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Metal-free, Direct Acylation of Purines to Access C^6-Acylated Purines Derivatives Induced by TBHP via Minisci-type Reaction

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Contents

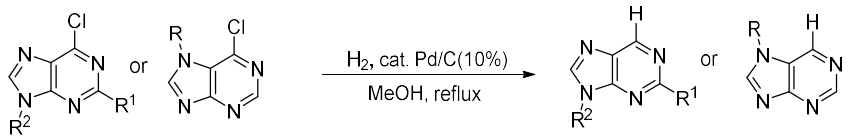
1. General Information

All the chemicals were purchased from commercial suppliers, all commercially available reagents were directly used without further purification. Melting points were determined on a hot stage melting point apparatus (uncorrected). NMR spectra were recorded with a 500MHz spectrometer for ^{1}H NMR, 125 MHz for ^{13}C NMR, 376 MHz for ^{19}F in $CDCl_3$, with TMS as an internal standard. The obtained signal multiplicities were distinguished with the common abbreviations s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), quint (quintet), sext (sextet), hept (heptet), and m (multiplet). HRMS measurements were carried out on a Thermo Fisher Q-Exactive mass spectrometer with Electrospray Ionization (ESI) as the ionization method. Visualization on thin layer chromatography (TLC) using ultraviolet light (254 nm). The reaction mixtures were fast purified by column chromatography (200-300 mesh) over silica gel.

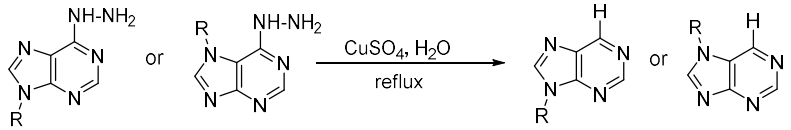
2. General experimental procedures for targeted molecules

2.1 synthesis of purine substrates

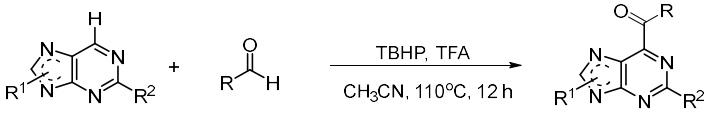
The synthesis of 6-H-purine substrates **1a-1e, 1i-1k, 1m** according to the previous report. [1]



The synthesis of 6-H-purine substrates **1f-1h, 1l** according to the previous report. [2]



2.2 General procedure for the synthesis of 3a-3m and 4a-4s'



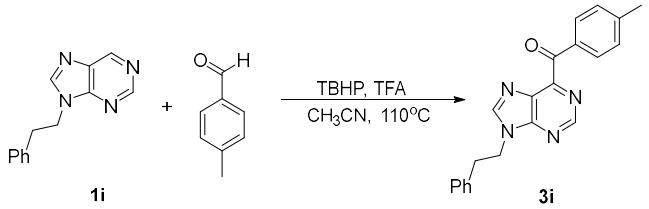
1 2 3 or 4

The purine substrate (0.5 mmol, 1.0 equiv.), RCHO (1.0 mmol, 2.0 equiv.), TBHP (1.25 mmol, 2.5 equiv. 70% in water) and TFA (1.0 mmol, 2.0 equiv.) were mixed in CH_3CN (1 mL) in a pressure-resistant tube. The resulting solution was heated at 110 °C in sealed tube with vigorous stirring for 12 h. Reaction progress was checked by TLC. Once the reaction was finished, it was mixed with H_2O (5 mL), and 1 mL Na_2CO_3 solution (2M) was added to adjust the pH, then the crude was extracted

with ethyl acetate (3×30 mL). After mixing the organic phase, the solution was dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure, then separated and purified the crude product using column chromatography to obtain **3a-3m** and **4a-4s'**.

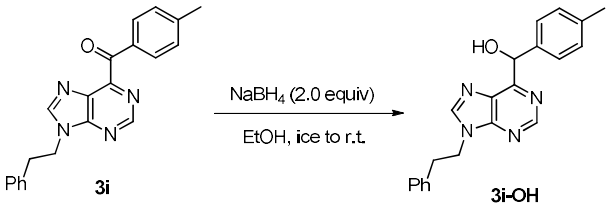
2.3 Gram-scale reaction and further transformation

2.3.1 Gram scale synthesis of product 3i



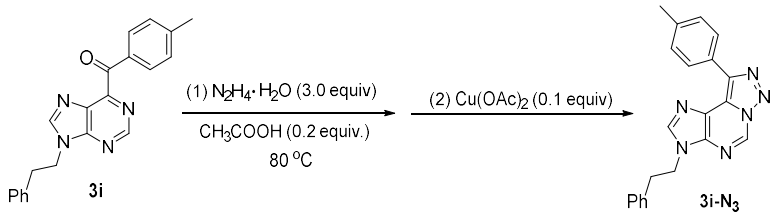
To further demonstrate the adaptability of the acylation method, we performed an experiment on a 5 mmol scale. **1i** (1.12 g, 5.0 mmol), *p*-tolualdehyde (1.20 g, 10.0 mmol), TBHP (1.13 g, 12.5 mmol, 70% in water) and TFA (1.14 g, 10.0 mmol) were dissolved in CH_3CN (5 mL) within a sturdy pressure tube, and the reaction was stirred at 110 °C for 12 h. Reaction progress was checked by TLC. Once the reaction was finished, it was combined with H_2O (20 mL), and the pH was adjusted by adding 10 mL Na_2CO_3 solution (2M). Afterwards, ethyl acetate (3×50 mL) was added for extraction. After mixing the organic phase, the solution was dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure, then separated and purified the raw material by column chromatography to get the final product (**3i**). Yield: 1.25 g, 74%.

2.3.2 Synthesis of (9-phenethyl-9*H*-purin-6-yl)(p-tolyl)methanol (3i-OH).



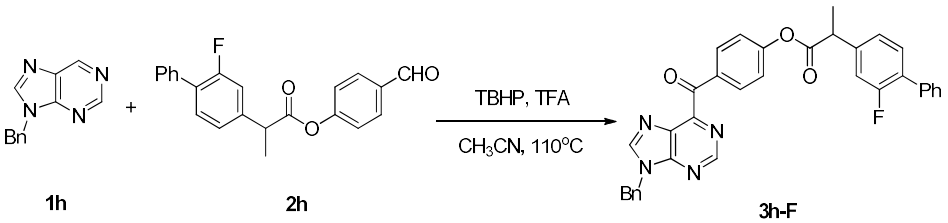
Under ice bath conditions, **3i** (103 mg, 0.3 mmol) was dissolved in EtOH (10 mL), $NaBH_4$ (22 mg, 0.6 mmol) was slowly added to the reaction solution and stirred continued for 30 min at room temperature. Reaction progress was checked by TLC. After the reaction was completed, H_2O (15 mL) was added to the reaction and ethyl acetate (3×30 mL) was used for extraction. After combining the organic phase, the solution was dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (**3i-OH**) was pure enough without further purification.

2.3.3 Synthesis of 3-phenethyl-9-(p-tolyl)-3*H*-[1,2,3]triazolo[5,1-i]-purine (3i-N_3).



Purine substrate **3i** (103 mg, 0.3 mmol) was dissolved in EtOH (10 mL), added N_2H_4•H_2O (45 mg, 0.9 mmol) and CH_3COOH (4 mg, 0.06 mmol) to the reaction, reacted at 80 °C for 2 h, then cooled to room temperature. EtOAc (3 mL) and $Cu(OAc)_2$ (5 mg, 0.03 mmol) were added and allowed to react for 6 h at room temperature. Reaction progress was checked by TLC. After the reaction had finished, the reaction mixture was added to H_2O (5 mL), Na_2CO_3 solution (2M) was added to adjust the pH, then the crude was extracted with ethyl acetate (3×30 mL). Later, the organic phase was combined, the solution was dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure, and the crude was separated and purified by fast column chromatography, the final product (**3i-N_3**) was obtained.

2.3.4 Synthesis of 4-(9-benzyl-9*H*-purine-6-carbonyl)phenyl-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoate (3h-F).



The substrate **2h** (348 mg, 1.0 mmol), **1h** (105 mg, 0.5 mmol), TBHP (113 mg, 1.25 mmol, 70% in water) and TFA (114 mg, 1.0 mmol,) were placed in CH_3CN (1 mL) within a sturdy pressure tube and subjected to magnetic stirring at 110 °C for 12 h. The reaction progress was checked by TLC. Once the reaction was finished, H_2O (5 mL) was added to the reaction, and the pH was adjusted by adding 1mL Na_2CO_3 solution (2M). Afterwards, ethyl acetate (3×30 mL) was added for extraction. After combining the organic phase, the solution was dried with anhydrous $MgSO_4$, filtered and concentrated to obtain crude product, which was separated and purified by column chromatography to obtain the final desired product (**3h-F**).

3. Characterization data for all compounds

ethyl 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) acetate (3a).

Yield: 134 mg, 83%; yellow solid, m. p. 126 – 130 °C; R_f = 0.23 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.10 (s, 1H), 8.26 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.12 (s, 2H), 4.30 (q, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 1.32 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.1, 166.6, 153.3, 152.2, 146.8, 145.2, 132.9, 131.3, 130.9, 129.3, 62.6, 44.3, 21.9, 14.1. The NMR data are identical with the reference[3]. ESI-HRMS $[M+H]^+$ calcd for $C_{17}H_{17}N_4O_3^+$ m/z 325.1295, found 325.1288.

methyl 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) acetate (3b).

Yield: 121 mg, 78%; yellow solid, m. p. 152 – 156 °C; R_f = 0.21 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.10 (s, 1H), 8.27 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 5.14 (s, 2H), 3.84 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 191.1, 167.1, 153.3, 152.2, 146.8, 145.3, 132.9, 131.3, 130.9, 129.3, 53.2, 44.1, 21.9. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{15}N_4O_3^+$ *m/z* 311.1139, found 311.1134.

2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl)ethyl acetate (3c).

Yield: 118 mg, 73%; yellow solid, m. p. 124 – 126 °C, R_f = 0.20 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.11 (s, 1H), 8.24 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 4.63 (t, *J* = 5.0 Hz, 2H), 4.50 (t, *J* = 5.0 Hz, 2H), 2.44 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 191.1, 170.4, 153.3, 152.0, 146.8, 145.2, 132.9, 131.6, 130.9, 129.3, 62.0, 42.9, 21.9, 20.7. ESI-HRMS $[M+H]^+$ calcd for $C_{17}H_{17}N_4O_3^+$ *m/z* 325.1295, found 325.1289.

3-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) propanenitrile (3d).

Yield: 127 mg, 87%; yellow solid, m. p. 118 – 122 °C; R_f = 0.11 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.10 (s, 1H), 8.33 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 4.67 (t, *J* = 6.5 Hz, 2H), 3.12 (t, *J* = 6.5 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 191.0, 153.6, 153.0, 152.1, 146.2, 145.5, 132.7, 131.8, 130.9, 129.4, 116.4, 40.0, 21.9, 18.8. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{14}N_5O^+$ *m/z* 292.1193, found 292.1189.

9-butyl-6-(4-methylbenzoyl) purine (3e).

Yield: 125 mg, 85%; oil; R_f = 0.28 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.00 (s, 1H), 8.13 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.25 (t, *J* = 8.0 Hz, 2H), 2.32 (s, 3H), 1.84

(quint, *J* = 7.5 Hz, 2H), 1.30 (sext, *J* = 7.0 Hz, 2H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 191.3, 153.3, 153.0, 151.7, 146.8, 145.1, 132.9, 131.6, 130.8, 129.2, 43.9, 31.9, 21.8, 19.9, 13.4. ESI-HRMS $[M+H]^+$ calcd for $C_{17}H_{19}N_4O^+$ *m/z* 295.1553, found 295.1550.

9-allyl-6-(4-methylbenzoyl) purine (3f).

Yield: 88 mg, 63%; yellow solid, m. p. 96 – 100 °C, R_f = 0.21 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.11 (s, 1H), 8.21 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.12 – 6.04 (m, 1H), 5.38 (d, *J* = 10.5 Hz, 1H), 5.30 (d, *J* = 17.0 Hz, 1H), 4.96 (d, *J* = 6.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 191.2, 153.2, 153.1, 152.0, 146.4, 145.2, 133.0, 131.7, 131.1, 130.9, 129.3, 119.9, 46.0, 21.9. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{15}N_4O^+$ *m/z* 279.1240, found 279.1237.

9-(prop-2-yn-1-yl)-6-(4-methylbenzoyl) purine (3g).

Yield: 94 mg, 68%; yellow solid, m. p. 154 – 158 °C, R_f = 0.20 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.13 (s, 1H), 8.40 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.13 (d, *J* = 2.5 Hz, 2H), 2.59 (t, *J* = 3.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 191.0, 153.4, 152.7, 152.1, 145.7, 145.3, 132.9, 131.7, 130.9, 129.3, 75.7, 75.3, 33.3, 21.9. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{13}N_4O^+$ *m/z* 277.1084, found 277.1080.

9-benzyl-6-(4-methylbenzoyl) purine (3h).

Yield: 131 mg, 80%; oil; R_f = 0.26 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.12 (s, 1H), 8.18 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.33 (m, 5H), 7.27 (d, *J* = 7.0 Hz, 2H), 5.50 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 191.3, 153.3, 153.2, 152.0, 146.6, 145.2, 134.8, 132.9, 131.6, 130.9, 129.3, 129.2, 128.8, 128.0, 47.5, 21.9. The NMR data are identical with the reference [3]. ESI-HRMS $[M+H]^+$ calcd for $C_{20}H_{17}N_4O^+$ *m/z* 329.1397 , found 329.1392.

9-phenethyl-6-(4-methylbenzoyl) purine (3i).

Yield: 139 mg, 81%; yellow solid, m. p. 168 – 172 °C; R_f = 0.43 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.11 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.81 (s, 1H), 7.30 – 7.24 (m, 5H), 7.08 (d, *J* = 7.0 Hz, 2H), 4.59 (t, *J* = 7.0 Hz, 2H), 3.23 (t, *J* = 7.5 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 191.2, 153.2, 153.0, 151.8, 146.7, 145.1, 136.9, 133.0, 131.7, 130.9, 129.2, 129.0, 128.7, 127.3, 45.6, 36.1, 21.9. ESI-HRMS $[M+H]^+$ calcd for $C_{21}H_{19}N_4O^+$ *m/z* 343.1553, found 343.1546.

9-(naphthalen-1-ylmethyl)-6-(4-methylbenzoyl) purine (3j).

Yield: 146 mg, 77%; yellow solid, m. p. 158 – 162 °C; R_f = 0.20 (EA/PE = 1:2, v/v). ^{1}H NMR (500 MHz,

$CDCl_3$) δ: 9.19 (s, 1H), 8.02 (s, 1H), 8.00 (d, J = 4.0 Hz, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 6.5 Hz, 2H), 7.54 – 7.51 (m, 2H), 7.49 – 7.42 (m, 2H), 7.27 (d, J = 8.0 Hz, 2H), 5.93 (s, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.2, 153.3, 152.1, 146.5, 145.2, 134.0, 132.9, 131.6, 130.9, 130.0, 129.9, 129.3, 129.2, 127.5, 127.4, 126.5, 125.4, 122.6, 45.3, 21.9. ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{19}N_4O^+$ m/z 379.1553, found 379.1545.

2-amino-9-propyl-6-(4-methylbenzoyl) purine (3k).

Yield: 66 mg, 45%; yellow solid, m. p. 152 – 156 °C; R_f = 0.20 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (d, J = 8.5 Hz, 2H), 7.81 (s, 1H), 7.27 (d, J = 8.5 Hz, 2H), 5.21 (br s, 2H), 4.09 (t, J = 7.5 Hz, 2H), 2.42 (s, 3H), 1.92 (sext, J = 7.5 Hz, 2H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.6, 159.4, 155.1, 154.4, 145.1, 143.8, 133.0, 130.8, 129.2, 125.9, 45.1, 23.1, 21.9, 11.2. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{18}N_5O^+$ m/z 296.1506, found 296.1503.

7-benzyl-6-(4-methylbenzoyl) purine (3l).

Yield: 108 mg, 66%; yellow solid, m. p. 142 – 144 °C; R_f = 0.19 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.17 (s, 1H), 8.44 (s, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.00 – 6.99 (m, 3H), 6.86 – 6.85 (m, 2H), 5.48 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.6, 163.6, 151.8, 150.2, 148.1, 145.4, 133.8, 132.1, 130.9, 129.1, 128.8, 128.4, 127.4, 122.5, 51.7, 21.9. ESI-HRMS $[M+H]^+$ calcd for $C_{20}H_{17}N_4O^+$ m/z 329.1397, found 329.1392.

3-(6-(4-methylbenzoyl)-7*H*-purin-7-yl) propanenitrile (3m).

Yield: 74 mg, 51%; yellow solid, m. p. 204 – 208 °C; R_f = 0.41 (EA/PE = 2:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.27 (s, 1H), 8.49 (s, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.67 (t, J = 6.0 Hz, 2H), 2.99 (t, J = 5.5 Hz, 2H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 192.3, 163.7, 152.1, 150.5, 146.6, 146.3, 132.2, 131.5, 129.6, 122.5, 116.4, 44.1, 22.0, 20.0. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{14}N_5O^+$ m/z 292.1193, found 292.1189.

9H-purin-6-yl)(p-tolyl)methanone (3n-*H*)

Yield: 26 mg, 22%; yellow solid, m.p. >220 °C; R_f = 0.17 (EA). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.68 (br s, 1H), 9.10 (s, 1H), 8.77 (s, 1H), 8.02 (d, J = 7.5 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H), 2.43 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 191.5, 150.9, 149.1, 144.7, 132.6, 130.7, 129.1, 21.2. $[M+H]^+$ calcd for $C_{13}H_{11}N_4O^+$ m/z 239.0927, found239.0924.

ethyl 2-(6-(4-methoxybenzoyl)-9*H*-purin-9-yl) acetate (4a).

Yield: 141 mg, 83%; yellow solid, m. p. 140 – 144 °C; R_f = 0.28 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz,

$CDCl_3$) δ: 9.08 (s, 1H), 8.29 (s, 1H), 8.04 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 5.13 (s, 2H), 4.27 (q, J = 7.0 Hz, 2H), 3.87 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.9, 166.8, 164.4, 153.5, 152.1, 147.0, 133.2, 131.2, 128.3, 113.9, 62.6, 55.6, 44.3, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{17}H_{17}N_4O_4^+$ m/z 341.1244, found 341.1239.

ethyl 2-(6-(4-(dimethylamino)benzoyl)-9*H*-purin-9-yl) acetate (4b).

Yield: 106 mg, 60%; yellow solid, m. p. 198 – 202 °C; R_f = 0.10 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.08 (s, 1H), 8.22 (s, 1H), 7.94 (d, J = 9.0 Hz, 2H), 6.66 (d, J = 9.0 Hz, 2H), 5.10 (s, 2H), 4.29 (q, J = 7.0 Hz, 2H), 3.08 (s, 6H), 1.32 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 188.9, 166.8, 155.1, 154.2, 153.0, 152.3, 146.3, 133.2, 131.1, 123.2, 110.7, 62.6, 44.2, 40.0, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{18}H_{20}N_5O_3^+$ m/z 354.1561, found 354.1552.

ethyl 2-(6-(4-(tert-butyl)benzoyl)-9*H*-purin-9-yl) acetate (4c).

Yield: 121 mg, 66%; yellow solid, m. p. 146 – 150 °C; R_f = 0.29 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 8.27 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 5.12 (s, 2H), 4.30 (q, J = 7.0 Hz, 2H), 1.35 (s, 9H), 1.33 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.0, 166.6, 158.0, 153.3, 146.9, 132.8, 131.3, 130.8, 125.6, 62.7, 44.3, 35.3, 31.0, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{20}H_{23}N_4O_3^+$ m/z 367.1765, found 367.1759.

ethyl 2-(6-benzoyl-9*H*-purin-9-yl) acetate (4d).

Yield: 127 mg, 82%; yellow solid, m. p. 120 – 124 °C; R_f = 0.30 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 8.28 (s, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 5.12 (s, 2H), 4.30 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.5, 166.6, 153.4, 152.9, 152.1, 147.0, 135.4, 134.1, 131.4, 130.8, 128.5, 62.7, 44.3, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{15}N_4O_3^+$ m/z 311.1139, found 311.1135.

ethyl 2-(6-(4-fluorobenzoyl)-9*H*-purin-9-yl) acetate (4e).

Yield: 87mg, 54%; yellow solid, m. p. 72 – 76 °C; R_f = 0.35 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 8.30 (s, 1H), 8.16 – 8.13 (m, 2H), 7.18 (t, J = 8.5 Hz, 2H), 5.13 (s, 2H), 4.30 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.8, 166.6, 167.38 and 165.30 (d, $J_{C\text{-}F}$ = 255.0 Hz), 153.5, 152.4, 152.0, 147.2, 133.68 and 133.60 (d, $J_{C\text{-}F}$ = 10.0 Hz), 131.81 and 131.79 (d, $J_{C\text{-}F}$ = 2.5 Hz), 131.3, 115.90 and 115.73 (d, $J_{C\text{-}F}$ = 21.2 Hz), 62.7, 44.3, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -103.1. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{14}FN_4O_3^+$ m/z 329.1044, found 329.1037.

ethyl 2-(6-(4-chlorbenzoyl)-9*H*-purin-9-yl) acetate (4f).

Yield: 96 mg, 56%; yellow solid, m. p. 120 – 124 °C; R_f = 0.28 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 8.30 (s, 1H), 8.05 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 5.13 (s, 2H), 4.30 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 190.2, 166.6, 153.6, 152.1, 152.0, 147.3, 140.7, 133.8, 132.2, 131.4, 128.9, 62.7, 44.3, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{14}ClN_4O_3^+$ m/z 345.0749, found 345.0743.

ethyl 2-(6-(4-bromobenzoyl)-9*H*-purin-9-yl) acetate (4g).

Yield: 105 mg, 54%; yellow solid, m. p. 118 – 122 °C; R_f = 0.36 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.10 (s, 1H), 8.32 (s, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 5.14 (s, 2H), 4.29 (q, J = 7.0 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 190.4, 166.6, 153.6, 152.0, 151.9, 147.4, 134.2, 132.2, 131.9, 131.4, 129.6, 62.7, 44.3, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{14}BrN_4O_3^+$ m/z 389.0244, found 389.0239.

ethyl 2-(6-(3-methylbenzoyl)-9*H*-purin-9-yl) acetate (4h).

Yield: 130 mg, 80%; yellow solid, m. p. 96 – 100 °C; R_f = 0.32 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.01 (s, 1H), 8.21 (s, 1H), 7.77 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 5.00 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H), 2.32 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.8, 166.7, 153.4, 153.1, 152.1, 147.1, 138.4, 135.4, 135.0, 131.3, 131.0, 128.4, 128.1, 62.6, 44.3, 21.3, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{17}H_{17}N_4O_3^+$ m/z 325.1295, found 325.1291.

ethyl 2-(6-(3-methoxybenzoyl)-9*H*-purin-9-yl) acetate (4i).

Yield: 138 mg, 81%; yellow solid, m. p. 112 – 116 °C; R_f = 0.24 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.10 (s, 1H), 8.28 (s, 1H), 7.65 (s, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.18 (dd, J_1 = 2.0 Hz, J_2 =8.5 Hz, 1H), 5.12 (s, 2H), 4.30 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 1.32 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.3, 166.6, 159.8, 153.4, 153.0, 152.1, 147.0, 136.6, 131.3, 129.5, 124.1, 121.0, 114.2, 62.6, 55.5, 44.3, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{17}H_{17}N_4O_4^+$ m/z 341.1244, found 341.1238.

ethyl 2-(6-(3-fluorobenzoyl)-9*H*-purin-9-yl) acetate (4j).

Yield: 85 mg, 52%; yellow solid, m. p. 56 – 60 °C; R_f = 0.32 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.12 (s, 1H), 8.32 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.84 – 7.81 (m, 1H), 7.51 – 7.46 (m, 1H),

7.36 – 7.33 (m, 1H), 5.13 (s, 2H), 4.31 (q, *J* = 7.0 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 190.16 and 190.14 (d, J_{C-F} = 2.5 Hz), 166.6, 163.55 and 161.58 (d, J_{C-F} = 246.2 Hz), 153.6, 152.0, 151.8, 147.5, 137.35 and 137.30 (d, J_{C-F} = 6.2 Hz), 131.4, 130.23 and 130.17 (d, J_{C-F} = 7.5 Hz), 126.80 and 126.78 (d, J_{C-F} = 2.5 Hz), 121.16 and 120.99 (d, J_{C-F} = 21.2 Hz), 117.35 and 117.17 (d, J_{C-F} = 22.5 Hz), 62.6, 44.3, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) *δ*: -111.7. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{14}FN_4O_3^+$ *m/z* 329.1044, found 329.1037.

ethyl 2-(6-(3-chlorbenzoyl)-9*H*-purin-9-yl) acetate (4k).

Yield: 83 mg, 48%; yellow solid, m. p. 100 – 104 °C; R_f = 0.30 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.12 (s, 1H), 8.31 (s, 1H), 8.08 (s, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.62 – 7.60 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 5.13 (s, 2H), 4.30 (q, *J* = 7.0 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 190.1, 166.6, 153.6, 152.1, 151.8, 147.4, 137.0, 134.8, 133.9, 131.4, 130.7, 129.8, 129.0, 62.7, 44.3, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{14}ClN_4O_3^+$ *m/z* 345.0749, found 345.0744.

ethyl 2-(6-(3-bromobenzoyl)-9*H*-purin-9-yl) acetate (4l).

Yield: 85 mg, 44%; yellow solid, m. p. 90 – 94 °C; R_f = 0.31 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.13 (s, 1H), 8.32 (s, 1H), 8.24 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.76 (m, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 5.13 (s, 2H), 4.31 (q, *J* = 7.5 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 190.0, 166.5, 153.6, 152.1, 151.8, 147.4, 137.2, 136.8, 133.6, 131.4, 130.1, 129.4, 122.8, 62.7, 44.4, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{14}BrN_4O_3^+$ *m/z* 389.0244, found 389.0238.

ethyl 2-(6-(2-chlorbenzoyl)-9*H*-purin-9-yl) acetate (4m).

Yield: 62 mg, 36%; yellow solid, m. p. 80 – 84 °C; R_f = 0.38 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.06 (s, 1H), 8.36 (s, 1H), 7.69 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.45 – 7.42 (m, 2H), 5.13 (s, 2H), 4.28 (q, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 193.3, 166.6, 154.1, 152.2, 150.5, 147.9, 137.3, 132.7, 130.9, 130.2, 127.0, 62.6, 44.4, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{14}ClN_4O_3^+$ *m/z* 345.0749, found 345.0741.

ethyl 2-(6-(2-methylbenzoyl)-9*H*-purin-9-yl) acetate (4n).

Yield: 107 mg, 66%; yellow solid, m. p. 78 – 82 °C; R_f = 0.33 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.08 (s, 1H), 8.30 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 5.12 (s, 2H), 4.30 (q, *J* = 7.0 Hz, 2H), 2.59 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 194.4, 166.6, 153.6, 153.1, 152.3, 147.2, 140.1, 135.4, 132.5, 132.1,

131.9, 131.2, 125.4, 62.7, 44.3, 21.4, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{17}H_{17}N_4O_3^+$ *m/z* 325.1295, found 325.1289.

ethyl 2-(6-(thiophene-2-carbonyl)-9*H*-purin-9-yl) acetate (4o).

Yield: 96 mg, 61%; yellow solid, m. p. 124 – 128 °C; R_f = 0.29 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.13 (s, 1H), 8.35 (s, 1H), 8.19 (dd, J_1 = 1.0 Hz, J_2 = 4.0 Hz, 1H), 7.81 (dd, J_1 = 1.0 Hz, J_2 = 4.0 Hz, 1H), 7.20 – 7.19 (m, 1H), 5.13 (s, 2H), 4.29 (d, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 182.7, 166.6, 153.9, 151.8, 151.0, 147.6, 141.0, 137.1, 136.6, 131.2, 128.1, 62.7, 44.3, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{14}H_{13}N_4O_3S^+$ *m/z* 317.0703, found 317.0700.

ethyl 2-(6-butyryl-9*H*-purin-9-yl) acetate (4p).

Yield: 64 mg, 46%; oil; R_f = 0.25 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.09 (s, 1H), 8.36 (s, 1H), 5.12 (s, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.34 (t, *J* = 7.5 Hz, 2H), 1.84 (sext, *J* = 7.5 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 201.0, 166.6, 154.3, 152.3, 149.4, 147.8, 130.4, 62.6, 44.3, 42.2, 17.2, 14.1, 13.8. ESI-HRMS $[M+H]^+$ calcd for $C_{13}H_{17}N_4O_3^+$ *m/z* 277.1295, found 277.1291.

ethyl 2-(6-isopropyl-9*H*-purin-9-yl) acetate (4q).

Yield: 82 mg, 66%; oil; R_f = 0.35 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.91 (s, 1H), 8.10 (s, 1H), 5.04 (s, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.81 (hept, *J* = 7.0 Hz, 1H), 1.47 (d, *J* = 7.0 Hz, 6H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 167.6, 167.0, 152.8, 150.9, 143.7, 131.1, 62.5, 44.1, 31.7, 21.2, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{12}H_{17}N_4O_2^+$ *m/z* 249.1346, found 249.1342.

ethyl 2-(6-(cyclohexanecarbonyl)-9*H*-purin-9-yl) acetate (4r).

Yield: 40 mg, 25%; yellow solid, m. p. 84 – 86 °C; R_f = 0.22 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.08 (s, 1H), 8.35 (s, 1H), 5.11 (s, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.90 – 3.84 (m, 1H), 1.99 – 1.96 (m, 2H), 1.86 – 1.82 (m, 2H), 1.75 – 1.72 (m, 2H), 1.57 – 1.40 (m, 4H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 203.8, 166.6, 154.1, 152.3, 149.7, 147.6, 130.7, 62.6, 46.6, 44.3, 28.4, 25.9, 25.6, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{16}H_{21}N_4O_3^+$ *m/z* 317.1608, found 317.1601.

ethyl 2-(6-cyclohexyl-9*H*-purin-9-yl) acetate (4r').

Yield: 75 mg, 52%; yellow solid, m. p. 88 – 92 °C; R_f = 0.39 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.90 (s, 1H), 8.10 (s, 1H), 5.04 (s, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.50 – 3.45 (m, 1H), 2.00 – 1.98 (m, 2H), 1.92 – 1.88 (m, 2H), 1.86 – 1.85 (m, 1H), 1.83 – 1.78 (m, 1H), 1.55 – 1.46 (m, 2H), 1.43

– 1.37 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 167.0, 166.7, 152.7, 150.9, 143.7, 131.2, 62.5, 44.1, 41.8, 31.3, 26.3, 25.9, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{15}H_{21}N_4O_2^+$ *m/z* 289.1659, found 289.1655.

ethyl 2-(6-(tert-butyl)-9*H*-purin-9-yl) acetate (4s).

Yield: 84 mg, 60%; oil; R_f = 0.28 (EA/PE = 1:3, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.80 (s, 1H), 8.02 (s, 1H), 4.96 (s, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 1.54 (s, 9H), 1.22 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 168.4, 166.1, 150.8, 150.4, 141.7, 130.1, 61.4, 43.0, 37.5, 28.2, 13.0. ESI-HRMS $[M+H]^+$ calcd for $C_{13}H_{19}N_4O_2^+$ *m/z* 263.1503, found 263.1501.

ethyl 2-(6,8-di-tert-butyl-9*H*-purin-9-yl) acetate (4s').

Yield: 37 mg, 23%; white solid, m. p. 90 – 94 °C; R_f = 0.39 (EA/PE = 1:3, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.80 (s, 1H), 5.15 (s, 2H), 4.25 (q, *J* = 7.0 Hz, 2H), 1.60 (s, 9H), 1.49 (s, 9H), 1.28 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 167.6, 159.8, 154.0, 151.0, 130.0, 62.1, 45.3, 38.3, 34.4, 29.2, 29.1, 14.1. ESI-HRMS $[M+H]^+$ calcd for $C_{17}H_{27}N_4O_2^+$ *m/z* 319.2129, found 319.2123.

(9-phenethyl-9*H*-purin-6-yl)(p-tolyl)methanol (3i-OH).

Yield: 98 mg, 95%; oil; R_f = 0.38 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.85 (s, 1H), 7.58 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.18 – 7.13 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 6.0 Hz, 2H), 6.26 (s, 1H), 5.21 (s, 1H), 4.42 (quint, *J* = 7.0 Hz, 1H), 4.34 (quint, *J* = 7.0 Hz, 1H), 3.06 (t, *J* = 7.0 Hz, 2H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 160.6, 151.8, 151.5, 144.7, 139.0, 137.6, 137.0, 130.3, 129.2, 128.9, 128.6, 127.2, 126.7, 72.5, 45.5, 36.0, 21.2. ESI-HRMS $[M+H]^+$ calcd for $C_{21}H_{21}N_4O^+$ *m/z* 345.1710, found 345.1706.

3-phenethyl-9-(p-tolyl)-3*H*-[1,2,3]triazolo[5,1-i]-purine (3i-N_3).

Yield: 91 mg, 86%; yellow solid, m. p. 180 – 182 °C; R_f = 0.19 (EA/PE = 1:3, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.36 (s, 1H), 8.57 (d, *J* = 8.0 Hz, 2H), 7.69 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.23 (m, 3H), 7.07 (d, *J* = 6.5 Hz, 2H), 4.60 (t, *J* = 7.0 Hz, 2H), 3.24 (t, *J* = 7.0 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 140.6, 138.2, 137.8, 137.7, 136.9, 134.9, 129.5, 129.0, 128.6, 127.6, 127.3, 126.8, 124.3, 46.3, 36.6, 21.4. ESI-HRMS $[M+H]^+$ calcd for $C_{21}H_{19}N_6^+$ *m/z* 355.1666, found 355.1661.

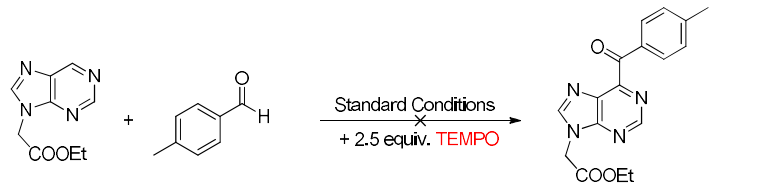
4-(9-benzyl-9*H*-purine-6-carbonyl)phenyl-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoate (3h-F).

Yield: 125 mg, 45%; oil; R_f = 0.37 (EA/PE = 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.12 (s, 1H), 8.19 (s, 1H), 8.12 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.42 (m, 5H), 7.38 – 7.32 (m, 5H), 7.24

– 7.22 (m, 1H), 7.18 (d, J = 8.5 Hz, 2H), 5.49 (s, 2H), 4.01 (q, J = 7.0 Hz, 1H), 1.66 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 190.2, 171.8, 160.8, 158.8, 155.2, 153.5, 152.4, 152.0, 146.8, 140.87 and 140.81 (d, $J_{C\text{-}F}$ = 7.5 Hz), 135.3, 134.7, 133.0, 132.6, 131.7, 131.15 and 131.12 (d, $J_{C\text{-}F}$ = 3.8 Hz), 129.3, 128.99 and 128.97 (d, $J_{C\text{-}F}$ = 2.5 Hz), 128.9, 128.5, 128.0, 127.8, 123.62 and 123.59 (d, $J_{C\text{-}F}$ = 3.8 Hz), 121.5, 115.45 and 115.26 (d, $J_{C\text{-}F}$ = 23.8 Hz), 47.6, 45.2, 18.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.1. ESI-HRMS $[M+H]^+$ calcd for $C_{34}H_{26}N_4O_3^+$ m/z 557.1983, found 557.1974.

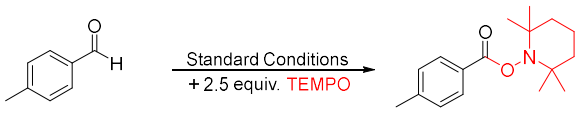
4. Mechanistic studies

4.1 Radical control experiment



1a **2a** 3a, trace, + 31% **2a-T** based on **2a**

1a (52 mg, 0.25 mmol), *p*-tolualdehyde (60 mg, 0.5 mmol), TBHP (56 mg, 0.625 mmol, 70% in water) and TFA (57 mg, 0.5 mmol) were placed in CH_3CN (1 mL) within a thick-walled pressure-resistant tube. TEMPO (98 mg, 0.625 mmol) was added and that was carried out at 110 °C under magnetic stirring for 12 h. Reaction progress was checked by TLC and no corresponding acylation product was found, which showed that the reaction was inhibited.



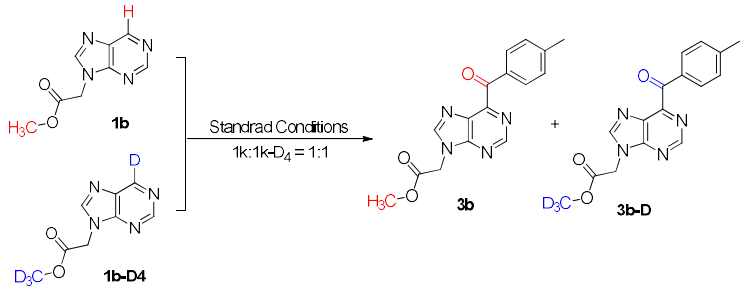
2a **2a-T, 44%**

As a contrast experiment **without 1a**, *p*-tolualdehyde (60 mg, 0.5 mmol), TBHP (56 mg, 0.625 mmol, 70% in water) and TFA (57 mg, 0.5 mmol) were placed in CH_3CN (1 mL) within a thick-walled pressure-resistant tube. TEMPO (98 mg, 0.625 mmol) was added and that was carried out at 110 °C under magnetic stirring for 12 h. Reaction progress was checked by TLC. After the reaction was completed, H_2O (5 mL) and 1 mL Na_2CO_3 solution (2M) were added to the reaction and ethyl acetate (3×30 mL) was used for extraction. After combining the organic phase, the solution was dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Finally, we can obtain the *p*-methylbenzoyl radical-trapped product **2a-T** in 44% yield by column chromatography with PE.

2,2,6,6-tetramethylpiperidin-1-yl-4-methylbenzoate (2a-T)

Yield: 60 mg, 44%; white solid, m. p. 54 – 58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 1.80 – 1.67 (m, 3H), 1.60 – 1.57 (m, 2H), 1.47 – 1.44 (m, 1H), 1.27 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.4, 143.5, 129.6, 129.2, 126.9, 60.4, 39.1, 32.0, 21.7, 20.8, 17.0.

4.2 Kinetic isotopic effect experiments



Purine substrate **1b** and **1b-D$_4$** (0.2+0.2 mmol, 1.0 equiv.), RCHO (0.8 mmol, 2.0 equiv.), TBHP (1.0 mmol, 2.5 equiv.) and TFA (0.8 mmol, 2.0 equiv.) were mixed in CH_3CN (1 mL) in a pressure-resistant tube. The solution was heated at 110 °C with stirring for 2 h. After, H_2O (5 mL) and 1 mL Na_2CO_3 solution (2M) were added to adjust the pH, then adding ethyl acetate (3×30 mL) for extraction. After mixing the organic phase, the solution was dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure, the residue crude product was purified by using column chromatography to obtain **3b**&**3b-D**. The ratio of **3b**/**3b-D** was determined to 1.36 according to ^{1}H NMR.

References

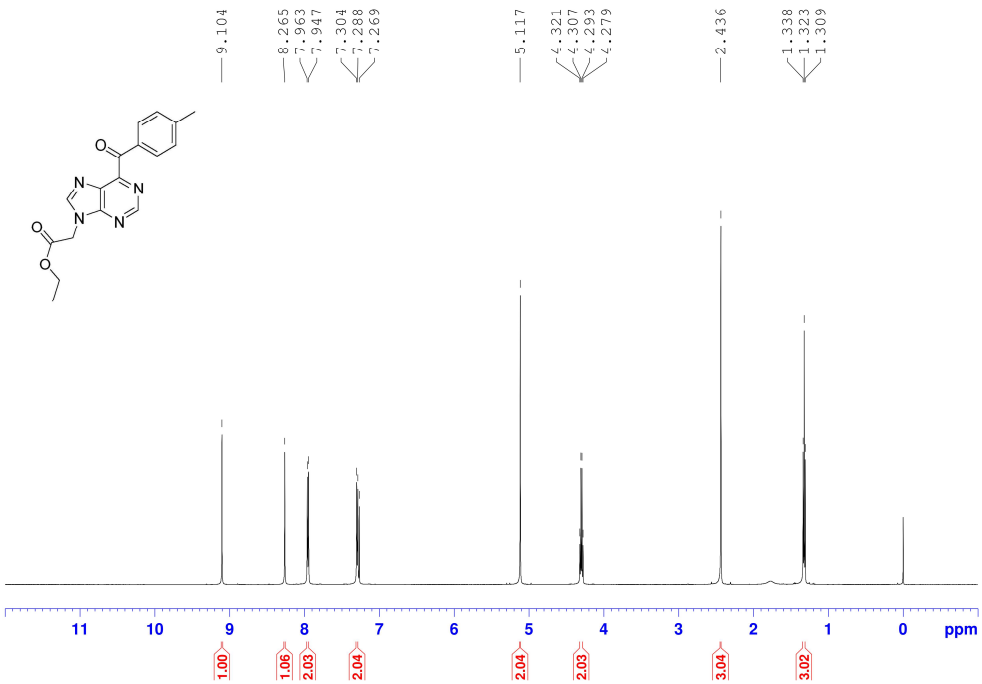
[1] D. K. Buffel, C. McGuigan, M. J. Robins. *J. Org. Chem*., 1985, **50**, 2664-2667.

[2] R. Xia, M.-S. Xie, H.-Y. Niu, G.-R. Qu, H.-M. Guo. *Green Chem*., 2014, **16**, 1077-1081.

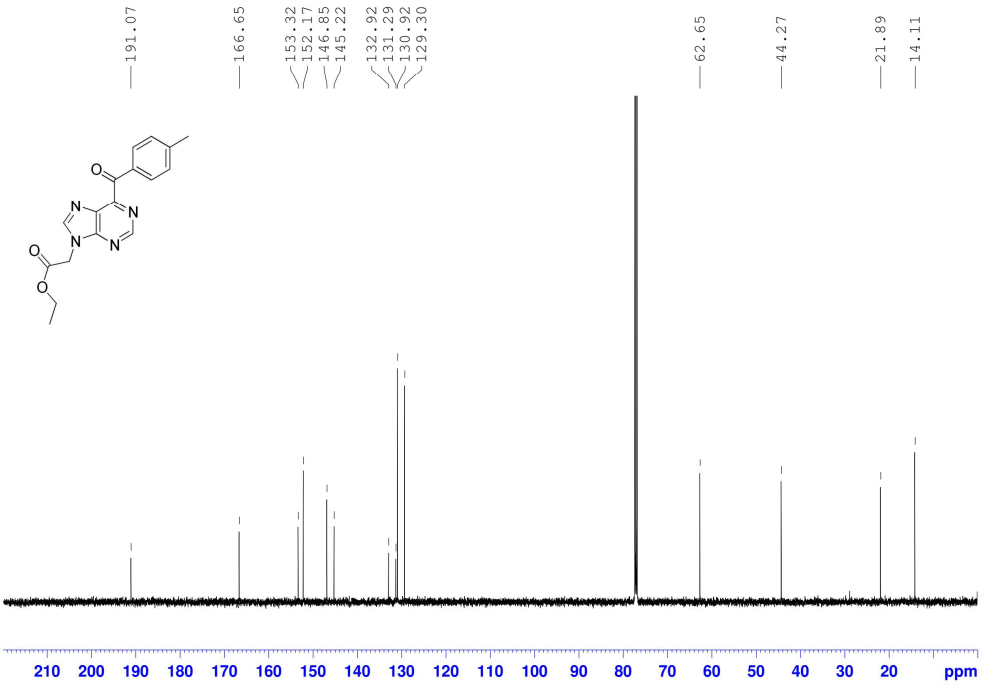
[3] L. Li, H. Zheng, F. Guo, Z. Fang, Q. Sun, J. Li, Q. Gao, T. Zhang and L. Fang, *Chem. Commun*., 2023, **59**, 3910-3913.

5. Copies of NMR Spectra of Products

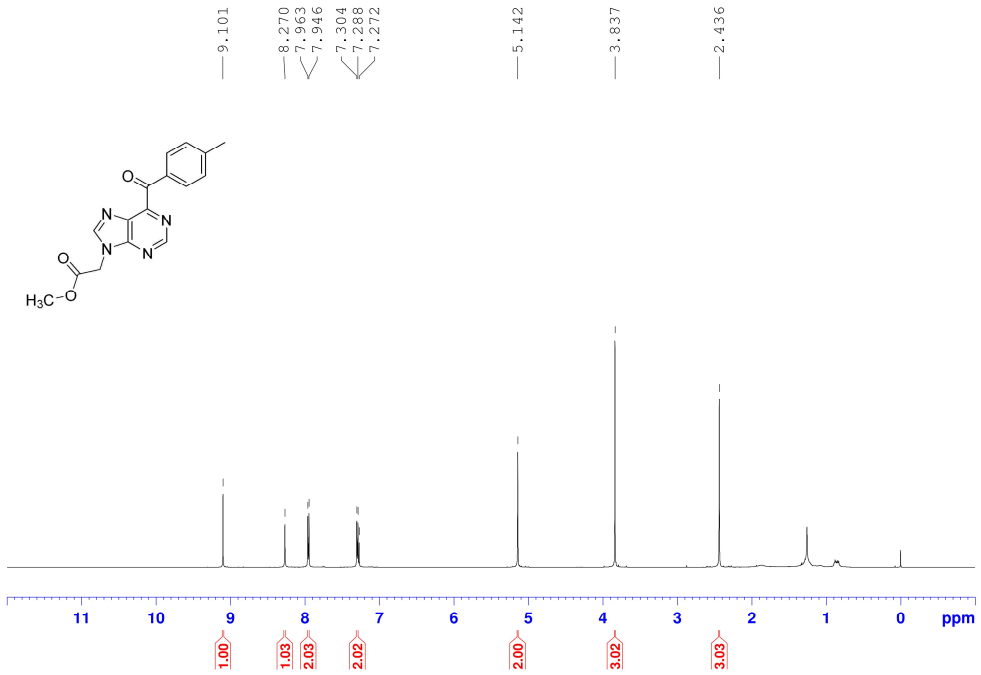
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) acetate (**3a**)



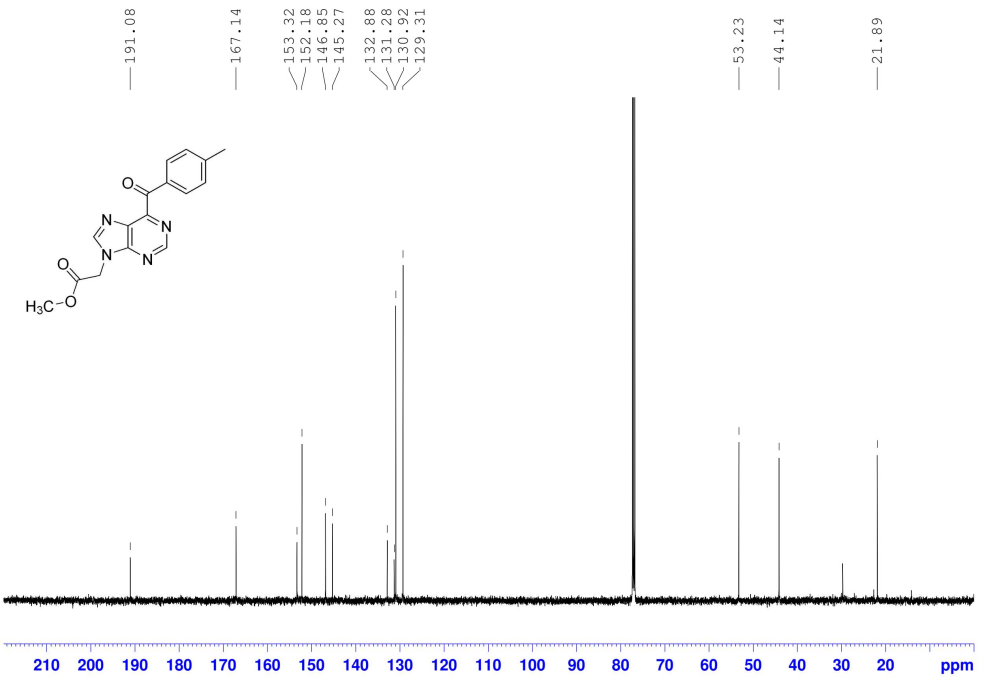
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) acetate (**3a**)



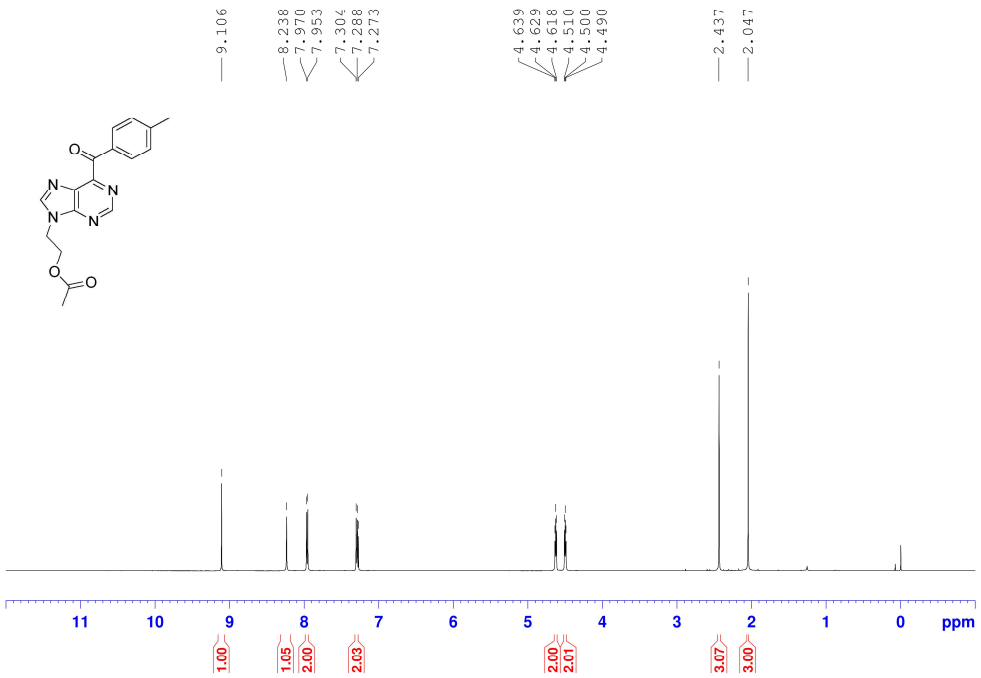
^{1}H NMR (500 MHz, in $CDCl_3$) of methyl 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) acetate (**3b**)



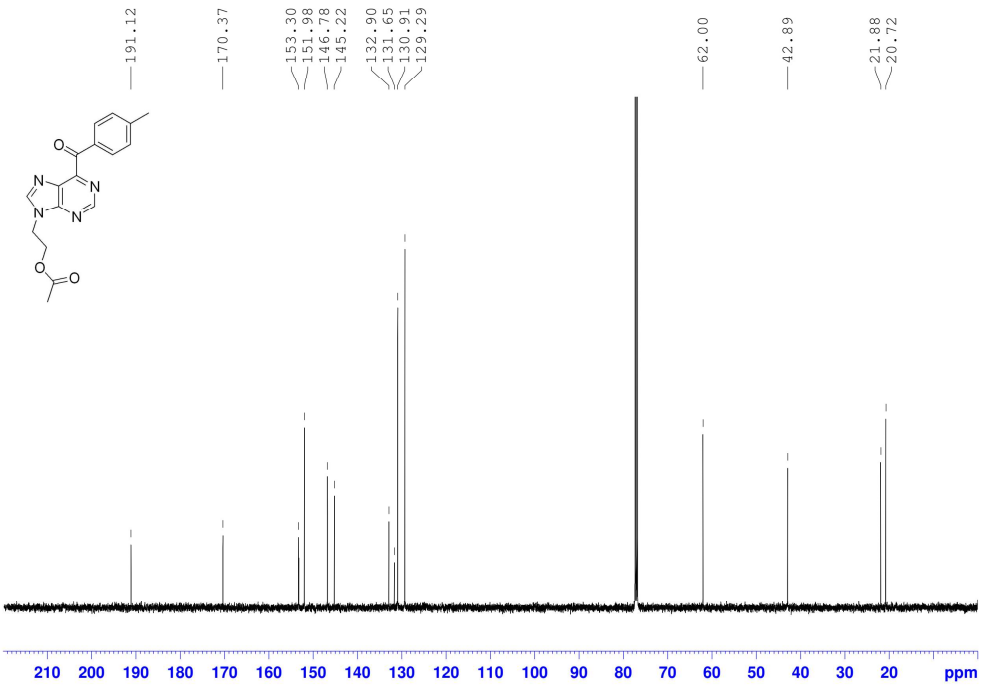
^{13}C NMR (125 MHz, in $CDCl_3$) of methyl 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) acetate (**3b**)



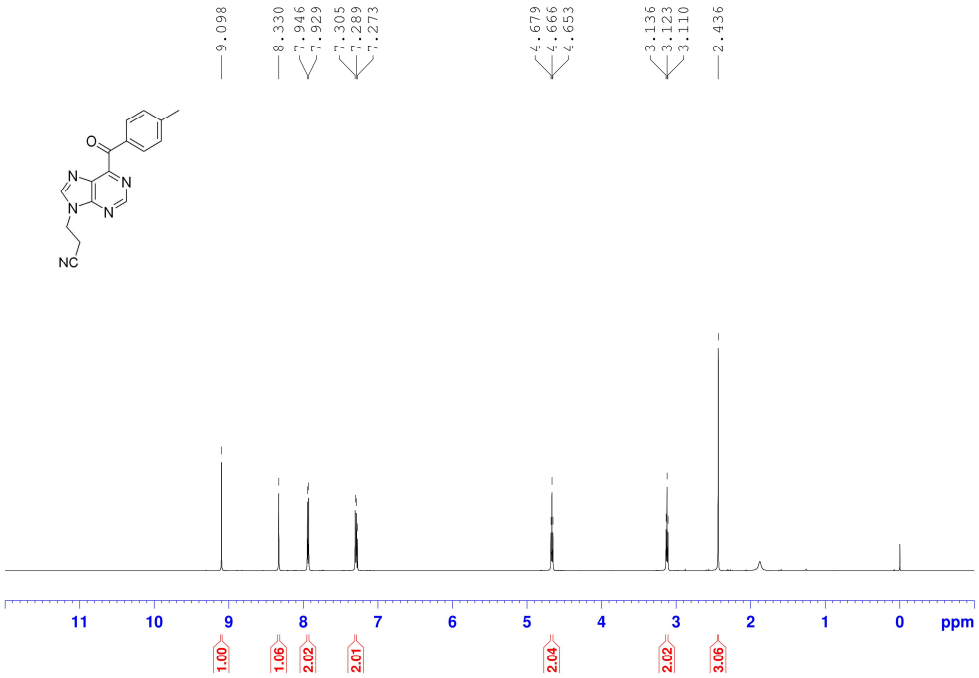
^{1}H NMR (500 MHz, in $CDCl_3$) of 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl)ethyl acetate (**3c**)



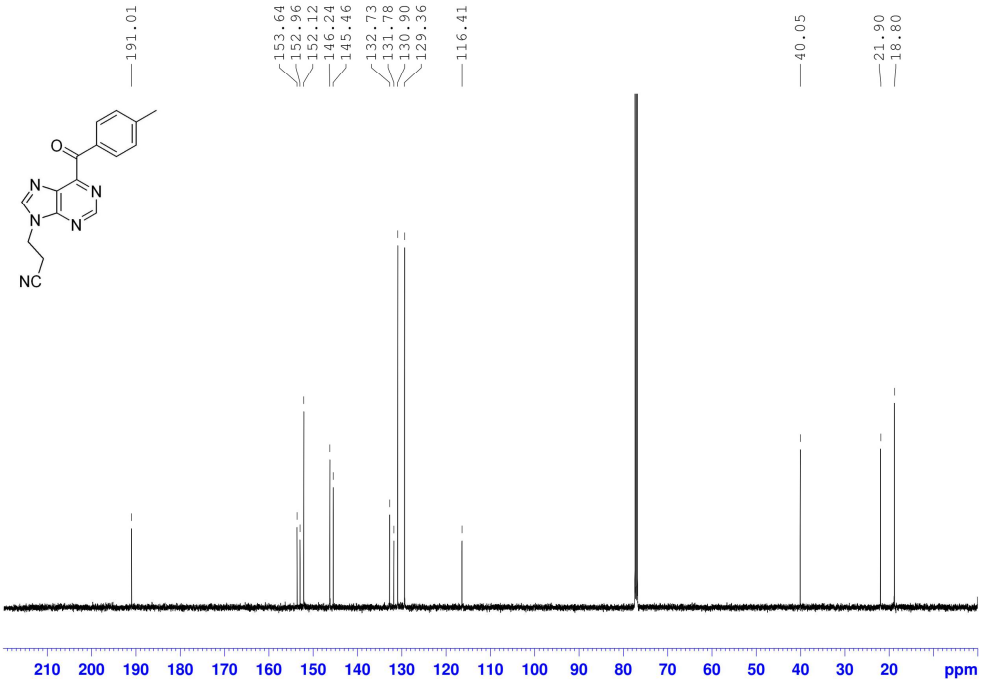
^{13}C NMR (125 MHz, in $CDCl_3$) of 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl)ethyl acetate (**3c**)



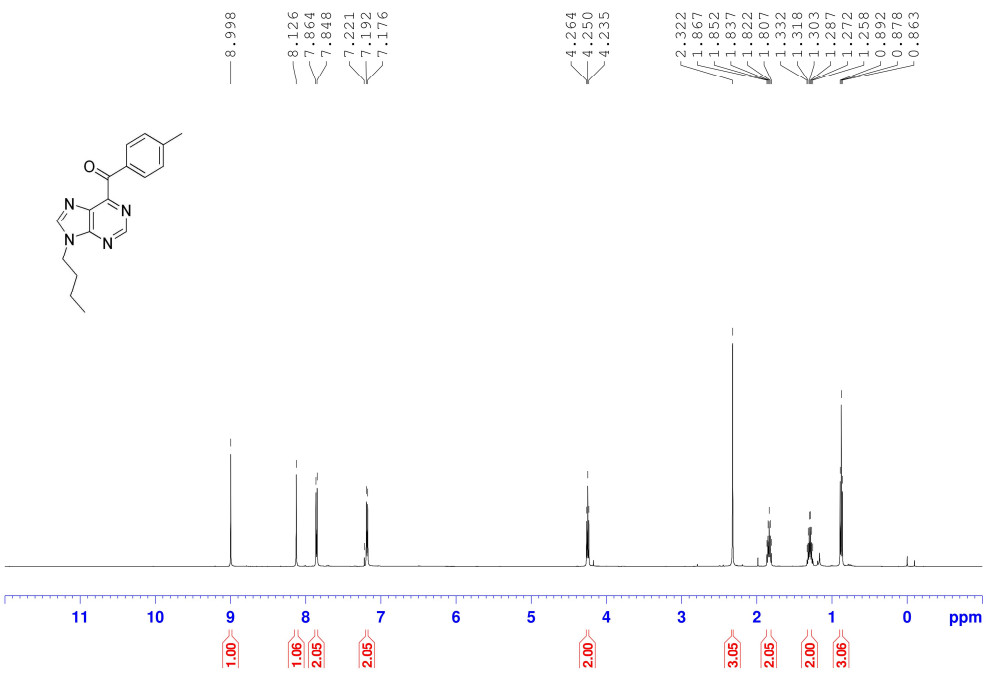
^{1}H NMR (500 MHz, in $CDCl_3$) of 3-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) propanenitrile (**3d**)



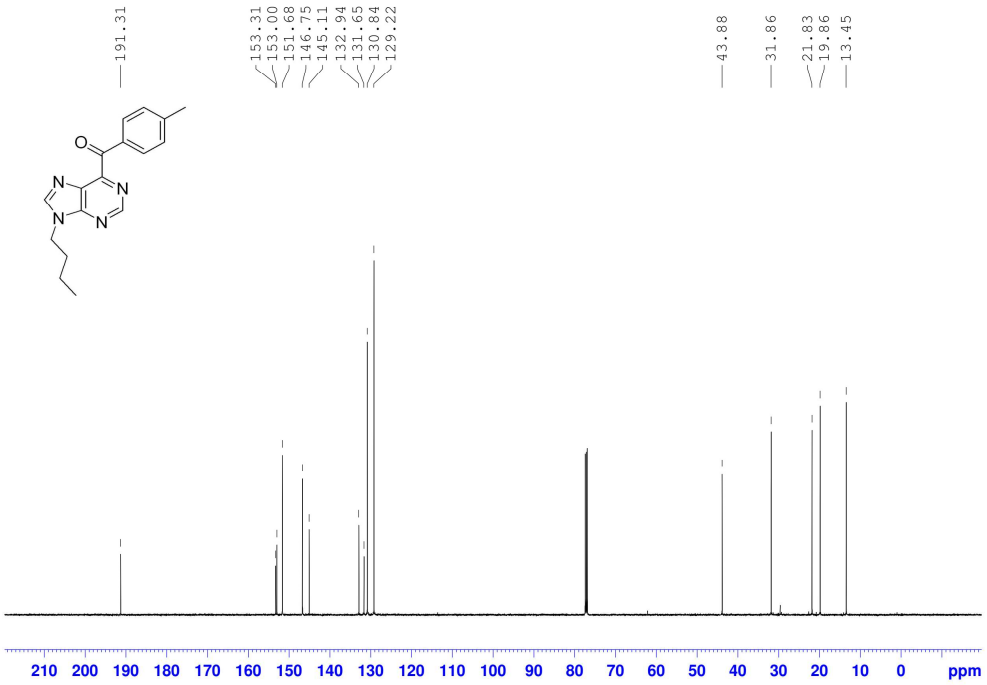
^{13}C NMR (125 MHz, in $CDCl_3$) of 3-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) propanenitrile (**3d**)



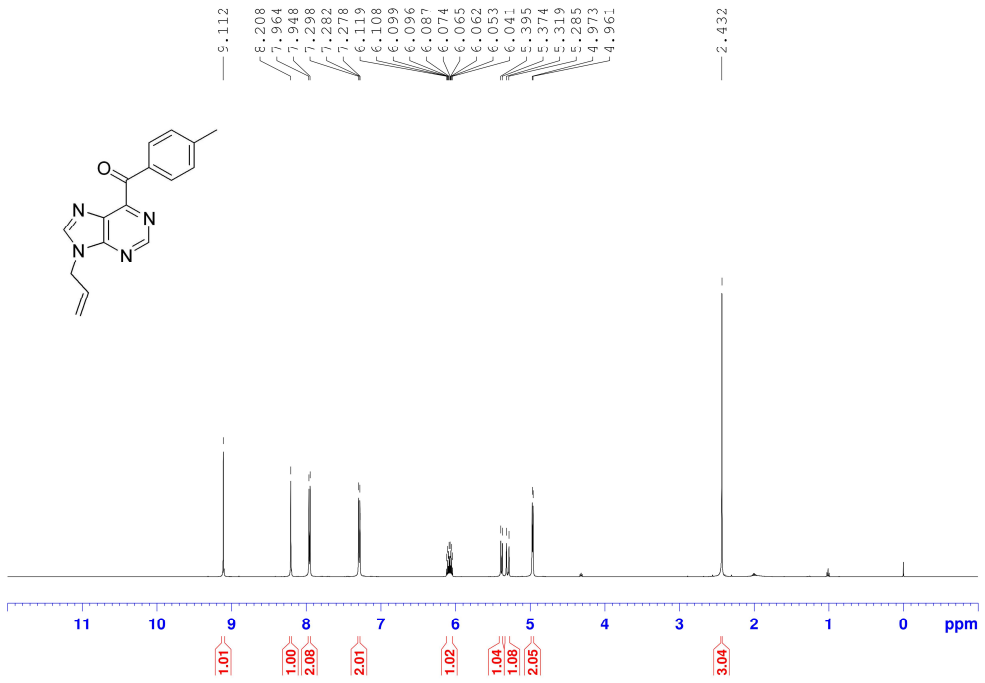
^{1}H NMR (500 MHz, in $CDCl_3$) of 9-butyl-6-(4-methylbenzoyl) purine (**3e**)



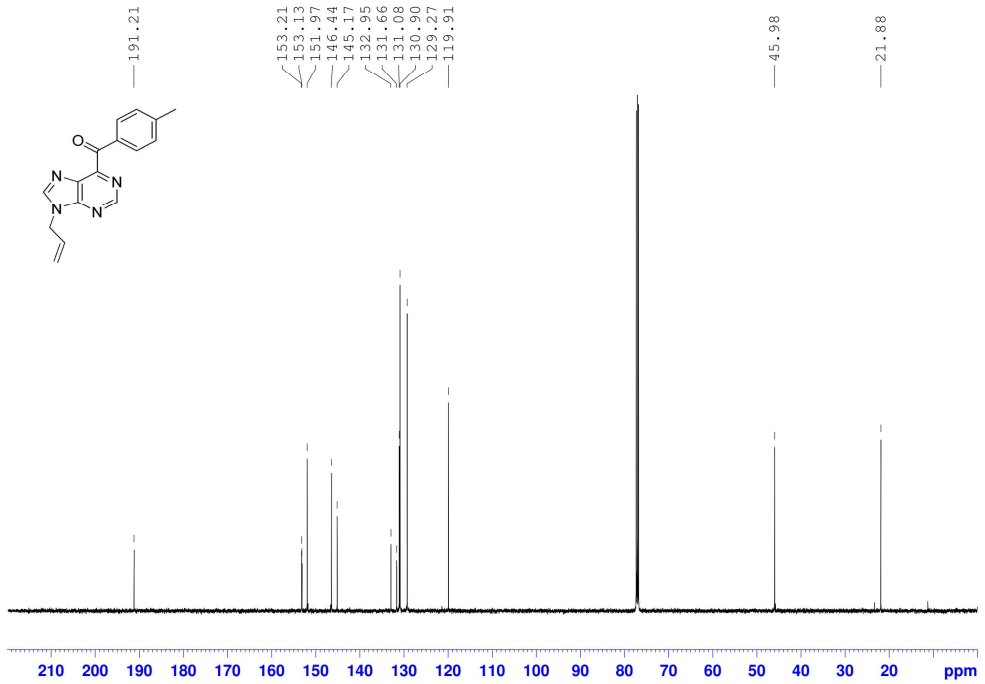
^{13}C NMR (125 MHz, in $CDCl_3$) of 9-butyl-6-(4-methylbenzoyl) purine (**3e**)



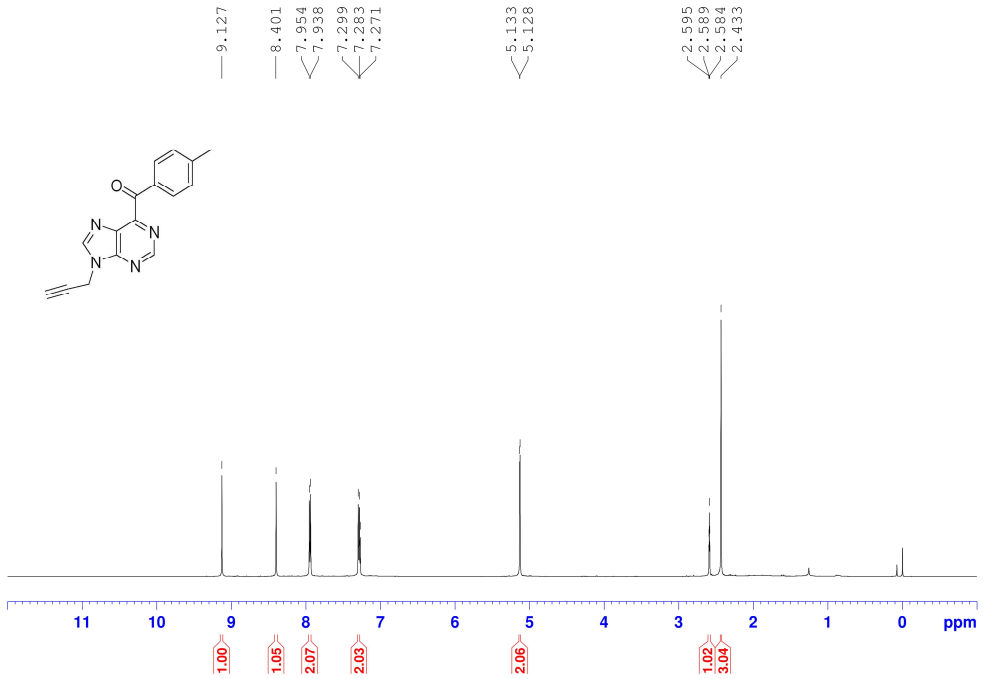
^{1}H NMR (500 MHz, in $CDCl_3$) of 9-allyl-6-(4-methylbenzoyl) purine (**3f**)



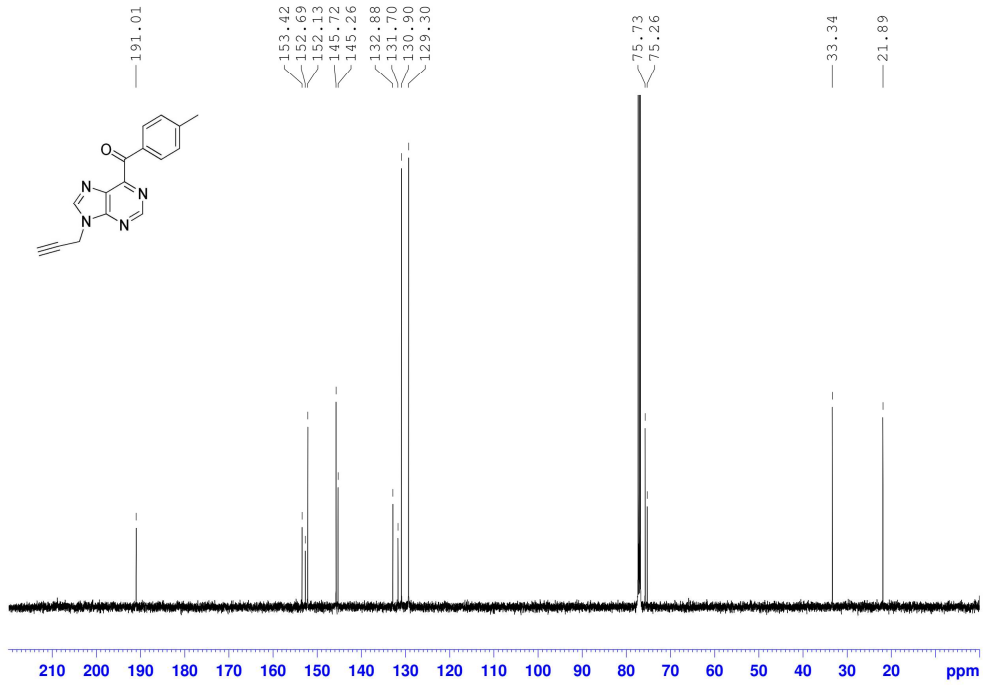
^{13}C NMR (125 MHz, in $CDCl_3$) of 9-allyl-6-(4-methylbenzoyl) purine (**3f**)



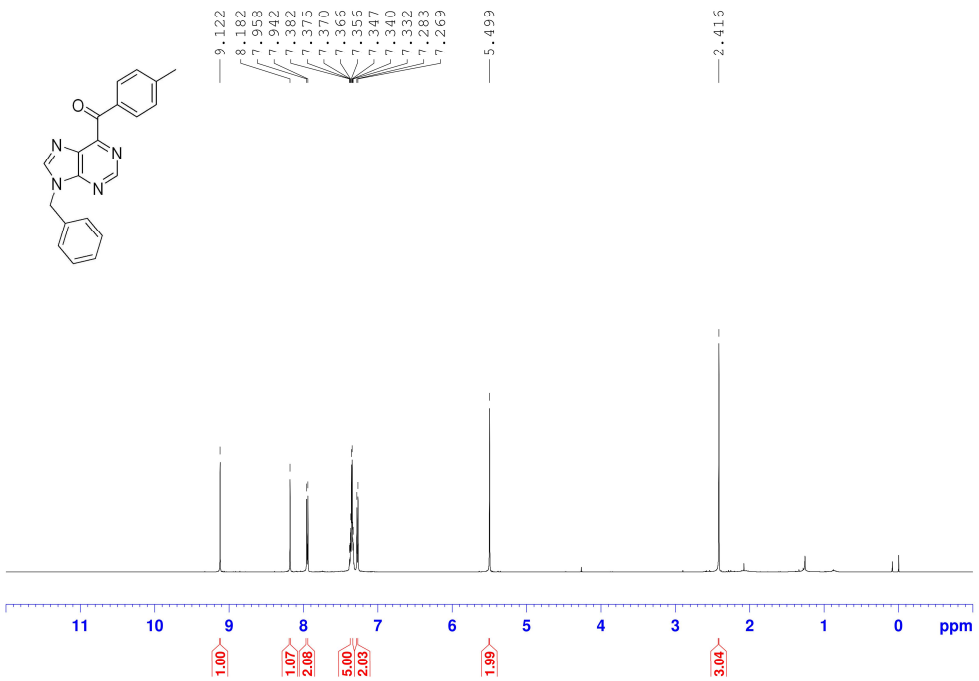
^{1}H NMR (500 MHz, in $CDCl_3$) of 9-(prop-2-yn-1-yl)-6-(4-methylbenzoyl) purine (**3g**)



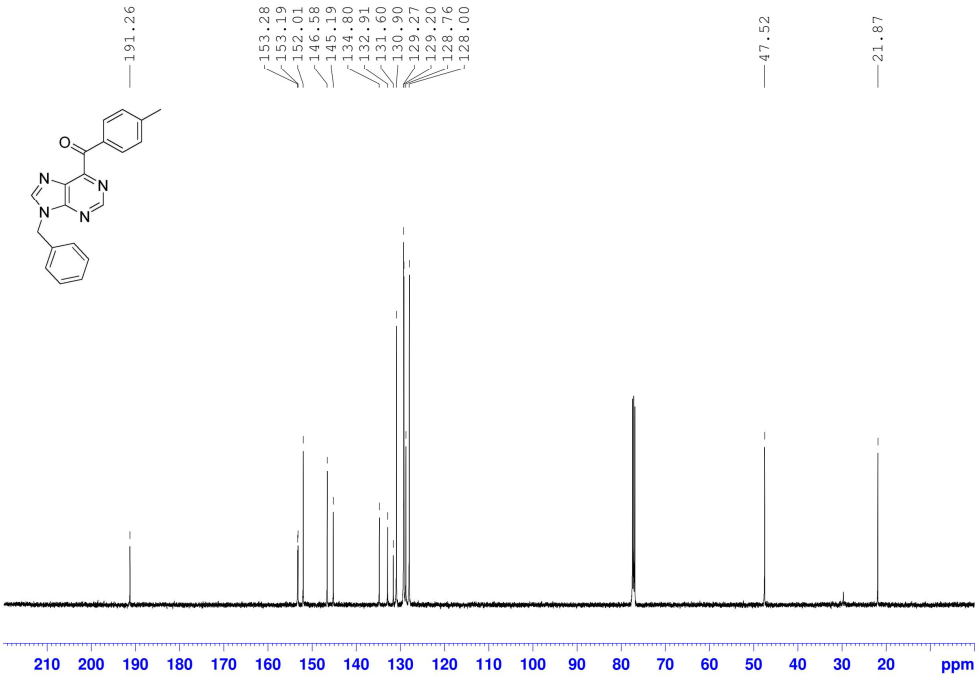
^{13}C NMR (125 MHz, in $CDCl_3$) of 9-(prop-2-yn-1-yl)-6-(4-methylbenzoyl) purine (**3g**)



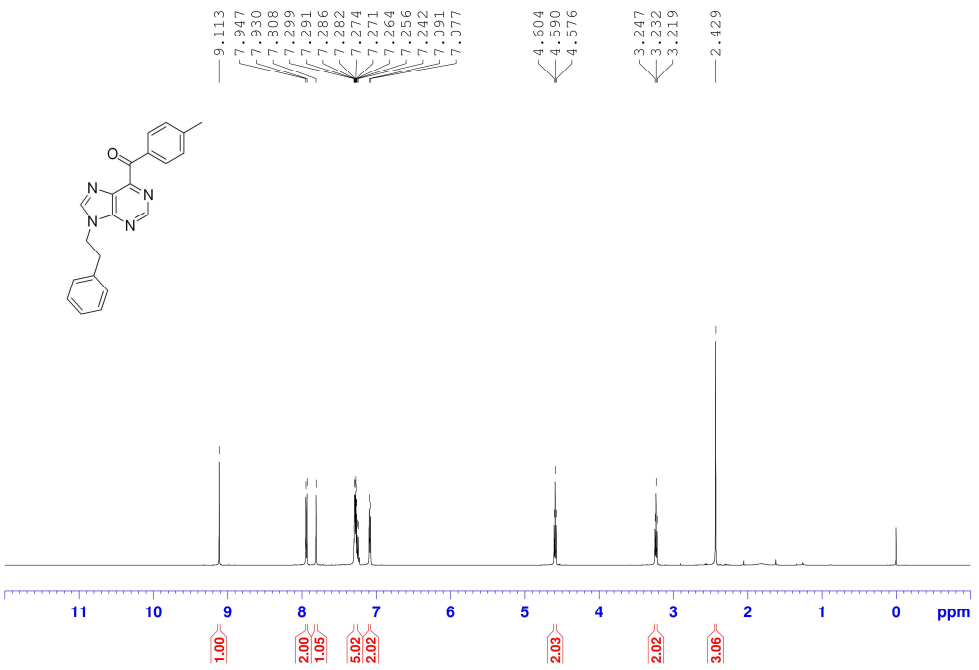
^{1}H NMR (500 MHz, in $CDCl_3$) of 9-benzyl-6-(4-methylbenzoyl) purine (**3h**)



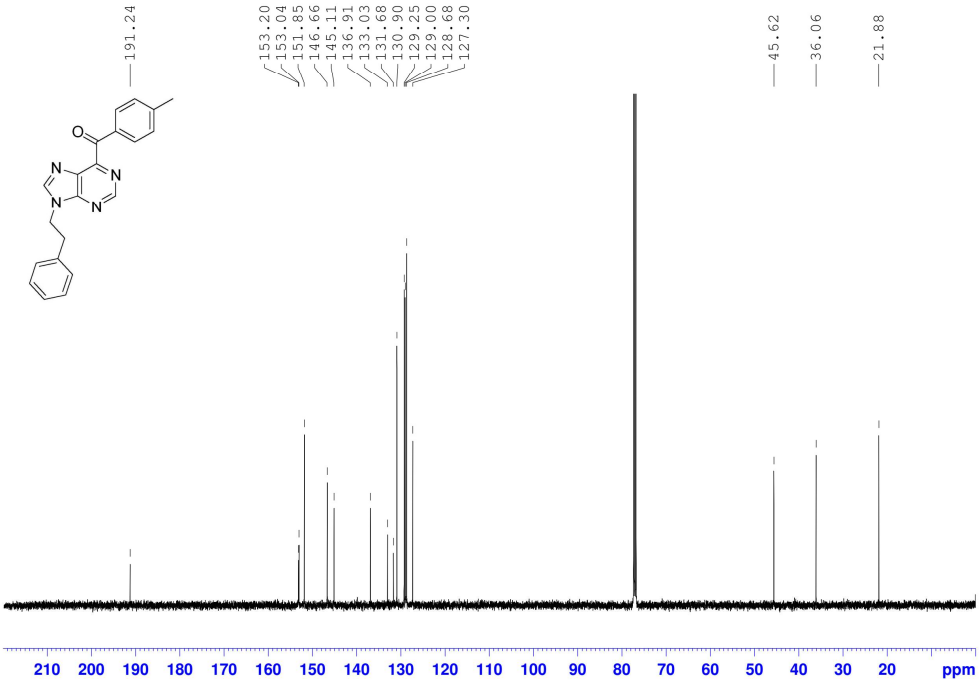
^{13}C NMR (125 MHz, in $CDCl_3$) of 9-benzyl-6-(4-methylbenzoyl) purine (**3h**)



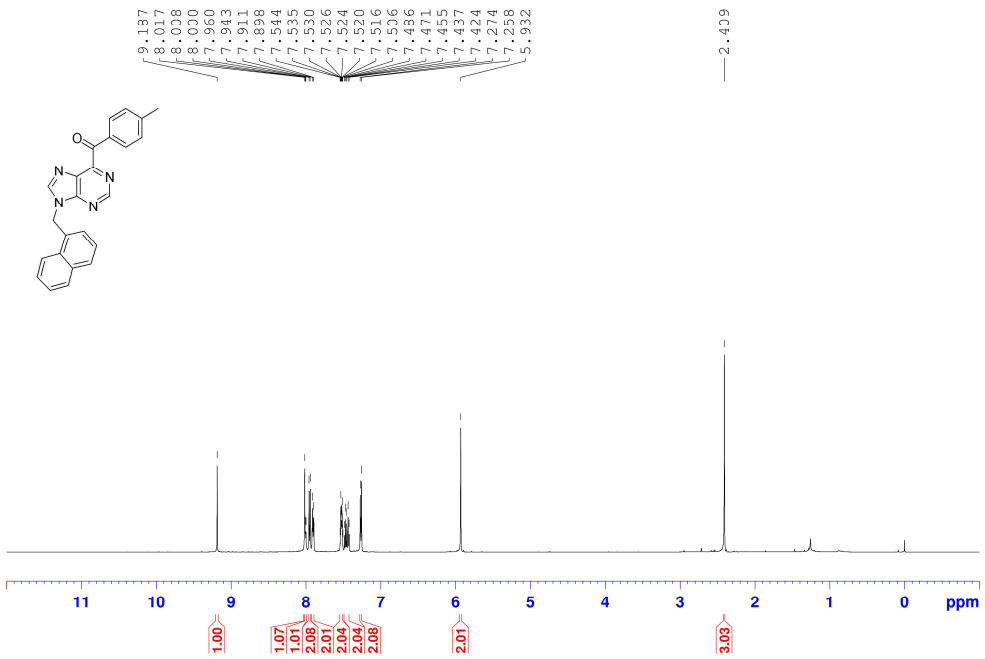
^{1}H NMR (500 MHz, in $CDCl_3$) of 9-phenethyl-6-(4-methylbenzoyl) purine (**3i**)



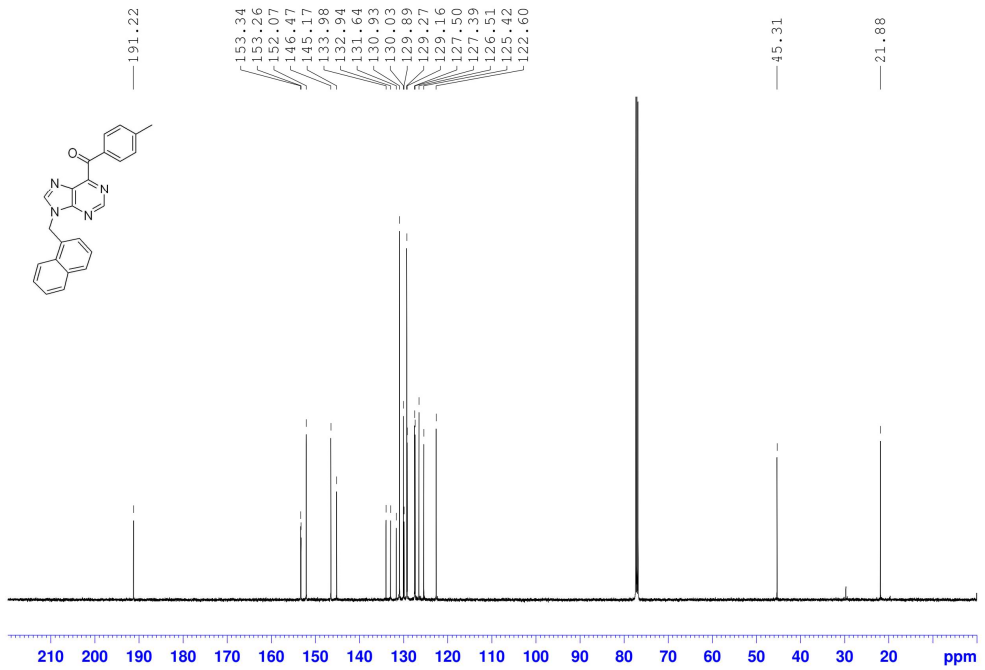
^{13}C NMR (125 MHz, in $CDCl_3$) of 9-phenethyl-6-(4-methylbenzoyl) purine (**3i**)



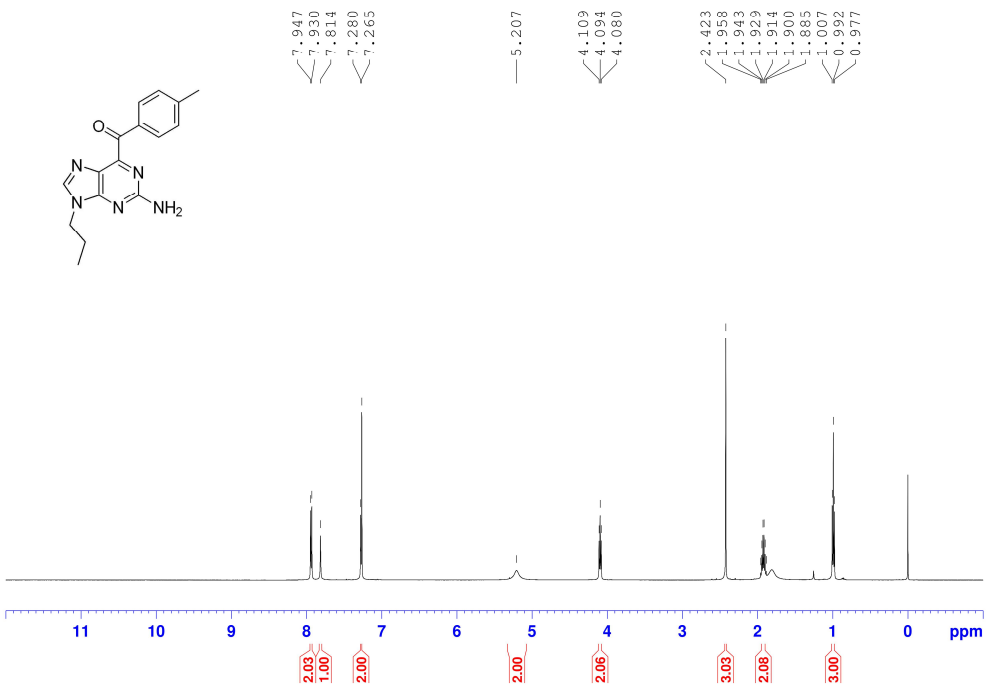
^{1}H NMR (500 MHz, in $CDCl_3$) of 9-(naphthalen-1-ylmethyl)-6-(4-methylbenzoyl) purine (**3j**)



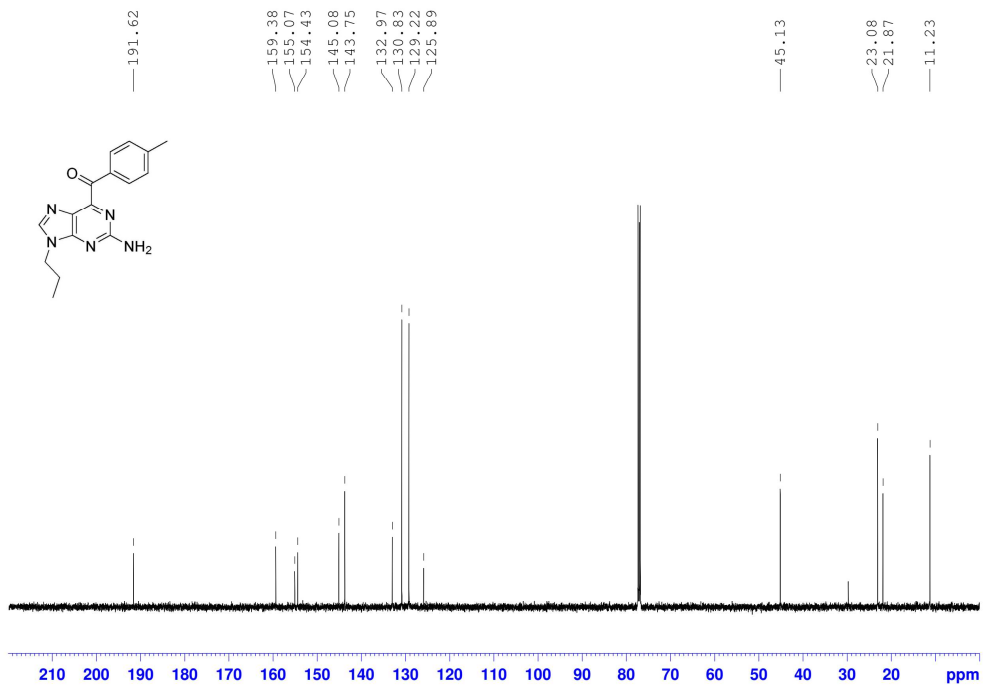
^{13}C NMR (125 MHz, in $CDCl_3$) of 9-(naphthalen-1-ylmethyl)-6-(4-methylbenzoyl) purine (**3j**)



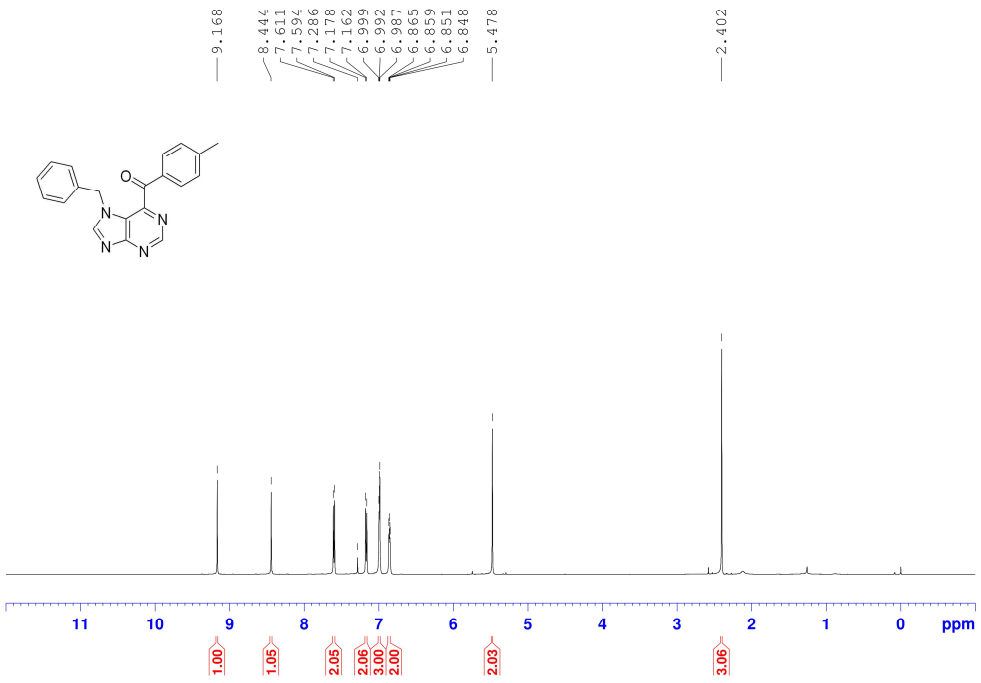
^{1}H NMR (500 MHz, in $CDCl_3$) of 2-amino-9-propyl-6-(4-methylbenzoyl) purine (**3k**)



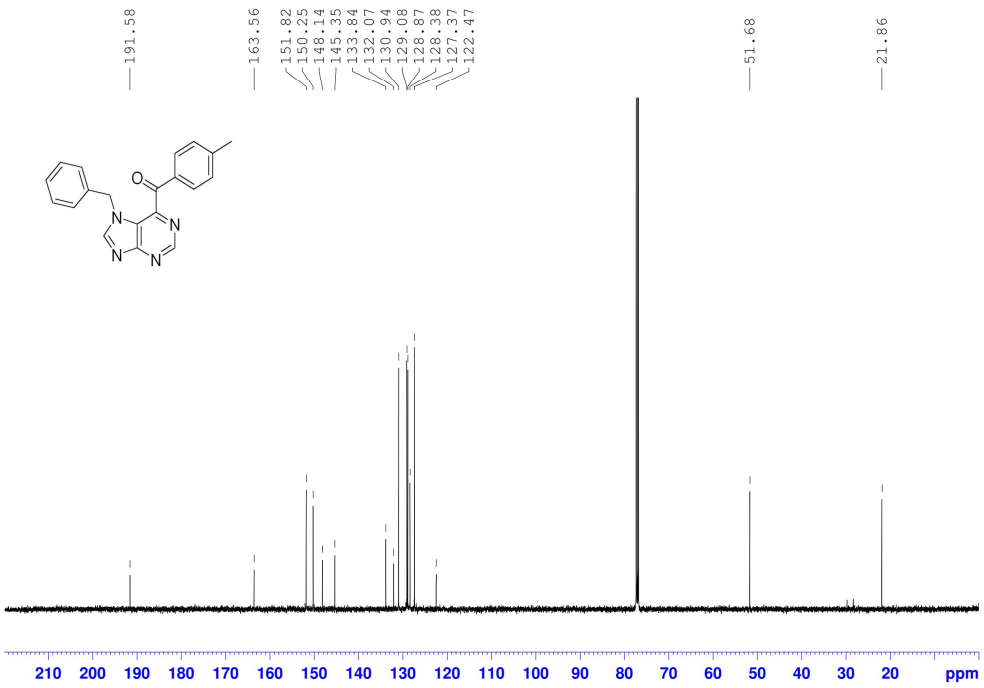
^{13}C NMR (125 MHz, in $CDCl_3$) of 2-amino-9-propyl-6-(4-methylbenzoyl) purine (**3k**)



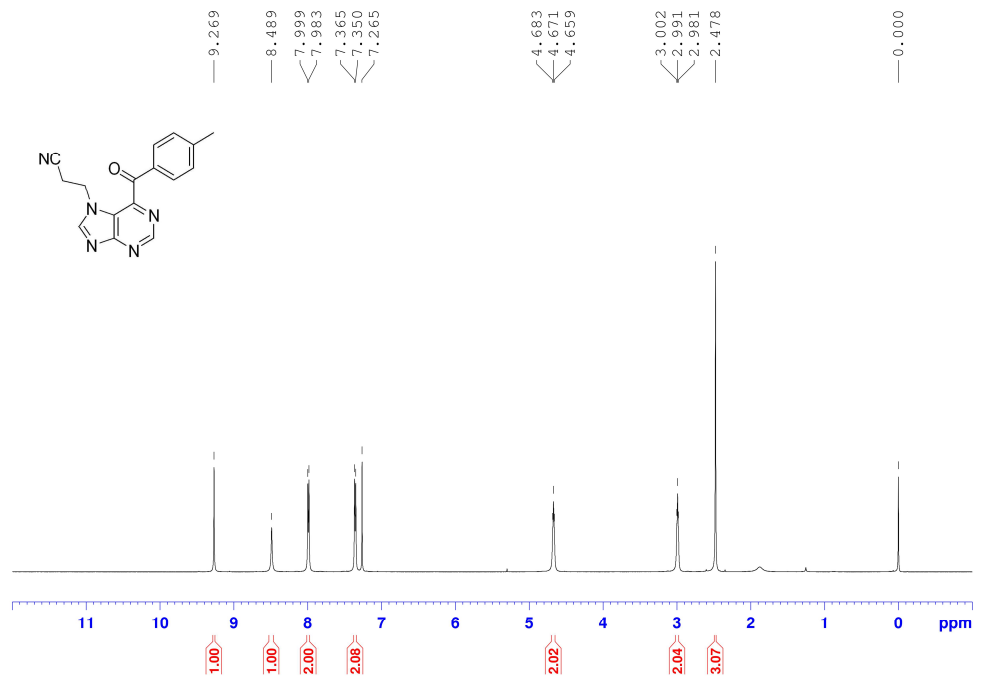
^{1}H NMR (500 MHz, in $CDCl_3$) of 7-benzyl-6-(4-methylbenzoyl) purine (**3l**)



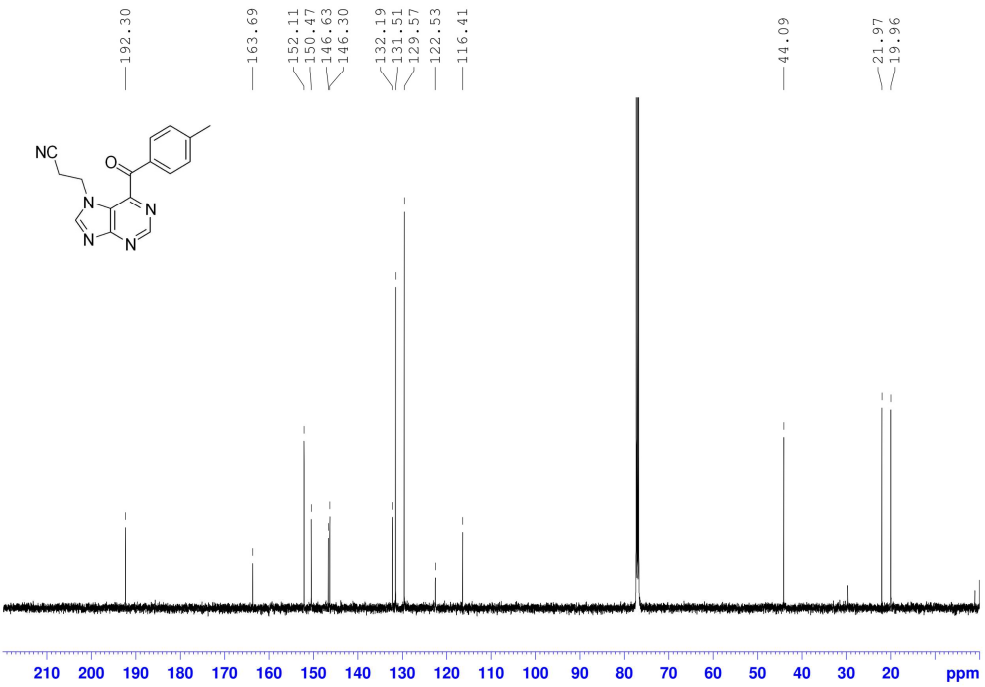
^{13}C NMR (125 MHz, in $CDCl_3$) of 7-benzyl-6-(4-methylbenzoyl) purine (**3l**)



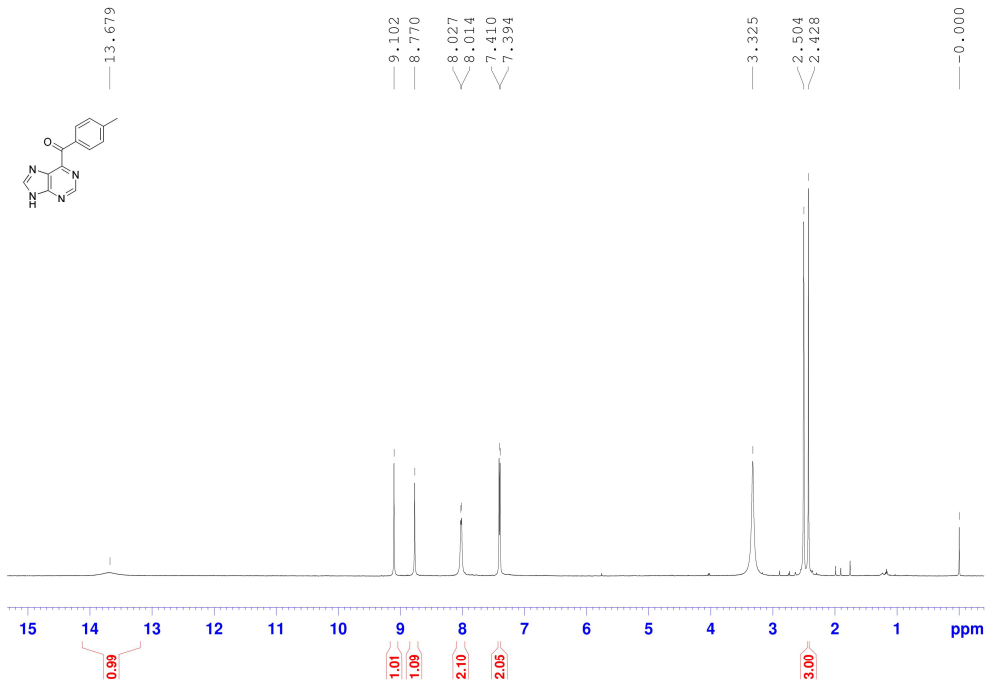
^{1}H NMR (500 MHz, in $CDCl_3$) of 3-(6-(4-methylbenzoyl)-7*H*-purin-7-yl) propanenitrile (**3m**)



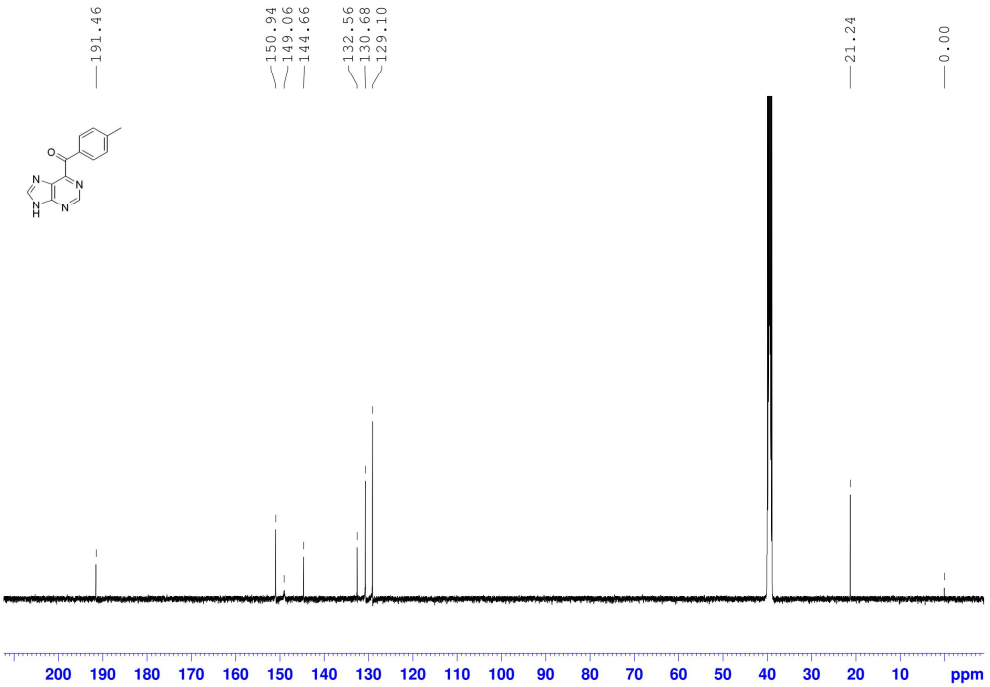
^{13}C NMR (125 MHz, in $CDCl_3$) of 3-(6-(4-methylbenzoyl)-7*H*-purin-7-yl) propanenitrile (**3m**)



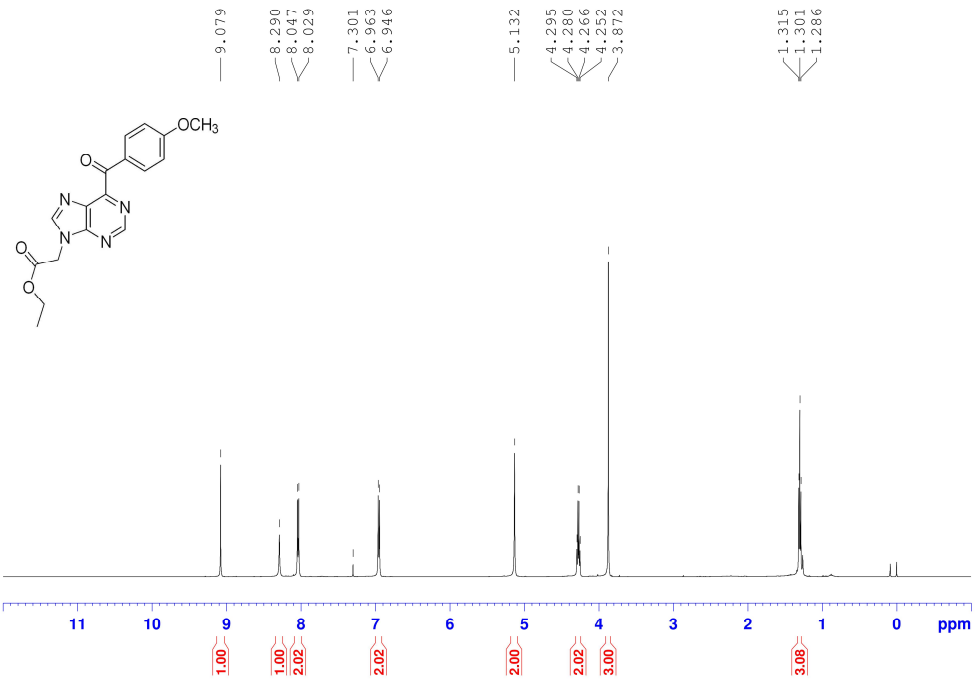
^{1}H NMR (500 MHz, in DMSO-d_6) of (9H-purin-6-yl)(p-tolyl)methanone (**3n-*H***)



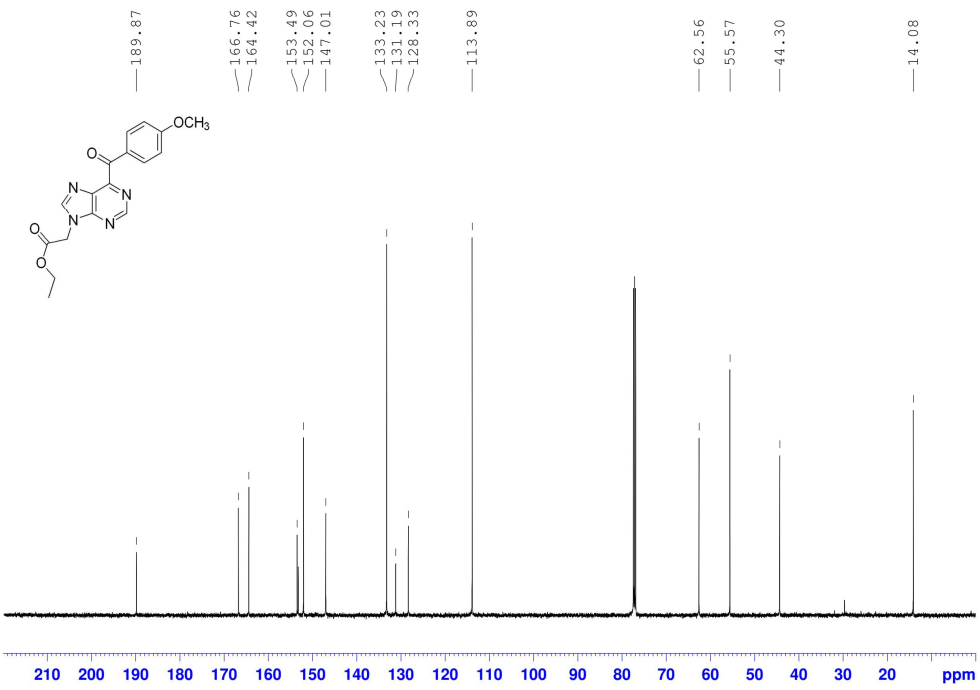
^{13}C NMR (125 MHz, in DMSO-d_6) of (9H-purin-6-yl)(p-tolyl)methanone (**3n-*H***)



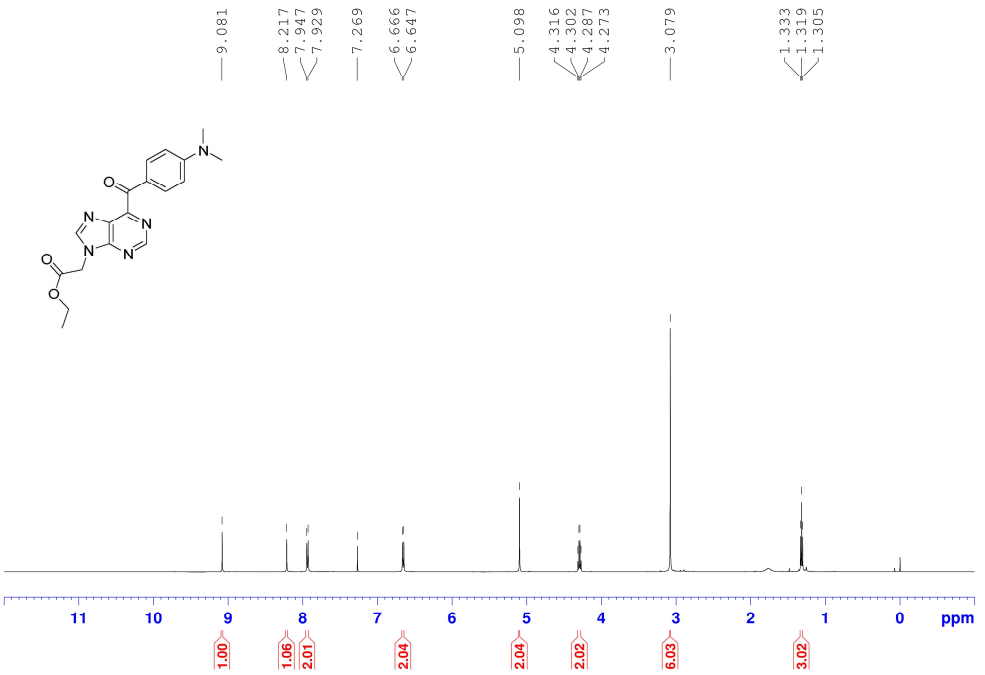
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(4-methoxybenzoyl)-9*H*-purin-9-yl) acetate (**4a**)



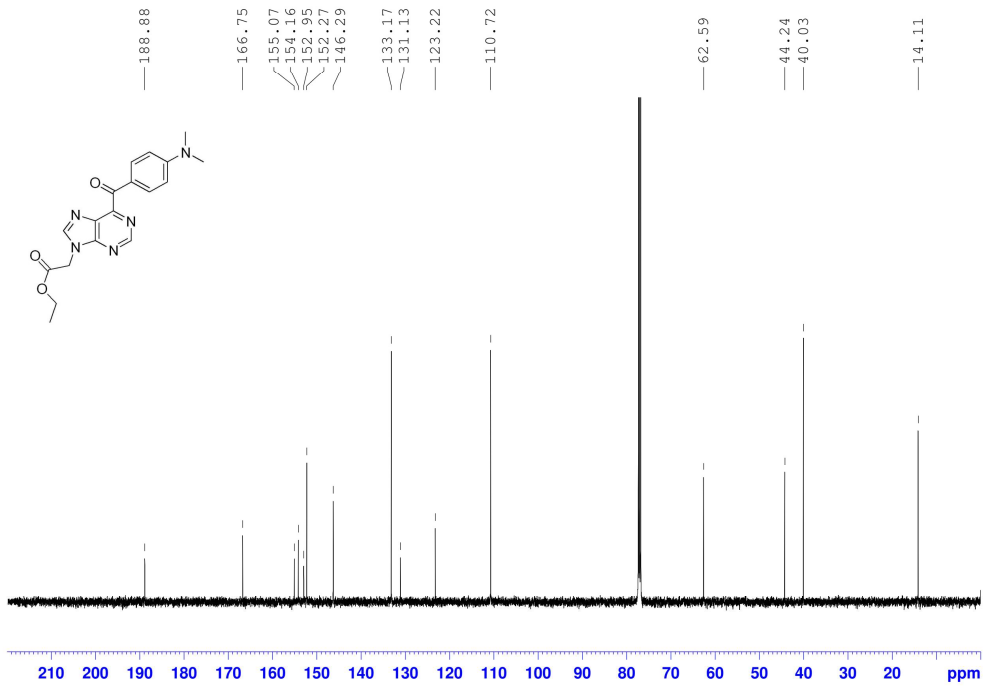
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(4-methoxybenzoyl)-9*H*-purin-9-yl) acetate (**4a**)



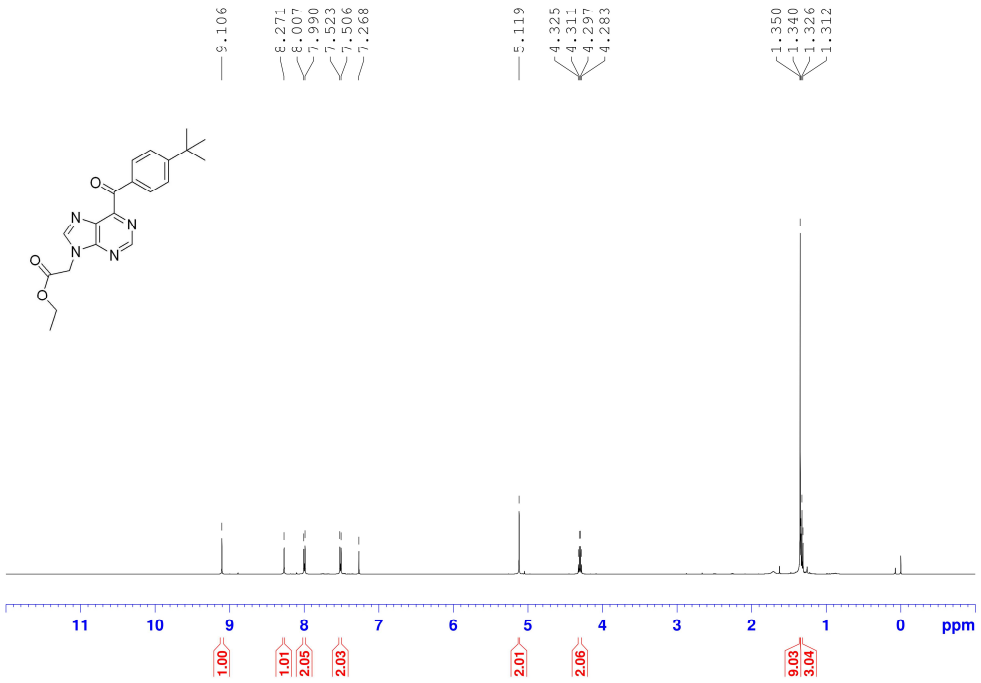
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(4-(dimethylamino)benzoyl)-9*H*-purin-9-yl) acetate (**4b**)



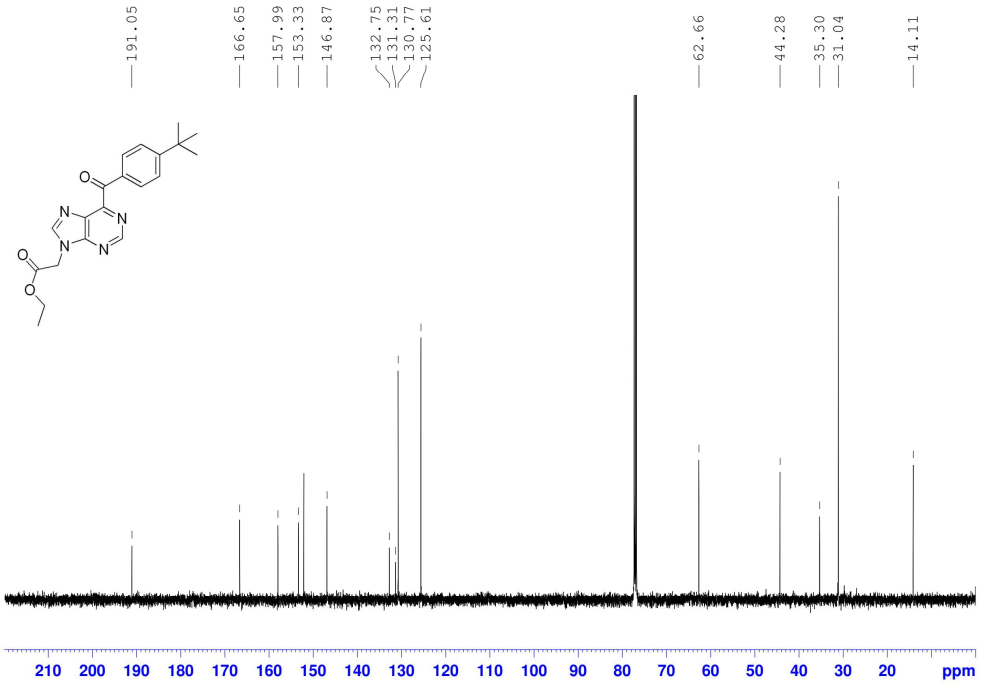
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(4-(dimethylamino)benzoyl)-9*H*-purin-9-yl) acetate (**4b**)



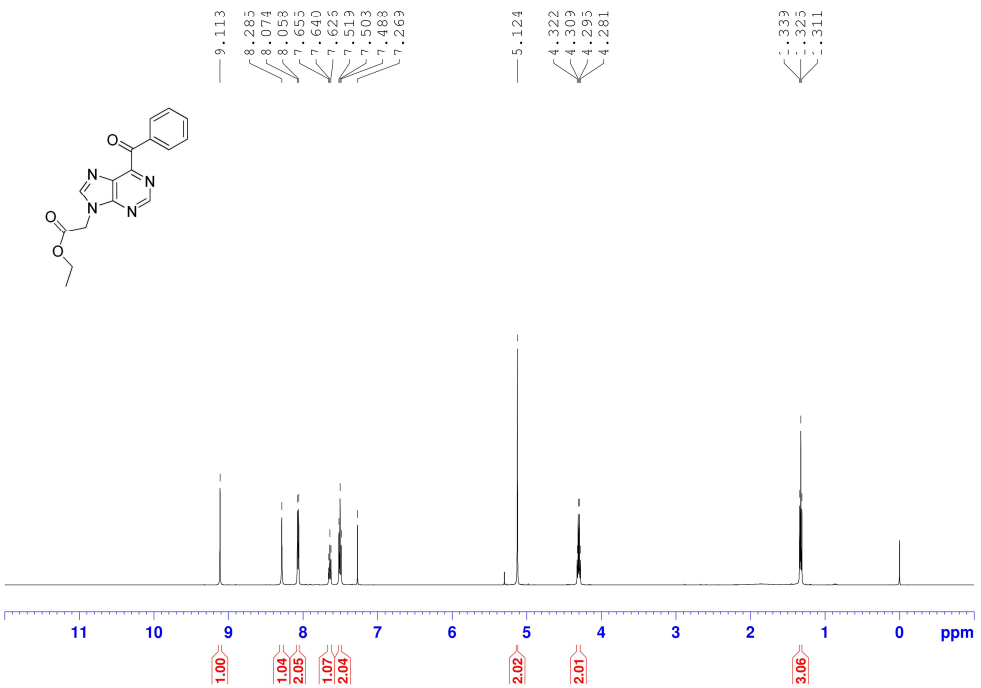
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(4-(tert-butyl)benzoyl)-9*H*-purin-9-yl) acetate (**4c**)



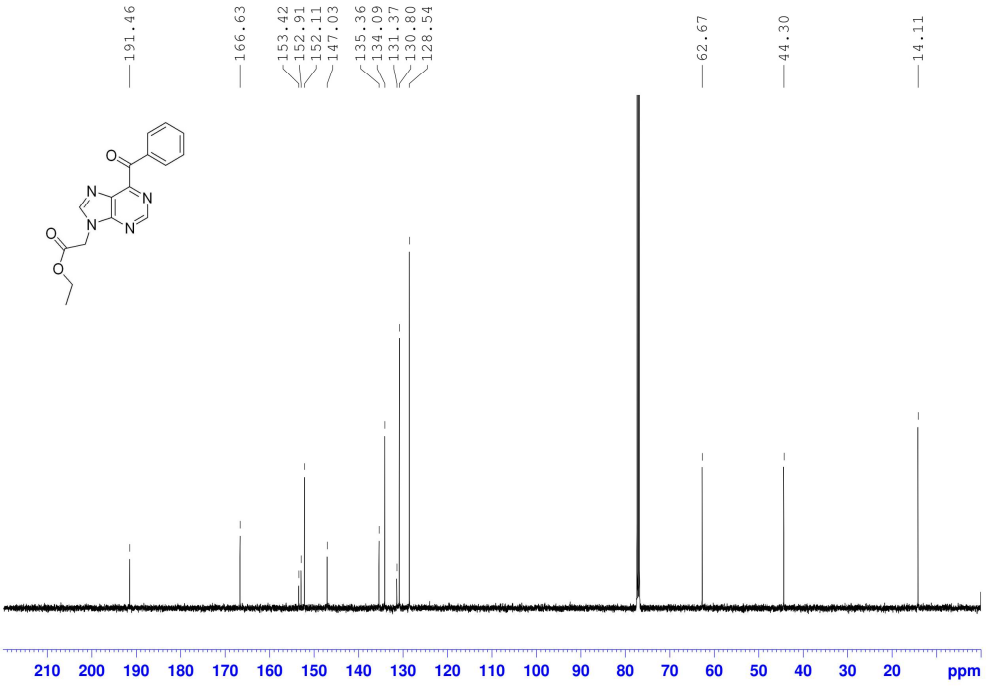
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(4-(tert-butyl)benzoyl)-9*H*-purin-9-yl) acetate (**4c**)



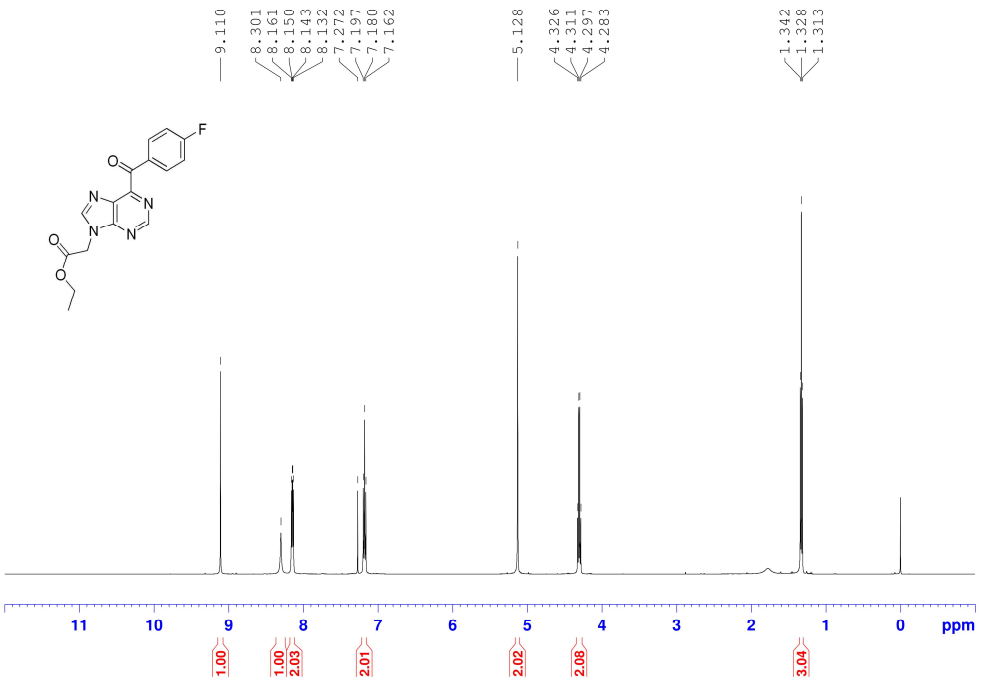
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-benzoyl-9*H*-purin-9-yl) acetate (**4d**)



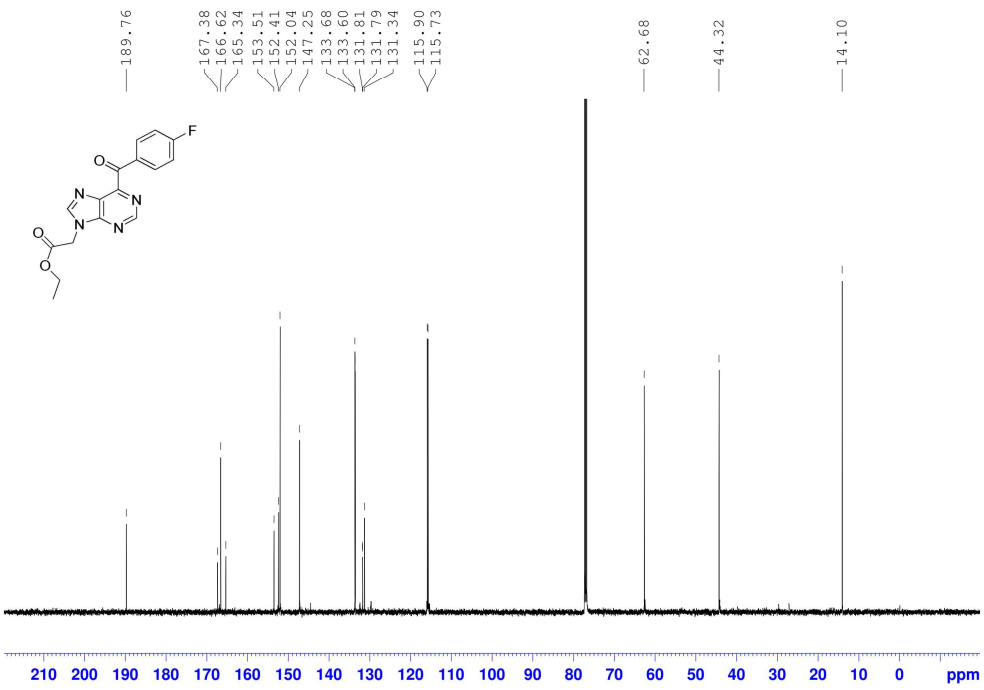
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-benzoyl-9*H*-purin-9-yl) acetate (**4d**)



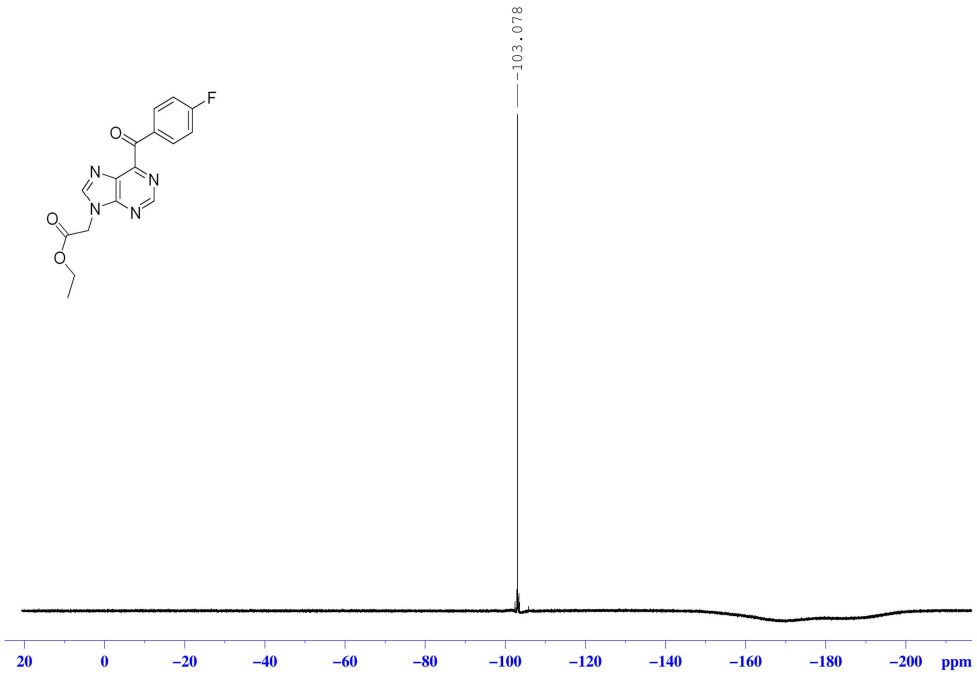
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(4-fluorobenzoyl)-9*H*-purin-9-yl) acetate (**4e**)



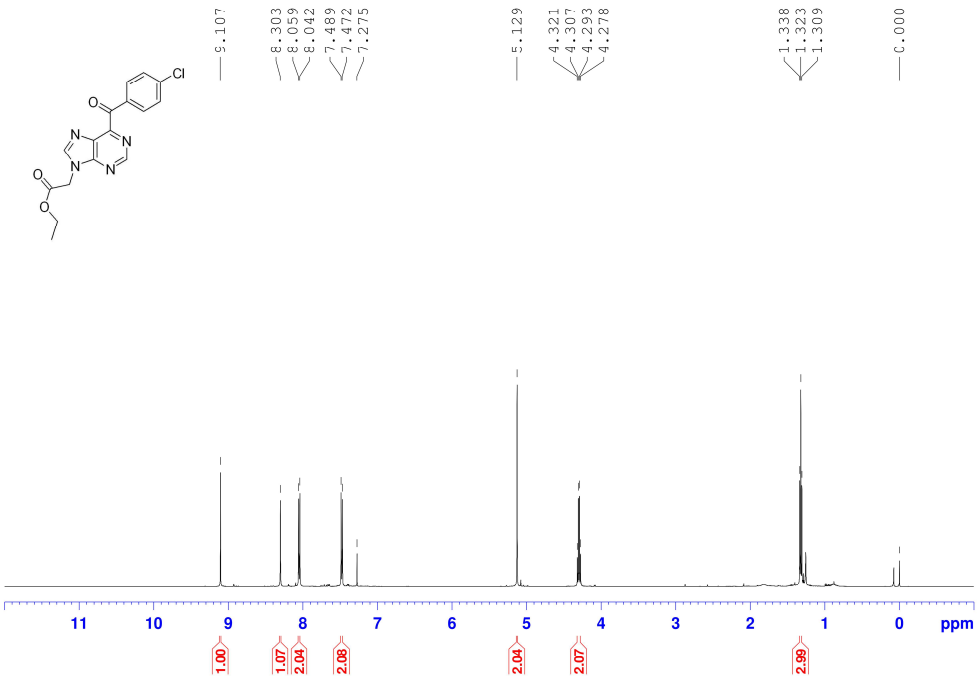
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(4-fluorobenzoyl)-9*H*-purin-9-yl) acetate (**4e**)



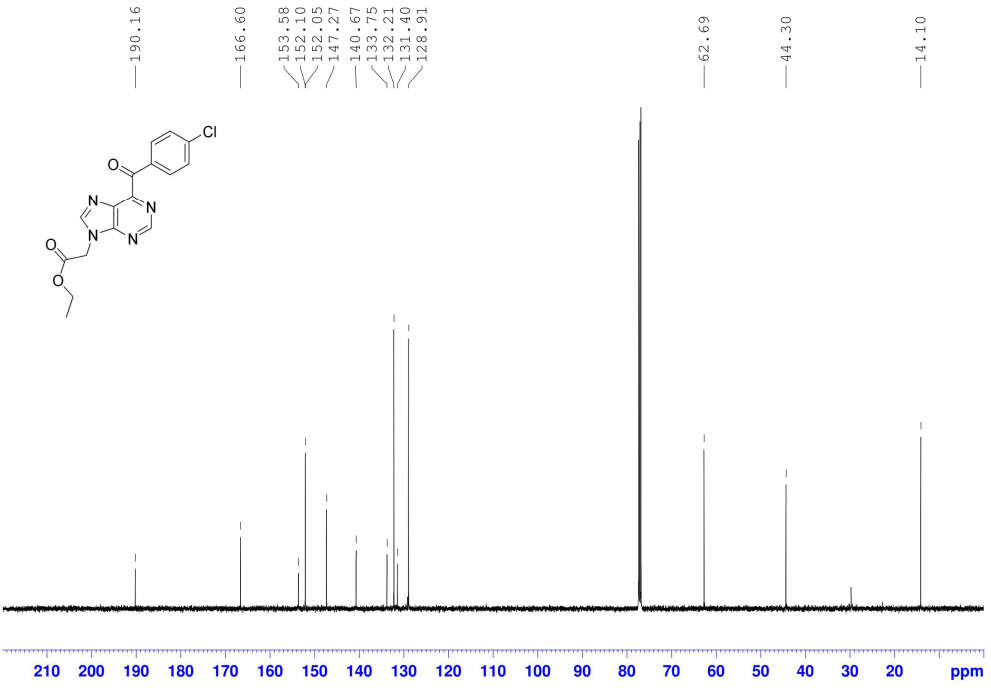
^{19}F NMR (376 MHz, in $CDCl_3$) of ethyl 2-(6-(4-fluorobenzoyl)-9*H*-purin-9-yl) acetate (**4e**)



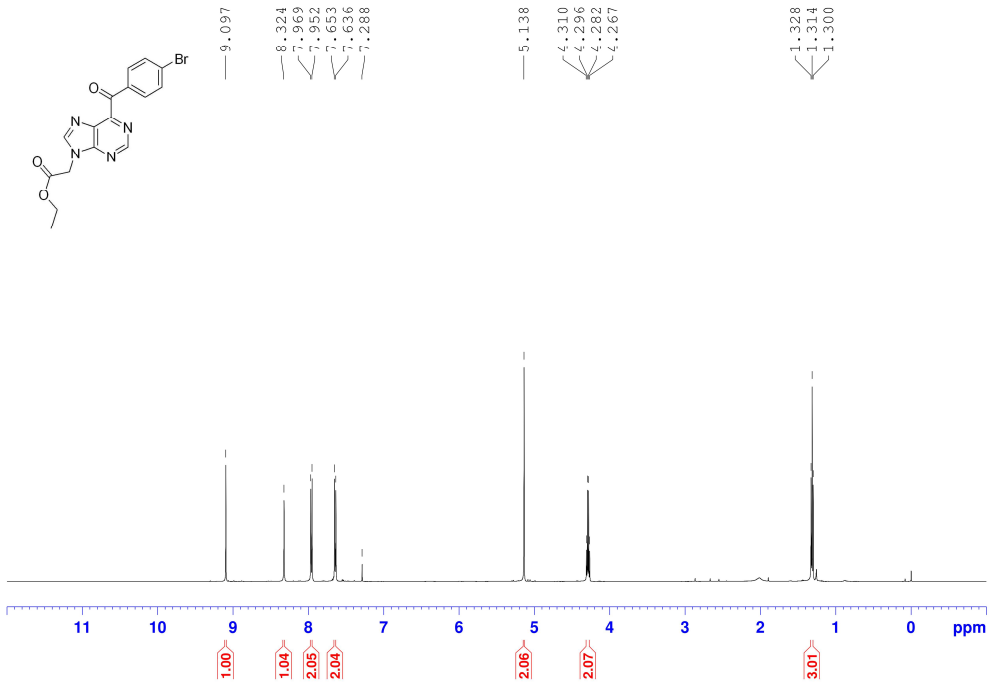
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(4-chlorbenzoyl)-9*H*-purin-9-yl) acetate (**4f**)



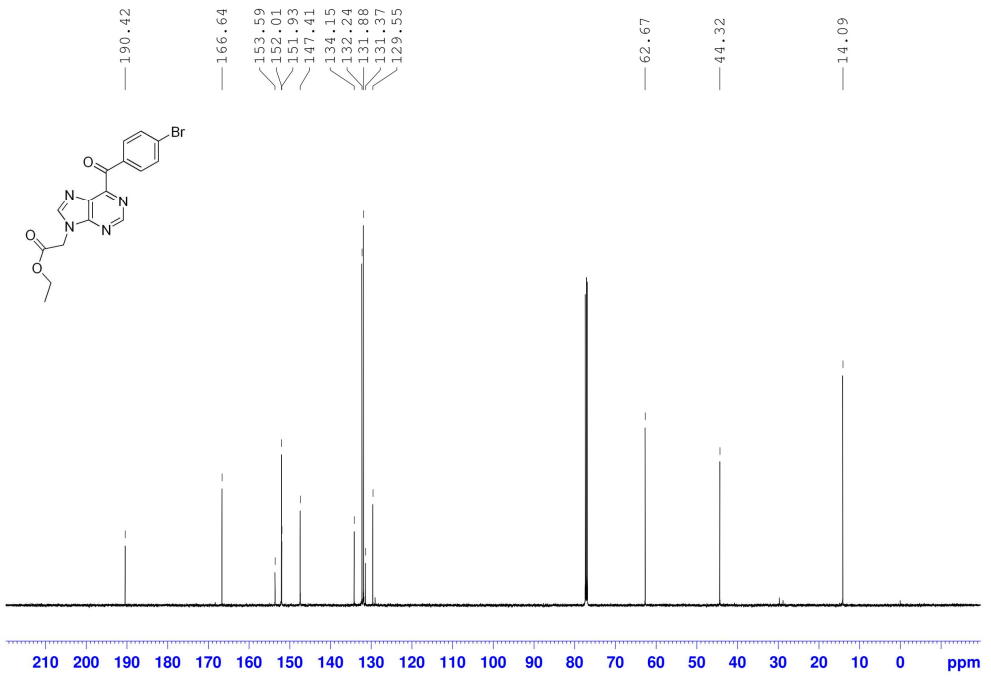
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(4-chlorbenzoyl)-9*H*-purin-9-yl) acetate (**4f**)



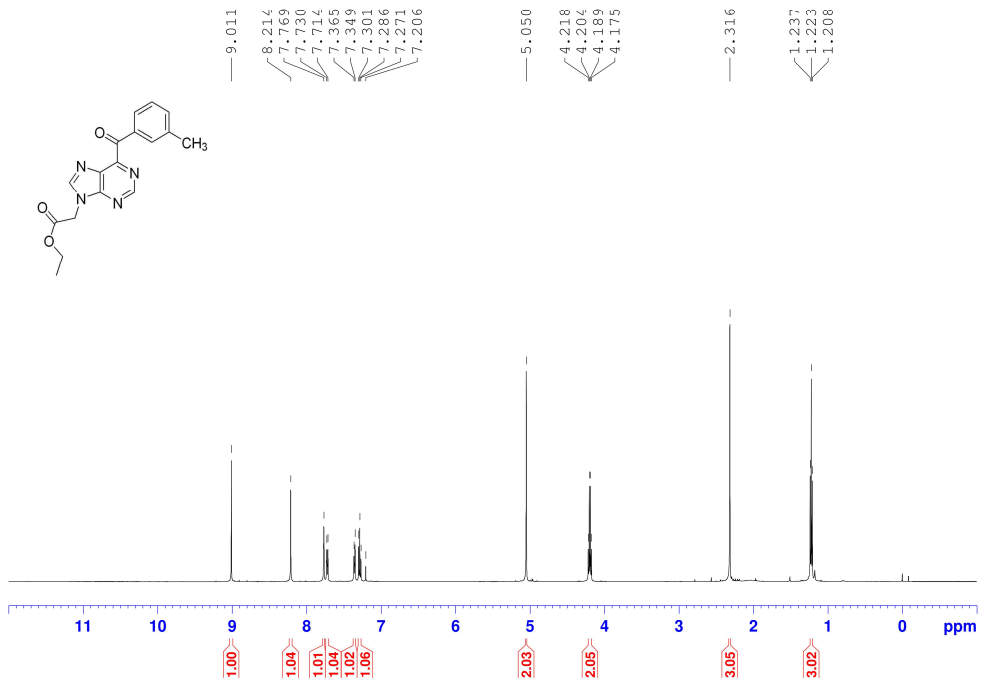
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(4-bromobenzoyl)-9*H*-purin-9-yl) acetate (**4g**)



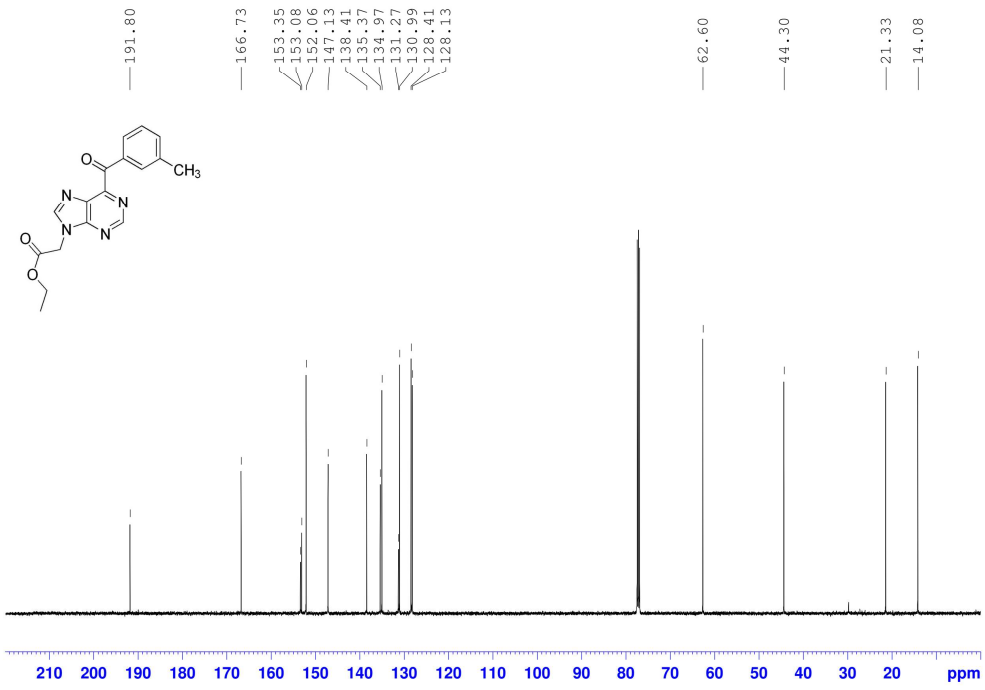
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(4-bromobenzoyl)-9*H*-purin-9-yl) acetate (**4g**)



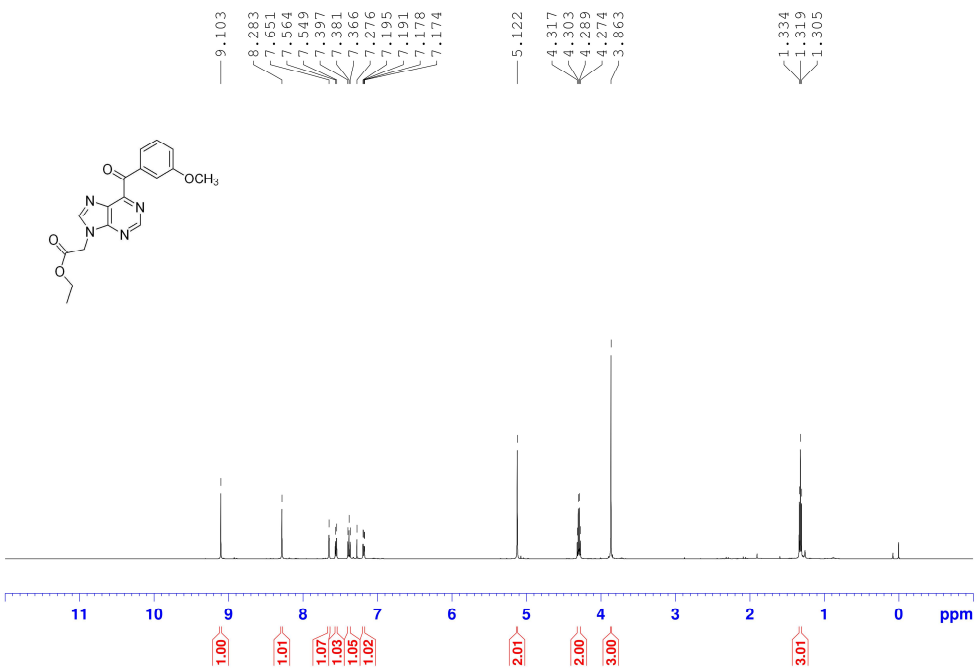
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(3-methylbenzoyl)-9*H*-purin-9-yl) acetate (**4h**)



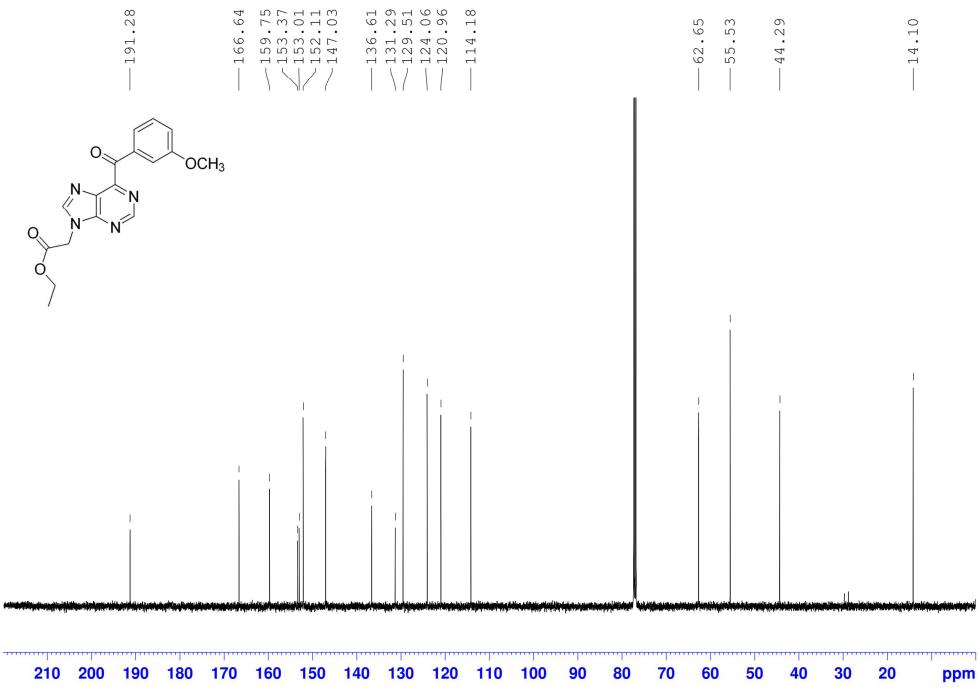
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(3-methylbenzoyl)-9*H*-purin-9-yl) acetate (**4h**)



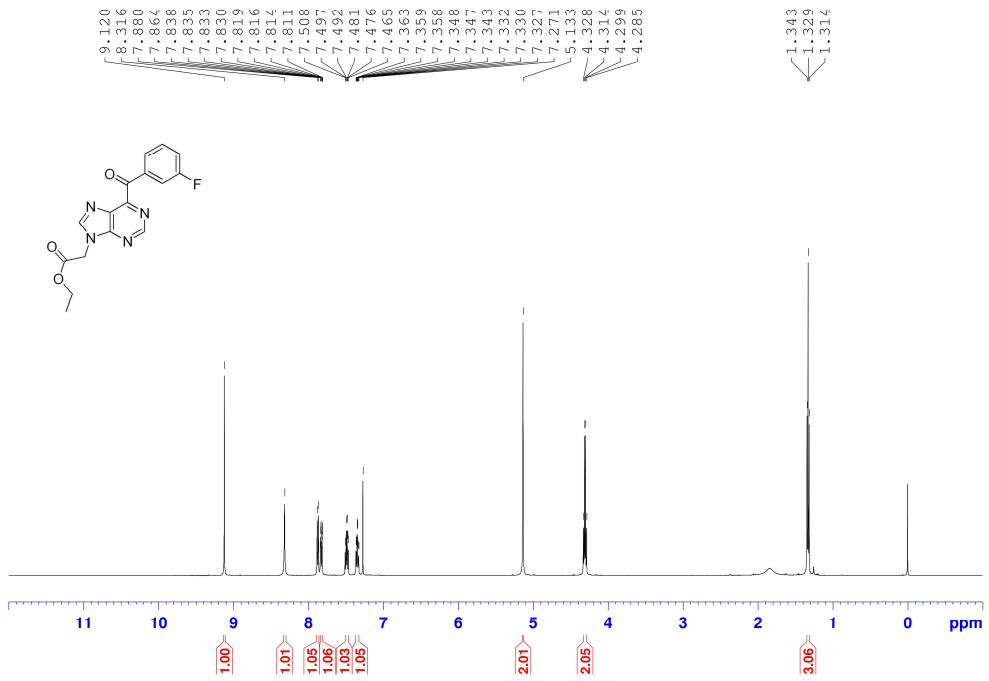
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(3-methoxybenzoyl)-9*H*-purin-9-yl) acetate (**4i**)



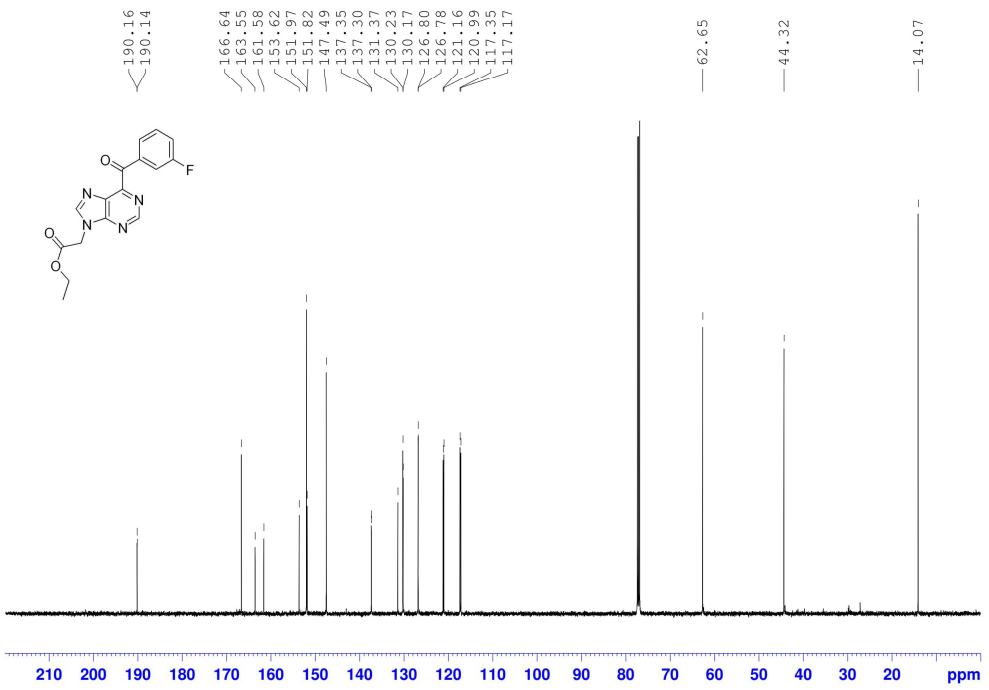
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(3-methoxybenzoyl)-9*H*-purin-9-yl) acetate (**4i**)



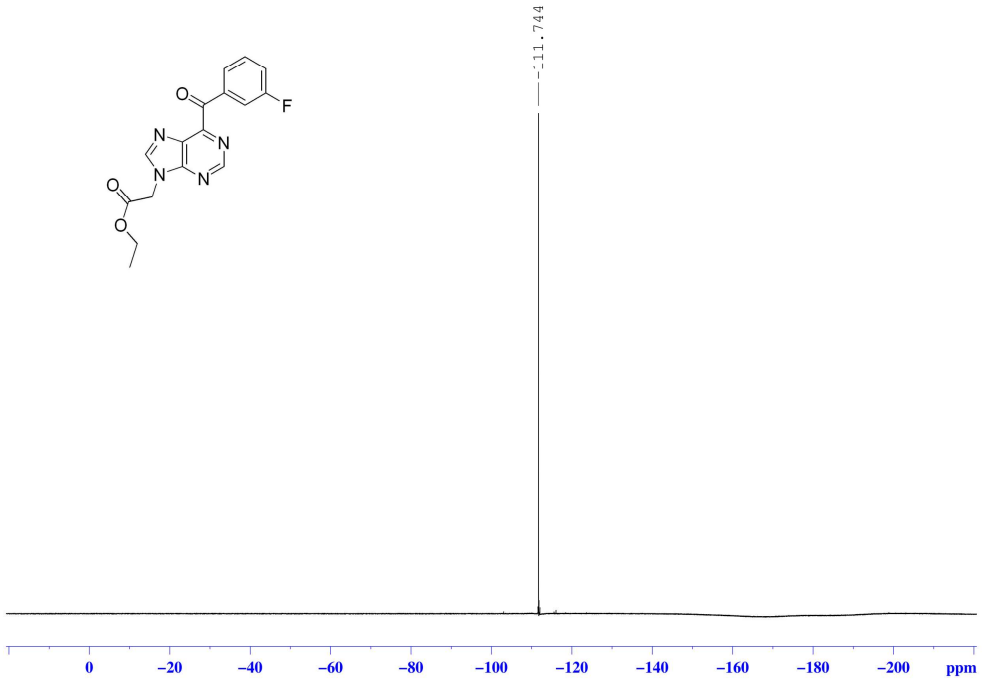
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(3-fluorobenzoyl)-9*H*-purin-9-yl) acetate (**4j**)



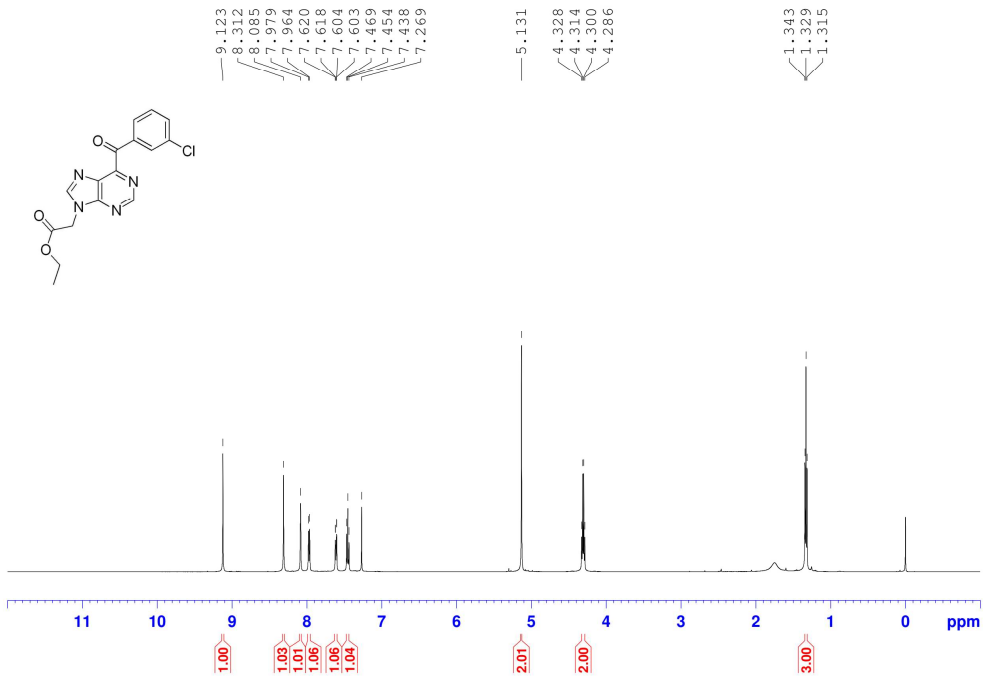
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(3-fluorobenzoyl)-9*H*-purin-9-yl) acetate (**4j**)



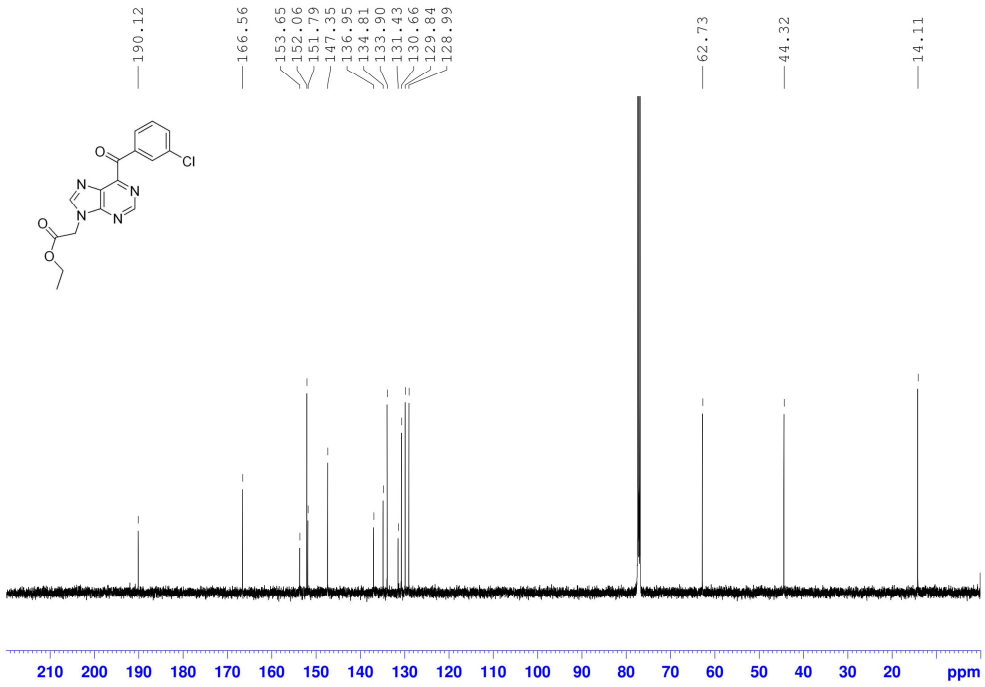
^{19}F NMR (376 MHz, in $CDCl_3$) of ethyl 2-(6-(3-fluorobenzoyl)-9*H*-purin-9-yl) acetate (**4j**)



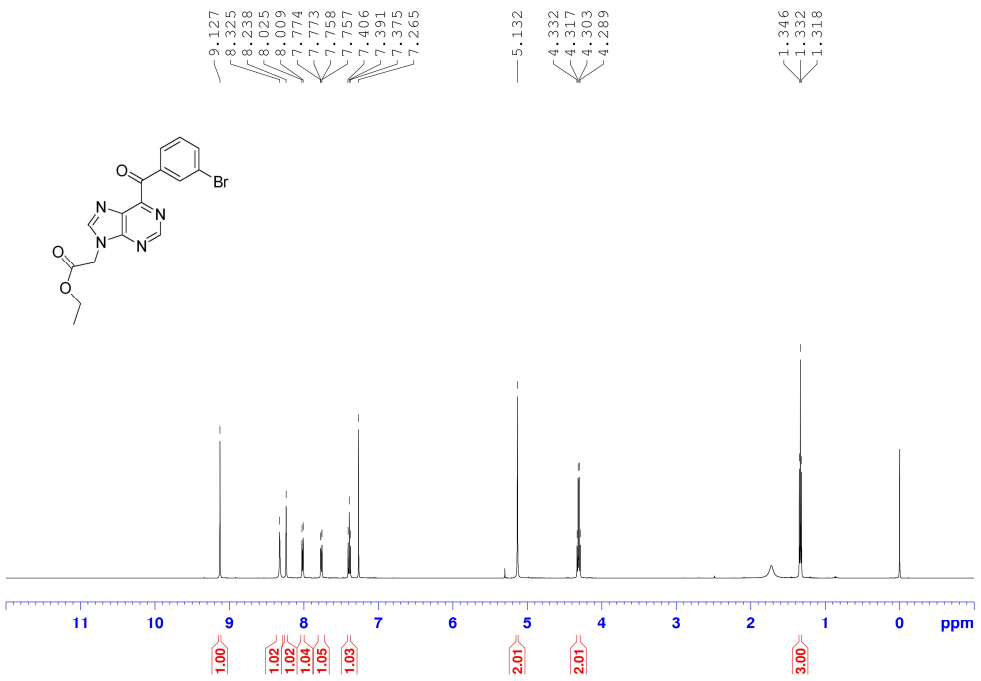
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(3-chlorbenzoyl)-9*H*-purin-9-yl) acetate (**4k**)



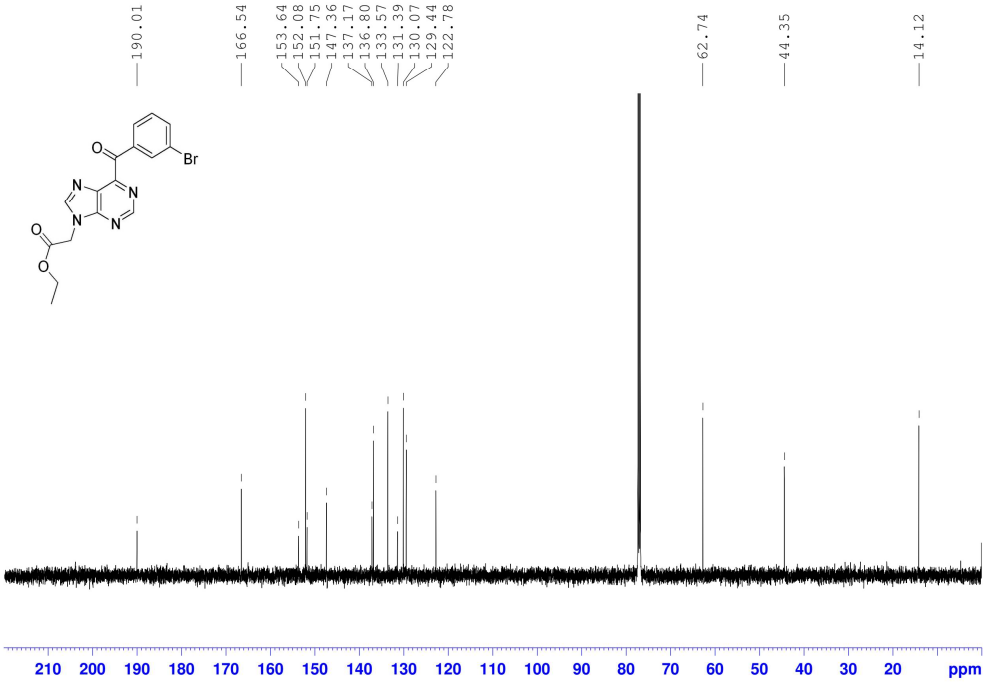
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(3-chlorbenzoyl)-9*H*-purin-9-yl) acetate (**4k**)



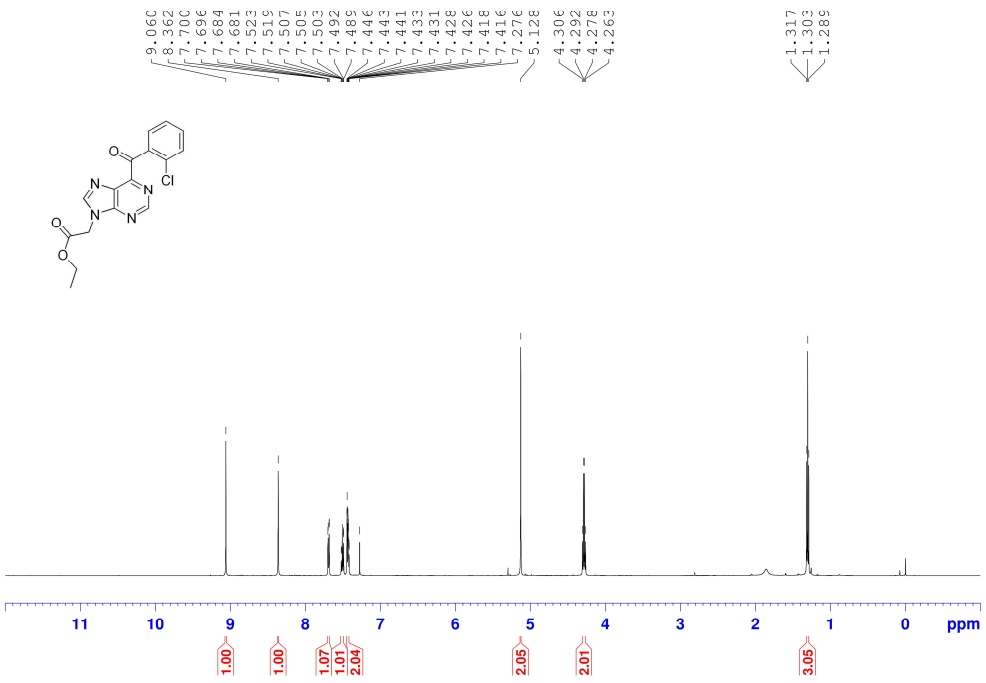
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(3-bromobenzoyl)-9*H*-purin-9-yl) acetate (**4l**)



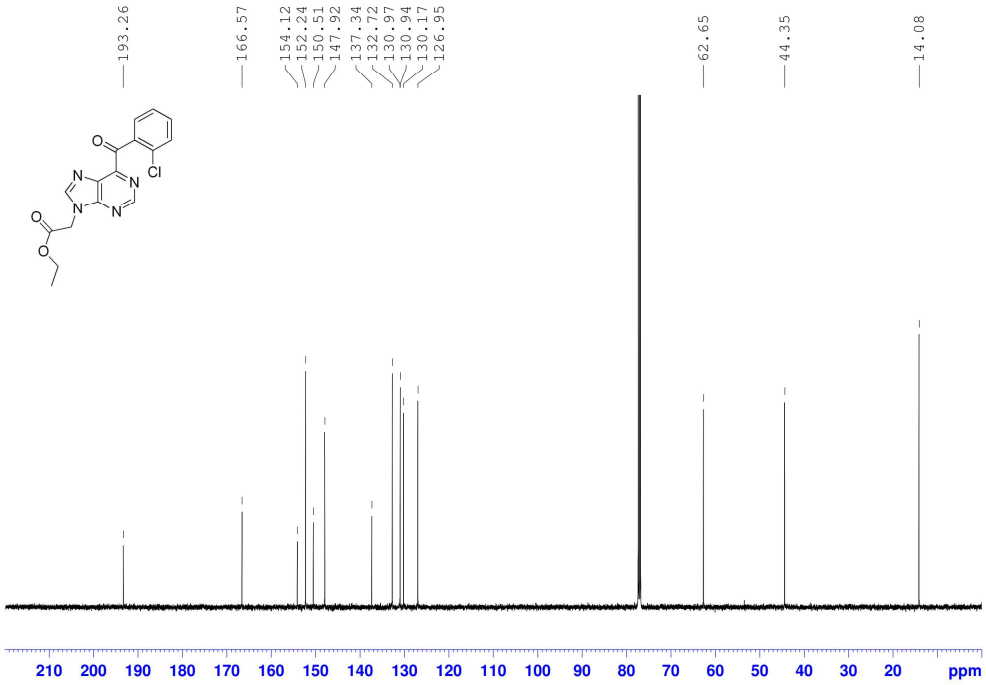
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(3-bromobenzoyl)-9*H*-purin-9-yl) acetate (**4l**)



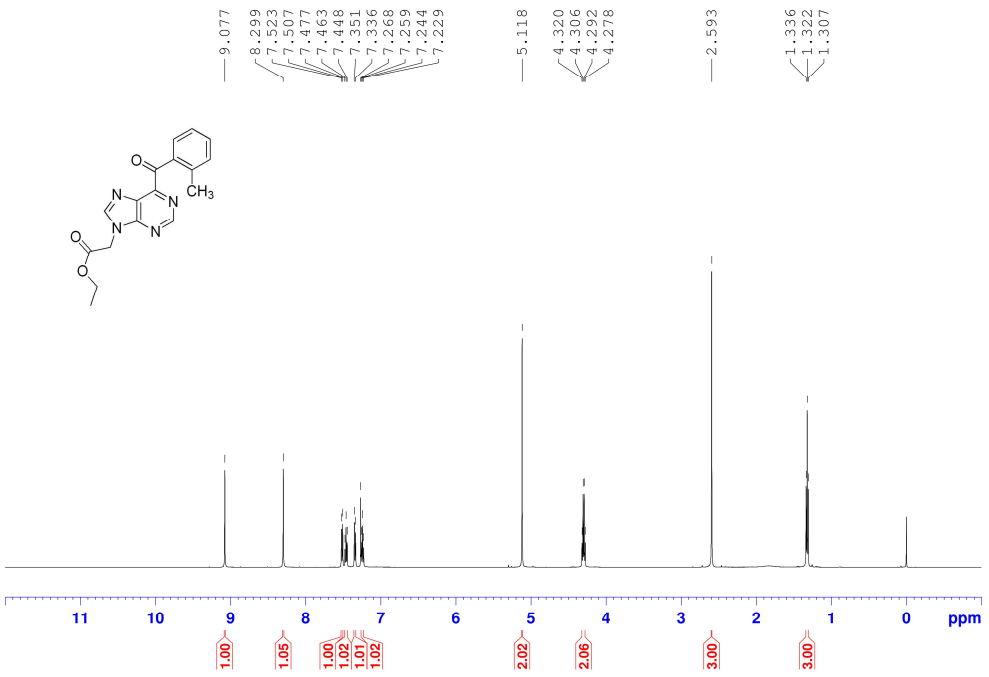
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(2-chlorbenzoyl)-9*H*-purin-9-yl) acetate (**4m**)



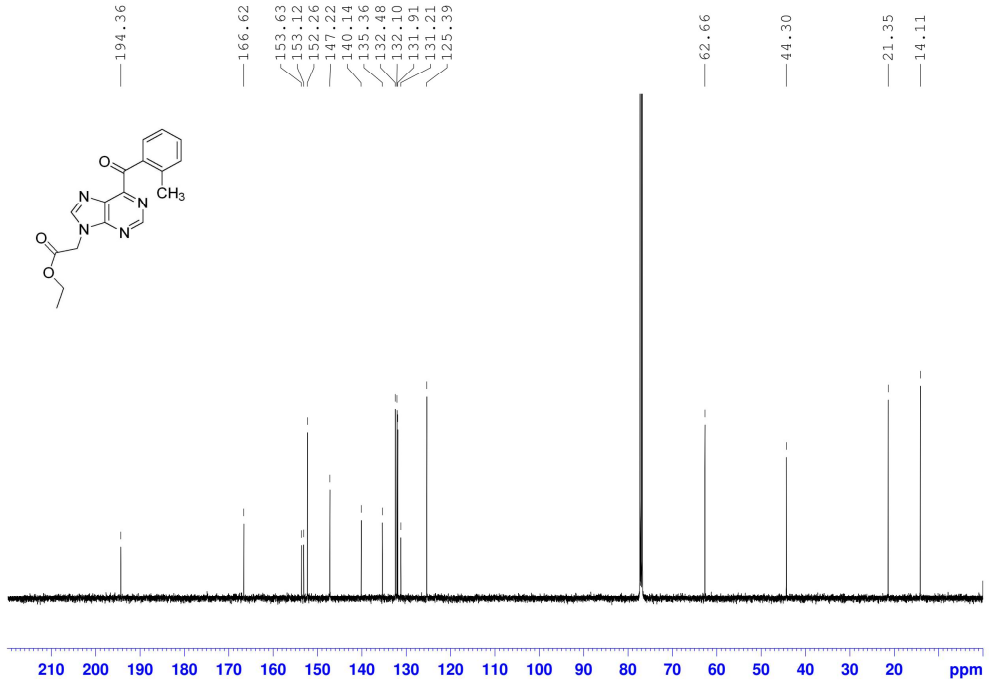
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(2-chlorbenzoyl)-9*H*-purin-9-yl) acetate (**4m**)



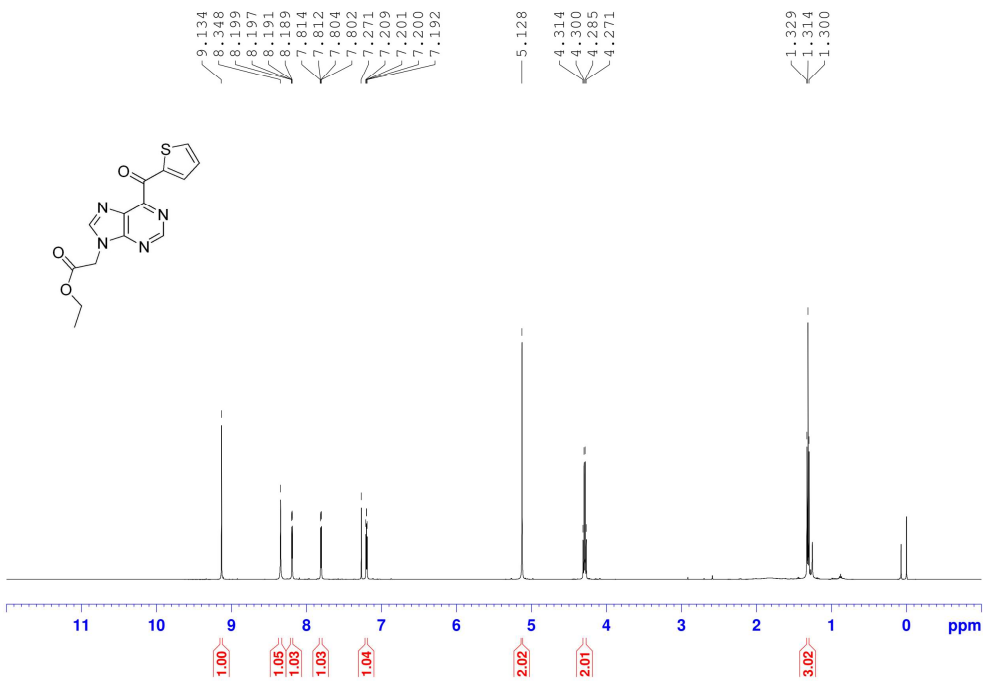
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(2-methylbenzoyl)-9*H*-purin-9-yl) acetate (**4n**)



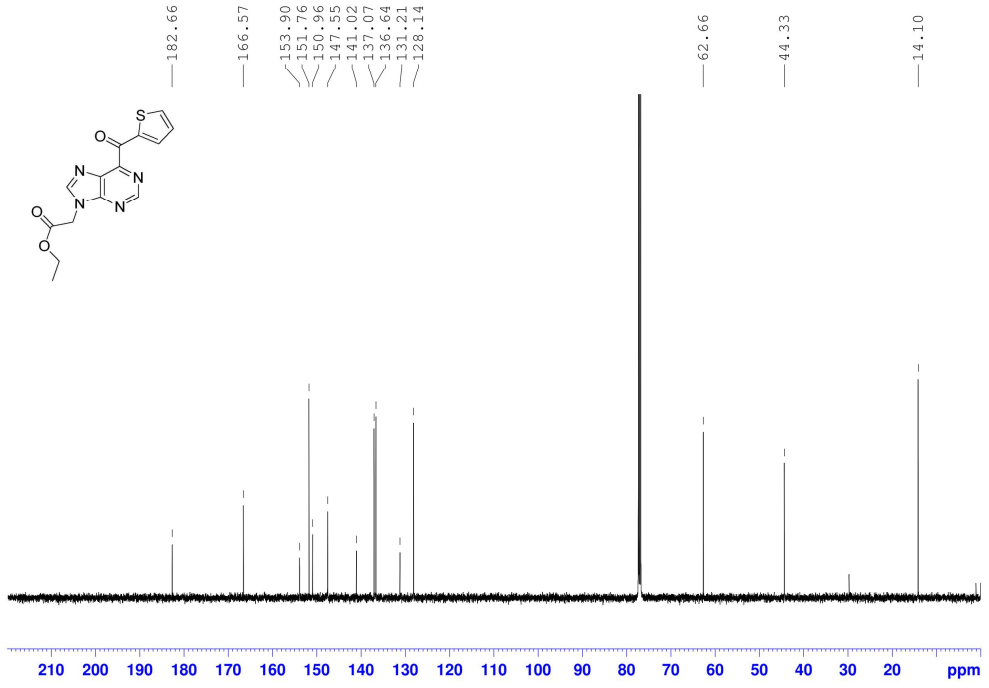
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(2-methylbenzoyl)-9*H*-purin-9-yl) acetate (**4n**)



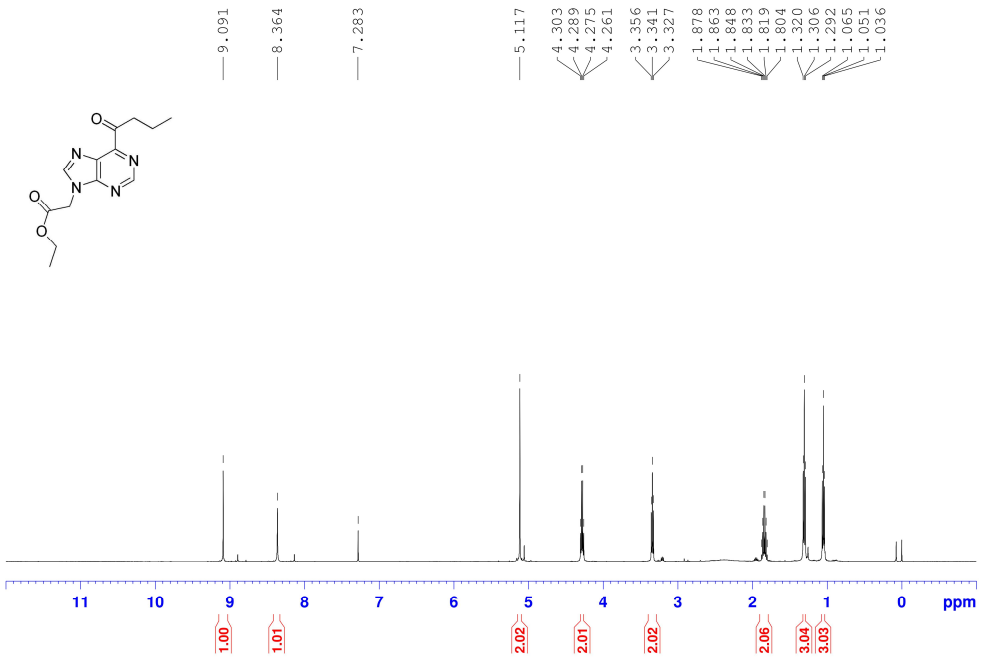
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(thiophene-2-carbonyl)-9*H*-purin-9-yl) acetate (**4o**)



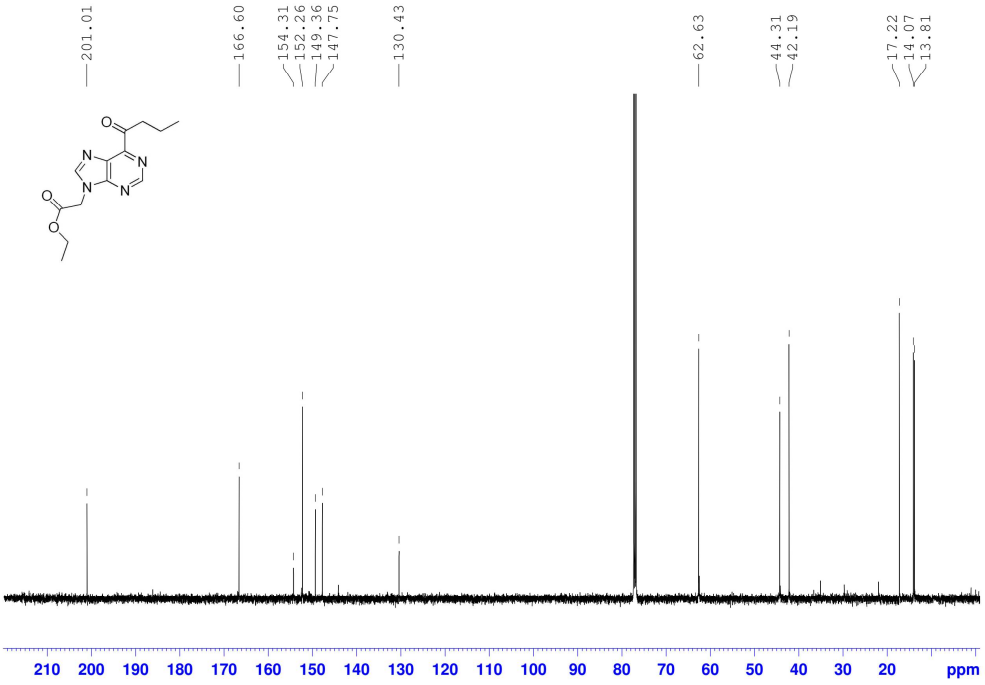
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(thiophene-2-carbonyl)-9*H*-purin-9-yl) acetate (**4o**)



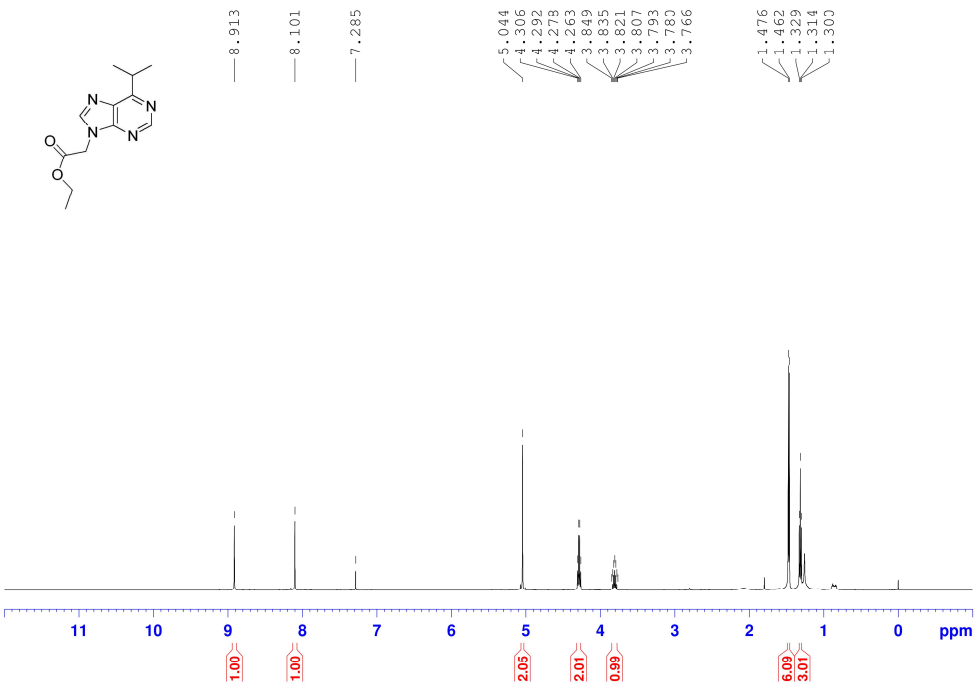
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-butyryl-9*H*-purin-9-yl) acetate (**4p**)



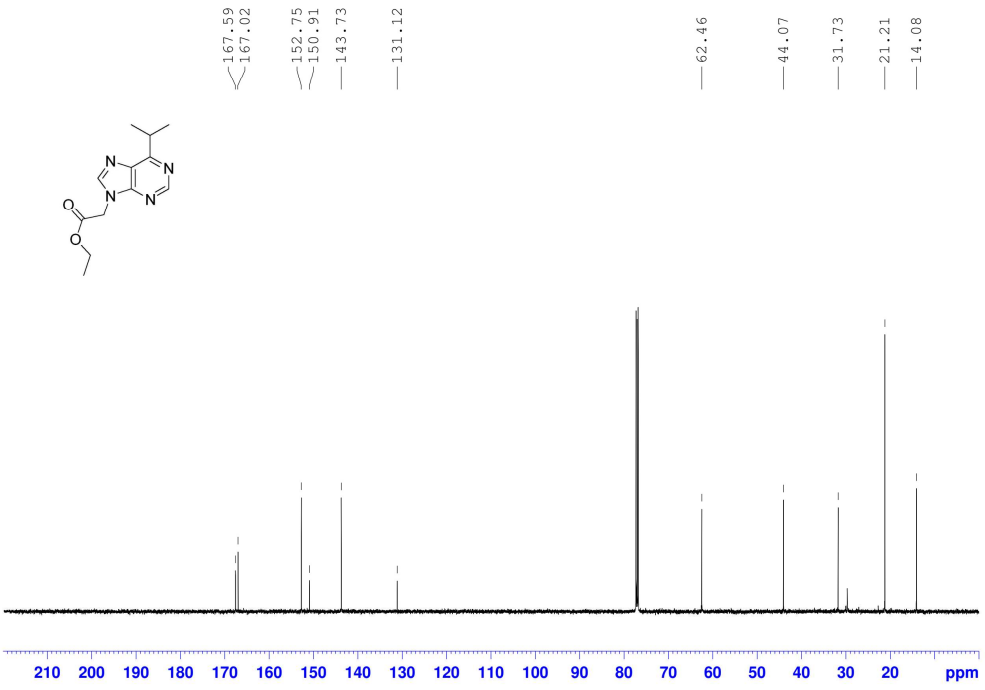
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-butyryl-9*H*-purin-9-yl) acetate (**4p**)



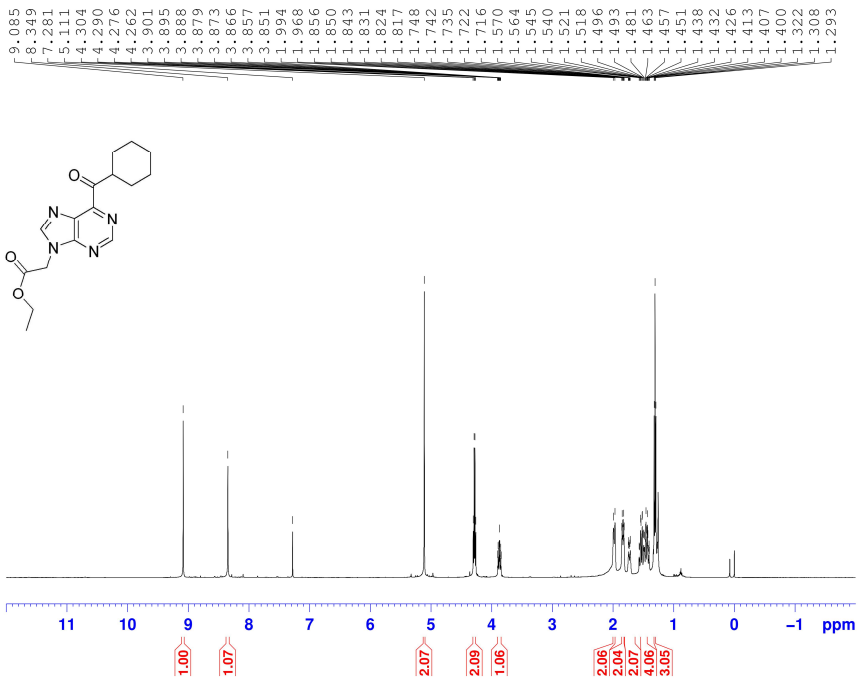
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-isopropyl-9*H*-purin-9-yl) acetate (**4q**)



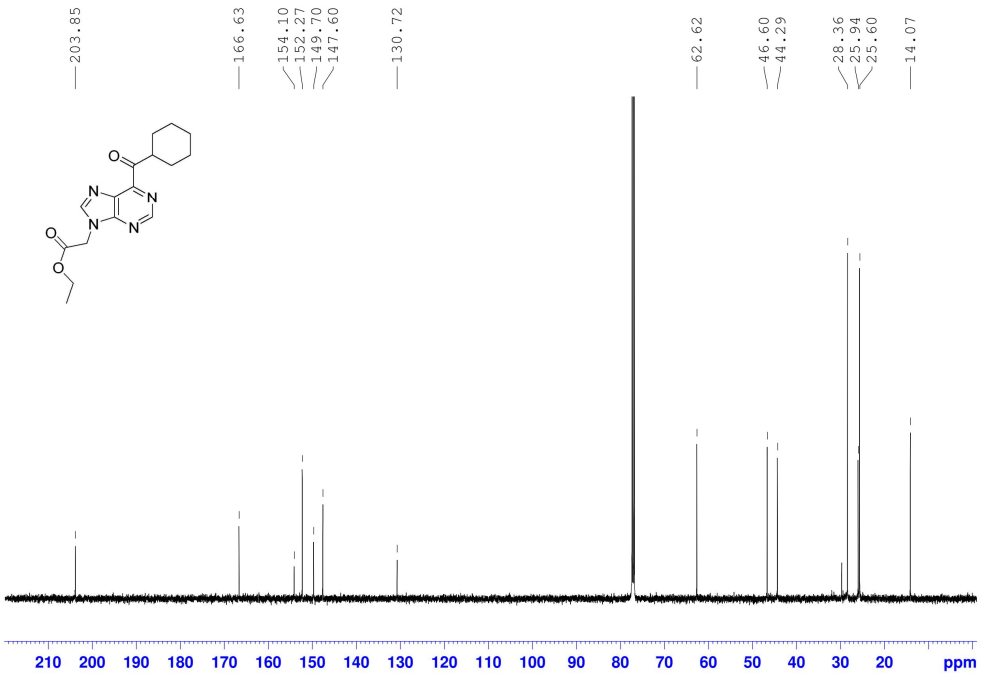
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-isopropyl-9*H*-purin-9-yl) acetate (**4q**)



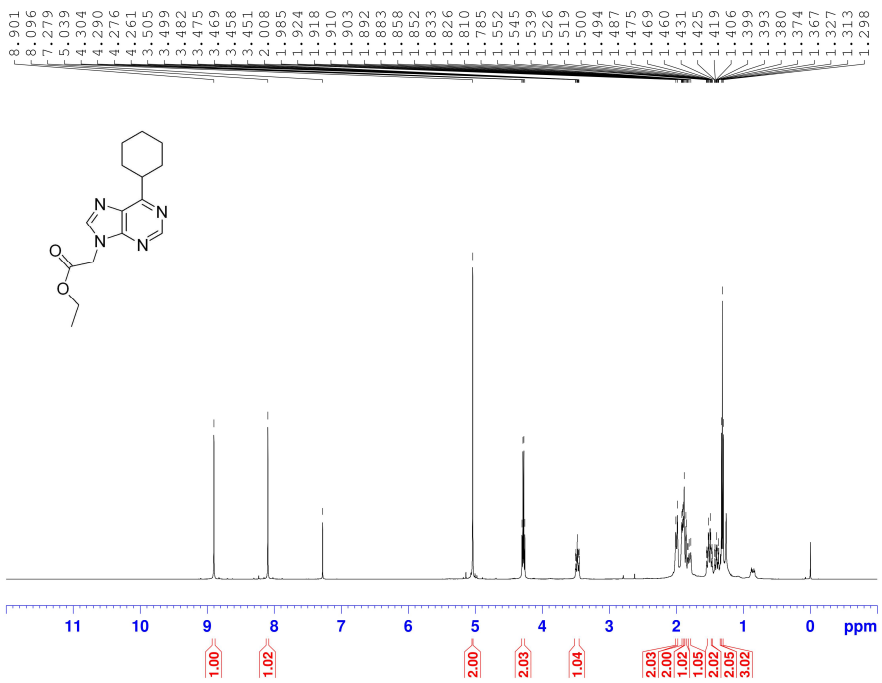
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-cyclohexanecarbonyl-9*H*-purin-9-yl) acetate (**4r**)



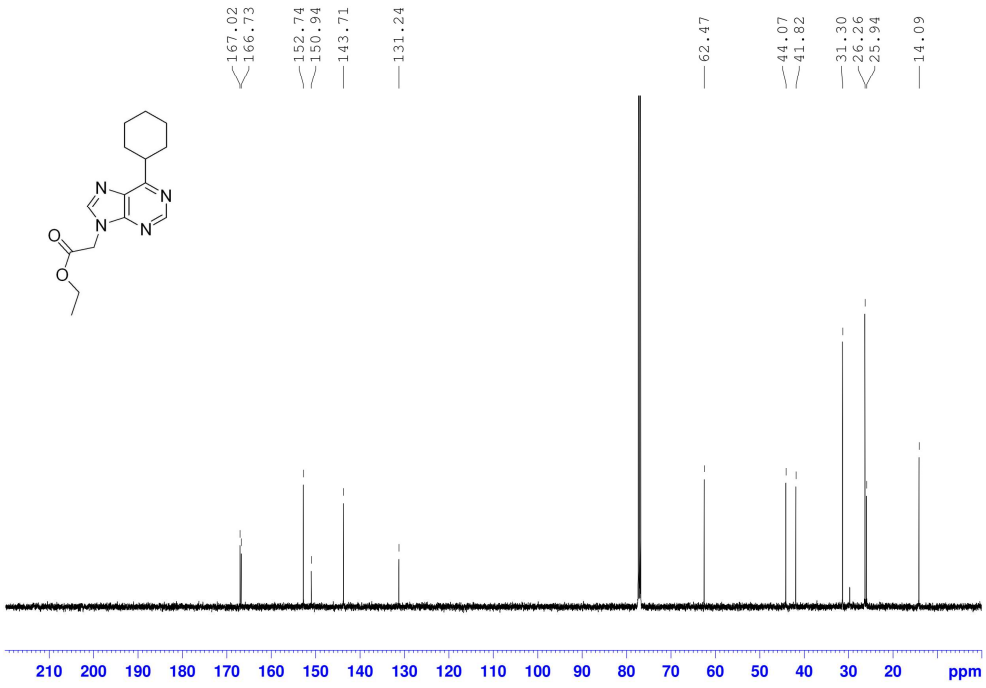
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-cyclohexanecarbonyl-9*H*-purin-9-yl) acetate (**4r**)



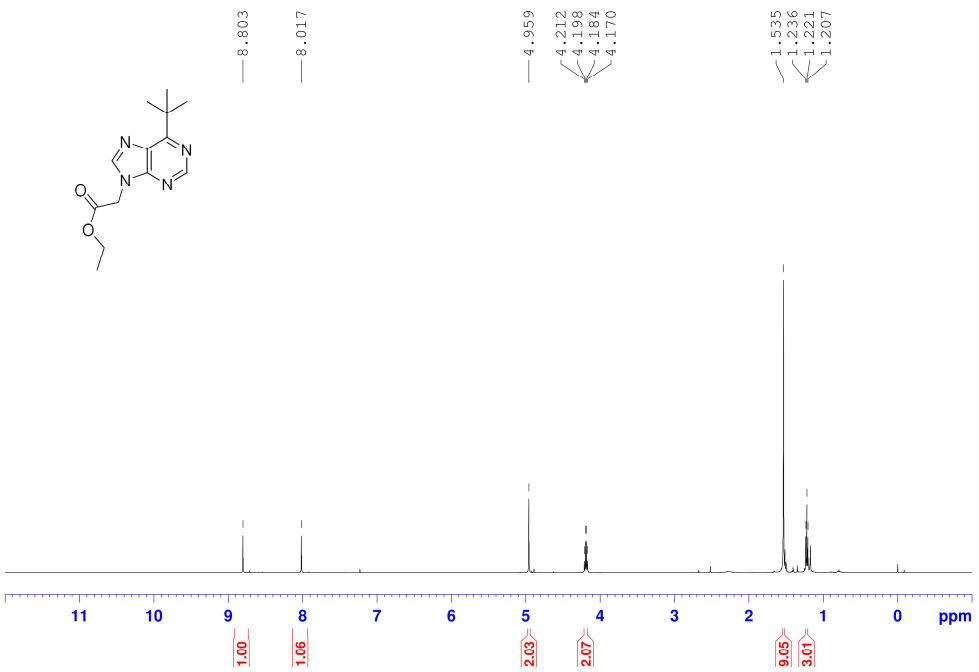
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-cyclohexyl-9*H*-purin-9-yl) acetate (**4r'**)



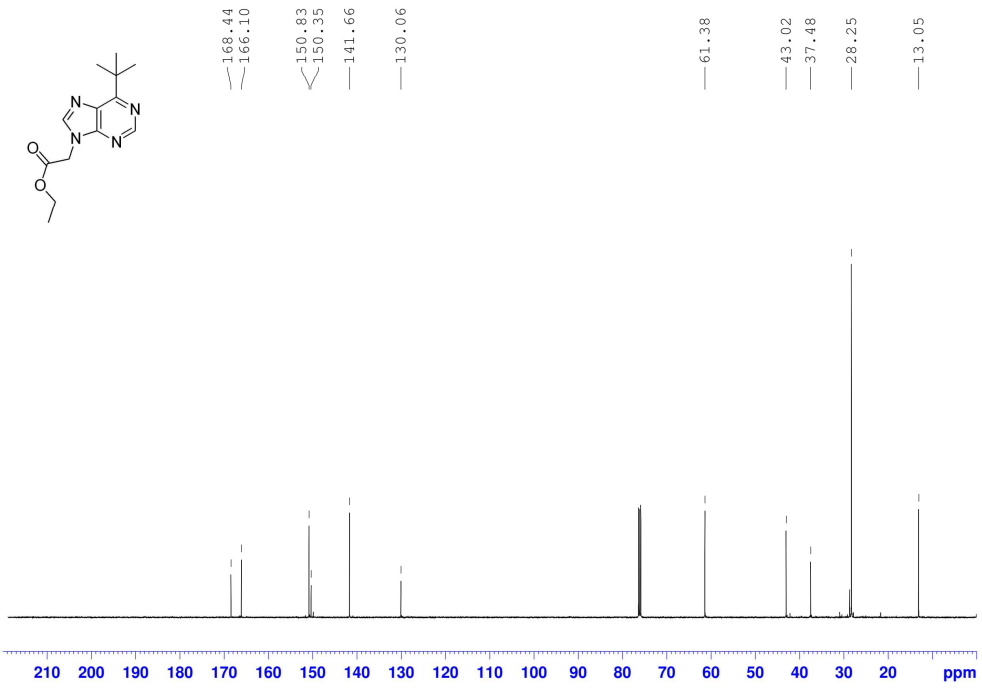
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-cyclohexyl-9*H*-purin-9-yl) acetate (**4r'**)



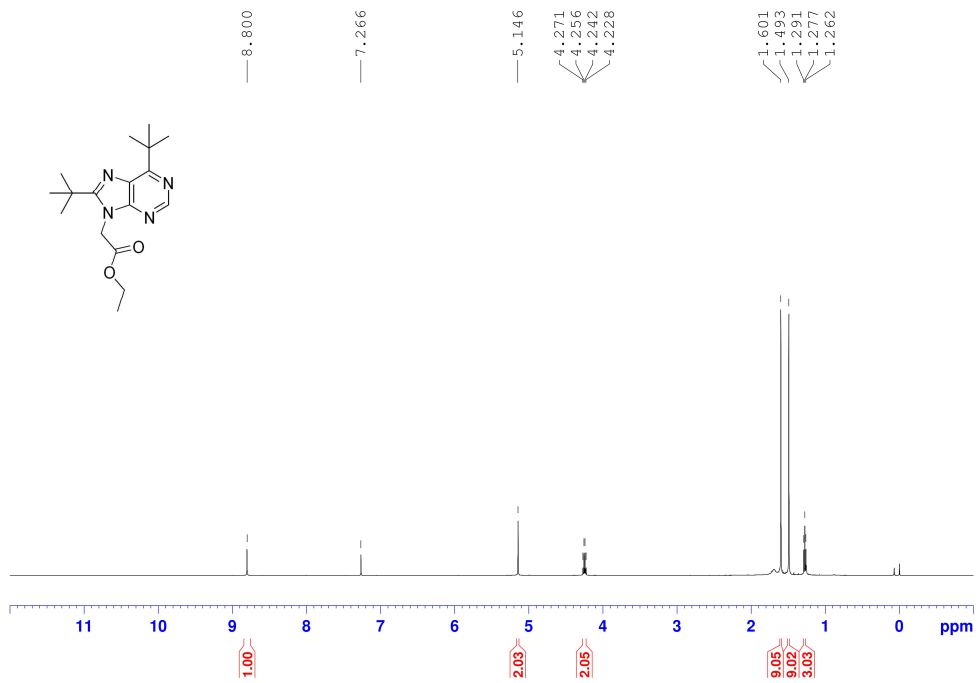
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6-(tert-butyl)-9*H*-purin-9-yl) acetate (**4s**)



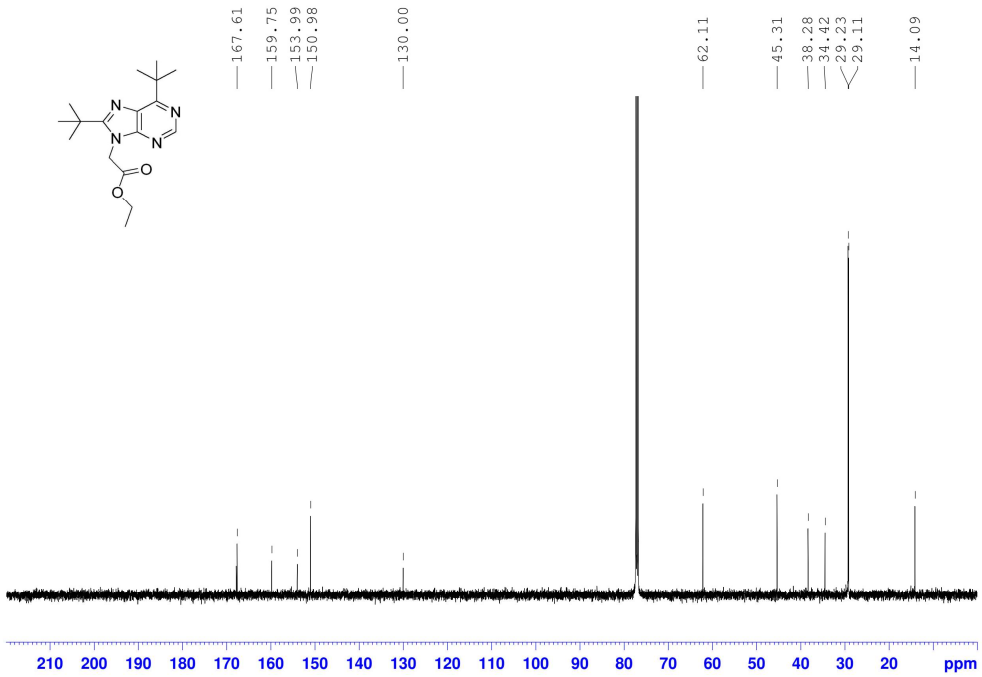
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6-(tert-butyl)-9*H*-purin-9-yl) acetate (**4s**)



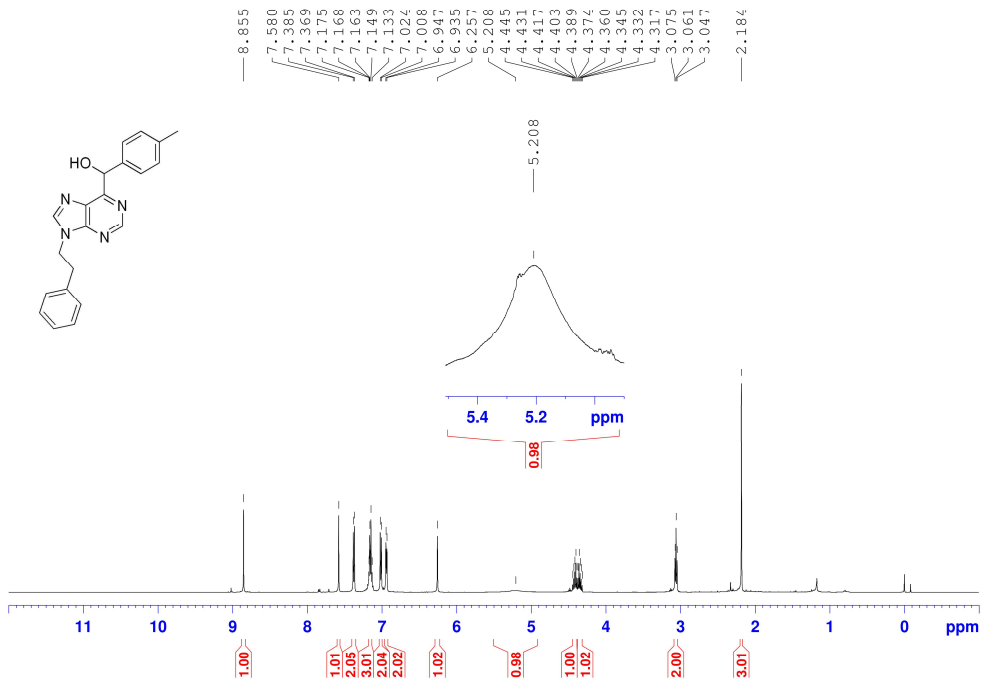
^{1}H NMR (500 MHz, in $CDCl_3$) of ethyl 2-(6,8-di-tert-butyl-9*H*-purin-9-yl) acetate (**4s'**)



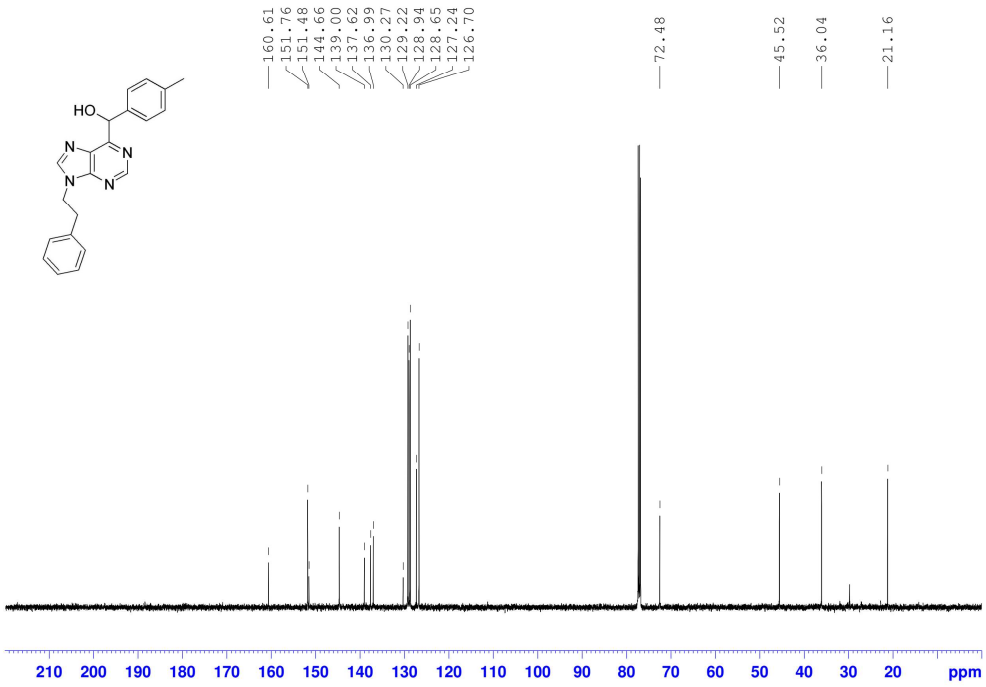
^{13}C NMR (125 MHz, in $CDCl_3$) of ethyl 2-(6,8-di-tert-butyl-9*H*-purin-9-yl) acetate (**4s'**)



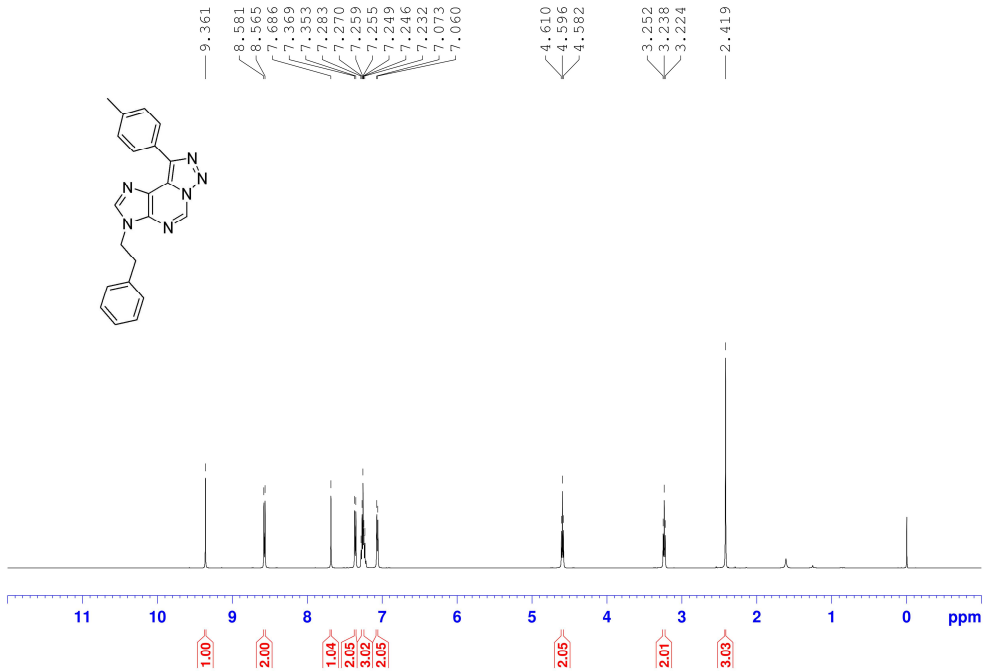
^{1}H NMR (500 MHz, in $CDCl_3$) of (9-phenethyl-9*H*-purin-6-yl)(p-tolyl) methanol (**3i-OH**)



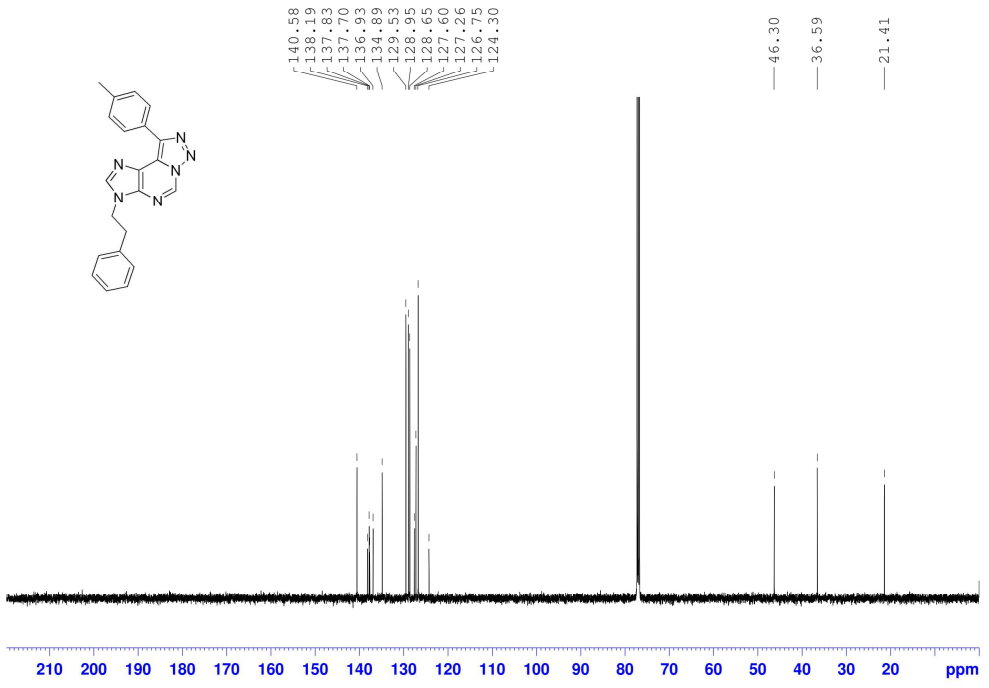
^{13}C NMR (125 MHz, in $CDCl_3$) of (9-phenethyl-9*H*-purin-6-yl)(p-tolyl) methanol (**3i-OH**)



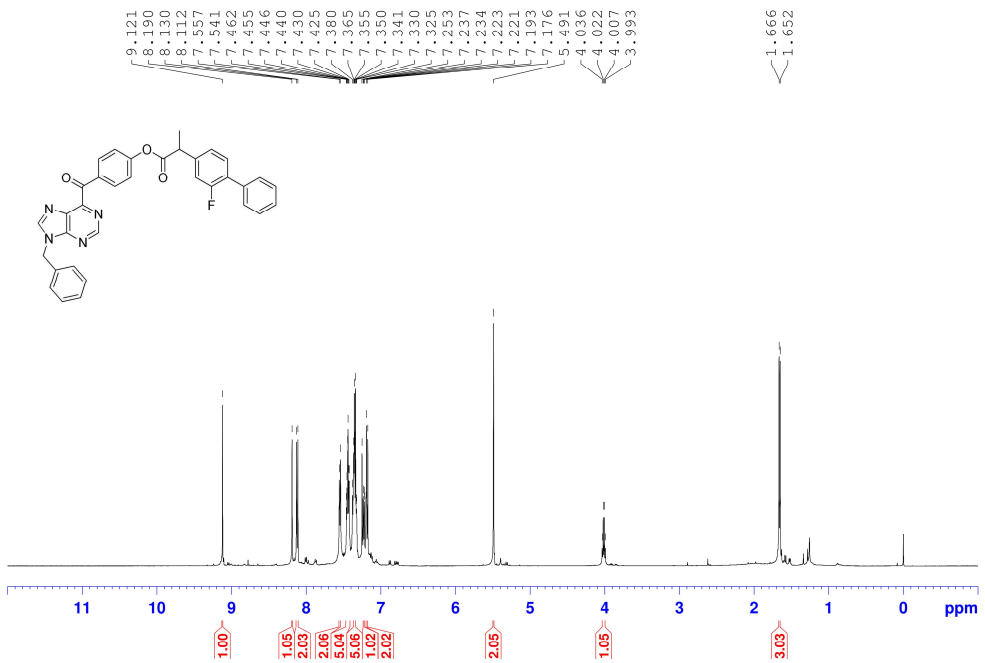
^{1}H NMR (500 MHz, in $CDCl_3$) of 3-phenethyl-9-(p-tolyl)-3*H*-[1,2,3]triazolo[5,1-i]purine (**3i-N$_3$**)



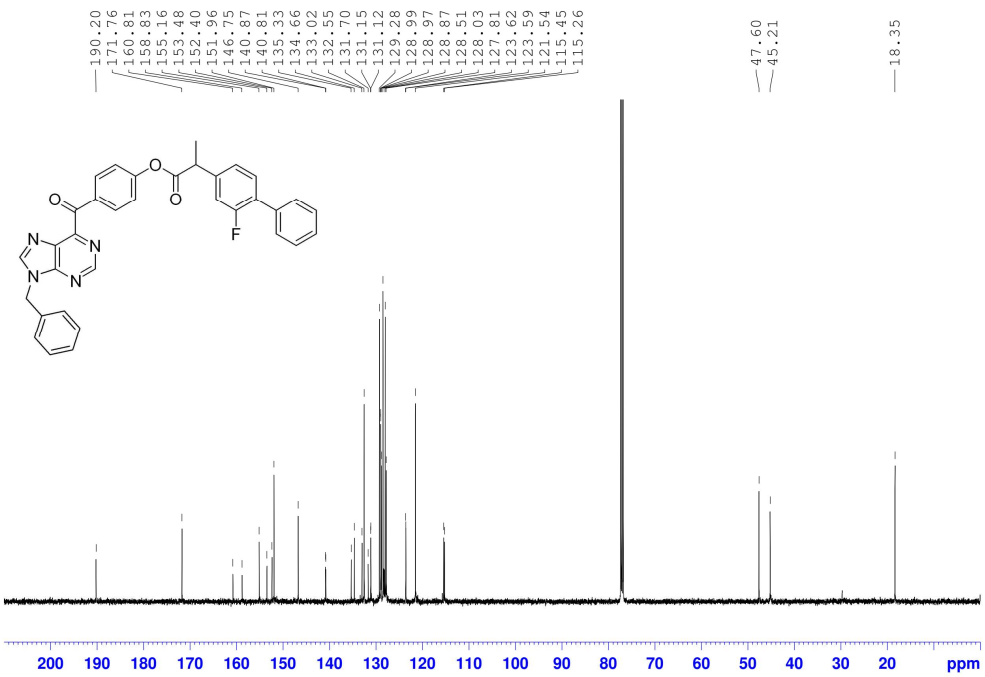
^{13}C NMR (125 MHz, in $CDCl_3$) of 3-phenethyl-9-(p-tolyl)-3*H*-[1,2,3]triazolo[5,1-i]purine (**3i-N$_3$**)



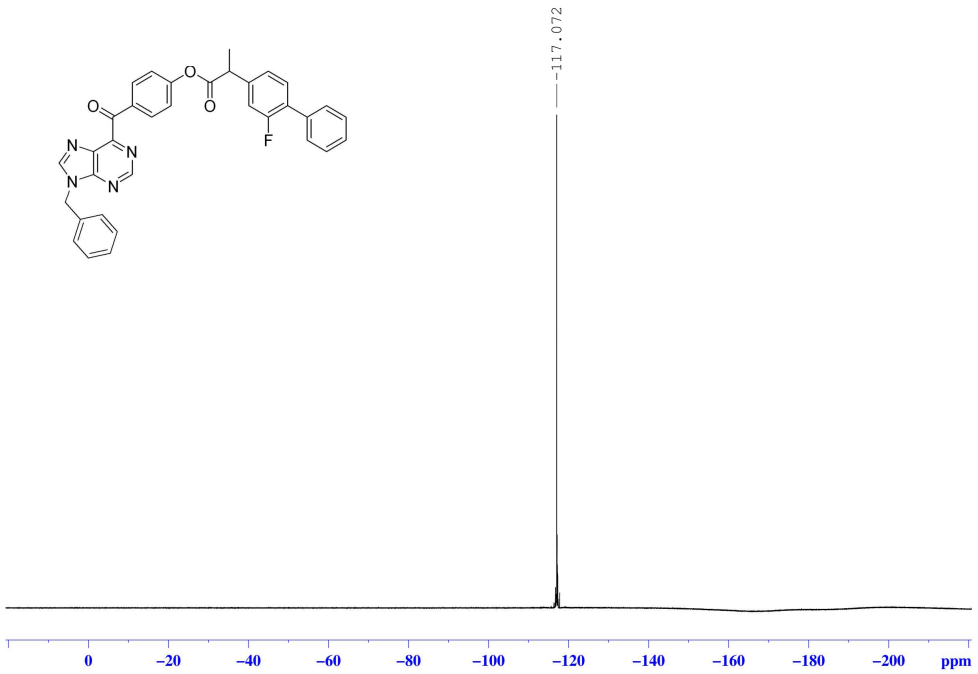
^{1}H NMR (500 MHz, in $CDCl_3$) of 4-(9-benzyl-9*H*-purine-6-carbonyl)phenyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl) propanoate (**3h-F**)



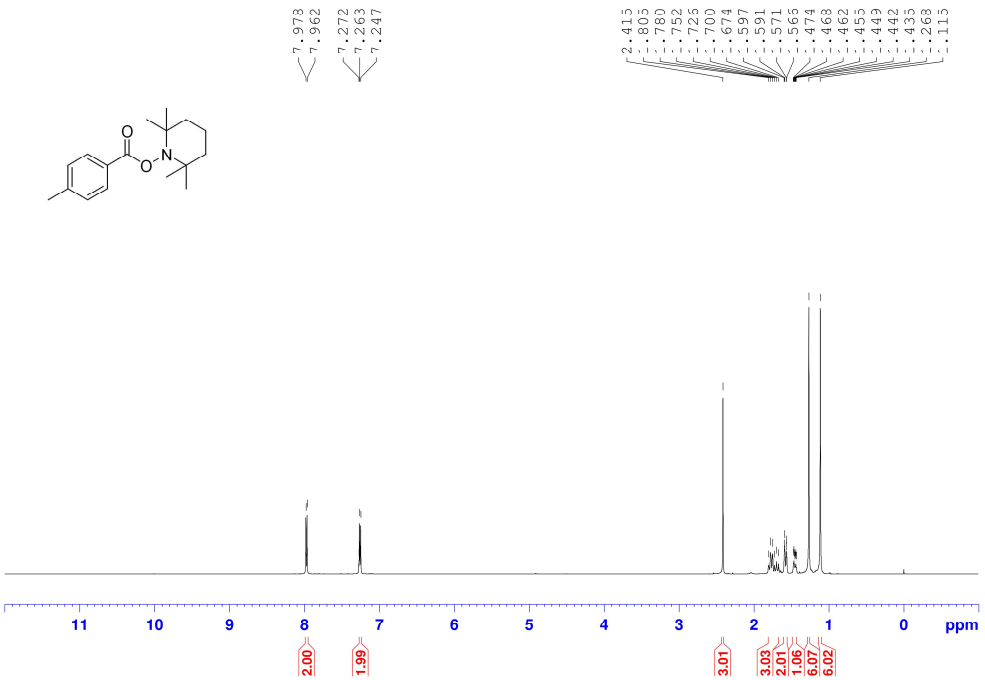
^{13}C NMR (125 MHz, in $CDCl_3$) of 4-(9-benzyl-9*H*-purine-6-carbonyl)phenyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl) propanoate (**3h-F**)



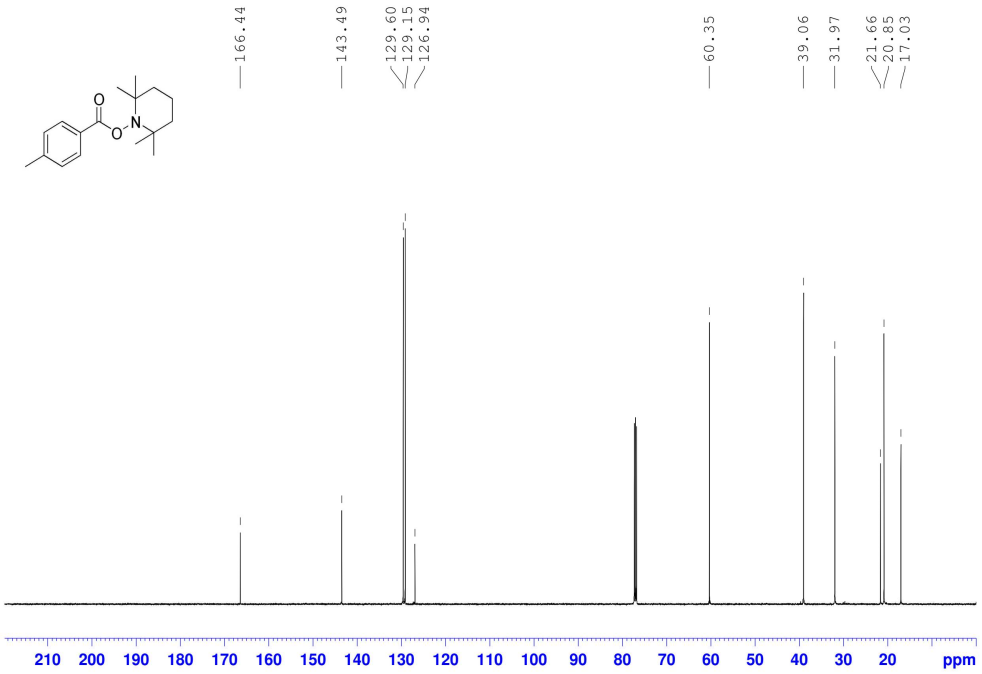
^{19}F NMR (376 MHz, in $CDCl_3$) of 4-(9-benzyl-9*H*-purine-6-carbonyl)phenyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl) propanoate (**3h-F**)



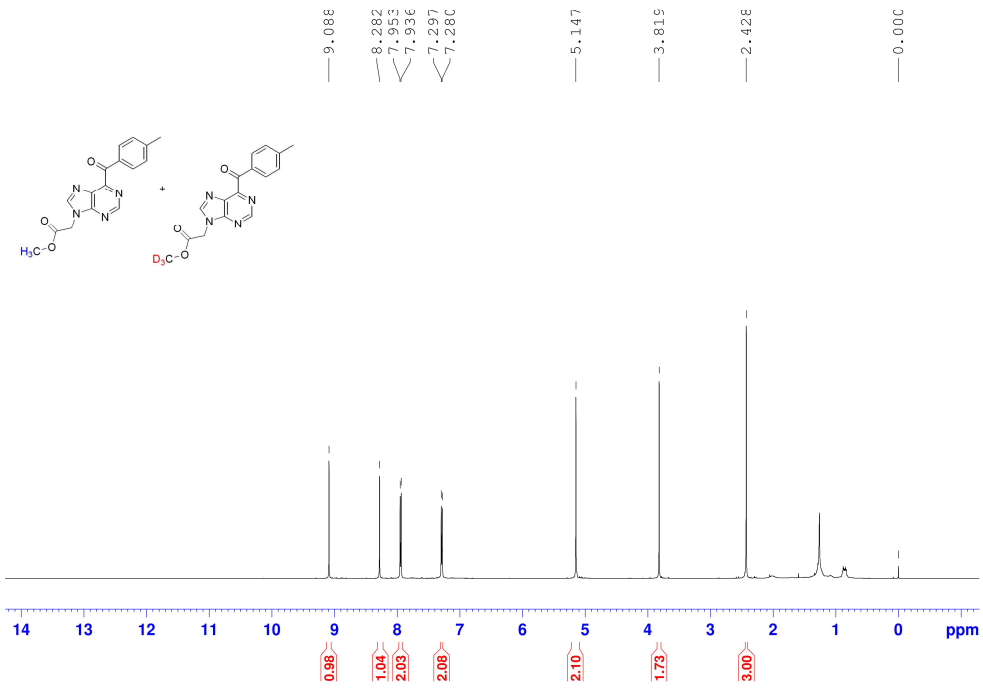
^{1}H NMR (500 MHz, in $CDCl_3$) of 2,2,6,6-tetramethylpiperidin-1-yl-4-methylbenzoate (**2a-T**)



^{13}C NMR (125 MHz, in $CDCl_3$) of 2,2,6,6-tetramethylpiperidin-1-yl-4-methylbenzoate (**2a-T**)

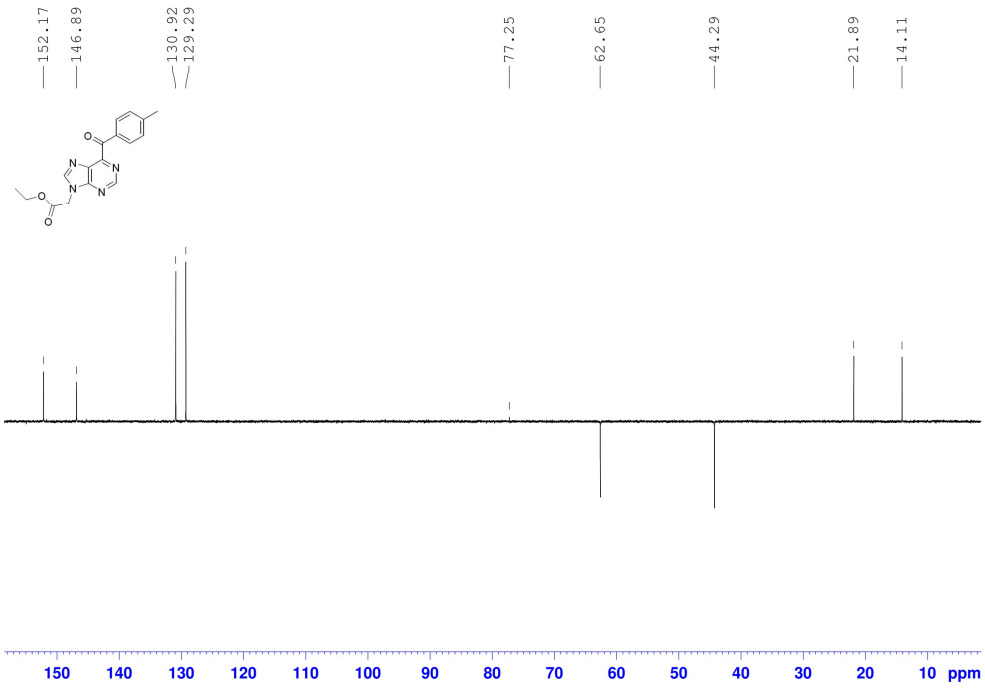


^{1}H NMR (500 MHz, in $CDCl_3$) of the **3b** and **3b-D** mixture in KIE experiment

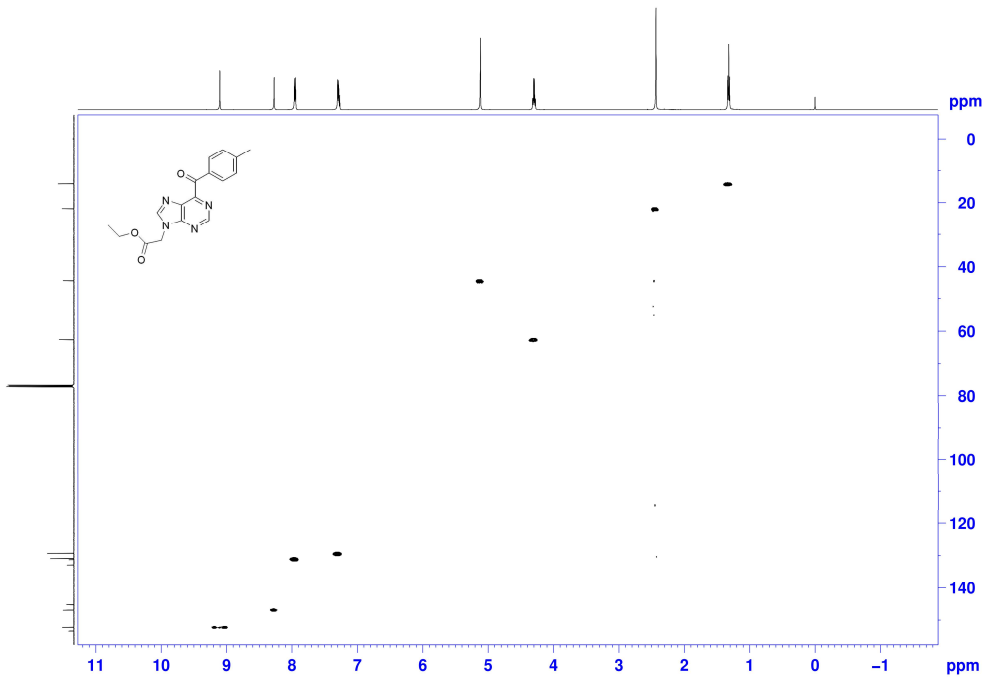


6. Copies of DEPT135, HSQC, HMBC Spectra of Product 3a

^{13}C NMR (dept 135) of ethyl 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) acetate (**3a**)



HSQC of ethyl 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) acetate (**3a**)



HMBC of ethyl 2-(6-(4-methylbenzoyl)-9*H*-purin-9-yl) acetate (**3a**)