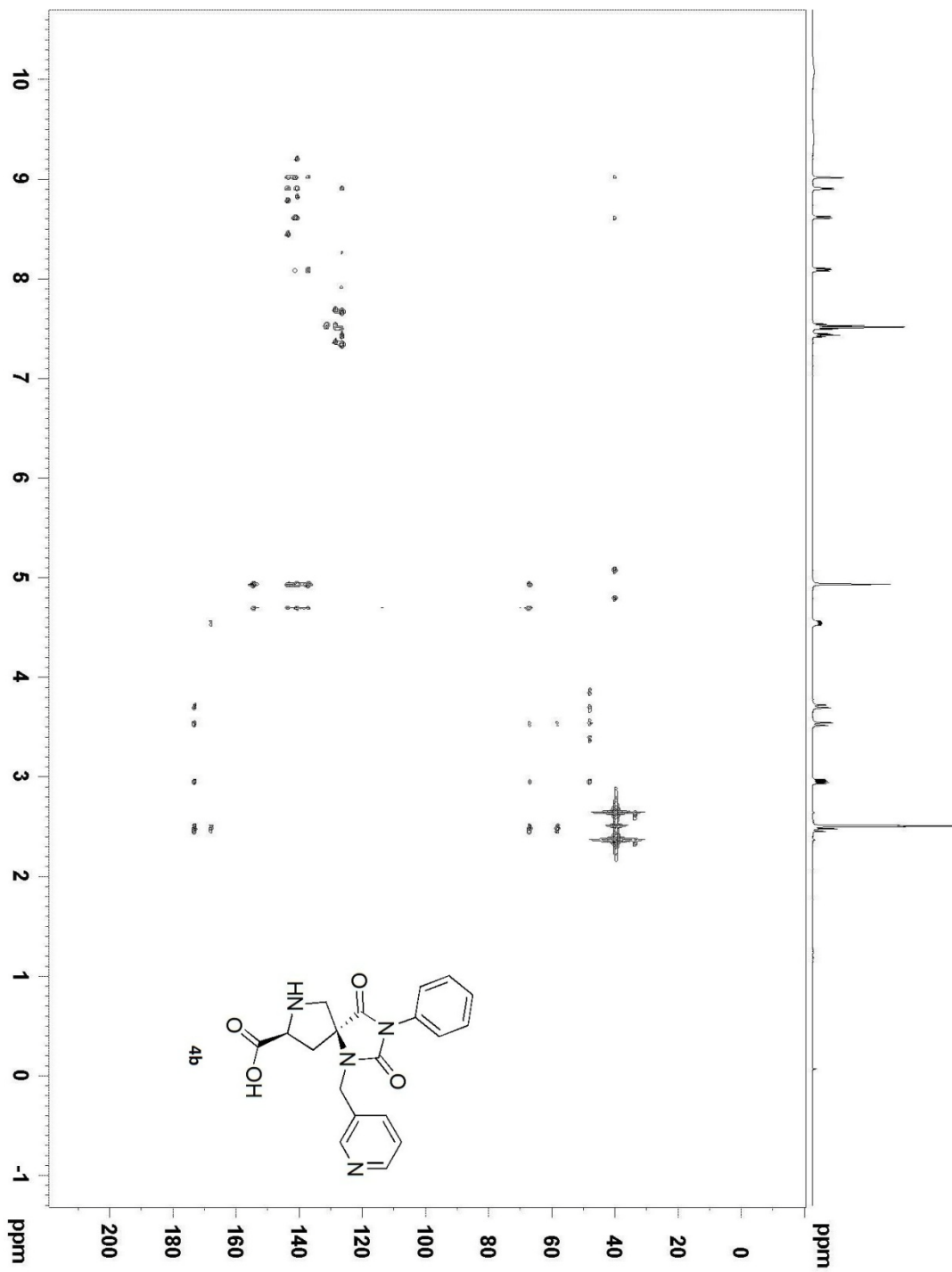
^{13}C -NMR of Compound **4a**



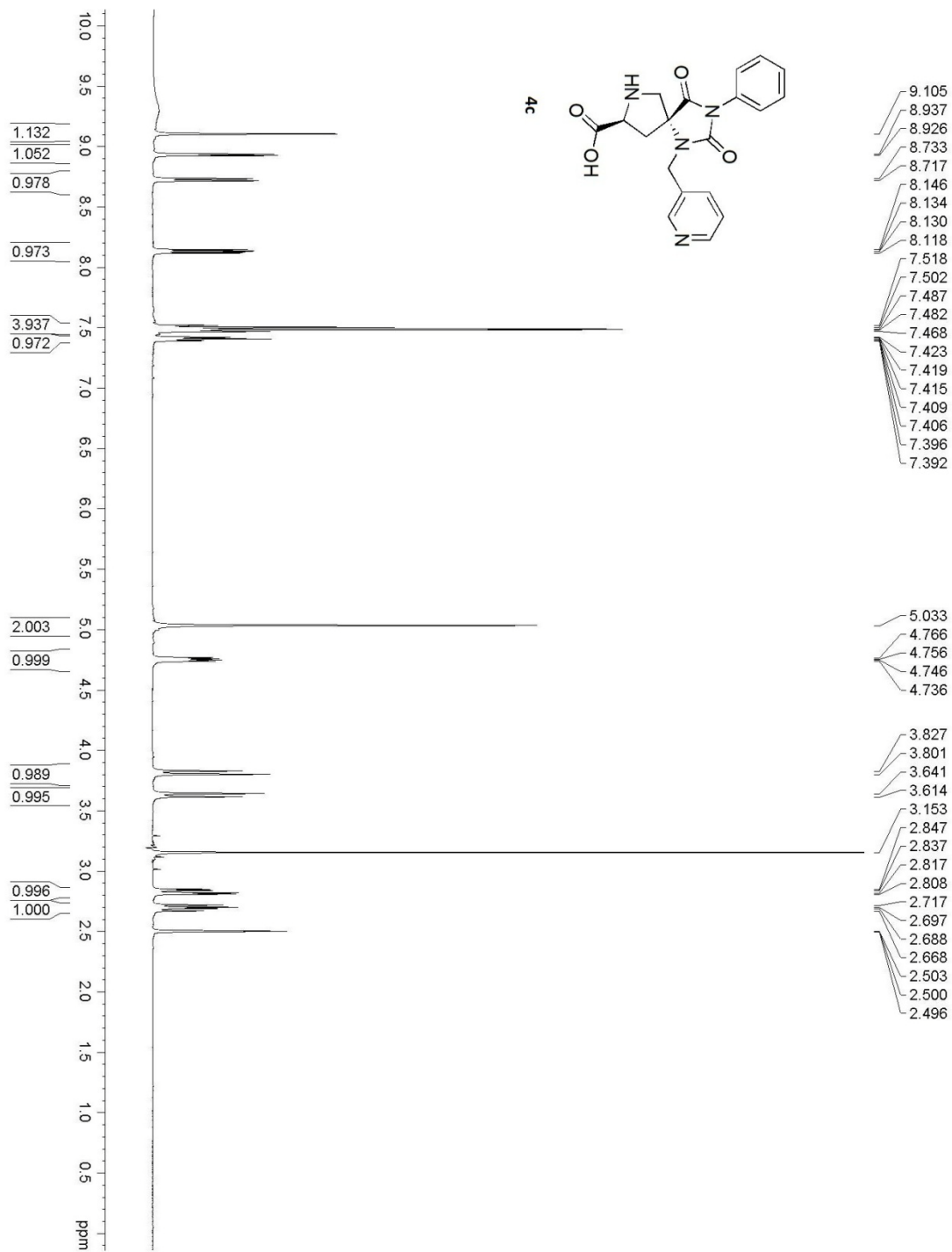
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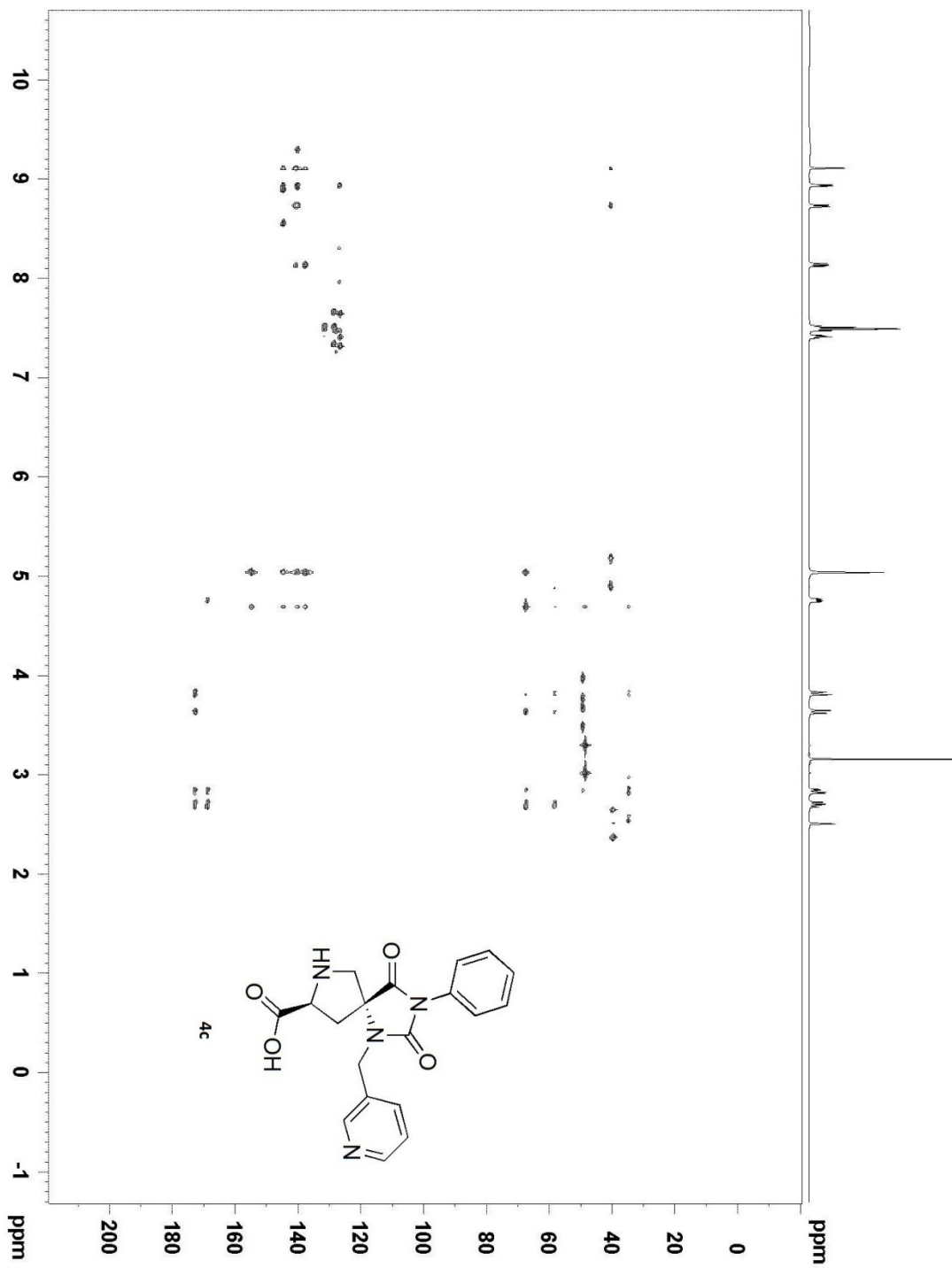
HMBC of Compound 4b



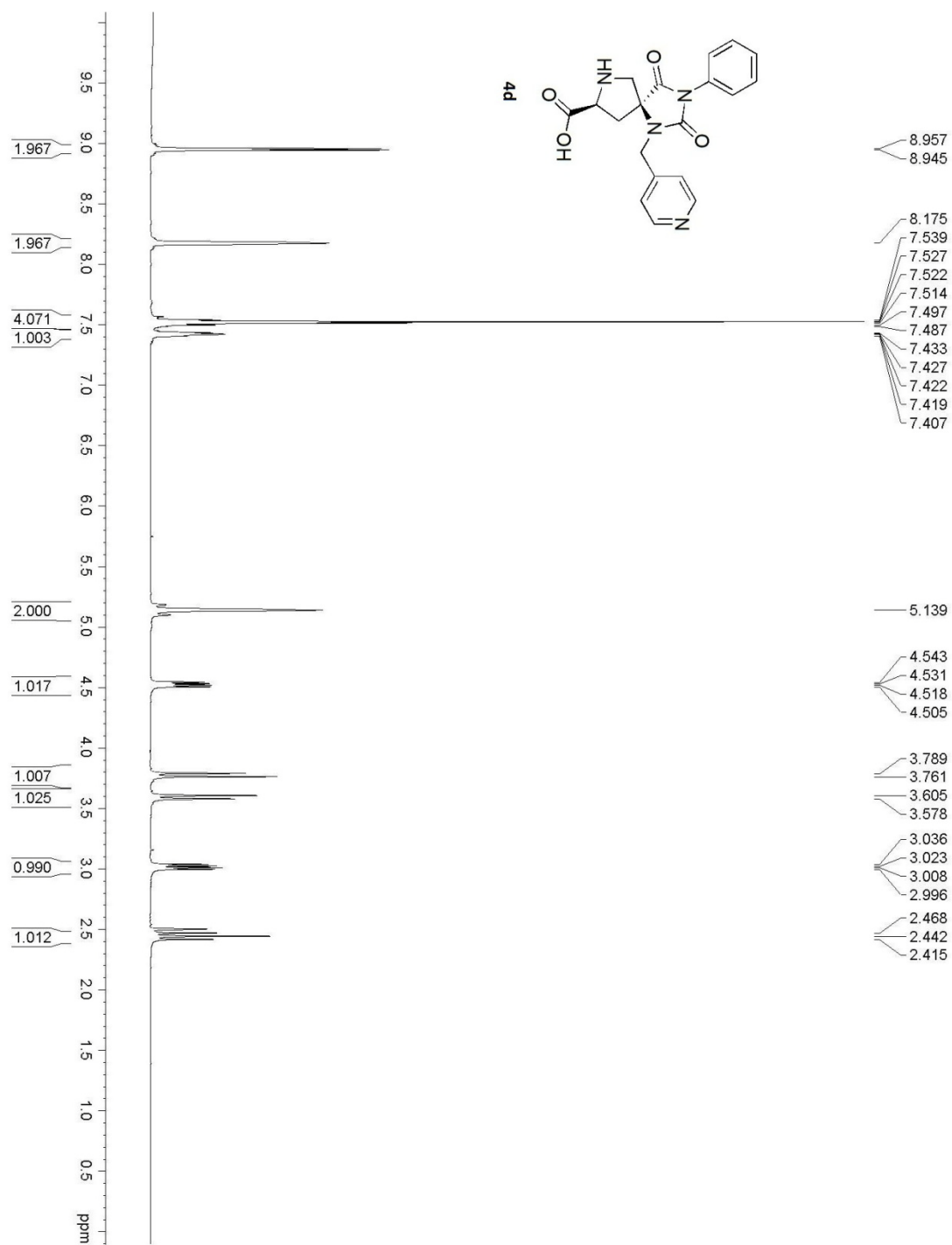
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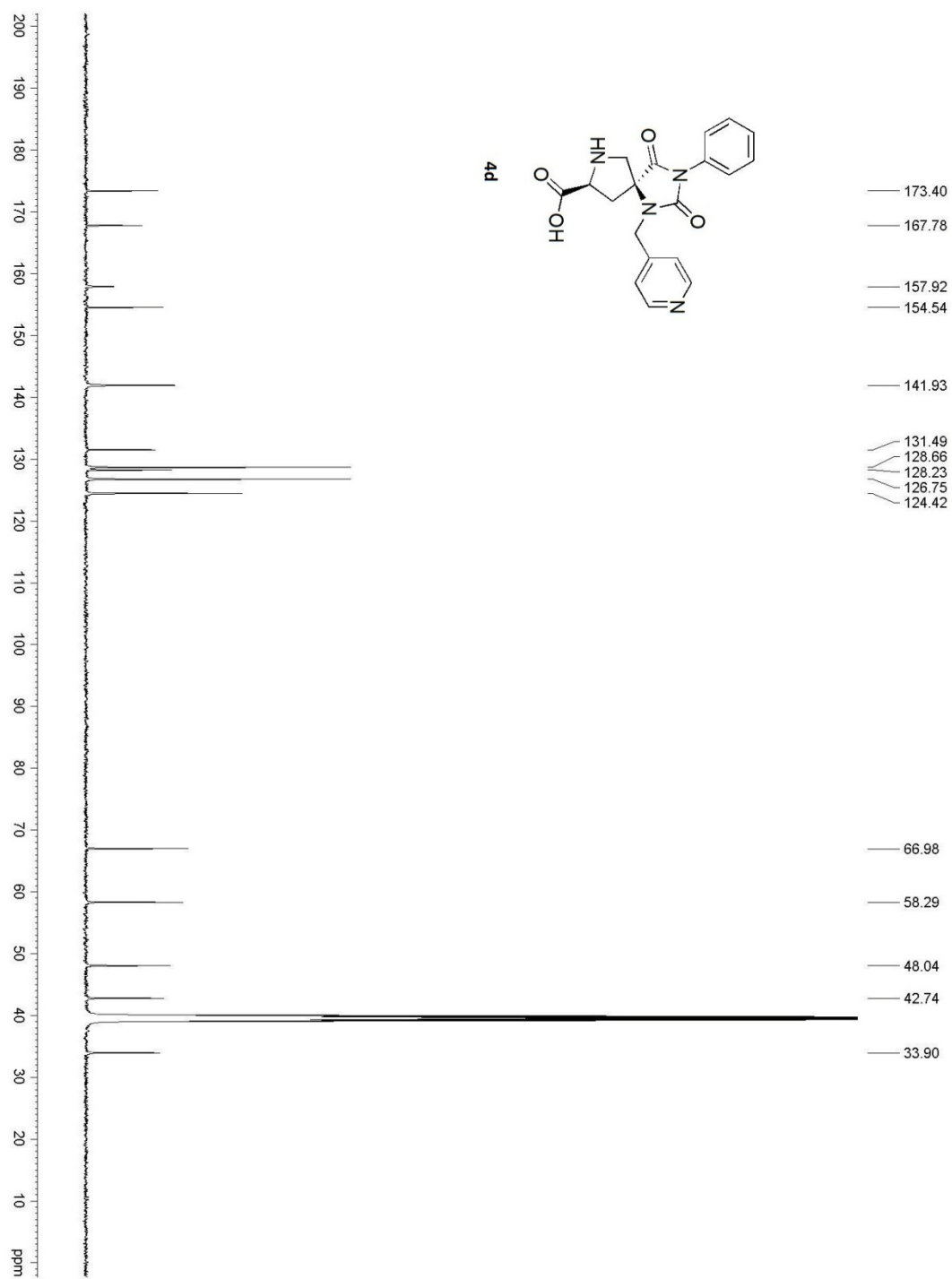
HMBC of Compound **4c**



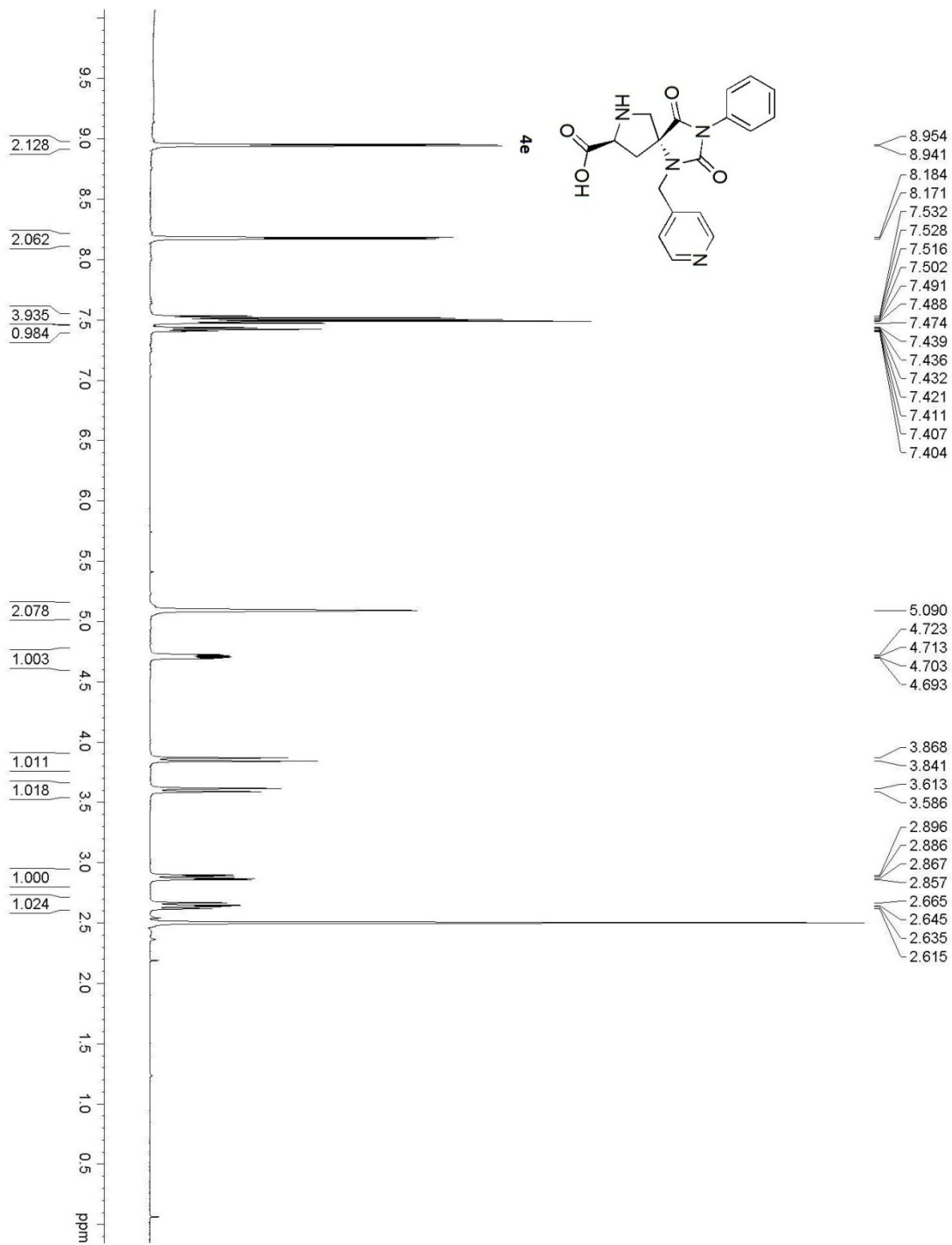
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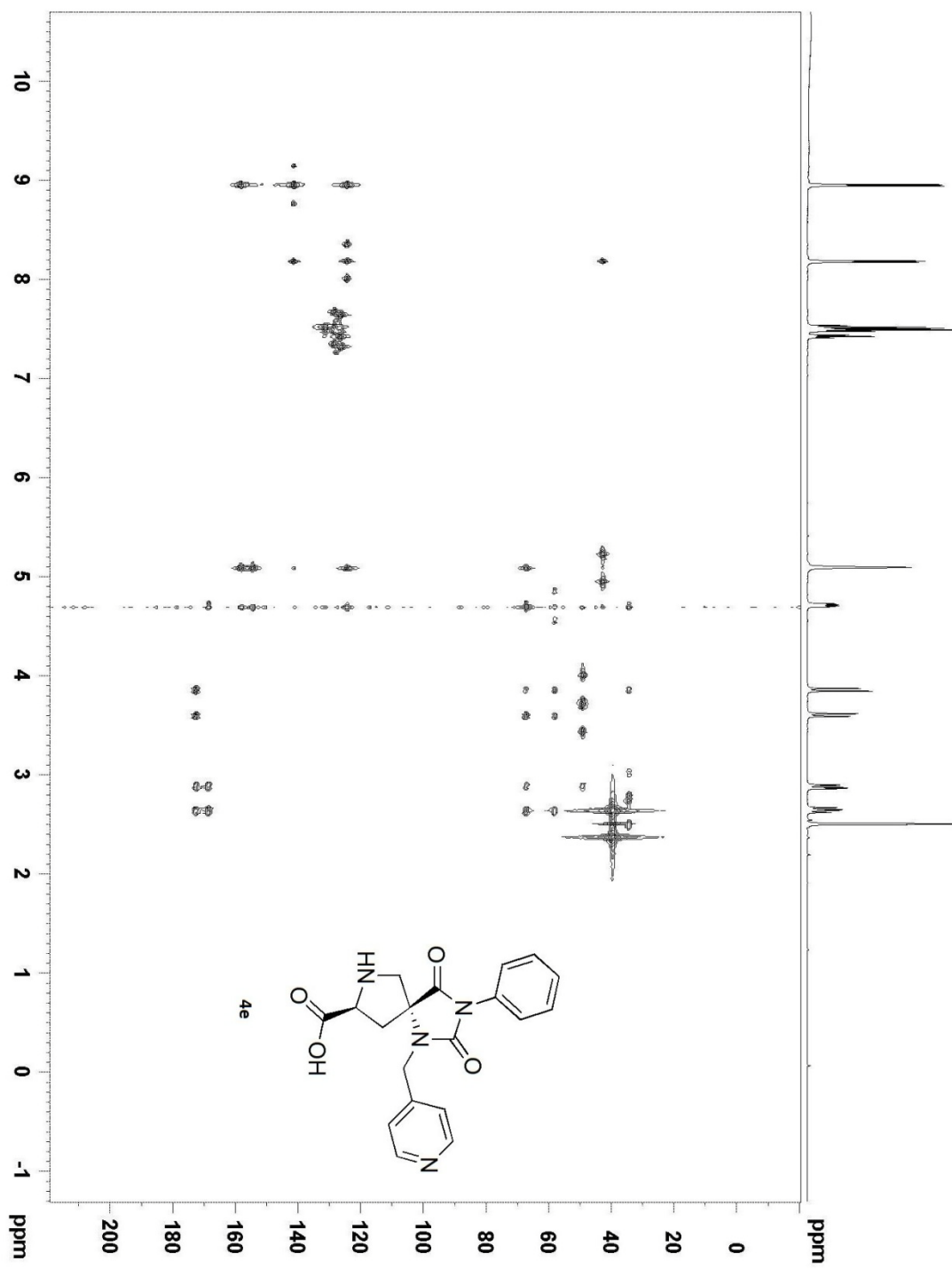
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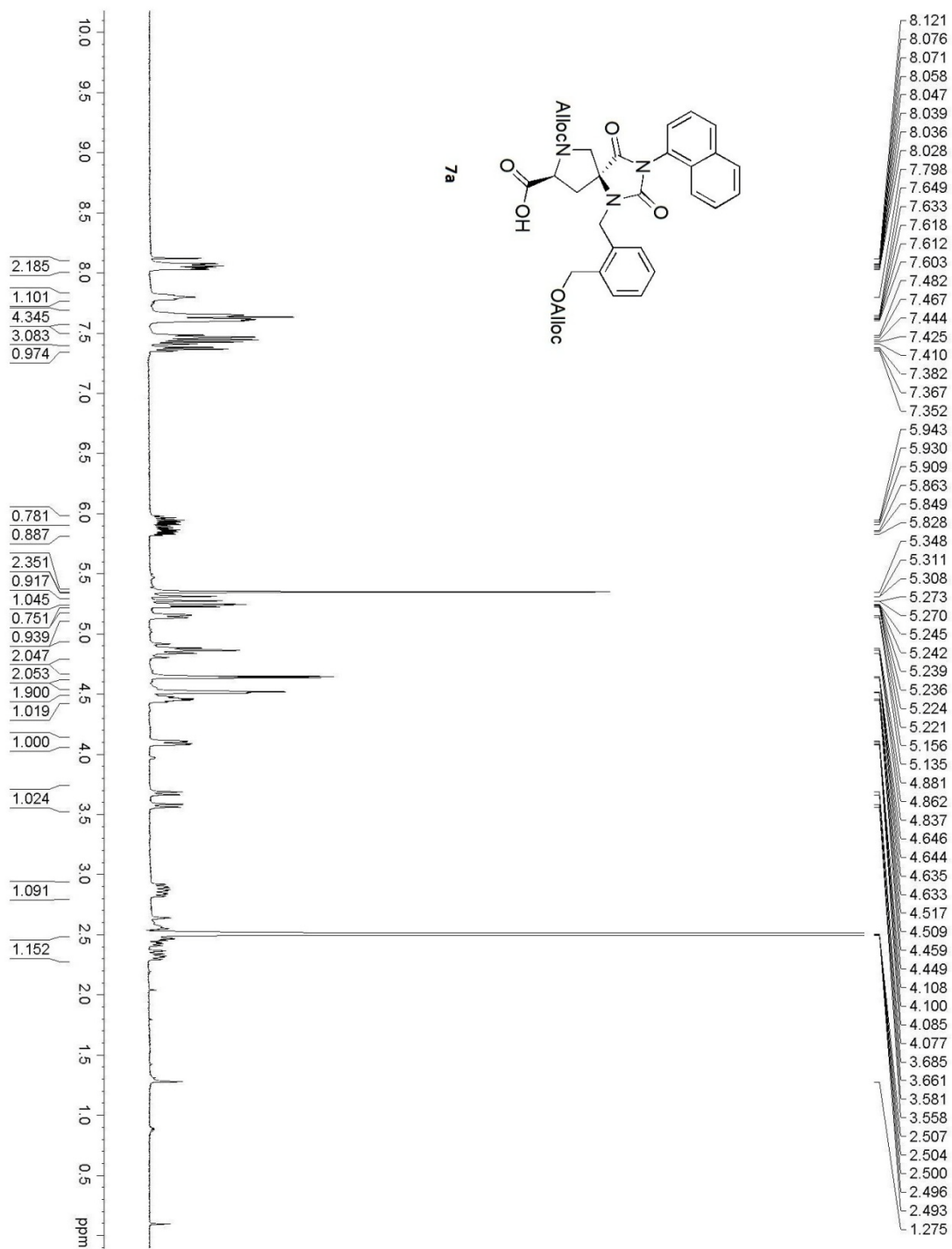
¹H-NMR of Compound 4e



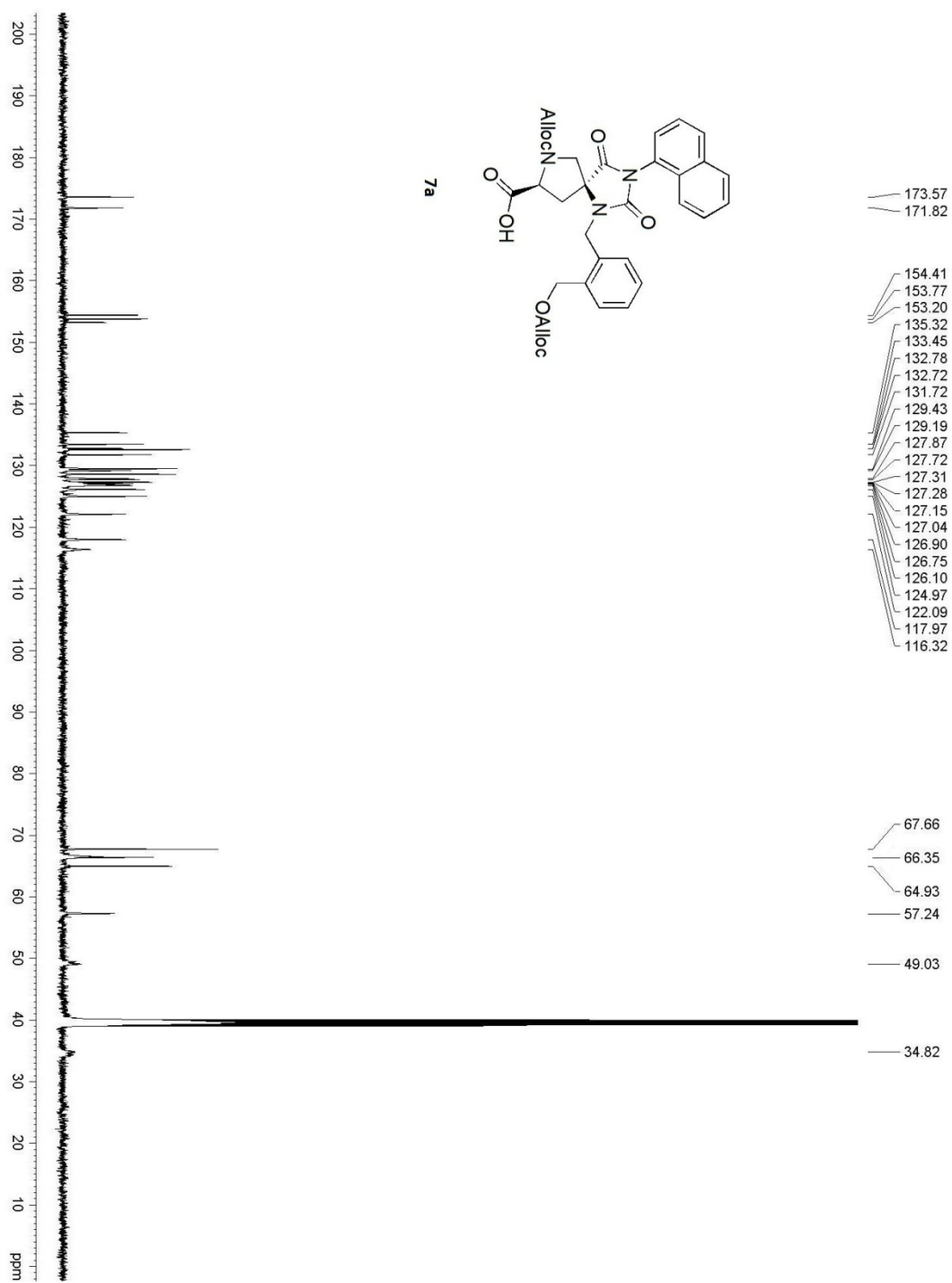
HMBC of Compound 4e



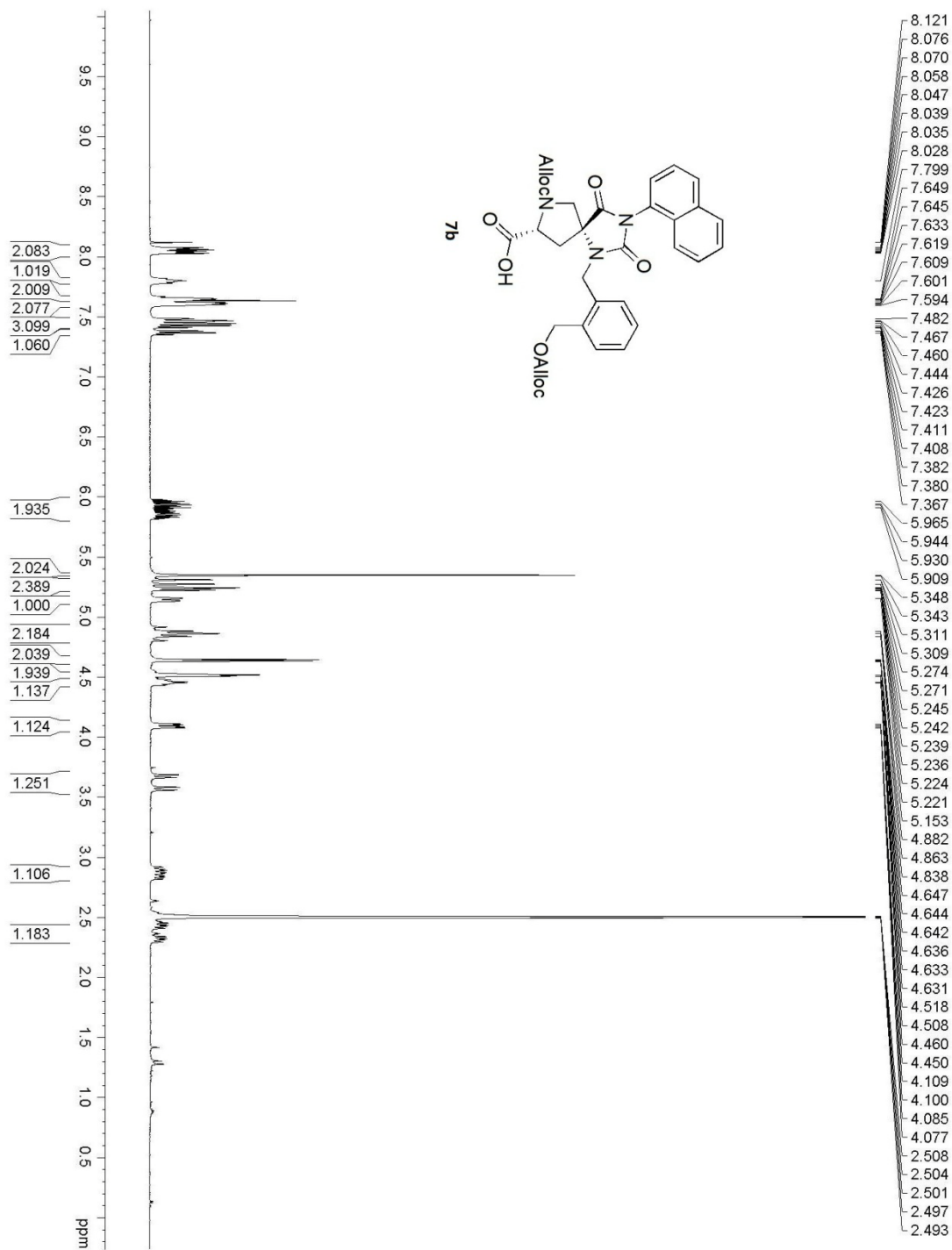
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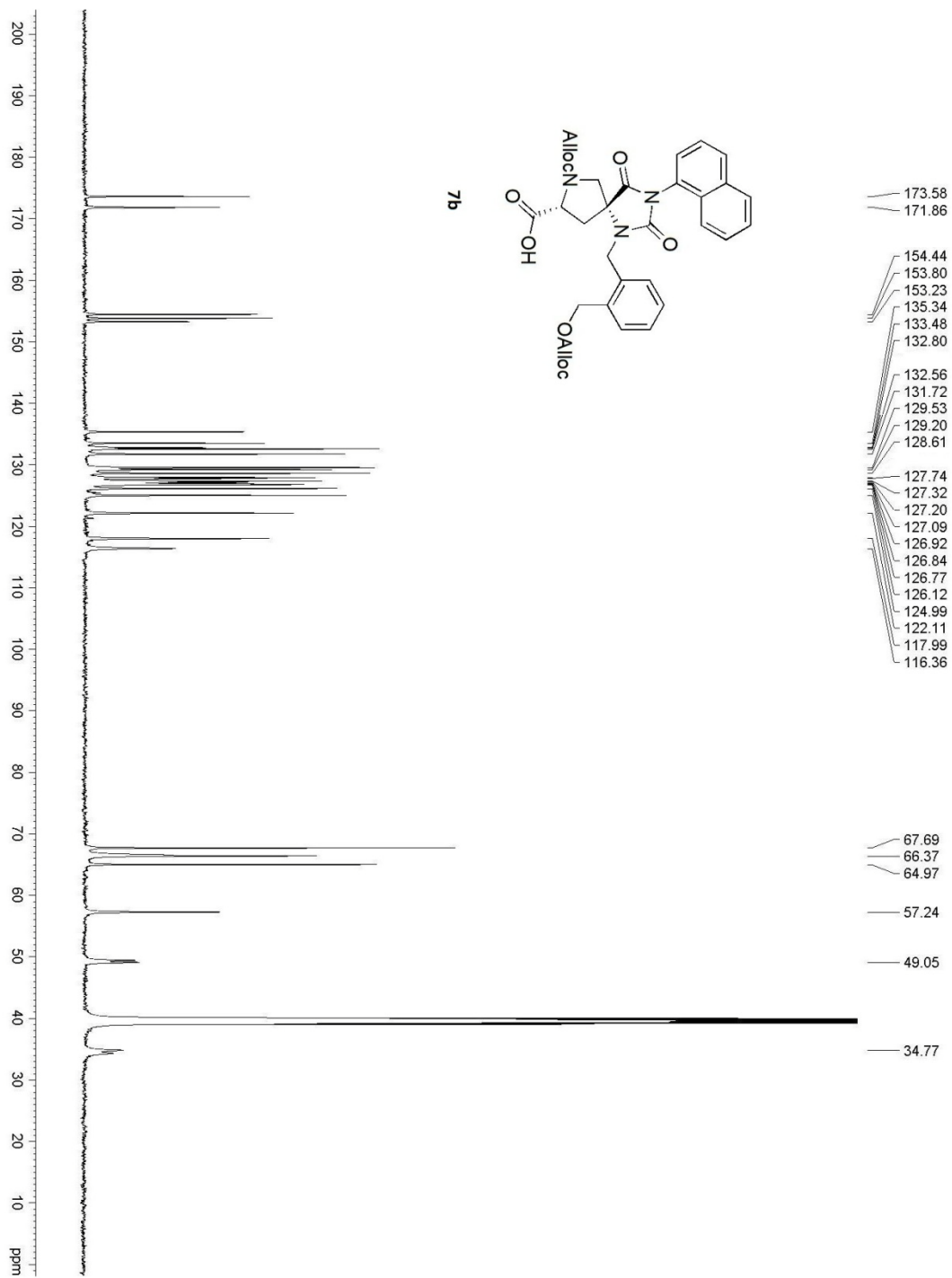
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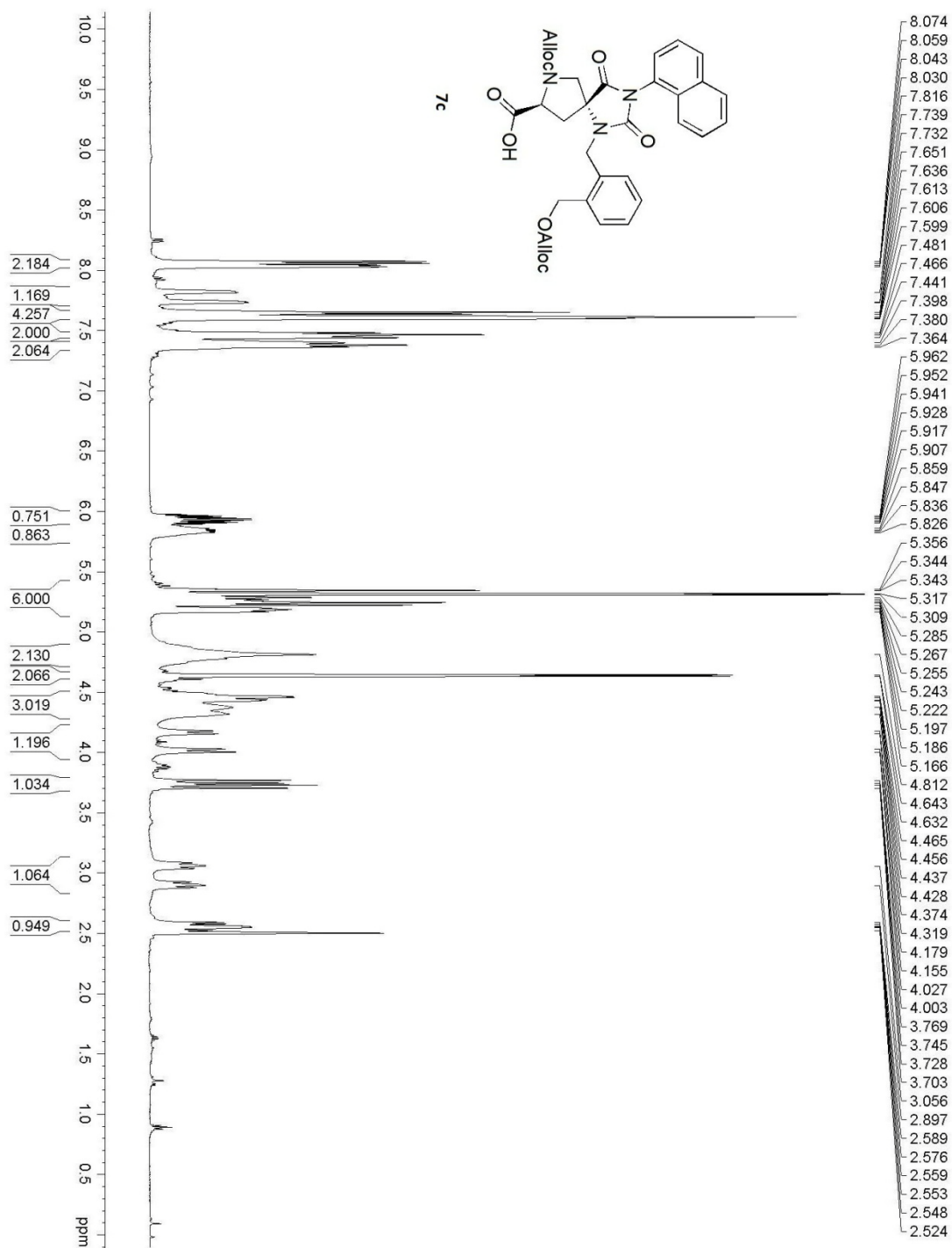
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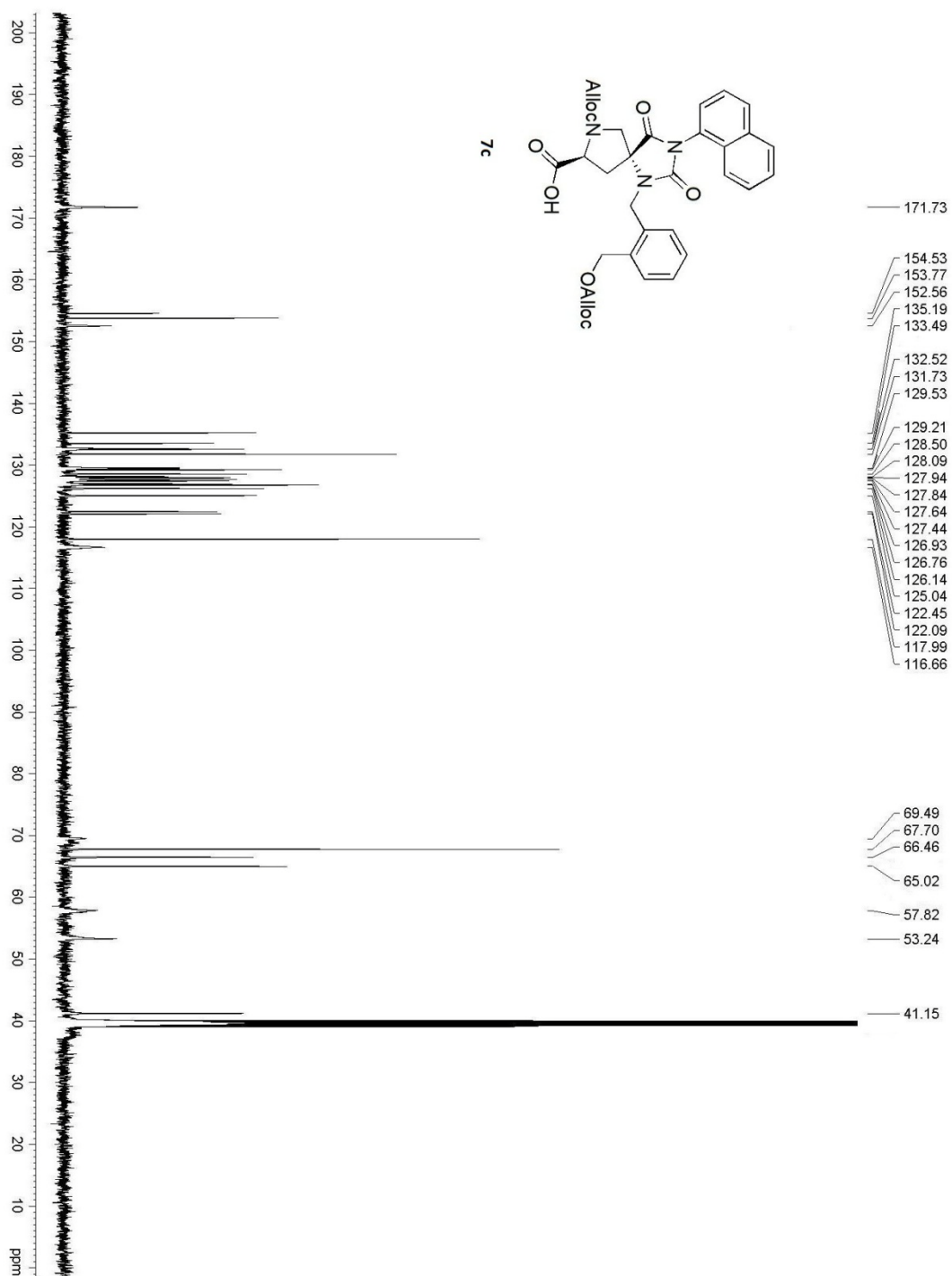
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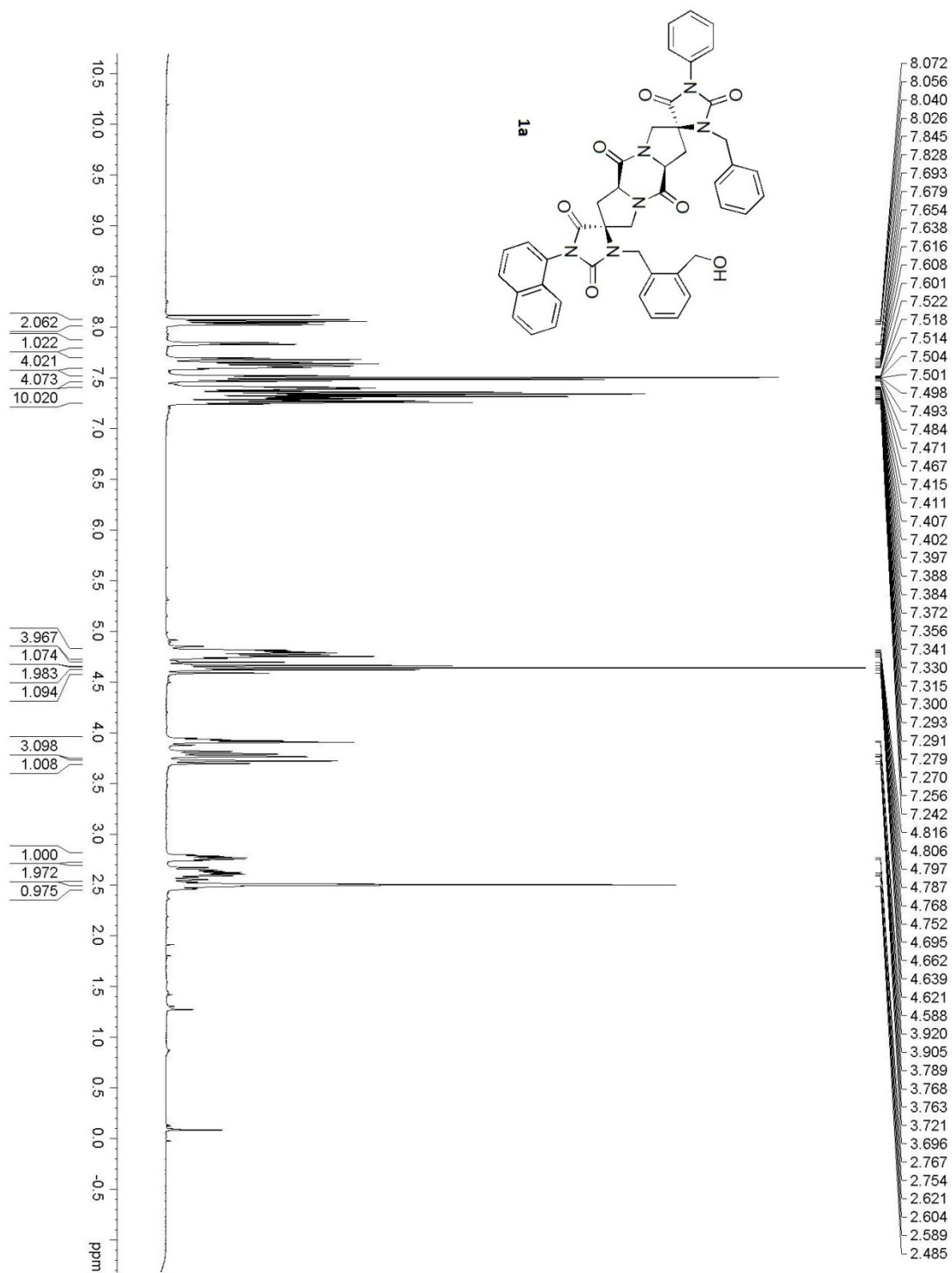
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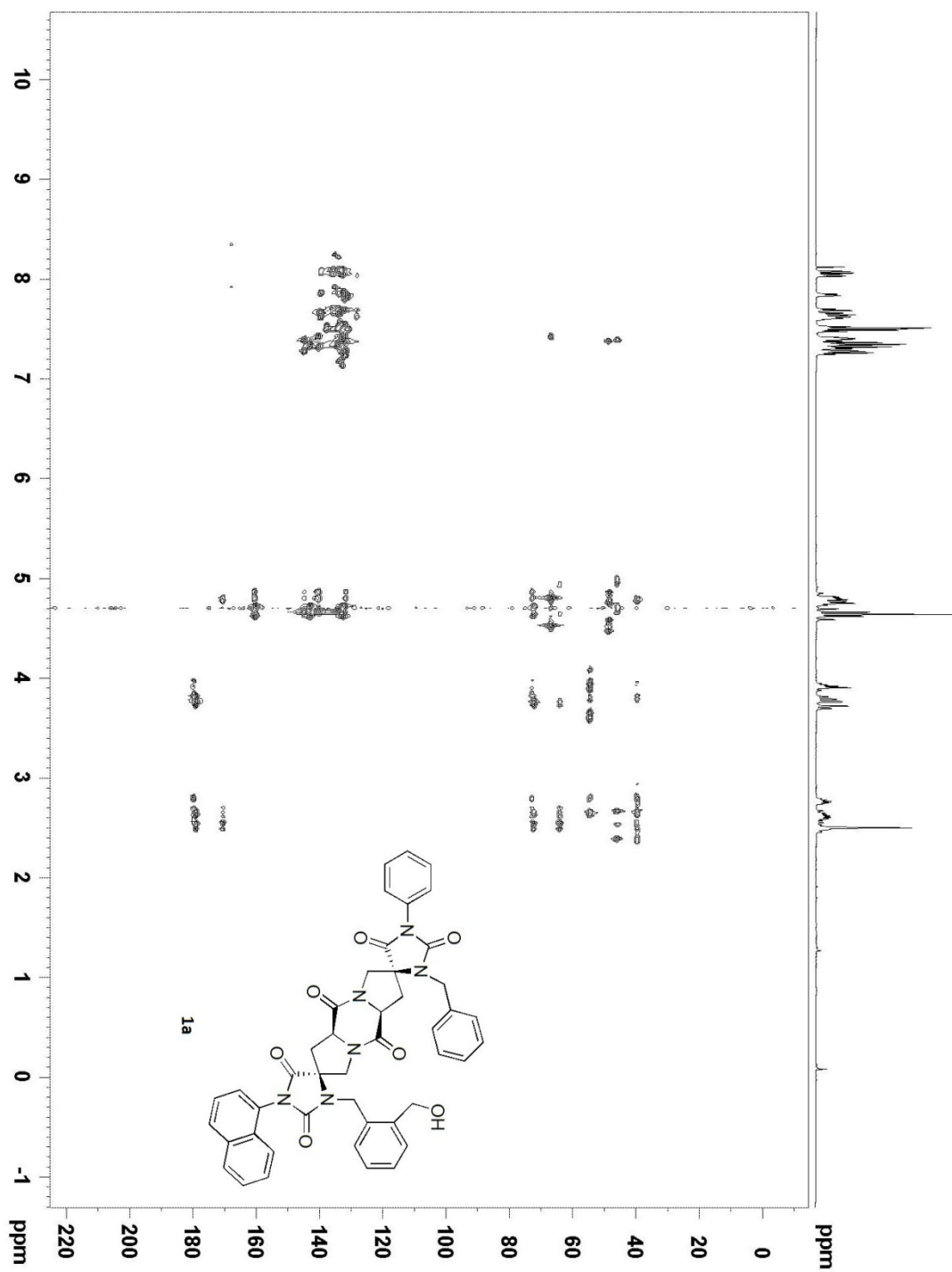
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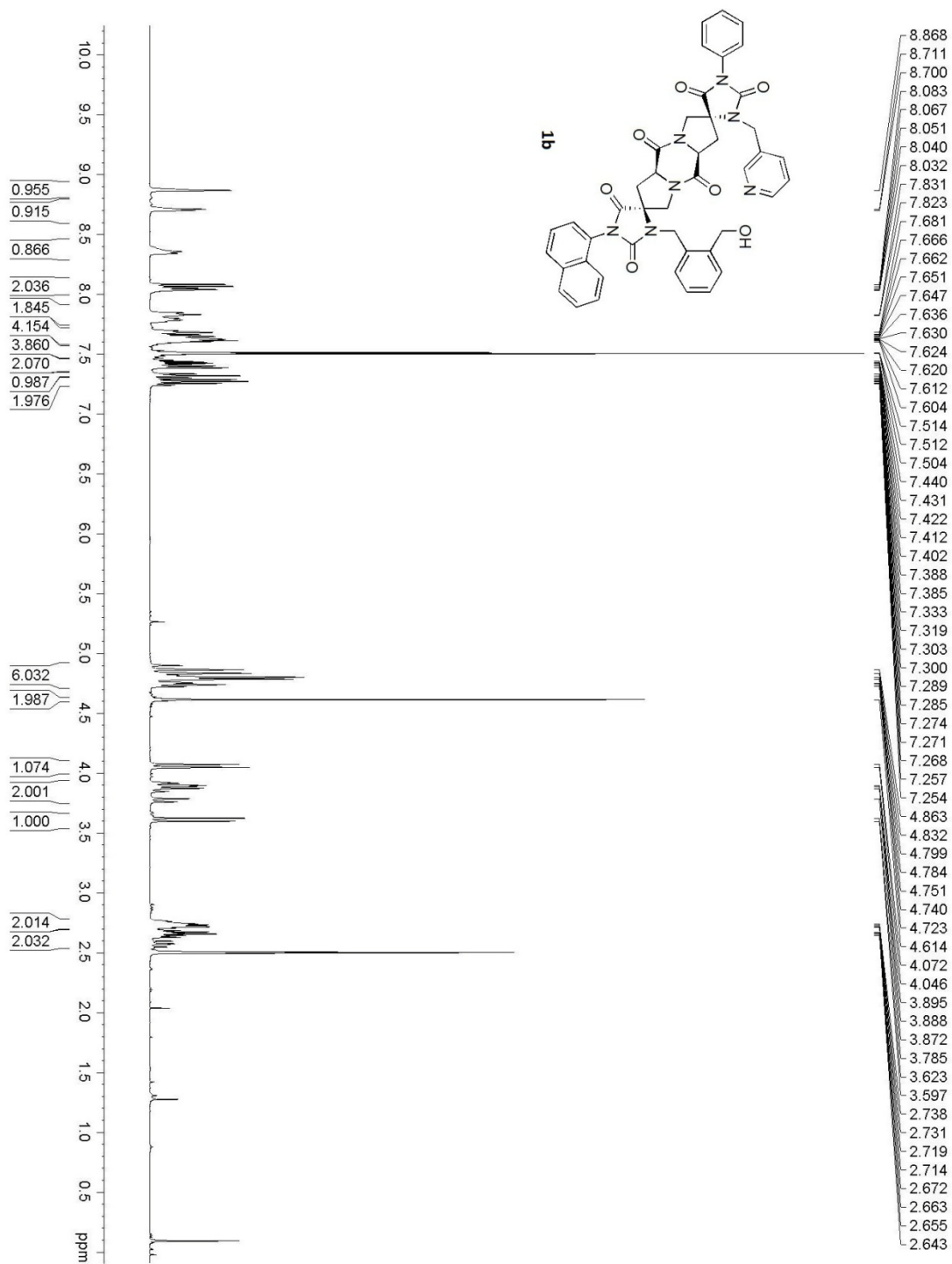
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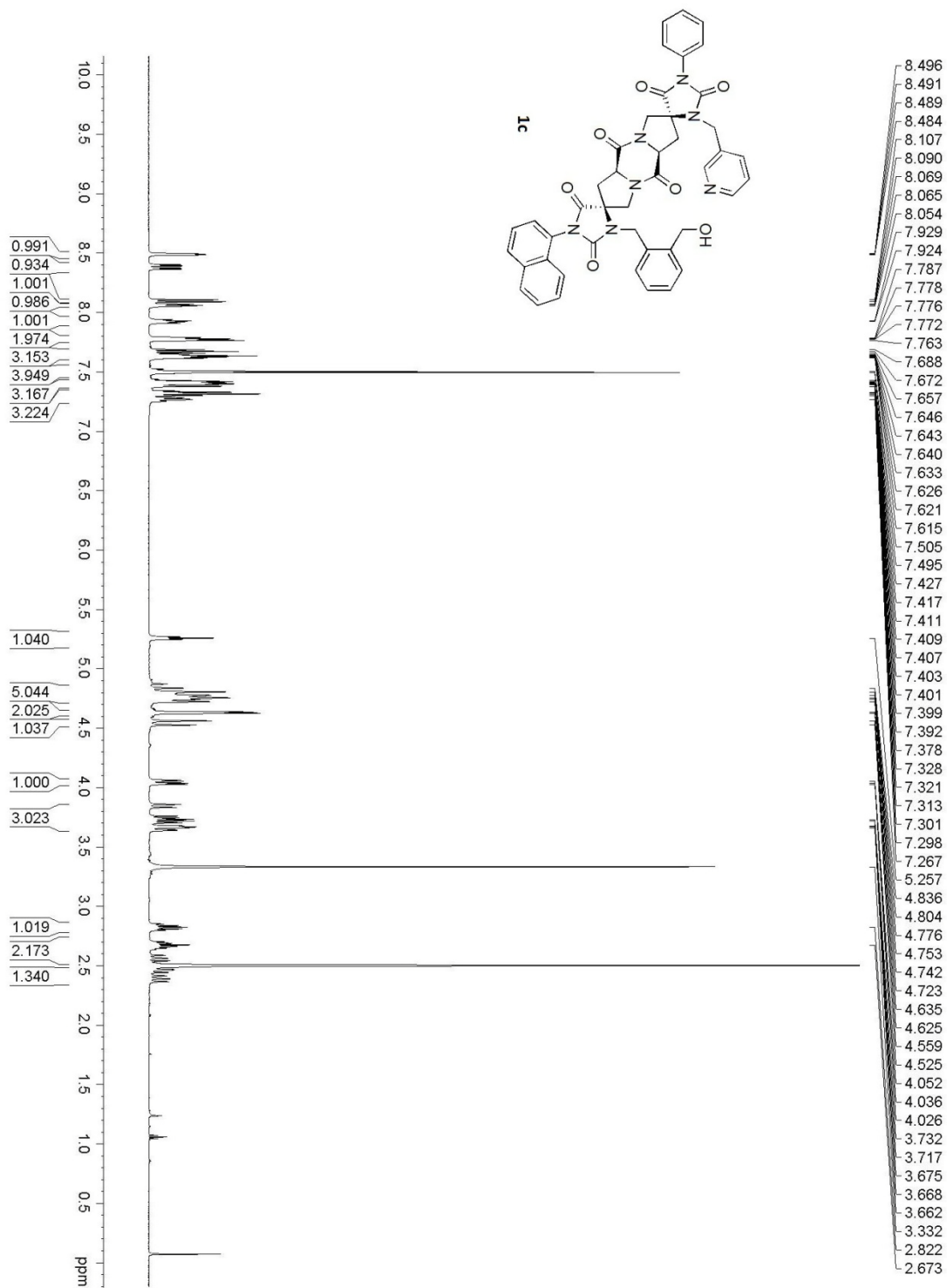
HMBC of Compound 1a



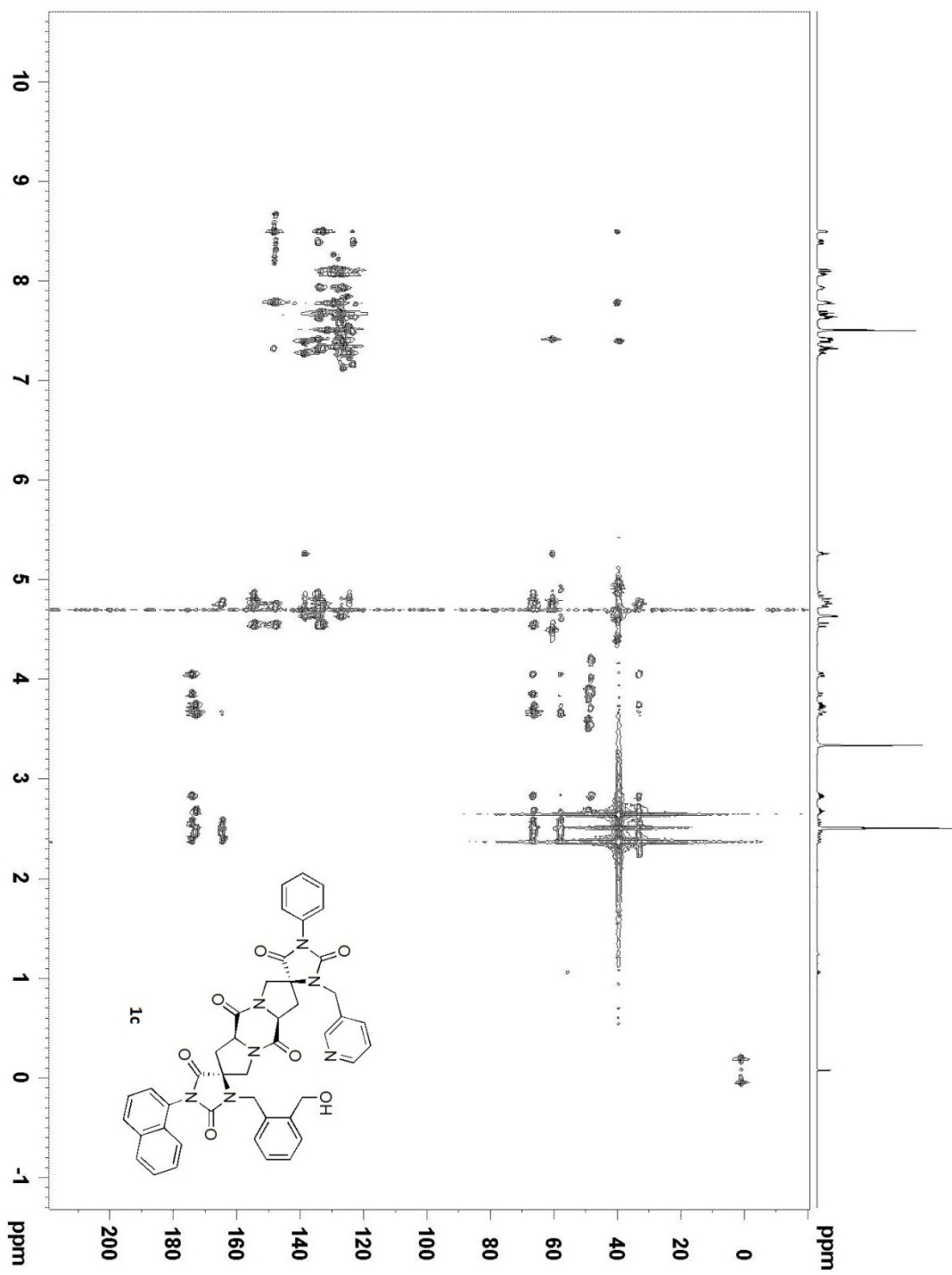
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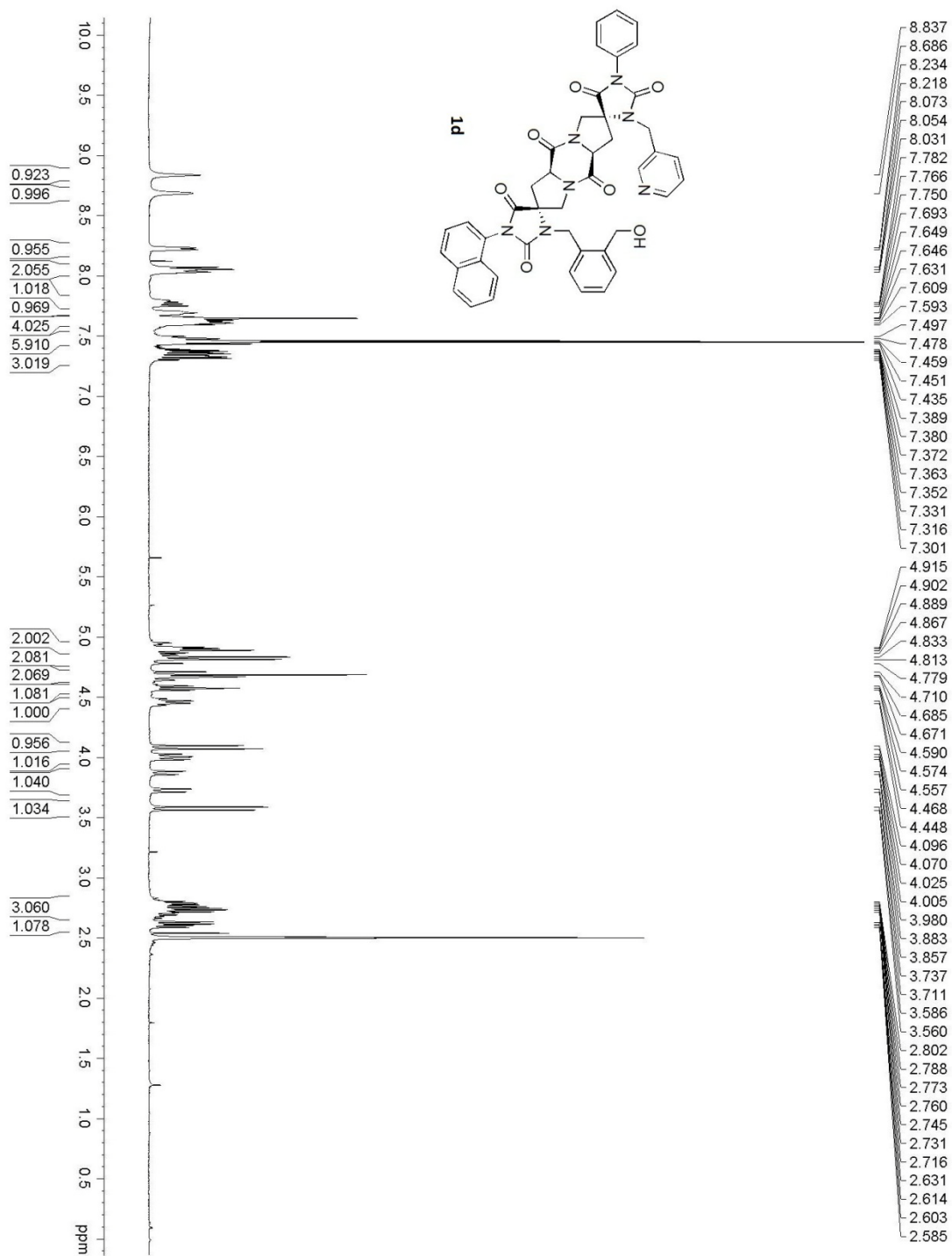
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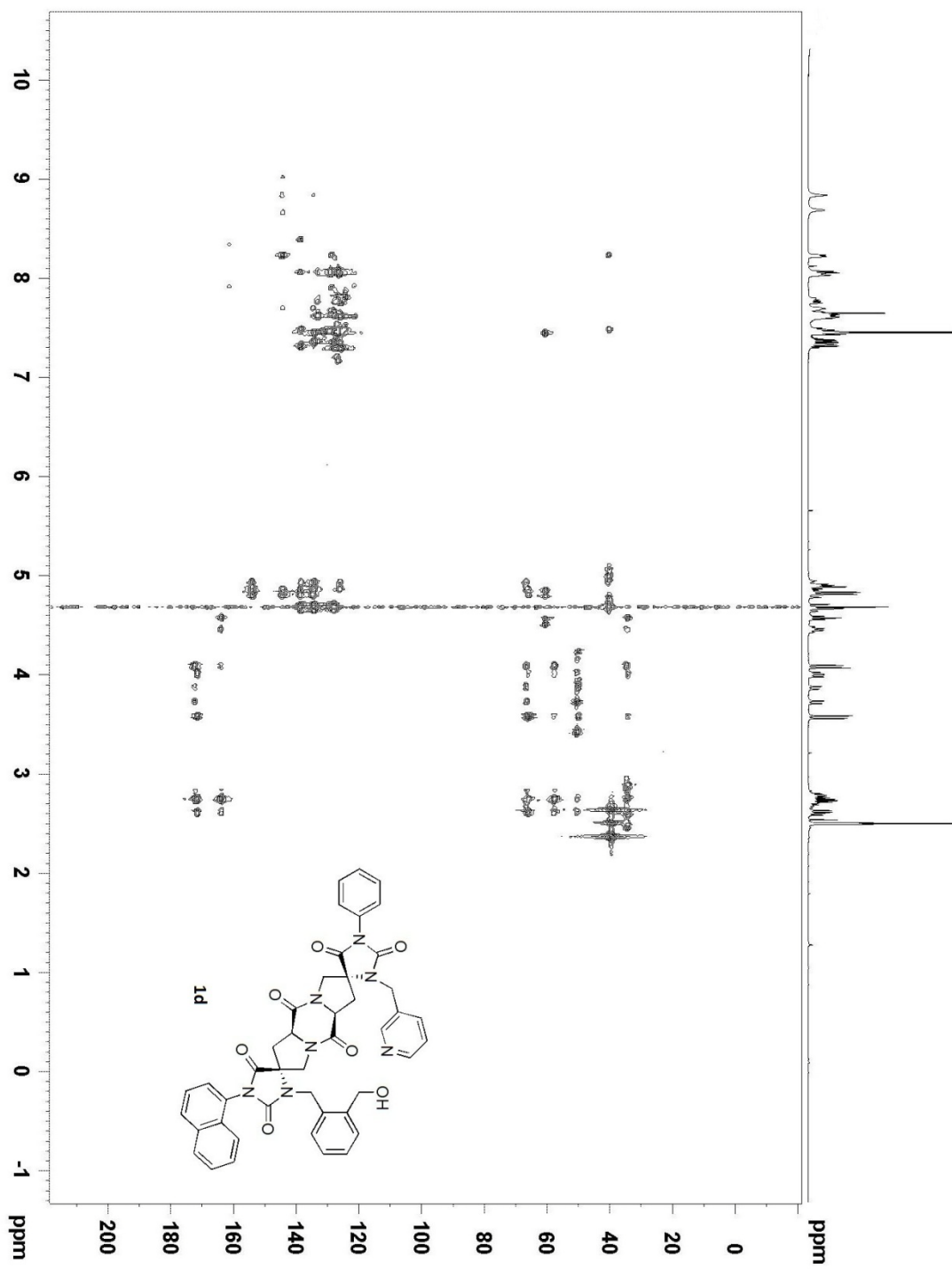
HMBC of Compound **1c**



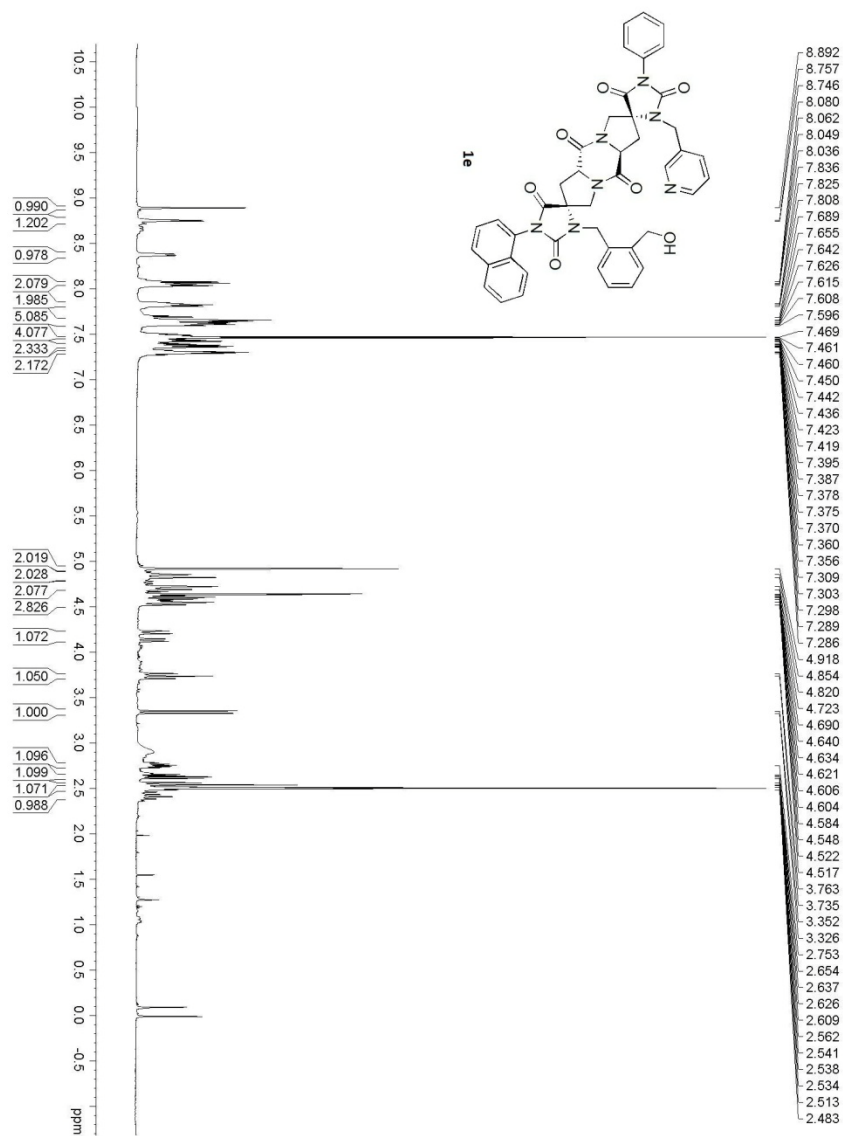
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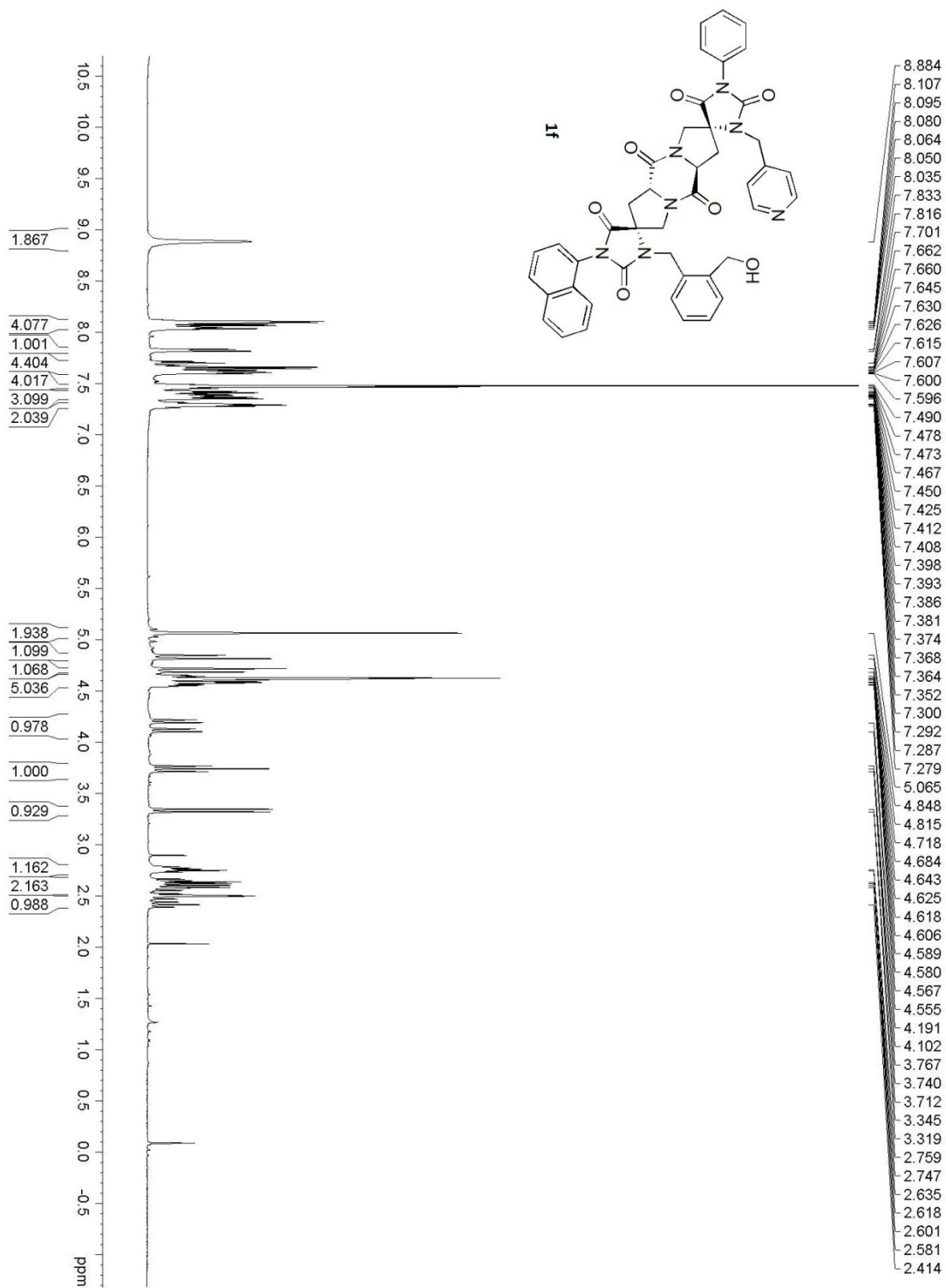
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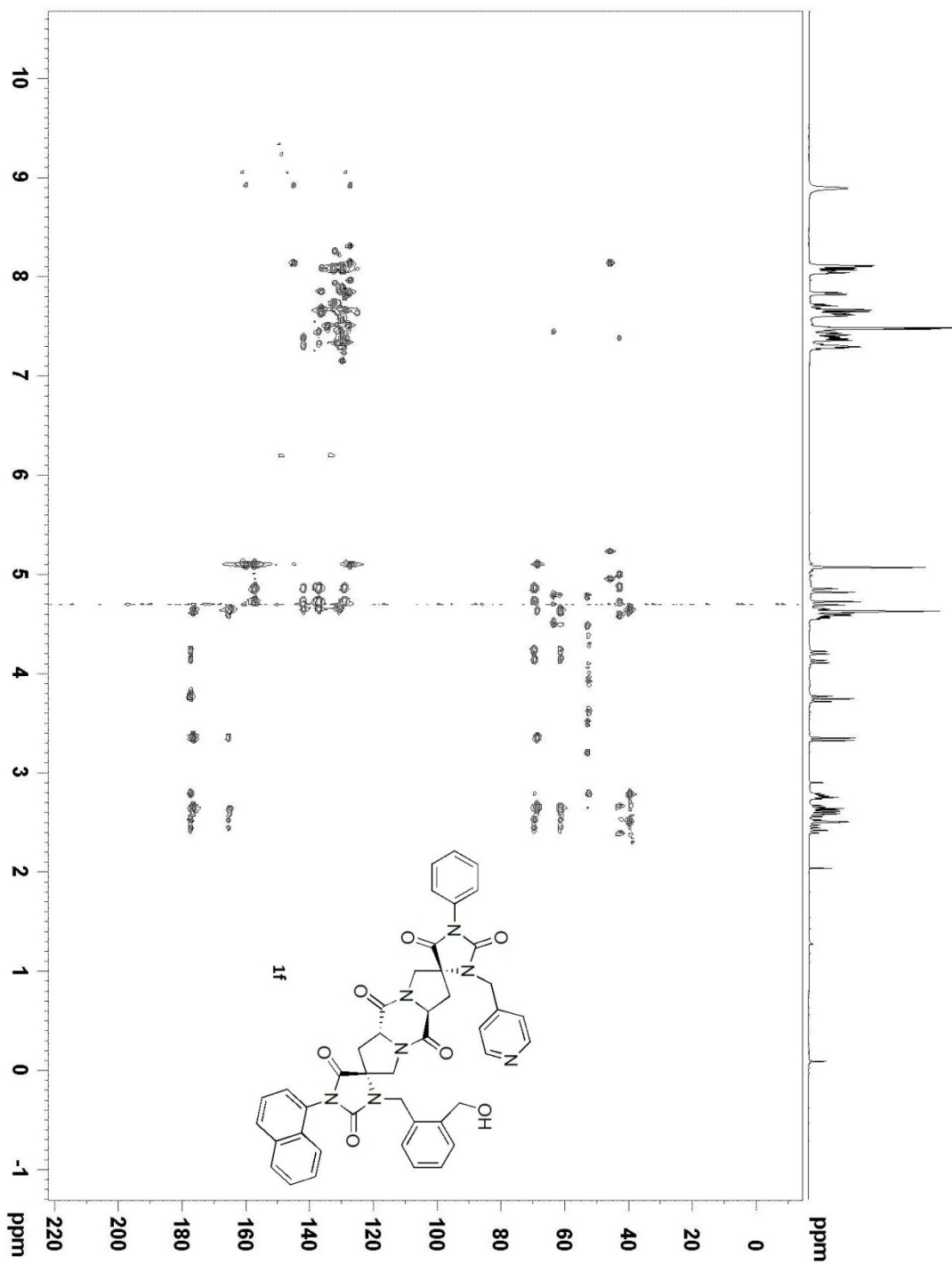
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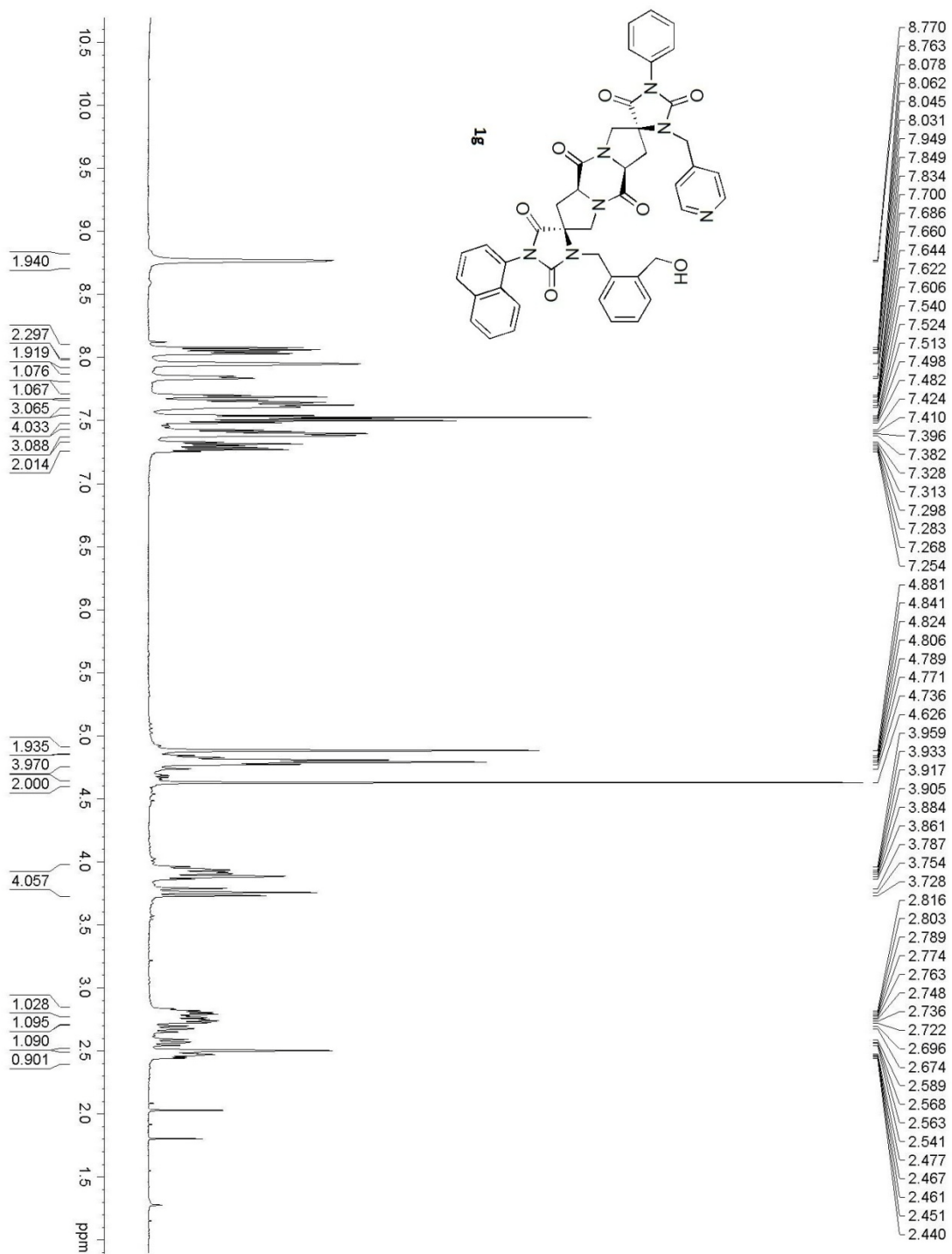
¹H-NMR of Compound **1f**



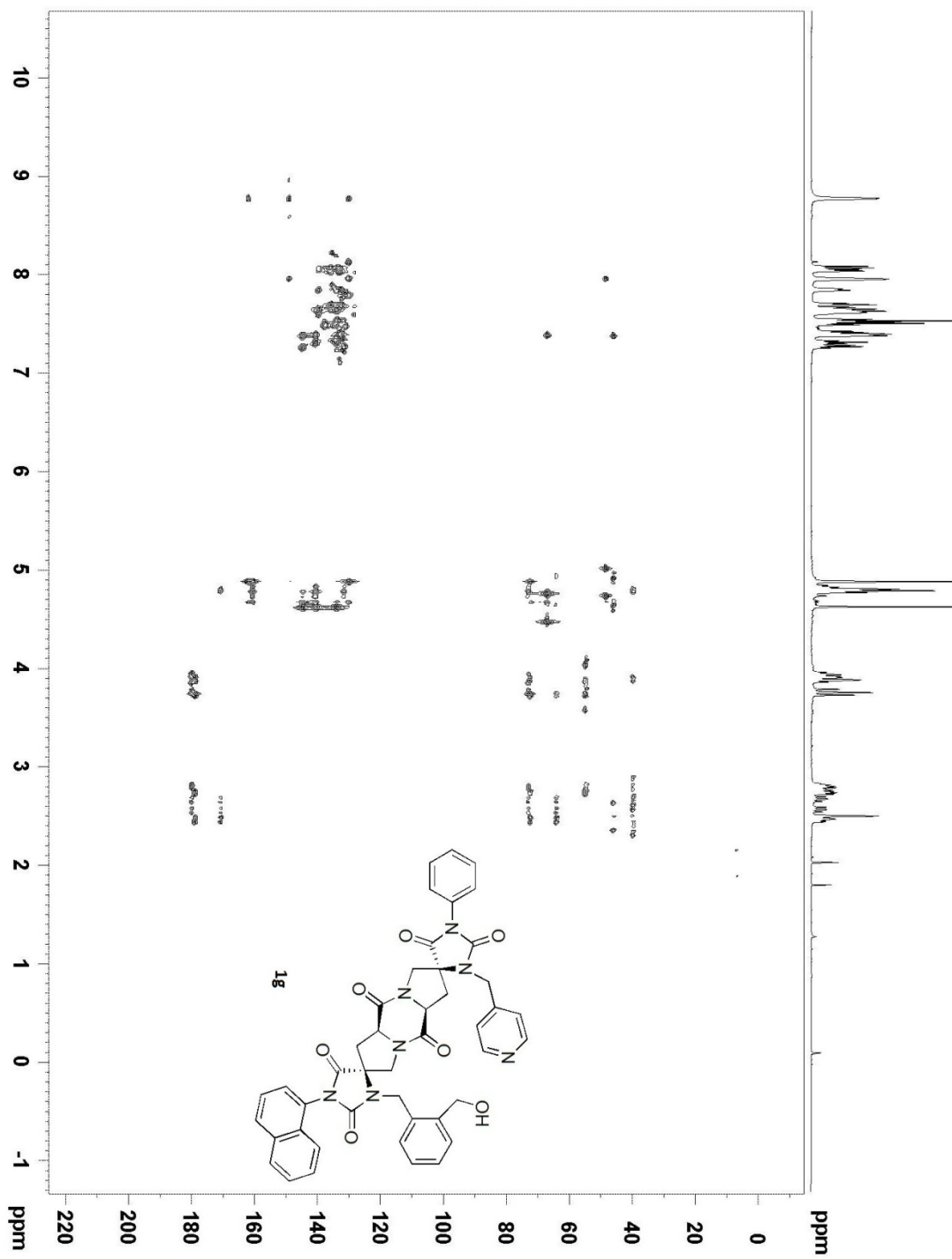
HMBC of Compound **1f**



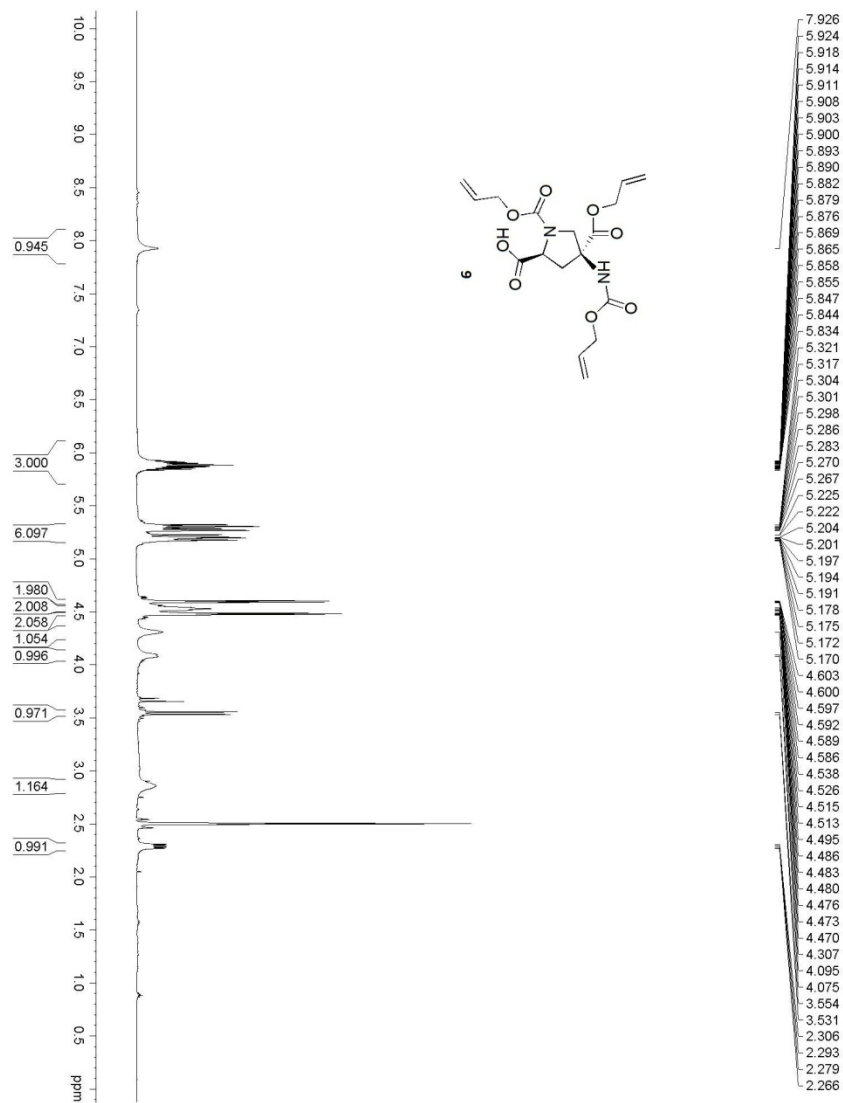
¹H-NMR of Compound **1g**



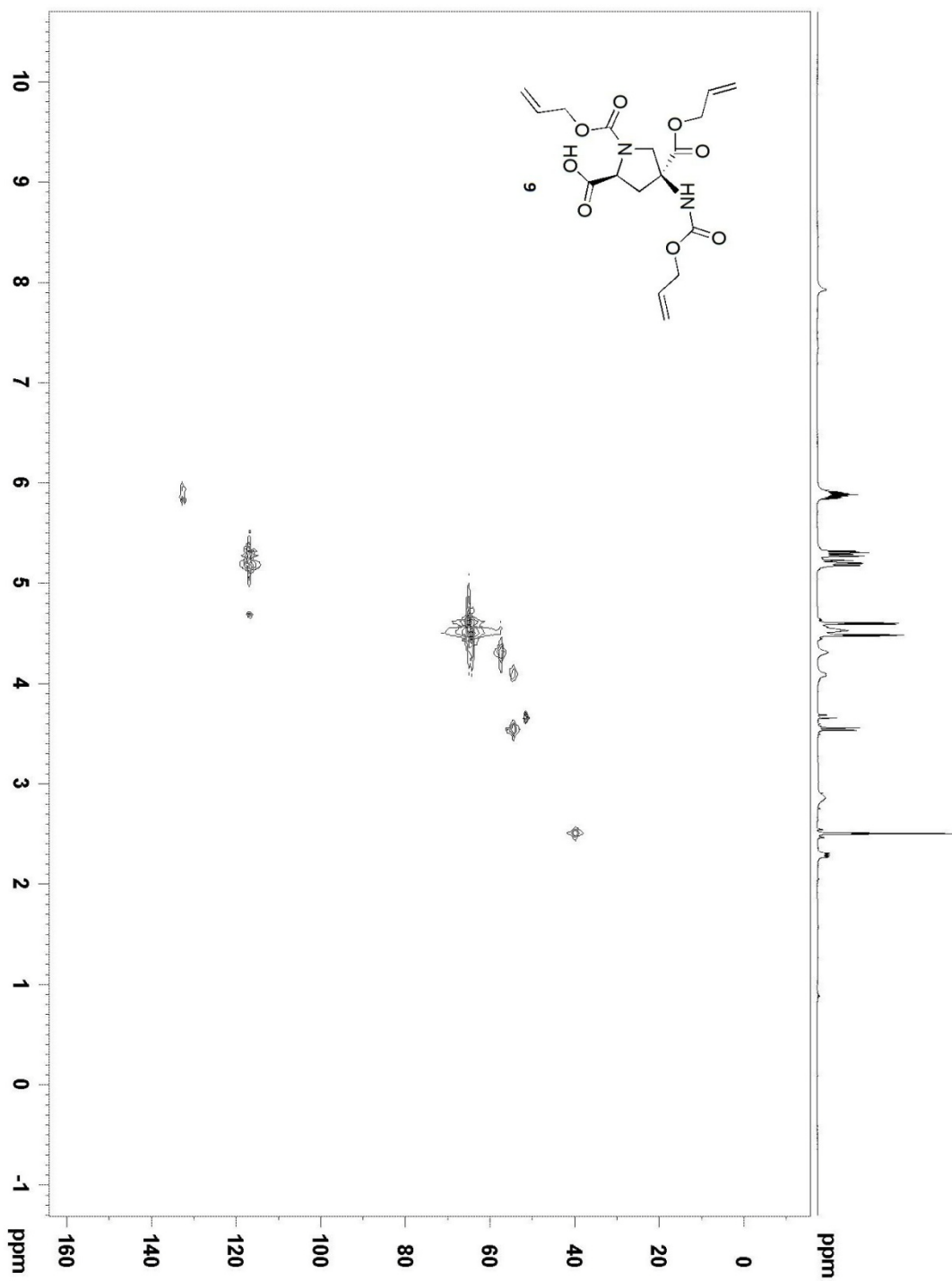
HMBC of Compound **1g**



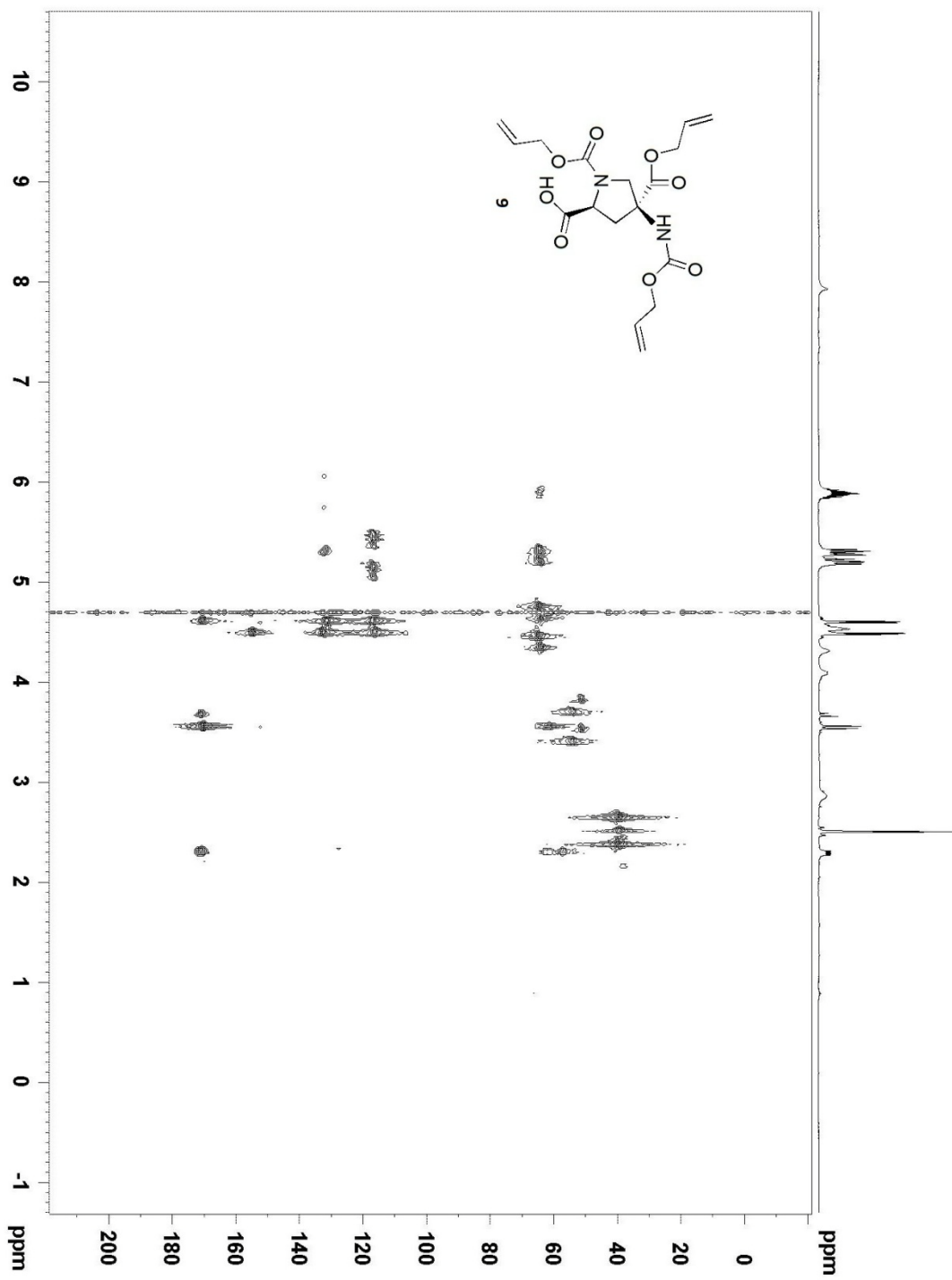
¹H-NMR of Compound 9



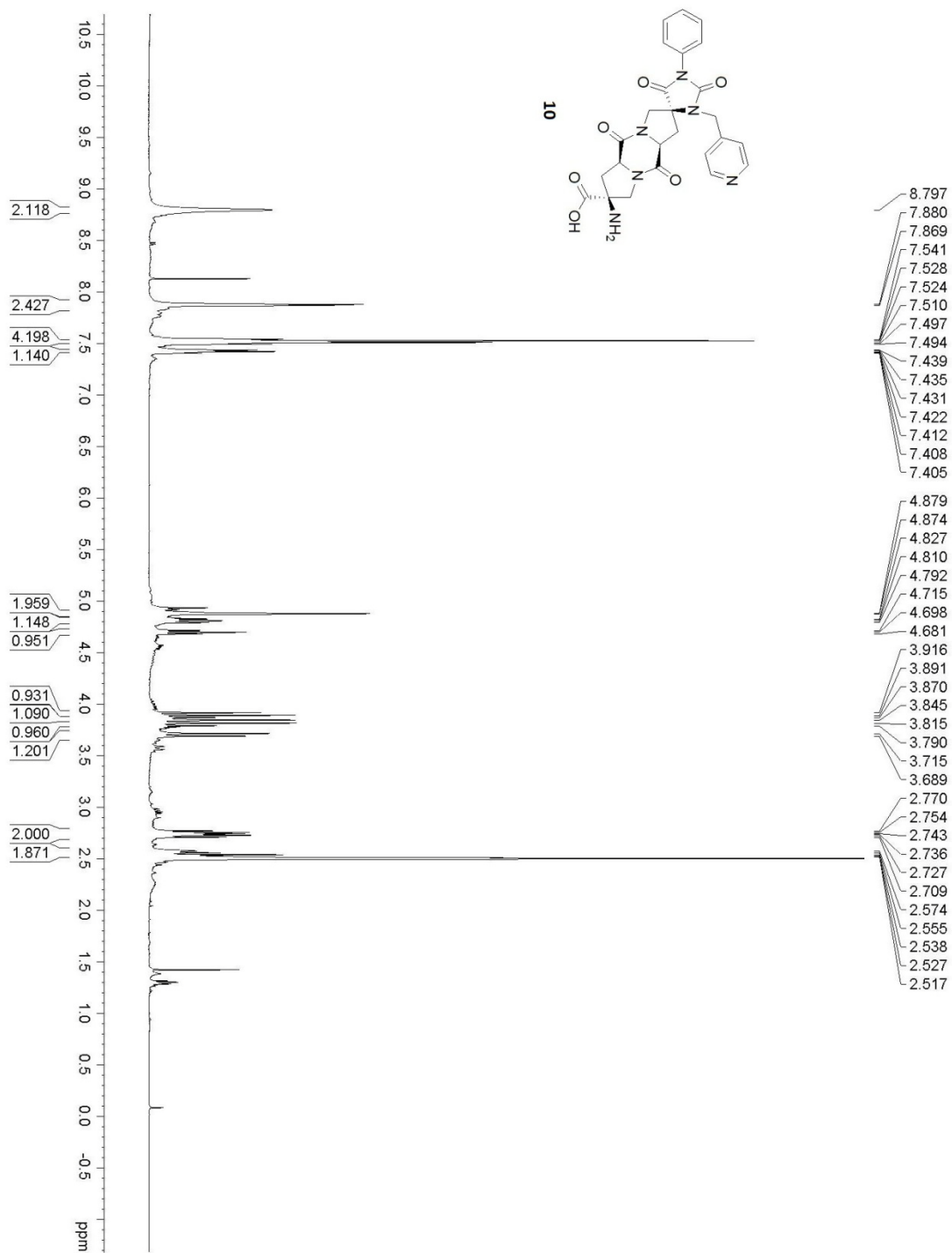
HMQC of Compound 9



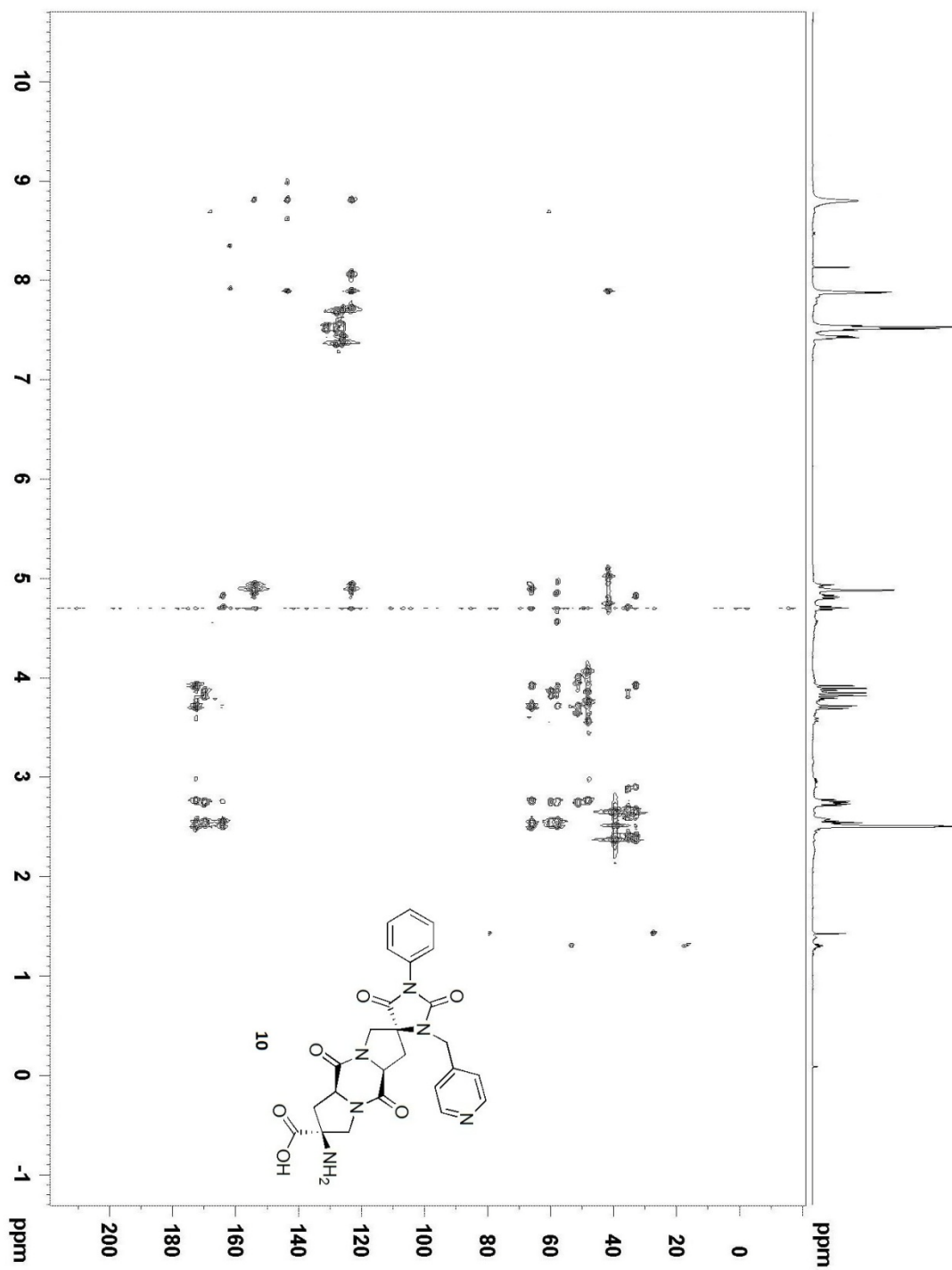
HMBC of Compound 9



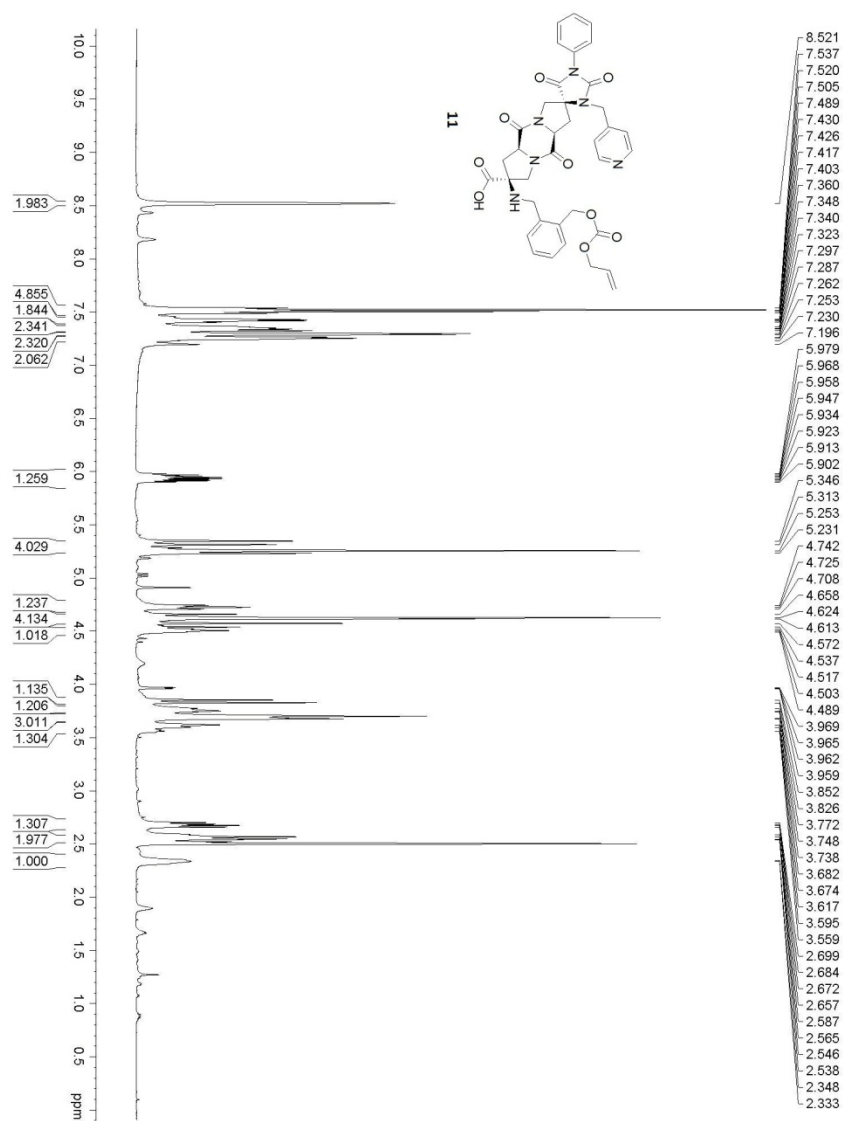
¹H-NMR of Compound **10**



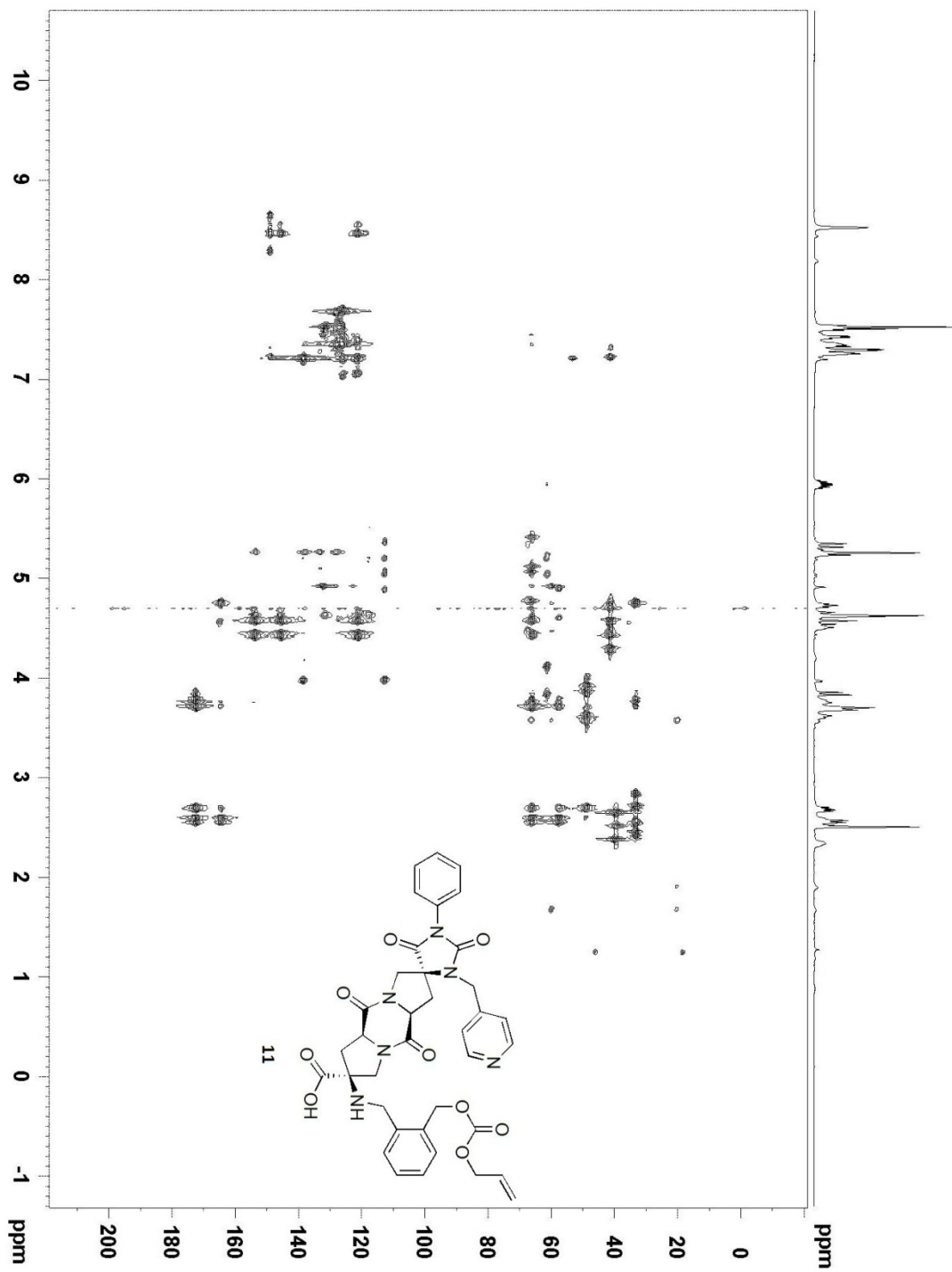
HMBC of Compound 10



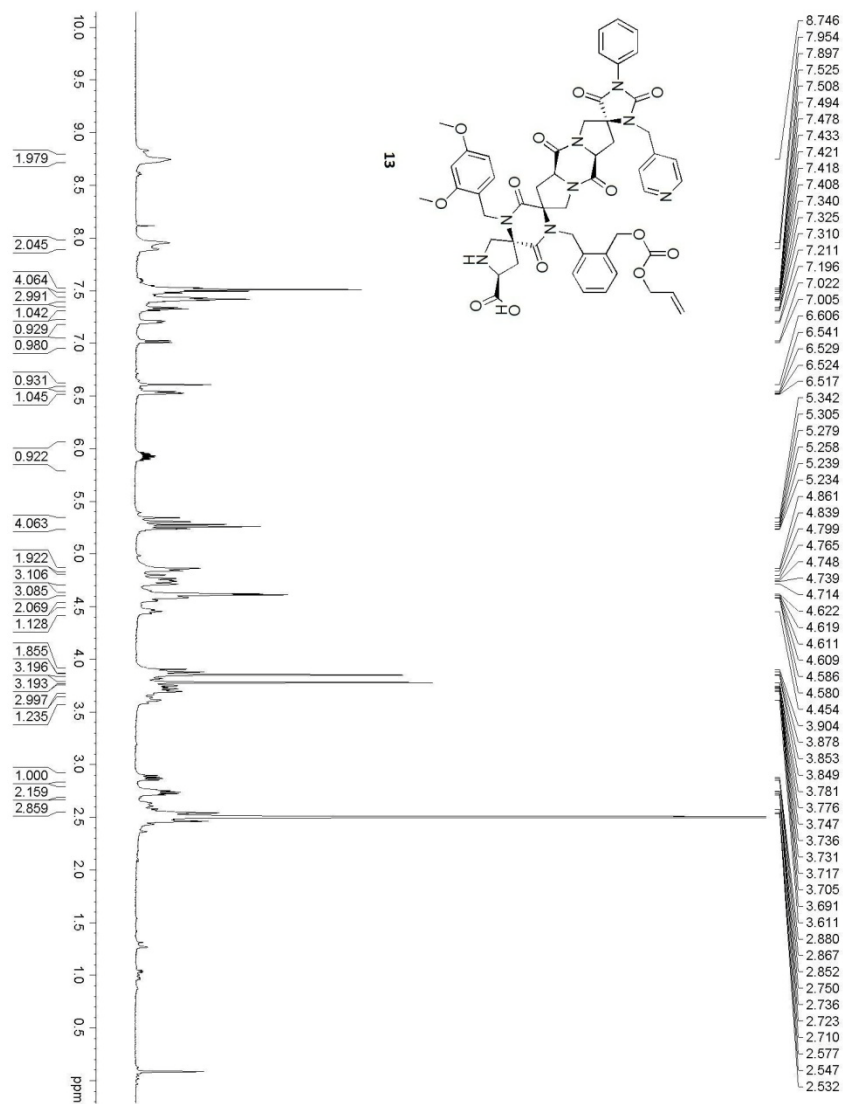
¹H-NMR of Compound **11**



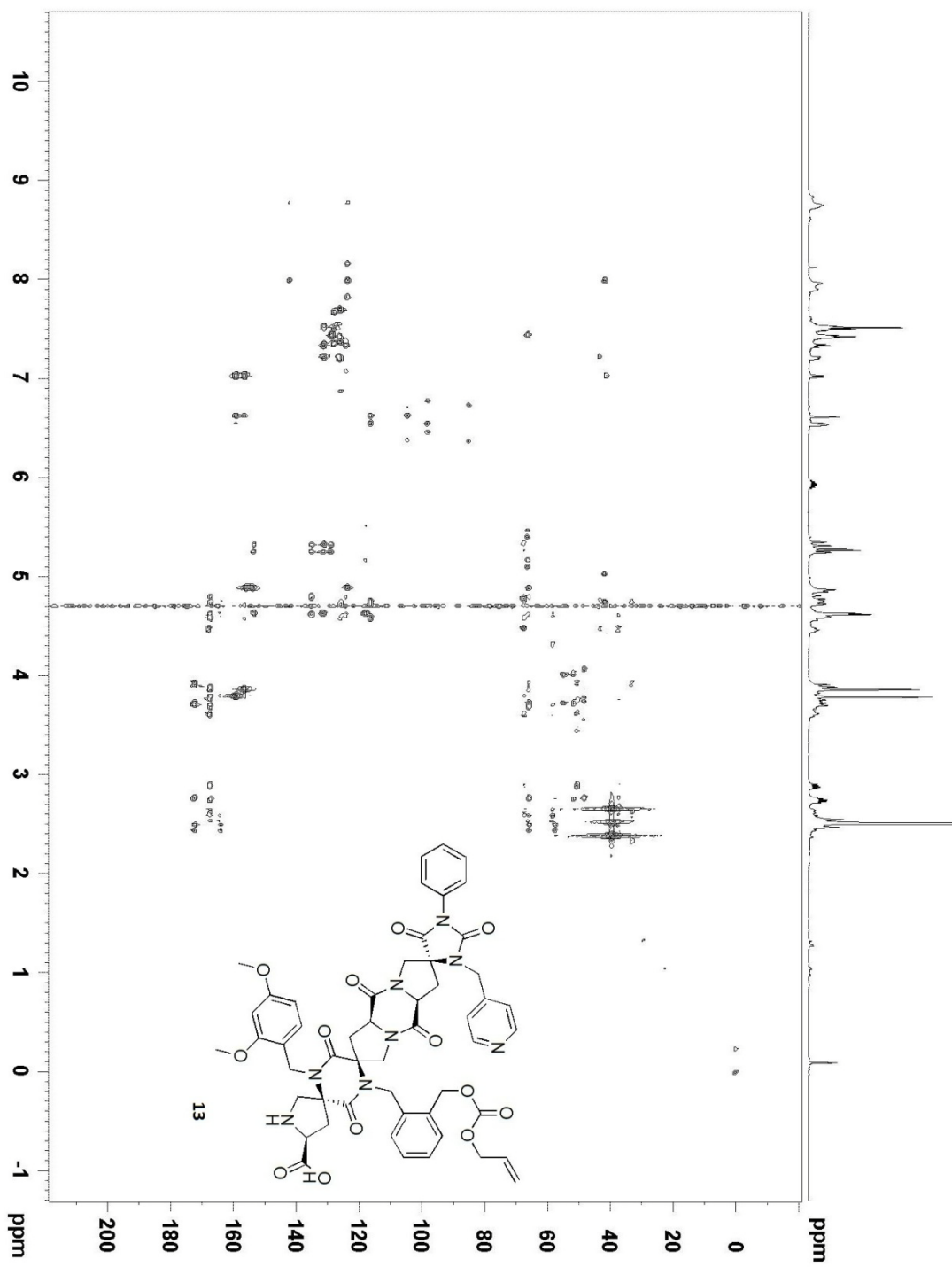
HMBC of Compound 11



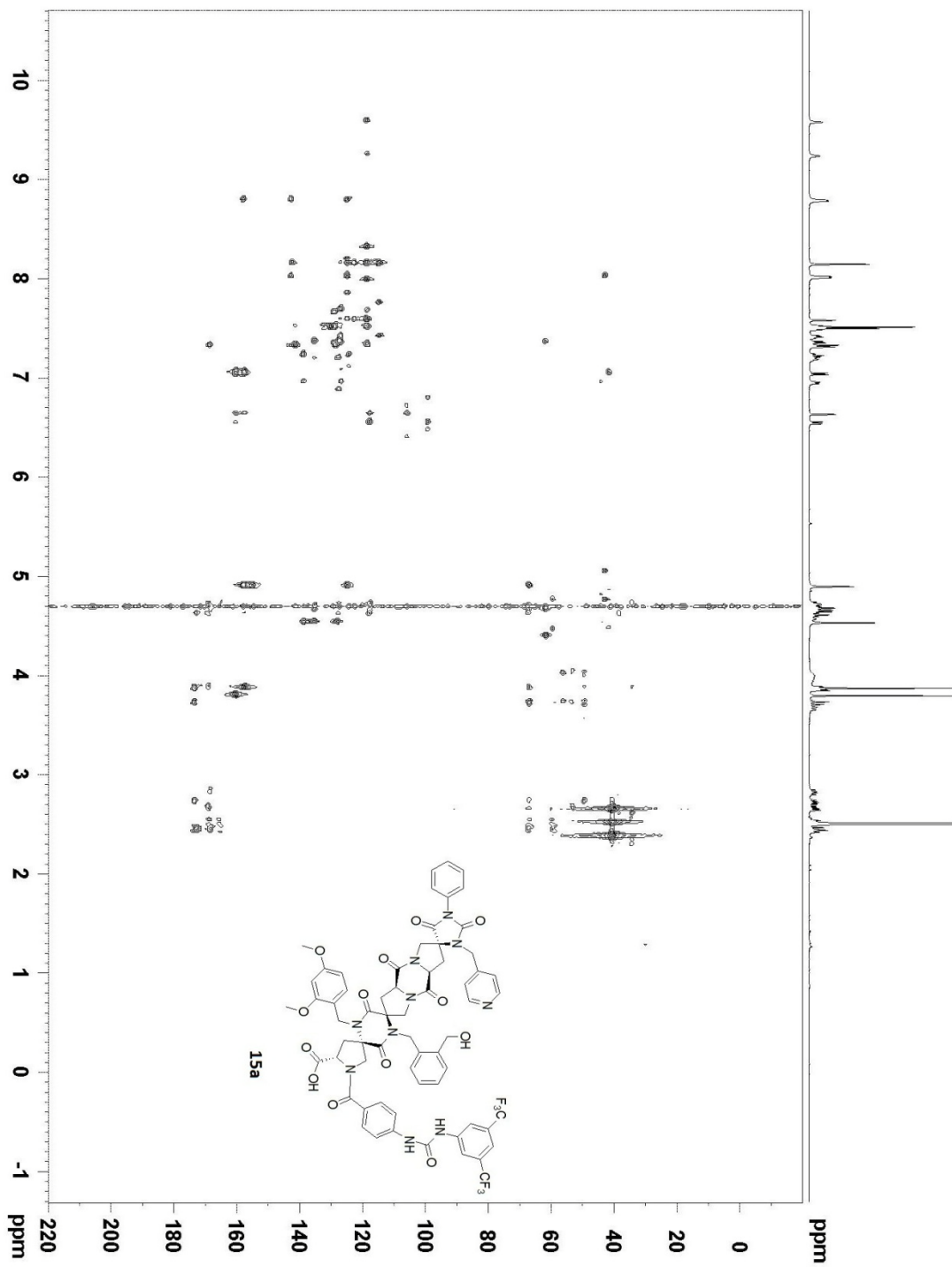
¹H-NMR of Compound 13



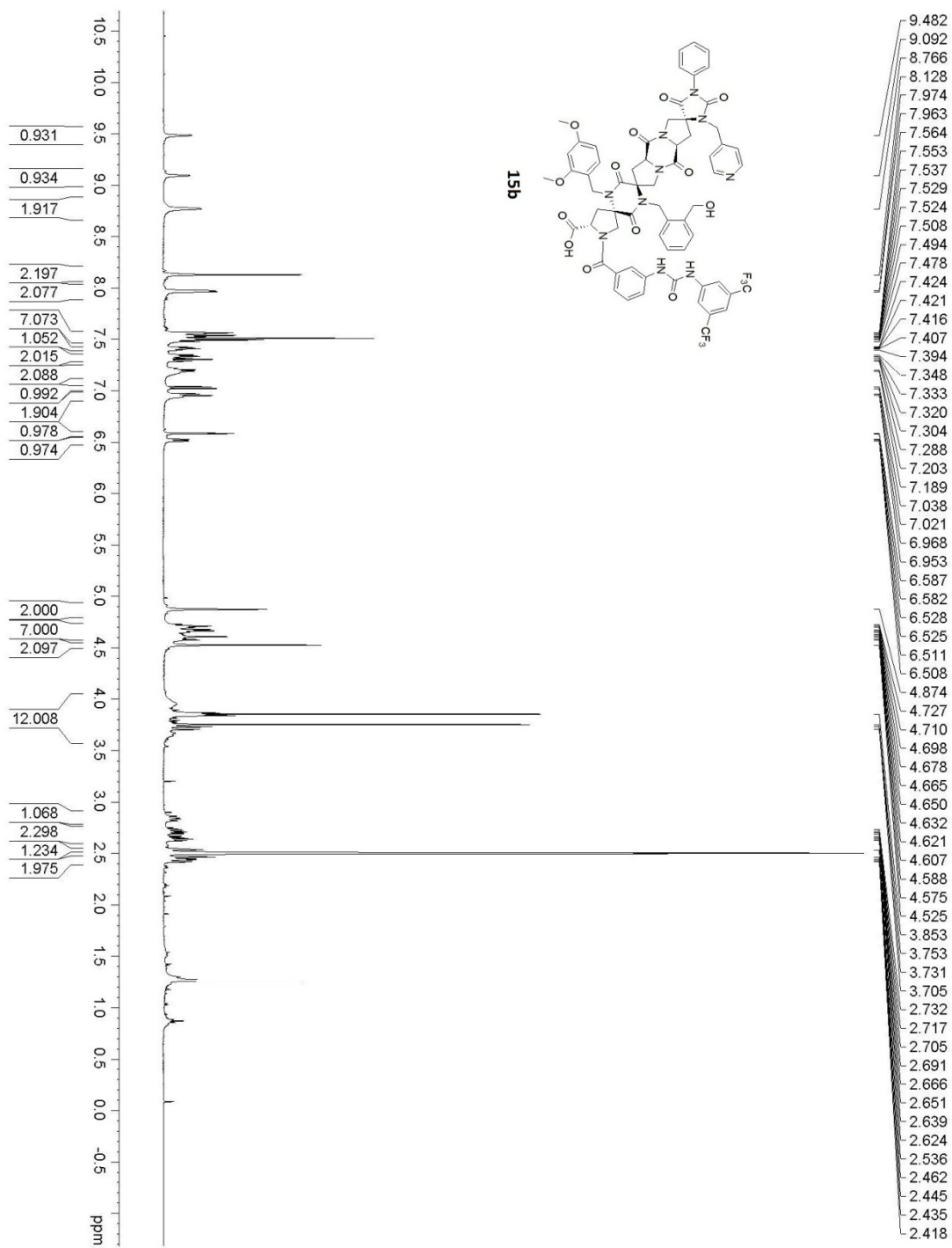
HMBC of compound 13



HMBC of Compound 15a



¹H-NMR of Compound **15b**



HMBC of Compound **15b**

