

# Assessing the Role of Malonamide Linker in the Design of Po-tent Dual Inhibitors of Factor Xa and Cholinesterases

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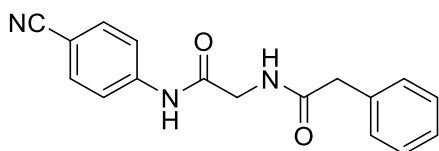
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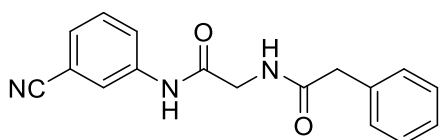
## 1. Synthesis and spectroscopic data

### Synthesis of compounds 2a-c.

Compounds **2a** and **2b** have been prepared by following the general procedure described in the paper manuscript.



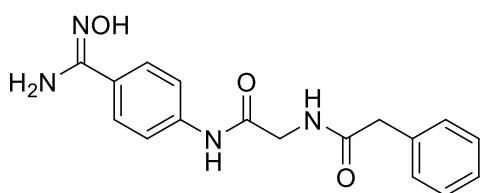
*4-cyano-N-[3-(phenyl-4-yl)-2-oxopropyl]benzamide (2b)*. Colorless oil, yield 23% (350 mg). IR  $\text{cm}^{-1}$ : 3274, 2228, 1683, 1649, 1603.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta_{\text{H}}$ : 9.79 (s, 1H), 7.58 (d,  $J = 8.8$  Hz, 2H), 7.47 (d,  $J = 8.8$  Hz, 2H), 7.30 – 7.19 (m, 5H), 6.92 (m, 1H), 3.99 (d,  $J = 5.2$  Hz, 2H), 3.56 (s, 2H).



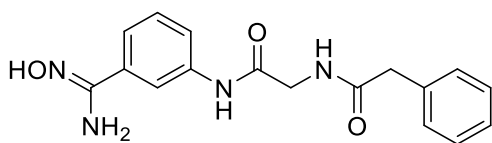
*3-cyano-N-[3-(phenyl-4-yl)-2-oxopropyl]benzamide (2b)*. Brown oil, yield 45% (100 mg). IR  $\text{cm}^{-1}$ : 3290, 2222, 1650, 1100, 704.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta_{\text{H}}$  8.12 (t,  $J = 1.7$  Hz, 1H), 7.99 (s, 1H), 7.90 (d,  $J = 7.7$  Hz, 1H), 7.81 (d,  $J = 2.0$  Hz, 1H), 7.45 (7,  $J = 7.5$  Hz, 1H), 7.24 (d,  $J = 7.7$  Hz, 1H), 7.20 – 7.10 (m, 3H), 6.98 – 6.87 (m, 2H) 4.51 (d,  $J = 5.8$  Hz, 2H), 4.20 (d,  $J = 5.0$  Hz, 2H).

### Synthesis of compounds 3a-c.

The synthesis of compound **3c** has been reported as an example in the paper manuscript. Compounds **3a** and **3b** have been prepared by following the same reported procedure.



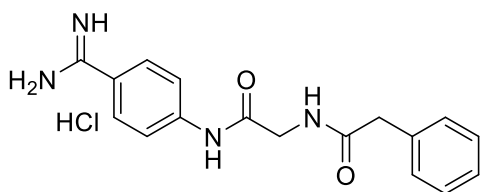
*N-[4-(hydroxyamidino)phenyl]-2-(phenylacetamido) acetamide (4a)*. White microcrystalline solid, yield 84% (400 mg). IR  $\text{cm}^{-1}$ : 3398, 3329, 1690, 1643, 1530, 833.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta_{\text{H}}$ : 10.06 (s, 1H), 9.50 (s, 1H), 8.38 (t,  $J = 5.8$  Hz, 1H), 7.59 (d,  $J = 9$  Hz, 2H), 7.54 (d,  $J = 9$  Hz, 2H), 7.27 (s, 2H), 5.72 (s, 2H), 3.89 (d,  $J = 5.8$  Hz, 2H), 3.50 (s, 2H).



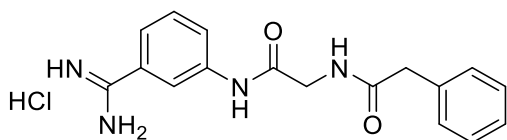
*N*-[[3-(*N*-hydroxycarbamimidoil)-phenylcarbamoyl]-methyl]-2-phenylacetamide (**3b**). White-grey amorphous powder, yield 51% (255 mg). IR  $\text{cm}^{-1}$ : 3444.8, 3400.5, 1678.5, 1646.8.  $^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta_{\text{H}}$ : 10.04 (s, 1H), 9.66 (s, 1H), 8.38 (t,  $J = 8.0$  Hz, 1H), 7.85 (s, 1H), 7.60 (s, 1H), 7.30-7.19 (m, 7H), 5.82 (s, 1H), 3.87 (d,  $J = 5.5$  Hz 2H), 3.59 (s, 2H).

### Synthesis of compounds 4a-c.

The synthesis of compound **4c** has been reported as an example in the paper manuscript. Compounds **4a** and **4b** have been prepared by following the same reported procedure.



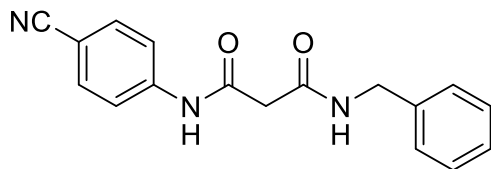
*N*-(4-amidinophenyl)-2-(phenylacetamido) acetamide hydrochloride (**4a**). White solid, yield 68% (290 mg), M.p. 235-238 °C. IR  $\text{cm}^{-1}$ : 3375, 3318, 3239, 1685, 1663, 1525, 845, 737.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta_{\text{H}}$ : 10.58(s, 1H), 9.20 (s, 2H), 8.97 (s, 2H), 8.47 (t,  $J = 5.8$  Hz, 1H), 7.78 (s, 4H), 7.27 (s, 5H), 3.93 (d,  $J = 5.8$  Hz, 2H), 3.50 (s, 2H). HRMS [ESI],  $m/z$ : 311.1500  $[\text{M}+\text{H}]^+$  for  $\text{C}_{17}\text{H}_{19}\text{N}_4\text{O}_2^+$ . Anal. Calc. for  $\text{C}_{17}\text{H}_{19}\text{N}_4\text{O}_2\text{Cl}$ , %: C, 58.87; H, 5.52; N, 16.15; found, %: C, 58.98; H, 5.62; N, 16.22.



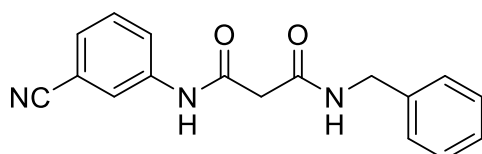
*N*-[(3-carbamimidoil-phenyl carbamoyl)-methyl]-2-phenyl-acetamide (**4b**). White solid, yield 63% (432 mg), m.p. 269-270 °C. IR  $\text{cm}^{-1}$ : 3434.7, 3255.9, 1701, 1687.3.  $^1\text{H}$ -NMR ( $d_6$ -DMSO)  $\delta$ : 10.48 (s, 1H), 9.35 (s, 2H), 9.10 (s, 2H), 8.48 (s, 1H), 8.07 (s, 1H), 7.80 (d,  $J = 9$  Hz, 1H), 7.25 (t,  $J = 6$  Hz, 1H), 7.44 (d,  $J = 6$  Hz, 1H), 7.2 (m, 5H), 3.91(d,  $J = 5.6$  Hz, 2H), 3.5 (s, 2H). HRMS [ESI],  $m/z$ : 311.1511  $[\text{M}+\text{H}]^+$  for  $\text{C}_{17}\text{H}_{19}\text{N}_4\text{O}_2^+$ . Anal. Calc. for  $\text{C}_{17}\text{H}_{19}\text{N}_4\text{O}_2\text{Cl}$ , %: C, 58.87; H, 5.52; N, 16.15; found, %: C, 59.00; H, 5.66; N, 16.12.

### Synthesis of compounds 6a-e, 7a-l, 8a-b, 9a-b, 10a-c, 11a-b.

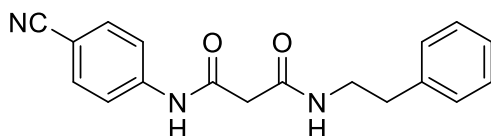
The synthesis of compound **7h** has been reported as an example in the paper manuscript. Compounds **6a-e**, **7a-l**, **8a-b**, **9a-b**, **10a-c**, **11a-b** have been prepared by following the same reported procedure.



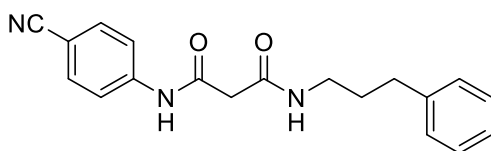
*N*<sup>1</sup>-benzyl-*N*<sup>3</sup>-(4-cyanophenyl)malonamide (**6a**). Brown oil, yield 52% (440 mg). IR  $\text{cm}^{-1}$ : 3270, 2221, 1670, 1632, 711.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta_{\text{H}}$ : 10.30 (s, 1H), 8.01 (s, 1H), 7.57 (d,  $J$  = 9.0 Hz, 2H), 7.42 (d,  $J$  = 9.0 Hz, 2H), 7.20-7.11 (m, 3H), 7.05 (d,  $J$  = 7.5 Hz, 2H), 4.25 (d,  $J$  = 4.0 Hz, 2H), 3.29 (s, 2H).



*N*<sup>1</sup>-benzyl-*N*<sup>3</sup>-(3-cyanophenyl)malonamide (**6b**). Brown oil, yield 22% (140 mg). IR  $\text{cm}^{-1}$ : 3268, 2222, 1672, 1635, 702.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta_{\text{H}}$ : 10.45 (s, 1H), 8.65 (t,  $J$  = 5.5 Hz, 1H), 8.10 (s, 1H), 7.80 – 7.50 (m, 3H), 7.50 (d,  $J$  = 8.5 Hz, 2H), 7.22-7.10 (m, 3H), 4.29 (d,  $J$  = 5.0 Hz, 2H), 3.27 (s, 2H).

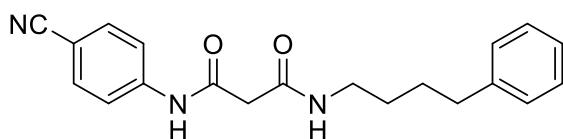


*N*<sup>1</sup>-(4-[cyanophenyl])-*N*<sup>3</sup>-(4-phenylethyl)malonamide (**6c**). White solid, yield 74% (555 mg). IR  $\text{cm}^{-1}$ : 3296, 2230, 1671, 1643, 1600, 1545, 836, 698.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta_{\text{H}}$ : 10.19 (s, 1H), 7.70 (d,  $J$  = 8.8 Hz, 2H), 7.34 – 7.19 (m, 5H), 6.41 (m, 1H), 3.62 – 3.55 (m, 2H), 3.28 (s, 2H), 2.85 (t,  $J$  = 6.9 Hz, 2H).

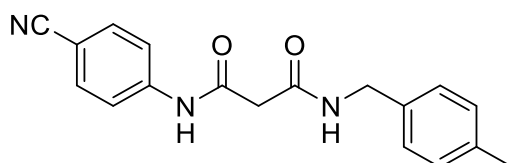


*N*<sup>1</sup>-(4-[cyanophenyl])-*N*<sup>3</sup>-(4-phenylpropyl)malonamide (**6d**). White solid, yield 67% (1.05 g). IR  $\text{cm}^{-1}$ : 3289, 2226, 1671, 1632, 1599, 1536, 696.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta_{\text{H}}$ : 10.13 (s, 1H),

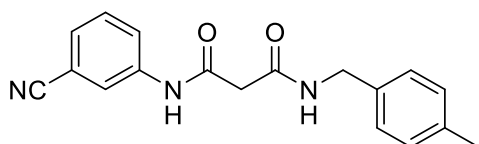
7.71 (d,  $J = 8.7$  Hz, 2H), 7.60 (d,  $J = 8.7$  Hz, 2H), 7.31 – 7.16 (m, 5H), 6.28 (m, 1H), 3.34 (q,  $J = 6.5$  Hz, 2H), 3.30 (s, 2H), 2.68 (t,  $J = 7.5$  Hz, 2H), 1.90 (quintet,  $J = 7.4$  Hz, 2H).



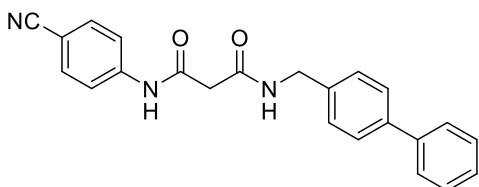
*N*<sup>1</sup>-(4-[cyanophenyl])-*N*<sup>3</sup>-[4-(phenyl)butyl] malonamide (**6e**). White solid, yield 49% (800 mg). IR  $\text{cm}^{-1}$ : 3442, 3311, 2229, 1673, 1638, 1603, 1543, 832, 700. <sup>1</sup>H NMR (300 MHz, DMSO- $\text{d}_6$ ),  $\delta_{\text{H}}$ : 10.20 (s, 1H), 7.70 (d,  $J = 8.7$  Hz, 2H), 7.59 (d,  $J = 8.7$  Hz, 2H), 7.29 – 7.14 (m, 5H), 6.48 (s, 1H), 3.33 – 3.30 (m, 4H), 2.26 (t,  $J = 7.1$  Hz, 2H), 1.71 – 1.54 (m, 4H).



*N*<sup>1</sup>-(4-[cyanophenyl])-*N*<sup>3</sup>-(4-methylbenzyl)malonamide (**7a**). White solid, yield 48% (425 mg). IR  $\text{cm}^{-1}$ : 3274, 2226, 1672, 1635, 835, 811. <sup>1</sup>H NMR (300 MHz, DMSO- $\text{d}_6$ ),  $\delta_{\text{H}}$ : 10.32 (s, 1H), 8.02 (s, 1H), 7.58 (d,  $J = 8.9$  Hz, 2H), 7.41 (d,  $J = 8.9$  Hz, 2H), 7.02 (d,  $J = 6.5$  Hz, 2H), 6.96 (d,  $J = 6.5$  Hz, 2H), 4.23 (d,  $J = 3.3$  Hz, 2H), 3.25 (s, 2H), 2.16 (s, 3H).

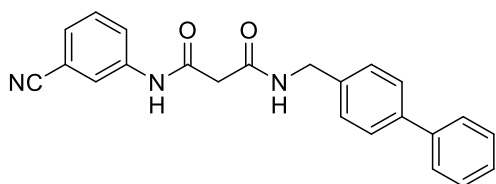


*N*<sup>1</sup>-(3-cyanophenyl)-*N*<sup>3</sup>-(4-methylbenzyl)-malonamide (**7b**). Pale brown solid, yield 40% (300 mg). IR  $\text{cm}^{-1}$ : 3435, 3297, 2232, 1675, 1650. <sup>1</sup>H-NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 10.01 (s, 1H), 8.05 (s, 1H), 7.71-7.67 (m, 1H), 7.44-7.39 (m, 2H), 7.25 (s, 1H), 7.16 (s, 3H), 6.5 (s, 1H), 4.43 (d,  $J = 3$  Hz, 2H), 3.58 (s, 2H), 2.36 (s, 3H).

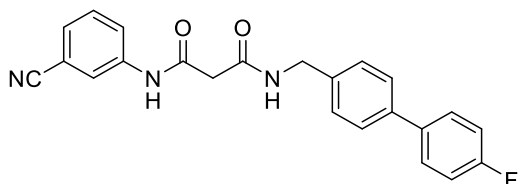


*N*<sup>1</sup>-[4-(cyano)-phenyl]-*N*<sup>3</sup>-biphenylmethylenmalonamide (**7c**). White solid, yield 68% (450 mg). IR  $\text{cm}^{-1}$ : 3269, 2221, 1662, 1630, 830, 810. <sup>1</sup>H NMR (300 MHz, DMSO- $\text{d}_6$ ),  $\delta_{\text{H}}$ : 10.32 (s, 1H), 8.02

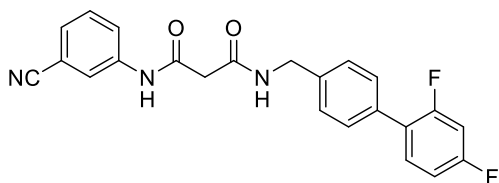
(s, 1H), 7.60 (d,  $J = 8.5$  Hz, 2H), 7.45 (d,  $J = 8.5$  Hz, 2H), 7.40-7.35 (m, 4H), 7.25-7.10 (m, 5H), 4.25 (d,  $J = 4.5$  Hz, 2H), 3.22 (s, 2H).



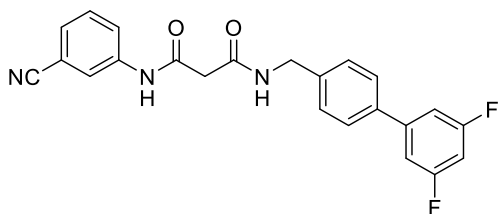
*N*<sup>1</sup>-[3-(cyano)-phenyl]-*N*<sup>3</sup>-biphenylmethylenmalonamide (**7d**). Pale brown oil, yield 30% (150 mg). IR  $\text{cm}^{-1}$ : 3446, 3284, 2226, 1674, 1632, 1601, 1538, 761, 690. <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta_{\text{H}}$ : 10.13 (s, 1H), 7.71 (d,  $J = 8.8$  Hz, 2H), 7.65 – 7.32 (m, 11H), 6.57 (br s, 1H), 4.52 (d,  $J = 5.8$  Hz, 2H), 3.4 (s, 2H).



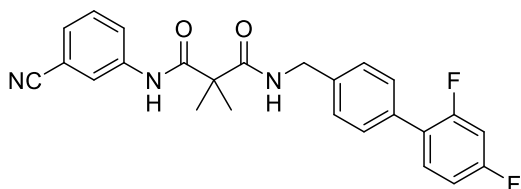
*N*<sup>1</sup>-(3-cyanophenyl)-*N*<sup>3</sup>-((4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)malonamide (**7g**). Brown oil, yield 14% (192 mg). IR  $\text{cm}^{-1}$ : 3282, 2221, 1672, 1635, 1600, 690. <sup>1</sup>H NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta_{\text{H}}$ : 10.49 (s, 1H), 8.63 (t,  $J = 5.8$  Hz, 1H), 8.09 (s, 1H), 7.80 – 7.50 (m, 7H), 7.38 – 7.23 (m, 4H), 4.33 (d,  $J = 5.8$  Hz, 2H), 3.31 (s, 2H).



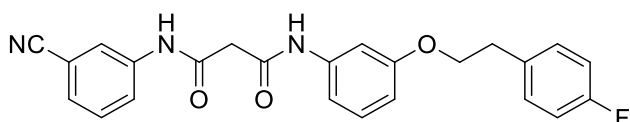
*N*<sup>1</sup>-(3-cyanophenyl)-*N*<sup>3</sup>-(2',4'-difluorobiphenyl)methylen malonamide (**7h**). Yellow oil, yield 27% (70 mg). IR  $\text{cm}^{-1}$ : 3321, 2231, 1681, 1651, 1431, 964, 795. <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta_{\text{H}}$ : 10.09 (s, 1H), 8.04 (s, 1H), 7.74 – 7.61 (m, 1H), 7.50 – 7.28 (m, 8H), 6.96 – 6.83 (m, 2H), 4.51 (d,  $J = 5.8$  Hz, 2H), 3.45 (s, 2H).



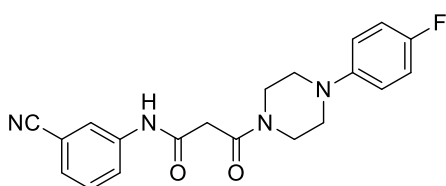
*N*<sup>1</sup>-[3-(cyano)phenyl]-*N*<sup>3</sup>-(3',5'-difluoro) biphenylmethylenmalonamide (**7i**). Brown oil, yield 62% (635 mg). IR cm<sup>-1</sup>: 3327, 2929, 2226, 1681, 1625, 1485, 1116, 986, 792, 682. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.48 (s, 1H), 8.66 (t, *J* = 6 Hz, 1H), 8.1 (s, 1H), 7.82 – 7.75 (m, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.65 – 7.35 (m, 5H), 7.23 – 7.15 (m, 1H), 4.35 (d, *J* = 5.9 Hz, 2H), 3.32 (s, 2H).



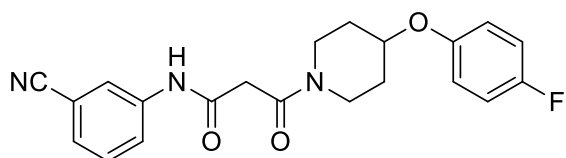
*N*<sup>1</sup>-(3-cyanophenyl)-*N*<sup>3</sup>-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)methyl)-2,2-dimethylmalonamide (**7l**). Brown oil, yield 67% (870 mg). IR cm<sup>-1</sup>: 3345, 3285, 3074, 2233, 1652, 1604, 1527, 1494, 964, 848, 800, 683. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ<sub>H</sub>: 9.73 (s, 1H), 8.05 (s, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.49 – 7.31 (m, 6H), 6.99 – 6.88 (m, 2H), 6.52 (br s, 1H), 4.53 (d, *J* = 5.5 Hz, 2H), 1.60 (s, 6H).



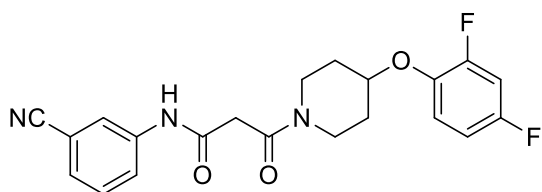
*N*<sup>1</sup>-(3-cyanophenyl)-*N*<sup>3</sup>-(3-(4-fluorophenethoxy)phenyl)malonamide (**8a**). Orange oil, yield 30%. IR cm<sup>-1</sup>: 3326, 2928, 2232, 1663, 1609, 1594, 1501, 1431, 1220, 1157, 1041, 830, 792, 683. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 9.71 (s, 1H), 8.76 (s, 1H), 8.06 (d, 1H), 7.72-7.69 (m, 1H), 7.42-7.40 (m, 2H), 7.25-7.19 (m, 4H), 7.04-6.95 (m, 3H), 6.71-6.67



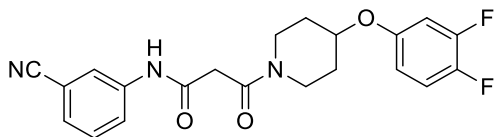
*N*-[4-(cyano)phenyl]-3-[4-(4-fluorophenyl)piperazin-1-yl] propanamide (**9a**). Pale yellow solid. M.P. = 146-148°C. IR cm<sup>-1</sup>: 3426, 2226, 1693, 1619, 1557, 1511, 1236, 822, 703, 661. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ<sub>H</sub>: 10.49 (s, 1H), 8.06 (d, *J* = 1.1 Hz, 1H), 7.71 (d, *J* = 7.1 Hz, 1H), 7.46 – 7.36 (2H, m), 7.00 (d, *J* = 9.07, 1H), 6.97 (d, *J* = 9.07 Hz, 1H), 6.90 (d, *J* = 9.13 Hz, 1H), 6.88 (d, *J* = 9.13 Hz, 1H), 3.84 (t, *J* = 5.09 Hz, 2H), 3.75 (t, *J* = 5.09 Hz, 2H), 3.55 (s, 2H), 3.18 – 3.09 (m, 4H).



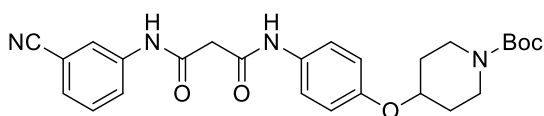
*N*-(3-cyanophenyl)-3-(4-(4-fluorophenoxy)piperidin-1-yl)-3-oxopropanamide (**10a**). Brown oil, yield 31% (250 mg). IR  $\text{cm}^{-1}$ : 3331, 2861, 2238, 1702, 1639, 1500, 1428, 1225, 1053, 830, 762.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ),  $\delta_{\text{H}}$ : 10.45 (s, 1 H), 8.08 (s, 1 H), 7.76 (m, 1 H), 7.52 (m, 2 H), 7.09 (m, 2 H), 6.99 (m, 2 H), 4.55 (m, 1 H), 3.85 (m, 1 H), 3.71 (m, 1 H), 3.56 (s, 2 H), 3.32 (m, 2 H), 1.90 (m, 2 H), 1.63 (m, 1 H), 1.50 (m, 1 H).



*N*-(3-cyanophenyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-oxopropanamide (**10b**). Dark brown oil, yield 60% (715 mg). IR  $\text{cm}^{-1}$ : 3335, 1700, 1634, 831, 760.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta_{\text{H}}$ : 10.60 (s, 1H), 8.05 (s, 1H), 7.73 – 7.65 (m, 1H), 7.46 – 7.35 (m, 2H), 7.02 – 6.77 (m, 3H), 4.46 (quintet,  $J = 4.4$  Hz, 1H), 3.90 – 3.67 (m, 4H), 3.50 (s, 2H), 1.95 – 1.85 (m, 4H).

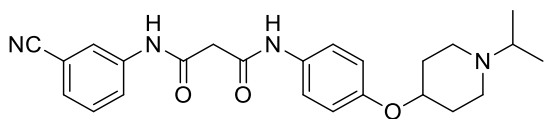


*N*-(3-cyanophenyl)-3-(4-(3,4-difluorophenoxy)piperidin-1-yl)-3-oxopropanamide (**10c**). Dark brown oil, yield 35% (590 mg). IR  $\text{cm}^{-1}$ : 3328, 1675, 1631, 831, 760.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta_{\text{H}}$ : 10.55 (s, 1H), 8.05 (s, 1H), 7.70 (dt,  $J = 7.1, 1.1$  Hz, 1H), 7.48 – 7.36 (m, 2H), 7.06 (q,  $J = 9.4$  Hz, 1H), 6.79 – 6.70 (m, 1H), 6.65 – 6.58 (m, 1H), 4.50 (quintet,  $J = 4.4$  Hz, 1H), 3.90 – 3.67 (m, 4H), 3.50 (s, 2H), 1.95 – 1.85 (m, 4H).



*tert*-butyl-4-[4-({3-[(3-cyanophenyl)amino]-3-oxopropanoylamino}phenoxy)piperidine-1-carboxylate (**11a**). Pale brown amorphous solid, yield 75% (950mg). IR  $\text{cm}^{-1}$ : 3311, 2331, 1693, 1239, 1173, 1030, 867, 831, 794, 684.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta_{\text{H}}$ : 9.80 (s, 1H), 8.58 (s, 1H), 8.07 (d,  $J = 1$  Hz, 1H) 7.79-7.69 (m, 1H), 7.45 – 7.26 (m, 4H), 6.90 (d,  $J = 9$  Hz, 2H), 4.45 – 4.39

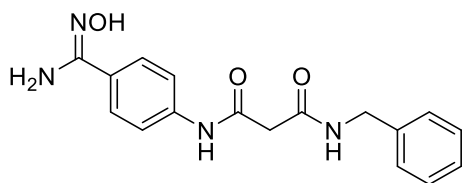
(m, 1H), 3.73 – 3.64 (m, 2H), 3.57 (s, 2H), 3.40-3.25 (m, 2H), 1.94-1.85 (m, 2H), 1.80 - 1.65 (m, 2H), 1.47 (s, 9H). ).



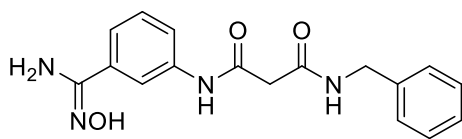
*N*<sup>1</sup>-{3-(cyano)phenyl}-*N*<sup>3</sup>-[4-(1-isopropylpiperidin-4-iloxy)phenyl]malonamide (**11b**). Dark brown oil, yield 42% (490 mg). IR  $\text{cm}^{-1}$ : 3327, 2238, 1678, 1639, 1225, 1053, 760. <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta_{\text{H}}$ : 9.83 (s, 1H), 8.46 (s, 1H), 7.42 (m, 2H), 7.25 (m, 4H), 6.96 (m, 2H), 4.18 (m, 1H), 3.46 (m, 2H), 2.82 (m, 4H), 2.47 (m, 4H), 2.16 (d, 6H), 1.09 (m, 1H). ESI-MS:  $m/z$ : 421.0  $[\text{M}+\text{H}]^+$ .

### Synthesis of compounds 12a-e, 13a-l, 14a-b, 15a-b, 16a-c, 17a-b.

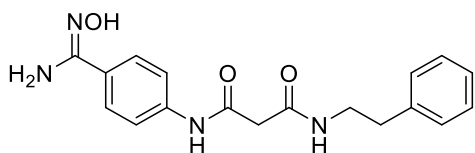
The synthesis of compound **13h** has been reported as an example in the paper manuscript. Compounds **12a-e**, **13a-l**, **14a-b**, **15a-b**, **16a-c**, **17a-b** have been prepared by following the same reported procedure.



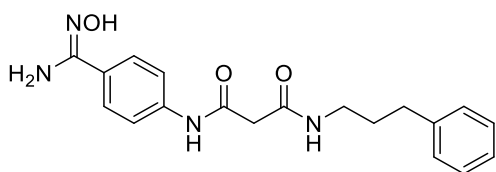
*N*<sup>1</sup>-{4-[amino(hydroxyimino)methyl]phenyl}-*N*<sup>3</sup>-(4-phenylethyl)malonamide (**12a**). Amorphous white powder, yield 42% (311mg). IR  $\text{cm}^{-1}$ : 3410, 3322, 1683 <sup>1</sup>H NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta_{\text{H}}$ : 10.18 (s, 1H), 9.52 (s, 1H), 7.59 (d,  $J = 9$  Hz, 2H), 7.48 (d,  $J = 9$  Hz, 2H), 7.28 – 7.15 (m, 5H), 5.65 (d,  $J = 5.5$  Hz, 2H), 3.33 (s, 2H).



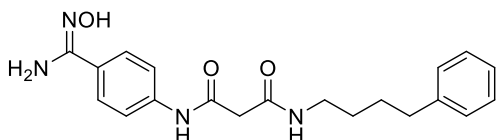
*N*<sup>1</sup>-{4-[amino(hydroxyimino)methyl]phenyl}-*N*<sup>3</sup>-(4-phenylethyl)malonamide (**12b**). Amorphous white powder, yield 66% (365 mg). IR  $\text{cm}^{-1}$ : 3429, 3390, 3318, 1645, 801 <sup>1</sup>H NMR (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$ : 10.15 (s, 1H), 9.60 (s, 1H), 8.29 (s, 1H), 7.87 (s, 1H), 7.62-7.60 (m, 1H), 7.30-7.28 (m, 2H), 7.25-7.09 (m, 4H), 5.73 (s, 2H), 4.24 (d,  $J = 5.3$  Hz, 2H), 3.28 (s, 2H).



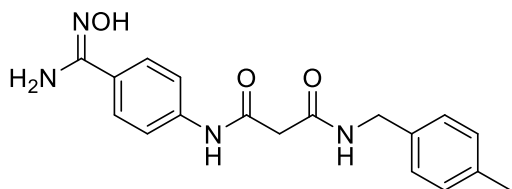
*N*<sup>1</sup>-{4-[amino(hydroxyimino)methyl]phenyl}-*N*<sup>3</sup>-(4-phenylethyl)malonamide (**12c**). Amorphous white powder, yield 82% (911mg). IR cm<sup>-1</sup>: 3416, 3324, 1683, 1635, 1527, 841, 698. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.17 (s, 1H), 9.53 (s, 1H), 8.16 (t, *J* = 5.3 Hz, 1H), 7.60 (d, *J* = 9 Hz, 2H), 7.56 (d, *J* = 9 Hz, 2H), 7.29 – 7.16 (m, 5H), 5.77 (s, 2H), 3.28 (t, *J* = 7.7 Hz, 2H), 3.22 (s, 2H), 2.71 (t, *J* = 7.7 Hz, 2H).



*N*<sup>1</sup>-{4-[amino(hydroxyimino)methyl]phenyl}-*N*<sup>3</sup>-(4-phenylpropyl)malonamide (**12d**). Amorphous white powder, yield 86% (862mg). IR cm<sup>-1</sup>: 3330, 1662, 1634, 1543, 842, 697. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.18 (s, 1H), 9.52 (s, 1H), 8.10 (t, *J* = 5.5 Hz, 1H), 7.59 (d, *J* = 9 Hz, 2H), 7.55 (d, *J* = 9 Hz, 2H), 7.28 – 7.15 (m, 5H), 5.74 (s, 2H), 3.23 (s, 2H), 3.11 – 3.04 (m, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.70 (m, *J* = 7.5 Hz, 2H).



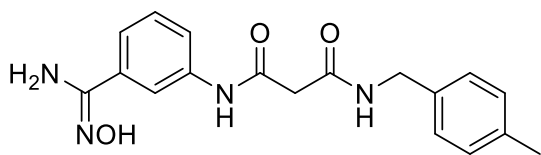
*N*<sup>1</sup>-{4-[amino(hydroxyimino)methyl]phenyl}-*N*<sup>3</sup>-[4-(phenyl)butyl] malonamide (**12e**). Amorphous white powder, yield 58% (446mg). IR cm<sup>-1</sup>: 3425, 3354, 1682, 1635, 1532, 700. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.18 (s, 1H), 9.56 (s, 1H), 8.05 (t, *J* = 5.2 Hz, 1H), 7.59 (d, *J* = 9.1 Hz, 2H), 7.54 (d, *J* = 9.1 Hz, 2H), 7.27 – 7.14 (m, 5H), 5.81 (s, 2H), 3.20 (s, 2H), 3.08 (q, *J* = 6 Hz, 2H), 2.55 (t, *J* = 7.4 Hz, 2H), 1.56 (quintet, *J* = 7.4 Hz, 2H), 1.41 (quintet, *J* = 7.4 Hz, 2H).



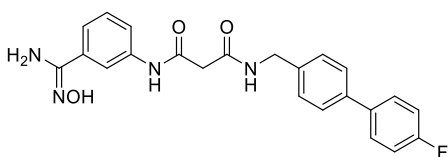
*N*<sup>1</sup>-{4-[amino(hydroxyimino)methyl]phenyl}-*N*<sup>3</sup>-(4-methylbenzyl)malonamide (**13a**). Amorphous white powder, yield 68% (450mg). IR cm<sup>-1</sup>: 3282, 1634, 1532, 837. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.19 (s, 1H), 9.52 (s, 1H), 8.51 (m, 1H), 7.59 (d, *J* = 8.9 Hz, 2H), 7.55 (d,

$J = 9$  Hz, 2H), 7.16 (d,  $J = 8.1$  Hz, 2H), 7.11 (d,  $J = 8.1$  Hz, 2H), 5.72 (s, 2H), 4.24 (d,  $J = 5.8$  Hz, 2H), 3.32 (s, 2H).

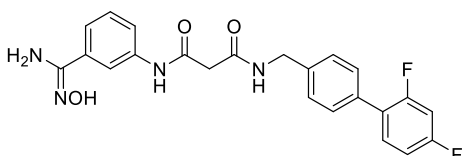
**13b.**



*N*<sup>1</sup>-(3-hydroxycarbamimidoylphenyl)-*N*<sup>3</sup>-(4-methyl-benzyl)-malonamide (**13b**). Amorphous white powder, yield 66% (730 mg). IR  $\text{cm}^{-1}$ : 3428, 3389, 3319, 1645, 1609, 800. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO)  $\delta$ : 10.15 (s, 1H), 9.60 (s, 1H), 8.29 (s, 1H), 7.87 (s, 1H), 7.62-7.60 (m, 1H), 7.30-7.28 (m, 2H), 7.25-7.09 (m, 4H), 5.73 (s, 2H), 4.24 (d,  $J = 5.5$  Hz, 2H), 3.28 (s, 2H), 2.06 (s, 3H).

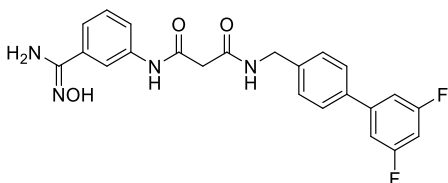


*N*<sup>1</sup>-((4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-*N*<sup>3</sup>-(3-(*N*'-hydroxycarbamimidoyl)phenyl)malonamide (**13g**). Amorphous white powder, yield 64% (134 mg). IR  $\text{cm}^{-1}$ : 3428, 3389, 3319, 1645, 1609, 800. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>),  $\delta_{\text{H}}$ : 10.25 (s, 1H), 9.64 (s, 1H), 8.61 (t,  $J = 5.8$  Hz, 1H), 7.88 (s, 1H), 7.7 – 7.56 (m, 5H), 7.38 – 7.21 (m, 6H), 5.80 (br s, 2H), 4.33 (d,  $J = 5.8$  Hz, 2H), 3.31 (s, 2H).



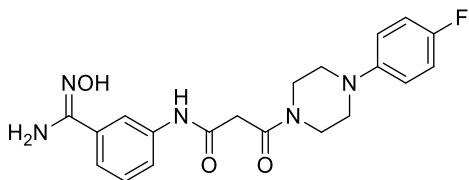
*N*<sup>1</sup>-((2',4'-difluoro-[1,1'-biphenyl]-4-yl)methyl)-*N*<sup>3</sup>-(3-(*N*'-hydroxycarbamimidoyl)phenyl)malonamide (**13h**). Amorphous white powder, yield 73% (67 mg). IR  $\text{cm}^{-1}$ : 3258, 2928, 2850, 1637, 1591, 1561, 1494, 1448, 1141, 1100, 806, 789; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>),  $\delta_{\text{H}}$ : 10.18 (s, 1H), 9.60 (s, 1H), 8.63 (t,  $J = 6.0$  Hz, 1H), 7.88 (s, 1H), 7.66 – 7.25 (m, 9H), 7.17 (td,  $J = 8.5, 2.6$  Hz, 1H), 5.73 (s, 2H), 4.35 (d,  $J = 5.9$  Hz, 2H), 3.32 (s, 2H).

**13i.**

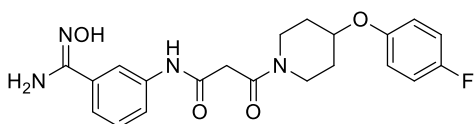


*N*<sup>1</sup>-{3-[amino(hydroxyimino)methyl]phenyl}-*N*<sup>3</sup>-(3',5'-difluoro) biphenylmethylenmalonamide (**13i**). Amorphous white powder, yield 90% (582 mg). IR cm<sup>-1</sup>: 3250, 2852, 1637, 805; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.18 (s, 1H), 9.60 (s, 1H), 8.66 (t, *J* = 6.0 Hz, 1H), 7.88 (s, 1H), 7.66 – 7.18 (m, 10H), 5.73 (s, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 3.32 (s, 2H).

**15a.**

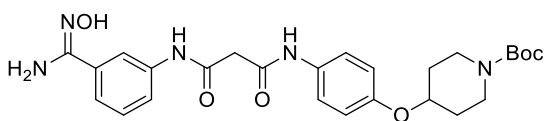


3-(4-(4-fluorophenyl)piperazin-1-yl)-*N*-(4-(*N'*-hydroxycarbamimidoyl)phenyl)-3-oxopropanamide (**15a**). Amorphous white powder, yield 81% (920 mg). IR cm<sup>-1</sup>: 3407.1, 1675.7, 1627.7, 1529.7, 1510.4, 1227.9, 828.7, 667.8. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.20 (s, 1H), 9.51 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.08 – 6.97 (m, 4H), 5.72 (s, 2H), 3.61 – 3.56 (m, 4H), 3.41 (t, *J* = 6.23, 2H), 3.10 – 3.03 (m, 4H).

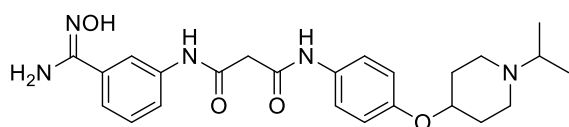


3-(4-(4-fluorophenoxy)piperidin-1-yl)-*N*-(3-(*N'*-hydroxycarbamimidoyl)phenyl)-3-oxopropanamide (**16a**). Amorphous white powder, yield 79% (320 mg). IR cm<sup>-1</sup>: 3256, 2928, 1635, 1591, 1562, 1494, 1447, 1142, 963. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.18 (s, 1H), 8.63 (br s, 1H), 7.92 (s, 1H), 7.62 – 7.54 (m, 1H), 7.35 – 7.23 (m, 2H), 7.15 – 6.95 (m, 4H), 5.73 (s, 2H), 4.55 (quintet, *J* = 3.8 Hz, 1H), 3.88 – 3.68 (m, 2H), 3.32 (s, 2H), 3.45 – 3.23 (m, 2H), 1.98 – 1.82 (m, 2H), 1.7 – 1.4 (m, 2H).

**17a.**



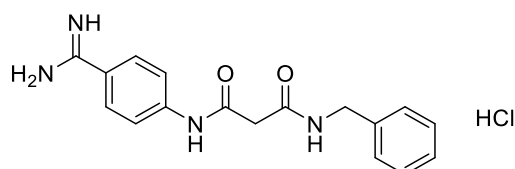
*t*-butyl 4-(4-({3-({3-[amino(hydroxyimino)methyl]phenyl}amino)-3-oxopropanoyl}amino)phenoxy)piperidine-1-carboxylate (**17a**). Amorphous white powder, yield 79% (930 mg). IR cm<sup>-1</sup>: 3310, 1668, 1546, 1508, 1428, 1237, 1109, 1031, 943, 831, 795. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ<sub>H</sub>: 9.76 (s, 1H), 9.47 (s, 1H), 7.63 (s, 1H), 7.50–7.23 (m, 4H), 7.19–7.06 (m, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 5.20 (s, 2H), 4.26 (m, 1H), 3.70 (s, 2H), 3.68–3.50 (m, 2H), 3.44–3.20 (m, 2H), 1.86–1.79 (m, 2H), 1.65–1.51 (m, 2H), 1.44 (s, 9H).



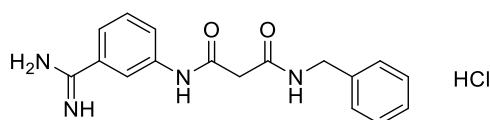
*N*<sup>1</sup>-{3-[amino(hydroxyimino)methyl]phenyl}-*N*<sup>3</sup>-[4-(1-isopropylpiperidin-4-iloxy)phenyl]malonamide (**17b**). Amorphous white powder, yield 97% (512 mg). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ <sub>H</sub>: 10,24 (s, 1H), 9,61 (t, *J* = 4,6 Hz, 1H), 7,56 (m, 2H), 7,39 (m, 2H), 6,68 (m, 2H), 6,47 (m, 2H), 5,73 (s, 2H), 4,34 (m, 2H), 4,07 (m, 1H), 3,32 (m, 8H), 2,48 (s, 6H).

### Synthesis of compounds 18a-e, 19a-l, 20a-b, 21a-b, 22a-c, 23a-b.

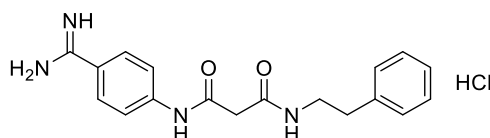
The synthesis of compound **19h** has been reported as an example in the paper manuscript. The amidine compounds have been prepared by following the same reported procedure.



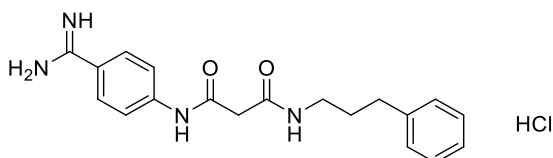
*N*<sup>1</sup>-{4-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-(benzyl)malonamide hydrochloride (**18a**). Pale yellow solid, yield 61% (290mg), M.p. 242 – 245 °C. IR  $\text{cm}^{-1}$ : 3363, 3240, 165, 1627.1, 1600, 843, 735. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ <sub>H</sub>: 10.78 (s, 1H), 9.25 (s, 2H), 8.99 (s, 2H), 8.64 (t, *J* = 5.5 Hz, 1H), 7.80 (s, 4H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.10-6.95 (m, 3H), 4.25 (d, *J* = 6.0 Hz, 2H), 3.37 (s, 2H). HRMS [ESI], *m/z*: 311.1504 [*M*+*H*]<sup>+</sup> for C<sub>17</sub>H<sub>19</sub>N<sub>4</sub>O<sub>2</sub>. Anal. Calc. for C<sub>17</sub>H<sub>19</sub>N<sub>4</sub>O<sub>2</sub>Cl, %: C, 58.87; H, 5.52; N, 16.15; found, %: C, 59.01; H, 5.54; N, 16.42.



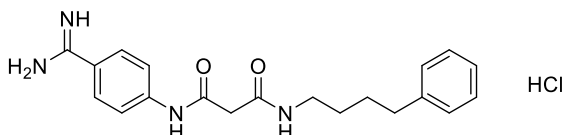
*N*<sup>1</sup>-(3-carbamimidoyl-phenyl)-*N*<sup>3</sup>-(benzyl) malonamide hydrochloride (**18b**) –White solid, yield 27% (150 mg) m.p. = 166-168 °C. IR  $\text{cm}^{-1}$ : 3292, 1680, 1625, 802; <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 10.64 (s, 1H), 9.32 (s, 2H), 9.10 (s, 2H), 8.63 (t, *J* = 5.5 Hz, 1H), 8.09 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.53 (t, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.20-7.00 (m, 5H), 4.22 (d, *J* = 5.5 Hz, 2H), 3.28 (s, 2H). HRMS [ESI], *m/z*: 311.1499 [*M*+*H*]<sup>+</sup> for C<sub>17</sub>H<sub>19</sub>N<sub>4</sub>O<sub>2</sub>. Anal. Calc. for C<sub>17</sub>H<sub>19</sub>N<sub>4</sub>O<sub>2</sub>Cl, %: C, 58.87; H, 5.52; N, 16.15; found, %: C, 58.91; H, 5.60; N, 16.51.



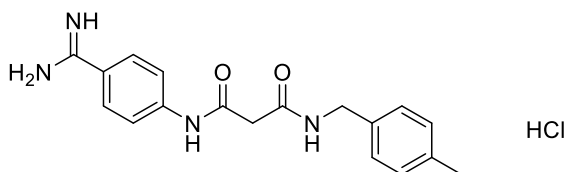
*N*<sup>1</sup>-{4-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-phenylethyl malonamide hydrochloride (**18c**). White solid, yield 46% (340 mg), M.p. 242–245 °C. IR cm<sup>-1</sup>: 3231.8, 1676.8, 1624.2, 1522.4, 842.5. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.77 (s, 1H), 9.25 (s, 2H), 9.00 (s, 2H), 8.30 (t, *J* = 5.5 Hz, 1H), 7.80 (s, 4H), 7.28 – 7.16 (m, 5H), 3.32 – 3.25 (m, 4H). HRMS [ESI], *m/z*: 325.1662 [M+H]<sup>+</sup> for C<sub>18</sub>H<sub>21</sub>N<sub>4</sub>O<sub>2</sub>. Anal. Calc. for C<sub>18</sub>H<sub>21</sub>N<sub>4</sub>O<sub>2</sub>Cl, %: C, 59.91; H, 5.87; N, 15.52; found, %: C, 59.87; H, 5.80; N, 15.57.



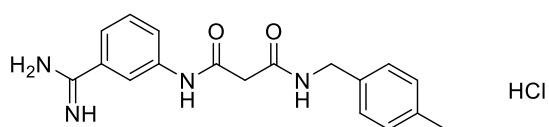
*N*<sup>1</sup>-{4-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-[3-(phenyl)]propyl malonamide hydrochloride (**18d**). White solid, yield 47% (350 mg), M.p. 220–223 °C. IR cm<sup>-1</sup>: 3232, 1675, 1603, 841, 1524. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.78 (s, 1H), 9.24 (s, 2H), 8.98 (s, 2H), 8.26 (t, *J* = 5.5 Hz, 1H), 7.80 (s, 4H), 7.28 – 7.17 (m, 5H), 3.32 (s, 2H), 3.07 (q, *J* = 5.8 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 1.69 (quintet, *J* = 7.5 Hz, 2H). HRMS [ESI], *m/z*: 339.1820 [M+H]<sup>+</sup> for C<sub>19</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>. Anal. Calc. for C<sub>19</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>Cl, %: C, 60.87; H, 6.18; N, 14.94; found, %: C, 61.00; H, 6.44; N, 14.87.



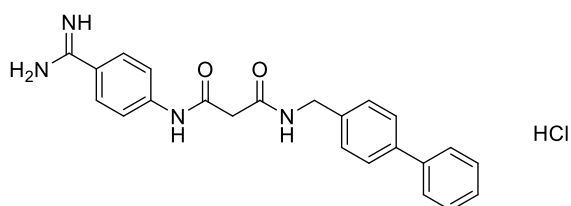
*N*<sup>1</sup>-{4-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-[4-(phenyl)butyl] malonamide hydrochloride (**18e**). White crystalline solid, yield 81% (340 mg), M.p. 244 – 246 °C. IR cm<sup>-1</sup>: 3385.3, 3025.0, 1675.9, 1602.3, 1523.0, 841.2. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.75 (s, 1H), 9.24 (s, 2H), 8.98 (s, 2H), 8.18 (t, *J* = 5.5 Hz, 1H), 7.80 (s, 4H), 7.26 – 7.11 (m, 5H), 3.29 (s, 2H), 3.08 (q, *J* = 6.0 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.56 (quintet, *J* = 7.5 Hz, 2H), 1.41 (quintet, *J* = 7.5 Hz, 2H). HRMS [ESI], *m/z*: 353.1977 [M+H]<sup>+</sup> for C<sub>20</sub>H<sub>25</sub>N<sub>4</sub>O<sub>2</sub>. Anal. Calc. for C<sub>20</sub>H<sub>25</sub>N<sub>4</sub>O<sub>2</sub>Cl, %: C, 61.77; H, 6.48; N, 14.41; found, %: C, 61.82; H, 6.54; N, 14.67.



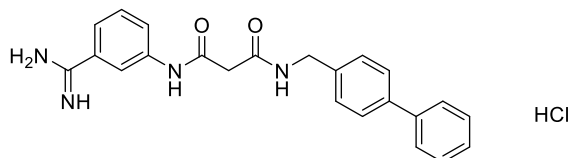
*N*<sup>1</sup>-{4-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-(4-methylbenzyl)malonamide hydrochloride (**19a**). Pink solid, yield 61% (290 mg), M.p. 248 – 249.7 °C. IR cm<sup>-1</sup>: 3363, 3239, 1679, 1625, 1602, 1524, 845, 738. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.78 (s, 1H), 9.25 (s, 2H), 8.99 (s, 2H), 8.64 (t, 1H, *J* = 5.6 Hz), 7.81 (s, 4H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 4.23 (d, *J* = 6.0 Hz, 2H), 3.37 (s, 2H), 2.25 (s, 3H). HRMS [ESI], *m/z*: 325.1660 [M+H]<sup>+</sup> for C<sub>18</sub>H<sub>21</sub>N<sub>4</sub>O<sub>2</sub>. Anal. Calc. for C<sub>18</sub>H<sub>21</sub>N<sub>4</sub>O<sub>2</sub>Cl, %: C, 59.91; H, 5.87; N, 15.52; found, %: C, 59.97; H, 5.91; N, 15.66.



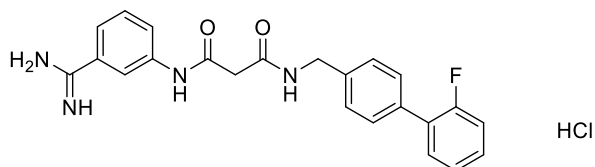
*N*<sup>1</sup>-(3-carbamimidoylphenyl)-*N*<sup>3</sup>-(4-methylbenzyl) malonamide hydrochloride (**19b**) White solid, yield 20% (0.140 g) m.p. = 162-164 °C. IR cm<sup>-1</sup> : 3292.2, 3066.2, 1678.4, 1625.3, 802.5; <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ : 10.64 (s, 1H), 9.36 (s, 2H), 9.09 (s, 2H), 8.63 (t, *J* = 5.5 Hz, 1H), 8.09 (s, 1H), 7.83 (d, *J* = 9 Hz, 1H), 7.53 (t, *J* = 9 Hz, 1H), 7.41 (d, *J* = 9 Hz, 1H), 7.17-7.09 (q, *J* = 9 Hz, 4H), 4.24 (d, *J* = 3 Hz, 2H), 3.28 (s, 2H), 2.06 (s, 3H). HRMS [ESI], *m/z*: 325.1661 [M+H]<sup>+</sup> for C<sub>18</sub>H<sub>21</sub>N<sub>4</sub>O<sub>2</sub>. Anal. Calc. for C<sub>18</sub>H<sub>21</sub>N<sub>4</sub>O<sub>2</sub>Cl, %: C, 59.91; H, 5.87; N, 15.52; found, %: C, 60.07; H, 5.95; N, 15.56.



*N*<sup>1</sup>-{3-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-biphenylmethylenmalonamide hydrochloride (**19c**). White solid, yield 55% (165 mg). M.p. 164-165 °C. IR cm<sup>-1</sup> : 3292, 1678, 1630, 800; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.80 (s, 1H), 9.40 (s, 2H), 9.11 (s, 2H), 8.67 (t, 1H, *J* = 5.5 Hz), 7.84 (s, 4H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.40-7.25 (m, 5H), 7.16 (d, *J* = 8.5 Hz, 2H), 4.23 (d, *J* = 5.5 Hz, 2H), 3.37 (s, 2H). HRMS [ESI], *m/z*: 387.1822 [M+H]<sup>+</sup> for C<sub>23</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>. Anal. Calc. for C<sub>23</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>Cl, %: C, 65.32; H, 5.48; N, 13.25; found, %: C, 65.39; H, 5.55; N, 13.44.

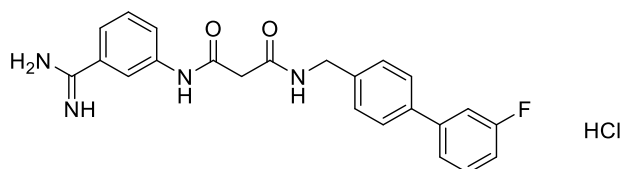


*N*<sup>1</sup>-{3-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-biphenylmethylenmalonamide hydrochloride (**19d**). Brown solid, yield 43% (110 mg). M.p. 170-180 °C. IR cm<sup>-1</sup> : 3290, 1680, 1627, 805; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ<sub>H</sub>: 10.78 (s, 1H), 9.36 (s, 2H), 9.06 (s, 2H), 8.74 (m, 1H), 8.05 (s, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.3 – 7.7 (m, 12H), 4.33 (d, *J* = 5.8 Hz, 2H), 3.38 (s, 2H). HRMS [ESI], *m/z*: 387.1821 [M+H]<sup>+</sup> for C<sub>23</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>. Anal. Calc. for C<sub>23</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>Cl, %: C, 65.32; H, 5.48; N, 13.25; found, %: C, 65.45; H, 5.65; N, 13.52.

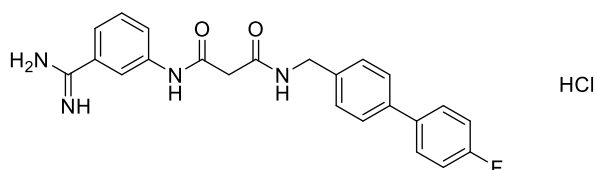


*N*<sup>1</sup>-(3-carbamimidoylphenyl)-*N*<sup>3</sup>-(2-fluorobenzyl)malonamide (**19e**). Pale brown solid, yield 33% (85 mg) M.p. 88-91 °C. IR cm<sup>-1</sup>: 3112, 1677, 1645, , 1548, 1484, 1407, 1251, 753, 694. <sup>1</sup>H NMR

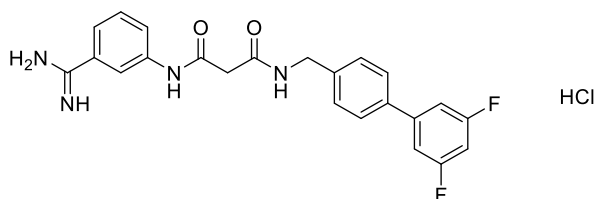
(300 MHz, DMSO- $d_6$ )  $\delta$  10.85 (d,  $J$  = 5.3 Hz, 1H), 9.42 (s, 2H), 9.27 (s, 2H), 8.84 (t,  $J$  = 5.0 Hz, 1H), 8.09 (s, 1H), 7.93 – 7.14 (m, 7H), 4.34 (d,  $J$  = 5.8 Hz, 3H), 3.43 (s, 4H). HRMS [ESI],  $m/z$ : 405.1721  $[M+H]^+$  for  $C_{23}H_{22}N_4O_2F$ . Anal. Calc. for  $C_{23}H_{22}N_4O_2FCl$ , %: C, 68.13; H, 5.47; N, 13.82; found, %: C, 68.35; H, 5.65; N, 13.62.



*N*<sup>1</sup>-(3-carbamimidoylphenyl)-*N*<sup>3</sup>-(3-fluorobenzyl)malonamide hydrochloride (**19f**). Brown powder, yield 32% (110 mg). M.p. 165–170 °C. IR  $cm^{-1}$ : 3139, 3053, 1678, 1651, 1548, 1403, 1259, 1188, 880, 776, 715, 679. <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  10.82 (s, 1H), 9.45 (s, 2H), 9.32 (s, 2H), 8.82 (t,  $J$  = 5.8 Hz, 1H), 8.11 (d,  $J$  = 7.4 Hz, 1H), 7.98 – 7.34 (m, 6H), 7.17 (tt,  $J$  = 4.7, 4.1 Hz, 1H), 4.34 (d,  $J$  = 5.9 Hz, 2H), 3.42 (s, 1H). HRMS [ESI],  $m/z$ : 405.1723  $[M+H]^+$  for  $C_{23}H_{22}N_4O_2F$ . Anal. Calc. for  $C_{23}H_{22}N_4O_2FCl$ , %: C, 68.13; H, 5.47; N, 13.82; found, %: C, 68.24; H, 5.61; N, 13.91.



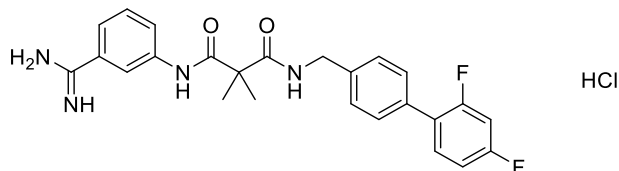
*N*<sup>1</sup>-(3-carbamimidoylphenyl)-*N*<sup>3</sup>-((4'-fluoro-[1,1'-biphenyl]-4-yl)methyl)malonamide hydrochloride (**19g**). Brown powder, yield 26% (74 mg). M.p. 250 °C dec. IR  $cm^{-1}$ : 3399, 1895, 1672, 1638, 1602, 1555, 1499, 1433, 1251, 805, 721, 676. <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ),  $\delta_H$ : 10.79 (s, 1H), 9.40 (s, 2H), 9.21 (s, 2H), 8.80 (t,  $J$  = 5.5 Hz, 1H), 7.7 – 7.0 (m, 11H), 4.33 (d,  $J$  = 5.8 Hz, 2H), 3.35 (s, 2H). HRMS [ESI],  $m/z$ : 405.1719  $[M+H]^+$  for  $C_{23}H_{22}N_4O_2F$ . Anal. Calc. for  $C_{23}H_{22}N_4O_2FCl$ , %: C, 68.13; H, 5.47; N, 13.82; found, %: C, 68.21; H, 5.55; N, 13.99.



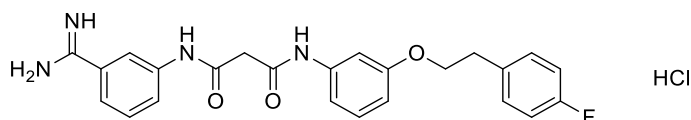
*N*<sup>1</sup>-{3-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-(3',5'-difluorobiphenyl)methylenmalonamide hydrochloride (**19i**). Brown solid, yield 68% (200 mg). M.p. 160-165 °C.. IR  $cm^{-1}$ : 3276, 1677, 1646, 965, 805, 701; <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ),  $\delta_H$ : 10.71 (s, 1H), 9.37 (s, 2H), 9.12 (s, 2H), 8.78 (t,  $J$  = 5.8 Hz, 1H), 8.10 (s, 1H), 7.85 (m, 1H), 7.69 (d,  $J$  = 8.3 Hz, 2H), 7.39 (d,  $J$  = 8.3 Hz, 2H), 7.2 (m, 1H), 4.34 (d,  $J$  = 5.8 Hz, 2H), 3.40 (s, 2H). HRMS [ESI],  $m/z$ : 423.1629  $[M+H]^+$

for  $C_{23}H_{21}N_4O_2F_2$ . Anal. Calc. for  $C_{23}H_{22}N_4O_2F_2Cl$ , %: C, 60.20; H, 4.61; N, 12.21; found, %: C, 60.23; H, 4.72; N, 12.19.

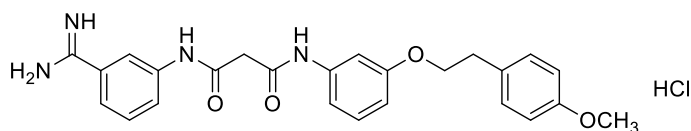
**19l.**



$N^1$ -(3-carbamimidoylphenyl)- $N^3$ -((2',4'-difluoro-[1,1'-biphenyl]-4-yl)methyl)-2,2-dimethylmalonamide hydrochloride (**19l**). Pale brown solid, yield 43% (110 mg). M.p. 132-136 °C. IR  $cm^{-1}$ : 3273, 3074, 1673, 1595, 1494, 1425, 1403, 1297, 1262, 1140, 1100, 964, 801, 720, 678.  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.81 (s, 1H), 9.13 (br s, 4H), 8.41 (t,  $J$  = 5.9 Hz, 1H), 8.15 (t,  $J$  = 1.8 Hz, 1H), 7.95 (d,  $J$  = 8.1 Hz, 1H), 7.58 – 7.47 (m, 2H), 7.46 – 7.39 (m, 3H), 7.38 – 7.29 (m, 3H), 7.17 (td,  $J$  = 8.4, 2.7 Hz, 1H), 4.34 (d,  $J$  = 5.8 Hz, 2H), 3.31 (s, 1H), 1.48 (s, 6H). HRMS [ESI],  $m/z$ : 451.1942  $[M+H]^+$  for  $C_{25}H_{25}N_4O_2F_2$ . Anal. Calc. for  $C_{25}H_{25}N_4O_2F_2Cl$ , %: C, 61.66; H, 5.17; N, 11.51; found, %: C, 61.97; H, 5.36; N, 11.50.

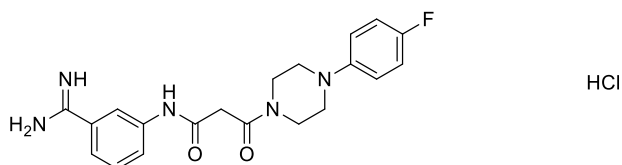


$N^1$ -{3-[amino(imino)methyl]phenyl}- $N^3$ -{3-[2-(4-fluorophenyl)ethoxy]phenyl}-malonamide (**20a**). hydrochloride (**20a**). Pale brown solid, yield 61% (290 mg). M.p. 108-110 °C. IR  $cm^{-1}$ : 3258, 2931, 1676, 1598, 1551, 1510, 1481, 1220, 1157, 1038, 721, 687.  $^1H$  NMR (300 MHz, DMSO- $d_6$ ),  $\delta_H$ :  $\delta$  10.89 (s, 1H), 10.49 (s, 1H), 9.39 (s, 2H), 9.18 (s, 2H), 8.12 (s, 1H), 7.86 (d,  $J$ =3Hz, 1H), 7.59-7.55 (t, 1H), 7.52 (d,  $J$ =6Hz, 1H), 7.48-7.28 (m, 3H), 7.21-7.06 (m, 4H), 6.61(d,  $J$ =6Hz, 1H), 4.11-4.07 (t,  $J$ =6Hz, 2H), 3.54 (s, 2H), 3.01-2.97 (t,  $J$ =6Hz, 2H). HRMS [ESI],  $m/z$ : 435.1829  $[M+H]^+$  for  $C_{24}H_{24}N_4O_3F$ . Anal. Calc. for  $C_{25}H_{25}N_4O_3FCl$ , %: C, 61.21; H, 5.14; N, 11.90; found, %: C, 61.37; H, 5.26; N, 11.79.



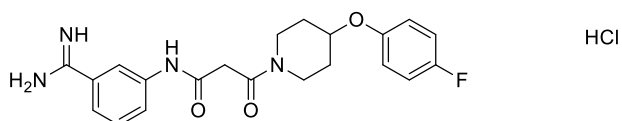
$N^1$ -(3-carbamimidoylphenyl)- $N^3$ -(3-(4-methoxyphenethoxy)phenyl)malonamide hydrochloride (**20b**). Brown solid, yield 44% (120 mg). M.p. 93-95 °C. IR  $cm^{-1}$ : 3017, 1682, 1645, 1555, 1402, 1248, 1034, 753, 682.  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  10.85 (s, 1H), 10.45 (s, 1H), 9.38 (s, 2H), 9.15 (s, 2H), 8.09 (dt,  $J$  = 16.5, 1.6 Hz, 1H), 7.86 (t,  $J$  = 7.4 Hz, 1H), 7.59 – 7.25 (m, 7H), 7.21 (d,

$J = 8.6$  Hz, 2H), 6.85 (d,  $J = 8.7$  Hz, 3H), 6.61 (d,  $J = 7.7$  Hz, 2H), 4.06 (t,  $J = 6.9$  Hz, 2H), 3.70 (s, 3H), 3.54 (s, 2H), 2.93 (t,  $J = 6.9$  Hz, 2H). HRMS [ESI],  $m/z$ : 447.2028  $[M+H]^+$  for  $C_{25}H_{27}N_4O_4$ . Anal. Calc. for  $C_{25}H_{27}N_4O_4Cl$ , %: C, 62.17; H, 5.63; N, 11.60; found, %: C, 62.27; H, 5.86; N, 11.77.

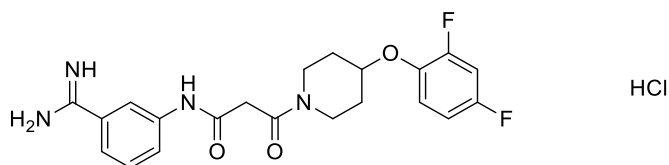


*N*-{4-[amino(imino)methyl]phenyl}-3-[4-(4-fluorophenyl)piperazin-1-yl]propanamide hydrochloride (**21a**). Brown solid, yield 20% (160 mg), M.p. 148-151 °C. IR  $cm^{-1}$ : 3444, 1682, 1627, 1560, 1510, 1450, 1232, 826, 725.  $^1H$  NMR (300 MHz, DMSO- $d_6$ ),  $\delta_H$ : 10.52 (s, 1H), 7.98 (s, 1H), 7.82 (d,  $J = 7.98$  Hz, 1H), 7.51 (t,  $J = 7.98$  Hz, 1H), 7.39 (d,  $J = 7.98$  Hz, 1H), 7.08-6.95 (m, 4H), 3.65 – 3.57 (m, 4H), 3.15-3.00 (m, 6H). HRMS [ESI],  $m/z$ : 384.1832  $[M+H]^+$  for  $C_{20}H_{23}N_5O_2F$ . Anal. Calc. for  $C_{20}H_{23}N_5O_2FCl$ , %: C, 57.21; H, 5.52; N, 16.68; found, %: C, 57.27; H, 5.82; N, 16.79.

## 22a.

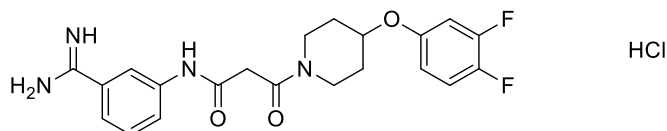


*N*-(3-[amino(imino)methyl]phenyl)-3-(4-(4-fluorophenoxy)piperidin-1-yl)-3-oxopropanamide hydrochloride (**22a**). Dark brown oil, yield 45% (112 mg). IR  $cm^{-1}$ : 3423, 1674, 1619, 1560, 1504, 1460, 1205, 1027, 873, 828, 802, 763.  $^1H$  NMR (300 MHz, DMSO- $d_6$ ),  $\delta_H$ : 10.75 (s, 1 H), 9.39 (s, 2 H), 9.21 (s, 2 H), 8.09 (s, 1 H), 7.84 (d,  $J=7.7$  Hz, 1 H), 7.51 (t,  $J=8.2$  Hz, 2 H), 7.15 (m, 2 H), 6.99 (m, 2 H), 4.56 (s, 2 H), 3.85 (m, 1 H), 3.68 (m, 1 H), 3.54 (s, 2 H), 3.30 (m, 2 H), 1.90 (m, 2 H), 1.65 (m, 1 H), 1.48 (m, 1 H). HRMS [ESI],  $m/z$ : 399.1831  $[M+H]^+$  for  $C_{21}H_{24}N_4O_3F$ .

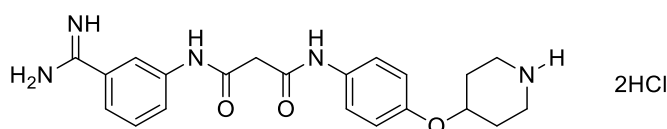


*N*-(3-carbamimidoylphenyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-oxopropanamide hydrochloride (**22b**). Dark brown oil, yield 90% (210 mg). IR  $cm^{-1}$ : 3420, 1675, 1620, 1200, 1024, 703.  $^1H$  NMR (300 MHz, DMSO- $d_6$ ),  $\delta_H$ : 10.78 (s, 1H), 9.37 (s, 2H), 9.14 (s, 2H), 8.08 (s, 1H), 7.84 – 7.82 (m, 1H), 7.53 (t,  $J = 7.8$  Hz, 1H), 7.41 (d,  $J = 7.7$  Hz, 1H), 7.38 – 7.23 (m, 2H), 7.05 –

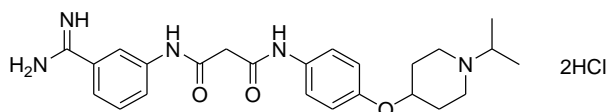
6.95 (m, 1H), 5.32 (br s, 2H), 4.56 (quintet,  $J = 3.6$  Hz, 1H), 3.98 – 3.65 (m, 2H), 3.61 (s, 2H), 3.33 – 3.12 (m, 2H), 2.00 – 1.83 (m, 1H), 1.69 – 1.47 (m, 1H). HRMS [ESI],  $m/z$ : 417.1731  $[M+H]^+$  for  $C_{21}H_{23}N_4O_3F_2$ .



*N*-(3-carbamimidoylphenyl)-3-(4-(3,4-difluorophenoxy)piperidin-1-yl)-3-oxopropanamide hydrochloride (**22c**). Dark brown oil, yield 37% (251 mg). IR  $cm^{-1}$ : 3422, 1673, 1625, 1200, 1025, 801.  $^1H$  NMR (300 MHz, DMSO- $d_6$ ),  $\delta_H$ : 10.68 (s, 1H), 10.31 (s, 1H), 9.37 (s, 2H), 9.13 (s, 2H), 8.08 (s, 1H), 7.83 (d,  $J = 9.1$  Hz, 1H), 7.53 (t,  $J = 8.0$  Hz, 1H), 7.41 (d,  $J = 8.0$  Hz, 1H), 7.38–7.25 (m, 1H), 7.30 – 7.08 (m, 1H), 6.84 – 6.78 (m, 1H), 4.6 (quintet,  $J = 4.5$  Hz, 1H), 3.90 – 3.65 (m, 2H), 3.54 (s, 2H), 3.30 – 3.10 (m, 2H), 2.0 – 1.8 (m, 2H), 1.70 – 1.40 (m, 2H). HRMS [ESI],  $m/z$ : 417.1735  $[M+H]^+$  for  $C_{21}H_{23}N_4O_3F_2$ .

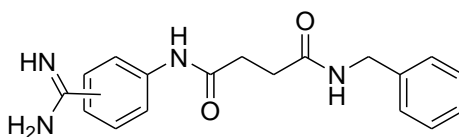


*N*<sup>1</sup>-{3-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-[4-(piperidin-4-iloxy)-phenyl]-malonamide dihydrochloride (**23a**). Dark brown oil, yield 15% (60 mg). IR  $cm^{-1}$ : 3288, 2974, 1689, 1553, 1508, 1479, 1414, 1234, 1169, 1031, 831, 802, 770, 723, 654.  $^1H$  NMR (300 MHz, DMSO- $d_6$ ),  $\delta_H$ : 10.85 (s, 1H), 10.34 (s, 1H), 9.38 (s, 2H), 9.15 (s, 2H), 7.41–8.12 (m, 4H), 7.53 (d,  $J = 9.0$  Hz, 2H), 6.94 (d,  $J = 9.0$  Hz, 2H), 3.52 (s, 2H), 4.55 (quintet,  $J = 3.3$  Hz, 1H), 3.17 (br s, 2H), 3.03 (br s, 2H), 2.08 (m, 2H), 1.80 (m, 2H). HRMS [ESI],  $m/z$ : 396.2032  $[M+H]^+$  for  $C_{21}H_{26}N_5O_3$ .



*N*<sup>1</sup>-{3-[amino(imino)methyl]phenyl}-*N*<sup>3</sup>-[4-(1-isopropylpiperidin-4-iloxy)phenyl]malonamide hydrochloride (**23b**). Dark brown oil, yield 22% (120 mg).  $^1H$  NMR (300 MHz, DMSO- $d_6$ ),  $\delta_H$ : 10.83 (s, 1H), 10.35 (d,  $J = 6.87$  Hz, 1H), 9.37 (s, 2H), 9.12 (s, 2H), 7.6–7.3 (m, 8H), 3.51 (s, 2H), 3.44 (m, 6H), 1.28 (m, 5H), 1.02 (m, 4H). HRMS [ESI],  $m/z$ : 438.2506  $[M+H]^+$  for  $C_{24}H_{32}N_5O_3$ .

**Table S1.** FXa and thrombin inhibition of succinimide analogues.

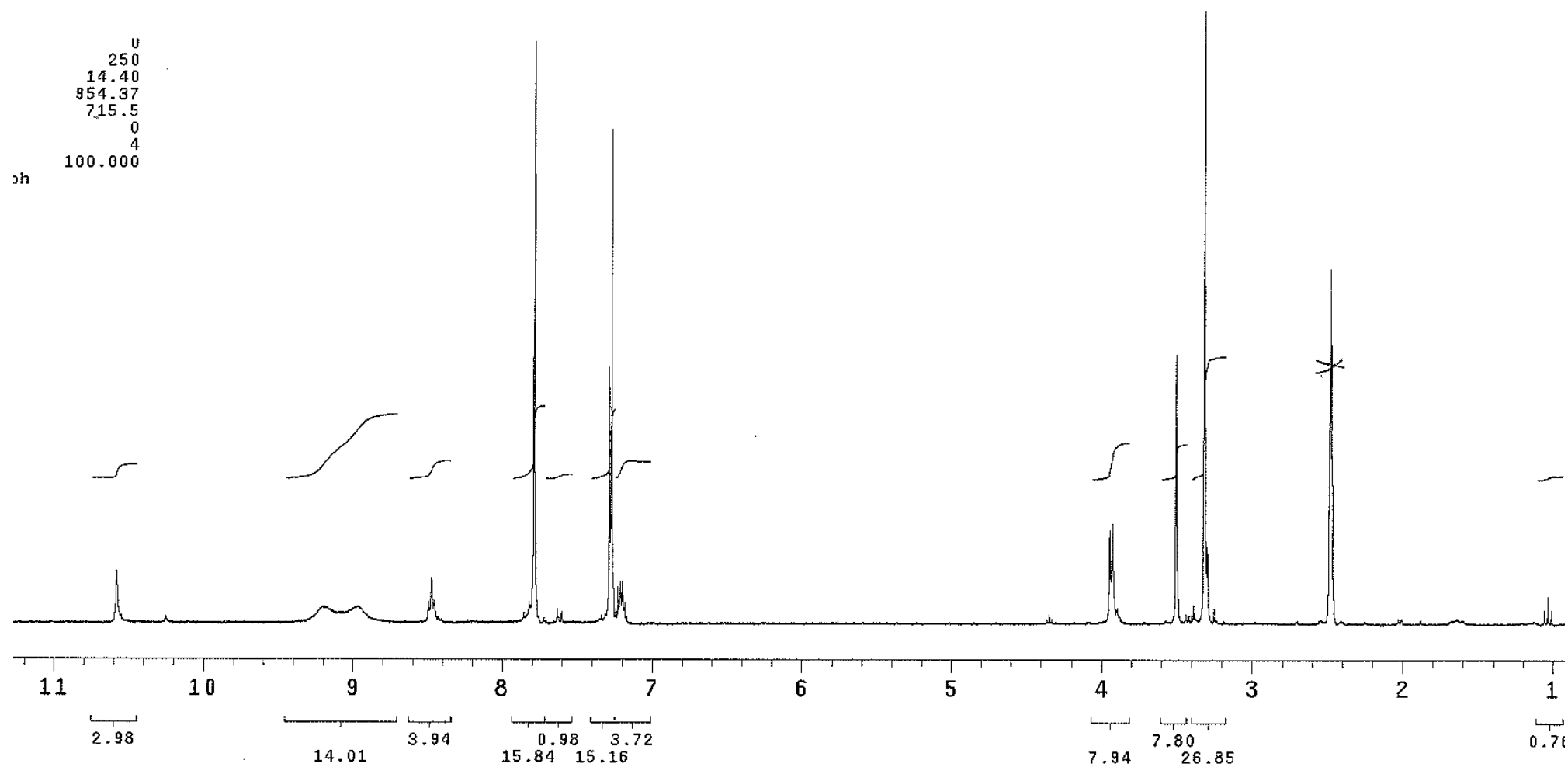


Cmpd	amidine	$K_i$ ( $\mu\text{M}$ ) <sup>a</sup>	
		fXa	thr
S1	p	>50	>50
		(10% at 50 $\mu\text{M}$ )	(5% at 50 $\mu\text{M}$ )
S2	m	>50	>50
		(8% at 50 $\mu\text{M}$ )	(7% at 50 $\mu\text{M}$ )
Apixaban <sup>b</sup>		0.00012	
Dabigatran <sup>b</sup>			0.0042

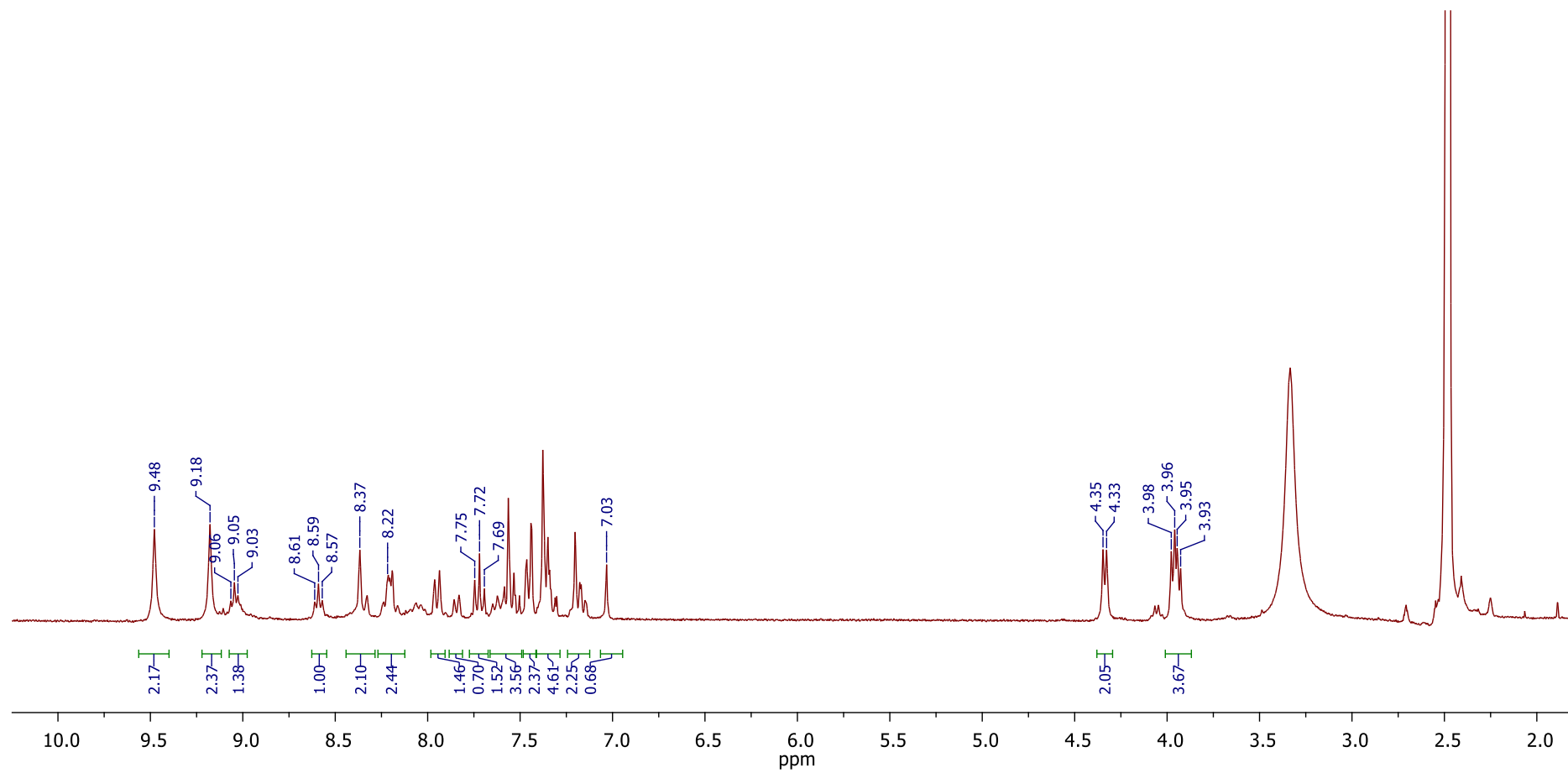
<sup>a</sup> $K_i$  values determined by applying the Cheng–Prousoff equation to  $\text{IC}_{50}$  values, by regression (GraphPad Prism software ver. 5.01). Data are means of three independent measurements, each one performed in triplicate (SEM < 5%). <sup>b</sup>Apixaban and dabigatran have been tested as positive controls against blood coagulation factors fXa and thrombin, respectively.

# HNMR spectra of selected compounds

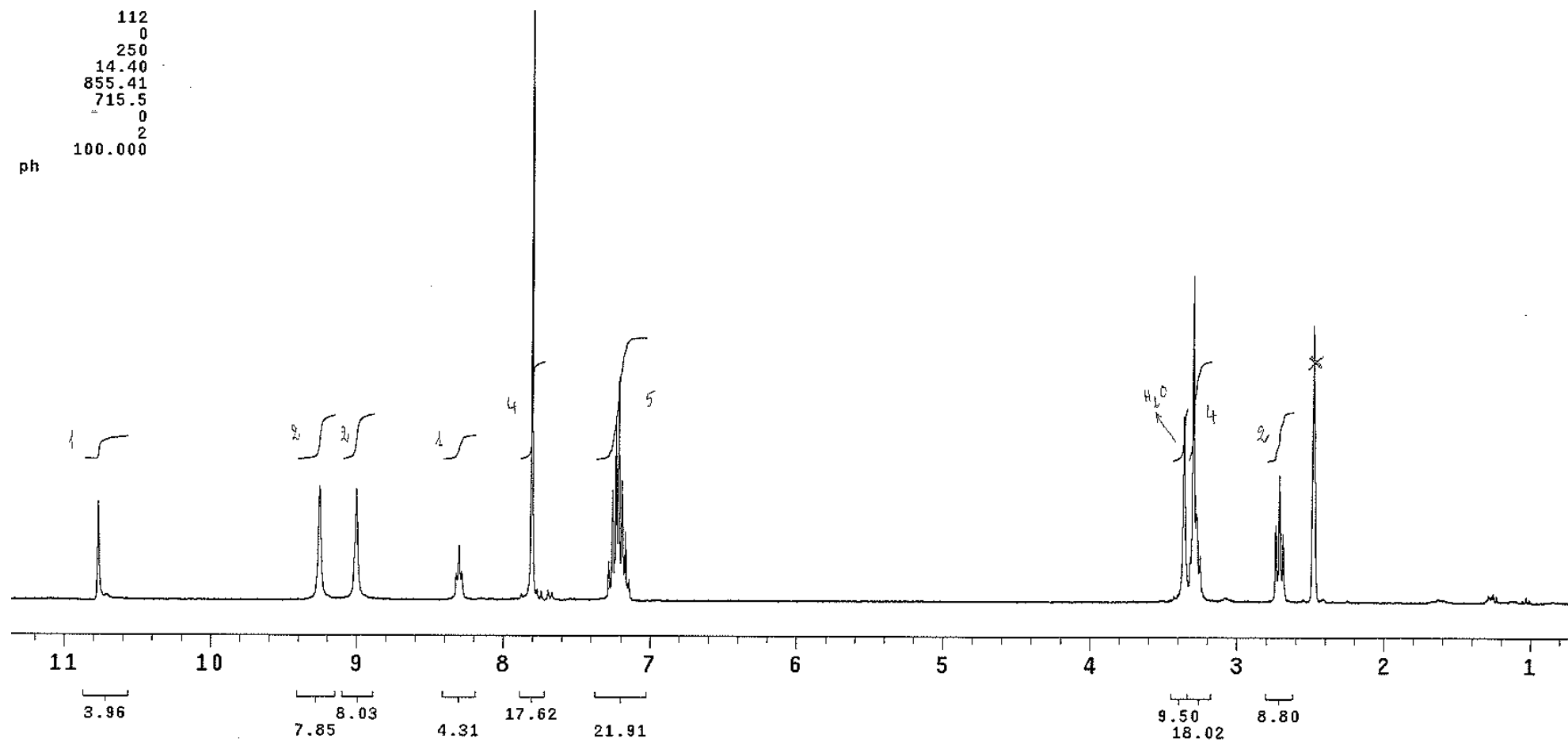
4b



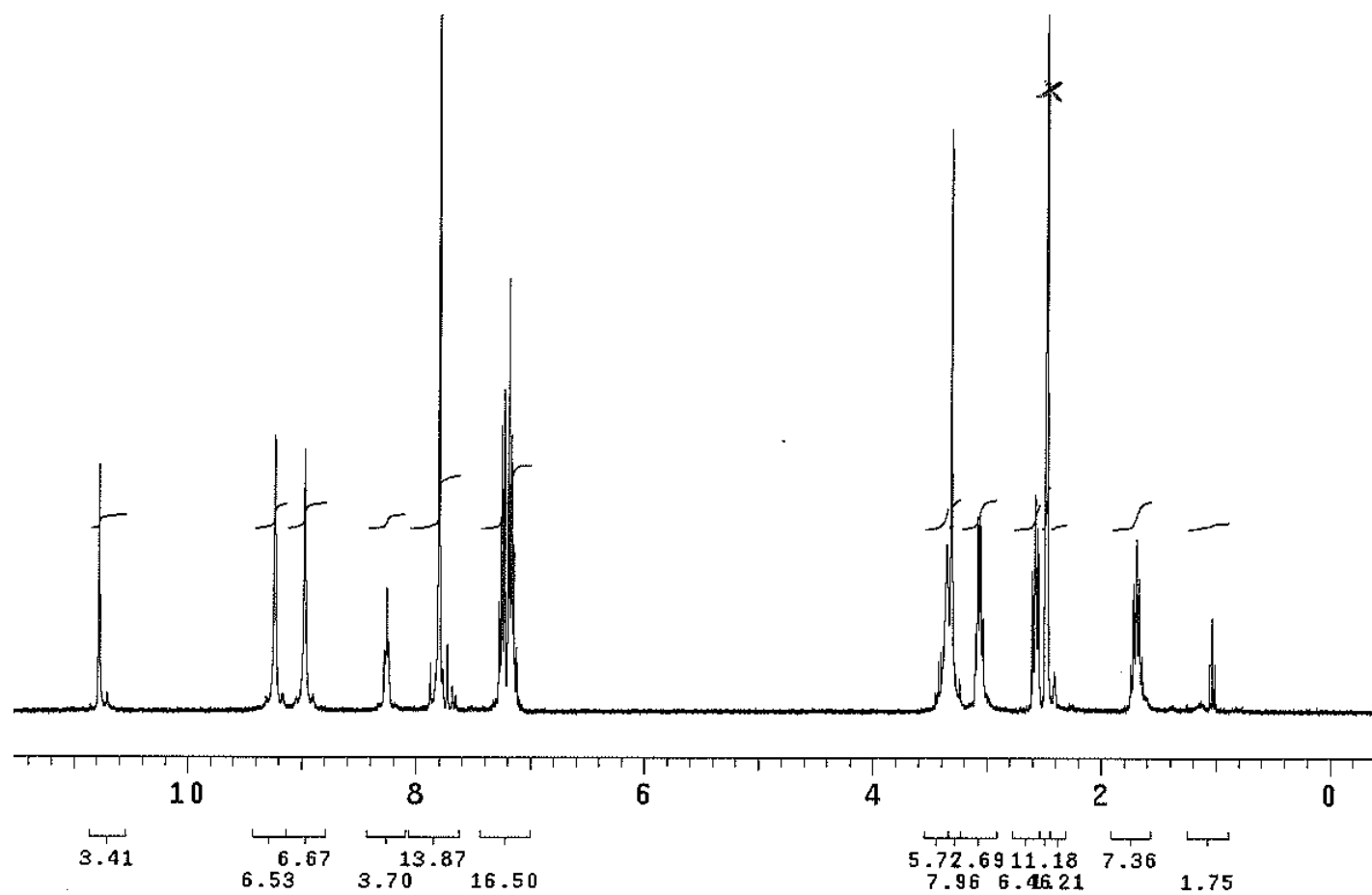
4c



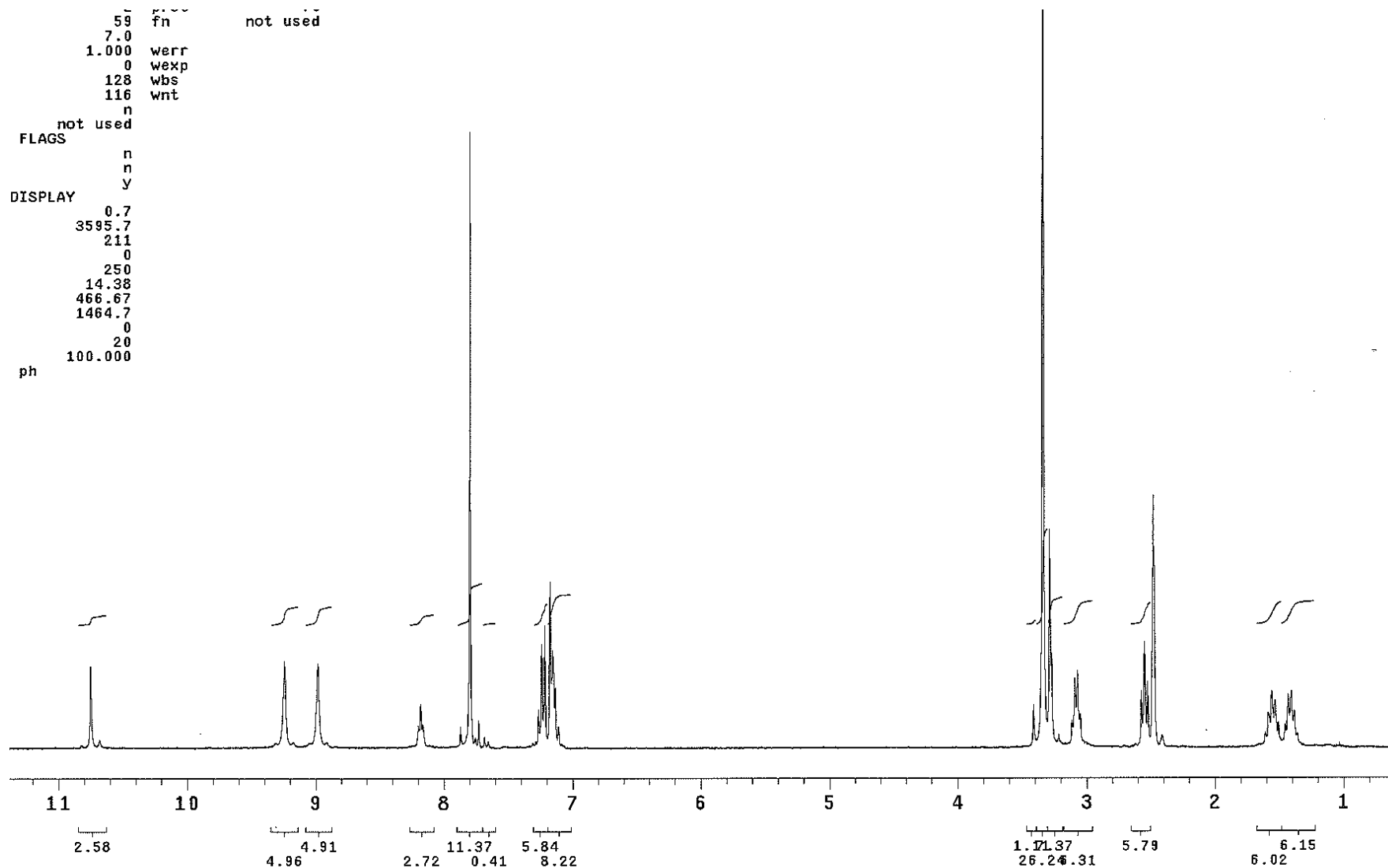
18c



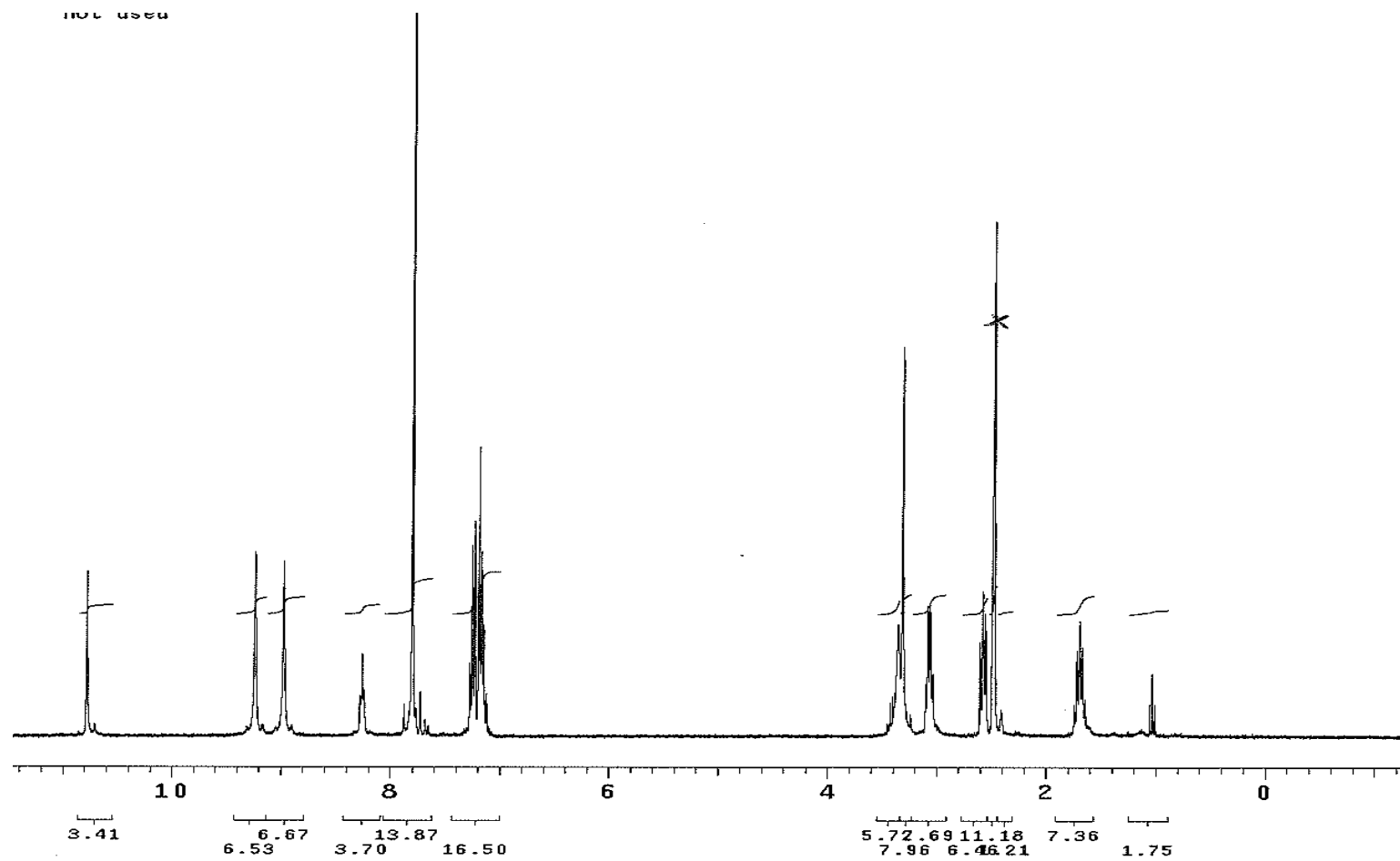
18d



18e



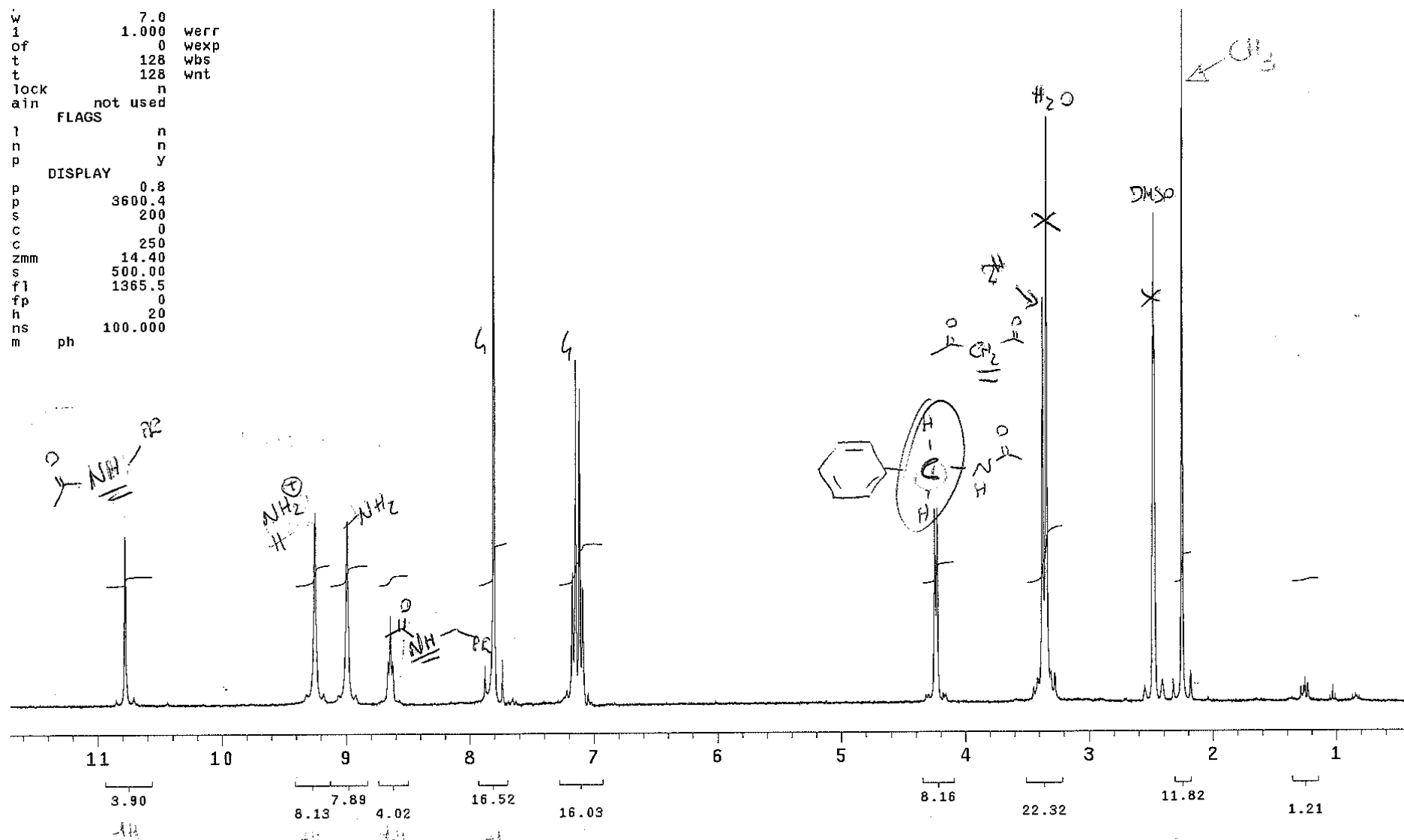
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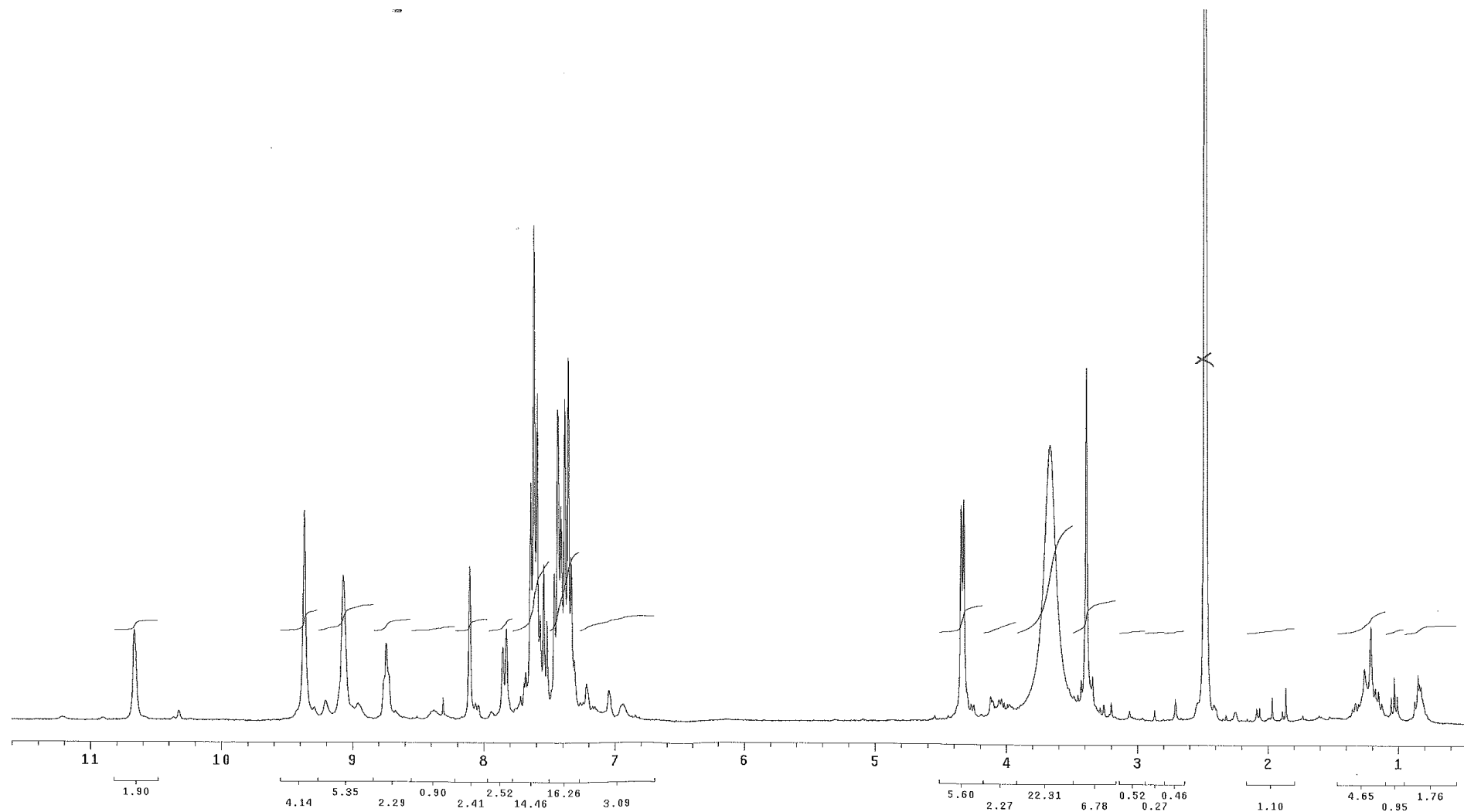
19a

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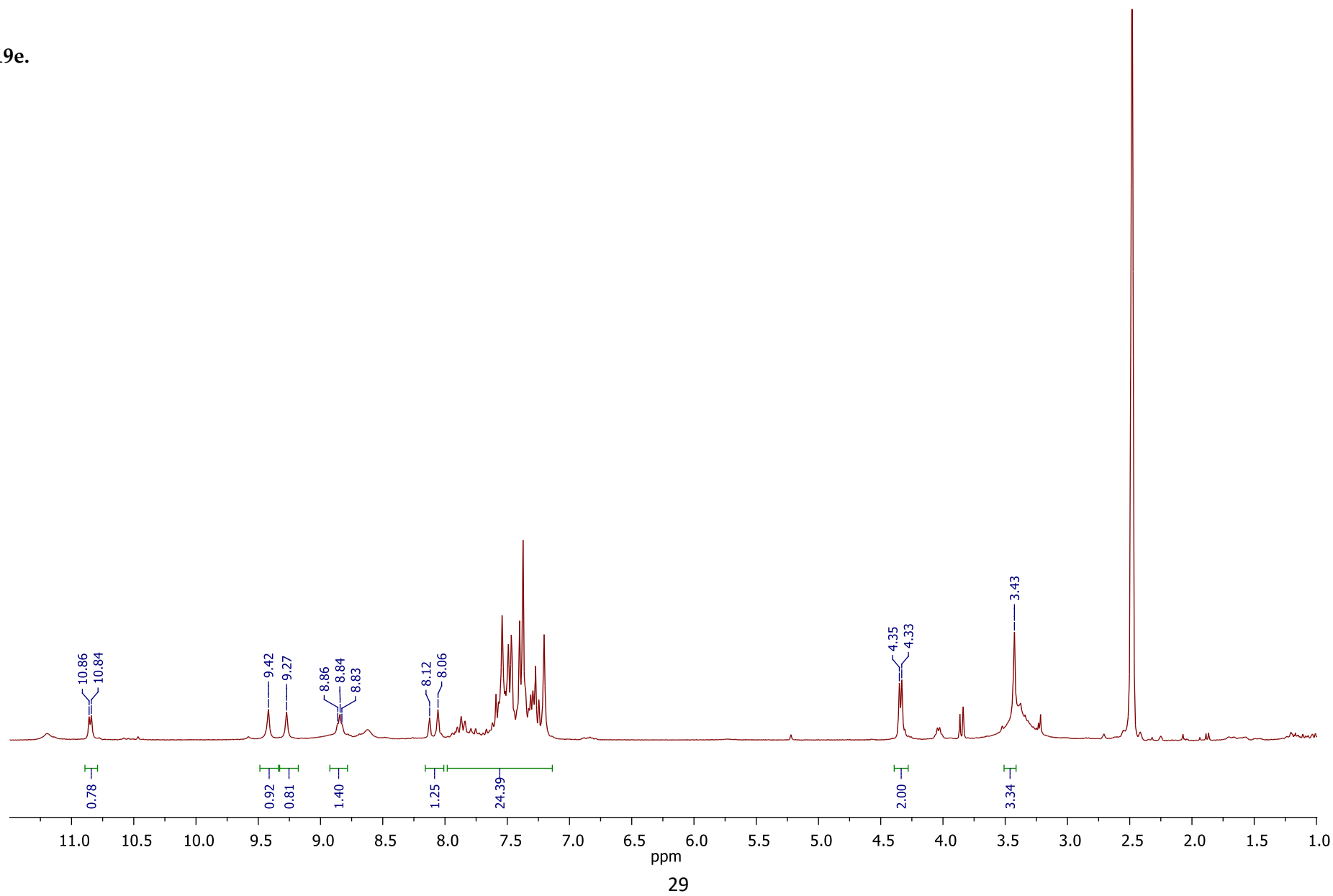
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t      128    wnt
lock    n
ain     not used
      FLAGS
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n      n
p      y
      DISPLAY
p      0.8
ps     3600.4
s      200
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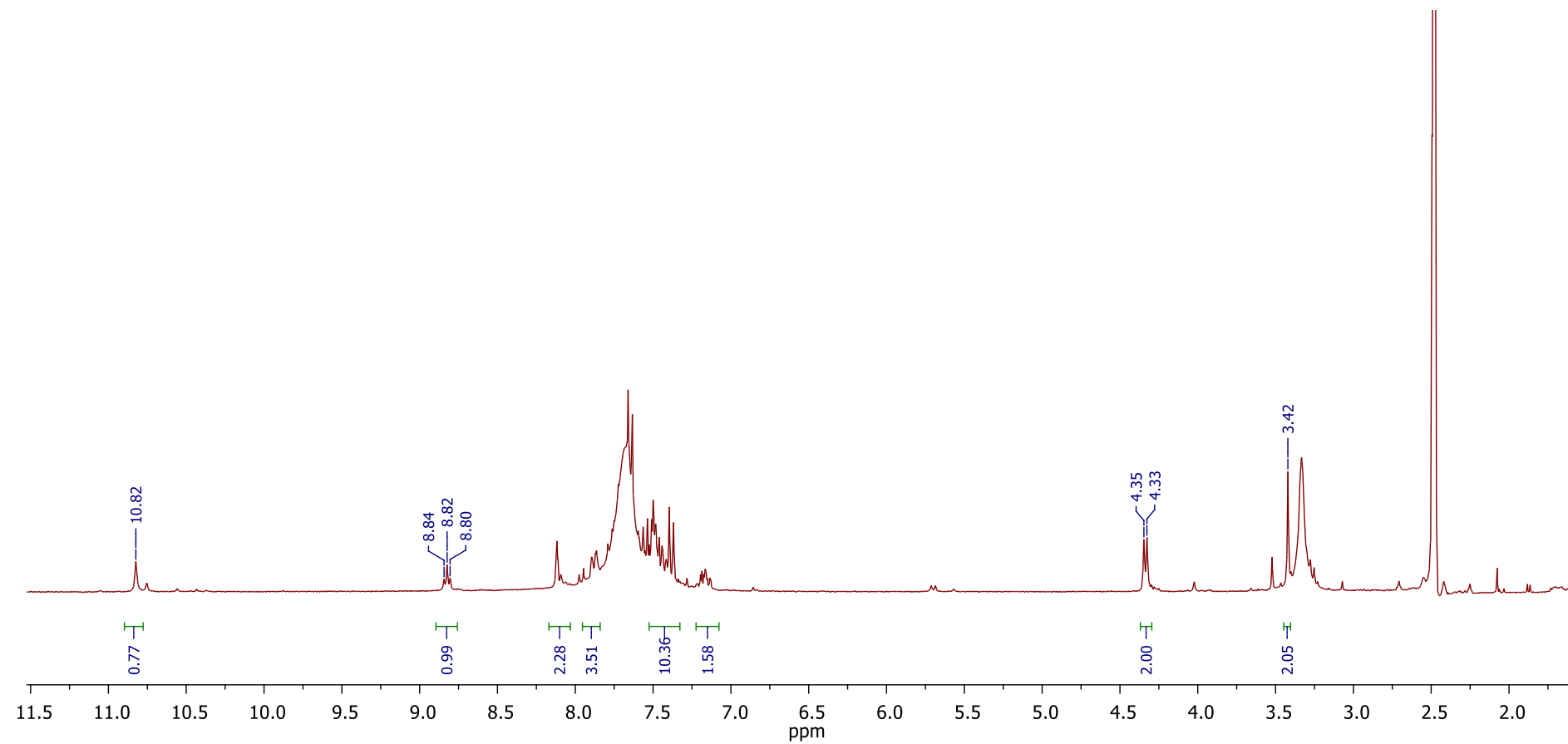
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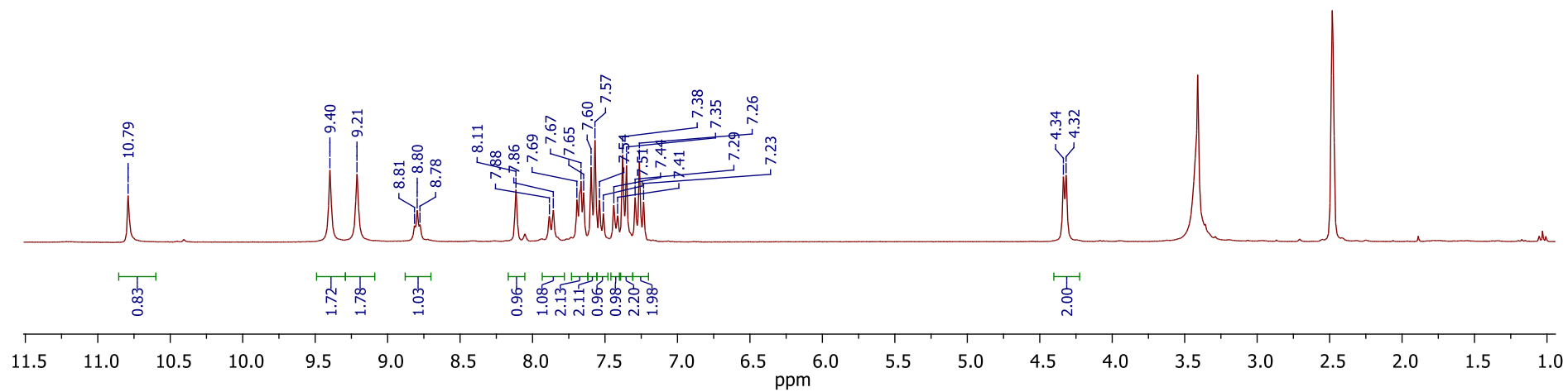
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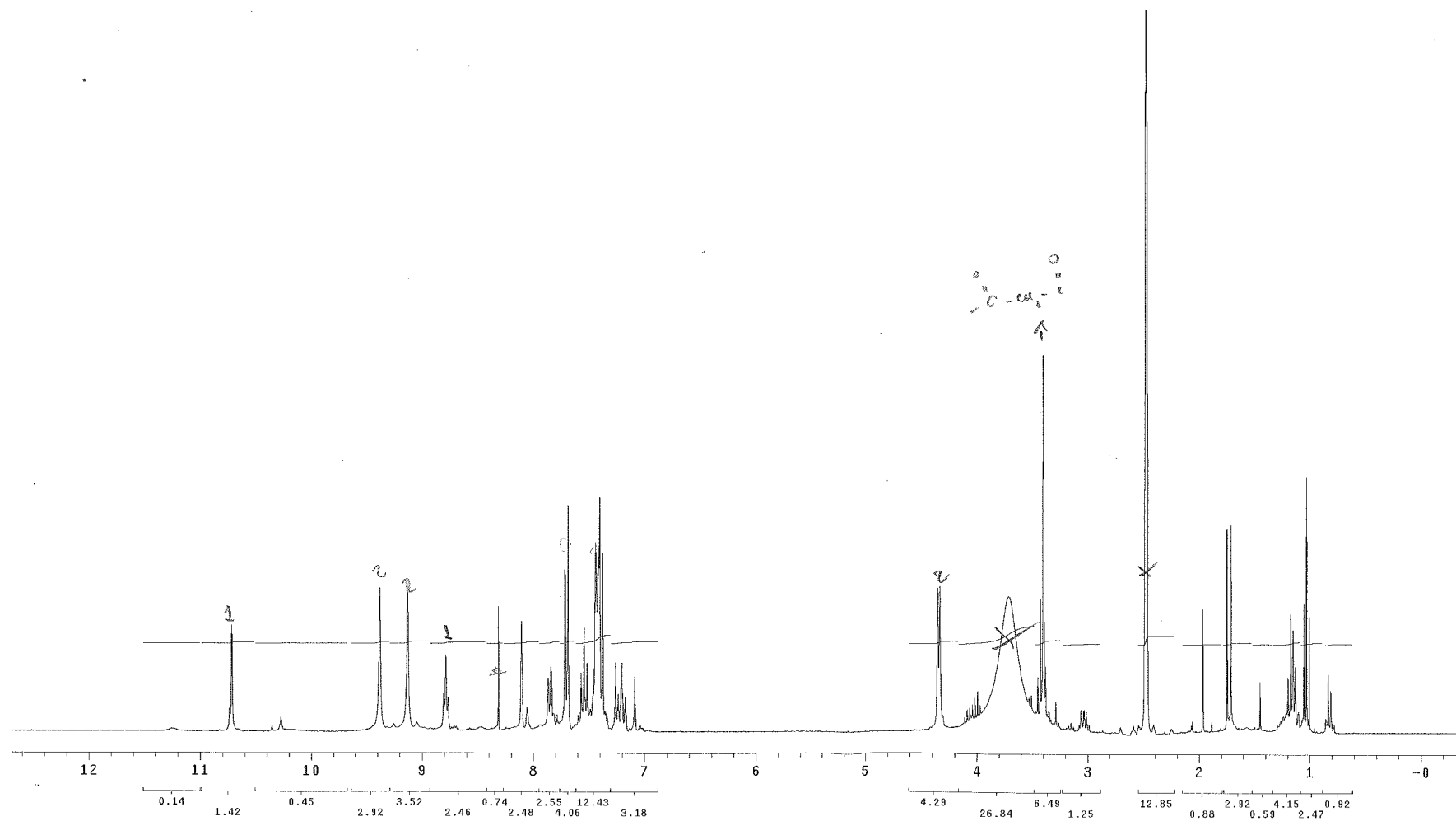


19f



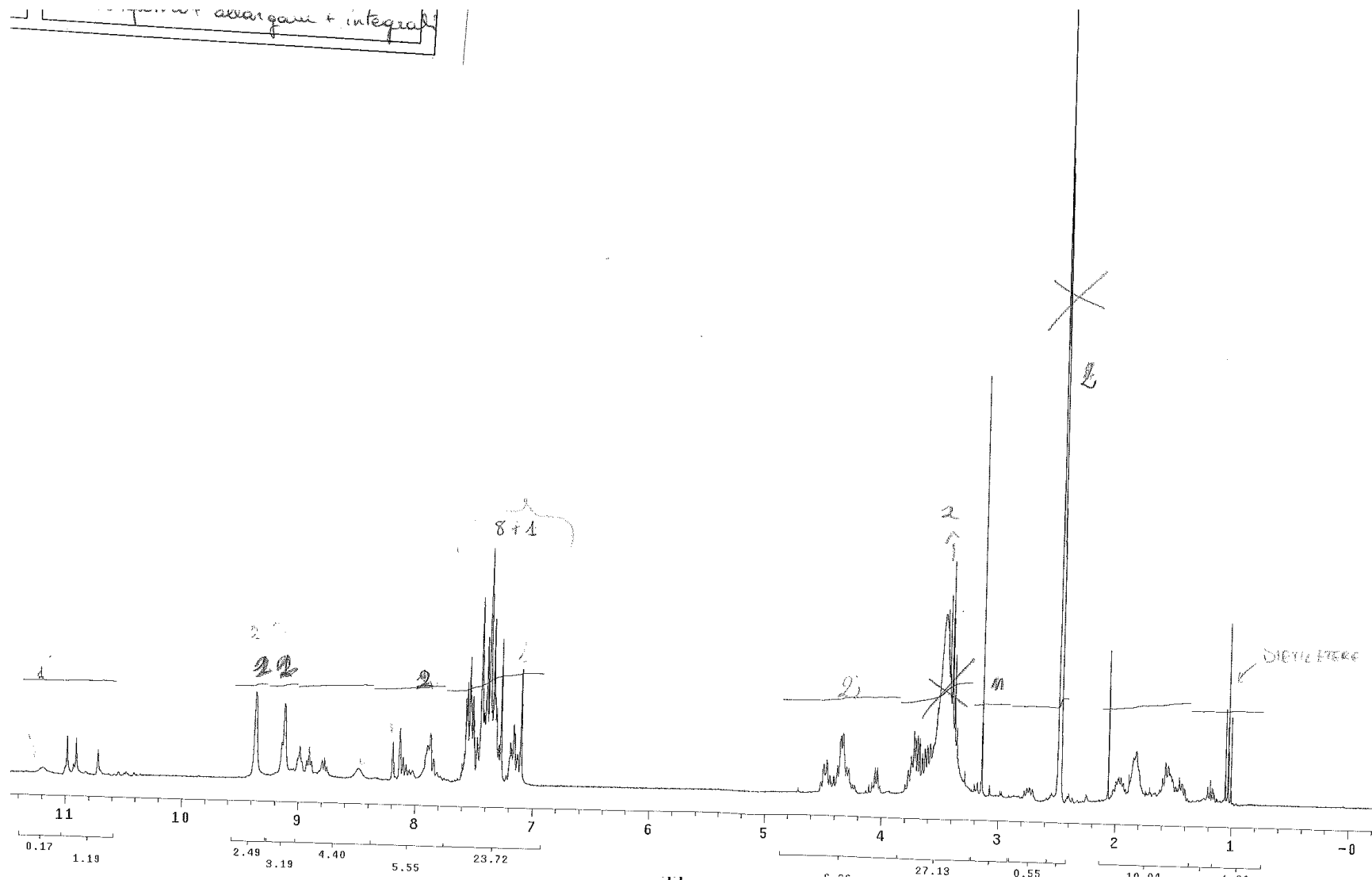
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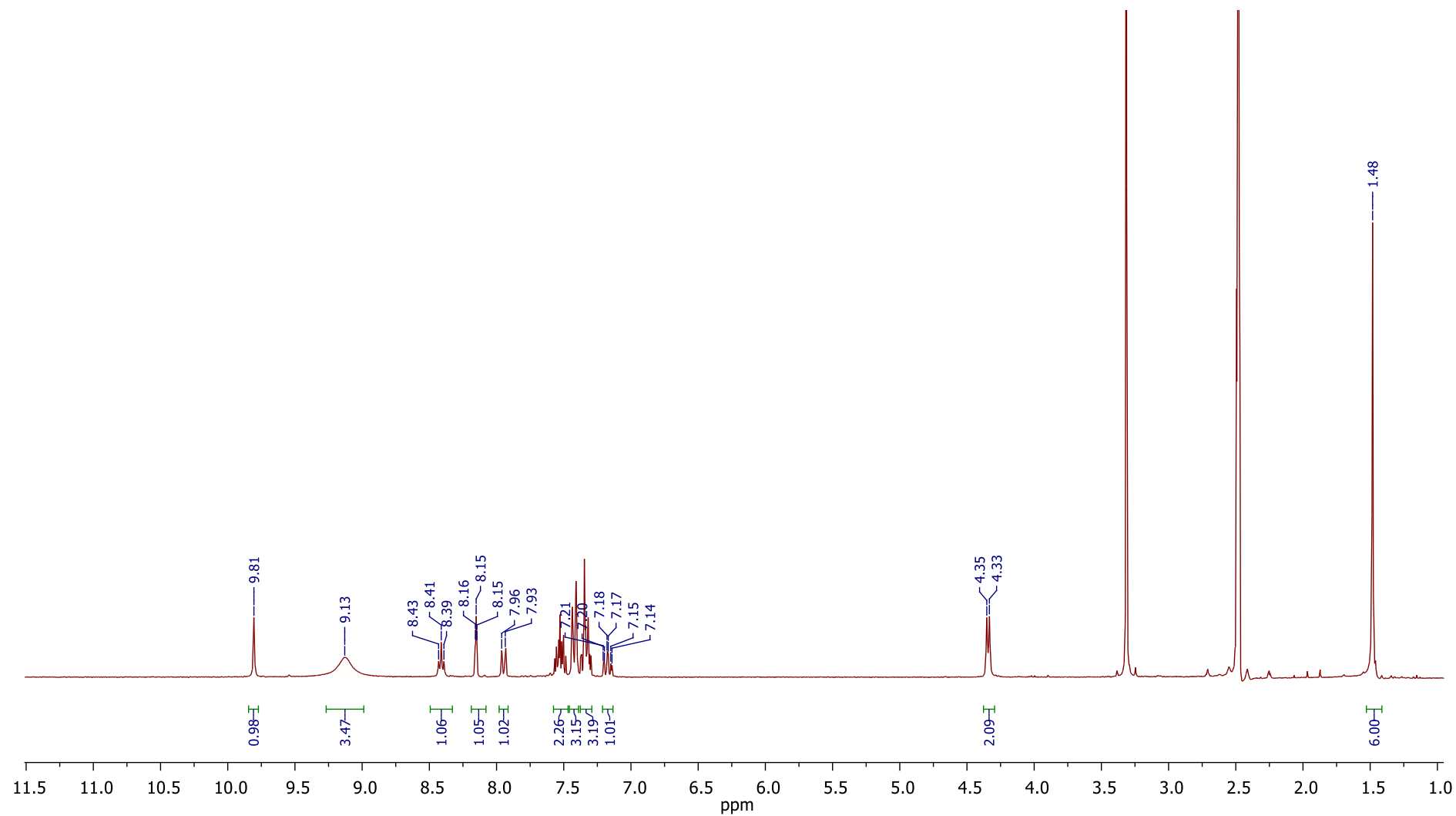




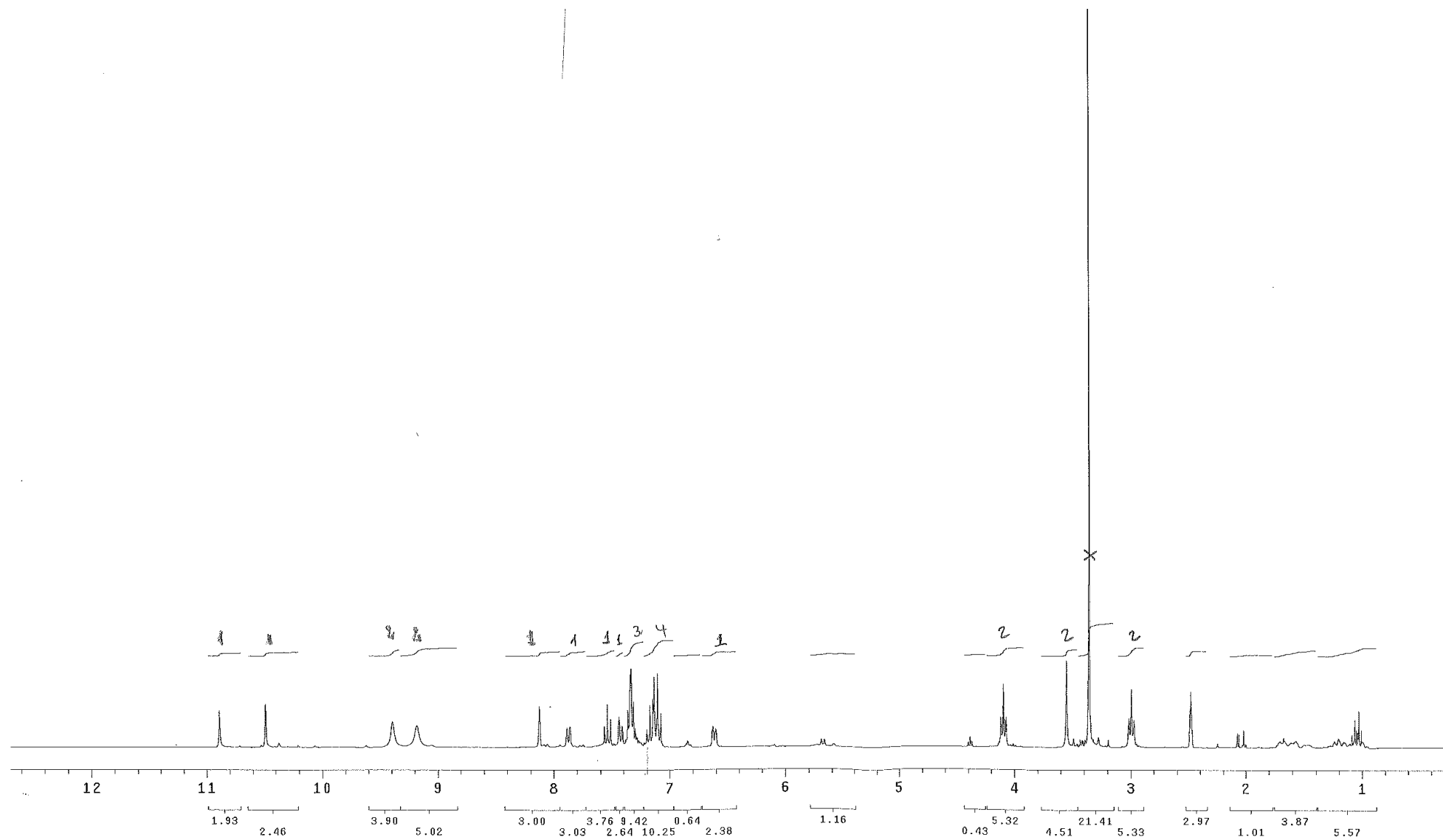
19h

19h + aromatic + integral

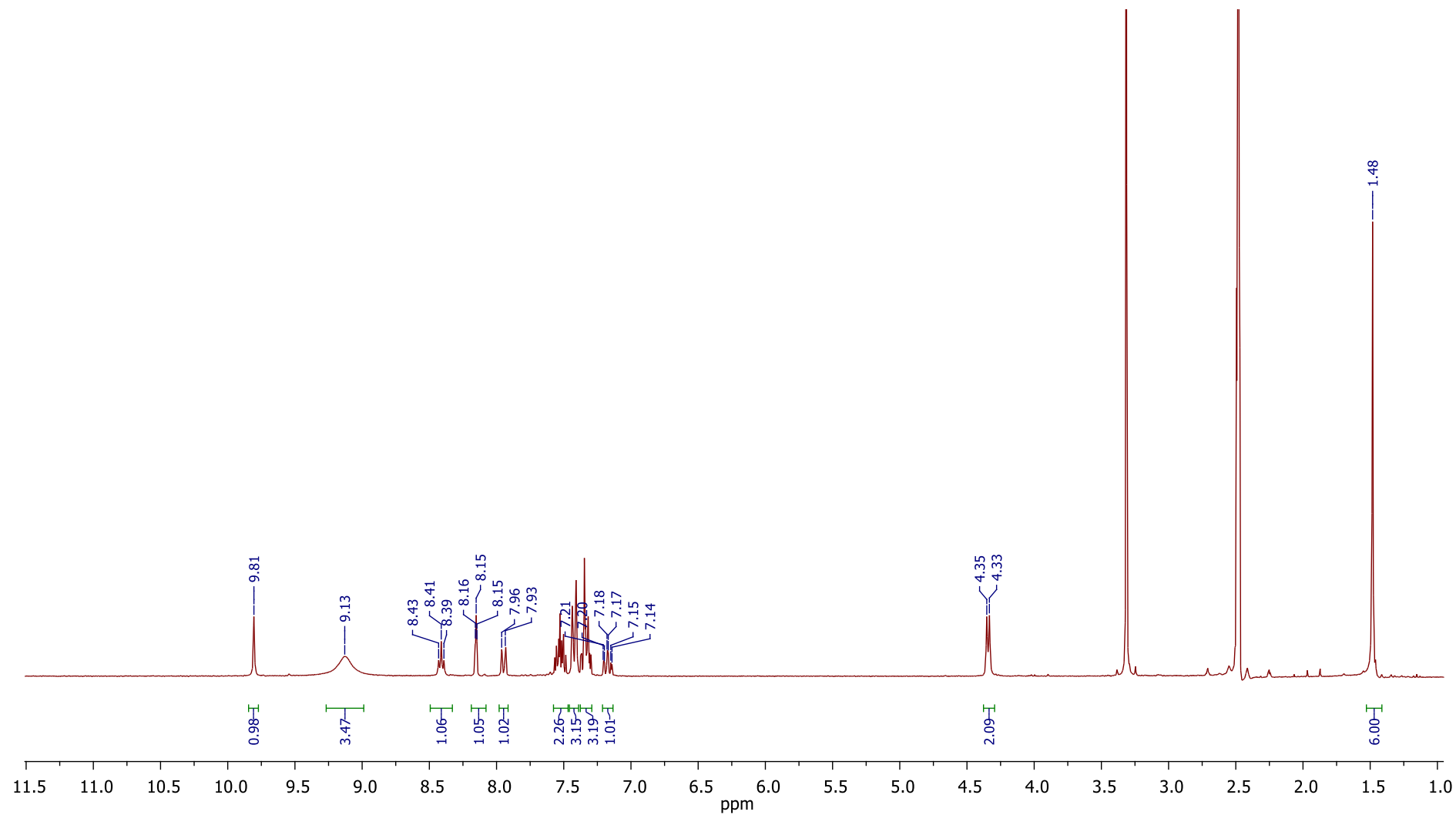




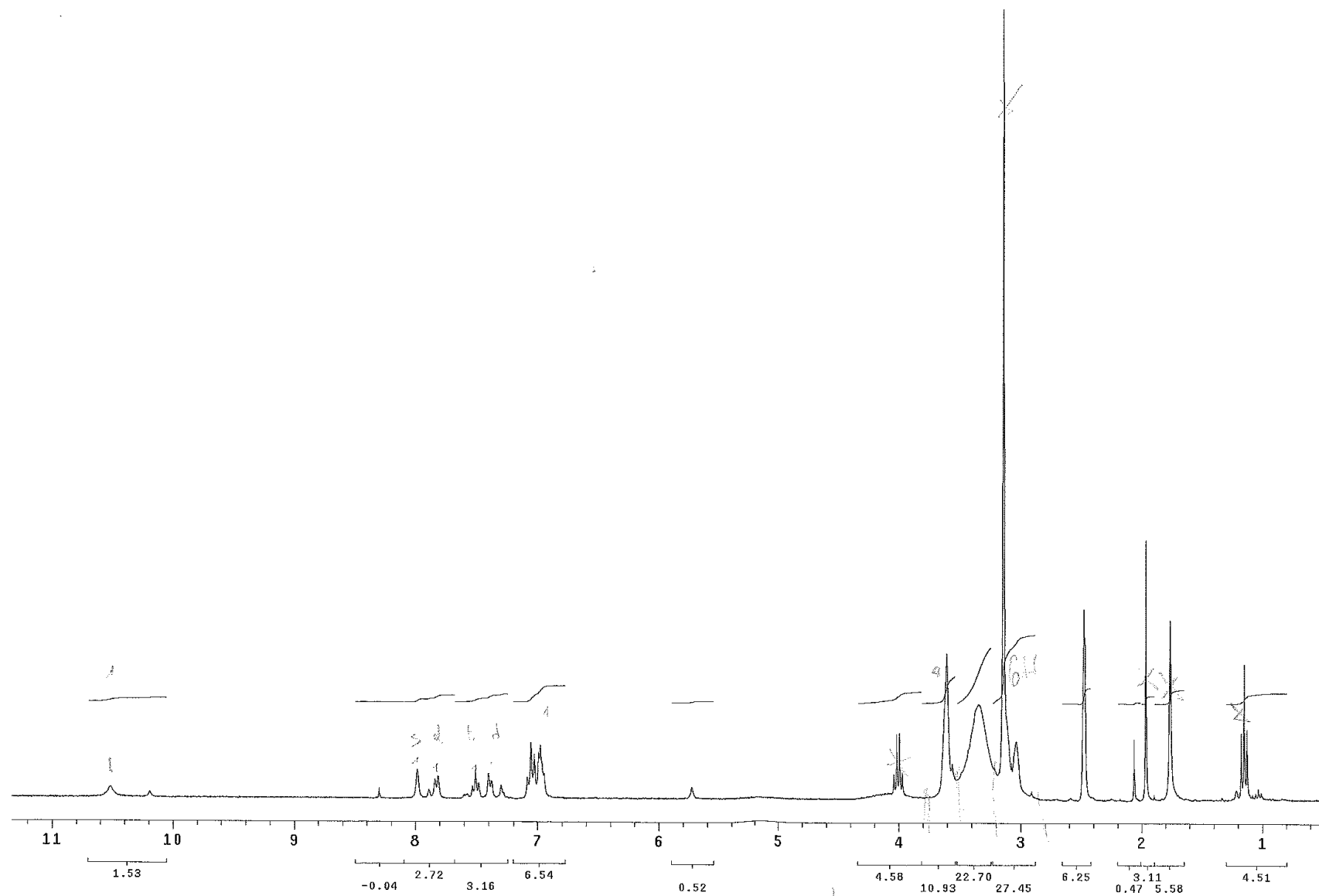
20a



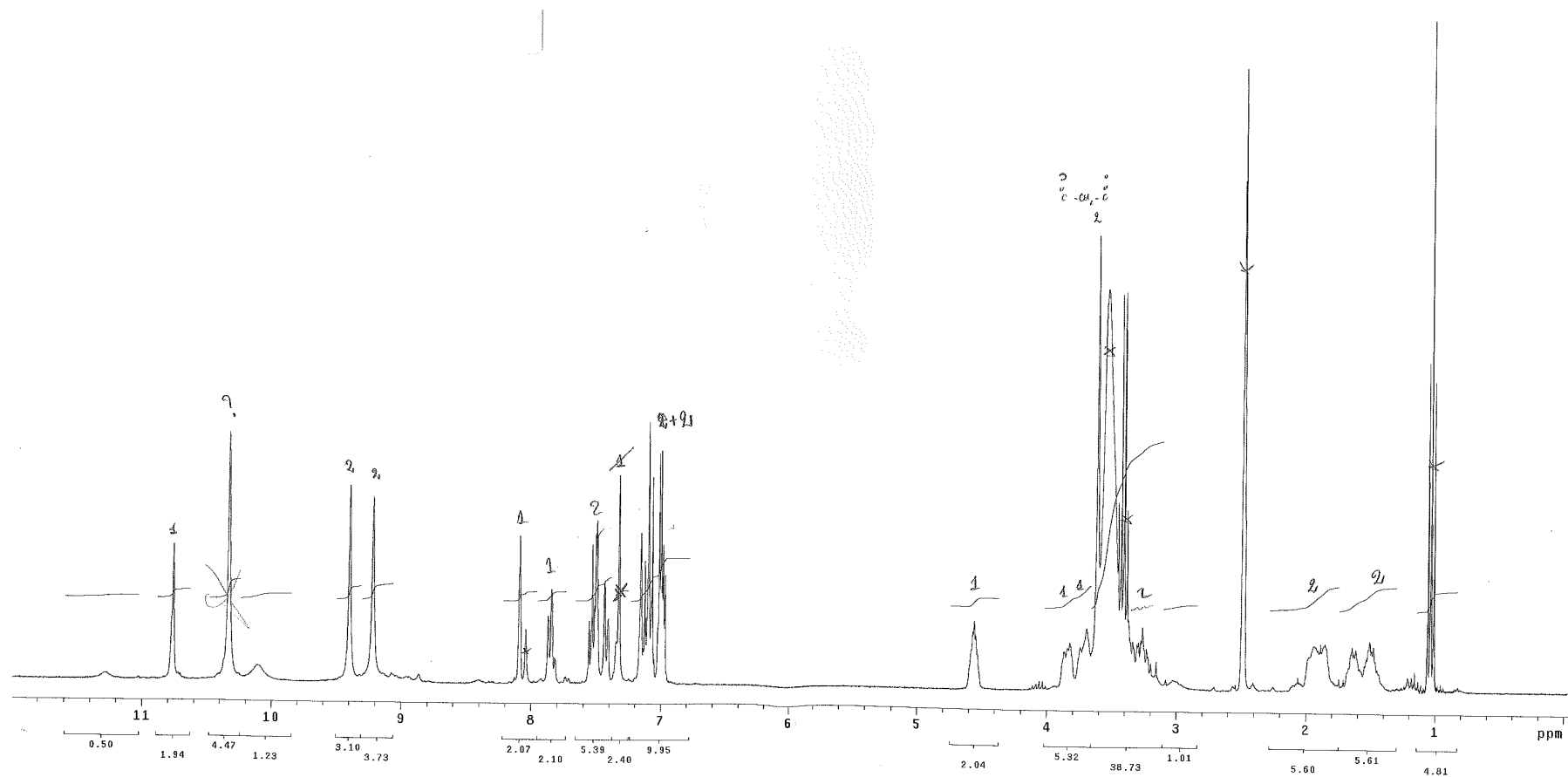
20b



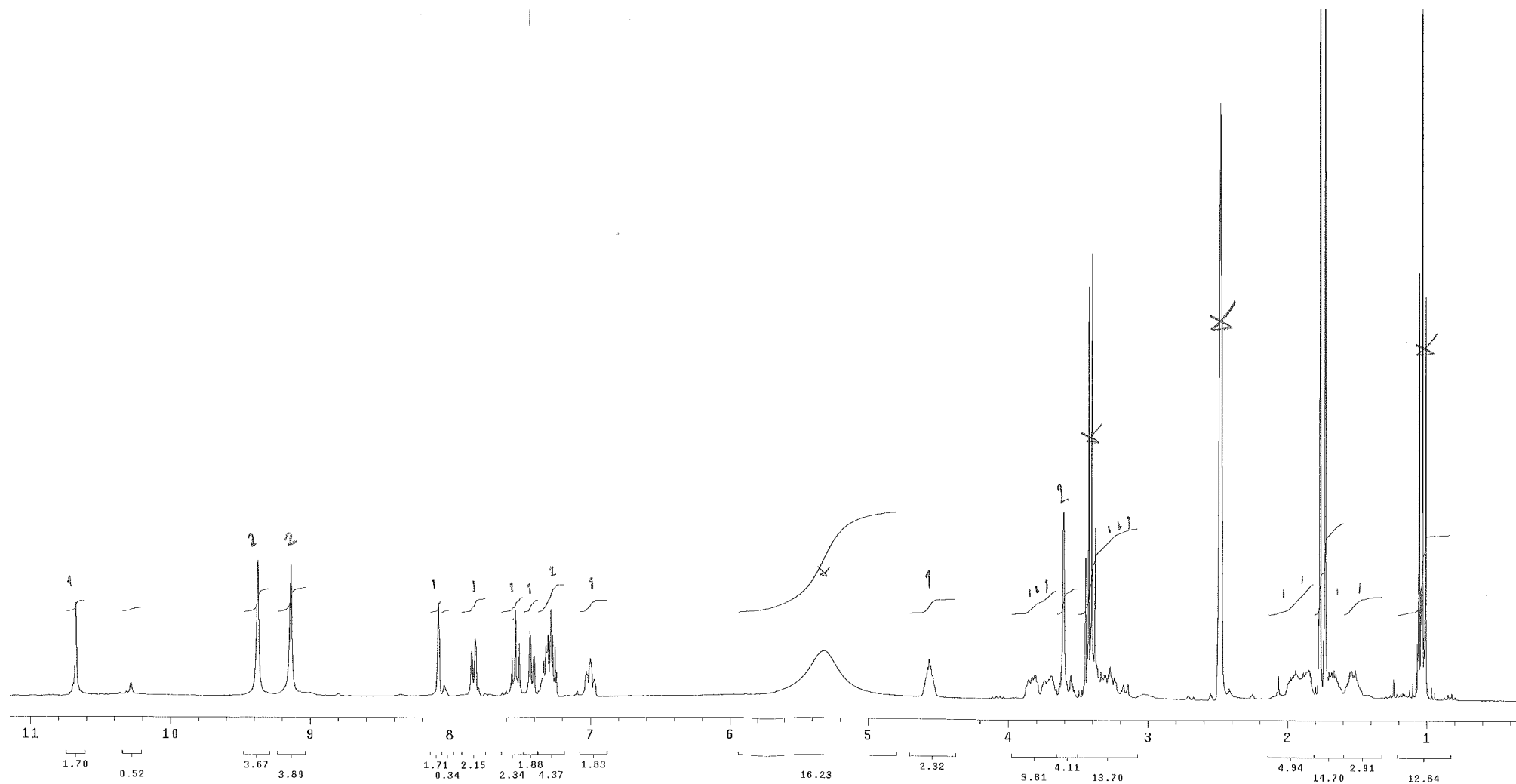
21a



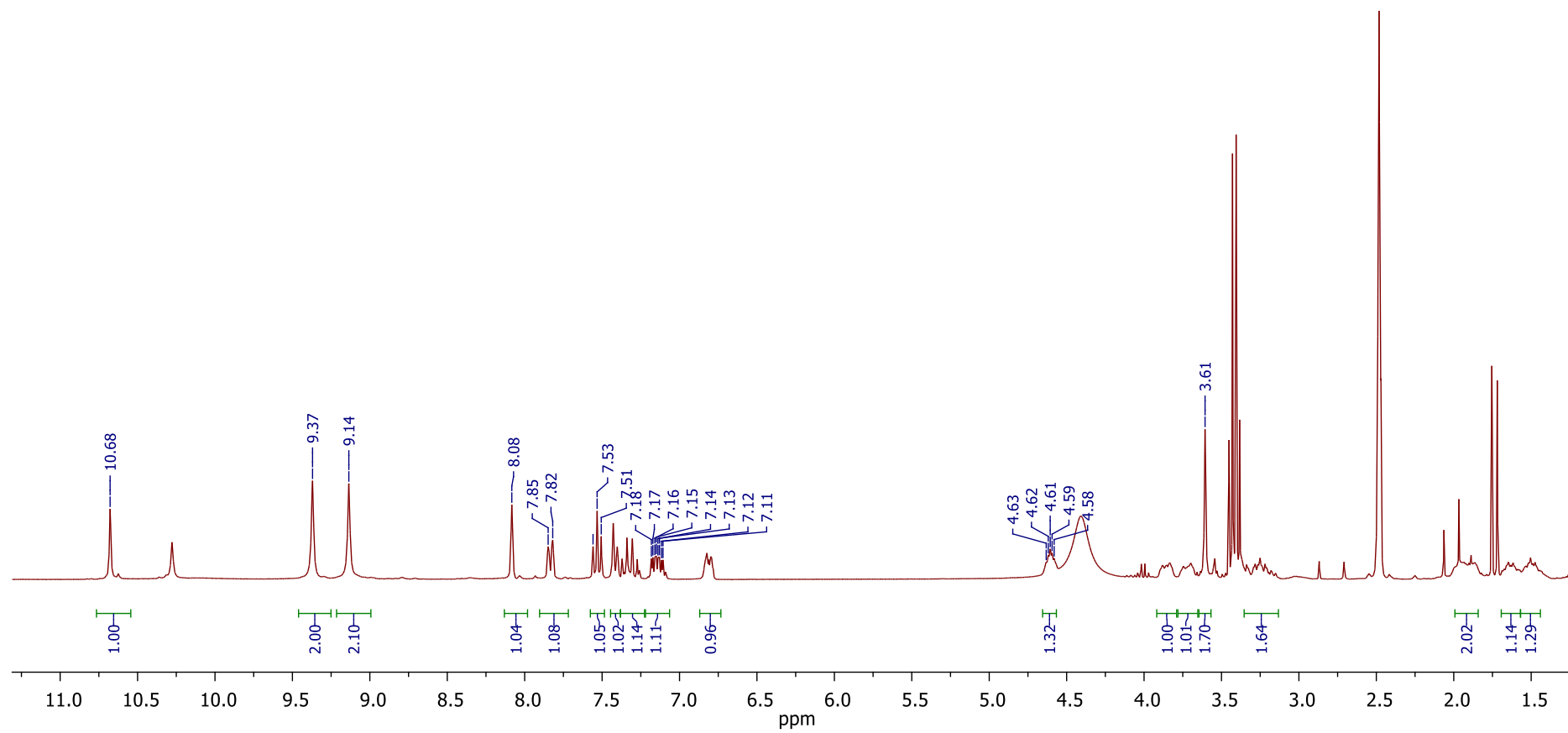
22a



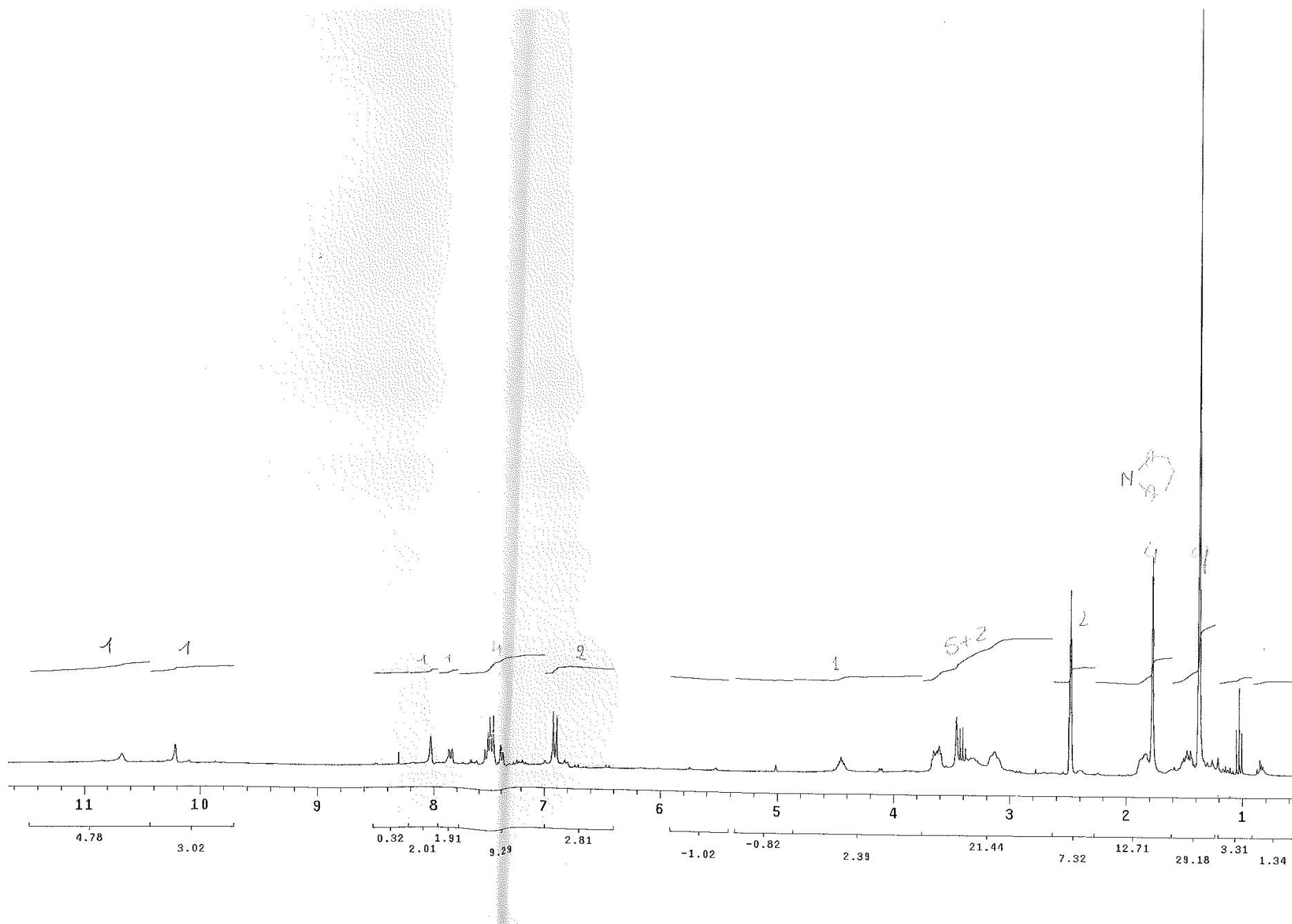
22b



22c



23a



23b

