

Supporting Information for

Highly Selective Acylation of Polyamines and Aminoglycosides by 5-Acyl-5-phenyl-1,5-dihydro-4H-pyrazol-4-ones

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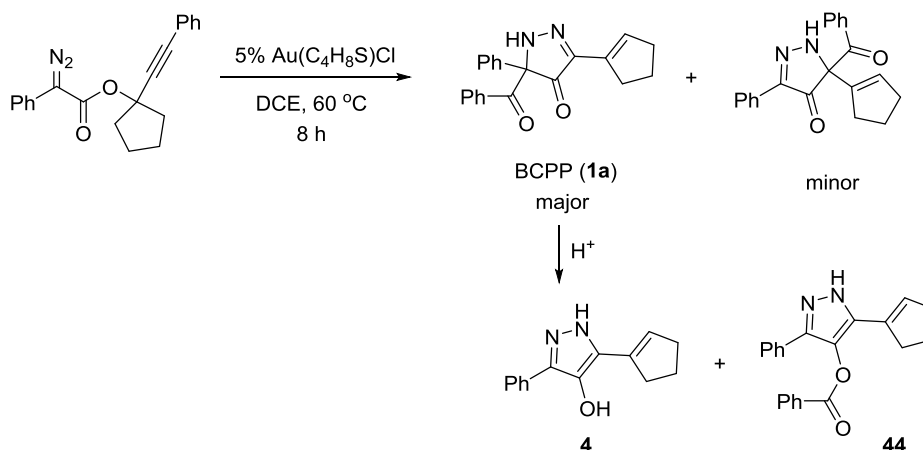
Contents

• General Information.....	S2
• A Modified Procedure for the Preparation of BCPP (1a).....	S2
• Characterization of Products.....	S3
• Experimental Procedure for the Kinetic Study of the Reaction Between BCPP and Amines.....	S10
• Substituents Effect and Hammett Plot for the Reaction of 1a–d with 1-Aminobutane.....	S26
• Kinetic Determination for the Intramolecular Benzoyl Transfer of BCPP.....	S34
• Crystal Structure Report for 44a (cd1436a).....	S37
• References.....	S40
• ¹ H and ¹³ C NMR Spectra of Products.....	S41
• HPLC Traces.....	S88

General Information. All solvents were purified and dried using standard techniques. Thin layer chromatography (TLC) analyses were performed on pre-coated analytical plates Silica Gel 60 F₂₅₄, and visualized with the use of UV light or iodine stain (I₂ and Silica Gel 60). High-resolution mass spectra (HRMS) were performed on a Bruker microTOF-ESI mass spectrometer. Exact masses were reported for the molecular ions [M+H]⁺ or [M+2H]²⁺. Melting points were measured uncorrected from an Electro Thermo Mel-Temp DLX 104. Column chromatography was performed on a CombiFlash[®] Rf 200 purification system using normal phase disposable columns. C18-Reversed phased silica gel was used for column chromatography of highly polar compounds. The purity of monoamides was determined on an Agilent 1260 Infinity Series HPLC instrument using a Phenomenex silica-based column (Lichrosorb 5 Sil 60A 250×4.60 mm). Kinetic experiments were performed on a Cary 5000 UV-Vis spectrometer. NMR spectra were recorded at 300 or 500 MHz (¹H NMR) and 76 or 126 MHz (¹³C NMR). Chemical shifts are reported in ppm using residual CHCl₃ (δ 7.26 ppm)/H₂O (δ 1.56 ppm), CH₃OH (δ 3.31 ppm)/H₂O (δ 4.87 ppm), DMSO (δ 2.50 ppm)/H₂O (δ 3.33 ppm), or D₂O (δ 4.79 ppm) for ¹H NMR reference, and the central resonance of CDCl₃ (δ 77.16 ppm), CD₃OD (δ 49.00 ppm), or DMSO-*d*₆ (δ 39.52 ppm) for ¹³C NMR reference. Multiplicities in ¹H NMR spectra are reported as: s (singlet); br (broad singlet); d (doublet); t (triplet); q (quartet); p (pentet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dt and td (doublet of triplets or triplet of doublets); dq (doublet of quartets); tt (triplet of triplets); m (multiplet); comp (composite of magnetically nonequivalent protons). The number of protons (n) for a given resonance is reported as nH; coupling constants (*J*) are given in Hertz (Hz).

Materials. AuCl(C₄H₈S) was purchased from Strem Chemicals. C18-Reversed phased silica gel was purchased from Sigma-Aldrich. BCPP (1a) and analogues 1b–d were synthesised from arylpropargyl phenyldiazoacetates and AuCl(C₄H₈S)¹ using a modified procedure. BCPP can be stored at 2–8 °C over three months without any decomposition. All other chemicals were obtained from commercial sources and used as received without further purification.

A Modified Procedure for the Preparation of BCPP (1a)

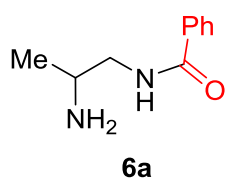


To a solution of 1-(phenylethynyl)cyclopentyl 2-diazo-2-phenylacetate (1.5 g, 4.54 mmol) in 50 mL of 1,2-dichloroethane (DCE) chloro(tetrahydrothiophene)gold(I) AuCl(C₄H₈S) (73 mg, 0.227 mmol) was added in one portion, the reaction flask was degassed and filled with nitrogen, and

the reaction solution was stirred at 60 °C for 8h. Solvent was evaporated until its volume was ca. 5 mL, and the product mixture was purified by flash chromatography on silica gel (with a 20:1 to 4:1 gradient of hexane:ethyl acetate as eluent) to afford BCPP (**1a**) as a light yellow solid (825 mg, 55% yield). Characterization data are in accordance with those in the literature.¹ Note: BCPP undergoes decomposition on silica gel to form **4** and **44**, therefore column chromatography must be performed rapidly.

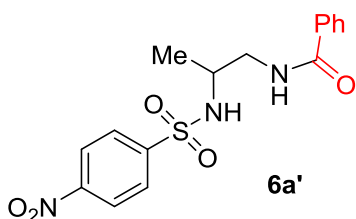
Characterization of Products

N-(2-Aminopropyl)benzamide (**6a**)



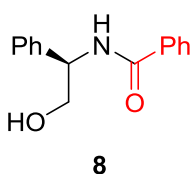
Reported compound.² Purified by flash chromatography on silica gel (with a 10:1 to 1:1 gradient of DCM:methanol as eluent): 87 mg, 98% yield; sticky pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, *J* = 7.5 Hz, 2H, *ortho*-Bz), 7.42 (t, *J* = 7.5 Hz, 1H, *para*-Bz), 7.34 (t, *J* = 7.5 Hz, 2H, *meta*-Bz), 7.22 (br, 1H, NH), 3.48 – 3.37 (m, 1H, C¹-H), 3.24 – 3.01 (comp, 2H, C¹-H, C²-H), 1.82 (br, 2H, NH₂), 1.07 (d, *J* = 5.9 Hz, 3H, Me). ¹³C NMR (126 MHz, CDCl₃) δ 167.8, 134.6, 131.3, 128.4, 127.0, 47.4, 46.6, 21.8. HRMS (ESI) *m/z* calcd for C₁₀H₁₅N₂O [M+H]⁺ 179.1179, found: 179.1182.

N-[2-(4-Nitrophenylsulfonamido)propyl]benzamide (**6a'**)



Compound **6a'** was prepared for HPLC determination of selectivity in benzylation of 1,2-diaminopropane by BCPP **1a**. To a stirred solution of **6a** (87 mg, 0.49 mmol) in DCM (5 mL) triethylamine (0.14 mL, 1.0 mmol) was added in one portion followed by a dropwise addition of 4-nitrobenzenesulfonyl chloride (163 mg, 0.74 mmol) in DCM (3 mL) at 0 °C. The mixture was stirred at 20 °C for 30 min. Column chromatography on silica gel (with a 3:1 to 1:1 gradient of hexane:ethyl acetate as eluent) afforded **6a'** in quantitative yield (178 mg) as a white solid: mp 170–171 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.12 (d, *J* = 8.7 Hz, 2H, Ar in Ns), 8.00 (d, *J* = 8.7 Hz, 2H, Ar in Ns), 7.65 (d, *J* = 7.4 Hz, 2H, *ortho*-Bz), 7.53 (t, *J* = 7.4 Hz, 1H, *para*-Bz), 7.41 (t, *J* = 7.4 Hz, 2H, *meta*-Bz), 6.64 (br, 1H, NHBz), 6.13 (br, 1H, NHNs), 3.65 – 3.57 (m, 1H, CH₁-NHNs), 3.56 – 3.47 (m, 1H, CH₂-NHBz), 3.42 – 3.34 (m, 1H, CH₂-NHBz), 1.24 (d, *J* = 6.5 Hz, 3H, Me). ¹³C NMR (126 MHz, CDCl₃) δ 168.6, 149.7, 146.6, 132.9, 132.3, 128.7, 128.0, 126.8, 124.2, 52.0, 45.3, 20.1. HRMS (ESI) *m/z* calcd for C₁₆H₁₈N₃O₅S [M+H]⁺ 364.0962, found: 364.0963.

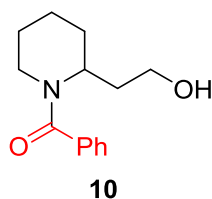
(*R*)-*N*-(2-Hydroxy-1-phenylethyl)benzamide (**8**)



Reported compound.³ Product was purified by flash chromatography on silica gel (with a 3:1 to 1:1 gradient of hexane:ethyl acetate as eluent): 120 mg, 100% yield; white solid, mp 146–147 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.71 (d, *J* = 8.1 Hz, 1H, NH), 7.92 (dd, *J* = 8.1, 1.7 Hz, 2H, *ortho*-Bz), 7.56 – 7.18 (comp, 8H, Ar), 5.08 (td, *J* = 8.1, 5.7 Hz, 1H, CHN), 4.95 (t, *J* = 5.9 Hz, 1H, OH), 3.77 – 3.58 (comp, 2H, CH₂OH). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 166.6, 141.8, 135.1, 131.6,

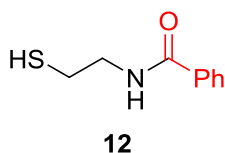
128.6, 128.5, 127.8, 127.4, 127.3, 65.0, 56.4. HRMS (ESI) m/z calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1176, found: 242.1186.

[2-(2-Hydroxyethyl)piperidin-1-yl](phenyl)methanone (10)



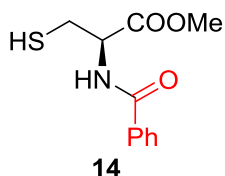
Reported compound.⁴ Product was purified by flash chromatography on silica gel (with a 2:1 to 1:1 gradient of hexane:ethyl acetate as eluent): 111 mg, 95% yield; thick colorless oil. 1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.35 (comp, 5H, Ar), 4.95 (br, 1H, OH), 4.19 – 4.11 (m, 1H, CH–N), 3.75 – 3.55 (comp, 2H, CH_2 –O), 3.46 (tt, J = 12.0, 3.1 Hz, 1H, CH_2 –N), 2.90 (td, J = 11.6, 2.7 Hz, 1H, CH_2 –N), 2.05 (ddt, J = 14.8, 11.9, 2.7 Hz, 1H, CH_2), 1.96 – 1.76 (comp, 2H, CH_2), 1.75 – 1.50 (comp, 5H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 135.9, 129.7, 128.4, 126.4, 58.4, 45.7, 43.4, 32.1, 29.1, 25.9, 19.2. HRMS (ESI) m/z calcd for $C_{14}H_{20}NO_2$ $[M+H]^+$ 234.1489, found: 234.1500.

N-(2-Mercaptoethyl)benzamide (12)



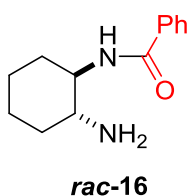
Reported compound.⁵ Product was purified by flash chromatography on silica gel (with a 4:1 to 2:1 gradient of hexane:ethyl acetate as eluent): 88 mg, 97% yield; white solid, mp 69–70 °C. 1H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.5, 1.3 Hz, 2H, *ortho*-Bz), 7.48 (t, J = 7.5, 1H, *para*-Bz), 7.40 (t, J = 7.5 Hz, 2H, *meta*-Bz), 7.01 (br, 1H, NH), 3.59 (dd, J = 12.6, 6.4 Hz, 2H, CH_2 –N), 2.74 (dt, J = 8.5, 6.4 Hz, 2H, CH_2 –S), 1.41 (t, J = 8.5 Hz, 1H, SH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 134.3, 131.6, 128.6, 127.0, 42.9, 24.6. HRMS (ESI) m/z calcd for $C_9H_{12}NOS$ $[M+H]^+$ 182.0634, found: 182.0635.

Methyl N-benzoyl-L-cysteinate (14)



Reported compound.⁵ The base form of L-cysteine methyl ester was prepared from the hydrochloride (86 mg, 0.5 mmol) by treatment with sodium bicarbonate (126 mg, 1.5 mmol) in water (2 mL). After extraction by DCM (3×5 mL), drying over anhydrous magnesium sulfate and evaporation of the solvent, the base form of L-cysteine methyl ester was obtained (67 mg, 99% yield) as a grey liquid. Monoamide **14** was purified by flash chromatography on silica gel (with a 3:1 to 1:1 gradient of hexane:ethyl acetate as eluent) to give 111 mg (93% yield) of a white solid, mp 62–63 °C. 1H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.6, 1.3 Hz, 2H, *ortho*-Bz), 7.52 (t, J = 7.6 Hz, 1H, *para*-Bz), 7.44 (t, J = 7.6 Hz, 2H, *meta*-Bz), 7.09 (br, 1H, NH), 5.07 (dt, J = 7.9, 4.1 Hz, 1H, CH–NH), 3.81 (s, 3H, Me), 3.17 – 3.07 (comp, 2H, CH_2 –S), 1.41 (t, J = 9.0 Hz, 1H, SH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 167.1, 133.5, 131.9, 128.5, 127.2, 54.2, 52.8, 26.7. HRMS (ESI) m/z calcd for $C_{11}H_{14}NO_3S$ $[M+H]^+$ 240.0689, found: 240.0699.

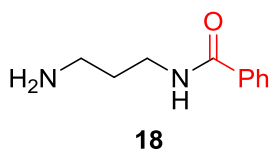
(±) trans-N-(2-Aminocyclohexyl)benzamide (16)



Reported compound.⁶ Product was purified by flash chromatography on silica gel (with a 5:1 gradient of DCM:methanol to pure methanol as eluent): 107 mg, 98% yield; white solid, mp 125–126 °C. 1H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.72 (comp, 2H, *ortho*-Bz), 7.51 – 7.39 (comp, 3H, Ar), 6.19 (br, 1H, NH), 3.75 – 3.69

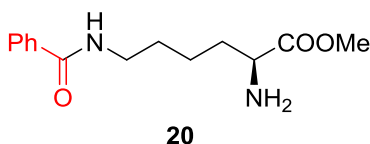
(m, 1H, C¹H-N), 2.52 – 2.46 (m, 1H, C²H-N), 2.16 – 2.08 (m, 1H, CH₂), 2.02 – 1.94 (m, 1H, CH₂), 1.80 – 1.70 (comp, 2H, CH₂), 1.56 (br, 2H, NH₂), 1.35 – 1.13 (comp, 4H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ 168.0, 134.8, 131.4, 128.5, 127.1, 56.7, 55.4, 35.5, 32.5, 25.2, 25.1. HRMS (ESI) *m/z* calcd for C₁₃H₁₉N₂O [M+H]⁺ 219.1492, found: 219.1499.

***N*-(3-Aminopropyl)benzamide (18)**



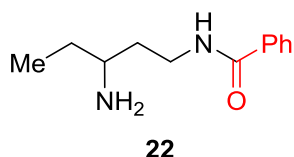
Reported compound.⁷ Product was purified by flash chromatography on silica gel (with a 5:1 gradient of DCM:methanol to pure methanol as eluent): 87 mg, 98% yield; white solid, mp 44–45 °C. ¹H NMR (500 MHz, CD₃OD) δ 7.87 (dd, *J* = 7.5, 1.3 Hz, 2H, *ortho*-Bz), 7.53 (t, *J* = 7.5 Hz, 1H, *para*-Bz), 7.46 (t, *J* = 7.5 Hz, 2H, *meta*-Bz), 4.97 (br, 5H, NH, NH₂, HDO, H₂O), 3.51 (t, *J* = 6.6 Hz, 2H, C¹H-N), 3.02 (t, *J* = 7.4 Hz, 2H, C³H-N), 2.03 – 1.97 (comp, 2H, C²H). ¹³C NMR (126 MHz, CD₃OD) δ 169.3, 133.7, 131.4, 128.1, 127.0, 37.0, 36.1, 27.4. HRMS (ESI) *m/z* calcd for C₁₀H₁₅N₂O [M+H]⁺ 179.1179, found: 179.1185.

Methyl *N*⁶-benzoyl-*L*-lysinate (20)



The base form of *L*-lysine methyl ester was prepared from its dihydrochloride (110 mg, 0.5 mmol) by treatment with sodium bicarbonate (126 mg, 1.5 mmol) in water (2 mL). Water was evaporated and the residue was dissolved in a mixture DCM:methanol 9:1 (5 mL), then the inorganic salts were filtered and washed with a mixture DCM:methanol 9:1 (2×5 mL). The solvents of the organic filtrate were evaporated to afford the base form of *L*-lysine methyl ester (80 mg, >99% yield) as a colorless oil. Monoamide **20** was purified by flash chromatography on silica gel (with a 10:1 to 3:1 gradient of DCM:methanol as eluent) to give 124 mg (94% yield) as a white solid, mp 238–239 °C (decomp). The reaction scale-up to 1.00 g (4.53 mmol) of *L*-lysine methyl ester after purification on silica gel afforded 1.13 g of **20** (95% yield). ¹H NMR (500 MHz, CD₃OD) δ 7.84 (d, *J* = 7.5 Hz, 2H, *ortho*-Bz), 7.51 (t, *J* = 7.5 Hz, 1H, *para*-Bz), 7.44 (t, *J* = 7.5 Hz, 2H, *meta*-Bz), 3.79 (t, *J* = 6.4 Hz, 1H, C²H), 3.74 (s, 3H, Me), 3.40 (t, *J* = 6.9 Hz, 2H, C⁶H), 1.92 – 1.85 (m, 1H, CH₂), 1.84 – 1.77 (m, 1H, CH₂), 1.68 – 1.63 (comp, 2H, CH₂), 1.53 – 1.42 (comp, 2H, CH₂). ¹³C NMR (126 MHz, CD₃OD) δ 172.5, 168.7, 134.3, 131.2, 128.2, 126.9, 53.1, 51.7, 39.1, 31.7, 28.7, 22.3. HRMS (ESI) *m/z* calcd for C₁₄H₂₁N₂O₃ [M+H]⁺ 265.1547, found: 265.1558.

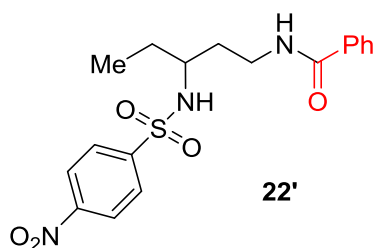
***N*-(3-Aminopentyl)benzamide (22)**



Reported compound.² Product was purified by flash chromatography on silica gel (with a 10:1 to 5:1 gradient of DCM:methanol as eluent): 103 mg, 100% yield; white solid, mp 116–117 °C. ¹H NMR (500 MHz, CD₃OD) δ 7.86 (d, *J* = 7.6 Hz, 2H, *ortho*-Bz), 7.54 (t, *J* = 7.6 Hz, 1H, *para*-Bz), 7.46 (t, *J* = 7.6 Hz, 2H, *meta*-Bz), 4.86 (br, 5H, NH, NH₂, HDO, H₂O), 3.64 – 3.55 (m, 1H, C¹-H), 3.50 – 3.42 (m, 1H, C¹-H), 3.14 (dq, *J* = 8.2, 6.3 Hz, 1H, C³-H), 2.04 – 1.96 (m, 1H, C²-H), 1.91 – 1.82 (m, 1H, C²-H), 1.78 – 1.66 (comp, 2H, C⁴-H), 1.02 (t, *J* = 7.5 Hz, 3H, Me). ¹³C NMR

(126 MHz, CD₃OD) δ 169.5, 133.5, 131.6, 128.2, 127.0, 50.6, 35.5, 32.2, 25.5, 8.5. HRMS (ESI) m/z calcd for C₁₂H₁₉N₂O [M+H]⁺ 207.1492, found: 207.1500.

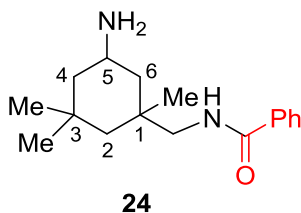
***N*-(3-[(4-Nitrophenyl)sulfonamido]pentyl)benzamide (22')**



22'

Prepared for HPLC analysis of selectivity in benzylation of 1,3-diaminopentane by BCPP **1a** following the procedure for **6a'**. Purified by flash chromatography on silica gel (with a 3:1 to 1:1 gradient of hexane:ethyl acetate as eluent): 195 mg, >99% yield; white solid, mp 79–80 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.26 (d, J = 8.7 Hz, 2H, Ar in Ns), 8.02 (d, J = 8.7 Hz, 2H, Ar in Ns), 7.80 (d, J = 7.5 Hz, 2H, *ortho*-Bz), 7.50 (t, J = 7.5 Hz, 1H, *para*-Bz), 7.43 (t, J = 7.5 Hz, 2H, *meta*-Bz), 7.14 (br, 1H, NHBz), 6.13 (br, 1H, NHNs), 3.77 – 3.71 (m, 1H, CH₂-NHBz), 3.44 – 3.26 (comp, 2H, CH₂-NHBz, CH-NHNs), 1.94 – 1.85 (m, 1H, C²-H), 1.65 – 1.56 (m, 1H, C²-H), 1.43 – 1.26 (comp, 2H, C⁴-H), 0.60 (t, J = 7.4 Hz, 3H, Me). ¹³C NMR (126 MHz, CDCl₃) δ 167.7, 149.8, 147.2, 134.1, 131.7, 128.7, 128.1, 126.9, 124.3, 54.1, 36.3, 34.6, 28.3, 10.2. HRMS (ESI) m/z calcd for C₁₈H₂₂N₃O₅S [M+H]⁺ 392.1275, found: 392.1276.

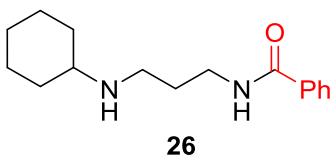
***N*-[5-Amino-1,3,3-trimethylcyclohexyl)methyl]benzamide (24)**



24

Purified by flash chromatography on silica gel (with a 5:1 to 1:1 gradient of DCM:methanol as eluents): 133 mg, 97% yield; sticky colorless oil. Obtained as a mixture of *trans*- and *cis*-isomers (*trans/cis* = 85:15), ratio *trans/cis* is the same with starting material. ¹H NMR of *trans*-**24** (500 MHz, CDCl₃) δ 7.76 (d, J = 7.4 Hz, 2H, *ortho*-Bz), 7.50 (t, J = 7.4 Hz, 1H, *para*-Bz), 7.43 (t, J = 7.4 Hz, 2H, *meta*-Bz), 6.23 (br, 1H, NH), 3.22 (d, J = 6.4 Hz, 2H, CH₂-N), 3.10 – 2.98 (m, 1H, C⁵H-N), 1.76 (br, 2H, NH₂), 1.68 – 1.60 (comp, 2H, Cy), 1.33 – 1.26 (comp, 2H, Cy), 1.09 (s, 3H, Me), 1.03 (s, 3H, Me), 0.97 – 0.94 (m, 1H, Cy), 0.94 (s, 3H, Me), 0.92 – 0.85 (m, 1H, Cy). ¹³C NMR (126 MHz, CDCl₃) δ 167.8, 134.9, 131.3, 128.5, 126.9, 53.5, 49.8, 47.4, 45.5, 44.0, 36.8, 35.2, 32.0, 27.9, 23.7. HRMS (ESI) m/z calcd for C₁₇H₂₇N₂O [M+H]⁺ 275.2118, found: 275.2127.

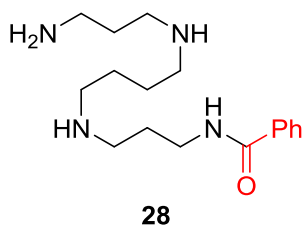
***N*-(3-(Cyclohexylamino)propyl)benzamide (26)**



26

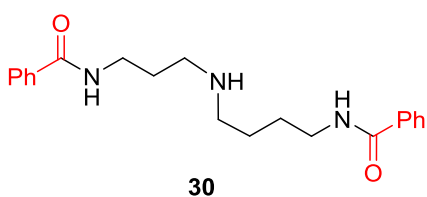
Reported compound.⁸ Product was purified by flash chromatography on silica gel (with a 5:1 to 1:1 gradient of DCM:methanol as eluent): 130 mg, 100% yield; white solid, mp 190–191 °C. ¹H NMR (500 MHz, CD₃OD) δ 7.88 (d, J = 7.5 Hz, 2H, *ortho*-Bz), 7.58 (t, J = 7.5 Hz, 1H, *para*-Bz), 7.50 (t, J = 7.5 Hz, 2H, *meta*-Bz), 3.54 (t, J = 6.2 Hz, 2H, CH₂NHBz), 3.14 – 3.04 (comp, 3H, CH₂NHCy, NHCH₂Cy), 2.22 – 2.08 (comp, 2H, CH₂), 2.08 – 1.98 (comp, 2H, CH₂), 1.98 – 1.83 (comp, 2H, CH₂), 1.78 – 1.69 (m, 1H, CH₂), 1.46 – 1.34 (comp, 4H, CH₂), 1.33 – 1.20 (m, 1H, CH₂). ¹³C NMR (126 MHz, CD₃OD) δ 169.7, 133.6, 131.6, 128.3, 126.9, 57.1, 41.9, 36.1, 29.0, 26.6, 24.7, 24.0. HRMS (ESI) m/z calcd for C₁₆H₂₅N₂O [M+H]⁺ 261.1961, found: 261.1972.

***N*-[3-([4-(3-Aminopropylamino)butyl]amino)propyl]benzamide (28)**



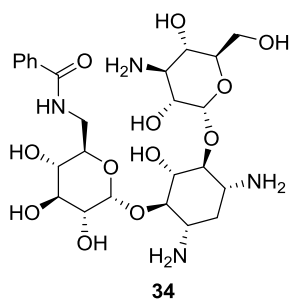
Purified by C18-reversed phase chromatography (with a gradient of pure water to water:acetonitrile 1:1 as eluent): 142 mg, 93% yield; pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.20 (br, 1H, NHBz), 7.77 (t, J = 7.6 Hz, 2H, *ortho*-Bz), 7.43 (t, J = 7.6 Hz, 1H, *para*-Bz), 7.36 (t, J = 7.6 Hz, 2H, *meta*-Bz), 3.51 (t, J = 6.4 Hz, 2H, CH_2NHBz), 2.80 – 2.10 (comp, 14H, NH, CH_2), 1.75 – 1.71 (comp, 2H, CH_2), 1.65 – 1.54 (comp, 2H, CH_2), 1.48 (br, 4H, NH). ^{13}C NMR (126 MHz, CDCl_3) δ 167.3, 134.8, 131.1, 128.4, 127.0, 49.7, 48.8, 47.8, 40.5, 39.9, 39.8, 33.5, 28.3, 28.2, 27.8. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{31}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 307.2492, found: 307.2499.

***N*-[3-(4-Benzamidobutylamino)propyl]benzamide (30)**



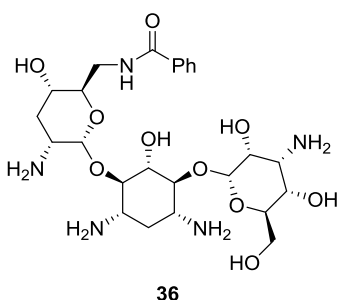
Reported compound.⁹ Product was purified by flash chromatography on silica gel (with a gradient of DCM:methanol 3:1 to pure methanol as eluent): 173 mg, 98% yield; white solid, mp 130–131 °C. ^1H NMR (500 MHz, CD_3OD) δ 7.89 – 7.83 (comp, 4H, *ortho*-Bz), 7.55 – 7.51 (comp, 2H, *para*-Bz), 7.45 (td, J = 7.6, 2.9 Hz, 4H, *meta*-Bz), 4.83 (br, 9H, NH, HDO, H_2O), 3.52 (t, J = 6.4 Hz, 2H, CH_2NHBz), 3.45 (t, J = 6.4 Hz, 2H, CH_2NHBz), 3.08 (t, J = 7.4 Hz, 4H, CH_2NH), 2.10 – 1.98 (comp, 2H, CH_2), 1.88 – 1.76 (comp, 2H, CH_2), 1.78 – 1.69 (comp, 2H, CH_2). ^{13}C NMR (126 MHz, CD_3OD) δ 169.4, 168.9, 134.2, 133.6, 131.5, 131.3, 128.2, 127.0, 126.9, 46.5, 45.2, 38.6, 36.1, 26.3, 26.1, 23.3. HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{28}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 354.2176, found: 354.2186.

***N*-6'-Benzoylkanamycin (34)**



Product was purified by flash chromatography on silica gel (with a gradient of methanol/28wt% aqueous ammonium hydroxide 100:0 to 80:20 as eluent): 91 mg, 77% yield; white solid, mp 255–256 °C. ^1H NMR (500 MHz, D_2O) δ 7.77 (d, J = 7.4 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.4 Hz, 2H), 5.23 (d, J = 3.8 Hz, 1H), 5.00 (d, J = 3.6 Hz, 1H), 3.99 – 3.67 (comp, 7H), 3.63 – 3.46 (comp, 4H), 3.37 – 3.29 (comp, 2H), 3.21 (dt, J = 15.3, 9.5 Hz, 2H), 3.00 (t, J = 9.9 Hz, 1H), 2.90 – 2.81 (m, 1H), 2.79 – 2.71 (m, 1H), 1.82 (dt, J = 9.1, 4.0 Hz, 1H), 1.07 (dd, J = 12.4 Hz, 1H). ^{13}C NMR (126 MHz, D_2O) δ 170.9, 133.3, 132.4, 129.0, 127.1, 100.4, 100.0, 88.0, 87.3, 74.2, 72.9, 72.2, 72.0, 71.6, 71.4, 71.4, 69.1, 60.3, 54.3, 50.3, 49.3, 40.9, 35.0. HRMS (ESI) m/z calcd for $\text{C}_{25}\text{H}_{42}\text{N}_4\text{O}_{12}$ $[\text{M}+2\text{H}]^{2+}$ 295.1394, found: 295.1392.

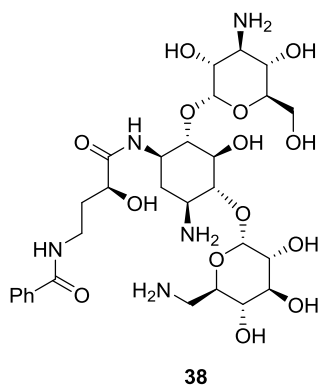
***N*-6'-Benzoyltobramycin (36)**



Product was purified by flash chromatography on silica gel (with a gradient of methanol/28wt% aqueous ammonium hydroxide 100:0 to 80:20 as eluent): 105 mg, 92% yield; white solid, mp 212–213 °C. ^1H NMR (500 MHz, D_2O) δ 7.66 (d, J = 7.4 Hz, 2H), 7.51 (t, J = 7.4 Hz,

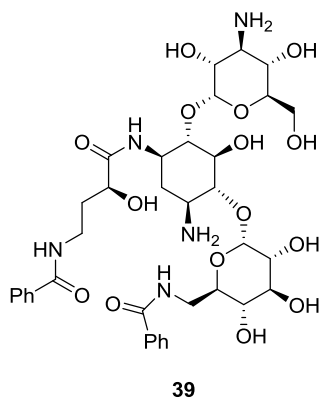
1H), 7.42 (t, *J* = 7.4 Hz, 2H), 4.96 (d, *J* = 2.8 Hz, 1H), 4.89 (d, *J* = 3.4 Hz, 1H), 3.80 – 3.75 (m, 1H), 3.74 – 3.59 (comp, 4H), 3.49 – 3.33 (comp, 4H), 3.26 – 3.17 (comp, 2H), 3.12 (t, *J* = 9.3 Hz, 1H), 3.06 (t, *J* = 9.3 Hz, 1H), 2.94 – 2.85 (comp, 2H), 2.78 – 2.67 (m, 1H), 2.67 – 2.57 (m, 1H), 1.99 – 1.90 (m, 1H), 1.71 – 1.63 (m, 1H), 1.53 (dd, 11.9 Hz, 1H), 0.95 (dd, *J* = 12.5 Hz, 1H). ¹³C NMR (126 MHz, D₂O) δ 170.7, 133.2, 132.3, 128.8, 127.0, 99.9, 99.7, 87.7, 87.0, 74.2, 72.1, 71.6, 69.1, 66.4, 60.2, 54.2, 50.2, 49.5, 49.1, 48.8, 40.8, 35.1, 34.3. HRMS (ESI) *m/z* calcd for C₂₅H₄₂N₅O₁₀ [M+H]⁺ 572.2926, found: 572.2925.

***N*-AHB-Benzoylamikacin (38)**



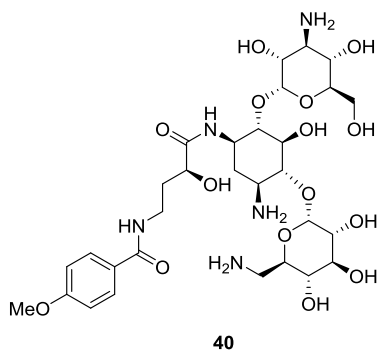
Product was purified by flash chromatography on silica gel (with a gradient of methanol/28wt% aqueous ammonium hydroxide 100:0 to 90:10 as eluent): 106 mg, 77% yield; white solid, mp 262–263 °C. ¹H NMR (500 MHz, D₂O) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 5.49 (d, *J* = 3.8 Hz, 1H), 5.11 (d, *J* = 3.6 Hz, 1H), 4.20 (dd, *J* = 8.8, 3.6 Hz, 1H), 4.02 – 3.92 (comp, 3H), 3.80 – 3.69 (comp, 5H), 3.63 – 3.57 (comp, 2H), 3.56 – 3.47 (comp, 4H), 3.41 – 3.30 (comp, 2H), 3.21 (t, *J* = 10.3 Hz, 1H), 3.16 – 3.04 (comp, 2H), 2.15 – 2.05 (m, 1H), 2.00 – 1.84 (comp, 2H), 1.52 (dd, *J* = 12.6 Hz, 1H). ¹³C NMR (126 MHz, D₂O) δ 176.2, 170.9, 133.6, 132.2, 128.8, 127.1, 98.1, 97.5, 82.6, 80.6, 74.2, 72.4, 72.1, 71.3, 71.1, 69.5, 69.3, 68.8, 66.9, 60.0, 54.9, 49.3, 48.4, 40.5, 38.8, 36.4, 33.0. HRMS (ESI) *m/z* calcd for C₂₉H₄₉N₅O₁₄ [M+2H]²⁺ 345.6633, found: 345.6631.

***N*-6'-*N*-AHB-Dibenzoylamikacin (39)**



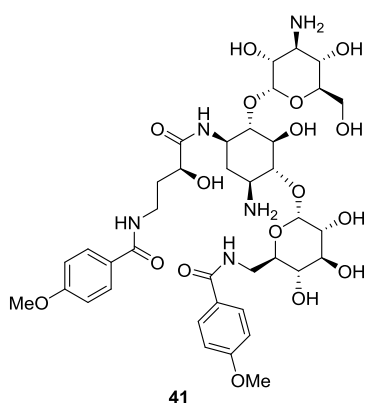
Product was purified by flash chromatography on silica gel (with a gradient of methanol/28wt% aqueous ammonium hydroxide 100:0 to 90:10 as eluent): 22 mg, 14% yield; white solid, mp 237–238 °C. ¹H NMR (500 MHz, D₂O) δ 7.78 – 7.71 (comp, 4H), 7.62 – 7.56 (comp, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 5.33 (d, *J* = 3.9 Hz, 1H), 5.10 (d, *J* = 3.7 Hz, 1H), 4.20 (dd, *J* = 8.8, 3.6 Hz, 1H), 4.05 – 3.98 (m, 1H), 3.97 – 3.91 (comp, 2H), 3.82 – 3.67 (comp, 7H), 3.66 – 3.59 (comp, 3H), 3.58 – 3.47 (comp, 3H), 3.38 – 3.30 (comp, 2H), 3.19 – 3.10 (m, 1H), 2.14 – 2.05 (m, 1H), 1.97 (dt, *J* = 13.0, 4.3 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.50 (dd, *J* = 12.6 Hz, 1H). ¹³C NMR (126 MHz, D₂O) δ 176.2, 171.2, 170.9, 133.6, 133.4, 132.4, 132.2, 128.9, 128.8, 127.2, 127.1, 99.0, 97.9, 83.3, 80.0, 73.8, 72.5, 72.0, 71.5, 71.1, 69.5, 68.3, 65.8, 59.7, 55.2, 49.0, 48.8, 40.6, 38.8, 36.4, 33.0, 31.8. HRMS (ESI) *m/z* calcd for C₃₆H₅₃N₅O₁₅ [M+2H]²⁺ 397.6764, found: 397.6760.

***N*-AHB-(4-Methoxybenzoyl)amikacin (40)**



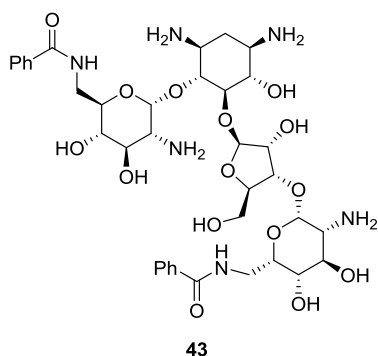
Product was purified by flash chromatography on silica gel (with a gradient of methanol/28wt% aqueous ammonium hydroxide 100:0 to 80:20 as eluent): 101 mg, 70% yield; off-white solid, mp 210–211 °C. ^1H NMR (500 MHz, D_2O) for two rotamers: δ 7.71 (dd, J = 8.9, 3.6 Hz, 4H), 7.07 – 6.97 (comp, 4H), 5.38 (d, J = 4.0 Hz, 1H), 5.23 (dd, J = 7.1, 4.0 Hz, 1H), 5.05 (d, J = 3.4 Hz, 2H), 4.22 – 4.13 (comp, 2H), 4.00 – 3.86 (comp, 6H), 3.84 (s, 6H, OMe), 3.80 – 3.66 (comp, 11H), 3.60 – 3.53 (comp, 3H), 3.52 – 3.45 (comp, 4H), 3.41 – 3.28 (comp, 8H), 3.26 – 3.15 (comp, 2H), 3.06 – 2.82 (comp, 5H), 2.14 – 2.04 (comp, 2H), 1.95 – 1.81 (comp, 4H), 1.48 (dd, J = 12.6 Hz, 1H), 1.37 (dd, J = 12.6 Hz, 1H). ^{13}C NMR (126 MHz, D_2O) for two rotamers: δ 176.1, 176.0, 170.1, 170.0, 163.4, 162.0, 129.1, 129.1, 126.0, 114.1, 100.6, 100.1, 98.7, 98.5, 98.4, 85.3, 84.8, 80.8, 79.9, 75.6, 74.7, 72.7, 72.5, 72.1, 72.0, 71.9, 71.7, 71.6, 71.3, 71.1, 70.7, 69.6, 69.5, 68.9, 68.8, 68.6, 60.3, 55.6, 54.2, 49.7, 49.6, 48.5, 41.0, 40.9, 36.4, 36.3, 34.1, 33.0. HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{51}\text{N}_5\text{O}_{15}$ $[\text{M}+2\text{H}]^{2+}$ 360.6685, found: 360.6686.

***N*-6'-*N*-AHB-Bis(4-methoxybenzoyl)amikacin (41)**



Product was purified by flash chromatography on silica gel (with a gradient of methanol/28wt% aqueous ammonium hydroxide 100:0 to 80:20 as eluent): 38 mg, 23% yield; off-white solid, mp 222–223 °C. ^1H NMR (500 MHz, D_2O) δ 7.63 (dd, J = 15.0, 8.9 Hz, 4H), 6.94 (dd, J = 12.6, 8.9 Hz, 4H), 5.13 (d, J = 3.8 Hz, 1H), 4.97 (d, J = 3.7 Hz, 1H), 4.07 (dd, J = 8.7, 3.8 Hz, 1H), 3.92 – 3.88 (dt, J = 10.0, 3.0 Hz, 1H), 3.84 – 3.77 (comp, 2H), 3.75 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.73 – 3.67 (m, 1H), 3.64 – 3.55 (comp, 5H), 3.54 – 3.48 (comp, 3H), 3.47 – 3.34 (comp, 5H), 3.26 – 3.20 (comp, 2H), 3.16 (t, J = 10.4 Hz, 1H), 2.04 – 1.92 (m, 1H), 1.80 – 1.72 (m, 1H), 1.22 (dd, J = 12.6 Hz, 1H). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 174.6, 167.1, 166.6, 162.0, 161.9, 129.6, 129.5, 127.1, 126.8, 113.9, 101.6, 98.0, 90.3, 80.5, 75.3, 73.2, 72.8, 72.4, 71.9, 71.2, 69.8, 68.1, 60.7, 55.8, 55.6, 50.0, 49.4, 41.5, 36.8, 35.6, 34.4. HRMS (ESI) m/z calcd for $\text{C}_{38}\text{H}_{57}\text{N}_5\text{O}_{17}$ $[\text{M}+2\text{H}]^{2+}$ 427.6869, found: 427.6868.

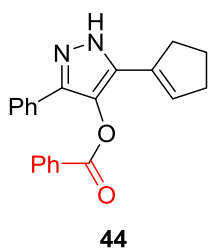
***N*-6'-*N*-6'''-Dibenzoylneomycin B (43)**



Product was purified by flash chromatography on silica gel (with a gradient of methanol/28wt% aqueous ammonium hydroxide 100:0 to 90:10 as eluent): 128 mg, 78% yield; white solid, mp 110–111 °C. ^1H NMR (500 MHz, D_2O) δ 7.73 (comp, 4H), 7.58 (t, J = 7.5 Hz, 1H), 7.49 (comp, 5H), 5.30 (d, J = 3.6 Hz, 1H), 5.20 (d, J = 2.1 Hz, 1H), 4.88 (d, J = 1.3 Hz, 1H), 4.28 – 4.23 (m, 1H), 4.18 – 4.12 (comp, 2H), 4.08 – 4.03 (comp, 2H), 3.97 – 3.90 (m, 1H),

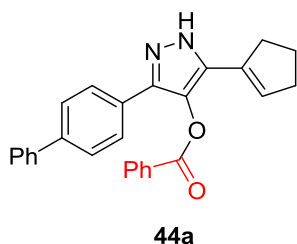
3.81 – 3.44 (comp, 11H), 3.34 – 3.27 (m, 1H), 3.20 (t, $J = 9.3$ Hz, 1H), 3.03 (s, 1H), 2.85 (t, $J = 9.3$ Hz, 1H), 2.76 – 2.65 (comp, 2H), 2.63 – 2.53 (m, 1H), 1.75 (dt, $J = 12.8, 4.0$ Hz, 1H), 0.93 (dd, $J = 12.5$ Hz, 1H). ^{13}C NMR (75 MHz, D_2O) δ 170.8, 170.6, 133.3, 133.2, 132.4, 132.3, 128.9, 128.8, 127.1, 127.0, 108.8, 99.1, 98.2, 84.2, 82.1, 81.3, 77.1, 76.1, 73.2, 73.0, 72.9, 71.8, 71.1, 70.5, 68.1, 61.6, 55.3, 52.5, 50.2, 50.0, 40.9, 40.7, 35.2. HRMS (ESI) m/z calcd for $\text{C}_{37}\text{H}_{56}\text{N}_6\text{O}_{15}$ $[\text{M}+2\text{H}]^{2+}$ 412.1896, found: 412.1894.

5-(Cyclopent-1-en-1-yl)-3-phenyl-1H-pyrazol-4-yl benzoate (**44**)



Synthetic procedure. A solution of BCPP **1a** (66.0 mg, 0.2 mmol) in methanol (15 mL) was kept at 20 °C for 12 h. Compound **44** was formed quantitatively and isolated as a white solid (mp 169–170 °C) after evaporation of methanol. ^1H NMR (500 MHz, CDCl_3) δ 8.31 (d, $J = 7.5$ Hz, 2H, Ar), 7.78 – 7.65 (comp, 3H, Ar), 7.58 (t, $J = 7.7$ Hz, 2H, Ar), 7.35 – 7.21 (comp, 3H, Ar), 6.10 – 6.07 (m, 1H, =CH), 2.72 – 2.69 (comp, 2H, $\text{CH}_2\text{C}=\text{}$), 2.42 – 2.40 (comp, 2H, $\text{CH}_2\text{C}=\text{}$), 1.85 (p, $J = 7.4$ Hz, 2H, CH_2). ^{13}C NMR (126 MHz, CDCl_3) δ 164.7, 133.9, 131.1, 130.4, 129.1, 129.0, 128.8, 128.7, 128.0, 126.2, 33.4, 33.0, 22.5. HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 331.1441, found: 331.1444.

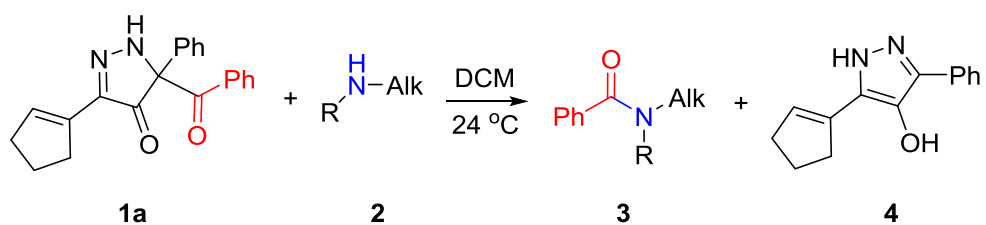
3-([1,1'-Biphenyl]-4-yl)-5-(cyclopent-1-en-1-yl)-1H-pyrazol-4-yl benzoate (**44a**)



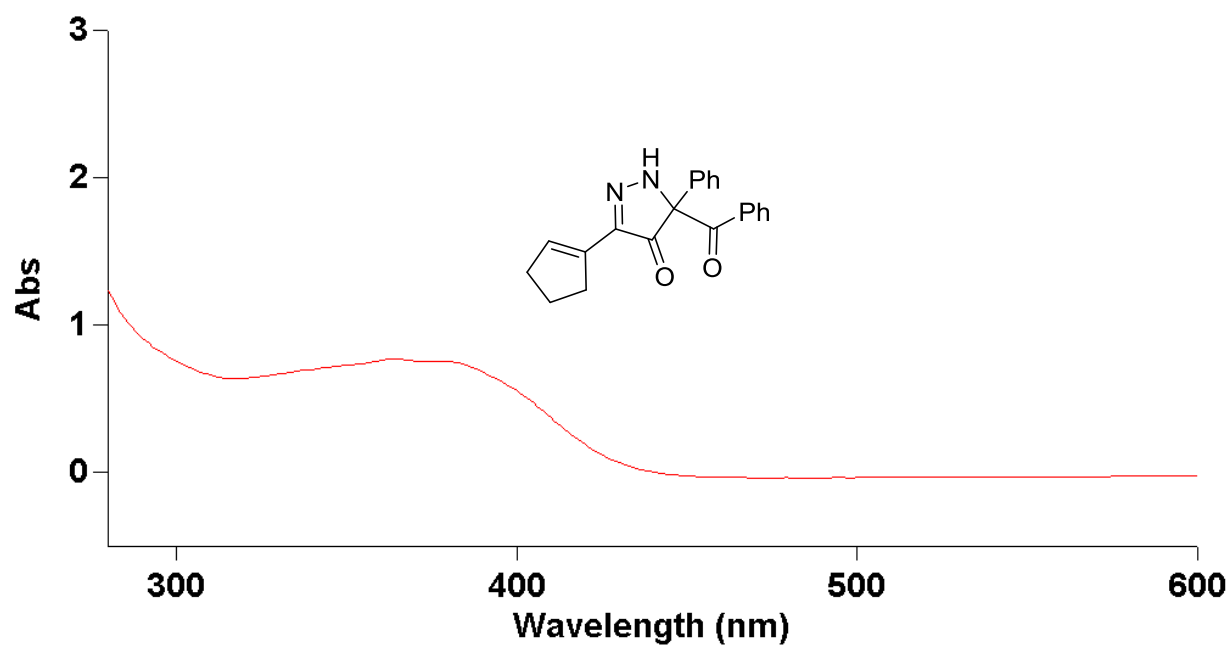
Under the same reaction conditions with **44** compound **44a** was formed quantitatively from the corresponding BCPP and isolated as a white solid: mp 213–214 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.27 (d, $J = 7.2$ Hz, 2H, Ar), 7.74 (d, $J = 8.3$ Hz, 2H, Ar), 7.69 (t, $J = 7.5$ Hz, 1H, Ar), 7.63 – 7.49 (comp, 6H, Ar), 7.39 (t, $J = 7.5$ Hz, 2H, Ar), 7.31 (t, $J = 7.5$ Hz, 1H, Ar), 6.12 – 6.09 (m, 1H, =CH), 2.75 – 2.71 (comp, 2H, $\text{CH}_2\text{C}=\text{}$), 2.45 – 2.42 (comp, 2H, $\text{CH}_2\text{C}=\text{}$), 1.92 (p, $J = 7.4$ Hz, 2H, CH_2). ^{13}C NMR (126 MHz, CDCl_3) δ 164.7, 140.8, 140.5, 139.9, 136.1, 134.0, 131.0, 130.4, 130.1, 129.3, 129.0, 128.8, 128.7, 128.4, 127.4, 127.3, 127.0, 126.5, 33.5, 33.0, 22.6. HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 407.1754, found: 407.1756.

Experimental Procedure for the Kinetic Study of the Reaction Between BCPP and Amines

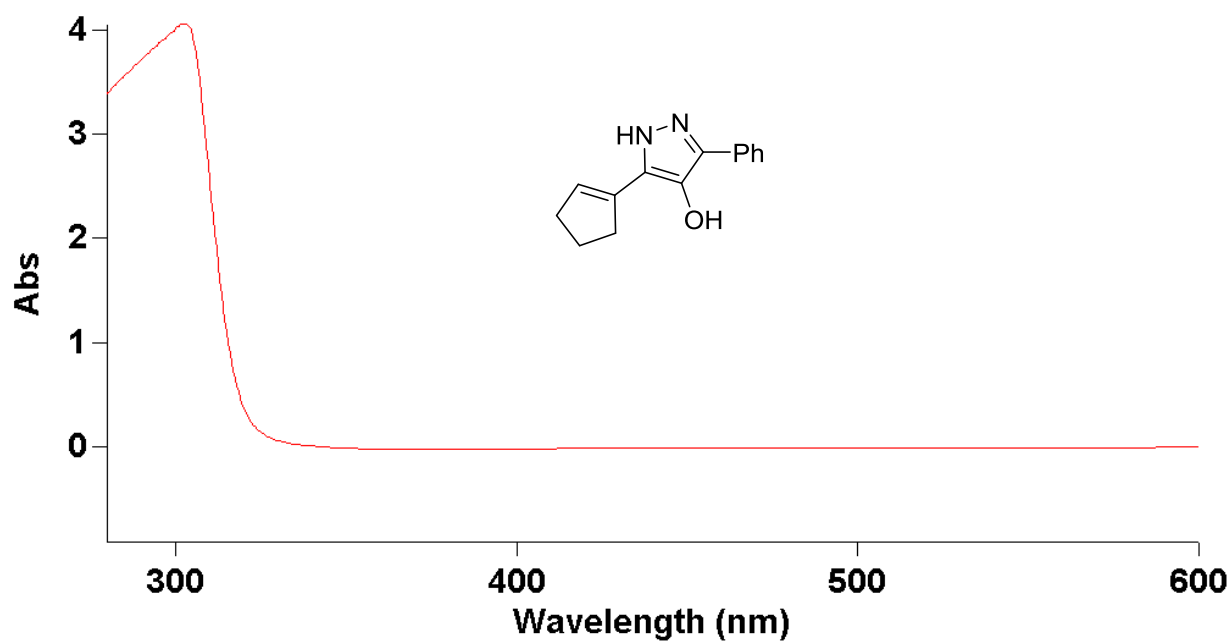
Rate constants for the reaction of BCPP with a series of amines were determined using UV-Vis spectroscopy at 24 ± 0.5 °C in dichloromethane. BCPP (**1a**) has an absorbance in the range 300 – 440 nm (covers visible light range), while other reactants and products absorb only in UV range. It allows monitoring the disappearance of BCPP at a certain wavelength (e.g. 380 nm). All kinetic measurements have been carried out above DCM cutoff ($\lambda = 245$ nm).



UV-Vis spectrum of BCPP (**1a**):



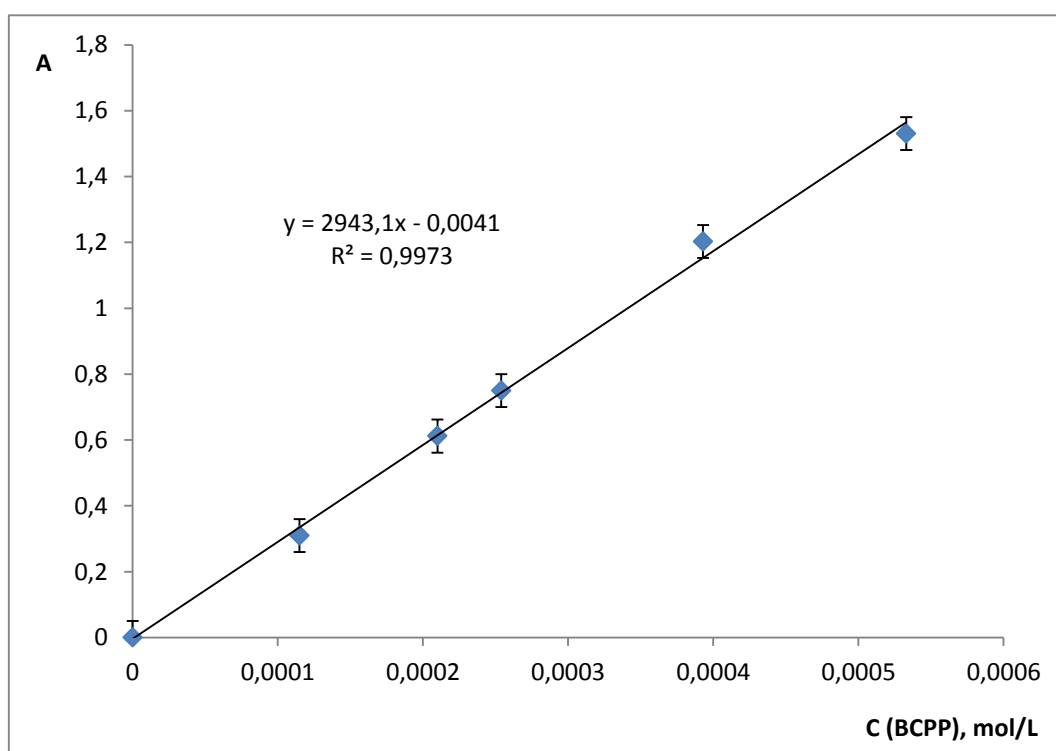
UV-Vis spectrum of **4**:



Extinction coefficient determination for BCPP (1a) at 380 nm.

Absorbance for a series of solutions of BCPP in DCM was measured at 24 °C. Extinction coefficient ϵ was determined from Beer-Lambert law: $A = \epsilon c l$ ($l = 1$ cm) as slope of the linear plot $A = f(c)$.

c (BCPP), mol/L	A
0	0
0.000115	0.3098
0.00021	0.6118
0.000254	0.7495
0.000393	1.2026
0.000533	1.5308



Extinction coefficient $\epsilon = 2920 \pm 70$ was determined from three parallel experiments.

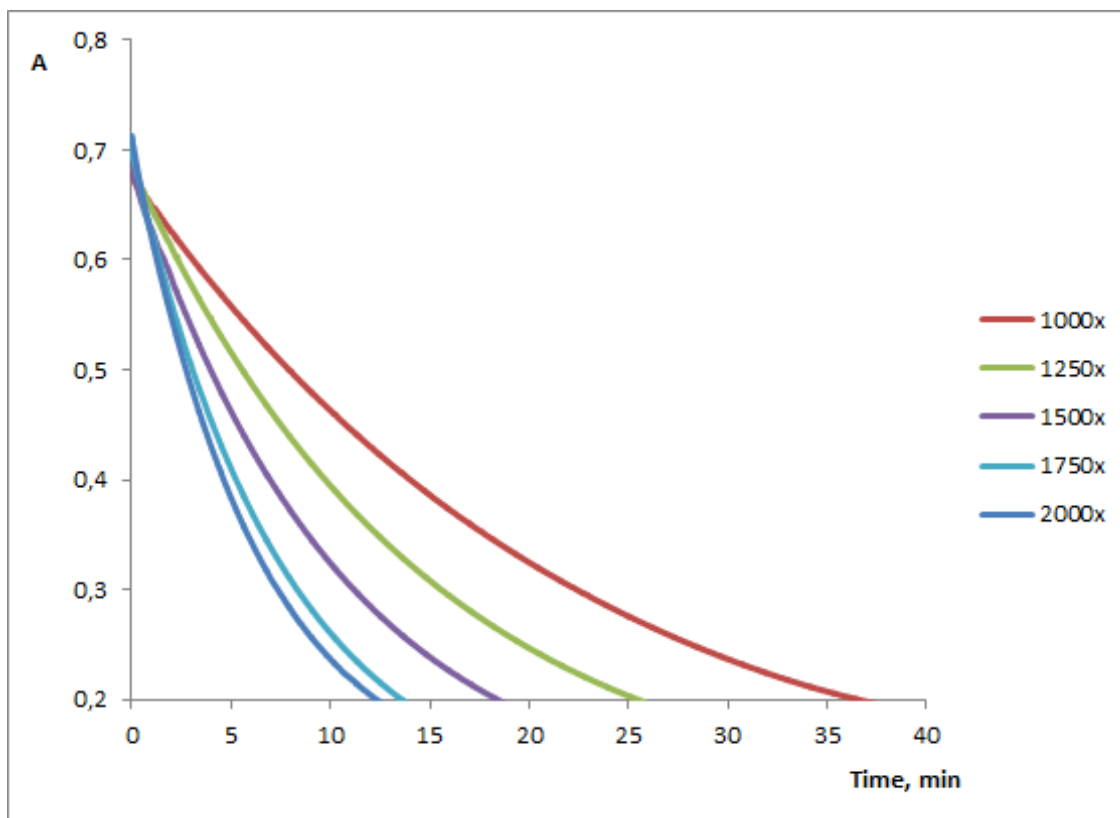
Determination of second order reaction rate.

Kinetic runs were performed for the reaction of BCPP with a series of amine solutions of different concentrations ($C_{\text{amine}} \geq 10 \cdot C_{\text{BCPP}}$).

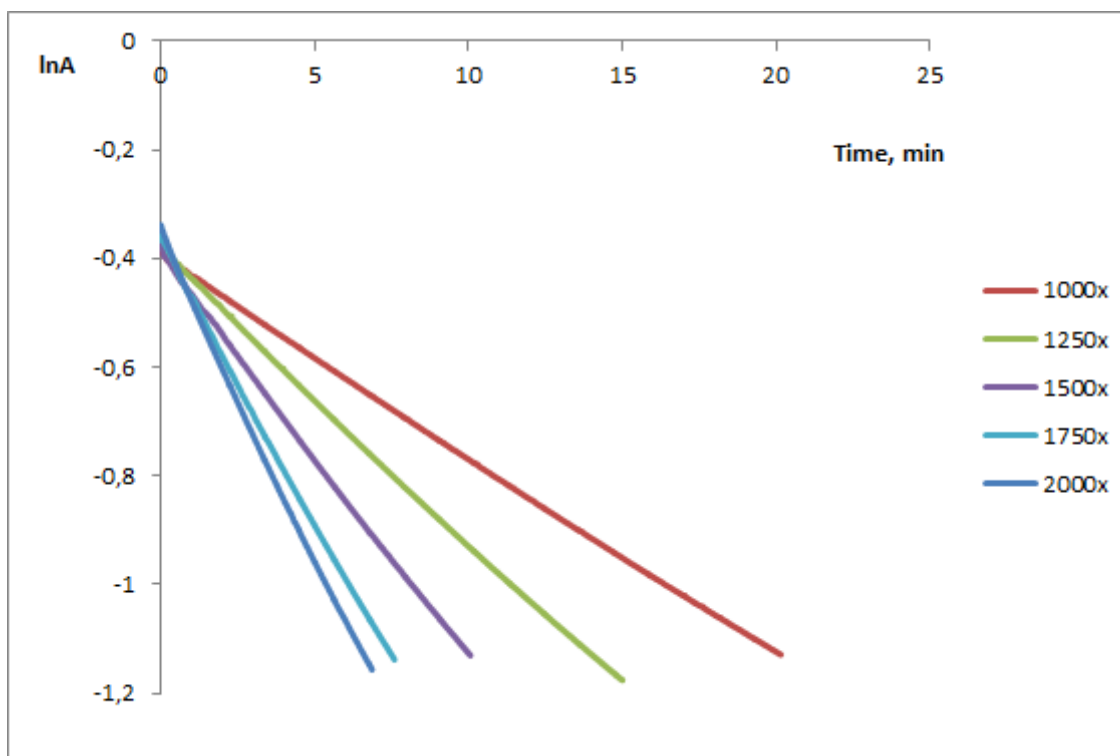
Considering that the extinction coefficient for BCPP at 380 nm $\epsilon = 2920$, a BCPP solution was prepared to have an absorbance $A = 0.4$ – 0.8 (at 380 nm). Concentrations of amine solutions ($C_{\text{amine}} \geq 10 \cdot C_{\text{BCPP}}$) were used to have reaction times less than one hour.

Kinetic data for the reaction of BCPP with amines.

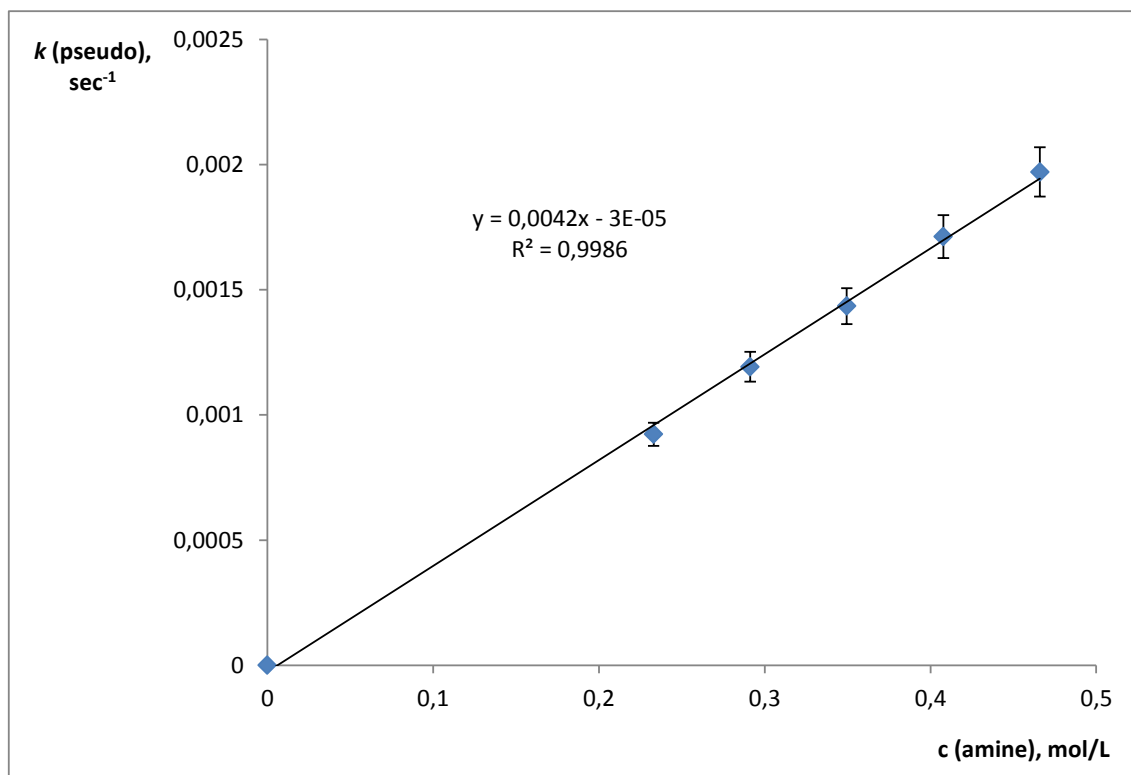
1) 2-amino-2-methylpropane ($C_{\text{BCPP}} = 2.4 \cdot 10^{-4} \text{ M}$):



* 1000x, 1250x, 1500x, 1750x, 2000x – excess of amine taken

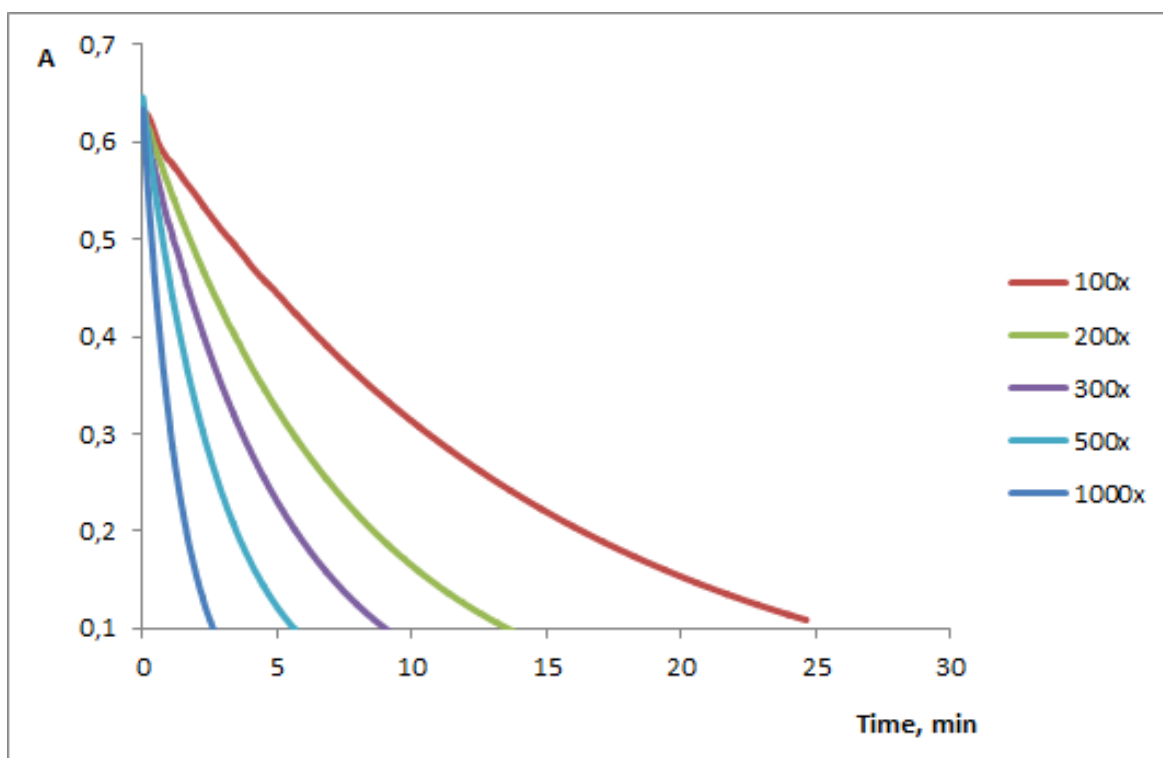


* 1000x, 1250x, 1500x, 1750x, 2000x – excess of amine taken

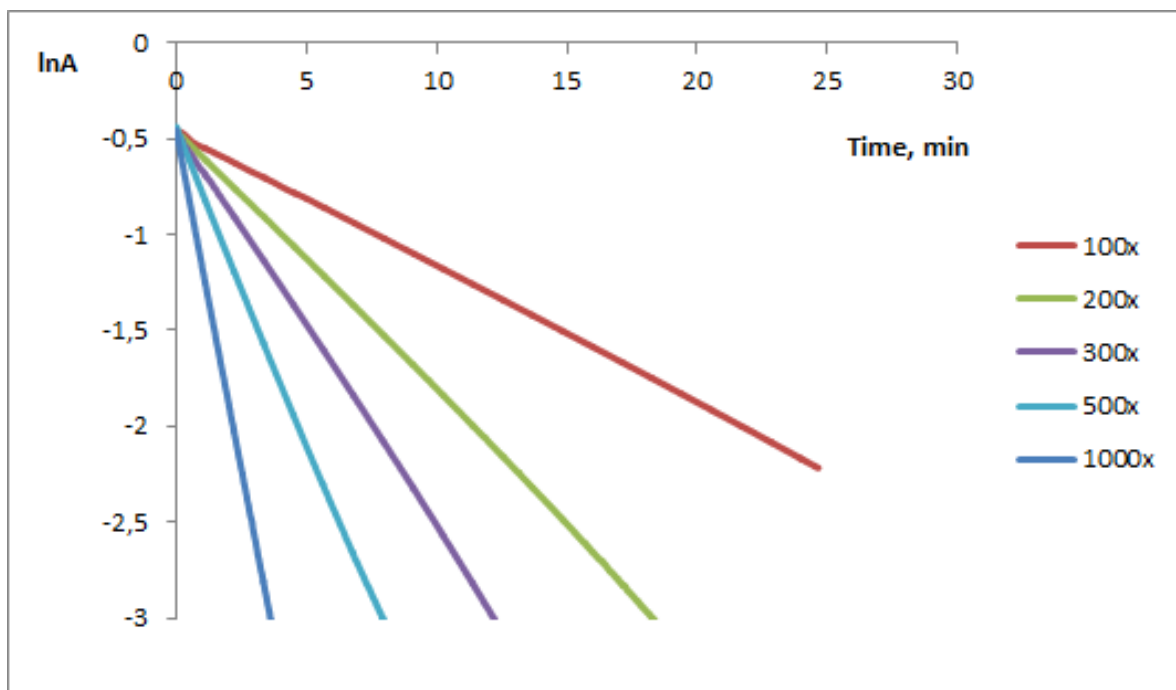


Second order rate constant in DCM at 24 °C obtained from three parallel experiments:
 $k = 0.0042 \pm 0.0002 \text{ (L} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1})$.

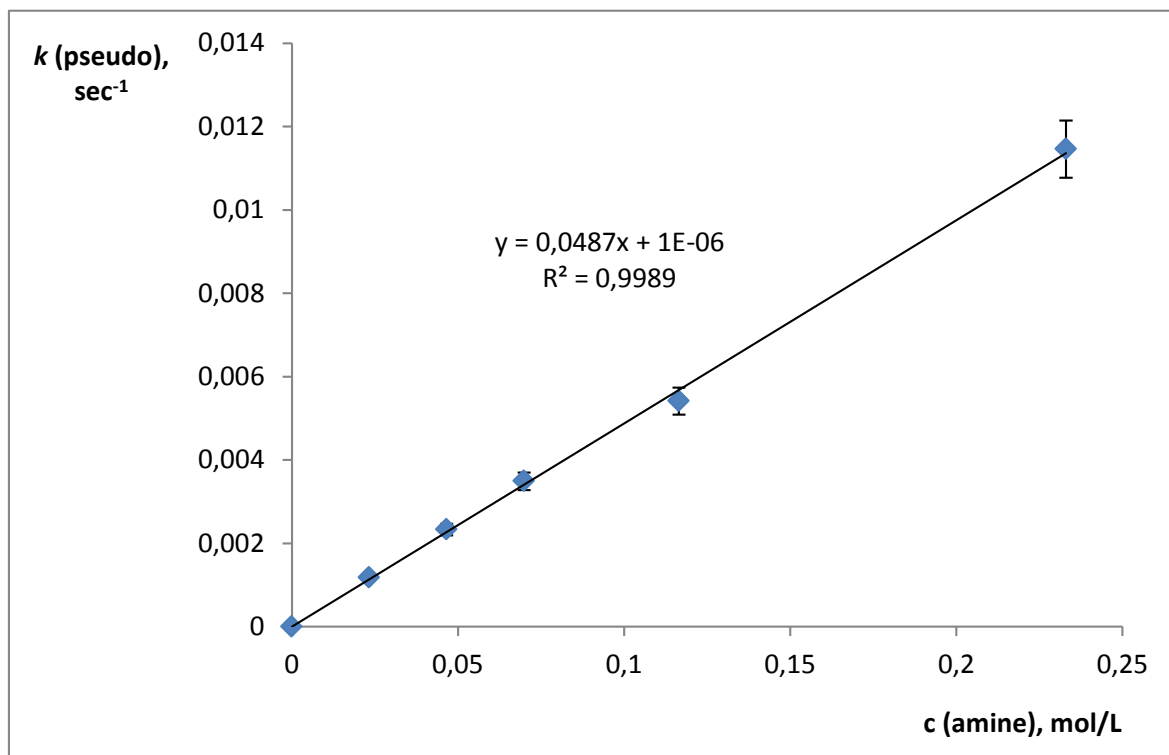
2) 2-Aminobutane ($C_{\text{BCPP}} = 2.2 \cdot 10^{-4} \text{ M}$):



* 100x, 200x, 300x, 500x, 1000x – excess of amine taken

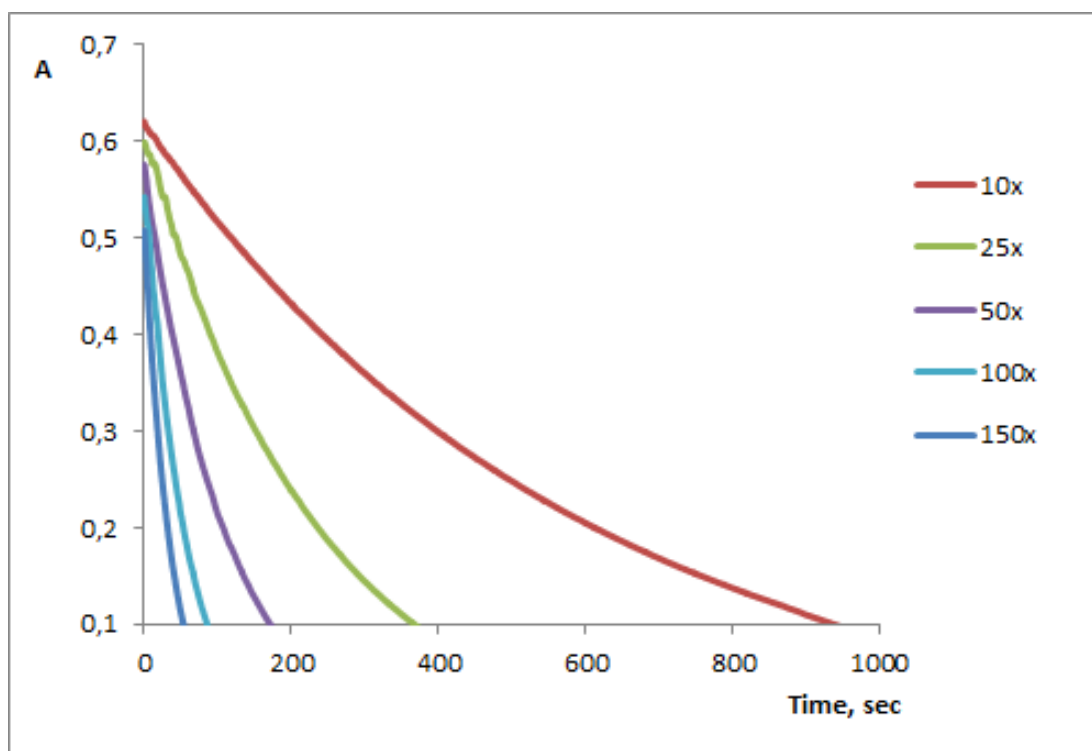


* 100x, 200x, 300x, 500x, 1000x – excess of amine taken

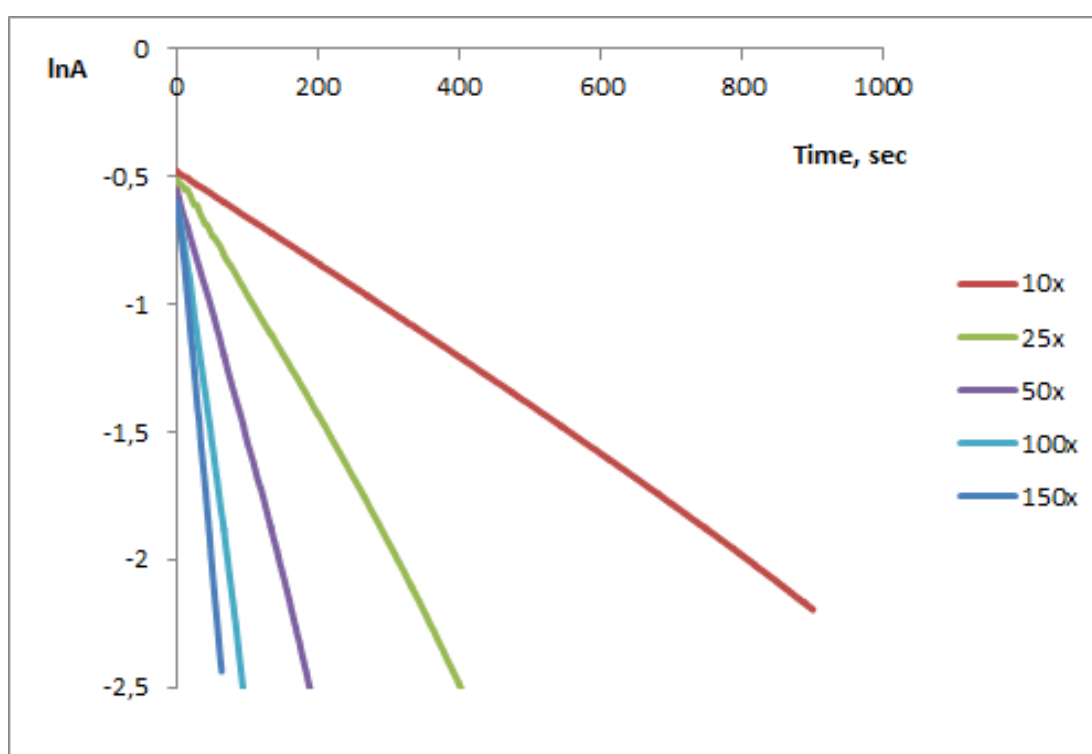


Second order rate constant in DCM at 24 °C obtained from three parallel experiments:
 $k = 0.049 \pm 0.002 \text{ (L} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1})$.

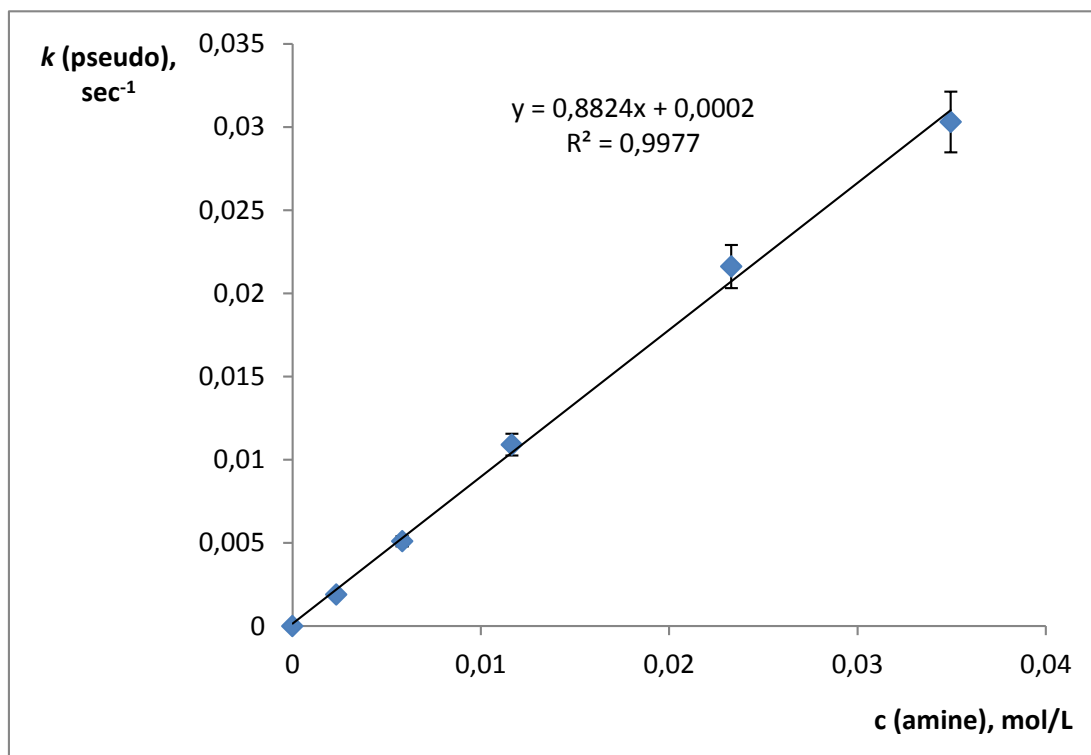
3) 1-Aminobutane ($C_{BCPP} = 2.1 \cdot 10^{-4} \text{ M}$):



* 10x, 25x, 50x, 100x, 150x – excess of amine taken

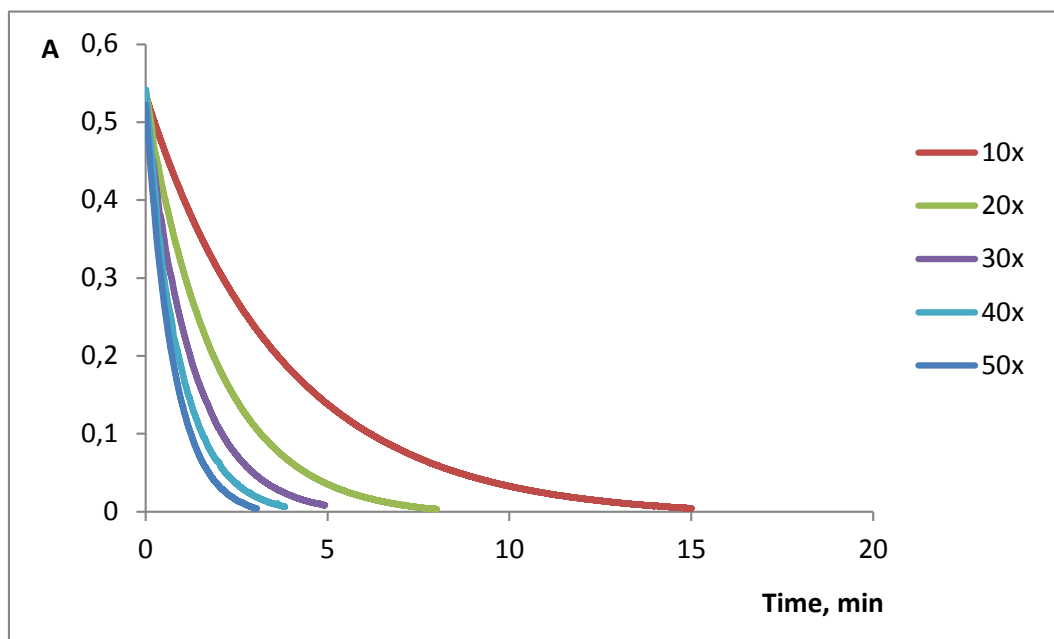


* 10x, 25x, 50x, 100x, 150x – excess of amine taken

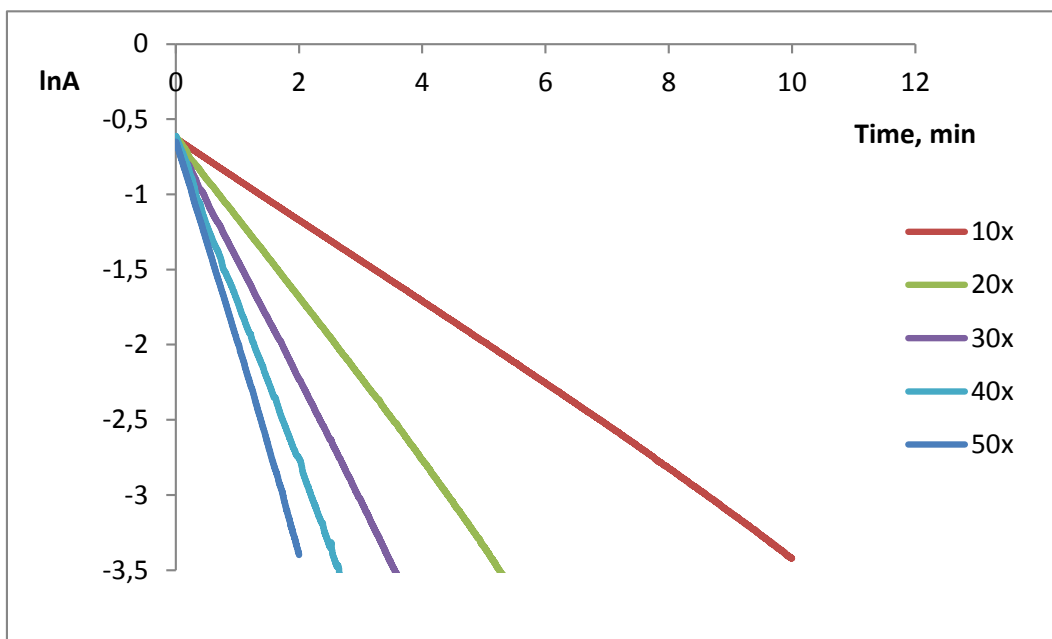


Second order rate constant in DCM at 24 °C obtained from three parallel experiments:
 $k = 0.86 \pm 0.04$ (L·mol⁻¹·sec⁻¹).

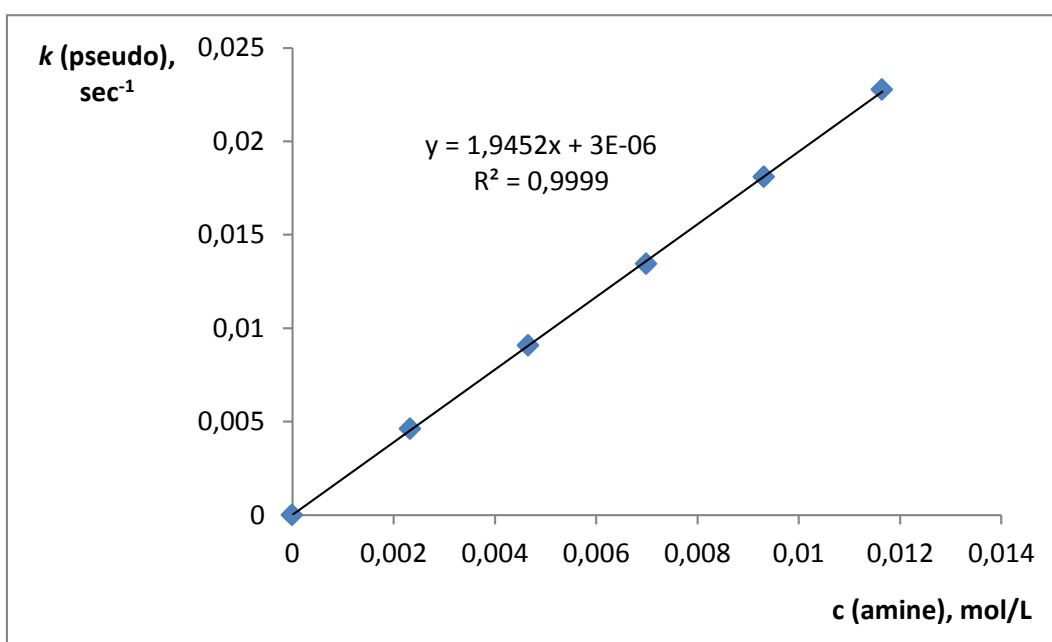
4) 2-Methyl-1,5-diaminopentane ($C_{BCPP} = 1.9 \cdot 10^{-4}$ M):



* 10x, 20x, 30x, 40x, 50x – excess of amine taken

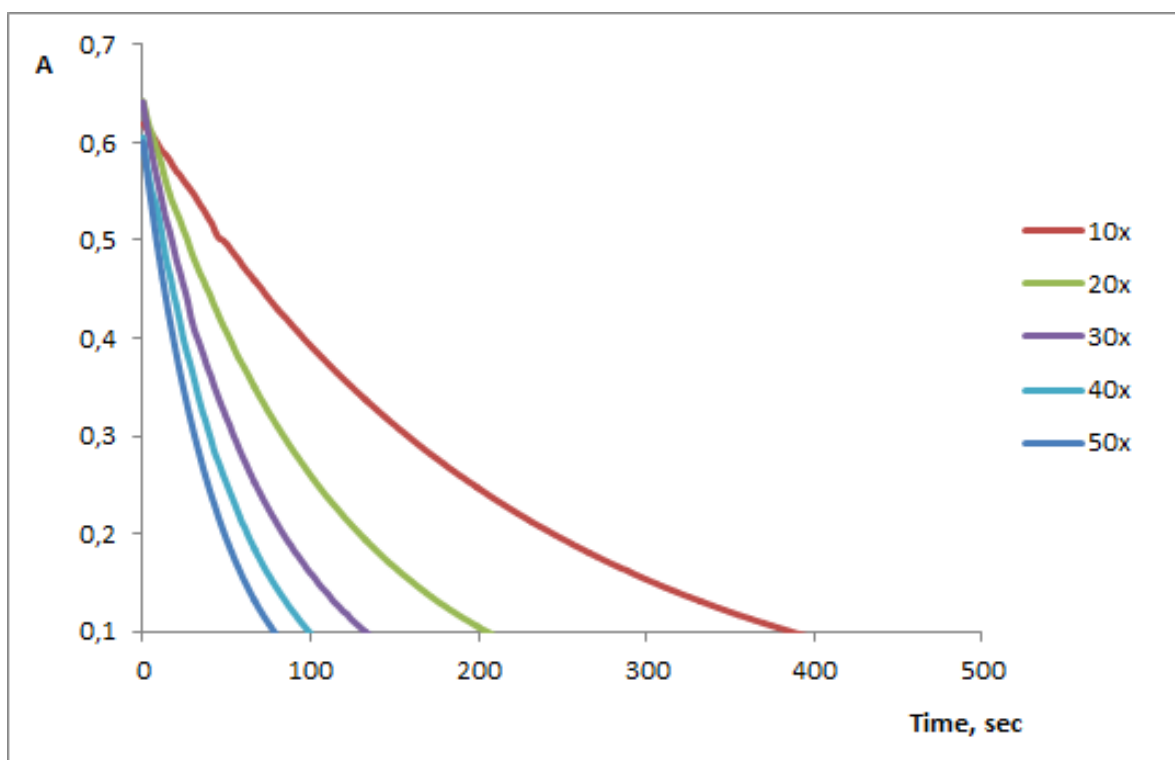


* 10x, 20x, 30x, 40x, 50x – excess of amine taken

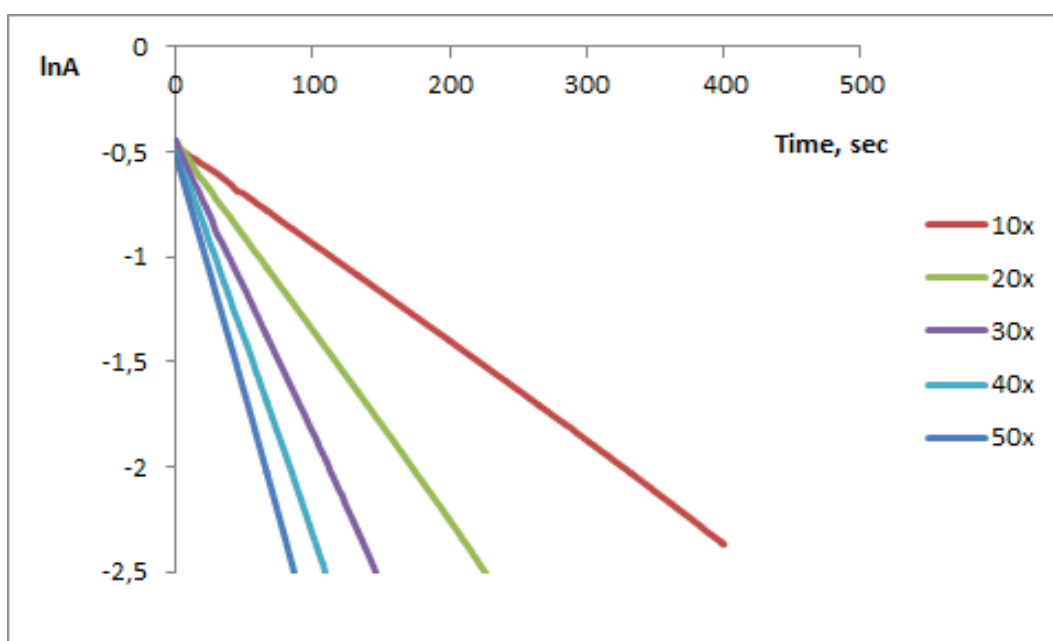


Second order rate constant in DCM at 24 °C obtained from three parallel experiments:
 $k = 1.92 \pm 0.04 \text{ (L} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1})$.

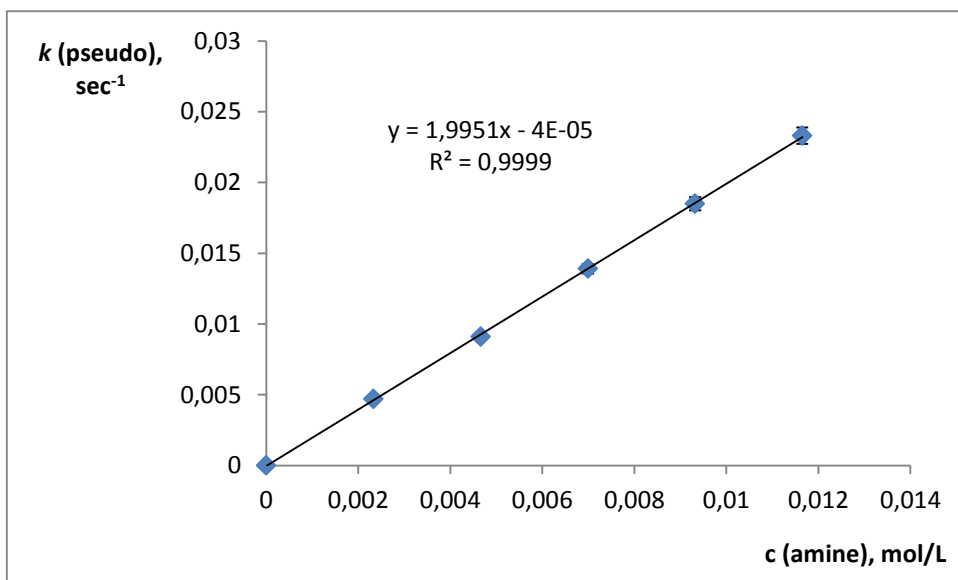
5) 1,2-Diaminopropane ($C_{BCPP} = 2.2 \cdot 10^{-4} \text{ M}$):



* 10x, 20x, 30x, 40x, 50x – excess of amine taken

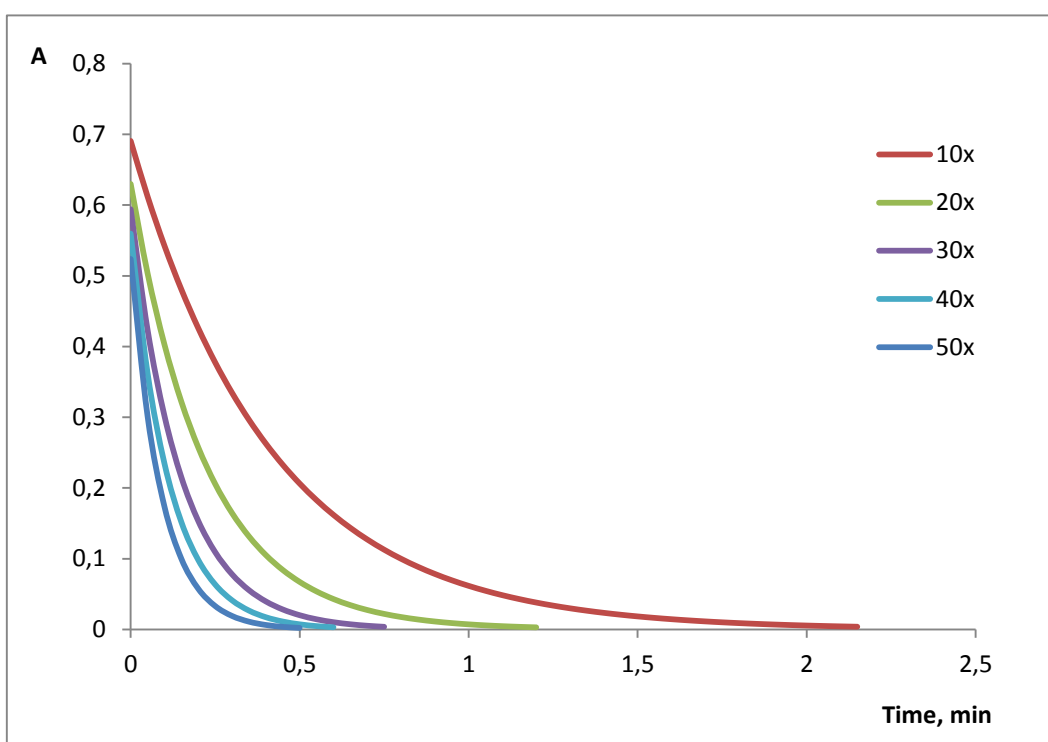


* 10x, 20x, 30x, 40x, 50x – excess of amine taken

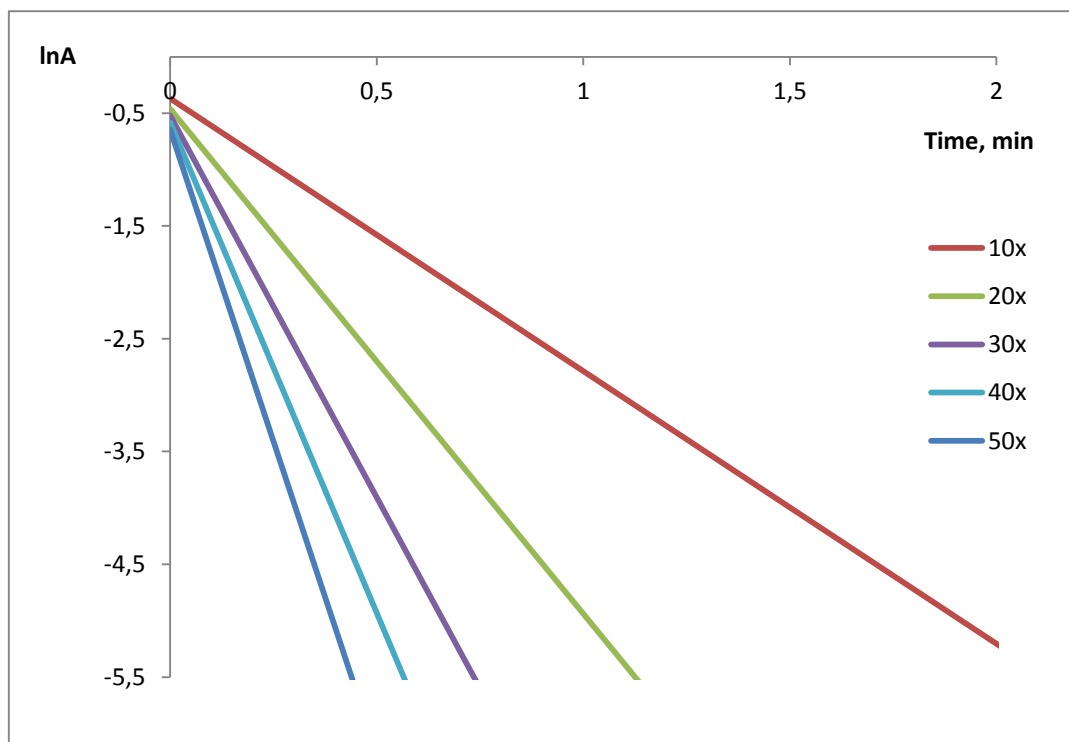


Second order rate constant in DCM at 24 °C obtained from three parallel experiments:
 $k = 1.98 \pm 0.05 \text{ (L} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1})$.

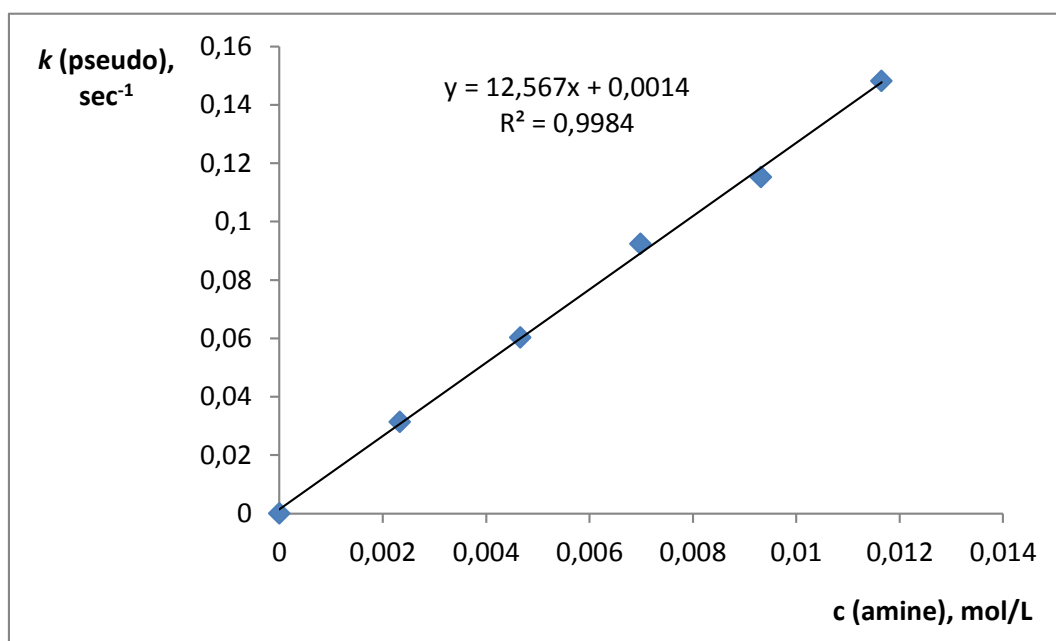
6) 1,3-Diaminopropane ($C_{\text{BCPP}} = 1.7 \cdot 10^{-4} \text{ M}$):



* 10x, 20x, 30x, 40x, 50x – excess of amine taken



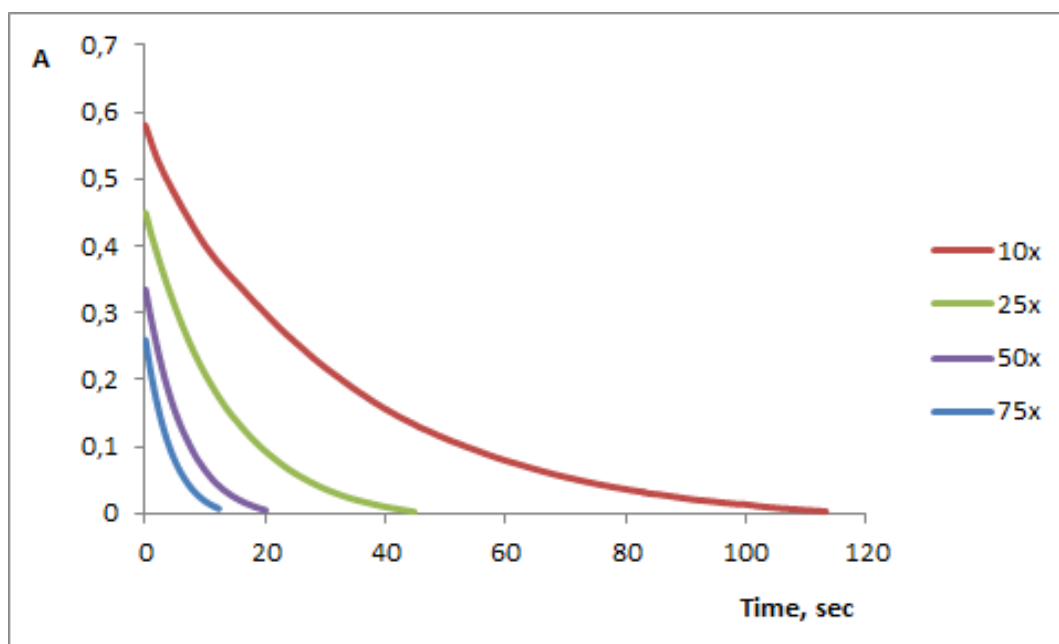
* 10x, 20x, 30x, 40x, 50x – excess of amine taken



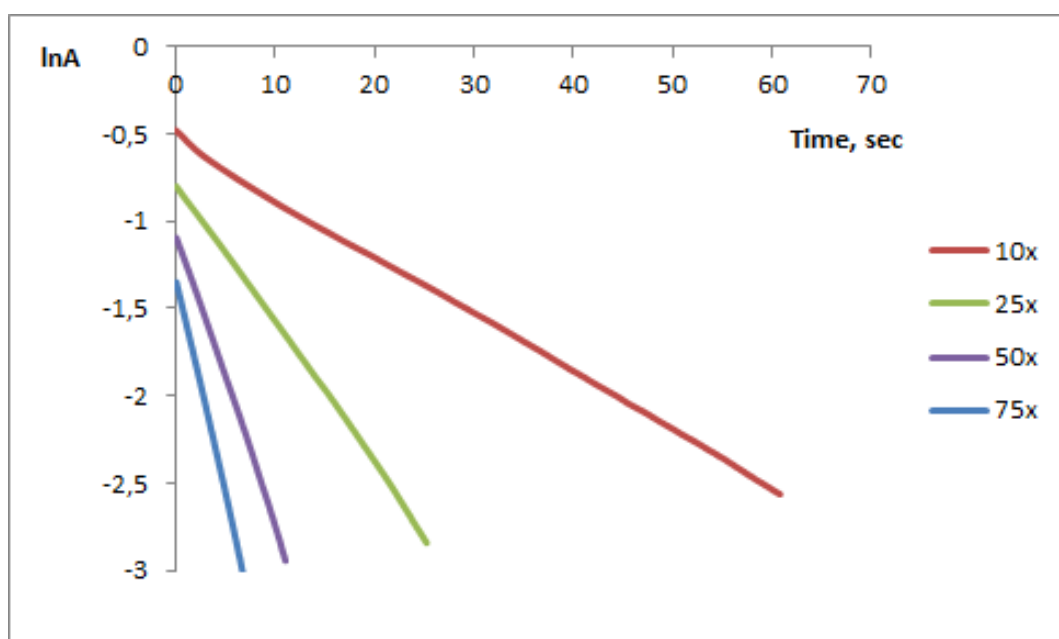
Second order rate constant in DCM at 24 °C obtained from three parallel experiments:

$k = 12.8 \pm 0.5 \text{ (L} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1})$

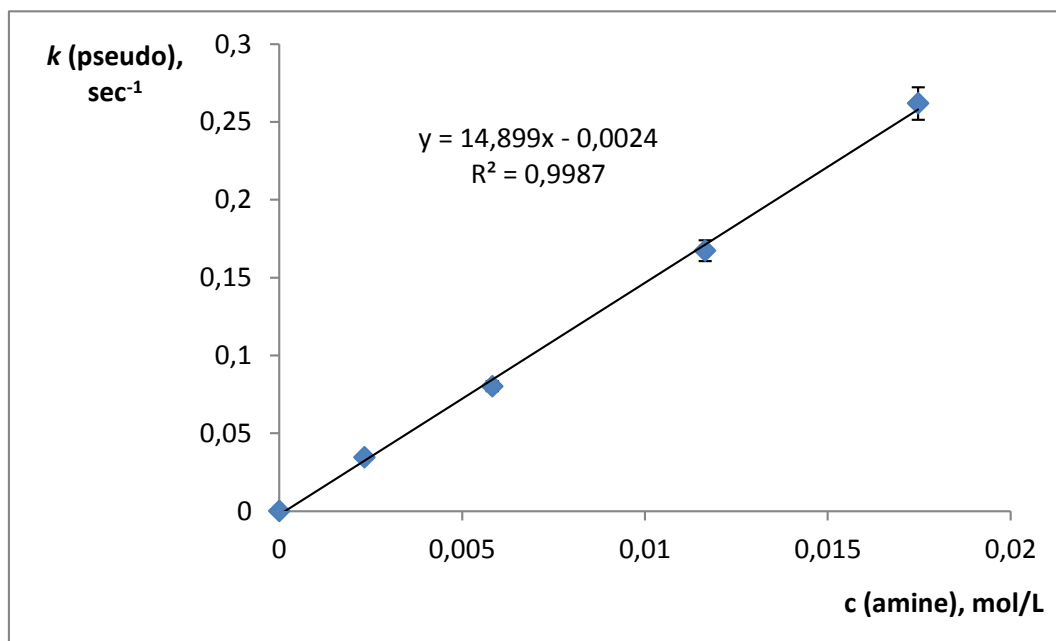
7) 1,3-Diaminopentane ($C_{BCPP} = 2.1 \cdot 10^{-4} \text{ M}$):



* 10x, 25x, 50x, 75x – excess of amine taken



* 10x, 25x, 50x, 75x – excess of amine taken

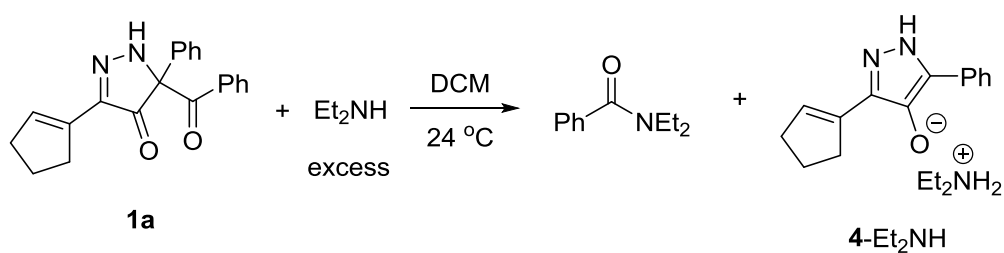


Second order rate constant in DCM at 24 °C obtained from three parallel experiments:

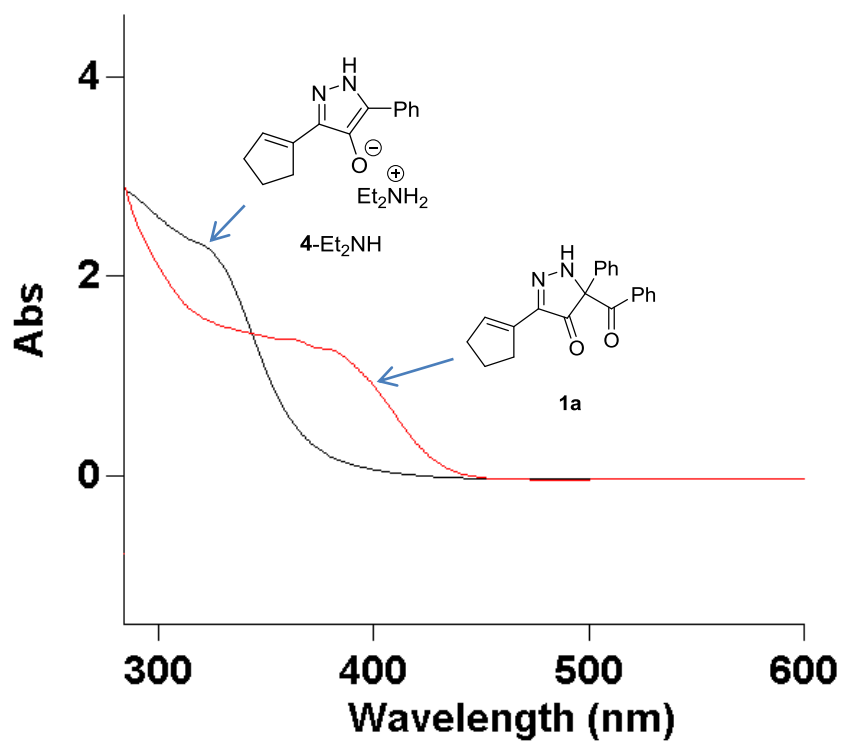
$k = 14.9 \pm 0.3 \text{ (L} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1})$

8) Diethylamine:

Because of its high basicity diethylamine forms with 4-hydroxypyrazole **4** compound **4-Et₂NH**, which has an absorbance at 380 nm.

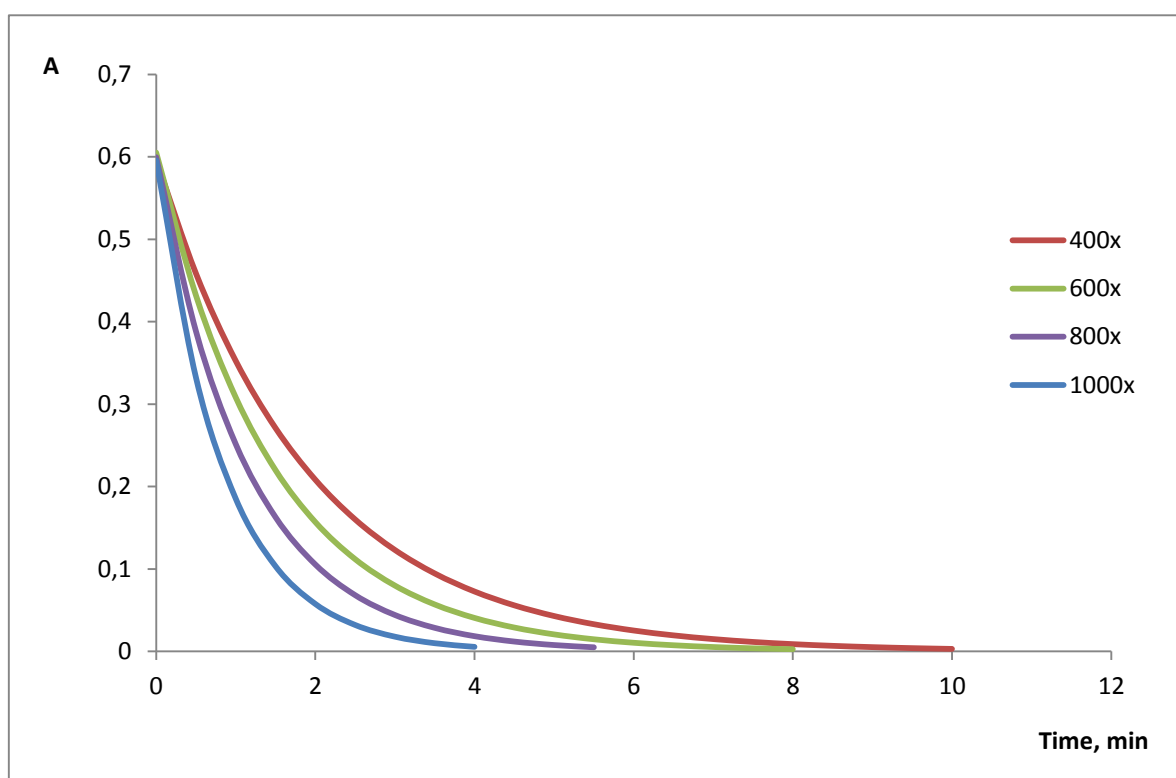


From UV-Vis spectra a suitable range has been found (e.g. $\lambda = 420 \text{ nm}$). Red line – spectrum of BCPP **1a**; black line – spectrum of **4-Et₂NH**.

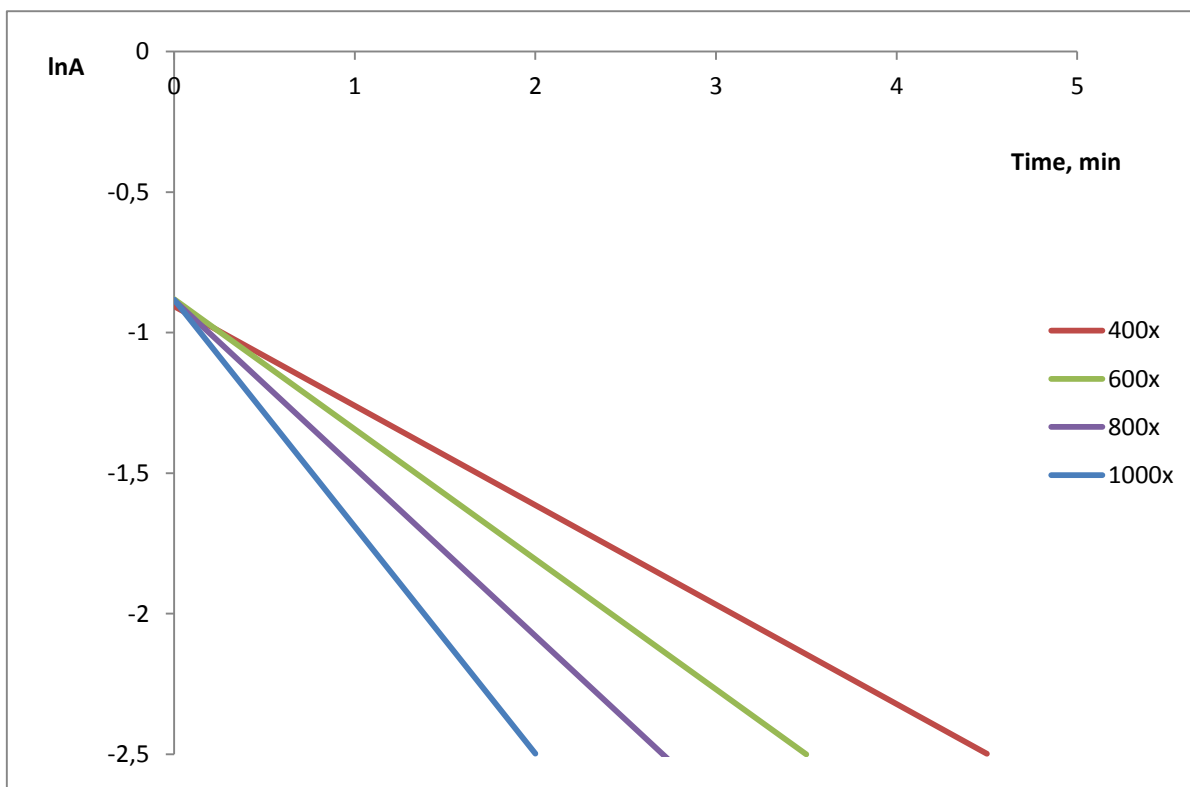


Kinetic measurements were carried out at 420 nm with a zero absorbance for the products.

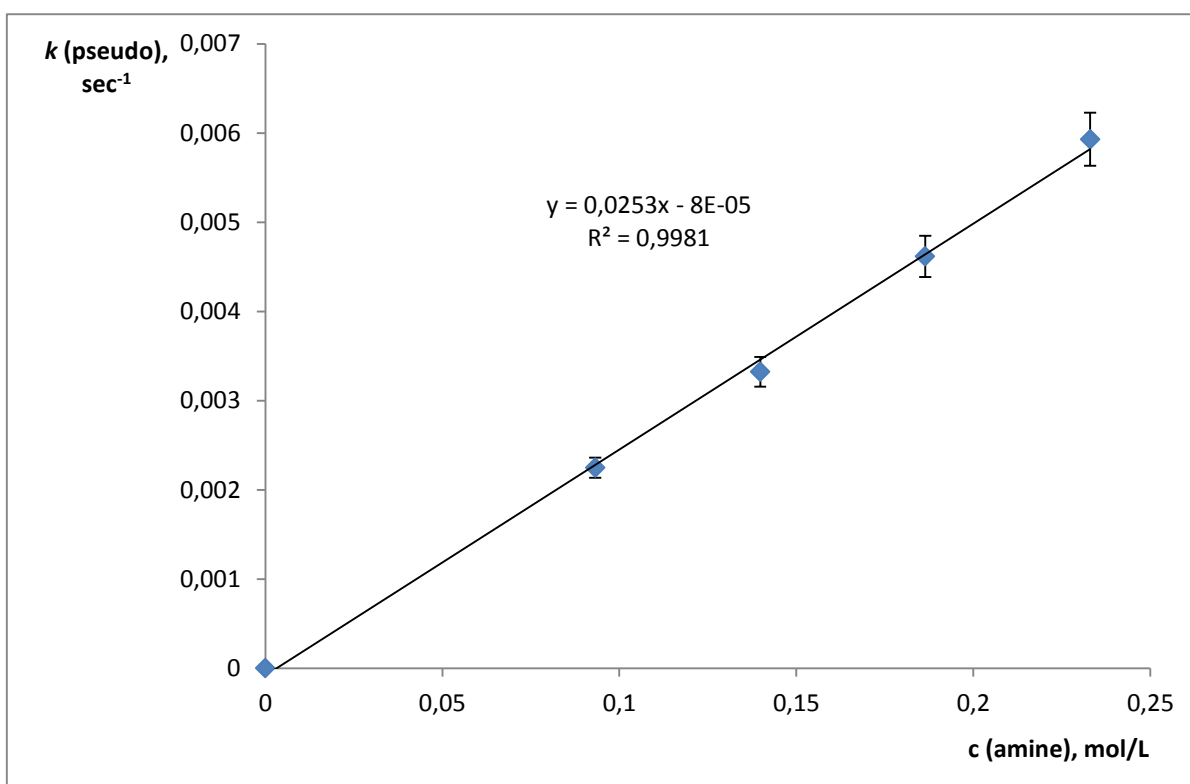
$$C_{\text{BCPP}} = 2.2 \cdot 10^{-4} \text{ M}$$



* 400x, 600x, 800x, 1000x – excess of amine taken



* 400x, 600x, 800x, 1000x – excess of amine taken

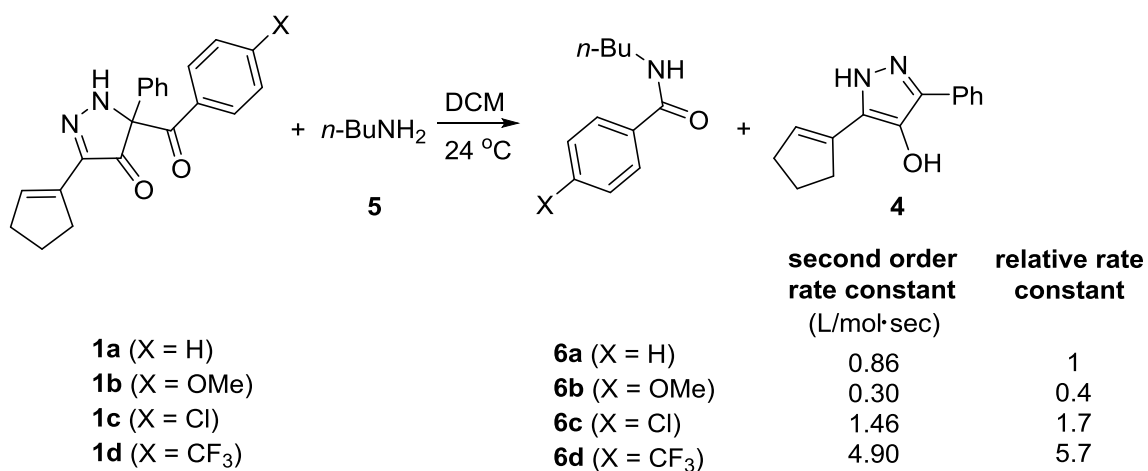


Second order rate constant in DCM at 24 °C obtained from three parallel experiments:

$k = 0.025 \pm 0.001 \text{ (L} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1})$

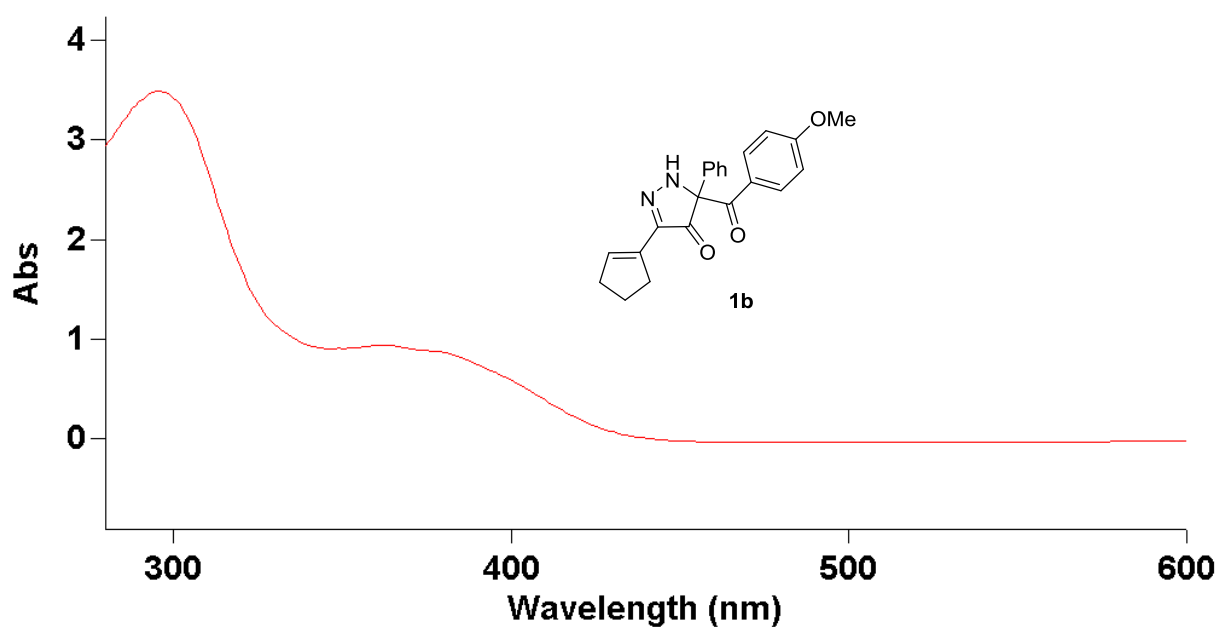
Substituents Effect and Hammett Plot for the Reaction of 1a–d with 1-Aminobutane

General scheme for the reaction of *para*-substituted acyl transfer reagents **1a–d** with 1-aminobutane.

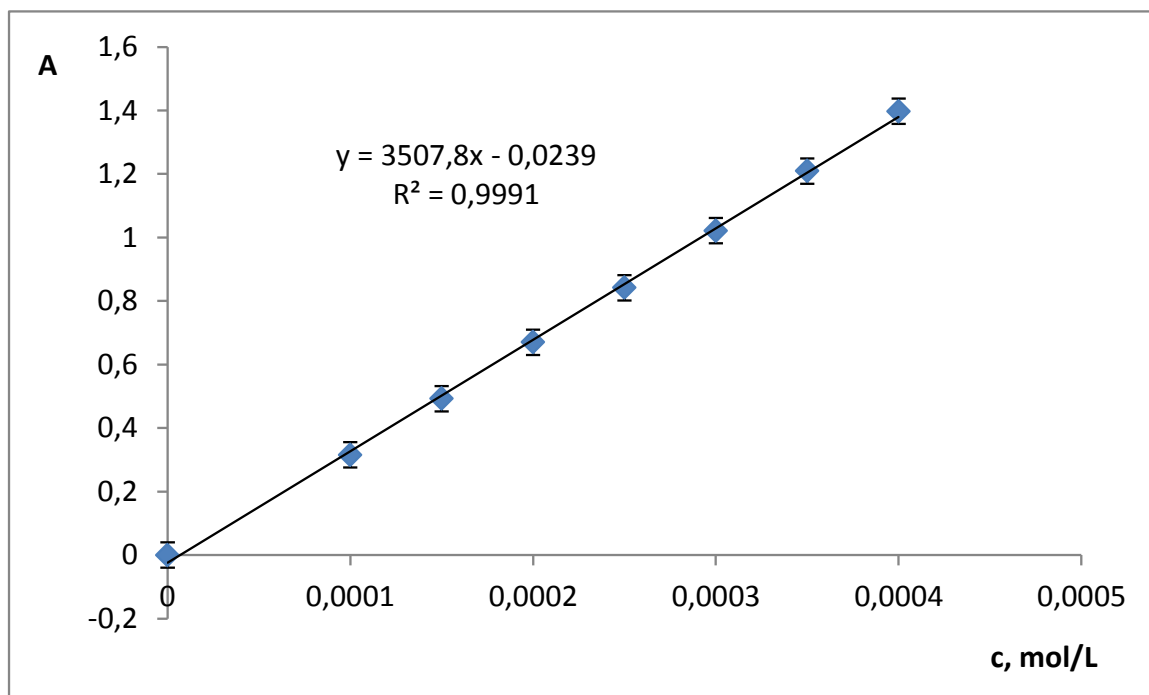


Extinction coefficient determination for **1b** (X = OMe) at 380 nm:

UV-Vis Spectra of 4-MeO-BCPP (**1b**):

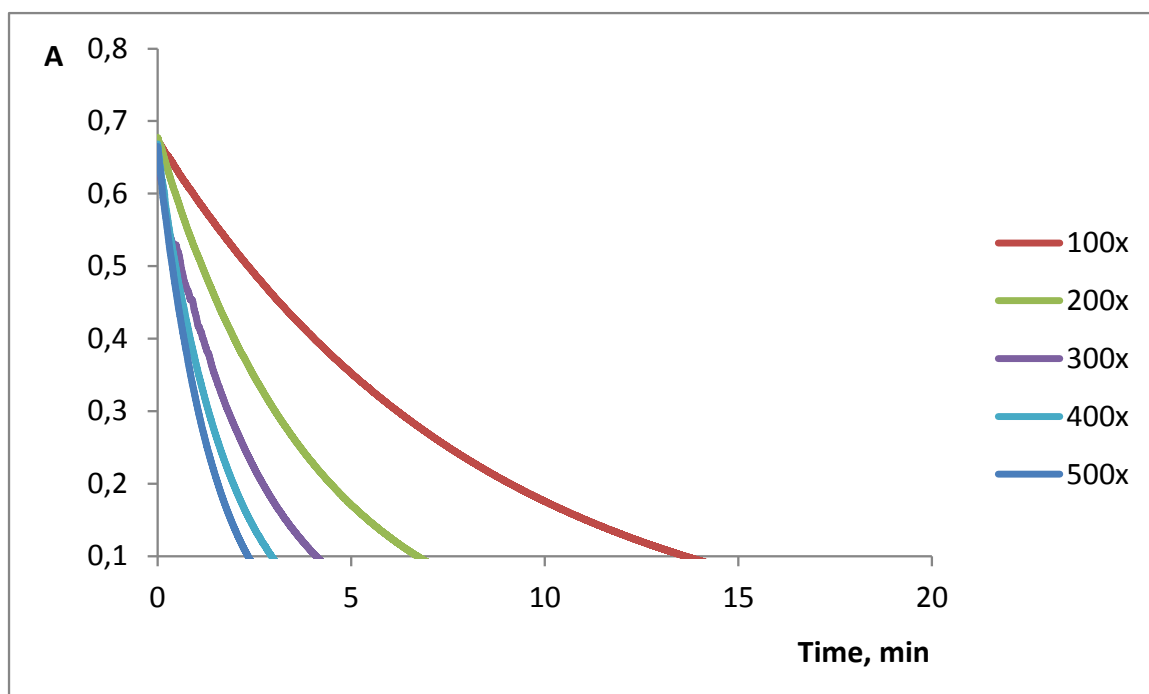


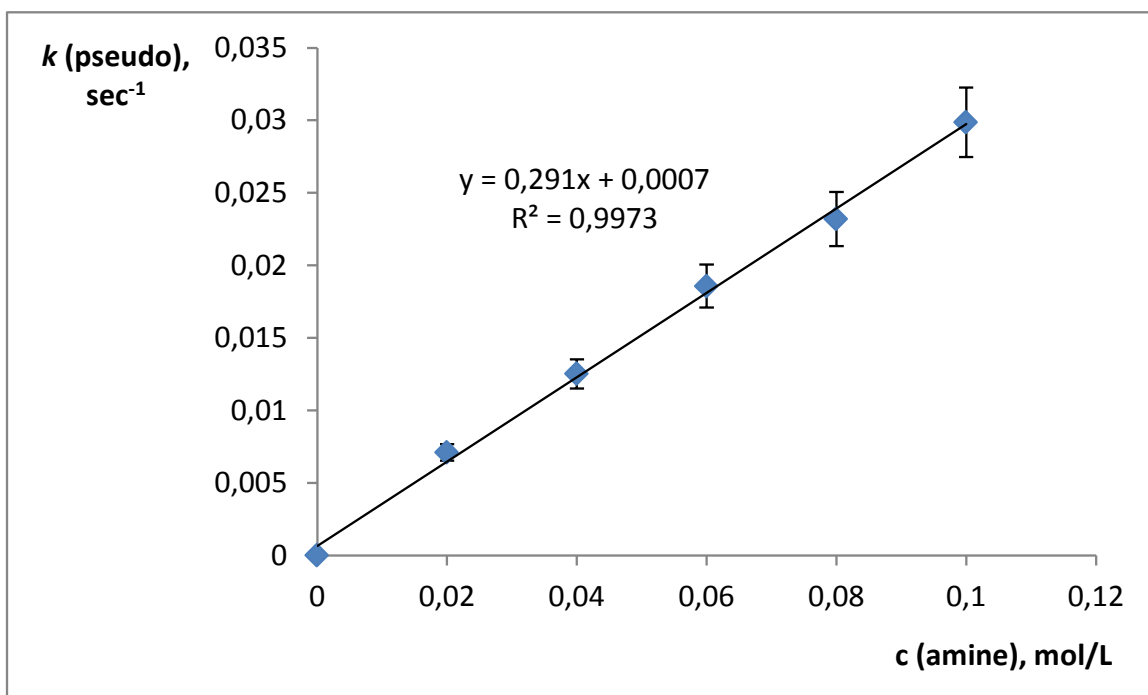
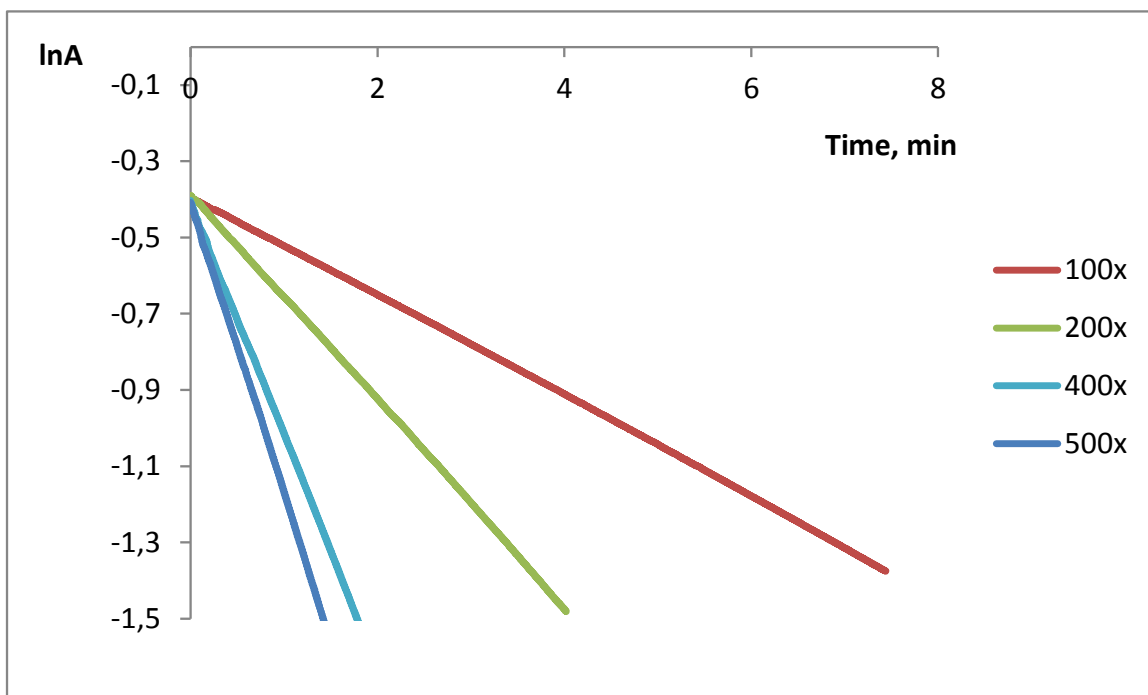
c (4-MeO-BCPP), mol/L	A
0	0
0.00010	0.3156
0.00015	0.4922
0.00020	0.6700
0.00025	0.8418
0.00030	1.0216
0.00035	1.2092
0.00040	1.3972



Extinction coefficient $\epsilon = 3506 \pm 93$ was determined from three parallel experiments.

Kinetics of the reaction of 4-MeO-BCPP with 1-aminobutane (at 380 nm, $C_{4\text{-MeO-BCPP}} = 2.0 \cdot 10^{-4}$ M).

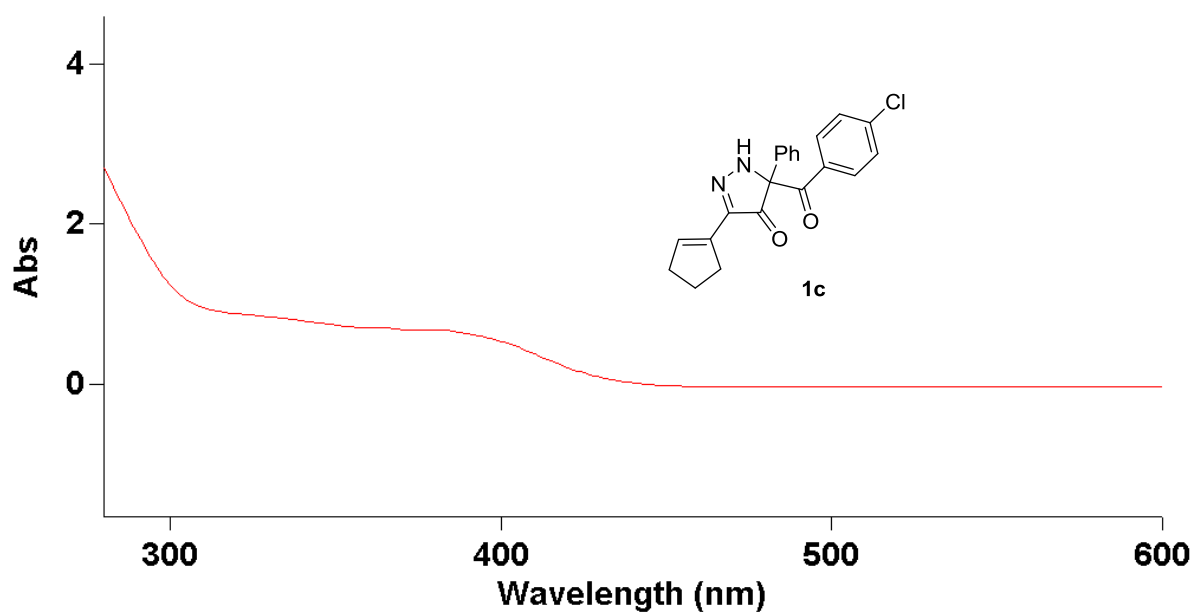




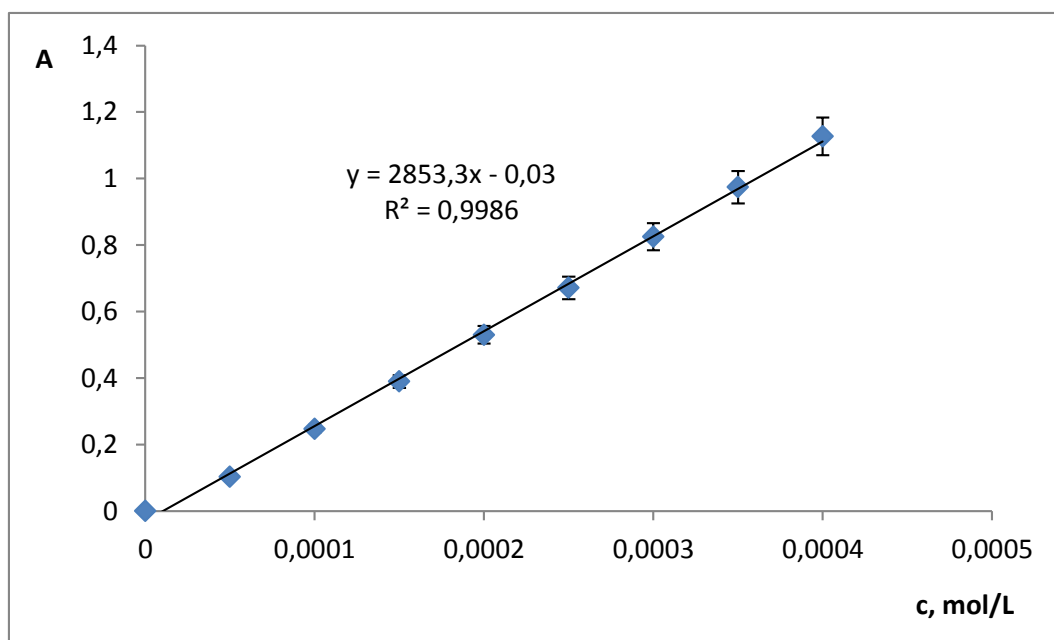
Second order rate constant in DCM at 24 ± 0.5 °C obtained from three parallel experiments:
 $k = 0.30 \pm 0.01$ (L·mol⁻¹·sec⁻¹).

Extinction coefficient determination for **1c** (X = Cl) at 380 nm:

UV-Vis Spectra of 4-Cl-BCPP (**1c**):

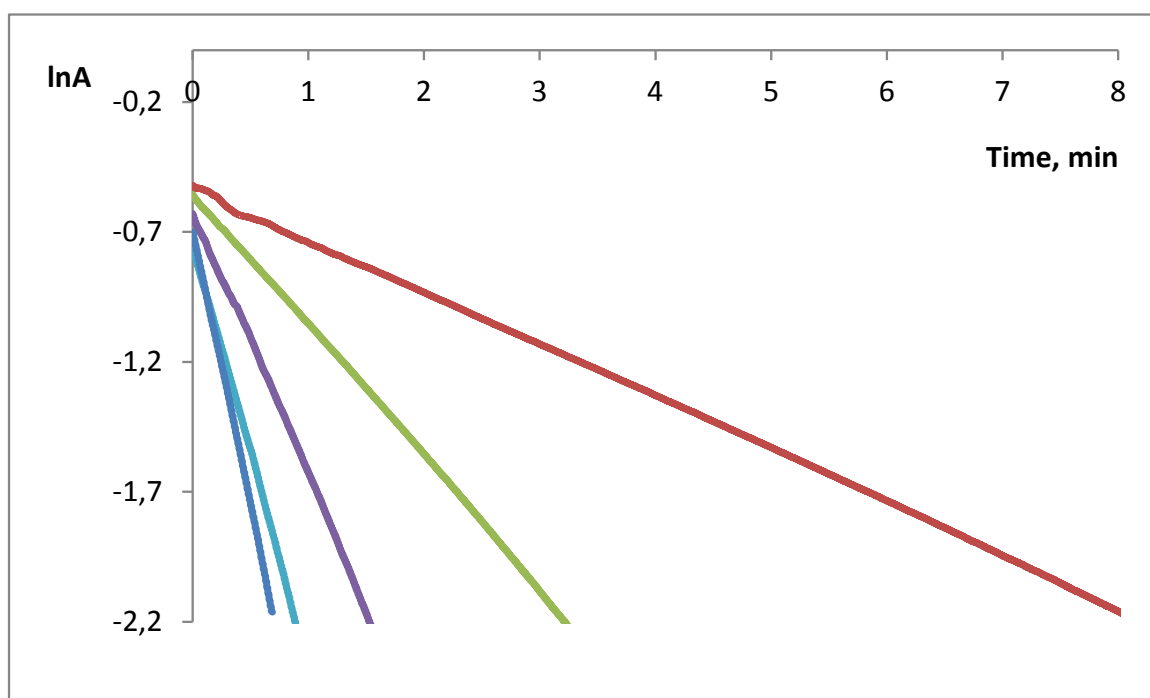
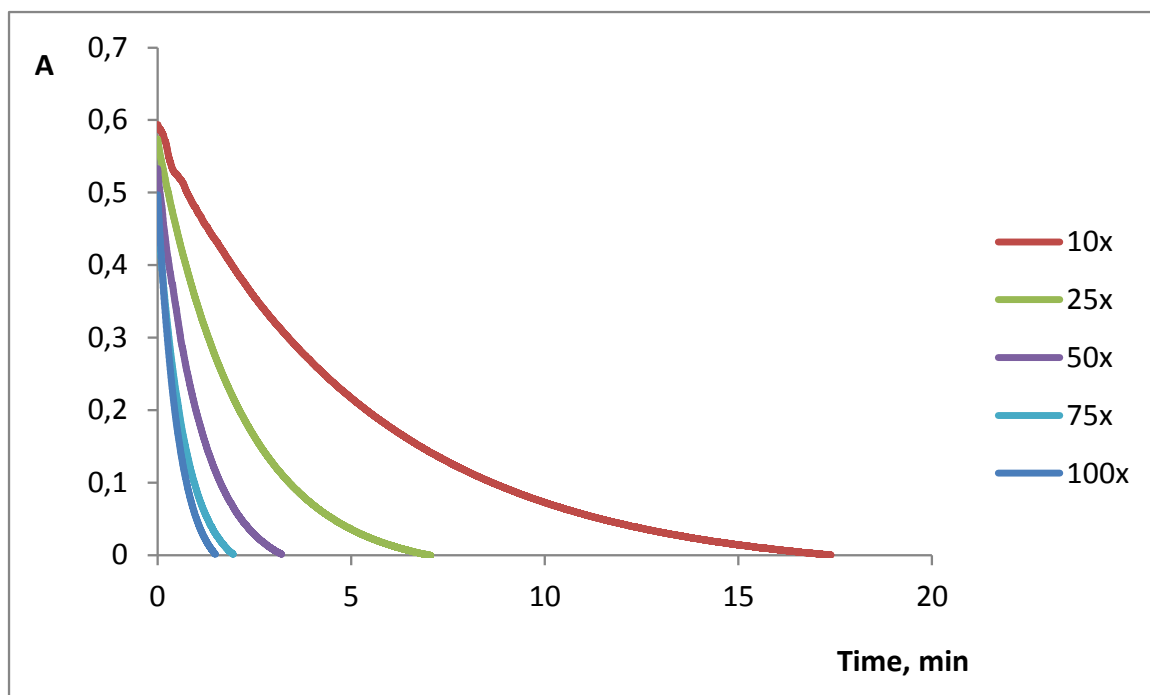


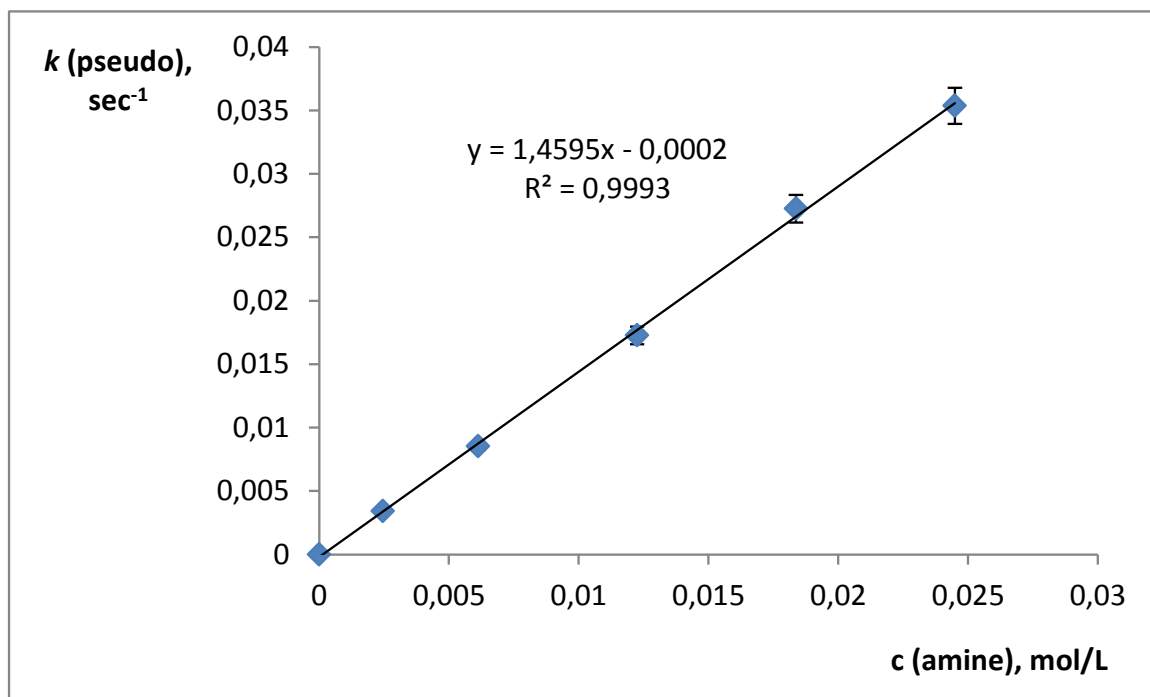
c (4-Cl-BCPP), mol/L	A
0	0
0.00005	0.1025
0.00010	0.2469
0.00015	0.3893
0.00020	0.5300
0.00025	0.6710
0.00030	0.8250
0.00035	0.9741
0.00040	1.1268



Extinction coefficient $\epsilon = 2853 \pm 65$ was determined from three parallel experiments.

Kinetics of the reaction of 4-Cl-BCPP with 1-aminobutane (at 380 nm, $C_{4\text{-Cl-BCPP}} = 2.1 \cdot 10^{-4}$ M).

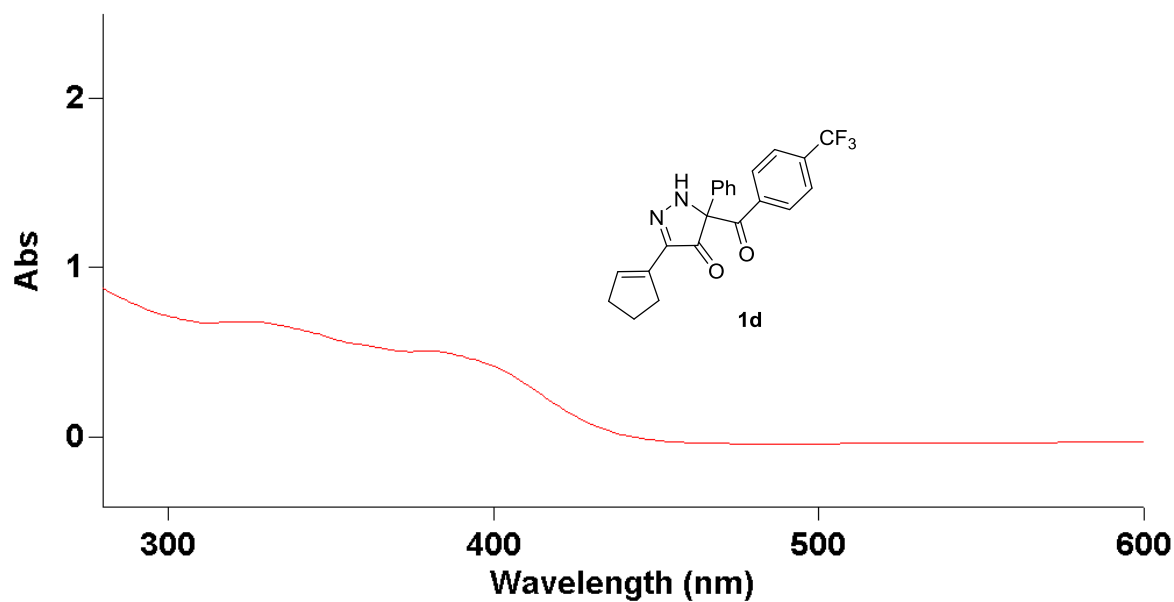




Second order rate constant in DCM at 24 ± 0.5 °C obtained from three parallel experiments:
 $k = 1.46 \pm 0.04$ ($\text{L} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1}$).

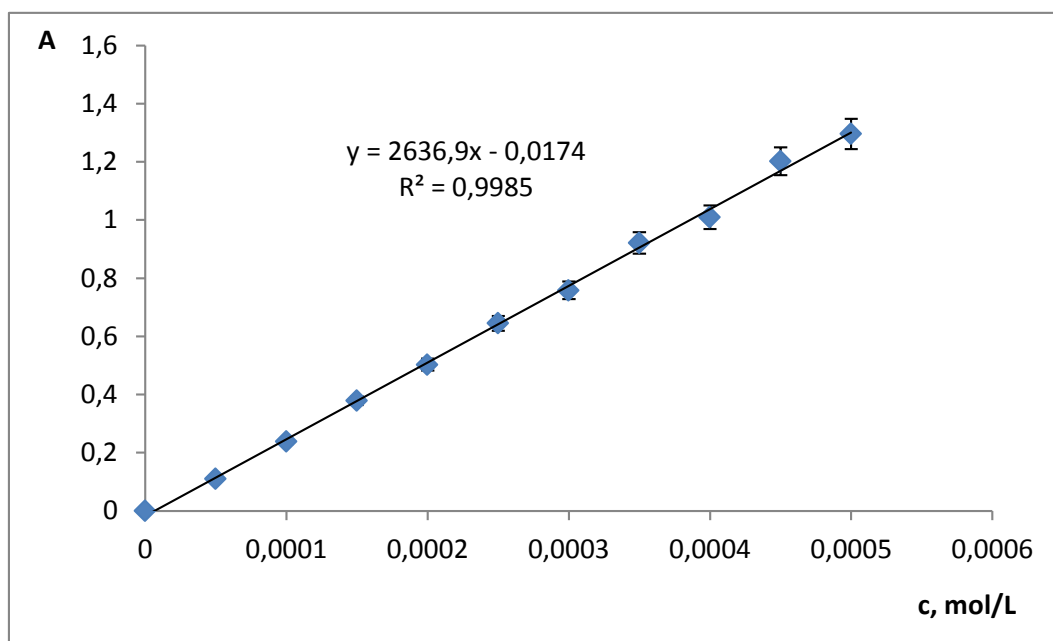
Extinction coefficient determination for **1d** (X = CF_3) at 380 nm:

UV-Vis Spectra of 4- CF_3 -BCPP (**1d**):



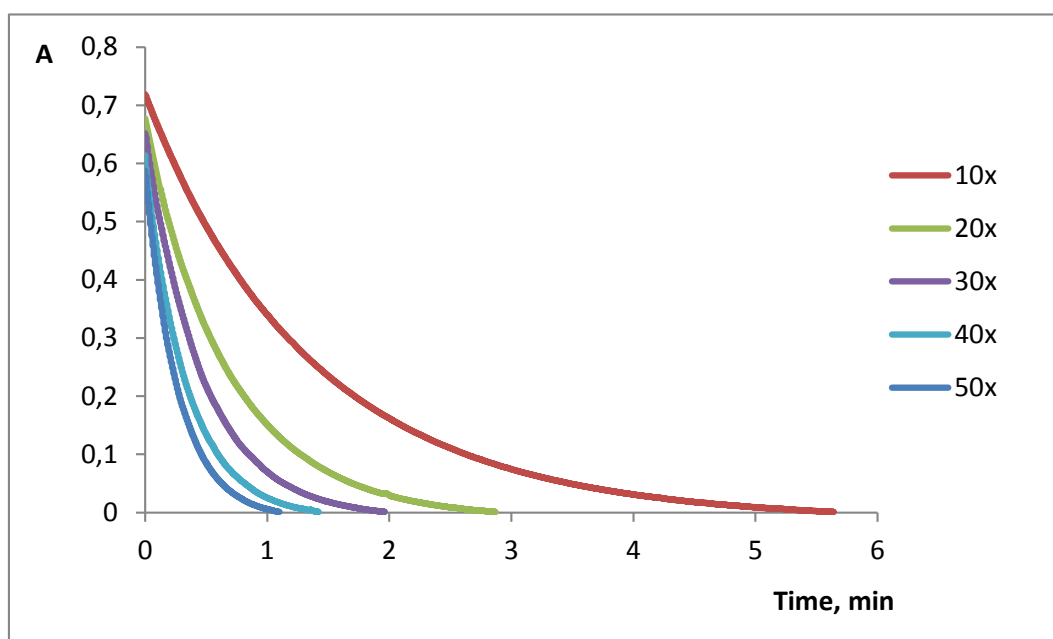
c (4- CF_3 -BCPP), mol/L	A
0	0
0.00005	0.1096
0.00010	0.2381
0.00015	0.3786

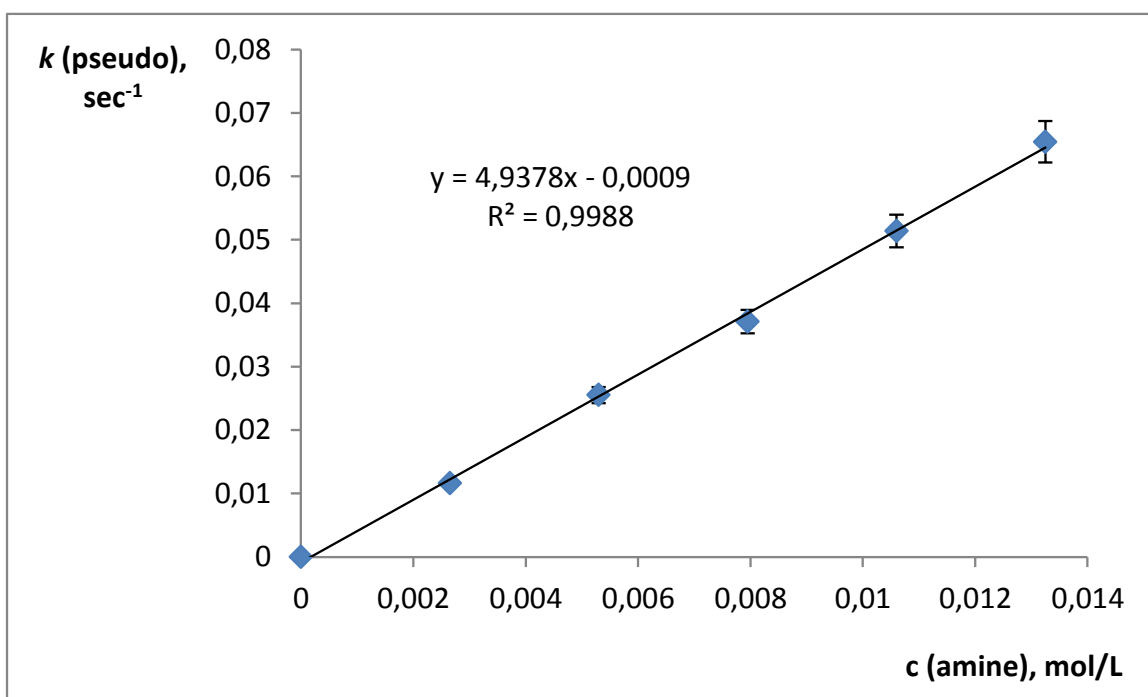
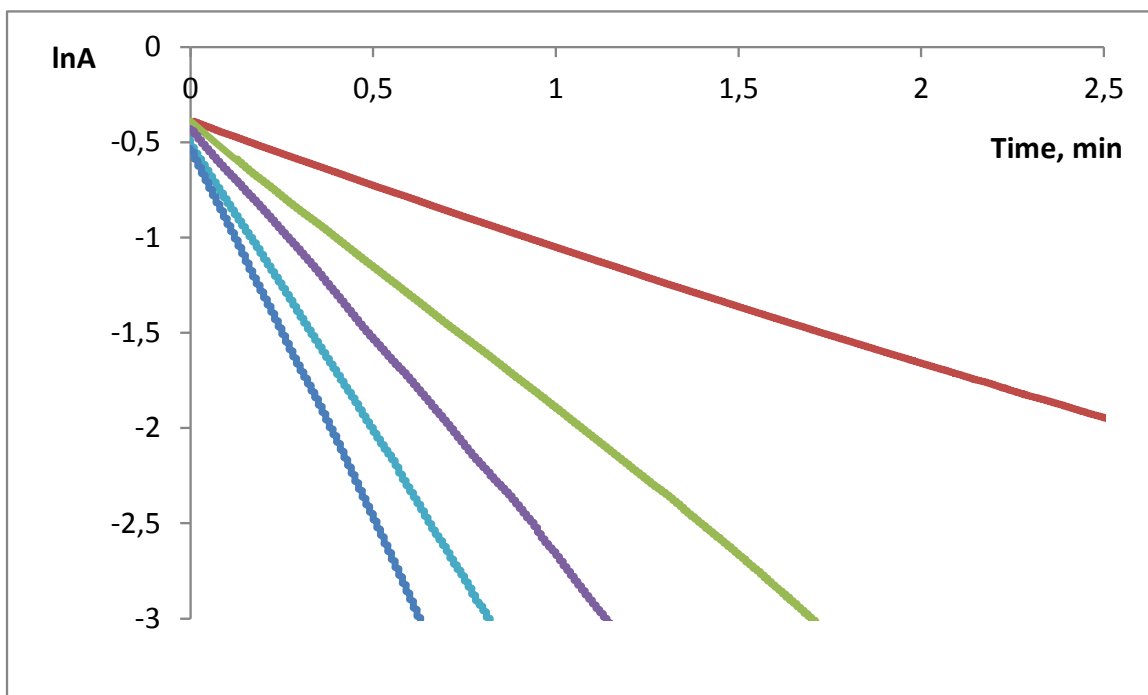
0.00020	0.5028
0.00025	0.6447
0.00030	0.7578
0.00035	0.9216
0.00040	1.0096
0.00045	1.2015
0.00050	1.2960



Extinction coefficient $\epsilon = 2637 \pm 50$ was determined from three parallel experiments.

Kinetics of the reaction of 4-CF₃-BCPP with 1-aminobutane (at 380 nm, $C_{4\text{-CF}_3\text{-BCPP}} = 2.6 \cdot 10^{-4}$ M).

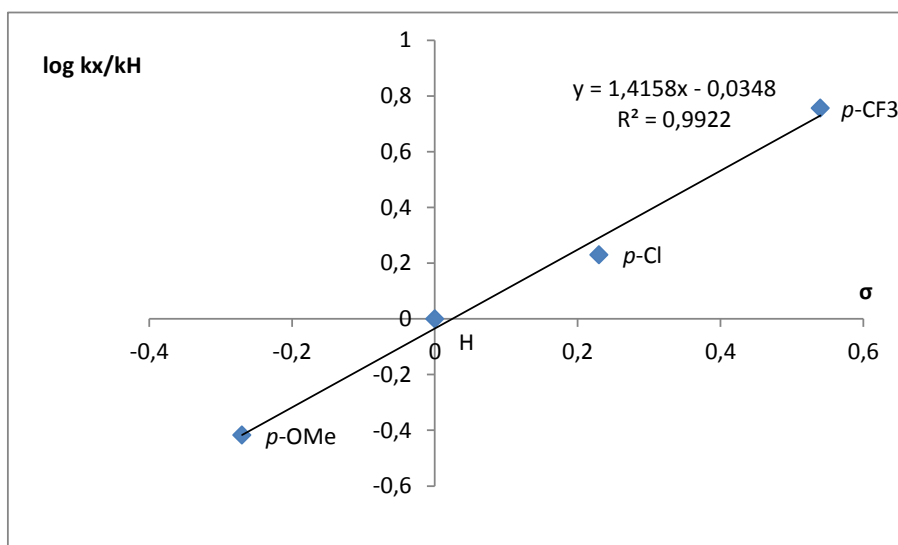




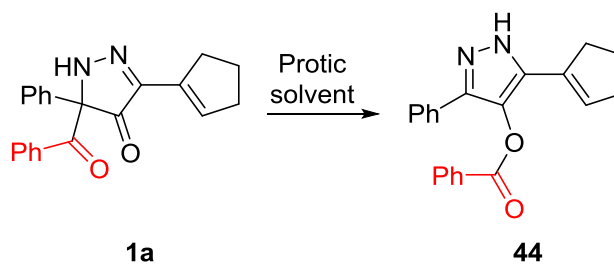
Second order rate constant in DCM at 24 ± 0.5 °C obtained from three parallel experiments:
 $k = 4.9 \pm 0.2$ ($\text{L} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1}$).

Hammett plot for the reaction of 1a–d with 1-aminobutane ($\rho = 1.42$)

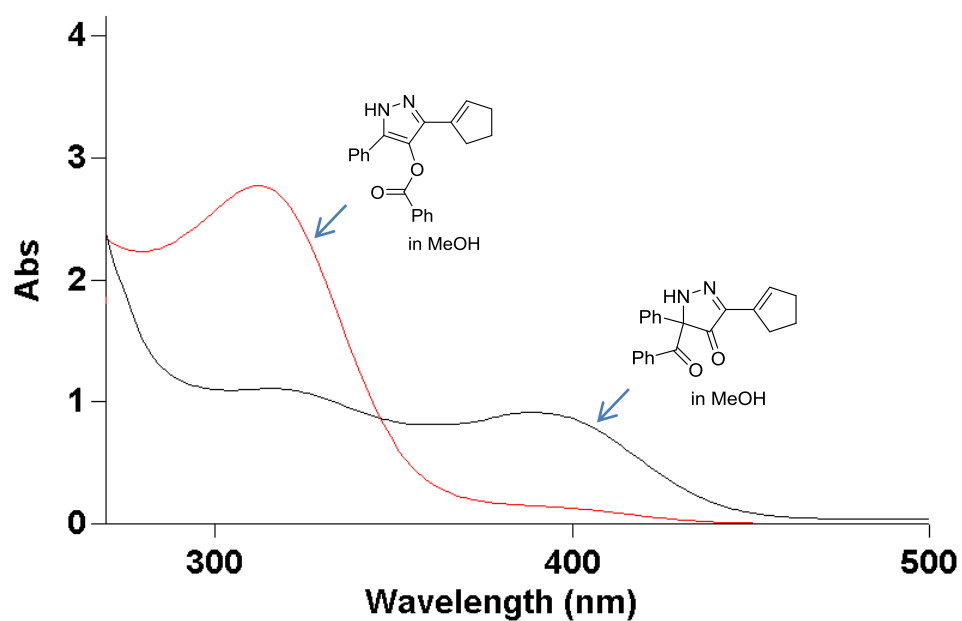
σ	$\log(k_x/k_H)$
-0.27	-0.417
0	0
0.23	0.2298
0.54	0.7557



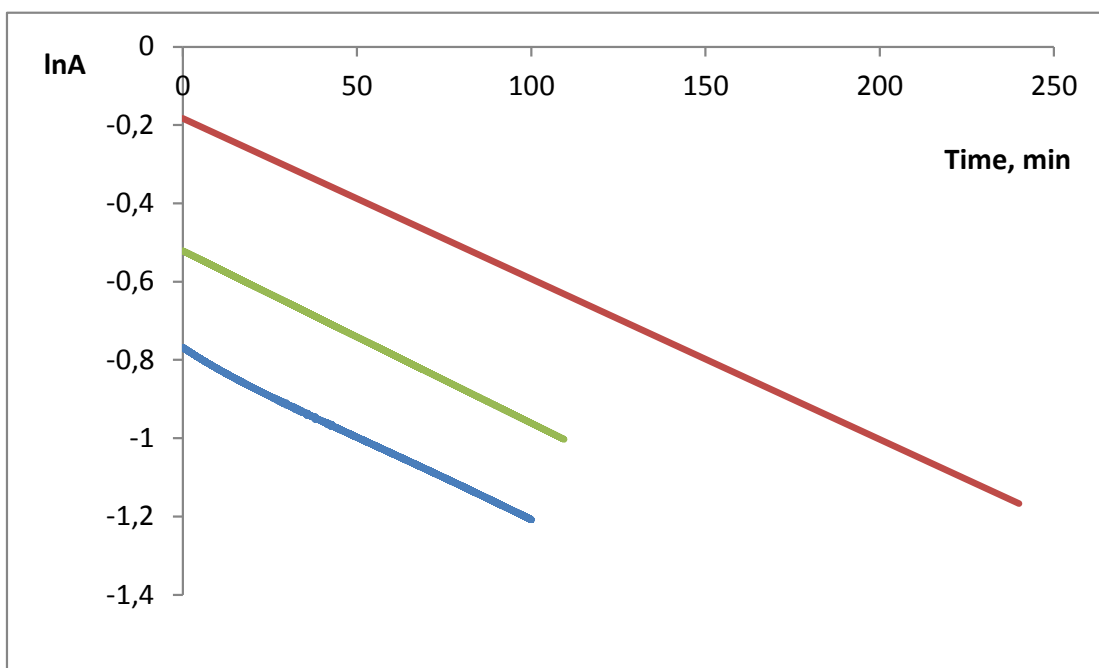
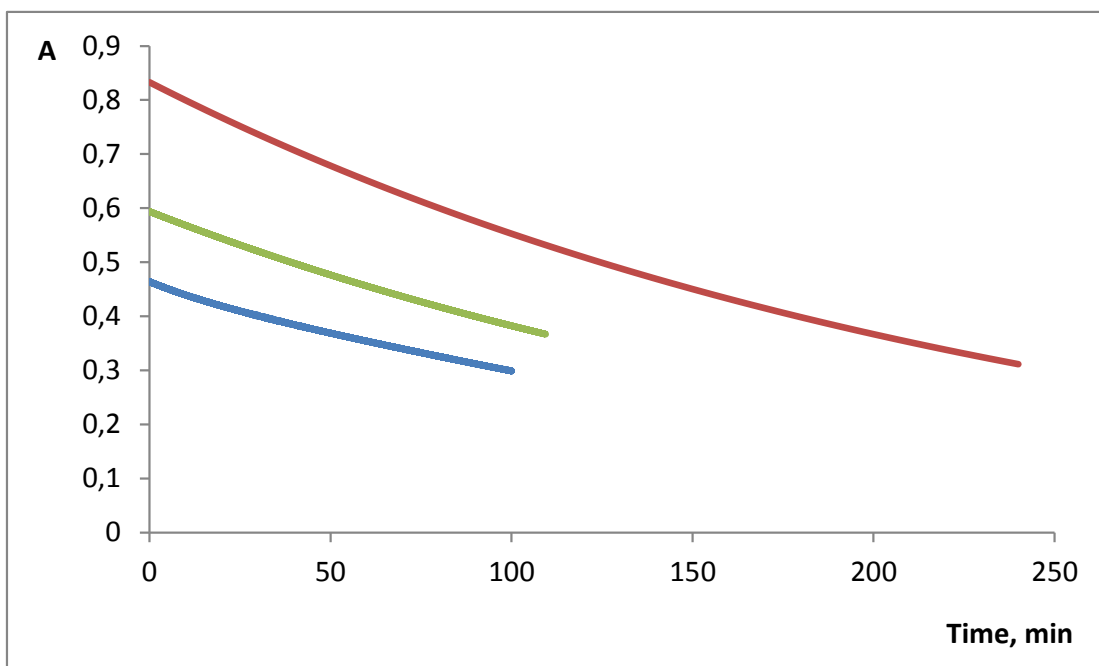
Kinetic Determination for the Intramolecular Benzoyl Transfer of BCPP



UV-Vis spectra of **1a** and **44** in methanol



Kinetics of the rearrangement **1a** → **44** in MeOH/DCM 5:1 at 400 nm – Monitoring the disappearance of **1a**:

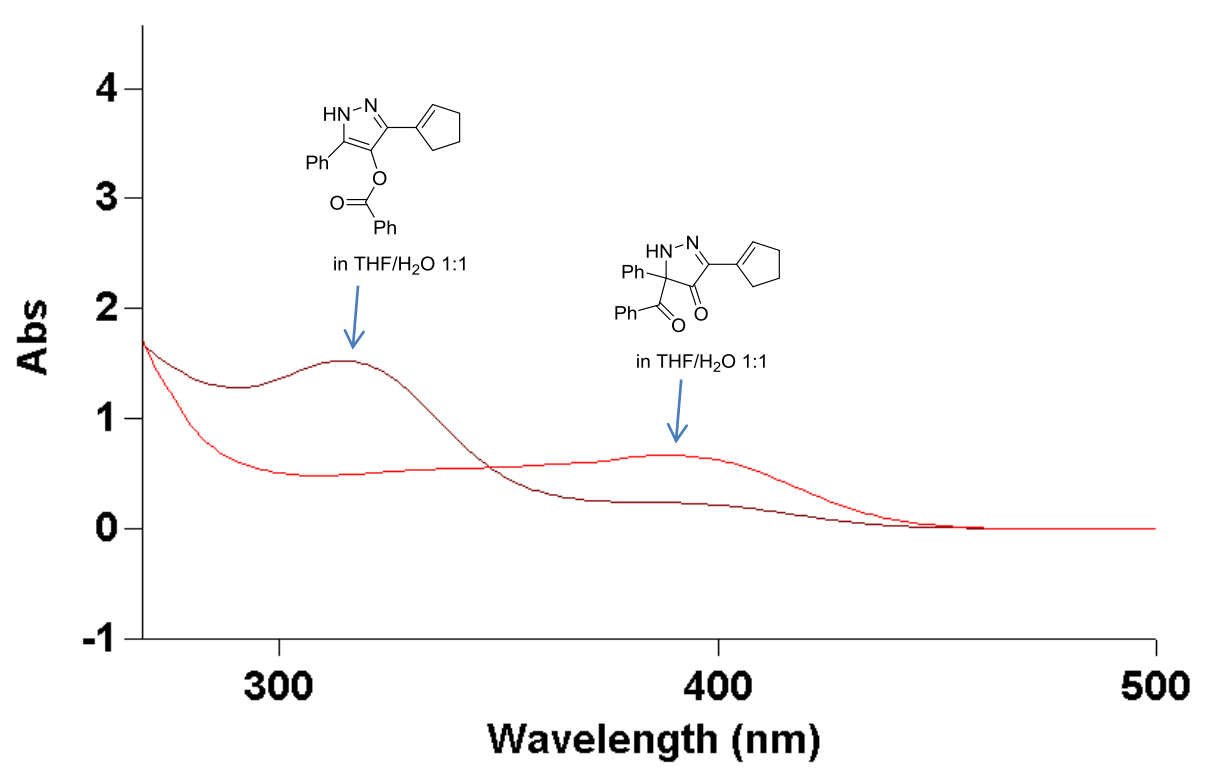


First order reaction rate constants determined at different concentrations of BCPP:

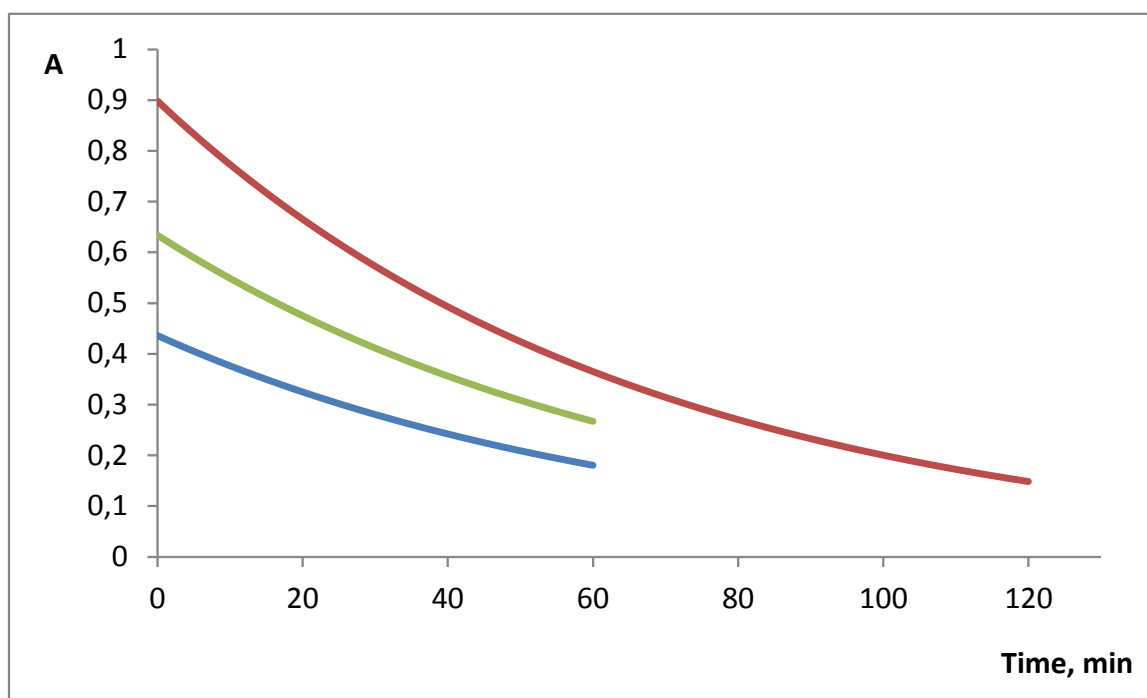
$$k = 7.33 \cdot 10^{-5}; 7.16 \cdot 10^{-5}; 6.83 \cdot 10^{-5} \text{ sec}^{-1}$$

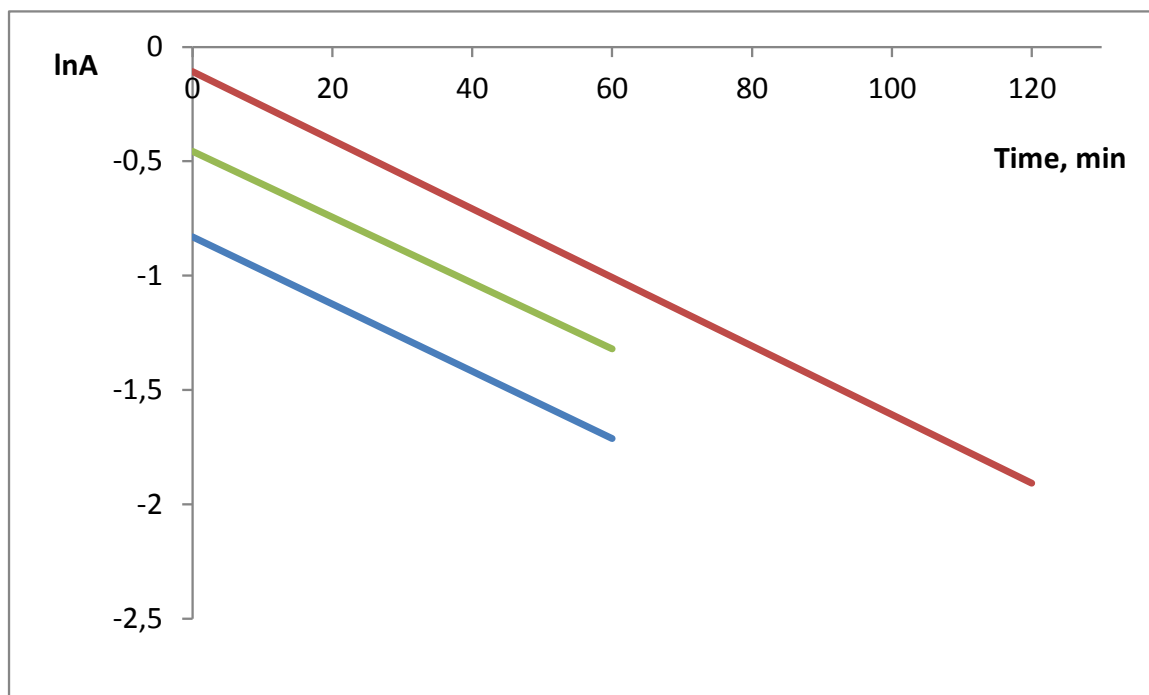
$$\underline{k = 7.1 \cdot 10^{-5} \pm 0.3 \cdot 10^{-5} \text{ sec}^{-1}}$$

UV-Vis spectra of **1a** and **44** in THF/H₂O 1:1



Kinetics of the rearrangement **1a** → **44** in THF/H₂O 1:1 at 400 nm – Monitoring the disappearance of **1a**:



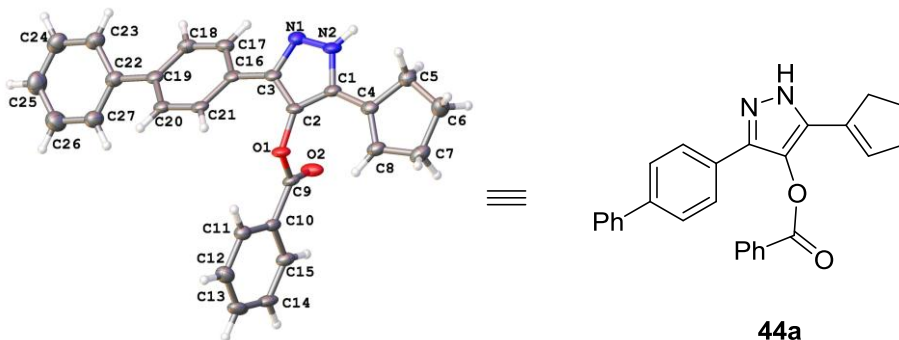


First order reaction rate constants determined at different concentrations of BCPP:

$$k = 2.40 \cdot 10^{-4}; 2.45 \cdot 10^{-4}; 2.49 \cdot 10^{-4} \text{ sec}^{-1}$$

$$\underline{k = 2.45 \cdot 10^{-4} \pm 0.05 \cdot 10^{-4} \text{ sec}^{-1}}$$

Crystal Structure Report for **44a** (cd1436a)



Single crystals of **44a** ($\text{C}_{27}\text{H}_{22}\text{N}_2\text{O}_2$) were prepared by slow evaporation of a 1:1 hexane:DCM mixture. A suitable colorless plate-like crystal, with dimensions of 0.33 mm $\times$ 0.13 mm $\times$ 0.10 mm, was mounted, using Paratone oil, onto a nylon loop. The data were collected at 98(2) K using a Rigaku AFC12 / Saturn 724 CCD fitted with MoK α radiation ($\lambda = 0.71075 \text{ \AA}$). Data collection and unit cell refinement were performed using *CrystalClear* software.¹⁰ The total number of data were measured in the range $6.46^\circ < 2\theta < 50.1^\circ$ using ω scans. Data processing and absorption correction, giving minimum and maximum transmission factors (0.546, 1.000), were accomplished with *CrystalClear*¹⁰ and *ABSCOR*¹¹, respectively. The structure, using

Olex2¹², was solved with the ShelXT¹³ structure solution program using direct methods and refined (on F^2) with the ShelXL¹⁴ refinement package using full-matrix, least-squares techniques. All non-hydrogen atoms were refined with anisotropic displacement parameters. Electron density peaks were used to determine the hydrogen atoms bound to N2, C5, C6 and C7 atoms. All other hydrogen atom positions were determined by geometry and refined by a riding model.

Table S1. Crystallographic Data and Structure Refinement for cd1436a

Identification code	cd1332
Empirical formula	C ₂₇ H ₂₂ N ₂ O ₂
Formula weight	406.48
Crystal system	Triclinic
Space group	<i>P</i> -1
<i>a</i> (Å)	5.7431(13)
<i>b</i> (Å)	12.655(3)
<i>c</i> (Å)	15.118(4)
α (°)	69.385(6)
β (°)	82.282(6)
γ (°)	87.431(7)
Volume (Å ³)	1019.1(4)
Z	2
ρ (calc.)	1.325
λ	0.71075
Temp. (K)	98(2)
F(000)	428
μ (mm ⁻¹)	0.084
T _{min} , T _{max}	0.546, 1.000
2 θ _{range} (°)	6.46 to 50.1

Reflections collected	6632
Independent reflections	3572 [R(int) = 0.0627]
Completeness	99.5%
Data / restraints / parameters	3572 / 0 / 301
Observed data [I > 2σ(I)]	2697
$wR(F^2 \text{ all data})$	0.1385
$R(F \text{ obsd data})$	0.0610
Goodness-of-fit on F^2	1.00
largest diff. peak and hole (e Å ⁻³)	0.30 / -0.34

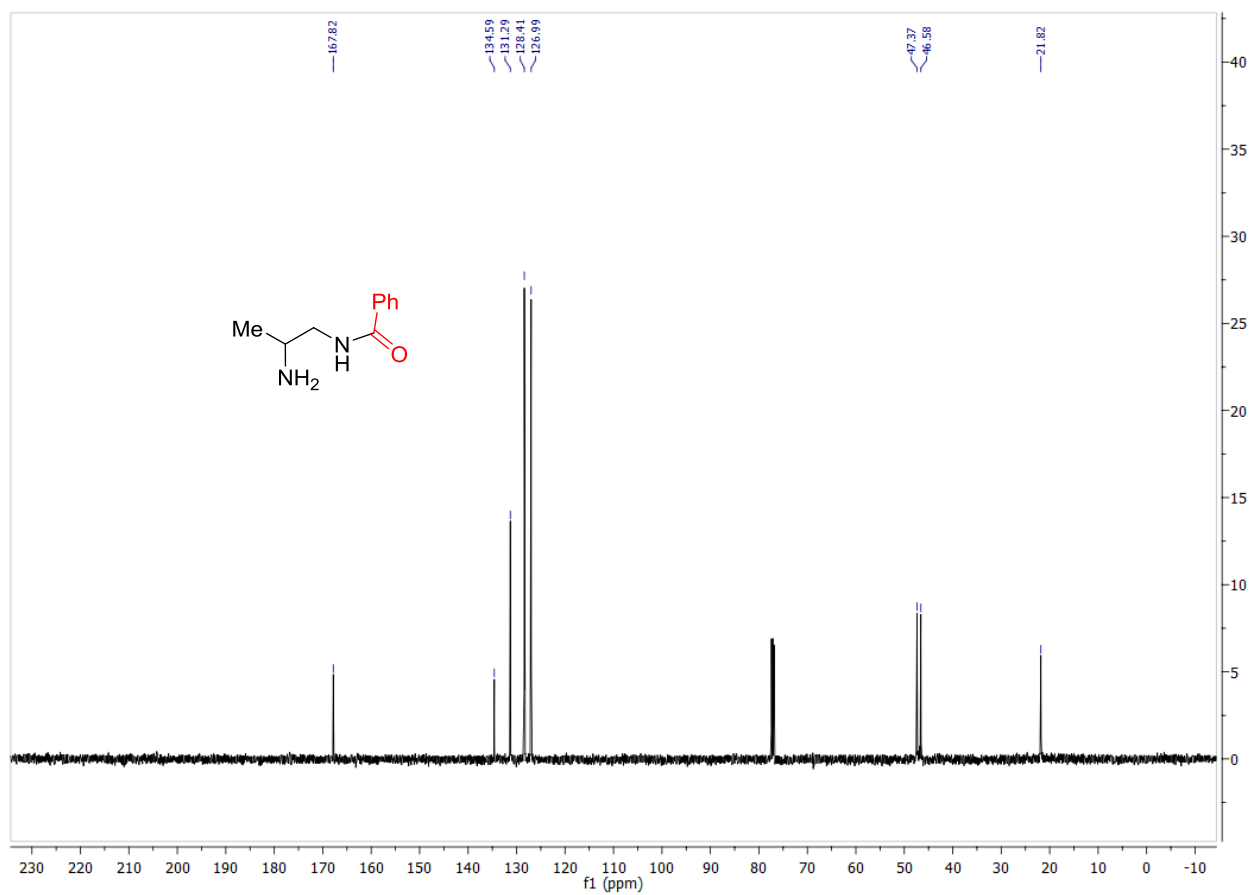
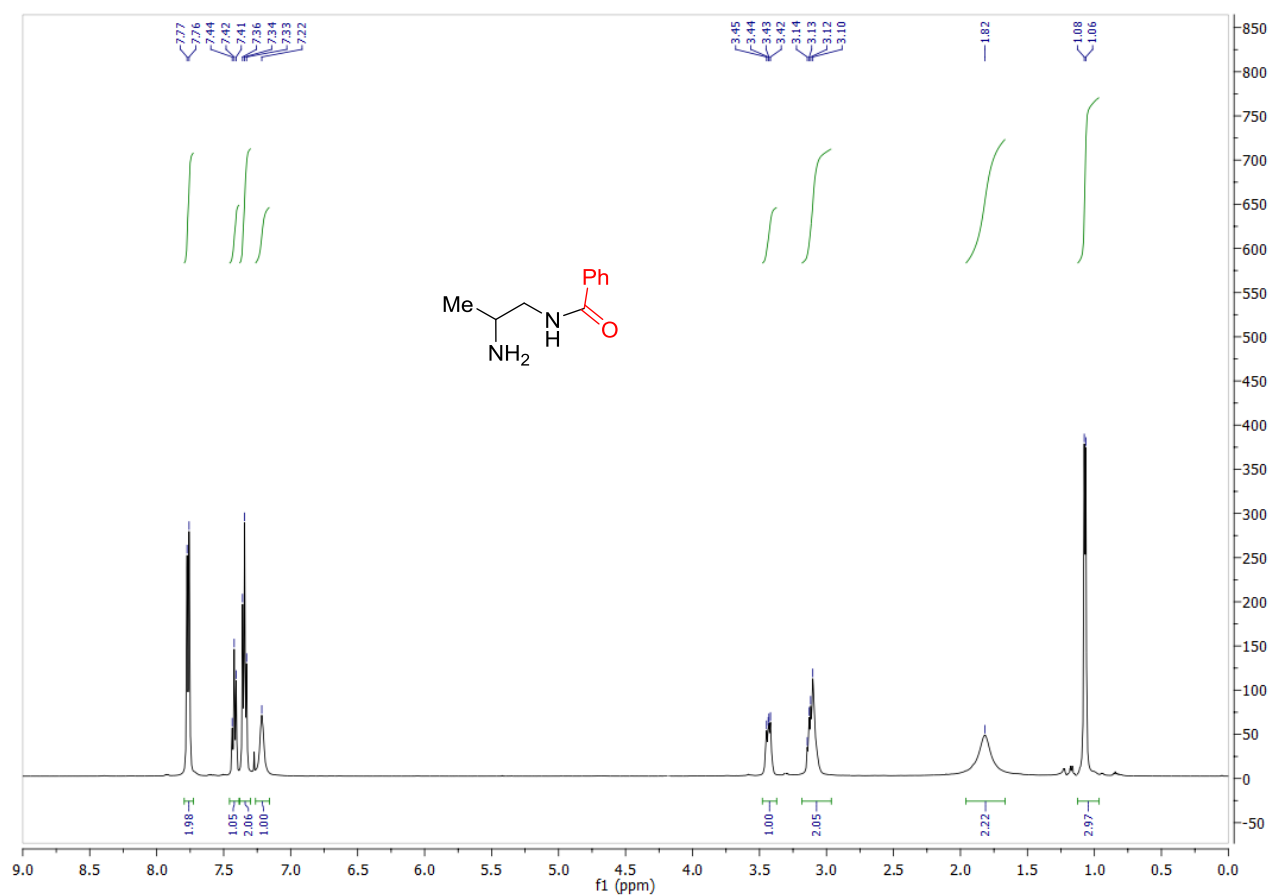
$$wR_2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2] \}^{1/2}$$

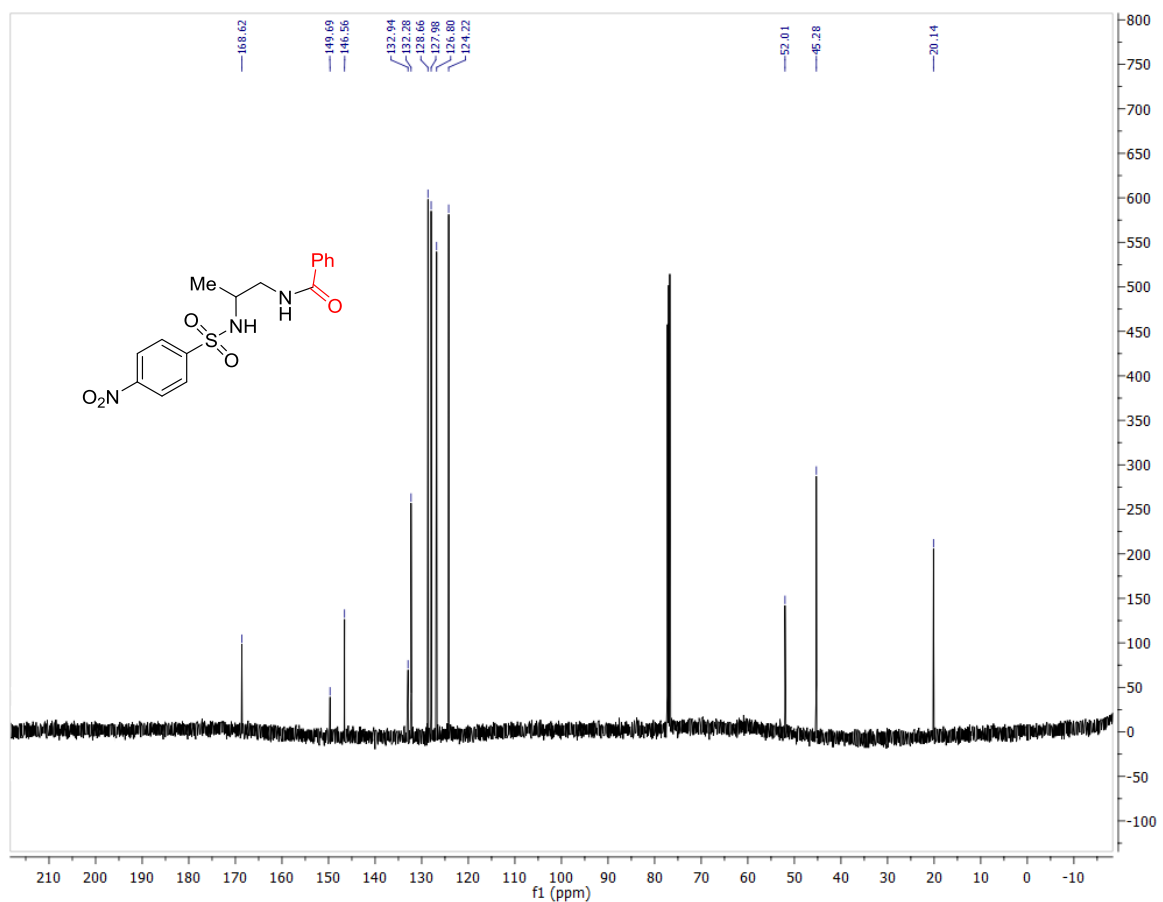
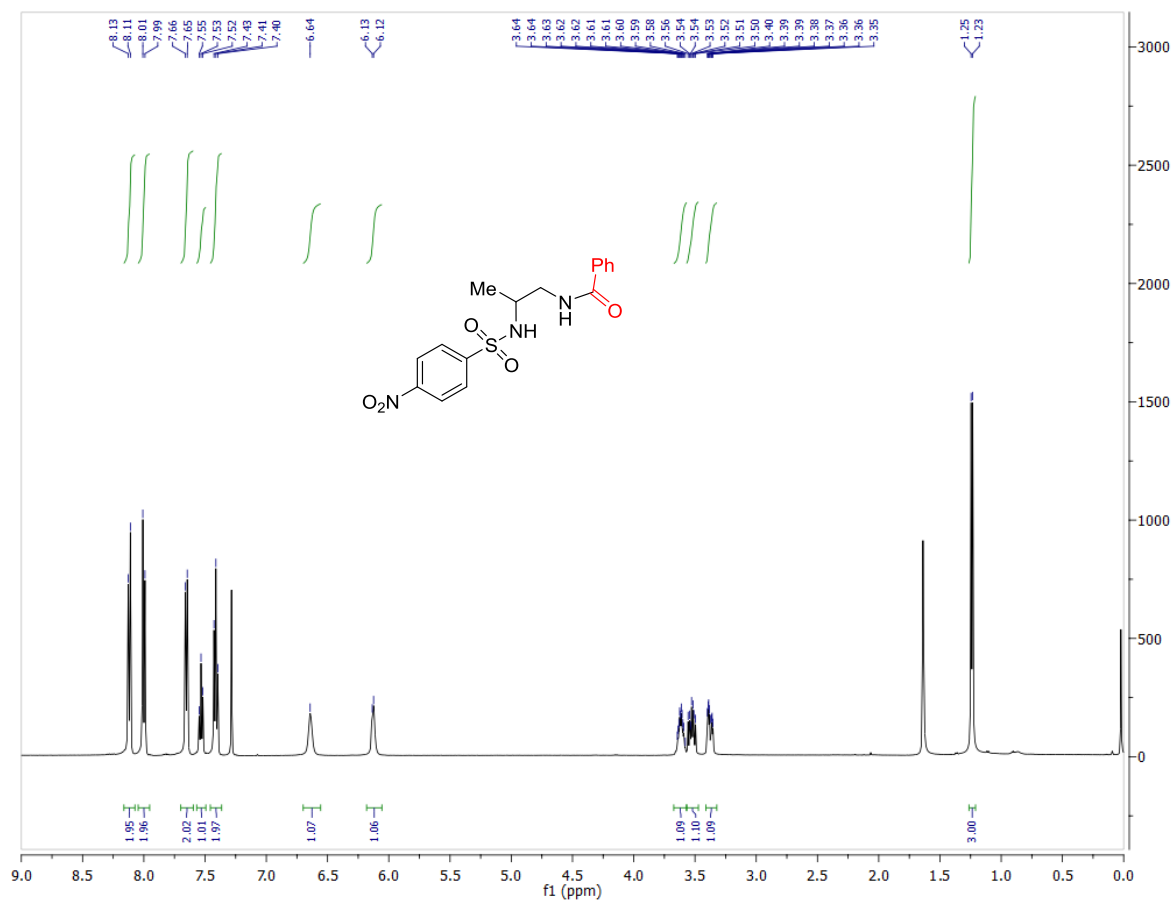
$$R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$$

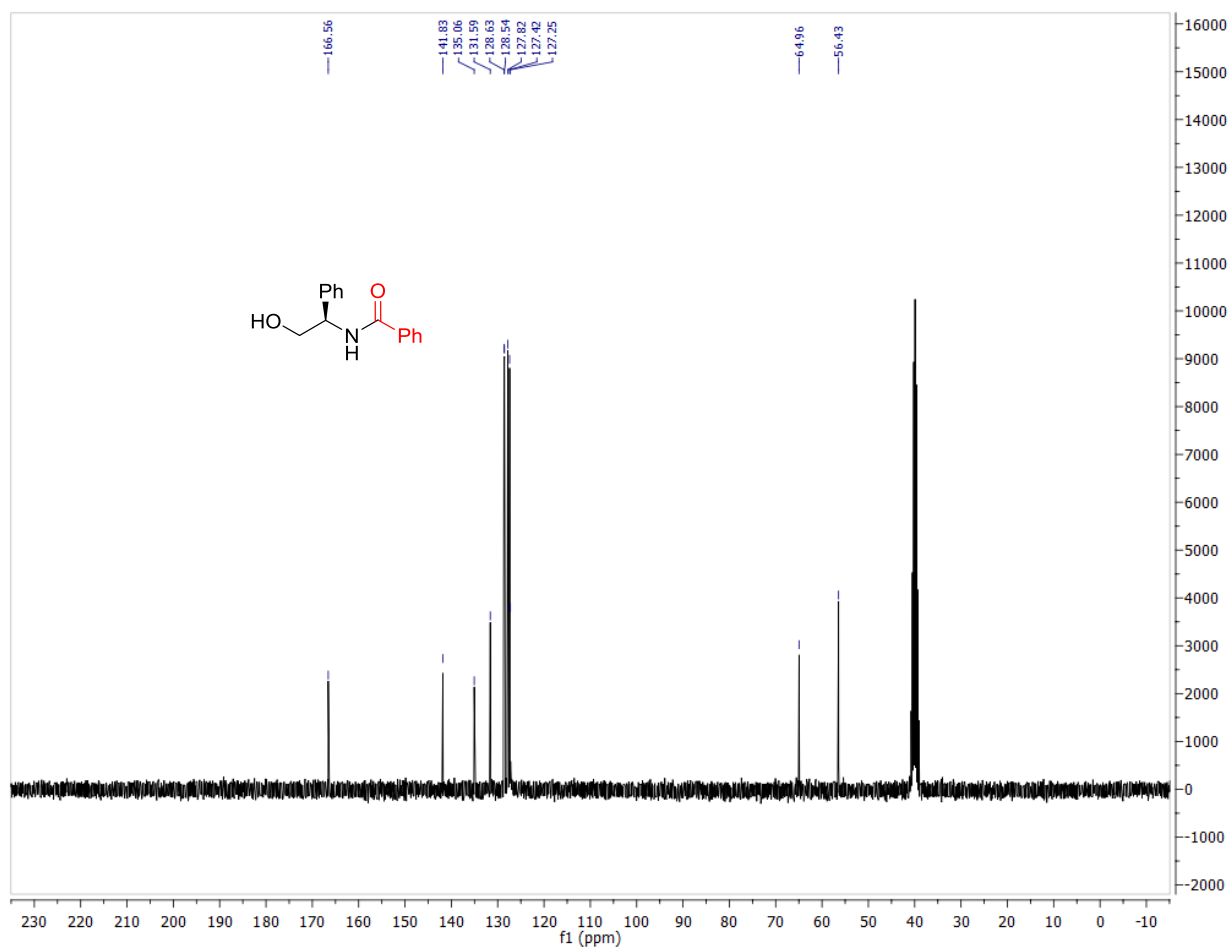
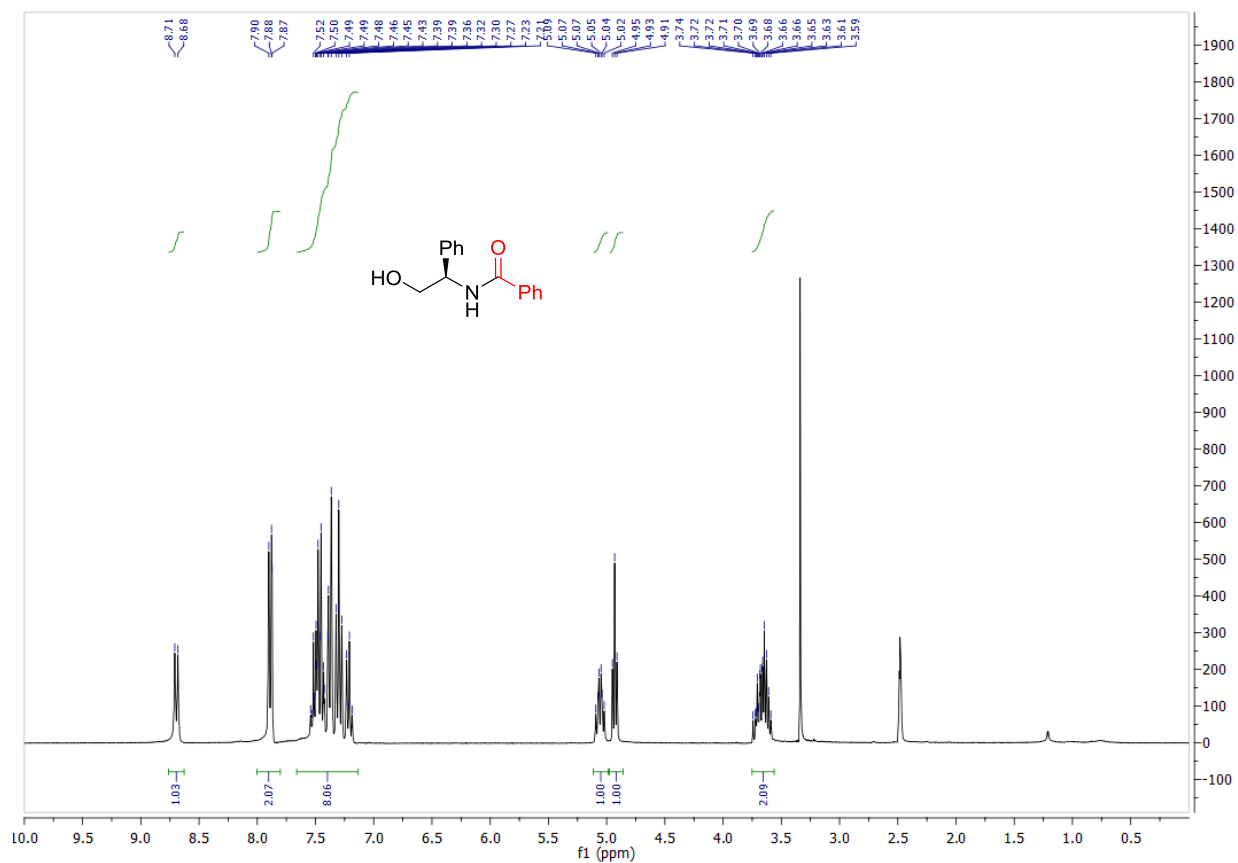
References

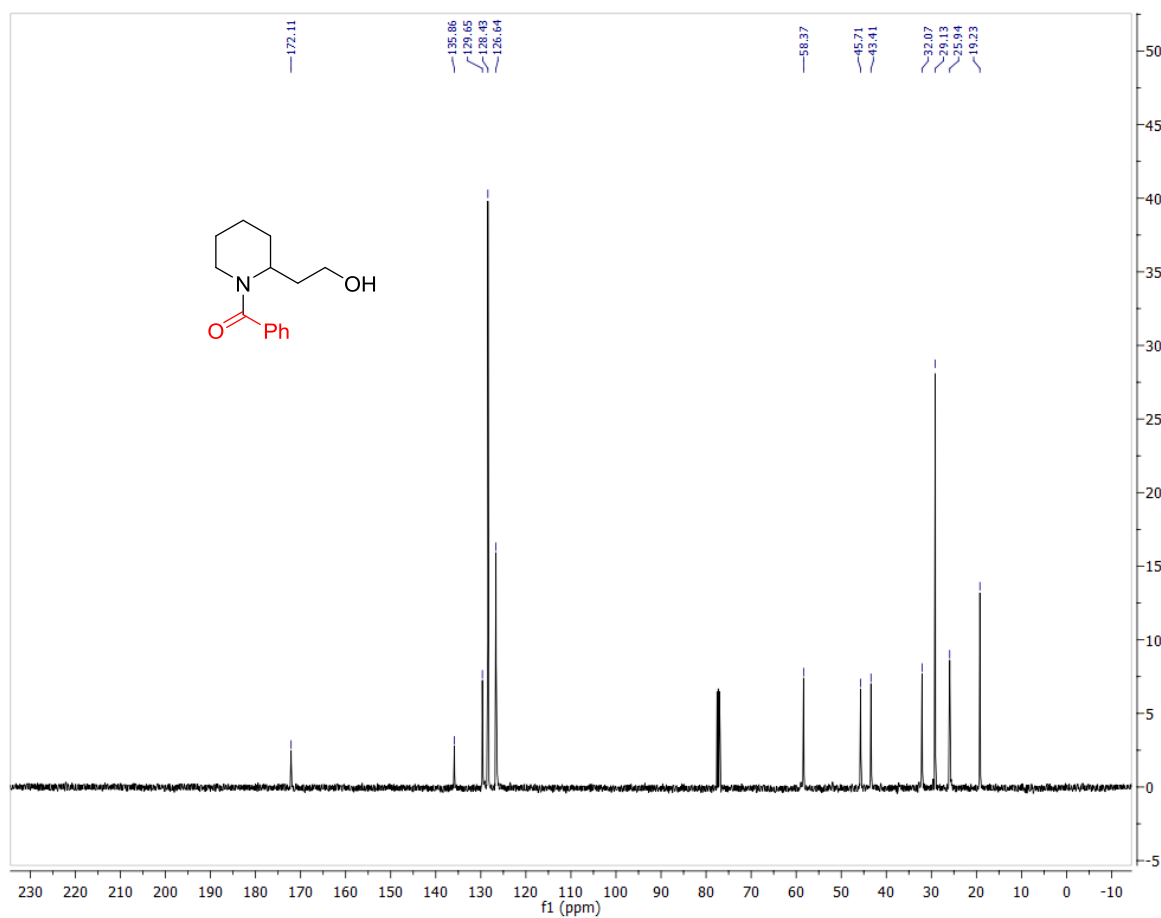
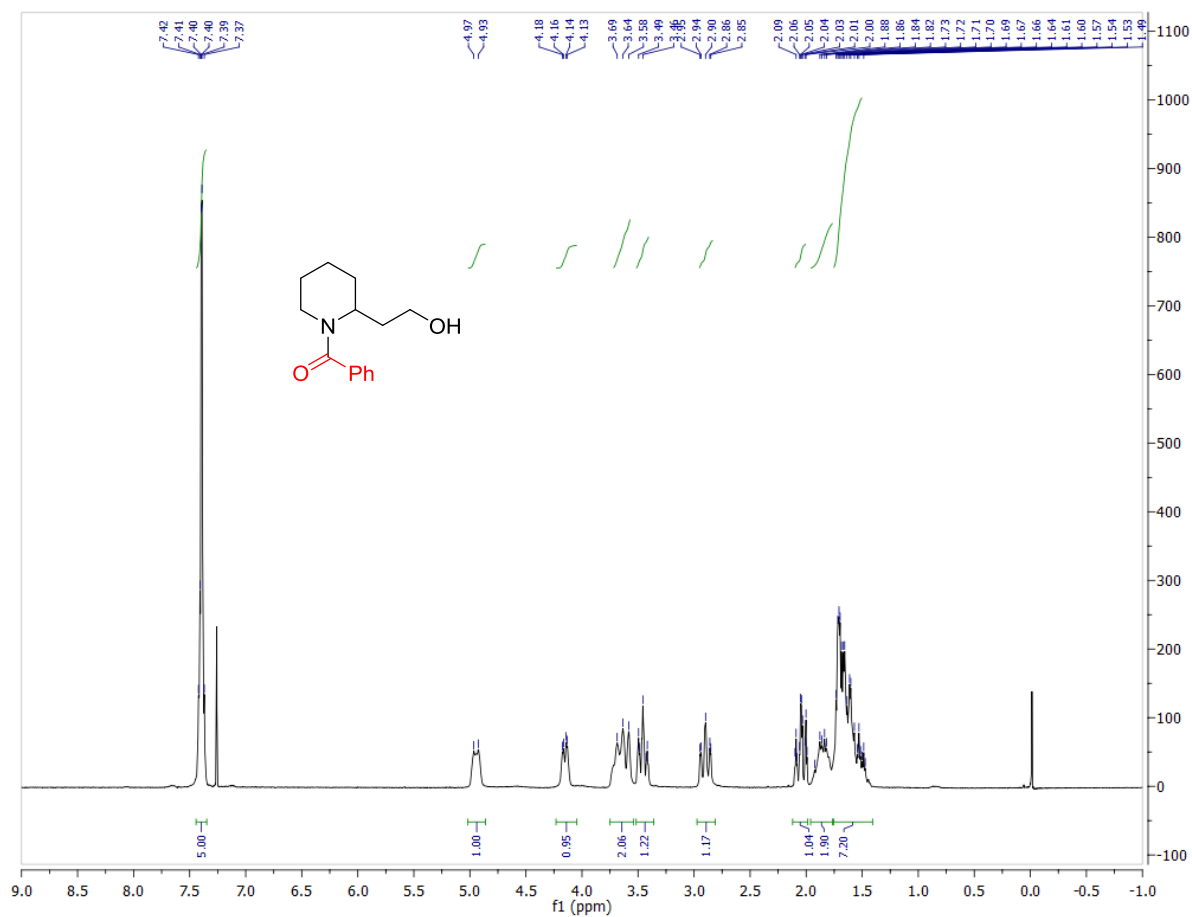
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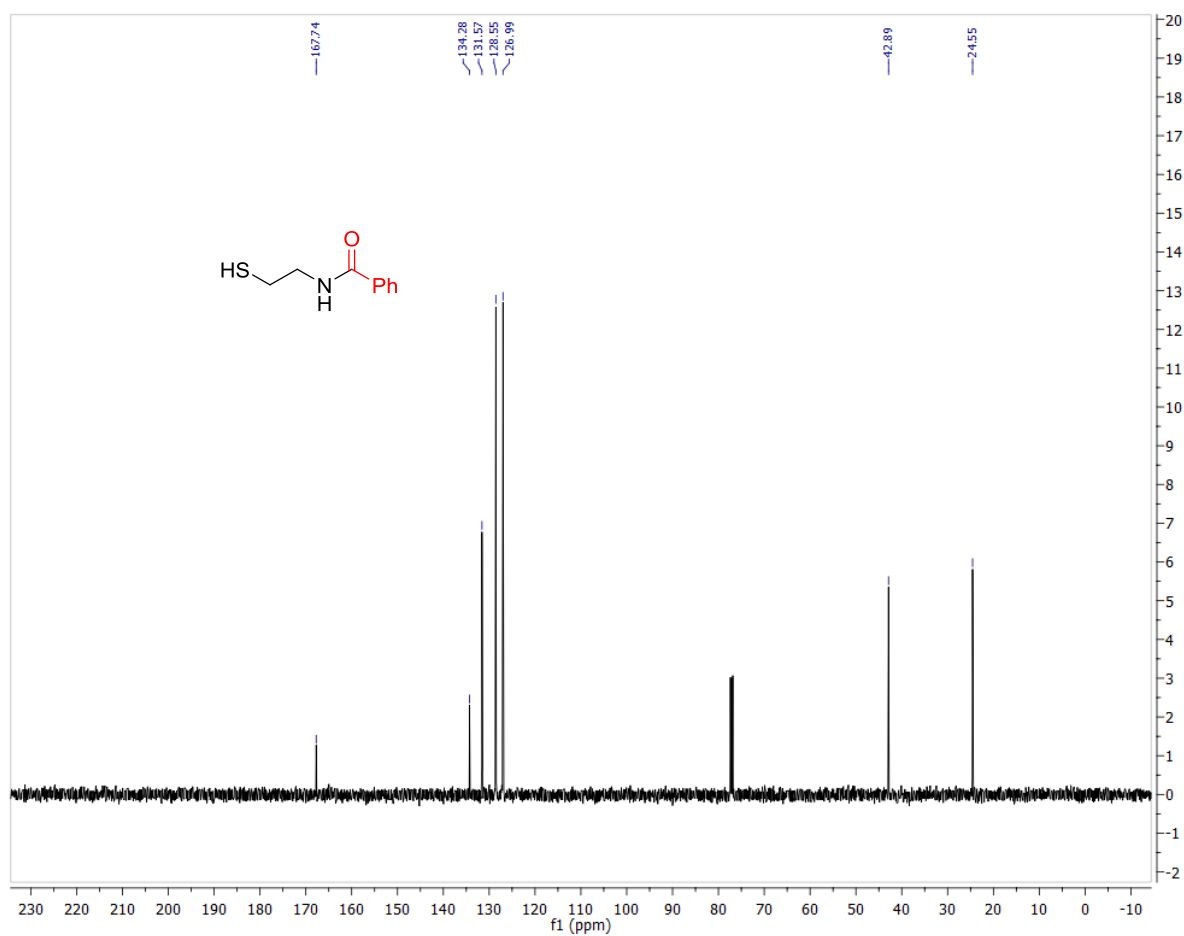
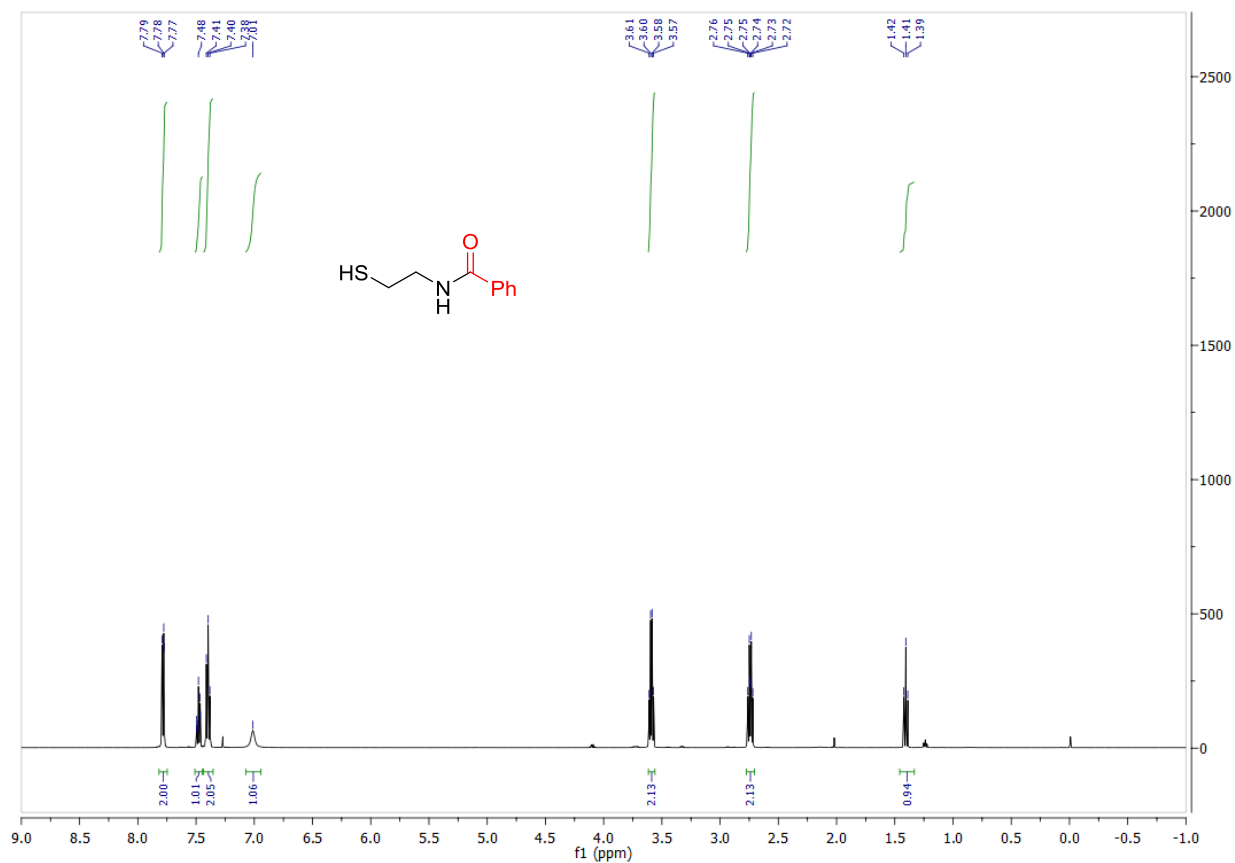
¹H and ¹³C NMR Spectra of Products

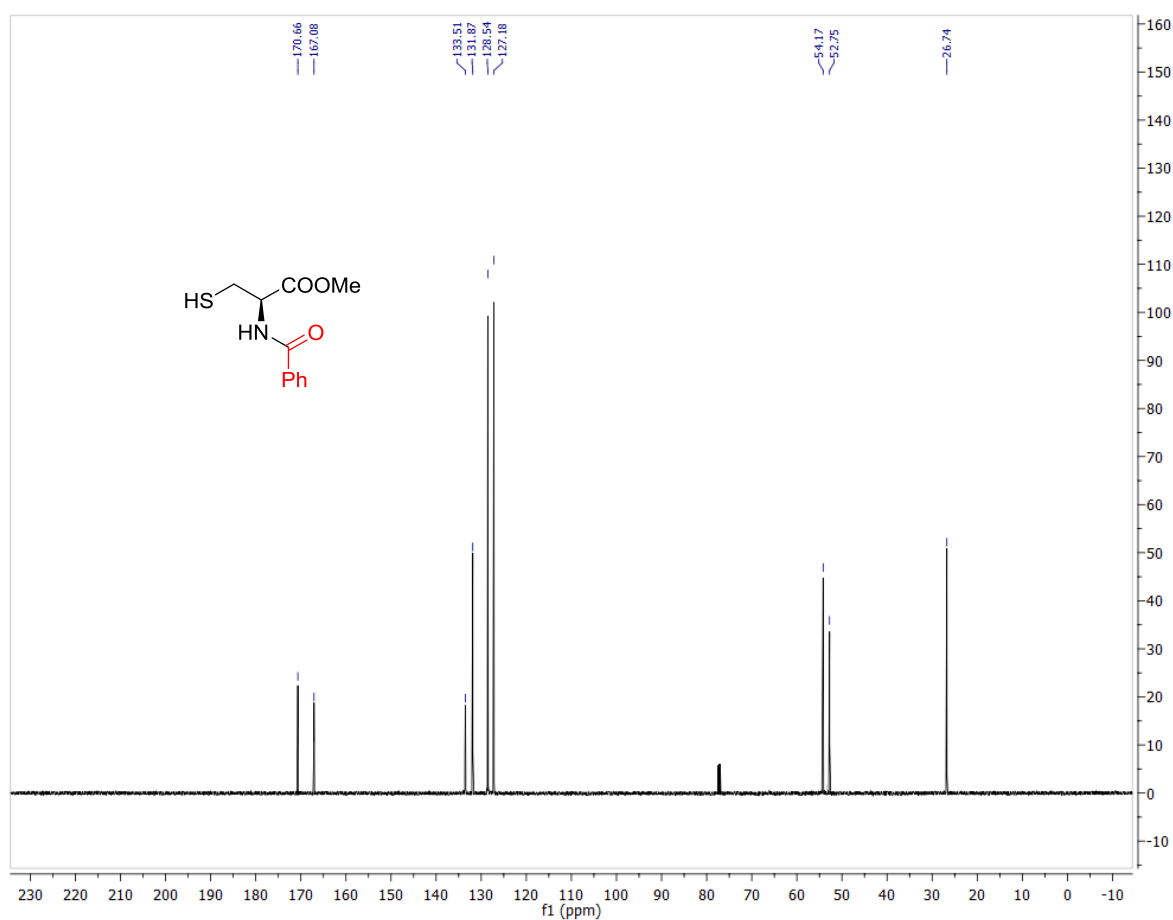
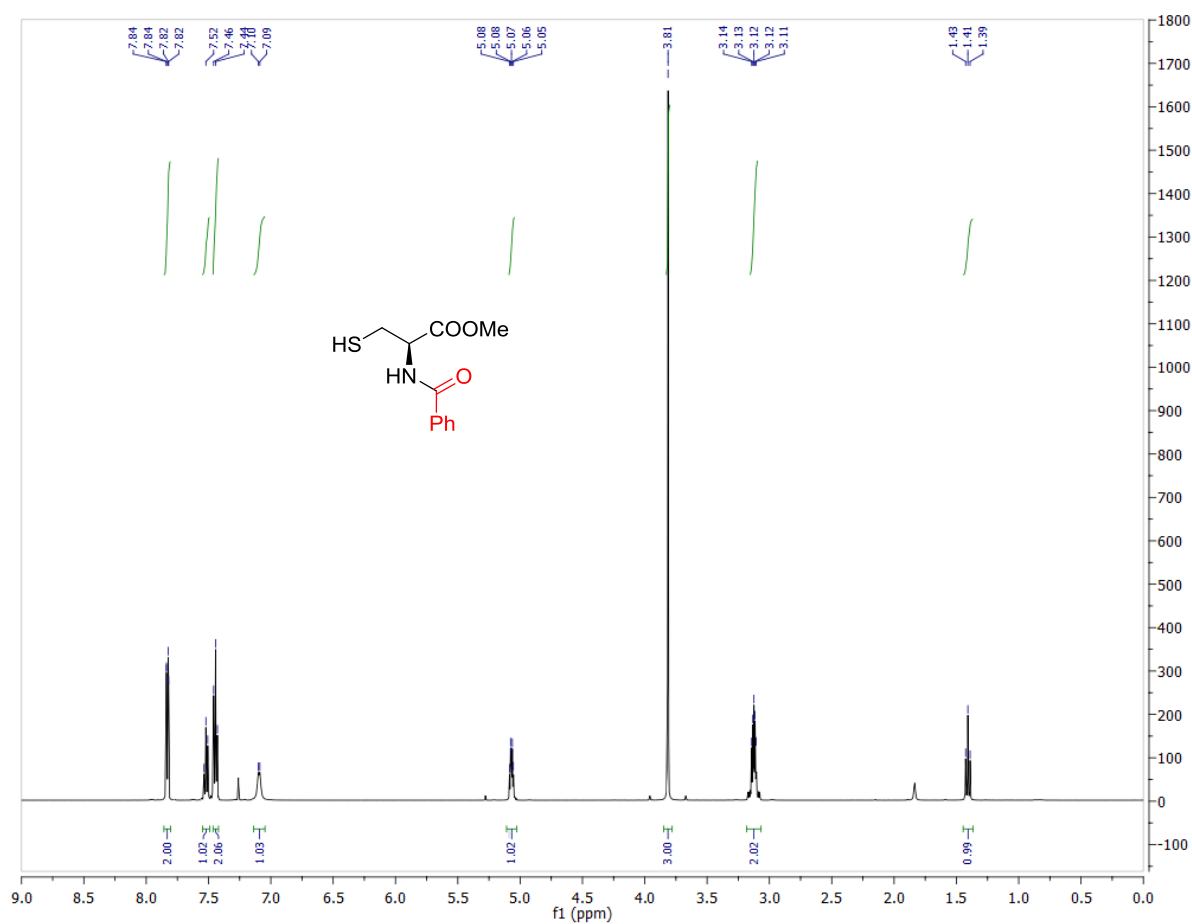


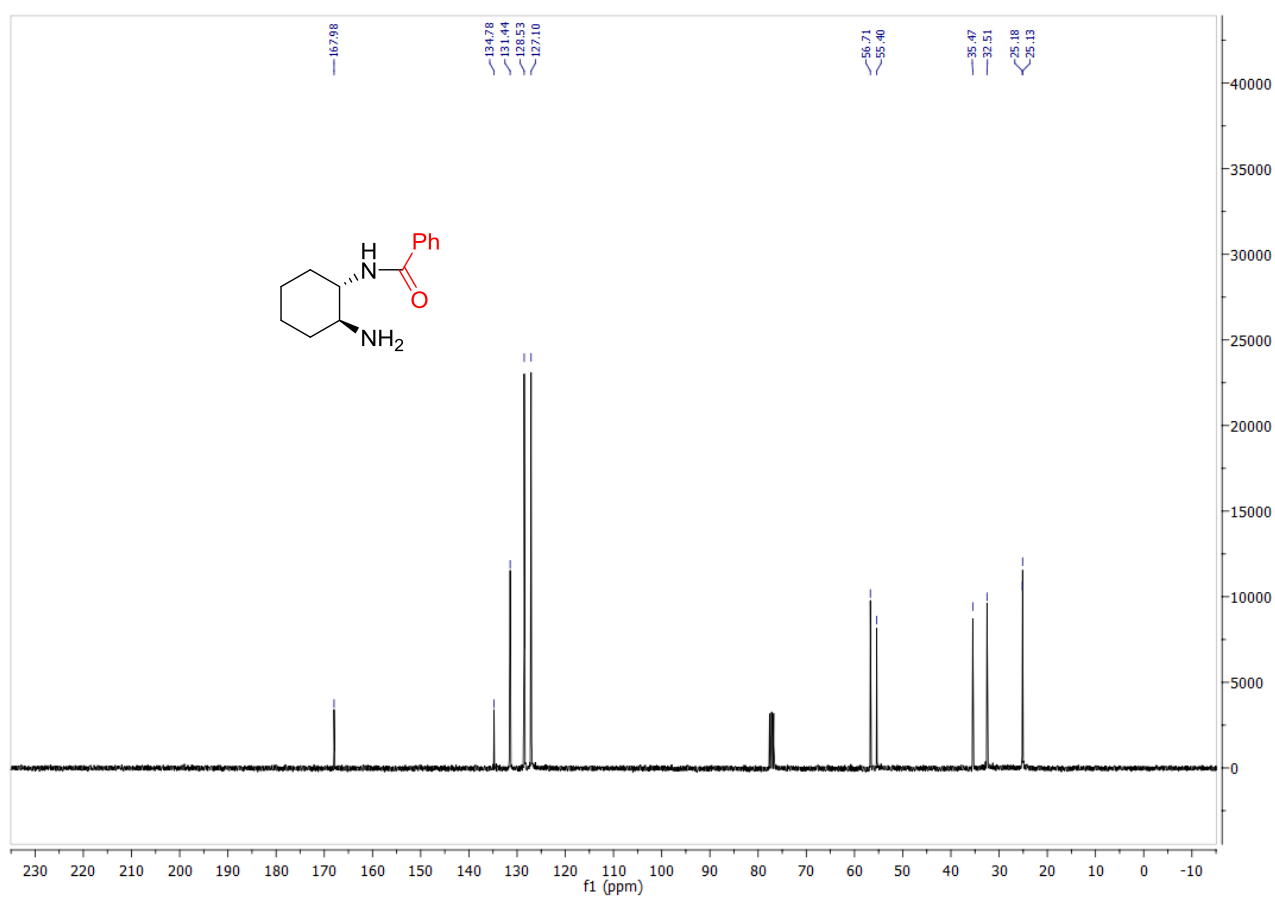
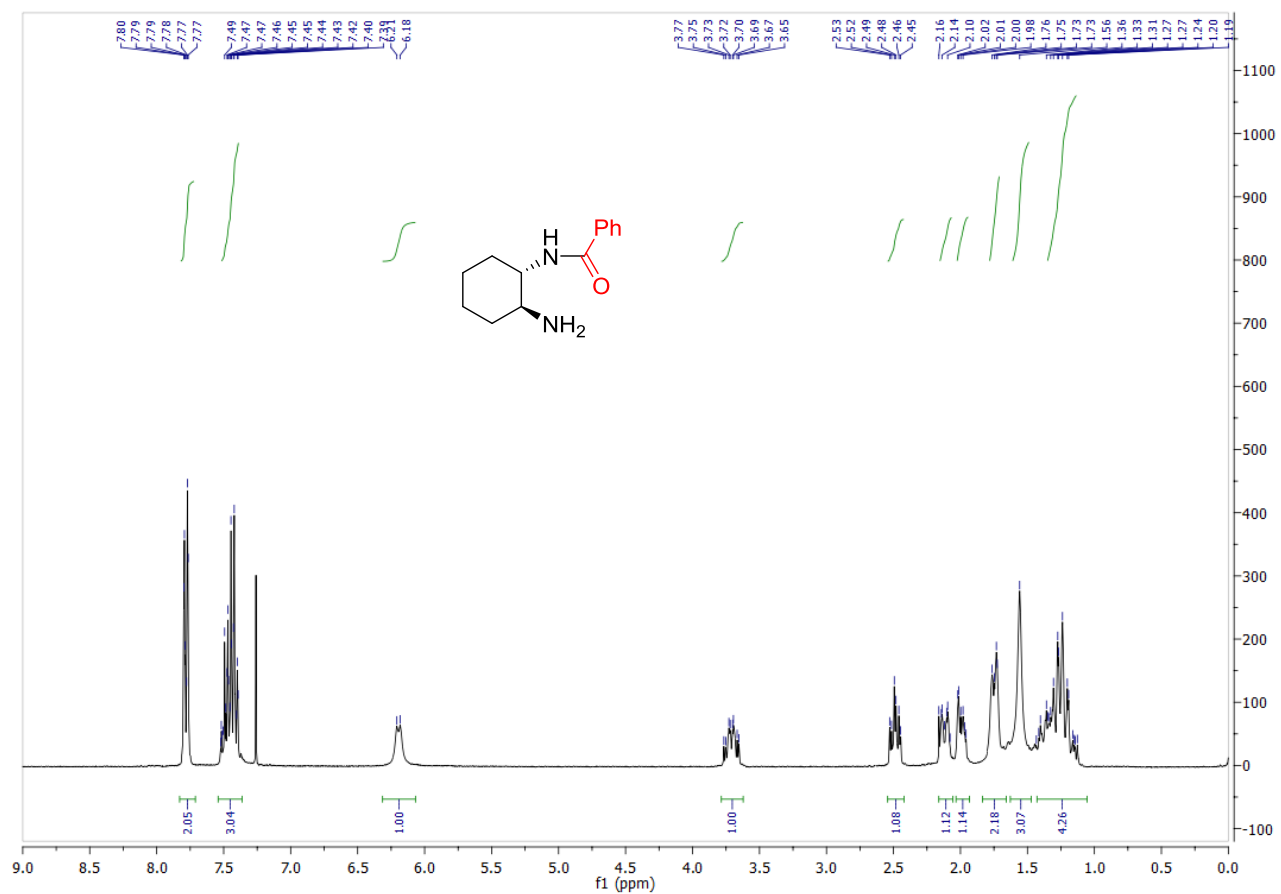


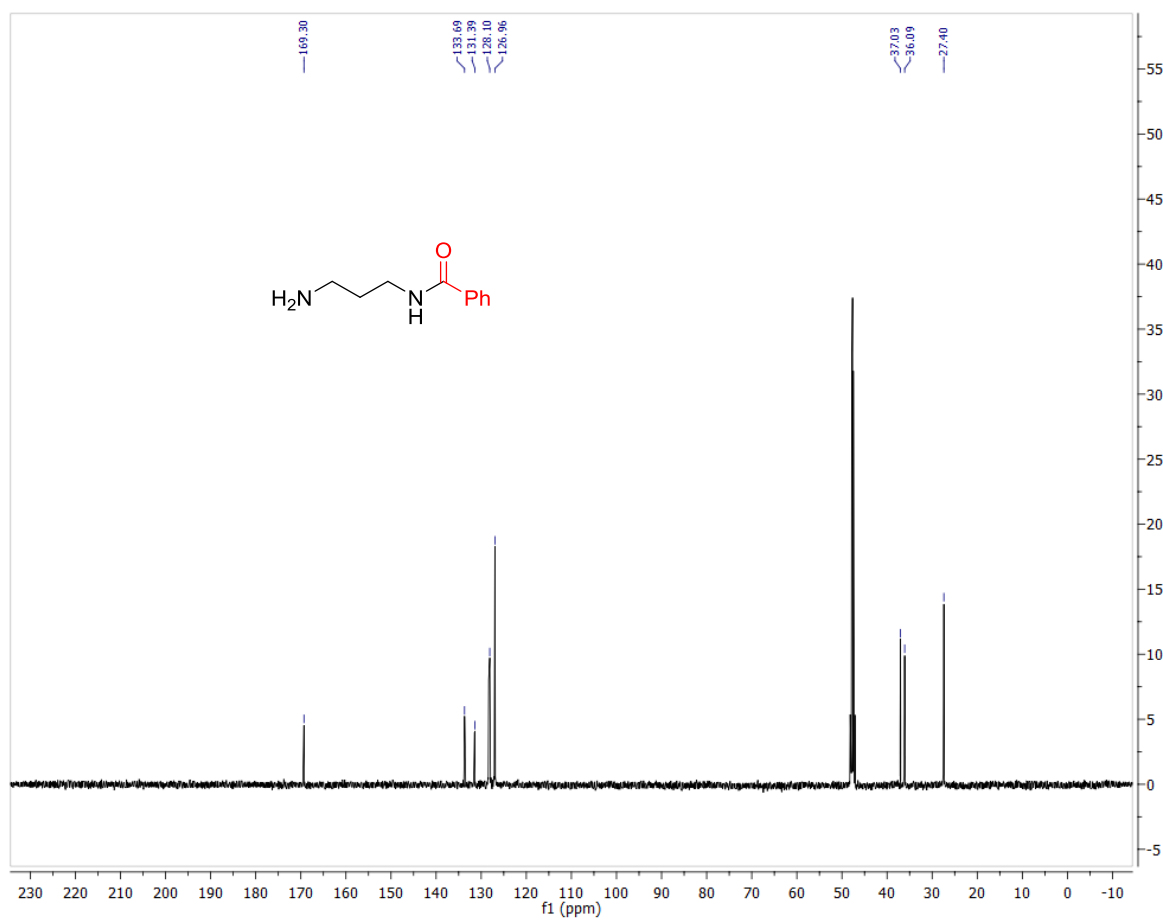
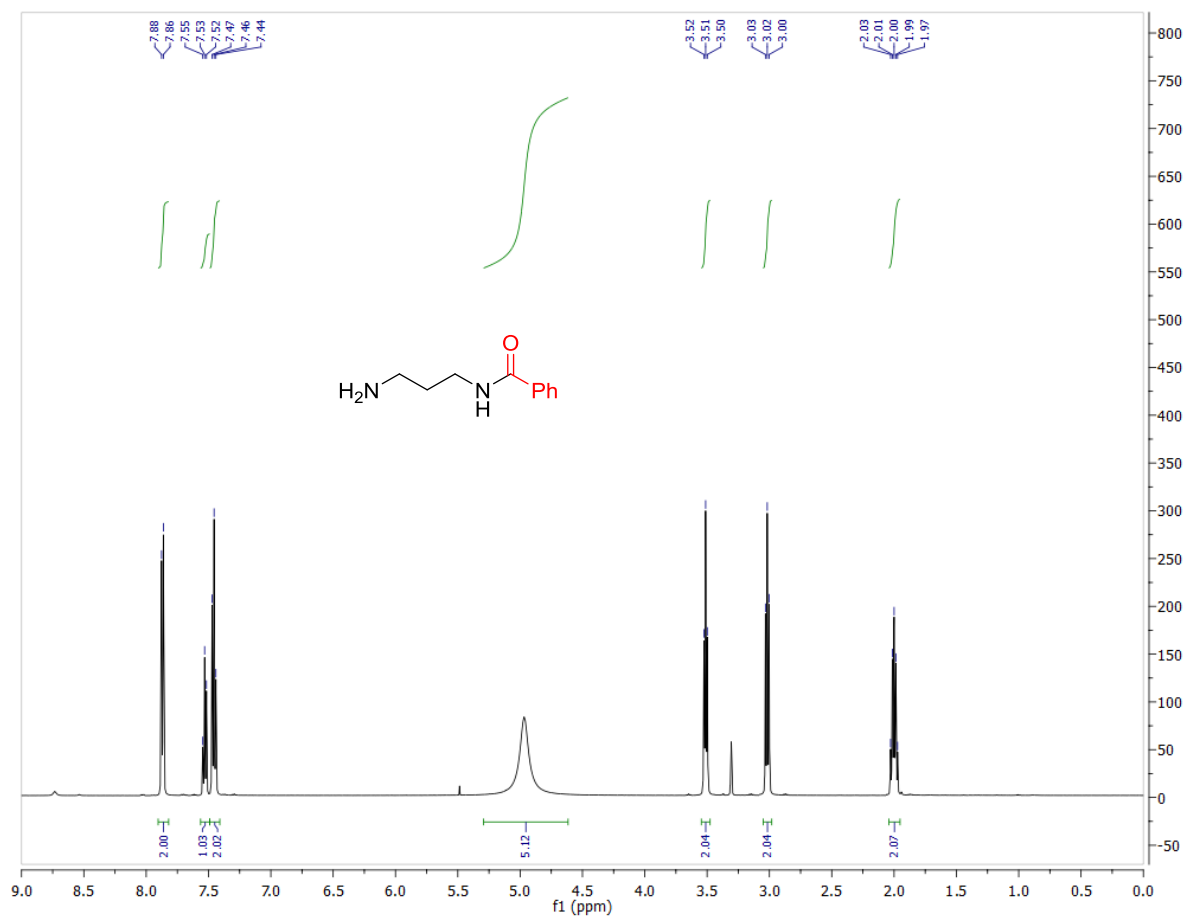


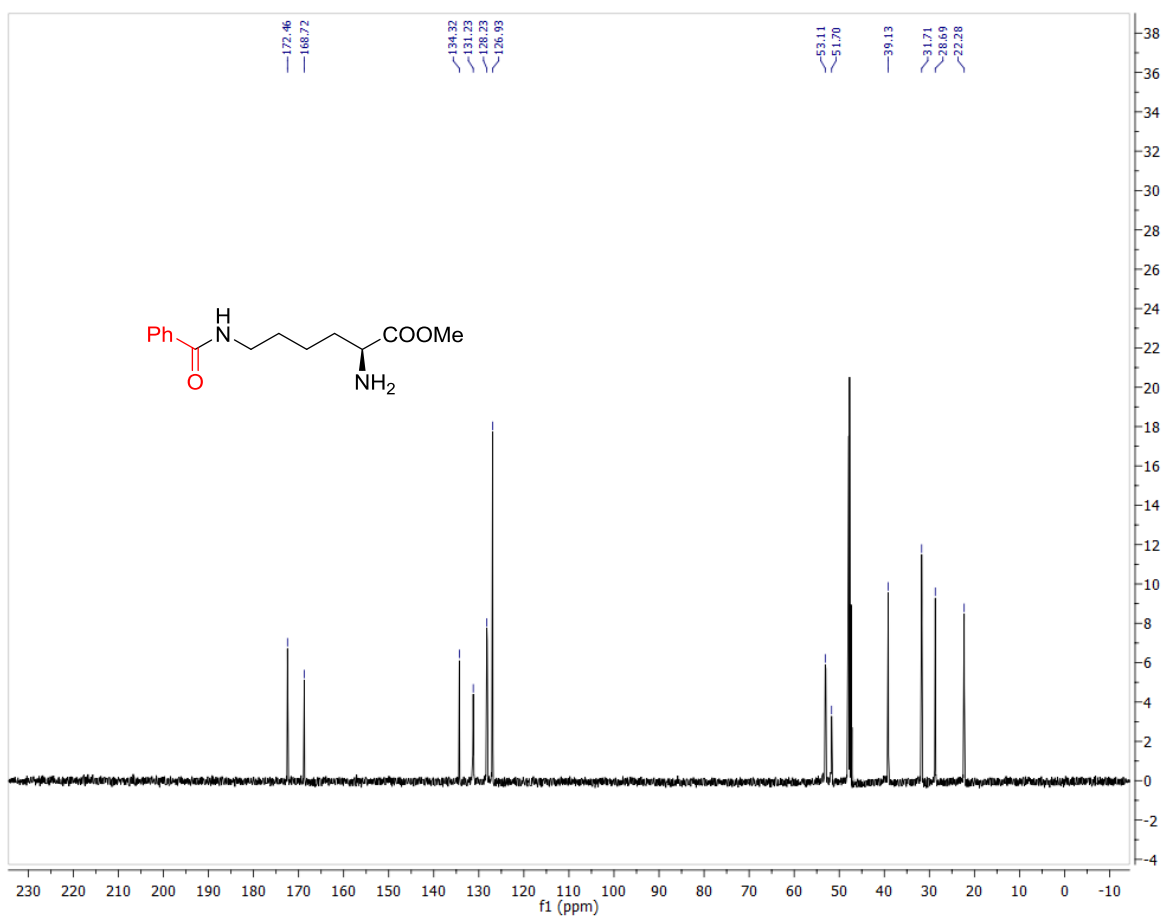
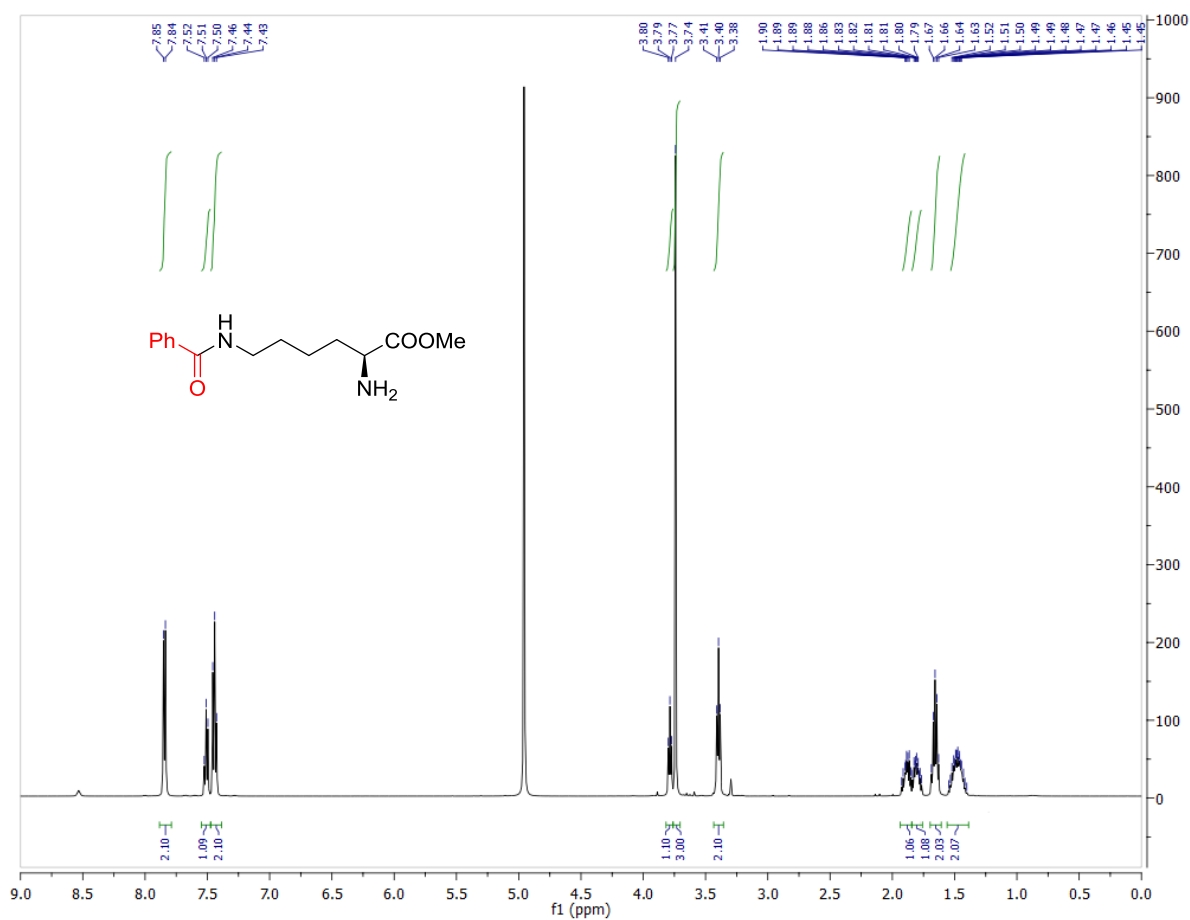


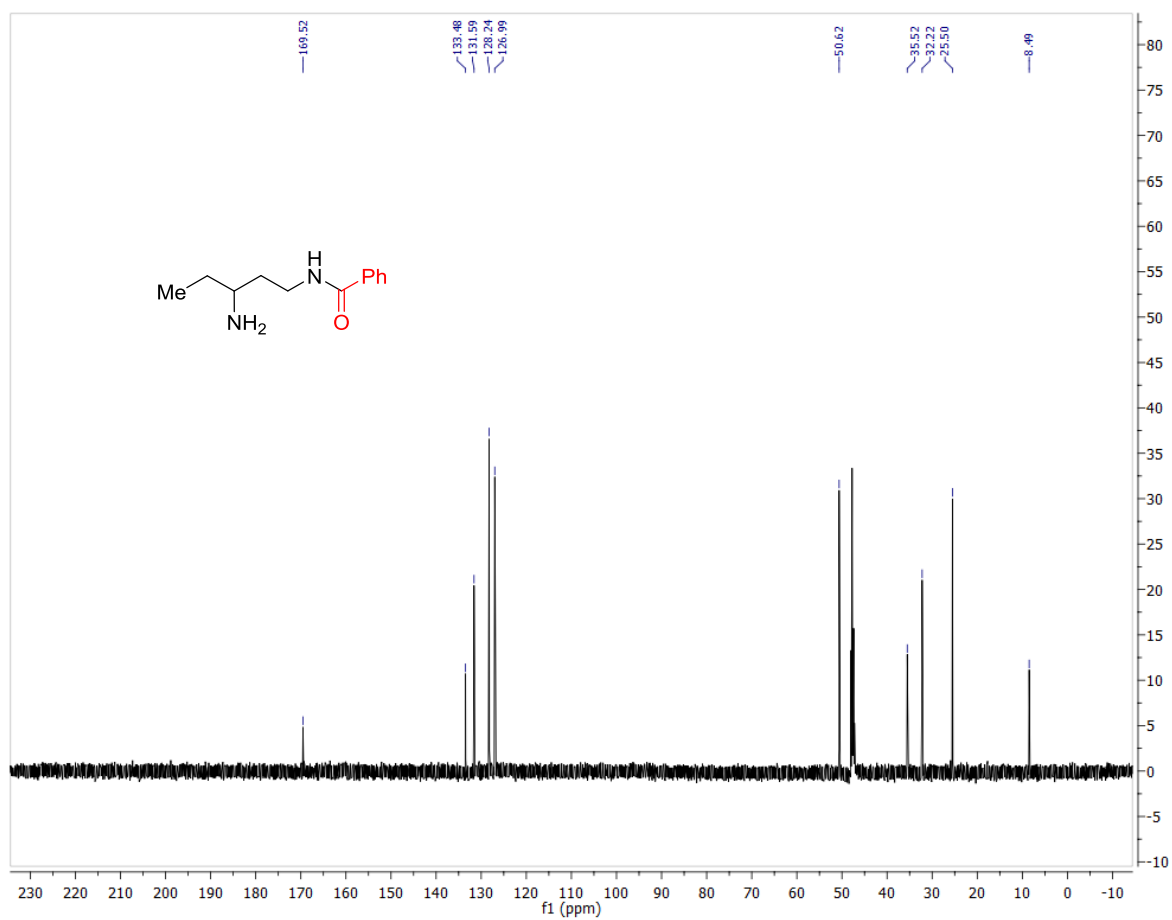
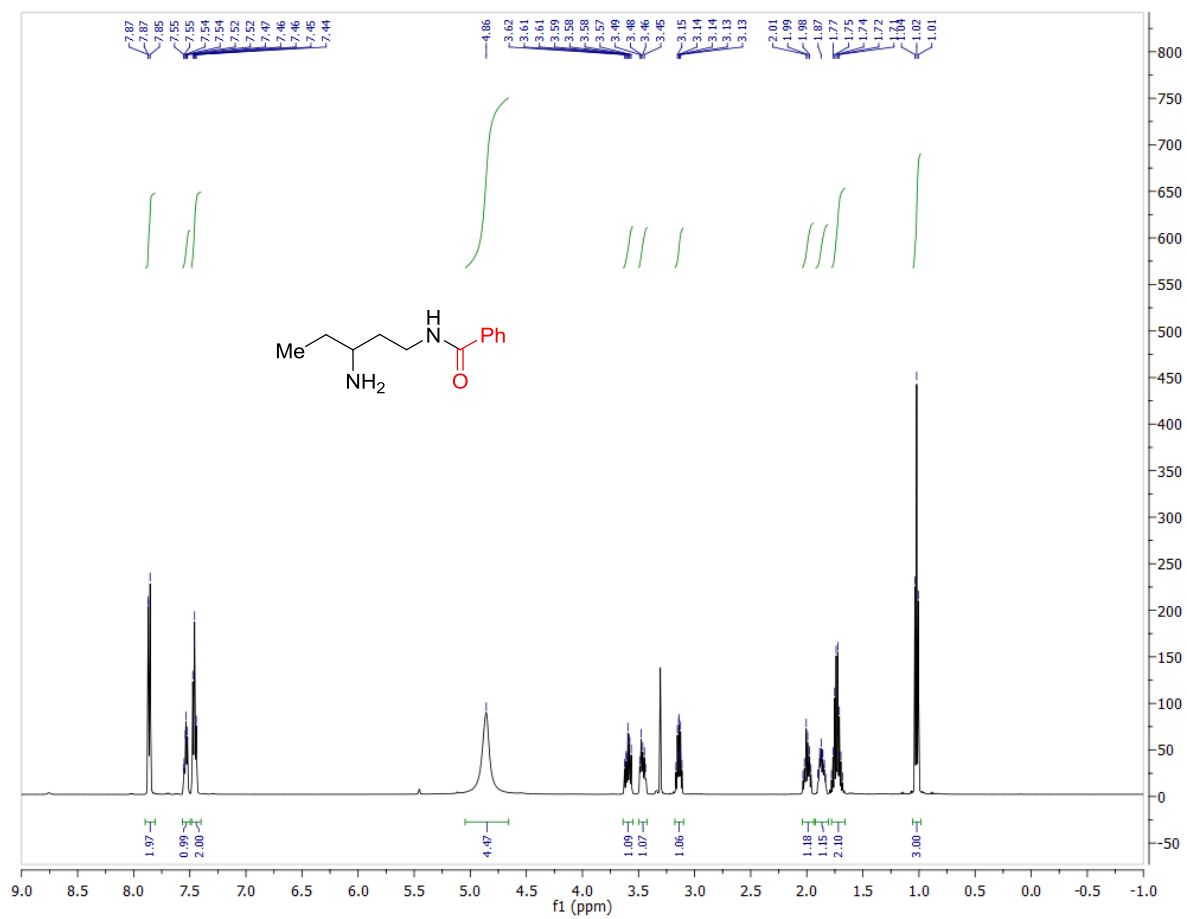


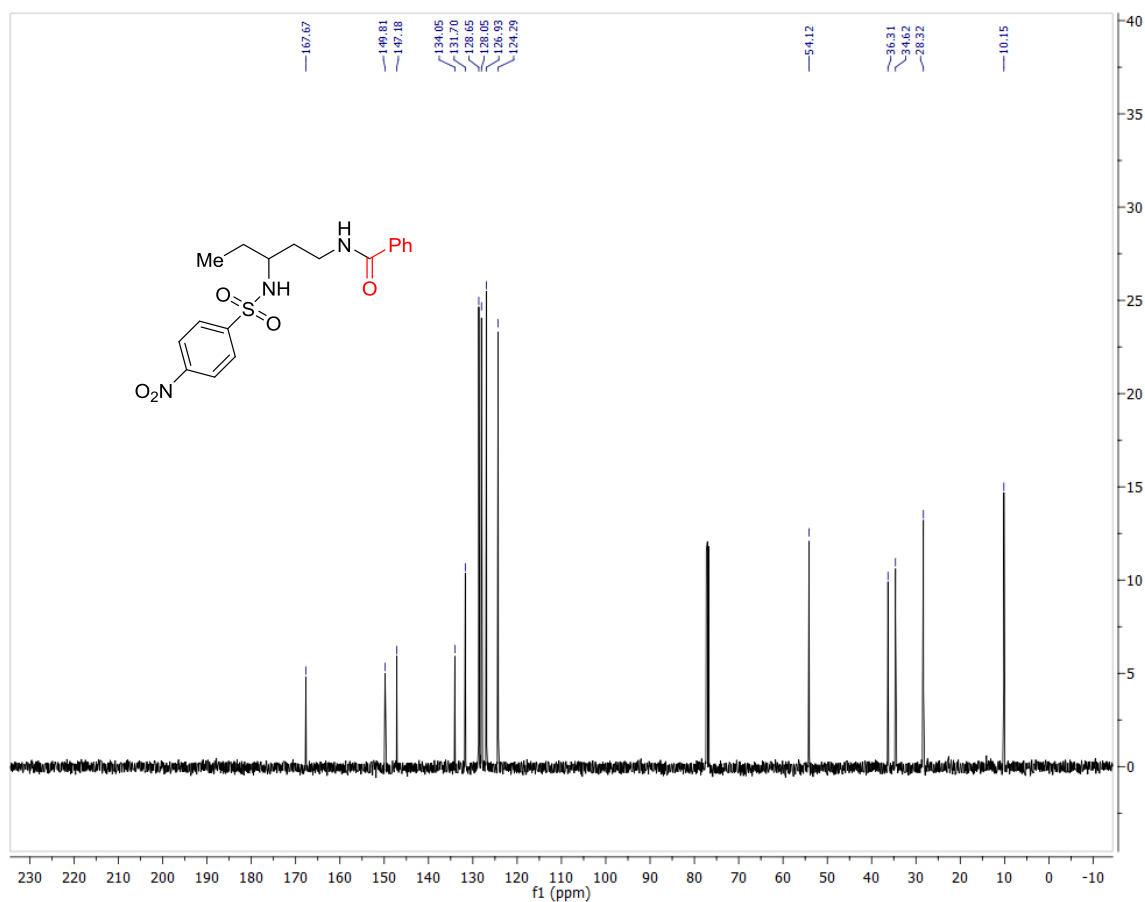
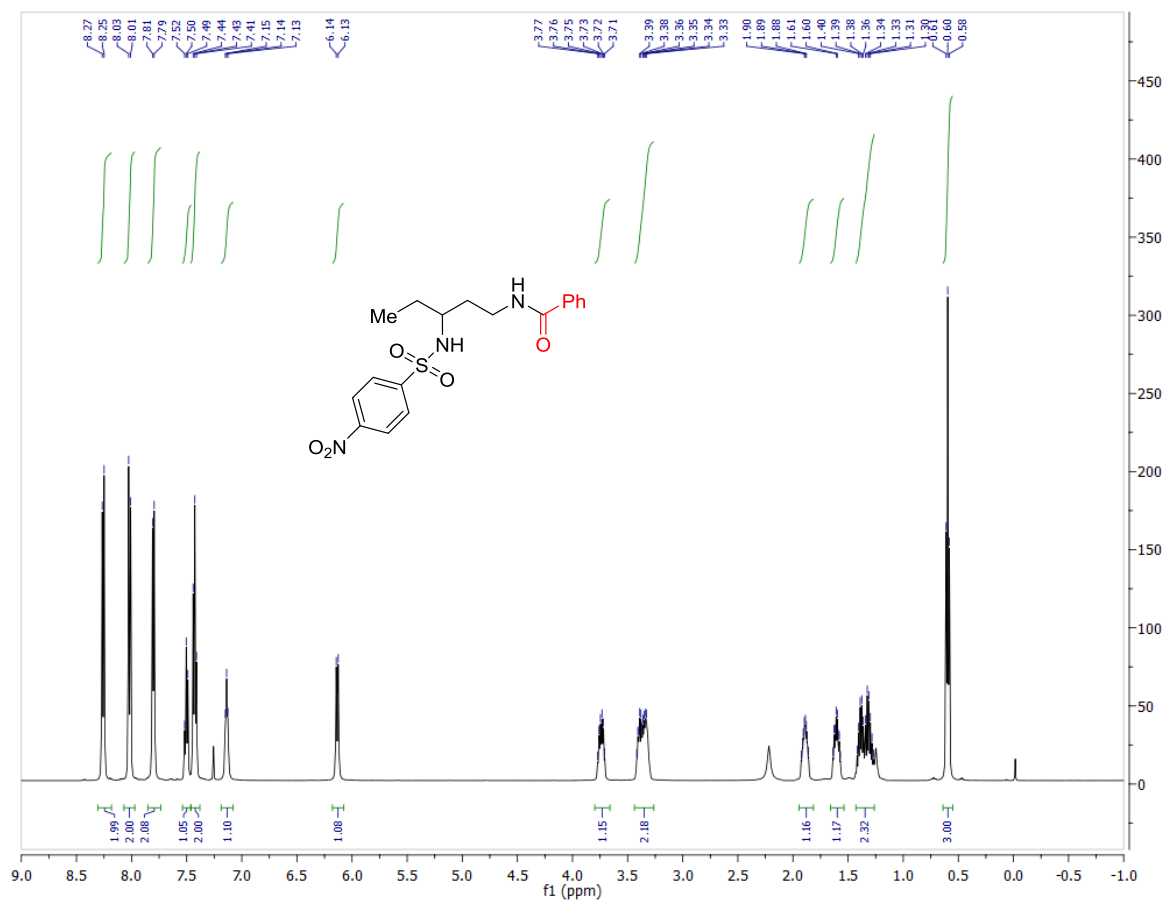


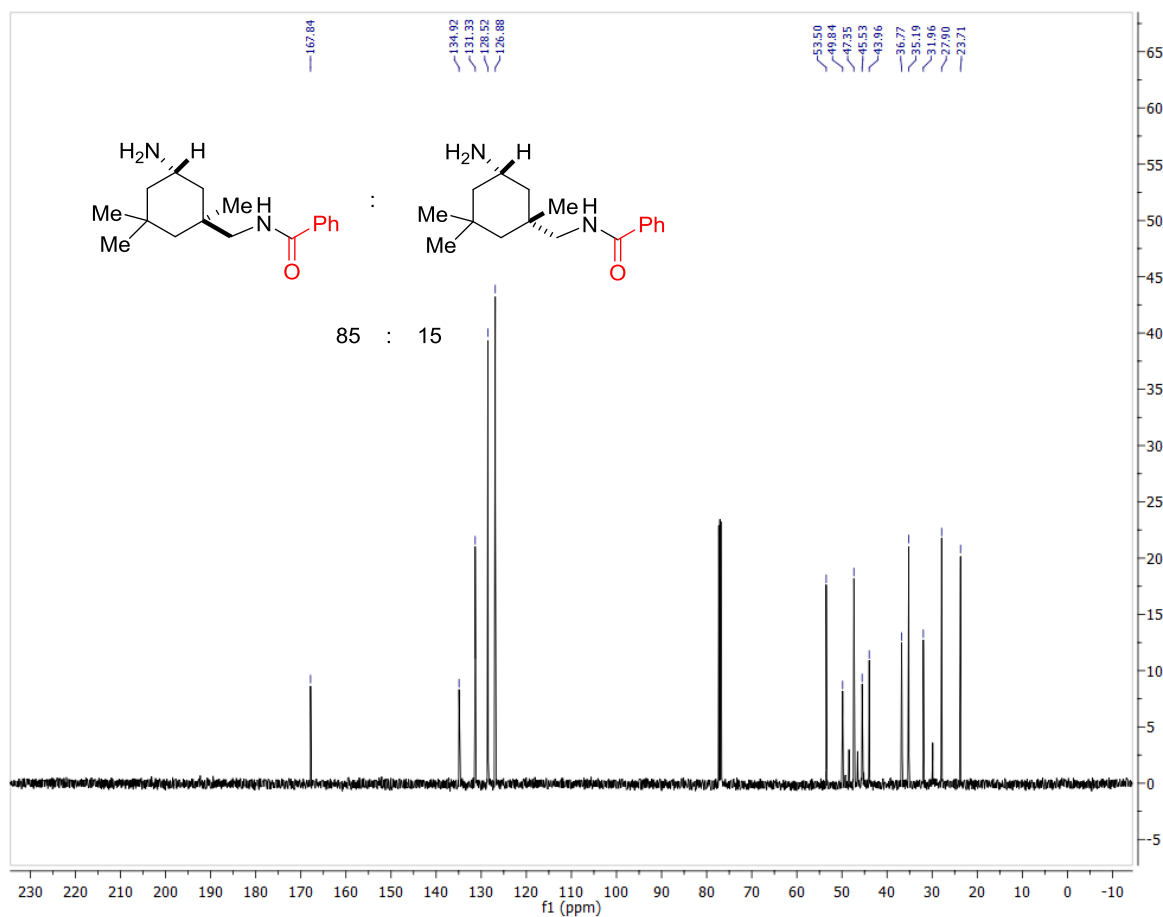
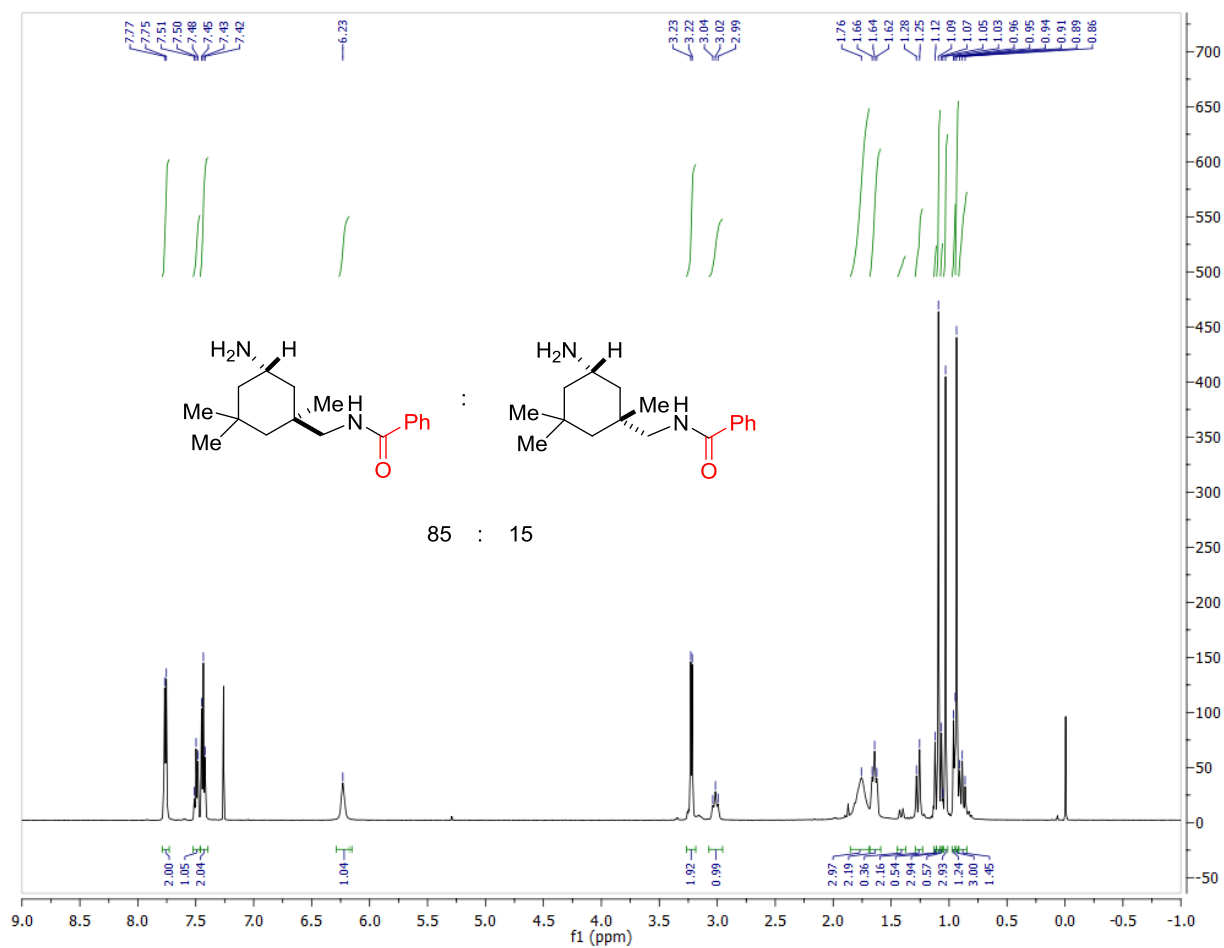


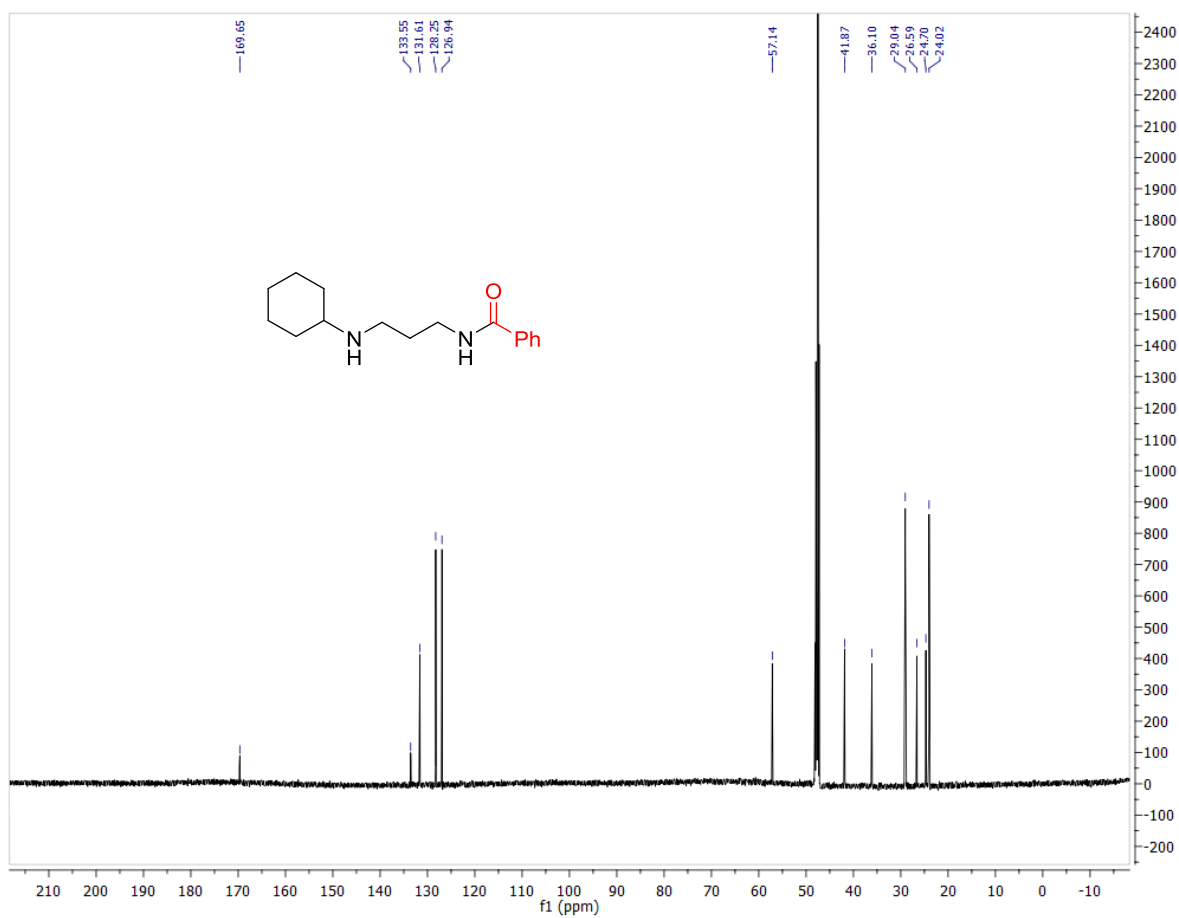
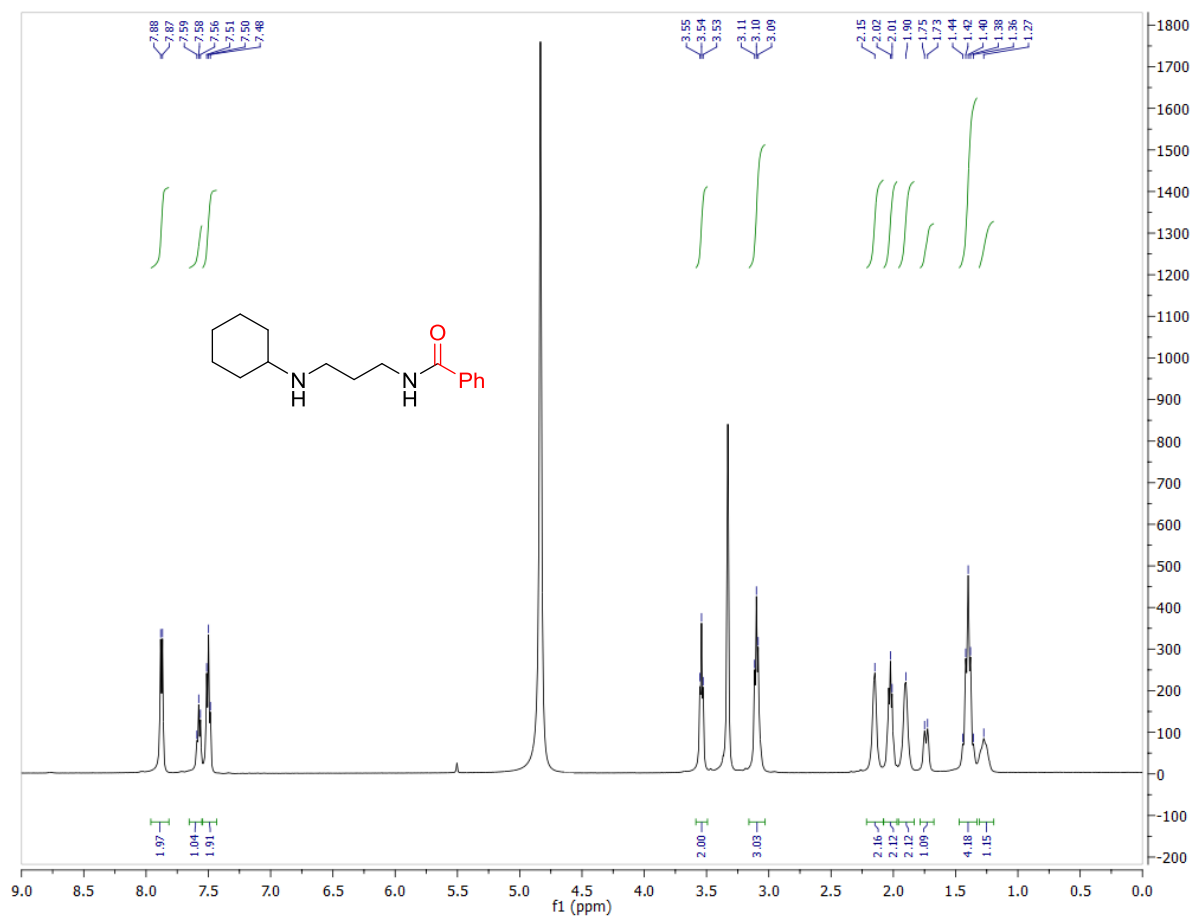


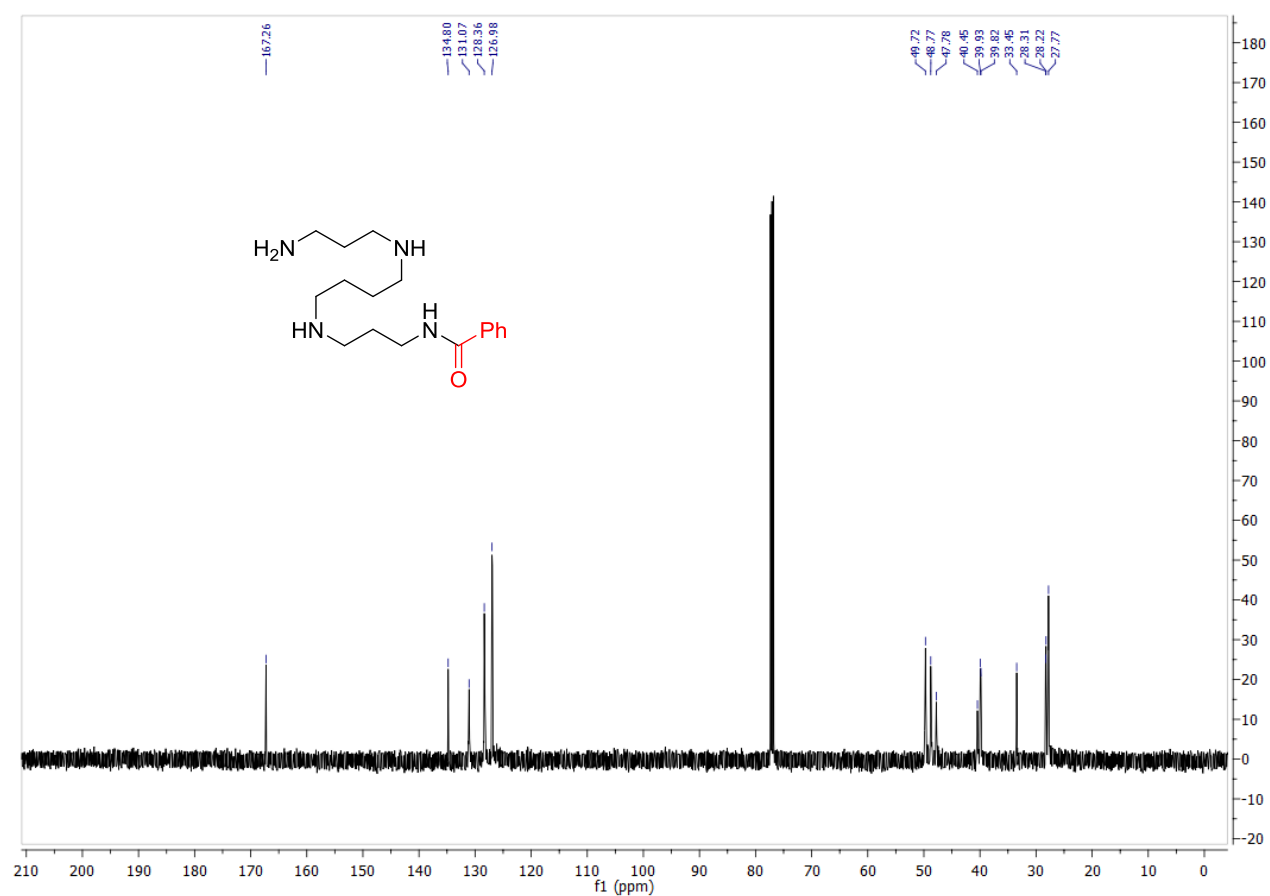
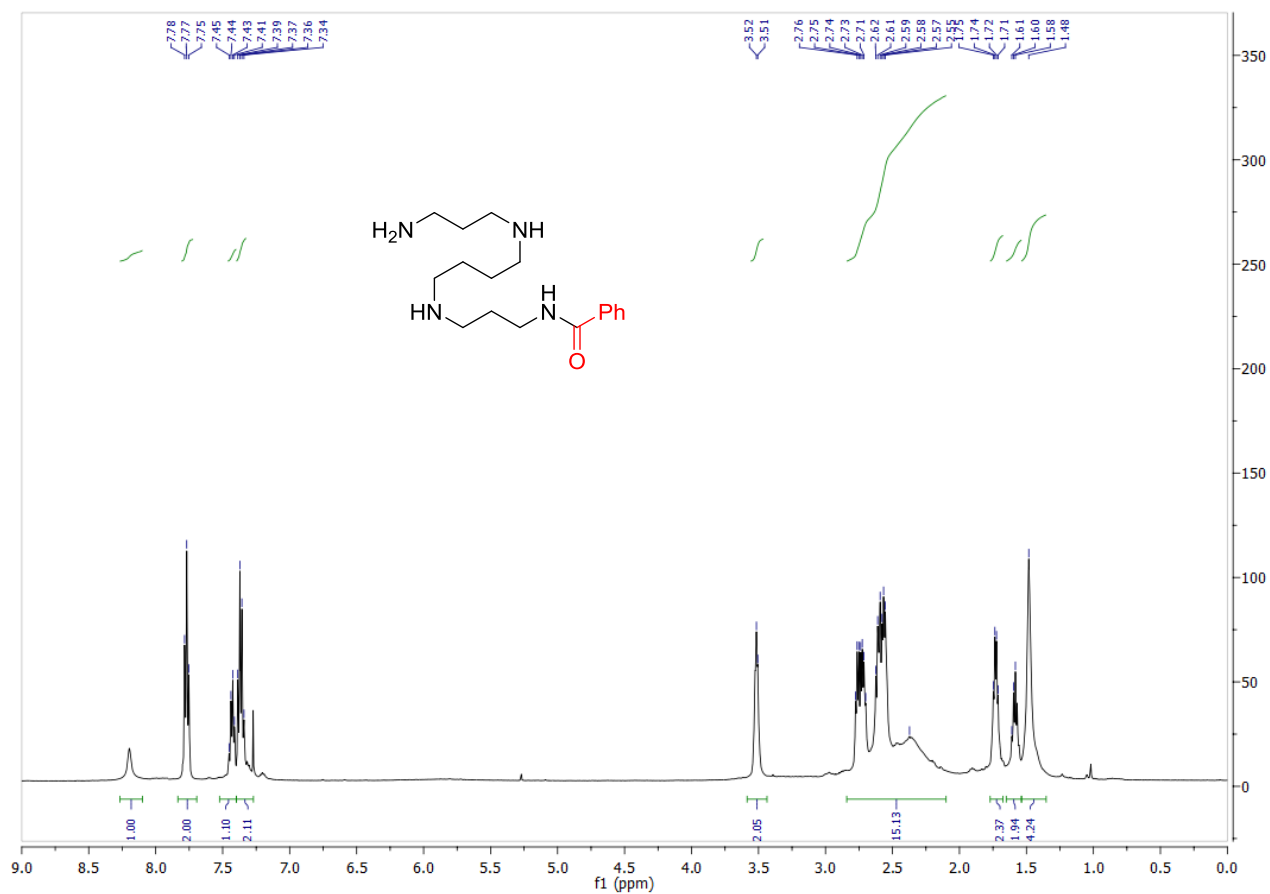


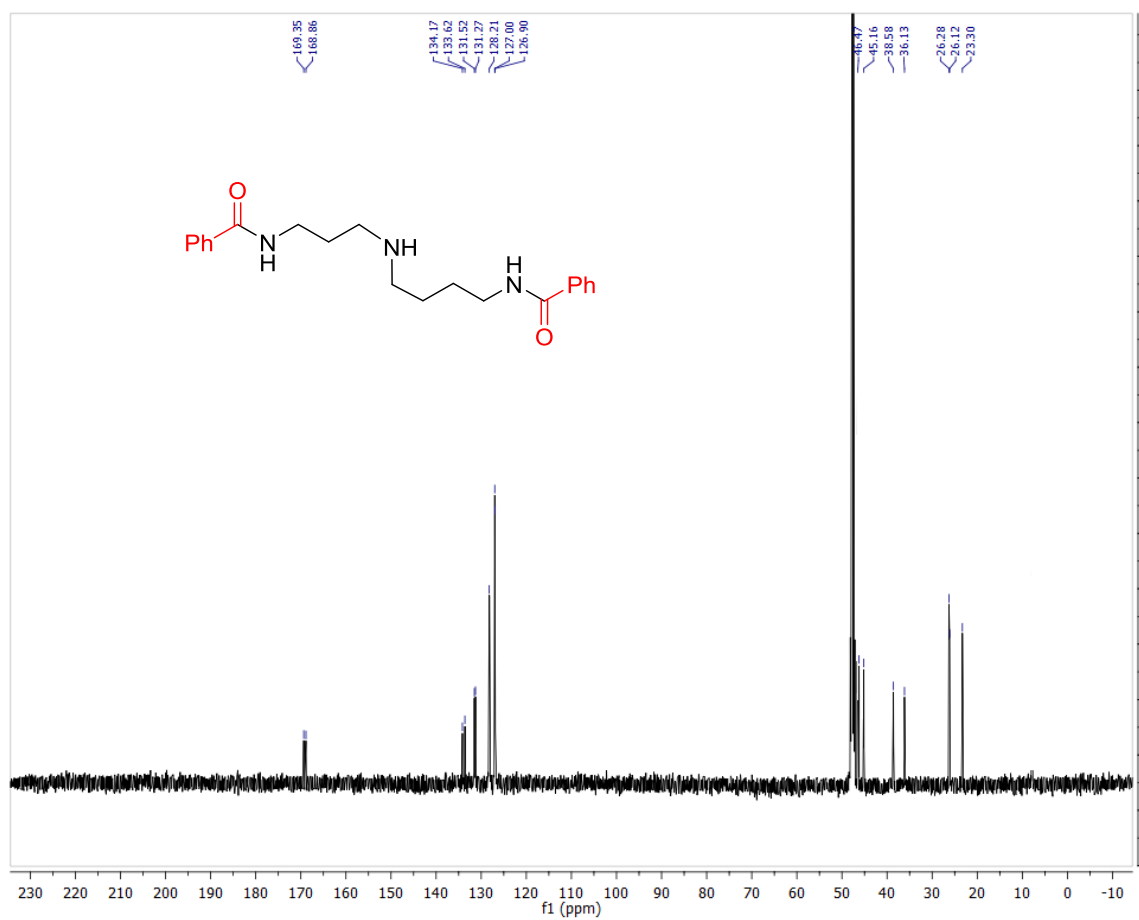
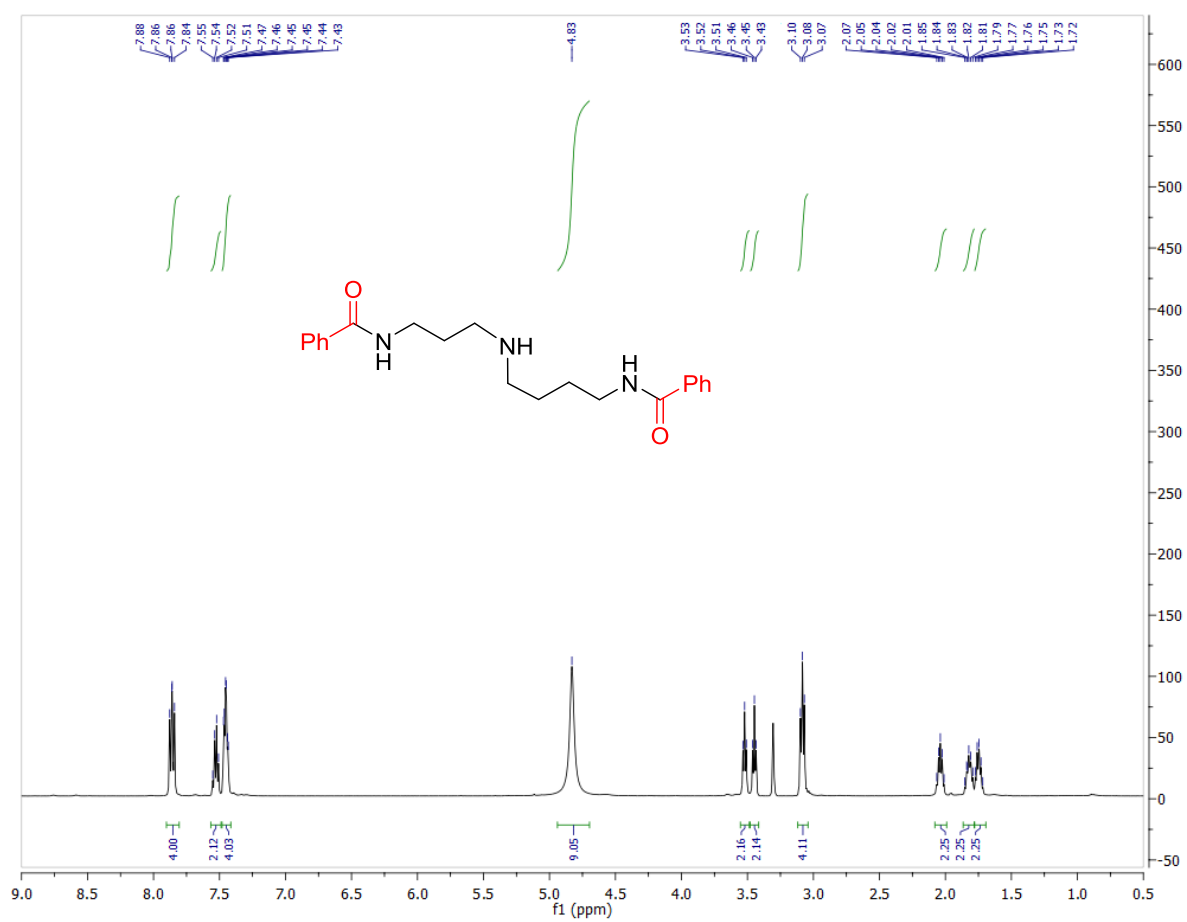


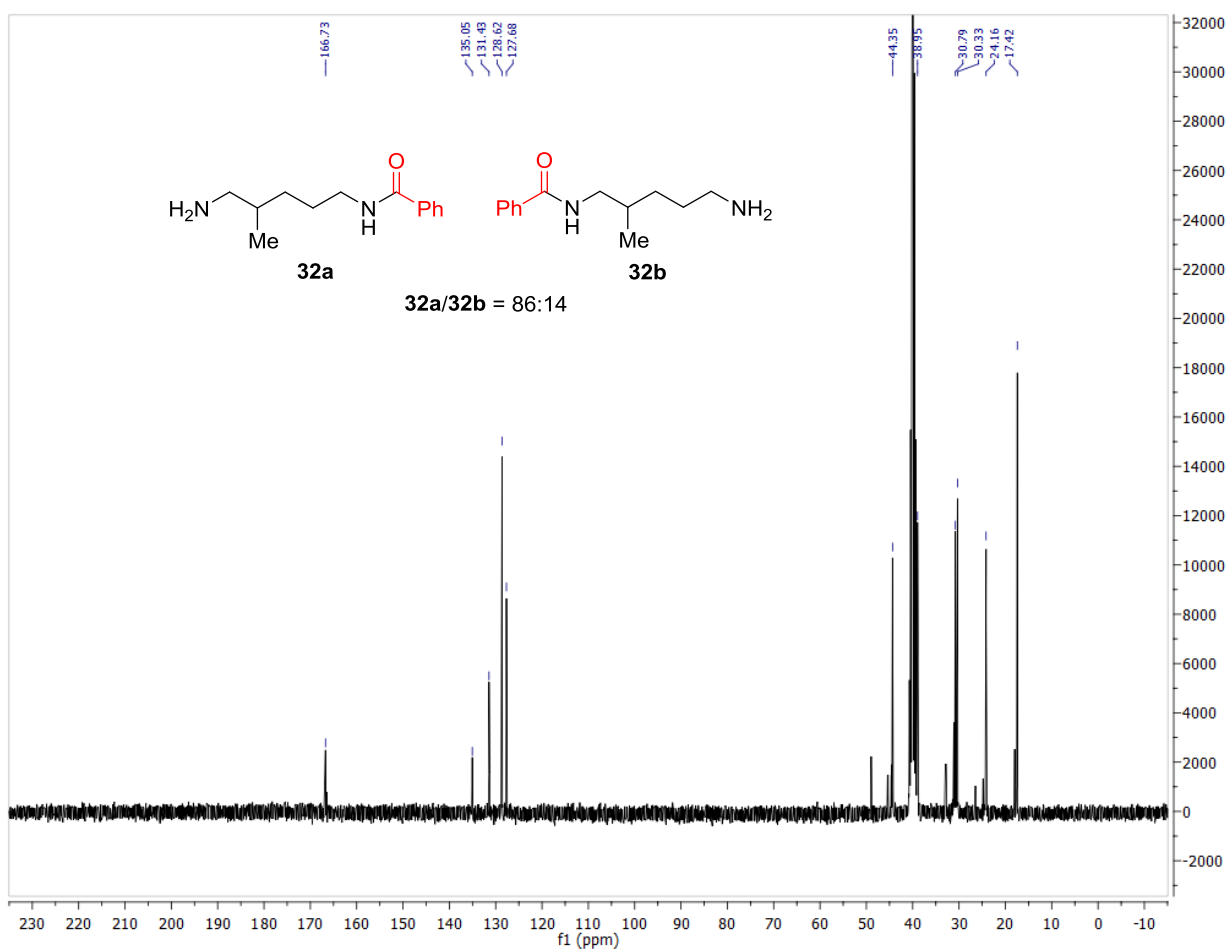
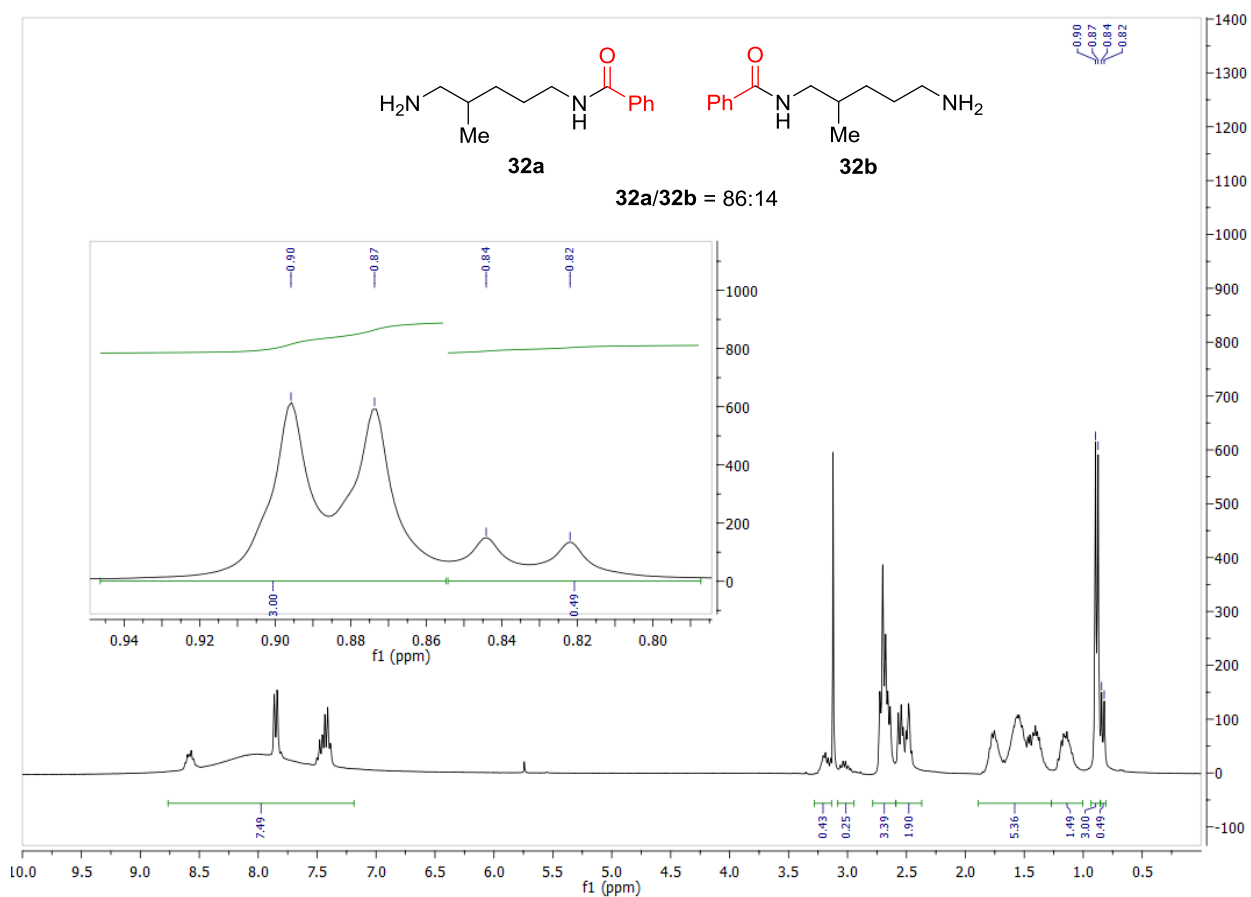




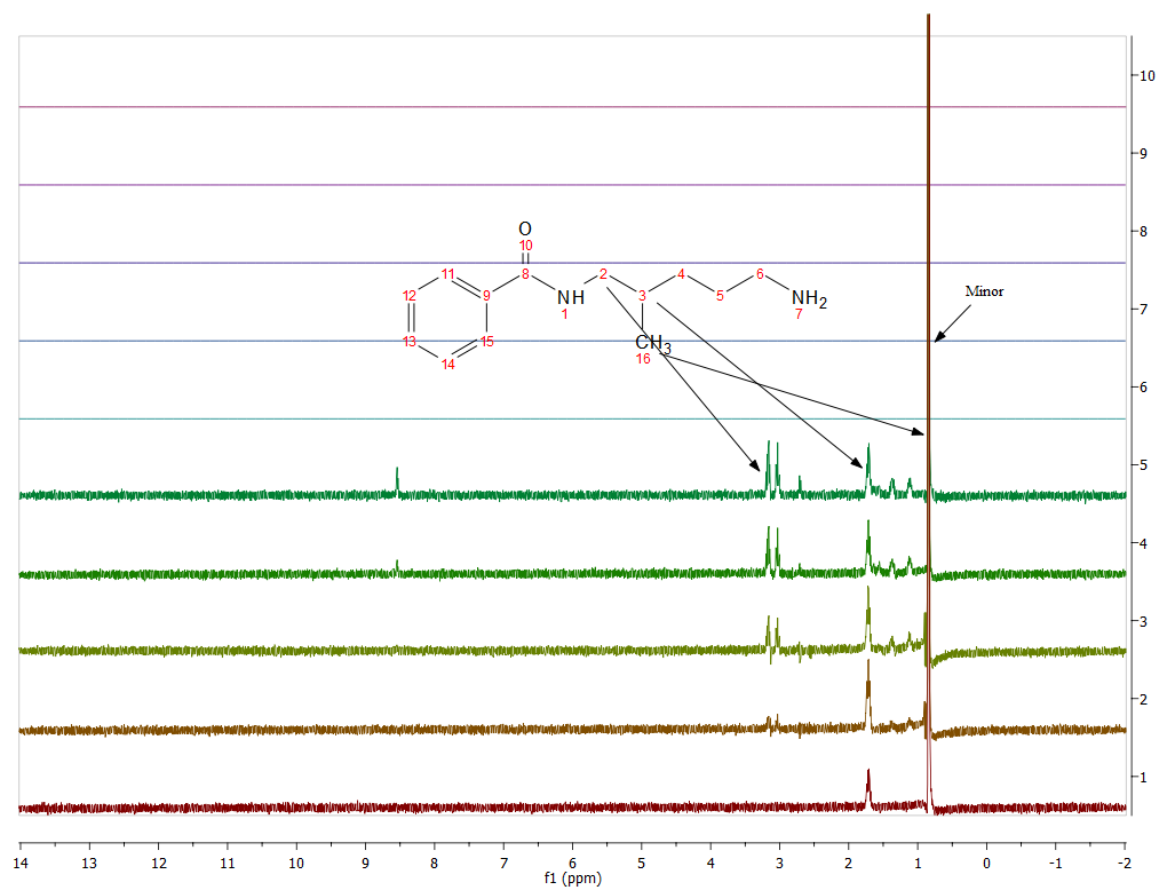
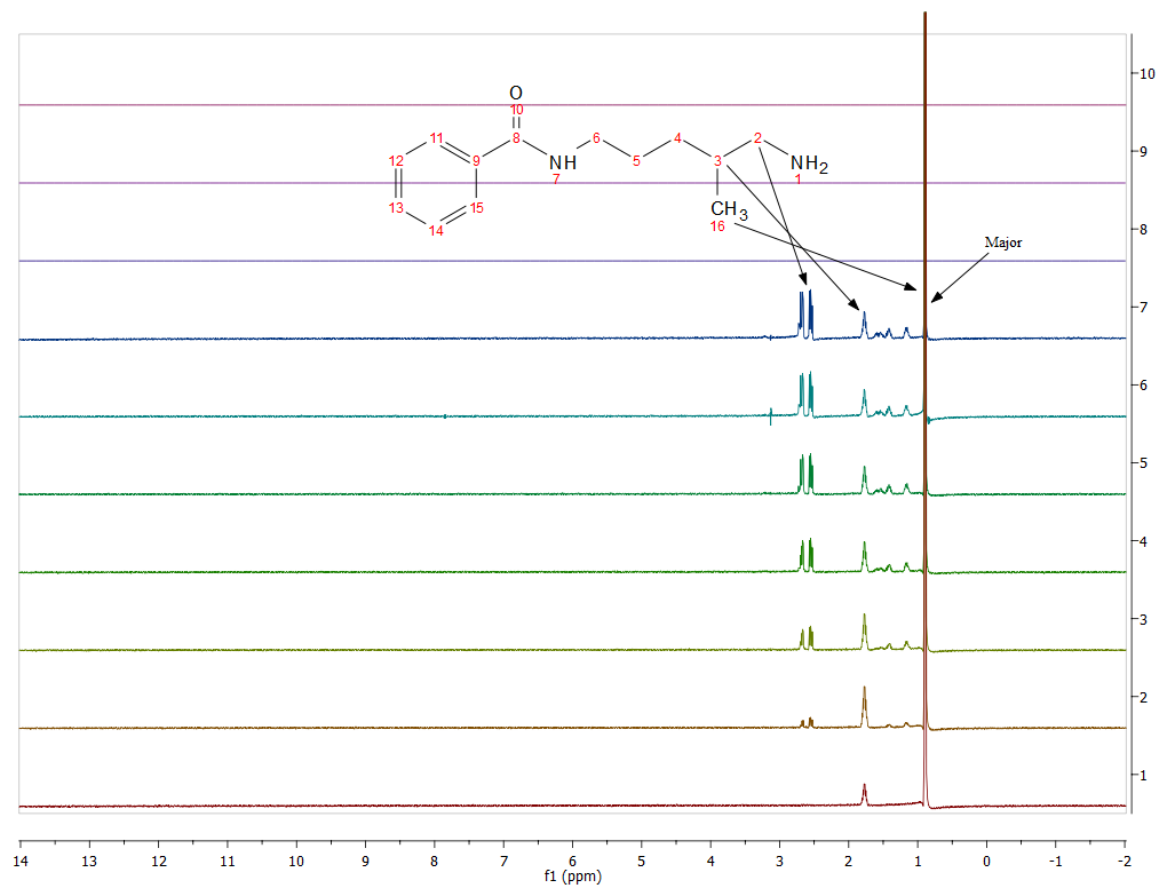


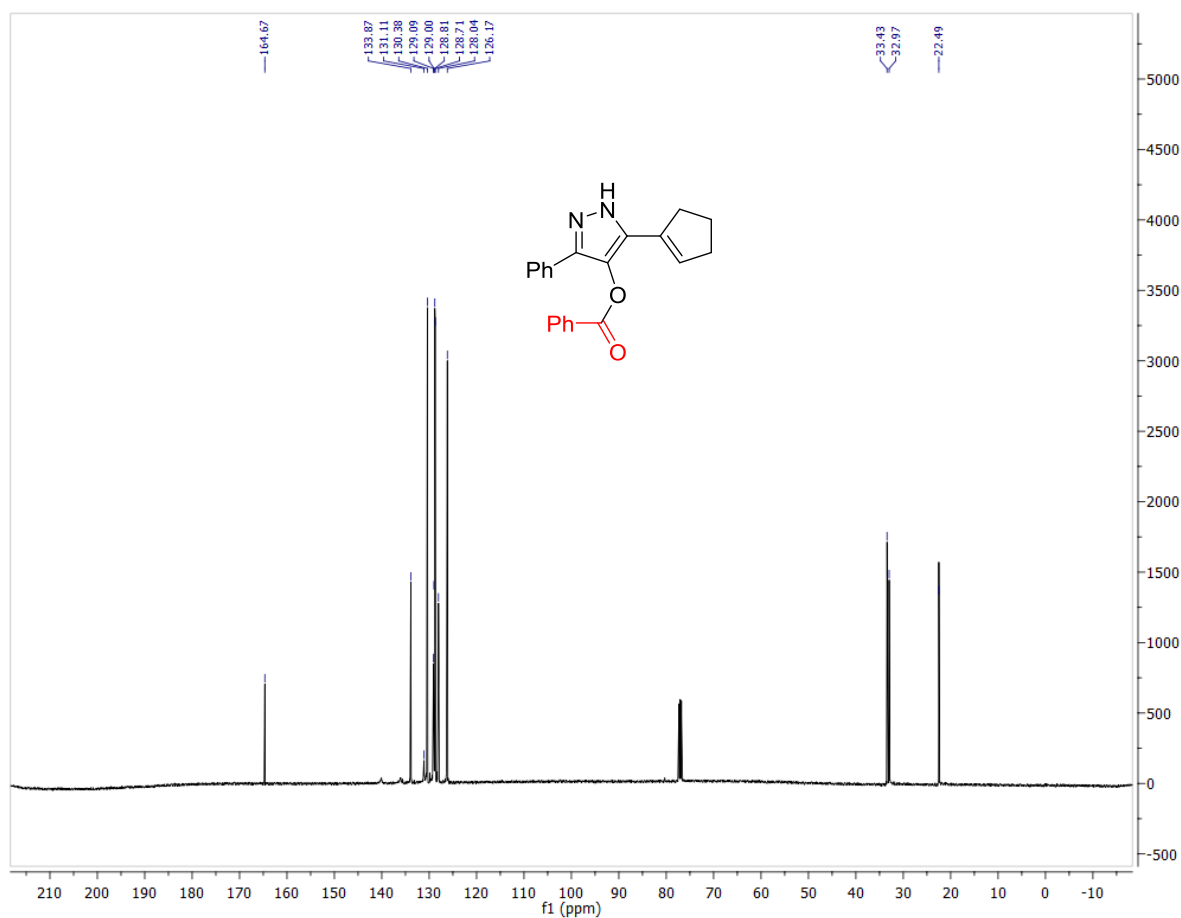
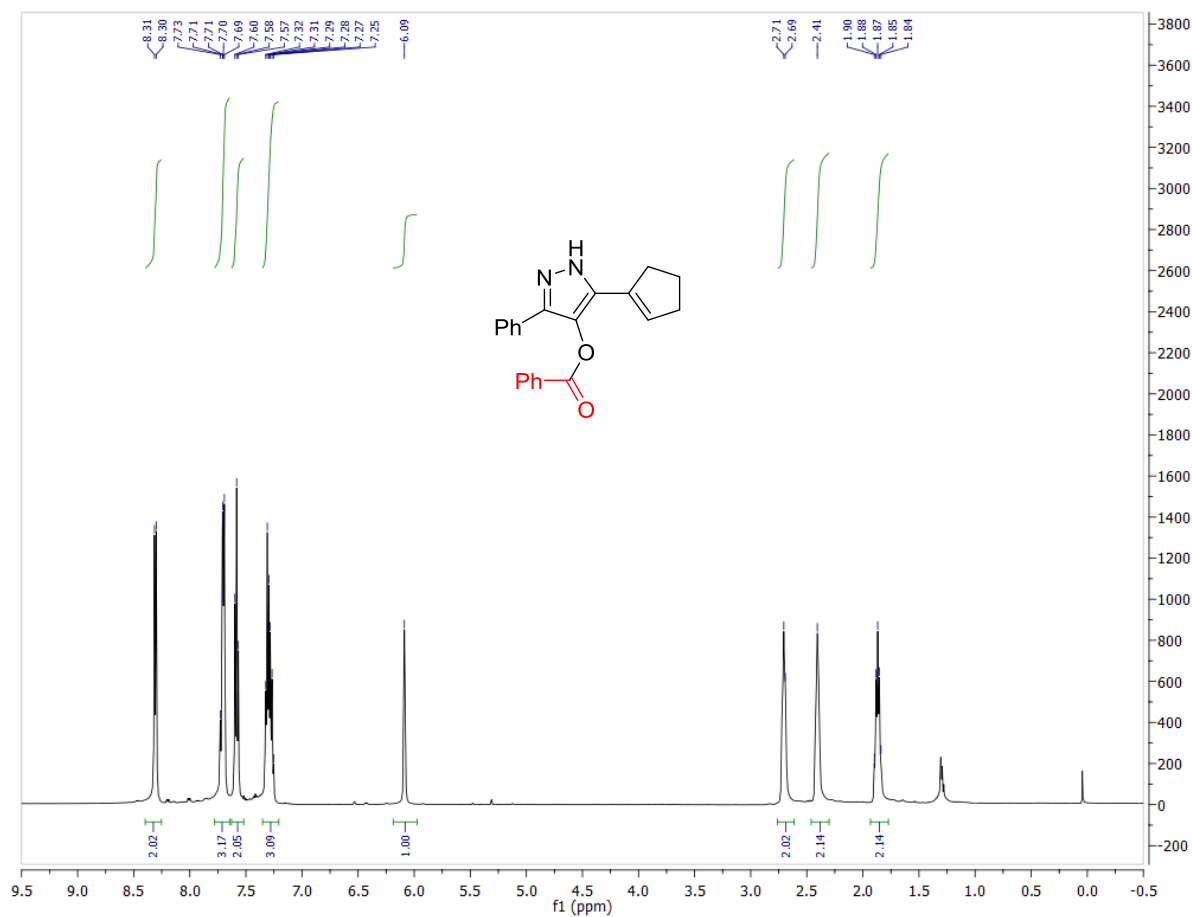


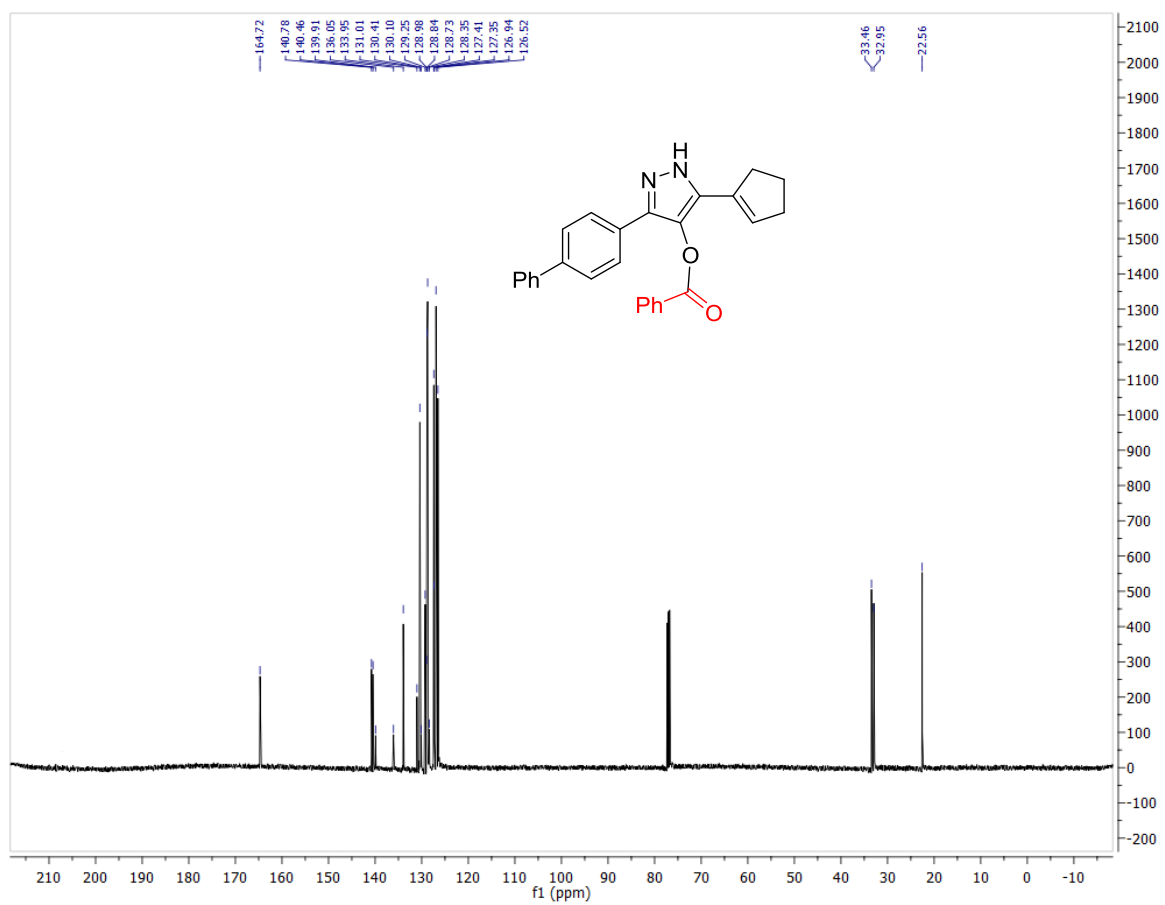
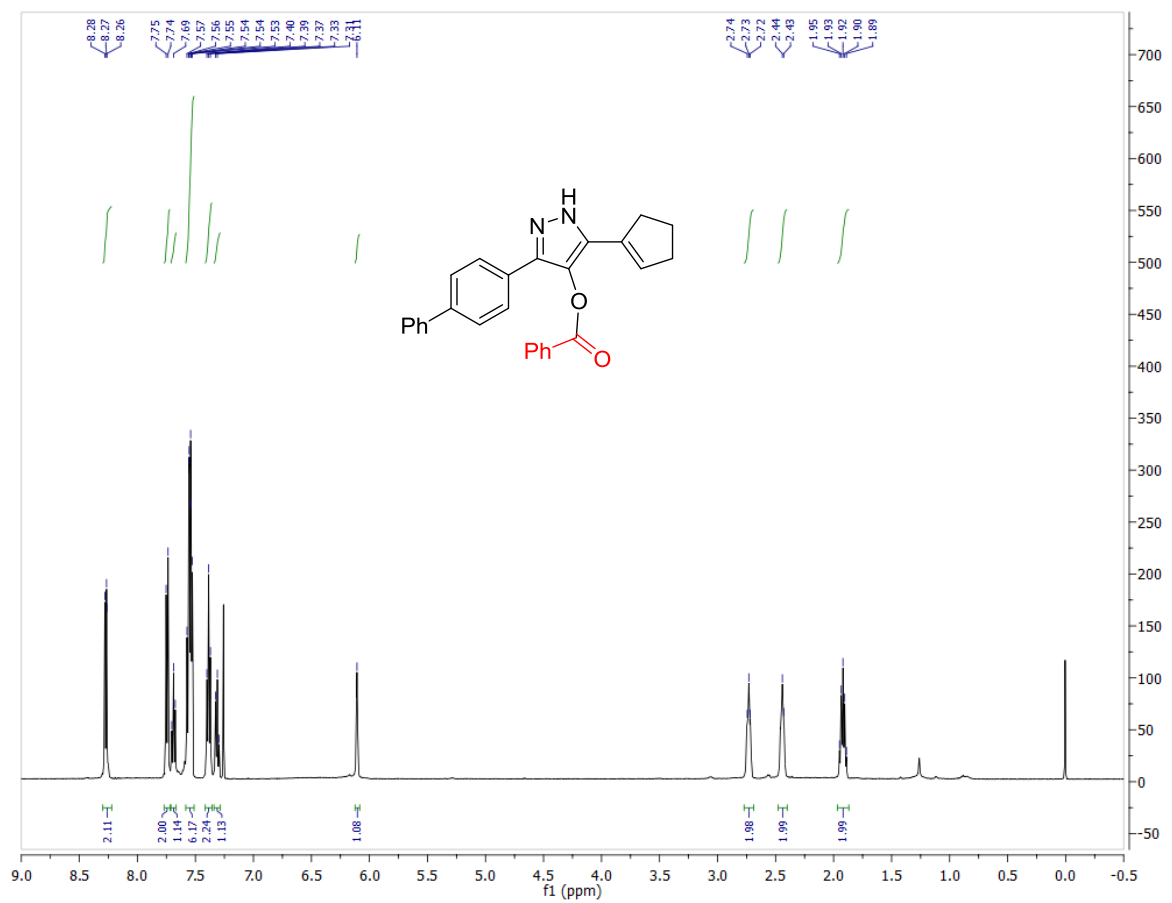


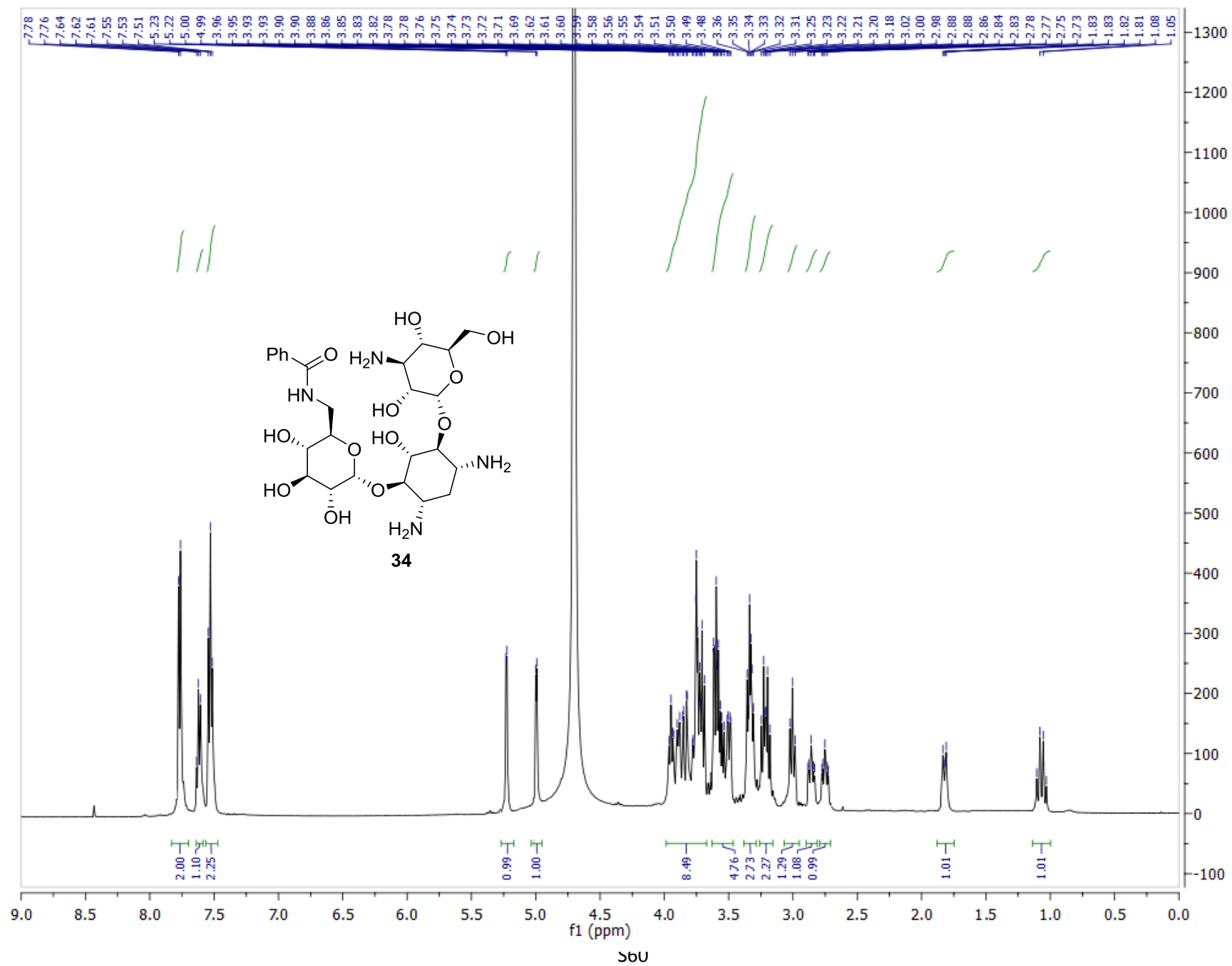


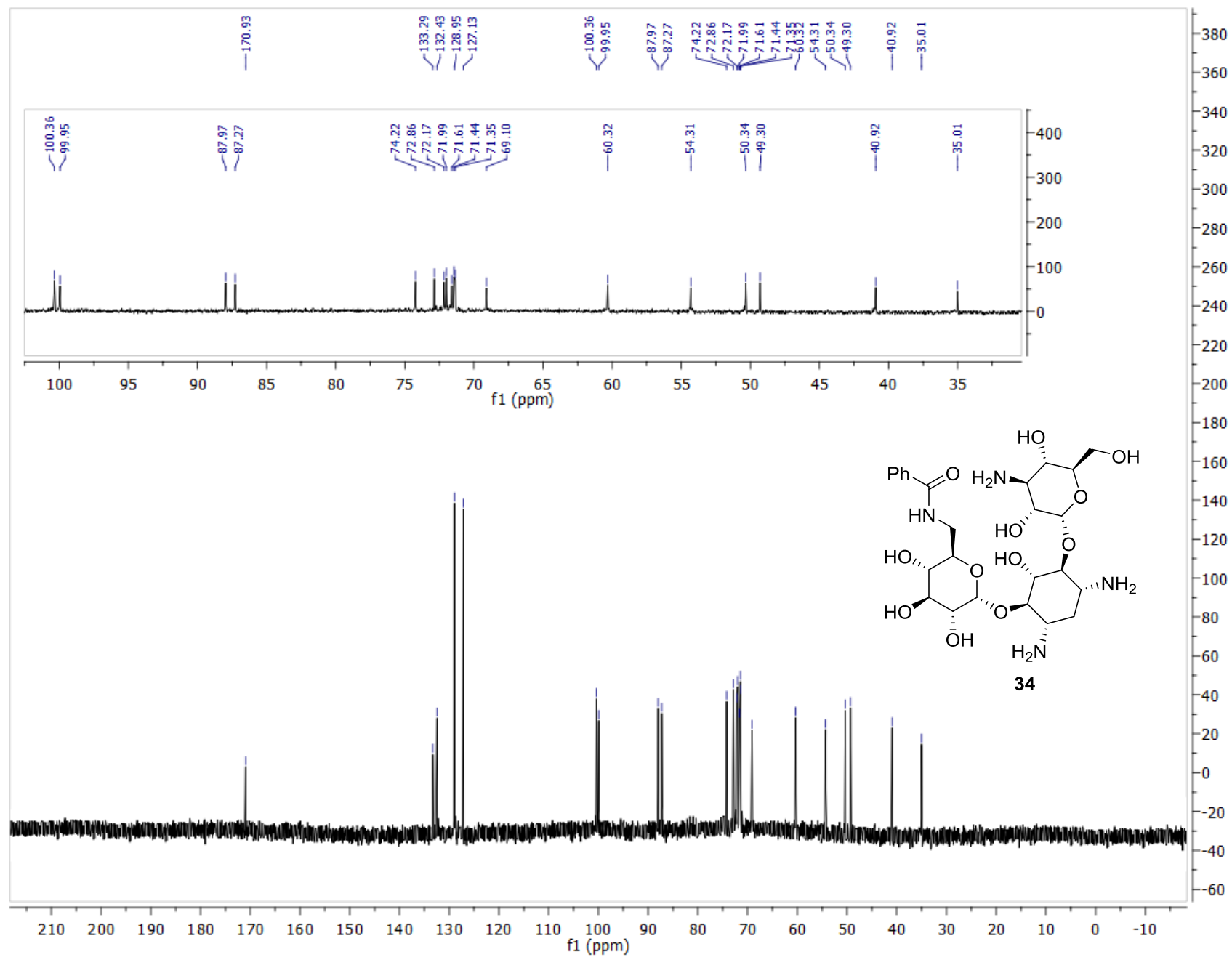
Selective 1D TOCSY ^1H NMR experiment for the mixture of **32a** and **32b**:



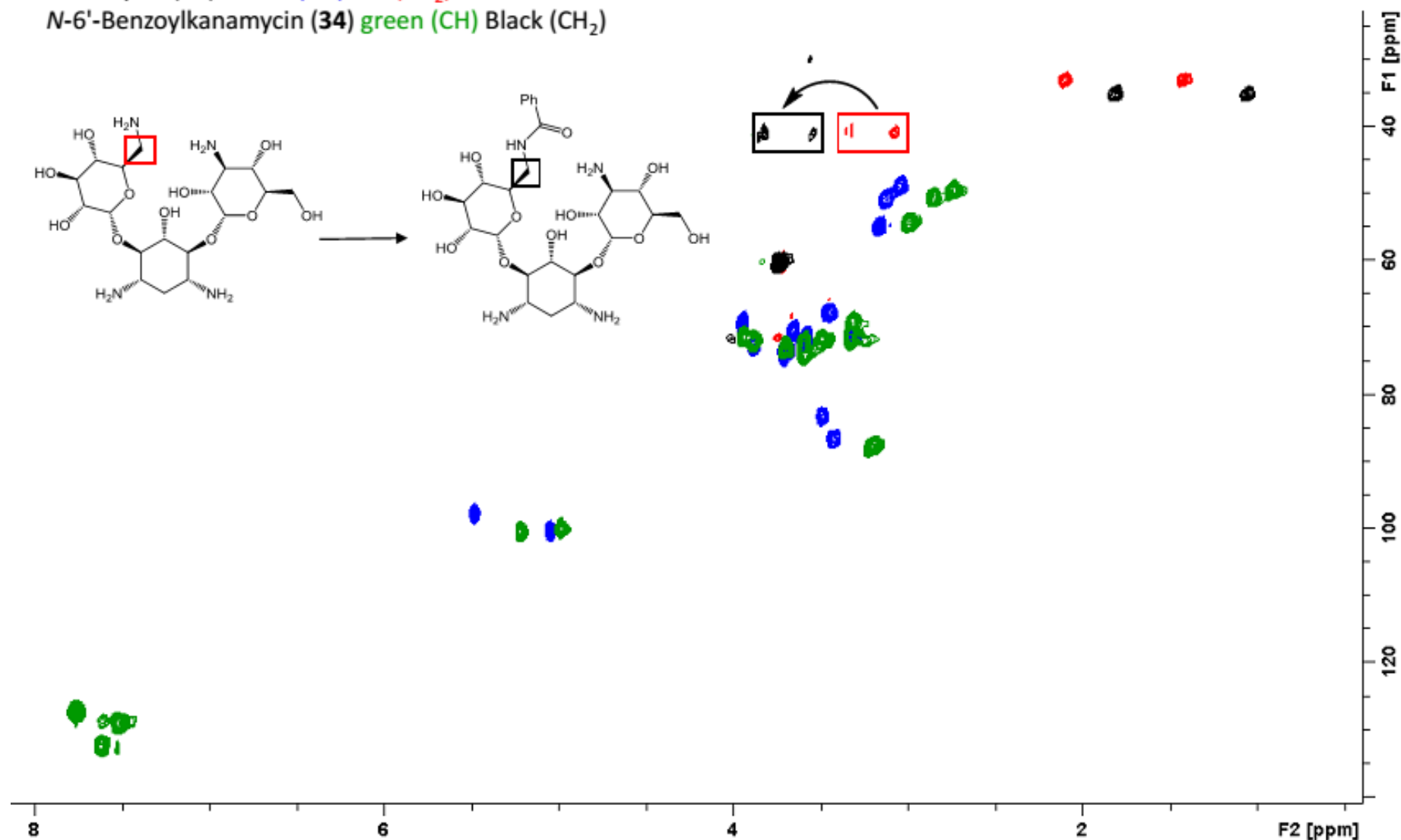




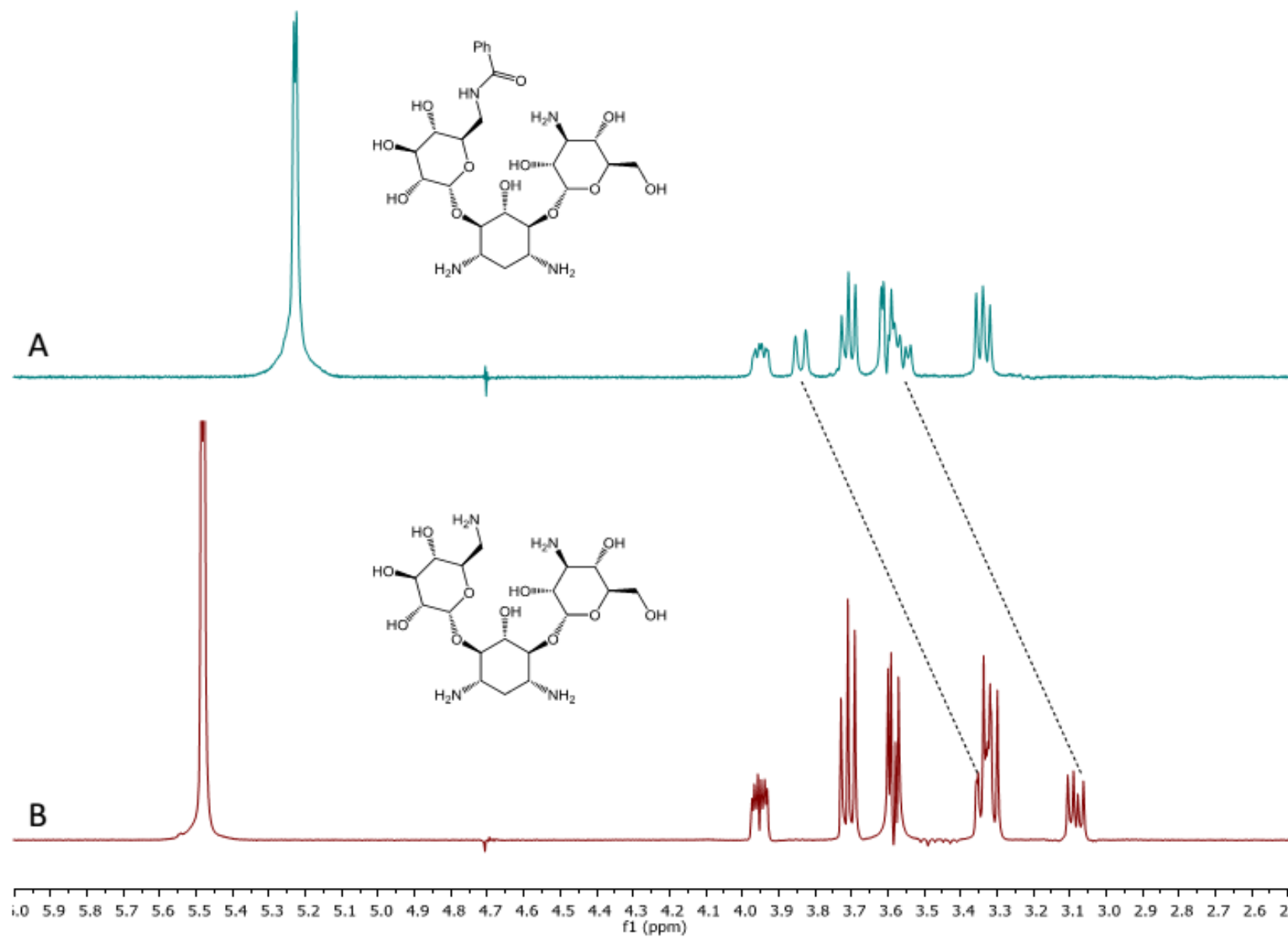




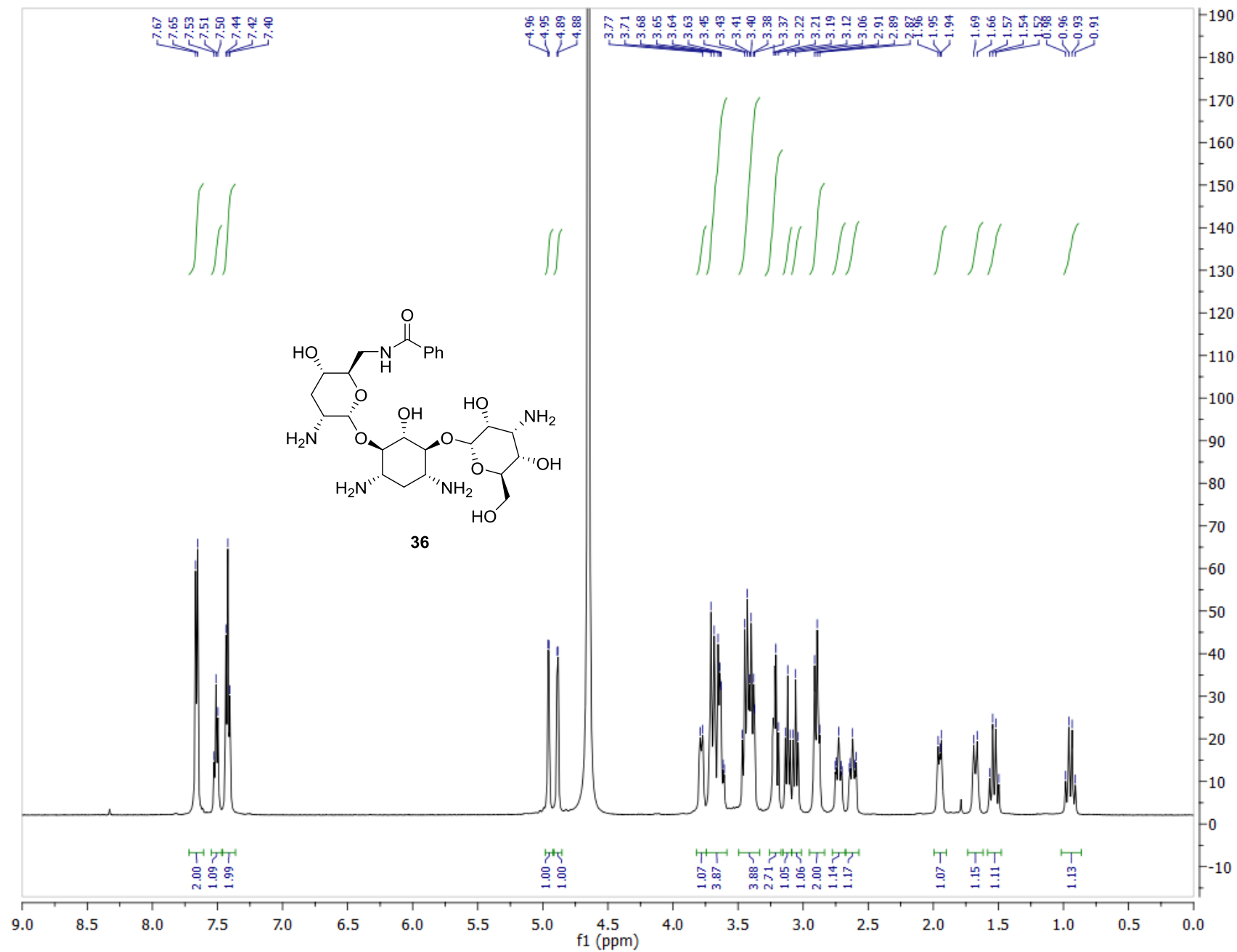
Kanamycin (**33**) – blue (CH) red (CH₂)
N-6'-Benzoylkanamycin (**34**) green (CH) Black (CH₂)

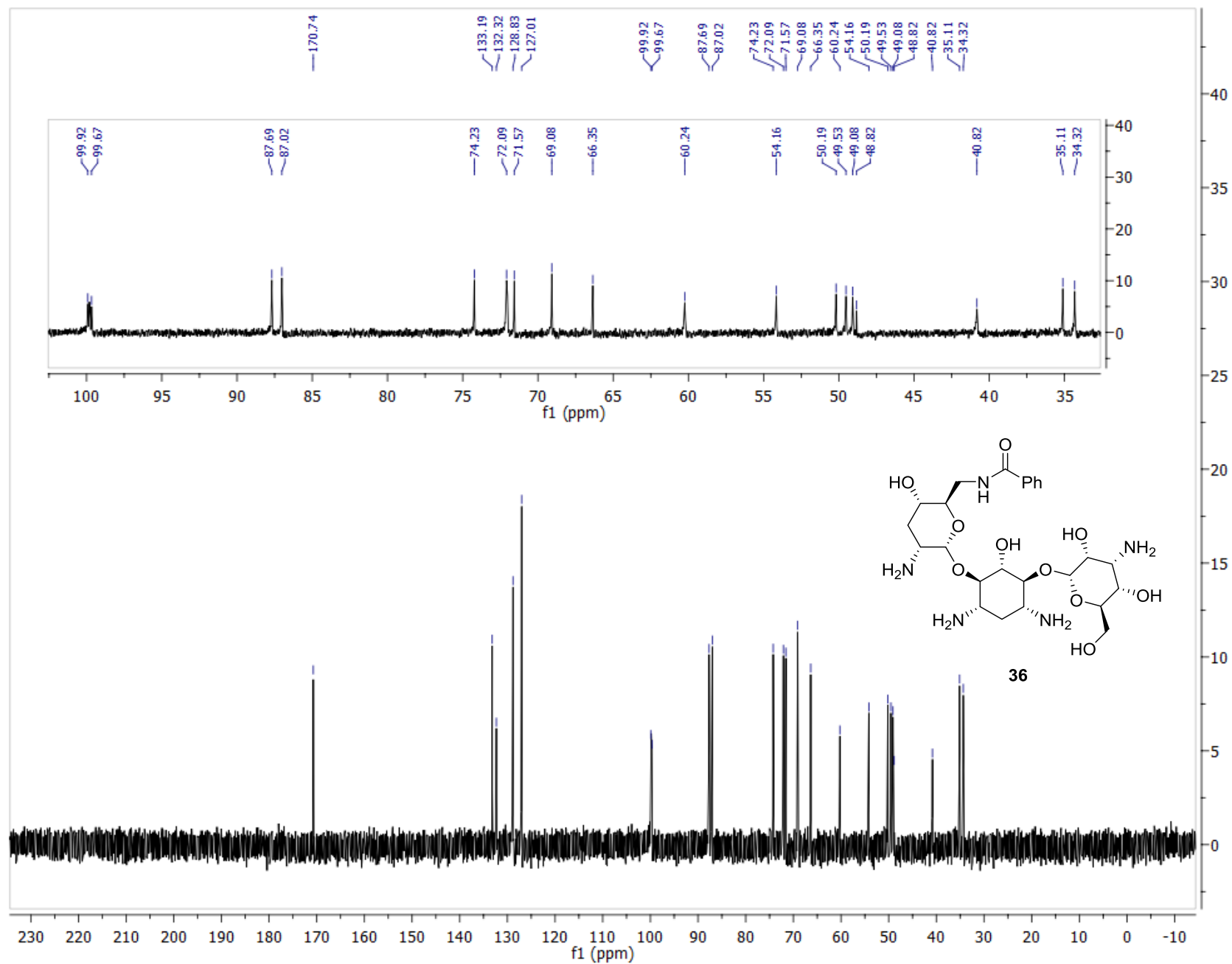


Overlay of the HSQC spectra of kanamycin (**33**) (CH blue, CH₂ red) and *N*-6'-Benzoylkanamycin (**34**) (CH green, CH₂ black). The methylene in the red box are the only peaks to shift down-field due to the anisotropy of the carbonyl of the benzoyl group.

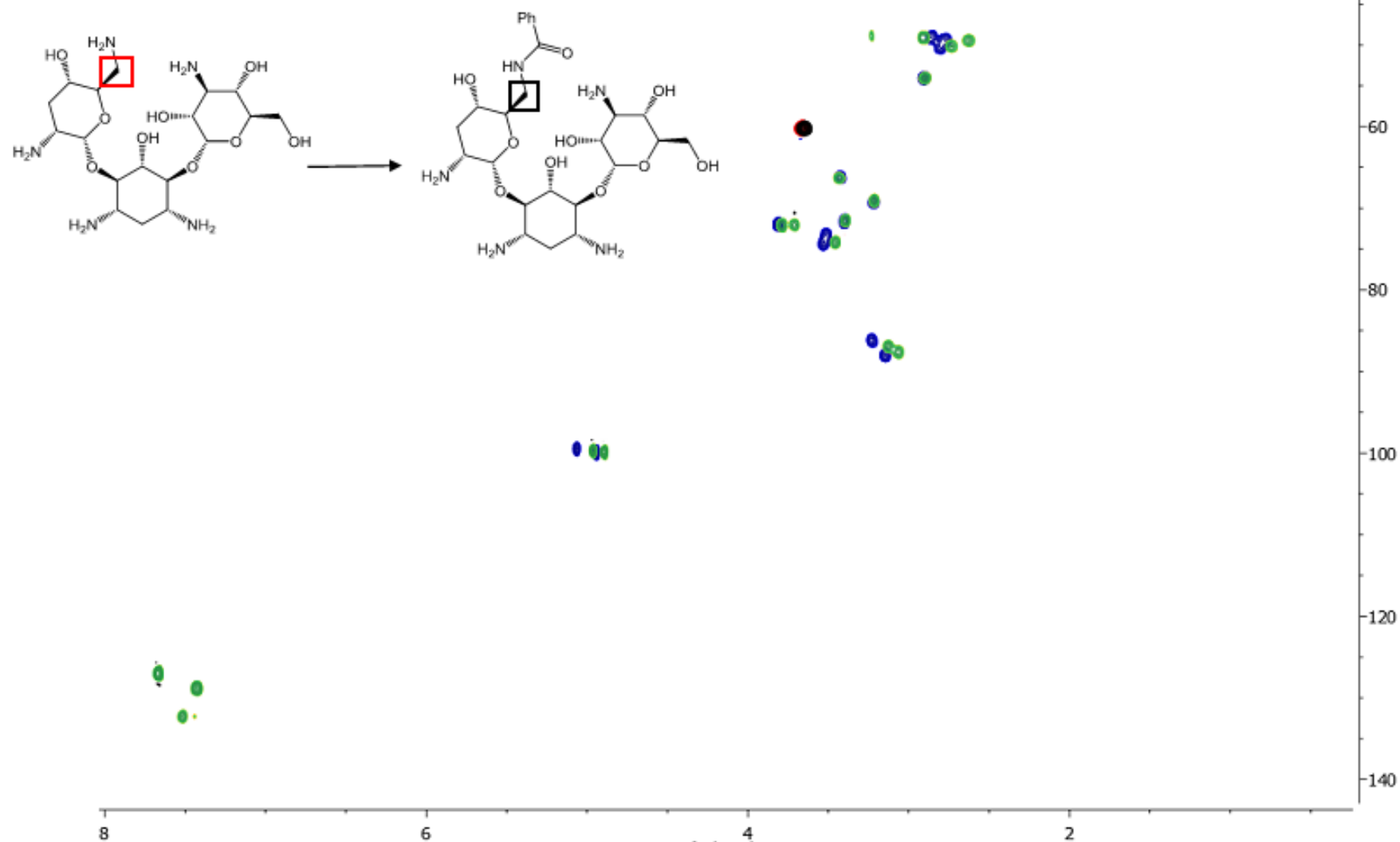


Selective 1D TOCSY spectra of (A) *N*-6'-Benzoylkanamycin (**34**) and (B) Kanamycin (**33**). Dotted lines show the large downfield shift of the benzoylated methylene.

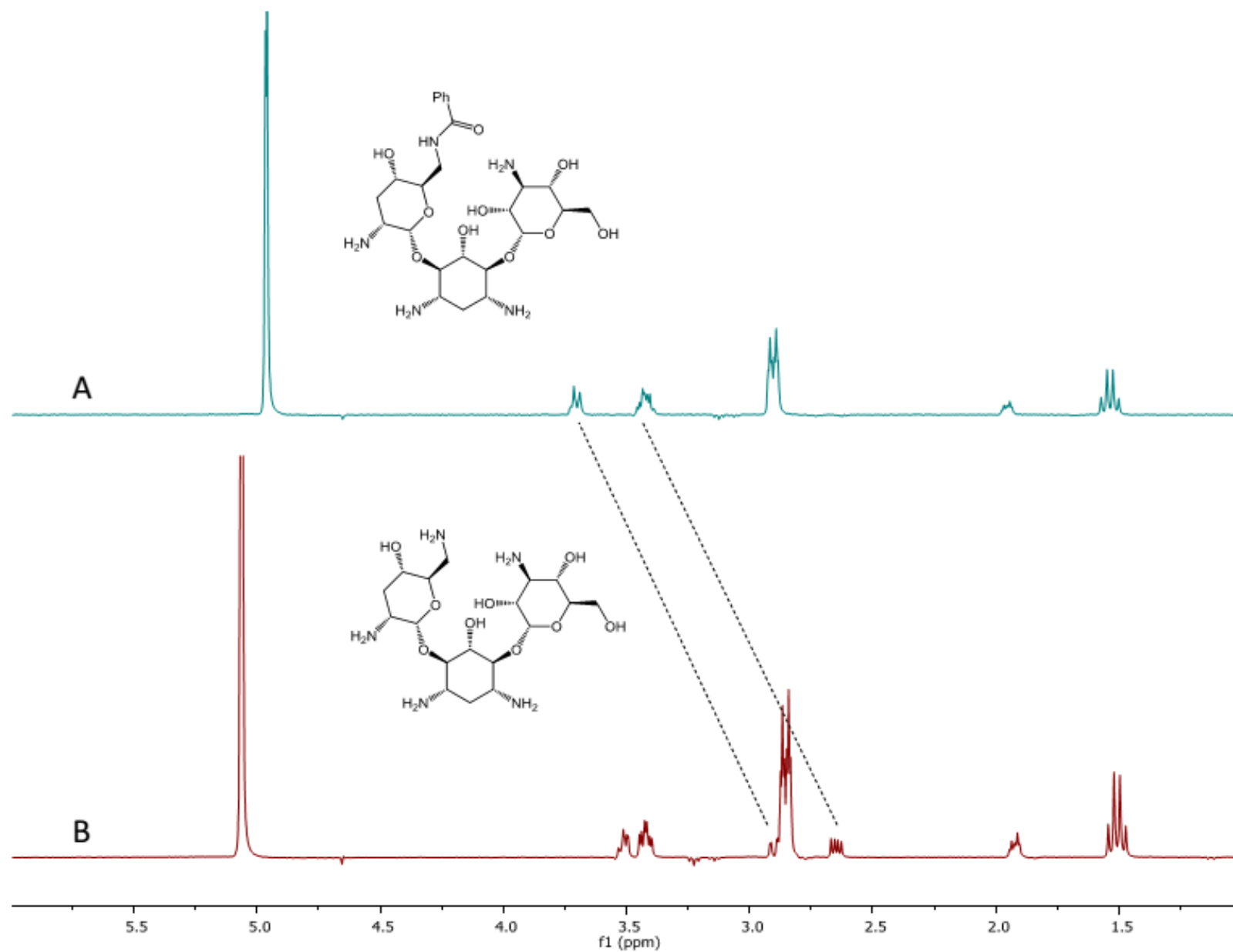




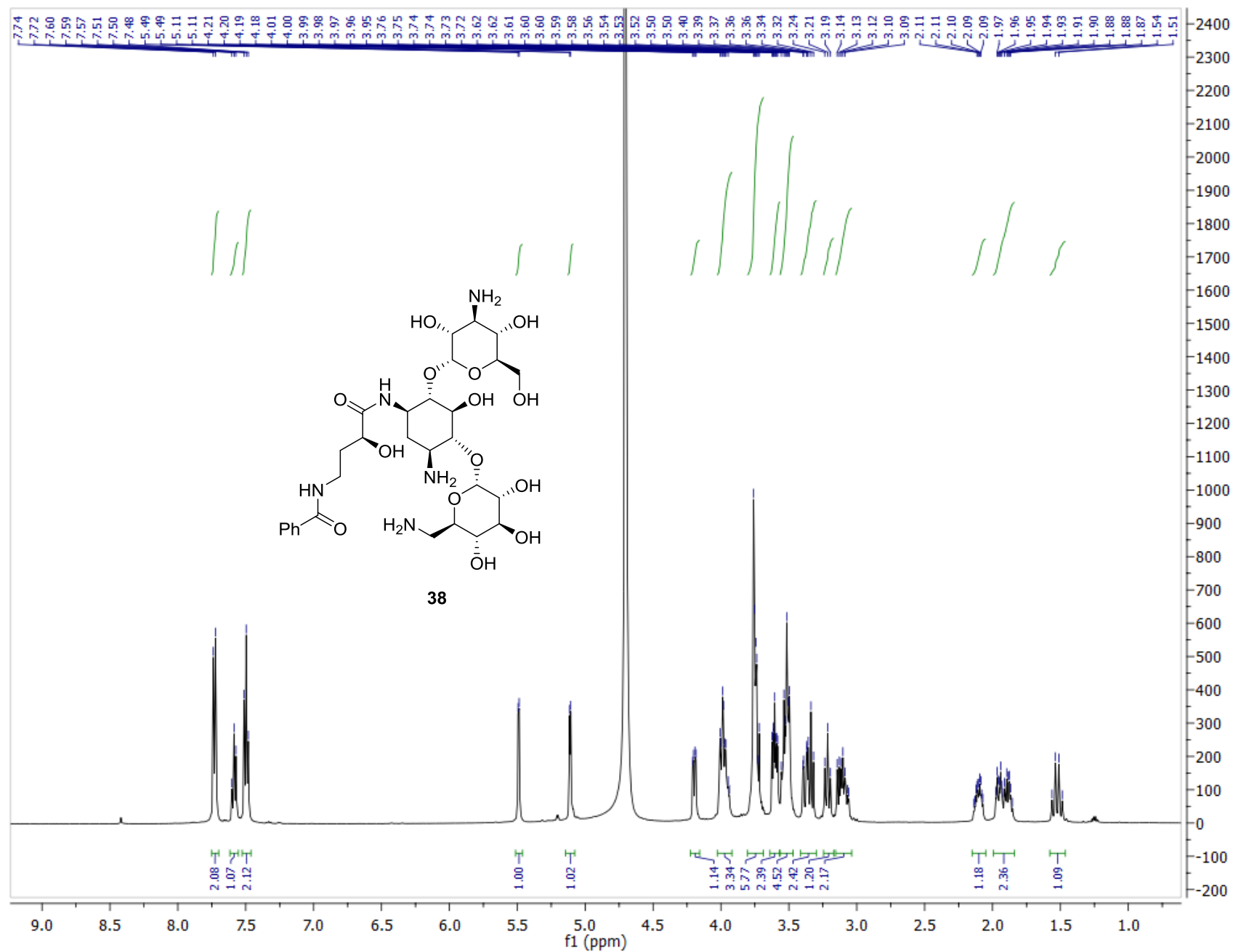
Tobramycin (**35**) – blue (CH) red (CH₂)
N-6'-Benzoyltobramycin (**36**) green (CH) Black (CH₂)

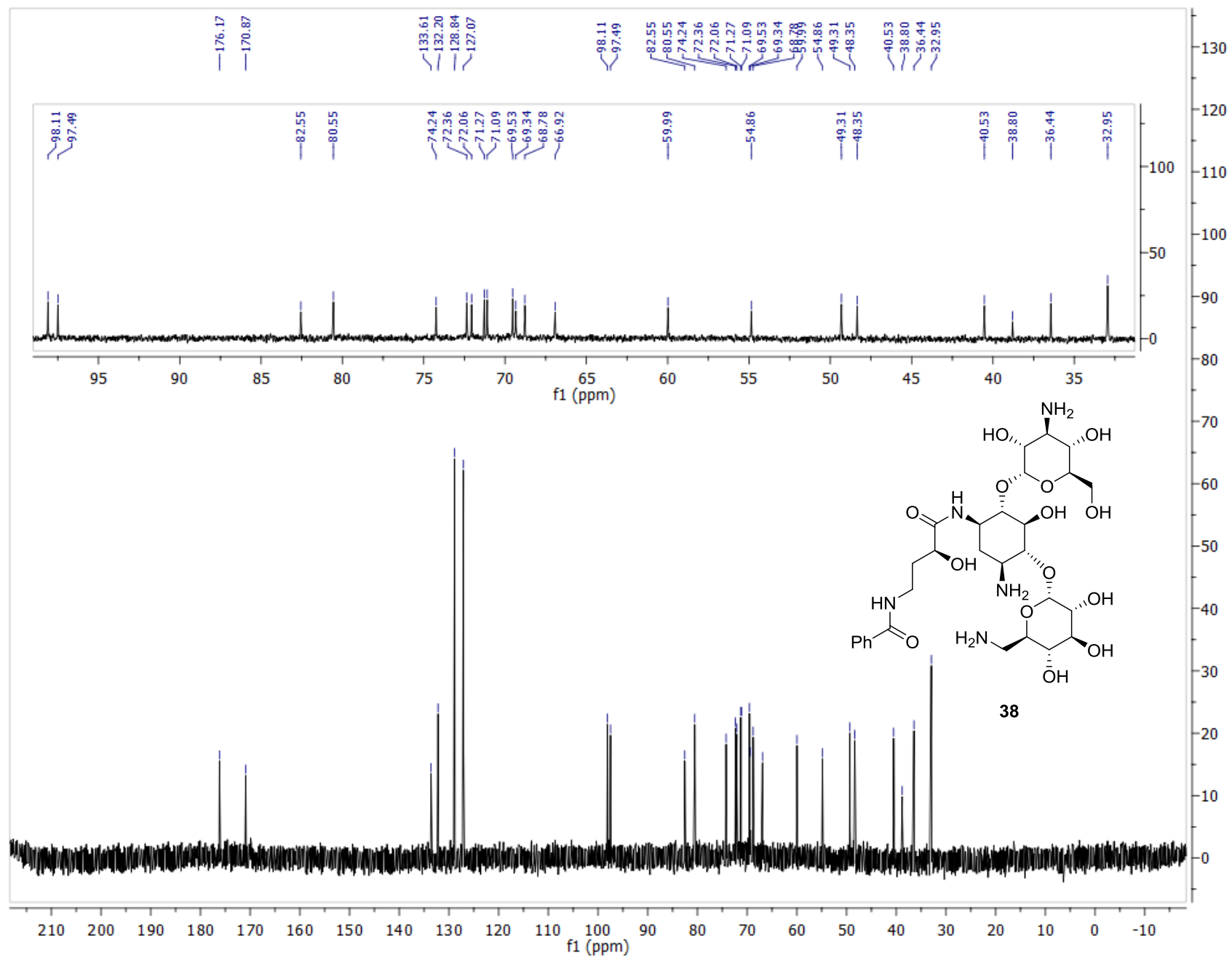


Overlay of the HSQC spectra of Tobramycin (**35**) (CH blue, CH₂ red) and *N*-6'-Benzoyltobramycin (**36**) (CH green, CH₂ black). The methylene in the red box are the only peaks to shift down-field due to the anisotropy of the carbonyl of the benzoyl group.



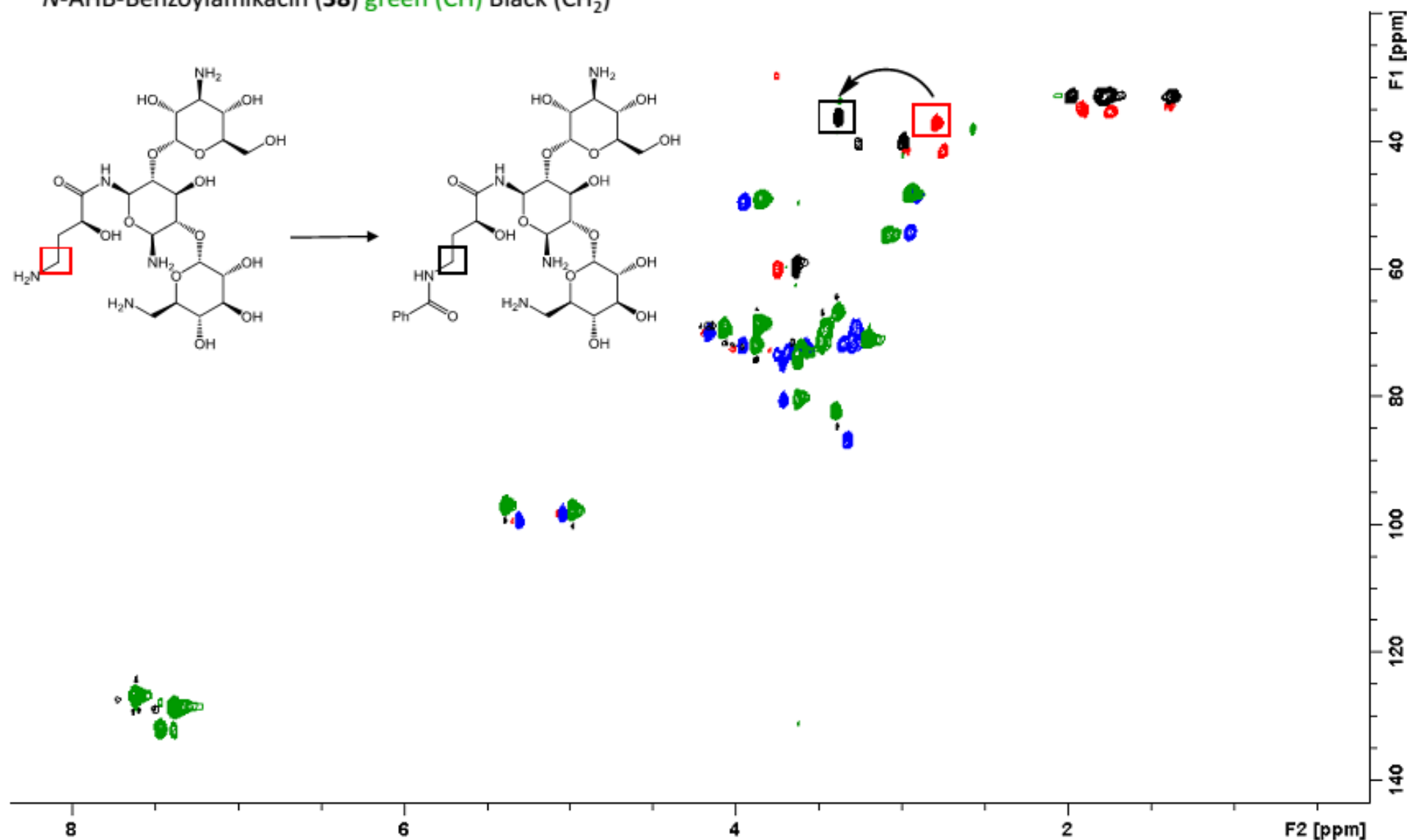
Selective 1D TOCSY spectra of (A) *N*-6'-Benzoyltobramycin (**36**) and (B) Tobramycin (**35**). Dotted lines show the large downfield shift of the benzoylated methylene.



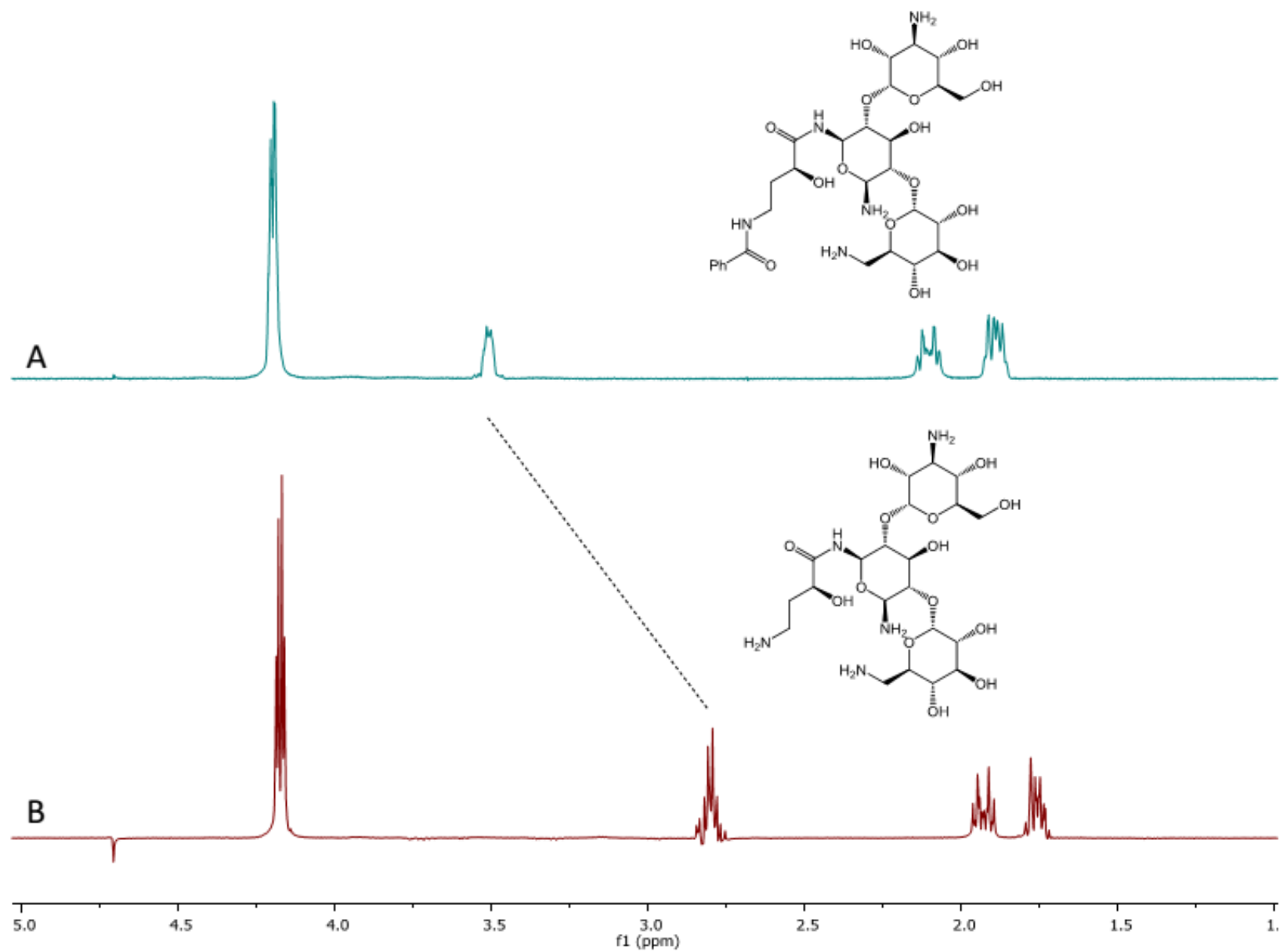


Amikacin (**37**) – blue (CH) red (CH₂)

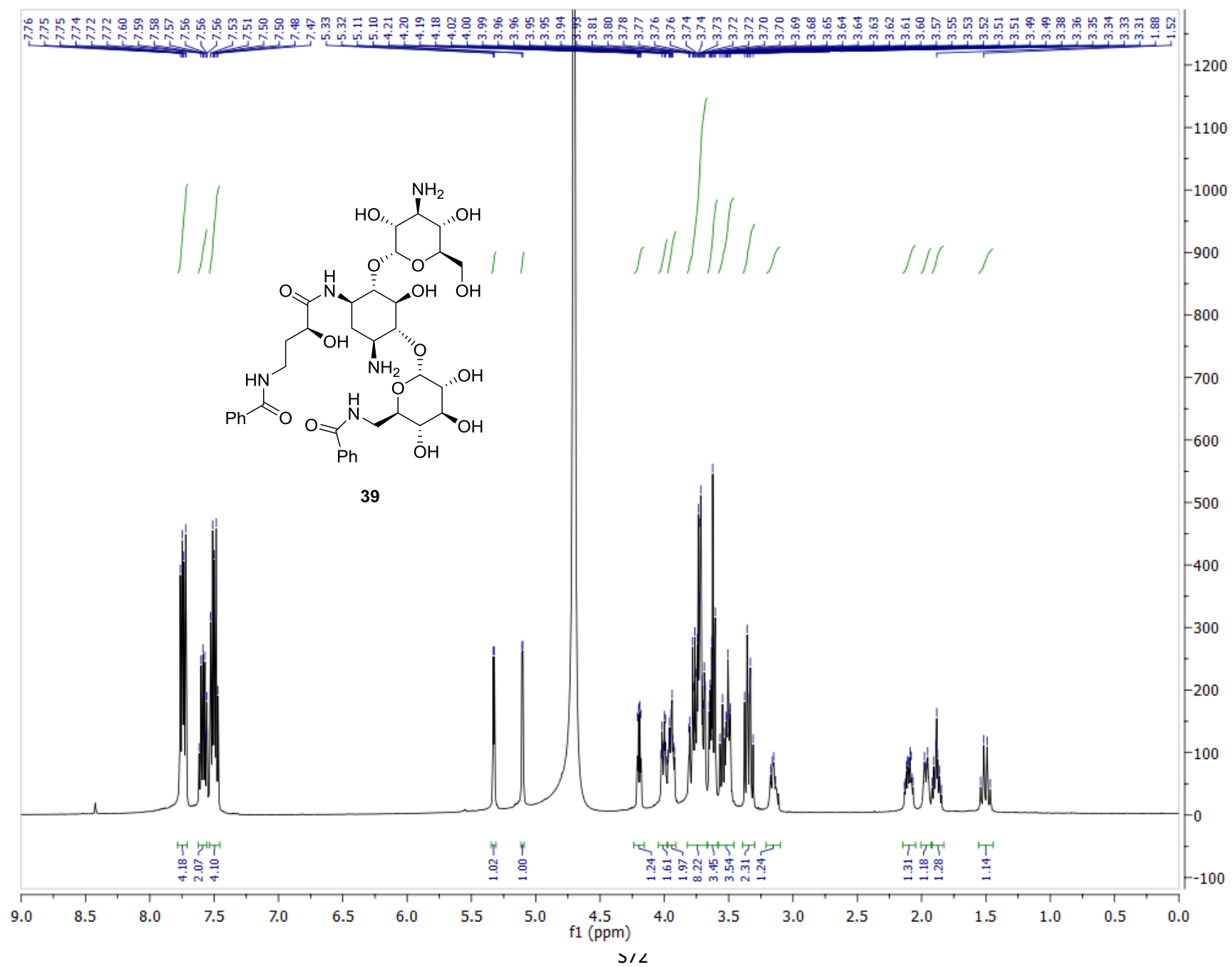
N-AHB-Benzoylamikacin (**38**) green (CH) Black (CH₂)

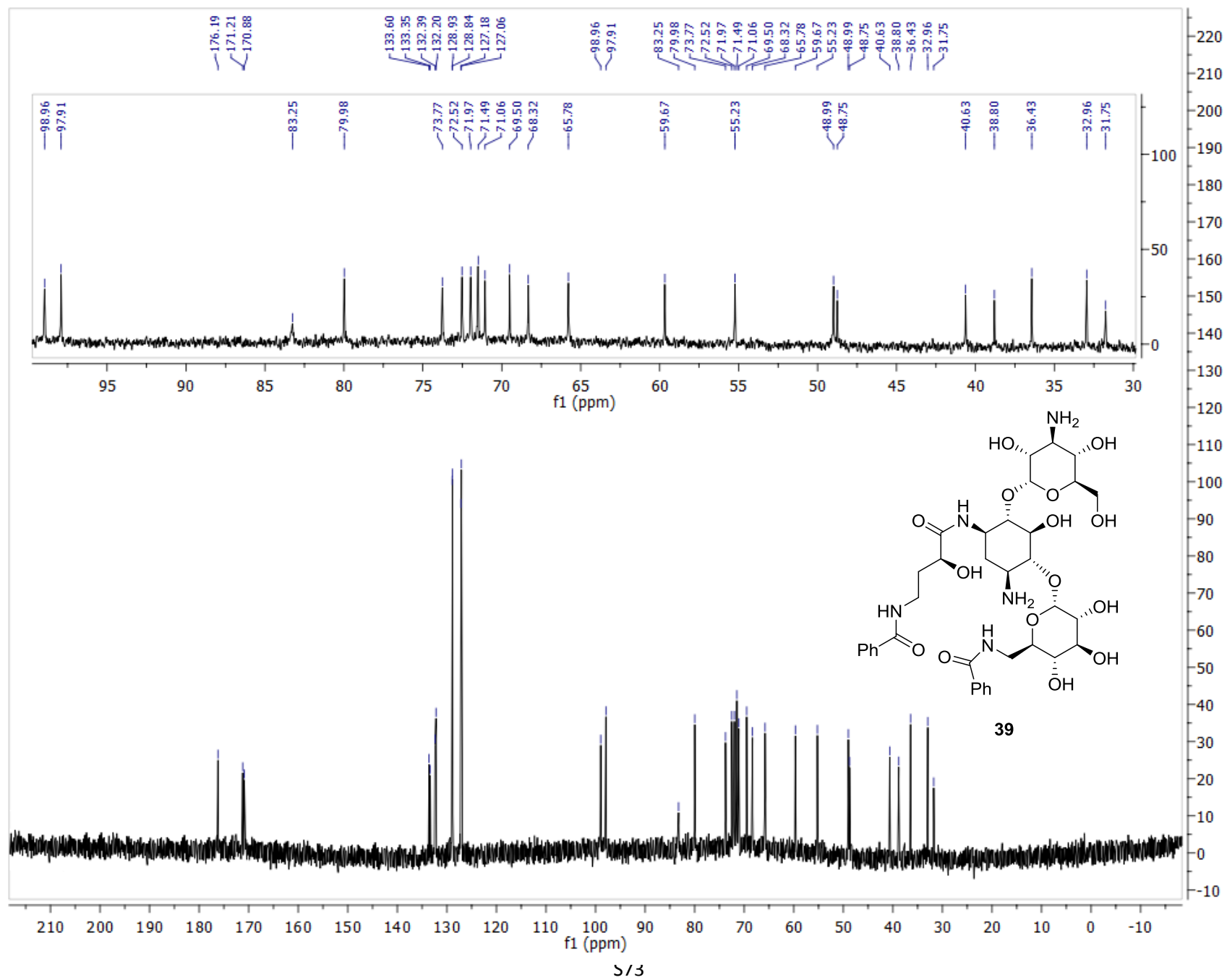


Overlay of the HSQC spectra of Amikacin (**37**) (CH blue, CH₂ red) and *N*-AHB-Benzoylamikacin (**38**) (CH green, CH₂ black). The methylene in the red box are the only peaks to shift down-field due to the anisotropy of the carbonyl of the benzoyl group.



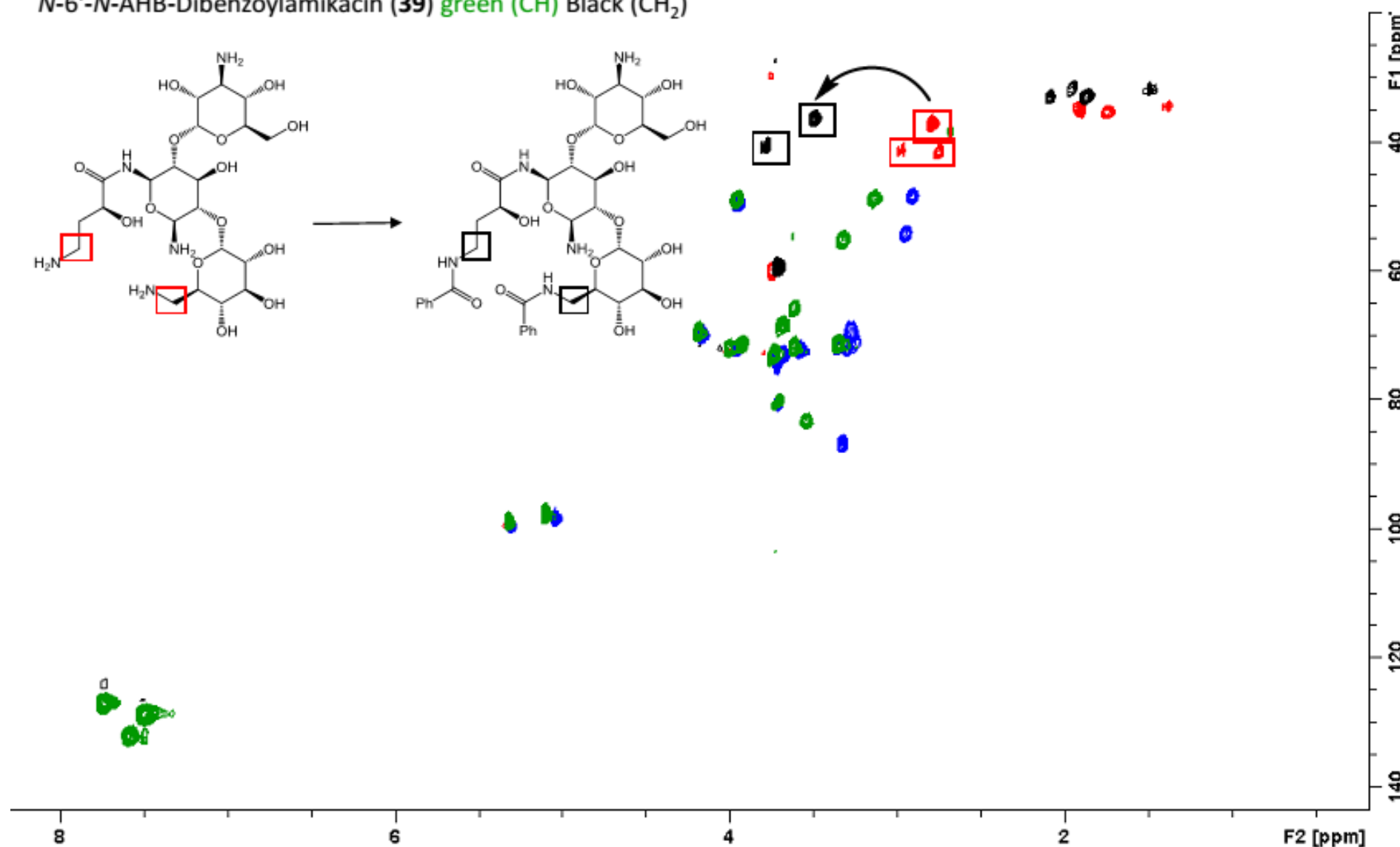
Selective 1D TOCSY spectra of (A) *N*-AHB-Benzoylamikacin (**38**) and (B) Amikacin (**37**). Dotted lines show the large downfield shift of the benzoylated methylene.



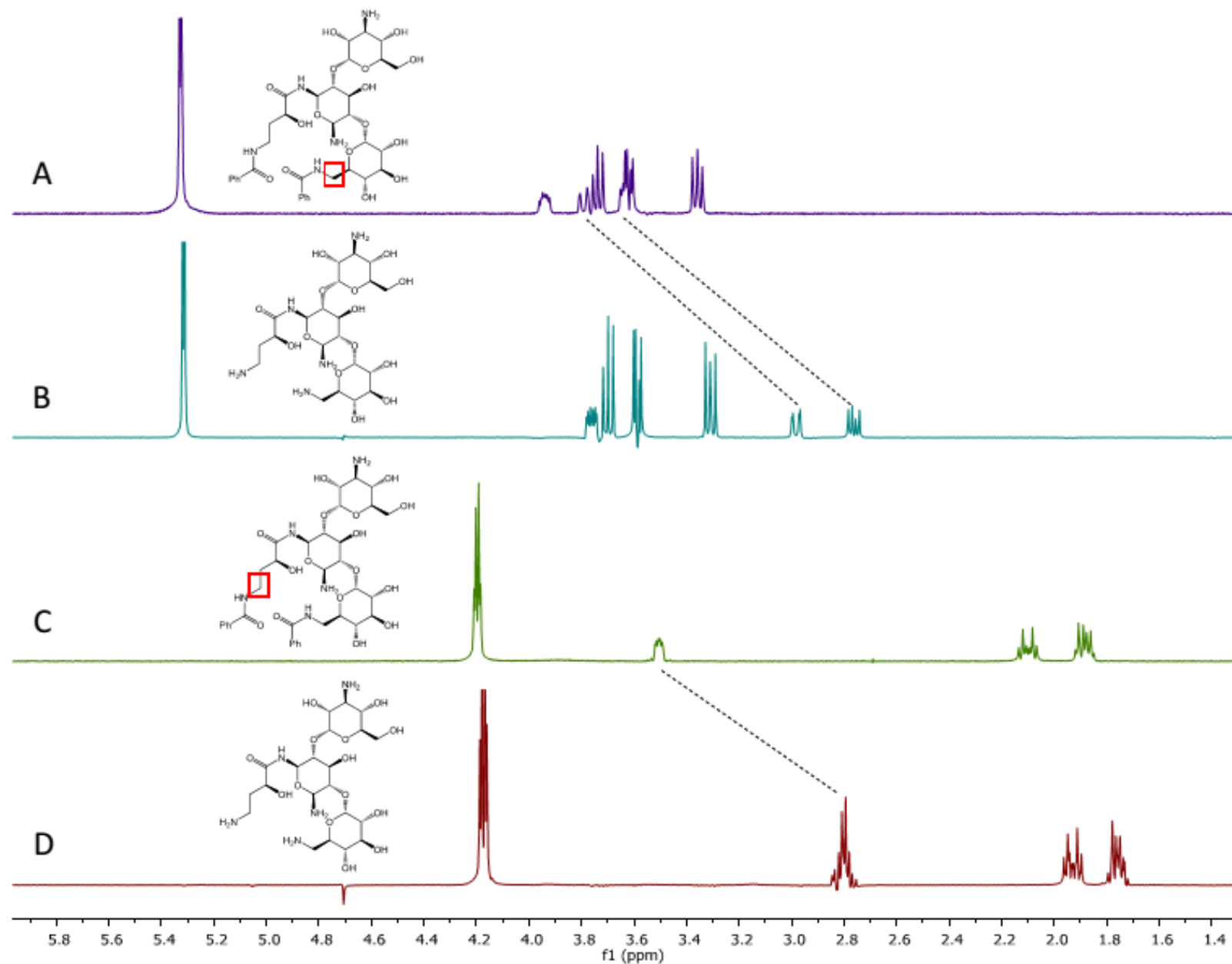


Amikacin (**37**) – blue (CH) red (CH₂)

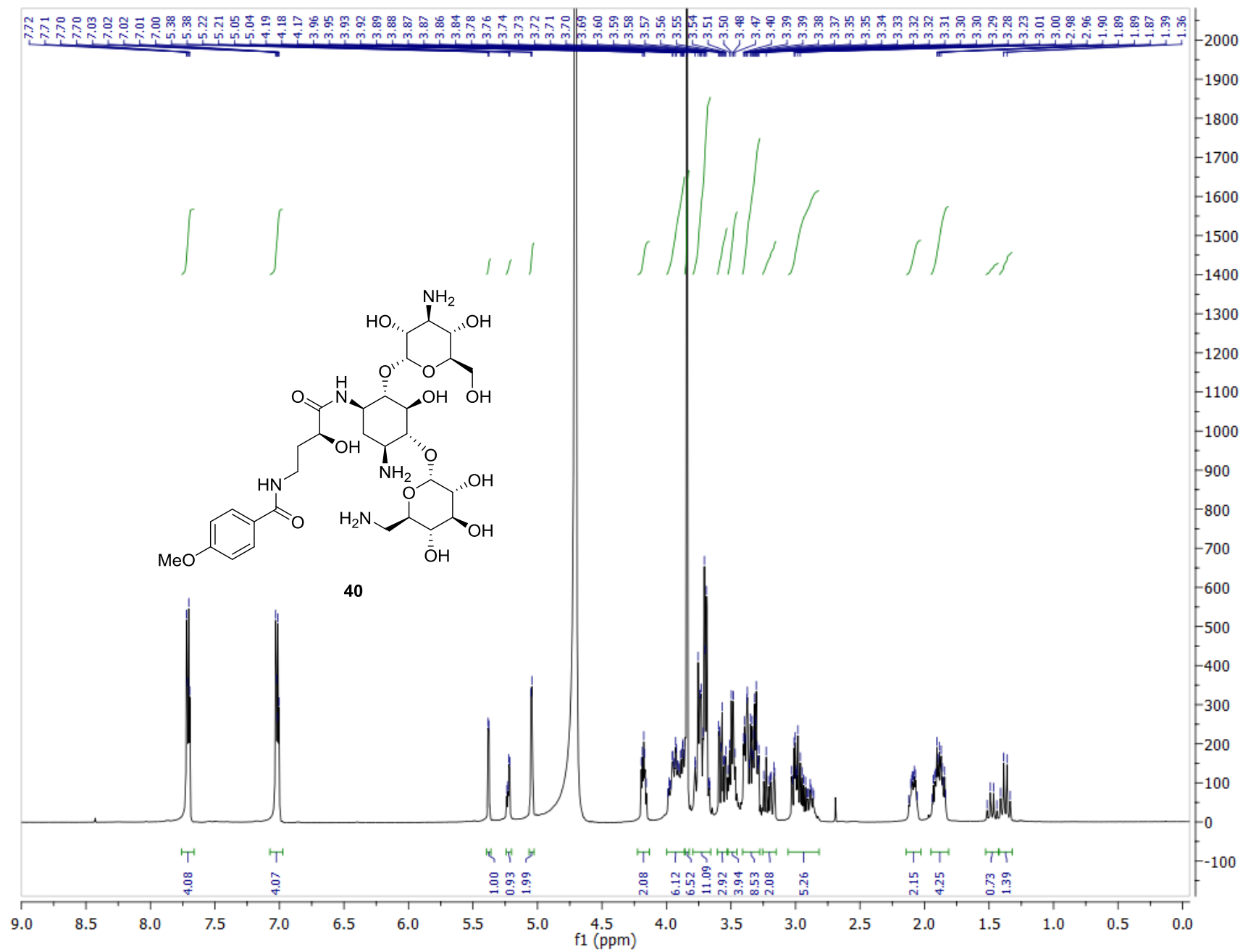
N-6'-*N*-AHB-Dibenzoylamikacin (**39**) green (CH) Black (CH₂)

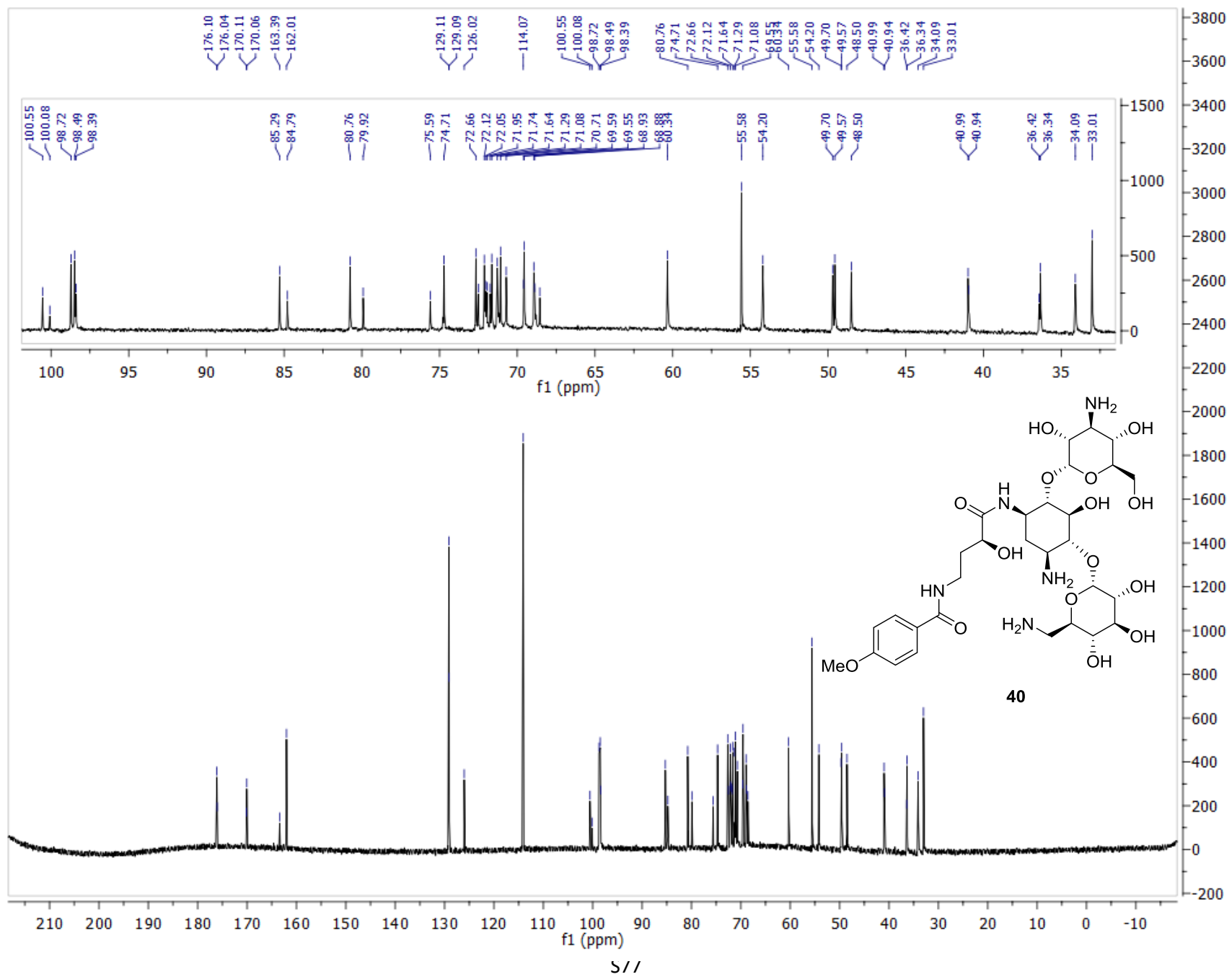


Overlay of the HSQC spectra of Amikacin (**37**) (CH blue, CH₂ red) and *N*-6'-*N*-AHB-Dibenzoylamikacin (**39**) (CH green, CH₂ black). The methylenes in the red box are the only peaks to shift down-field due to the anisotropy of the carbonyl of the benzoyl group.



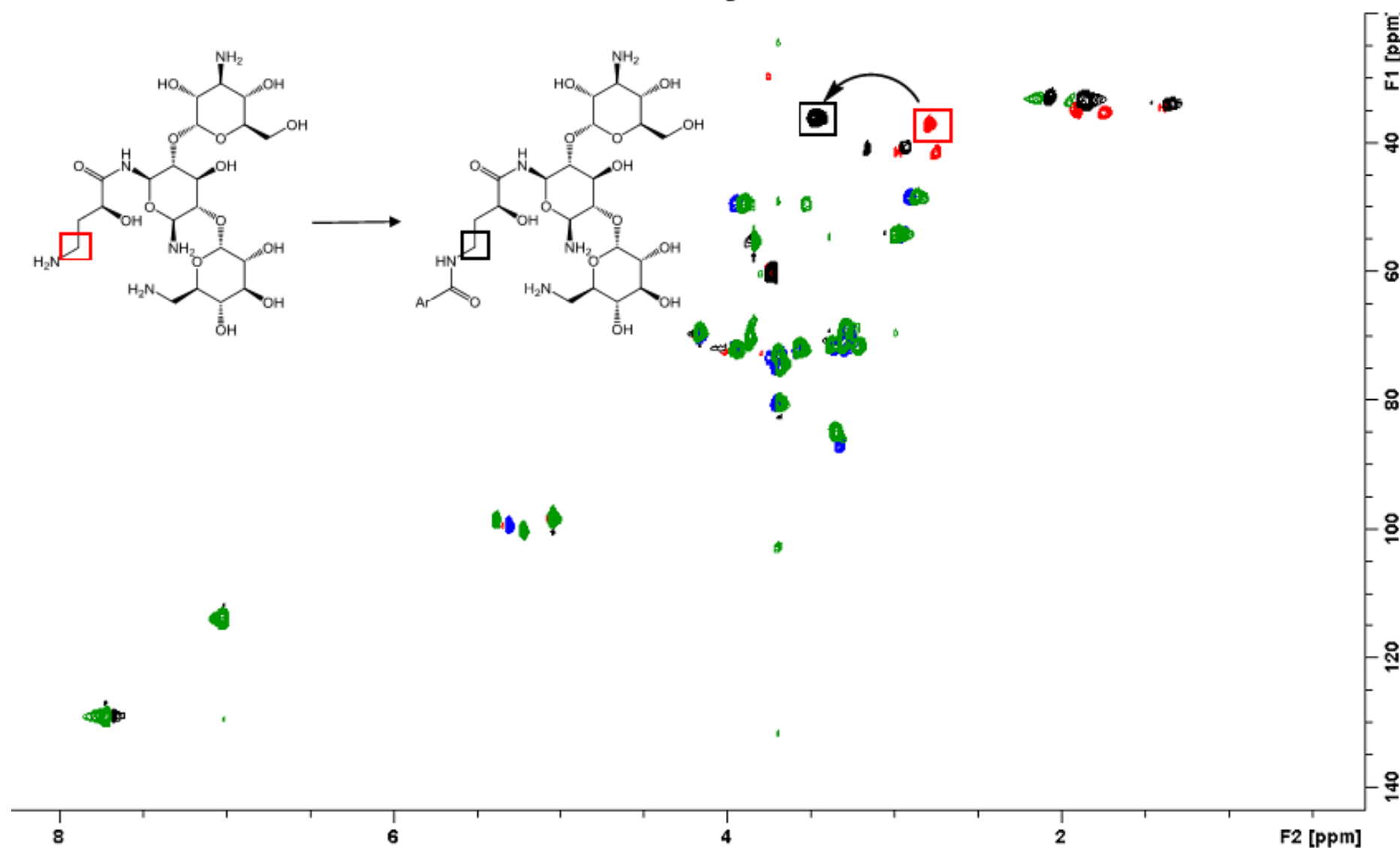
Selective 1D TOCSY spectra of (A and C) *N*-6'-*N*-AHB-Dibenzoylamikacin (**39**) and (B and D) Amikacin (**37**). Dotted lines show the large downfield shift of the benzoylated methylenes.



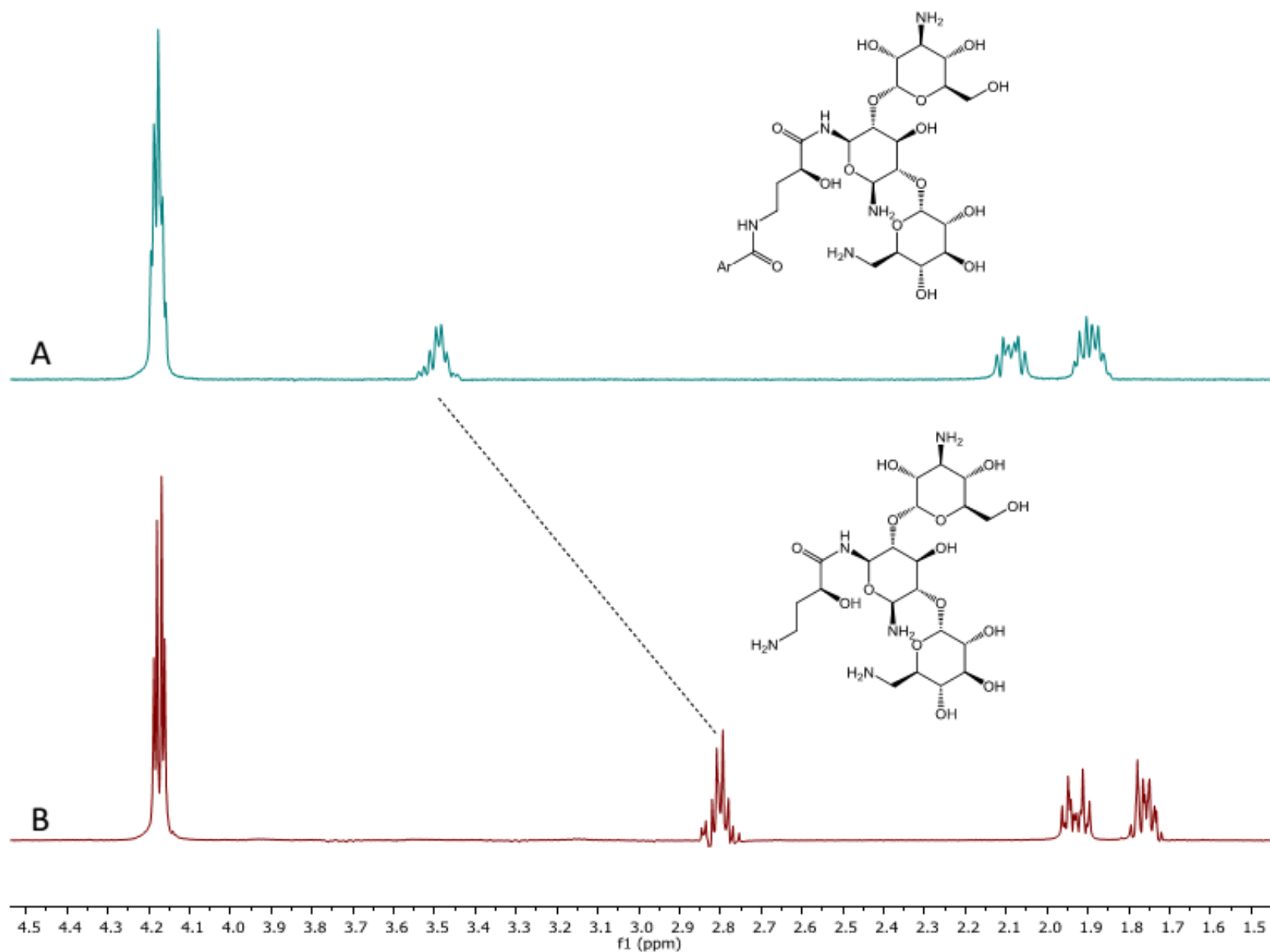


Amikacin (**37**) – blue (CH) red (CH₂)

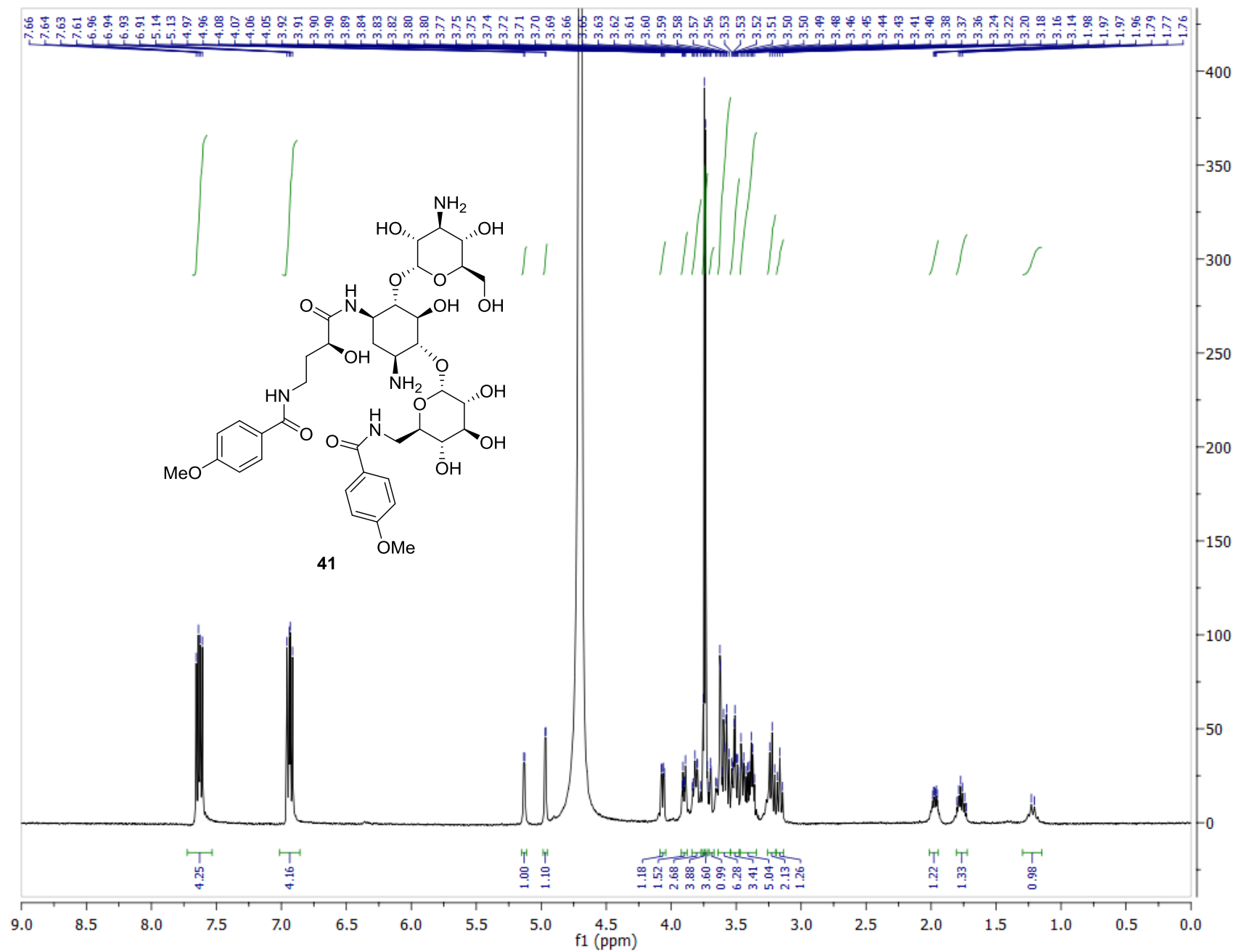
N-AHB-(4-Methoxybenzoyl)amikacin (**40**) green (CH) Black (CH₂)

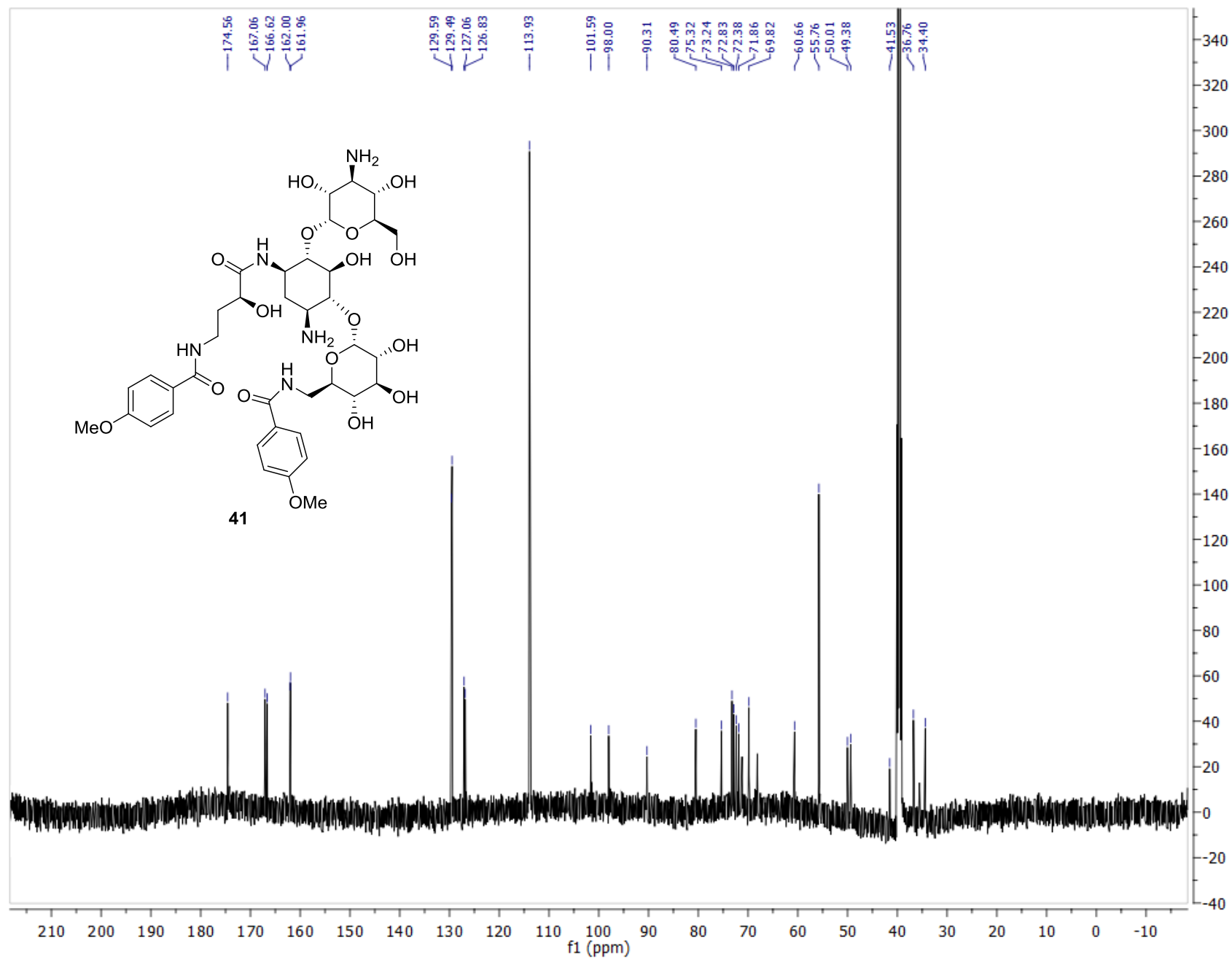


Overlay of the HSQC spectra of Amikacin (**37**) (CH blue, CH₂ red) and *N*-AHB-(4-Methoxybenzoyl)amikacin (**40**) (CH green, CH₂ black).
The methylene in the red box are the only peaks to shift down-field due to the anisotropy of the carbonyl of the benzoyl group.



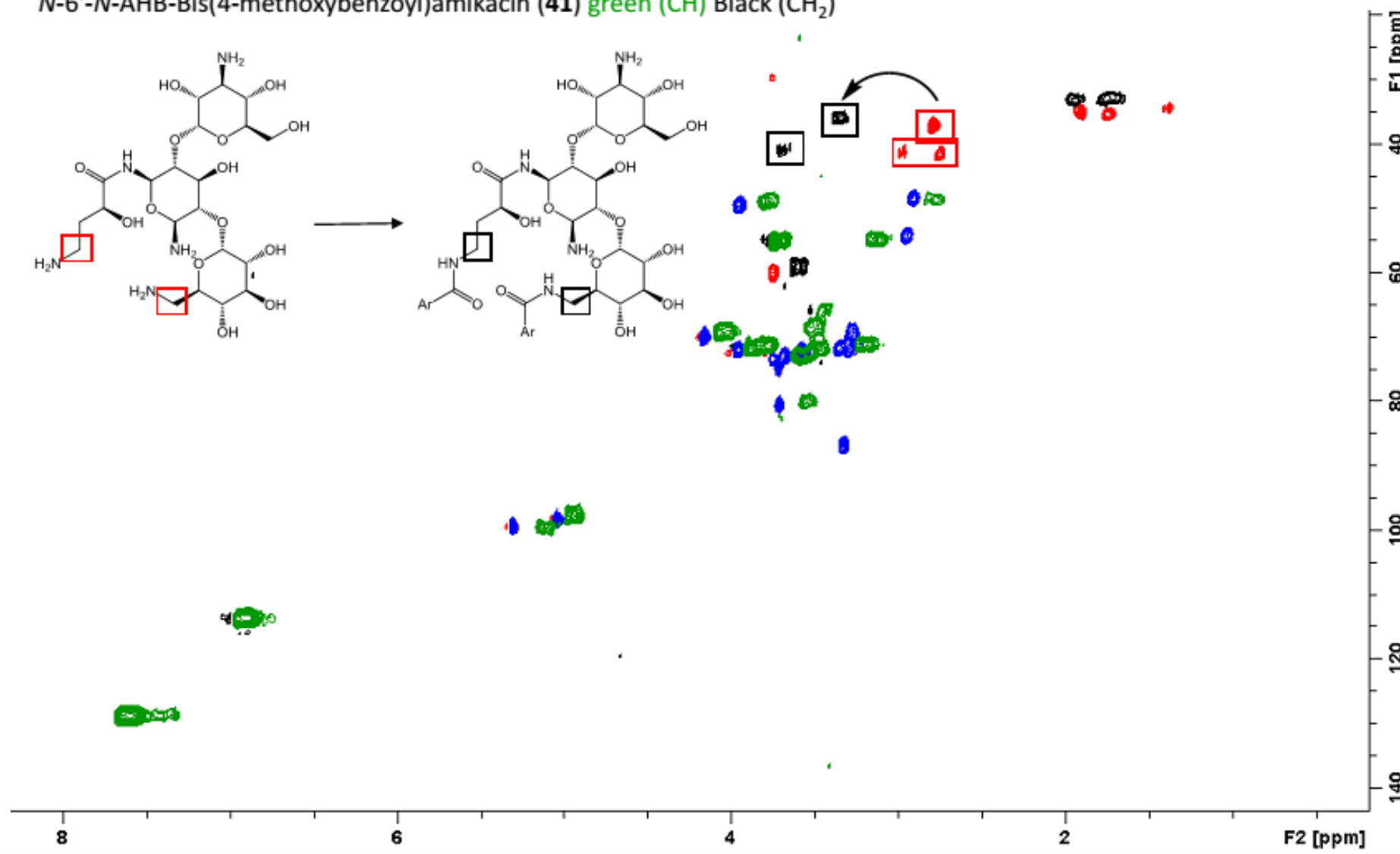
Selective 1D TOCSY spectra of (A) *N*-AHB-(4-Methoxybenzoyl)amikacin (**40**) and (B) Amikacin (**37**). Dotted lines show the large downfield shift of the 4-methoxybenzoylated methylene.



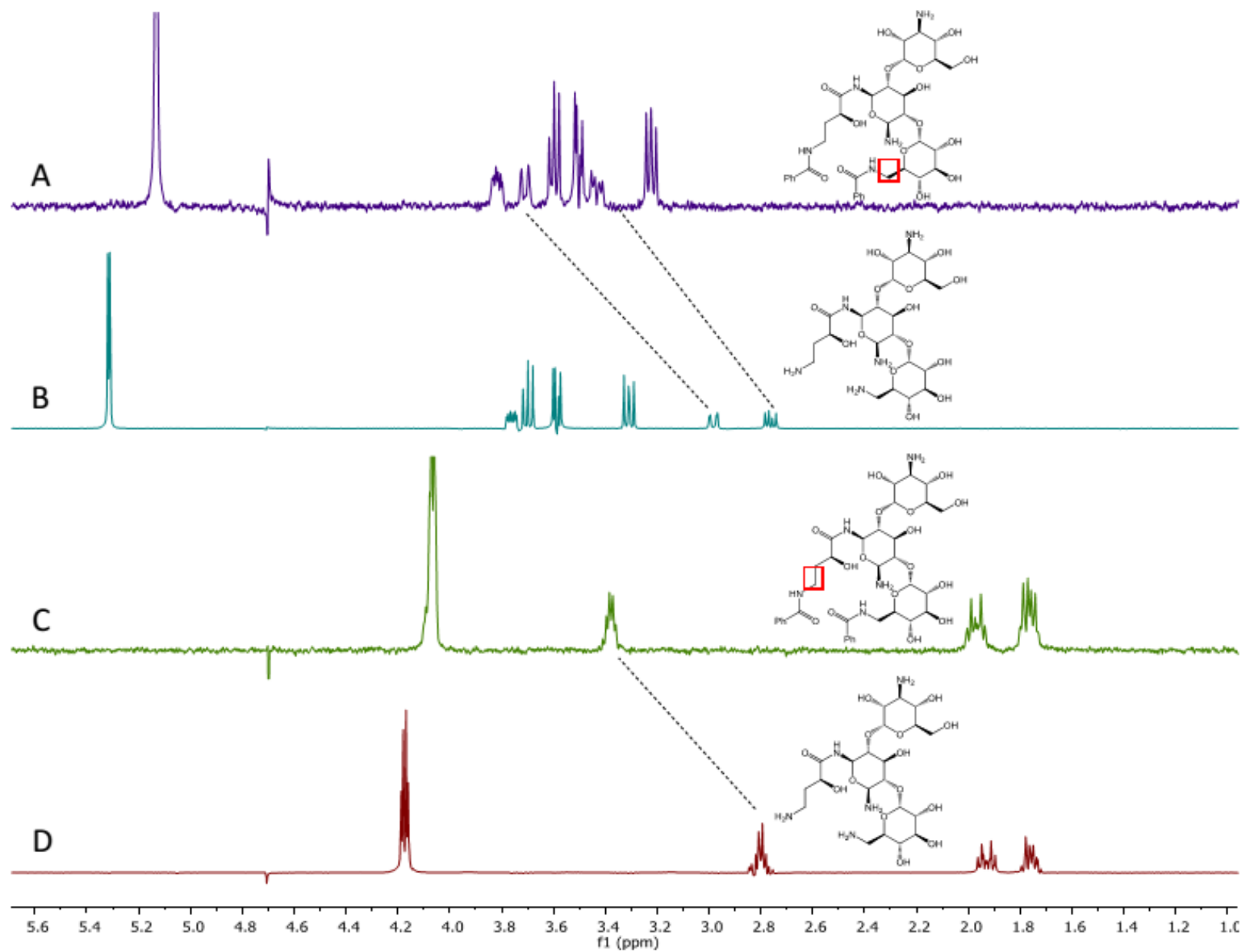


Amikacin (**37**) – blue (CH) red (CH₂)

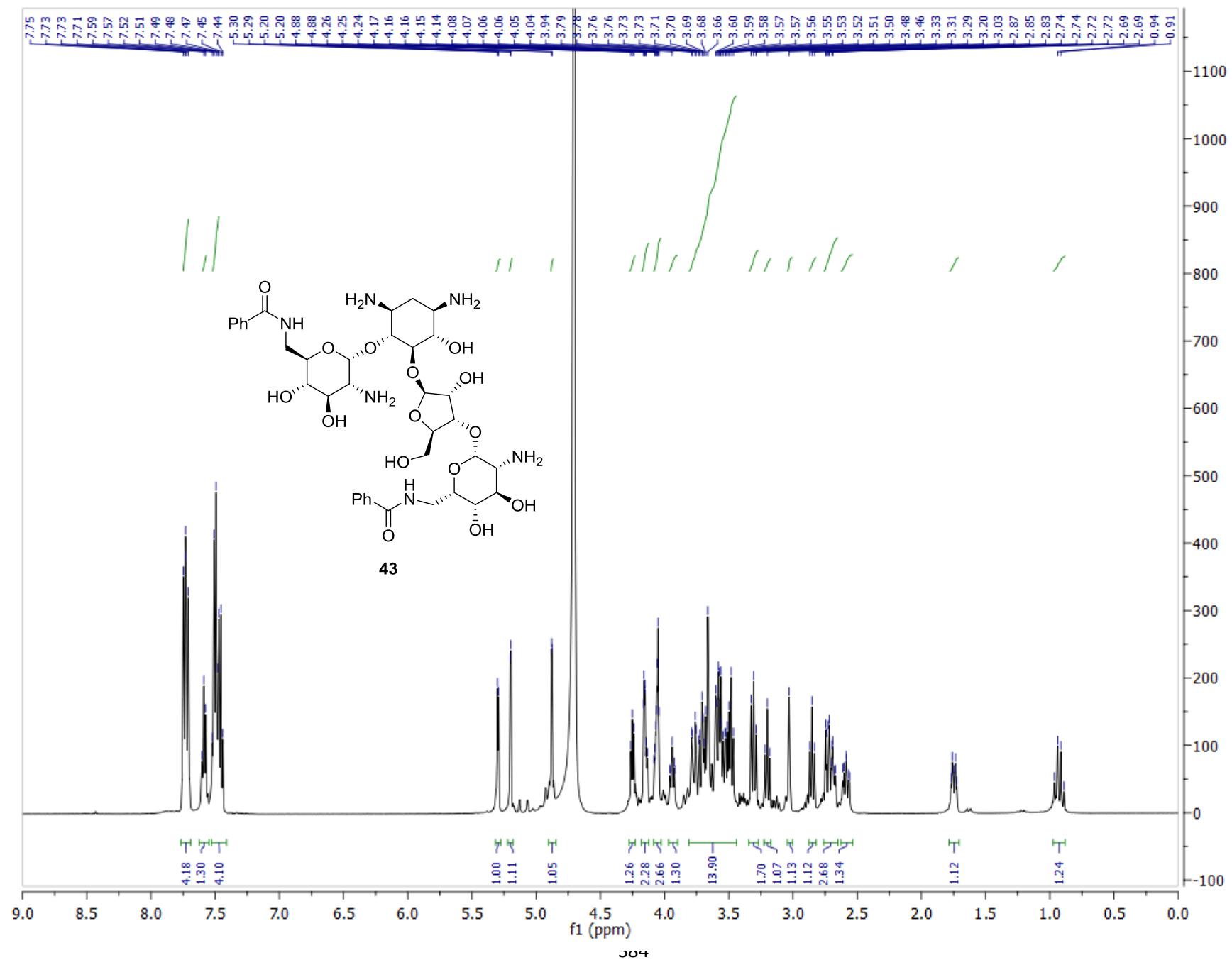
N-6'-*N*-AHB-Bis(4-methoxybenzoyl)amikacin (**41**) green (CH) Black (CH₂)

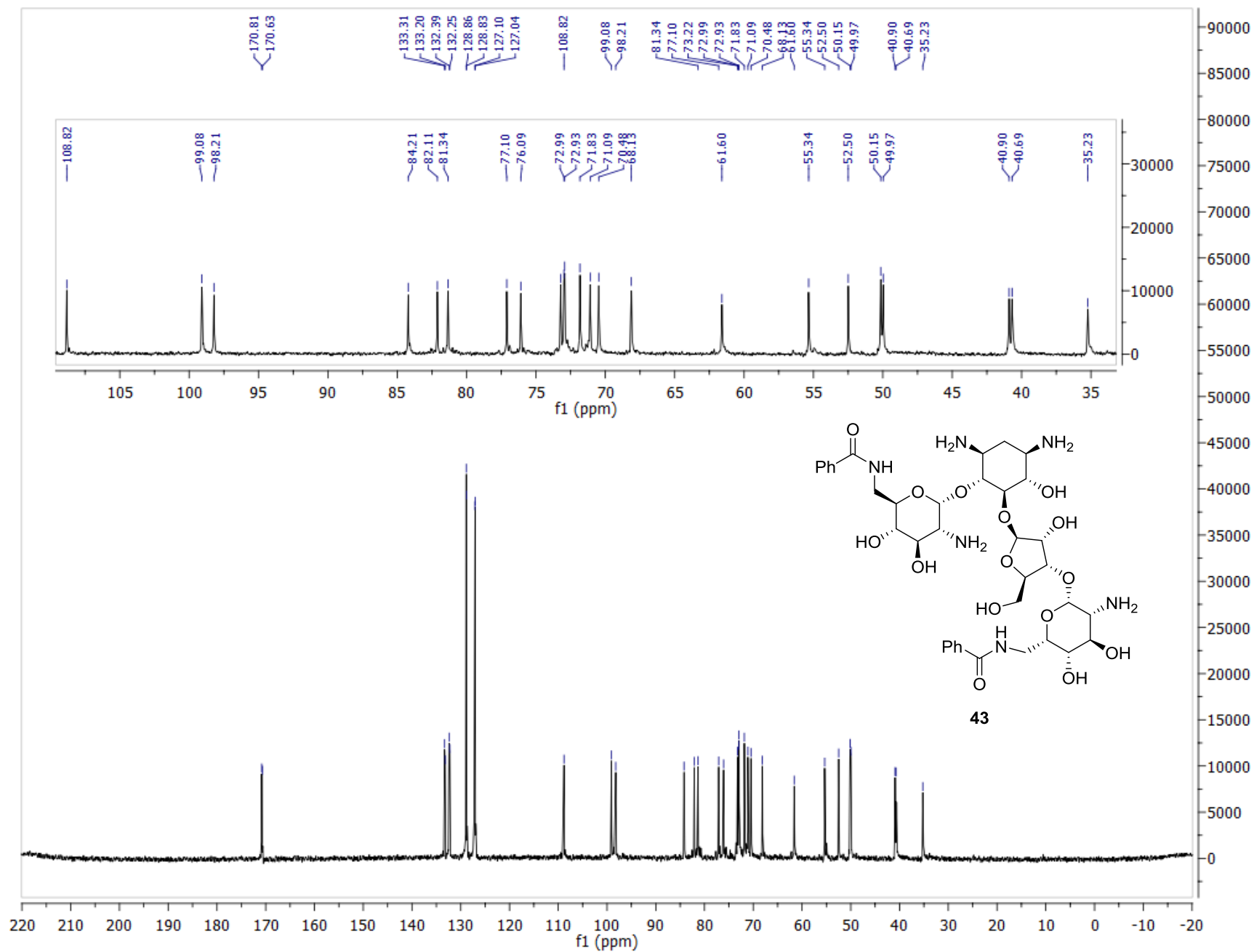


Overlay of the HSQC spectra of Amikacin (**37**) (CH blue, CH₂ red) and *N*-6'-*N*-AHB-Bis(4-methoxybenzoyl)amikacin (**41**) (CH green, CH₂ black). The methylenes in the red box are the only peaks to shift down-field due to the anisotropy of the carbonyl of the benzoyl group.



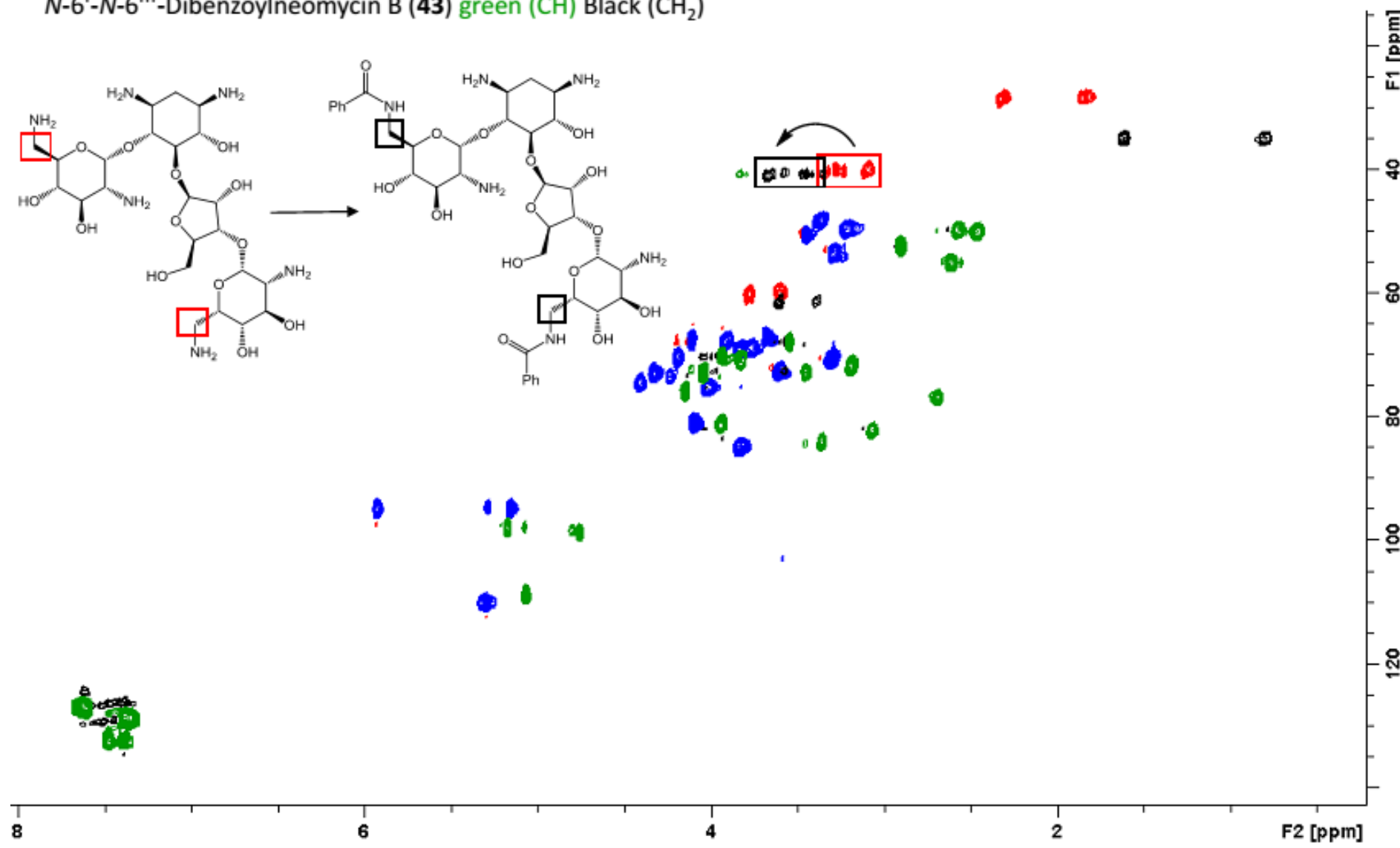
Selective 1D TOCSY spectra of (A and C) *N*-6'-*N*-AHB-Bis(4-methoxybenzoyl)amikacin (**41**) and (B and D) Amikacin (**37**). Dotted lines show the large downfield shift of the 4-methoxy benzoylated methylenes.



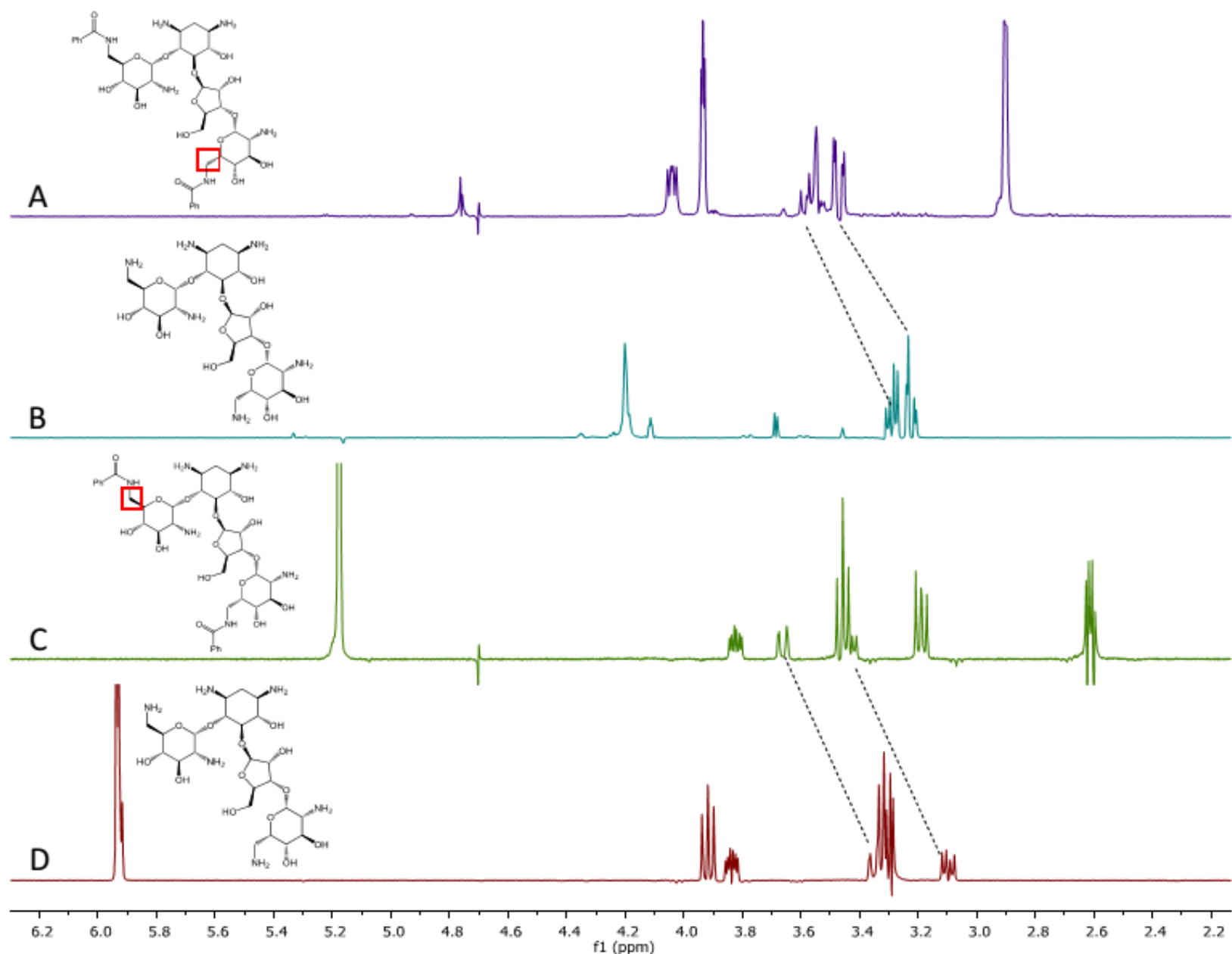


Neomycin B (**42**) – blue (CH) red (CH₂)

N-6'-*N*-6'''-Dibenzoylneomycin B (**43**) green (CH) black (CH₂)



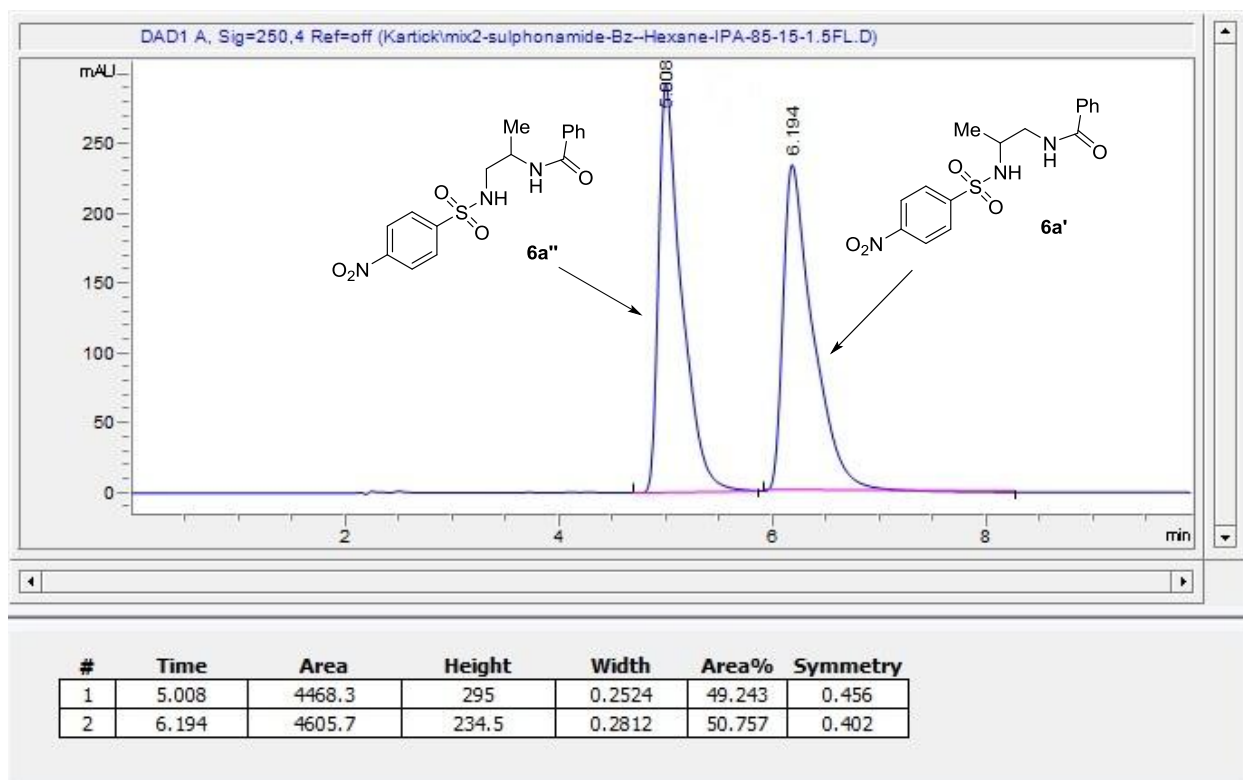
Overlay of the HSQC spectra of Neomycin B (**42**) (CH blue, CH₂ red) and *N*-6'-*N*-6'''-Dibenzoylneomycin B (**43**) (CH green, CH₂ black). The methylenes in the red box are the only peaks to shift down-field due to the anisotropy of the carbonyl of the benzoyl group.



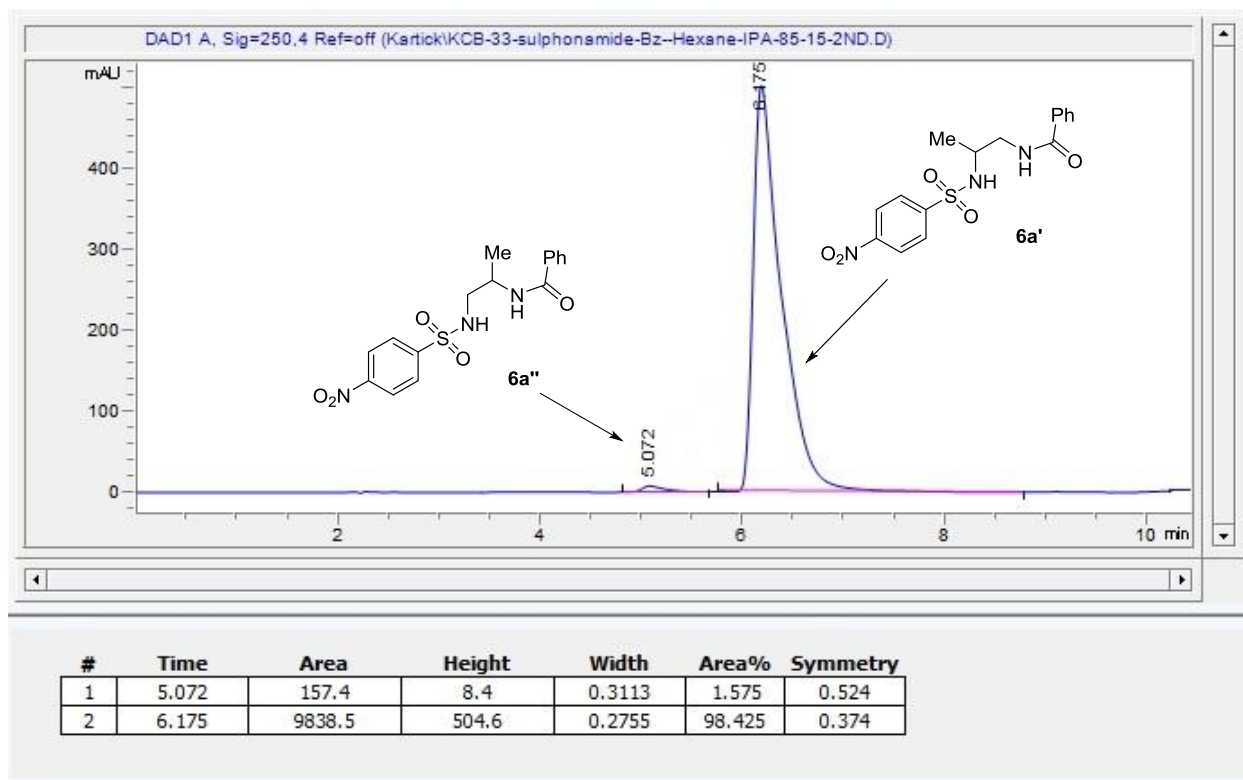
Selective 1D TOCSY spectra of (A and C) *N*-6'-*N*-6'''-Dibenzoylneomycin B (**43**) and (B and D) Neomycin B (**42**). Dotted lines show the large downfield shift of the benzoylated methylenes.

HPLC Traces

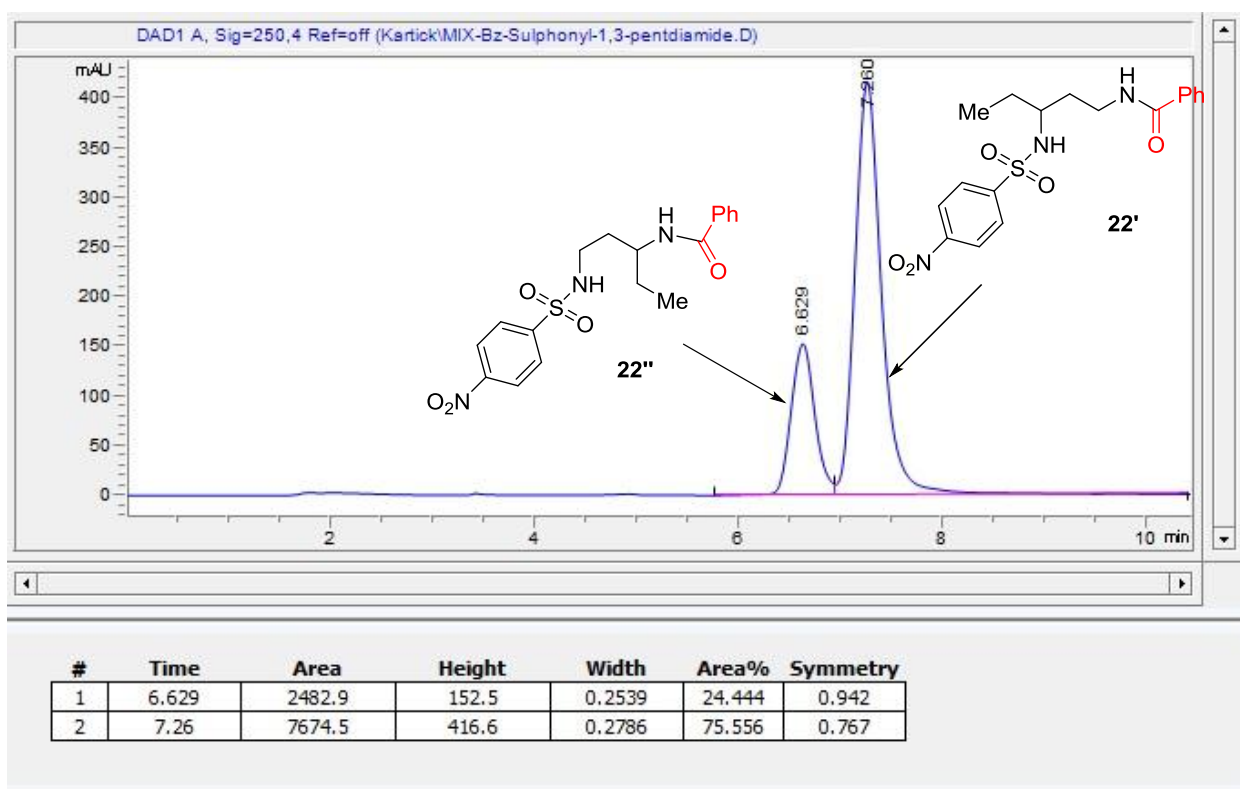
Mixture of standards: Phenomenex silica-based column (Lichrosorb 5 Sil 60A 250×4.60 mm), flow rate 1.5 mL/min, hexanes/*i*-PrOH = 85:15



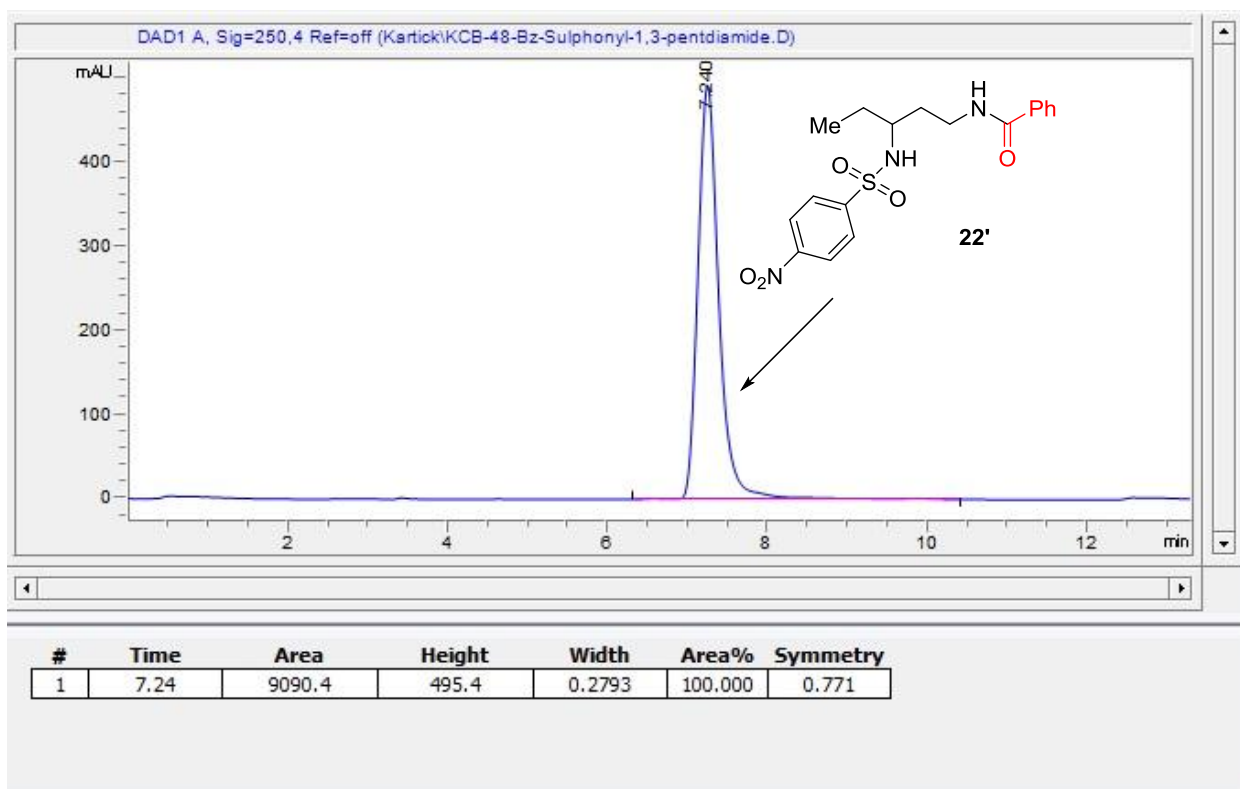
Site-selective reaction with BCPP 1a: Phenomenex silica-based column (Lichrosorb 5 Sil 60A 250×4.60 mm), flow rate 1.5 mL/min, hexanes/*i*-PrOH = 85:15



Mixture of standards: Phenomenex silica-based column (Lichrosorb 5 Sil 60A 250×4.60 mm), flow rate 1.0 mL/min, hexanes/*i*-PrOH = 85:15

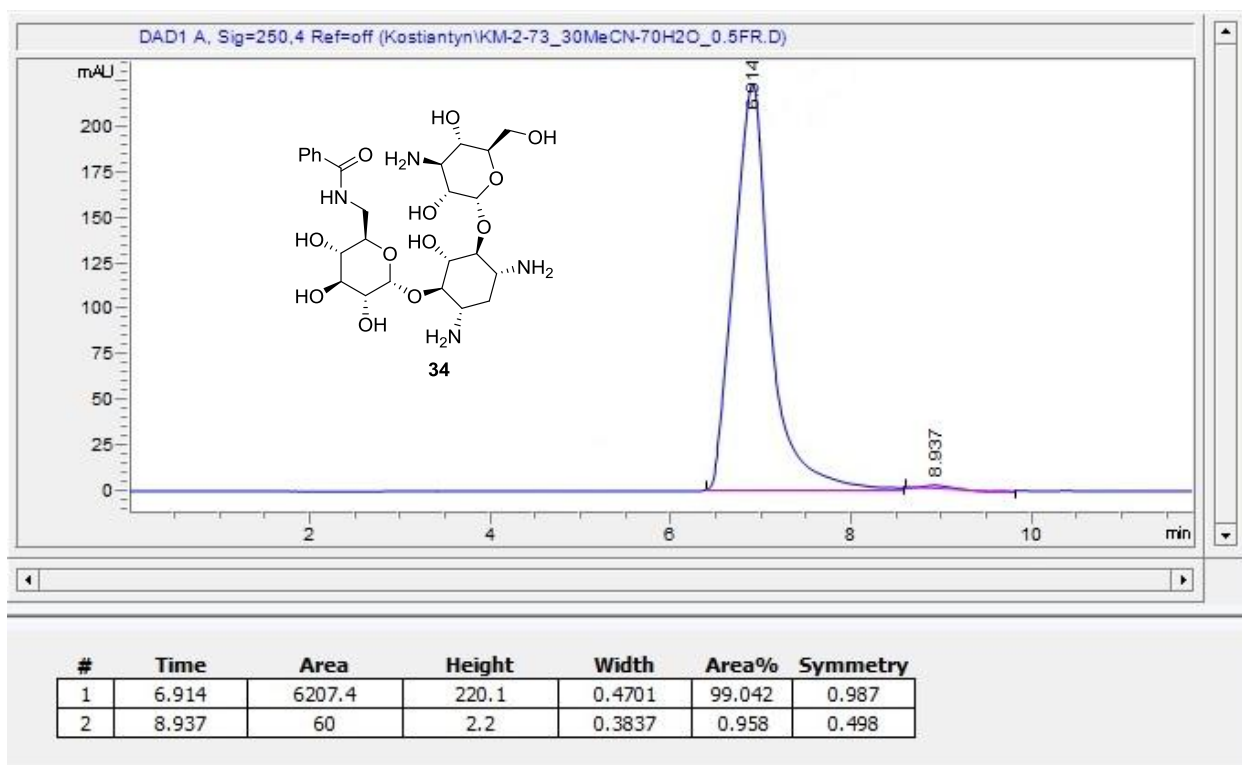


Site-selective reaction with BCPP 1a: Phenomenex silica-based column (Lichrosorb 5 Sil 60A 250×4.60 mm), flow rate 1.0 mL/min, hexanes/*i*-PrOH = 85:15

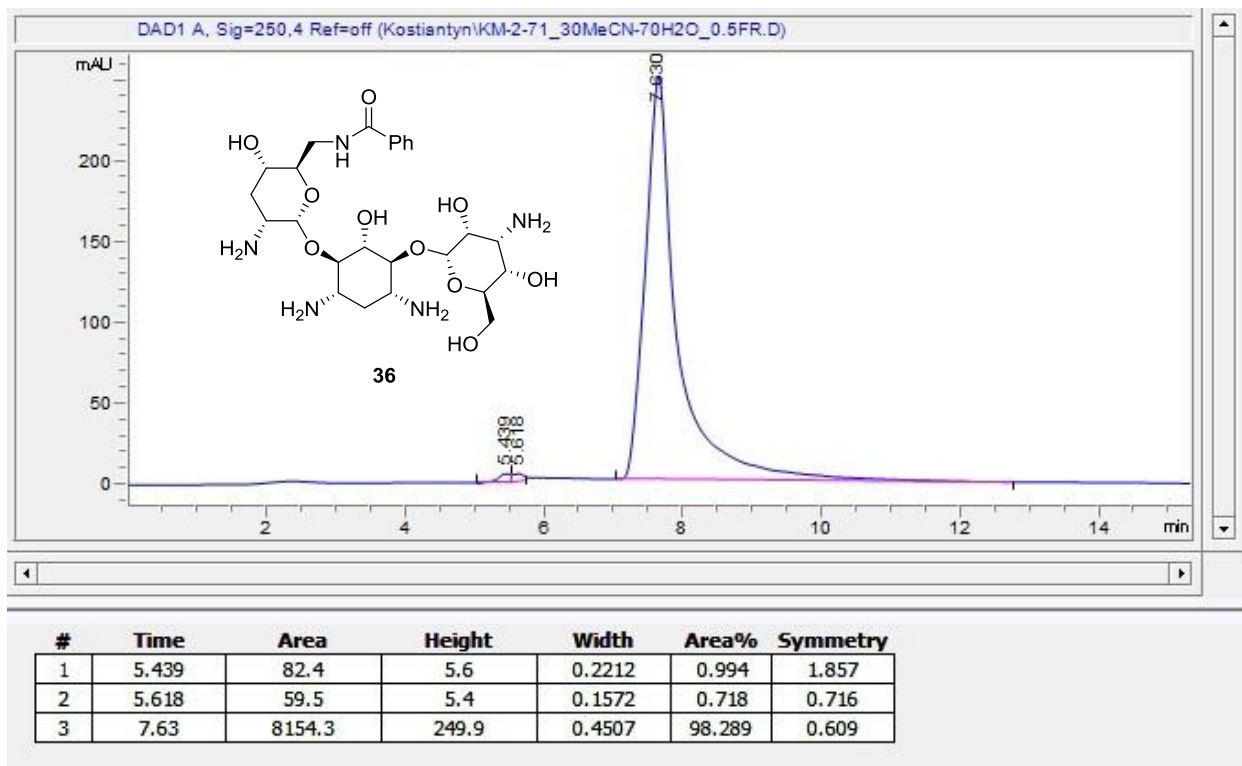


HPLC Traces of Aminoglycosides

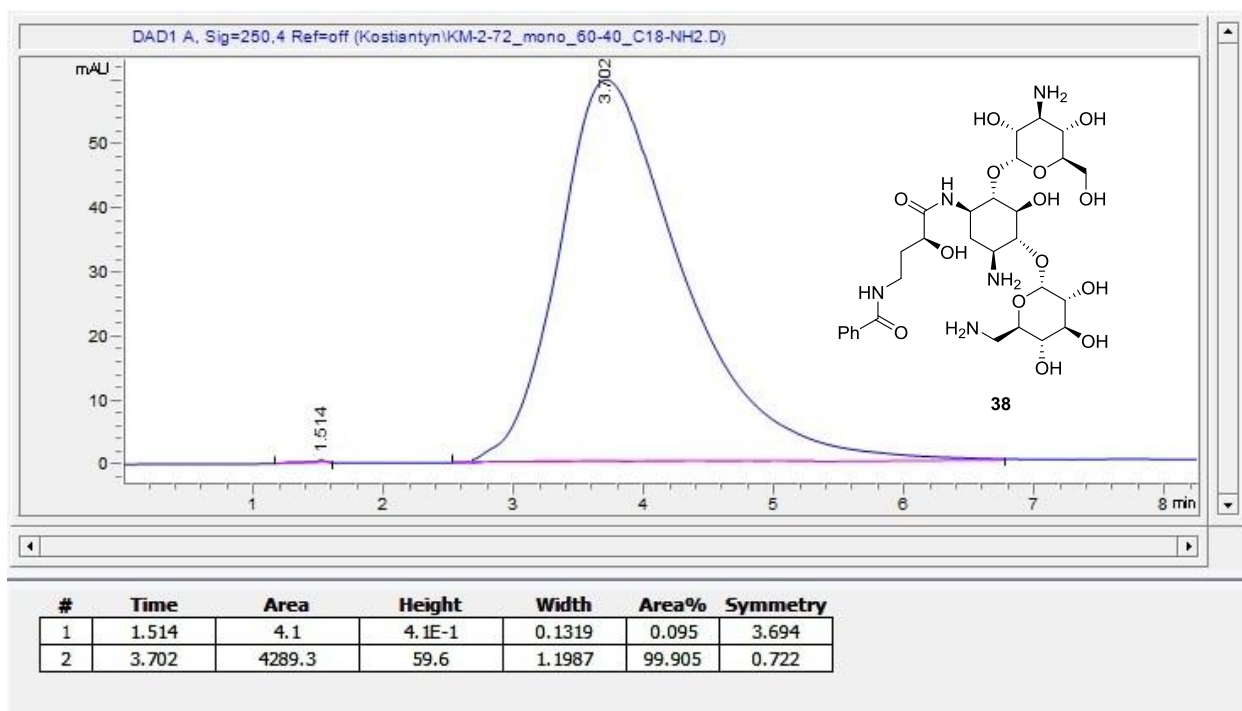
Lichrospher® 100 NH₂ (5µm) C18 column, flow rate 0.5 mL/min, H₂O/CH₃CN = 70:30



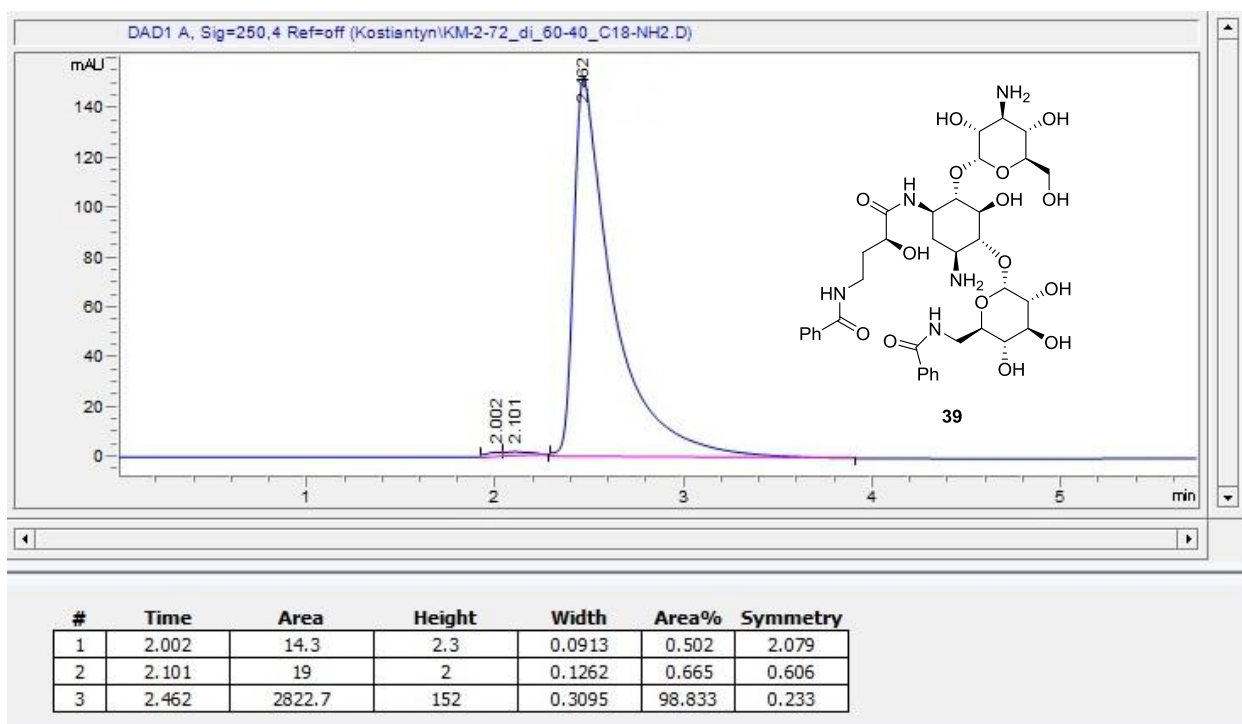
Lichrospher® 100 NH₂ (5µm) C18 column, flow rate 0.5 mL/min, H₂O/CH₃CN = 70:30



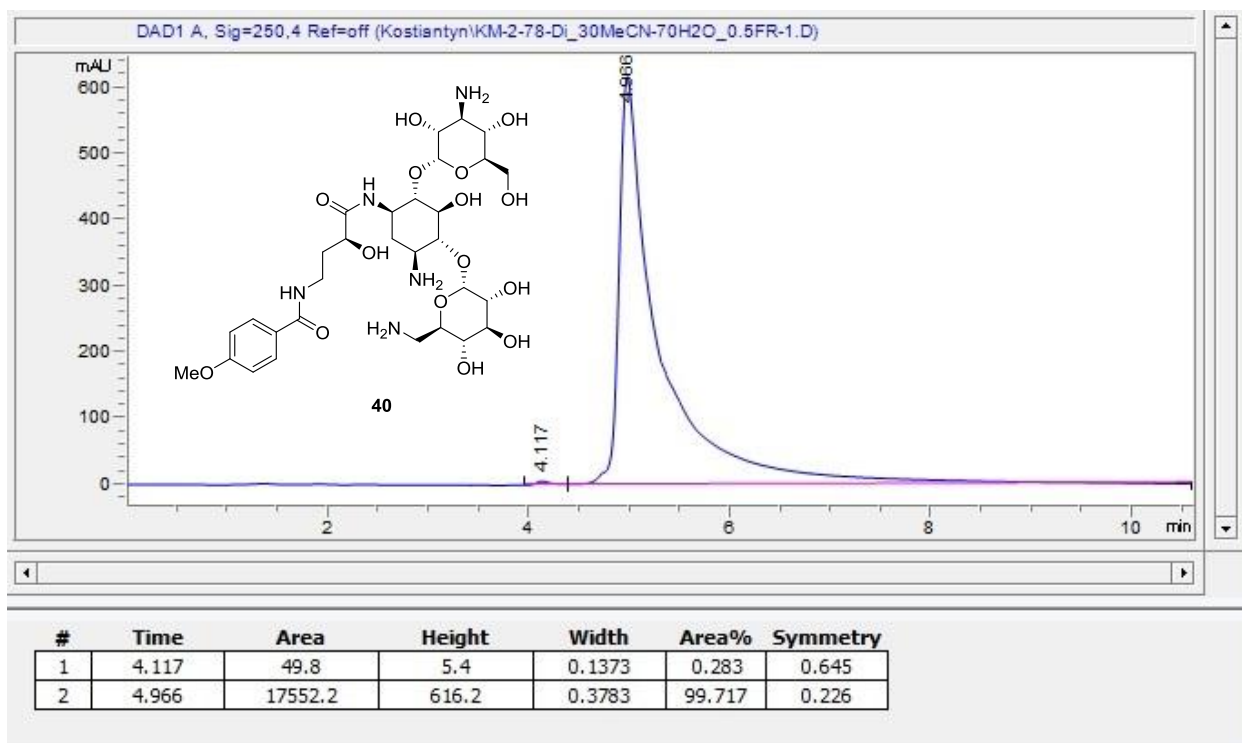
Lichrospher® 100 NH₂ (5µm) C18 column, flow rate 0.5 mL/min, H₂O/CH₃CN = 60:40



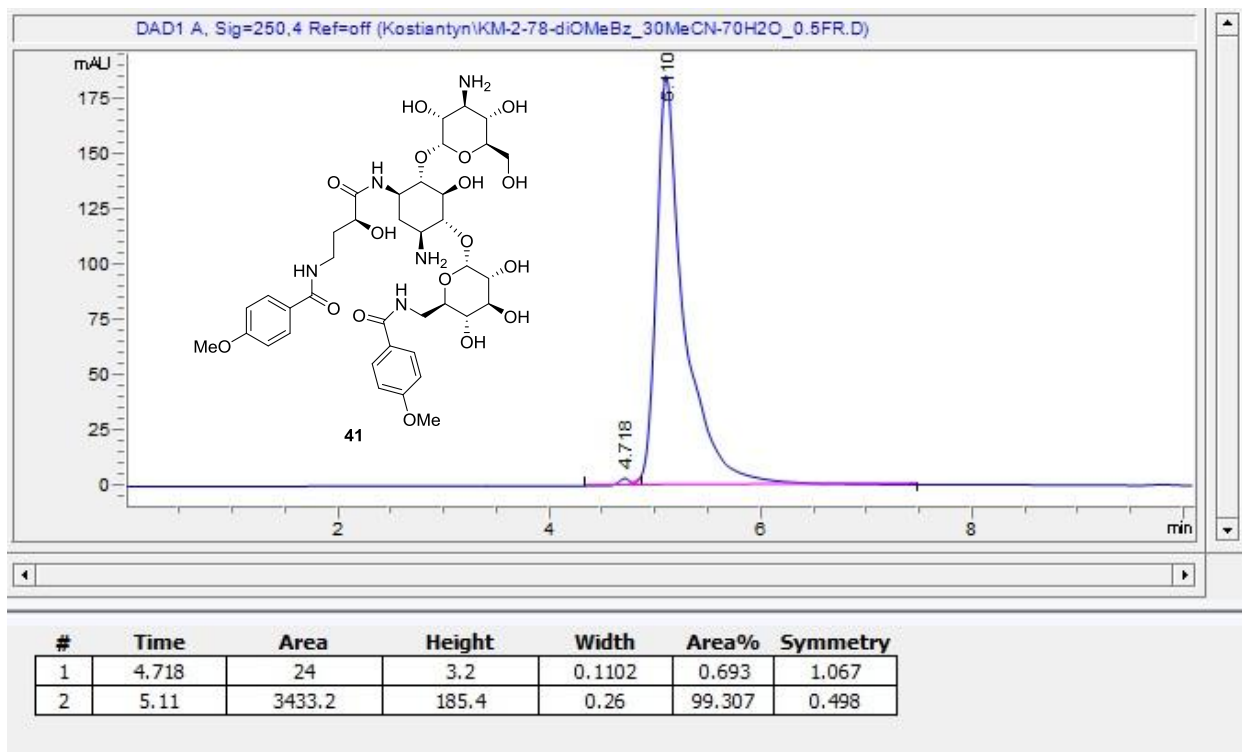
Lichrospher® 100 NH₂ (5µm) C18 column, flow rate 0.5 mL/min, H₂O/CH₃CN = 60:40



Lichrospher® 100 NH₂ (5µm) C18 column, flow rate 0.5 mL/min, H₂O/CH₃CN = 70:30



Lichrospher® 100 NH₂ (5µm) C18 column, flow rate 0.5 mL/min, H₂O/CH₃CN = 70:30



Lichrospher® 100 NH₂ (5µm) C18 column, flow rate 0.5 mL/min, H₂O/CH₃CN = 70:30

