Supplementary data

Design, synthesis, and biological evaluation of novel thiazole derivatives as PI3K/mTOR dual inhibitors

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1- Chemistry Experimental Section

1.1 Chemistry procedures

Starting materials and solvents were acquired from commercial suppliers and were used without extra purification. Melting points were obtained on a Griffin apparatus and were uncorrected. Microanalyses for C, H, and N were carried out at the Regional Center for Mycology and Biotechnology, Faculty of Pharmacy, Al-Azhar University. IR spectra were recorded on Shimadzu IR 435 spectrophotometer (Shimadzu Corp., Kyoto, Japan) Faculty of Pharmacy, Cairo University, Cairo, Egypt and values were represented in cm^{-1}. ^1H NMR spectra were carried out on Bruker 400 MHz (Bruker Corp., Billerica, MA, USA) spectrophotometer, Faculty of Pharmacy, Cairo University, Cairo, Egypt. The chemical shifts were recorded in ppm on δ scale, coupling constants (*J*) were given in Hz and peak multiplicities are designed as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were carried out on Bruker 100 MHz spectrophotometer, Faculty of Pharmacy, Cairo University, Cairo, Egypt. Progress of the reactions were monitored by TLC using precoated aluminum sheet silica gel MERCK 60F 254 and was visualized by UV lamp.

1.2 2-Ethoxy-4-((2-(4-phenylthiazol-2-yl)hydrazineylidene)methyl)phenol (3a)

Yellowish green solid: 75% yield; mp 182–184ºC; IR (KBr, cm^{-1}) 3313 (OH), 3336 (NH), 3062 (CH aromatic), 2927, 2881 (CH aliphatic), 1620 (C=N), 1581 (C=C); ^1H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H, NH, D_2O exchangeable), 8.02 (s, 1H, CH=N), 7.85–7.83 (m, 1H, ArH), 7.45–7.38 (m, 2H, ArH), 7.34 (d, *J* = 7.2 Hz, 2H, ArH), 7.31 (s, 1H, ArH thiazole), 7.25 (d, *J* = 1.6 Hz, 1H, ArH), 7.10 (dd, *J* = 8.4, 1.6 Hz, 1H, ArH), 6.87–6.82 (m, 1H, ArH), 5.73 (s, 1H, OH, D_2O exchangeable), 4.07 (q, *J* = 6.8 Hz, 2H, $\underline{CH_2}CH_3$), 1.36 (t, *J* = 6.8 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 153.7, 147.7, 147.6, 135.6, 132.3, 129.9, 129.8, 129.1, 126.3, 121.6, 115.9, 112.4, 110.3, 64.3, 15.0. Anal. Calcd for $C_{18}H_{17}N_3O_2S$ (339.41): C, 63.70; H, 5.05; N, 12.38, found C, 63.91; H, 5.22; N, 12.59.

1.3 2-Ethoxy-4-((2-(4-(3-nitrophenyl)thiazol-2-yl)hydrazineylidene)methyl)phenol (3b)

Orange solid: 71% yield; mp 190–192ºC; IR (KBr, cm^{-1}) 3479 (OH), 3336 (NH), 3062 (CH aromatic), 2927, 2881 (CH aliphatic), 1616 (C=N), 1585 (C=C); ^1H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H, NH, D_2O exchangeable), 8.66 (s, 1H, ArH), 8.29 (d, *J* = 8.0 Hz, 1H, ArH), 8.14 (dd, *J* = 8.0, 1.6 Hz, 1H, ArH), 7.95 (s, 1H, CH=N), 7.72–7.66 (m, 2H, ArH + OH, D_2O exchangeable), 7.61 (s, 1H, ArH thiazole), 7.23 (d, *J* = 1.6 Hz, 1H, ArH), 7.07 (dd, *J* = 8.2, 1.6 Hz, 1H, ArH), 6.85 (d, *J* = 8.0 Hz, 1H, ArH), 4.07 (q, *J* = 6.8 Hz, 2H, $\underline{CH_2}CH_3$), 1.37 (t, *J* = 6.8 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 153.7, 148.2, 148.1, 147.6, 147.1, 136.1, 131.4, 129.3, 129.1, 124.5, 122.3, 121.7, 115.9, 115.7, 113.0, 64.3, 15.0. Anal. Calcd for $C_{18}H_{16}N_4O_4S$ (384.41): C, 56.24; H, 4.20; N, 14.58, found C, 56.41; H, 4.39; N, 14.81.

1.4 2-(2-(4-Chloro-3-nitrobenzylidene)hydrazineyl)-4-phenylthiazole (3c)

Yellow solid: 71% yield; mp 238–240ºC; IR (KBr, cm^{-1}) 3367 (NH), 3059 (CH aromatic), 2970, 2873 (CH aliphatic), 1627 (C=N), 1608 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H, NH, D_2O exchangeable), 8.30 (d, J = 2.0 Hz, 1H, ArH), 8.10 (s, 1H, CH=N), 7.98 (dd, J = 8.8, 2.0 Hz, 1H, ArH), 7.88–7.86 (m, 2H, ArH), 7.83 (d, J = 8.4 Hz, 1H, ArH), 7.43 (d, J = 7.2 Hz, 2H, ArH), 7.40 (s, 1H, ArH thiazole), 7.32 (t, J = 7.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.2, 150.9, 148.4, 138.3, 135.6, 134.8, 132.6, 130.9, 129.1, 128.8, 128.3, 126.0, 123.2, 104.8. Anal. Calcd for $C_{16}H_{11}ClN_4O_2S$ (358.80): C, 53.56; H, 3.09; N, 15.62, found C, 53.80; H, 3.27; N, 15.89.

1.5 2-(2-(4-Chloro-3-nitrobenzylidene)hydrazineyl)-4-(3-nitrophenyl)thiazole (3d)

Yellow solid: 76% yield; mp 236–238ºC; IR (KBr, cm^{-1}) 3410 (NH), 3086 (CH aromatic), 2920, 2866 (CH aliphatic), 1624 (C=N), 1570 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H, NH, D_2O exchangeable), 8.68 (t, J = 2.0, 1H, ArH), 8.31–8.30 (m, 2H, ArH), 8.16 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 8.10 (s, 1H, CH=N), 7.98 (dd, J = 8.4, 2.0 Hz, 1H, ArH), 7.83 (d, J = 8.4 Hz, 1H, ArH), 7.73 (s, 1H, ArH thiazole), 7.72 (t, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.6, 148.7, 148.6, 148.3, 138.5, 136.4, 135.4, 132.6, 132.0, 131.0, 130.7, 125.2, 123.2, 122.5, 120.4, 107.5. Anal. Calcd for $C_{16}H_{10}ClN_5O_4S$ (403.80): C, 47.59; H, 2.50; N, 17.34, found C, 47.82; H, 2.67; N, 17.52.

1.6 2-(2-(4-Chloro-3-nitrobenzylidene)hydrazineyl)-4-(4-chlorophenyl)thiazole (3e)

Yellow solid: 78% yield; mp 232–234ºC; IR (KBr, cm^{-1}) 3313 (NH), 3039 (CH aromatic), 2873, 2804 (CH aliphatic), 1631 (C=N), 1608 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H, NH, D_2O exchangeable), 8.31 (dd, J = 7.4, 1.6 Hz, 1H, ArH), 8.10 (s, 1H, CH=N), 7.97 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.89 (t, J = 7.4 Hz, 2H, ArH), 7.82 (d, J = 8.4 Hz, 1H, ArH), 7.56–7.46 (m, 3H, ArH + ArH thiazole); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 148.4, 147.0, 139.4, 135.2, 133.3, 132.6, 131.1, 130.9, 130.0, 128.9, 127.7, 123.3, 105.6. Anal. Calcd for $C_{16}H_{10}Cl_2N_4O_2S$ (393.24): C, 48.87; H, 2.56; N, 14.25, found C, 49.05; H, 2.71; N, 14.53.

1.7 1,5-Dimethyl-4-((2-(4-(3-nitrophenyl)thiazol-2-yl)hydrazineylidene)methyl)-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (3f)

Yellowish green solid: 71% yield; mp 238–240ºC; IR (KBr, cm^{-1}) 3410 (NH), 3109 (CH aromatic), 2924, 2850 (CH aliphatic), 1647 (C=O), 1608 (C=N), 1580 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H, NH, D_2O exchangeable), 8.67 (s, 1H, ArH), 8.30 (d, J = 8.0 Hz, 1H, ArH), 8.15 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 7.88 (s, 1H, CH=N), 7.71 (t, J = 8.0 Hz, 1H, ArH), 7.60 (s, 1H, ArH thiazole), 7.54 (t, J = 7.6 Hz, 2H, ArH), 7.40 (t, J = 7.6 Hz, 1H, ArH), 7.37–7.35 (m, 2H, ArH), 3.26 (s, 3H, NCH_3), 2.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 164.0, 152.5, 148.7, 148.6, 136.8, 136.4, 134.9, 132.0, 130.6, 129.7, 127.8, 125.7, 122.4, 120.3, 106.1, 101.3, 34.9, 12.7. Anal. Calcd for $C_{21}H_{18}N_6O_3S$ (434.47): C, 58.05; H, 4.18; N, 19.34, found C, 58.31; H, 4.32; N, 19.62.

1.8 4-((2-(4-(4-Bromophenyl)thiazol-2-yl)hydrazineylidene)methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (3g)

Buff solid: 80% yield; mp 234–236ºC; IR (KBr, cm^{-1}) 3221 (NH), 3051 (CH aromatic), 2939, 2850 (CH aliphatic), 1647 (C=O), 1610 (C=N), 1562 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H, NH, D_2O exchangeable), 7.88 (s, 1H, CH=N), 7.80 (d, J = 8.4 Hz, 2H, ArH), 7.59 (d, J = 8.4 Hz, 2H, ArH), 7.53 (t, J = 7.6

Hz, 2H, ArH), 7.46–7.40 (m,1H, ArH), 7.36–7.30 (m, 3H, ArH + ArH thiazole), 3.24 (s, 3H, NCH_3), 2.61 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3, 161.8, 152.5, 152.0, 149.7, 131.9, 130.0, 129.7, 128.1, 128.0, 127.9, 125.7, 120.8, 104.2, 101.3, 34.5, 10.7. Anal. Calcd for $C_{21}H_{18}BrN_5OS$ (468.37): C, 53.85; H, 3.87; N, 14.95, found C, 54.09; H, 4.03; N, 15.17.

1.9 2-(2-(4-(Benzyloxy)benzylidene)hydrazineyl)-4-phenylthiazole (3h)

Buff solid: 78% yield; mp 212–214ºC; IR (KBr, cm^{-1}) 3224 (NH), 3039 (CH aromatic), 2924, 2873 (CH aliphatic), 1612 (C=N), 1562 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H, NH, D_2O exchangeable), 8.02 (s, 1H, CH=N), 7.85 (d, *J* = 7.2 Hz, 2H, ArH), 7.62 (d, *J* = 8.8 Hz, 2H, ArH), 7.47 (d, *J* = 7.2 Hz, 2H, ArH), 7.44–7.39 (m, 4H, ArH), 7.36–7.29 (m, 3H, ArH + ArH thiazole), 7.09 (d, *J* = 8.8 Hz, 2H, ArH), 5.16 (s, 2H, OCH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.4, 162.7, 160.0, 137.2, 131.9, 130.9, 129.8, 129.5, 128.9, 128.5, 128.3, 128.2, 126.3, 116.0, 115.7, 69.8. Anal. Calcd for $C_{23}H_{19}N_3OS$ (385.49): C, 71.66; H, 4.97; N, 10.90, found C, 71.92; H, 4.84; N, 11.16.

1.10 2-(2-(4-(Benzyloxy)benzylidene)hydrazineyl)-4-(3-nitrophenyl)thiazole (3i)

Brown solid: 75% yield; mp 210–212ºC; IR (KBr, cm^{-1}) 3224 (NH), 3059 (CH aromatic), 2931, 2873 (CH aliphatic), 1620 (C=N), 1597 (C=C);^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H, NH, D_2O exchangeable), 8.66 (s, 1H, ArH), 8.28 (d, *J* = 8.0 Hz, 1H, ArH), 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H, ArH), 8.01 (s, 1H, CH=N), 7.69 (t, *J* = 8.0 Hz, 1H, ArH), 7.61–7.59 (m, 2H, ArH + ArH thiazole), 7.45 (d, *J* = 7.2 Hz, 2H, ArH), 7.39 (t, *J* = 7.2 Hz, 2H, ArH), 7.33 (d, *J* = 7.2 Hz, 1H, ArH), 7.08–7.05 (m, 3H, ArH), 5.13 (s, 2H, OCH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7, 164.6, 157.4, 148.4, 140.0, 136.2, 134.0, 132.3, 131.4, 129.3, 128.9, 128.5, 128.3, 128.2, 124.5, 122.8, 115.7, 93.2, 70.1. Anal. Calcd for $C_{23}H_{18}N_4O_3S$ (430.48): C, 64.17; H, 4.21; N, 13.02, found C, 64.40; H, 4.35; N, 13.29.

1.11 2-(2-(4-(Benzyloxy)-3-methoxybenzylidene)hydrazineyl)-4-phenylthiazole (3j)

Yellowish green solid: 71% yield; mp 206–208ºC; IR (KBr, cm^{-1}) 3224 (NH), 3059 (CH aromatic), 2935, 2870 (CH aliphatic), 1612 (C=N), 1570 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H, NH, D_2O exchangeable), 8.04 (s, 1H, CH=N), 7.85 (d, *J* = 7.2 Hz, 2H, ArH), 7.46 (d, *J* = 7.2 Hz, 3H, ArH), 7.41 (d, *J* = 8.0 Hz, 3H, ArH), 7.36–7.31 (m, 4H, ArH + ArH thiazole), 7.18 (dd, *J* = 8.4, 1.6 Hz, 1H, ArH), 7.12–7.09 (m, 1H, ArH), 5.13 (s, 2H, OCH_2), 3.83 (s, 3H, OCH3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 157.4, 149.8, 149.3, 135.6, 132.3, 129.9, 129.8, 129.5, 128.9, 128.4, 128.3, 128.1, 126.3, 121.2, 113.1, 110.2, 109.1, 70.3, 56.0. Anal. Calcd for $C_{24}H_{21}N_3O_2S$ (415.51): C, 69.38; H, 5.09; N, 10.11, found C, 69.09; H, 5.21; N, 10.34.

1.12 2-(2-(4-(Benzyloxy)-3-methoxybenzylidene)hydrazineyl)-4-(3-nitrophenyl)thiazole (3k)

Brown solid: 68% yield; mp 200–202ºC; IR (KBr, cm^{-1}) 3236 (NH), 3062 (CH aromatic), 2916, 2866 (CH aliphatic), 1635 (C=N), 1590 (C=C) ;^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H, NH, D_2O exchangeable), 8.68 (t, *J* = 2.0 Hz, 1H, ArH), 8.30 (d, *J* = 8.0 Hz, 1H, ArH), 8.16-8.13 (m, 1H, ArH), 7.99 (s, 1H, CH=N), 7.71 (t, *J* = 8.0 Hz, 1H, ArH), 7.64 (s, 1H, ArH thiazole), 7.46 (d, *J* = 6.8 Hz, 2H, ArH), 7.42–7.39 (m, 2H, ArH), 7.37–7.34 (m, 1H, ArH), 7.31 (d, *J* = 1.6 Hz, 1H, ArH), 7.17 (dd, *J* = 8.4, 1.6 Hz, 1H, ArH), 7.10 (d, *J* = 8.4 Hz, 1H, ArH), 5.13 (s, 2H, OCH_2), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 149.8, 149.6, 148.7, 148.4,

142.3, 137.3, 134.0, 132.0, 130.7, 130.5, 128.9, 128.3, 127.5, 123.2, 122.6, 120.4, 113.8, 109.2, 106.6, 70.4, 55.9. Anal. Calcd for $C_{24}H_{20}N_4O_4S$ (460.51): C, 62.60; H, 4.38; N, 12.17, found C, 62.43; H, 4.51; N, 12.43.

1.13 2-(2-(4-(Benzyloxy)-3-methoxybenzylidene)hydrazineyl)-4-(4-chlorophenyl)thiazole (3l)

Buff solid: 74% yield; mp 210–212ºC; IR (KBr, cm^{-1}) 3421 (NH), 3082 (CH aromatic), 2920, 2862 (CH aliphatic), 1616 (C=N), 1573 (C=C);^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H, NH, D_2O exchangeable), 7.99 (s, 1H, CH=N), 7.87 (d, J = 8.8 Hz, 2H, ArH), 7.48–7.46 (m, 4H, ArH), 7.41 (t, J = 7.2 Hz, 2H, ArH), 7.38 (s, 1H, ArH thiazole), 7.36–7.30 (m, 2H, ArH), 7.17 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.10 (d, J = 8.4 Hz, 1H, ArH), 5.13 (s, 2H, OCH_2), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.0, 149.8, 143.2, 137.2, 137.1, 131.8, 130.4, 130.0, 129.9, 128.9, 128.9, 128.6, 128.4, 128.3, 120.7, 113.8, 113.3, 109.1, 70.3, 56.0. Anal. Calcd for $C_{24}H_{20}ClN_3O_2S$ (449.95): C, 64.07; H, 4.48; N, 9.34, found C, 63.98; H, 4.59; N, 9.52.

1.14 2-(2-(4-(Benzyloxy)-3-ethoxybenzylidene)hydrazineyl)-4-phenylthiazole (3m)

Buff solid: 77% yield; mp 190–192ºC; IR (KBr, cm^{-1}) 3402 (NH), 3059 (CH aromatic), 2927, 2873 (CH aliphatic), 1624 (C=N), 1573 (C=C);^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H, NH, D_2O exchangeable), 7.97 (s, 1H, CH=N), 7.86 (d, J = 7.2 Hz, 2H, ArH), 7.47 (d, J = 7.2 Hz, 2H, ArH), 7.43–7.39 (m, 4H, ArH), 7.36–7.29 (m, 4H, ArH + ArH thiazole), 7.15 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 7.09 (d, J = 8.4 Hz, 1H, ArH), 5.16 (s, 2H, OCH_2), 4.10 (q, J = 6.8 Hz, 2H, O<u>CH_2</u>CH_3), 1.37 (t, J = 6.8 Hz, 3H, OCH_2<u>CH_3</u>); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.8, 149.9, 149.8, 149.1, 142.7, 137.4, 134.5, 129.1, 128.9, 128.8, 128.6, 128.3, 128.1, 126.1, 120.7, 114.4, 110.7, 104.0, 70.4, 64.4, 15.2. Anal. Calcd for $C_{25}H_{23}N_3O_2S$ (429.54): C, 69.91; H, 5.40; N, 9.78, found C, 70.06; H, 5.63; N, 10.02.

1.15 2-(2-(4-(Benzyloxy)-3-ethoxybenzylidene)hydrazineyl)-4-(3-nitrophenyl)thiazole (3n)

Buff solid: 79% yield; mp 206–208ºC; IR (KBr, cm^{-1}) 3267 (NH), 3051 (CH aromatic), 2978, 2873 (CH aliphatic), 1624 (C=N), 1577 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H, NH, D_2O exchangeable), 8.67 (t, J = 2.0 Hz, 1H, ArH), 8.30 (d, J = 8.0 Hz, 1H, ArH), 8.15 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 7.97 (s, 1H, CH=N), 7.71 (t, J = 8.0 Hz, 1H, ArH), 7.64 (s, 1H, ArH thiazole), 7.46 (d, J = 7.2 Hz, 2H, ArH), 7.40 (t, J = 7.2 Hz, 2H, ArH), 7.35–7.30 (m, 2H, ArH), 7.17 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.09 (d, J = 8.4 Hz, 1H, ArH), 5.15 (s, 2H, OCH_2), 4.10 (q, J = 7.2 Hz, 2H, O<u>CH_2</u>CH_3), 1.37 (t, J = 7.2 Hz, 3H, OCH_2<u>CH_3</u>); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 150.0, 149.1, 148.7, 148.1, 143.3, 137.4, 133.9, 132.0, 130.6, 130.5, 128.9, 128.3, 128.1, 123.1, 122.6, 120.9, 114.2, 110.5, 106.6, 70.4, 64.4, 15.2. Anal. Calcd for $C_{25}H_{22}N_4O_4S$ (474.54): C, 63.28; H, 4.67; N, 11.81, found C, 63.45; H, 4.72; N, 12.07.

1.16 2-(2-(4-(Benzyloxy)-3-ethoxybenzylidene)hydrazineyl)-4-(4-chlorophenyl)thiazole (3o)

Buff solid: 72% yield; mp 210–212ºC; IR (KBr, cm^{-1}) 3290 (NH), 3032 (CH aromatic), 2927, 2873 (CH aliphatic), 1624 (C=N), 1573 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H, NH, D_2O exchangeable), 7.96 (s, 1H, CH=N), 7.87 (d, J = 8.8 Hz, 2H, ArH), 7.48–7.46 (m, 4H, ArH + ArH thiazole), 7.40 (t, J = 7.2 Hz, 2H, ArH), 7.37 (s, 1H, ArH), 7.35–7.34 (m, 1H, ArH), 7.29 (d, J = 1.6 Hz, 1H, ArH), 7.15 (dd, J = 8.4, 1.6 Hz, 1H, ArH), 7.09 (d, J = 8.4 Hz, 1H, ArH), 5.15 (s, 2H, OCH_2), 4.10 (q, J = 6.8 Hz, 2H, O<u>CH_2</u>CH_3), 1.37 (t, J = 6.8 Hz, 3H, OCH_2<u>CH_3</u>). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9, 150.0, 149.9, 149.1, 143.2, 137.4, 131.9, 130.4, 130.0,

129.1, 128.9, 128.3, 128.1, 127.7, 121.0, 114.3, 110.7, 104.8, 70.4, 64.4, 15.2. Anal. Calcd for $C_{25}H_{22}ClN_3O_2S$ (463.98): C, 64.72; H, 4.78; N, 9.06, found C, 64.59; H, 4.87; N, 9.29.

1.17 2-(2-(4-(Benzyloxy)-3-ethoxybenzylidene)hydrazineyl)-4-(4-bromophenyl)thiazole (3p)

Buff solid: 69% yield; mp 200–202ºC; IR (KBr, cm^{-1}) 3394 (NH), 3062 (CH aromatic), 2987, 2873 (CH aliphatic), 1606 (C=N), 1570 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H, NH, D_2O exchangeable), 7.96 (s, 1H, CH=N), 7.81 (d, *J* = 8.4 Hz, 2H, ArH), 7.60 (d, *J* = 8.4 Hz, 2H, ArH), 7.46 (d, *J* = 6.8 Hz, 2H, ArH), 7.42–7.41 (m, 2H, ArH), 7.39 (s, 1H, ArH thiazole), 7.35 (d, *J* = 6.8 Hz, 1H, ArH), 7.29 (d, *J* = 1.6 Hz, 1H, ArH), 7.15 (dd, *J* = 8.4, 1.6 Hz, 1H, ArH), 7.09 (d, *J* = 8.4 Hz, 1H, ArH), 5.15 (s, 2H, OCH_2), 4.10 (q, *J* = 6.8 Hz, 2H, $O\underline{CH_2}CH_3$), 1.37 (t, *J* = 6.8 Hz, 3H, $OCH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9, 149.9, 149.8, 149.1, 143.2, 137.4, 132.0, 131.8, 130.7, 130.3, 128.9, 128.3, 128.1, 121.1, 120.7, 114.4, 110.7, 104.8, 70.4, 64.4, 15.2. Anal. Calcd for $C_{25}H_{22}BrN_3O_2S$ (508.43): C, 59.06; H, 4.36; N, 8.26, found C, 59.28; H, 4.50; N, 8.49.

2- Biological evaluation

2.1 Measurement of anticancer activity against a panel of 60 cell lines.

Anticancer activity screening of the newly synthesized compounds was measured *in vitro* utilizing 60 different human cancer cell lines provided by US NCI according to previously reported standard procedure as follows:

- Cells were seeded into 96-well microtiter plates in a density of 5,000-1,000 cells per 100 µL/well. Cells were then incubated at 37°C, 5% CO_2, 95% air, and 100% relative humidity for 24 h before the addition of experimental compounds. After 24 h, two plates of each cell line were fixed in situ with trichloroacetic acid (TCA), to present a measurement of the cell population for each cell line at the time of compound exposure (Tz).
- Experimental compounds were solubilized in DMSO at 400-fold, the desired final maximum test concentration, and stored frozen before use. At the time of compound addition, an aliquot of frozen concentrate was thawed and diluted to twice the desired final maximum test concentration with a complete medium containing 50 µg/mL gentamicin.
- Additional four, 10-fold or ½ log serial dilutions were made to provide a total of five compound concentrations plus control. Aliquots of 100 µL of these different compound dilutions were added to the appropriate microtiter wells containing 100 µL of the medium, resulting in the required final compound concentrations.
- Following compound addition, the plates were incubated for an additional 48 hr at 37°C, 5% CO_2, 95% air, and 100% relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells were fixed in situ by the gentle addition of 50 µL of cold 50% (w/v) TCA (final concentration, 10% TCA and incubated for 60 min. at 4°C. The supernatant was discarded, and the plates were washed five times with tap water and air-dried.
- Sulforhodamine B (SRB) solution (100 µL) at 0.4% (w/v) in 1% acetic acid was added to each well and plates were incubated for 10 min. at room temperature. After staining, the unbound dye was removed by washing

five times with 1% acetic acid and the plates were air-dried. The bound stain was subsequently solubilized with 10 mM Trizma base, and the absorbance was obtained using an automated plate reader at a wavelength of 515 nm. For suspension cells, we used the same methodology except that the assay was terminated by fixing settled cells at the bottom of the wells by gently adding 50 µL of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements [time zero (Tz), control growth (C), and test growth in the presence of a compound at the five concentration levels (Ti)], the percentage growth was calculated at each of the compound concentration levels. Percentage growth inhibition is calculated as follows:

$$[(Ti - Tz)/(C - Tz)] \times 100 \text{ for concentrations for which } Ti \geq Tz,$$
$$[(Ti - Tz)/Tz] \times 100 \text{ for concentrations for which } Ti > Tz$$

For each experimental agent. Growth inhibition of 50% (GI_{50}) is calculated from $[(Ti - Tz)/(C - Tz)] \times 100 = 50$, which is the compound concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the compound incubation; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested.

2.2 MTT assay and selectivity index (SI) calculation

The 3–(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method of monitoring *in vitro* cytotoxicity is well suited for use with multiwell plates. The assessment of cell population growth is based on the capability of living cells to reduce the yellow product MTT to a blue product, formazan, by a reduction reaction occurring in the mitochondria. The cell lines were ncubated for 24 h in 96-microwell plates. The number of living cells in the presence or absence (control) of the various test compounds is directly proportional to the intensity of the blue color, measured by spectrophotometry using (ROBONIK P2000 Spectrophotometer) at a wavelength of 570 nm. Measure the background absorbance of multiwell plates at 690 nm and subtract from the 570 nm measurement. Five concentrations ranging from 0.01 µM to 100 µM (with a semi-log decrease in concentration) were tested for each of the compounds under study. Each experiment was carried out in triplicate. The IC_{50} values [the concentration required for 50% inhibition of cell viability] were calculated using sigmoidal dose-response curve-fitting models. The selectivity index (SI) was calculated as the ratio of cytotoxicity (IC_{50}) of normal lymphocytes (PCS-800-017) to the leukemia cell line HL-60(TB).

Table S1. Percentages of growth inhibition obtained from tests of compounds **3a-q** against a panel of tumor cell lines at asingle concentration of (10 μM).

Cell lines	Compounds																
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**	**3m**	**3n**	**3o**	**3p**	**3q**
Leukemia																	
CCRF-CEM	59.40	**94.91**	25.72	65.66	**81.86**	20.43	--	--	28.01	--	53.56	--	--	31.73	27.64	37.55	--
HL-60(TB)	**73.44**	>100	>100	52.13	>100	--	27.22	16.13	49.69	51.49	54.83	36.03	26.31	41.43	45.56	22.85	21.66
K-562	45.39	**92.26**	26.86	**77.08**	**86.14**	32.21	41.9	--	58.43	47.14	65.07	34.26	37.47	48.21	67.36	59.13	17.23
MOLT-4	55.45	>100	37.97	58.44	**86.93**	--	22.16	--	49.58	43.52	51.06	20.61	33.59	60.49	24.42	28.39	--
RPMI-8226	53.40	**98.10**	**85.1**	**78.44**	>100	21.79	21.4	--	55.91	35.97	61.14	22.19	34.37	65.91	58.87	59.65	--
SR	31.27	**98.89**	22.96	53.84	**81.15**	--	35.61	--	60.14	40.82	55.36	33.08	--	29.37	43.93	25.36	--
Non-small cell lung cancer																	
A549/ATCC	--	**91.8**	--	--	--	--	--	25.63	18.49	38.48	23.60	--	--	21.93	**87.43**	**76.42**	--
EKVX	53.04	**78.52**	31.44	21.23	**97.75**	21.07	22.91	15.39	36.28	37.02	19.30	29.67	34.62	25.80	32.59	18.56	28.34
HOP-62	--	>100	--	17.54	60.28	--	--	--	--	--	--	--	--	--	--	--	30.45
HOP-92	23.92	>100	--	--	>100	21.68	--	--	--	35.81	--	24.16	11.71	--	31.88	20.97	29.45
NCI-H226	--	**83.99**	--	**75.71**	**89.96**	18.97	32.30	--	--	19.19	--	32.12	18.90	15.31	31.25	22	NT
NCI-H23	39.24	>100	--	44.9	**80.17**	20.85	19.69	--	32.67	32.55	23.84	23.55	26.07	--	54.58	47.28	15.88
NCI-H322M	34.1	**76.97**	**83.11**	50.49	>100	16.24	--	24.29	--	23.68	--	15.28	19.83	--	22.81	15.02	16.75
NCI-H460	27.32	>100	--	22.22	38.05	21.03	--	--	26.09	--	--	43.32	--	24.08	**88.78**	**78.6**	22.75
NCI-H522	**88.98**	>100	17.49	46.33	**82.28**	33.91	27.60	18.26	25.37	--	33.62	39.74	20.63	31.86	31.86	60.18	17.37
Colon Cancer																	
COLO 205	--	--	--	--	--	--	--	--	--	--	64.66	--	--	--	25.07	34.87	--
HCC-2998	>100	**88.2**	>100	>100	>100	21.1	--	--	--	--	16.18	--	--	16.45	25.55	18.01	--
HCT-116	34.14	>100	--	--	20.87	16.68	--	--	42.7	19.96	47.76	15.42	26.36	39.24	**87.5**	**70.93**	--
HCT-15	41.66	**92.55**	--	56.61	**86.41**	--	--	50.17	52.32	32.35	46.47	34.27	19.16	45.63	61	65.84	15.17
HT29	--	--	42.62	64.28	**82.35**	16.93	--	--	--	17.78	16.72	31.22	--	--	68.17	**73.91**	--
KM12	42.89	>100	**86.6**	**96.1**	>100	--	--	17.75	28.88	18.03	30.65	18.21	15.47	20.79	26.6	30.01	--
SW-620	--	**99.57**	--	--	22.12	--	--	--	--	--	--	--	--	--	**76.18**	**76.13**	--
CNS Cancer																	
SF-268	29.11	**96.73**	--	--	34.71	--	--	42.42	--	--	--	--	--	--	--	--	27.12
SF-295	18.92	>100	--	--	--	--	16.9	15.31	21.39	--	50.73	20.59	--	37.8	47.97	30.68	--

SF-539	58.81	>100	--	--	--	35.93	--	--	31.12	--	48.57	22.86	--	26.63	61.61	37.69	57.12
SNB-19	28.77	**96.14**	19.27	30.98	**80.07**	--	--	--	--	--	25.66	34.46	--	16.81	23.61	--	21.94
SNB-75	53.81	>100	--	--	39.93	24.94	--	--	--	--	--	29.18	25.77	34.84	51.3	40.93	21.73
U251	21.78	>100	--	58.23	49.15	--	--	--	17.78	--	22.24	--	--	28.24	45.29	58.5	20.33
Melanoma																	
LOX IMVI	**85.46**	>100	--	>100	**90.84**	16.36	--	15.53	--	17.25	16.19	--	17.00	16.03	35.4	37.64	32.16
MALME-3M	--	>100	--	33.15	50.91	29.42	--	--	22.17	27.59	19.58	29.06	--	--	32.73	34.00	22.26
M14	43.1	>100	--	46.25	31.31	--	--	--	--	--	21.40	--	30.41	23.95	45.97	33.88	18.79
MDA-MB-435	28.79	>100	--	--	--	--	--	--	15.55	--	--	--	--	22.41	43.55	43.55	--
SK-MEL-2	--	>100	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
SK-MEL-28	28.01	**98.65**	--	37.64	**74.32**	--	--	--	--	--	19.76	--	--	20.44	--	17.45	--
SK-MEL-5	53.67	>100	--	35.44	59.62	22.91	26.63	--	41.23	34.24	28.75	20.56	15.47	26.9	19.64	17.53	18.62
UACC-257	18.45	>100	--	16.26	49.16	18.39	17.94	--	--	--	--	--	--	18.91	--	--	--
UACC-62	46.06	>100	--	--	--	16.79	22.46	46.13	24.99	37.25	26.41	28.76	33.07	28.76	24.88	25.09	17.56
Ovarian cancer																	
IGROV1	59.43	>100	--	18.63	67.11	--	--	--	--	35.38	--	--	36.22	--	33.04	20.85	--
OVCAR-3	40.3	>100	**96.18**	>100	>100	--	--	--	--	23.4	--	--	23.61	--	--	--	--
OVCAR-4	45.81	>100	--	--	26.41	44.46	22.78	17.98	38.2	38.18	33.62	30.19	23.54	38.01	58.49	36.39	22.68
OVCAR-5	--	**83.55**	--	--	--	--	--	--	--	--	--	--	--	--	15.11	--	--
OVCAR-8	22.41	**97.1**	--	--	16.97	--	--	--	--	--	18.61	18.57	--	--	49.16	42.39	35.08
NCI/ADR-RES	24.09	>100	NT	NT	NT	25.77	--	NT	NT	NT	NT	NT	16.65	23.42	58.7	51.54	40.49
SK-OV-3	--	**80.72**	--	--	--	---	--	--	--	--	--	--	--	--	--	--	40.84
Renal Cancer																	
786-0	19.88	>100	--	--	--	30.32	--	--	19.33	--	56.5	--	--	49.32	53.87	28.09	--
A498	--	--	--	--	--	--	16.71	--	--	--	--	--	--	NT	21.33	--	--
ACHN	35.01	**99.95**	--	--	--	31.59	--	**79.82**	20.22	29.58	24.81	31.04	17.87	19.97	39.1	21.34	18.09
CAKI-1	49.83	>100	--	--	39.94	27.17	--	45.57	20.11	29.18	34.96	26.63	24.09	28.8	24.04	18.26	18.6
RXF 393	22.21	>100	--	--	68.9	--	--	--	25.86	--	68.51	--	--	**79.23**	29.52	25.01	22.03
SN12C	30.88	>100	--	23.06	48.25	--	--	--	24.76	24.37	26.83	--	16.04	17.13	28.47	25.27	19.48
TK-10	--	>100	--	--	--	--	--	--	--	--	15.38	--	--	--	--	--	--
UO-31	66.01	**98.32**	--	36.67	32.14	25.48	22.09	40.39	33.18	54.03	31.49	26.78	48.12	33.55	44.94	29.21	15.44
Prostate Cancer																	
PC-3	54.86	**93.38**	40.1	33.67	>100	--	--	37.45	32.14	41.05	37.82	30.81	31.71	32.58	29.67	40.37	--

DU-145	--	>100	63.72	38.17	**99.19**	--	--	19.73	25.99	--	25.89	--	--	--	63.74	34	16.45
Breast Cancer																	
MCF7	**75.82**	>100	**89.86**	**97.95**	>100	22.9	--	34.93	47.38	41.77	35.94	45.02	26.34	38.92	42.99	31.98	36.18
MDA-MB-231/ATCC	45.34	>100	--	22.45	**74.93**	38.76	--	17.41	--	31.89	39.05	33.93	32.06	18.51	31.73	30.68	29.54
HS 578T	34.02	65.19	27.01	**75.99**	>100	43.39	--	--	--	--	36.38	27.78	18.74	25.02	35.79	34.63	40.54
BT-549	67.47	>100	--	52.5	--	20.69	21.68	--	--	--	NT	--	19.19	15.5	32.31	--	28.38
T-47D	58.45	>100	>100	**91.54**	>100	36.84	34.85	37.92	33.45	45.22	63.92	27.62	47.96	48.12	40.4	24.51	23.36
MDA-MB-468	**89.79**	>100	>100	>100	>100	51.18	40.98	--	26.36	19.26	38.87	--	21.79	38.36	41.91	32.51	33.94
Mean inhibition	36.86	**111.56**	21.54	36.04	**65.96**	16.24	9.82	13.09	18.51	19.06	28.81	16.48	14.46	23.85	37.06	31.83	18.2

-- Inhibition of growth by the compound is less than 15%.
* The bold figures indicate **Strong (GI% > 70%)**

2.3 *In vitro* PI3K inhibitory assay

The inhibitory rate against PI3K of compounds **3b** and **3e** were assayed *in-vitro* using the PI3Kα (p110α/p85α) Assay Kit Catalog #79781, BPS Bioscience, Inc, San Diego, CA, USA according to the manufacturer's instructions. Mix 750 µL Kinase assay buffer and 750 µL distilled water (1:1) to prepare 2.5x Kinase assay buffer. Mix 25 µL of 500 µM ATP (provided) and 975 µL distilled water to prepare 12.5 µM ATP solution. Calculate the amount of PI3Kα required for the assay and dilute enzyme to ~ 0.5 ng/µL with 2.5x Kinase assay buffer prepared in step 2. Store remaining undiluted enzyme in aliquots at -80°C. add 5 µL PI3K lipid substrate first, 5 µL inhibitor second, 5 µL 12.5 µM ATP third and 10 µL of diluted PI3Kα). Add 5 µL PI3K lipid substrate to all wells. Add 5 µL of 5x Inhibitor solution of each well labeled as "Test Inhibitor." For the "Positive Control" and "Blank," add 5 µL of the same solution without inhibitor Add 5 µL diluted ATP to all wells. To the wells designated as "Blank," add 10 µL of 2.5x Kinase assay buffer. Initiate reaction by adding 10 µL of diluted PI3Kα enzyme to the wells designated "Positive Control" and "Test Inhibitor." Carefully shake the plate well and incubate it at 30°C for 40 min. After the 40 minutes reaction, add 25 µL of ADP-Glo reagent to each well. Cover plate with aluminum foil and incubate the plate at room temperature for 45 min. After the 45 min incubation, add 50 µL of Kinase Detection reagent to each well. Measure luminescence using the microplate reader. "

2.4 *In vitro* mTOR inhibitory assay

The inhibitory rate against PI3K of compounds **3b** and **3e** were assayed in-vitro using m-TOR/Raptor/MLST8 Complex, Catalog #: 40300 according to the manufacturer's directions. Assay was done using ADP-Glo (Promega) reagents with 100 µM ATP, 0.1 mg/mL 4EBP1 and 5 mM MnCl2 in 25 µL using kinase buffer (40 mM Tris HCl pH 7.4, 20 mM $MgCl_2$, 0.1 mg/mL BSA, and 2 mM DTT). Reaction was performed at 30°C for 45 min.

Conc	% inhibition
100	94
10	89
1	71
0.1	49
0.01	33

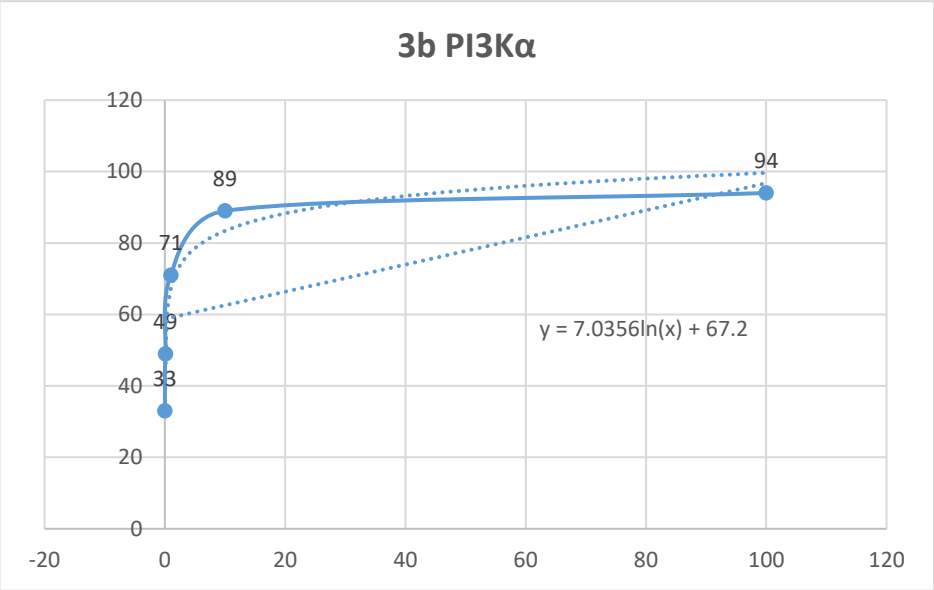
e

2.718282

Conc.	nd % inhibi	Excel-Fit
100	94	**99.6001**
10	89	99.6001
1	71	67.2
0.1	49	50.9999
0.01	33	34.7999
IC50	0.086	0.08675
		7.0356
		67.2

Equation that describes the curve

y = 7.0356ln(x) + 67.2



Conc	% inhibition
100	93
10	85
1	63
0.1	47
0.01	30

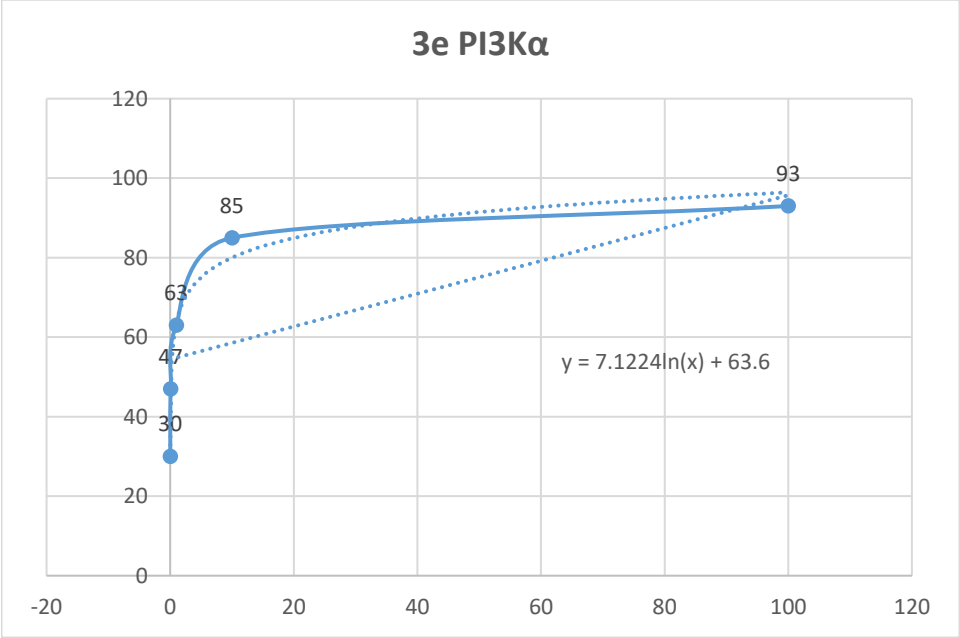
e

2.718282

Conc.	nd % inhibit	Excel-Fit
100	93	**96.399864**
10	85	96.399864
1	63	63.6
0.1	47	47.200068
0.01	30	30.800136
IC50	0.148	0.1481591
		7.1224
		63.6

Equation that describes the curve

y = 7.1224ln(x) + 63.6



Conc	% inhibition
100	93
10	82
1	61
0.1	43
0.01	27

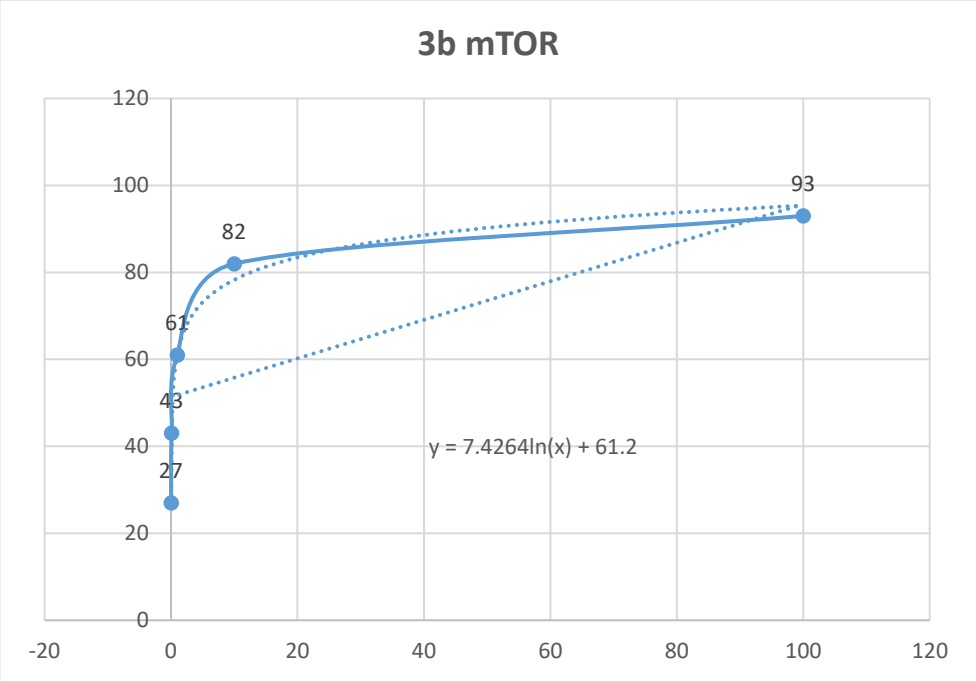
e

2.718282

Conc.	nd % inhibi	Excel-Fit
100	93	**95.399836**
10	82	95.399836
1	61	61.2
0.1	43	44.100082
0.01	27	27.000164
IC50	0.221	0.2213228
		7.4264
		61.2

Equation that describes the curve

y = 7.4264ln(x) + 61.2



Conc	% inhibition
100	92
10	75
1	50
0.1	27
0.01	11

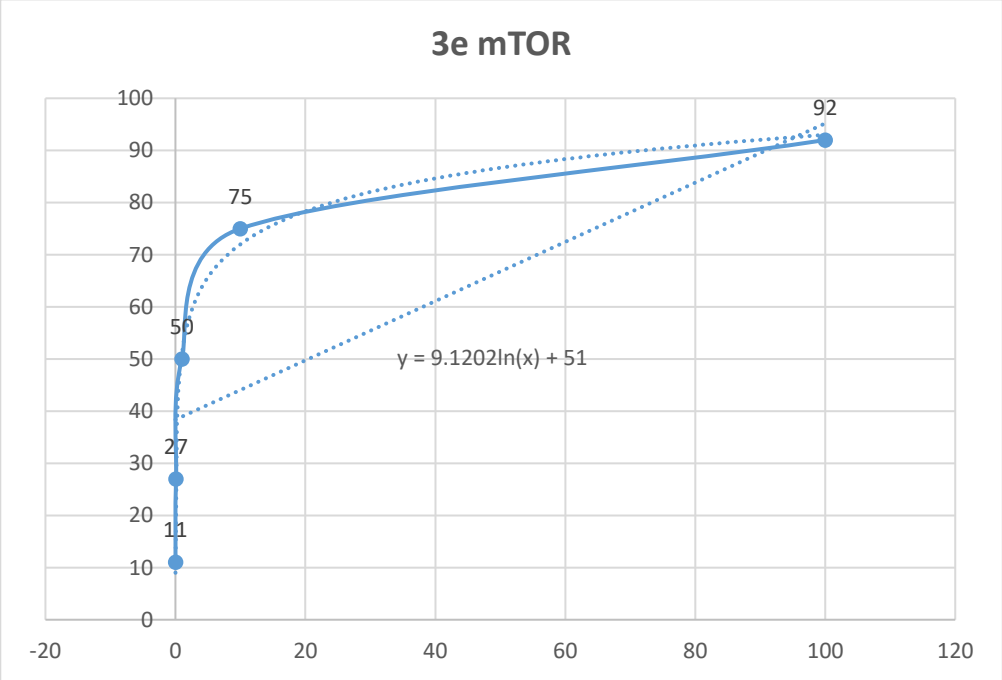
e

2.718282

Conc.	nd % inhibi	Excel-Fit
100	92	**93.000073**
10	75	93.000073
1	50	51
0.1	27	29.999963
0.01	11	8.9999269
IC50	0.896	0.8961507
		9.1202
		51

Equation that describes the curve

y = 9.1202ln(x) + 51



Conc	% inhibition
100	95
10	82
1	68
0.1	49
0.01	36

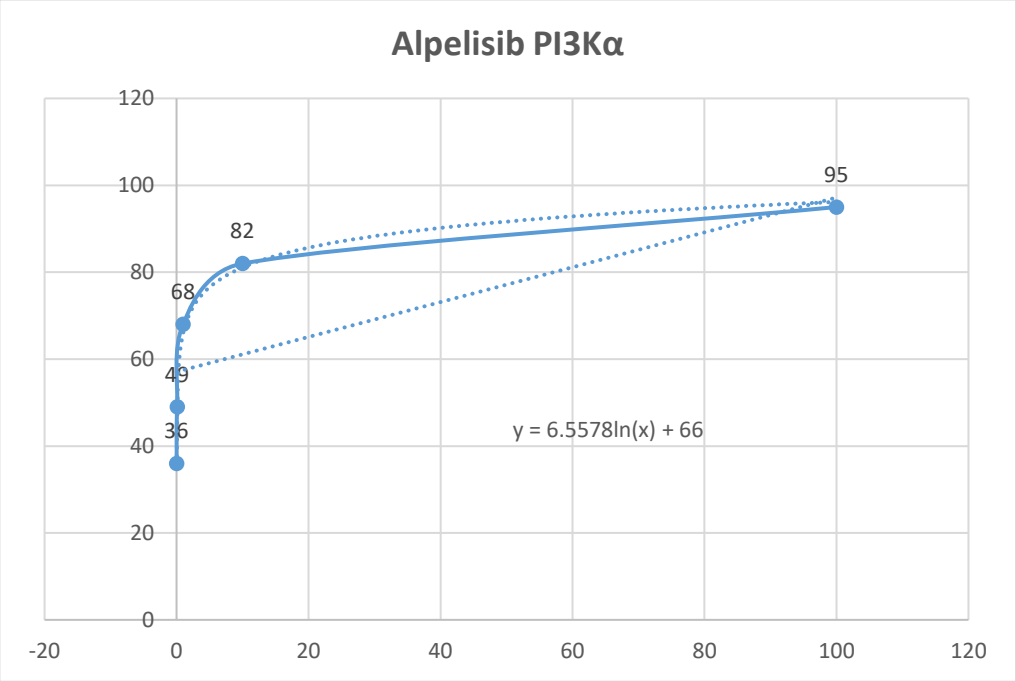
e

2.718282

Conc.	und % inhibiti	Excel-Fit
100	95	**96.19979**
10	82	96.19979
1	68	66
0.1	49	50.90011
0.01	36	35.80021
IC50	0.087	0.087175
		6.5578
		66

Equation that describes the curve

y = 6.5578ln(x) + 66



Conc	% inhibition
100	96
10	86
1	70
0.1	47
0.01	30

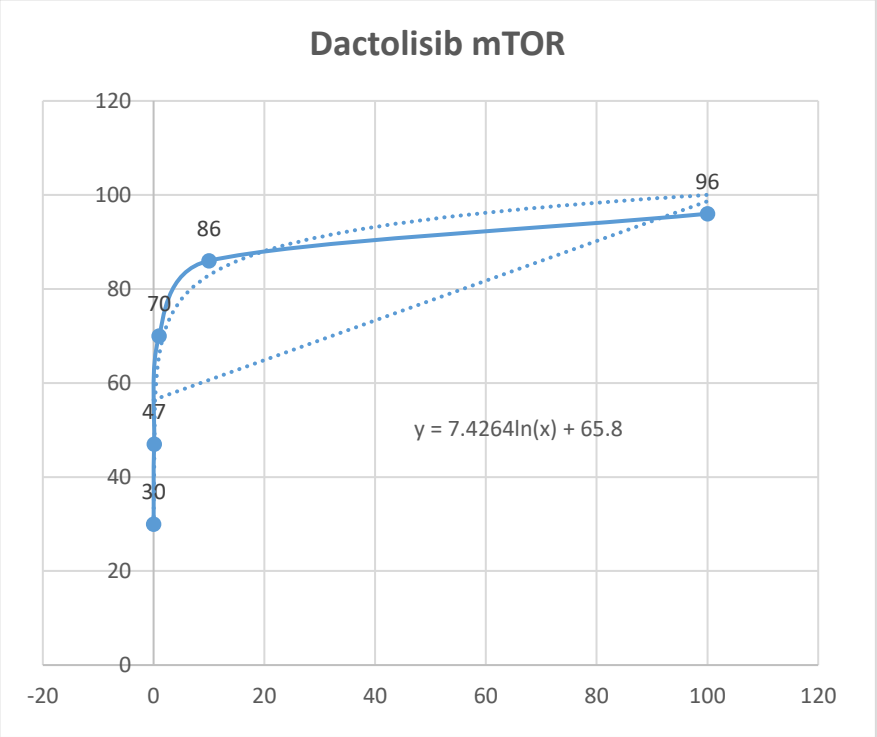
e

2.7183

Conc.	ınd % inhibit	Excel-Fit
100	96	**99.99984**
10	86	99.99984
1	70	65.8
0.1	47	48.70008
0.01	30	31.60016
IC50	0.119	0.119129
		7.4264
		65.8

Equation that describes the curve

y = 7.4264ln(x) + 65.8



2.5 Cell cycle analysis

Flow cytometry was used to analyze the cell cycle using ab139418 propidium iodide flow cytometry kit/BD (Abcam, Cambridge, UK), as directed by the manufacturer guidelines. leukemia HL60(TB) cells were treated with compounds **3b** and **3e** at their IC_{50} values (2.32 and 2.29 μM, respectively) for 24 h. The cells were washed twice with ice-cold phosphate buffer saline (PBS) and collected by centrifugation. The cells were then fixed using ice-cold 66% (v/v) ethanol, washed with PBS, and re-suspended with 0.1 mg/mL RNase to digest cellular RNA and thus minimize stained RNA in the background. The cells were next stained with PI, a fluorescent molecule that may bind to nucleic acid, at a concentration of 40 mg/mL. In cells, PI attaches to DNA in proportion to its amount. Because the DNA content of cells at different stages of the cell cycle differs, the fluorescence intensitycan be used to assess the stage of cell growth. FacsCalibur (BD Biosciences, USA) was used to estimate cell fluorescence, which was then examined using Cell-Quest software (Becton Dickinson). Cell cycle analysis of leukemia HL-60(TB) cells without any treatment was used as a control.

2.6 Apoptosis assay

According to the manufacturer's instructions, flow cytometry was used to analyze apoptosis using Annexin V and propidium iodide double-staining apoptosis detection kit (Biovision, USA). Annexin V is a phosphatidylserine (PS) binding protein with a high affinity. After beginning apoptosis, the latter is a cell membrane component that translocate from the inner face of the plasma membrane to the cell surface. PS can be detected on the cell surface using a fluorescent Annexin V conjugate. Leukemia HL-60(TB) cells ($5x10^5$) were exposed to compounds **3b** and **3e** at their IC_{50} values and subsequently incubated for 24 h. After that, the cells were centrifuged and resuspended in 500 mL of binding buffer. Annexin V and PI double staining was accomplished by mixing 5 μL of Annexin V with 5 μL of PI. The cells were then incubated for 15 min. in the dark at room temperature. FacsCalibur was used to assess cell fluorescence after incubation (BD Biosciences, USA). The results were represented using dot-plot graphs.

2.7 Caspase-3 enzyme assay

The level of the apoptotic marker caspase-3 was measured using Invitrogen ELISA Kit Catalog # KHO1091. The procedure of the used kit was performed according to the manufacturer's instructions. Let all components reach room temperature before use. Gently combine all liquid reagents before use. Add 100 μL of the standard diluent buffer to the zero standard wells. Add 100 μL of standards and controls or diluted samples to the appropriate microtiter wells. Incubate for 2 h at room temperature. Pipette 100 μL of caspase-3 (Active) detection antibody solution into each well. Incubate for 1 h at room temperature. Add 100 μL anti-rabbit IgG HRP working solution to each well. Prepare the working dilution and incubate for 30 min. at room temperature. Add 100 μL of stabilized chromogen to each well. The liquid in the wells will begin to turn blue. Incubate for 30 min. at room temperature and in the dark. Add 100 μL of stop solution to each well. The solution in the wells should change from blue to yellow. Read the absorbance of each well at 450 nm. Read

the plate within 2 h after adding the stop solution. Use curve fitting software to generate the standard curve. Read the concentrations for unknown samples and controls from the standard curve.

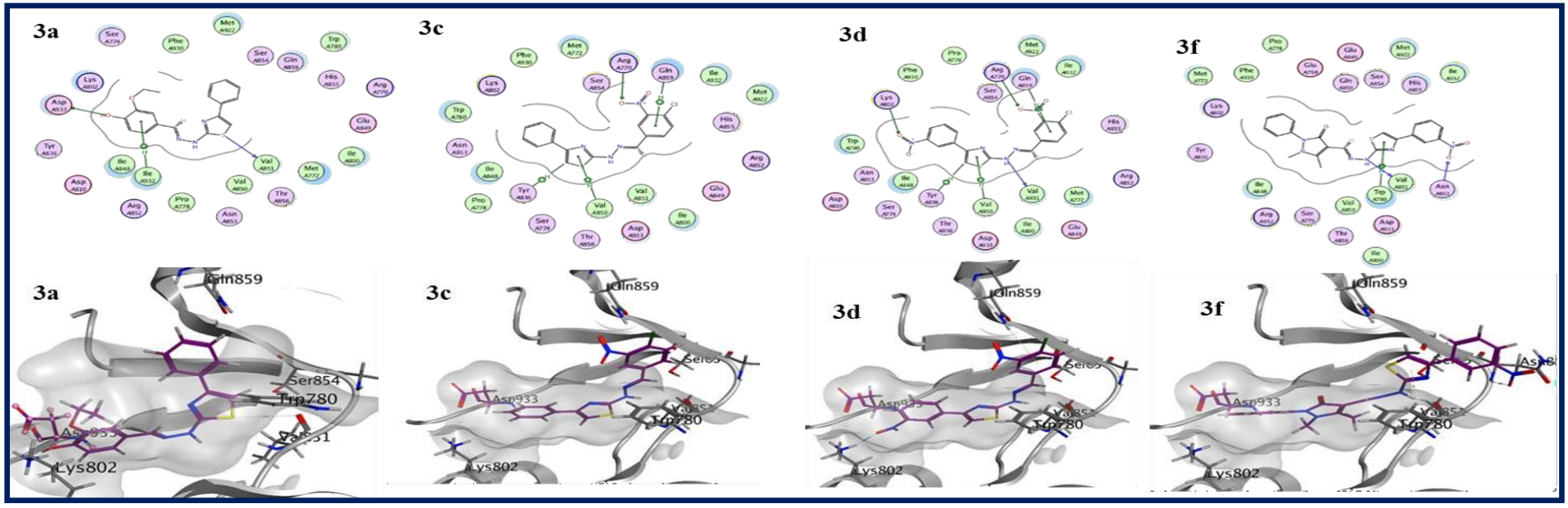
3- Molecular modeling

3.1 Molecular modeling studies

Table S2. The docking scores and Lipinski parameters of the thiazole derivatives **3a**, **3c**, **3d**, **3f**–**q**

Compound	Docking scorewith PI3K active site (PDB: 7PG6) (kcal/mol)	Interactions withPI3K active site	Docking scorewith mTOR active site (PDB: 4JT6) (kcal/mol)	Interactions withmTOR active site
3a	-6.7718	HB (Val851) HB (Asp933) Arene-H (Ile932)	-7.5046	HB (Gly2238) Arene-H (Met2345) Arene-H (Ile2356)
3c	-6.2879	HB (Arg770) Arene-H (Tyr836) Arene-H (Val850) Arene-H (Gln859)	-7.6092	HB (Trp2239) HB (Val2240) Arene-H (Glu2190) Arene-H (Met2345)
3d	-6.9187	HB (Lys802) HB (Val851) HB (Arg770) Arene-H (Tyr836) Arene-H (Val850) Arene-H (Gln859)	-7.6802	HB (Asp2195) HB (Val2240) Arene-H (Ile2237) Arene-H (Met2345) Arene-H (Ile2356)
3f	-7.1743	HB (Val851) HB (Asn853) Arene-H (Trp780)	-8.2853	HB (Met2345) HB (Leu2192) Arene-H (Trp2239) Arene-H (Glu2190) Arene-H (Met2345) Arene-H (Asp2357)
3g	-7.1772	HB (Val851) Arene-H (Tyr836) Arene-H (Trp780) Arene-H (Asn853)	-8.5718	HB (Met2345) Arene-H (Glu2190) Arene-H (Met2345) Arene-H (Asp2357) Arene-H (Ile2356)
3h	-7.4789	HB (Val851) Arene-H (Tyr836) Arene-H (Trp780) Arene-H (Lys802) Arene-H (Asn853)	-8.2342	HB (Gly2238) Arene-H (Glu2190) Arene-H (Met2345)
3i	-7.5763	HB (Val851) HB (Asn853) Arene-H(Lys802) Arene-H (Ser854) Arene-H (Trp780) Arene-H(Lys802)	-8.7294	HB (Gly2238) HB (Met2345) HB (Thr2245) Arene-H (Met2345) Arene-H (Glu2190)

3j	-7.3285	HB (Ser851) Arene-H (Trp780) Arene-H (Ile932)	-8.3727	HB (Gly2238) HB (Val2240) Arene-H (Glu2190) Arene-H (Ile2237) Arene-H (Met2345) Arene-H (Ile2356)
3k	-8.1237	HB (Val851) HB (Gln859) Arene-H (Trp780) Arene-H (Lys802) Arene-H (Asp805) Arene-H (Val850)	-8.5287	HB (Gly2238) Arene-H (Glu2190) Arene-H (Ile2237) Arene-H (Met2345)
3l	-7.6351	Arene-H (Tyr836) Arene-H (Ser774) Arene-H (Ala775) Arene-H (Lys802) Arene-H (Val850)	-8.5391	HB (Val2240) Arene-H (Ile2237) Arene-H (Trp2239)
3m	-7.9815	HB (Val851) Arene-H (Ser774) Arene-H (Trp780) Arene-H (Asn853) Arene-H (Ser854)	-8.5556	HB (Val2240) HB (Gly2238) Arene-H (Glu2190) Arene-H (Ile2356)
3n	-7.8469	HB (Val851) Arene-H(Arg770) Arene-H (Val850) Arene-H (Gln859)	-8.8540	HB (Gly2238) HB (Thr2245) Arene-H (Glu2190)
3o	-7.3411	Arene-H (Tyr836) Arene-H (Trp780) Arene-H (Val850)	-8.7115	HB (Val2240) HB (Gly2238) Arene-H (Glu2190) Arene-H (Ile2356)
3p	-7.9445	HB (Val851) Arene-H (Trp780) Arene-H (Asn853) Arene-H (Ser854)	-8.8438	HB (Gly2238) Arene-H (Glu2190)
3q	-6.7034	HB (Val851) Arene-H (Val850) Arene-H (Gln859) Arene-H (Ile932)	-7.6112	HB (Glu2190) HB (Val2240) Arene-H (Glu2190) Arene-H (Ile2237)
Alpelisib	-8.1121	HB (Ser854) HB (Gln859) HB (Lys802) HB (Val851)		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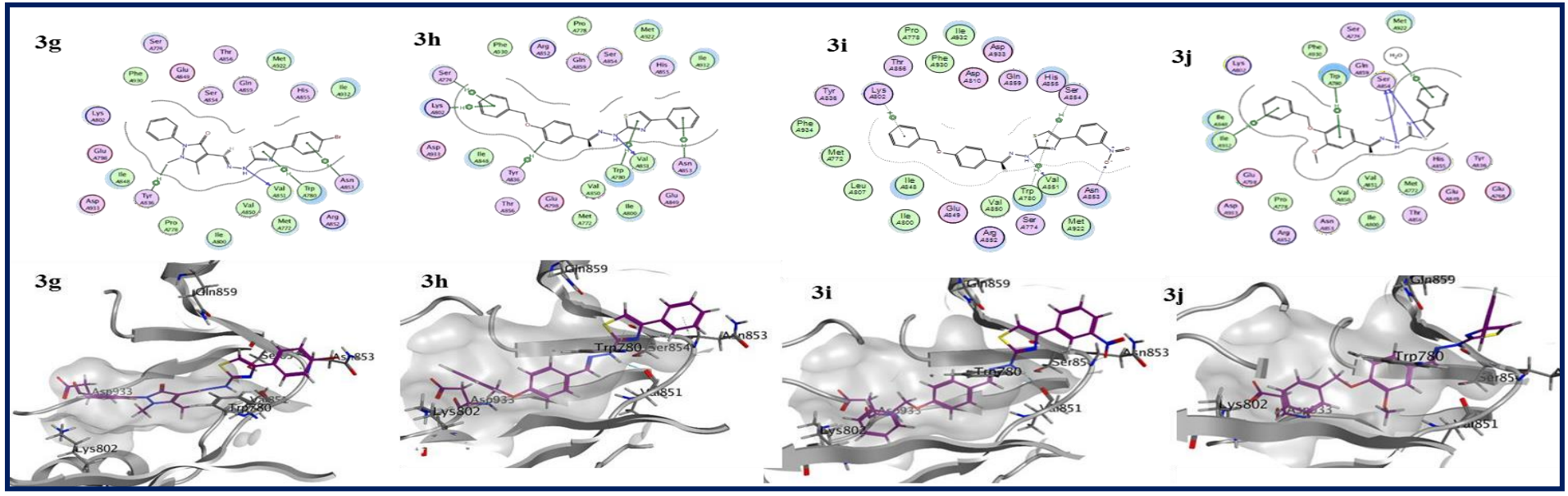
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3h
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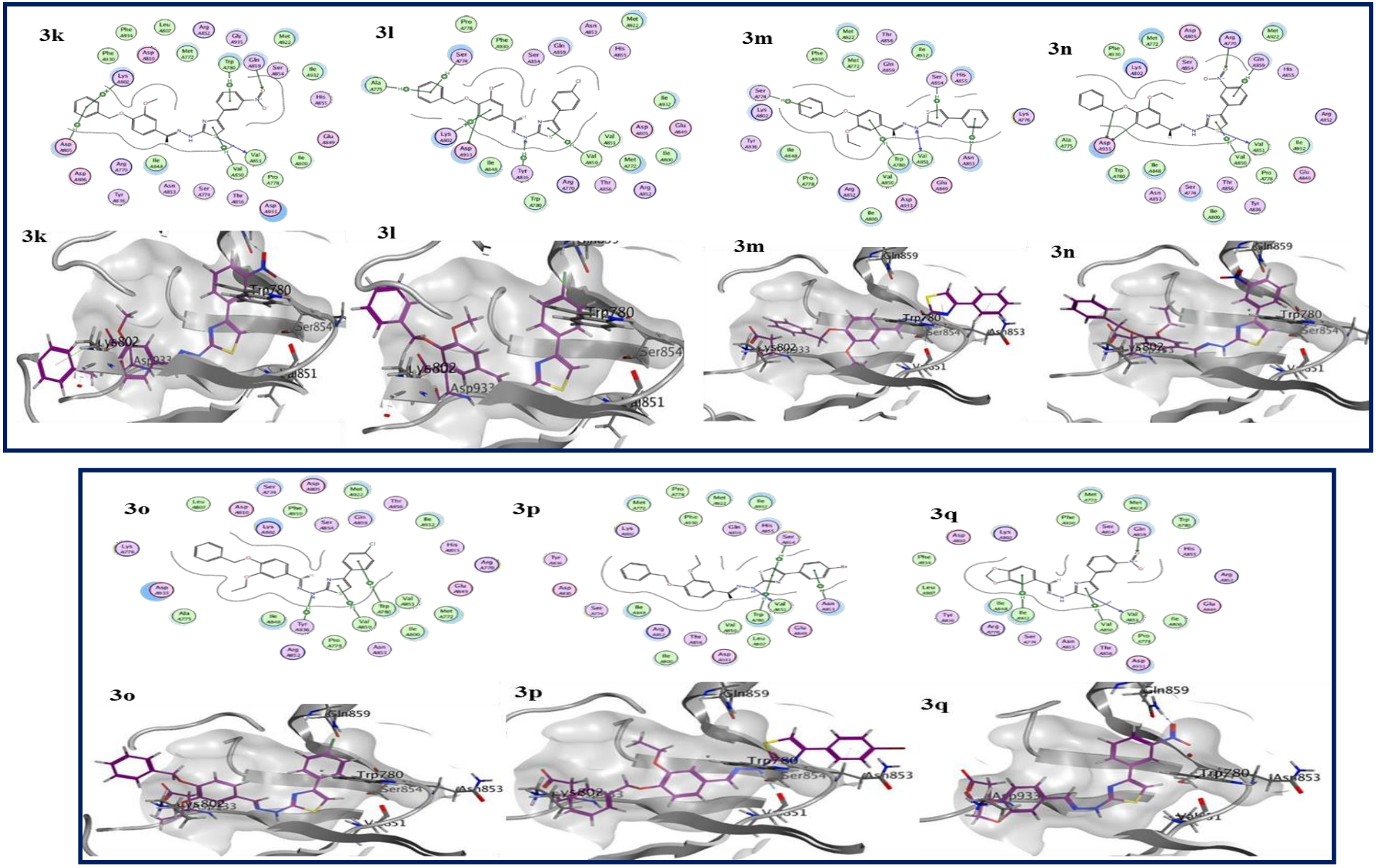
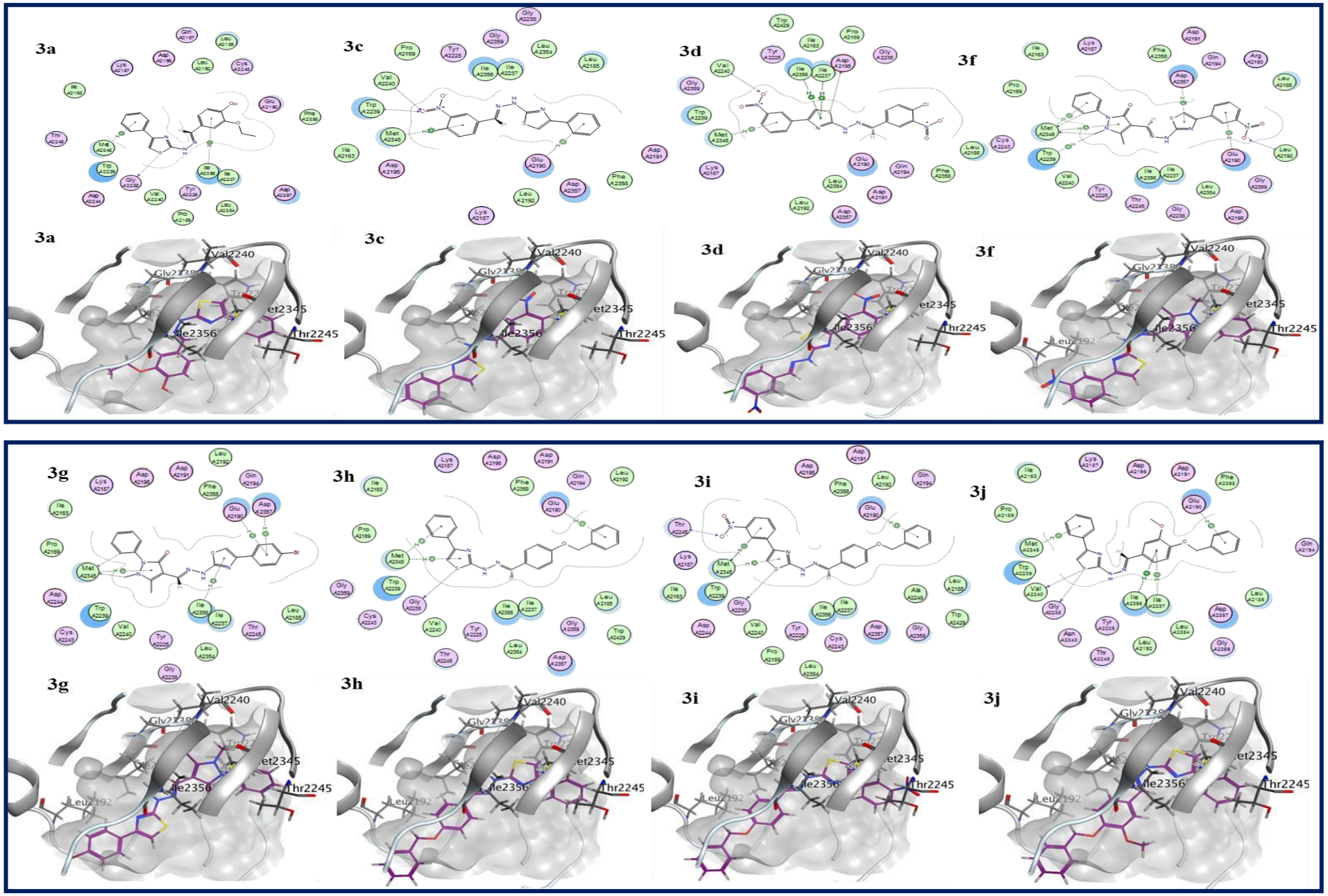


Fig. S1. 2D and 3D interactions of the synthesized derivatives with PI3K active site (PDB: 7PG6).


3a
3c
3d
3f
3a
3c
3d
3f
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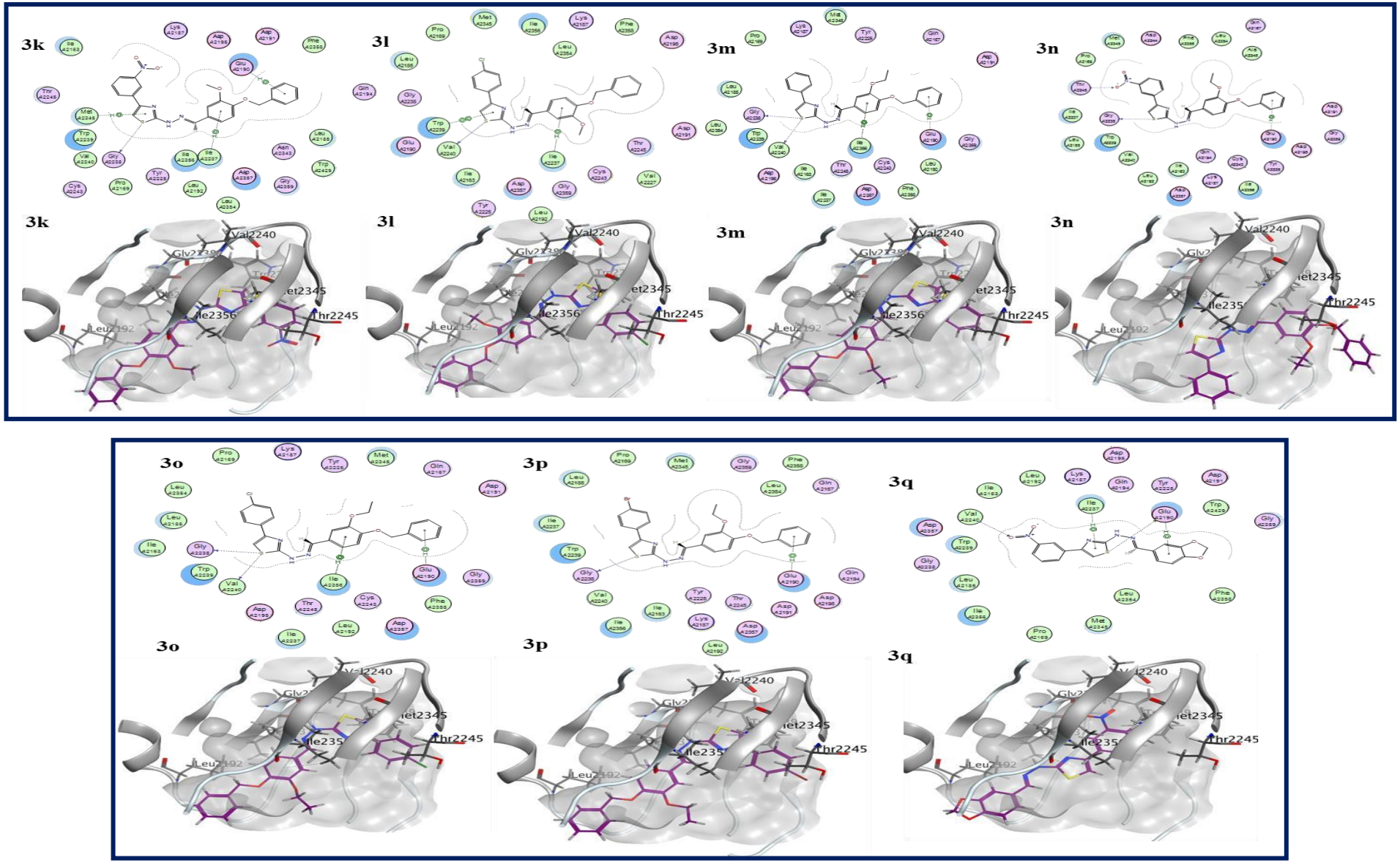


Fig. S2. 2D and 3D interactions of the synthesized derivatives with mTOR active site (PDB: 4JT6).

3.2 Prediction of physicochemical, pharmacokinetic, and ADME properties

Table S3. The physicochemical and ADME properties of the target molecules.

Compd.	MW (g/mol) <500	#H-bond acceptors <10	#H-bond donors <5	Log P o/w <5	Lipinski violations	TPSA (Å^2) <140	Rotatable bonds <10	GI	BBB	BA Score
3a	460.51	6	1	4.12	0	129.8	9	Low	No	0.55
3b	339.41	4	2	3.72	0	94.98	6	High	No	0.55
3c	358.8	4	1	3.47	0	111.34	5	High	No	0.55
3d	403.8	6	1	2.76	0	157.16	6	Low	No	0.55
3e	393.25	4	1	4.02	0	111.34	5	Low	No	0.55
3f	434.47	5	1	3.19	0	138.27	6	Low	No	0.55
3g	468.37	3	1	4.53	0	92.45	5	High	No	0.55
3h	385.48	3	1	4.97	0	74.75	7	High	No	0.55
3i	430.48	5	1	4.41	0	120.57	8	Low	No	0.55
3j	415.51	4	1	4.96	0	83.98	8	High	No	0.55
3k	460.51	6	1	4.12	0	129.8	9	Low	No	0.55
3l	449.95	4	1	5.48	0	83.98	8	High	No	0.55
3m	429.53	4	1	5.27	0	83.98	9	High	No	0.55
3n	474.53	6	1	4.51	0	129.8	10	Low	No	0.55
3o	463.98	4	1	5.77	0	83.98	9	Low	No	0.55
3p	508.43	4	1	5.94	1	83.98	9	Low	No	0.55
3q	368.37	6	1	3.04	0	129.8	5	Low	No	0.55
Alpelisib	441.47	7	2	3.03	0	129.45	7	Low	No	0.55
Dactolisib	469.54	4	0	4.74	0	76.5	3	High	No	0.55

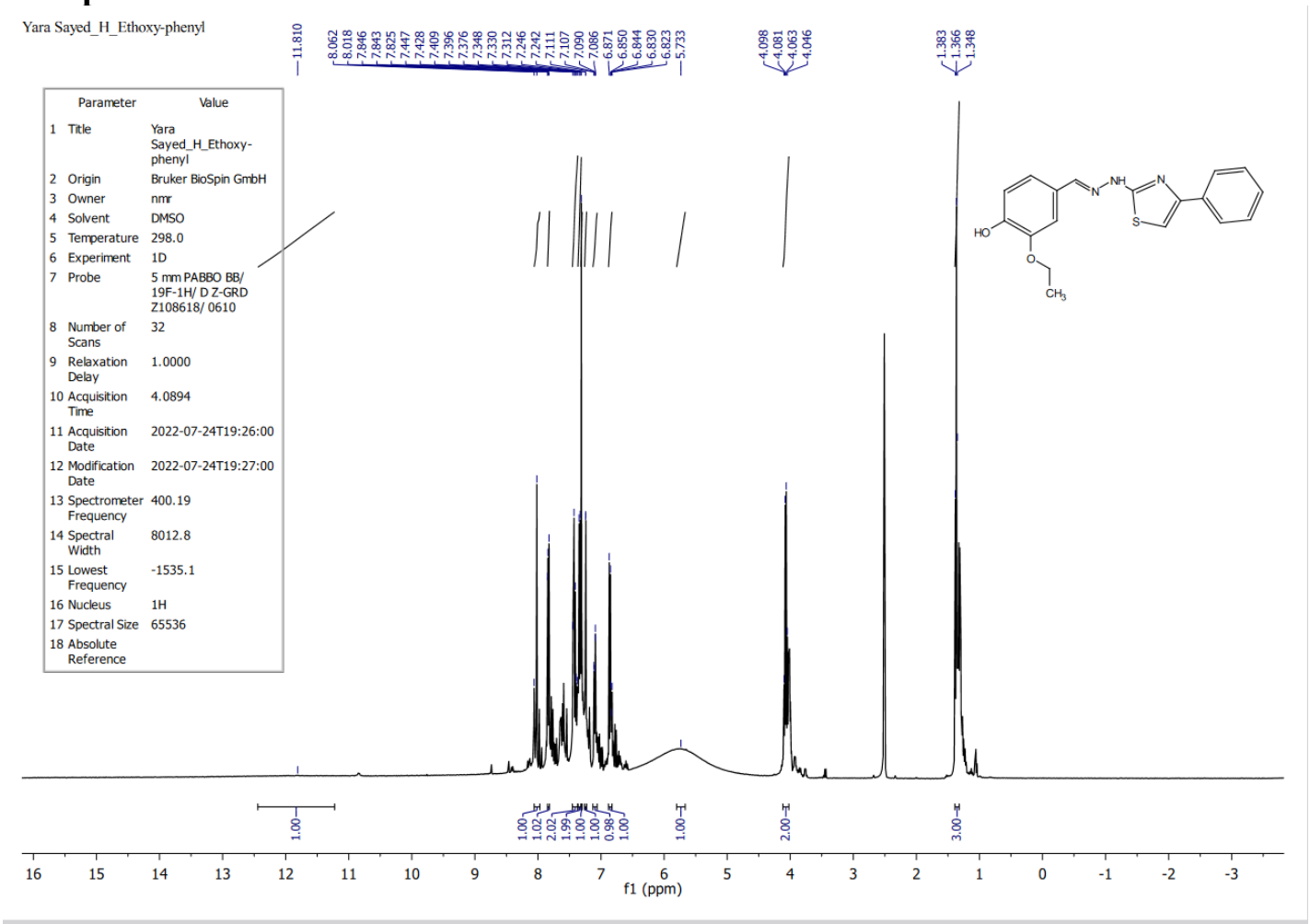
3.3 ProTox-3.0 - Prediction of Toxicity of chemicals

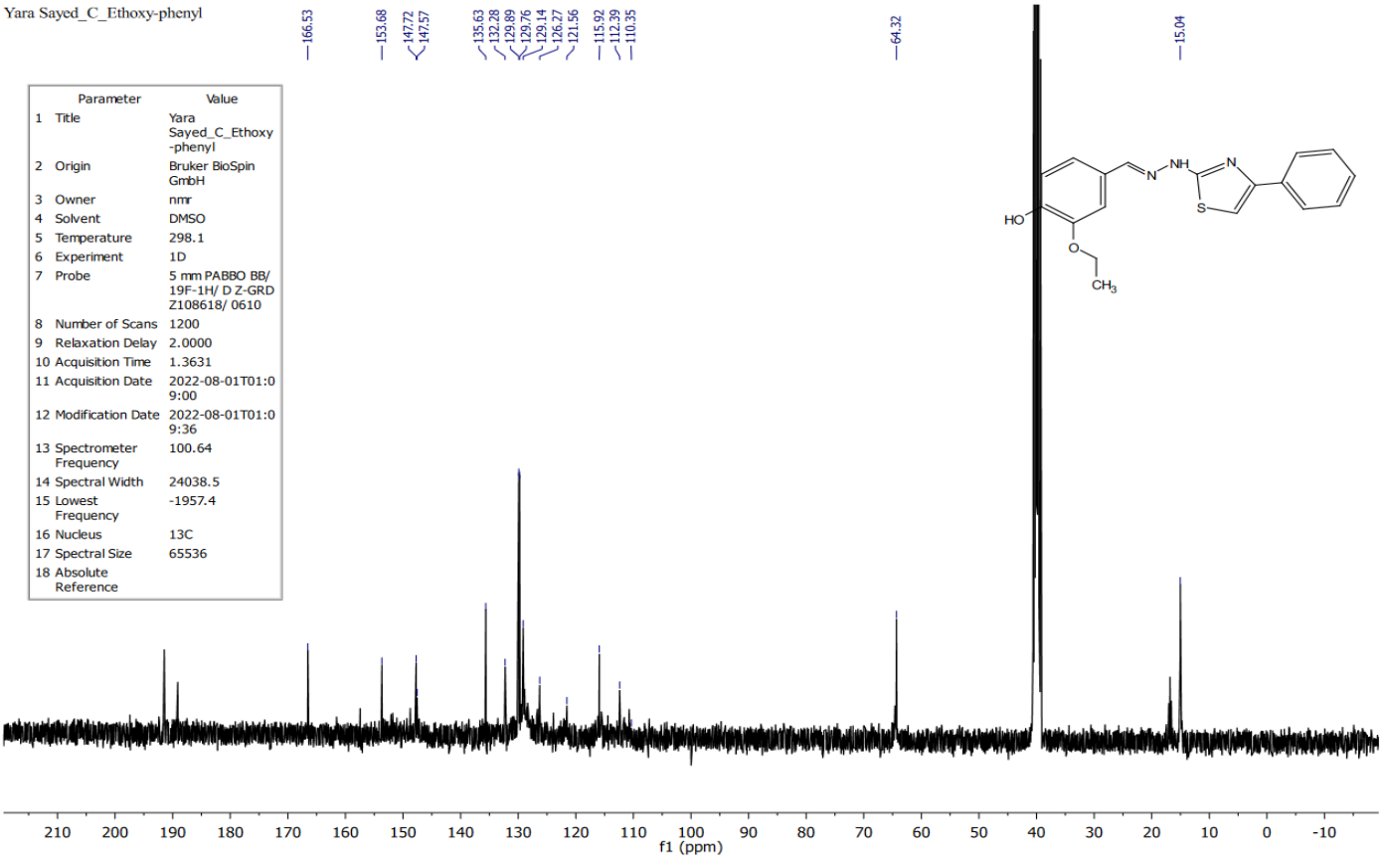
			3b		3e	
Classification	**Target**	**Shorthand**	**Prediction**	**Probability**	**Prediction**	**Probability**
Organ toxicity	Neurotoxicity	neuro	Inactive	0.77	Inactive	0.53
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.57	Inactive	0.71
Toxicity end points	Cytotoxicity	cyto	Inactive	0.65	Inactive	0.68
Toxicity end points	Clinical toxicity	clinical	Inactive	0.61	Inactive	0.64
Toxicity end points	Nutritional toxicity	nutri	Inactive	0.54	Inactive	0.50
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.96	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.98	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.70	Inactive	0.78
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.93	Inactive	0.63
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.89	Inactive	0.92
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.85	Inactive	0.75
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.85	Inactive	0.75
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.78	Inactive	0.73
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.76	Inactive	0.73
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.73	Inactive	0.83
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.75	Inactive	0.85
Molecular Initiating Events	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.82	Inactive	0.89
Molecular Initiating Events	GABA receptor (GABAR)	mie_gabar	Inactive	0.76	Inactive	0.86
Molecular Initiating Events	Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmdar	Inactive	0.94	Inactive	0.95
Molecular Initiating Events	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR)	mie_ampar	Inactive	0.98	Inactive	0.99

Molecular Initiating Events	Kainate receptor (KAR)	mie_kar	Inactive	0.97	Inactive	1
Molecular Initiating Events	Achetylcholinesterase (AChE)	mie_ache	Inactive	0.86	Inactive	0.80
Molecular Initiating Events	Constitutive androstane receptor (CAR)	mie_car	Inactive	1	Inactive	1
Molecular Initiating Events	Pregnane X receptor (PXR)	mie_pxr	Inactive	0.83	Inactive	0.70
Molecular Initiating Events	NADH-quinone oxidoreductase (NADHOX)	mie_nadhox	Inactive	0.93	Inactive	0.98
Molecular Initiating Events	Voltage gated sodium channel (VGSC)	mie_vgsc	Inactive	0.73	Inactive	0.54
Molecular Initiating Events	Na+/I- symporter (NIS)	mie_nis	Inactive	0.80	Inactive	0.74
Metabolism	Cytochrome CYP1A2	CYP1A2	Inactive	0.78	Inactive	0.52
Metabolism	Cytochrome CYP2C19	CYP2C19	Inactive	0.66	Inactive	0.53
Metabolism	Cytochrome CYP2D6	CYP2D6	Inactive	0.70	Inactive	0.64
Metabolism	Cytochrome CYP2E1	CYP2E1	Inactive	0.99	Inactive	0.98

4- ^{1}H NMR and ^{13} C NMR spectra of the new derivatives.

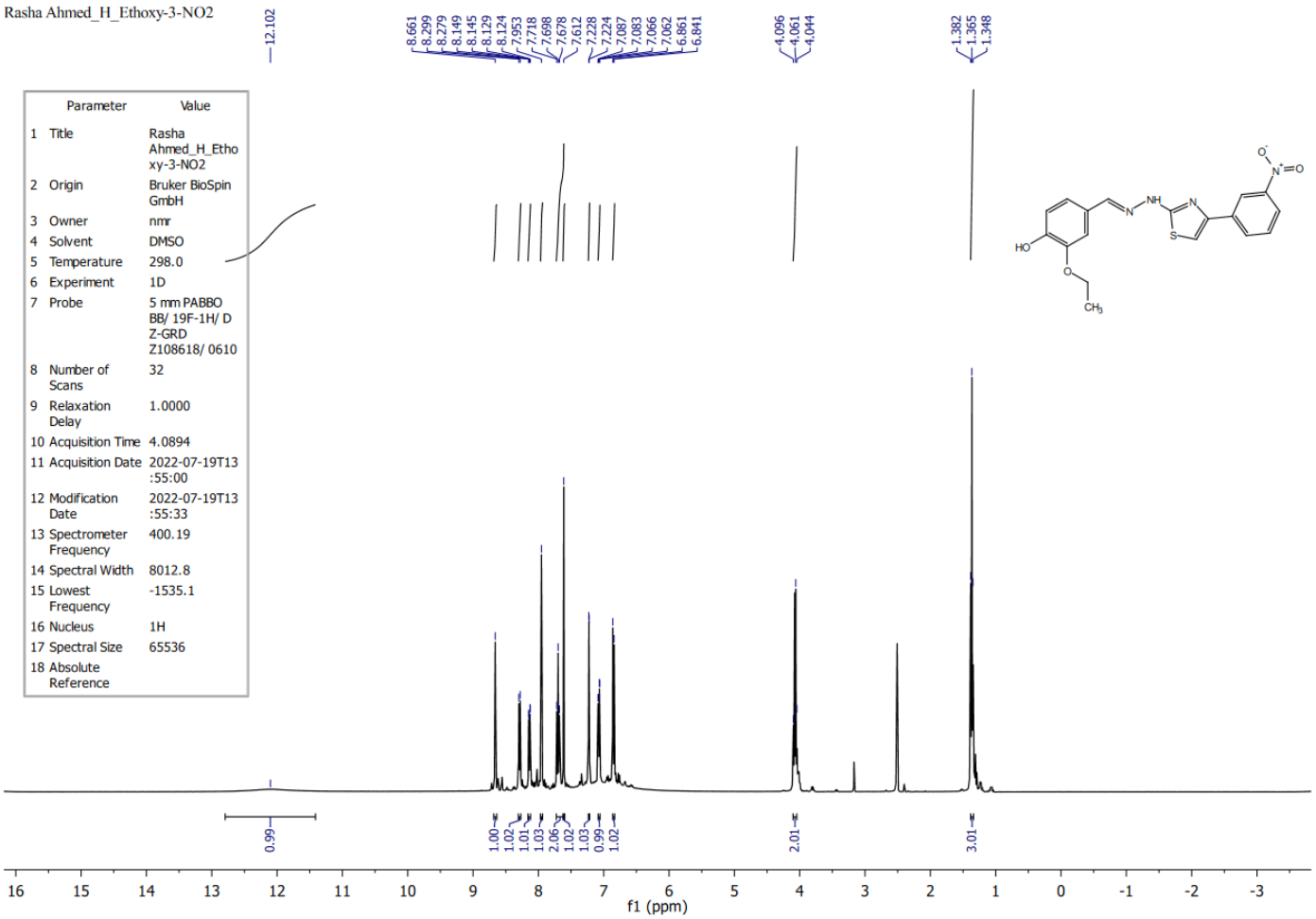
Compound 3a





Compound 3b

Rasha Ahmed_H_Ethoxy-3-NO2



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9	Relaxation Delay	1.0000
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18	Absolute Reference	

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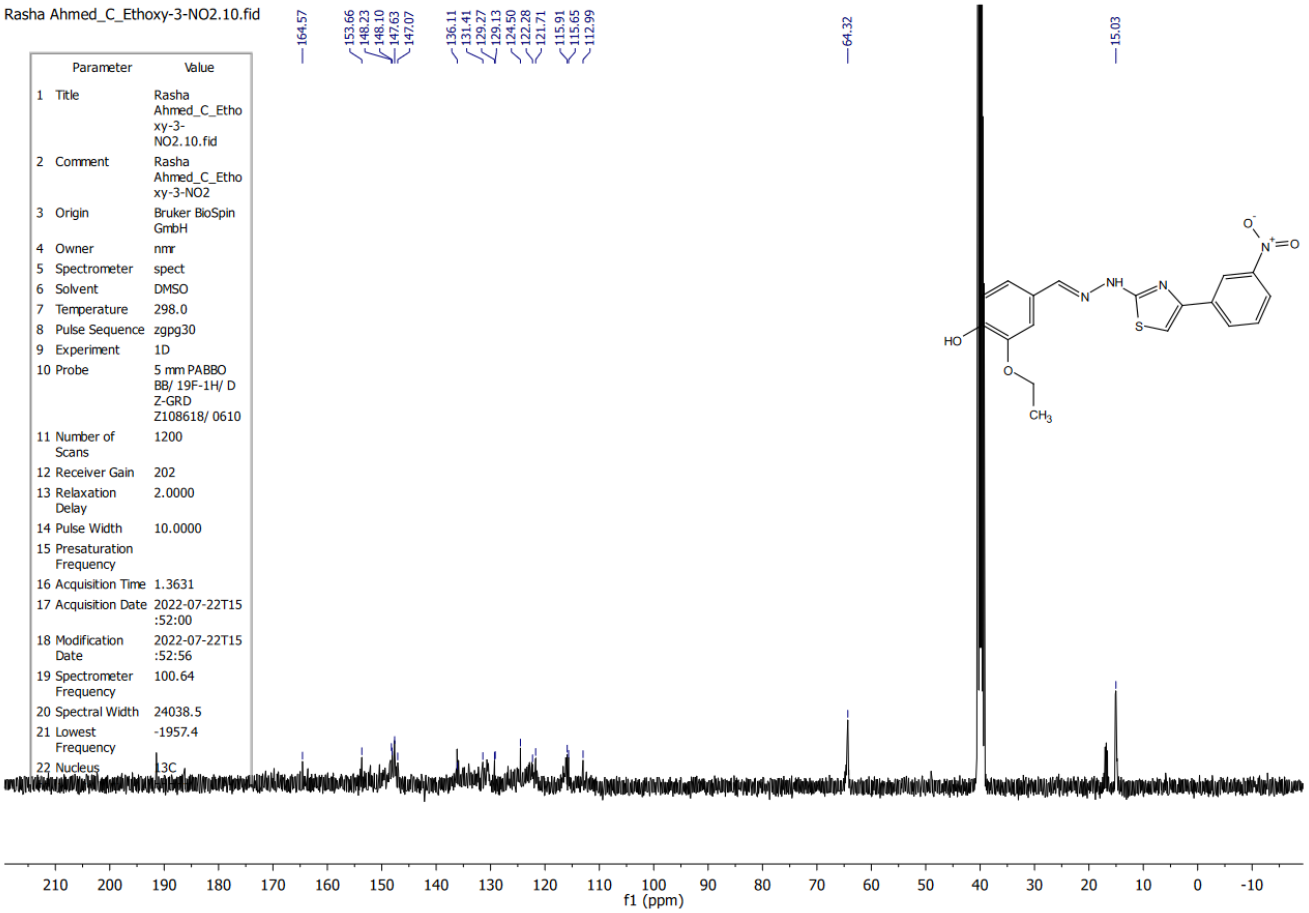

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13	Relaxation Delay	2.0000
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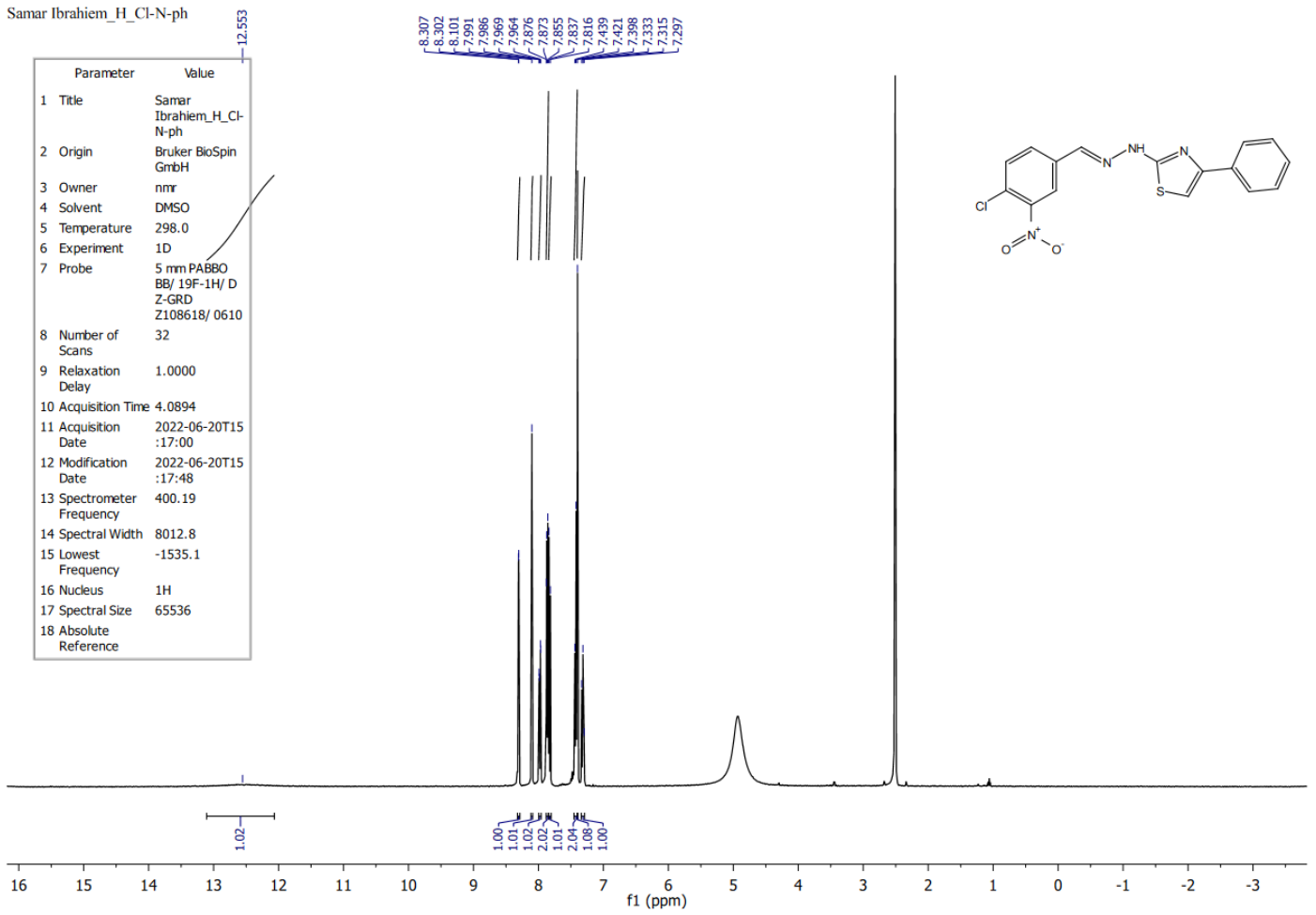
Compound 3c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17 Spectral Size 65536
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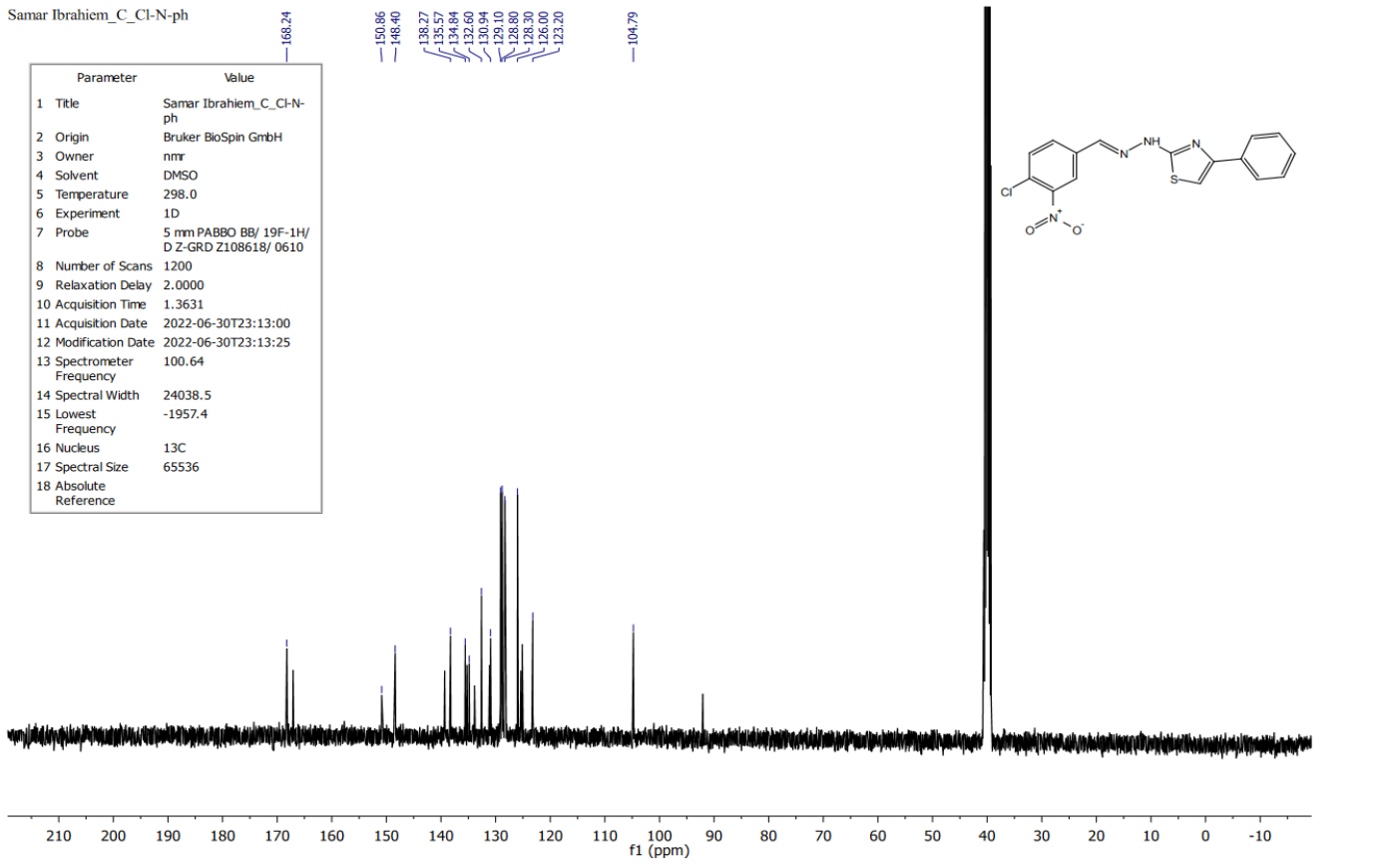
1.00
f1 (ppm)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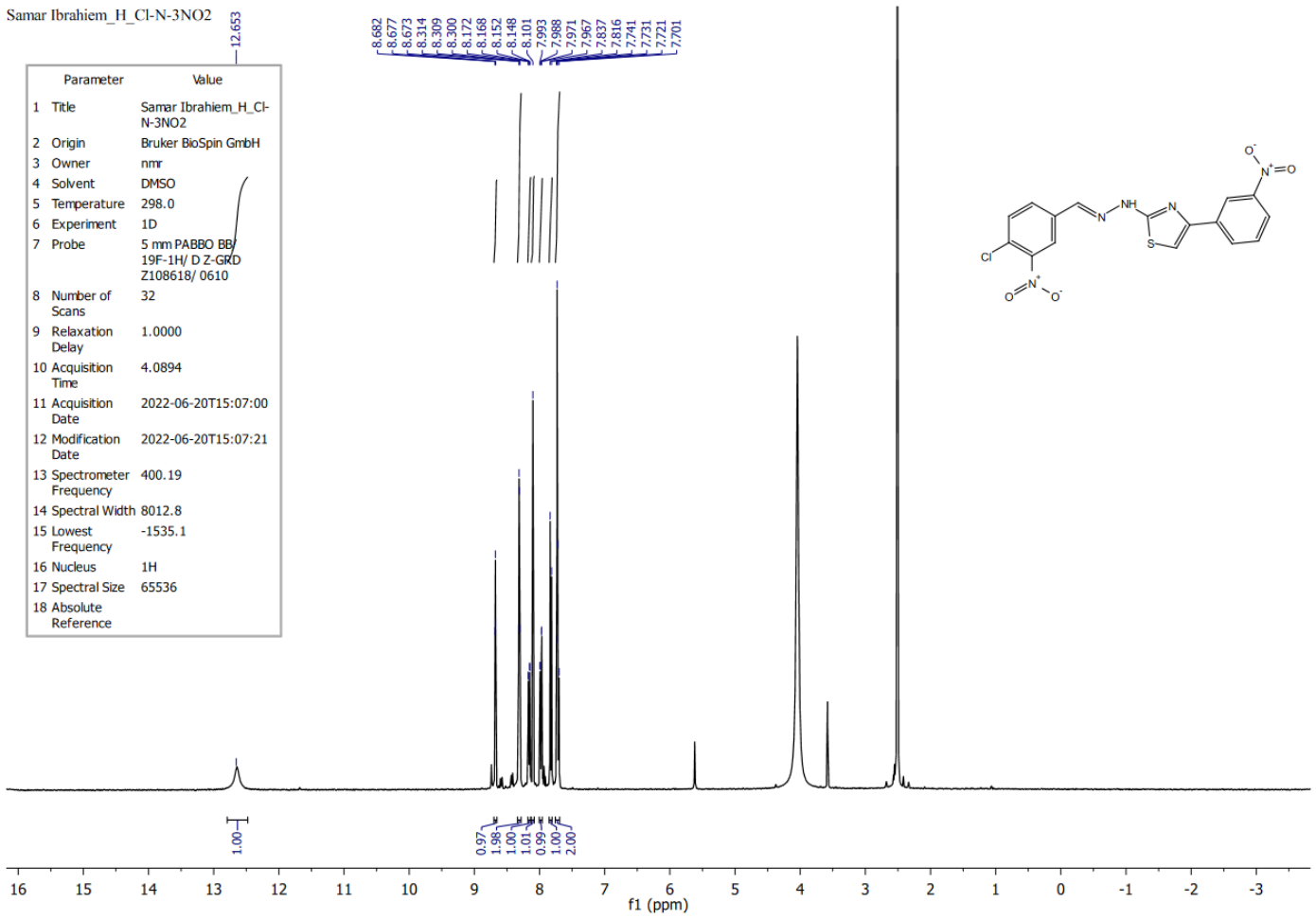
Compound 3d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16 Nucleus 1H
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1.98
1.00
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0.99
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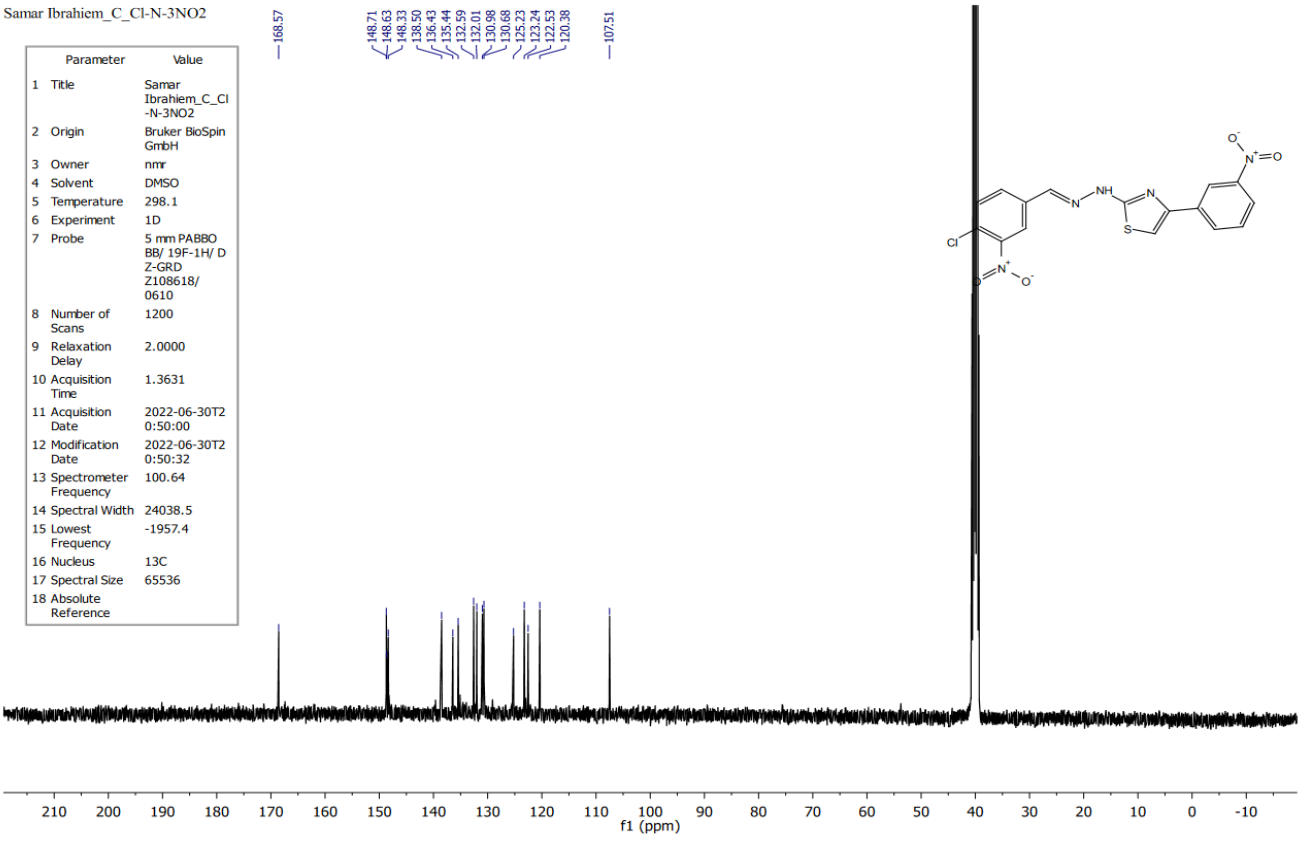
2.00
f1 (ppm)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8 Number of Scans 1200
9 Relaxation Delay 2.0000
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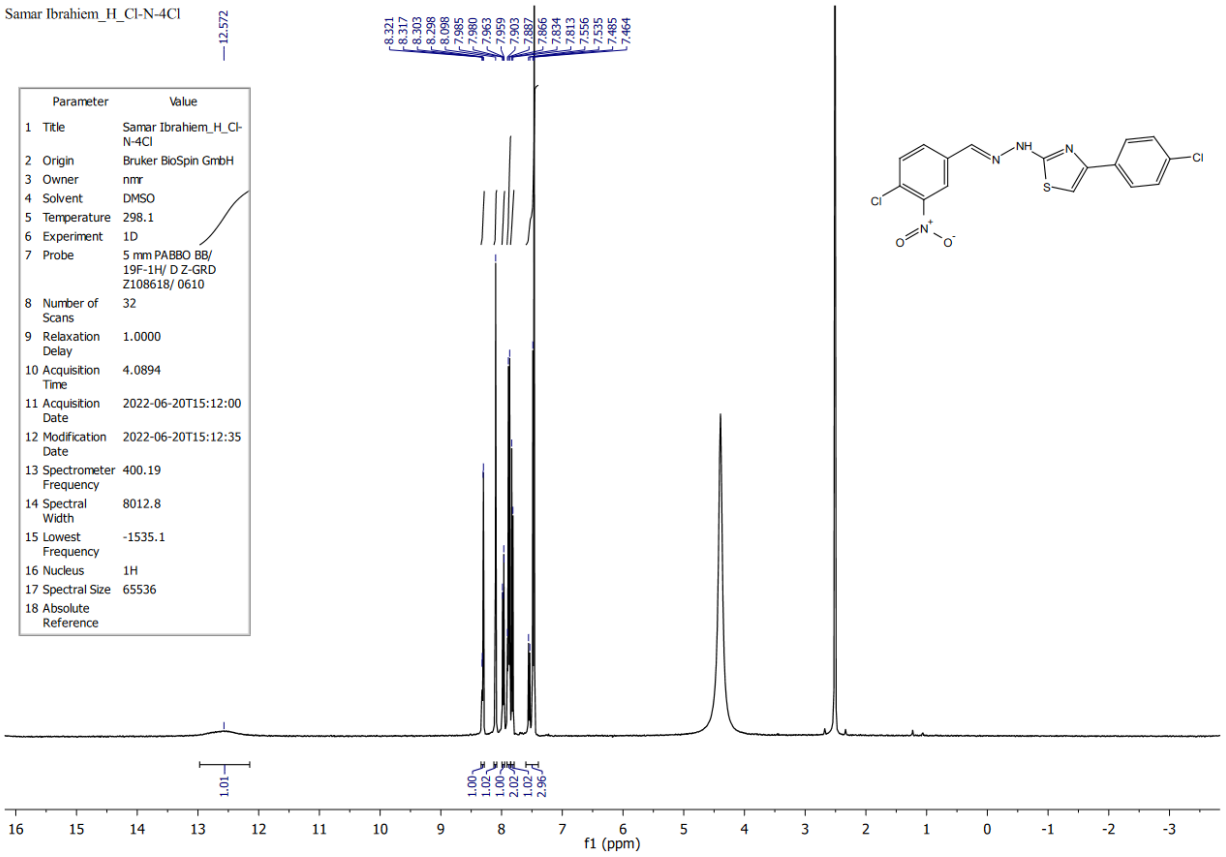
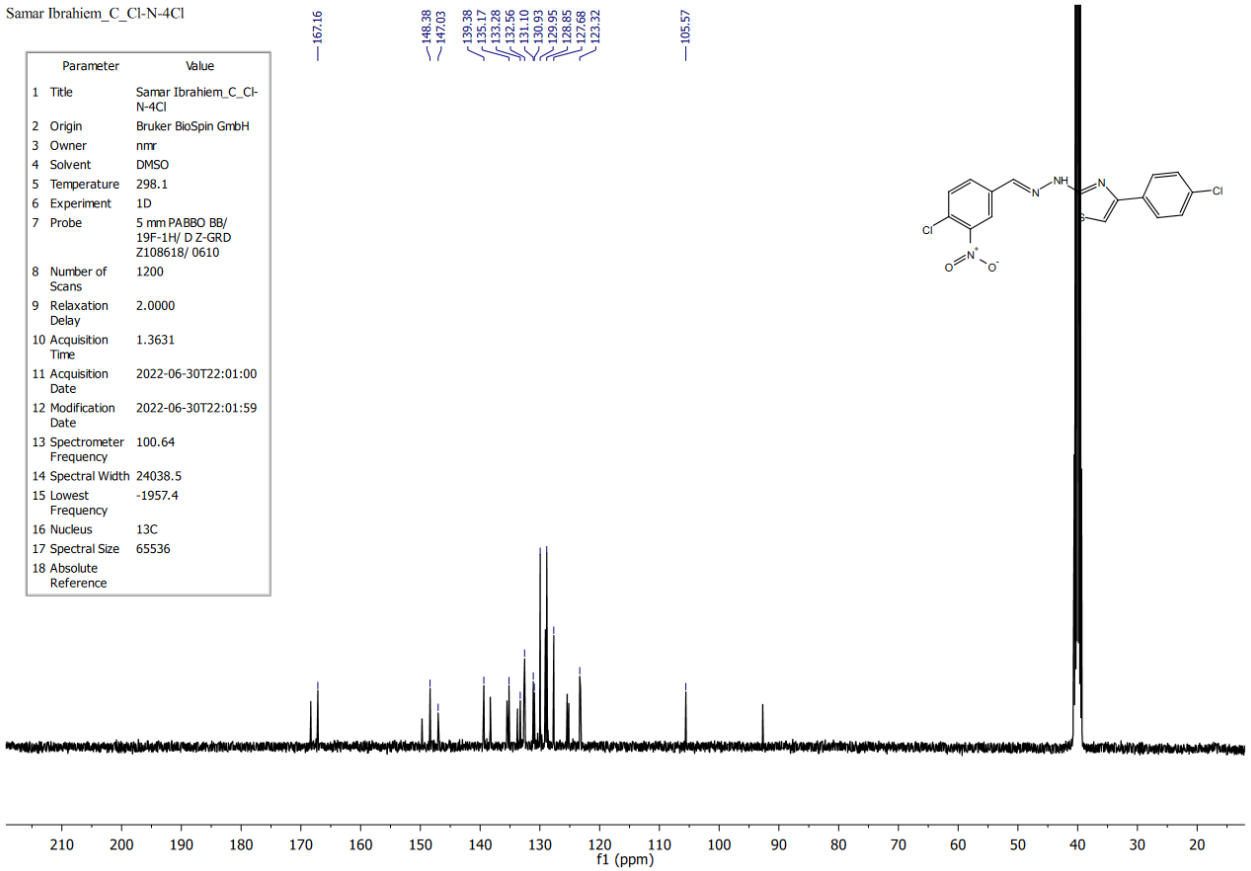
14 Spectral Width 24038.5
15 Lowest Frequency -1957.4
16 Nucleus 13C
17 Spectral Size 65536
18 Absolute Reference
f1 (ppm)

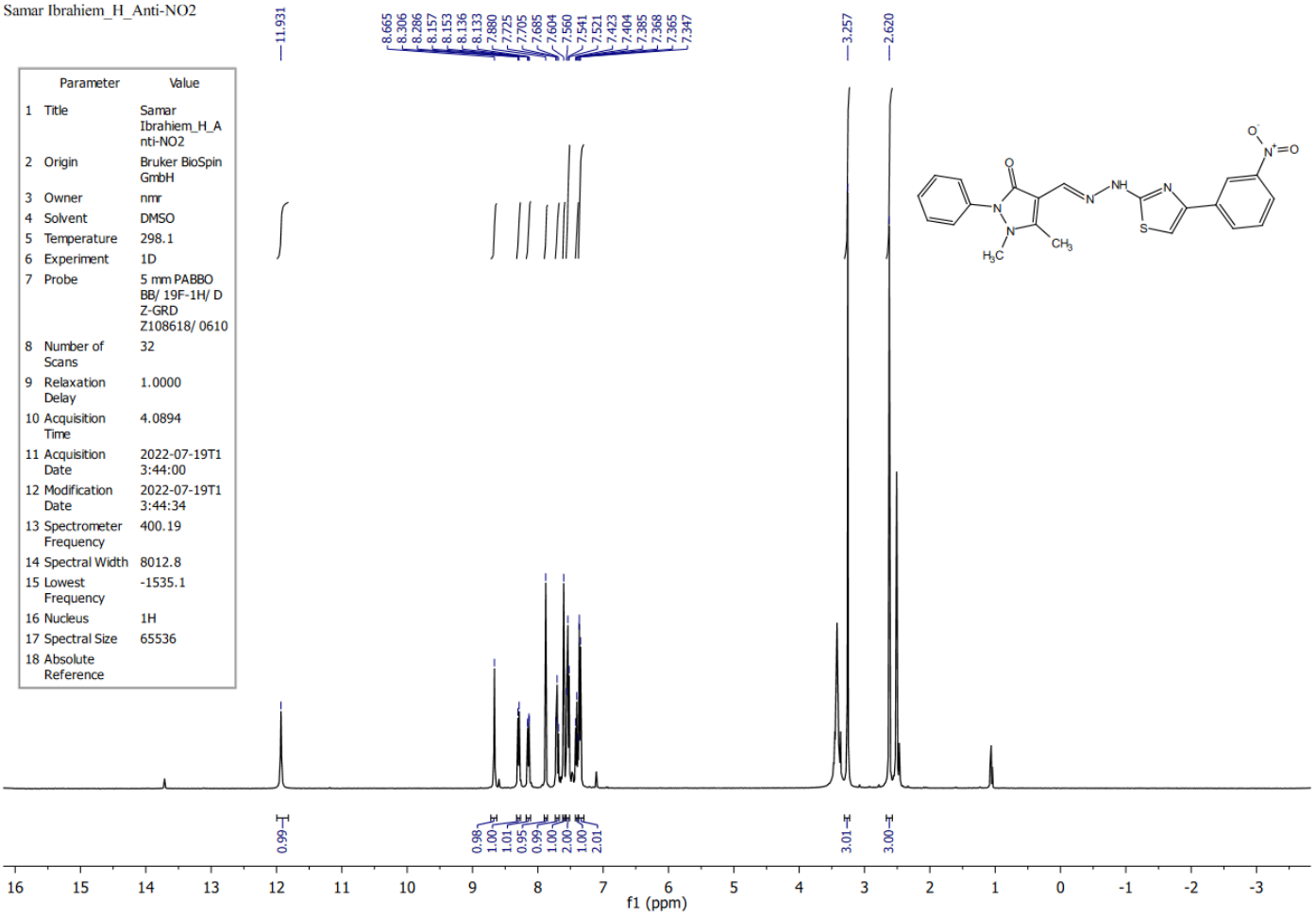
Compound 3e


Samar Ibrahiem_H_Cl-N-4Cl
12.572
8.321
8.317
8.303
8.298
8.098
7.985
7.980
7.963
7.959
7.903
7.887
7.866
7.834
7.813
7.556
7.535
7.485
7.464
Parameter Value
1 Title Samar Ibrahiem_H_Cl-N-4Cl
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.1
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 32
9 Relaxation Delay 1.0000
10 Acquisition Time 4.0894
11 Acquisition Date 2022-06-20T15:12:00
12 Modification Date 2022-06-20T15:12:35
13 Spectrometer Frequency 400.19
14 Spectral Width 8012.8
15 Lowest Frequency -1535.1
16 Nucleus 1H
17 Spectral Size 65536
18 Absolute Reference
1.01
1.00
1.02
1.00
2.02
1.02
2.96
f1 (ppm)


Samar Ibrahiem_C_Cl-N-4Cl
167.16
148.38
147.03
139.38
135.17
133.28
132.56
131.10
130.93
129.95
128.85
127.68
123.32
105.57
Parameter Value
1 Title Samar Ibrahiem_C_Cl-N-4Cl
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.1
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 1200
9 Relaxation Delay 2.0000
10 Acquisition Time 1.3631
11 Acquisition Date 2022-06-30T22:01:00
12 Modification Date 2022-06-30T22:01:59
13 Spectrometer Frequency 100.64
14 Spectral Width 24038.5
15 Lowest Frequency -1957.4
16 Nucleus 13C
17 Spectral Size 65536
18 Absolute Reference
f1 (ppm)

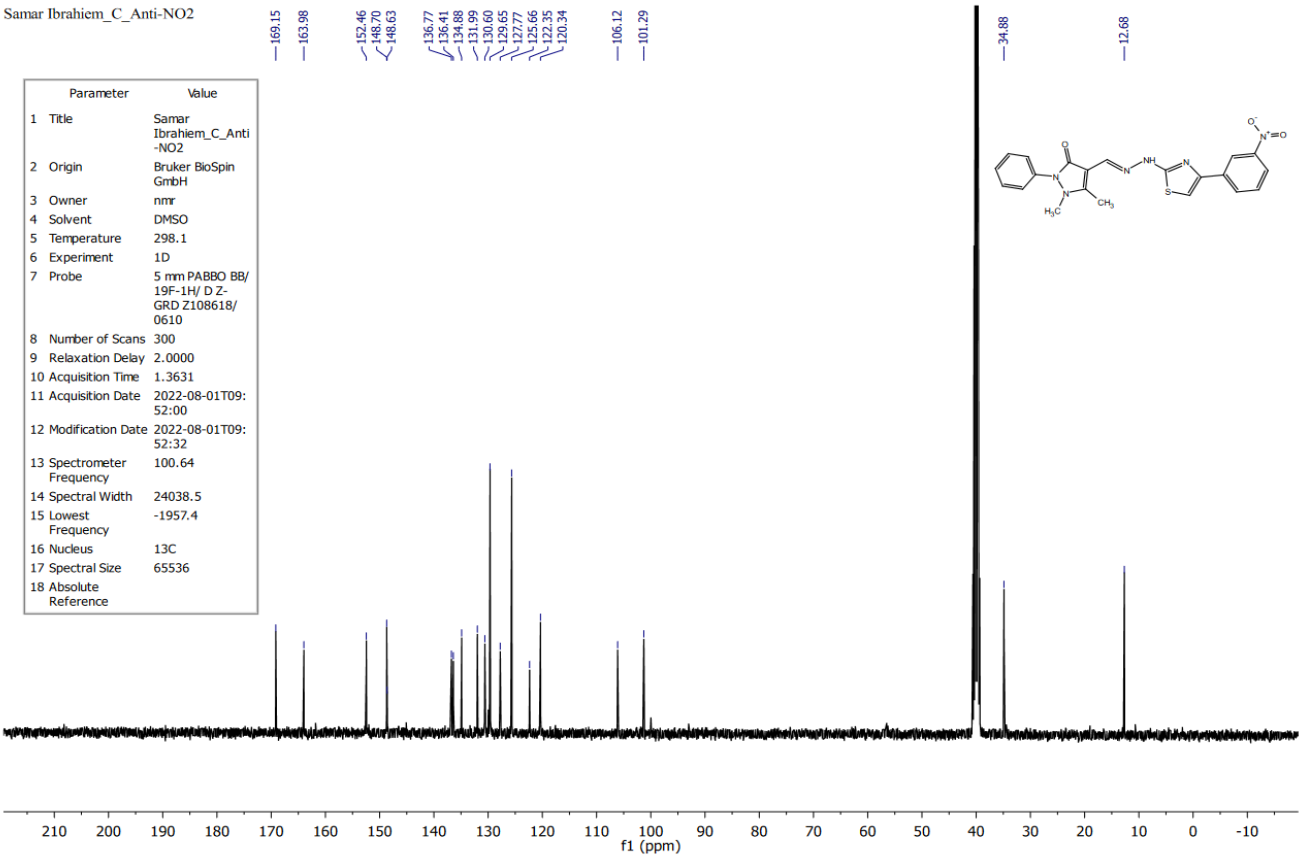
Compound 3f

Samar Ibrahiem_H_Anti-NO2



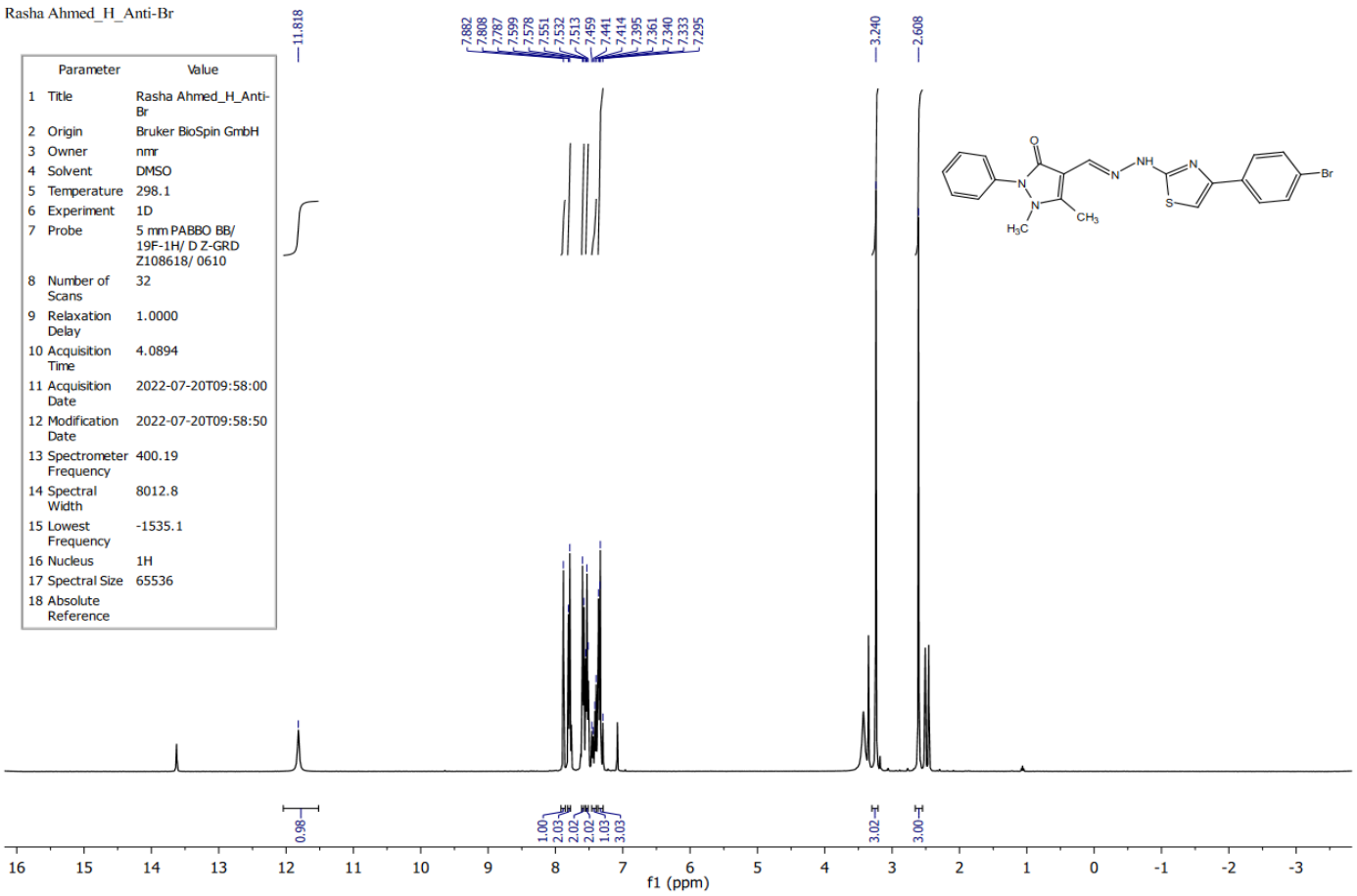
	Parameter	Value
1	Title	Samar Ibrahiem_H_Anti-NO2
2	Origin	Bruker BioSpin GmbH
3	Owner	nmr
4	Solvent	DMSO
5	Temperature	298.1
6	Experiment	1D
7	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8	Number of Scans	32
9	Relaxation Delay	1.0000
10	Acquisition Time	4.0894
11	Acquisition Date	2022-07-19T13:44:00
12	Modification Date	2022-07-19T13:44:34
13	Spectrometer Frequency	400.19
14	Spectral Width	8012.8
15	Lowest Frequency	-1535.1
16	Nucleus	1H
17	Spectral Size	65536
18	Absolute Reference	

Samar Ibrahiem_C_Anti-NO2

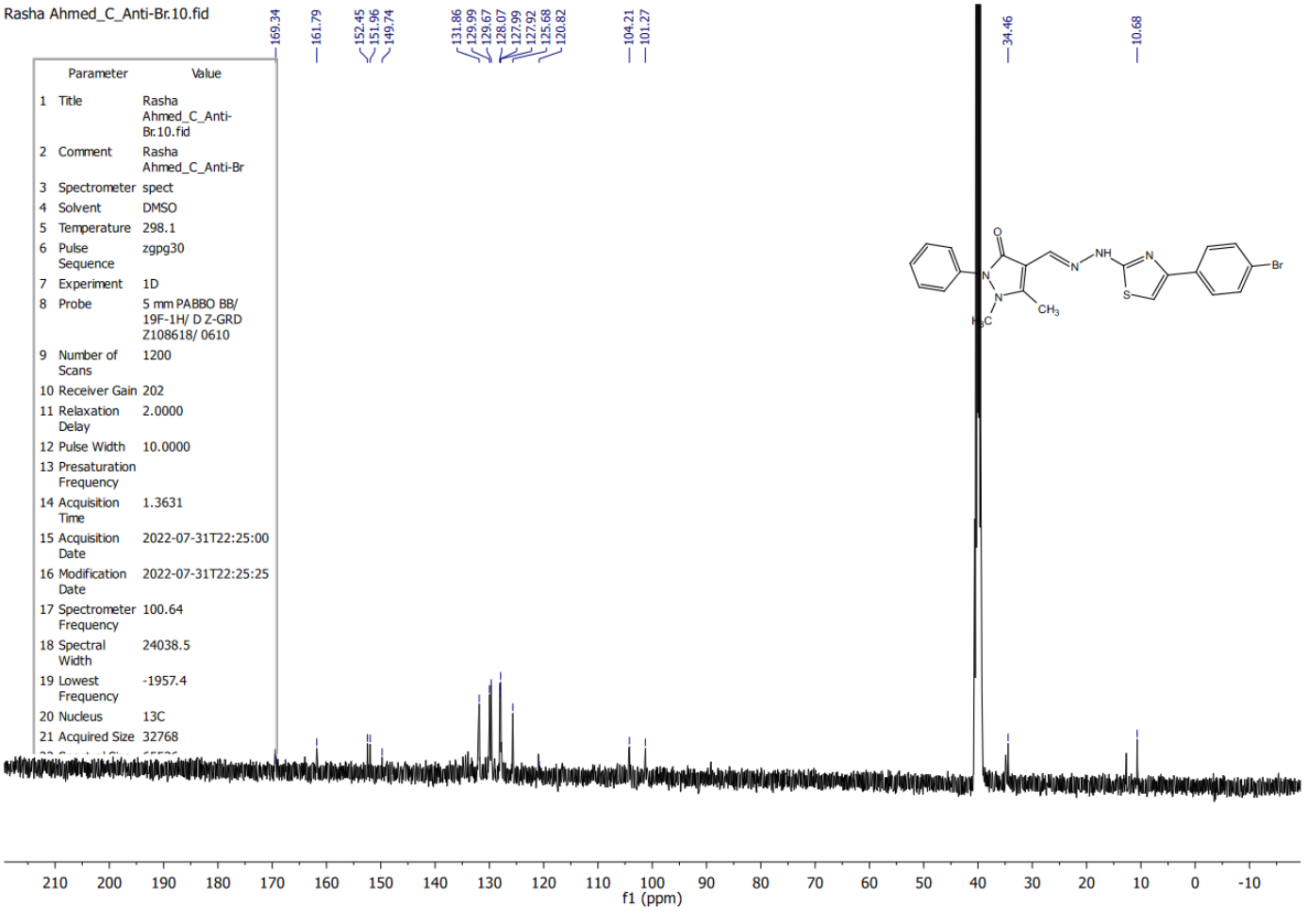


	Parameter	Value
1	Title	Samar Ibrahiem_C_Anti-NO2
2	Origin	Bruker BioSpin GmbH
3	Owner	nmr
4	Solvent	DMSO
5	Temperature	298.1
6	Experiment	1D
7	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8	Number of Scans	300
9	Relaxation Delay	2.0000
10	Acquisition Time	1.3631
11	Acquisition Date	2022-08-01T09:52:00
12	Modification Date	2022-08-01T09:52:32
13	Spectrometer Frequency	100.64
14	Spectral Width	24038.5
15	Lowest Frequency	-1957.4
16	Nucleus	13C
17	Spectral Size	65536
18	Absolute Reference	

Compound 3g

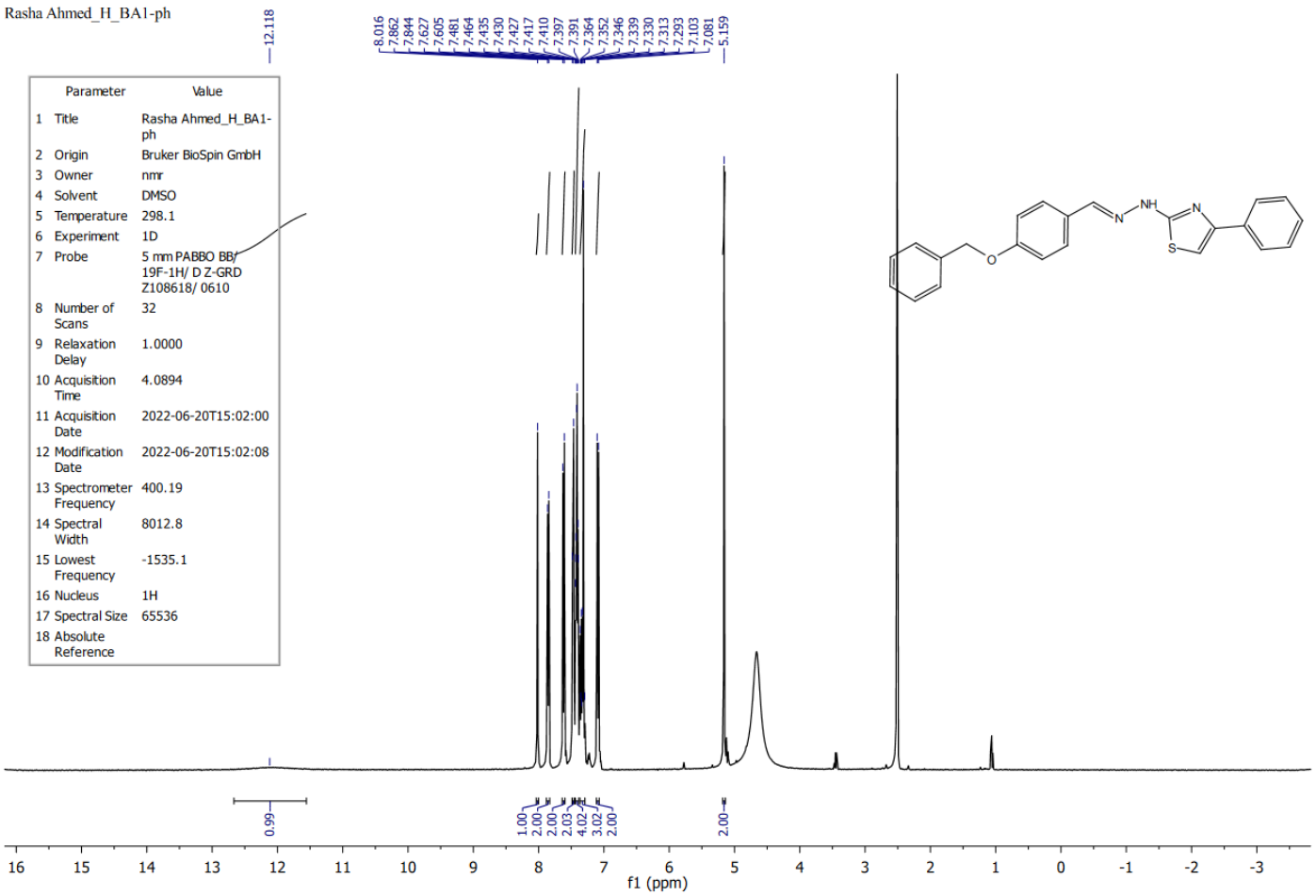


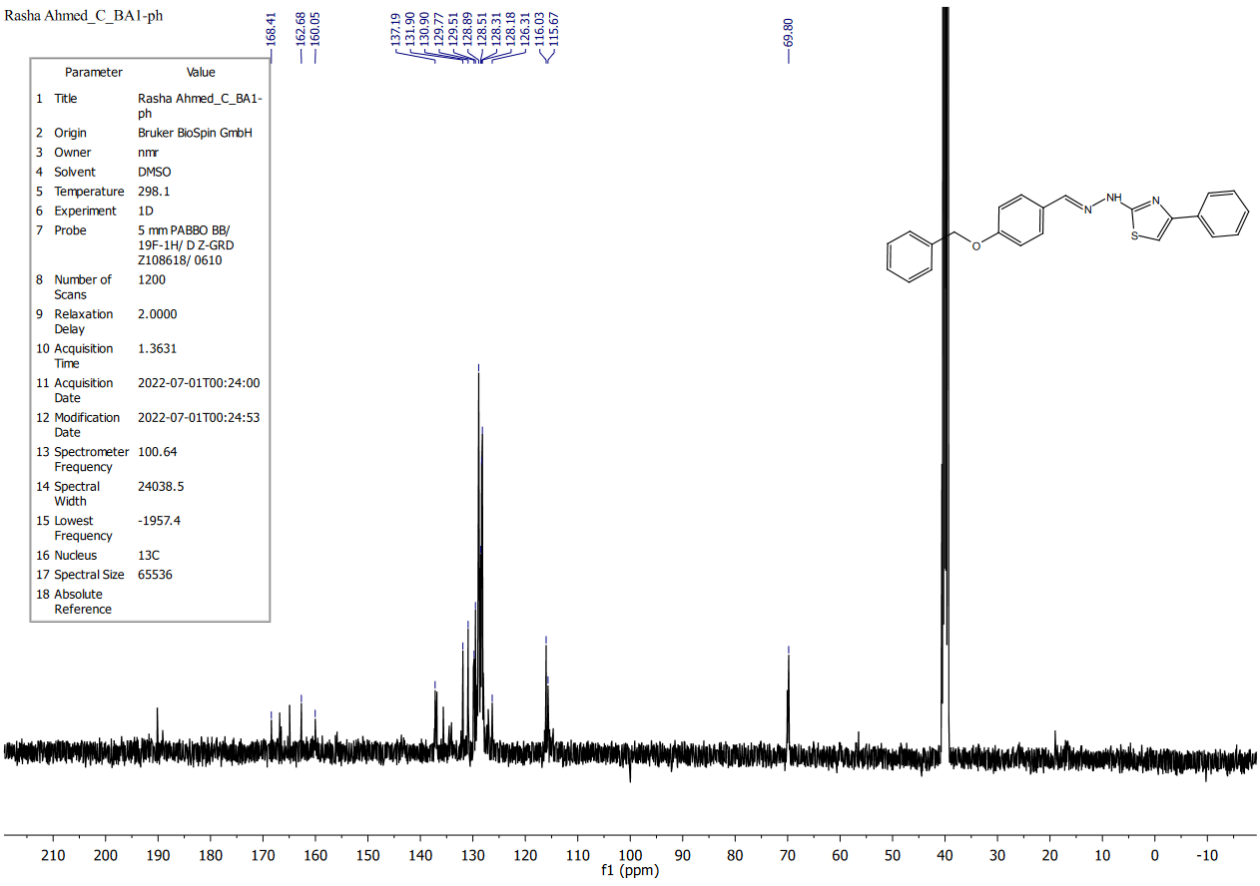
	Parameter	Value
1	Title	Rasha Ahmed_H_Anti-Br
2	Origin	Bruker BioSpin GmbH
3	Owner	nmr
4	Solvent	DMSO
5	Temperature	298.1
6	Experiment	1D
7	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8	Number of Scans	32
9	Relaxation Delay	1.0000
10	Acquisition Time	4.0894
11	Acquisition Date	2022-07-20T09:58:00
12	Modification Date	2022-07-20T09:58:50
13	Spectrometer Frequency	400.19
14	Spectral Width	8012.8
15	Lowest Frequency	-1535.1
16	Nucleus	1H
17	Spectral Size	65536
18	Absolute Reference	



	Parameter	Value
1	Title	Rasha Ahmed_C_Anti-Br.10.fid
2	Comment	Rasha Ahmed_C_Anti-Br
3	Spectrometer	spect
4	Solvent	DMSO
5	Temperature	298.1
6	Pulse Sequence	zgpg30
7	Experiment	1D
8	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
9	Number of Scans	1200
10	Receiver Gain	202
11	Relaxation Delay	2.0000
12	Pulse Width	10.0000
13	Presaturation Frequency	
14	Acquisition Time	1.3631
15	Acquisition Date	2022-07-31T22:25:00
16	Modification Date	2022-07-31T22:25:25
17	Spectrometer Frequency	100.64
18	Spectral Width	24038.5
19	Lowest Frequency	-1957.4
20	Nucleus	13C
21	Acquired Size	32768

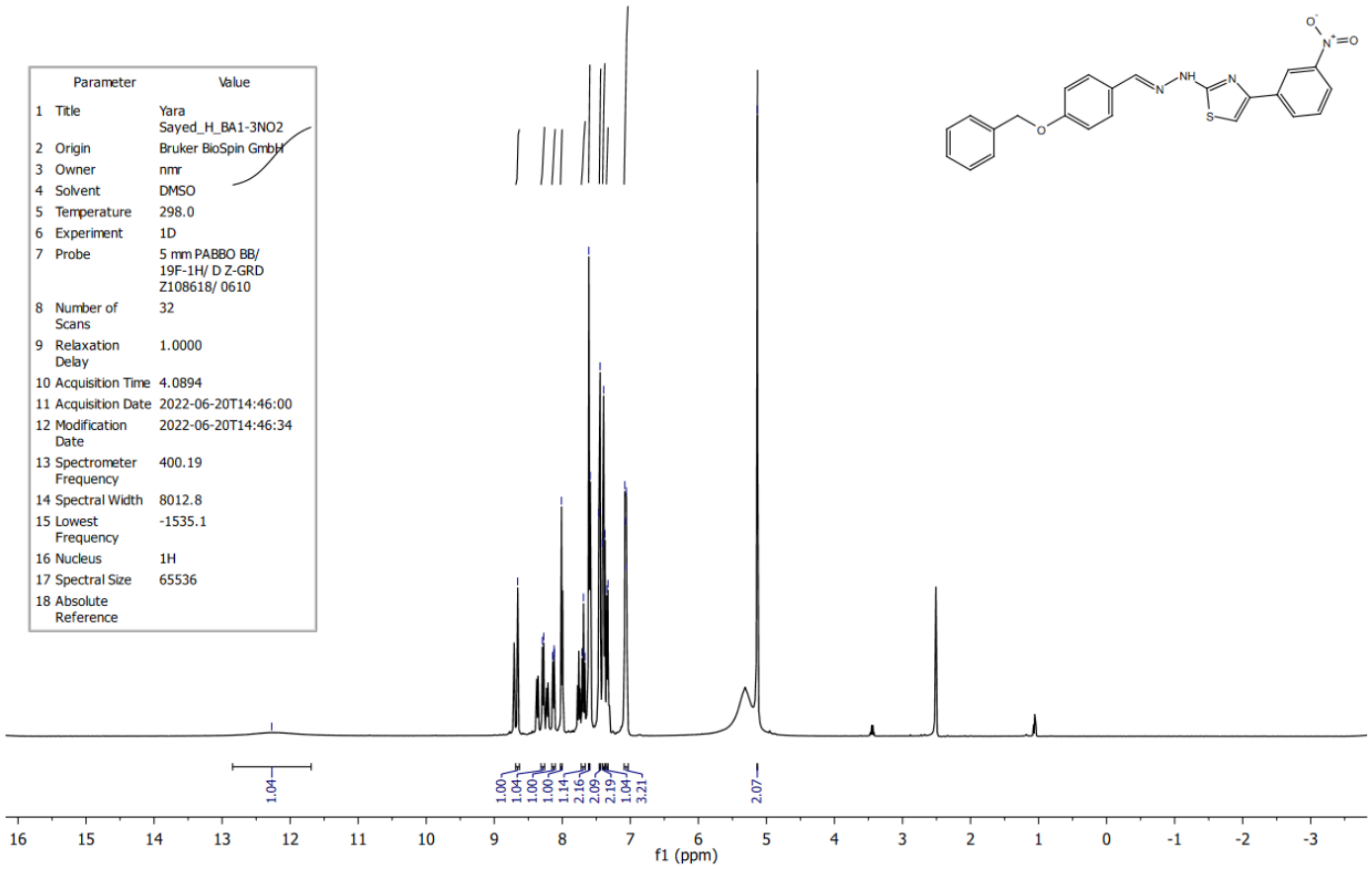
Compound 3h


Rasha Ahmed_H_BA1-ph
12.118
8.016
7.862
7.844
7.627
7.605
7.481
7.464
7.435
7.430
7.427
7.417
7.410
7.397
7.391
7.364
7.352
7.346
7.339
7.330
7.313
7.293
7.103
7.081
5.159
Parameter Value
1 Title Rasha Ahmed_H_BA1-ph
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.1
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 32
9 Relaxation Delay 1.0000
10 Acquisition Time 4.0894
11 Acquisition Date 2022-06-20T15:02:00
12 Modification Date 2022-06-20T15:02:08
13 Spectrometer Frequency 400.19
14 Spectral Width 8012.8
15 Lowest Frequency -1535.1
16 Nucleus 1H
17 Spectral Size 65536
18 Absolute Reference
0.99
1.00
2.00
2.00
2.03
4.02
3.02
2.00
2.00
f1 (ppm)


Rasha Ahmed_C_BA1-ph
168.41
162.68
160.05
137.19
131.90
130.90
129.77
129.51
128.89
128.51
128.31
128.18
126.31
116.03
115.67
69.80
Parameter Value
1 Title Rasha Ahmed_C_BA1-ph
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.1
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 1200
9 Relaxation Delay 2.0000
10 Acquisition Time 1.3631
11 Acquisition Date 2022-07-01T00:24:00
12 Modification Date 2022-07-01T00:24:53
13 Spectrometer Frequency 100.64
14 Spectral Width 24038.5
15 Lowest Frequency -1957.4
16 Nucleus 13C
17 Spectral Size 65536
18 Absolute Reference
f1 (ppm)

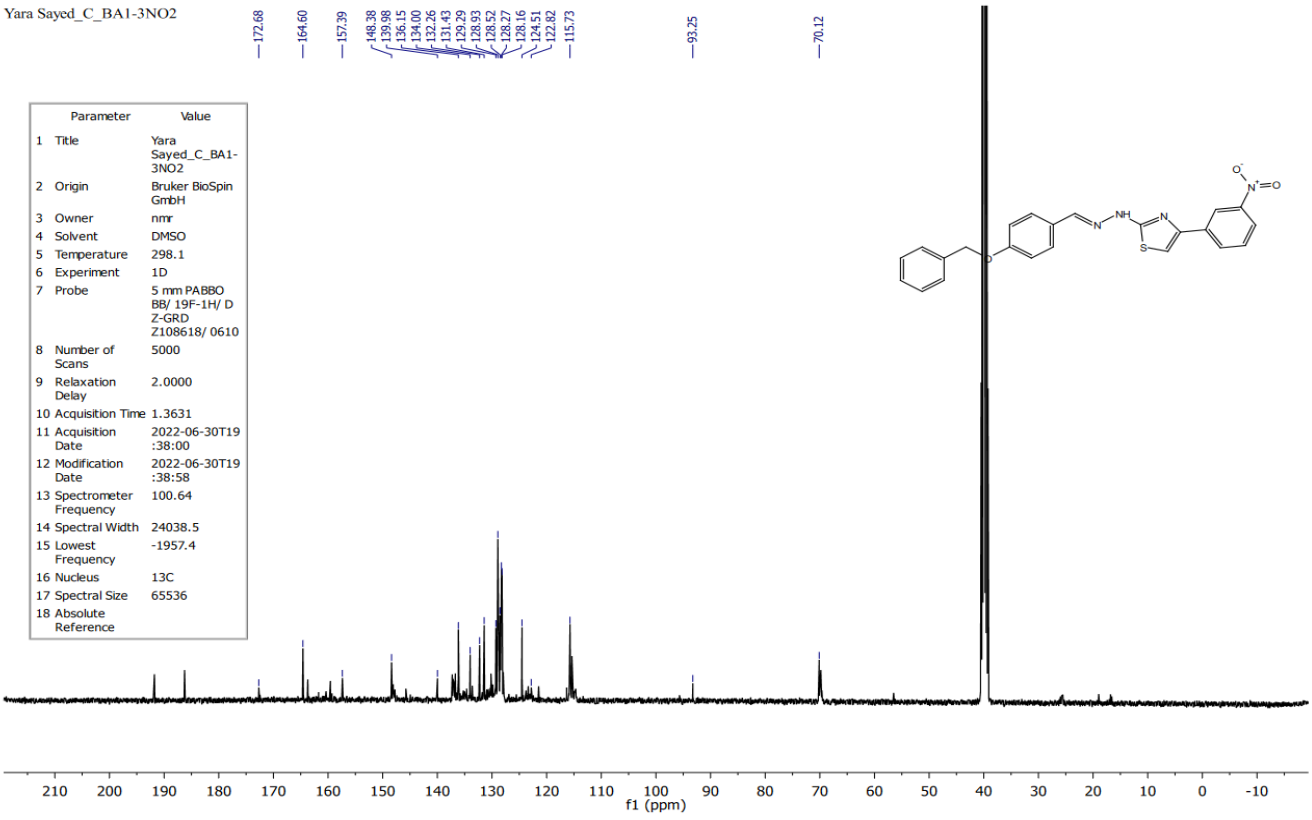
Compound 3i

Yara Sayed_H_BA1-3NO2



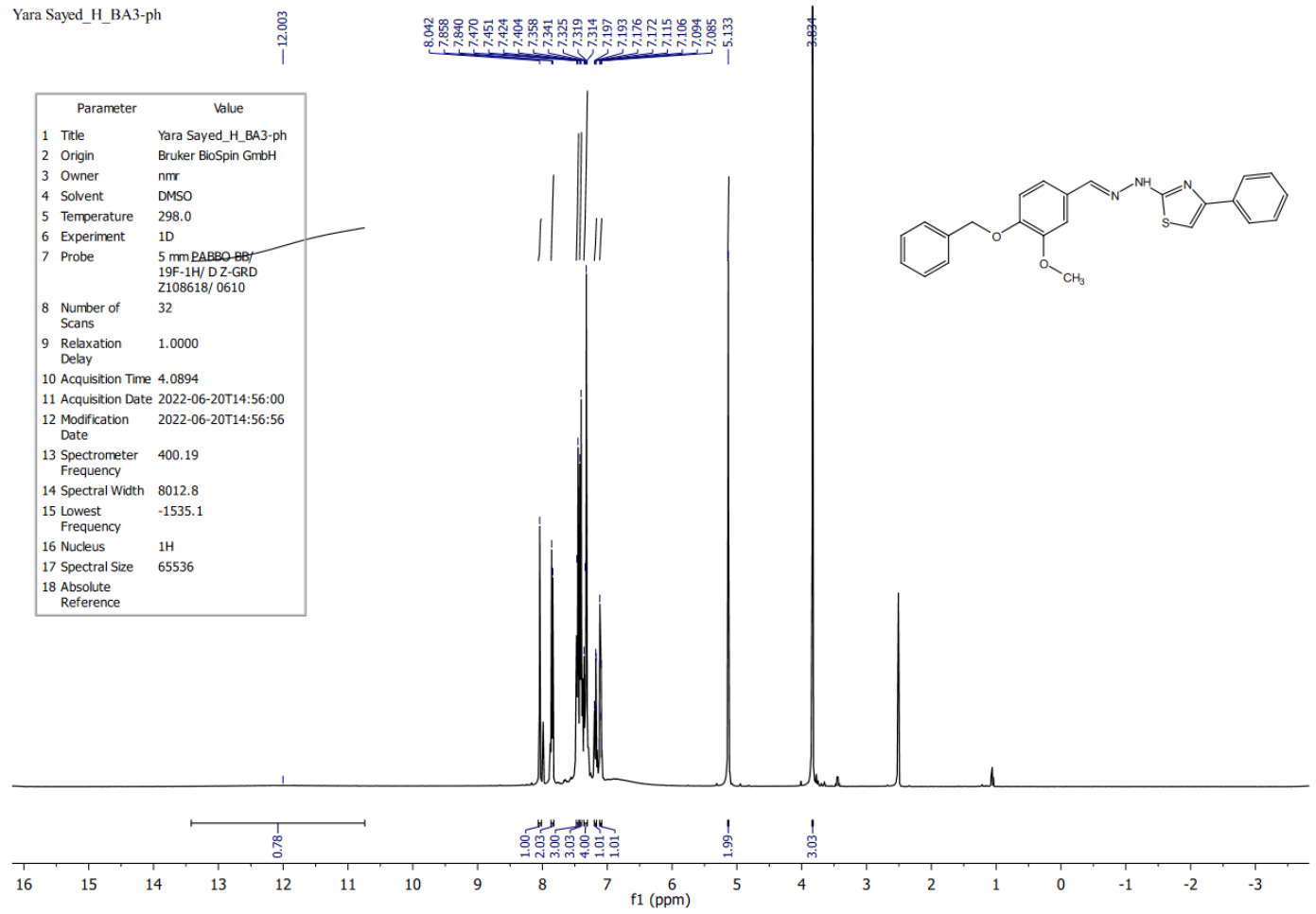
	Parameter	Value
1	Title	Yara Sayed_H_BA1-3NO2
2	Origin	Bruker BioSpin GmbH
3	Owner	nmr
4	Solvent	DMSO
5	Temperature	298.0
6	Experiment	1D
7	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8	Number of Scans	32
9	Relaxation Delay	1.0000
10	Acquisition Time	4.0894
11	Acquisition Date	2022-06-20T14:46:00
12	Modification Date	2022-06-20T14:46:34
13	Spectrometer Frequency	400.19
14	Spectral Width	8012.8
15	Lowest Frequency	-1535.1
16	Nucleus	1H
17	Spectral Size	65536
18	Absolute Reference	

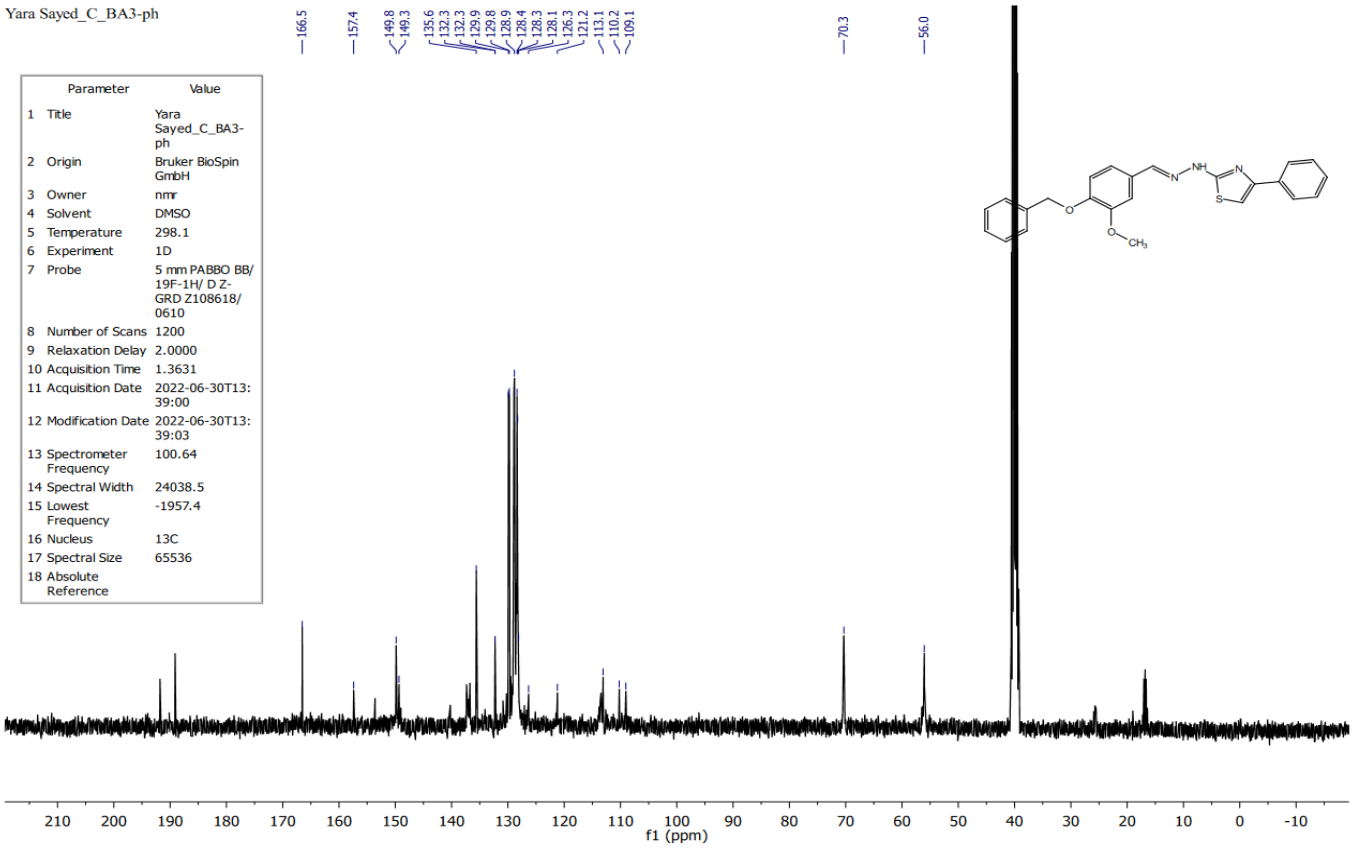
Yara Sayed_C_BA1-3NO2



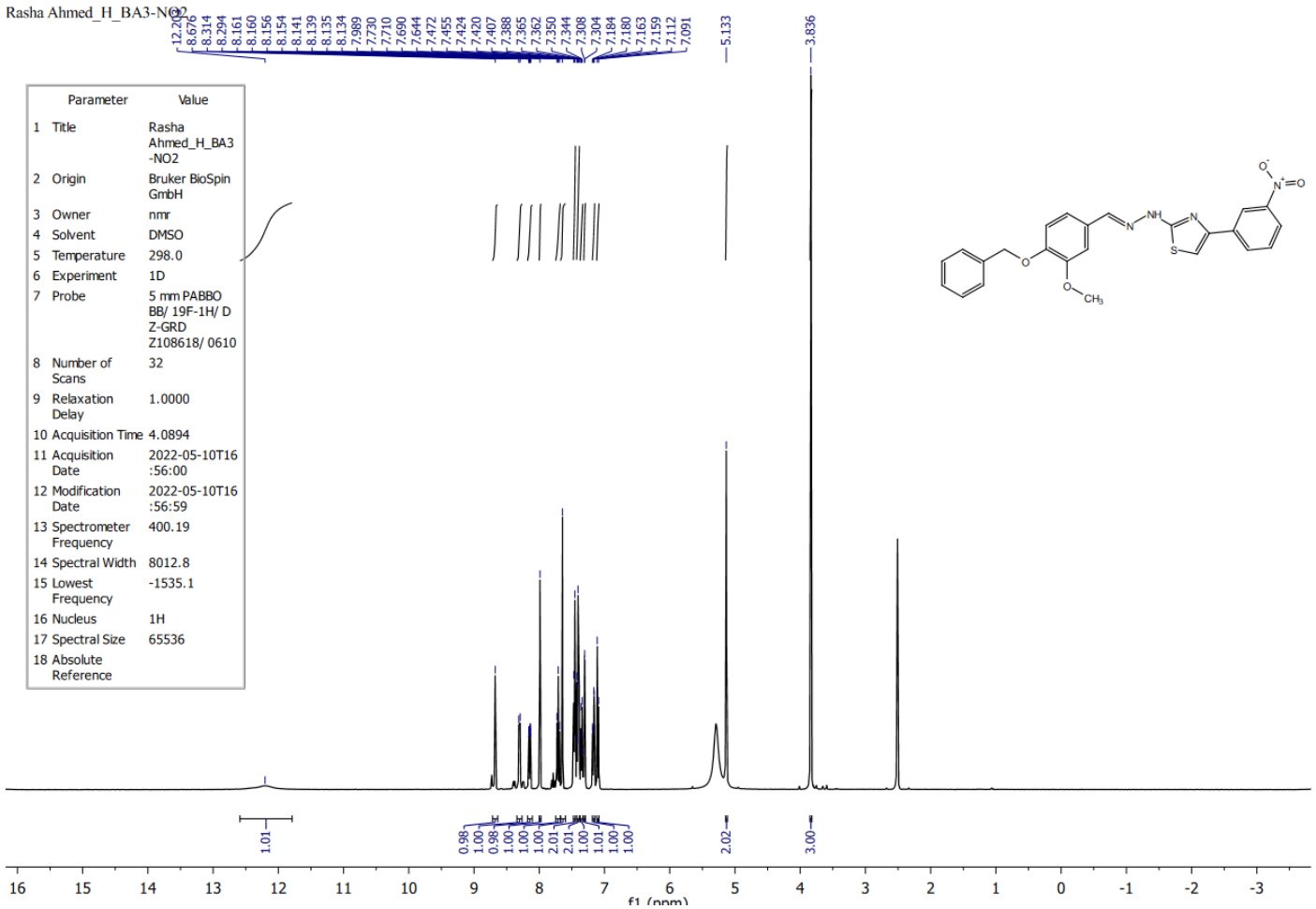
	Parameter	Value
1	Title	Yara Sayed_C_BA1-3NO2
2	Origin	Bruker BioSpin GmbH
3	Owner	nmr
4	Solvent	DMSO
5	Temperature	298.1
6	Experiment	1D
7	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8	Number of Scans	5000
9	Relaxation Delay	2.0000
10	Acquisition Time	1.3631
11	Acquisition Date	2022-06-30T19:38:00
12	Modification Date	2022-06-30T19:38:58
13	Spectrometer Frequency	100.64
14	Spectral Width	24038.5
15	Lowest Frequency	-1957.4
16	Nucleus	13C
17	Spectral Size	65536
18	Absolute Reference	

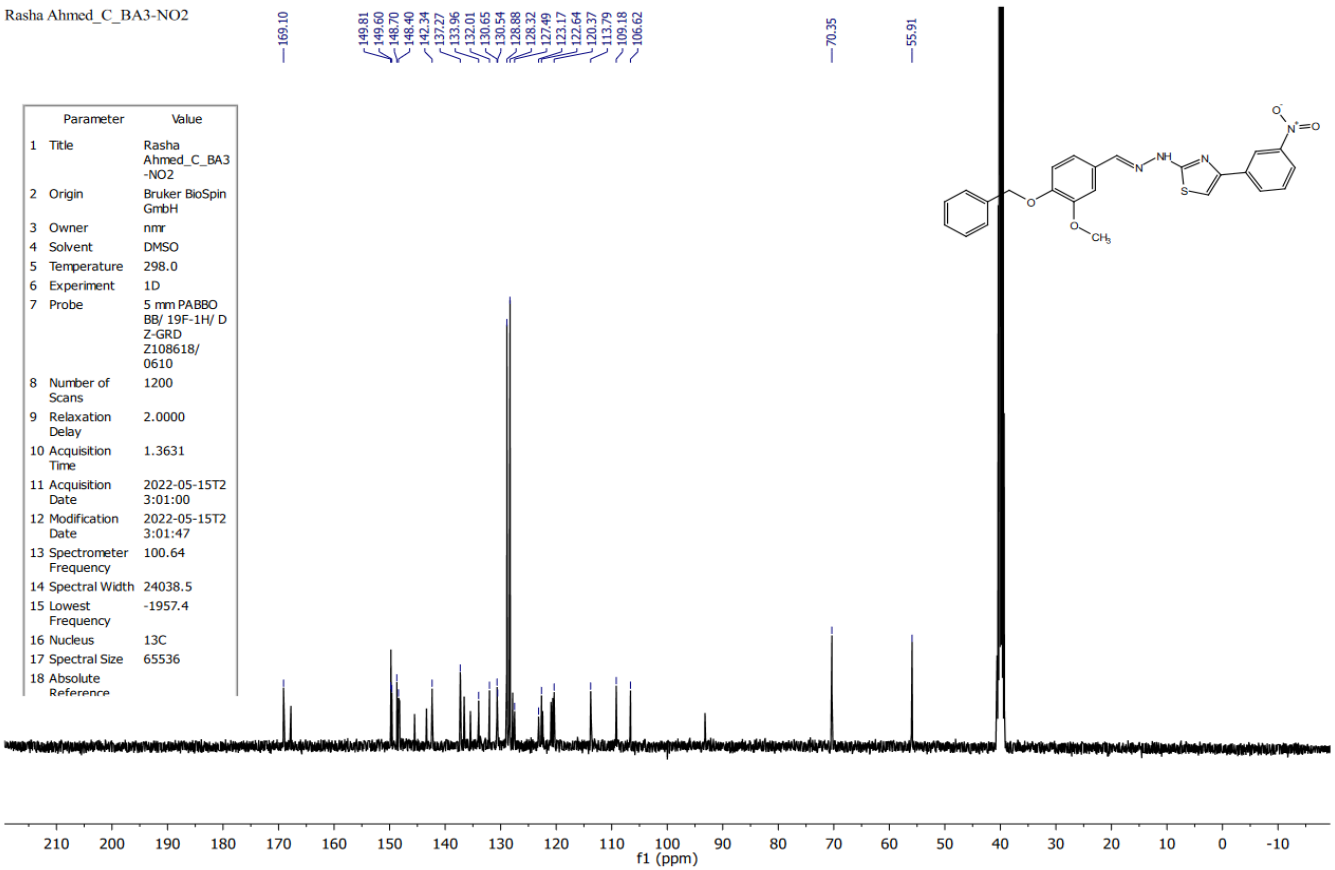
Compound 3j


Yara Sayed_H_BA3-ph
12.003
8.042
7.858
7.840
7.470
7.451
7.424
7.404
7.358
7.341
7.325
7.319
7.314
7.197
7.193
7.176
7.172
7.115
7.106
7.094
7.085
5.133
3.834
Parameter Value
1 Title Yara Sayed_H_BA3-ph
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.0
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 32
9 Relaxation Delay 1.0000
10 Acquisition Time 4.0894
11 Acquisition Date 2022-06-20T14:56:00
12 Modification Date 2022-06-20T14:56:56
13 Spectrometer Frequency 400.19
14 Spectral Width 8012.8
15 Lowest Frequency -1535.1
16 Nucleus 1H
17 Spectral Size 65536
18 Absolute Reference
0.78
1.00
2.03
3.00
3.03
4.00
1.01
1.01
1.99
3.03
f1 (ppm)


Yara Sayed_C_BA3-ph
166.5
157.4
149.8
149.3
135.6
132.3
132.3
129.9
129.8
128.9
128.4
128.3
128.1
126.3
121.2
113.1
110.2
109.1
70.3
56.0
Parameter Value
1 Title Yara Sayed_C_BA3-ph
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.1
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 1200
9 Relaxation Delay 2.0000
10 Acquisition Time 1.3631
11 Acquisition Date 2022-06-30T13:39:00
12 Modification Date 2022-06-30T13:39:03
13 Spectrometer Frequency 100.64
14 Spectral Width 24038.5
15 Lowest Frequency -1957.4
16 Nucleus 13C
17 Spectral Size 65536
18 Absolute Reference
f1 (ppm)

Compound 3k

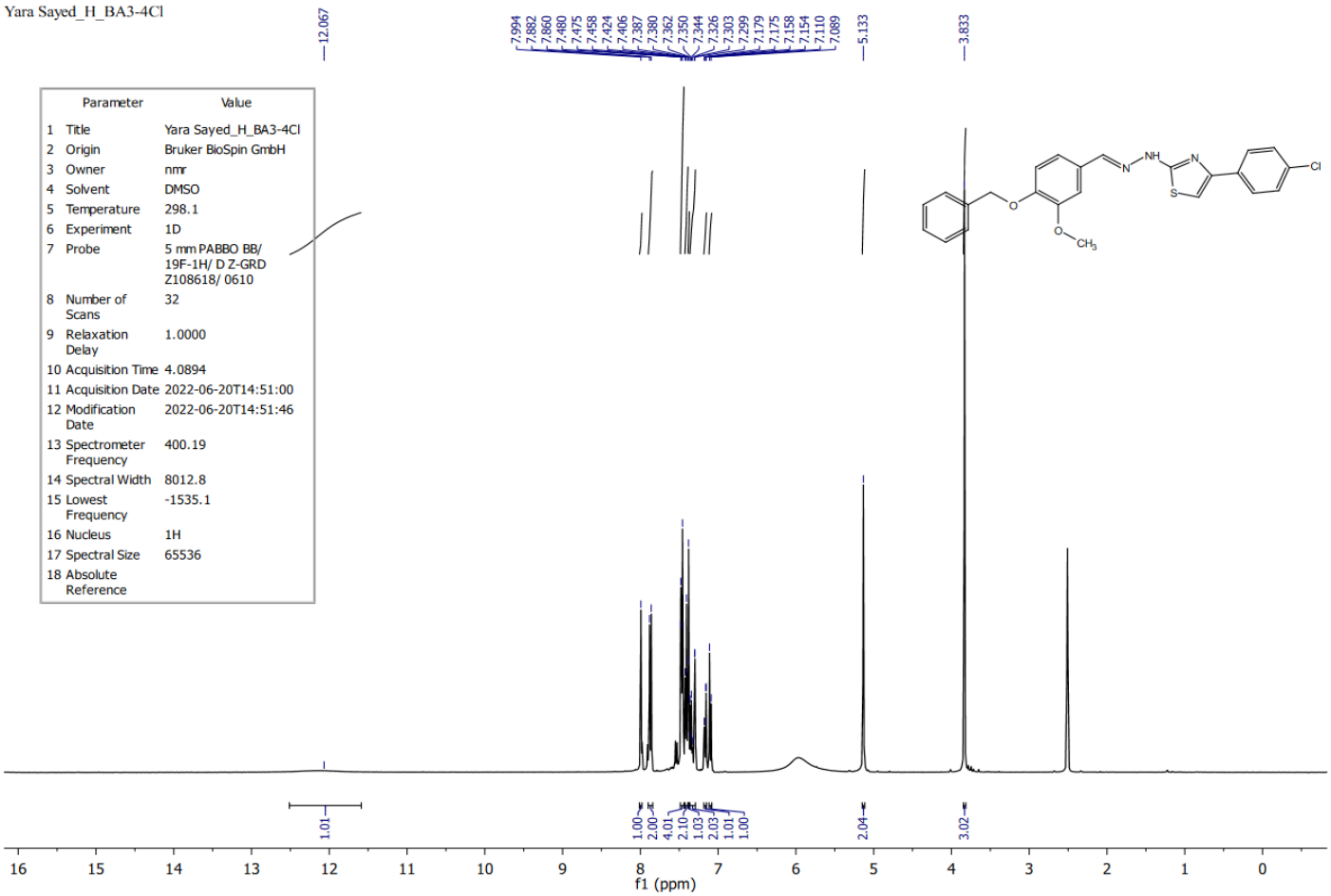

Rasha Ahmed_H_BA3-NO2
12.202
8.676
8.314
8.294
8.161
8.160
8.156
8.154
8.141
8.139
8.135
8.134
7.989
7.730
7.710
7.690
7.644
7.472
7.455
7.424
7.420
7.407
7.388
7.365
7.362
7.350
7.344
7.308
7.304
7.184
7.180
7.163
7.159
7.112
7.091
5.133
3.836
Parameter Value
1 Title Rasha Ahmed_H_BA3-NO2
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.0
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 32
9 Relaxation Delay 1.0000
10 Acquisition Time 4.0894
11 Acquisition Date 2022-05-10T16:56:00
12 Modification Date 2022-05-10T16:56:59
13 Spectrometer Frequency 400.19
14 Spectral Width 8012.8
15 Lowest Frequency -1535.1
16 Nucleus 1H
17 Spectral Size 65536
18 Absolute Reference
1.01
0.98
1.00
0.98
1.00
1.00
1.00
2.01
2.01
1.00
1.01
1.00
1.00
2.02
3.00
f1 (ppm)


Rasha Ahmed_C_BA3-NO2
169.10
149.81
149.60
148.70
148.40
142.34
137.27
133.96
132.01
130.65
130.54
128.88
128.32
127.49
123.17
122.64
120.37
113.79
109.18
106.62
70.35
55.91
Parameter Value
1 Title Rasha Ahmed_C_BA3-NO2
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.0
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 1200
9 Relaxation Delay 2.0000
10 Acquisition Time 1.3631
11 Acquisition Date 2022-05-15T23:01:00
12 Modification Date 2022-05-15T23:01:47
13 Spectrometer Frequency 100.64
14 Spectral Width 24038.5
15 Lowest Frequency -1957.4
16 Nucleus 13C
17 Spectral Size 65536
18 Absolute Reference
f1 (ppm)

Compound 3l

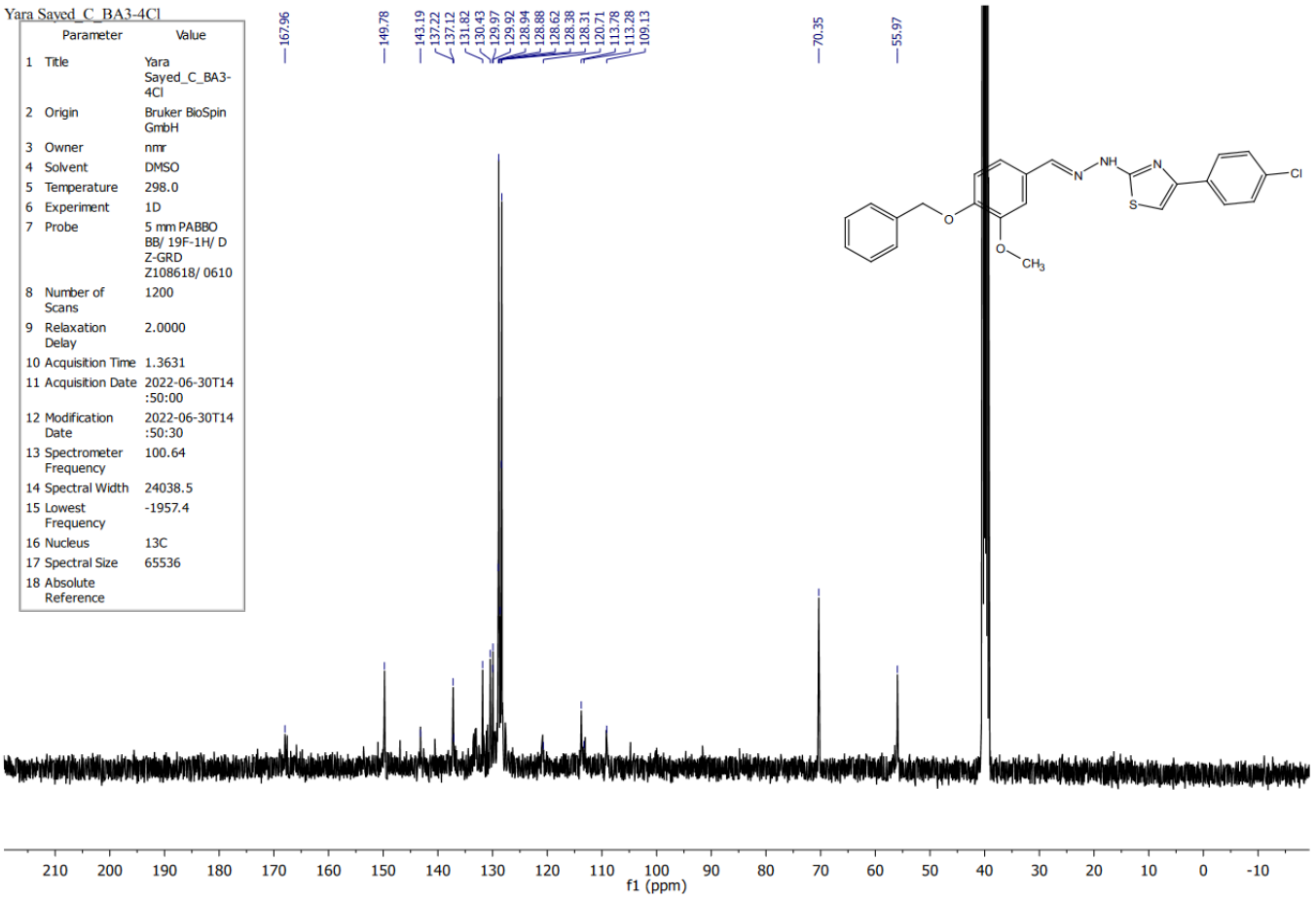
Yara Sayed_H_BA3-4Cl

	Parameter	Value
1	Title	Yara Sayed_H_BA3-4Cl
2	Origin	Bruker BioSpin GmbH
3	Owner	nmr
4	Solvent	DMSO
5	Temperature	298.1
6	Experiment	1D
7	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8	Number of Scans	32
9	Relaxation Delay	1.0000
10	Acquisition Time	4.0894
11	Acquisition Date	2022-06-20T14:51:00
12	Modification Date	2022-06-20T14:51:46
13	Spectrometer Frequency	400.19
14	Spectral Width	8012.8
15	Lowest Frequency	-1535.1
16	Nucleus	1H
17	Spectral Size	65536
18	Absolute Reference	



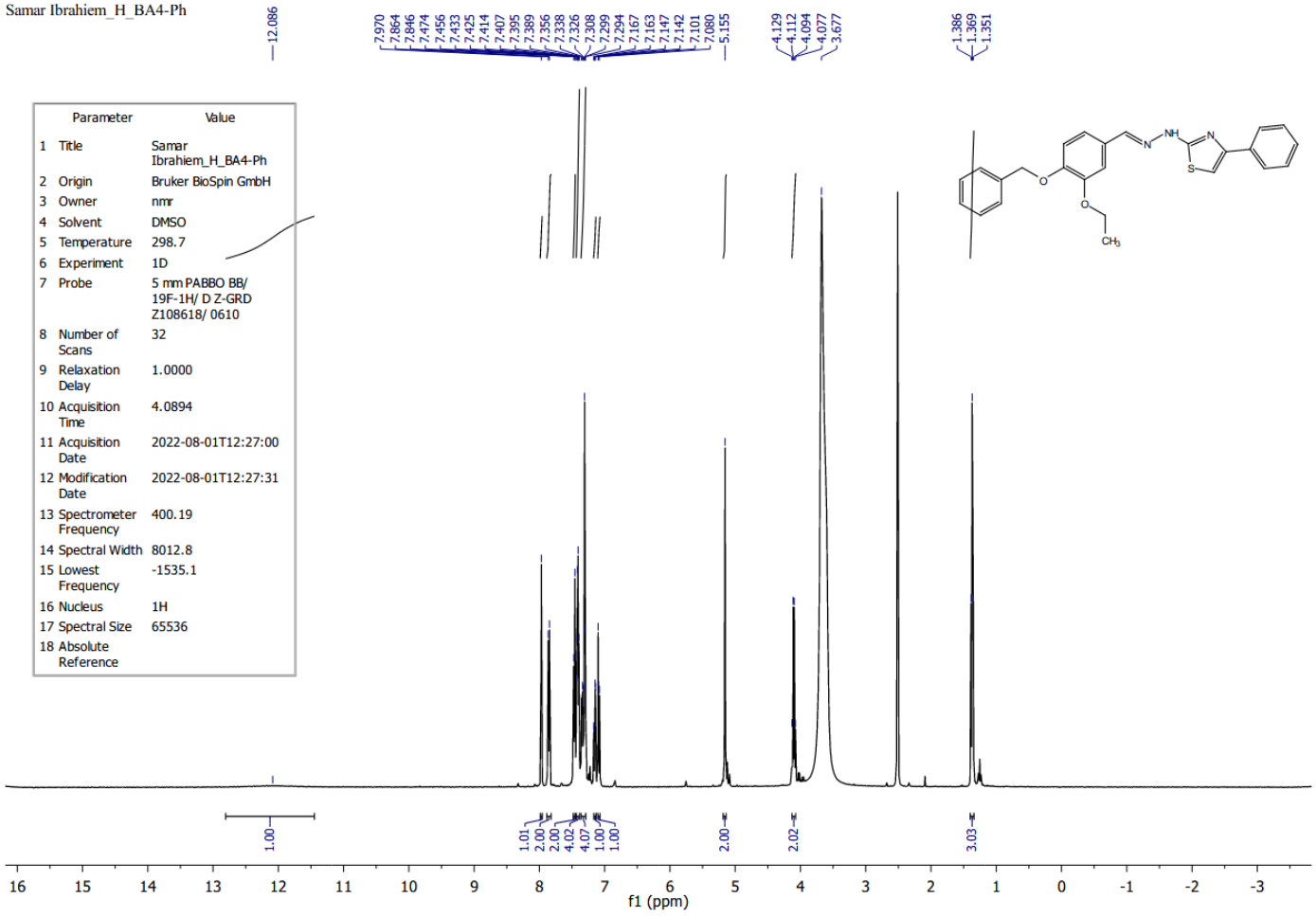
Yara Sayed_C_BA3-4Cl

	Parameter	Value
1	Title	Yara Sayed_C_BA3-4Cl
2	Origin	Bruker BioSpin GmbH
3	Owner	nmr
4	Solvent	DMSO
5	Temperature	298.0
6	Experiment	1D
7	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8	Number of Scans	1200
9	Relaxation Delay	2.0000
10	Acquisition Time	1.3631
11	Acquisition Date	2022-06-30T14:50:00
12	Modification Date	2022-06-30T14:50:30
13	Spectrometer Frequency	100.64
14	Spectral Width	24038.5
15	Lowest Frequency	-1957.4
16	Nucleus	13C
17	Spectral Size	65536
18	Absolute Reference	



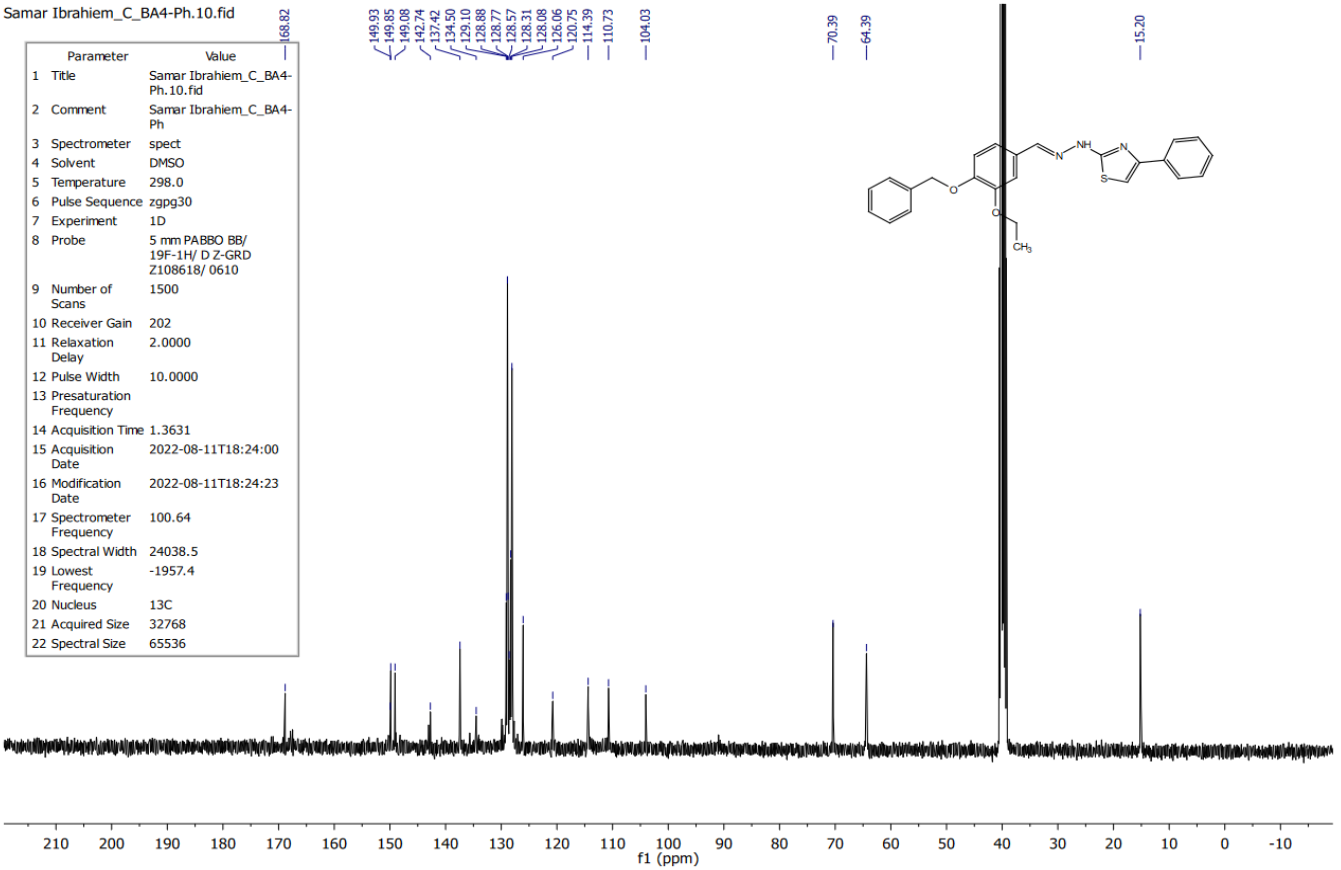
Compound 3m

Samar Ibrahiem_H_BA4-Ph



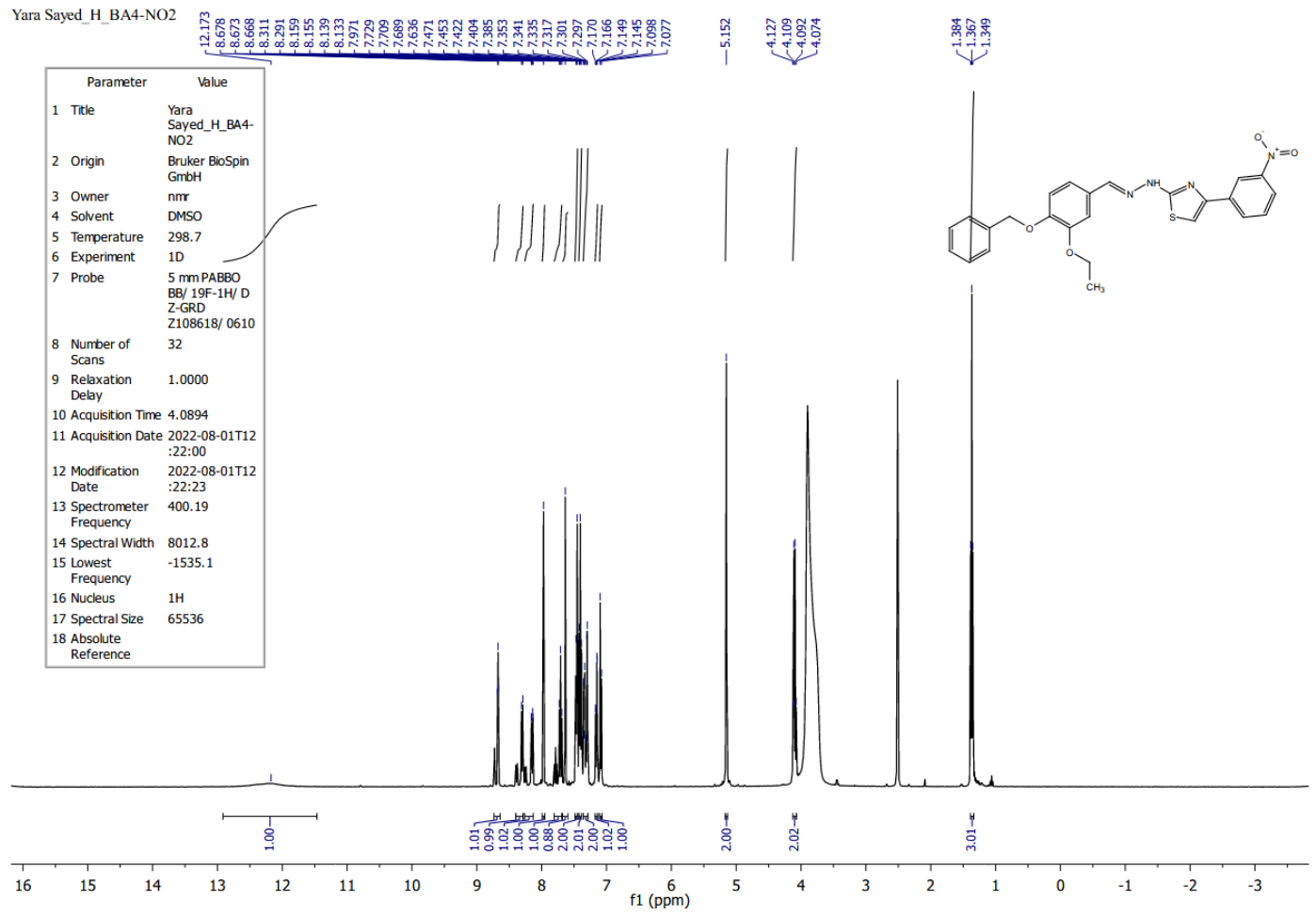
	Parameter	Value
1	Title	Samar Ibrahiem_H_BA4-Ph
2	Origin	Bruker BioSpin GmbH
3	Owner	nmr
4	Solvent	DMSO
5	Temperature	298.7
6	Experiment	1D
7	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8	Number of Scans	32
9	Relaxation Delay	1.0000
10	Acquisition Time	4.0894
11	Acquisition Date	2022-08-01T12:27:00
12	Modification Date	2022-08-01T12:27:31
13	Spectrometer Frequency	400.19
14	Spectral Width	8012.8
15	Lowest Frequency	-1535.1
16	Nucleus	1H
17	Spectral Size	65536
18	Absolute Reference	

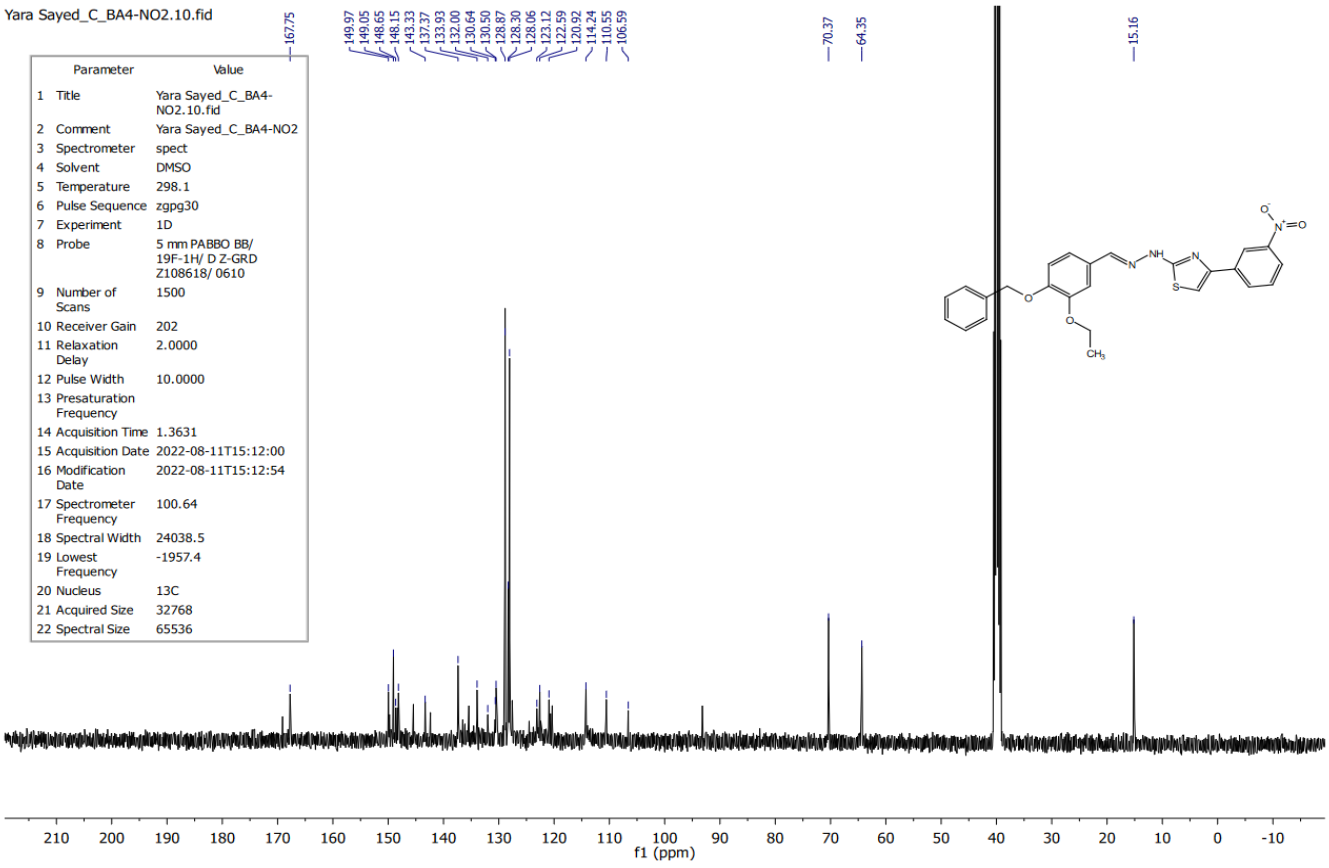
Samar Ibrahiem_C_BA4-Ph.10.fid



	Parameter	Value
1	Title	Samar Ibrahiem_C_BA4-Ph.10.fid
2	Comment	Samar Ibrahiem_C_BA4-Ph
3	Spectrometer	spect
4	Solvent	DMSO
5	Temperature	298.0
6	Pulse Sequence	zgpg30
7	Experiment	1D
8	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
9	Number of Scans	1500
10	Receiver Gain	202
11	Relaxation Delay	2.0000
12	Pulse Width	10.0000
13	Presaturation Frequency	
14	Acquisition Time	1.3631
15	Acquisition Date	2022-08-11T18:24:00
16	Modification Date	2022-08-11T18:24:23
17	Spectrometer Frequency	100.64
18	Spectral Width	24038.5
19	Lowest Frequency	-1957.4
20	Nucleus	13C
21	Acquired Size	32768
22	Spectral Size	65536

Compound 3n

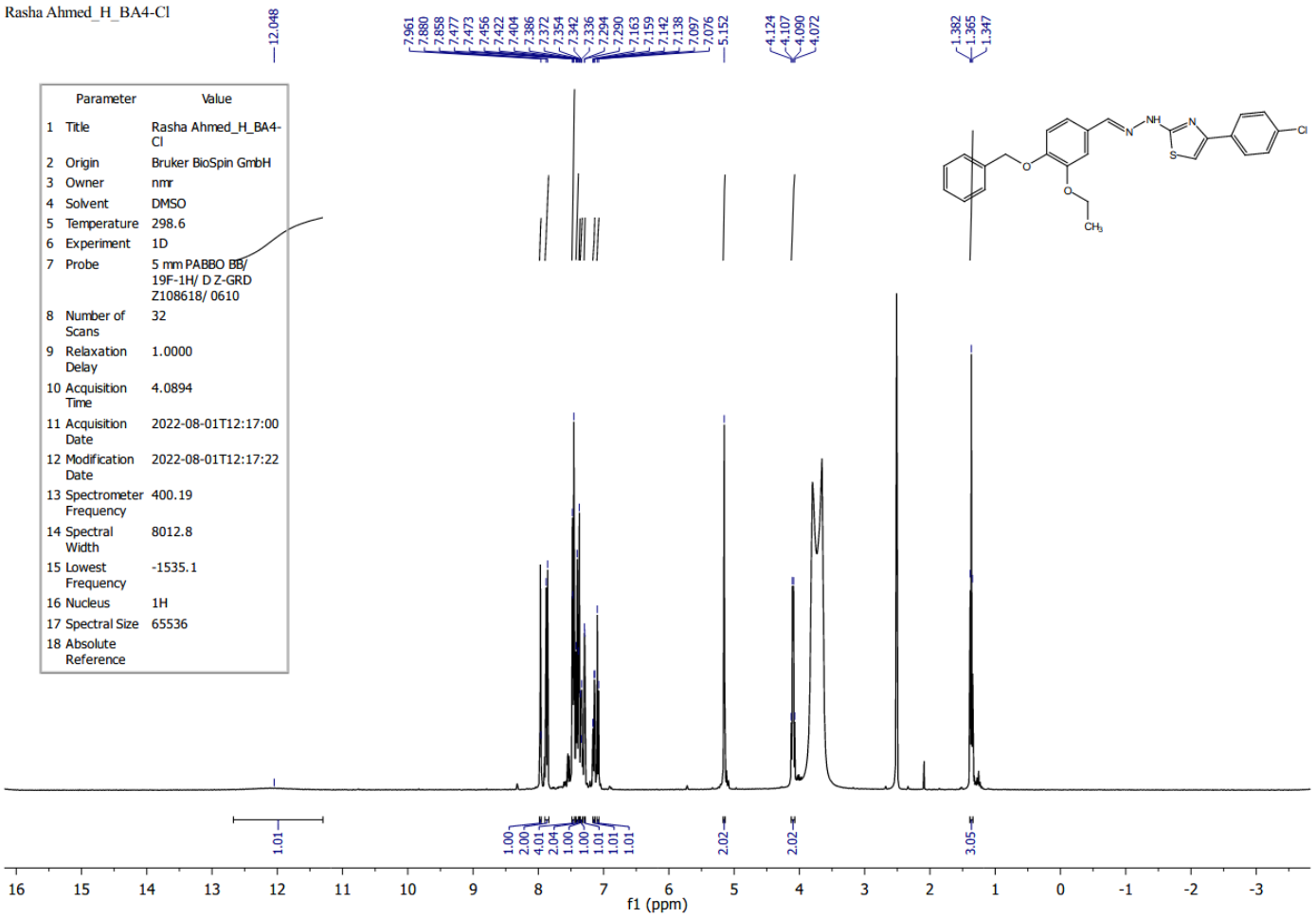

Yara Sayed_H_BA4-NO2
12.173
8.678
8.673
8.668
8.311
8.291
8.159
8.155
8.139
8.133
7.971
7.729
7.709
7.689
7.636
7.471
7.453
7.422
7.404
7.385
7.353
7.341
7.335
7.317
7.301
7.297
7.170
7.166
7.149
7.145
7.098
7.077
5.152
4.127
4.109
4.092
4.074
1.384
1.367
1.349
Parameter Value
1 Title Yara Sayed_H_BA4-NO2
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.7
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 32
9 Relaxation Delay 1.0000
10 Acquisition Time 4.0894
11 Acquisition Date 2022-08-01T12:22:00
12 Modification Date 2022-08-01T12:22:23
13 Spectrometer Frequency 400.19
14 Spectral Width 8012.8
15 Lowest Frequency -1535.1
16 Nucleus 1H
17 Spectral Size 65536
18 Absolute Reference
1.00
1.01
0.99
1.02
1.00
1.00
0.88
2.00
2.01
2.00
1.02
1.00
2.00
2.02
3.01
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


Yara Sayed_C_BA4-NO2.10.fid
167.75
149.97
149.05
148.65
148.15
143.33
137.37
133.93
132.00
130.64
130.50
128.87
128.30
128.06
123.12
122.59
120.92
114.24
110.55
106.59
70.37
64.35
15.16
Parameter Value
1 Title Yara Sayed_C_BA4-NO2.10.fid
2 Comment Yara Sayed_C_BA4-NO2
3 Spectrometer spect
4 Solvent DMSO
5 Temperature 298.1
6 Pulse Sequence zgpg30
7 Experiment 1D
8 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
9 Number of Scans 1500
10 Receiver Gain 202
11 Relaxation Delay 2.0000
12 Pulse Width 10.0000
13 Presaturation Frequency
14 Acquisition Time 1.3631
15 Acquisition Date 2022-08-11T15:12:00
16 Modification Date 2022-08-11T15:12:54
17 Spectrometer Frequency 100.64
18 Spectral Width 24038.5
19 Lowest Frequency -1957.4
20 Nucleus 13C
21 Acquired Size 32768
22 Spectral Size 65536
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 3o

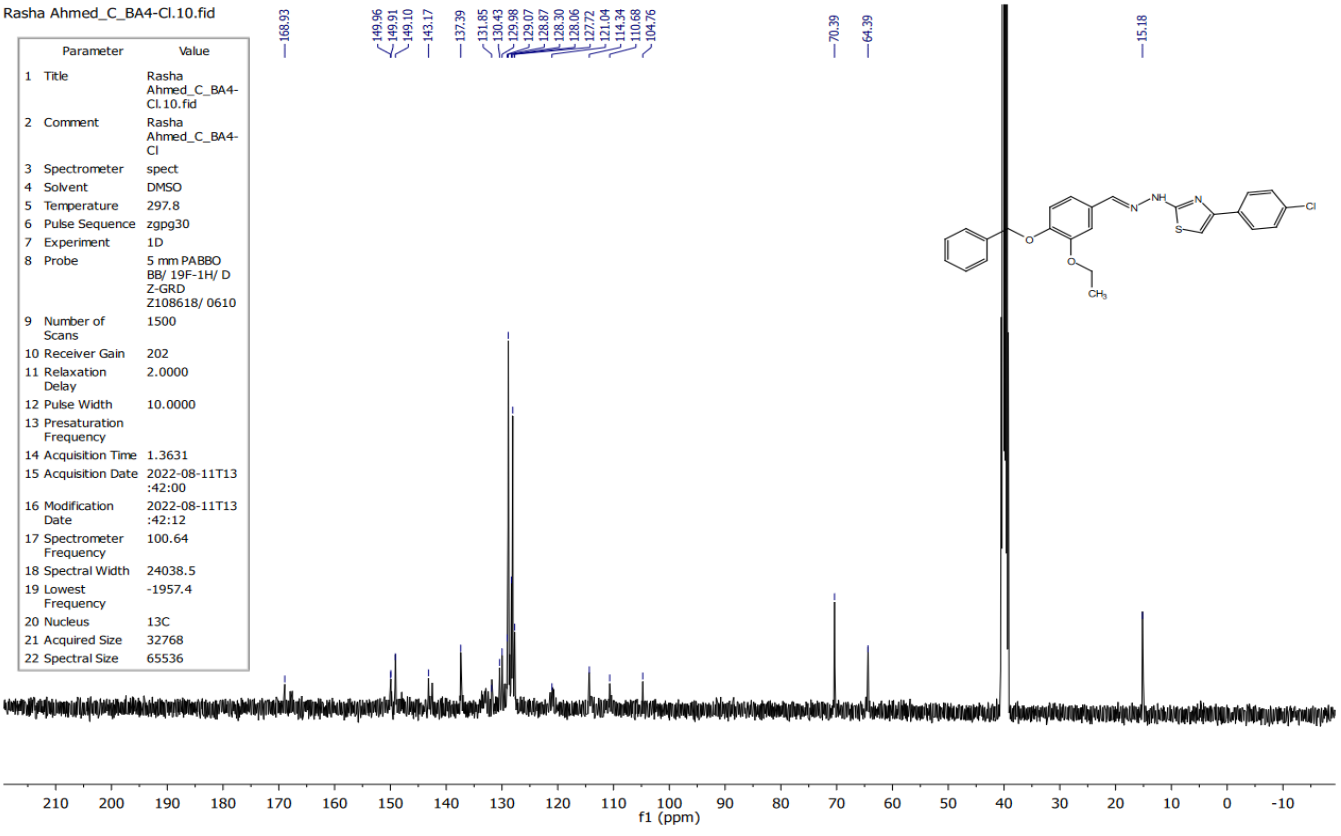
Rasha Ahmed_H_BA4-Cl

	Parameter	Value
1	Title	Rasha Ahmed_H_BA4-Cl
2	Origin	Bruker BioSpin GmbH
3	Owner	nmr
4	Solvent	DMSO
5	Temperature	298.6
6	Experiment	1D
7	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8	Number of Scans	32
9	Relaxation Delay	1.0000
10	Acquisition Time	4.0894
11	Acquisition Date	2022-08-01T12:17:00
12	Modification Date	2022-08-01T12:17:22
13	Spectrometer Frequency	400.19
14	Spectral Width	8012.8
15	Lowest Frequency	-1535.1
16	Nucleus	1H
17	Spectral Size	65536
18	Absolute Reference	

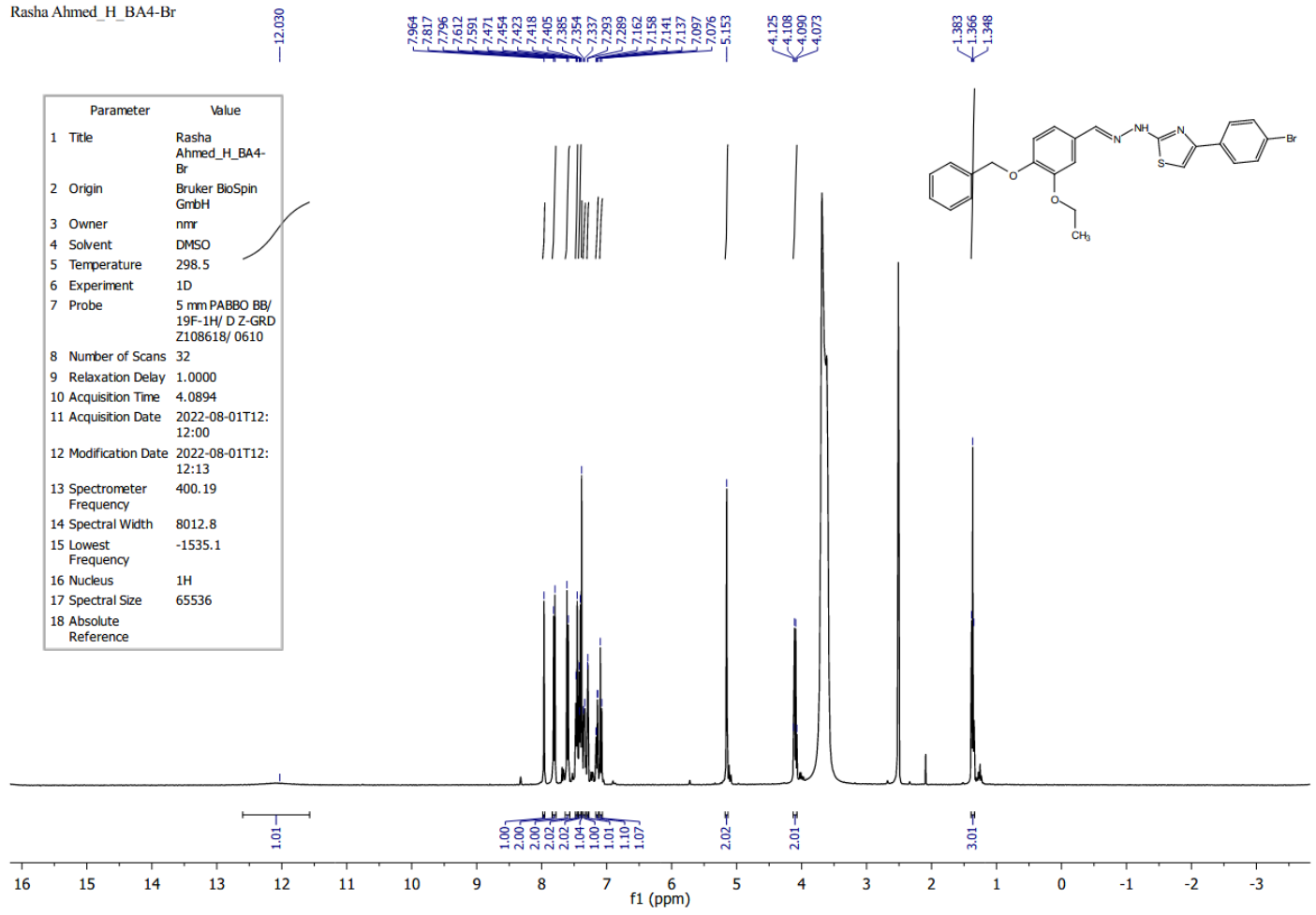


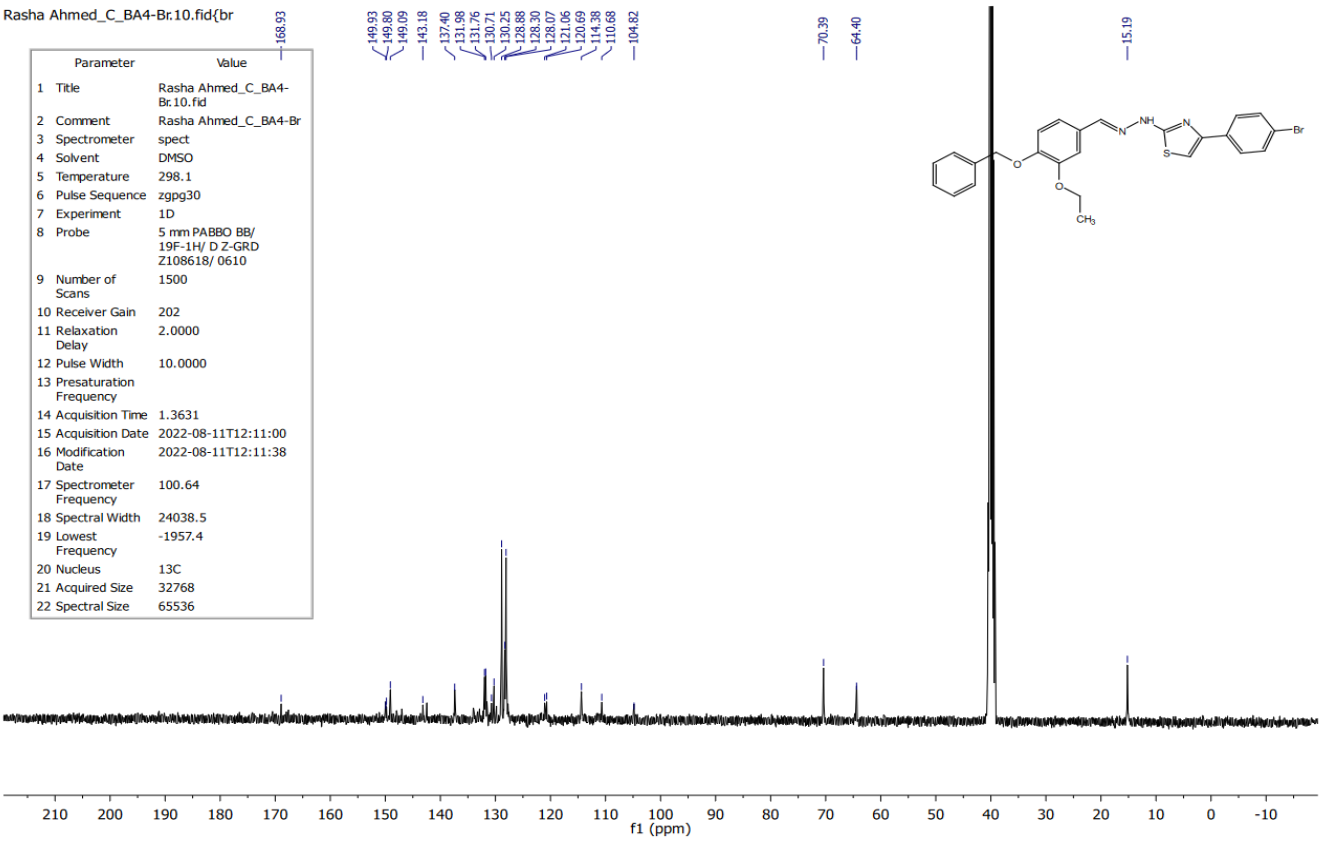
Rasha Ahmed_C_BA4-Cl.10.fid

	Parameter	Value
1	Title	Rasha Ahmed_C_BA4-Cl.10.fid
2	Comment	Rasha Ahmed_C_BA4-Cl
3	Spectrometer	spect
4	Solvent	DMSO
5	Temperature	297.8
6	Pulse Sequence	zgpg30
7	Experiment	1D
8	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
9	Number of Scans	1500
10	Receiver Gain	202
11	Relaxation Delay	2.0000
12	Pulse Width	10.0000
13	Presaturation Frequency	
14	Acquisition Time	1.3631
15	Acquisition Date	2022-08-11T13:42:00
16	Modification Date	2022-08-11T13:42:12
17	Spectrometer Frequency	100.64
18	Spectral Width	24038.5
19	Lowest Frequency	-1957.4
20	Nucleus	13C
21	Acquired Size	32768
22	Spectral Size	65536



Compound 3p


Rasha Ahmed_H_BA4-Br
12.030
7.964
7.817
7.796
7.612
7.591
7.471
7.454
7.423
7.418
7.405
7.385
7.354
7.337
7.293
7.289
7.162
7.158
7.141
7.137
7.097
7.076
5.153
4.125
4.108
4.090
4.073
1.383
1.366
1.348
Parameter Value
1 Title Rasha Ahmed_H_BA4-Br
2 Origin Bruker BioSpin GmbH
3 Owner nmr
4 Solvent DMSO
5 Temperature 298.5
6 Experiment 1D
7 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
8 Number of Scans 32
9 Relaxation Delay 1.0000
10 Acquisition Time 4.0894
11 Acquisition Date 2022-08-01T12:12:00
12 Modification Date 2022-08-01T12:12:13
13 Spectrometer Frequency 400.19
14 Spectral Width 8012.8
15 Lowest Frequency -1535.1
16 Nucleus 1H
17 Spectral Size 65536
18 Absolute Reference
1.01
1.00
2.00
2.00
2.02
2.02
1.04
1.00
1.01
1.10
1.07
2.02
2.01
3.01
f1 (ppm)


Rasha Ahmed_C_BA4-Br.10.fid{br
168.93
149.93
149.80
149.09
143.18
137.40
131.98
131.76
130.71
130.25
128.88
128.30
128.07
121.06
120.69
114.38
110.68
104.82
70.39
64.40
15.19
Parameter Value
1 Title Rasha Ahmed_C_BA4-Br.10.fid
2 Comment Rasha Ahmed_C_BA4-Br
3 Spectrometer spect
4 Solvent DMSO
5 Temperature 298.1
6 Pulse Sequence zgpg30
7 Experiment 1D
8 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0610
9 Number of Scans 1500
10 Receiver Gain 202
11 Relaxation Delay 2.0000
12 Pulse Width 10.0000
13 Presaturation Frequency
14 Acquisition Time 1.3631
15 Acquisition Date 2022-08-11T12:11:00
16 Modification Date 2022-08-11T12:11:38
17 Spectrometer Frequency 100.64
18 Spectral Width 24038.5
19 Lowest Frequency -1957.4
20 Nucleus 13C
21 Acquired Size 32768
22 Spectral Size 65536
f1 (ppm)

Elemental analysis

Al-Azhar University

The Regional Center for Mycology and Biotechnology

Requester Data:

Name: Dr Rasha Hasan

Authority: Faculty of Pharmacy, Cairo University

Sample Data:

Sixteen samples had been submitted for elemental analysis.

Analysis Report:

Sample Code	C%	H%	N%
3g Anti Br	54.09	4.03	15.17
3f Anti NO_2	58.31	4.32	19.62
3i BA_1 NO_2	64.40	4.35	13.29
3h BA_1 Ph	71.92	4.84	11.16
3k BA_3 $3NO_2$	62.43	4.51	12.43
3l BA_3 4Cl	63.98	4.59	9.52
3j BA_3 Ph	69.09	5.21	10.34
3n BA_4 $3NO_2$	63.45	4.72	12.07
3p BA_4 Br	59.28	4.50	8.49
3o BA_4 Cl	64.59	4.87	9.29
3m BA_4 Ph	70.06	5.63	10.02
3d $ClNO_2$ $3NO_2$	47.82	2.67	17.52
3e $ClNO_2$ 4Cl	49.05	2.71	14.53
3c $ClNO_2$ Ph	53.80	3.27	15.89
3b Ethoxy NO_2	56.41	4.39	14.81
3a Ethoxy Ph	63.91	5.22	12.59

INVESTIGATOR **DIRECTOR**