Fluorinated Indeno-quinoxaline bearing thiazole moieties as hypoglycemic agents targeting *α*-amylase, and *α*-glucosidase: synthesis, molecular docking, and ADMET studies.

Nirvana A. Gohar[a], Eman A. Fayed[b*], Yousry A. Ammar[c], Ola A. Abu Ali[d], Ahmed Ragab[c], Amal M. Mahfoz[e], and Moustafa S. Abusaif [c]

[a]Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, MTI University, Cairo, Egypt.

[b]Pharmaceutical Organic Chemistry, Faculty of Pharmacy (Girls), Al-Azhar University, Nasr City 11754, Cairo, Egypt.

[c]Department of Chemistry, Faculty of Science (Boys), Al-Azhar University, Nasr City 11884, Cairo, Egypt.

[d] Department of Chemistry, College of Science, Taif University, P.O.Box 11099 Taif 21944, Saudi Arabia

[e]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Modern University for Technology and Information, Cairo, Egypt.

S1 Material and methods

3.1. Chemistry

Inaccurate melting points (MPs) of the novel designed compounds are determined and reported on the digital Gallen Kamp MFB-595 instrument. A Shimadzu 440 spectrophotometer is used to measure the IR spectra between 400 – 4000 cm^{-1}. A Bruker (400 and 101 MHz) spectrometer is used to evaluate the ^{1}H and ^{13}C signals in the NMR spectra and is recorded relative to deuterated solvent signals only in dimethyl sulfoxide (DMSO-d_6). Values of the chemical shift were listed as δ ppm units. Also, the starting material 7-fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-one (**3**) was constructed according to the previous work in a good yield = 65 %, as pale-orange color and melting point in arrange of M.p. = 253–254 ^{O}C.

3.1.1. Synthesis of Schiff's bases (4-6)

To a solution of starting material (**3**) (0.01 mol) and amino thiazole derivatives (0.01 mol) namely, 2-aminothiazol-4(5*H*)-one, 1-(2-amino-4-methylthiazol-5-yl)ethan-1-one or ethyl 2-amino-4-methylthiazole-5-carboxylate in ethanol / acetic acid mixture (5 / 15 mL) was heated under reflux 3-4 h (monitored by TLC). Upon the reaction's completion, the solid formed was collected, filtered out, and recrystallized from the appropriate solvent.

3.1.2. 2-((7-Fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)amino)thiazol-4(5*H*)-one (**4**)

Yield: 76 % as light-orange crystals from EtOH; mp. 190–192 ^{O}C; IR: ν/cm^{-1} = 3051 (CH-Arom), 2981 (CH-Aliph), 1736 (C=O), 1604 (C=N); ^{1}H NMR δ/ppm = 4.08 (2H, s, CH_2), 7.69 (1H, t, *J*=8.0 Hz, H-Arom), 7.76 (1H, t, *J*=8.0 Hz, H-Arom), 7.87 (1H, s, H-Arom), 7.89 (1H, d, *J*=8.0 Hz, H-Arom), 7.94 (1H, d, *J*=8.0 Hz, H-Arom), 8.07 (1H, d, *J*=8.0 Hz, H-Arom), 8.24 (1H, dd, *J*=8.6, 4.8 Hz, H-Arom); ^{13}C NMR δ/ppm 37.46 (CH_2), 113.94, 114.16, 115.78, 117.28, 118.68, 118.85, 120.59, 121.35, 122.96, 124.76, 133.60, 133.81, 137.46, 145.60, 163.57 (C=N), 173.55 (C-F), 178.41 (C=O), 179.02 (S-C=N). Anal. Calcd. for **$C_{18}H_9FN_4OS$** (348.36): C, 62.06; H, 2.60; N, 16.08; Found: C, 62.48; H, 2.34; N, 16.54 %.

3.1.3. 1-(2-((7-Fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)amino)-4-methylthiazol-5-yl)ethan-1-one (**5**)

Yield: 72 % as orange crystals from EtOH; mp. 198–200 ^{O}C; IR: *ν*/cm^{-1} = 3053 (CH-Arom), 2950 (CH-Aliph), 1735 (C=O), 1604 (C=N); ^{1}H NMR *δ*/ppm = 2.33 (3H, s, CH_3), 2.41 (3H, s, CH_3), 7.72 (1H, t, *J*=8 Hz, H-Arom), 7.79 (1H, d, *J*=6.1 Hz, H-Arom), 7.87 (1H, s, H-Arom), 7.90 (1H, d, *J*=5.3 Hz, H-Arom), 7.96 (1H, d, *J*=6.8 Hz, H-Arom), 8.08 (1H, t, *J*=4 Hz, H-Arom), 8.25 (1H, dd, *J*=9.2, 6.0 Hz, H-Arom); ^{13}C NMR *δ*/ppm 18.15 (CH_3), 29.44 (CH_3), 113.48, 113.70, 119.85, 120.10, 121.22, 122.25, 122.48, 124.29, 133.11, 133.34, 133.45, 136.83, 136.96, 139.13, 140.66, 157.33 (C=N), 170.41 (C-F), 188.26 (S-C=N), 189.04 (COCH_3). Anal. Calcd. for **$C_{21}H_{13}FN_4OS$** (388.42): C, 64.94; H, 3.37; N, 14.42; Found: C, 64.68; H, 3.44; N, 14.24 %.

3.1.4. Ethyl 2-((7-fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)amino)-4-methylthiazole-5-carboxylate (**6**)

Yield: 70 % as red crystals from EtOH; mp. 180–182 ^{O}C; IR: *ν*/cm^{-1} = 3076 (CH-Arom), 2925 (CH-Aliph), 1735 (C=O), 1605 (C=N); ^{1}H NMR *δ*/ppm = 1.21 (3H, t, CH_3CH_2O-), 2.38 (3H, s, CH_3), 4.13 (2H, q, CH_3CH_2O-), 7.72 (1H, t, *J*=8 Hz, H-Arom), 7.79 (1H, d, *J*=8.6 Hz, H-Arom), 7.88 (1H, s, H-Arom), 7.89 (1H, d, *J*=7.5 Hz, H-Arom), 7.95 (1H, t, *J*=8.0 Hz, H-Arom), 8.08 (1H, d, *J*=7.2 Hz, H-Arom), 8.25 (1H, dd, *J*=9.1, 6.3 Hz, H-Arom); ^{13}C NMR *δ*/ppm 14.07 (CH_3CH_2O-), 27.42 (CH_3), 61.12 (CH_3CH_2O-), 113.38, 113.63, 119.57, 122.52, 130.03, 132.67, 135.22, 139.49, 146.69, 155.28, 158.27 (Cs.Arom), 165.00 (C=N), 166.36 (C-F), 169.24 (CO.ester), 173.68 (S-C=N); Anal. Calcd. for **$C_{22}H_{15}FN_4O_2S$** (418.45): C, 63.15; H, 3.61; N, 13.39; Found: C, 63.27; H, 3.41; N, 13.12 %.

3.1.5. Synthesis of thiazolyl hydrazone derivatives (7-9)

7-fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-one (**3**) (0.01 mol) was dissolved in absolute ethanol (15 mL) and the appropriate hydrazine derivatives (0.01 mol) such as 2-hydrazineylthiazol-4(5*H*)-one, 1-(2-hydrazineyl-4-methylthiazol-5-yl)ethan-1-one, or ethyl 2-hydrazineyl-4-methylthiazole-5-carboxylate were added. The reaction mixture was heated under reflux for 1 h (monitored by TLC). Upon the reaction's completion, the solid formed was collected, filtered out, and recrystallized from the appropriate solvent.

3.1.6. 2-(2-(7-Fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)hydrazineyl)thiazol-4(5*H*)-one (**7**)

Yield: 78 % as light-yellow crystals from EtOH; mp. 171–173 ^{O}C; IR: *ν*/cm^{-1} = 3130 (NH), 3049 (CH-Arom), 2967 (CH-Aliph), 1709 (C=O), 16125 (C=N); ^{1}H NMR *δ*/ppm = 4.06 (2H, s, CH_2), 7.05 (1H, m, H-Arom), 7.68 (2H, m, H-Arom), 7.87 (1H, t, *J*=4.0 Hz, H-Arom), 7.90 (1H, s, H-Arom), 8.04 (1H, d, *J*=7.7 Hz, H-Arom), 8.22 (1H, dd, *J*=16.8, 8.2 Hz, H-Arom), 11.77 (1H, s, NH, disappeared by D_2O); ^{13}C NMR *δ*/ppm 33.03 (CH_2), 113.64, 120.03, 122.07, 122.44, 130.00,

132.27, 134.61, 136.58, 136.75, 138.93, 142.23, 145.59 (Cs.Arom), 158.70, 160.05 (C=N), 162.35 (C-F), 168.75 (S-C=N), 173.28 (C=O); Anal. Calcd. for **$C_{18}H_{10}FN_5OS$** (363.37): C, 59.50; H, 2.77; N, 19.27; Found: C, 59.65; H, 2.78; N, 19.03 %.

3.1.7. 1-(2-(2-(7-Fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)hydrazineyl)-4-methyl-thiazol-5-yl)ethan-1-one (8)

Yield: 67 % as light-orange crystals from EtOH; mp. 174–176 ^{O}C; IR: ν/cm^{-1} = 3427 (NH), 3076 (CH-Arom, 2980 (CH-Aliph), 1735 (C=O), 1605 (C=N); ^{1}H NMR δ/ppm = 1.94 (3H, s, CH_3), 2.29 (3H, s, CH_3), 7.72 (1H, t, *J*=6.0 Hz, H-Arom), 7.77 (1H, t, *J*=5.8 Hz, H-Arom), 7.87 (1H, s, H-Arom), 7.90 (1H, d, *J*=5.6 Hz, H-Arom), 7.94 (1H, d, *J*=8.0 Hz, H-Arom), 7.96 (1H, s, NH, disappeared by D_2O), 8.07 (1H, d, *J*=8 Hz, Ar-H), 8.23 (1H, dd, *J*=9.2, 6.0 Hz, Ar-H); ^{13}C NMR δ/ppm 16.18 (CH_3), 27.76 (CH_3), 114.21, 118.72, 120.10, 121.48, 122.37, 123.72, 124.21, 131.49, 132.08, 133.52, 135.18, 136.04, 137.21, 138.38, 141.00 (Cs.Arom), 155.36 (C=N), 171.49 (C-F), 188.30 (S-C=N), 190.27 (CH_3CO); Anal. Calcd. for **$C_{21}H_{14}FN_5OS$** (403.44): C, 62.52; H, 3.50; N, 17.36; Found: C, 62.43; H, 3.41; N, 17.75 %.

3.1.8. Ethyl 2-(2-(7-fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)hydrazineyl)-4-methyl-thiazole-5-carboxylate (**9**)

Yield: 69 % as deep-red crystals from EtOH; mp. 151–153 ^{O}C; IR: ν/cm^{-1} = 3425 (NH), 3073 (CH-arom), 2985 (CH-Aliph), 1714 (C=O), 1605 (C=N); ^{1}H NMR δ/ppm = 1.27 (3H, t, CH_3CH_2O-), 2.57 (3H, s, CH_3), 4.23 (2H, q, CH_3CH_2O-), 7.71 (1H, t, *J*=7.5 Hz, H-Arom), 7.76 (1H, t, *J*=5.6 Hz, H-Arom), 7.85 (1H, d, *J*=6.8 Hz, H-Arom), 7.88 (1H, s, H-Arom), 7.90 (1H, s, NH, disappeared by D_2O), 7.94 (1H, d, *J*=6.8 Hz, H-Arom), 8.07 (1H, d, *J*=7.4 Hz, H-Arom), 8.24 (1H, dd, *J*=9.2, 6.0 Hz, H-Arom); ^{13} NMR δ/ppm 19.23 (CH_3CH_2O-), 21.02 (CH_3), 61.94 (CH_3CH_2O-), 104.53, 113.45, 113.68, 114.69, 117.55, 119.83, 120.08, 122.46, 124.27, 133.09, 133.33, 133.43, 136.81, 136.95, 137.03, 139.13, 140.63, 148.26 (Cs.Arom), 149.52 (C=N), 157.31 (C-F), 161.95 (S-C=N), 164.62 (C=O); Anal. Calcd. for **$C_{22}H_{16}FN_5O_2S$** (433.46): C, 60.96; H, 3.72; N, 16.16; Found: C, 60.57; H, 3.55; N, 16.63 %.

3.1.9. Synthesis of 5-(7-Fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)-2-hydrazineyl-thiazol-4(5*H*)-one (10)

To a solution of compound **3** (0.01 mol) and 2-hydrazineylthiazol-4(5*H*)-one (0.01 mol) in acetic acid (15 mL) as solvent containing sodium acetate (0.3 g) as a catalyst. The reaction mixture was heated under reflux for 4 h (monitored by TLC). Upon the reaction's completion, left to cool and poured onto ice-cold water, then neutralized with a few drops of 1 M HCl. The solid that formed was collected by filtration, washed with water, and recrystallized from the appropriate solvent.

Yield: 82 % as a pale-white powder from EtOH; mp. 100–102 ^{O}C; IR: ν/cm^{-1} = 3415 (NH_2), 3190 (NH), 3076 (CH-Arom), 1711 (C=O), 1624 (C=N), 1570 (C=C); ^{1}H NMR δ/ppm = 5.43 (2H, s, NH_2, disappeared by D_2O), 7.73 (1H, t, *J*=7.8 Hz, H-Arom), 7.78 (1H, t, *J*=8.0 Hz, H-Arom), 7.84 (1H, d, *J*=7.3 Hz, H-Arom), 7.87(1H, s, H-Arom), 7.89 (1H, s, NH, disappeared by D_2O), 7.92 (1H, d, *J*=7.9 Hz, H-Arom), 8.05 (1H, d, *J*=7.4 Hz, H-Arom), 8.13 (1H, dd, *J*=9.2, 6.0 Hz, H-Arom); C ^{13} NMR δ/ppm 112.70, 112.93, 113.38, 121.76, 122.40, 124.19, 130.10, 131.02, 133.03, 134.36, 135.51, 136.64, 153.36, 154.83 (Cs.Arom), 157.13 (C=N), 158.91 (S-C=N), 161.58 (C-F), 172.16 (C=O); Anal. Calcd. for **$C_{18}H_{10}FN_5OS$** (363.37): C, 59.50; H, 2.77; N, 19.27; Found: C, 59.46; H, 2.56; N, 19.46 %.

3.1.10. Synthesis of 5-(7-fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)-2-(2-((substituted)-hydrazineyl)thiazol-4(5*H*)-one (12 &13)

To a solution of compound **3** (0.01 mol) and the corresponding reagent **11a** or **11b** (0.01 mol) in acetic acid (15 mL) as solvent containing sodium acetate (0.3 g) as a catalyst. The reaction mixture was heated under reflux for 4 h (monitored by TLC). Upon the reaction's completion, left to cool and poured onto ice-cold water, then neutralized with a few drops of 1 M HCl. The solid that formed was collected by filtration, washed with water, and recrystallized from the appropriate solvent.

3.1.11. 5-(7-Fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)-2-(2-((1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)methylene)hydrazineyl)thiazol-4(5*H*)-one (12)

Yield: 64 % as a pale-brown powder from AcOH; mp. 270–272 ^{O}C; IR: ν/cm^{-1} = 3422 (NH), 3052 (CH-Arom), 2924 (CH-Aliph), 1729 (C=O), 1630 (C=N), 1570 (C=C); ^{1}H NMR δ/ppm = 2.37 (3H, s, CH_3.tolyl), 7.29 (2H, d, *J*=6.5 Hz, H-Arom), 7.35 (1H, t, *J*=8.0 Hz, H-Arom), 7.41 (1H, d, *J*=8.0 Hz, H-Arom), 7.51 (2H, d, *J*=8.2 Hz, H-Arom), 7.56 (2H, d, *J*=8.2 Hz, H-Arom), 7.63 (1H, t, *J*=7.4 Hz, H-Arom), 7.68 (1H, s, methine-CH), 7.70 (1H, s, H-Arom), 7.80 (1H, d, *J*=8.0 Hz, H-Arom), 7.85 (1H, d, *J*=9.0 Hz, H-Arom), 7.89 (1H, s, H-Arom), 7.95 (2H, t, *J*=7.4 Hz, H-Arom), 8.01 (1H, t, *J*=7.1 Hz, H-Arom), 8.19 (1H, dd, *J*=8.7, 6.5 Hz, H-Arom), 8.90 (1H, s, NH, disappeared by D_2O); ^{13}C NMR δ/ppm 21.05 (CH_3.tolyl), 113.51, 116.71, 118.95, 119.36, 122.58, 124.38, 127.21, 127.86, 128.62, 129.22, 129.79, 132.68, 133.23, 134.95, 136.79, 137.10, 138.20, 138.71, 139.03, 140.64, 149.45, 151.73 (Cs.Arom), 152.83 (C=N), 157.32(C=C), 164.99 (S-C=N), 172.31 (C-F), 174.44 (C=O); Anal. Calcd. for **$C_{35}H_{22}FN_7OS$** (607.67): C, 69.18; H, 3.65; N, 16.14; Found: C, 69.21; H, 3.45; N, 16.12 %.

3.1.12. 5-(7-Fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)-2-(2-(2-oxoindolin-3-ylidene)-hydrazineyl)thiazol-4(5*H*)-one (13)

Yield: 65 % as a light-red powder from AcOH; mp. 283–285 ^{O}C; IR: ν/cm^{-1} = 3178 (br. 2NH), 3075 (CH-Arom), 1695 (br. 2C=O), 1615 (C=N), 1569 (C=C); ^{1}H NMR δ/ppm = 6.84 (1H, t, *J*=6.0 Hz, H-Arom), 6.99 (1H, d, *J*=7.4 Hz, H-Arom), 7.03 (1H, d, *J*=7.6 Hz, H-Arom), 7.29 (1H, t, *J*=8.0 Hz, H-Arom), 7.36 (1H, d, *J*=7.7 Hz, H-Arom), 7.69 (1H, t, *J*=7.4 Hz, H-Arom), 7.75 (1H, t, *J*=6.0 Hz, H-Arom), 7.88 (1H, s, H-Arom), 7.91 (1H, d, *J*=9.5 Hz, H-Arom), 8.04 (1H, d,

J=6.5 Hz, H-Arom), 8.21 (1H, dd, *J*=11.9, 5.7 Hz, H-Arom), 10.67 (1H, s, NH, disappeared by D_2O), 11.05 (1H, s, NH, disappeared by D_2O); ^{13}C NMR *δ*/ppm 110.29, 113.42, 117.34, 119.78, 120.56, 121.61, 122.42, 124.21, 127.94, 128.19, 131.25, 132.35, 132.74, 133.03, 136.89, 138.35, 139.10, 140.58, 142.92, 143.94 (Cs.Arom), 157.24 (C=N), 164.97 (S-C=N), 168.86 (C-F), 171.92, 171.97 (2C=O); Anal. Calcd. for **$C_{26}H_{13}FN_6O_2S$** (492.49): C, 63.41; H, 2.66; N, 17.06; Found: C, 63.55; H, 2.41; N, 17.01%.

3.1.13. Synthesis of 2-(7-fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)hydrazine-1-carbo-thioamide (14)

To a solution of the starting material (**3**) (0.01 mol) in ethanolic solution (15 mL) containing a few drops of acetic acid, thiosemicarbazide (0.01 mol) was added. The reaction mixture was heated under reflux for 1.5 h (monitored by TLC). Upon the reaction's completion, the solid that formed was left to cool and collected by filtration, washed with cold ethanol, and recrystallized from the appropriate solvent.

Yield: 77 % as a light-green crystal from AcOH; mp. 210–212 ^{O}C; IR: *v*/cm^{-1} = 3448, 3396 (NH_2), 3275 (NH), 3158 (CH-Arom), 2950 (CH-Aliph), 1610 (C=N); ^1H NMR *δ*/ppm = 7.64 (d, *J*=7.3 Hz, 1H, H-Arom), 7.67 (t, *J*=7.4 Hz, 1H, H-Arom), 7.77 (t, *J*=8.6 Hz, 1H, H-Arom), 7.96 (d, *J*=9.2 Hz, 1H, H-Arom), 8.06 (d, *J*=6.4 Hz, 1H, H-Arom), 8.15 (s, 2H, NH_2 exchangeable by D_2O), 8.79 (d, *J*=7.5 Hz, 1H, H-Arom), 9.05 (s, 1H, H-Arom), 12.48 (s, 1H, NH exchangeable by D_2O); ^{13}C NMR *δ*/ppm 113.94, 114.17, 115.77, 120.19, 122.94, 124.75, 129.88, 132.97, 133.58, 137.43, 141.11, 142.88, 144.48 (Cs-Arom), 154.76 (C=N-NH), 161.93 (C-F), 182.02 (C=S).; Anal. Calcd. for **$C_{16}H_{10}FN_5S$** (323.35): C, 59.43; H, 3.12; N, 21.66; Found: C, 59,52; H, 3.22; N, 21.21%.

3.1.14. The reaction of thiosemicarbazone derivatives (14) with a different alkylating agent (15-17)

A solution of compound **14** (0.01 mol), an appropriate alkylating agent (0.01 mol) namely, ethyl 2-chloropropanoate, ethyl 2-chlorobutanoate, and diethyl but-2-ynedioate in ethanol / acetic acid mixture (15 / 5 mL) containing sodium acetate (0.2 gm) were added. The reaction mixture was heated under reflux for 3-5 h (monitored by TLC). Upon the reaction's completion, left to cool and poured onto ice-cold water, then neutralized with a few drops of 1 M HCl. The solid that formed was collected by filtration, washed with water, and recrystallized from the appropriate solvent.

3.1.15. 2-(2-(7-Fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)hydrazineyl)-5-methyl-thi-azol-4(5*H*)-one (15)

Yield: 66 % as a light-yellow crystal from AcOH; mp. 265–267 ^{O}C; IR: *v*/cm^{-1} = 3060 (CH-Arom), 2928 (CH-Aliph), 1722 (C=O), 1631 (C=N); ^1H NMR *δ*/ppm = 1.45 (3H, d, CH_3.thiazole), 3.81 (1H, q, CH. thiazole), 7.54 (1H, t, *J*=7.4 Hz, H-Arom), 7.64 (1H, d, *J*=7.3 Hz, H-Arom), 7.93 (1H, s, H-Arom), 7.99 (1H, d, *J*=9.6 Hz, H-Arom), 8.08 (1H, d, *J*=7.4 Hz, H-Arom), 8.17 (1H, t, *J*=8.2 Hz, H-Arom), 8.26 (1H, dd, *J*=9.1, 5.9 Hz, H-Arom), 8.84 (1H, s, 1NH disappeared by

D_2O); ^{13}C NMR δ/ppm 19.85 (CH_3.thiazole), 57.87 (CH.thiazole), 113.39, 113.61, 119.71, 119.96, 120.51, 120.75, 121.87, 122.04, 122.40, 131.14, 131.89, 132.49, 135.02, 135.99, 136.91, 138.29 (Cs.Arom), 154.29 (C-F), 178.79 (C=O); Anal. Calcd. for **$C_{19}H_{12}FN_5OS$** (377.40): C, 60.47; H, 3.21; N, 18.56; Found: C, 60.46; H, 3.56; N, 18.34%.

3.1.16. 5-Ethyl-2-(2-(7-fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)hydrazineyl)thiazol-4(5*H*)-one (**16**)

Yield: 69 % as a yellow crystal from AcOH; mp. 255–257 ^{O}C; IR: ν/cm^{-1} = 3239 (NH), 3054 (CH-arom), 2965 (CH-aliph), 1720 (C=O), 1631 (C=N); ^1H NMR δ/ppm = 0.99 (3H, t, $\underline{CH_3}CH_2$), 2.02 (2H, p, $CH_3\underline{CH_2}$), 4.33 (1H, t, CH.thiazole), 7.66 (1H, t, *J*=5.6 Hz, H-Arom), 7.69 (1H, d, *J*=5.0 Hz, H-Arom), 7.73 (1H, t, *J*=8.0 Hz, H-Arom), 7.89 (1H, s, H-Arom), 7.94 (1H, d, *J*=4.7 Hz, H-Arom), 8.05 (1H, d, *J*=3.9 Hz, H-Arom), 8.12 (1H, dd, *J*=9.2, 5.9 Hz, H-Arom), 12.64 (1H, s, NH disappeared by D_2O); ^{13}C NMR δ/ppm 10.42 (CH_3), 25.44 (CH_2), 49.88 (CH.thiazole), 112.97, 113.18, 119.30, 119.55, 121.98, 122.19, 129.90, 131.85, 132.45, 135.30, 138.66, 139.25, 141.83, 146.34 (Cs-Arom), 154.80 (C=N), 161.63 (C-F), 164.12 (C=O); Anal. Calcd. for **$C_{20}H_{14}FN_5OS$** (391.42): C, 61.37; H, 3.61; N, 17.89; Found: C, 61.65; H, 3.21; N, 17.15%.

3.1.17. Ethyl -2-(2-(2-(7-fluoro-11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)hydrazineyl)-4-oxo-thiazol-5(4*H*)-ylidene)acetate (**17**)

Yield: 79 % as deep-orange crystal from AcOH; mp. 199–197 ^{O}C; IR: ν/cm^{-1} = 3263 (NH), 3054 (CH-Arom), 2987 (CH-Aliph), 1727, 1700 (2C=O), 1638 (C=N); ^1H NMR δ/ppm = 1.27 (3H, t, $\underline{CH_3}CH_2O$-), 4.24 (2H, q, $CH_3\underline{CH_2}O$-), 6.64 (1H, s, vinilic-$\underline{CH}$), 7.65 (1H, d, *J*=7.5 Hz, H-Arom), 7.68 (1H, t, *J*=9.2 Hz, H-Arom), 7.73 (1H, t, *J*=8.0 Hz, H-Arom), 7.90 (1H, d, *J*=6.8 Hz, H-Arom), 7.96 (1H, s, H-arom), 7.98 (1H, s, NH disappeared by D_2O), 8.15 (1H, dd, *J*=9.2, 5.9 Hz, H-arom); ^{13}C NMR δ/ppm 14.57 ($\underline{CH_3}CH_2O$-), 61.55 ($CH_3\underline{CH_2}O$-), 96.97 (vinylic-$\underline{CH}$), 113.65, 119.69, 120.76, 122.53, 130.04, 132.77, 134.65, 135.23, 136.79, 138.30, 139.50, 143.07, 146.70, 155.28 (Cs-Arom), 158.28 (C=N), 161.62 (S-$\underline{C}$=N), 165.01 (C-F), 166.24, 166.38 (2C=O); Anal. Calcd. for **$C_{22}H_{14}FN_5O_3S$** (447.44): C, 59.06; H, 3.15; N, 15.65; Found: C, 59.24; H, 3.03; N, 15.55%.

3.2. Biology

3.2.1. Animals and experimental design:

96 Male Swiss albino mice weighing 25 – 30 g were purchased from the National Scientific Research Center (Giza, Egypt). Mice were maintained at 20–25 °C in a 12 h light/dark cycle, with a commercial normal rodent diet and water freely available. They were divided into 16 groups, 6 mice each. First, the normal control group (received citrate buffer, ip for 2 weeks). Second; the diabetic control group (STZ-induced diabetic mice & received normal saline, ip, for 2 weeks).

3rd: diabetic mice treated with gliclazide as a reference standard for 2 weeks. Other diabetic mice (groups 4-16) received new synthesized compounds; dissolved in tween 80 (25 mg/kg, oral, for 2 weeks).

3.2.2. Diabetes induction:

Mice (groups 2-16) were fasted overnight for 12 hours, then intraperitoneally injected with 50 mg/kg streptozotocin (STZ) which was freshly dissolved in citrate buffer solution {pH 4.5}, 15 minutes after IP injection of nicotinamide (NA) 110 mg/kg. NA is used to partially protect against the damaging effects of STZ on β cells. This model is used to develop a model of type II DM. After 3 days blood glucose was checked by one-touch Glucometer (using blood from the tail). Mice with bllod glucose level ≥ 250 mg/dL were selected for diabetic groups [34]. At the end mice were fasted overnight, then blood samples were collected on EDTA tubes. Plasma was isolated by centrifugation at 10,000 rpm/min, for 10 min.

3.2.3. Chemicals

STZ, NA, and ELISA kits were purchased from Sigma Aldrich Co (St Louis, MO, USA). Spectrophotometric kits were purchased from Biodiagnostic Co, Egypt.

3.2.4. Biochemical analysis

3.2.4.1. Measurements of blood glucose and plasma insulin levels

Fasting blood glucose was assessed spectrophotometrically using blood from the lateral tail vein on the last day of the experiment; by a commercial kit [35]. Glucose oxidase catalyzes the oxidation of glucose to hydrogen peroxide and gluconic acid. Then hydrogen peroxide liberated reacts with 4-amino antipyrine (4-AAP) and a phenol derivative producing red colored compound. The color intensity is directly proportional to glucose concentration in the sample.

The provided reagents: 1-R_1 solution: standard glucose solution. 2-R_2 solution: phosphate buffer, glucose oxidase, peroxidase, 4-AAP and phenol.
Procedure: R_2 solution **(**1 ml) was added to sample or standard (R1) (10 µl) and incubated 10 minutes at 37ºC for. Then the absorbance of samples and standard were measured colorimetry at 546 nm.

Plasma insulin for the most efficient compounds in lowering blood glucose level (**4**,**6**,**8**,**16**) was assessed using the ELISA technique. Standards and samples (5 µl) were put in the wells, and incubated with monoclonal antibody conjugated to horseradish peroxidase enzyme (100 µl). Then plate was sealed, incubated for 90 minutes with shaking at 600 rpm at room temperature. After wash, TMB substrate (3,3',5,5'-Tetramethylbenzidine) (100 µl) was added and incubated at room

temperature for 15 minutes. Then color developed in proportion to the amount of insulin bound initially. The reaction was stopped by adding Stop solution (100 µl). Absorbance of was measured at 450 nm.

3.2.4.2. Measurements of kidney functions

Plasma urea was determined according to Orsonneau et al. (1992) [36] using a commercial reagent kit. The assay depends on the fact that, urea in the plasma is hydrolyzed by urease into ammonium and carbon dioxide. The ammonia liberated reacts with salicylate and sodium hypochlorite forming indophenol; a green colored compound. **The Provided reagents:** 1-R_1: standard solution. 2-R_2: urease. 3-R_3: phosphate buffer, EDTA, sodium salicylate and sodium nitroprusside (catalyst). 4-R_4: sodium hypochlorite and sodium hydroxide. **Procedure:** One drop of R_2 solution was added to 1 ml of R_3 solution followed by the addition of 10 µl of sample or standard solution (R_1). The contents of tubes were mixed and incubated for 3 minutes at 37ºC, and then 200 µl of R_4 solution were added, mixed and incubated for 5 minutes at 37ºC. The absorbance was measured colorimetry at 578 nm.

Plasma creatinine was measured using a colorimetric kit according to Saibaba et al. (1997) [37]. Creatinine in the sample is reacted with sodium picrate in alkaline medium forming a red complex. **Provided reagents in the kit:** 1-R_1: standard solution. 2-R_2: picric acid. R_3 (alkaline reagent): sodium hydroxide.

Equal volumes of R_2 and R_3 are mixed to prepare working reagent. **Procedure:**1 ml of R_2 was added to 100 µl of sample or standard. The absorbance of the regent blank, samples or standard was measured at 492 nm after 30 and 120 seconds and the change in absorbance was calculated.

3.2.4.3. Measurements of oxidative stress biomarkers

Plasma GSH content was assessed colorimetry according to Beutler et al. [38]. Where 0.5 ml of sample and 1 ml of buffer were added followed by 100 µl of Ellman's reagent [5,5`-dithio-bis (2-nitrobenzoic acid)]. The absorbance of the formed yellow color was measured within 5 minutes at 405 nm.

Plasma MDA was assessed colorimetry. 1 ml of chromogen solution provided from a commercial kit was added to 200 µl of sample or standard MDA solution. Tubes were mixed; covered; heated in a boiling water bath for 30 minutes; then cooled. The absorbance of samples was measured at 534 nm[39].

3.2.4.4. Liver functions markers & cholesterol

Plasma AST & ALT were measured colorimetry at 510 nm according to Piyachaturawat *et al*., 1988 [40] using a commercial kits. Cholesterol was measured colorimetry using a commercial kit according to Cox and García-Palmieri, 1990 [41]. Where procaine hydrochloride reacted with sodium nitrite in acid medium to form diazonium salt; which is coupled with cholesterol in alkaline medium to form soluble colored product. Absorption was measured at 428nm.

3.2.5. Statistical analysis

The data were expressed as means ± S.E. Results were calculated by one-way ANOVA, followed by Tuckey's test as a post hoc test. $P < 0.05$ was considered significant. All the analyses were carried out by using SPSS software (version 22.0) for Windows 8.1 (SPSS, Inc., Chicago, IL, USA).

3.2.6. *In vitro* assay of *α*-glucosidase inhibitory activity

The assay was carried out following the *α*-Glucosidase Inhibitor Screening Colorimetric Kit protocol supplied by BioVision Company, USA

3.2.6.1. Assay Protocol

1. Screening Compounds, Inhibitor Control & Background Control preparations: Samples [S] and **Inhibitor Control [IC]:**

Dissolve test samples to 100X in a proper solvent. Further, dilute to 10X using *α*-Glucosidase Assay Buffer. Add 10 µL of Diluted test compound, 10 µL of acarbose into wells of 96-well clear plate designated as test samples [S] or Inhibitor Control [IC], respectively.

Enzyme Control [EC] and **Background Control [BC]:**

Add 10 and 20 µL of *α*-Glucosidase Assay Buffer into the designated well(s) of 96-well clear plate, respectively.

IC_{50} estimation (Optional): Prepare several dilutions of candidate(s) in *α*-Glucosidase Assay Buffer. Add 10 µL of each dilution into designated wells.

2. *α*-Glucosidase Enzyme Solution Preparation:

Prepare a 20-fold dilution of *α*-glucosidase (i.e. Dilute 2 µL of *α*-glucosidase with 38 µL of *α*-Glucosidase Assay Buffer), mix thoroughly, and keep on ice. Add 10 µL of Diluted *α*-Glucosidase Enzyme Solution to each well-containing Test Sample(s) [S], Inhibitor Control [IC], Enzyme Control [EC], and Solvent Control [SC]. Adjust the volume of each well to 80 µL/well with *α*-Glucosidase Assay Buffer. Mix well and incubate at room temperature for 15-20 min. Protect from light.

3. Reaction Mix Preparation: Mix enough reagents for the number of assays to be performed. For each well, prepare 20 µL Reaction Mix containing:

Reaction Mix

***α*-Glucosidase Assay Buffer** 17 µL

***α*-Glucosidase Substrate Mix** 3 µL

Mix & add 20 µL Reaction Mix to test sample(s) [S], Inhibitor Control [IC], Enzyme Control [EC], Solvent Control [SC] and Background.

Control [BC] wells and mix well.

4. Measurement: Measure absorbance immediately at OD: 410 nm in kinetic mode for 60 min at room temperature. Choose two-time points (t1 & t2) in the linear range of the plot and obtain the corresponding values for the absorbance (OD1 and OD2).

5. Calculation: Calculate the slope for all test samples [S], Enzyme Control [EC], Solvent Control [SC], and Background Control [BC] by dividing the net ΔOD (A2-A1) values with the time Δt (t2-t1). Subtract the Slope of Background Control from [S], [EC] and [SC]. If [SC] slope is significantly different when compared to [EC], use [SC] values to determine the effect of the tested compound.

% Relative Inhibition = {(**Slope of** [**EC**] −**Slope of** [**S**]) / **Slope of**[**EC**]} X 100

% Relative Activity = {**Slope of** [**S**] / **Slope of** [**EC**]} X 100

3.2.7. *In vitro* assay of *α*-amylase inhibitory activity

The assay was carried out following the *α*-Amylase Inhibitor Colorimetric Kit protocol supplied by BioVision Company, USA

The literature description [42] was used to calculate the proportion of enzyme inhibition caused by the synthesized compounds. Typically, a 0.01 M buffer with a pH of 6.9 was used to create a starch solution (Sigma Aldrich, 1% w/v). Then, in separate test tubes, mixes of enzyme and sample were pre-incubated at 37 °C by adding aliquots (300 L) of the solution. Another 30 minutes were spent incubating these combinations. After adding 300 L of a 2 M solution of dinitro salicylic acid substrate (DNSA), the reaction was stopped by immediately submerging each test tube in a pot of boiling water. After reaching room temperature, the test tubes were diluted with 1 mL of distilled water. To adjust the absorbance of colored test samples, a blank was created for each concentration by incubating samples without the enzyme solution. As a control, a test tube with 300 L of dimethyl sulfoxide (DMSO) was utilized. Each final solution's absorbency was measured at 540 nm using a UV-vis spectrophotometer. The IC_{50} values were calculated from the gathered data using Microsoft Excel Professional Plus 2019 software. The following formula was used to compute the percentage inhibition of ***α***-amylase: $((A_{control} - A_{sample})/ A_{control})X\ 100$.

3.2.8. *In Silico* Studies

3.2.8.1. *In silico* Pharmacokinetic Studies:

In the current study, the Swiss ADMET website (http://www.sib.swiss) interface was used to screen all the synthesized compounds as well as the standard reference medicines [43]. Drug-likeliness and *in silico* ADME features were predicted. ChemDraw 19.0 was used to transform the molecular structures into the SMILES database. Then, to calculate the physicochemical descriptors, lipophilicity, pharmacokinetics qualities, ADME parameters, and medicinal chemistry friendliness, these SMILES were entered as input into the SwissADME website [44-48].

3.2.8.2. Docking studies

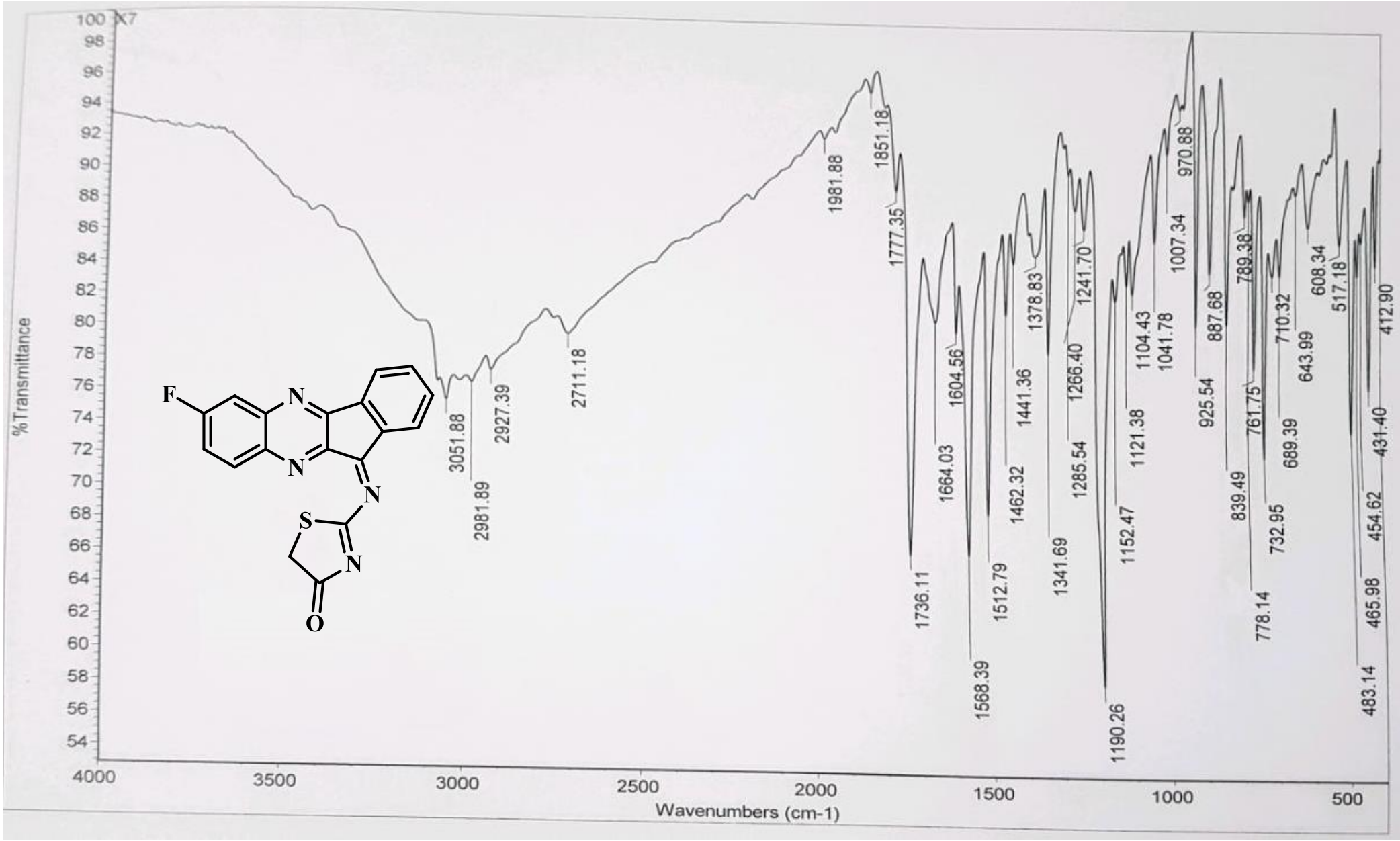
For this docking study, the 3D crystal structures of α-amylase and α-glucosidase in association with acarbose (PDB ID: 1B2Y, resolution: 3.2 and PDB ID: 5NN8, resolution: 2.45) [49] were retrieved in.pdb format from the RCSB PDB (https://www.rscb.org). The protein crystal structures were all imported into the Molecular Operating Environment (MOE 2014.09) (Montreal, QC, Canada) [50]. At MMFF94x, the forcefield was configured. We eliminated far-off water molecules, fixed structural issues, added missing hydrogen atoms, and calculated partial charges. Using the default RMS gradient (0.1 kcal/mol/A), energy reduction was carried out. One defined the binding pocket [49]. ChemDraw Ultra 19.0 was used to sketch newly synthesized compounds, which were subsequently stored in .mol file format and entered a database. By fixing structural issues and inserting missing hydrogens, the database was prepared. Charges in part were computed. Following the selection of the proper tautomeric states for each molecule, energy reduction was performed [51-55]. Triangle Matcher was used as a placement method and London dG as a scoring mechanism for docking. The Rigid Receptor technique was used for refinement.

List of Abbreviations

ABS	Absorption
AGIs	α-glucosidase inhibitors
AST	Aspartate Aminotransferase
ALT	Alanine Transaminase
CNS	Central nervous system
DM	Diabetes mellitus
GC/ MS	Gas Chromatograph-Mass Spectrometry
GSH	Glutathione
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
IC_{50}	The half-maximal inhibitory concentration
IR	Infrared

MR	Molar refractivity
MDA	Malondialdehyde
NC	Normal control
PC	Positive control
P-gp	P-glycoprotein
PDB	Protein data bank
PPM	Part per million
RMSD	Root Mean Square Deviation
SAR	Structure-activity relationship
STZ	Streptozotocin
TLC	Thin layer chromatography
TMS	Tetramethyl silane
TPSA	Topological polar surface area

4: IR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1604.56
1568.39
1512.79
1462.32
1441.36
1378.83
1341.69
1285.54
1266.40
1241.70
1190.26
1152.47
1121.38
1104.43
1041.78
1007.34
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925.54
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839.49
789.38
778.14
761.75
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689.39
643.99
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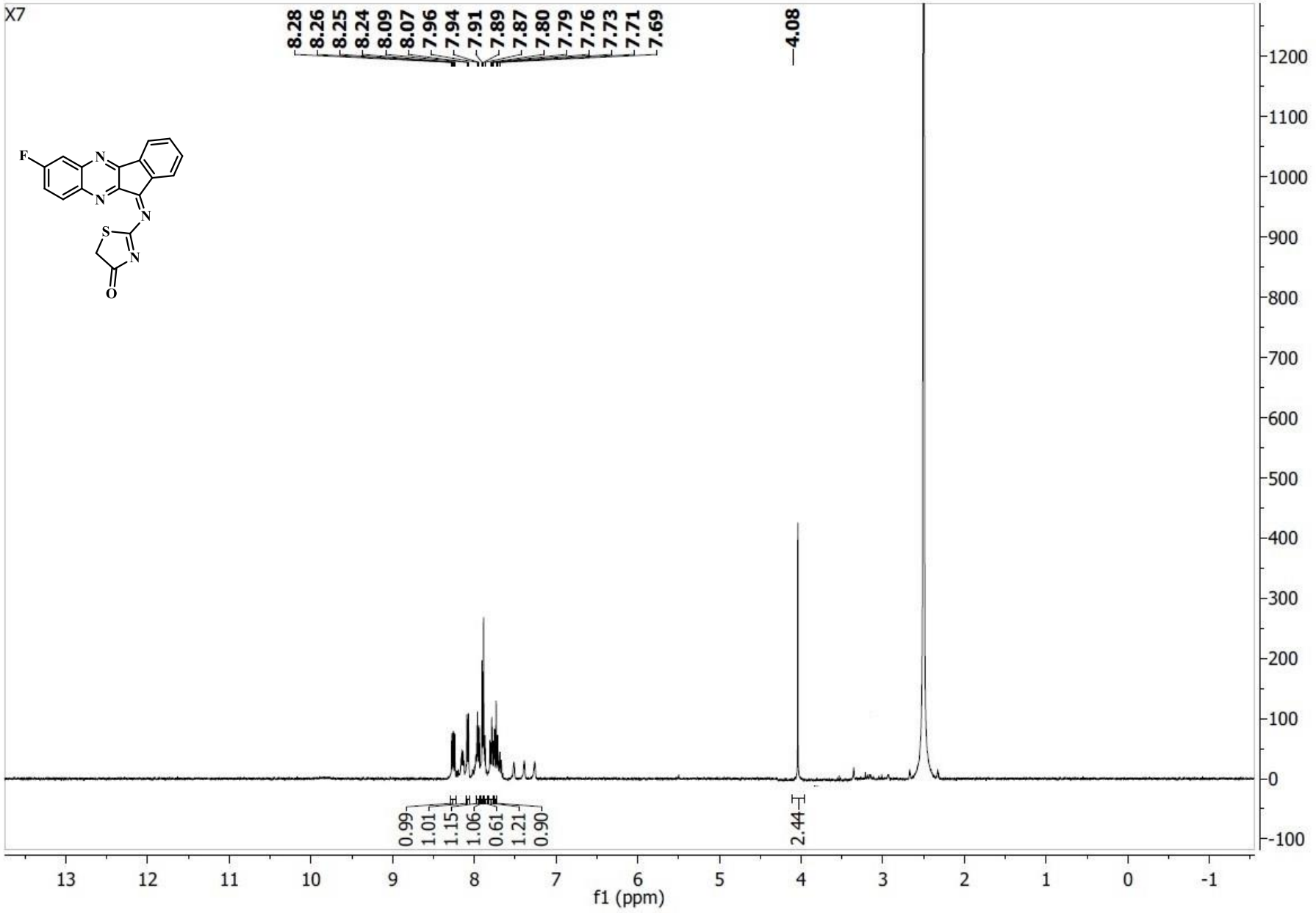
N
N
S
N
O

4: ^{1}H NMR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8.24
8.09
8.07
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7.80
7.79
7.76
7.73
7.71
7.69
4.08
F
N
N
N
S
N
O
0.99
1.01
1.15
1.06
0.61
1.21
0.90
2.44
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
13
12
11
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9
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5
4
3
2
1
0
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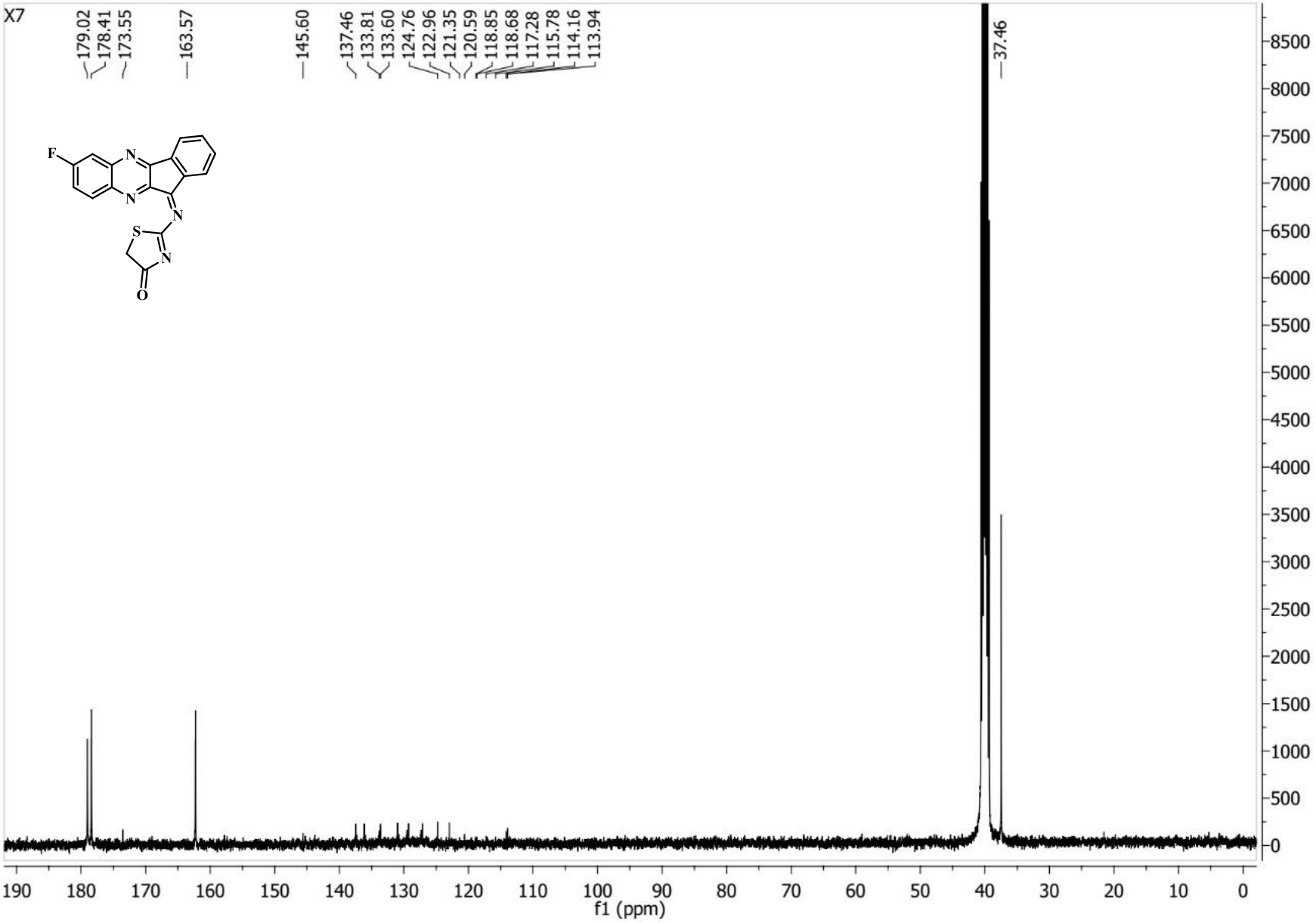
f1 (ppm)

4: ^{13}C NMR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118.85
118.68
117.28
115.78
114.16
113.94
37.46
F
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N
N
S
N
O
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8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
190
180
170
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150
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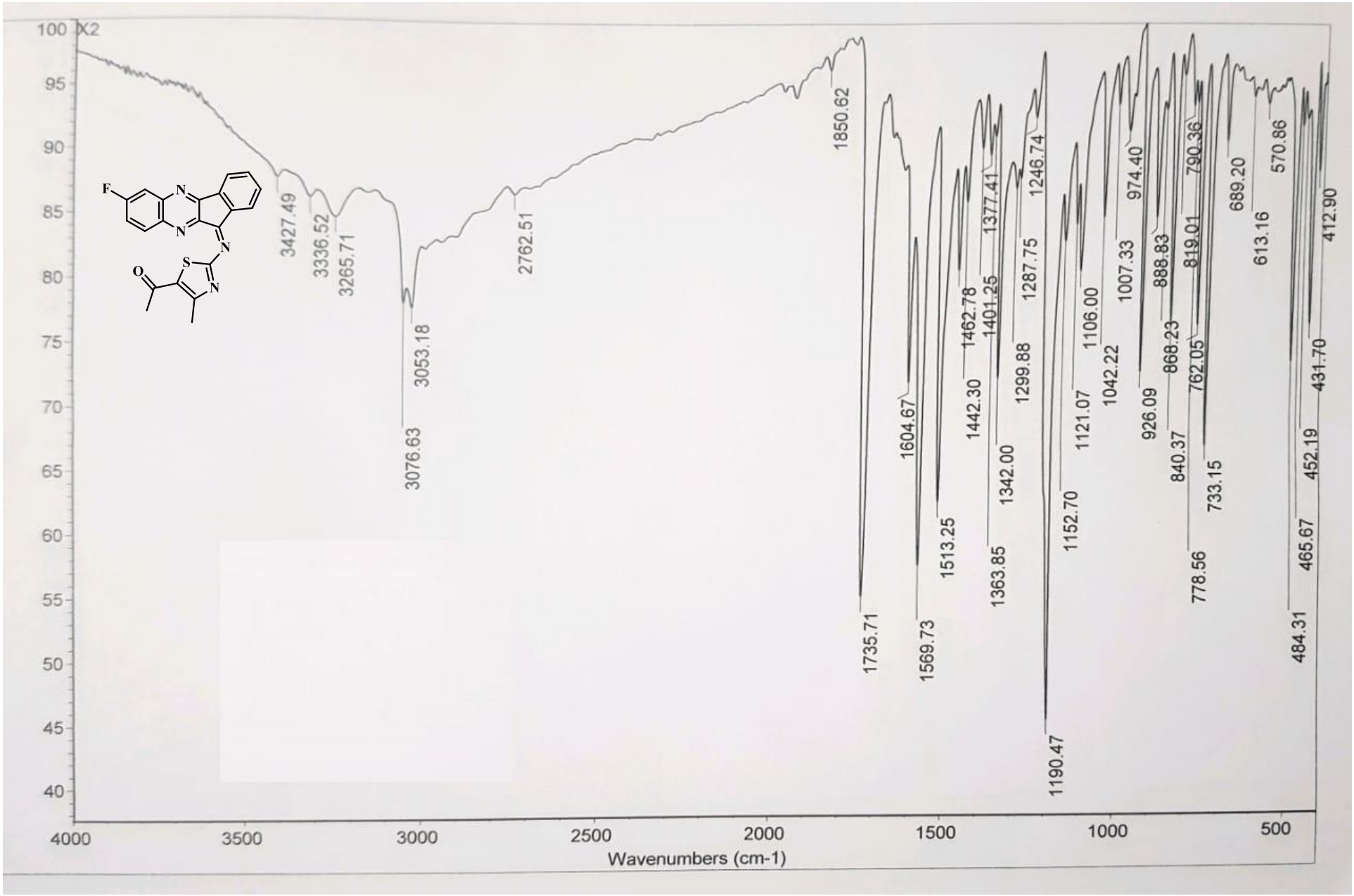
30
20
10
0
f1 (ppm)

5: IR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1513.25
1462.78
1442.30
1401.25
1377.41
1363.85
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1299.88
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1121.07
1106.00
1042.22
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974.40
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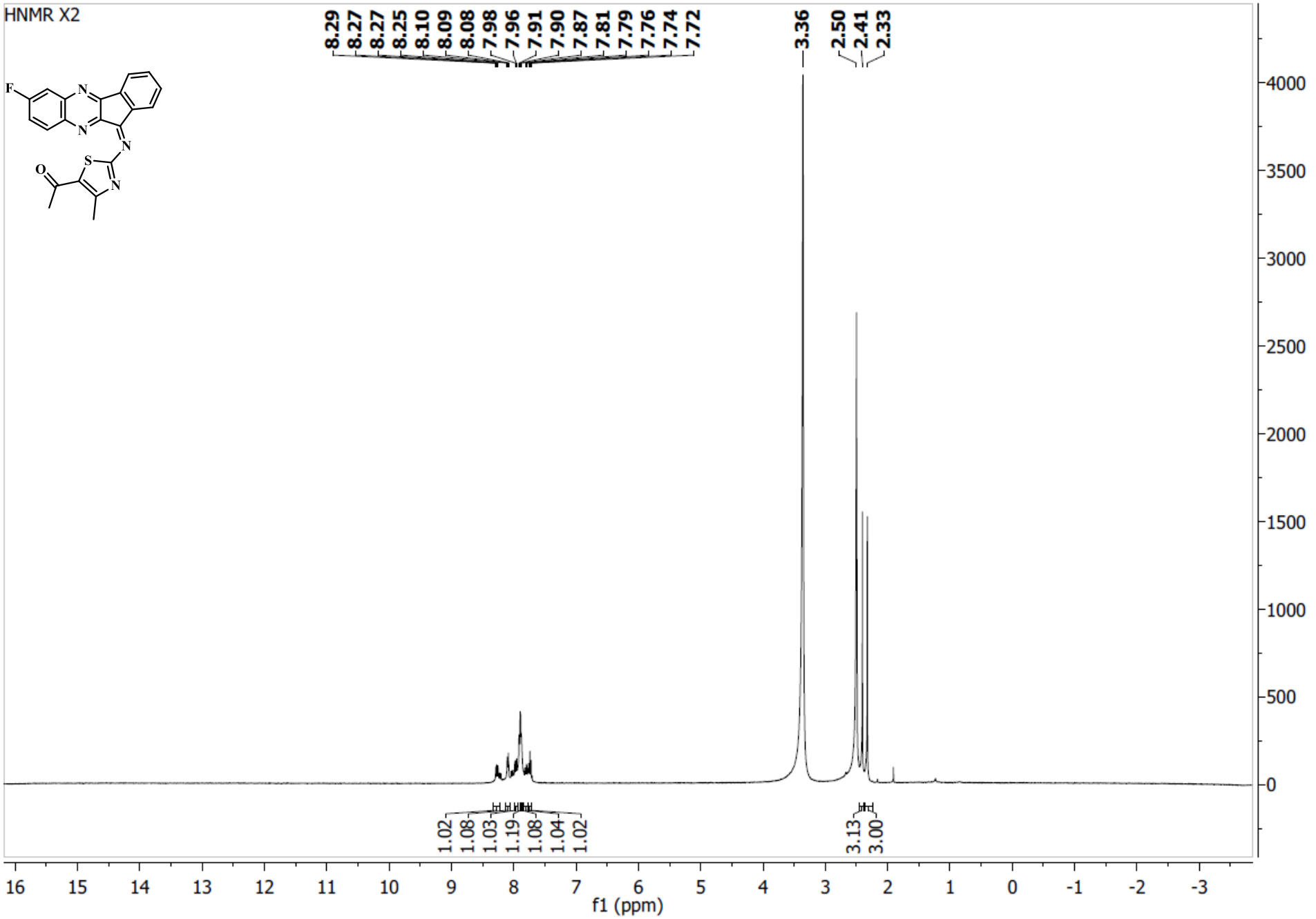
5: ^{1}H NMR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8.08
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N
N
N
S
N
O
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3500
3000
2500
2000
1500
1000
500
0
1.02
1.08
1.03
1.19
1.08
1.04
1.02
3.13
3.00
16
15
14
13
12
11
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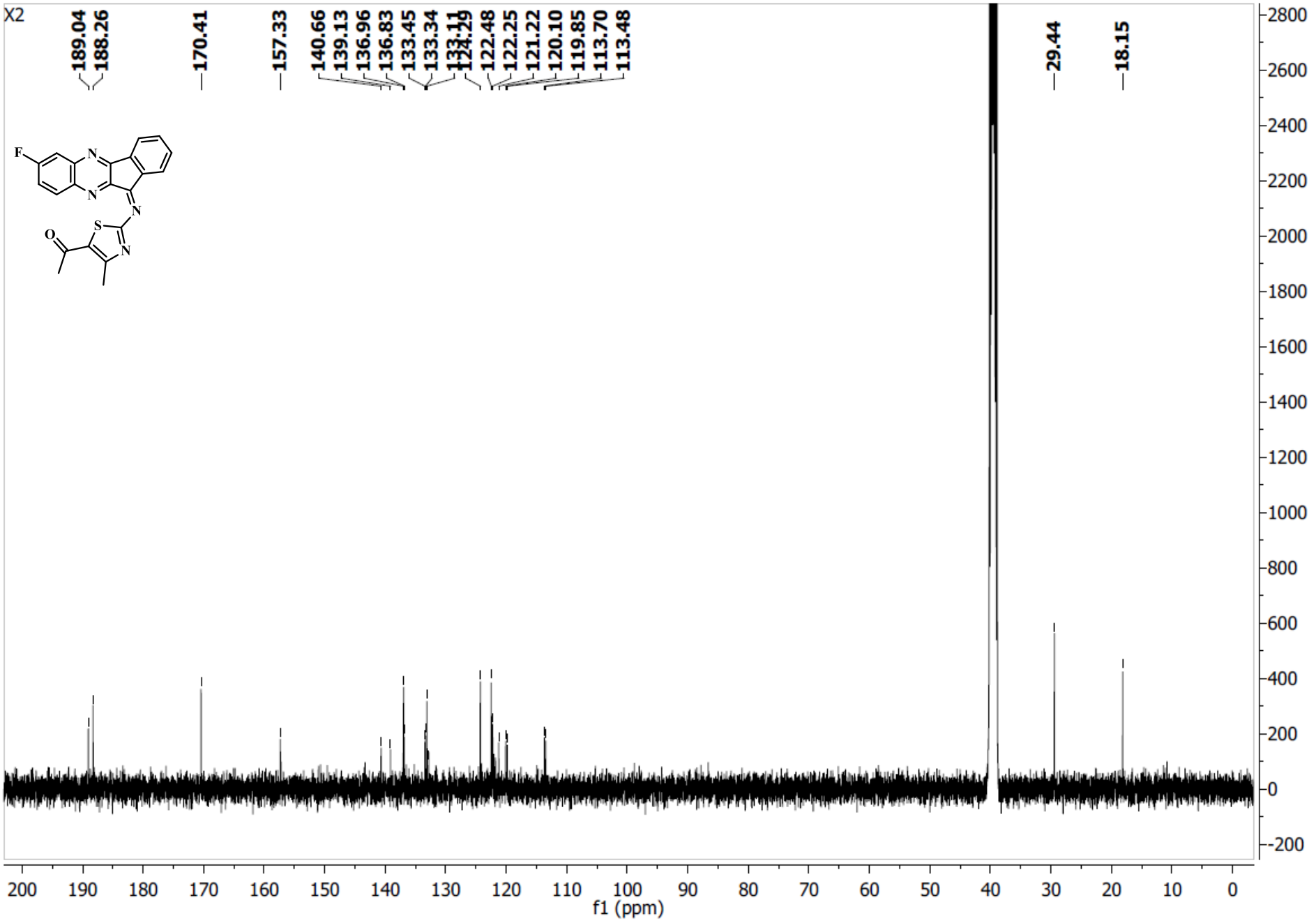
f1 (ppm)

5: ^{13}C NMR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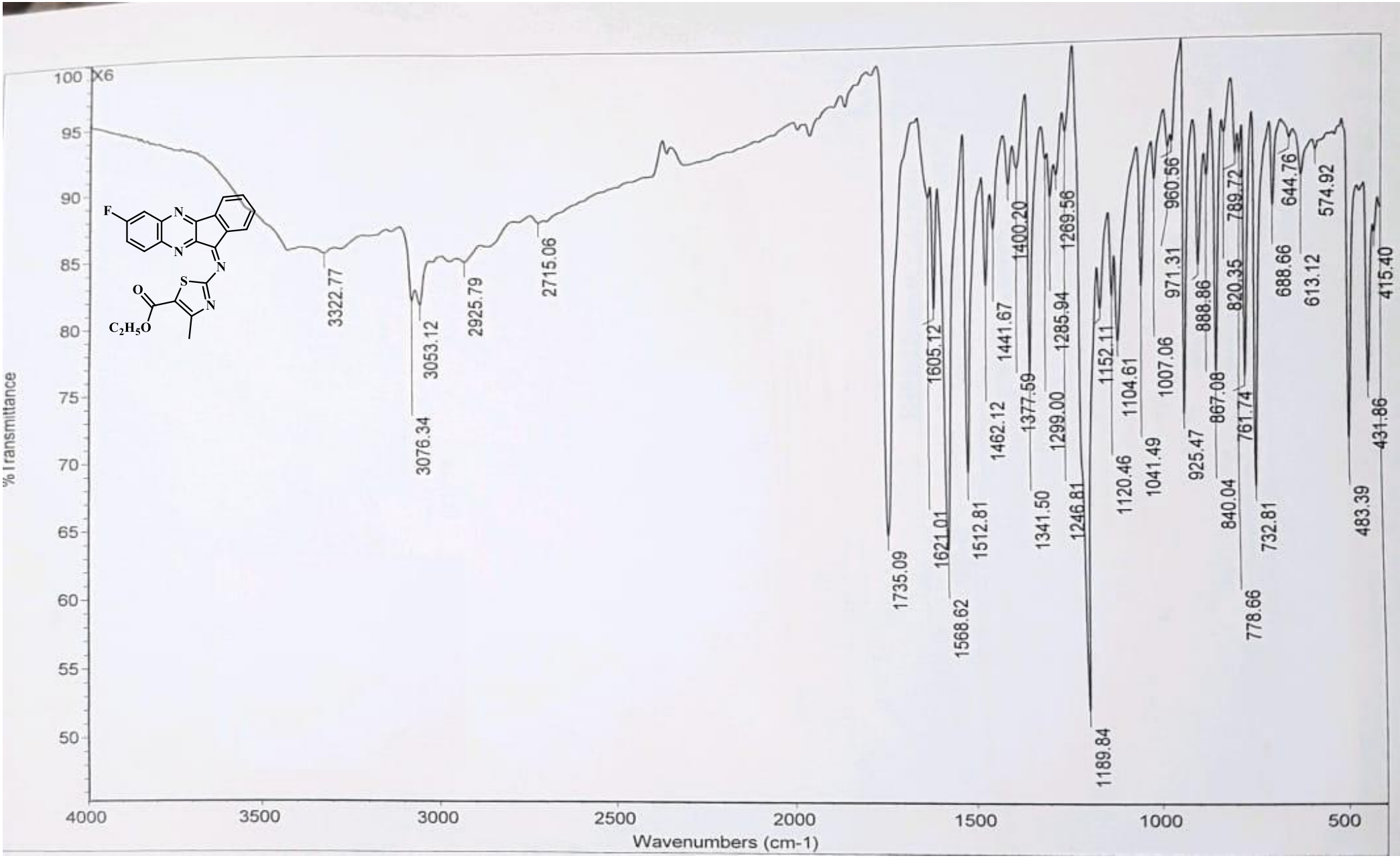
N
N
S
N
O
f1 (ppm)

6: IR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% Transmittance
Wavenumbers (cm-1)
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3000
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2000
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1000
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55
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3053.12
2925.79
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840.04
820.35
789.72
778.66
761.74
732.81
688.66
644.76
613.12
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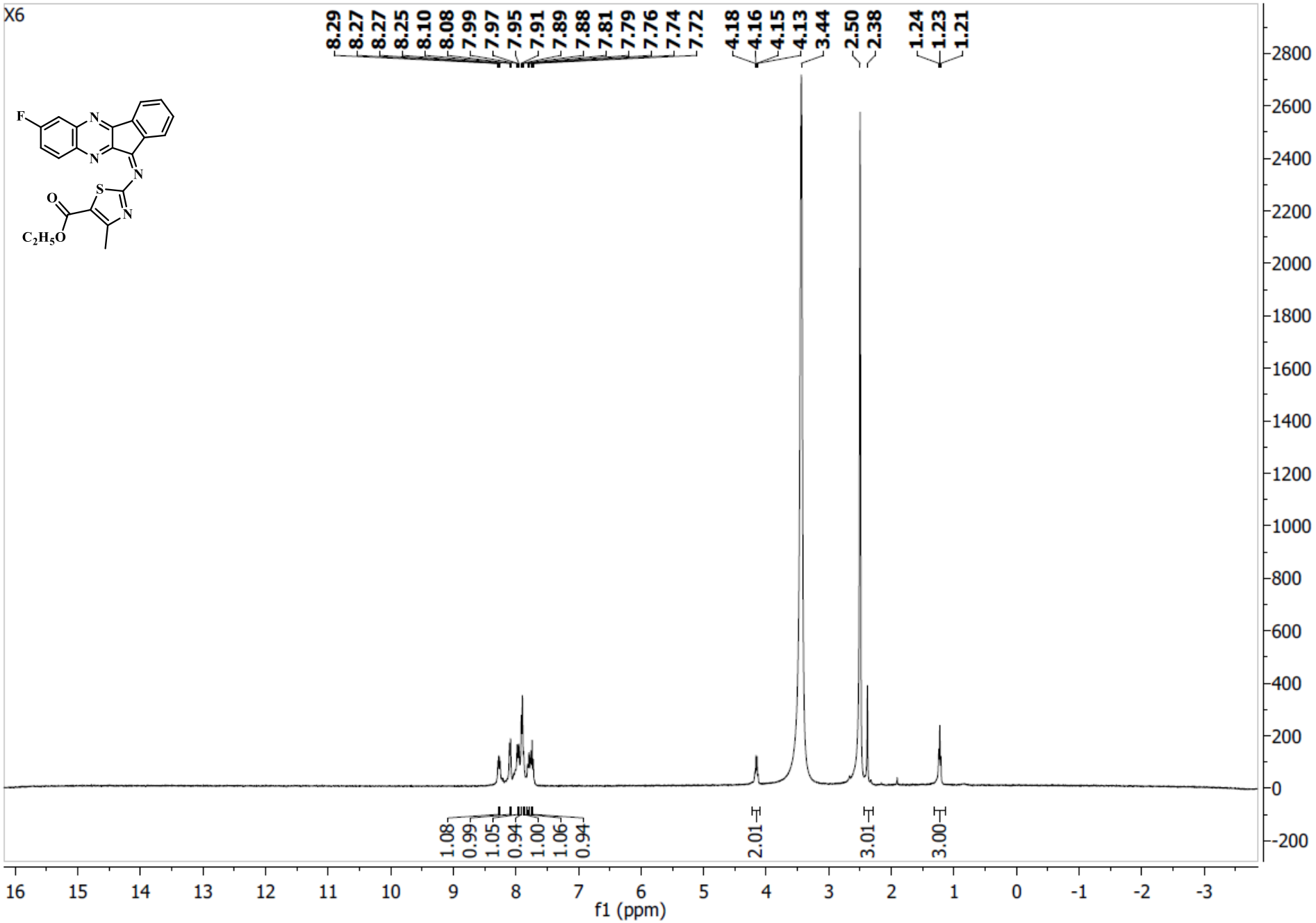
N
S
N
O
O
C2H5O

6: ^{1}H NMR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8.27
8.25
8.10
8.08
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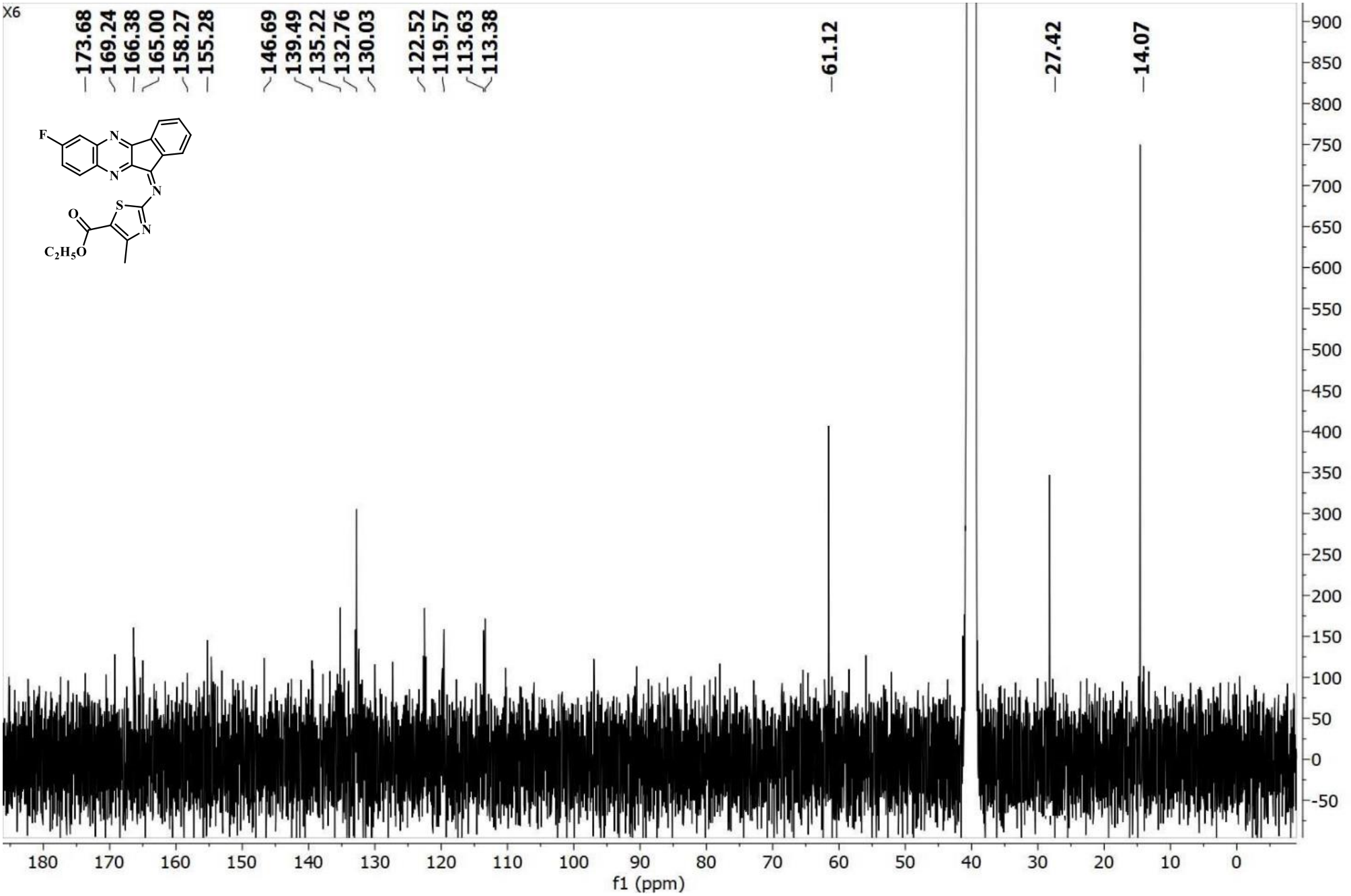
7.88
7.81
7.79
7.76
7.74
7.72
4.18
4.16
4.15
4.13
3.44
2.50
2.38
1.24
1.23
1.21
F
N
N
N
S
N
O
O
C2H5O
1.08
0.99
1.05
0.94
1.00
1.06
0.94
2.01
3.01
3.00
f1 (ppm)

6: ^{13}C NMR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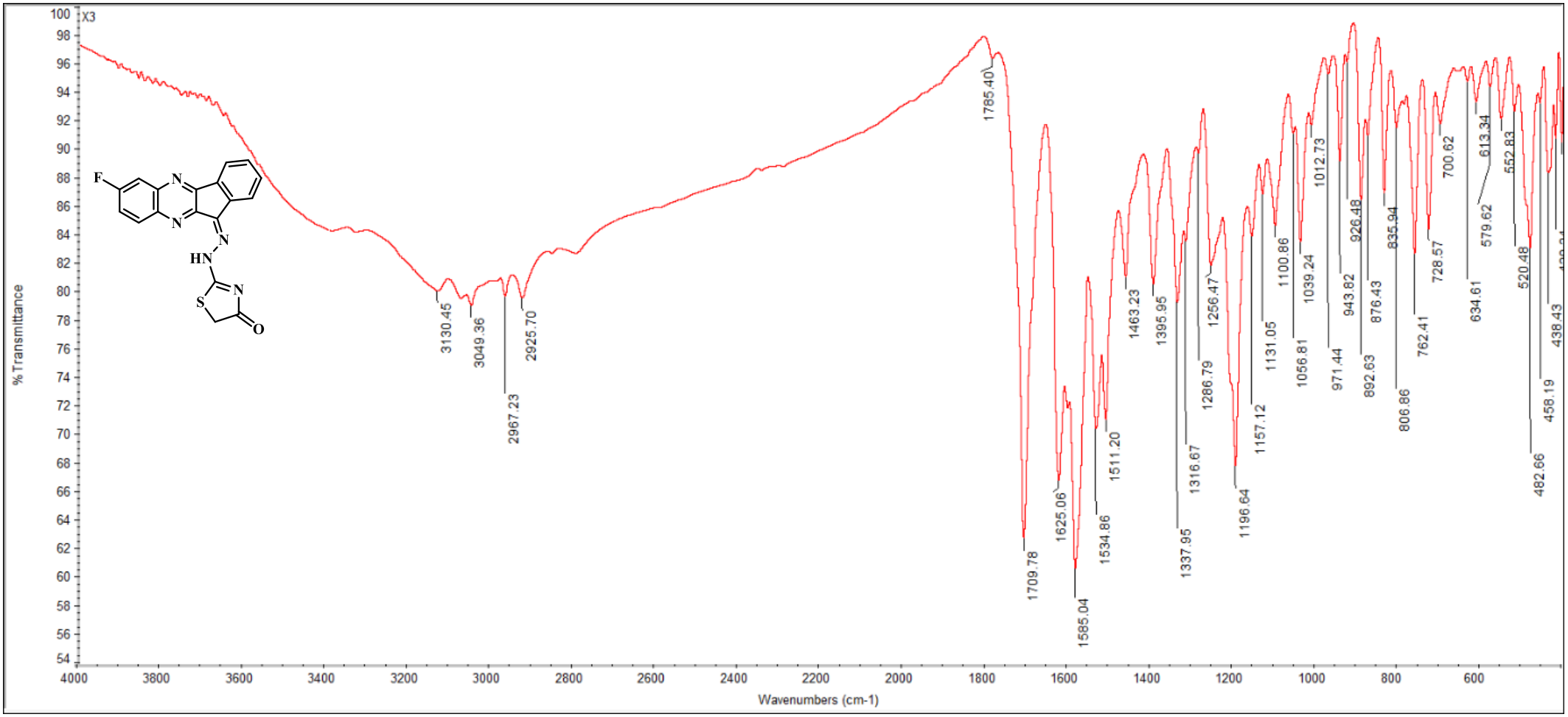
S
O
N
C_2H_5O
f1 (ppm)

7: IR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1463.23
1395.95
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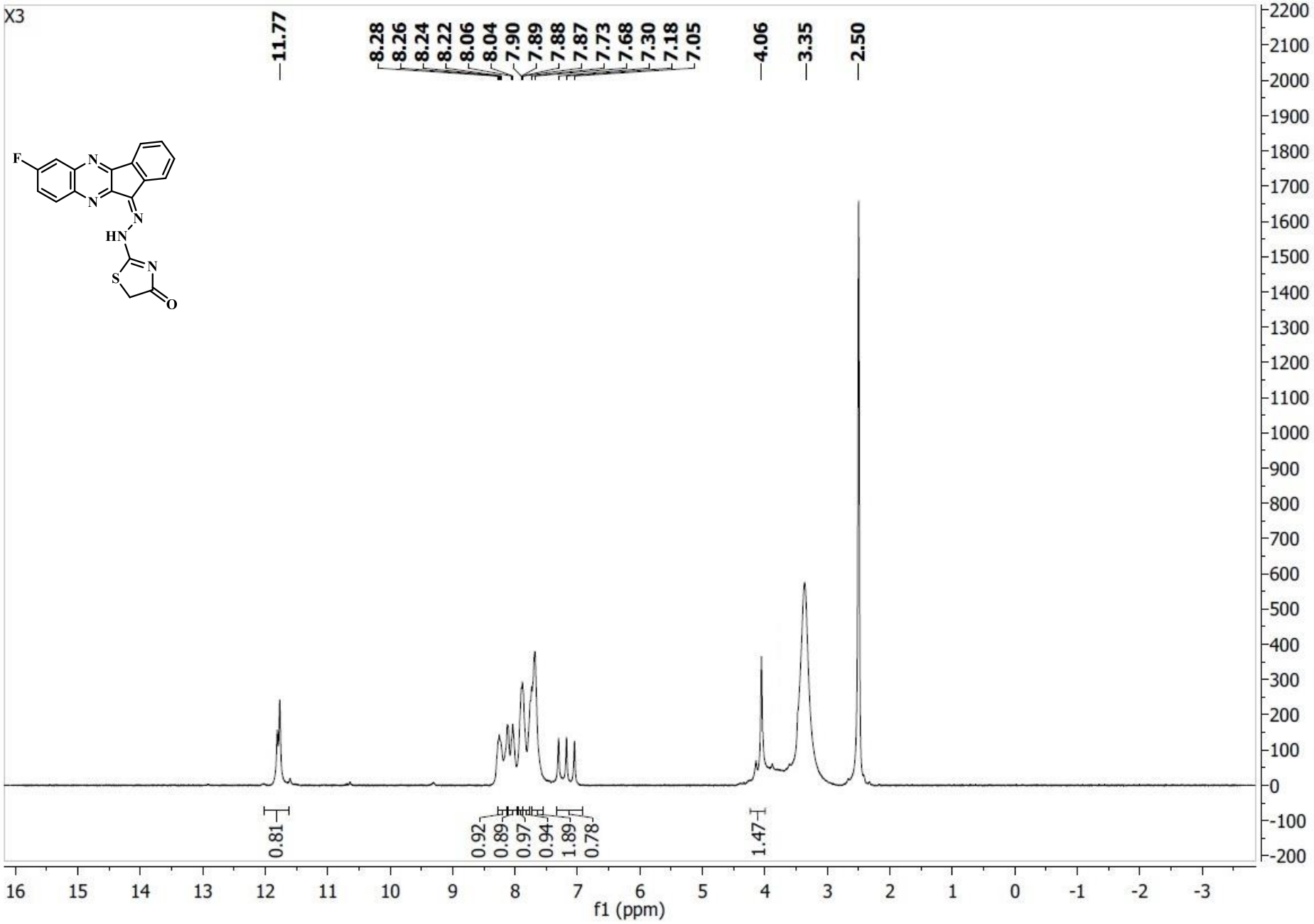
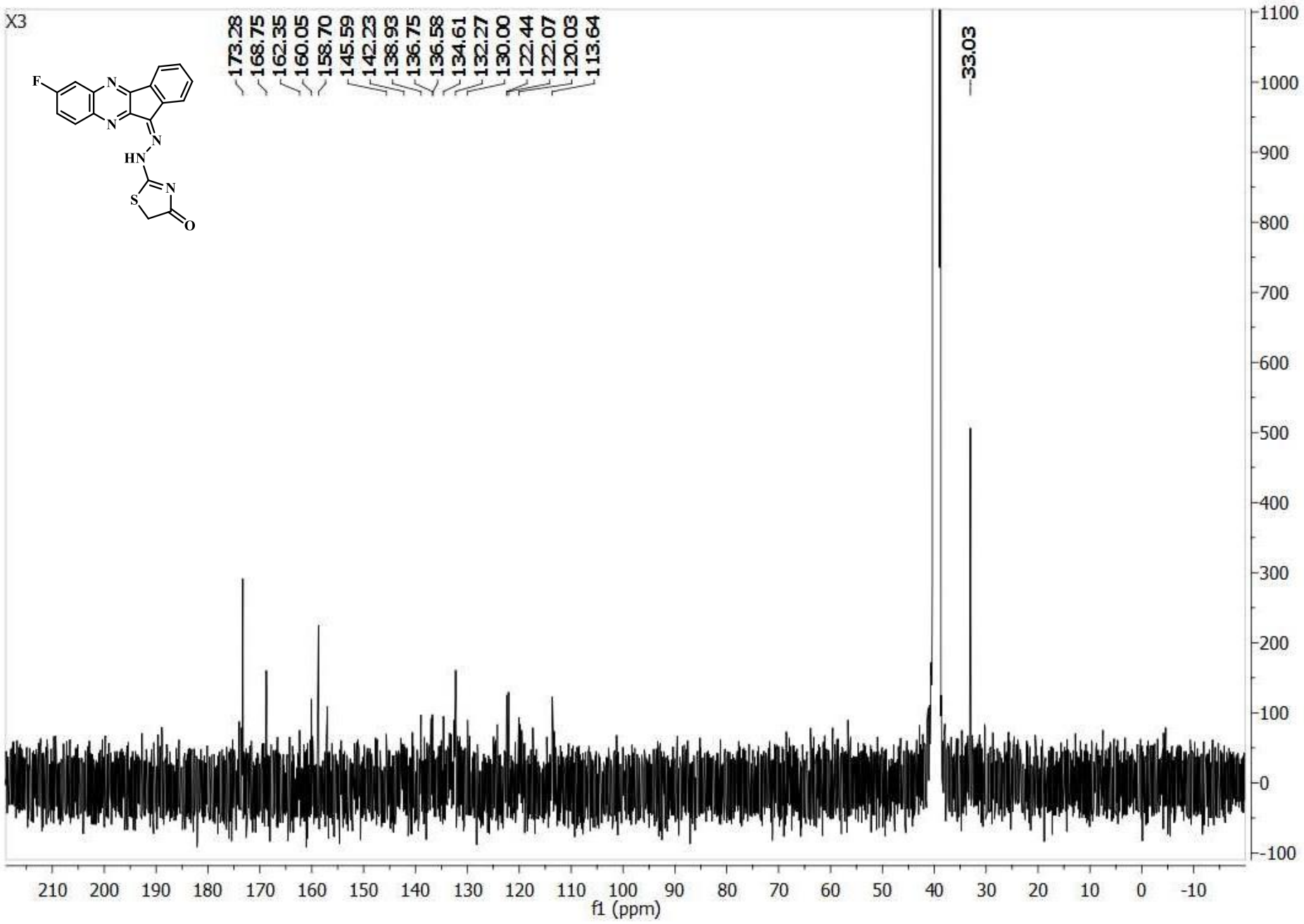
1286.79
1256.47
1196.64
1157.12
1131.05
1100.86
1056.81
1039.24
1012.73
971.44
943.82
926.48
892.63
876.43
835.94
806.86
762.41
728.57
700.62
634.61
613.34
579.62
552.83
520.48
482.66
458.19
438.43
F
N
N
N
HN
S
N
O

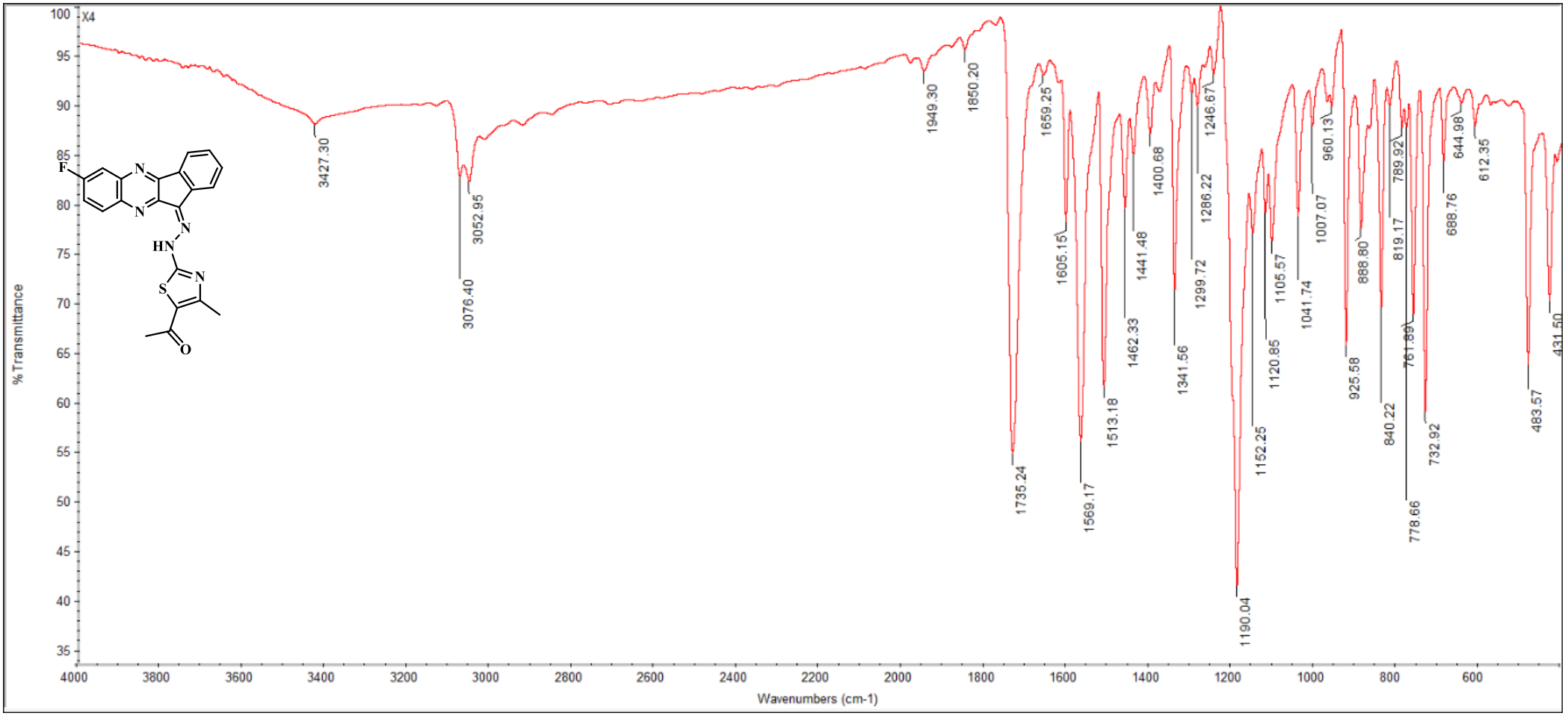
7: ^{1}H NMR


X3
11.77
8.28
8.26
8.24
8.22
8.06
8.04
7.90
7.89
7.88
7.87
7.73
7.68
7.30
7.18
7.05
4.06
3.35
2.50
F
N
N
N
HN
S
N
O
0.81
0.92
0.89
0.97
0.94
1.89
0.78
1.47
f1 (ppm)

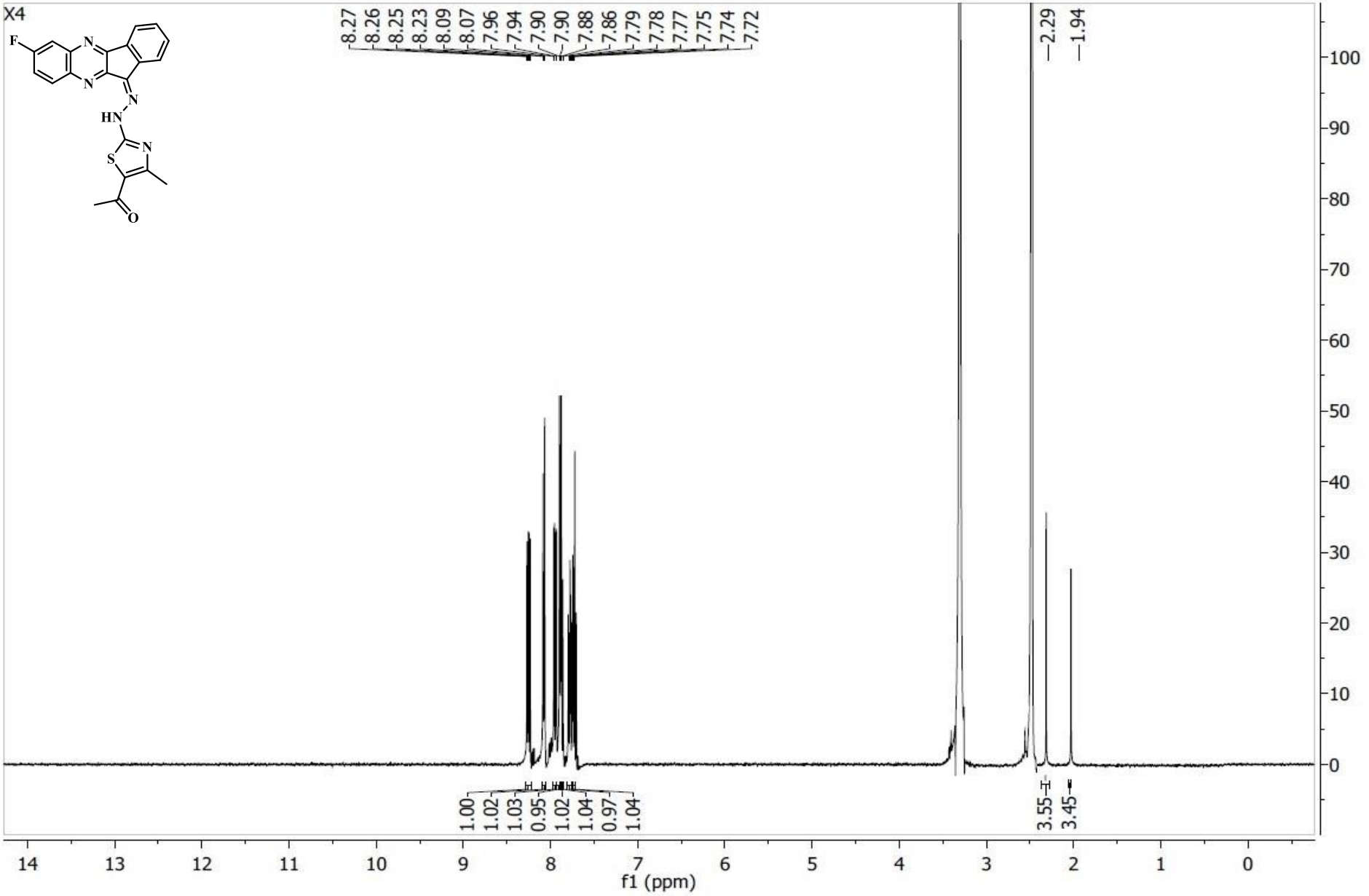
7: ^{13}C NMR


X3
F
N
N
N
HN
S
N
O
173.28
168.75
162.35
160.05
158.70
145.59
142.23
138.93
136.75
136.58
134.61
132.27
130.00
122.44
122.07
120.03
113.64
33.03
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)

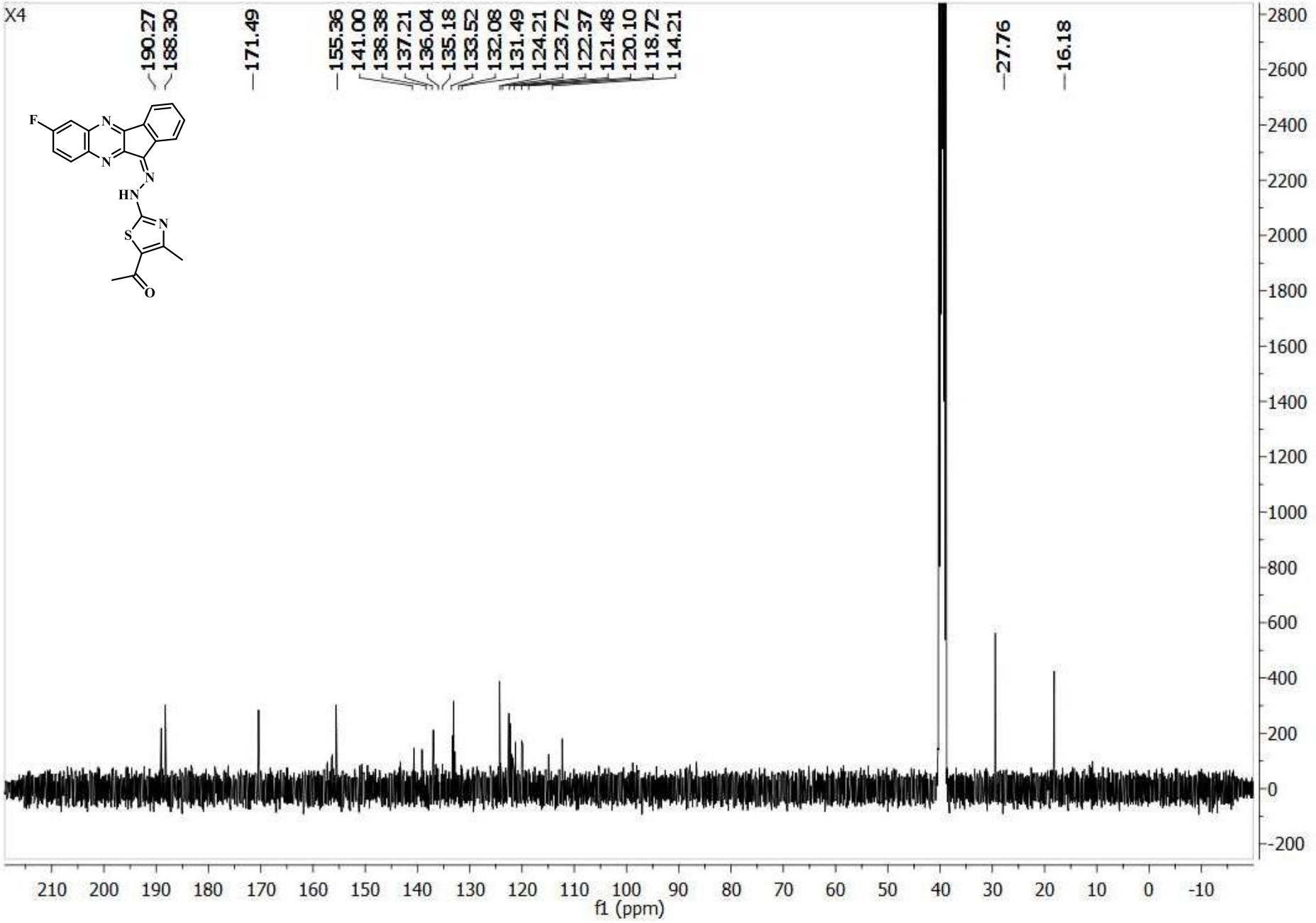
8: IR


X4
% Transmittance
Wavenumbers (cm-1)
3427.30
3076.40
3052.95
1949.30
1850.20
1659.25
1605.15
1735.24
1569.17
1513.18
1462.33
1441.48
1400.68
1341.56
1299.72
1286.22
1246.67
1190.04
1152.25
1120.85
1105.57
1041.74
1007.07
960.13
925.58
888.80
840.22
819.17
789.92
778.66
761.89
732.92
688.76
644.98
612.35
483.57
431.50
F
N
N
HN
N
S
N
O

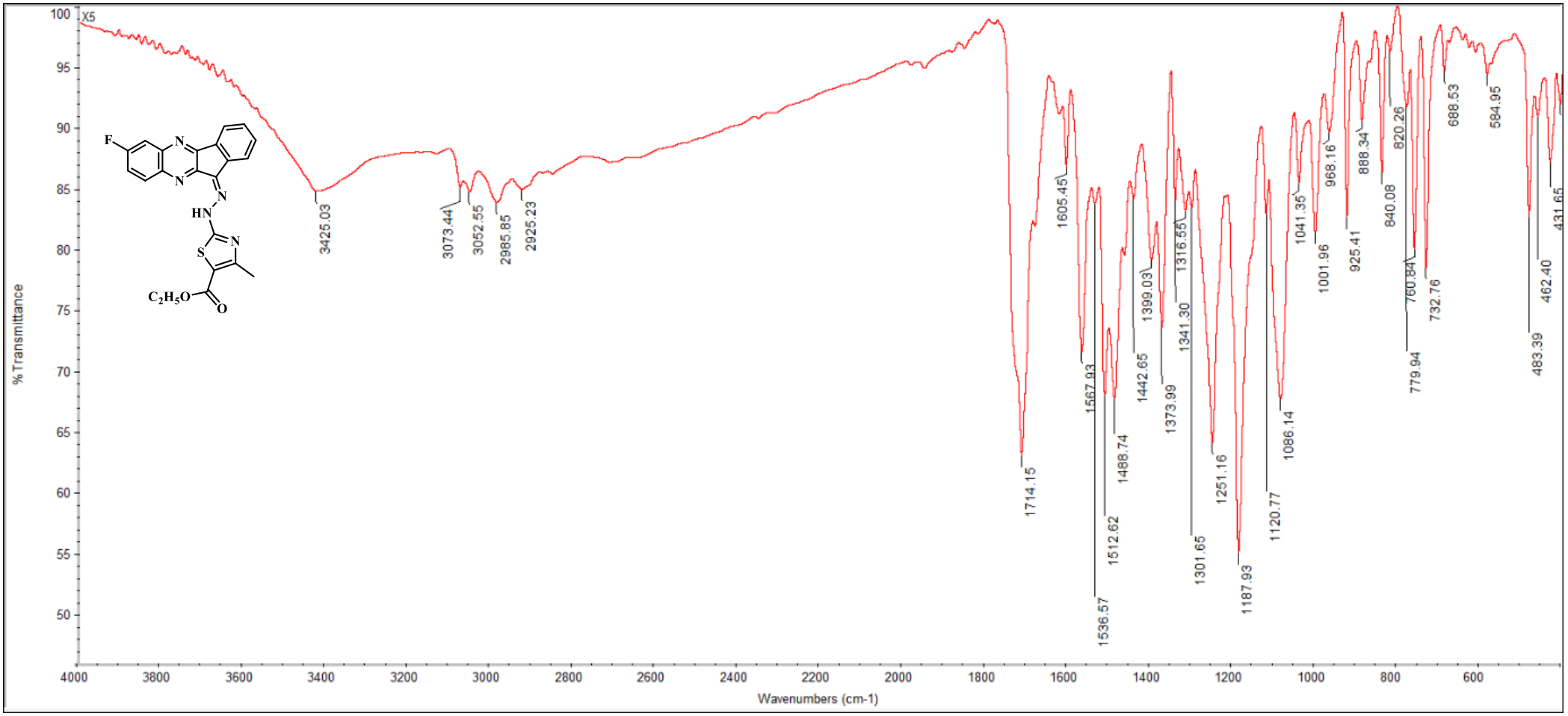
8: ^{1}H NMR


X4
F
N
N
N
HN
S
N
O
8.27
8.26
8.25
8.23
8.09
8.07
7.96
7.94
7.90
7.90
7.88
7.86
7.79
7.78
7.77
7.75
7.74
7.72
2.29
1.94
1.00
1.02
1.03
0.95
1.02
1.04
0.97
1.04
3.55
3.45
f1 (ppm)

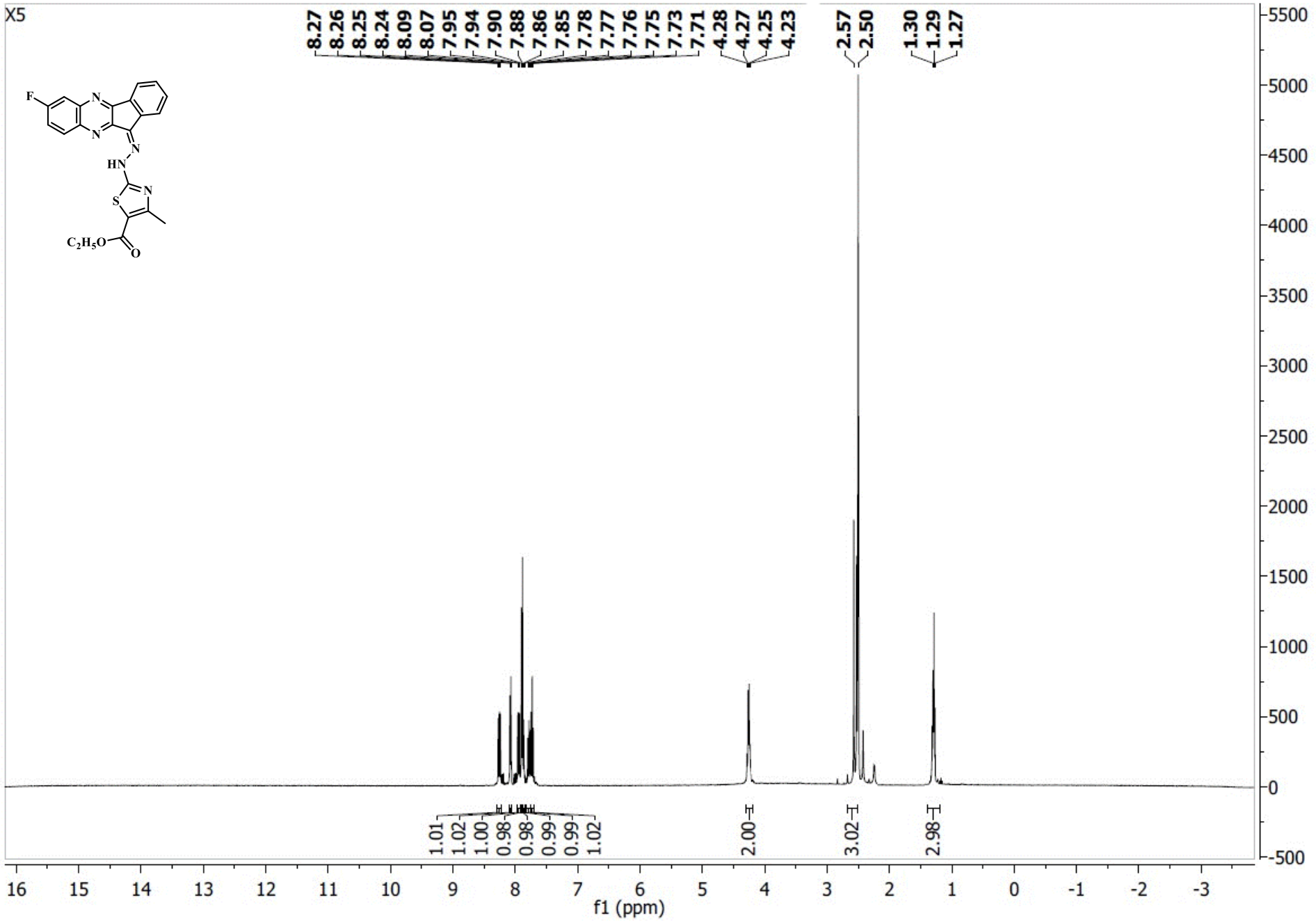
8: ^{13}C NMR


X4
190.27
188.30
171.49
155.36
141.00
138.38
137.21
136.04
135.18
133.52
132.08
131.49
124.21
123.72
122.37
121.48
120.10
118.72
114.21
27.76
16.18
F
N
N
N
HN
S
N
O
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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)

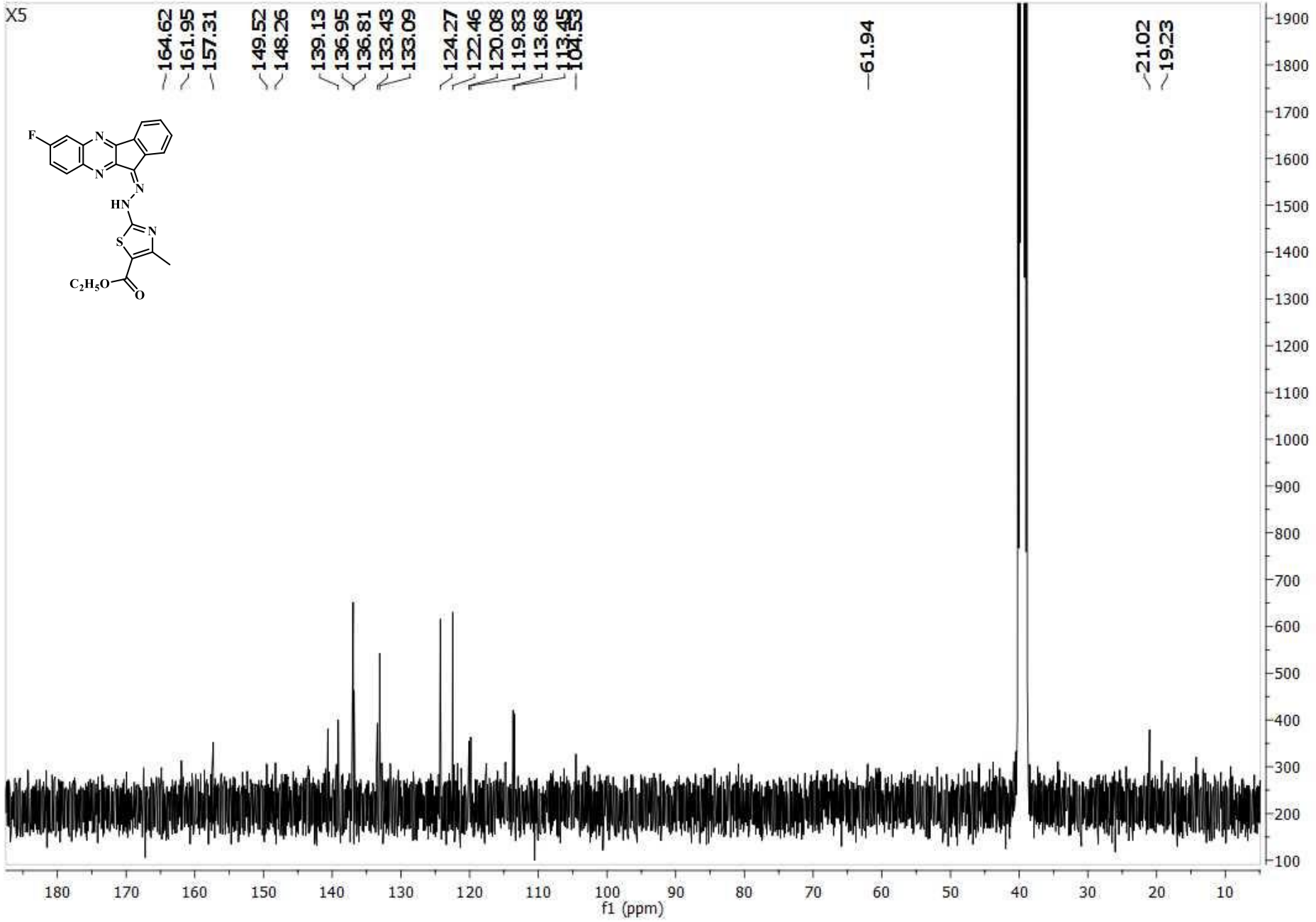
9: IR


X5
% Transmittance
Wavenumbers (cm-1)
3425.03
3073.44
3052.55
2985.85
2925.23
1714.15
1605.45
1567.93
1536.57
1512.62
1488.74
1442.65
1399.03
1373.99
1341.30
1316.55
1301.65
1251.16
1187.93
1120.77
1086.14
1041.35
1001.96
968.16
925.41
888.34
840.08
820.26
779.94
760.84
732.76
688.53
584.95
483.39
462.40
431.65

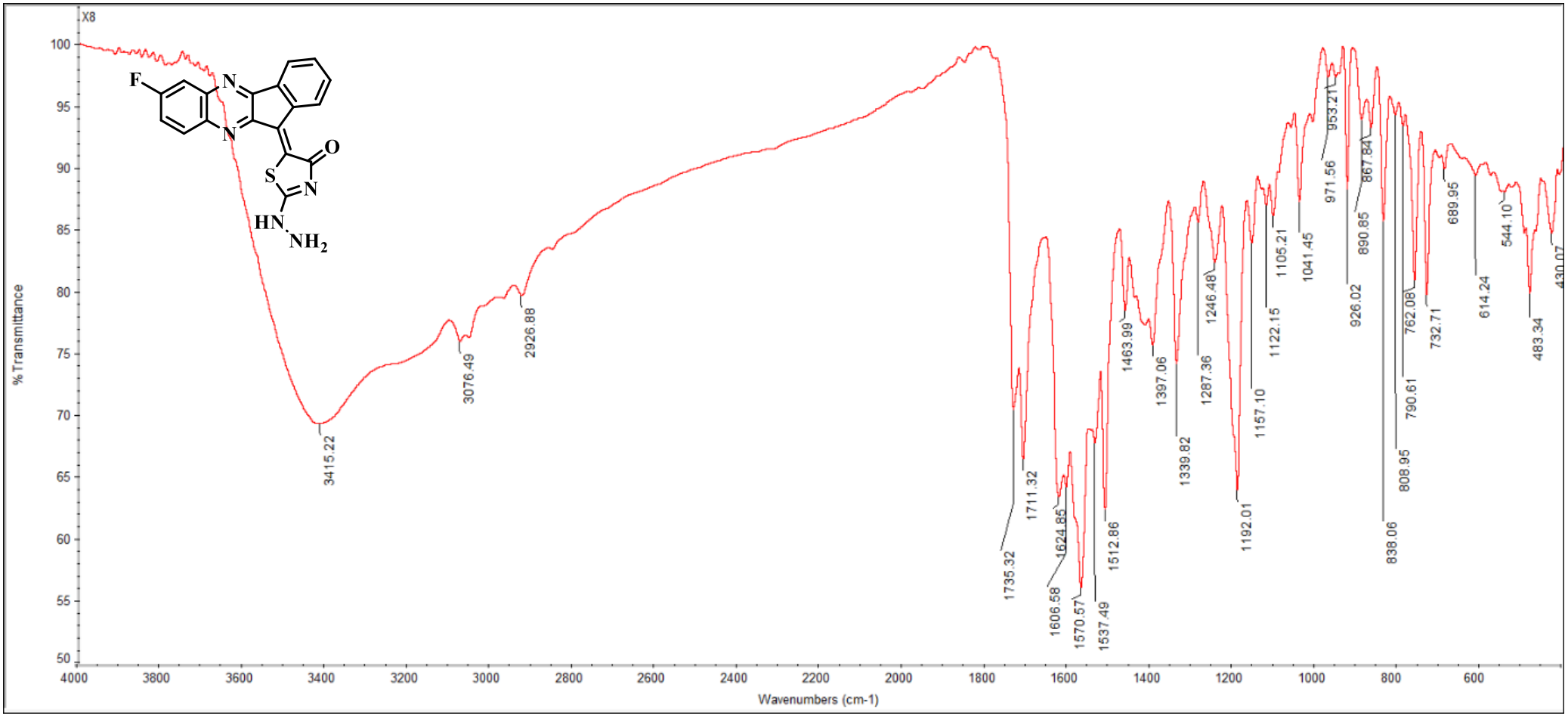
9: ^{1}H NMR


X5
8.27
8.26
8.25
8.24
8.09
8.07
7.95
7.94
7.90
7.88
7.86
7.85
7.78
7.77
7.76
7.75
7.73
7.71
4.28
4.27
4.25
4.23
2.57
2.50
1.30
1.29
1.27
F
N
N
HN
N
S
O
O
1.01
1.02
1.00
0.98
0.98
0.99
0.99
1.02
2.00
3.02
2.98
f1 (ppm)

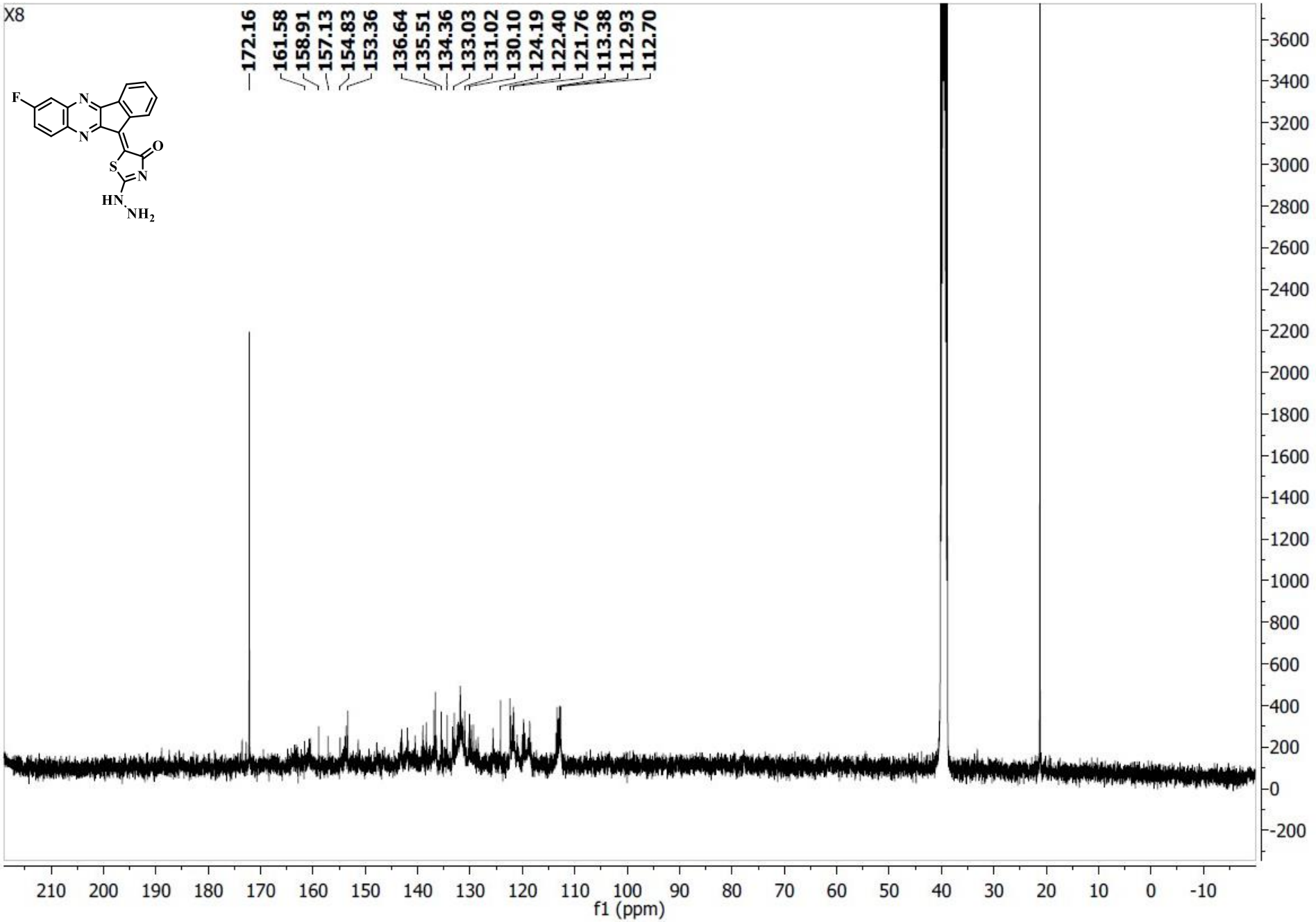
9: ^{13}C NMR


X5
164.62
161.95
157.31
149.52
148.26
139.13
136.95
136.81
133.43
133.09
124.27
122.46
120.08
119.83
113.68
61.94
21.02
19.23
F
N
N
HN
N
S
C_2H_5O
O
f1 (ppm)

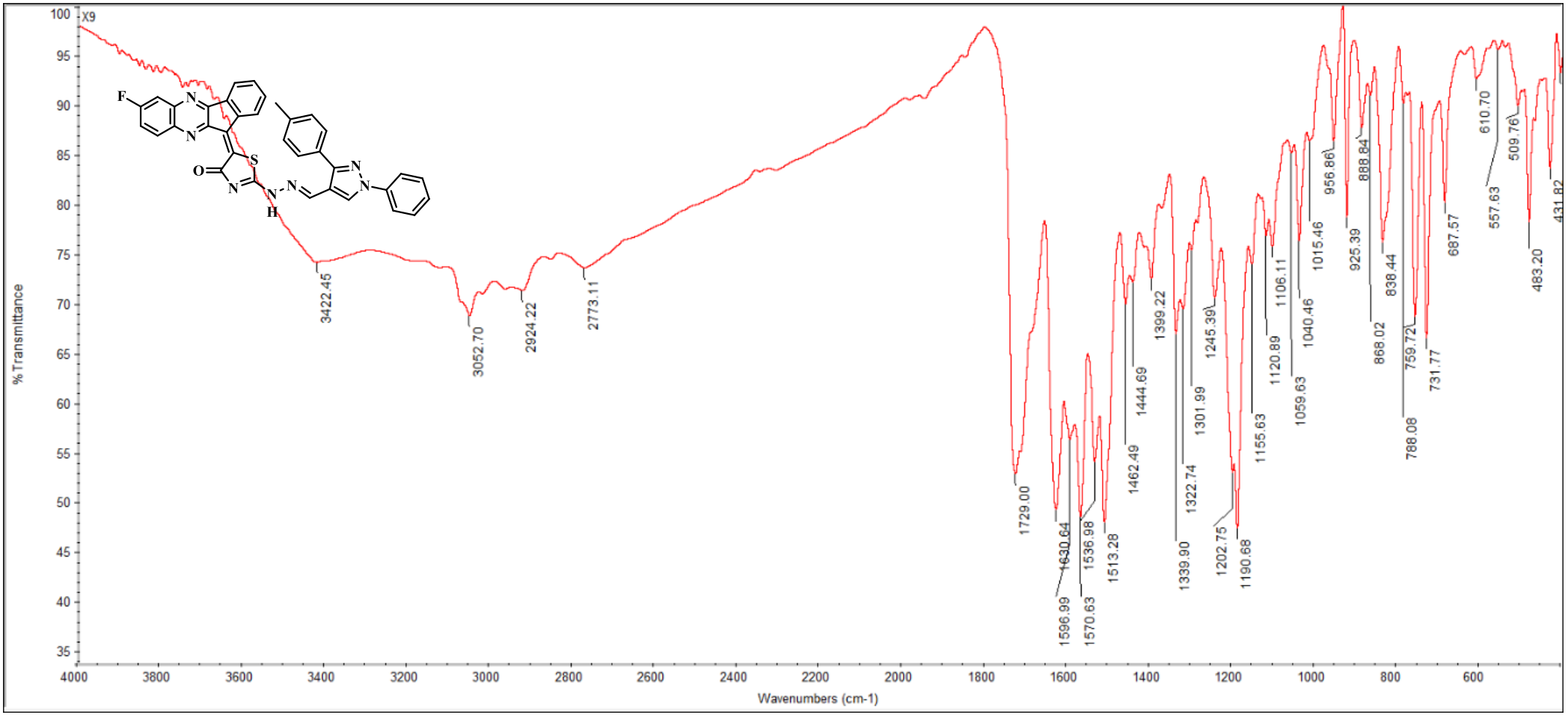
10: IR


X8
% Transmittance
Wavenumbers (cm-1)
3415.22
3076.49
2926.88
1735.32
1711.32
1624.85
1606.58
1570.57
1537.49
1512.86
1463.99
1397.06
1339.82
1287.36
1246.48
1192.01
1157.10
1122.15
1105.21
1041.45
971.56
953.21
926.02
890.85
867.84
838.06
808.95
790.61
762.08
732.71
689.95
614.24
544.10
483.34
F
N
N
O
S
N
HN
NH2

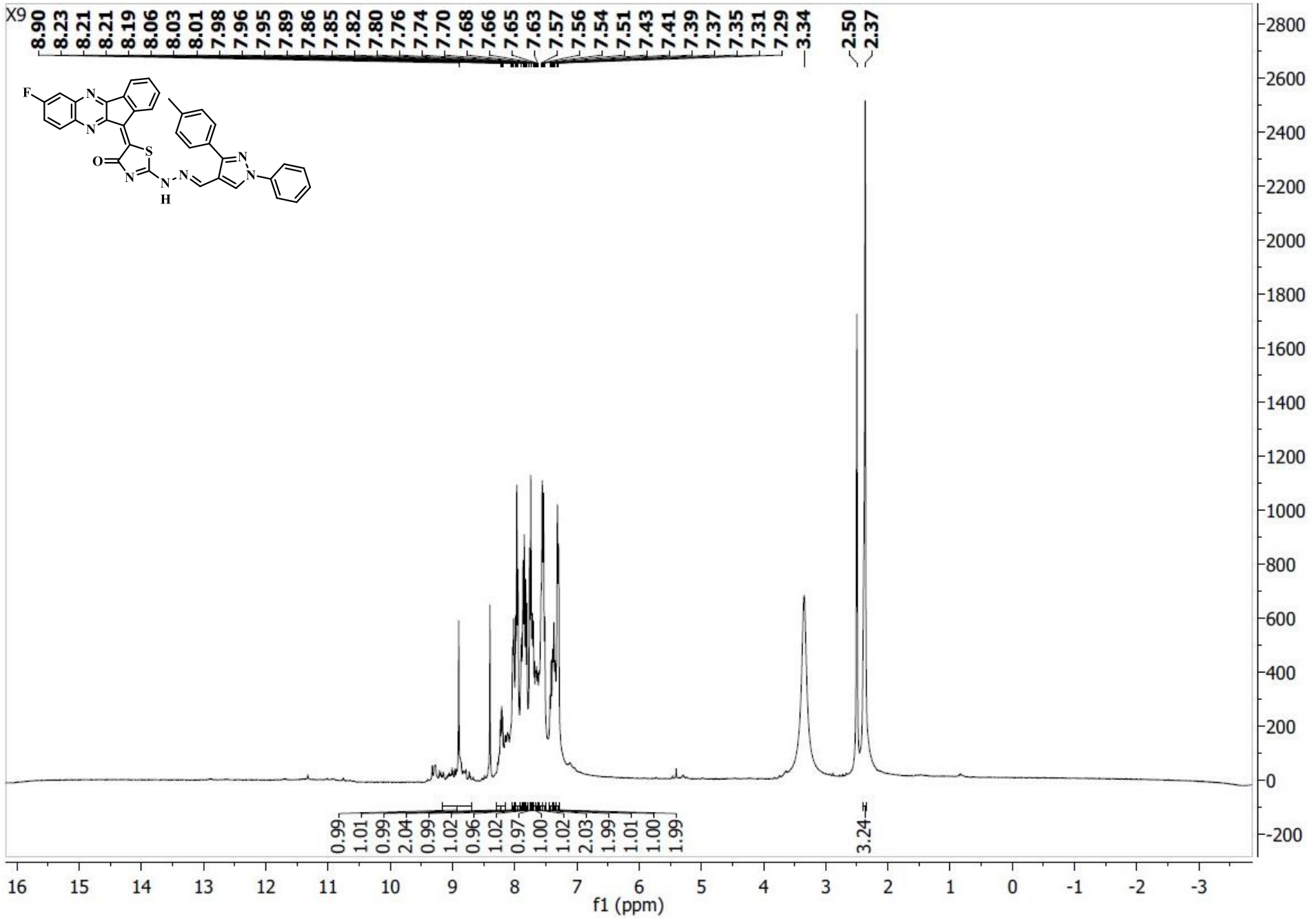
10: ^{13}C NMR


X8
172.16
161.58
158.91
157.13
154.83
153.36
136.64
135.51
134.36
133.03
131.02
130.10
124.19
122.40
121.76
113.38
112.93
112.70
F
N
N
O
S
N
HN
NH2
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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)

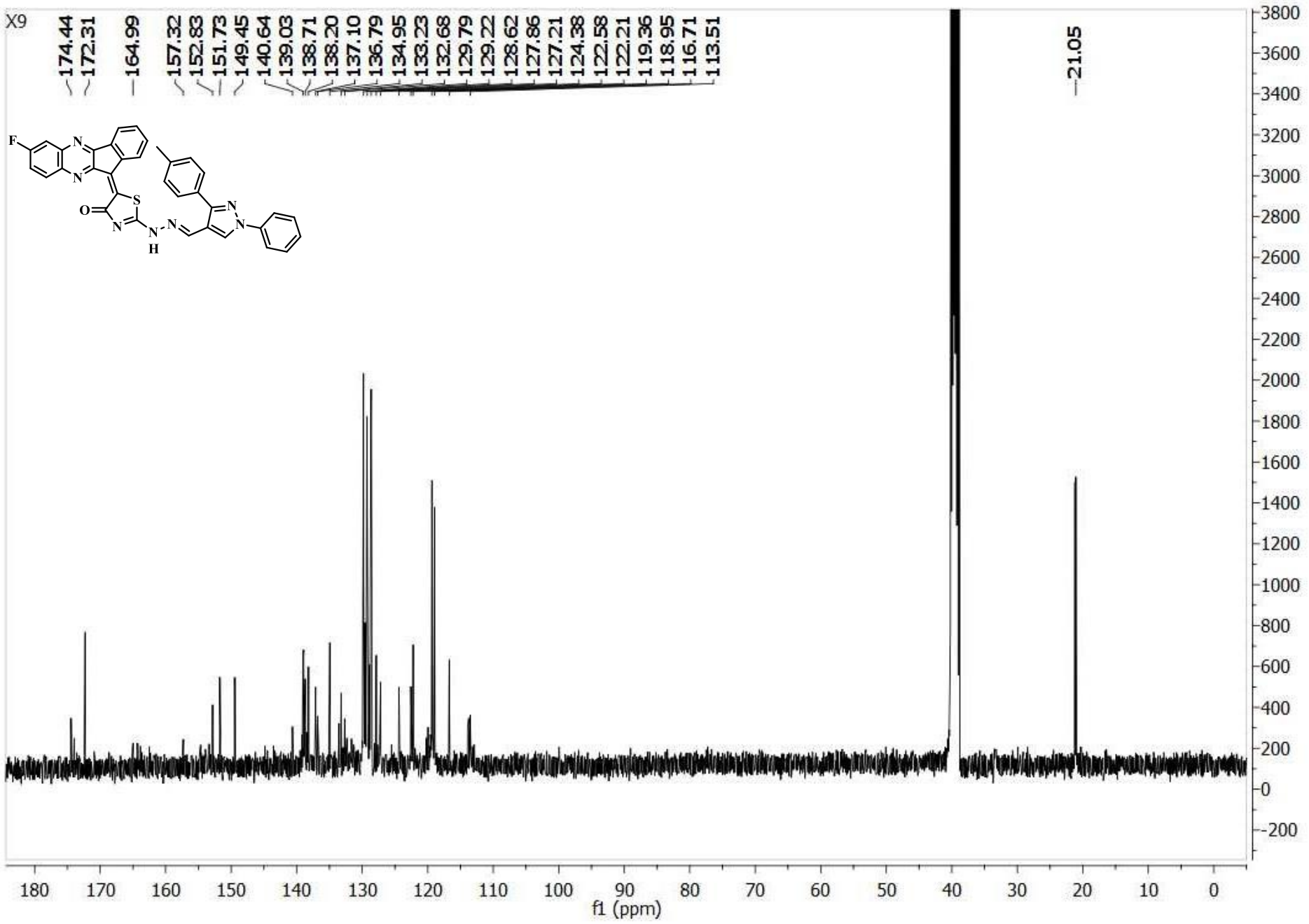
12: IR


X9
% Transmittance
Wavenumbers (cm-1)
3422.45
3052.70
2924.22
2773.11
1729.00
1630.64
1596.99
1570.63
1536.98
1513.28
1462.49
1444.69
1399.22
1339.90
1322.74
1301.99
1245.39
1202.75
1190.68
1155.63
1120.89
1106.11
1059.63
1040.46
1015.46
956.86
925.39
888.84
868.02
838.44
788.08
759.72
731.77
687.57
610.70
557.63
509.76
483.20
431.82

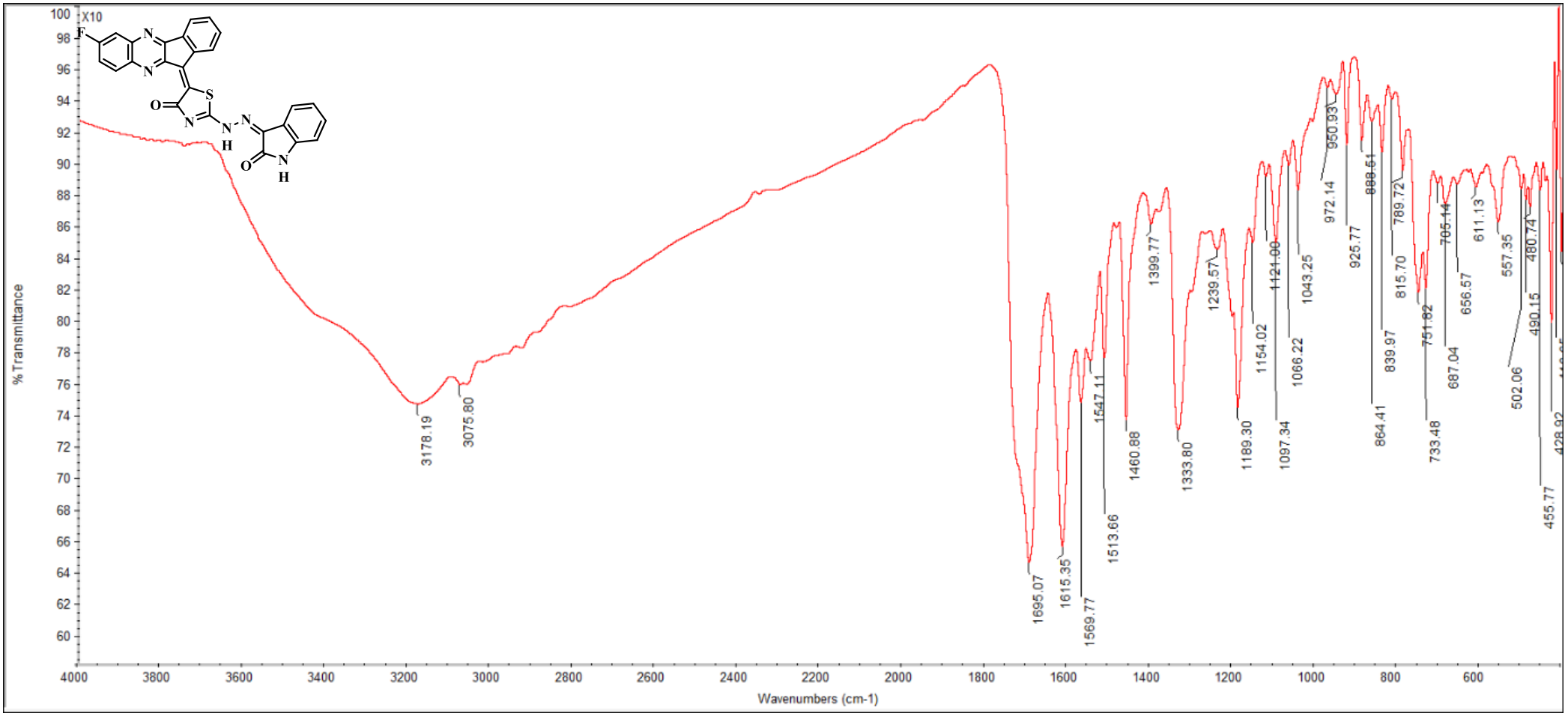
12: ^{1}H NMR


X9
8.90
8.23
8.21
8.21
8.19
8.06
8.03
8.01
7.98
7.96
7.95
7.89
7.86
7.85
7.82
7.80
7.76
7.74
7.70
7.68
7.66
7.65
7.63
7.57
7.56
7.54
7.51
7.43
7.41
7.39
7.37
7.35
7.31
7.29
3.34
2.50
2.37
F
O
S
N
H
0.99
1.01
0.99
2.04
0.99
1.02
0.96
1.02
0.97
1.00
1.02
2.03
1.99
1.01
1.00
1.99
3.24
f1 (ppm)

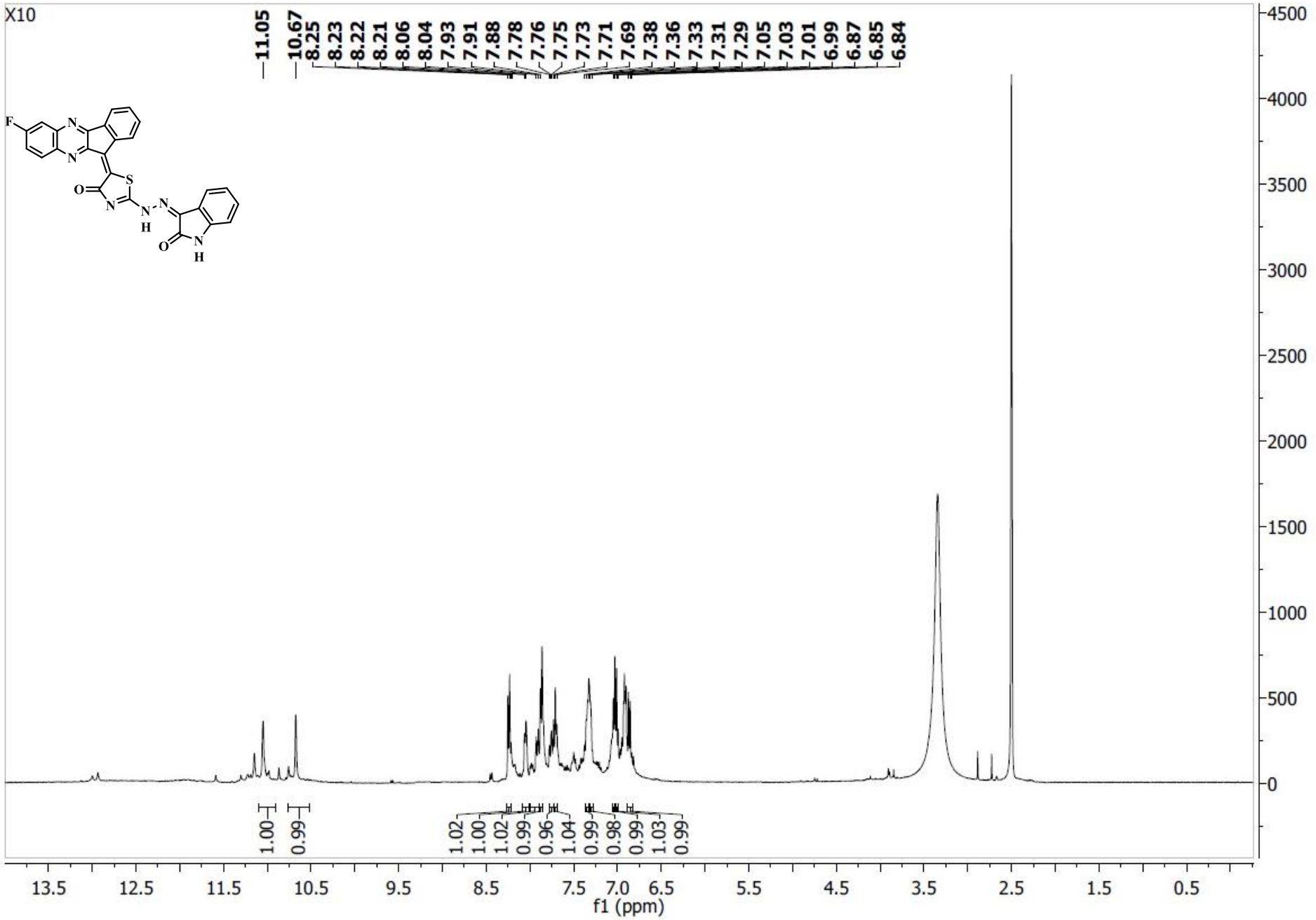
12: ^{13}C NMR


X9
174.44
172.31
164.99
157.32
152.83
151.73
149.45
140.64
139.03
138.71
138.20
137.10
136.79
134.95
133.23
132.68
129.79
129.22
128.62
127.86
127.21
124.38
122.58
122.21
119.36
118.95
116.71
113.51
21.05
F
N
N
S
O
N
N
N
H
N
N
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

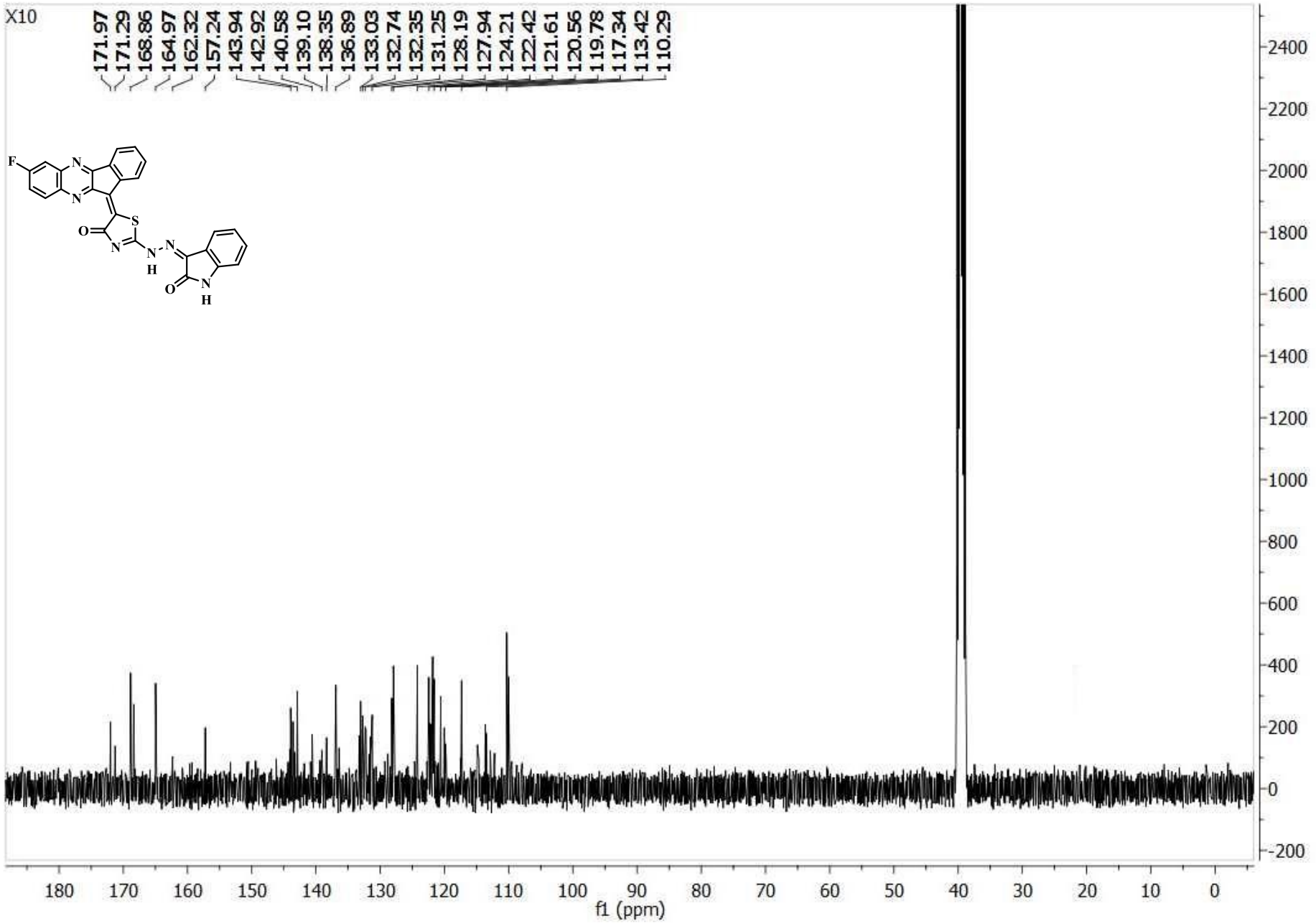
13: IR


X10
% Transmittance
Wavenumbers (cm-1)
3178.19
3075.80
1695.07
1615.35
1569.77
1547.11
1513.66
1460.88
1399.77
1333.80
1239.57
1189.30
1154.02
1121.00
1097.34
1066.22
1043.25
972.14
950.93
925.77
888.61
864.41
839.97
815.70
789.72
751.82
733.48
705.14
687.04
656.57
611.13
557.35
502.06
490.15
480.74
455.77

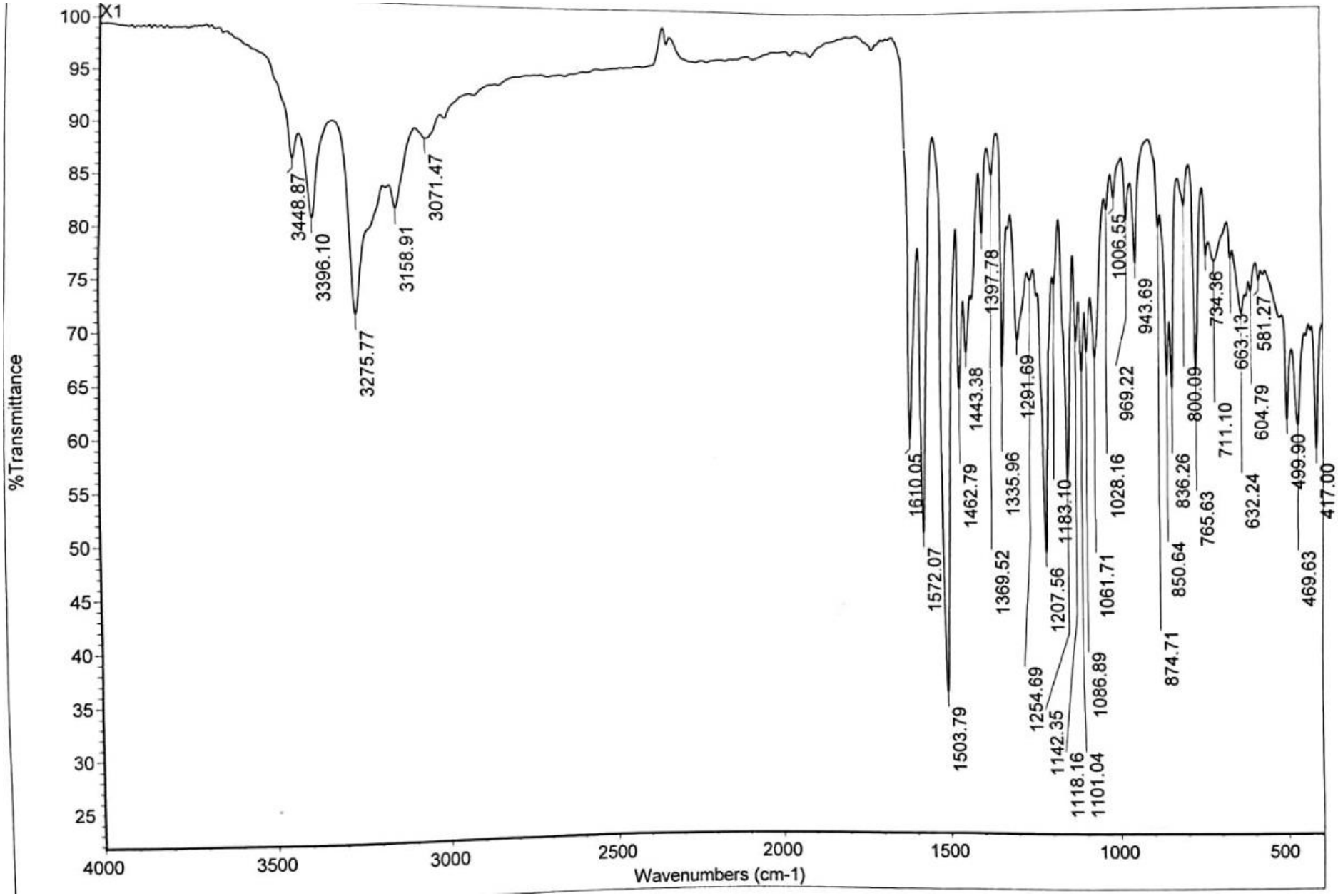
13: ^{1}H NMR


X10
11.05
10.67
8.25
8.23
8.22
8.21
8.06
8.04
7.93
7.91
7.88
7.78
7.76
7.75
7.73
7.71
7.69
7.38
7.36
7.33
7.31
7.29
7.05
7.03
7.01
6.99
6.87
6.85
6.84
F
O
S
N
H
O
N
H
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.00
0.99
1.02
1.00
1.02
0.99
0.96
1.04
0.99
0.98
0.99
1.03
0.99
13.5
12.5
11.5
10.5
9.5
8.5
7.5
7.0
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

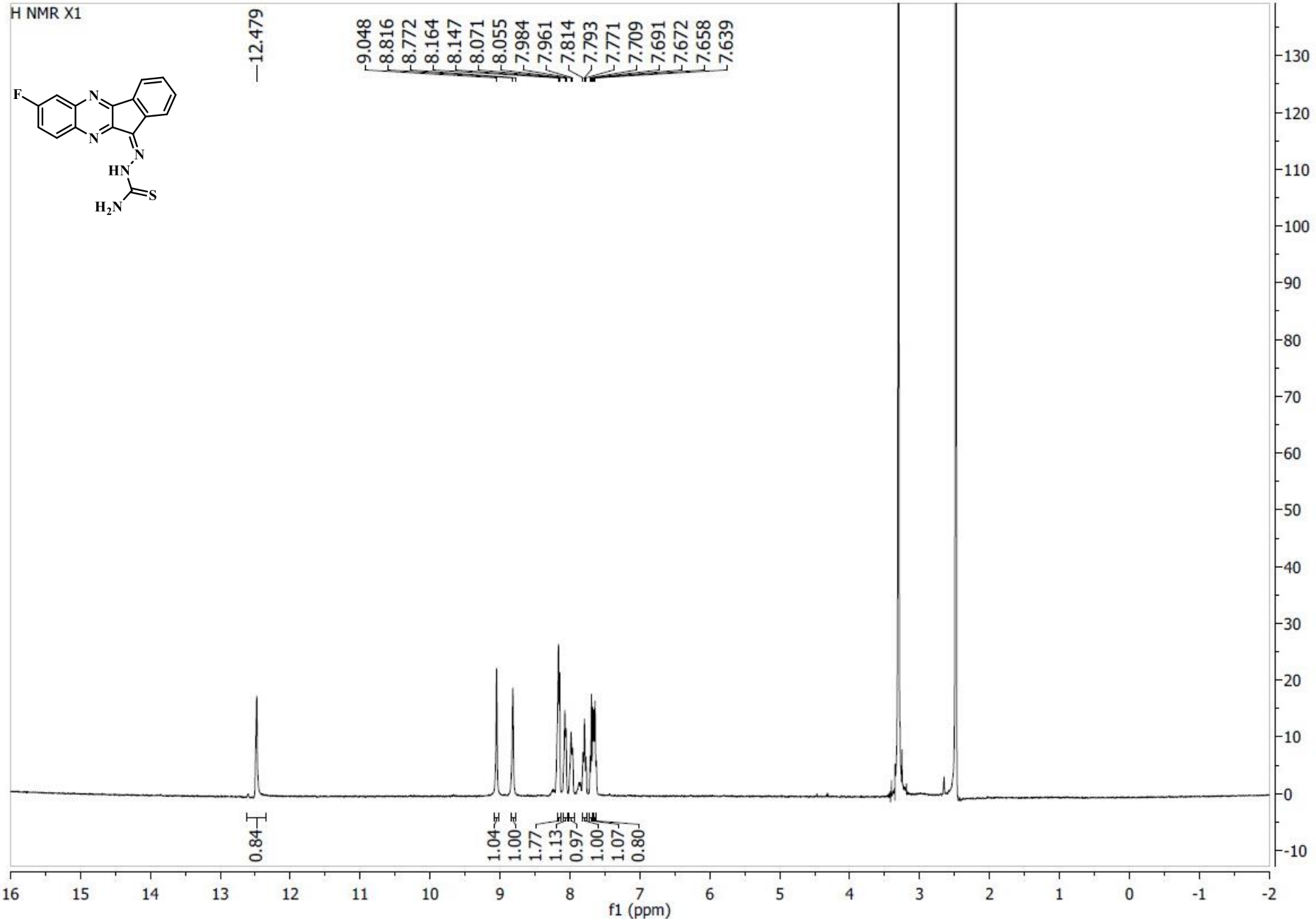
13: ^{13}C NMR


X10
171.97
171.29
168.86
164.97
162.32
157.24
143.94
142.92
140.58
139.10
138.35
136.89
133.03
132.74
132.35
131.25
128.19
127.94
124.21
122.42
121.61
120.56
119.78
117.34
113.42
110.29
F
N
N
S
O
N
N
H
O
N
H
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

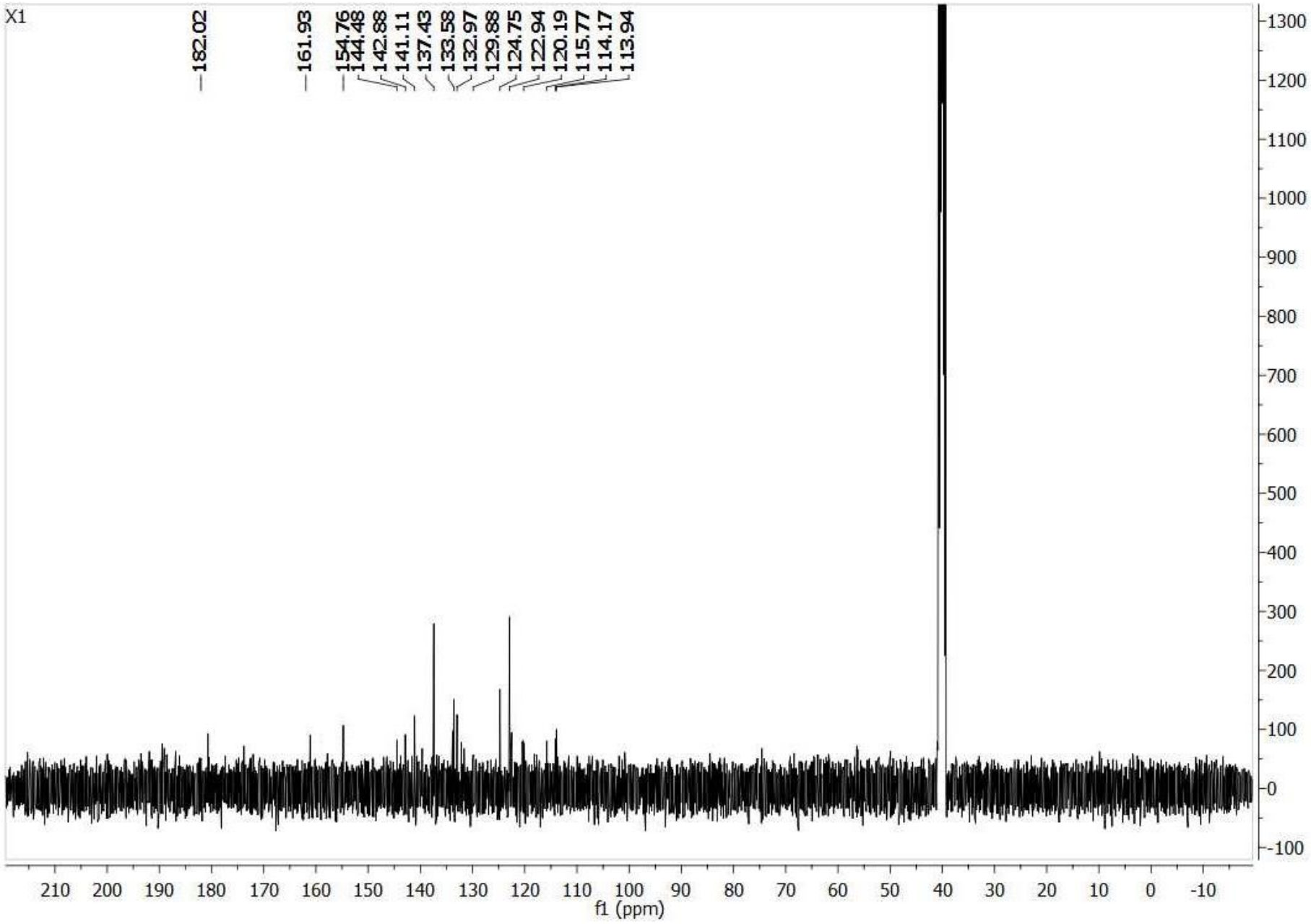
14: IR


X1
%Transmittance
Wavenumbers (cm-1)
3448.87
3396.10
3275.77
3158.91
3071.47
1610.05
1572.07
1503.79
1462.79
1443.38
1397.78
1369.52
1335.96
1291.69
1254.69
1207.56
1183.10
1142.35
1118.16
1101.04
1086.89
1061.71
1028.16
1006.55
969.22
943.69
874.71
850.64
836.26
800.09
765.63
734.36
711.10
663.13
632.24
604.79
581.27
499.90
469.63
417.00

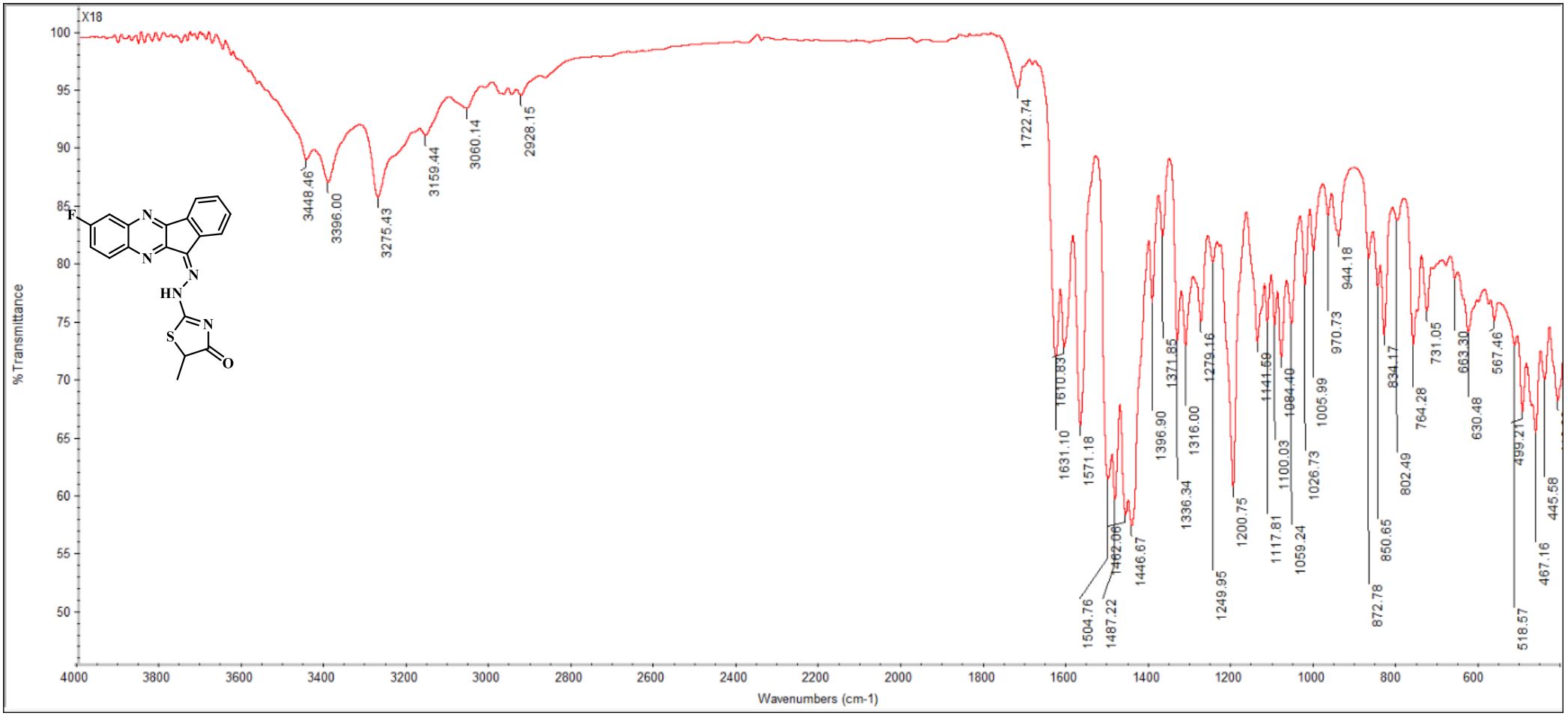
14: ^{1}H NMR


H NMR X1
12.479
9.048
8.816
8.772
8.164
8.147
8.071
8.055
7.984
7.961
7.814
7.793
7.771
7.709
7.691
7.672
7.658
7.639
F
N
N
N
HN
S
H2N
0.84
1.04
1.00
1.77
1.13
0.97
1.00
1.07
0.80
f1 (ppm)

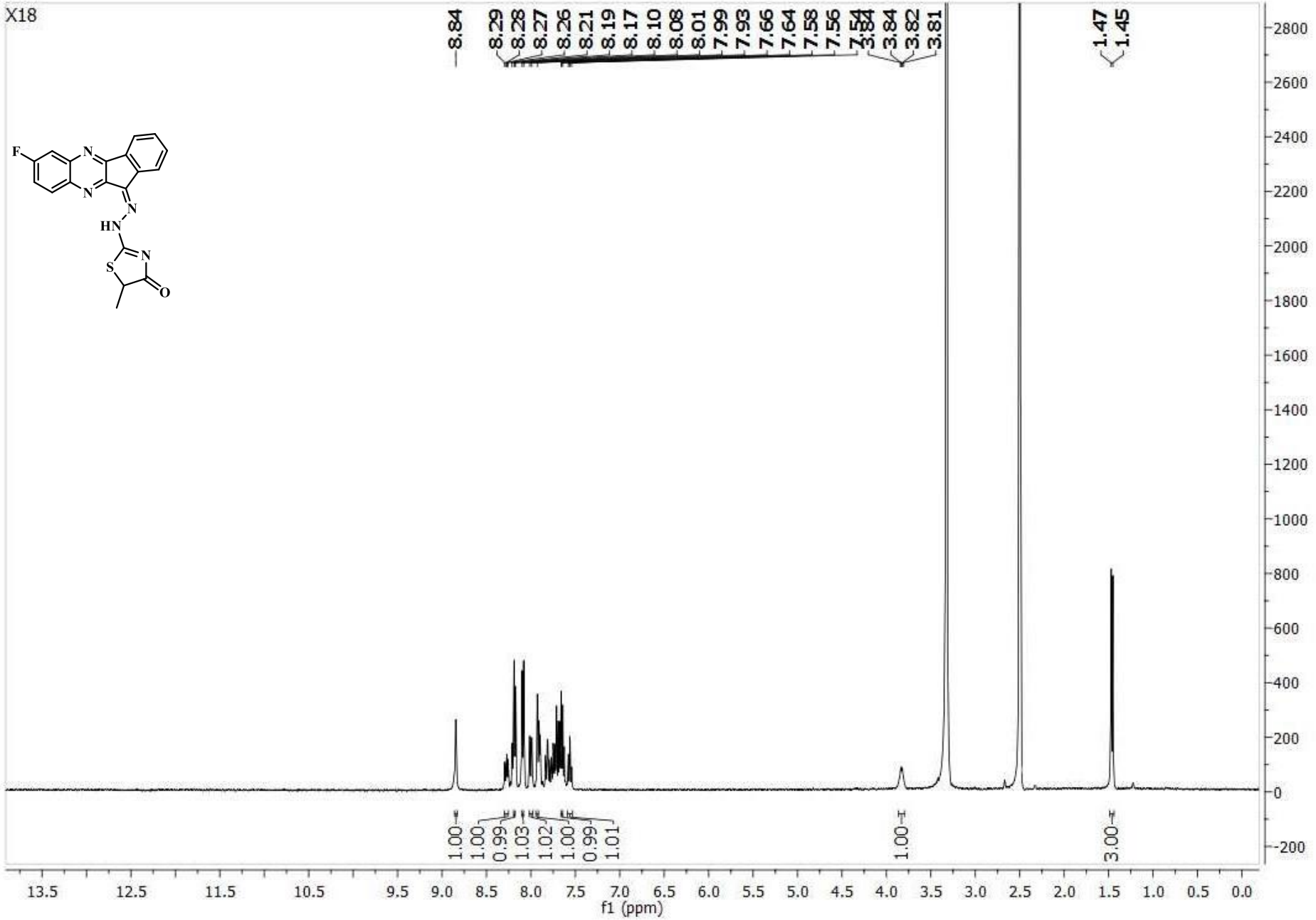
14: ^{13}C NMR


X1
182.02
161.93
154.76
144.48
142.88
141.11
137.43
133.58
132.97
129.88
124.75
122.94
120.19
115.77
114.17
113.94
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)

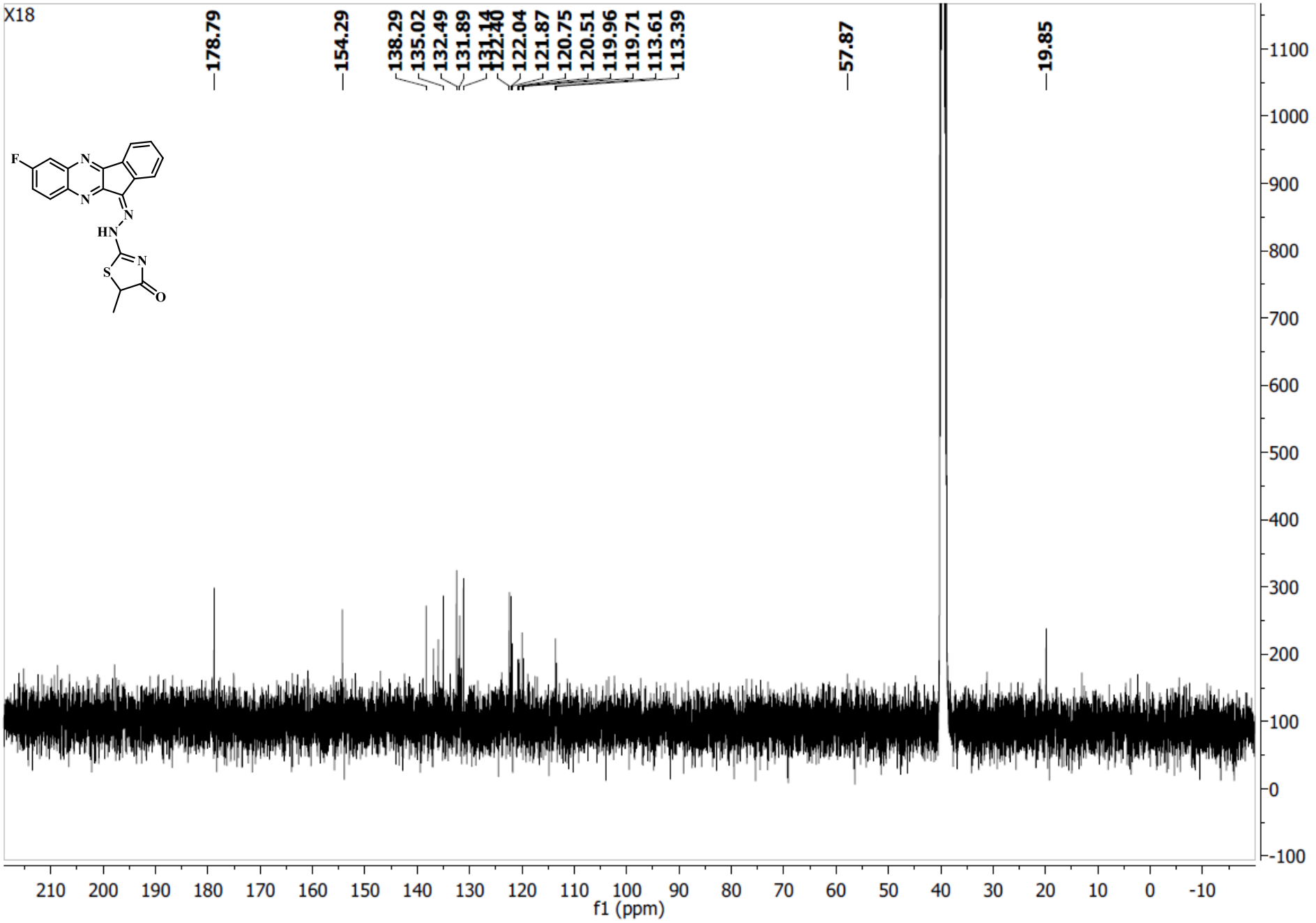
15: IR


X18
% Transmittance
Wavenumbers (cm-1)
3448.46
3396.00
3275.43
3159.44
3060.14
2928.15
1722.74
1631.10
1610.83
1571.18
1504.76
1487.22
1462.06
1446.67
1396.90
1371.85
1336.34
1316.00
1279.16
1249.95
1200.75
1141.59
1117.81
1100.03
1084.40
1059.24
1026.73
1005.99
970.73
944.18
872.78
850.65
834.17
802.49
764.28
731.05
663.30
630.48
567.46
518.57
499.21
467.16
445.58
F
N
N
HN
N
S
O

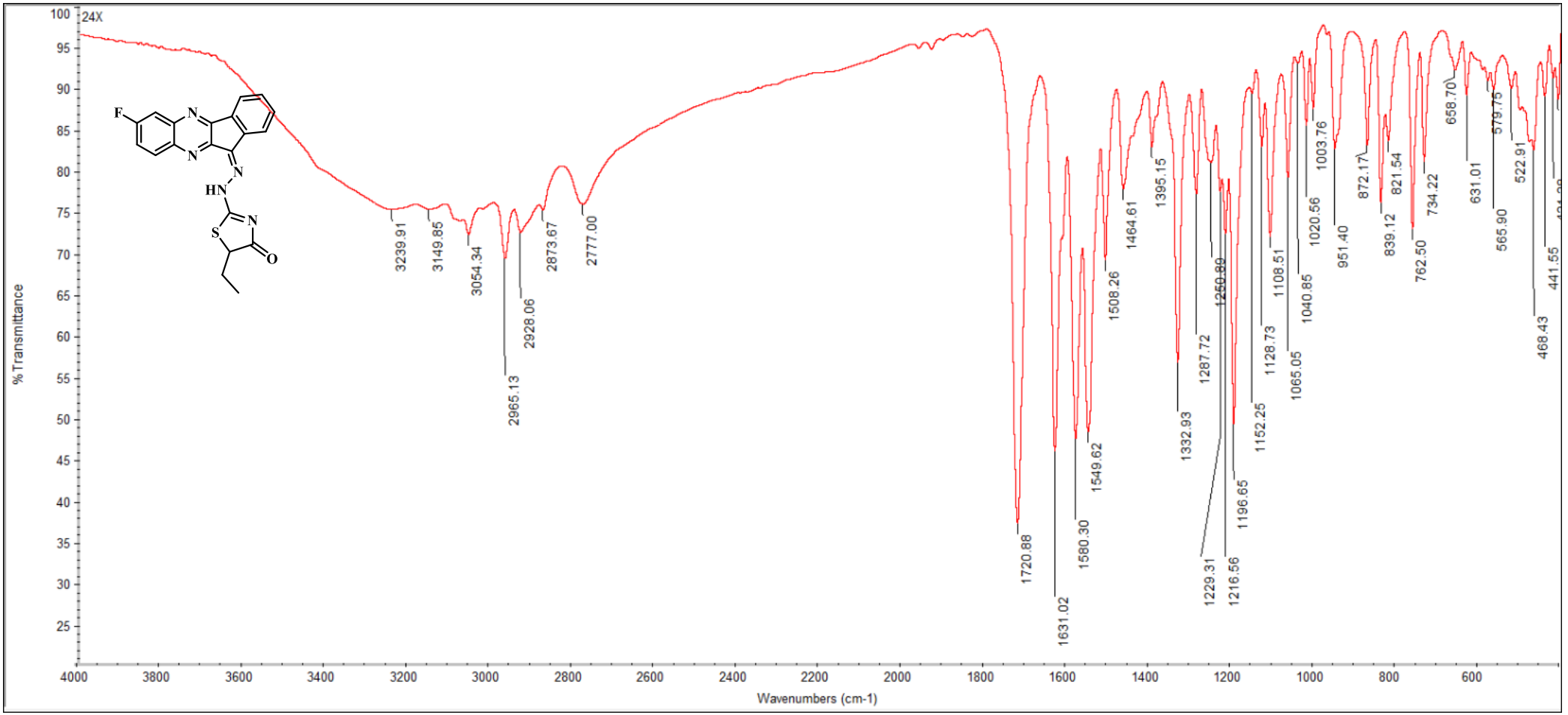
15: ^{1}H NMR


X18
8.84
8.29
8.28
8.27
8.26
8.21
8.19
8.17
8.10
8.08
8.01
7.99
7.93
7.66
7.64
7.58
7.56
3.84
3.82
3.81
1.47
1.45
F
N
N
N
HN
S
N
O
1.00
1.00
0.99
1.03
1.02
1.00
0.99
1.01
1.00
3.00
f1 (ppm)

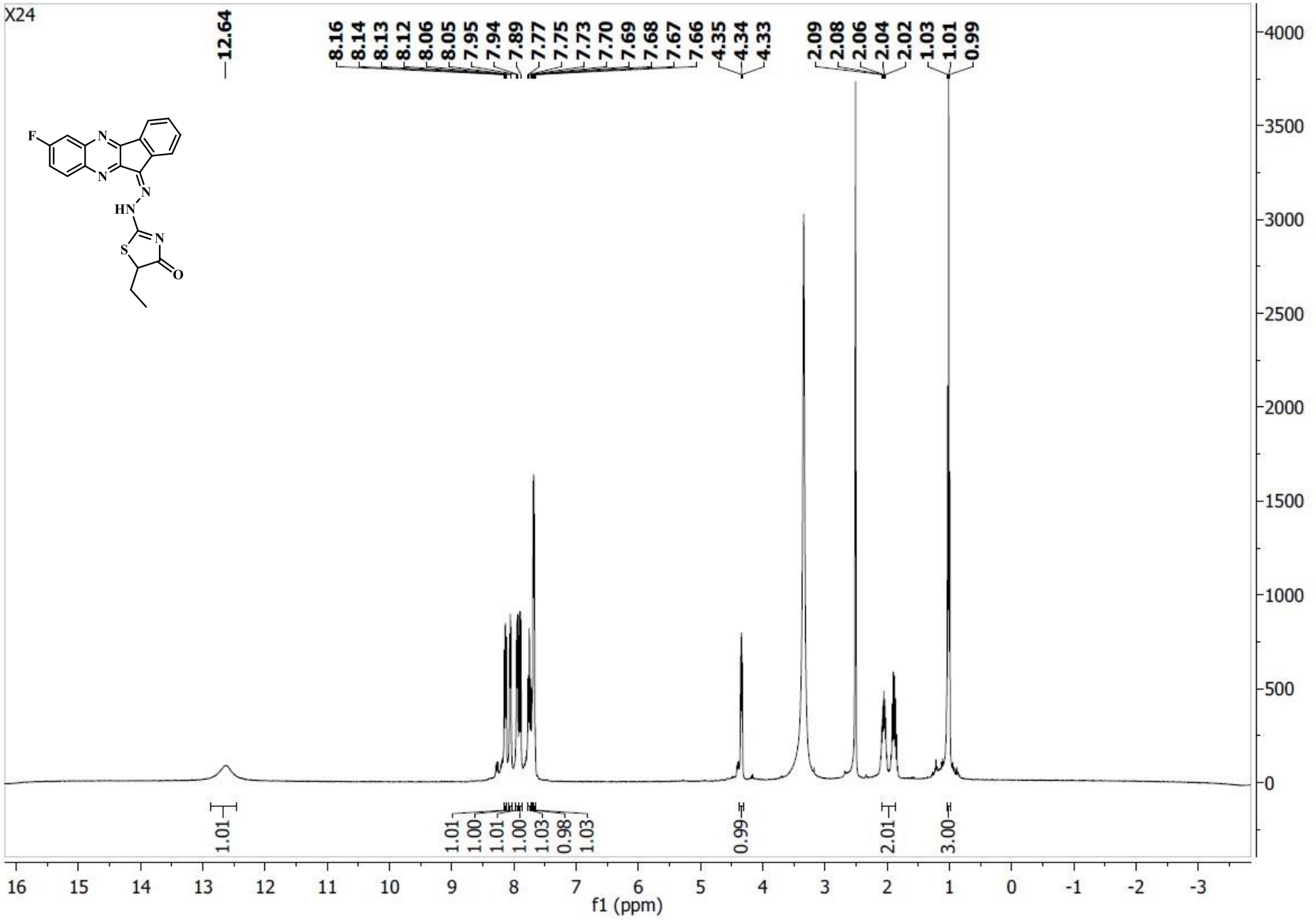
15: ^{13}C NMR


X18
178.79
154.29
138.29
135.02
132.49
131.89
131.14
122.40
122.04
121.87
120.75
120.51
119.96
119.71
113.61
113.39
57.87
19.85
F
N
N
N
HN
N
S
O
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)

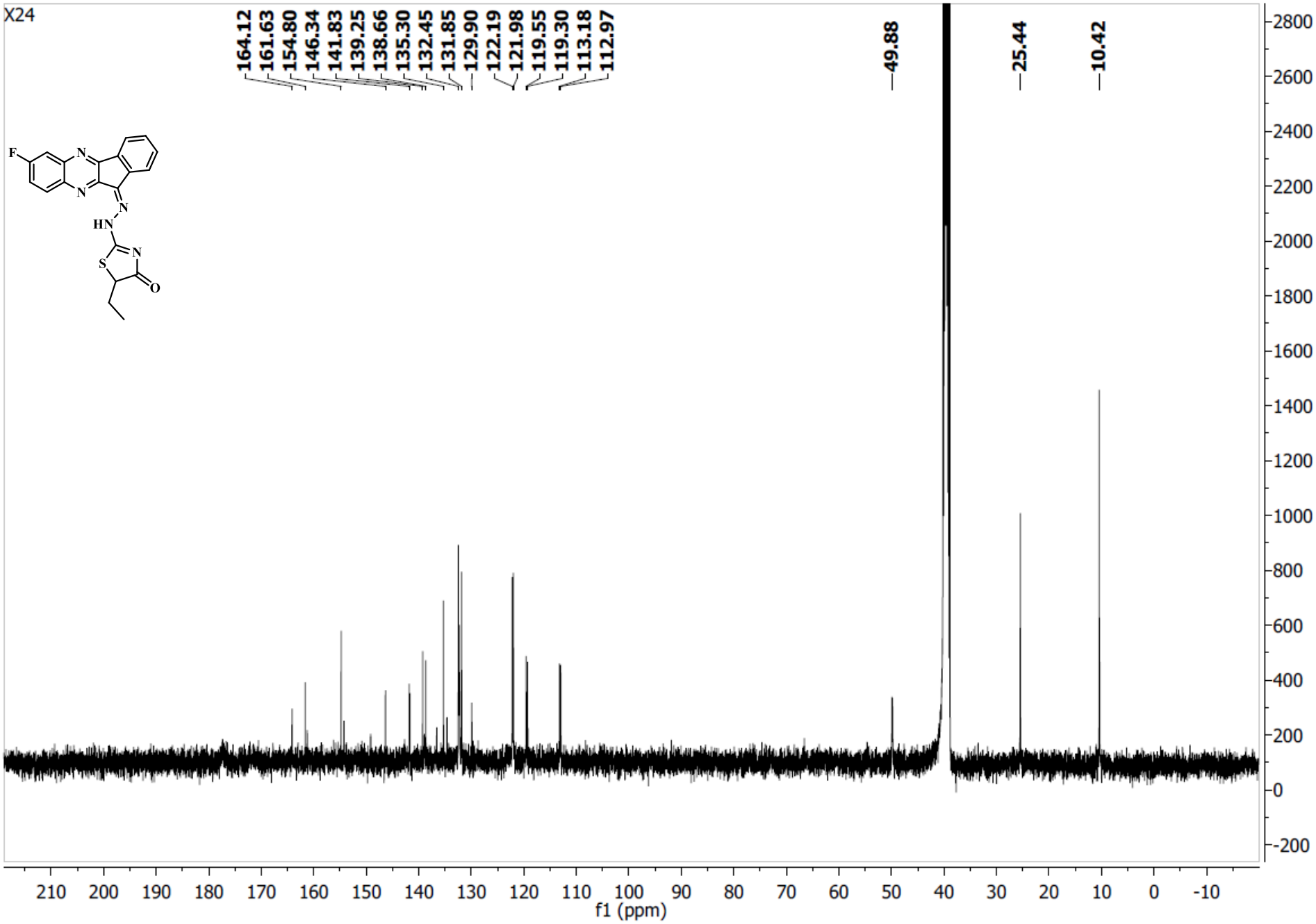
16: IR


24X
% Transmittance
Wavenumbers (cm-1)
3239.91
3149.85
3054.34
2965.13
2928.06
2873.67
2777.00
1720.88
1631.02
1580.30
1549.62
1508.26
1464.61
1395.15
1332.93
1287.72
1250.89
1229.31
1216.56
1196.65
1152.25
1128.73
1108.51
1065.05
1040.85
1020.56
1003.76
951.40
872.17
839.12
821.54
762.50
734.22
658.70
631.01
579.75
565.90
522.91
468.43
441.55
F
N
N
HN
N
S
O

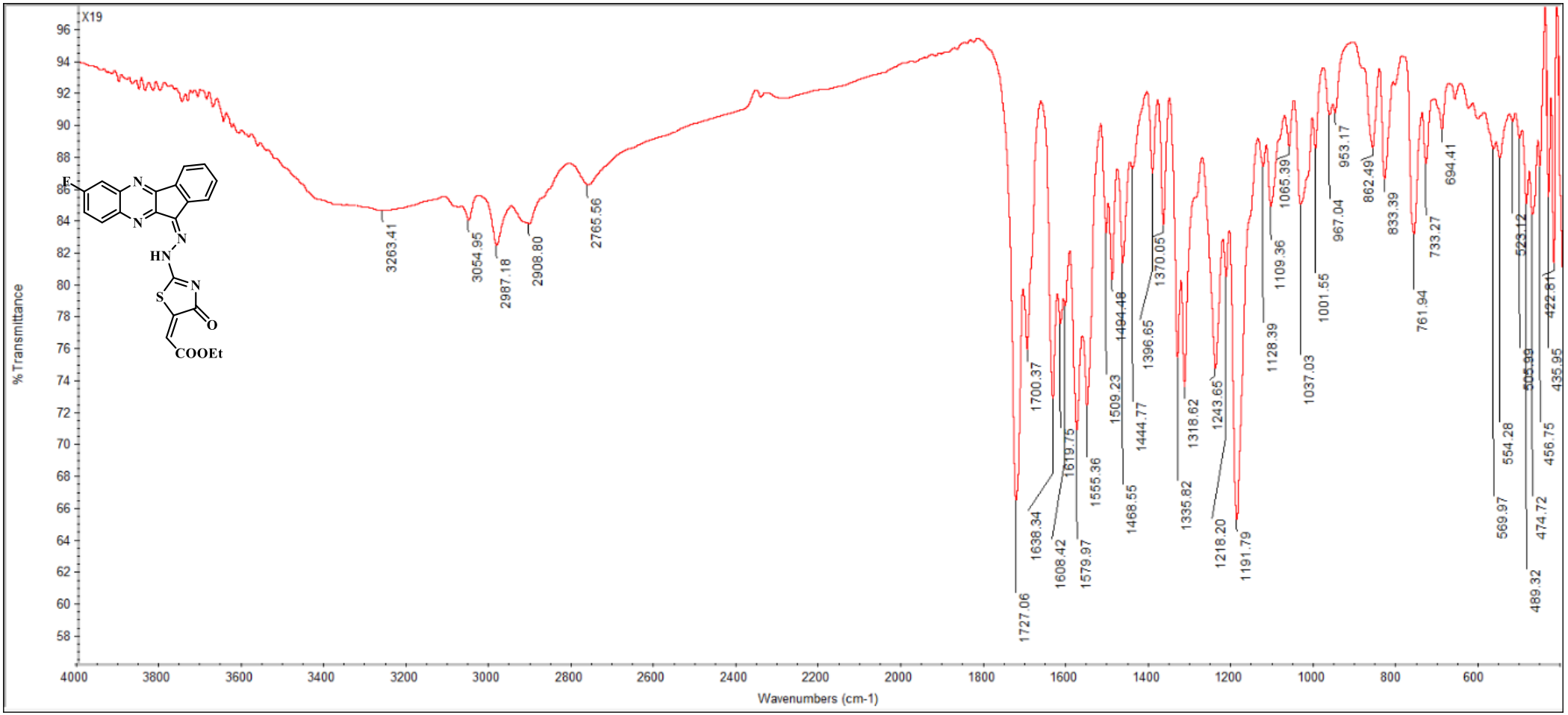
16: ^{1}H NMR


X24
12.64
8.16
8.14
8.13
8.12
8.06
8.05
7.95
7.94
7.89
7.77
7.75
7.73
7.70
7.69
7.68
7.67
7.66
4.35
4.34
4.33
2.09
2.08
2.06
2.04
2.02
1.03
1.01
0.99
F
N
N
N
HN
S
N
O
1.01
1.01
1.00
1.01
1.00
1.03
0.98
1.03
0.99
2.01
3.00
f1 (ppm)

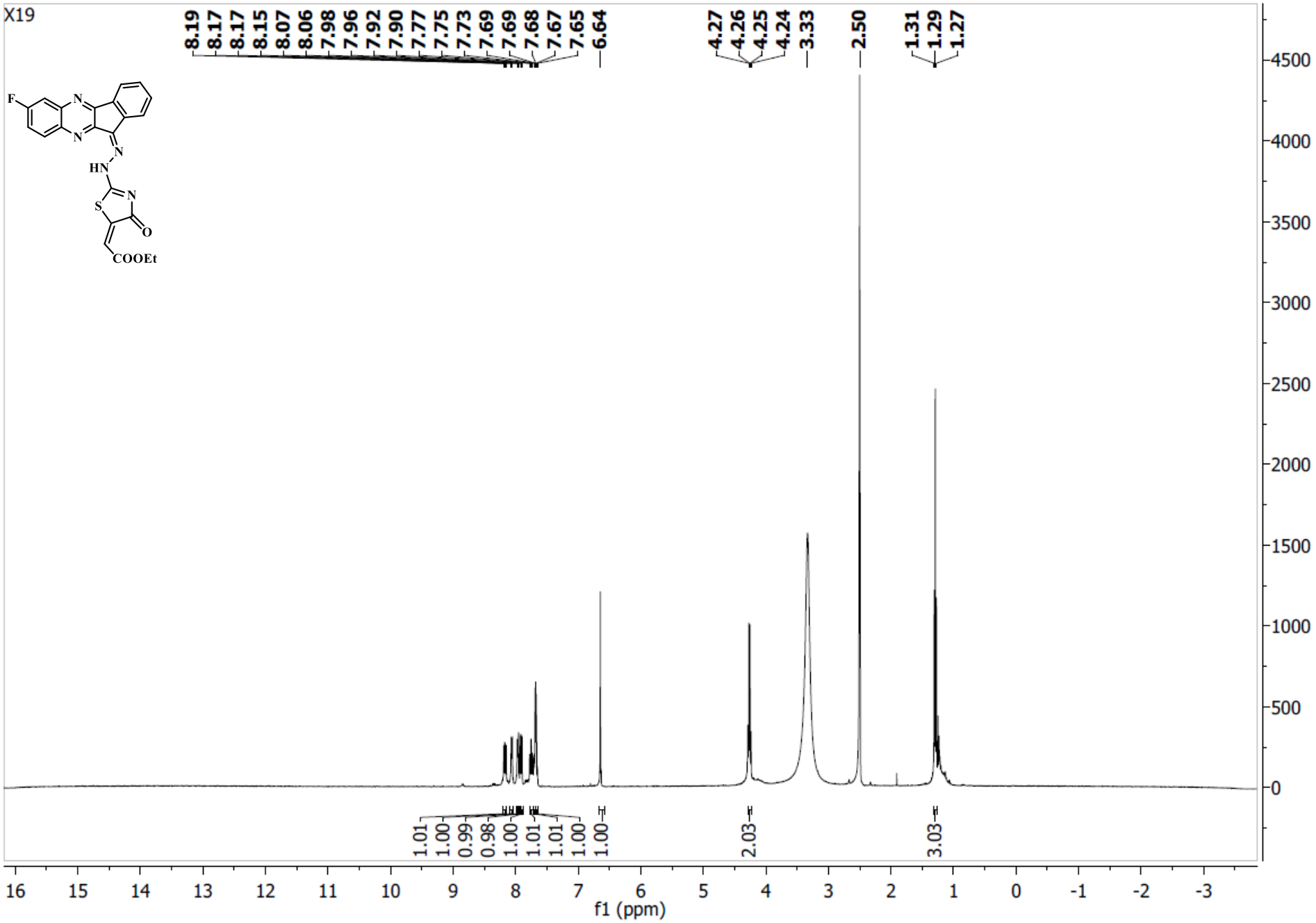
16: ^{13}C NMR


X24
164.12
161.63
154.80
146.34
141.83
139.25
138.66
135.30
132.45
131.85
129.90
122.19
121.98
119.55
119.30
113.18
112.97
49.88
25.44
10.42
F
N
N
N
HN
S
N
O
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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)

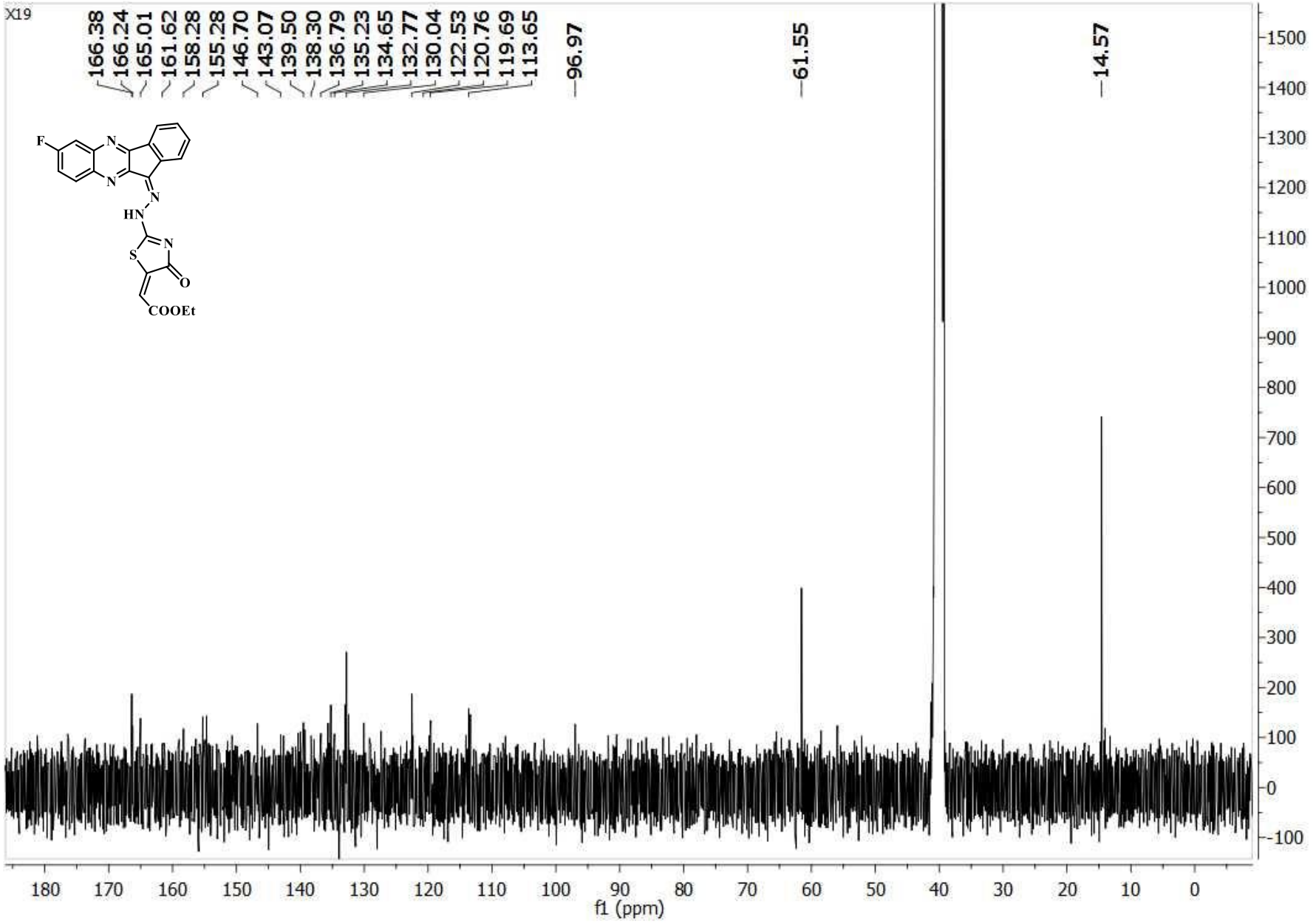
17: IR


X19
% Transmittance
Wavenumbers (cm-1)
3263.41
3054.95
2987.18
2908.80
2765.56
1727.06
1700.37
1638.34
1608.42
1619.75
1579.97
1555.36
1509.23
1494.48
1488.55
1444.77
1396.65
1370.05
1335.82
1318.62
1243.65
1218.20
1191.79
1128.39
1109.36
1065.39
1037.03
1001.55
967.04
953.17
862.49
833.39
761.94
733.27
694.41
569.97
554.28
523.12
505.99
489.32
474.72
456.75
435.95
422.81
F
N
N
HN
N
S
O
COOEt

17: ^{1}H NMR

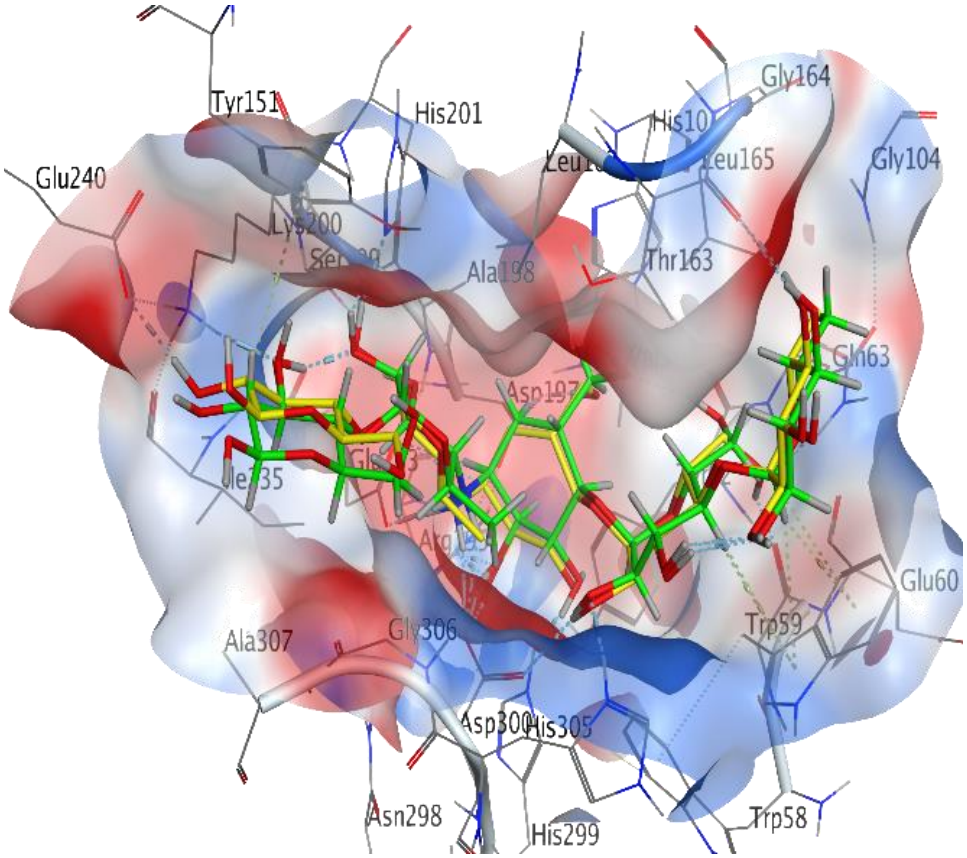

X19
8.19
8.17
8.17
8.15
8.07
8.06
7.98
7.96
7.92
7.90
7.77
7.75
7.73
7.69
7.69
7.68
7.67
7.65
6.64
4.27
4.26
4.25
4.24
3.33
2.50
1.31
1.29
1.27
F
N
N
N
HN
S
N
O
COOEt
1.01
1.00
0.99
0.98
1.00
1.01
1.01
1.00
1.00
2.03
3.03
4500
4000
3500
3000
2500
2000
1500
1000
500
0
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)

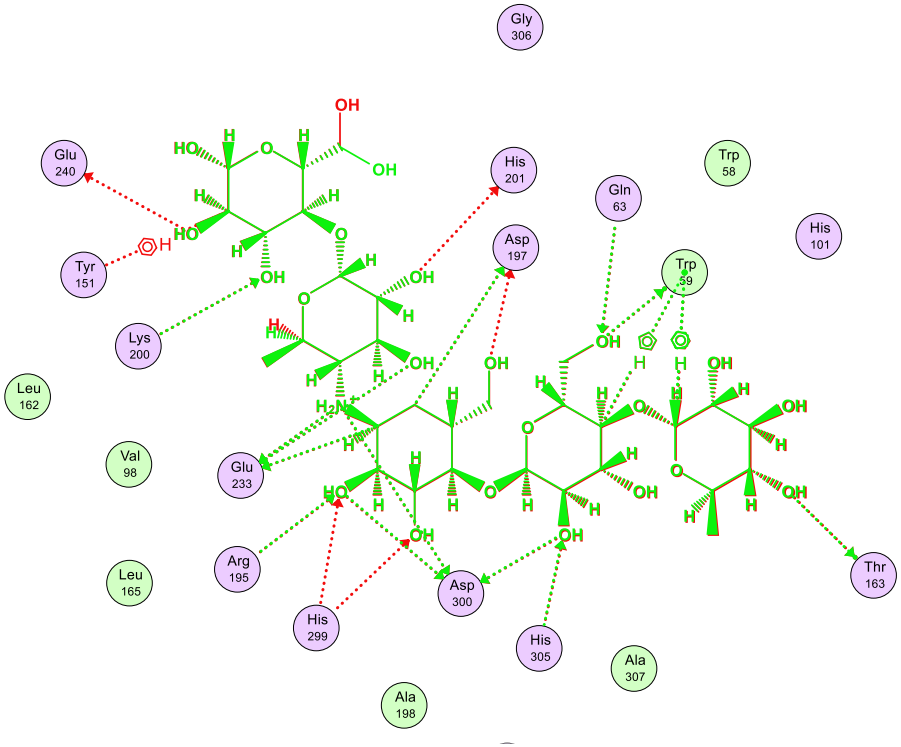
17: ^{13}C NMR


X19
166.38
166.24
165.01
161.62
158.28
155.28
146.70
143.07
139.50
138.30
136.79
135.23
134.65
132.77
130.04
122.53
120.76
119.69
113.65
96.97
61.55
14.57
F
N
N
HN
N
S
O
COOEt
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Docking Studies

A)





B)

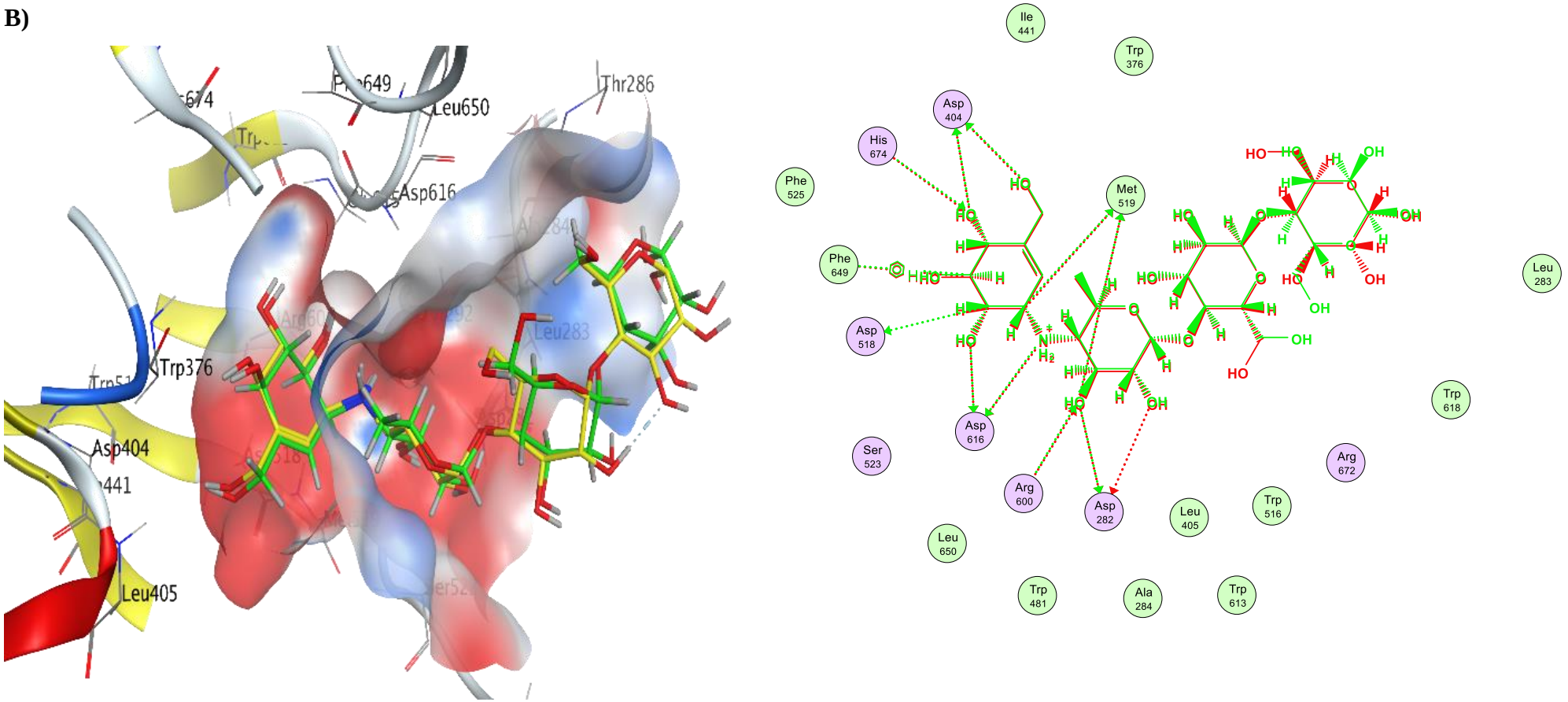
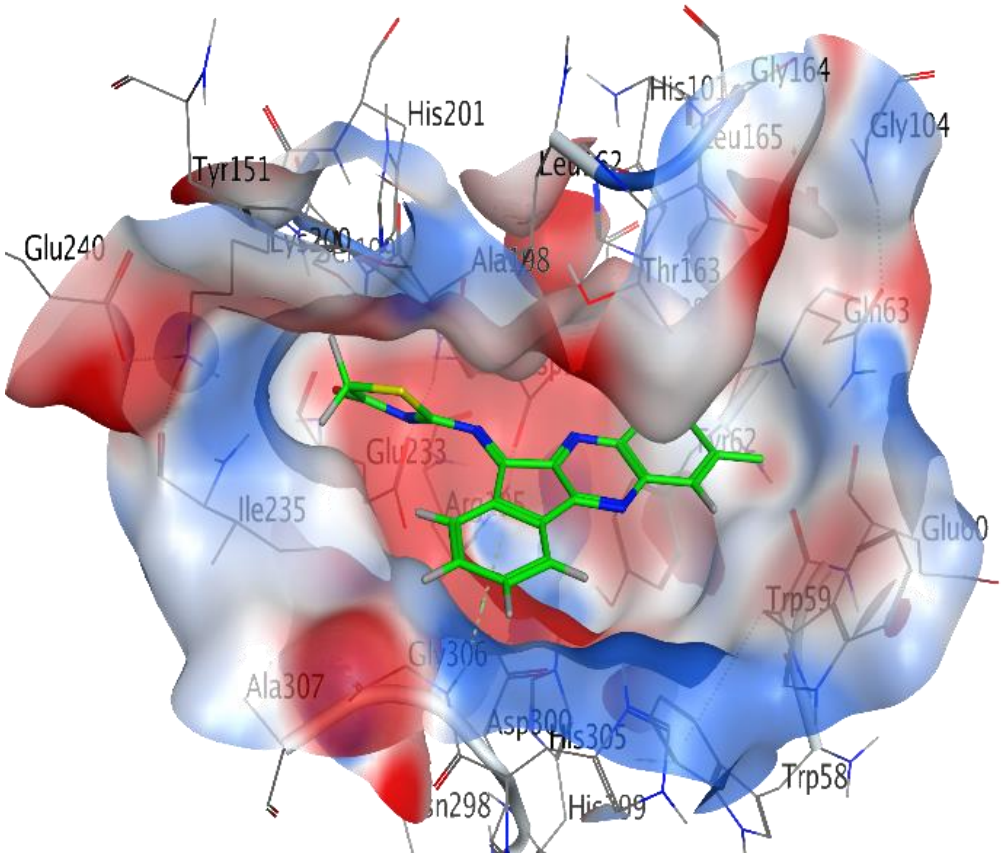
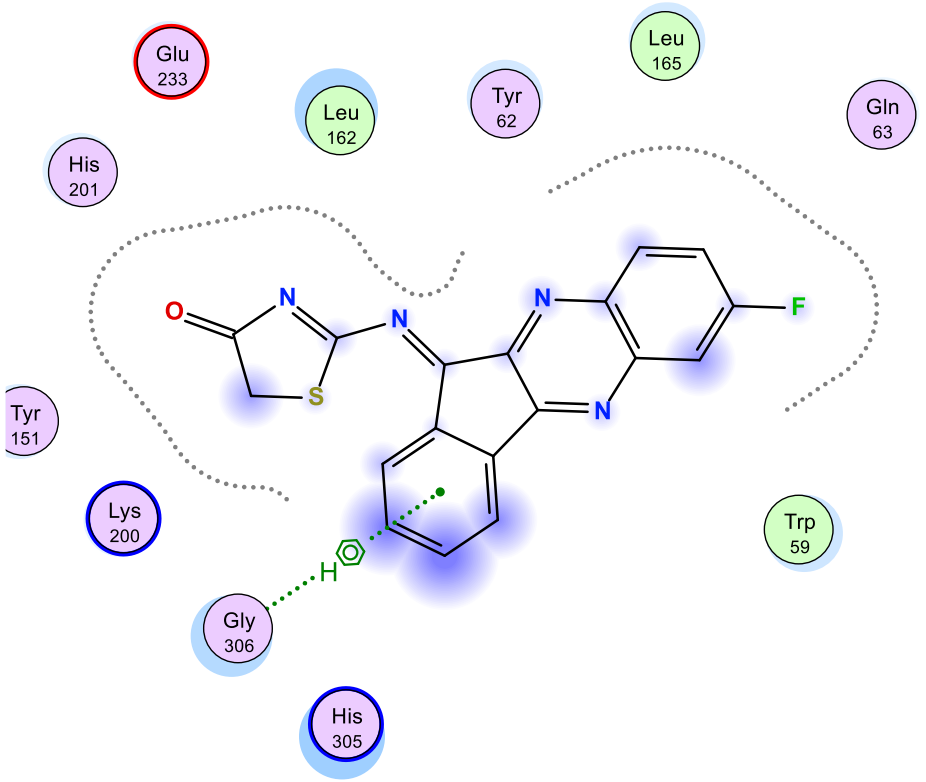


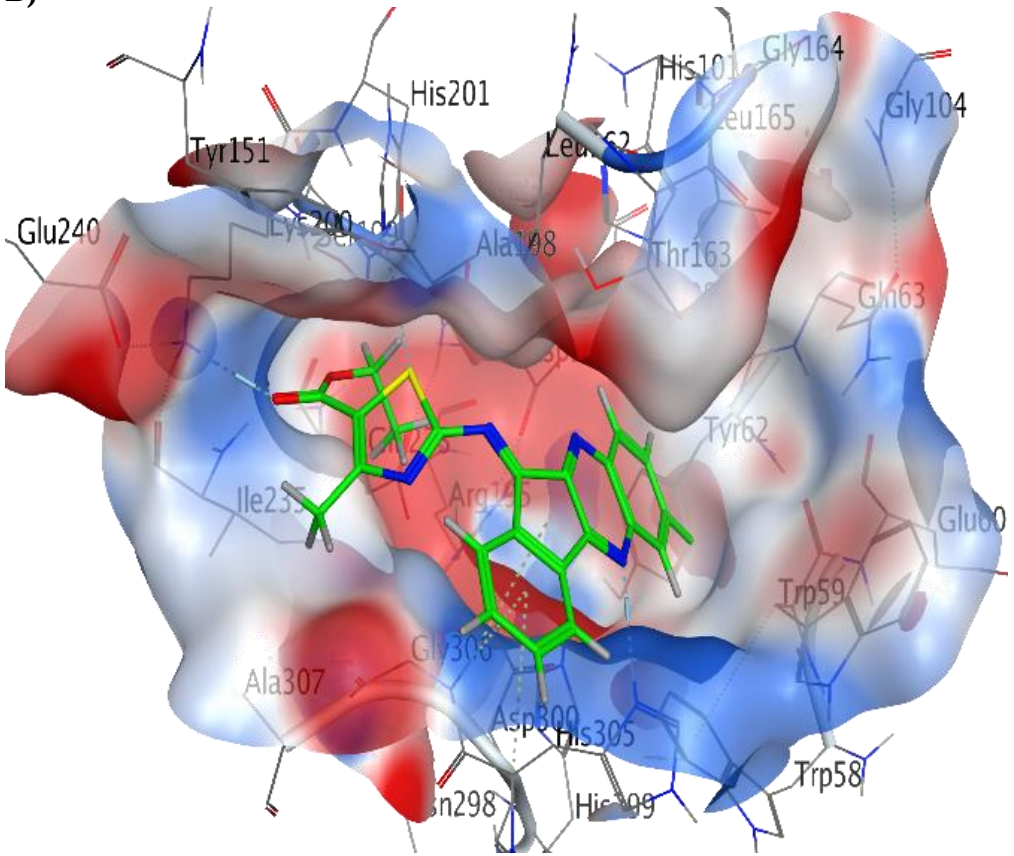
Figure 3: A) Overlay between co-crystallized ligand (yellow) and re-docked pose (green) of Acarbose (RMSD= 0.66 Å) in α-amylase (PDB ID: 1B2Y), complex overlay and ligand interactions. B) Overlay between co-crystallized ligand (yellow) and re-docked pose (green) of Acarbose (RMSD= 0.56 Å) in α-glucosidase (PDB ID: 5NN8), complex overlay and ligand interactions.

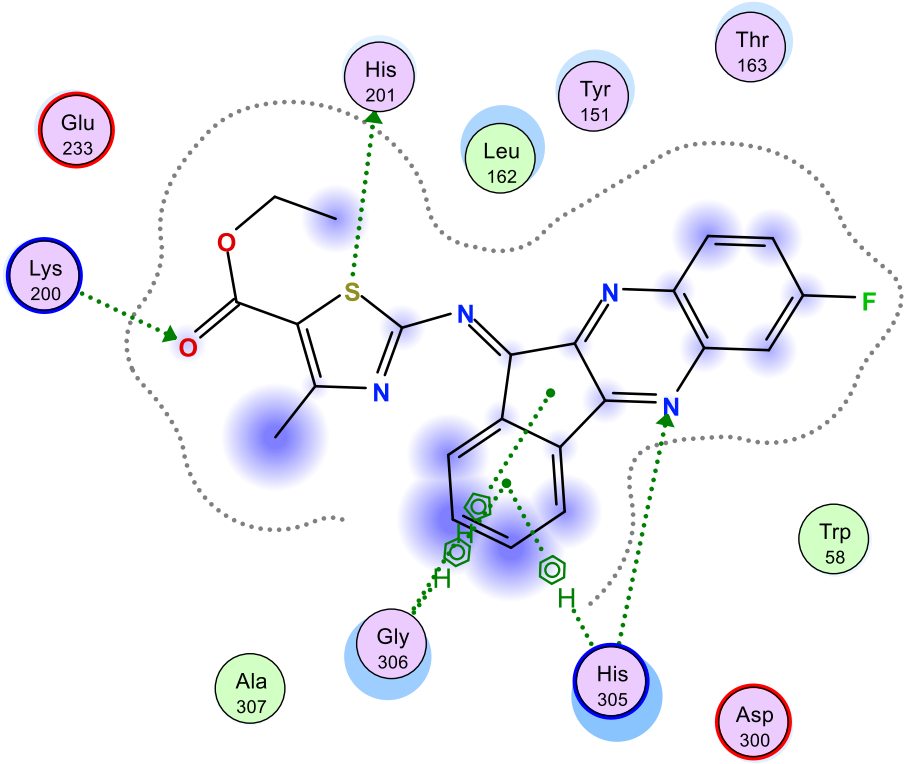
A)


His201
Tyr151
Glu240
Gly164
Gly104
Thr163
Glu233
Ile235
Trp59
Ala307
Asp300
His305
Trp58

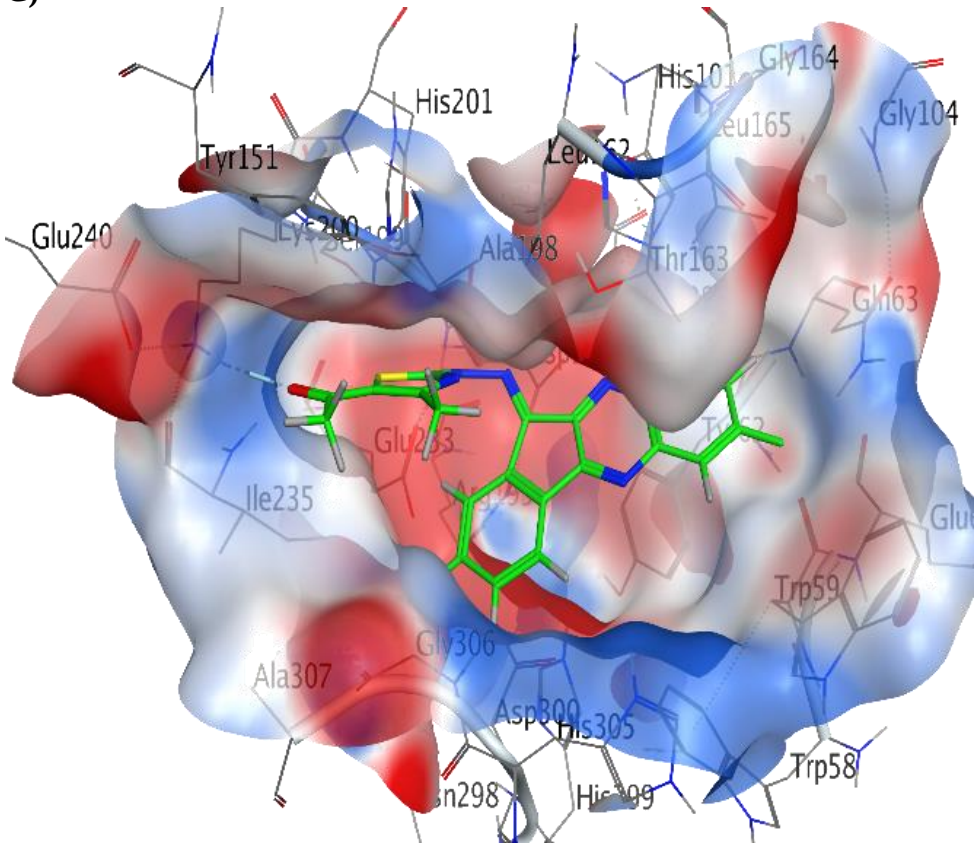

Glu 233
Leu 165
Leu 162
Tyr 62
Gln 63
His 201
Tyr 151
Lys 200
Trp 59
Gly 306
His 305
O
N
N
N
N
S
F
H

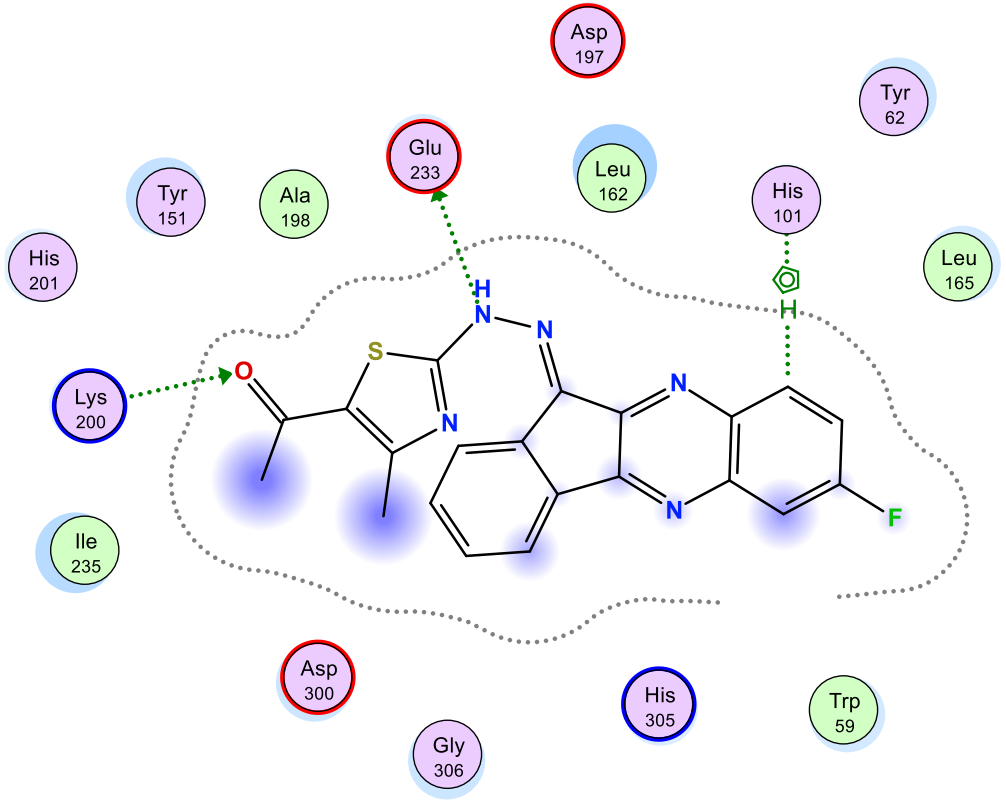
B)


His201
Tyr151
Glu240
Gly164
Gly104
Thr163
Gln63
Tyr62
Trp59
Trp58
Ala307
His305


Glu 233
His 201
Tyr 151
Thr 163
Leu 162
Lys 200
Trp 58
Gly 306
Ala 307
His 305
Asp 300
O
S
N
F
H

C)


His201
Tyr151
Glu240
Gly164
Gly104
Thr163
Glu233
Ile235
Trp59
Gly306
Ala307
Asp300
His305
Trp58


Asp 197
Tyr 62
Glu 233
Leu 162
Tyr 151
Ala 198
His 101
His 201
Leu 165
Lys 200
Ile 235
Asp 300
His 305
Trp 59
Gly 306
S
N
O
F
H

D)

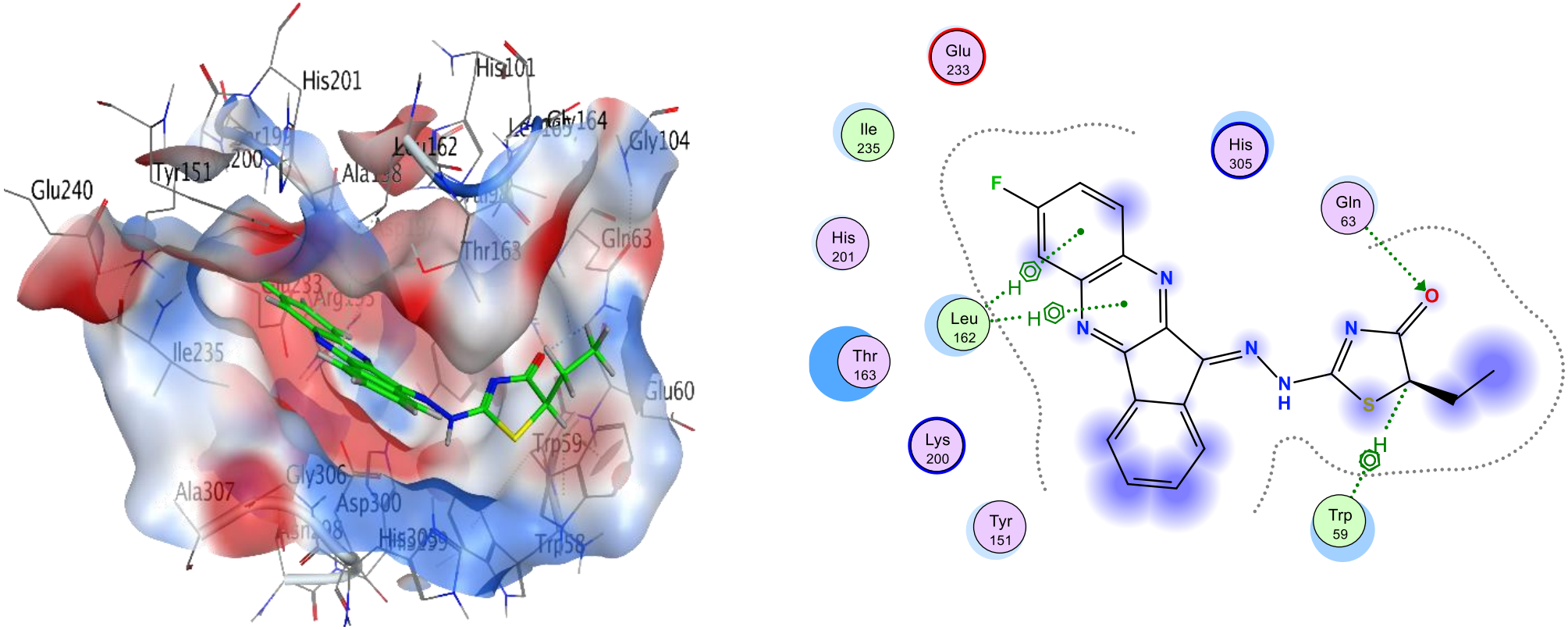
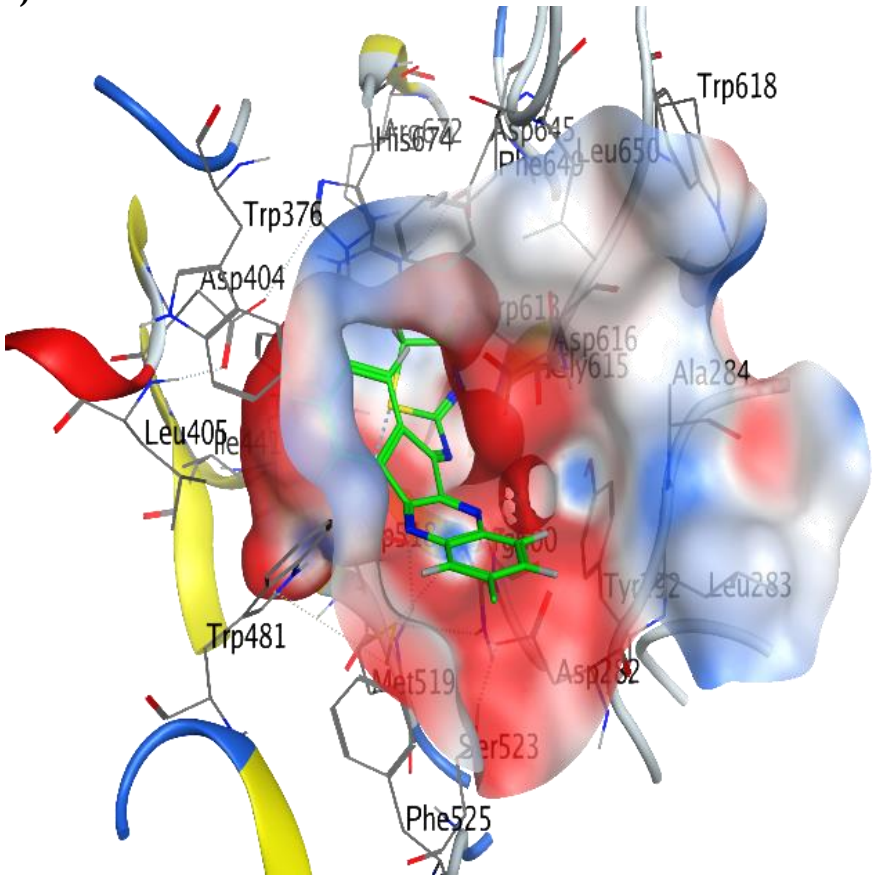
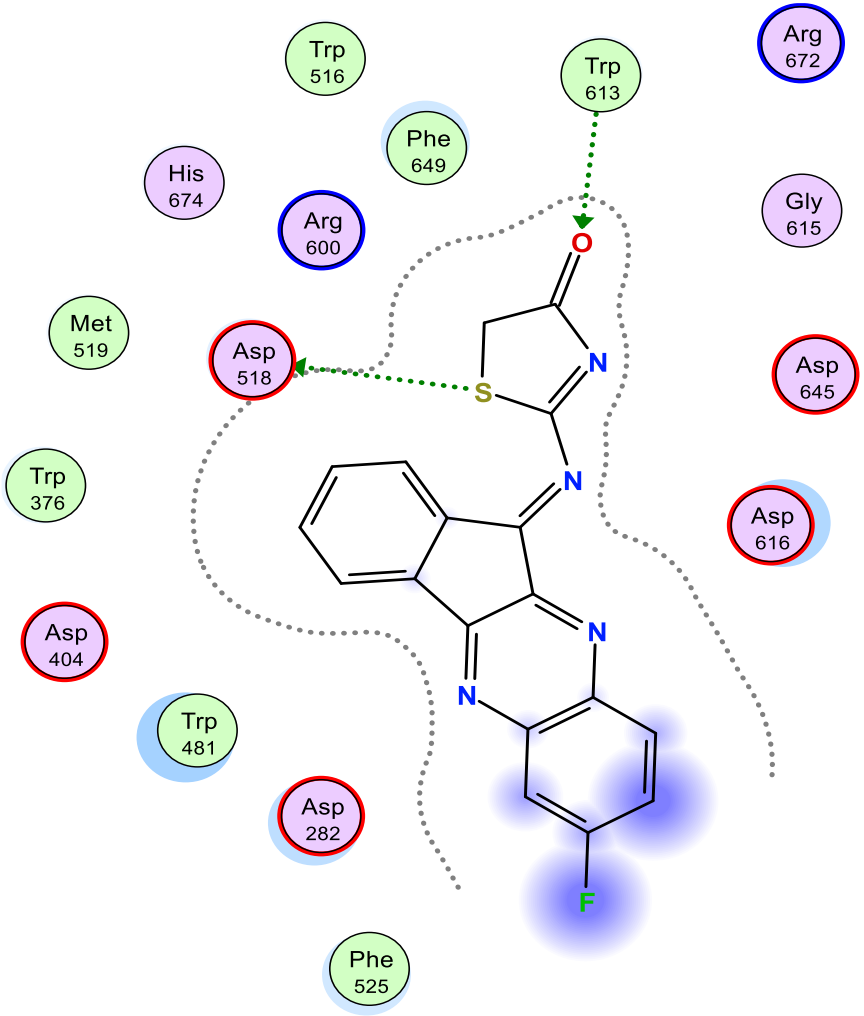


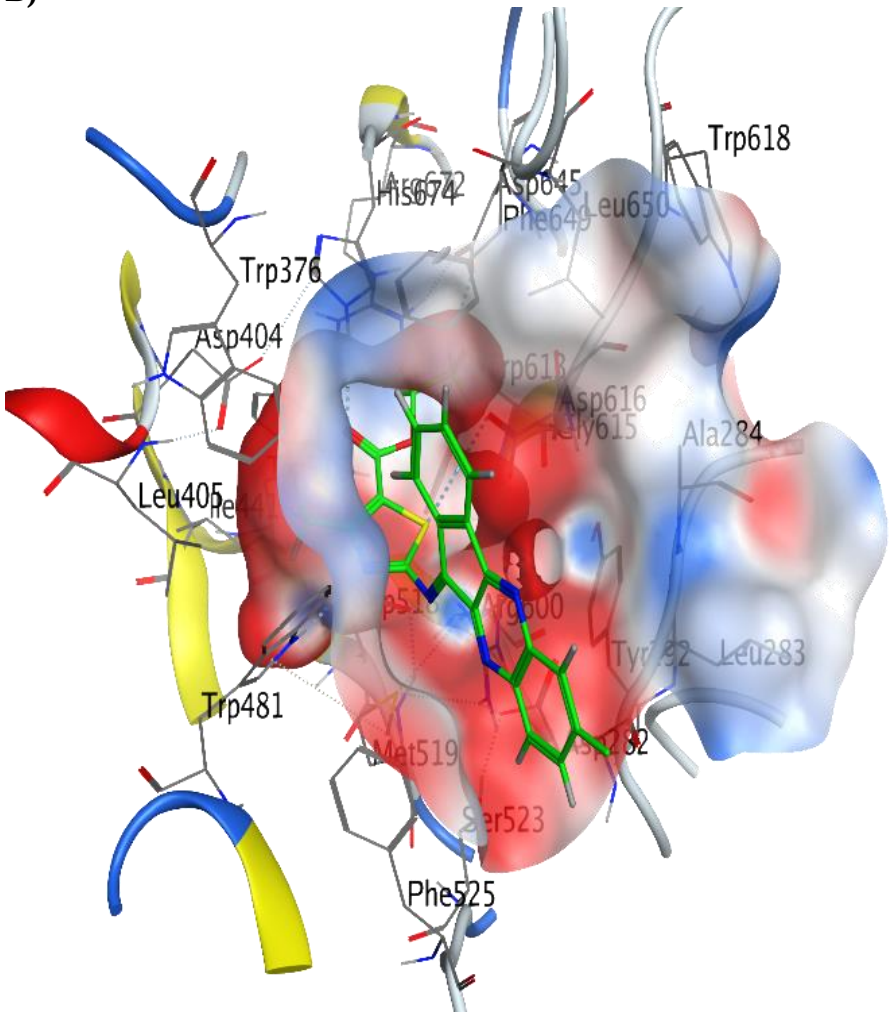
Figure 4: 3D binding modes & 2D ligand interactions with *α*-amylase (PDB ID: 1B2Y) of the most active compounds, (A) Compound 4, (B) Compound 6, (C) Compound 8, (D) Compound 16

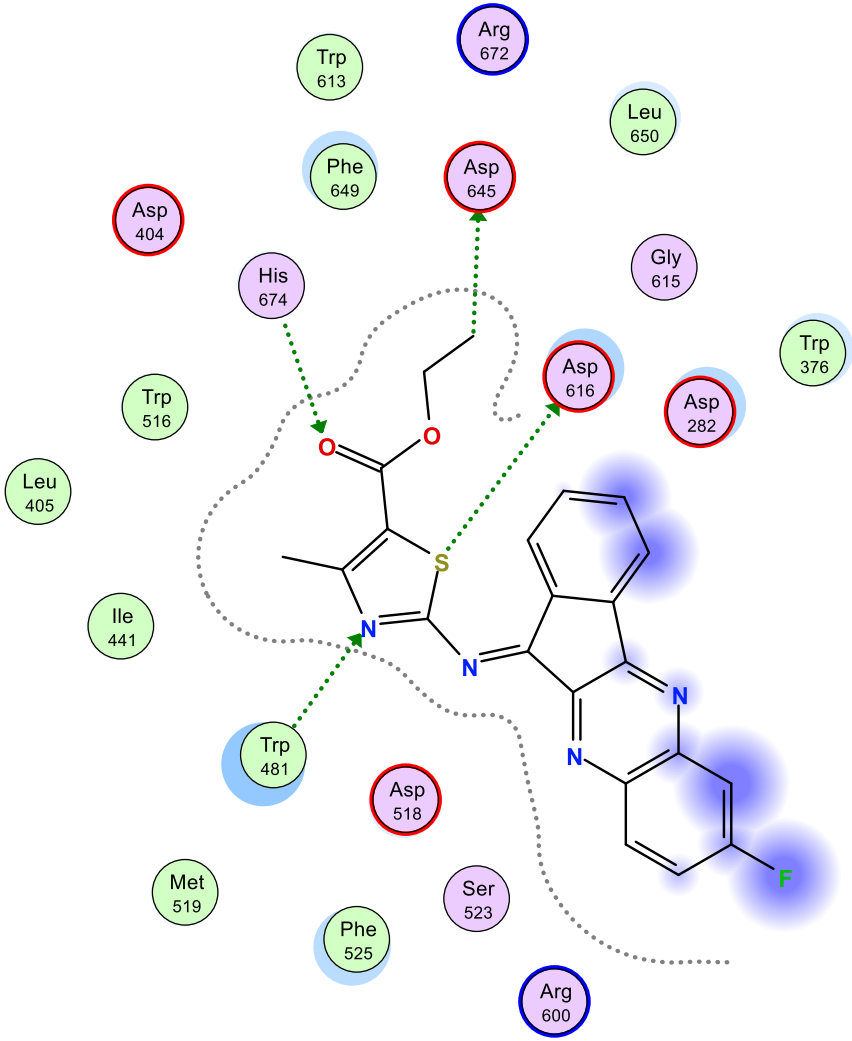
A)


Trp618
His674
Asp645
Leu650
Trp376
Asp404
Asp616
Ala284
Leu405
Tyr232
Leu283
Trp481
Met519
Asp282
Ser523
Phe525

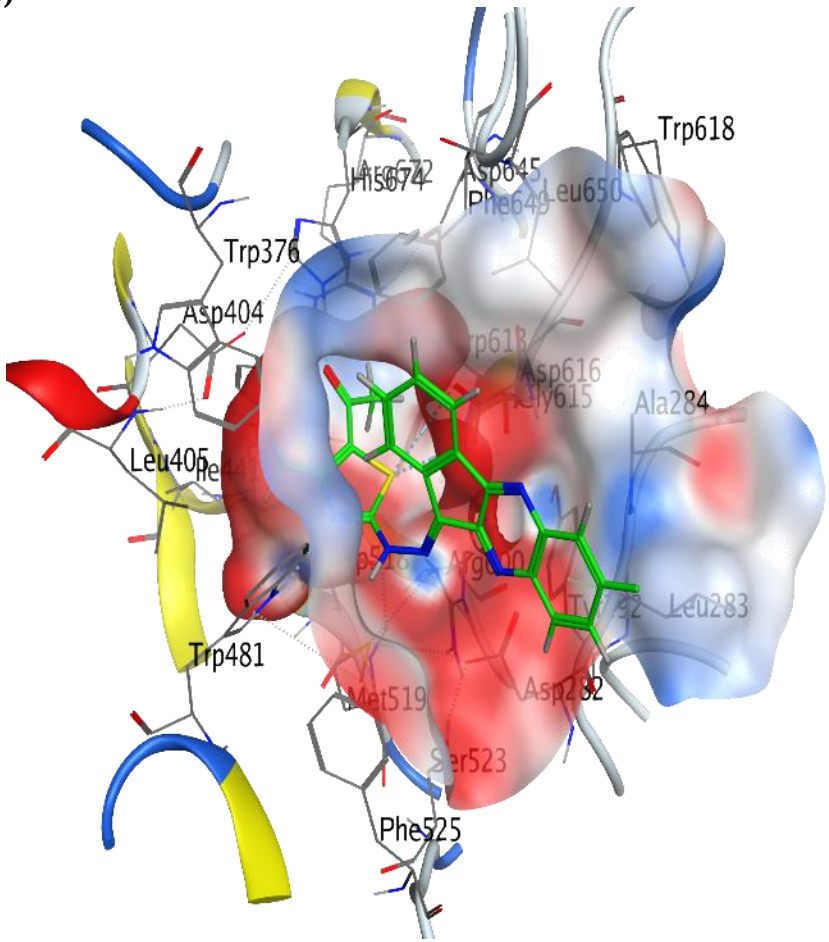

Trp 516
Trp 613
Arg 672
Phe 649
His 674
Arg 600
Gly 615
O
Met 519
Asp 518
N
Asp 645
S
Trp 376
N
Asp 616
N
Asp 404
N
Trp 481
Asp 282
F
Phe 525

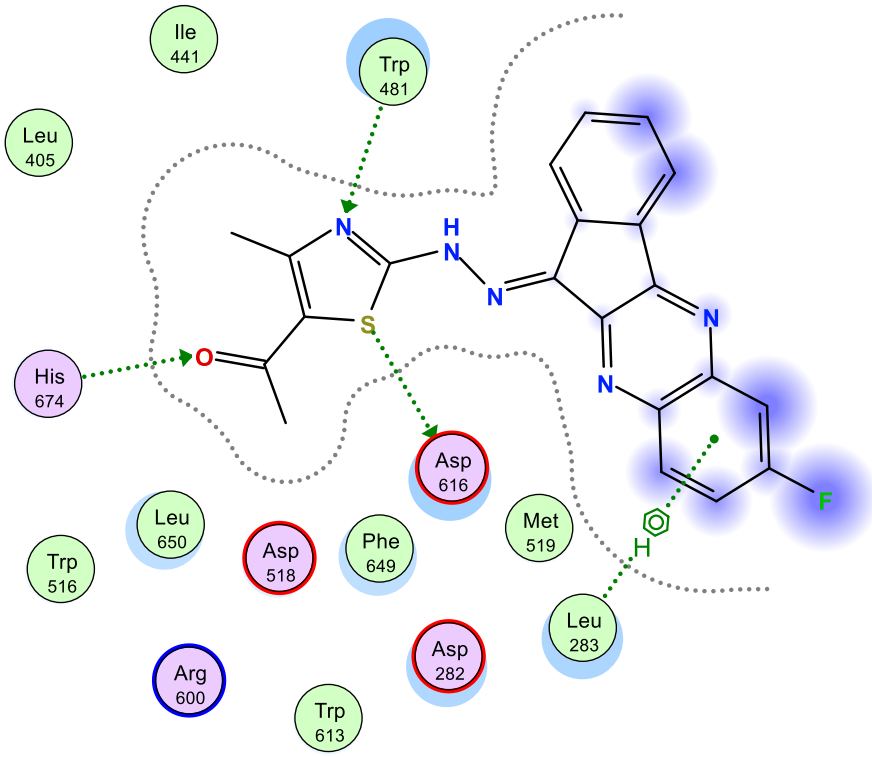
B)


Trp618
His674
Asp645
Leu650
Trp376
Asp404
Asp616
Ala284
Leu405
Leu283
Trp481
Met519
Ser523
Phe525


Arg 672
Trp 613
Leu 650
Phe 649
Asp 645
Asp 404
His 674
Gly 615
Trp 376
Asp 616
Asp 282
Trp 516
Leu 405
Ile 441
Trp 481
Asp 518
Met 519
Ser 523
Phe 525
Arg 600
O
O
S
N
N
N
N
F

C)


Trp618
Trp376
Asp404
Leu405
Trp481
Met519
Phe525
Asp616
Ala284
Leu283


Ile 441
Trp 481
Leu 405
His 674
Asp 616
Leu 650
Asp 518
Phe 649
Met 519
Trp 516
Leu 283
Asp 282
Arg 600
Trp 613
F

D)

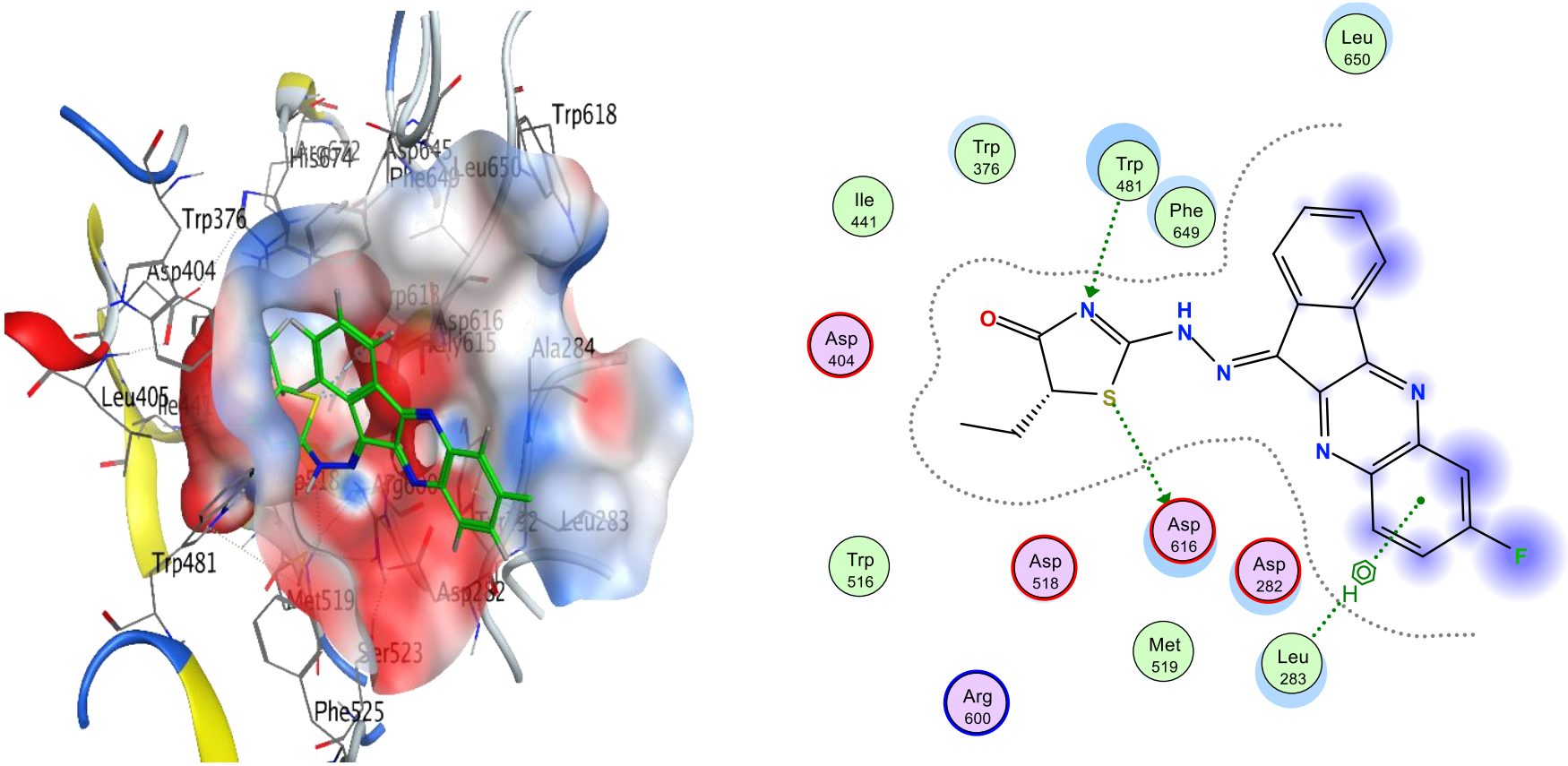


Figure 5: 3D binding modes & 2D ligand interactions with *α*-glucosidase (PDB ID: 5NN8) of the most active compounds, (A) Compound 4, (B) Compound 6, (C) Compound 8, (D) Compound 16