

Supplementary material related to the article

DIRECT REDUCTIVE AMINATION OF FUNTIONALIZED ALDEHYDES WITH ANILINE DERIVATIVES OF PURINES AND 7-DEAZAPURINES

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Includes:

- Preparation of the aldehyde **8**. S2
- Figure S1: Recirculation set-up applied in the H-cube flow reactor S3
- ¹H and ¹³C NMR spectra of the synthesized compounds. S4

Preparation of the aldehyde **8**.

***tert*-Butyl (*tert*-butoxycarbonyl)-*L*-homoserinate.**

To a solution of Boc-*L*-Asp-OtBu (3.0 g, 10.38 mmol) and PyBOP (6.47 g, 12.46 mmol) in THF (30 mL), DIPEA (2.20 mL, 12.46 mmol) was added. The reaction was stirred at rt for 30 minutes, cooled with an ice bath and sodium borohydride (576 mg, 15.57 mmol) was added portion wise. The mixture was kept stirring at rt overnight. Then, HCl 1M (20 mL) was added and the aqueous phase was extracted with EtOAc (3x20 mL). The organic phases were combined and washed with a saturated solution of sodium bicarbonate (40 mL) and then with brine solution (40 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated. The crude was purified through a silica gel column using a mixture of Hexane/EtOAc (3/2), affording 2.10 g of ***tert*-butyl (*tert*-butoxycarbonyl)-*L*-homoserinate** (73% yield) as a colorless oil. The ¹H NMR data were in accordance with those published.¹ ¹H NMR (400 MHz, CDCl₃) δ: 1.45 (s, 9H), 1.47 (s, 9H), 2.14 (m, 1H), 3.41 (dd, *J* = 8.6, 4.6 Hz, 1H), 3.55 – 3.86 (m, 2H), 4.35 (m, 1H), 5.33 (d, *J* = 7.9 Hz, 1H).

***tert*-Butyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate (**8**).**

To a mixture containing ***tert*-butyl (*tert*-butoxycarbonyl)-*L*-homoserinate** (150 mg, 0.545 mmol) and sodium bicarbonate (457 mg, 5.45 mmol) in DCM (2.5 mL), the Dess-Martin periodinane suspended in DCM was added (346 mg, 0.817 mmol, 0.3 M in DCM). The mixture was stirred at rt for one hour and a solution of sodium thiosulphate 1M was added (2 mL). Then the mixture was stirred vigorously for 5 minutes, and 10 mL of a saturated solution of sodium bicarbonate were added. Then, the aqueous phase was extracted with DCM (3x10 mL). The organic phases were combined and washed with brine solution (20 mL). The organic extract was evaporated, and the residue obtained was purified through a silica gel column using a mixture of Hexane/EtOAc (4/1), affording 243 mg of **8** (63% yield) as an amorphous solid. The ¹H NMR data were in accordance with those published.¹ ¹H NMR (400 MHz, CDCl₃) δ: 1.44 (s, 9H), 1.45 (s, 9H), 2.90– 3.04 (m, 2H), 4.48 (m, 1H), 5.35 (d, *J* = 6.2 Hz, 1H), 9.73 (s, 1H).

Reference.

- 1 W. Qu, Z. Zha, K. Ploessl, B. P. Lieberman, L. Zhu, D. R. Wise, C. B. Thompson and H. F. Kung, *J. Am. Chem. Soc.*, 2011, **133**, 1122–1133.

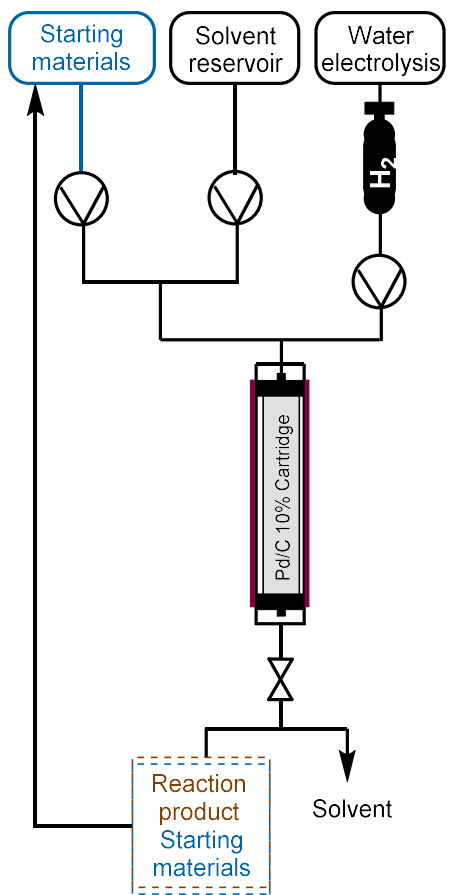
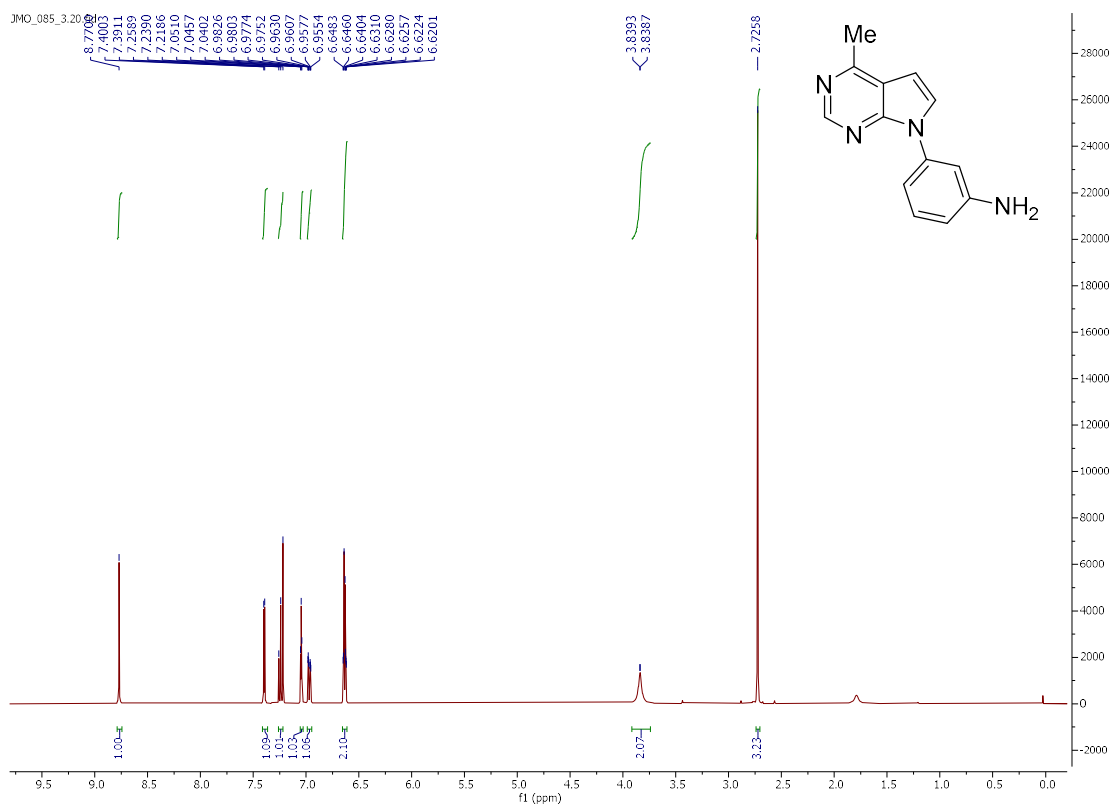


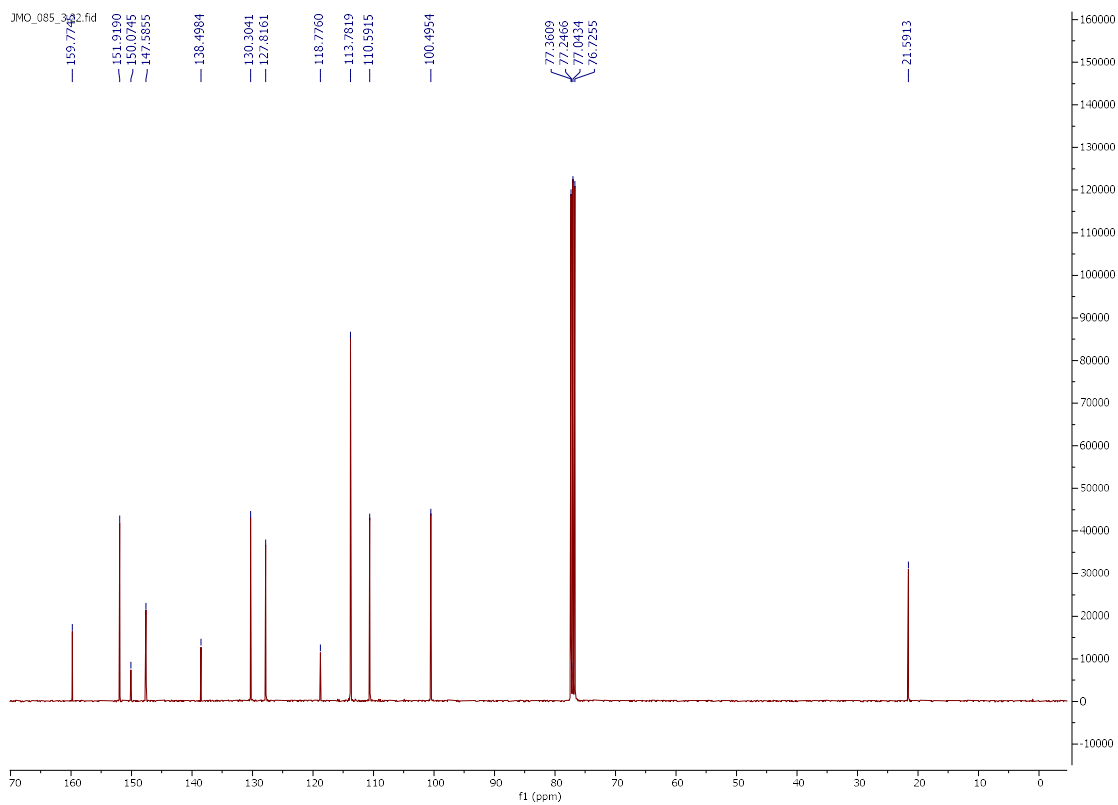
Figure S1: Recirculation set-up of the H-cube

3-(4-Methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)aniline (3).

¹H NMR (400 MHz, CDCl₃)

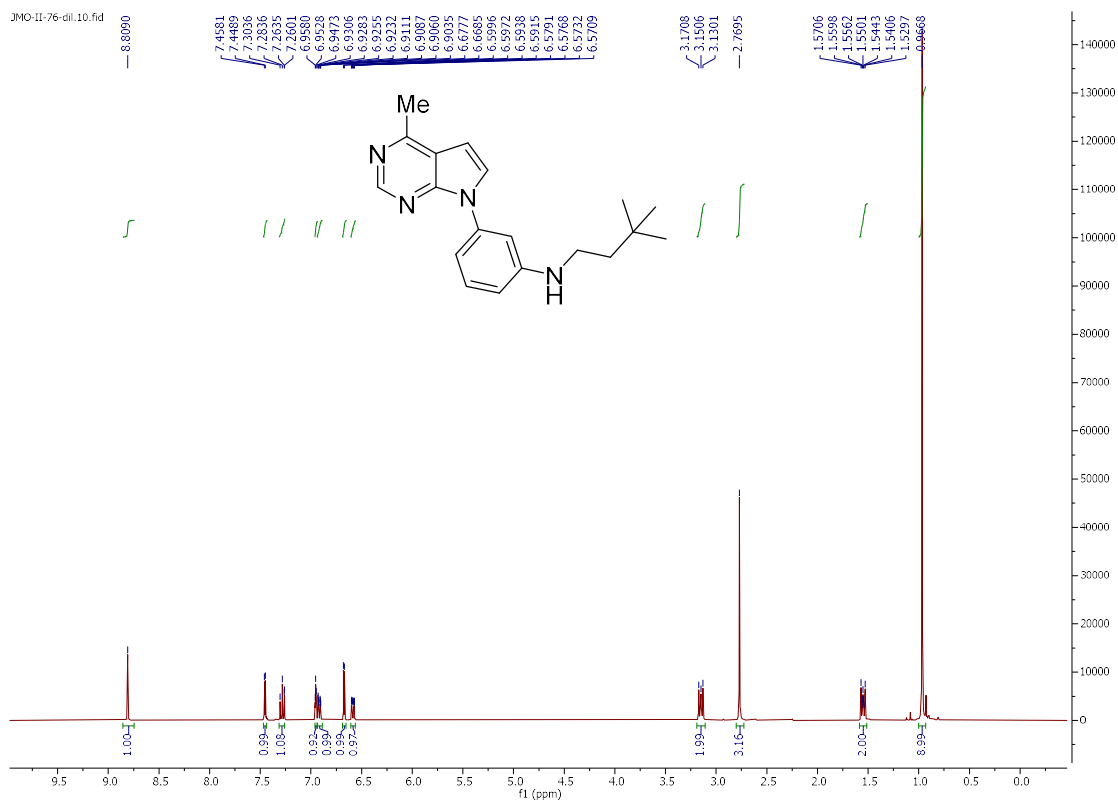


¹³C NMR (100 MHz, CDCl₃)

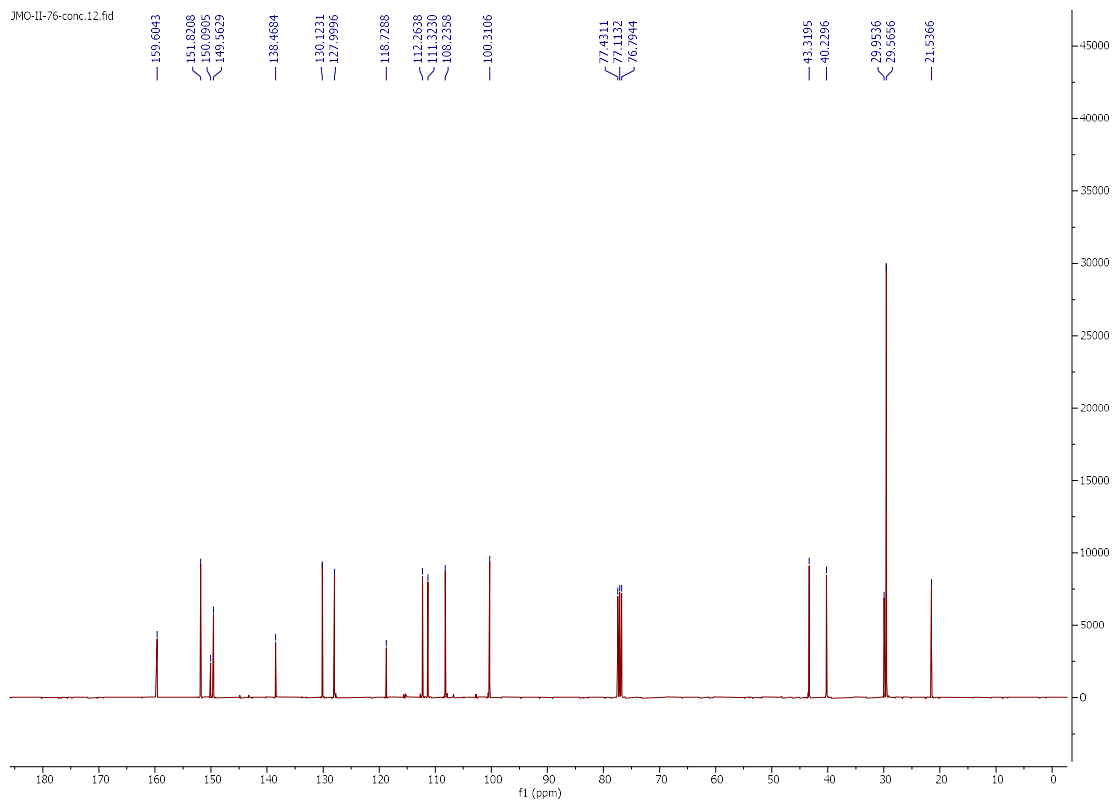


***N*-(3,3-Dimethylbutyl)-3-(4-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)aniline (5).**

¹H NMR (400 MHz, CDCl₃)

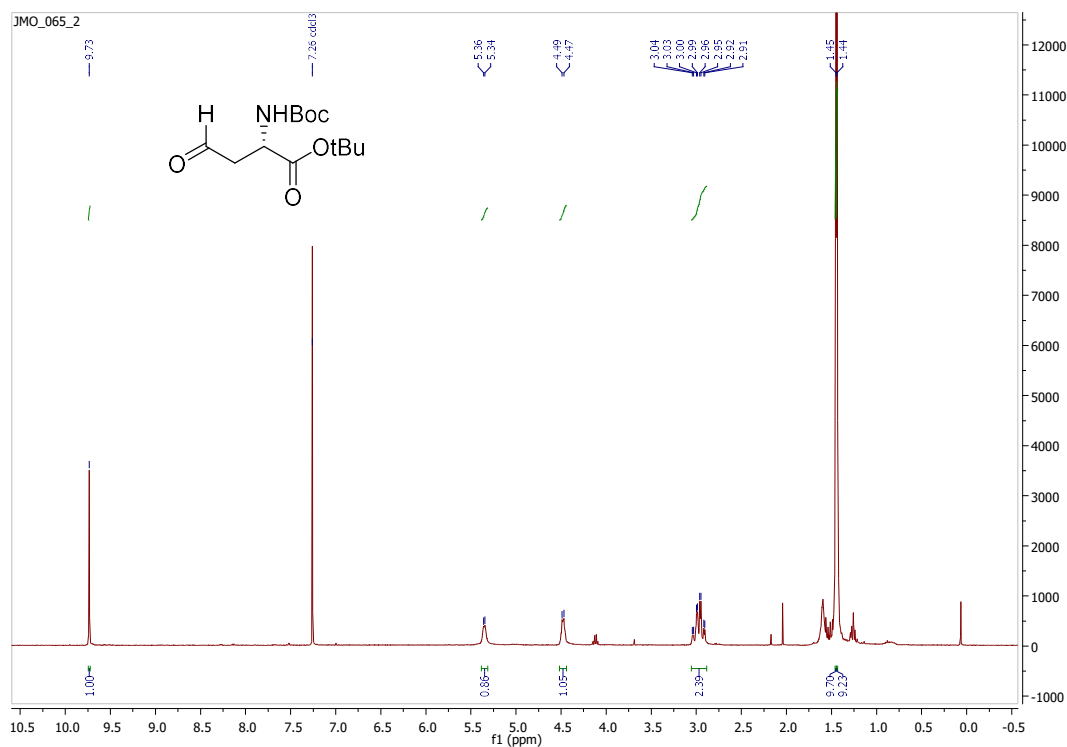


¹³C NMR (100 MHz, CDCl₃)



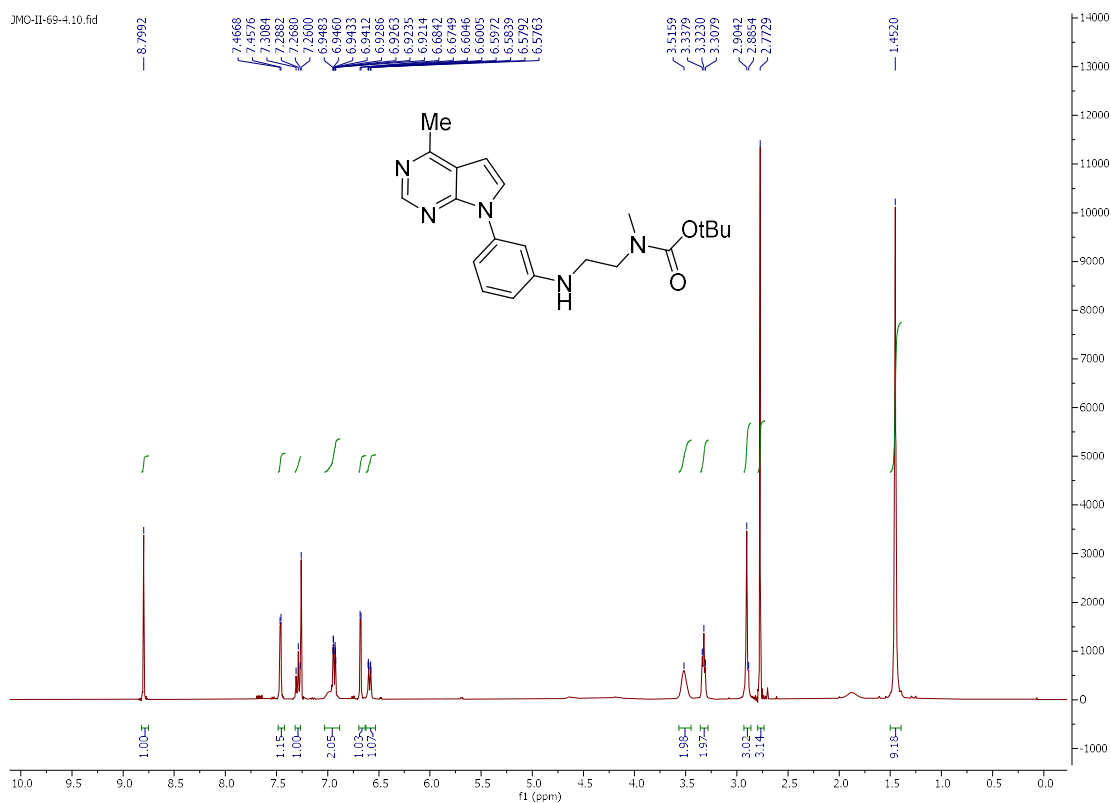
***tert*-butyl (S)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate (8)**

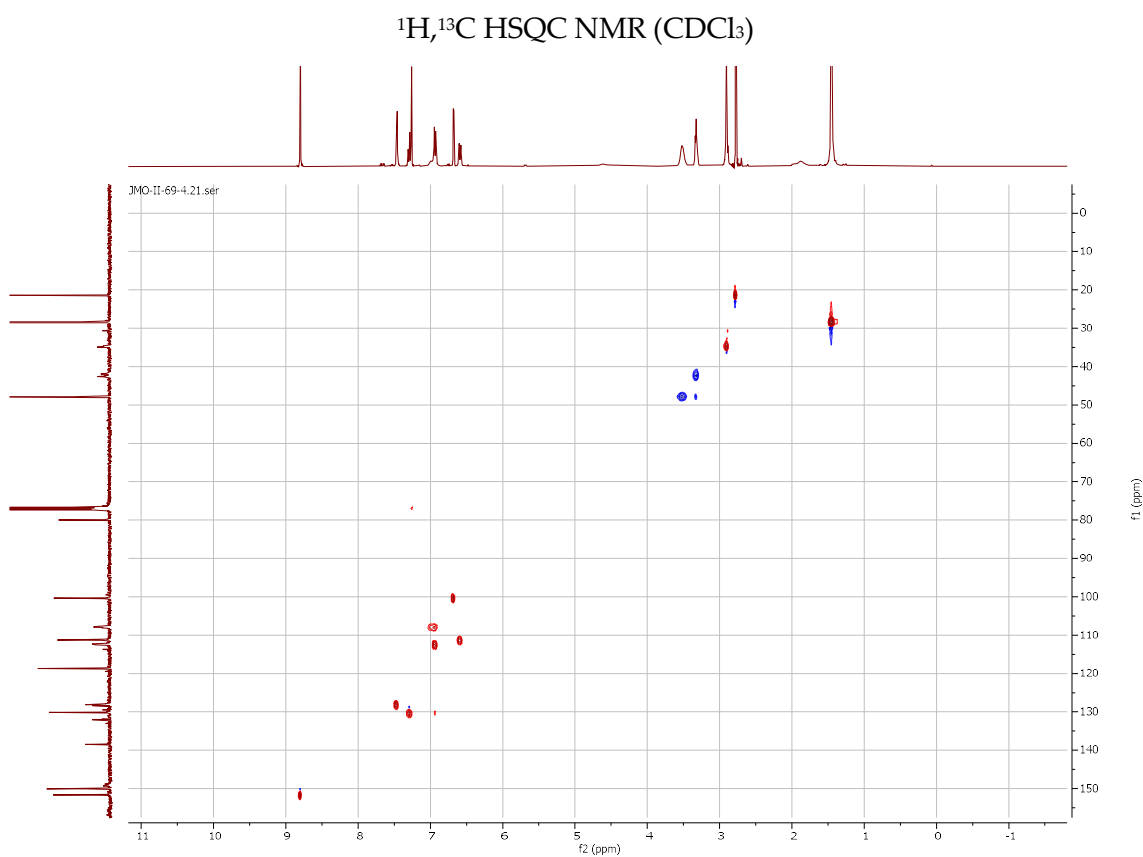
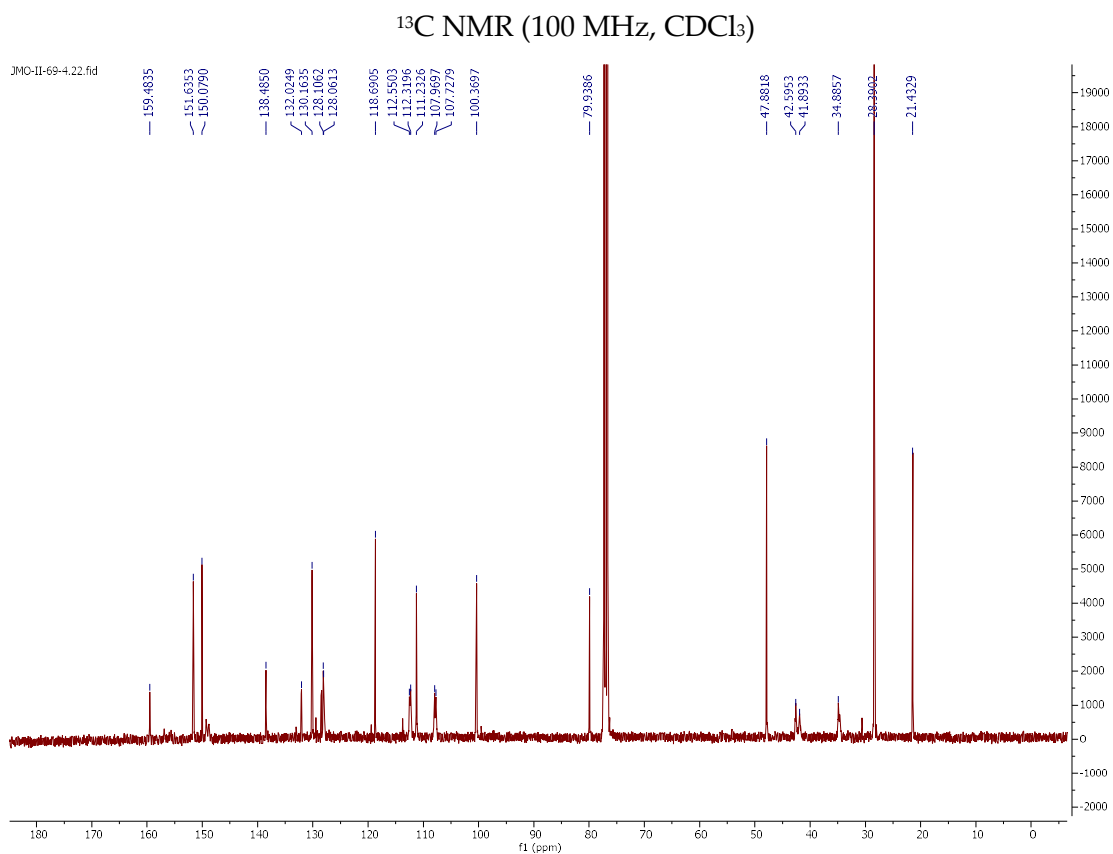
¹H NMR (400 MHz, CDCl₃)



***tert*-Butyl methyl(2-((3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)phenyl)amino)ethyl) carbamate (10).**

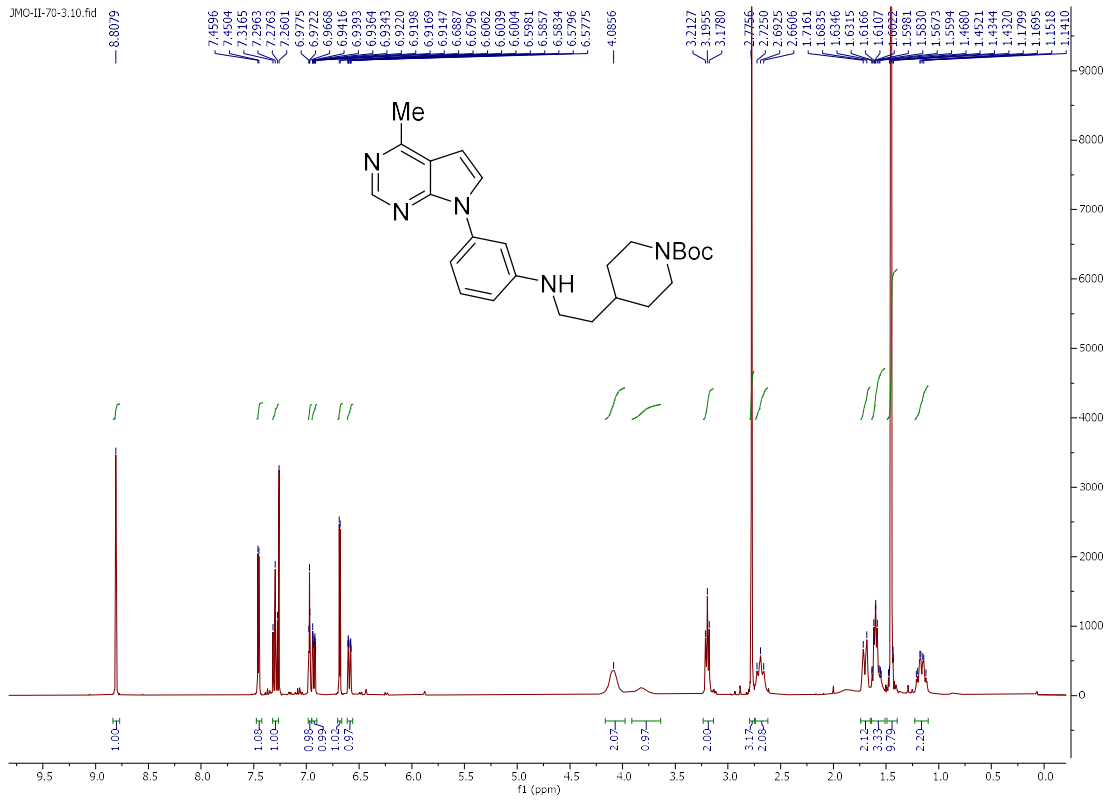
¹H NMR (400 MHz, CDCl₃)



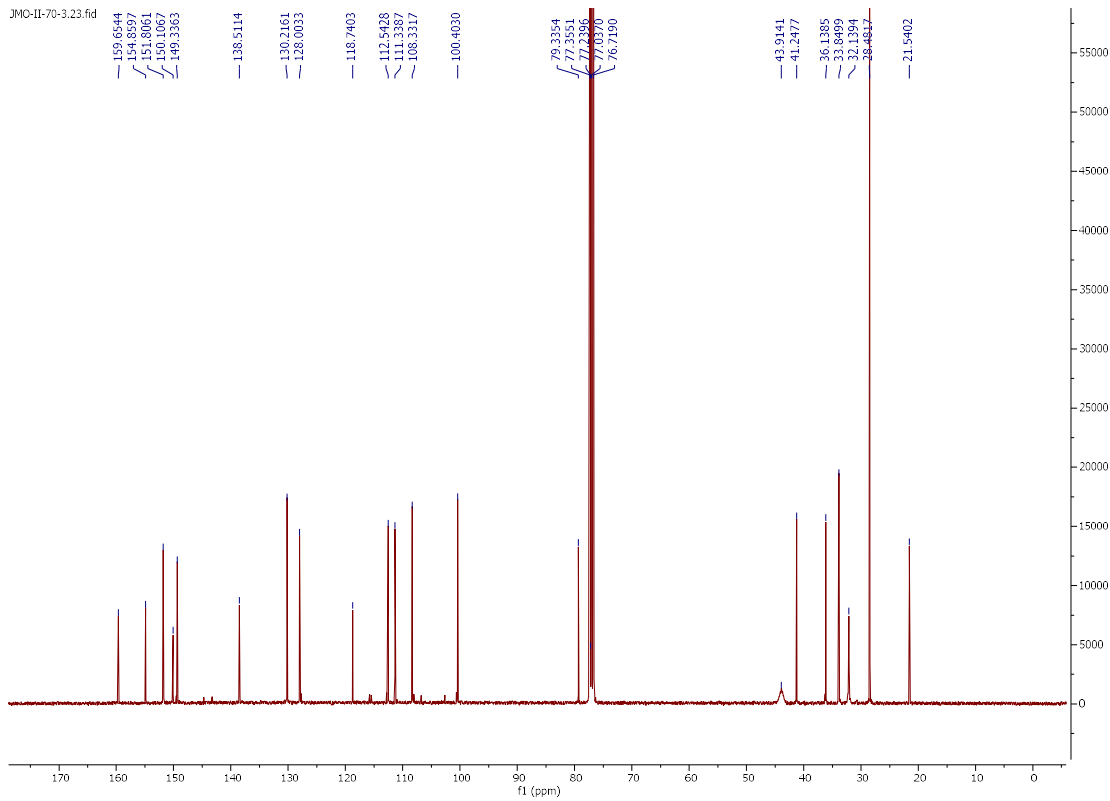


***tert*-Butyl 4-(2-((3-(4-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)amino)ethyl)piperidine-1-carboxylate (11).**

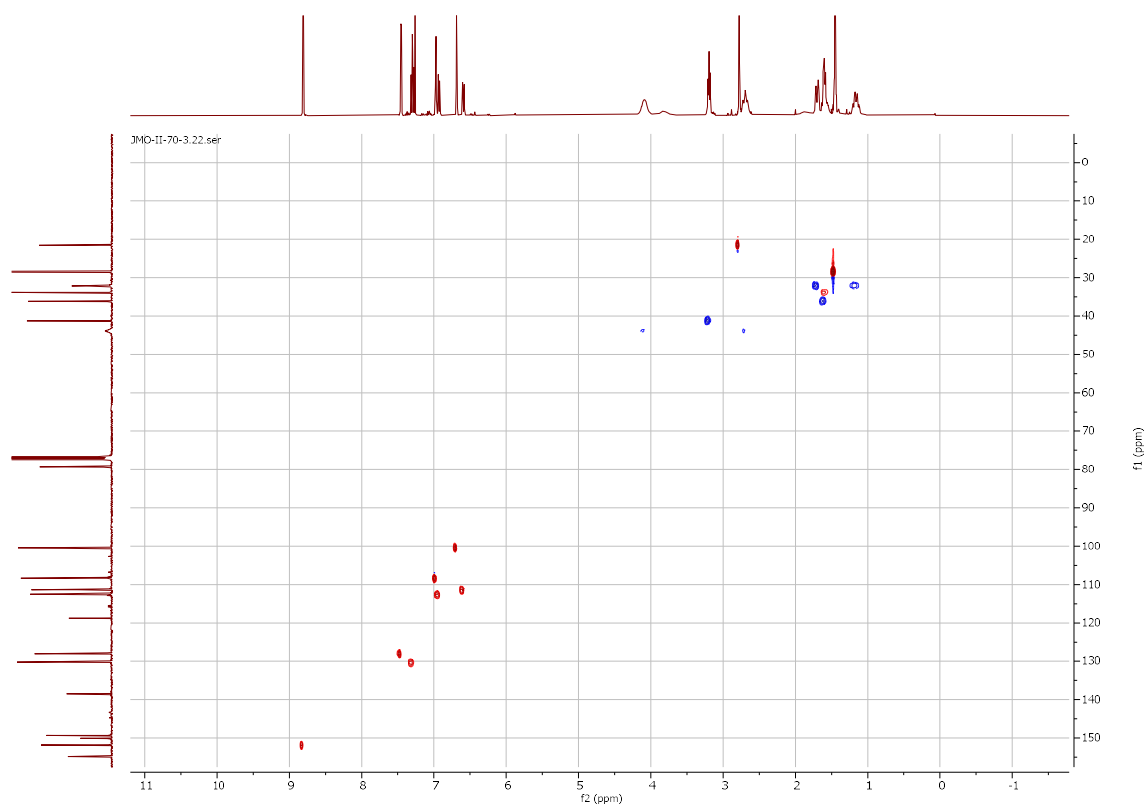
¹H NMR (400 MHz, CDCl₃)



¹³C NMR (100 MHz, CDCl₃)

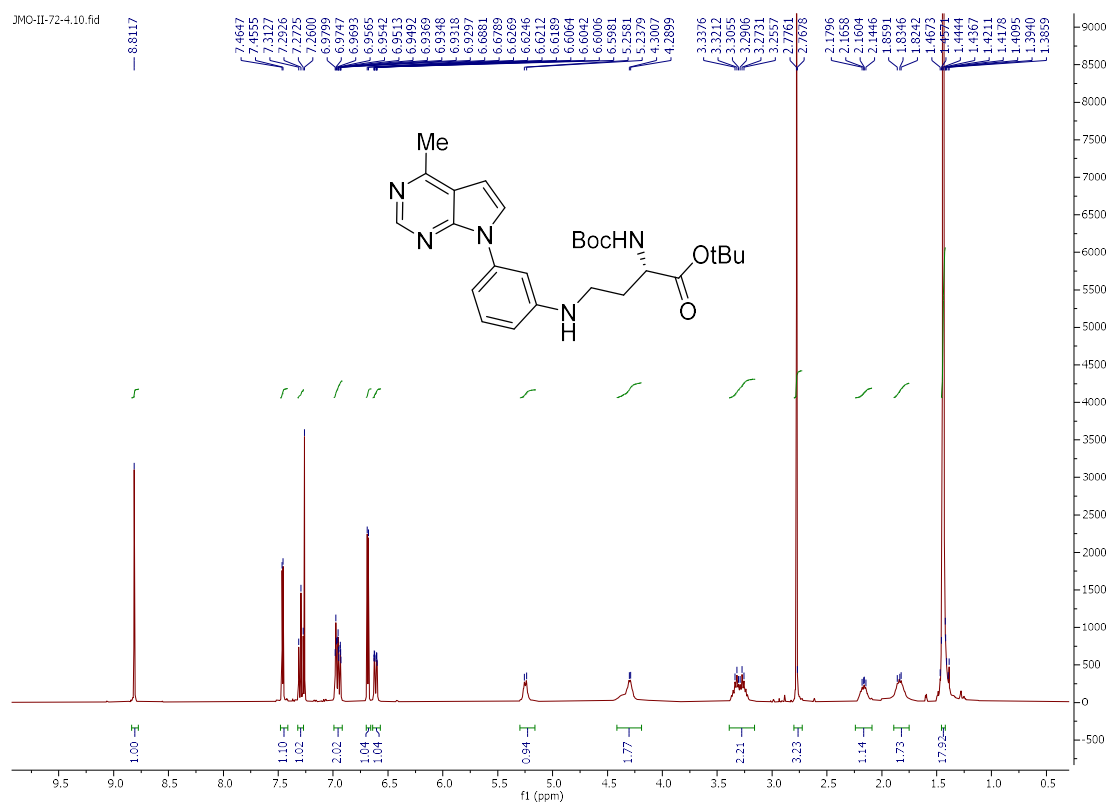


$^1\text{H}, ^{13}\text{C}$ HSQC NMR (CDCl_3)

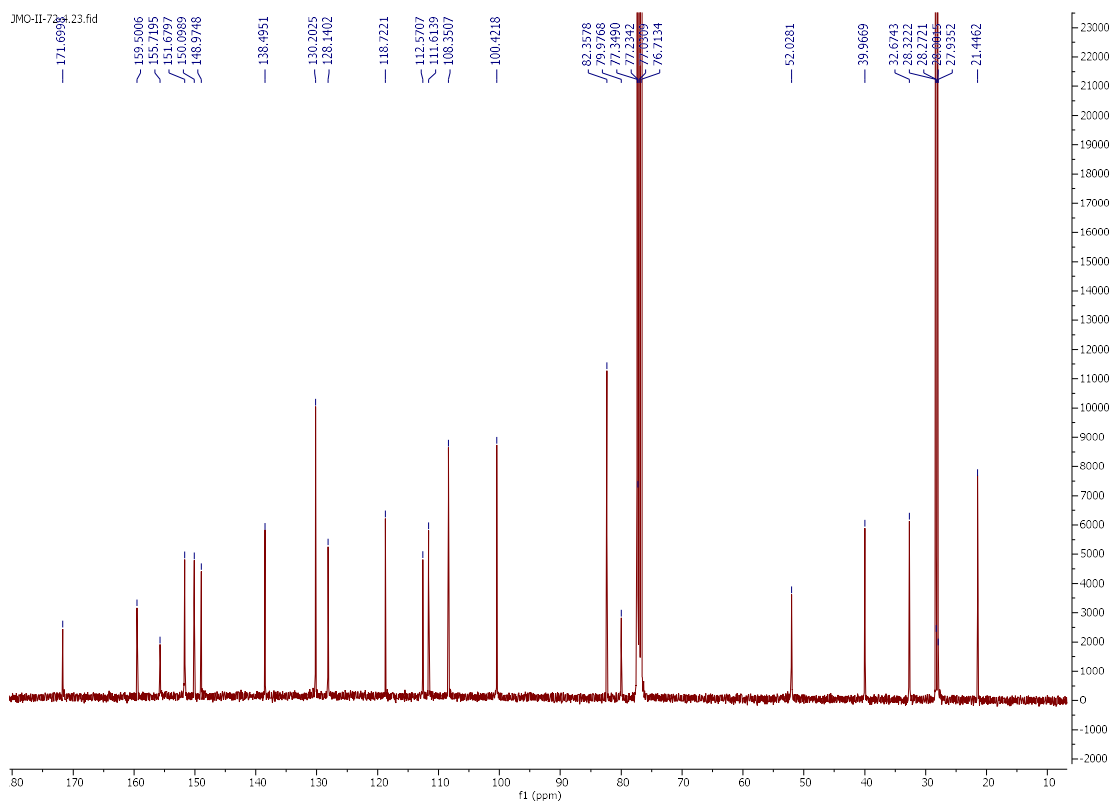


tert-Butyl (S)-2-((*tert*-butoxycarbonyl)amino)-4-((3-(4-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)amino)butanoate (12).

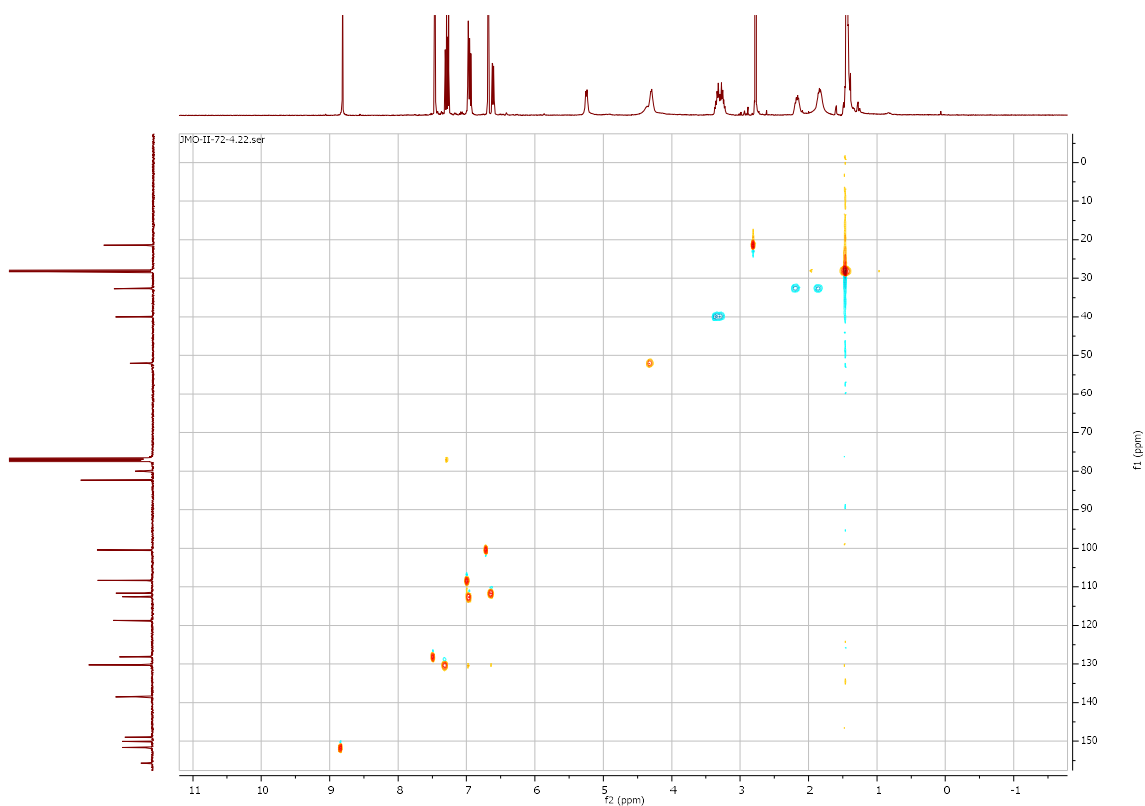
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR (100 MHz, CDCl_3)

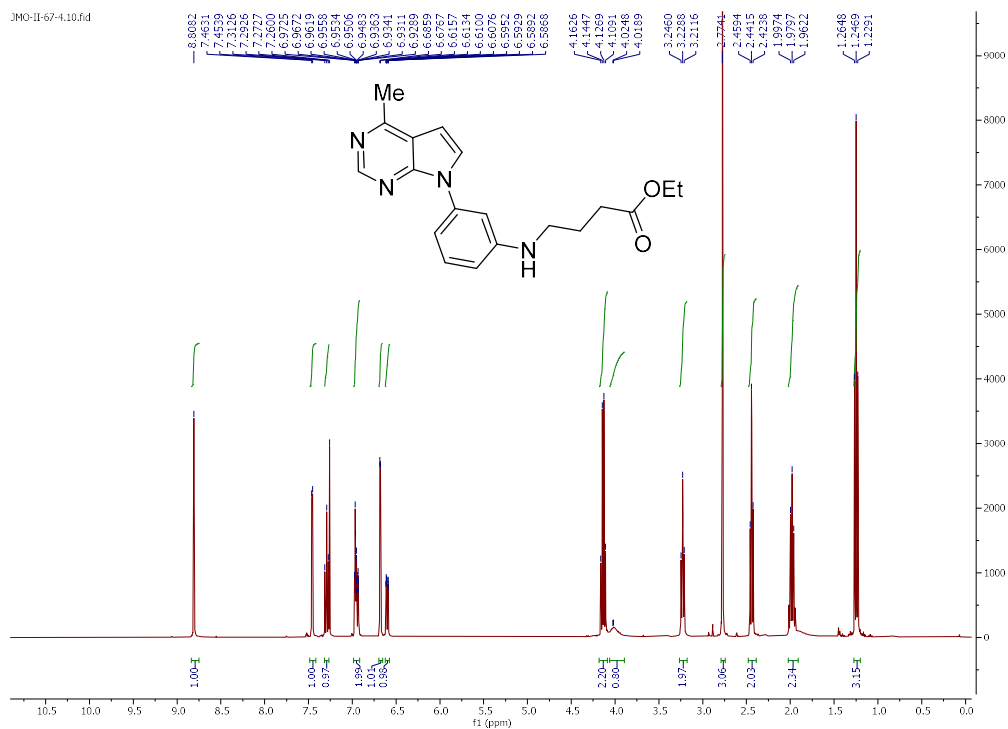


^1H , ^{13}C HSQC NMR (CDCl_3)

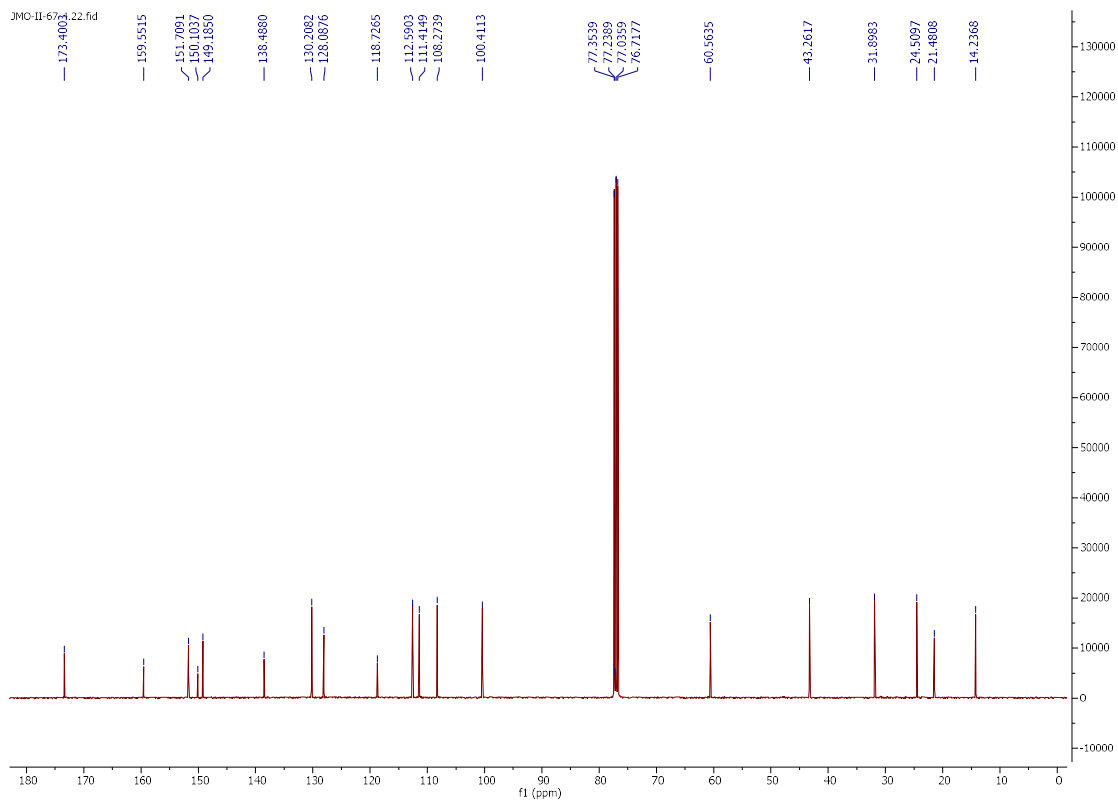


Ethyl 4-((3-(4-methyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)phenyl)amino) butanoate (13).

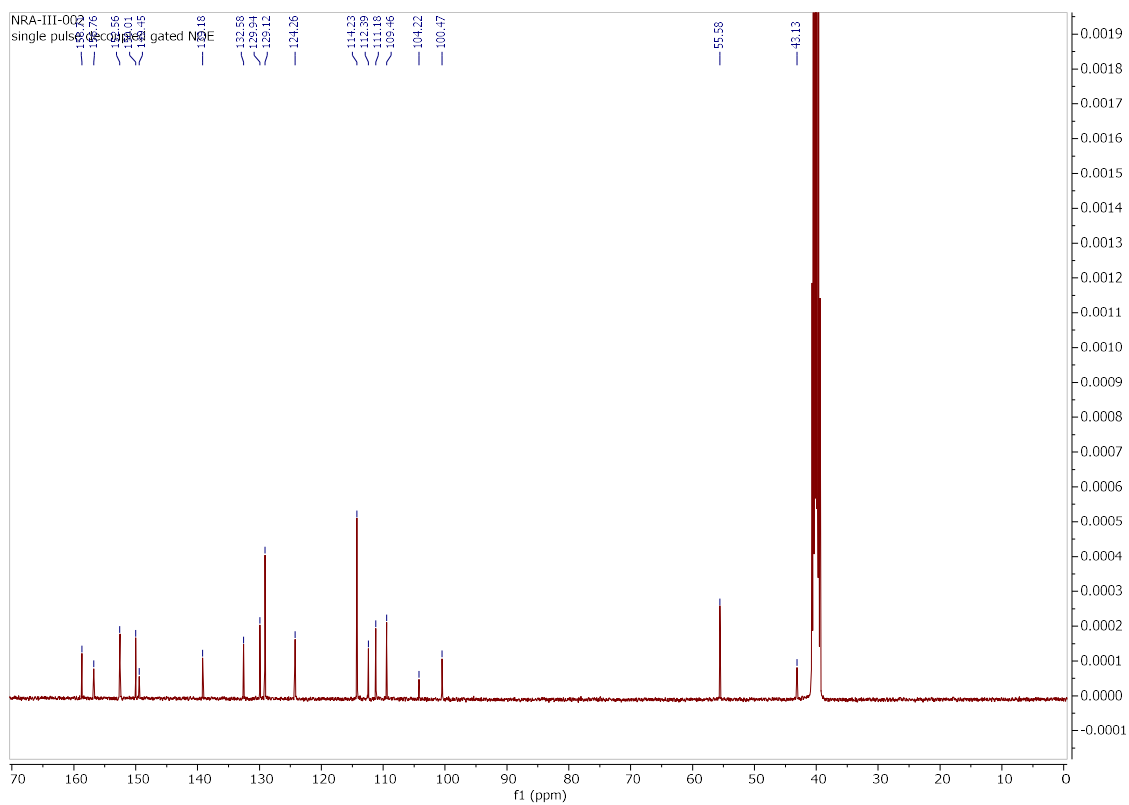
¹H NMR (400 MHz, CDCl₃)



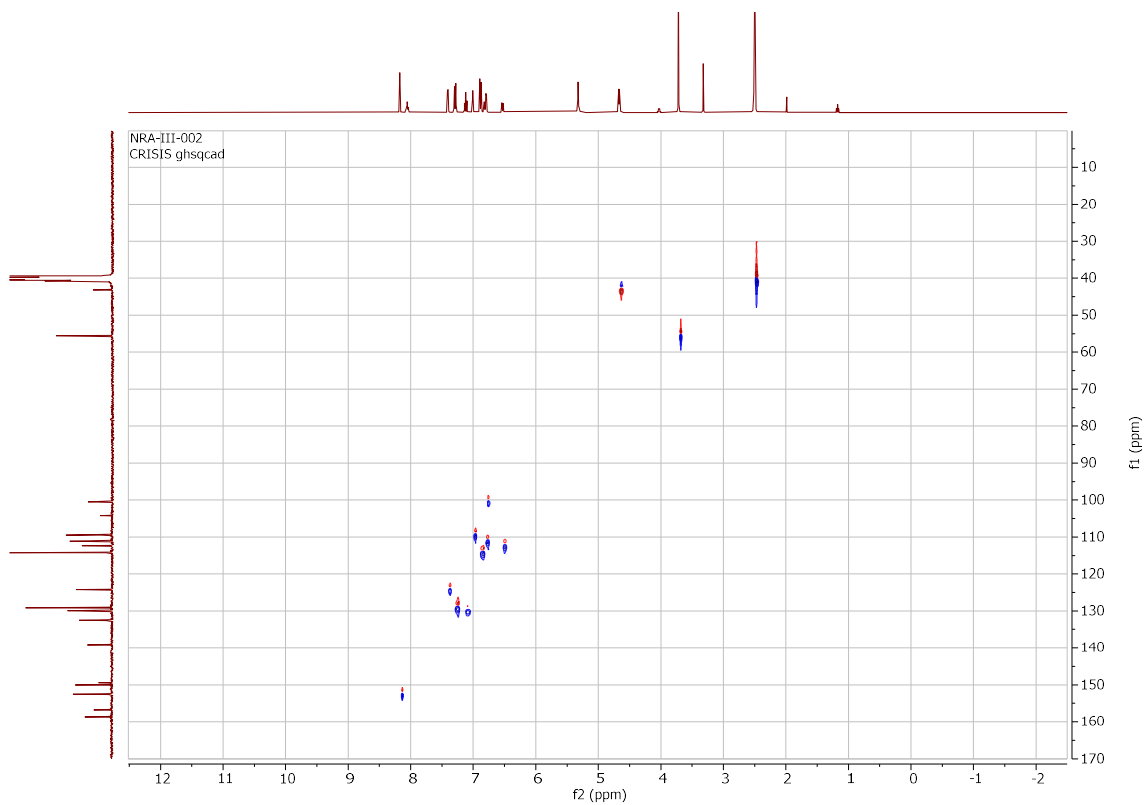
¹³C NMR (100 MHz, CDCl₃)



^{13}C NMR (100 MHz, $\text{DMSO-}d_6$)

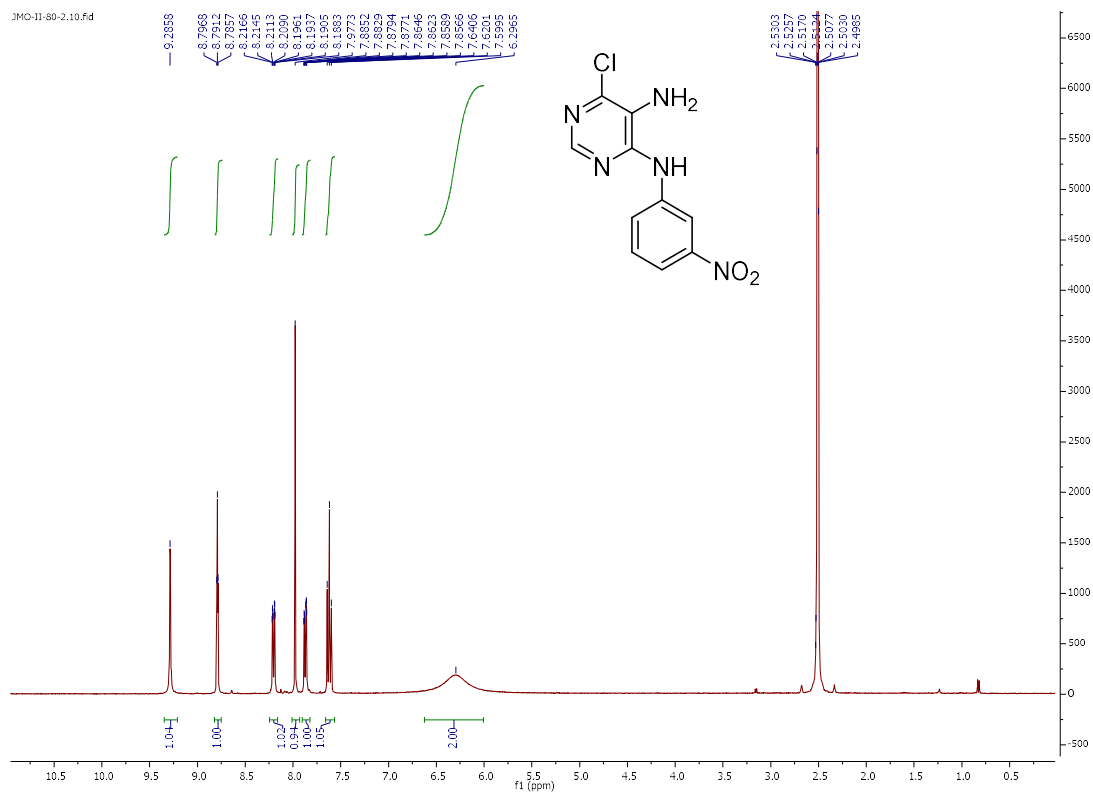


$^1\text{H},^{13}\text{C}$ HSQC NMR ($\text{DMSO-}d_6$)

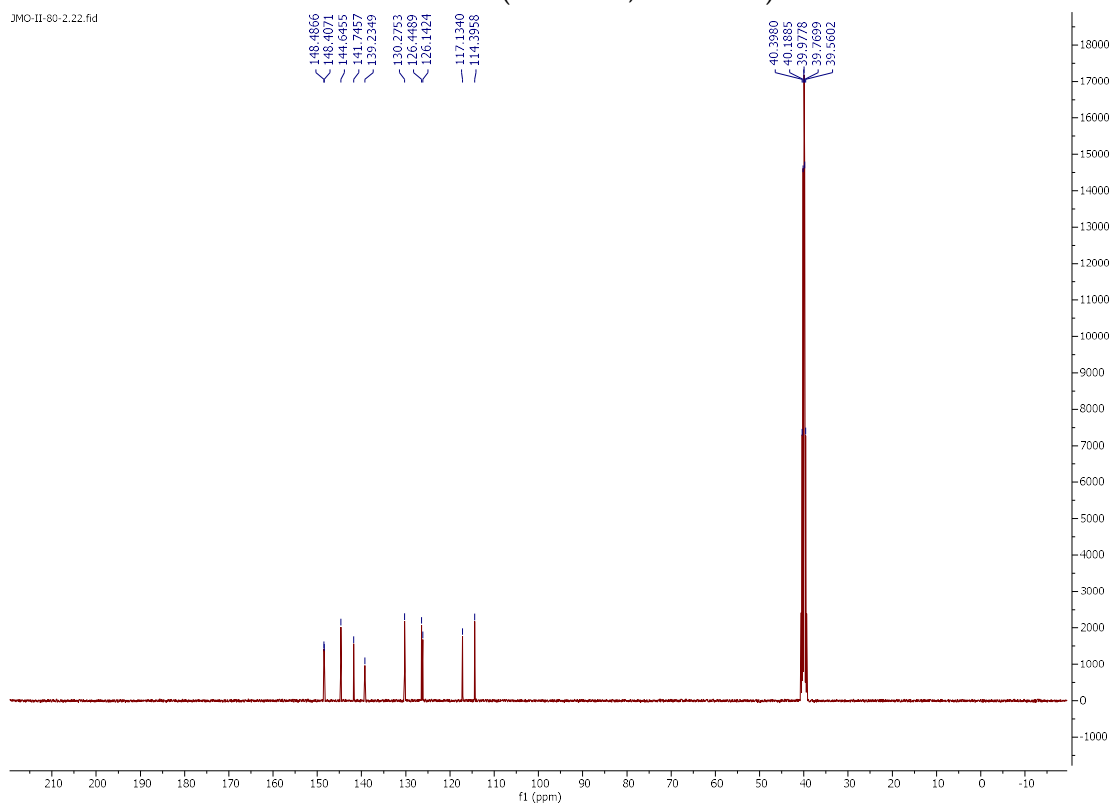


6-Chloro-N⁴-(3-nitrophenyl)pyrimidine-4,5-diamine (18).

¹H NMR (400 MHz, DMSO-d₆)

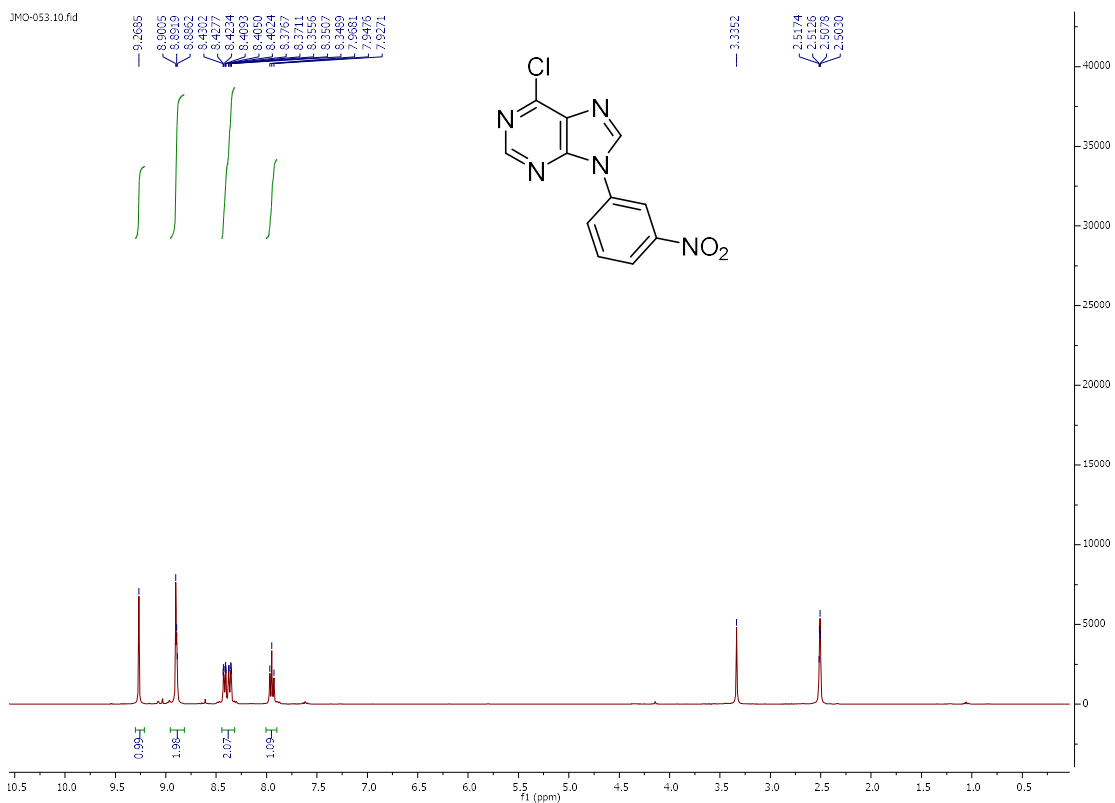


¹³C NMR (100 MHz, DMSO-d₆)

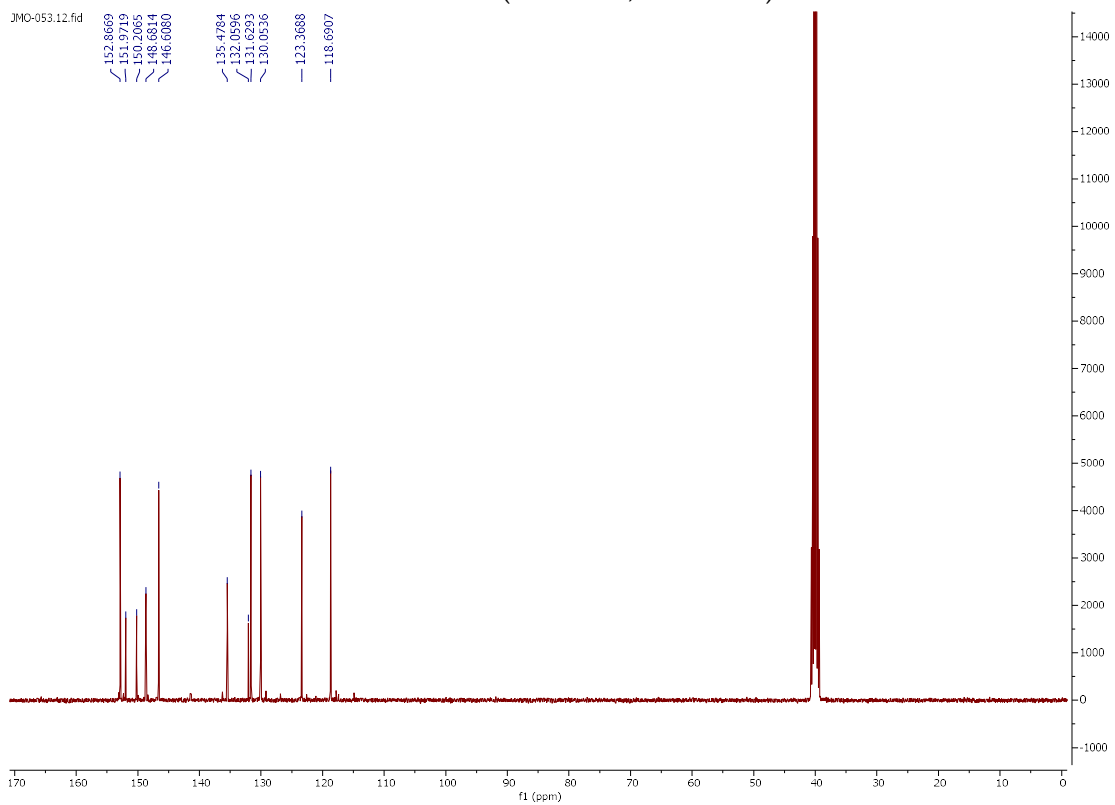


6-Chloro-9-(3-nitrophenyl)-9H-purine (19).

¹H NMR (400 MHz, DMSO-*d*₆)

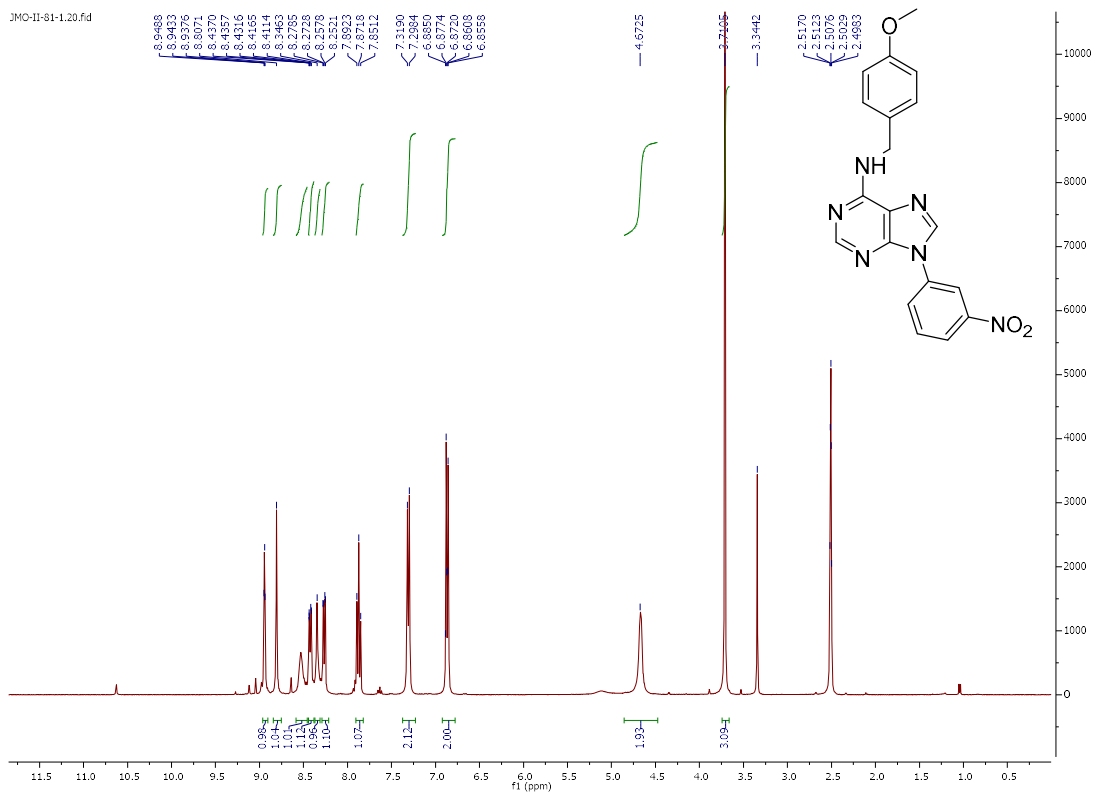


¹³C NMR (100 MHz, DMSO-*d*₆)

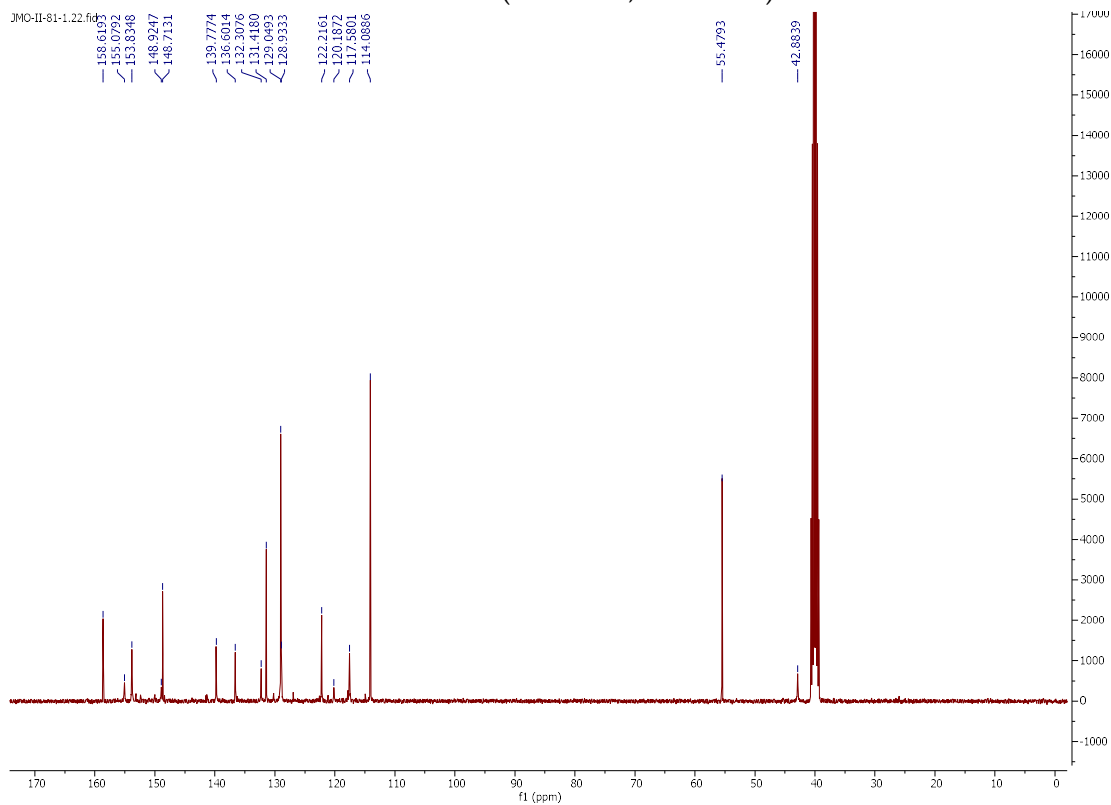


9-(3-Nitrophenyl)-N-(4-methoxybenzyl)-9H-purin-6-amine (20).

¹H NMR (400 MHz, DMSO-*d*₆)

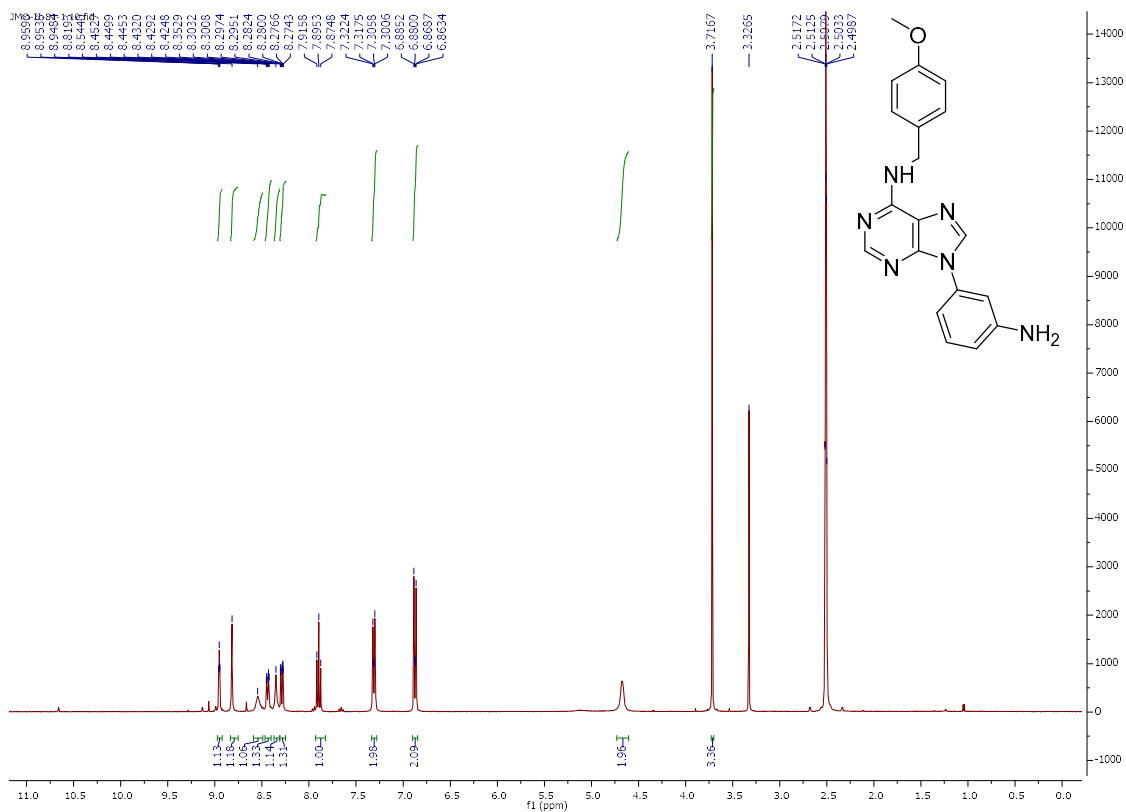


¹³C NMR (100 MHz, DMSO-*d*₆)

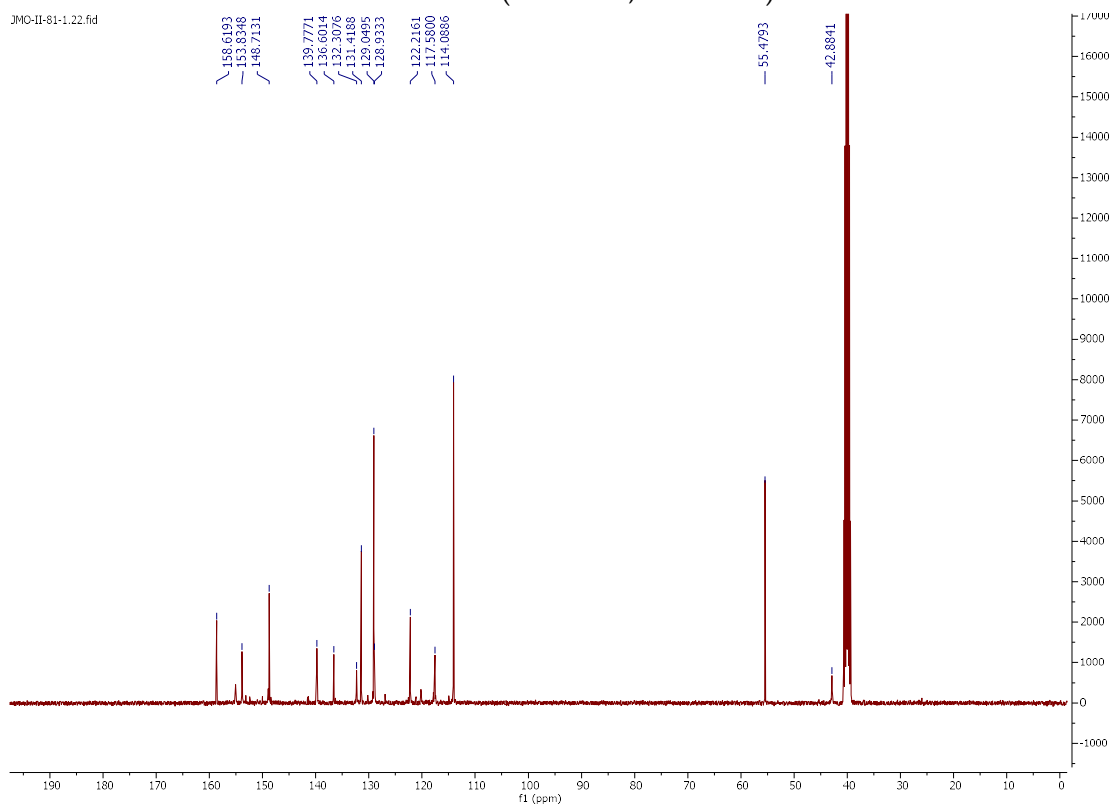


9-(3-Aminophenyl)-N-(4-methoxybenzyl)-9H-purin-6-amine (21).

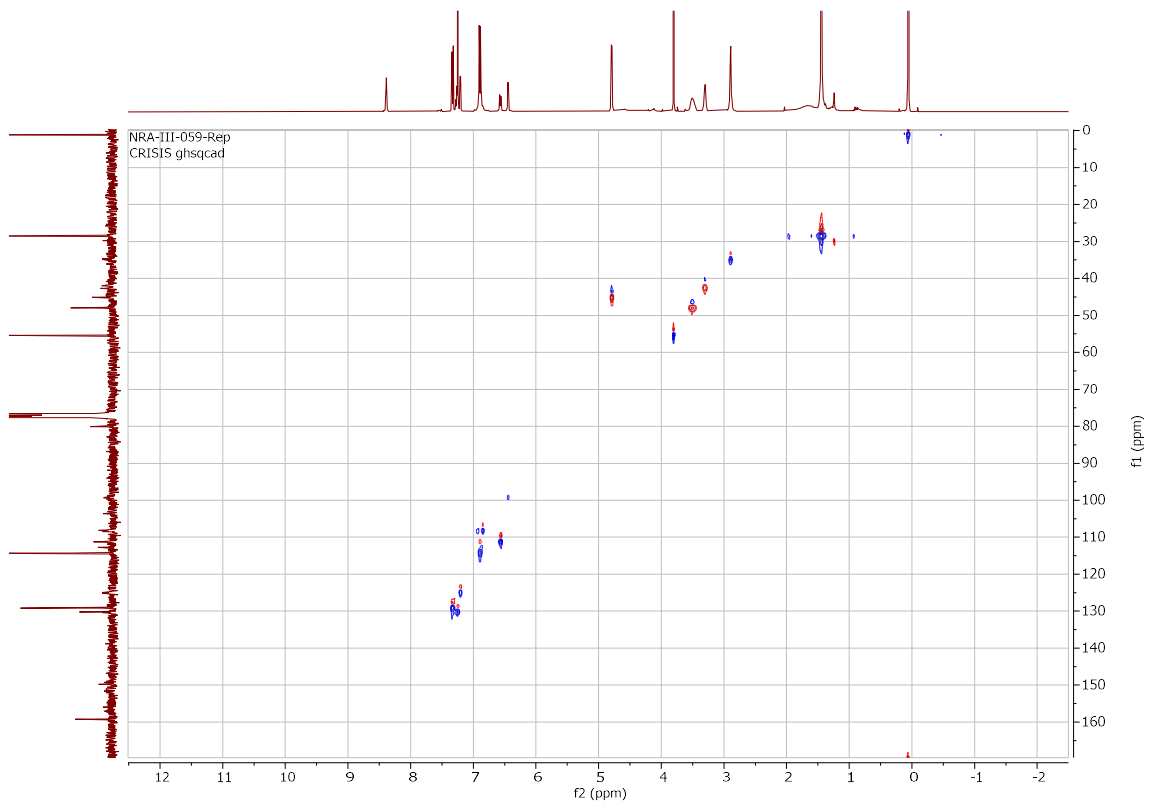
¹H NMR (400 MHz, DMSO-*d*₆)



¹³C NMR (100 MHz, DMSO-*d*₆)

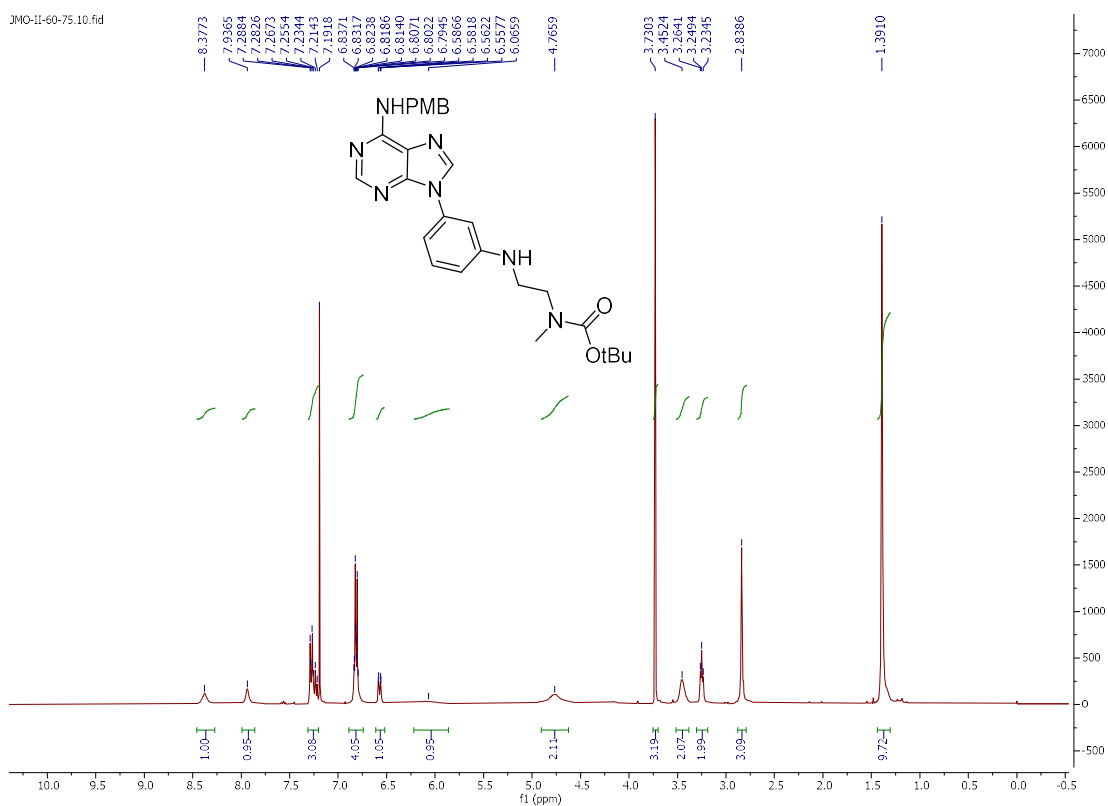


$^1\text{H}, ^{13}\text{C}$ HSQC NMR (CDCl_3)

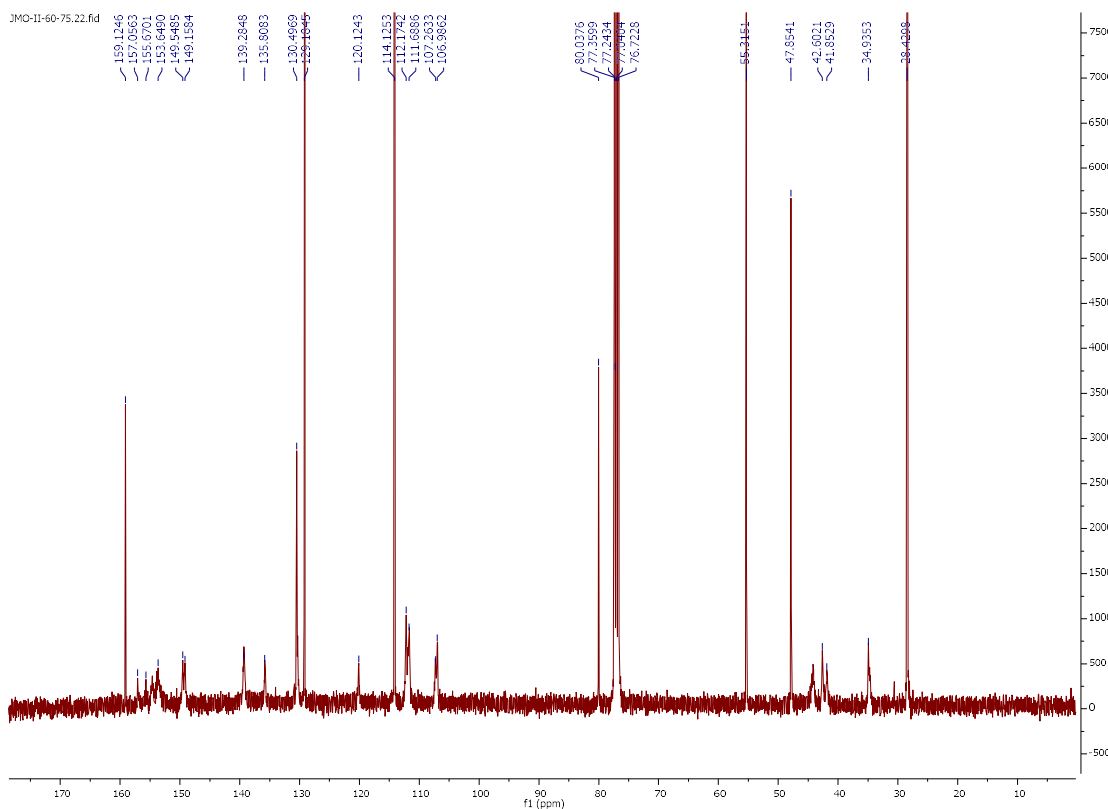


***tert*-Butyl (2-((3-(6-((4-methoxybenzyl)amino)-9*H*-purin-9-yl)phenyl)amino)ethyl) (methyl) carbamate (23).**

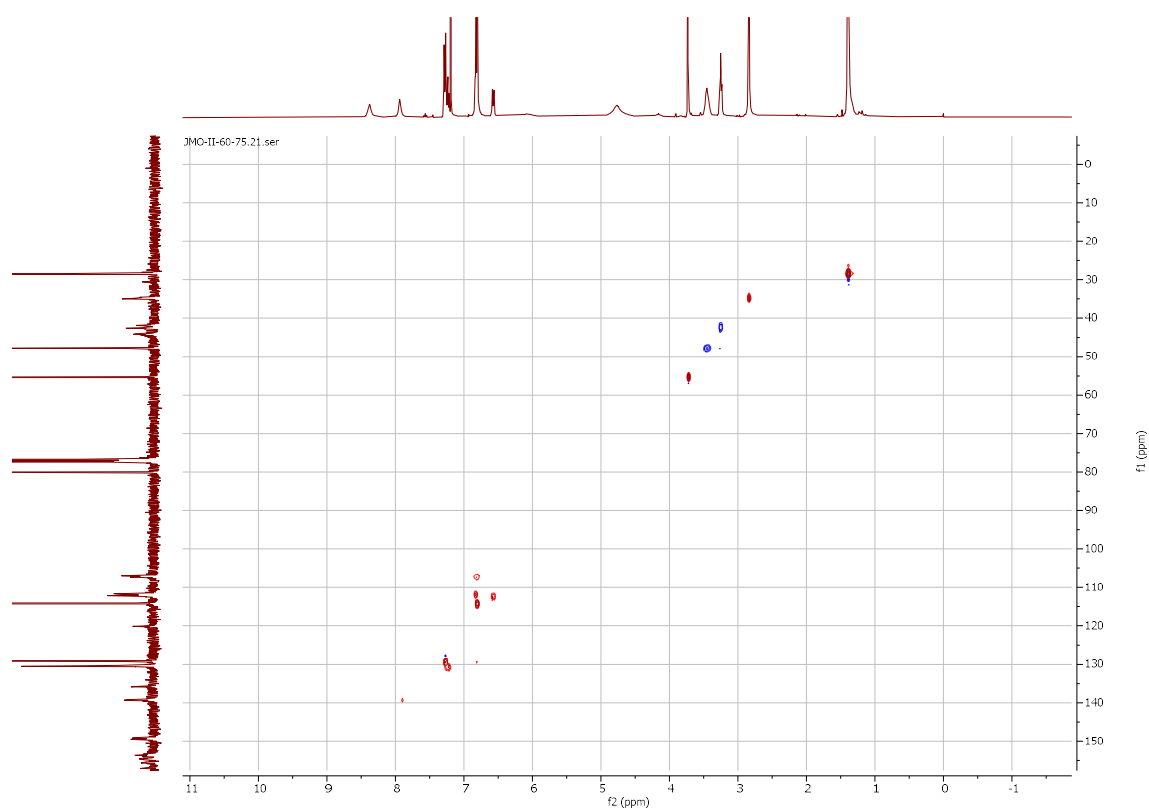
¹H NMR (400 MHz, CDCl₃)



¹³C NMR (100 MHz, CDCl₃)

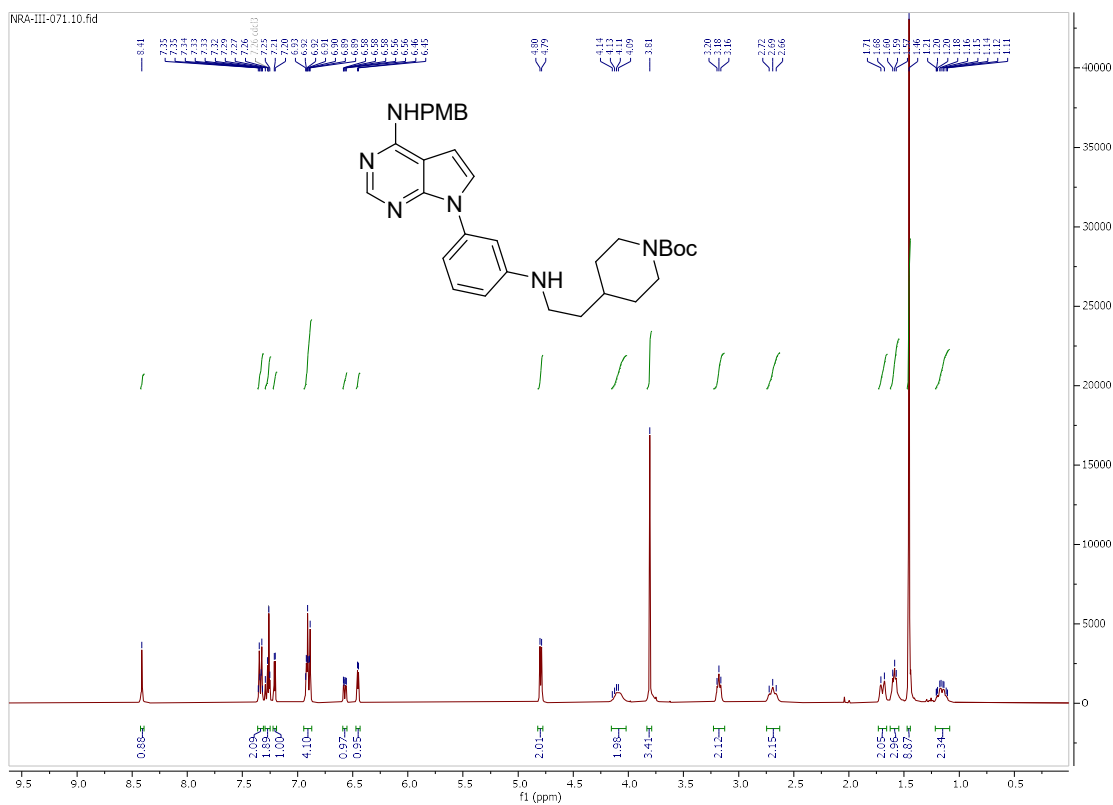


$^1\text{H}, ^{13}\text{C}$ HSQC NMR (CDCl_3)

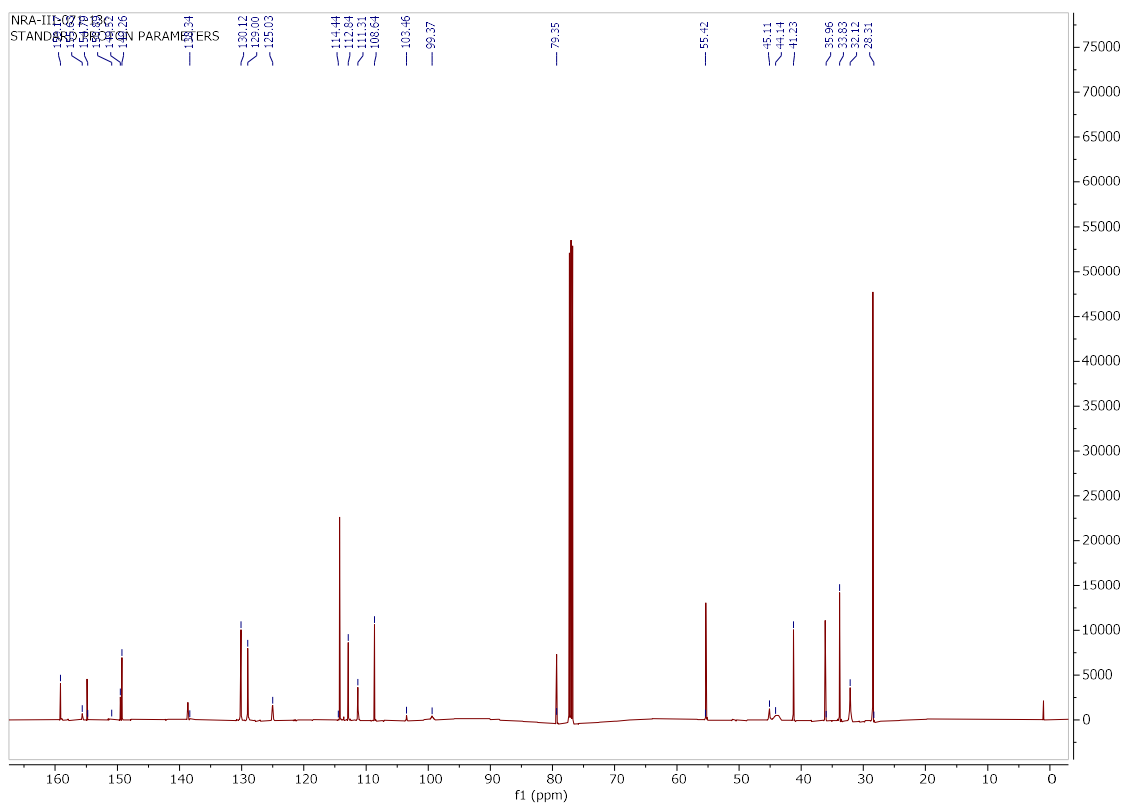


tert-Butyl 4-(2-((3-(4-((4-methoxybenzyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)amino)ethyl)piperidine-1-carboxylate (**24**).

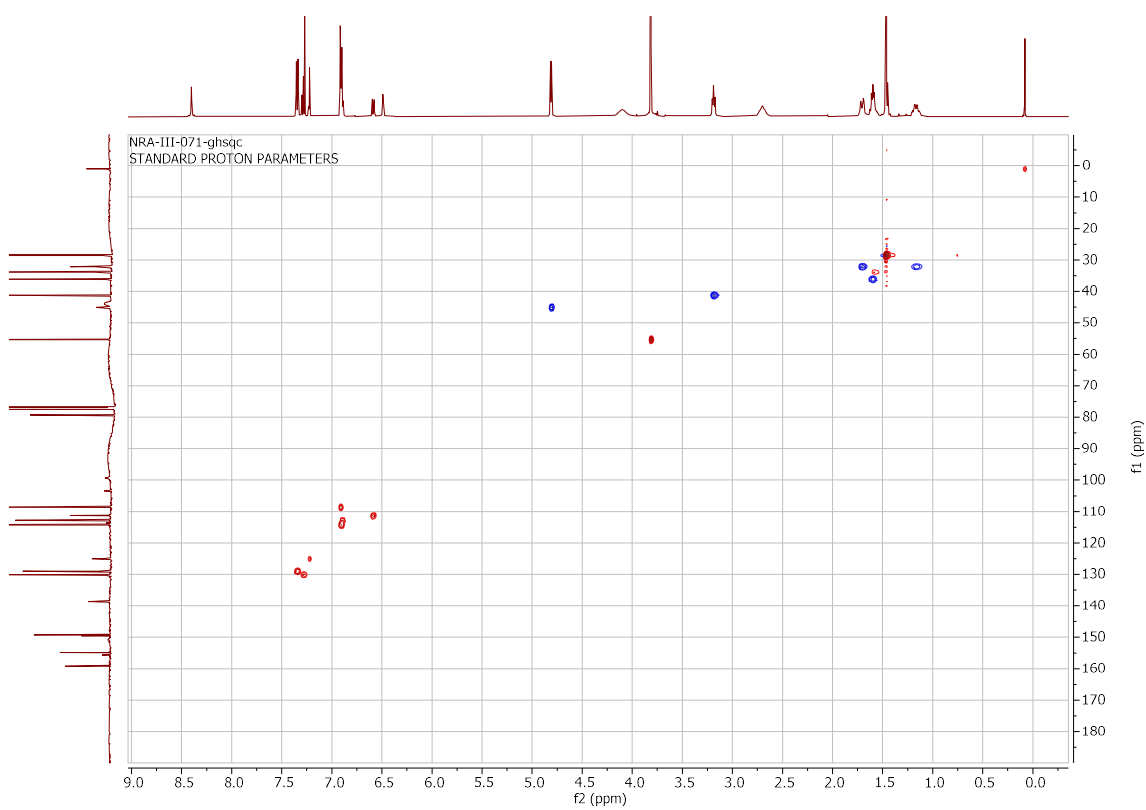
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR (126 MHz, CDCl_3)

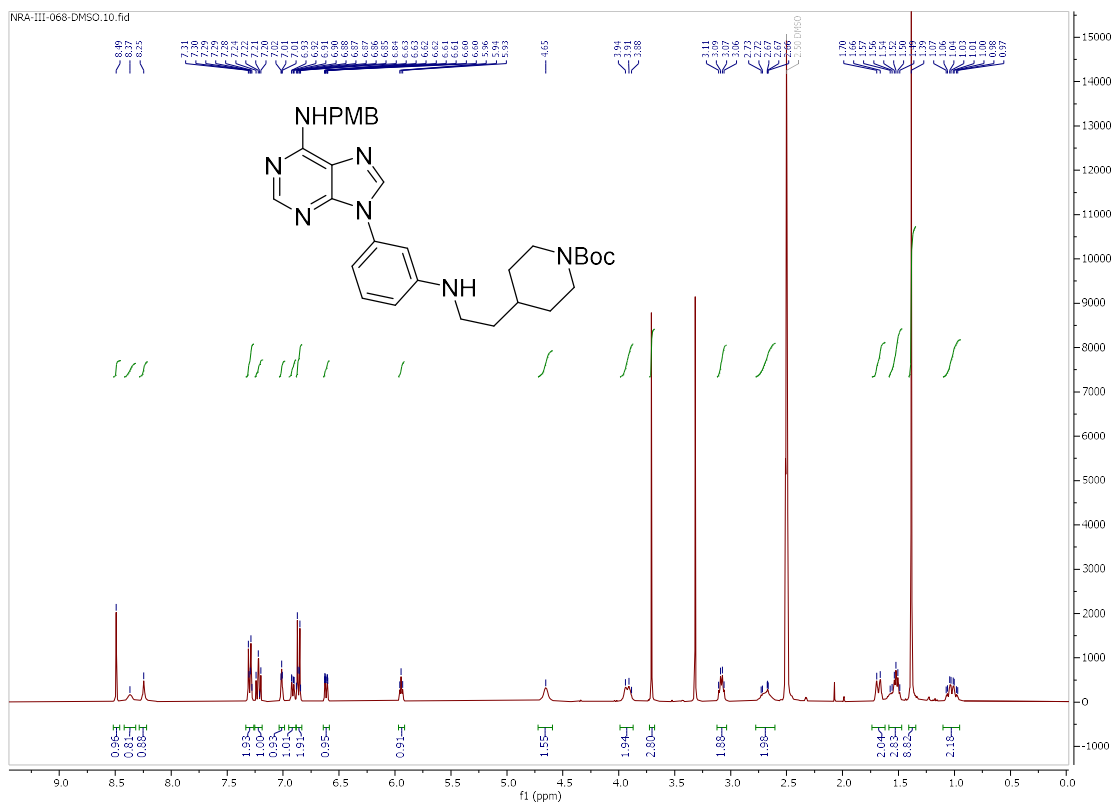


$^1\text{H}, ^{13}\text{C}$ HSQC NMR (CDCl_3)

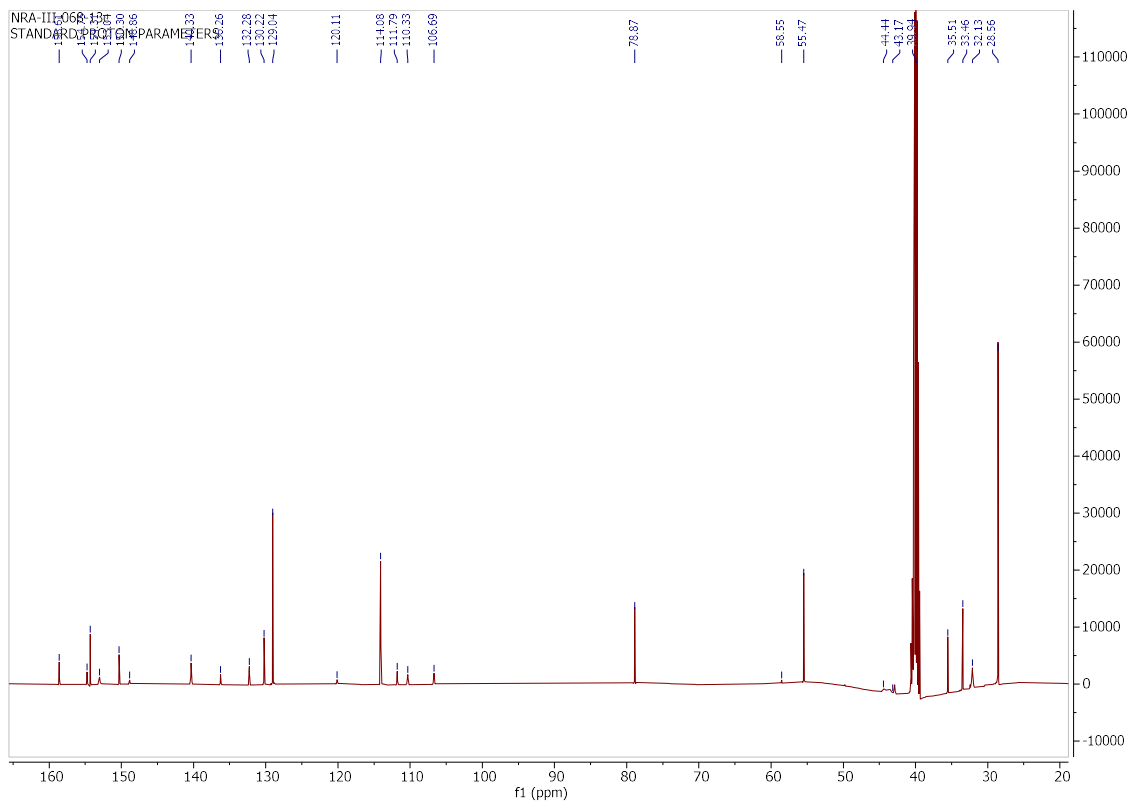


***tert*-Butyl 4-((3-(6-((4-methoxybenzyl)amino)-9*H*-purin-9-yl) phenyl)amino)ethyl) piperidine-1-carboxylate (25).**

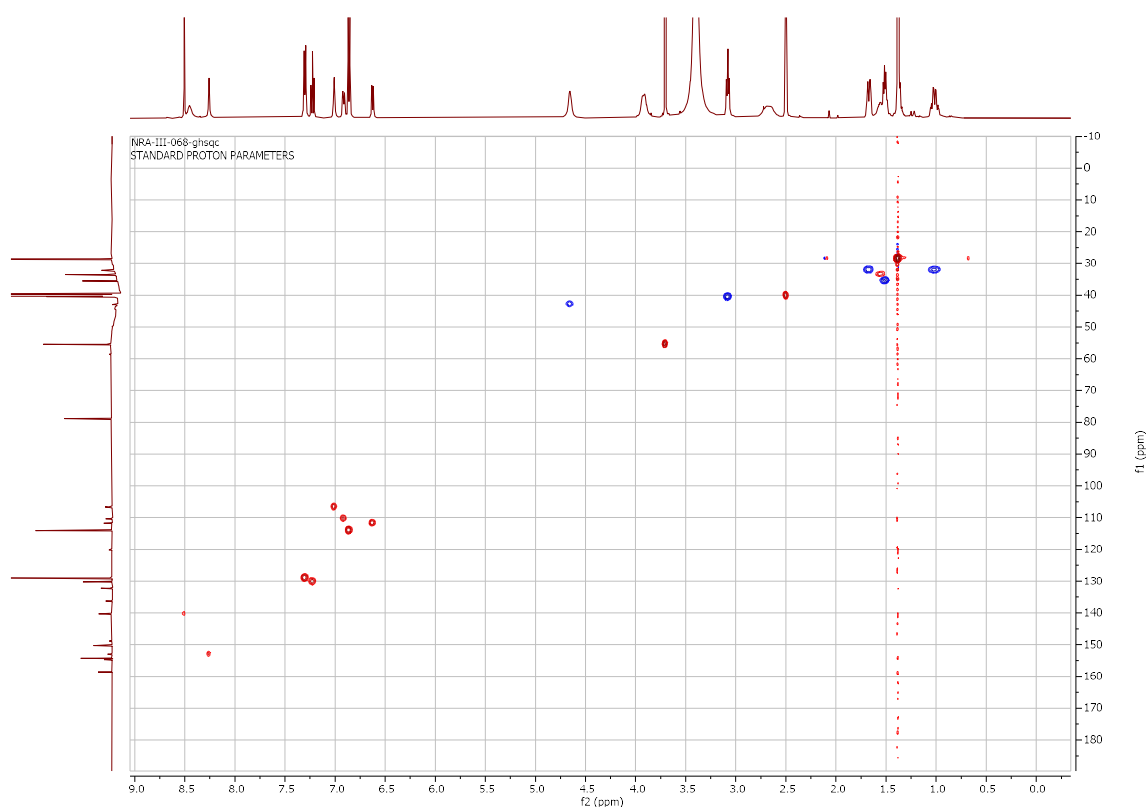
¹H NMR (400 MHz, DMSO-*d*₆)



¹³C NMR (126 MHz, DMSO-*d*₆)

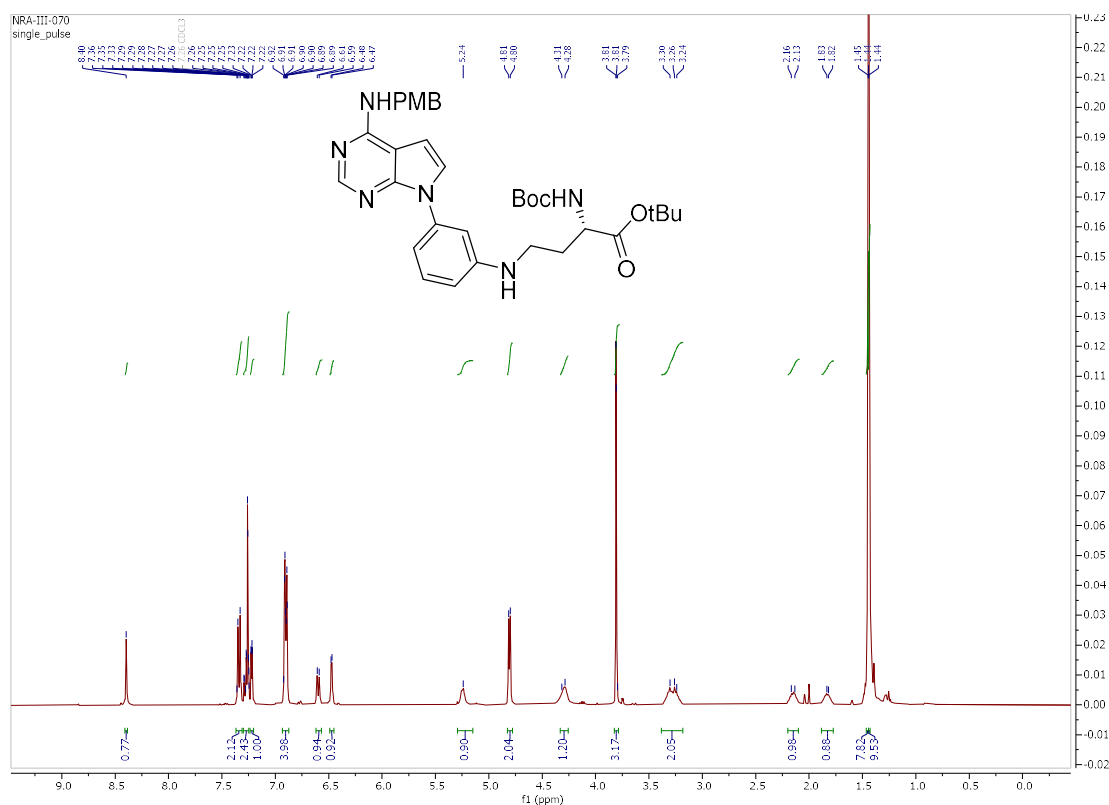


$^1\text{H}, ^{13}\text{C}$ HSQC NMR ($\text{DMSO-}d_6$)

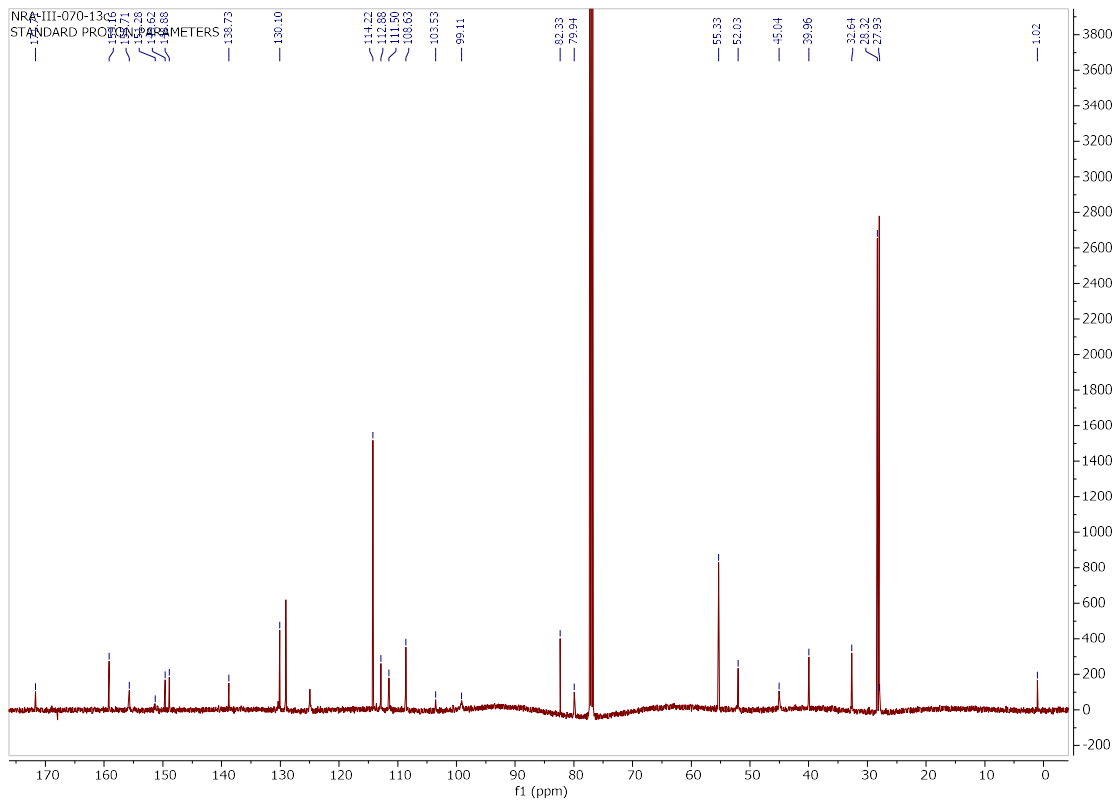


tert-Butyl (S)-2-((*tert*-butoxycarbonyl)amino)-4-((3-(4-((4-methoxybenzyl)amino)-7H-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)amino)butanoate (26).

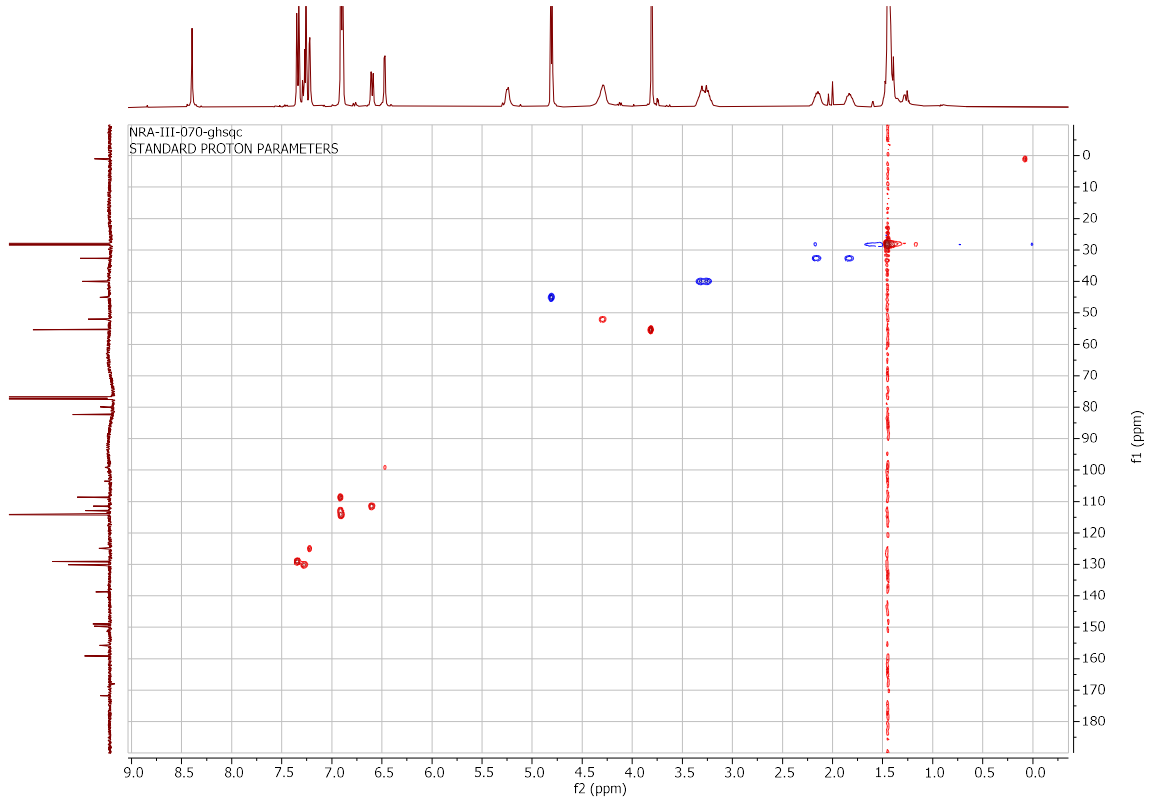
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR (126 MHz, CDCl_3)

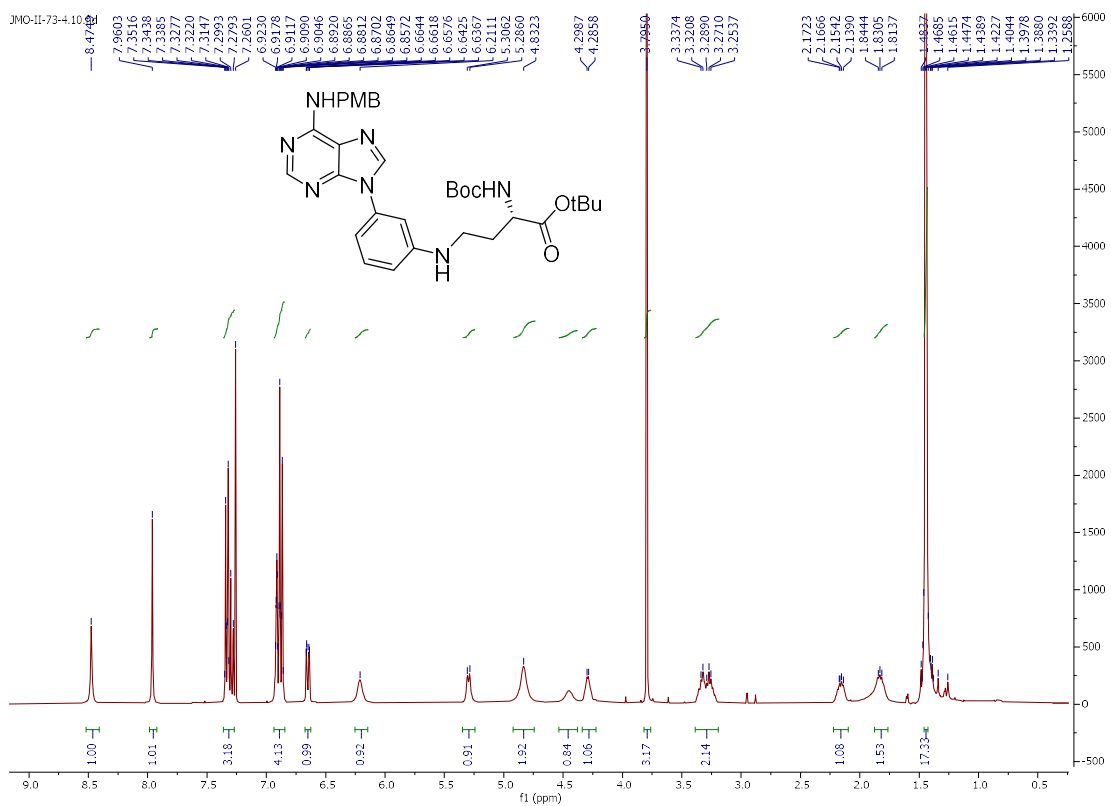


$^1\text{H}, ^{13}\text{C}$ HSQC NMR (CDCl_3)

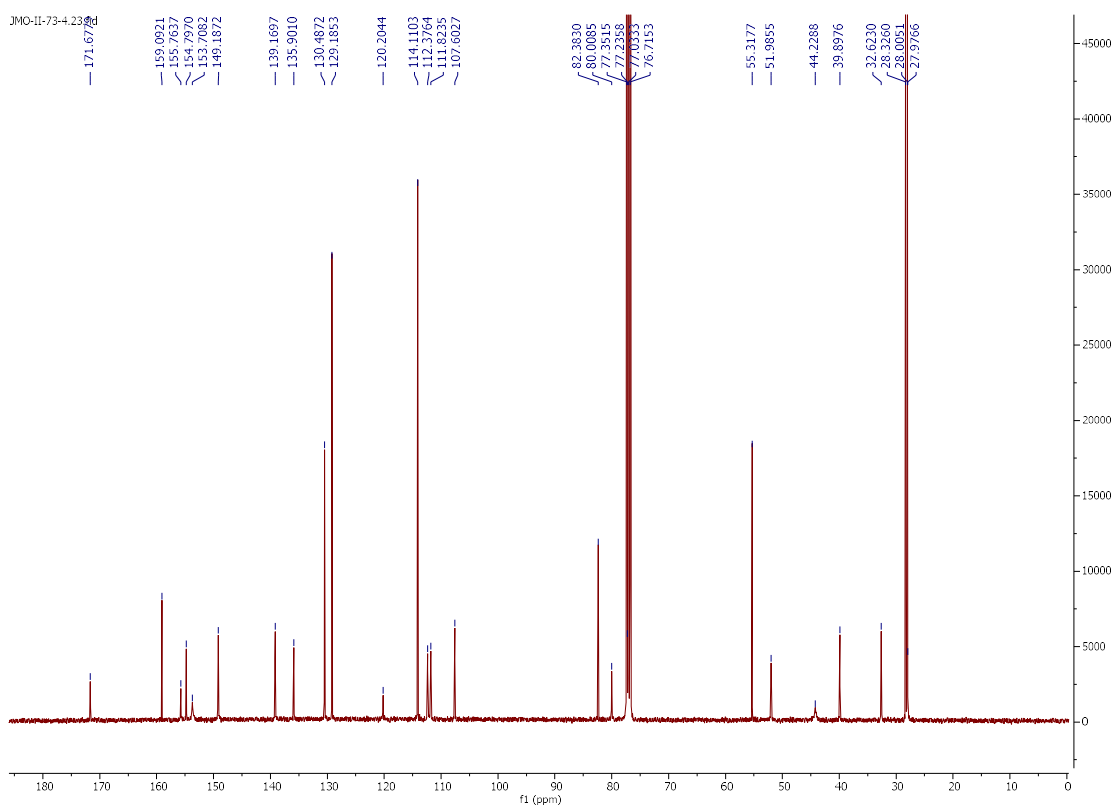


***tert*-Butyl (S)-2-((*tert*-butoxycarbonyl)amino)-4-((3-(6-((4-methoxybenzyl)amino)-9H-purin-9-yl)phenyl)amino)butanoate (27).**

¹H NMR (400 MHz, CDCl₃)

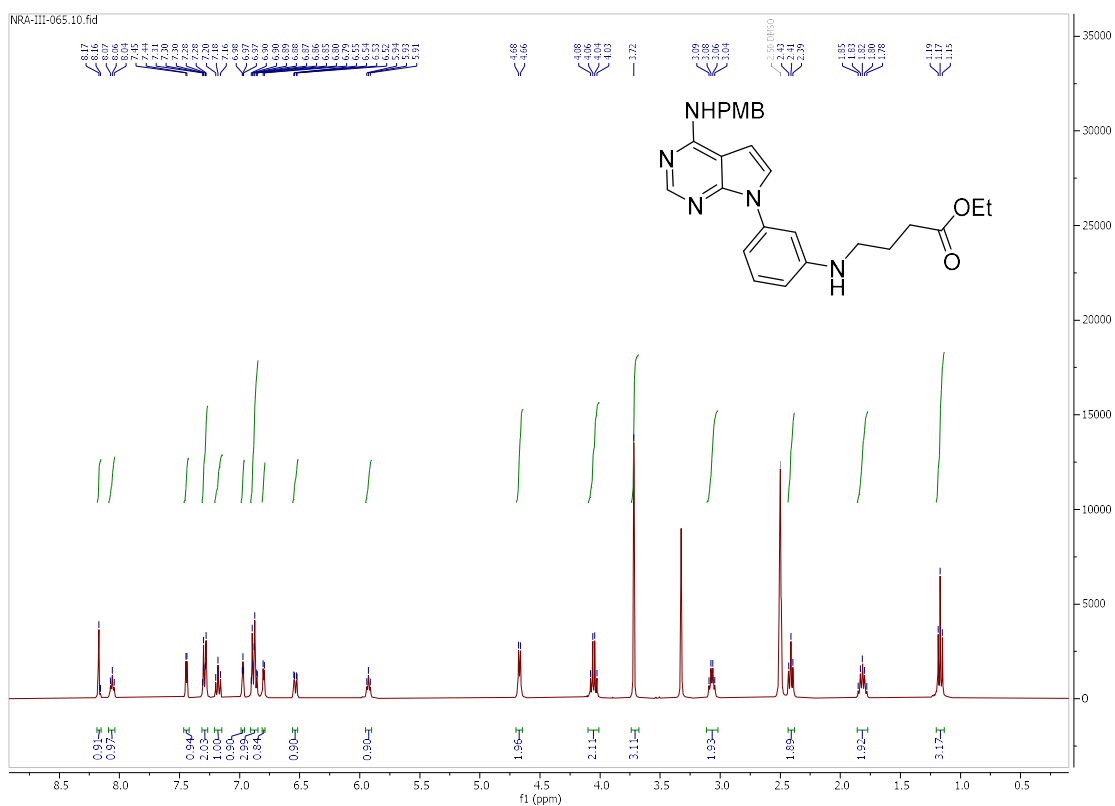


¹³C NMR (100 MHz, CDCl₃)

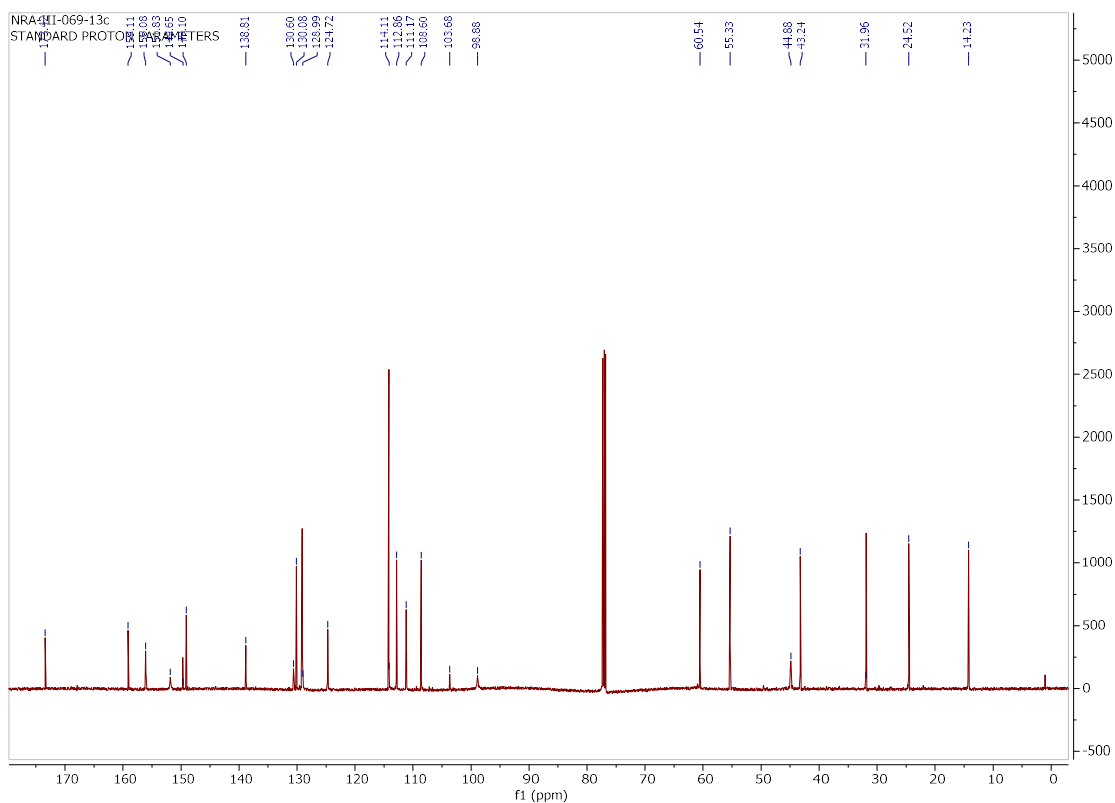


Ethyl 4-((3-(4-((4-methoxybenzyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)phenyl)amino)butanoate (28).

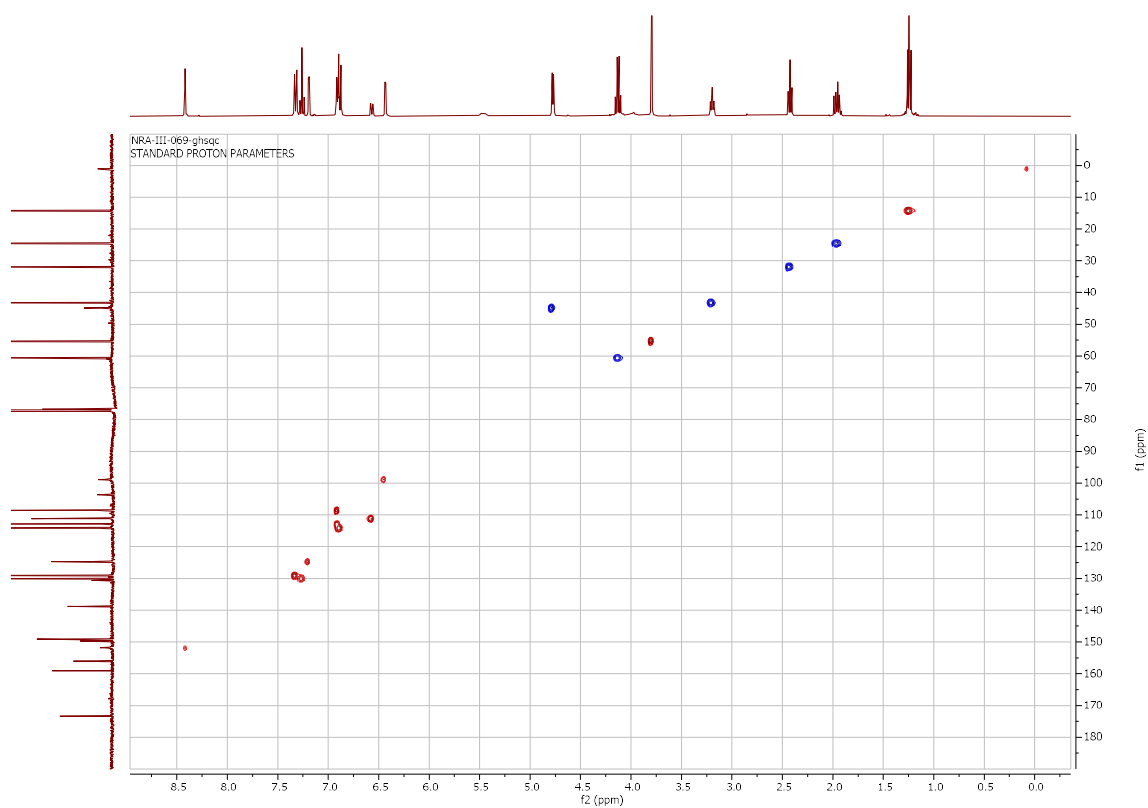
¹H NMR (400 MHz, DMSO-*d*₆)



¹³C NMR (126 MHz, CDCl₃)

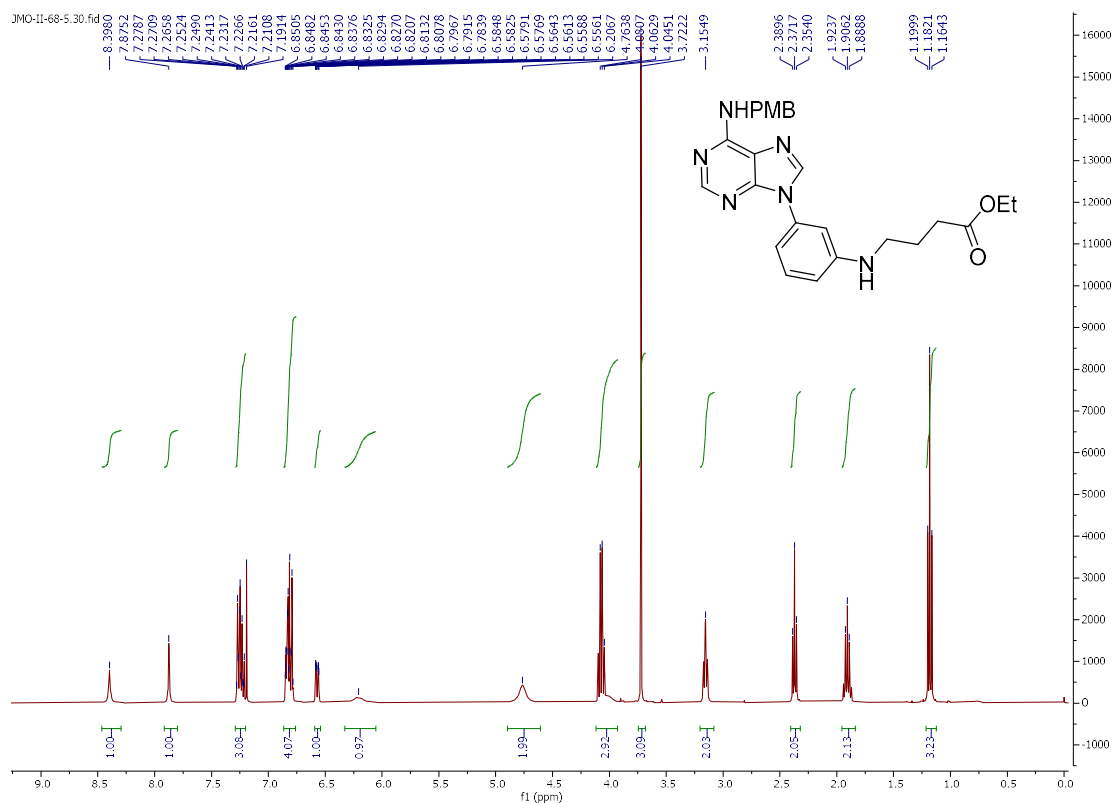


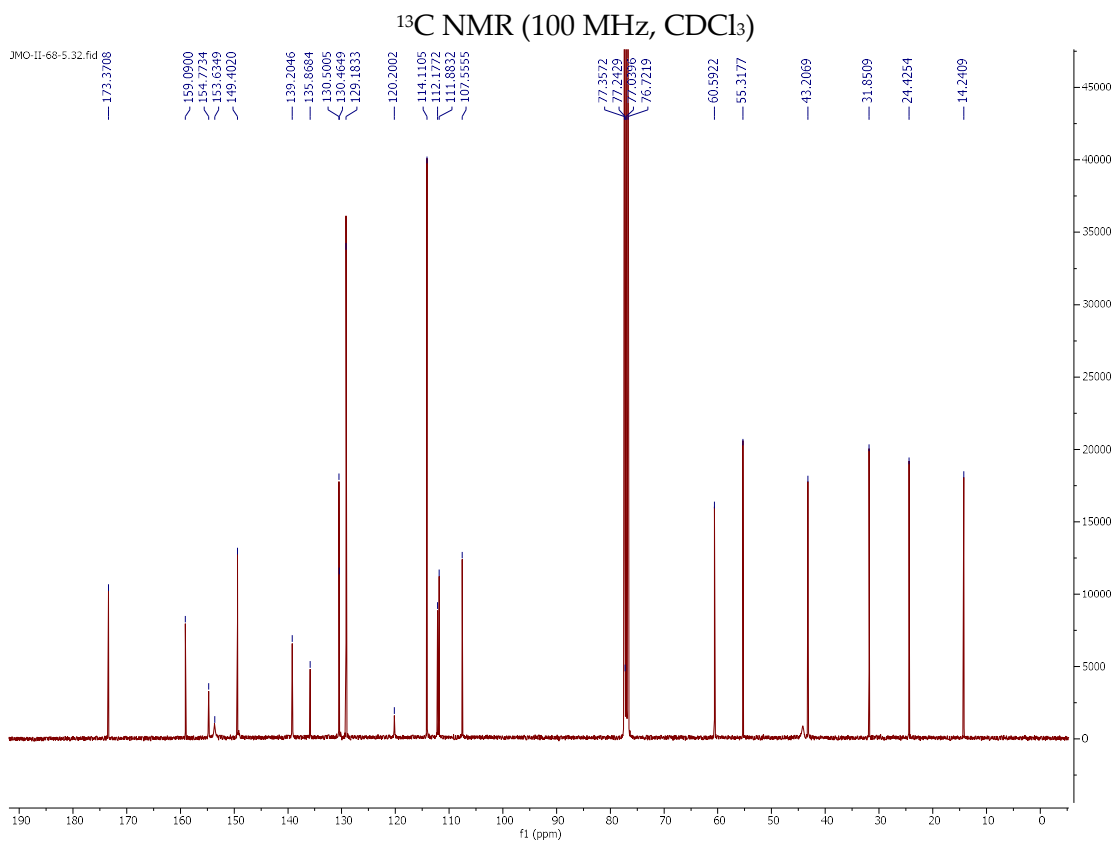
$^1\text{H}, ^{13}\text{C}$ HSQC NMR (CDCl_3)



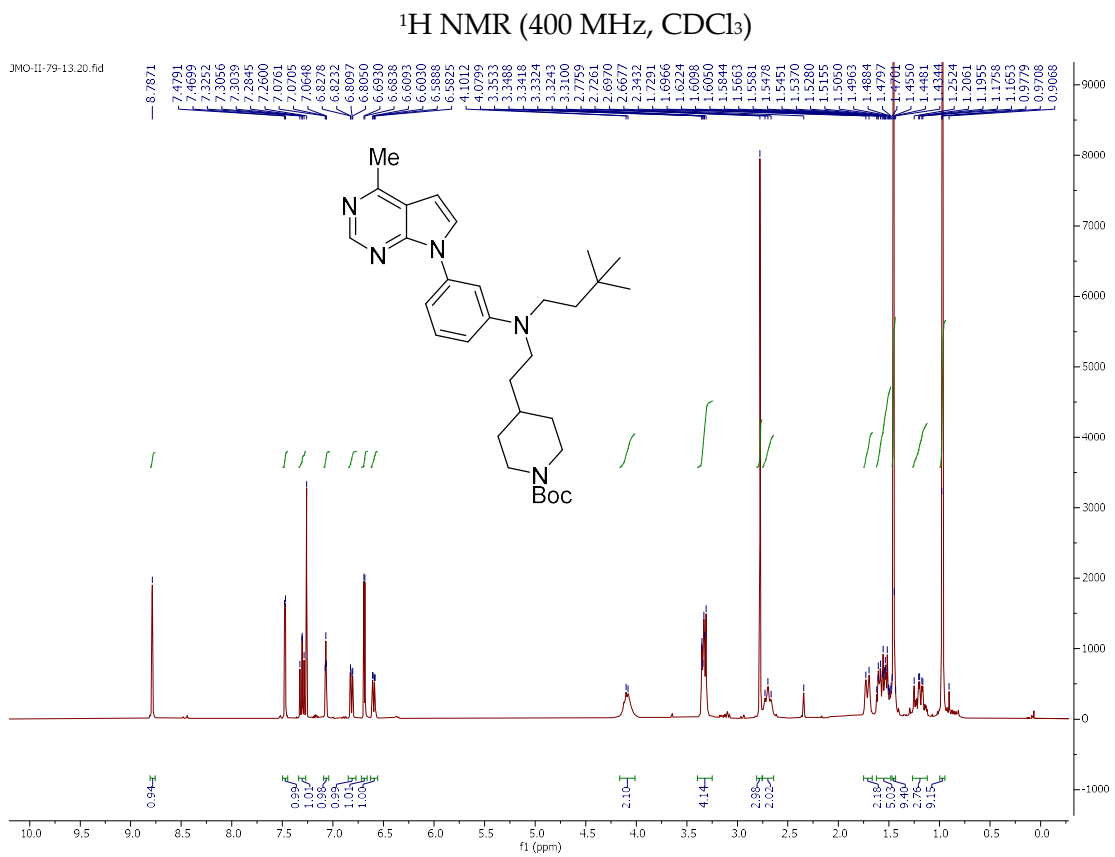
Ethyl 4-((3-(6-((4-methoxybenzyl)amino)-9H-purin-9-yl)phenyl)amino)butanoate (29).

^1H NMR (400 MHz, CDCl_3)

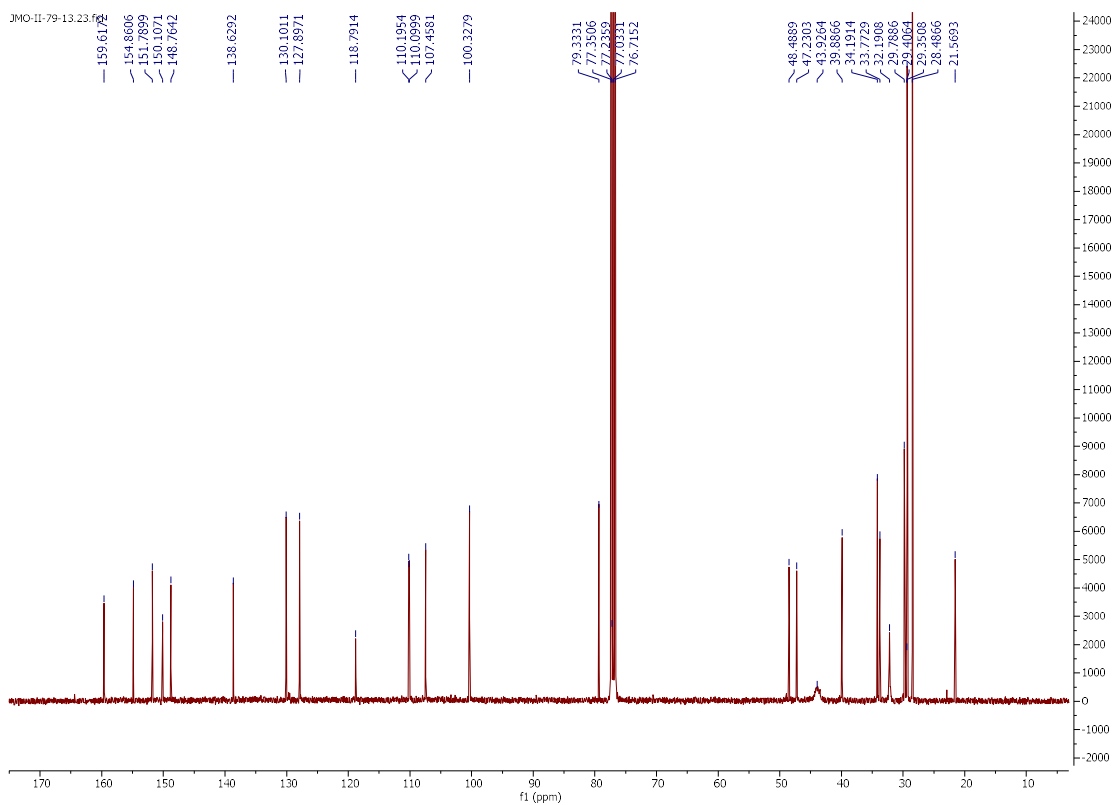




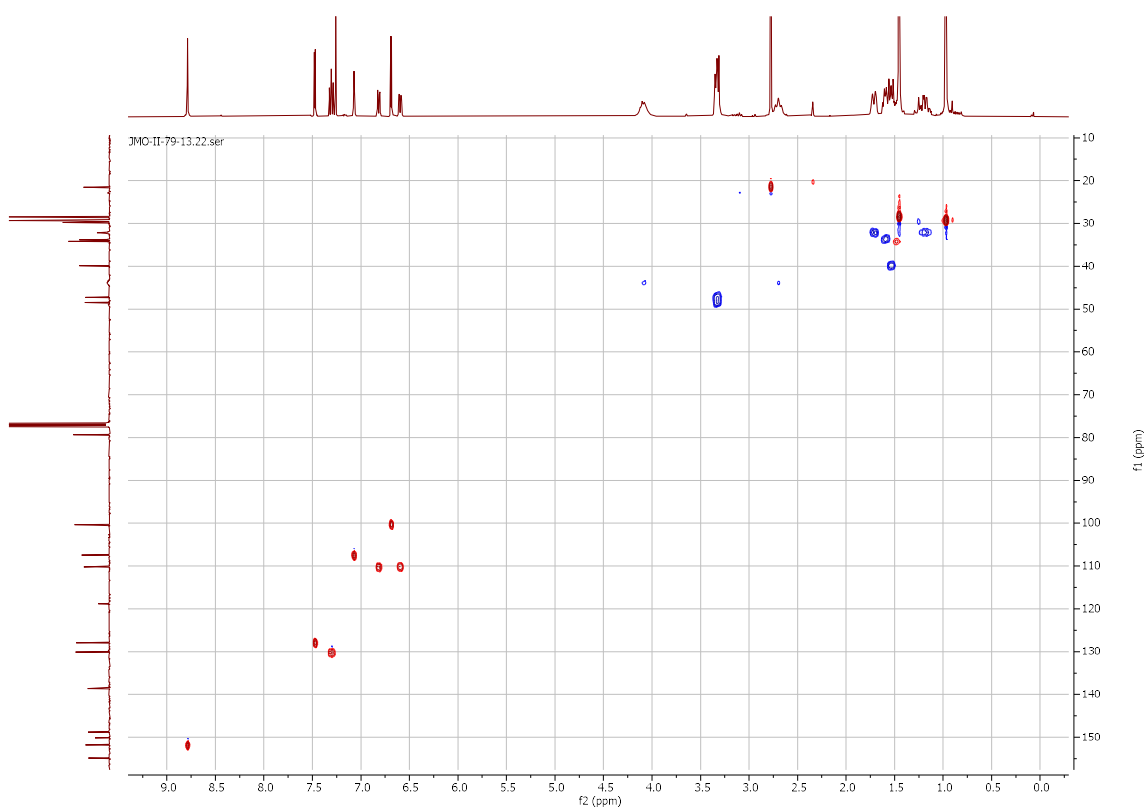
tert-Butyl 4-(2-((3,3-dimethylbutyl)(3-(4-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)amino)ethyl)piperidine-1-carboxylate, (30).



¹³C NMR (100 MHz, CDCl₃)

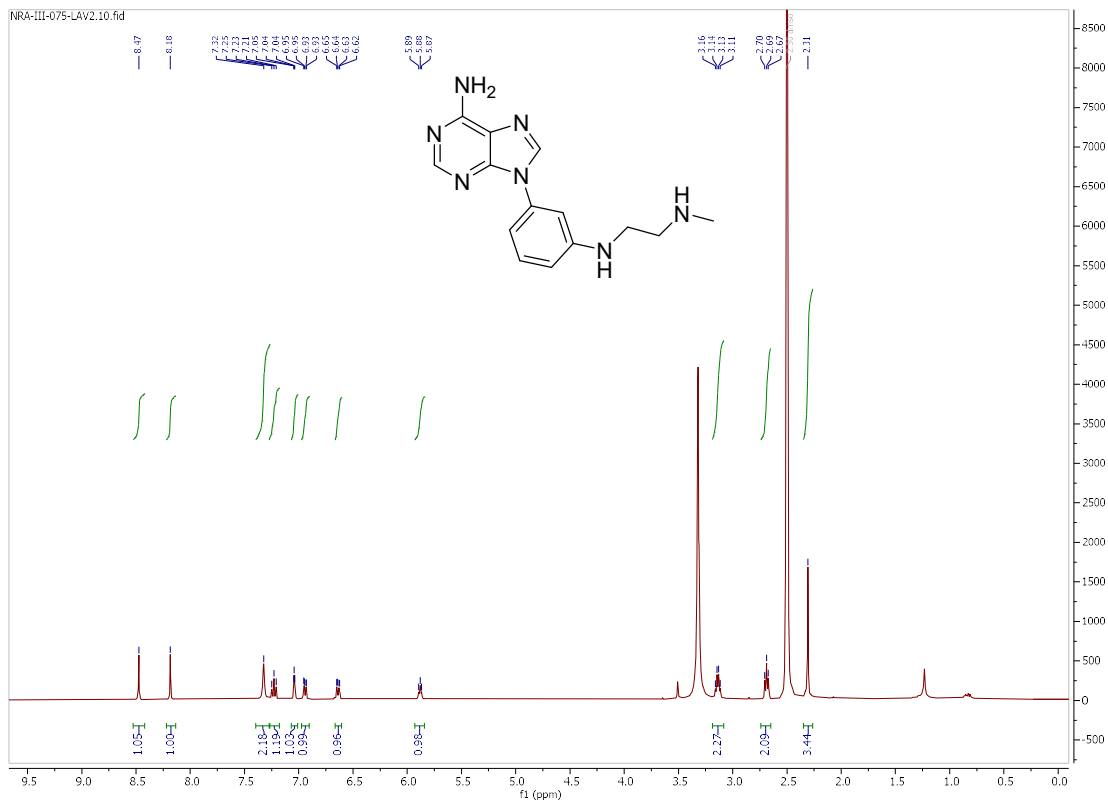


¹H, ¹³C HSQC NMR (CDCl₃)



***N*¹-(3-(4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)-*N*²-methylethane-1,2-diamine (31).**

¹H NMR (400 MHz, DMSO-*d*₆)



¹³C NMR (100 MHz, CDCl₃)

