Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

An efficient Route to Novel A2a Adenosine Receptor Antagonists, Analogues and Prodrugs

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Content:

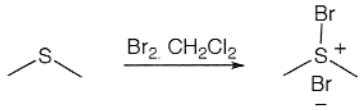
General Methods.

All reactions were carried out under anhydrous, inert atmosphere (nitrogen or argon) with dry, freshly distilled solvents unless otherwise noted. Thin layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates. Preparative thin layer chromatography was carried with Silica Gel GF. Flash chromatography was performed using silica gel 60 (230-400 Mesh). All chemicals were purchased from Sigma Aldrich or Fisher Scientific unless otherwise specified.

Nuclear magnetic resonance (NMR) spectra for all compounds were obtained either on a 300 or a 500 MHz spectrometer. The chemical shifts are reported in δ (ppm) values relative to CHCl3 (δ 7.27 for 1H NMR and δ 77.0 ppm for 13C NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz (Hz).

Mass spectra for all compounds were obtained on a Hewlett Packard 6890 Plus GC with 5973 Mass Selective Detector. The column used was an Agilent HP Ultra 1, 25m x 0.2mm with a 0.11μm film thickness. The electron impact ionization source was run at 70 eV. For compounds containing atoms with characteristic isotopes (i.e. bromine) low resolution mass spectrometry was used to verify presence of isotopes and verify compound identity.

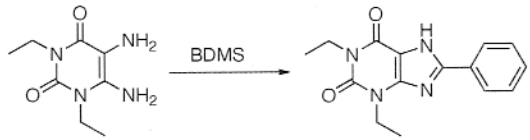
Procedure 1: synthesis of Bromodimethylsulfonium Bromide (BDMS):



Dimethyl sulfide (1.5 g, 25 mmol) was dissolved in freshly distilled dichloromethane (5 mL). A solution of bromine (1.997 g, 25 mmol) in dichloromethane (5 mL) and added into the above solution at 0°C over 5 min. The orange precipitate was collected by vacuum filtration washed with hexane and dried *in vacuo* to yield the title compound (4.3 g, 77%) as a yellow solid. mp 80-83 °C.[1]

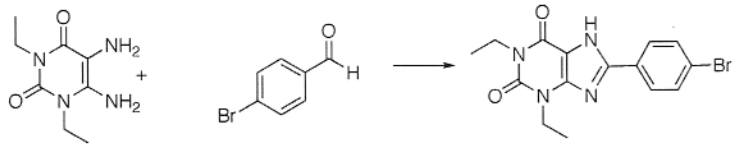
[1] Khan, A.T., Ali, M.A. Goswami, P., Choudhury L.H., *J. Org. Chem.* **2006**, *71*, 8961.

Procedure 2: synthesis of xanthines, 1,3-diethyl-8-phenyl-1*H*-purine-2,6(3*H*,7*H*)-dione :



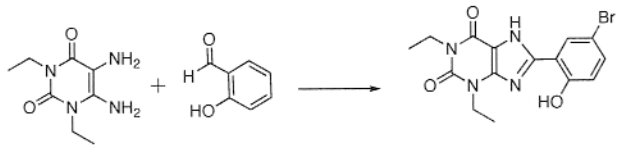
Bromodimethylsulfonium bromide (0.25 mmol) from the previous procedure was added to a solution of benzaldehyde (0.053 g, 0.25 mmol) and 1, 3-diethyl-5,6-aminouracil (**1**) (0.025 g, 0.25 mmol) in freshly distilled acetonitrile (5 mL). The reaction mixture was stirred at 25°C for 4h. The precipitate was collected via filtration, washed with ethyl acetate (25 mL) and dried *in vacuo*. The crude solid was purified by recrystallization from DMSO and water to yield the title compound (0.050 g, 70%) as a white solid. mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.16 (t, J = 7.0Hz, 3H), 1.26 (t, J = 7.0Hz, 3H), 3.97 (q, J = 7.0Hz, 2H), 4.10 (q, J = 7.0Hz, 2H), 7.44-56 (m, 3H), 8.14 (d, J = 8.5Hz, 2H), 13.90 (br, 1H). HRMS (ESI), $C_{15}H_{17}N_4O_2$ m/z $(M+H)^+$: calcd 284.1273, obsd 284.1277

Procedure 3: microwave accelerated coupling of xanthines: 8-(4-bromophenyl)-1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione:



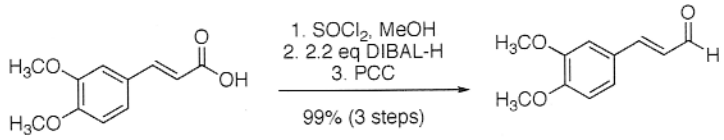
(Bromodimethyl) sulfonium bromide (0.010 g, 0.045 mmol) was added to a mixture of 4-bromobenzaldehyde (0.0466 g, 0.25 mmol), 1,3-diethyl-5,6-diaminouracil (0.4955 g, 0.25 mol) and anhydrous acetonitrile (500 μL) in a 14 x 86 mm (o.d.) glass microwave tube. The tube was capped with a CEM Corp. PL cap, the atmosphere was flushed with argon gas and then the tube was placed in the cavity of a CEM discover® Lab Mate reactor. The solution was subjected to microwave irradiation while stirring, the temperature was brought to 110 °C over 15 min. and then held for 10 min (150 W, 100 psi). The resulting precipitate was filtered, washed with ethyl acetate (5 mL) and methanol (2.5 mL) and then recrystallized from ethyl acetate to yield the title compound (0.065g, 72%) as a yellow solid. mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.13 (t, J = 7.0Hz, 3H), 1.26 (t, J = 7.0Hz, 3H), 3.94 (q, J = 7.0Hz, 2H), 4.08 (q, J = 7.0Hz, 2H), 7.01 (d, J = 8.5Hz, 2H), 8.05 (d, J = 8.5Hz, 2H), 13.89 (br, 1H). HRMS (ESI), $C_{15}H_{16}BrN_4O_2$ m/z $(M+H)^+$: calcd 362.0378, obsd 362.0369.

Procedure 4 : 8-(5-bromo-2-hydroxyphenyl)1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione :



(Bromodimethyl) sulfonium bromide (0.879 g, 4.0 mmol) was added (in two portions) to a mixture of 2-hydroxybenzaldehyde (0.3053 g, 2.5 mmol) and 1,3,-diethyl-5,6-diaminouracil (0.495 g 2.5 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 14 hours. The precipitate formed was collected by vacuum filtration, washed with ethyl acetate and dried *in vacuo*. The crude solid was purified by recrystallization from DMSO and water to yield the title compound (0.66 g, 73%) as a white solid. mp 315-317 °C; TLC (dichloromethane/ methanol = 19:1): R_f 0.30; ^{1}H NMR (500 MHz, d6-DMSO): δ 13.80-14.20 (brs, 1H,), 11.75-12.10 (brs, 1H), 8.29 (d, J = 2.5 Hz, 1H), 7.80 (dd, J = 8.5, 2.5 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 4.08 (q, J = 7.5 Hz, 2H), 3.96 (q, J = 7.5 Hz, 2H), 1.28 (q, J = 7.5 Hz, 3H), 1.15 (q, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, d6-DMSO): δ 156.6, 154.4, 150.7, 150.6, 148.1, 135.1, 129.7, 120.2, 118.0, 115.3, 111.3, 55.6, 39.2, 36.7, 13.9; HRMS (ESI) m/z $C_{15}H_{16}BrN_4O_3$ $(M+H)^+$: calcd 379.0406, obsd 379.0401.

Procedure 5: (E)-3,4-Dimethoxy-cinnimaldehyde:

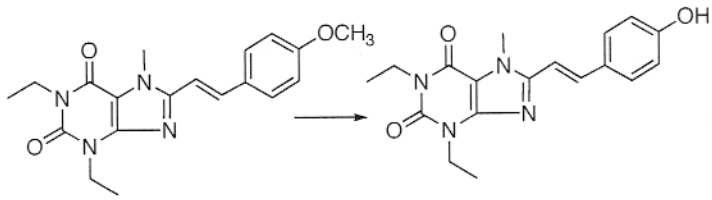


3,4-Dimethoxycinnamic acid (2.96 g, 11.7 mmol) was dissolved in methanol (60 mL). Thionyl Chloride (0.893 mL, 1.05 eq) added dropwise. Mixture refluxed for 30 minutes. triethylamine (1.7 mL) was added to neutralize the evolved hydrochloric acid and the reaction was allowed to reflux for an additional 30 minutes. The solution was then cooled and the solvent was removed *in vacuo*. Purification via flash chromatography provided 3.06 g (98%) of 3,4-Dimethoxy-methylcinnimate as a yellow solid.
3,4-Dimethoxy-methylcinnimate (3.0g , 11.23 mmol) dissolved in dichloromethane (180 mL). The reaction mixture was cooled to -78°C and Diisobutyl aluminum hydride (28 mL, 1M in Hex, 2.5 eq) was added over one hour. Quenched was performed utilizing 1.2 mL of methanol then 1 mL of water at -60°C. The precipitated salts collected, then dissolved in 1% Hydrochloric acid. This solution was extracted with dichloromethane (4 x 200 mL). The organic layers collected from the salt solution washings and the original solution were combined, washed with water (100 mL) and brine (100 mL) and then concentrated *in vacuo* to be used directly in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): 2.2 (s, broad, 1H) 3.99 (s., 3H), 4.0 (s, 3H), 4.38 (d, J = 8.0Hz, 2H) 6.25 (dt, J = 8.0, 2.0Hz, 1H) 6.9 (s, 1H), 7.2 (d, J = 8.0Hz 1H) 7.47 (s, 1H);

The crude reaction mixture was dissolved in dichloromethane (110 mL). The resulting solution was added dropwise to a solution of pyridinium chlorochromate (2.5231 g) in dichloromethane (170 mL). The mixture was stirred overnight (12 h). An additional 20 mol % of PCC was added to the solution and the solution was allowed to stir an additional hour. The solution was filtered through a plug of florosil, concentrated *in vacuo* and purified via flash chromatography to provide 2.037 g (73.4%) of the title compound as a yellow solid as compared to literature characterisation. m.p. 82-83°C ^{1}H NMR (300 MHz, $CDCl_3$,) 9.67 (d, J = 7.8 Hz, CHO), 7.42 (d, J = 15.8 Hz, 1 H), 7.17-6.91 (m, 3 H) 6.62 (dd, J = 15.8, 7.7 Hz, 1H) 3.94-3.93 (s, 6 H); ^{13}C (75 MHz, CDC1,) 193.6, 152.8, 152.5 127.1, 126.7, 123.4, 111.1, 110.1, 109.0, 56.0, 55.9 .[2]

[2] J. Org. Chem, **1990** *55* , 3679

<u>Procedure 6:</u> (E)-1,3-diethyl-8-(4-hydroxystyryl)-7-methyl-1H-purine-2,6(3H,7H)-dione:

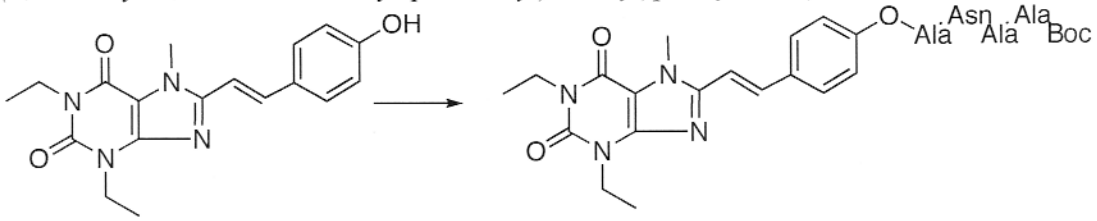


A 1M BBr_3 in CH_2Cl_2 (170 µl, 0.85 mmol) was added to a solution of (E)-1,3-diethyl-8-(4-methoxystyryl)-7-methyl-1H-purine-2,6(3H,7H)-dione[3] (100 mg, 0.28 mmol) in dry CH_2Cl_2 (0.35 mL). The reaction mixture was stirred at room temperature for 3 h and diluted with water (0.3 mL). The formed precipitate collected via vacuum filtration, washed with excess water and dried *in vacuo* to give the title compound as a yellow solid. (90 mg, 95%) mp > 300 °C; TLC (MeOH: CH_2Cl_2 = 1: 9): Rf 0.2 ^{1}H NMR (500 MHz, DMSO-d6): δ 1.12 (t, *J* = 7.5 Hz, 3H), 1.25 (t, *J* = 7.5 Hz, 3H), 3.91 (q, *J* = 7.5 Hz, 2H), 3.99 (s, 3H), 4.06 (q, *J* = 7.5 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 7.11 (d, J = 16.0 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d6): δ 51.1, 69.2, 73.3, 75.6, 144.9, 147.1, 153.6, 164.6, 167.3, 174.8, 185.4, 187.9, 188.3, 191.8, 196.7 HRMS (ESI), m/z $C_{18}H_{21}N_4O_3$ $(M+H)^+$: calcd 340.1535, obsd 340.1549

[3] Synthesized according to EP 0590919.

Procedure 7: (E)-tert-butyl 1-(7-amino-5-(2-(4-(2-1,3 diethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)vinyl)phenoxyamino)propanamido)-3,4,7-trioxoheptan-2-ylamino)-1-oxopropan-2-ylcarbamate (24)

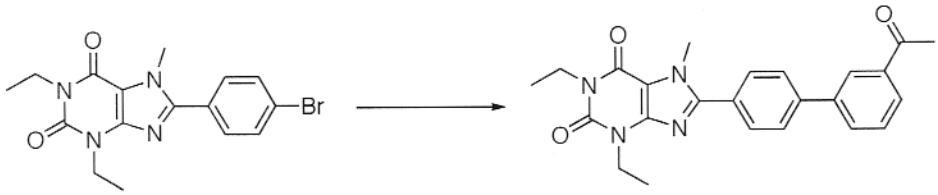
(N-(N-(N-(N-(1,1-dimethylethoxycarbonyl)alanyl)asparaginyl)alanine E-4-(2-(1,3-diethyl-2,6-dioxo-7-methyl-purin-8-yl)ethenyl)phenyl ester)



4-Dimethylaminopyridine (DMAP) (11 mg, 0.088 mmol) was added to a flask containing compound **(22)** (30 mg, 0.088 mmol) in DMF (1.2 mL). The solution was stirred at 25°C for 30 min. The resulting compound (41mg, 0.088mmol) was added to a solution of Boc-Ala-Ala-Asp-Ala[4] (**23**) (41mg, 0.088 mmol) in N-methyl morpholine (23µl, 0.211mmol) and O-(1H-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) (59mg, 0.152mmol) in DMF (1.2 mL) at 0°C. The reaction mixture was stirred in the dark at 25°C for 6h. The reaction was concentrated *in vacuo,* diluted ethyl acetate (20 mL) and the resulting precipitate was collected via vacuum filtration. The filtrate was washed with ethyl acetate and dried *in vacuo* to yield the title compound (44 mg, 65%) as a pale yellow solid. m.p. 208-212°C TLC (MeOH: CH_2Cl_2 = 1: 9): Rf 0.41 ^{1}H NMR (500 MHz, DMSO-d6): δ 1.13 (t, *J* = 7.5Hz, 3H), 1.16-1.21 (m, 6H), 1.26 (t, *J* = 7.5 Hz, 3H), 1.37 (s, 9H), 1.44 (d, J = 6.0Hz, 3H), 2.50 (m, 2H), 3.93 (q, J = 6.0Hz, 2H), 3.98 (m, 1H), 4.04 (s, 3H), 4.07 (q, J = 6.0Hz, 2H), 4.21 (m, 1H), 4.40-4.45 (m, 1H), 4.57(m, 1H), 6.90-6.96 (m, 2H), 7.16 (d, J = 7.0Hz, 2H), 7.34 (s, 1H), 7.36 (d, J = 15.5Hz, 1H), 7.67 (d, J = 15.5Hz, 1H), 7.85 (d, J = 6.5Hz, 1H), 7.95-8.01 (m, 1H), 8.08-8.13(m, 1H), 8.25 (dd, J = 25.5, 6.5Hz, 1H) ^{13}C NMR (75 MHz, DMSO-d6): δ 14.2, 17.5, 18.9, 19.1, 36.5, 37.6, 38.7, 42.4, 42.7, 49.1, 50.2, 50.5, 79.0, 108.4, 114.0, 123.0, 129.7, 134.3, 136.5, 148.4, 150.6, 150.9, 152.0, 155.0, 156.0, 171.9, 172.1, 172.3, 172.9, 173.7. HRMS (ESI), m/z $C_{36}H_{50}N_9O_{10}$ $(M+H)^+$: calcd 767.3602, obsd 767.3612.

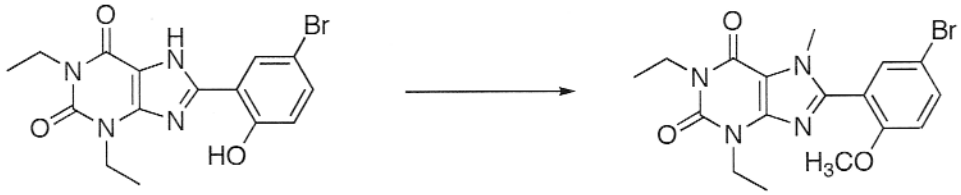
[4] Synthesized according to Rella, M. R., Williard, P. G. *J. Org. Chem.* **2007**, 72, 525.

Procedure 8: 8-(3'-acetylbiphenyl-4-yl)-1,3-diethyl-1H-purine-2,6(3H,7H)-dione



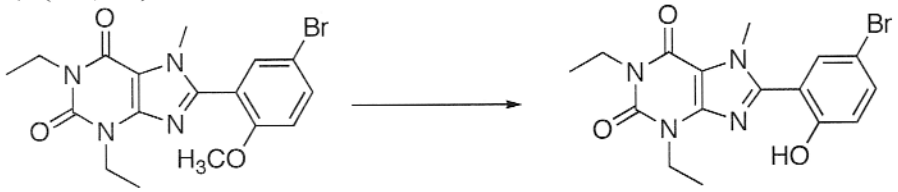
$Pd(PPh_3)_4$ (0.0017 g, 3mol%) was added to a degassed solution of 8-(4-bromophenyl)-1,3-diethyl-1H-purine-2,6(3H,7H)-dione (0.020 g, 0.053 mmol), 3-acetylphenylboronic acid (0.0095 g, 1.1 equiv) and barium hydroxide octahydrate (0.025 g, 1.5 equiv) in dimethoxyethane (DME) (2 mL) and water (0.5 mL) in a CEM microwave tube. The resulting solution was exposed to microwave irradiation (300W) for 10 minutes at 100 °C and cooled to 25 °C. The reaction mixture was diluted with dichloromethane (10 mL) and filtered through a plug of silica gel. The filtrate was diluted with water (10 mL) and extracted with dichloromethane (3x, 10 mL). The combined extracts were washed with brine (20 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by preparative thin layer chromatography (hexanes/ ethyl acetate = 3:2) to afford the title compound (0.016 g, 73%) as a white solid. Mp = 182-184 °C; TLC (hexane/ ethyl acetate = 1:1): R_f 0.36; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22-8.25 (m, 1H), 7.97-8.01 (m, 1H), 7.76-7.87 (m, 5H), 7.60 (t, J = 7.5 Hz, 1H), 4.24 (q, J = 7.0Hz, 2H), 4.13 (q, J = 7.0Hz, 2H), 4.12 (s, 3H), 2.68 (s, 3H), 1.40 (t, J = 7.0Hz, 3H), 1.29 (t, J = 7.0Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.90155.6, 151.7, 150.9, 148.1, 142.2, 140.6, 138.0, 131.8, 129.9, 129.5, 128.13, 128.09, 127.8, 127.0, 109.1, 77.4, 38.6, 36.5, 34.1, 26.9, 13.6, 13.5; HRMS (ESI) m/z $C_{24}H_{25}N_4O_3$ $(M+H)^+$: calcd 417.1927, obsd 417.1919.

Procedure 9: 8-(5-bromo-2-methoxyphenyl)-1,3-diethyl-7-methyl-1H-purine-2,6(3H,7H)-dione



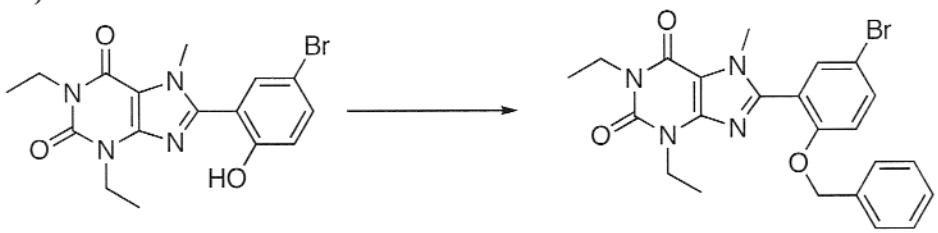
Methyl iodide (36.5 μL, 3 equiv) was added to a mixture of 8-(5-bromo-2-hydroxyphenyl)-1,3-diethyl-1H-purine-2,6(3*H*,7*H*)-dione (0.074 g, 0.194 mmol) and potassium carbonate (0.085 g, 3 equiv) in dimethylformamide (4 mL) at 25 °C (Ar atmosphere) then heated to 60°C overnight. The resulting solution was diluted with water (20 mL) and acidified to pH ~2 by the slow addition of 5% HCl. The aqueous layer was extracted with chloroform (3x 20 mL), dried over $MgSO_4$ and concentrated in vacuo to afford the title compound (0.065 g, 82%) as a yellow solid. Mp = 159-161 °C; TLC (Hexane/ ethyl acetate = 1:1): R_f 0.28; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.63 (m, 2H), 6.92 (d, J = 8.5 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6, 155.4, 150.8, 148.7, 147.8, 134.96, 134.76, 119.7, 113.4, 113.1, 108.8, 55.1, 38.6, 36.5, 33.3, 13.6, 13.4; HRMS (ESI) m/z $C_{17}H_{20}BrN_4O_3$ $(M+H)^+$: calcd 407.0719, obsd 407.0714.

Procedure 10: 8-(5-bromo-2-hydroxyphenyl)-1,3-diethyl-7-methyl-1H-purine-2,6(3H,7H)-dione



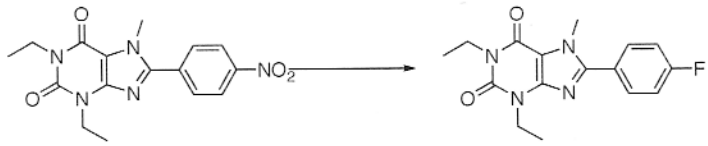
Boron tribromide (32 μL, 3 equiv) was added to a solution of 8-(5-bromo-2-methoxyphenyl)-1,3-diethyl-7-methyl-1H-purine-2,6(3H,7H)-dione (0.046g, 0.113mmol) in dichloromethane (2 mL) at 25°C and stirred for 2h. The resulting solution was diluted with water (10 mL) and extracted with dichloromethane (3x 10mL). The combined extract were washed with brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo to afford the title compound (0.0417g, 94%) as a yellow solid. Mp = 176-177 °C; TLC neutralized with triethylamine (ethyl acetate): R_f 0.22; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.8-11.8 (brs, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 9.0, 2.0 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 4.27 (s, 3H), 4.18 (q, J = 7.0 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2, 155.1, 150.5, 147.9, 145.7, 135.2, 129.4, 120.3, 113.9, 111.2, 108.2, 39.0, 36.8, 35.2, 13.5, 13.4; HRMS (ESI) m/z $C_{16}H_{18}BrN_4O_3$ $(M+H)^+$: calcd 393.0562, obsd 393.0548.

Procedure 11: 8-(2-(benzyloxy)-5-bromophenyl)-1,3-diethyl-7-methyl-1H-purine-2,6(3H,7H)-dione



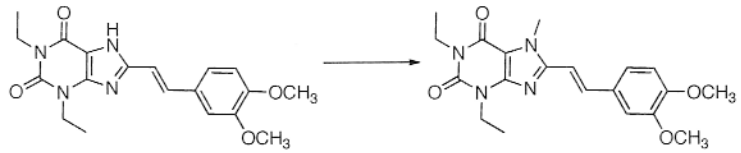
Benzyl bromide (7.7 μL, 1.5 equiv) was added to a solution of 8-(5-bromo-2-hydroxyphenyl)-1,3-diethyl-7-methyl-1H-purine-2,6(3H,7H)-dione (0.017g, 0.0432mmol) and potassium carbonate (0.018g, 3 equiv) in dimethylformamide (2 mL) at 25°C. The resulting solution was heated to 70°C for 3h and cooled to 25°C. The solution was diluted with water (10 mL) and brought to pH ~ 2 by the slow addition of 5% HCl. The aqueous layer was extracted with dichloromethane (3x 10mL) and the combined extracts washed with brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by preparative thin layer chromatography (hexanes/ ethyl acetate = 3:1) to afford the title compound (0.0194g, 93%) as a yellow solid. Mp = 56-57 °C; TLC (hexane/ ethyl acetate = 1:1): R_f 0.48; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, J = 2.0Hz, 1H), 7.55 (dd, J = 8.5, 2.0 Hz, 1H), 7.23-7.39 (m, 5H), 6.96 (d, J = 8.5 Hz, 1H), 5.11 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H), 4.10 (q, J = 7.0 Hz, 1H), 3.80 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 155.4, 150.9, 148.7, 147.9, 135.7, 135.0, 134.9, 128.9, 128.6, 127.3, 120.4, 115.0, 113.8, 108.8, 71.4, 38.7, 36.6, 33.5, 13.7, 13.5; HRMS (ESI) m/z $C_{23}H_{24}BrN_4O_3$ $(M+H)^+$: calcd 483.1032, obsd 483.1026.

Procedure 12: 1,3-diethyl-8-(4-fluorophenyl)-7-methyl-1H-purine-2,6(3H,7H)-dione



Anhydrous TBAF (1M in DMSO, 3 equiv, 262 μL) was added to a solution of 1,3-diethyl-7-methyl-8-(4-nitrophenyl)-1H-purine-2,6(3H,7H)-dione (0.030g, 0.0873mmol) in DMSO (0.5 mL) and exposed to microwave irradiation (300W) at 180 °C for 10 minutes and cooled to 25 °C. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3x 10 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by preparative thin layer chromatography (hexanes/ ethyl acetate = 3:1) to afford the title compound (0.0031g, 11%) as a white solid and recovered starting material (0.0189g, 63%). Mp = 162-165 °C; TLC (hexane/ ethyl acetate = 4:1): R_f 0.27; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65-7.71 (m, 2H), 7.23 (t, J = 8.5 Hz, 2H), 4.21 (q, J = 7.0 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 4.05 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 163.0 155.5, 151.2, 150.9, 147.9, 131.5, 131.4, 124.8, 116.4, 116.2, 108.9, 38.6, 36.6, 33.9, 13.6, 13.5; HRMS (ESI) m/z $C_{16}H_{18}FN_4O_2$ $(M+H)^+$: calcd 317.1414, obsd 317.1402.

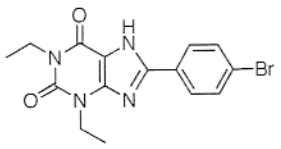
Procedure 13: (E)-8-[2-(3,4-Dimethoxyphenyl) vinyl]-1,3-diethyl-7-methyl-3, 7 dihydropurine-2,6-dione (KW 6002). [5]



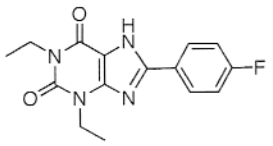
K_2CO_3 (1.35g, 9.43mmol) was added to a solution of compound 3-5 (2.02g, 5.45mmol) in dry DMF (27mL). Iodomethane (0.68mL, 10.77mmol) was added and the reaction mixture was stirred at room temperature for 1h. The formed precipitate was filtered off. The filtrate was diluted with water (30 mL) and the resulting mixture was extracted with chloroform (3°—100 mL). The organic extracts were washed with water (100 mL) and brine (100 mL), dried with MgSO4 and evaporated in vacuo. The residue was purified via flash chromatography to give the title compound as a yellow solid. (2.0g, 95%) mp=191-195 °C; TLC (hexanes: ethyl acetate = 3: 2): Rf 0.22 1H NMR (500 MHz, CDCl3): 1.23 (t, J = 7.0 Hz, 3H), 1.36 (t, J = 7.0 Hz, 3H), 3.90 (s, 3H,), 3.93 (s, 3H), 4.03 (s, 3H), 4.07 (q, J = 7.0 Hz, 2H), 4.18 (q, J = 7.0 Hz, 2H), 6.74 (d, J = 15.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 7.15 (dd, J = 8.5, 2.0 Hz, 1H), 7.70 (d, J = 15.5 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$): R 13.3, 13.4, 31.5, 36.3, 38.4, 55.9, 56.0, 108.0, 109.3, 109.5, 111.2, 121.2, 128.6, 138.1, 148.2, 149.2, 150.2, 150.4, 150.7, 155.0 HRMS (ESI), m/z (M+H)+: calcd 384.1798, obsd 384.1789. Elemental Analysis: (C20H24N4O4) calcd (%): C, 62.48; H, 6.29; N, 14.57; found (%): C, 62.45; H, 6.39; N, 14.55

[5] EP 0590919.

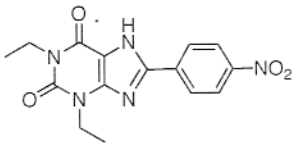
8-(4-bromophenyl)-1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione:
Procedure 2: yellow solid. (72 mg, 79%) mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.13 (t, J = 7.0Hz, 3H), 1.26 (t, J = 7.0Hz, 3H), 3.94 (q, J = 7.0Hz, 2H), 4.08 (q, J = 7.0Hz, 2H), 7.01 (d, J = 8.5Hz, 2H), 8.05 (d, J = 8.5Hz, 2H), 13.89 (br, 1H). HRMS (ESI), m/z $(M+H)^+$: calcd 362.0378, obsd 362.0369.



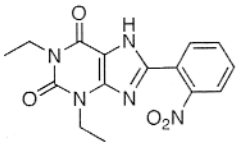
1,3-diethyl-8-(4-fluorophenyl)-1*H*-purine-2,6(3*H*,7*H*)-dione:
Procedure 2: white solid. (53 mg, 70%) mp > 300 °C ;^{1}H NMR (500 MHz, DMSO-d6): δ 1.14 (t, J = 7.0Hz, 3H), 1.27 (t, J = 7.0Hz, 3H), 3.95 (q, J = 7.0Hz, 2H), 4.08 (q, J = 7.0Hz, 2H), 7.37 (m, 2H), 8.18 (m, 2H), 13.85 (br, 1H). HRMS (ESI), m/z $(M+H)^+$: calcd 302.1179, obsd 302.1159.



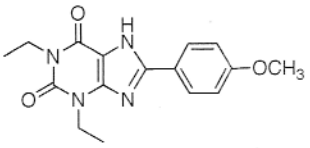
1,3-diethyl-8-(4-nitrophenyl)-1*H*-purine-2,6(3*H*,7*H*)-dione:
Procedure 2: yellow solid. (57 mg, 79%) mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.15 (t, J = 7Hz, 3H), 1.29 (t, J = 7Hz, 3H), 3.96 (q, J = 7.5Hz, 2H), 4.11 (q, J = 7Hz, 2H), 8.37 (s, 4H) HRMS (ESI), m/z $(M+H)^+$: calcd 329.1124, obsd 329.1124



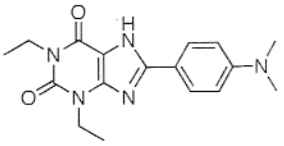
1,3-diethyl-8-(2-nitrophenyl)-1*H*-purine-2,6(3*H*,7*H*)-dione :
Procedure 2: yellow solid. (59 mg, 72%) mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.15 (t, J = 7.0Hz, 3H), 1.21 (t, J = 7.0Hz, 3H), 3.95 (q, J = 7.5Hz, 2H), 3.99 (q, J = 7.5Hz, 2H), 7.74-7.76 (m, 1H), 7.83-7.86 (m, 1H), 7.93 (d, J = 7.5Hz, 1H), 8.03 (d, J = 7.5Hz, 1H) HRMS (ESI), m/z $(M+H)^+$: calcd 329.1124, obsd 329.1111.



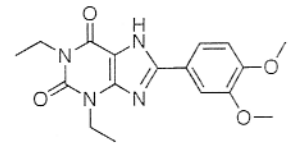
1,3-diethyl-8-(4-methoxyphenyl)-1*H*-purine-2,6(3*H*,7*H*)-dione:
Procedure 2: yellow solid. (56 mg, 71%) mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.14 (t, J = 7.0Hz, 3H), 1.27 (t, J = 7.0Hz, 3H), 3.82 (s, 3H), 3.95 (q, J = 7.5Hz, 2H), 4.09 (q, J = 7.5Hz, 2H), 7.06 (d, J = 9.0Hz, 2H), 8.08 (d, J = 9Hz, 2H), 13.61 (br, 1H) HRMS (ESI), m/z $(M+H)^+$: calcd 314.1379, obsd 314.1392.



8-(4-(dimethylamino) phenyl)-1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione:
Procedure 2: yellow solid (53 mg, 66%). mp > 300 °C ^{1}H NMR (500 MHz, DMSO-d6): δ 1.14 (t, J = 7.0Hz, 3H), 1.27 (t, J = 7.0Hz, 3H),2.98 (s, 3H), 3.33 (s, 3H), 3.94 (q, J = 7.5Hz, 2H), 4.08 (q, J = 7.5Hz, 2H), 6.77 (d, J = 9.5Hz, 2H), 7.96 (d, J = 9.5Hz, 2H), 13.35 (br, 1H) HRMS (ESI), m/z $(M+H)^+$: calcd 327.1695, obsd 327.1678.

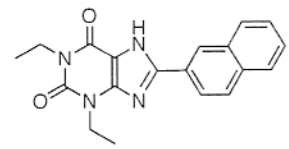


8-(3,4-dimethoxyphenyl)-1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione:



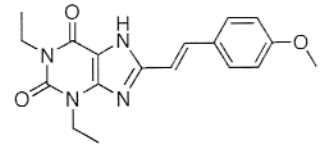
Procedure 2: Yellow solid (54mg, 63%). mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.14 (t, J = 7.5Hz, 3H), 1.27 (t, J = 7.5Hz, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 3.95 (q, J = 7.5Hz, 2H), 4.09 (q, J = 7.5Hz, 2H), 7.08 (d, J = 8.0Hz, 1H), 7.71-7.74 (m, 2H) HRMS (ESI), m/z $(M+H)^+$: calcd 344.1485, obsd 344.1475.

1,3-diethyl-8-(naphthalen-2-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione:



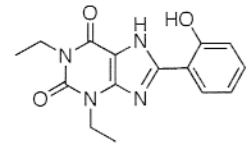
Procedure 2: yellow solid (61mg, 74%). mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.16 (t, J = 7.5Hz, 3H), 1.31 (t, J = 7.5Hz, 3H), 3.97 (q, J = 7.0Hz, 2H), 4.14 (q, J = 7.0Hz, 2H), 7.08 (d, J = 8.0Hz, 1H), 7.58-7.61 (m, 2H), 7.96-7.99 (m, 1H), 8.01-8.06 (m, 2H), 8.25 (dd, J = 10.0, 2.0Hz, 1H), 8.73 (s, 1H), 14.01 (br, 1H) HRMS (ESI), m/z $(M+H)^+$: calcd 334.1430, obsd 334.1449.

(E)-1,3-diethyl-8-(4-methoxystyryl)-1*H*-purine-2,6(3*H*,7*H*)-dione:



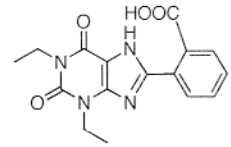
Procedure 2: yellow solid (54mg, 63%). mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.13 (t, J = 7.5Hz, 3H), 1.25 (t, J = 7.5Hz, 3H), 3.79 (s, 1H), 3.93 (q, J = 7.0Hz, 2H), 4.06 (q, J = 7.0Hz, 2H), 6.89 (d, J = 17.0Hz, 1H), 6.98 (d, J = 9.0Hz, 1H), 7.56-7.62 (m, 2H), 13.46 (br, 1H) HRMS (ESI), m/z $(M+H)^+$: calcd 340.1535, obsd 340.1521.

1,3-diethyl-8-(2-hydroxyphenyl)-1*H*-purine-2,6(3*H*,7*H*)-dione:



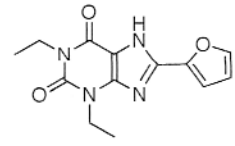
Procedure 2: yellow solid (50mg, 66%). mp > 300 °C ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.14 (t, J = 7.0Hz, 3H), 1.27 (t, J = 7.0Hz, 3H), 3.95 (q, J = 7.0Hz, 2H), 4.08 (q, J = 7.0Hz, 2H), 6.62-6.98 (m, 2H), 7.30-7.33(m, 1H), 8.06 (d, J = 7.5Hz, 1H). HRMS (ESI), m/z $(M+H)^+$: calcd 300.1222, obsd 300.1220.

2-(1,3-diethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)benzoic acid:



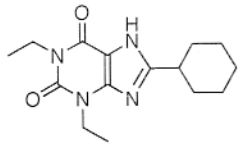
Procedure 2: yellow solid (56mg, 68%). mp > 300 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ 1.11 (t, J=6.8Hz, 3H), 1.24 (t, J=7.2 , 3H), 3.92 (q, J=6.8 , 2H), 4.05 (q, J=6.8, 2H), 7.46-7.57 (m, 2H), 7.90 (d, J=7.6, 1H), 8.02 (d, J=7.2, 1H) HRMS (ESI), m/z $(M+H)^+$: calcd 328.1172, obsd 328.1188.

1,3-diethyl-8-(furan-2-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione:



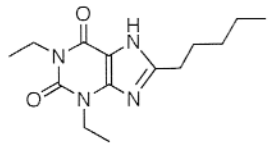
Procedure 2: white solid (41mg, 60%). mp > 300 °C ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (t, J = 7.0Hz, 3H), 1.40 (t , J = 7.0Hz, 3H), 4.18 (q, J = 7.0Hz, 2H), 4.26 (q, J = 7.0Hz, 2H), 6.59-6.60 (m, 1H), 7.24-7.26 (m, 1H), 7.58-7.59 (m, 1H), 11.58 (br, 1H) HRMS (ESI), m/z $(M+H)^+$: calcd 274.1066, obsd 274.1085.

8-cyclohexyl-1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione:



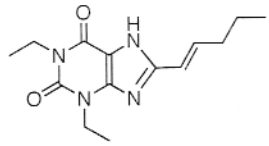
Procedure 2: white solid (49mg, 68%).mp > 300 ºC ; ^{1}H NMR (500 MHz, DMSO-d6): δ 1.10 (t, J = 7.0Hz, 3H), 1.20 (t, J = 7.0Hz, 3H), 1.27-1.36 (m, 2H), 1.50-1.58 (m, 2H), 1.62-1.68 (m, 2H), 1.72-1.78 (m, 2H), 1.86-1.90 (m, 2H), 2.69-2.75 (m, 1H), 3.90 (q, J = 7.0Hz, 2H),3.99 (q, J = 7.0Hz, 2H), 13.05 (br, 1H)HRMS (ESI), m/z $(M+H)^+$: calcd 290.1740, obsd 290.1755.

1,3-diethyl-8-pentyl-1*H*-purine-2,6(3*H*,7*H*)-dione:



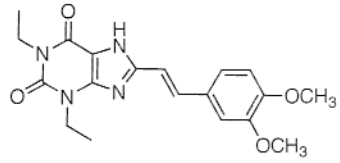
Procedure 2: white solid (47mg, 68%).mp > 300 ºC ; ^{1}H NMR (500 MHz, DMSO-d6): δ 0.85 (t, J = 7.0Hz, 3H), 1.10 (t, J = 7.5Hz, 3H), 1.20 (t, J = 7.0Hz, 3H), 1.21-1.31 (m, 4H), 1.64-1.70 (m, 2H), 2.65 (t, J = 7.5Hz, 2H), 3.90 (q, J = 7.0Hz, 2H), 4.00 (q, J = 7.0Hz, 2H) HRMS (ESI), m/z $(M+H)^+$: calcd 278.1743, obsd 278.1744.

(E)-1,3-diethyl-8-(pent-1-enyl)-1*H*-purine-2,6(3*H*,7*H*)-dione:



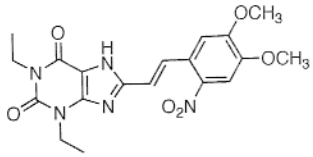
Procedure 2: white solid (48mg, 70%). mp > 300 ºC ; ^{1}H NMR (500 MHz, DMSO-d6): δ 0.91 (t, J = 7Hz, 3H), 1.11 (t, J = 7.5Hz, 3H), 1.21 (t, J = 7.0Hz, 3H), 1.40-1.52 (m, 2H), 1.17-1.24 (m, 2H), 3.91 (q, J = 7.0Hz, 2H), 4.01 (q, J = 7.0Hz, 2H), 6.28 (d, J = 16.0Hz, 1H), 6.76-6.87 (m, 1H) HRMS (ESI), m/z $(M+H)^+$: calcd 276.1586, obsd 276.1602.

(E)-8-(3-4,-dimethoxystyryl)-1,3-diethyl-*1H*-purine-2,6(*3H,7H*)-dione:



Procedure 2: yellow solid compared to literature characterisation values (3.27 mg, 58%) . m.p. 260-262°C [6]

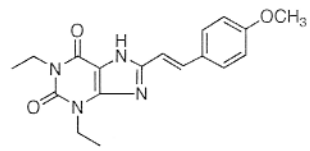
(E)-8-[2-(4, 5-Dimethoxy-2-nitro-phenyl) vinyl]-1, 3-diethyl-3, 7-dihydropurine-2, 6-Dione:



Procedure 2: Yellow solid. (3.39g, 60%) mp=268-269 °C; TLC (MeOH: CH_2Cl_2 = 05:9.5): Rf 0.63 ^{1}H NMR (500 MHz, $CDCl_3$):): δ 1.12 (t, J = 7.0Hz, 3H), 1.28 (t, J = 7.0Hz, 3H), 3.96 (q, J = 7.0Hz, 2H), 4.02 (d, 6H), 4.08 (q, J = 7.0Hz, 2H) 6.6-6.56 (q, 1H). 7.02 (s, 1H) 7.68 (s, 1H), 8.17-8.14 (d, 1H), 9.7 (d, 1H). δ ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.4, 13.5, 36.9, 39.0, 55.8, 56.0, 107.3, 109.1, 111.2, 113.4, 121.2, 128.6, 136.8, 149.3, 149.6, 150.4, 150.5, 151.7, 155.6. HRMS (ESI), m/z (M+H)+: calcd 370.1641, obsd 370.1647.

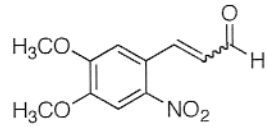
[6] EP 0590919.

(*E*)-8-[2-(4-Dimethoxyphenyl) vinyl]-1, 3-diethyl-3, 7-dihydropurine-2, 6-Dione:



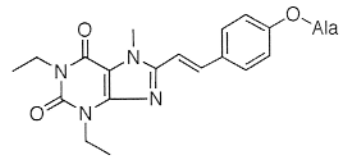
Procedure 2: yellow solid (189mg, 62%).mp=244-246°C ; TLC (MeOH: CH_2Cl_2 = 0.5:9.5): Rf 0.43 1H NMR (300 MHz, DMSO-d6): δ 1.17 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 3.84 (s, 3H), 3.97 (q, J = 7.2 Hz, 2H), 4.10 (q, J = 6.8 Hz, 2H), 5.79(s, 1H), 6.94 (d, *J* = 16.2 Hz, 1H), 7.03(d, J = 8.9Hz, 2H), 7.61 (d, *J* = 8.9Hz, 2H), 7.65 (d, *J* = 16.2 Hz, 1H) ^{13}C NMR (75 MHz, DMSO-d6): δ 14.1, 36.5, 38.9, 39.6, 56.1, 107.9, 114.2, 115.3, 128.9, 129.5, 128.6, 135.8, 148.9, 149.6, 150.9, 151.1, 154.5, 161.0.
HRMS (ESI), m/z $(M+H)^+$: calcd 340.1535, obsd 340.1551.

4,5-Dimethoxy-2-nitro-cinnamaldeyde [7]



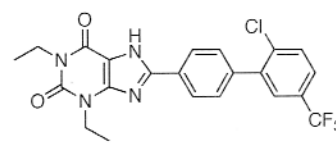
Procedure 5 yellow solid (2.4 mg, 75%). mp. 103-105 •C ^{1}H NMR (500 MHz, $CDCl_3$): 9.78-9.72 (d, 1H) 8.17-8.14 (d, 1H), 7.68 (s, 1H), 7.02 (s, 1H) 6.6-6.56 (q, 1H) 4.01 (d, 6H).

(E)-4-(2-(1,3-diethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)vinyl)phenyl 2-aminoproponate, *(Alanine E-4-(2-(1,3-diethyl-2,6-dioxo-7-methylpurin-8-yl)ethenyl)phenyl ester).*



Procedure 7: white solid (128 mg, 80% two steps). TLC (MeOH: CH_2Cl_2 = 1: 9): Rf 0.41 mp=277-281°C ^{1}H NMR (500 MHz, DMSO-d6): δ 1.13 (t, *J* = 7.0Hz, 3H), 1.26 (t, *J* = 7.5 Hz, 3H), 1.58 (d, J = 6.0Hz, 3H), 2.50 (m, 2H), 3.92 (q, J = 6.0Hz, 2H), 4.05 (s, 3H), 4.07 (q, J = 6.0Hz, 2H), 4.21 (m, 1H), 4.44 (m, 1H), 7.26 (d, J = 8.5Hz, 2H), 7.39 (d, J = 15.5Hz, 1H), 7.69 (d, J = 16.0Hz, 1H), 7.93 (d, J = 9.0Hz, 2H), 8.48 (br, 2H) ^{13}C NMR (75 MHz, DMSO-d6): δ 14.42, 17.02, 32.88, 38.16, 40.31, 110.24, 114.45, 123.72, 130.69, 136.58, 138.65, 150.14, 152.62, 152.93, 153.04, 156.98, 170.67
HRMS (ESI), m/z $(M+H)^+$: calcd 411.1907, obsd 411.1922.

8-(2'-chloro-5'-(trifluoromethyl)biphenyl-4-yl)-1,3-diethyl-1H-purine-2,6(3H,7H)- dione



Procedure 8: white solid (0.0204g, 81%) M.p. = 195-197 °C; TLC (Hexane/ ethyl acetate = 4:1): R_f 0.37; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 2H), 7.57-7.67 (m, 5H), 4.24 (q, J = 7.0 Hz, 2H), 4.13 (s, 3H), 4.12 (q, J = 7.0 Hz, 2 Hz), 1.40 (t, J = 7.0 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 151.5, 150.9, 148.0, 140.3, 140.1, 136.5, 130.9, 130.1, 129.9, 129.6, 129.3, 128.1-128.6 (q, *J*=62.5 Hz, 1C), 125.9-126.1 (q, *J*=25 Hz, 1C), 124.8, 122.7, 109.1, 38.6, 36.6, 34.1, 13.6, 13.5; HRMS (ESI) m/z $C_{23}H_{21}N_4O_2ClF_3$ $(M+H)^+$: calcd 477.1305, obsd 477.1313.

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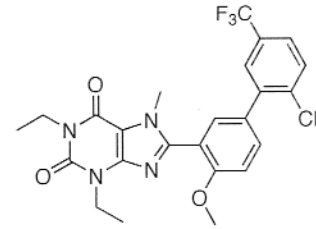
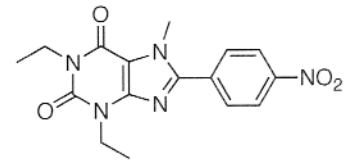
[7] USP 6084120

8-(2'-chloro-4-methoxy-5'-(trifluoromethyl)biphenyl-3-yl)-1,3-diethyl-7-methyl-1H-purine-2,6(3H,7H)-dione



Procedure 8: white solid.(0.015 g, 78%) Mp = 119-120 °C; TLC (hexane/ ethyl acetate = 1:1): R_f 0.32; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.65 (m, 5H), 7.12 (d, J = 8.5 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.12 (q, J = 7.0 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 1.36 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 155.7, 151.0, 149.8, 148.1, 140.0, 136.7, 133.5, 133.3, 131.2, 130.9, 129.9, 129.7, 128.4-128.6 (q, *J*= 25.0 Hz, 1C), 126.6-126.15 (q, *J*=56.25 Hz, 1C), 118.1, 111.4, 109.0, 56.1, 38.8, 36.7, 33.5, 13.8, 13.6; HRMS (ESI) m/z $C_{24}H_{23}ClF_3N_4O_3$ $(M+H)^+$: calcd 507.1411, obsd 507.1410.

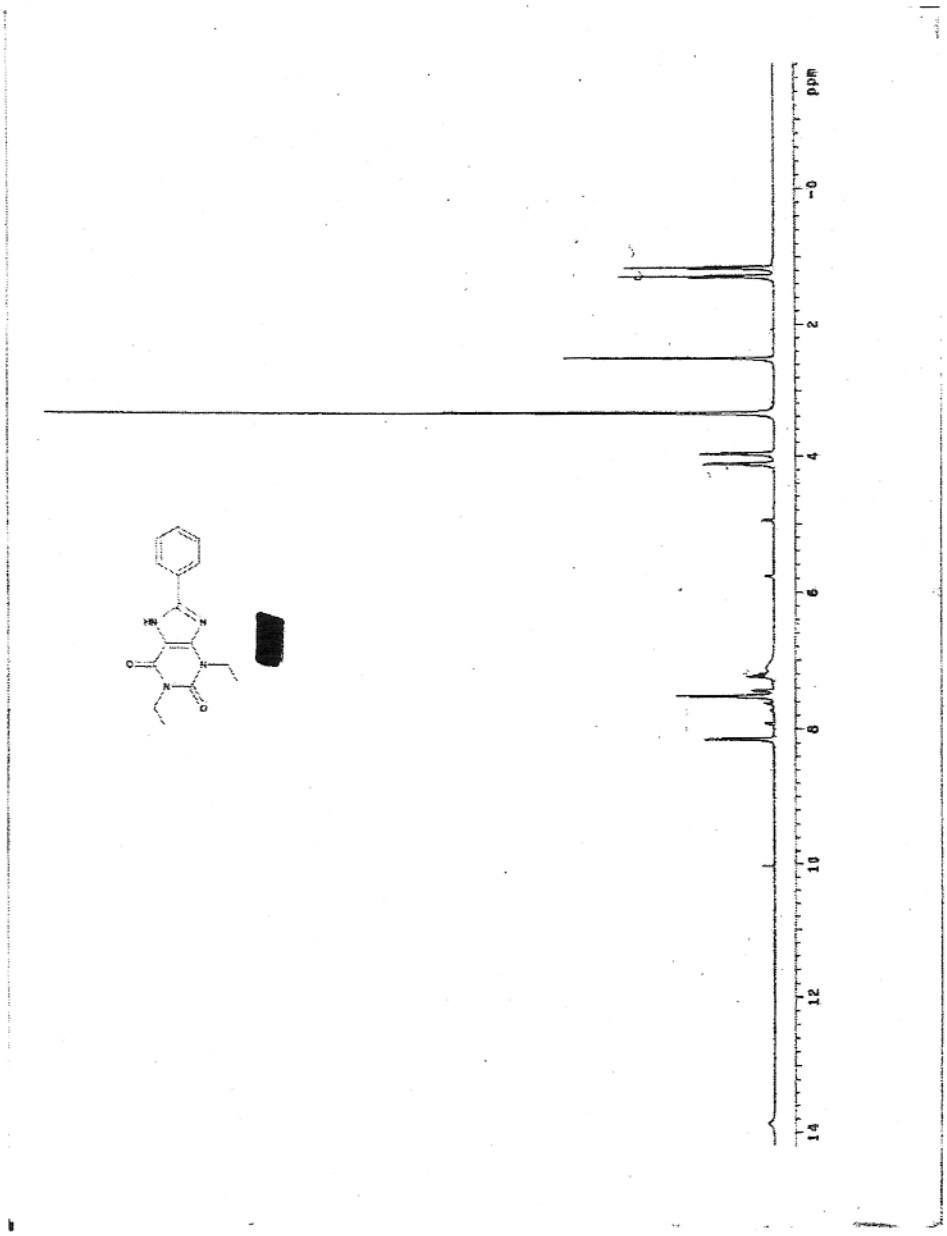
1,3-diethyl-7-methyl-8-(4-nitrophenyl)-1H-purine-2,6(3H,7H)-dione



Procedure 10: white solid (0.071g, 99%). Mp = 222-224 °C; TLC (hexane/ ethyl acetate = 4:1): R_f 0.25; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, J = 9.0 Hz, 2H), 7.94 (d, J = 9.0 Hz, 2H), 4.22 (q, J = 7.0 Hz, 2H), 4.15 (s, 3H), 4.11 (q, J = 7.0 Hz, 2H), 1.38 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 150.6, 149.2, 148.5, 147.8, 134.6, 130.1, 124.1, 109.6, 38.6, 36.6, 34.1, 13.5, 13.3; HRMS (ESI) m/z $C_{16}H_{18}N_5O_4$ $(M+H)^+$: calcd 344.1359, obsd344.1364.

Scanned Nuclear Magnetic Resonance Spectra

[redacted]



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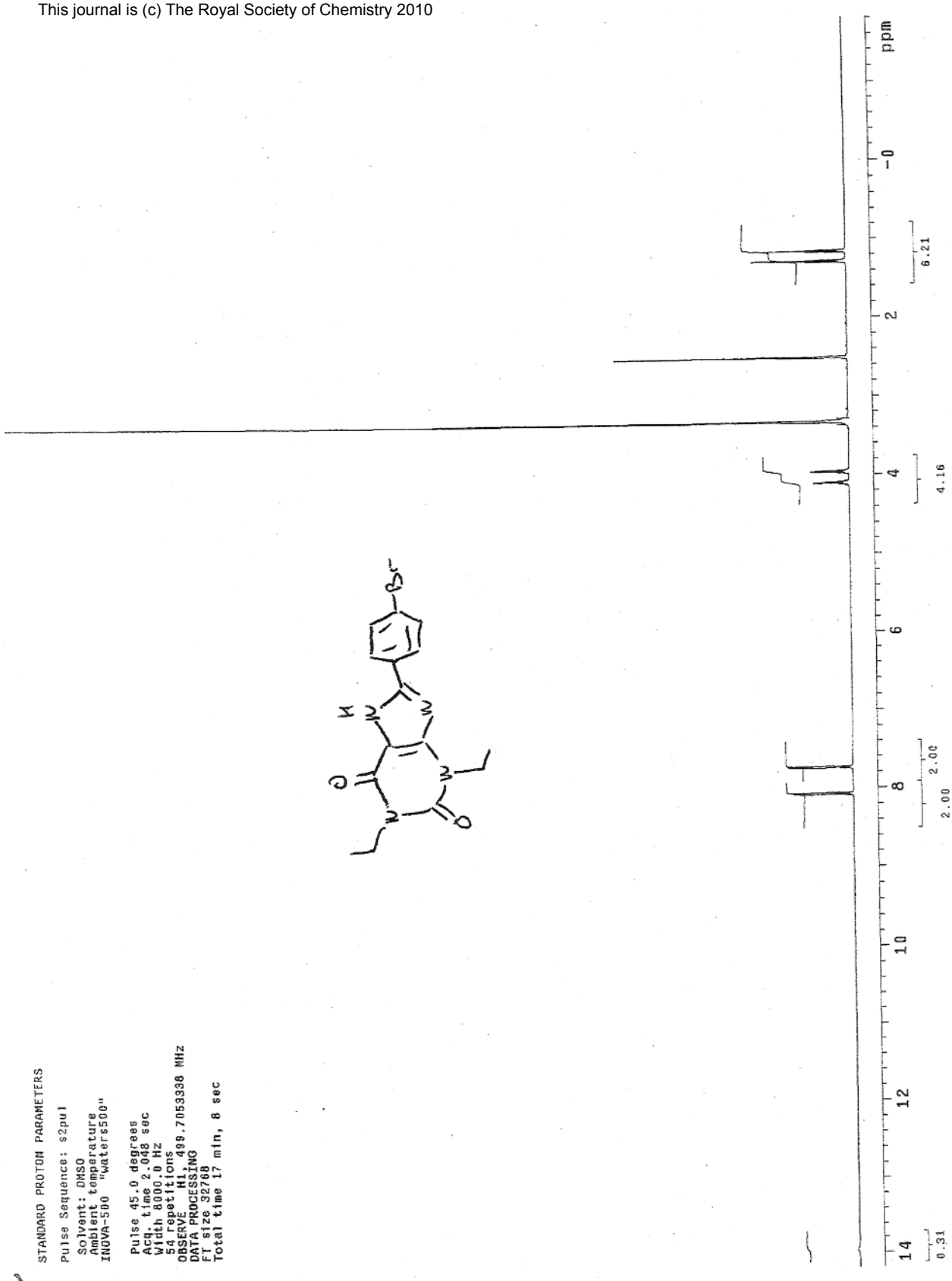
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Solvent: DMSO
Ambient temperature
INOVA-500 "waters500"
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
54 repetitions
OBSERVE H1, 499.7053338 MHz
DATA PROCESSING
FT size 32768
Total time 17 min, 8 sec
ppm
14
12
10
8
6
4
2
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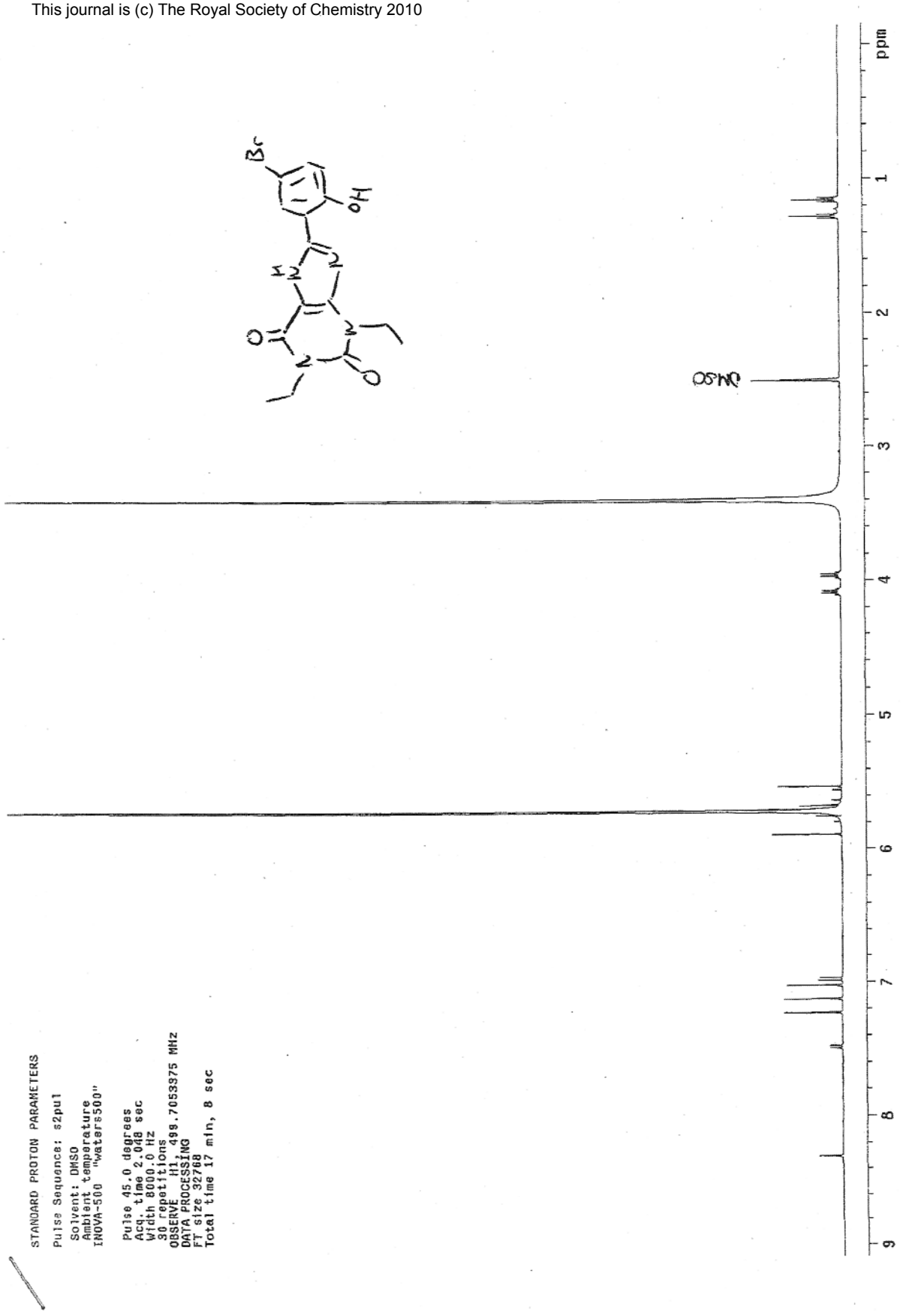
0.31
2.00
2.00
4.16
6.21
H
N
N
O
N
N
O
Br


STANDARD PROTON PARAMETERS
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
INOVA-500 "watsrs500"
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
30 repetitions
OBSERVE H1, 499.7053375 MHz
DATA PROCESSING
FT size 32768
Total time 17 min, 8 sec
Br
OH
O
N
H
DMSO
ppm
9
8
7
6
5
4
3
2
1

STANDARD CARBON PARAMETERS dpwr=34, sw=34,000 Hz
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
User: 1-14-87
INOVA-500 "water500"
Pulse 27.7 degrees
Acq. time 0.984 sec
Width 33999.2 Hz
45856 repetitions
OBSERVE C13, 125.6508761 MHz
DECOUPLE H1, 499.7083324 MHz
Power 34 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 27 hr, 1 min, 9 sec
Br
OH
O
N
H
N
N
O
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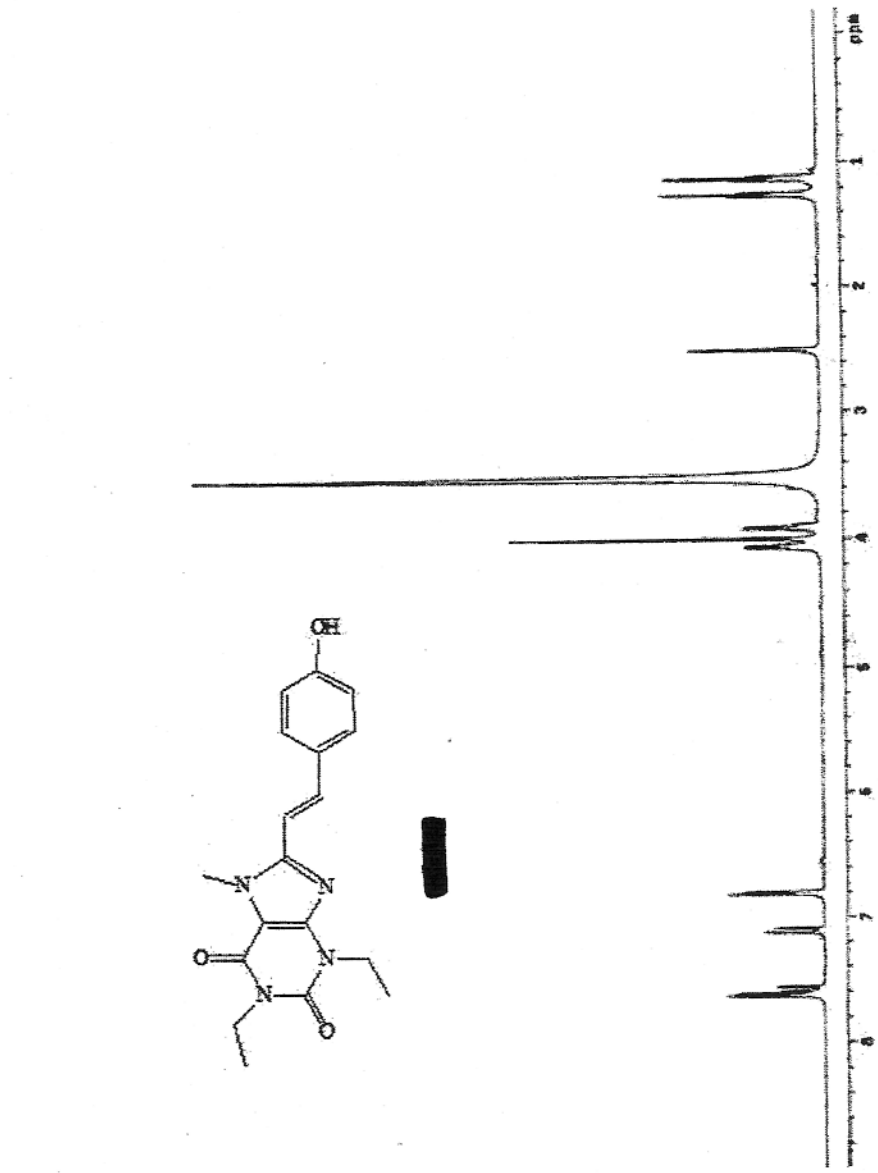
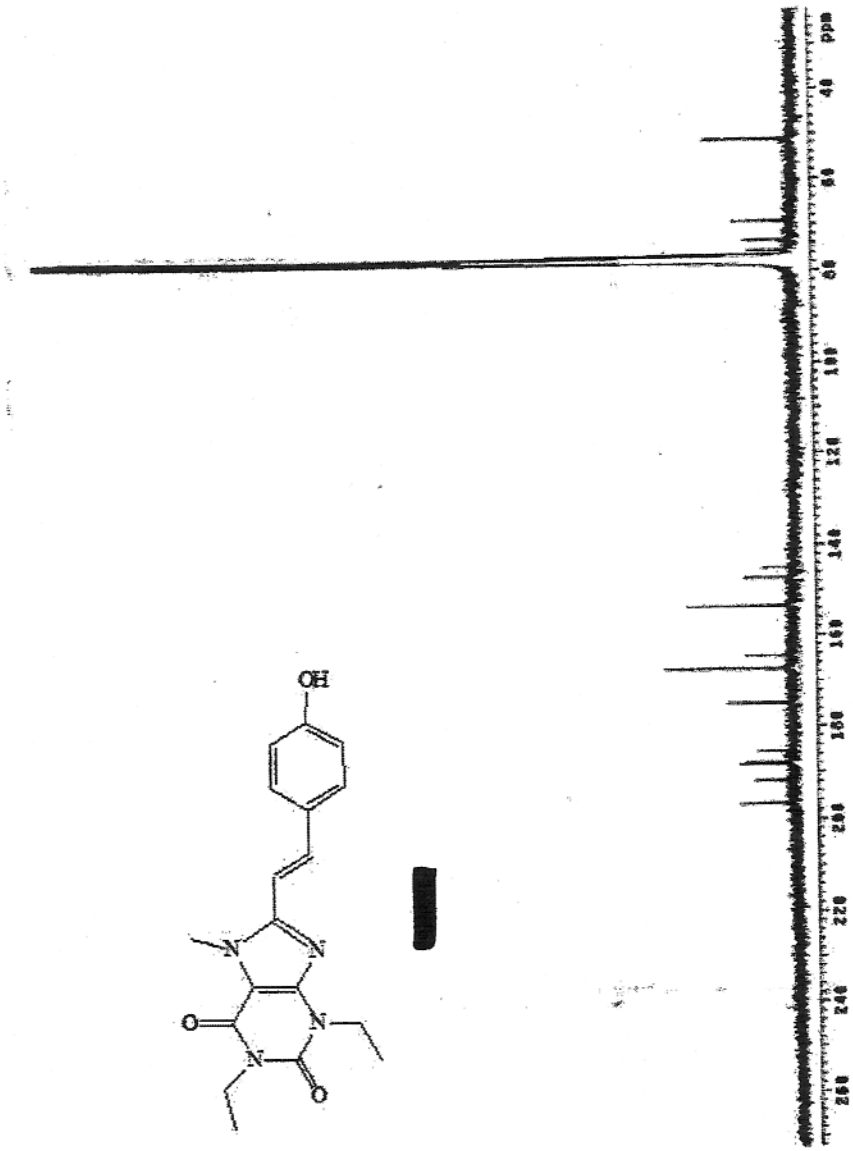
200
180
160
140
120
100
80
60
40
20
0
ppm



Supplementary Material (ESI) for Organic & Biomolecular Chemistry

[redacted]



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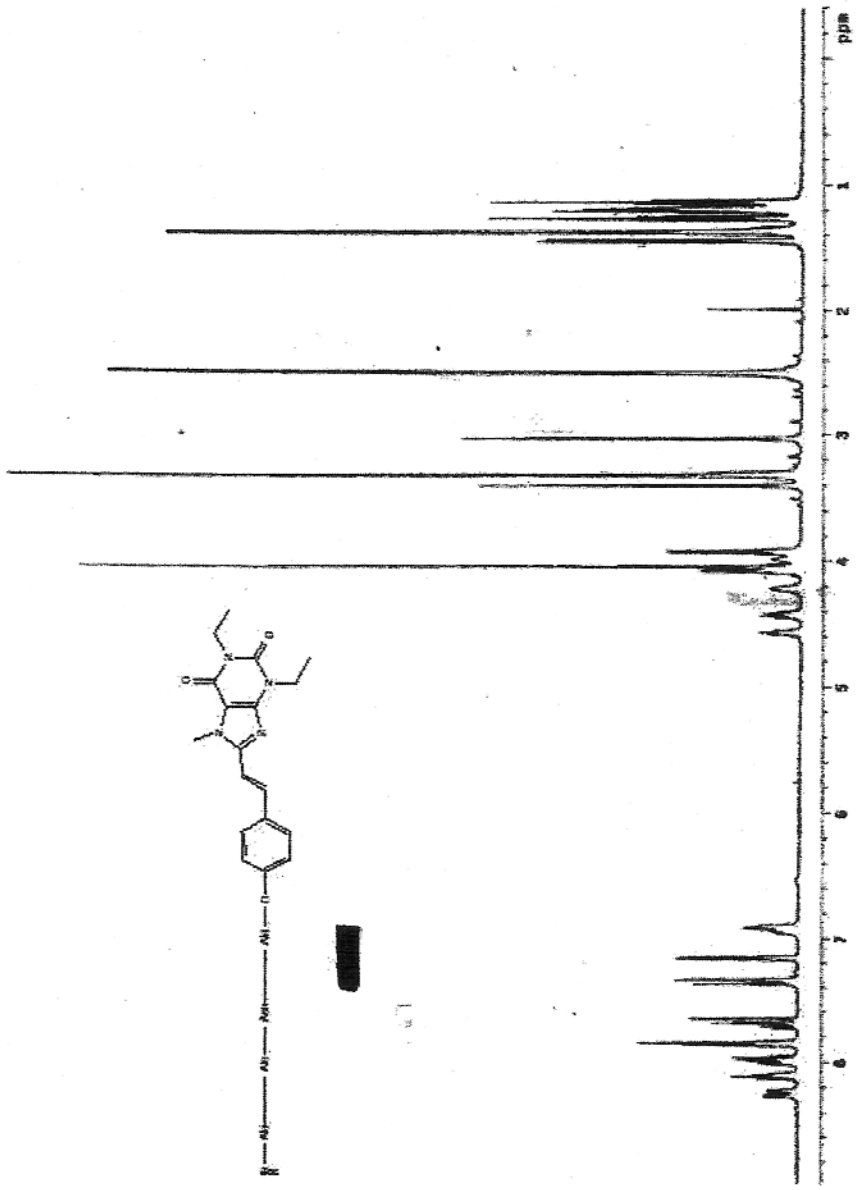
ppm
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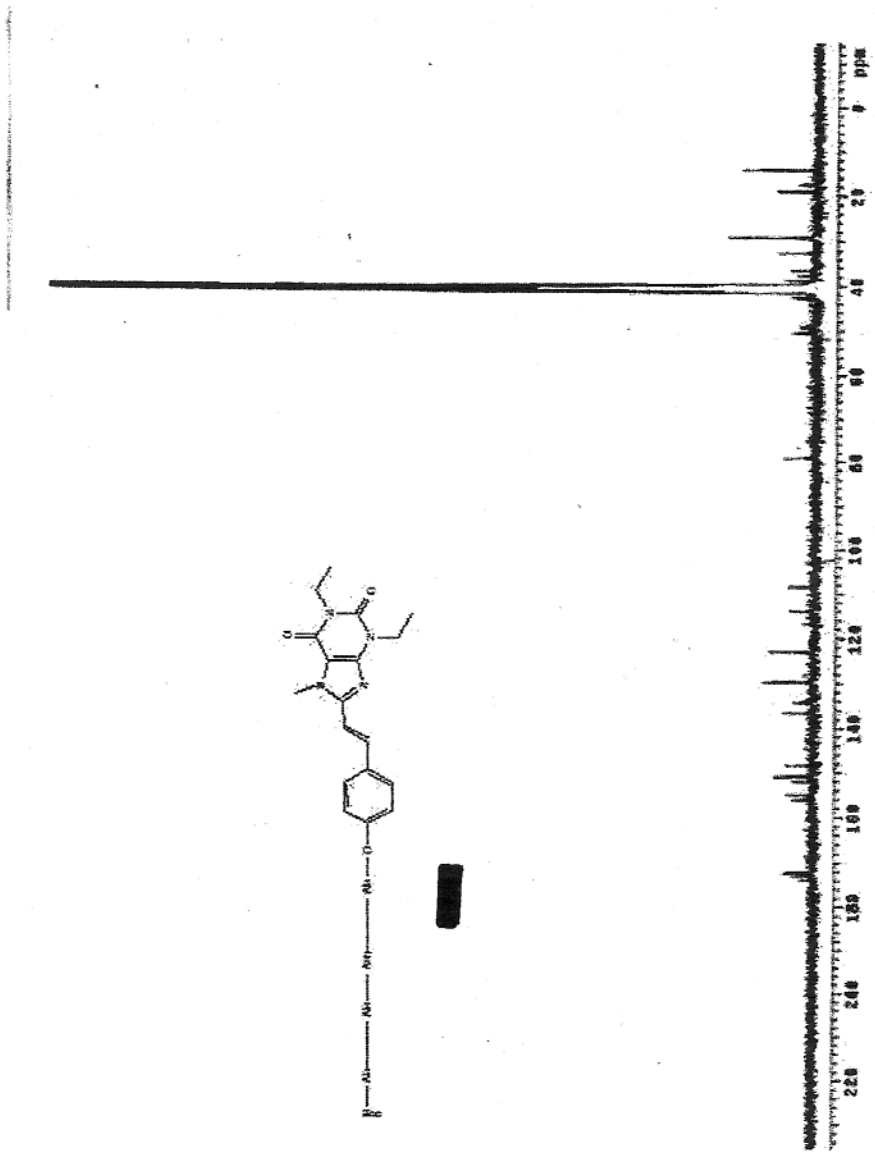

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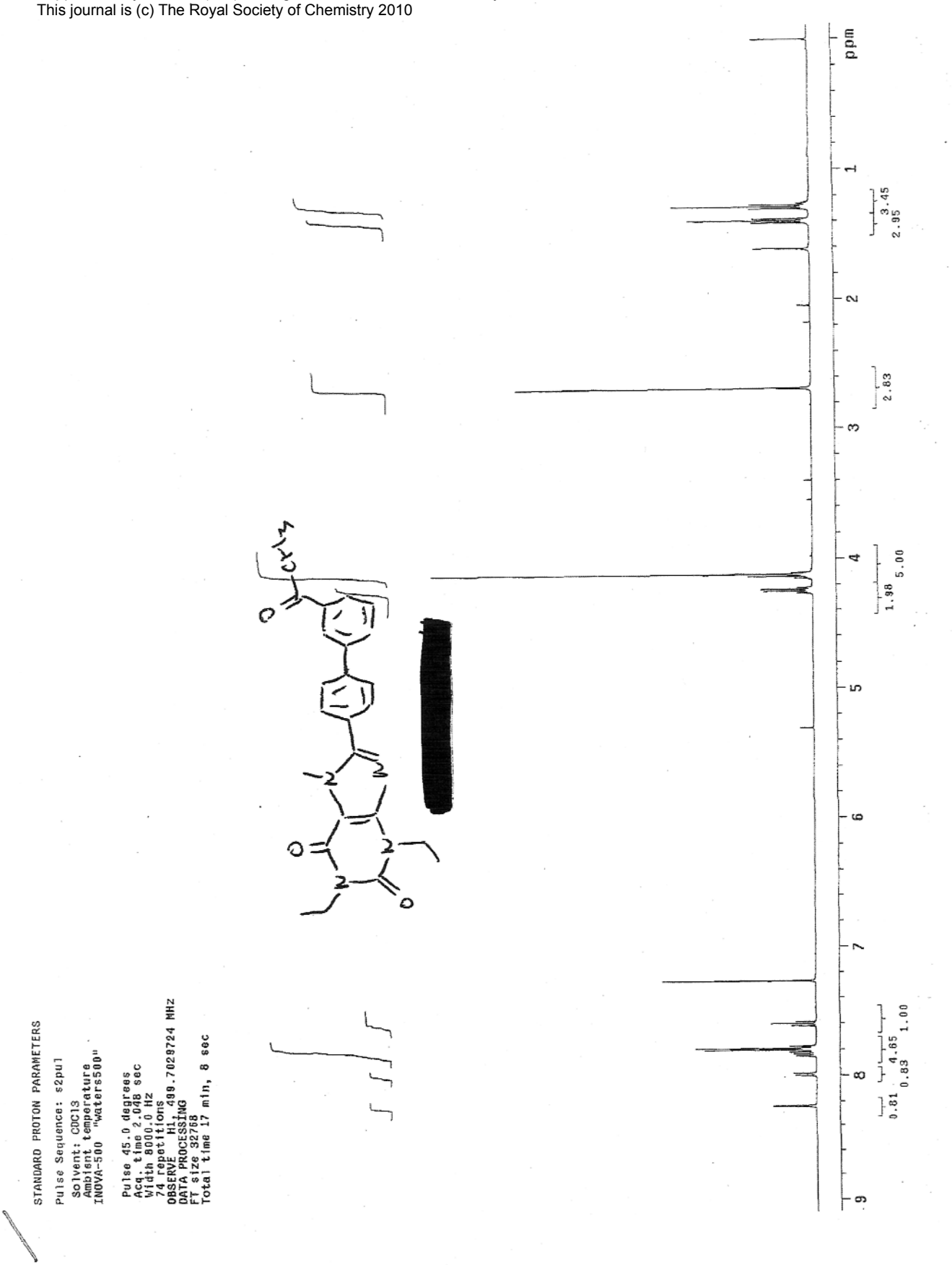
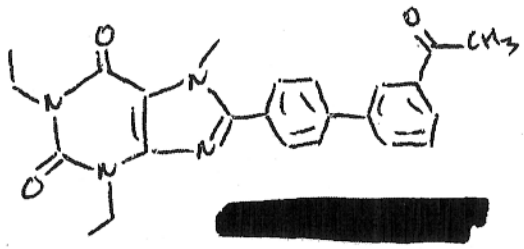
Supplementary Material (ESI) for Organic & Biomolecular Chemistry

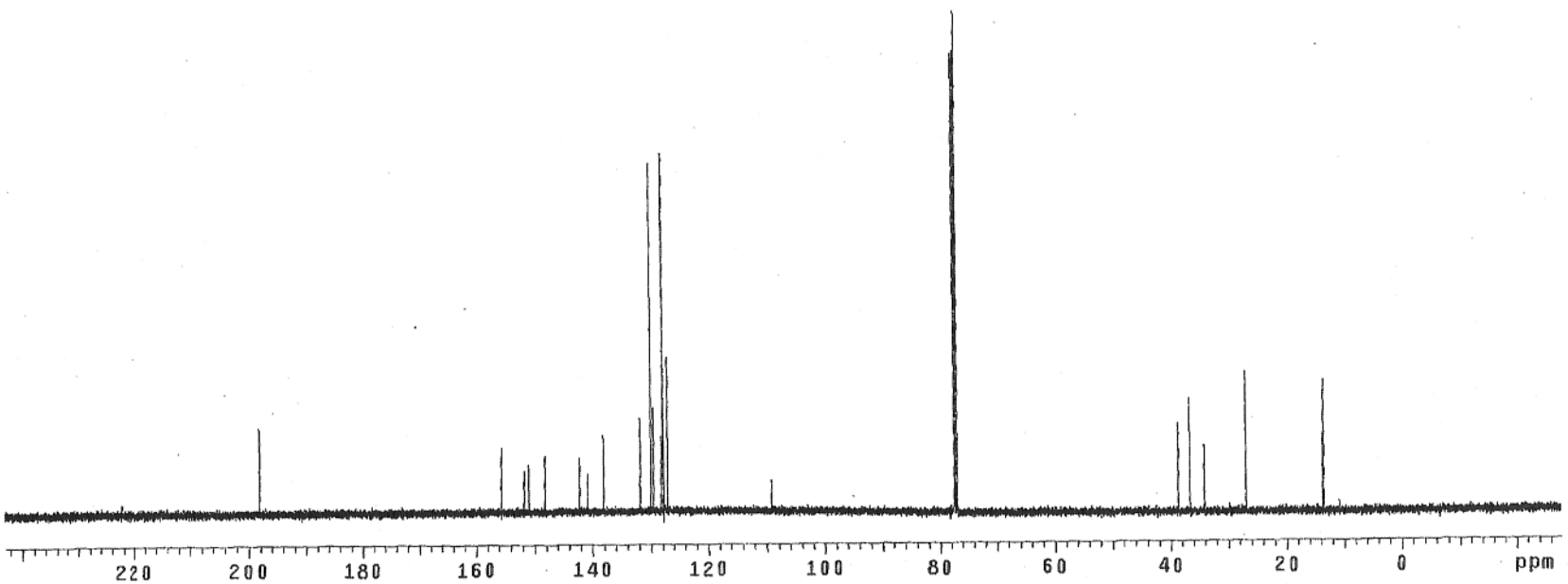


STANDARD CARBON PARAMETERS dpwr=34, sw=34,000 Hz

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
User: 1-14-87
INOVA-500 "waters500"

 Pulse 27.7 degrees
 Acq. time 0.964 sec
 Width 33989.2 Hz
 32000 repetitions
OBSERVE C13, 125.6503938 MHz
DECOUPLE H1, 499.7059588 MHz
 Power 34 dB
 on during acquisition
 off during delay
 GARP-1 modulated
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 65536
Total time 8 hr, 38 min, 46 sec

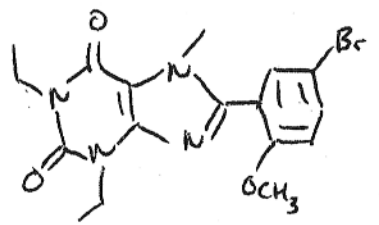




STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "waters500"

Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
18 repetitions
OBSERVE H1, 498.7029607 MHz
DATA PROCESSING
FT size 32768
Total time 17 min, 8 sec



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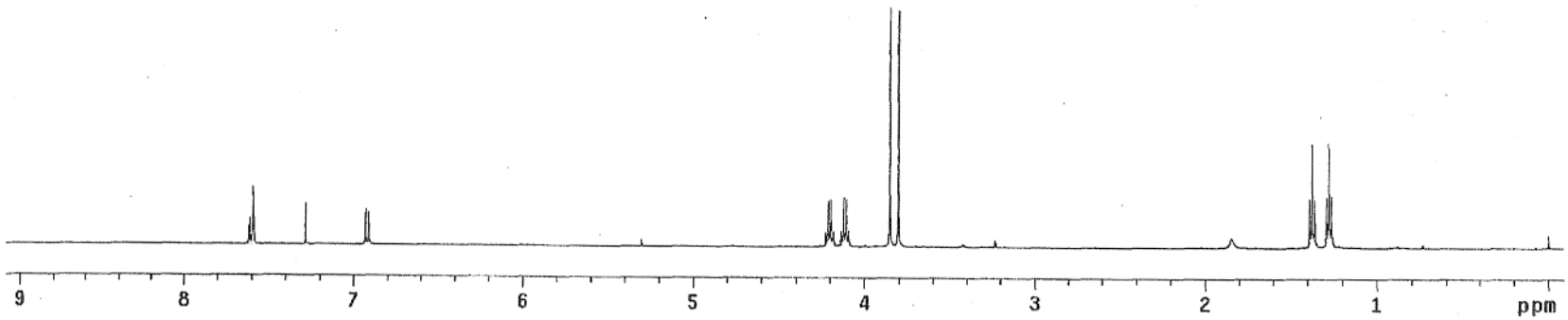
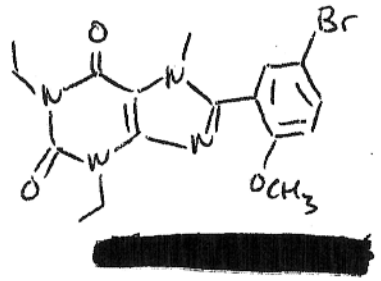
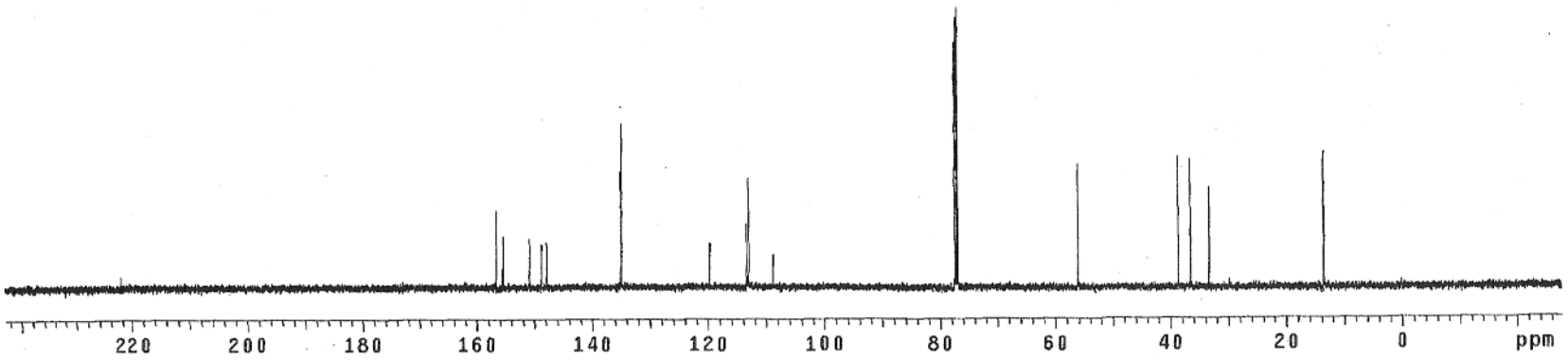


STANDARD CARBON PARAMETERS dpwr=34, sw=34,000 Hz

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
User: 1-14-87
INOVA-500 "waters500"

 Pulse 27.7 degrees
 Acq. time 0.964 sec
 Width 33999.2 Hz
 2736 repetitions
OBSERVE C13, 125.6503979 MHz
DECOUPLE H1, 499.7058588 MHz
 Power 34 dB
 on during acquisition
 off during delay
 GARP-1 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 42 min, 6 sec





STANDARD PROTON PARAMETERS

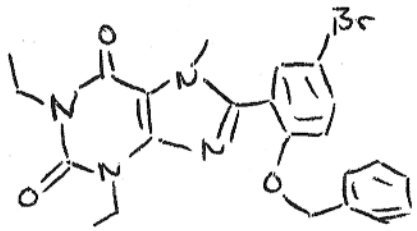
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "waters500"

Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7029690 MHz
DATA PROCESSING
FT size 32768
Total time 17 min, 8 sec

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "waters500"

Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
56 repetitions
OBSERVE H1, 499.7029710 MHz
DATA PROCESSING
FT size 32768
Total time 17 min, 8 sec



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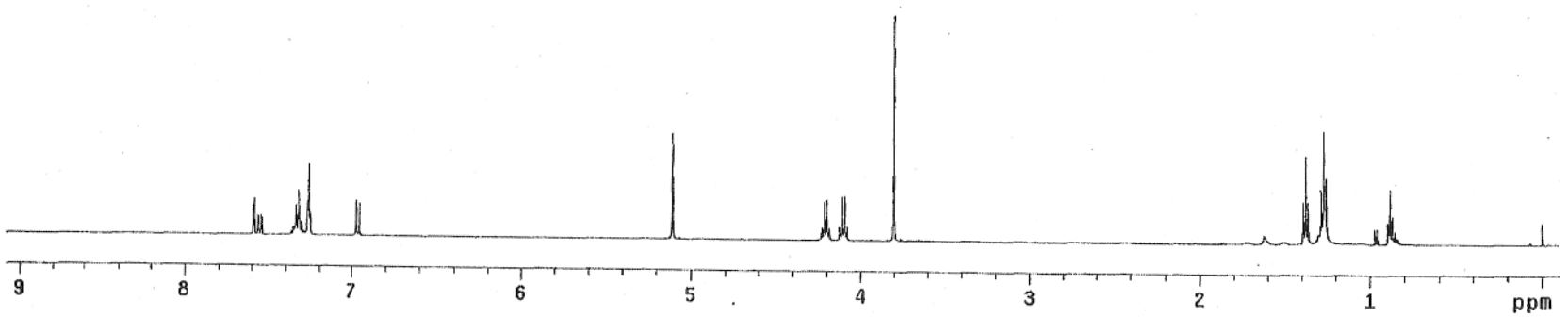
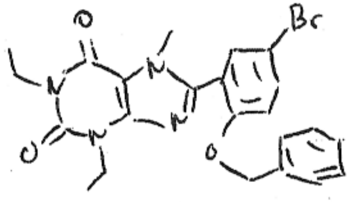


STANDARD CARBON PARAMETERS dpwr=34, sw=34,000 Hz

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-14-87
INOVA-500 "waters500"

Pulse 27.7 degrees
Acq. time 0.964 sec
Width 33999.2 Hz
1024 repetitions
OBSERVE C13, 125.6503938 MHz
DECOUPLE H1, 499.7059588 MHz
Power 34 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 42 min, 6 sec



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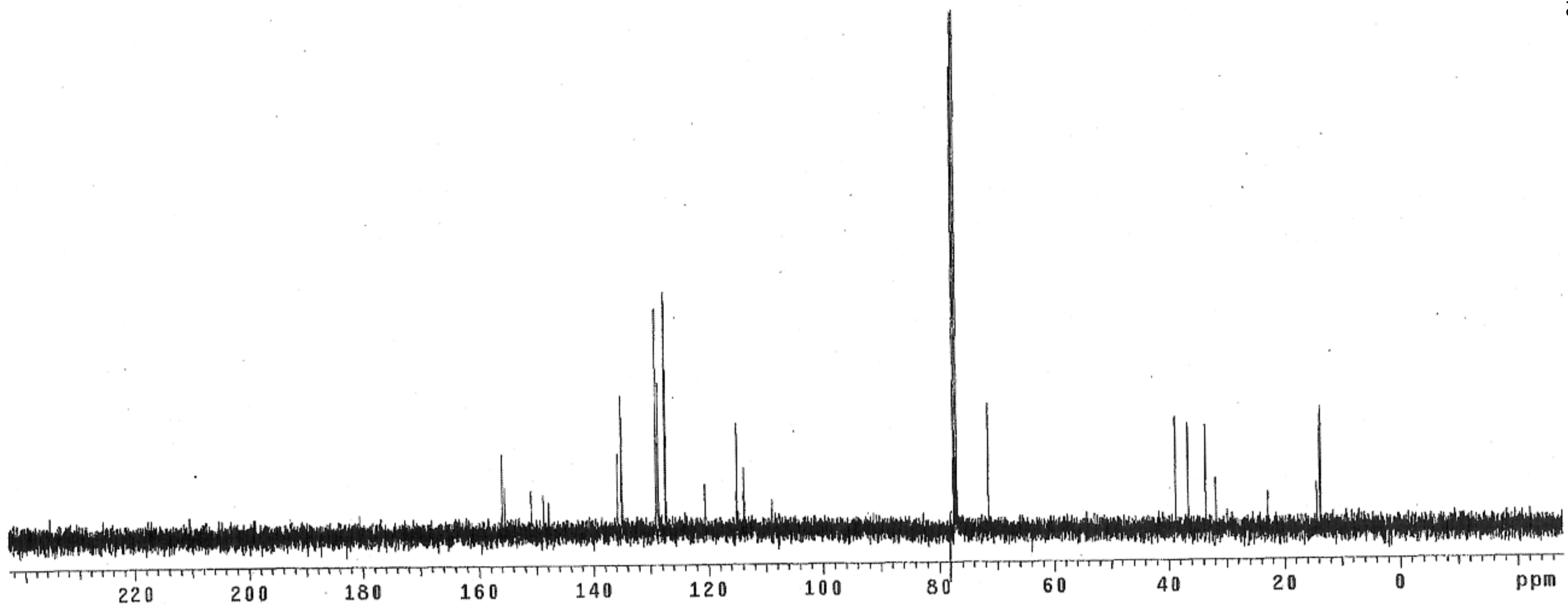

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "water500"

Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.7029871 MHz
DATA PROCESSING
FT size 32768
Total time 17 min, 8 sec

STANDARD CARBON PARAMETERS dpwr=34, sw=34,000 Hz

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-14-87
INOVA-500 "waters500"

Pulse 27.7 degrees
Acq. time 0.864 sec
Width 33998.2 Hz
1056 repetitions
OBSERVE C13, 125.6503948 MHz
DECOUPLE H1, 499.7059588 MHz
Power 34 dB
on during acquisition
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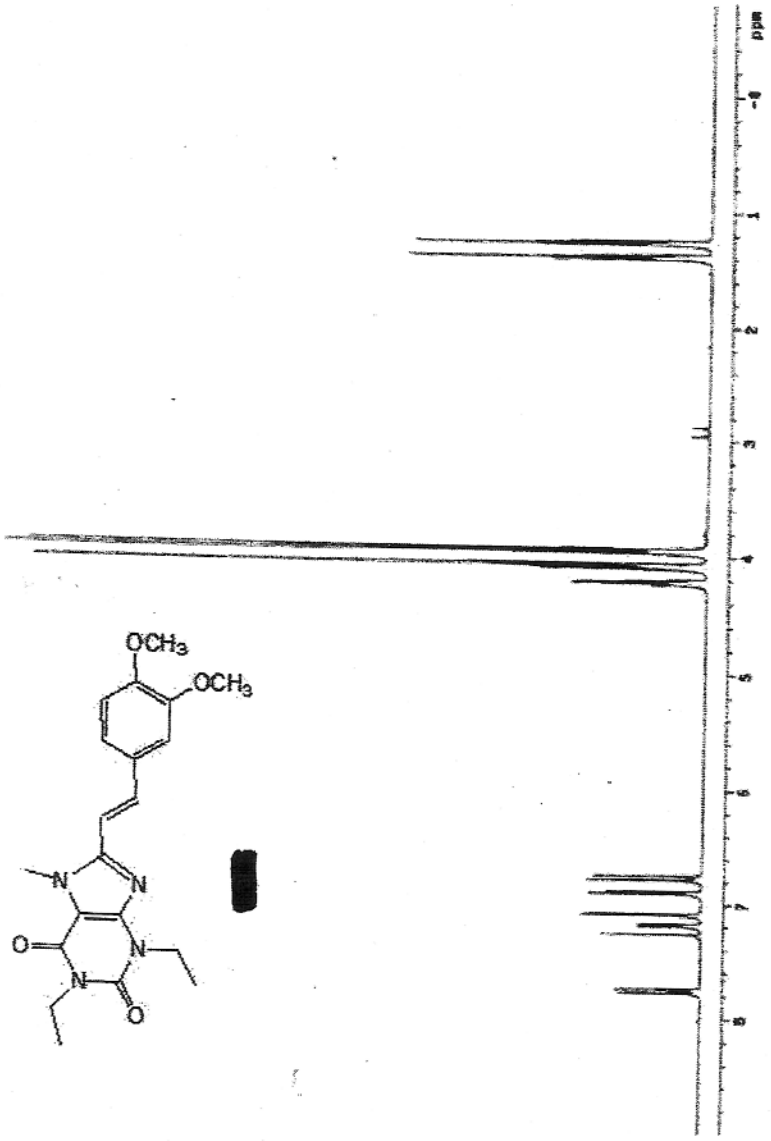
GARP-1 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 13 hr, 30 min, 34 sec

[redacted]



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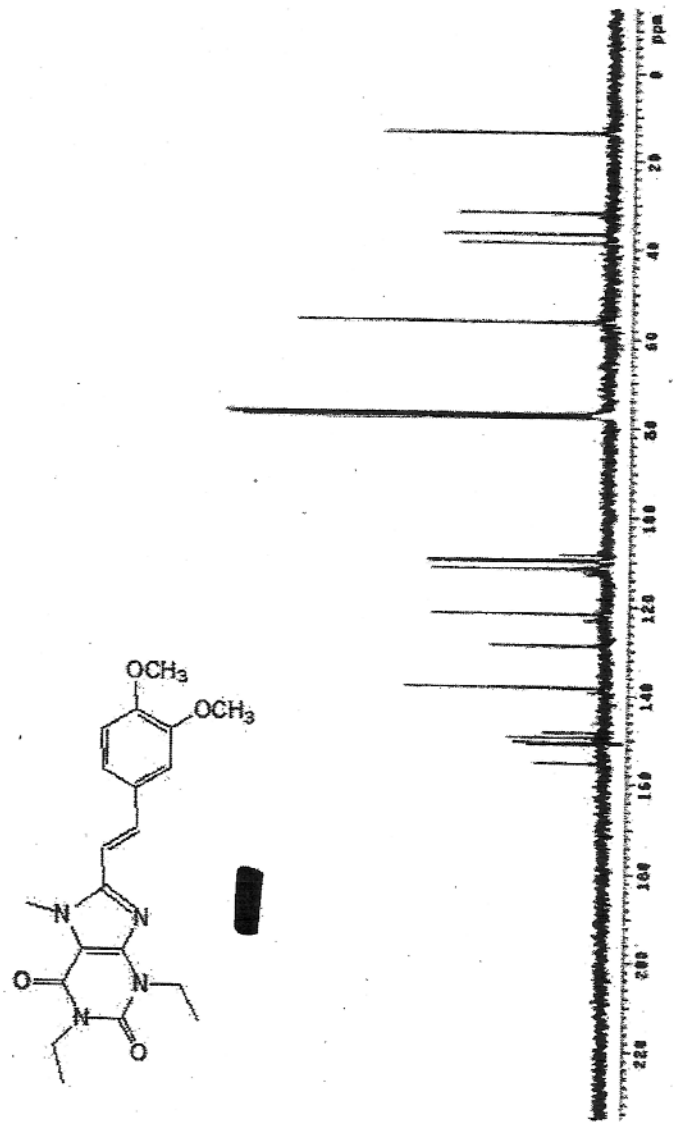
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OCH3
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N
N
O

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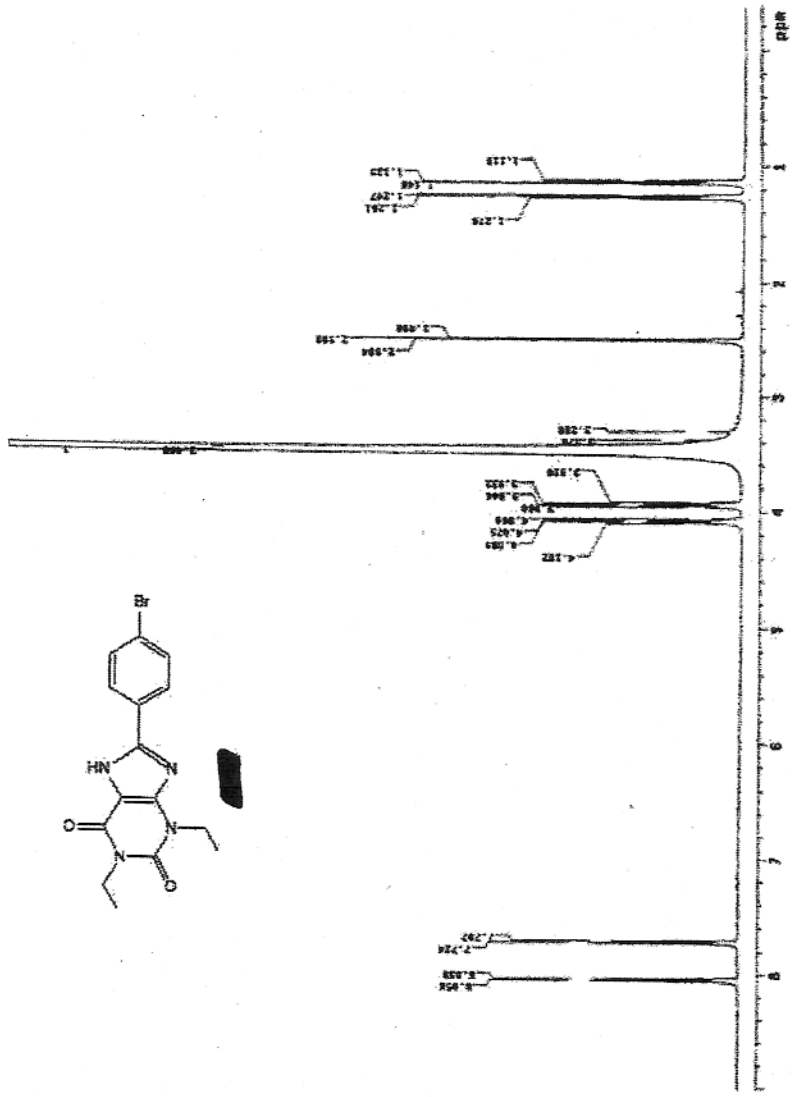

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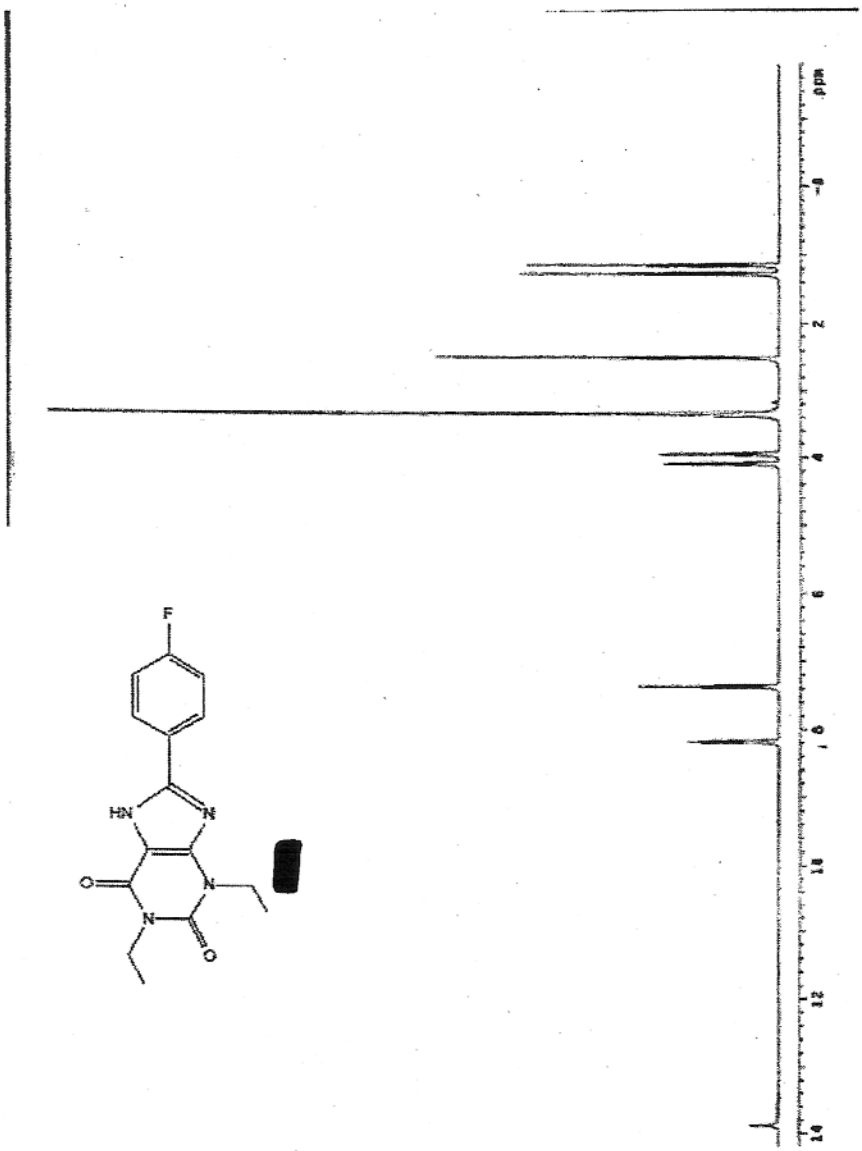

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S38

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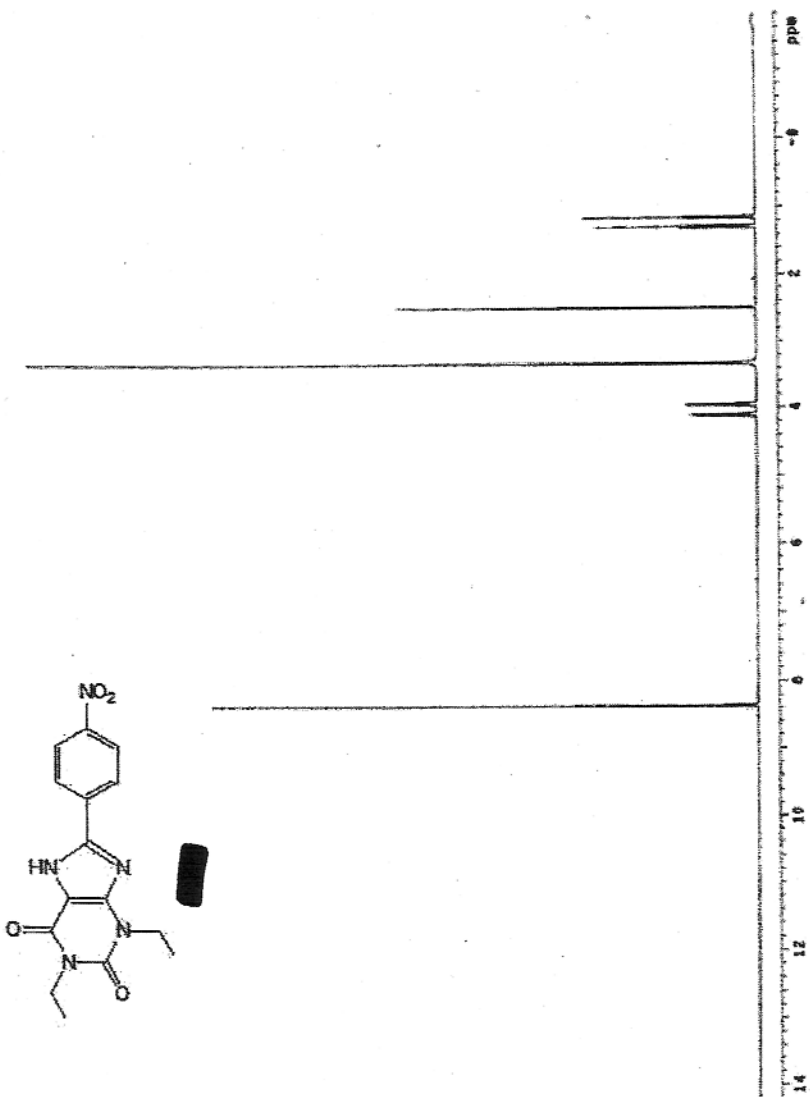

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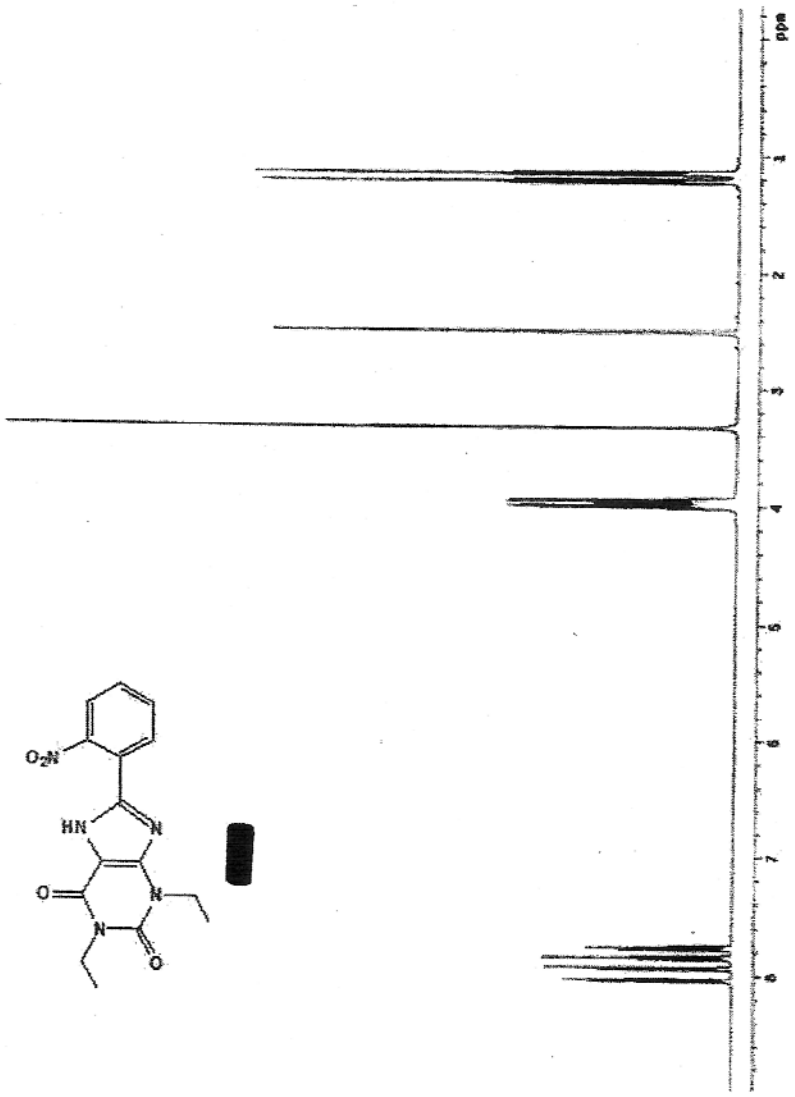

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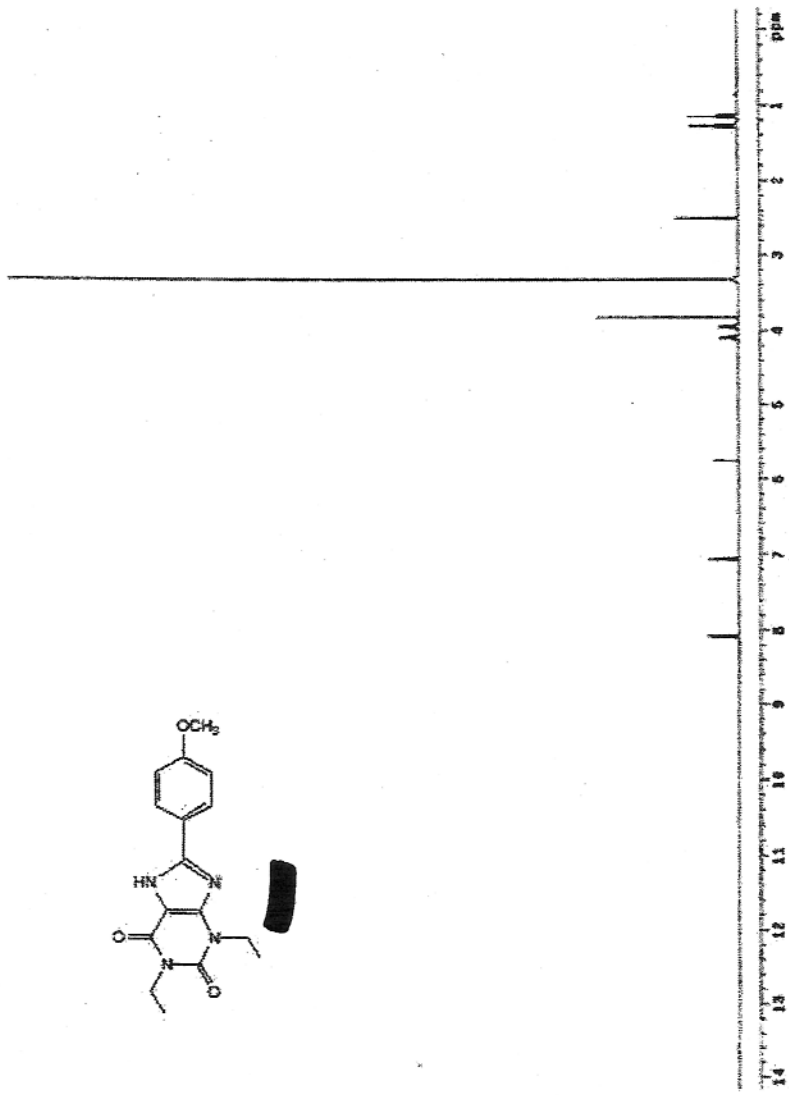

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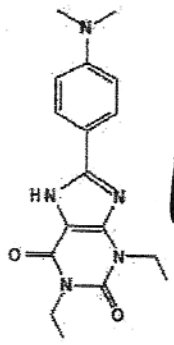

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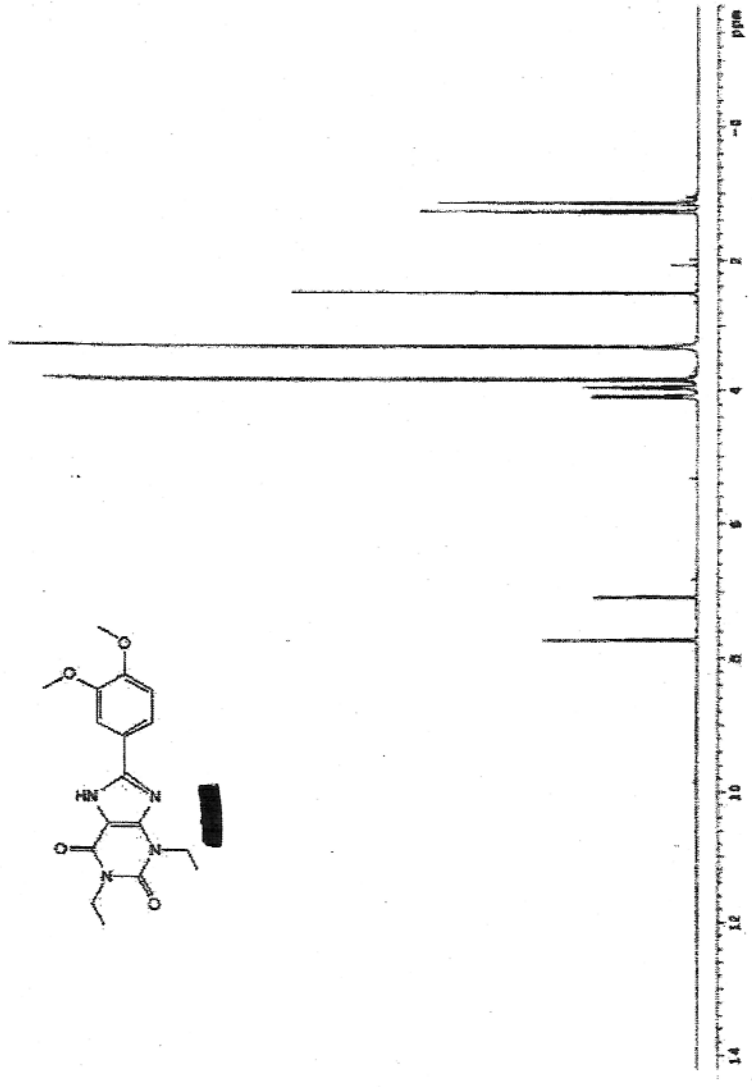

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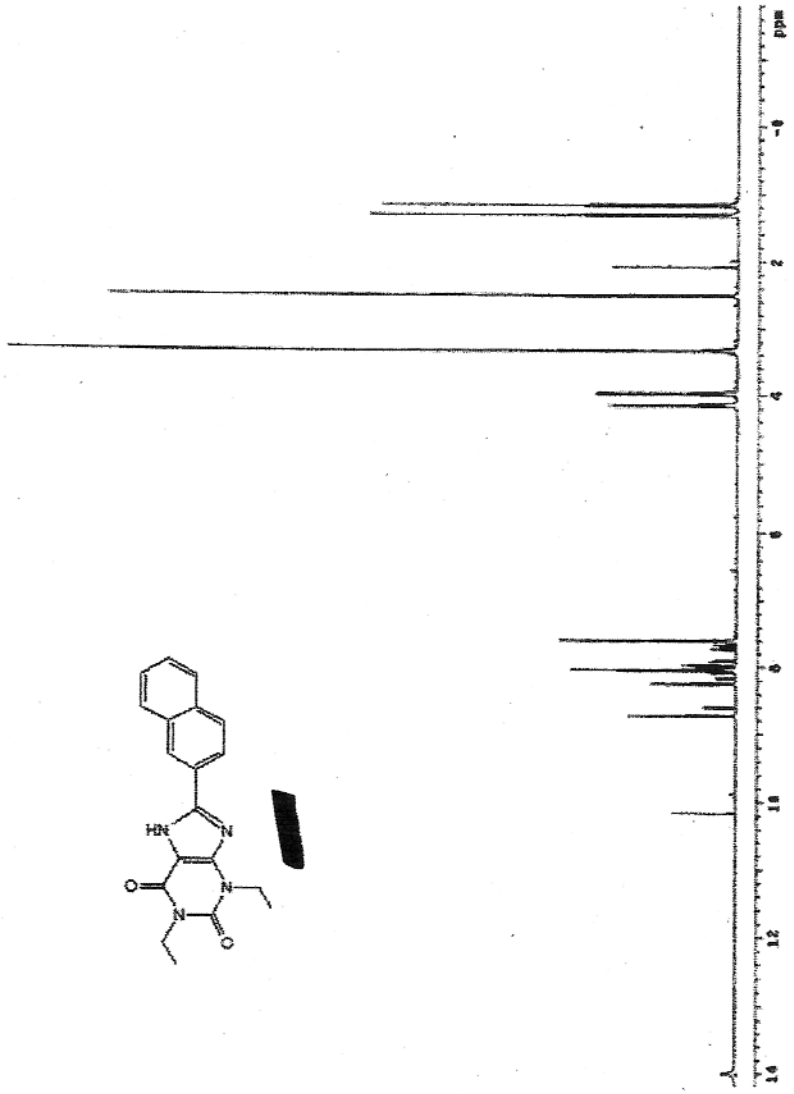
ppm
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4
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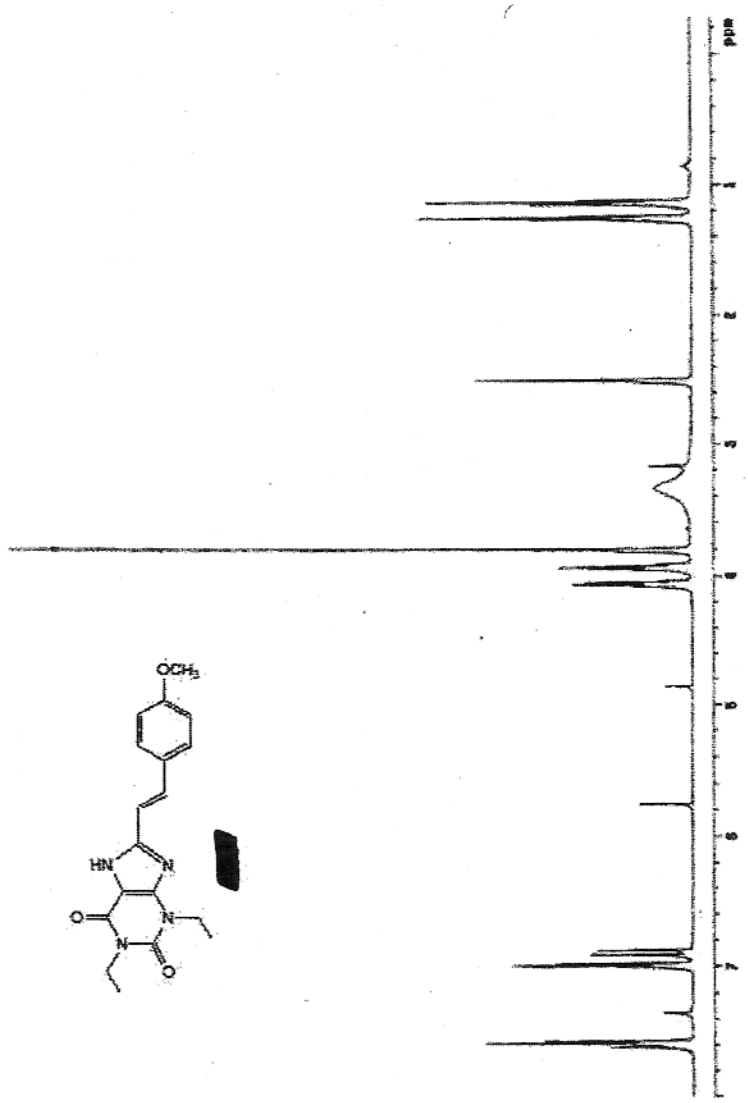
N
N
O
N
O

[redacted]



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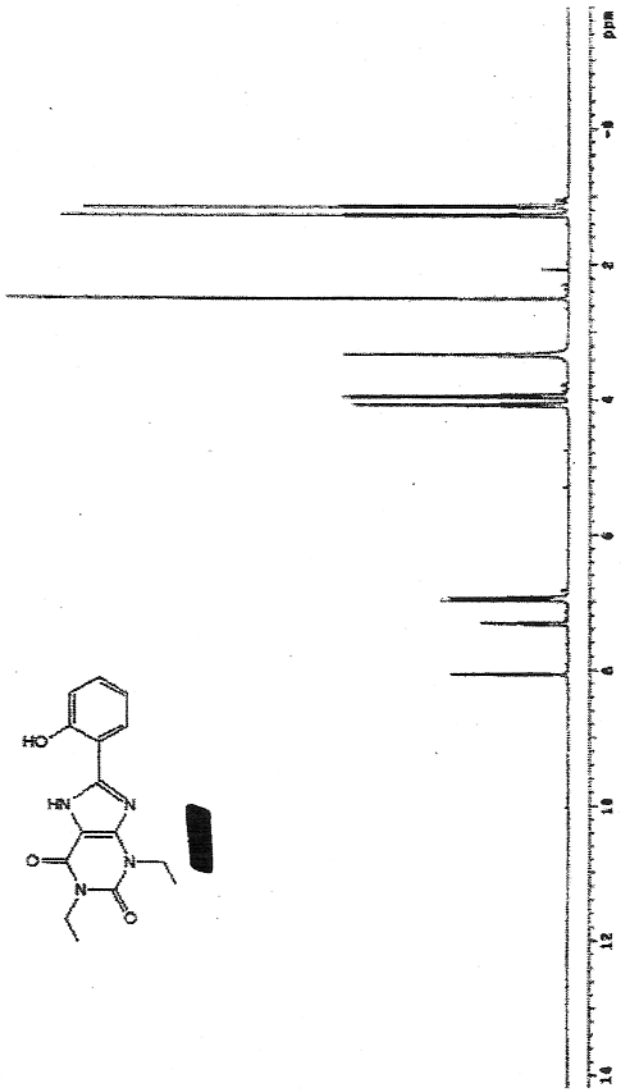
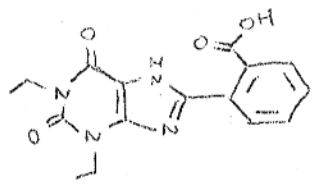
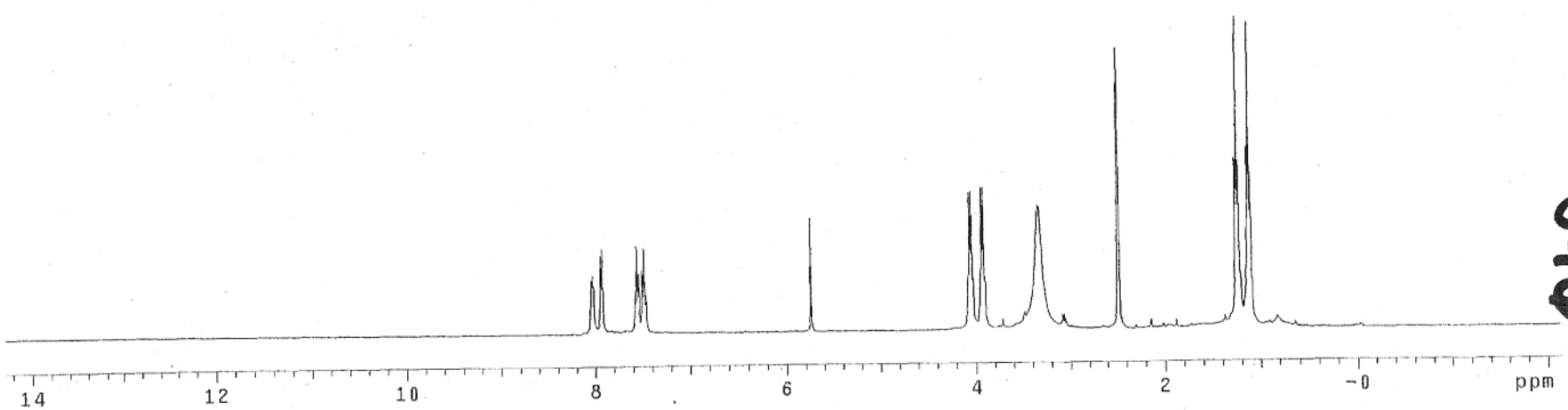


[redacted]

RT-37
[redacted]
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-400BB "nmr400"

Relax. delay 1.000 sec
Pulse 34.6 degrees
Acq. time 1.991 sec
Width 7507.5 Hz
128 repetitions
OBSERVE H1, 400.1622959 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 42 sec





S46

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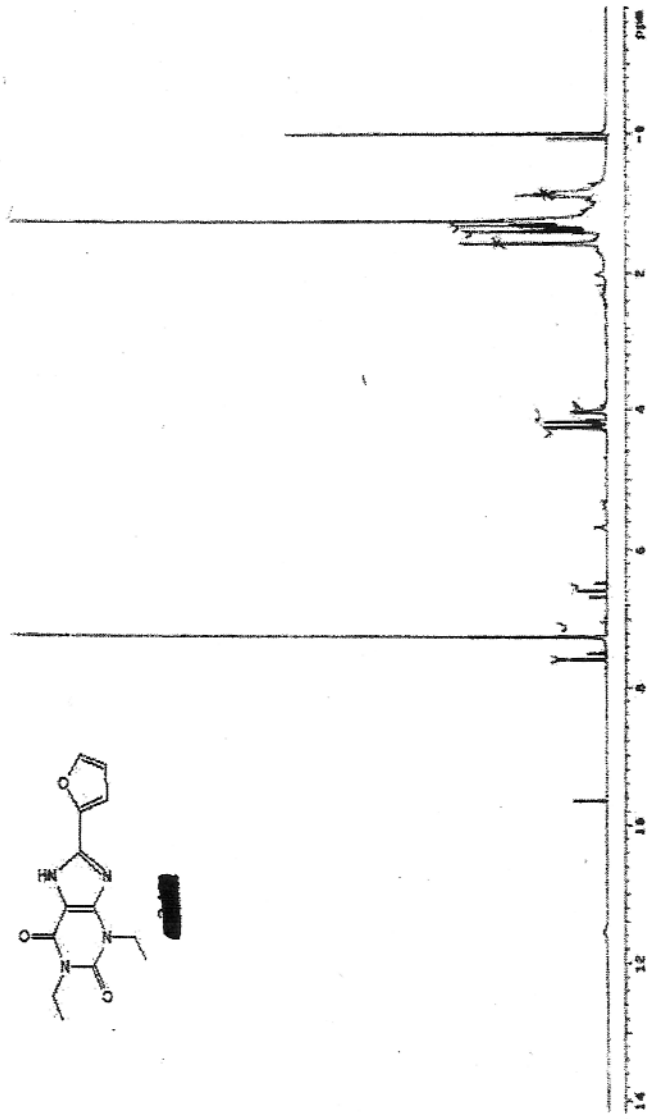

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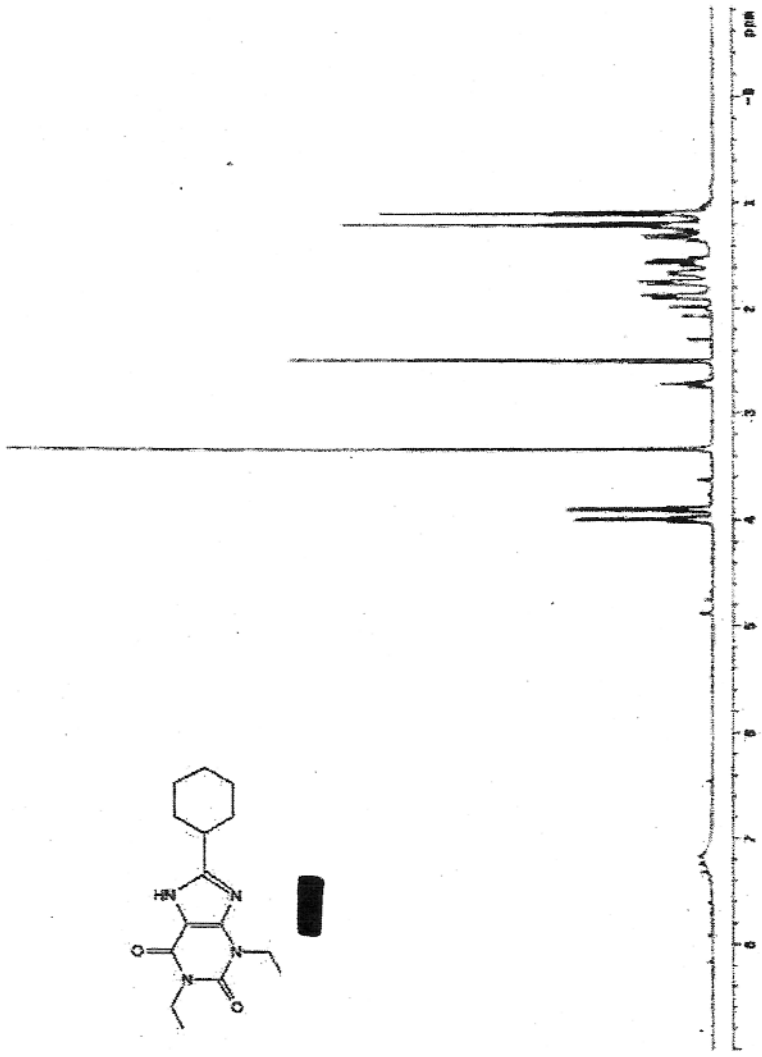
[redacted]



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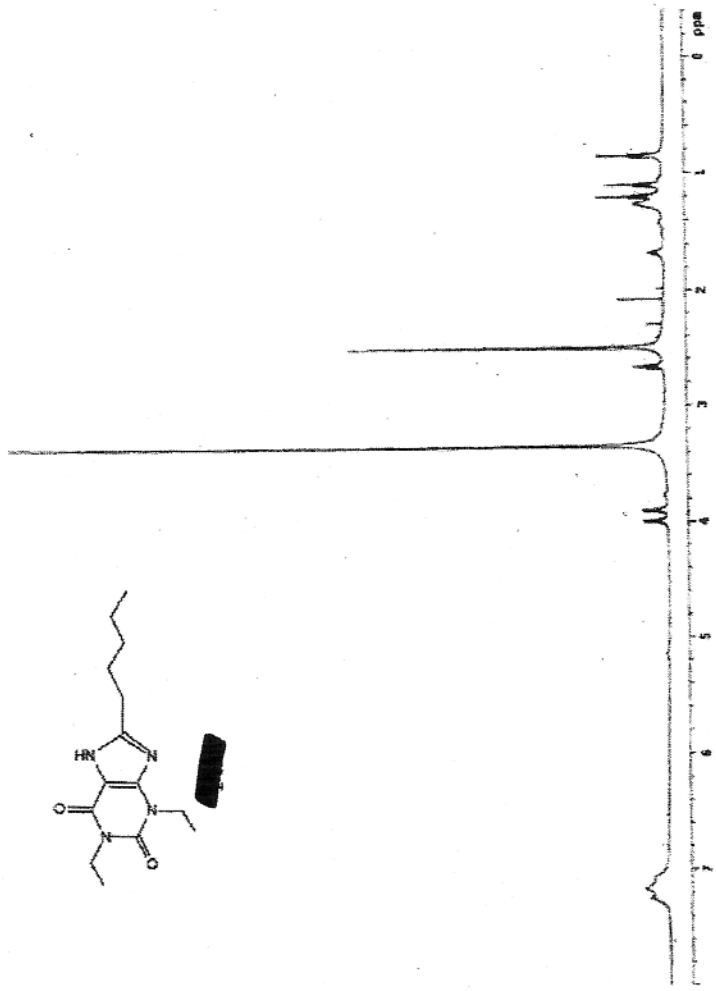

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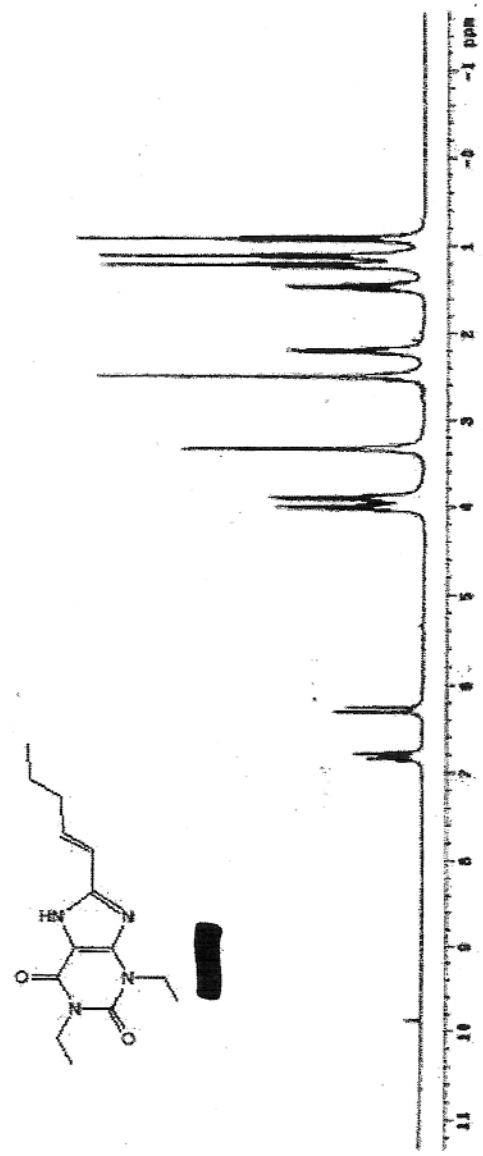
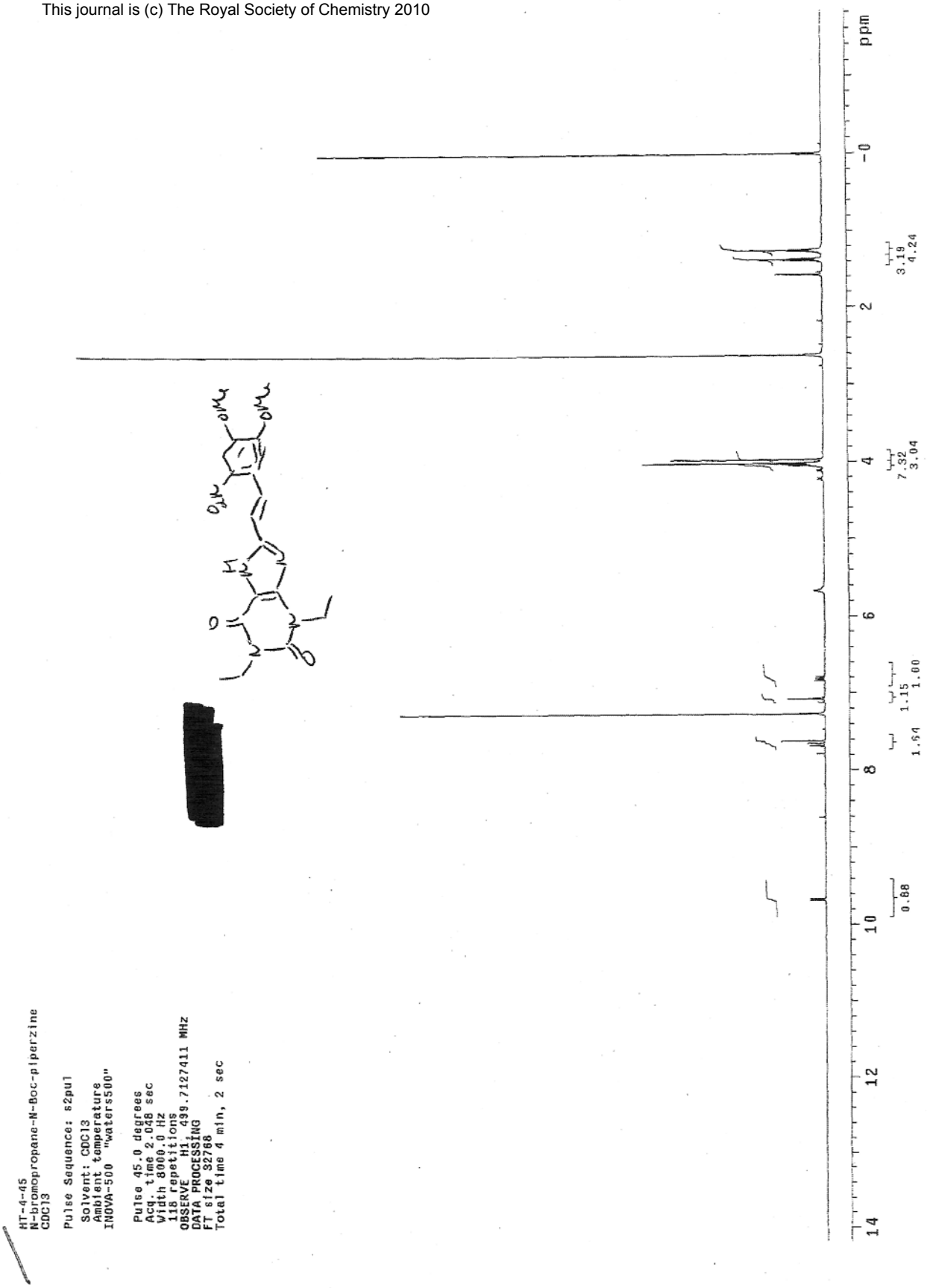
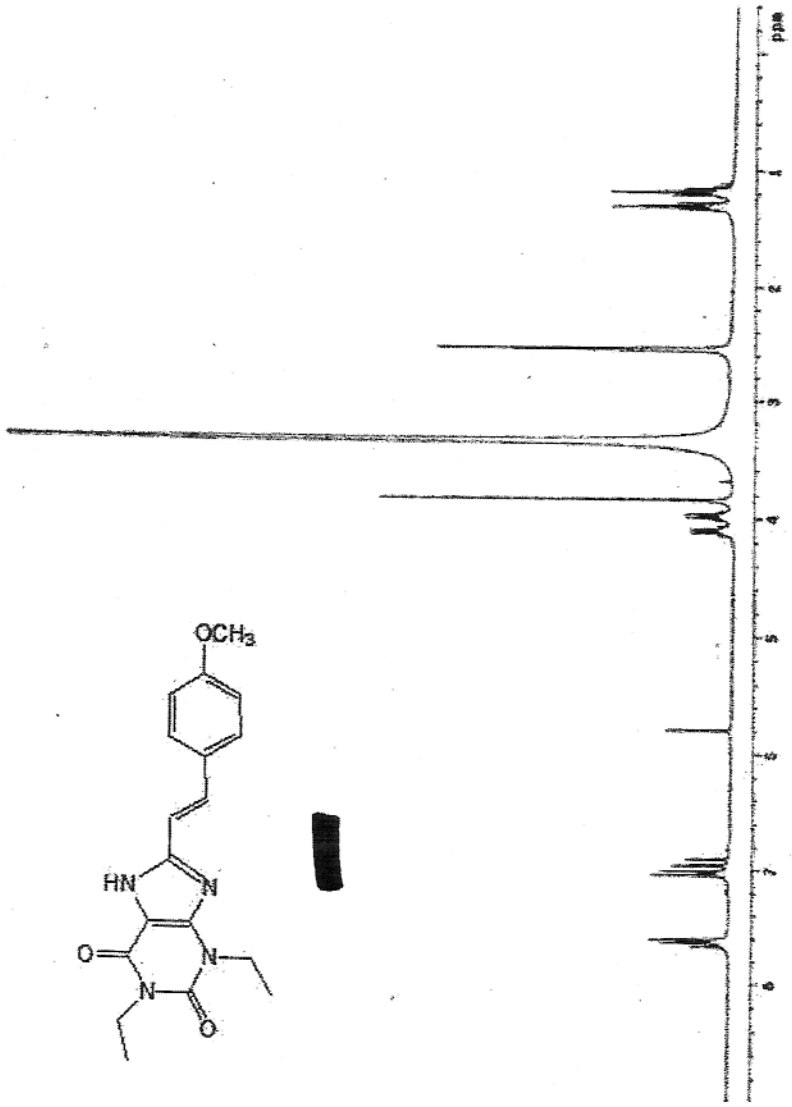


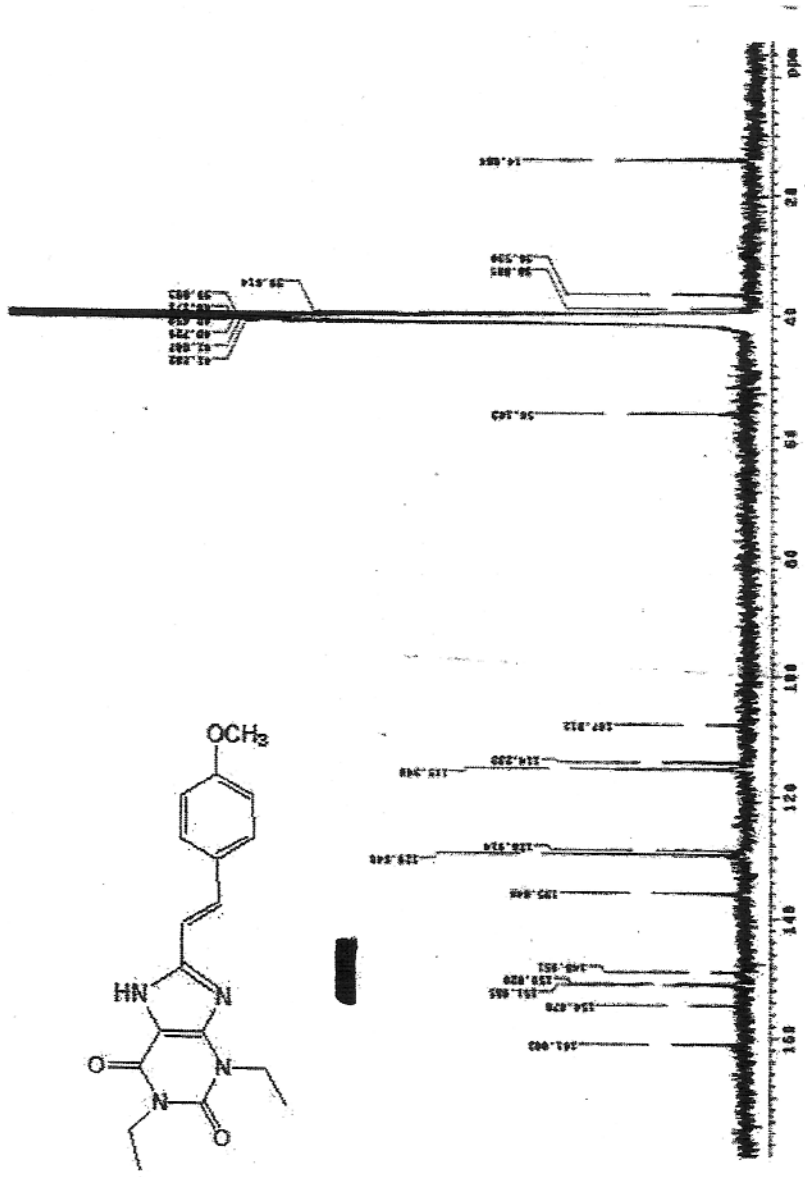
[redacted]

Supplementary Material (ESI) for Organic & Biomolecular Chemistry




OCH3
HN
N
O
N
N
O
ppm

S53



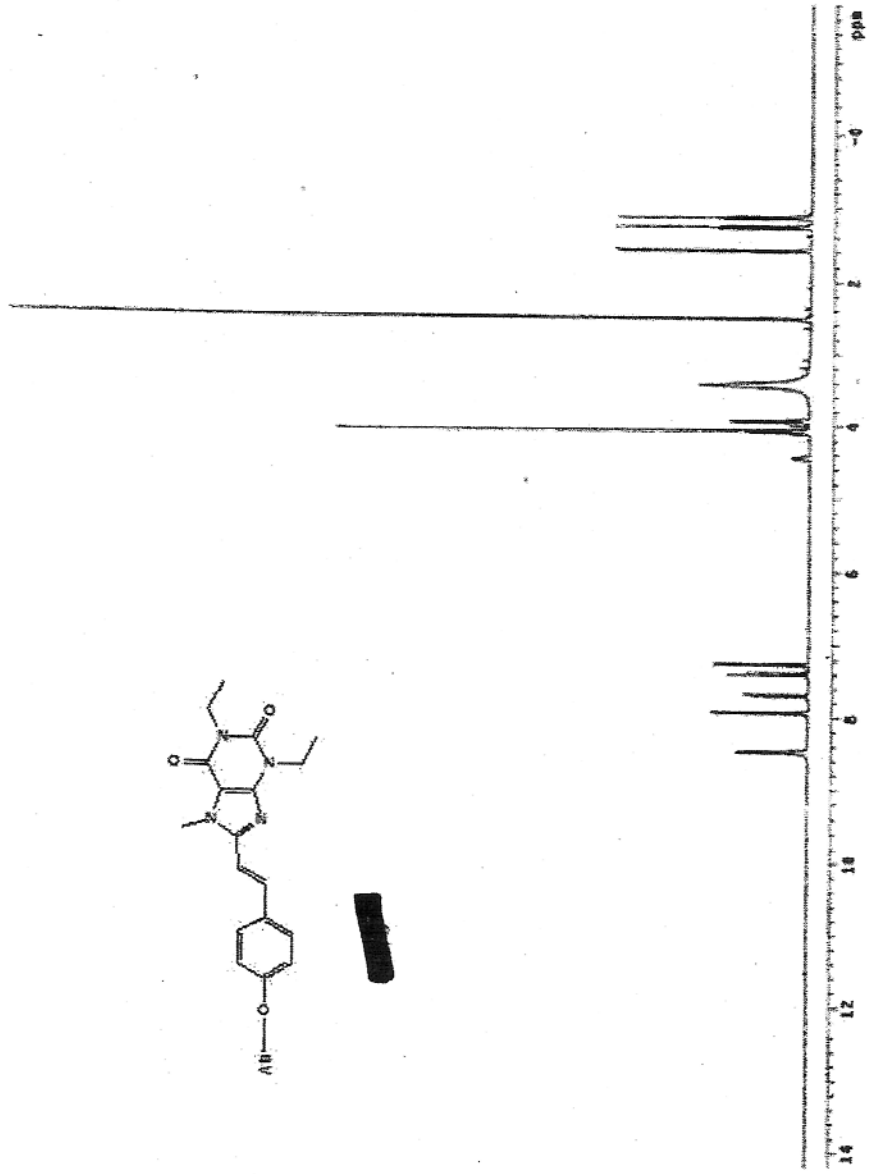
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "waters500"

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 499.7127362 MHz
DATA PROCESSING
FT size 32768
Total time 4 min, 3 sec

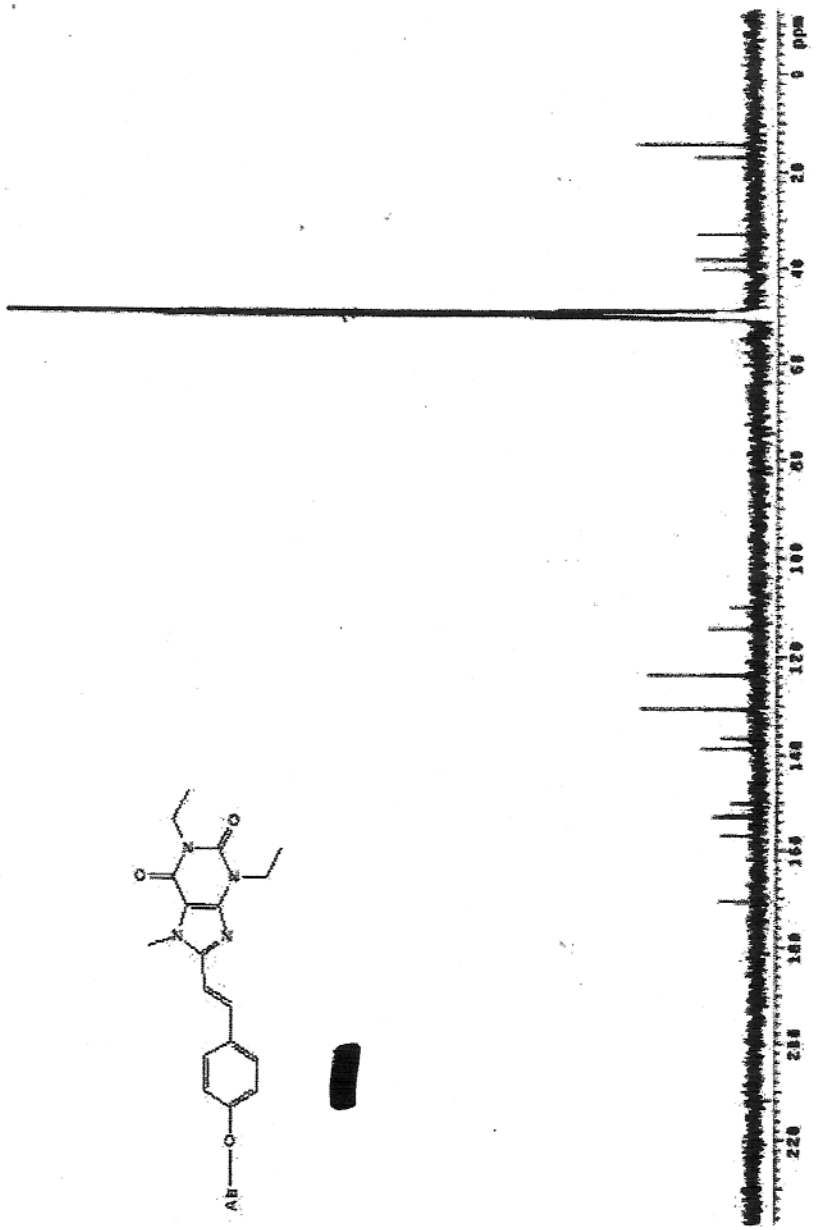
S55

[redacted]



[redacted]

[redacted]



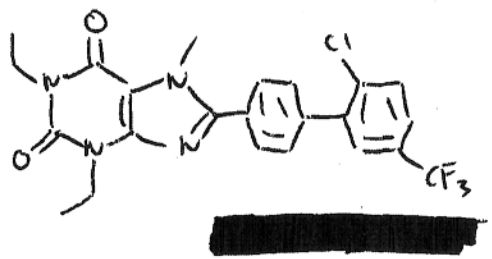
[redacted]

STANDARD PROTON PARAMETERS

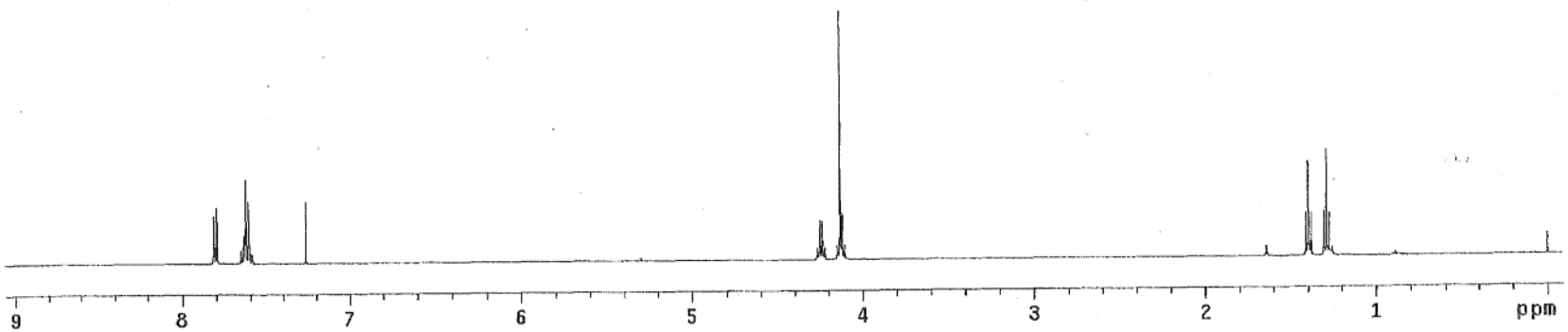
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
INOVA-500 "waters500"

Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
84 repetitions
OBSERVE H1, 499.7029705 MHz
DATA PROCESSING
FT size 32768
Total time 17 min, 8 sec



[redacted]



S57

S58

STANDARD CARBON PARAMETERS dpwr=34, sw=34,000 Hz

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-14-87
INOVA-500 "waters500"

Pulse 27.7 degrees
Acq. time 0.964 sec
Width 33999.2 Hz
4624 repetitions
OBSERVE C13, 125.6503838 MHz
DECOUPLE H1, 499.7059588 MHz
Power 34 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 5 hr, 24 min, 13 sec

STANDARD CARBON PARAMETERS dpwr=34, sw=34,000 Hz
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-14-87
INOVA-500 "waters500"
Pulse 27.7 degrees
Acq. time 0.964 sec
Width 33999.2 Hz
45296 repetitions
OBSERVE C13, 125.6503793 MHz
DECOUPLE H1, 499.7059588 MHz
Power 34 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 27 hr, 1 min, 9 sec
Cl
CF3
OMe
N
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
INOVA-500 "water500"

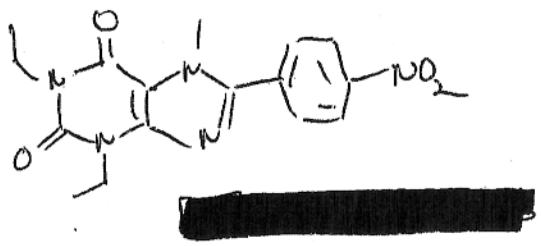
Relax. delay 15.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
6 repetitions
OBSERVE H1, 499.7029719 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 2 hr, 22 min, 8 sec

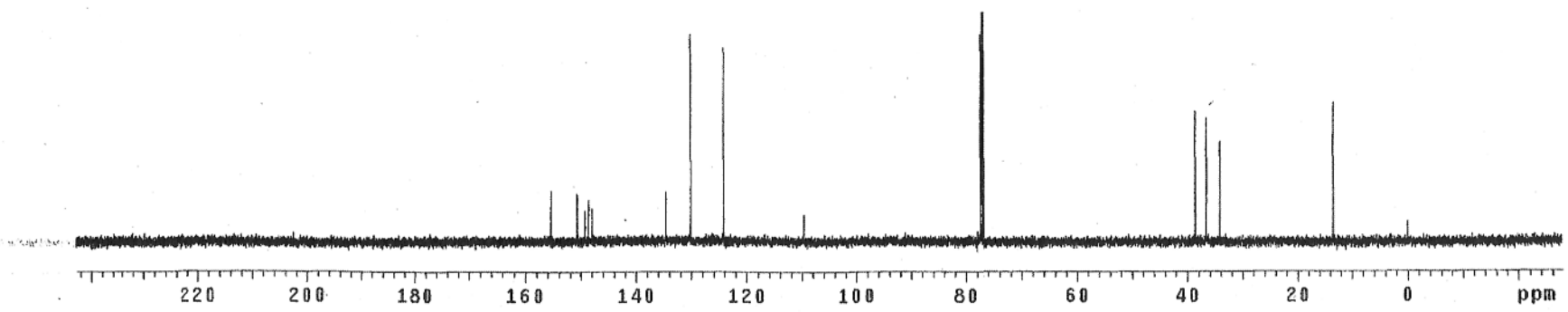
STANDARD CARBON PARAMETERS dpwr=34, sw=34,000 Hz

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
User: 1-14-87
INOVA-500 "waters500"

Pulse 27.7 degrees
Acq. time 0.964 sec
Width 33999.2 Hz
1472 repetitions
OBSERVE C13, 125.6504095 MHz
DECOUPLE H1, 499.7059588 MHz
Power 34 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 42 min, 6 sec





S61

S62

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
INOVA-500 "water500"

Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8000.0 Hz
82 repetitions
OBSERVE H1, 499.7029646 MHz
DATA PROCESSING
FT size 32768
Total time 17 min, 8 sec