Supplementary Information

Potent oxazolidinone antibacterials with heteroaromatic C-ring substructure

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List of Contents

Experimental

Chemistry

Melting points were determined with a Yanagimoto micro melting point apparatus (hot plate) and are uncorrected. Elemental analyses are within ±0.4 % of the theoretical values and were determined on a Yanaco CHN MT-5 instrument. Low-resolution mass spectra with electron ionization (EI-LRMS) and high-resolution mass spectra with electron ionization (EI-HRMS) were recorded on a JEOL JMS-AX505HA. Low-resolution mass spectra with electrospray ionization (ESI-LRMS) were recorded on a Waters 3100 Mass Detector. High-resolution mass spectra with electrospray ionization (ESI-HRMS) were recorded on a Thermo Fisher Scientific LTQ-Orbitrap. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were measured with a Varian Mercury at 300 MHz and at 75 MHz, respectively. The chemical shifts are recorded in ppm, and coupling constants (J) in Hz. ^{1}H NMR and ^{13}C NMR chemical shifts are relative to that of either tetramethylsilane (0.00 ppm for ^{1}H NMR in $CDCl_3$ or $CD_3OD/CDCl_3$) or residual solvent (77.00 ppm for ^{13}C NMR in $CDCl_3$ or $CD_3OD/CDCl_3$, 2.49 ppm for ^{1}H NMR in DMSO-d_6, and 39.50 ppm for ^{13}C NMR in DMSO-d_6). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br; broad peak. Column chromatography was carried out with silica gel [Fuji Davison BW200] as the absorbent. Thin layer chromatography (TLC) was carried out on Merck Silica gel 60 PF_{254}. Solutions were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate and the solvent was removed by rotary evaporation under reduced pressure.

Synthesis of known compounds.

Known compounds **6-12** and **19** were synthesized in accordance with previous reports[1-8].

(*S*)-(*N*-3-(3-Fluoro-4-(3,3,4,4-tetramethylborolan-1-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl acetamide (6)[1]: Pale brown amorphous powder; ^{1}H NMR (300 MHz, $CDCl_3$): 1.35 (12H, s, $(C\underline{H}_3)_2C$-$C(C\underline{H}_3)_2$), 2.02 (3H, s, $C\underline{H}_3$-C=O), 3.62-3.70 (2H, m, -$C\underline{H}_2$-NH-C=O), 3.80 (1H, dd, J = 7.0, 9.1 Hz, oxazolidinone-H4), 4.06 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.75-4.86 (1H, m, oxazolidinone-H5), 6.71 (1H, br t, J = 6 Hz, -N$\underline{H}$-C=O), 7.18 (1H, dd, J = 1.8, 8.2 Hz, phenyl-H6), 7.37 (1H, dd, J = 1.8, 11.4 Hz, phenyl-H2), and 7.71 (1H, t, J = 8.2 Hz, phenyl-H5); ^{13}C NMR (75 MHz, $CDCl_3$): 22.94 (1C), 24.77 (4C), 41.83 (1C), 47.34 (1C), 72.13 (1C), 83.87 (2C), 104.99 (1C, d, $J_{C\text{-}F}$ = 29.9 Hz), 112.58 (1C), 137.53 (1C, d, $J_{C\text{-}F}$ = 10.0 Hz), 142.19 (1C, d, $J_{C\text{-}F}$ = 11.6 Hz), 154.11 (1C), 167.59 (1C, d, $J_{C\text{-}F}$ = 251 Hz), and 171.37 (1C), *carbon attached to boron not observed*; EI-LRMS (m/z): 378 (M^+).

6-Bromopyrazolo[1,5-a]pyridine (7)[2]**:** ^{1}H NMR (300 MHz, $CDCl_3$): 6.51 (1H, d, J = 2.1 Hz, C_3-H), 7.13 (1H, dd, J = 1.8, 9.4 Hz, C_5-H), 7.40 (1H, d, J = 9.4 Hz, C_4-H), 7.91 (1H, d, J = 2.1 Hz, C_2-H), and 8.61 (1H, d, J = 1.8 Hz, C_7-H); ^{13}C NMR (75 MHz, $CDCl_3$): 97.55 (1C), 106.03 (1C), 118.38 (1C), 126.58 (1C), 128.78 (1C), 138.42 (1C), and 142.13 (1C); EI-LRMS (m/z): 196 (M^+).

6-Bromoimidazo[1,5-a]pyridine (8)[3]**:** ^{1}H NMR (300 MHz, $CDCl_3$): 6.74 (1H, dd, J = 1.5, 9.7 Hz, C_7-H), 7.33 (1H, d, J = 9.7 Hz, C_8-H), 7.44 (1H, s, C_1-H), 8.06 (1H, s, C_3-H), and 8.08 (1H, d, J = 1.5 Hz, C_5-H); ^{13}C NMR (75 MHz, $CDCl_3$): 108.13 (1C), 118.85 (1C), 121.15 (1C), 121.91 (1C), 122.56 (1C), 127.58 (1C), and 128.53 (1C); EI-LRMS (m/z): 196 (M^+).

6-Bromoimidazo[1,2-a]pyridine (9)[4]**:** ^{1}H NMR (300 MHz, $CDCl_3$): 7.21 (1H, dd, J = 1.8, 9.7 Hz, C_7-H), 7.51 (1H, d, J = 9.7 Hz, C_8-H), 7.55 (1H, s, C_2 or C_3-H), 7.64 (1H, s, C_2 or C_3-H), and 8.28 (1H, d, J = 1.8 Hz, C_5-H); ^{13}C NMR (75 MHz, $CDCl_3$): 106.87 (1C), 112.50 (1C), 118.42 (1C), 125.70 (1C), 127.65 (1C), 134.33 (1C), and 143.79 (1C); EI-LRMS (m/z): 196 (M^+).

7-Bromoimidazo[1,2-a]pyridine (10)[5]**:** ^{1}H NMR (300 MHz, $CDCl_3$): 6.87 (1H, dd, J = 1.8, 7.0 Hz, C_6-H), 7.56 (1H, s, C_2 or C_3-H), 7.60 (1H, s, C_2 or C_3-H), 7.80 (1H, br s, C_8-H), and 7.99 (1H, d, J = 7.0 Hz, C_5-H); ^{13}C NMR (75 MHz, $CDCl_3$): 112.52 (1C), 116.08 (1C), 117.86 (1C), 119.98 (1C), 125.81 (1C), 134.24 (1C), and 145.46 (1C); EI-LRMS (m/z): 196 (M^+).

6-Bromo[1,2,4]triazolo[1,5-a]pyridine (11)[6]**:** ^{1}H NMR (300 MHz, $CDCl_3$): 7.62 (1H, dd, J = 2.0, 9.4 Hz, C_7-H), 7.68 (1H, dd, J = 0.9, 9.4 Hz, C_8-H), 8.34 (1H, s, C_2-H), and 8.77 (1H, dd, J = 0.9, 2.0 Hz, C_5-H); ^{13}C NMR (75 MHz, $CDCl_3$): 105.01 (1C), 108.17 (1C), 117.28 (1C), 128.94 (1C), 133.14 (1C), and 154.35 (1C); EI-LRMS (m/z): 197 (M^+).

7-Bromo[1,2,4]triazolo[1,5-a]pyridine (12)[7]**:** ^{1}H NMR (300 MHz, $CDCl_3$): 7.15 (1H, dd, J = 2.1, 7.3 Hz, C_6-H), 7.97 (1H, d, J = 2.1 Hz, C_8-H), 8.34 (1H, s, C_2-H), and 8.47 (1H, d, J = 7.3 Hz, C_5-H); ^{13}C NMR (75 MHz, $CDCl_3$): 117.86 (1C), 119.32 (1C), 123.74 (1C), 128.62 (1C), 151.08 (1C), and 154.64 (1C); EI-LRMS (m/z): 197 (M^+).

***(R)*-3-(3-Fluoro-4-(3,3,4,4-tetramethylborolan-1-yl)phenyl)-5-([1,2,3]triazol-1-yl)methyloxazolidin-2-one (19)**[8]**:** Pale brown amorphous powder; ^{1}H NMR (300 MHz, $CDCl_3$): 1.35 (12H, s, $(C\underline{H}_3)_2C$-$C(C\underline{H}_3)_2$), 3.92 (1H, dd, J = 6.2, 9.1 Hz, oxazolidinone-H4), 4.18 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.79 (2H, br s, -$C\underline{H}_2$-[1,2,3]triazole), 5.01-5.12 (1H, m, oxazolidinone-H5), 7.11 (1H, dd, J = 1.8, 8.2 Hz, phenyl-H6), 7.30 (1H, dd, J = 1.8, 11.6 Hz, phenyl-H2), 7.70 (1H, dd, J = 7.3, 8.2 Hz, phenyl-H5), 7.73 (1H, br s, [1,2,3]triazole-H), and 7.79 (1H, br s, [1,2,3]triazole-H); ^{13}C NMR (75 MHz, $CDCl_3$): 24.76 (4C), 47.10 (1C), 51.93 (1C), 70.51

(1C), 83.88 (2C), 105.08 (1C, d, J_{C-F} = 30.4 Hz), 112.61 (1C), 124.99 (1C), 134.42 (1C), 137.56 (1C, d, J_{C-F} = 10.0 Hz), 141.63 (1C, d, J_{C-F} = 11.1 Hz), 152.94 (1C), and 167.52 (1C, d, J_{C-F} = 251 Hz), *carbon attached to boron not observed*; EI-LRMS (m/z): 388 (M^+).

General procedure for the synthesis of compounds 13-18 and 20-23

To a stirred suspension of heteroaryl bromide **7-12** (0.844 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.028 mmol) in 1,4-dioxane (3 ml) and H_2O (1 ml) at ambient temperature was added sodium carbonate (1.688 mmol) and compound **6** (for compounds **13-18**) or **19** (for compounds **20-23**) (0.562 mmol). The reaction mixture was heated to reflux for an hour, then concentrated in vacuo, and cooled to ambient temperature. Water (10 ml) was added, and the aqueous layer was extracted with 10% MeOH/$CHCl_3$ (3 × 20 ml). The combined organic layer was dried and evaporated, followed by silica gel (8 g) column chromatography of the residue using $CHCl_3$/MeOH (98:2 to 90:10) as the eluent to yield compounds **13-18** and **20-23**. The products **13-18** and **20-23** were recrystallized from appropriate organic solvents.

(*S*)-(*N*-3-(3-Fluoro-4-(pyrazolo[1,5-a]pyridin-6-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl acetamide (13): Pale brown neddles (EtOH); mp 195-197 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 2.03 (3H, s, C<u>H</u>$_3$-C=O), 3.54-3.73 (2H, m, -C<u>H</u>H-NH-C=O), 3.85 (1H, dd, *J* = 6.7, 9.1 Hz, oxazolidinone-H4), 4.15 (1H, t, *J* = 9.1 Hz, oxazolidinone-H4), 4.78-4.89 (1H, m, oxazolidinone-H5), 6.57 (1H, d, *J* = 2.4 Hz, fused ring-H3), 7.29-7.38 (2H, m, phenyl-H6 and fused ring-H5), 7.51 (1H, t, *J* = 8.5 Hz, phenyl-H5), 7.60 (1H, dd, *J* = 2.4, 12.9 Hz, phenyl-H2), 7.62 (1H, d, *J* = 9.4 Hz, fused ring-H4), 7.95 (1H, br t, *J* = 6 Hz, -N<u>H</u>-C=O), 7.97 (1H, d, *J* = 2.4 Hz, fused ring-H2), and 8.66 (1H, br s, fused ring-H7); ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$): 21.99 (1C), 41.70 (1C), 47.41 (1C), 72.00 (1C), 96.74 (1C), 106.24 (1C, d, J_{C-F} = 26.6 Hz), 113.73 (1C), 117.51 (1C), 119.98 (1C), 120.07 (1C, d, J_{C-F} = 12.8 Hz), 124.67 (1C), 127.14 (1C), 130.09 (1C), 138.84 (1C), 138.87 (1 C, d, J_{C-F} = 10.6 Hz), 141.88 (1C), 154.51 (1C), 159.63 (1C, d, J_{C-F} = 245 Hz), and 172.15 (1C); LRMS-EI (*m/z*): 368 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{19}H_{17}FN_4O_3$ (M^+): 368.1285; Found 368.1291

(*S*)-(*N*-3-(3-Fluoro-4-(imidazo[1,5-a]pyridin-6-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl acetamide (14): Pale brown powder (EtOH); mp 206-209 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): 2.03 (3H, s, C<u>H</u>$_3$-C=O), 3.55-3.70 (2H, m, -C<u>H</u>H-NH-C=O), 3.86 (1H, dd, *J* = 6.7, 9.1 Hz, oxazolidinone-H4), 4.15 (1H, t, *J* = 9.1 Hz, oxazolidinone-H4), 4.78-4.89 (1H, m, oxazolidinone-H5), 6.96 (1H, d, *J* = 9.4 Hz, fused ring-H7), 7.33 (1H, dd, *J* = 2.1, 8.5 Hz, phenyl-H6), 7.39 (1H, s, fused ring-H1), 7.49 (1H, t, *J* = 8.5 Hz, phenyl-H5), 7.52 (1H, d, *J* = 9.4 Hz fused ring-H8), 7.59 (1H, dd, *J* = 2.1, 13.2 Hz, phenyl-H2), 8.05 (1H, br t, *J* = 6 Hz, -N<u>H</u>-C=O), and 8.22 (2H, s, fused ring-H3 and H5); ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$): 21.96 (1C), 41.68 (1C), 47.44 (1C), 72.00 (1C),

106.19 (1C, d, J_{C-F} = 27.6 Hz), 113.66 (1C), 117.61 (1C), 118.82 (1C), 120.01 (1C, d, J_{C-F} = 14.3 Hz), 120.82 (1C), 121.02 (1C), 121.16 (1C), 127.83 (1C), 128.99 (1C), 129.95 (1C), 138.98 (1 C, d, J_{C-F} = 11.3 Hz), 154.49 (1C), 159.68 (1C, d, J_{C-F} = 248 Hz), and 172.16 (1C); LRMS-EI (*m/z*): 368 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{19}H_{17}FN_4O_3$ (M^+): 368.1285; Found 368.1282

(*S*)-(*N*-3-(3-Fluoro-4-(imidazo[1,2-a]pyridin-6-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl acetamide (15): Colorless needles (CH_3CN); mp 236-238 °C; ^{1}H NMR (300 MHz, CD_3OD+$CDCl_3$): 2.03 (3H, s, C<u>H</u>$_3$-C=O), 3.61 (1H, dd, *J* = 5.6, 14.6 Hz, -C<u>H</u>H-NH-C=O), 3.66 (1H, dd, *J* = 4.4, 14.6 Hz, -CH<u>H</u>-NH-C=O), 3.86 (1H, dd, *J* = 6.7, 9.1 Hz, oxazolidinone-H4), 4.15 (1H, t, *J* = 9.1 Hz, oxazolidinone-H4), 4.84 (1H, dddd, *J* = 4.4, 5.6, 6.7, 9.1 Hz, oxazolidinone-H5), 7.34 (1H, dd, *J* = 2.1, 8.5 Hz, phenyl-H6), 7.43 (1H, d, *J* = 9.3 Hz, fused ring-H7), 7.49 (1H, t, *J* = 8.5 Hz, phenyl-H5), 7.61 (1H, s, fused ring-H2 or H3), 7.61 (1H, dd, *J* = 2.1, 12.9 Hz, phenyl-H2), 7.63 (1H, d, *J* = 9.3 Hz, fused ring-H8), 7.71 (1H, s, fused ring-H2 or H3), 8.04 (1H, br t, *J* = 6 Hz, -N<u>H</u>-C=O), and 8.42 (1H, s, fused ring-H5); ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$): 22.04 (1C), 41.66 (1C), 47.38 (1C), 72.00 (1C), 106.20 (1C, d, J_{C-F} = 29.4 Hz), 112.92 (1C), 113.66 (1C), 116.38 (1C), 119.89 (1C, d, J_{C-F} = 13.3 Hz), 120.56 (1C), 125.02 (1C), 126.39 (1C), 130.16 (1C), 132.84 (1C), 138.92 (1C, d, J_{C-F} = 11.1 Hz), 143.96 (1C), 154.51 (1C), 159.53 (1C, d, J_{C-F} = 247 Hz), and 172.20 (1C); LRMS-EI (*m/z*): 368 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{19}H_{17}FN_4O_3$ (M^+): 368.1285; Found 368.1277

(*S*)-(*N*-3-(3-Fluoro-4-(imidazo[1,2-a]pyridin-7-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl acetamide (16): White powder (CH_3CN); mp 191-193 °C (dec.); ^{1}H NMR (300 MHz, CD_3OD+$CDCl_3$): 2.03 (3H, s, C<u>H</u>$_3$-C=O), 3.61 (1H, dd, *J* = 5.3, 14.5 Hz, -C<u>H</u>H-NH-C=O), 3.65 (1H, dd, *J* = 4.1, 14.5 Hz, -CH<u>H</u>-NH-C=O), 3.87 (1H, dd, *J* = 6.7, 9.1 Hz, oxazolidinone-H4), 4.16 (1H, t, *J* = 9.1 Hz, oxazolidinone-H4), 4.84 (1H, dddd, *J* = 4.1, 5.3, 6.7, 9.1 Hz, oxazolidinone-H5), 7.09 (1H, d, *J* = 7.3 Hz, fused ring-H6), 7.34 (1H, dd, *J* = 2.2, 8.5 Hz, phenyl-H6), 7.55 (1H, t, *J* = 8.5 Hz, phenyl-H5), 7.61 (1H, dd, *J* = 2.2, 13.5 Hz, phenyl-H2), 7.62 (1H, s, fused ring-H2 or H3), 7.69 (1H, s, fused ring-H2 or H3), 7.73 (1H, br s, fused ring-H8), 8.09 (1H, br t, *J* = 6 Hz, -N<u>H</u>-C=O), and 8.27 (1H, d, *J* = 7.3 Hz, fused ring-H5); ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$): 21.94 (1C), 41.64 (1C), 47.35 (1C), 71.94 (1C), 106.15 (1C, d, J_{C-F} = 28.8 Hz), 112.33 (1C), 113.50 (1C), 113.56 (1C), 115.57 (1C), 121.65 (1C, d, J_{C-F} = 13.3 Hz), 125.35 (1C), 130.09 (1C), 132.15 (1C), 132.97 (1C), 139.15 (1C, d, J_{C-F} = 11.1 Hz), 144.89 (1C), 154.48 (1C), 159.58 (1C, d, J_{C-F} = 248 Hz), and 172.22 (1C); LRMS-EI (*m/z*): 368 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{19}H_{17}FN_4O_3$ (M^+): 368.1285; Found 368.1292

(*S*)-(*N*-3-(3-Fluoro-4-([1,2,4]triazolo[1,5-a]pyridin-6-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl acetamide (17): Colorless needles ($CHCl_3$/EtOH); mp 214-216 °C; ^{1}H NMR (300 MHz, CD_3OD+$CDCl_3$): 2.04 (3H, s, C<u>H</u>$_3$-C=O),

3.62 (1H, dd, J = 5.6, 14.4 Hz, -CHH-NH-C=O), 3.67 (1H, dd, J = 4.1, 14.4 Hz, -CHH-NH-C=O), 3.88 (1H, dd, J = 6.7, 9.1 Hz, oxazolidinone-H4), 4.17 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.86 (1H, dddd, J = 4.1, 5.6, 6.7, 9.1 Hz, oxazolidinone-H5), 7.39 (1H, dd, J = 2.2, 8.5 Hz, phenyl-H6), 7.55 (1H, t, J = 8.5 Hz, phenyl-H5), 7.66 (1H, dd, J = 2.2, 13.1 Hz, phenyl-H2), 7.82 (1H, d, J = 9.3 Hz, fused ring-H7 or H8), 7.85 (1H, d, J = 9.3 Hz, fused ring-H7 or H8), 8.07 (1H, br t, J = 6 Hz, -NH-C=O), 8.39 (1H, s, fused ring-H2), and 8.85 (1H, s, fused ring-H5); ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$): 22.03 (1C), 41.71 (1C), 47.35 (1C), 72.04 (1C), 106.24 (1C, d, $J_{C\text{-}F}$ = 28.8 Hz), 113.82, 115.64, 118.71 (1C, d, $J_{C\text{-}F}$ = 12.8 Hz), 122.69 (1C), 127.30 (1C), 130.25 (1C), 131.50 (1C), 139.59 (1C, d, $J_{C\text{-}F}$ = 11.1 Hz), 148.98 (1C), 153.46 (1C), 154.46 (1C), 159.56 (1C, d, $J_{C\text{-}F}$ = 247 Hz), and 172.25 (1C); LRMS-EI (*m/z*): 369 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{18}H_{16}FN_5O_3$ (M^+): 369.1237; Found 369.1246

(*S*)-(*N*-3-(3-Fluoro-4-([1,2,4]triazolo[1,5-a]pyridin-7-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl acetamide (18): Colorless needles ($CHCl_3$/EtOH); mp 246-248 °C; ^{1}H NMR (300 MHz, CD_3OD+$CDCl_3$): 2.03 (3H, s, CH_3-C=O), 3.61 (1H, dd, J = 5.3, 14.4 Hz, -CHH-NH-C=O), 3.65 (1H, dd, J = 4.3, 14.4 Hz, -CHH-NH-C=O), 3.89 (1H, dd, J = 6.7, 9.1 Hz, oxazolidinone-H4), 4.19 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.86 (1H, dddd, J = 4.3, 5.3, 6.7, 9.1 Hz, oxazolidinone-H5), 7.39 (1H, d, J = 7.3 Hz, fused ring-H6), 7.40 (1H, dd, J = 2.1, 8.5 Hz, phenyl-H6), 7.61 (1H, t, J = 8.5 Hz, phenyl-H5), 7.67 (1H, dd, J = 2.1, 13.3 Hz, phenyl-H2), 7.93 (1H, s, fused ring-H8), 8.39 (1H, s, fused ring-H2), and 8.72 (1H, d, J = 7.3 Hz, fused ring-H5); ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$): 21.79 (1C), 41.59 (1C), 47.29 (1C), 71.95 (1C), 106.13 (1C, d, $J_{C\text{-}F}$ = 28.1 Hz), 113.67 (1C), 114.77 (1C), 115.31 (1C), 120.52 (1C, d, $J_{C\text{-}F}$ = 12.8 Hz), 127.73 (1C), 130.29 (1C), 137.76 (1C), 140.04 (1C, d, $J_{C\text{-}F}$ = 11.1 Hz), 149.94 (1C), 153.36 (1C), 154.42 (1C), 159.57 (1C, d, $J_{C\text{-}F}$ = 249 Hz), and 172.29 (1C); LRMS-EI (*m/z*): 369 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{18}H_{16}FN_5O_3$ (M^+): 369.1237; Found 369.1231

(*R*)-3-(3-Fluoro-4-(imidazo[1,2-a]pyridin-6-yl)phenyl)-5-([1,2,3]triazol-1-yl)methyloxazolidin-2-one (20): Pale yellow powder ($CHCl_3$/EtOH); mp 229-232 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6): 3.95 (1H, dd, J = 5.8, 9.4 Hz, oxazolidinone-H4), 4.29 (1H, t, J = 9.4 Hz, oxazolidinone-H4), 4.86 (2H, d, J = 5.0 Hz, -CHH-[1,2,3]triazole), 5.18 (1H, ddt, J = 5.8, 9.4, 5.0 Hz, oxazolidinone-H5), 7.39 (1H, dd, J = 2.1, 8.8 Hz, phenyl-H6), 7.41 (1H, br d, J = 9.4 Hz, fused ring-H7), 7.57 (1H, dd, J = 2.1, 13.6 Hz, phenyl-H2), 7.61 (1H, s, fused ring-H2 or H3), 7.64 (1H, t, J = 8.8 Hz, phenyl-H5), 7.64 (1H, d, J = 9.4 Hz, fused ring-H8), 7.77 (1H, br s, [1,2,3]triazole-H), 7.99 (1H, s, fused ring-H2 or H3), 8.18 (1H, br s, [1,2,3]triazole-H), and 8.79 (1H, s, fused ring-H5); ^{13}C NMR (75 MHz, , DMSO-d_6): 46.95 (1C), 51.61 (1C), 70.90 (1C), 105.68 (1C, d, $J_{C\text{-}F}$ = 29.4 Hz), 113.57 (1C), 114.09 (1C), 116.52 (1C), 119.22 (1C), 119.41 (1C, d, $J_{C\text{-}F}$ = 12.8 Hz), 125.52 (1C), 125.75 (1C),

125.88 (1C), 130.61 (1C), 133.28 (1C), 133.55 (1C), 139.14 (1C, d, J_{C-F} = 11.1 Hz), 143.47 (1C), 153.32 (1C), and 159.00 (1C, d, J_{C-F} = 245 Hz); LRMS-EI (*m/z*): 378 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{19}H_{15}FN_6O_2$ (M^+): 378.1241; Found 378.1245

(*R*)-3-(3-Fluoro-4-(imidazo[1,2-a]pyridin-7-yl)phenyl)-5-([1,2,3]triazol-1-yl)methyloxazolidin-2-one (21): Pale yellow powder ($CHCl_3$/EtOH); mp 253-256 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6): 3.96 (1H, dd, *J* = 5.6, 9.4 Hz, oxazolidinone-H4), 4.29 (1H, t, *J* = 9.4 Hz, oxazolidinone-H4), 4.86 (2H, d, *J* = 5.1 Hz, -CHH-[1,2,3]triazole), 5.18 (1H, ddt, *J* = 5.6, 9.4, 5.1 Hz, oxazolidinone-H5), 7.11 (1H, dt, *J* = 7.1, 1.7 Hz, fused ring-H6), 7.39 (1H, dd, *J* = 2.2, 8.8 Hz, phenyl-H6), 7.55 (1H, dd, *J* = 2.2, 13.8 Hz, phenyl-H2), 7.62 (1H, d, *J* = 1.7 Hz, fused ring-H2 or H3), 7.70 (1H, t, *J* = 8.8 Hz, phenyl-H5), 7.73 (1H, s, fused ring-H2 or H3), 7.77 (1H, br s, [1,2,3]triazole-H), 7.98 (1H, s, fused ring-H8), 8.18 (1H, br s, [1,2,3]triazole-H), and 8.60 (1H, d, *J* = 7.1 Hz, fused ring-H5); ^{13}C NMR (75 MHz, , DMSO-d_6): 46.96 (1C), 51.65 (1C), 70.96 (1C), 105.72 (1C, d, J_{C-F} = 28.1 Hz), 112.66 (1C), 113.06 (1C), 114.11 (1C), 115.67 (1C), 121.07 (1C, d, J_{C-F} = 11.6 Hz), 125.79 (1C), 126.60 (1C), 130.55 (1C), 130.61 (1C), 133.32 (1C), 133.90 (1C), 139.39 (1C, d, J_{C-F} = 10.6 Hz), 144.46 (1C), 153.34 (1C), and 159.10 (1C, d, J_{C-F} = 247 Hz); LRMS-EI (*m/z*): 378 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{19}H_{15}FN_6O_2$ (M^+): 378.1241; Found 378.1242

(*R*)-3-(3-Fluoro-4-([1,2,4]triazolo[1,5-a]pyridin-6-yl)phenyl)-5-([1,2,3]triazol-1-yl)methyloxazolidin-2-one (22): Colorless needles ($CHCl_3$/EtOH); mp 254-256 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6): 3.96 (1H, dd, *J* = 5.6, 9.4 Hz, oxazolidinone-H4), 4.30 (1H, t, *J* = 9.4 Hz, oxazolidinone-H4), 4.87 (2H, d, *J* = 4.7 Hz, -CHH-[1,2,3]triazole), 5.19 (1H, ddt, *J* = 5.6, 9.4, 4.7 Hz, oxazolidinone-H5), 7.40 (1H, dd, *J* = 2.0, 8.8 Hz, phenyl-H6), 7.58 (1H, dd, *J* = 2.1, 13.5 Hz, phenyl-H2), 7.71 (1H, t, *J* = 8.8 Hz, phenyl-H5), 7.77 (1H, s, [1,2,3]triazole-H), 7.85 (1H, d, *J* = 9.4 Hz, fused ring-H7), 7.92 (1H, d, *J* = 9.4 Hz, fused ring-H8), 8.18 (1H, s, [1,2,3]triazole-H), 8.55 (1H, s, fused ring-H2), and 9.15 (1H, s, fused ring-H5); ^{13}C NMR (75 MHz, , DMSO-d_6): 46.97 (1C), 51.63 (1C), 70.94 (1C), 105.65 (1C, d, J_{C-F} = 28.2 Hz), 114.14 (1C), 115.77 (1C), 118.35 (1C, d, J_{C-F} = 13.8 Hz), 121.70 (1C), 125.77 (1C), 127.83 (1C), 131.03 (1C), 131.24 (1C), 133.30 (1C), 139.67 (1C, d, J_{C-F} = 10.0 Hz), 149.01 (1C), 153.33 (1C), 154.31 (1C), and 159.09 (1C, d, J_{C-F} = 245 Hz); LRMS-EI (*m/z*): 379 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{18}H_{14}FN_7O_2$ (M^+): 379.1193; Found 379.1189

(*R*)-3-(3-Fluoro-4-([1,2,4]triazolo[1,5-a]pyridin-7-yl)phenyl)-5-([1,2,3]triazol-1-yl)methyloxazolidin-2-one (23): Colorless needles ($CHCl_3$/EtOH); mp 259-261 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6): 3.97 (1H, dd, *J* = 5.7, 9.1 Hz, oxazolidinone-H4), 4.30 (1H, t, *J* = 9.1 Hz, oxazolidinone-H4), 4.87 (2H, d, *J* = 4.7 Hz, -CHH-[1,2,3]triazole), 5.19 (1H, ddt, *J* = 5.7, 9.1, 4.7 Hz, oxazolidinone-H5), 7.38 (1H, d, *J* = 7.1 Hz, fused

ring-H6), 7.41 (1H, br d, J = 9 Hz, phenyl-H6), 7.58 (1H, br d, J = 14 Hz, phenyl-H2), 7.75 (1H, t, J = 9.1 Hz, phenyl-H5), 7.77 (1H, s, [1,2,3]triazole-H), 8.00 (1H, s, fused ring-H8), 8.18 (1H, s, [1,2,3]triazole-H), 8.53 (1H, s, fused ring-H2), and 9.00 (1H, d, J = 7.1 Hz, fused ring-H5); ^{13}C NMR (75 MHz, , DMSO-d_6): 46.98 (1C), 51.64 (1C), 71.00 (1C), 105.66 (1C, d, $J_{C\text{-}F}$ = 30.4 Hz), 114.14 (1C), 114.84 (2C), 120.07 (1C, d, $J_{C\text{-}F}$ = 12.8 Hz), 125.79 (1C), 128.72 (1C), 130.99 (1C), 133.33 (1C), 136.39 (1C), 140.18 (1C, d, $J_{C\text{-}F}$ = 12.1 Hz), 150.02 (1C), 153.33 (1C), 154.41 (1C), and 159.12 (1C, d, $J_{C\text{-}F}$ = 247 Hz); LRMS-EI (*m/z*): 379 (M^+). HRMS-EI (*m/z*): Calcd. for $C_{18}H_{14}FN_7O_2$ (M^+): 379.1193; Found 379.1197

Assays for antibacterial activity, safety profile, and PK profile

In Vitro Antibacterial Activity

The *in vitro* antibacterial activities of the compounds shown in Tables 2 and 4 were determined by the broth microdilution method recommended by the Clinical Laboratory Standards Institute (CLSI). Cation-adjusted Mueller-Hinton broth (CAMHB) (Difco) was used, except for *S. pneumoniae* and *H. influenzae*. For *S. pneumoniae*, CAMHB supplemented with 5% lysed horse blood was used. For *H. influenzae*, Haemophilus test medium (Nissui Pharmaceutical Co., Ltd., Japan) was used. The tested Gram-positive organisms included clinical isolates of *S. aureus* SR20549, *S. aureus* SR3637 (methicillin-resistant), *S. pneumoniae* SR26207, *S. pneumoniae* SR11031 (penicillin-resistant), *E. faecalis* SR1004 and *E. faecium* SR7940. *S. aureus* Smith and *S. aureus* resistant to linezolid NRS271 (NARSA) were also used. Gram-negative bacteria used in the study were clinical isolates of *M. catarrhalis* SR26840 and *H. influenzae* SR27914.

In Vivo Antibacterial Efficacy

The data on *in vivo* efficacy of the compounds are summarized in Table 5. Five-week-old male JCL/ICR mice (body weight 20-25 g) from Clea Japan, Inc. (Tokyo) were used to prepare a systemic infection model (five mice per group). All animal studies were approved by the Animal Care and Use Committee of Shionogi Co., Ltd. The test strain was methicillin-resistant *S. aureus* SR3637.[9] Mice were injected intraperitoneally with 0.5 or 1.0 ml of bacterial suspension (approximately 100 times the 50% lethal dose). Test and reference compounds were administered intravenously or orally 1 h after infection. Mortality was recorded over 7 days to estimate the 50% effective dose (ED_{50}) and 95% confidence limits, which were determined by the logit method.

In Vitro Inhibition Assay for CYP450 Isoforms

The inhibitory effects of the compounds on selected CYP 450 isoforms are summarized in Table 6. Human CYP450 activities were measured using the following reactions: ethoxyresorufin *O*-deethylation for CYP1A2, tolbutamide hydroxylation for CYP2C9, dextromethorphan *O*-demethylation for CYP2D6, and terfenadine hydroxylation for CYP3A4. The incubation mixture consisted of 1 mM NADPH, 50 mM HEPES buffer (pH 7.4) containing 10 mM $MgCl_2$ and 0.1 mM EDTA, human liver microsomes (0.2 mg protein/mL) and a cocktail of the 4 substrates (0.375 μM ethoxyresorufin, 100 μM tolbutamide, 5 μM dextromethorphan and 1 μM terfenadine) in the presence or absence of test compound in a final volume of 500 μL. A solution of test compound in DMSO (final 0.5%) was added to give a final concentration of 0, 1, 5, 10 and 20 μM. Reactions were initiated by adding NADPH. After incubation for 20 min at 37°C, reactions were terminated by the addition of an equivalent volume of acetonitrile/methanol (1/1, v/v). A standard curve was prepared by adding an authentic metabolite cocktail to the same reaction components without incubation. After centrifugation, the supernatants were evaluated with a fluorescence plate reader (for CYP1A2) or an LC/MS/MS system (for CYP2C9, 2D6 and 3A4).

In Vitro Inhibition Assay for MAO-A and MAO-B

The inhibitory effects of test compounds on MAO-A and MAO-B activities are summarized in Table 6. MAO-A and MAO-B activities were measured by a slight modification of the method of Curet et al.[10] Rat forebrains were homogenized in 20 volumes of buffer (0.25 M sucrose, 10 mM sodium phosphate buffer, pH 7.4) at 4°C (final concentration: 500 μg of tissue/assay). Briefly, 100 μl of homogenate was preincubated for 20 min at 37°C with or without test compound (final concentration of 30 μM) in a total volume of 400 μl. After this preincubation, the reaction was started by the addition of [^{14}C]5-HT as a specific MAO-A substrate (final concentration 500 μM, specific activity 1 μCi/μmol) or [^{14}C]PEA as a specific MAO-B substrate (final concentration 125 μM, specific activity 0.1 μCi/μmol). The final volume of incubation buffer (0.25 M sucrose, 10 mM sodium phosphate buffer, pH 7.4) was 500 μl and the incubation times were 5 min for MAO-A and 10 min for MAO-B. The reaction was stopped by adding 200 μl of 4 M HCl and 5 mL of extraction solvent (toluene/ethyl acetate vol/vol). After vigorous shaking and centrifugation (1000 rpm, 5 min) of the mixture, the radioactivity of the organic layer was measured with a liquid scintillation counter.

*Oral Administration to Uninfected Mice for PK analysis of compound **18***

Five-week-old male ICR (IGS) mice (Charles River Laboratories Japan, Inc.) weighing 30-35 g were used after having been acclimated for at least a week. They were maintained under a 12-hr light/dark cycle and fed a

standard diet. Compound **18** was orally administered (10 mL/kg) to unfasted mice as a 0.5% MC (400 cps) suspension. Blood was collected from the heart with a heparinized syringe under anesthesia with diethyl ether. The blood was centrifuged at 3000 rpm for 10 min at 4 °C (Model H-103RL, Kokusan-enshinki Co., Ltd., Tokyo, Japan), and the plasma was stored at -20 °C until assay using LC/MS/MS.

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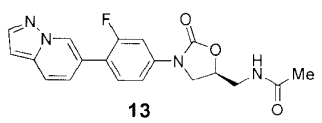
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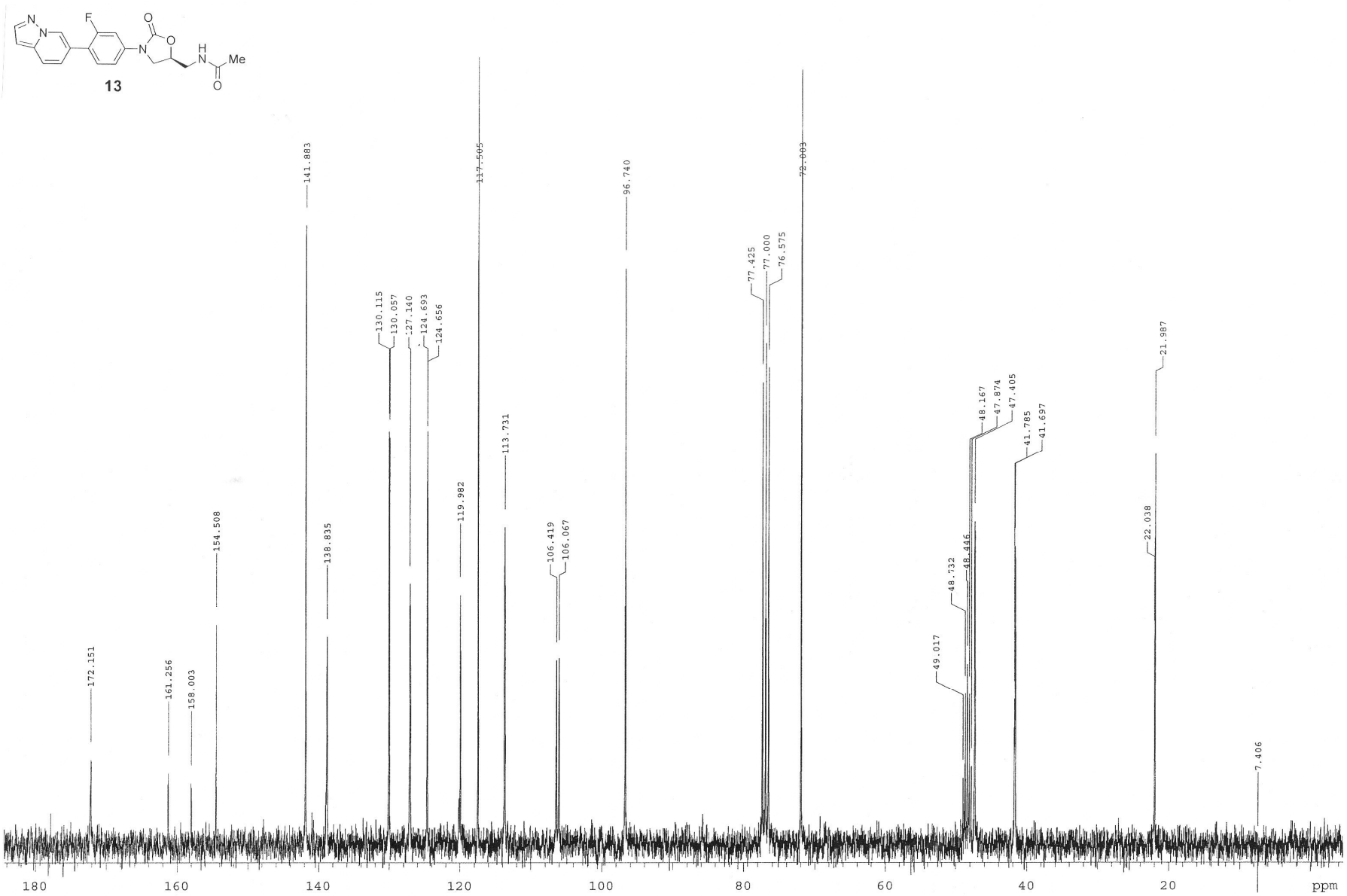
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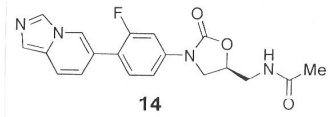
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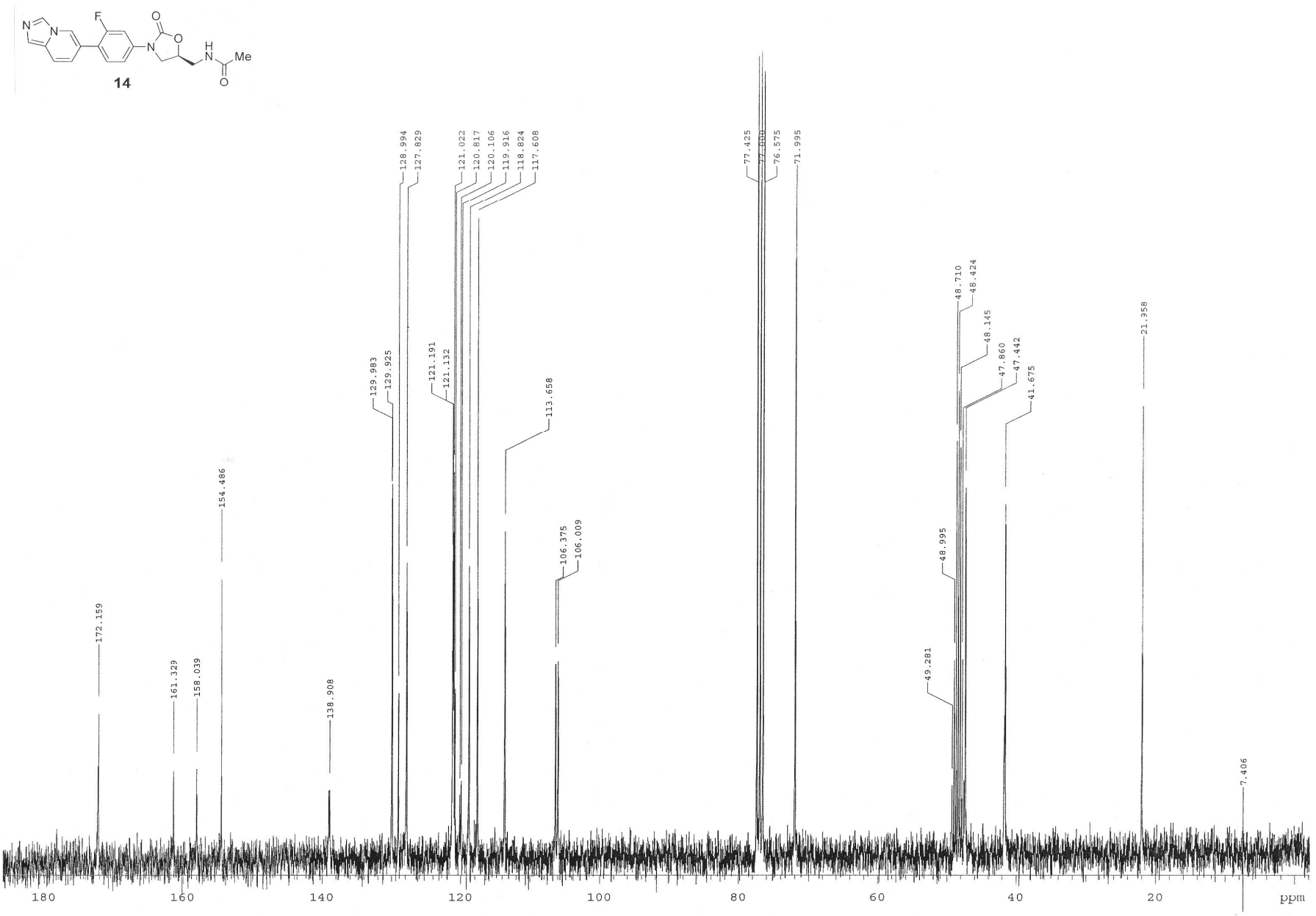
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121.022
120.817
120.106
119.916
118.824
117.608
113.658
106.375
106.009
77.425
77.000
76.575
71.995
49.281
48.995
48.710
48.424
48.145
47.860
47.442
41.675
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7.406
180
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140
120
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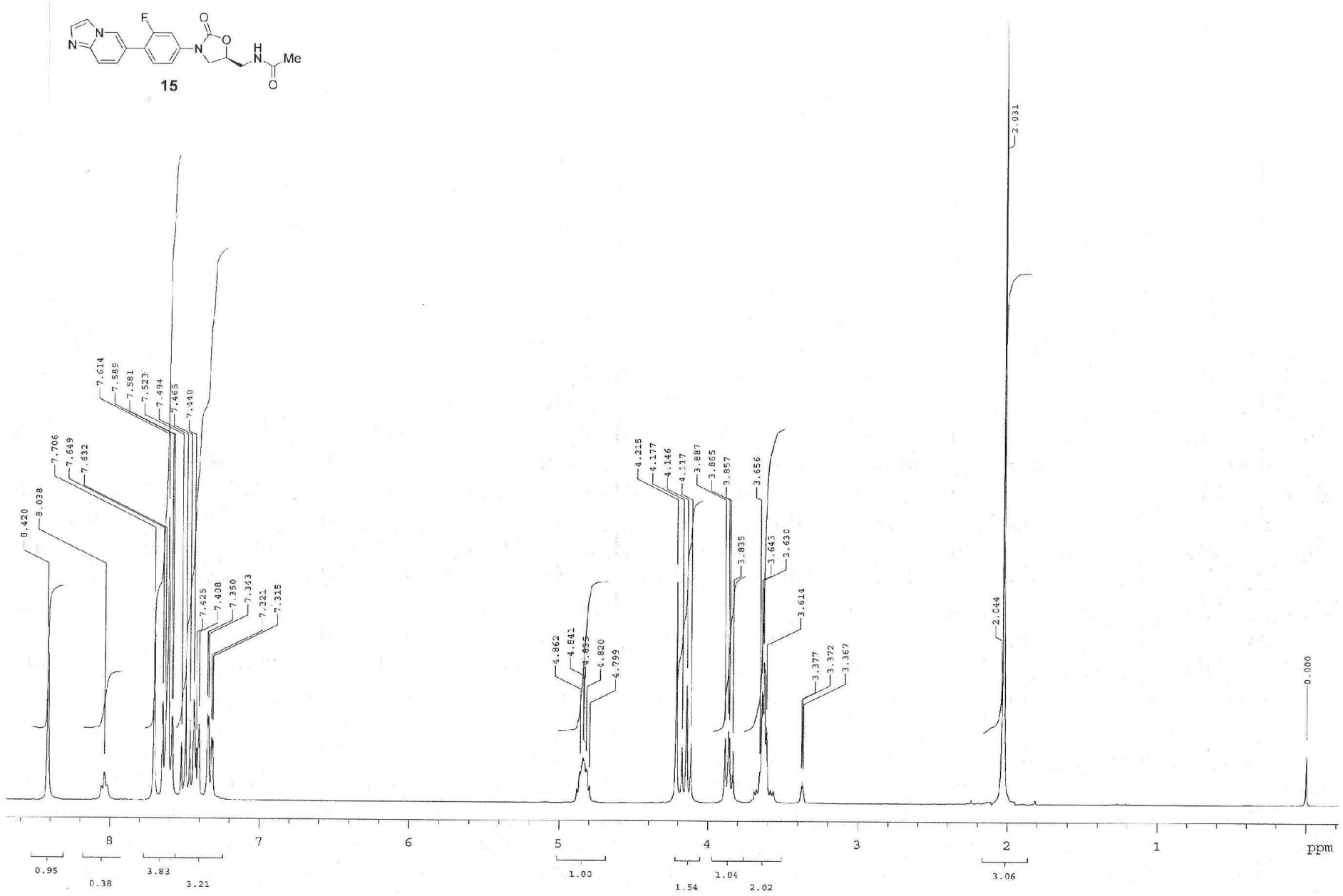
60
40
20
ppm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8.420
8.038
7.706
7.649
7.632
7.614
7.589
7.581
7.523
7.494
7.465
7.440
7.425
7.408
7.350
7.343
7.332
7.315
4.862
4.841
4.835
4.820
4.799
4.215
4.177
4.146
4.117
3.887
3.865
3.857
3.835
3.656
3.643
3.630
3.614
3.377
3.372
3.367
2.044
2.031
0.000
8
7
6
5
4
3
2
1
ppm
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0.38
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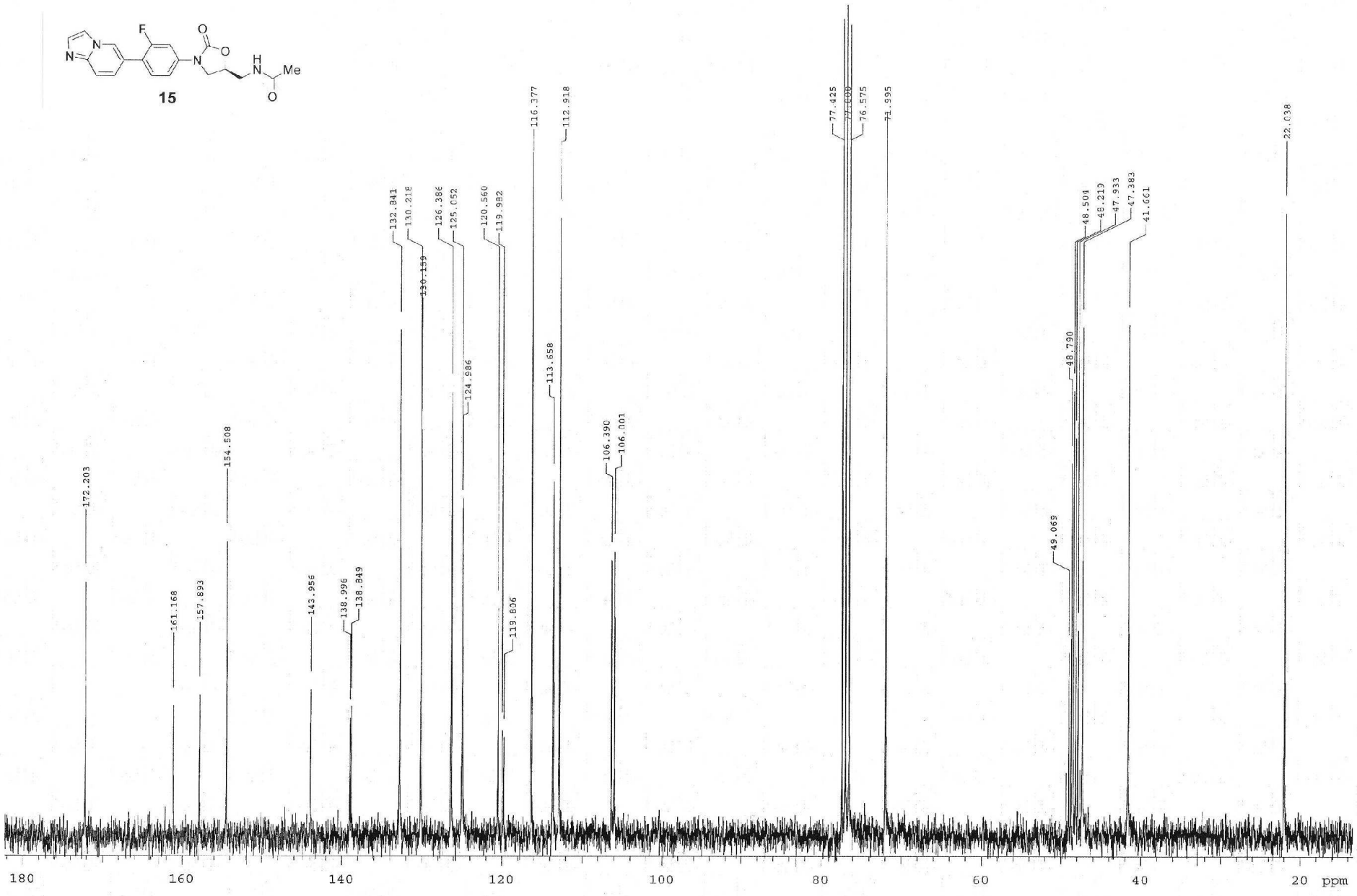
1.04
2.02
3.06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143.956
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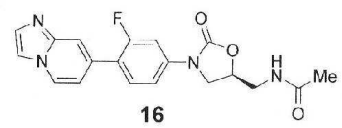
138.849
132.341
130.218
130.159
126.386
125.052
124.986
120.560
119.982
119.806
116.377
113.658
112.918
106.390
106.001
77.425
76.575
71.995
49.069
48.790
48.504
48.219
47.933
47.383
41.661
22.038
180
160
140
120
100
80
60
40
20
ppm


F
O
N
N
O
O
H
N
Me
O

16

8.281
8.256
8.091
7.731
7.691
7.689
7.628
7.618
7.583
7.553
7.524
7.419
7.356
7.348
7.327
7.319
7.103
7.084
7.078
4.867
4.846
4.839
4.823
4.314
4.188
4.158
4.129
3.892
3.870
3.862
3.839
3.654
3.641
3.631
3.627
3.615
3.368
2.033
0.000
8
7
6
5
4
3
2
1
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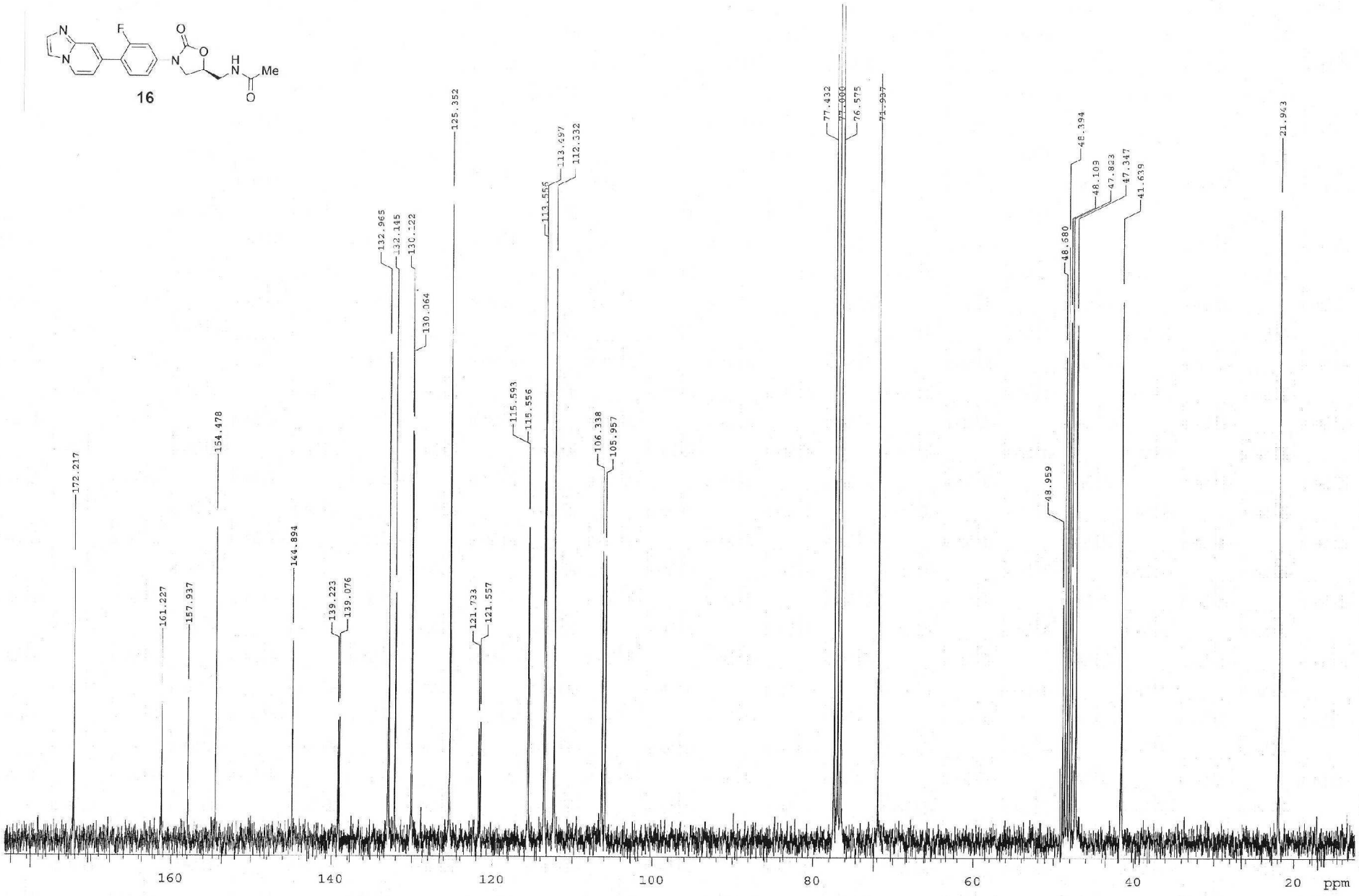
1.04
0.99
1.00
1.08
1.04
2.03
3.00


16
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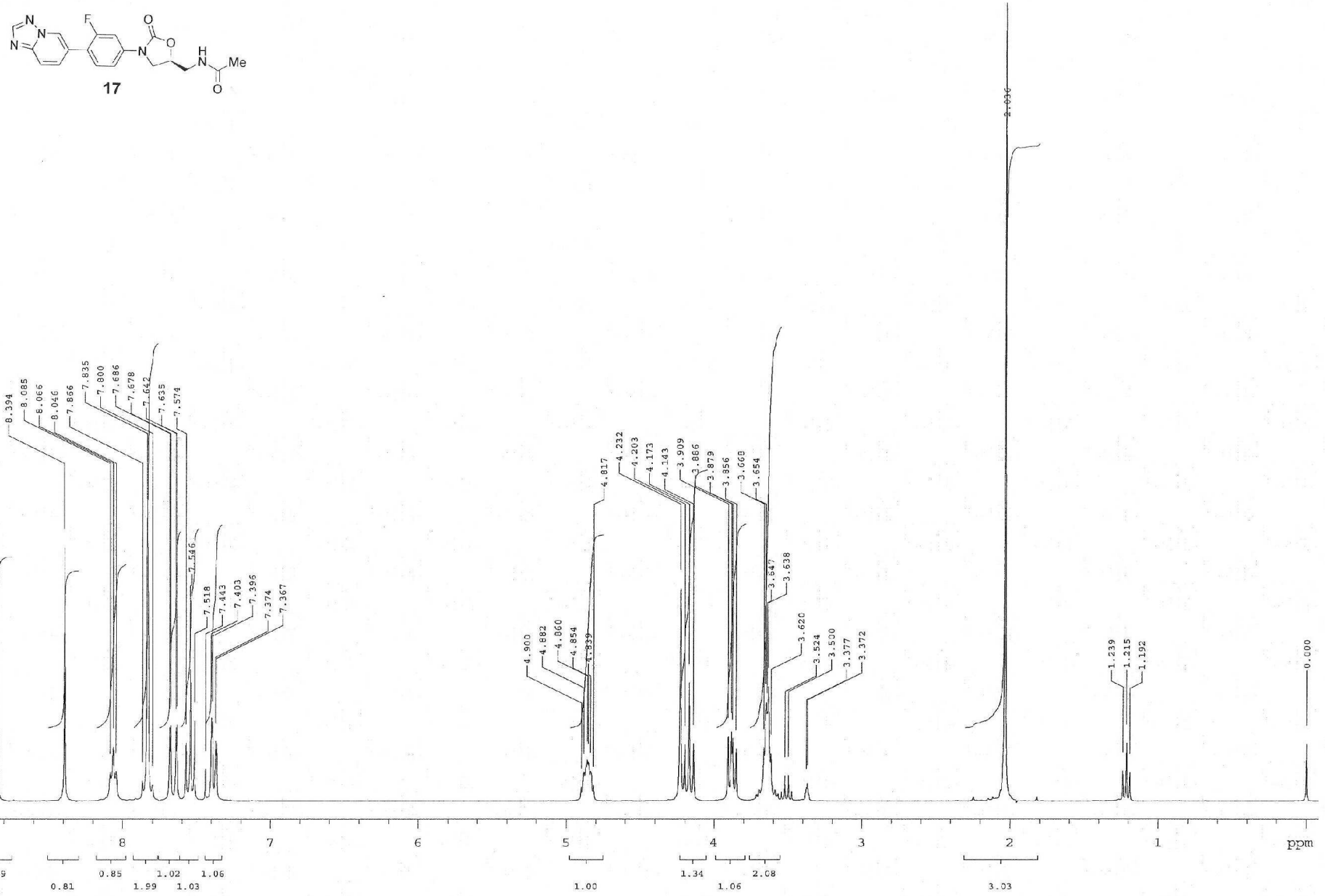
157.937
154.478
144.894
139.223
139.076
132.965
132.145
130.122
130.064
125.352
121.733
121.557
115.593
115.556
113.556
113.497
112.332
106.338
105.957
77.432
77.000
76.575
74.937
48.959
48.580
48.394
48.109
47.823
47.347
41.639
21.963
160
140
120
100
80
60
40
20
ppm


17
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8.846
8.394
8.085
8.066
8.046
7.866
7.835
7.800
7.686
7.678
7.642
7.635
7.574
7.546
7.518
7.443
7.403
7.396
7.374
7.367
4.900
4.882
4.860
4.854
4.839
4.817
4.232
4.203
4.173
4.143
3.909
3.886
3.879
3.856
3.660
3.654
3.647
3.638
3.620
3.524
3.500
3.377
3.372
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1.239
1.215
1.192
0.000
9
8
7
6
5
4
3
2
1
ppm
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0.85
1.99
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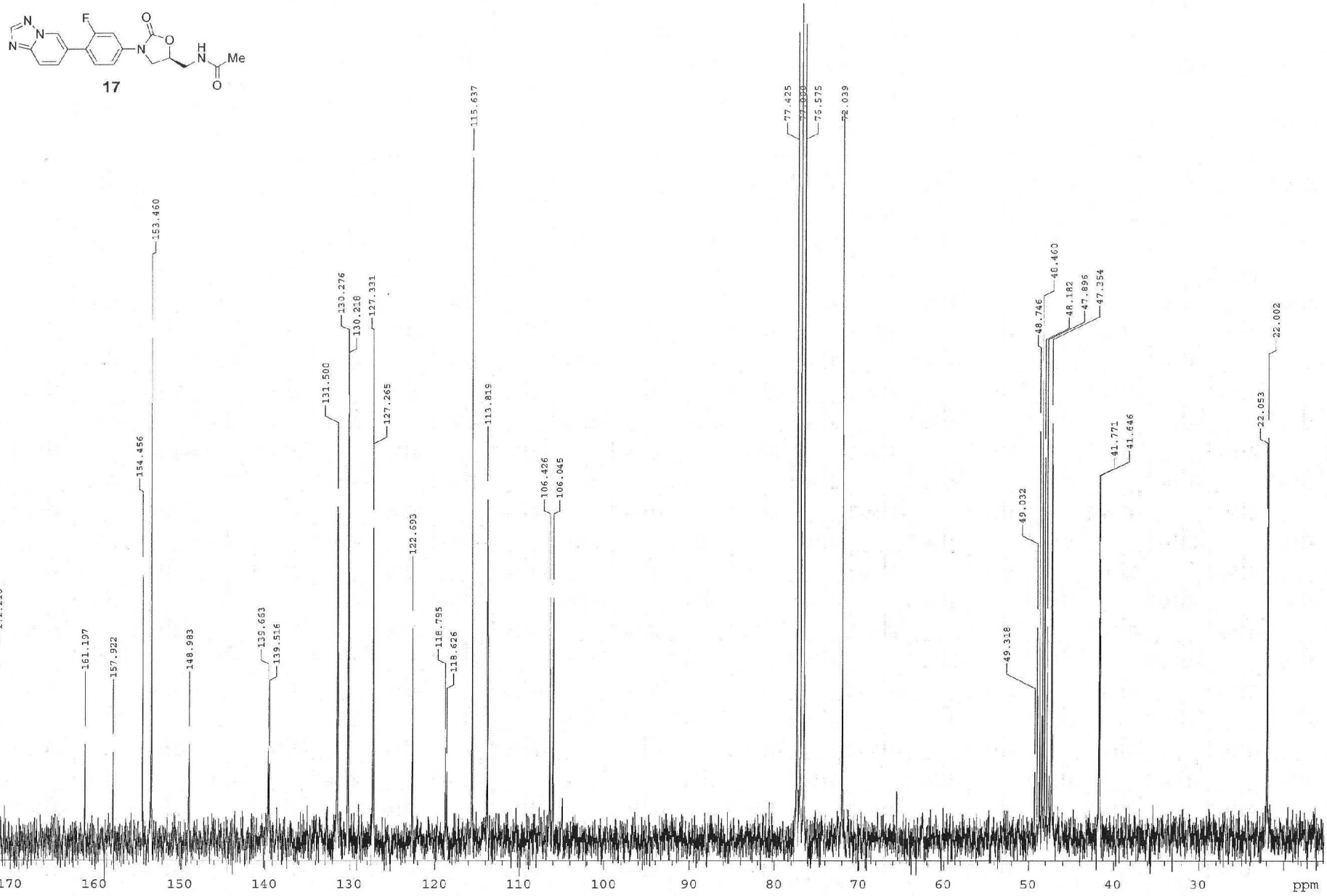
1.03
1.06
1.00
1.34
1.06
2.08
3.03


17
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172.210
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157.922
154.456
153.460
148.983
139.663
139.516
131.500
130.276
130.218
127.331
127.265
122.693
118.795
118.626
115.637
113.819
106.426
106.045
77.425
77.000
76.575
72.039
49.318
49.032
48.746
48.460
48.182
47.896
47.354
41.771
41.646
22.053
22.002
170
160
150
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130
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90
80
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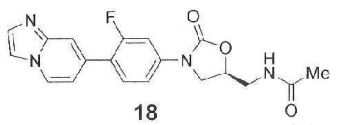
50
40
30
ppm


N
F
O
O
N
O
H
N
Mc
N
O

18

8.728
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8.705
8.702
8.389
7.933
7.930
7.697
7.689
7.652
7.644
7.614
7.584
7.490
7.426
7.419
7.399
7.394
7.375
7.369
7.364
4.899
4.881
4.858
4.852
4.837
4.833
4.815
4.421
4.215
4.184
4.154
3.914
3.891
3.803
3.661
3.688
3.674
3.640
3.632
3.627
3.615
3.584
3.566
3.365
3.360
3.354
2.201
2.057
2.025
0.000
8
7
6
5
4
3
2
1
-0
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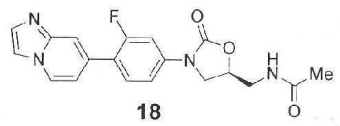
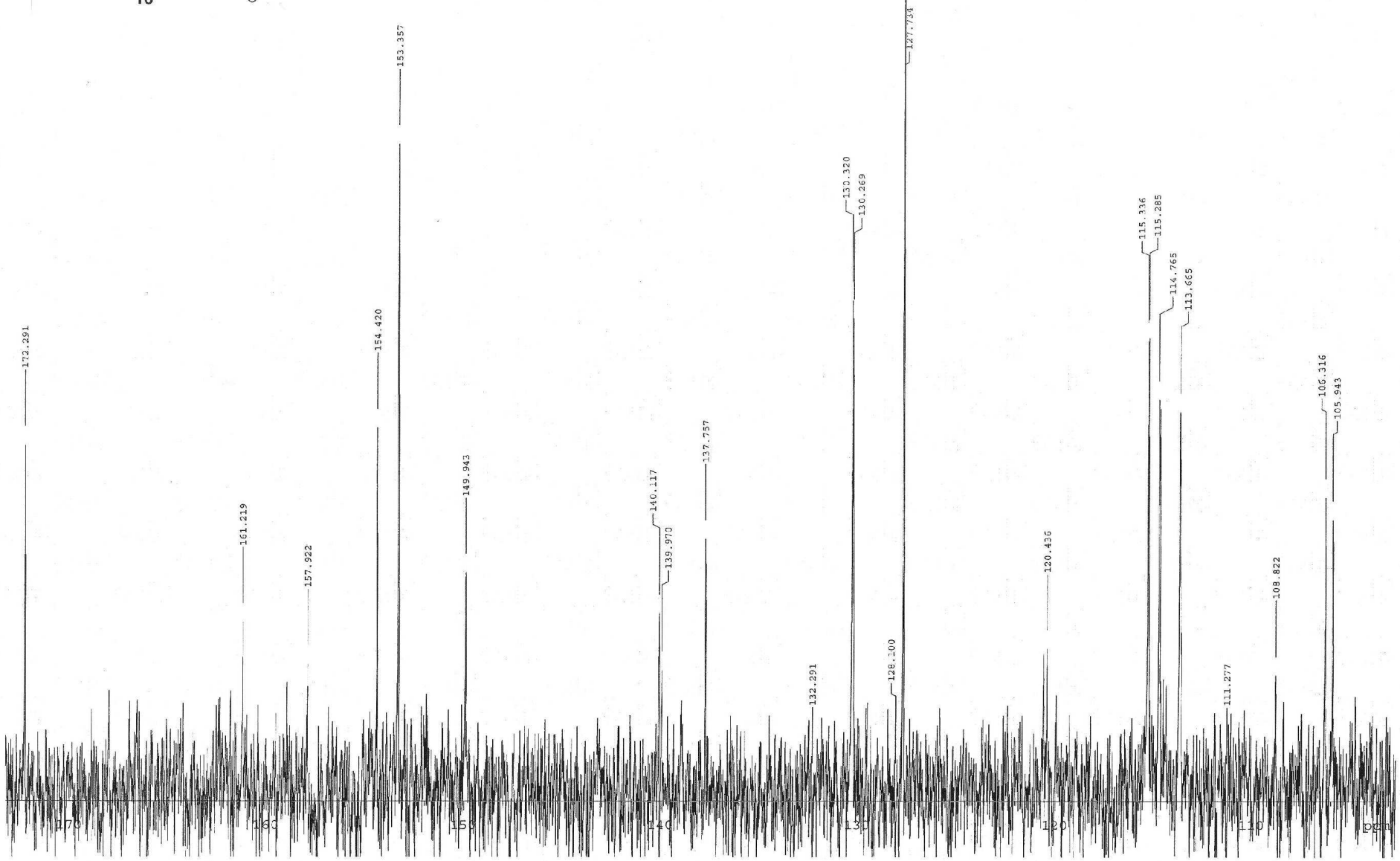
0.88
0.95
2.00
2.00
1.00
1.02
1.02
2.02
2.99


F
O
N
O
N
H
N
Me
O

18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153.357
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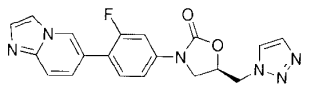
139.970
137.757
132.291
130.320
130.269
128.100
127.734
120.436
115.336
115.285
114.765
113.665
111.277
108.822
106.316
105.943
170
160
150
140
130
120
110
ppm



20

8.789
8.178
8.176
7.994
7.768
7.766
7.664
7.653
7.635
7.622
7.606
7.595
7.588
7.550
7.543
7.424
7.404
7.397
7.376
7.369
5.186
5.156
4.867
4.850
4.323
4.292
4.261
3.979
3.959
3.948
3.928
3.343
2.514
2.502
2.496
2.490
2.484
9
8
7
6
5
4
3
ppm
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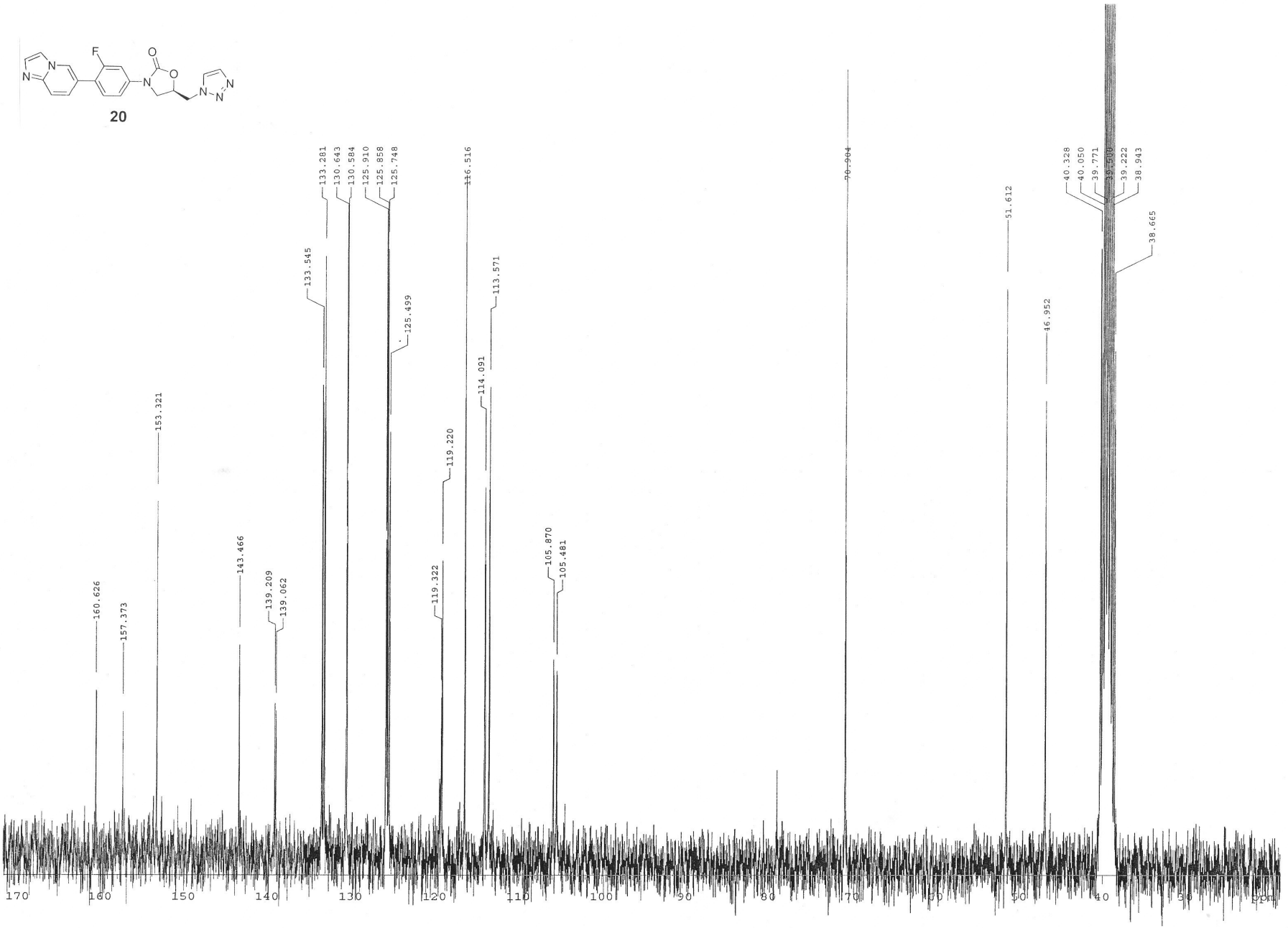
0.95
0.93
0.85
3.87
2.03
1.00
2.00
1.00
1.00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O
N
O
N
N
N
N
20
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153.321
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139.209
139.062
133.545
133.281
130.643
130.584
125.910
125.858
125.748
125.499
119.322
119.220
116.516
114.091
113.571
105.870
105.481
76.904
51.612
46.952
40.328
40.050
39.771
39.700
39.222
38.943
38.665
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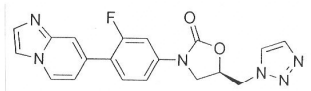
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



21

8.617
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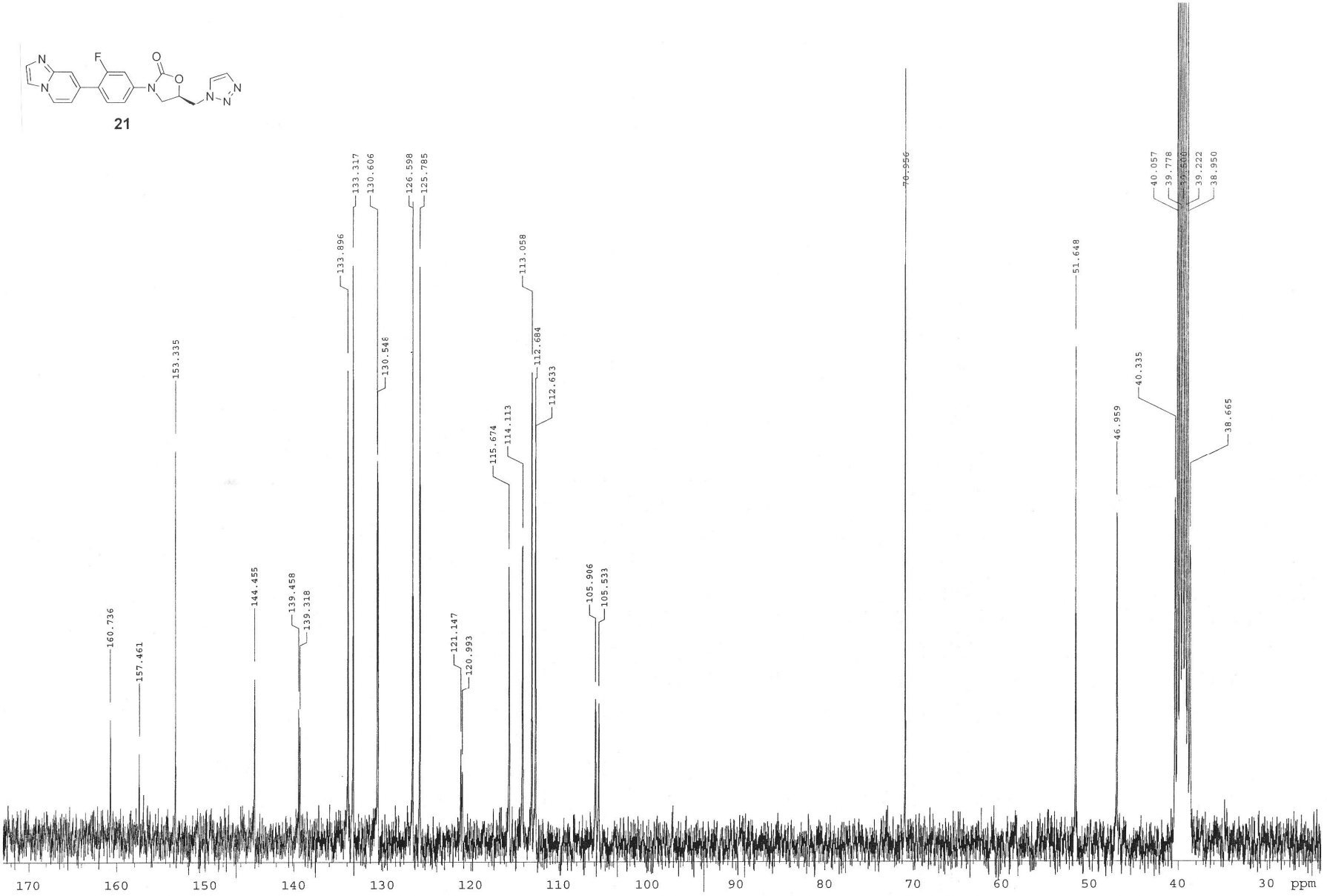
8.180
8.178
7.979
7.769
7.767
7.725
7.700
7.671
7.625
7.622
7.580
7.573
7.534
7.527
7.402
7.395
7.374
7.366
7.121
7.116
7.110
7.097
7.092
7.087
5.205
5.187
5.176
5.137
5.140
4.868
4.851
4.324
4.292
4.262
3.980
3.961
3.949
3.930
3.359
3.330
3.302
2.513
2.502
2.496
2.490
2.484
2.478
8
7
6
5
4
3
ppm
1.04
1.03
1.01
4.99
1.10
1.04
1.00
2.03
0.99
0.99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139.458
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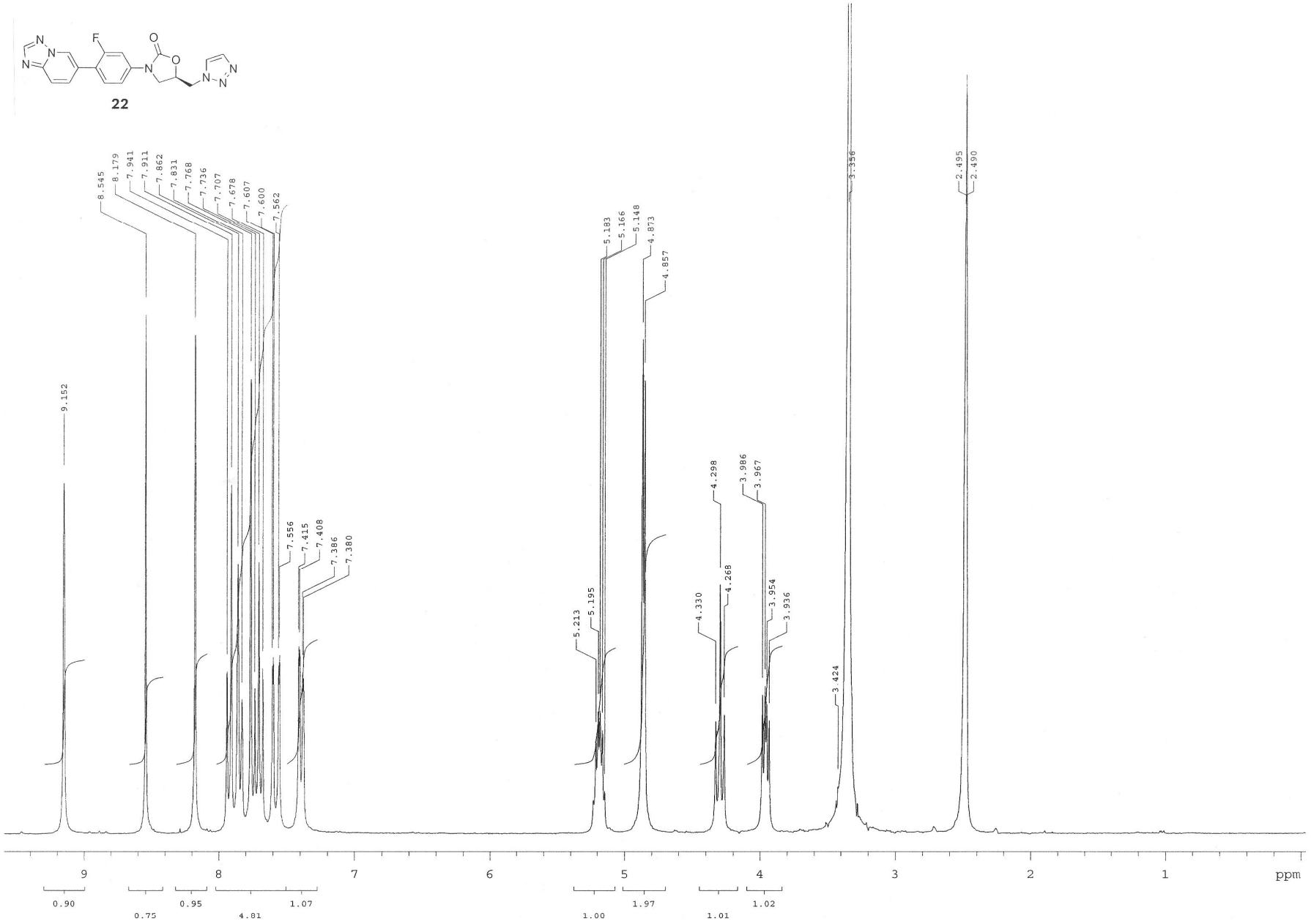
133.896
133.317
130.606
130.546
126.598
125.785
121.147
120.993
115.674
114.113
113.058
112.684
112.633
105.906
105.533
70.956
51.648
46.959
40.335
40.057
39.778
39.500
39.222
38.950
38.665
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


22
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8.179
7.941
7.911
7.862
7.831
7.768
7.736
7.707
7.678
7.607
7.600
7.562
7.556
7.415
7.408
7.386
7.380
5.213
5.195
5.183
5.166
5.148
4.873
4.857
4.330
4.298
4.268
3.986
3.967
3.954
3.936
3.424
3.356
2.495
2.490
ppm
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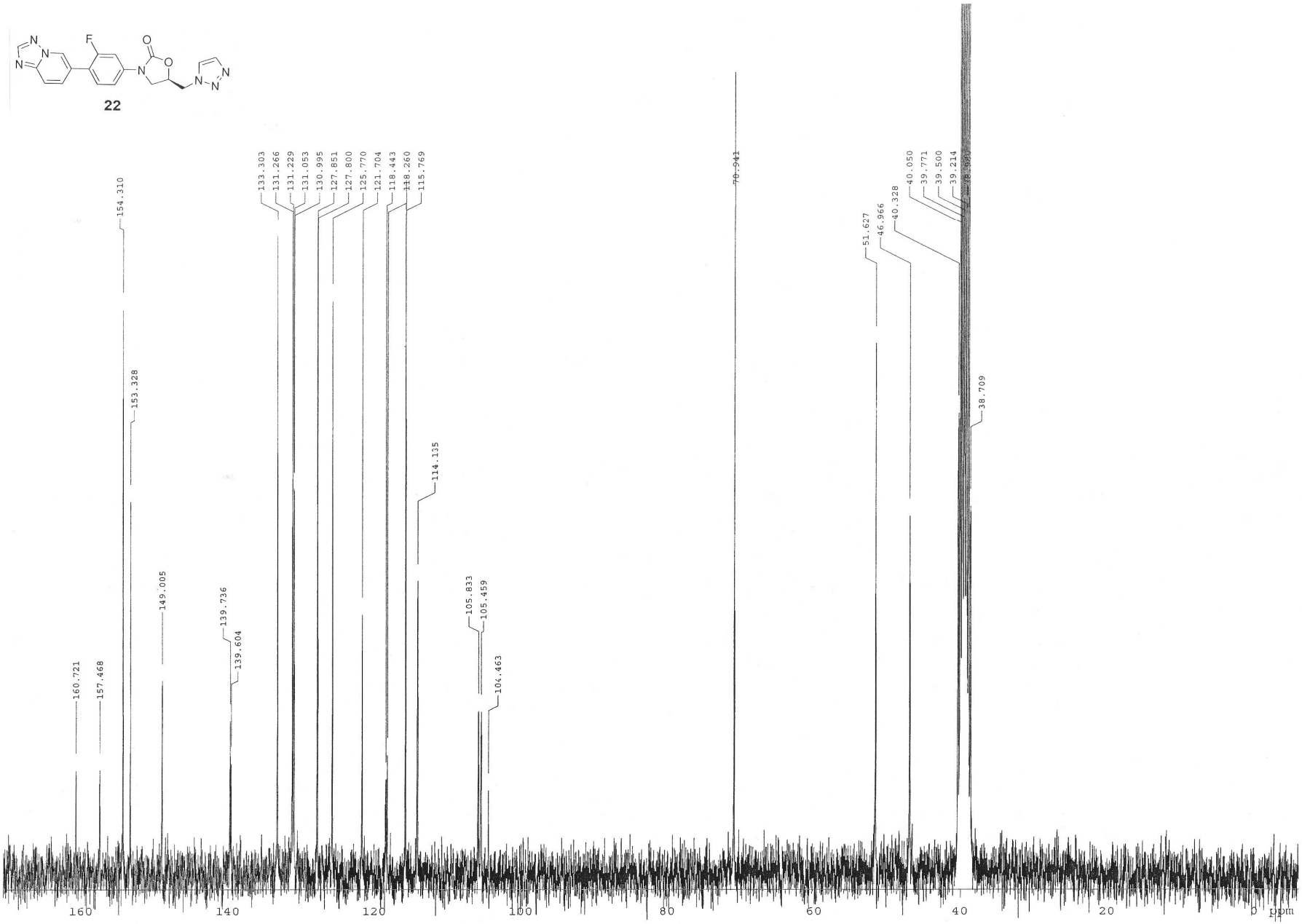
0.75
0.95
4.81
1.07
1.00
1.97
1.01
1.02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154.310
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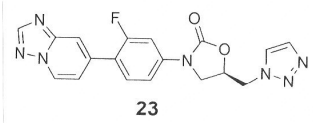
149.005
139.736
139.604
133.303
131.266
131.229
131.053
130.995
127.851
127.800
125.770
121.704
118.443
118.260
115.769
114.135
105.833
105.459
104.463
70.941
51.627
46.966
40.328
40.050
39.771
39.500
39.214
38.709
160
140
120
100
80
60
40
20
0 ppm



23

9.012
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8.181
7.995
7.768
7.755
7.725
7.603
7.558
7.430
7.396
7.371
3.533
5.216
5.199
5.186
5.171
4.876
4.860
4.333
4.301
4.271
3.992
3.973
3.961
3.942
1.467
2.490
9
8
7
6
5
4
3
2
1
ppm
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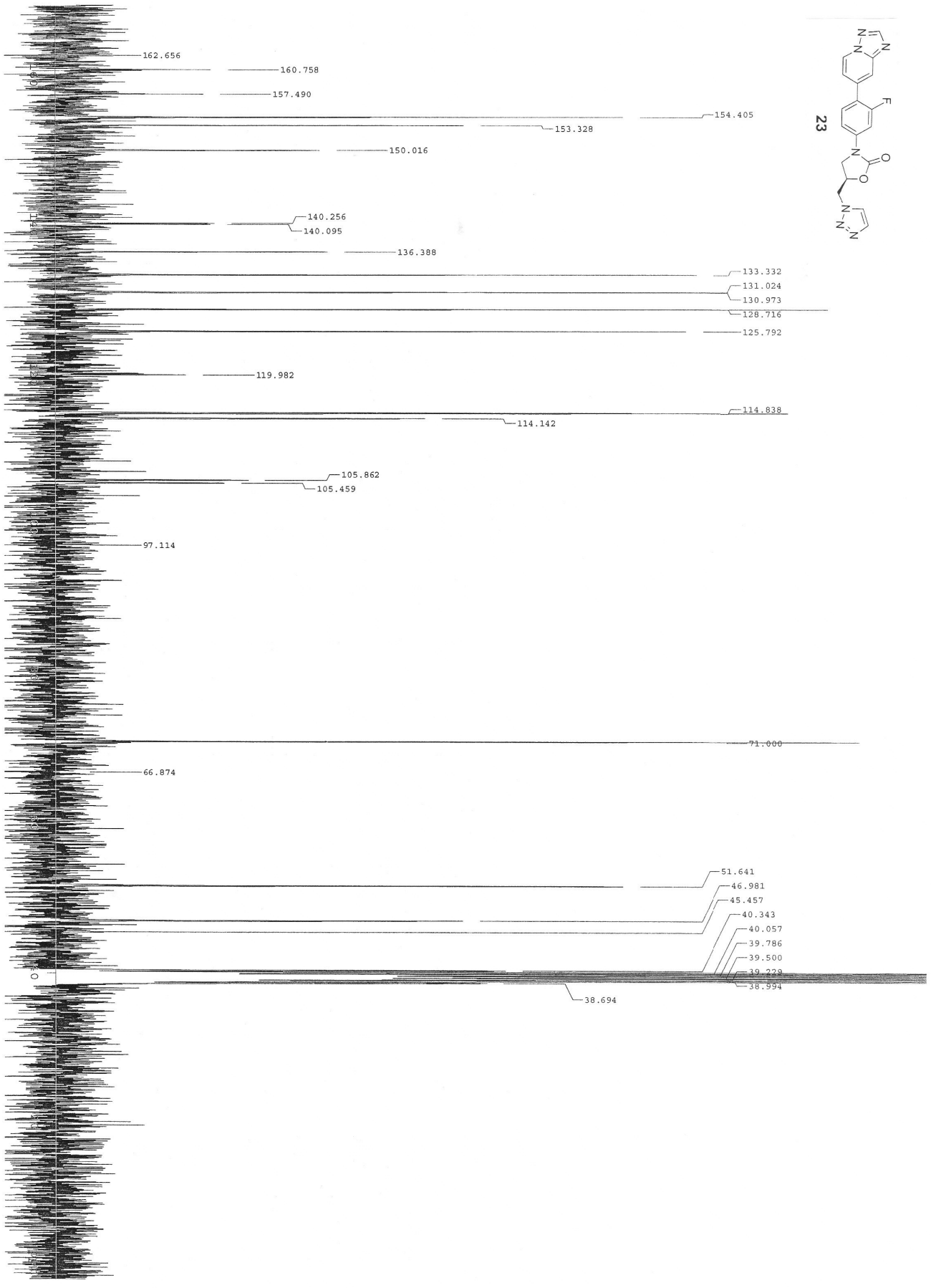
0.94
0.95
1.81
1.05
2.00
1.00
1.97
1.01
1.04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140.095
136.388
133.332
131.024
130.973
128.716
125.792
119.982
114.838
114.142
105.862
105.459
97.114
71.000
66.874
51.641
46.981
45.457
40.343
40.057
39.786
39.500
39.228
38.994
38.694
23