Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Metal-Free Direct C-6-H Alkylation of Purines and Purine Nucleosides Enabled by Oxidative Homolysis of 4-Alkyl-1,4-Dihydropyridines at Room Temperature

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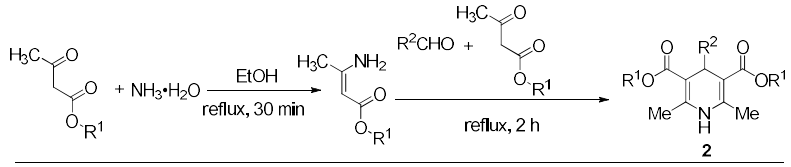
Contents

1. Substrate scope of DHPs

4-Alkyl-1,4-dihydropyridines **2** were synthesized by the methods in previous reports [1-3]. And the DHPs were listed below.



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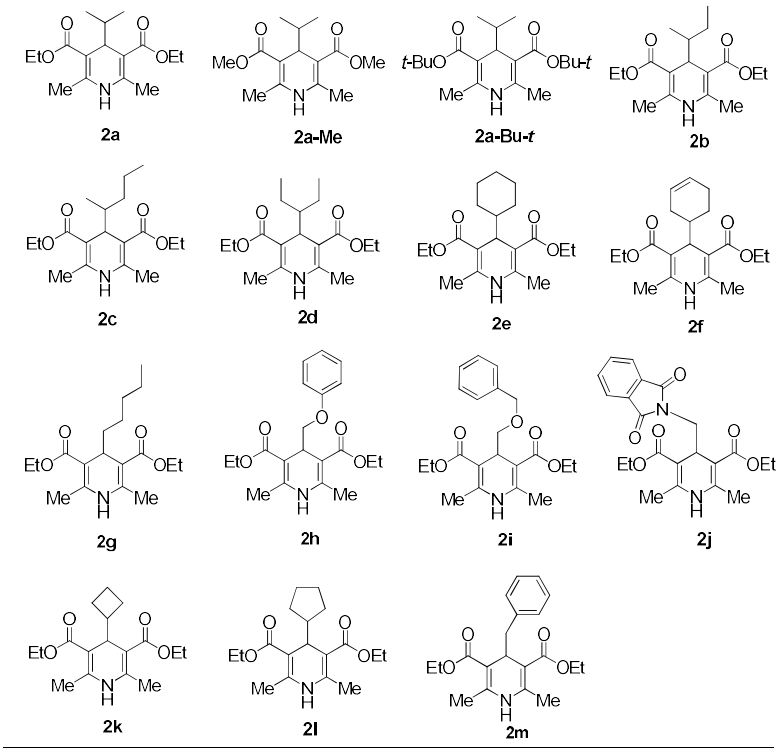


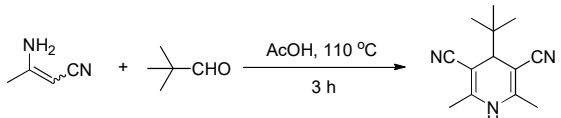
2a **2a-Me** **2a-Bu-*t*** **2b**

2c **2d** **2e** **2f**

2g **2h** **2i** **2j**

2k **2l** **2m**

Nitrile Hantszch ester were synthesized by the methods in previous reports.[4]



2n

References

1. Á. Gutierrez-Bonet, C. Remeur, J. K. Matsui and G. A. Molander, *J. Am. Chem. Soc.*, 2017, **139**, 12251–12258

2. Y. Byun, J. Moon, W. An, N. K. Mishra, H. S. Kim, P. Ghosh and I. S. Kim, *J. Org. Chem.,* 2021, **86**, 12247–12256.

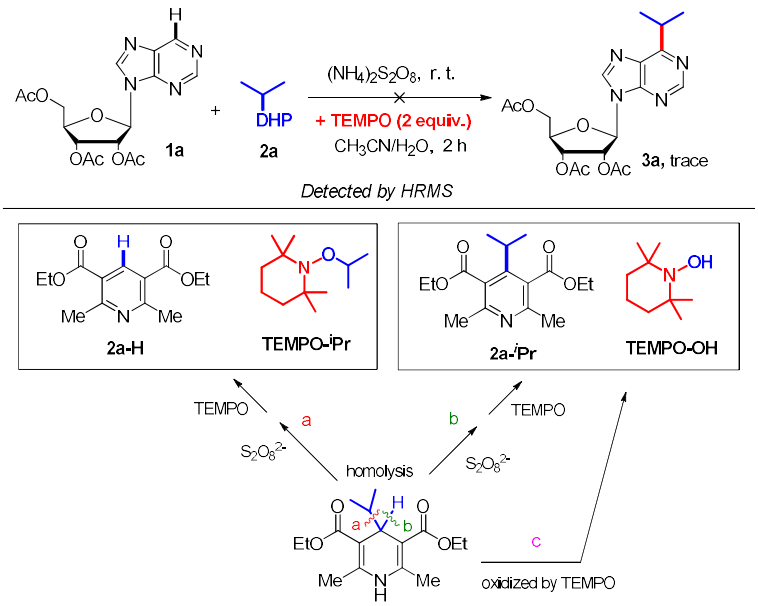
3. B. Loev and K. M. Snader. *J. Org. Chem.,* 1965, **30**,1914-1916.

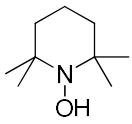
4. W. X. Chen, Z. Liu, J. Q. Tian, J. Li, J. Ma, X. Cheng and G. G. Li, *J. Am. Chem. Soc.*, 2016, **138**, 12312

2. Radical Trapping Experiment with TEMPO

Under ambient atmosphere, substrate **1a** (0.26 mmol) and DHP **2a** (0.39 mmol, 1.5 equiv.) were dissolved in CH_3CN/H_2O (0.75 mL + 0.75 mL) in a 5 mL vial. $(NH_4)_2S_2O_8$ (0.39 mmol, 1.5 equiv.) and 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 0.52 mmol, 2.0 equiv.) were then added to the mixture. Degassing-backfilling with nitrogen for 5 times to remove the oxygen in the system. The system was then reacted at room temperature for 3 h. Then, 5% K_2CO_3 aqueous solution (2 mL) was added to the mixture to adjust pH value. Subsequently, the solution was extracted with ethyl acetate (30 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered. The crude organic phase was detected by HPLC-HRMS with ESI ion source under positive mode.

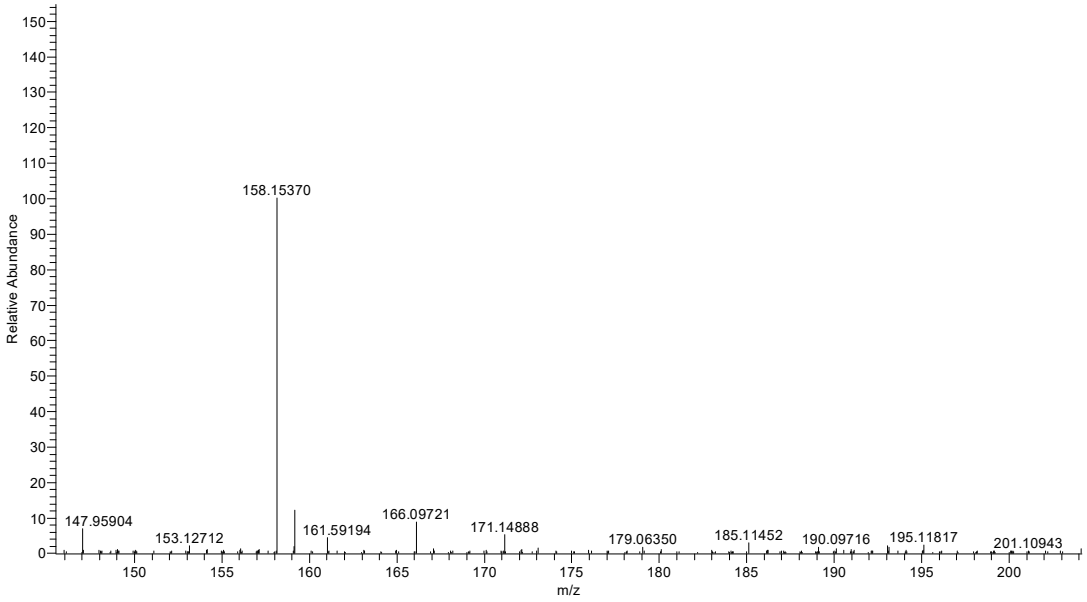
The reaction was obviously inhibited, which mean a radical process might be involved. Four different compounds were detected by HRMS, which perhaps were **2a-H**, **2a-^{i}Pr**, **TEMPO-^{i}Pr**, and **TEMPO-OH** according to the exact mass ($[M+H]^+$). The mechanism about the generation of these compounds was as follow. There is a radical process in the reaction. Firstly, the single electron transfer (SET) oxidation of the DHP **2a** by $S_2O_8^{2-}$ resulted in the formation of a series of species (pyridine **2a-H**, isopropyl radical (*i*-Pr$^\bullet$), etc.) via homolysis. Then, the capturing of isopropyl radical (*i*-Pr$^\bullet$) by TEMPO could form TEMPO-^{i}Pr (route a). In fact, we think that the single electron transfer (SET) oxidation of the DHP **2a** by $S_2O_8^{2-}$ possibly also resulted in another species (pyridine **2a-^{i}Pr**, and high active radical (H$^\bullet$), which was immediately captured by **TEMPO** to form **TEMPO-OH** (route b). Besides, the DHP **2a** was also possibly oxidized by **TEMPO**, resulting in the formation of **2a-^{i}Pr** and **TEMPO-OH** (route c).

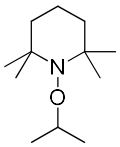




HRMS of TEMPO-OH

DHP-TEMPO_20221101154701 #857 RT: 4.64 AV: 1 SB: 96 3.41-3.65 , 5.51-5.78 NL: 3.25E6
T: FTMS + c ESI Full ms [80.0000-1200.0000]





HRMS of TEMPO-^{i}Pr

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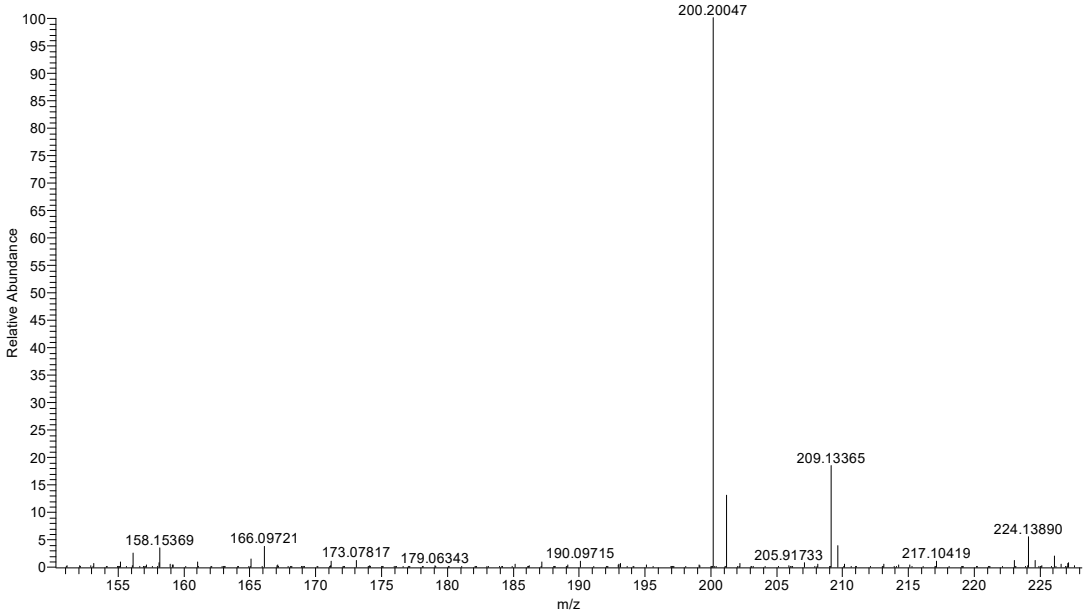
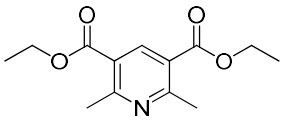
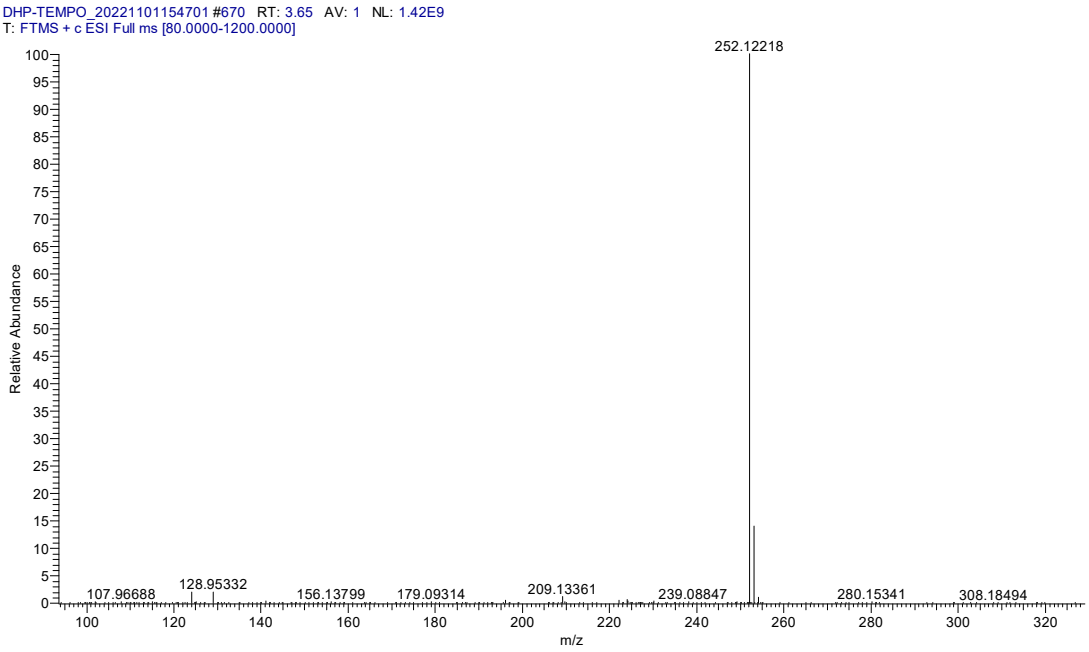
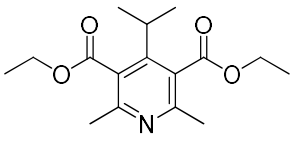


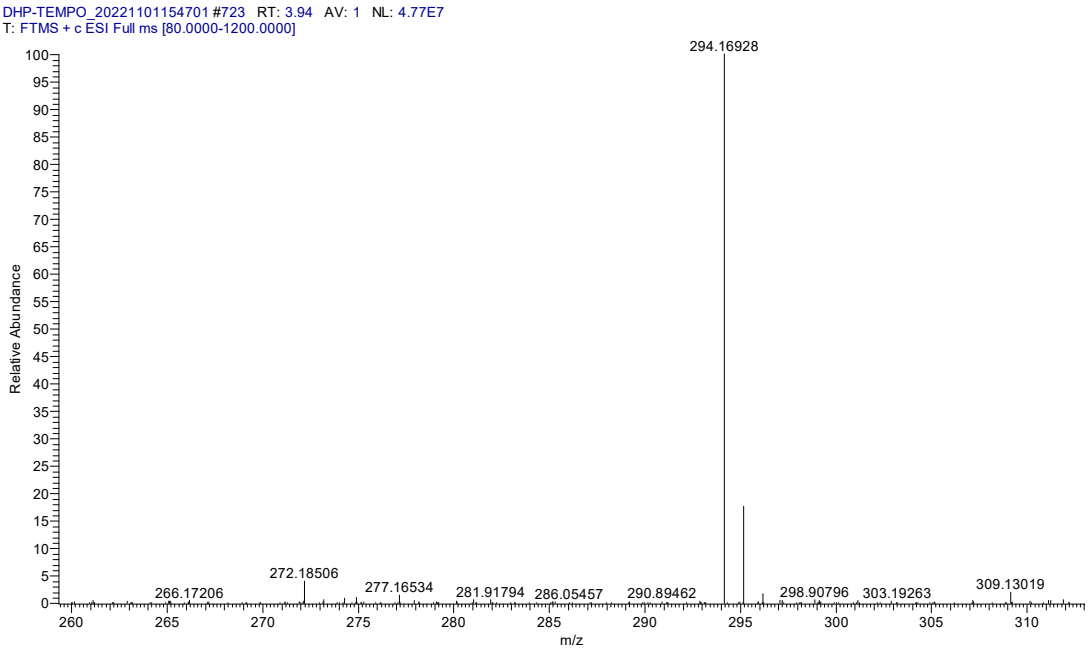


HRMS of 2a-H



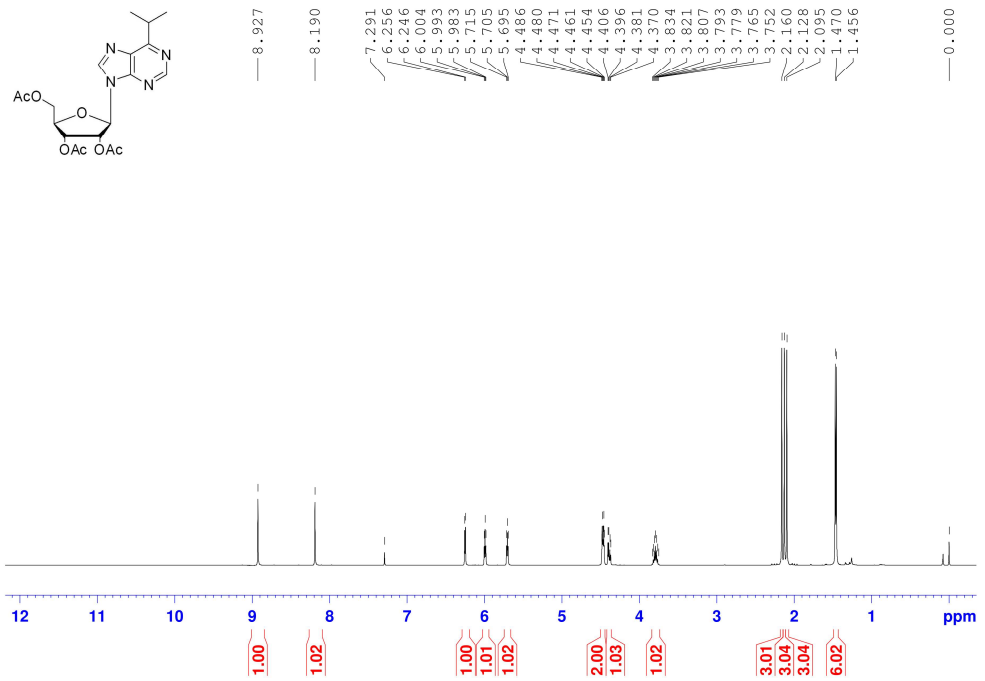


HRMS of 2a-^{i}Pr

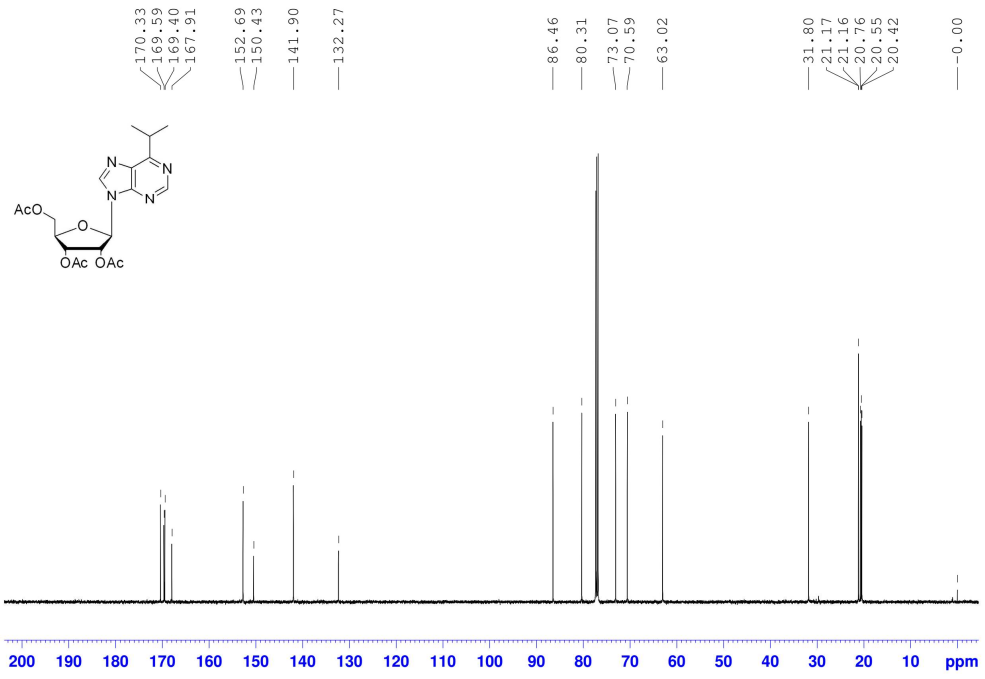


3. ^{1}H NMR and ^{13}C NMR Spectra of the Products

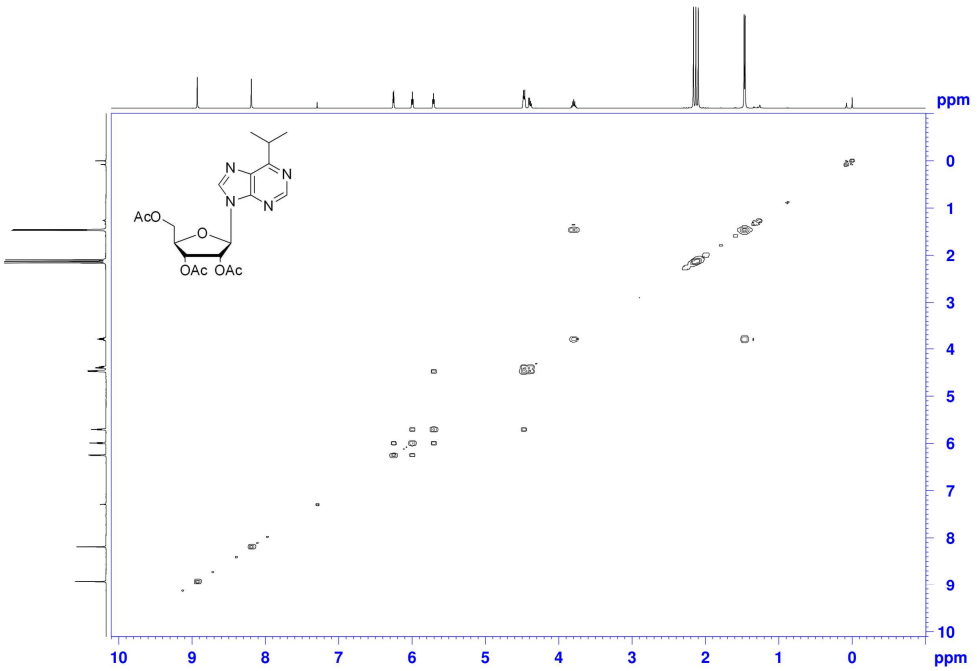
^{1}H NMR of 6-isopropyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**3a**) in 500 MHz, $CDCl_3$



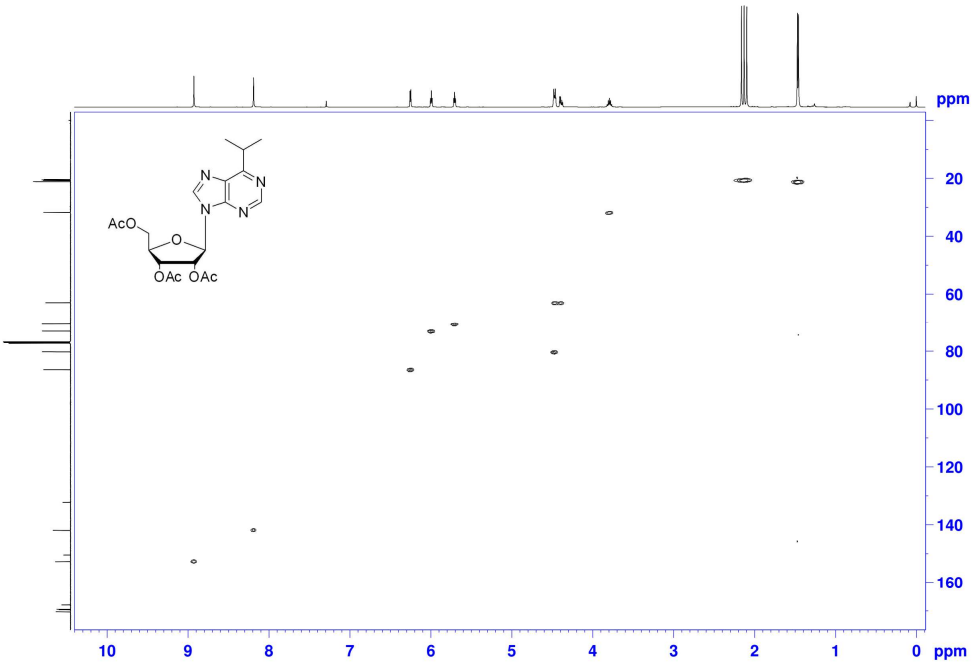
^{13}C NMR of 6-isopropyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**3a**) in 125 MHz, $CDCl_3$



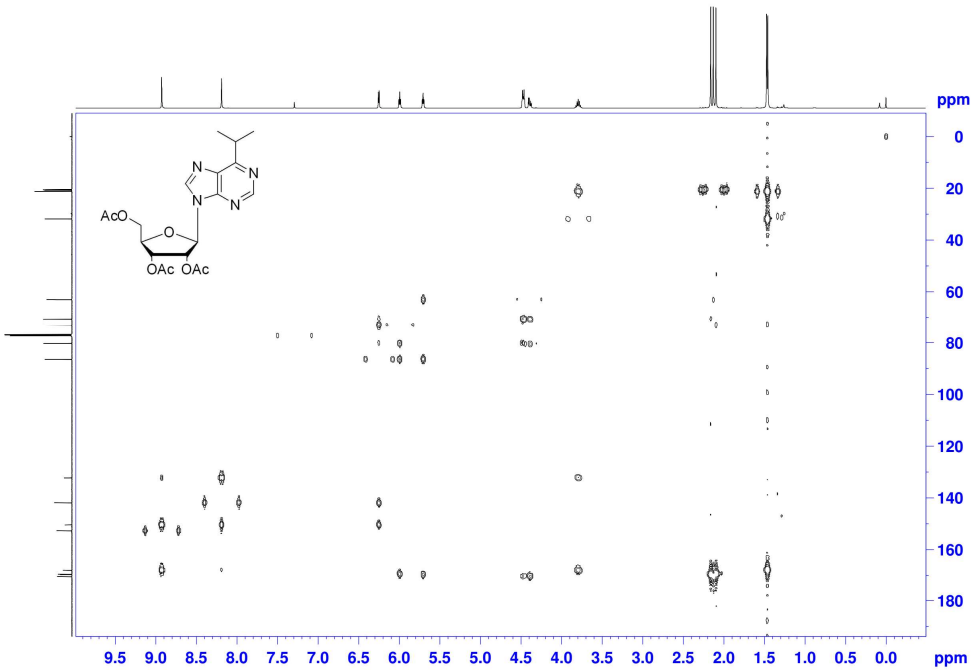
^{1}H-^{1}H COSY of 6-isopropyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**3a**) in 500 MHz, $CDCl_3$



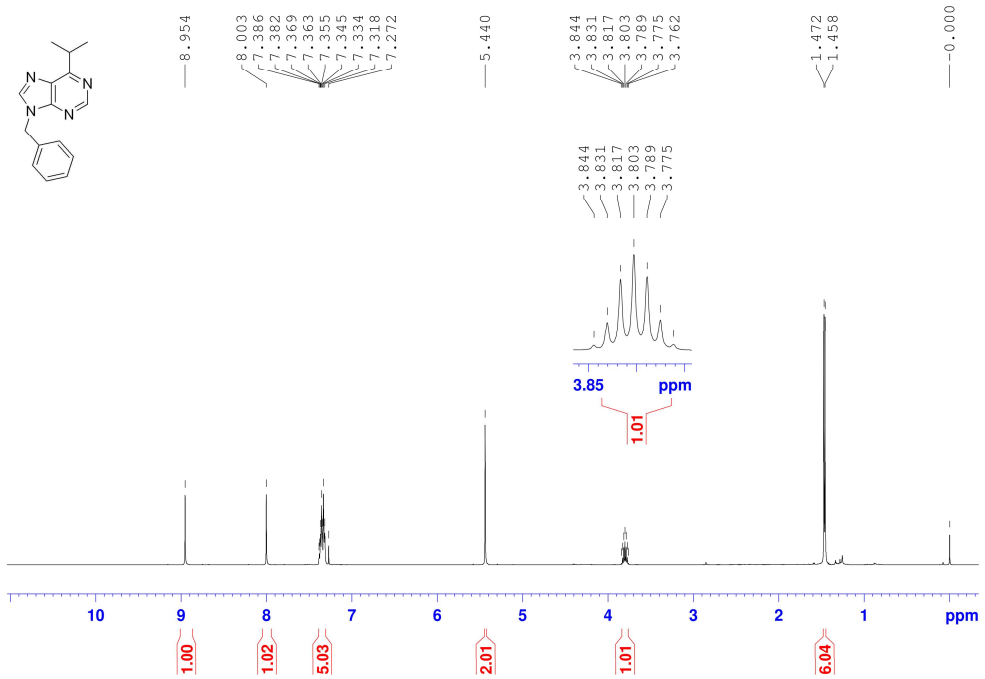
^{1}H-^{13}C COSY of 6-isopropyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**3a**) in $CDCl_3$



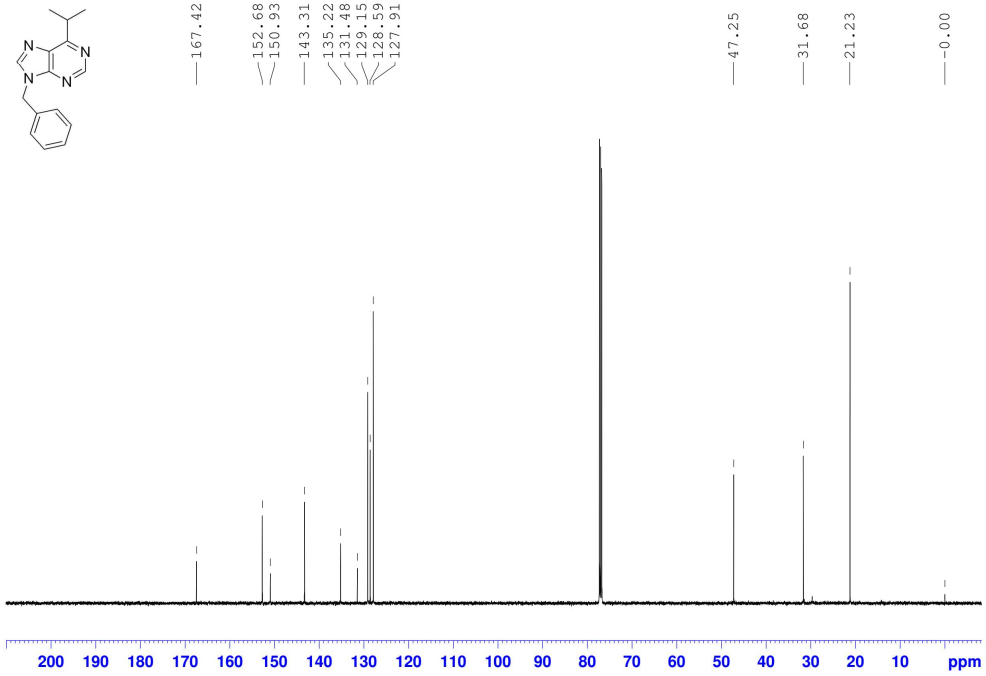
HMBC of 6-isopropyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**3a**) in $CDCl_3$



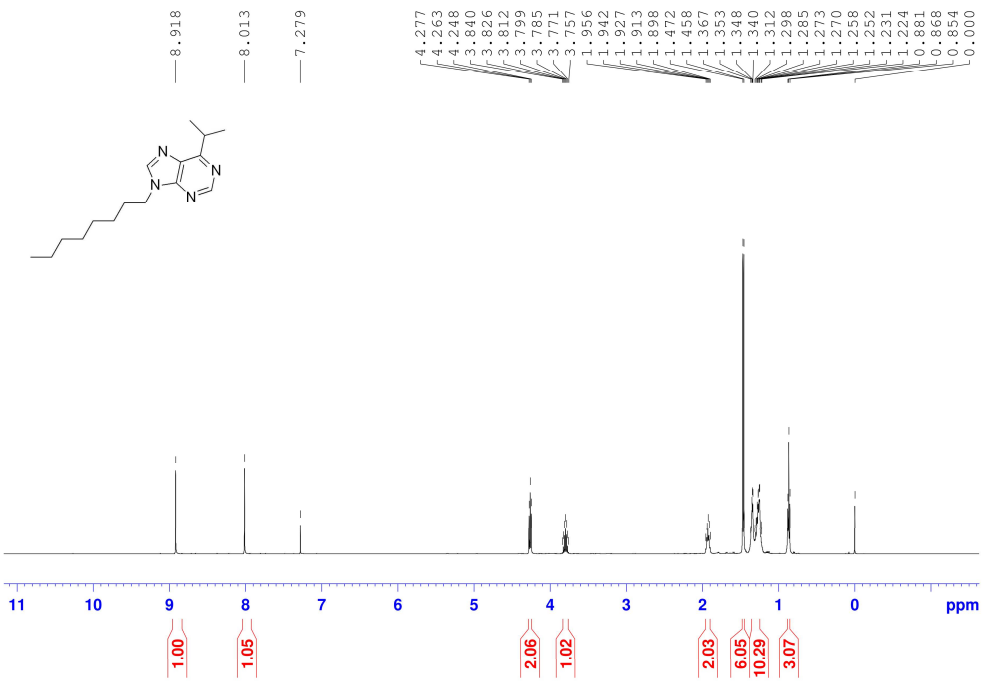
^{1}H NMR of 9-benzyl-6-isopropyl-*9H*-purine (**3b**) in 500 MHz, $CDCl_3$



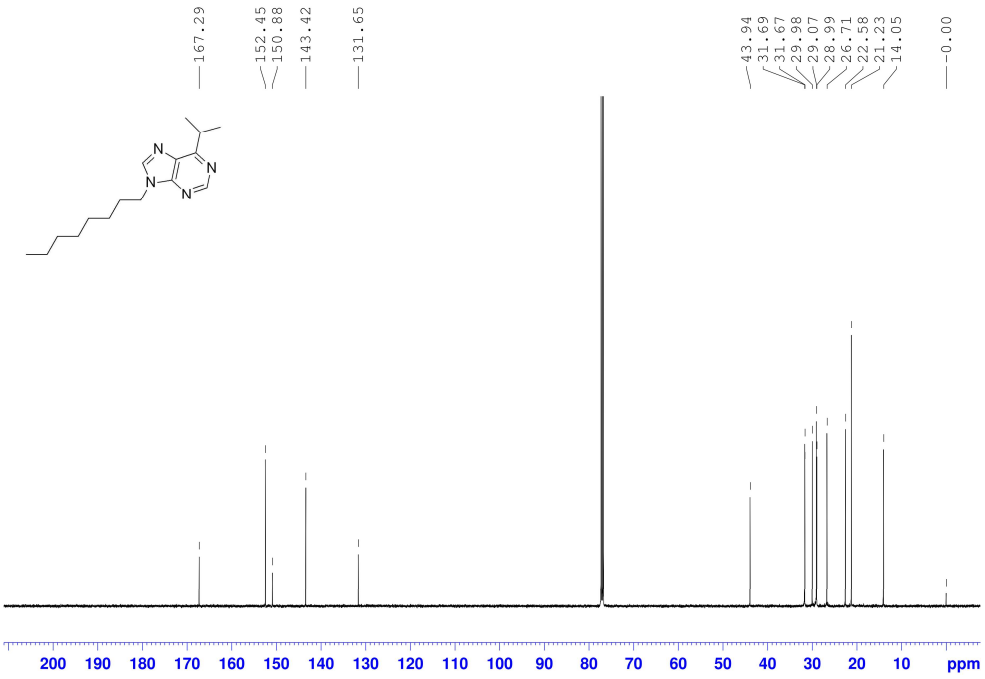
^{13}C NMR of 9-benzyl-6-isopropyl-*9H*-purine (**3b**) in 125 MHz, $CDCl_3$



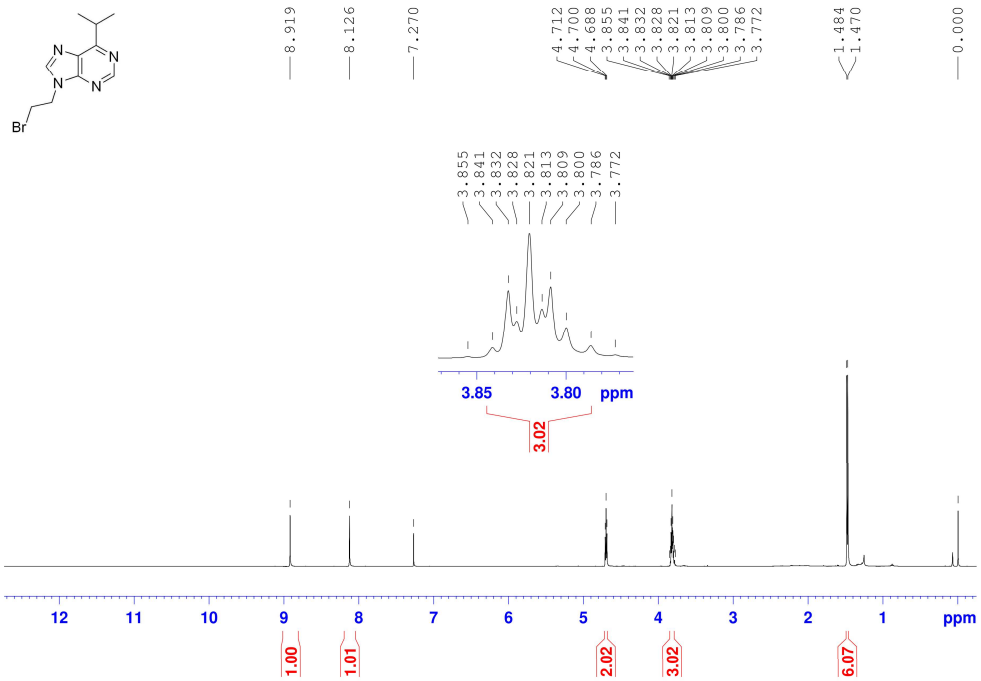
^{1}H NMR of 6-isopropyl-9-octyl-*9H*-purine (**3c**) in 500 MHz, $CDCl_3$



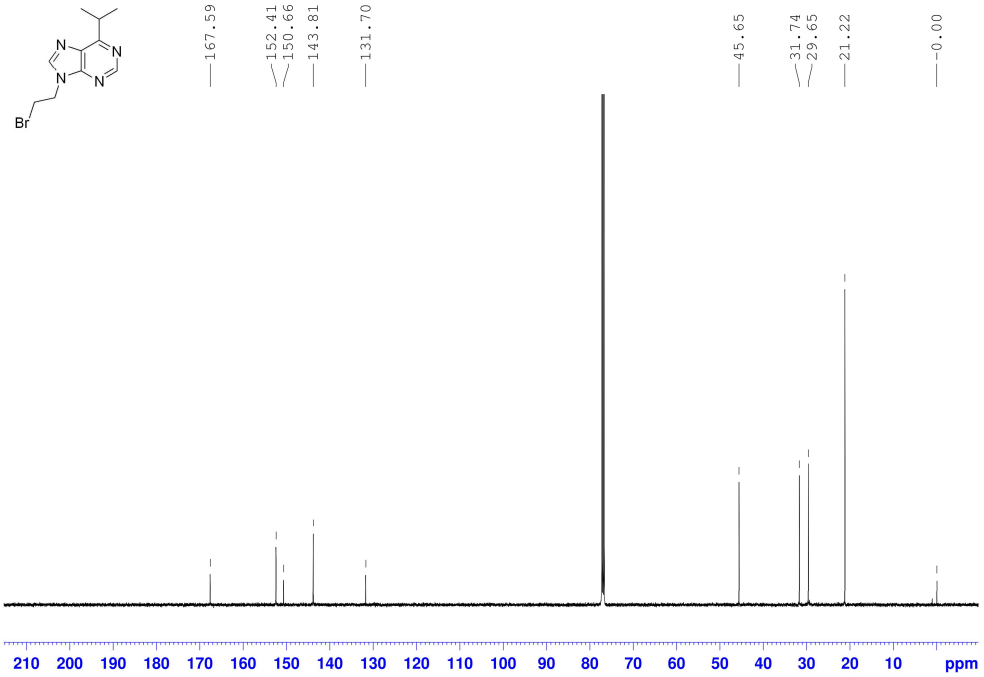
^{13}C NMR of 6-isopropyl-9-octyl-*9H*-purine (**3c**) in 125 MHz, $CDCl_3$



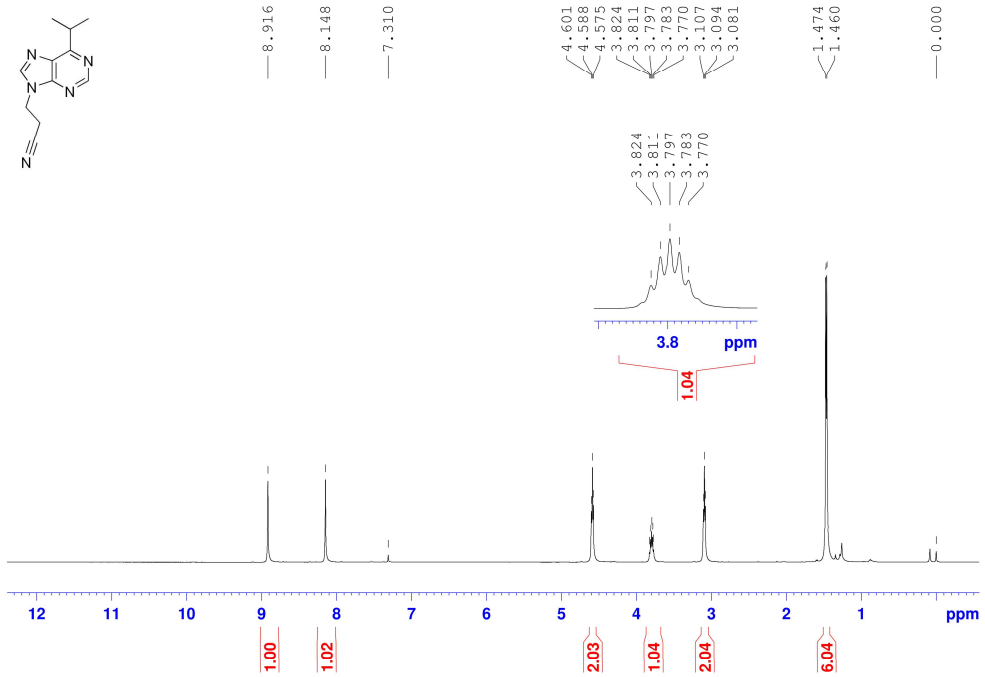
^{1}H NMR of 9-(2-bromoethyl)-6-isopropyl-*9H*-purine (**3d**) in 500 MHz, $CDCl_3$



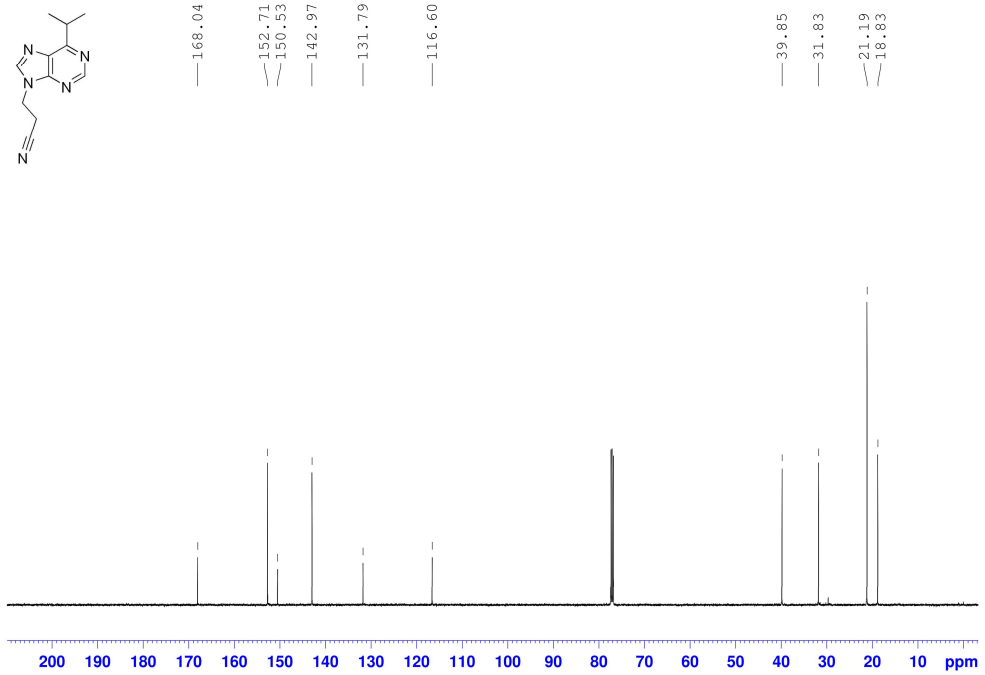
^{13}C NMR of 9-(2-bromoethyl)-6-isopropyl-*9H*-purine (**3d**) in 125 MHz, $CDCl_3$



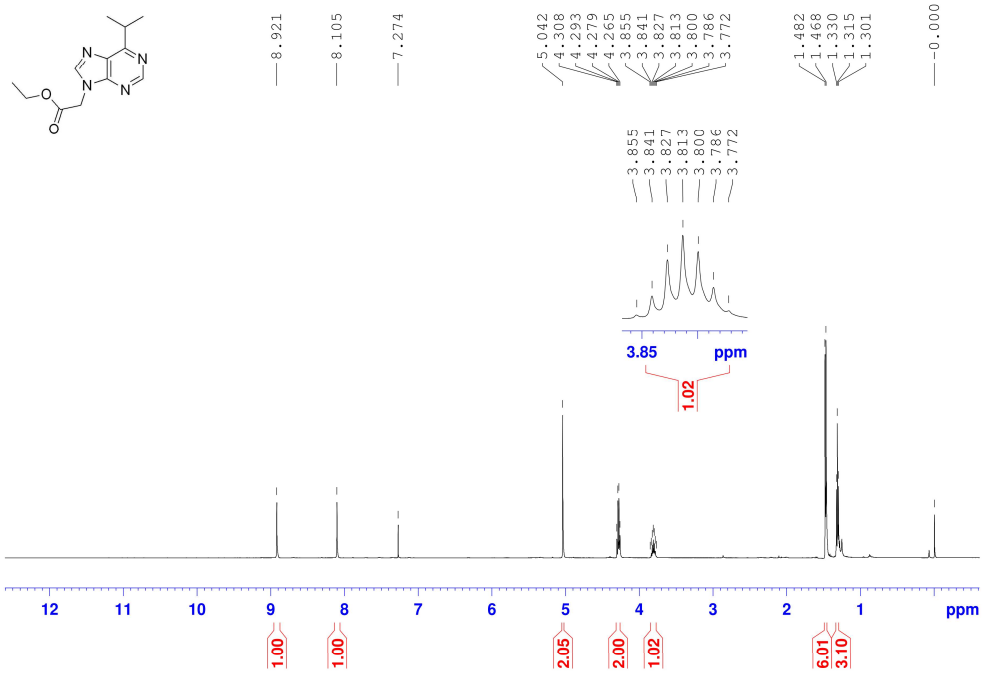
^{1}H NMR of 3-(6-isopropyl-9H-purin-9-yl)propanenitrile (**3e**) in 500 MHz, $CDCl_3$



^{13}C NMR of 3-(6-isopropyl-9H-purin-9-yl)propanenitrile (**3e**) in 125 MHz, $CDCl_3$



^{1}H NMR of ethyl 2-(6-isopropyl-*9H*-purin-9-yl)acetate (**3f**) in 500 MHz, $CDCl_3$



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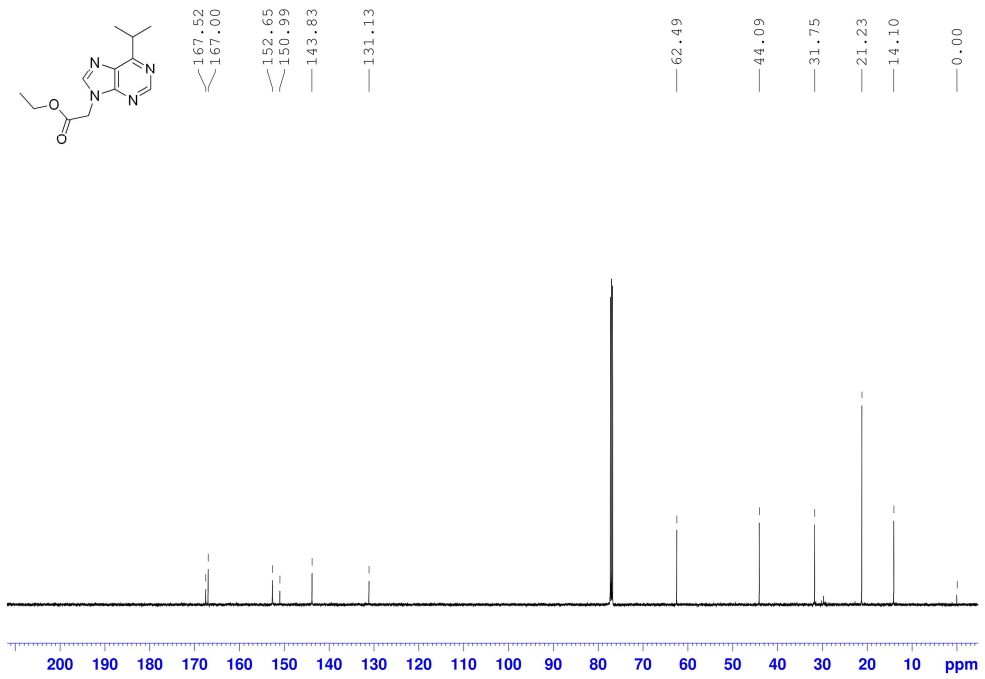
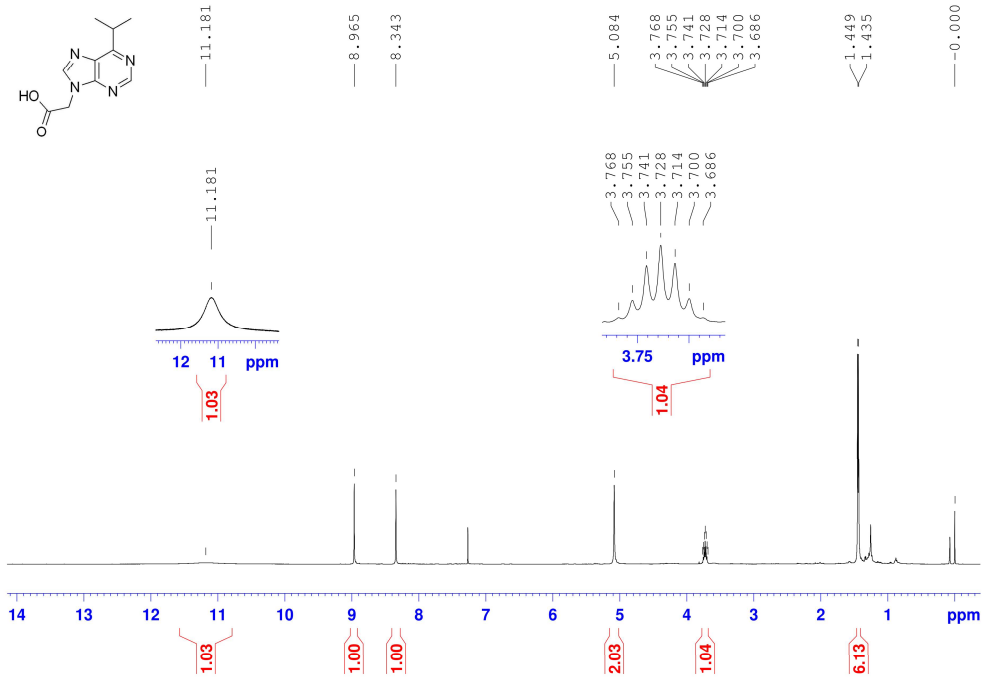


^{1}H NMR of 2-(6-isopropyl-*9H*-purin-9-yl)acetic acid (**3g**) in 500 MHz, $CDCl_3$



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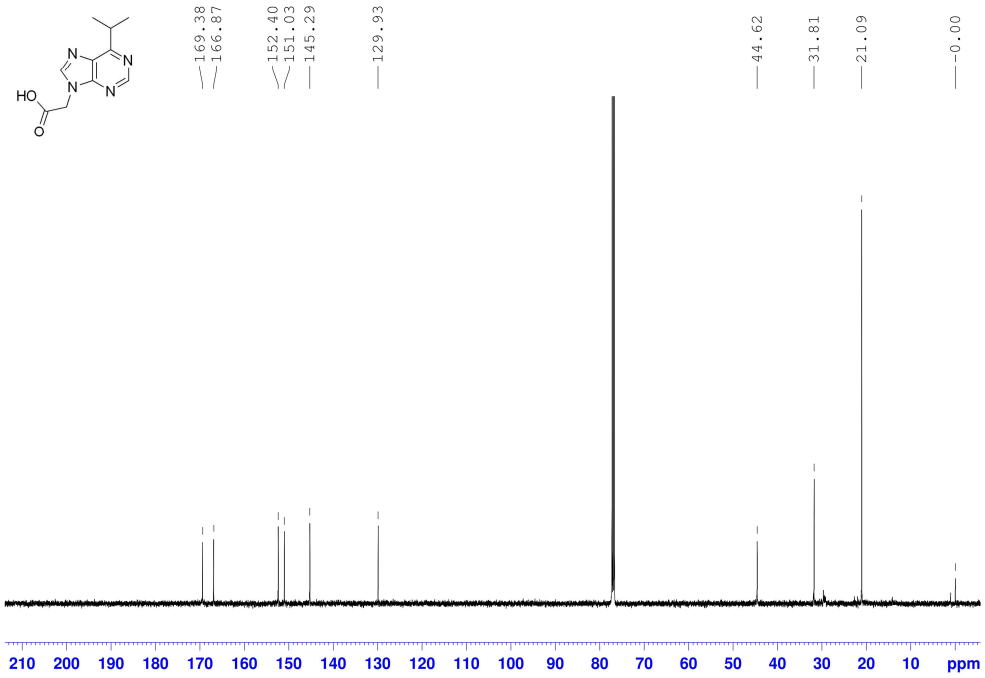
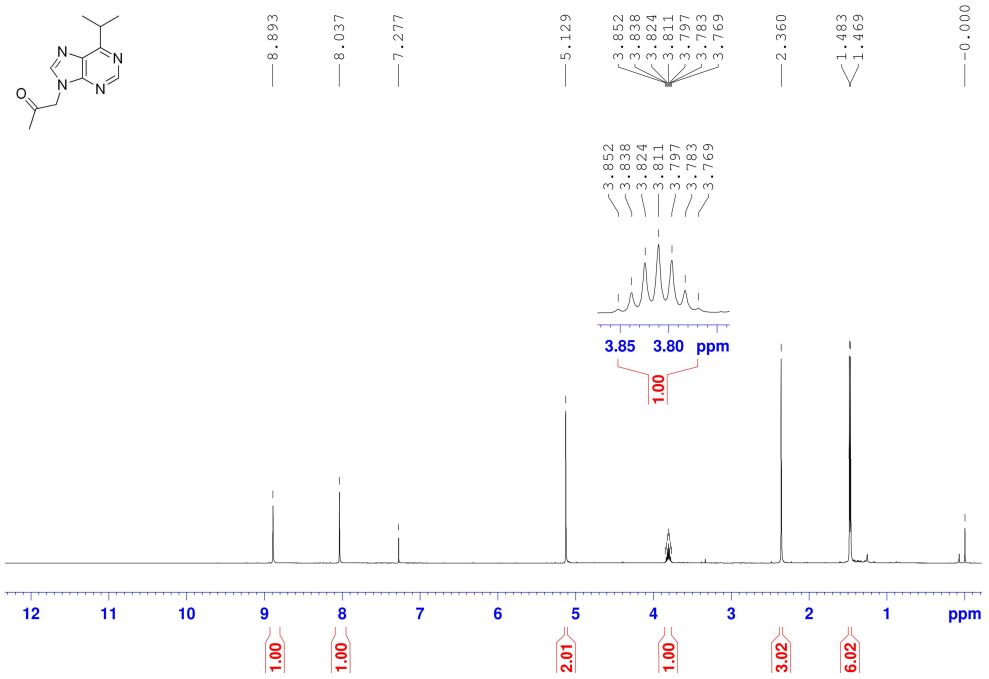
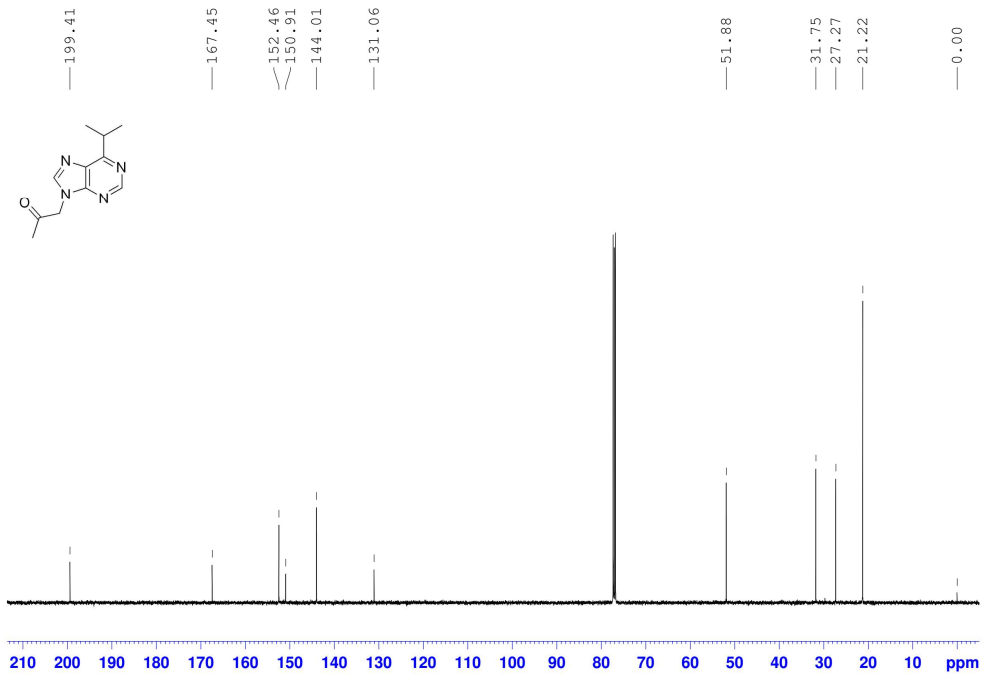


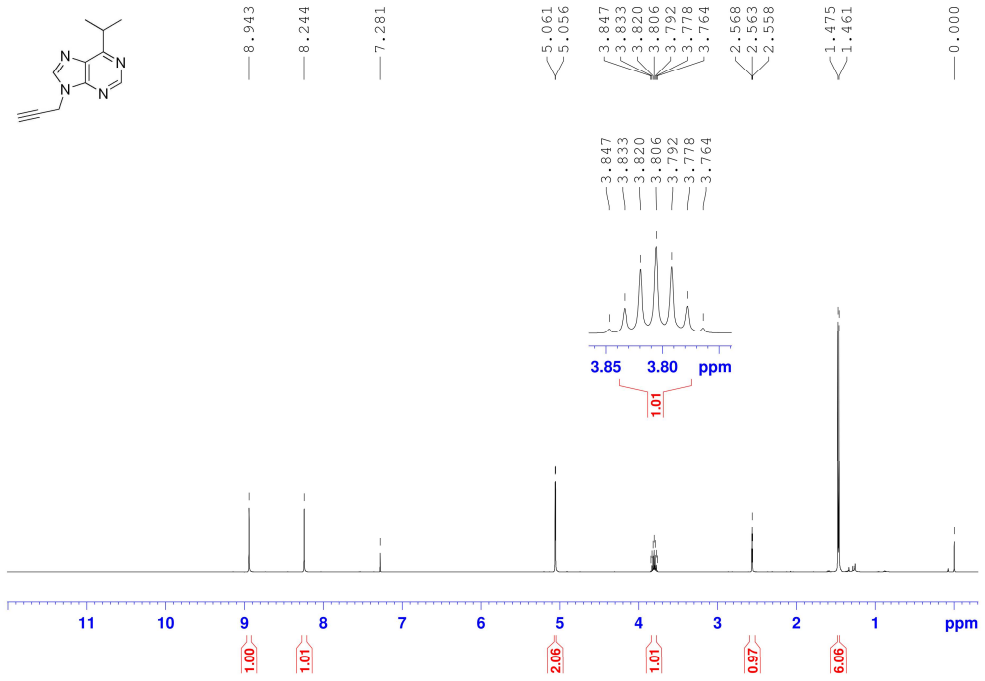
^{1}H NMR of 1-(6-isopropyl-*9H*-purin-9-yl)propan-2-one (**3h**) in 500 MHz, $CDCl_3$



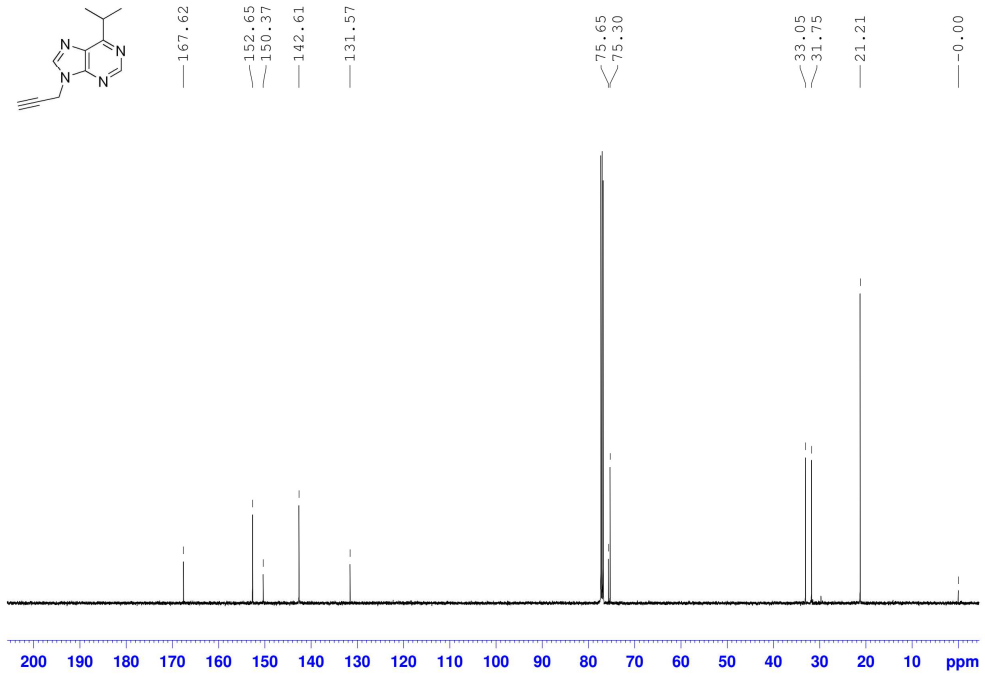
^{13}C NMR of 1-(6-isopropyl-*9H*-purin-9-yl)propan-2-one (**3h**) in 125 MHz, $CDCl_3$



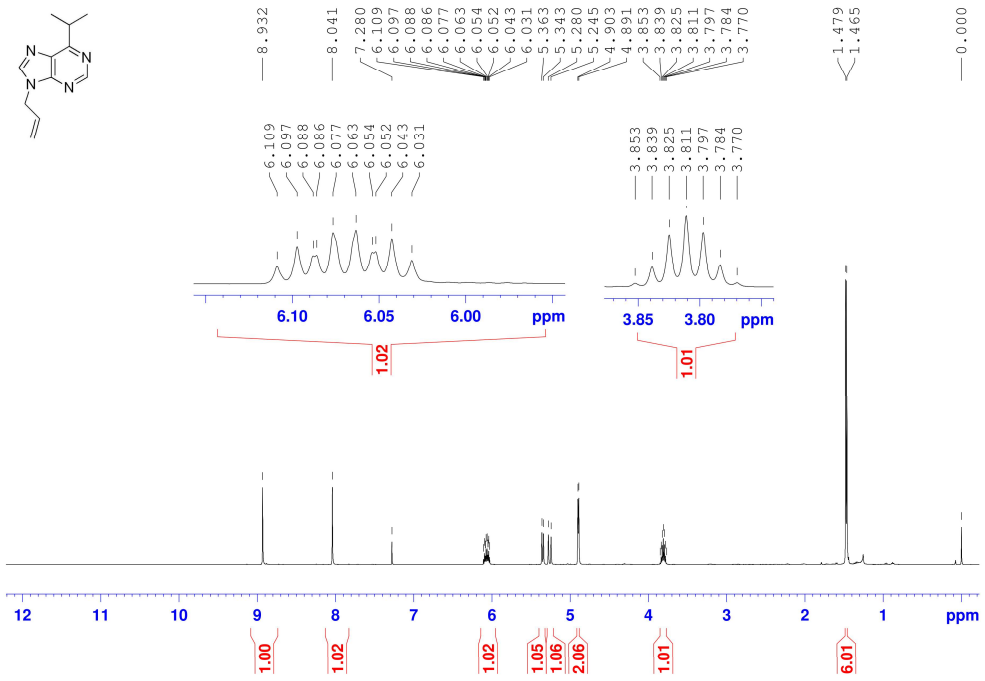
^{1}H NMR of 6-isopropyl-9-(prop-2-yn-1-yl)-9*H*-purine (**3i**) in 500 MHz, $CDCl_3$



^{13}C NMR of 6-isopropyl-9-(prop-2-yn-1-yl)-9*H*-purine (**3i**) in 125 MHz, $CDCl_3$



^{1}H NMR of 9-allyl-6-isopropyl-*9H*-purine (**3j**) in 500 MHz, $CDCl_3$



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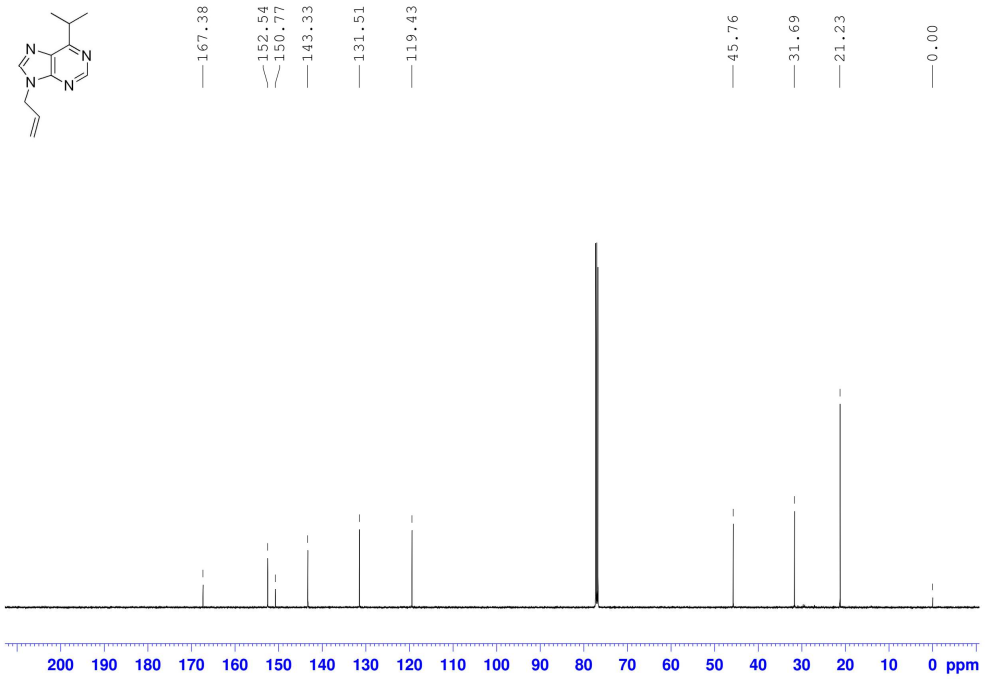
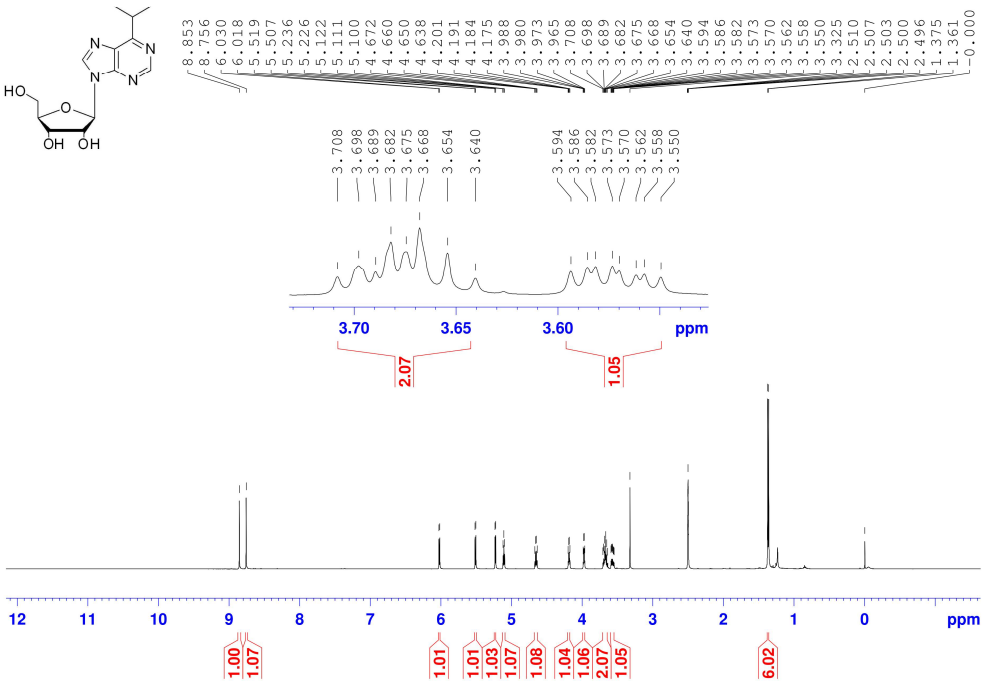
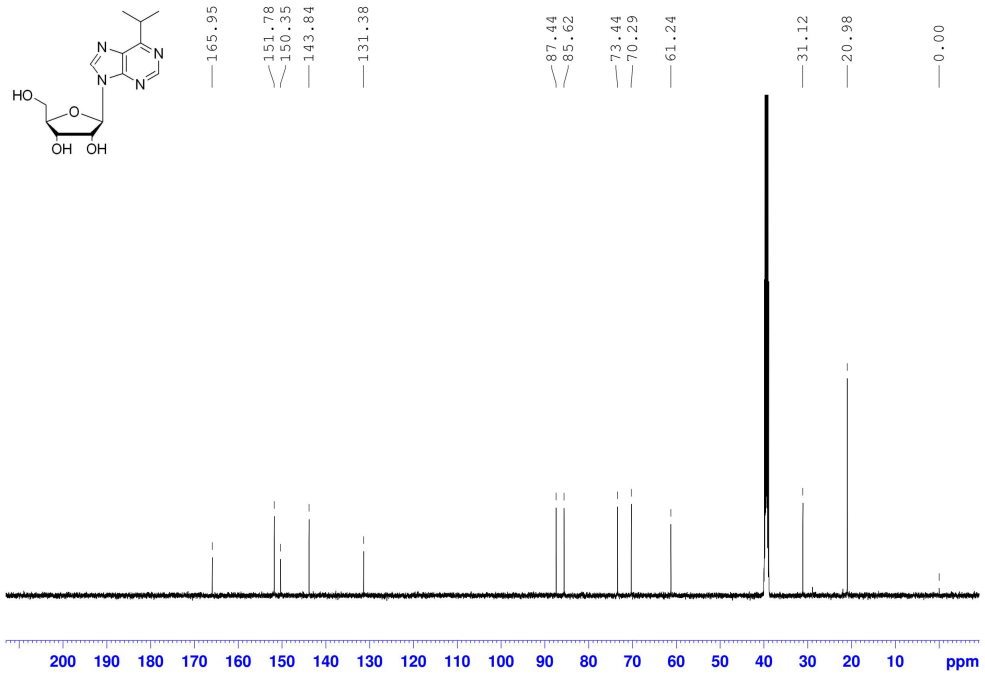


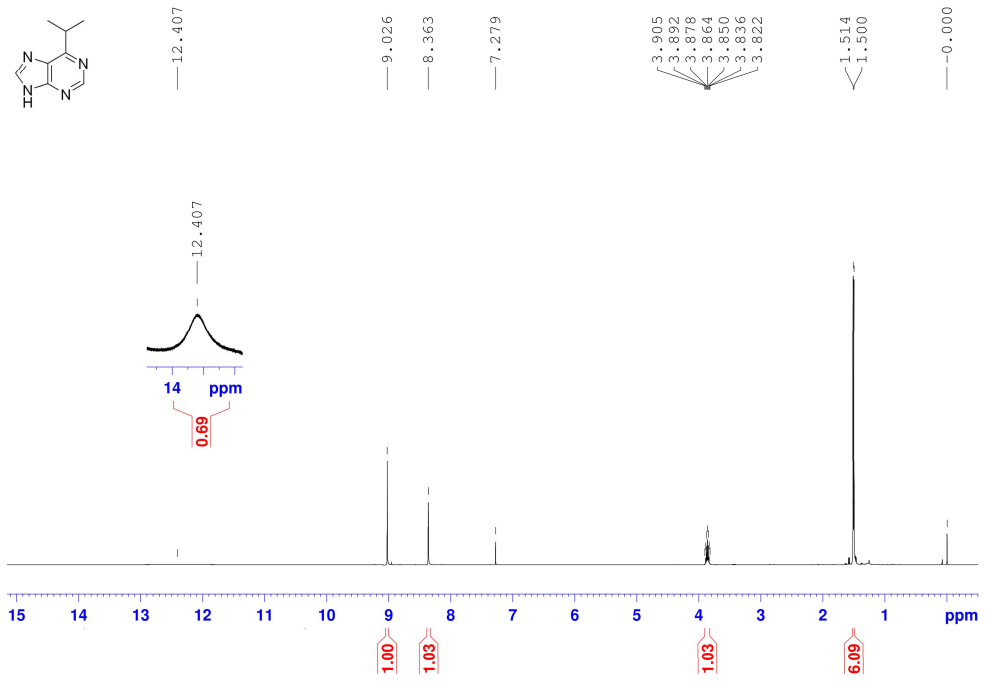
^{1}H NMR of 6-isopropyl-nebularine (**3k**) in 500 MHz, DMSO-d_6



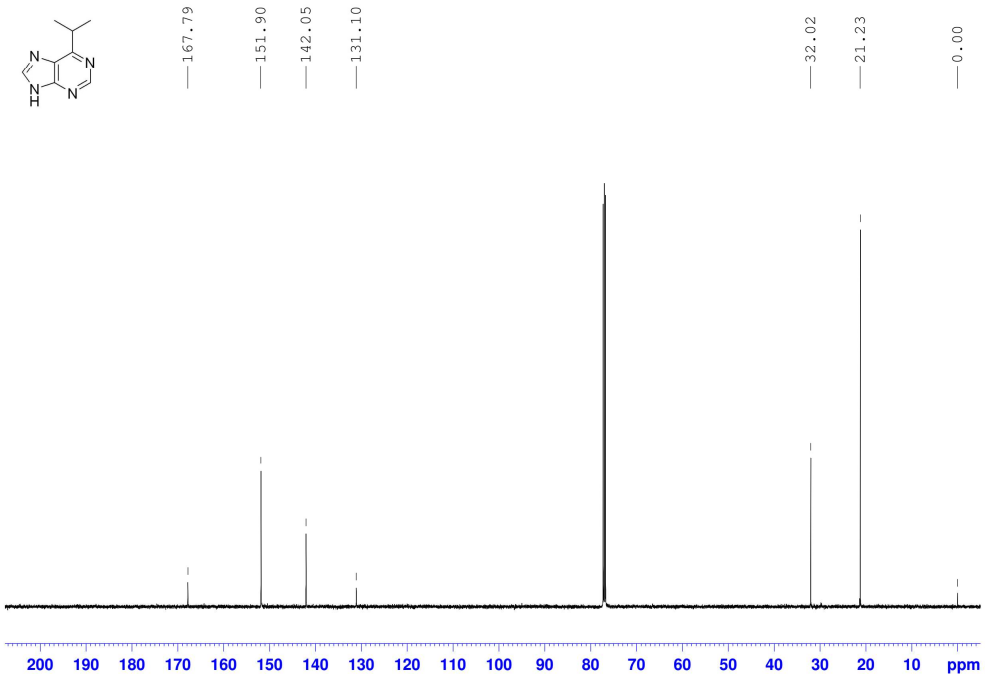
^{13}C NMR of 6-isopropyl-nebularine (**3k**) in 125 MHz, DMSO-d_6



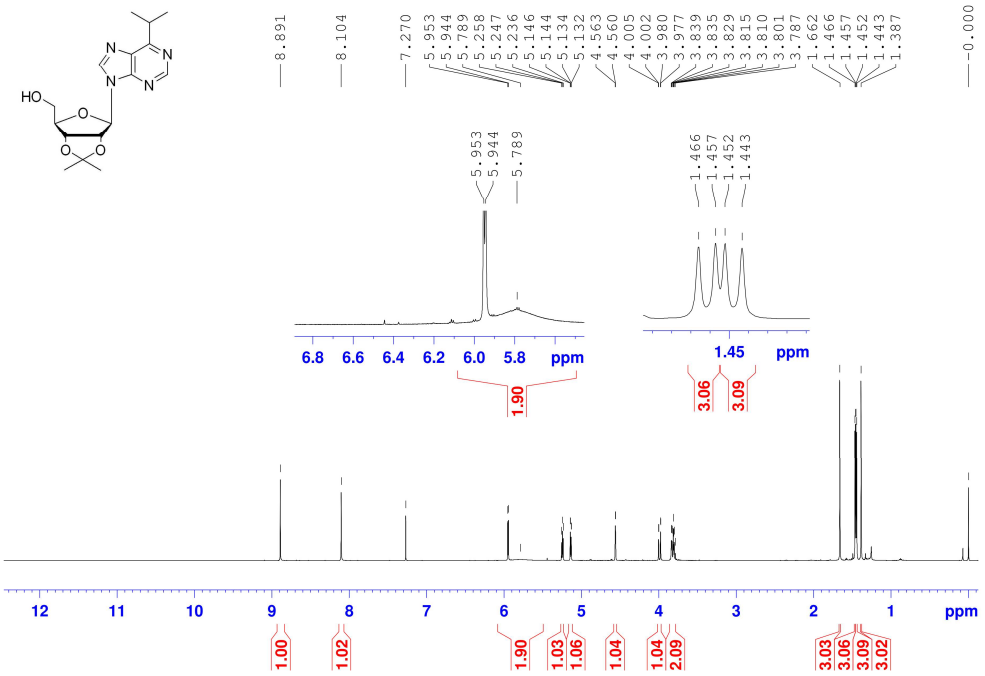
^{1}H NMR of 6-isopropyl-*9H*-purine (**3l**) in 500 MHz, $CDCl_3$



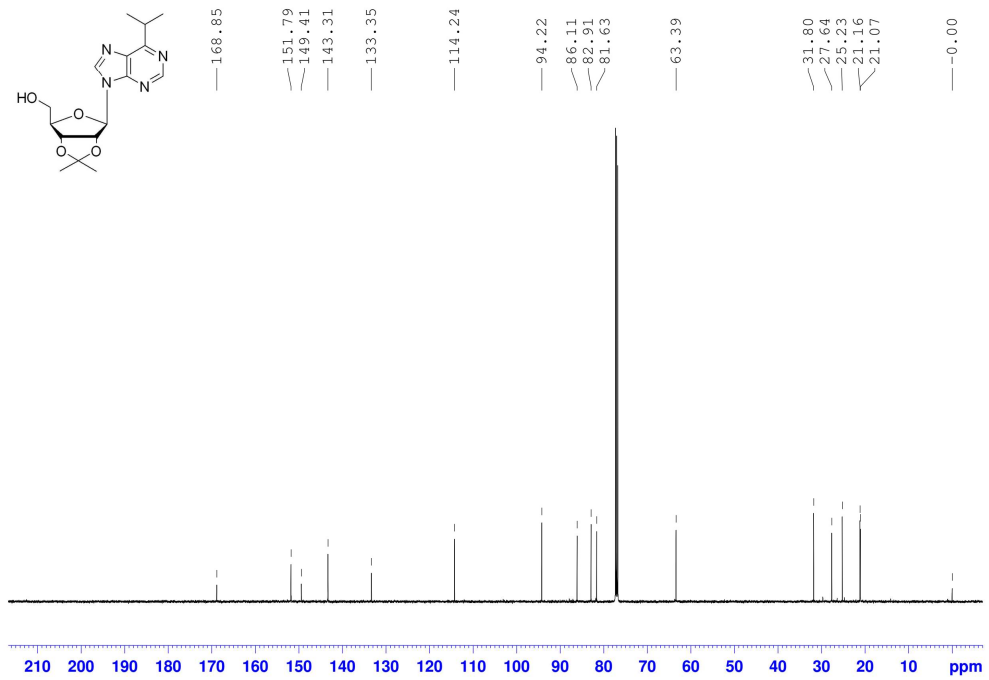
^{13}C NMR of 6-isopropyl-*9H*-purine (**3l**) in 125 MHz, $CDCl_3$



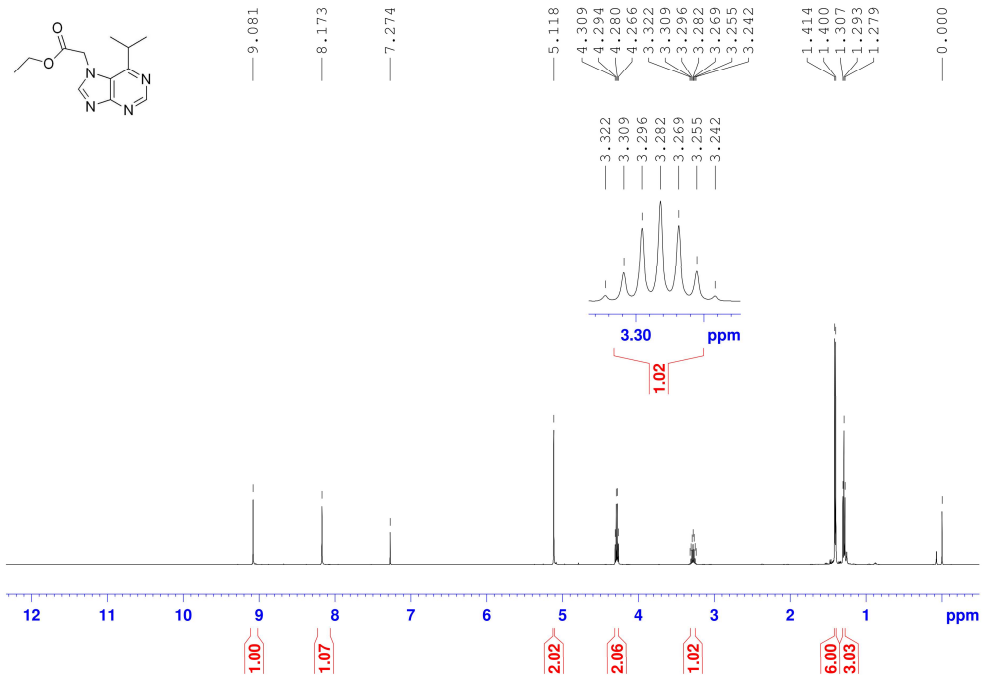
^{1}H NMR of 6-isopropyl-9-(2′, 3′-O-isoproylidenyl-β-D-ribofuranosyl) purine nucleoside (**3m**) in 500 MHz, $CDCl_3$



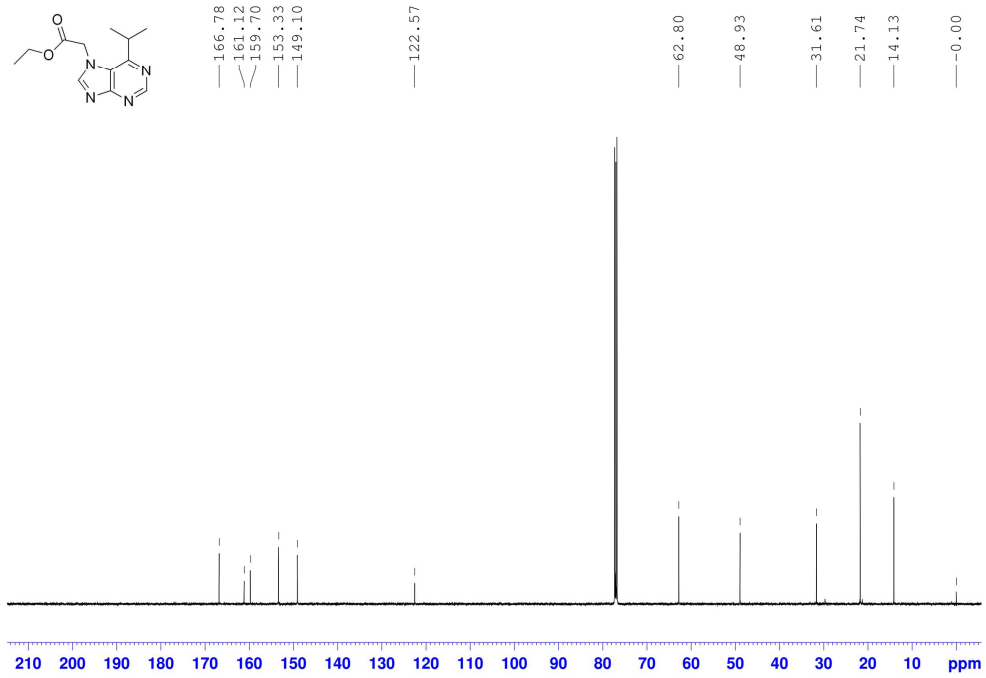
^{13}C NMR of 6-isopropyl-9-(2′, 3′-O-isoproylidenyl-β-D-ribofuranosyl) purine nucleoside (**3m**) in 125 MHz, $CDCl_3$



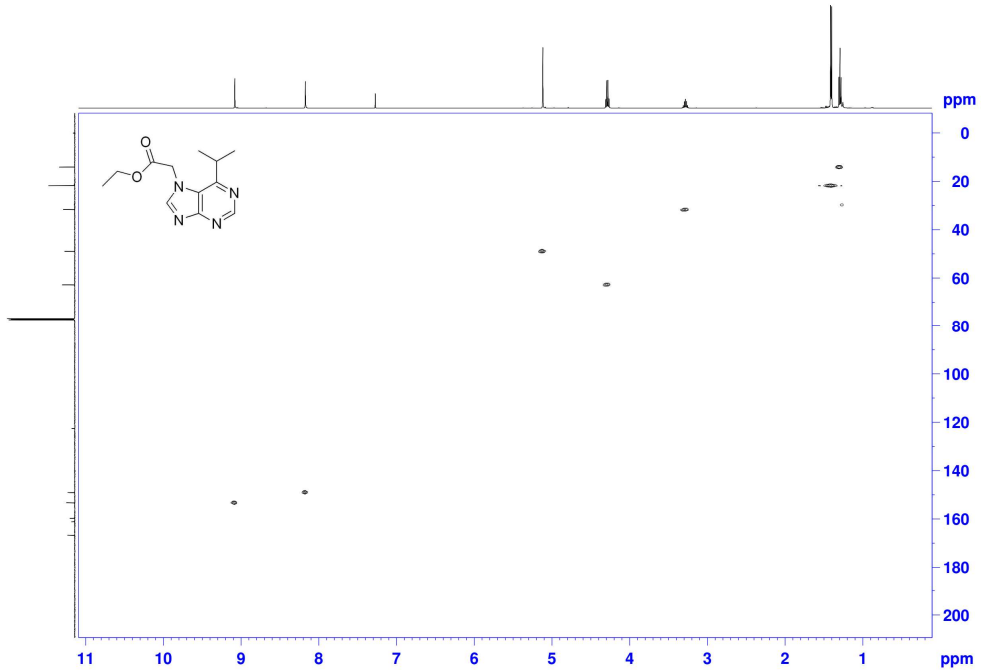
^{1}H NMR of ethyl 2-(6-isopropyl-*7H*-purin-7-yl)acetate (**3n**) in 500 MHz, $CDCl_3$



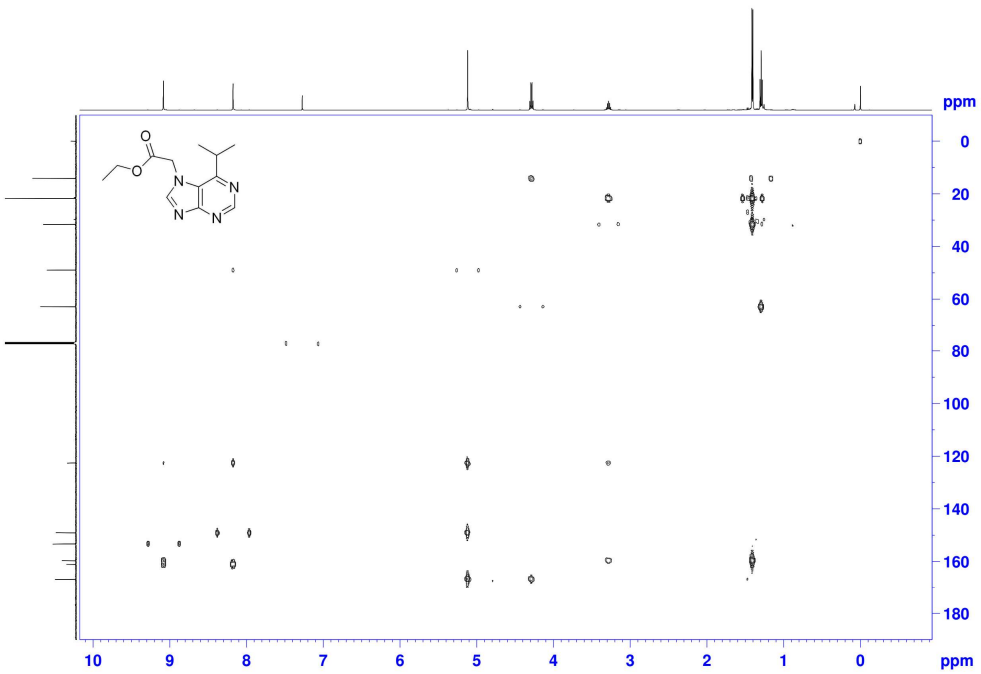
^{13}C NMR of ethyl 2-(6-isopropyl-*7H*-purin-7-yl)acetate (**3n**) in 125 MHz, $CDCl_3$



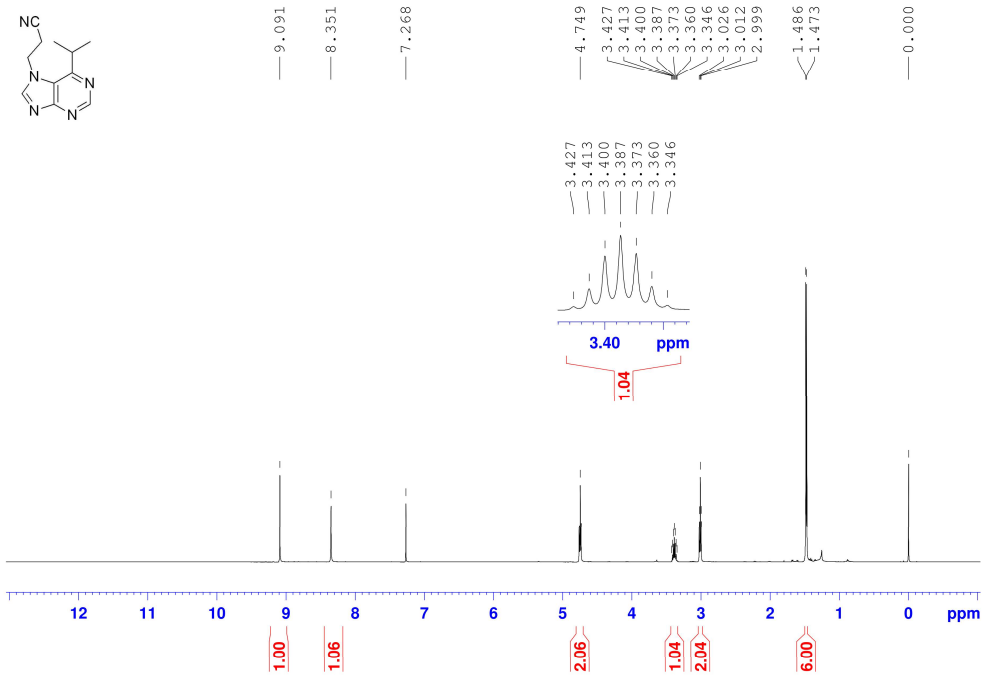
^{1}H-^{13}COSY of ethyl 2-(6-isopropyl-*7H*-purin-7-yl)acetate (**3n**) in $CDCl_3$



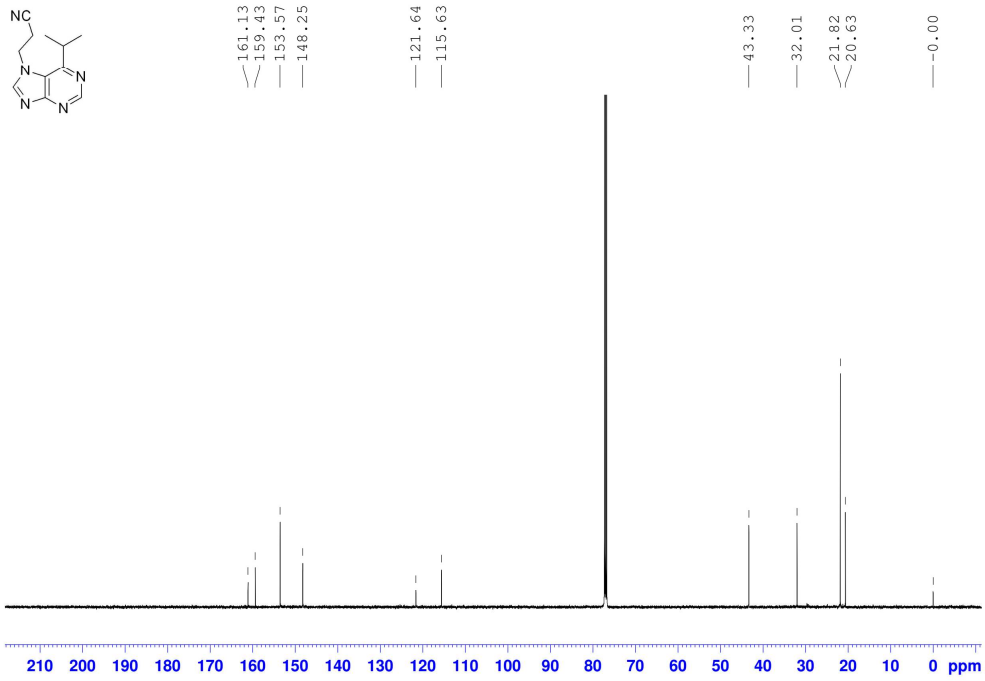
HMBC of ethyl 2-(6-isopropyl-*7H*-purin-7-yl)acetate (**3n**) in $CDCl_3$



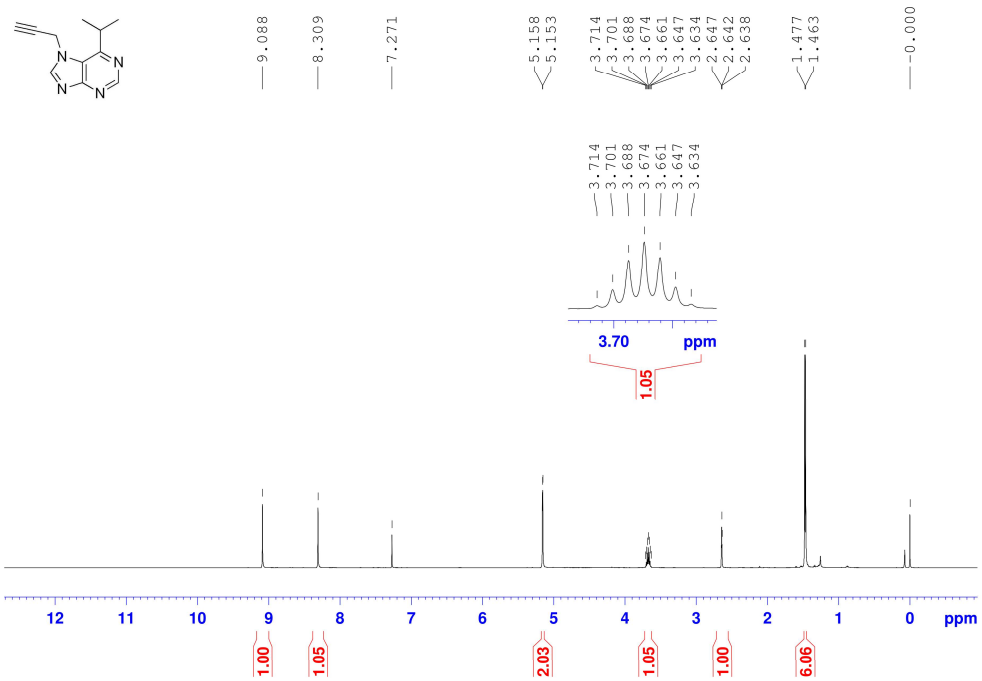
^{1}H NMR of 3-(6-isopropyl-*7H*-purin-7-yl)propanenitrile (**3o**) in 500 MHz, DMSO-d_6



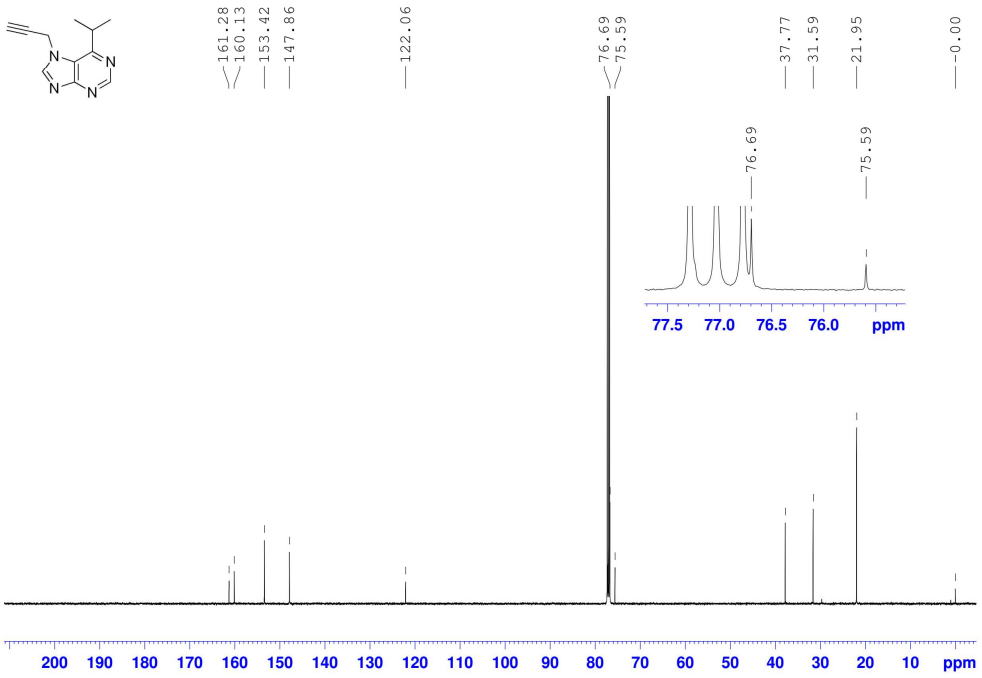
^{13}C NMR of 3-(6-isopropyl-*7H*-purin-7-yl)propanenitrile (**3o**) in 125 MHz, DMSO-d_6



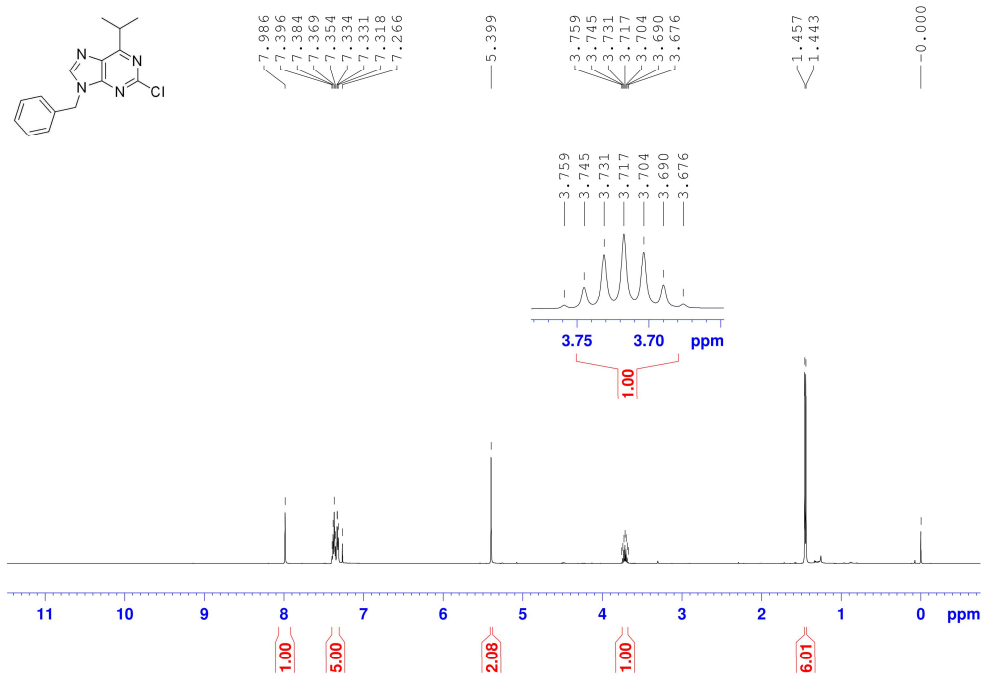
^{1}H NMR of 6-isopropyl-7-(prop-2-yn-1-yl)-*7H*-purine (**3p**) in 500 MHz, $CDCl_3$



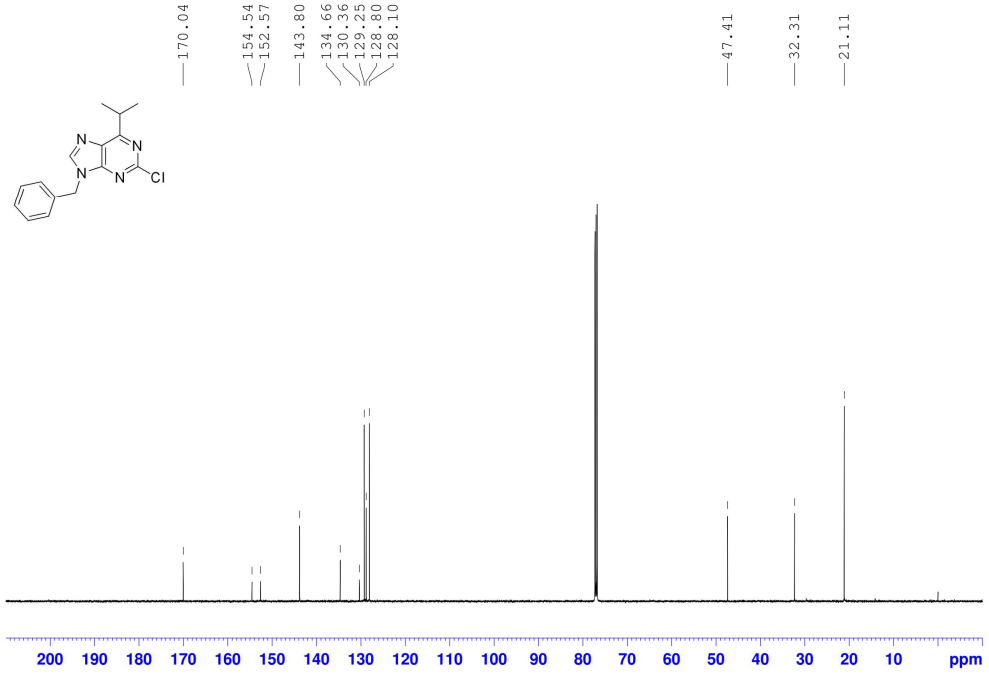
^{13}C NMR of 6-isopropyl-7-(prop-2-yn-1-yl)-*7H*-purine (**3p**) in 125 MHz, $CDCl_3$



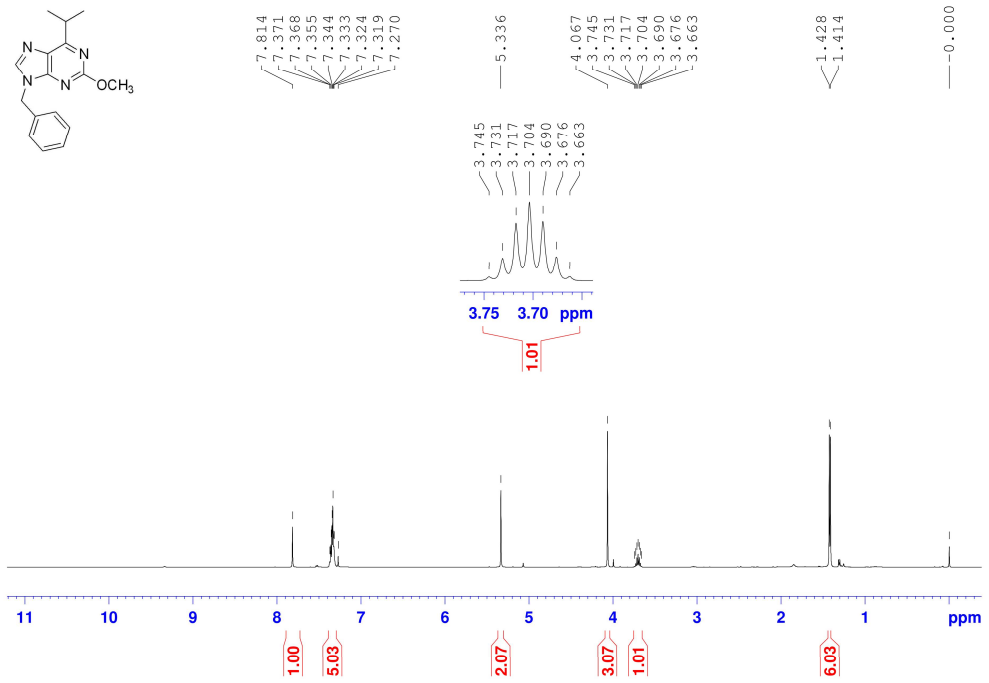
^{1}H NMR of 9-benzyl-2-chloro-6-isopropyl-*9H*-purine (**3q**) in 500 MHz, $CDCl_3$



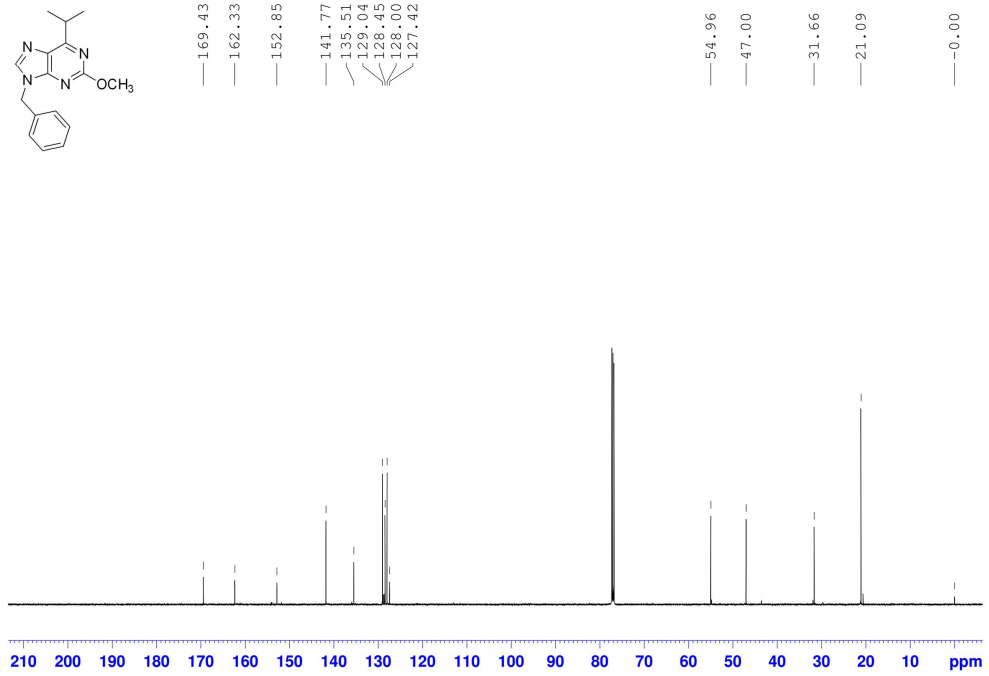
^{13}C NMR of 9-benzyl-2-chloro-6-isopropyl-*9H*-purine (**3q**) in 125 MHz, $CDCl_3$



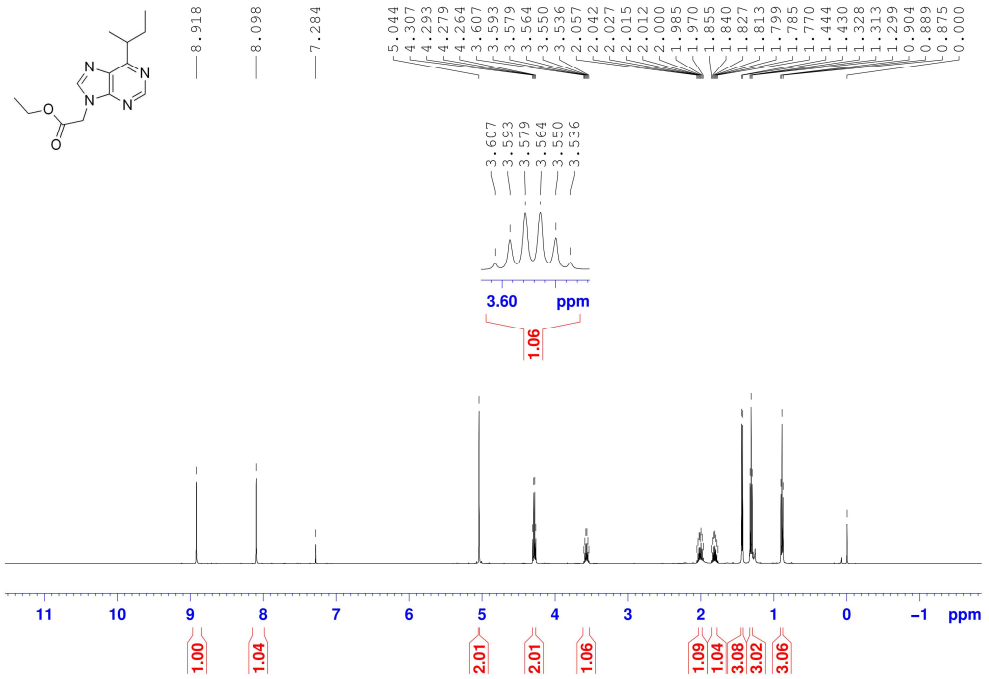
^{1}H NMR of 9-benzyl-6-isopropyl-2-methoxy-*9H*-purine (**3r**) in 500 MHz, $CDCl_3$



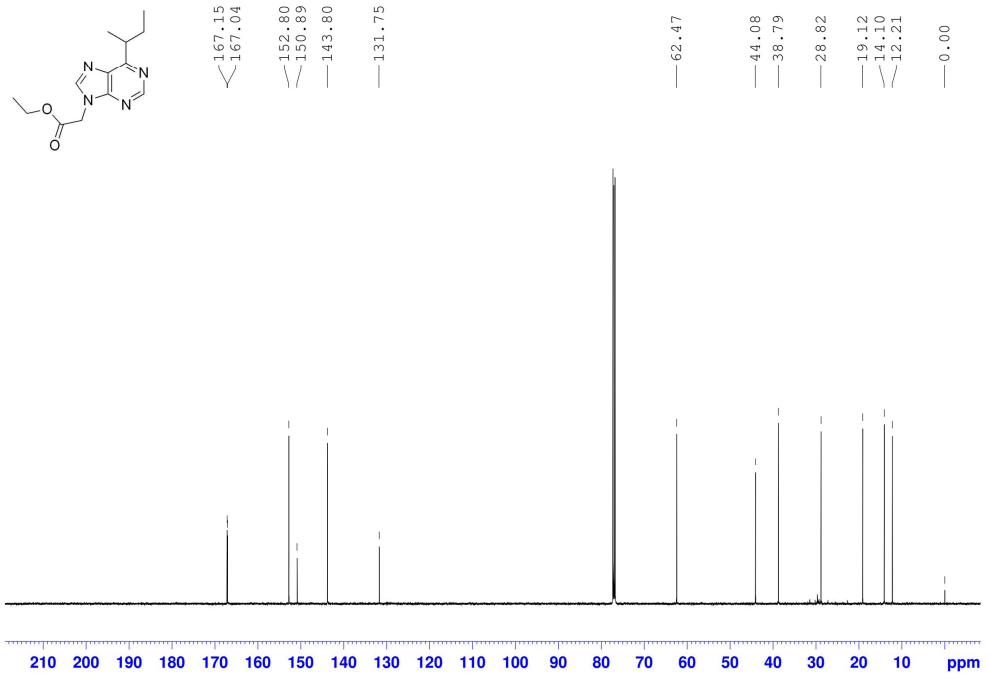
^{13}C NMR of 9-benzyl-6-isopropyl-2-methoxy-*9H*-purine (**3r**) in 125 MHz, $CDCl_3$



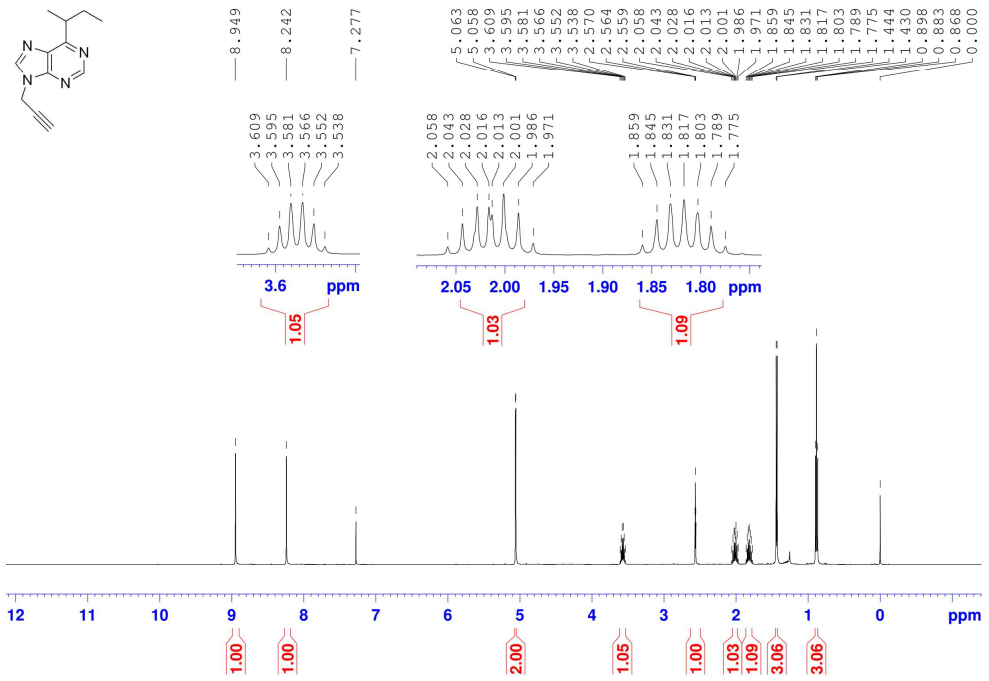
^{1}H NMR of ethyl 2-(6-(sec-butyl)-*9H*-purin-9-yl)acetate (**4a**) in 500 MHz, $CDCl_3$



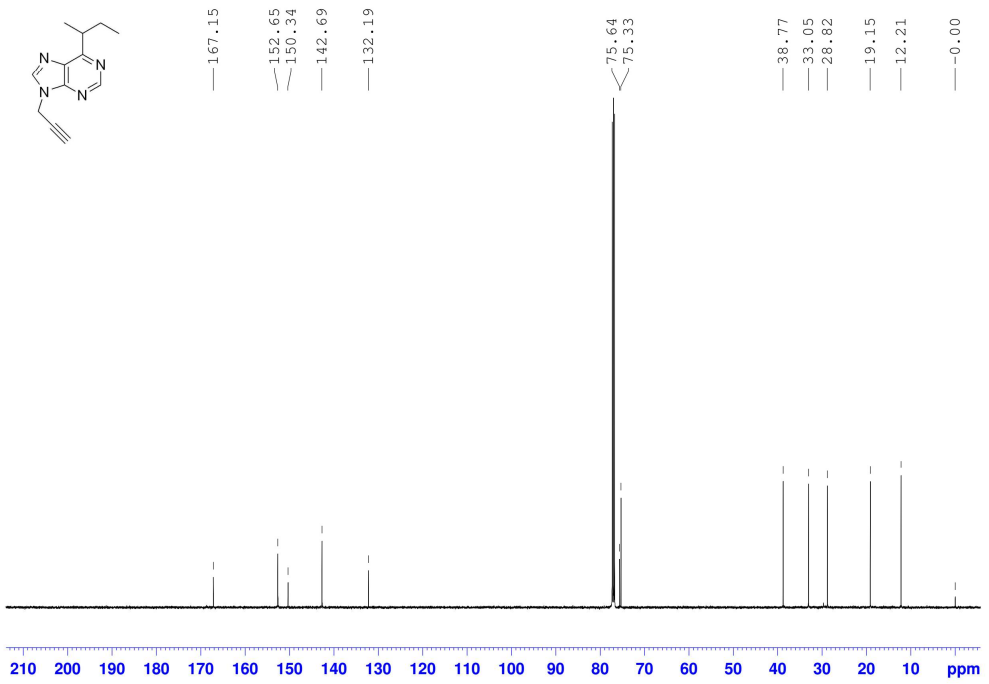
^{13}C NMR of ethyl 2-(6-(sec-butyl)-*9H*-purin-9-yl)acetate (**4a**) in 125 MHz, $CDCl_3$



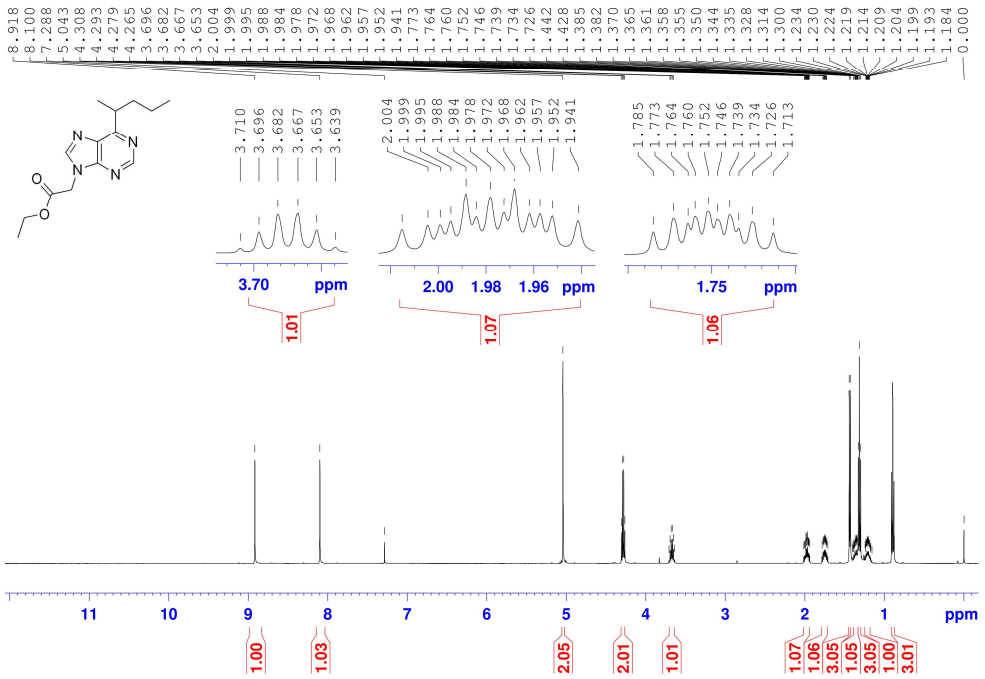
^{1}H NMR of 6-(sec-butyl)-9-(prop-2-yn-1-yl)-*9H*-purine (**4b**) in 500 MHz, $CDCl_3$



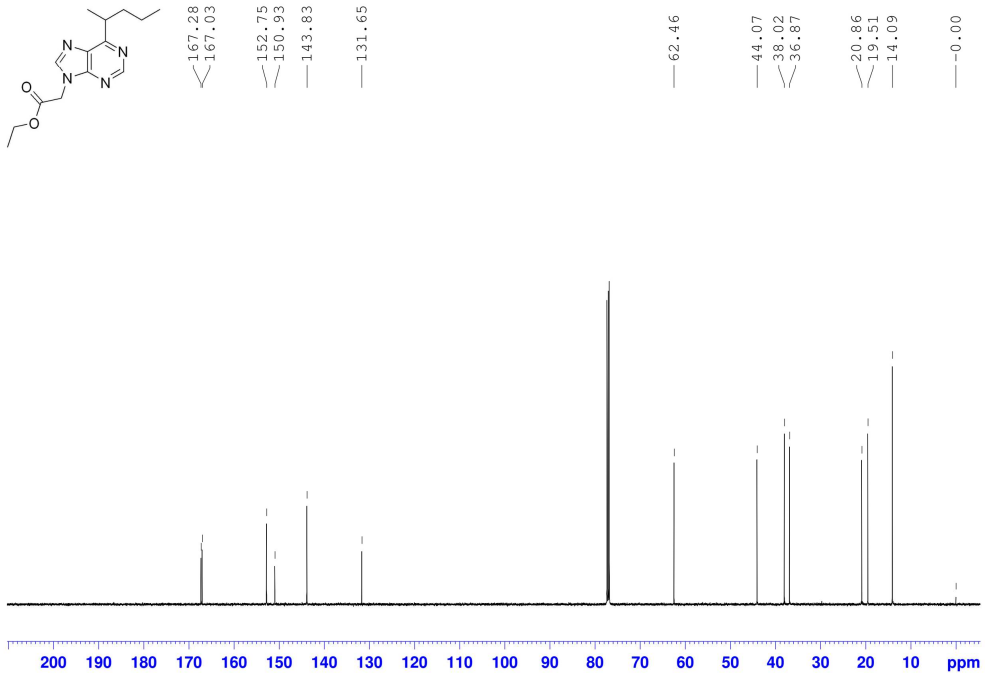
^{13}C NMR of 6-(sec-butyl)-9-(prop-2-yn-1-yl)-*9H*-purine (**4b**) in 125 MHz, $CDCl_3$



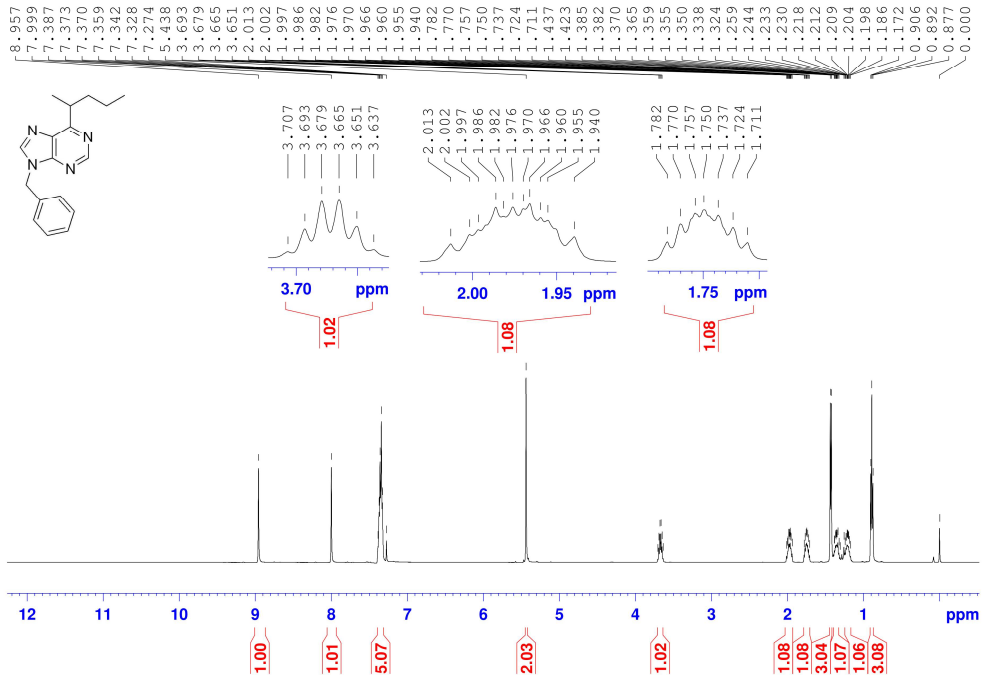
^{1}H NMR of ethyl 2-(6-(pentan-2-yl)-*9H*-purin-9-yl)acetate (**4c**) in 500 MHz, $CDCl_3$



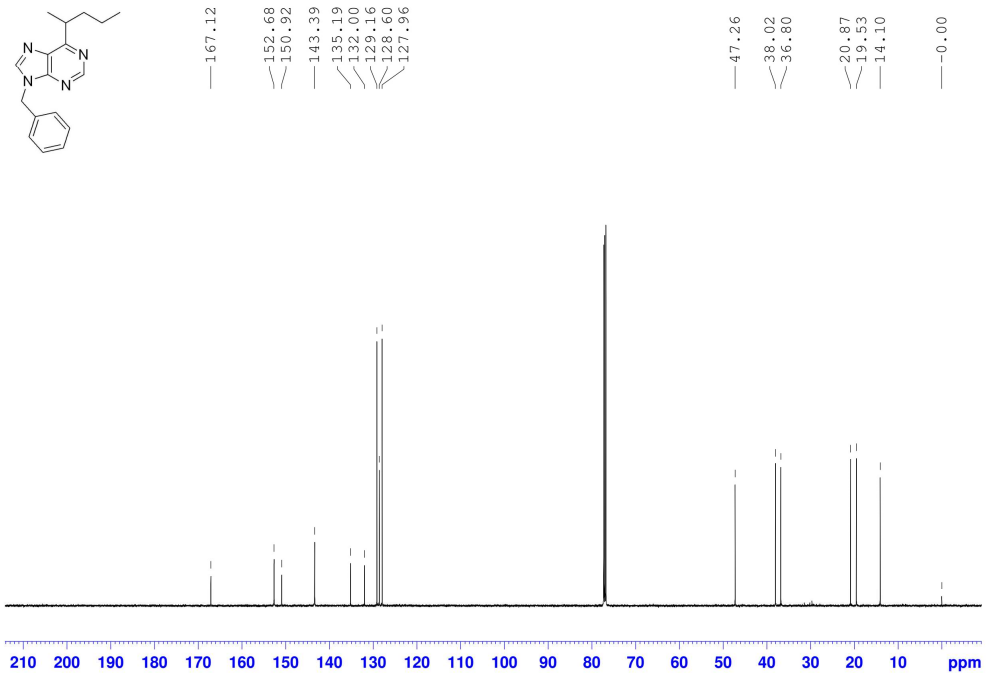
^{13}C NMR of ethyl 2-(6-(pentan-2-yl)-*9H*-purin-9-yl)acetate (**4c**) in 125 MHz, $CDCl_3$



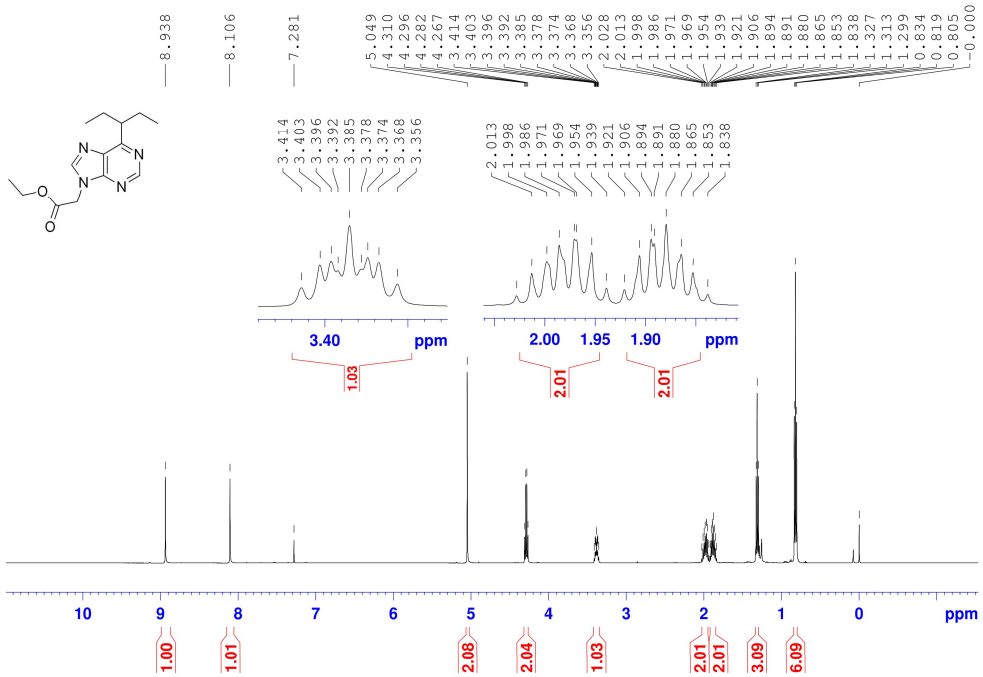
^{1}H NMR of 9-benzyl-6-(pentan-2-yl)-*9H*-purine (**4d**) in 500 MHz, $CDCl_3$



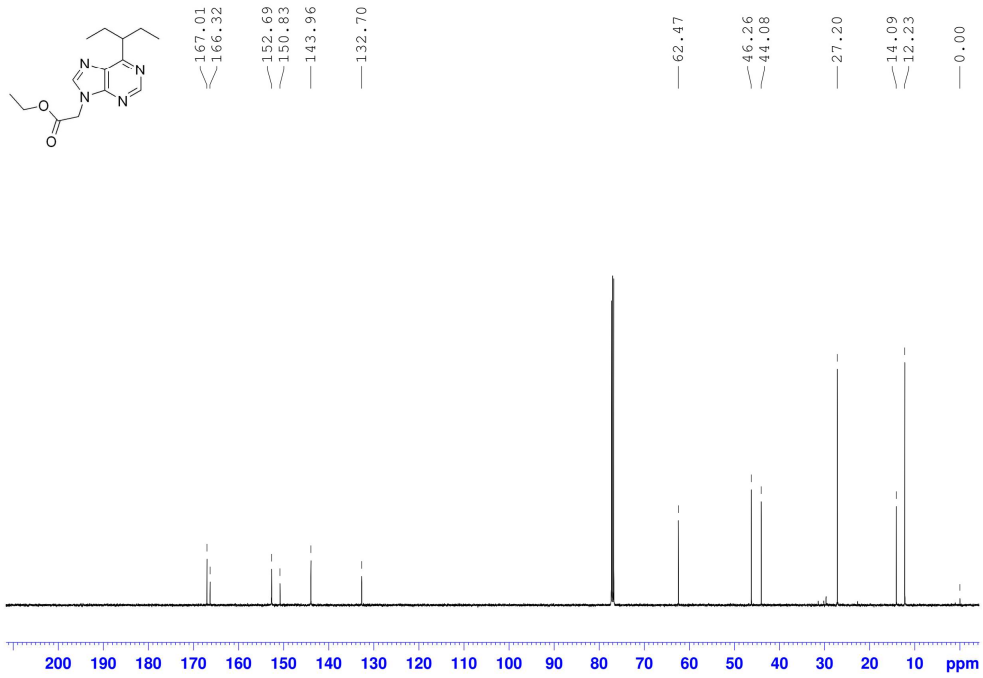
^{13}C NMR of 9-benzyl-6-(pentan-2-yl)-*9H*-purine (**4d**) in 125 MHz, $CDCl_3$



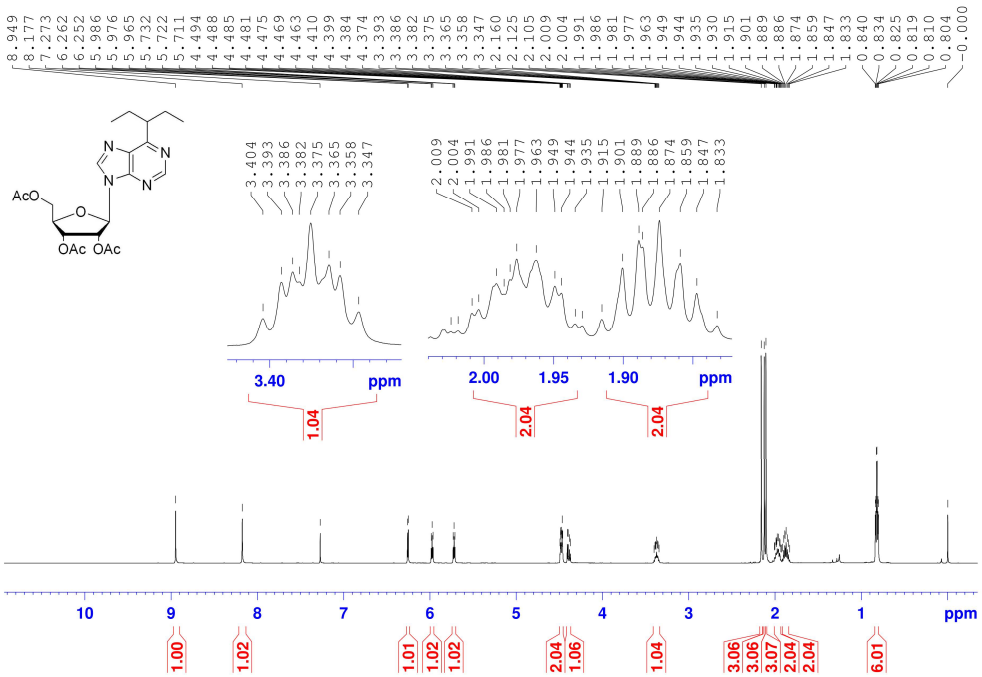
^{1}H NMR of ethyl 2-(6-(pentan-3-yl)-*9H*-purin-9-yl)acetate (**4e**) in 500 MHz, $CDCl_3$



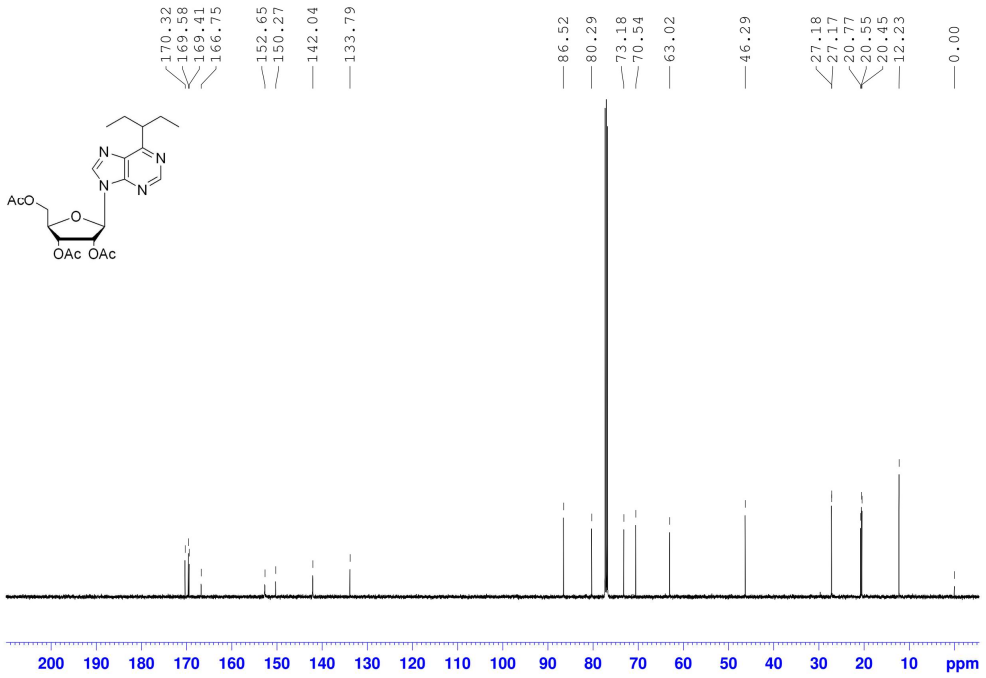
^{13}C NMR of ethyl 2-(6-(pentan-3-yl)-*9H*-purin-9-yl)acetate (**4e**) in 125 MHz, $CDCl_3$



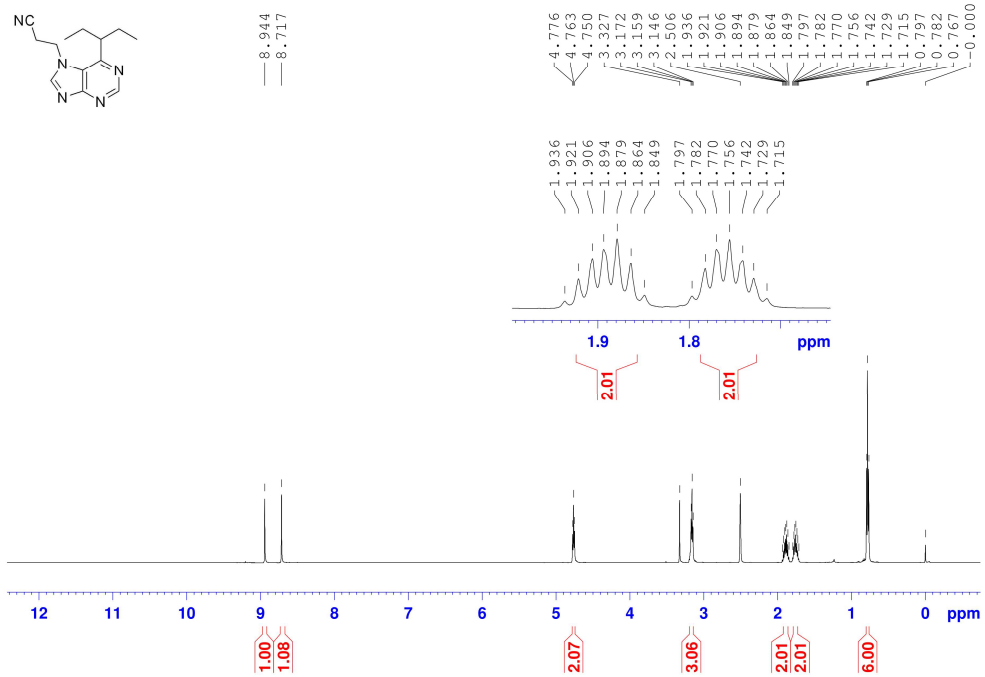
^{1}H NMR of 6-(pentan-3-yl)-2′,3′,5′-tri-*O*-acetyl-nebularine (**4f**) in 500 MHz, $CDCl_3$



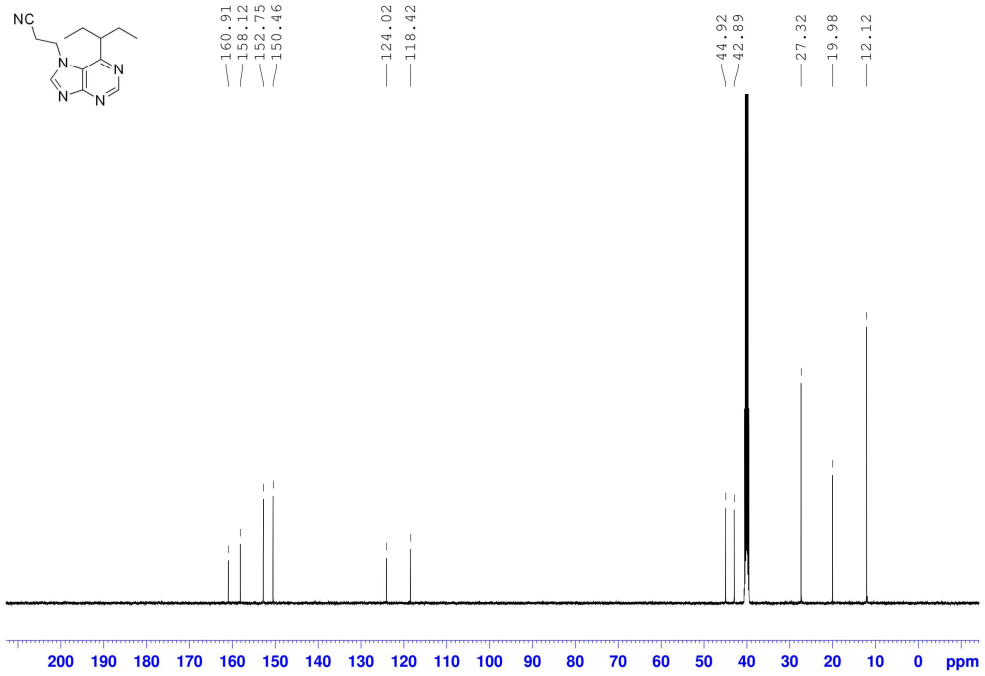
^{13}C NMR of 6-(pentan-3-yl)-2′,3′,5′-tri-*O*-acetyl-nebularine (**4f**) in 125 MHz, $CDCl_3$



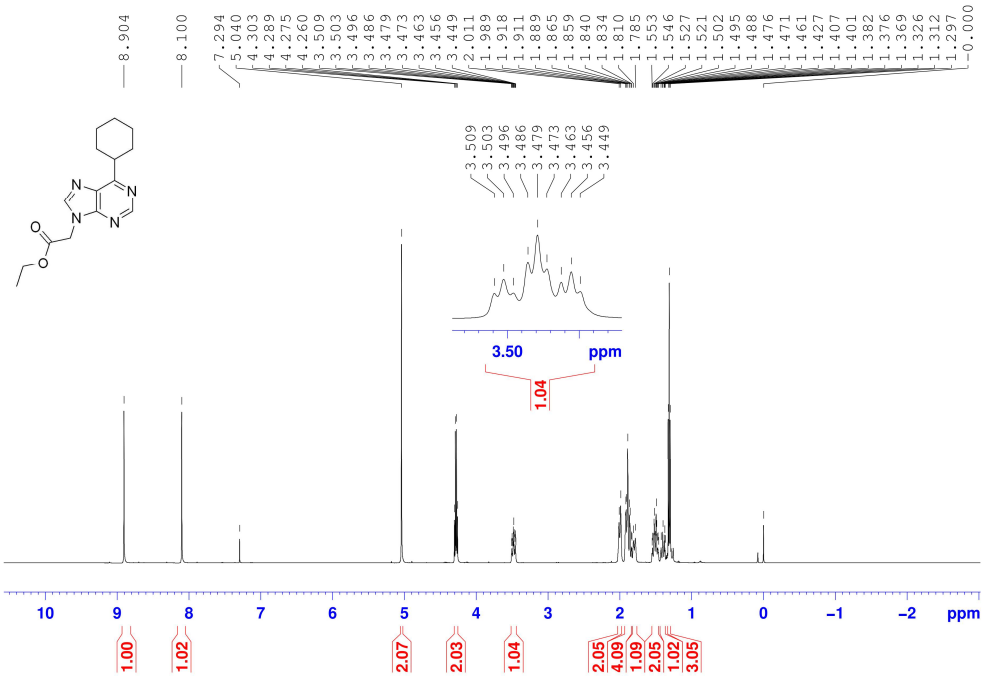
^{1}H NMR of 3-(6-(pentan-3-yl)-*7H*-purin-7-yl)propanenitrile (**4g**) in 500 MHz, DMSO-d_6



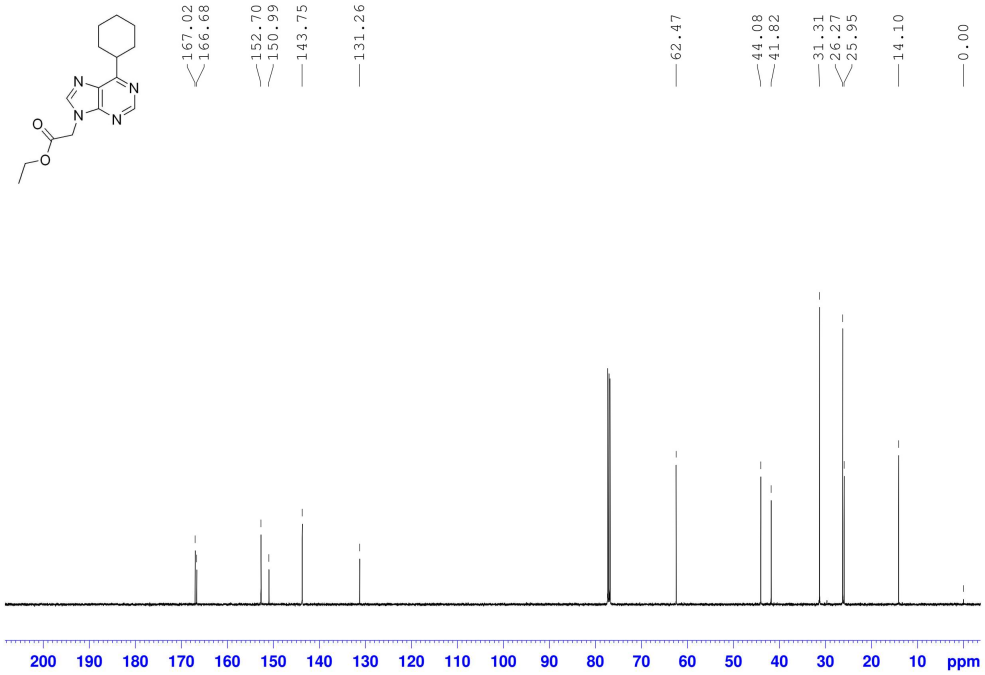
^{13}C NMR of 3-(6-(pentan-3-yl)-*7H*-purin-7-yl)propanenitrile (**4g**) in 125 MHz, DMSO-d_6



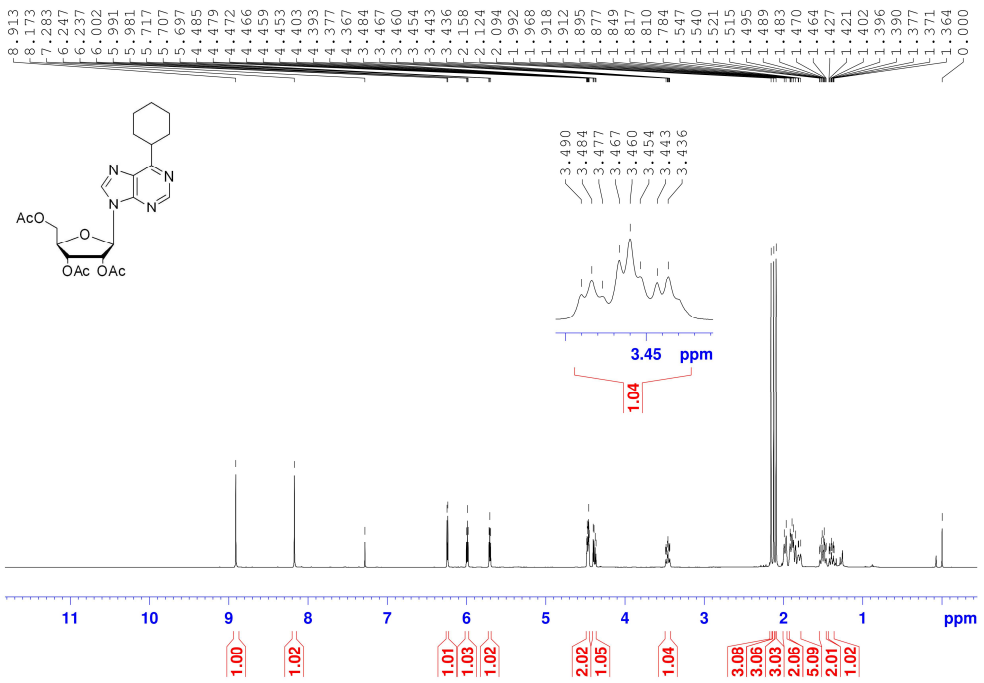
^{1}H NMR of ethyl 2-(6-cyclohexyl-9H-purin-9-yl)acetate (**4h**) in 500 MHz, $CDCl_3$



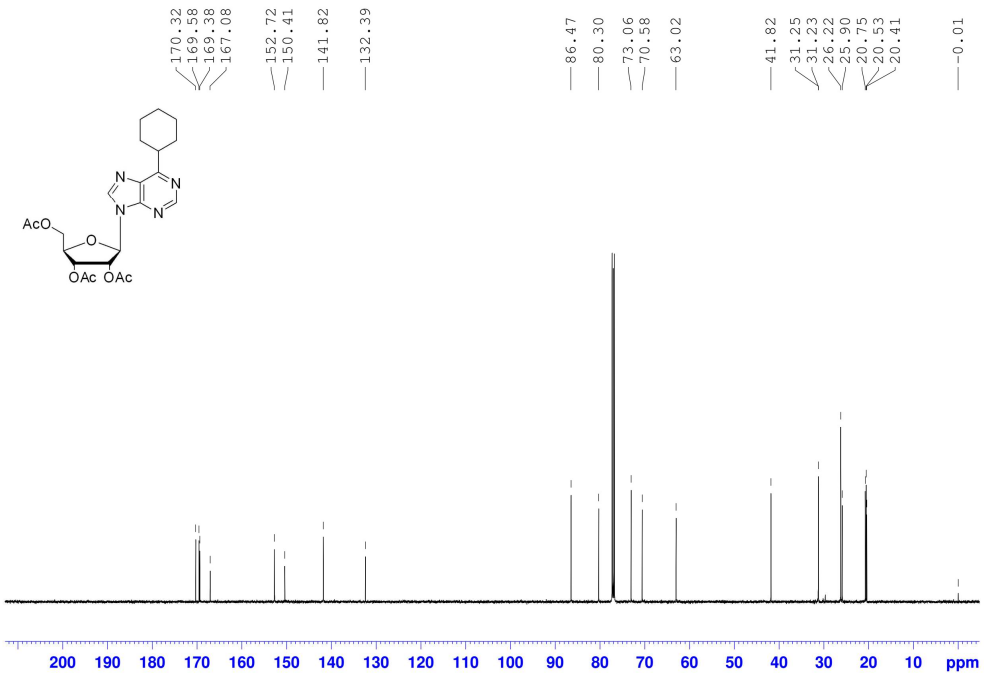
^{13}C NMR of ethyl 2-(6-cyclohexyl-9H-purin-9-yl)acetate (**4h**) in 125 MHz, $CDCl_3$



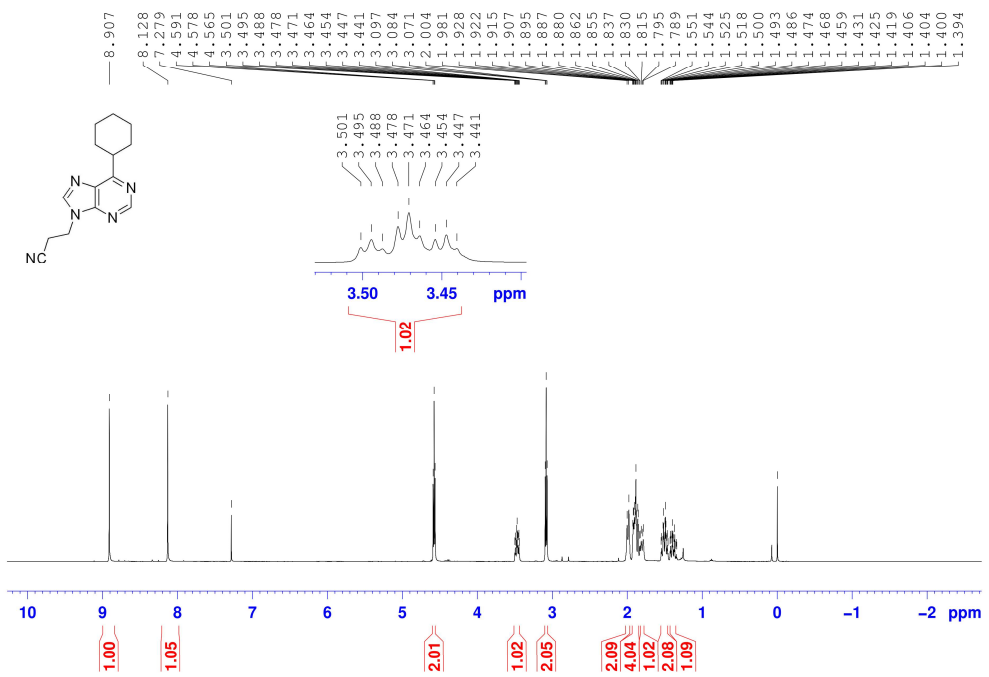
^{1}H NMR of 6-cyclohexyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**4i**) in 500 MHz, $CDCl_3$



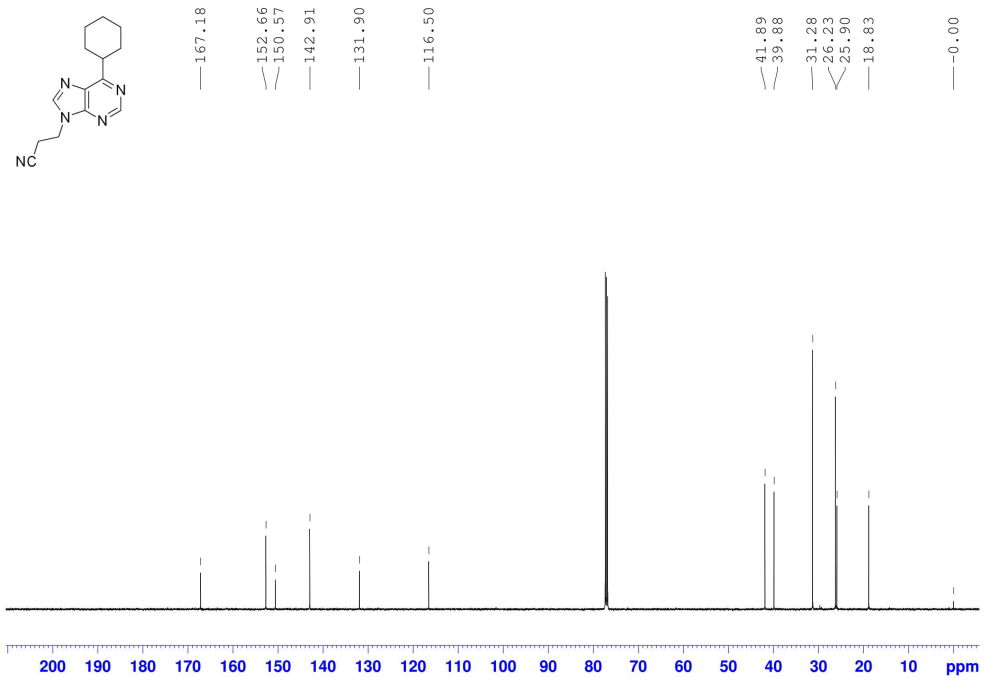
^{13}C NMR of 6-cyclohexyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**4i**) in 125 MHz, $CDCl_3$



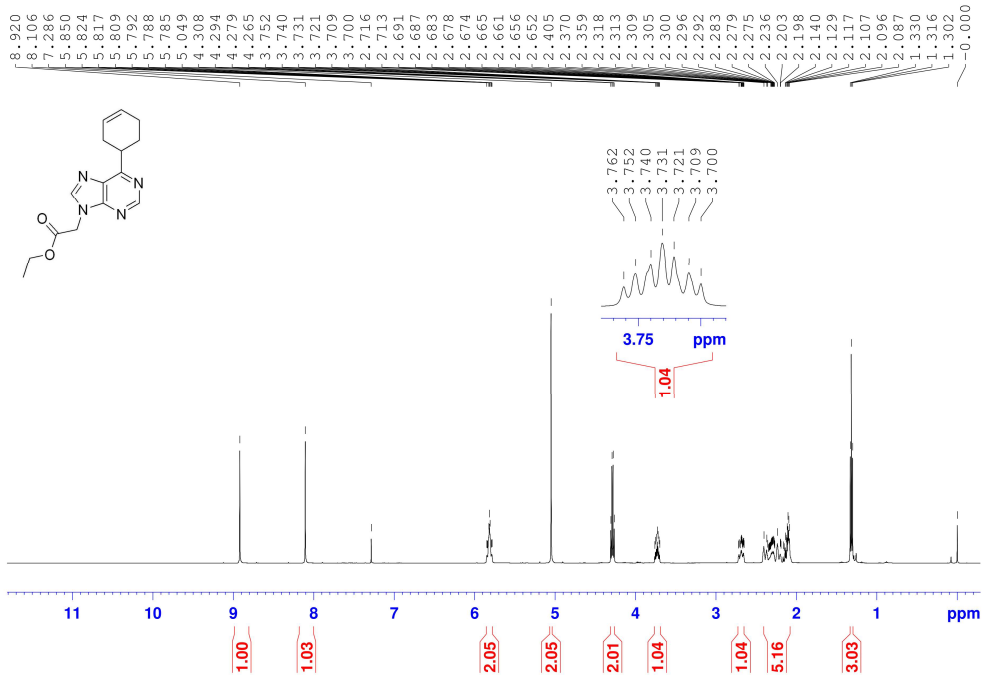
^{1}H NMR of 3-(6-cyclohexyl-*9H*-purin-9-yl)propanenitrile (**4j**) in 500 MHz, $CDCl_3$



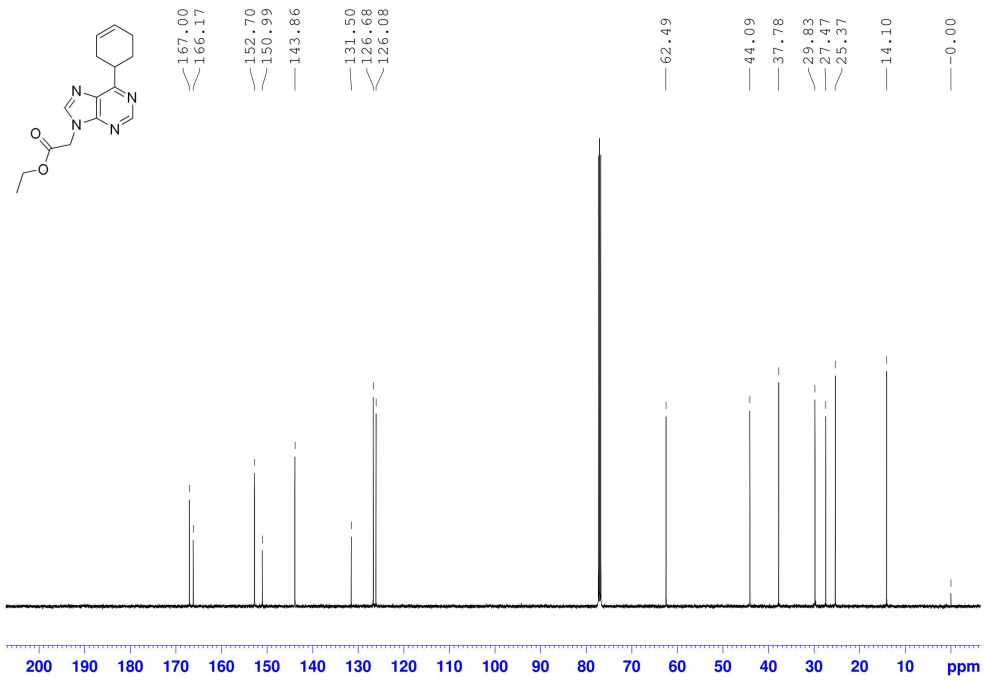
^{13}C NMR of 3-(6-cyclohexyl-*9H*-purin-9-yl)propanenitrile (**4j**) in 125 MHz, $CDCl_3$



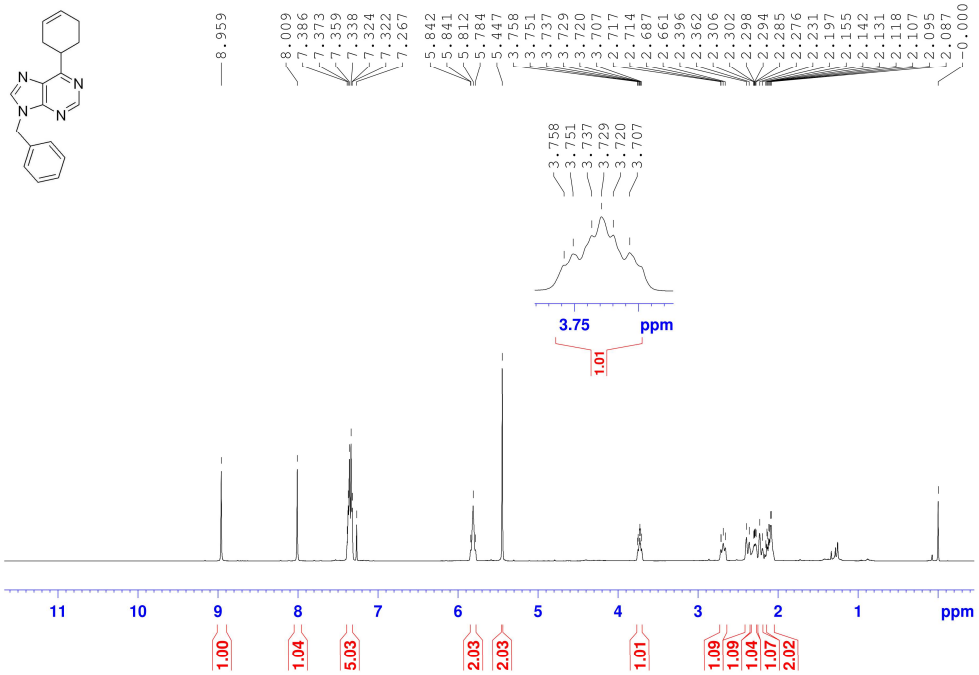
^{1}H NMR of ethyl 2-(6-(cyclohex-3-en-1-yl)-*9H*-purin-9-yl)acetate (**4k**) in 500 MHz, $CDCl_3$



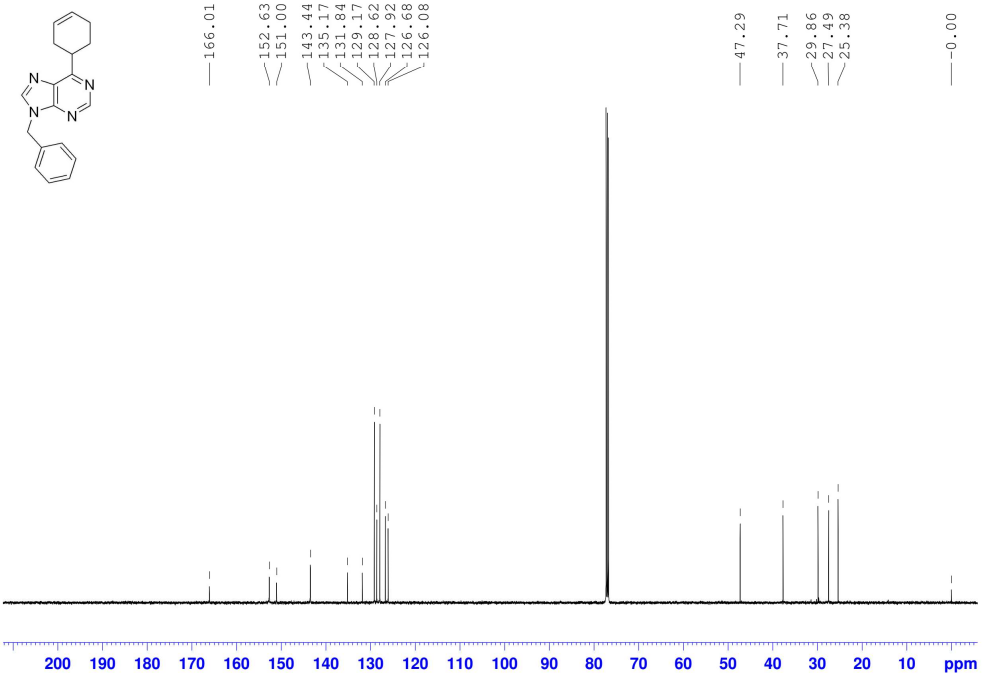
^{13}C NMR of ethyl 2-(6-(cyclohex-3-en-1-yl)-*9H*-purin-9-yl)acetate (**4k**) in 125 MHz, $CDCl_3$



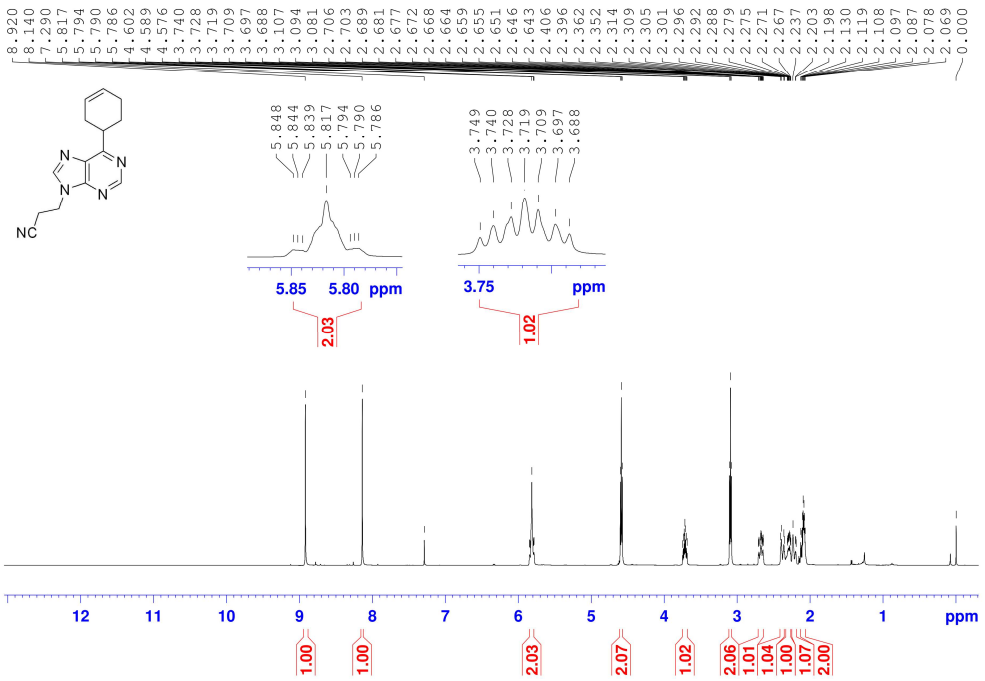
^{1}H NMR of 9-benzyl-6-(cyclohex-3-en-1-yl)-*9H*-purine (**4l**) in 500 MHz, $CDCl_3$



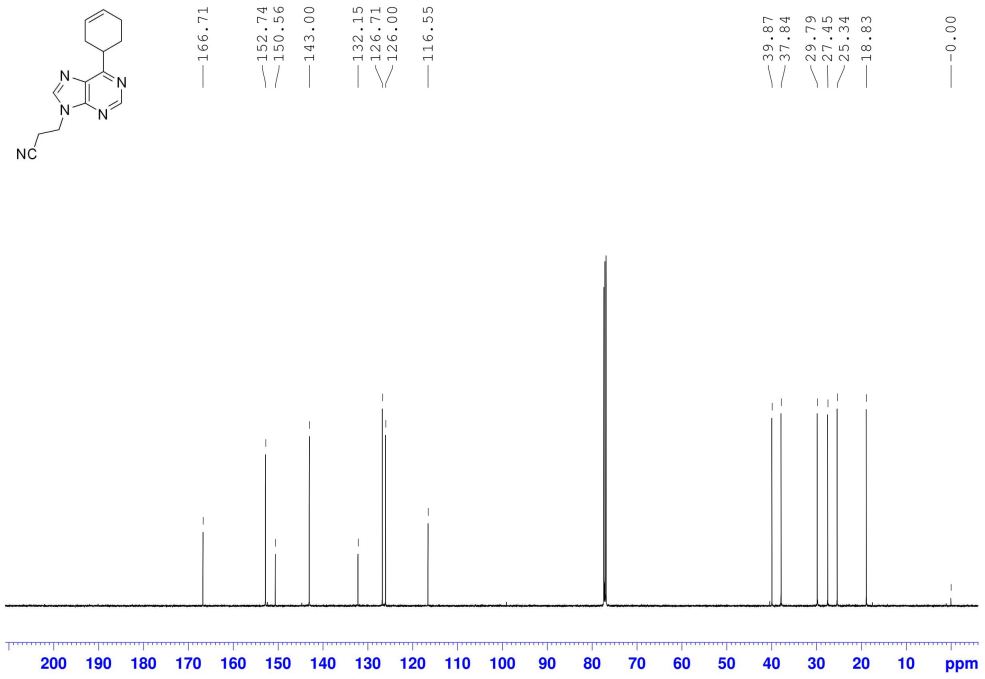
^{13}C NMR of 9-benzyl-6-(cyclohex-3-en-1-yl)-*9H*-purine (**4l**) in 125 MHz, $CDCl_3$



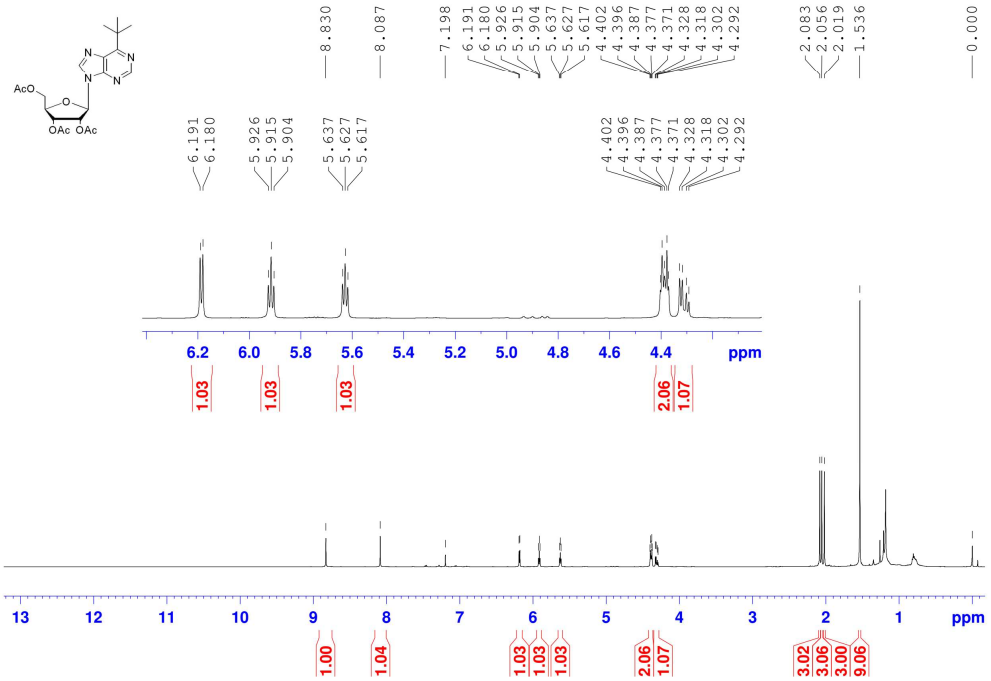
^{1}H NMR of 3-(6-(cyclohex-3-en-1-yl)-9H-purin-9-yl)propanenitrile (**4m**) in 500 MHz, $CDCl_3$



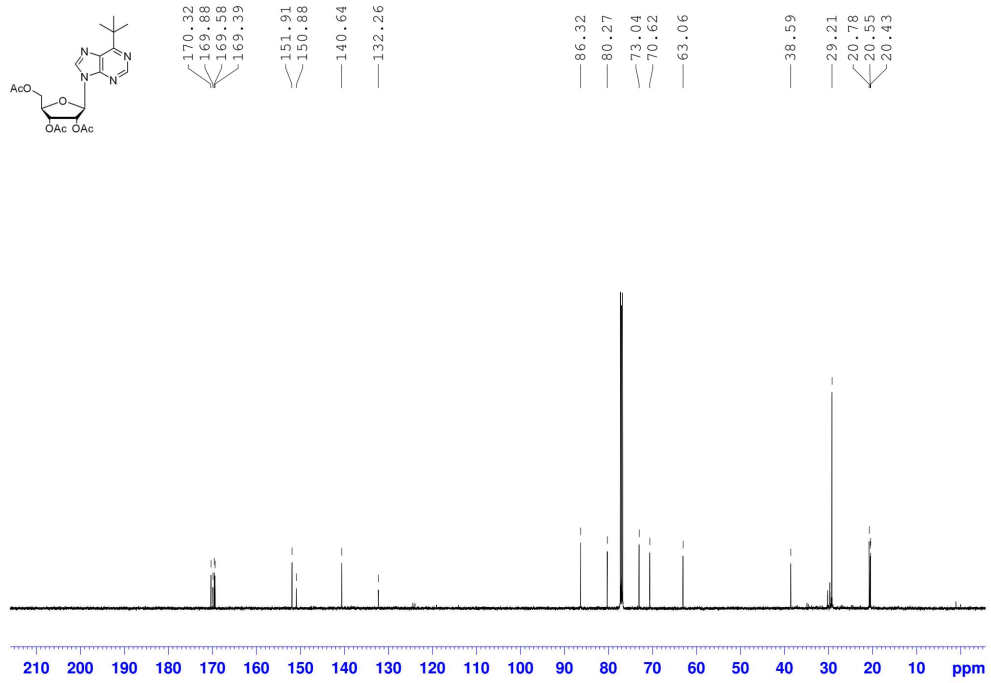
^{13}C NMR of 3-(6-(cyclohex-3-en-1-yl)-9H-purin-9-yl)propanenitrile (**4m**) in 125 MHz, $CDCl_3$



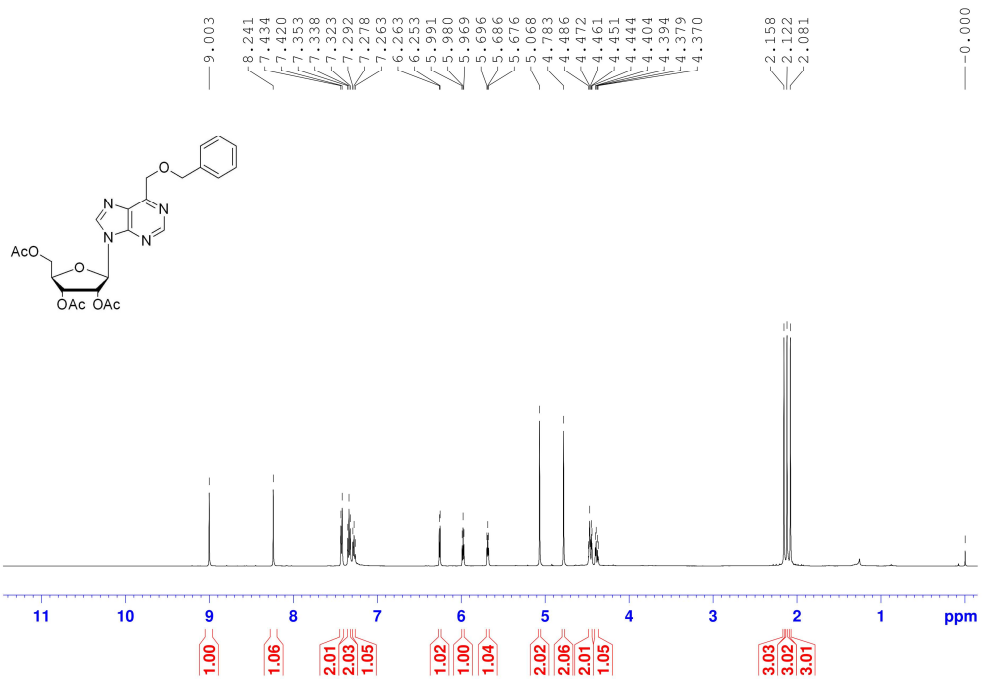
^{1}H NMR of 6-*t*-butyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**4n**) in 500 MHz, $CDCl_3$



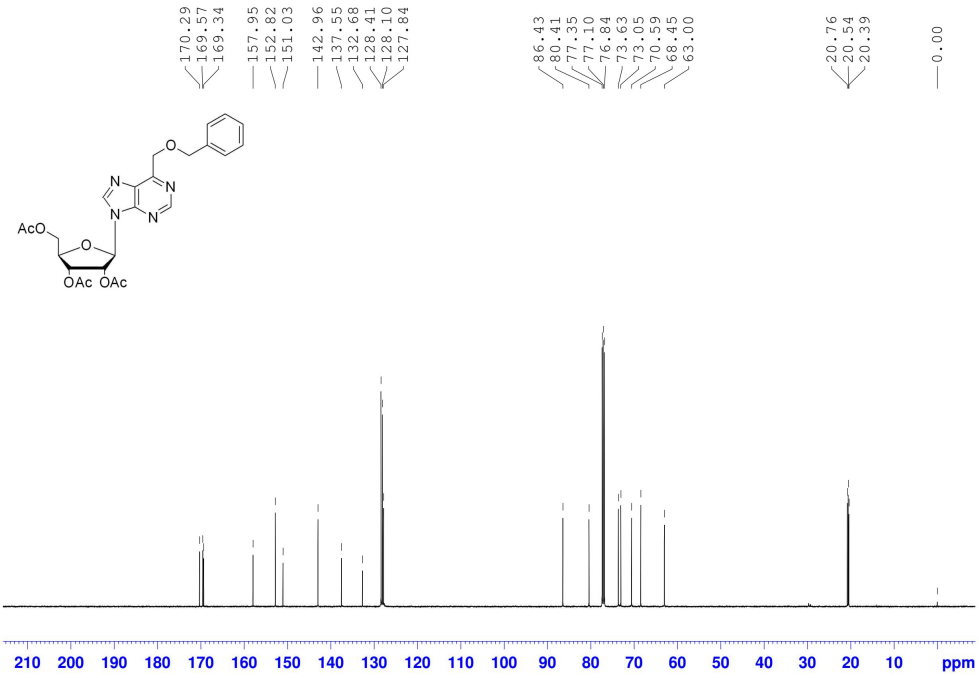
^{13}C NMR of 6-*t*-butyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**4n**) in 125 MHz, $CDCl_3$



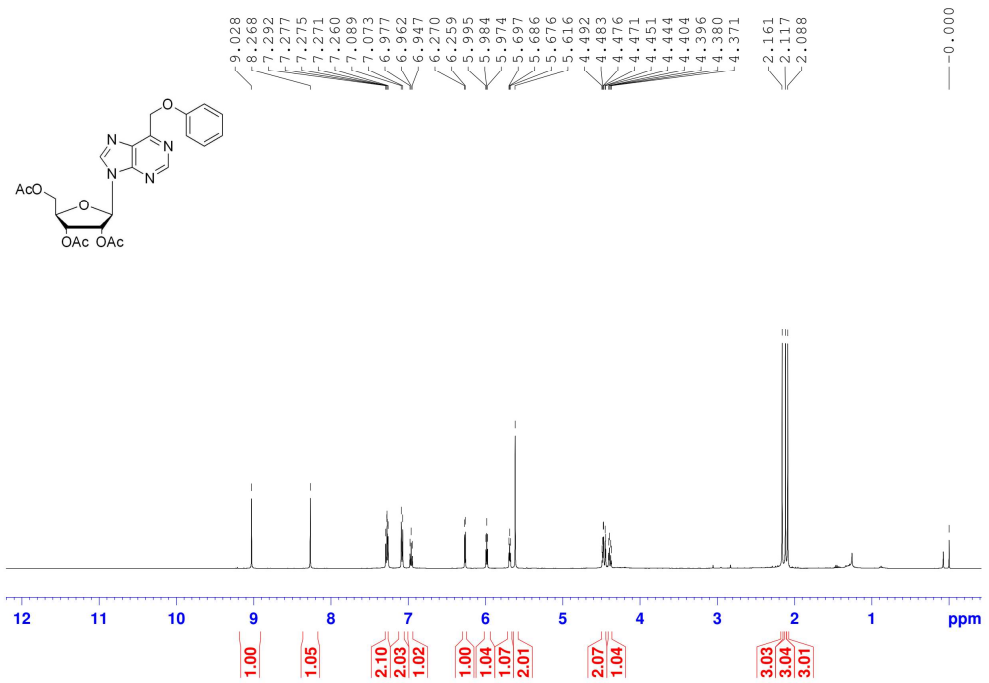
^{1}H NMR of 6-((benzyloxy)methyl)-2′,3′,5′-tri-*O*-acetyl-nebularine (**4p**) in 500 MHz, $CDCl_3$



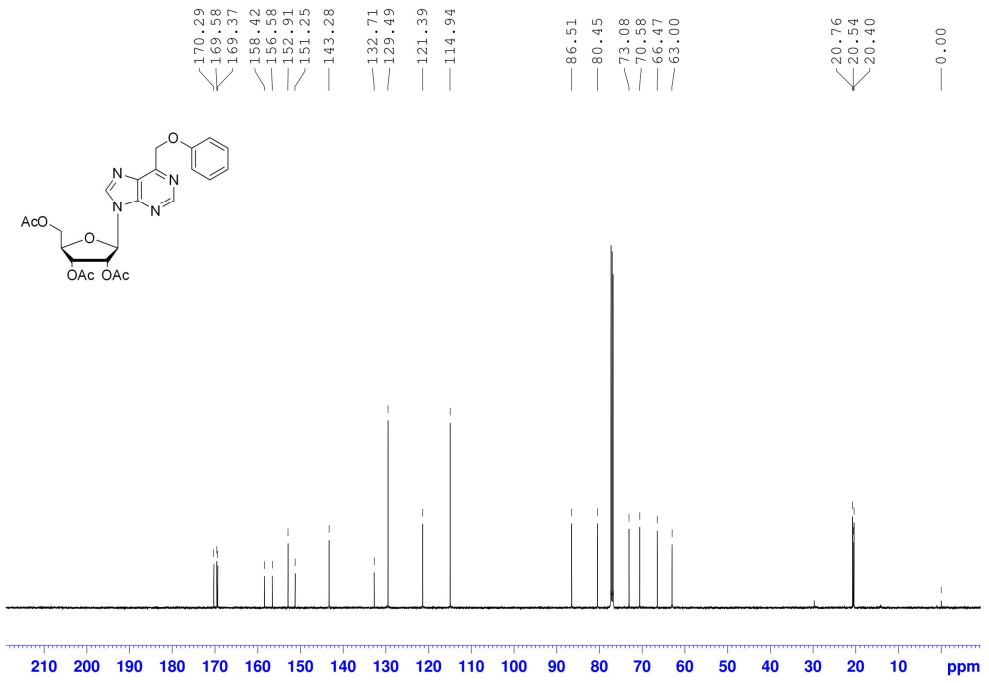
^{13}C NMR of 6-((benzyloxy)methyl)-2′,3′,5′-tri-*O*-acetyl-nebularine (**4p**) in 125 MHz, $CDCl_3$



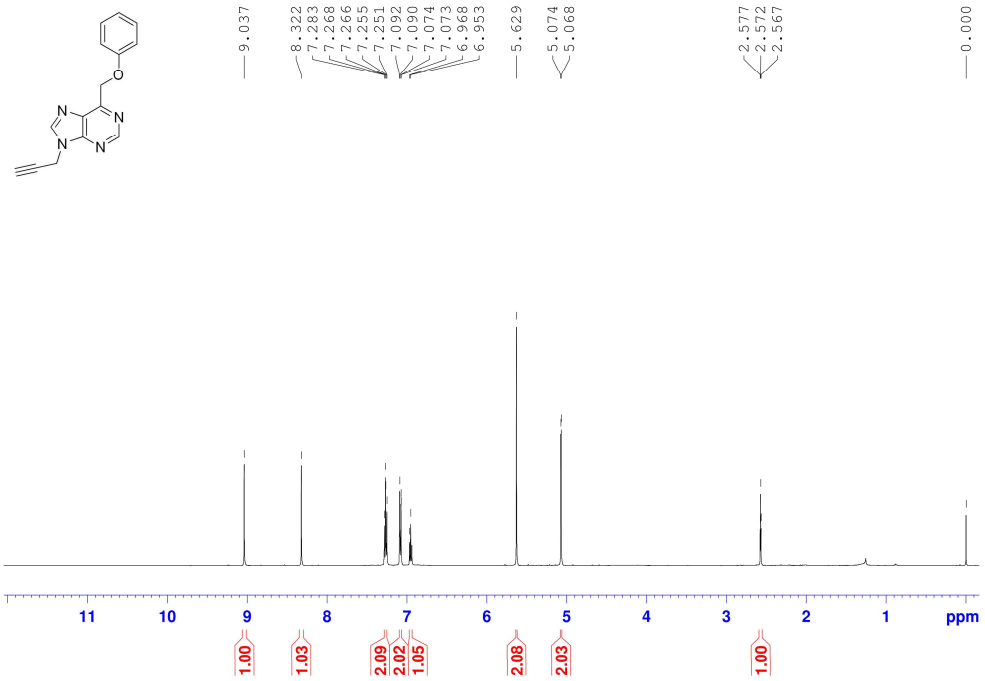
^{1}H NMR of 6-phenoxymethyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**4q**) in 500 MHz, $CDCl_3$



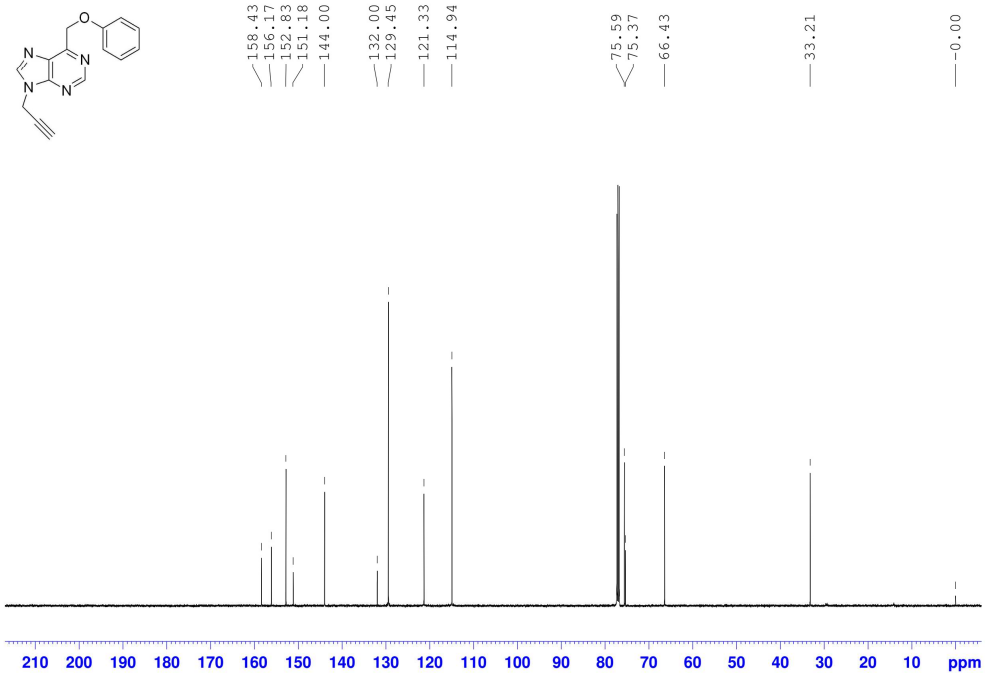
^{13}C NMR of 6-phenoxymethyl-2′,3′,5′-tri-*O*-acetyl-nebularine (**4q**) in 125 MHz, $CDCl_3$



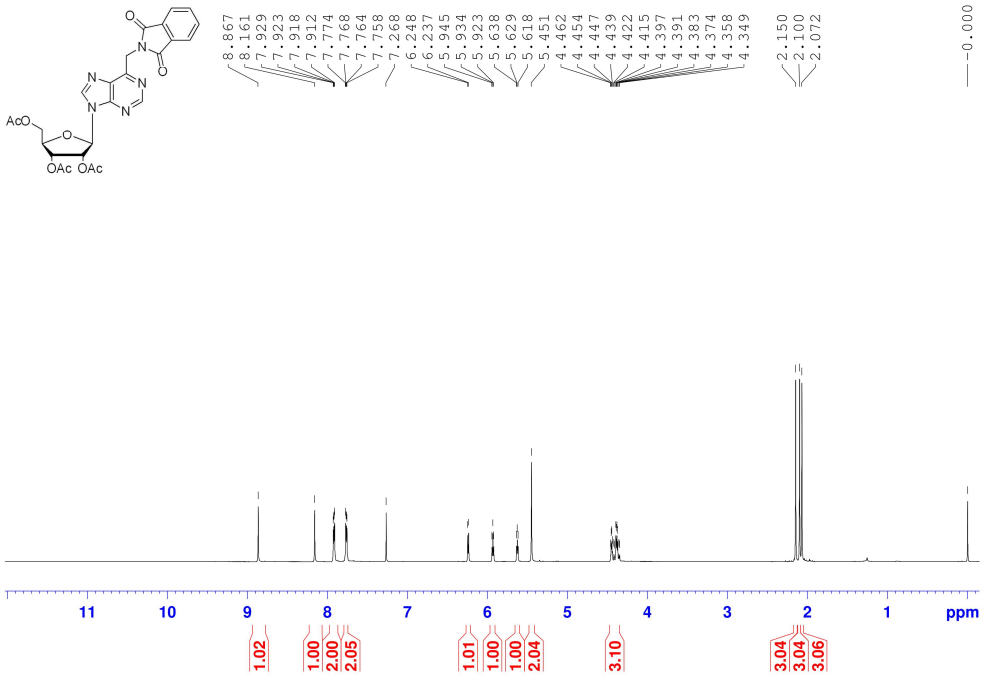
^{1}H NMR of 6-(phenoxymethyl)-9-(prop-2-yn-1-yl)-*9H*-purine (**4r**) in 500 MHz, $CDCl_3$



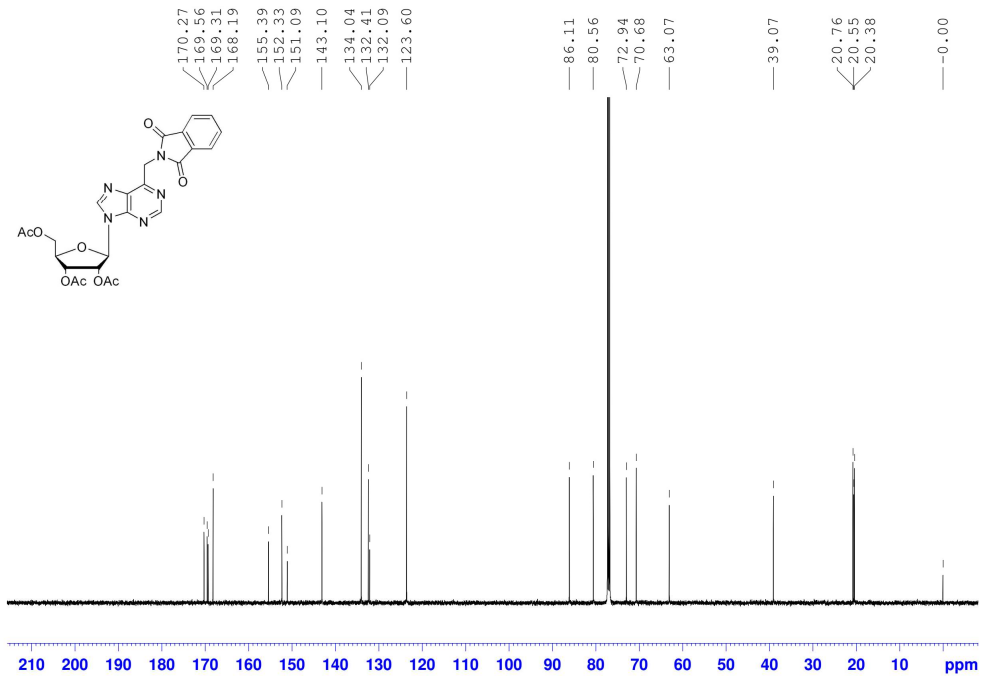
^{13}C NMR of 6-(phenoxymethyl)-9-(prop-2-yn-1-yl)-*9H*-purine (**4r**) in 125 MHz, $CDCl_3$



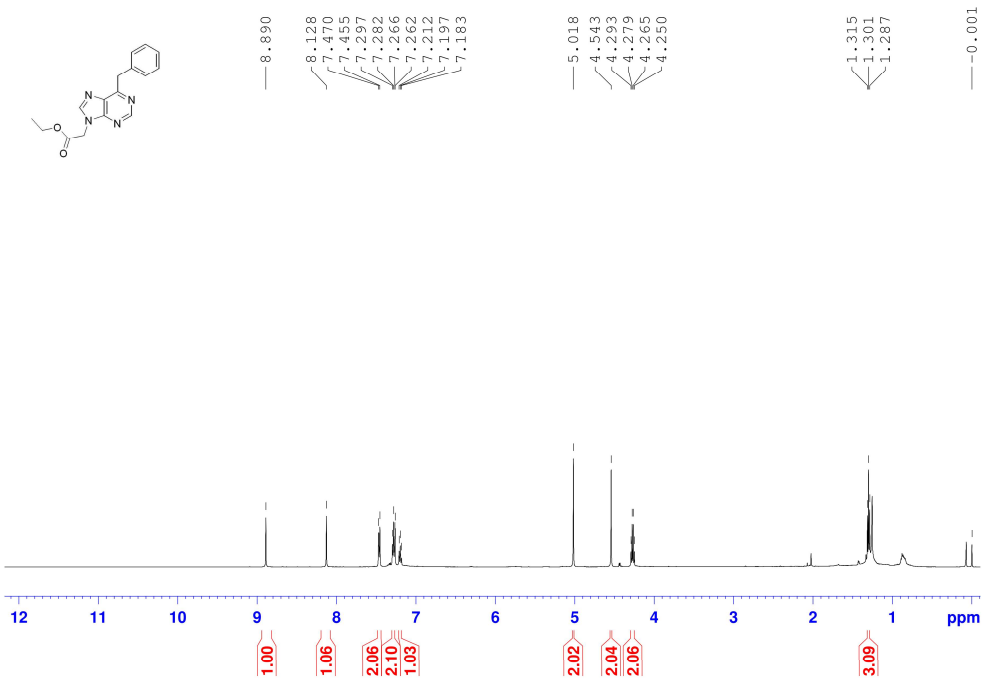
^{1}H NMR of 6-((1,3-dioxoisoindolin-2-yl)methyl)-2′,3′,5′-tri-*O*-acetyl-nebularine (**4s**) in 500 MHz



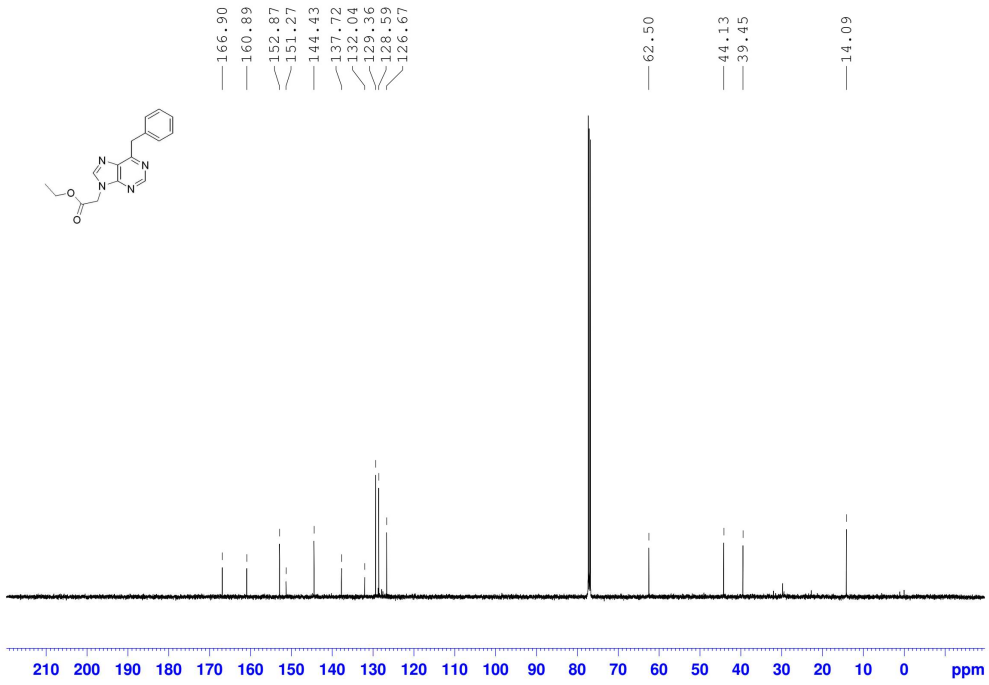
^{13}C NMR of 6-((1,3-dioxoisoindolin-2-yl)methyl)-2′,3′,5′-tri-*O*-acetyl-nebularine (**4s**) in 125 MHz



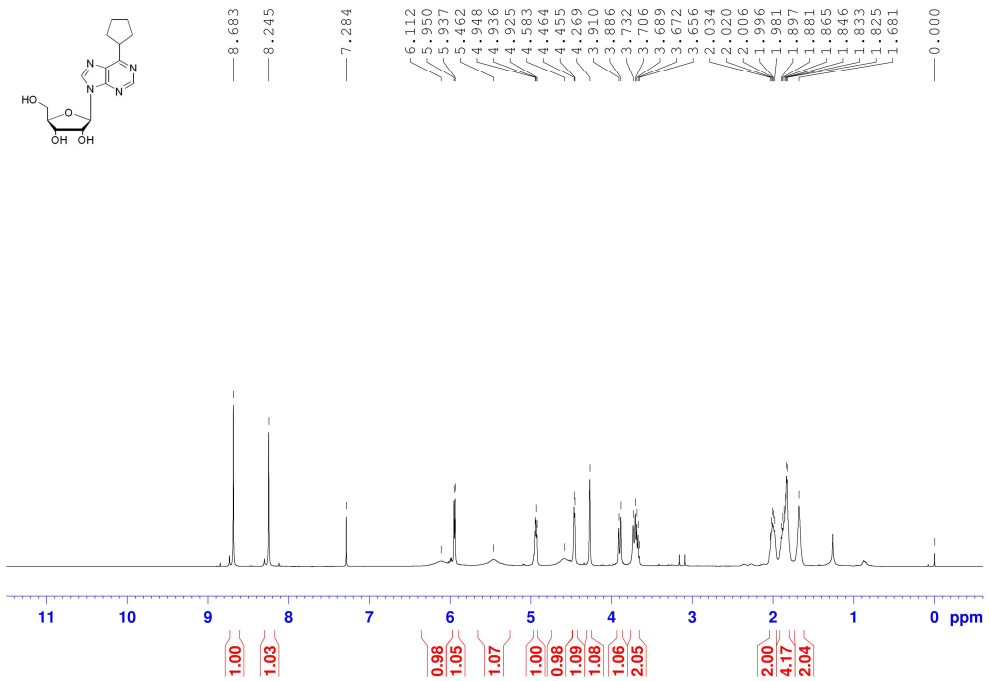
^{1}H NMR of ethyl 2-(6-benzyl-*9H*-purin-9-yl)acetate (**4t**) in 500 MHz, $CDCl_3$



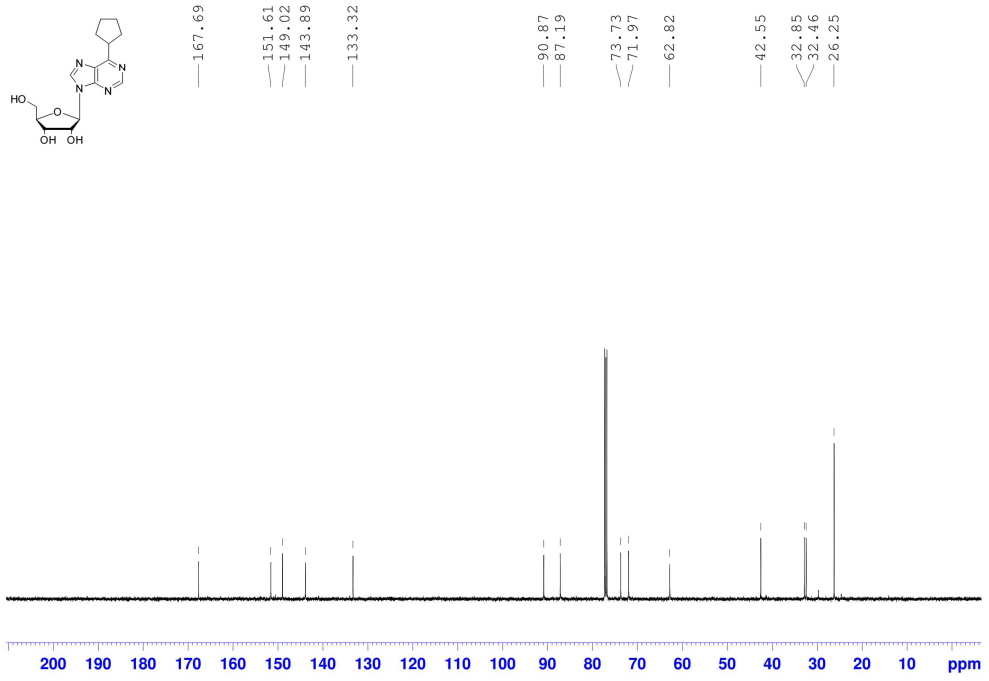
^{13}C NMR of ethyl 2-(6-benzyl-*9H*-purin-9-yl)acetate (**4t**) in 125 MHz, $CDCl_3$



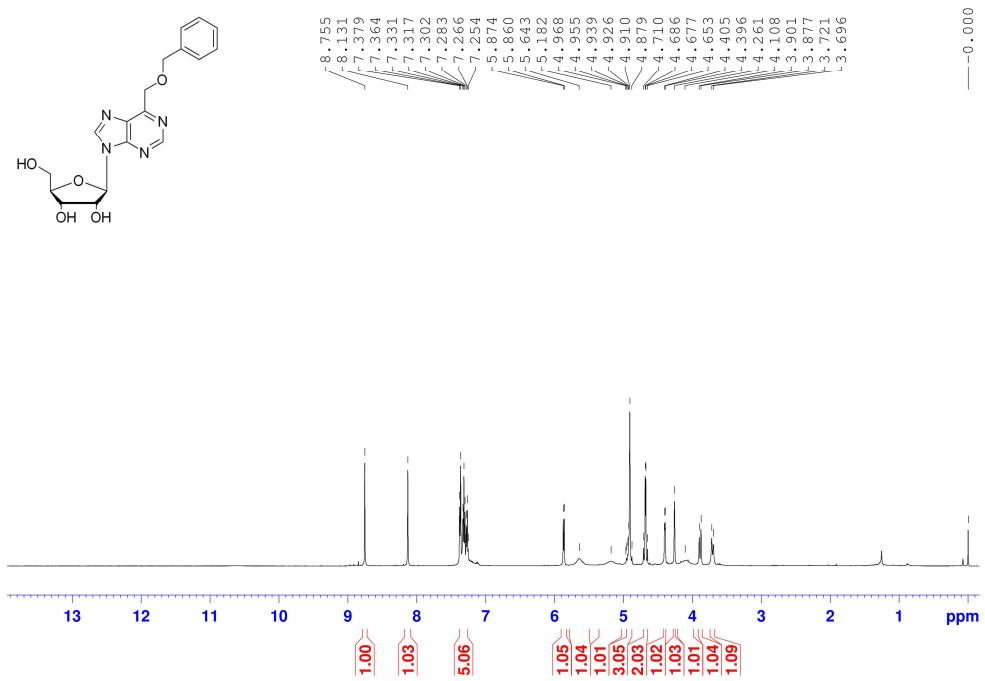
^{1}H NMR of 6-cyclopentyl-nebularine (**6-CPN**) in 500 MHz, $CDCl_3$



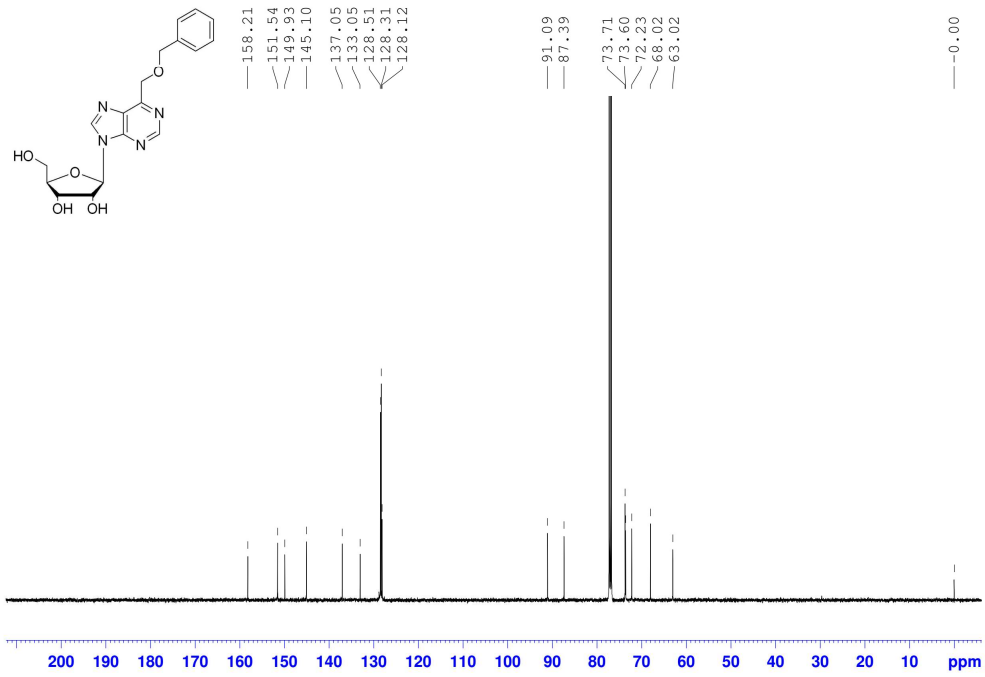
^{13}C NMR of 6-cyclopentyl-nebularine (**6-CPN**) in 125 MHz, $CDCl_3$



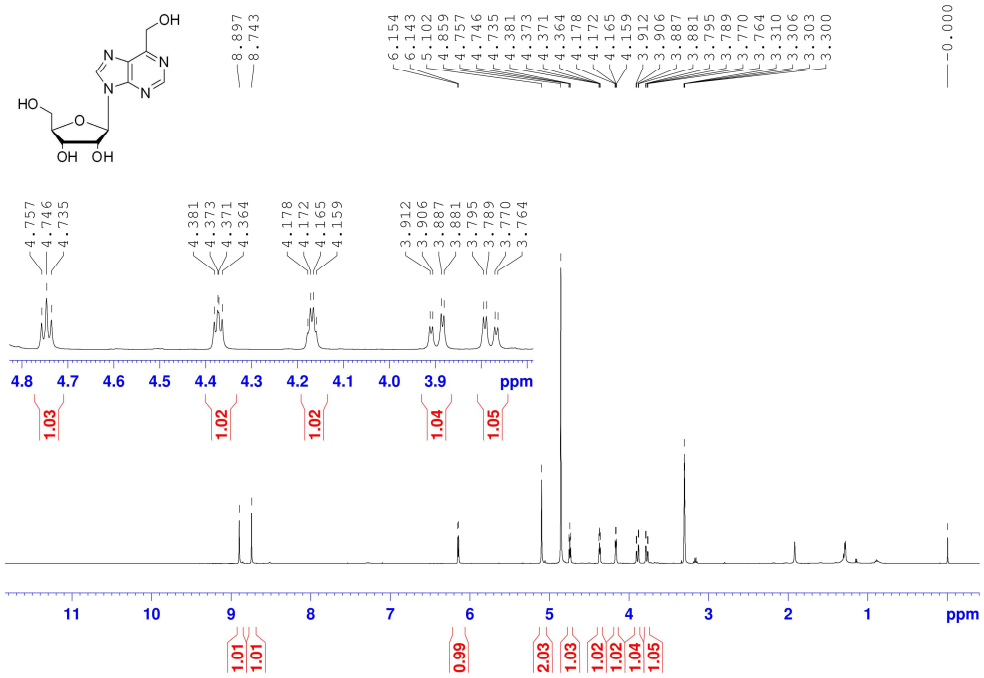
^{1}H NMR of 6-((benzyloxy)methyl)-2′,3′,5′-tri-*O*-acetyl-nebularine (**Neb-OBn**) in 500 MHz, $CDCl_3$



^{13}C NMR of 6-((benzyloxy)methyl)-2′,3′,5′-tri-*O*-acetyl-nebularine (**Neb-OBn**) in 125 MHz, $CDCl_3$



^{1}H NMR of 6-hydroxymethyl-nebularine (**6-HOMN**) in 500 MHz, CD_3OD



^{13}C NMR of 6-hydroxymethyl-nebularine (**6-HOMN**) in 125 MHz, CD_3OD