

Electronic Supplementary Information (ESI)

Synthesis and characterization of new functionalized 1,2,3-triazole-based acetaminophen derivatives via click chemistry from expired commercial acetaminophen tablets

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1 General information

1.1 Materials and Instruments

All work-up and purification procedures were carried out with reagent-grade solvents (purchased from Aldrich and Merck) in the air. Thin-layer chromatography (TLC) was performed using Silufol UV254 plates (0.25 mm), exposed in a UV light chamber of 254 nm. The melting points (uncorrected) were measured by using the Fisher-Johns melting point apparatus.

Infrared spectra (FT-IR) were taken on an FT-IR Nicolet™ iS50 spectrophotometer, and the wavenumbers of the absorption peaks are listed in cm^{-1} . ^1H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. Chemical shifts were reported in ppm with the solvent resonance as the internal standard (CDCl_3 : δ 7.26 ppm; DMSO-d_6 : δ 2.50 ppm). Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from solvent resonance as the internal standard (CDCl_3 : δ 77.00 ppm; DMSO-d_6 : δ 40.45 ppm). Elemental analyses were performed on a PerkinElmer 2400 Series II analyzer and were within ± 0.4 of theoretical values.

18 tablets of commercial acetaminophen brand 500 mg, Genfar® (10.13 g), expiration date 25 Dec. 2018, were obtained at the blue point of reception of University Wellness at the Industrial University of Santander (Colombia). The triturate obtained was dissolved in 400 mL of a CH_2Cl_2 : MeOH (3:1) solution and placed in a Schott bottle with a lid with vigorous shaking for 24 hours at room temperature. The resulting solution was filtered through Celite and concentrated to dryness to obtain a pure *N*-(4-hydroxyphenyl)acetamide (or 4'-hydroxyacetanilide, acetaminophen, and paracetamol) as a white crystalline solid [(Mp = 169-171 °C, R_f = 0.6 (petroleum ether-ethyl acetate, 1:3)], the spectral data of which were in agreement with those of acetaminophen from literature (SDBS Information. https://sdb.db.aist.go.jp/sdb/cgi-bin/direct_frame_disp.cgi?sdbno=3290&spectrum_type=IR&fname=NIDA61329).

2 Experimental procedures

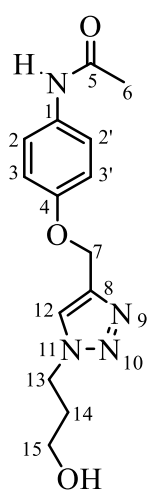
2.1 Synthesis of *N*-(4-(prop-2-yn-1-yloxy)phenyl)acetamide (*O*-propargylated acetaminophen) (**3**)

The compound synthesized from acetaminophen **1** (0.20 g, 1.32 mmol), propargyl bromide **2** (0.28 g, 2.37 mmol), potassium carbonate (0.18 g, 1.30 mmol), and 0.5 mL of propylene carbonate as a solvent. The reaction proceeded at 80 °C for 24 hours by conventional heating. Product **3** was obtained as a yellow crystalline solid (0.213 g, 1.12 mmol, 85%). R_f = 0.8 (1:4 petroleum ether-ethyl acetate). Mp = 111-113 °C. IR: (ATR, $\nu_{\max}/\text{cm}^{-1}$): 3310 ($\nu(\text{N-H})$ amide), 2925 and 2856 ($\nu_{\text{Ar}}(\text{C-H})$), 1651 ($\nu(\text{C=O})$ amide), 1576-1393 ($\nu_{\text{Ar}}(\text{C=C})$), 1271 ($\nu(\text{C-N})$), 863-759 ($\gamma_{\text{Ar}}(\text{C-H})$). ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.57 (1H, s, -NH), 7.40 (2H, d, J = 9.0 Hz, 3- and 3'- H_{Ar}), 6.91 (2H, d, J = 9.0 Hz, 2- and 2'- H_{Ar}), 4.65 (2H, t, CH_2), 2.51 (1H, s, $\text{HC}\equiv$), 2.12 (3H, s, $\text{H}_3\text{C-C(O)NH-}$). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm) = 168.5(-C=O), 154.3 ($\text{C}_{\text{Ar}}\text{-O}$), 131.9 ($\text{C}_{\text{Ar}}\text{-NH-C=O}$), 121.8 (2 $\text{C}_{\text{Ar}}\text{-C}_{\text{Ar}}\text{-O}$), 115.3 (2 $\text{C}_{\text{Ar}}\text{-C}_{\text{Ar}}\text{-NH}$), 78.5(-C \equiv CH), 76.7 (-C \equiv CH), 56.1 (-CH $_2$ -C \equiv), 24.3 ($\text{H}_3\text{C-CO-}$).

2.2 General Procedure for the Synthesis of 1,2,3-triazole-based APAP derivatives **5a-f**

General methodology: In a 20 mL flask, alkyne **3** (1mmol, 189 mg) and $\text{CuBr(PPh}_3)_3$ catalyst (1 mol%) dissolved in a 4 mL of *tert*-BuOH:H $_2$ O mixture (1:1) were added at room temperature and the reaction mixture was stirred for 30 min. Then, the corresponding azide **4a-f** (1.3 mmol) was slowly added, and the reaction was allowed until TLC monitoring showed that the precursors had been completely consumed. The formed products **5a-f** were precipitated with cold water, filtered, washed with methanol, recrystallized, and characterized as stable solid substances.

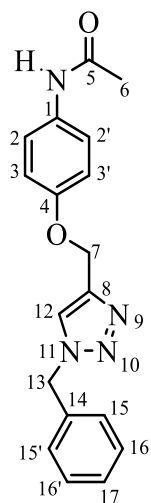
2.2.1 *N*-(4-((1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)acetamide (**5a**).



Synthesized from alkyne **3** (189 mg, 1 mmol), 3-azido-1-propanol **4a** (132 mg, 1.3 mmol), and $[\text{Cu(PPh}_3)_3\text{Br}]$ catalyst (9.3 mg, 1 mol%) in 4 mL of *tert*-BuOH:H $_2$ O (1:1) as a solvent. The reaction proceeded at room temperature for 9 h. Product **5a** was obtained as a gray solid (270 mg, 0.93 mmol, 93 %). R_f = 0.20 (ethyl acetate). Mp = 156-158 °C. IR (ATR, $\nu_{\max}/\text{cm}^{-1}$): 3250 ($\nu(\text{N-H})$ amide and (O-H)), 3143-2867 ($\nu_{\text{C-H}}$), 1638 ($\nu(\text{C=O})$ amide), 1542-1393 ($\nu_{\text{Ar}}(\text{C=C})$), 1226 ($\nu(\text{C-N})$), 863-759 ($\gamma_{\text{Ar}}(\text{C-H})$). ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) = 9.79 (1H, s, -NH), 8.19 (1H, s, 12-CH), 7.48 (2H, d, J = 8.2 Hz, 3- and 3'- H_{Ar}), 6.96 (2H, d, J = 8.2 Hz, 2- and 2'- H_{Ar}), 5.08 (2H, s, 7-CH $_2$) 4.68 (1H, t, J = 5.1 Hz, 15-CH $_2$ OH) 4.42 (2H, t, J = 7.0 Hz, 13-CH $_2$), 1.98 (7H, m, 14-CH $_2$, 15-CH $_2$ and 6-CH $_3$). ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm) = 167.8 (-C=O), 153.8 ($\text{C}_{\text{Ar}}\text{-O}$), 142.7 ($\text{C}_{\text{Ar}}\text{-NH-C=O}$), 132.8 (=C $_{\text{Triazole-CH}_2\text{O-}}$), 124.5 (=C-

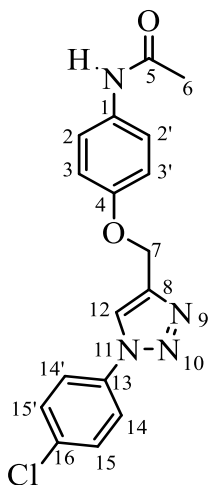
N_{Triazole}), 120.5 (2 C_{Ar}-C_{Ar}-O), 114.7 (2 C_{Ar}-C_{Ar}-NH-), 61.3 (-O-CH₂-), 57.4 (-CH₂-CH₂-OH), 46.7 (N-CH₂-CH₂-), 32.9 (N-CH₂-CH₂-), 23.8 (H₃C-CO-). Anal. calcd. for C₁₄H₁₈N₄O₃ (MW = 290.32 g/mol): C, 57.92; H, 6.25; N, 19.30 %. Found: C, 57.66; H, 6.47; N, 19.15 %.

2.2.2 N-(4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)acetamide (**5b**). Synthesized



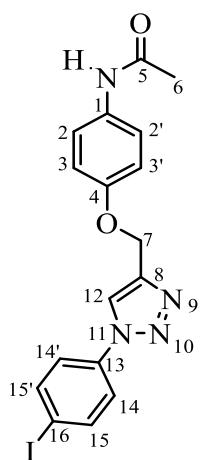
from alkyne **3** (189 mg, 1 mmol), benzyl azide **4b** (173 mg, 1.3 mmol), and [Cu(PPh₃)₃Br] catalyst (9.3 mg, 1 mol%) in 2 mL of *tert*-BuOH:H₂O (1:1) as a solvent. The reaction proceeded at room temperature for 13 h. Product **5b** was obtained as a light pink crystalline solid (267 mg, 0.83 mmol, 83 %). R_f = 0.40 (ethyl acetate). Mp = 133-134 °C. IR (ATR, ν_{max}/cm⁻¹): 3296 (ν(N-H) amide), 3143-2918 (ν(C-H)), 1676 (ν(C=O) amide), 1596-1393 (νAr(C=C)), 1271 (ν(C-N)), 867-762 (γAr(C-H)). ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 9.78 (1H, s, -NH), 8.26 (1H, s, 12-CH), 7.48 (2H, d, *J* = 9.0 Hz, 3- and 3'-H_{Ar}), 7.34 (5H, m, 15-, 15'-, 16-, 16'- and 17-H_{Ar}), 6.95 (2H, d, *J* = 9.0 Hz, 2- and 2'-H_{Ar}), 5.61 (2H, s, 13-CH₂), 5.08 (2H, s, 7-CH₂), 2.01 (3H, s, 6-CH₃). ¹³C NMR (101 MHz, DMSO-d₆) δ (ppm) = 167.7 (-C=O), 153.7 (C_{Ar}-O), 143.1 (=C_{Triazole}-CH₂O-), 136.0 (-C_{ipso}Bn), 132.8 (C_{Ar}-NH-C=O), 128.7 (2 C_m-Bn), 128.1 (C_p-Bn), 127.9 (2 C_o-Bn), 124.5 (=C-N_{Triazole}), 120.4 (2 C_{Ar}-C_{Ar}-O), 114.7 (2 C_{Ar}-C_{Ar}-NH-), 61.2 (-O-CH₂-), 52.8 (N-CH₂-Bn), 23.7 (H₃C-CO-). Anal. calcd. for C₁₈H₁₈N₄O₂ (MW = 322.37 g/mol): C, 67.07; H, 5.63; N, 17.38 %. Found: C, 67.25; H, 5.87; N, 17.55 %.

2.2.3 N-(4-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)acetamide (**5c**). Synthesized



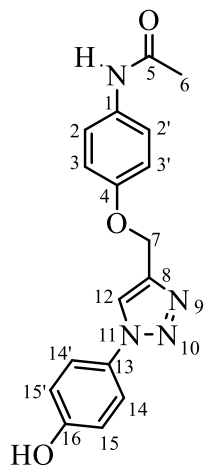
Synthesized from alkyne **3** (189 mg, 1 mmol), 4-chlorophenyl azide **4c** (198 mg, 1.3 mmol), and [Cu(PPh₃)₃Br] catalyst (9.3 mg, 1 mol%) in 4 mL of *tert*-BuOH:H₂O (1:1) as a solvent. The reaction proceeded at room temperature for 13 h. Product **5c** was obtained as a yellow amorphous solid (291 mg, 0.85 mmol, 73 %). R_f = 0.35 (ethyl acetate: petroleum ether, 2:1). Mp = 264-265 °C. IR (ATR, ν_{max}/cm⁻¹): 3289 (ν(N-H) amide), 3256-3100 (ν(C-H)), 1660 (ν(C=O) amide), 1553-1393 (νAr(C=C)), 1271 (ν(C-N)), 867-762 (γAr(C-H)). ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 9.79 (1H, s, -NH), 8.96 (1H, s, 12-CH), 7.96 (2H, d, *J* = 8.8 Hz, 15- and 15'-H_{Ar}), 7.68 (2H, d, *J* = 8.8 Hz, 14- and 14'-H_{Ar}), 7.50 (2H, d, *J* = 9.0 Hz, 3- and 3'-H_{Ar}), 7.00 (2H, d, *J* = 9.0 Hz, 2- and 2'-H_{Ar}), 5.19 (2H, s, 7-CH₂), 2.00 (3H, s, 6-CH₃). ¹³C NMR (101 MHz, DMSO-d₆) δ (ppm) = 167.7 (-C=O), 153.6 (C_{Ar}-O), 144.1 (=C_{Triazole}-CH₂O-), 135.3 (N-C_{ipso}PhCl), 133.08 (C_{Ar}-NH-C=O), 129.8 (Cl-C_{ipso}PhCl), 129.8 (2 C_m-PhCl), 122.8 (=C-N_{Triazole}), 121.8 (2 C_o-PhCl), 120.4 (2 C_{Ar}-C_{Ar}-O), 114.7 (2 C_{Ar}-C_{Ar}-NH-), 61.1 (N-CH₂-Bn), 23.7 (H₃C-CO-). Anal. calcd. for C₁₇H₁₅ClN₄O₂ (MW = 342.78 g/mol): C, 59.57; H, 4.41; N, 16.35 %. Found: C, 59.23; H, 4.65; N, 16.19 %.

2.2.4 *N*-(4-((1-(4-iodophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)acetamide (**5d**).



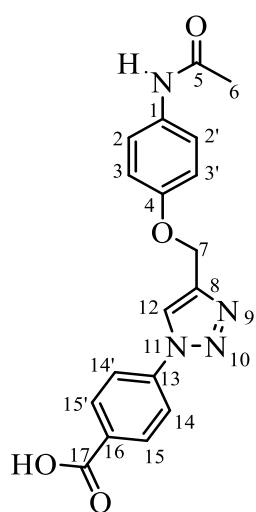
Synthesized from alkyne **3** (189 mg, 1 mmol), 4-iodophenyl azide **4d** (321 mg, 1.3 mmol), and [Cu(PPh₃)₃Br] catalyst (9.3 mg, 1 mol%) in 4 mL of *tert*-BuOH:H₂O (1:1) as a solvent. The reaction proceeded at room temperature for 11 h. Product **5d** was obtained as a yellow solid (0.278 g, 0.64 mmol, 64 %). *R*_f = 0.42 (ethyl acetate: petroleum ether, 2:1). Mp = 257-258 °C. IR (ATR, *v*_{max}/cm⁻¹): 3289 (*v*(N-H) amide), 3134-2918 (*v*(C-H)), 1660 (*v*(C=O) amide), 1576-1393 (*v*Ar(C=C)), 1231 (*v*(C-N)), 816-762 (*γ*Ar(C-H)). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 9.79 (1H, s, -NH), 8.95 (1H, s, 12-CH), 7.96 (2H, d, *J* = 8.8 Hz, 15- and 15'-H_{Ar}), 7.74 (2H, d, *J* = 8.8 Hz, 14- and 14'-H_{Ar}), 7.50 (2H, d, *J* = 9.0 Hz, 3- and 3'-H_{Ar}), 7.00 (2H, d, *J* = 9.0 Hz, 2- and 2'-H_{Ar}), 5.18 (2H, s, 7-CH₂), 2.01 (3H, s, 6-CH₃). ¹³C NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 167.7 (-C=O), 153.6 (C_{Ar}-O), 144.1 (=C_{Triazole}-CH₂O-), 138.5 (2 C_m-PhI), 136.2 (N-C_{ipso}PhI), 132.9 (C_{Ar}-NH-C=O), 122.7 (=C-N_{Triazole}), 122.0 (2 C_o-PhI), 120.4 (2 C_{Ar}-C_{Ar}-O), 114.7 (2 C_{Ar}-C_{Ar}-NH-), 94.3 (I-C_{ipso}PhI), 61.1 (N-CH₂-Bn), 23.8 (H₃C-CO-). Anal. calcd. for C₁₇H₁₅IN₄O₂ (MW = 434.24 g/mol): C, 47.02; H, 3.48; N, 12.90 %. Found: C, 47.24; H, 3.66; N, 12.75 %.

2.2.5 *N*-(4-((1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)acetamide (**5e**).



Synthesized from alkyne **3** (189 mg, 1 mmol), 4-hydroxyphenyl azide **4e** (175 mg, 1.3 mmol), and [Cu(PPh₃)₃Br] catalyst (9.3 mg, 1 mol%) in 4 mL of *tert*-BuOH:H₂O (1:1) as a solvent. The reaction proceeded at room temperature for 12 h. Product **5e** was obtained as a red crystalline solid (237 mg, 0.73 mmol, 73 %). *R*_f = 0.25 (ethyl acetate: petroleum ether, 2:1). Mp = 230-232 °C. IR (ATR, *v*_{max}/cm⁻¹): 3235-3184 (*v*(N-H) amide and (O-H)), 3135-2925 (*v*(C-H)), 1649 (*v*(C=O) amide), 1576-1393 (*v*Ar(C=C)), 1213 (*v*(C-N)), 869-742 (*γ*Ar(C-H)). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 9.94 (1H, s, -NH), 9.79 (1H, s, 16-OH), 8.73 (1H, s, 12-CH), 7.66 (2H, d, *J* = 8.9 Hz, 14- and 14'-H_{Ar}), 7.49 (2H, d, *J* = 9.0 Hz, 3- and 3'-H_{Ar}), 6.99 (2H, d, *J* = 9.0 Hz, 2- and 2'-H_{Ar}), 6.93 (2H, d, *J* = 8.9 Hz, 15- and 15'-H_{Ar}), 5.15 (2H, s, 7-CH₂), 2.00 (3H, s, 6-CH₃). ¹³C NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 167.7 (-C=O), 157.8 (HO-C_{ipso}PhOH), 153.7 (C_{Ar}-O), 143.5 (=C_{Triazole}-CH₂O-), 132.9 (C_{Ar}-NH-C=O), 128.7 (N-C_{ipso}PhOH), 122.6 (=C-N_{Triazole}), 122.0 (2 C_m-PhOH), 120.4 (2 C_{Ar}-C_{Ar}-O), 116.0 (2 C_o-PhOH), 114.7 (2 C_{Ar}-C_{Ar}-NH-), 61.2 (N-CH₂-Bn), 23.8 (H₃C-CO-). Anal. calcd. for C₁₇H₁₆N₄O₃ (MW = 324.34 g/mol): C, 62.95; H, 4.97; N, 17.27 %. Found: C, 62.78; H, 4.71; N, 17.43 %.

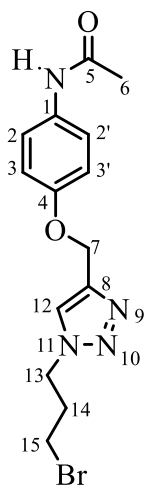
2.2.6 4-(4-((4-acetamidophenoxy)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (**5f**).



Synthesized from alkyne **3** (189 mg, 1 mmol), 4-azidobenzoic acid **4f** (212 mg, 1.3 mmol), and [Cu(PPh₃)₃Br] catalyst (9.3 mg, 1 mol%) in 4 mL of *tert*-BuOH:H₂O (1:1) as a solvent. The reaction proceeded at room temperature for 9 h. Product **5f** was obtained as a yellow crystalline solid (257 mg, 0.73 mmol, 73 %). *R*_f = 0.30 (ethyl acetate). *Mp* = > 300 °C. IR (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3096-2809 ($\nu(\text{N-H})$ amide and OH acid), 2553-2402 ($\nu(\text{C-H})$), 1671 ($\nu(\text{C=O})$ amide), 1576-1393 ($\nu(\text{Ar}(\text{C=C}))$), 1271 ($\nu(\text{C-N})$), 867-762 ($\gamma(\text{Ar}(\text{C-H}))$). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 9.78 (1H, s, -NH), 9.02 (1H, s, 12-CH), 8.09 (4H, m, 14-, 14', 15- and 15'-H_{Ar}), 7.50 (2H, d, *J* = 8.9 Hz, 3- and 3'-H_{Ar}), 7.00 (2H, d, *J* = 8.9 Hz, 2- and 2'-H_{Ar}), 5.20 (2H, s, 7-CH₂), 2.00 (3H, s, 6-CH₃). ¹³C NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 167.7 (-C=O_{amide}), and -C=O_{acid}), 157.8 (C_{Ar}-O), 153.6 (C(O)-C_{ipso}PhCOOH), 144.3 (=C_{Triazol}-CH₂O-), 139.4 (C_{Ar}-NH-C=O), 122.8 (2 C_O-

PhCOOH), 120.4 (2 C_{Ar}-C_{Ar}-O), 119.9 (2 C_m-PhCOOH), 119.9 (=C-N_{Triazole}), 114.8 (2 C_{Ar}-C_{Ar}-NH-), 114.7 (N-C_{ipso}PhCOOH), 61.1 (N-CH₂-Bn), 23.7 (H₃C-CO-). Anal. calcd. for C₁₈H₁₆N₄O₄ (MW = 352.35 g/mol): C, 61.36; H, 4.58; N, 15.90 %. Found: C, 61.56; H, 4.73; N, 15.74 %.

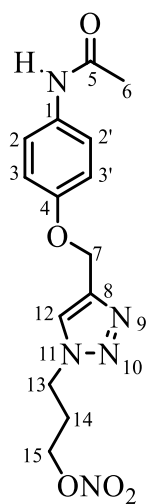
2.3 Synthesis of *N*-(4-((1-(3-bromopropyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)acetamide (**6a**)



Synthesized from hybrid **5a** (0.150 g, 0.52 mmol) and PBr₃ (0.281 g, 1.05 mmol, 0.133 mL), in dichloromethane (3 mL) as solvent. The reaction proceeded in an ice bath for 4 hours, then allowed to warm to room temperature over 20 hours. The reaction mixture was extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, concentrated, and then purified by column chromatography on silica gel using a mixture of petroleum ether-ethyl acetate (1: 4) as an eluent. Product **6a** was obtained as a white crystalline solid (97 mg, 0.27 mmol, 53%). *R*_f = 0.57 (ethyl acetate). *Mp* = 146-148 °C. IR: (ATR, $\nu_{\text{max}}/\text{cm}^{-1}$): 3278 ($\nu(\text{N-H})$ amide), 3135-2848 ($\nu(\text{C-H})$), 1657 ($\nu(\text{C=O})$ amide), 1576-1393 ($\nu(\text{Ar}(\text{C=C}))$), 1226 ($\nu(\text{C-N})$), 863-759 ($\gamma(\text{Ar}(\text{C-H}))$). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.67 (1H, s, 12-CH), 7.41 (2H, d, *J* = 8.6 Hz, 3- and 3'-H_{Ar}), 7.36 (s, -NH), 6.94 (2H, d, *J* = 8.6 Hz, 2- and 2'-H_{Ar}), 5.20 (2H, s, 7-CH₂),

4.57 (2H, t, *J* = 6.6 Hz, 15-CH₂), 3.38 (2H, t, *J* = 6.2 Hz, 13-CH₂), 2.49 (2H, *q*, *J* = 6.4 Hz, 14-CH₂), 2.17 (1H, s, 6-CH₃). ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) = 168.4 (-C=O), 155.1 (C_{Ar}-O), 144.3 (C_{Ar}-NH-C=O), 131.7 (=C_{Triazol}-CH₂O-), 123.4 (=C-N_{Triazole}), 122.0 (2 C_{Ar}-C_{Ar}-O), 115.3 (2 C_{Ar}-C_{Ar}-NH-), 62.41 (N-CH₂-Bn), 48.3 (-CH₂-CH₂-Br), 32.6 (N-CH₂-CH₂-), 29.4 (N-CH₂-CH₂-), 24.4 (H₃C-CO-). Anal. calcd. for C₁₄H₁₇BrN₄O₂ (MW = 353.22 g/mol): C, 47.61; H, 4.85; N, 15.86 %. Found: C, 47.48; H, 4.94; N, 15.63 %.

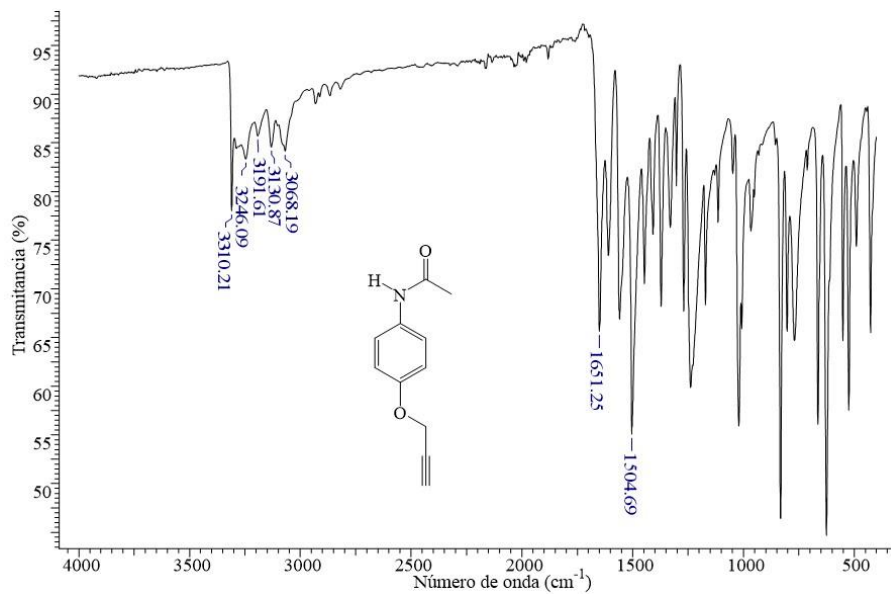
2.4 Synthesis of 3-(4-((4-acetamidophenoxy)methyl)-1H-1,2,3-triazol-1-yl)propyl nitrate (7a)



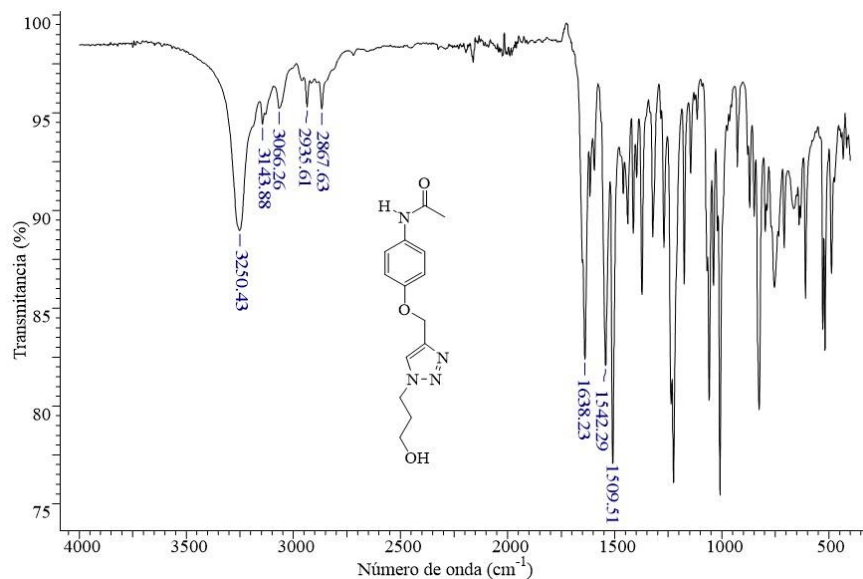
Synthesized from hybrid **6a** (80 mg, 0.22 mmol) and AgNO₃ (44 mg, 0.26 mmol) in acetonitrile (3 mL) as a solvent. The reaction proceeded at 60 °C in the dark. The reaction mixture was filtered through Celite and extracted with ethyl acetate (3 x 10 mL). It was dried over Na₂SO₄, concentrated, and then purified by column chromatography on silica gel using a mixture of petroleum ether-ethyl acetate (1:4) as an eluent. Product **7a** was obtained as a yellow crystalline solid (43 mg, 0.13 mmol, 61%). R_f = 0.59 (ethyl acetate). Mp = 117-119 °C. IR: (ATR, ν_{max}/cm⁻¹): 3275 (ν(N-H) amide), 3189-2874 (ν(C-H)), 1654 (ν(C=O) amide), 1620 (ν(ONO₂)), 1576-1393 (νAr(C=C)), 1279 (ν(ONO₂)), 1226 (ν(C-N)), 863-759 (γAr(C-H)). ¹H NMR (400 MHz, CDCl₃) δ(ppm) = 7.62 (1H, s, 12-CH), 7.41 (1H, s, -NH), 7.37 (2H, d, *J* = 9.0 Hz, 3- and 3'-H_{Ar}), 6.90 (2H, d, *J* = 9.0 Hz, 2- and 2'-H_{Ar}), 5.17 (2H, s, 7-CH₂), 4.51-4.43 (4H, m, 13-CH₂ and 15-CH₂), 2.38 (2H, q, *J* = 6.5 Hz), 2.13 (3H, s, 6-CH₃). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 168.5 (-C=O), 155.0 (C_{Ar}-O), 144.6 (C_{Ar}-NH-C=O), 131.8 (=C_{Triazol-CH₂O-}), 123.2 (=C-N_{Triazole}), 122.1 (2 C_{Ar}-C_{Ar}-O), 115.3 (2 C_{Ar}-C_{Ar}-NH-), 69.3(-CH₂-CH₂-ONO₂), 62.3 (N-CH₂-Bn), 46.6 (N-CH₂-CH₂-), 27.7 (N-CH₂-CH₂-), 24.4 (H₃C-CO-). Anal. calcd. for C₁₄H₁₇N₅O₅ (MW: 335.32 g/mol): C, 50.15; H, 5.11; N, 20.89 %. Found: 50.39; H, 5.39; N, 20.85 %.

3. IR spectra of products

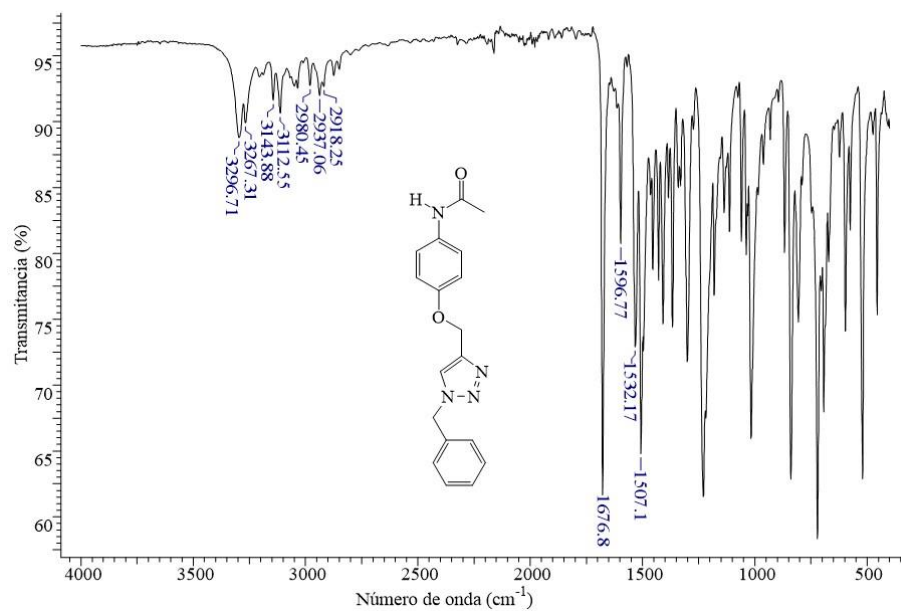
3.1 IR spectrum of *O*-propargylated acetaminophen 3



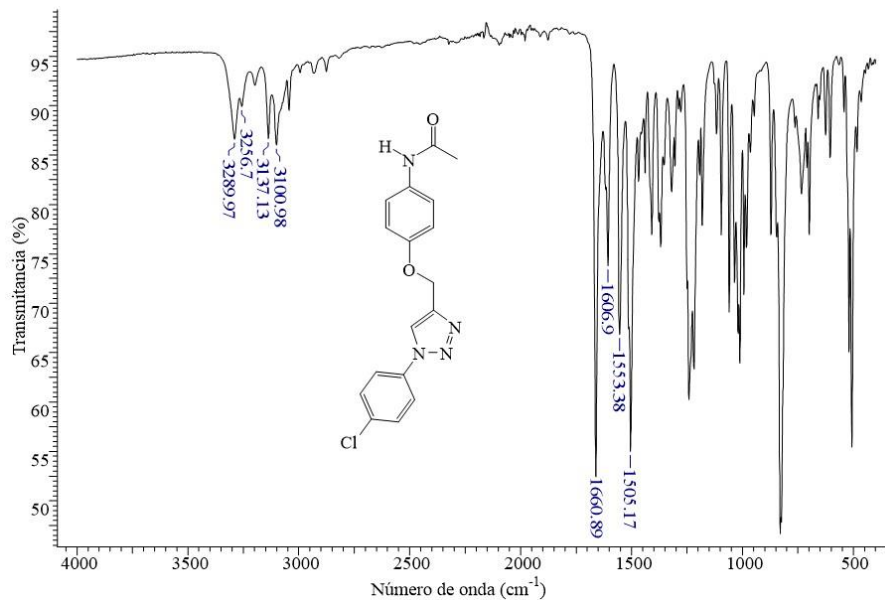
3.2 IR spectrum of hybrid 5a



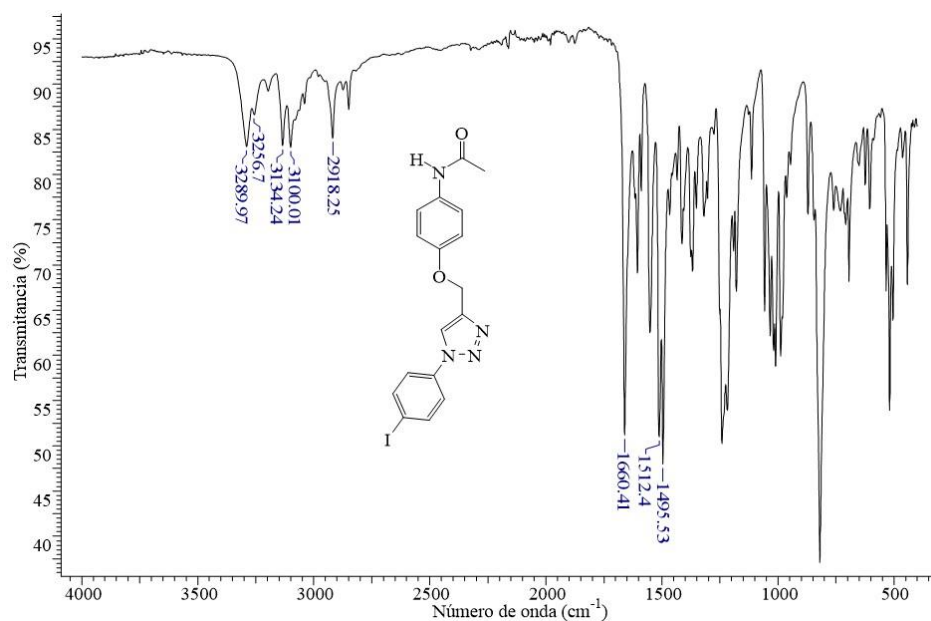
3.3 IR spectrum of hybrid 5b



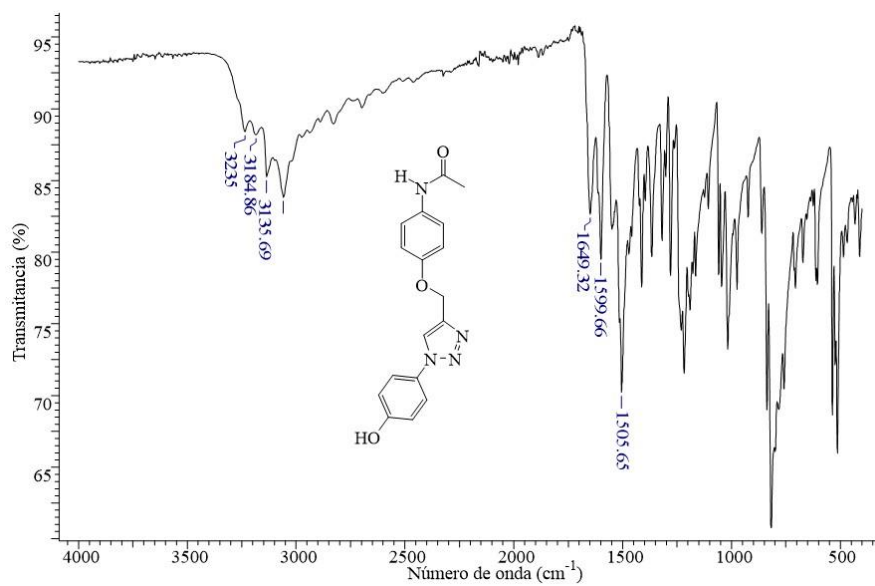
3.4 IR spectrum of hybrid 5c



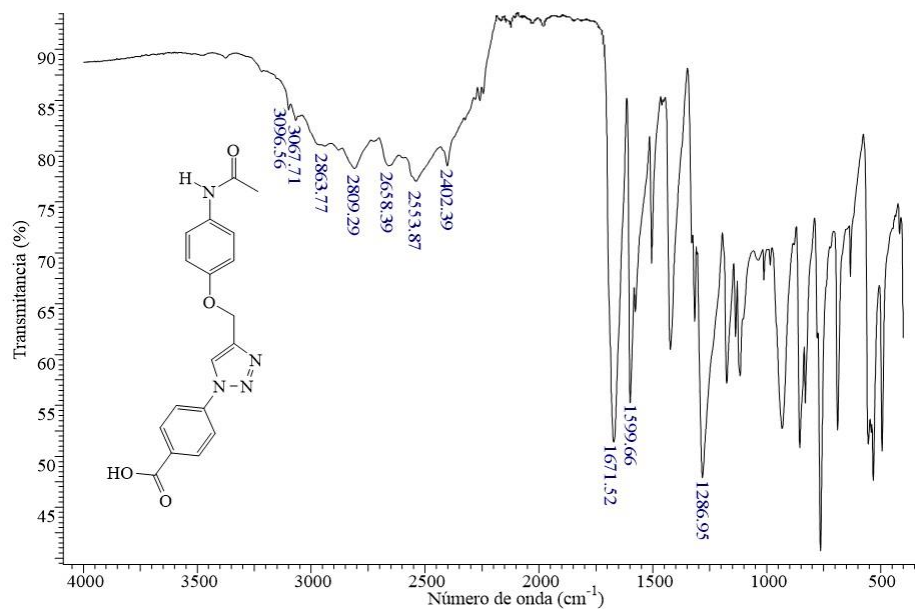
3.5 IR spectrum of hybrid 5d



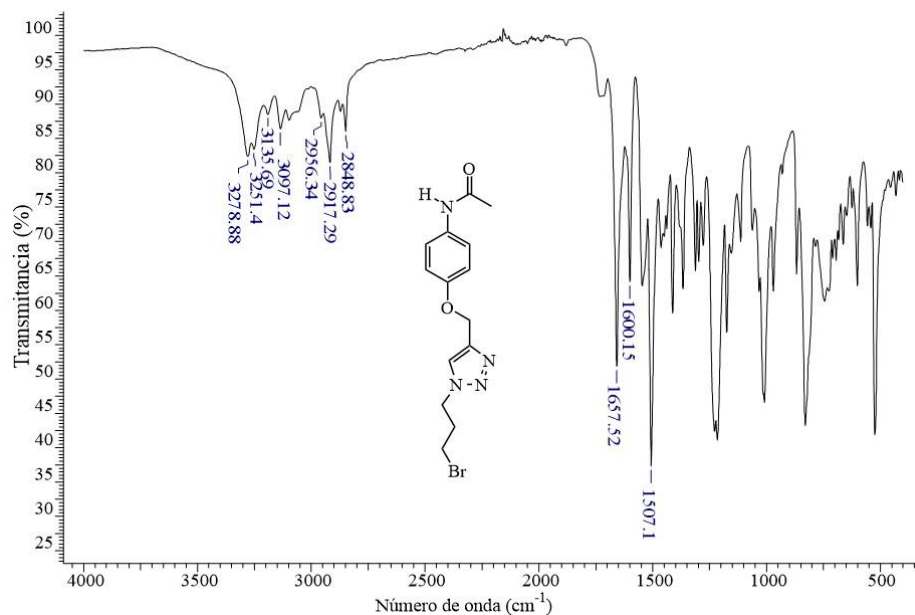
3.6 IR spectrum of hybrid 5e



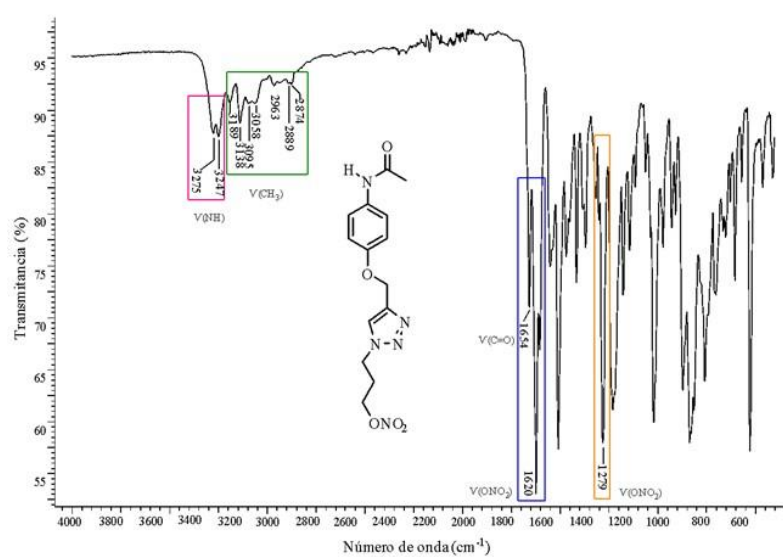
3.7 IR spectrum of hybrid 5f



3.8 IR spectrum of hybrid 6a

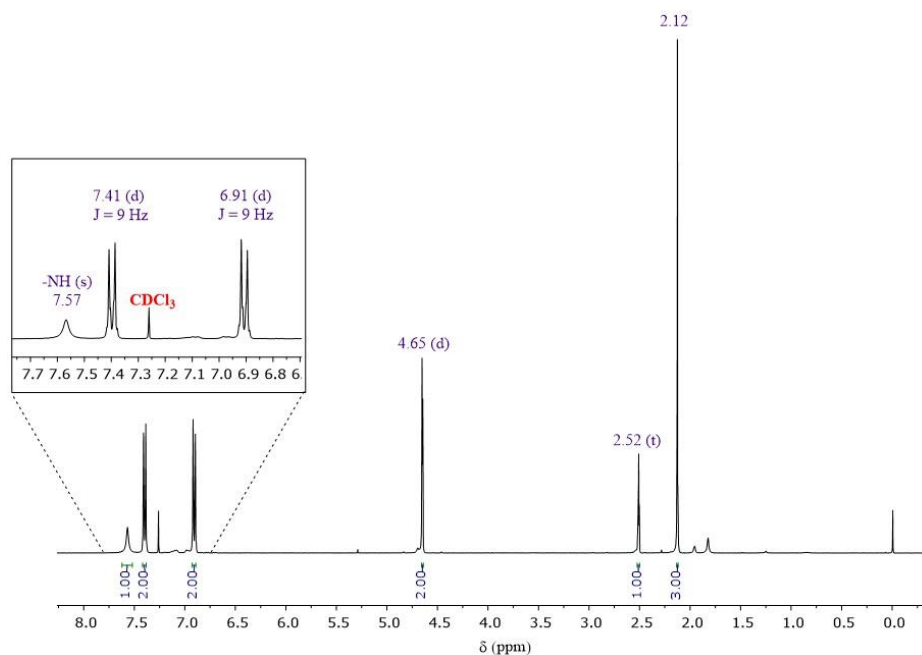


3.9 IR spectrum of hybrid 7a

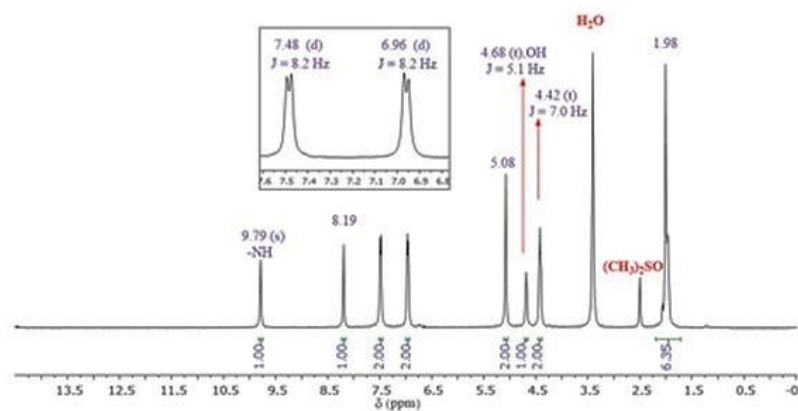


4. NMR spectra of products

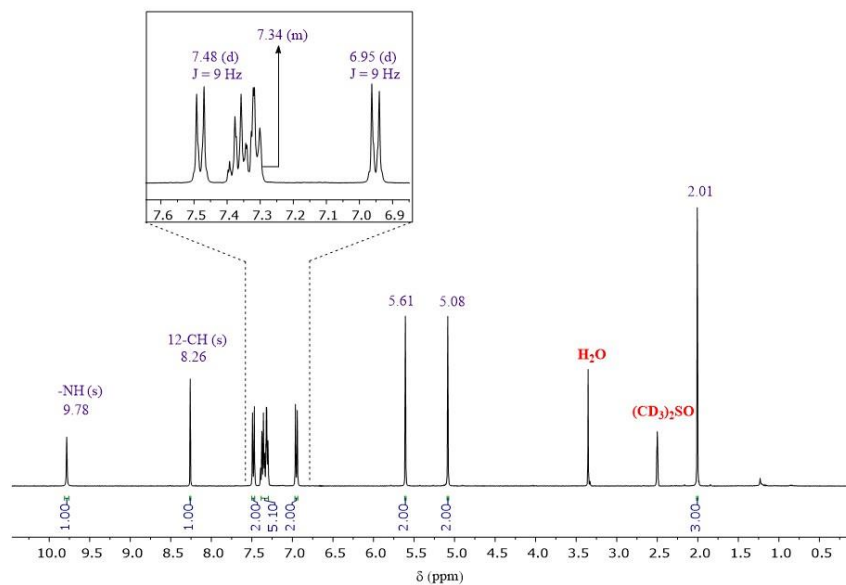
4.1 ^1H NMR spectrum of *O*-propargylated acetaminophen **3**



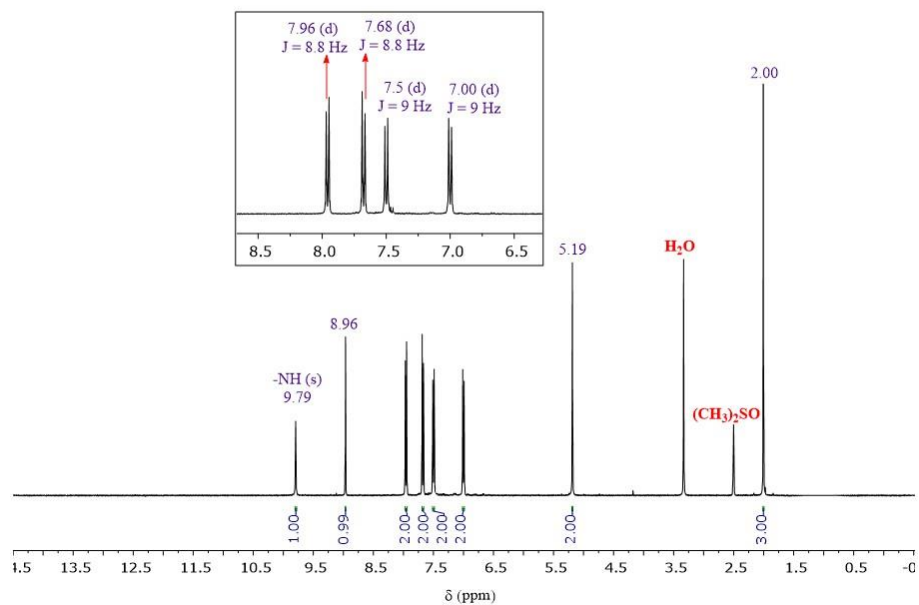
4.2 ^1H NMR spectrum of hybrid **5a**



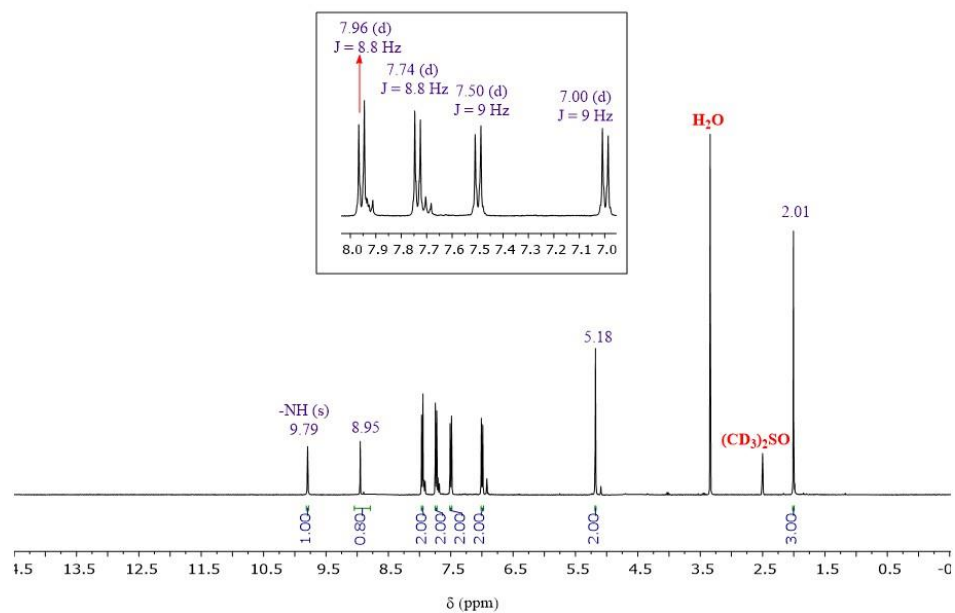
4.3 ^1H NMR spectrum of hybrid 5b



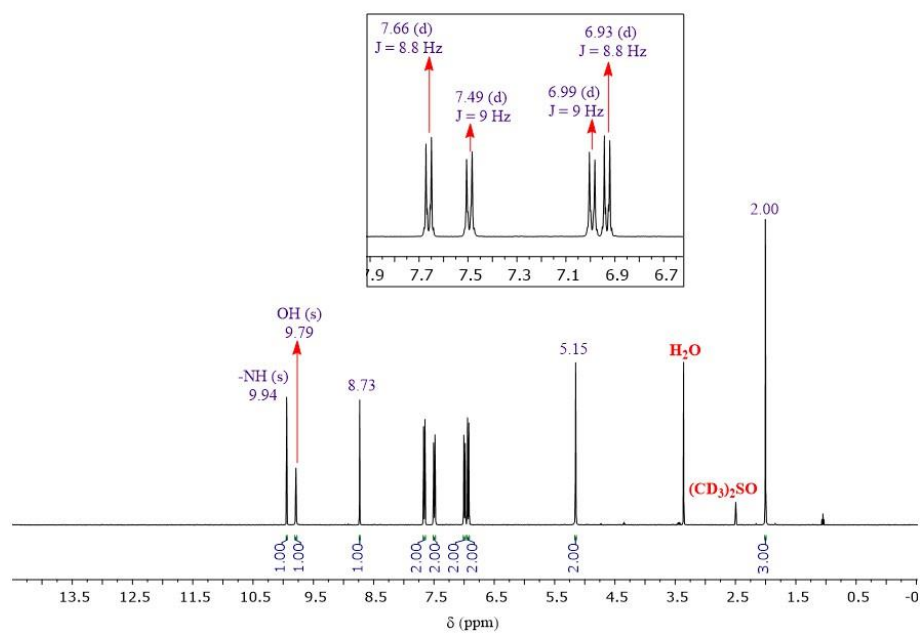
4.4 ^1H NMR spectrum of hybrid 5c



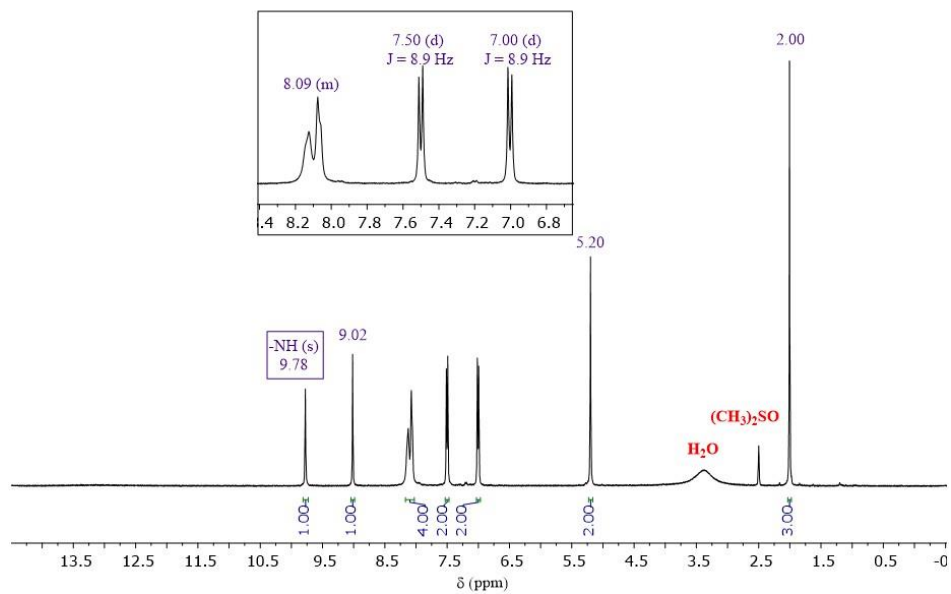
4.5 ^1H NMR spectrum of hybrid 5d



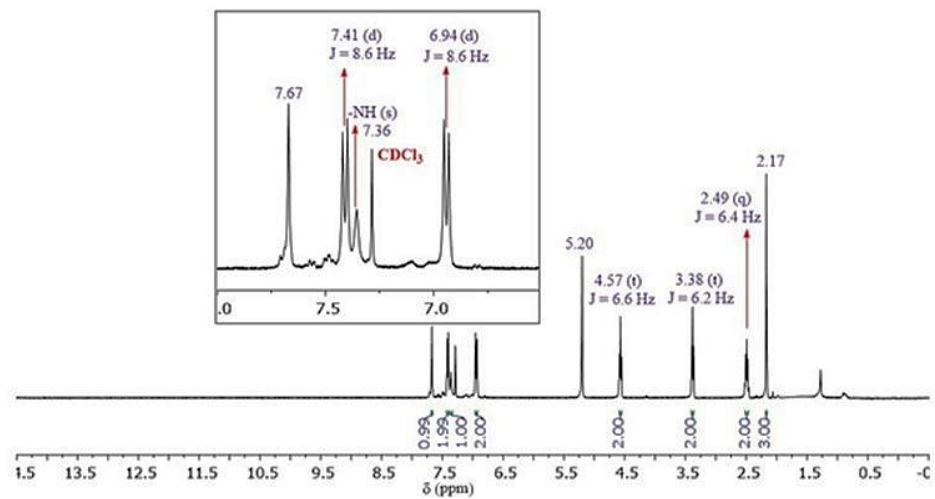
4.6 ^1H NMR spectrum of hybrid 5e



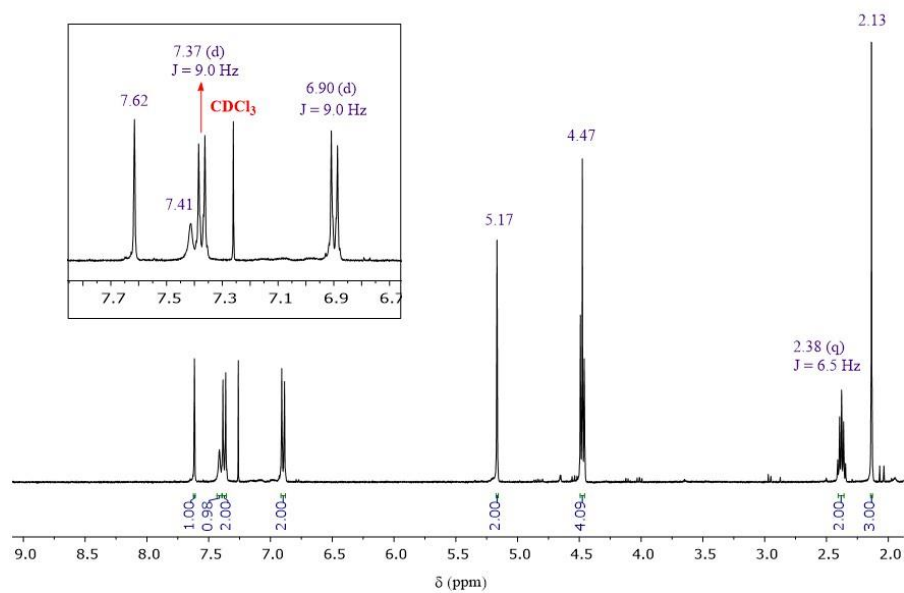
4.7 ^1H NMR spectrum of hybrid 5f



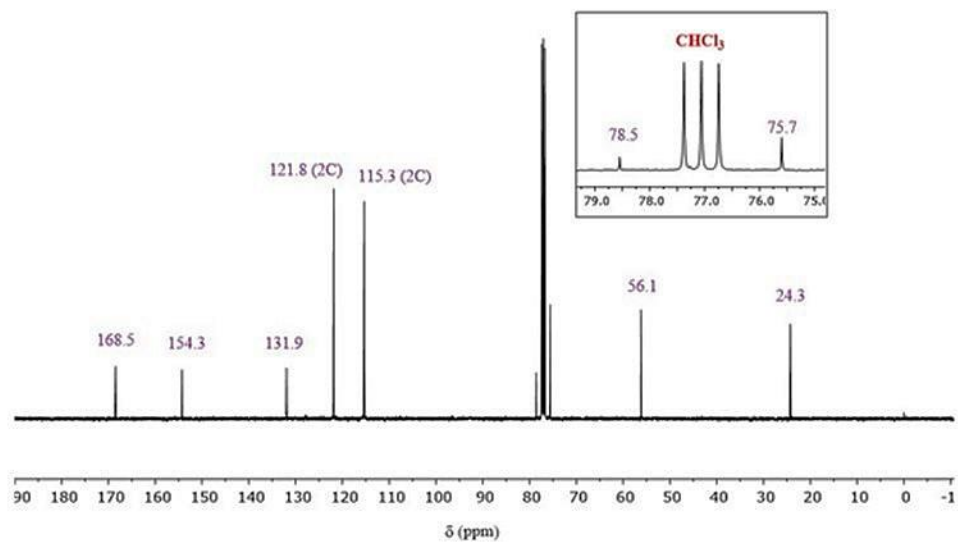
4.8 ^1H NMR spectrum of hybrid 6a



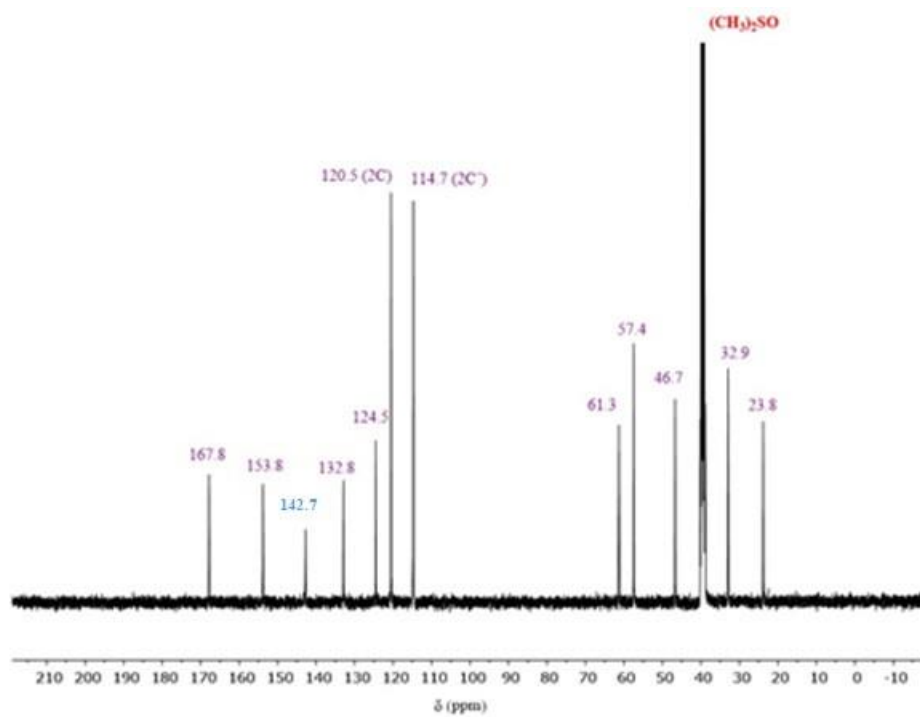
4.9 ^1H NMR spectrum of hybrid 7a



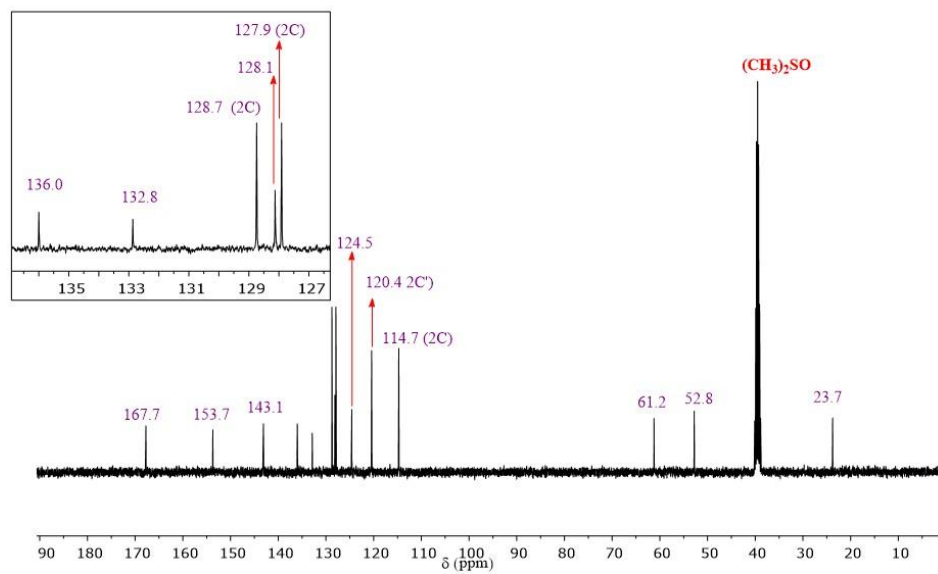
4.10 ^{13}C NMR spectrum of *O*-propargylated acetaminophen 3



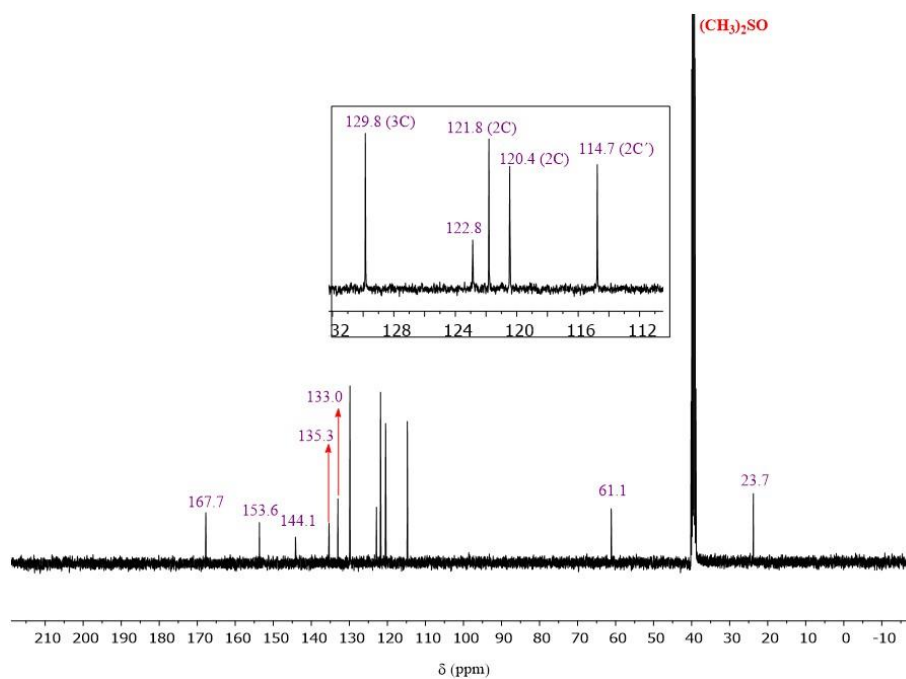
4.11 ^{13}C NMR spectrum of hybrid 5a



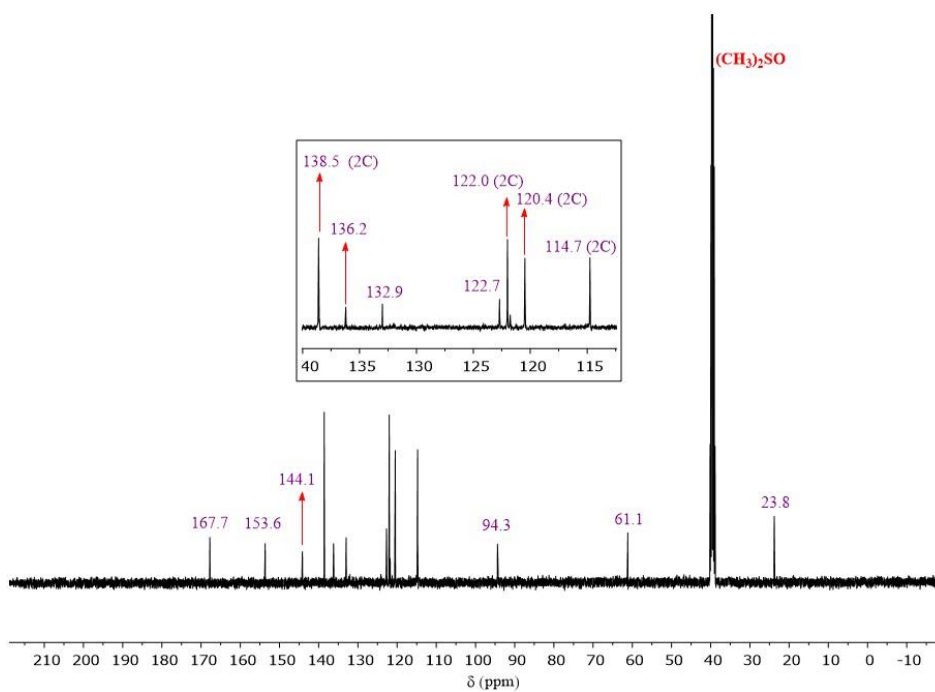
4.12 ^{13}C NMR spectrum of hybrid 5b



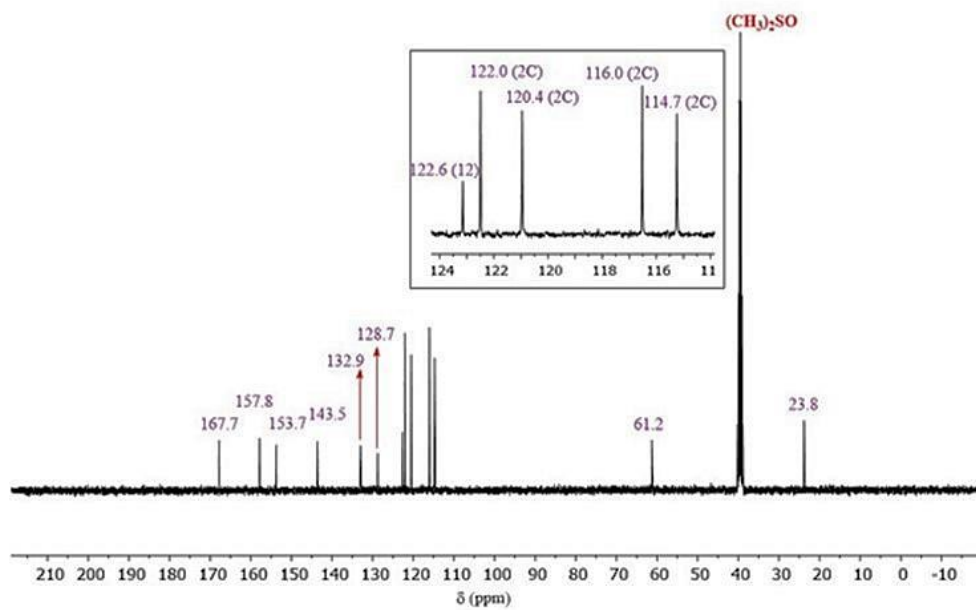
4.13 ^{13}C NMR spectrum of hybrid 5c



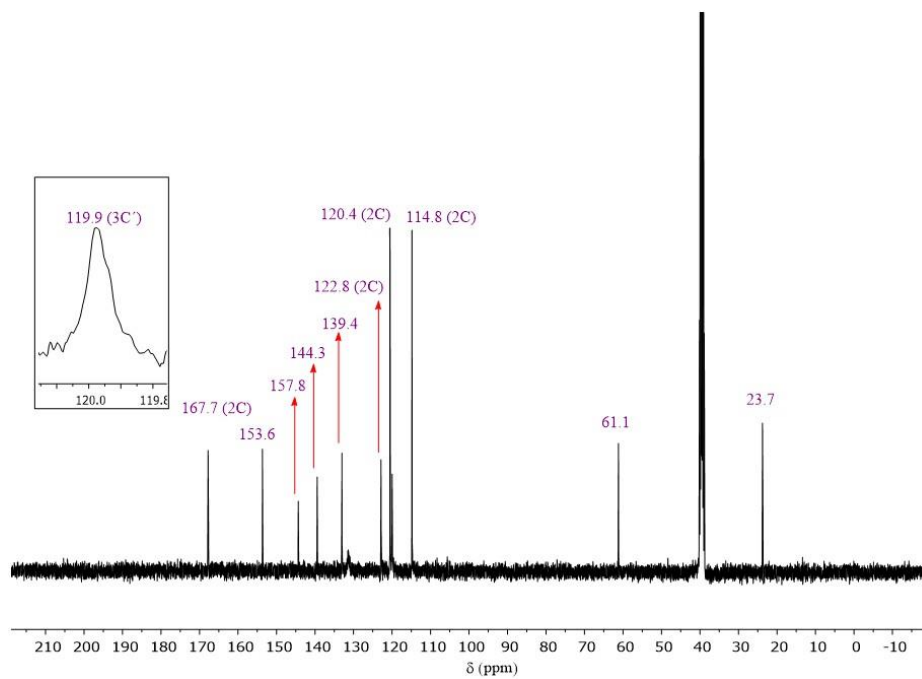
4.14 ^{13}C NMR spectrum of hybrid 5d



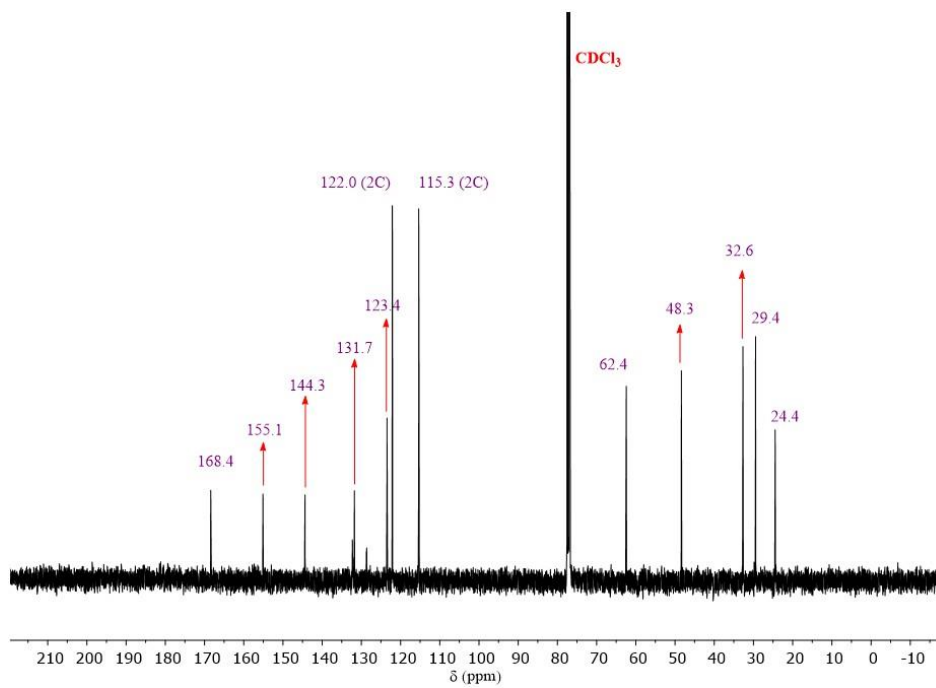
4.15 ^{13}C NMR spectrum of hybrid 5e



4.16 ^{13}C NMR spectrum of hybrid 5f



4.17 ^{13}C NMR spectrum of hybrid 6a



4.18 ^{13}C NMR spectrum of hybrid 7a

