Supplementary Material

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

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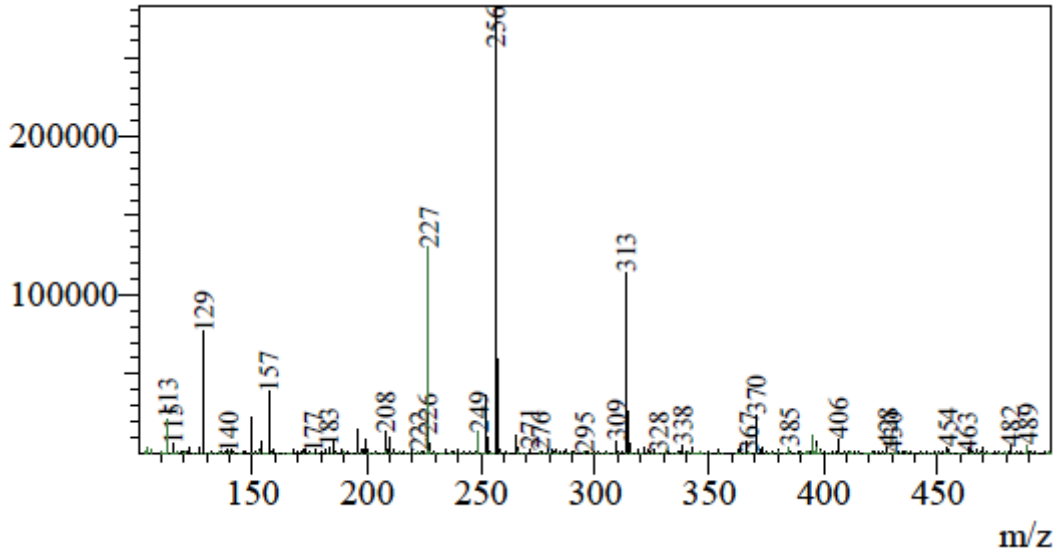


Figure S1. Mass spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-5-amine TFA salt (**3**).

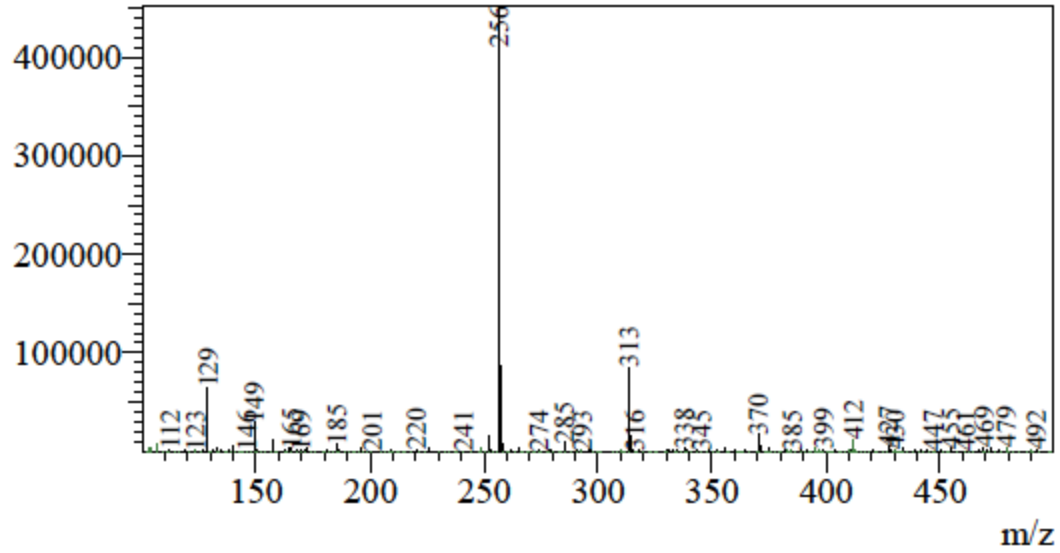


Figure S2. Mass spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-7-amine TFA salt (**4**).

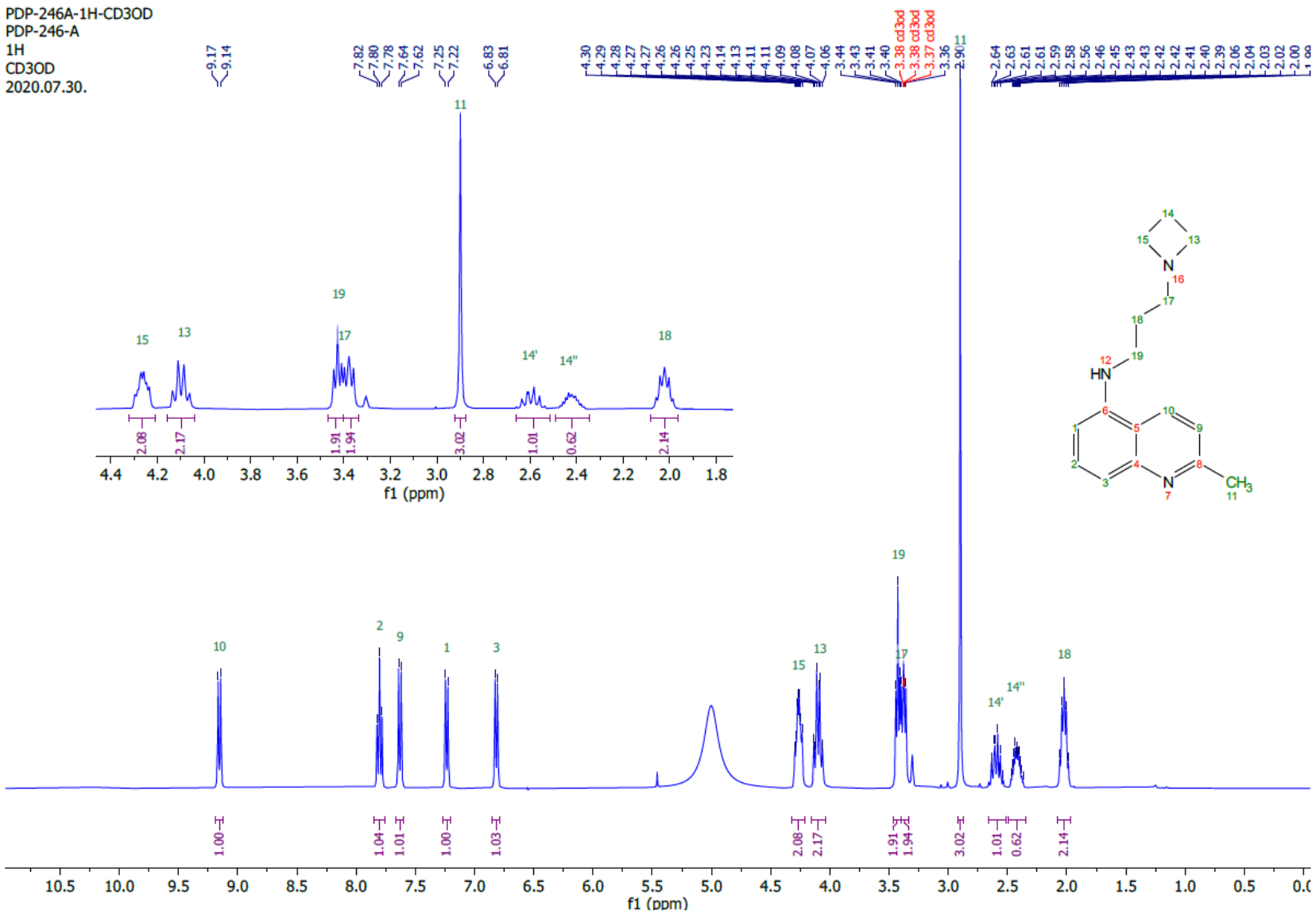


Figure S3: ^{1}H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-5-amine TFA salt (**3**) recorded at 400 MHz in CD_3OD.

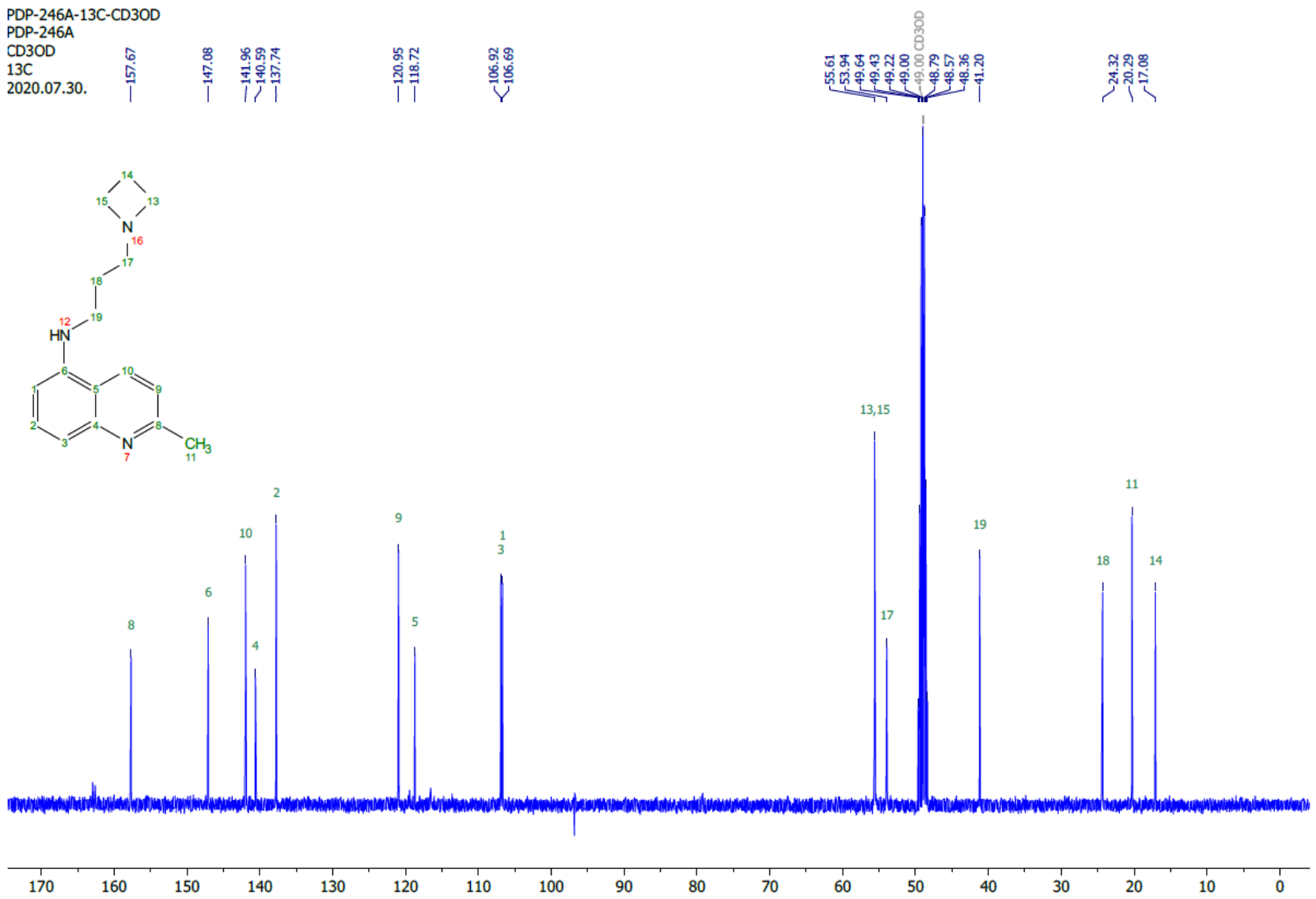


Figure S4: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-5-amine TFA salt (**3**) recorded at 400 MHz in CD_3OD.

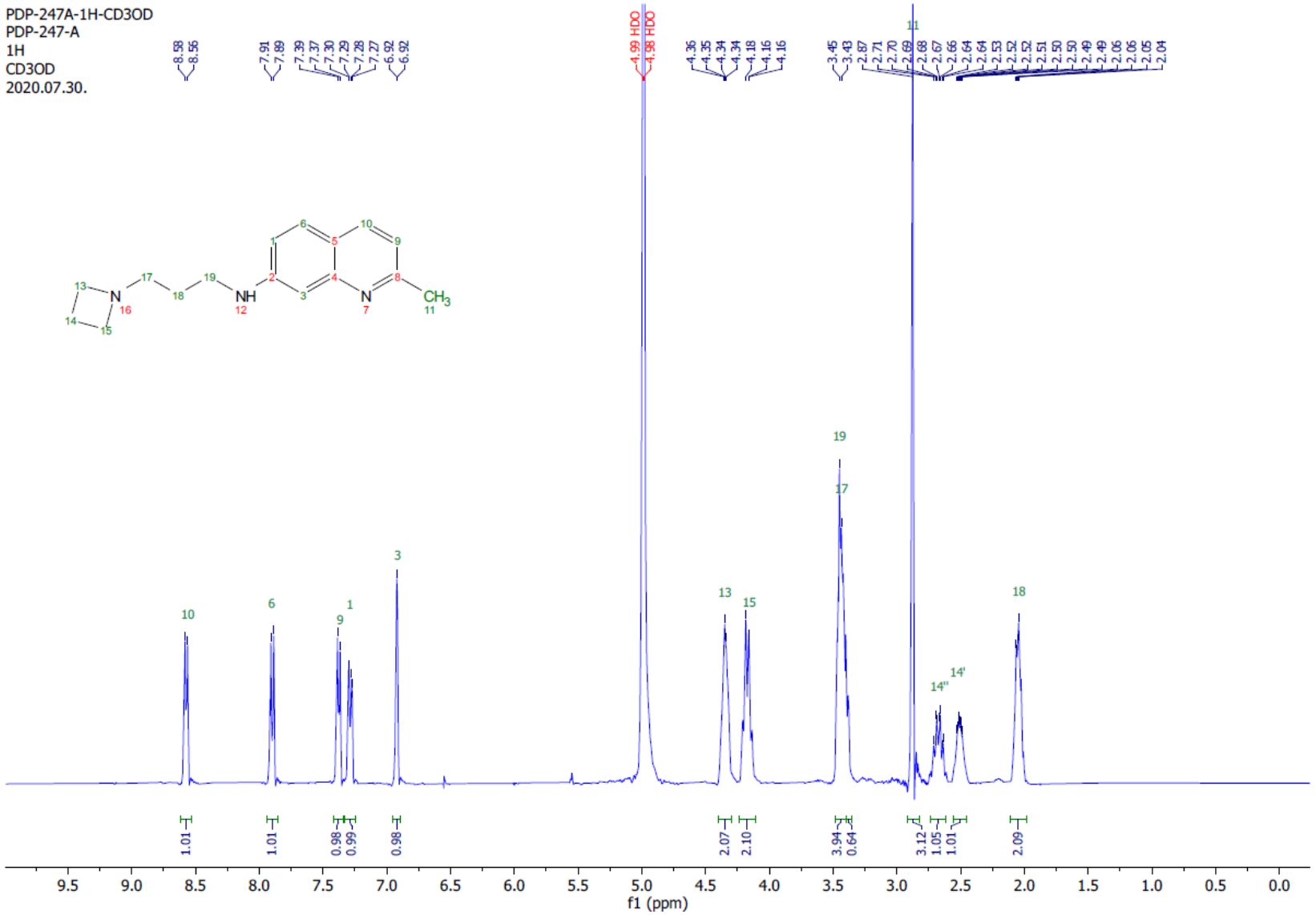


Figure S5: ^{1}H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-7-amine TFA salt (**4**) recorded at 400 MHz in CD_3OD.

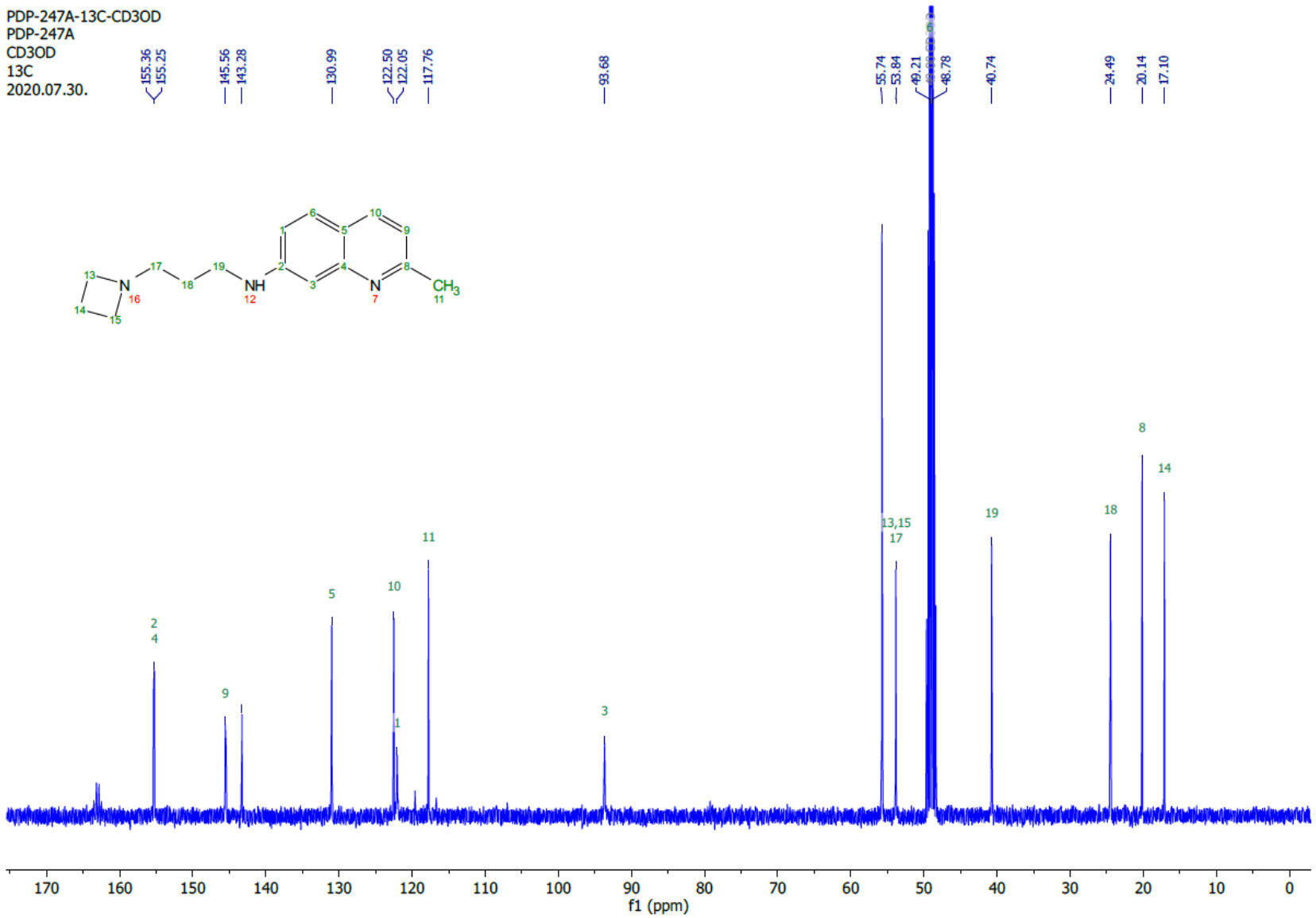


Figure S6: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-methylquinolin-7-amine TFA salt (**4**) recorded at 400 MHz in CD_3OD.

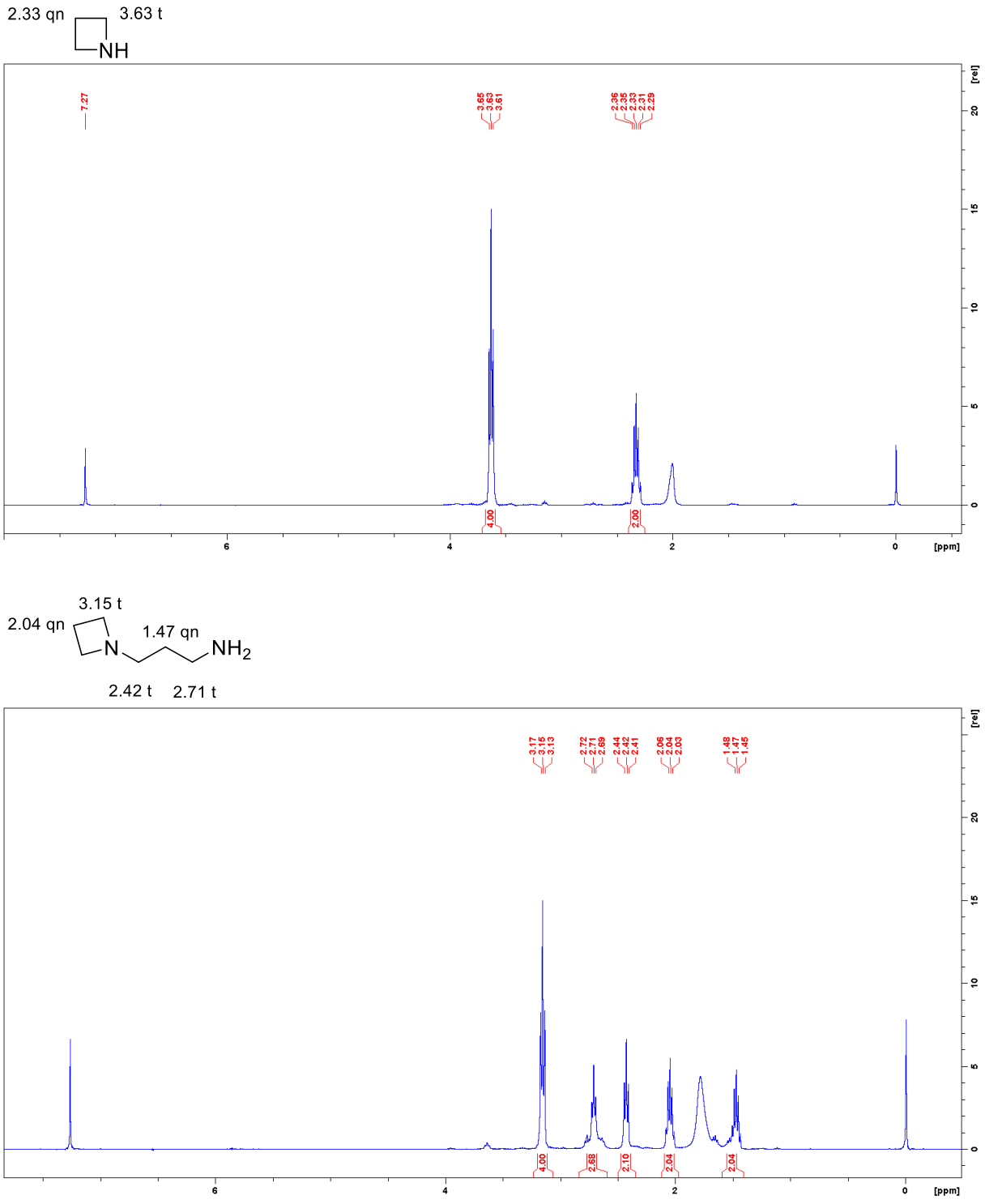


Figure S7. ^{1}H NMR spectrum (400 MHz, CDCl3) of azetidine (**8**) and 3-(azetidin-1-yl)propan-1-amine (**7**).

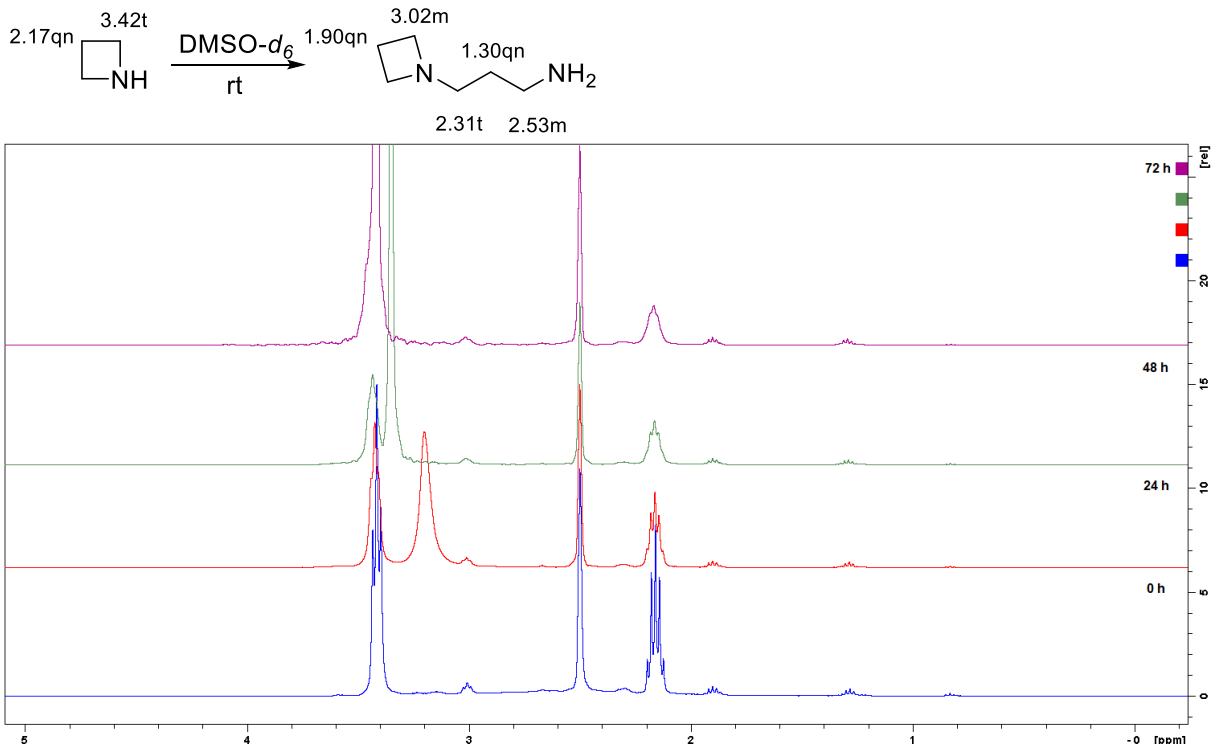


Figure S8. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine at rt.

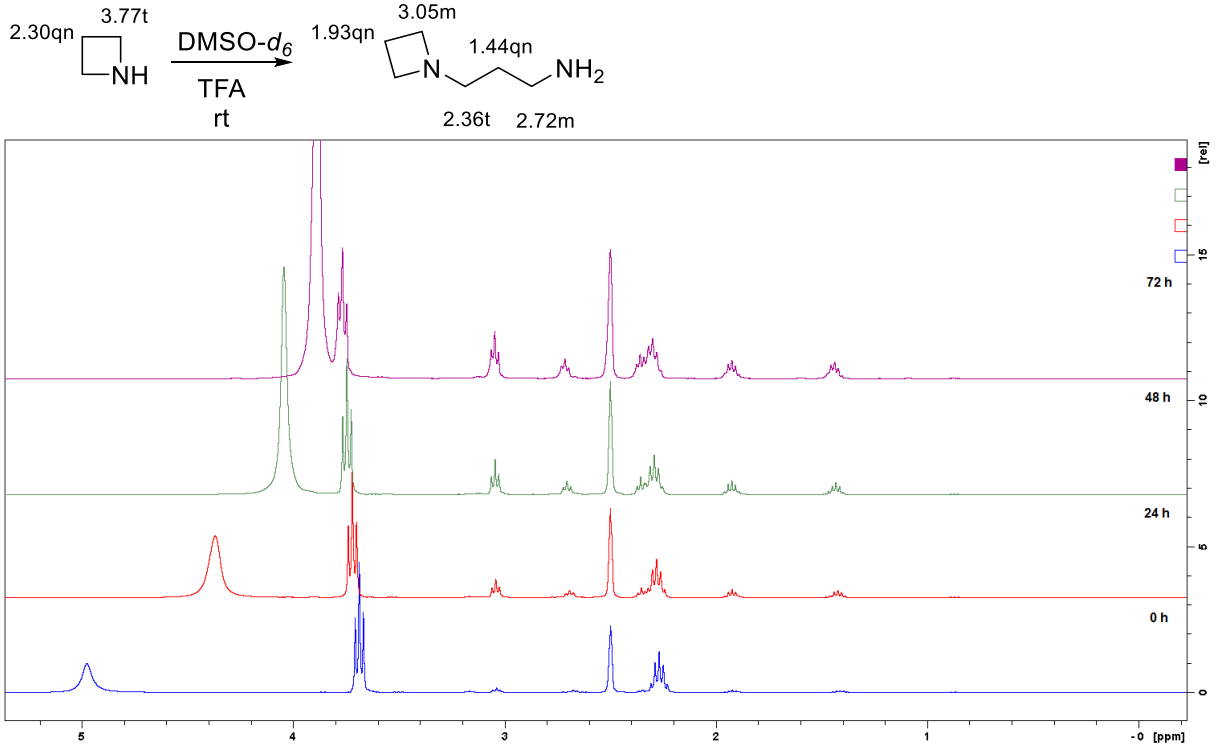


Figure S9. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + TFA at rt.

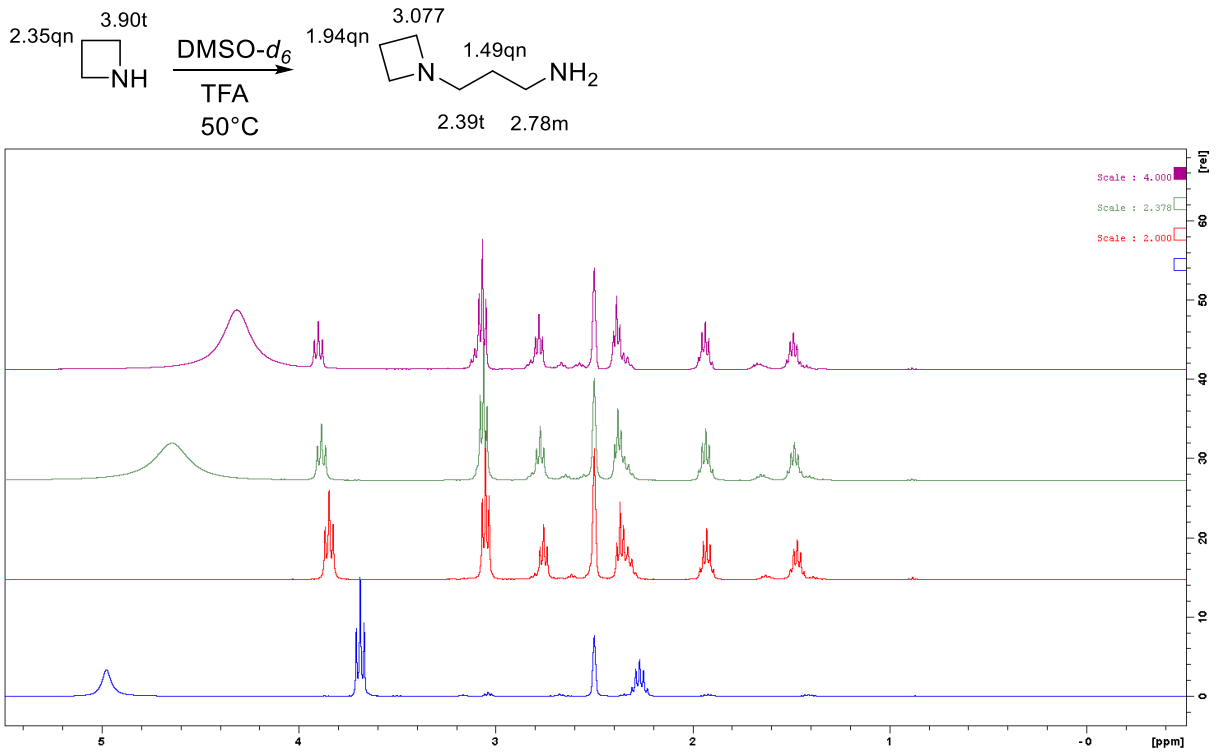


Figure S10. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + TFA at 50°C.

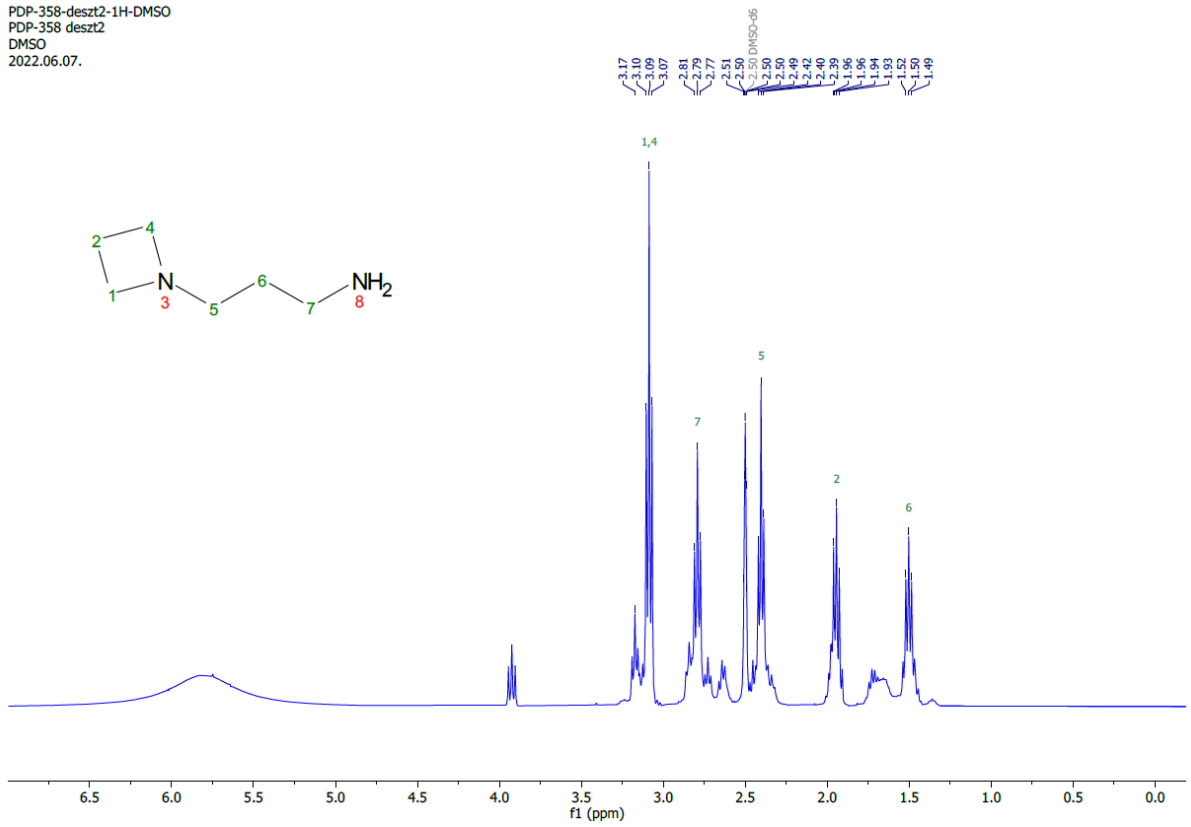


Figure S11. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + TFA at 50°C (synthetic experiment A).

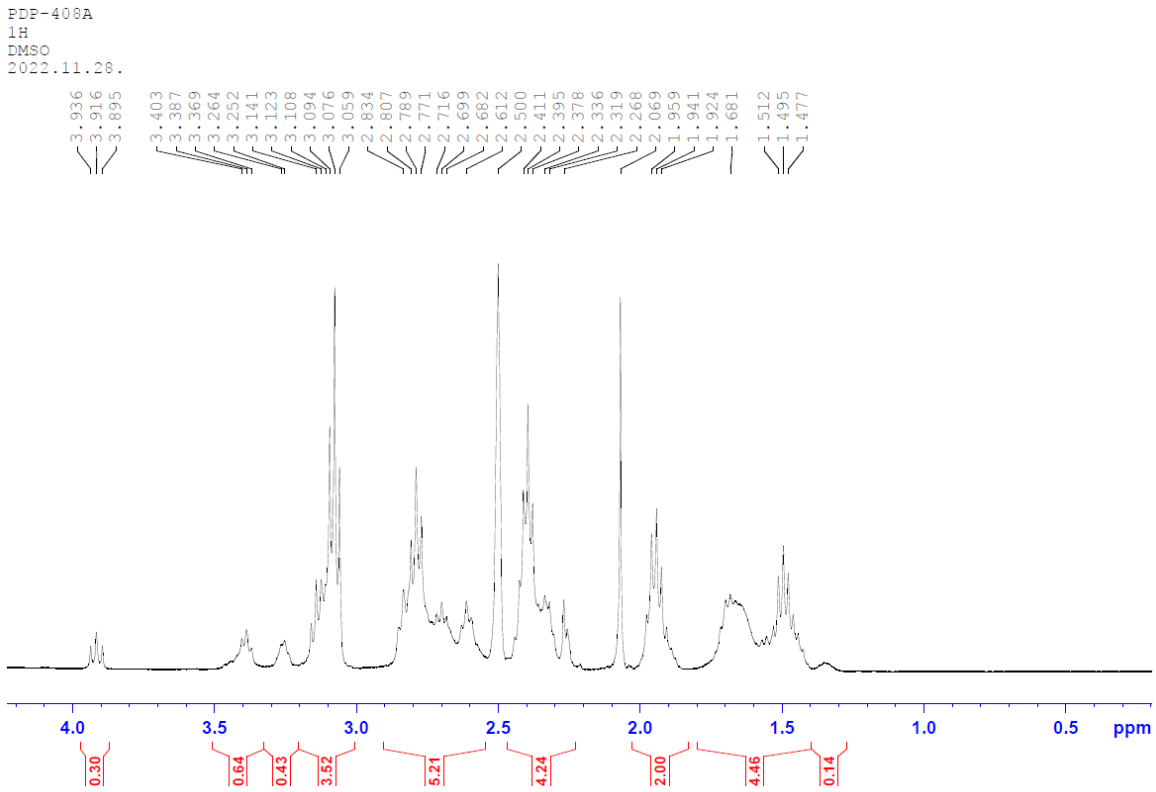


Figure S12. ^{1}H NMR (400 MHz, DMSO-d_6) of the crude product of the reaction of azetidine + TFA at 50°C (synthetic experiment B).

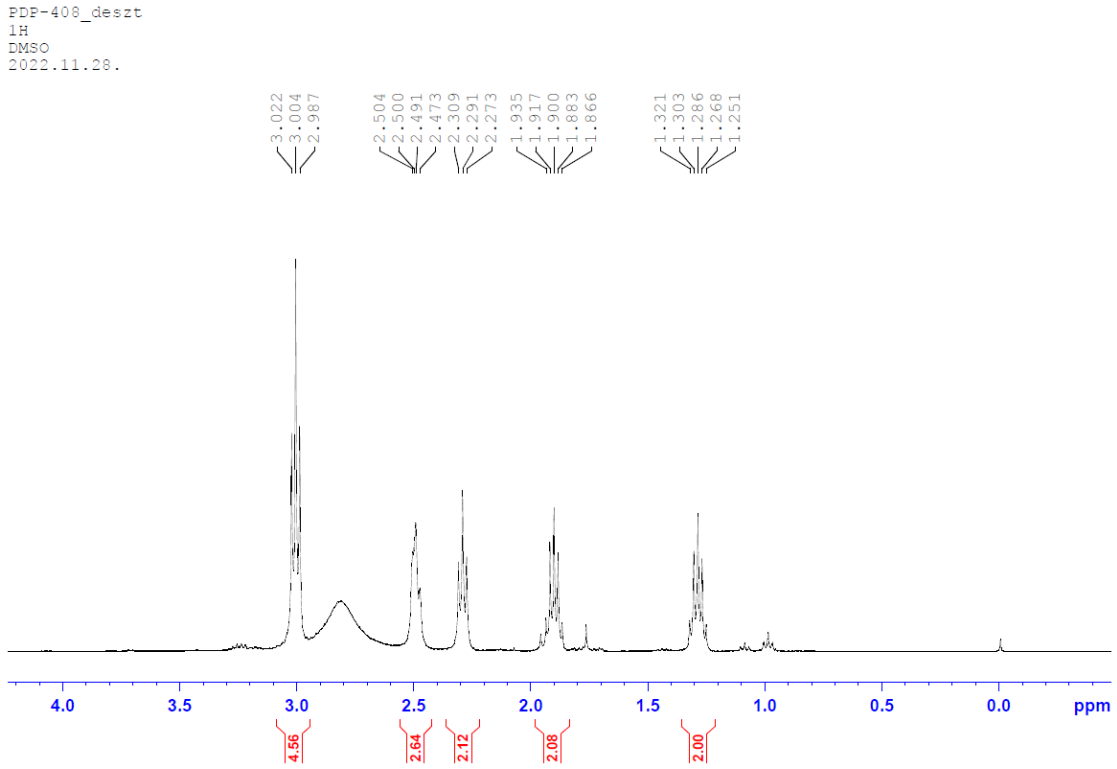


Figure S13. ^{1}H NMR (400 MHz, DMSO-d_6) after vacuum distillation of the product (**7**) (synthetic experiment B).

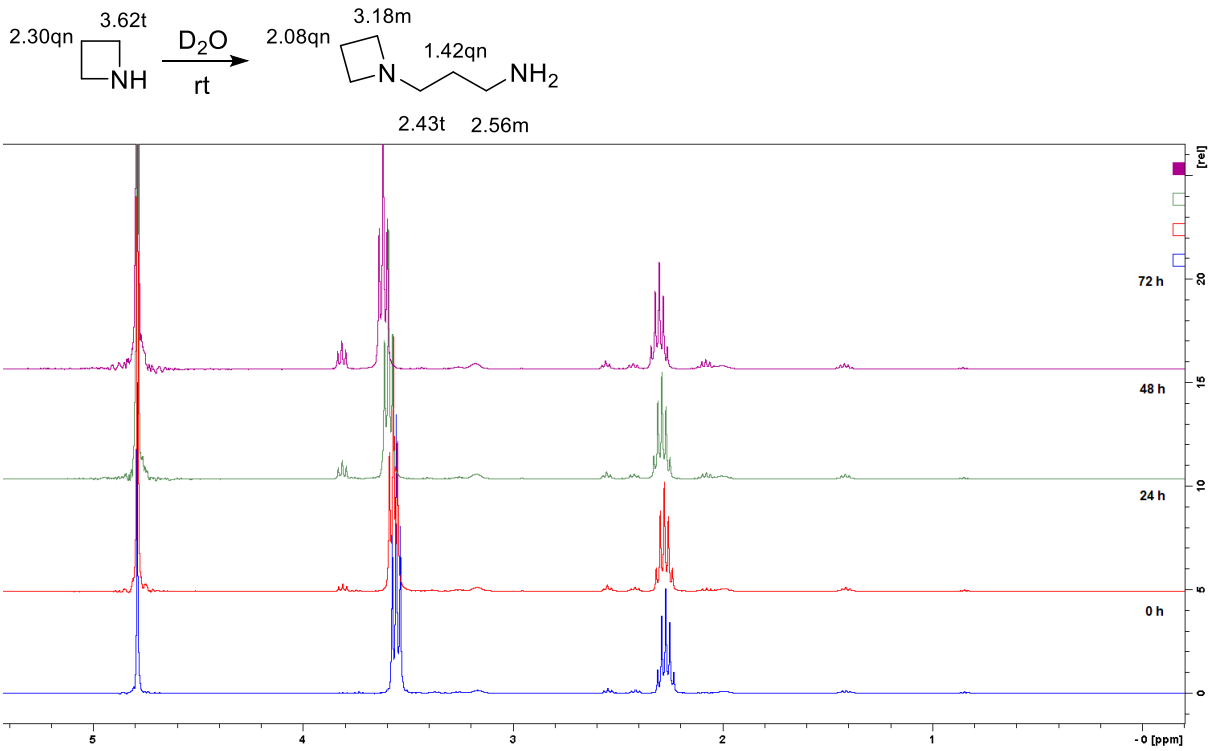


Figure S14. ^{1}H NMR (400 MHz, D_2O) monitoring of azetidine at rt.

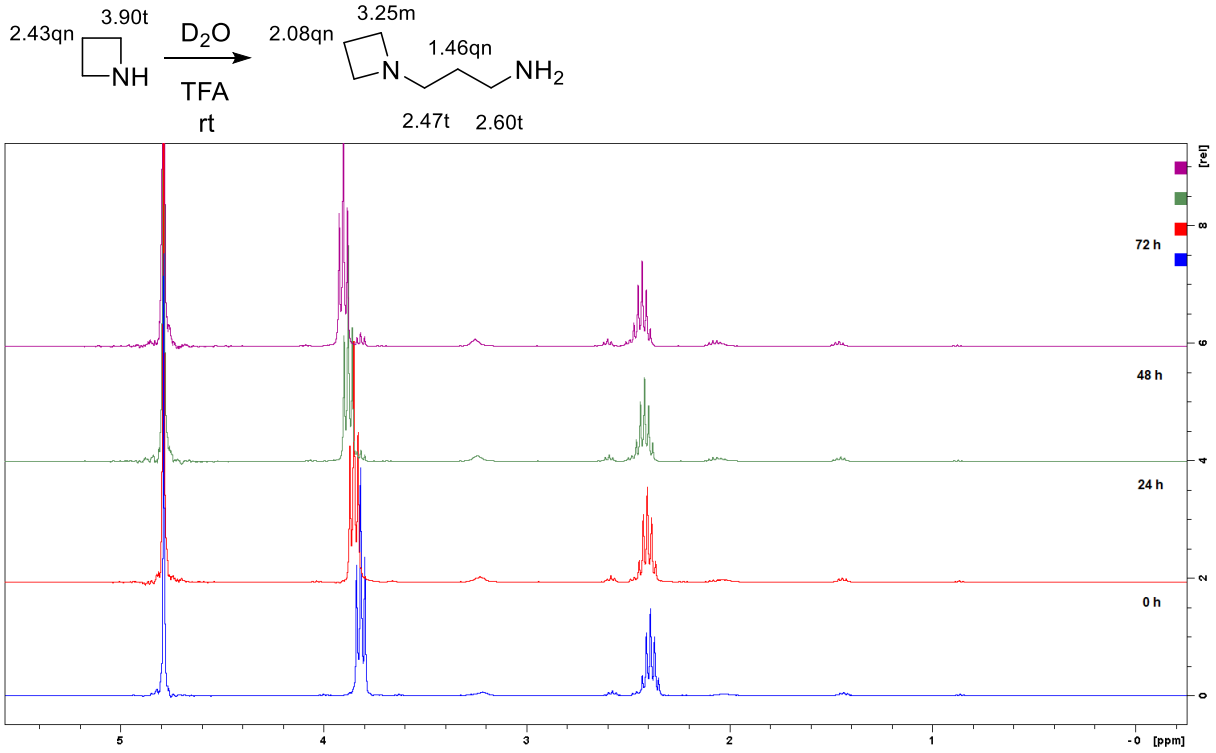


Figure S15. ^{1}H NMR (400 MHz, D_2O) monitoring of azetidine + TFA at rt.

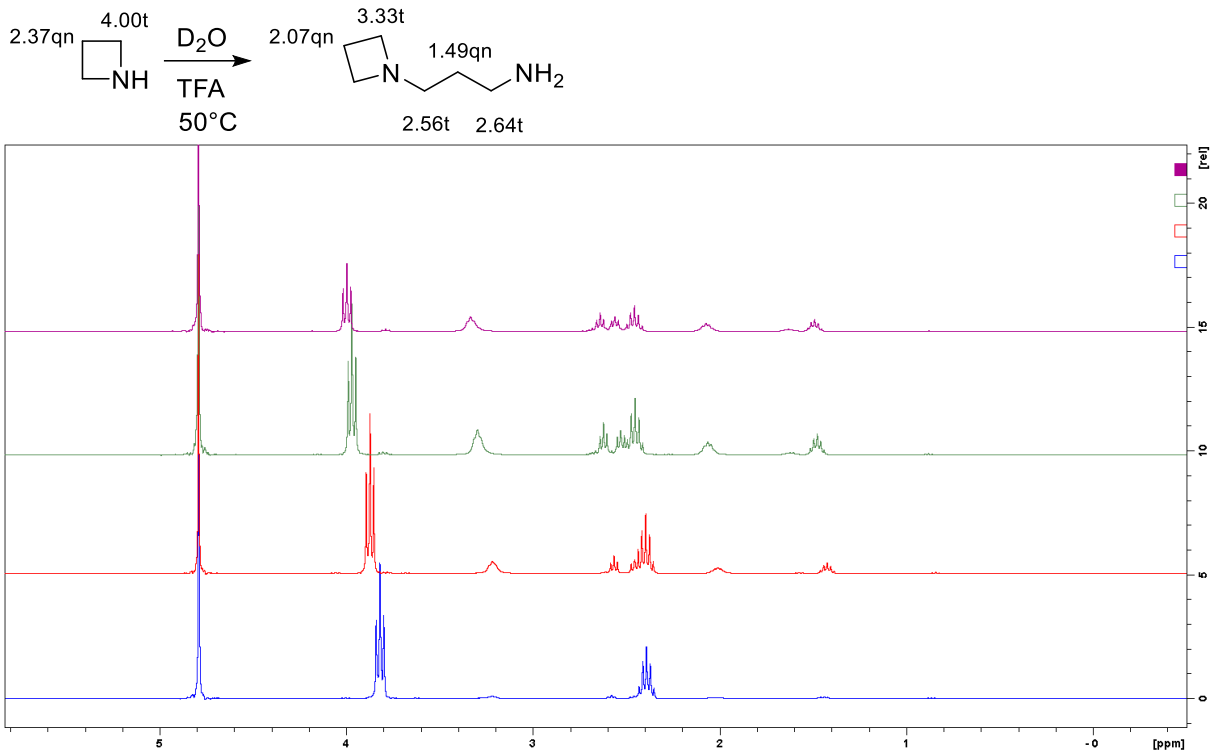


Figure S16. ^{1}H NMR (400 MHz, D_2O) monitoring of azetidine + TFA at 50°C.

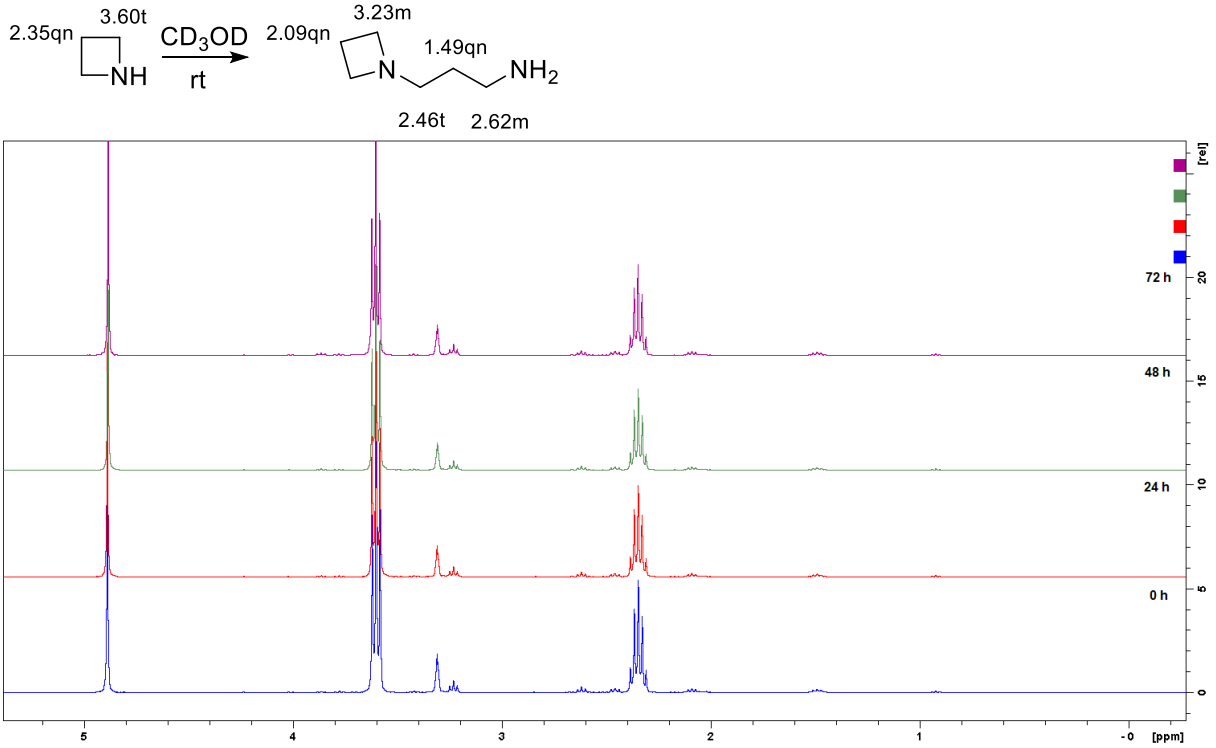


Figure S17. ^{1}H NMR (400 MHz, CD_3OD) monitoring of azetidine at rt.

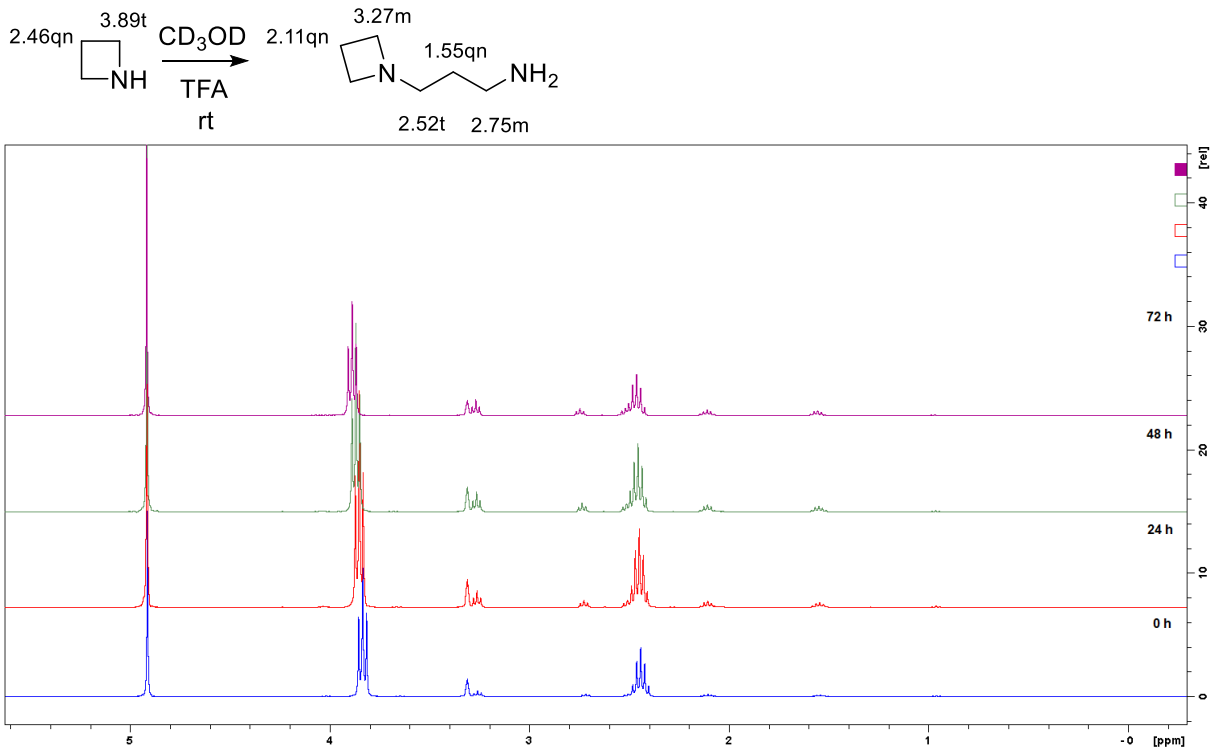


Figure S18. ^{1}H NMR (400 MHz, CD_3OD) monitoring of azetidine + TFA at rt.

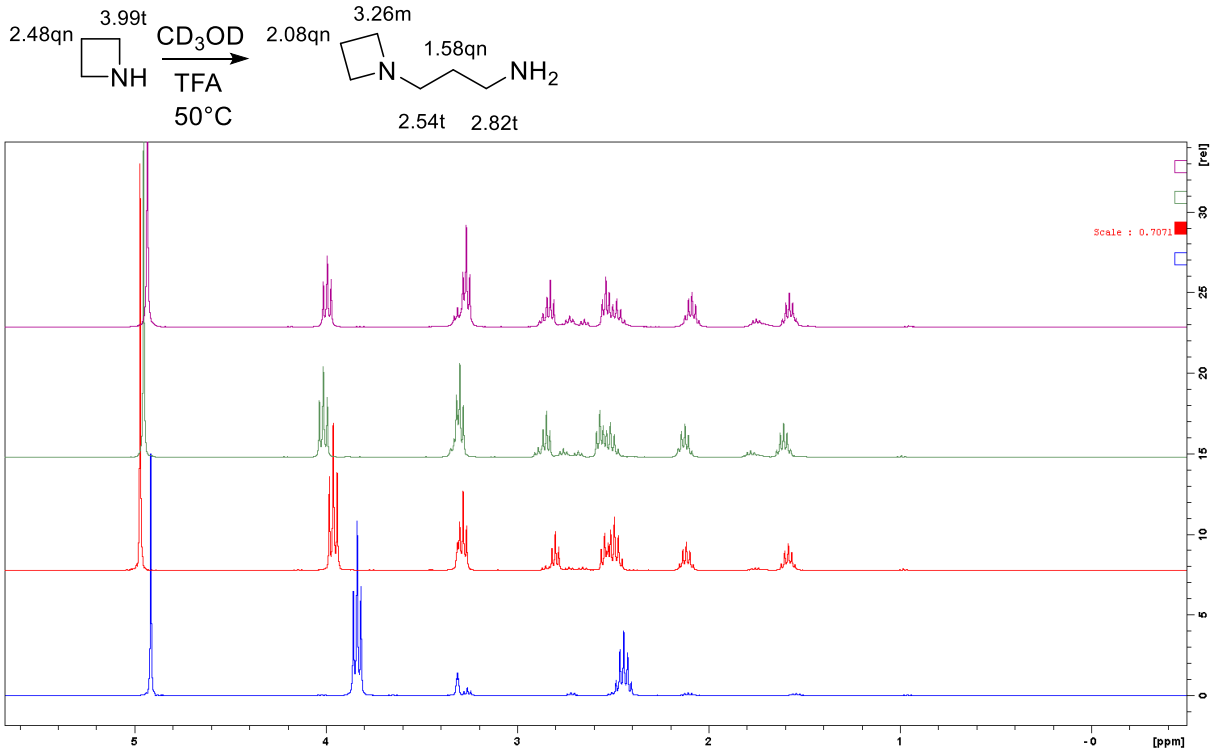


Figure S19. ^{1}H NMR (400 MHz, CD_3OD) monitoring of azetidine + TFA at 50°C.

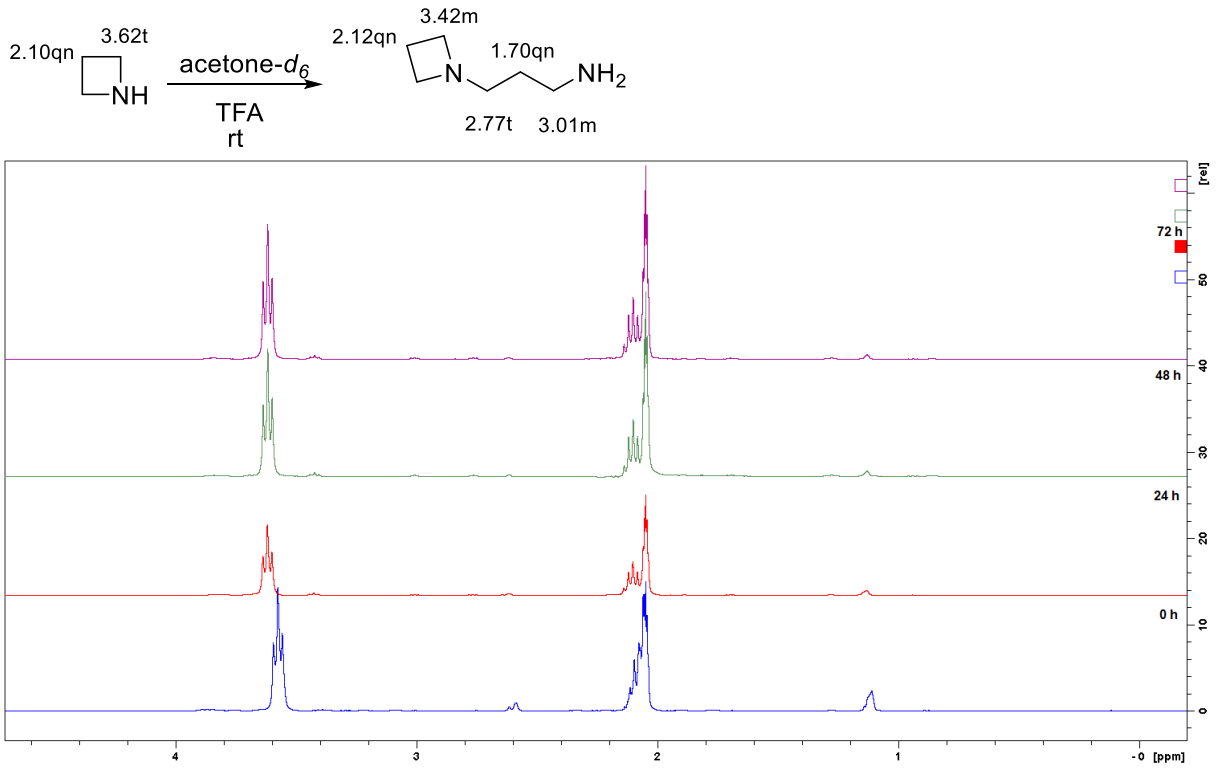


Figure S20. ^{1}H NMR (400 MHz, acetone-d_6) monitoring of azetidine + TFA at rt.

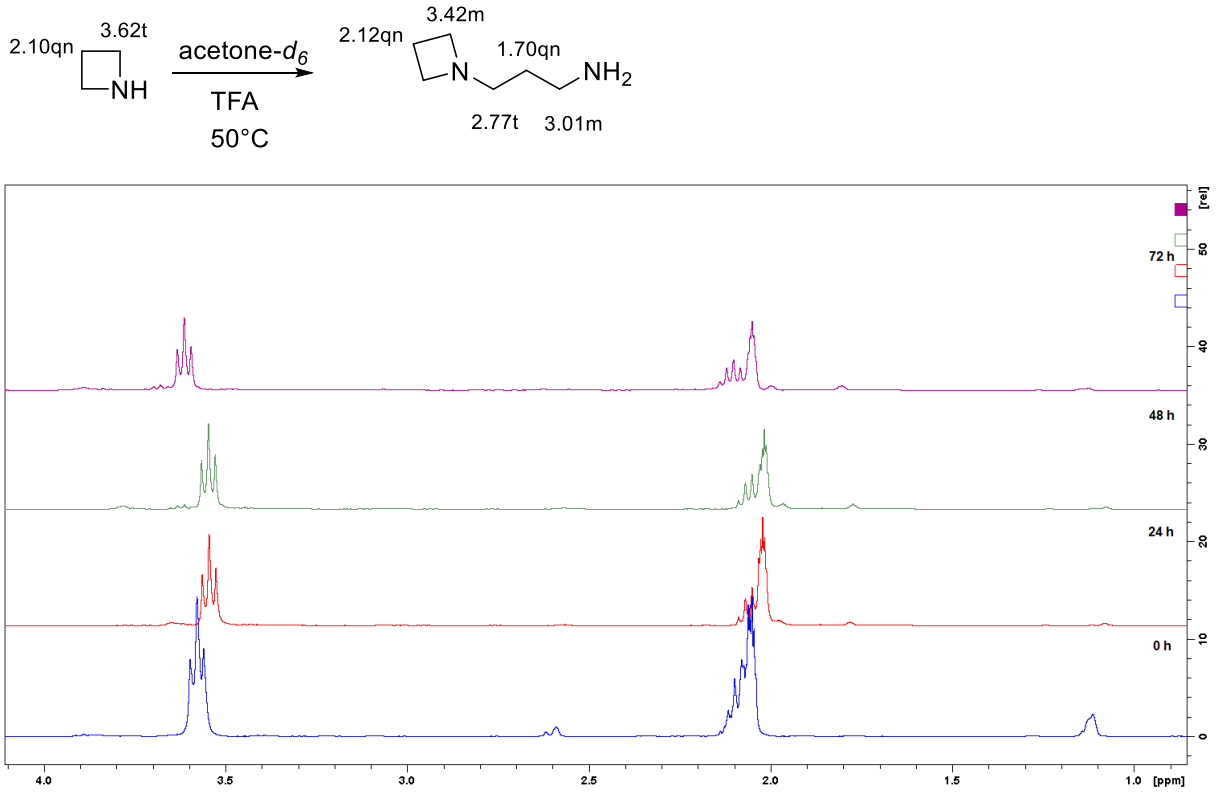


Figure S21. ^{1}H NMR (400 MHz, acetone-d_6) monitoring of azetidine + TFA at 50°C.

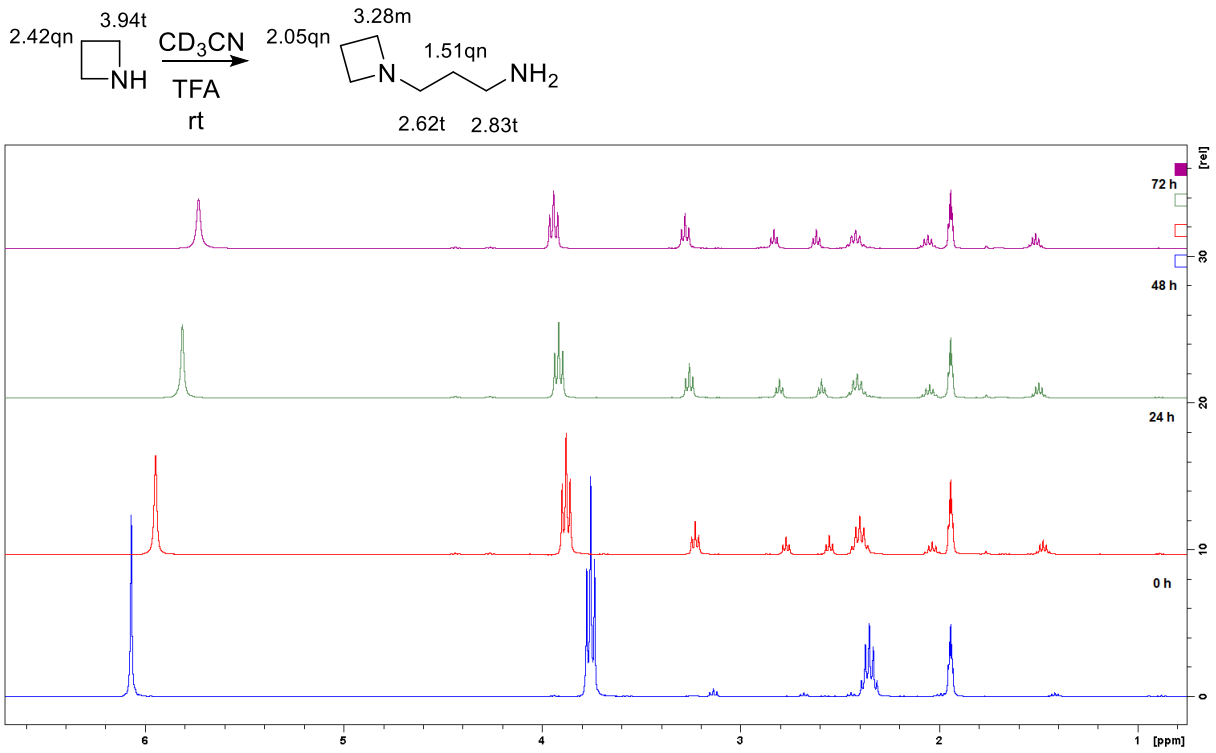


Figure S22. ^{1}H NMR (400 MHz, CD_3CN) monitoring of azetidine + TFA at rt.

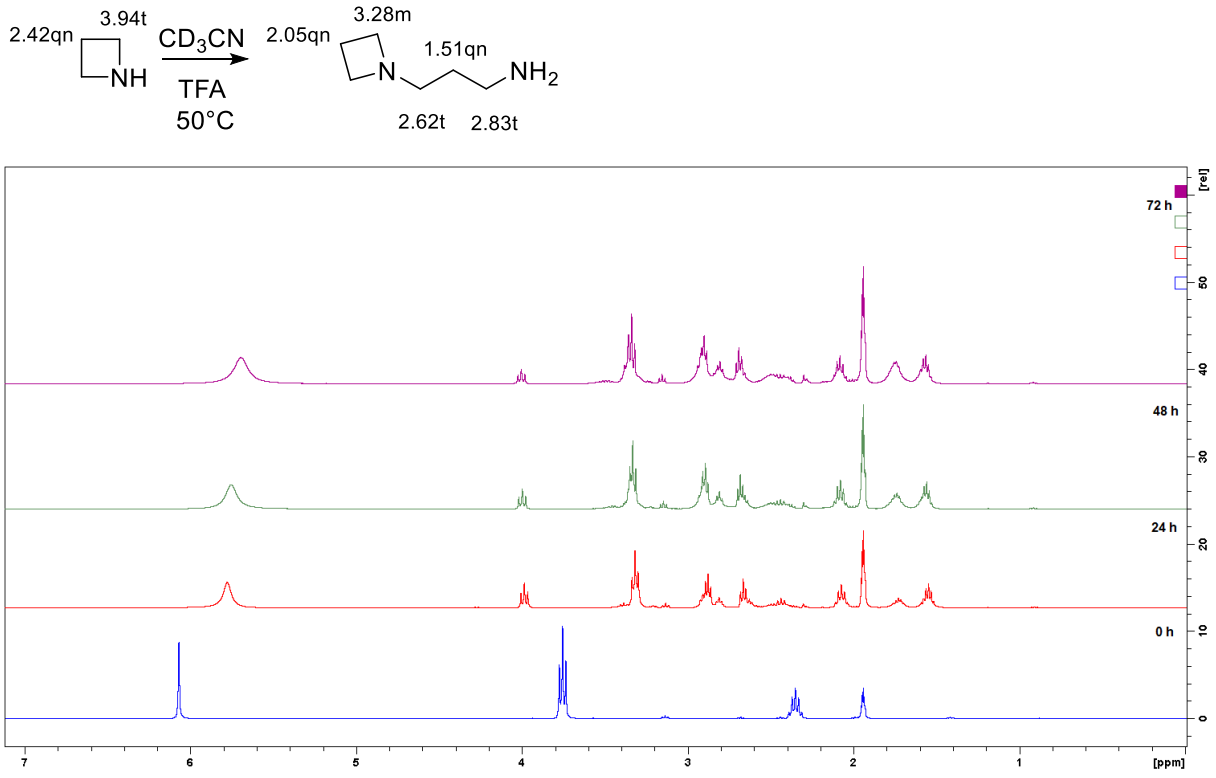


Figure S23. ^{1}H NMR (400 MHz, CD_3CN) monitoring of azetidine + TFA at 50°C.

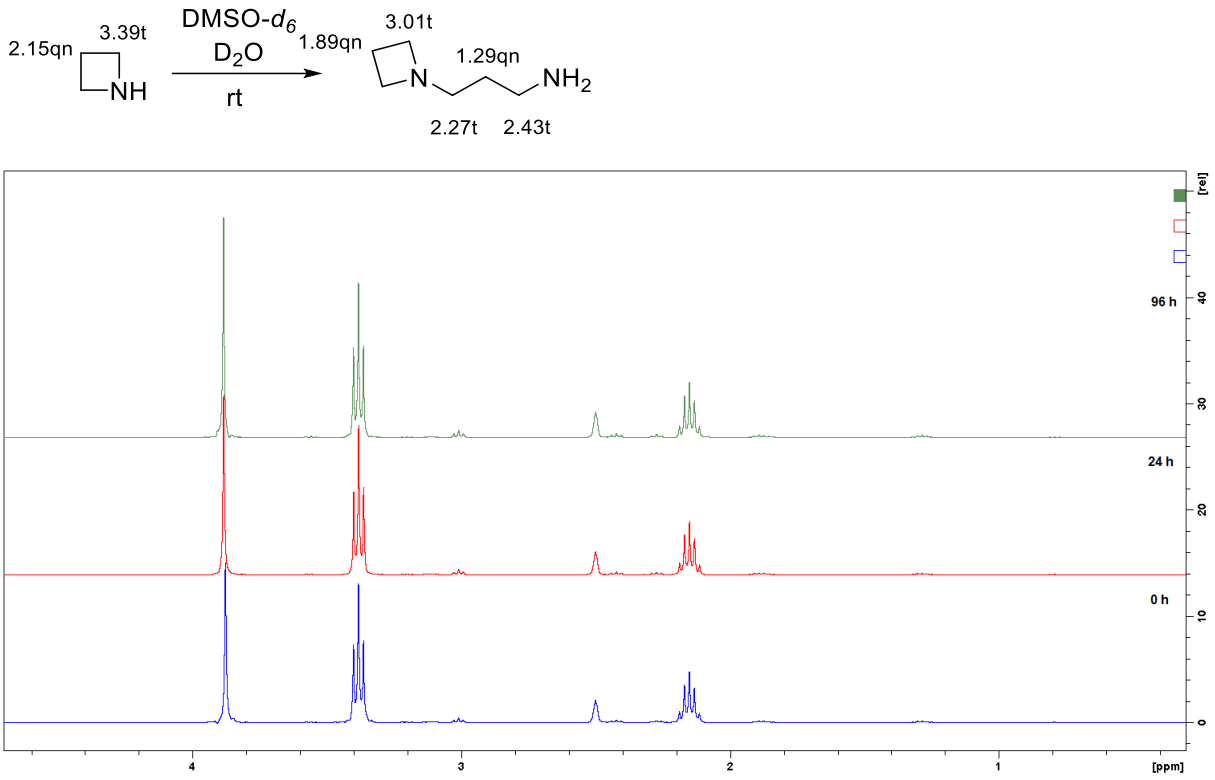


Figure S24. ^{1}H NMR (400 MHz, DMSO-d_6+D_2O (9:1)) monitoring of azetidine at rt.

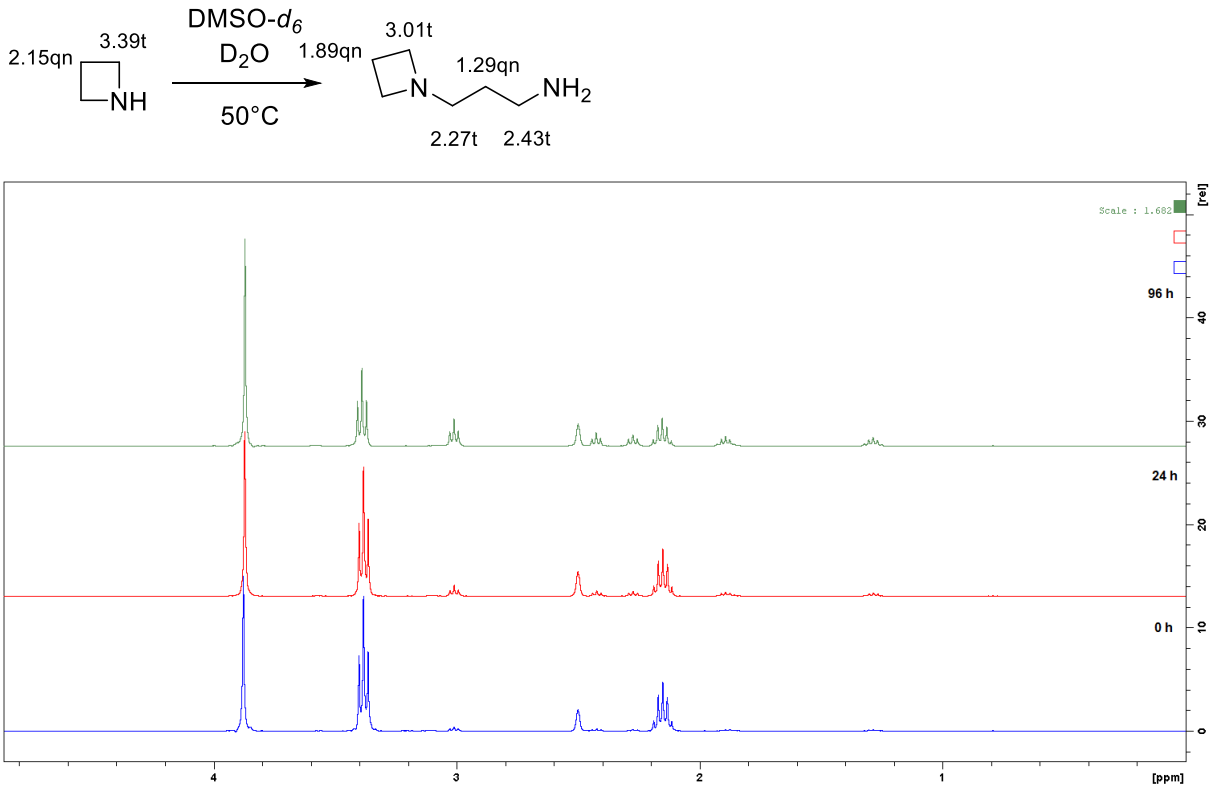
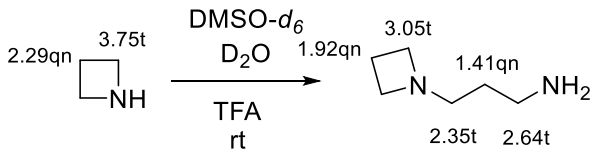


Figure S25. ^{1}H NMR (400 MHz, DMSO-d_6+D_2O (9:1)) monitoring of azetidine at 50°C.



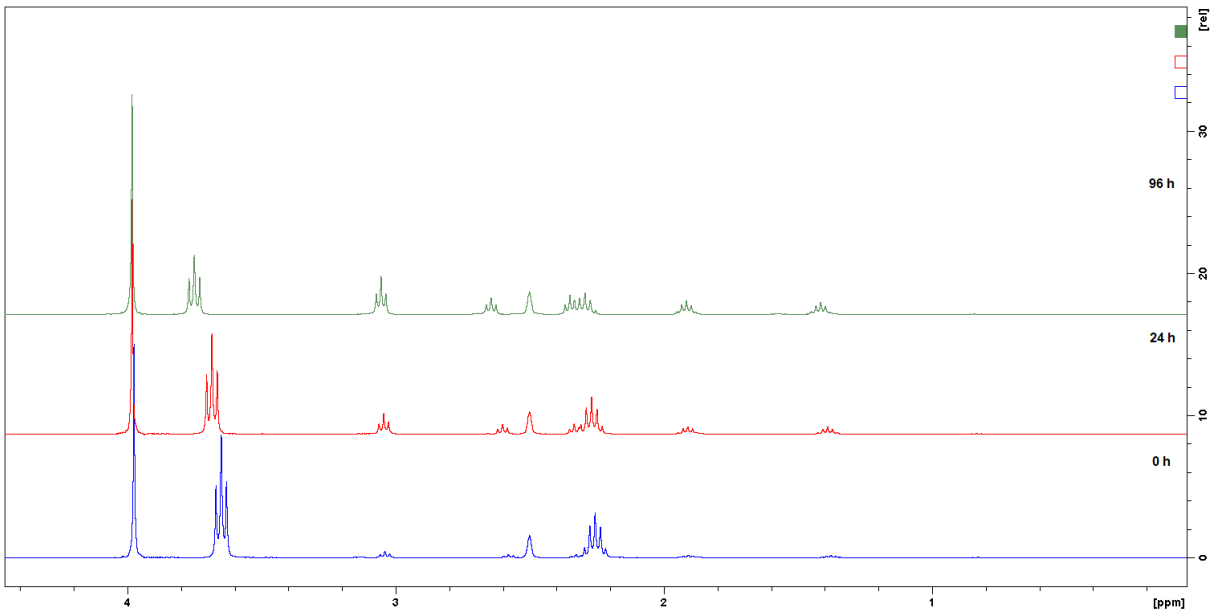
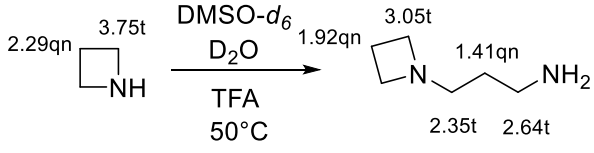


Figure S26. ^{1}H NMR (400 MHz, DMSO-d_6+D_2O (9:1)) monitoring of azetidine + TFA at rt.



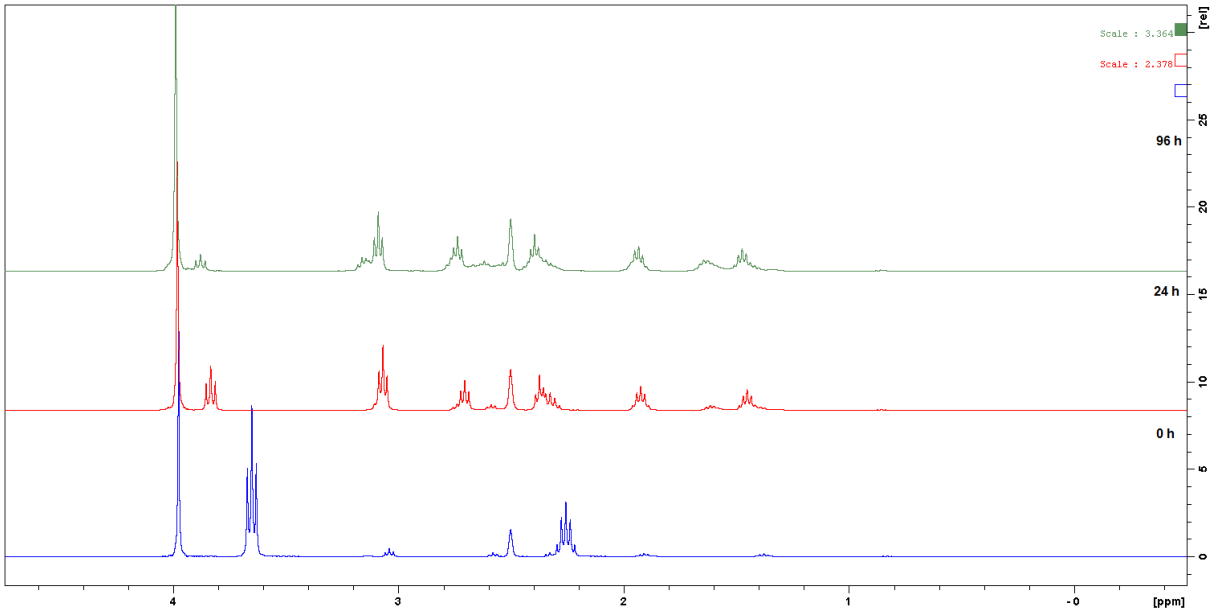


Figure S27. ^{1}H NMR (400 MHz, DMSO-d_6+D_2O (9:1)) monitoring of azetidine + TFA at 50°C.

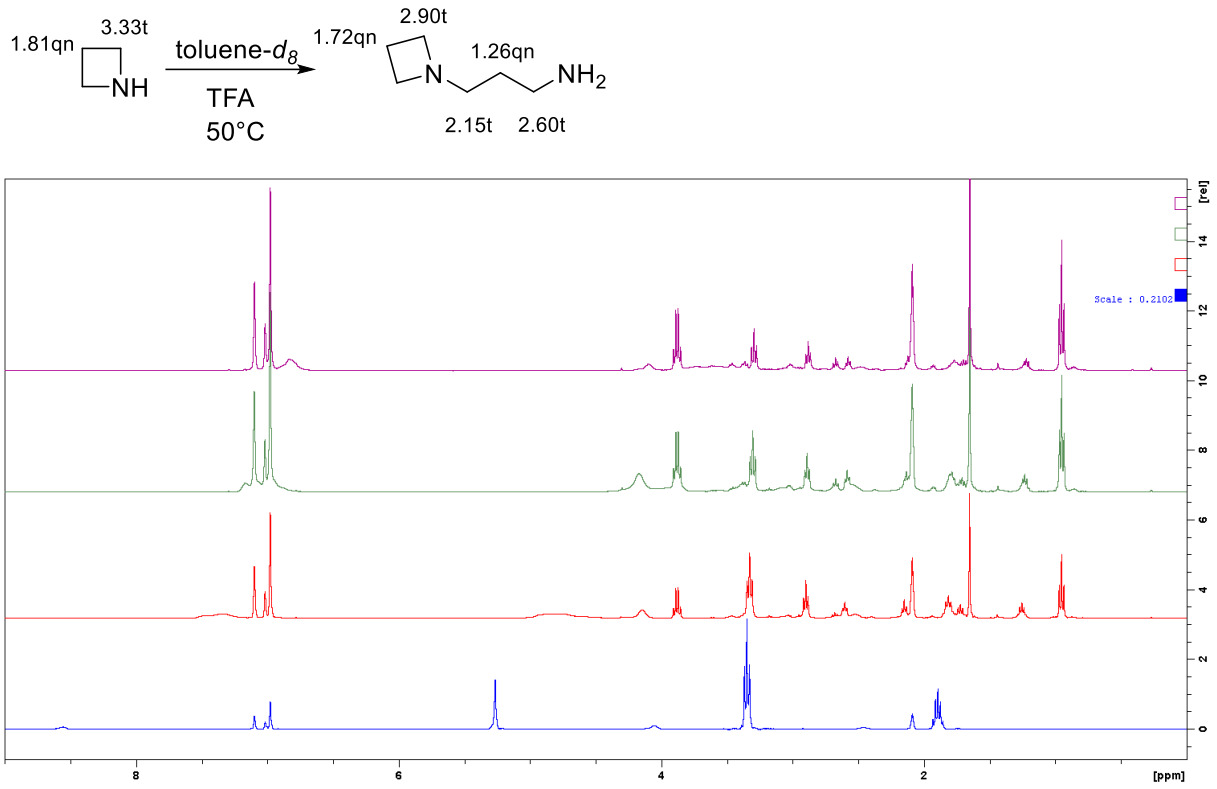


Figure S28. ^{1}H NMR (400 MHz, toluene-d_8) monitoring of azetidine + TFA at 50°C.

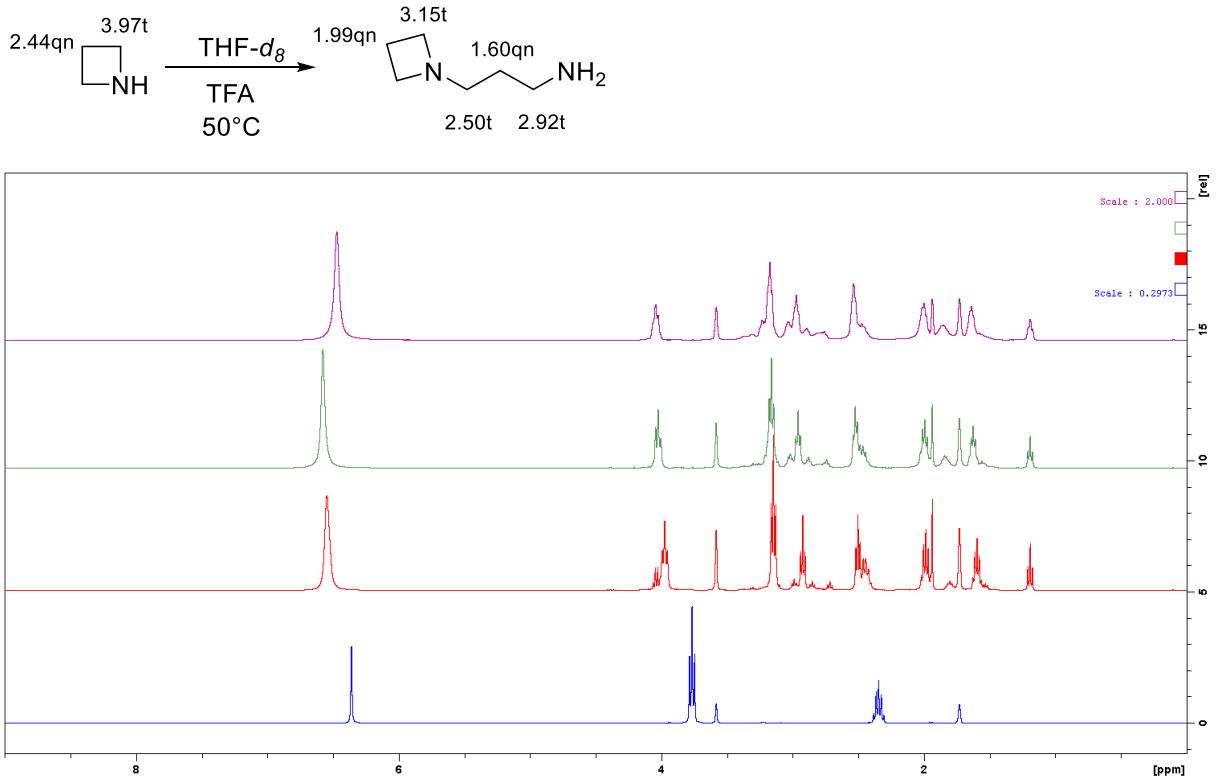


Figure S29. ^{1}H NMR (400 MHz, THF-d_8) monitoring of azetidine + TFA at 50°C.

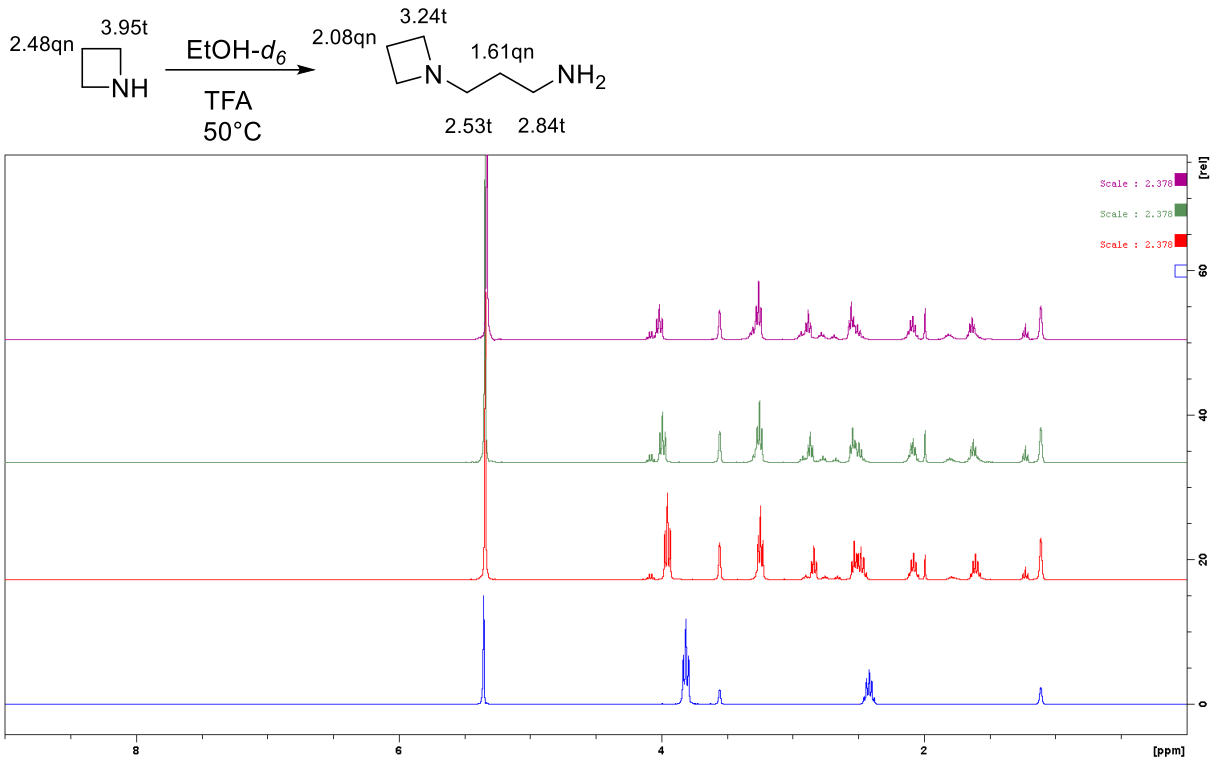


Figure S30. ^{1}H NMR (400 MHz, EtOH-d_6) monitoring of azetidine + TFA at 50°C.

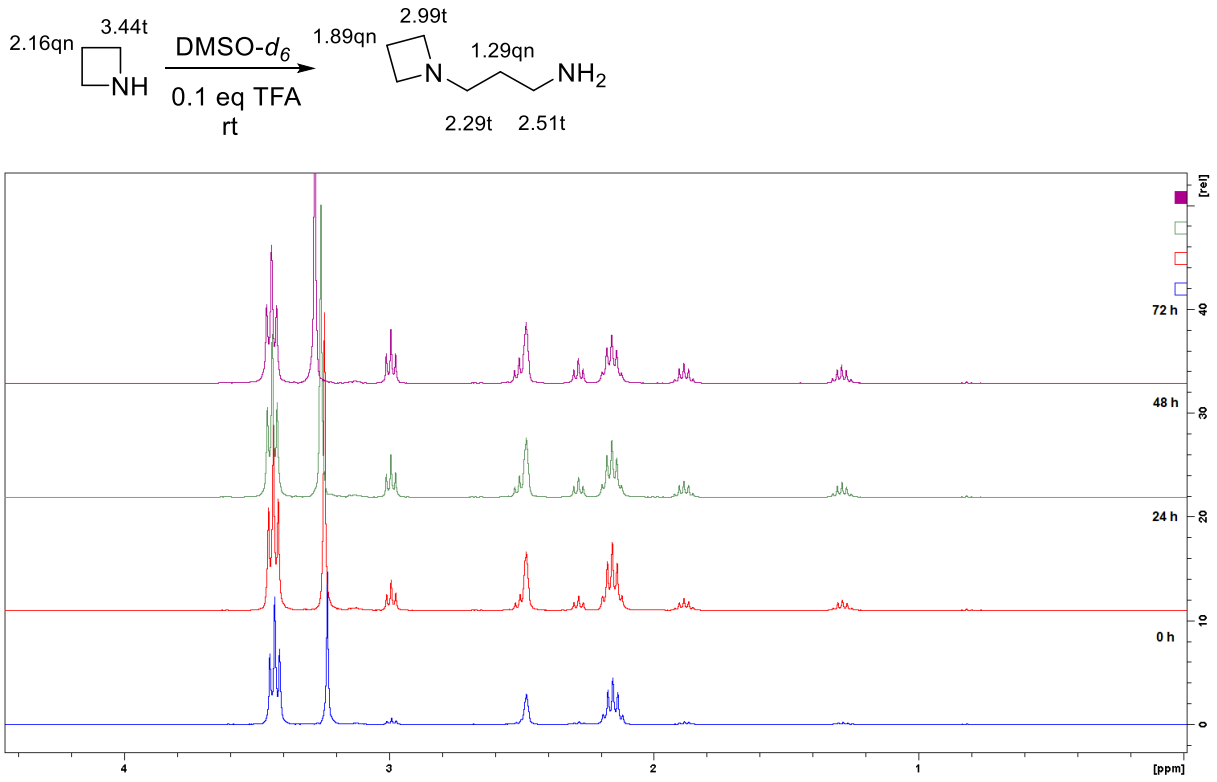
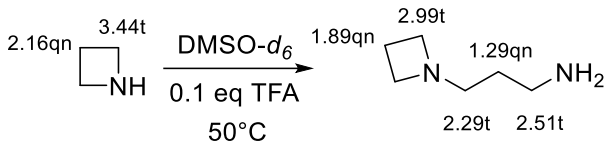


Figure S31. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + 0.1 eq TFA at rt.



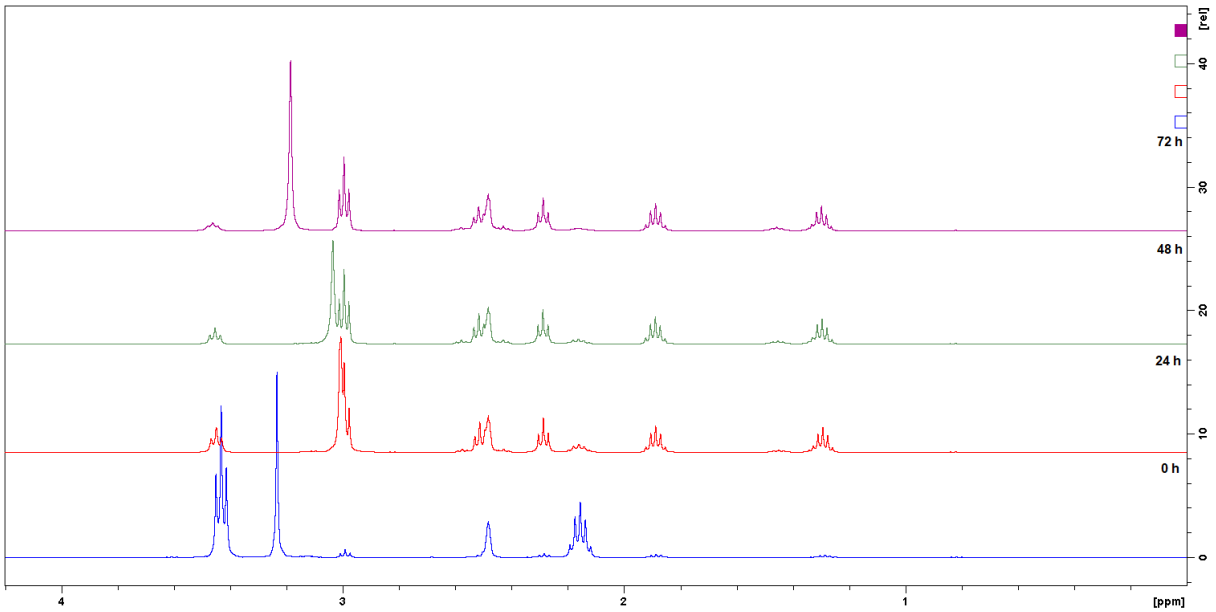
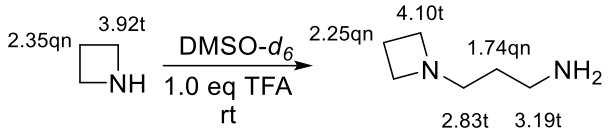


Figure S32. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + 0.1 eq TFA at 50°C.



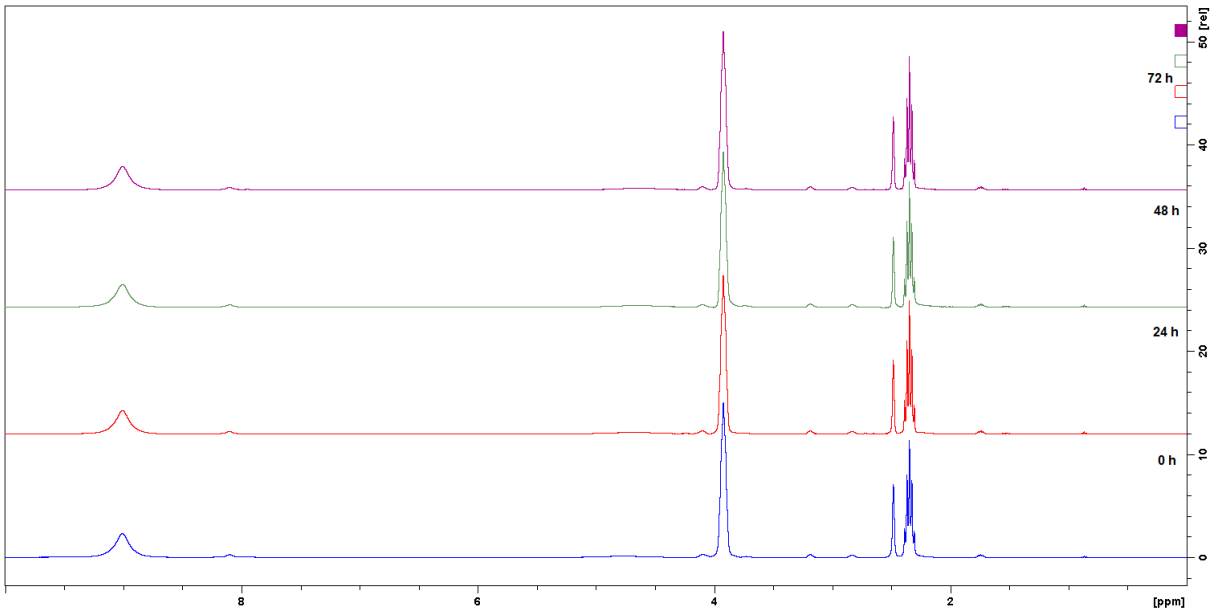


Figure S33. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + 1.0 eq TFA at rt.

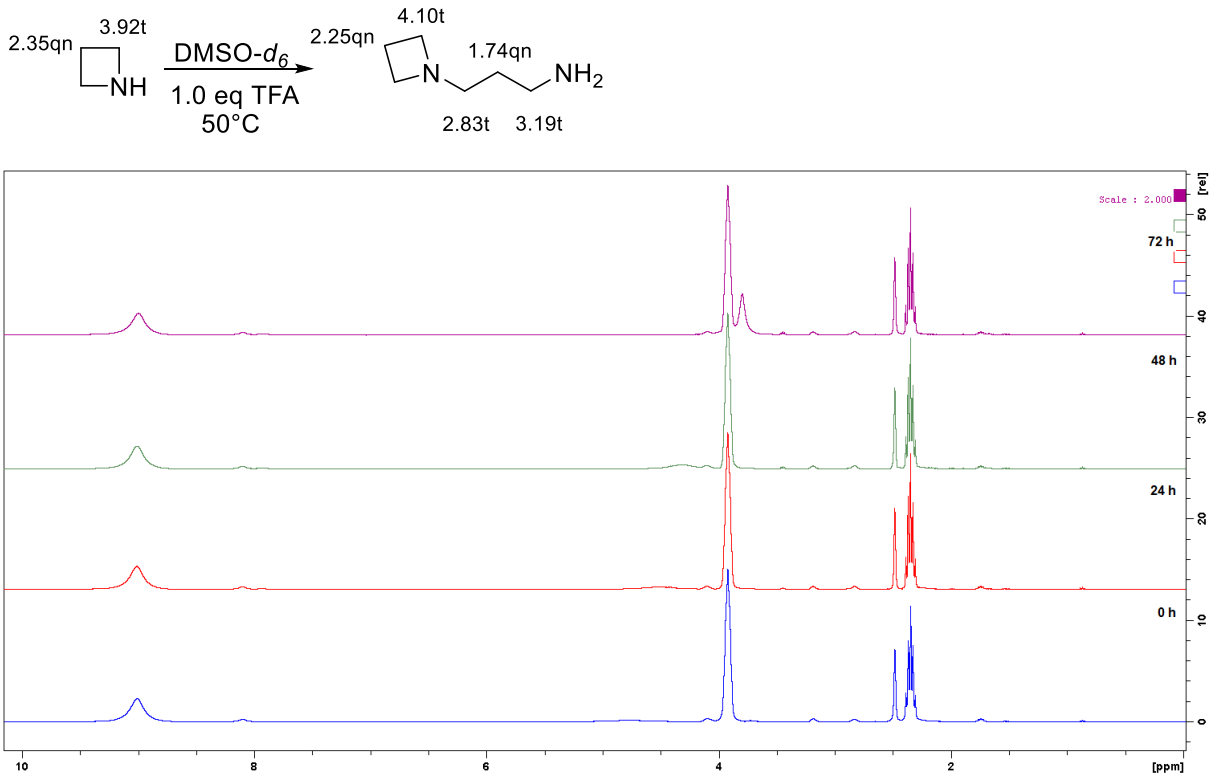


Figure S34. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + 1.0 eq TFA at 50°C.

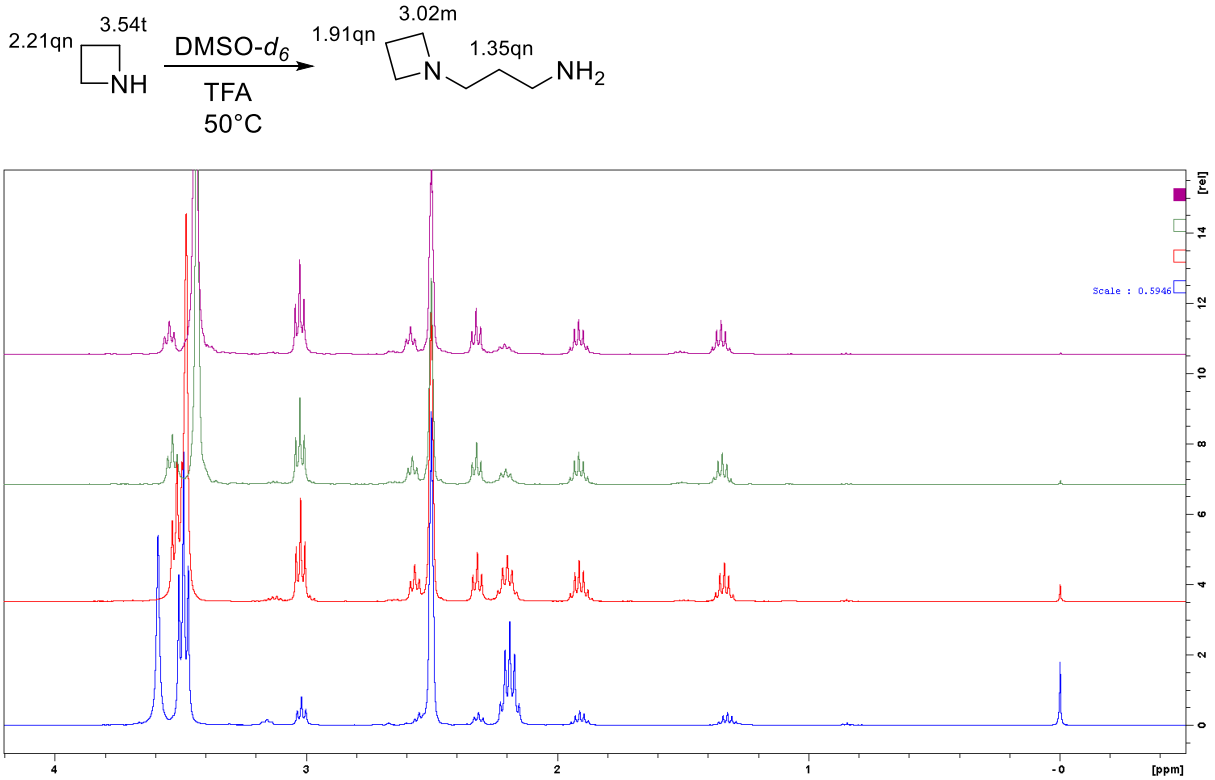


Figure S35. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine (1.0 M) + TFA at 50°C.

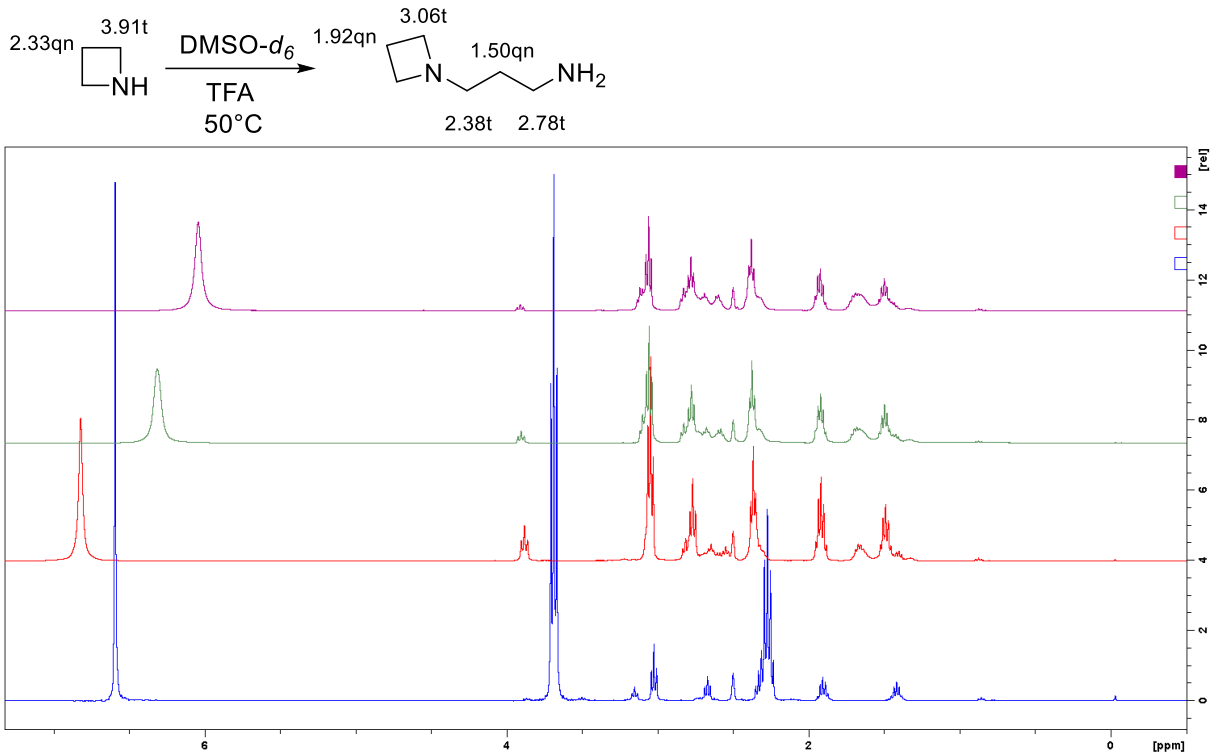


Figure S36. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine (5.0 M) + TFA at 50°C.

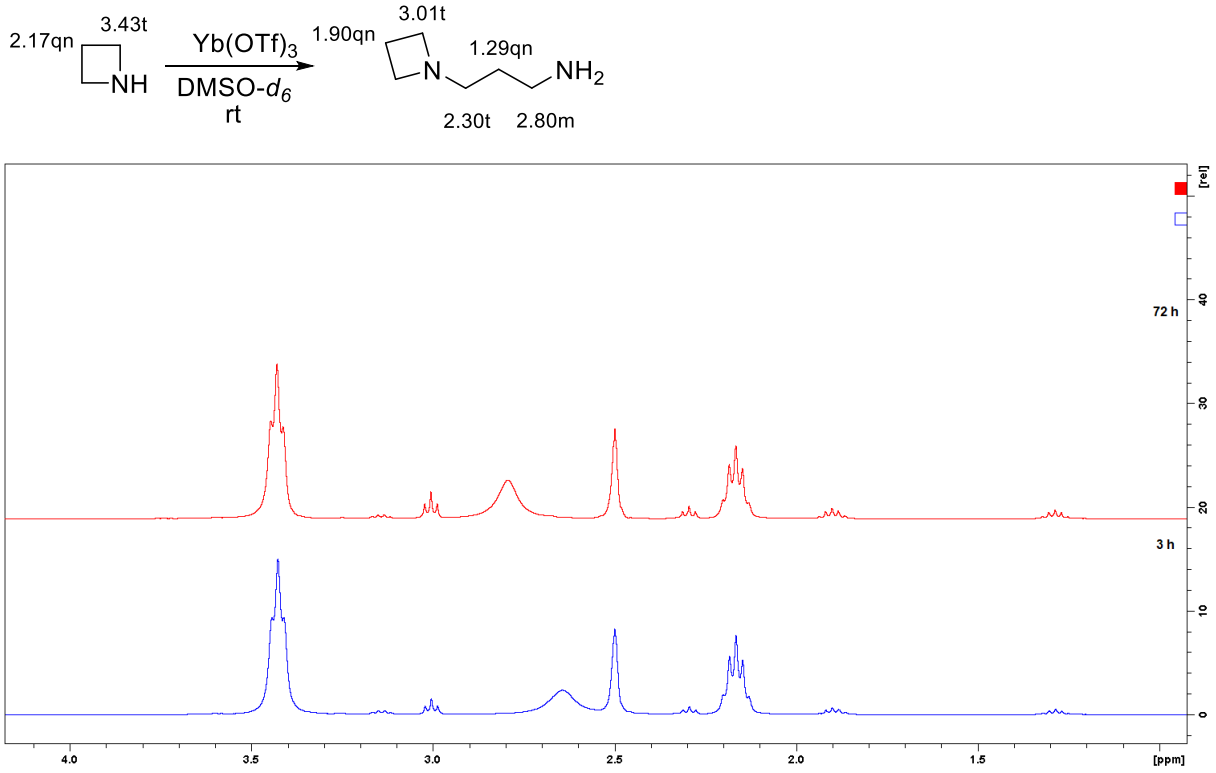
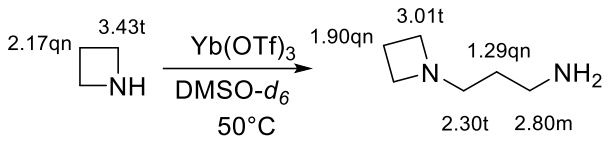


Figure S37. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + Yb(OTf)$_3$ at rt.



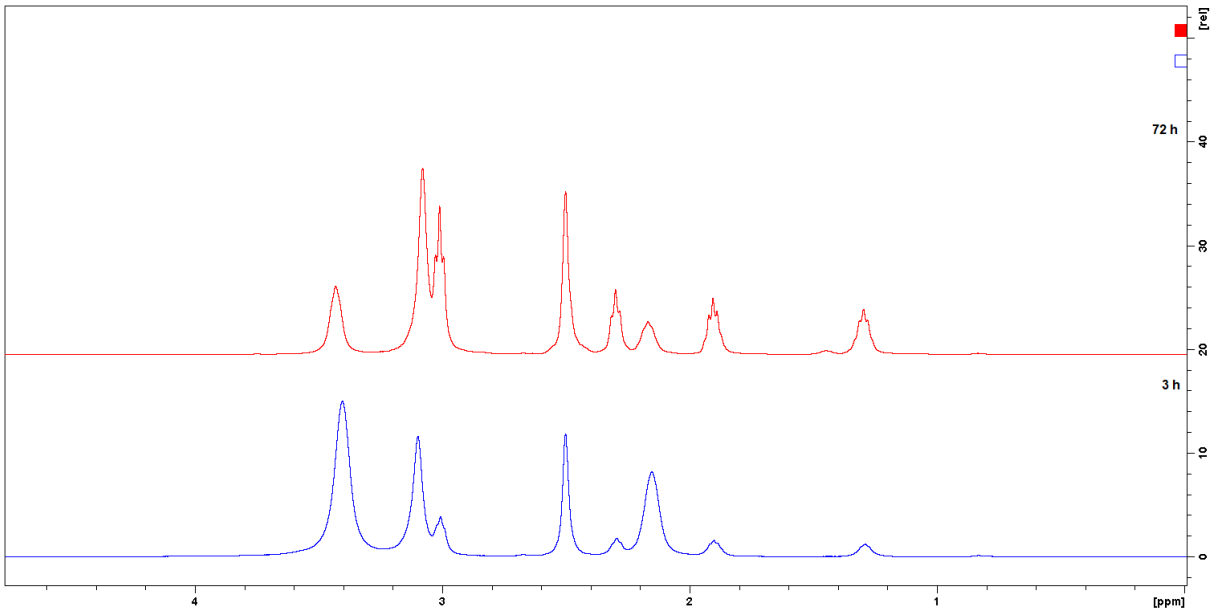
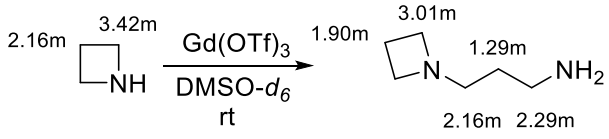


Figure S38. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + Yb(OTf)$_3$ at 50°C.



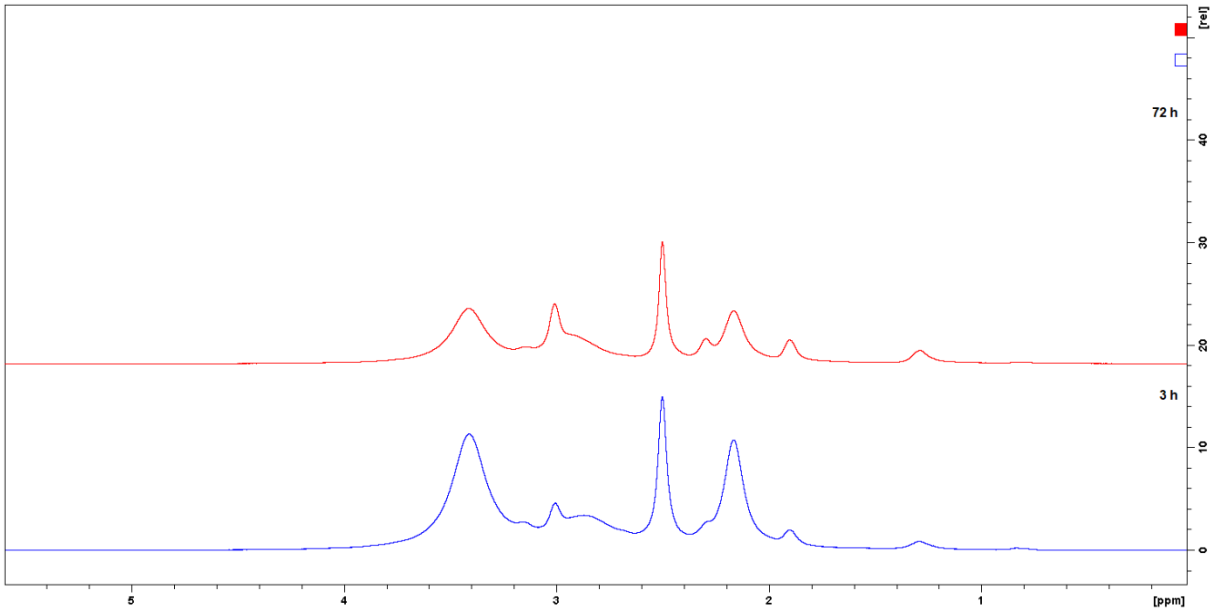
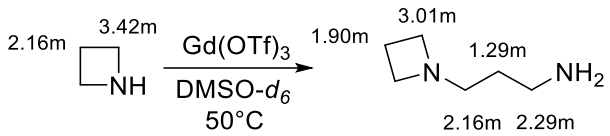


Figure S39. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + Gd(OTf)$_3$ at rt.



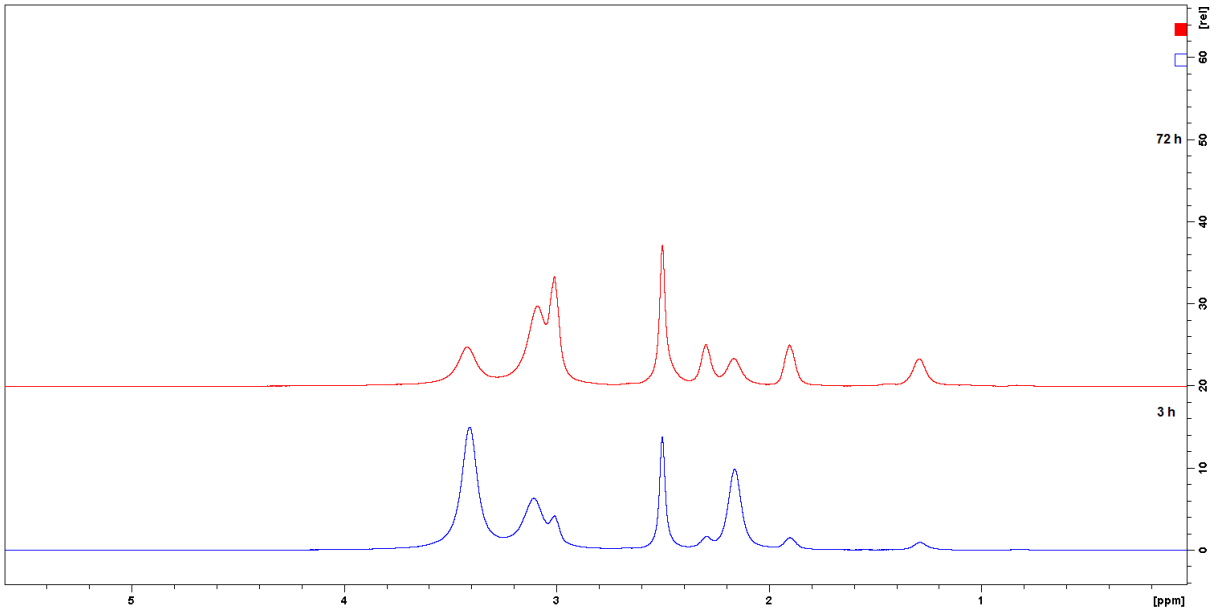
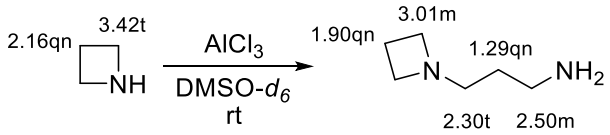


Figure S40. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + $Gd(OTf)_3$ at 50°C.



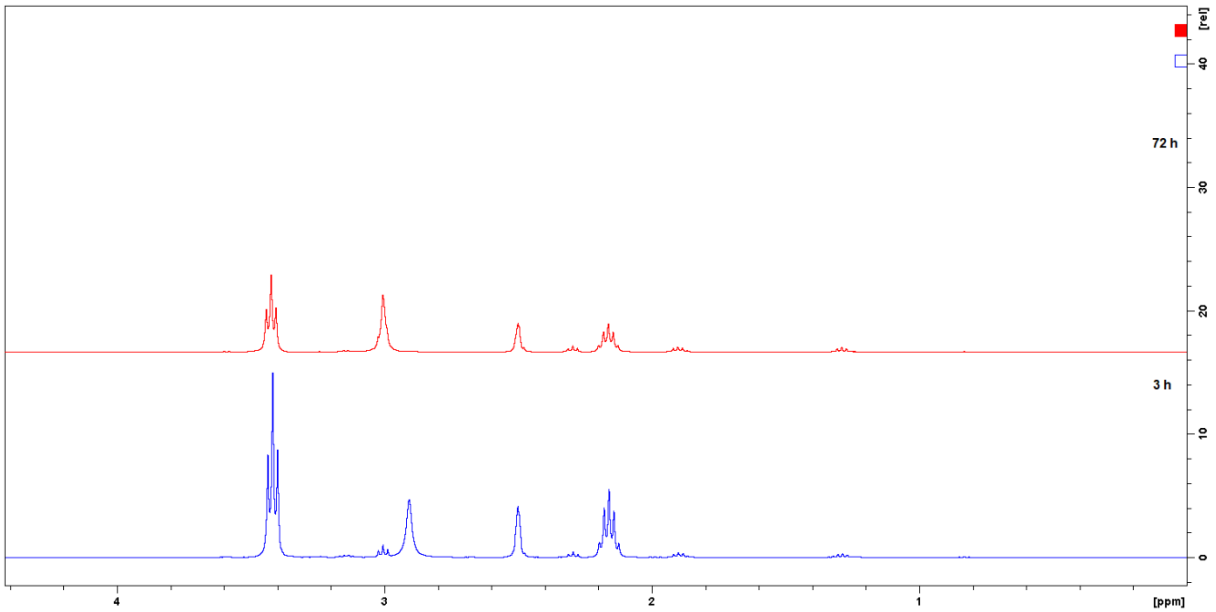
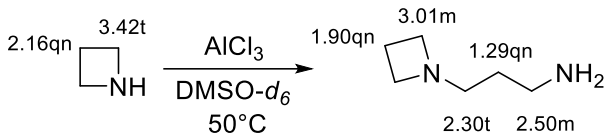


Figure S41. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + $AlCl_3$ at rt.



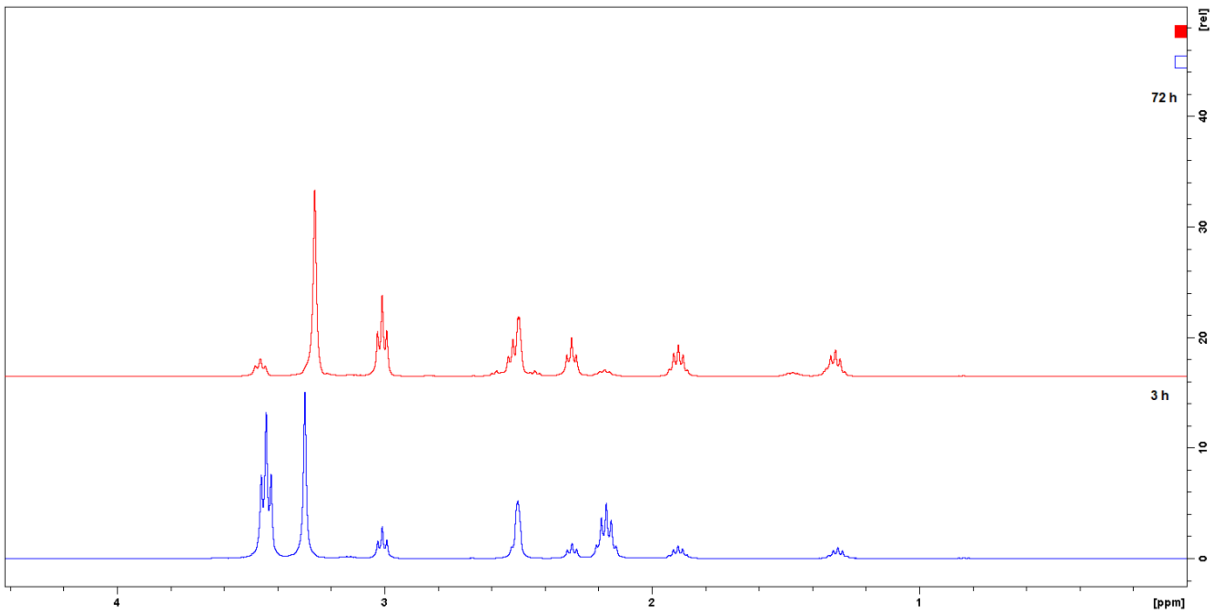
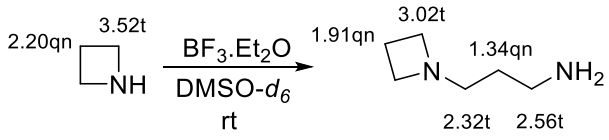


Figure S42. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + $AlCl_3$ at 50°C.



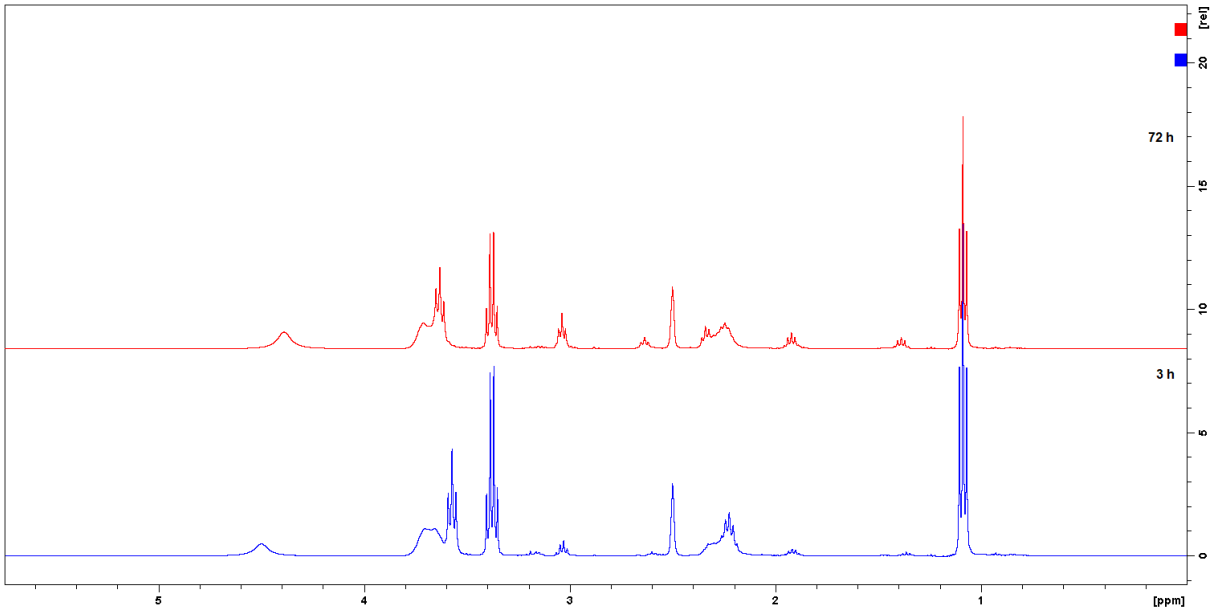
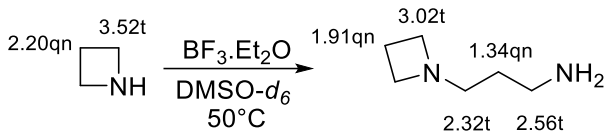


Figure S43. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + $BF_3.Et_2O$ at rt.



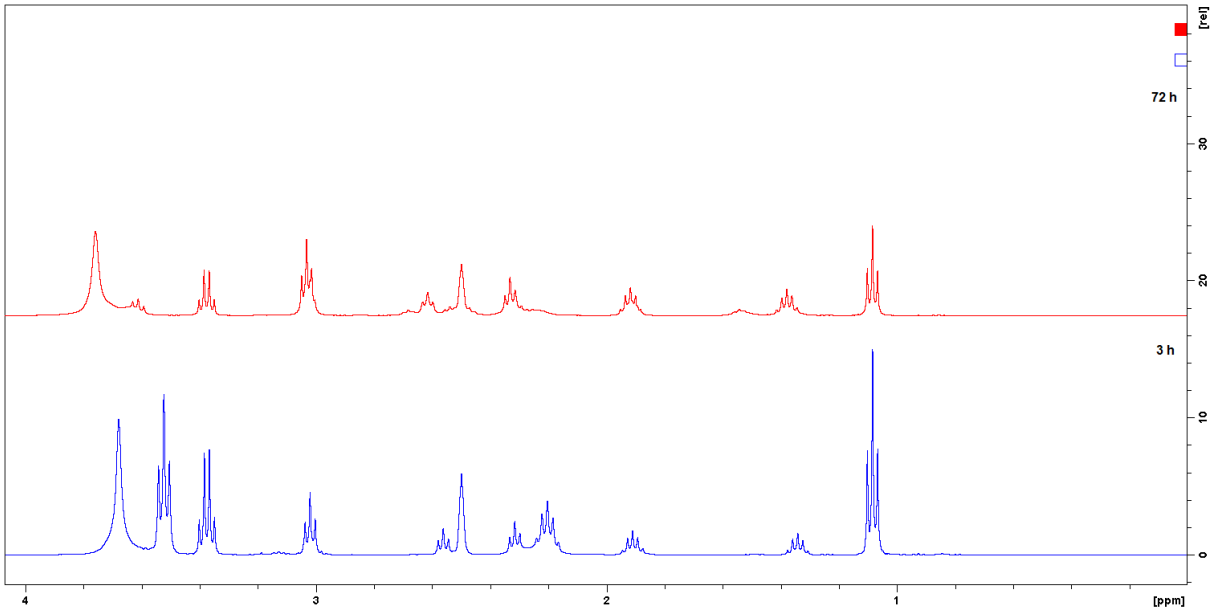
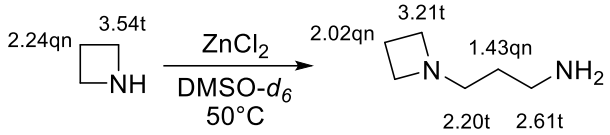


Figure S44. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + $BF_3.Et_2O$ at 50°C.



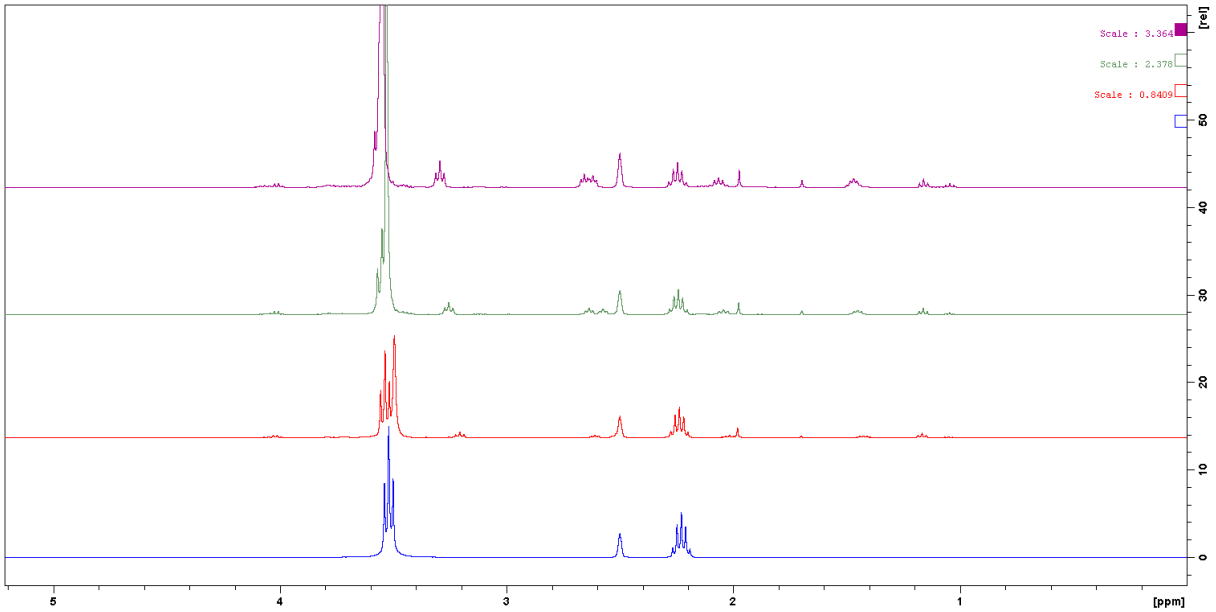


Figure S45. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + $ZnCl_2$ at 50°C.

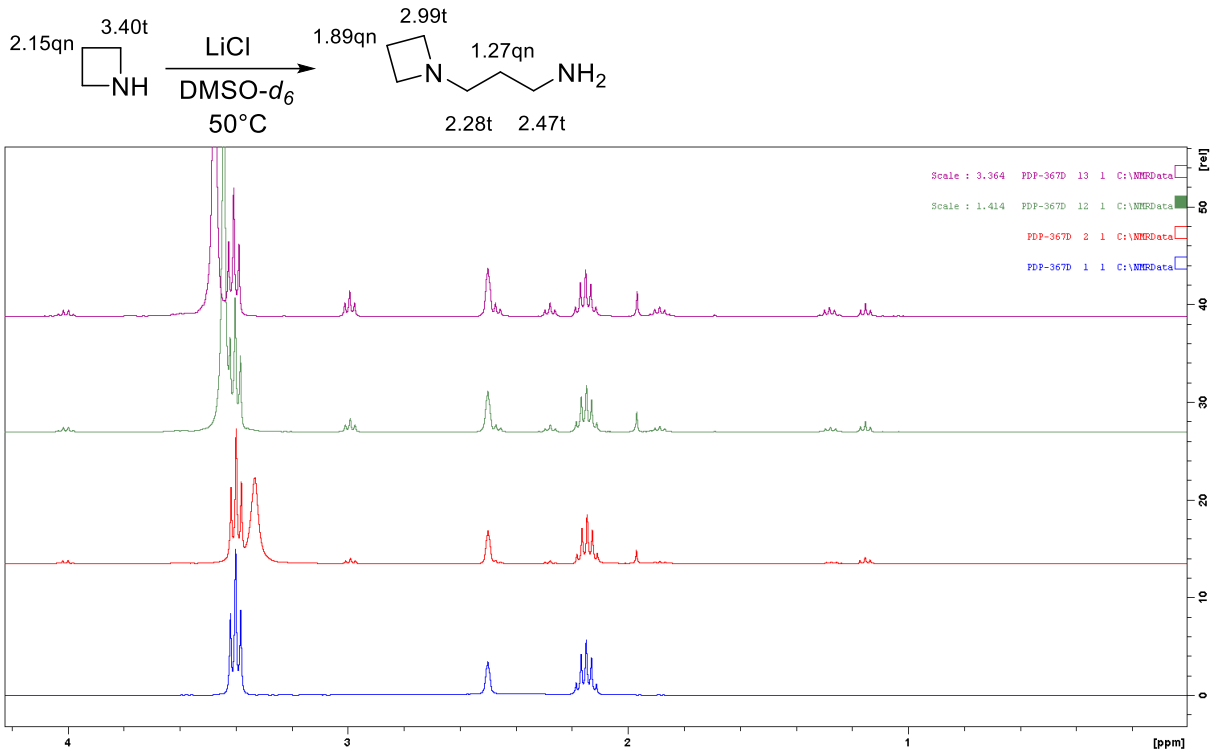


Figure S46. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + LiCl at 50°C.

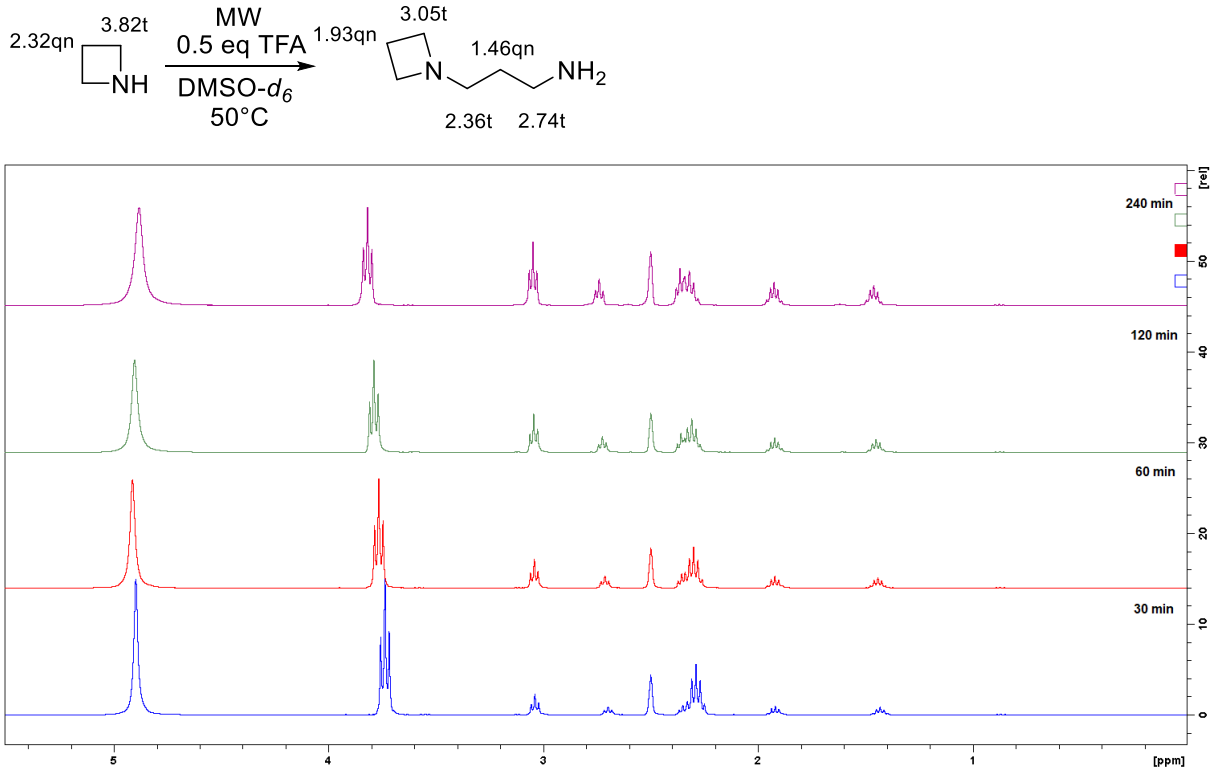
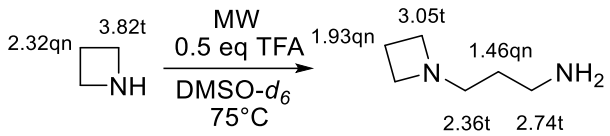


Figure S47. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + TFA at 50°C, MW heating.



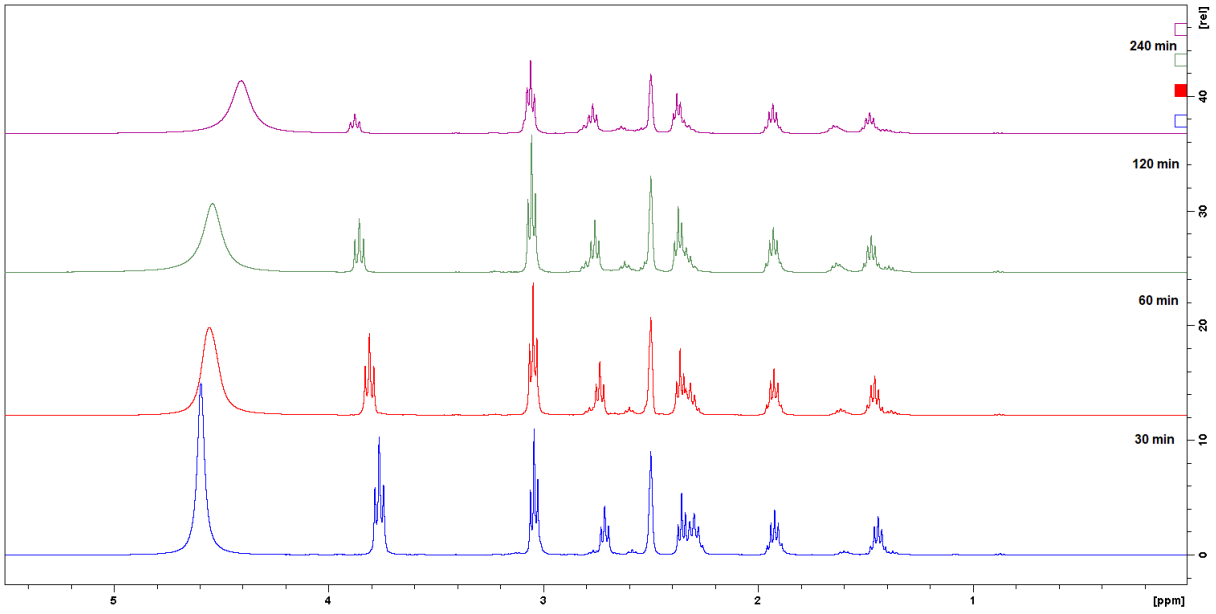
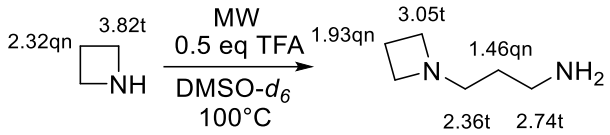


Figure S48. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + TFA at 75°C, MW heating.



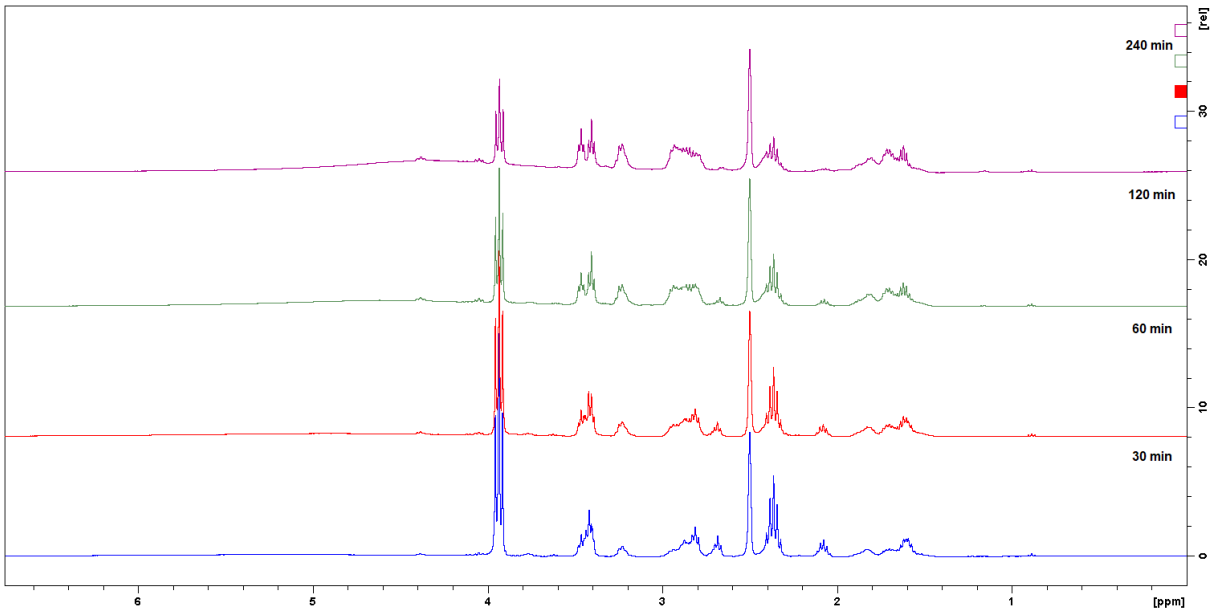
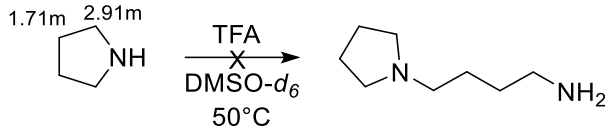


Figure S49. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + TFA at 100°C, MW heating.



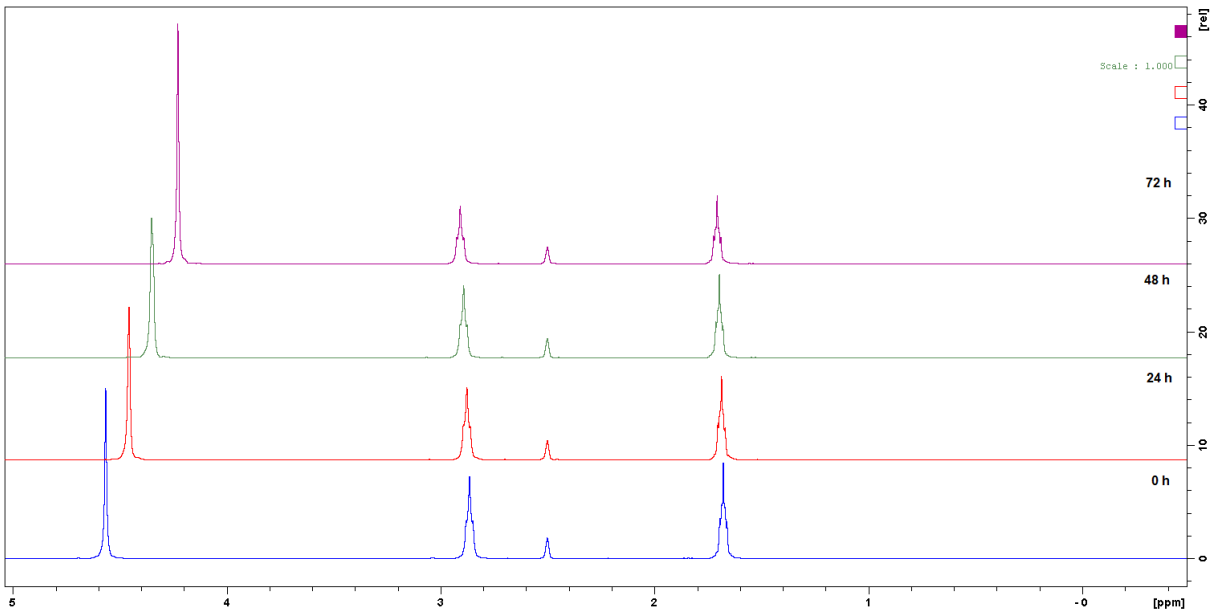
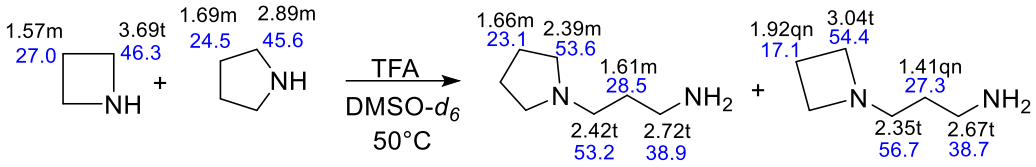


Figure S50. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of pyrrolidine + TFA at 50°C.



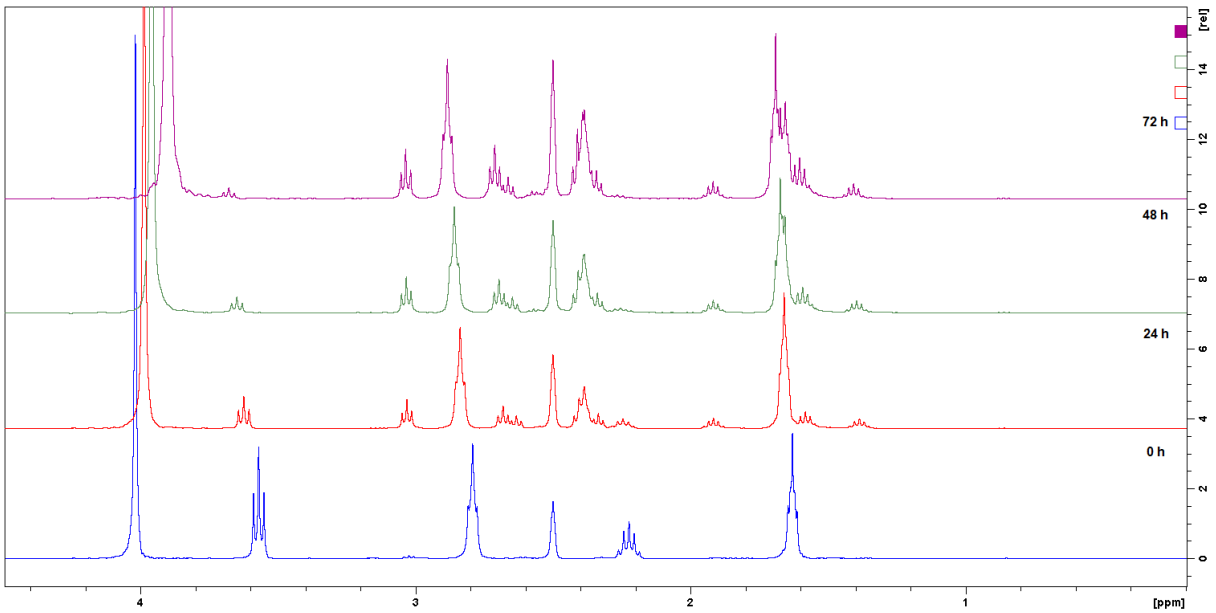
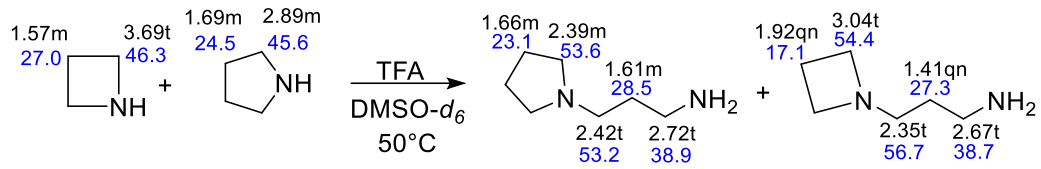


Figure S51. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + pyrrolidine (1.0 eq) + TFA at 50°C.



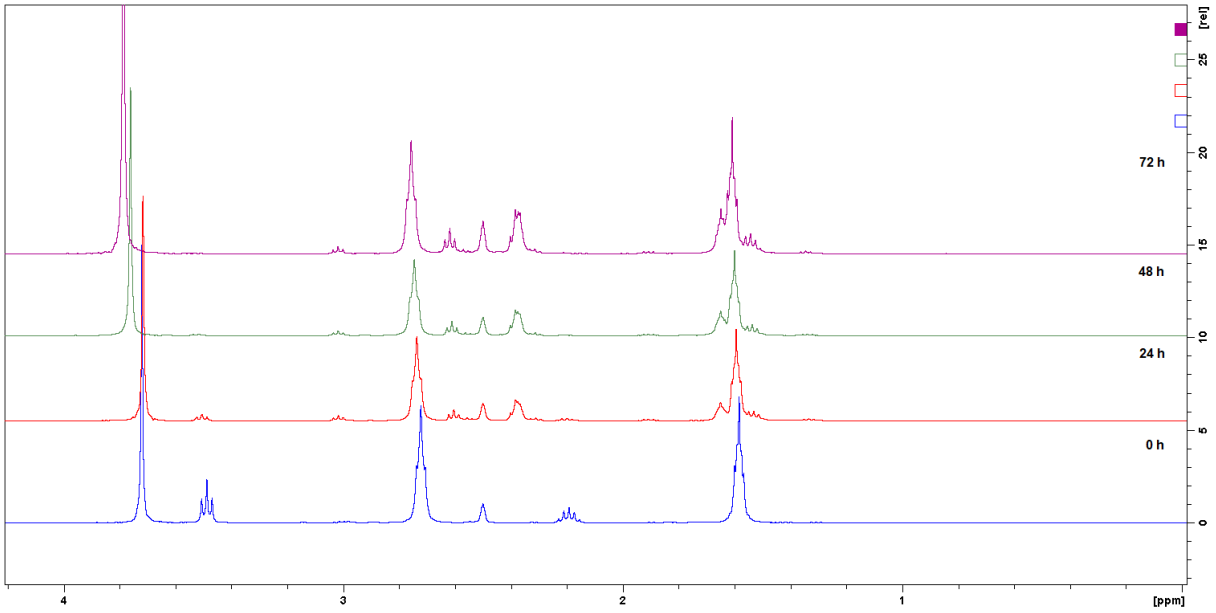


Figure S52. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + pyrrolidine (3.0 eq) + TFA at 50°C.

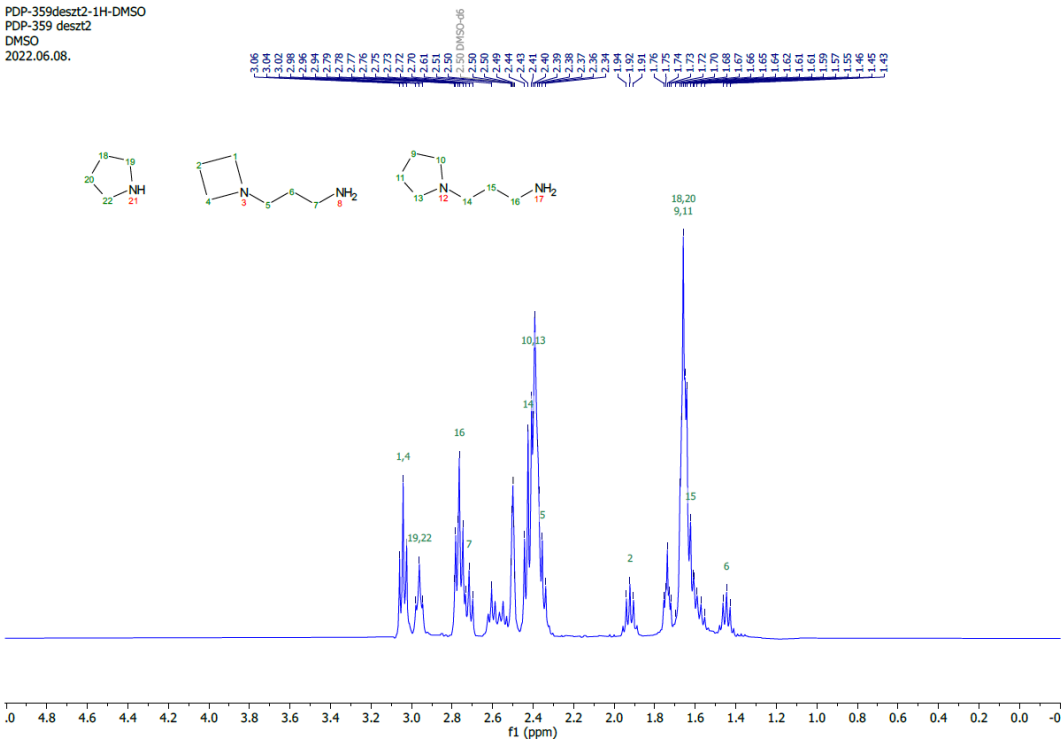
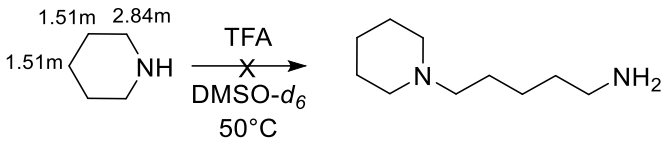


Figure S53. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + pyrrolidine (1.0 eq) + TFA at 50°C (synthetic experiment).



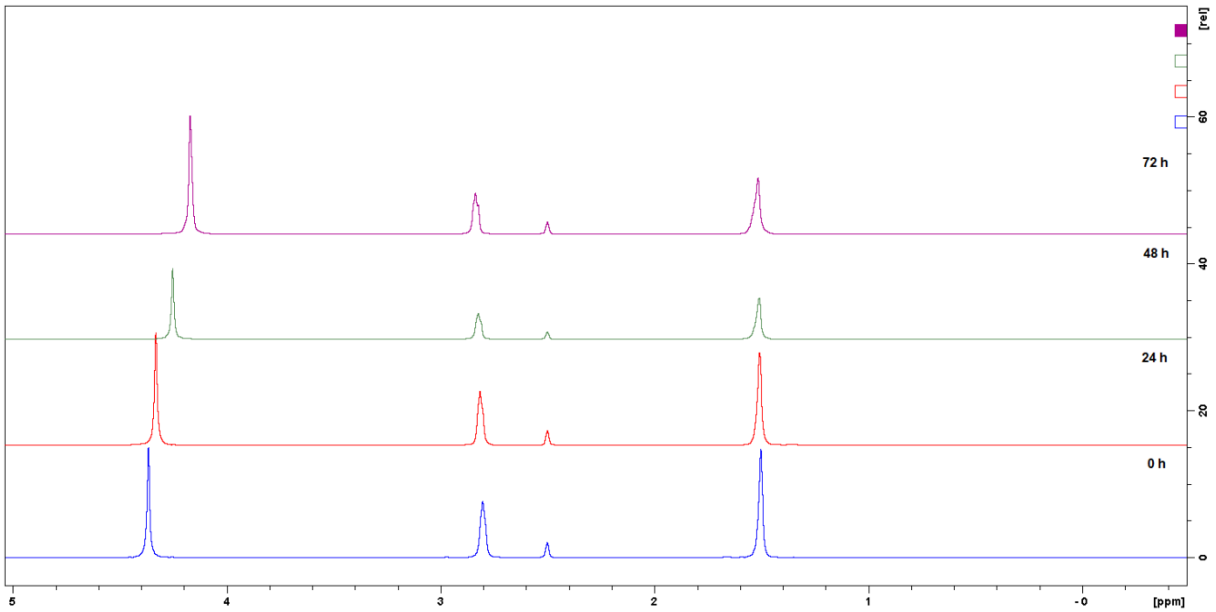
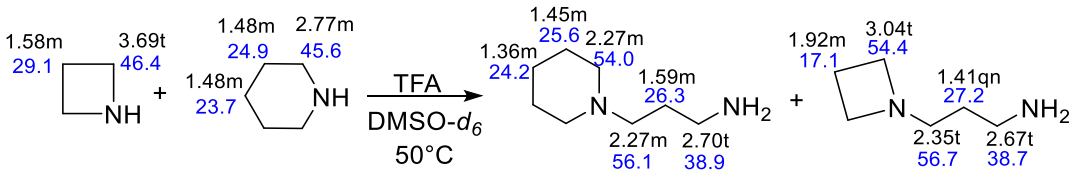


Figure S54. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of piperidine + TFA at 50°C.



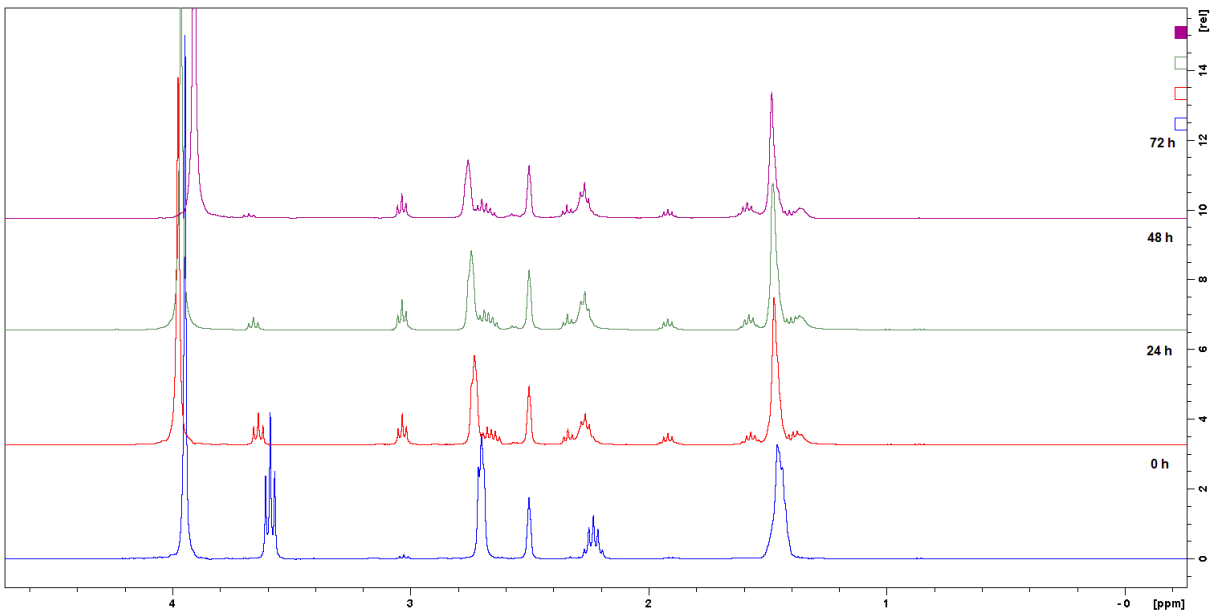
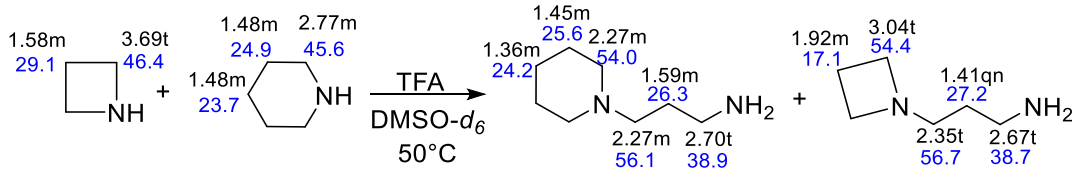


Figure S55. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + piperidine (1.0 eq) + TFA at 50°C.



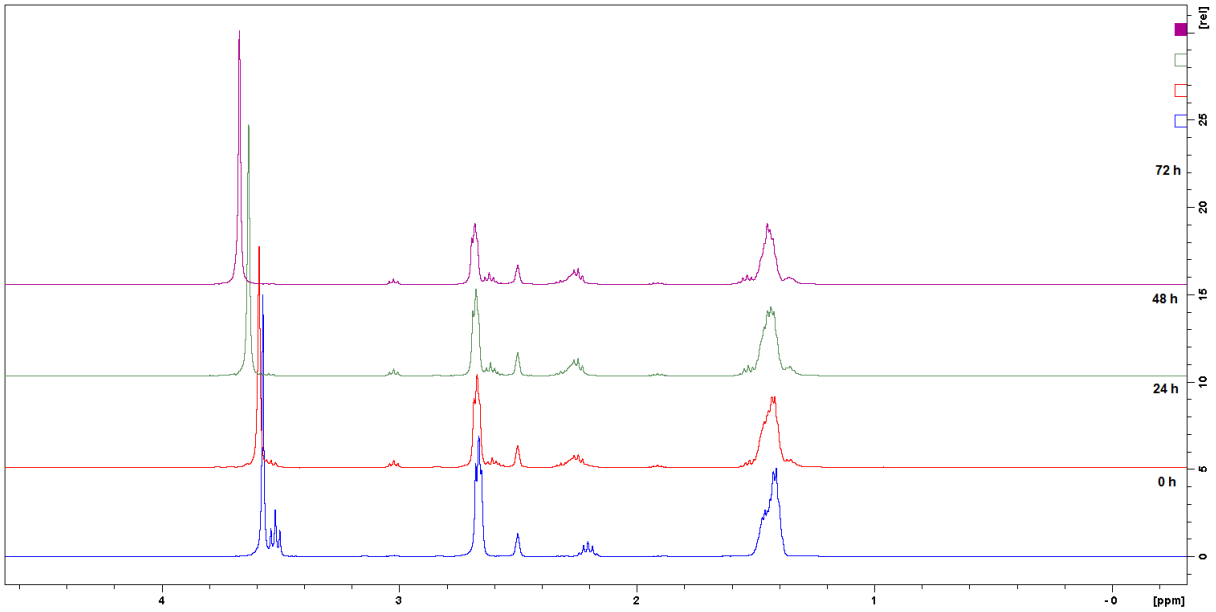
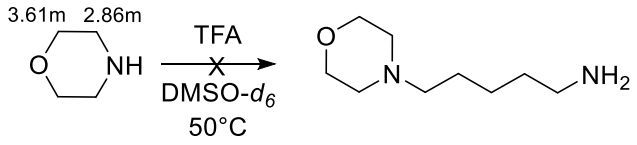


Figure S56. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + piperidine (3.0 eq) + TFA at 50°C.



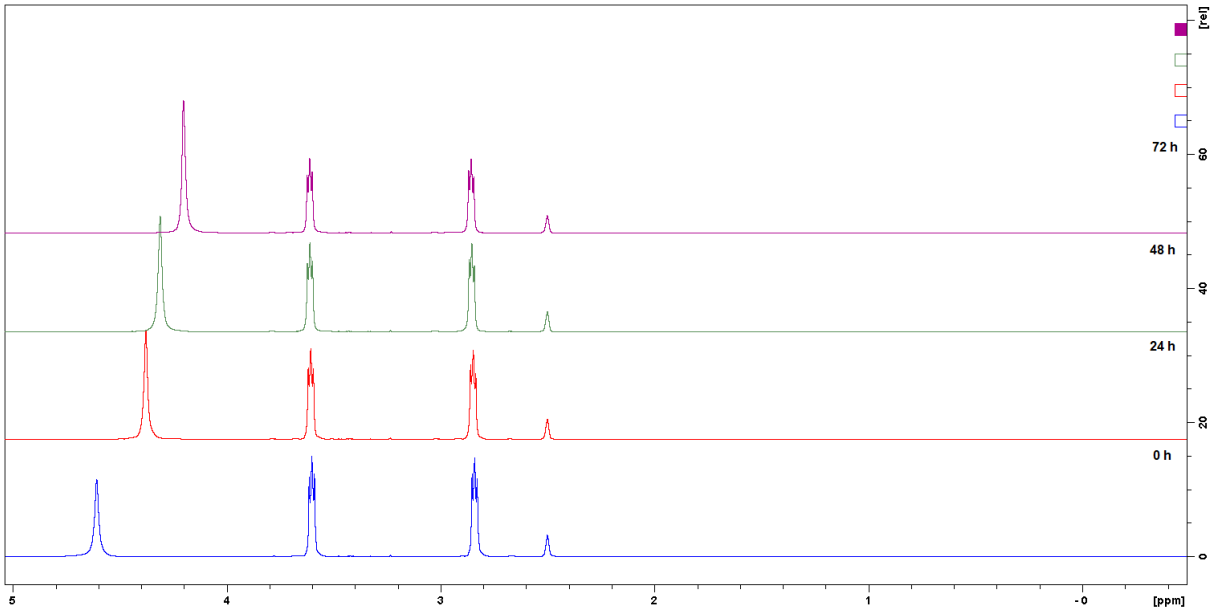


Figure S57. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of morpholine + TFA at 50°C.

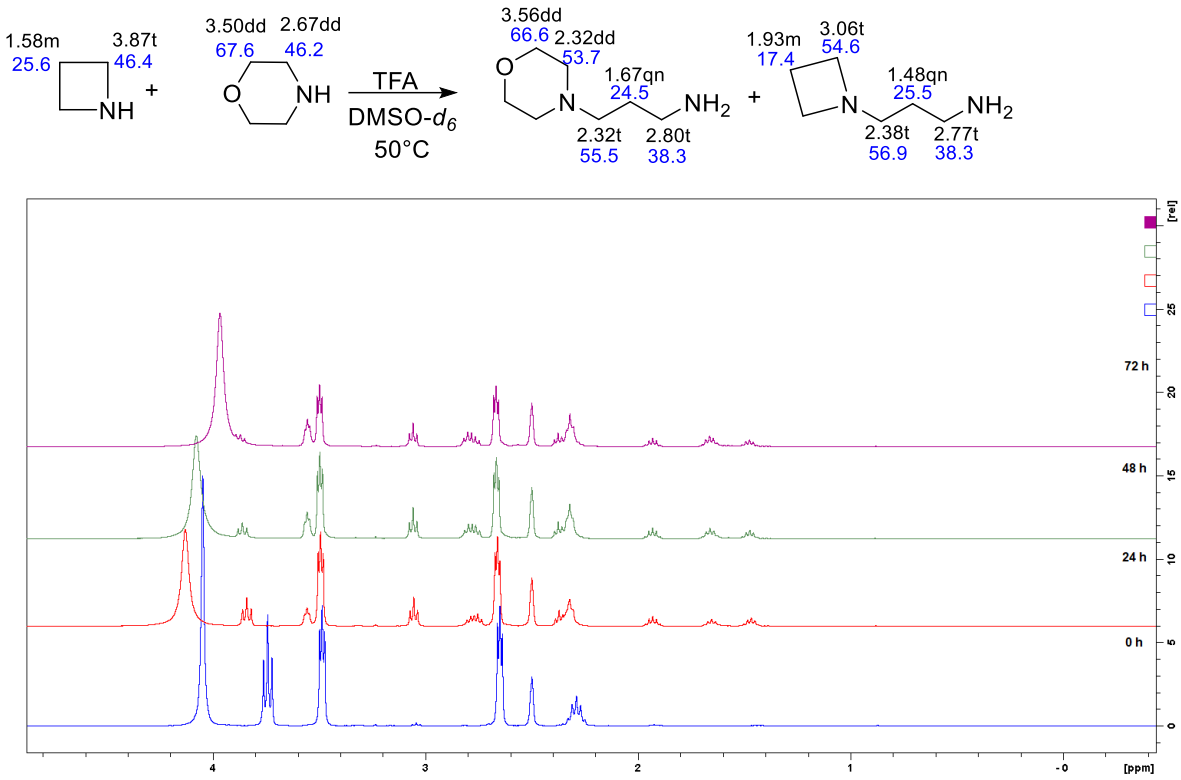


Figure S58. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + morpholine (1.0 eq) + TFA at 50°C.

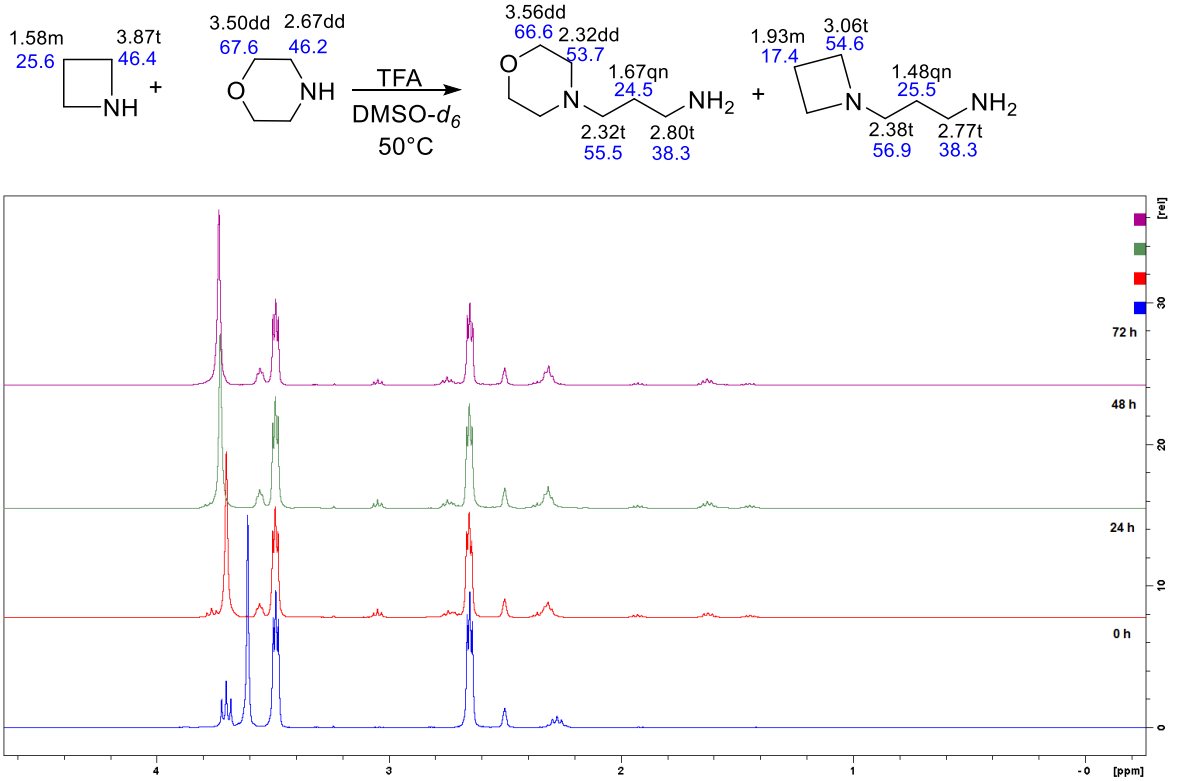
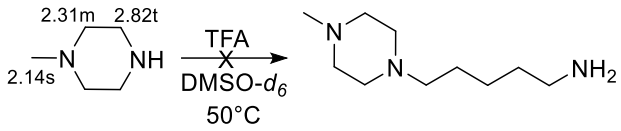


Figure S59. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + morpholine (3.0 eq) + TFA at 50°C.



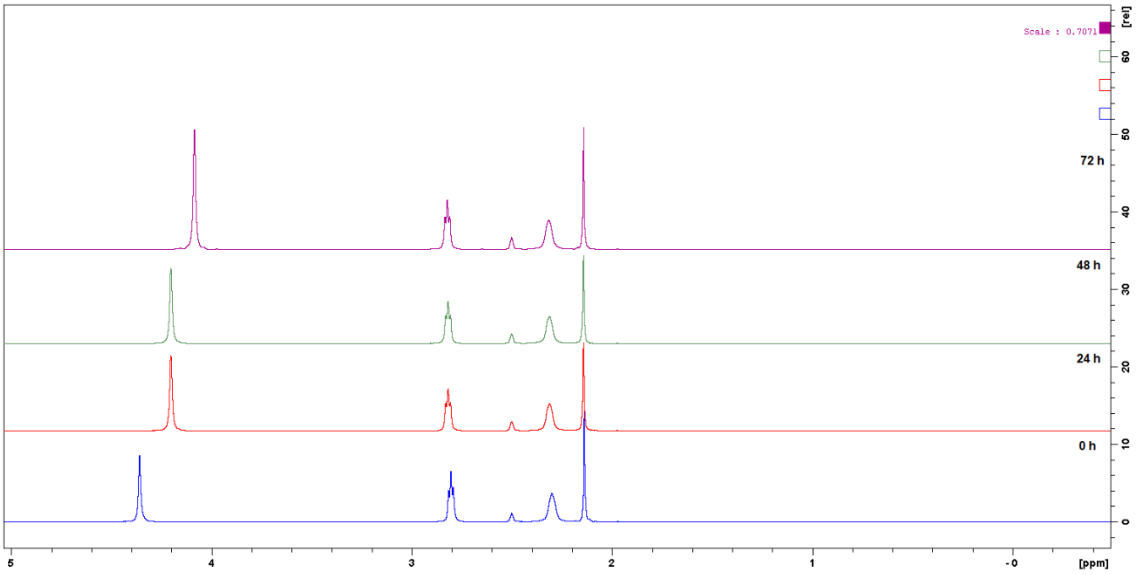
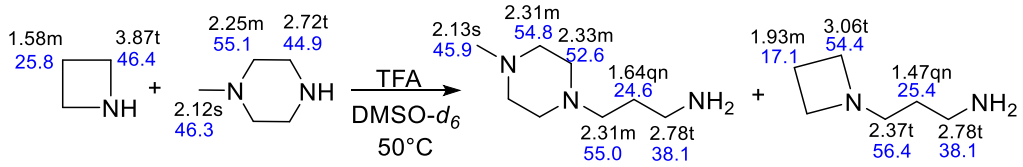


Figure S60. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of *N*-methylpiperazine + TFA at 50°C.



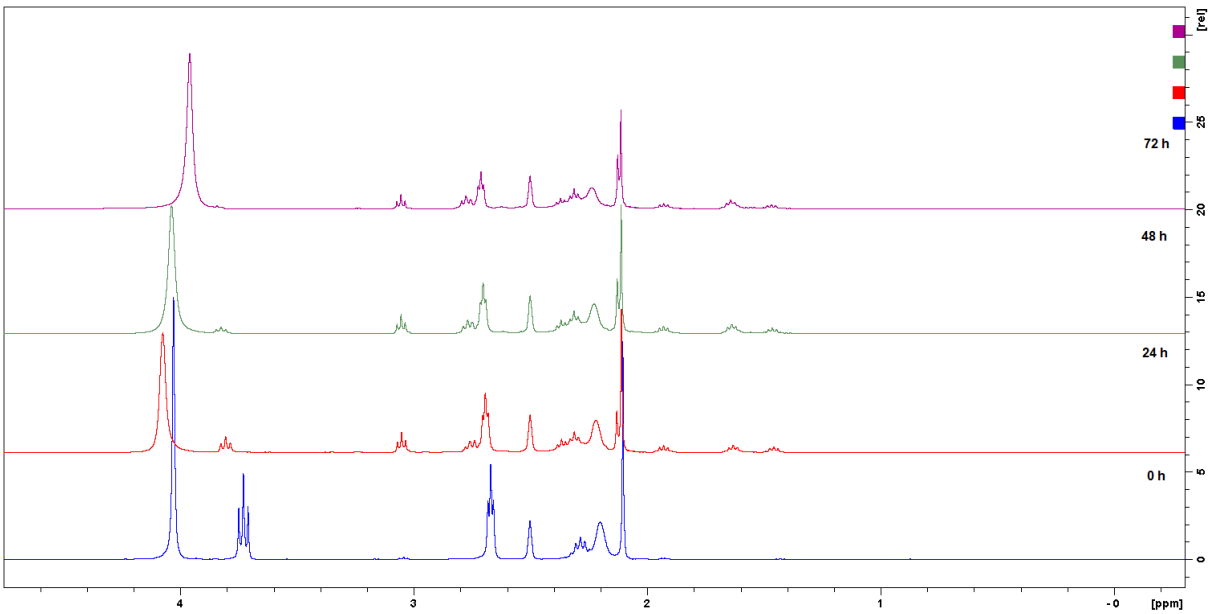


Figure S61. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + *N*-methylpiperazine (1.0 eq) + TFA at 50°C.

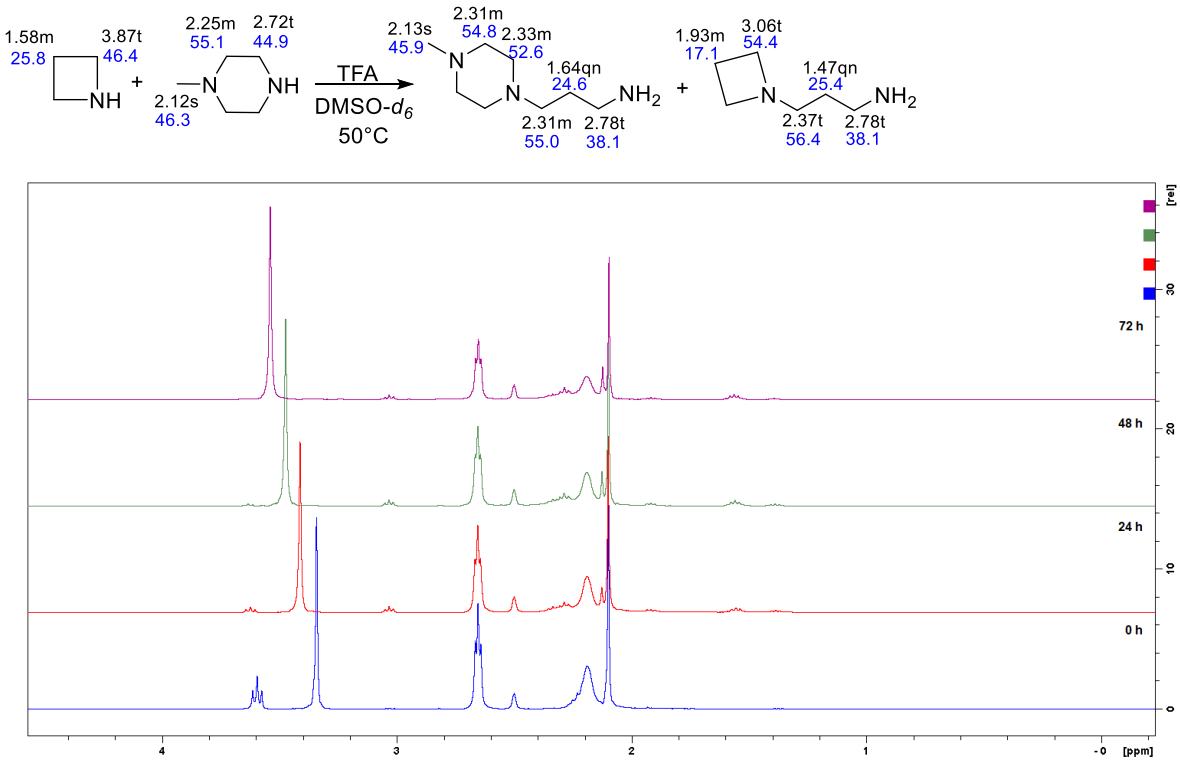


Figure S62. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + *N*-methylpiperazine (3.0 eq) + TFA at 50°C

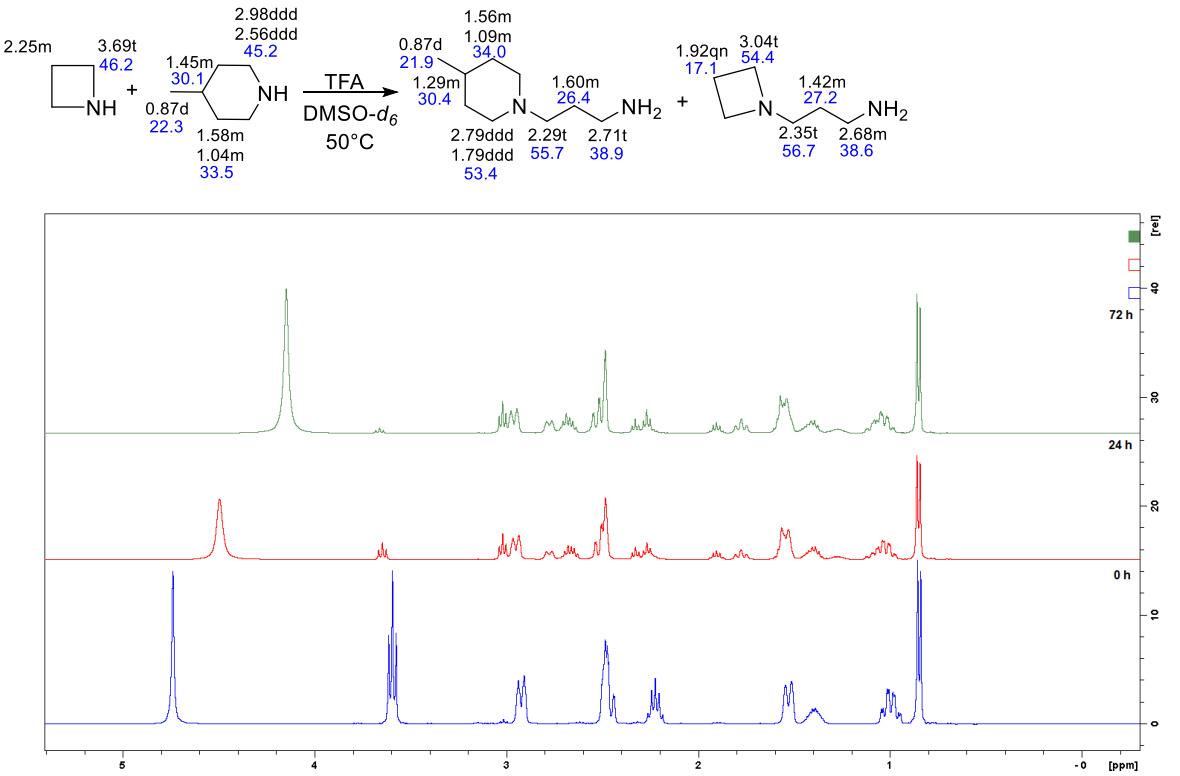
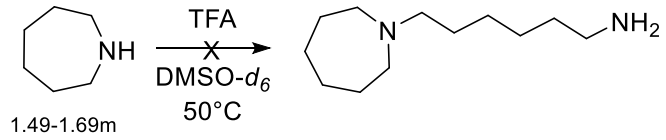


Figure S63. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + 4-methylpiperidine (1.0 eq) + TFA at 50°C.



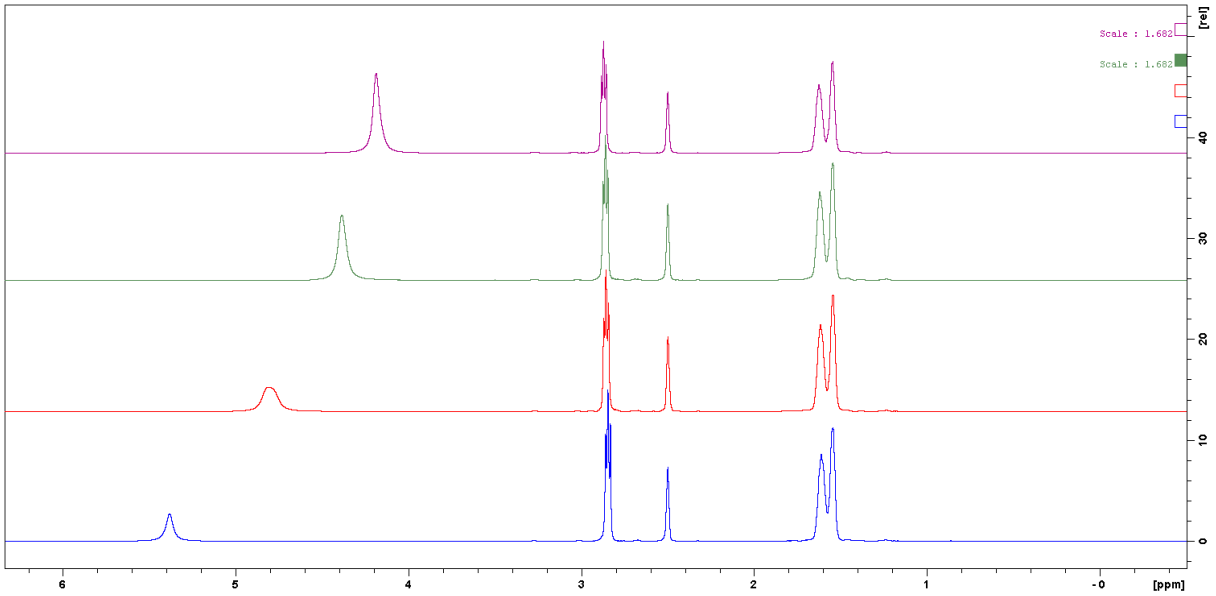
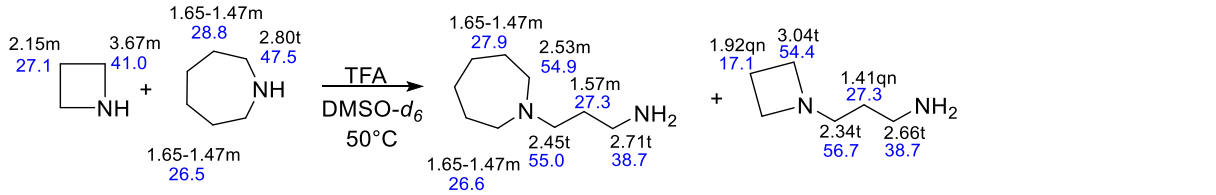


Figure S64. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of hexahydroazepine + TFA at 50°C.



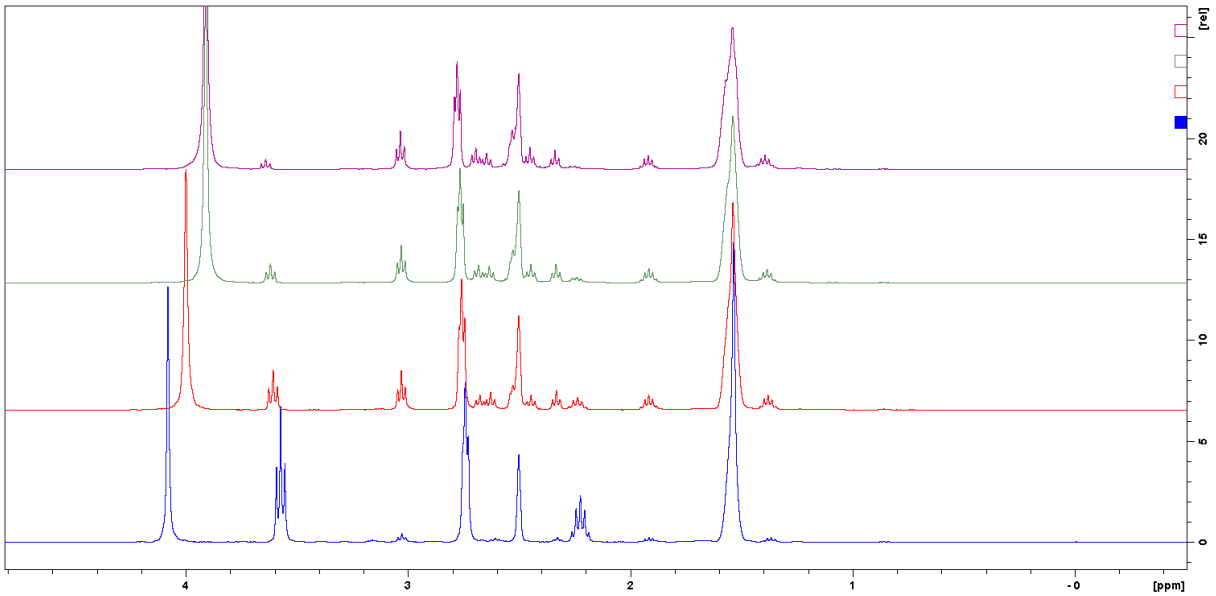


Figure S65. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + hexahydroazepine (1.0 eq) + TFA at 50°C.

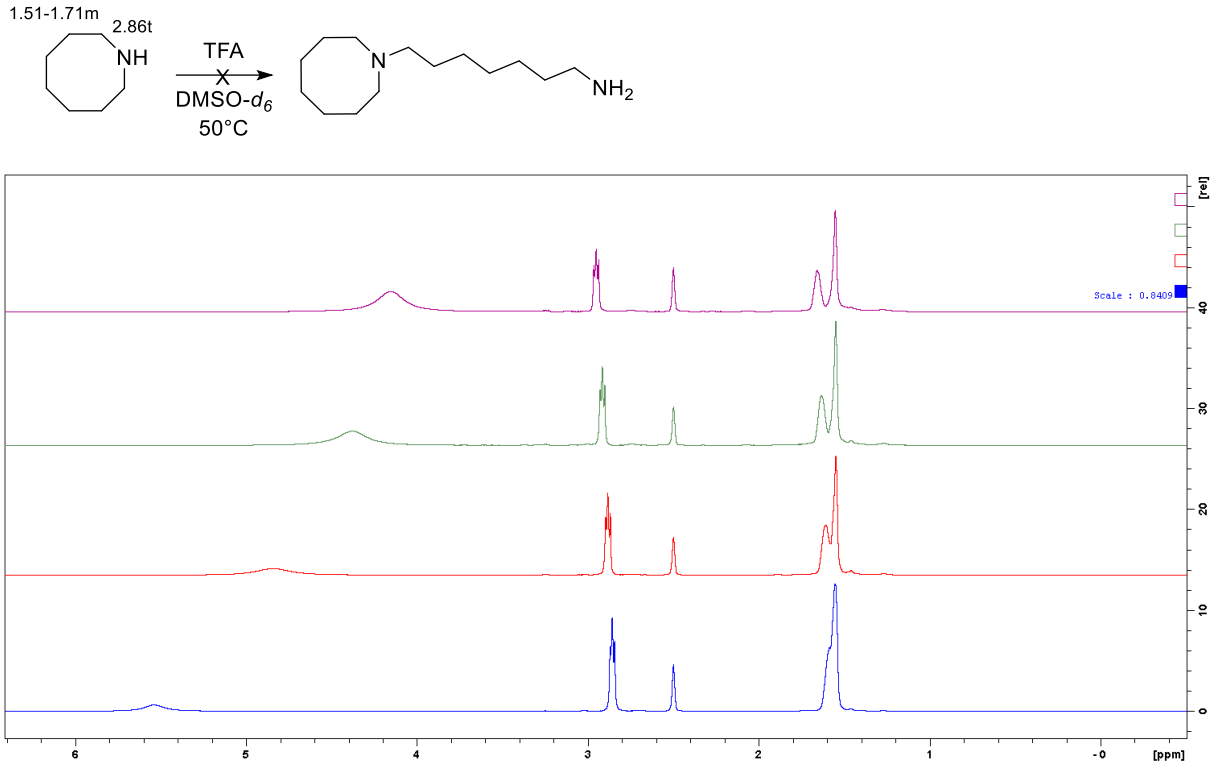


Figure S66. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of octahydroazocine + TFA at 50°C.

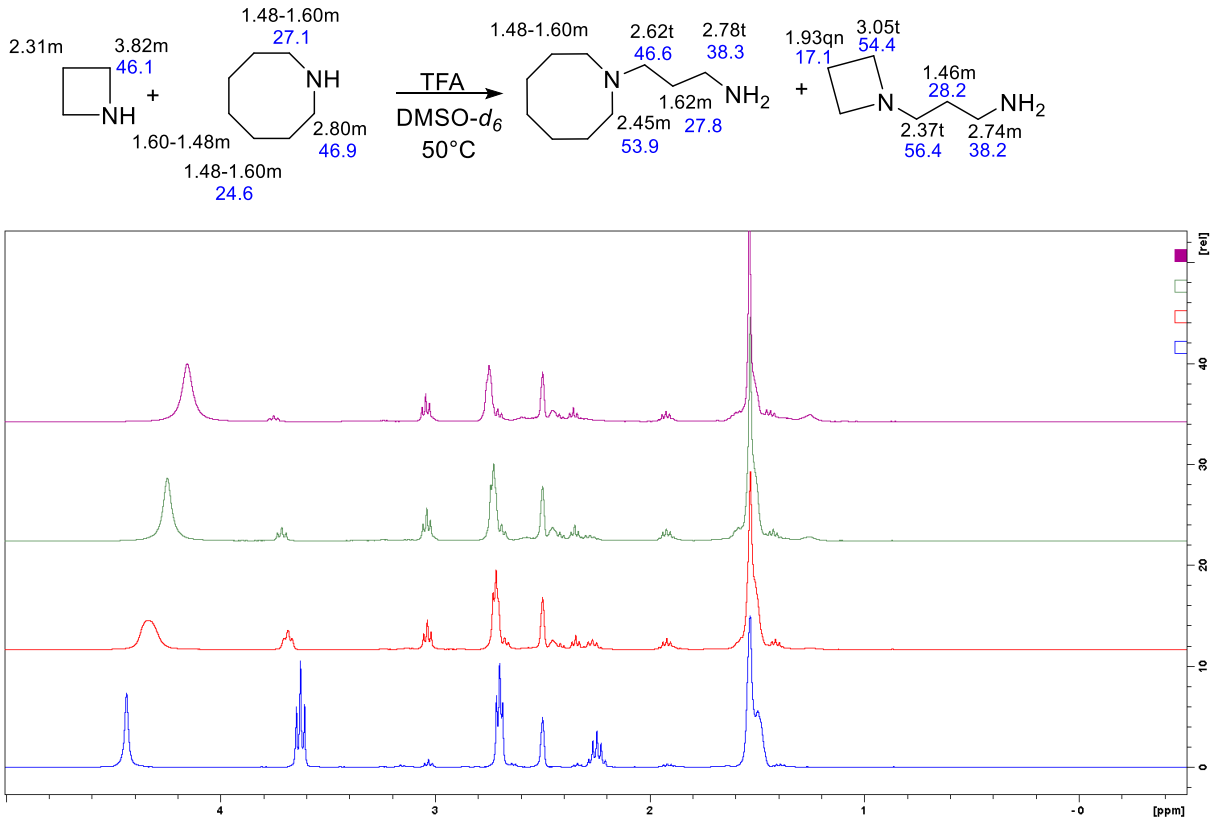


Figure S67. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + octahydroazocine (1.0 eq) + TFA at 50°C.

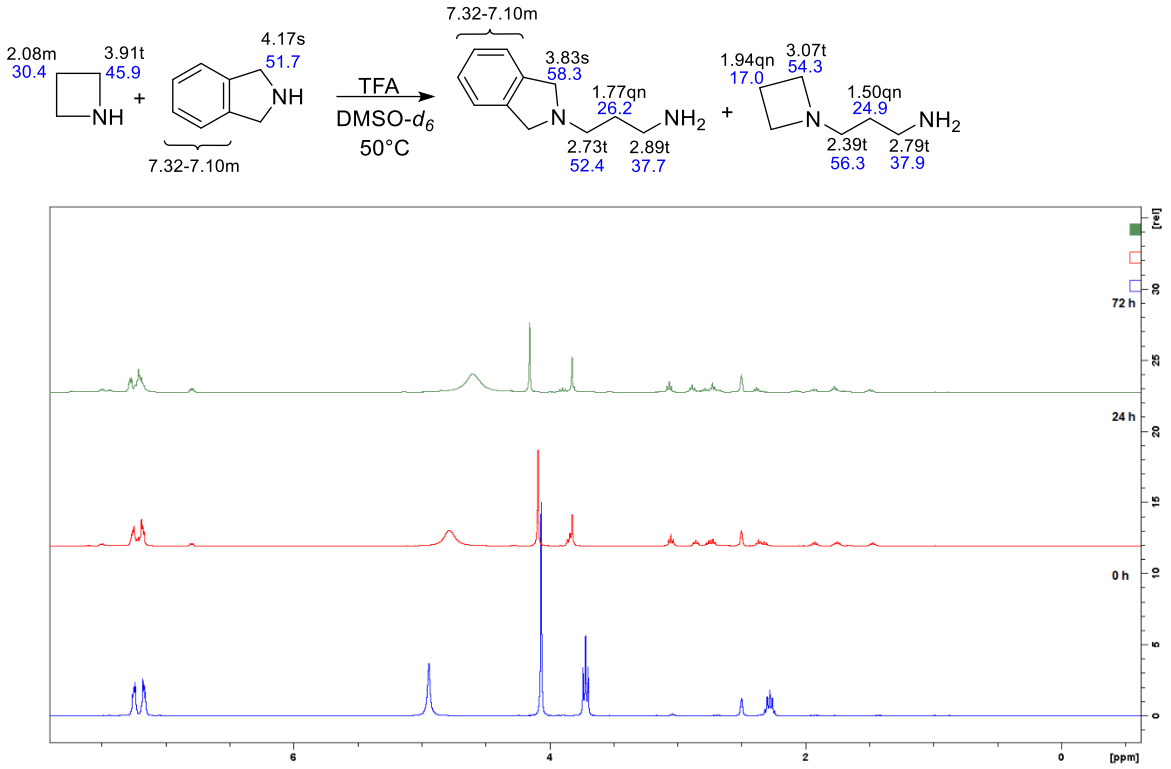


Figure S68. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + isoindoline (1.0 eq) + TFA at 50°C.

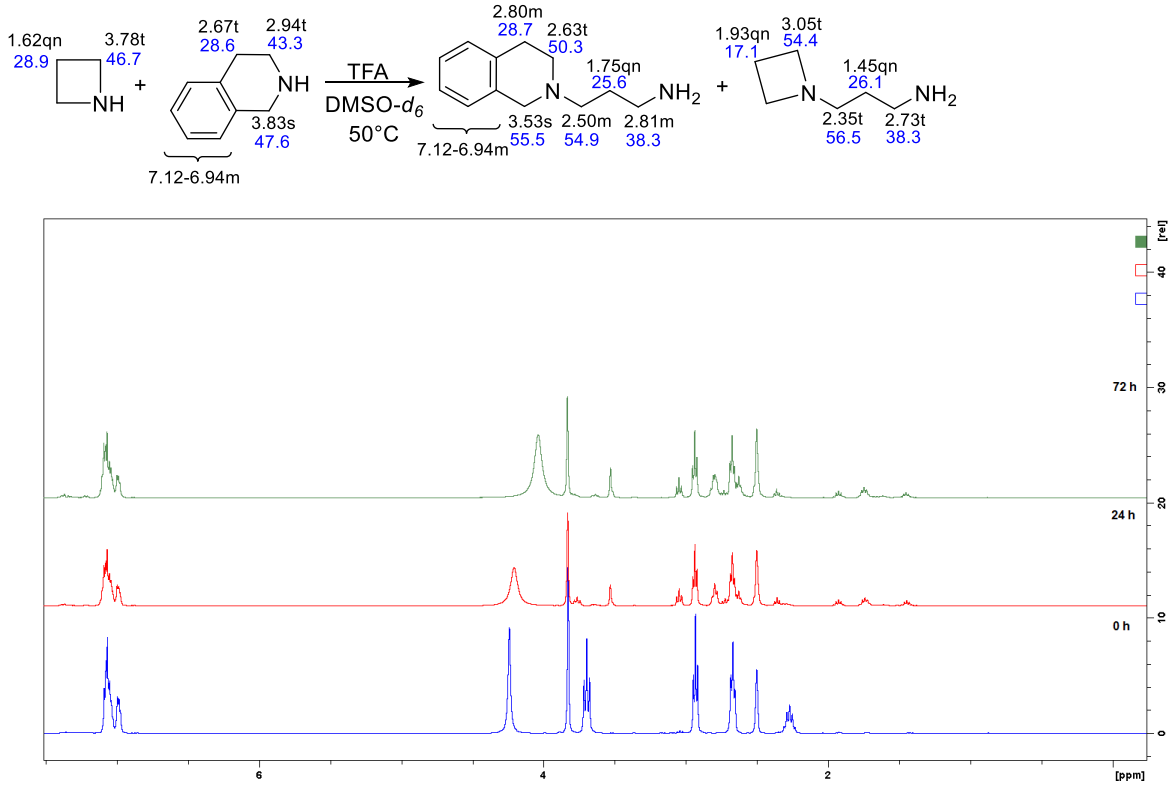


Figure S69. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of azetidine + 1,2,3,4-tetrahydroisoquinoline (1.0 eq) + TFA at 50°C.

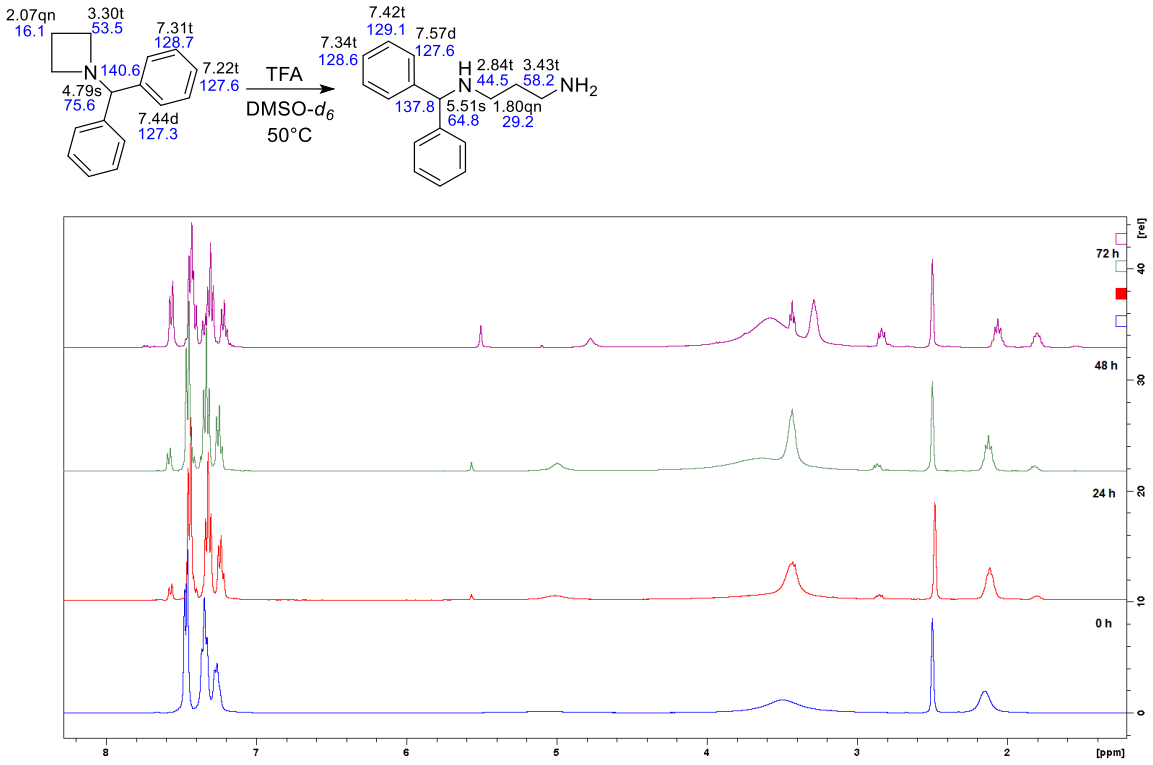


Figure S70. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of 1-(diphenylmethyl)azetidine + TFA at 50°C.

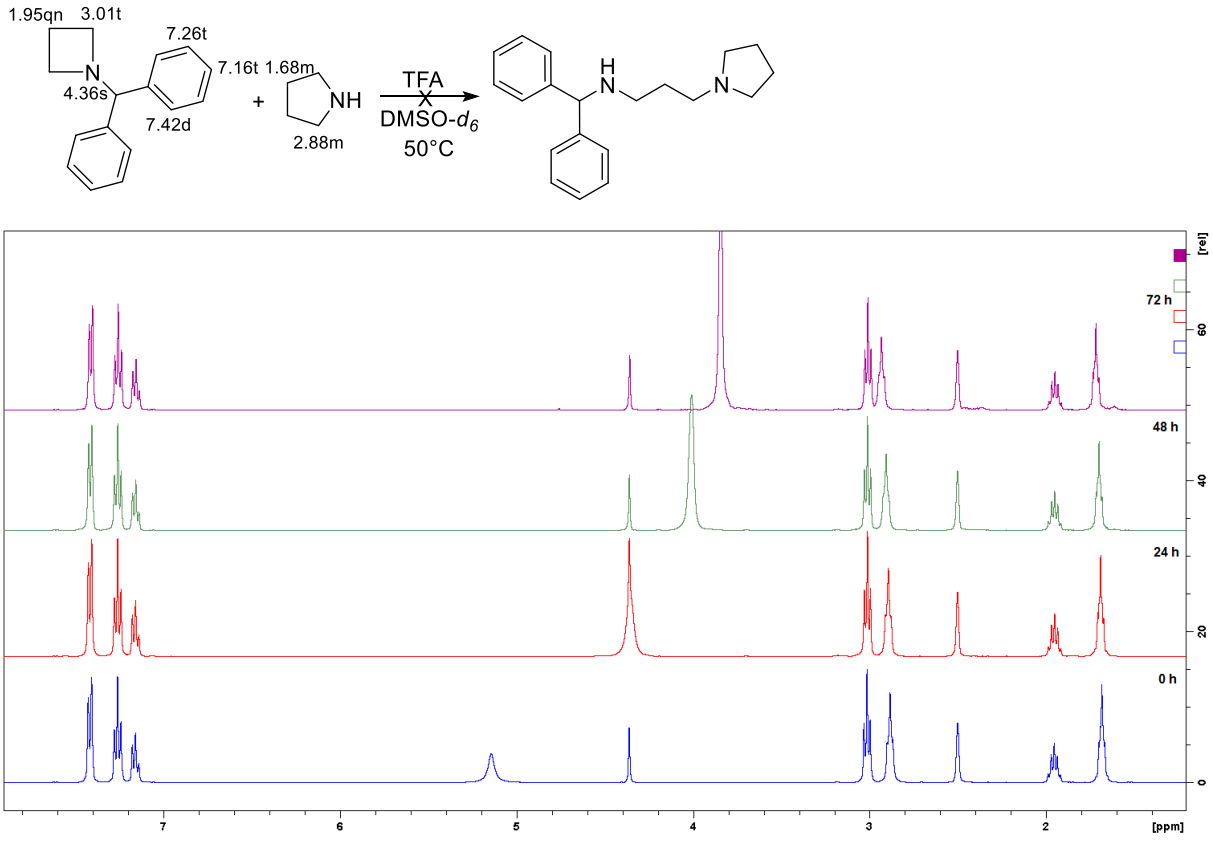


Figure S71. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of 1-(diphenylmethyl)azetidine + pyrrolidine (1.0 eq) + TFA at 50°C.

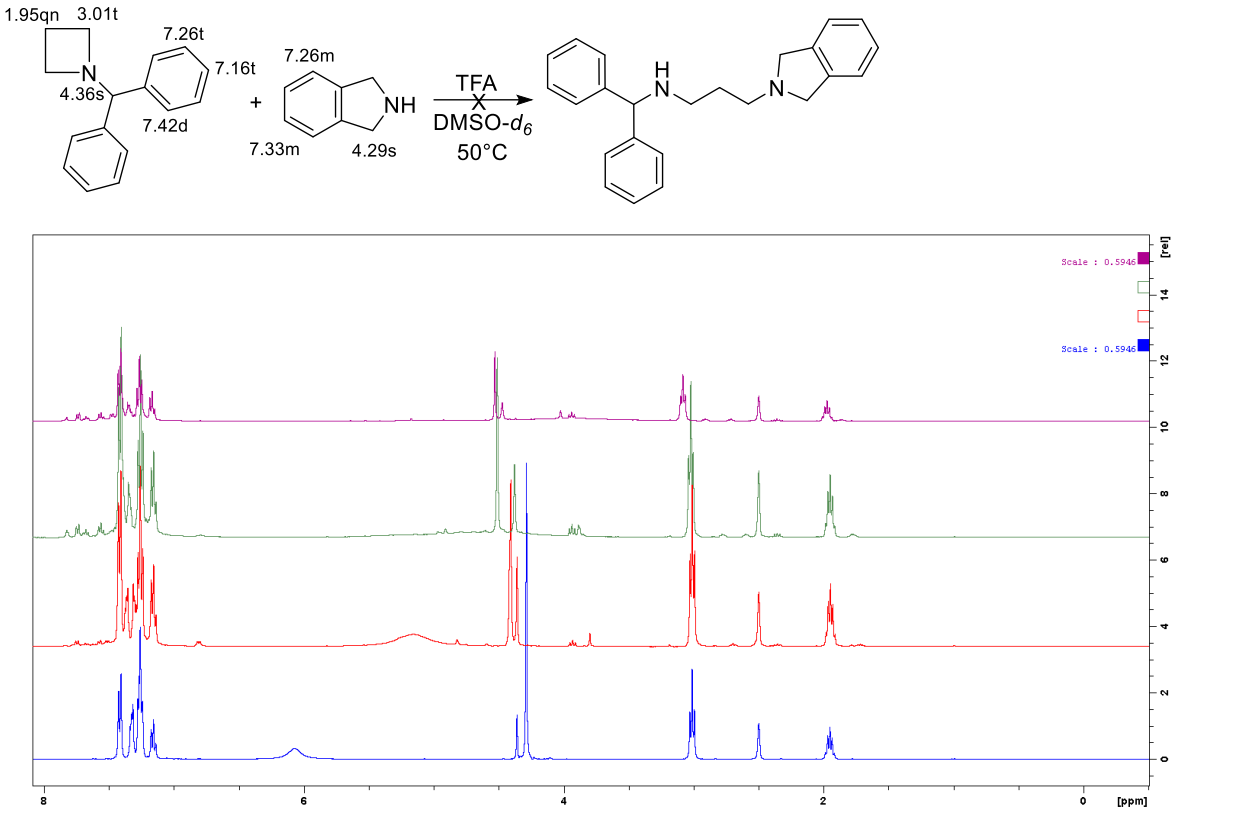


Figure S72. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of 1-(diphenylmethyl)azetidine + pyrrolidine (1.0 eq) + TFA at 50°C.

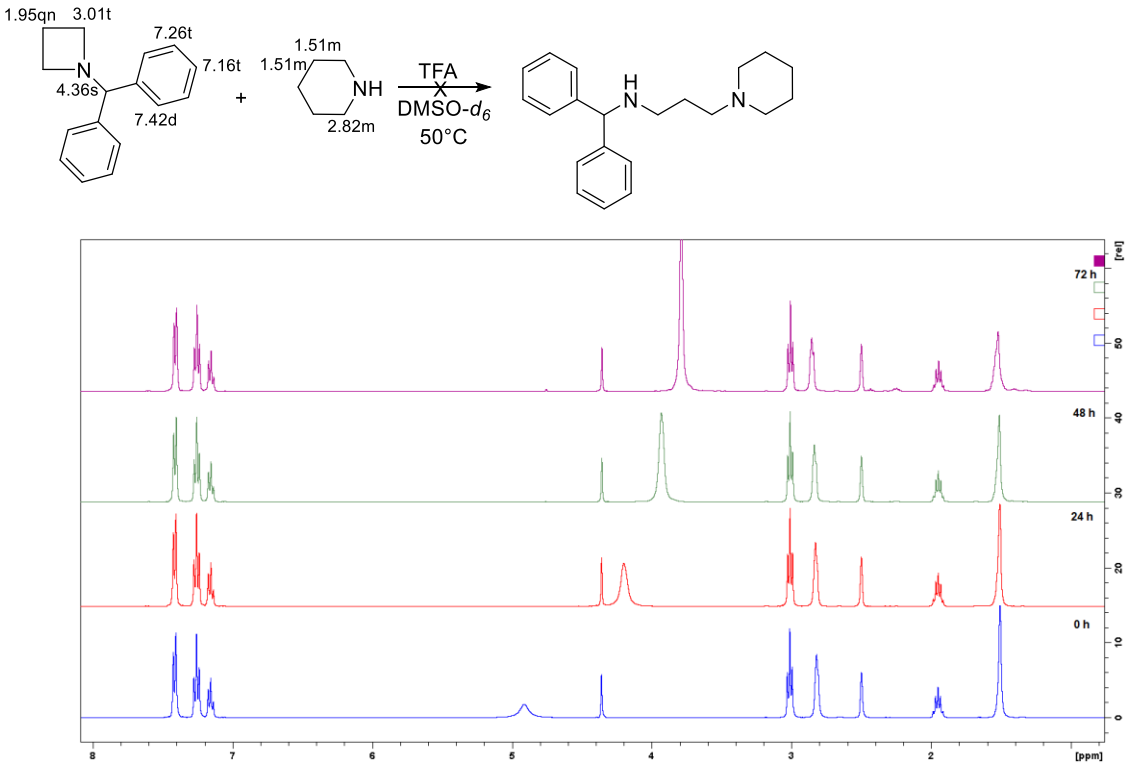


Figure S73. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of 1-(diphenylmethyl)azetidine + piperidine (1.0 eq) + TFA at 50°C.

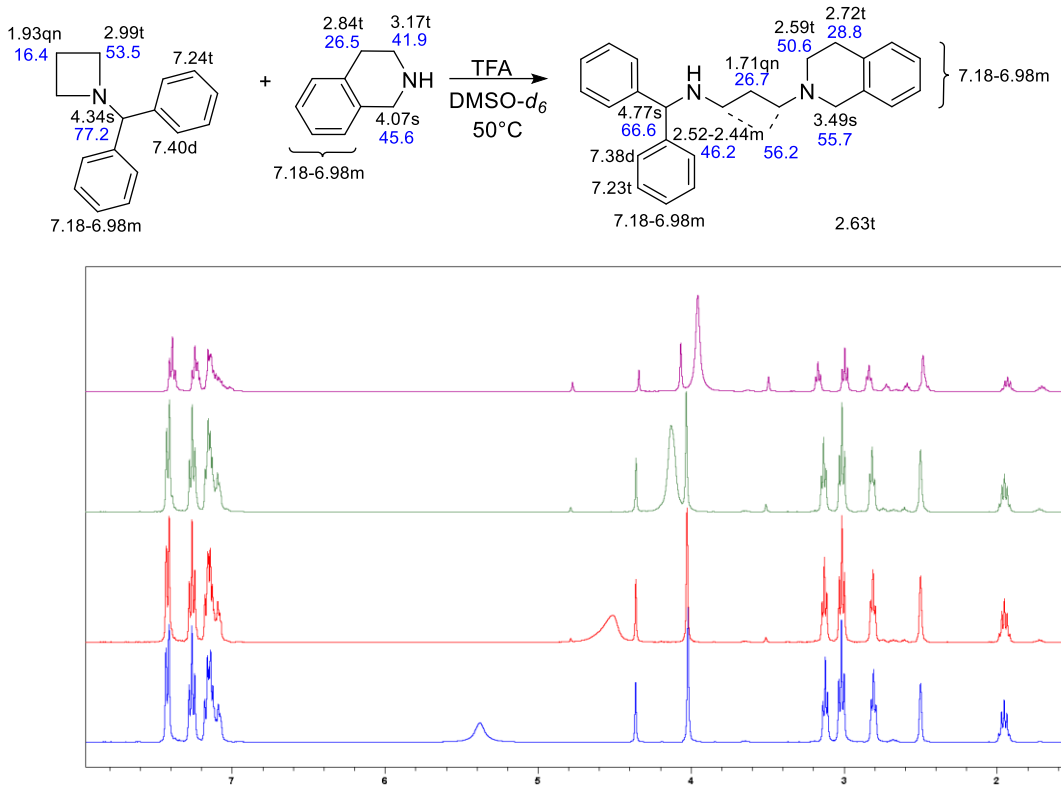


Figure S74. ^{1}H NMR (400 MHz, DMSO-d_6) monitoring of 1-(diphenylmethyl)azetidine + 1,2,3,4-tetrahydroisoquinoline (1.0 eq) + TFA at 50°C.

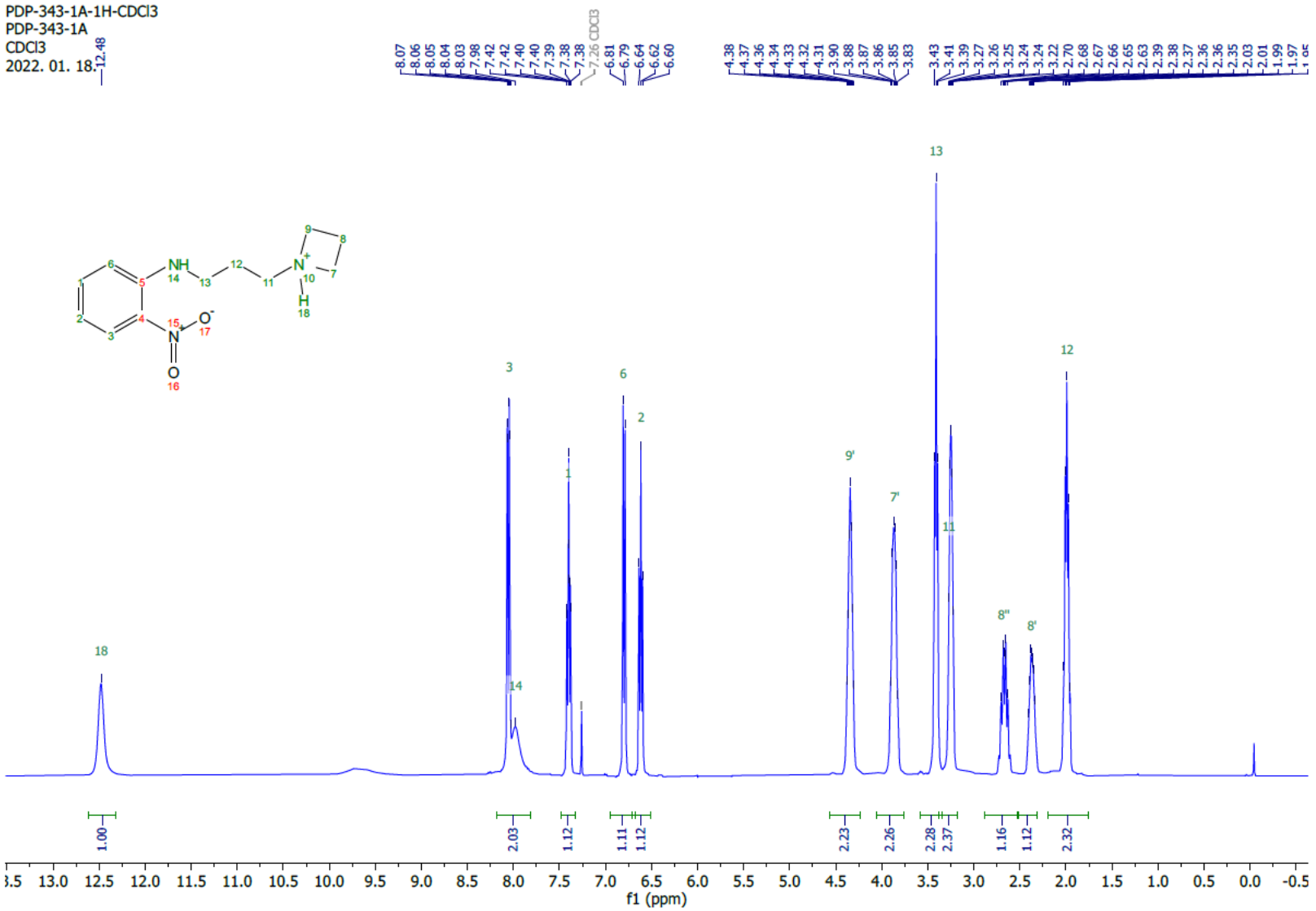


Figure S75: ^{1}H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-nitroaniline TFA salt (**10**) recorded at 400 MHz in $CDCl_3$.

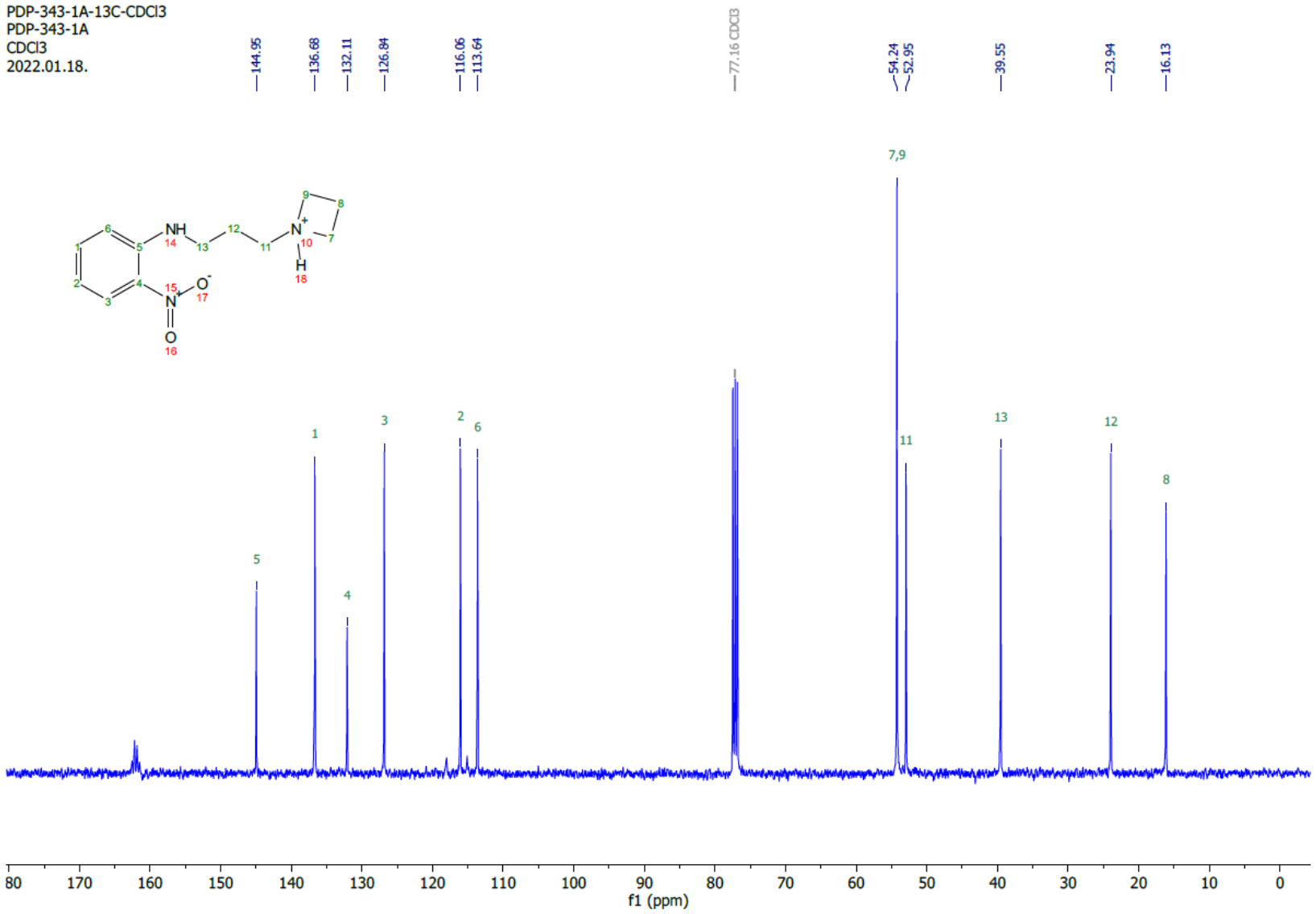


Figure S76: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-nitroaniline TFA salt (**10**) recorded at 400 MHz in $CDCl_3$.

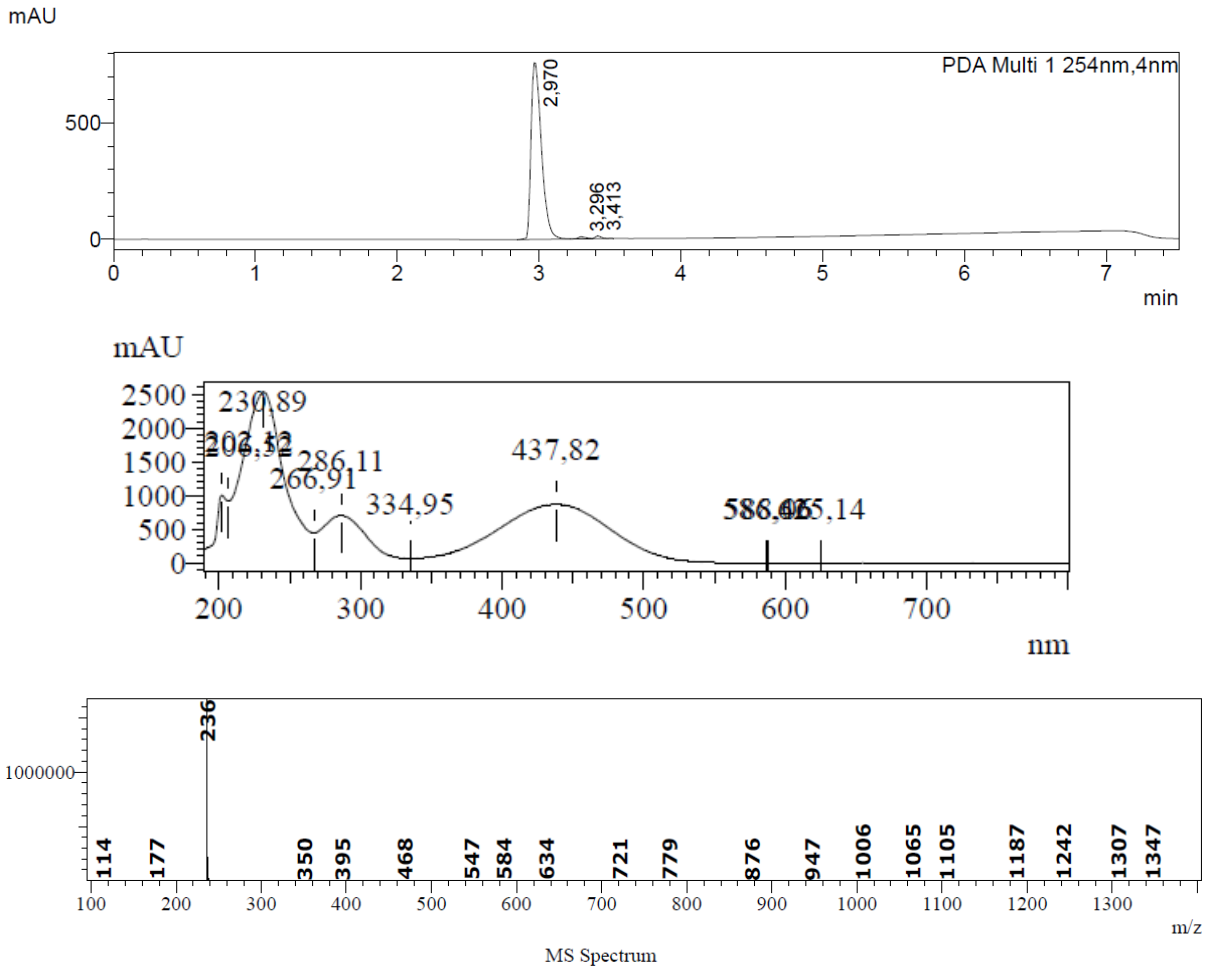


Figure S77.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(azetidin-1-yl)propyl]-2-nitroaniline TFA salt (**10**).

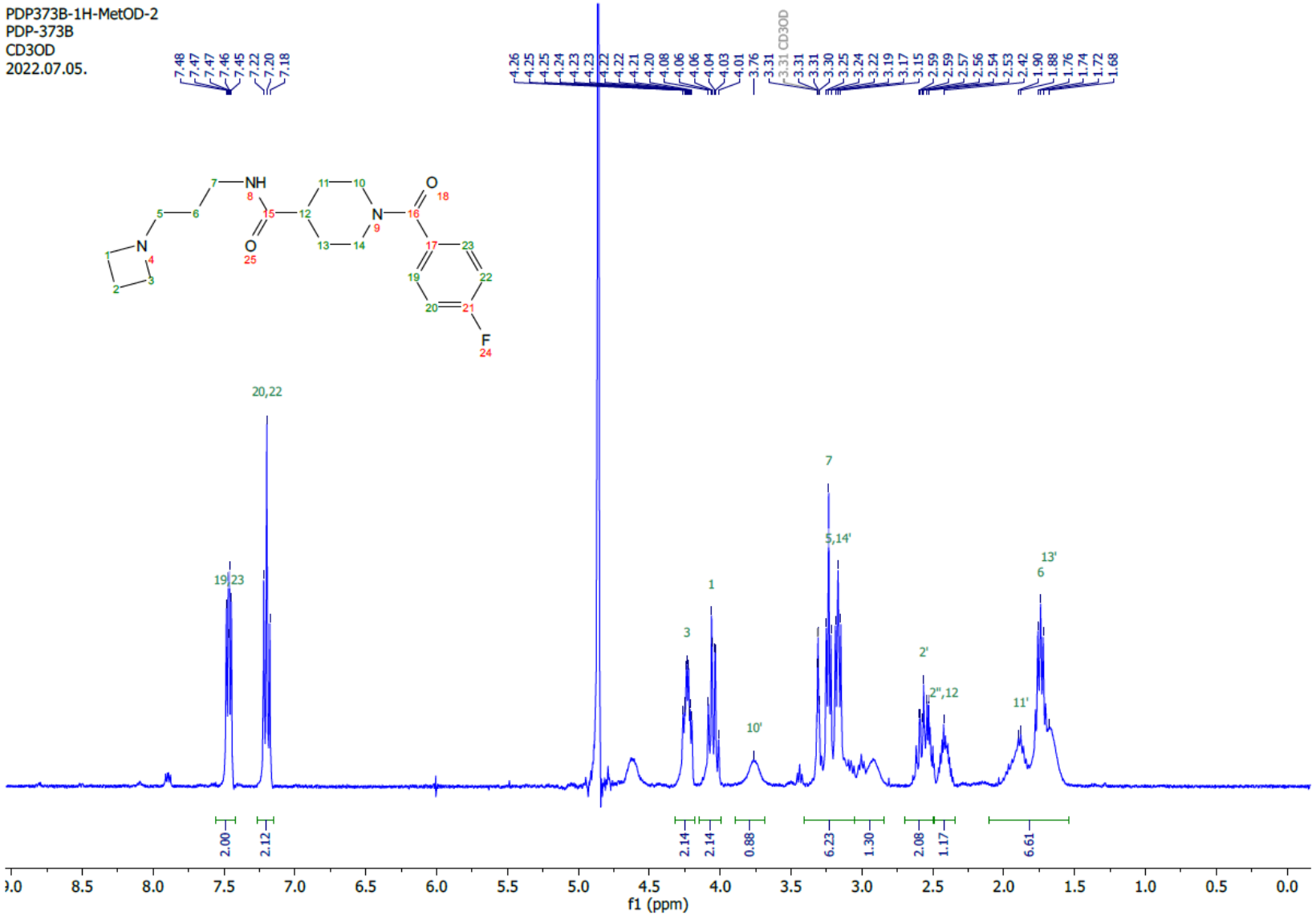


Figure S78: ^{1}H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-1-(4-fluorobenzoyl)piperidine-3-carboxamide TFA salt (**12**) recorded at 400 MHz in CD_3OD.

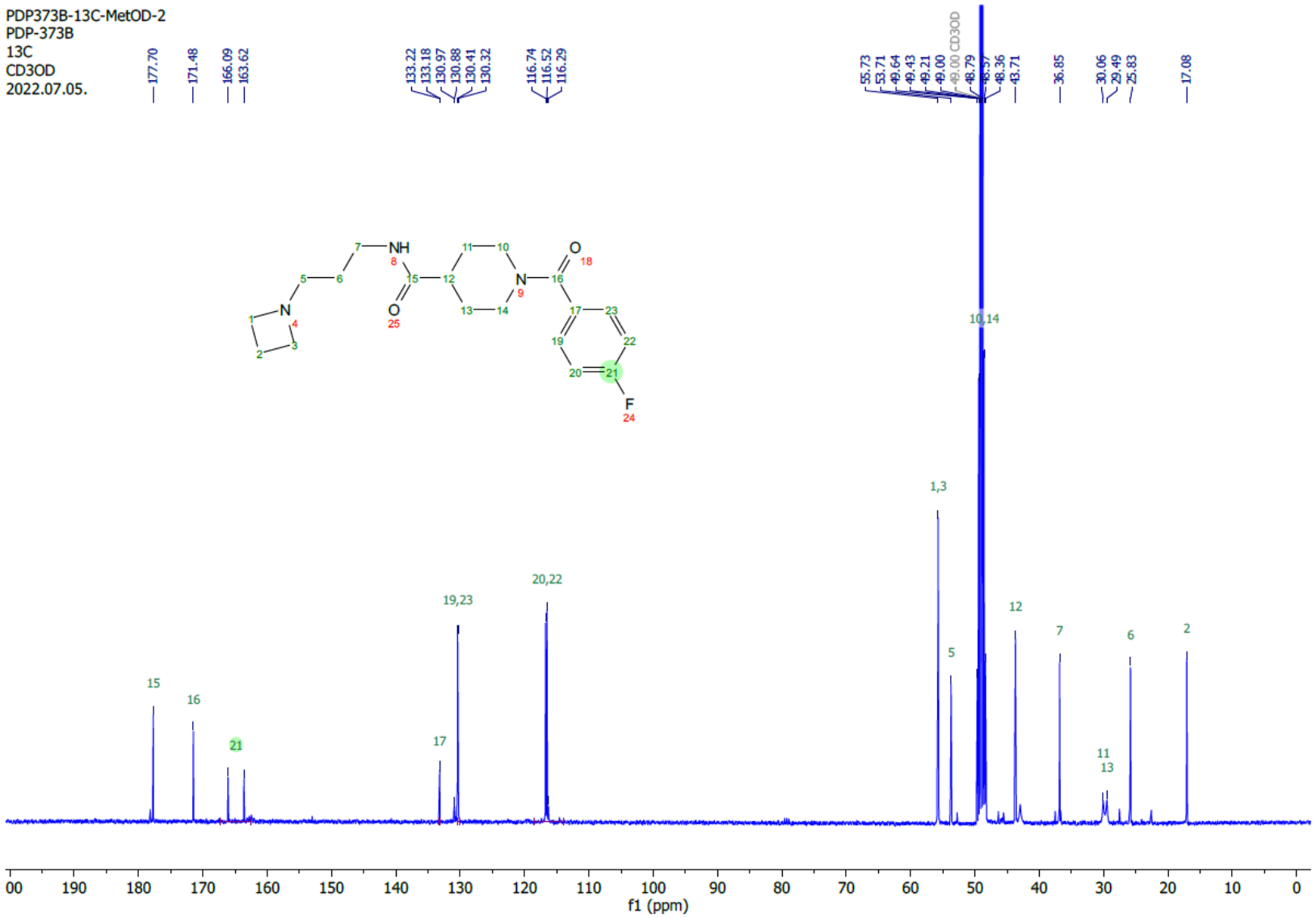


Figure S79: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]-1-(4-fluorobenzoyl)piperidine-3-carboxamide TFA salt (**12**) recorded at 400 MHz in $CDCl_3$.

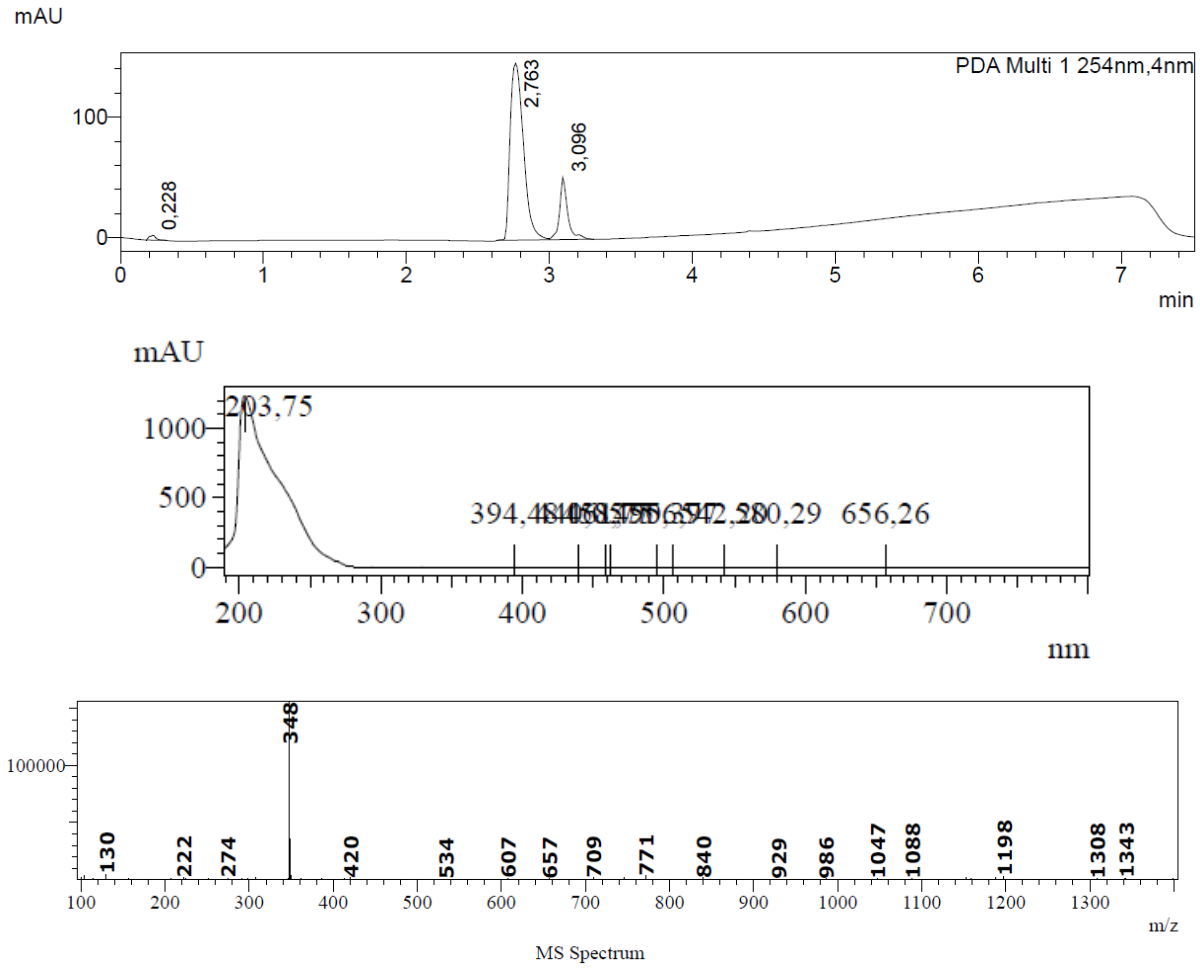


Figure S80: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(azetidin-1-yl)propyl]-1-(4-fluorobenzoyl)piperidine-3-carboxamide TFA salt (**12**).

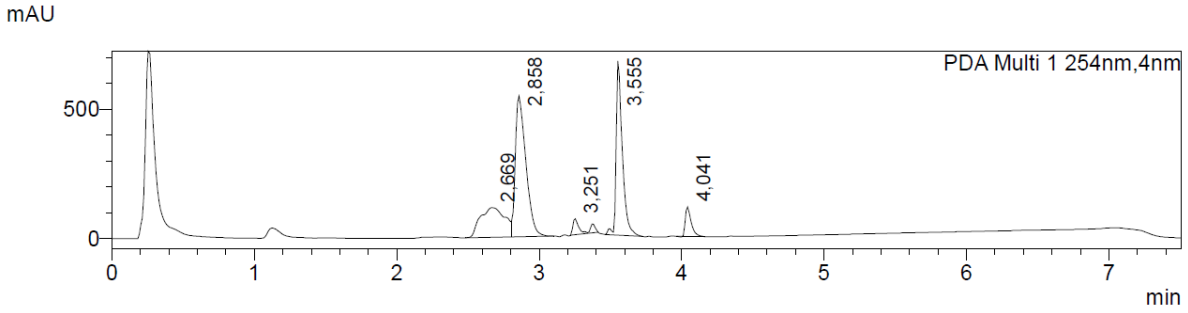


Figure S81. HPLC chromatogram of the crude reaction mixture (reaction with 5-chloro-3a*H*-thieno[2,3-*b*]pyrrole-4-sulfonyl chloride (**14**)).

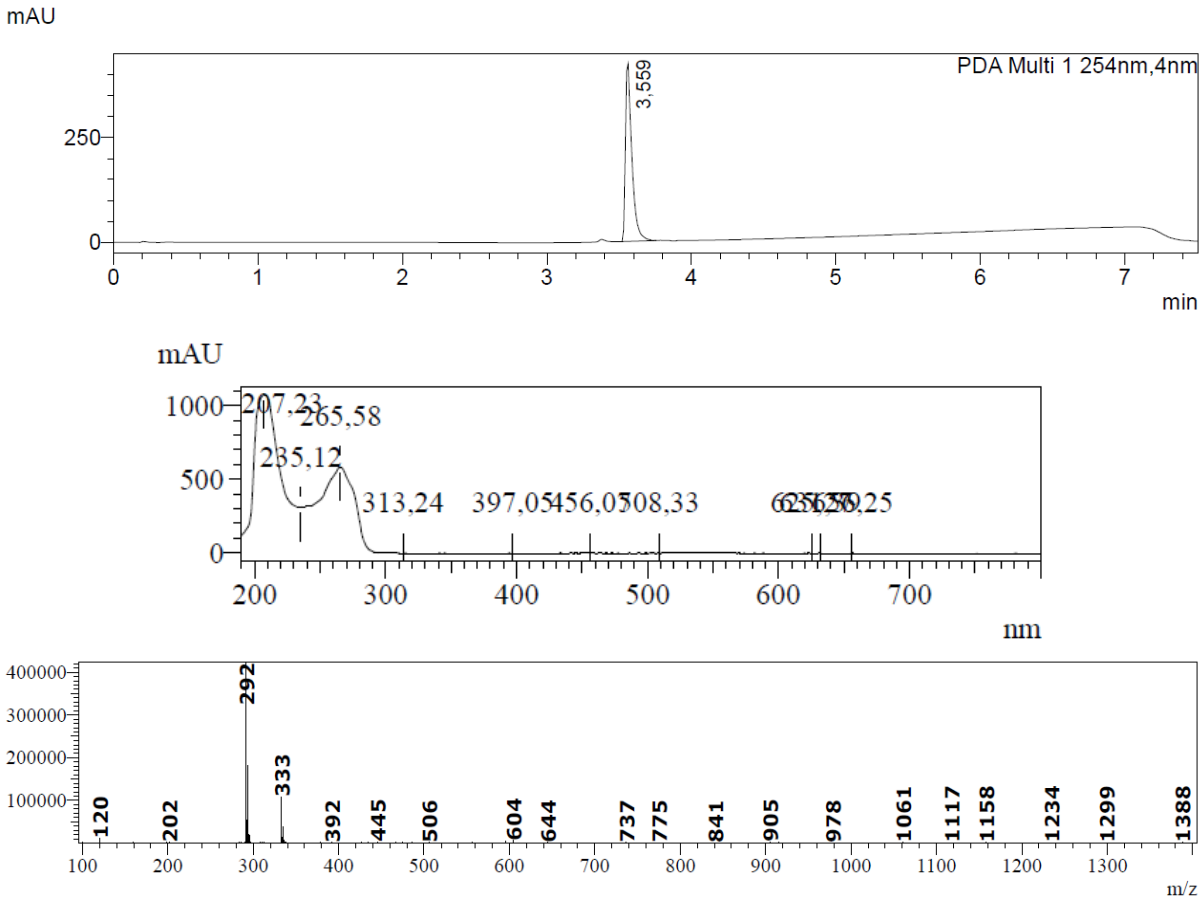
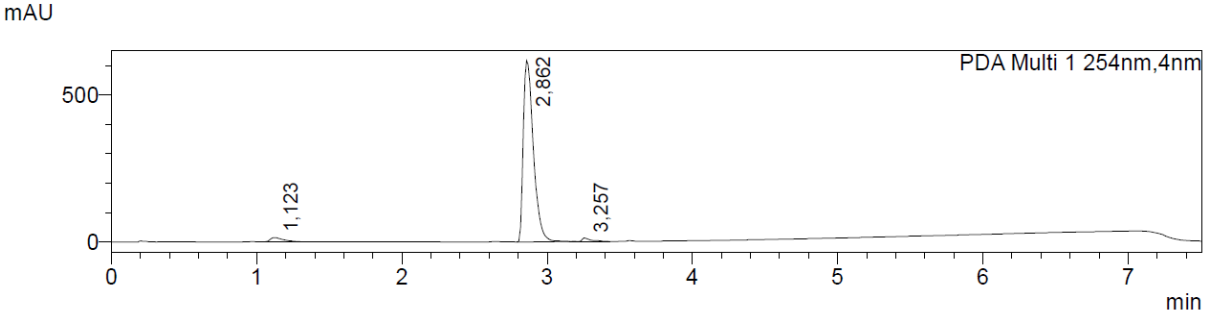


Figure S82: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of 6-chloro-5-(pyrrolidine-1-sulfonyl)imidazo[2,1-*b*][1,3]thiazole (**15**).



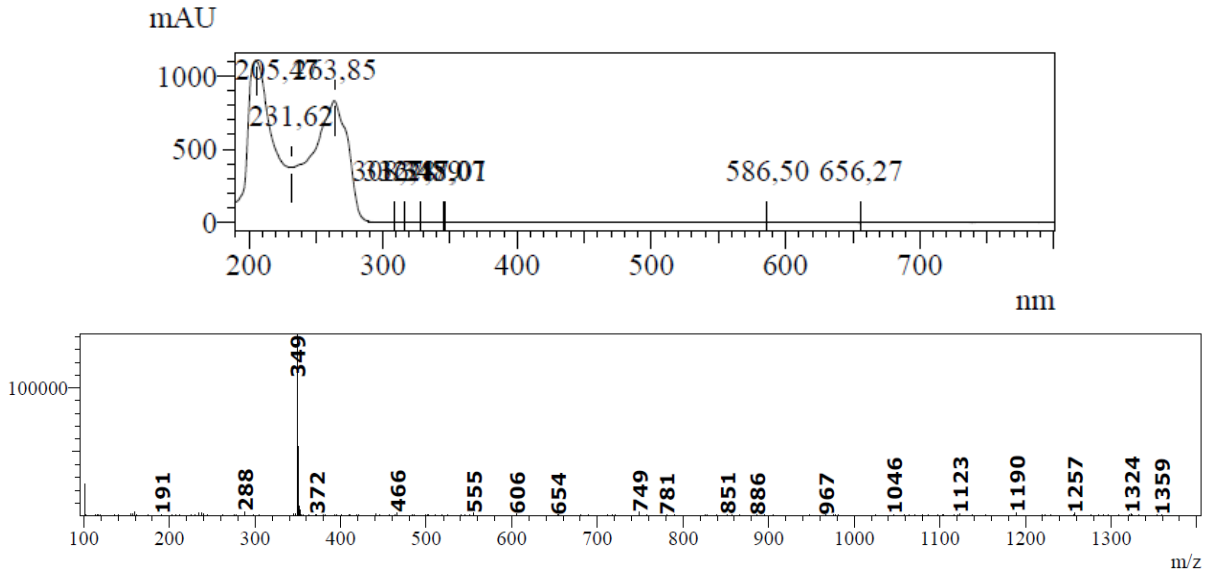


Figure S83.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of 6-chloro-*N*-[3-(pyrrolidin-1-yl)propyl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide TFA salt (**17**).

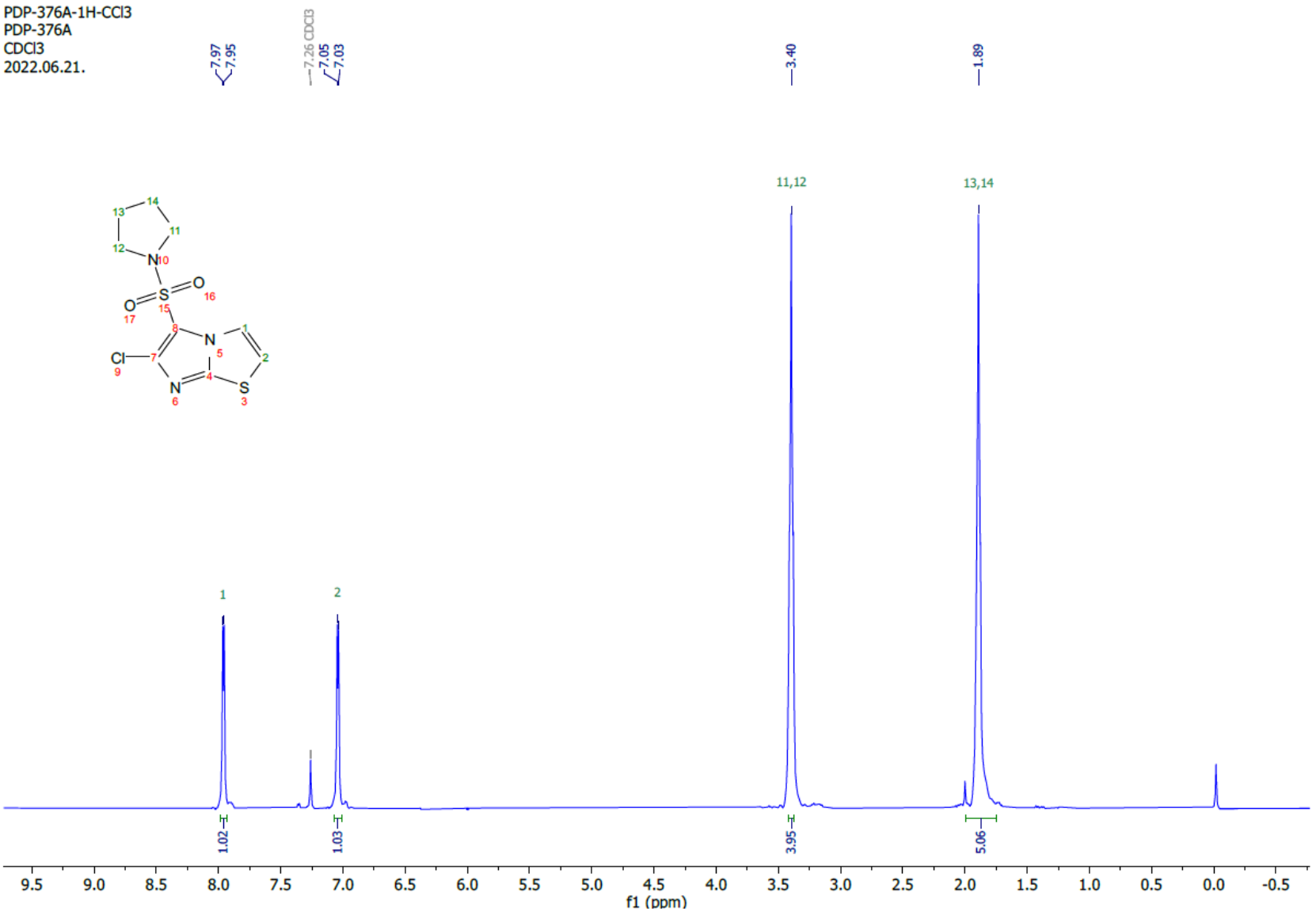


Figure S84: ^{1}H NMR spectrum of 6-chloro-5-(pyrrolidine-1-sulfonyl)imidazo[2,1-*b*][1,3]thiazole (**15**) recorded at 400 MHz in $CDCl_3$.

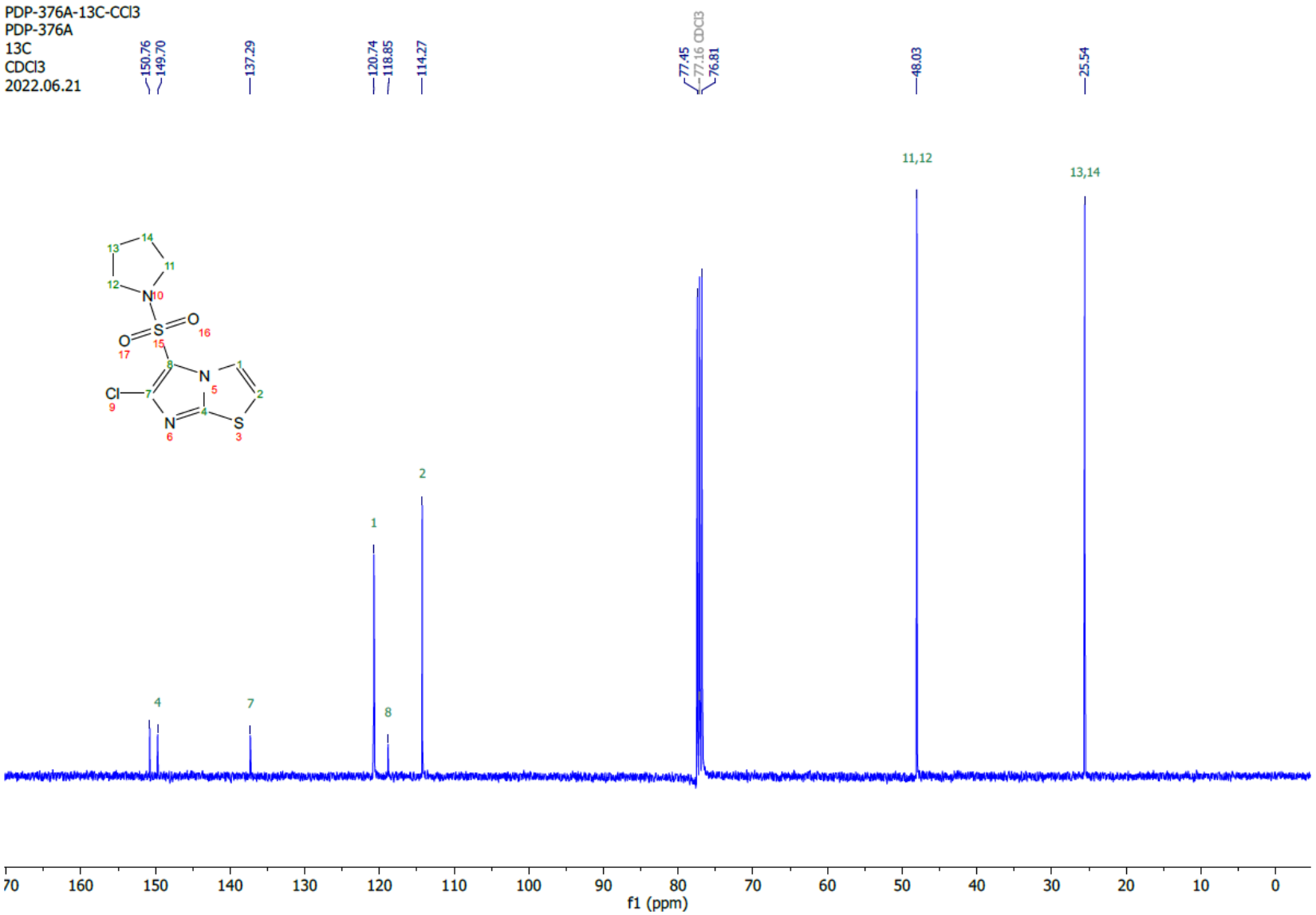


Figure S85: ^{13}C NMR spectrum of 6-chloro-5-(pyrrolidine-1-sulfonyl)imidazo[2,1-*b*][1,3]thiazole (**15**) recorded at 400 MHz in $CDCl_3$.

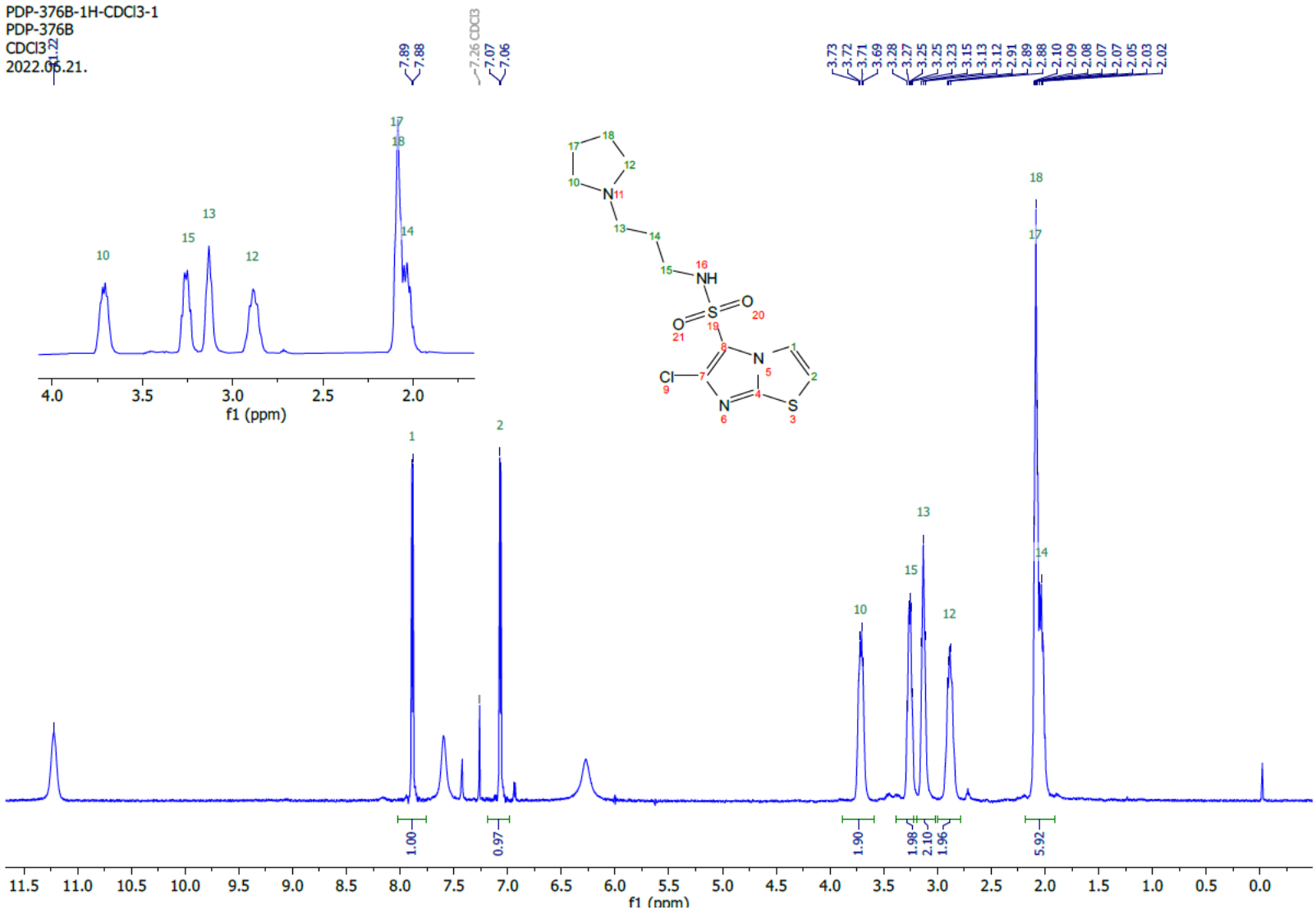


Figure S86: ^{1}H NMR spectrum of 6-chloro-*N*-[3-(pyrrolidin-1-yl)propyl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide TFA salt (**17**) recorded at 400 MHz in $CDCl_3$.

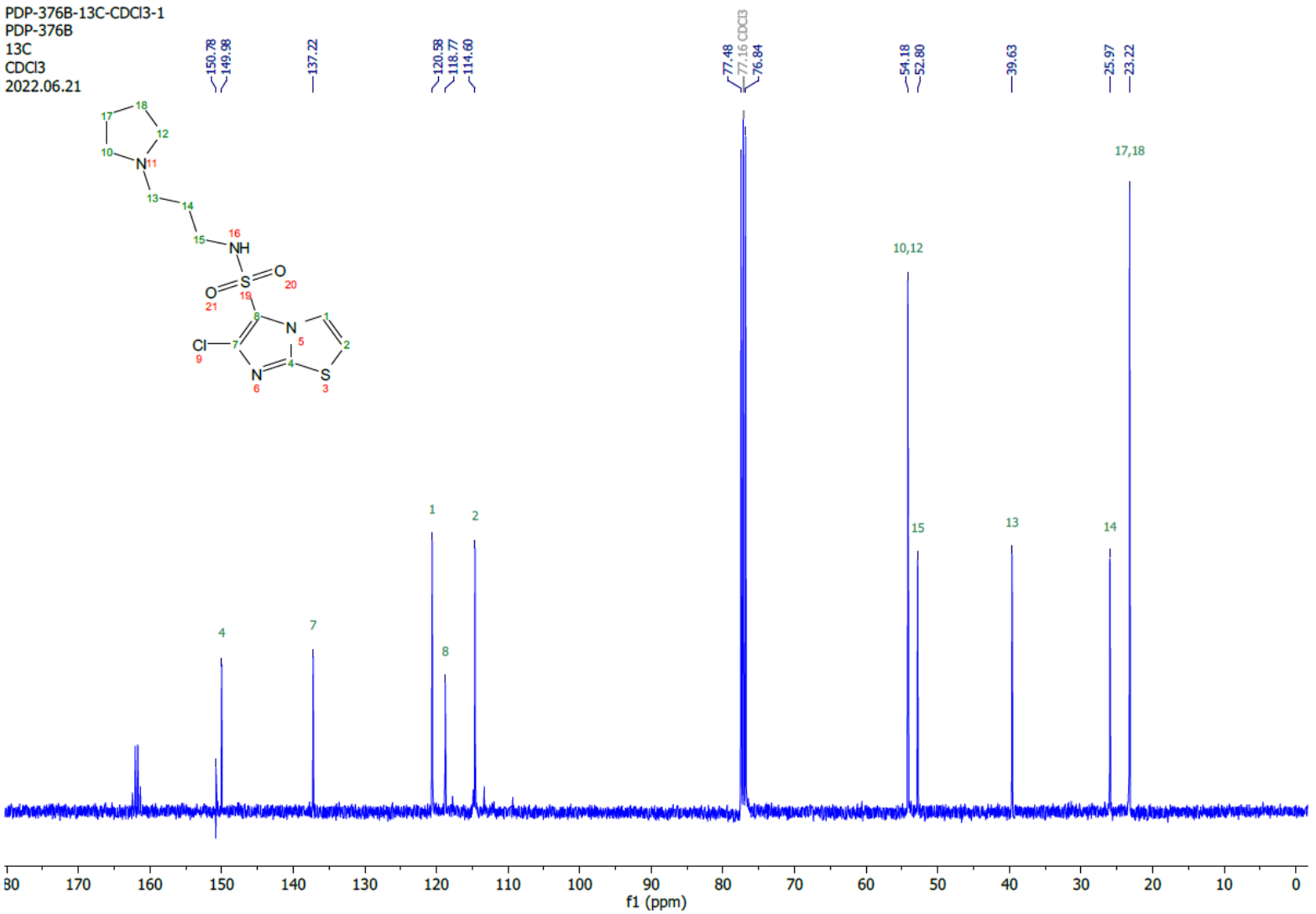


Figure S87: ^{13}C NMR spectrum of 6-chloro-*N*-[3-(pyrrolidin-1-yl)propyl]imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide TFA salt (**17**) recorded at 400 MHz in $CDCl_3$.

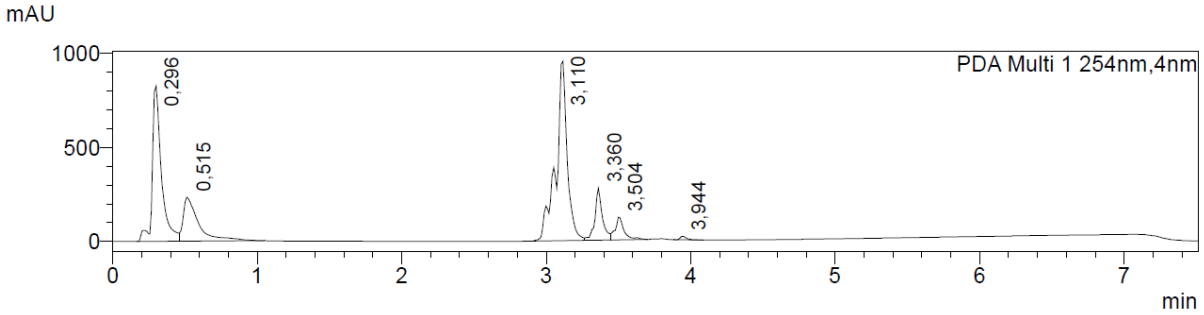


Figure S88. HPLC chromatogram of the crude reaction mixture (amide formation with quinoline-2-carboxylic acid (**18**)).

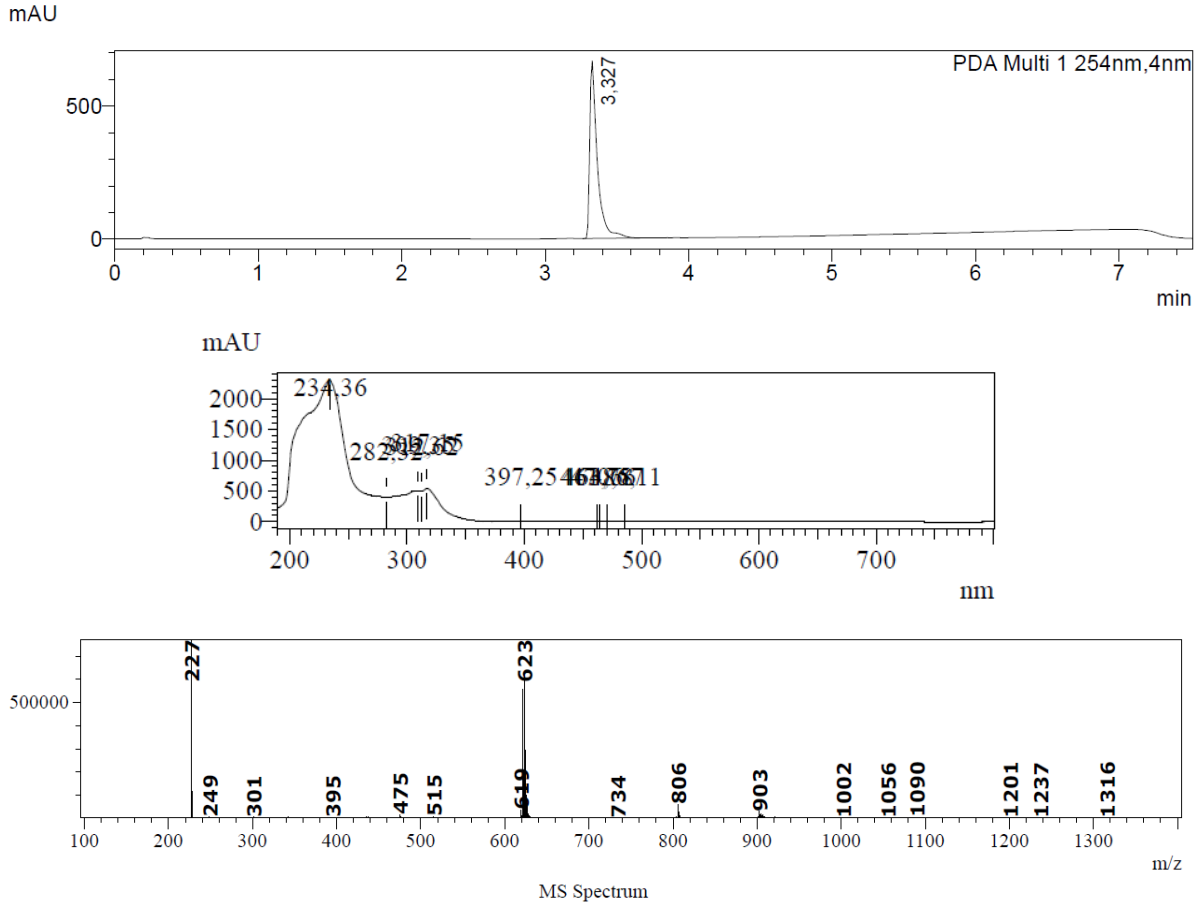
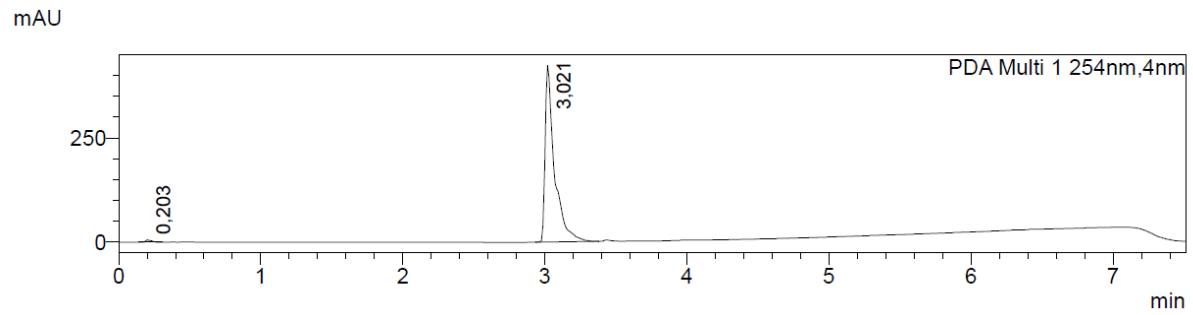


Figure S89.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of (pyrrolidin-1-yl)(quinolin-2-yl)methanone (**19**).



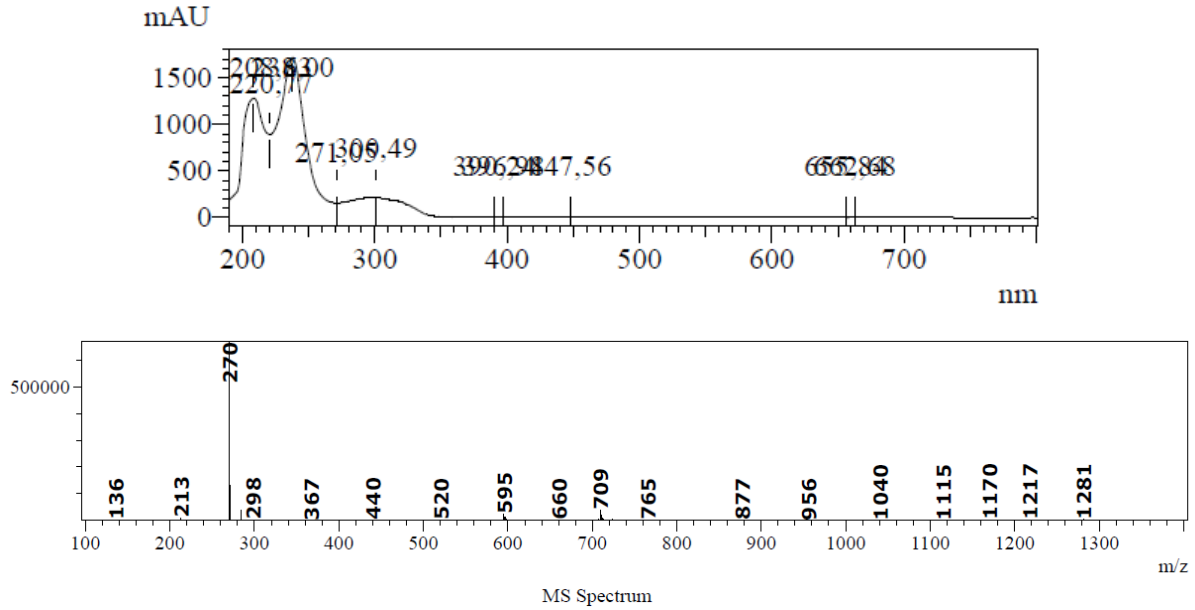


Figure S90. HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(azetidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**20**).

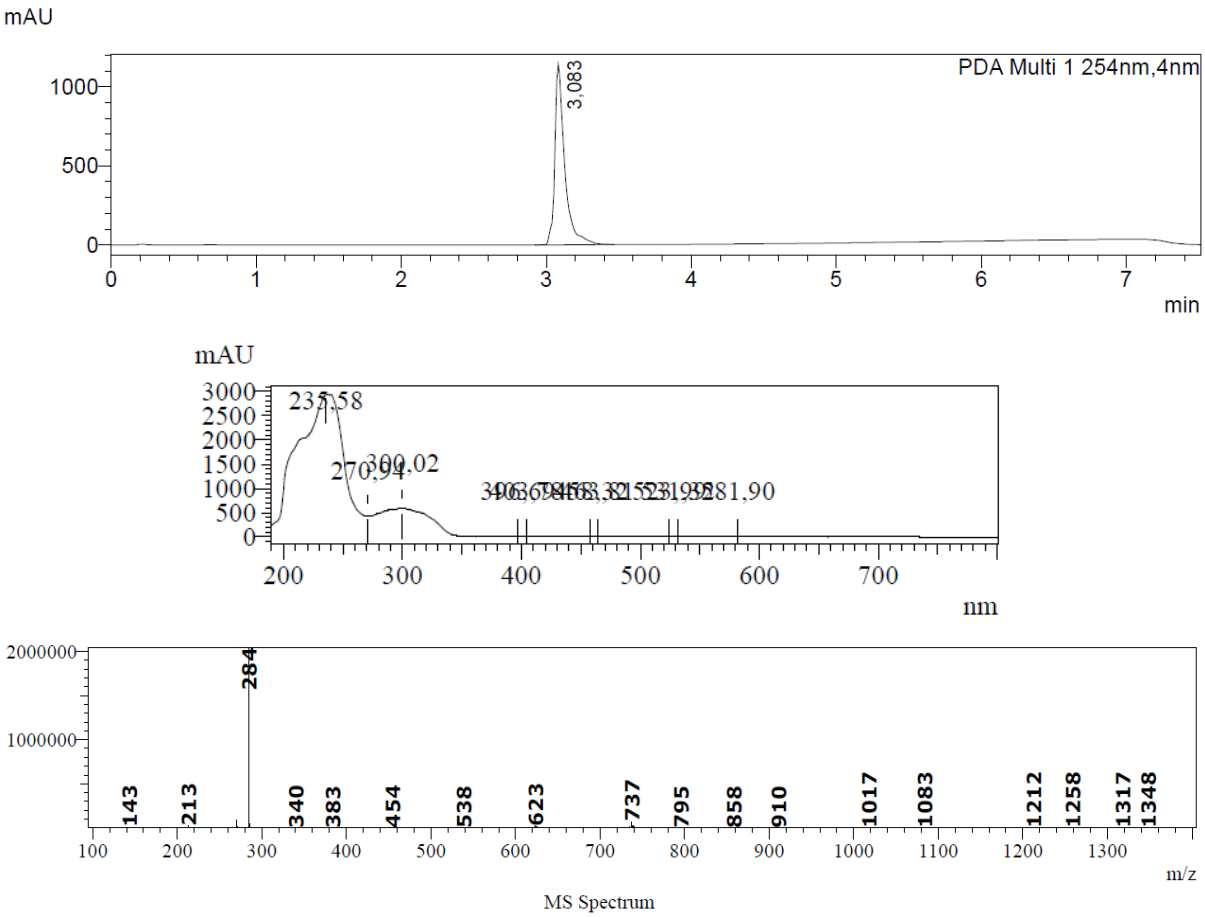


Figure S91.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(pyrrolidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**21**).

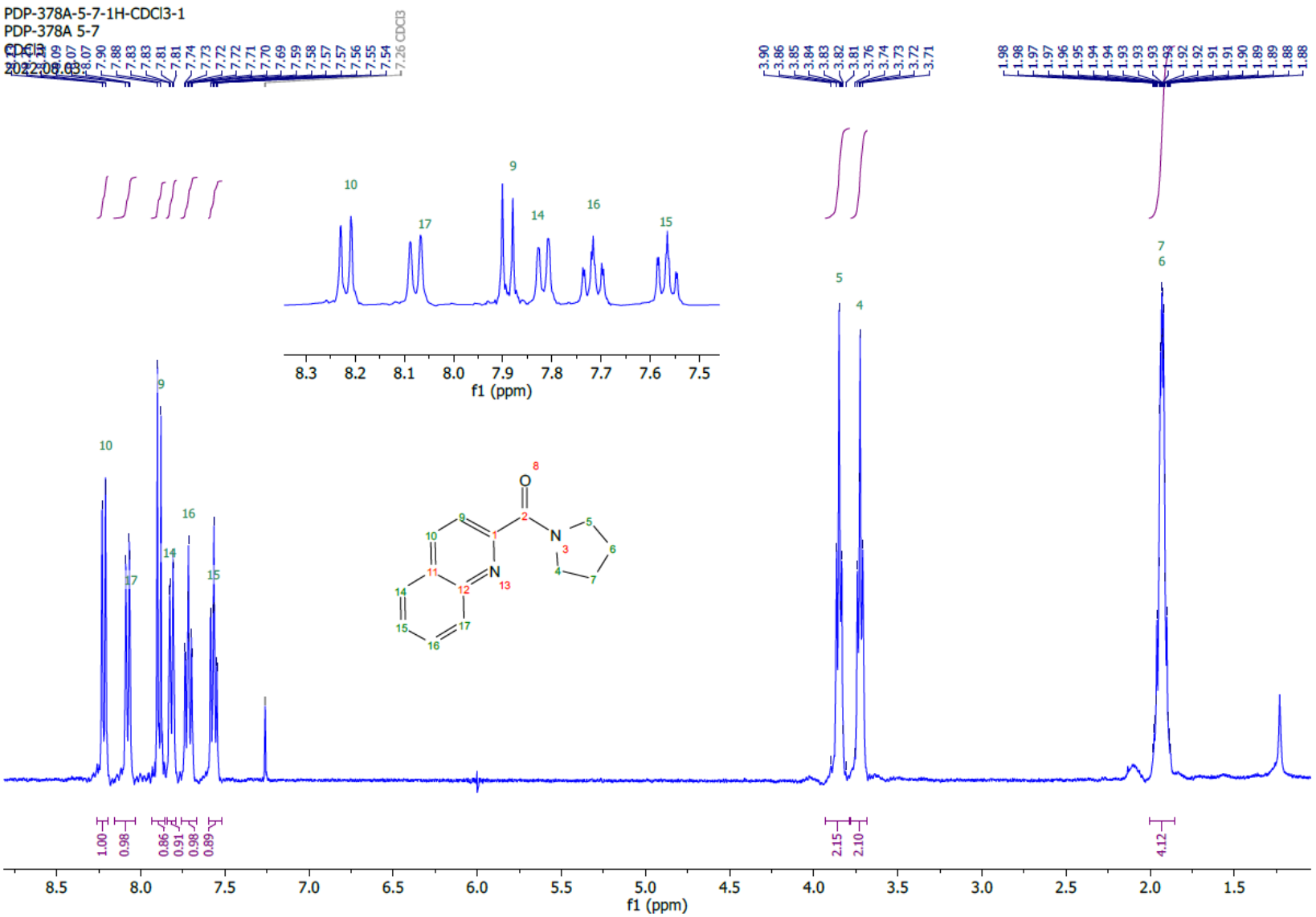


Figure S92: ^{1}H NMR spectrum of (pyrrolidin-1-yl)(quinolin-2-yl)methanone (**19**) recorded at 400 MHz in $CDCl_3$.

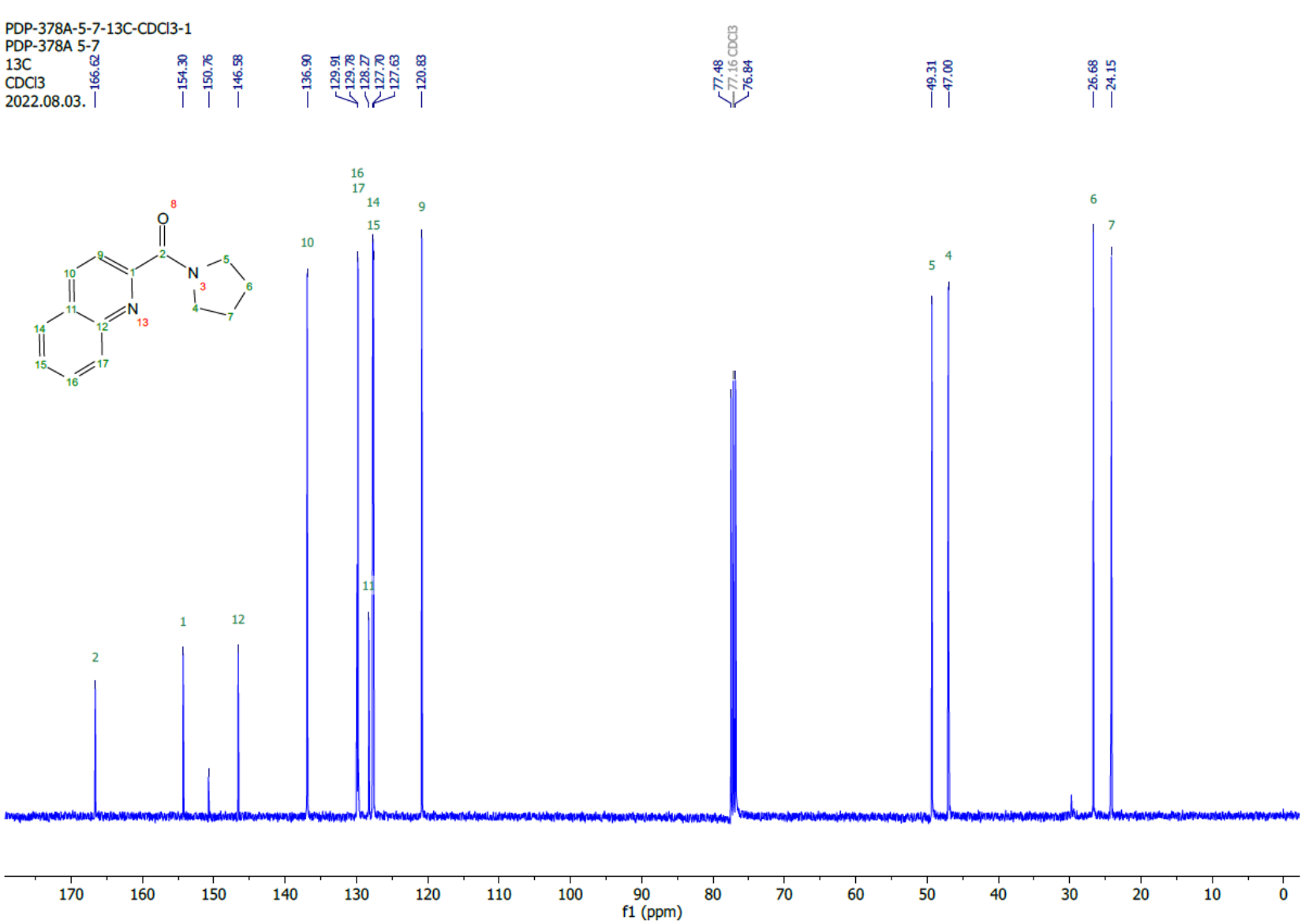


Figure S93. ^{13}C NMR spectrum of (pyrrolidin-1-yl)(quinolin-2-yl)methanone (**19**) recorded at 400 MHz in $CDCl_3$.

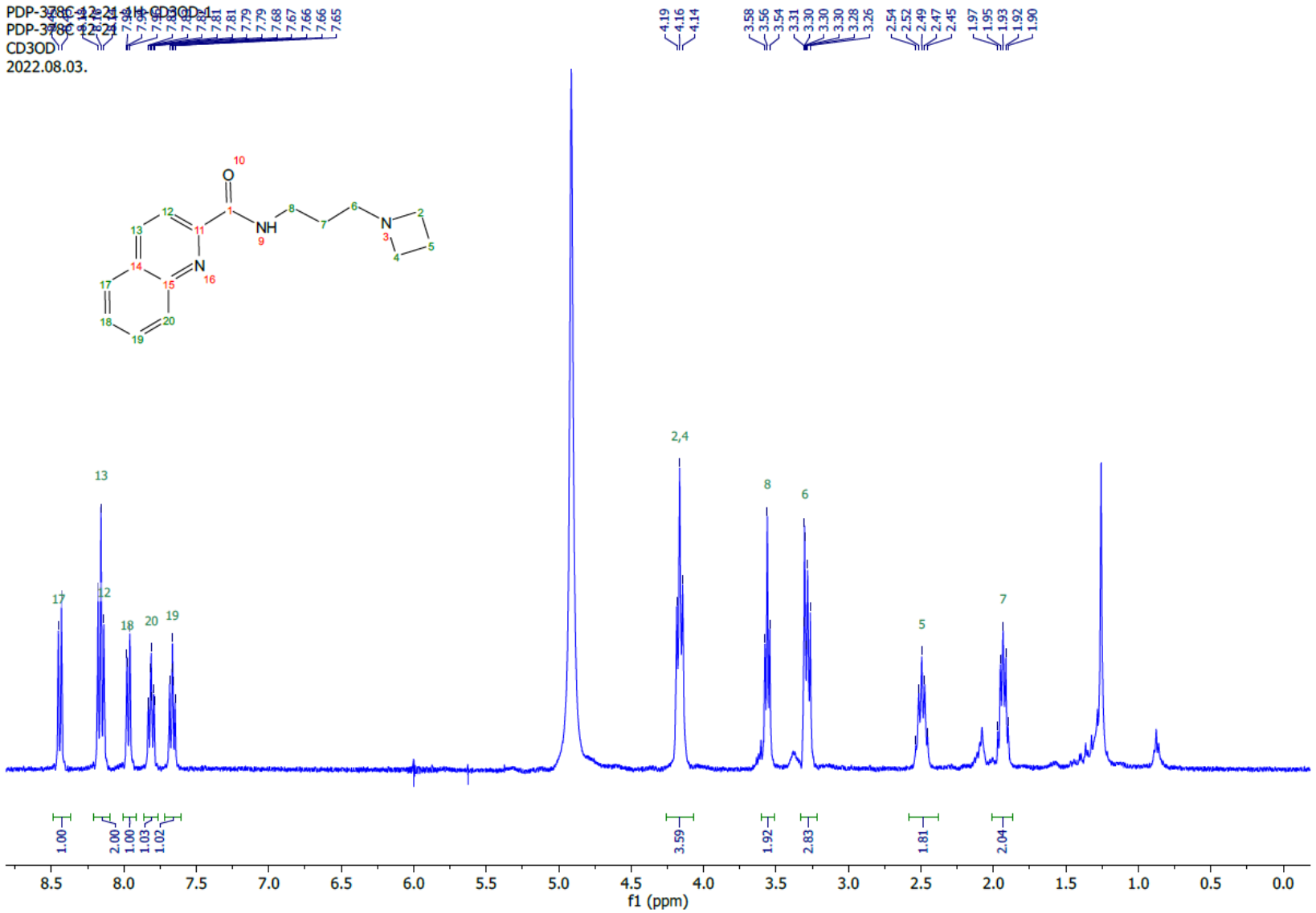


Figure S94. ^{1}H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**20**) recorded at 400 MHz in $CDCl_3$.

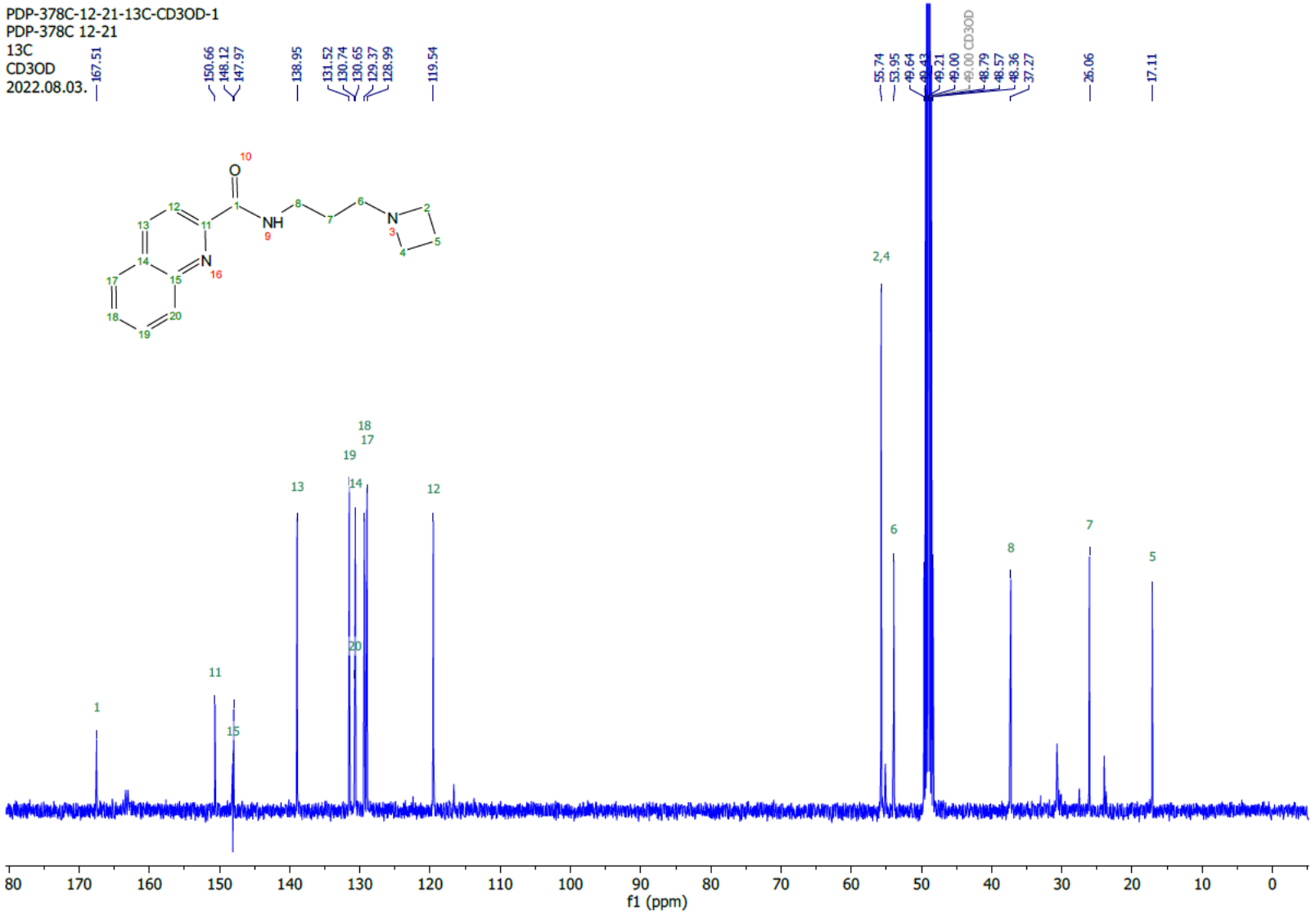


Figure S95: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**20**) recorded at 400 MHz in $CDCl_3$.

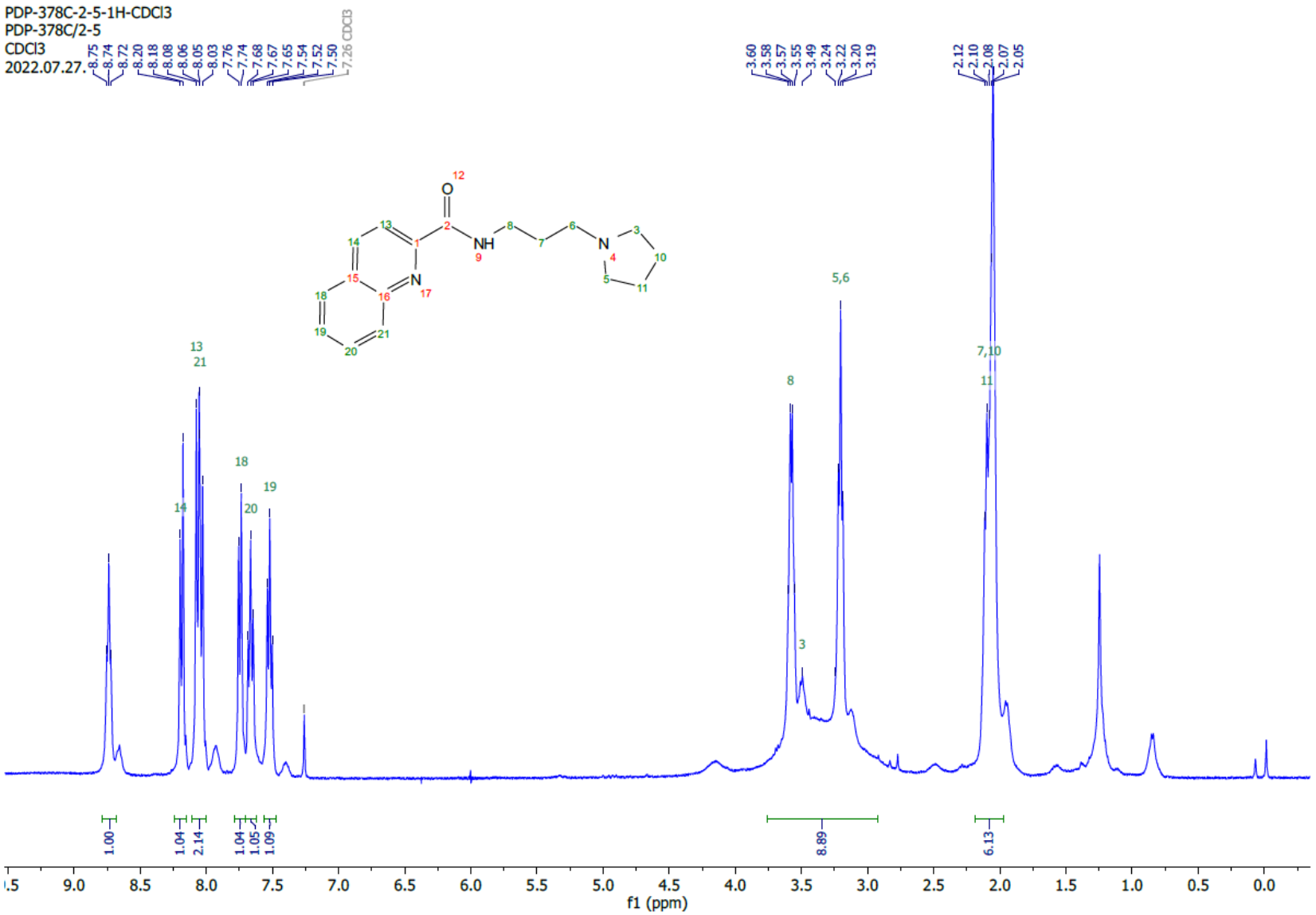


Figure S96: ^{1}H NMR spectrum of *N*-[3-(pyrrolidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**21**) recorded at 400 MHz in $CDCl_3$.

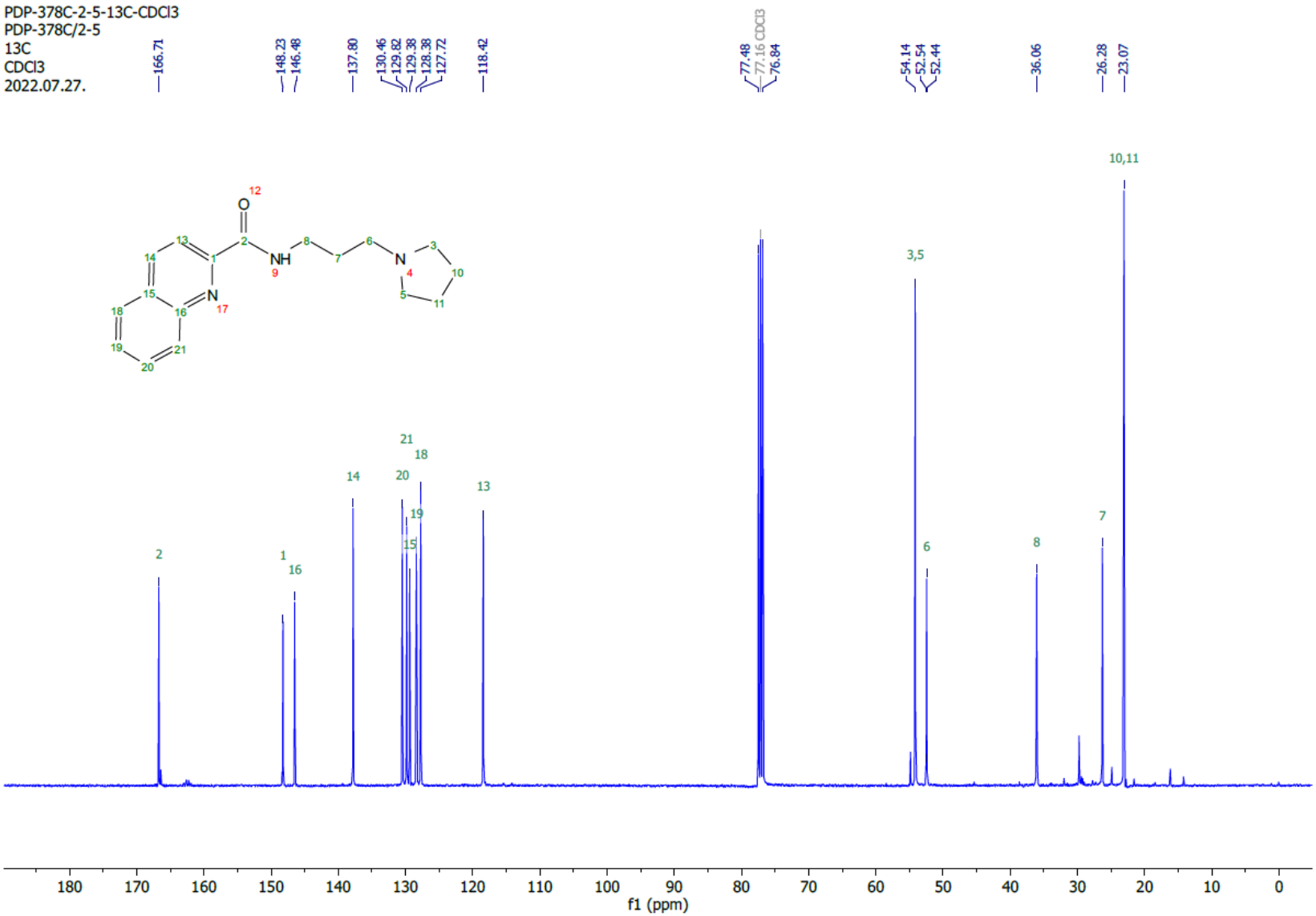


Figure S97: ^{13}C NMR spectrum of *N*-[3-(pyrrolidin-1-yl)propyl]quinoline-2-carboxamide TFA salt (**21**) recorded at 400 MHz in $CDCl_3$

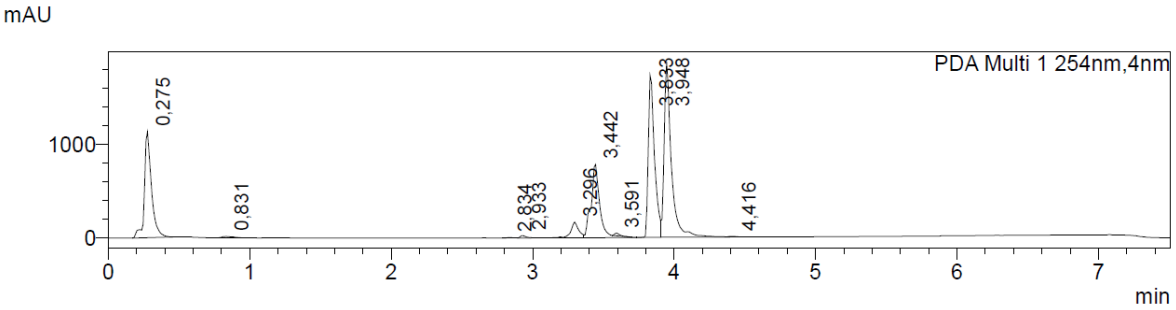


Figure S98. HPLC chromatogram of the crude reaction mixture (amide formation with [1,1'-biphenyl]-4-carboxylic acid (**22**)).

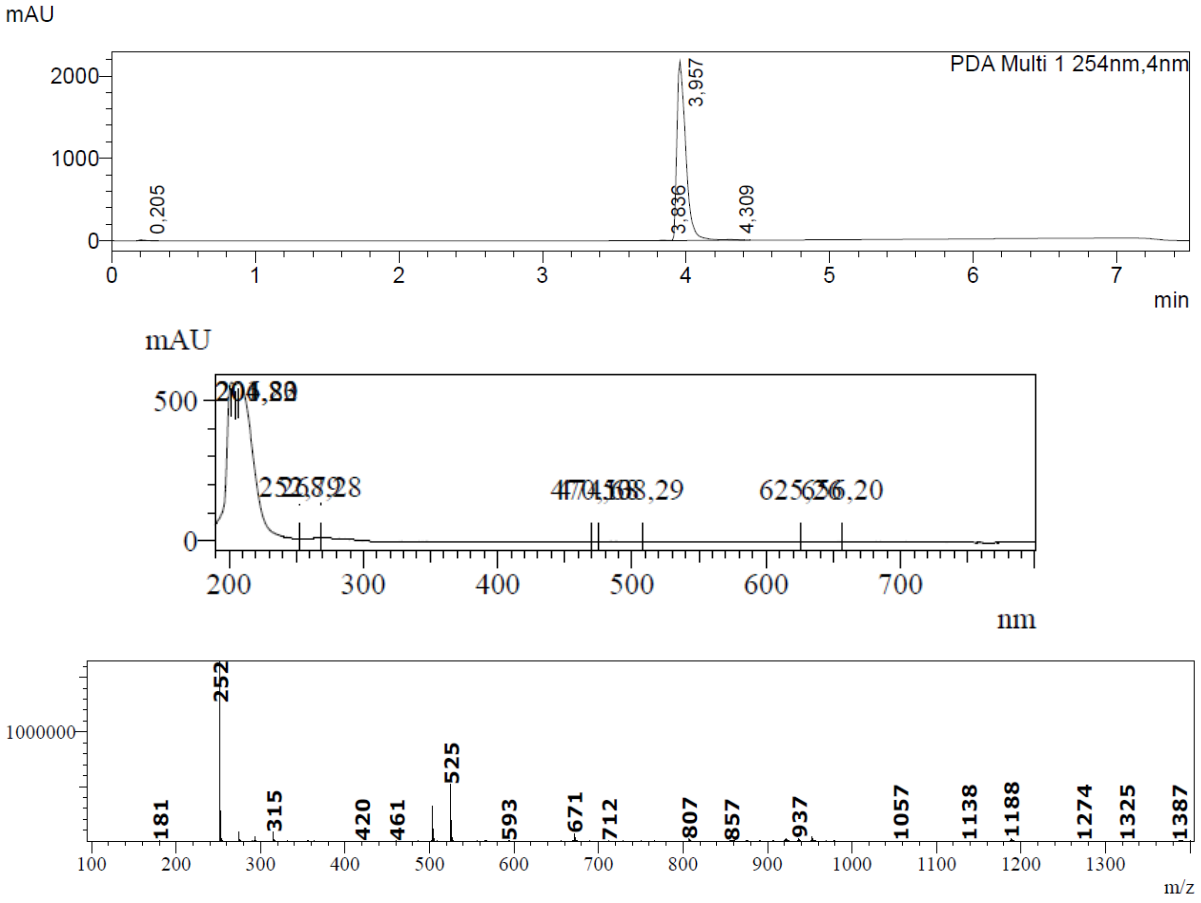
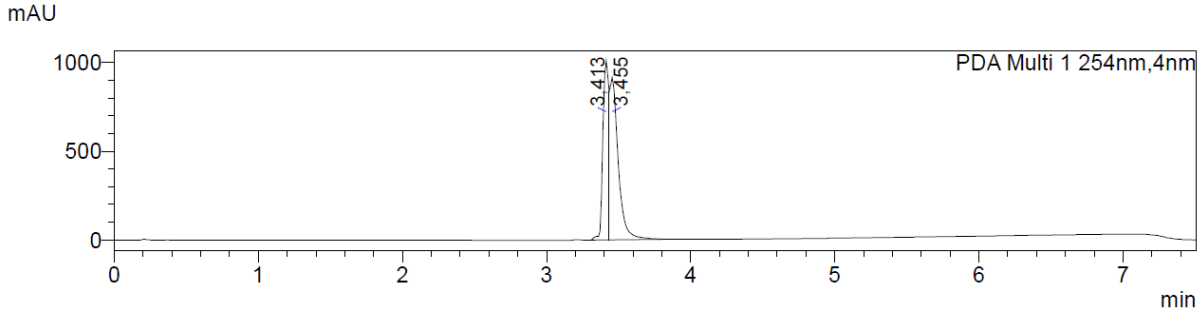


Figure S99: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of ([1,1'-biphenyl]-4-yl)(pyrrolidin-1-yl)methanone (**23**).



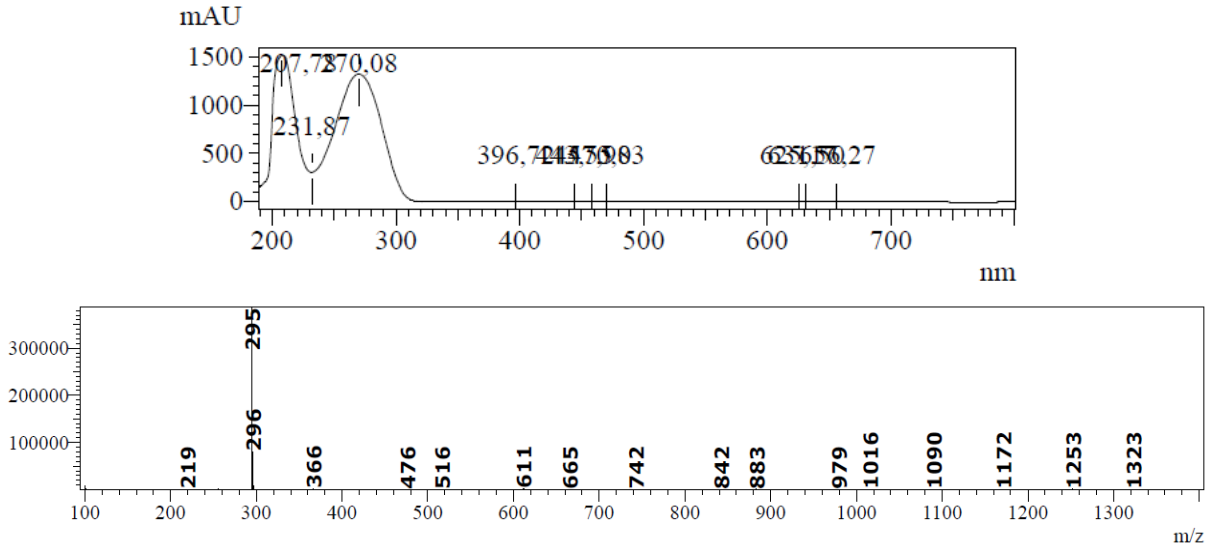


Figure S100.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(azetidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**24**).

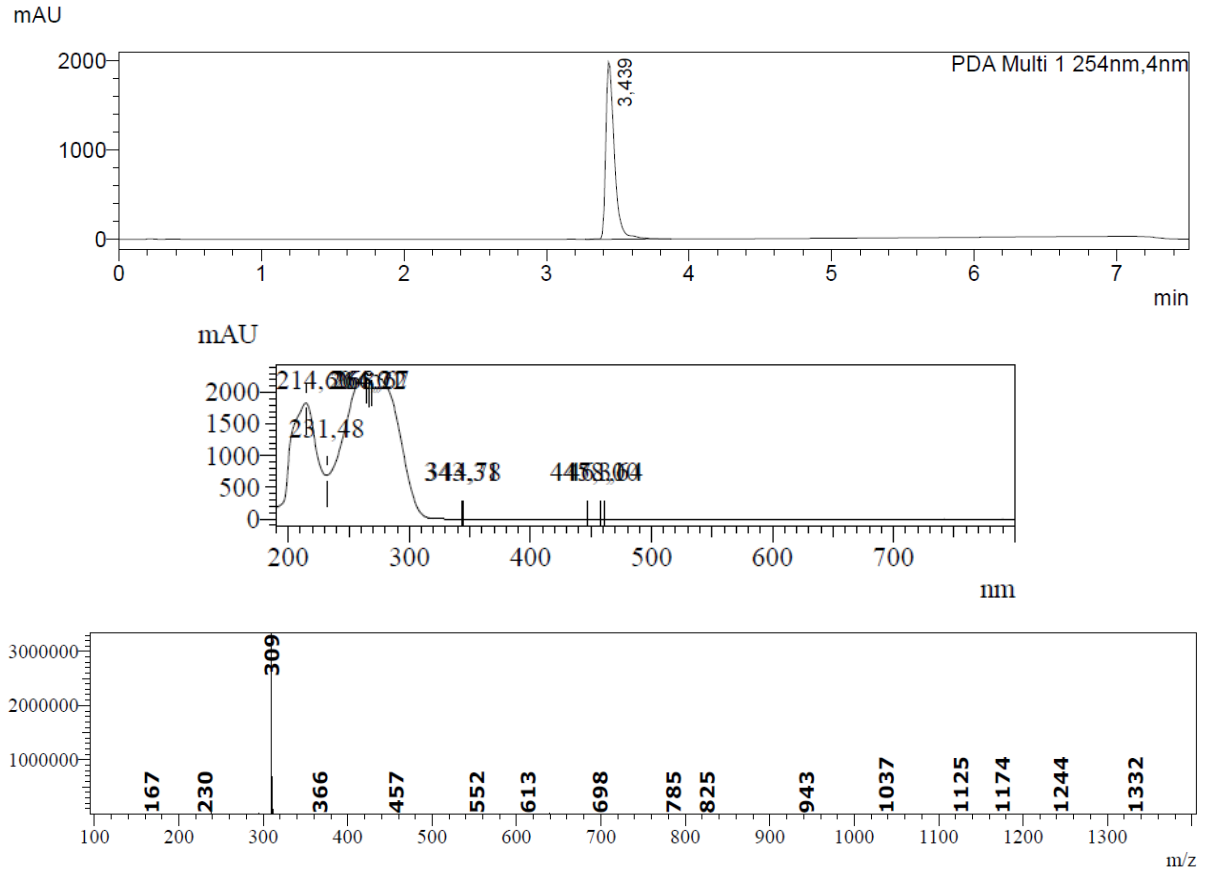


Figure S101.: HPLC UV chromatogram, UV-VIS spectrum and mass spectrum of *N*-[3-(pyrrolidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**25**).

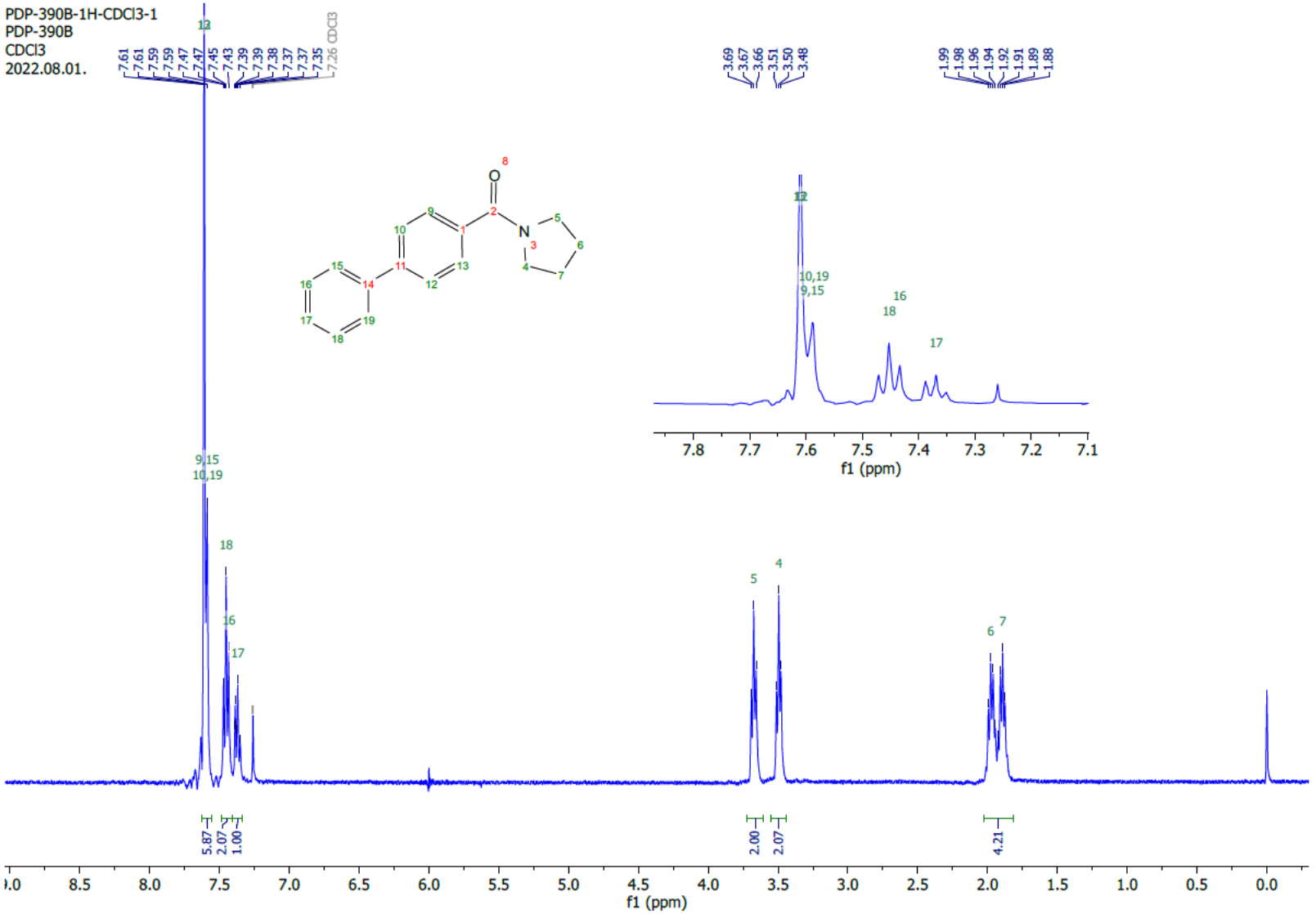


Figure S102: ^{1}H NMR spectrum of ([1,1'-biphenyl]-4-yl)(pyrrolidin-1-yl)methanone (**23**) recorded at 400 MHz in $CDCl_3$.

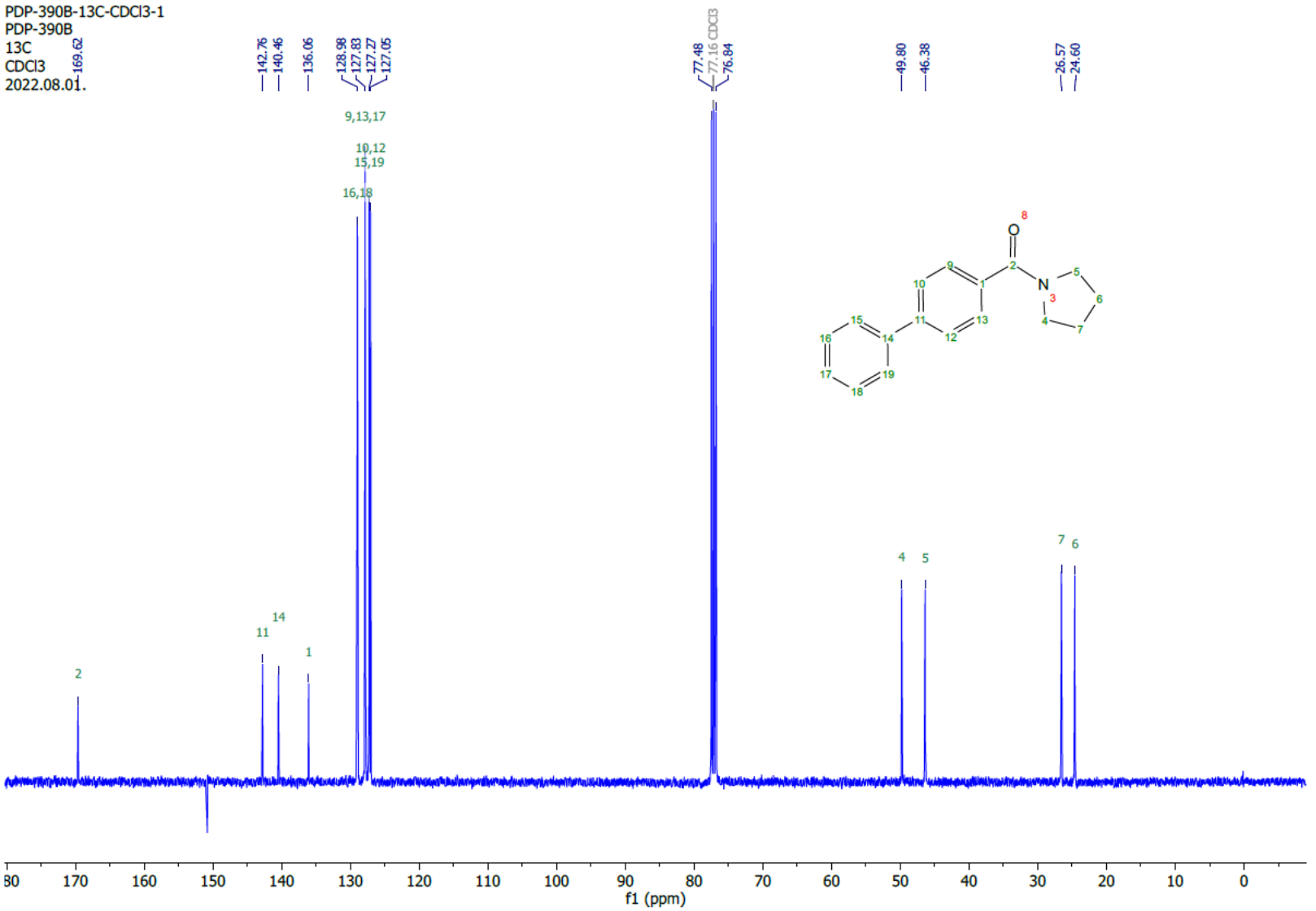


Figure S103: ^{13}C NMR spectrum of ([1,1'-biphenyl]-4-yl)(pyrrolidin-1-yl)methanone (**23**) recorded at 400 MHz in $CDCl_3$

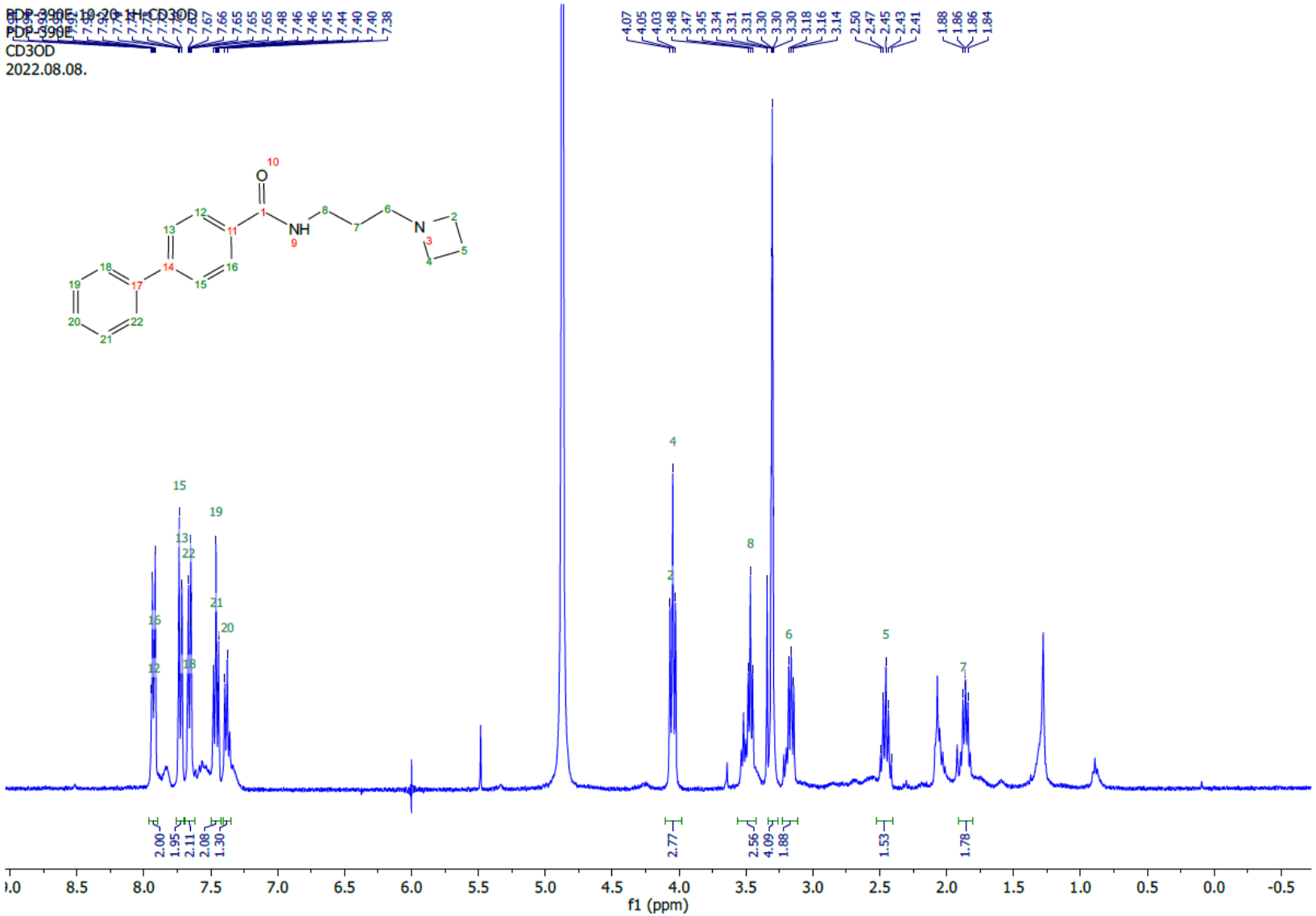


Figure S104: ^{1}H NMR spectrum of *N*-[3-(azetidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**24**) recorded at 400 MHz in $CDCl_3$.

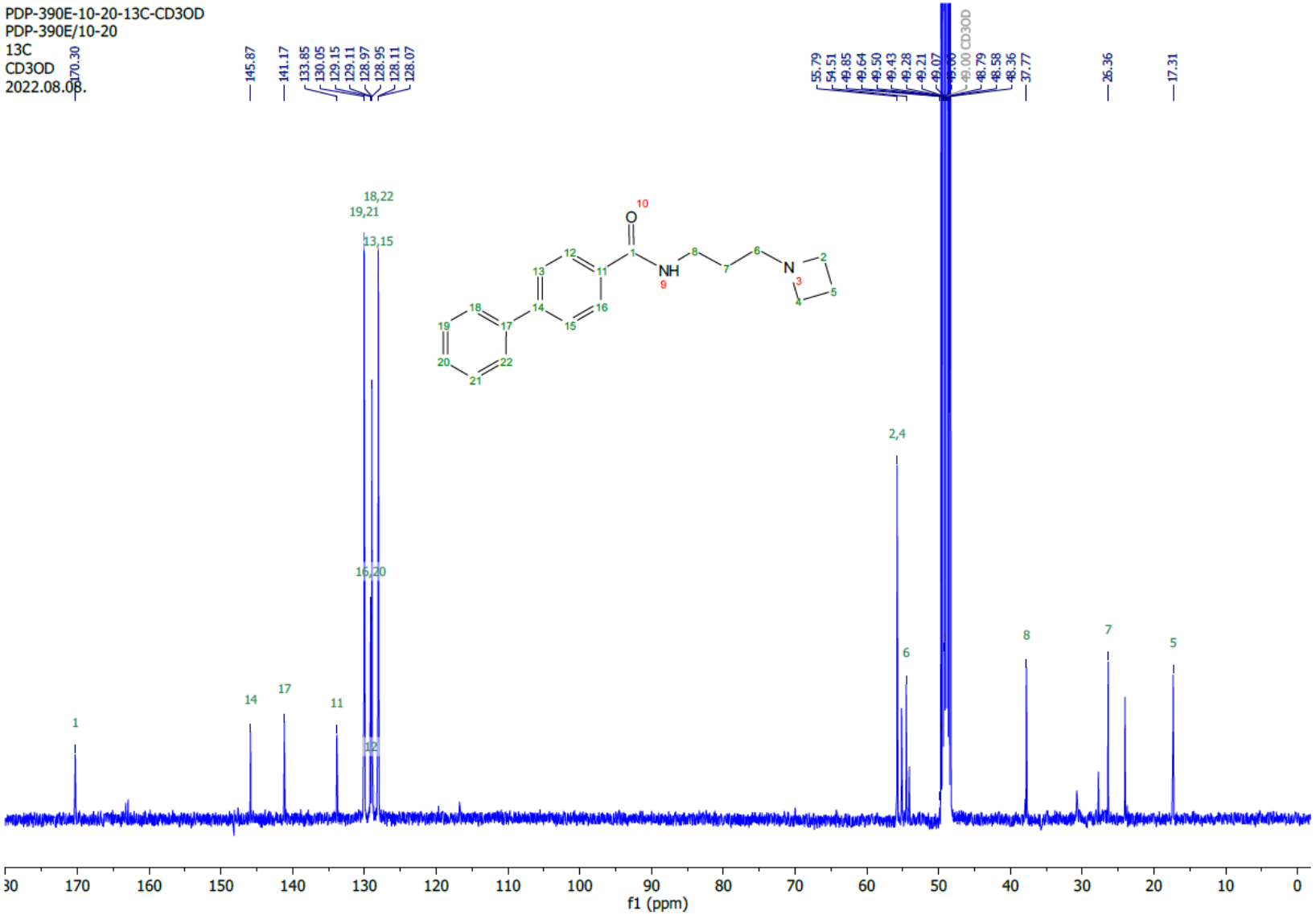


Figure S105: ^{13}C NMR spectrum of *N*-[3-(azetidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**24**) recorded at 400 MHz in $CDCl_3$

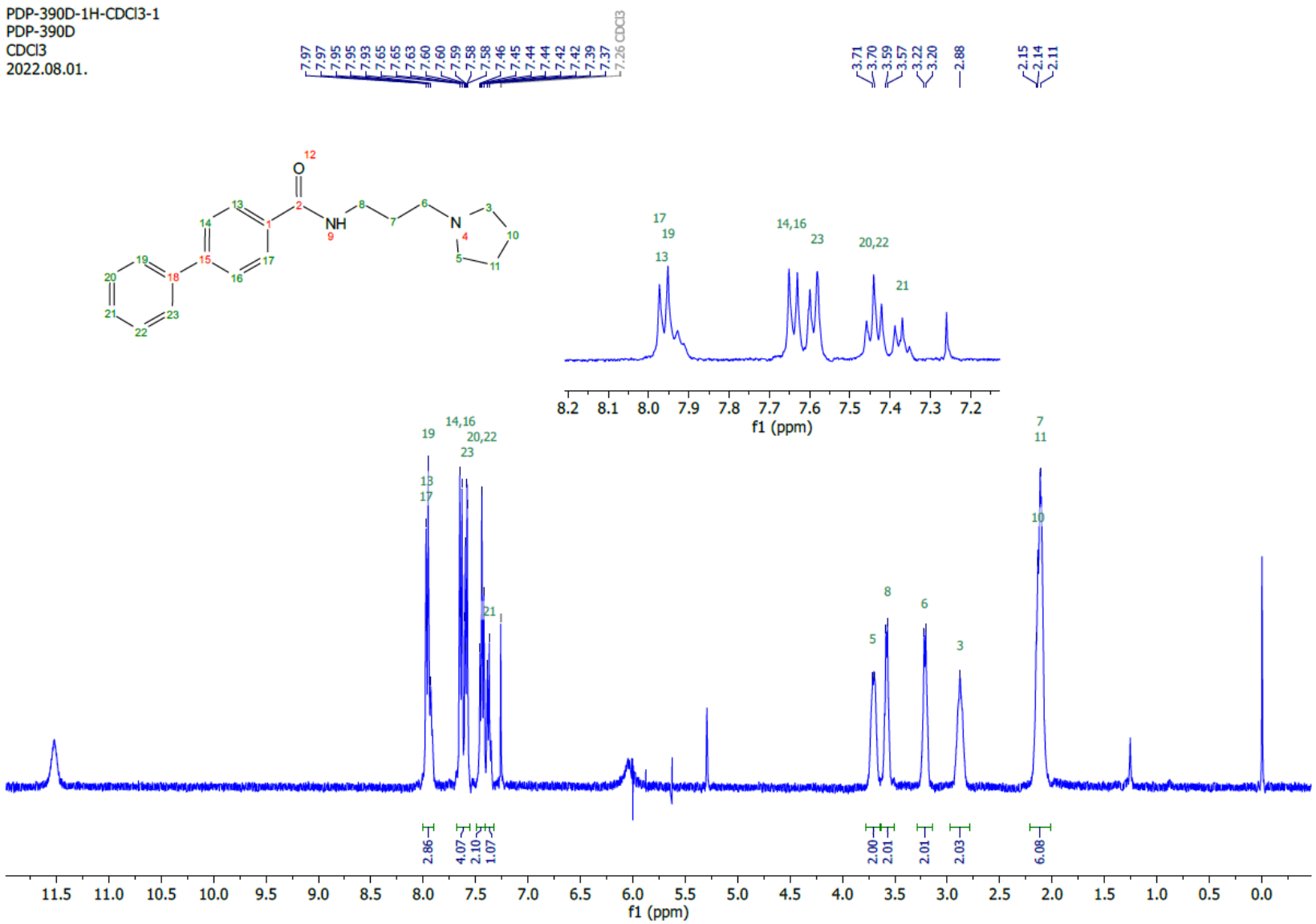


Figure S106: ^{1}H NMR spectrum of *N*-[3-(pyrrolidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**25**) recorded at 400 MHz in $CDCl_3$.

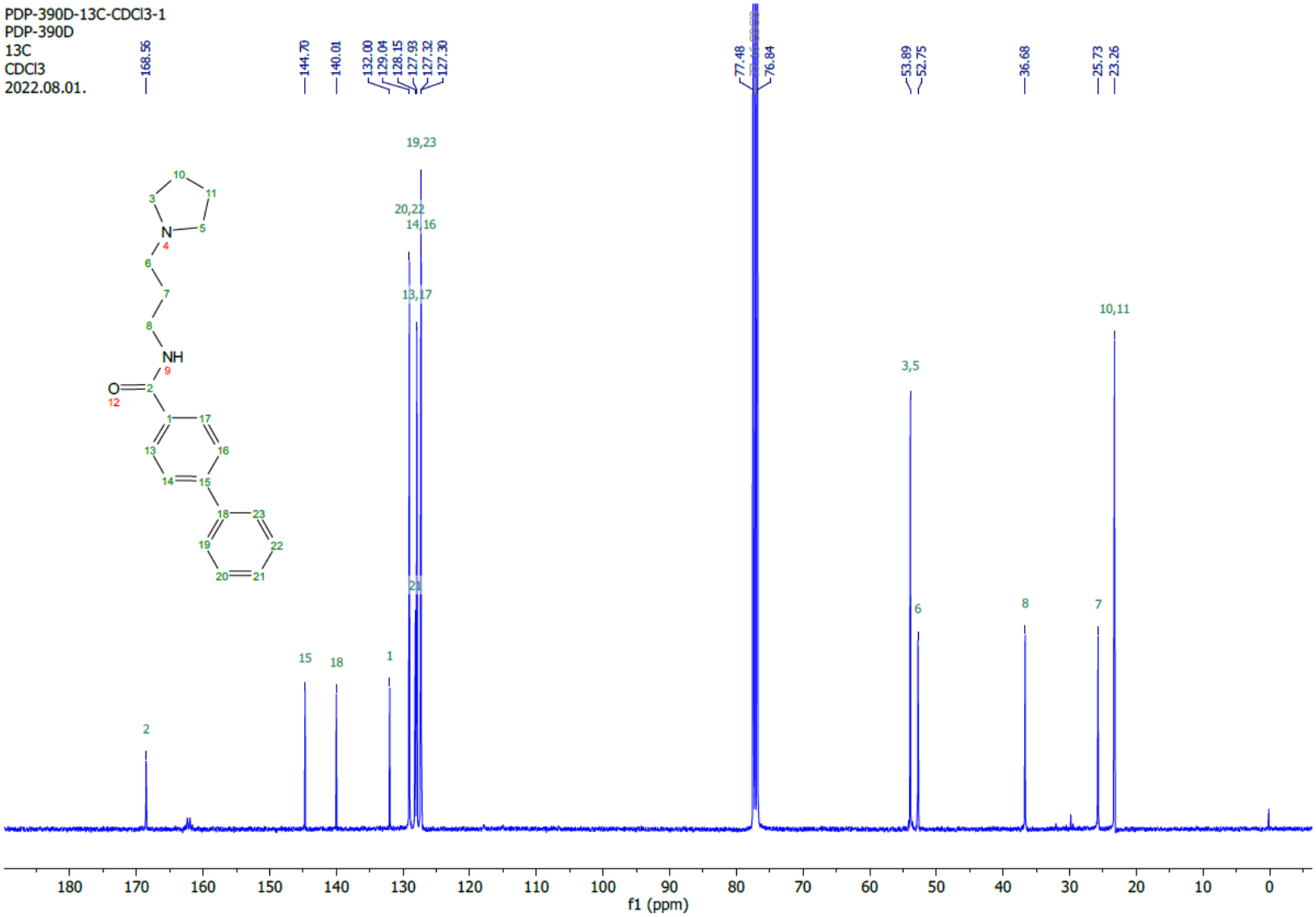


Figure S107: ^{13}C NMR spectrum of *N*-[3-(pyrrolidin-1-yl)propyl][1,1'-biphenyl]-4-carboxamide TFA salt (**25**) recorded at 400 MHz in $CDCl_3$