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Identification of some novel xanthine-based derivatives with bronchodilator activity

Aim: The discovery of new bronchodilators with higher efficacy than theophylline is an important issue for asthmatic patients. **Materials & methods:** Theophylline **2**, 8-bromotheophylline **4** and theobromine **6** were reacted with different 2/3-chloro-*N*-phenylacetamides **1a-d** or their propanamide analogs **1e-g** to obtain **3a-g**, **5a-g** and **7a-g**, respectively. The target compounds were screened for their *in vitro* bronchodilator activity using isolated guinea pig tracheal rings precontracted with histamine and compared with their precursors. **Results:** Many compounds exhibited promising activity especially **3d**, **3f**, **5d**, **7d** and **7e**. 2D-QSAR study resulted in a significant model ($N = 24$, $n = 5$, $R^2 = 0.848$, $R^2_{cvOO} = 0.748$, $R^2_{cvMO} = 0.745$, $F = 21.215$, $s^2 = 0.0002$) using CODESSA-Pro software. **Conclusion:** These compounds can be considered as promising hits for potent bronchodilators that may be useful for further investigations.

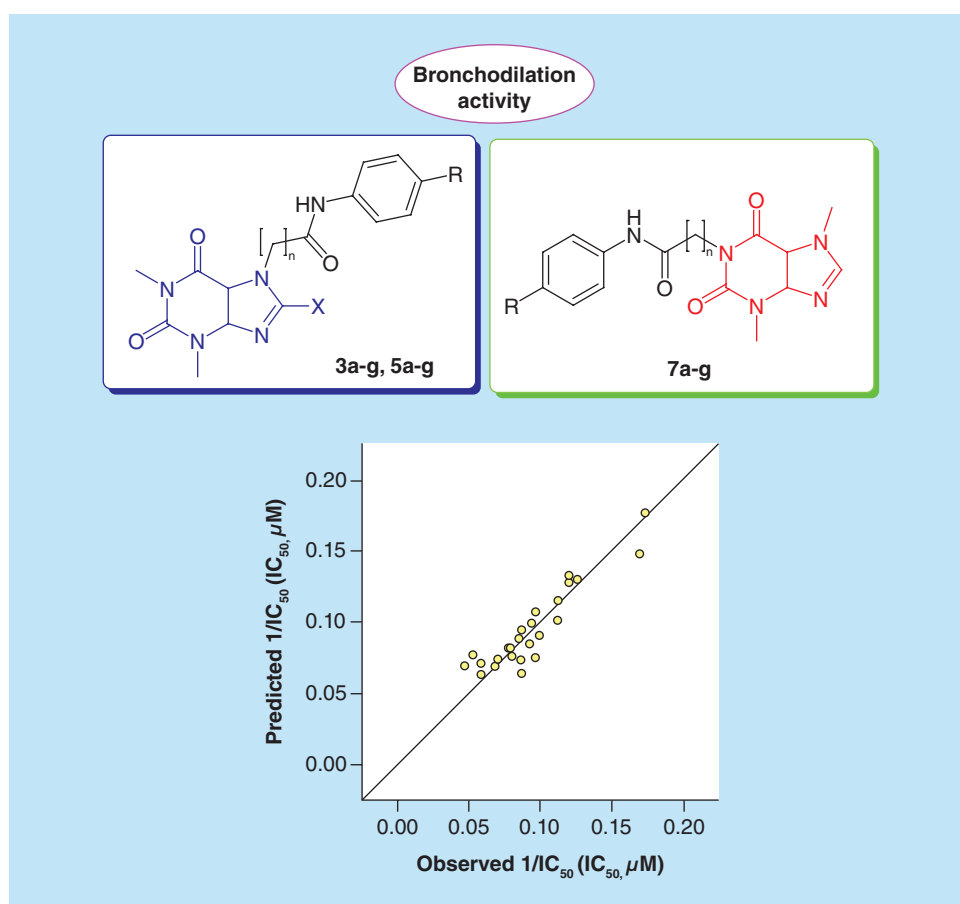
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Asthma as well as chronic obstructive pulmonary disease can be considered as complicated chronic pulmonary diseases that are characterized by inflammation, reversible airway obstruction, wheezing and respiratory distress. The asthmatic attacks are allergic in nature and are induced by different factors such as exercise, exposure to environmental allergens, chemicals, viral infection, irritants and antigen–antibody reaction [1,2]. Asthma affects many populations worldwide particularly children and its incidence is predicted to be increased dramatically from year to year as air pollution has increased significantly especially in the developing countries [3]. While there has been no permanent remedy for asthma, several cases can be managed by inhaled corticosteroids exemplified by beclomethasone [4], mast cell stabilizers (sodium cromoglycate) [5], leukotriene inhibitors (zafirlukast, montelukast and zileuton) [6–9] or 5-lipoxygenase inhibitors [4] to control the inflammation of the trachea and bronchi. Another strategy to control the acute attacks of asthma was achieved through the usage of short acting bronchodilators that aid in quick relief of the bronchial constriction, their action starts within minutes after inhalation and lasts for

2–4 h. Furthermore, the long-acting bronchodilators can be used every day to manage asthma [10–12]. The commonly used bronchodilators are inhaled β_2 sympathomimetics (albuterol) [10,11], parasympatolytics (ipratropium) [12] and xanthines (theophylline, aminophylline) [10]. A more recent approach has been conducted through using omalizumab, an IgG1 monoclonal antibody, to interrupt the immune cascade [13]. On the other hand, chronic obstructive pulmonary disease could be controlled by combination of inhaled corticosteroids, long-acting β_2 agonists and anticholinergics [14–16]. Despite the fact that theophylline was the first prescribed medication for asthma in 1921 [17], its side effects such as tachycardia, narrow therapeutic range and CNS stimulation [18,19] provoked the search for new candidates. Several trials were performed to obtain new xanthine derivatives with better biological profiles than theophylline. This was achieved through various substitutions at positions 3, 7 or 8. Thus, 1-methyl-3-isobutyl-8-(4-benzohydrilpiperazinoethyl)xanthine (S 9795) **I** was selected for clinical trials in asthmatic patients due to its long duration of action, its lack of CNS stimulating effects and its inhibitory activity on the mast cells degranulation and

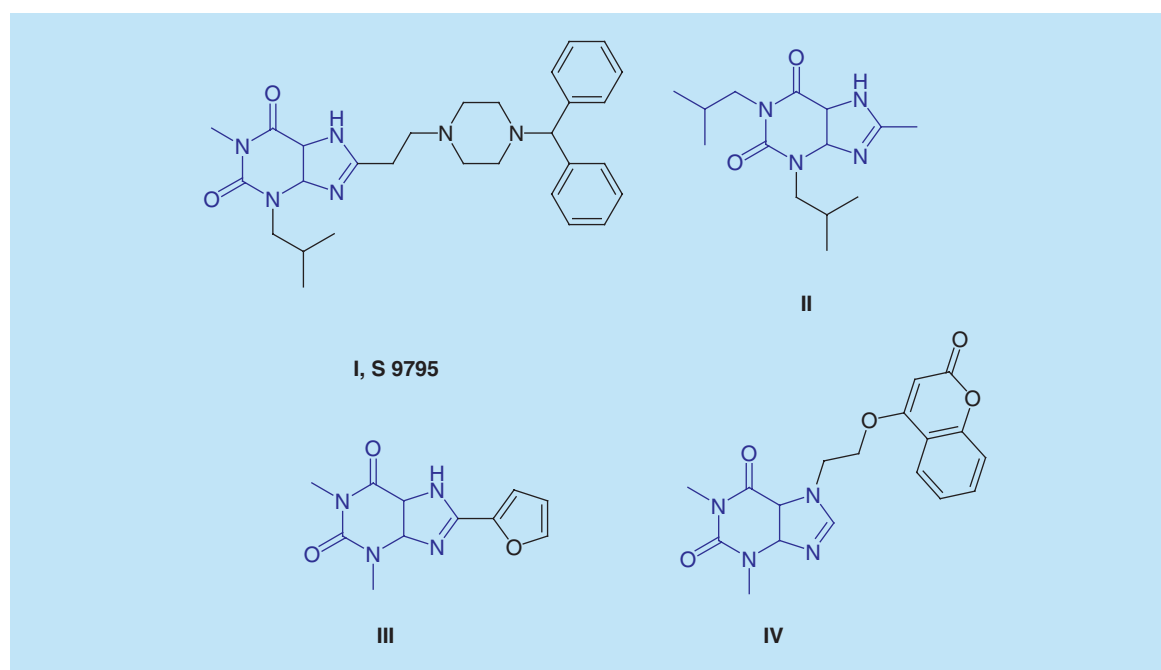


Figure 1. Representative examples of xanthine derivatives with bronchodilator activity.

phosphodiesterase [20]. Furthermore, 1,3-diisobutyl-8-methyl xanthine **II** revealed a good activity profile and a favorable therapeutic index, which was 14-folds greater than that of theophylline [21]. Moreover, hybridization of the xanthine scaffold with heterocyclic moieties resulted in compounds **III** and **IV** with better bronchodilator activities (Figure 1) [22,23]. Based on the previous findings, this research work aimed at preparing some xanthine derivatives through several structural modifications and screening them for their bronchodilator activity to obtain an integrated structure–activity relationship. That, substitution at position 7 with different *N*-phenylacetamides and their propanamide analogs was performed to study the effect of these moieties and the spacer on the bronchodilator activity. Additionally, bromination at 8-position was performed along with the substitution at position 7 using the same fragments to study the effect of a bulky group on the activity. Furthermore, the effect of the position of these moieties was studied, where theobromine structure was modified through introducing the same *N*-phenylacetamides/propanamides at position 1 (Figure 2). Finally, a 2D-QSAR study was performed to validate the obtained activity and investigate the structural parameters controlling the activity.

Materials & methods

Chemistry

Melting points were carried out by the open capillary tube method using a Stuart (Stone Staffordshire ST/50SA UK) apparatus and they were uncorrected. Infrared Spectra were performed on Shimadzu FT-IR 8400 S spectrometer Affinity A1 using potassium

bromide discs, and expressed in wave number (cm^{-1}). NMR spectra were recorded on a Bruker Ascend 400/R (^1H : 400 MHz, ^{13}C : 100 MHz) spectrophotometer (Supplementary Information). Chemical shift values (δ) were given in parts per million (p.p.m.) downfield from tetramethylsilane as an internal reference. Elemental analyses were carried out using FLASH 2000 CHNS/O analyzer, Thermo Scientific at the Regional Centre for Mycology and Biotechnology, Al-Azhar University, Nasr City, Cairo. Mass spectra were carried out on Direct Inlet part to mass analyzer in Thermo Scientific GCMS model ISQ at the Regional Centre for Mycology and Biotechnology, Al-Azhar University, Nasr City, Cairo. All the reactions were monitored by thin layer chromatography silica gel F 254, Aluminium sheets 20×20 cm (Sigma-Aldrich, Darmstadt, Germany) were used. Dichloromethane: methanol (1: 0.1) was the adopted elution system. The 2/3-chloro-*N*-arylacetamides/propanamide **1a-g** were prepared according to the reported procedures [24–36].

General procedure for the preparation of 3a-g

Theophylline **2** (2.77 mmol, 0.50 g) was added to a suspension of potassium carbonate (6.93 mmol, 0.96 g) or sodium hydride (9.16 mmol, 0.22 g) in DMF (12 ml) and stirred at 100°C for 2 h. A mixture of **1a-g** (5.55 mmol) and potassium iodide (1.38 mmol, 0.23 g) in DMF (4 ml) was added to the previous mixture and the resulted mixture was stirred at ($80\text{--}100^\circ\text{C}$). The product was monitored by TLC. At the end of the reaction, the mixture was cooled to room temperature and poured onto ice water (100 ml) then the pH was adjusted to 6 with hydrochloric acid 35%. The formed precipitate was filtered, washed with water and dried to yield the required product.

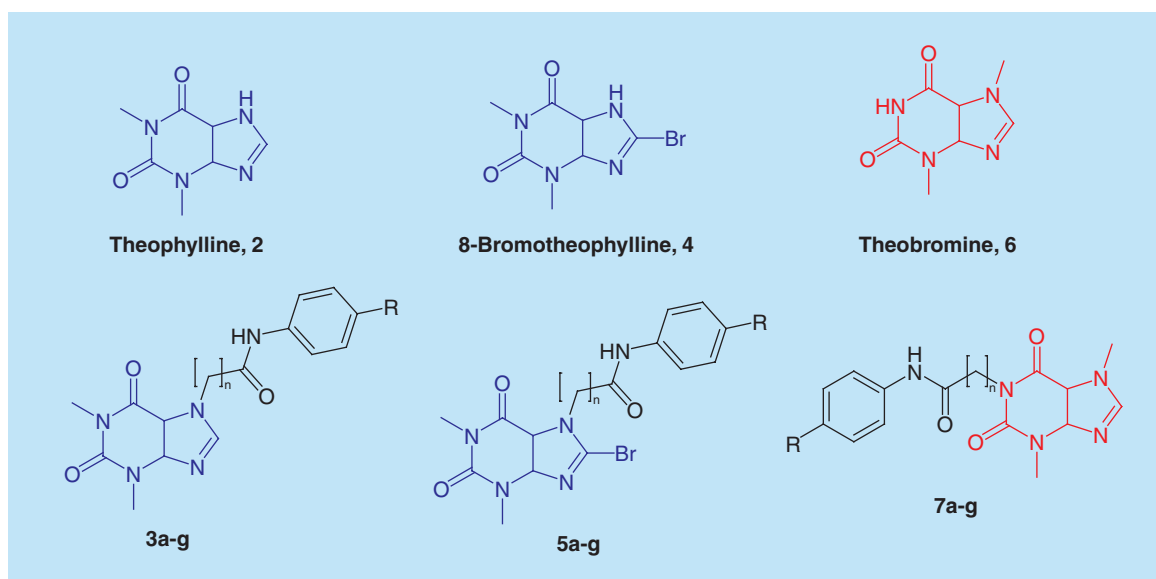


Figure 2. Structures of target compounds and their precursors.

2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-phenylacetamide 3a

It was prepared using **1a** in the presence of potassium carbonate and the reaction time was 17 h. The dried powder was recrystallized from ethanol to give pure buff powder, yield 0.79 g, 92%; mp 146–147°C, IR $\nu_{\max}$ cm⁻¹: 3138 (N-H amide), 3094–3061 (C-H aromatic), 2990–2947 (C-H aliphatic), 1699, 1659, 1643 (3 C=O), 1597 (N-H bending), 1553–1472 (C=C aromatic). ¹H NMR (CDCl₃) δ : 3.45 (s, 3H, CH₃), 3.61 (s, 3H, CH₃), 5.00 (s, 2H, CH₂), 7.10–7.17 (m, 1H, Ar-H), 7.30–7.40 (m, 2H, Ar-H), 7.45–7.60 (m, 2H, Ar-H), 7.79 (s, 1H, Ar-H), 9.52 (s, 1H, NH exchanged with D₂O). ¹³C NMR (DMSO-*d*₆) δ : 27.9 (CH₃), 29.9 (CH₃), 49.2 (CH₂), 106.9, 119.5, 124.0, 125.7, 129.3, 130.4, 139.1, 144.2, 148.4 (aromatic carbons), 151.5 (C=O), 154.9 (C=O), 165.3 (C=O). MS, *m/z*: 315.12 (M⁺+2), 314.13 (M⁺+1), 313.08 (M⁺), 193.05. Anal. Calcd for (C₁₅H₁₅N₅O₃): C, 57.50; H, 4.83; N, 22.35; found, C, 57.74; H, 4.87; N, 22.62.

2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-methoxyphenyl)acetamide 3b

It was prepared using **1b** in the presence of potassium carbonate and the reaction time was 17 h. The dried powder was recrystallized from ethanol to give pure grey powder, yield 0.45 g, 47%; mp 235–236°C, IR $\nu_{\max}$ cm⁻¹: 3140 (N-H amide), 3082–3005 (C-H aromatic), 2951–2835 (C-H aliphatic), 1701–1655 (3 C=O), 1605 (N-H bending), 1551–1458 (C=C aromatic). ¹H NMR (CDCl₃) δ : 3.47 (s, 3H, CH₃), 3.62 (s, 3H, CH₃), 3.78 (s, 3H, OCH₃), 4.98 (s, 2H, CH₂), 6.84 (d, 2H, *J* = 8.92 Hz, Ar-H), 7.44 (d, 2H, *J* = 8.92 Hz, Ar-H), 7.80 (s, 1H, Ar-H), 9.35 (s, 1H, NH exchanged with D₂O). ¹³C NMR (DMSO-*d*₆) δ : 27.8 (CH₃), 29.7 (CH₃), 49.1 (CH₂), 55.4 (OCH₃), 107.0, 113.9, 121.2, 131.6, 143.3, 148.4, 155.1 (aromatic carbons), 151.6 (C=O), 156.0 (C=O), 164.2 (C=O). Anal. Calcd for (C₁₆H₁₇N₅O₄): C, 55.97; H, 4.99; N, 20.40; found, C, 56.24; H, 5.06; N, 20.61.

2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-fluorophenyl)acetamide 3c

It was prepared using **1c** in the presence of potassium carbonate and the reaction time was 17 h. The dried powder was recrystallized from ethanol to give pure white granules, yield 0.50 g, 55%; mp 200–201°C, IR $\nu_{\max}$ cm⁻¹: 3125 (N-H amide), 3075–3001 (C-H aromatic), 2995 (C-H aliphatic), 1701, 1651 (3 C=O), 1605 (N-H bending), 1551–1458 (C=C aromatic). ¹H NMR (CDCl₃) δ : 3.32 (s, 3H, CH₃), 3.47 (s, 3H, CH₃), 4.98 (s, 2H, CH₂), 7.23 (t, 2H, *J* = 8.54 Hz, Ar-H), 7.46–7.44 (m, 2H, Ar-H), 7.79 (s, 1H, Ar-H), 9.58 (s, 1H, NH exchanged with D₂O).

¹³C NMR (DMSO-*d*₆) δ : 27.9 (CH₃), 29.9 (CH₃), 49.1 (CH₂), 106.9, 115.8, 116.0, 121.2, 121.3, 135.4, 144.2, 148.4, 166.7 (aromatic carbons), 151.5 (C=O), 154.9 (C=O), 165.3 (C=O). MS, *m/z*: 333.12 (M⁺+2), 332.10 (M⁺+1), 331.08 (M⁺), 123.06. Anal. Calcd for (C₁₅H₁₄FN₅O₃): C, 54.38; H, 4.26; N, 21.14; found, C, 54.49; H, 4.30; N, 21.30.

2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-sulfamoylphenyl)acetamide 3d

It was prepared using **1d** in the presence of potassium carbonate and the reaction time was 25 h. The dried powder was washed by hot methanol to give pure yellow powder, yield 0.43 g, 40%; mp 267–268°C, IR $\nu_{\max}$ cm⁻¹: 3271, 3194 (SO₂NH₂), 3117 (N-H amide), 3067 (C-H aromatic), 2997–2855 (C-H aliphatic), 1705–1659 (3 C=O amide), 1605 (N-H bending), 1597–1454 (C=C aromatic), 1381, 1153 (SO₂). ¹H NMR (DMSO-*d*₆) δ : 3.20 (s, 3H, CH₃), 3.36 (s, 2H, NH₂ exchanged with D₂O), 3.46 (s, 3H, CH₃), 5.25 (s, 2H, CH₂), 7.37 (s, 1H, NH exchanged with D₂O), 7.73 (d, 2H, *J* = 8.60 Hz, Ar-H), 7.90 (d, 2H, *J* = 8.40 Hz, Ar-H), 8.08 (s, 1H, Ar-H). ¹³C NMR (DMSO-*d*₆) δ : 27.9 (CH₃), 29.9 (CH₃), 49.3 (CH₂), 106.9, 119.2, 127.3, 139.2, 141.9, 144.2, 148.4 (aromatic carbons), 151.5 (C=O), 154.9 (C=O), 166.0 (C=O). MS, *m/z*: 392.18 (M⁺), 193.09. Anal. Calcd for (C₁₅H₁₆N₆O₅S): C, 45.91; H, 4.11; N, 21.42; found, C, 46.12; H, 4.18; N, 21.68.

3-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-phenylpropanamide 3e

It was prepared using **1e** in the presence of sodium hydride and the reaction time was 32 h to give pure yellow powder 0.60 g, 67%; mp 259–260°C, IR $\nu_{\max}$ cm⁻¹: 3117 (N-H amide), 3086–3024 (C-H aromatic), 2924, 2855 (C-H aliphatic), 1701, 1651 (3 C=O), 1605 (N-H bending), 1543–1439 (C=C aromatic). ¹H NMR (DMSO-*d*₆) δ : 2.96 (t, 2H, *J* = 6.28 Hz, CH₂), 3.24 (s, 3H, CH₃), 3.41 (s, 3H, CH₃), 4.53 (t, 2H, *J* = 6.24 Hz, CH₂), 7.02 (t, 3H, *J* = 7.26 Hz, Ar-H), 7.53 (d, 2H, *J* = 7.92 Hz, Ar-H), 8.00 (s, 1H, Ar-H), 9.97 (s, 1H, NH exchanged with D₂O). ¹³C NMR (DMSO-*d*₆) δ : 27.9 (CH₃), 29.7 (CH₃), 31.8 (CH₂), 37.1 (CH₂), 106.5, 119.7, 123.6, 128.7, 138.9, 142.7, 148.9 (aromatic carbons), 151.5 (C=O), 154.9 (C=O), 168.3 (C=O). Anal. Calcd for (C₁₆H₁₇N₅O₃): C, 58.71; H, 5.23; N, 21.39; found, C, 58.94; H, 5.30; N, 21.62.

3-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-methoxyphenyl)propanamide 3f

It was prepared using **1f** in the presence of sodium hydride and the reaction time was 35 h to give grey

powder, yield 0.42 g, 42%; mp 128–130°C, IR $\nu_{\max}$ cm^{-1} : 3140 (N-H amide), 3094 (C-H aromatic), 2924, 2850 (C-H aliphatic), 1697, 1647 (3 C=O), 1558, 1458 (C=C aromatic). ^1H NMR (DMSO- d_6) δ : 2.90 (t, 2H, J = 6.44 Hz, CH_2), 3.25 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.52 (t, 2H, J = 6.42 Hz, CH_2), 6.85 (d, 2H, J = 9.00 Hz, Ar-H), 7.43 (d, 2H, J = 8.96 Hz, Ar-H), 7.99 (s, 1H, Ar-H), 9.83 (s, 1H, NH exchanged with D_2O). ^{13}C NMR (DMSO- d_6) δ : 28.0 (CH_3), 29.9 (CH_3), 37.0 (CH_2), 43.1 (CH_2), 55.6 (OCH_3), 106.3, 114.2, 121.1, 132.4, 143.3, 148.9, 155.7 (aromatic carbons), 151.5 (C=O), 154.8 (C=O), 168.1 (C=O). MS, m/z : 359.22 ($\text{M}^+ + 2$), 358.15 ($\text{M}^+ + 1$), 357.18 (M^+), 122.07. Anal. Calcd for ($\text{C}_{17}\text{H}_{19}\text{N}_5\text{O}_4$): C, 57.14; H, 5.36; N, 19.60; found, C, 57.36; H, 5.43; N, 19.84.

3-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-fluorophenyl)propanamide **3g**

It was prepared using **1g** in the presence of sodium hydride and the reaction time was 32 h. The dried powder was washed with methanol to give white powder, yield 0.36 g, 38%; m.p 267–268°C, IR $\nu_{\max}$ cm^{-1} : 3155 (N-H amide), 3086 (C-H aromatic), 2947, 2920 (C-H aliphatic), 1697, 1655, 1643 (3 C=O), 1620 (N-H bending), 1551–1458 (C=C aromatic). ^1H NMR (CDCl_3) δ : 2.98 (t, 2H, J = 6.44 Hz, CH_2), 3.42 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 4.62 (t, 2H, J = 6.48 Hz, CH_2), 6.97–7.02 (m, 3H, 2Ar-H + NH), 7.40–7.41 (m, 2H, Ar-H), 7.69 (s, 1H, Ar-H). ^{13}C NMR (DMSO- d_6) δ : 28.0 (CH_3), 29.9 (CH_3), 37.1 (CH_2), 43.0 (CH_2), 106.3, 115.6, 115.8, 121.2, 121.3, 135.7, 143.3, 148.9, 159.6 (aromatic carbons), 151.5 (C=O), 154.8 (C=O), 168.6 (C=O). MS, m/z : 347 ($\text{M}^+ + 2$), 346.14 ($\text{M}^+ + 1$), 345.11 (M^+), 180.04. Anal. Calcd for ($\text{C}_{16}\text{H}_{16}\text{FN}_5\text{O}_3$): C, 55.65; H, 4.67; N, 20.28; found, C, 55.80; H, 4.71; N, 20.45.

8-Bromo-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione **4**

To a mixture of theophylline **2** (27.75 mmol, 5.0 g) and sodium acetate (42.67 mmole, 3.52 g) in glacial acetic acid (50 ml), bromine (49.92 mmole, 2.61 ml) was added drop-wise. The resulted mixture was stirred for 25 h at room temperature then poured into ice water (200 ml) and cooled at 0°C for 20 min. The obtained precipitate was filtered, washed with cold water and dried, to give off white powder, yield 5.15 g, 71%; mp 295–296°C (reported 295–297°C) [37,38].

General procedure for the preparation of **5a-d**

8-Bromotheophylline **4** (1.93 mmol, 0.50 g) was added to a suspension of potassium carbonate (4.80 mmol, 0.66 g) in DMF (10 ml) and the mixture was stirred

at 100°C for 2 h. The appropriate 2-chloro-*N*-phenylacetamide **1a-d** (3.86 mmol) was dissolved in DMF (4 ml) and then added to the previous mixture. The resulted mixture was stirred at the appropriate temperature and the product was monitored by TLC. At the end of the reaction, the mixture was cooled to room temperature and poured onto ice water (100 ml) then the pH was adjusted to 6 with 35% hydrochloric acid. The formed precipitate was filtered off, washed with water and dried to give the product.

2-(8-Bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-phenylacetamide **5a**

It was prepared using **1a** and the reaction was stirred for 72 h at room temperature to give white powder, yield 0.57 g, 75%; mp 276–277°C, IR $\nu_{\max}$ cm^{-1} : 3275 (N-H amide), 3066 (C-H aromatic), 2951–2924 (C-H aliphatic), 1701–1670 (3 C=O), 1608 (N-H bending), 1543–1446 (C=C aromatic). ^1H NMR (CDCl_3) δ : 3.47 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 5.10 (s, 2H, CH_2), 7.14 (s, 1H, Ar-H), 7.31 (t, 2H, J = 7.20 Hz, Ar-H), 7.54 (d, 2H, J = 7.40 Hz, Ar-H), 9.00 (s, 1H, NH exchanged with D_2O). ^{13}C NMR (DMSO- d_6) δ : 27.9 (CH_3), 29.8 (CH_3), 49.3 (CH_2), 109.2, 119.6, 124.0, 128.9, 129.3, 138.4, 147.9 (aromatic carbons), 151.1 (C=O), 154.2 (C=O), 163.6 (C=O). Anal. Calcd for ($\text{C}_{15}\text{H}_{14}\text{BrN}_5\text{O}_3$): C, 45.94; H, 3.60; N, 17.86; found, C, 46.17; H, 3.55; N, 18.09.

2-(8-Bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-methoxyphenyl)acetamide **5b**

It was prepared using **1b** and the reaction was stirred for 72 h at room temperature to give white powder, yield 0.64 g, 79%; mp 238–240°C, IR $\nu_{\max}$ cm^{-1} : 3267 (N-H amide), 3067 (C-H aromatic), 2951–2932 (C-H aliphatic), 1701, 1659 (3 C=O), 1609 (N-H bending), 1539–1438 (C=C aromatic). ^1H NMR (CDCl_3) δ : 3.45 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.09 (s, 2H, CH_2), 6.86 (d, 2H, J = 8.44 Hz, Ar-H), 7.44 (d, 2H, J = 8.40 Hz, Ar-H), 8.88 (s, 1H, NH exchanged with D_2O). ^{13}C NMR (DMSO- d_6) δ : 28.0 (CH_3), 30.0 (CH_3), 49.3 (CH_2), 55.6 (OCH_3), 109.1, 114.5, 121.1, 130.1, 132.0, 147.9, 156.0 (aromatic carbons), 151.1 (C=O), 154.2 (C=O), 163.5 (C=O). MS, m/z : 424.03 ($\text{M}^+ + 2$), 423.02 ($\text{M}^+ + 1$), 422.06 (M^+), 123.06. Anal. Calcd for ($\text{C}_{16}\text{H}_{16}\text{BrN}_5\text{O}_4$): C, 45.51; H, 3.82; N, 16.59; found, C, 45.73; H, 3.80; N, 16.81.

2-(8-Bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-fluorophenyl)acetamide **5c**

It was prepared using **1c** and the reaction was stirred for 21 h at 60°C. The dried powder was recrystallized

from ethanol to give white solid, yield 0.33 g, 42%; mp 278–280°C, IR $\nu_{\max}$ cm^{-1} : 3290 (N-H amide), 3086–3001 (C-H aromatic), 2955–2928 (C-H aliphatic), 1701–1651 (3 C=O), 1609 (N-H bending), 1558–1450 (C=C aromatic). ^1H NMR ($\text{DMSO}-d_6$) δ : 3.18 (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 7.14 (t, 2H, $J = 8.64$ Hz, Ar-H), 7.56–7.62 (m, 2H, Ar-H), 9.33 (s, 1H, NH exchanged with D_2O). ^{13}C NMR ($\text{DMSO}-d_6$) δ : 27.7 (CH_3), 29.9 (CH_3), 46.7 (CH_2), 102.4, 115.6, 115.8, 120.2, 121.1, 135.7, 136.7, 147.9, 150.7 (aromatic carbons), 151.4 (C=O), 153.8 (C=O), 165.5 (C=O). MS, m/z : 411.38 ($\text{M}^+ + 1$), 410.44 (M^+), 94.10. Anal. Calcd for ($\text{C}_{15}\text{H}_{13}\text{BrFN}_5\text{O}_3$): C, 43.92; H, 3.19; N, 17.07; found, C, 44.17; H, 3.22; N, 17.32.

2-(8-Bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-sulfamoylphenyl)acetamide 5d

It was prepared using **1d** and the reaction was stirred for 11 h at 60°C. The dried powder was washed from hot ethanol to give pale grey powder, yield 0.80 g, 88%; mp 224–225°C, IR $\nu_{\max}$ cm^{-1} : 3447, 3393 (NH_2), 3196 (N-H amide), 3096–3069 (C-H aromatic), 2957–2853 (C-H aliphatic), 1695–1647 (3 C=O), 1628 (N-H bending), 1597–1442 (C=C aromatic). ^1H NMR ($\text{DMSO}-d_6$) δ : 3.20 (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 4.17 (s, 2H, NH_2 exchanged with D_2O), 4.82 (s, 2H, CH_2), 7.32 (d, 2H, $J = 8.64$ Hz, Ar-H), 7.54 (d, 2H, $J = 8.60$ Hz, Ar-H), 9.04 (s, 1H, NH exchanged with D_2O). ^{13}C NMR ($\text{DMSO}-d_6$) δ : 27.8 (CH_3), 29.9 (CH_3), 46.2 (CH_2), 102.9, 117.8, 127.2, 137.0, 139.3, 143.5, 147.8 (aromatic carbons), 151.4 (C=O), 153.9 (C=O), 168.5 (C=O). MS, m/z : 471.85 (M^+), 123.12. Anal. Calcd for ($\text{C}_{15}\text{H}_{15}\text{BrN}_6\text{O}_5\text{S}$): C, 38.23; H, 3.21; N, 17.83; found, C, 38.40; H, 3.18; N, 18.06.

General procedure for the preparation of 5e-g

8-Bromotheophylline **4** (1.93 mmol, 0.50 g) was added to a suspension of sodium hydride (5.79 mmol, 0.14 g) in DMF (10 ml) and the mixture was stirred at 100°C for 2 h. The appropriate 3-chloro-N-phenylpropanamide **1e-g** (3.86 mmol) was dissolved in DMF (4 ml) and then added to the previous mixture. The resulted mixture was stirred at 120°C for 20 h. At the end of the reaction, the mixture was cooled to room temperature and poured onto ice water (100 ml) then the pH was adjusted to 6 with 35% hydrochloric acid.

3-(8-Bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-phenylpropanamide 5e

It was prepared using **1e** and the dried powder was recrystallized from dichloromethane to give reddish white crystals, yield 0.10 g, 13%; mp 179–180°C,

IR $\nu_{\max}$ cm^{-1} : 3271 (N-H amide), 3086–3067 (C-H aromatic), 2924–2894 (C-H aliphatic), 1701–1651 (3 C=O), 1608 (N-H bending), 1543–1458 (C=C aromatic). ^1H NMR (CDCl_3) δ : 2.96 (t, 2H, $J = 7.14$ Hz, CH_2), 3.45 (s, 3H, CH_3), 3.59 (s, 3H, CH_3), 4.72 (t, 2H, $J = 6.92$ Hz, CH_2), 7.14 (t, 1H, $J = 7.18$ Hz, Ar-H), 7.35 (t, 2H, $J = 7.64$ Hz, Ar-H), 7.56 (d, 2H, $J = 7.76$ Hz, Ar-H), 8.14 (s, 1H, NH exchanged with D_2O). ^{13}C NMR ($\text{DMSO}-d_6$) δ : 28.1 (CH_3), 30.0 (CH_3), 36.9 (CH_2), 44.0 (CH_2), 108.6, 119.7, 123.8, 129.0, 129.1, 139.3, 148.4 (aromatic carbons), 151.2 (C=O), 154.0 (C=O), 168.2 (C=O). MS, m/z : 406.12 (M^+), 93.05. Anal. Calcd for ($\text{C}_{16}\text{H}_{16}\text{BrN}_5\text{O}_3$): C, 47.31; H, 3.97; N, 17.24; found, C, 47.59; H, 4.01; N, 17.52.

3-(8-Bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-methoxyphenyl)propanamide 5f

It was prepared using **1f** and the dried powder was recrystallized from dichloromethane to give white powder, yield 0.22 g, 26%; mp 220–222°C, IR $\nu_{\max}$ cm^{-1} : 3287 (N-H amide), 3063 (C-H aromatic), 2951–2855 (C-H aliphatic), 1701, 1670, 1647 (3 C=O), 1601 (N-H bending), 1543–1450 (C=C aromatic). ^1H NMR (CDCl_3) δ : 2.94 (t, 2H, $J = 7.44$ Hz, CH_2), 3.44 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.71 (t, 2H, $J = 7.44$ Hz, CH_2), 6.88 (d, 2H, $J = 8.96$ Hz, Ar-H), 7.45 (d, 2H, $J = 8.92$ Hz, Ar-H), 7.98 (s, 1H, NH exchanged with D_2O). ^{13}C NMR ($\text{DMSO}-d_6$) δ : 23.4 (CH_3), 25.3 (CH_3), 33.3 (CH_2), 39.5 (CH_2), 50.7 (OCH_3), 103.8, 109.4, 116.9, 123.5, 126.0, 144.01, 146.4 (aromatic carbons), 149.8 (C=O), 151.8 (C=O), 162.1 (C=O). Anal. Calcd for ($\text{C}_{17}\text{H}_{18}\text{BrN}_5\text{O}_4$): C, 46.80; H, 4.16; N, 16.05; found, C, 46.97; H, 4.22; N, 16.31.

3-(8-Bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-fluorophenyl)propanamide 5g

It was prepared using **1g** and the dried powder was recrystallized from ethanol to give white powder, yield 0.22 g, 27%; mp 217–219°C, IR $\nu_{\max}$ cm^{-1} : 3302 (N-H amide), 3063 (C-H aromatic), 2924 (C-H aliphatic), 1697–1659 (3 C=O), 1612 (N-H bending), 1535–1462 (C=C aromatic). ^1H NMR (CDCl_3) δ : 2.95 (t, 2H, $J = 7.24$ Hz, CH_2), 3.45 (s, 3H, CH_3), 3.59 (s, 3H, CH_3), 4.71 (t, 2H, $J = 7.10$ Hz, CH_2), 7.04 (t, 2H, $J = 8.48$ Hz, Ar-H), 7.51–7.55 (m, 2H, Ar-H), 8.19 (s, 1H, NH exchanged with D_2O). ^{13}C NMR ($\text{DMSO}-d_6$) δ : 28.1 (CH_3), 30.0 (CH_3), 36.8 (CH_2), 44.0 (CH_2), 108.6, 115.6, 115.8, 121.4, 121.5, 128.8, 135.7, 148.4, 160.0 (aromatic carbons), 151.2 (C=O), 154.0 (C=O), 168.1 (C=O). MS, m/z : 426.01 ($\text{M}^+ + 1$), 424.98 (M^+),

344.15. Anal. Calcd for (C₁₆H₁₅BrFN₅O₃): C, 45.30; H, 3.56; N, 16.51; found, C, 45.47; H, 3.54; N, 16.79.

General procedure for the preparation of 7a-g

Theobromine **6** (2.77 mmol, 0.50 g) was added to a suspension of potassium carbonate (6.93 mmol, 0.96 g) or sodium hydride (9.16 mmol, 0.22 g) in DMF (12 ml) and the mixture was stirred at 100°C for 2 h. A mixture of the appropriate 2/3-chloro-*N*-phenylacetamide/propanamide **1a-g** (5.55 mmol) and potassium iodide (1.38 mmol, 0.23 g) in DMF (4 ml) was added to the previous mixture and the resulted mixture was stirred at (80–100°C). The product was monitored by TLC. At the end of the reaction, the mixture was cooled to room temperature and poured onto ice water (100 ml) then the pH was adjusted to 6 with 35% hydrochloric acid. The formed precipitate was filtered, washed with water and dried to obtain **7a-g**.

2-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-*N*-phenylacetamide 7a

It was prepared using **1a** in the presence of potassium carbonate and the reaction time was 17 h. The dried powder was recrystallized from ethanol to give white powder, yield 0.22 g, 25%; mp 250–252°C, IR Y_{max} cm⁻¹: 3264 (N-H amide), 3067 (C-H aromatic), 2951 (C-H aliphatic), 1709, 1655 (3 C=O), 1601 (N-H bending), 1543–1447 (C=C aromatic). ¹H NMR (CDCl₃) δ: 3.61 (s, 3H, CH₃), 4.00 (s, 3H, CH₃), 4.86 (s, 2H, CH₂), 7.08 (t, 1H, *J* = 7.18 Hz, Ar-H), 7.26–7.39 (m, 2H, Ar-H), 7.46–7.52 (m, 2H, Ar-H), 7.56 (s, 1H, Ar-H), 7.97 (s, 1H, NH exchanged with D₂O). ¹³C NMR (DMSO-*d*₆) δ: 29.9 (CH₃), 33.6 (CH₃), 43.8 (CH₂), 107.0, 119.5, 125.7, 129.3, 139.2, 143.7, 149.0 (aromatic carbons), 151.4 (C=O), 154.6 (C=O), 166.2 (C=O). MS, *m/z*: 314.11 (M⁺+1), 313.09 (M⁺), 193.06. Anal. Calcd for (C₁₅H₁₅N₅O₃): C, 57.50; H, 4.83; N, 22.35; found, C, 57.68; H, 4.89; N, 22.57.

2-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-*N*-(4-methoxyphenyl)acetamide 7b

It was prepared using **1b** in the presence of potassium carbonate and the reaction time was 22 h. The dried powder was recrystallized from ethanol to give yellow powder, yield 0.21 g, 22%; mp 257–259°C, IR Y_{max} cm⁻¹: 3260 (N-H amide), 3078 (C-H aromatic), 2959, 2924 (C-H aliphatic), 1709, 1663 (3 C=O), 1601 (N-H bending), 1547–1458 (C=C aromatic). ¹H NMR (CDCl₃) δ: 3.62 (s, 3H, CH₃), 3.80 (s, 3H, CH₃), 4.01 (s, 3H, OCH₃), 4.84 (s, 2H, CH₂), 6.84 (d, 2H, *J* = 8.84 Hz, Ar-H), 7.44 (d, 2H, *J* = 8.84 Hz, Ar-H), 7.56 (s, 1H, Ar-H), 7.64 (s, 1H,

NH exchanged with D₂O). ¹³C NMR (DMSO-*d*₆) δ: 29.9 (CH₃), 33.7 (CH₃), 43.7 (CH₂), 55.6 (OCH₃), 107.1, 114.4, 121.0, 132.4, 143.7, 149.0, 155.7 (aromatic carbons), 151.4 (C=O), 154.7 (C=O), 165.6 (C=O). MS, *m/z*: 345.13 (M⁺+2), 344.13 (M⁺+1), 343.10 (M⁺), 193.06. Anal. Calcd for (C₁₆H₁₇N₅O₄): C, 55.97; H, 4.99; N, 20.40; found, C, 56.12; H, 5.06; N, 20.64.

2-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-*N*-(4-fluorophenyl)acetamide 7c

It was prepared using **1c** in the presence of potassium carbonate and the reaction time was 20 h. The dried powder was recrystallized from ethanol to give white powder, yield 0.62 g, 67%; 280–281°C, IR Y_{max} cm⁻¹: 3264 (N-H amide), 3071 (C-H aromatic), 2955–2854 (C-H aliphatic), 1713, 1663 (3 C=O), 1605 (N-H bending), 1543–1454 (C=C aromatic). ¹H NMR (DMSO-*d*₆) δ: 3.44 (s, 3H, CH₃), 3.89 (s, 3H, CH₃), 4.66 (s, 2H, CH₂), 7.15 (t, 2H, *J* = 8.88 Hz, Ar-H), 7.58 (d, 2H, *J* = 5.00 Hz, Ar-H), 8.08 (s, 1H, Ar-H), 10.29 (s, 1H, NH exchanged with D₂O). ¹³C NMR (DMSO-*d*₆) δ: 29.7 (CH₃), 33.5 (CH₃), 43.7 (CH₂), 107.2, 115.2, 121.5, 135.2, 142.7, 149.00, 159.8 (aromatic carbons), 151.4 (C=O), 154.7 (C=O), 166.1 (C=O). Anal. Calcd for (C₁₅H₁₄FN₅O₃): C, 54.38; H, 4.26; N, 21.14; found, C, 54.59; H, 4.33; N, 21.38.

2-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-*N*-(4-sulfamoylphenyl)acetamide 7d

It was prepared using **1d** in the presence of potassium carbonate and the reaction time was 18 h. The dried powder was washed with hot ethanol to give pale brown powder, yield 0.42 g, 39%; mp 202–203°C, IR Y_{max} cm⁻¹: 3285, 3275 (SO₂NH₂), 3117 (N-H amide), 3071 (C-H aromatic), 2959 (C-H aliphatic), 1701–1655 (3 C=O), 1593 (N-H bending), 1543–1458 (C=C aromatic), 1315, 1157 (SO₂). ¹H NMR (DMSO-*d*₆) δ: 3.45 (s, 3H, CH₃), 3.89 (s, 3H, CH₃), 4.71 (s, 2H, CH₂), 7.08 (s, 1H, NH exchanged with D₂O), 7.27 (s, 2H, NH₂ exchanged with D₂O), 7.72 (d, 2H, *J* = 8.80 Hz, Ar-H), 7.77 (d, 2H, *J* = 8.80 Hz, Ar-H), 8.08 (s, 1H, Ar-H). ¹³C NMR (DMSO-*d*₆) δ: 29.9 (CH₃), 33.7 (CH₃), 44.0 (CH₂), 107.0, 112.9, 119.1, 127.2, 127.9, 139.0, 142.1, 143.8, 149.0 (aromatic carbons), 151.4 (C=O), 154.6 (C=O), 166.8 (C=O). MS, *m/z*: 392.11 (M⁺), 65.06. Anal. Calcd for (C₁₅H₁₆N₆O₅S): C, 45.91; H, 4.11; N, 21.42; found, C, 46.23; H, 4.18; N, 21.70.

3-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-*N*-phenylpropanamide 7e

It was prepared using **1e** in the presence of sodium hydride and the reaction time was 32 h to give white powder, yield 0.54 g, 60%; mp 101–102°C, IR Y_{max}

cm⁻¹: 3256 (N-H amide), 3098 (C-H aromatic), 2924 (C-H aliphatic), 1694, 1670, 1643 (3 C=O), 1601 (N-H bending), 1555–1447 (C=C aromatic). ¹H NMR (CDCl₃) δ: 2.85 (t, 2H, *J* = 6.86 Hz, CH₂), 3.61 (s, 3H, CH₃), 4.00 (s, 3H, CH₃), 4.44 (t, 2H, *J* = 6.94 Hz, CH₂), 7.10 (t, 1H, *J* = 7.32 Hz, Ar-H), 7.32 (t, 2H, *J* = 7.86 Hz, Ar-H), 7.55 (s, 1H, Ar-H), 7.58 (d, 2H, *J* = 7.84 Hz, Ar-H), 8.51 (s, 1H, NH exchanged with D₂O). ¹³C NMR (DMSO-*d*₆) δ: 29.8 (CH₃), 33.6 (CH₃), 35.1 (CH₂), 37.6 (CH₂), 107.1, 115.5, 115.7, 121.4, 121.5, 135.8, 135.9, 143.4, 148.7 (aromatic carbons), 151.2 (C=O), 154.7 (C=O), 169.3 (C=O). MS, *m/z*: 328.16 (M⁺+1), 327.17 (M⁺), 93.07. Anal. Calcd for (C₁₆H₁₇N₅O₃): C, 58.71; H, 5.23; N, 21.39; found, C, 58.98; H, 5.30; N, 21.62.

3-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(4-methoxyphenyl)propanamide 7f

It was prepared using **1f** in the presence of sodium hydride and the reaction time was 35 h to give grey powder, yield 0.56 g, 0.56%, mp 125–127°C, IR Y_{max} cm⁻¹: 3291 (N-H amide), 3090–3024 (C-H aromatic), 2928–2832 (C-H aliphatic), 1701–1651 (3 C=O), 1609 (N-H bending), 1551–1492 (C=C aromatic). ¹H NMR (CDCl₃) δ: 2.59 (t, 2H, *J* = 6.20 Hz, CH₂), 3.37 (s, 3H, CH₃), 3.56 (s, 3H, CH₃), 3.68 (s, 3H, OCH₃), 4.18 (t, 2H, *J* = 6.24 Hz, CH₂), 6.62 (d, 2H, *J* = 8.44 Hz, Ar-H), 7.04 (s, 1H, Ar-H), 7.24 (d, 2H, *J* = 8.40 Hz, Ar-H), 8.09 (s, 1H, NH exchanged with D₂O). ¹³C NMR (DMSO-*d*₆) δ: 29.8 (CH₃), 33.6 (CH₃), 35.0 (CH₂), 37.7 (CH₂), 55.6 (OCH₃), 107.1, 114.2, 121.4, 132.7, 143.4, 148.7, 155.6 (aromatic carbons), 151.2 (C=O), 154.7 (C=O), 168.8 (C=O). MS, *m/z*: 359.18 (M⁺+2), 358.17 (M⁺+1), 357.14 (M⁺), 181.06. Anal. Calcd for (C₁₇H₁₉N₅O₄): C, 57.14; H, 5.36; N, 19.60; found, C, 57.09; H, 5.43; N, 19.78.

3-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-(4-fluorophenyl)propanamide 7g

It was prepared using **1g** in the presence of sodium hydride and the reaction time was 35 h. The dried powder was recrystallized from methanol to give pale green crystals, yield 0.48 g, 50%; mp 234–236°C, IR Y_{max} cm⁻¹: 3287 (N-H amide), 3067–3048 (C-H aromatic), 2924–2855 (C-H aliphatic), 1701, 1651 (3 C=O), 1616 (N-H bending), 1543–1458 (C=C aromatic). ¹H NMR (CDCl₃) δ: 2.87 (t, 2H, *J* = 6.70 Hz, CH₂), 3.63 (s, 3H, CH₃), 4.02 (s, 3H, CH₃), 4.44 (t, 2H, *J* = 6.66 Hz, CH₂), 7.02 (t, 2H, *J* = 8.72 Hz, Ar-H), 7.54–7.59 (m, 3H, Ar-H), 8.53 (s, 1H, NH exchanged with D₂O). ¹³C NMR (CDCl₃) δ: 24.9 (CH₃), 28.7 (CH₃), 30.7 (CH₂), 33.0 (CH₂), 102.7, 110.2, 110.4, 116.6, 116.7, 137.1, 144.0, 146.6, 150.2 (aromatic carbons), 152.8 (C=O), 155.2 (C=O), 164.1 (C=O).

Anal. Calcd for (C₁₆H₁₆FN₅O₃): C, 55.65; H, 4.67; N, 20.28; found, C, 55.91; H, 4.73; N, 20.49.

Bronchodilation properties screening

The bronchodilation activity screening procedures were carried out according to the reported techniques [39,40] by testing the effects of the prepared xanthine derivatives **3a-g**, **5a-g** and **7a-g** and their precursors theophylline **2**, 8-bromotheophylline **4** and theobromine **6** on isolated guinea pig tracheal rings (350–400 g). The tracheas were quickly dissected from guinea pigs that were sacrificed by vertebral dislocation after very light anesthesia (according to the ethics approved by the Research Ethics Committee at the Faculty of Pharmacy, Cairo University, Cairo, Egypt) and placed in a Petri dish containing physiological salt solution. The tracheas were cleaned from adherent connective tissues as much as possible and cut into rings of 2–3-mm length and each ring was placed in a vertical chamber '10 ml jacketed automatic multichamber organ bath system (Model no. ML870B6/C, Panlab, Spain)' filled with Krebs solution composed of (in mM): NaCl, 118.0; KCl, 4.7; NaHCO₃, 25.0; CaCl₂, 1.8; NaH₂PO₄, 1.2; MgSO₄, 1.2; glucose, 11.0 and oxygenated with bubbles of carbogen gas (95% O₂/5% CO₂) at 37 ± 0.5°C. Each trachea ring was mounted between two stainless steel hooks. The lower hook was fixed between two plates, while the upper one was attached to a force displacement transducer (Model no. MLT0201, Panlab, Barcelona, Spain) connected to an amplifier (PowerLab, AD Instruments Pty. Ltd., Bella Vista, Australia) in turn connected to a computer. The Chart for windows (v 3.4) software was used to record and elaborate the data. Preparations were stabilized under 1 g resting tension during 1 h and then the contracture response to histamine (10⁻⁶ M) was measured before and after exposure to increasing concentrations of the tested synthesized compounds. The tested compounds were dissolved in dimethylsulfoxide as stock solution (10 ml of 10⁻³ M). Control experiments were performed in the presence of dimethylsulfoxide alone, at the same concentrations as those used with the tested derivatives, which demonstrated that the solvent did not affect the contractile response of isolated trachea. The mean of three successive runs were used in each case to extract the experimental data. The observed bronchodilation activity screening data are represented in **Table 1** and the potency (IC₅₀, concentration necessary for 50% reduction of maximal histamine-induced contracture) was determined.

2D-QSAR study

2D-QSAR studies were undertaken utilizing comprehensive descriptors for structural and statistical analysis

Table 1. Observed and estimated/predicted bronchodilation activity values for the tested compounds.

Entry	Compound	Observed (experimental) IC_{50} , μM	Estimated IC_{50} , μM	Error [†]
1	Theophylline, 2	12.65	12.27	0.38
2	3a	10.63	10.19	0.44
3	3b	12.44	12.33	0.11
4	3c	11.72	11.40	0.32
5	3d	5.76	5.71	0.05
6	3e	21.30	14.56	6.74
7	3f	5.91	6.80	-0.89
8	3g	12.50	13.24	-0.74
9	8-Bromotheophylline, 4	8.93	8.78	0.15
10	5a	10.83	11.94	-1.11
11	5b	14.56	14.59	-0.03
12	5c	17.00	14.32	2.68
13	5d	8.37	7.58	0.79
14	5e	11.48	15.73	-4.25
15	5f	10.36	9.43	0.93
16	5g	17.00	15.94	1.06
17	Theobromine, 6	11.47	10.78	0.69
18	7a	10.09	11.13	-1.04
19	7b	14.17	13.58	0.59
20	7c	10.40	13.50	-3.10
21	7d	8.37	7.87	0.50
22	7e	7.94	7.79	0.15
23	7f	11.63	13.64	-2.01
24	7g	18.94	13.06	5.88

[†]Error is the difference between the experimentally observed and estimated bioactivity values.

(CODESSA-Pro) software. The bioactive compounds (**3a–g**, **5a–g** and **7a–g**, in addition to theophylline **2**, 8-bromotheophylline **4** and theobromine **6**) were used as a training set for constructing the QSAR model. Geometry of the training set compounds was initially optimized by AM1 technique [41–51] then, exported to CODESSA-Pro that includes MOPAC capability for the final geometry optimization. CODESSA-Pro calculated 771 molecular descriptors (constitutional, topological, geometrical, charge-related, semiempirical, molecular-type, atomic-type and bond-type descriptors) for the exported 24 training set compounds. Different mathematical transformations [including property, 1/property, log(property) and 1/log(property)] of the experimentally observed bronchodilator property/activity (IC_{50} , μM) of the training set compounds were utilized searching for the best QSAR model. The best multi-linear regression (BMLR) technique was utilized which

is a stepwise search for the best n -parameter regression equations (where n stands for the number of descriptors used), based on the highest R^2 (squared correlation coefficient), R^2_{cvOO} (squared cross-validation 'leave one-out, LOO' coefficient), R^2_{cvMO} (squared cross-validation 'leave many-out, LMO' coefficient), F (Fisher statistical significance criteria) values, and s^2 (standard deviation). The QSAR models up to 5-descriptor model describing the bioactivity of the bronchodilator active agents were generated.

Results & discussion

Chemistry

The 2/3-chloro-*N*-arylacetamides/propanamides **1a–g** were prepared as outlined in Figure 3 according to the reported procedures [24–36]. Heating of theophylline **2** with **1a–g** at 80–100°C in DMF in the presence of catalytic amount of potassium iodide

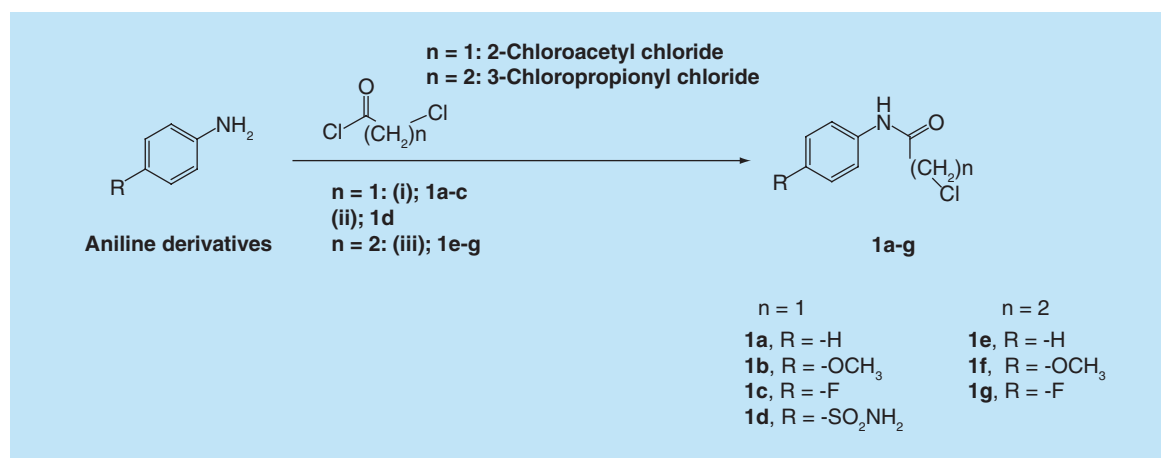


Figure 3. Synthesis of 2/3-chloro-N-arylacetamides/propanamides 1a-g. Reagents and reaction conditions: (i) 2N NaOH, CH₂Cl₂, r.t., 30 min; (ii) trimethylamine, DMF, r.t., 4–25 h; (iii) trimethylamine, ethylacetate, r.t., 1 h.

and either potassium carbonate or sodium hydride resulted in **3a-d** or **3e-g**, respectively (Figure 4). IR spectra of **3a-g** showed bands at 1705–1643 cm⁻¹ corresponding to 3 C=O, additionally, IR spectrum of **3d** showed bands at 3347, 3271 cm⁻¹ and 1381, 1153 cm⁻¹

attributed to NH₂ and SO₂, respectively. ¹H NMR spectra of **3a-d** revealed three singlet signals at 3.20–3.47, 3.20–3.62 and 4.98–5.25 p.p.m. due to 2 CH₃ and CH₂, respectively, in addition to an exchangeable NH singlet at 9.35–9.58 p.p.m. Compound **3b**

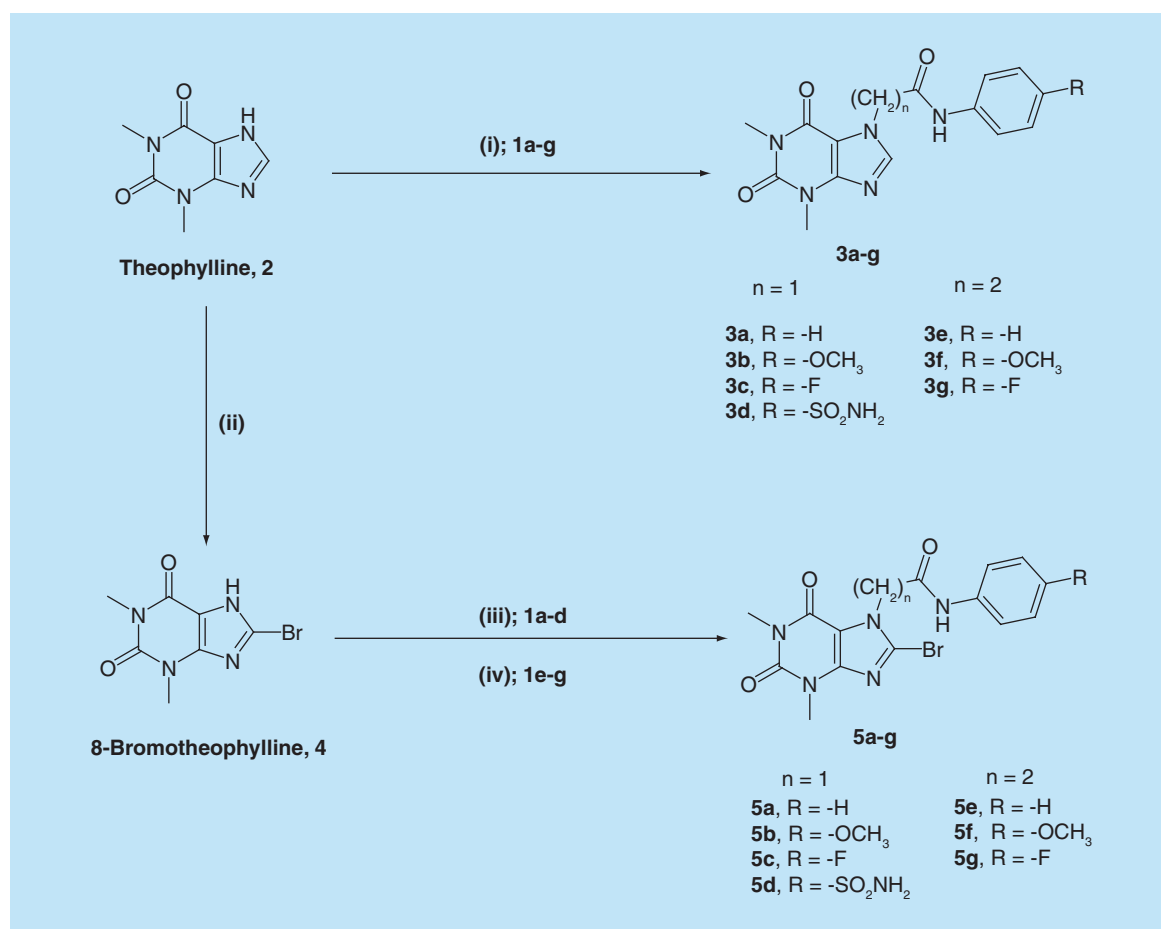


Figure 4. Synthesis of target compounds. 3a-g and 5a-g. Reagents and reaction conditions: (i) K₂CO₃ or NaH, KI, DMF, 80–100°C, 17–35 h; (ii) Br₂, NaOAc, HOAc, r.t., 25 h; (iii) K₂CO₃, DMF, r.t., -60°C, 11–72 h; (iv) NaH, DMF, 120°C, 20 h.

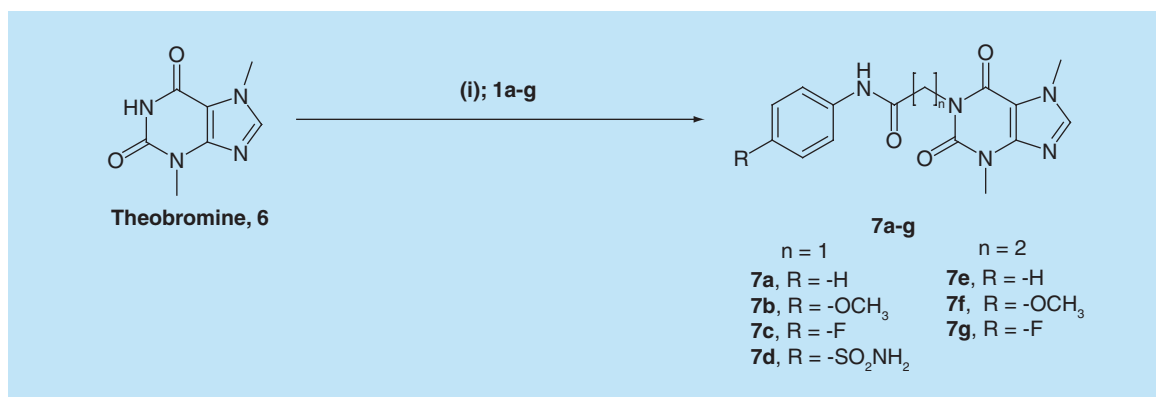


Figure 5. Synthesis of target compounds 7a-g. Reagents and reaction conditions: (i) K₂CO₃ or NaH, KI, DMF, 80–100°C, 17–35 h.

showed an additional singlet at 3.78 p.p.m. due to OCH₃ group. Its ¹³C NMR spectrum revealed signals at 27.8, 29.7, 49.1 and 55.4 due to 2 CH₃, CH₂ and OCH₃ carbons, respectively. In case of compound **3d**, ¹H NMR spectrum showed two exchangeable singlet signals at 3.36 and 7.73 p.p.m. due to NH₂ and NH, respectively. On the other hand, ¹H NMR spectra of the propanamide derivatives **3e-g** showed two triplets at 2.76–2.98 and 3.41–4.62 p.p.m., corresponding to two CH₂. Furthermore, ¹³C NMR spectrum of compound **3e** revealed signals at 27.9, 29.7, 31.8 and 37.1 p.p.m. attributed to 2 CH₃ and 2CH₂ carbons, respectively (Supplementary Information). Similarly, the *N*-alkylation of 8-bromotheophylline **4** with 2-chloro-*N*-arylacetamides **1a-d** was achieved using potassium carbonate in DMF at lower reaction temperature (r.t. –60°C) and longer stirring time (up to 72 h) to obtain the target compounds **5a-d** in a good yield. Degradation of these target compounds were observed when a higher temperature was used. On the other hand, the target compounds **5e-g** were obtained by the reaction of 8-bromotheophylline **4** and 3-chloro-*N*-arylpropanamides **1e-g** in the presence of sodium hydride at higher temperature (100–120°C). The obtained structures of **5a-g** were confirmed by their spectral and elemental analyses. Further, *N*-alkylation of theobromine **6** with **1a-g** to obtain **7a-g** was carried out applying the same procedures for the preparation of theophylline analogs **3a-g** (Figure 5). ¹H NMR spectra of the target compounds **7a-d** revealed singlet signals at 3.33–3.62, 3.80–4.00 and 4.66–4.99 p.p.m. due to 2CH₃ and CH₂ protons, respectively, in addition to, the aromatic and the exchangeable signals of NH at 6.84–11.09 p.p.m. In case of compound **7b**, its ¹H NMR spectra revealed an additional singlet at 4.01 p.p.m. due to OCH₃ protons. ¹H NMR spectra of compounds **7e-g** showed two triplets at 2.50–2.87 and 3.40–4.44 p.p.m. corresponding to 2 CH₂. ¹³C NMR of compound **7g**, as a

representative example showed signals at δ 24.9, 28.7, 30.7 and 32.96 p.p.m. corresponding to 2 CH₃ and 2 CH₂ carbons, respectively.

Bronchodilator activity

The *in vitro* bronchodilator activity of the target compounds **3a-g**, **5a-g** and **7a-g**, along with their precursors, theophylline **2**, 8-bromotheophylline **4** and theobromine **6** was investigated *in vitro* using isolated guinea pig tracheal rings precontracted with histamine according to the standard reported technique [39,40]. The principle in this *in vitro* screening assay depends on the ability of tested compounds to inhibit the constriction stimulated by histamine in order to assess their bronchodilation activity. The observed activity was expressed as IC₅₀, concentration of compounds necessary to reduce maximal histamine-induced contracture

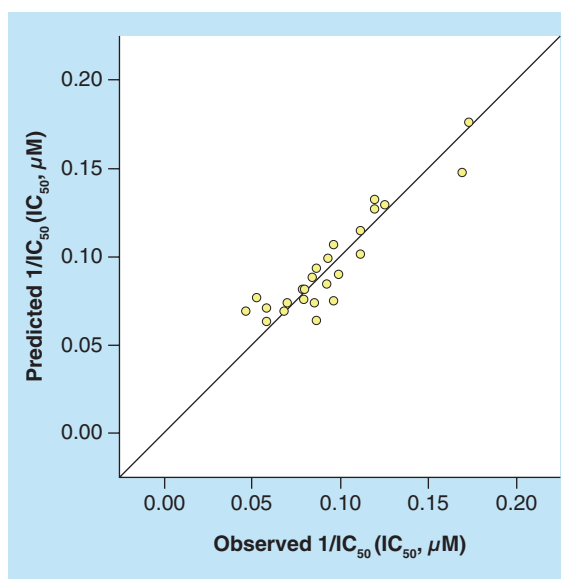


Figure 6. BMLR-QSAR model plot of correlations representing the observed versus predicted 1/IC₅₀, μM values for the bronchodilator active agents.

by 50% in guinea pig isolated tracheal rings and the results were presented in Table 1. From the obtained results (Table 1), it can be observed that the bronchodilator activity of theophylline ($IC_{50} = 12.65 \mu M$) was enhanced by bromination at position 8 (8-bromotheophylline, $IC_{50} = 8.93 \mu M$) and was slightly increased in case of its positional isomer; theobromine ($IC_{50} = 11.47 \mu M$). Moreover, theophylline derivatives with phenyl acetamide substituents **3a-c** revealed better activity than their phenyl propanamide congeners **3e-g**, but, compound **3f** ($IC_{50} = 5.91 \mu M$) was an exception. Furthermore, substitution with an electron withdrawing group was more favorable than an electron donating group and the *p*-sulfonamide derivative **3d** was the most active compound in this series with IC_{50} of $5.76 \mu M$.

Concerning the positional isomers **7a-g**, the phenyl propanamide substitutions **7e-g** were more favorable than their phenyl acetamide derivatives **7a-c**, except for the *p*-fluoro derivative **7c**, which was more potent than its homolog **7g**. Also, the unsubstituted phenyl propanamide derivative **7e** was the most active compound in this series with IC_{50} of $7.94 \mu M$.

Interestingly, the *p*-sulfonamide derivative **7d** showed promising activity with IC_{50} of $8.37 \mu M$. Thus, position (*N*-1 of theobromine) could accommodate a phenyl acetamide, that was un/substituted with an electron withdrawing moiety. In case of the phenylpropanamide derivatives, either unsubstituted or an electron donating group was more favorable than the electron withdrawing one.

Although, 8-bromotheophylline derivatives **5a-c** and **5e-g** revealed lower activity than 8-bromotheophylline **4**; they exhibited comparable activity to each other. Compound **5f** was an exception that exhibited enhanced activity compared with its phenyl acetamide derivative **5b**. Additionally, the *p*-sulfonamide derivative **5d** was again the most active compound in this series with $IC_{50} = 8.37 \mu M$.

2D-QSAR study

2D-QSAR studies were undertaken utilizing CODESSA-Pro (comprehensive descriptors for structural and statistical analysis) software employing the 24 bronchodilatory active agents (**3a-g**, **5a-g**, **7a-g** and theophylline **2**, 8-bromotheophylline **4** and theobromine **6**) [41–51]. The best multilinear regression QSAR (BMLR-QSAR) model obtained for the present study is statistically significant. The five descriptors controlling the QSAR model were presented in Table 2 and arranged according to their importance for the model, which is controlled by standard deviation (S) and t-test (t) values. Figure 6 showed the BMLR-QSAR model plot of correlations representing the observed versus predicted $1/IC_{50}$, μM values for the bioactive agents. The plots were uniformly scattered (observed, 0.0469–0.174; predicted, 0.063–0.175; $1/IC_{50}$, μM). Table 1 revealed the observed and estimated/predicted IC_{50} (μM) values of the bronchodilatory active agents.

Maximum antibonding contribution of one molecular orbital (molecular-type descriptor) was the first descriptor controlling the attained QSAR model based on its Student's *t*-criterion value ($t = 3.589$). Highest occupied and lowest unoccupied molecular orbital energy (HOMO, LOMO) were determined by EQUATIONS (1) and (2) [52]. Although this descriptor (energy value) contributes in the QSAR model with the highest coefficient value relative to other descriptors of the model (coefficient = 0.528), its effect for the predicted property seemed limited. This was attributed to the fact that all the test set analogs were of the same chemical scaffold [the descriptor value range = (−2.2456) – (−2.4036)]. Table 3 exhibited the descriptor values of the QSAR model.

$$\epsilon_{HOMO} = \langle \phi_{HOMO} | \hat{F} | \phi_{HOMO} \rangle$$

Table 2. Descriptors of the BMLR-QSAR model for the bronchodilator active agents.

Entry	ID	Coefficient	S	t	Descriptor
1	0	2.743	0.418	6.555	Intercept
2	D_1	0.528	0.147	3.589	Maximum antibonding contribution of one MO
3	D_2	−0.099	0.053	−1.887	Minimum exchange energy for bond H-C
4	D_3	−0.071	0.026	−2.693	Maximum resonance energy for bond H-C
5	D_4	−7.172	1.810	−3.963	Positively charged part of partial charged surface area (Zefirov's PC)
6	D_5	−7.459	1.010	−7.385	Minimum 1-electron reaction index for atom O

$N = 24$, $n = 5$, $R^2 = 0.848$, $R^2_{cvOO} = 0.748$, $R^2_{cvMO} = 0.745$, $F = 21.215$, $S^2 = 0.0002$
 $\log(1/IC_{50}) = 2.743 + (0.528 \times D_1) - (0.099 \times D_2) - (0.071 \times D_3) - (7.172 \times D_4) - (7.459 \times D_5)$.
 S: Standard deviation; t: t-test value.

Table 3. Molecular descriptor values of the BMLR-QSAR model for the bronchodilatory active agents.

Entry	Compound	Descriptors [†]				
		D_1	D_2	D_3	D_4	D_5
1	Theophylline, 2	-2.3303	5.1527	11.2977	0.02549	-0.00787
2	3a	-2.2868	5.1282	11.2629	0.01999	-0.00109
3	3b	-2.2706	5.0966	11.2203	0.02371	-0.00042
4	3c	-2.279	5.0681	11.1807	0.02272	-0.0002
5	3d	-2.2589	4.8936	11.0366	0.02341	-0.00748
6	3e	-2.3088	5.151	11.291	0.02104	-0.00028
7	3f	-2.2822	5.0619	11.1669	0.02244	-0.00789
8	3g	-2.2938	5.1445	11.2834	0.02114	-0.00008
9	8-Bromotheophylline, 4	-2.4036	5.2895	10.6008	0.02001	-0.00738
10	5a	-2.3601	5.1793	11.1212	0.01708	-0.0009
11	5b	-2.3609	5.1816	11.0981	0.01922	-0.00078
12	5c	-2.3592	5.1785	11.0921	0.01851	-0.00005
13	5d	-2.263	4.987	11.086	0.0196	0
14	5e	-2.3683	5.174	11.1042	0.01855	0.00005
15	5f	-2.3676	5.1743	11.0983	0.02018	-0.00711
16	5g	-2.3757	5.1989	11.0926	0.01794	0
17	Theobromine, 6	-2.3158	5.1566	11.3009	0.02454	-0.00754
18	7a	-2.2851	5.1511	11.2914	0.01953	0
19	7b	-2.2854	5.1512	11.2916	0.02185	-0.00008
20	7c	-2.2922	5.1528	11.2946	0.02136	-0.00019
21	7d	-2.2456	4.8389	11.0749	0.02397	-0.00025
22	7e	-2.3075	5.1588	11.3026	0.02016	-0.00755
23	7f	-2.2875	5.1523	11.2938	0.02168	-0.00006
24	7g	-2.2899	5.1519	11.2925	0.02101	0

[†] D_1 = Max. antibonding contribution of one MO; D_2 = Min. exchange energy for bond H-C; D_3 = Max. resonance energy for bond H-C; D_4 = Positively charged part of partial charged surface area (Zefirov's PC); D_5 = Min. 1-electron reaction index for atom O.

$$\varepsilon_{\text{LUMO}} = \langle \phi_{\text{LUMO}} | \hat{F} | \phi_{\text{LUMO}} \rangle$$

where, ϕ_{MoMO} stands for highest occupied molecular orbital, ϕ_{LUMO} for the lowest unoccupied molecular orbital,

$\hat{F}$ for Fock operator.

Minimum exchange energy for bond H-C was a semiempirical descriptor. Electronic exchange energy between two given atoms was determined by EQUATION (3) [52].

$$E_{\text{exc}}(\text{AB}) = \sum_{\mu, \nu \in A} \sum_{\lambda, \sigma \in B} P_{\mu\lambda} P_{\nu\sigma} \langle \mu\lambda | \nu\sigma \rangle$$

where, A stands for a given atomic species, B for another atomic species, $P_{\mu\nu}$, $P_{\lambda\sigma}$ for density matrix elements over atomic basis $\{\mu\nu\}$ and

$\langle \mu\nu | \lambda\sigma \rangle$ for electron repulsion integrals on atomic basis $\{\mu\nu\}$.

Maximum resonance energy for bond H-C was the third descriptor governing the QSAR model ($t = -2.693$) which was a semiempirical descriptor. Resonance energy between given two atomic species was determined by EQUATION (4) [52].

$$E_{\text{R}}(\text{AB}) = \sum_{\mu \in A} \sum_{\nu \in B} P_{\mu\nu} \beta_{\mu\nu}$$

where, A stands for a given atomic species, B for another atomic species, $P_{\mu\nu}$ for density matrix elements over atomic basis $\{\mu\nu\}$ and $\beta_{\mu\nu}$ for resonance integrals on atomic basis $\{\mu\nu\}$.

Positively charged part of partial charged surface area (Zefirov's PC) was a charge-related descriptor. The partial positively charged surface was determined by EQUATION (5) [52].

$$PPSA1 = \sum_A S_A A \in \{\delta_A > 0\}$$

where, S_A stands for positively charged solvent-accessible atomic surface area.

Minimum 1-electron reaction index for atom O was a semiempirical descriptor is the fifth descriptor of QSAR model ($t = -7.385$).

Internal validation technique was the most appropriate for the present QSAR study due to the limited dataset utilized [39,43–45]. R^2_{cvOO} (squared cross-validation correlation coefficient with leave one out 'one example omitted at a time' = 0.748) and R^2_{cvMO} (squared cross-validation correlation coefficient with leave many out 'many data points omitted at a time up to 20% of the total data points' = 0.745), were close to the squared correlation coefficient of the BMLR-QSAR model ($R^2 = 0.848$). Standard deviation of the regression ($s^2 = 0.0002$) relative to Fisher test value ($F = 21.215$) also statistical parameters support the robustness of the 2D-QSAR model.

The predicted IC_{50} values for the high potent bronchodilator agents **3d,f**; **5d**; **7d,e** and (5.71–9.93 μM) were correlated with the observed bioproperties ($IC_{50(\text{observed})} = 5.76\text{--}8.93 \mu M$) exhibiting acceptable error values. Compounds **3a-c,g**; **5a,e,f** and **7a,c,f** which revealed promising bronchodilation properties ($IC_{50(\text{observed})} = 10.09\text{--}12.50 \mu M$) relative to the reference standard, theophylline **2** ($IC_{50} = 12.65 \mu M$) showed comparable predicted bioproperties ($IC_{50(\text{predicted})} = 9.43\text{--}15.73 \mu M$). Meanwhile, compounds **3e**; **5c,g** and **7g**, which were low bronchodilator effective agents ($IC_{50(\text{observed})} = 17.00\text{--}21.30 \mu M$), exhibited predicted properties ($IC_{50(\text{predicted})} = 13.06\text{--}15.94 \mu M$) with relatively higher error values (1.06–6.74; Table 1). From all the above observations, it could be concluded that the attained 2D-QSAR model is applicable not only for the high potent bronchodilator hits but also for the low effective agents.

Conclusion

Three novel series of 7-substituted theophylline **3a-g**, 8-bromotheophylline **5a-g** and 1-substituted theobromine **7a-g** were prepared through alkylation of theophylline **2**, 8-bromotheophylline **4** and theobromine **6**, respectively, under basic conditions. These compounds were screened for their *in vitro* bronchodilator activity in guinea pig tracheal rings precontracted with histamine. Many compounds exerted better activity than theophylline **2** ($IC_{50} = 12.65 \mu M$) especially the *N*-(4-sulfamoylphenyl) derivatives **3d**, **5d** and **7d** ($IC_{50} = 5.76$, 8.37 and $8.37 \mu M$, respectively). Thus, these compounds can be considered as promising hits for potent bronchodilators that may be useful for further investigations. 2D-QSAR study revealed a statistically significant model that validated the obtained bronchodilator activity and it could be also used for prediction of the activity of any compound bearing the same scaffold.

Future perspective

Asthma represents an important health problem affecting high populations, particularly children. It could be managed by different bronchodilators and/or corticosteroids to relieve the bronchospasm and inflammation associated with asthma. However, these medications resulted in serious side effects such as tachycardia, CNS stimulation and water retention. Therefore, there has been an urgent need to discover a new medication with more efficiency. This research work aimed at modifying the structure of theophylline, the first bronchodilator used in asthma and at their *in vitro* screening using isolated guinea pig tracheal rings precontracted with histamine, hoping to obtain new derivatives with promising bronchodilation activity. Thus, they may represent lead scaffolds for further optimization. Furthermore, a 2D-QSAR study was performed in order to validate the obtained activity and study the structural features affecting the activity.

Summary points

Chemistry

- Novel xanthenes **3a-g**, **5a-g** and **7a-g** were prepared from *N*-alkylation of theophylline **2**, 8-bromotheophylline **4** and theobromine **6**, respectively, with different 2/3-chloro-*N*-phenylacetamides **1a-d** or their propanamide analogs **1e-g**.

Bronchodilation activity

- All the prepared compounds were screened for their bronchodilation activity using isolated guinea pig tracheal rings precontracted with histamine.
- Many compounds exerted better activity than theophylline **2** ($IC_{50} = 12.65 \mu M$) especially the *N*-(4-sulfamoylphenyl) derivatives **3d**, **5d** and **7d** ($IC_{50} = 5.76$, 8.37 and $8.37 \mu M$, respectively).

2D-QSAR study

- 2D-QSAR study revealed a statistically significant model that validated the obtained bronchodilator activity and it could be also used for prediction of the activity of any compound bearing the same scaffold.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/full/10.4155/fmc-2017-0092.

References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest

- Anandan C, Nurmatov U, Van Schayck OCP, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 65(2), 152–167 (2010).
- Katzung BG. *Basic & Clinical Pharmacology (9th Edition)*. Lange Medical Books/McGraw-Hill, New York, Part IV, Chapter 20, pp. 319–335 (2004).
- World Health Organization www.who.int/en
- Walsh LJ, Wong CA, Cooper S, Guhan AR, Pringle M, Tattersfield AE. Morbidity from asthma in relation to regular treatment: a community based study. *Thorax* 54(4), 296–300 (1999).
- Goose J, Blair AMJN. Passive cutaneous anaphylaxis in the rat, induced with two homologous reagin-like antibodies and its specific inhibition with disodium cromoglycate. *J. Immunol.* 16, 749–760 (1969).
- Pescoldderung L. Role of leukotriene antagonists in non-asthmatic disorders. *Minerva Pediatr.* 56(2), 151–155 (2004).
- Krell RD, Aharony D, Buckner CK *et al.* The preclinical pharmacology of ICI204,219- a peptide leukotriene antagonist. *Am. Rev. Resp. Dis.* 141, 978–987 (1990).
- Jones TR, Labella M, Belley M *et al.* Pharmacology of montelukast sodium (Singulair), a potent and selective leukotriene D₄ receptor antagonist. *Can. J. Physiol. Pharmacol.* 73(2), 191–201 (1995).
- Carter GW, Young PR, Albert DH *et al.* 5-lipoxygenase inhibitory activity of zileuton. *J. Pharmacol. Exp. Ther.* 256(3), 929–937 (1991).
- Fanta CH, Rossing TH, McFadden ER. Treatment of acute asthma. Is combination therapy with sympathomimetics and methylxanthines indicated?. *Am. J. Med.* 80(1), 5–10 (1986).
- Tennant RC, Erin EM, Barnes PJ, Hansel TT. Long-acting β_2 -adrenoceptor agonists or tiotropium bromide for patients with COPD: is combination therapy justified? *Curr. Opin. Pharmacol.* 3(3), 270–276 (2003).
- Moan MJ, Fanta CH. Bronchodilator therapy in the management of acute asthma. *Compr. Ther.* 21(8), 421–427 (1995).
- Holgate ST. Trials and tribulations in identifying new biologic treatments for asthma. *Trends Immunol.* 33(5), 238–246 (2012).
- Vestbo J, Hurd SS, Agustí AG *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 187(4), 347–365 (2013).
- Welte T, Miravittles M, Hernandez P *et al.* Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 180(8), 741–750 (2009).
- Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ. Superiority of 'triple' therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax* 63(7), 592–598 (2008).
- Mancht DI, Ting GA. A study of antispasmodic drugs on the bronchus. *J. Pharm. Exp. Ther.* 18, 373–381 (1921).
- Okano T, Aita K, Ikeda K. Electronic properties of *N*-heteroaromatics. XII. On the mode of interaction between theophylline and ethylenediamine in aqueous solution. *Chem. Pharm. Bull.* 15(11), 1621–1625 (1967).
- Hardy C, Schofield O, George CF. Allergy to aminophylline. *Br. Med. J.* 286, 2051–2052 (1983).
- Regnier GL, Guillonneau CG, Duhault JL, Tisserand FP, Saint-Romas G, Holstorp SM. New xanthine derivatives with potent and long lasting anti-bronchoconstrictive activity. *Eur. J. Med. Chem.* 22(3), 243–250 (1987).
- Reports the pharmacological importance of lead compound I.
- Merlos M, Gomez L, Vericat ML, Bartroli J, Garcia-Rafanell J, Fern J. Structure-activity relationships in a series of xanthine derivatives with antibronchoconstrictory and bronchodilatory activities. *Eur. J. Med. Chem.* 25(8), 653–658 (1990).
- Baziard-Mouysset G, Rached A, Younes S *et al.* Synthesis and *in vitro* bronchospasmolytic activity of 8-aryl, heteroaryl or arylalkyltheophyllines. *Eur. J. Med. Chem.* 30(3), 253–260 (1995).

- 23 Akgün H, Balkan A, Günay S, Erol K, Boydağ S. Some new 7-aryloxyalkyltheophyllines as bronchodilators. *Eur. J. Med. Chem.* 32(2), 175–179 (1997).
- **Reports the pharmacological importance of lead compound IV.**
- 24 Matulenko MA, Hakeem AA, Kolasa T *et al.* Synthesis and functional activity of (2-aryl-1-piperazinyl)-N-(3-methylphenyl)acetamides: selective dopamine D₄ receptor agonists. *Bioorg. Med. Chem.* 12(13), 3471–3483 (2004).
- 25 Ananthalakshmi KV, Bartl T, Aziza MH *et al.* Synthesis and structure–activity relationship studies of theophylline analogs on population responses in the rat hippocampus *in vitro*. *Bioorg. Med. Chem.* 16(17), 8142–8150 (2008).
- 26 Okawara T, Matsuda T, Furukawa M. Convenient syntheses of cyclic carboxamides from α , β , γ , δ and ϵ -halocarboxamides under phase transfer conditions. *Chem. Pharm. Bull.* 30(4), 1225–1233 (1982).
- 27 Pasquinnucci L, Prezzavento O, Marrazzo A *et al.* Evaluation of N-substitution in 6,7-benzomorphan compounds. *Bioorg. Med. Chem.* 18(14), 4975–4982 (2010).
- 28 Ma L, Li S, Zheng H *et al.* Synthesis and biological activity of novel barbituric and thiobarbituric acid derivatives against non-alcoholic fatty liver disease. *Eur. J. Med. Chem.* 46(6), 2003–2010 (2011).
- 29 Unger Y, Strassner T. Platinum (II) complexes with amide-functionalized NHC ligands. *J. Organomet. Chem.* 713, 203–208 (2012).
- 30 Zhang W, Ai J, Shi D *et al.* Discovery of novel type II c-Met inhibitors based on BMS-777607. *Eur. J. Med. Chem.* 80, 254–266 (2014).
- **Describes the synthesis of the key reagents 1a-g.**
- 31 Patel RV, Patel PK, Kumari P, Rajani DP, Chikhaliya KH. Synthesis of benzimidazolyl-1,3,4-oxadiazol-2-ylthio-N-phenyl (benzothiazolyl) acetamides as antibacterial, antifungal and antituberculosis agents. *Eur. J. Med. Chem.* 53, 41–51 (2012).
- 32 Ma L, Xie C, Ma Y *et al.* Synthesis and biological evaluation of novel 5-benzylidenethiazolidine-2,4-dione derivatives for the treatment of inflammatory diseases. *J. Med. Chem.* 54(7), 2060–2068 (2011).
- 33 Yalpani M, Hall LD. Synthesis of fluorescent probe – carbohydrate conjugates. *Can. J. Chem.* 59(20), 2934–2939 (1981).
- 34 Addy PS, Saha B, Pradeep S *et al.* 1,3,5-Trisubstituted benzenes as fluorescent photoaffinity probes for human carbonic anhydrase II capture. *Chem. Commun.* 49(19), 1930–1932 (2013).
- 35 Alafeefy AM, Ceruso M, Al-Tamimi A-MS, Del Prete S, Capasso C, Supuran CT. Quinazoline–sulfonamides with potent inhibitory activity against the α -carbonic anhydrase from *Vibrio cholerae*. *Bioorg. Med. Chem.* 22(19), 5133–5140 (2014).
- 36 Vijayaraghavan S, Shirodkar PY. Synthesis of some 1,2,4-triazoles as potential anti-tubercular agents. *Ind. J. Chem. -Section B Org. Med. Chem.* 54B(9), 1149–1153 (2015).
- 37 Drabczyńska A, Müller CE, Karolak-Wojciechowska J *et al.* N⁶-Benzyl-substituted 1,3-dimethyl- and 1,3-dipropyl-pyrimido[2,1-f]purinediones: Synthesis and structure–activity relationships at adenosine A₁ and A_{2A} receptors. *Bioorg. Med. Chem.* 15(14), 5003–5017 (2007).
- 38 Drabczyńska A, Yuzlenko O, Köse M *et al.* Synthesis and biological activity of tricyclic cycloalkylimidazo-, pyrimido- and diazepinopurinediones. *Eur. J. Med. Chem.* 46(9), 3590–3607 (2011).
- **Describes the synthesis of the key intermediate 4.**
- 39 Girgis AS, Aziz MN, Shalaby EM *et al.* Crystal structure studies and bronchodilation properties of novel benzocycloheptapyridines. *J. Chem. Crystal.* 46(6), 280–289 (2016).
- **Describes the procedure for screening of the bronchodilation activity.**
- 40 Girgis AS, Saleh DO, George RF *et al.* Synthesis, bioassay, and QSAR study of bronchodilatory active 4H-pyrano[3,2-c]pyridine-3-carbonitriles. *Eur. J. Med. Chem.* 89, 835–843 (2015).
- 41 Faidallah HM, Panda SS, Serrano JC *et al.* Synthesis, antimalarial properties and 2D-QSAR studies of novel triazole-quinine conjugates. *Bioorg. Med. Chem.* 24(16), 3527–3539 (2016).
- 42 George RF, Panda SS, Shalaby EM, Srouf AM, Ahmed Farag IS, Girgis AS. Synthesis and molecular modeling studies of indole-based antitumor agents. *RSC Adv.* 6(51), 45434–45451 (2016).
- **Describes the 2D-QSAR technique.**
- 43 Panda SS, Detistov OS, Girgis AS, Mohapatra PP, Samir A, Katritzky AR. Synthesis and molecular modeling of antimicrobial active fluoroquinolone–pyrazine conjugates with amino acid linkers. *Bioorg. Med. Chem. Lett.* 26(9), 2198–2205 (2016).
- 44 Ibrahim MA, Panda SS, Oliferenko AA *et al.* Macrocyclic peptidomimetics with antimicrobial activity: synthesis, bioassay, and molecular modeling studies. *Org. Biomol. Chem.* 13(36), 9492–9503 (2015).
- 45 Panda SS, Liaqat S, Girgis AS, Samir A, Hall CD, Katritzky AR. Novel antibacterial active quinolone–fluoroquinolone conjugates and 2D-QSAR studies. *Bioorg. Med. Chem. Lett.* 25(18), 3816–3821 (2015).
- 46 Girgis AS, Panda SS, Srouf AM *et al.* Rational design, synthesis and molecular modeling studies of novel anti-oncological alkaloids against melanoma. *Org. Biomol. Chem.* 13(23), 6619–6633 (2015).
- 47 Naumov RN, Panda SS, Girgis AS, George RF, Farhat M, Katritzky AR. Synthesis and QSAR study of novel anti-inflammatory active mesalazine–metronidazole conjugates. *Bioorg. Med. Chem. Lett.* 25, 2314–2320 (2015).
- 48 Girgis AS, Panda SS, Aziz MN, Steel PJ, Hall CD, Katritzky AR. Rational design, synthesis, and 2D-QSAR study of anti-oncological alkaloids against hepatoma and cervical carcinoma. *RSC Adv.* 5(36), 28554–28569 (2015).
- 49 Tiwari AD, Panda SS, Girgis AS *et al.* Microwave assisted synthesis and QSAR study of novel NSAID acetaminophen conjugates with amino acid linkers. *Org. Biomol. Chem.* 12, 7238–7249 (2014).

- 50 Girgis AS, Stawinski J, Ismail NSM, Farag H. Synthesis and QSAR study of novel cytotoxic spiro[3*H*-indole-3,2'-(1'*H*)-pyrrolo[3,4-*c*]pyrrole]-2,3',5'-(1*H*,2'*aH*,4'*H*)-triones. *Eur. J. Med. Chem.* 47, 312–322 (2012).
- 51 Girgis AS, Farag H, Ismail NSM, George RF. Synthesis, hypnotic properties and molecular modeling studies of 1,2,7,9-tetraaza-spiro[4.5]dec-2-ene-6,8,10-triones. *Eur. J. Med. Chem.* 46, 4964–4969 (2011).
- 52 CODESSA-pro manual pp. 54, 68, 74 (2005). www.codessa-pro.com/manuals/manual.htm

Identification of some novel xanthine based derivatives with bronchodilator activity

Supplementary material ^1H NMR, ^{13}C NMR for target compounds

Abdallah Reda_H_F7-70 (7D)

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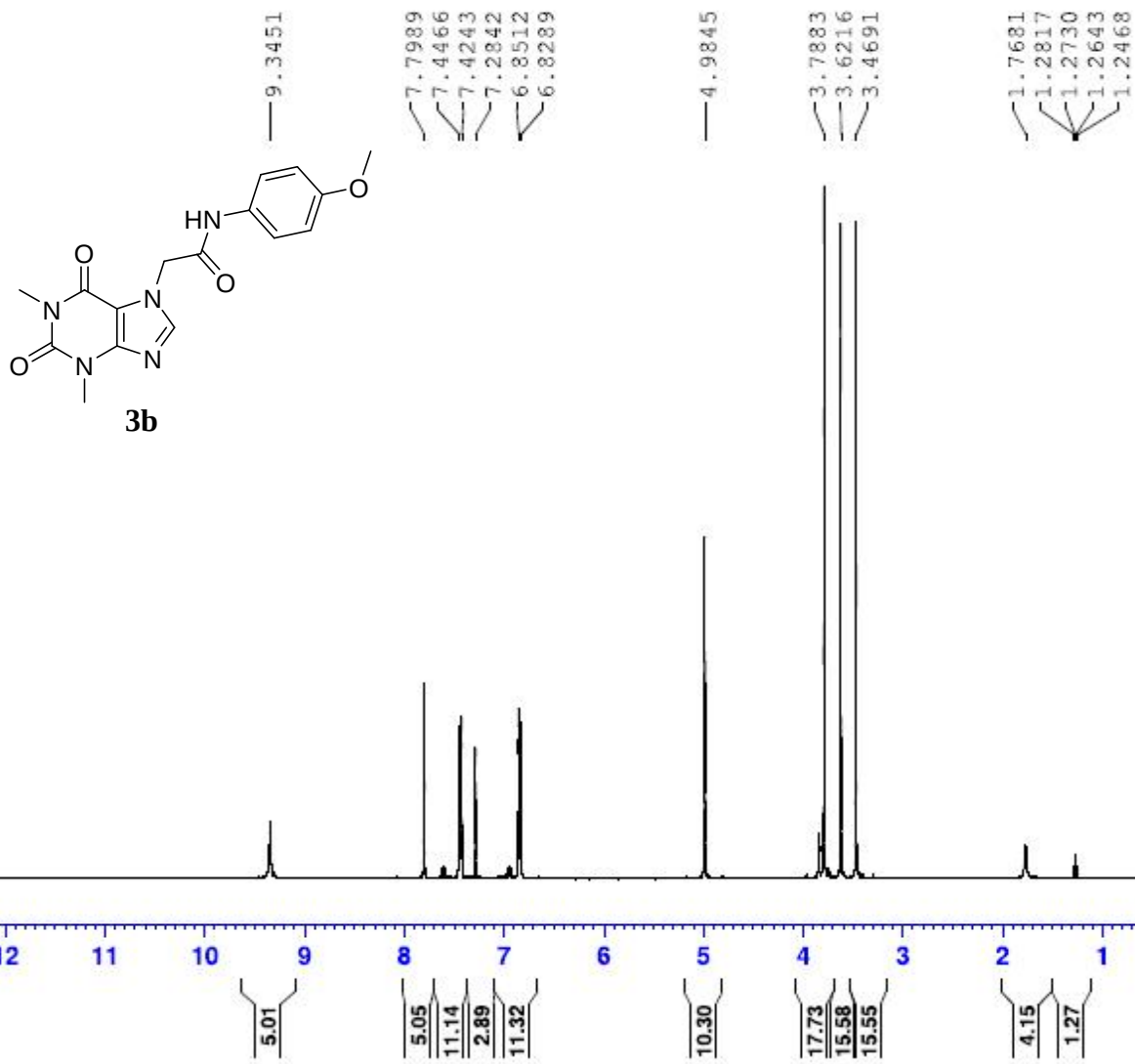


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PROCNO 1

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TD 65536
SOLVENT CDCl3
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DS 2
SWH 8012.820 Hz
FIDRES 0.122260 Hz
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TE 299.1 K
D1 1.0000000 sec
TD0 1

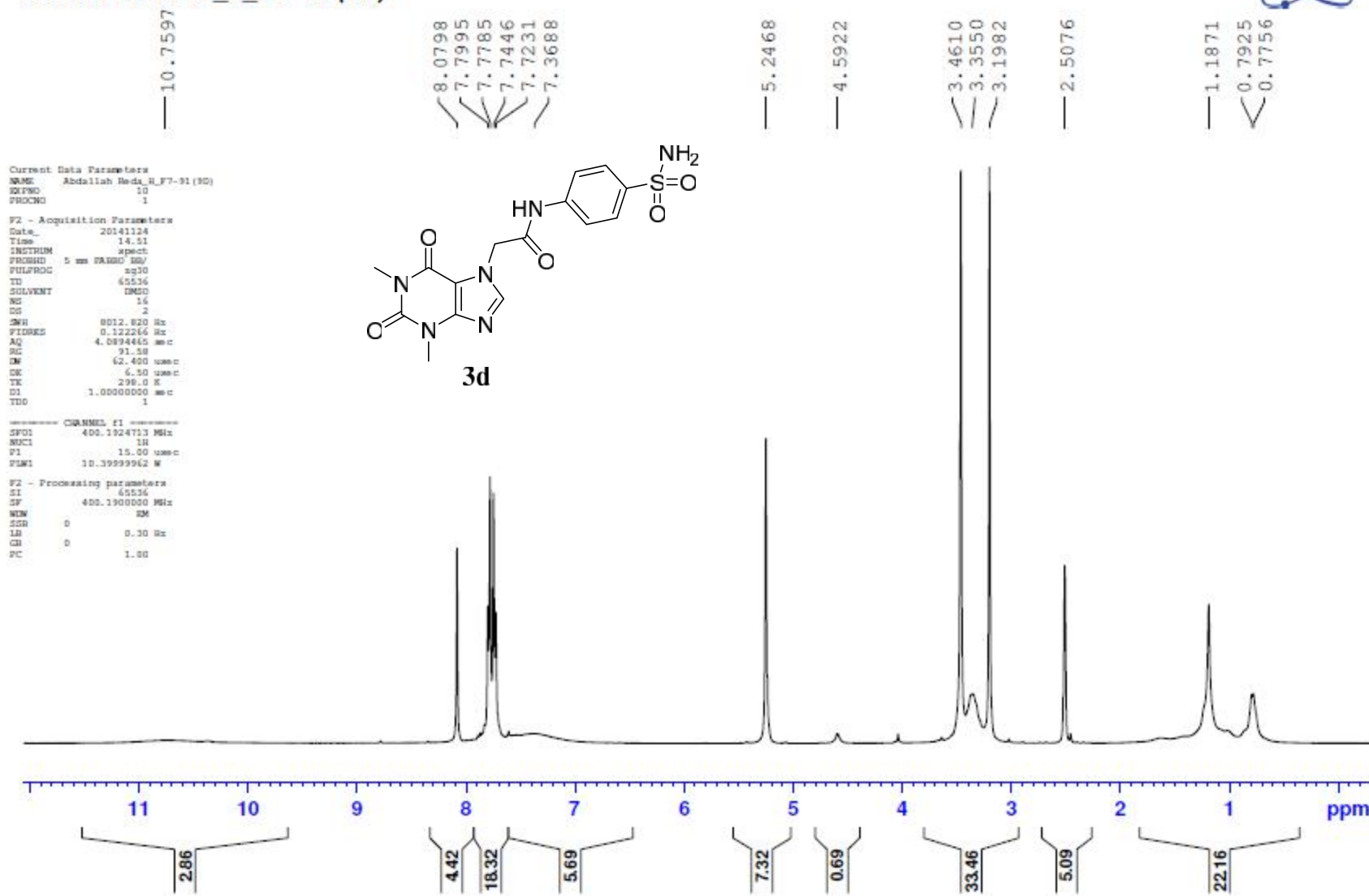
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SF 400.1300000 MHz
NUC 1H
SGB 0
LA 0.70 Hz
CB 0
PC 1.00





Abdallah Reda_H_F7-91 (9D)



Riham Francois_C_4d

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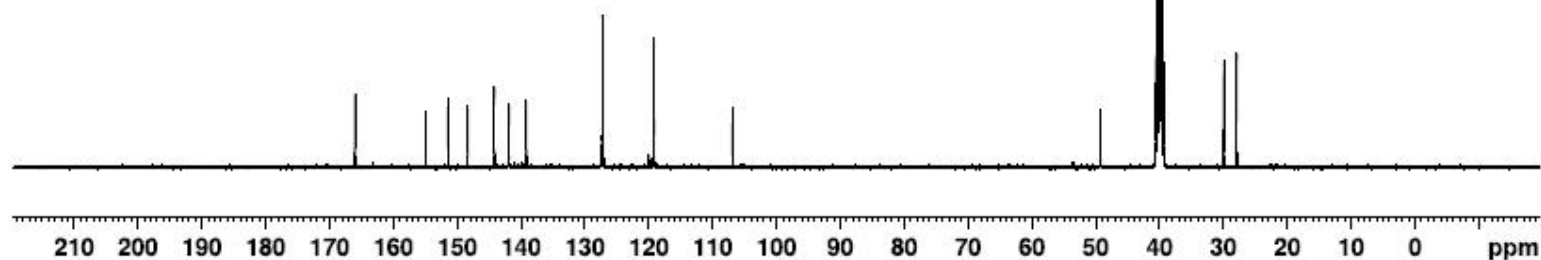
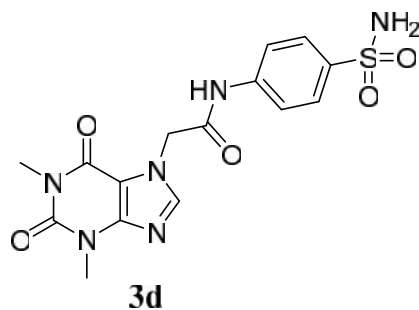


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EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161216
Time 3.12
INSTRUM spect
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1200
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 202.37
DW 20.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

----- CHANNEL f1 -----
SFO1 100.6379178 MHz
NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

----- CHANNEL f2 -----
SFO2 400.1916008 MHz
NUC2 1H
CPDPRG2 waltz16



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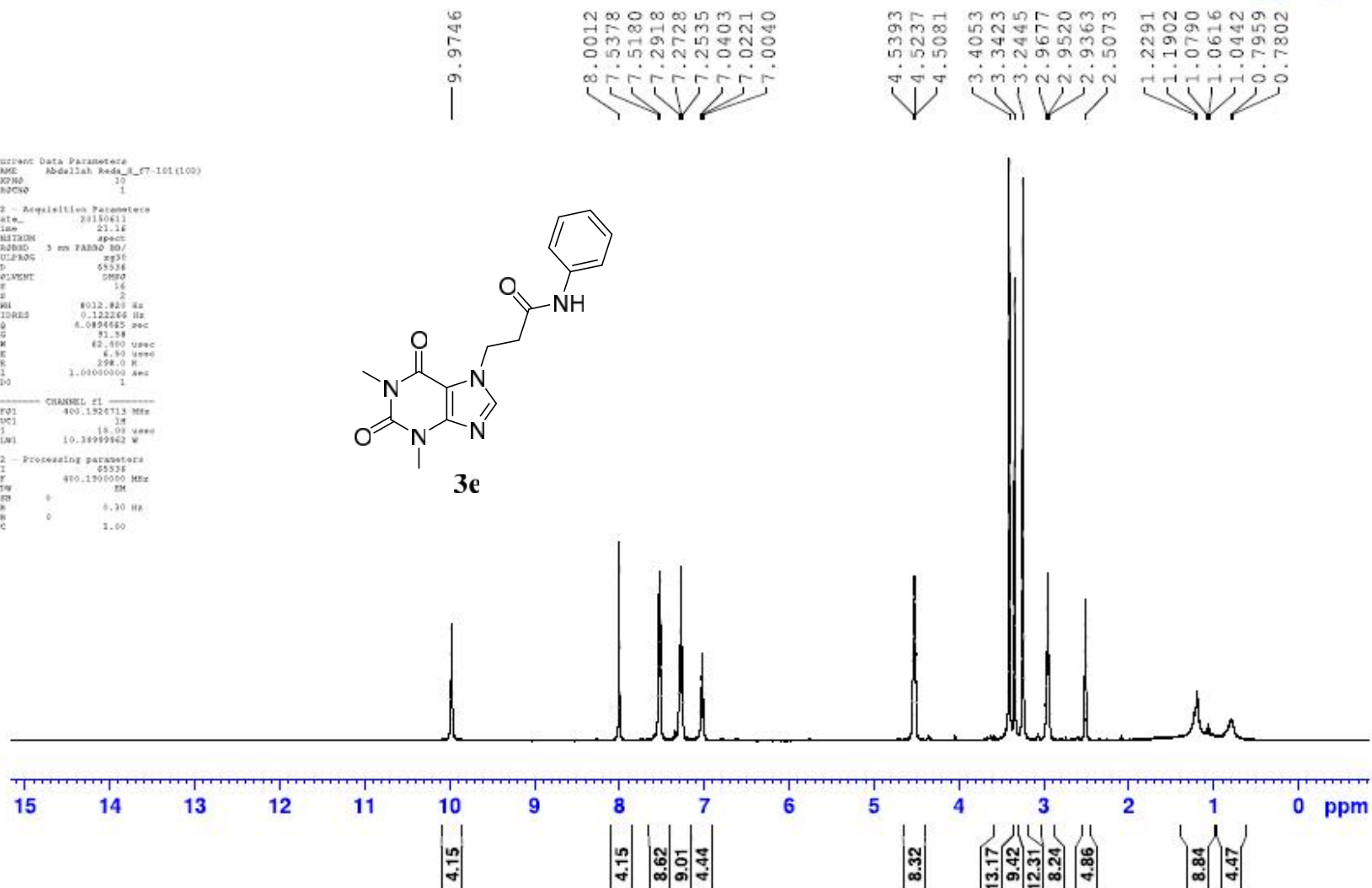
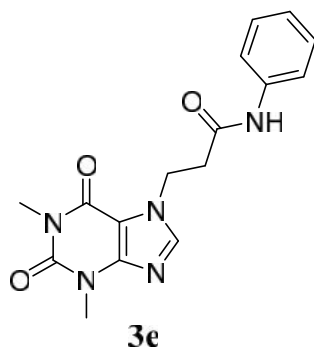


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TD          65536
SI          32768
RG          65536
SOLVENT    DMSO
NS          16
DS          2
SWH         8012.829 Hz
AQ          1.122646 Hz
RG          4.082946E5 sec
RG          31.58
DM          62.400 usec
DE          6.80 usec
TE          298.0 K
DQ          1.04000000 usec
IT0         1

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F2 - Processing parameters	
S1	\$5536
SF	400.1700000 MHz
NTW	EM
SEM	0
LB	0.10 Hz
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PC	1.00



Abdallah Rida_H_F7-110(11D)

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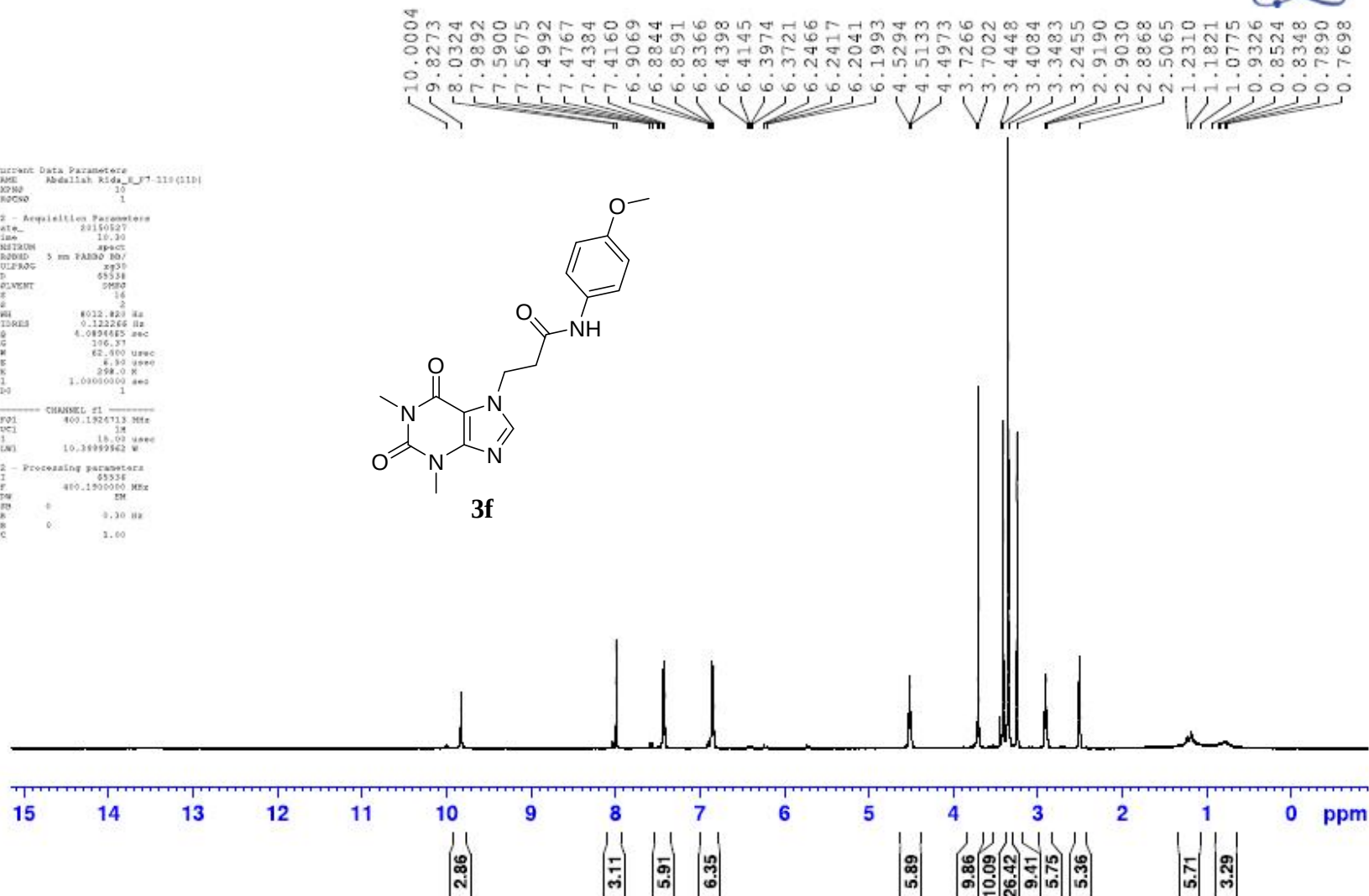
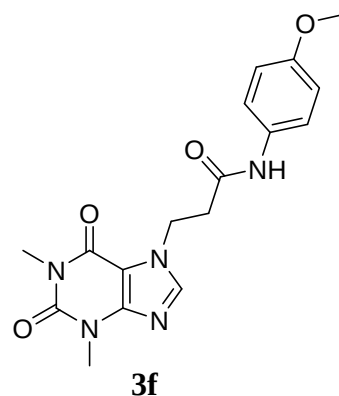


Current Data Parameters
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EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894615 sec
RG 106.25
DW 62.900 usec
DE 4.90 usec
TE 300.0 K
D1 1.0900000 sec
TD0 1

CHANNEL f1
SF01 400.192513 MHz
NUC1 13C
P1 15.00 usec
PLN1 10.36999962 W

F2 - Processing parameters
SI 65536
SF 400.1900000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.60



Riham Francois_C_4f

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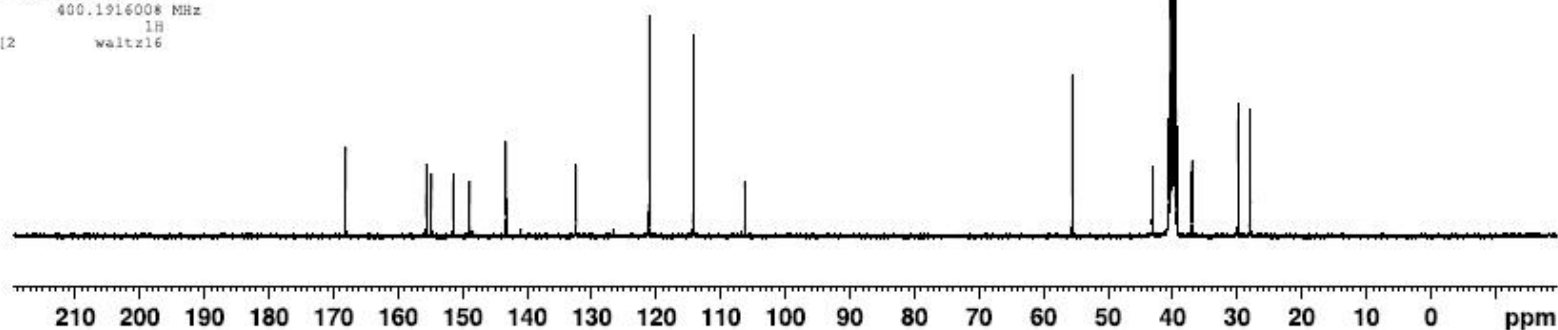
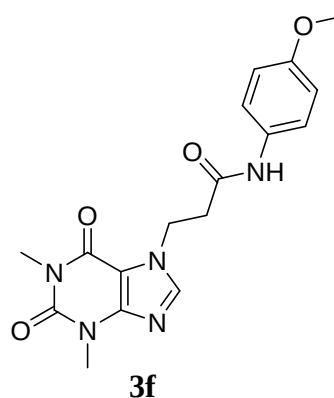


Current Data Parameters
NAME Riham Francois_C_4f
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161215
Time 22.27
INSTRUM spect
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1200
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 202.37
DW 20.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

----- CHANNEL f1 -----
SFO1 100.6379178 MHz
NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

----- CHANNEL f2 -----
SFO2 400.1916008 MHz
NUC2 1H
CPDPRG2 waltz16



Riham Francois_C_4g

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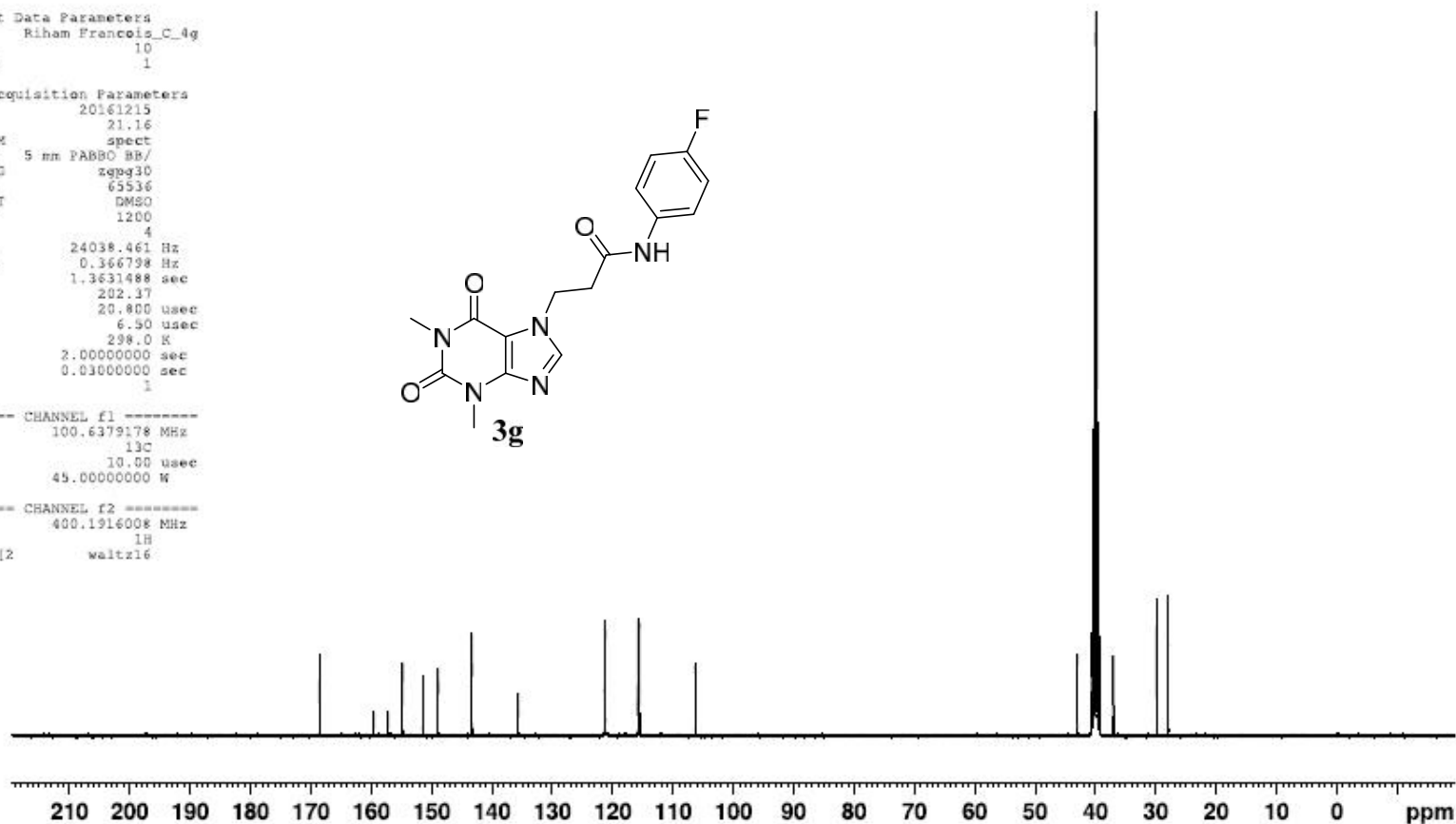
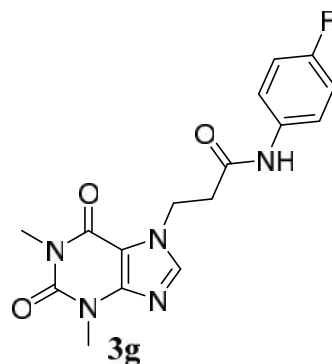


Current Data Parameters
NAME Riham Francois_C_4g
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
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Time 21.16
INSTRUM spect
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1200
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 202.17
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

----- CHANNEL f1 -----
SFO1 100.6379178 MHz
NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

----- CHANNEL f2 -----
SFO2 400.1916008 MHz
NUC2 1H
CPDPRG12 waltz16



Abdalla Reda_H_E11-62-6E

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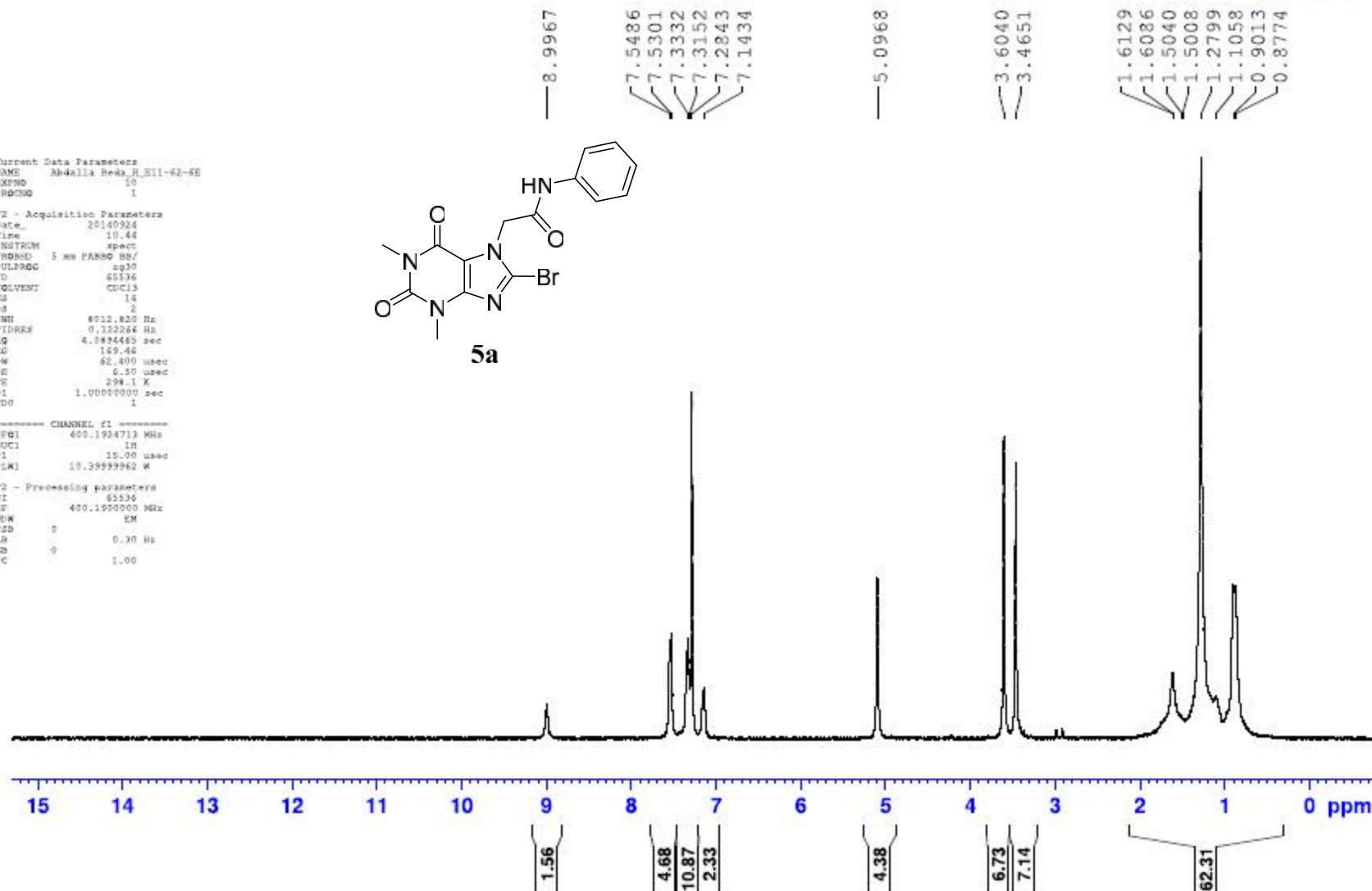
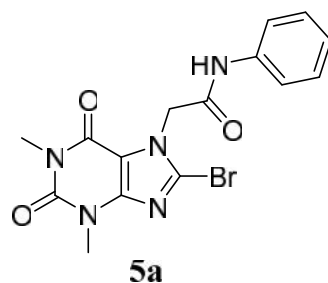


Current Data Parameters
NAME Abdalla Reda_H_E11-62-6E
EXTNO 10
PROCNO 1

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Time 10.44
INSTRUM spect
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 14
DS 2
SWH 8012.820 Hz
FIDRES 0.123266 Hz
AQ 4.849465 sec
RG 169.44
OW 62.400 usec
DE 6.30 usec
TE 298.1 K
D1 1.0000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 1H
P1 15.00 usec
PLW1 10.39999962 W

F2 - Processing parameters
SI 65536
SF 400.1500000 MHz
WDW EM
SSB 0
LA 0.30 Hz
CB 0
PC 1.00



Abdallah Reda_H_F11-71 (7E)

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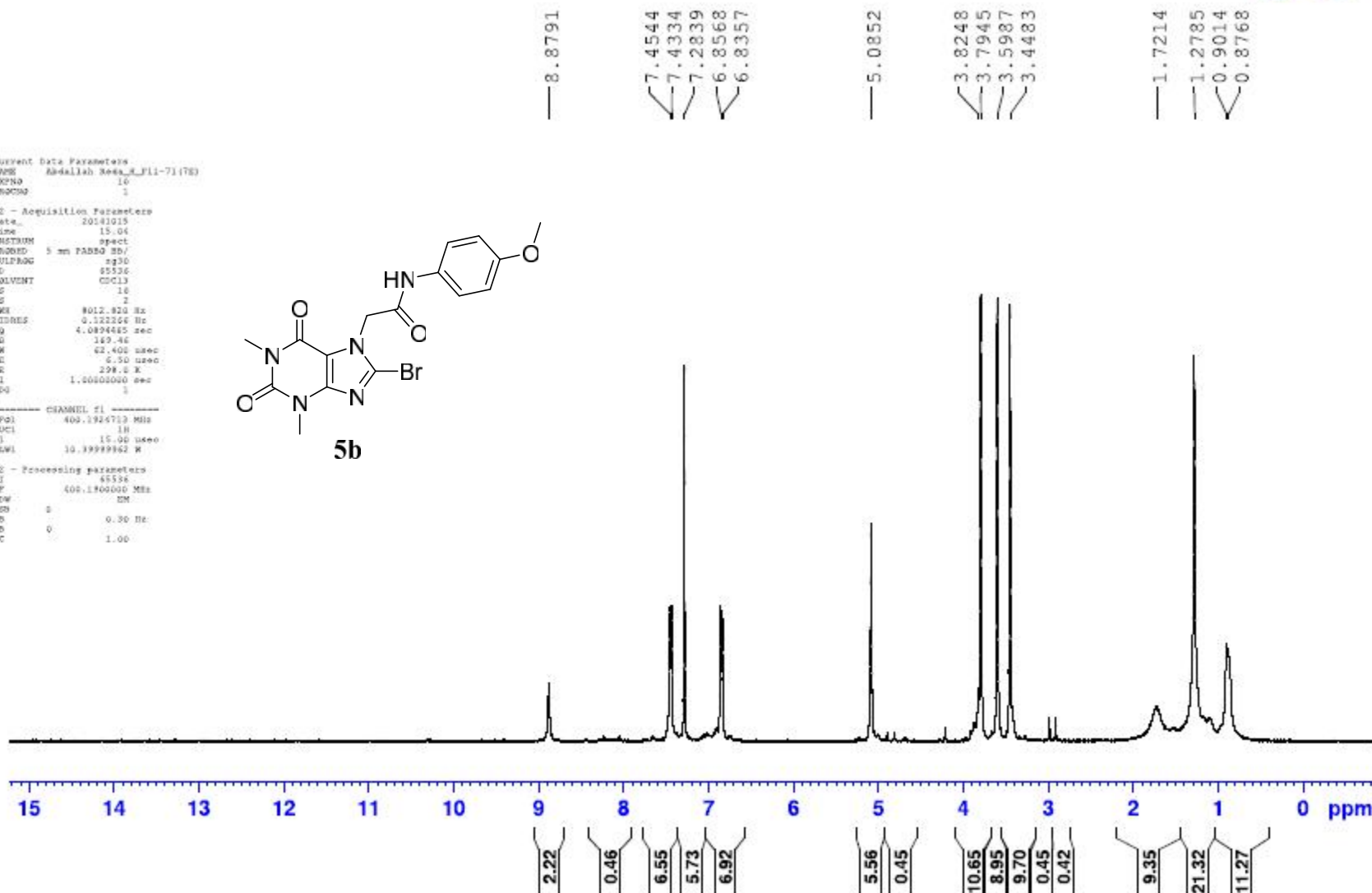
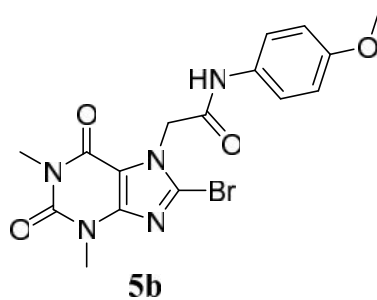


Current Data Parameters
NAME Abdallah Reda_H_F11-71 (7E)
EXPNO 16
PROCNO 1

F2 - Acquisition Parameters
Date_ 20181015
Time 15:04
INSTRUM spect
PROBHD 5 mm PABBO 2D/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 169.46
DN 62.400 usec
DE 5.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1

CHANNEL f1
FQ1 400.1924713 MHz
NUC1 1H
P1 15.00 usec
PL1 10.39989362 W

F2 - Processing parameters
SI 45536
SF 400.1900000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Riham Francois_C_9b

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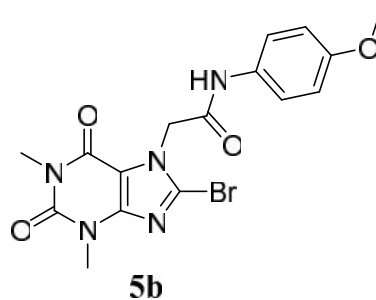


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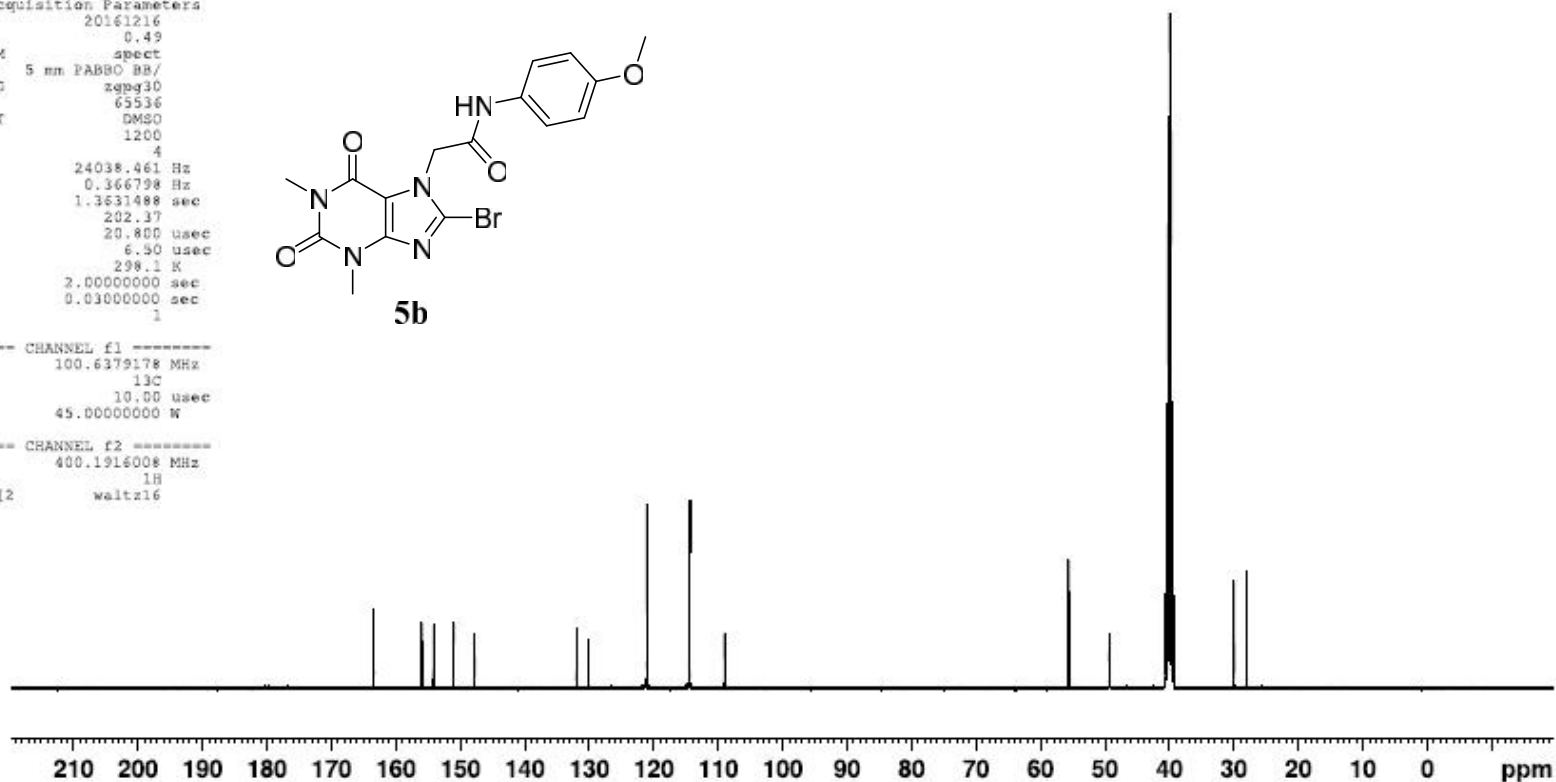
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PROCNO 1

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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1200
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 202.17
DW 20.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1



----- CHANNEL f1 -----
SFO1 100.6379178 MHz
NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

----- CHANNEL f2 -----
SFO2 400.1916008 MHz
NUC2 1H
CPDPRG2 waltz16



Abdallah Rida_H_F11-101 (10E)

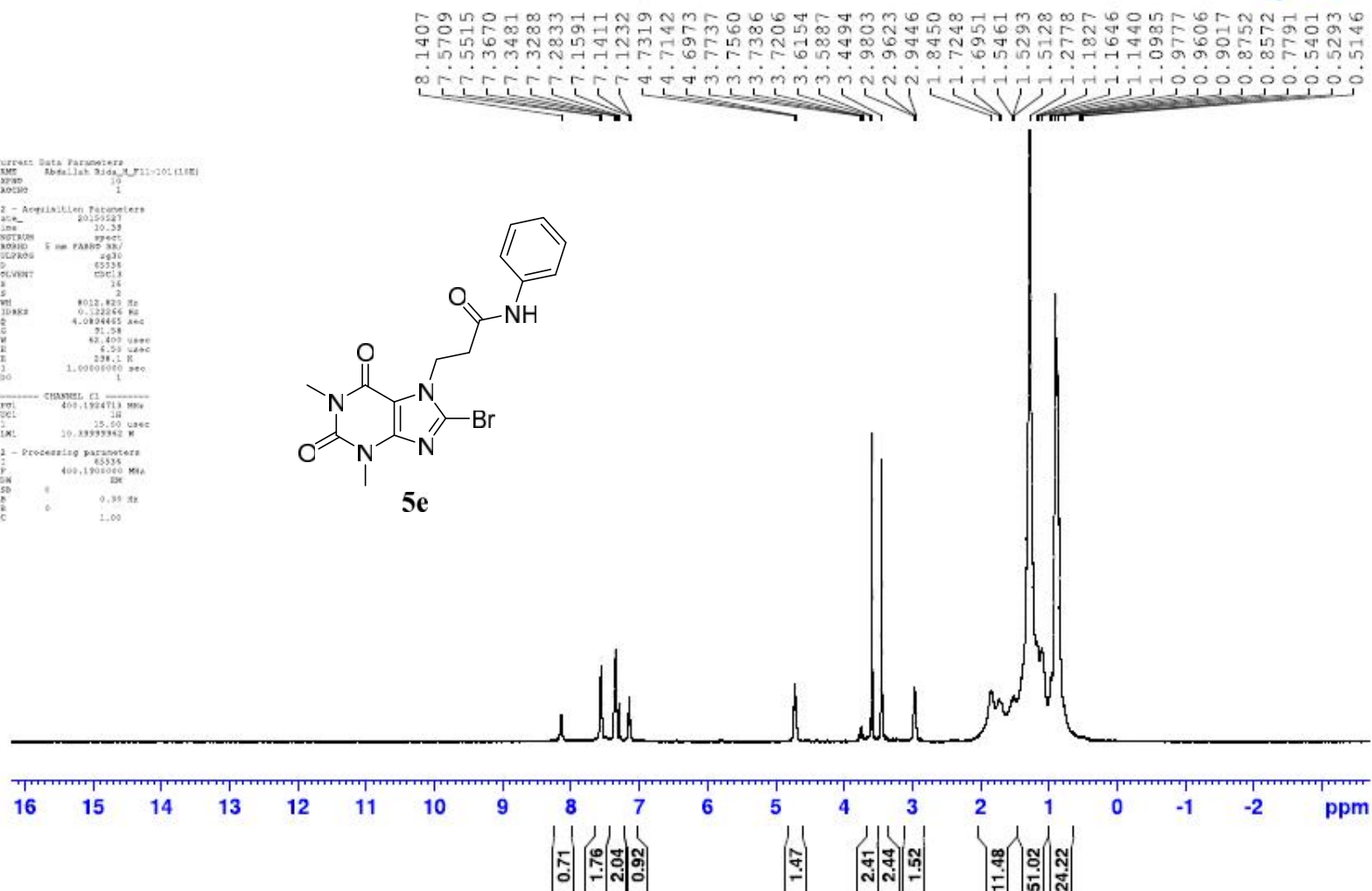
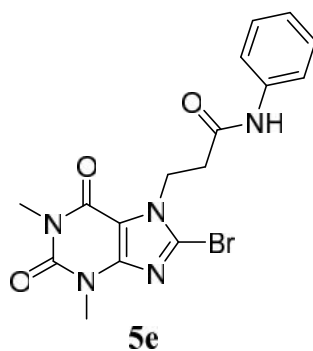
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Current Data Parameters
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EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20190227
Time 10:33
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 801.825 Hz
FIDRES 0.122646 Hz
AQ 4.0804465 sec
RG 31.58
RW 82.400 usec
DE 6.50 usec
TE 298.2 K
D1 1.0000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 400.1924713 MHz
P1 10
PC 15.00 usec
PL1 0.00000000 W
===== CHANNEL f2 =====
F2 - Processing parameters
SI 65536
SF 400.190000 MHz
WDW EM
SSB 0
LB 0.35 Hz
GB 0
PC 1.00



Riham Francois_C_12a

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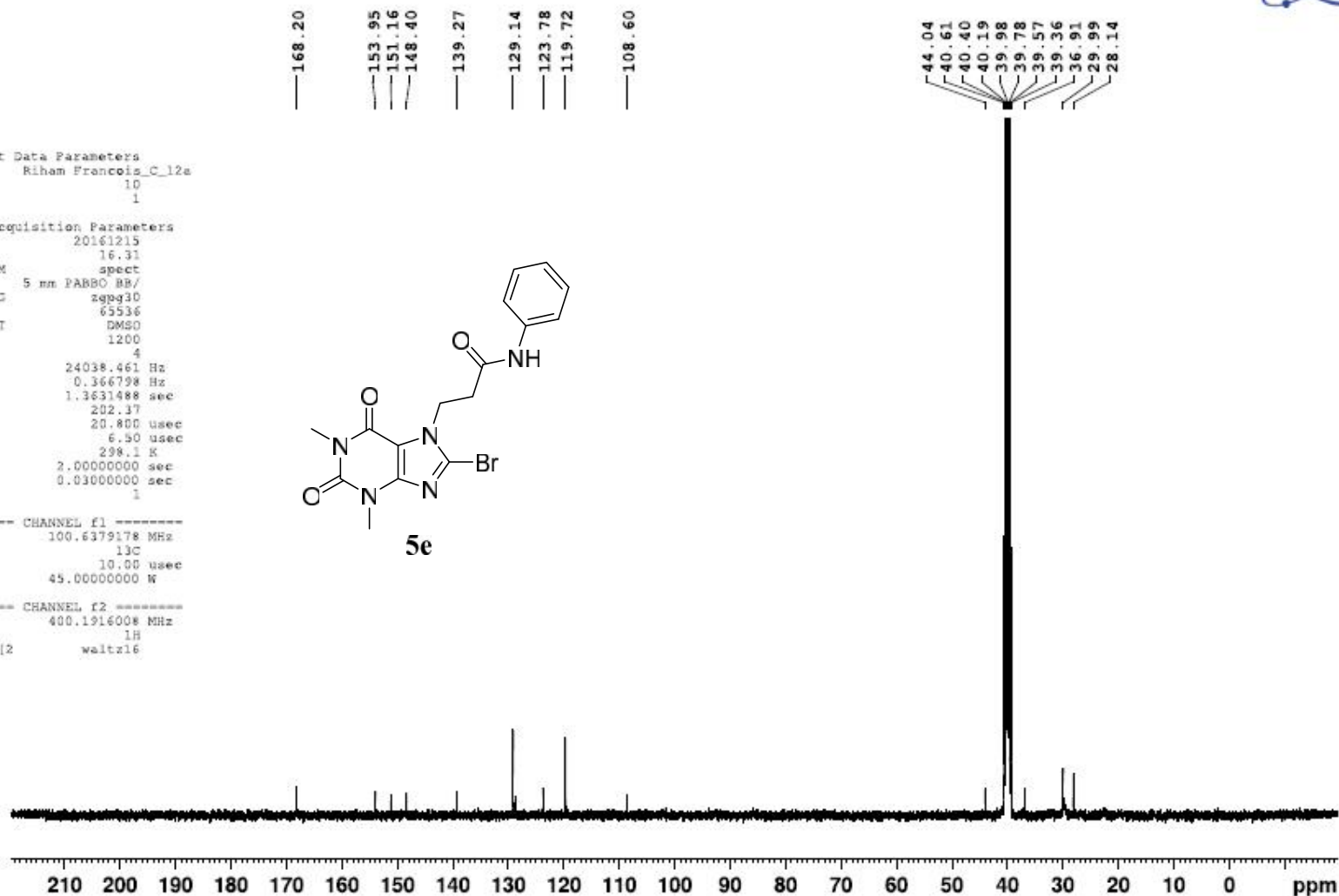
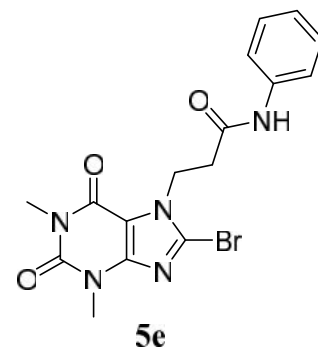


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PROCNO 1

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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1200
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 202.37
DW 20.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

----- CHANNEL f1 -----
SFO1 100.6379178 MHz
NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

----- CHANNEL f2 -----
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NUC2 1H
CPDPRG2 waltz16

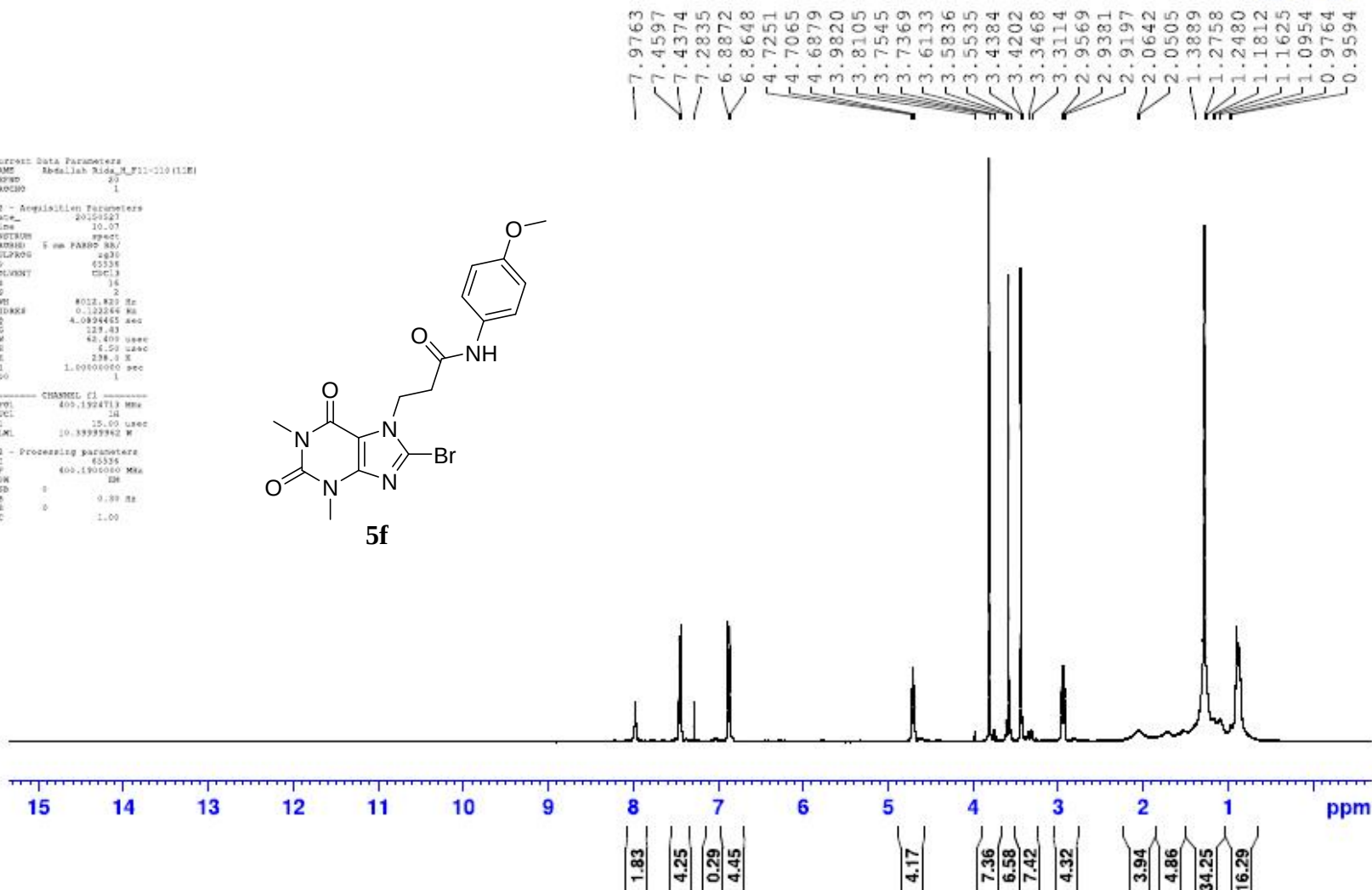
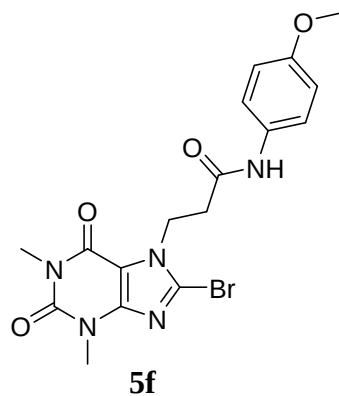


Abdallah Rida_H_F11-110 (11E)

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Current Data Parameters
NAME Abdallah Rida_H_F11-110 (11E)
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20250527
Time 10.07
INSTRUM spect
PROBHD 5 mm F400P 1H/13
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 4012.820 Hz
FIDRES 0.122244 Hz
AQ 4.0924465 sec
RG 129.43
RM 48.409 usec
DE 6.50 usec
TE 298.2 K
D1 1.0000000 sec
TD0 1
===== CHANNEL f1 =====
NUC1 13C 101.62613 MHz
P1 15.00 usec
P1MX 10.33999962 W
F2 - Processing parameters
SI 65536
SF 400.1906000 MHz
WDW 128
SSB 0
LB 0.89 Hz
GB 0
PC 1.00



Abdallah Reda_C_4f

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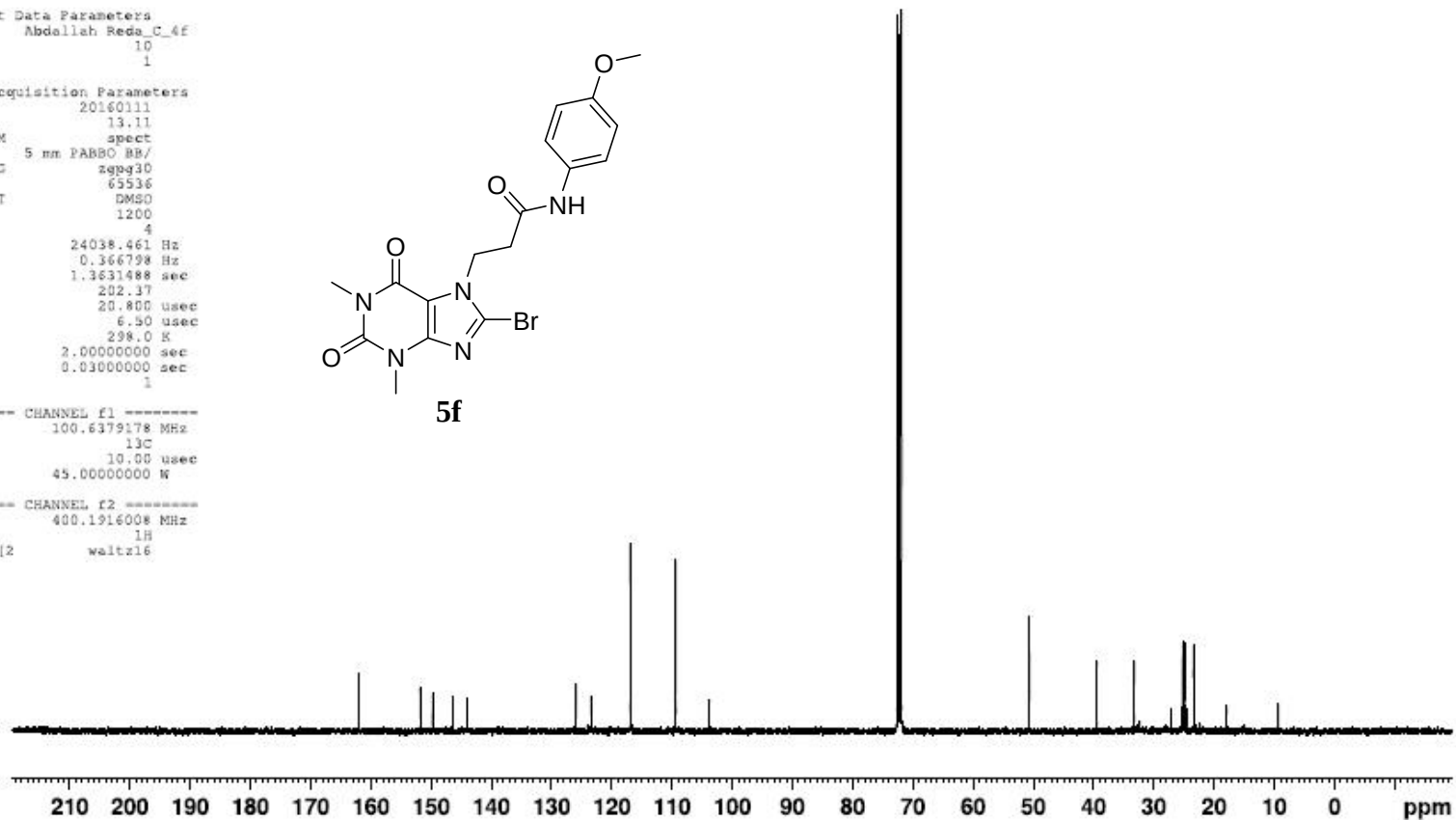
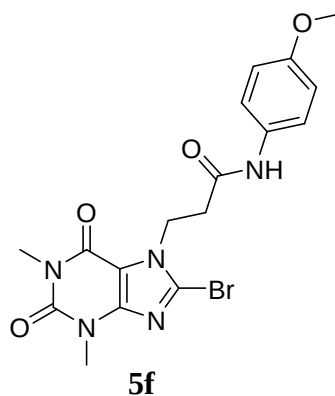


Current Data Parameters
NAME Abdallah Reda_C_4f
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
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Time 13.11
INSTRUM spect
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1200
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 202.17
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

----- CHANNEL f1 -----
SFO1 100.6379178 MHz
NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

----- CHANNEL f2 -----
SFO2 400.1916008 MHz
NUC2 1H
CPDPRG2 waltz16



Abdallah Rida_H_F11-120 (12E)

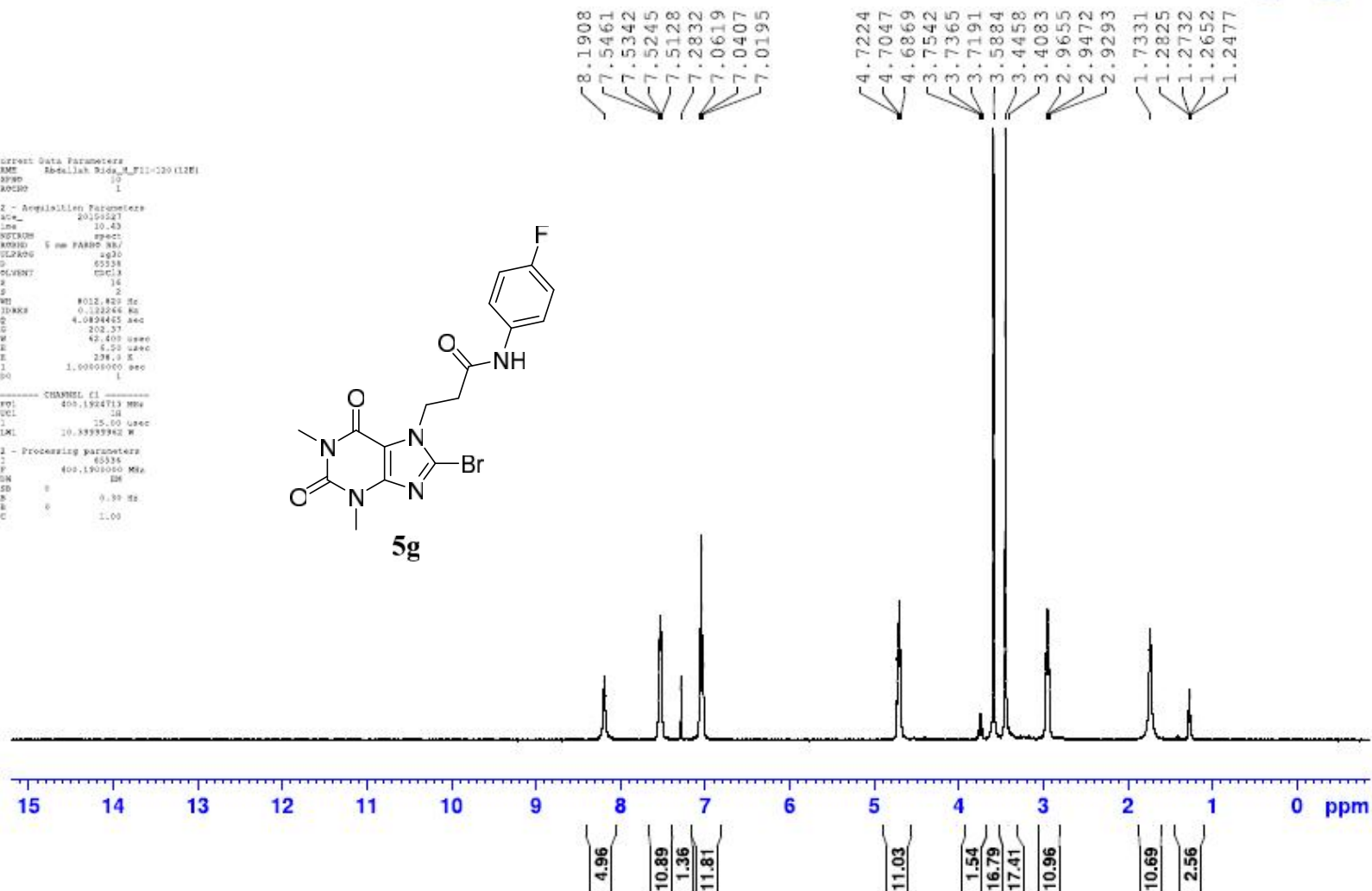
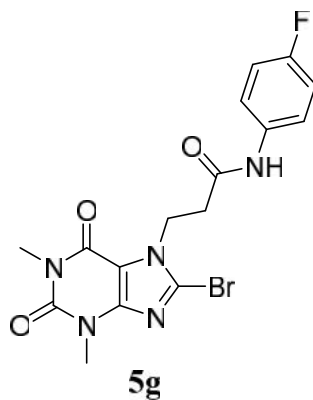
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Current Data Parameters
NAME Abdallah Rida_H_F11-120 (12E)
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150521
Time 10.43
INSTRUM spect
PROBHD 5 mm F4000 NMR
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 4012.820 Hz
FIDRES 0.122244 Hz
AQ 4.0824425 sec
RG 202.37
DM 42.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

CHANNEL f1
NUC1 400.1924713 MHz
P1 15.00 usec
PIPL 10.33333333 W
F2 - Processing parameters
SI 65536
SF 400.1900000 MHz
WDW EM
SSB 0
LB 0.33 Hz
GB 0
PC 1.00



Abdallah Reda_H_f70-60 (7T)

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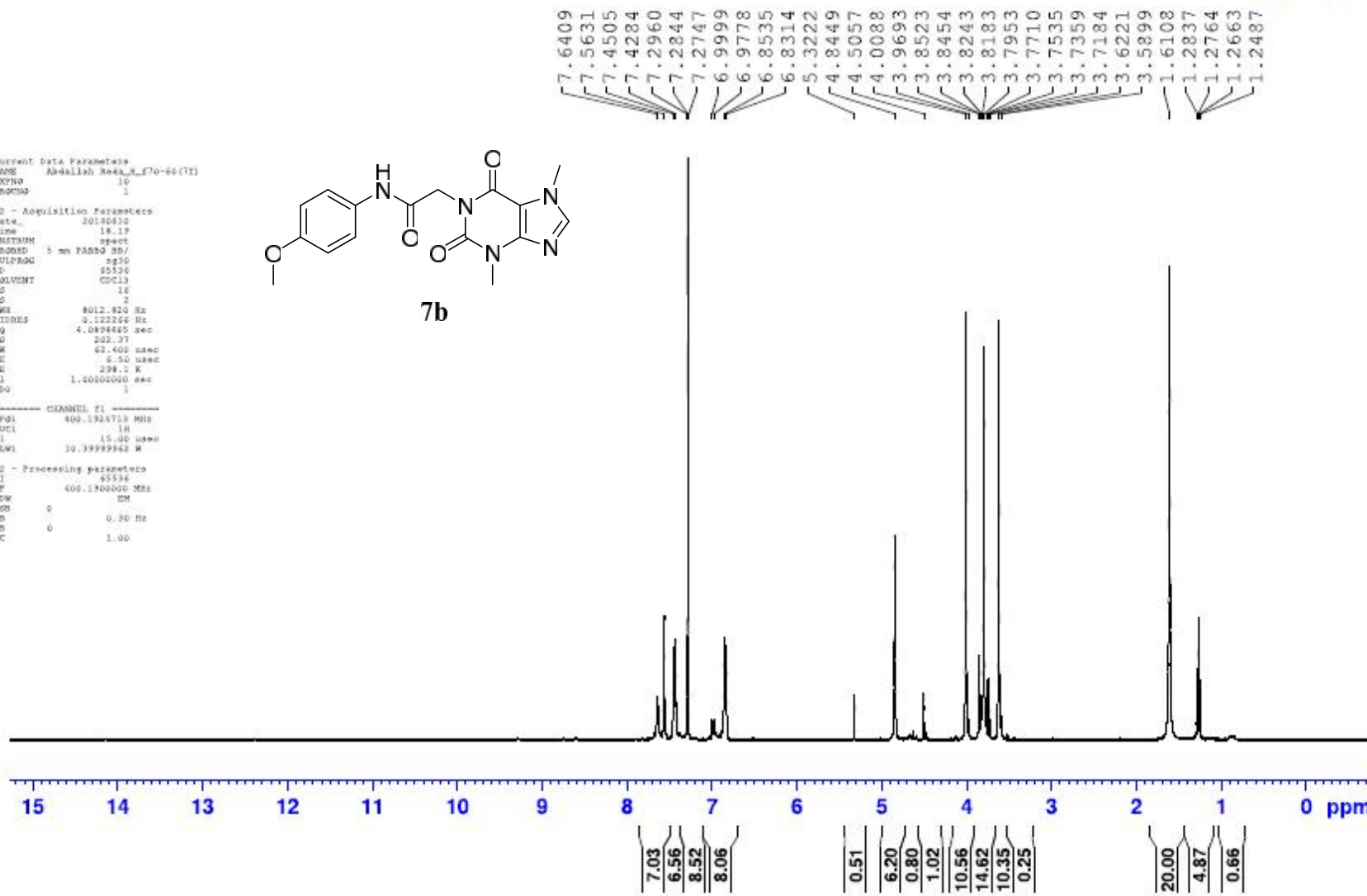
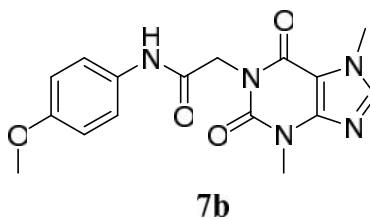


Current Data Parameters
NAME Abdallah Reda_H_f70-60(7T)
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140610
Time 18.19
INSTRUM spect
PROBHD 5 mm TABBO SD/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 3.122266 Hz
AQ 4.0894665 sec
RG 202.27
DM 62.400 used
DE 6.50 used
TE 298.1 K
D1 1.0000000 sec
TD0 1

CHANNEL f1
NUC1 1H
P1 15.00 used
PL1 30.39999962 W

F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Riham Francois_C_8b

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Current Data Parameters
NAME Riham Francois_C_8b
EXPNO 10
PROCNO 1

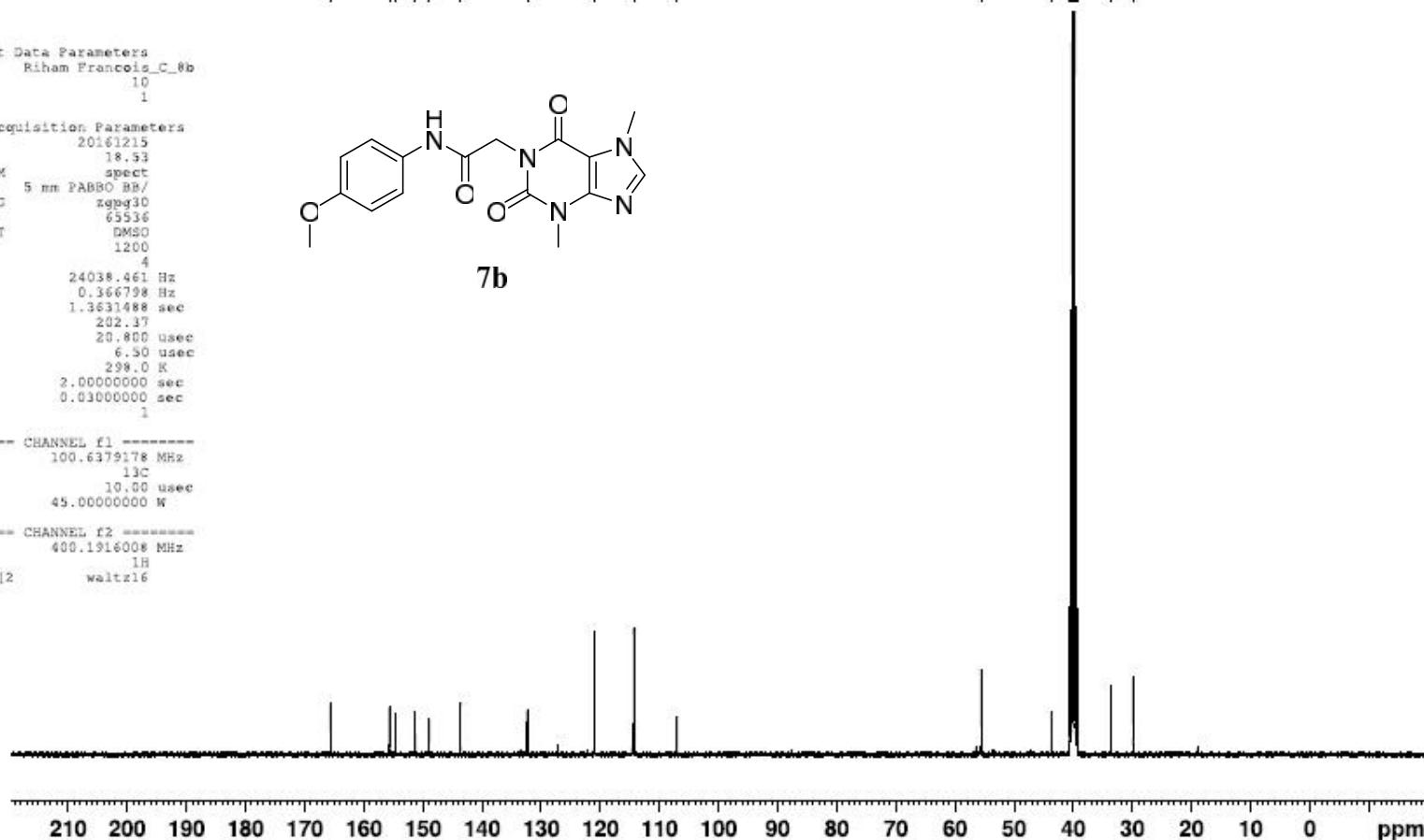
F2 - Acquisition Parameters
Date_ 20161215
Time 18.53
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1200
DS 4
SWH 24038.461 Hz
FIDRES 0.366728 Hz
AQ 1.3631488 sec
RG 202.37
DW 20.800 usec
DE 6.30 usec
TE 299.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

----- CHANNEL f1 -----
SFO1 100.6379178 MHz
NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

----- CHANNEL f2 -----
SFO2 400.1916008 MHz
NUC2 1H
CPDPRG2 waltz16



7b



Abdallah Rida_H_F70-80(8T)

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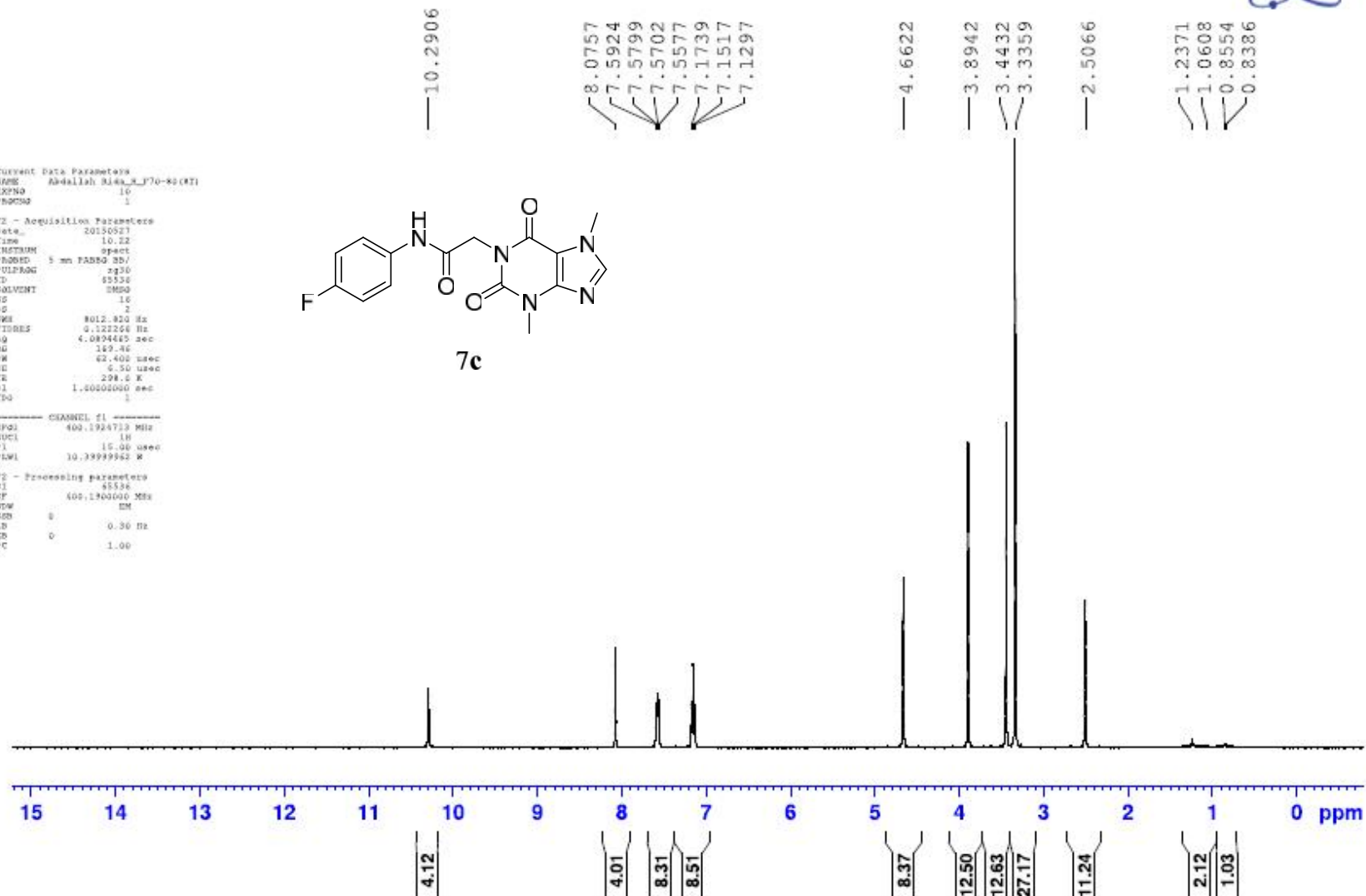
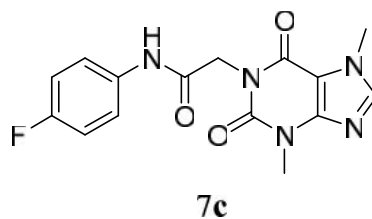


Current Data Parameters
NAME Abdallah_Rida_H_F70-80(8T)
EXPNO 16
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150527
Time 10.22
INSTRUM spect
PROBHD 5 mm F400 QNP
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8012.850 Hz
FIDRES 0.123256 Hz
AQ 4.0894465 sec
RG 169.46
DM 62.400 usec
DE 6.50 usec
TE 298.2 K
D1 1.50000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 1H
P1 15.00 usec
PLWL 10.39999962 W

F2 - Processing parameters
SI 32768
SF 400.1900000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Abdalla Reda_H_F70-100 (10T)

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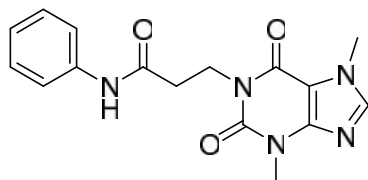


Current Data Parameters
NAME Abdalla Reda_H_F70-100(10T)
EXPNO 17
PROCNO 1

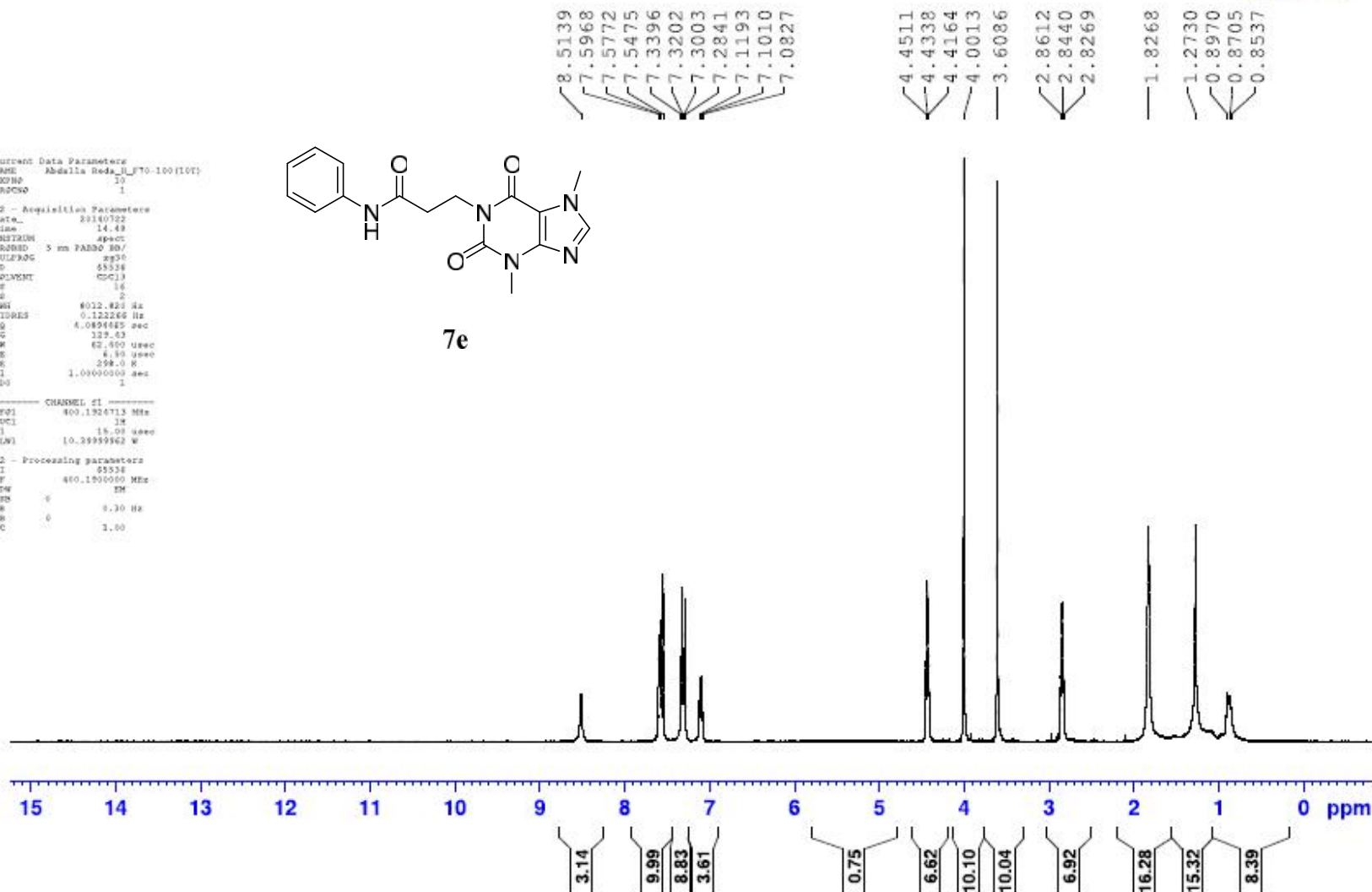
F2 - Acquisition Parameters
Date_ 20140722
Time 14.49
INSTRUM spect
PROBHD 5 mm PABBO 80/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.823 Hz
FIDRES 0.122266 Hz
AQ 4.0894825 sec
RG 329.63
DW 62.460 usec
DE 4.90 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

----- CHANNEL f1 -----
NUC1 1H
P1 18.00 usec
PLW1 10.35999962 W

F2 - Processing parameters
SI 65536
SF 400.1500000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



7e



Abdallah Reda_H_F70-110 (11T)

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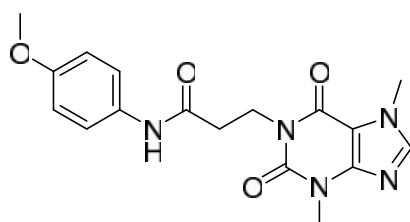


Current Data Parameters
NAME Abdallah Reda_H_F70-110 (11T)
EXPNO 10
PROCNO 1

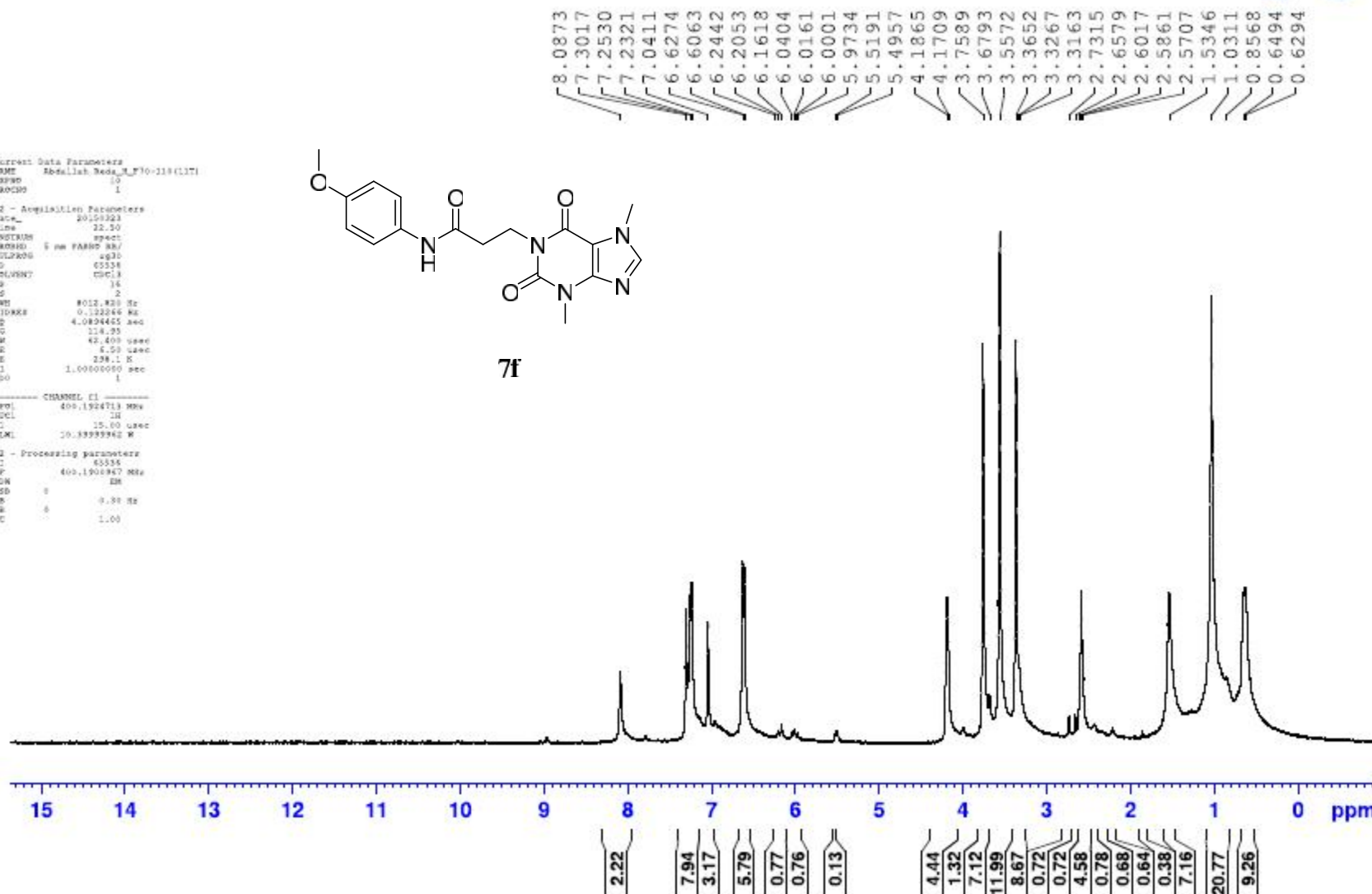
F2 - Acquisition Parameters
Date_ 20150923
Time 22.50
INSTRUM spect
PROBHD 5 mm F4001 H₂O
PULPROG zgpg30
TD 65536
SOLVENT H₂O
NS 14
DS 2
SWH 8012.820 Hz
FIDRES 0.122246 Hz
AQ 4.0804455 sec
RG 114.95
DM 42.400 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TDO 1

CHANNEL f1
NUC1 400.1924713 MHz
P1 15.00 usec
PL1 0.00000000 W

F2 - Processing parameters
SI 65536
SF 400.1901947 MHz
WDW EM
SSB 0
LB 0.90 Hz
GB 0
PC 1.00



7H



Riham Francois_C_8f

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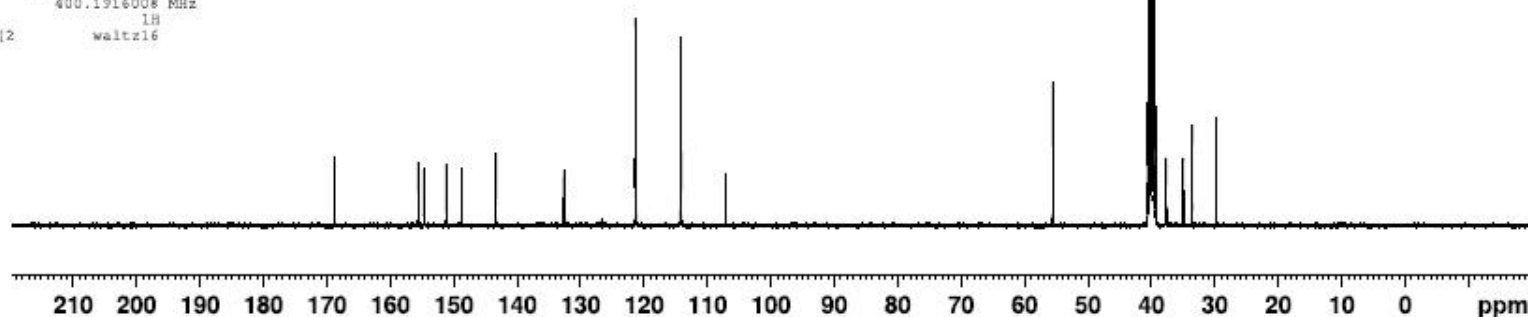


Current Data Parameters
NAME Riham Francois_C_8f
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161216
Time 4.23
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1200
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 202.37
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

----- CHANNEL f1 -----
SFO1 100.6379178 MHz
NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

----- CHANNEL f2 -----
SFO2 400.1916008 MHz
NUC2 1H
CPDPRG2 waltz16



Abdallah Reda_H_F70-120 (12T)

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Current Data Parameters
NAME Abdallah Reda_H_F70-120 (12T)
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20250111
Time 15.08
INSTRUM spect
PROBHD 5 mm PABO 8H
PULPROG zgpg30
TD 65536
SOLVENT DMSO-d6
NS 32
DS 2
SWH 8012.822 Hz
FIDRES 0.122446 Hz
AQ 4.0824465 sec
RG 202.37
DM 42.400 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 400.1324713 MHz
NUC1 1H
P1 15.00 usec
PL1 0.00000000 M

F2 - Processing parameters
SI 65536
SF 400.1301010 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

