

Supplementary Material

3-Aminopropylazetidines: facile synthesis and application for medicinal chemical purposes

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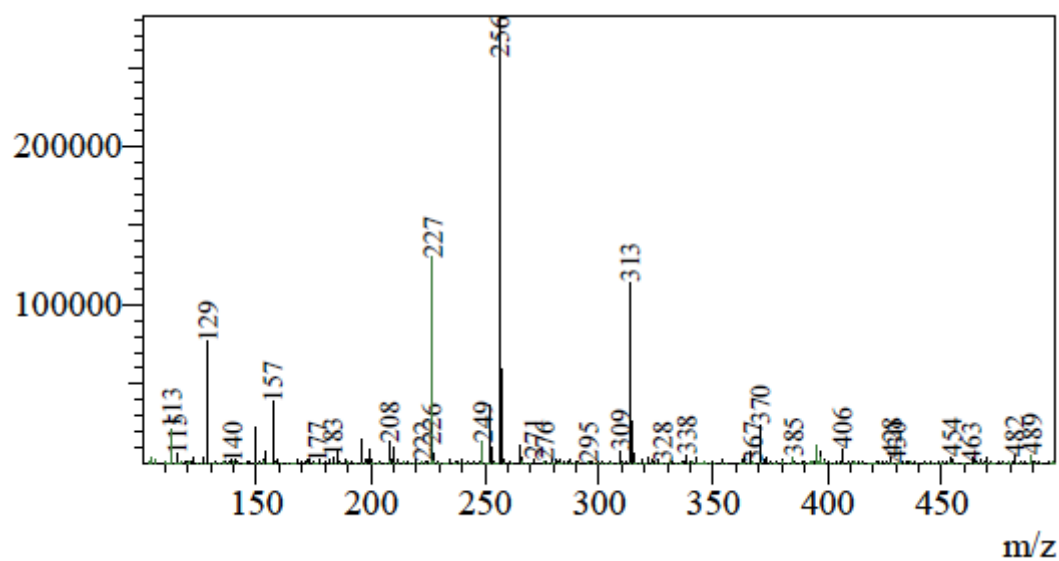


Figure S1. Mass spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-5-amine TFA salt (3).

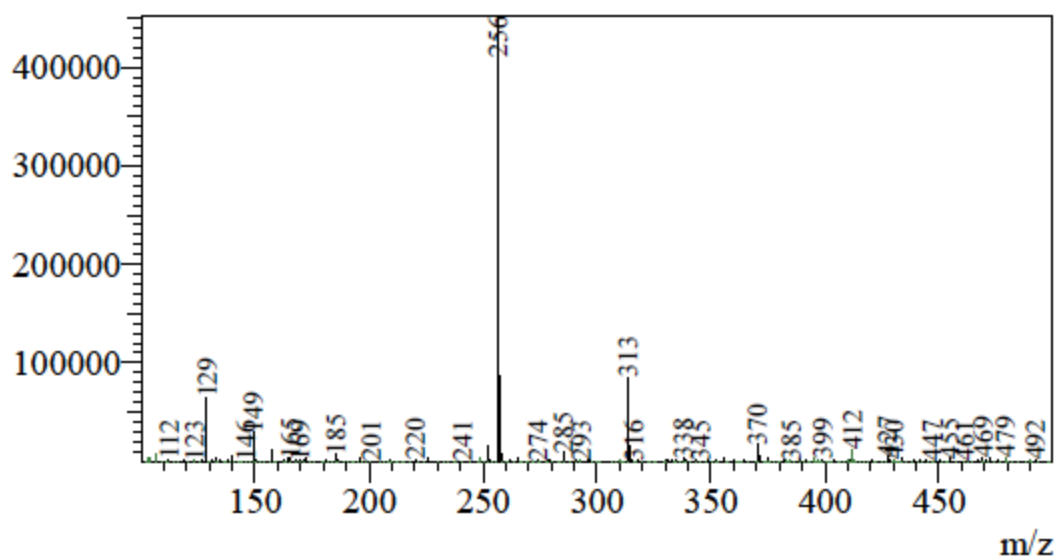


Figure S2. Mass spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-7-amine TFA salt (4).

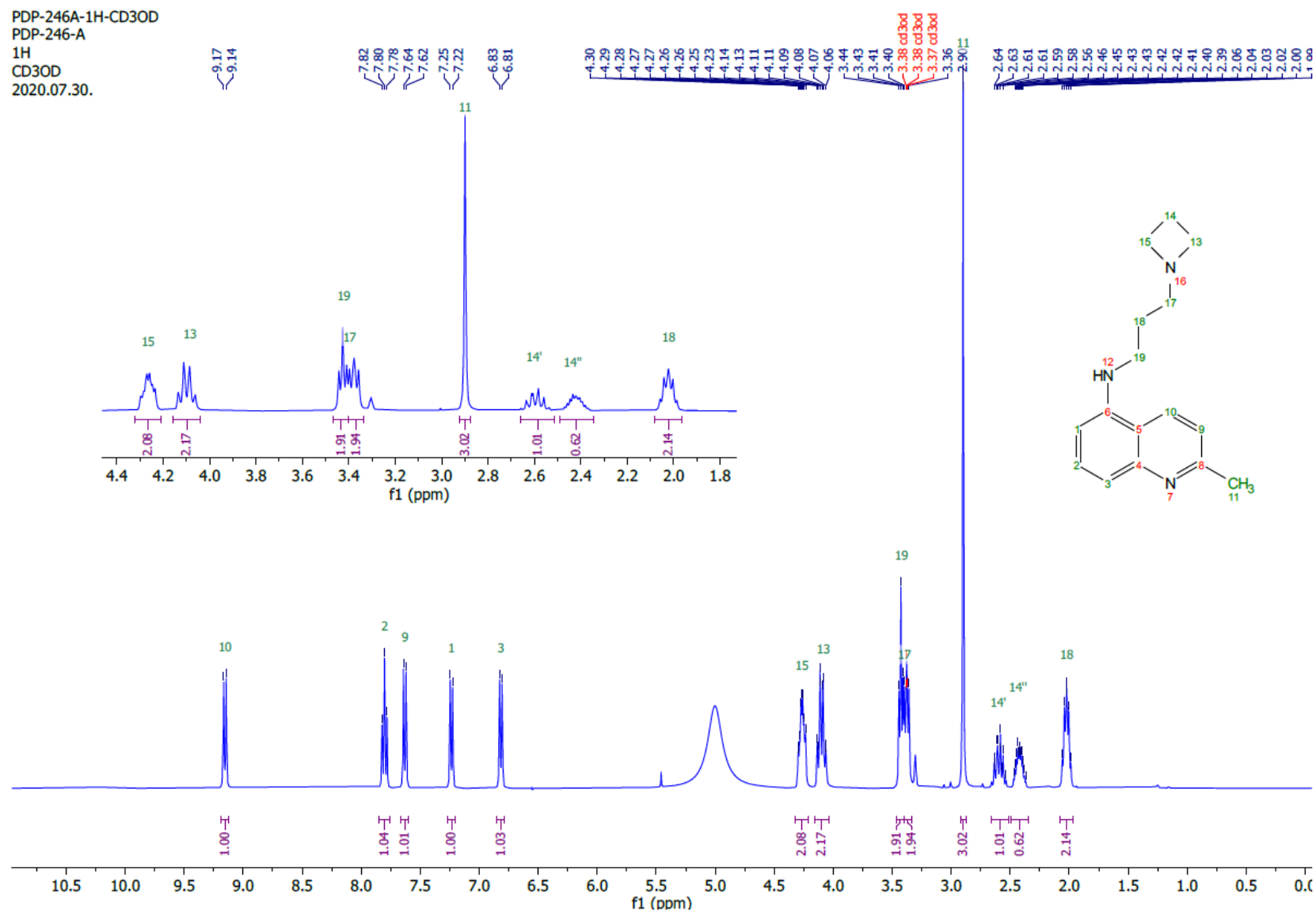


Figure S3: ^1H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-5-amine TFA salt (**3**) recorded at 400 MHz in CD_3OD .

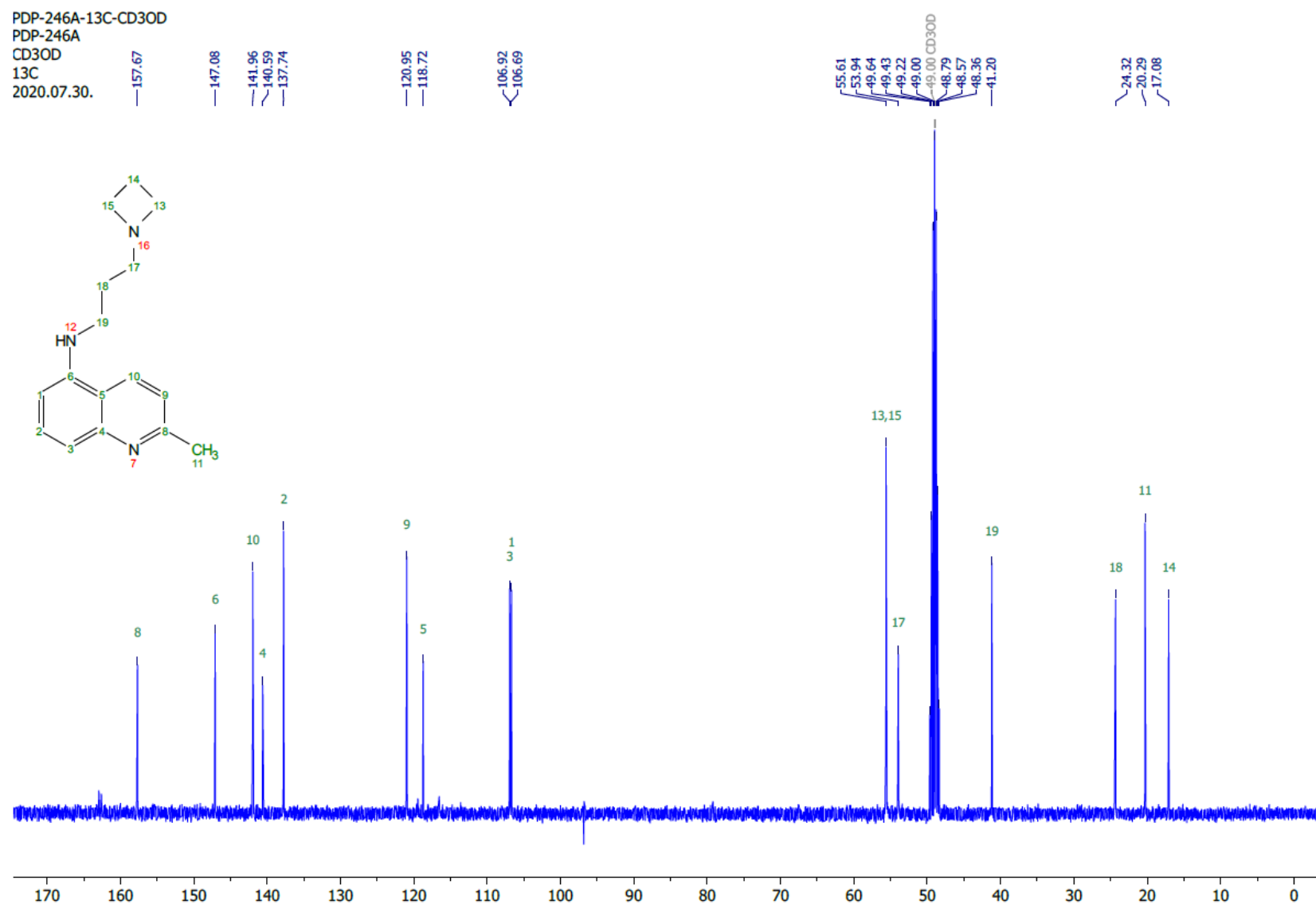


Figure S4: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-5-amine TFA salt (**3**) recorded at 400 MHz in CD_3OD .

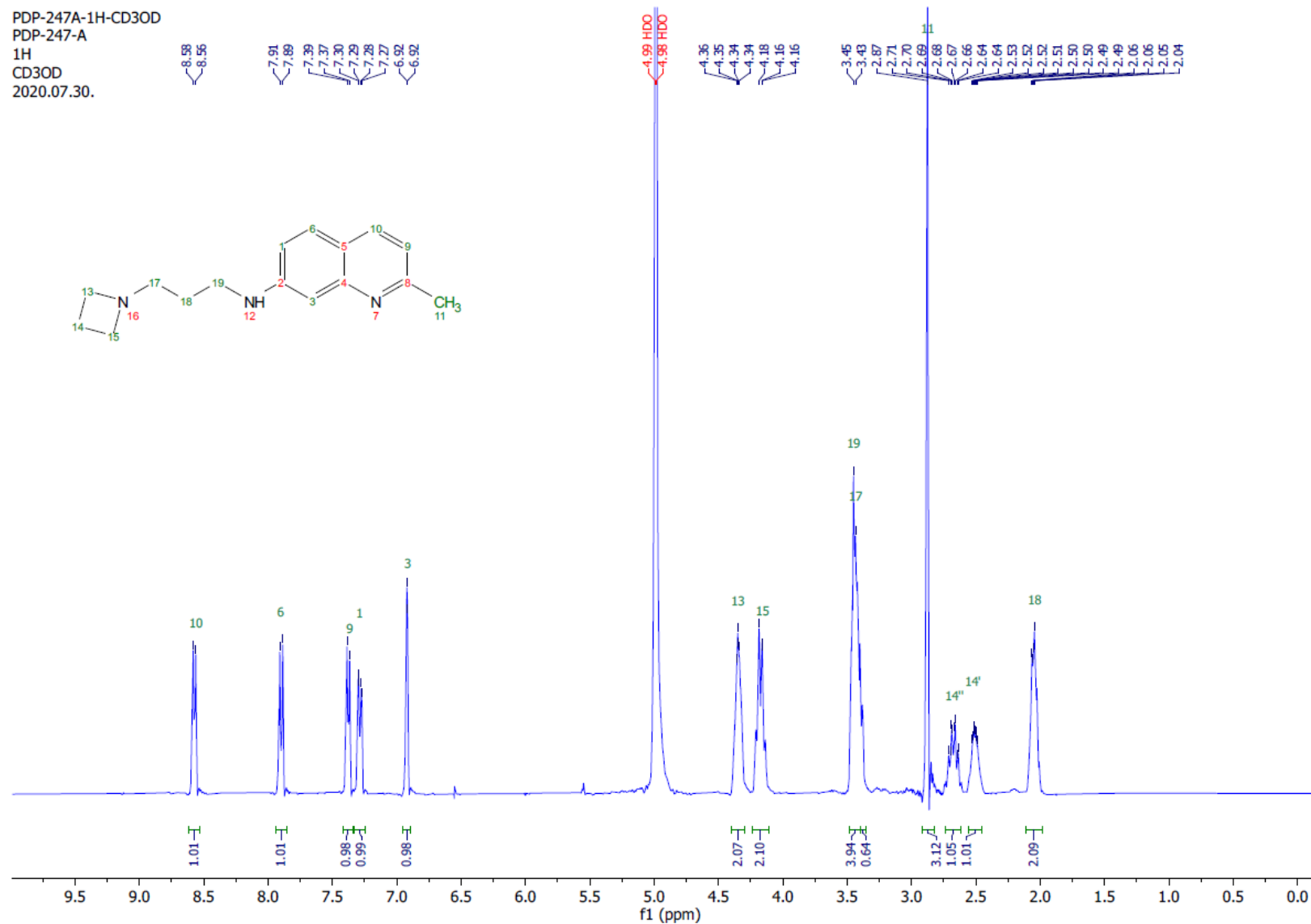


Figure S5: ¹H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-7-amine TFA salt (4) recorded at 400 MHz in CD₃OD.

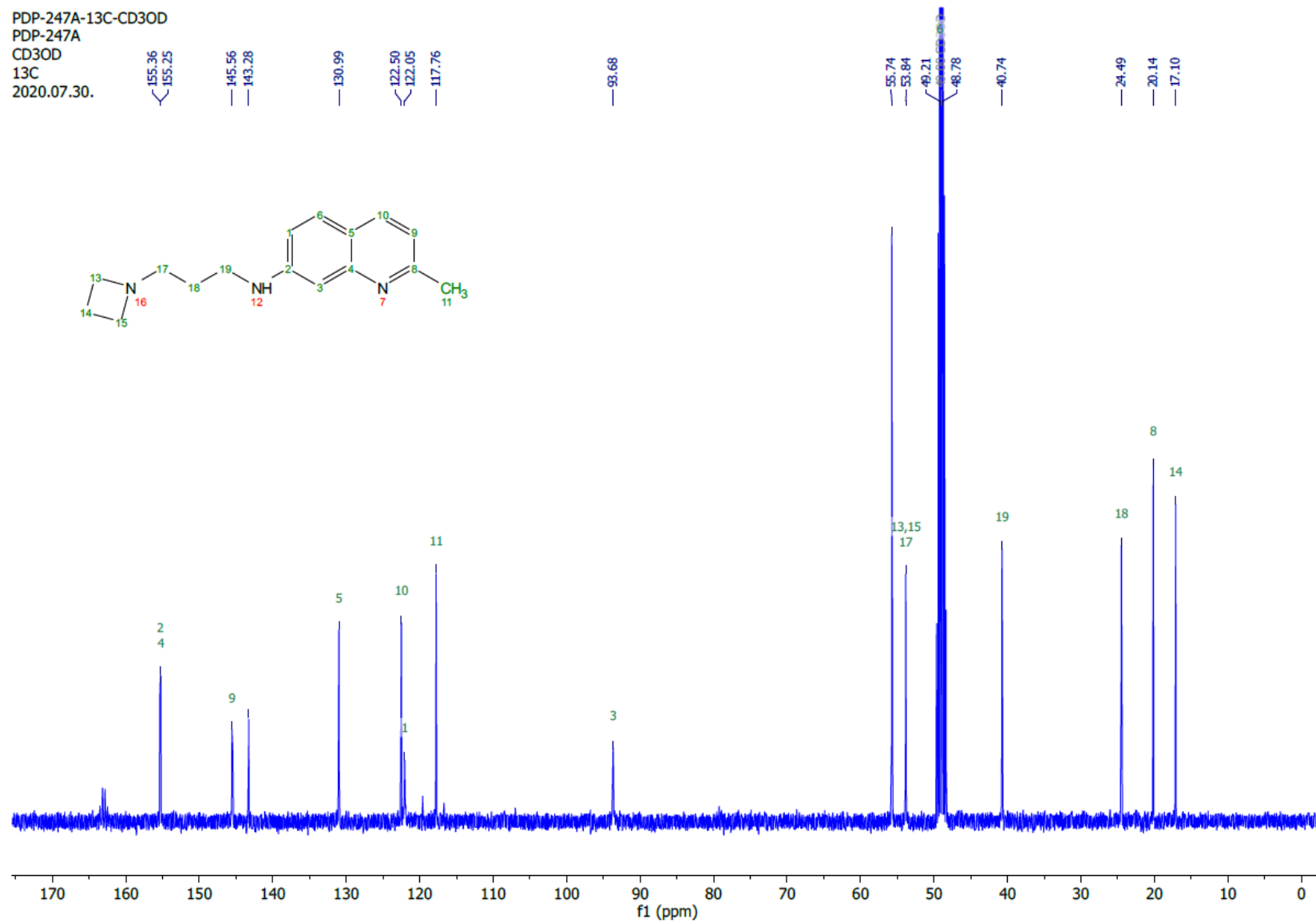


Figure S6: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-7-amine TFA salt (**4**) recorded at 400 MHz in CD_3OD .

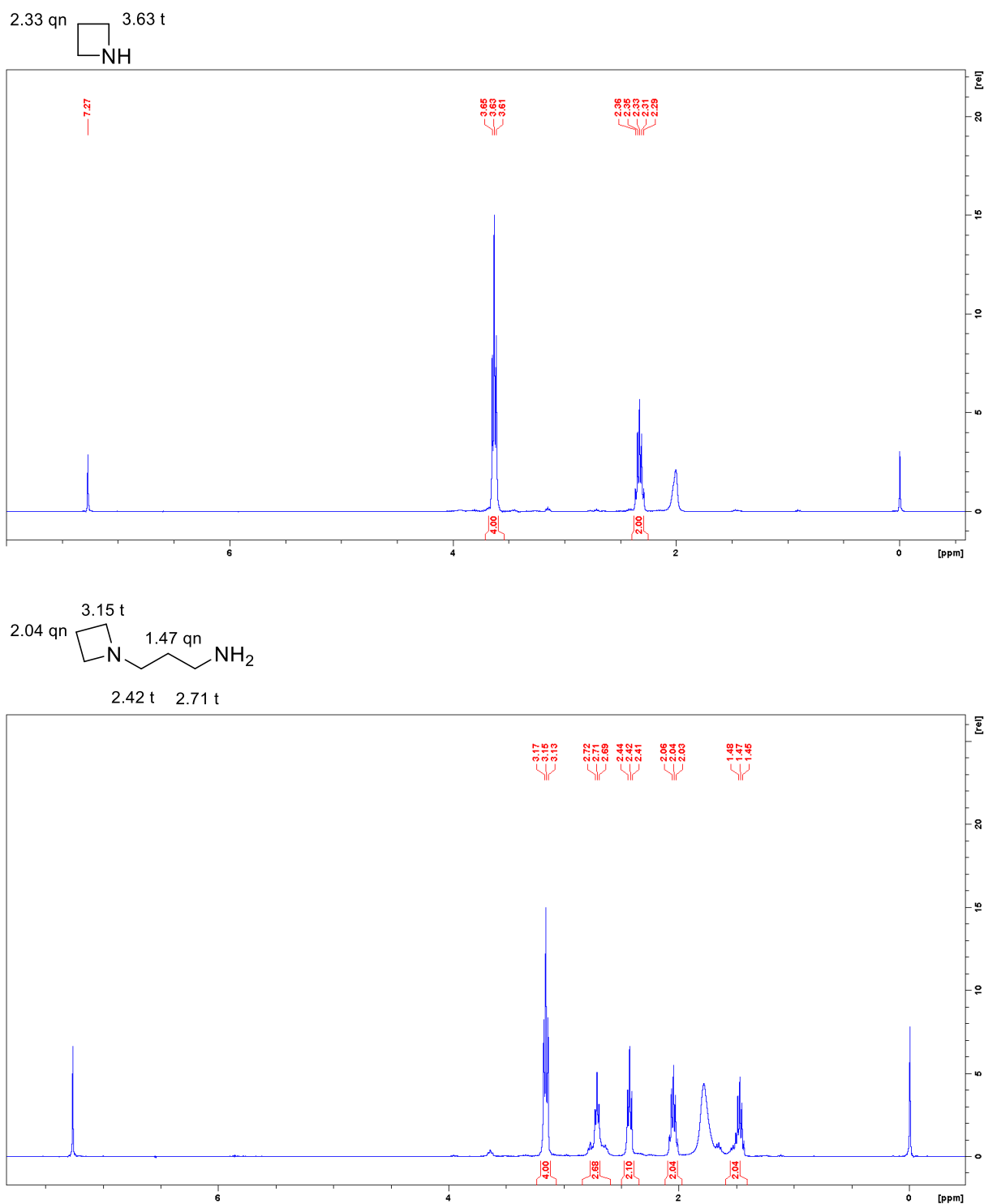
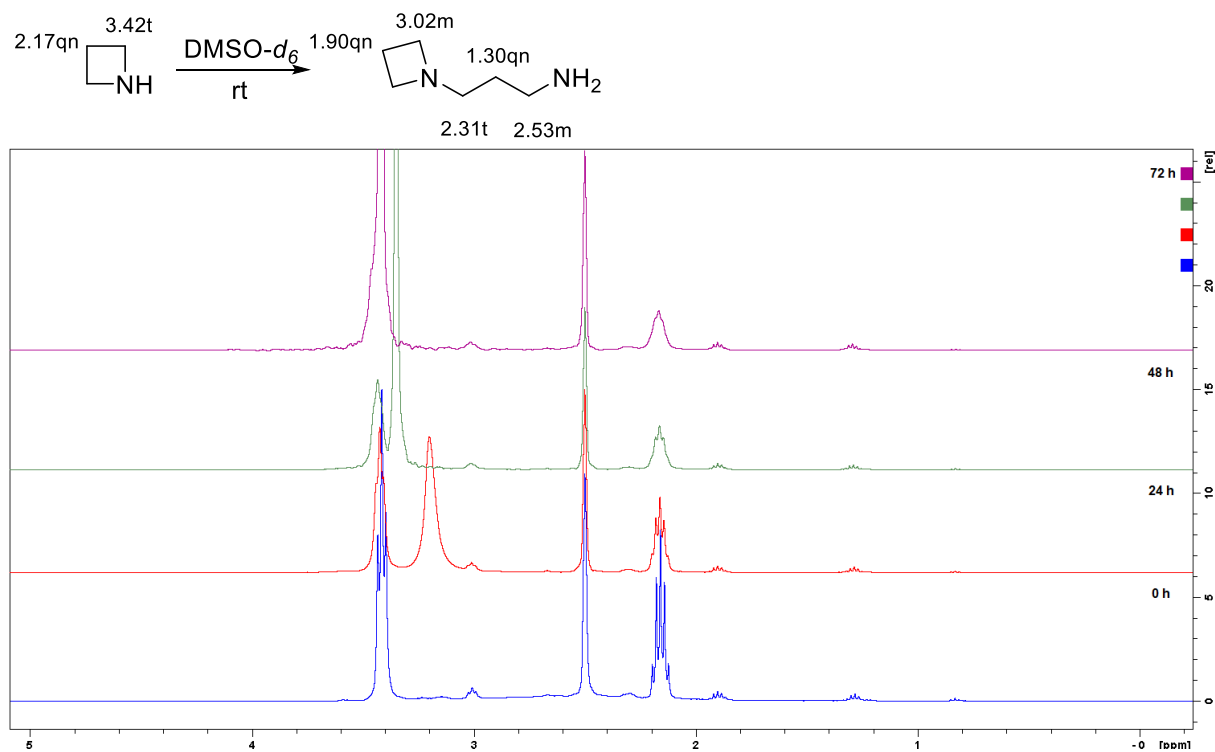
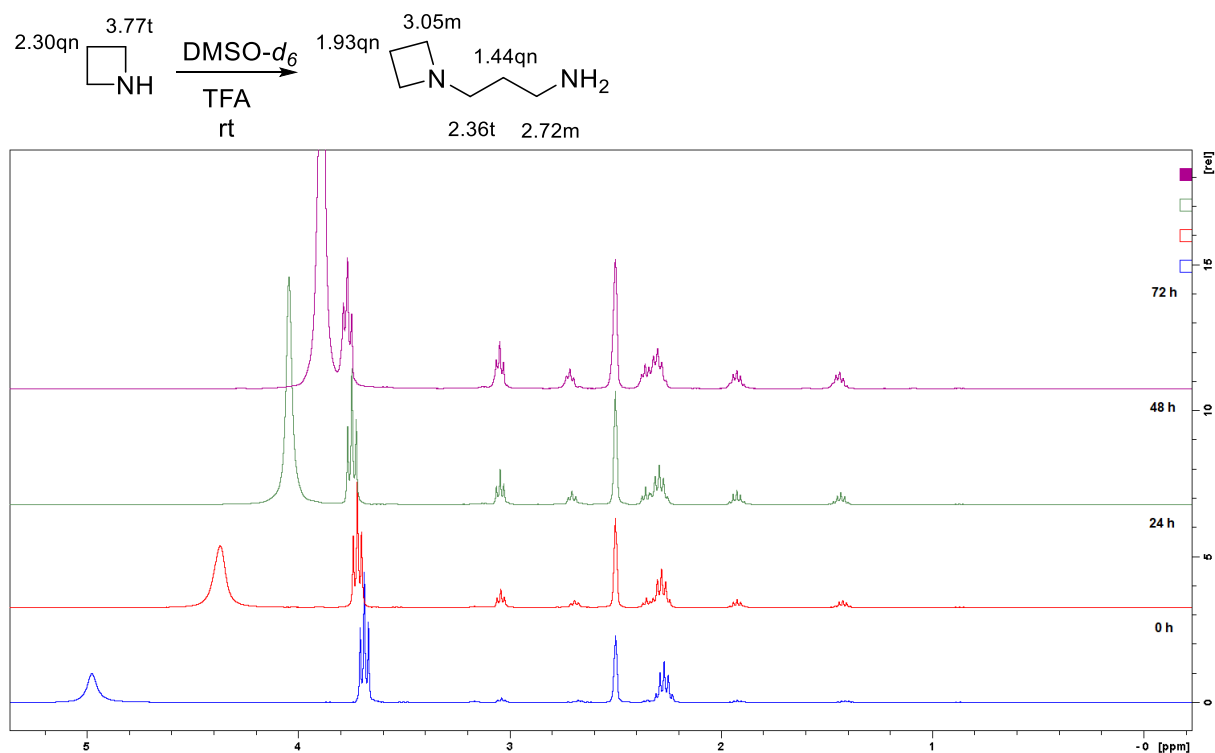


Figure S7. ^1H NMR spectrum (400 MHz, CDCl_3) of azetidine (**8**) and 3-(azetidin-1-yl)propan-1-amine (**7**).

**Figure S8.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine at rt.**Figure S9.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + TFA at rt.

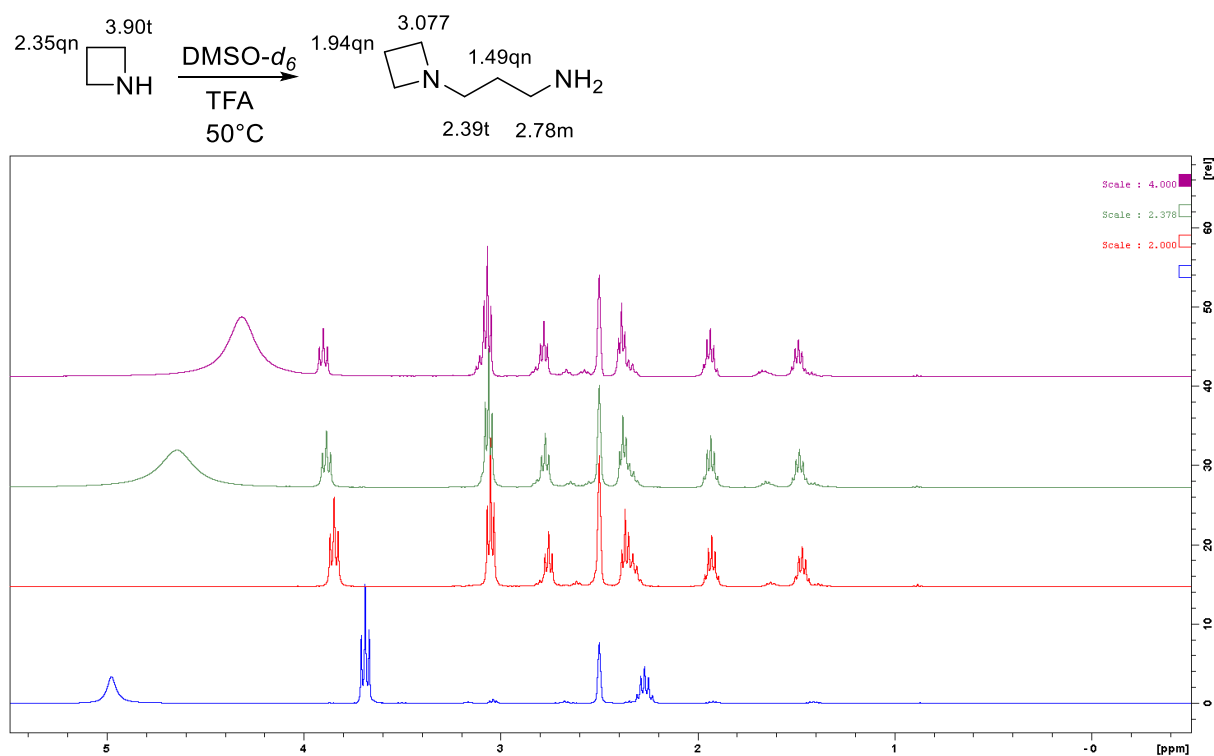


Figure S10. ^1H NMR (400 MHz, DMSO- d_6) monitoring of azetidine + TFA at 50°C.

PDP-358-deszt2-1H-DMSO
PDP-358 deszt2
DMSO
2022.06.07.

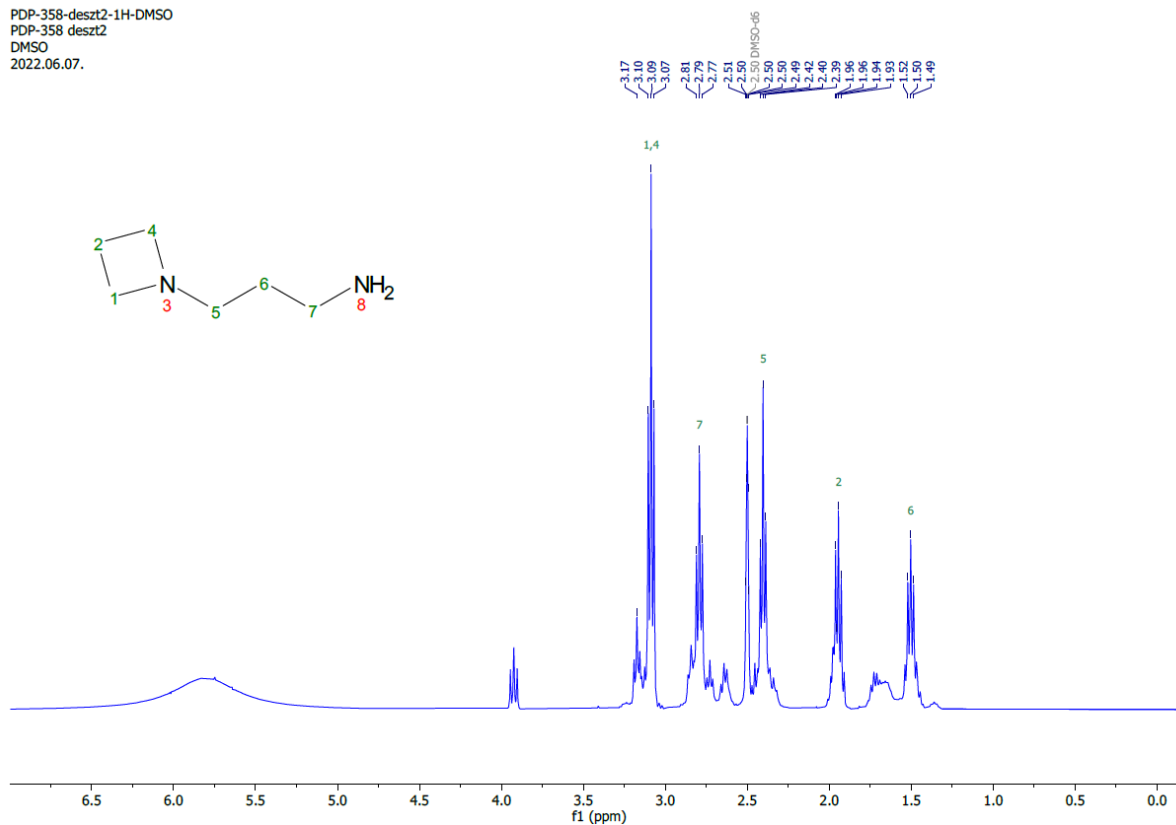


Figure S11. ^1H NMR (400 MHz, DMSO- d_6) monitoring of azetidine + TFA at 50°C (synthetic experiment A).

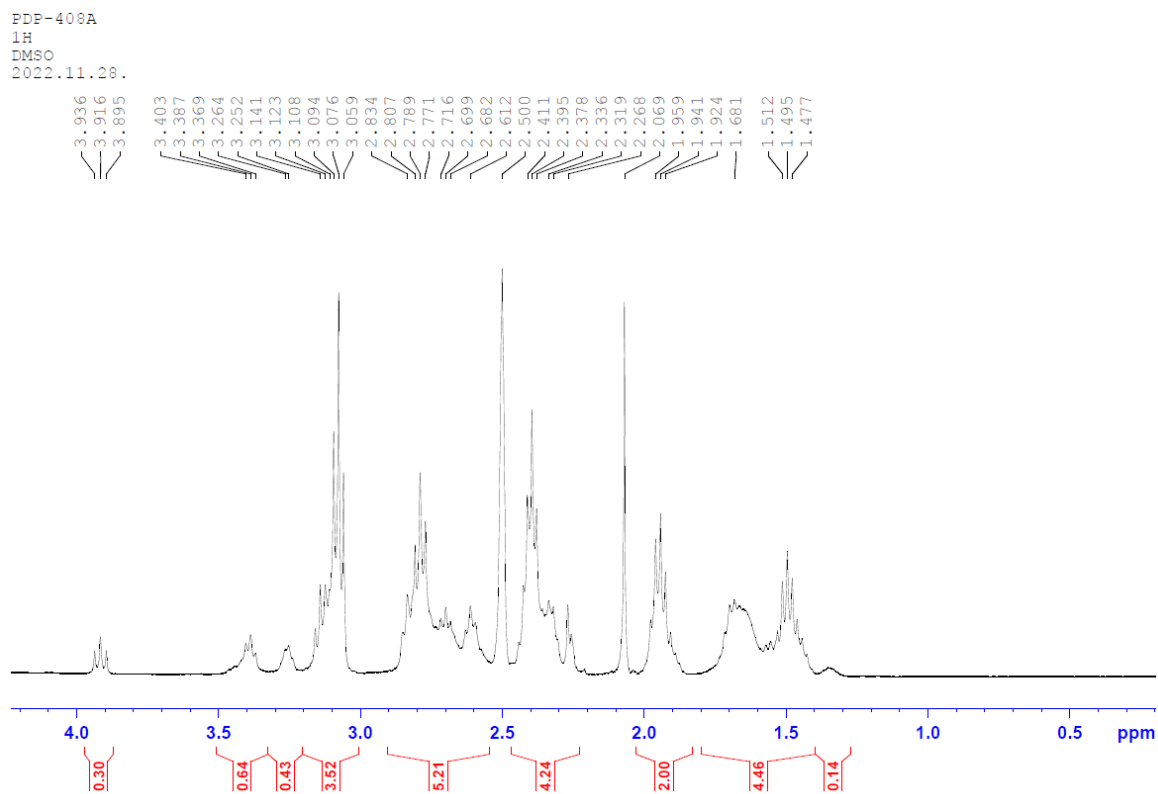


Figure S12. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) of the crude product of the reaction of azetidine + TFA at 50°C (synthetic experiment B).

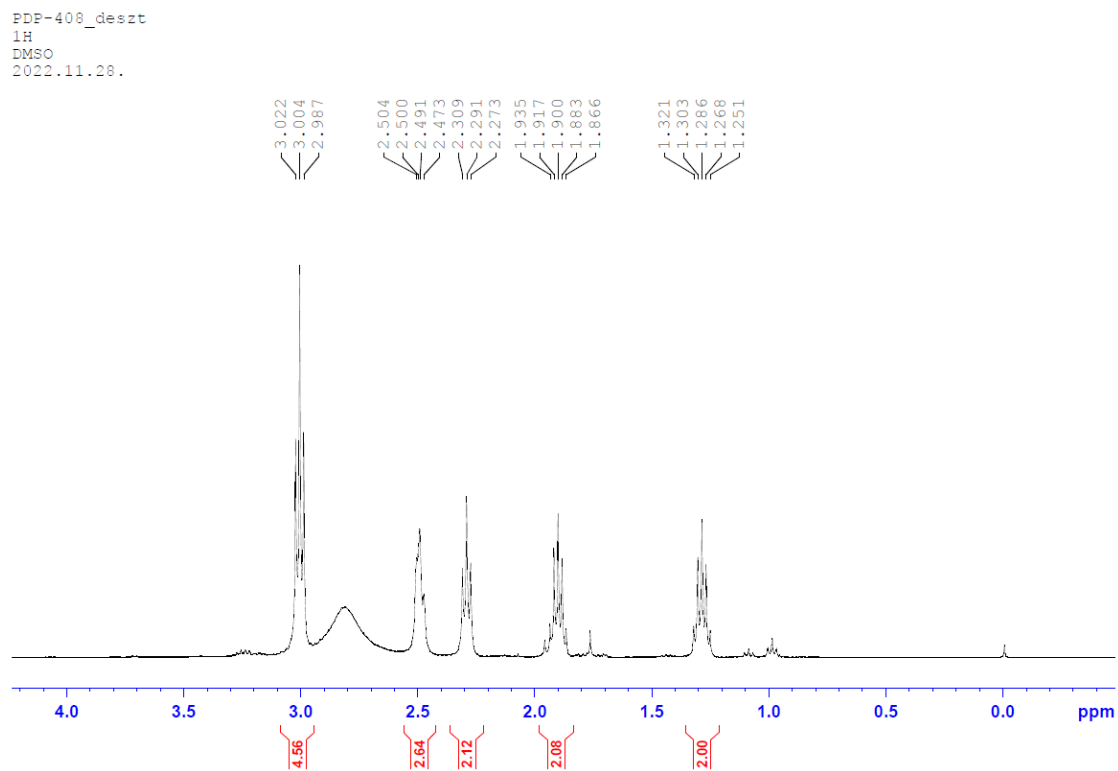
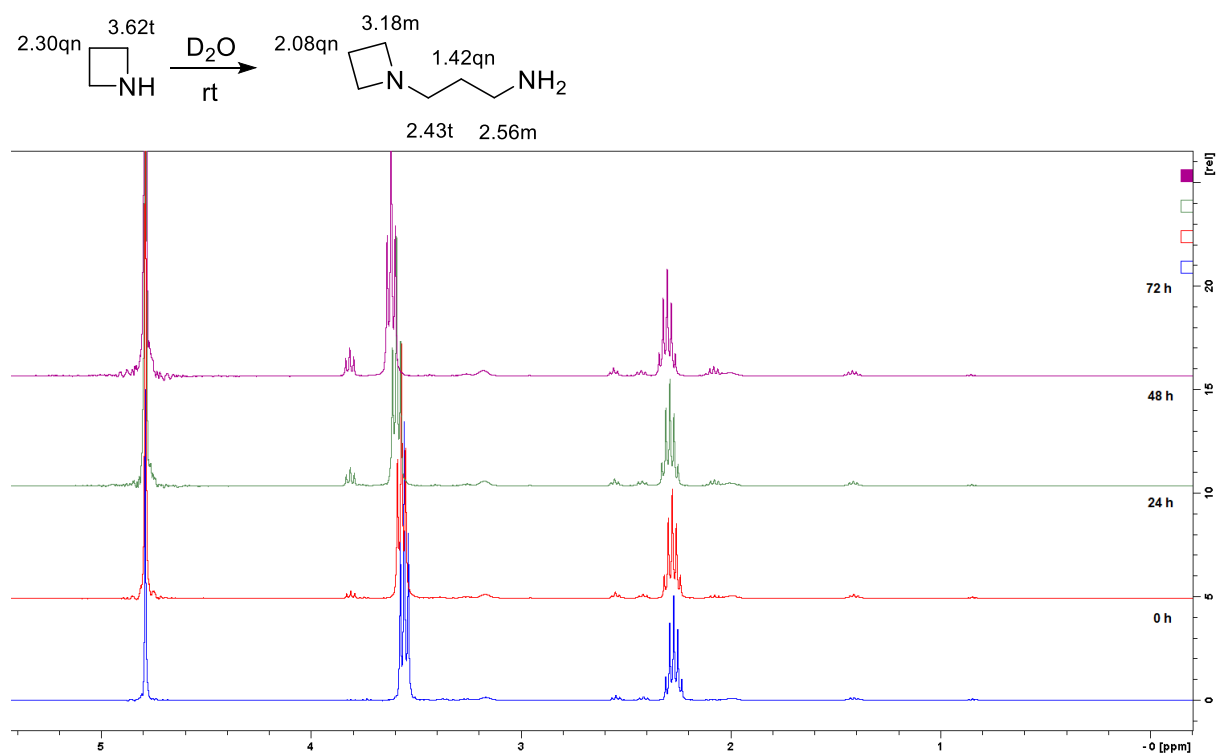
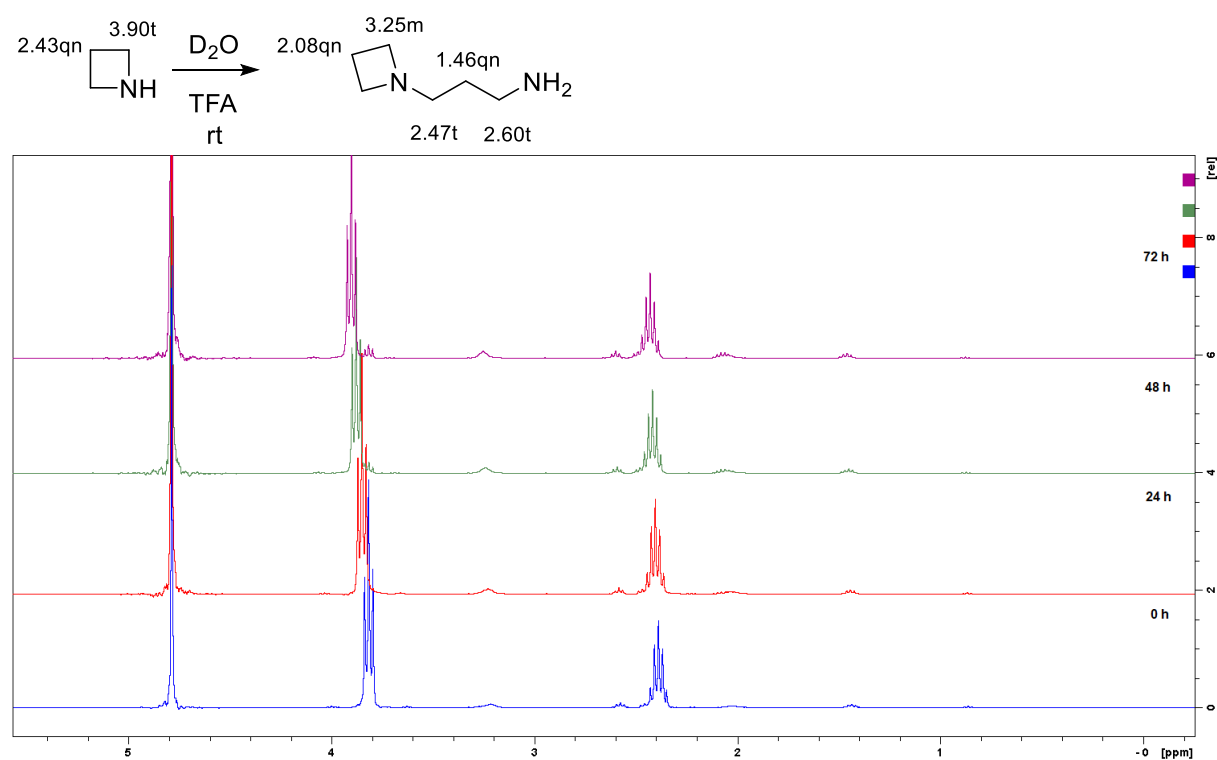
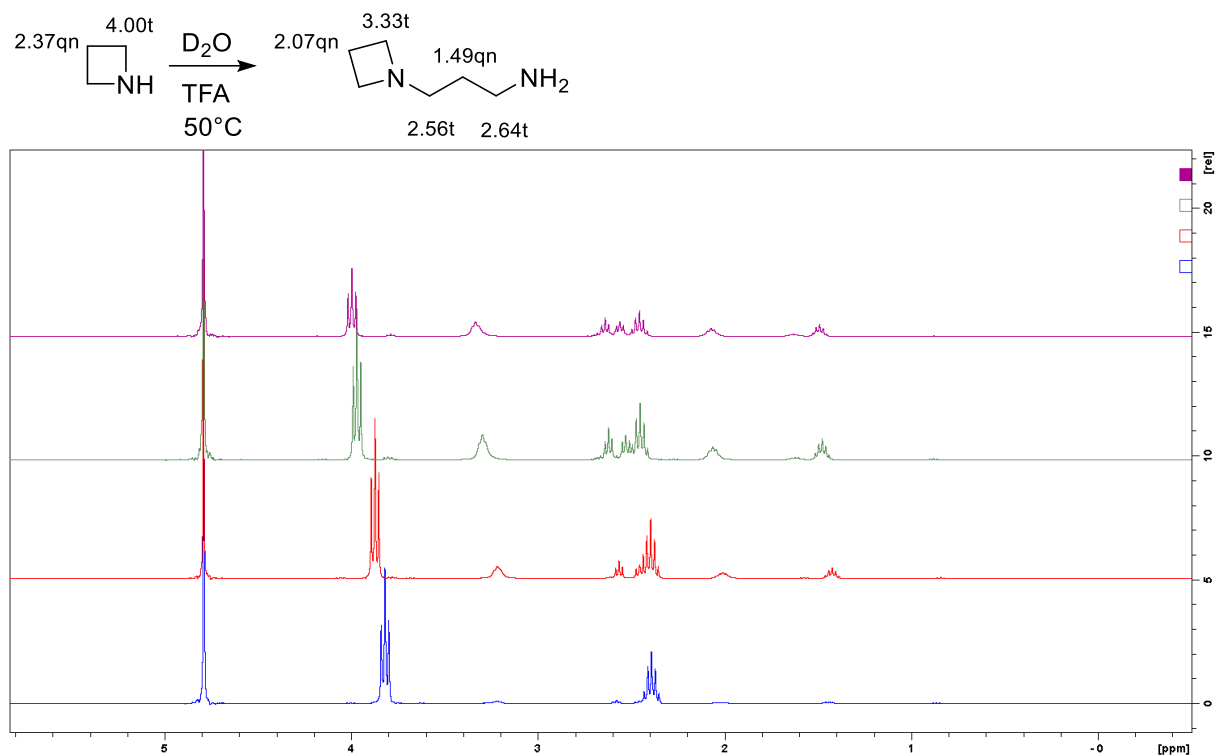
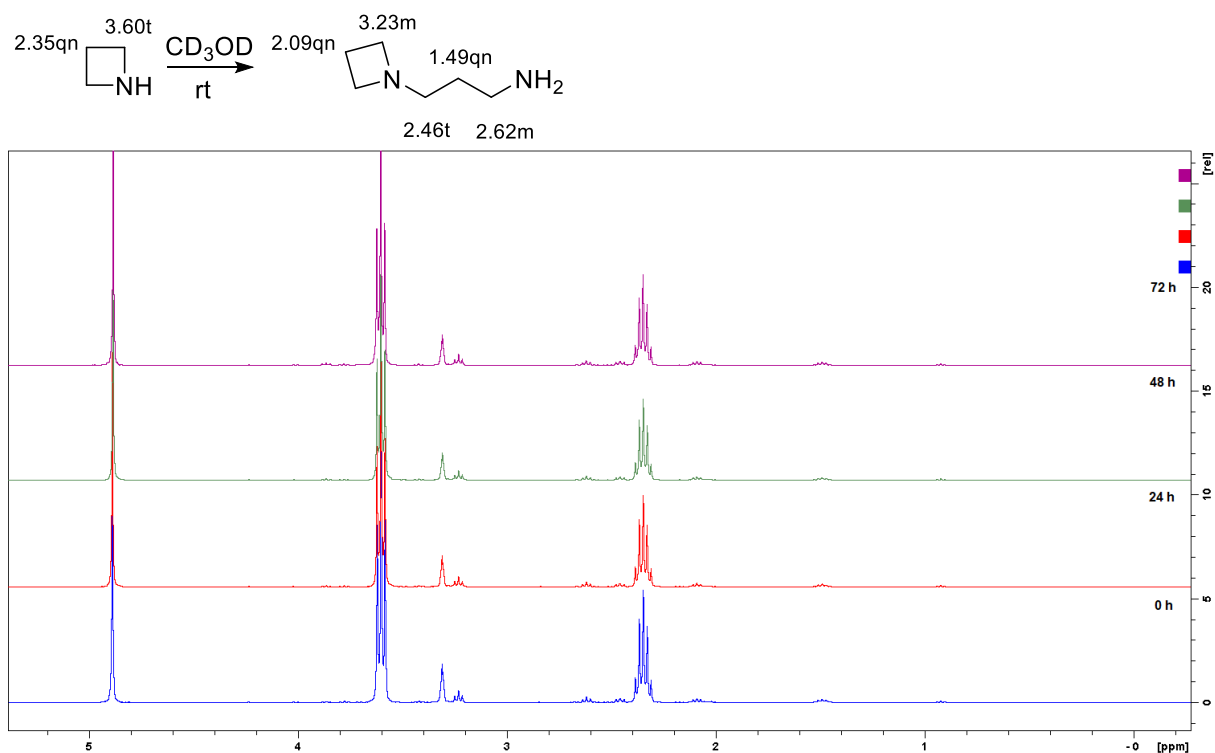
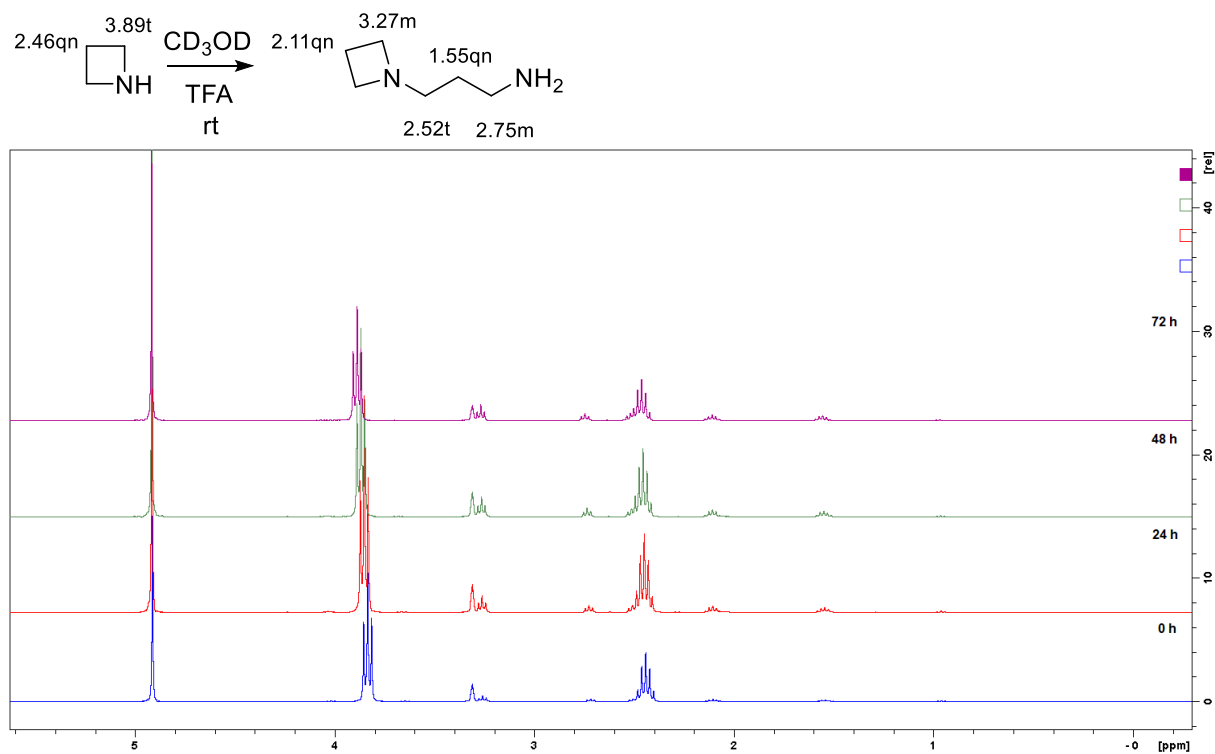
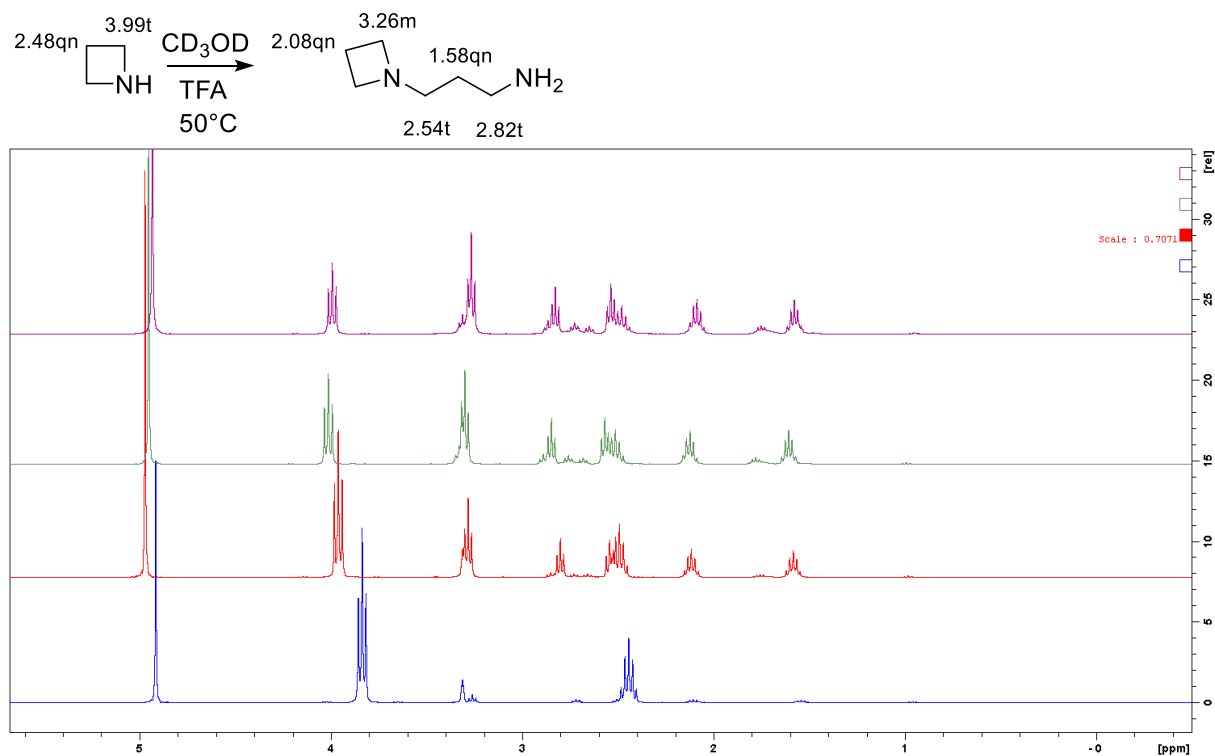


Figure S13. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) after vacuum distillation of the product (**7**) (synthetic experiment B).

**Figure S14.** ^1H NMR (400 MHz, D_2O) monitoring of azetidine at rt.**Figure S15.** ^1H NMR (400 MHz, D_2O) monitoring of azetidine + TFA at rt.

**Figure S16.** ^1H NMR (400 MHz, D_2O) monitoring of azetidine + TFA at 50°C .**Figure S17.** ^1H NMR (400 MHz, CD_3OD) monitoring of azetidine at rt.

**Figure S18.** ^1H NMR (400 MHz, CD_3OD) monitoring of azetidine + TFA at rt.**Figure S19.** ^1H NMR (400 MHz, CD_3OD) monitoring of azetidine + TFA at 50°C .

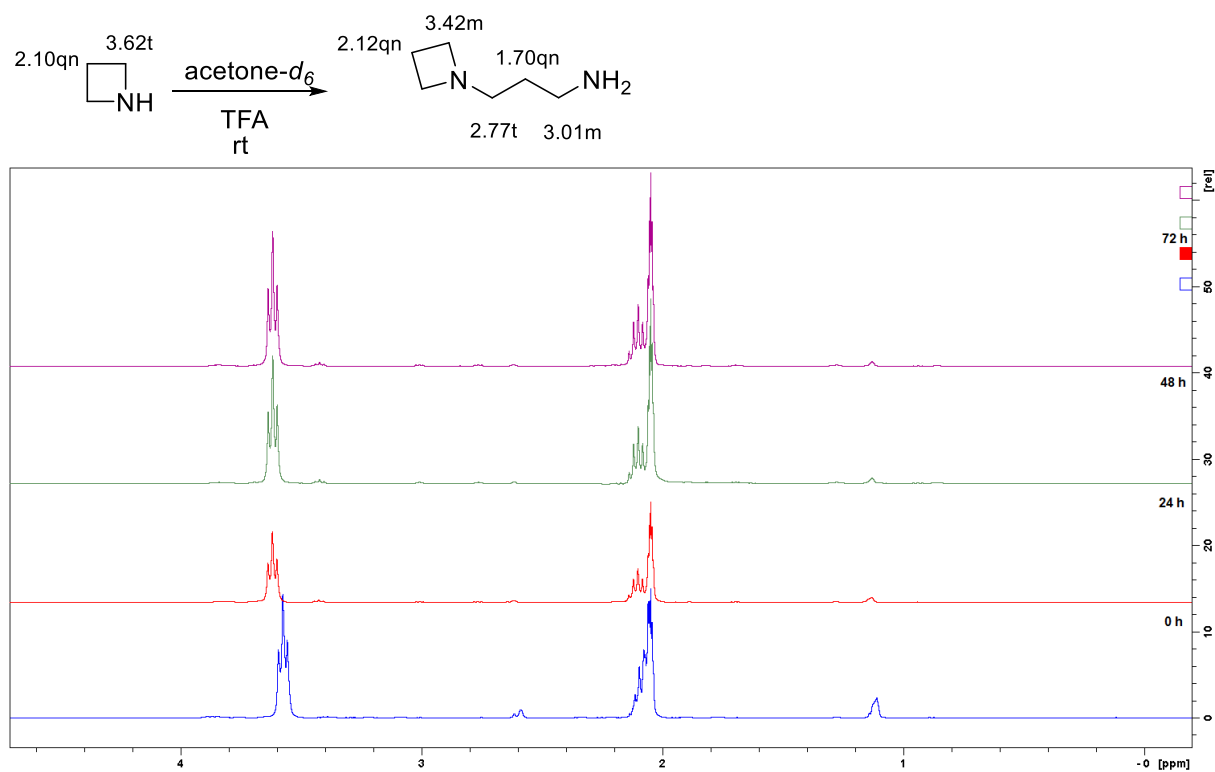


Figure S20. ^1H NMR (400 MHz, acetone-d_6) monitoring of azetidine + TFA at rt.

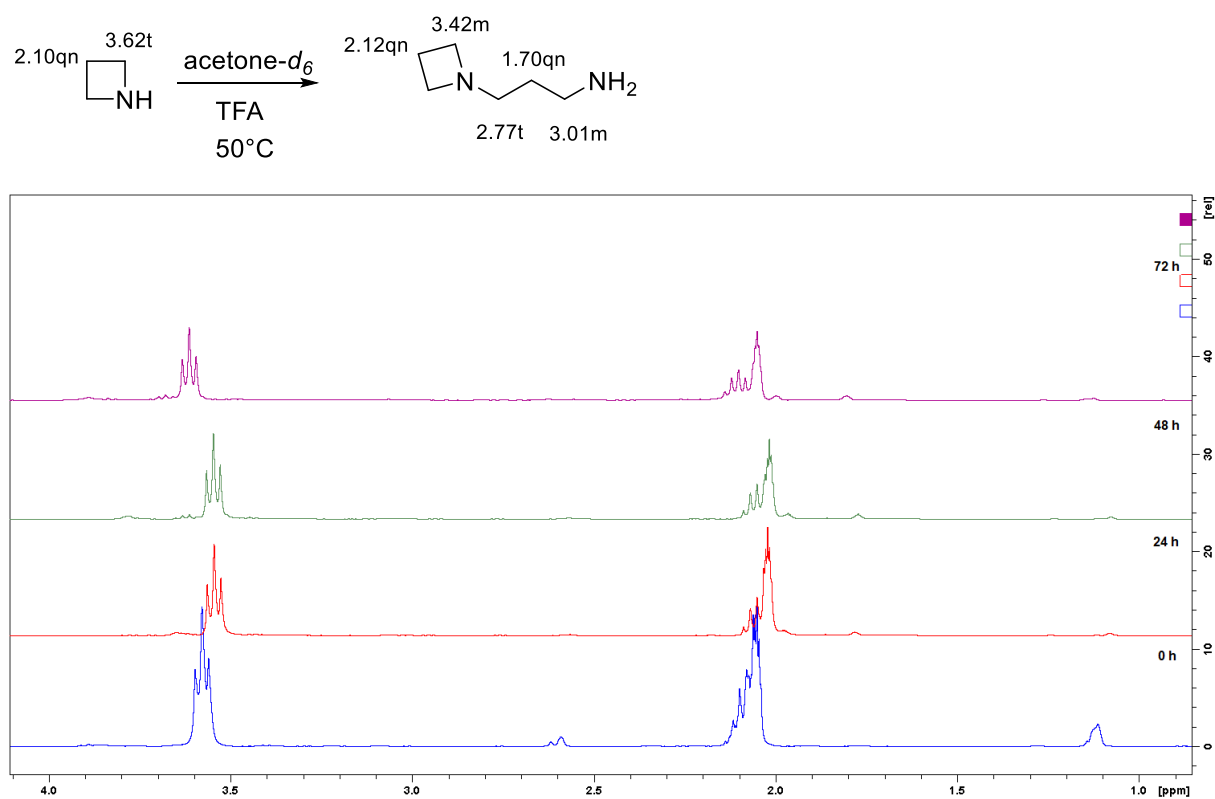
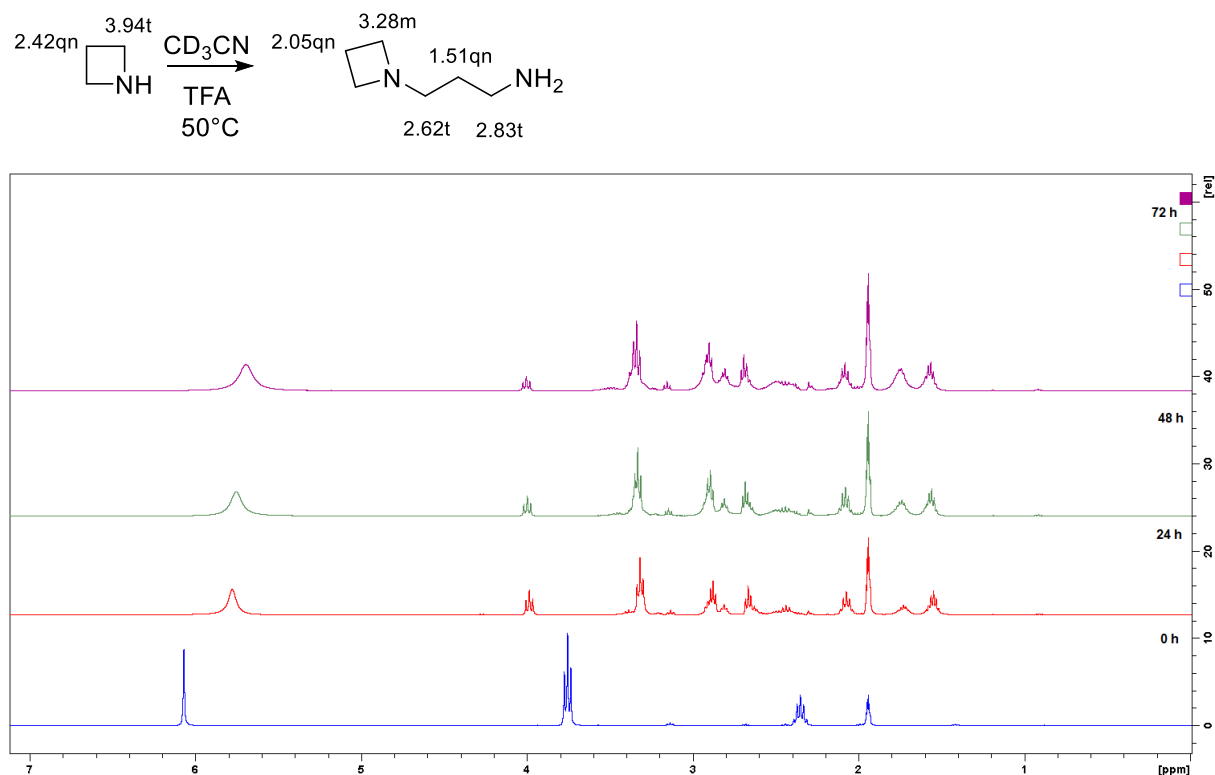
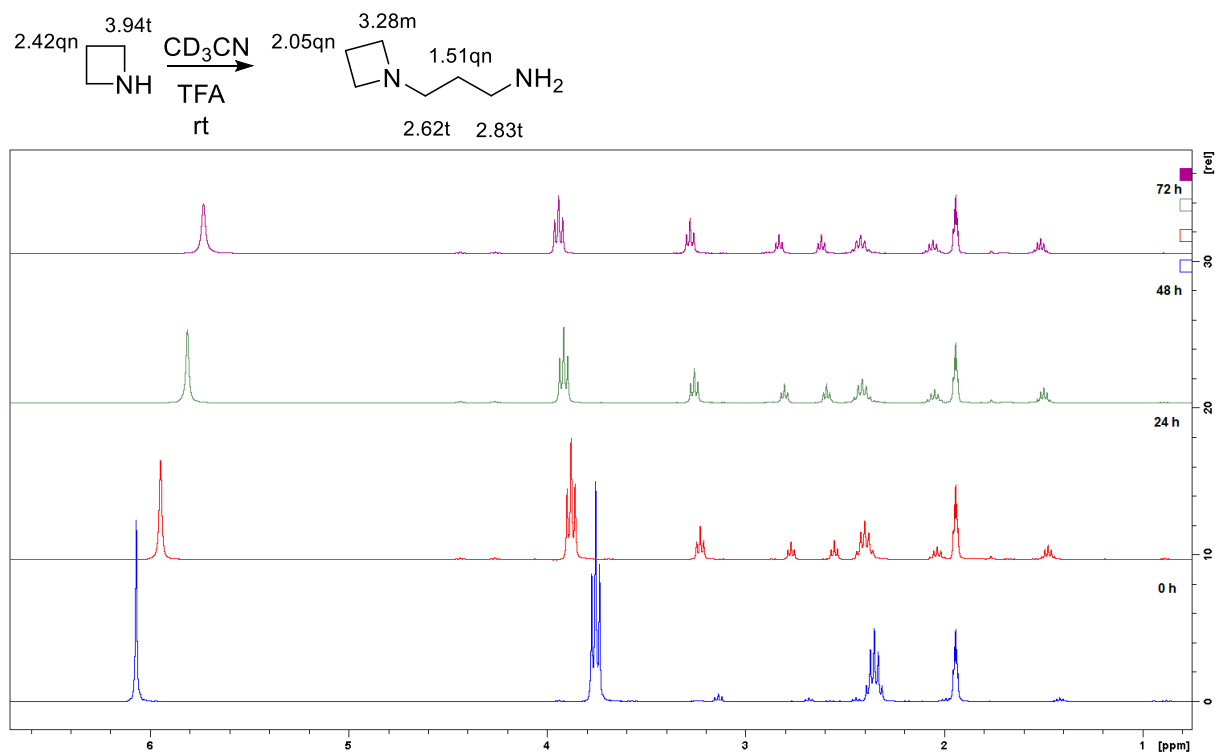


Figure S21. ^1H NMR (400 MHz, acetone-d_6) monitoring of azetidine + TFA at 50°C.



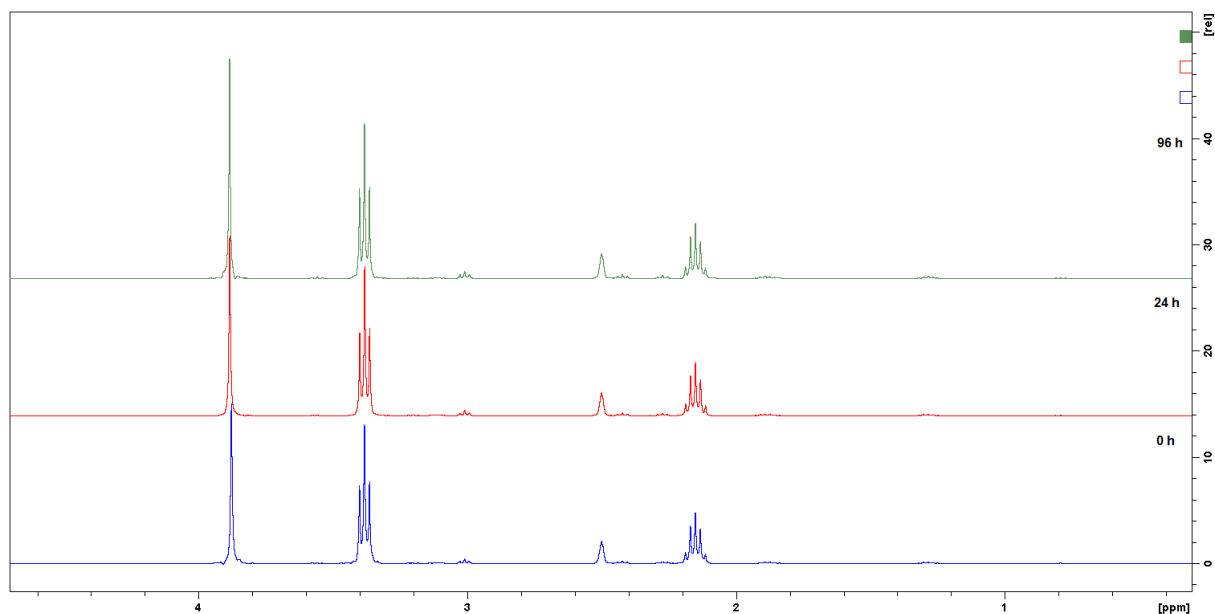
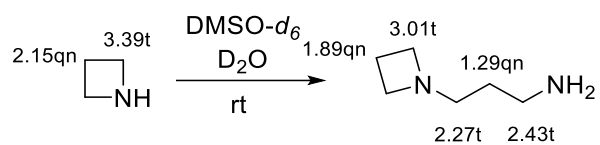


Figure S24. ^1H NMR (400 MHz, $\text{DMSO-}d_6+\text{D}_2\text{O}$ (9:1)) monitoring of azetidine at rt.

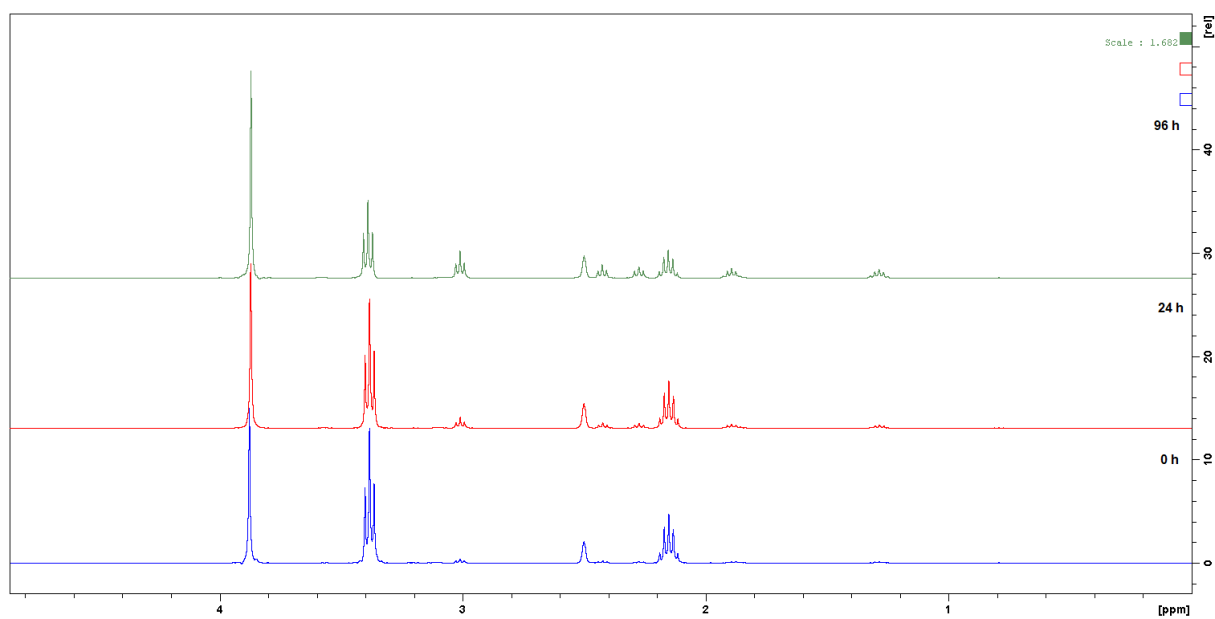
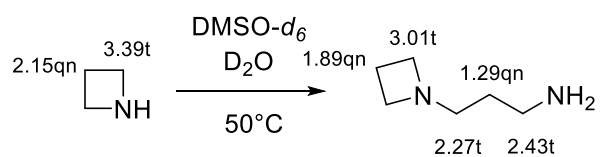
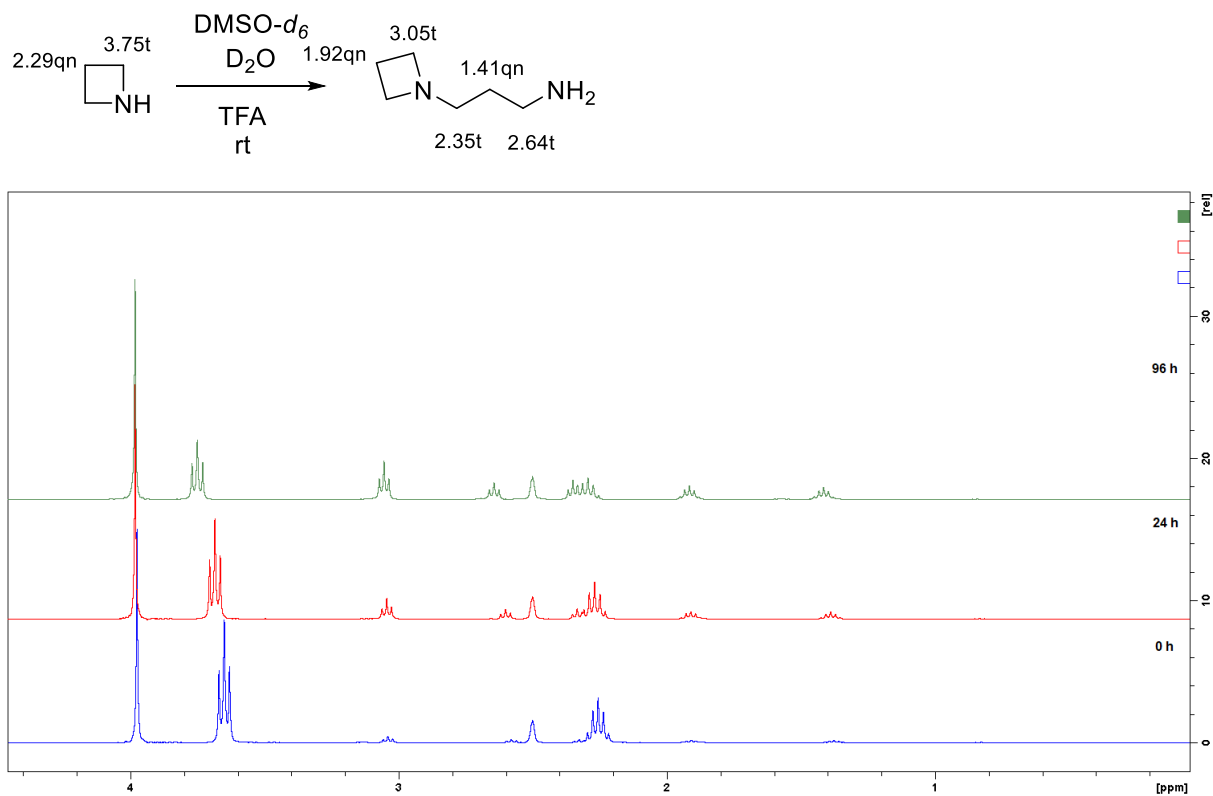
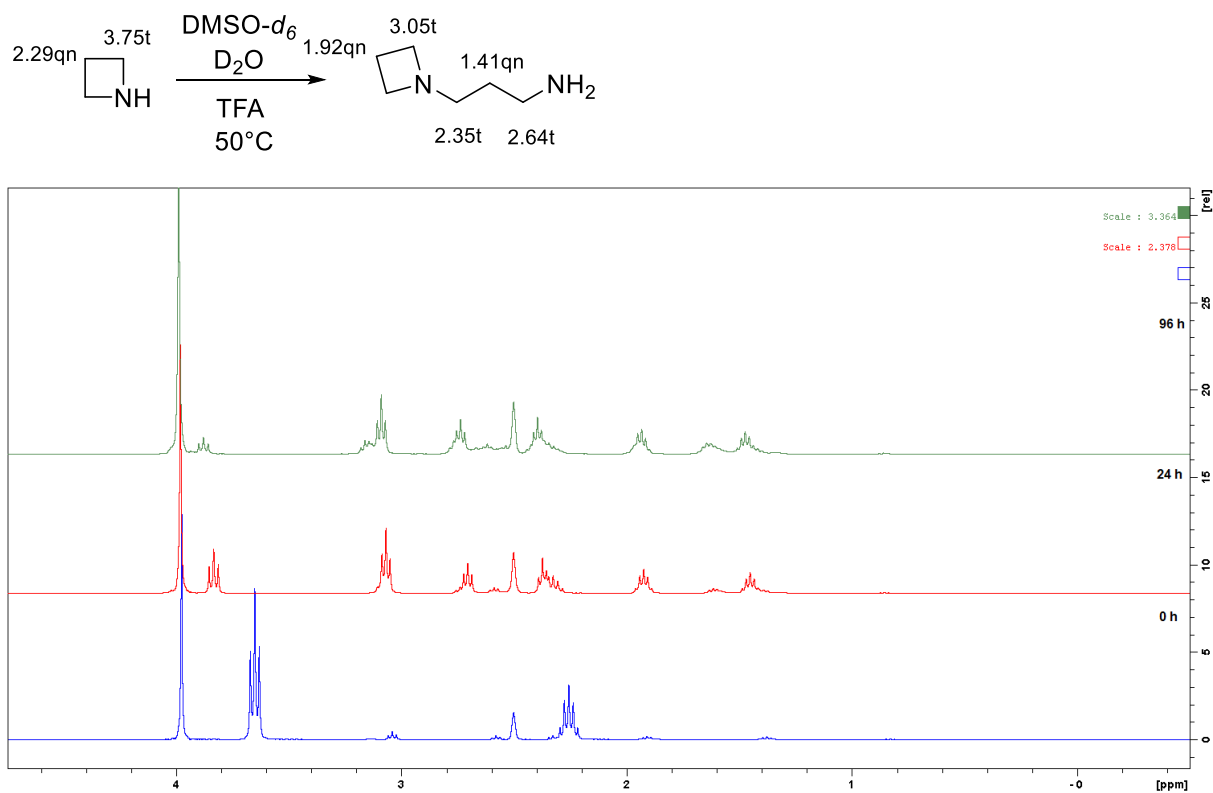


Figure S25. ^1H NMR (400 MHz, $\text{DMSO-}d_6+\text{D}_2\text{O}$ (9:1)) monitoring of azetidine at 50°C .

**Figure S26.** ^1H NMR (400 MHz, $\text{DMSO-}d_6+\text{D}_2\text{O}$ (9:1)) monitoring of azetidine + TFA at rt.**Figure S27.** ^1H NMR (400 MHz, $\text{DMSO-}d_6+\text{D}_2\text{O}$ (9:1)) monitoring of azetidine + TFA at 50°C .

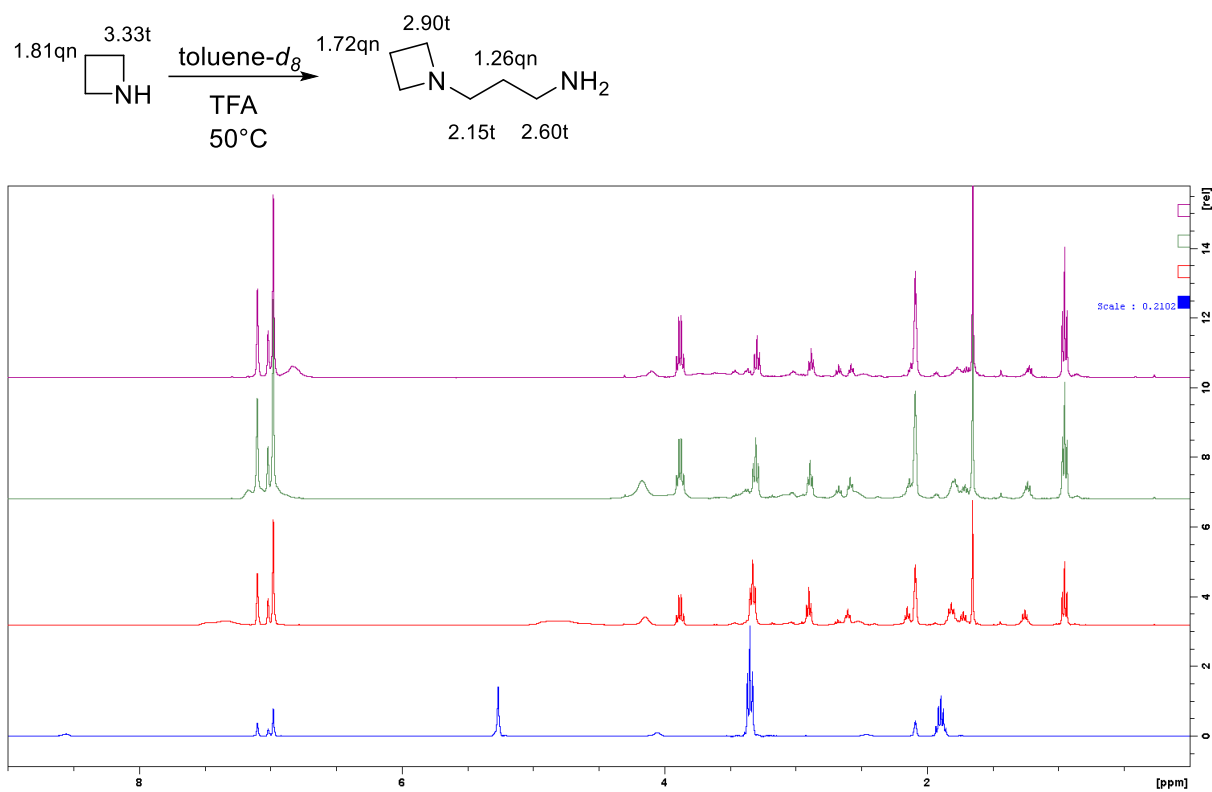


Figure S28. ^1H NMR (400 MHz, $\text{toluene-}d_8$) monitoring of azetidine + TFA at 50°C .

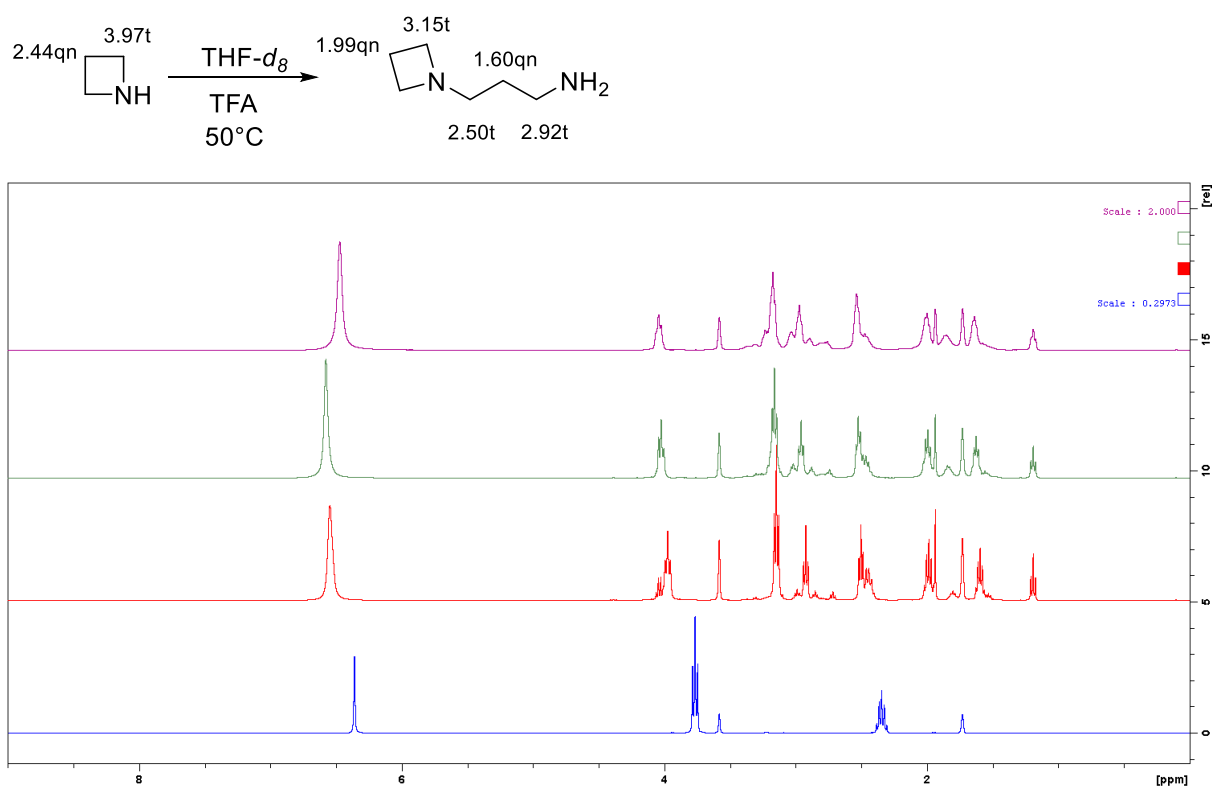
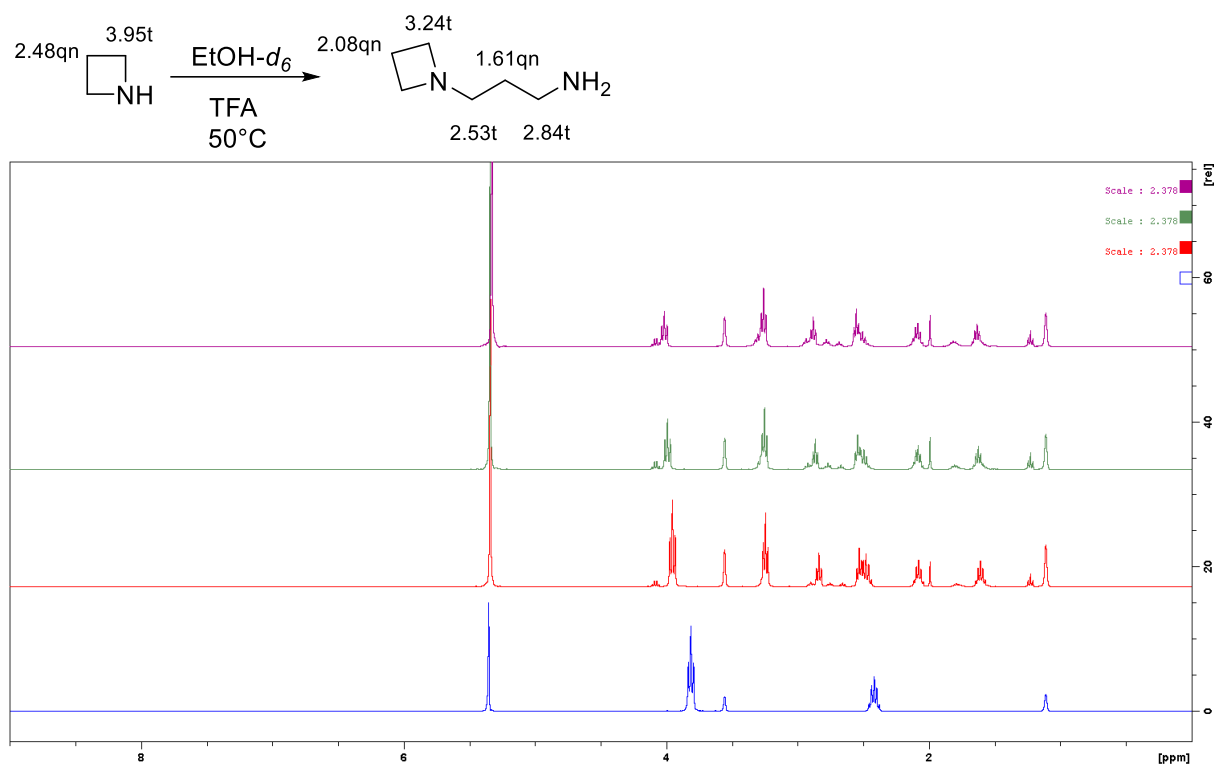
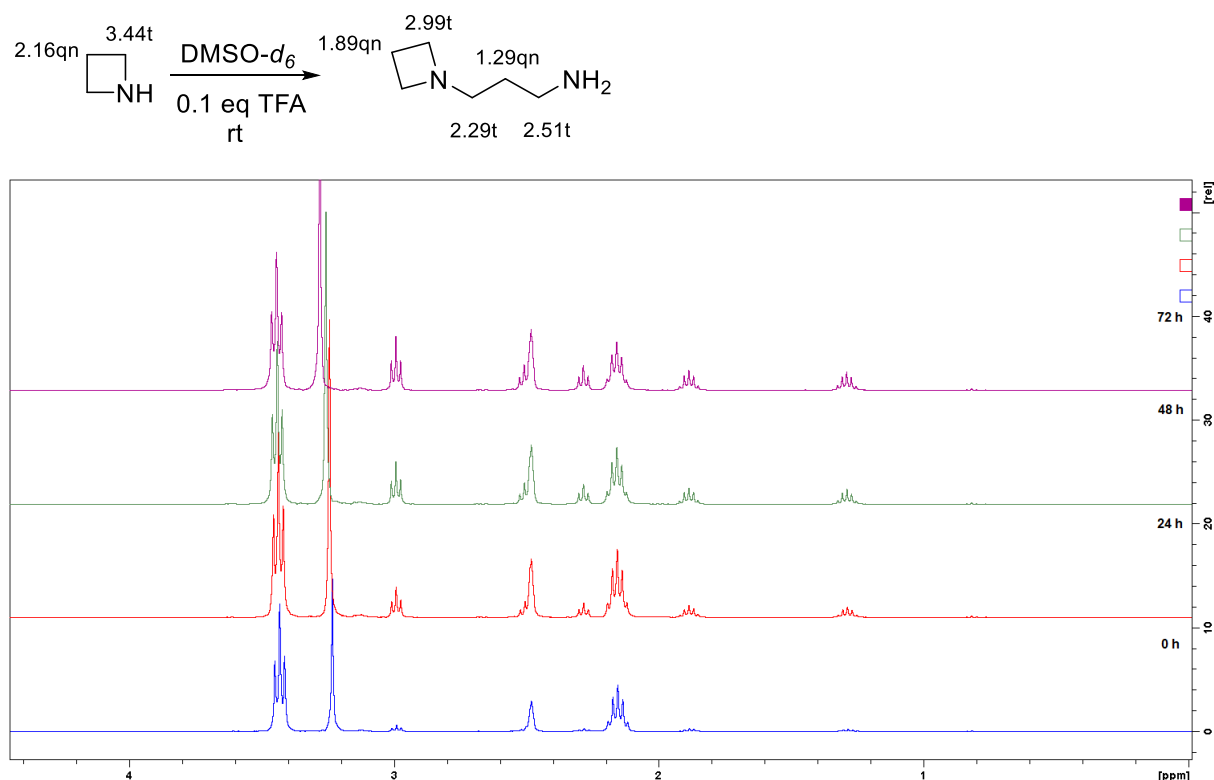
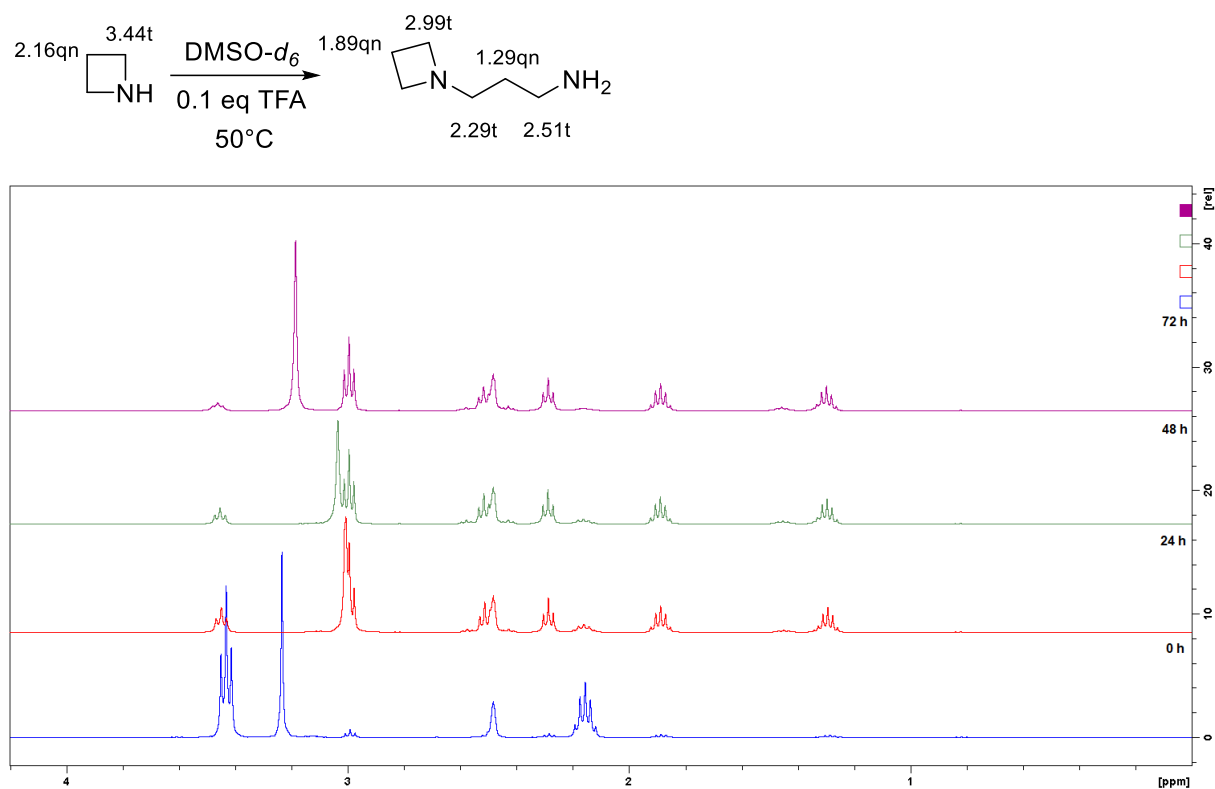
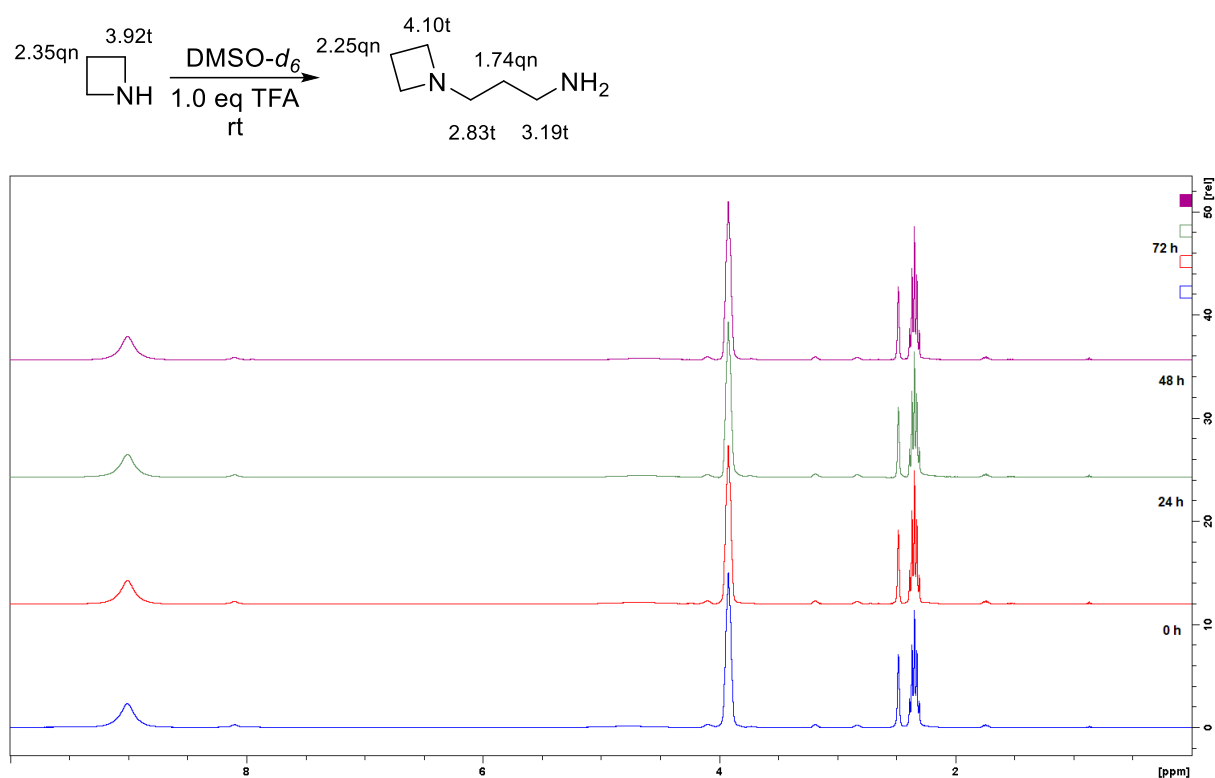


Figure S29. ^1H NMR (400 MHz, $\text{THF-}d_8$) monitoring of azetidine + TFA at 50°C .

**Figure S30.** ^1H NMR (400 MHz, $\text{EtOH-}d_6$) monitoring of azetidine + TFA at 50°C .**Figure S31.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + 0.1 eq TFA at rt.

**Figure S32.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + 0.1 eq TFA at 50°C .**Figure S33.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + 1.0 eq TFA at rt.

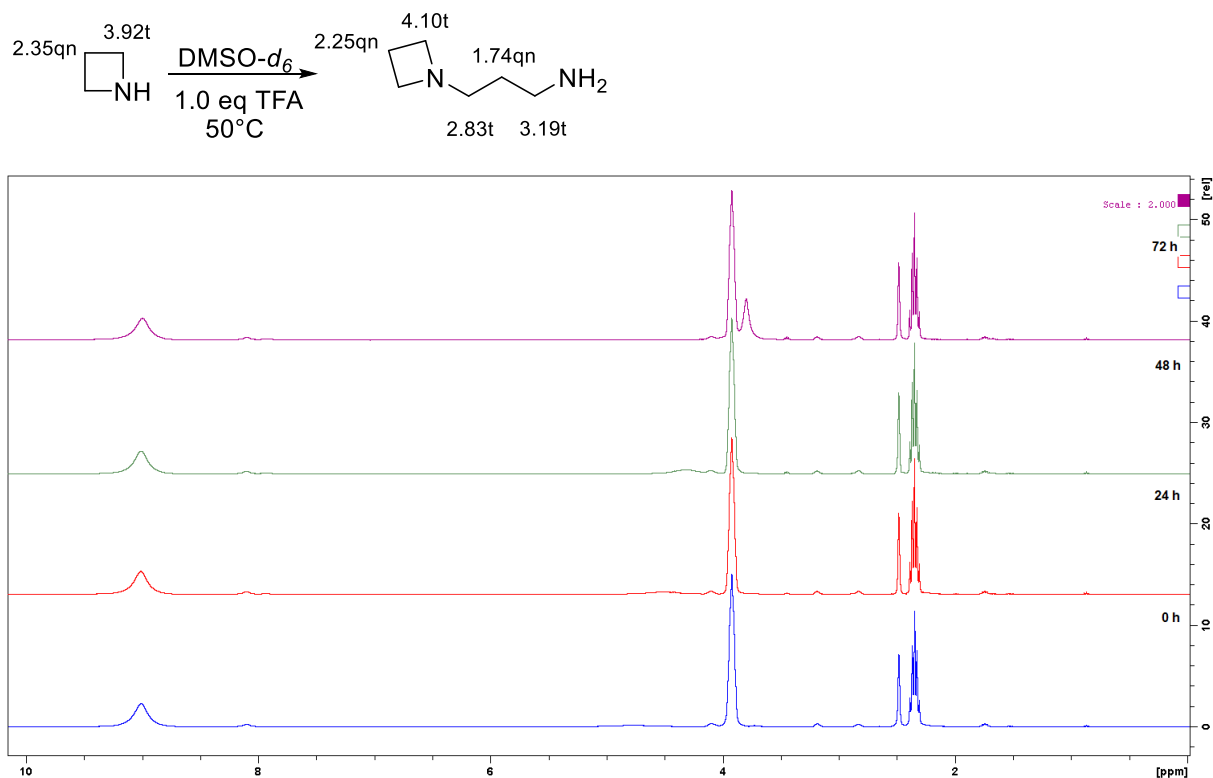


Figure S34. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + 1.0 eq TFA at 50°C .

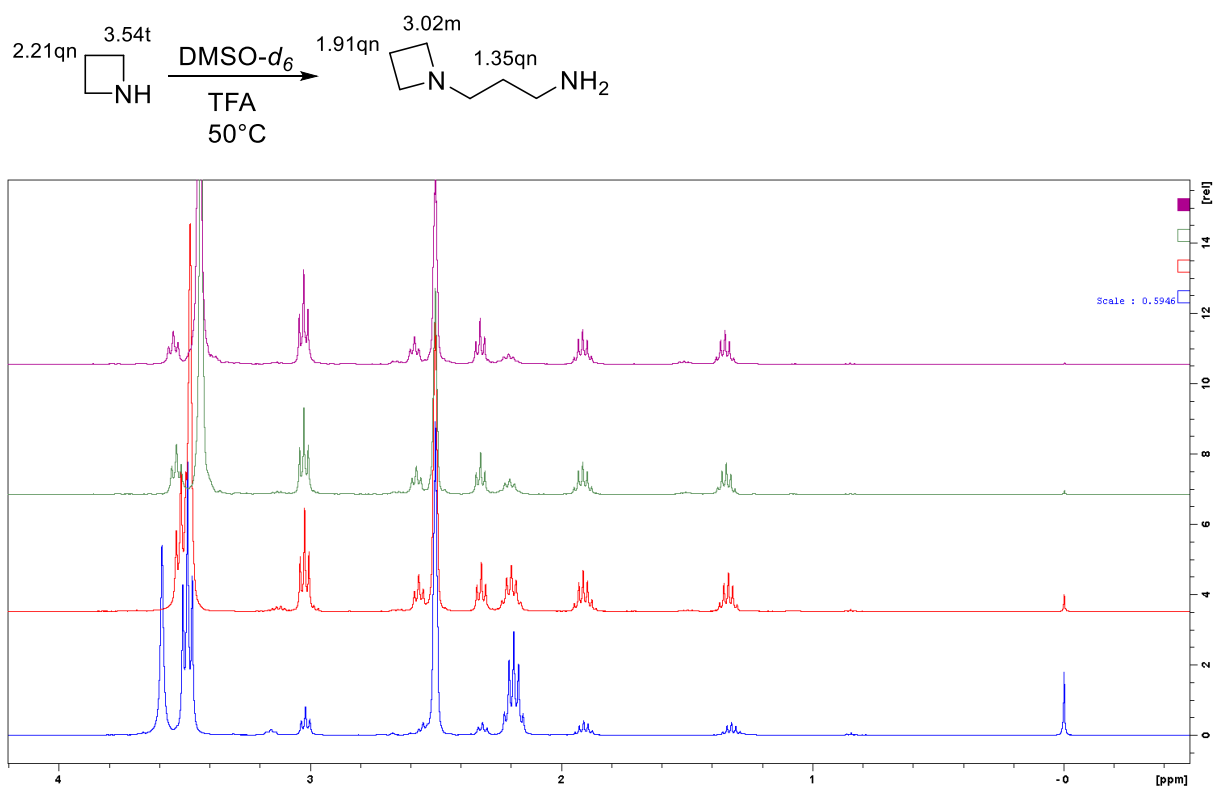


Figure S35. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine (1.0 M) + TFA at 50°C .

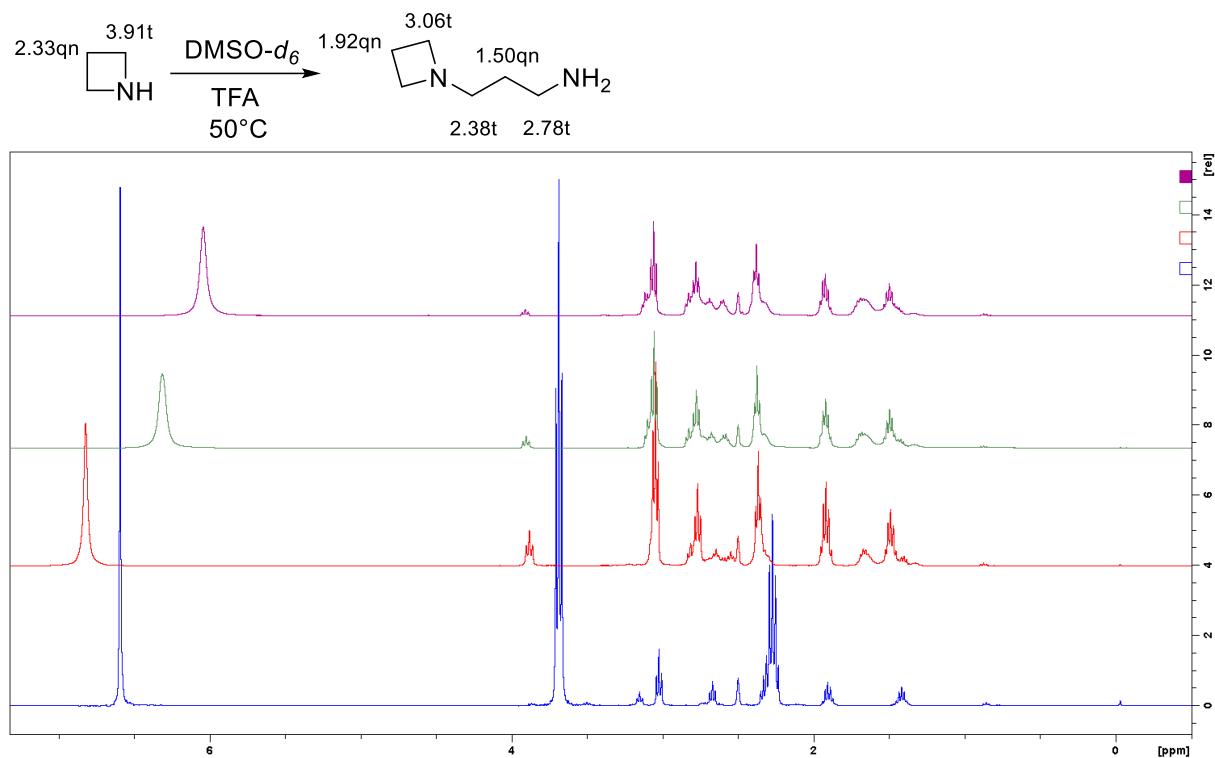


Figure S36. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine (5.0 M) + TFA at 50°C .

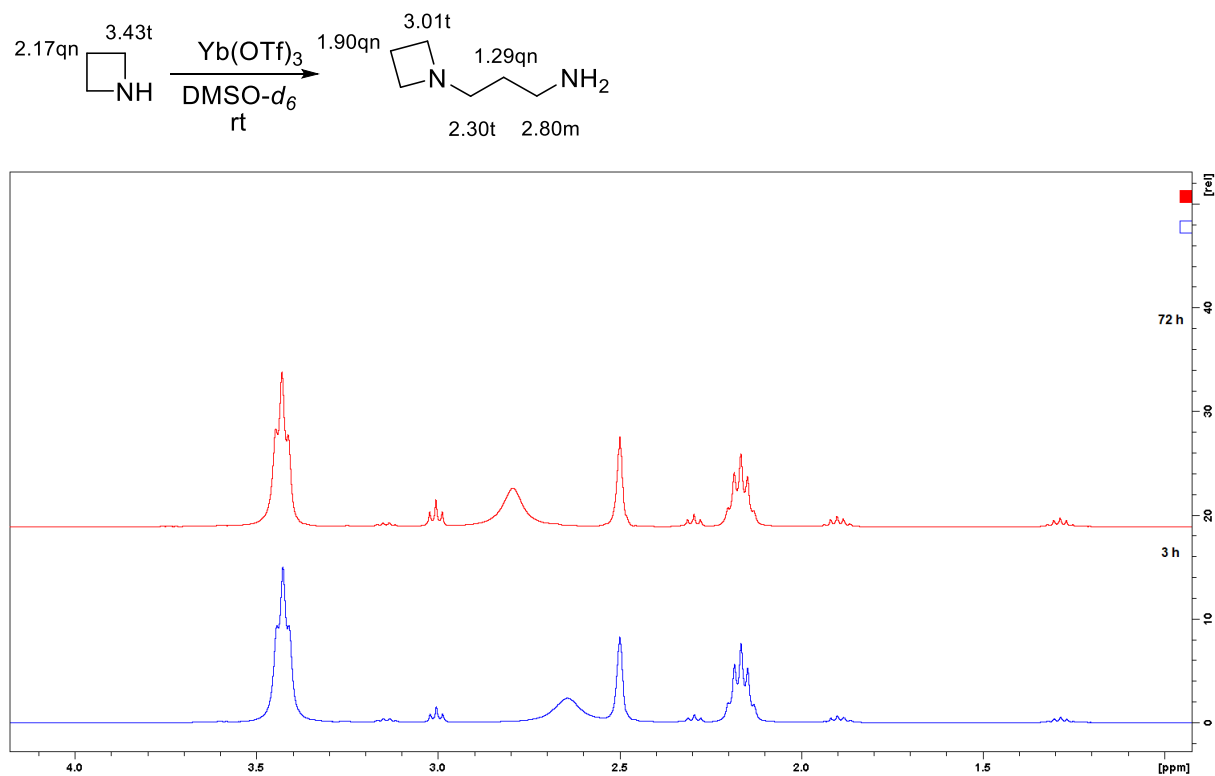
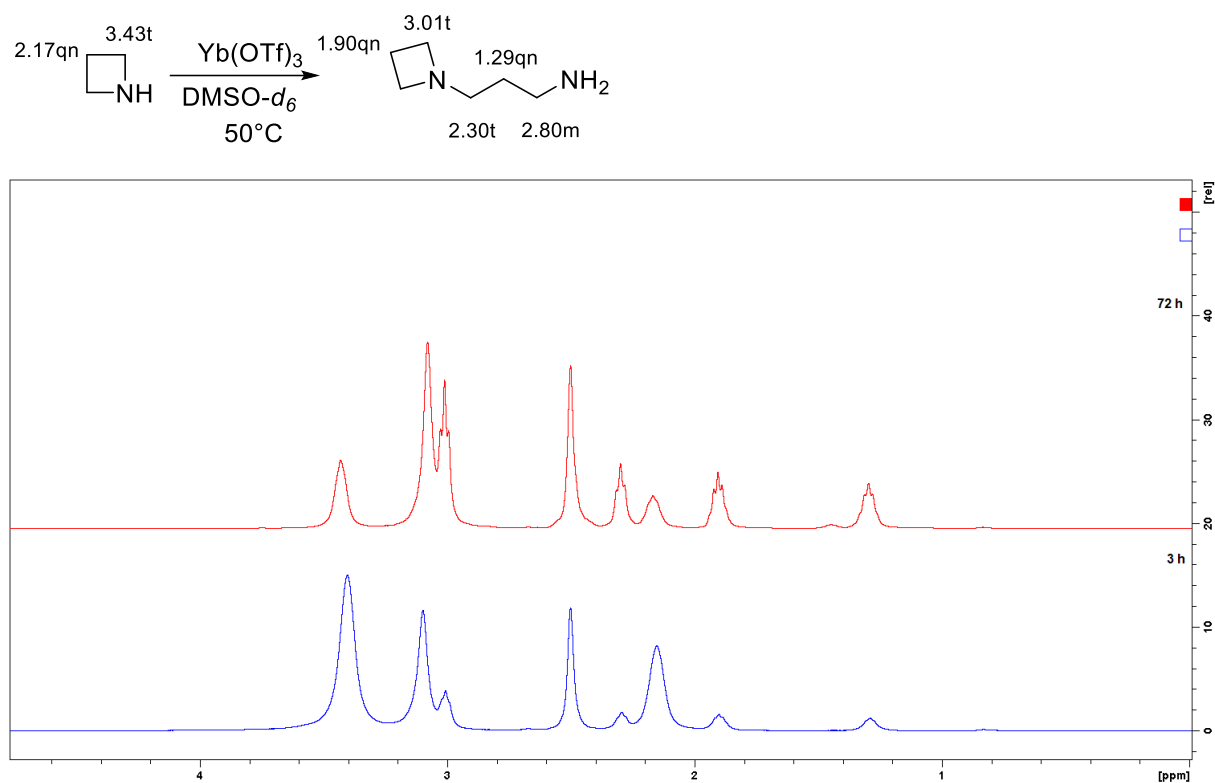
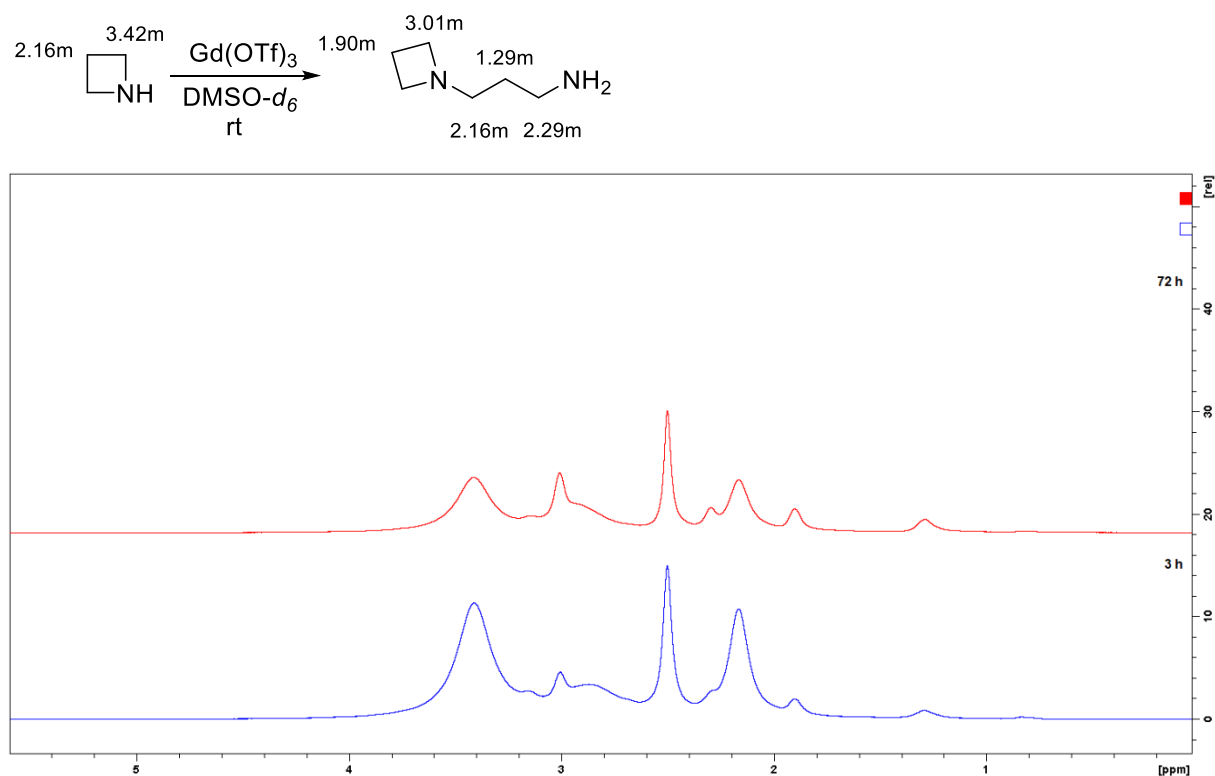


Figure S37. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + Yb(OTf)_3 at rt.

**Figure S38.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + Yb(OTf)_3 at 50°C .**Figure S39.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + Gd(OTf)_3 at rt.

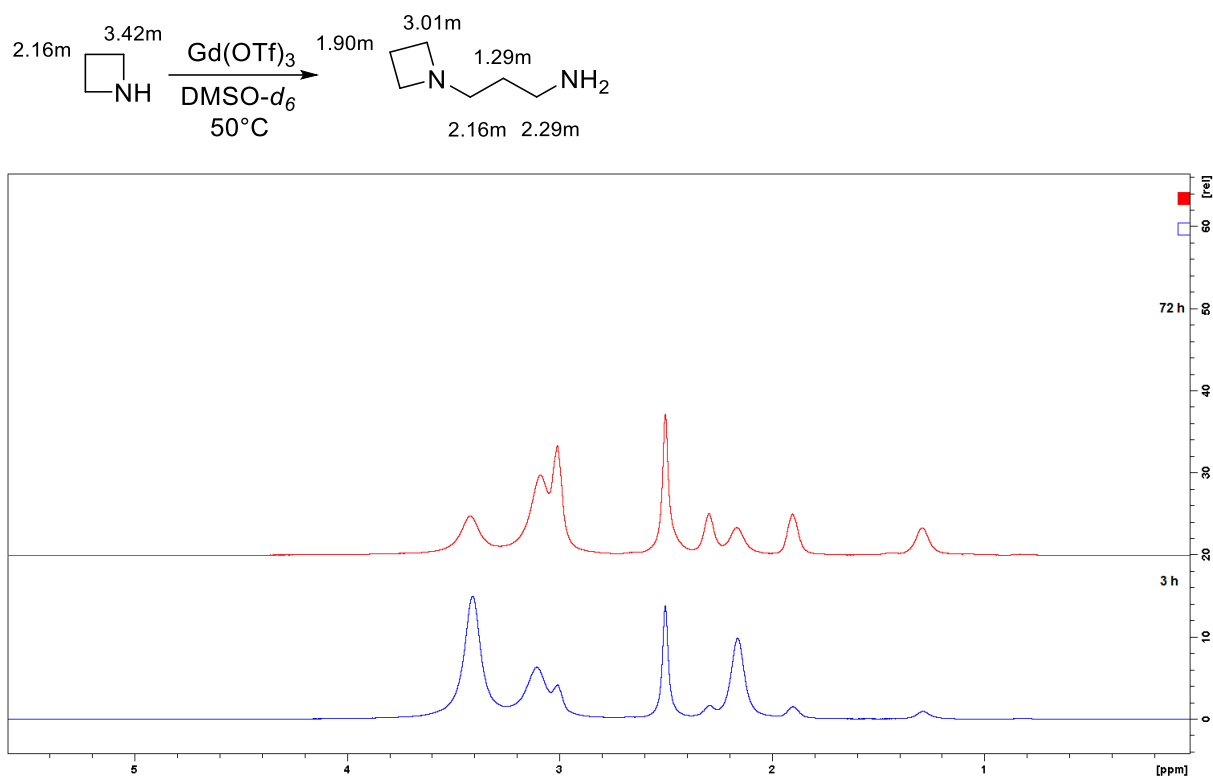


Figure S40. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + Gd(OTf)_3 at 50°C .

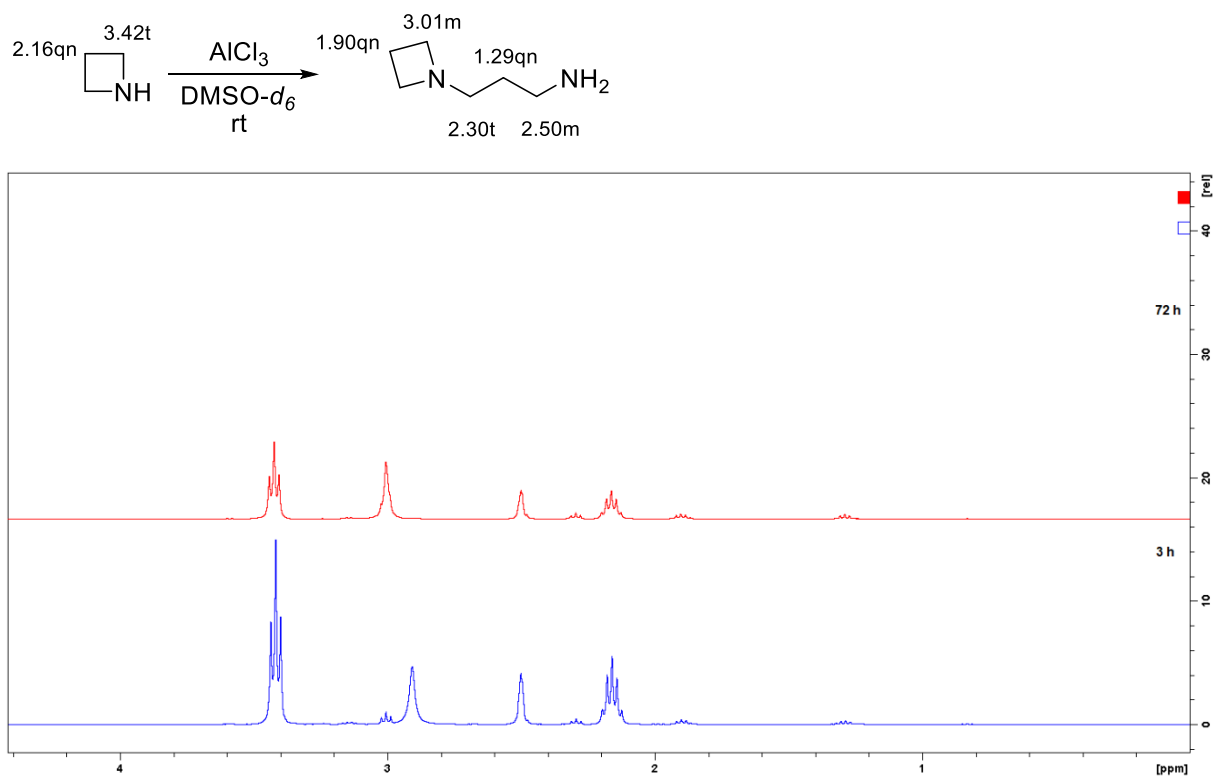
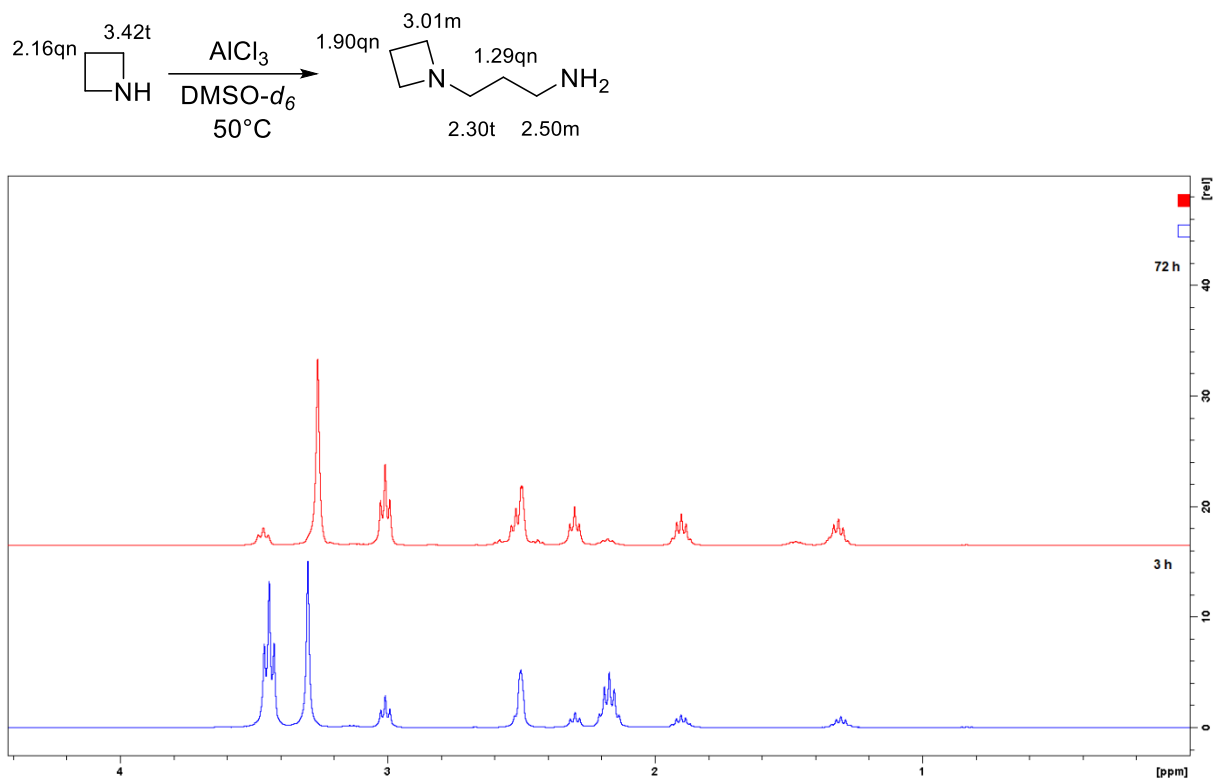
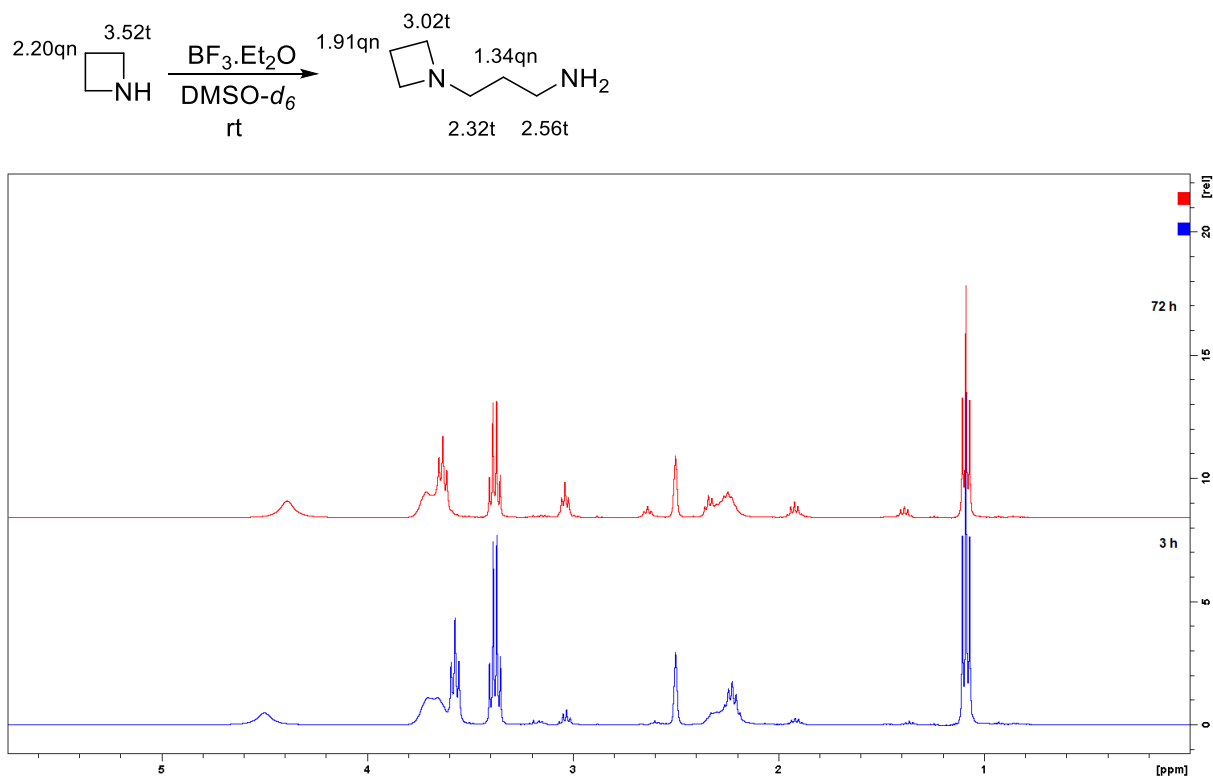
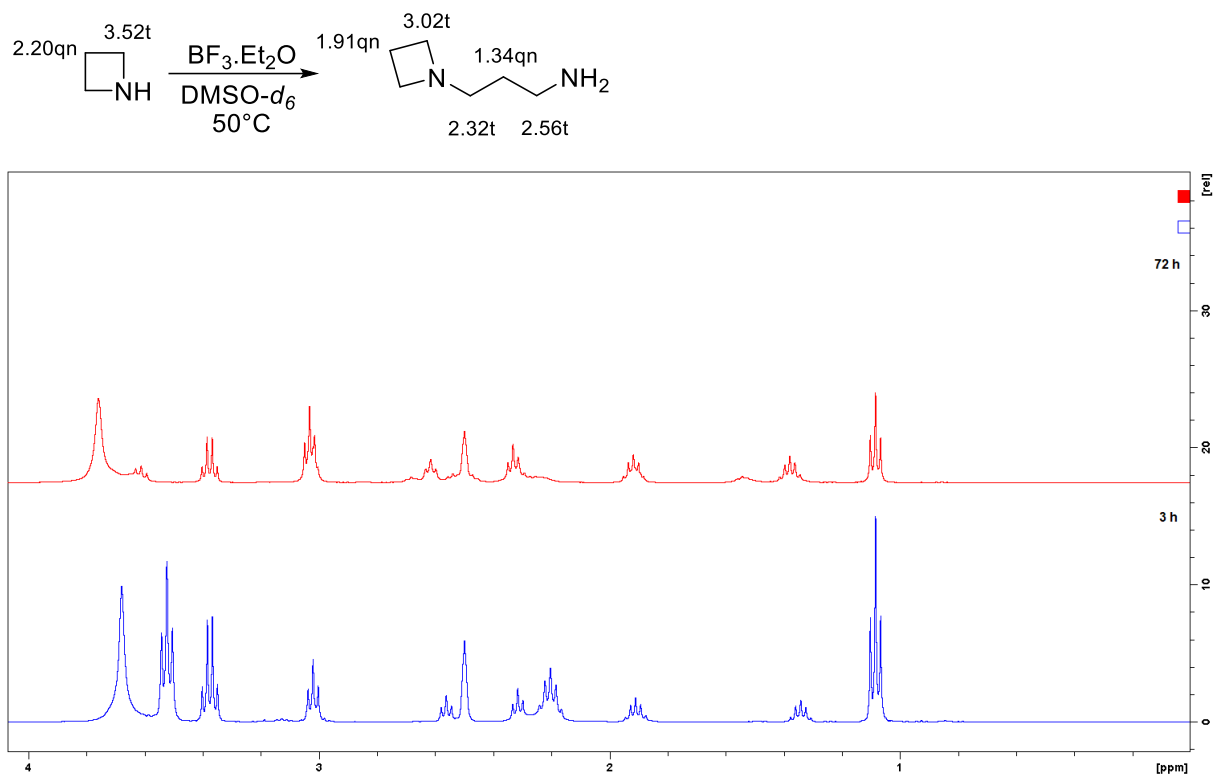
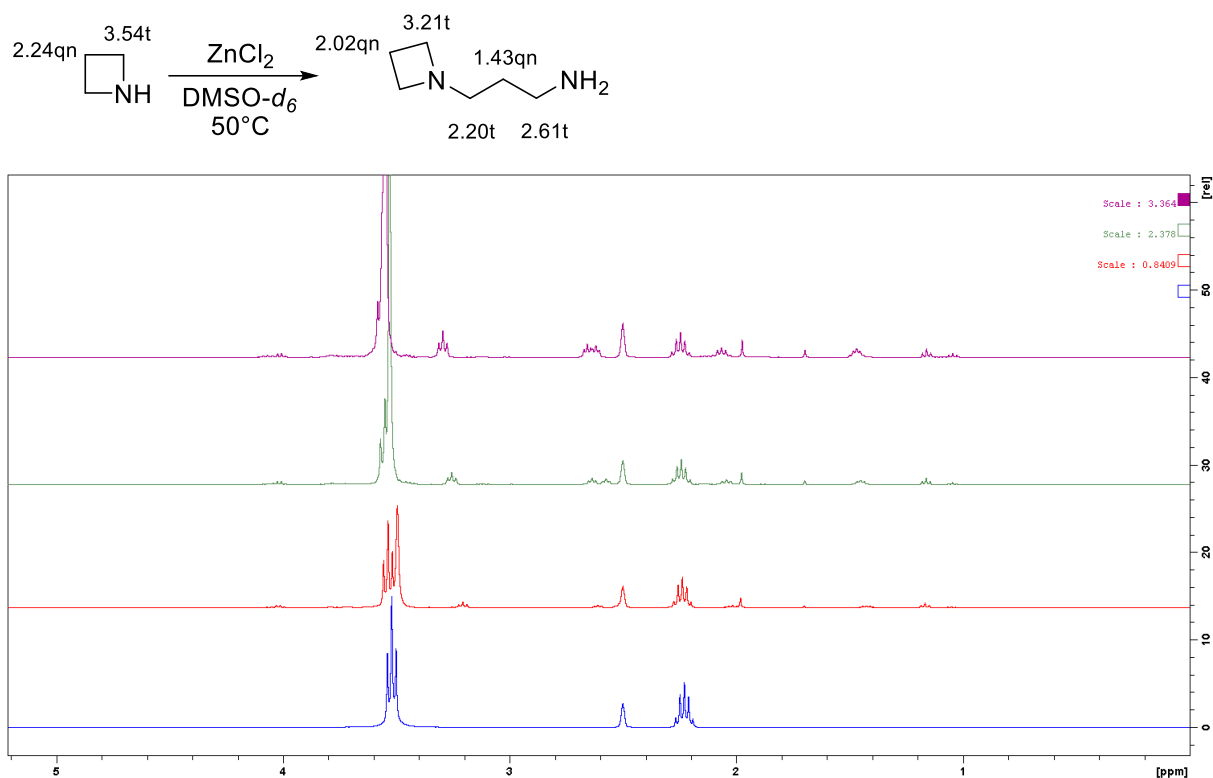
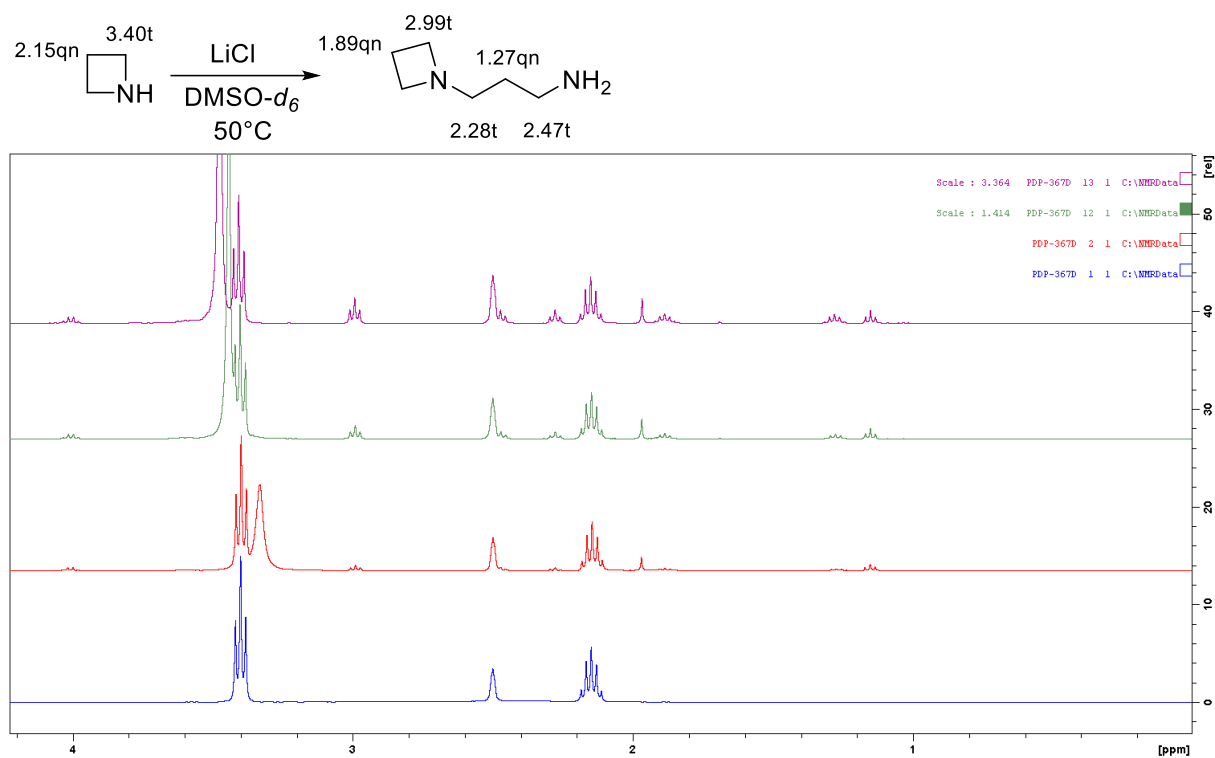
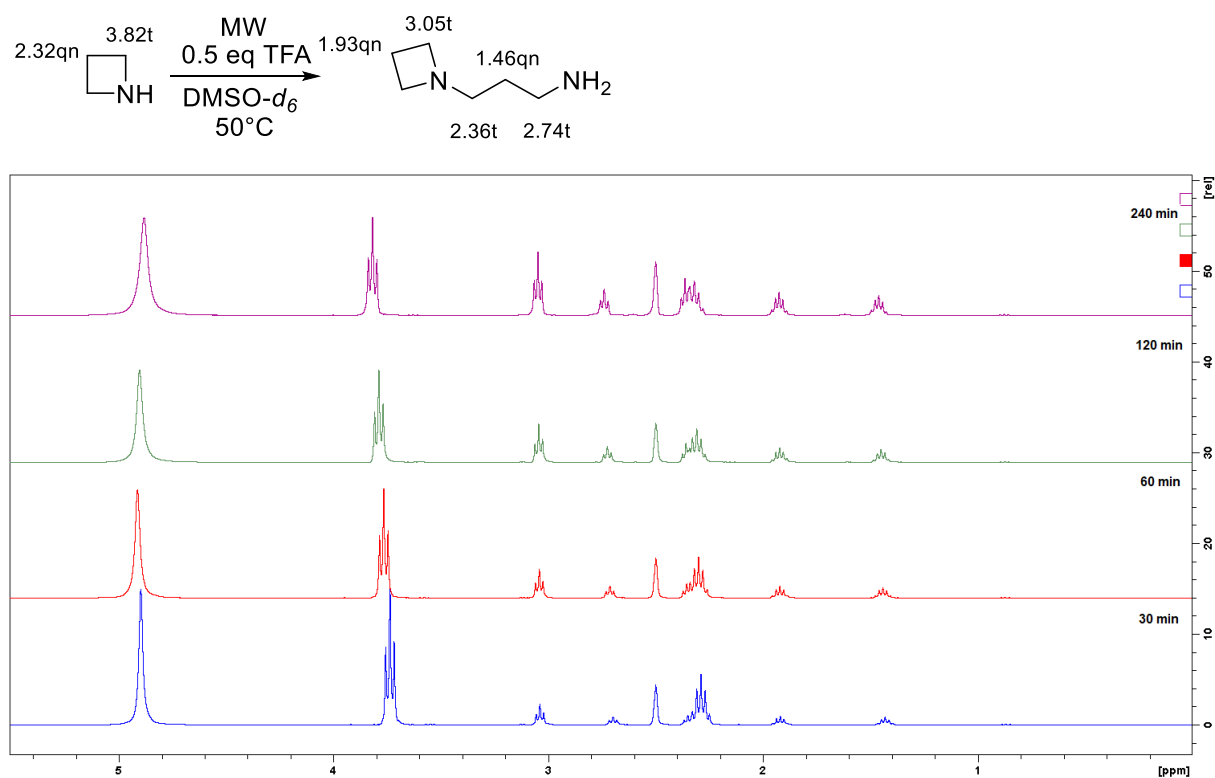
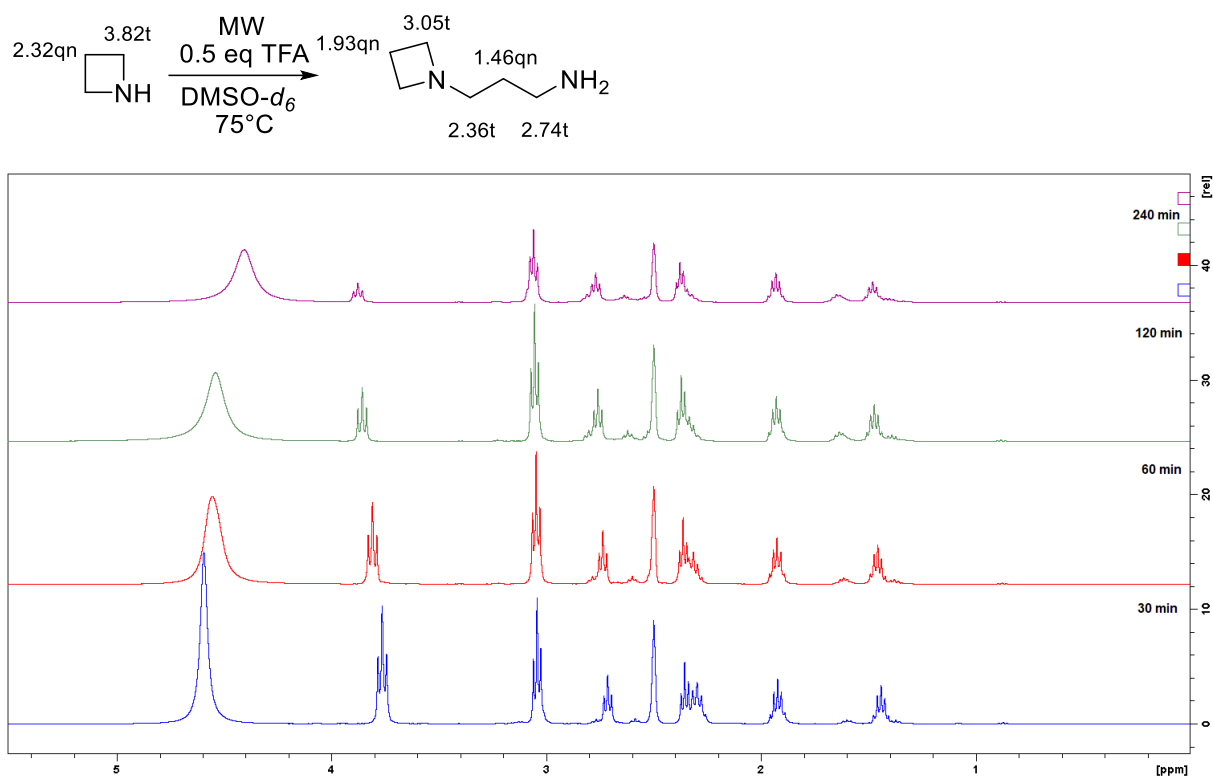
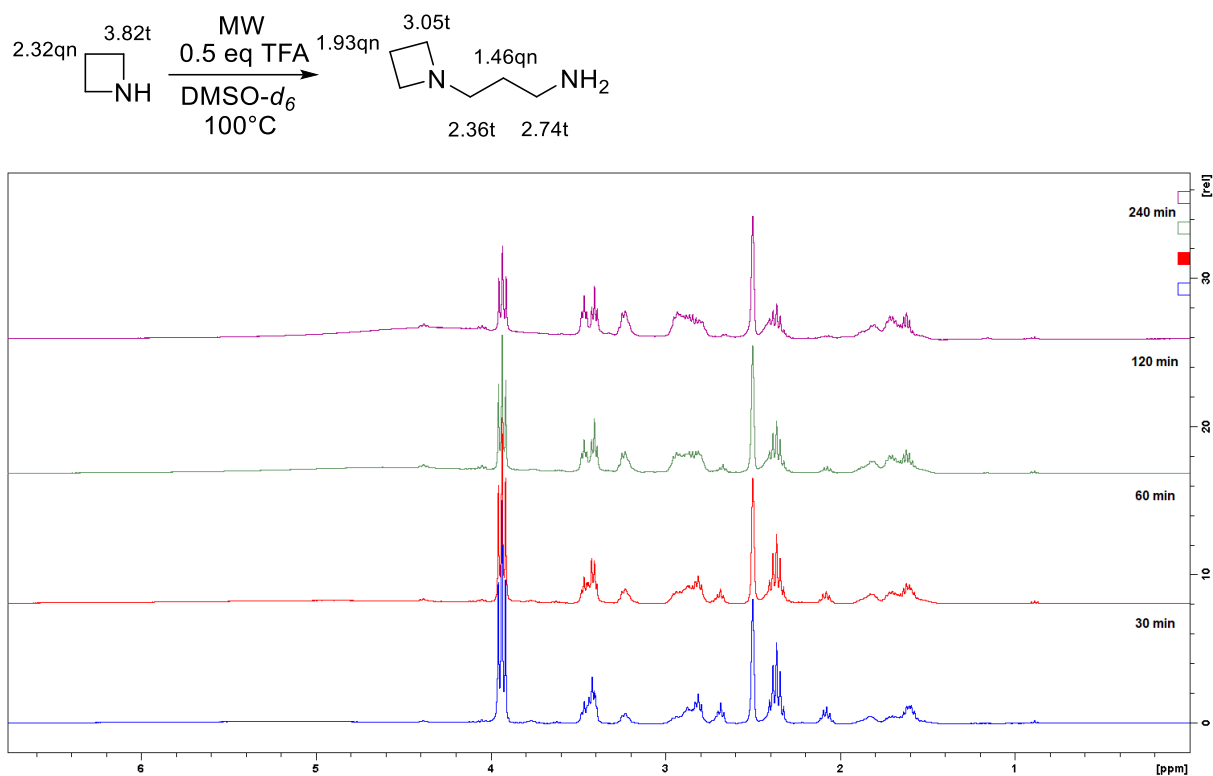


Figure S41. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + AlCl_3 at rt.

**Figure S42.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + AlCl_3 at 50°C .**Figure S43.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at rt.

**Figure S44.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at 50°C .**Figure S45.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + ZnCl_2 at 50°C .

**Figure S46.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + LiCl at 50°C .**Figure S47.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + TFA at 50°C , MW heating.

**Figure S48.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + TFA at 75°C , MW heating.**Figure S49.** ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + TFA at 100°C , MW heating.

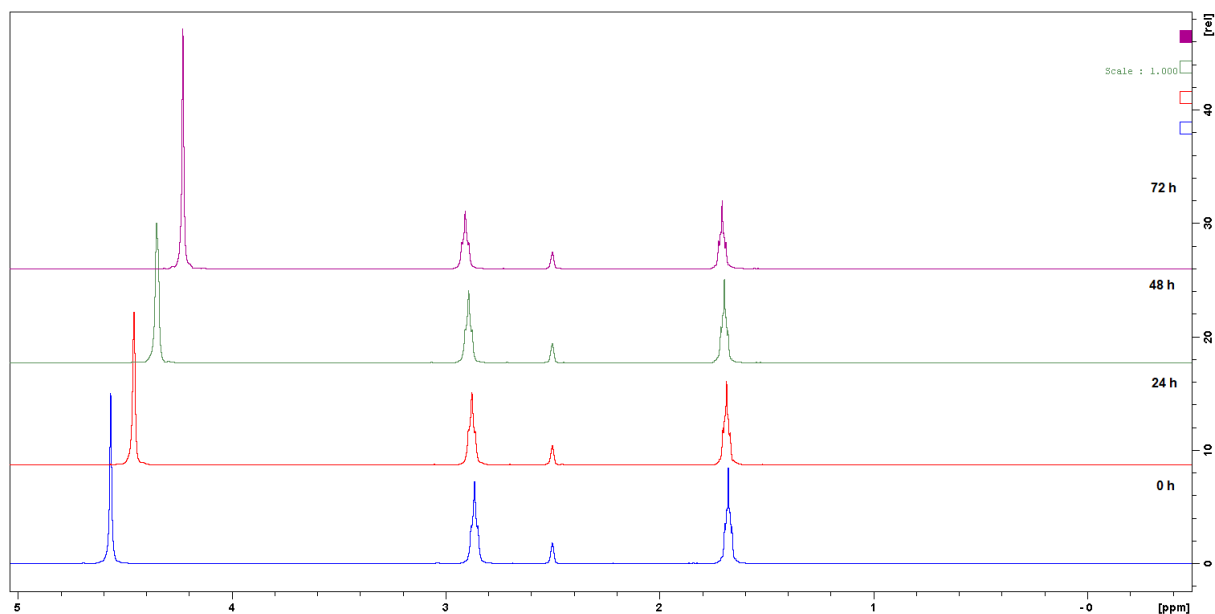
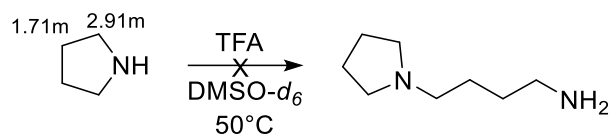


Figure S50. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of pyrrolidine + TFA at 50°C .

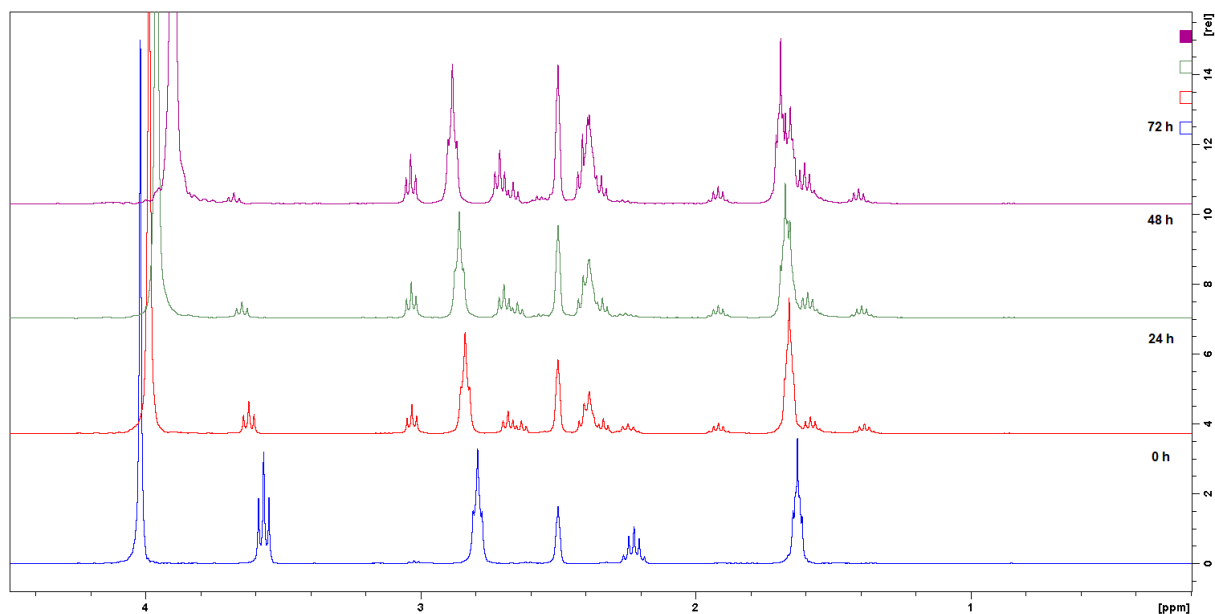
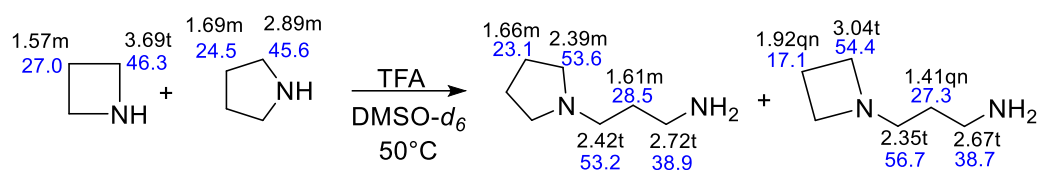


Figure S51. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + pyrrolidine (1.0 eq) + TFA at 50°C .

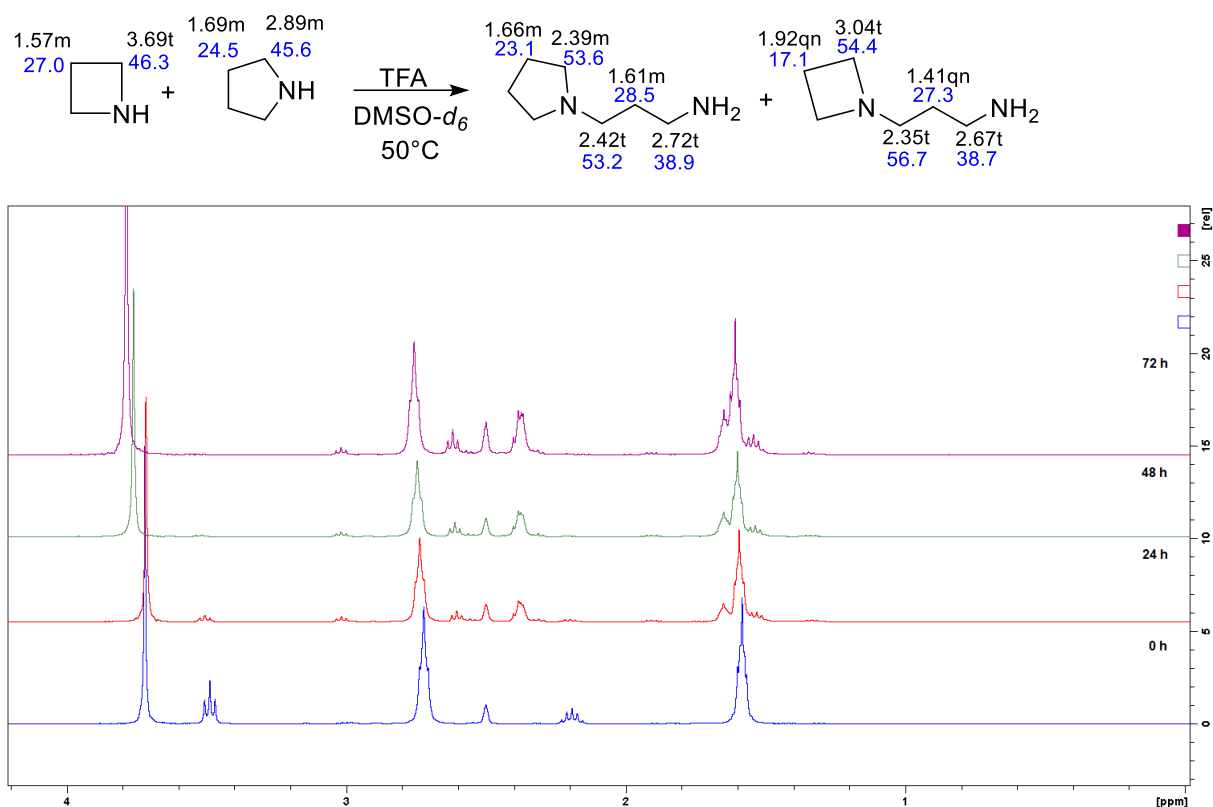


Figure S52. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) monitoring of azetidine + pyrrolidine (3.0 eq) + TFA at 50°C .

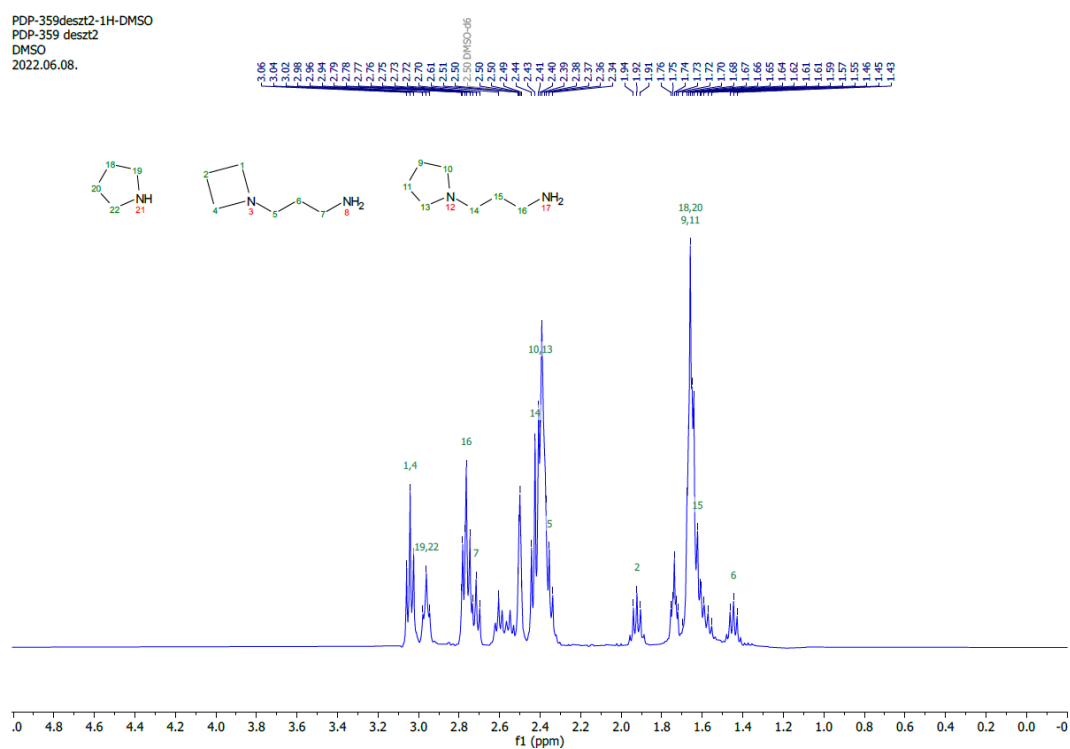


Figure S53. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) monitoring of azetidine + pyrrolidine (1.0 eq) + TFA at 50°C (synthetic experiment).

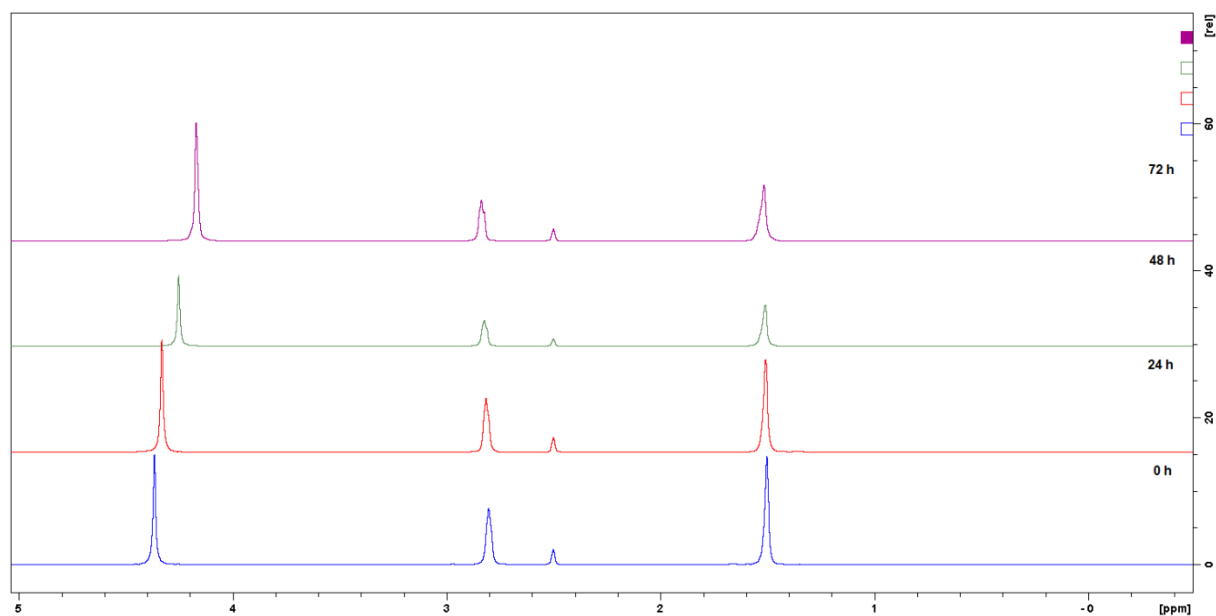
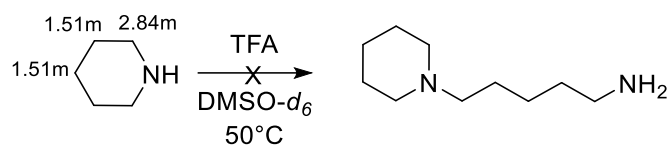


Figure S54. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of piperidine + TFA at 50°C .

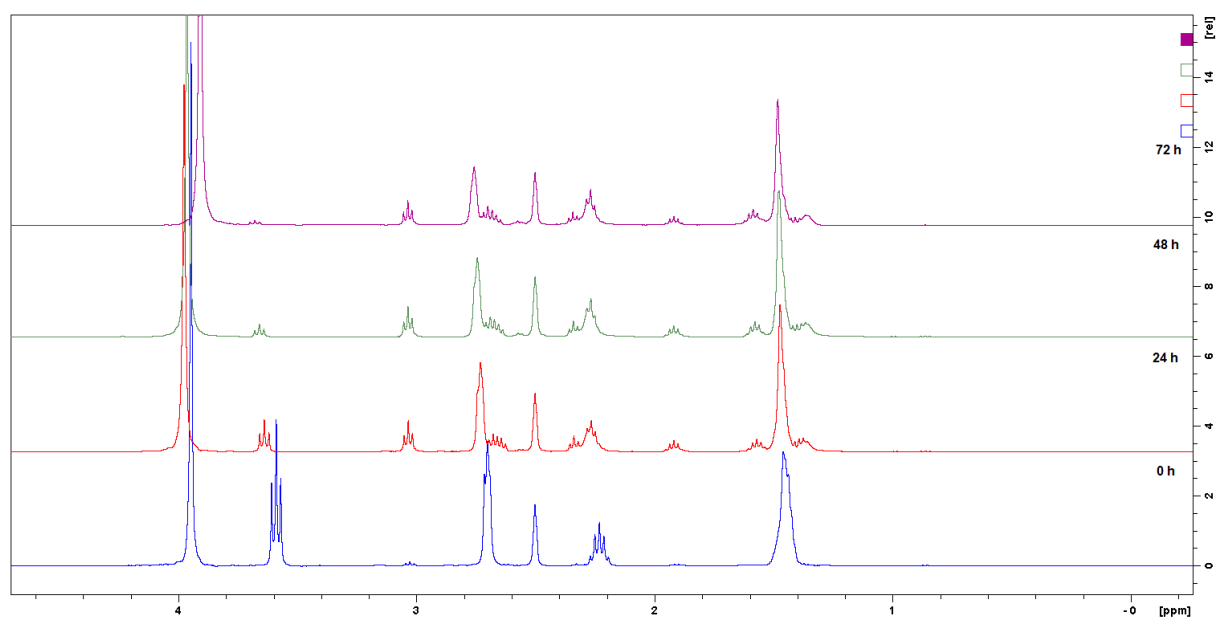
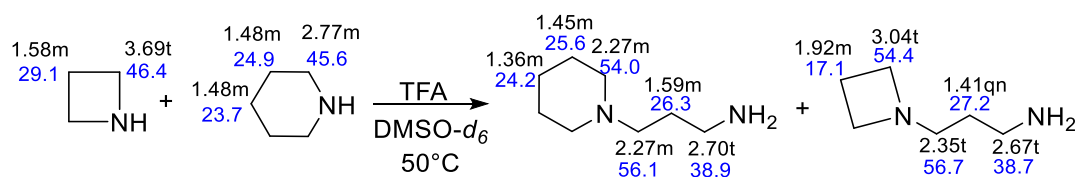


Figure S55. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + piperidine (1.0 eq) + TFA at 50°C .

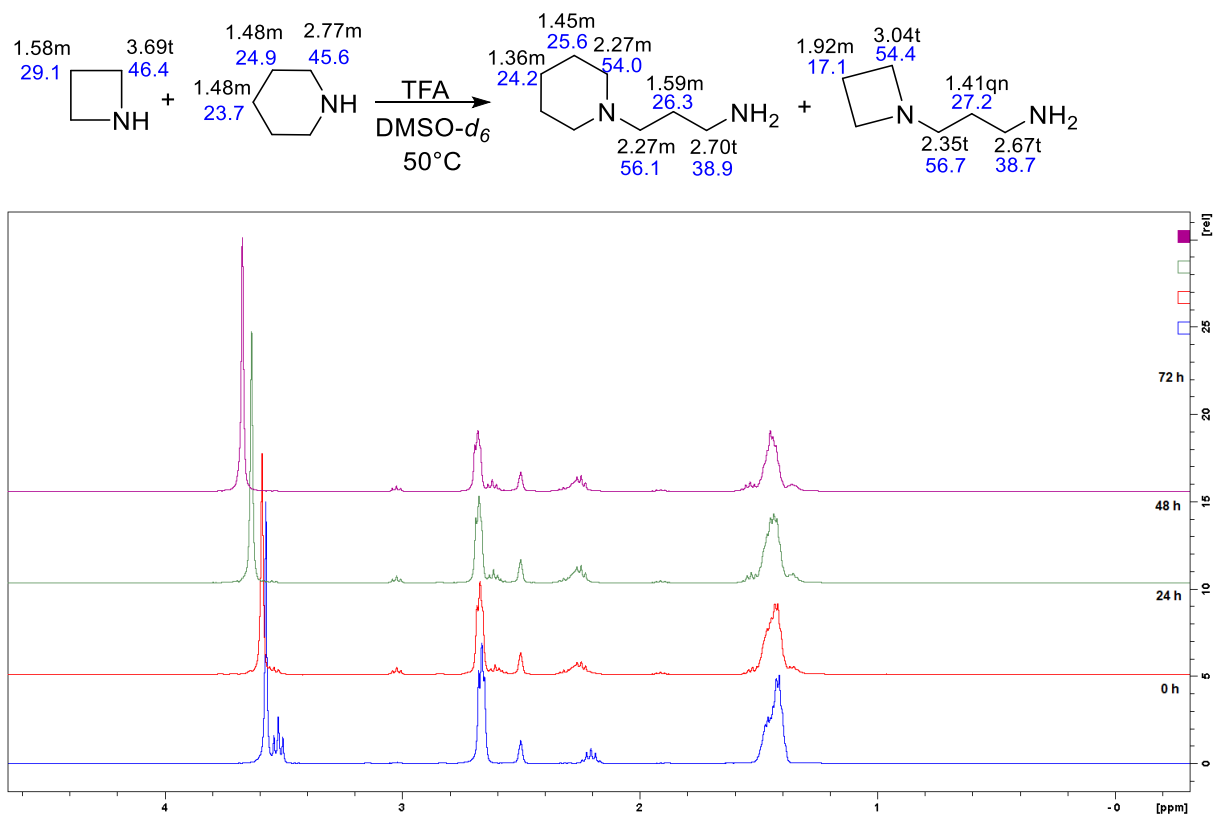


Figure S56. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + piperidine (3.0 eq) + TFA at 50°C .

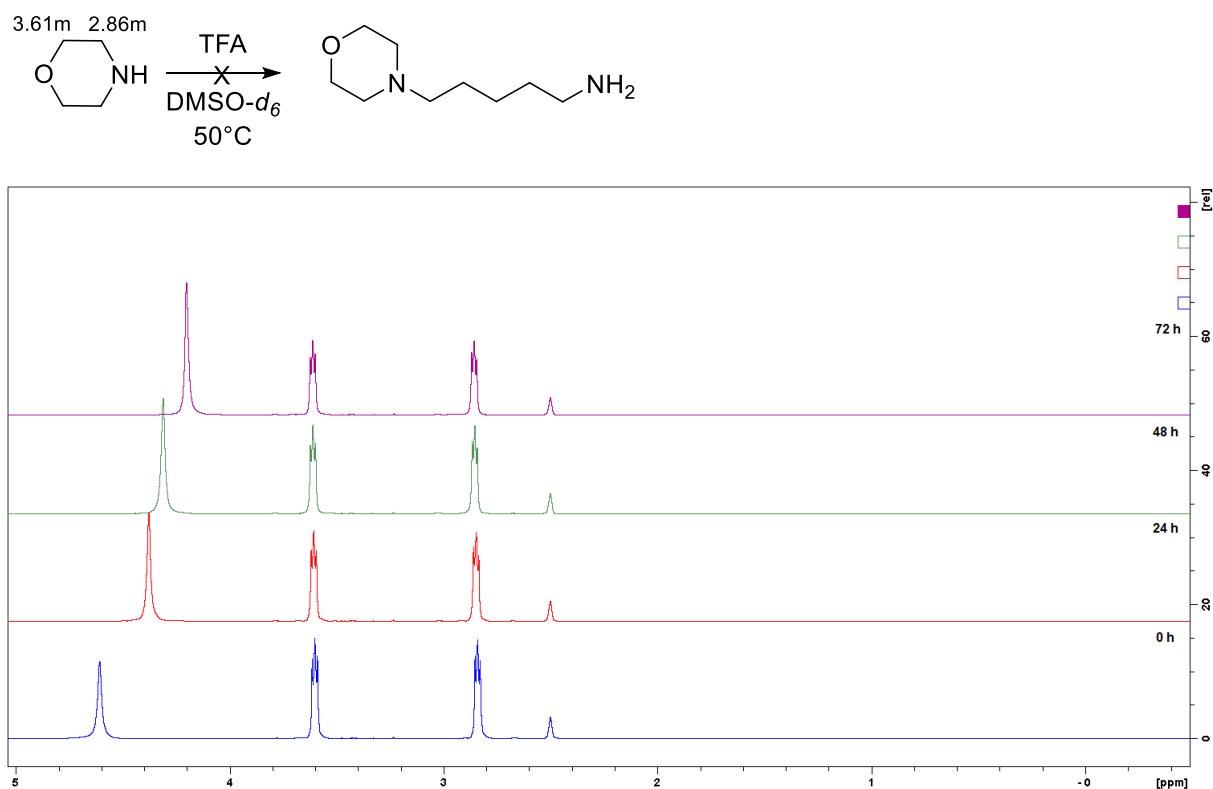


Figure S57. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of morpholine + TFA at 50°C .

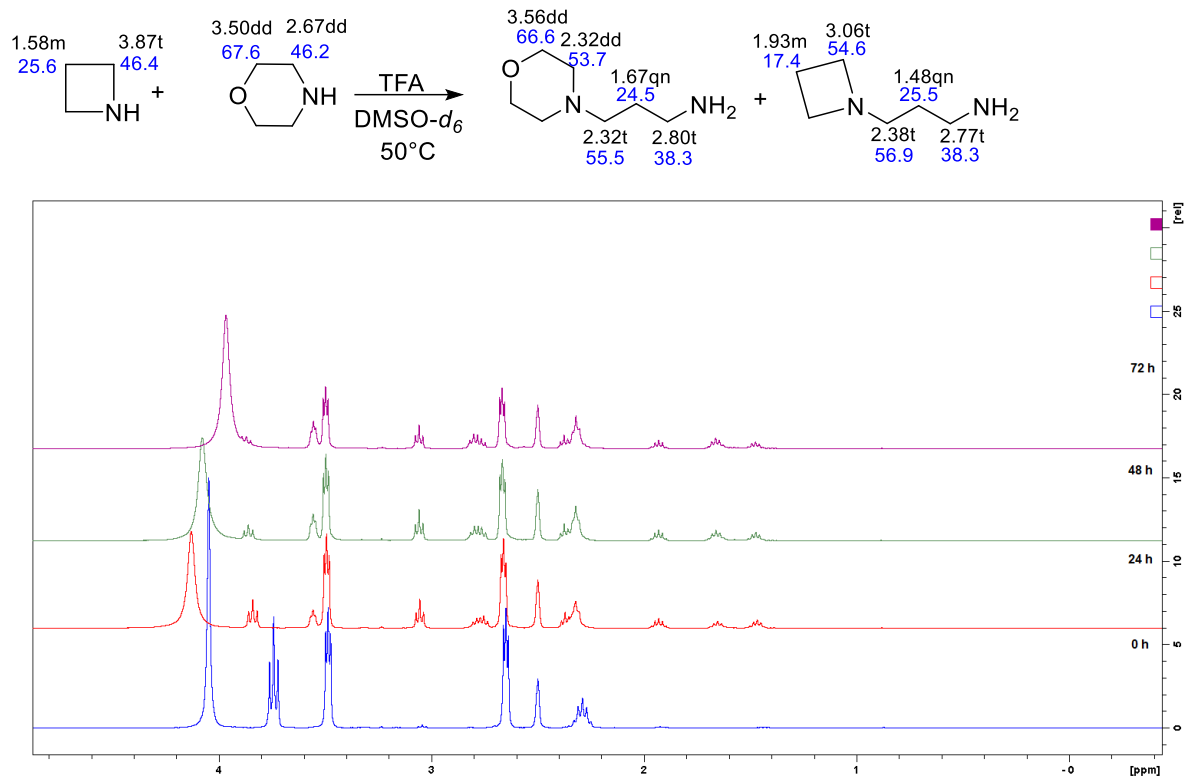


Figure S58. ¹H NMR (400 MHz, DMSO-*d*₆) monitoring of azetidine + morpholine (1.0 eq) + TFA at 50°C.

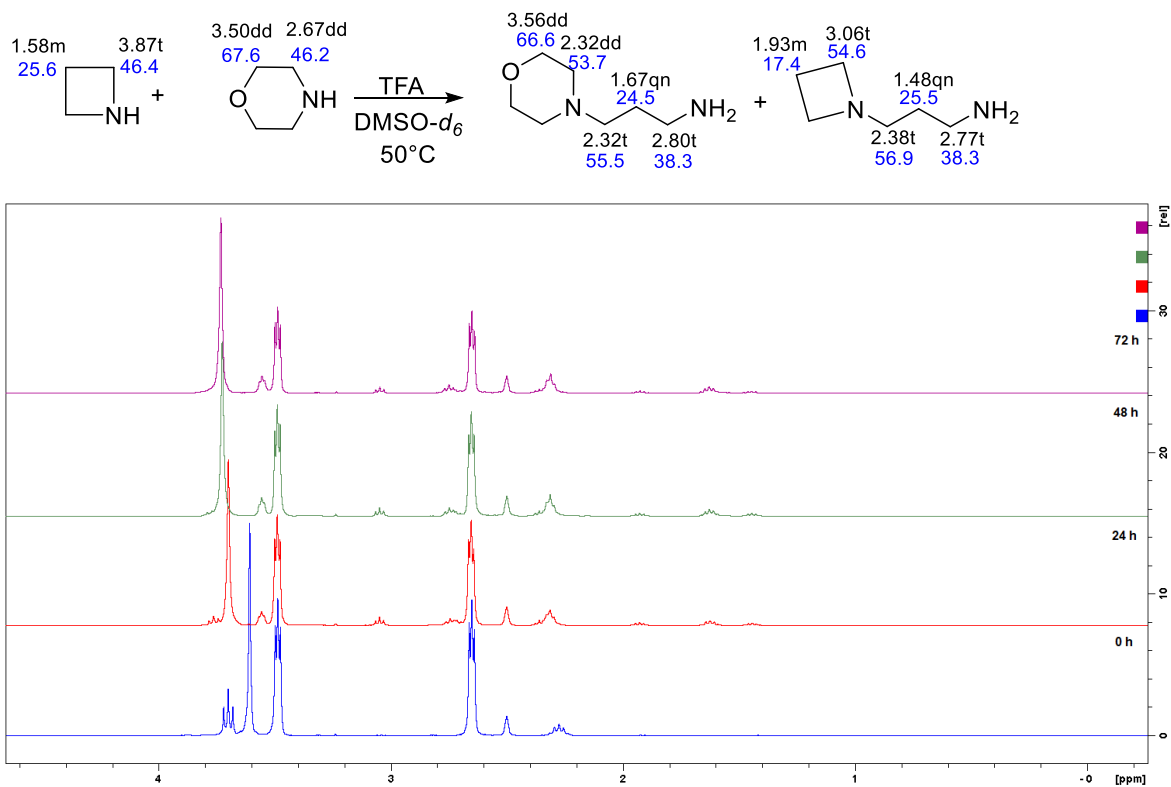


Figure S59. ¹H NMR (400 MHz, DMSO-*d*₆) monitoring of azetidine + morpholine (3.0 eq) + TFA at 50°C.

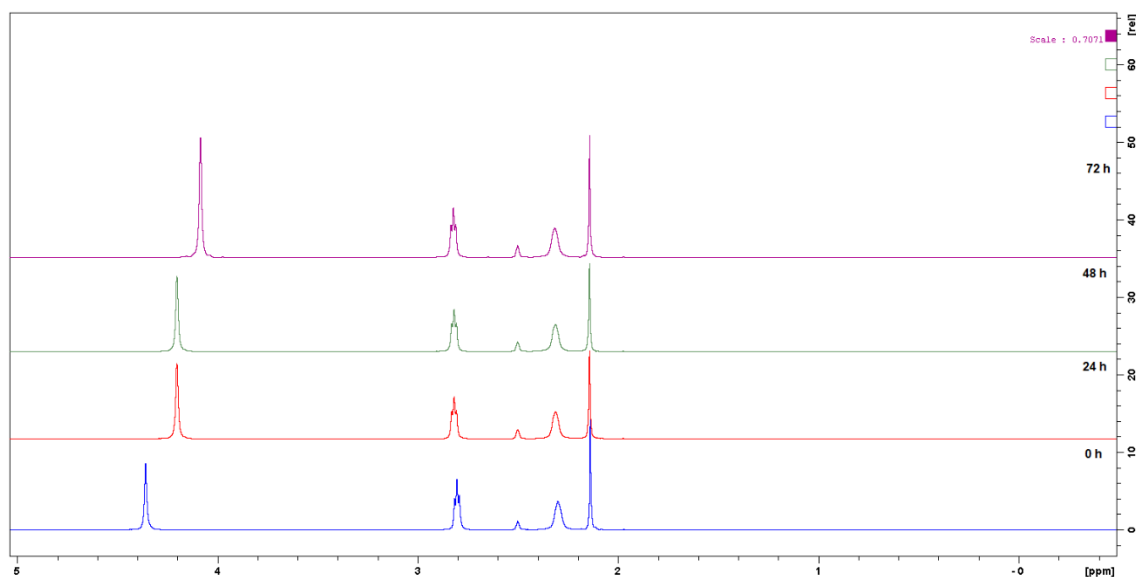
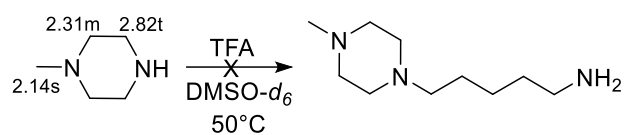


Figure S60. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of *N*-methylpiperazine + TFA at 50°C .

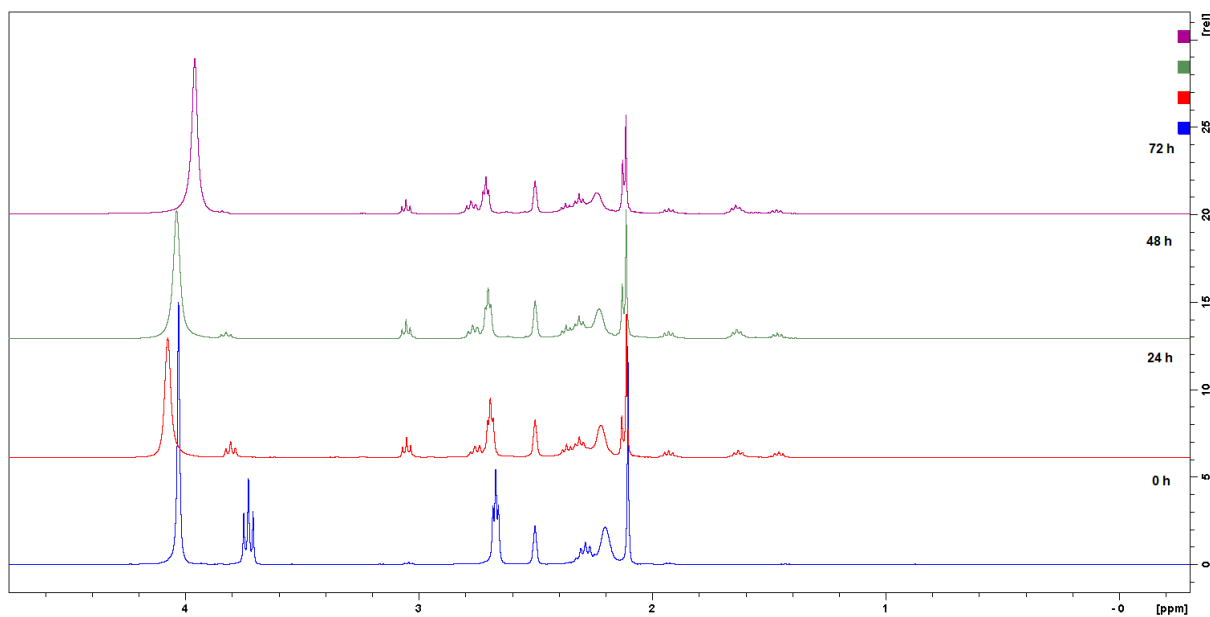
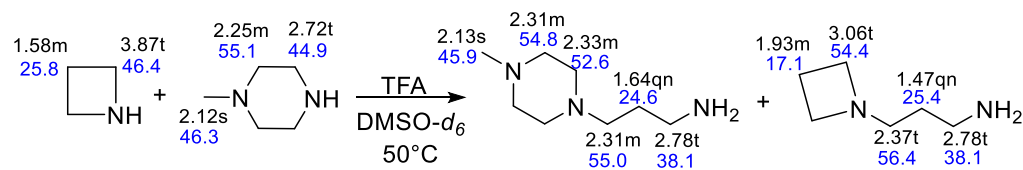


Figure S61. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + *N*-methylpiperazine (1.0 eq) + TFA at 50°C .

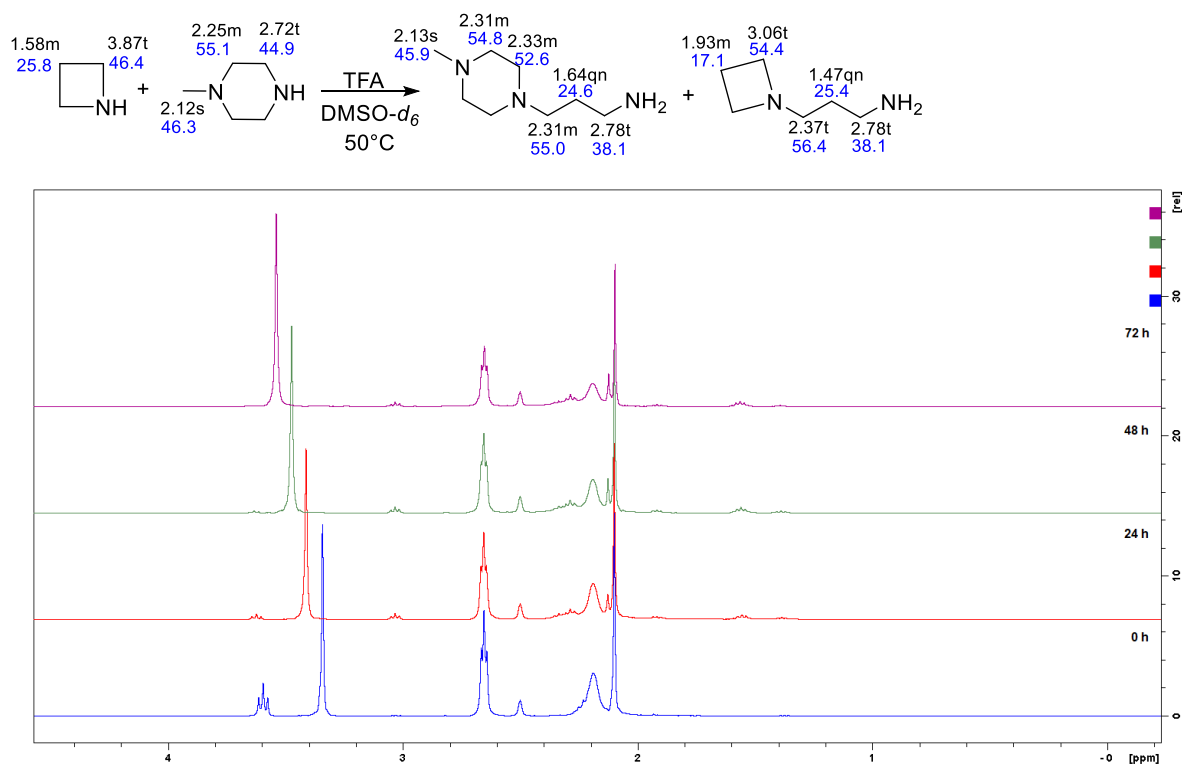


Figure S62. ¹H NMR (400 MHz, DMSO-*d*₆) monitoring of azetidine + *N*-methylpiperazine (3.0 eq) + TFA at 50°C

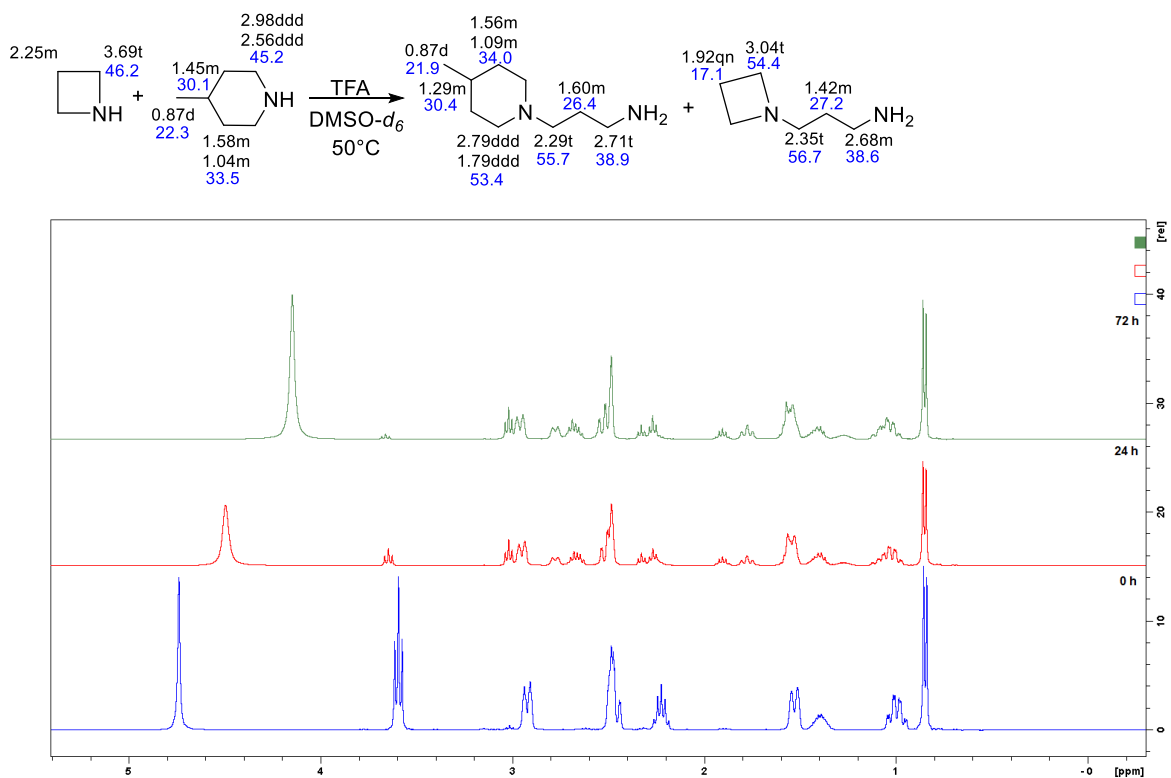


Figure S63. ¹H NMR (400 MHz, DMSO-*d*₆) monitoring of azetidine + 4-methylpiperidine (1.0 eq) + TFA at 50°C.

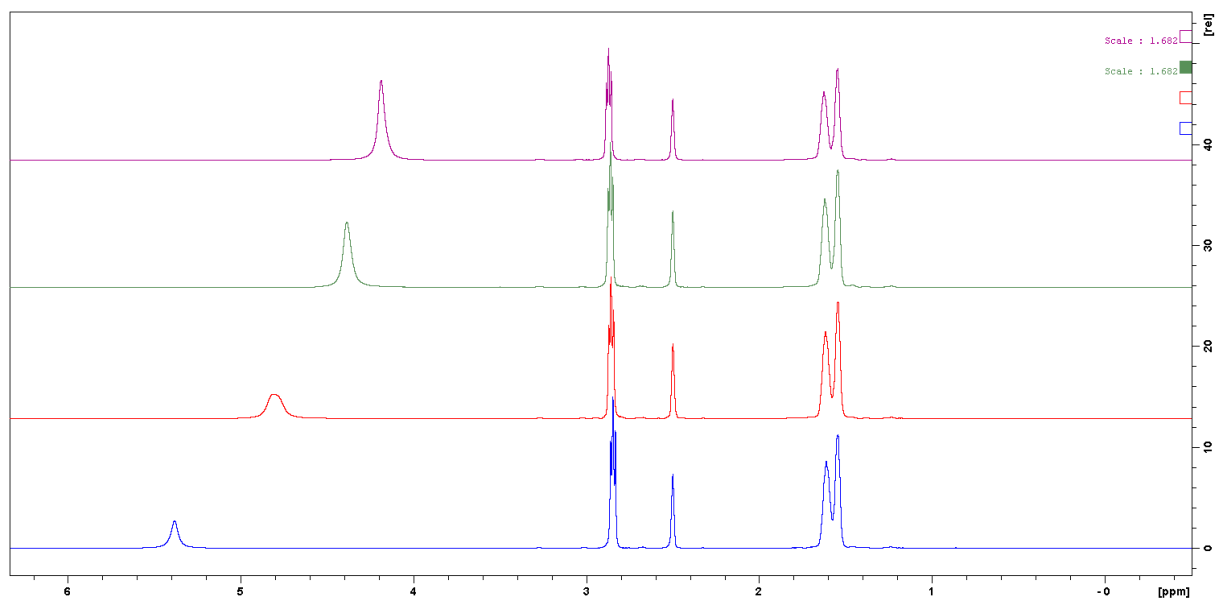
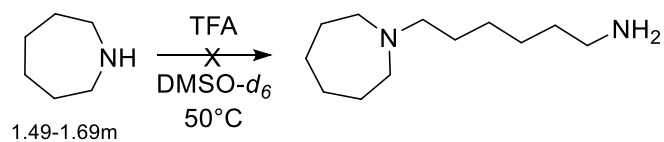


Figure S64. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of hexahydroazepine + TFA at 50°C .

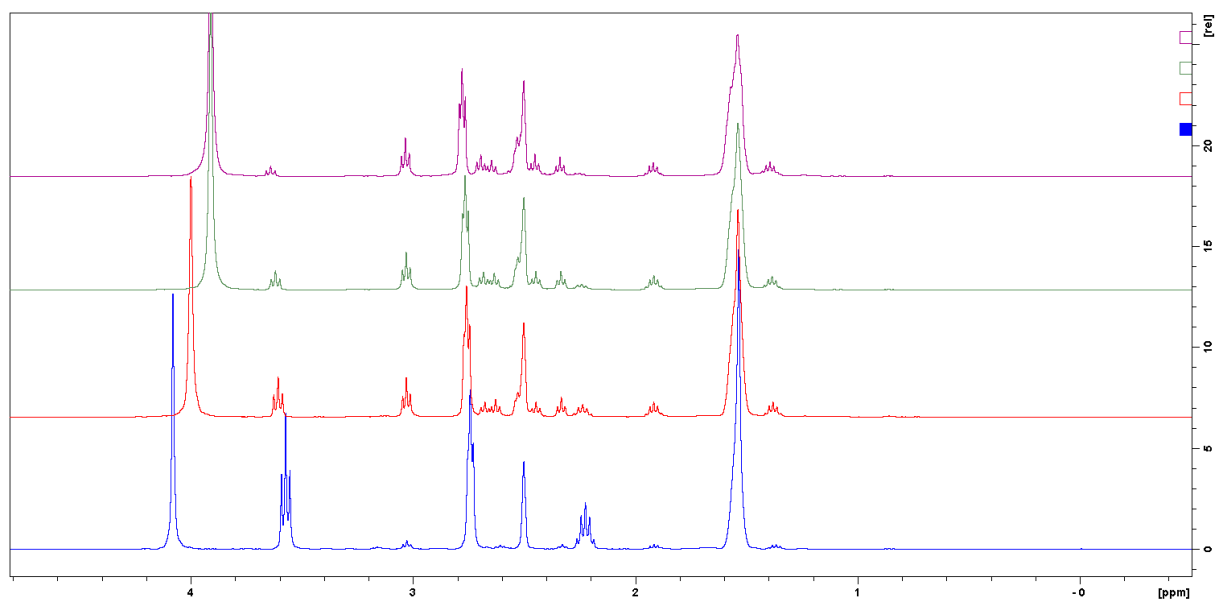
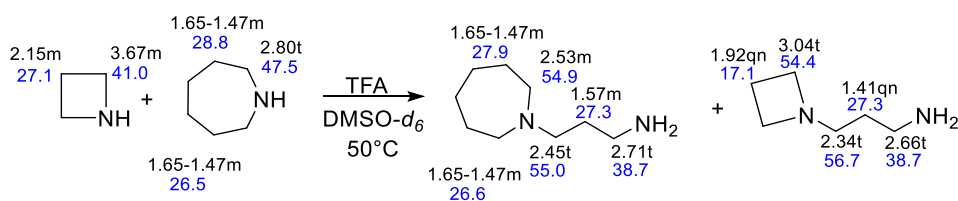


Figure S65. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + hexahydroazepine (1.0 eq) + TFA at 50°C .

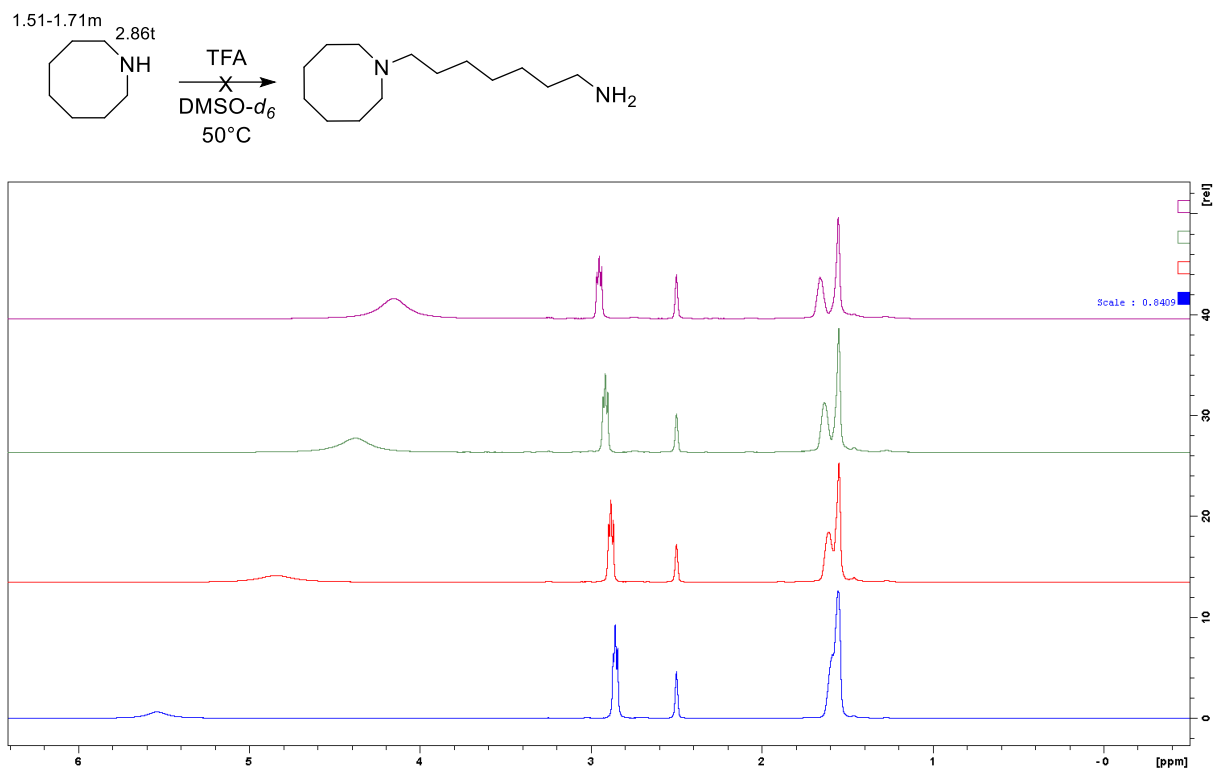


Figure S66. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of octahydroazocine + TFA at 50°C .

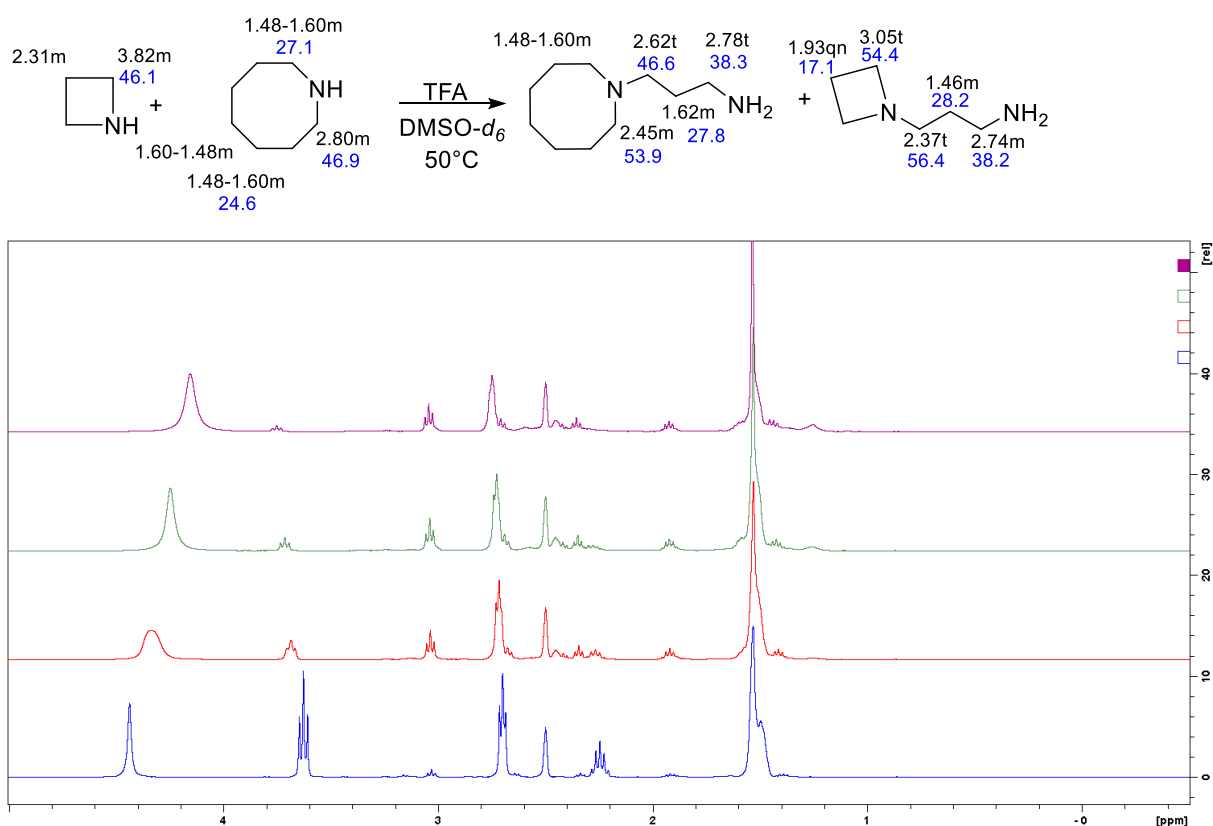


Figure S67. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + octahydroazocine (1.0 eq) + TFA at 50°C .

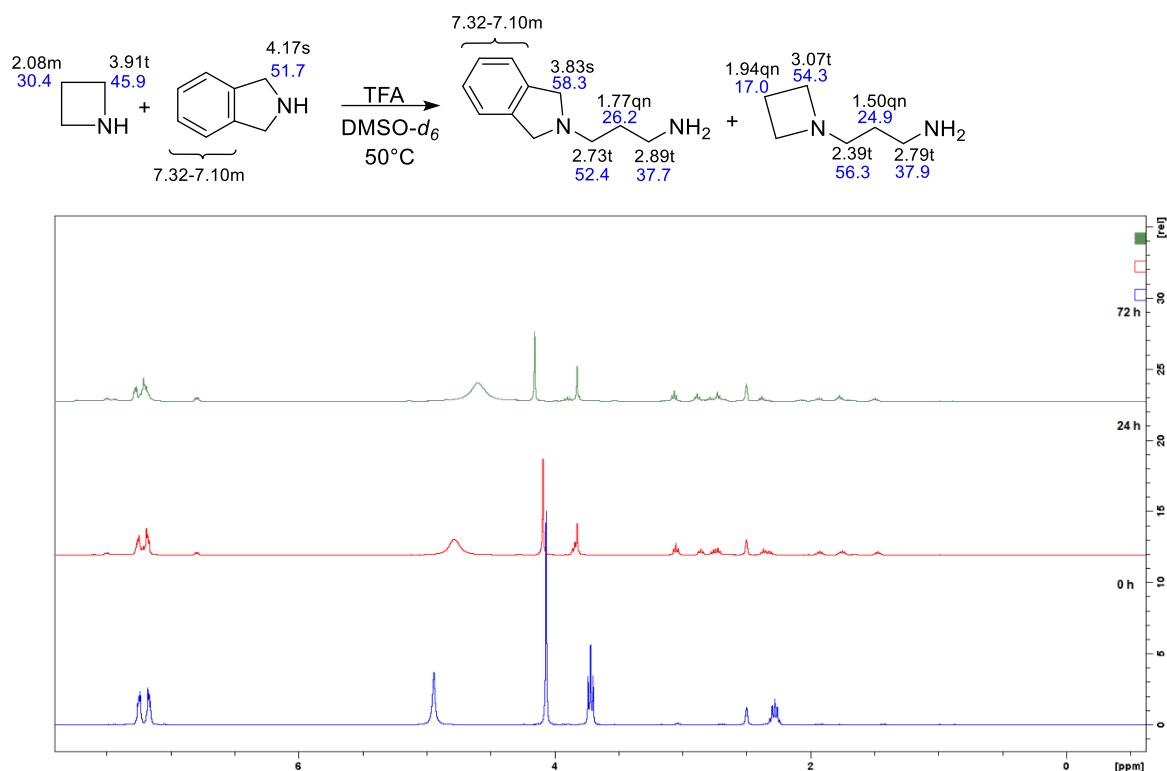


Figure S68. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + isoindoline (1.0 eq) + TFA at 50°C .

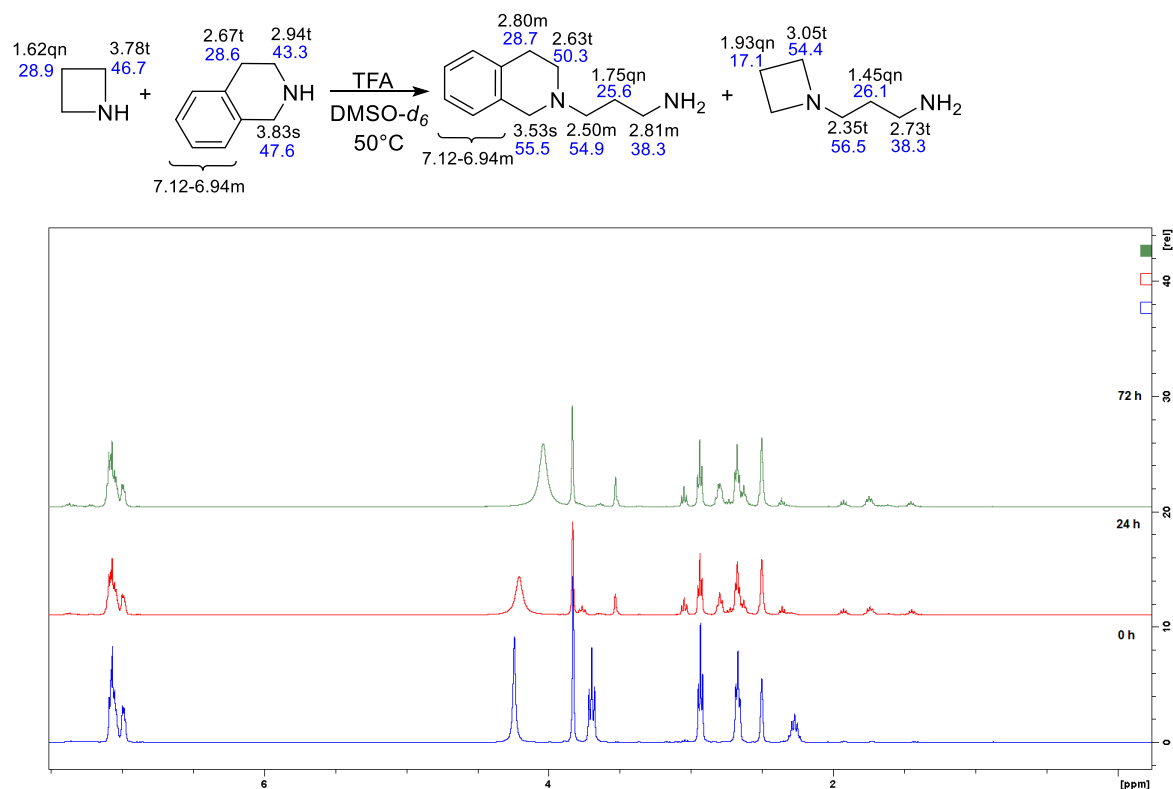


Figure S69. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of azetidine + 1,2,3,4-tetrahydroisoquinoline (1.0 eq) + TFA at 50°C .

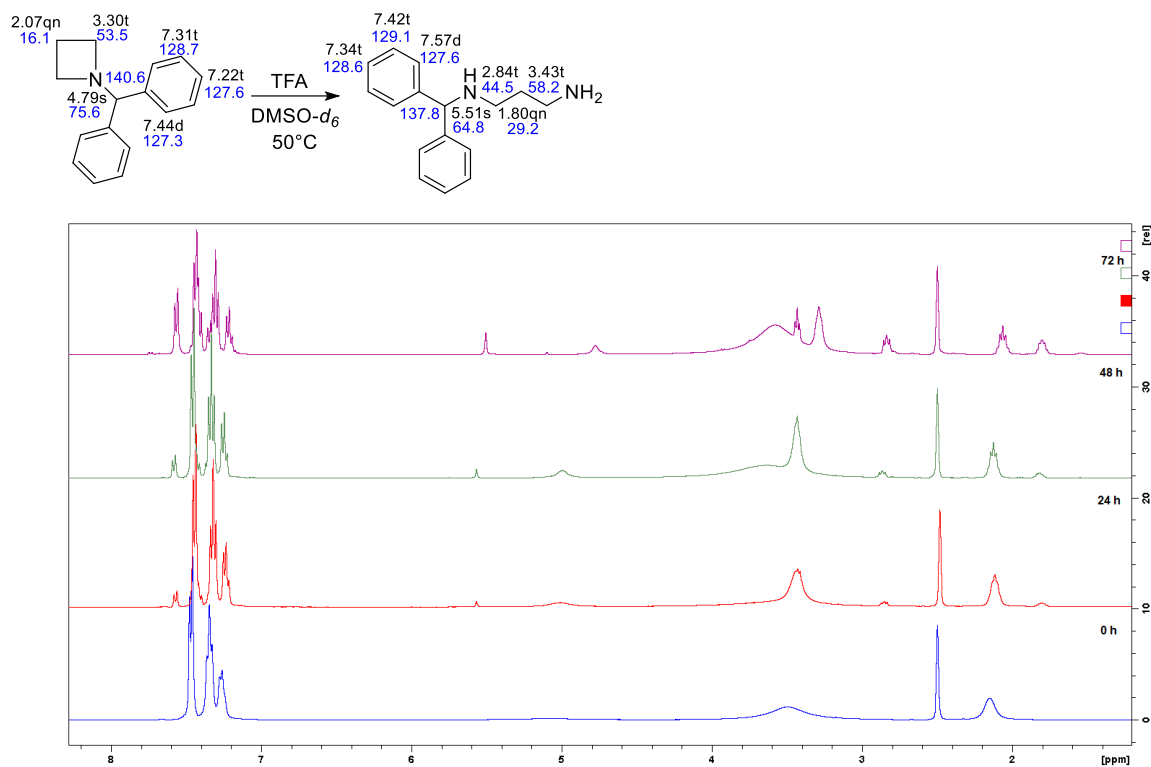


Figure S70. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of 1-(diphenylmethyl)azetidine + TFA at 50°C .

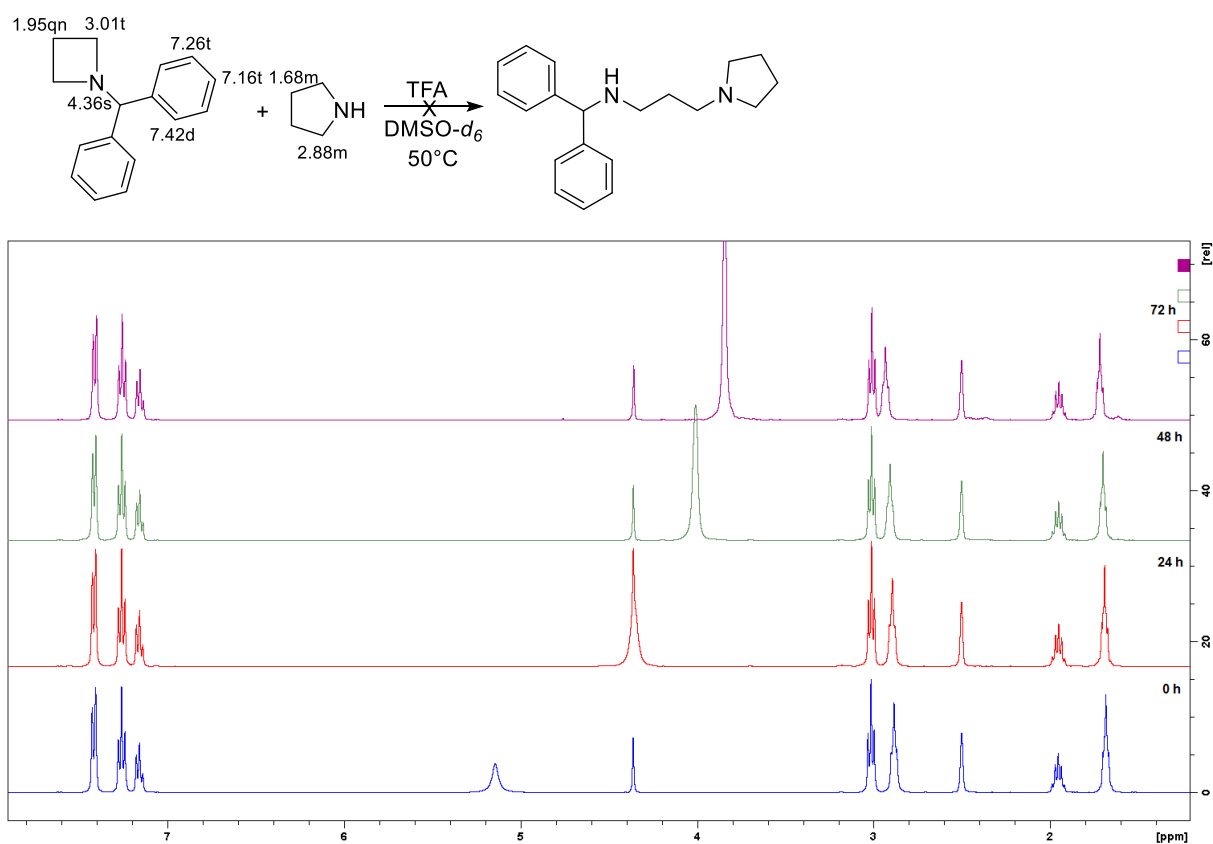


Figure S71. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) monitoring of 1-(diphenylmethyl)azetidine + pyrrolidine (1.0 eq) + TFA at 50°C .

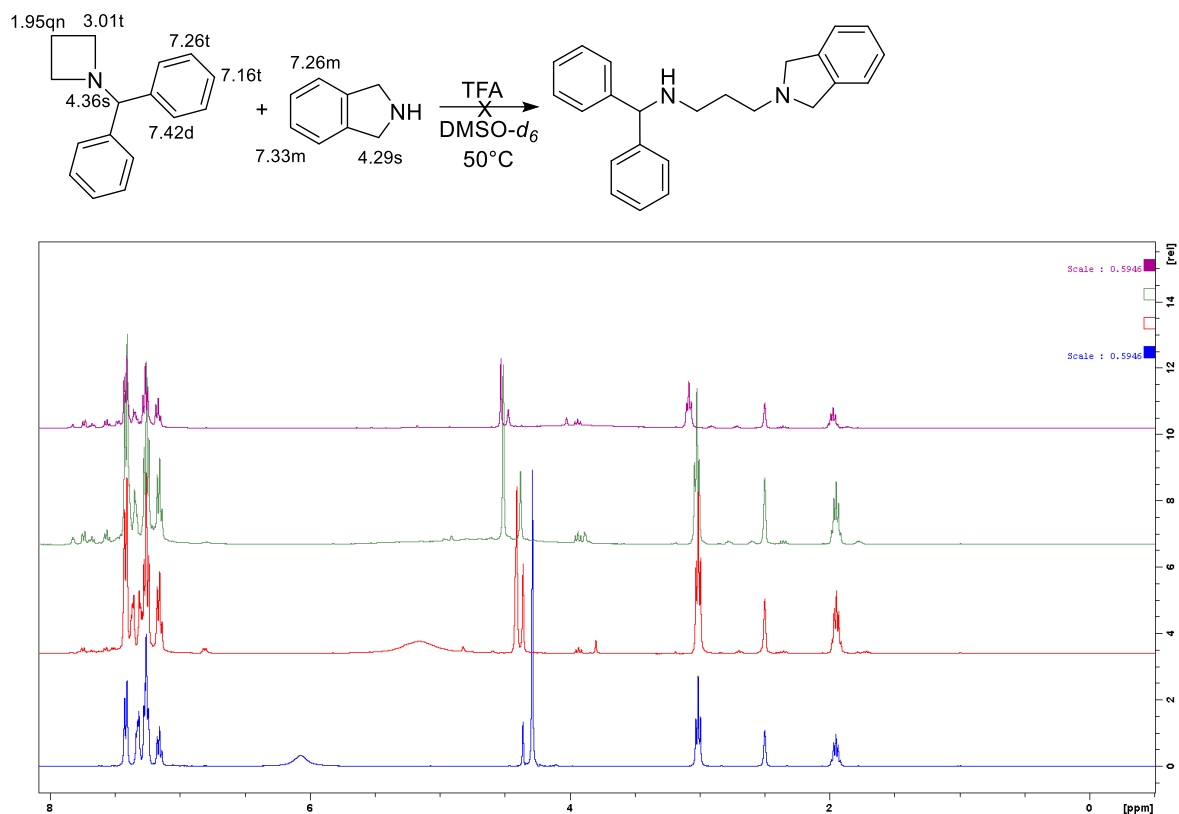


Figure S72. ¹H NMR (400 MHz, DMSO-*d*₆) monitoring of 1-(diphenylmethyl)azetidine + pyrrolidine (1.0 eq) + TFA at 50 °C.

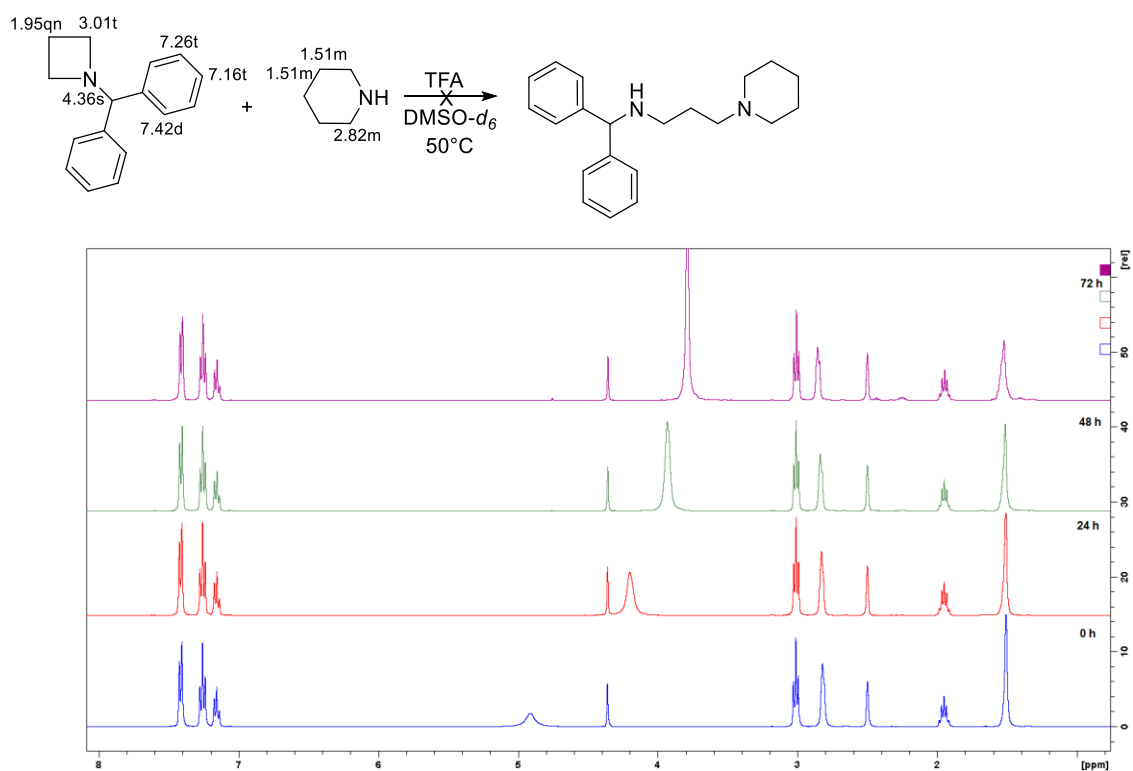


Figure S73. ¹H NMR (400 MHz, DMSO-*d*₆) monitoring of 1-(diphenylmethyl)azetidine + piperidine (1.0 eq) + TFA at 50 °C.

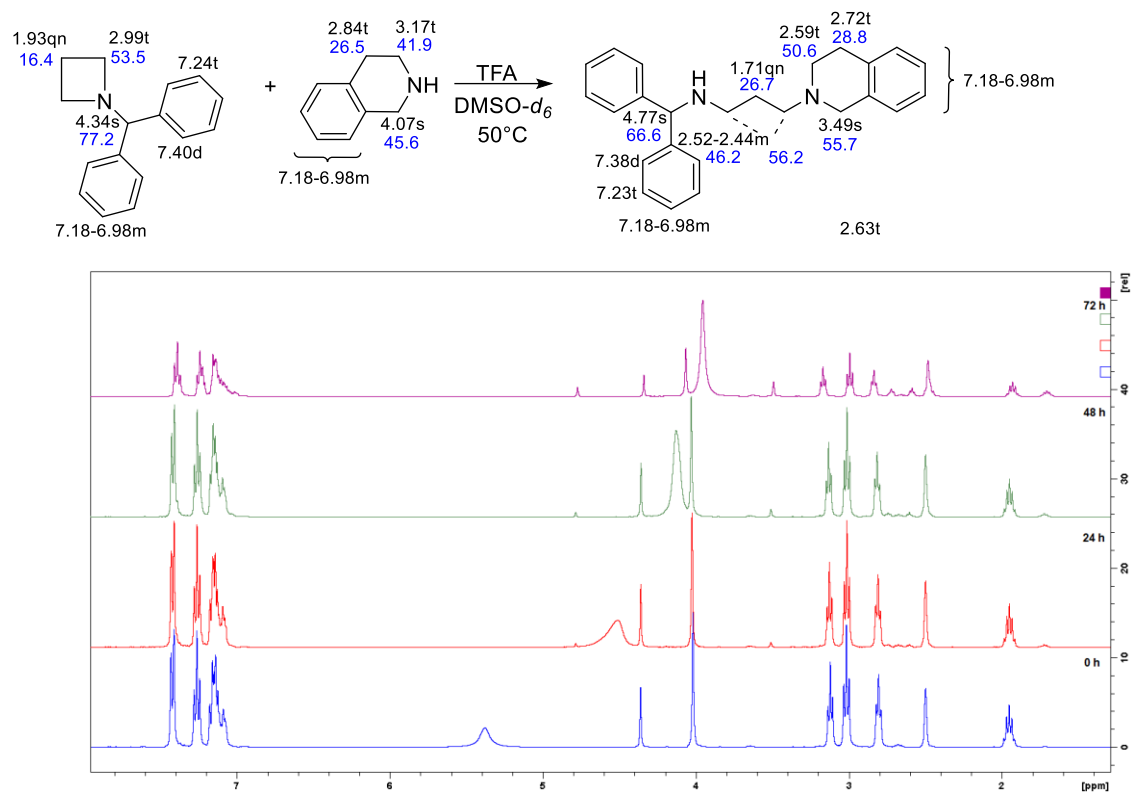


Figure S74. ^1H NMR (400 MHz, DMSO- d_6) monitoring of 1-(diphenylmethyl)azetidine + 1,2,3,4-tetrahydroisoquinoline (1.0 eq) + TFA at 50°C.

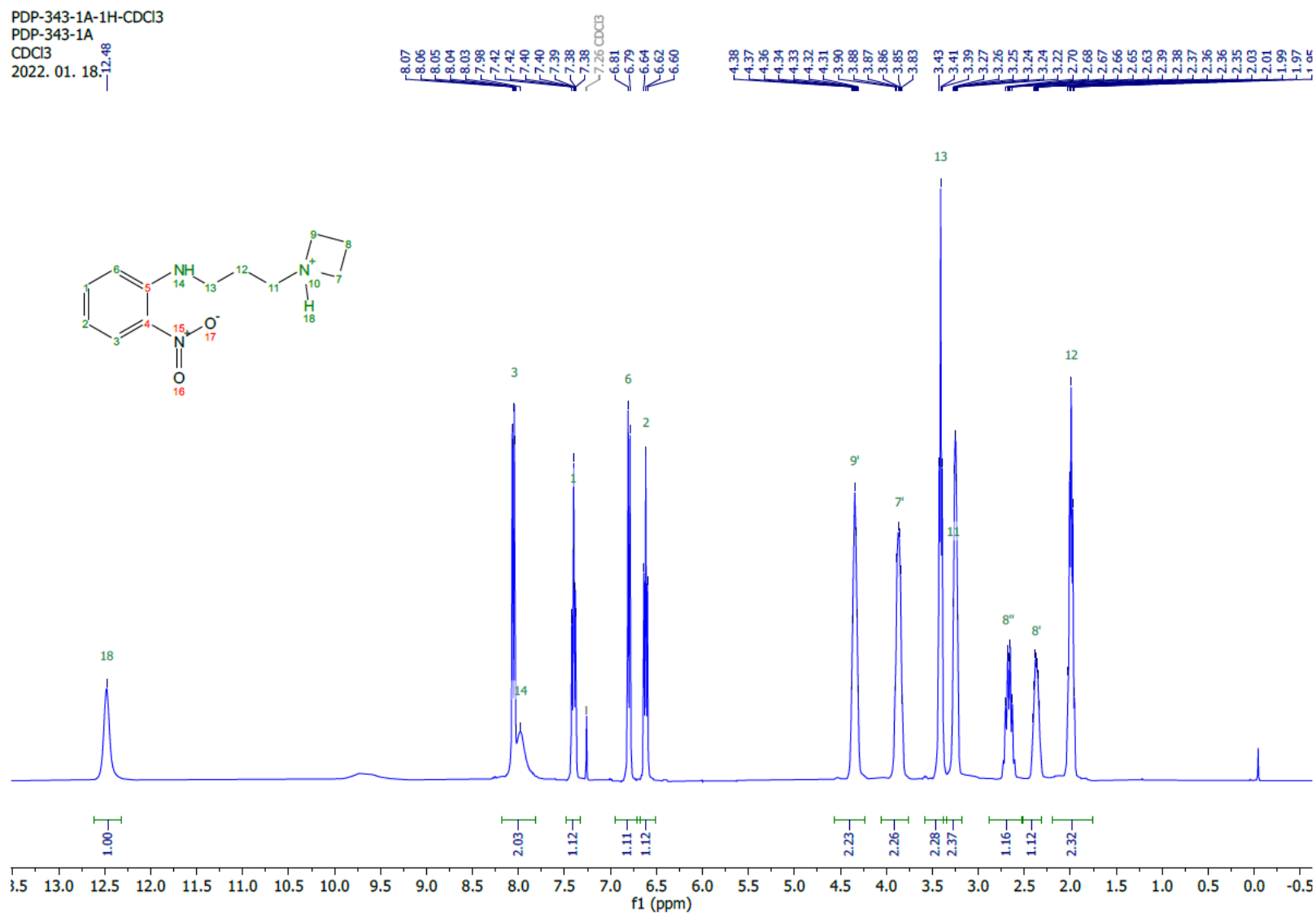


Figure S75: ^1H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-nitroaniline TFA salt (**10**) recorded at 400 MHz in CDCl_3 .

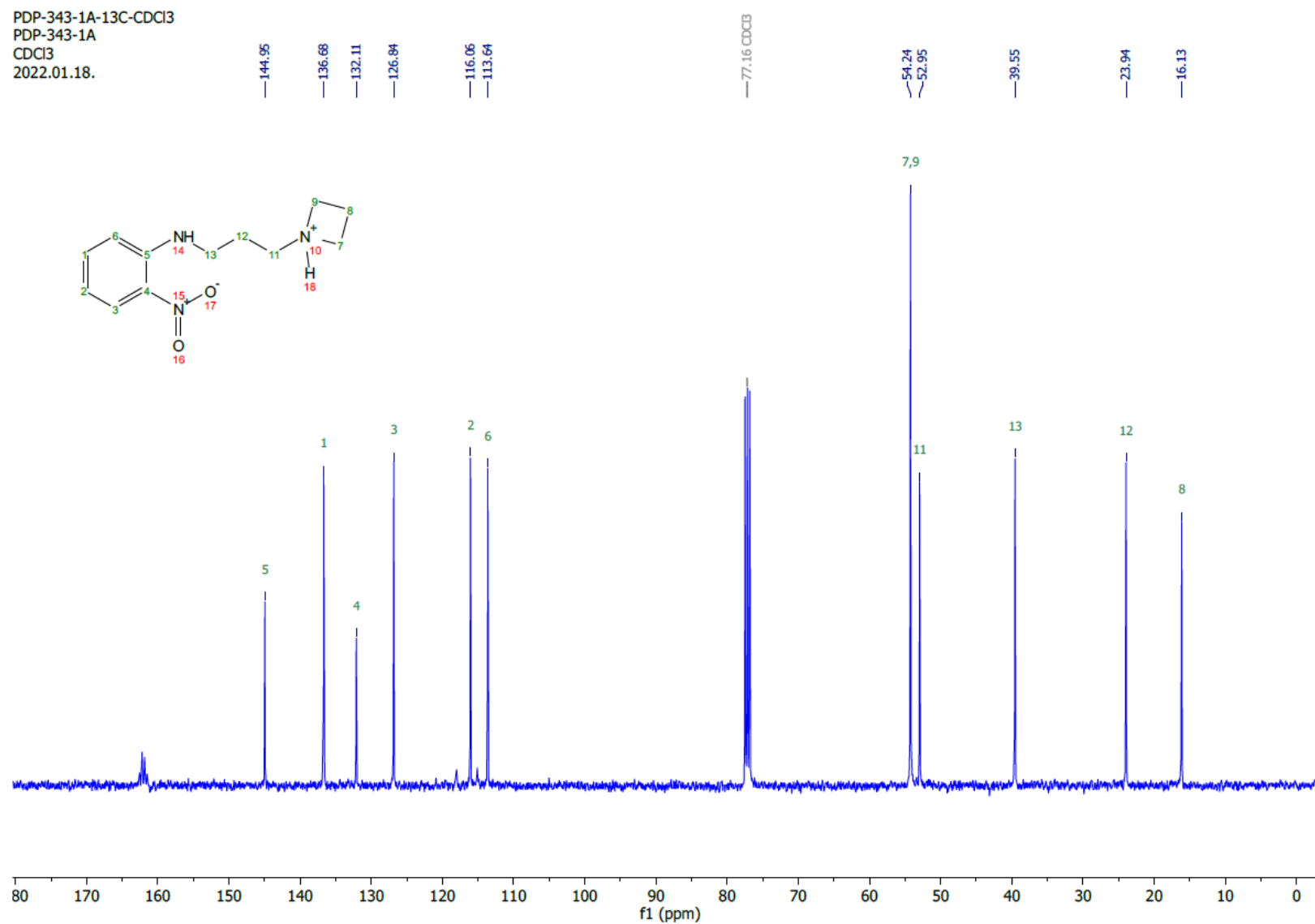


Figure S76: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-nitroaniline TFA salt (**10**) recorded at 400 MHz in CDCl_3 .

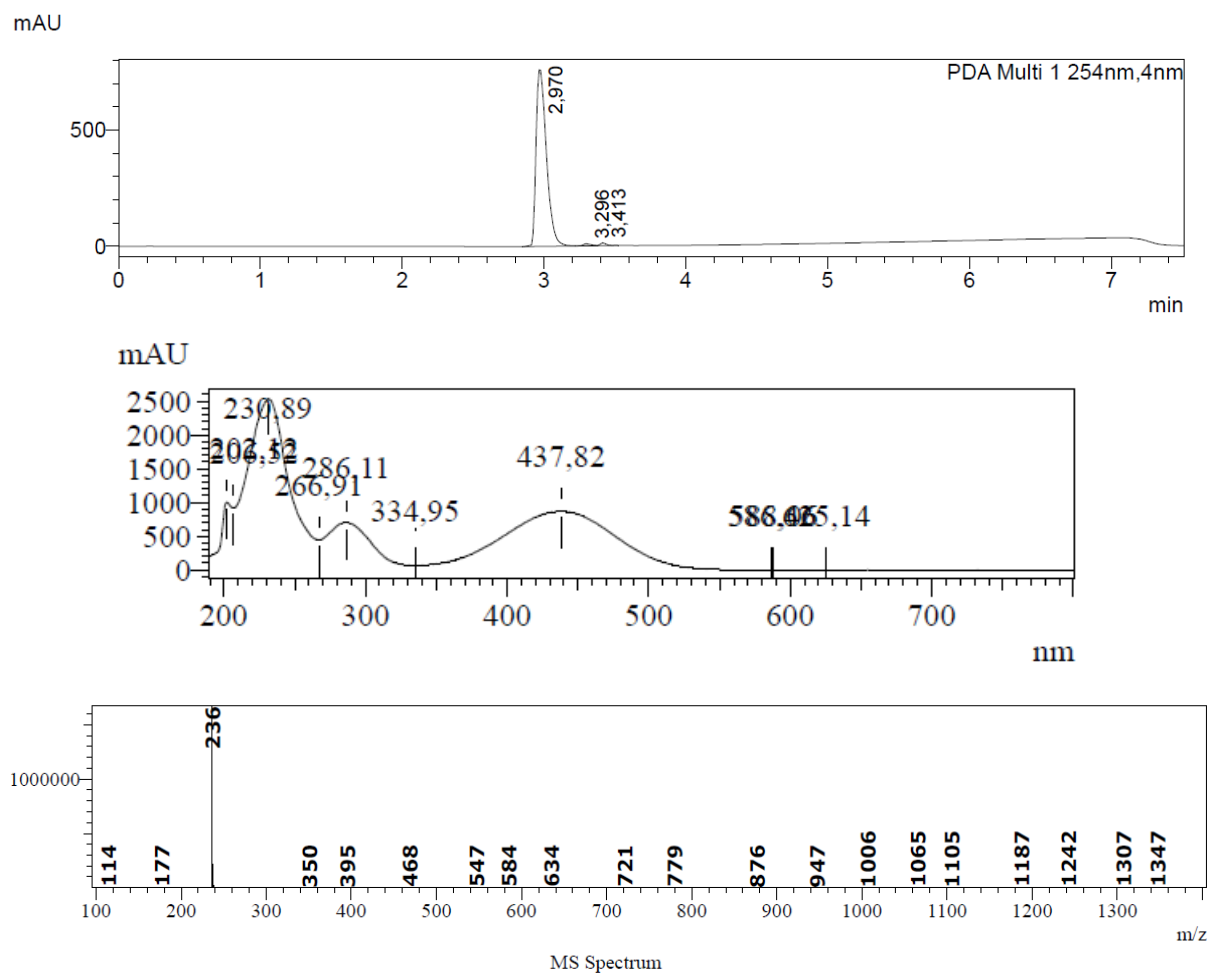


Figure S77.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-nitroaniline TFA salt (**10**).

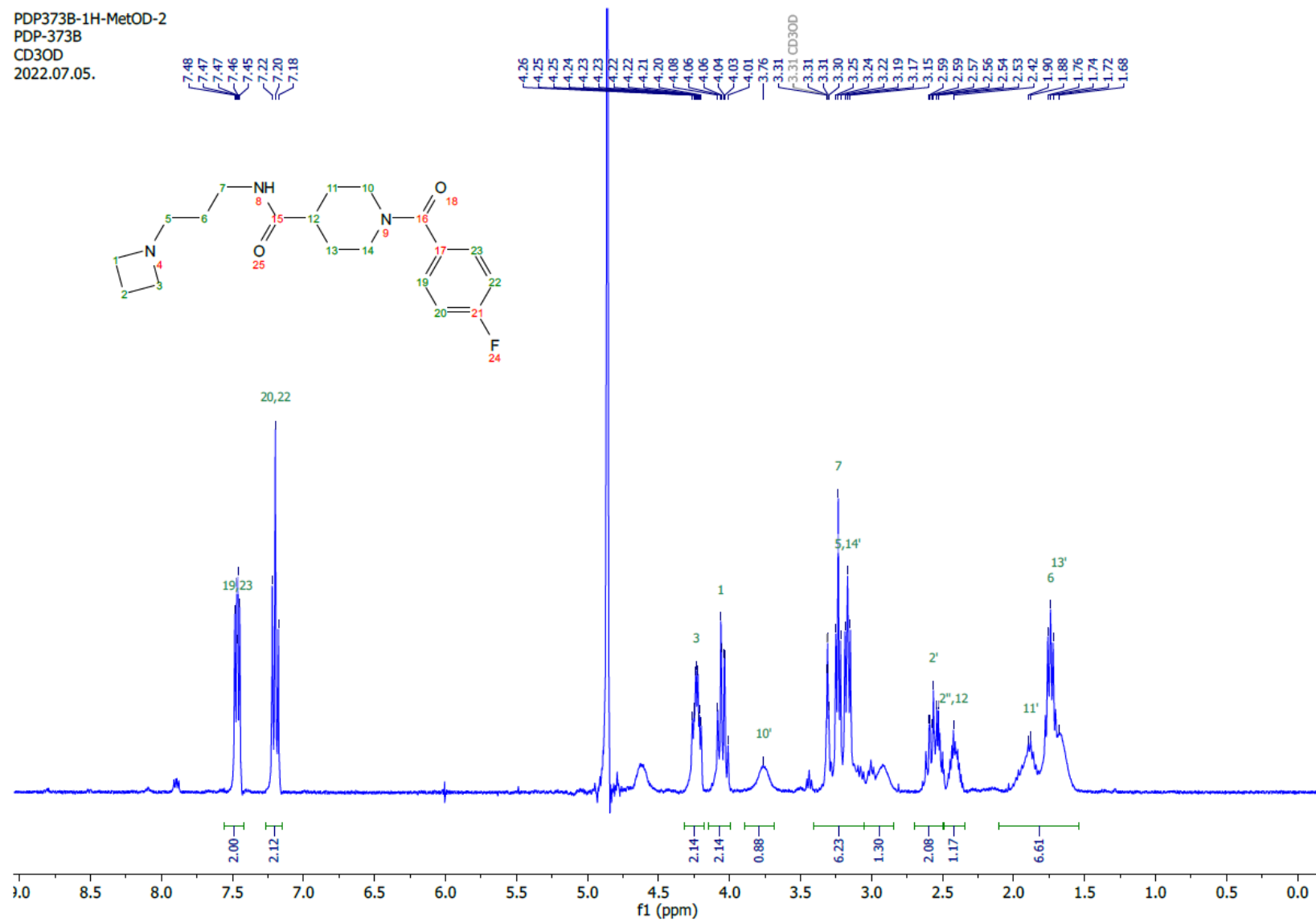


Figure S78: ^1H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-1-(4-fluorobenzoyl)piperidine-3-carboxamide TFA salt (**12**) recorded at 400 MHz in CD_3OD .

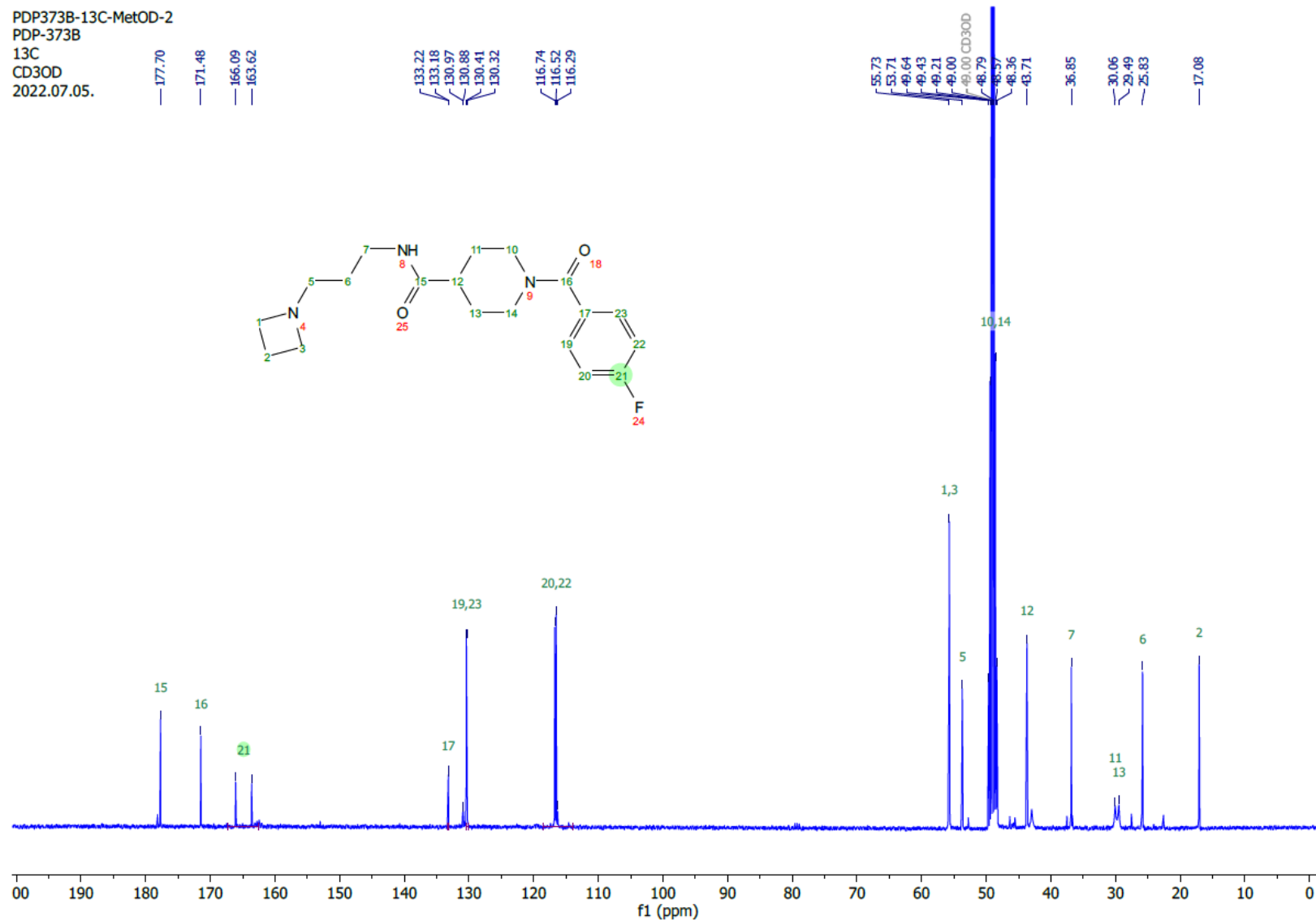


Figure S79: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-1-(4-fluorobenzoyl)piperidine-3-carboxamide TFA salt (**12**) recorded at 400 MHz in CDCl_3 .

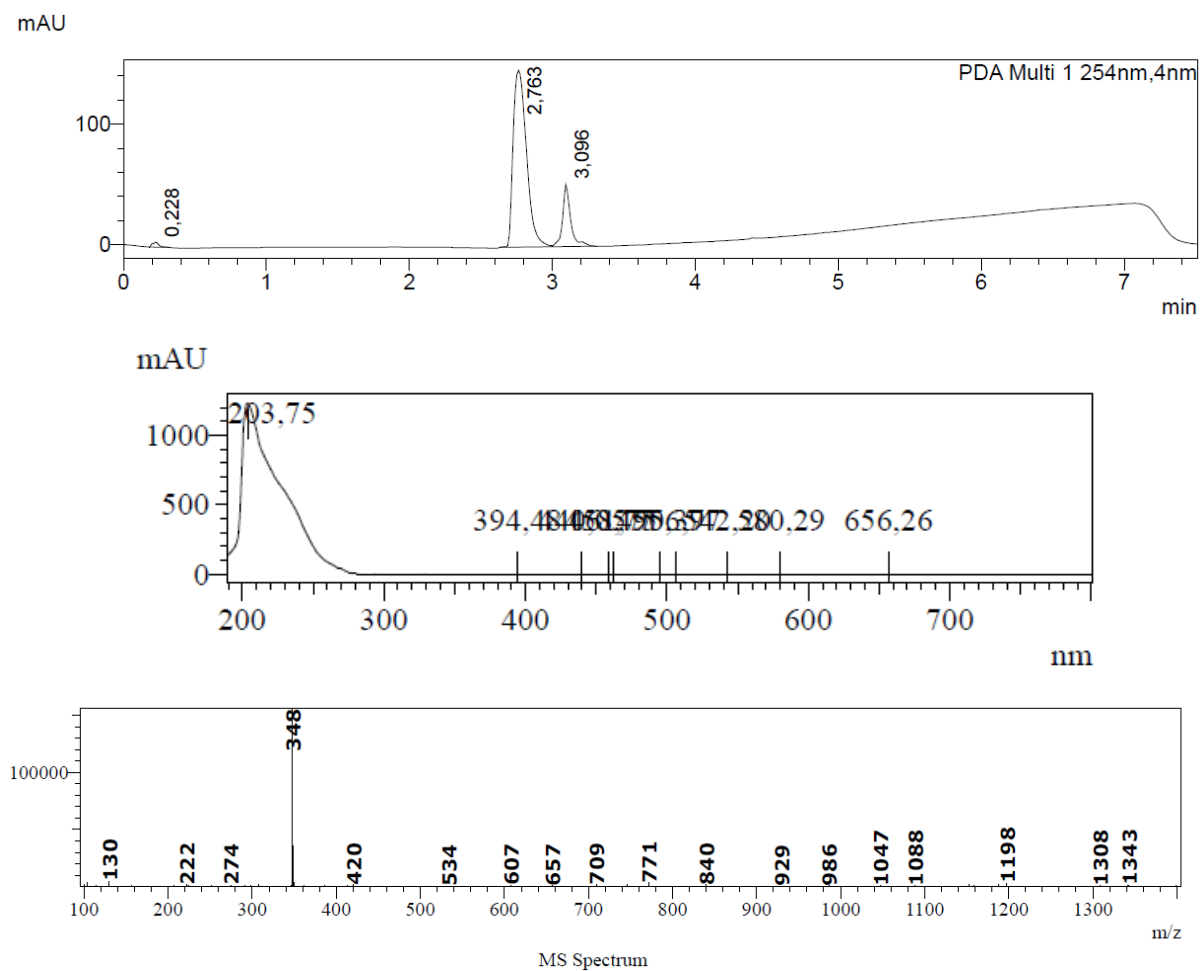


Figure S80: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(azetidin-1-yl)propyl]-1-(4-fluorobenzoyl)piperidine-3-carboxamide TFA salt (**12**).

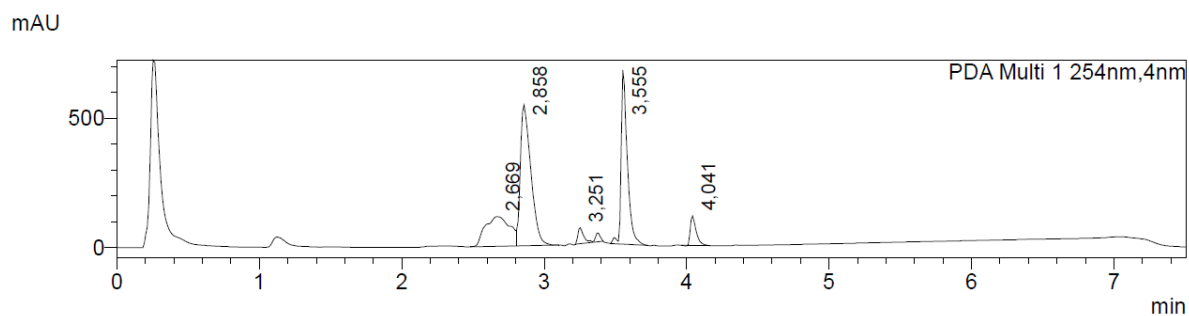


Figure S81. HPLC chromatogram of the crude reaction mixture (reaction with 5-chloro-3a*H*-thieno[2,3-*b*]pyrrole-4-sulfonyl chloride (**14**)).

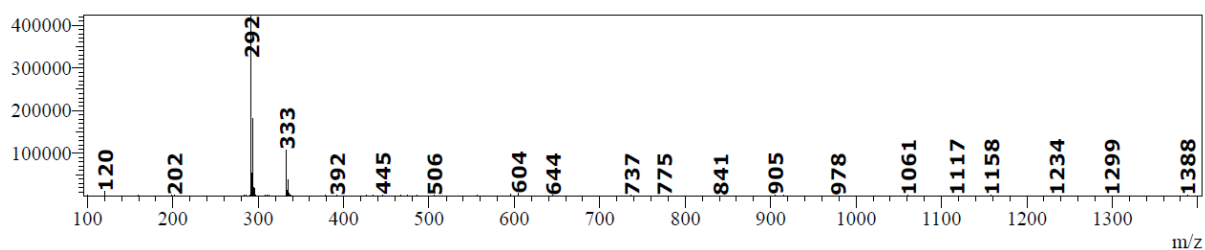
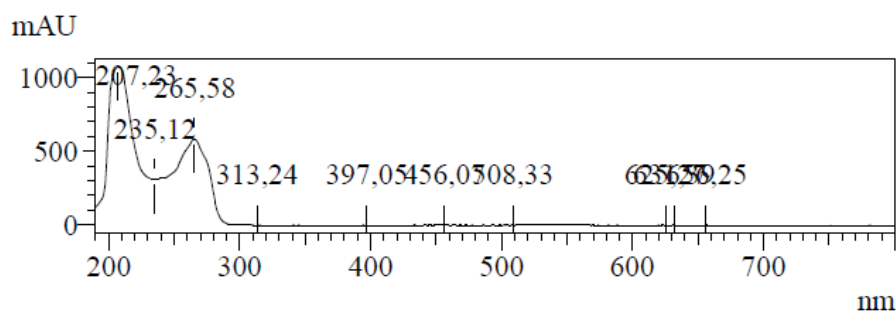
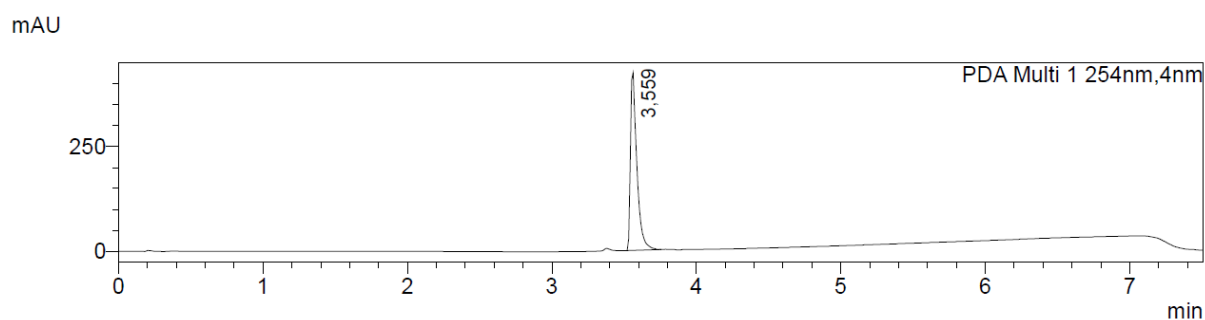
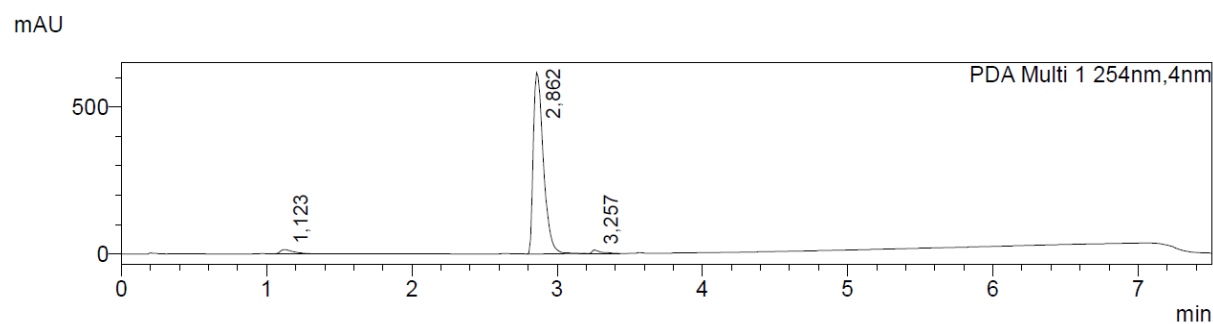


Figure S82: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of 6-chloro-5-(pyrrolidine-1-sulfonyl)imidazo[2,1-*b*][1,3]thiazole (**15**).



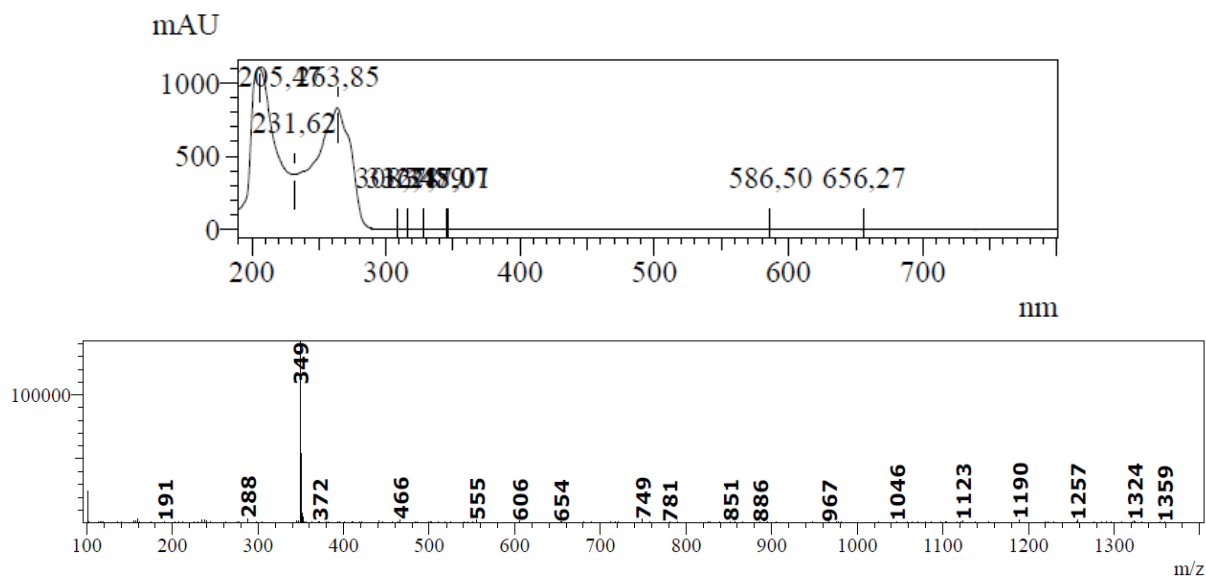


Figure S83.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of 6-chloro-*N*-[3-(pyrrolidin-1-yl)propyl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide TFA salt (**17**).

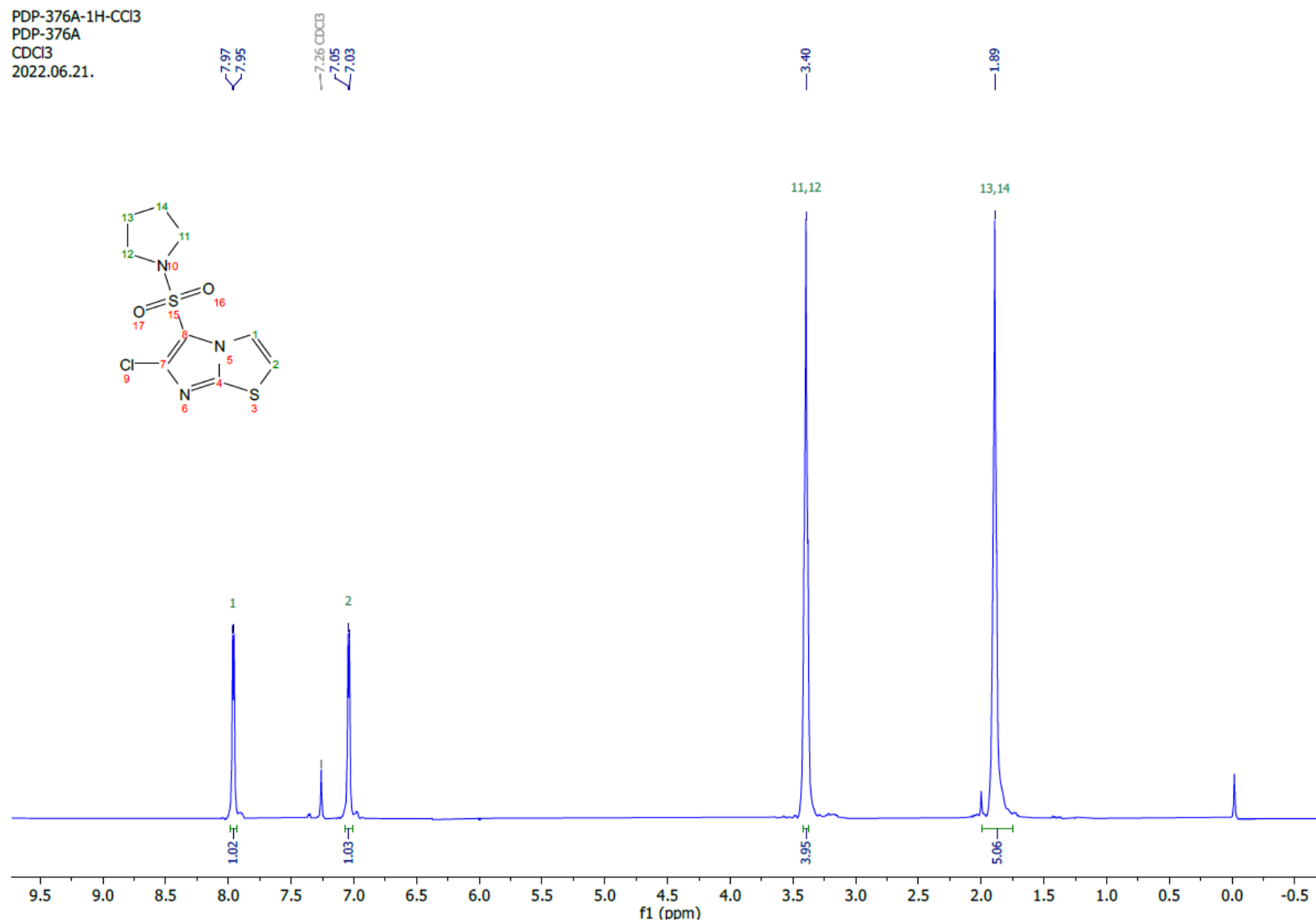


Figure S84: ^1H NMR spectrum of 6-chloro-5-(pyrrolidine-1-sulfonyl)imidazo[2,1-*b*][1,3]thiazole (**15**) recorded at 400 MHz in CDCl_3 .

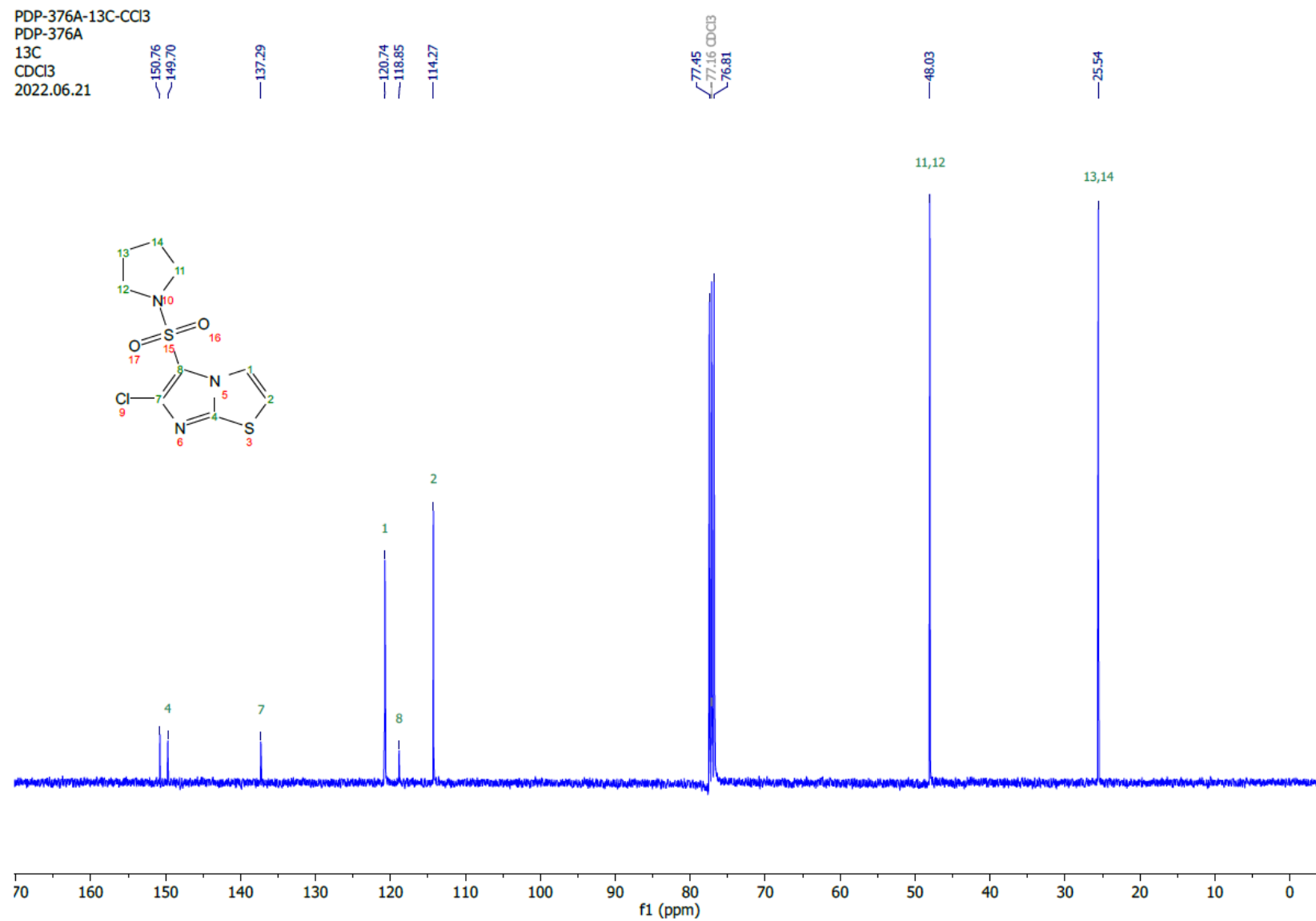


Figure S85: ^{13}C NMR spectrum of 6-chloro-5-(pyrrolidine-1-sulfonyl)imidazo[2,1-*b*][1,3]thiazole (**15**) recorded at 400 MHz in CDCl_3 .

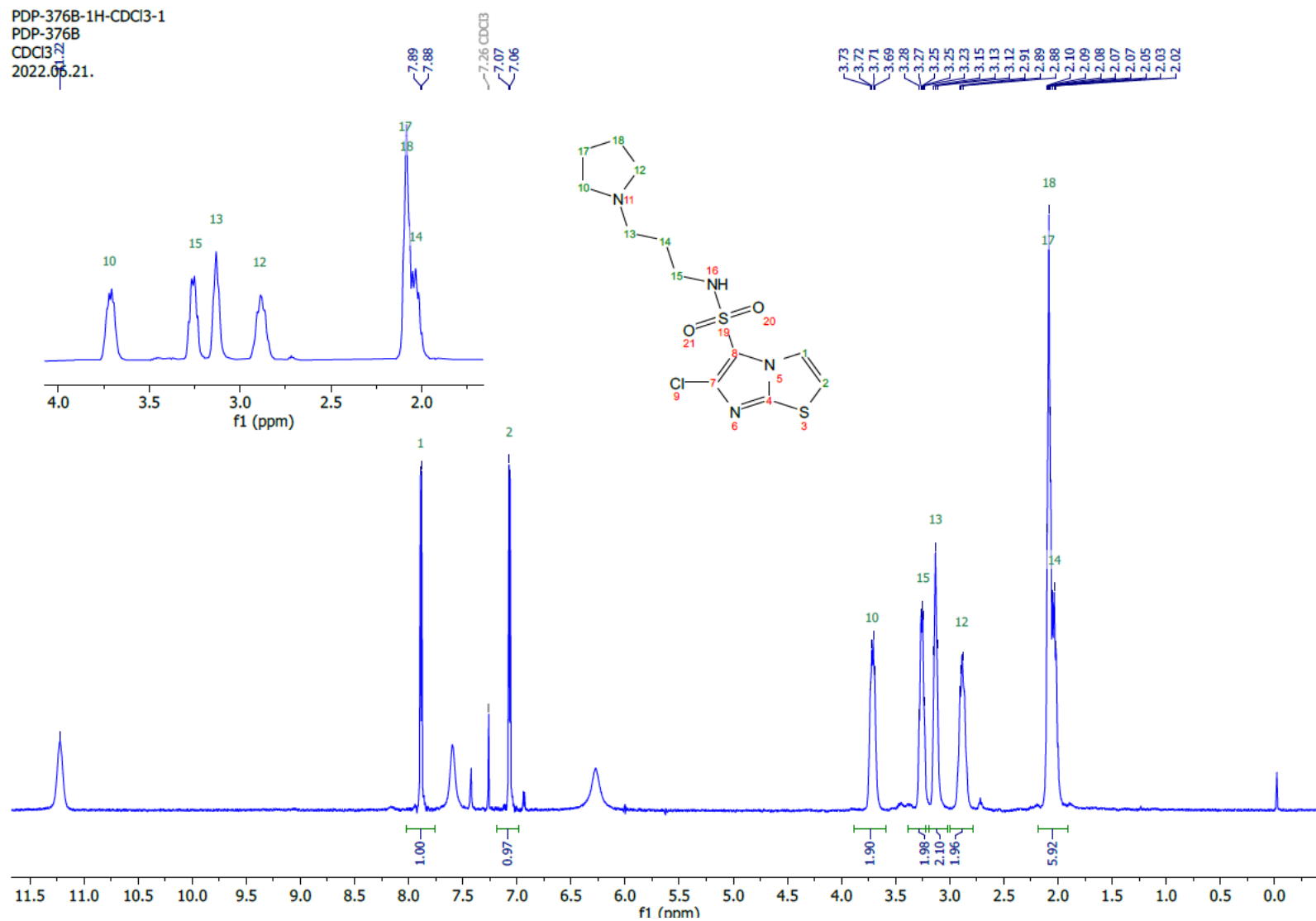


Figure S86: ^1H NMR spectrum of 6-chloro-*N*-[3-(pyrrolidin-1-yl)propyl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide TFA salt (**17**) recorded at 400 MHz in CDCl_3 .

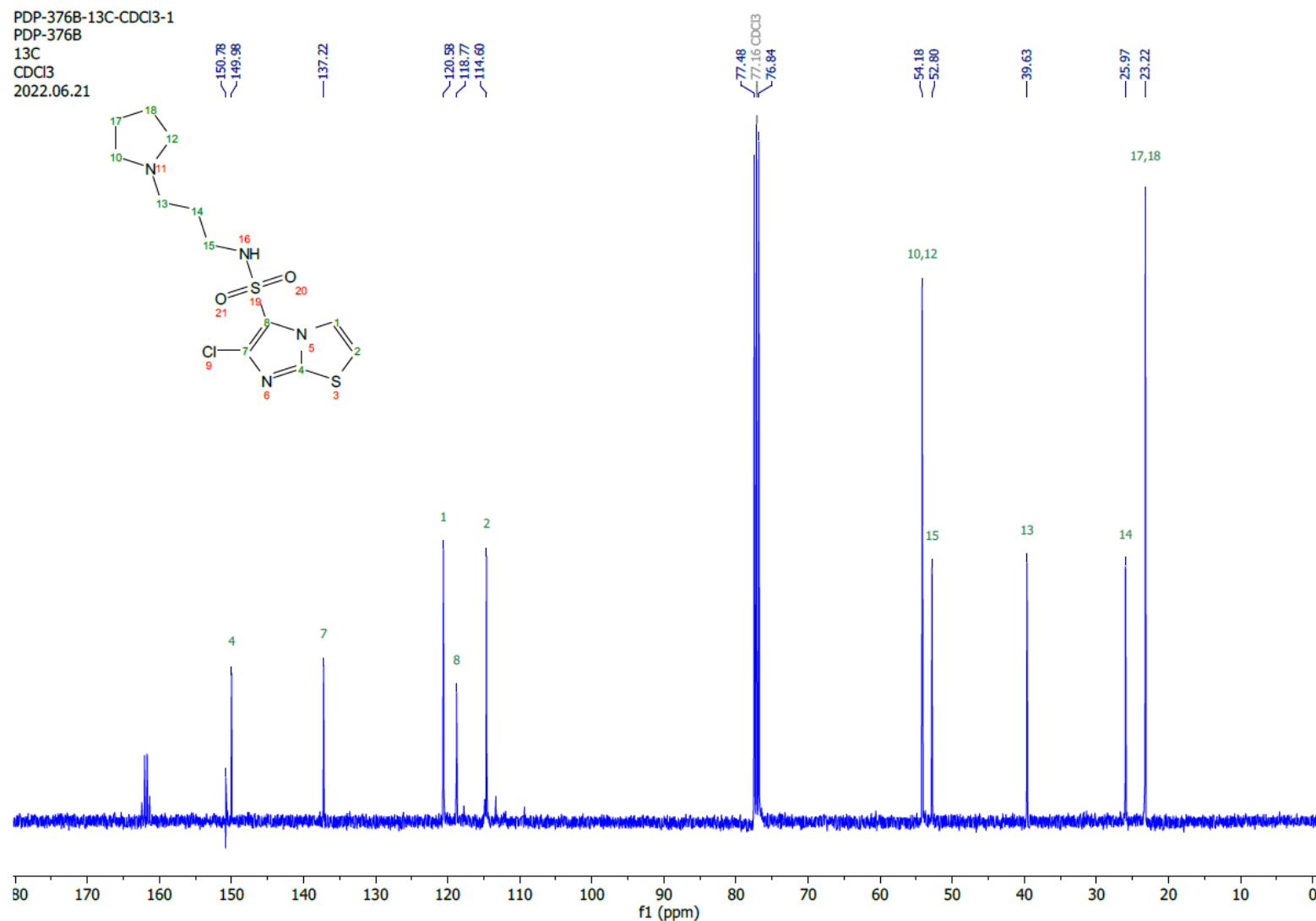


Figure S87: ^{13}C NMR spectrum of 6-chloro-N-[3-(pyrrolidin-1-yl)propyl]imidazo[2,1-b][1,3]thiazole-5-sulfonamide TFA salt (**17**) recorded at 400 MHz in CDCl_3 .

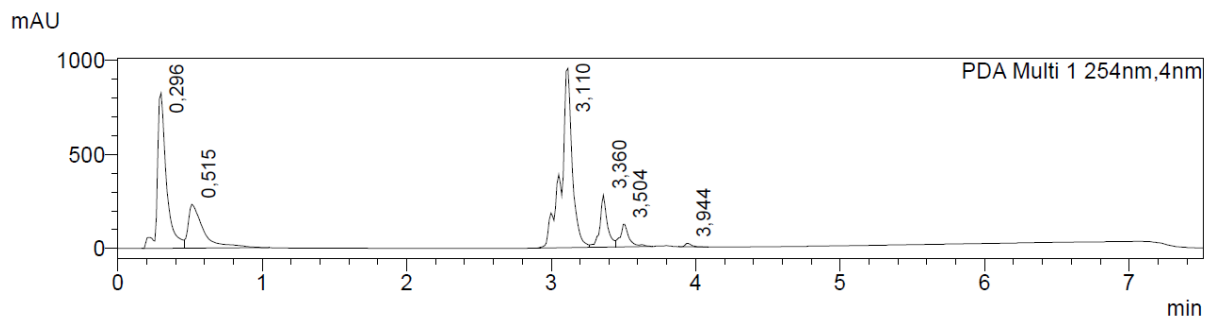


Figure S88. HPLC chromatogram of the crude reaction mixture (amide formation with quinoline-2-carboxylic acid (**18**)).

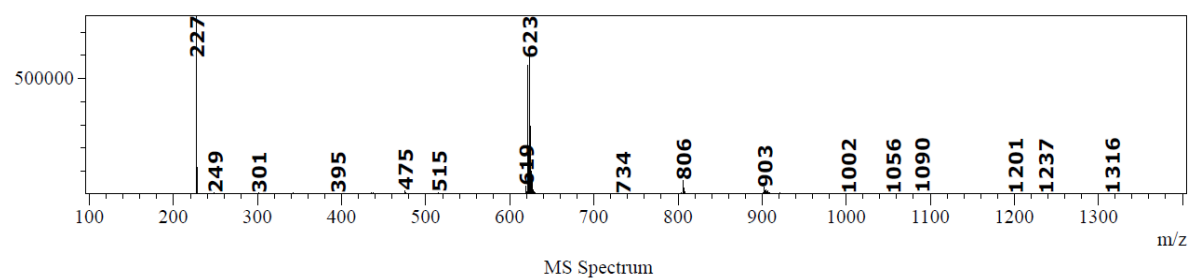
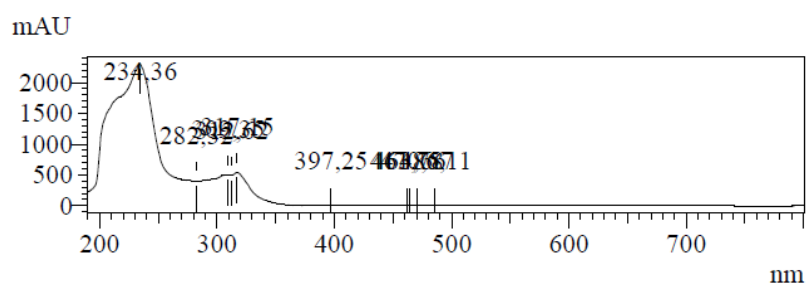
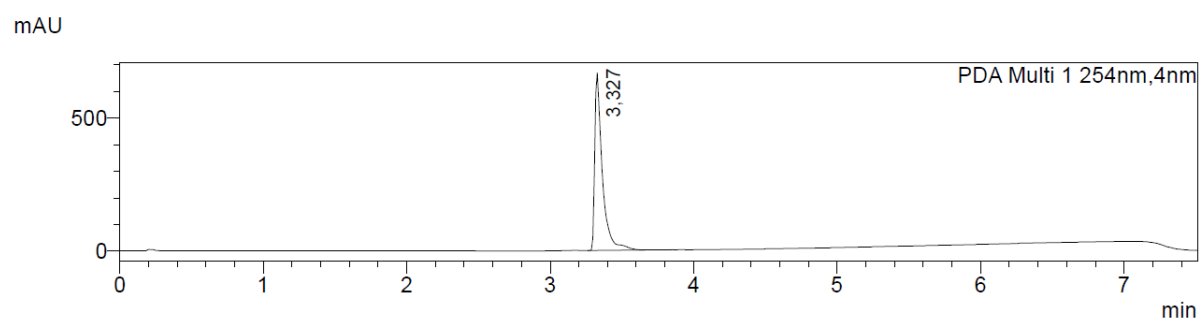
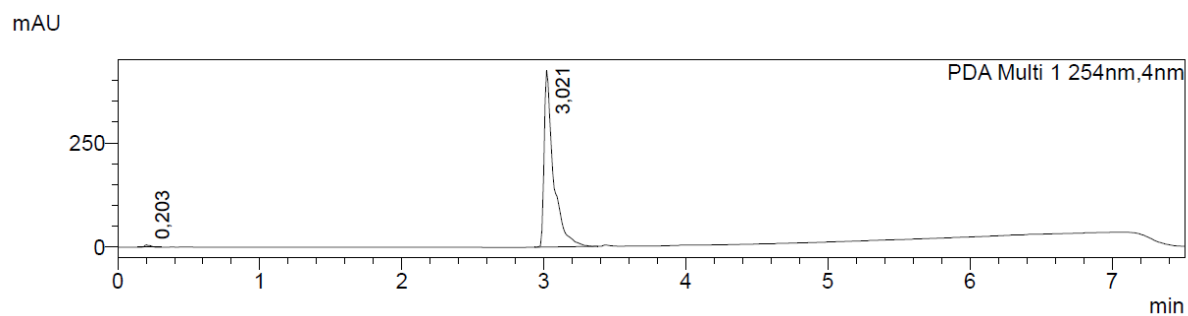


Figure S89. HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of (pyrrolidin-1-yl)(quinolin-2-yl)methanone (**19**).



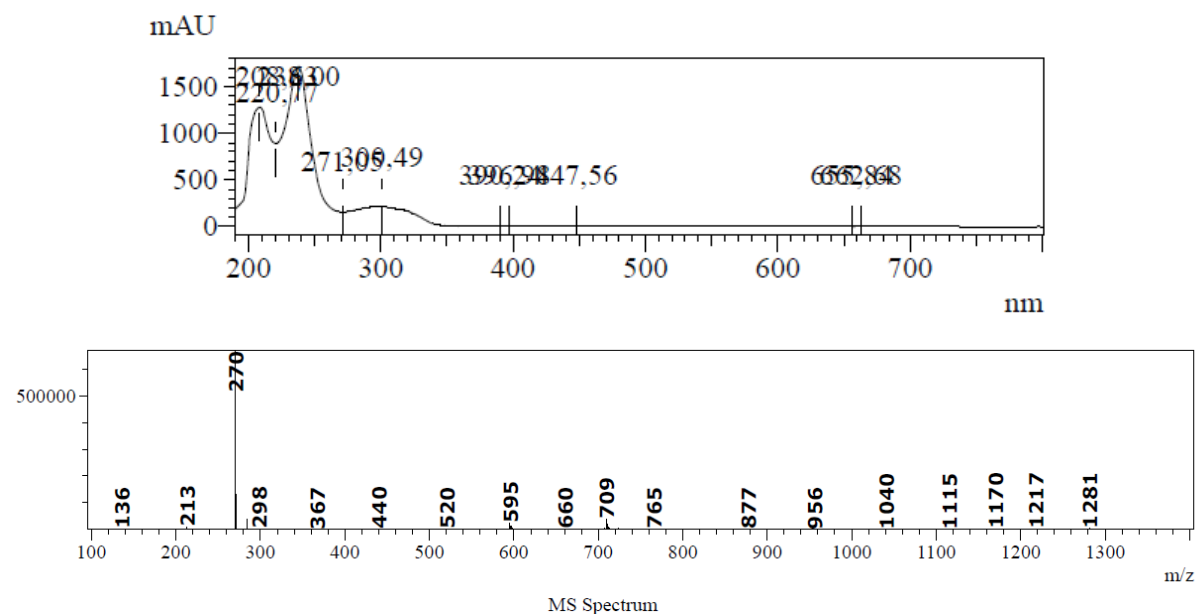


Figure S90. HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(azetidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**20**).

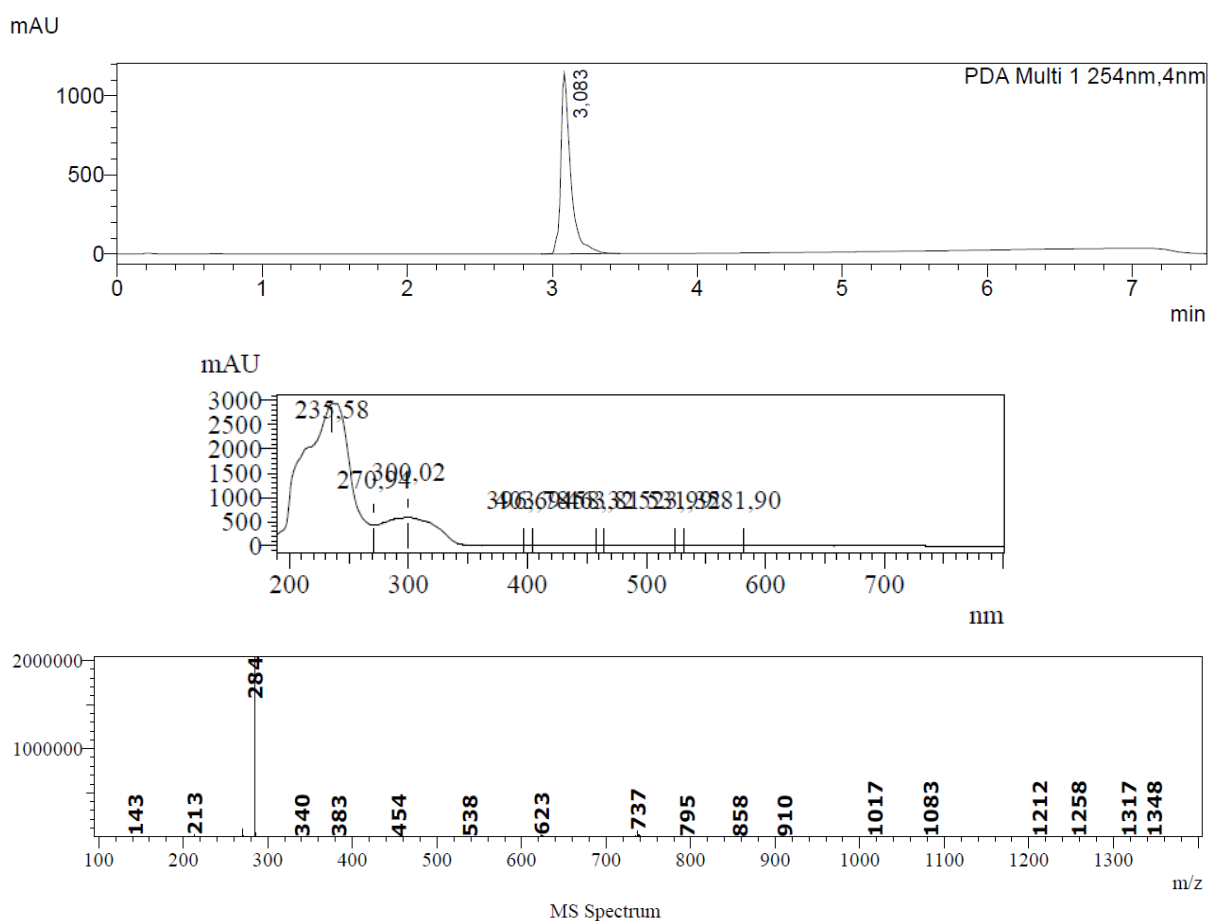


Figure S91. HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(pyrrolidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**21**).

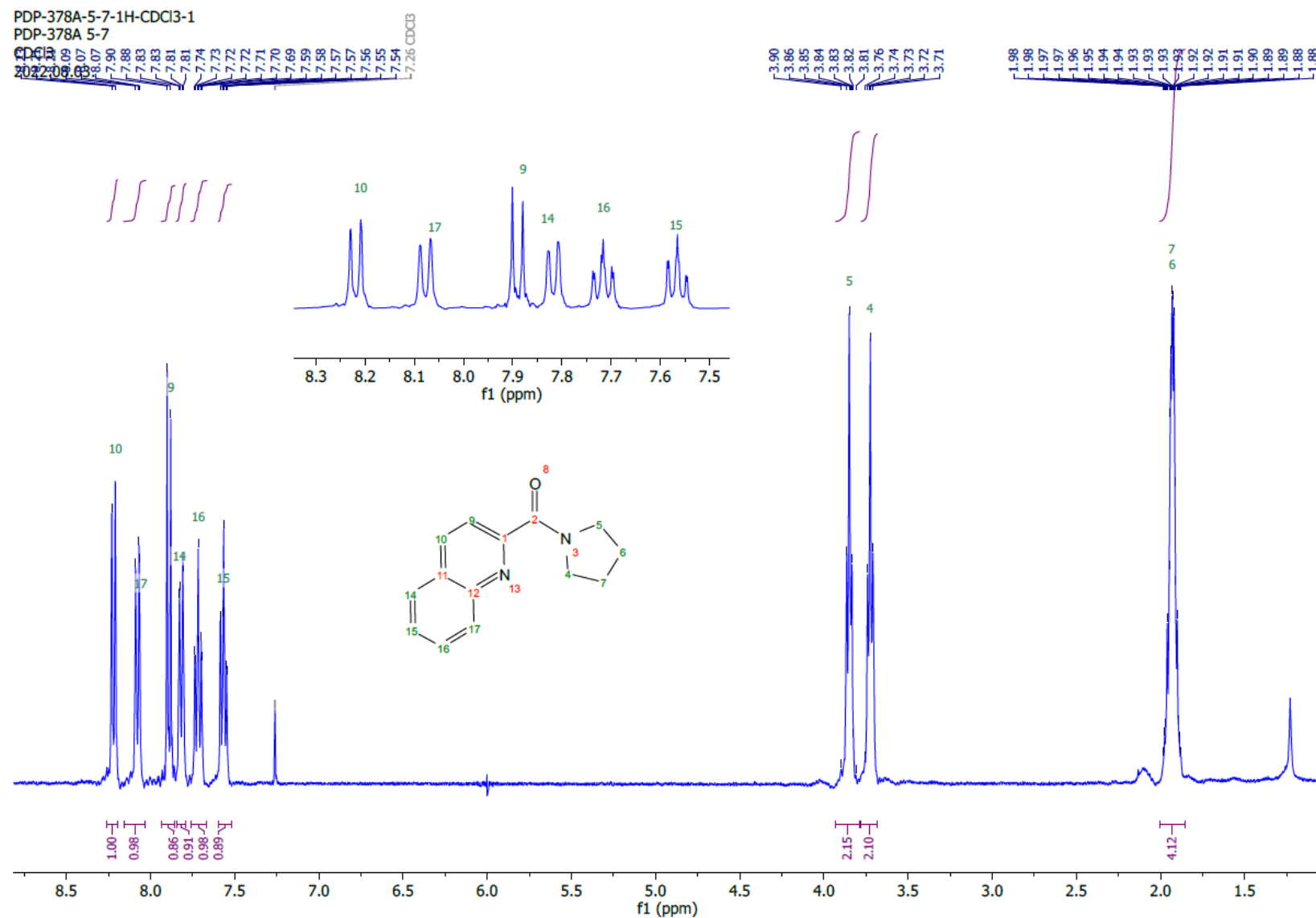
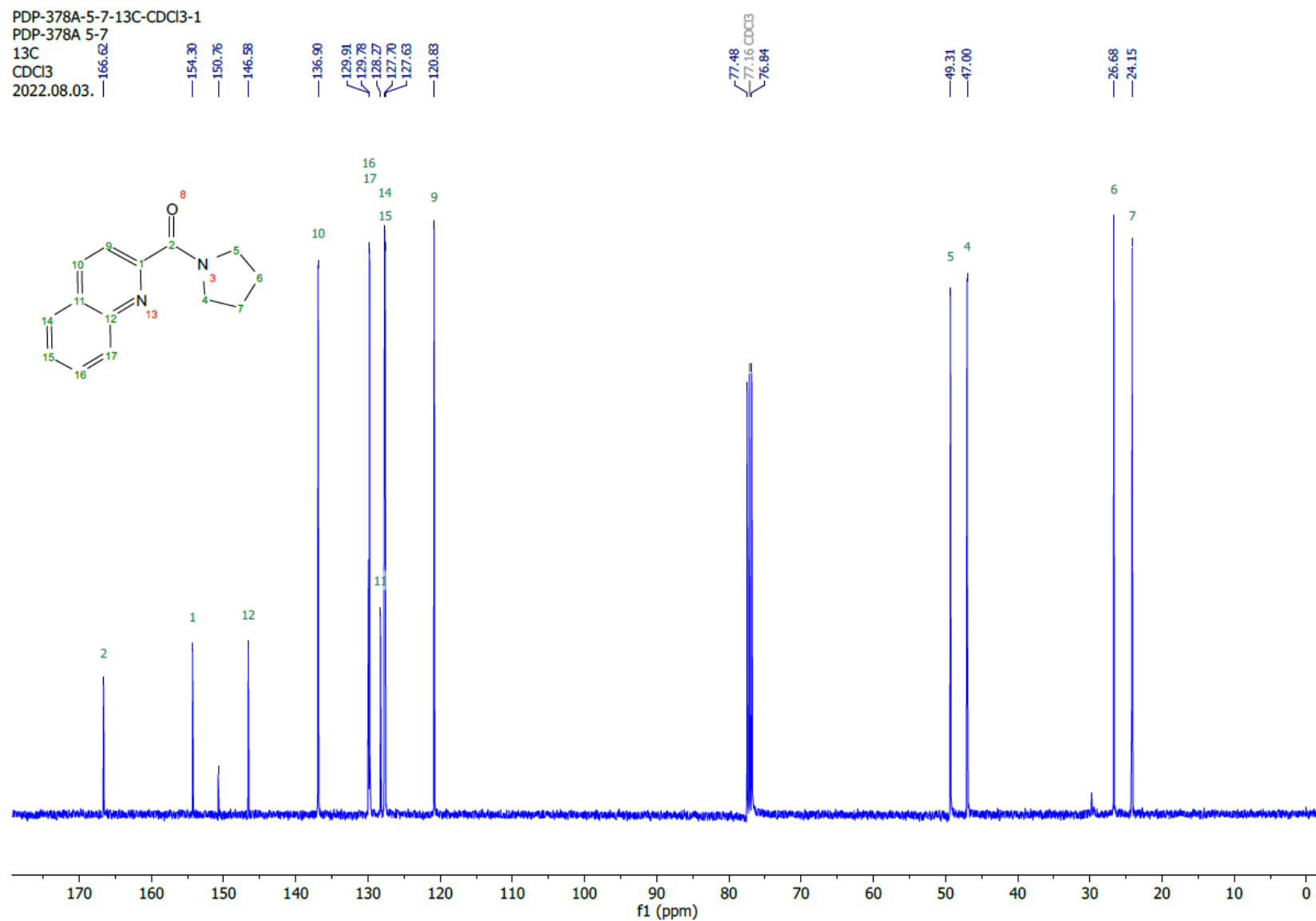


Figure S92: ^1H NMR spectrum of (pyrrolidin-1-yl)(quinolin-2-yl)methanone (**19**) recorded at 400 MHz in CDCl_3 .



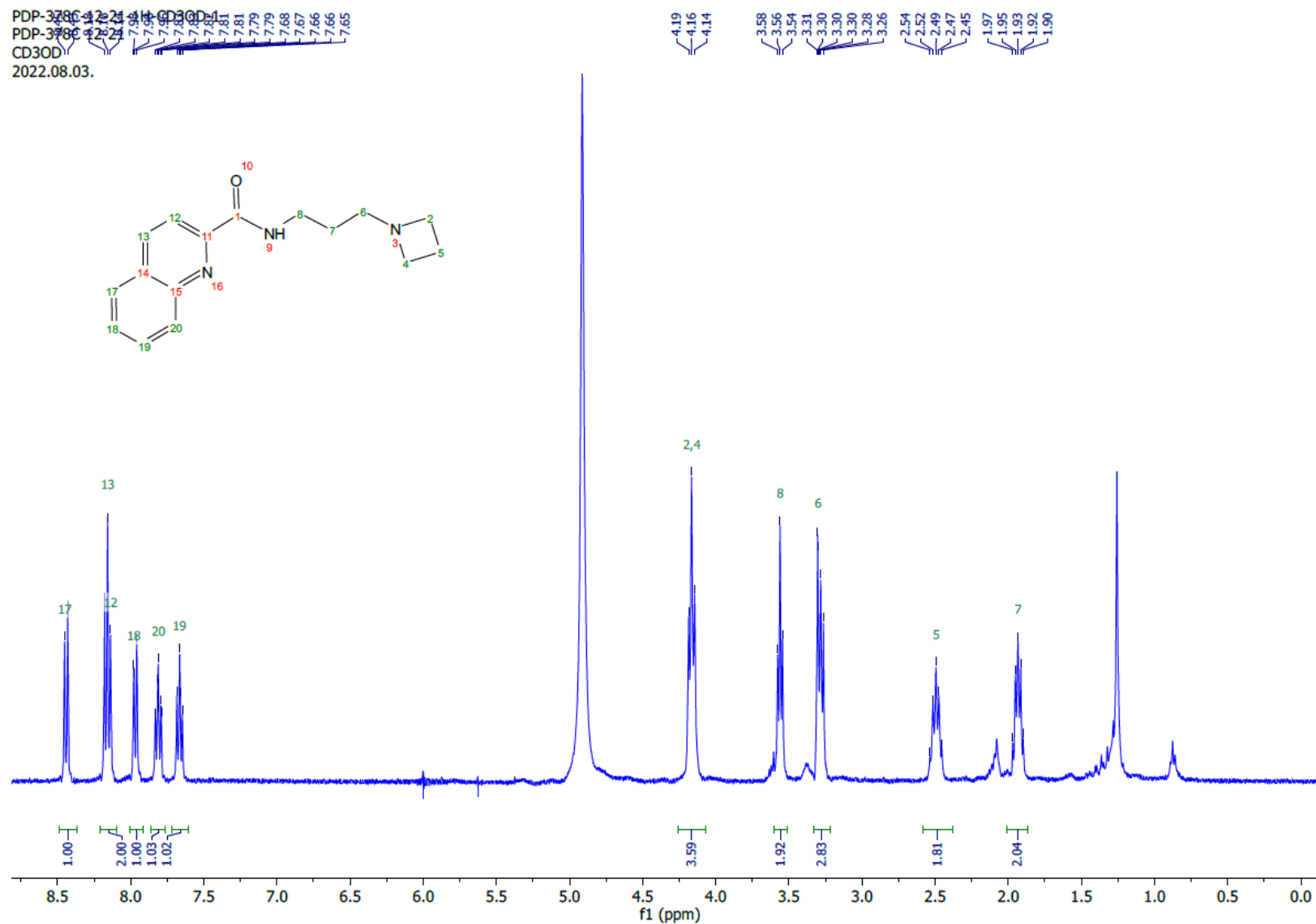


Figure S94. ^1H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**20**) recorded at 400 MHz in CDCl_3 .

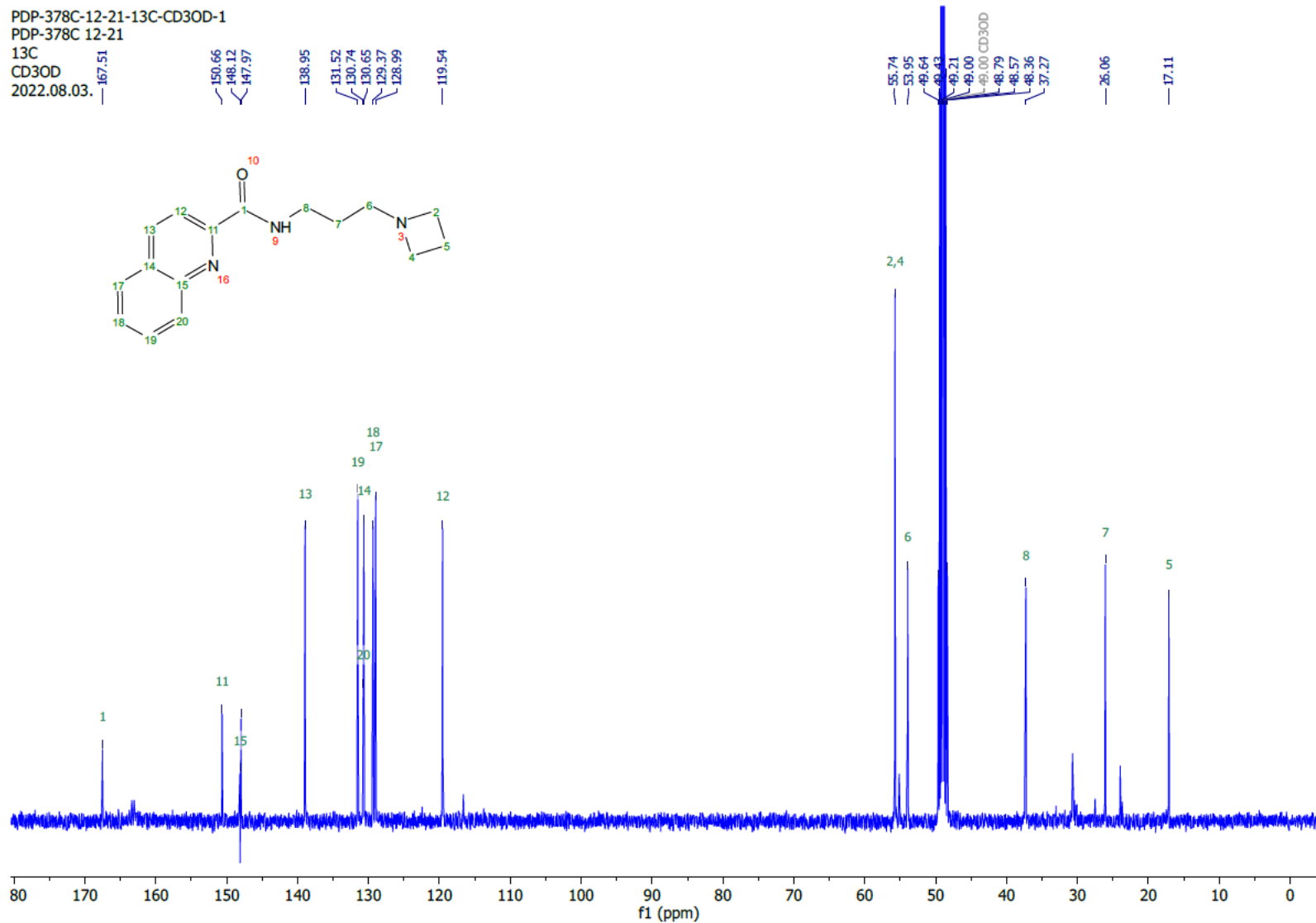


Figure S95: ¹³C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**20**) recorded at 400 MHz in CDCl₃.

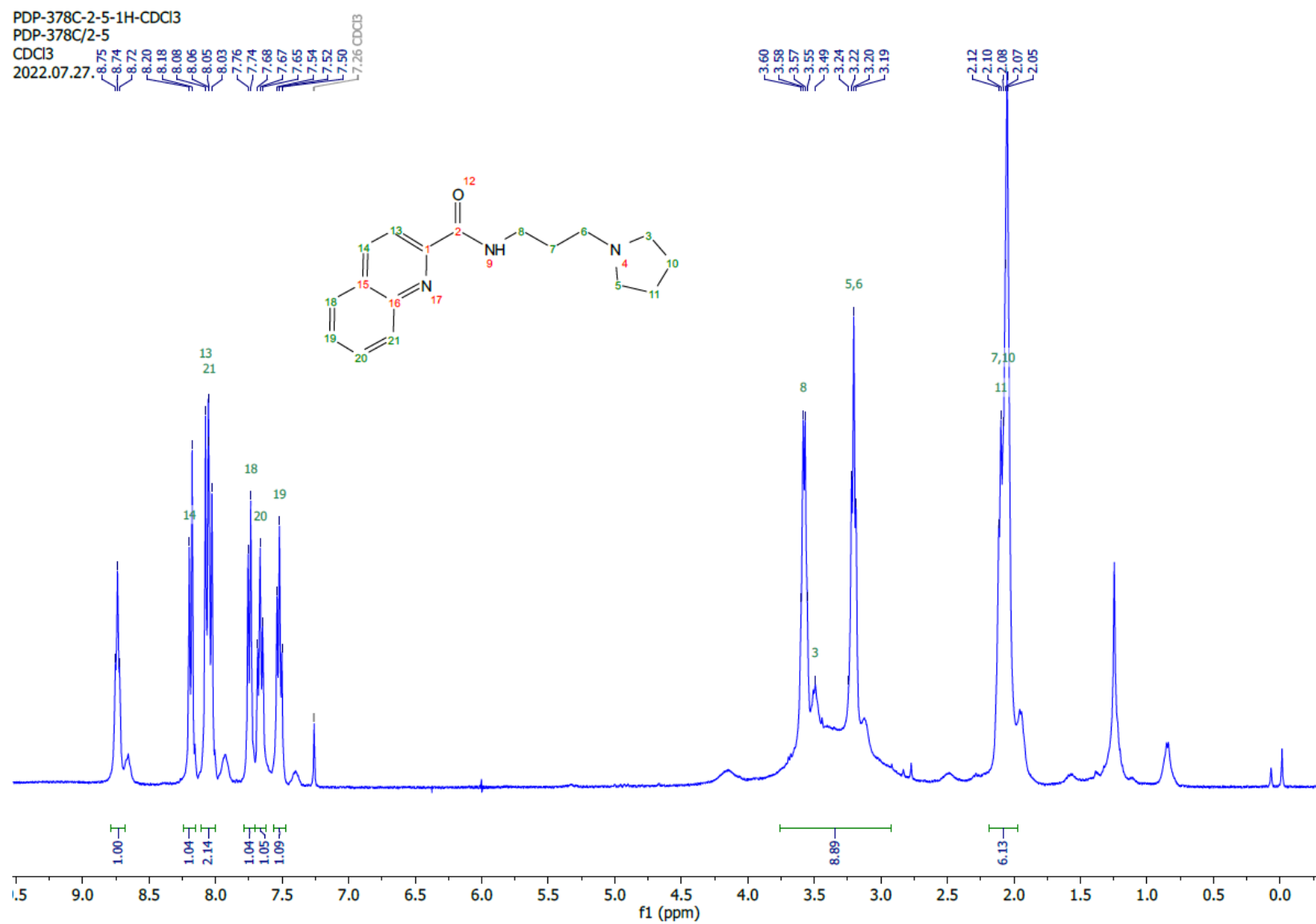


Figure S96: ¹H NMR spectrum of *N*-[3-(pyrrolidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**21**) recorded at 400 MHz in CDCl₃.

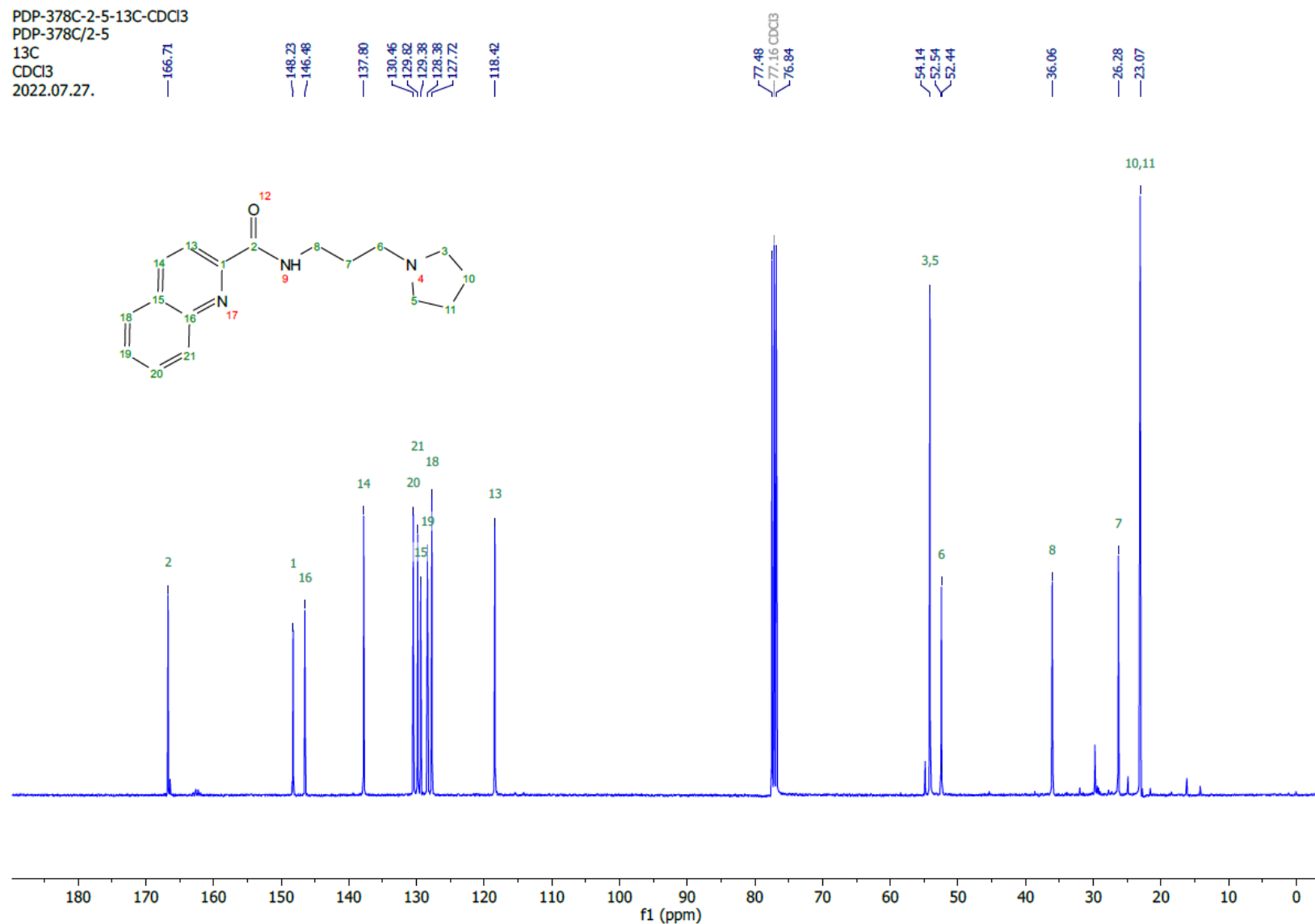


Figure S97: ¹³C NMR spectrum of *N*-[3-(pyrrolidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**21**) recorded at 400 MHz in CDCl₃

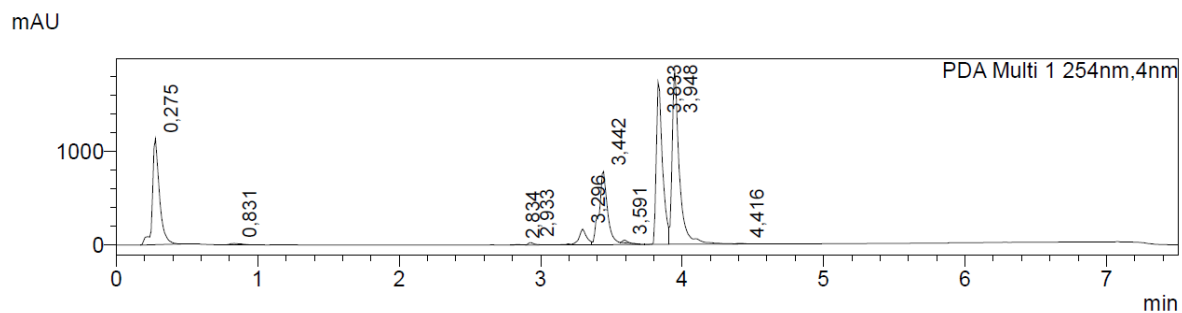


Figure S98. HPLC chromatogram of the crude reaction mixture (amide formation with [1,1'-biphenyl]-4-carboxylic acid (**22**)).

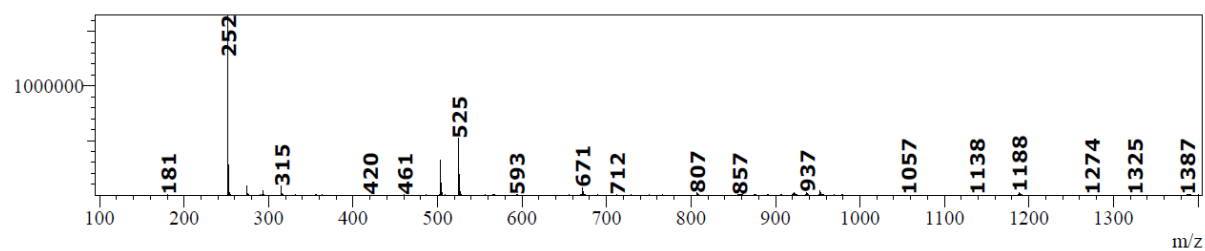
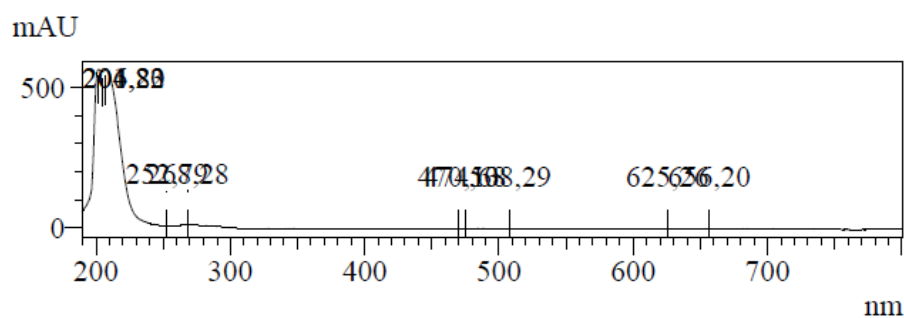
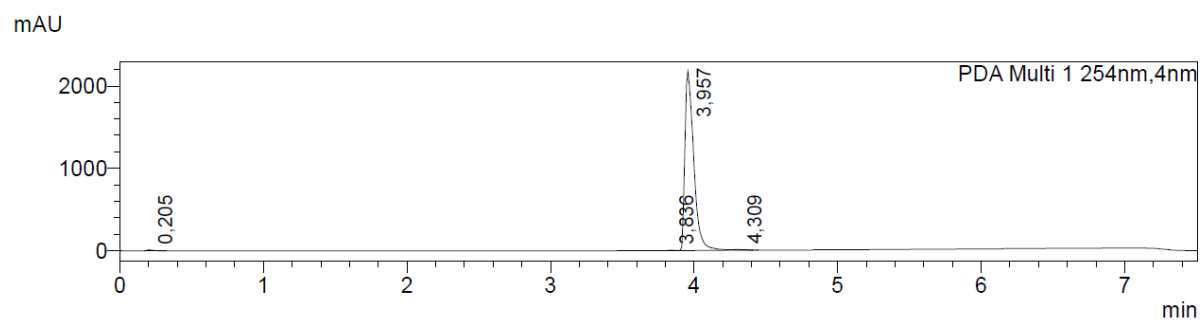
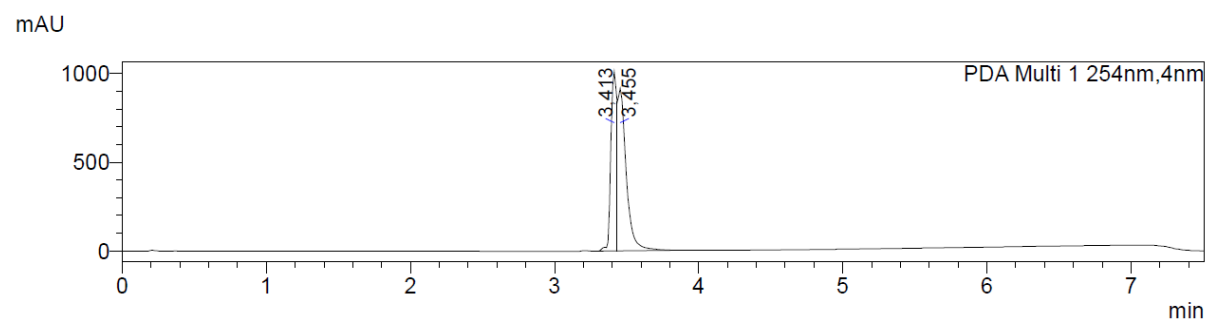


Figure S99: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of ([1,1'-biphenyl]-4-yl)(pyrrolidin-1-yl)methanone (**23**).



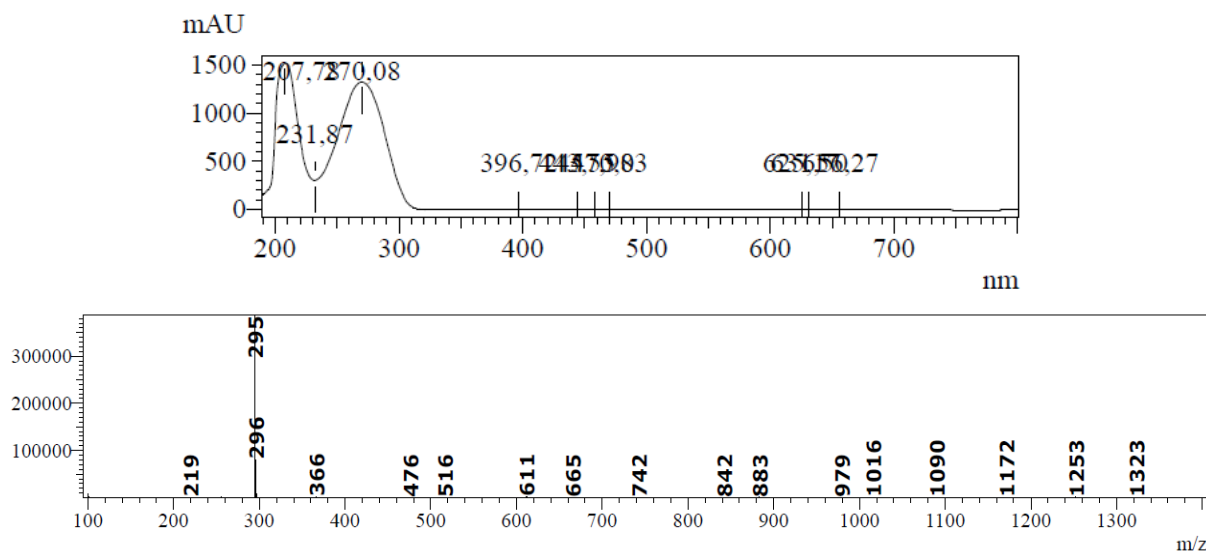


Figure S100.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(azetidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**24**).

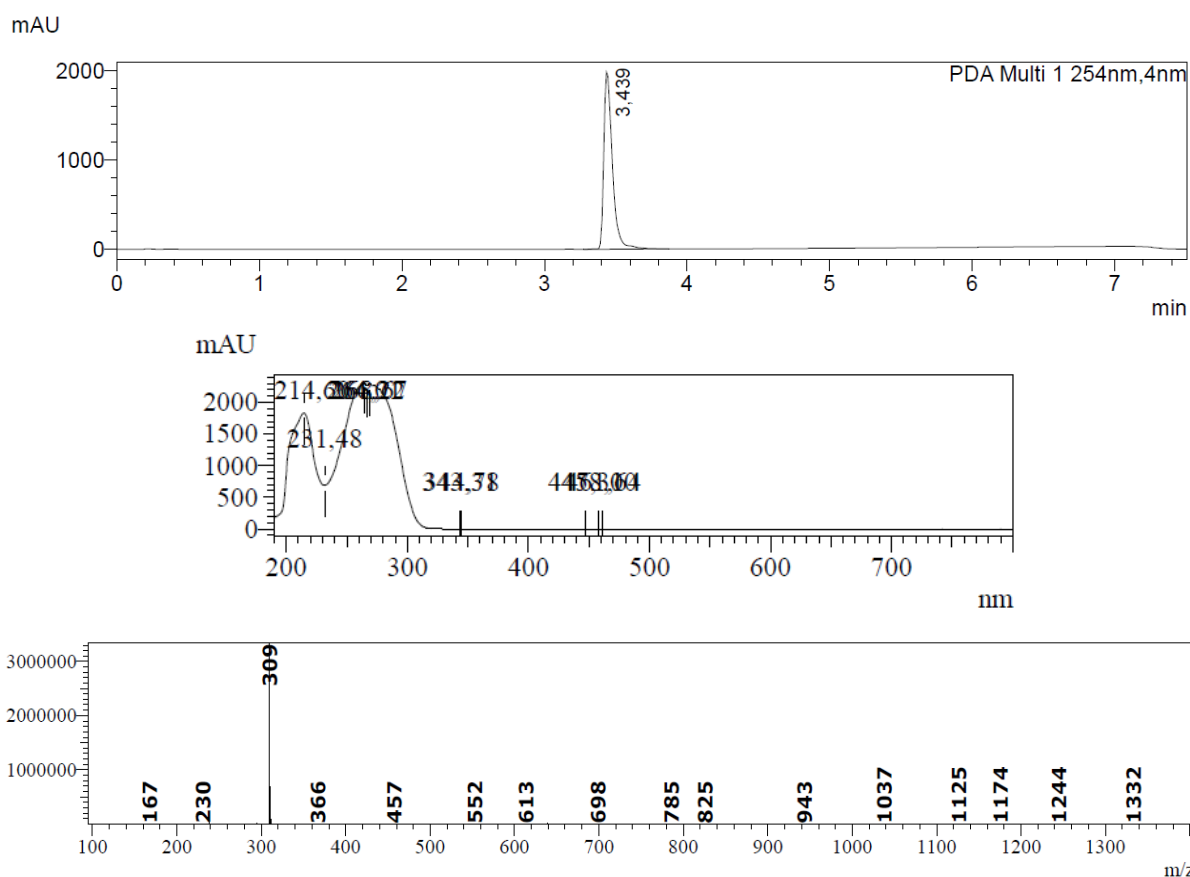


Figure S101.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(pyrrolidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**25**).

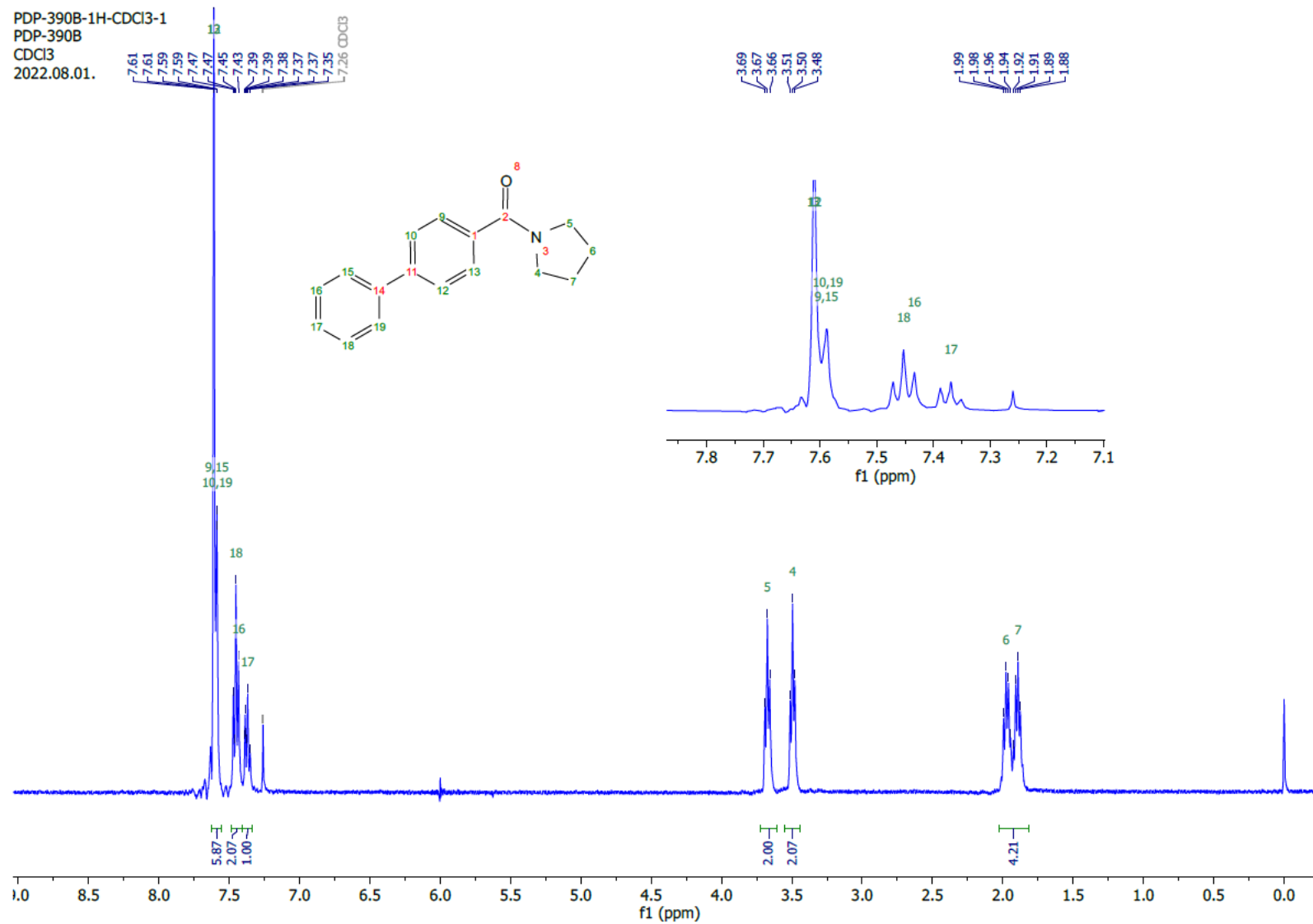


Figure S102: ¹H NMR spectrum of ([1,1'-biphenyl]-4-yl)(pyrrolidin-1-yl)methanone (**23**) recorded at 400 MHz in CDCl₃.

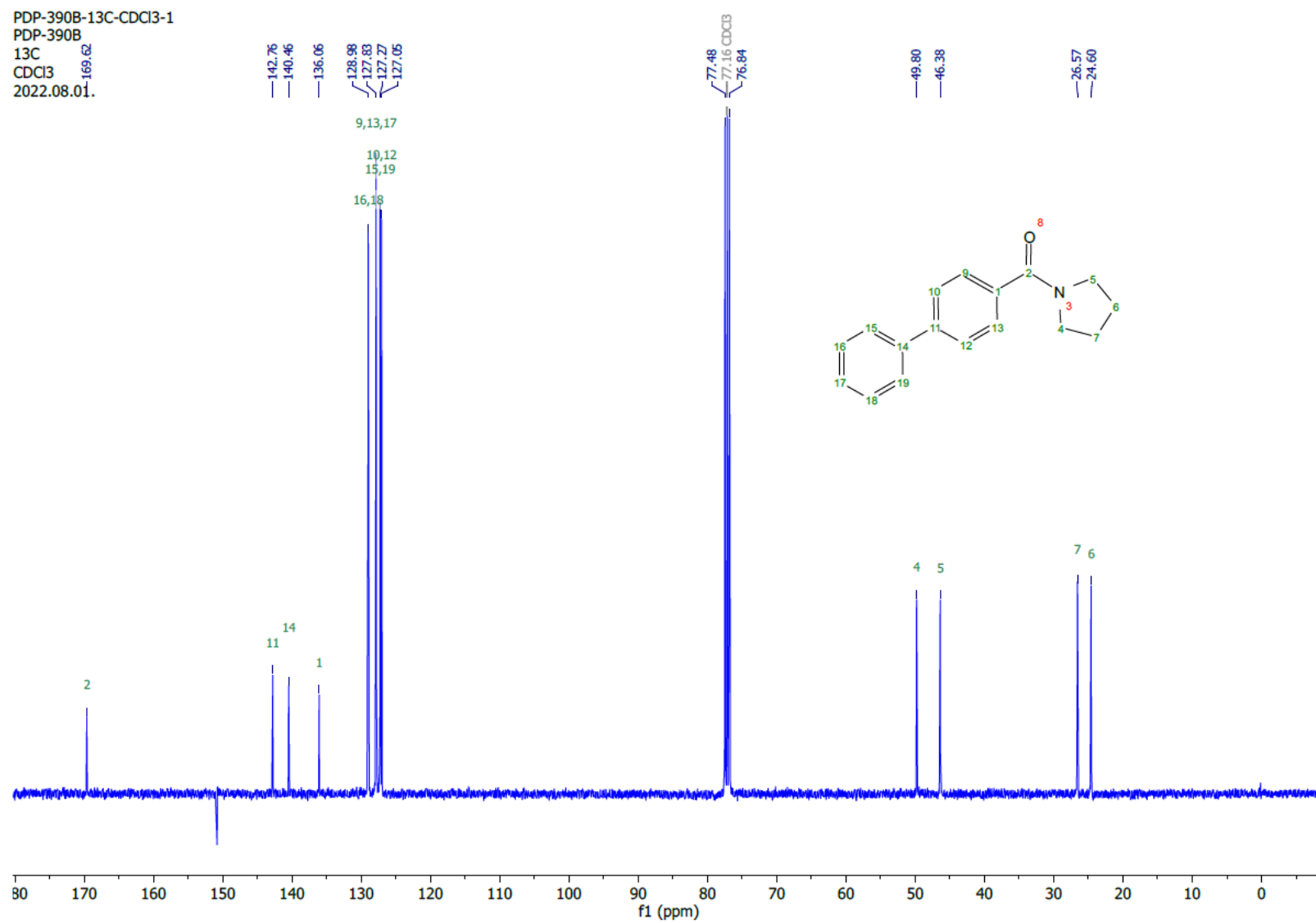


Figure S103: ^{13}C NMR spectrum of ([1,1'-biphenyl]-4-yl)(pyrrolidin-1-yl)methanone (**23**) recorded at 400 MHz in CDCl_3

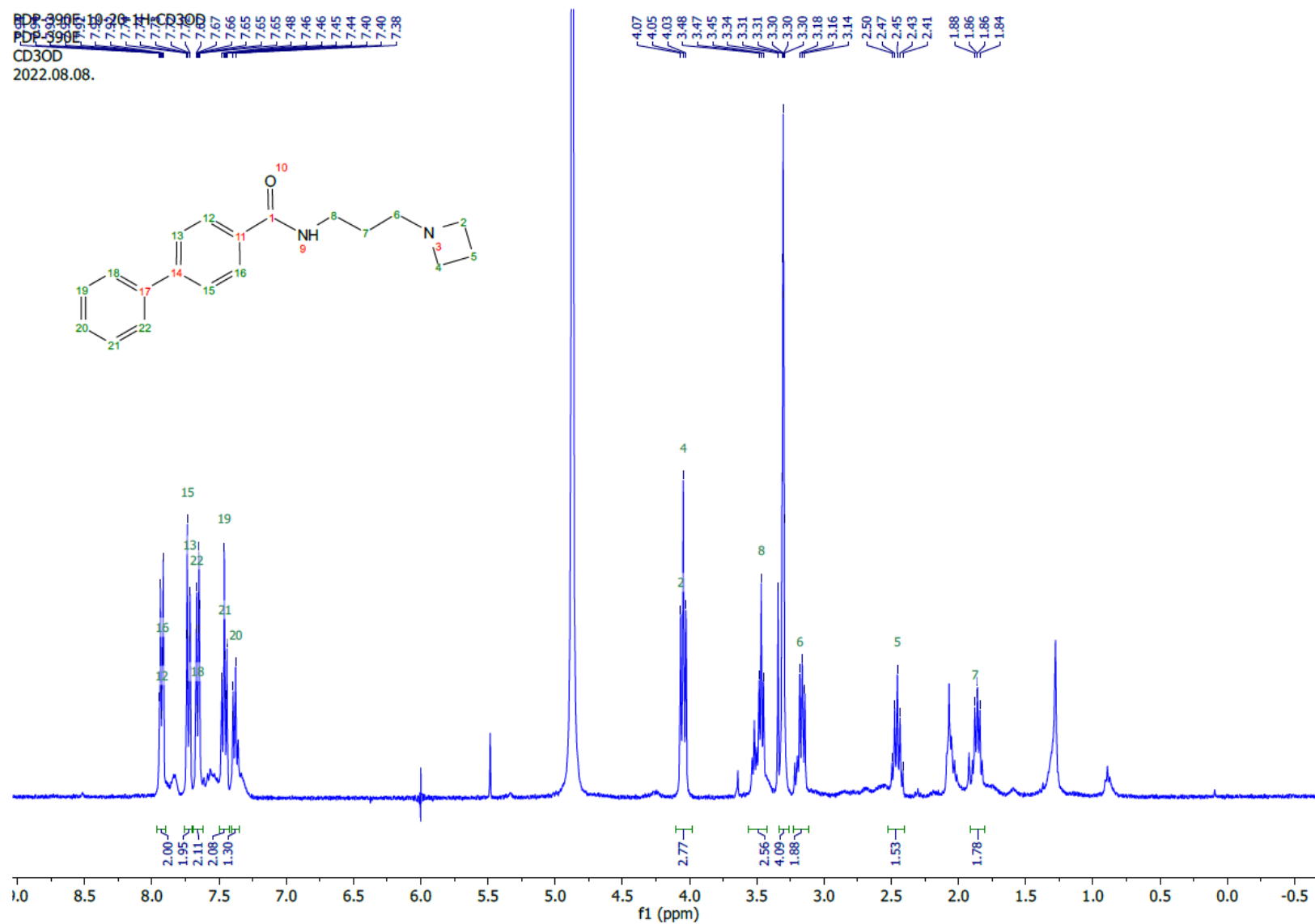


Figure S104: ^1H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**24**) recorded at 400 MHz in CDCl_3 .

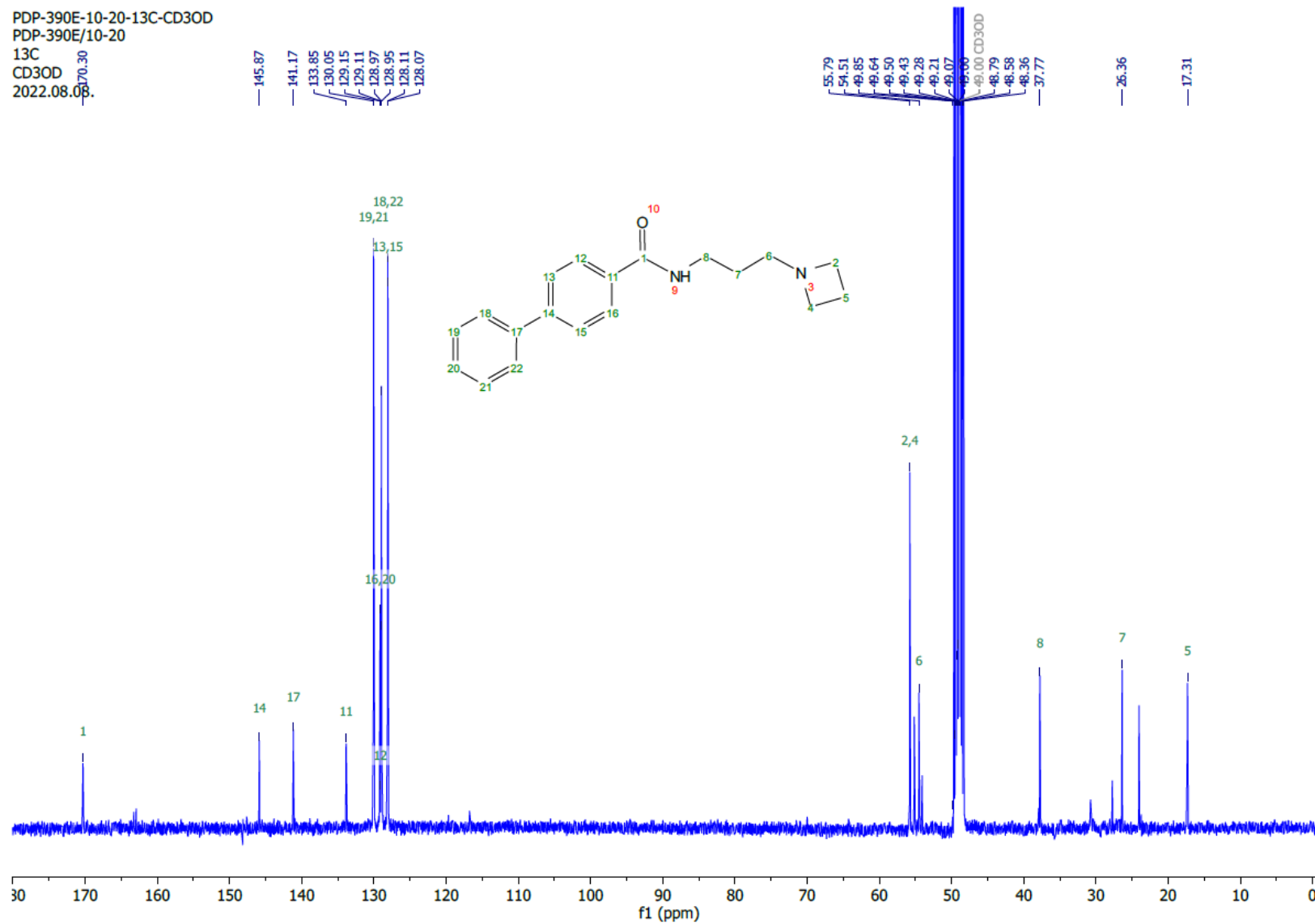


Figure S105: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**24**) recorded at 400 MHz in CDCl_3

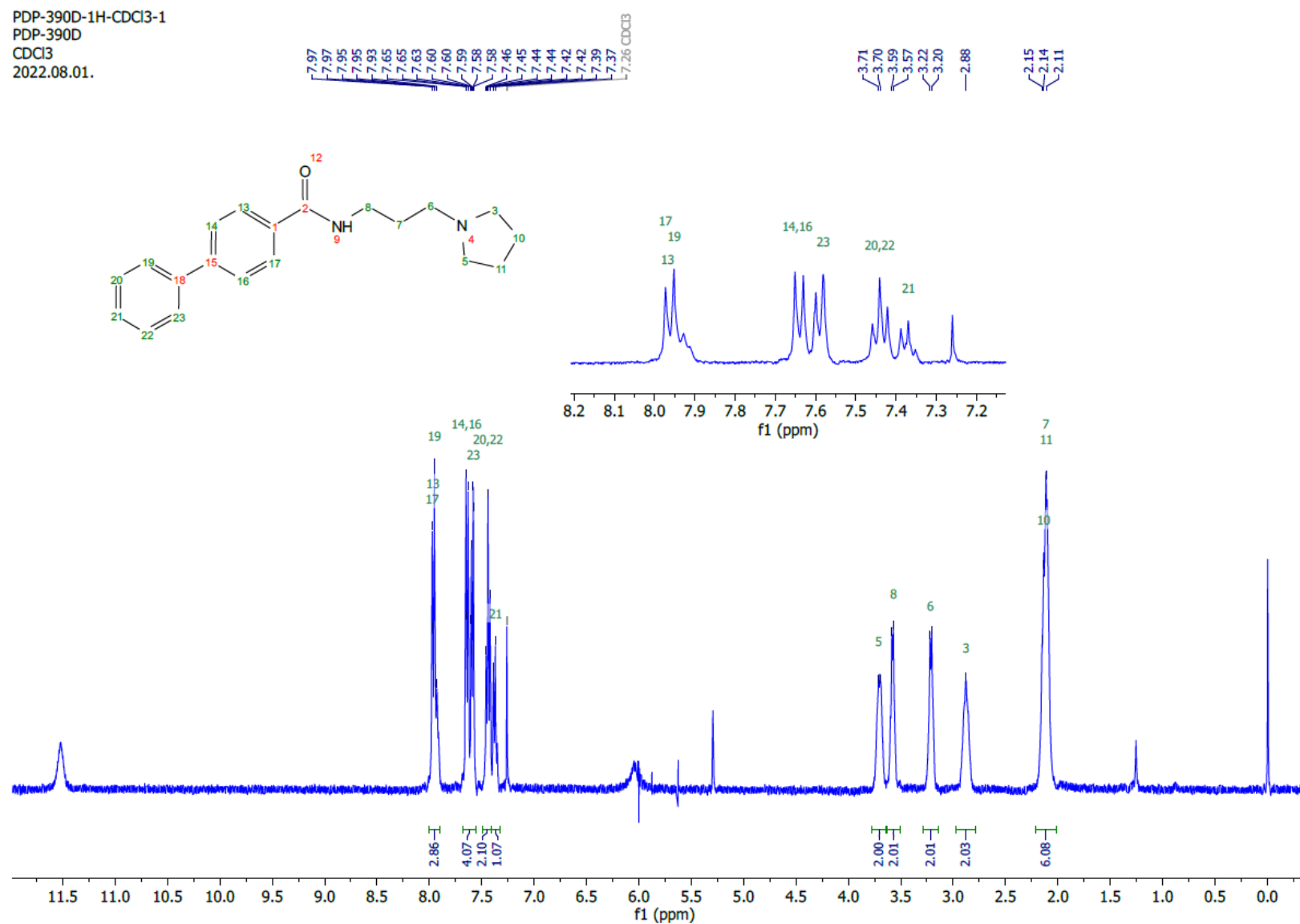


Figure S106: ^1H NMR spectrum of *N*-[3-(pyrrolidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**25**) recorded at 400 MHz in CDCl_3 .

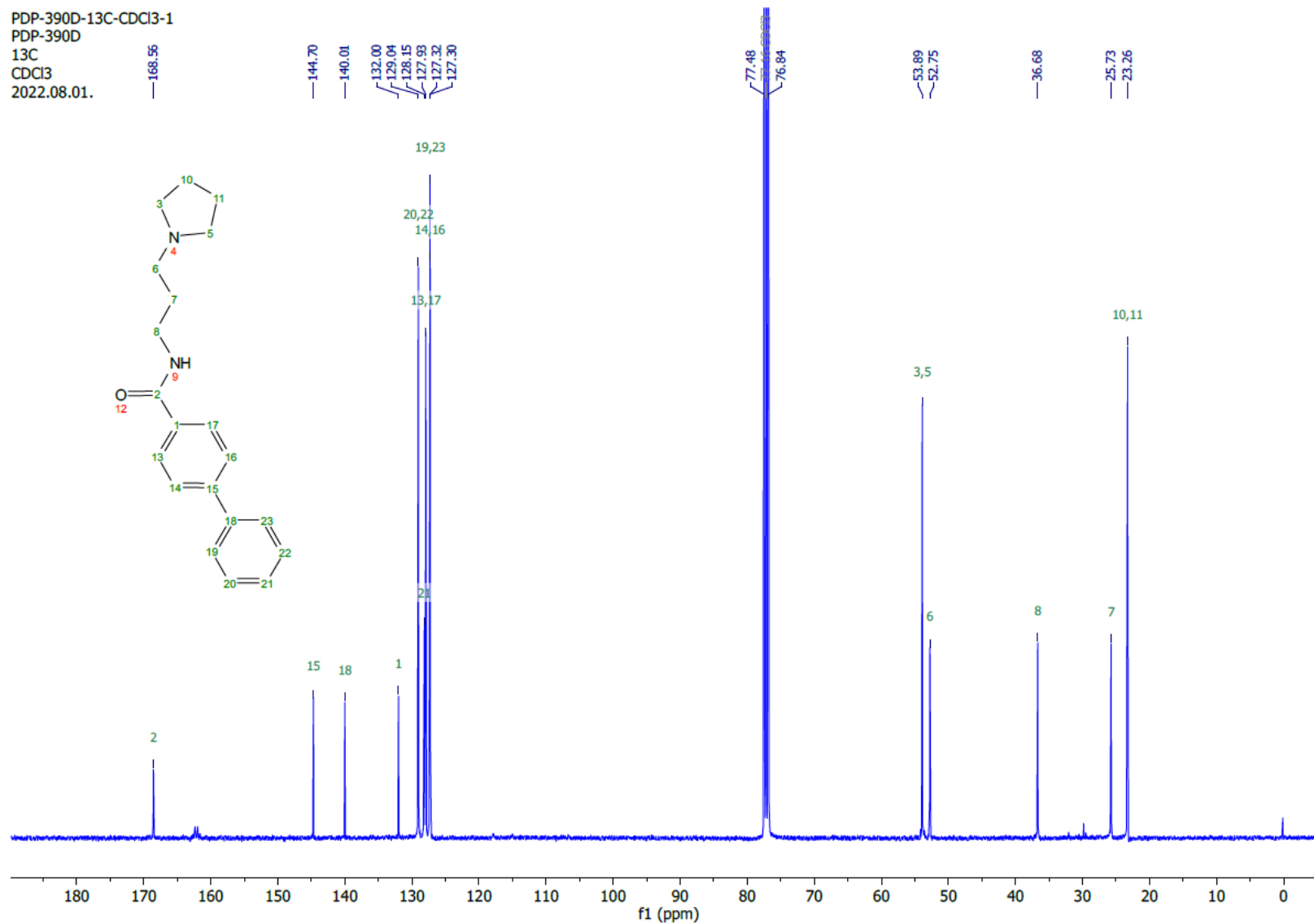


Figure S107: ¹³C NMR spectrum of *N*-[3-(pyrrolidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (25) recorded at 400 MHz in CDCl₃