Supplemental Material

Recyclization of Morpholinochromonylidene-Thiazolidinone Using Nucleophiles: Facile Synthesis, Cytotoxic Evaluation, Apoptosis, Cell cycle and Molecular docking Studies of A Novel series of Azole, Azine, Azepine and Pyran Derivatives

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Contents

1. General Marks

The melting points were determined in an open capillary tube on a digital Stuart SMP-3 apparatus. IR spectra were measured on FT-IR (Nicolet IS10) spectrophotometer using ATR technique. The ^{1}H- and ^{13}C-NMR spectra were measured a Bruker spectrometer (400 and 100 MHz), using DMSO-d_6 as a solvent and TMS (δ) as an internal standard. Mass spectra were recorded on direct probe controller inlet part to single quadropole mass analyzer in (thermo scientific GCMS). Elemental microanalyses were performed Perkin-Elmer 2400II at the Chemical War department, Ministry of Defense. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental microanalysis

2. Experimental methods and spectral data

Synthesis of 2-(morpholinoimino)-5-[(4-oxo-4*H*-chromen-3-yl)methylene]-3-phenyl-thiazolidin-4-one (3).

A mixture of 1-morpholino-3-phenylthiourea (**1**) (0.59 g, 2.5 mmol), ethyl bromoacetate (0.27 ml, 2.5 mmol) and 3-formylchromone (**2**) (0.43 g, 2.5 mmol) in absolute ethanol (25 ml) in the presence of freshly prepared sodium acetate (0.2 g, 2.5 mmol), was heated under reflux for 3 hours. The formed solid during heating, was filtered off and washed with distilled water and methanol. The pure yellow solid was obtained after crystallization from DMF-EtOH in 80% yield, mp 224–225 ^{o}C. IR (KBr), (ν max, cm^{-1}): 3064 (C–H$_{arom}$), 2964, 2887, 2858, 2831 (C–H$_{aliph}$), 1699 (C=O), 1651 (C=O$_{chromone}$), 1613 (C=N), 1602, 1558, 1557 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.66 (t, 4H, J=3.6 Hz, CH$_2$N), 3.70 (t, 4H, J=4.0 Hz, CH$_2$O), 7.42–7.48 (m, 3H, Ph–H and H–6$_{chromone}$), 7.51–7.60 (m, 4H, Ph–H and =CH), 7.74 (d, 1H, J=8.4 Hz, H–8$_{chromone}$), 7.89 (t, 1H, J=7.2 Hz, H–7$_{chromone}$), 8.17 (d, 1H, J=7.6 Hz H–5$_{chromone}$), 8.84 (s, 1H, H–2$_{chromone}$). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.8 (CH$_2$N), 65.9 (CH$_2$O), 119.0 (C–8$_{chromone}$), 119.2 (C–3$_{chromone}$), 122.1 (C–6$_{chromone}$), 123.4 (C–4a$_{chromone}$), 124.7 (C–5$_{chromone}$), 126.0 (C–5$_{thiazole}$), 126.7 (=CH$_{exocyclic}$), 128.5 (C–2,6$_{phenyl}$), 129.0 (C–4$_{phenyl}$), 129.5 (C–3,5$_{phenyl}$), 135.3 (C–1$_{phenyl}$), 135.4 (C–7$_{chromone}$), 156.0 (C–8a$_{chromone}$), 159.5 (C–2$_{chromone}$), 159.9 (C=N), 166.7 (C=O), 175.1 (C=O$_{chromone}$). MS (*m/z*, I%): 433 (M^{+}, 17%). Anal. Calcd for $C_{23}H_{19}N_3O_4S$ (433.48): C, 63.73%; H, 4.42%; N, 9.49%; S, 7.40%. Found: C, 63.65%; H, 4.23%; N, 9.30%; S, 7.23%.

General procedure for synthesis of both products 4 and 5.

A mixture of 2-(morpholinoimino)-5-[(4-oxo-4*H*-chromen-3-yl)methylene]-3-phenyl-thiazolidin-4-one (**3**) (0.65 g, 1.5 mmol) and morpholine and/or 4-aminomorpholine (1.5 mmol) in absolute ethanol (20 ml), was heated under reflux for 6 hours. The formed solids after cooling were filtered off and crystallized from ethanol.

5-{2-(2-Hydroxybenzoyl)-3-(morpholinoamino)allylidene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (4). Brown solid in 60% yield, mp 173–174 ^{o}C. IR (KBr), (ν max, cm^{-1}): 3228 (br, OH, NH), 3064 (C–H$_{arom}$), 2959, 2915, 2894, 2855, 2840 (C–H$_{aliph}$), 1710 (C=O), 1668 (C=O), 1608 (C=N), 1592 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.59 (t, 4H, J=4.8 Hz, CH$_2$N), 2.69 (t, 4H, J=4.4 Hz, CH$_2$N), 3.61–3.75 (m, 8H, CH$_2$O), 6.17 (s, 1H, NH), 7.32 (t, 2H, J=7.2 Hz, Ar–H), 7.43–7.57 (m, 7H, Ph–H and Ar–H), 7.81 (s, 1H, =CH), 8.46 (d, 1H, J=1.6 Hz, =CH–N), 11.23 (brs, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.3 (CH$_2$N), 56.6 (CH$_2$N), 64.8 (CH$_2$O), 66.2 (CH$_2$O), 114.2 (*C*–C=O), 118.9 (C–3$_{aryl}$), 121.1 (C–5$_{aryl}$),

122.5 (C–1_{aryl}), 123.6 (C–6_{aryl}), 126.6 (C–$5_{thiazole}$), 127.9 (=CH), 128.6 (C–$2,6_{phenyl}$), 128.9 (C–4_{phenyl}), 129.1 (C–$3,5_{phenyl}$), 131.5 (C–4_{aryl}), 136.6 (C–1_{phenyl}), 146.6 (=CH–N), 153.3 (C–2_{aryl}), 156.8 (C=N), 167.9 (C=$O_{thiazole}$), 173.9 (C=O). MS (*m/z*, I%): 534 (M^+, 21%). Anal. Calcd for $C_{27}H_{29}N_5O_5S$ (534.26): C, 60.55%; H, 5.46%; N, 13.08%; S, 5.99%. Found: C, 60.36%; H, 5.28%; N, 12.89%; S, 5.82%.

5-{2-(2-Hydroxybenzoyl)-3-morpholinoallylidene}-2-(morpholinoimino)-3-phenyl-thiazolidin-4-one (5). Brown solid in 70% yield, mp 177–178 °C. IR (KBr), (*v* max, cm^{-1}): 3067 (br, OH, C–H_{arom}), 2961, 2923, 2893, 2849 (C–H_{aliph}), 1712 (C=O), 1654 (C=O), 1604 (C=N), 1494 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.65–2.69 (m, 8H, CH_2N), 3.69–3.77 (m, 8H, CH_2O), 7.42–7.64 (m, 9H, Ph –H, Ar–H), 7.81 (s, 1H, =CH), 8.83 (s, 1H, =CHN), 11.24 (brs, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.4 (CH_2N), 56.1 (CH_2N), 63.2 (CH_2O), 64.1 (CH_2O), 116.4 (<u>C</u>–C=O), 118.9 (C–3_{aryl}), 121.1 (C–5_{aryl}), 122.3 (C–1_{aryl}), 124.3 (C–6_{aryl}), 126.6 (C–$5_{thiazole}$), 127.2 (=$CH_{exocyclic}$), 128.6 (C–$2,6_{phenyl}$), 128.9 (C–4_{phenyl}), 129.1 (C–$3,5_{phenyl}$), 133.1 (C–1_{phenyl}), 135.1 (C–4_{phenyl}), 143.2 (=CHN), 151.0 (C–2_{aryl}), 158.4 (C=N), 167.9 (C=O), 177.8 (C=O). MS (*m/z*, I%): 521 (M^+, 27%). Anal. Calcd for $C_{27}H_{28}N_4O_5S$ (520.60): C, 62.29%; H, 5.42%; N, 10.76%; S, 6.16%. Found: C, 62.10%; H, 5.23%; N, 10.58%; S, 5.97%.

General procedure for synthesis of the pyrazole derivatives 6-11.

A mixture of compound **3** (0.65 g, 1.5 mmol) and hydrazine compounds, namely hydrazine hydrate, methylhydrazine, phenylhydrazine, 4-nitrophenylhydrazine and 2,4-dinitro-phenylhydrazine (1.5 mmol) in absolute ethanol (20 ml), was heated under reflux for 4-6 hours. The formed solids during heating were filtered off and crystallized from DMF/ethanol.

Special method for synthesis of product 6. A mixture of 2-(morpholinoimino)-5-[(4-oxo-4*H*-chromen-3-yl)methylene]-3-phenylthiazolidin-4-one (**3**) (0.65 g, 1.5 mmol) and hydrazide compounds, namely semicarbazide, thiosemicarbazide and cyanoacetohydrazide (1.5 mmol) in absolute ethanol (20 ml) in the presence or absence of sodium ethoxide, was heated under reflux for 6 hours. The formed solid during heating in all cases, was filtered off and crystallized from DMF/ethanol.

5-[(3-(2-Hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene]-2-(morpholinoimino)-3-phenyl-thiazolidin-4-one (6). Yellow solid in 75% yield, mp 282–284 °C. IR (KBr), (*v* max, cm^{-1}): 3185 (OH), 3126 (NH), 3058, 3005 (C–H_{arom}), 2961, 2896 2855 (C–H_{aliph}), 1683 (C=O), 1623 (C=N), 1595 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.68 (s, 4H, CH_2N), 3.73 (s, 4H, CH_2O), 6.94 (t, 1H, *J*=7.6 Hz, H–5_{aryl}), 7.02 (d, 1H, *J*=8.0 Hz, H–3_{aryl}), 7.25 (d, 1H, *J*=7.2 Hz, H–6_{aryl}),

7.32 (t, 1H, *J*=7.6 Hz, H–4_{aryl}), 7.39 (d, 2H, *J*=7.6 Hz, Ph–H), 7.44 (d, 1H, *J*=7.2 Hz, Ph–H), 7.48–7.52 (m, 3H, Ph–H and =CH), 7.99 (brs, 1H, H–$5_{pyrazole}$), 10.06 (brs, 1H, OH), 13.48 (brs, 1H, NH). ^{13}C-NMR(100 MHz, DMSO-d_6): 53.8 (CH_2N), 64.2 (CH_2O), 117.8 (C–$4_{pyrazole}$), 118.9 (C–3_{aryl}), 119.9 (C–1_{aryl}), 120.9 (C–5_{aryl}), 126.6 (C–$5_{thiazole}$), 127.3 (=$CH_{exocyclic}$), 128.5 (C–$2,6_{phenyl}$), 128.9 (C–4_{phenyl}), 129.1 (C–$3,5_{phenyl}$), 131.7 (C–4_{aryl}), 132.3 (C–6_{aryl}), 133.1 (C–1_{phenyl}), 143.2 (C–$5_{pyrazole}$), 146.6 (C–$3_{pyrazole}$), 151.0 (C–2_{aryl}), 158.4 (C=N), 167.9 (C=O). MS (*m/z*, I%): 447 (M^+, 38%). Anal. Calcd for $C_{23}H_{21}N_5O_3S$ (447.51): C, 61.73%; H, 4.73%; N, 15.65%; S, 7.16%. Found: C, 61.54%; H, 4.55%; N, 15.48%; S, 6.97%.

5-{[3-(2-Hydroxyphenyl)-1-methyl-1*H*-pyrazol-4-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (7). White solid in 76% yield, mp 258–260 °C. IR (KBr), (*v* max, cm^{-1}): 3114 (OH), 3064 (C–H_{arom}), 2955, 2923, 2896, 2870, 2849 (C–H_{aliph}), 1707 (C=O), 1612 (C=N), 1581, 1539 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.70 (s, 4H, CH_2N), 3.74 (s, 4H, CH_2O), 4.01 (s, 3H, CH_3), 6.91 (t, 1H, *J*=7.6 Hz, Ar–H), 7.01 (d, 1H, *J*=8.0 Hz, Ar–H), 7.27–7.28 (m, 2H, Ar–H), 7.40–7.45 (m, 3H, Ph–H), 7.48–7.52 (m, 3H, Ph–H and =CH), 8.20 (s, 1H, H–$5_{pyrazole}$), 9.75 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 36.3 (NCH_3), 55.8 (CH_2N), 65.9 (CH_2O), 115.4 (C–3_{aryl}), 116.4 (C–$4_{pyrazole}$), 118.2 (C–5_{aryl}), 119.5 (C–1_{aryl}), 119.6 (C–$5_{thiazole}$), 123.5 (=$CH_{exocyclic}$), 128.5 (C–$2,6_{phenyl}$), 128.9 (C–4_{phenyl}), 129.5 (C–$3,5_{phenyl}$), 130.5 (C–6_{aryl}), 131.7 (C–1_{phenyl}), 131.8 (C–4_{aryl}), 135.4 (C–$5_{pyrazole}$), 150.9 (C–$2'_{aryl}$), 155.5 (C–$3_{pyrazole}$), 158.8 (C=N), 166.7 (C=O). MS (*m/z*, I%): 461 (M^+, 11%). Anal. Calcd for $C_{24}H_{23}N_5O_3S$ (461.21): C, 62.46%; H, 5.02%; N, 15.17%; S, 6.95%. Found: C, 62.27%; H, 4.83%; N, 14.98%; S, 6.75%.

5-{[5-(2-Hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (8). Yellow solid in 65% yield, mp 210–212 °C. IR (KBr), (*v* max, cm^{-1}): 3173 (C–H_{arom}), 2967, 2826, 2896, 2858 (C–H_{aliph}), 1715 (C=O), 1609 (C=N), 1595 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.70 (s, 4H, CH_2N), 3.75 (s, 4H, CH_2O), 6.87–6.94 (m, 2H, Ar–H), 7.13 (d, 1H, *J*=6.8 Hz, Ar–H), 7.21 (s, 1H, =CH), 7.32–7.45 (m, 9H, Ph–H and Ar–H), 7.50 (t, 2H, *J*=7.6 Hz, Ph–H), 8.18 (s, 1H, H–$3_{pyrazole}$), 9.93 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 56.5 (CH_2N), 66.0 (CH_2O), 115.5 (C–$4_{pyrazole}$), 116.6 (C–3_{aryl}), 117.8 (C–1_{aryl}), 119.8 (C–$5_{thiazole}$), 119.9 (C–5_{aryl}), 121.5 (=$CH_{exocyclic}$), 124.1 (C–$2',6'_{phenyl}$), 128.2 (C–$4'_{phenyl}$), 128.5 (C–$2,6_{phenyl}$), 129.0 (C–4_{phenyl}), 129.3 (C–$3',5'_{phenyl}$), 129.4 (C–$3,5_{phenyl}$), 131.9 (C–4_{aryl}), 132.3 (C–6_{aryl}), 135.3 (C–1_{phenyl}), 139.5 (C–$1'_{phenyl}$), 140.0 (C–$5_{pyrazole}$), 142.2 (C–$3_{pyrazole}$), 156.1 (C–2_{aryl}), 159.0 (C=N), 166.7 (C=O). MS (*m/z*, I%): 523 (M^+, 62%). Anal.

Calcd for $C_{29}H_{25}N_5O_3S$ (523.61): C, 66.52%; H, 4.81%; N, 13.81%; S, 6.12%. Found: C, 66.33%; H, 4.62%; N, 13.63%; S, 6.02%.

5-{[3-(2-Hydroxyphenyl)-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]methylene}-2-(morpholino-imino)-3-phenylthiazolidin-4-one (9). Yellow solid in 75% yield, mp 281–283 °C. IR (KBr), (ν max, cm^{-1}): 3205 (br, OH), 3040 (C–H_{arom}), 2973, 2925, 2893, 2846 (C–H_{aliph}), 1707 (C=O), 1613 (C=N), 1590, 1521 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.69 (t, 4H, J=4.4 Hz, CH_2N), 3.74 (t, 4H, J=4.8 Hz, CH_2O), 6.93 (d, 1H, J=8.4 Hz, Ar–H), 6.98 (t, 1H, J=7.6 Hz, Ar–H), 7.19 (s, 1H, =CH), 7.26 (dd, 1H, J=7.6 and 1.2 Hz, Ar–H), 7.37–7.45 (m, 4H, Ph–H and Ar–H), 7.50 (t, 2H, J=7.6 Hz, Ph–H), 7.57 (d, 2H, J=9.2 Hz, H–2',6'$_{aryl}$), 8.26 (d, 2H, J=9.2 Hz, H–3',5'$_{aryl}$), 8.30 (s, 1H, H–5$_{pyrazole}$), 9.99 (s, 1H, OH). ^{13}C-NMR (100MHz, DMSO-d_6): 53.2 (CH_2N), 64.8 (CH_2O), 111.8 (C–2',6'$_{aryl}$), 116.4 (C–3$_{aryl}$), 117.8 (C–4$_{pyrazole}$), 119.9 (C–1$_{aryl}$), 121.2 (C–5$_{aryl}$), 122.4 (C–3',5'$_{aryl}$), 126.6 (C–5$_{thiazole}$), 127.9 (=CH$_{exocyclic}$), 128.6 (C–2,6$_{phenyl}$), 129.1 (C–1$_{phenyl}$), 130.1 (C–3,5$_{phenyl}$), 131.6 (C–4$_{aryl}$), 132.3 (C–6$_{aryl}$), 135.1 (C–1$_{phenyl}$), 140.5 (C–4'$_{aryl}$), 143.2 (C–3$_{pyrazole}$), 144.9 (C–1'$_{aryl}$), 150.2 (C–2$_{aryl}$), 151.9 (C–5$_{pyrazole}$), 157.9 (C=N), 169.1 (C=O). MS (*m/z*, I%): 568 (M^+, 36%). Anal. Calcd for $C_{29}H_{24}N_6O_5S$ (568.94): C, 61.26%; H, 4.25%; N, 14.78%; S, 5.64%. Found: C, 61.07%; H, 4.07%; N, 14.59%; S, 5.45%.

5-{[1-(2,4-Dinitrophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (10). White solid in 80% yield, mp 266-267 °C. IR (KBr), (ν max, cm^{-1}): 3108, 3069 (C–H_{arom}), 2967, 2917, 2890, 2846, 2825 (C–H_{aliph}), 1711 (C=O), 1624 (C=N), 1607, 1598 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.68 (s, 4H, CH_2N), 3.73 (s, 4H, CH_2O), 7.43–7.57 (m, 9H, Ph–H, Ar–H and =CH), 7.65 (t, 1H, J=7.2 Hz, Ar–H), 7.76 (d, 1H, J=7.6 Hz, Ar–H), 8.09 (d, 1H, J=8.8 Hz, H–6`$_{aryl}$), 8.27 (dd, 1H, $J$=9.2 and 2.4 Hz, H–5`$_{aryl}$), 8.41 (s, 1H, H–3$_{pyrazole}$), 8.50 (d, 1H, J=2.4 Hz, H–3`$_{aryl}$). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.7 (CH_2N), 66.1 (CH_2O), 115.3 (C–6'$_{aryl}$), 116.7 (C–3$_{aryl}$), 118.6 (C–5$_{aryl}$), 119.3 (C–1$_{aryl}$), 119.8 (C–4$_{payrazole}$), 120.6 (C–5$_{thiazole}$), 122.3 (C–3'$_{aryl}$), 124.6 (=CH$_{exocyclic}$), 126.6 (C–5'$_{aryl}$), 128.6 (C–2,6$_{phenyl}$), 129.0 (C–4$_{phenyl}$), 129.6 (C–3,5$_{phenyl}$), 130.6 (C–4$_{aryl}$), 131.3 (C–6$_{aryl}$), 132.3 (C–1$_{phenyl}$), 137.4 (C–4`$_{aryl}$), 139.2 (C–2`$_{aryl}$), 141.2 (C–1`$_{aryl}$), 142.8 (C–3$_{payrazole}$), 144.8 (C–5$_{payrazole}$), 151.7 (C–2$_{aryl}$), 159.3 (C=N), 166.7 (C=O). MS (*m/z*, I%): 614 (M^+, 28%). Anal. Calcd for $C_{29}H_{23}N_7O_7S$ (613.87): C, 56.77%; H, 3.78%; N, 15.98%; S, 5.22%. Found: C, 56.58%; H, 3.60%; N, 15.79%; S, 5.12%.

Synthesis of 5-[(5-(2-hydroxyphenyl)isoxazol-4-yl)methylene]-2-(morpholinoimino)-3-phenylthiazolidin-4-one (11).

A mixture of compound **3** (0.65 g, 1.5 mmol) and hydroxylamine hydrochloride (0.11 g, 1.5 mmol) in ethanolic sodium ethoxide (0.1 g of Na metal in 20 ml of absolute ethanol), was heated under reflux for 6 hours. The mixture was poured into cold water and neutralized with diluted hydrochloric acid (10%). The formed solid was filtered off, washed with water and crystallized from methanol. Beige solid in 70% yield, mp >300 ^{o}C. IR (KBr), (ν max, cm^{-1}): 3081 (br, OH), 3023 (C–H$_{arom}$), 2921, 2864, 2840 (C–H$_{aliph}$), 1656 (C=O), 1613 (C=N), 1596, 1578 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.69 (s, 4H, CH_2N), 3.71 (s, 4H, CH_2O), 7.38–7.42 (m, 2H, Ar–H), 7.47–7.57 (m, 5H, Ph–H, =CH and Ar–H), 7.60–7.66 (m, 3H, Ph–H), 8.15 (s, 1H, H–3$_{oxazole}$), 9.30 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.3 (CH_2N), 64.1 (CH_2O), 115.1 (C–1$_{aryl}$), 117.7 (C–4$_{oxazole}$), 118.9 (C–3$_{aryl}$), 121.1 (C–5$_{aryl}$), 125.3 (C–6$_{aryl}$), 126.4 (C–5$_{thiazole}$), 127.8 (=CH$_{exocyclic}$), 128.6 (C–2,6$_{phenyl}$), 128.8 (C–4$_{phenyl}$), 129.1 (C–3,5$_{phenyl}$), 130.1 (C–4$_{aryl}$), 132.3 (C–1$_{phenyl}$), 151.0 (C–2$_{aryl}$), 154.9 (C–3$_{oxazole}$), 158.4 (C–5$_{oxazole}$), 159.4 (C=N), 169.1 (C=O). MS (*m/z*, I%): 446 (M^+, 38%). Anal. Calcd for $C_{23}H_{20}N_4O_4S$ (446.19): C, 61.60%; H, 4.50%; N, 12.49%; S, 7.15%. Found: C, 61.42%; H, 4.33%; N, 12.30%; S, 6.96%.

General procedure for synthesis of the pyrimidine derivatives 12-17.

A mixture of compound **3** (0.65 g, 1.5 mmol) and nitrogen 1,3-*bi*-nucleophilic reagents, namely urea, thiourea, selenourea, guanidine carbonate, 2-aminobenzimidazole and 3-amino-1*H*-1,2,4-triazole (1.5 mmol) in ethanolic sodium ethoxide (0.1 g of Na metal in 20 ml of absolute ethanol), was heated under reflux for 8-12 hours. The mixtures were poured into cold water and neutralized with diluted hydrochloric acid (10%). The formed solids were filtered off, washed with water and crystallized from ethanol or DMF/EtOH.

5-{[4-(2-Hydroxyphenyl)-2-oxo-1,2-dihydropyrimidin-5-yl]methylene}-2-(morpholino-imino)-3-phenylthiazolidin-4-one (12). Orange solid in 74% yield, mp 150–152 ^{o}C. IR (KBr), (ν max, cm^{-1}): 3444 (br, OH, NH), 3064, (C–H$_{arom}$), 2952, 2920, 2861, 2843 (C–H$_{aliph}$), 1717 (C=O$_{thiazolidinone}$), 1698 (C=O$_{pyrimidinone}$), 1645 (C=N), 1605, 1558 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.66 (t, 4H, J=4.4 Hz, CH_2N), 3.59 (t, 2H, J=5.2 Hz, CH_2O), 3.70 (t, 2H, J=4.8 Hz, CH_2O), 6.96–7.16 (m, 2H, Ar–H), 7.30–7.55 (m, 5H, Ph–H, =CH and Ar–H), 7.74–7.92 (m, 3H, Ph–H), 8.17 (d, 1H, J=1.2 Hz, H–6$_{pyrimidine}$), 8.84 (s, 1H, OH), 11.03 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.3 (CH_2N), 65.8 (CH_2O), 113.8 (C–5$_{pyrimidine}$), 118.3 (C–3$_{aryl}$), 118.9 (C–1$_{aryl}$), 120.6 (C–5$_{aryl}$), 125.9 (C–5$_{thiazole}$), 127.9 (=CH$_{exocyclic}$), 128.4 (C–2,6$_{phenyl}$),

129.2 (C–4_{phenyl}), 129.7 (C–$3,5_{phenyl}$), 130.7 (C–6_{aryl}), 132.3 (C–4_{aryl}), 135.1 (C–1_{phenyl}), 137.4 (C–$6_{pyrimidine}$), 151.7 (C–2_{aryl}), 157.4 (C–$4_{pyrimidine}$), 161.5 (C=N), 166.0 (C=$O_{thiazolidinone}$), 170.7 (C=$O_{pyrimidinone}$). MS (*m/z*, I%): 475 (M^+, 29%). Anal. Calcd for $C_{24}H_{21}N_5O_4S$ (475.32): C, 60.62%; H, 4.45%; N, 14.73%; S, 6.74%. Found: C, 60.43%; H, 4.27%; N, 14.54%; S, 6.56%.

5-{[4-(2-Hydroxyphenyl)-2-thioxo-1,2-dihydropyrimidin-5-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (13). Yellow solid in 60% yield, mp 220–221 °C. IR (KBr), (*v* max, cm^{-1}): 3126 (br, OH, NH), 3058 (C–H_{arom}), 2941, 2921, 2895, 2858, 2840 (C–H_{aliph}), 1726 (C=O), 1615 (C=N), 1601, 1585 (C=C), 1144 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.59–2.66 (m, 4H, CH_2N), 3.64–3.74 (m, 4H, CH_2O), 7.07 (d, 1H, *J*=8.4 Hz, H–3_{aryl}), 7.11 (t, 1H, *J*=7.6 Hz, H–5_{aryl}), 7.36 (d, 2H, *J*=7.6 Hz, Ph–H), 7.45–7.57 (m, 5H, Ph–H, H–4_{aryl} and =CH), 8.04 (d, 1H, *J*=7.6 Hz, H–6_{aryl}), 8.16 (s, 1H, H–$6_{pyrimidine}$), 10.52 (brs, 1H, OH), 13.87 (brs, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.2 (CH_2N), 65.8 (CH_2O), 111.6 (C–$5_{pyrimidine}$), 117.2 (C–3_{aryl}), 118.9 (C–1_{aryl}), 120.5 (C–5_{aryl}), 125.9 (C–$5_{thiazole}$), 126.7 (=$CH_{exocyclic}$), 128.4 (C–$2,6_{phenyl}$), 129.2 (C–4_{phenyl}), 129.7 (C–$3,5_{phenyl}$), 130.6 (C–6_{aryl}), 131.3 (C–4_{aryl}), 135.1 (C–1_{phenyl}), 136.1 (C–$6_{pyrimidine}$), 151.6 (C–2_{aryl}), 157.3 (C–$4_{pyrimidine}$), 157.9 (C=N), 161.5 (C=O), 181.1 (C=S). MS (*m/z*, I%): 493 (M^+, 70%). Anal. Calcd for $C_{24}H_{21}N_5O_3S_2$ (493.21): C, 58.64%; H, 4.31%; N, 14.25%; S, 13.04%. Found: C, 58.45%; H, 4.14%; N, 14.14%; S, 12.85%.

5-{[4-(2-Hydroxyphenyl)-2-selenoxo-1,2-dihydropyrimidin-5-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (14). Yellow solid in 65% yield, mp 250–252 °C. IR (KBr), (*v* max, cm^{-1}): 3188 (br, OH, NH), 3061 (C–H_{arom}), 2967, 2890, 2867, 2840 (C–H_{aliph}), 1719 (C=O), 1608 (C=N), 1591, 1558 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.63-2.67 (m, 4H, CH_2N), 3.67-3.72 (m, 4H, CH_2O), 6.94–7.01 (m, 2H, Ar–H), 7.34–7.37 (m, 3H, Ar–H and Ph–H), 7.44–7.57 (m, 5H, Ph–H and =CH), 7.81 (s, 1H, H–$6_{pyrimidine}$), 8.83 (s, 1H, OH), 10.50 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 54.2 (CH_2N), 65.8 (CH_2O), 109.7 (C–$5_{pyrimidine}$), 117.2 (C–3_{aryl}), 118.0 (C–1_{aryl}), 120.6 (C–5_{aryl}), 125.9 (C–$5_{thiazole}$), 127.9 (=$CH_{exocyclic}$), 128.6 (C–$2,6_{phenyl}$), 129.2 (C–4_{phenyl}), 129.7 (C–$3,5_{phenyl}$), 130.7 (C–6_{aryl}), 131.9 (C–4_{aryl}), 134.5 (C–1_{phenyl}), 137.1 (C–$6_{pyrimidine}$), 152.6 (C–2_{aryl}), 157.9 (C–$4_{pyrimidine}$), 158.9 (C=N), 163.4 (C=O), 180.1 (C=Se). MS (*m/z*, I%): 540 (M^+, 25%). Anal. Calcd for $C_{24}H_{21}N_5O_3Se$ (540.92): C, 53.53%; H, 3.93%; N, 13.01%; S, 5.95%. Found: C, 53.34%; H, 3.75%; N, 12.83%; S, 5.77%.

5-{[2-Amino-4-(2-hydroxyphenyl)pyrimidin-5-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (15). Yellow solid in 72% yield, mp188−189 °C. IR (KBr), (*v* max, cm^{-1}): 3474, 3343, 3199 (br, OH, NH_2), 3074 (C–H_{arom}), 2963, 2918, 2890, 2854, 2838 (C–H_{aliph}), 1717 (C=O), 1612 (C=N), 1602, 1527 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.66 (s, 4H, CH_2N), 3.70 (s, 4H, CH_2O), 7.35–7.59 (m, 9H, Ph–H and Ar–H), 8.34 (s, 1H, =CH), 8.57 (s, 1H, H–$6_{pyrimidine}$), 8.82 (s, 2H, NH_2), 10.10 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.8 (CH_2N), 65.9 (CH_2O), 119.1 (C–3_{aryl}), 120.3 (C–1_{aryl}), 122.1 (C–5_{aryl}), 123.4 (C–$5_{pyrimidine}$), 126.1 (C–$5_{thiazole}$), 126.7 (=$CH_{exocyclic}$), 128.5 (C–$2,6_{phenyl}$), 129.1 (C–4_{phenyl}), 129.5 (C–$3,5_{phenyl}$), 130.8 (C–4_{aryl}), 131.4 (C–6_{aryl}), 133.7 (C–1_{phenyl}), 155.9 (C–2_{aryl}), 156.9 (C–$4_{pyrimidine}$), 159.5 (C=N), 159.9 (C–$6_{pyrimidine}$), 163.9 (C–$2_{pyrimidine}$), 166.7 (C=O). MS (*m/z*, I%): 474 (M^+, 50%). Anal. Calcd for $C_{24}H_{22}N_6O_3S$ (474.67): C, 60.75%; H, 4.67%; N, 17.71%; S, 6.76%. Found: C, 60.56%; H, 4.49%; N, 17.51%; S, 6.58%.

5-{[4-(2-Hydroxyphenyl)benzo[4,5]imidazo[1,2-*a*]pyrimidin-3-yl]methylene-2-(morpholinoimino)-3-phenylthiazolidin-4-one (16). Brown solid in 74% yield, mp 200–202 °C. IR (KBr), (*v* max, cm^{-1}): 3135 (brs, OH), 3029 (C–H_{arom}), 2955, 2923, 2889, 2847 (C–H_{aliph}), 1716 (C=O), 1606 (C=N), 1590, 1575 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.69 (t, 4H, *J*=4.4 Hz, CH_2N), 3.73 (t, 4H, *J*=4.4 Hz, CH_2O), 6.44 (d, 1H, *J*=8.4 Hz, Ar–H), 7.16–7.21 (m, 3H, Ar–H), 7.29 (s, 1H, =CH), 7.40–7.52 (m, 7H, Ph–H and Ar–H), 7.65 (td, 1H, *J*=8.8 and 1.6 Hz, Ar–H), 7.91 (d, 1H, *J*=8.0 Hz, Ar–H), 9.20 (s, 1H, H–$2_{benzimidazopyrimidine}$), 10.33 (brs, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 54.6 (CH_2N), 65.3 (CH_2O), 114.3 (C–$6_{benzimidazopyrimidine}$), 115.6 (C–$3_{aryl}$), 118.9 (C–$5_{aryl}$), 120.0 (C–$1_{aryl}$), 121.2 (C–$9_{benzimidazopyrimidine}$), 122.3 (C–$7_{benzimidazopyrimidine}$), 122.9 (C–$8_{benzimidazopyrimidine}$), 124.2 (C–$3_{benzimidazopyrimidine}$), 125.7 (C–$5_{thiazole}$), 127.3 (=$CH_{exocyclic}$), 128.4 (C–$2,6_{phenyl}$), 129.3 (C–$4_{phenyl}$), 129.6 (C–$3,5_{phenyl}$), 130.6 (C–$4_{aryl}$), 131.5 (C–$6_{aryl}$), 132.8 (C–$1_{phenyl}$), 135.6 (C–$5a_{benzimidazopyrimidine}$), 139.6 (C–$9a_{benzimidazopyrimidine}$), 150.5 (C–$2_{aryl}$), 154.4 (C–$4_{benzimidazopyrimidine}$), 154.9 (C–$2_{benzimidazopyrimidine}$), 157.9 (C=N), 159.1 (C–$10a_{benzimidazopyrimidine}$), 166.1 (C=O). MS (*m/z*, I%): 548 (M^+, 27%). Anal. Calcd for $C_{30}H_{24}N_6O_3S$ (548.19): C, 65.68%; H, 4.41%; N, 15.32%; S, 5.84%. Found: C, 65.49%; H, 4.23%; N, 15.13%; S, 5.65%.

5-{[5-(2-Hydroxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyrimidin-6-yl]methylene}-2-(morpholino-imino)-3-phenylthiazolidin-4-one (17). Brown solid in 70% yield, mp 163−165 °C. IR (KBr), (*v* max, cm^{-1}): 3264 (brs, OH), 3073 (C–H_{arom}), 2964, 2925, 2890, 2855, 2834 (C–H_{aliph}),

1716 (C=O), 1608 (C=N), 1592, 1517 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.66 (t, 4H, *J*=4.8 Hz, CH_2N), 3.71 (t, 4H, *J*=4.0 Hz, CH_2O), 7.03 (t, 1H, *J*=7.6 Hz, Ar–H), 7.08 (d, 1H, *J*=8.4 Hz, Ar–H), 7.38 (s, 1H, =CH), 7.40–7.62 (m, 7H, Ph–H and Ar–H), 8.70 (s, 1H, H–$7_{triazolopyrimidine}$), 9.20 (s, 1H, H–$3_{triazolopyrimidine}$), 10.27 (brs, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.8 (CH_2N), 67.2 (CH_2O), 116.5 (C–3_{aryl}), 120.5 (C–1_{aryl}), 121.8 (C–5_{aryl}), 123.9 (C–$6_{triazolopyrimidine}$), 125.5 (C–$5_{thiazole}$), 126.3 (=$CH_{exocyclic}$), 128.5 (C–$2,6_{phenyl}$), 129.1 (C–4_{phenyl}), 129.6 (C–$3,5_{phenyl}$), 131.3 (C–4_{aryl}), 131.9 (C–6_{aryl}), 132.9 (C–1_{phenyl}), 150.6 (C–2_{aryl}), 153.6 (C–$5_{triazolopyrimidine}$), 154.3 (C–$7_{triazolopyrimidine}$), 155.9 (C–$3_{triazolopyrimidine}$), 159.1 (C=N), 160.7 (C–$8a_{triazolopyrimidine}$), 166.3 (C=O). MS (*m/z*, I%): 499 (M^+, 22%). Anal. Calcd for $C_{25}H_{21}N_7O_3S$ (499.99): C, 60.11%; H, 4.24%; N, 19.63%; S, 6.42%. Found: C, 59.92%; H, 4.05%; N, 19.45%; S, 6.24%.

Synthesis of 5-{(5-(2-Hydroxyphenyl)-2,3-dihydro-1*H*-1,4-diazepin-6-yl) methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (18).

A mixture of compound **3** (0.65 g, 1.5 mmol) and ethylenediamine (1.5 or 3 mmol) in absolute ethanol (20 ml), was heated under reflux for 8 hours. The formed solid after cooling in both cases, was filtered off and crystallized from ethanol to give yellow solid in 67% yield, mp 210–212 ^{o}C. IR (KBr), (*ν* max, cm^{-1}): 3311 (br, OH), 3223 (br, NH), 3094 (C–H_{arom}), 2969, 2920, 2899, 2863 (C–H_{aliph}), 1701 (C=O), 1604 (C=N), 1559, 1542 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.40 (t, 4H, *J*=4.0 Hz, $CH_2N_{diazepine}$), 2.68–2.73 (m, 4H, CH_2N), 3.65–3.71 (m, 4H, CH_2O), 4.11 (s, 1H, NH), 6.67 (t, 1H, *J*=8.0 Hz, Ar–H), 6.83 (d, 1H, *J*=8.0 Hz, Ar–H), 7.18–7.27 (m, 4H, Ph–H and Ar–H), 7.37 (t, 1H, *J*=7.6 Hz, Ar–H), 7.43 (d, 2H, *J*=7.6 Hz, Ph–H), 7.47 (s, 1H, =CH), 7.62 (s, 1H, H–$7_{diapezine}$), 9.43 (brs, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 51.9 (C–$2_{diapezine}$), 55.4 (CH_2N), 56.6 (C–$3_{diapezine}$), 64.1 (CH_2O), 102.2 (C–$6_{diapezine}$), 118.9 (C–3_{aryl}), 121.1 (C–5_{aryl}), 123.6 (C–1_{aryl}), 126.6 (C–$5_{thiazole}$), 127.9 (=$CH_{exocyclic}$), 128.5 (C–$2,6_{phenyl}$), 129.1 (C–4_{phenyl}), 130.1 (C–$3,5_{phenyl}$), 131.6 (C–6_{aryl}), 132.3 (C–1_{phenyl}), 135.1 (C–4_{aryl}), 140.4 (C–$7_{diapezine}$), 146.6 (C–$5_{diapezine}$), 151.0 (C–2_{aryl}), 159.5 (C=N), 169.1 (C=O). MS (*m/z*, I%): 476 (M^+, 9%). Anal. Calcd for $C_{25}H_{25}N_5O_3S$ (475.99): C, 63.14%; H, 5.30%; N, 14.73%; S, 6.74%. Found: C, 62.96%; H, 5.11%; N, 14.54%; S, 6.56%.

General procedure for synthesis of the seven-membered heterocyclic systems 19-21.

A mixture of compound **3** (0.65 g, 1.5 mmol) and nitrogen 1,4-*bi*-nucleophilic reagents, namely 2-aminothiophenol, 1,2-phenylenediamine and 2-aminophenol (1.5 mmol) in ethanolic sodium ethoxide (0.1 g of Na metal in 20 ml of absolute ethanol), was heated under reflux for

8-12 hours. The mixtures were poured into cold water and neutralized with diluted hydrochloric acid (10%). The formed solids were filtered off, washed with water and crystallized from DMF/ethanol.

5-{[4-(2-Hydroxyphenyl)benzo[*b*][1,4]thiazepin-3-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (19). Brown solid in 96% yield, mp 120−121 °C. IR (KBr), (*v* max, cm^{-1}): 3341 (br, OH), 3061 (C−H_{arom}), 2964, 2896, 2861, 2837 (C−H_{aliph}), 1716 (C=O), 1608 (C=N), 1578, 1522 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.64 (s, 4H, CH_2N), 3.60−3.68 (m, 4H, CH_2O), 6.84−7.15 (m, 3H, Ar−H), 7.17−7.22 (m, 1H, Ar−H), 7.37−7.56 (m, 6H, Ar−H and Ph−H), 7.72 (t, 1H, *J*=8.8 Hz, Ar−H), 7.78−7.82 (m, 1H, Ar−H), 7.99 (t, 1H, *J*=8.4 Hz, Ar−H), 8.09 (s, 1H, =CH), 8.17 (s, 1H, H−$2_{thiazepine}$), 9.39 (s, 1H, OH). MS (*m/z*, I%): 540 (M^+, 28%). Anal. Calcd for $C_{29}H_{24}N_4O_3S_2$ (540.13): C, 64.43%; H, 4.47%; N, 10.36%; S, 11.86%. Found: C, 64.24%; H, 4.29%; N, 10.17%; S, 11.67%.

5-{[4-(2-Hydroxyphenyl)-1*H*-benzo[*b*][1,4]diazepin-3-yl]methylene}-2-(morpholino-imino)-3-phenylthiazolidin-4-one (20). Brown solid in 64% yield, mp 260−261 °C. IR (KBr), (*v* max, cm^{-1}): 3346 (br, OH), 3232 (br, NH) 3061 (C−H_{arom}), 2961, 2864, 2843, (C−H_{aliph}), 1701 (C=O), 1606 (C=N), 1542 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.63−2.64 (m, 4H, CH_2N), 3.68 (t, 4H, *J*=3.6 Hz, CH_2N), 6.58−6.63 (m, 1H, Ar−H), 6.81 (t, 1H, *J*=8.8 Hz, Ar−H), 6.87−6.94 (m, 2H, Ar−H), 6.99−7.01 (m, 1H, Ar−H), 7.15 (t, 2H, *J*=6.8 Hz, Ar−H), 7.30−7.36 (m, 3H, Ph−H and Ar−H), 7.44−7.51 (m, 3H, Ph−H), 8.05 (s, 1H, =CH), 8.51 (s, 1H, H−$2_{diazepine}$), 9.28 (s, 1H, OH), 10.22 (s, 1H, NH). MS (*m/z*, I%): 524 (M^+, 44%). Anal. Calcd for $C_{29}H_{25}N_5O_3S$ (523.17): C, 66.52%; H, 4.81%; N, 13.38%; S, 6.12%. Found: C, 66.33%; H, 4.62%; N, 13.19%; S, 5.93%.

5-{[2-(2-Hydroxyphenyl)benzo[*b*][1,4]oxazepin-3-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (21). Brown solid in 86% yield, mp 185−187 °C. IR (KBr), (*v* max, cm^{-1}): 3252 (br, OH), 3073 (C−H_{arom}), 2955, 2914, 2890, 2840 (C−H_{aliph}), 1706 (C=O), 1601 (C=N), 1497 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.36 (t, 2H, *J*=4.4 Hz, CH_2N), 2.69 (t, 2H, *J*=4.4 Hz, CH_2N), 3.69 (t, 2H, *J*=5.2 Hz, CH_2O), 3.73 (t, 2H, *J*=5.2 Hz, CH_2O), 6.87−7.04 (m, 3H, Ar−H), 7.20−7.55 (m, 9H, Ph−H,=CH and Ar−H), 7.63 (d, 1H, *J*=8.4 Hz, Ar−H), 7.77 (t, 1H, *J*=7.6 Hz, Ar−H), 7.81 (s, 1H, H−$4_{benzoxazepine}$), 10.58 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 54.5 (CH_2N), 67.4 (CH_2O), 100.6 (C−$3_{benzoxazepine}$), 115.4 (C−$6_{benzoxazepine}$), 117.4 (C−3_{aryl}), 119.6 (C−1_{aryl}), 120.6 (C−$9_{benzooxazepine}$), 121.4 (C−5_{aryl}), 122.4 (C−$7_{benzooxazepine}$), 125.2 (C−$8_{benzooxazepine}$), 126.9 (C−$5_{thiazole}$), 127.7 (=$CH_{exocyclic}$), 128.5 (C−$2,6_{phenyl}$), 128.9 (C−4_{phenyl}),

129.5 (C–3,5$_{phenyl}$), 131.7 (C–4$_{aryl}$), 131.8 (C–6$_{aryl}$), 132.8 (C–1$_{phenyl}$), 137.9 (C–5a$_{benzoxazepine}$), 139.2 (C–9a$_{benzoxazepine}$), 150.2 (C–2$_{aryl}$), 153.8 (C–2$_{benzoxazepine}$), 154.7 (C–4$_{benzoxazepine}$), 159.5 (C=N), 166.0 (C=O). MS (*m/z*, I%): 524 (M^+, 20%). Anal. Calcd for $C_{29}H_{24}N_4O_4S$ (524.60): C, 66.40%; H, 4.61%; N, 10.68%; S, 6.11%. Found: C, 66.21%; H, 4.43%; N, 10.49%; S, 5.93%.

General procedure for synthesis of the pyran derivatives 22-24 and pyridine 25.

A mixture of compound **3** (0.65 g, 1.5 mmol) and acyclic carbon nucleophilic reagents, namely malononitrile, cyanoacetamide and cyanothioacetamide (1.5 mmol) in ethanolic sodium ethoxide (0.1 g of Na metal in 25 ml of absolute ethanol), was heated under reflux for 8-12 hours. In the case of malononitrile and cyanoacetamide, the mixtures were poured into cold water and neutralized with diluted hydrochloric acid (10%). The formed solids **22** and **23** were filtered off, washed with water and crystallized from DMF-EtOH. In case of using cyanothioacetamide, the former red solid **24** during heating was filtered off and washed with water. The filtrate solution was poured into cold water and neutralized with diluted hydrochloric acid (10%) to give the orange solid **25**. Both solids **24** and **25** were crystallized from DMF-ethanol.

6-(2-Hydroxyphenyl)-2-imino-5-{2-(morpholinoimino)-4-oxo-3-(phenylthiazolidin-5-ylidene)methyl}-2*H*-pyran-3-carbonitrile (22). Brown solid in 62% yield, mp 260–261 °C. IR (KBr), (*v* max, cm^{-1}): 3320 (br, OH), 3205 (br, NH), 3070 (C–H$_{arom}$) 2967, 2926, 2893, 2843 (C–H$_{aliph}$), 2189 (C ≡ N), 1719 (C=O$_{thiazole}$), 1654 (C=NH), 1607 (C=N), 1557 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.66 (t, 4H, *J*=4.0 Hz, CH_2N), 370 (t, 4H, *J*=4.4 Hz, CH_2O), 6.90 (d, 1H, *J*=7.6 Hz, Ar–H), 6.95 (t, 1H, *J*=7.6 Hz, Ar–H), 7.20–7.28 (m, 3H, Ph–H and Ar–H), 7.42–7.50 (m, 3H, Ph–H and =CH), 7.61 (d, 1H, *J*=8.0 Hz, Ph–H), 7.69 (d, 1H, *J*=8.8 Hz, Ar–H), 8.22 (s, 1H, H–4$_{pyran}$), 9.87 (brs, 1H, OH), 10.11 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.2 (CH_2N), 64.1 (CH_2O), 95.4 (C–3$_{pyran}$), 100.9 (C–5$_{pyran}$), 112.7 (C–1$_{aryl}$), 114.3 (C ≡ N), 118.9 (C–3$_{aryl}$), 120.1 (C–5$_{aryl}$), 123.1 (C–6$_{aryl}$), 127.0 (C–5$_{thiazole}$), 127.8 (=CH$_{exocyclic}$), 128.6 (C–2,6$_{phenyl}$), 128.8 (C–4$_{phenyl}$), 129.2 (C–3,5$_{phenyl}$), 130.1 (C–4$_{aryl}$), 132.3 (C–1$_{phenyl}$), 143.2 (C–4$_{pyran}$), 151.0 (C–2$_{aryl}$), 153.2 (C–6$_{pyran}$), 158.4 (C=N), 161.9 (C–2$_{pyran}$), 167.9 (C=O). MS (*m/z*, I%): 500 (M^+, 26%). Anal. Calcd for $C_{26}H_{21}N_5O_4S$ (500.46): C, 62.51%; H, 4.24%; N, 14.02%; S, 6.42%. Found: C, 62.32%; H, 4.06%; N, 13.84%; S, 6.23%.

6-(2-Hydroxyphenyl)-5-{2-(morpholinoimino)-4-oxo-3-(phenylthiazolidin-5-ylidene) methyl}-2-oxo-2*H*-pyran-3-carbonitrile (23). Yellow solid in 88% yield, mp 274–275 °C. IR (KBr), (*v* max, cm^{-1}): 3440 (br, OH), 3064 (C–H$_{arom}$) 2973, 2920, 2890, 2852 (C–H$_{aliph}$), 2222 (C ≡ N), 1719 (C=O), 1669 (C=O), 1653 (C=N), 1615, 1558 (C=C). ^{1}H-NMR (400 MHz,

DMSO-d_6): 2.66 (t, 4H, *J*=4.0 Hz, CH_2N), 3.70 (s, 4H, CH_2O), 7.05 (t, 1H, *J*=8.0 Hz, Ar–H), 7.23 (d, 1H, *J*=7.2 Hz, Ar–H), 7.36 (t, 1H, *J*=7.2 Hz, Ar–H), 7.41–7.60 (m, 5H, Ph–H), 7.74 (d, 1H, *J*=8.4 Hz, Ar–H), 8.17 (s, 1H, =CH), 8.86 (s, 1H, H–4_{pyran}), 9.71 (brs, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.5 (CH_2N), 64.8 (CH_2O), 102.0 (C–3_{pyran}), 108.1 (C–5_{pyran}), 112.6 (C–1_{aryl}), 114.1 (C ≡ N), 118.9 (C–3_{aryl}), 121.1 (C–5_{aryl}), 123.5 (C–6_{aryl}), 126.2 (C–$5_{thiazole}$), 127.2 (=$CH_{exocyclic}$), 128.6 (C–$2,6_{phenyl}$), 128.8 (C–4_{phenyl}), 129.2 (C–$3,5_{phenyl}$), 130.1 (C–4_{aryl}), 133.2 (C–1_{phenyl}), 150.2 (C–2_{aryl}), 153.3 (C–4_{pyran}), 155.8 (C–6_{pyran}), 158.4 (C=N), 167.9 (C=O), 172.6 (C–2_{pyran}). MS (*m/z*, I%): 501 (M^+, 49%). Anal. Calcd for $C_{26}H_{20}N_4O_5S$ (501.68): C, 62.39%; H, 4.03%; N, 11.19%; S, 6.41%. Found: C, 62.20%; H, 3.84%; N, 11.00%; S, 6.23%.

6-(2-Hydroxyphenyl)-5-(*Z*/*E*)-{[2-oxo-2*H*-pyran-3-carbothioamido-5-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (24). Brown solid in 40% yield, mp >300 °C. IR (KBr), (*v* max, cm^{-1}): 3364, 3238 (OH, NH_2), 3055 (C–H_{arom}), 2970, 2920, 2887, 2852, 2831 (C–H_{aliph}), 1716 (C=O), 1689 (C=O), 1611 (C=N), 1568, 1549 (C=C), 1211 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.62 (s, 4H, CH_2N), 2.69 (s, 4H, CH_2N), 3.61 (s, 4H, CH_2O), 3.75 (s, 4H, CH_2O), 7.01 (d, 1H, *J*=8.0 Hz, Ar–H), 7.37–7.58 [m, 20H, Ar–H (4*H*), Ph–H (10*H*), and =CH (2*H*) and NH_2 (4*H*)], 7.70 (t, 1H, *J*=7.2 Hz, Ar–H), 8.01 (d, 1H, *J*=7.6 Hz, Ar–H), 8.17 (d, 1H, *J*=7.2 Hz, Ar–H), 8.08 (s, 1H, H–4_{pyran}), 8.24 (s, 1H, H–4_{pyran}), 8.44 (s, 1H, OH), 8.89 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 54.5, 55.8 (CH_2N), 65.3, 65.8 (CH_2O), 105.5, 105.9 (C–5_{pyran}), 112.1, 112.8 (C–3_{pyran}), 116.4, 116.7 (C–3_{aryl}), 118.5, 118.9 (C–1_{aryl}), 120.1, 120.7 (C–5_{aryl}), 126.3, 126.6 (C–$5_{thiazole}$), 127.3, 127.5 (=$CH_{exocyclic}$), 128.4, 128.7 (C–$2,6_{phenyl}$), 129.0, 129.3 (C–4_{phenyl}), 129.6, 129.9 (C–$3,5_{phenyl}$), 130.1, 130.2 (C–4_{aryl}), 131.6, 131.8 (C–6_{aryl}), 132.4, 132.8 (C–1_{phenyl}), 139.1, 139.9 (C–4_{pyran}), 150.5, 150.8 (C–2_{aryl}), 152.2, 152.8 (C–6_{pyran}), 159.1, 159.7 (C=N), 161.2, 161.9 (C=O), 166.1, 167.0 (C=$O_{thiazole}$), 180.5, 180.9 (C=S). MS (*m/z*, I%): 534 (M^+, 28%). Anal. Calcd for $C_{26}H_{22}N_4O_5S_2$ (534.65): C, 58.41%; H, 4.15%; N, 10.48%; S, 11.99%. Found: C, 58.23%; H, 3.97%; N, 10.30%; S, 11.80%.

6-(2-Hydroxyphenyl)-5-{[3-cyano-2-thioxo-2,3-dihydropyridine-5-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (25). Red solid in 44% yield, mp >300 °C. IR (KBr), (*v* max, cm^{-1}): 3067 (C–H_{arom}), 2967, 2919, 2884, 2855, 2846 (C–H_{aliph}), 1717 (C=O), 2225 (C ≡ N), 1608 (C=N), 1581, 1558 (C=C), 1207 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.51–2.68 (m, 4H, CH_2N), 3.68–3.71 (t, 4H, *J*=4.8 Hz, CH_2O), 6.11 (d, 1H, *J*=3.2 Hz, H–$3_{pyridine}$), 7.33–7.37 (m, 3H, Ar–H and Ph–H), 7.41–7.48 (m, 4H, Ph–H and =CH),

7.50–7.56 (m, 3H, Ph–H and Ar–H), 8.28 (d, 1H, *J*=3.2 Hz, H–$4_{pyridine}$), 10.45 (brs, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 45.9 (C–$3_{pyridine}$), 54.5 (CH_2N), 65.3 (CH_2O), 113.4 (C ≡ N), 118.9 (C–3_{aryl}), 120.1 (C–1_{aryl}), 121.8 (C–5_{aryl}), 123.4 (C–$4_{pyridine}$), 124.2 (C–$5_{pyridine}$), 126.3 (C–$5_{thiazole}$), 127.5 (=$CH_{exocyclic}$), 128.5 (C–$2,6_{phenyl}$), 129.0 (C–4_{phenyl}), 129.6 (C–$3,5_{phenyl}$), 130.7 (C–4_{aryl}), 131.5 (C–6_{aryl}), 132.9 (C–1_{phenyl}), 150.6 (C–2_{aryl}), 155.5 (C–$6_{pyridine}$), 159.2 (C=N), 166.1 (C=O), 183.1 (C=S). MS (*m/z*, I%): 515 (M^+, 14%). Anal. Calcd for $C_{26}H_{21}N_5O_3S_2$ (515.13): C, 60.57%; H, 4.11%; N, 13.58%; S, 12.44%. Found: C, 60.39%; H, 3.93%; N, 13.40%; S, 12.25%.

General procedure for synthesis of the pyran derivatives 26-29.

A mixture of compound **3** (0.65 g, 1.5 mmol) and cyclic carbon nucleophilic reagents, namely dimedone, 3-phenyl-1,4-dihydro-5H-pyrazol-5-one, barbituric acid and thiobarbituric acid (1.5 mmol) in ethanolic sodium ethoxide (0.1 g of Na metal in 25 ml of absolute ethanol), was heated under reflux for 10-12 hours. The mixture reactions were poured into cold water and neutralized with diluted hydrochloric acid (10%). The isolated solids were filtered off, washed with water and crystallized from DMF-ethanol.

5-{[2-(2-Hydroxyphenyl)-7,7-dimethyl-5-oxo-6,7-dihydro-5*H*-chromen-3-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (26). Orange solid in 69% yield, mp 263–264 °C. IR (KBr), (*ν* max, cm^{-1}): 3064 (C–H_{arom}), 2964, 2923, 2890, 2837 (C–H_{aliph}), 1713 (C=O), 1651 (C=O), 1612 (C=N), 1594, 1557 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 1.31 (s, 6H, CH_3), 2.66 (t, 4H, *J*=4.4 Hz, CH_2N), 2.89 (s, 2H, H–$6_{chromene}$), 3.70 (t, 4H, *J*=4.8 Hz, CH_2O), 6.19 (s, 1H, H–$8_{chromen}$), 7.42–7.48 (m, 4H, Ph–H and Ar–H), 7.51–7.55 (m, 2H, Ph–H), 7.59 (t, 2H, *J*=7.2 Hz, Ph–H), 7.74 (d, 1H, *J*=8.4 Hz, Ar–H), 7.88 (s, 1H, =CH), 8.17 (s, 1H, H–$4_{chromene}$), 10.46 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 22.6 (CH_3), 22.9 (CH_3), 31.3 (C–$7_{chromene}$), 52.5 (C–$6_{chromene}$), 55.8 (CH_2N), 65.9 (CH_2O), 111.0 (C–$3_{chromene}$), 112.3 (C–1_{aryl}), 119.0 (C–3_{aryl}), 122.1 (C–5_{aryl}), 123.4 (C–6_{aryl}), 126.0 (C–$5_{thiazole}$), 126.7 (=$CH_{exocyclic}$), 128.5 (C–$2,6_{phenyl}$), 129.0 (C–4_{phenyl}), 129.5 (C–$3,5_{phenyl}$), 130.7 (C–4_{aryl}), 133.5 (C–1_{phenyl}), 134.1 (C–$8_{chromene}$), 135.3 (C–$4_{chromene}$), 135.4 (C–$4a_{chromene}$), 146.5 (C–$2_{chromene}$), 150.4 (C–2_{aryl}), 155.9 (C–$8a_{chromene}$), 159.5 (C=N), 159.9 (C=O), 166.7 (C=O). MS (*m/z*, I%): 555 (M^+, 18%). Anal. Calcd for $C_{31}H_{29}N_3O_5S$ (555.46): C, 67.01%; H, 5.26%; N, 7.56%; S, 5.77%. Found: C, 66.82%; H, 5.07%; N, 7.38%; S, 5.59%.

5-{(6-(2-Hydroxyphenyl)-3-phenylpyrano[2,3-*c*]pyrazol-5-yl)methylene{-2-(morpholino-imino)-3-phenylthiazolidin-4-one (27). Brown solid in 89% yield, mp 283–284 °C. IR (KBr), (*ν* max, cm^{-1}): 3205 (br, OH), 3038 (C–H_{arom}), 2964, 2920, 2887, 2855, 2843 (C–H_{aliph}), 1725

(C=O), 1608 (C=N), 1524 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.66 (t, 4H, J=3.6 Hz, CH_2N), 3.70–3.74 (m, 4H, CH_2O), 6.91 (d, 2H, J=8.0 Hz, Ph–H), 6.99 (t, 1H, J=7.2 Hz, Ar–H), 7.13–7.21 (m, 3H, Ph–H and Ar–H), 7.28–7.38 (m, 6H, Ar–H, Ph–H and =CH), 7.47 (t, 1H, J=7.6 Hz, Ar–H), 7.59 (t, 2H, J=8.4 Hz, Ph–H), 8.15 (s, 1H, H–4_{pyran}), 9.60 (brs, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.4 (CH_2N), 64.8 (CH_2O), 105.7 (C–$5_{pyranopyrazole}$), 111.0 (C–1_{aryl}), 112.7 (C–$3_{pyranopyrazole}$), 116.4 (C–3_{aryl}), 119.9 (C–5_{aryl}), 122.3 (C–6_{aryl}), 125.3 (C–$3`,5`_{phenyl}$), 126.6 (C–$5_{thiazole}$), 127.2 (=$CH_{exocyclic}$), 128.6 (C–$2,6_{phenyl}$), 128.9 (C–4_{phenyl}), 129.1 (C–$3,5_{phenyl}$), 129.7 (C–$2`,6`_{phenyl}$), 130.1 (C–4_{aryl}), 131.6 (C–$4`_{phenyl}$), 133.1 (C–$1_{phenyl}$), 135.5 (C–$1`_{phenyl}$), 139.5 (C–4_{pyran}), 148.2 (C–$3_{pyrazole}$), 150.2 (C–2_{aryl}), 153.9 (C–$6_{pyranopyrazole}$), 156.7 (C–$7a_{pyranopyrazole}$), 159.4 (C=N), 169.1 (C=O). MS (*m/z*, I%): 575 (M^+, 22%). Anal. Calcd for $C_{32}H_{25}N_5O_4S$ (575.07): C, 66.77%; H, 4.38%; N, 12.17%; S, 5.57%. Found: C, 66.58%; H, 4.20%; N, 11.98%; S, 5.39%.

5-{[7-(2-Hydroxyphenyl)-2,4-dioxo-2*H*,*3H*-pyrano[2,3-*d*]pyrimidin-6-yl]methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (28). Brown solid in 66% yield, mp 264–265 ^{o}C. IR (KBr), (v max, cm^{-1}): 3288 (brs, NH, OH), 3076 (C–H_{arom}), 2958, 2964, 2923, 2893, 2893, 2855, (C–H_{aliph}), 1716 (C=O), 1671 (C=O), 1651 (C=O), 1610 (C=N), 1550 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.66 (t, 4H, J=4.8 Hz, CH_2N), 3.70 (t, 4H, J=4.4 Hz, CH_2O), 6.94–7.01 (m, 1H, Ar–H), 7.42–7.59 (m, 7H, Ph–H and Ar–H), 7.89 (t, 1H, J=7.2 Hz, Ar–H), 8.46 (s, 1H, =CH), 8.84 (s, 1H, H–$5_{pyranopyrimidine}$), 9.08 (s, 1H, OH), 10.46 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.5 (CH_2N), 66.5 (CH_2O), 104.5 (C–$6_{pyranopyrimidine}$), 113.3 (C–1_{aryl}), 119.5 (C–3_{aryl}), 120.6 (C–$4a_{pyranopyrimidine}$), 121.4 (C–5_{aryl}), 123.5 (C–6_{aryl}), 126.4 (C–$5_{thiazole}$), 127.6 (=$CH_{exocyclic}$), 128.6 (C–$2,6_{phenyl}$), 128.9 (C–4_{phenyl}), 129.2 (C–$3,5_{phenyl}$), 129.9 (C–4_{aryl}), 131.6 (C–1_{phenyl}), 140.1 (C–$5_{pyranopyrimidine}$), 151.7 (C–2_{aryl}), 153.2 (C–$7_{pyranopyrimidine}$), 155.6 (C–$8a_{pyranopyrimidine}$), 158.6 (C=N), 160.9 (C=O), 162.7 (C=O), 167.7 (C=$O_{thiazole}$). MS (*m/z*, I%): 543 (M^+, 33%). Anal. Calcd for $C_{27}H_{21}N_5O_6S$ (543.29): C, 59.66%; H, 3.89%; N, 12.88%; S, 5.90%. Found: C, 59.47%; H, 3.71%; N, 12.70%; S, 5.71%.

5-{[7-(2-Hydroxyphenyl)-4-oxo-2-thioxo-2,3-dihydro-4H-pyrano[2,3-*d*]pyrimidin-6-yl] methylene}-2-(morpholinoimino)-3-phenylthiazolidin-4-one (29). Orange solid in 66% yield, mp >300 ^{o}C. IR (KBr), (v max, cm^{-1}): 3264 (brs, OH), 3167 (brs, NH), 3093 (C–H_{arom}), 2964, 2890, 2894 (C–H_{aliph}), 1710 (C=O), 1654 (C=O), 1615 (C=N), 1555 (C=C), 1299 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.73 (s, 4H, CH_2N), 3.70 (s, 4H, CH_2O), 6.88 (t, 1H, J=8.4 Hz, Ar–H), 7.29–7.64 (m, 7H, Ph–H and Ar–H), 7.81 (d, 1H, J=7.6 Hz, Ar–H), 7.95 (s, 1H,

=CH), 8.19 (s, 1H, H–$5_{pyranopyrimidine}$), 9.49 (s, 1H, OH), 11.12 (brs, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 55.2 (CH_2N), 67.8 (CH_2O), 105.5 (C–$6_{pyranopyrimidine}$), 118.5 (C–3_{aryl}), 120.1 (C–1_{aryl}), 121.2 (C–$4a_{pyranopyrimidine}$), 122.3 (C–5_{aryl}), 126.5 (C–$5_{thiazole}$), 127.4 (=$CH_{exocyclic}$), 128.5 (C–$2,6_{phenyl}$), 129.2 (C–4_{phenyl}), 129.7 (C–$3,5_{phenyl}$), 130.7 (C–4_{aryl}), 131.5 (C–6_{aryl}), 132.4 (C–1_{phenyl}), 141.4 (C–$5_{pyranopyrimidine}$), 150.6 (C–2_{aryl}), 152.2 (C–$7_{pyranopyrimidine}$), 155.4 (C–$8a_{pyranopyrimidine}$), 159.2 (C=N), 162.5 (C=O), 166.1 (C=O), 177.6 (C=S). MS (*m/z*, I%): 560 (M^+, 50%). Anal. Calcd for $C_{27}H_{21}N_5O_5S_2$ (559.60): C, 57.95%; H, 3.78%; N, 12.31%; S, 11.46%. Found: C, 57.77%; H, 3.60%; N, 12.13%; S, 11.27%.

In Vitro Cytotoxicity

The American type of culture collection (ATCC) provided human cell lines for human breast cancer cells (MCF-7), human liver cancer cells (HepG-2), and Human ovary cancer cells (SKOV-3). A humidified, 5% (v/v) CO_2 atmosphere was used to culture the cells at 37 ^oC in RPMI-1640 supplemented with (100 μg/mL); penicillin (100 units/mL); and heat-inactivated fetal bovine serum (10% v/v) [27].

Cytotoxicity Assay

Using the sulphorhodamine B (SRB) assay, the cytotoxicity of the synthesized compounds against (MCF-7, HEPG-2 and SKOV-3) human tumor cells was assessed. Before being treated with the synthesized compounds, cells that were growing at 80% confluency, trypsinized and cultured in a 96-well tissue culture plate for 24 h. Cells were subjected to six different doses of each chemical (0.01, 0.1, 1, 10, and 1000 μg/mL) with untreated cells added as a control. Before the cells were fixed with TCA (10% w/v) for an hour at 4 ^oC, they were exposed to concentrations for 72 h. After multiple washings, cells were stained with a 0.4% (w/v) SRB solution for 10 min in the dark. The surplus stain was eliminated using 1% (v/v) glacial acetic acid. The SRB-stained cells were dissolved in Tris-HCl buffer after drying overnight. A microplate reader was used to gauge the color intensity at 540 nm. Sigma Plot 12.0 software was used to examine the association between each tumor cell line's viability percentage and compound concentrations in order to determine the IC50 (drug dose that reduces survival to 50%) [27].

Apoptosis Analysis

MCF-7, HepG-2 and SKOV-3 cells were treated for 48 h with the **7**, **11**, **12**, **15**, **19**, **22**, **26** and **28** before being trypsinized and subjected to two PBS washes. According to the manufacturer, apoptosis was evaluated using Alexa Fluor-488/PI staining Apoptosis Detection Kit, Cell Signaling Technology (CST). Briefly, cells were gently mixed with 0.5 ML of binding

buffer for 15 min at room temperature in a dark area after being resuspended in 5 μL of Alexa Fluor-488 of PI (staining solution), and 5 μL of binding buffer [32]. The cells were then subjected to a FACS analysis using a Cytek®Northern Lights 2000 spectral flow cytometer and SpectroFloTM Software version 2.2.0.3 (Cytek Biosciences, Fremont, CA, USA).

Cell Cycle Analysis

The IC_{50} values for the products **7**, **11**, **12**, **15**, **19**, **22**, **26** and **28** were pre-calculated and administered to (MCF-7, HepG-2 and SKOV-3) cells for 48 h. The cells were then fixed in ice-cold 60% ethanol at 40 ºC and trypsinized before being washed twice in phosphate buffered saline. After being resuspended, the cells were incubated for 15 min in 500 L of Cell Signaling Technology's (CST) propidium iodide with RNase staining buffer. In order to evaluate the data from 10,000 cells and the distribution of cell cycle phases for each sample, FACS analysis was completed using a Cytek®Northern Lights 2000 spectral flow cytometer (Cytek Biosciences, Fremont, CA, USA) and SpectroFloTM Software version 2.2.0.3 (Cytek Biosciences, Fremont, CA, USA), both of which are available from the United States [33].

Molecular Docking

The bioactive compounds were subject to docking study to explore their binding mode towards murine double minute 2 (MDM2) (PDB ID: 4j3e) receptors protein which were downloaded from protein data bank. All ligands and receptor were prepared for docking with rigid protein geometry using Auto Dock Tools version 1.5.6 [36-38]. The docking cavities were defined according to the interactions of protein with the co-crystalized ligands which are also used as reference ligand. The grid bx with dimensions of $18 \times 16 \times 18$ points, with 1.0 Å spacing were placed to make the entire binding cavities involved. The co-crystalized ligands were redocked to the receptor to validate the docking parameters. Docking was performed using AutoDockVina [39,40]. The 2D and 3D images were generated by Discovery Studio and Chimera [41].

3. Copies of NMR Spectra for all the synthesized Compounds

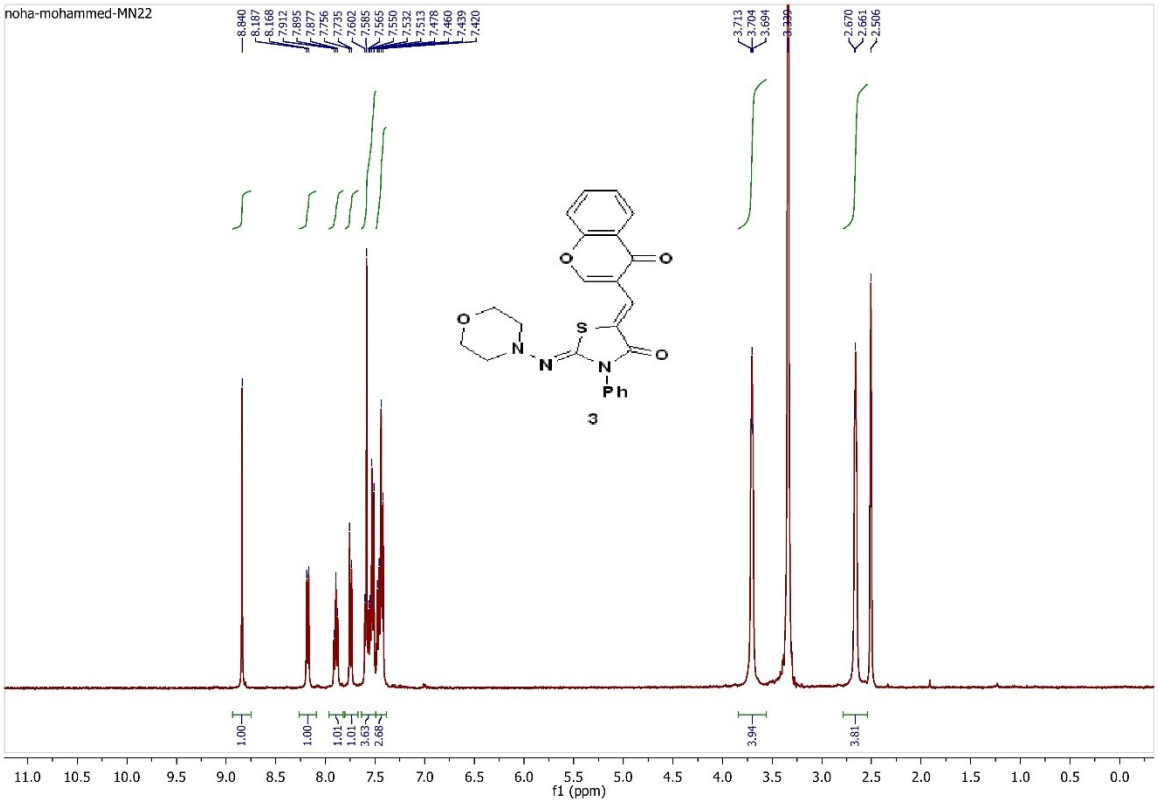


Figure S1: The ^{1}H-NMR spectrum of compound **3**.

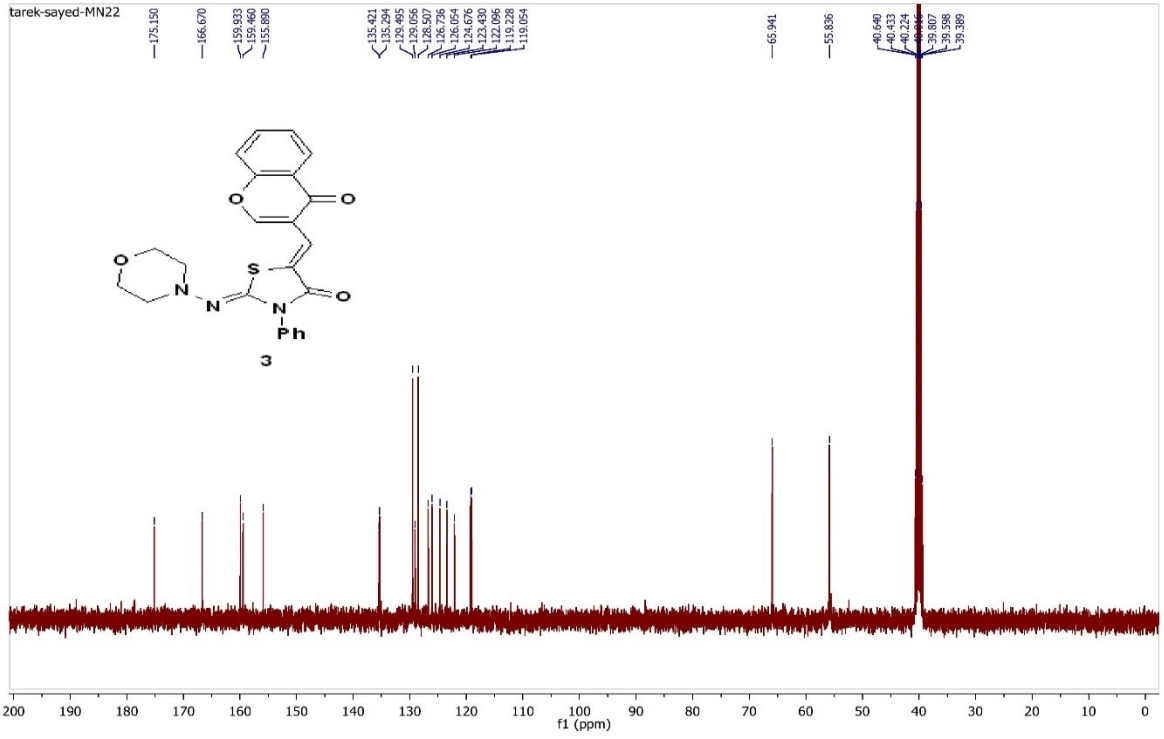


Figure S2: The ^{13}C-NMR spectrum of compound **3**.

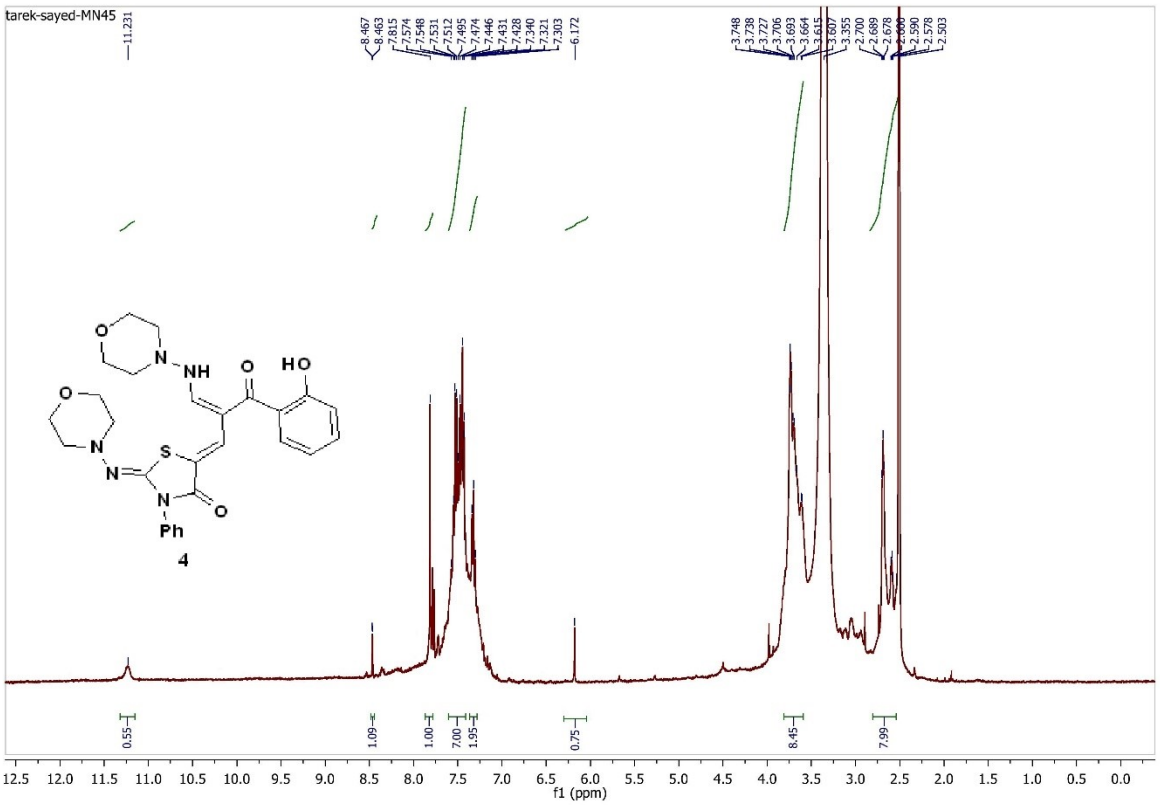


Figure S3: The ^{1}H-NMR spectrum of compound **4**.

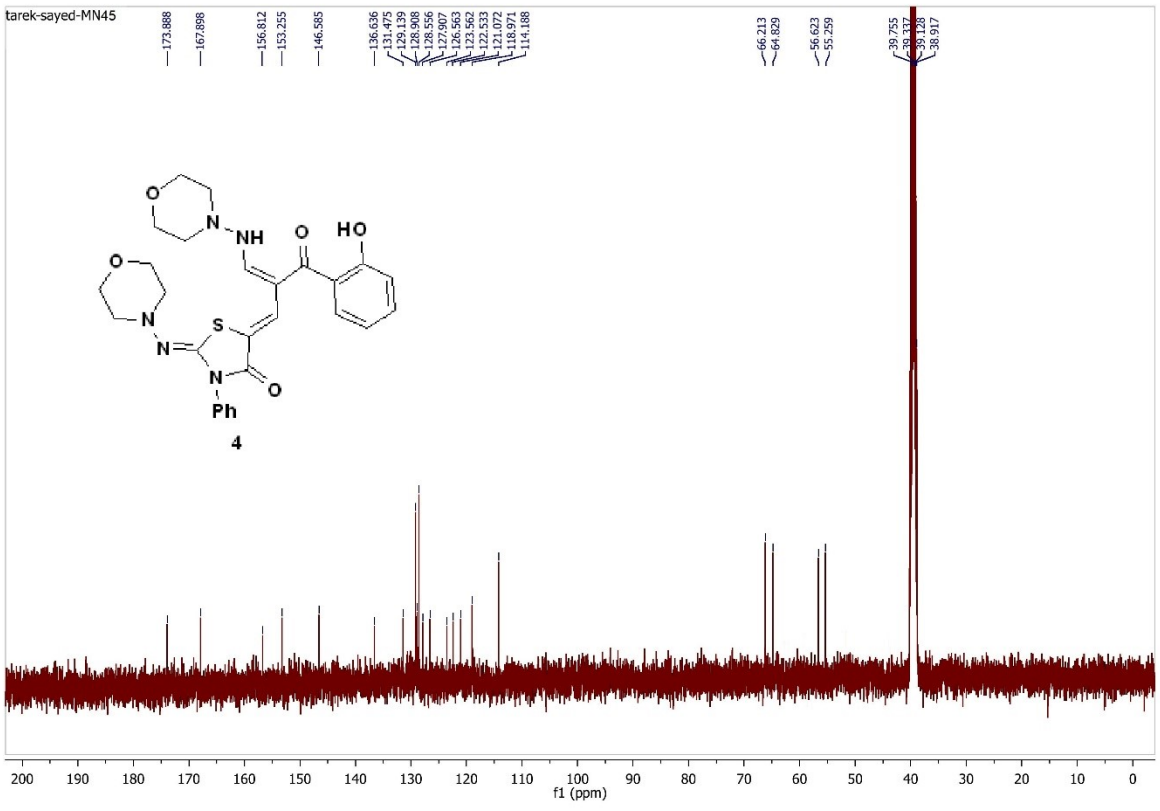


Figure S4: The ^{13}C-NMR spectrum of compound **4**.

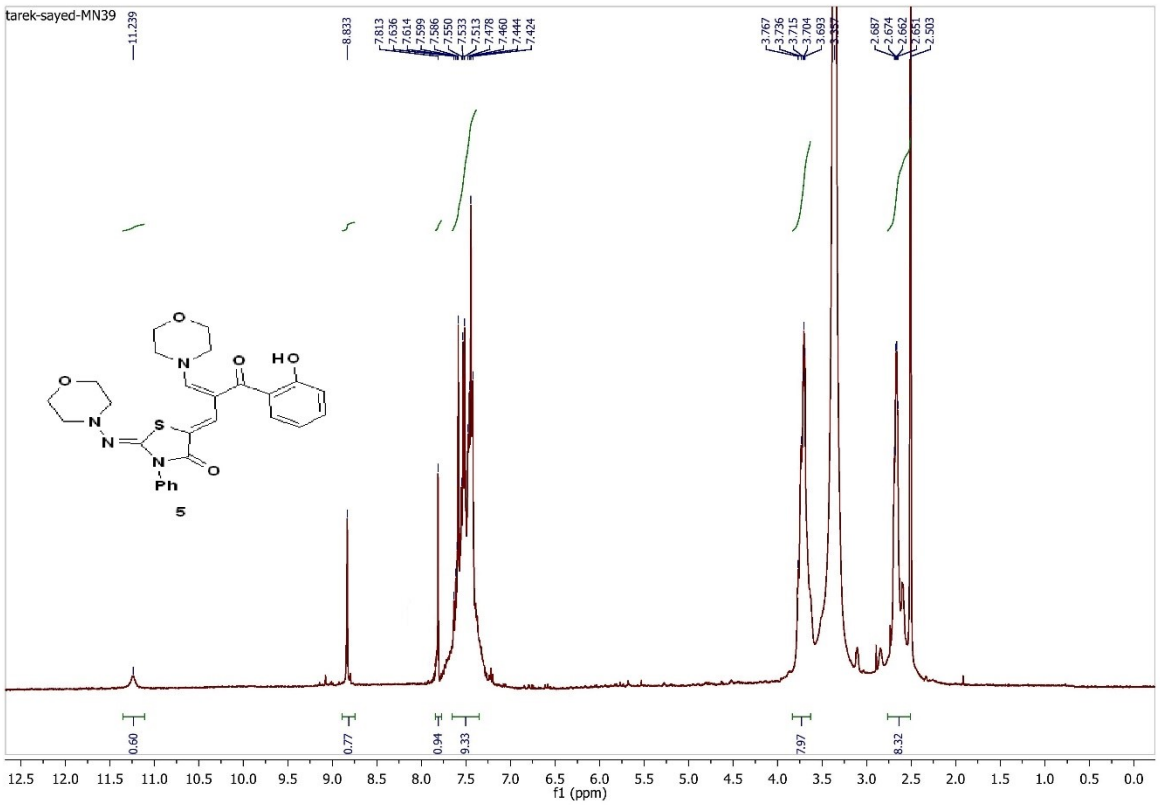


Figure S5: The ^{1}H-NMR spectrum of compound **5**.

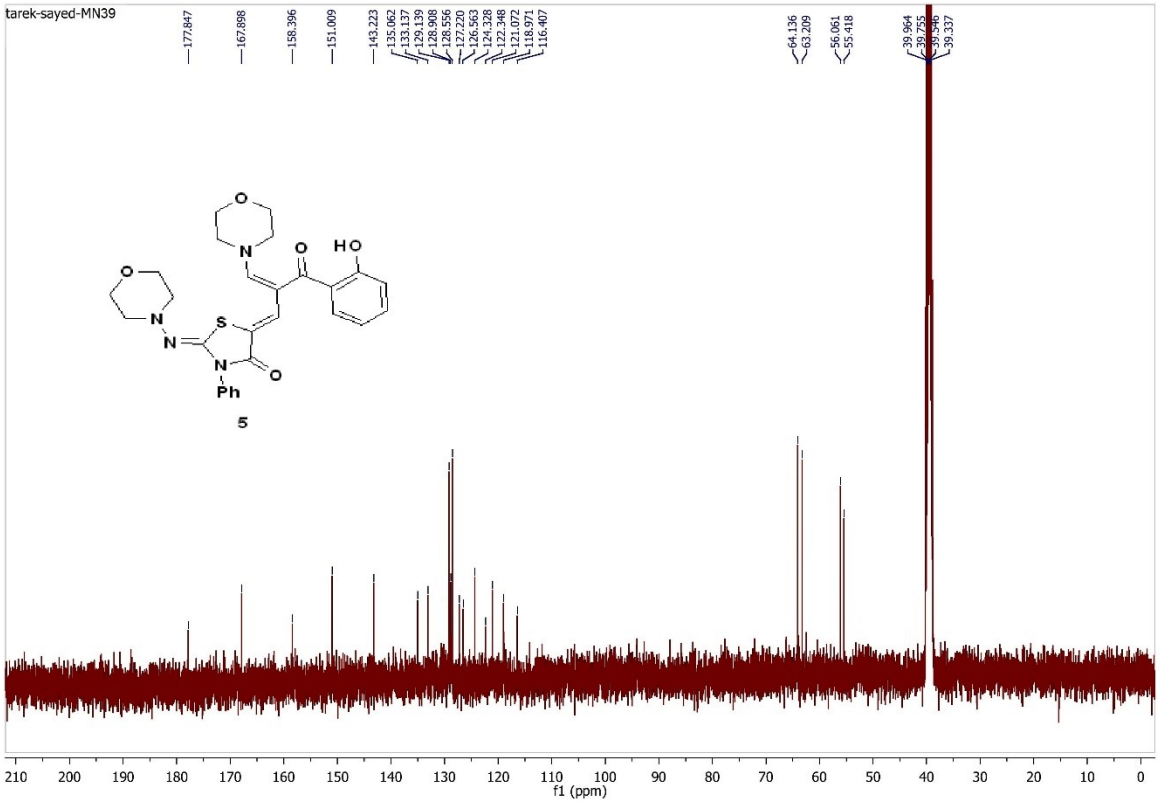


Figure S6: The ^{13}C-NMR spectrum of compound **5**.

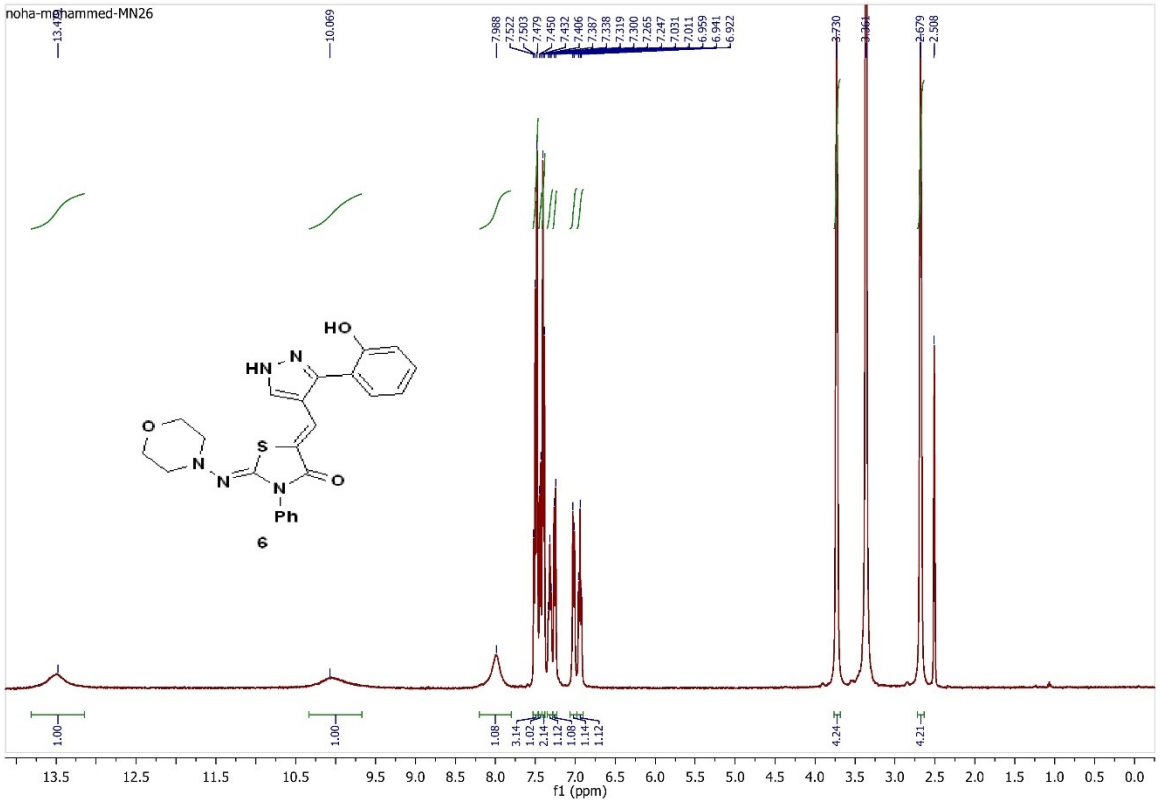


Figure S7: The ^{1}H-NMR spectrum of compound **6**.

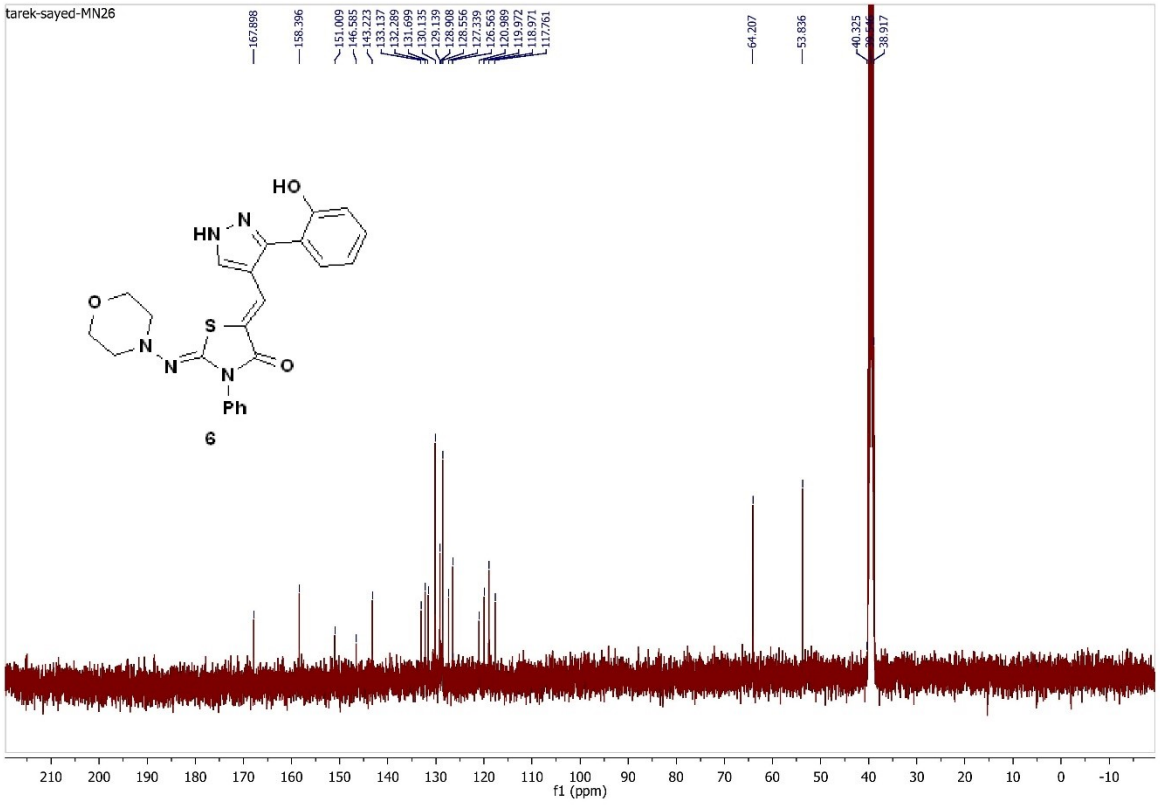


Figure S7: The ^{13}C-NMR spectrum of compound **6**.

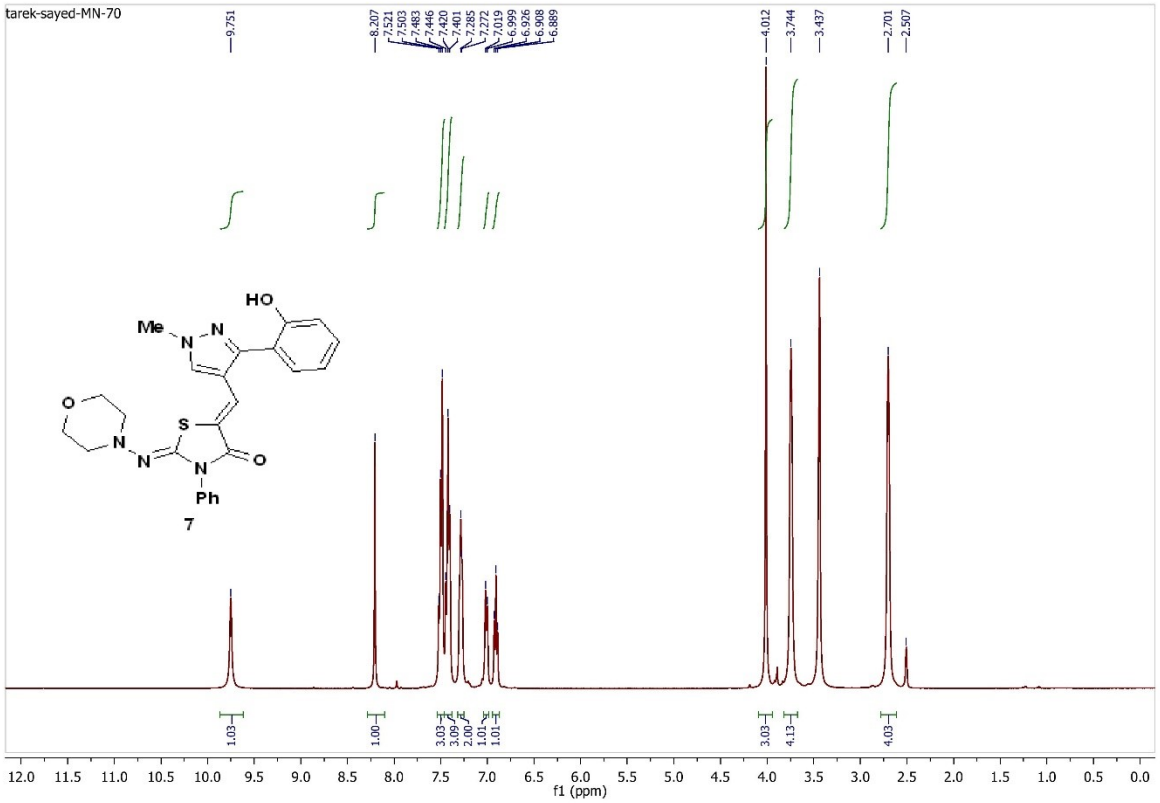


Figure S9: The ^{1}H-NMR spectrum of compound **7**.

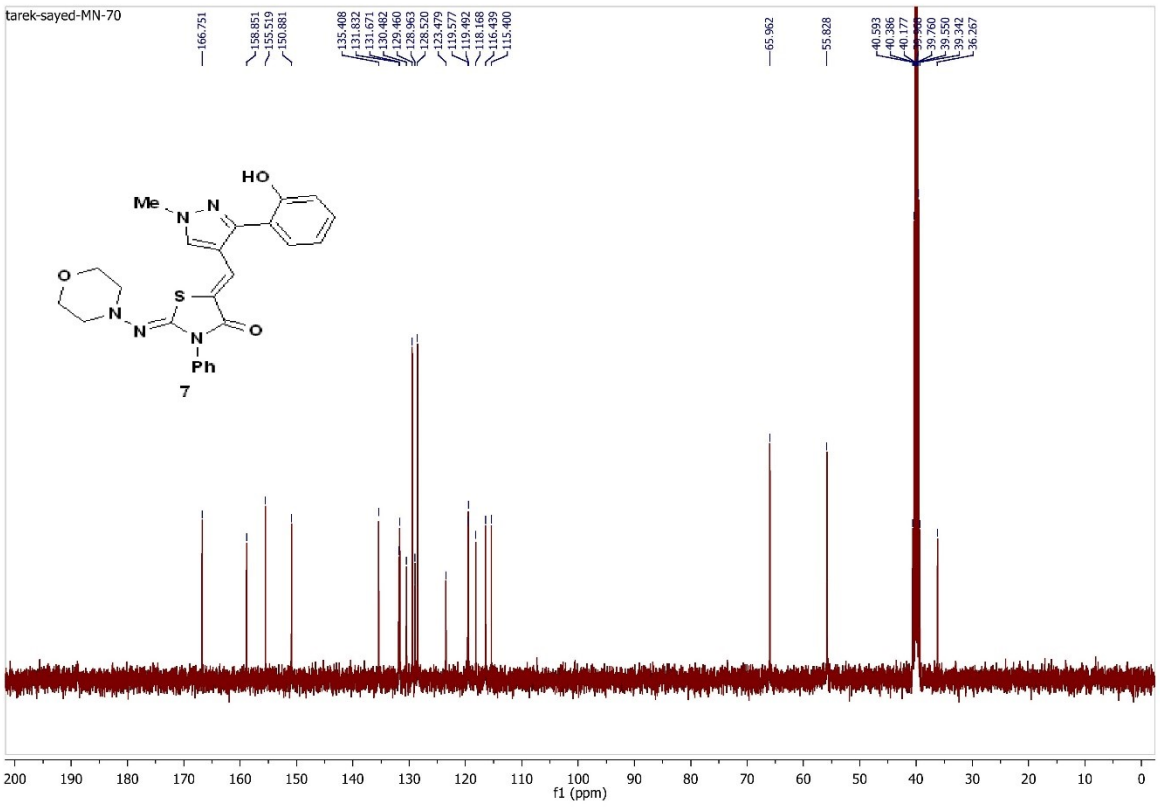


Figure S10: The ^{13}C-NMR spectrum of compound **7**.

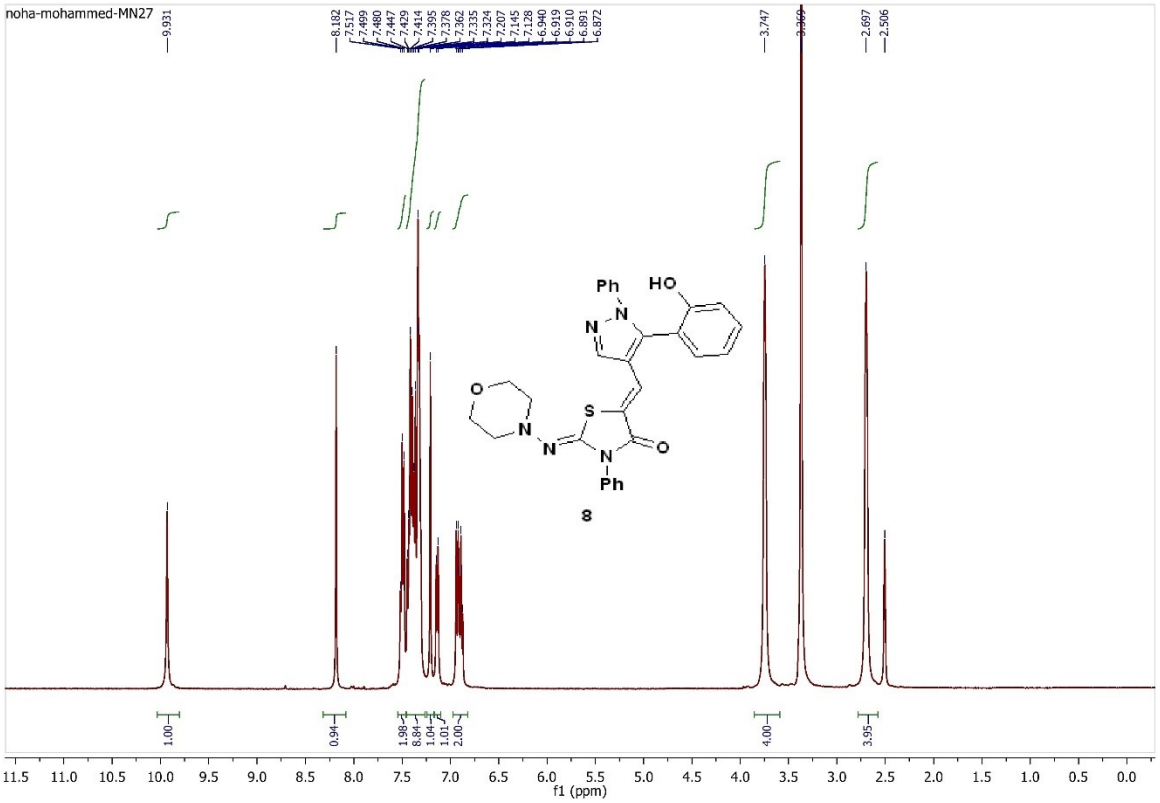


Figure S11: The ^{1}H-NMR spectrum of compound **8**.

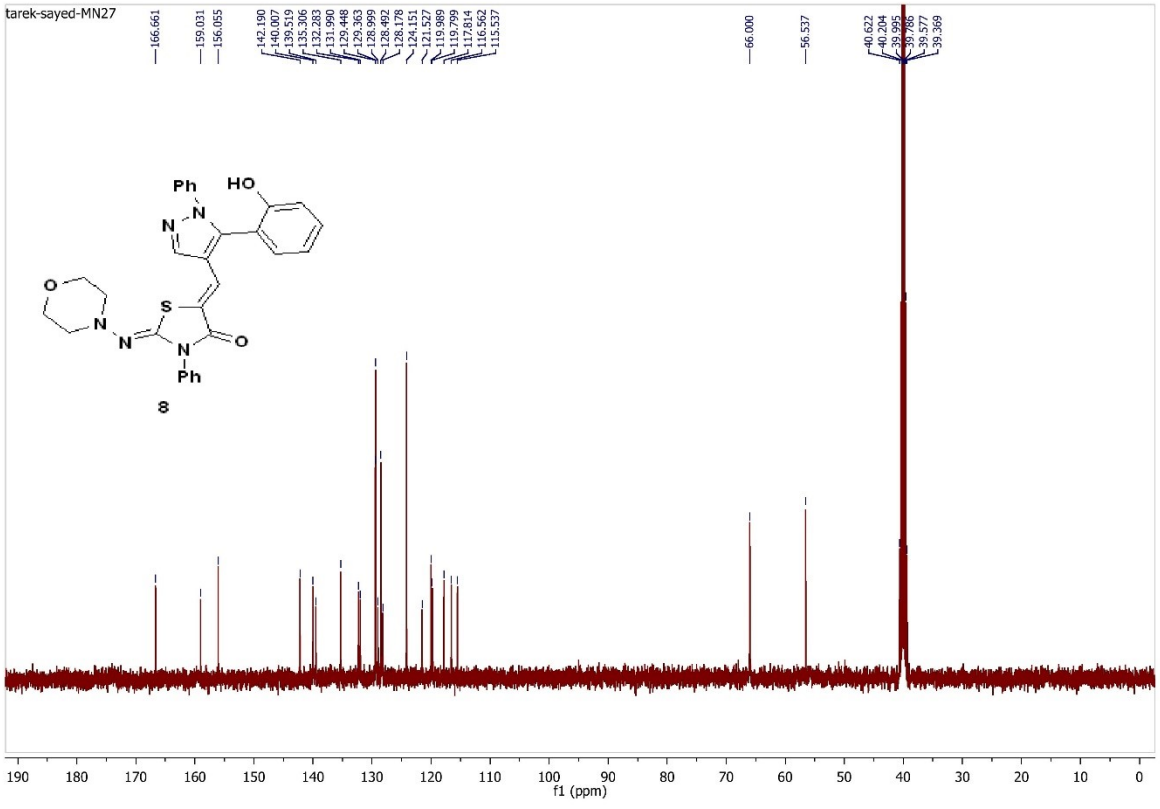


Figure S12: The ^{13}C-NMR spectrum of compound **8**.

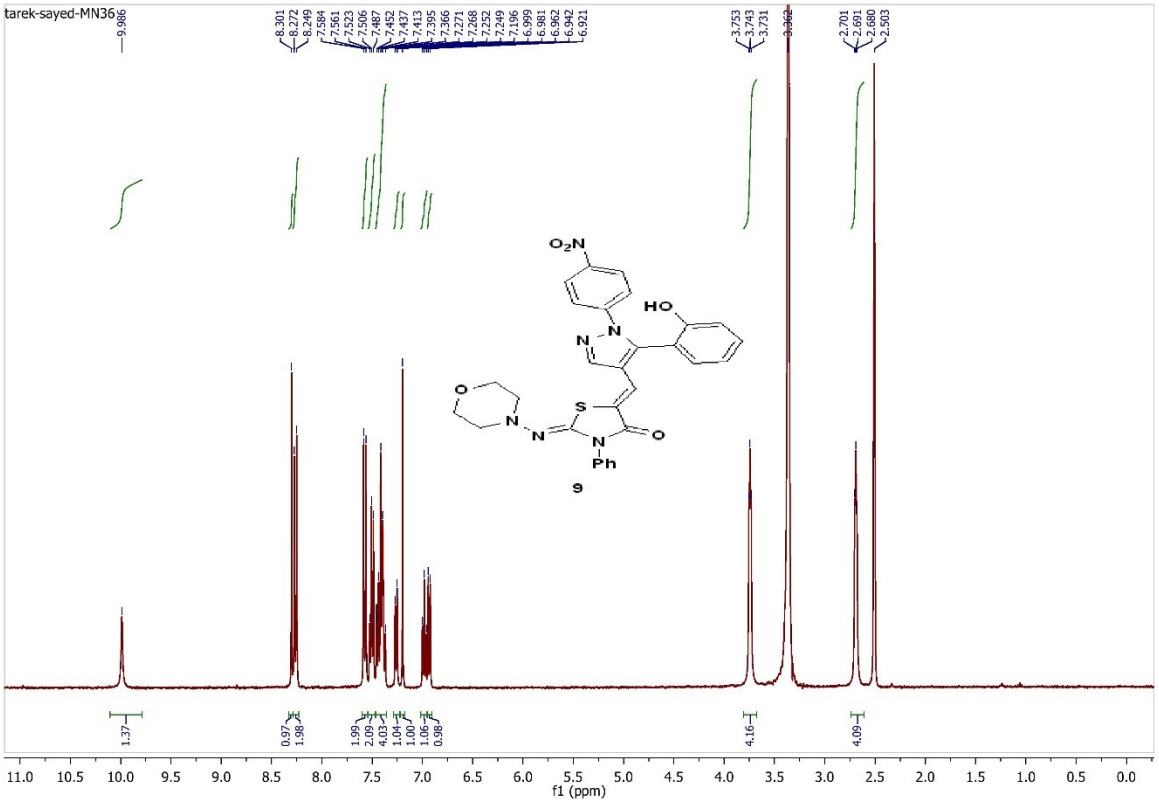


Figure S13: The ^{1}H-NMR spectrum of compound **9**.

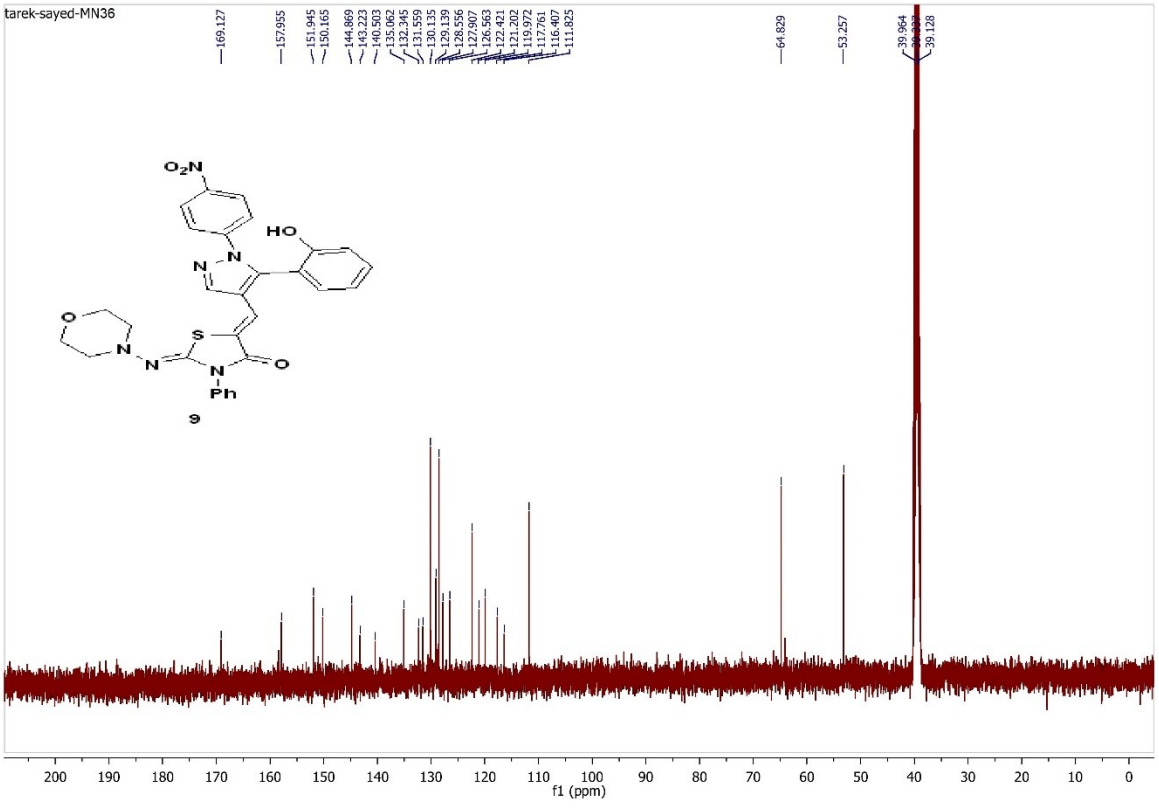


Figure S14: The ^{13}C-NMR spectrum of compound **9**.

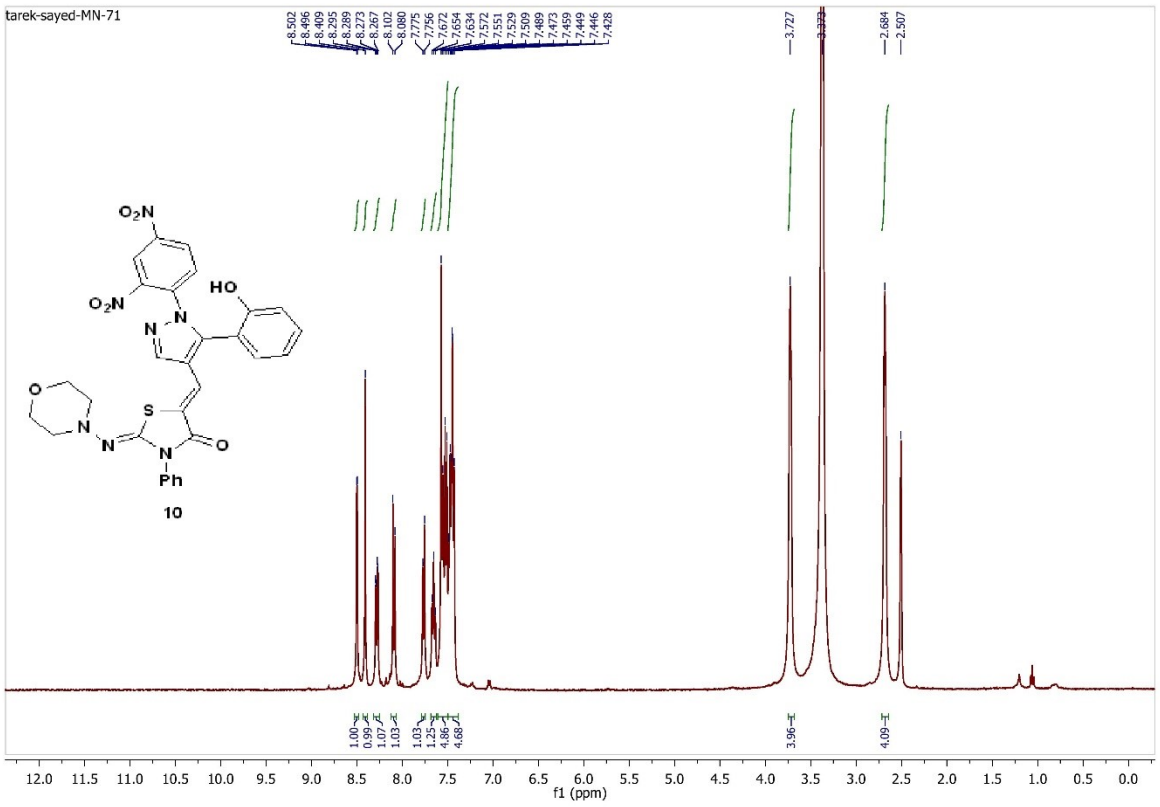


Figure S15: The ^{1}H-NMR spectrum of compound **10**.

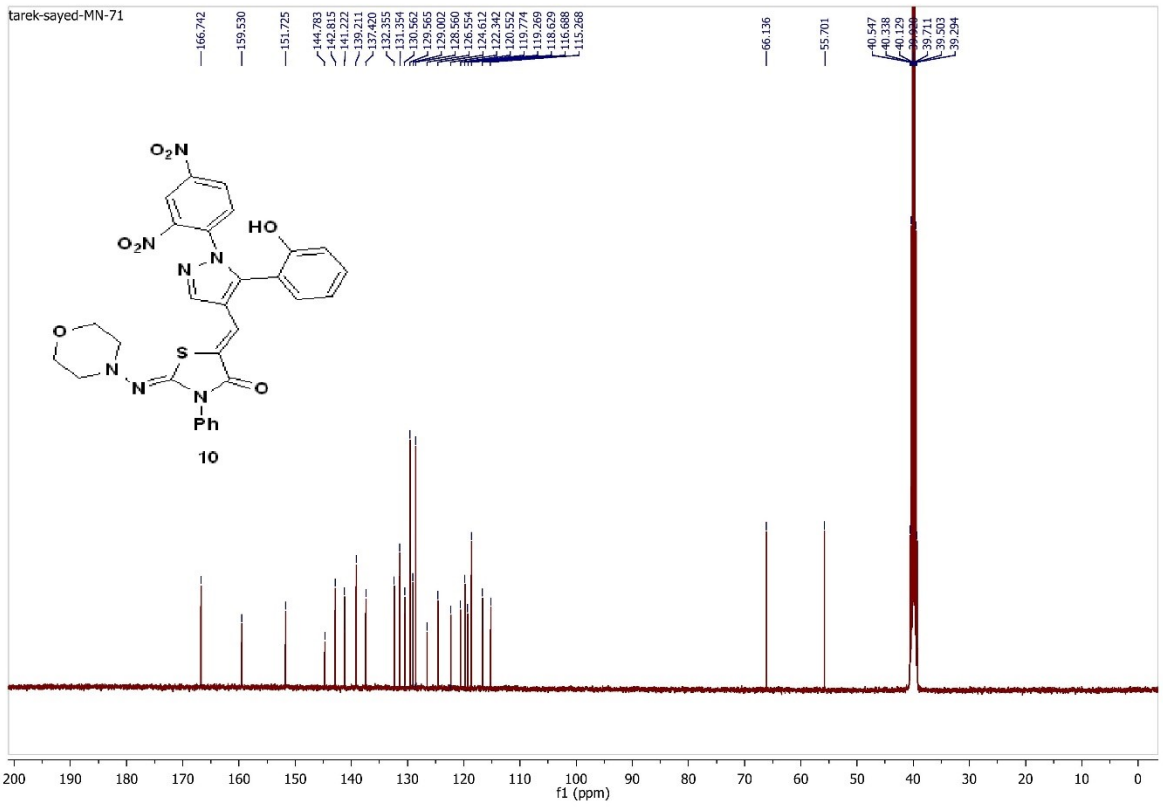


Figure S16: The ^{13}C-NMR spectrum of compound **10**.

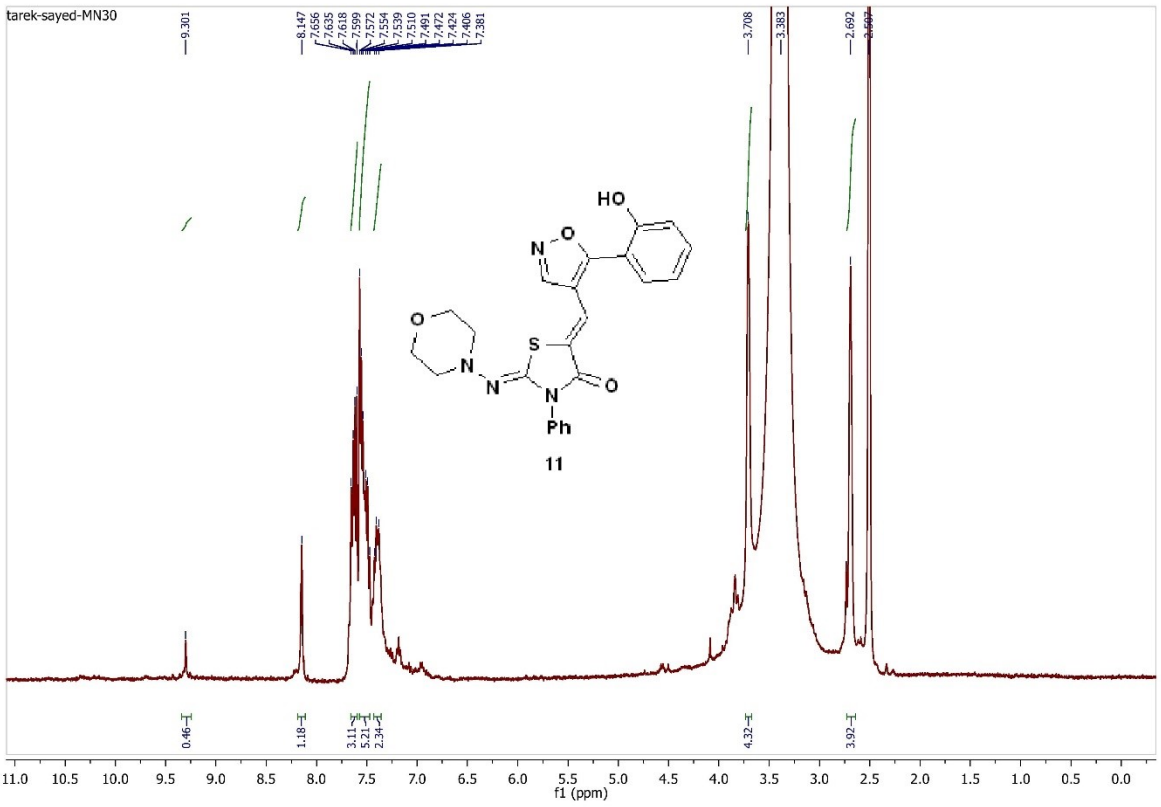


Figure S17: The ^{1}H-NMR spectrum of compound **11**.

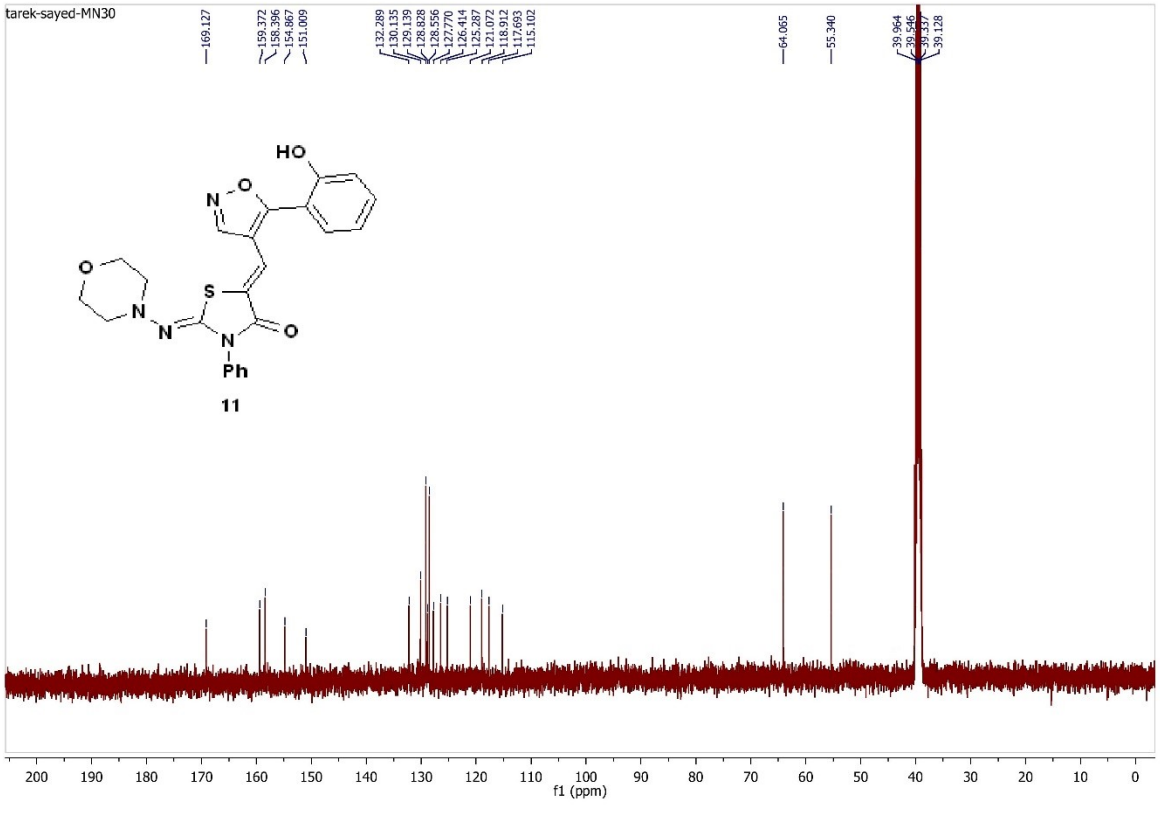


Figure S18: The ^{13}C-NMR spectrum of compound **11**.

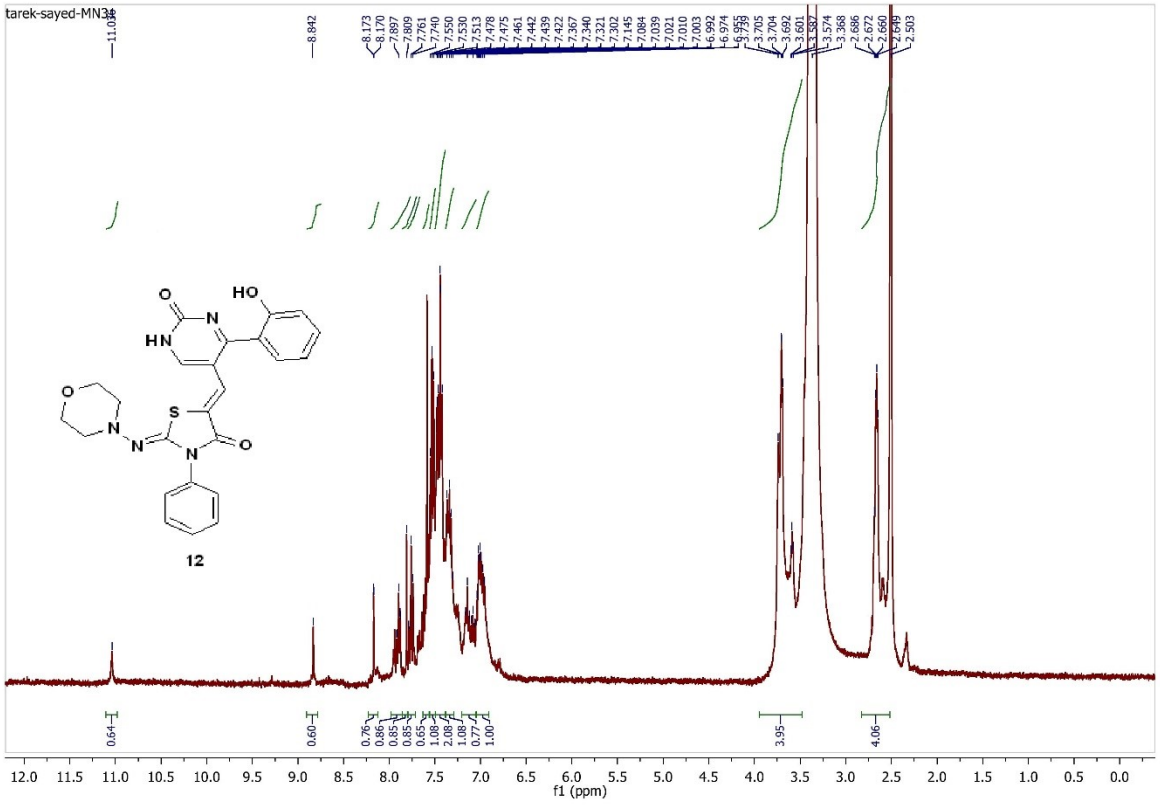


Figure S19: The ^{1}H-NMR spectrum of compound **12**.

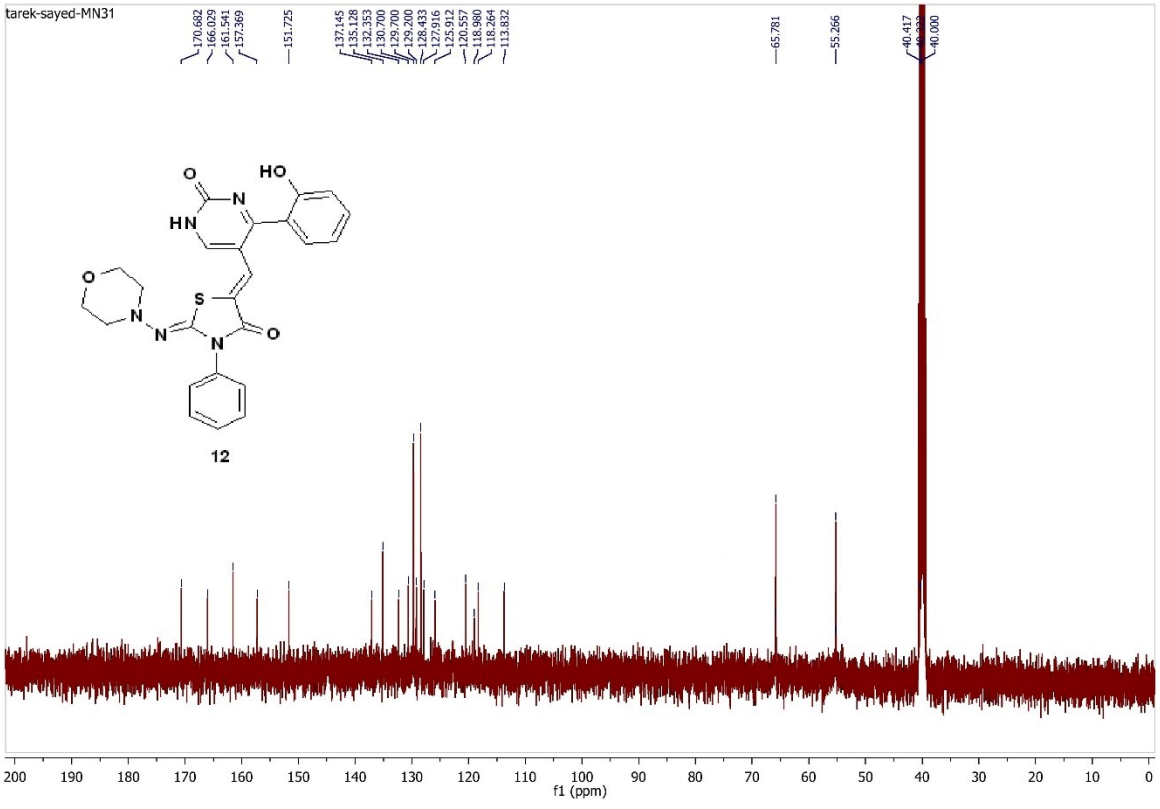
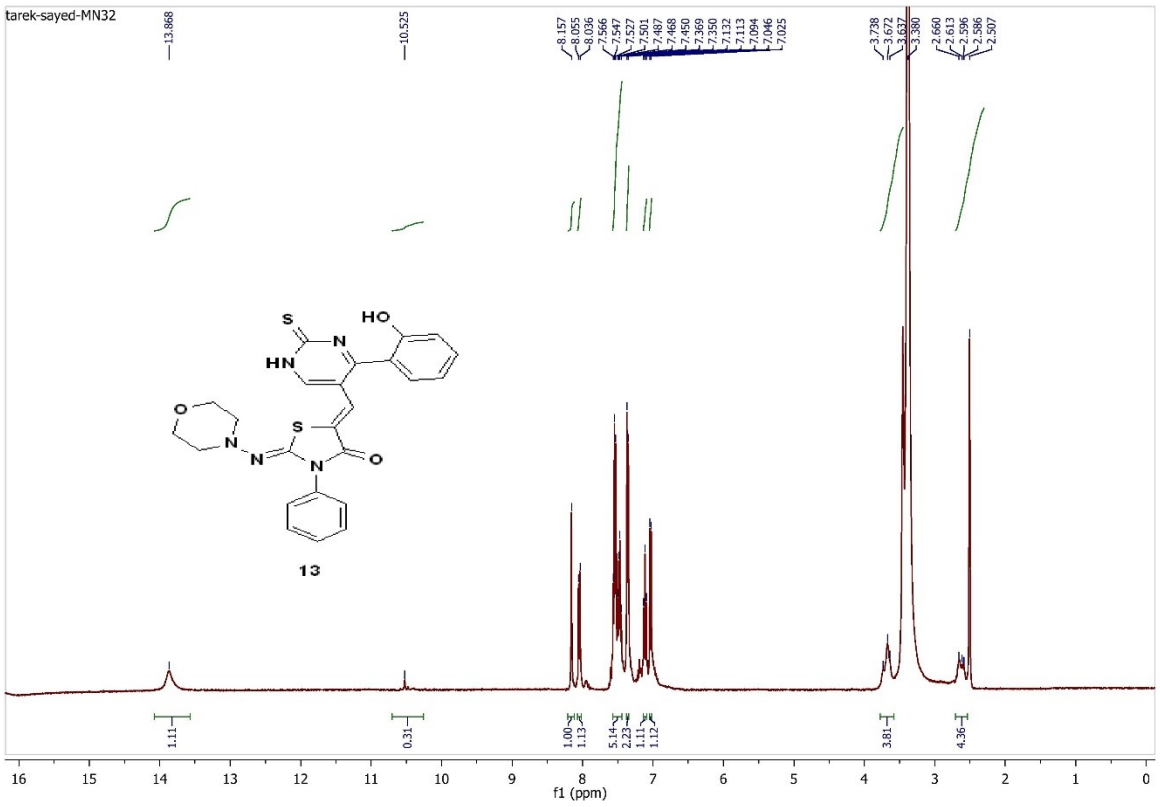
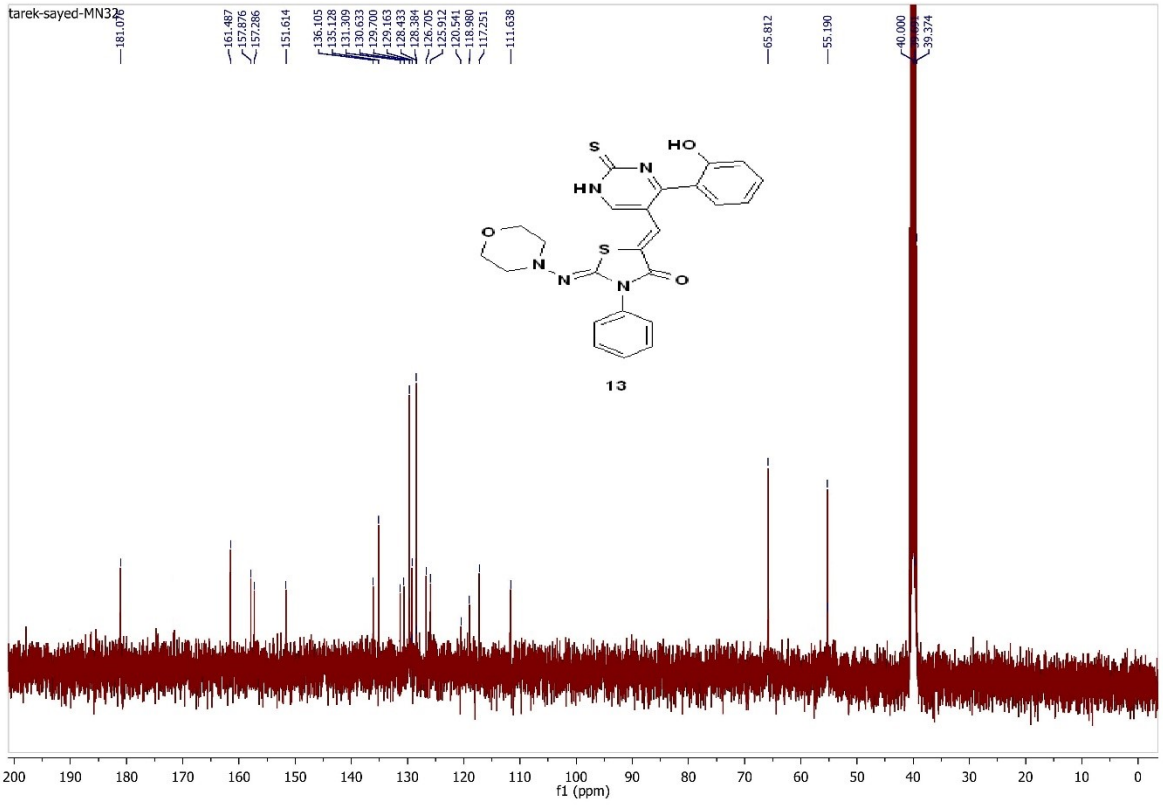


Figure S20: The ^{13}C-NMR spectrum of compound **12**.



13

Figure S21: The ^{1}H-NMR spectrum of compound **13**.



13

Figure S22: The ^{13}C-NMR spectrum of compound **13**.

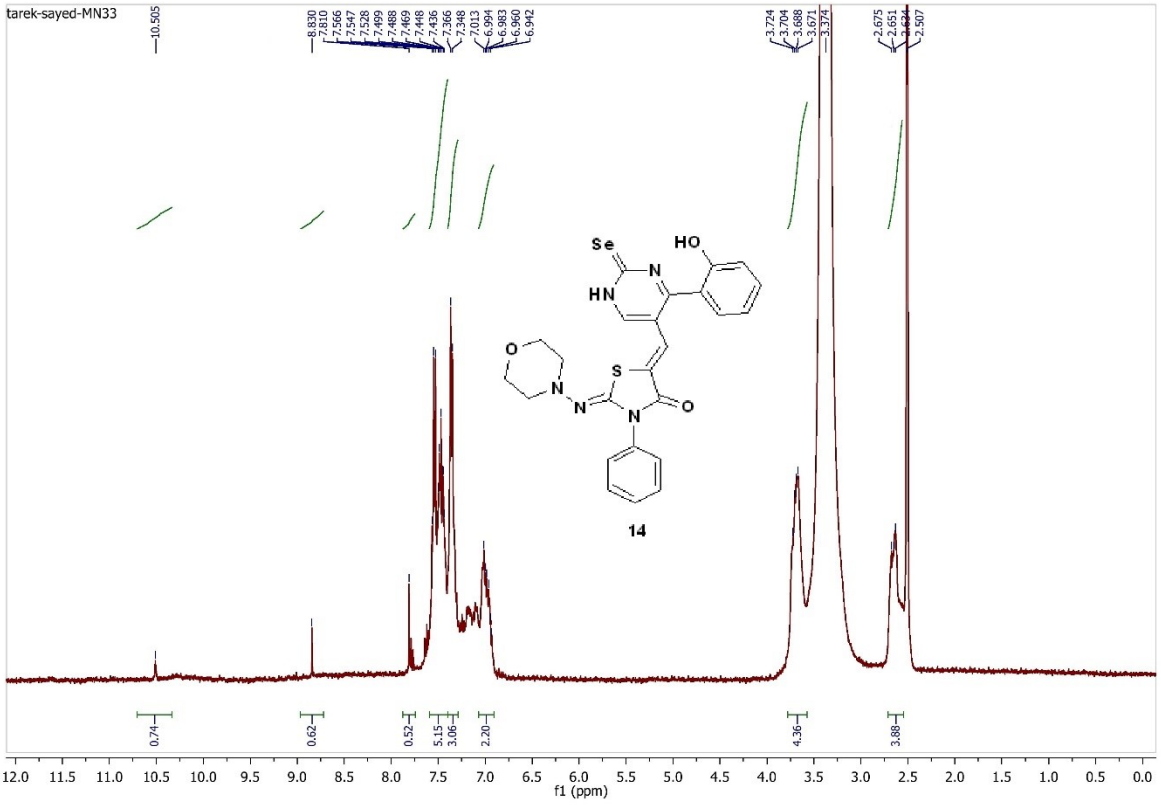


Figure S23: The ^{1}H-NMR spectrum of compound **14**.

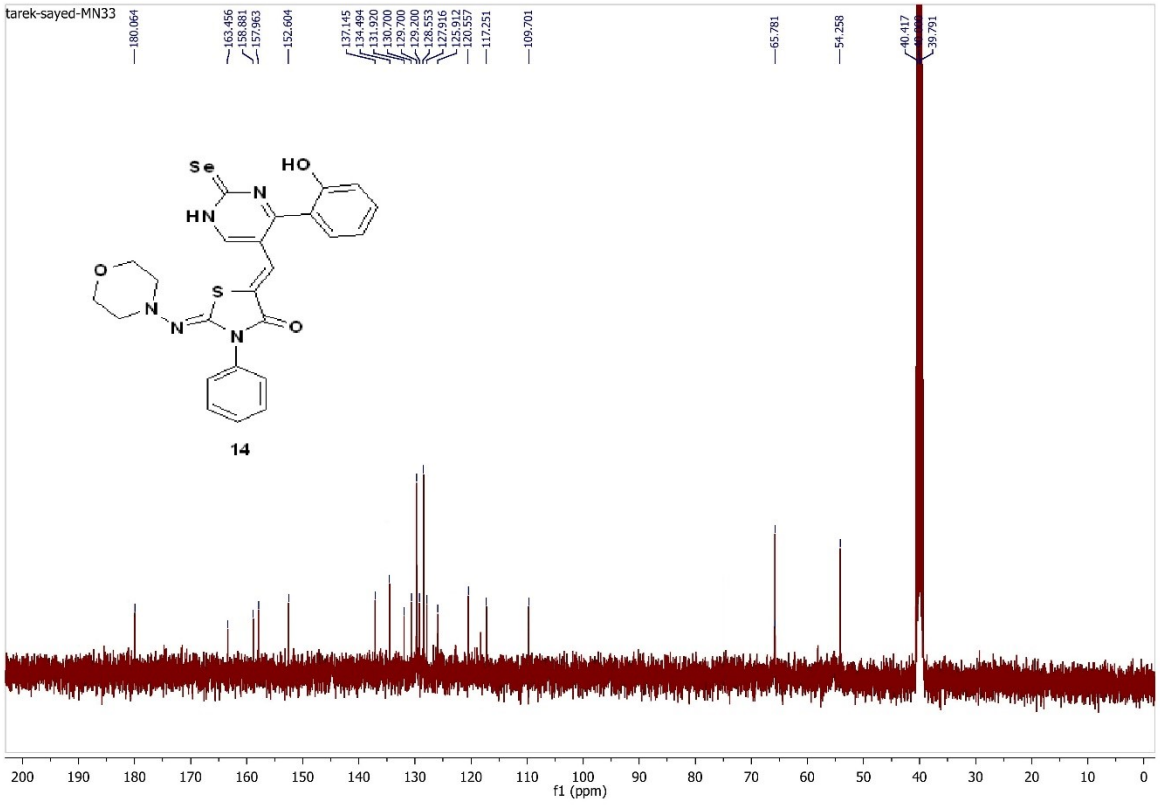


Figure S24: The ^{13}C-NMR spectrum of compound **14**.

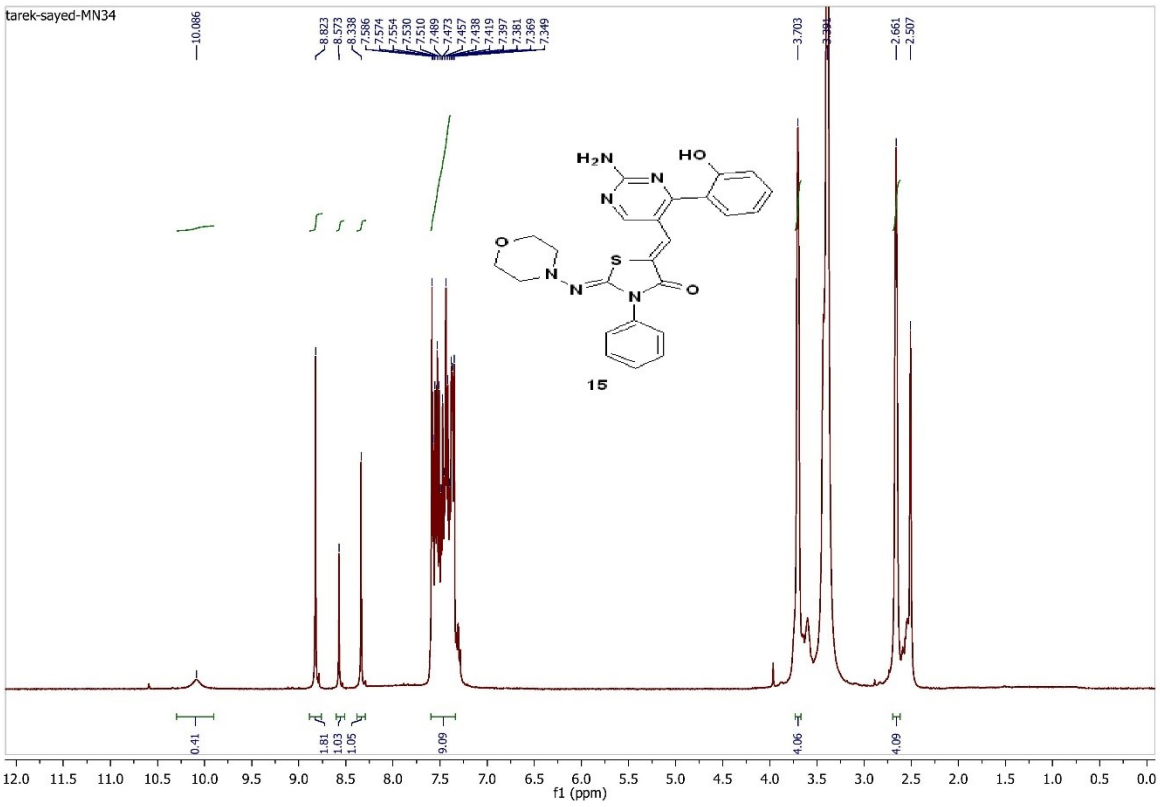


Figure S25: The ^{1}H-NMR spectrum of compound **15**.

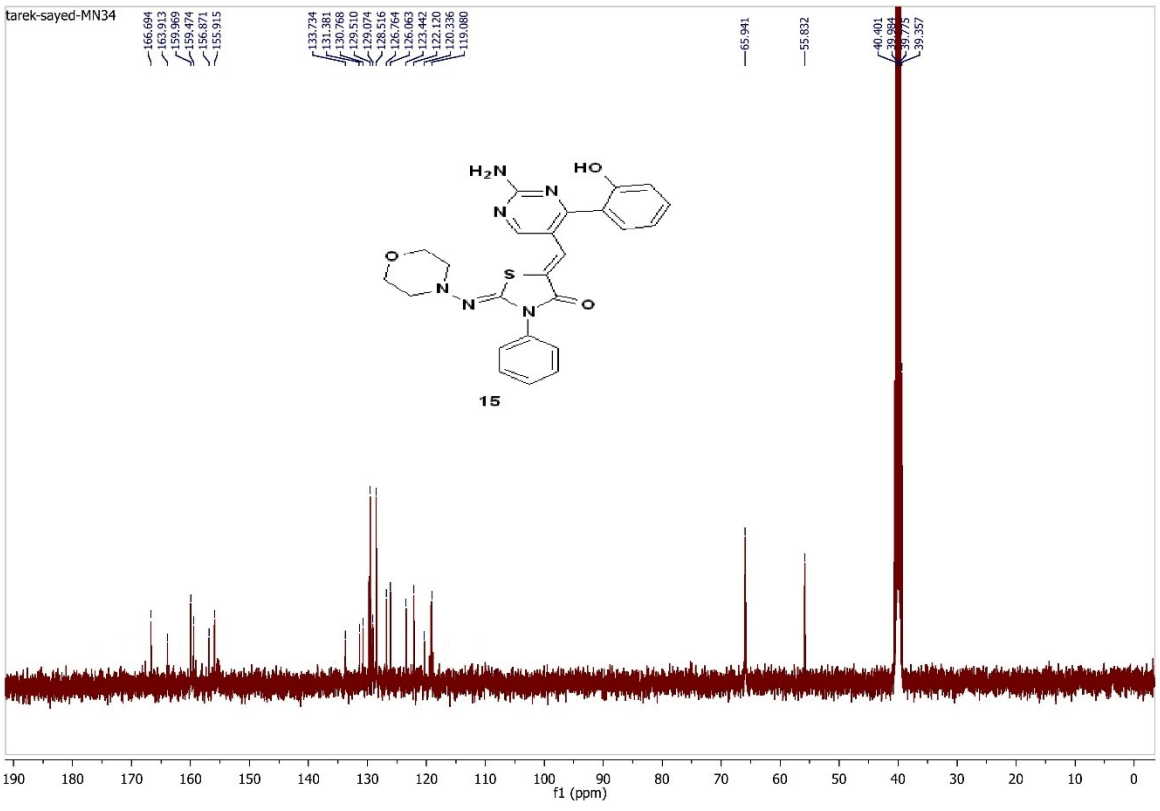


Figure S26: The ^{13}C-NMR spectrum of compound **15**.

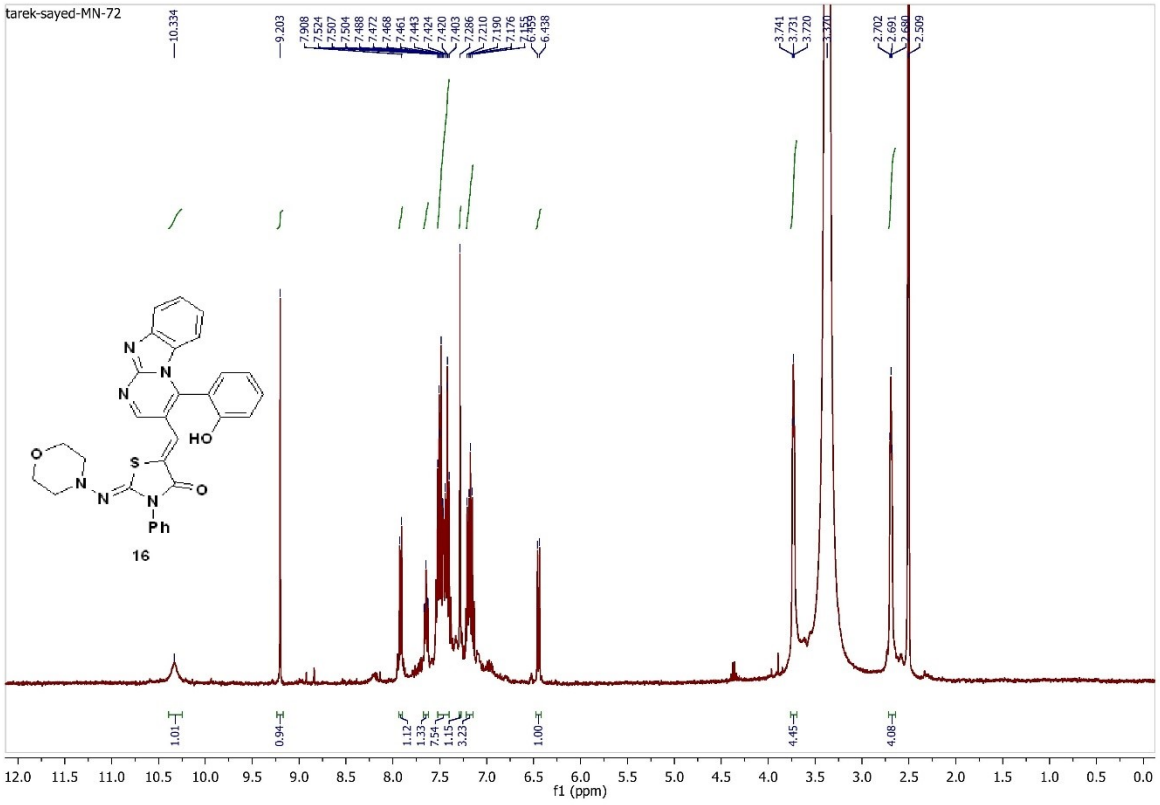


Figure S27: The ^{1}H-NMR spectrum of compound **16**.

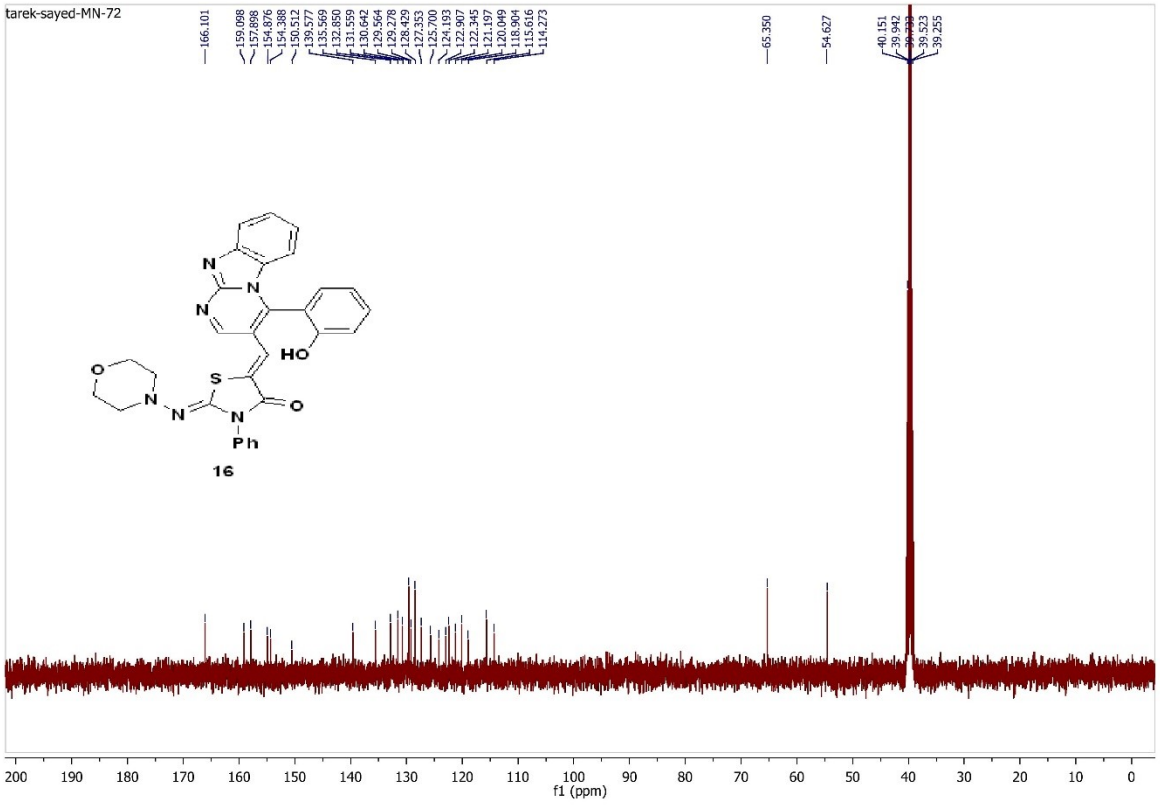


Figure S28: The ^{13}C-NMR spectrum of compound **16**.

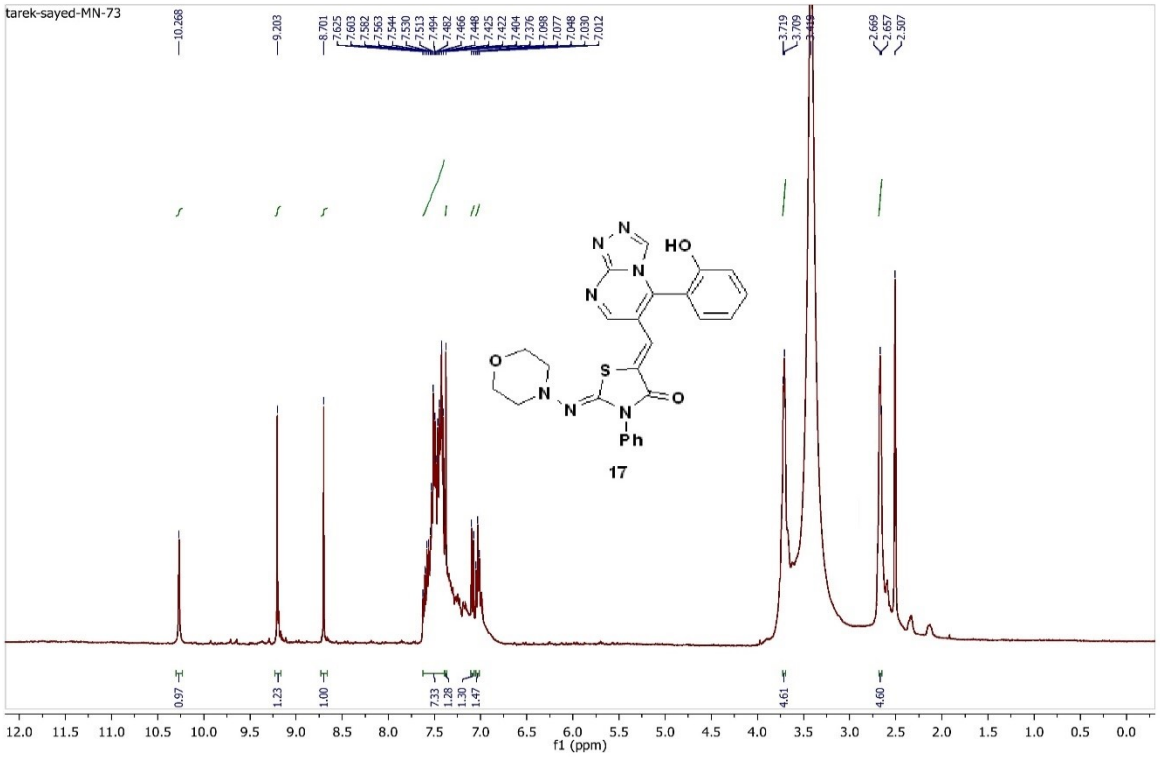


Figure S29: The ^{1}H-NMR spectrum of compound **17**.

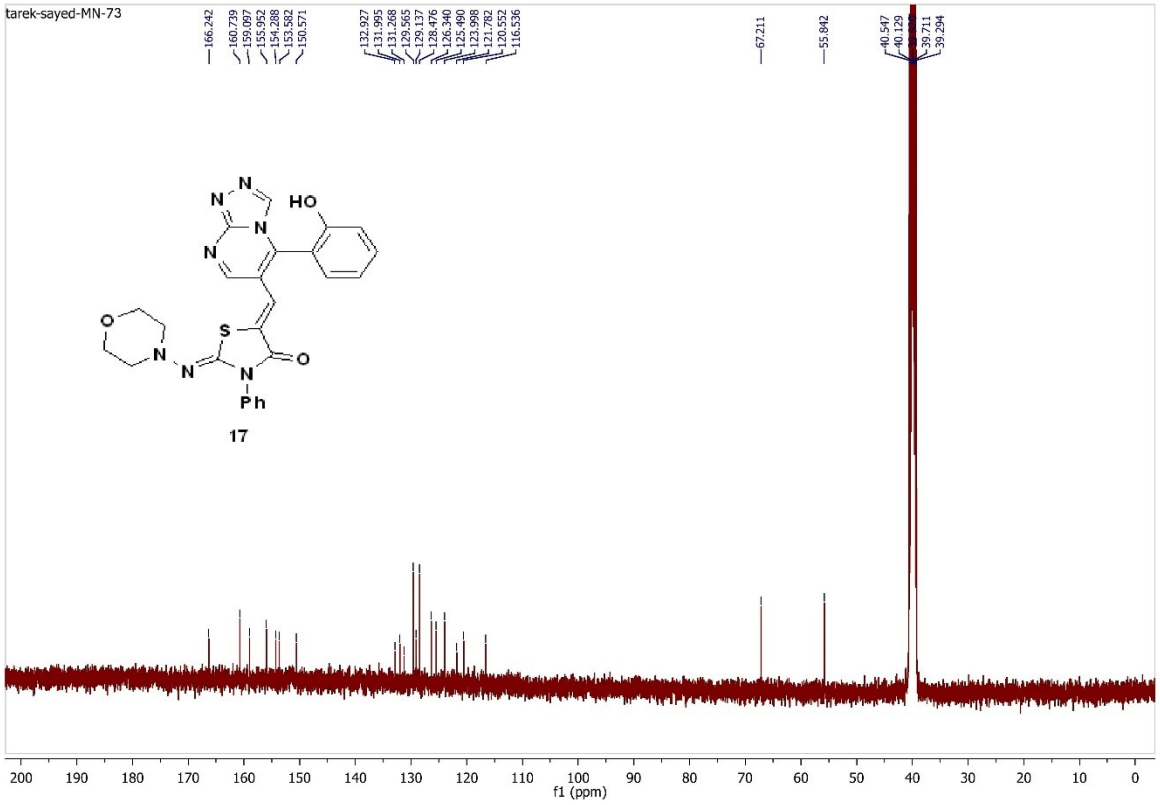


Figure S30: The ^{13}C-NMR spectrum of compound **17**.

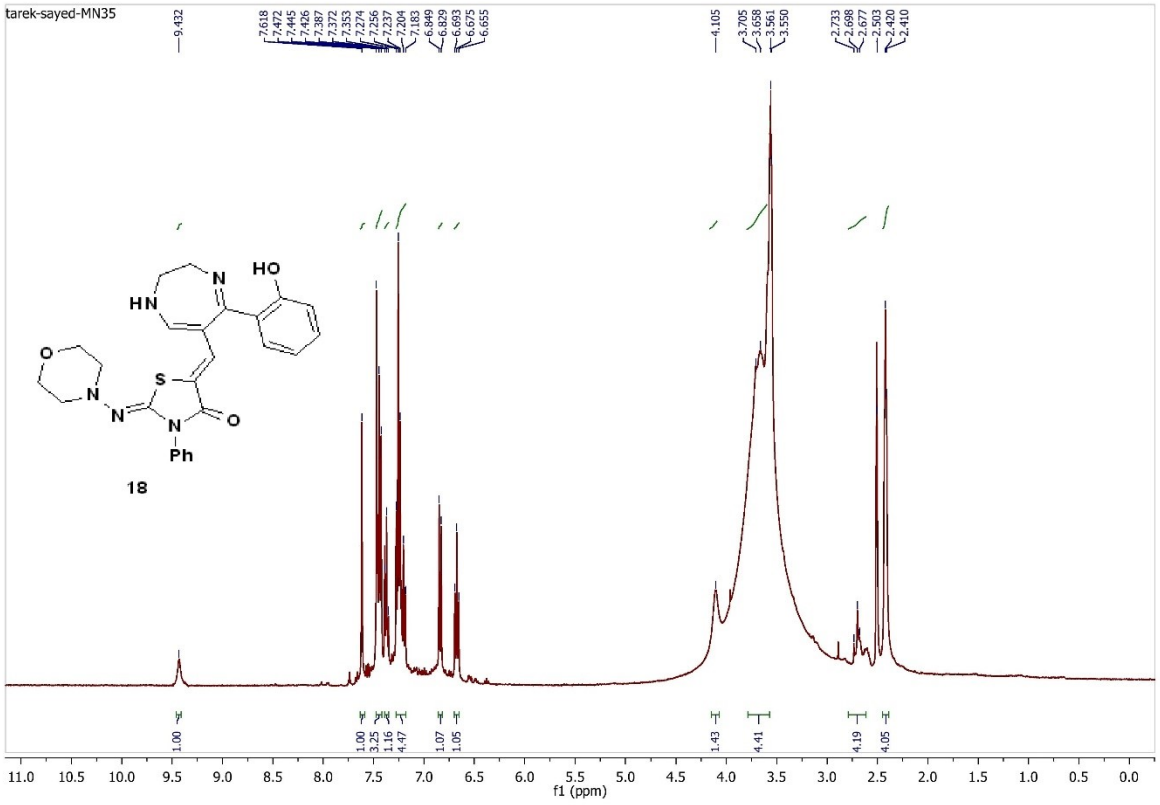


Figure S31: The ^{1}H-NMR spectrum of compound **18**.

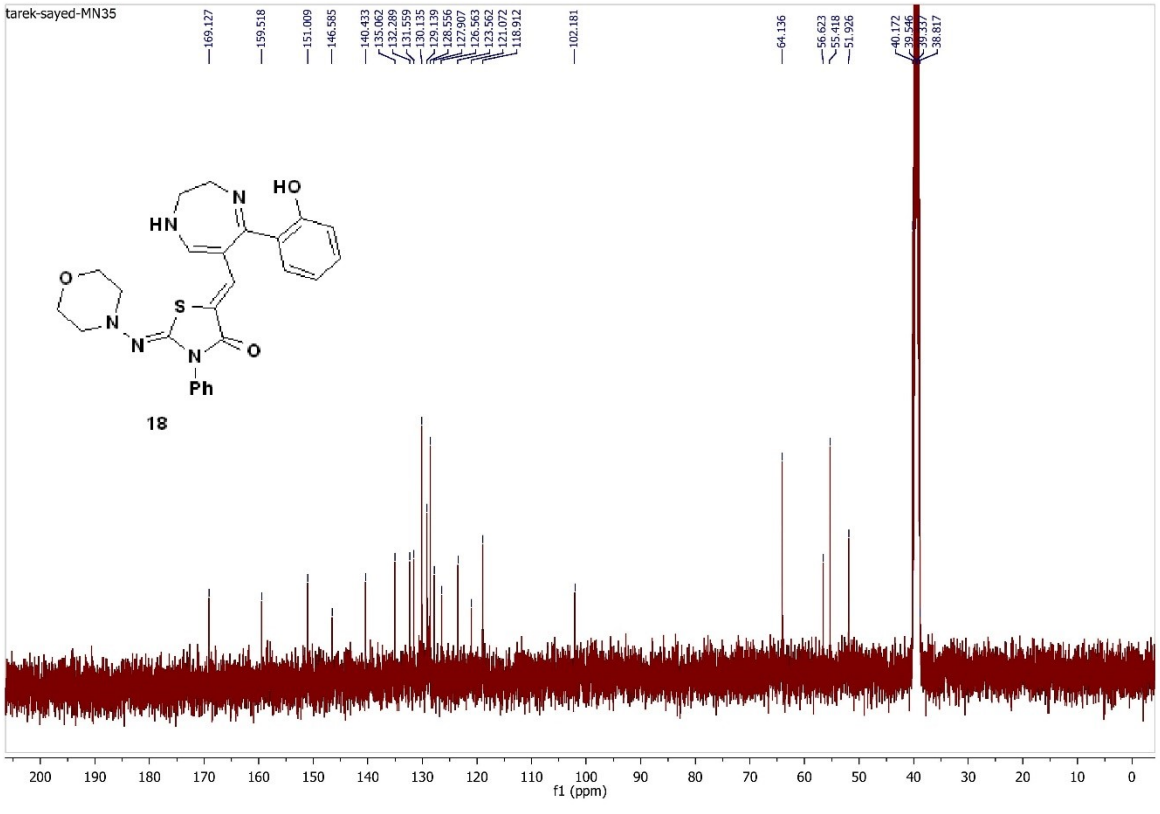


Figure S32: The ^{13}C-NMR spectrum of compound **18**.

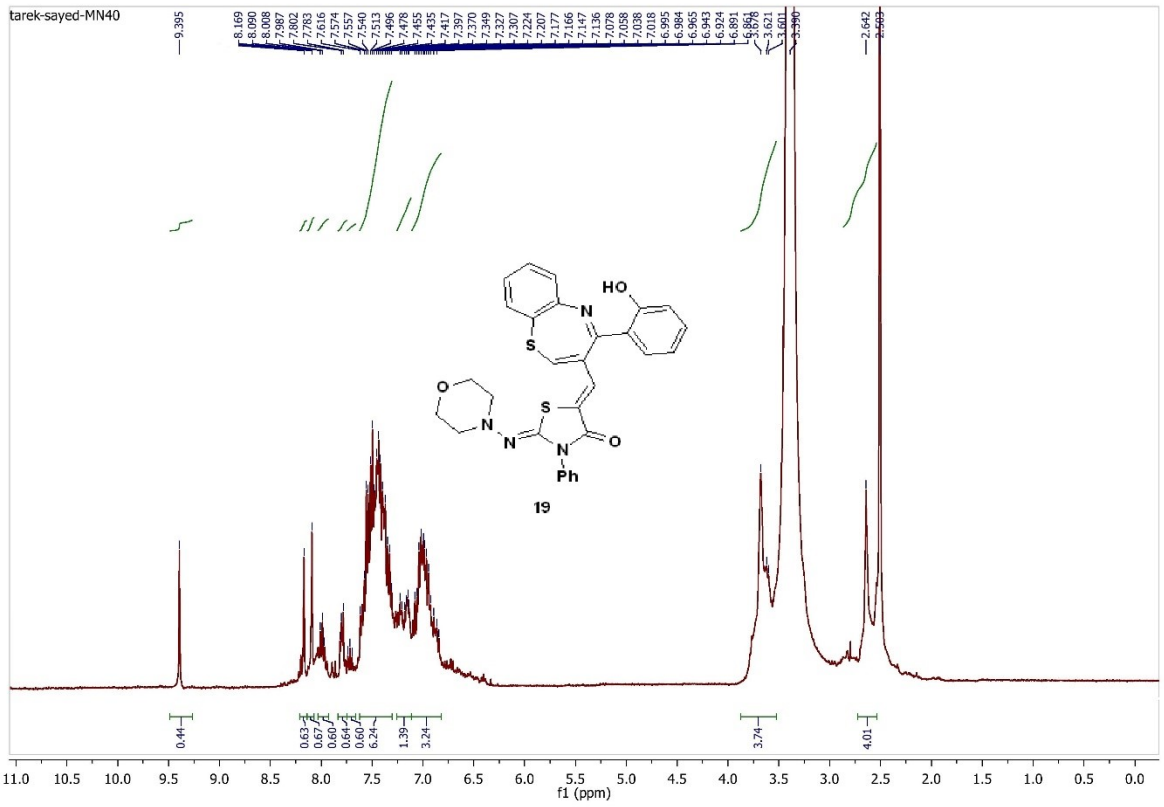


Figure S33: The ^{1}H-NMR spectrum of compound **19**.

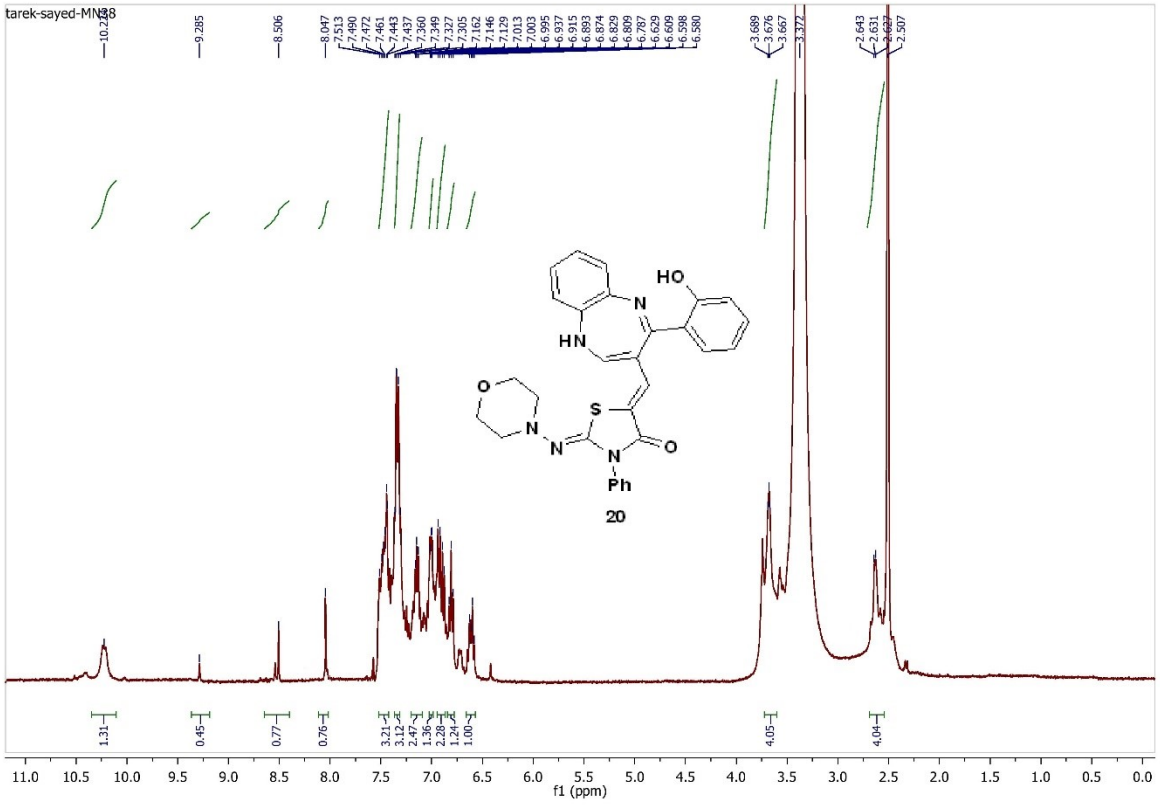


Figure S34: The ^{1}H-NMR spectrum of compound **20**.

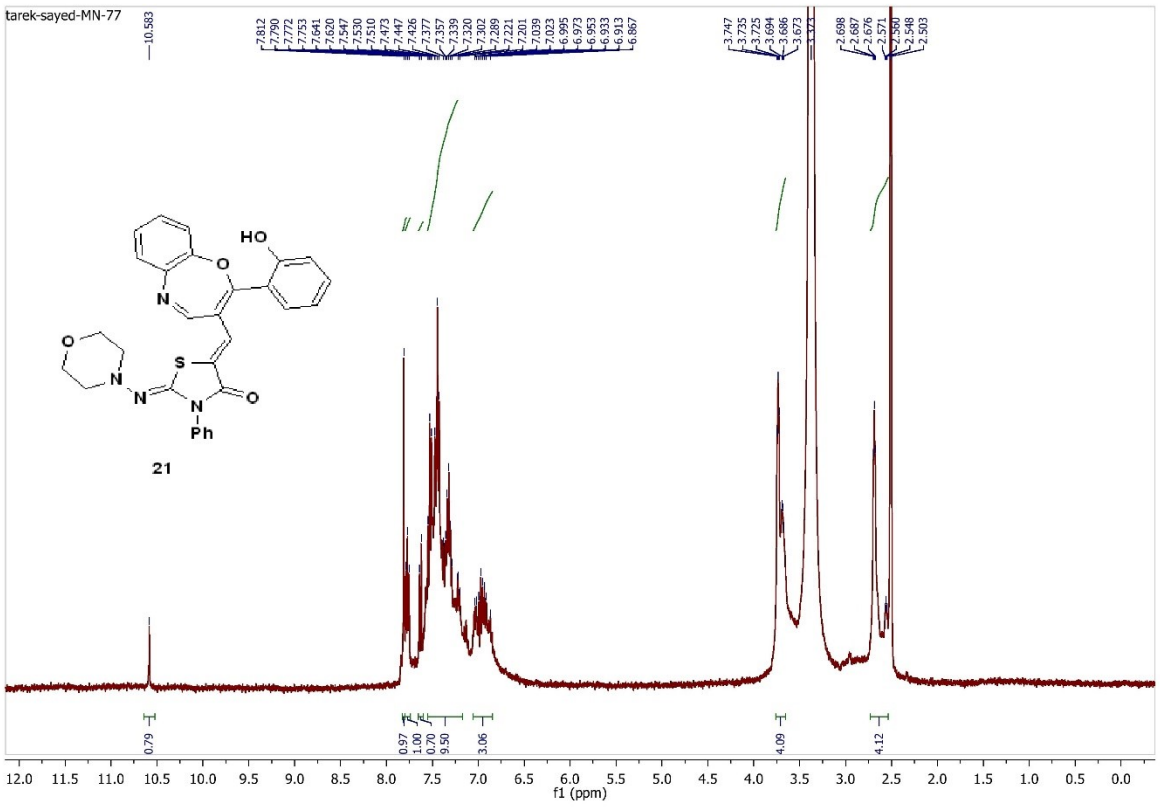


Figure S35: The ^{1}H-NMR spectrum of compound **21**.

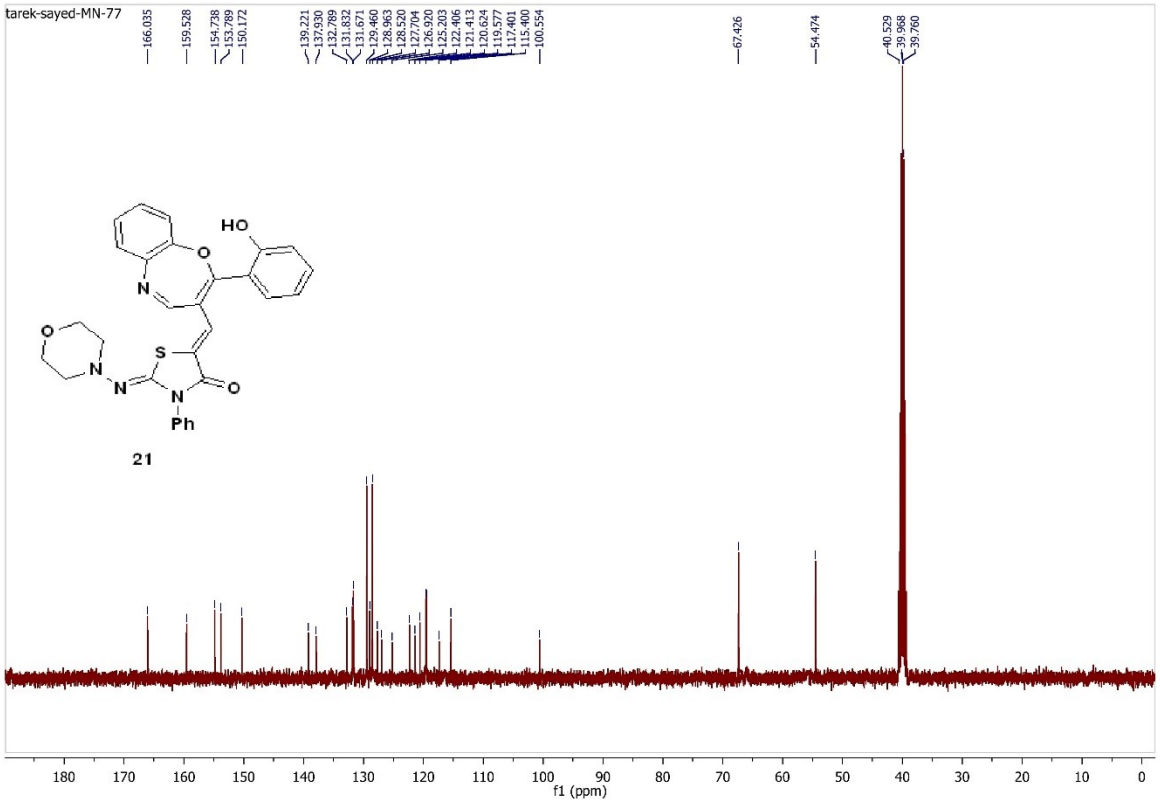


Figure S36: The ^{13}C-NMR spectrum of compound **21**.

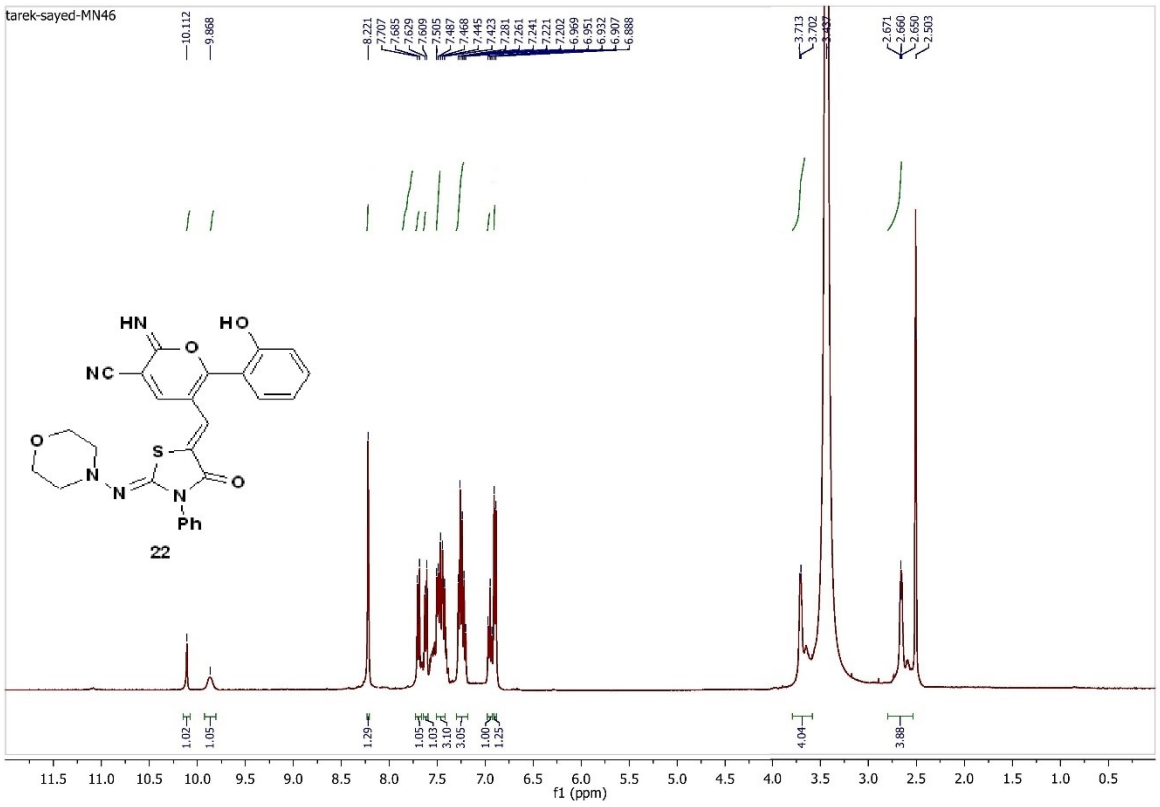


Figure S37: The ^{1}H-NMR spectrum of compound **22**.

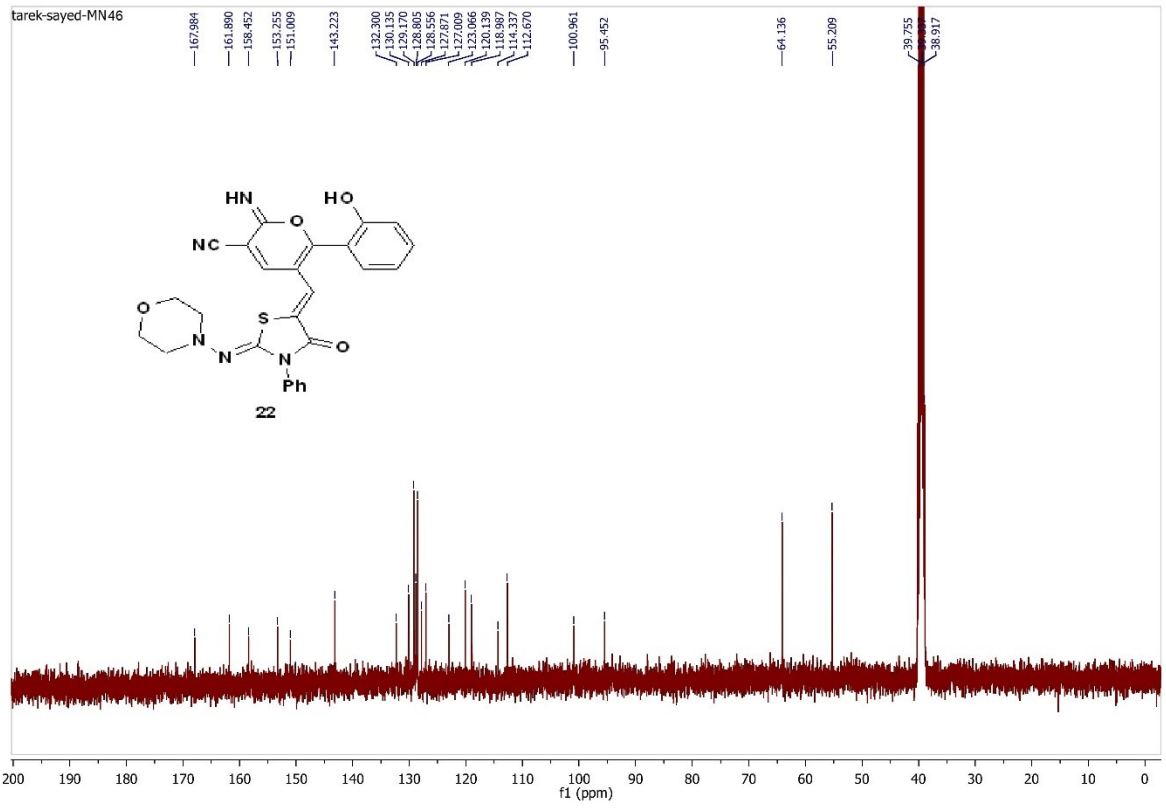


Figure S38: The ^{13}C-NMR spectrum of compound **22**.

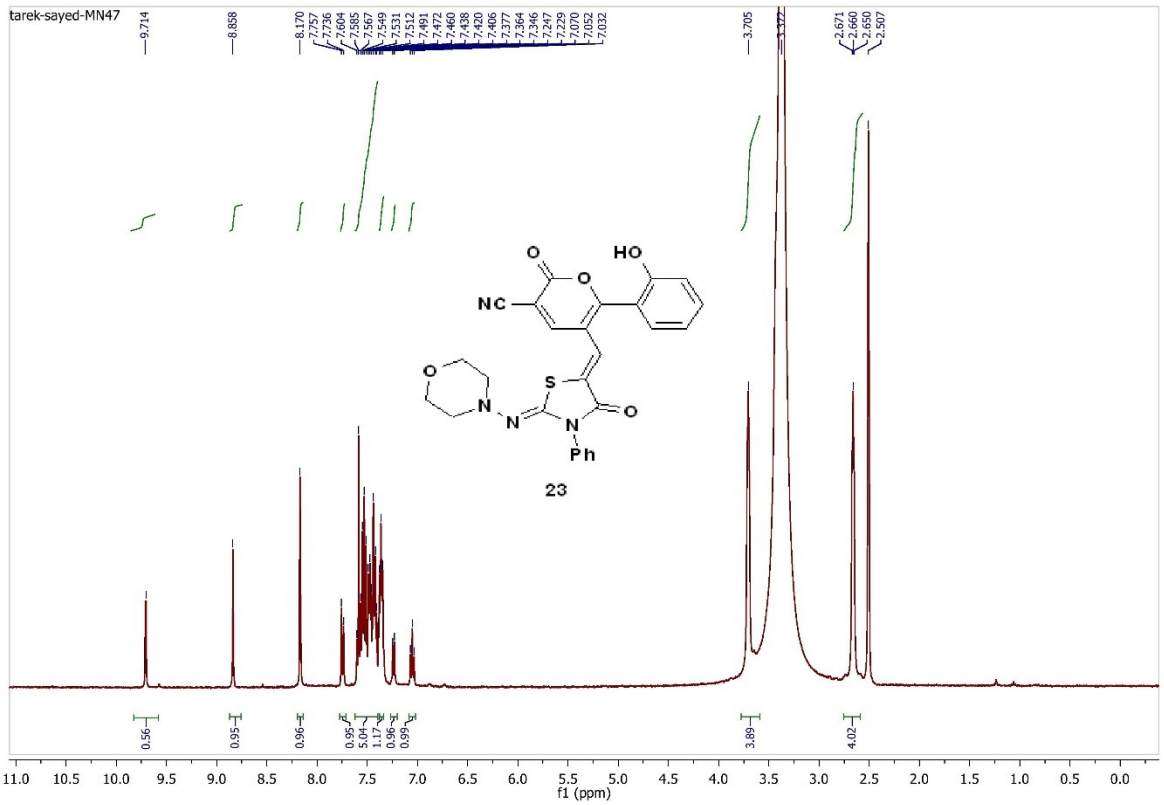


Figure S39: The ^{1}H-NMR spectrum of compound **23**

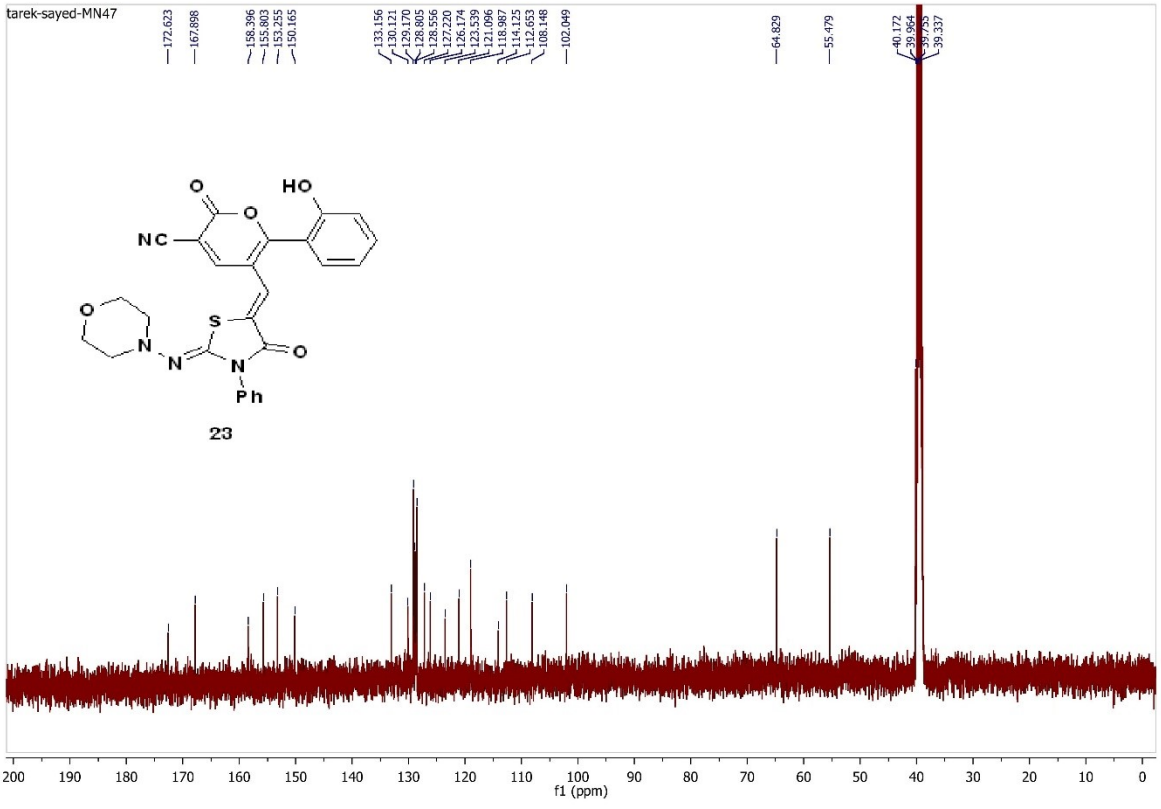


Figure S40: The ^{13}C-NMR spectrum of compound **23**.

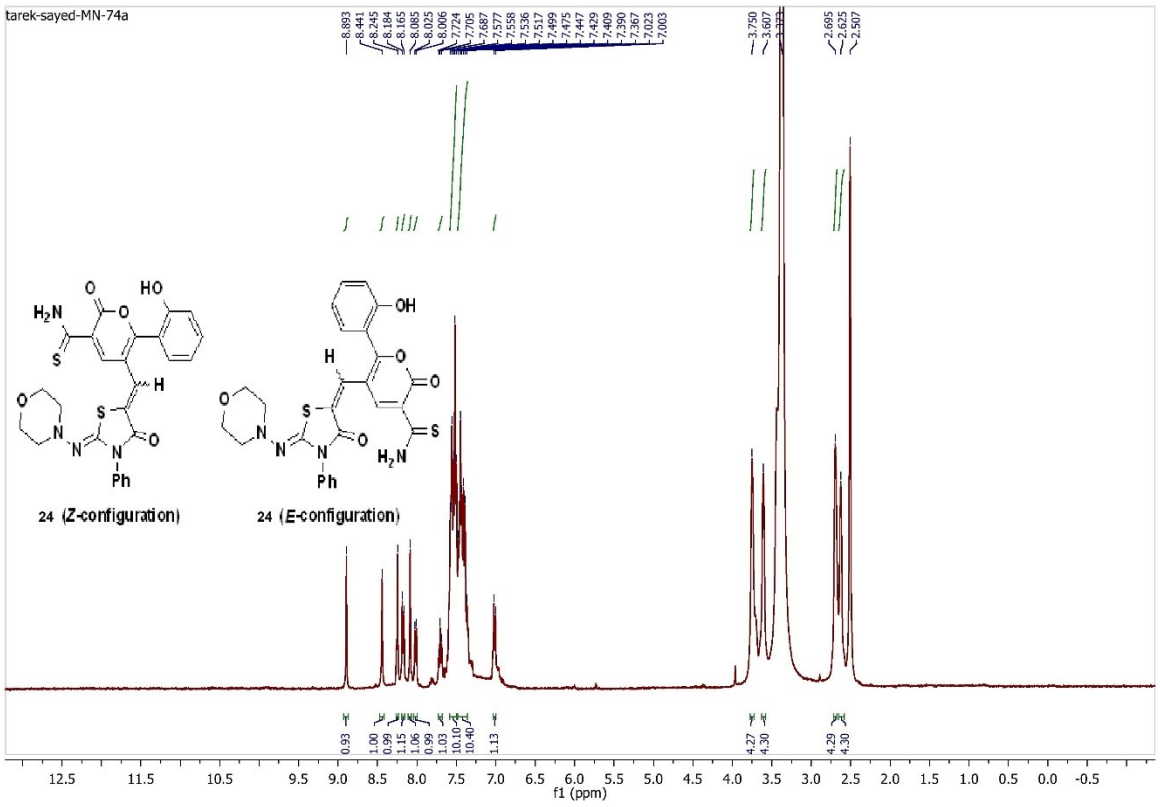


Figure S41: The ^{1}H-NMR spectrum of compound **24**.

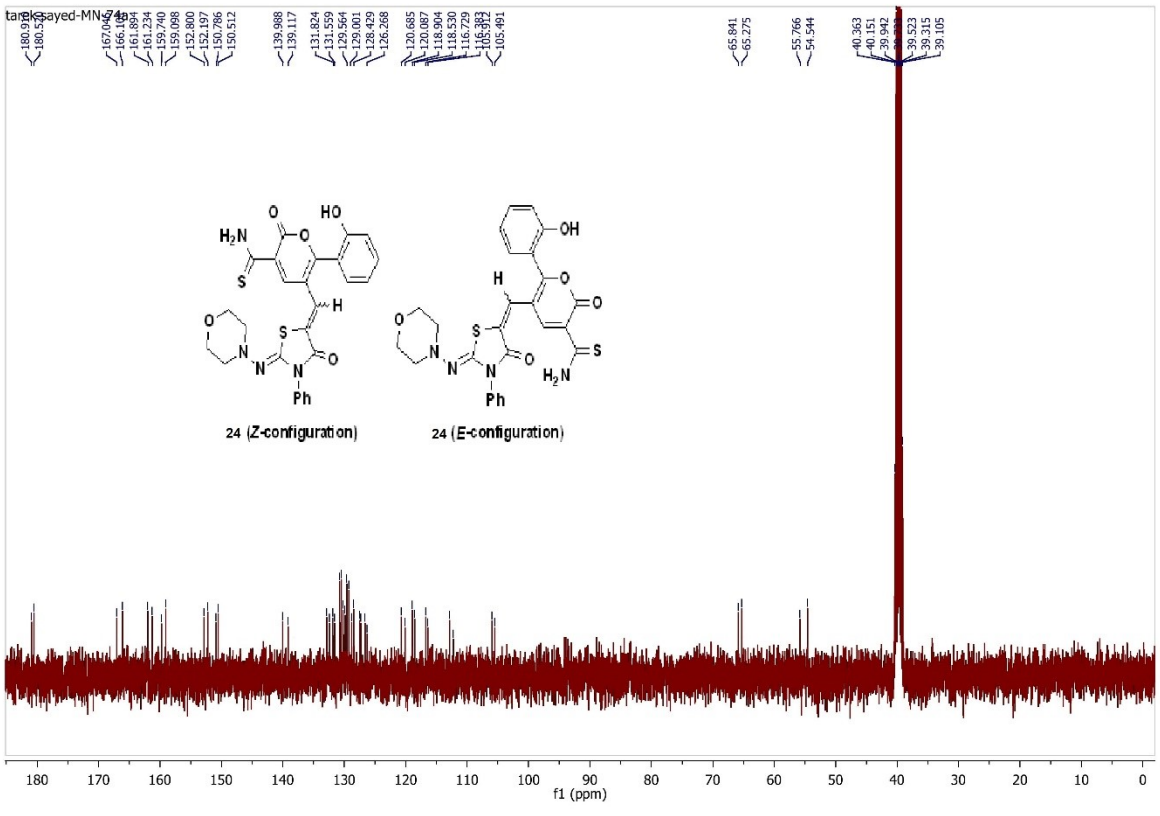


Figure S42: The ^{13}C-NMR spectrum of compound **24**.

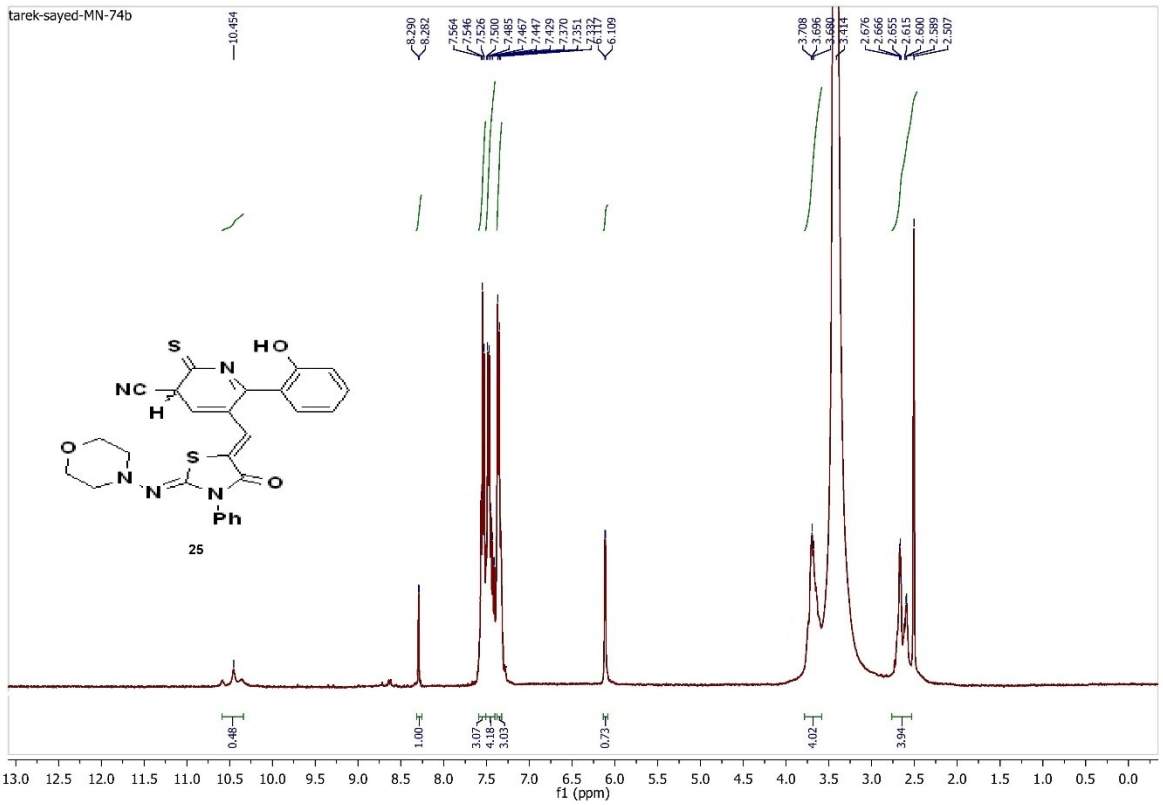


Figure S43: The ^{1}H-NMR spectrum of compound **25**.

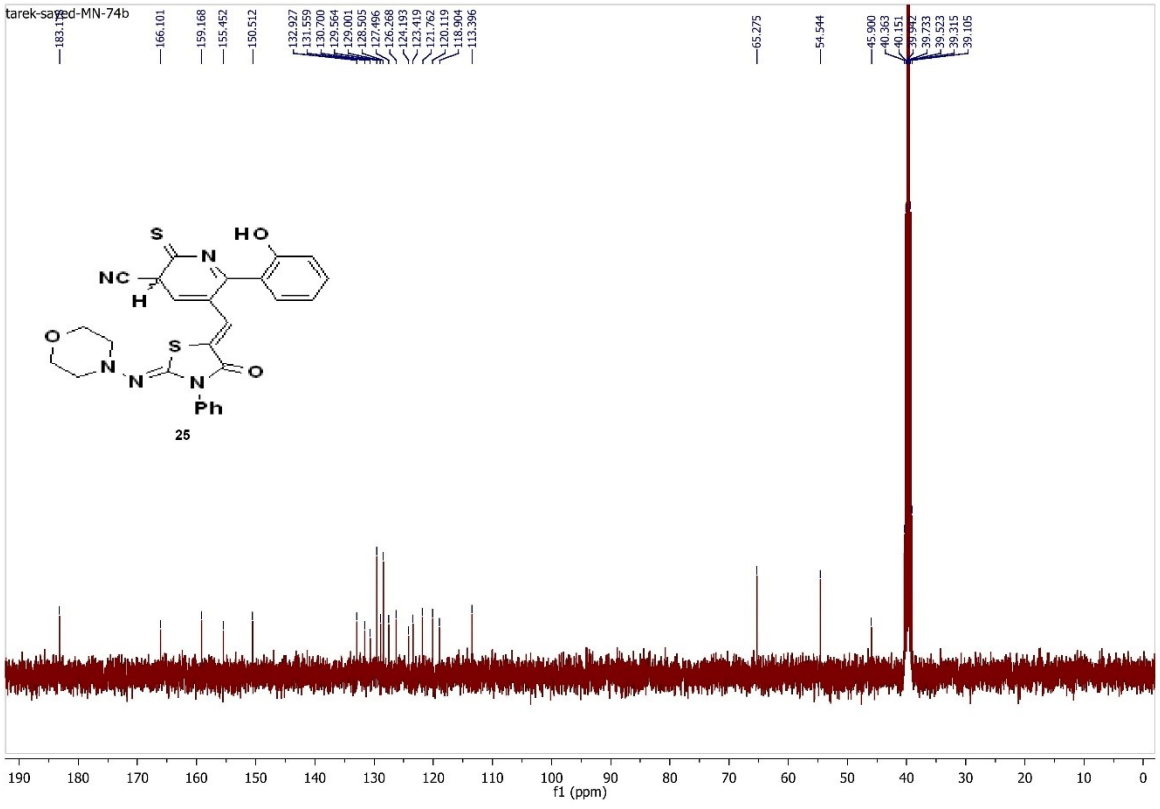


Figure S44: The ^{13}C-NMR spectrum of compound **25**.

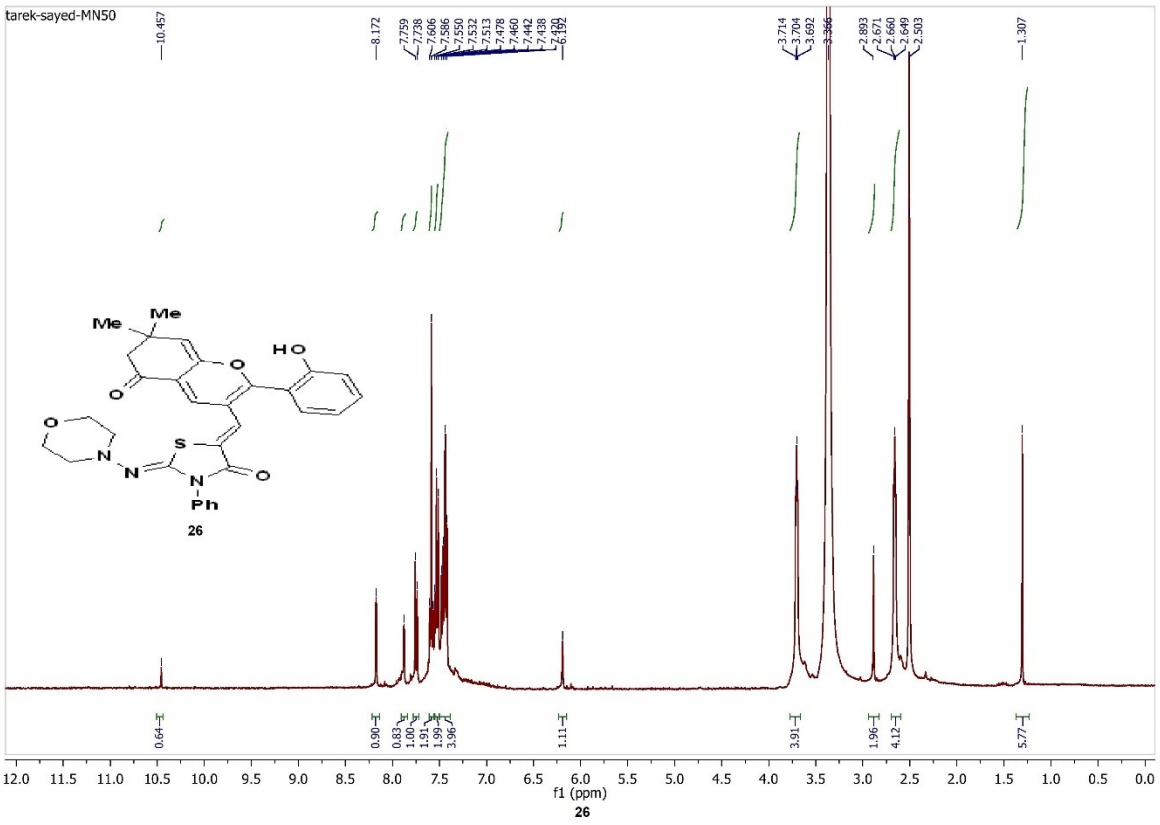


Figure S45: The ^{1}H-NMR spectrum of compound **26**.

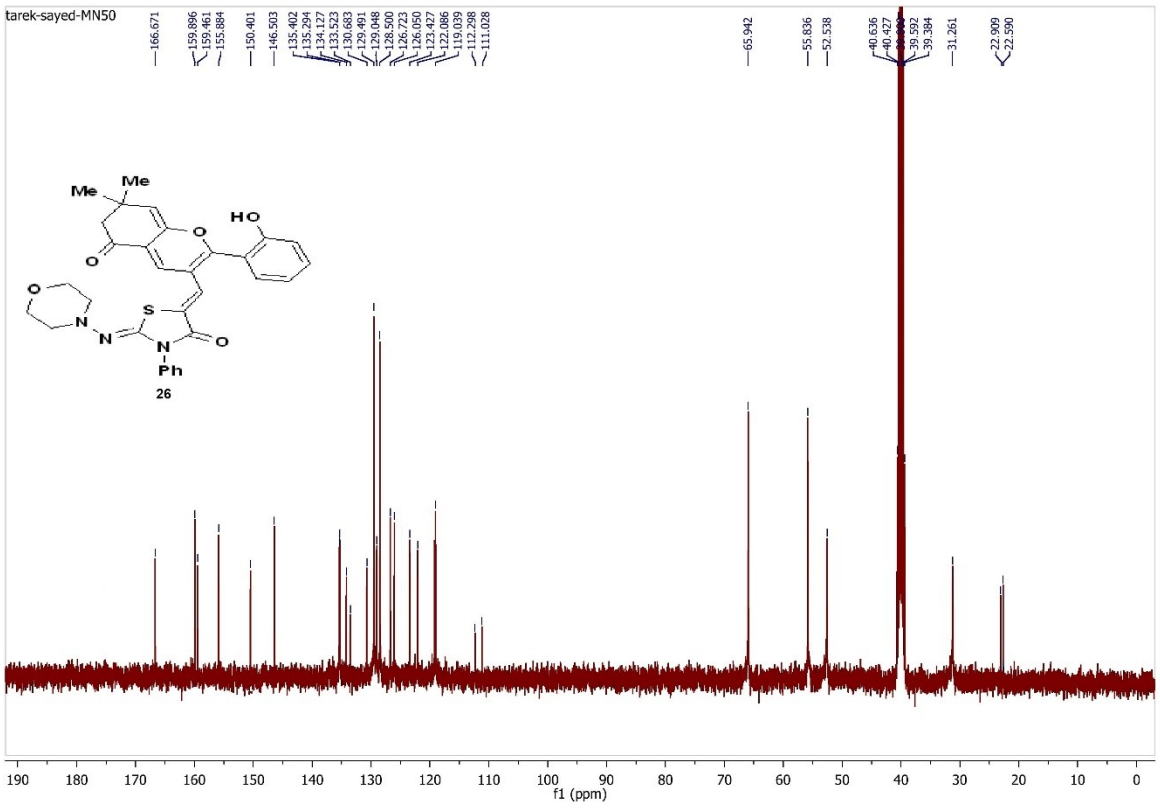


Figure S46: The ^{13}C-NMR spectrum of compound **26**.

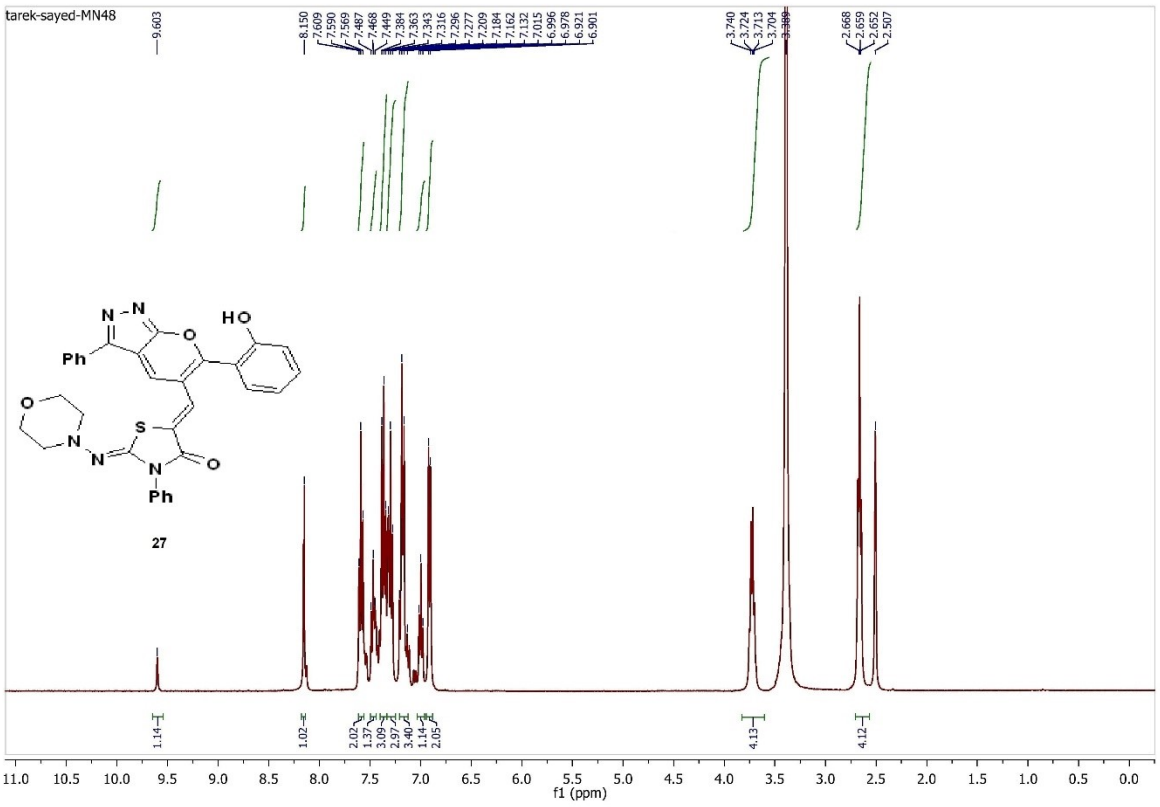


Figure S47: The ^{1}H-NMR spectrum of compound **27**.

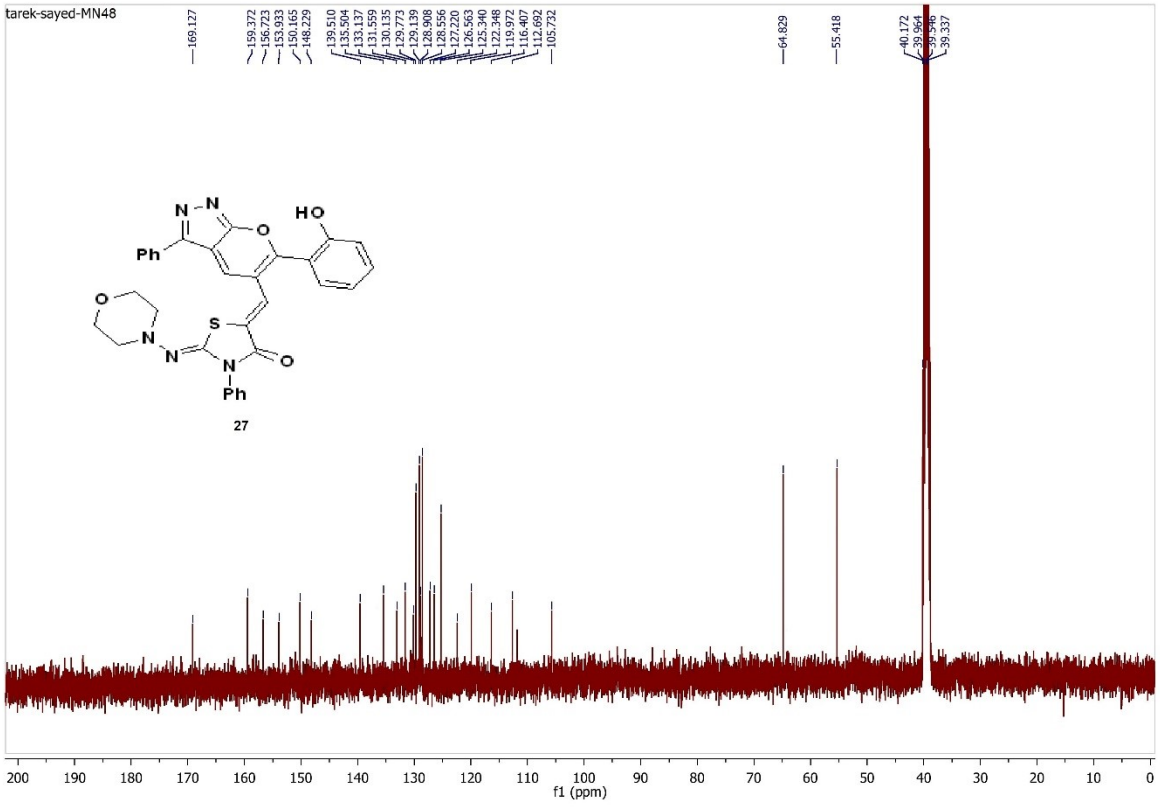


Figure S48: The ^{13}C-NMR spectrum of compound **27**.

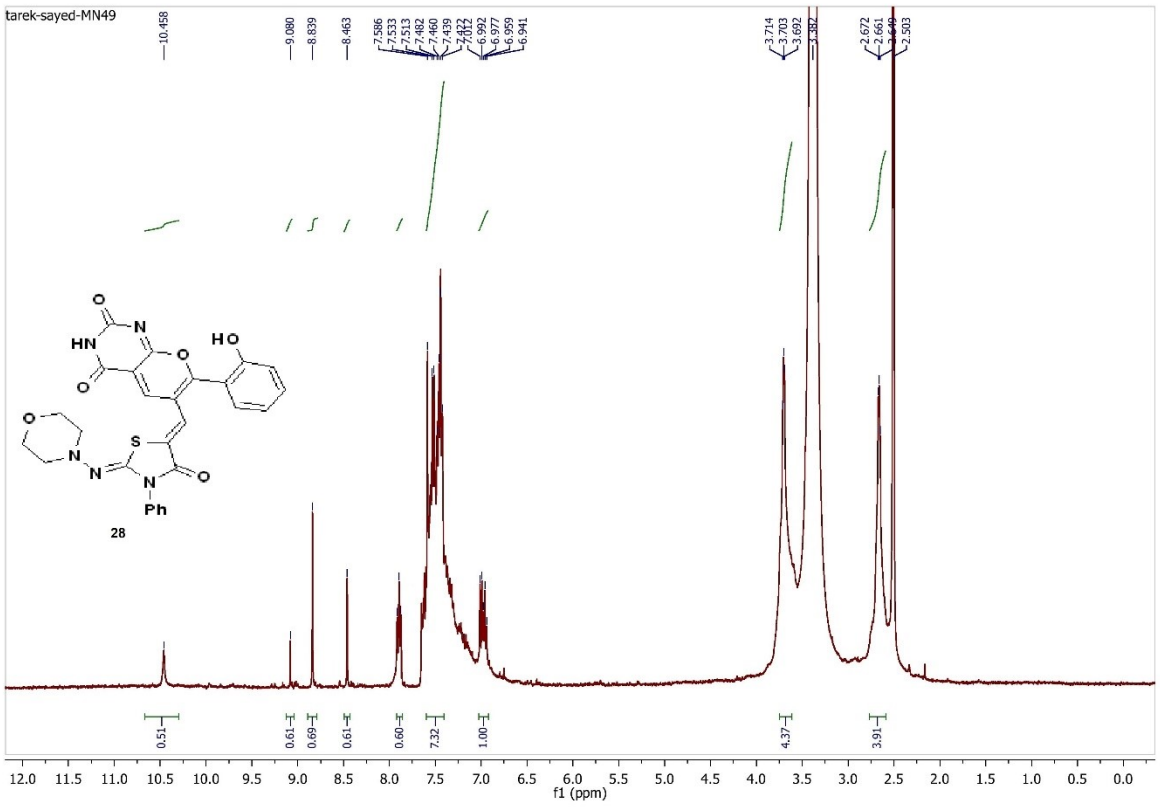


Figure S49: The ^{1}H-NMR spectrum of compound **28**.

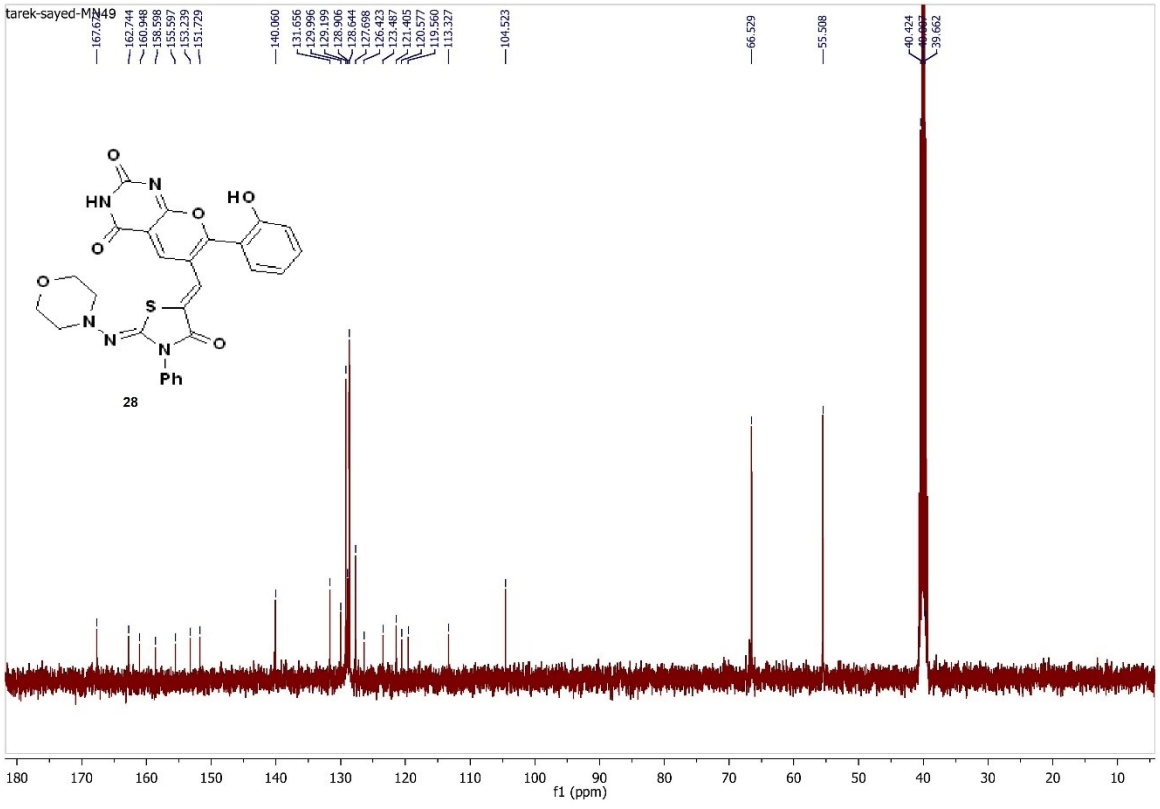


Figure S50: The ^{13}C-NMR spectrum of compound **28**.

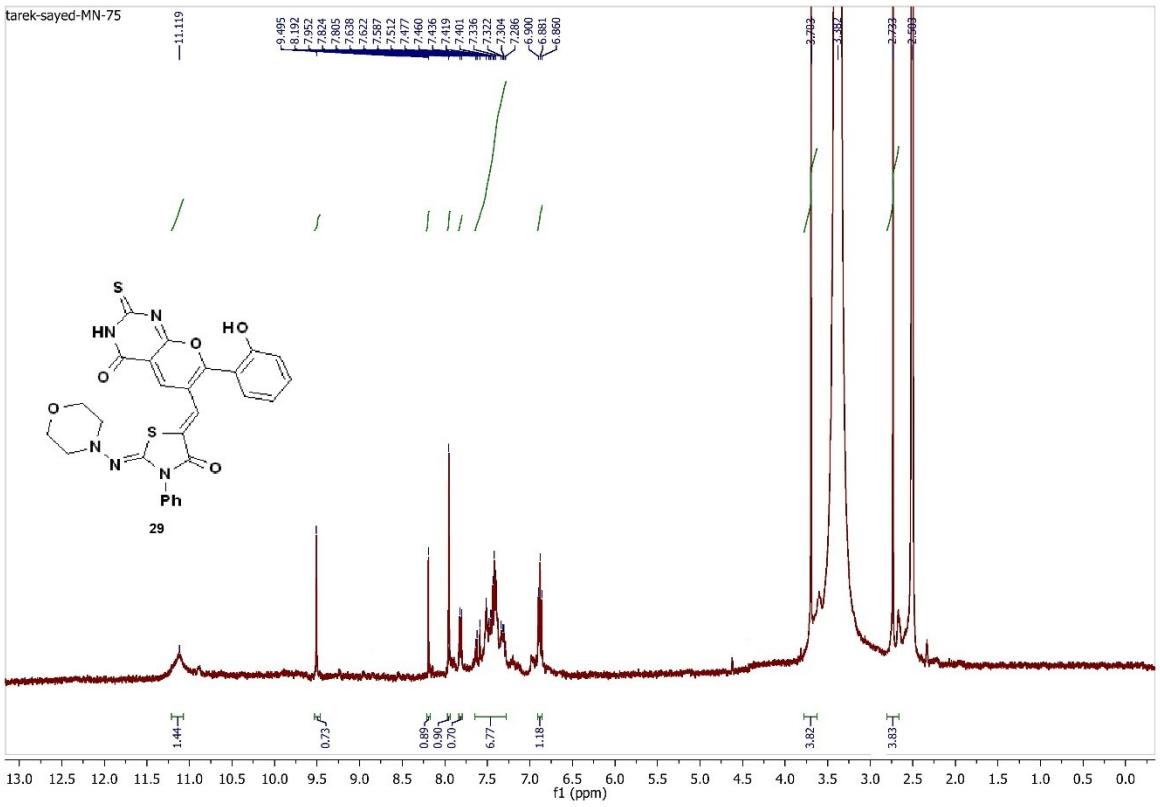


Figure S51: The ^{1}H-NMR spectrum of compound **29**.

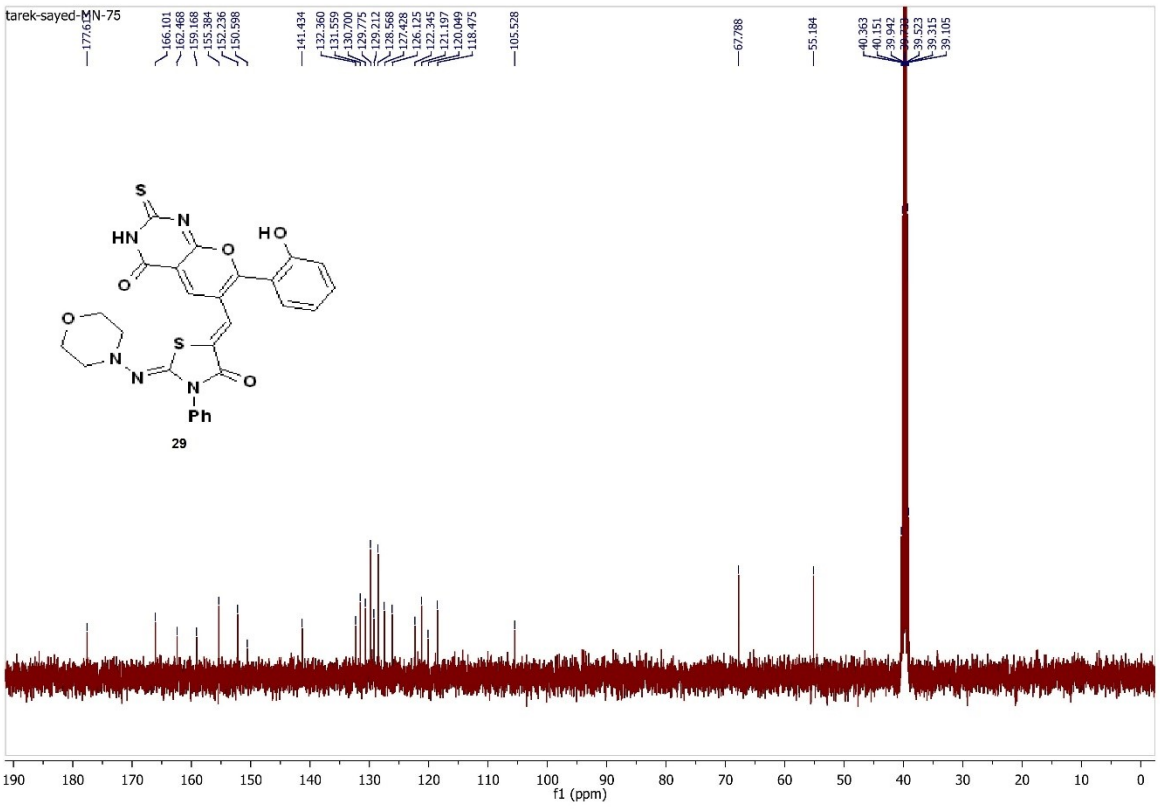


Figure S52: The ^{13}C-NMR spectrum of compound **29**.

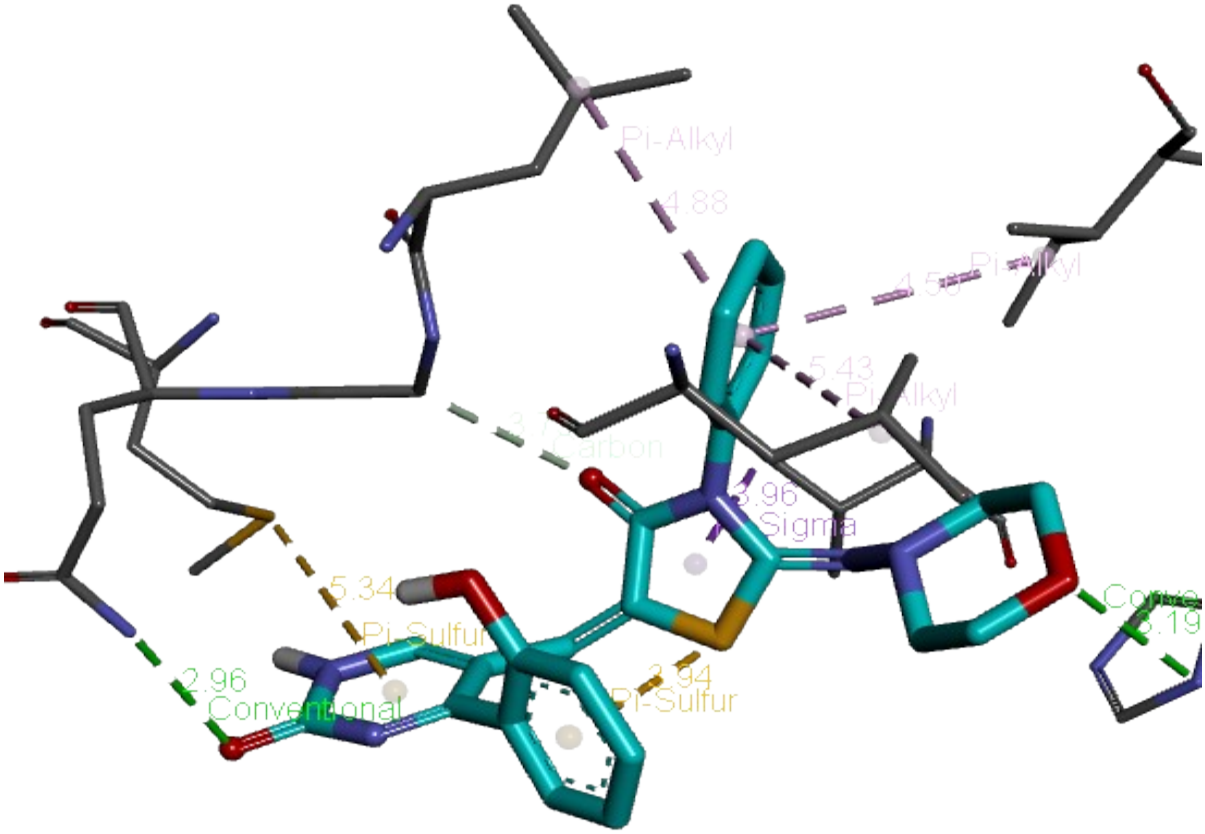


Figure S53: Interactions of product **12** with p53-MDM2 protein-protein interaction in 3D.

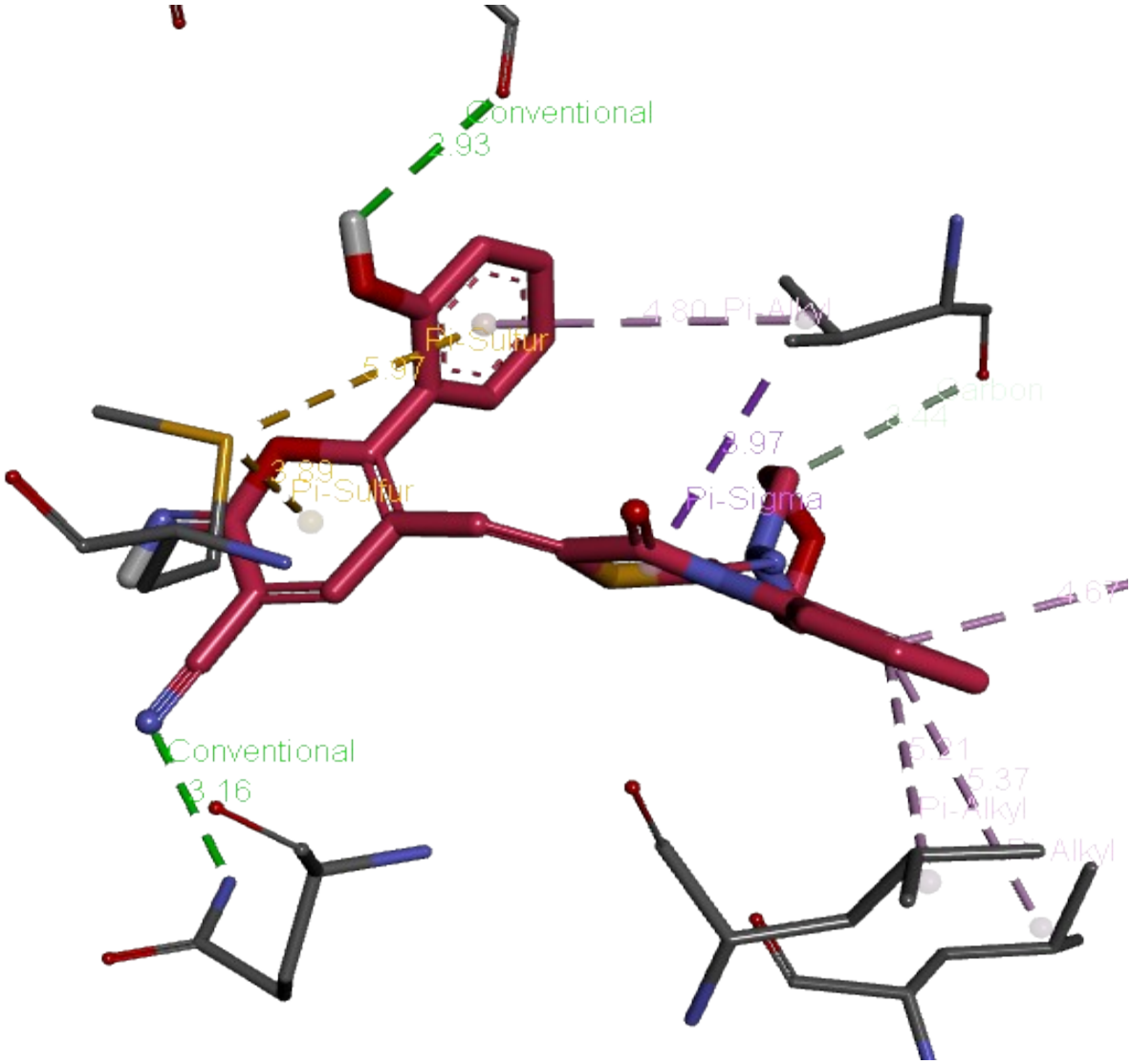


Figure S54: Interactions of product **22** with p53-MDM2 protein-protein interaction in 3D.

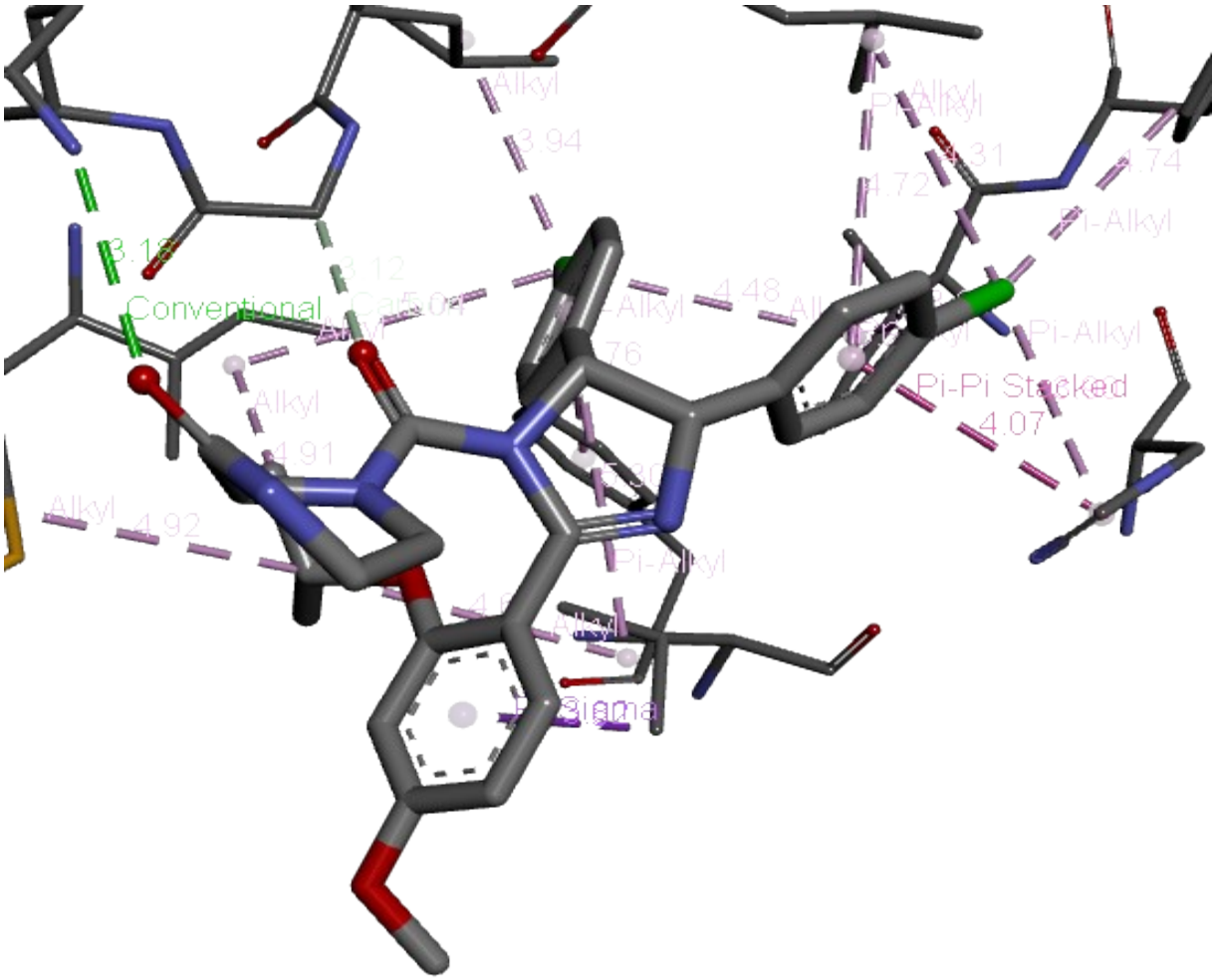


Figure S55: Interactions of Nutlin-3a with p53-MDM2 protein-protein interaction in 3D.