

Antifungal activity and biocompatibility assessment with molecular docking of new pyrazole derivatives

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Experimental

General Remarks:

The melting point of the synthesized compounds was measured in degrees Celsius (°C) using the Gallenkamp apparatus. The IR spectra were obtained using FTIR spectrometers, Thermo Scientific Nicolet iS10, Mattson 5000 at Mansoura University. The NMR analysis for the synthesized compounds was performed on a Bruker 400 MHz and JEOL 500 MHz, Mansoura University in DMSO-*d*₆ and D₂O as the solvent with tetramethylsilane used as an internal reference. The EI-Mass spectra were analyzed in a Thermo scientific GCMS model ISQ LT at the Regional Center for Mycology and Biotechnology (RCMB) at Al-Azhar University, Nasr City, Cairo. Elemental analysis (C, H, and N) was performed at Cairo University. The insecticidal activity was performed at the insect lab of the Plant Protection Research Institute, Mansoura. TLC Silica gel 60 F254, Merck, Germany.

3.2 Chemical Reactions:

General procedure of preparation of 2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-Substituted-acrylamide (3a-h).

A solution containing 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (**1**) (0.01 mol) or 2-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)malononitrile (**2**) (0.01 mol) and *N*-aryl cyanoacetamide (0.01 mol) in ethanol (20 ml) was refluxed with a catalytic amount of piperidine (2 drops) for 2 h. The resulting precipitate was filtered and washed with ethanol, then recrystallized from DMF: EtOH (1:2) to obtain the pure compounds **3a-h** in good yield.

2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-(4-methylphenyl)acrylamide (3a).

Pale yellow sheet; yield 90%; m.p. >300 °C. IR (KBr): (ν cm⁻¹): 3363 (NH), 2205 (CN), 1682 (C=O), 1591 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 2.28(s, 3H, CH₃), 7.15-7.99 (m, 14 H, Ar-H), 8.14 (s, 1H, =CH), 9.21 (s, 1H, pyrazole-H), 10.24 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ /ppm: 20.97, 105.74, 114.98, 117.24, 120.08 (2C), 121.38 (2C), 128.44, 129.38 (2C), 129.51 (5C), 129.68, 129.72, 130.37 (2C), 133.85, 136.24, 139.12, 142.18, 155.02, 160.44. MS: (m/z, %)= 404.65 (M⁺, 13.08); Anal. Calcd for C₂₆H₂₀N₄O (404.46): C, 77.21; H, 4.98; N, 13.85 %. Found C, 77.19; H, 4.96; N, 13.87 %

2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-(4-methoxyphenyl)acrylamide (3b).

Yellow sheet; yield 87%; m.p. 250-252 °C. IR (KBr): (ν cm⁻¹): 3351 (NH), 2213 (CN), 1678 (C=O), 1596 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 3.75 (s, 3H, OCH₃), 6.83-7.98 (m, 14 H, Ar-H), 8.15 (s, 1H, =CH), 9.23 (s, 1H, pyrazole-H), 10.19 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ /ppm: 55.67, 105.99, 114.26, 114.98, 117.24, 120.09 (2C), 123.02 (2C), 128.46, 129.39 (2C), 129.53 (4C), 129.69, 129.74, 130.38 (2C), 131.41, 131.63, 139.12, 142.13, 155.49, 160.22. MS: (m/z, %)= 420.03 (M⁺, 21.6); Anal. Calcd for C₂₆H₂₀N₄O₂ (420.46): C, 74.27; H, 4.79; N, 13.33%. Found C, 74.29; H, 4.77; N, 13.31%

N-(4-bromophenyl)-2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamide (3c).

Off white sheet; yield 89 %; m.p. 262-264 °C. IR (KBr): (ν cm⁻¹): 3360 (NH), 2204 (CN), 1683 (C=O), 1589 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.46-7.97 (m, 14 H, Ar-H), 8.16 (s, 1H, =CH), 9.22 (s, 1H, pyrazole-H), 10.41 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ /ppm: 105.35, 114.92, 116.60, 117.11, 120.11 (2C), 123.26 (2C), 128.49, 129.40 (2C), 129.76 (4C), 130.37 (2C), 131.35, 131.98 (2C), 138.17, 139.09, 142.69, 155.11, 160.76. MS: (m/z, %)= 469.66 (M⁺, 37.29); Anal. Calcd for C₂₅H₁₇BrN₄O (469.33): C, 63.98; H, 3.65; N, 11.94%. Found C, 63.96; H, 3.67; N, 11.96%

***N*-(4-chlorophenyl)-2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylamide (3d).**

Pale yellow sheet; yield 88%; m.p. 275-277 °C. IR (KBr): (ν cm⁻¹): 3358 (NH), 2204 (CN), 1684 (C=O), 1589 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.41-7.98 (m, 14 H, Ar-H), 8.17 (s, 1H, =CH), 9.23 (s, 1H, pyrazole-H), 10.44 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ /ppm: 105.29, 114.91, 117.12, 120.12 (2C), 122.89 (2C), 128.49, 129.09 (2C), 129.42 (4C), 129.54, 129.78, 129.82, 130.39, 131.34 (2C), 137.70, 139.09, 142.71, 155.12, 160.77. MS: (m/z, %)= 424.66/ 426.68 (M⁺/ M⁺+2, 38.59/ 59.55); Anal. Calcd for C₂₅H₁₇ClN₄O (424.88): C, 70.67; H, 4.03; N, 13.19% Found C, 70.69; H, 4.05; N, 13.21%

4-(2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylamido) benzoic acid (3e).

Pale yellow sheet; yield 89 %; m.p. > 300 °C. IR (KBr): (ν cm⁻¹): 3451 (OH), 3234 (NH), 2217 (CN), 1685 (C=O), 1565 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.46-7.96 (M, 14 H, Ar-H), 7.98 (s, 1H, =CH), 8.20 (s, 1H, pyrazole-H), 9.25 (s, 1H, NH), 10.61 (s, 1H, OH). ¹³C NMR (DMSO-*d*₆) δ /ppm: 105.37, 114.89, 117.11, 120.11 (2C), 120.43 (2C), 127.07, 128.51, 129.42 (2C), 129.54 (2C), 129.78, 129.86, 130.38 (2C), 130.66 (2C), 131.33, 139.08, 142.67, 142.87, 155.14, 161.07, 167.46. MS: (m/z, %)= 434.85 (M⁺, 10.76); Anal. Calcd for C₂₆H₁₈N₄O₃ (434.45): C, 71.88; H, 4.18; N, 12.90%. Found C, 71.87; H, 4.20; N, 12.92%

2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-*N*-(4-nitrophenyl)acrylamide (3f).

Yellow sheet; yield 87%; m.p. 268-270 °C. IR (KBr): (ν cm⁻¹): 3330 (NH), 2207 (CN), 1687 (C=O), 1585 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.47-8.23 (m, 14H, Ar-H), 8.27 (s, 1H, =CH), 9.25 (s, 1H, pyrazole-H), 10.85 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ /ppm: 114.90, 117.07, 120.15 (2C), 120.97 (2C), 125.22 (2C), 128.55, 129.44 (2C), 129.54 (4C), 129.81, 129.95, 130.39 (2C), 131.31, 131.31, 139.08, 143.27, 155.22, 161.58. MS: (m/z, %) = 435.40 (M⁺, 16.64); Anal. Calcd for C₂₅H₁₇N₅O₃ (435.43): C, 68.96; H, 3.94; N, 16.08%. Found C, 68.94; H, 3.97; N, 16.10%

2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-*N*-(thiazol-2-yl)acrylamide (3g).

Yellow sheet; yield 86%; m.p. 280-282 °C. IR (KBr): (ν cm⁻¹): 3326 (NH), 2216 (CN), 1614 (C=O), 1566 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.20-7.96 (M, 12 H, Ar-H), 8.28 (s, 1H, =CH), 9.22 (s, 1H, pyrazole-H), 13.24 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ /ppm: 113.23, 115.25 (2C), 117.82, 120.09 (2C), 128.44, 129.47 (3C), 129.50 (3C), 129.66, 129.71, 130.37 (2C), 131.45, 142.45, 155.26 (2C). MS: (m/z, %)= 397.68 (M⁺, 23.02); Anal. Calcd for C₂₂H₁₅N₅OS (397.45): C, 66.48; H, 3.80; N, 17.62%. Found C, 66.46; H, 3.82; N, 17.60%

***N*-(benzo[d]thiazol-2-yl)-2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylamide (3h).**

Pale yellow sheet; yield 87 %; m.p. > 300 °C. IR (KBr): (ν cm⁻¹): 3340 (NH), 2205 (CN), 1689 (C=O), 1585 (C=N) cm⁻¹. Anal. Calcd for C₂₆H₁₇N₅OS (447.52): C, 69.78; H, 3.83; N, 15.65%. Found C, 69.77; H, 3.81; N, 15.67%

4,5,6,7-tetrabromo-2-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)amino)-isoindoline-1,3-dione (6).

A solution containing 4-(hydrazineylidenemethyl)-1,3-diphenyl-1*H*-pyrazole (**4**) (0.26 g, 0.001 mol) and 4,5,6,7-tetrabromoisobenzofuran-1,3-dione (**5**) (0.45 g, 0.001 mol) in AcOH (30 ml) was refluxed and allowed to form a precipitate after 3 hours. The solid was then collected by filtration and purified by recrystallization from DMF: EtOH (1:2) to yield pure compound **6**.

Pale yellow sheet; yield 75 %; m.p. > 300 °C. IR (KBr): (ν cm⁻¹): 1754 (C=O), 1723 (C=O), 1589 (C=N) cm⁻¹. MS: (m/z, %) = (708.11/ 710.89, (M⁺, 38.06/12.58); Anal. Calcd for C₂₄H₁₂Br₄N₄O₂ (707.99): C, 40.72; H, 1.71; N, 7.91; %. Found C, 40.70; H, 1.73; N, 7.93%

5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carbonitrile (7).

Method a

Ethanol solution of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**1**) (2.5 g, 0.01 mol) and 2-cyanoacetohydrazide (1 g, 0.01 mol) in the presence of the catalytic amount of base and or acid in EtOH was refluxed for 2 h. The solid was then collected through filtration and purified by recrystallization from DMF: EtOH (1:2) to give compound **7**.

Method b

Ethanol solution of acetohydrazide **8** (3 g, 0.01 mol) in the presence of the catalytic amount of Et₃N or AcOH was refluxed for 15 min. The solid was then collected through filtration and purified by recrystallization from DMF: EtOH (1:2) to give compound **7**.

Yellow sheet; yield 65 %; m.p. 250-252 °C. IR (KBr): (ν cm⁻¹): 3422 (NH), 2205 (CN), 1687 (C=O amide), 1586 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.34–8.23 (m, 10H, Ar-H), 8.58 (s, 1H, NHNHCO), 9.22 (s, 1H, OH), 9.28, 9.29 (two, s, 1H, pyrazole-H), 11.86 (br, 1H, NHCO). Anal. Calcd for C₁₉H₁₃N₅O (327.35): C, 69.71; H, 4.00; N, 21.39 %. Found C, 69.69; H, 3.98; N, 21.37 %.

2-cyano-*N'*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide (8).

A solution of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**1**) (2.5 g, 0.01 mol) and 2-cyanoacetohydrazide (1 g, 0.01 mol) in EtOH (20 ml) was heated on a water bath, which formed a crude precipitate after 0.5 hr. The solid that was produced was gathered by filtering it, and it was purified by recrystallization from AcOEt, resulting in the isolation of pure compound **8**.

White sheet; yield 92 %; m.p. 210-211 °C. IR (KBr): (ν cm⁻¹): 3184 (NH), 2258 (CN), 1678 (C=O amide), 1599 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.40–8.04 (m, 10H, Ar-H), 9.03 (s, 1H, pyrazole-H), 11.64 (s, 1H, NNHCO exchangeable); for anti- isomer: 4.13 (s, 2H, CH₂), 8.13 (s, 1H, CH=N); for syn isomer: δ 3.79 (s, 2H, CH₂), 8.25 (s, 1H, CH=N). ¹³C NMR (DMSO-*d*₆) δ /ppm: 24.41, 116.59, 117.12, 119.11(2C), 127.53, 128.74, 128.89, 128.92, 129.11(2C), 130.14, 132.57, 137.84, 139.43, 151.75, 158.84, 164.76, 160.44. Anal. Calcd for C₁₉H₁₅N₅O (329.36): C, 69.29; H, 4.59; N, 21.26%. Found C, 69.26; H, 4.57; N, 21.22%.

General procedure of preparation of *N'*-(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-oxo-6-(*p*-substituted)-2*H*-chromene-3-carbohydrazide (10a-e).

A solution containing 2-cyano-*N'*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-acetohydrazide (**8**) (0.33 g, 0.01 mol), and *p*-substituted salicylaldehyde **9a-e** (0.01 mol) in absolute ethanol (20 ml) along with a small quantity of piperidine (2-3 drops) was stirred at 50 °C for ½ hr. The resulting precipitate was filtered, washed with EtOH, dried, and recrystallized from EtOH: DMF (2:1) to yield the desired compounds **10a-e**.

***N'*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-oxo-2*H*-chromene-3-carbohydrazide (10a).**

Yellow powder; yield 69%; m.p. 222-224 °C. IR (KBr): (ν cm⁻¹): 3313 (NH), 1682 (COO), 1638 (CONH), 1604 (C=N). ¹H NMR (DMSO-*d*₆): δ 7.25-8.04 (m, 18H, Ar-H), 8.54 (s, 1H, =CH), 8.37 (s, 1H, CH=N), 9.05 (s 1H, pyrazole-H), 13.46 (br s, 1H, NHCO). Anal. Calcd for C₂₆H₁₈N₄O₃ (434.46): C, 71.88; H, 4.18; N, 12.90 %. Found C, 71.86; H, 4.15; N, 12.92 %.

***N'*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-oxo-6-(*p*-tolyl diazenyl)-2*H*-chromene-3-carbohydrazide (10b).**

Red powder; yield 72%; m.p. 250-252 °C. IR (KBr): (ν cm⁻¹): 3451 (NH), 1680 (COO), 1599 (CONH), 1546 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 2.39 (s, 3H, CH₃), 7.38-8.03 (m, 17 H, Ar-H), 8.53 (s, 1H, =CH), 8.67 (s, 1H, CH=N), 9.03 (s, 1H, pyrazole-H), 11.82 (s, 1H, NHCO). MS: (m/z, %)= 552.03 (M⁺, 16.11); Anal. Calcd for C₃₃H₂₄N₆O₃ (552.58): C, 71.73; H, 4.38; N, 15.21 %. Found C, 71.71; H, 4.36; N, 15.19%

6-((4-chlorophenyl) diazenyl)-*N'*-(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-oxo-2*H*-chromene-3-carbohydrazide (10c).

Orange powder; yield 70 %; m.p. 222-224 °C. IR (KBr): (ν cm⁻¹): 3451 (NH), 1600 (COO), 1599 (CONH), 1546 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.35-7.95 (m, 17 H, Ar-H), 8.02 (s, 1H, =CH), 9.02 (s, 1H, CH=N), 9.03 (s, 1H, pyrazole-H), 11.78 (s, 1H, NHCO). MS: (m/z, %)= 572.35/ 575.61 (M⁺-1/ M⁺, 38.09/ 20.86); Anal. Calcd for C₃₂H₂₁ClN₆O₃ (573.00/ 575.14): C, 67.08; H, 3.69; N, 14.67%. Found C, 67.06; H, 3.67; N, 14.65%

***N'*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-6-((4-nitrophenyl) diazenyl)-2-oxo-2*H*-chromene-3-carbohydrazide (10d).**

Brown powder; yield 71%; m.p. 200-202 °C. IR (KBr): (ν cm⁻¹): 3451 (NH), 1599 (COO), 1699 (CONH), 1547 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.36-8.01 (m, 17 H, Ar-H), 8.54 (s, 1H, =CH), 8.75 (s, 1H, CH=N), 9.01 (s, 1H, pyrazole-H), 11.80 (s, 1H, NHCO). MS: (m/z, %)= 582.66 (M⁺-1, 19.02); Anal. Calcd for C₃₂H₂₁N₇O₅ (583.16): C, 65.86; H, 3.63; N, 16.80%. Found C, 65.84; H, 3.66; N, 16.78 %

4-((3-(2-(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbonyl)-2-oxo-2*H*-chromen-6-yl) diazenyl) benzoic acid (13e).

Orange powder; yield 70 %; m.p. 290-292 °C. IR (KBr): (ν cm⁻¹): 3419 (OH), 3318 (NH), 1713 (COOH), 1675 (COO), 1601 (CONH), 1548 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 7.35-8.14 (m, 17 H, Ar-H), 8.54 (s, 1H, =CH), 8.73 (s, 1H, CH=N), 9.01 (s, 1H, pyrazole-H), 11.72 (s, 1H, NH), 12.94 (s, 1H, OH). MS: (m/z, %)= 581.59/ 582.16 (M⁺-1/ M⁺, 25.86/ 25.70)/ 581.17; Anal. Calcd for C₃₃H₂₂N₆O₅ (582.58): C, 68.04; H, 3.81; N, 14.43%. Found C, 68.06; H, 3.83; N, 14.41%

2-cyano-3-(dimethylamino)-N'-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-acrylo-hydrazide (11).

A solution of acetohydrazide **8** (0.23 g, 0.01 mol) and *N,N*-dimethylformamide dimethyl acetal (2.7 ml, 0.02 mol) in toluene (15 mL) was heated under reflux for 1 h., resulting in the formation of a solid precipitate. The solid product was collected by filtration, washed with hot EtOH, and recrystallized from a mixture of EtOH: DMF (2:1) to obtain pure compound **11**.

Pale yellow sheet; yield 85 %; m.p. 237-239 °C. IR (KBr): (ν cm⁻¹): 3450 (NH), 2194 (CN), 1659 (CONH), 1604 (C=N). ¹H NMR (DMSO-*d*₆) δ /ppm: 3.23 (s, 3H, NCH₃), 3.30 (s, 3H, NCH₃), 7.36-8.01 (m, 11H, Ar-H, =CH-N(Me)₂), 8.46 (s, 1H, =CH), 8.89 (s, 1H, pyrazole-H), 10.86 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ /ppm: 38.66, 47.57, 69.28, 117.80 (2C), 119.21, 119.60 (2C), 127.22, 127.39, 128.81, 128.97, 129.22 (2C), 130.10 (2C), 132.58, 139.55 (2C), 151.98, 157.49 (2C). MS: (m/z, %)= 384.67 (M⁺, 24.68); Anal. Calcd for C₂₂H₂₀N₆O (384.17): C, 68.73; H, 5.24; N, 21.86 %. Found C, 68.71; H, 5.22; N, 21.84 %

4-((dimethylamino)methylene)-6-(1,3-diphenyl-1H-pyrazol-4-yl)pyridazine-3,5(4H,6H)-dione (12).

Compound **11** (0.4 gm, 0.001 mol) was heated under reflux in AcOH (10 ml) for 30 minutes. The formed crude solid was filtered and washed with hot ethanol, and pure compound **12** was obtained by recrystallization from a mixture of EtOH: Dioxane (2:1).

Red Powder; yield 83%; m.p. >300 °C. IR (KBr): (ν cm⁻¹): 1685 (C=O), 1615 (C=N). MS: (m/z, %)= 385.79 (M⁺, 79.03); Anal. Calcd for C₂₂H₁₉N₅O₂ (385.43): C, 68.56; H, 4.97; N, 18.17%. Found C, 68.54; H, 4.95; N, 18.15%.

2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-(4-methylphenyl)acrylamide (3a)

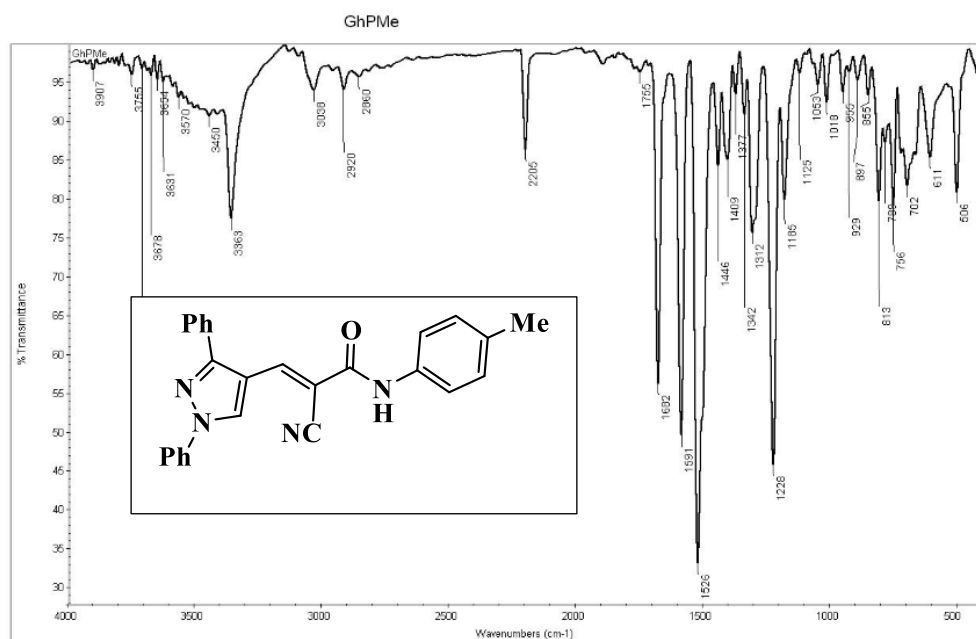


Figure S1: IR spectrum of compound 3a

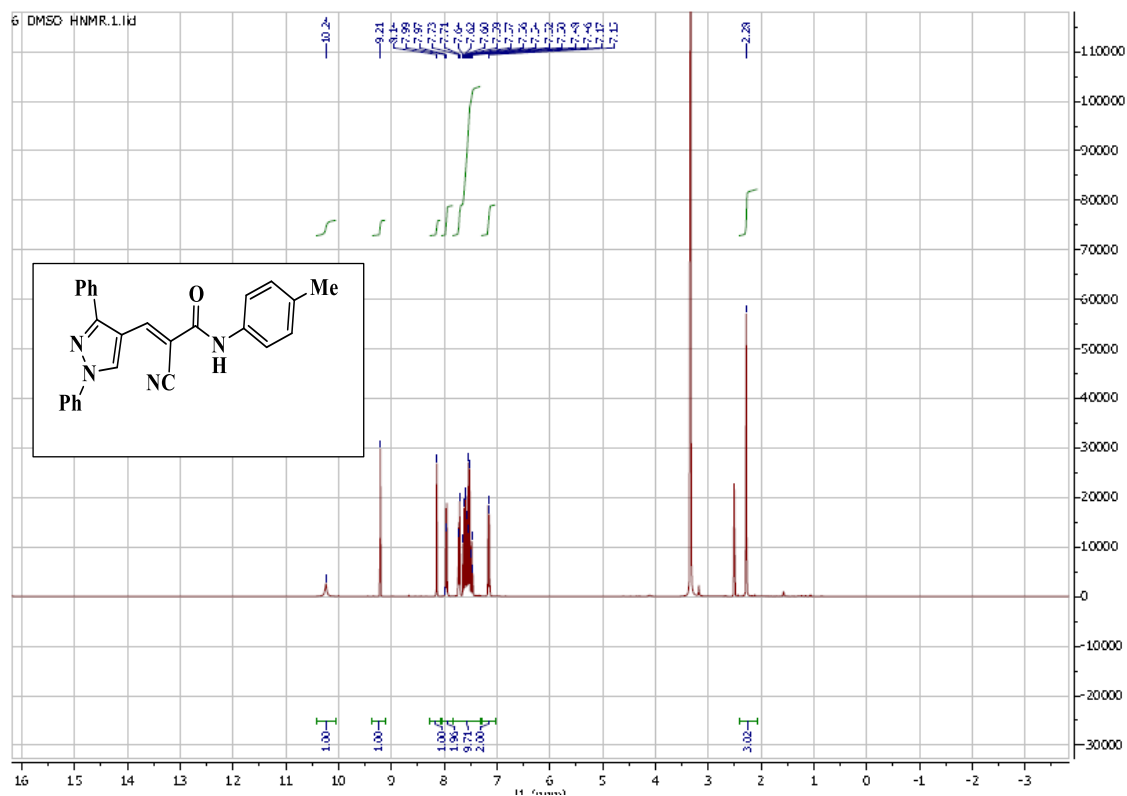


Figure S2: ¹H NMR spectrum of compound 3a

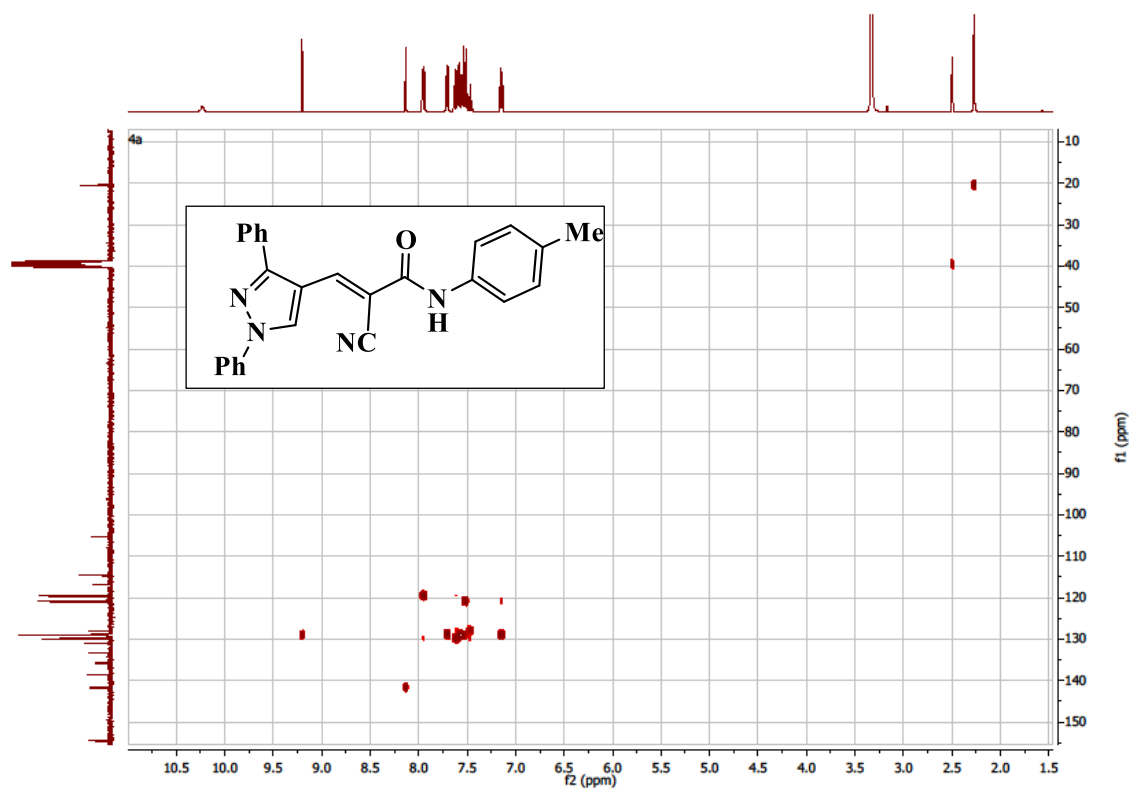


Figure S5: ^1H SQC spectrum of compound 3a

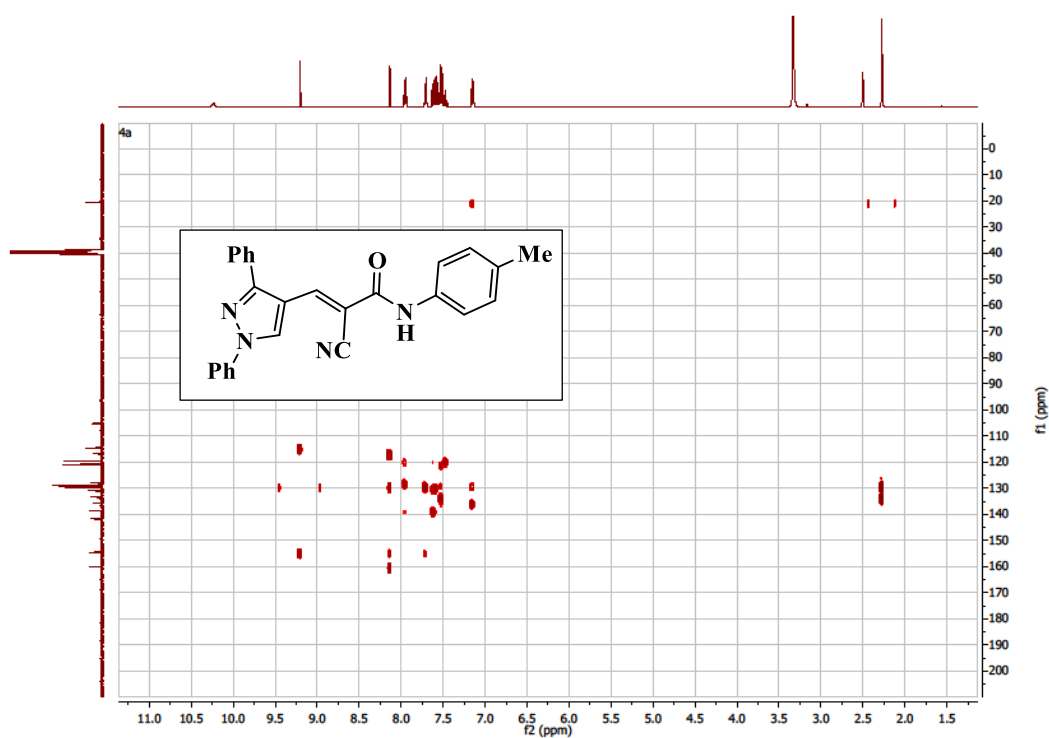


Figure S6: ^1H MBC spectrum of compound 3a

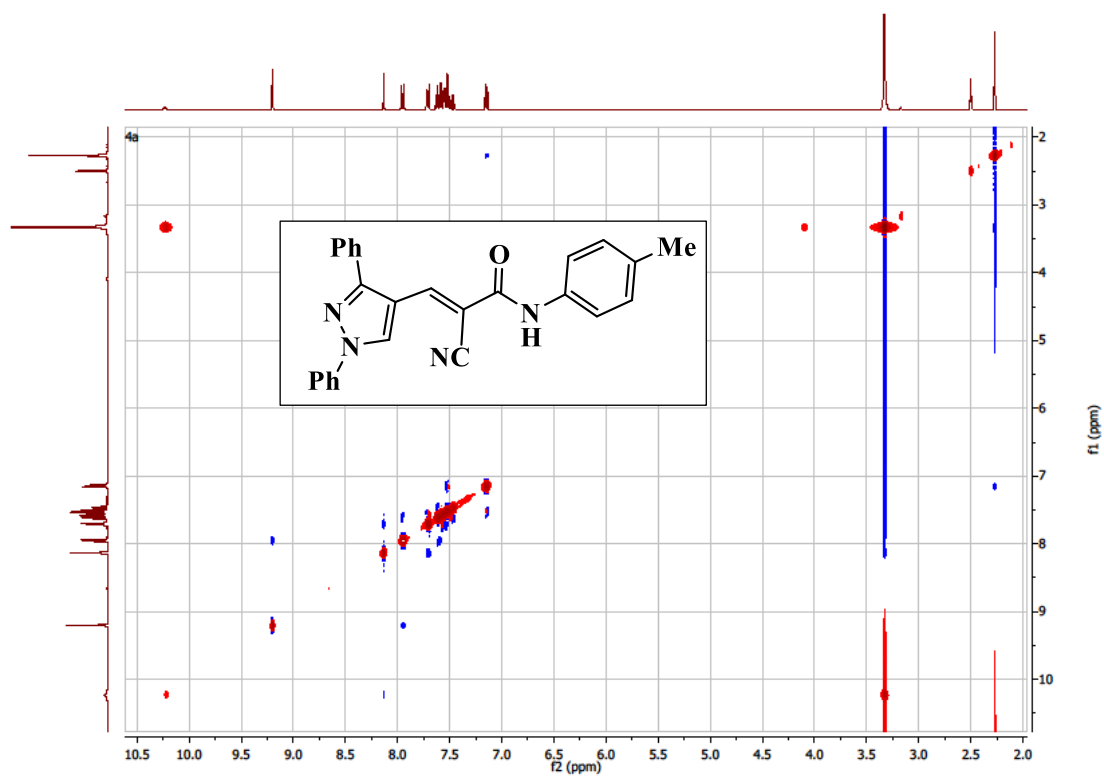
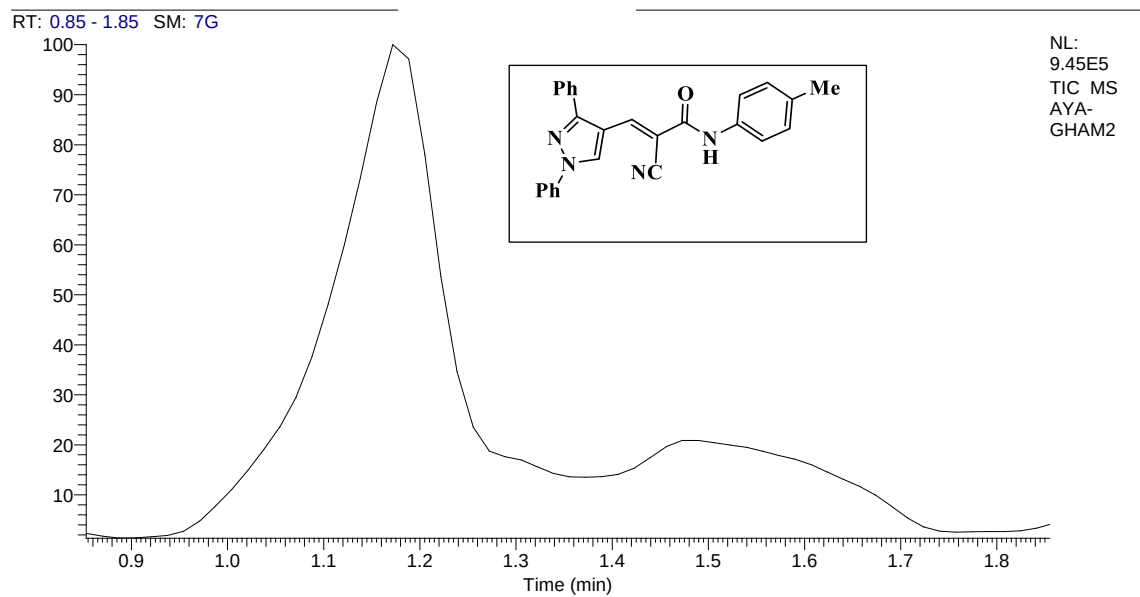


Figure S7: ¹H NOSTY spectrum of compound 3a



AYA-GHAM2 #211-212 RT: 3.55-3.56 AV: 2 NL: 2.19E2
T: {0,0} + c EI Full ms [40.00-1000.00]

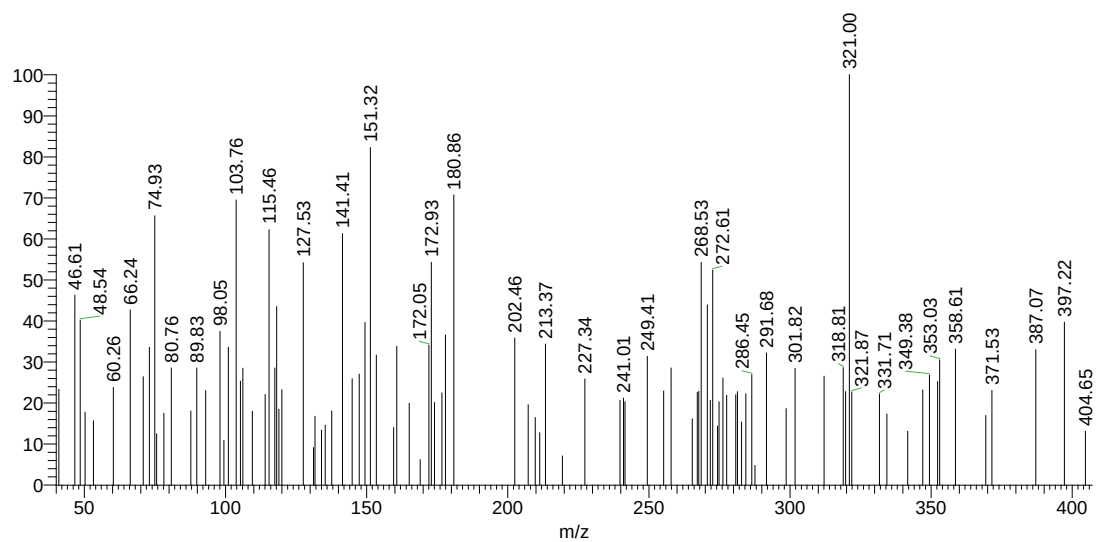


Figure S8: Mass spectrum of compound 3a

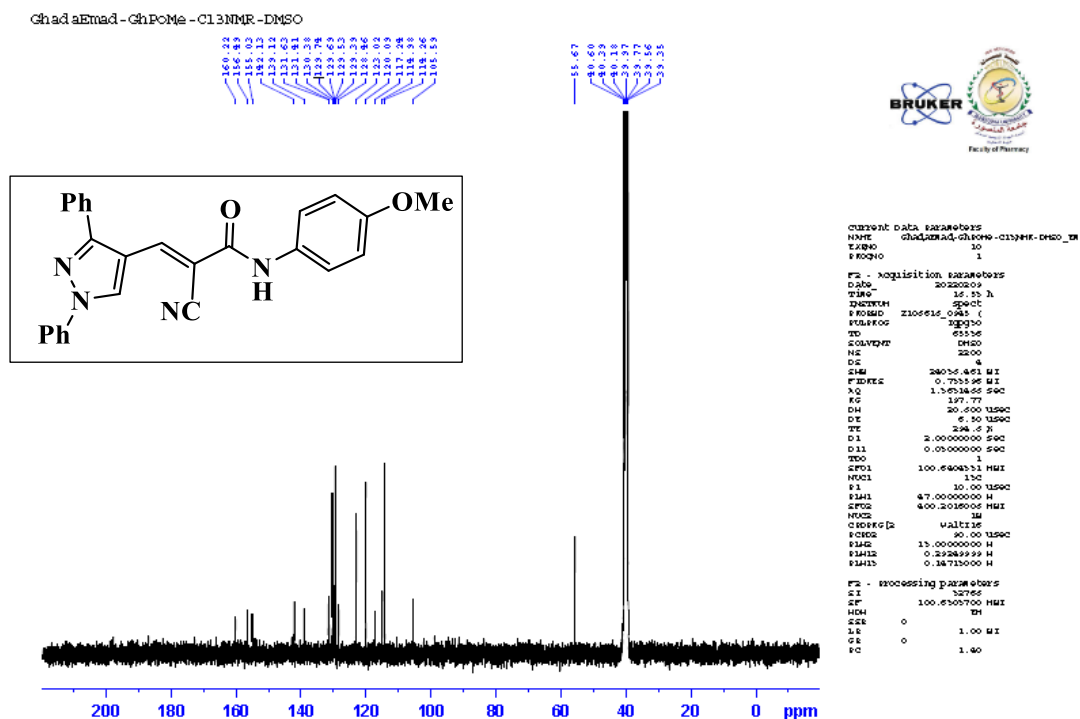
The IR spectrum of GhPOMe shows characteristic absorption bands. The chemical structure of GhPOMe is shown in the inset:

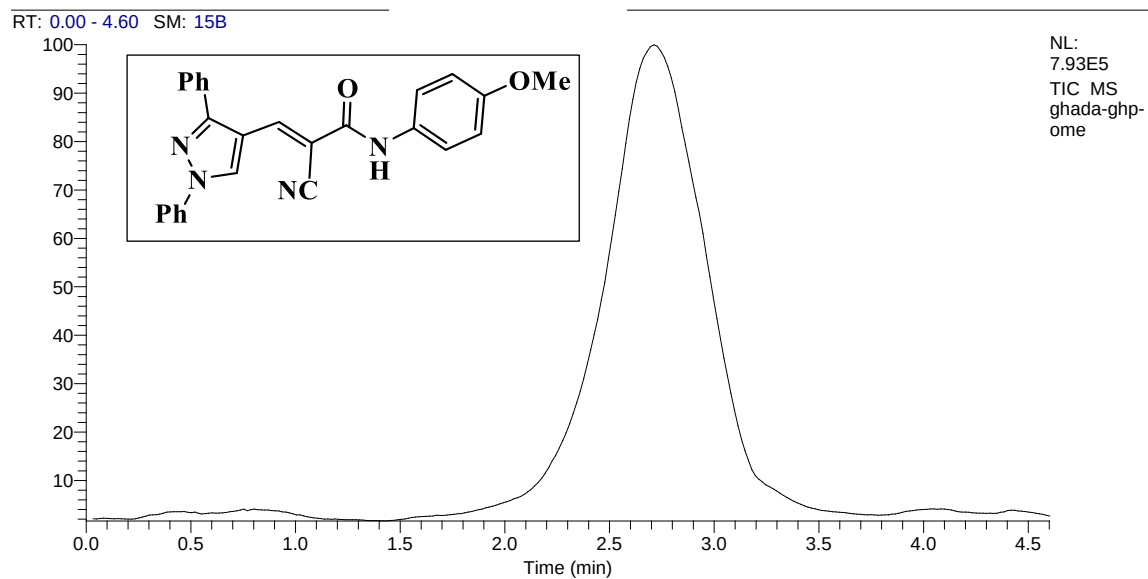
COC1=CC=C(NC(=O)C=Cc2c[n(C3=CC=CC=C3)nc2C4=CC=CC=C4])C=C1

Key IR peaks (Wavenumbers in cm⁻¹):

- 3411 (N-H stretch)
- 3008 (Aromatic C-H stretch)
- 2942 (Aliphatic C-H stretch)
- 2834 (Aliphatic C-H stretch)
- 2218 (C≡N stretch)
- 1678 (C=O stretch)
- 1596 (Aromatic ring stretch)
- 1513 (Aromatic ring stretch)
- 1445 (C=C stretch)
- 1416 (C=C stretch)
- 1390 (C-O stretch)
- 1249 (C-O stretch)
- 1231 (C-O stretch)
- 1177 (C-O stretch)
- 1026 (C-O stretch)
- 956 (C=C stretch)
- 910 (C=C stretch)
- 816 (Aromatic ring stretch)
- 787 (Aromatic ring stretch)
- 757 (Aromatic ring stretch)
- 680 (Aromatic ring stretch)
- 627 (Aromatic ring stretch)
- 540 (Aromatic ring stretch)
- 510 (Aromatic ring stretch)

[illegible]





ghada-ghp-ome #53 RT: 0.90 AV: 1 SB: 2 1.34, 0.92 NL: 7.22E2
T: + c EI Full ms [40.00-1000.00]

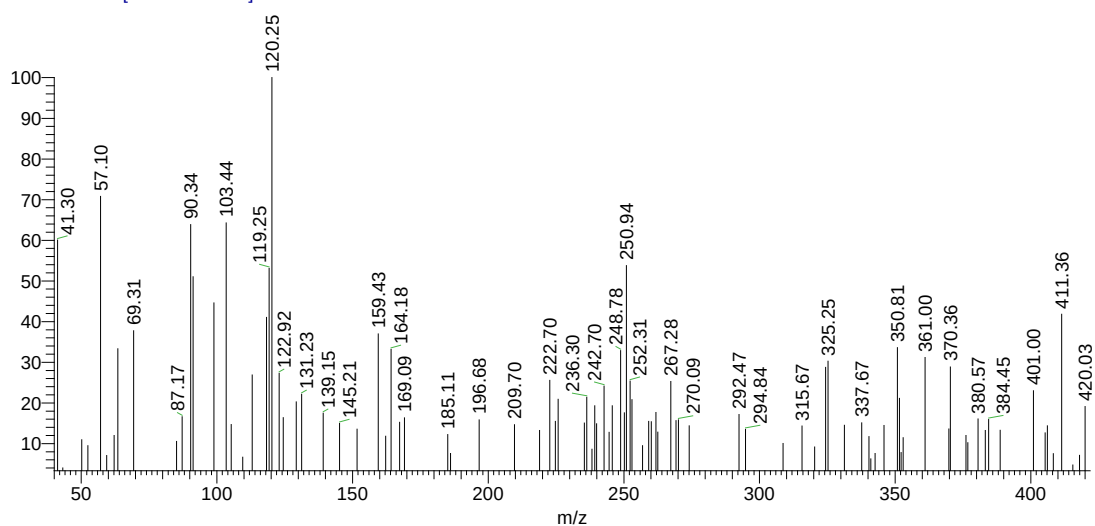


Figure S12: Mass spectrum of compound 3b

N-(4-bromophenyl)-2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylamide (3c)

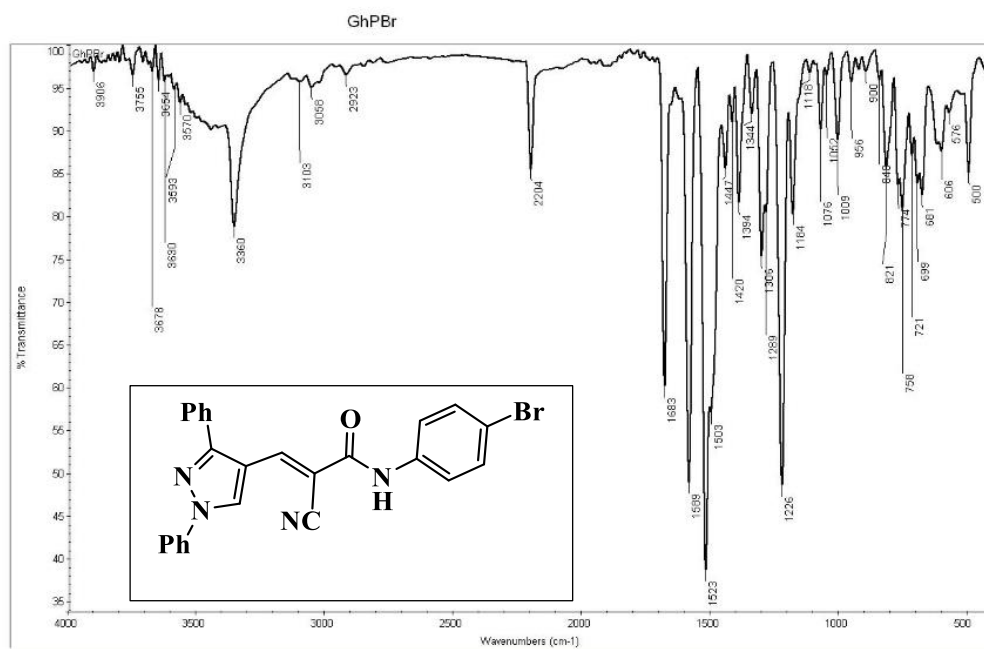


Figure S13: IR spectrum of compound 3c

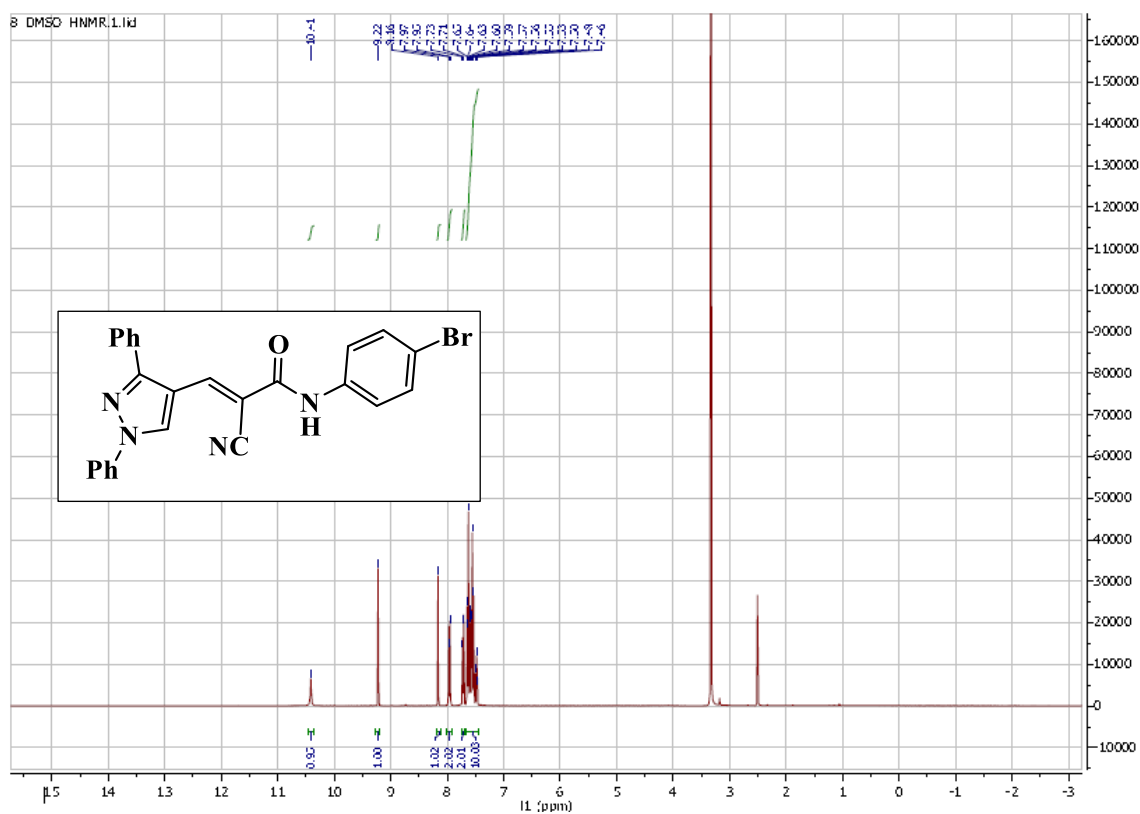


Figure S14: ¹H NMR spectrum of compound 3c

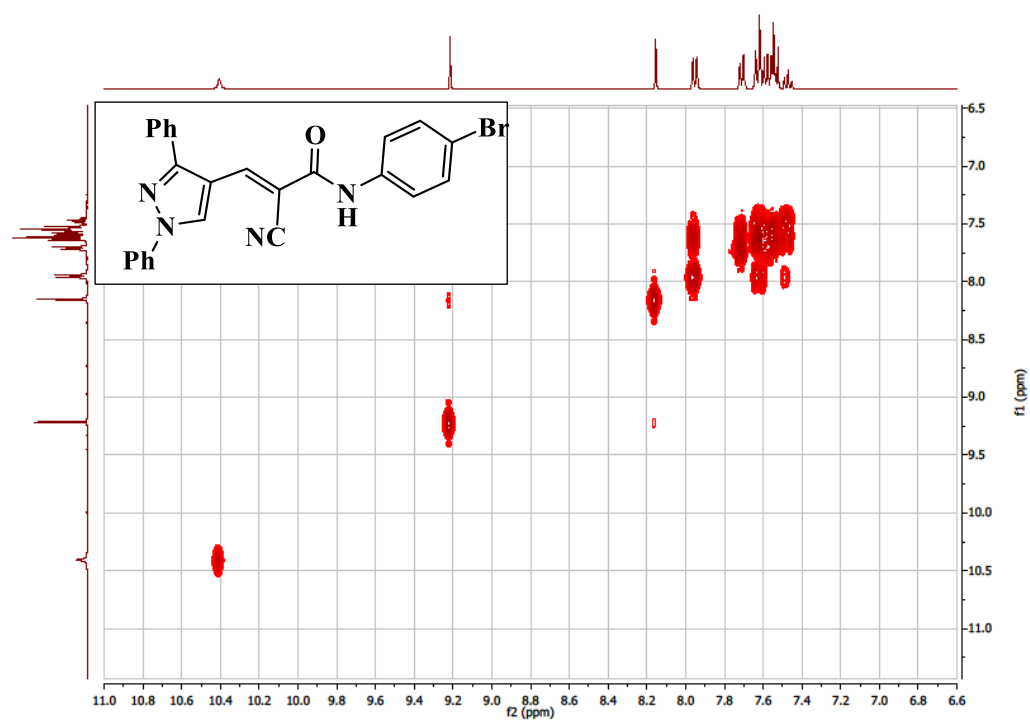


Figure S15: ^1H COSY spectrum of compound 3c

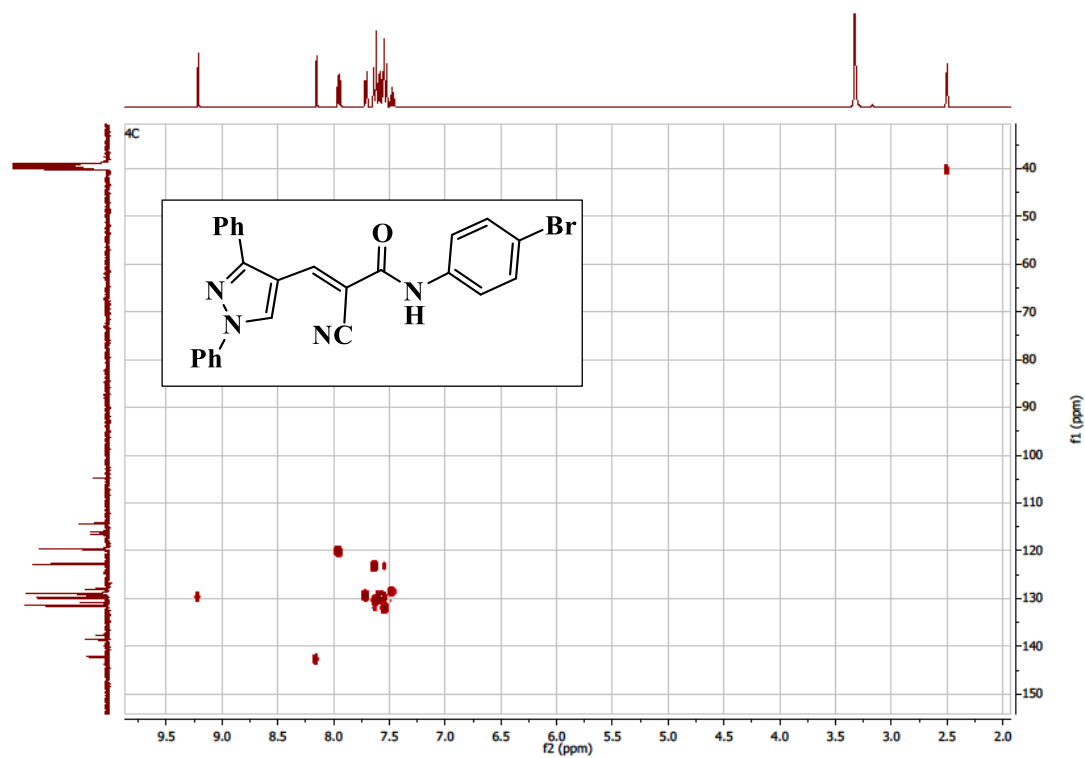


Figure S16: $^1\text{H}/^{13}\text{C}$ HSQC spectrum of compound 3c

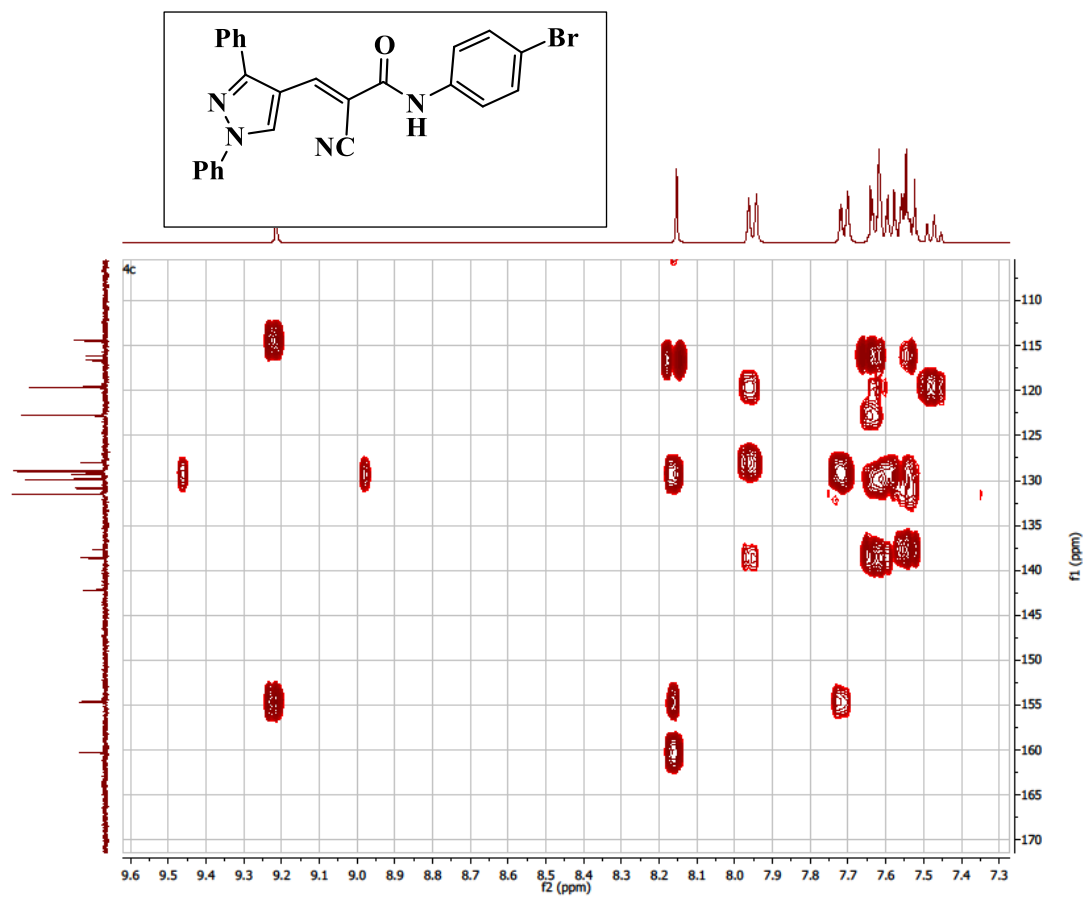


Figure S17: ¹H MBC spectrum of compound 3c

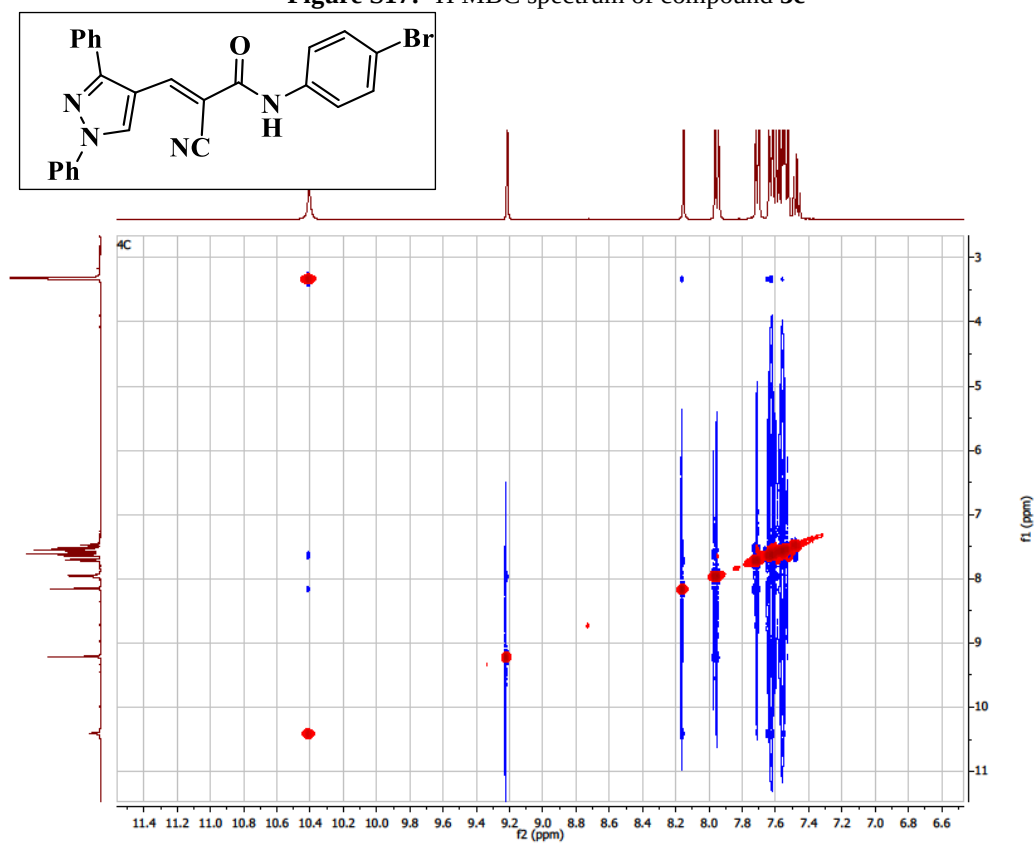


Figure S18: ¹H NOSEY spectrum of compound 3c

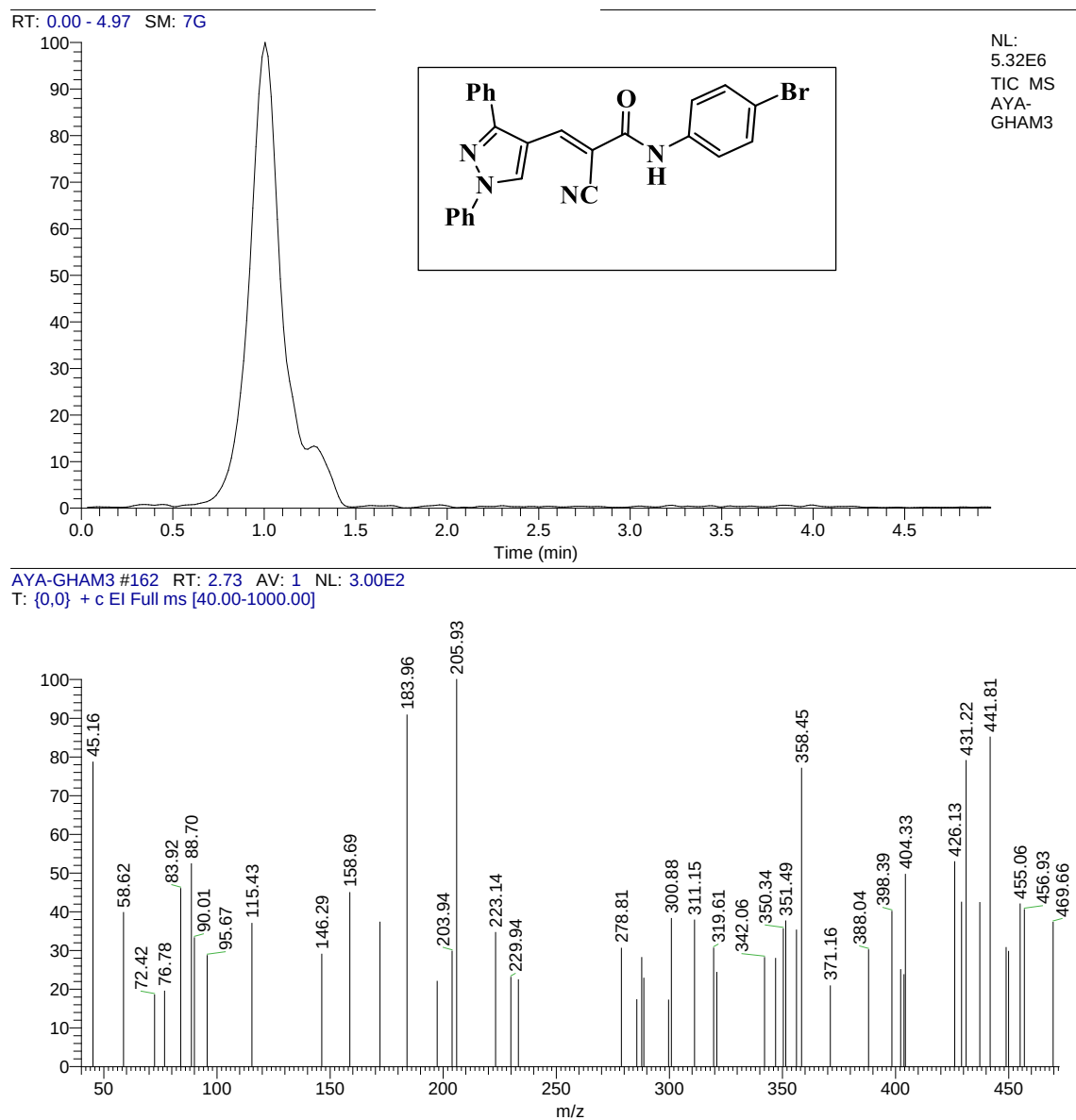


Figure S19: Mass spectrum of compound 3c

***N*-(4-chlorophenyl)-2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylamide (3d):**

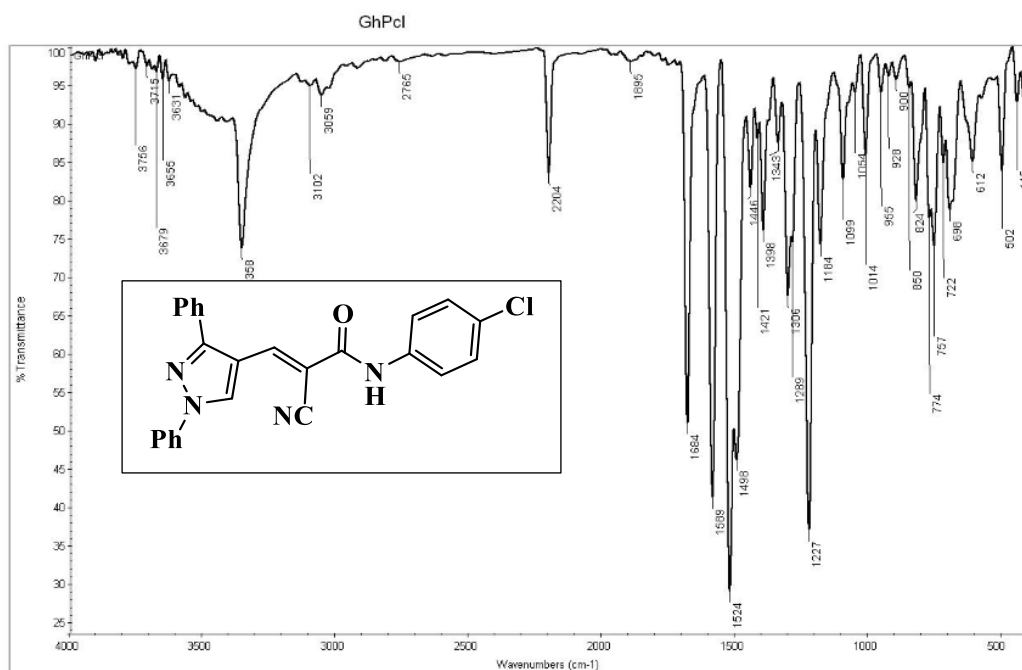


Figure S20: IR spectrum of compound 3d

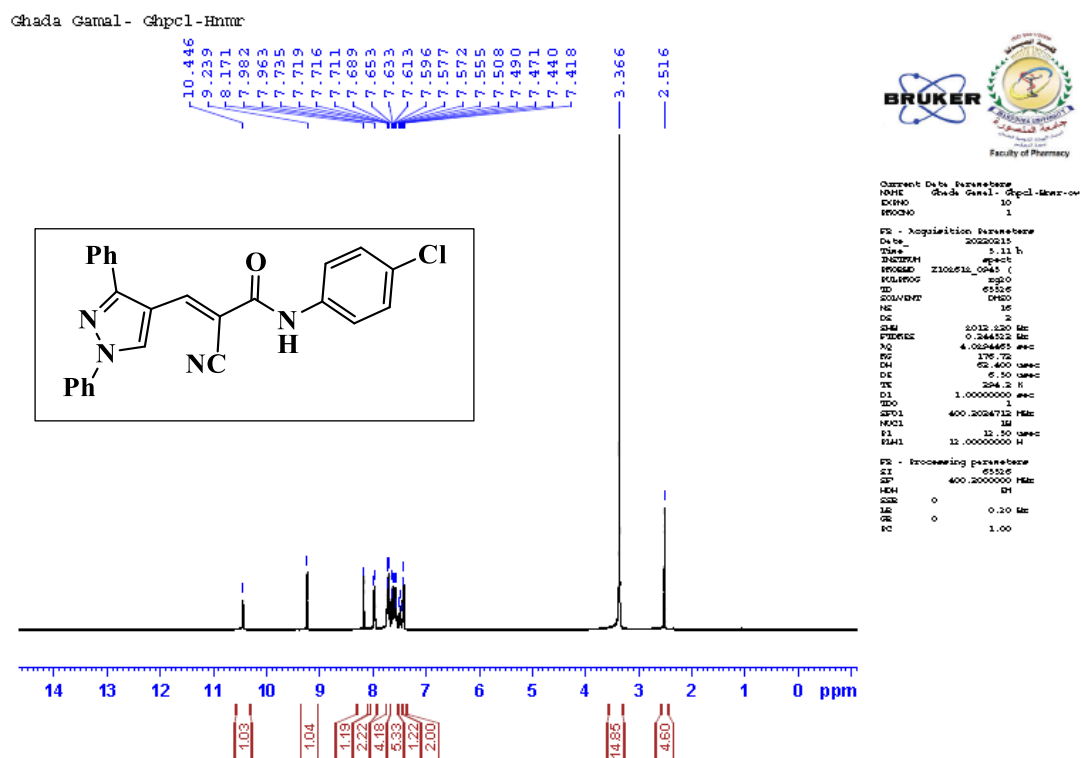
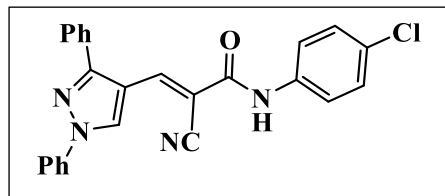


Figure S21: ^1H NMR spectrum of compound 3d

[illegible]

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PULPROG   zgpg30
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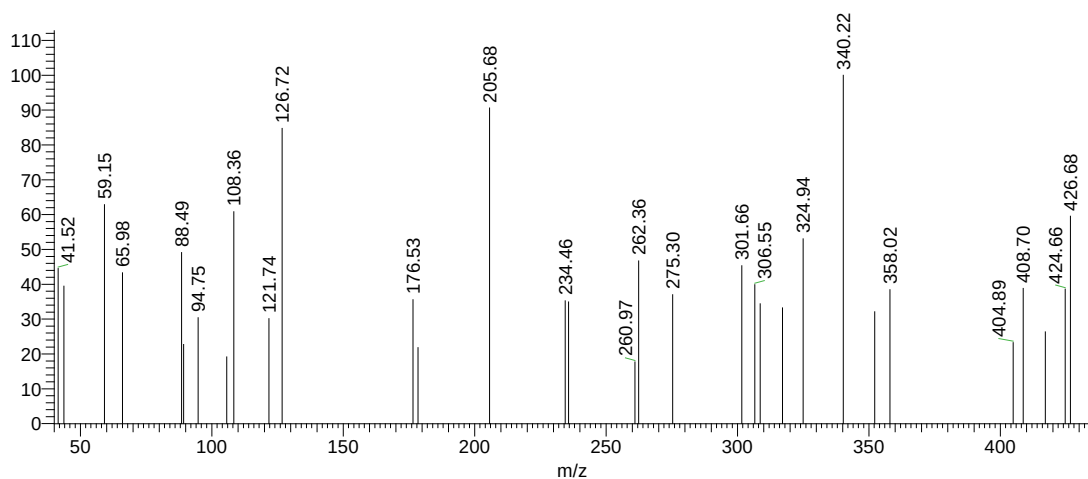
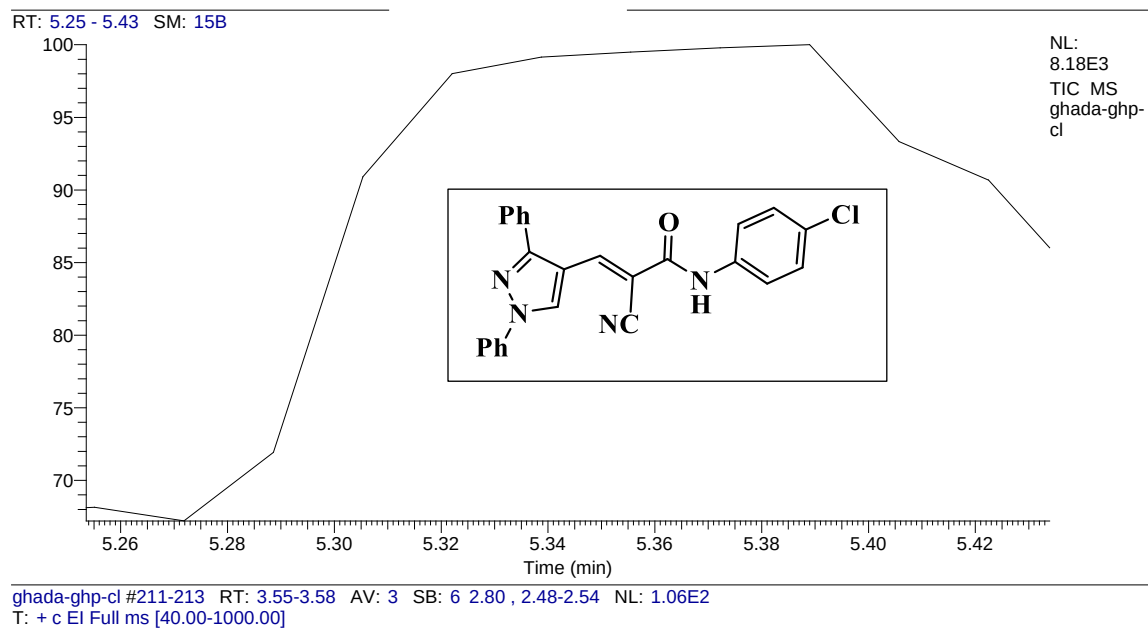


Figure S23: Mass spectrum of compound 3d

4-(2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamido)benzoic acid (3e)

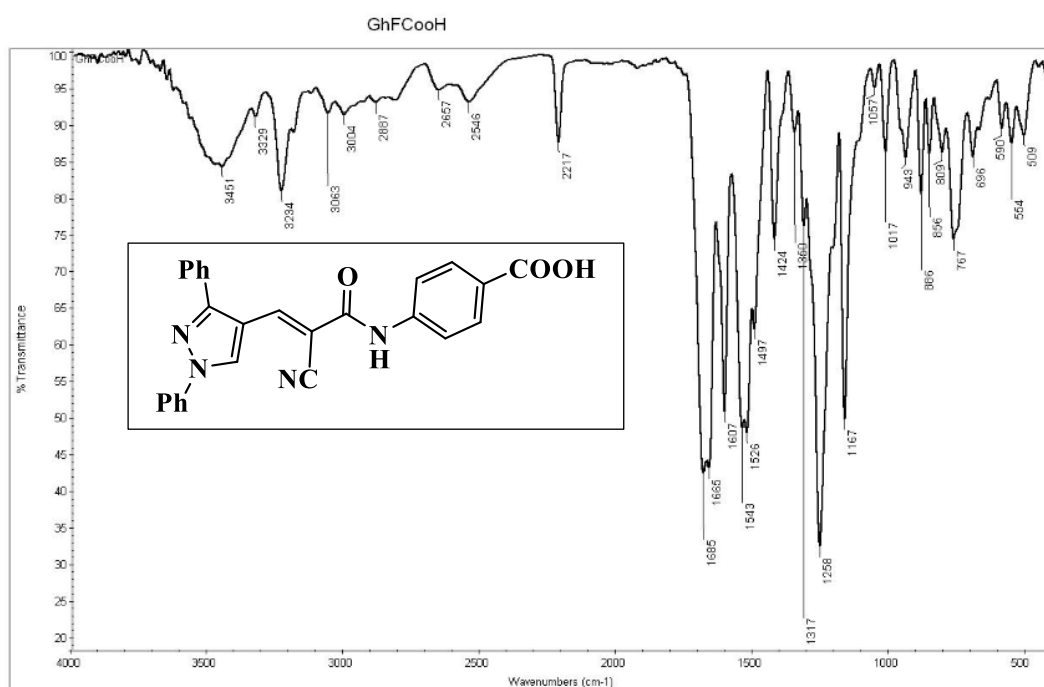


Figure S24: IR spectrum of compound 3e

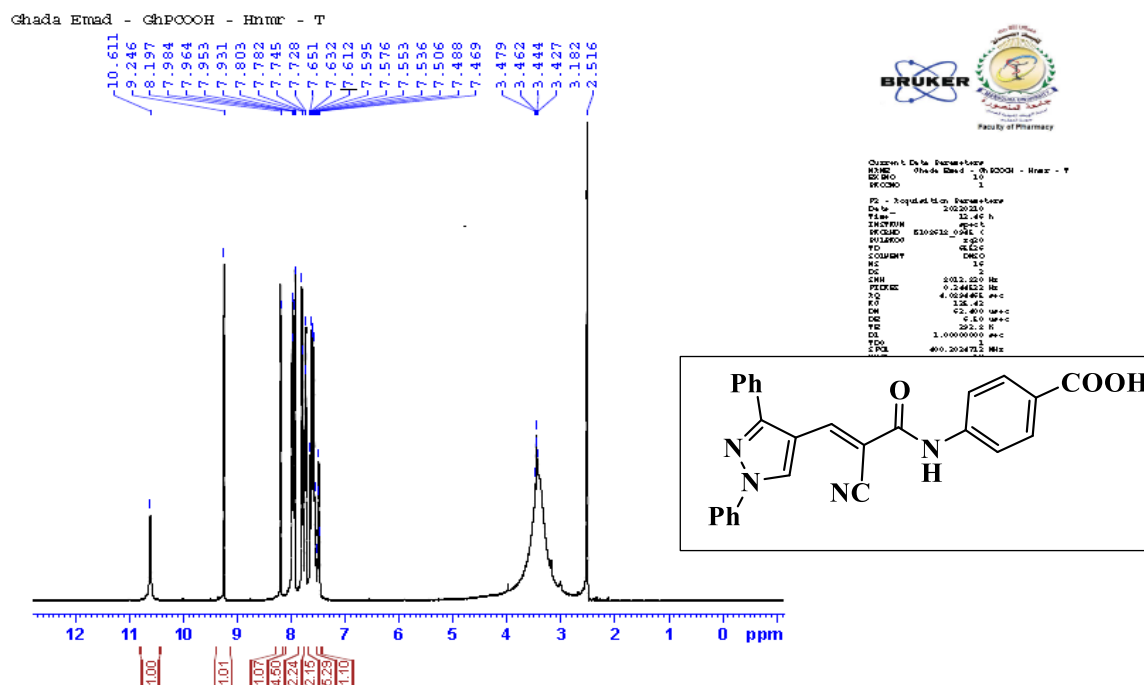
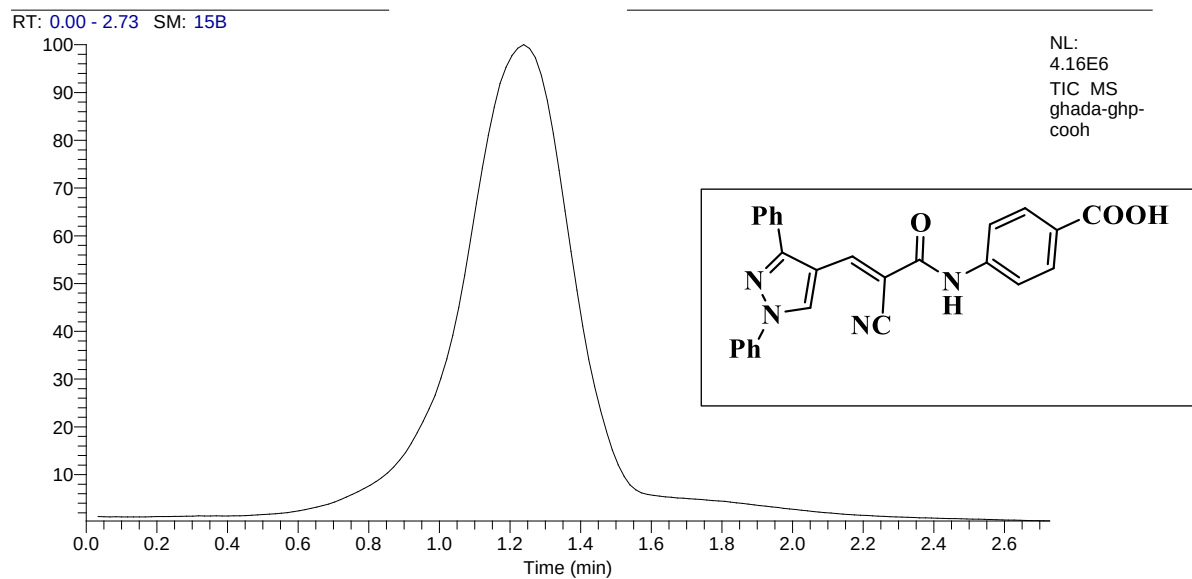


Figure S25: ¹H NMR spectrum of compound 3e



ghada-ghp-cooh #146 RT: 2.46 AV: 1 SB: 6 2.73, 2.48-2.54 NL: 8.76E2
T: + c EI Full ms [40.00-1000.00]

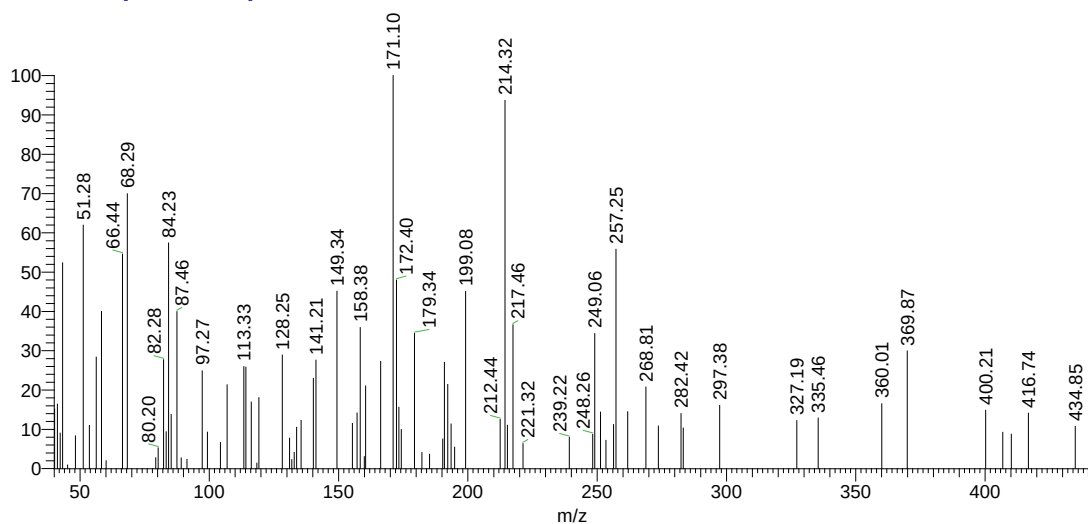


Figure S27: Mass spectrum of compound 3e

2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-(4-nitrophenyl)acrylamide (3f)

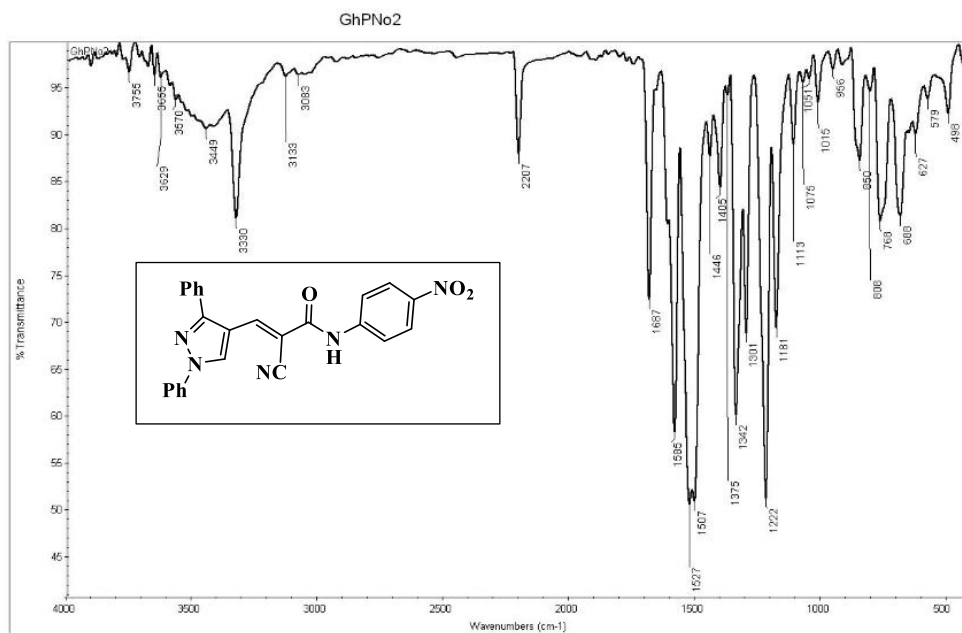


Figure S28: IR spectrum of compound 3f

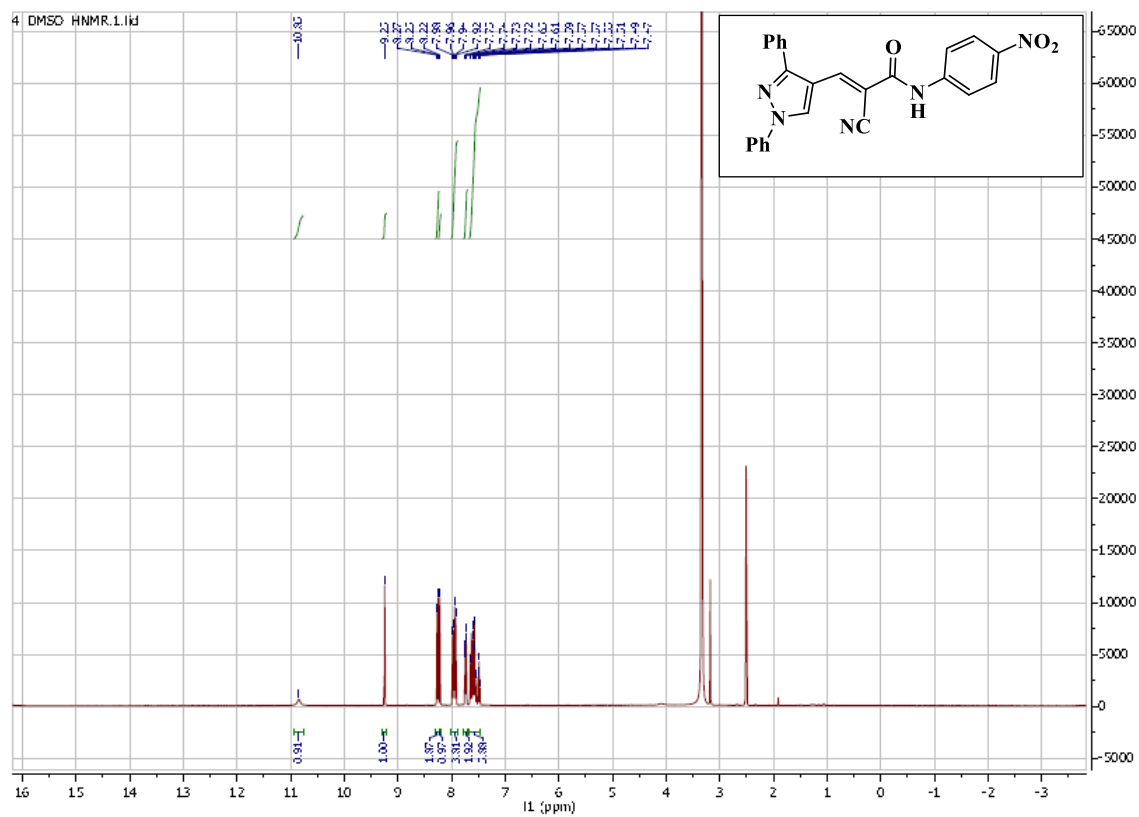


Figure S29: ¹H NMR spectrum of compound 3f

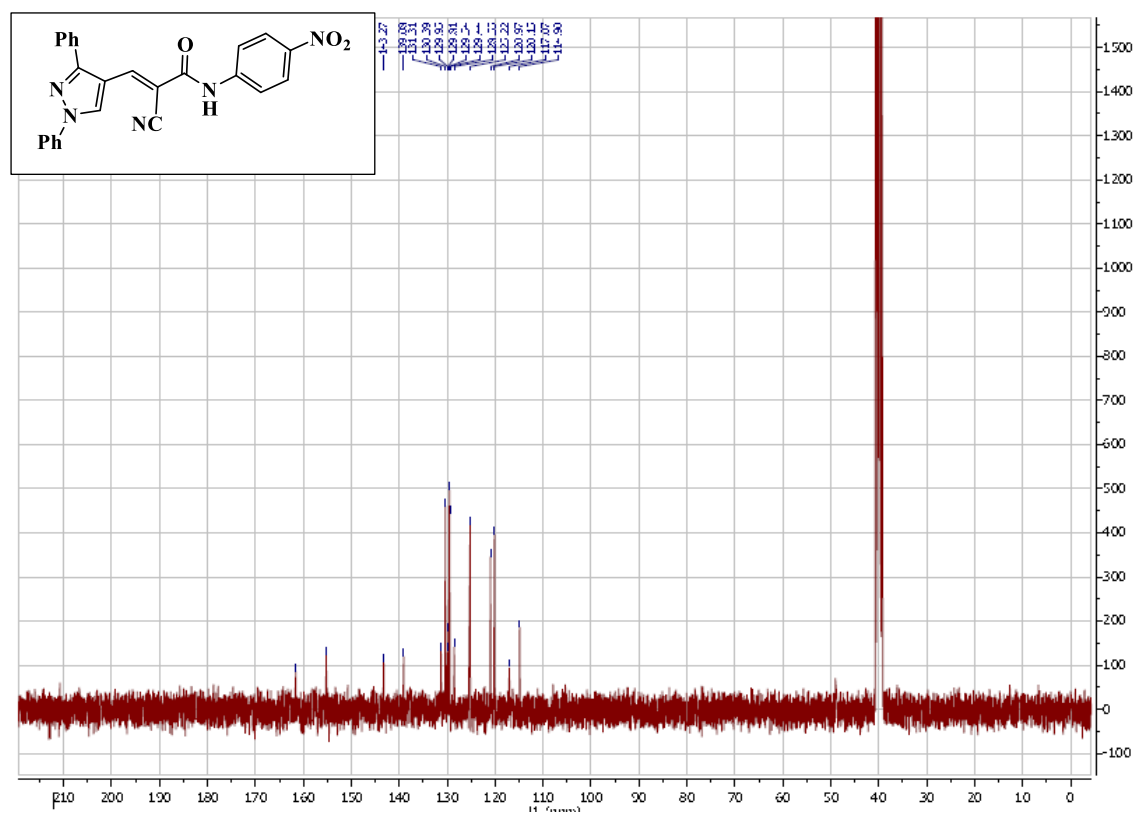


Figure S30: ^{13}C NMR spectrum of compound 3f

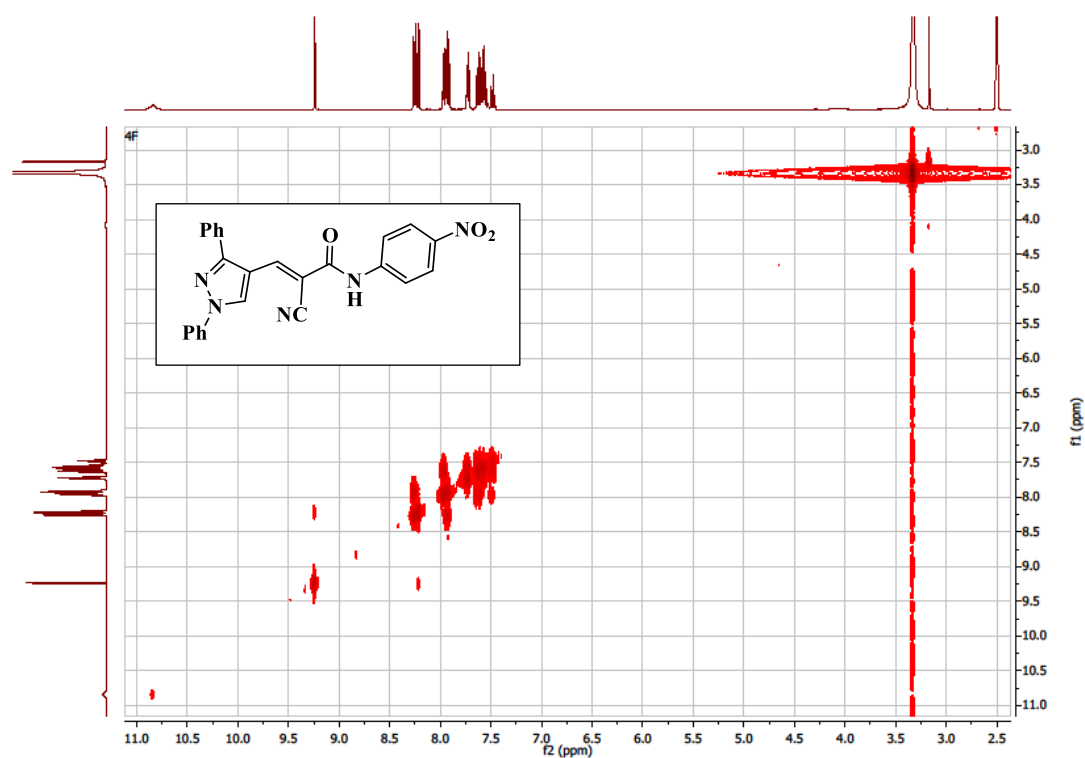


Figure S31: ^1H COSY spectrum of compound 3f

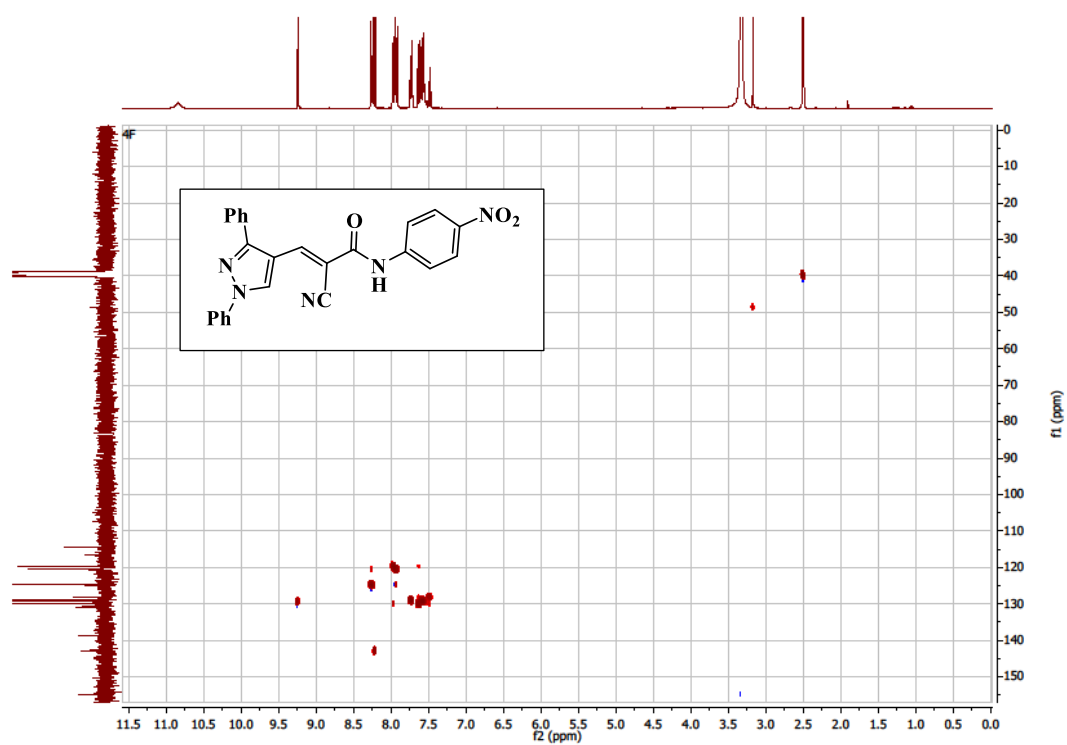


Figure S32: ^1H SQC spectrum of compound 3f

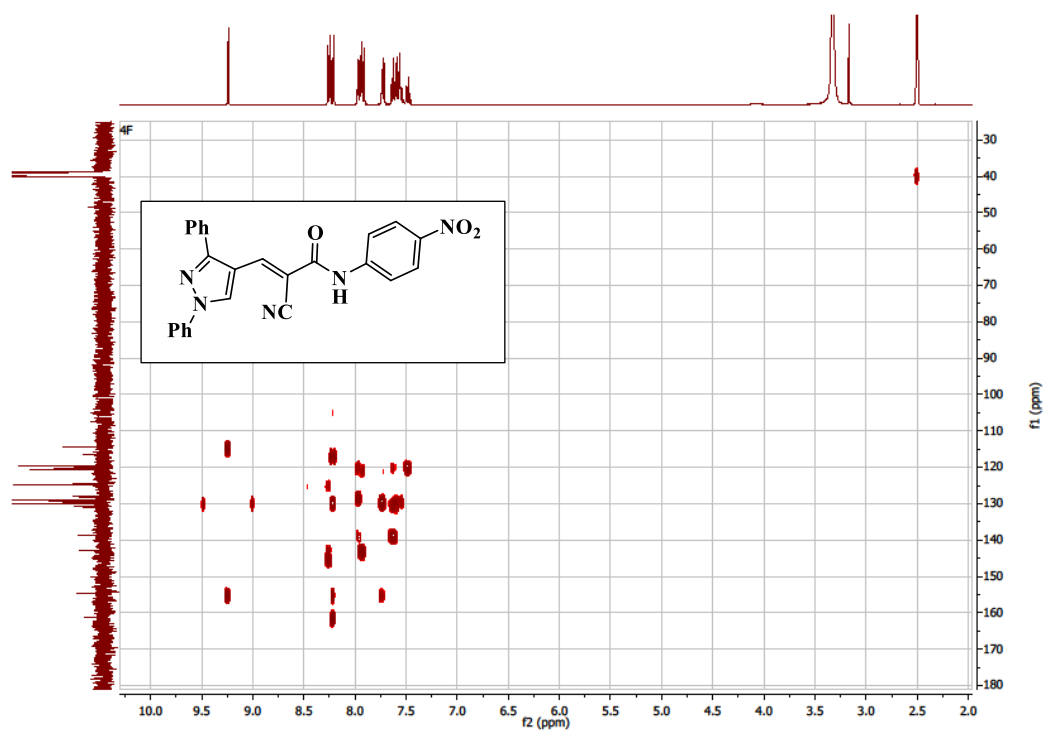


Figure S33: ^1H MBC spectrum of compound 3f

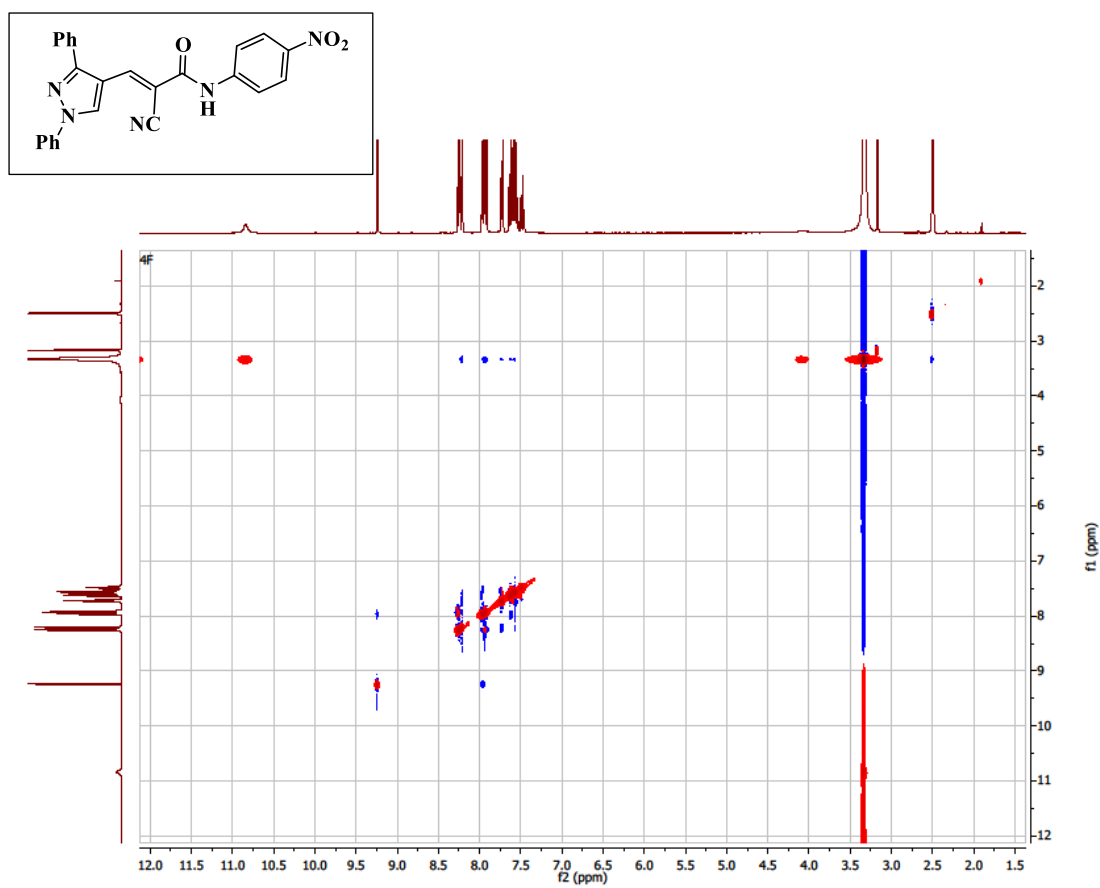
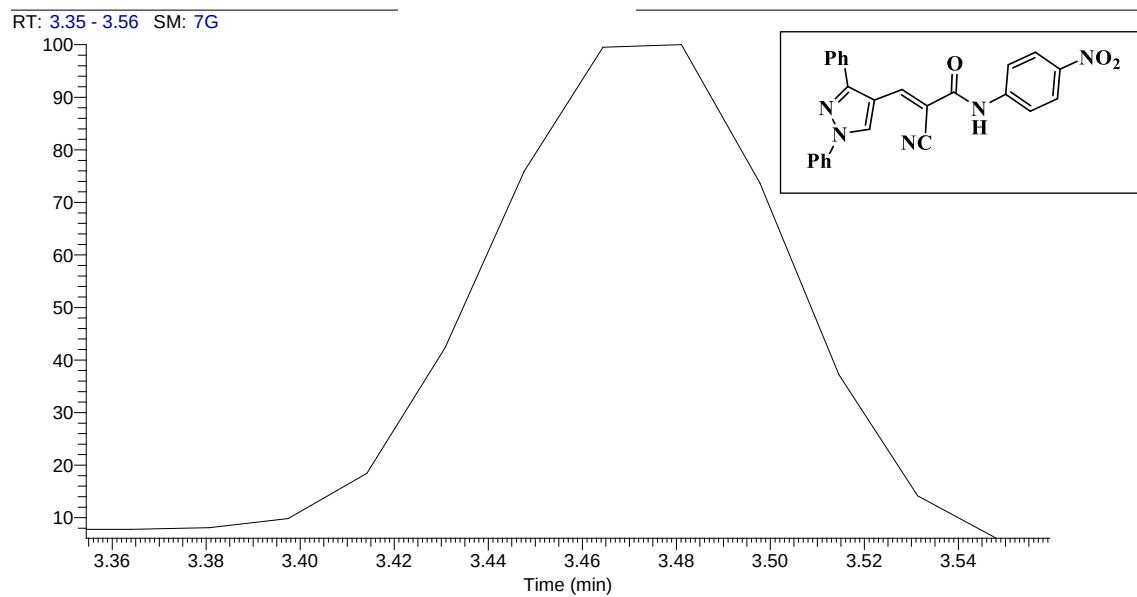


Figure S34: ^1H NOSEY spectrum of compound 3f



AYA-GHAM1 #275 RT: 4.62 AV: 1 NL: 6.83E2
T: {0,0} + c EI Full ms [40.00-1000.00]

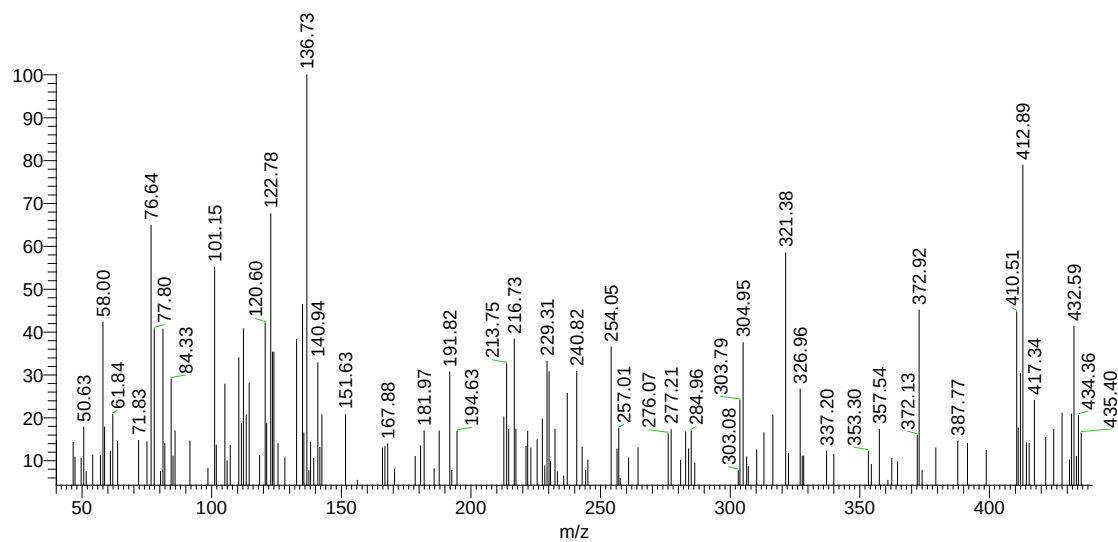


Figure S35: Mass spectrum of compound 3f

2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-(thiazol-2-yl)acrylamide (4g)

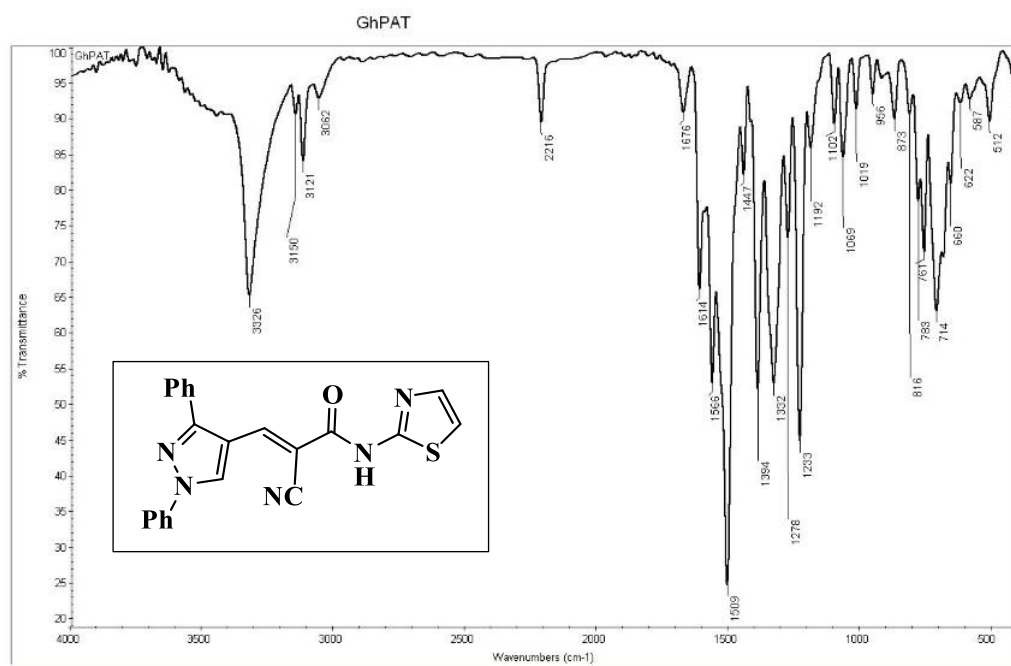
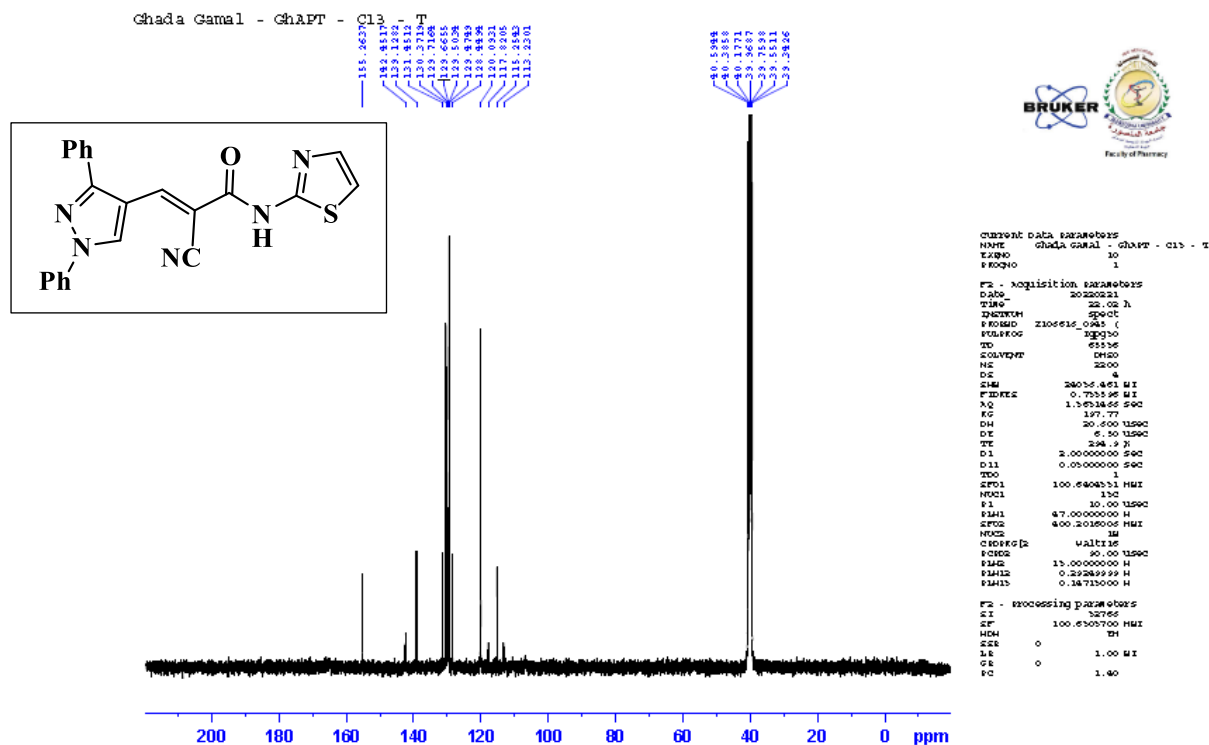
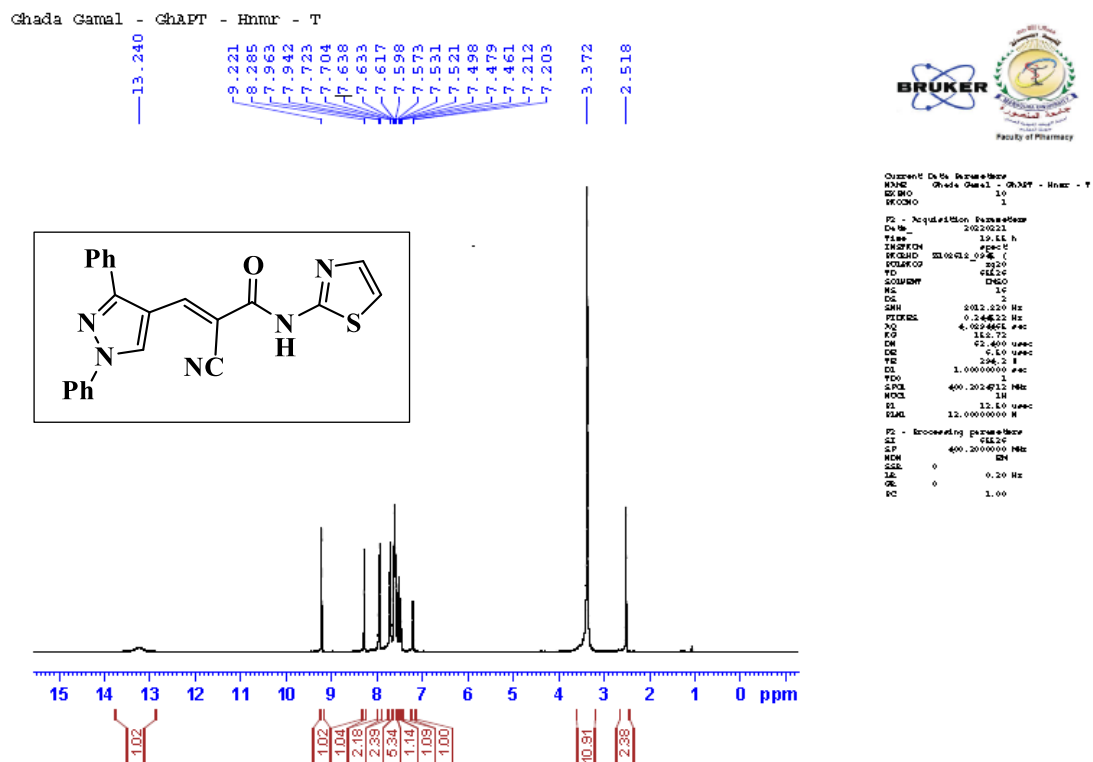
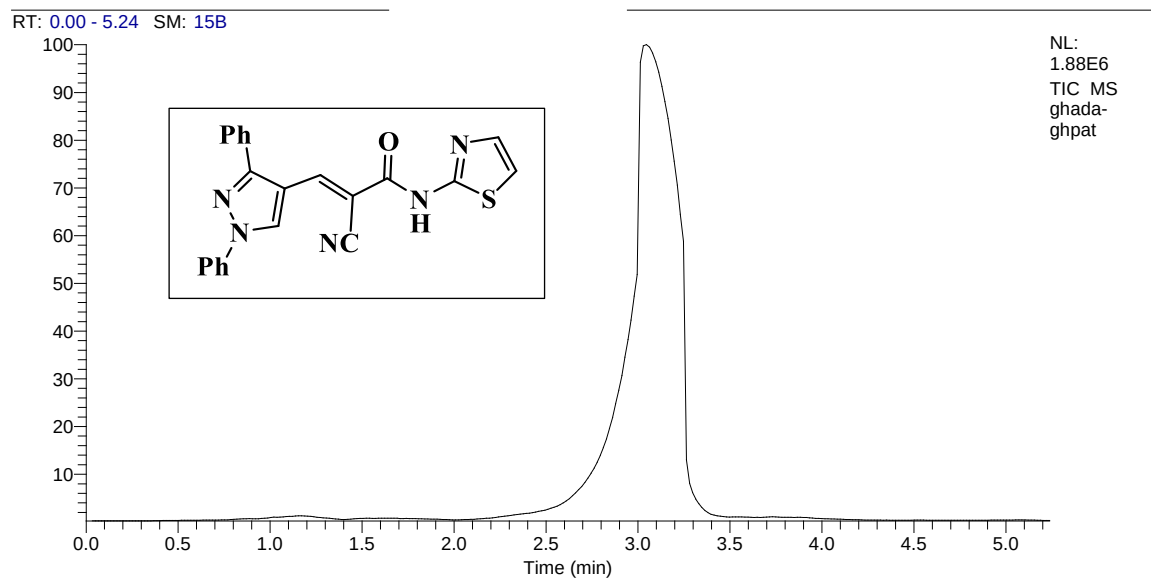


Figure S36: IR spectrum of compound 3g





ghada-ghpat #269-271 RT: 4.52-4.55 AV: 3 SB: 6 2.80 , 2.48-2.54 NL: 1.68E2
T: + c EI Full ms [40.00-1000.00]

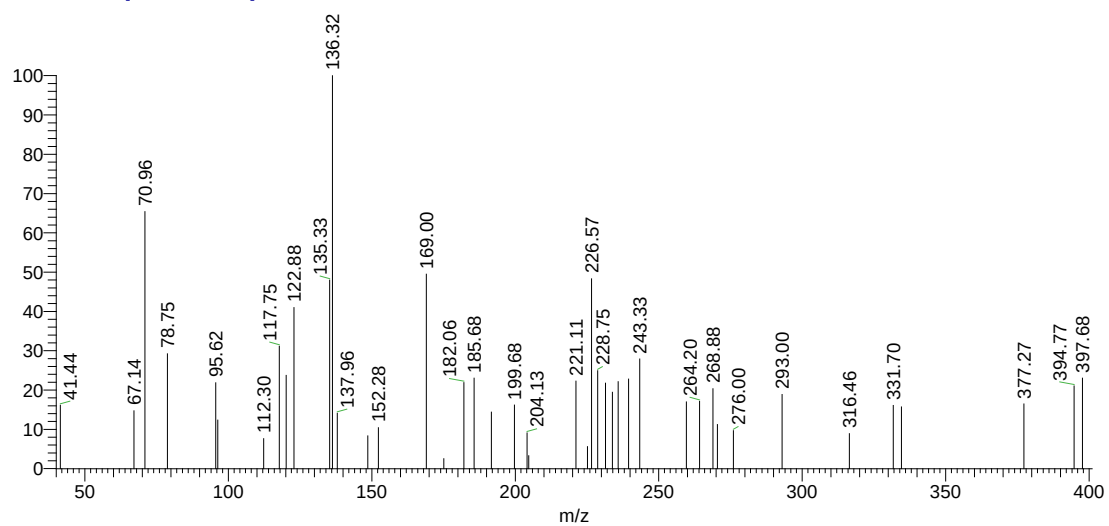


Figure S39: Mass spectrum of compound 3g

***N*-(benzo[d]thiazol-2-yl)-2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylamide (3h):**

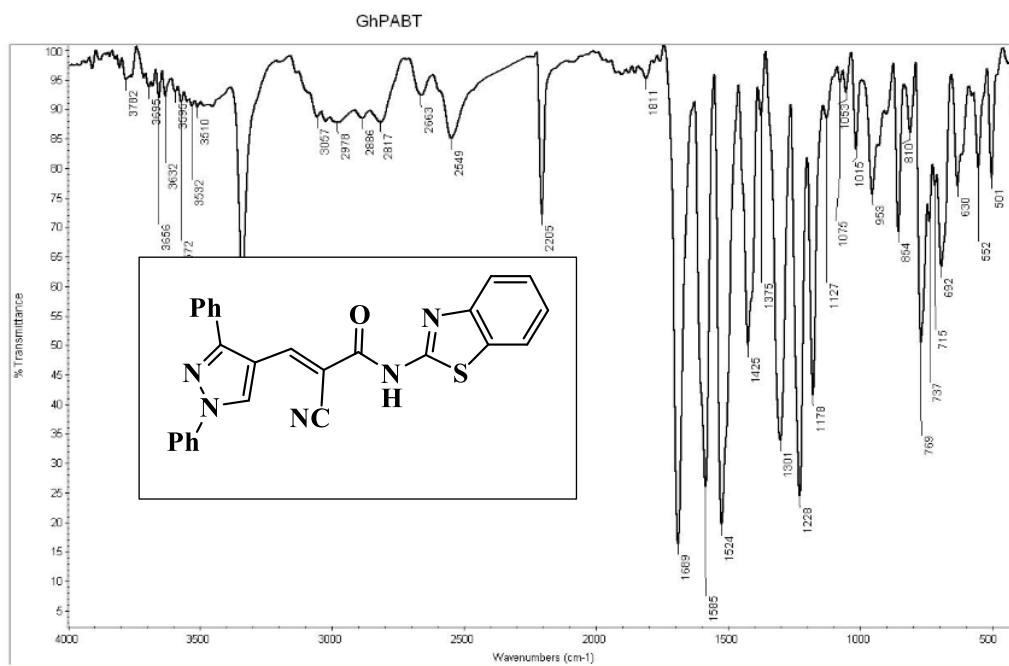


Figure S40: IR spectrum of compound 3h

4,5,6,7-tetrabromo-2-(((1,3-diphenyl-1H-pyrazol-4-yl)methylene)amino)isoindoline-1,3-dione (6)

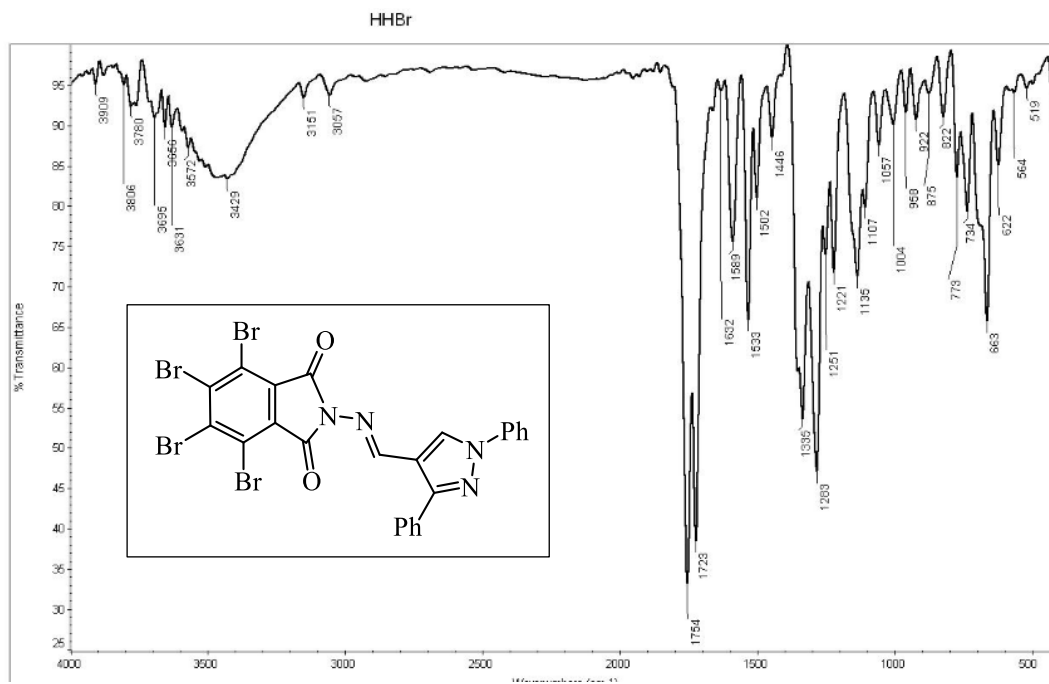


Figure S41: IR spectrum of compound 6

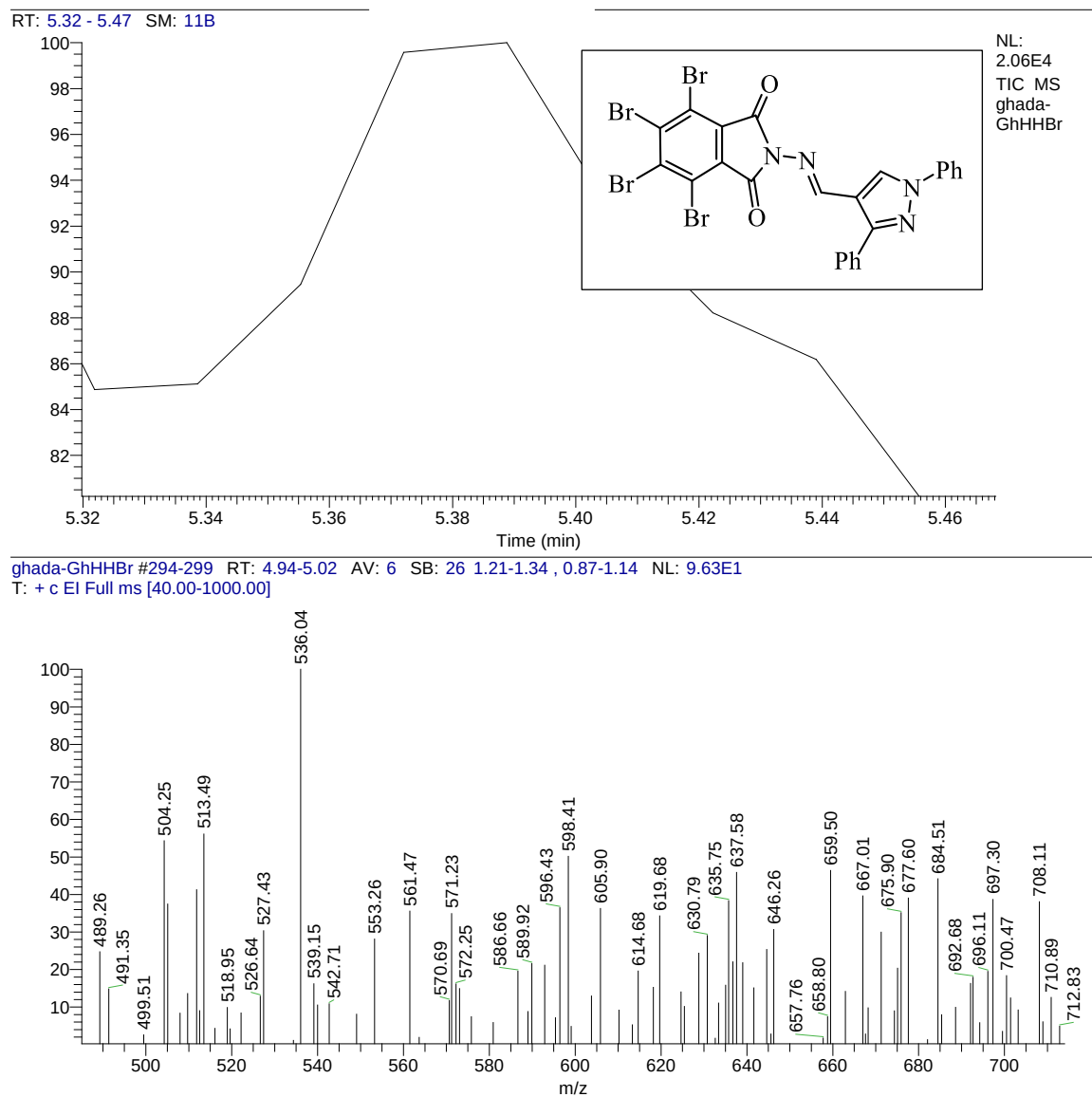


Figure S42: Mass spectrum of compound 6

5-(1,3-diphenyl-1H-pyrazol-4-yl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carbonitrile (7):

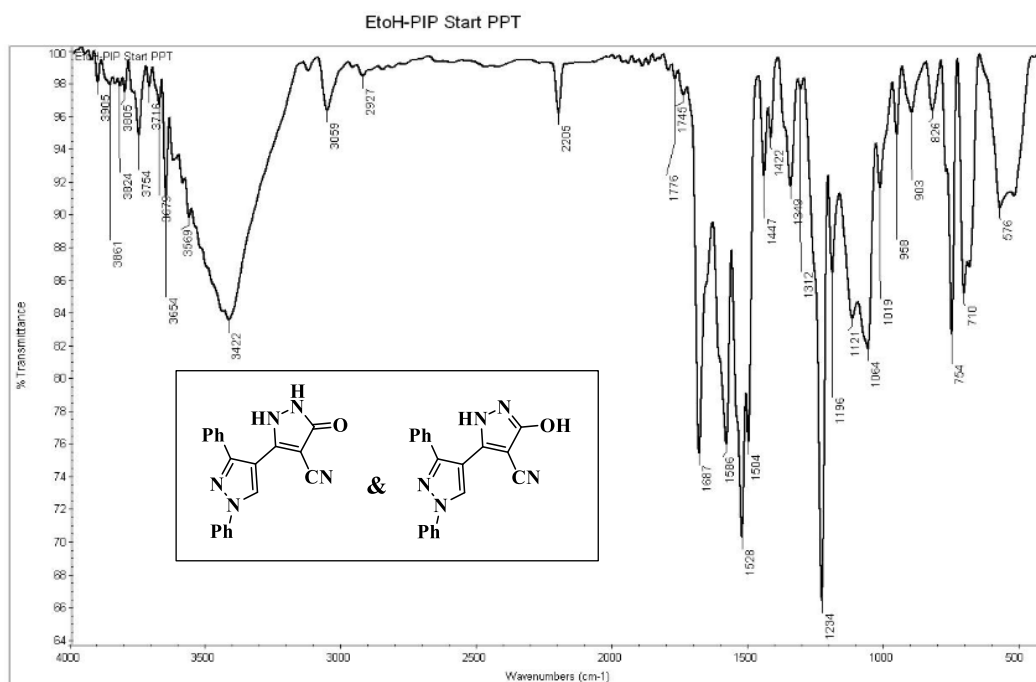


Figure S43: IR spectrum of compound 7

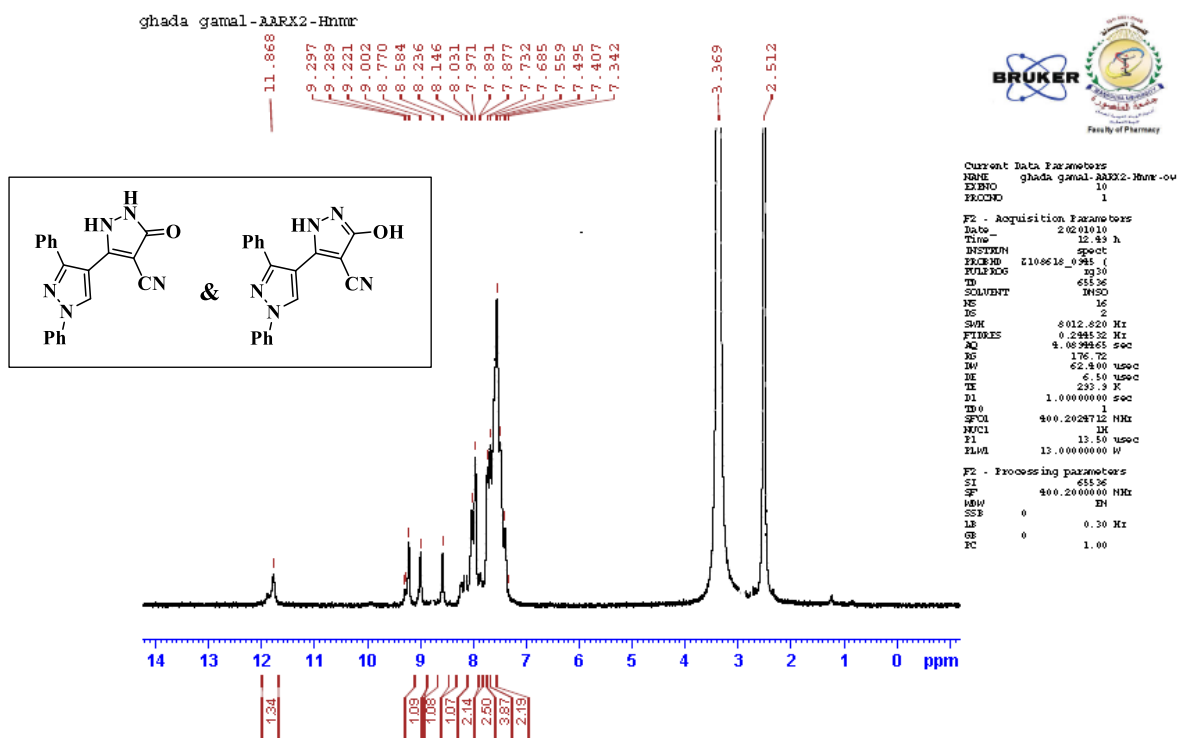


Figure S44: ^1H NMR spectrum of compound 7

2-cyano- N' -((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide (8)

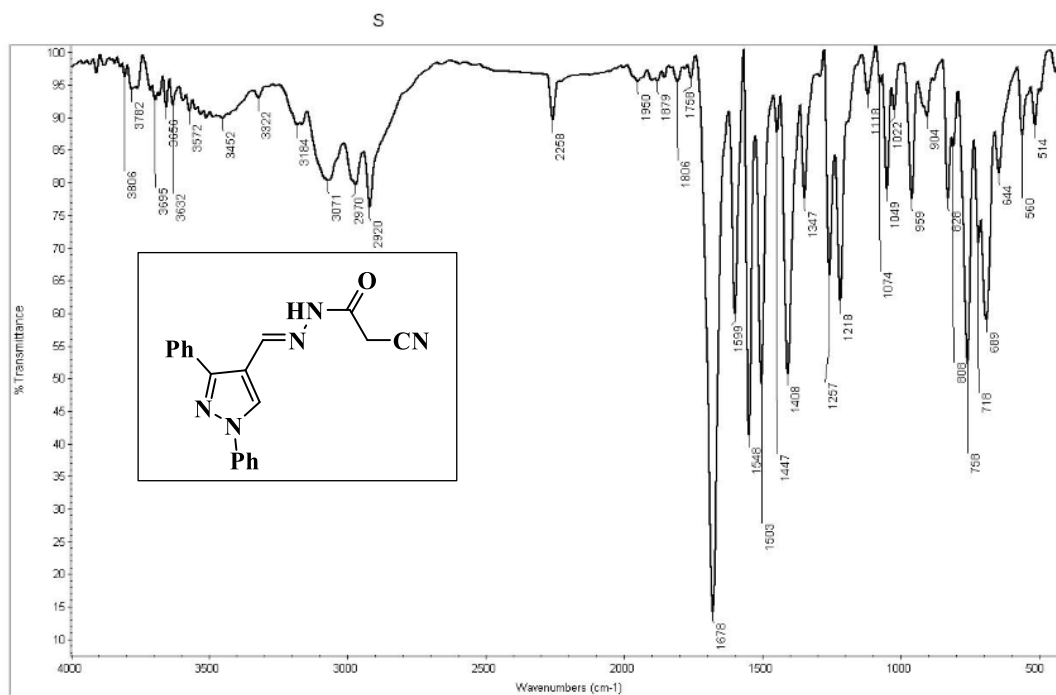


Figure S45: IR spectrum of compound 8

Figure S47: ^{13}C NMR spectrum of compound 8

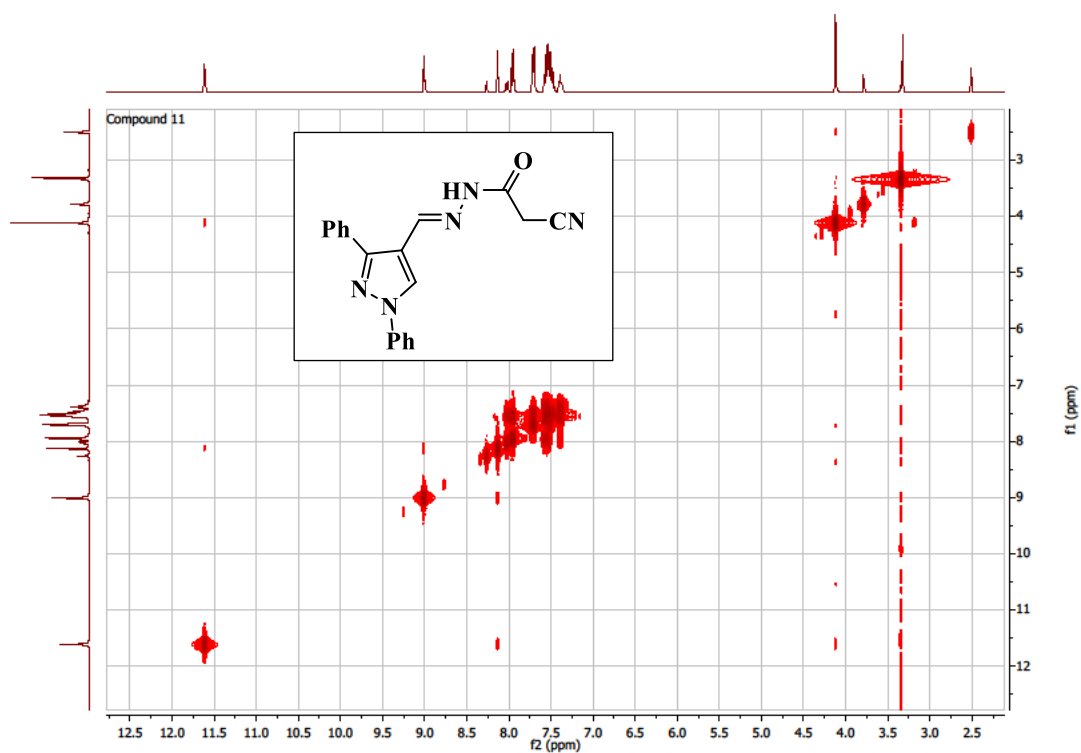


Figure S48: ^1H COSY spectrum of compound 8

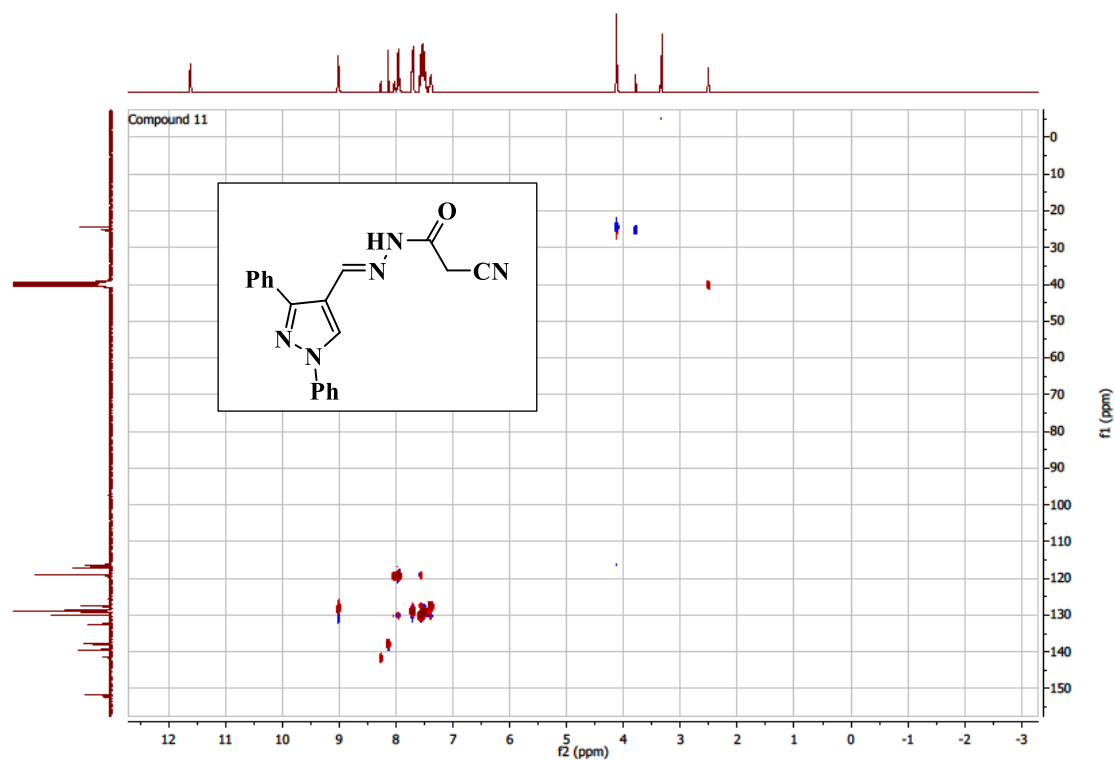


Figure S49: ^1H SQC spectrum of compound 8

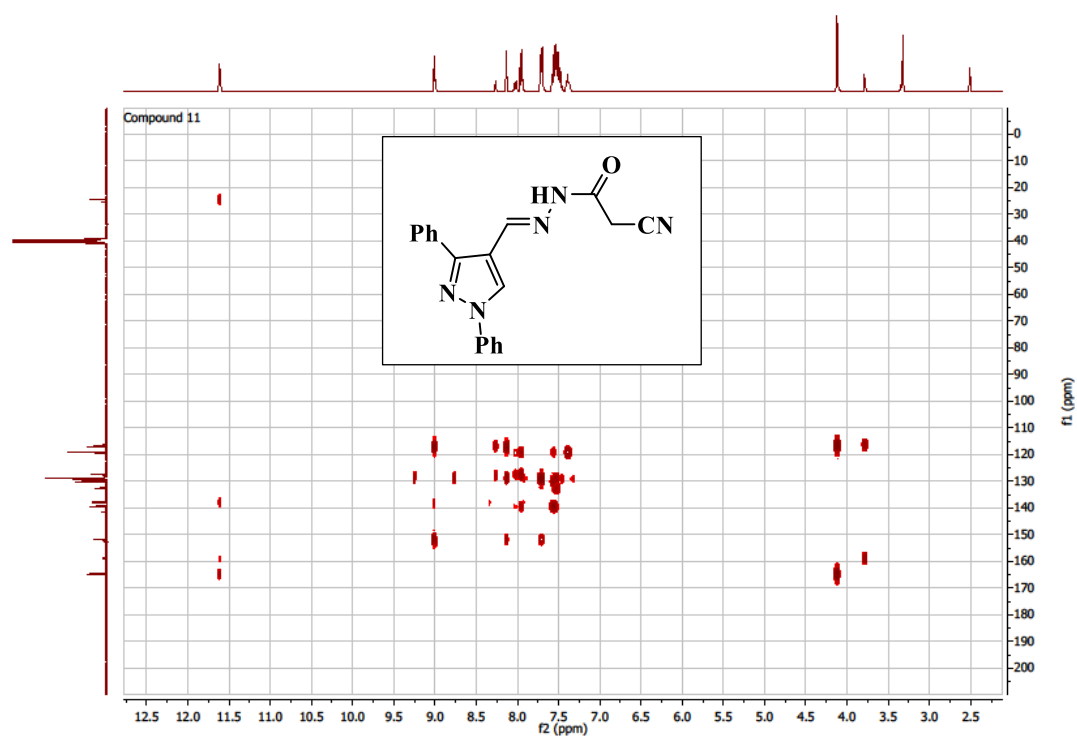


Figure S50: ^1H MBC spectrum of compound 8

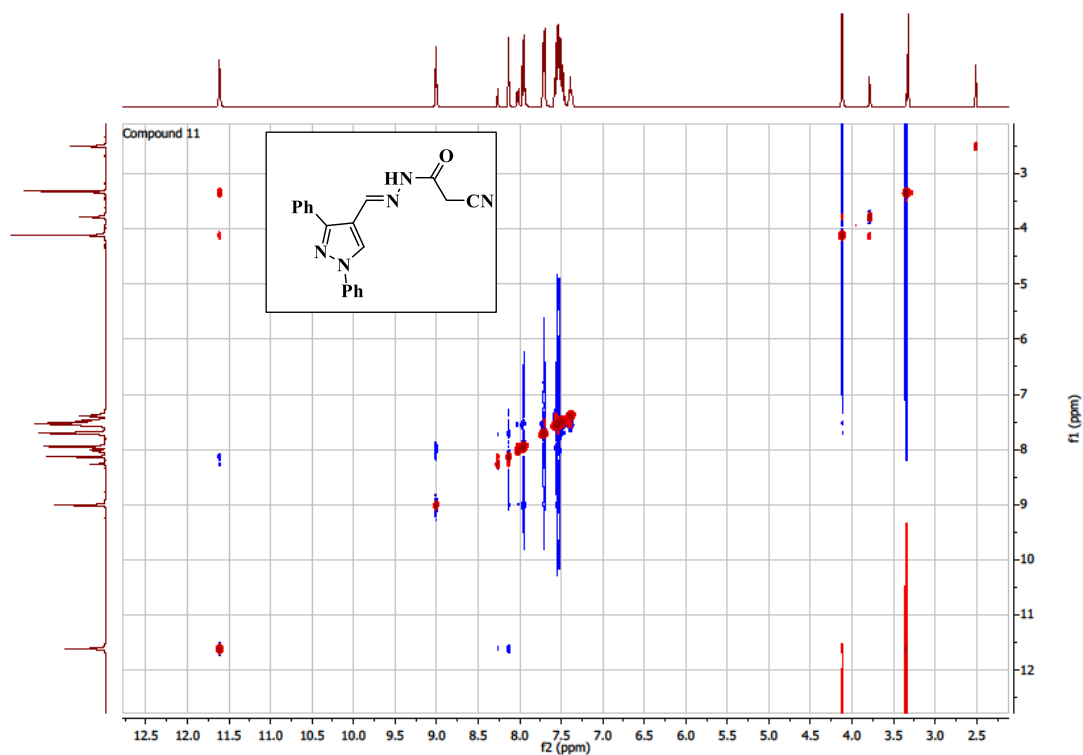


Figure S51: ¹H NMR spectrum of compound 8

N'-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-oxo-2*H*-chromene-3-carbohydrazide (10a)

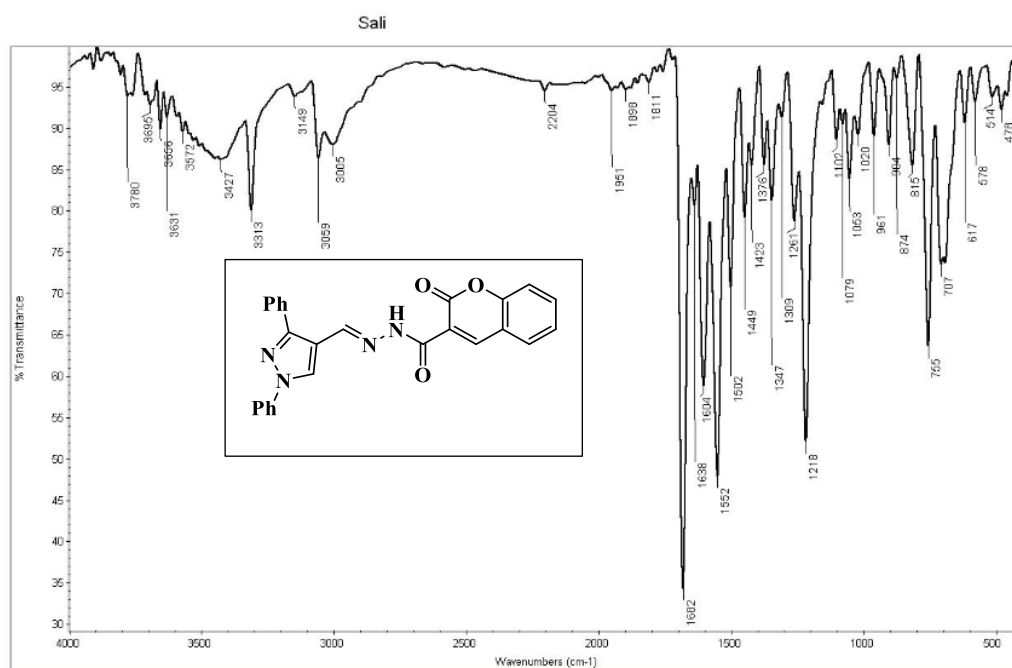


Figure S52: IR spectrum of compound 10a

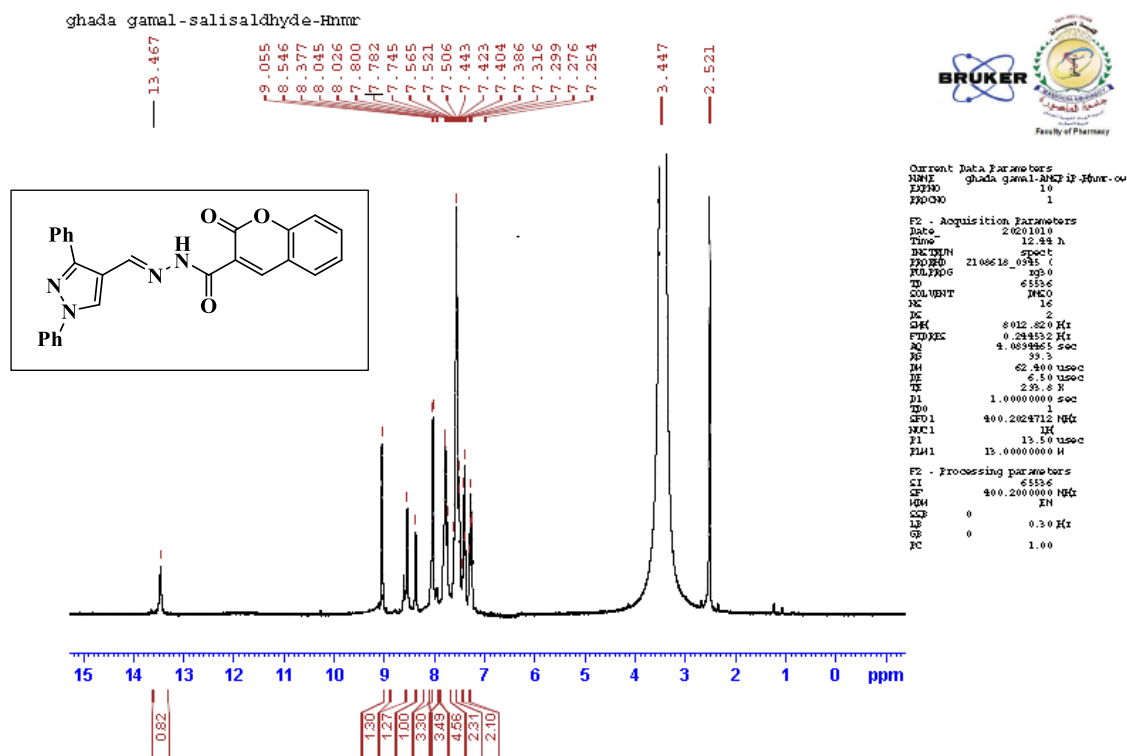


Figure S53: ¹H NMR spectrum of compound 10a

***N'*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-oxo-6-(*p*-tolyl-diazenyl)-2*H*-chromene-3-carbohydrazide (10b)**

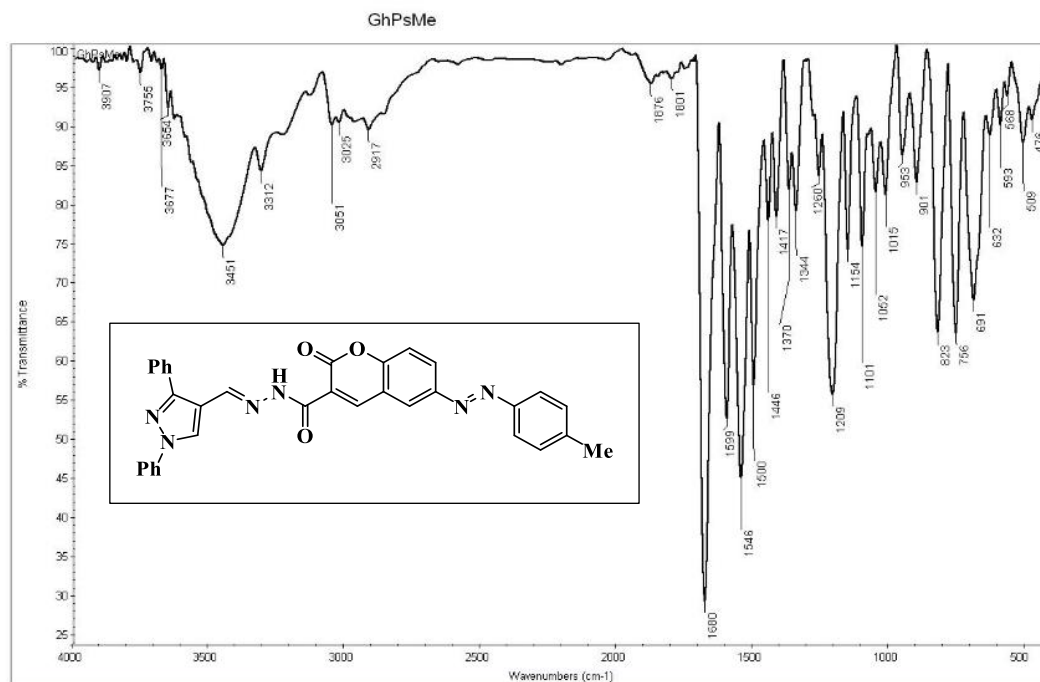
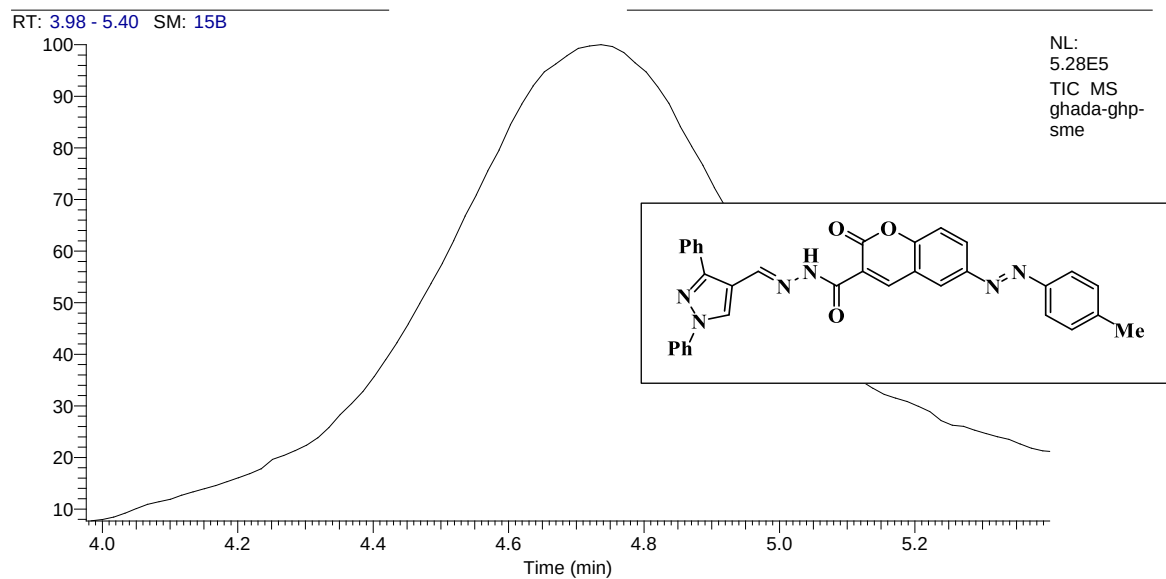


Figure S54: IR spectrum of compound 10b



ghada-ghp-sme #182 RT: 3.06 AV: 1 SB: 14 3.57 , 3.38-3.58 NL: 5.07E2
T: + c EI Full ms [40.00-1000.00]

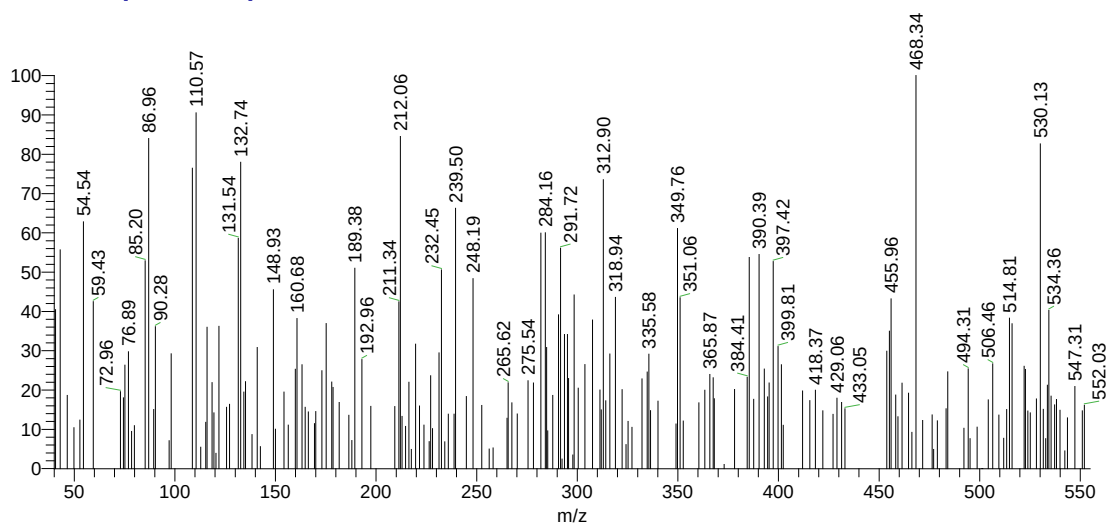


Figure S56: Mass spectrum of compound 10b

6-((4-chlorophenyl)diazenyl)-N'-(1,3-diphenyl-1H-pyrazol-4-yl)methylene)-2-oxo-2H-chromene-3-carbohydrazide (10c)

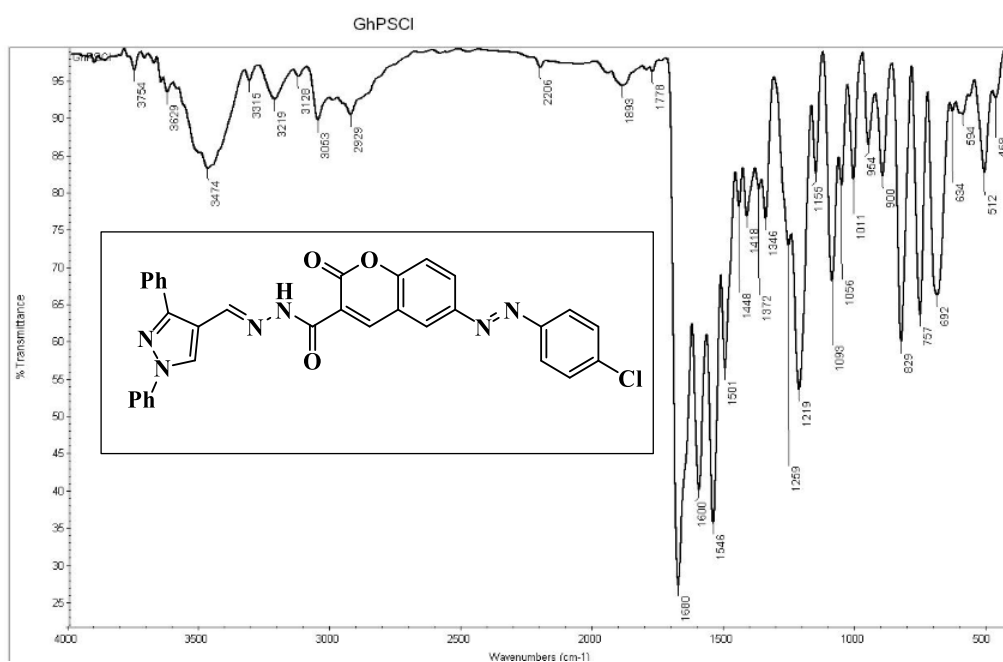
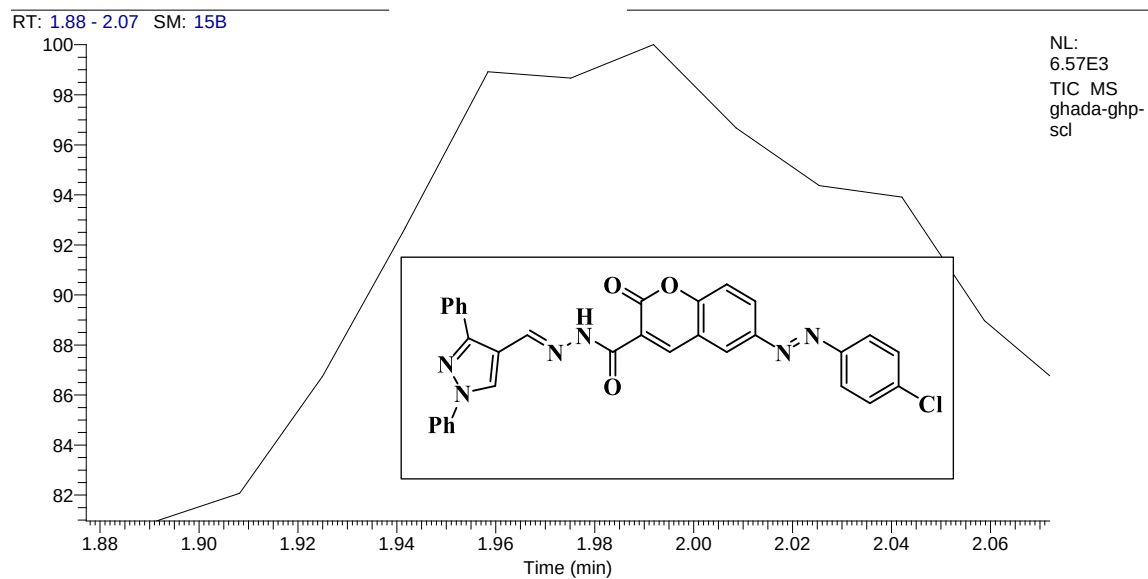


Figure S57: IR spectrum of compound 10c



ghada-ghp-scl #101-102 RT: 1.71-1.72 AV: 2 SB: 6 2.74, 2.48-2.54 NL: 1.70E2
T: + c EI Full ms [40.00-1000.00]

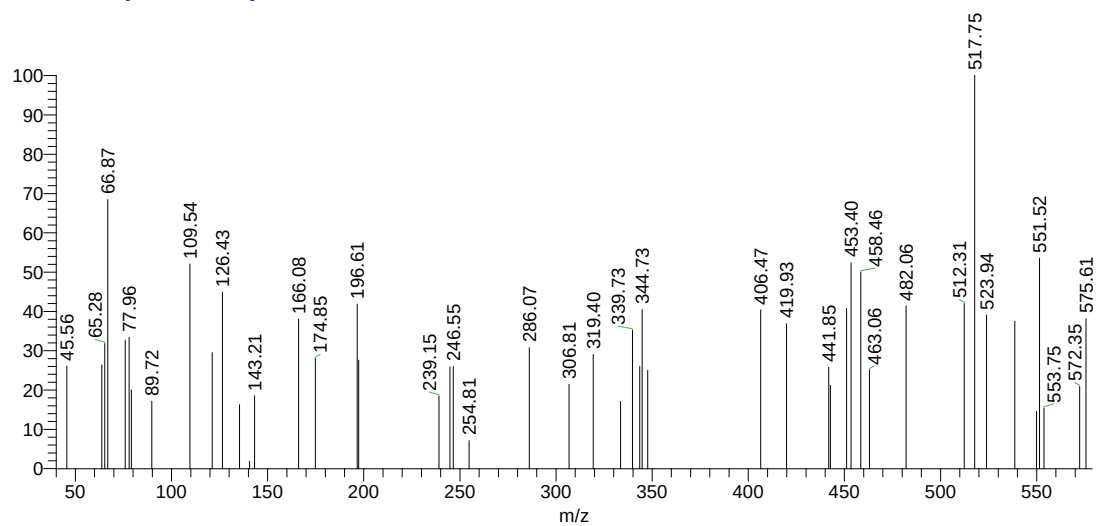


Figure S58: Mass spectrum of compound 10c

***N'*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-6-((4-nitrophenyl)diazenyl)-2-oxo-2*H*-chromene-3-carbohydrazide (10d)**

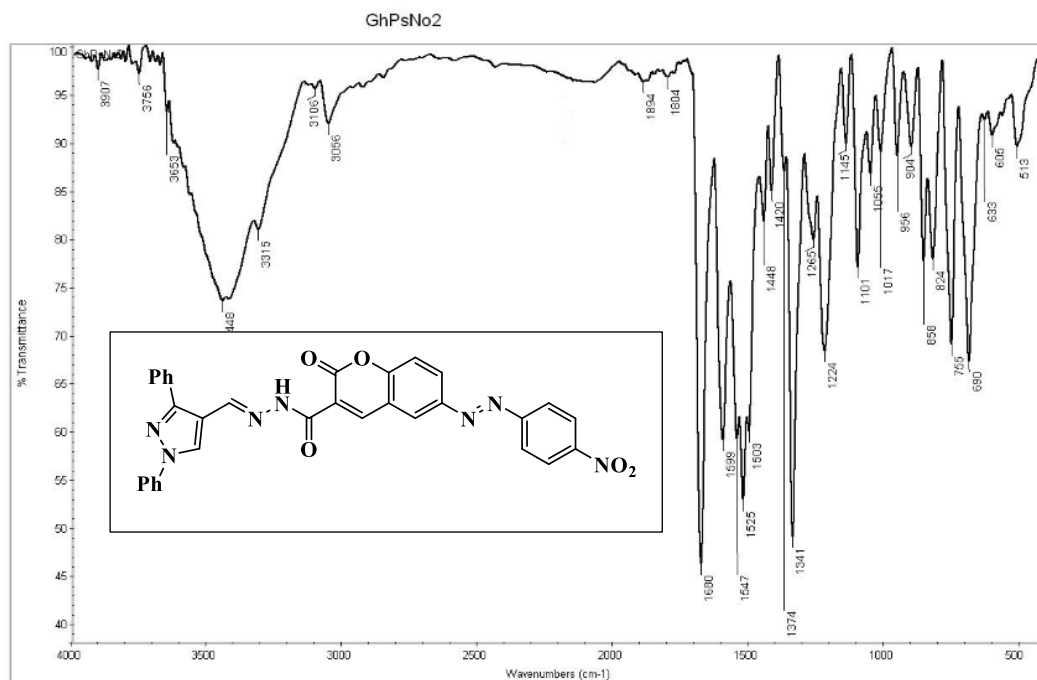
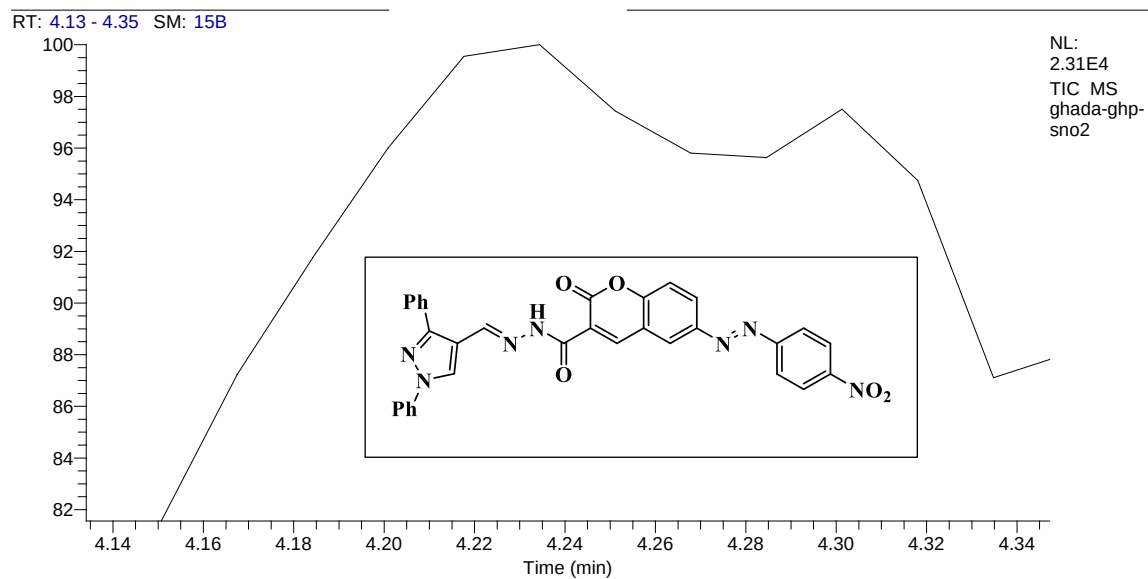


Figure S59: IR spectrum of compound 10d



ghada-ghp-sno2 #278 RT: 4.67 AV: 1 SB: 6 2.80 , 2.48-2.54 NL: 6.51E2
T: + c EI Full ms [40.00-1000.00]

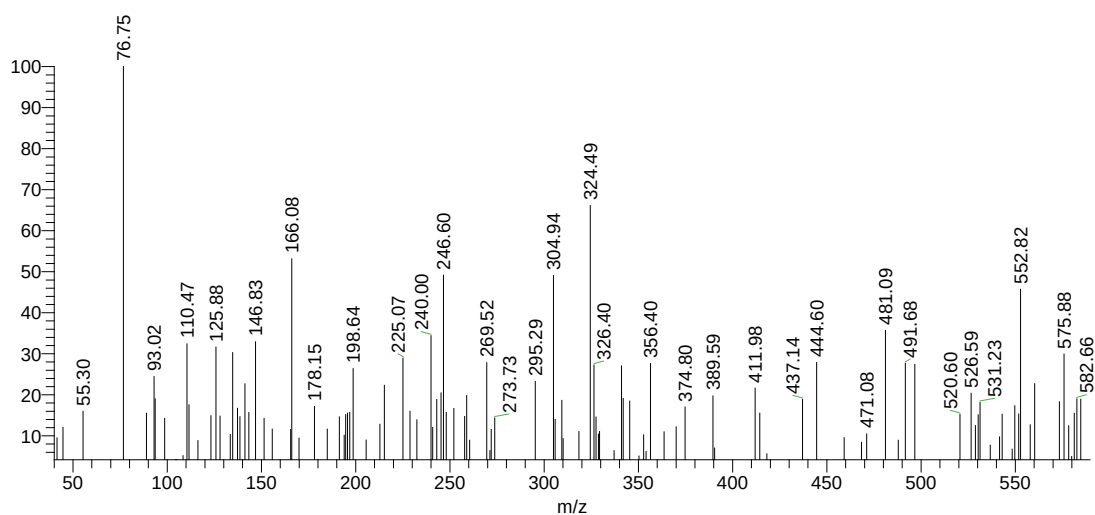


Figure S62: Mass spectrum of compound 10d

4-((3-(2-(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbonyl)-2-oxo-2*H*-chromen-6-yl)diazenyl)benzoic acid (10e)

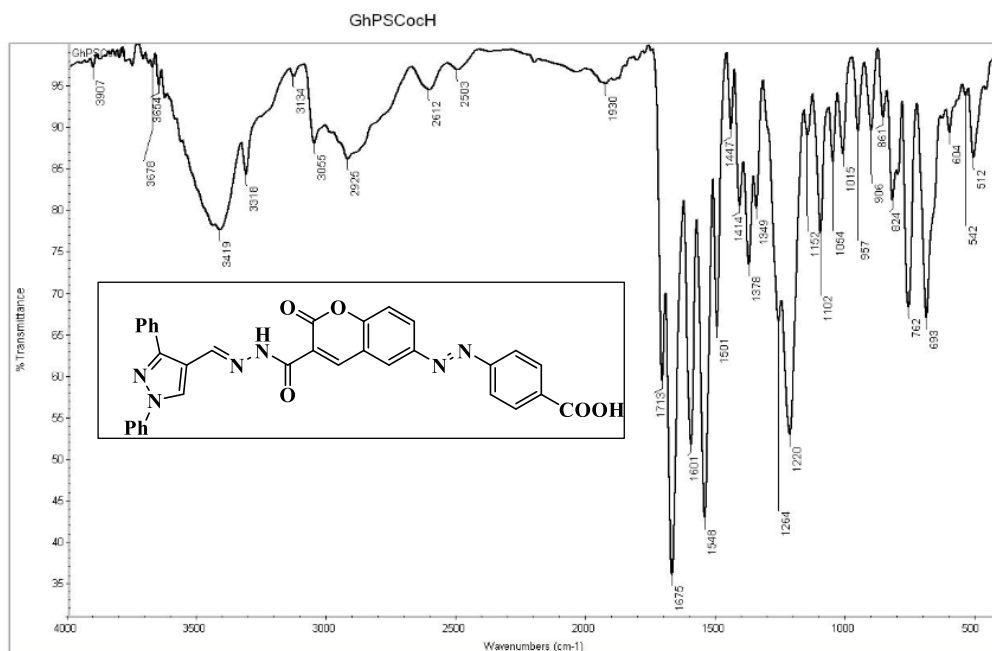
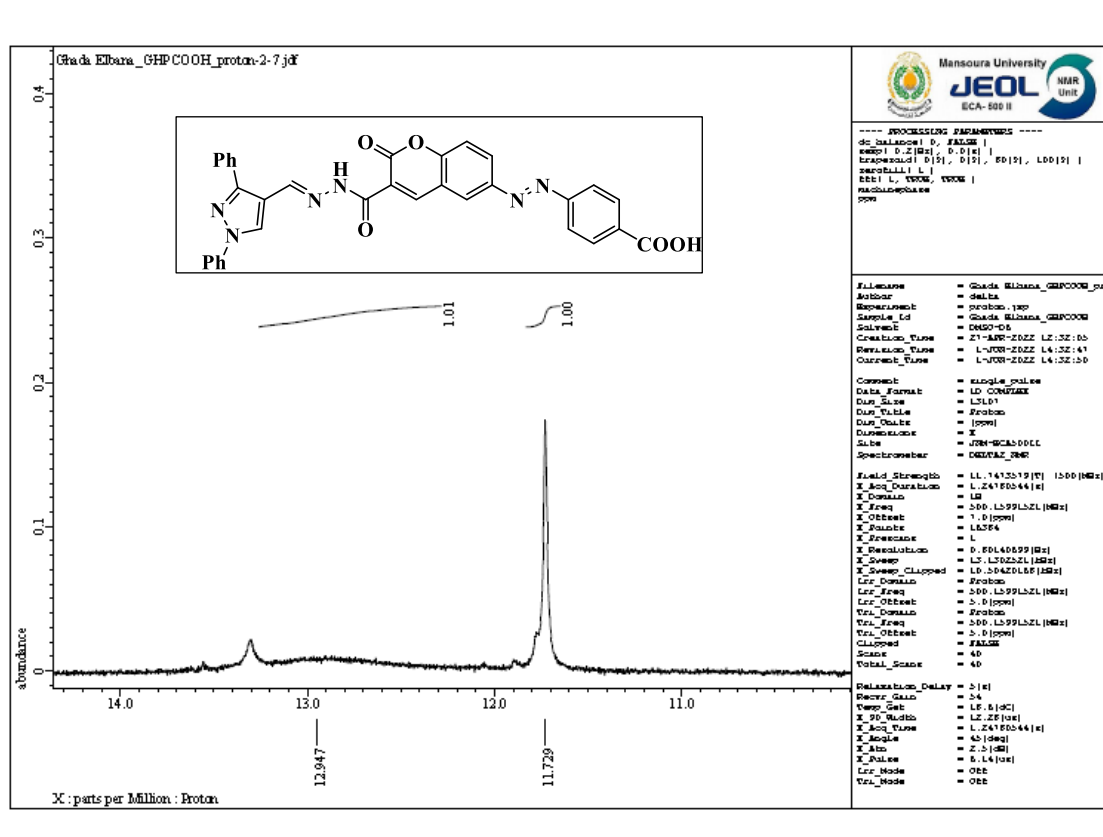
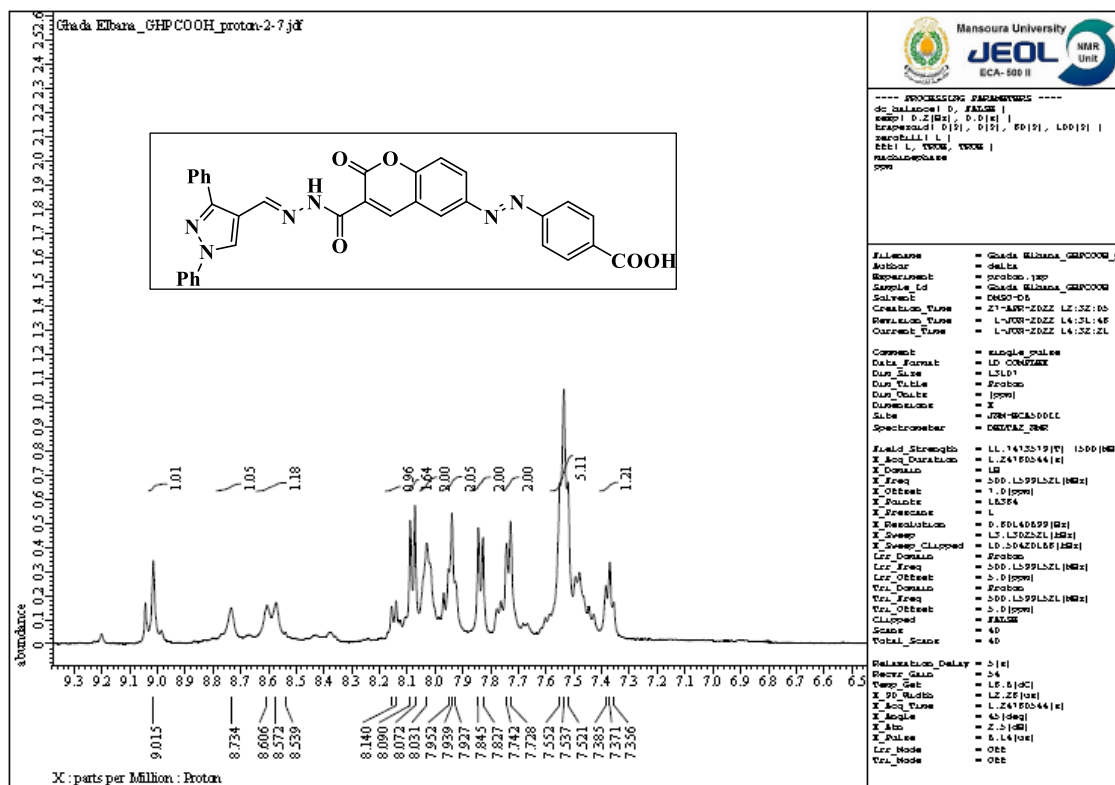


Figure S63: IR spectrum of compound 10e



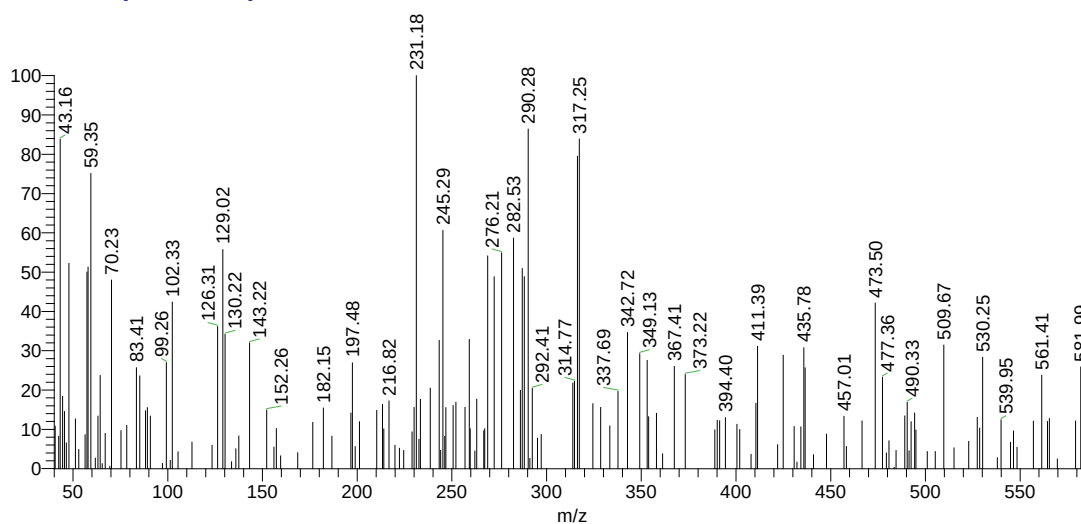
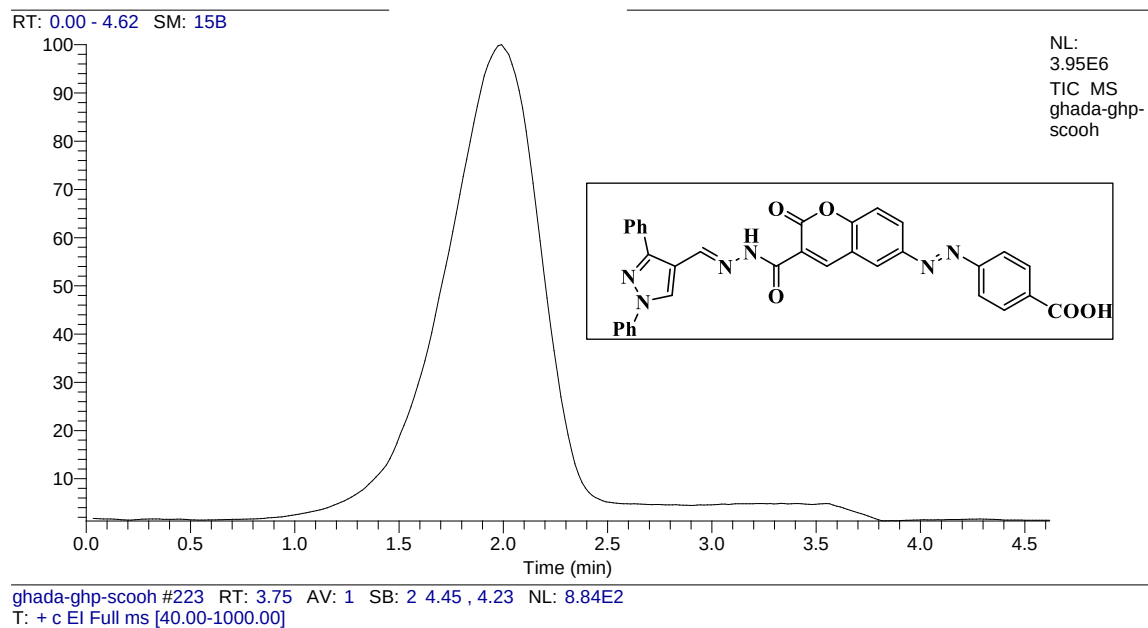


Figure S67: Mass spectrum of compound 10e

2-cyano-3-(dimethylamino)-N'-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-acrylo-hydrazide (11)

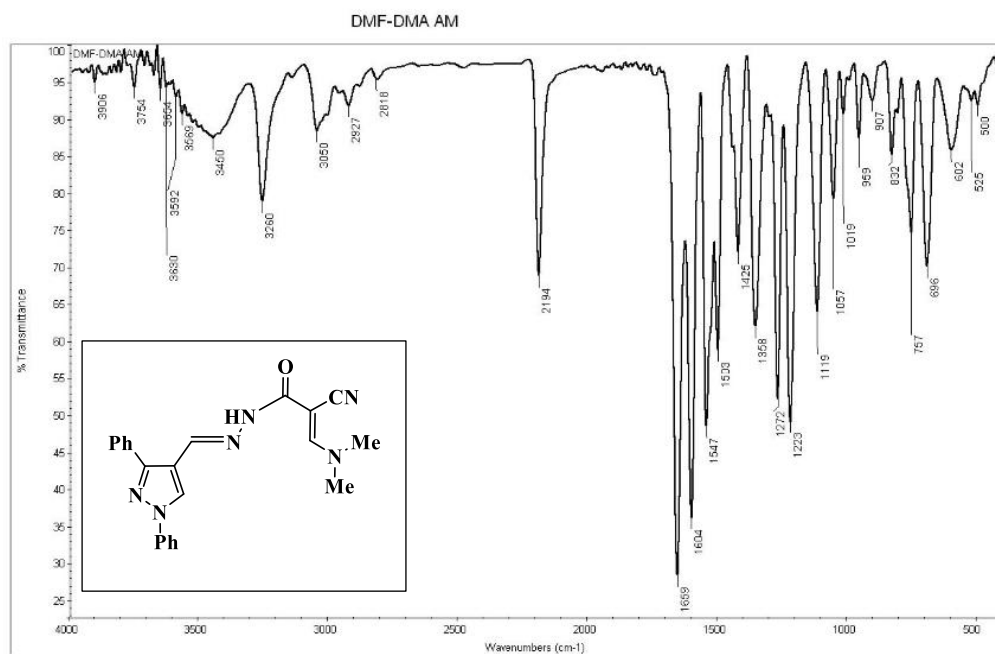


Figure S68: IR spectrum of compound 11

Amira hamza-DMF-DMA-AM-Hnmr-ES

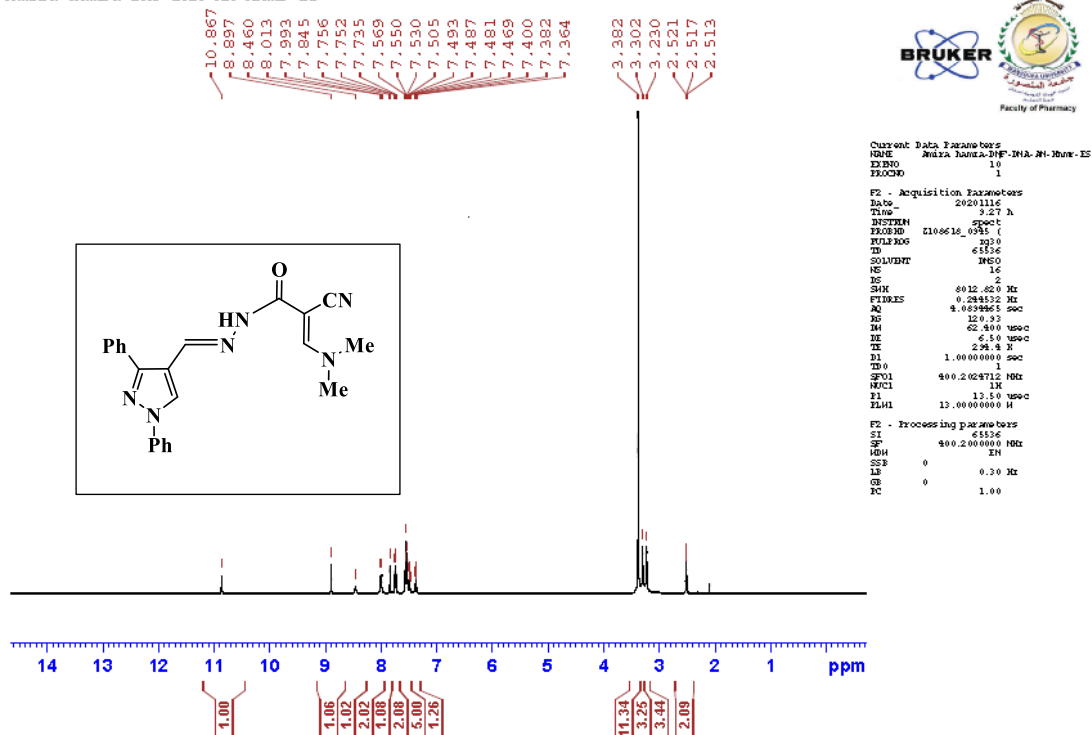


Figure S69: ¹H NMR spectrum of compound 11

amira hamza-AM-DMF-DMA-c13-R

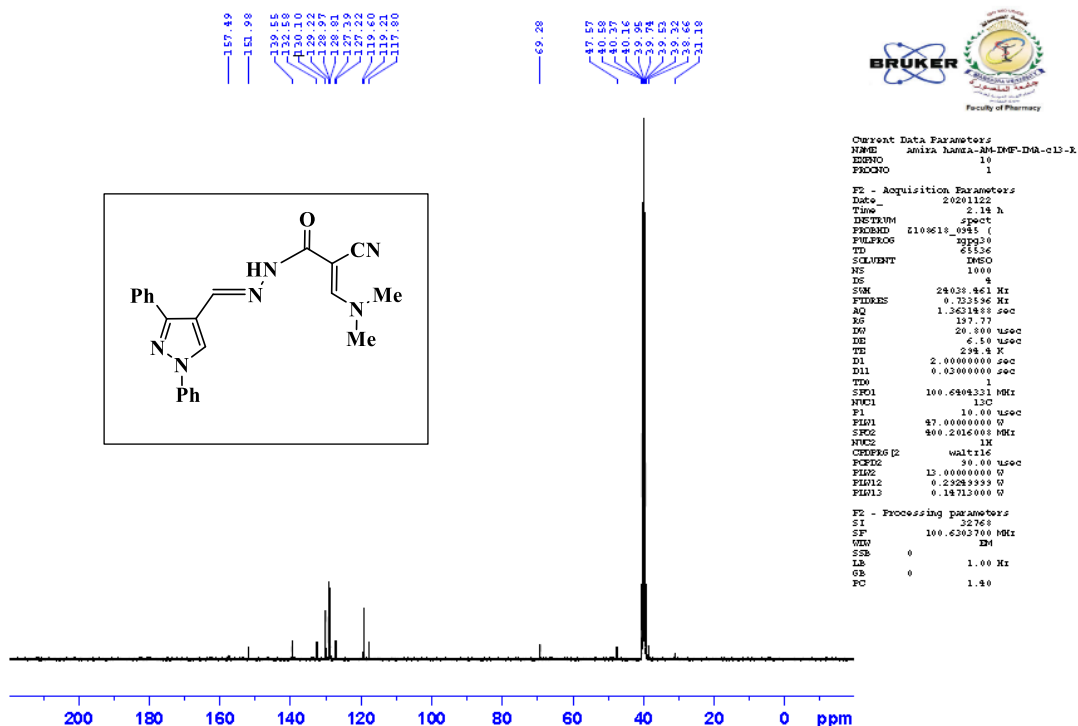


Figure S70S: ^{13}C NMR spectrum of compound 11

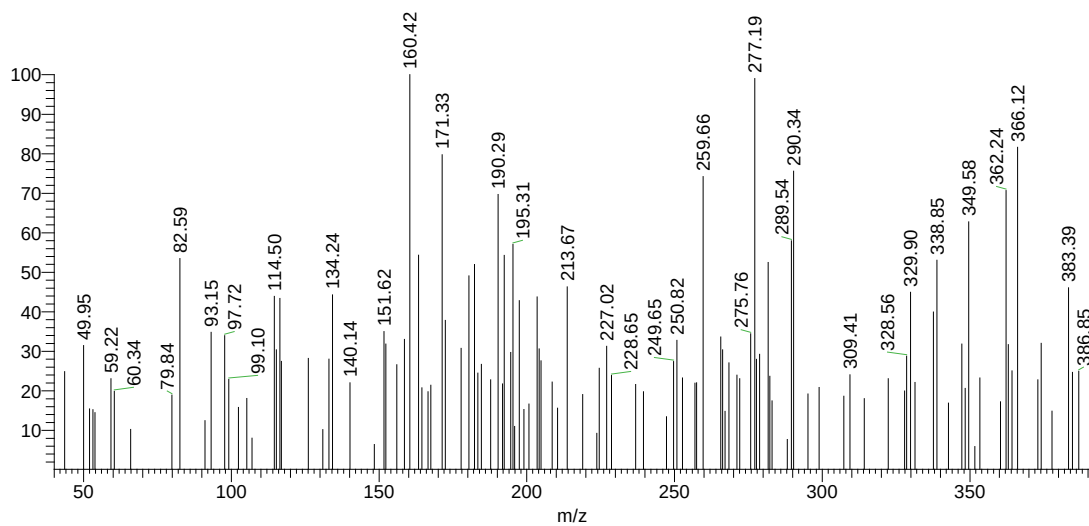
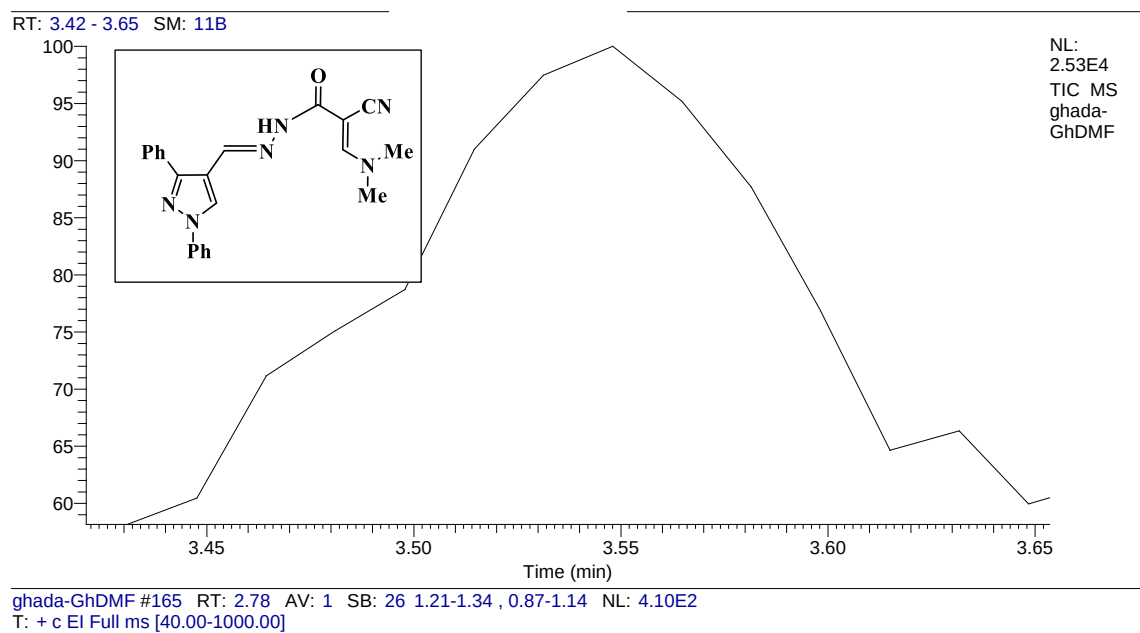


Figure S71: Mass spectrum of compound 11

4-((dimethylamino)methylene)-6-(1,3-diphenyl-1H-pyrazol-4-yl)pyridazine-3,5(4H,6H)-dione (12)

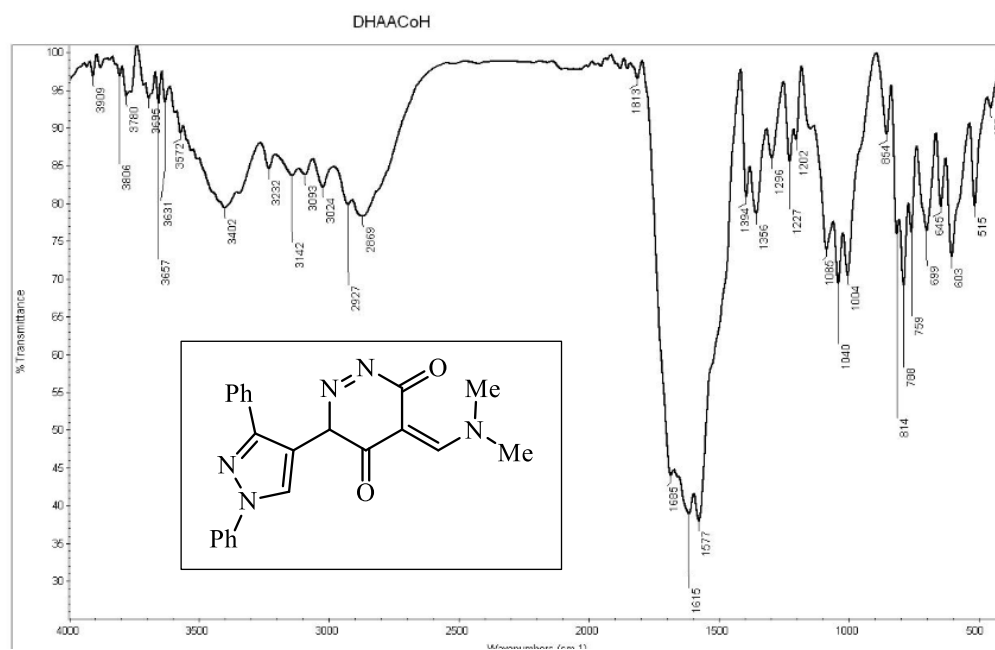
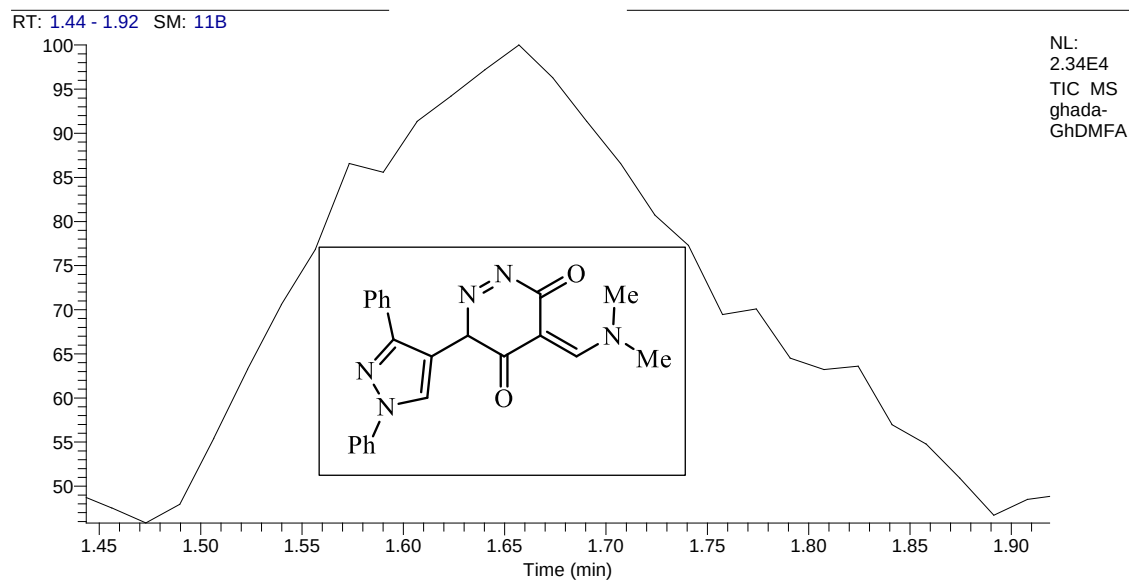


Figure S72: IR spectrum of compound 12



ghada-GhDMFA #250-253 RT: 4.20-4.25 AV: 4 SB: 26 1.21-1.34 , 0.87-1.14 NL: 1.32E2
T: + c EI Full ms [40.00-1000.00]

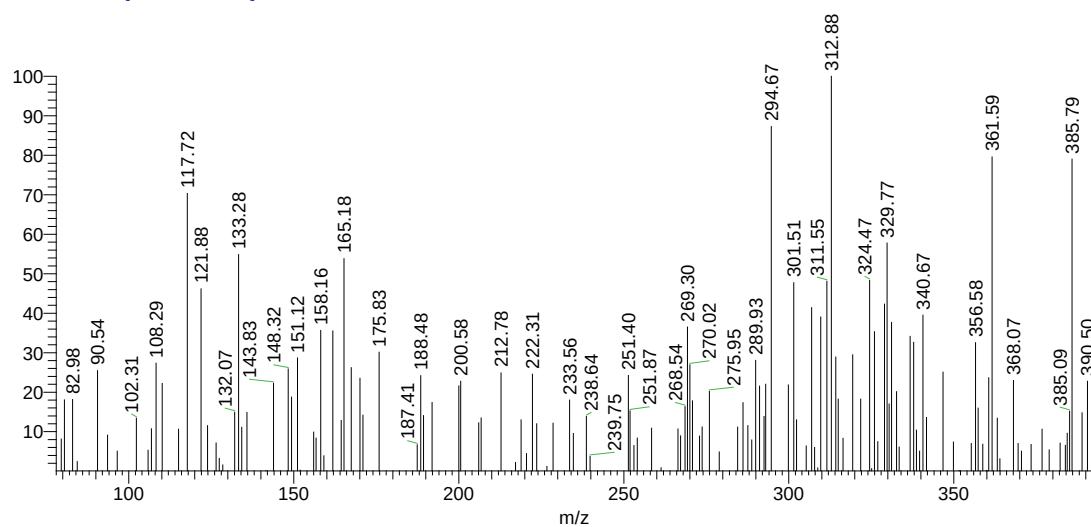


Figure S73: Mass spectrum of compound 12