Supporting information

for

Iterative Oxime Bond Chemistry Leads to Protease Inhibitors

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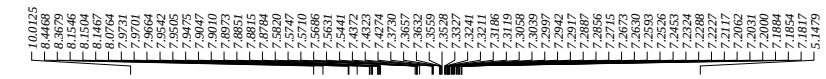
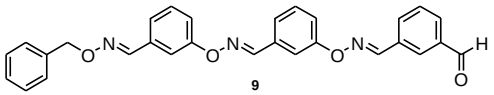
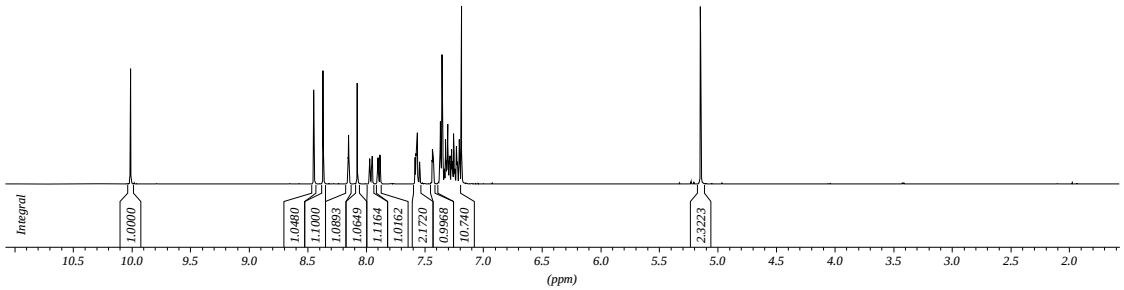
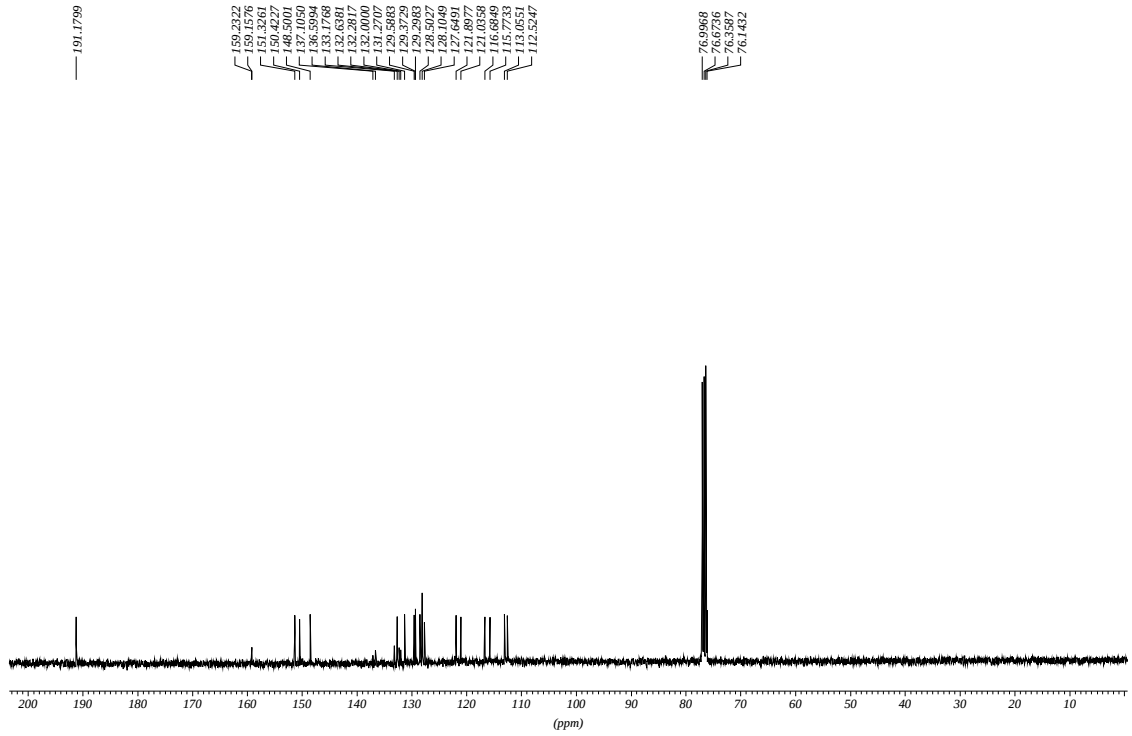
Spectroscopic data of active compounds **9**, **21**, **35** and **38-40**, protease assay conditions and basic crystallographic data for oligomers **19** and **41**.



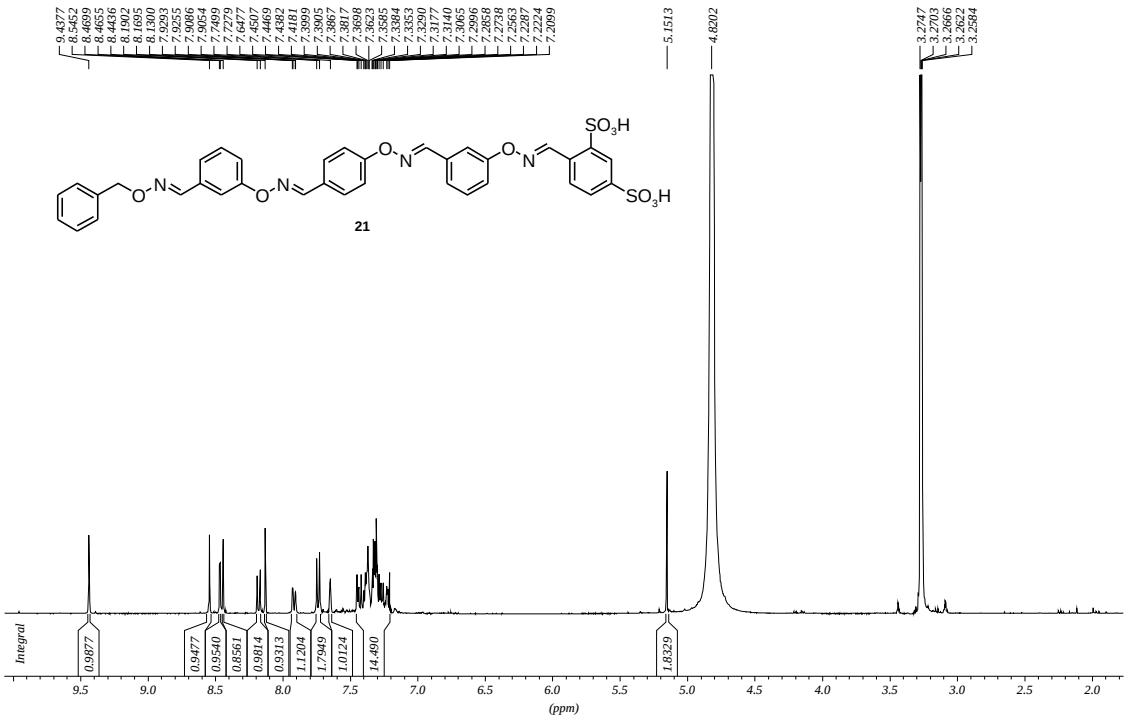


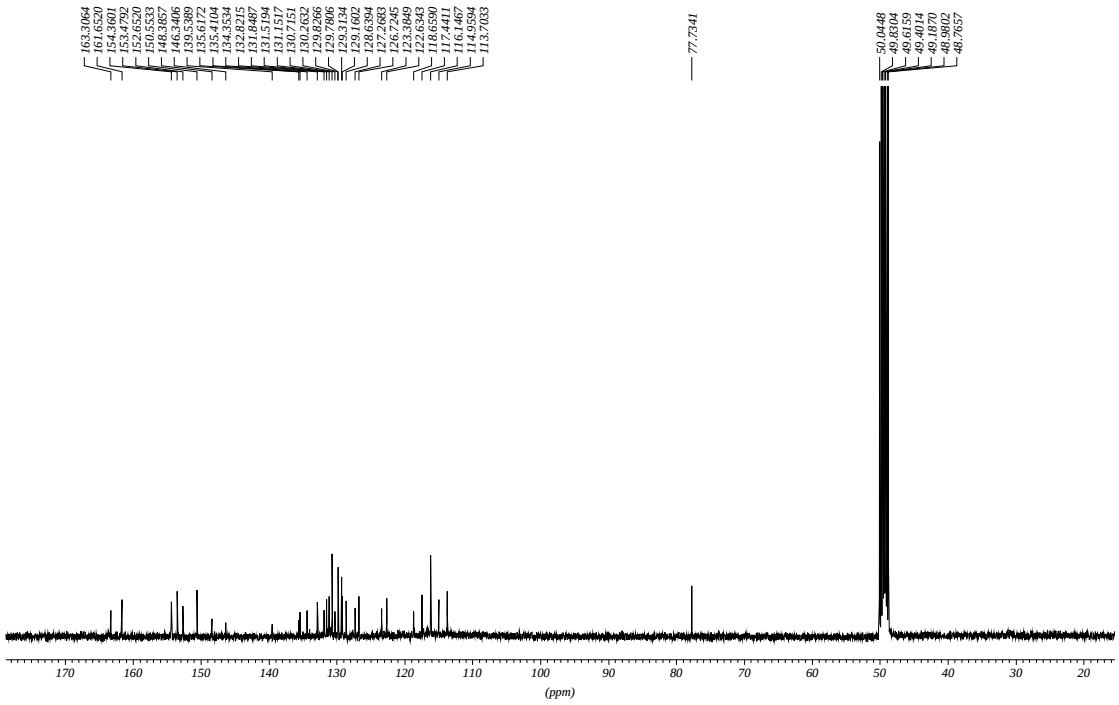
9



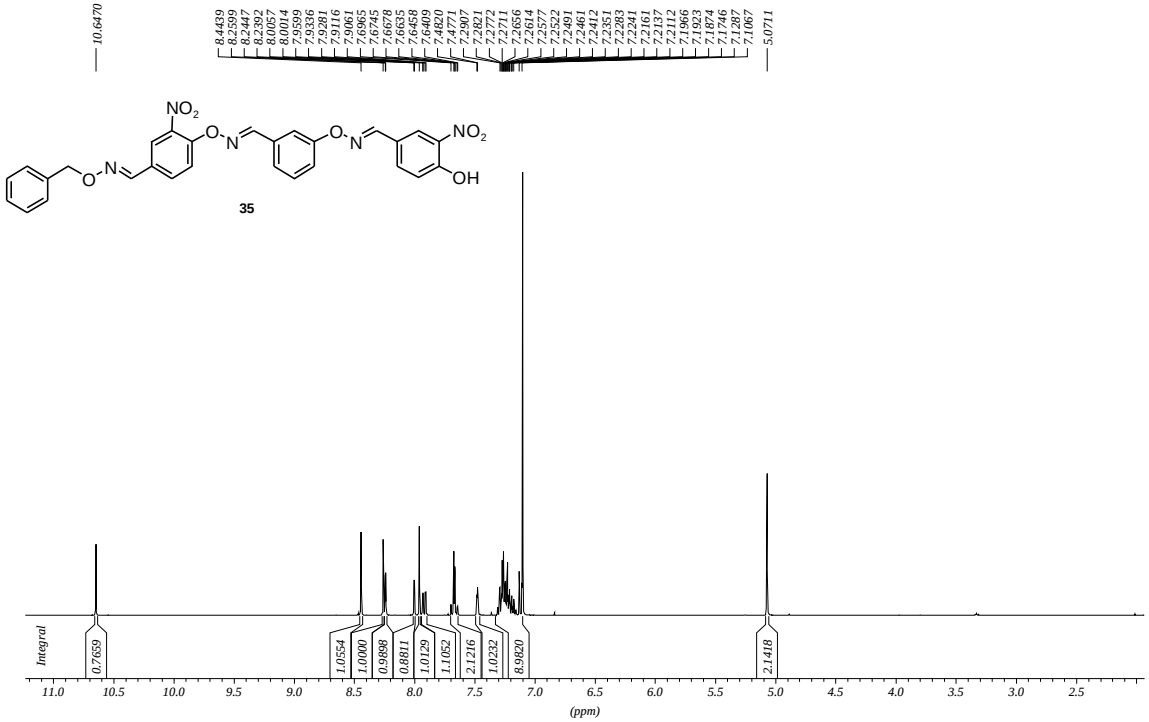


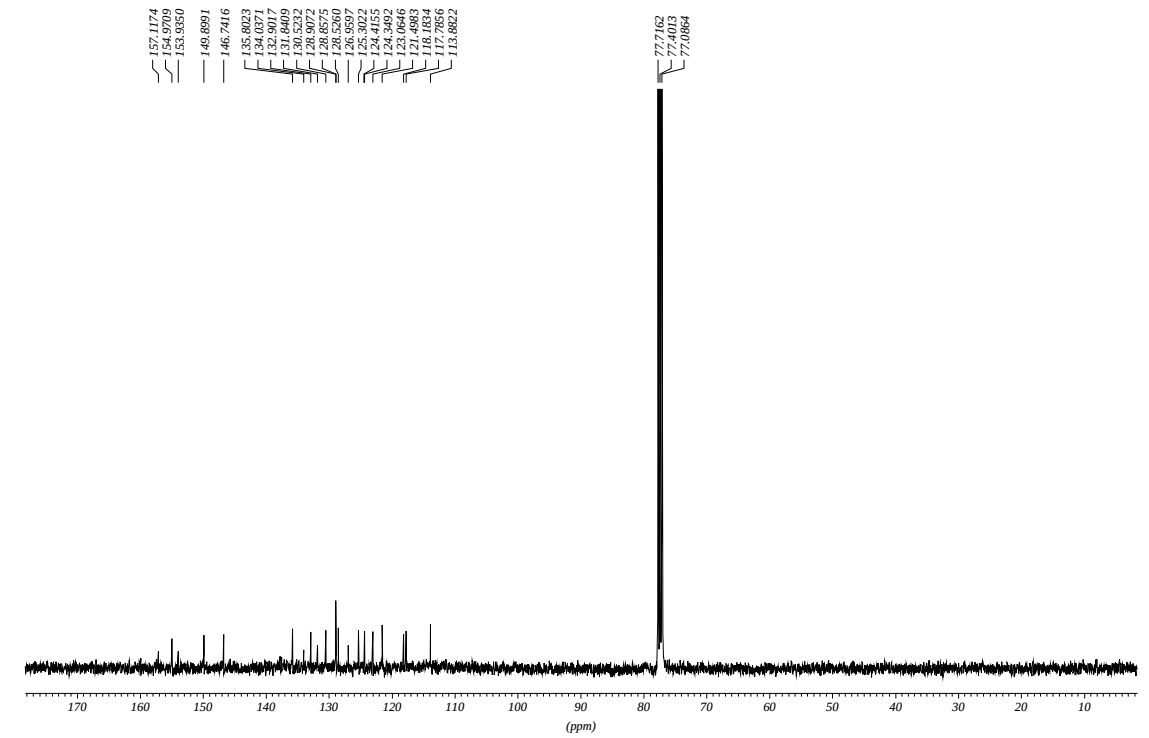
^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.01 (s, 1 H, CHO), 8.44 (s, 1 H, $H_{ox.}$), 8.37 (s, 1 H, $H_{ox.}$), 8.15 (t, 1 H, *J* = 1.7 Hz, $H_{ar.}$), 8.07 (s, 1 H, $H_{ox.}$), 7.96 (dt, 1 H, *J* = 1.5, 7.8 Hz, $H_{ar.}$), 7.89 (dt, 1 H, *J* = 1.5, 7.8 Hz, $H_{ar.}$), 7.58-7.54 (m, 2 H, $H_{ar.}$), 7.43 (t, 1 H, *J* = 1.9 Hz, $H_{ar.}$), 7.37-7.18 (m, 11 H, $H_{ar.}$), 5.15 (s, 2 H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 159.2, 159.1, 151.3, 150.4, 148.5, 137.1, 136.6, 133.2, 132.6, 132.3, 132.0, 131.3, 129.6, 129.4, 129.3, 128.5, 128.1, 127.6, 122.1, 121.9, 121.0, 116.7, 115.8, 113.0, 112.5, 76.1; HREI-MS: calcd. for $C_{29}H_{24}N_3O_4$: 478.1766; found: 478.1779 $[M+H]^+$.



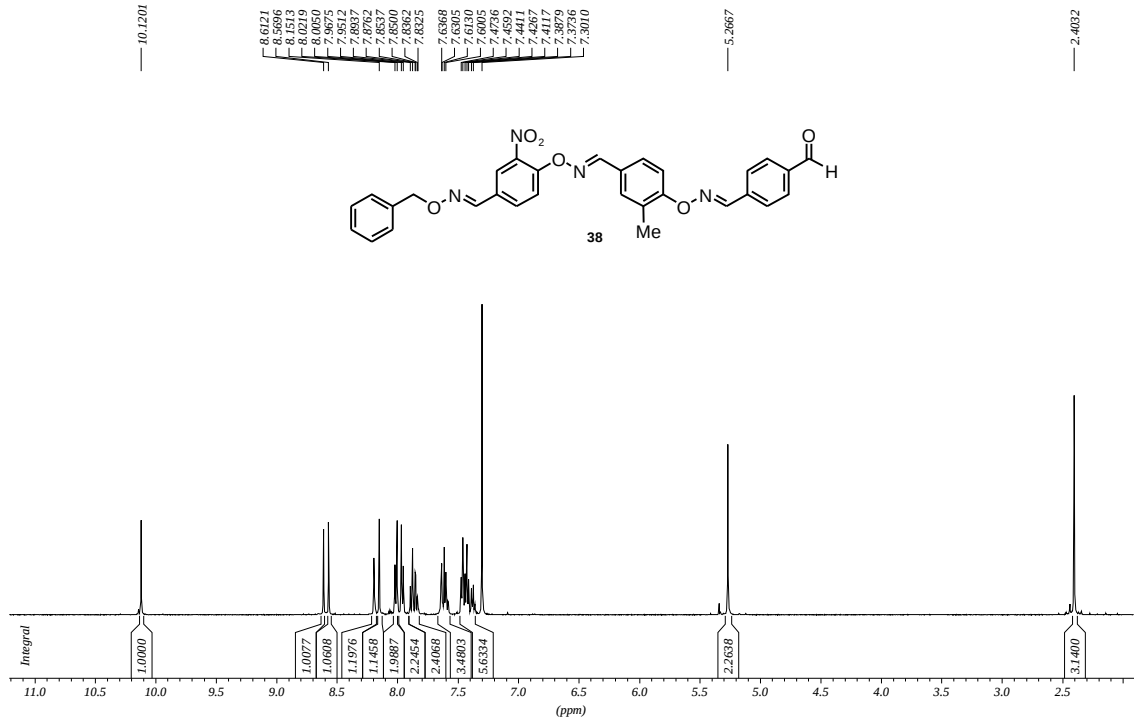


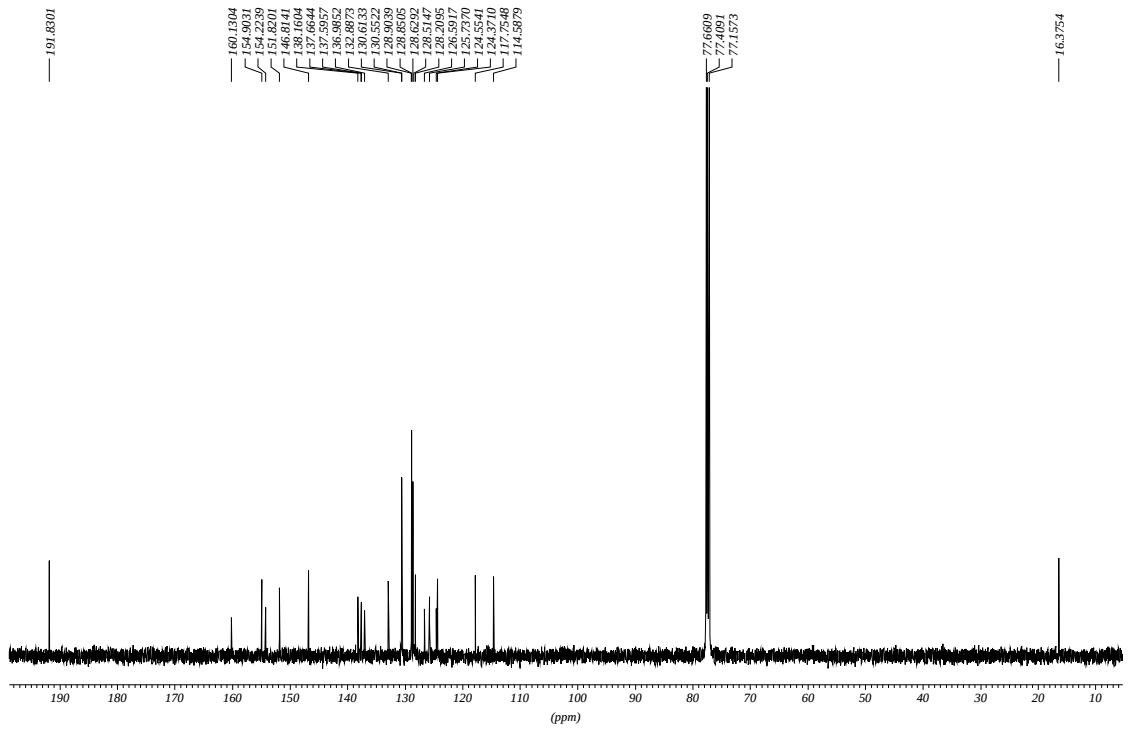
^{1}H NMR (400 MHz, CD_3OD): δ = 9.43 (s, 1 H, $H_{ox.}$), 8.54 (s, 1 H, $H_{ox.}$), 8.46 (d, 1 H, *J* = 1.8 Hz, $H_{ar.}$), 8.44 (s, 1 H, $H_{ox.}$), 8.17 (d, 1 H, *J* = 8.3 Hz, $H_{ar.}$), 8.13 (s, 1 H, $H_{ox.}$), 7.91 (dd, 1 H, *J* = 1.4, 8.3 Hz, $H_{ar.}$), 7.75-7.64 (m, 3 H, $H_{ar.}$), 7.45-7.20 (m, 14 H, $H_{ar.}$), 5.15 (s, 2 H, CH_2); ^{13}C NMR (100 MHz, CD_3OD): δ = 163.3, 161.6, 154.4, 153.5, 152.7, 150.6, 148.4, 146.3, 139.5, 135.6, 135.4, 134.4, 132.8, 131.8, 131.5, 131.2, 130.7, 130.3, 129.8, 129.7, 129.3, 129.1, 128.6, 127.3, 126.7, 123.4, 122.6, 118.7, 117.4, 116.1, 114.9, 113.7, 77.7; EI-MS: calcd. for $C_{35}H_{28}N_4O_{10}S_2$: 728.12; found: 728.89 $[M+H]^+$.



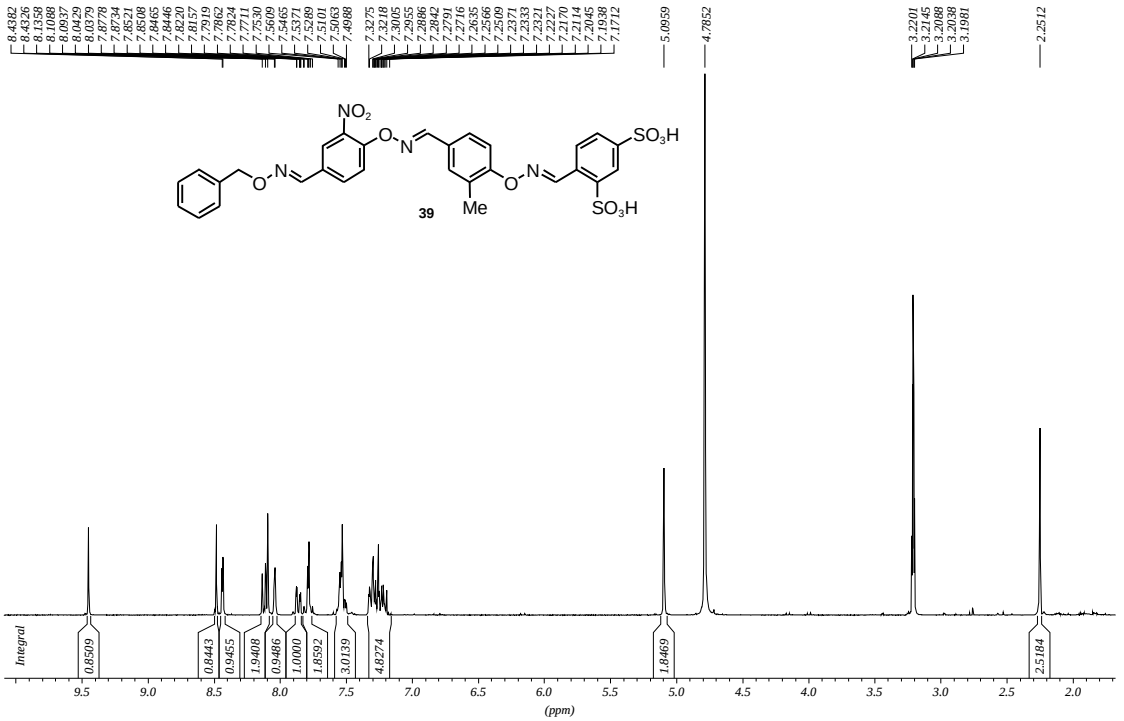


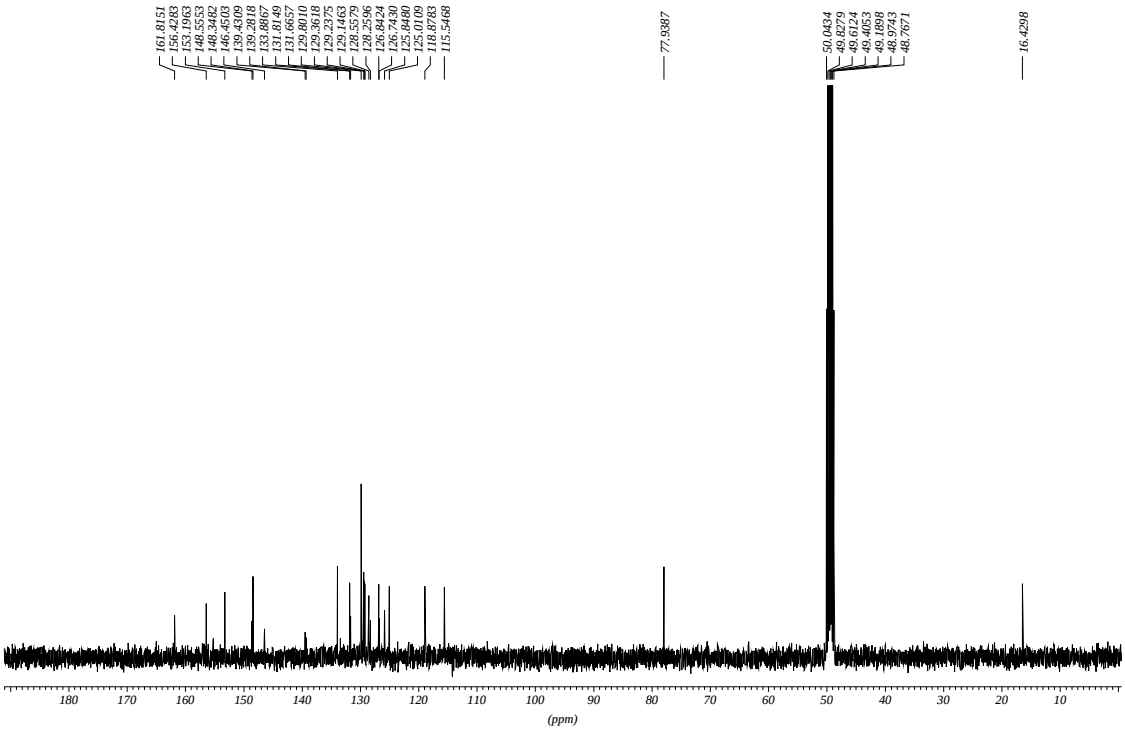
^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.64 (s, 1 H, OH), 8.44 (s, 1 H, $H_{ox.}$), 8.26 (s, 1 H, $H_{ox.}$), 8.24 (d, 1 H, *J* = 2.2 Hz, $H_{ar.}$), 8.00 (d, 1 H, *J* = 1.7 Hz, $H_{ar.}$), 7.96 (s, 1H, $H_{ox.}$), 7.91 (dd, 1 H, *J* = 2.2, 8.8 Hz, $H_{ar.}$), 7.69-7.64 (m, 2 H, $H_{ar.}$), 7.48-7.46 (m, 1 H, $H_{ar.}$), 7.30-7.10 (m, 9 H, $H_{ar.}$), 5.07 (s, 2 H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1, 154.9, 153.9, 149.9, 146.7, 137.8, 137.6, 135.8, 134.0, 132.9, 131.8, 130.5, 128.9, 128.8, 128.5, 126.9, 125.3, 124.4, 124.3, 123.0, 121.5, 118.2, 117.8, 113.9, 77.1; HREI-MS: calcd. for $C_{28}H_{22}N_5O_8$: 556.1468; found: 556.1501 $[M+H]^+$.



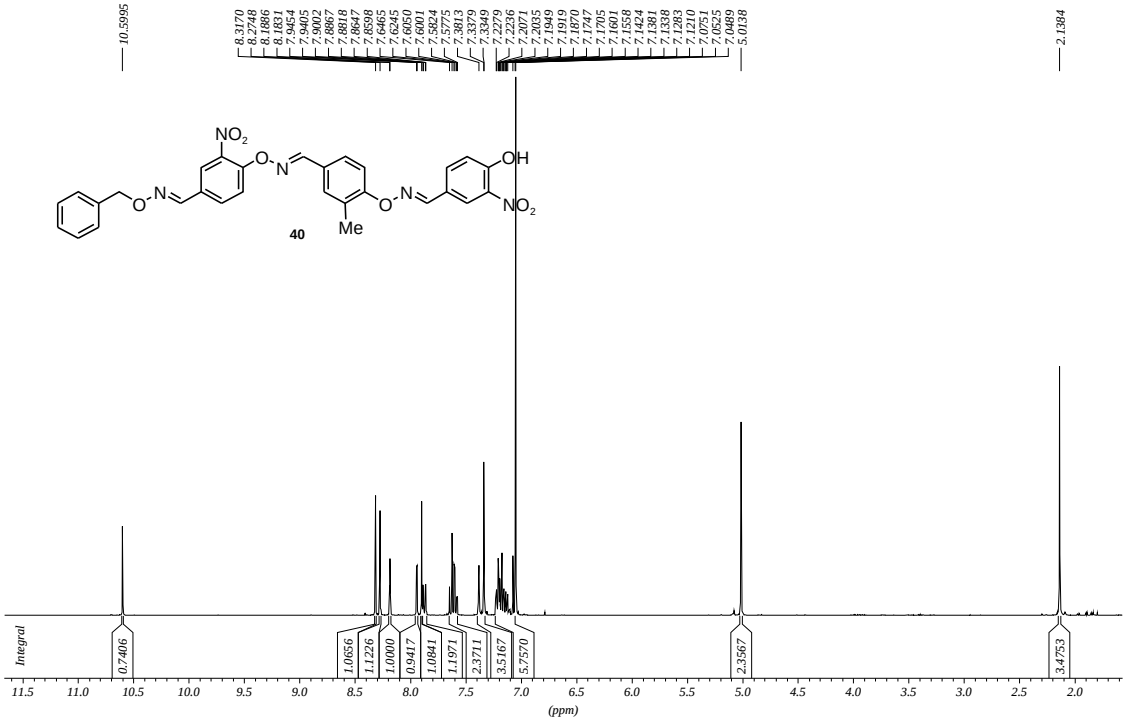


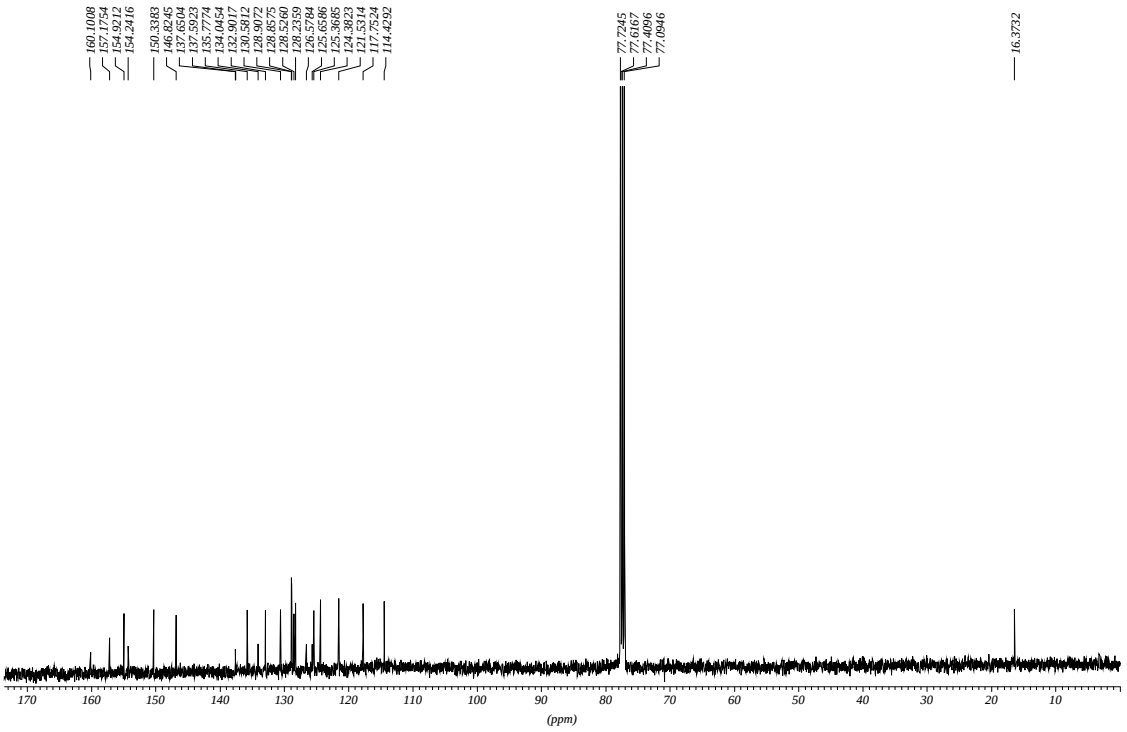
^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.12 (s, 1 H, CHO), 8.61 (s, 1 H, $H_{ox.}$), 8.57 (s, 1 H, $H_{ox.}$), 8.19 (d, 1 H, *J* = 1.5 Hz, $H_{ar.}$), 8.15 (s, 1 H, $H_{ox.}$), 8.02-7.95 (m, 4 H, $H_{ar.}$),7.89-7.83 (m, 2 H, $H_{ar.}$), 7.63-7.58 (m, 3 H, $H_{ar.}$), 7.47-7.35 (m, 5 H, $H_{ar.}$), 5.26 (s, 2 H, CH_2), 2.40 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 160.1, 154.9, 154.2, 151.8, 146.8, 138.1, 137.6, 137.5, 136.9, 132.9, 130.6, 130.5, 128.9, 128.8, 128.6, 128.5, 128.2, 126.6, 125.7, 124.5, 124.4, 117.7, 114.6, 76.9, 16.4; HREI-MS: calcd. for $C_{30}H_{25}N_4O_6$: 537.1774; found: 537.1806 $[M+H]^+$.





^{1}H NMR (400 MHz, CD_3OD): δ = 9.45 (s, 1 H, $H_{ox.}$), 8.48 (s, 1 H, $H_{ox.}$), 8.43 (d, 1 H, *J* = 1.7 Hz, $H_{ar.}$), 8.11 (d, 1 H, *J* = 8.1 Hz, $H_{ar.}$), 8.09 (s, 1 H, $H_{ox.}$), 8.04 (d, 1 H, *J* = 1.5 Hz, $H_{ar.}$), 7.86 (dd, 1 H, *J* = 1.3, 8.1 Hz, $H_{ar.}$), 7.82-7.77 (m, 2 H, $H_{ar.}$), 7.56-7.49 (m, 3 H, $H_{ar.}$), 7.32-7.17 (m, 5 H, $H_{ar.}$), 5.09 (s, 2 H, CH_2); ^{13}C NMR (100 MHz, CD_3OD): δ = 161.8, 156.4, 153.2, 148.6, 148.3, 146.5, 139.4, 139.3, 133.9, 131.8, 131.7, 129.8, 129.4, 129.2, 129.1, 128.6, 128.3, 126.8, 126.7, 125.8, 125.0, 118.9, 115.5, 77.9, 16.4; EI-MS: calcd. for $C_{29}H_{25}N_4O_{11}S_2$: 669.0961; found: 669.0967 $[M+H]^+$.



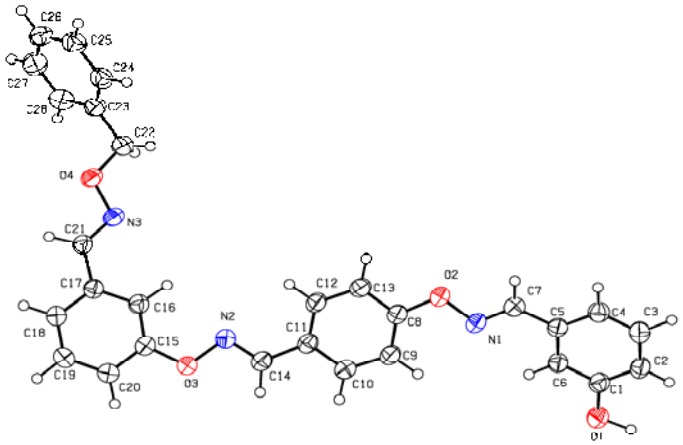


^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.60 (s, 1 H, OH), 8.31 (s, 1 H, $H_{ox.}$), 8.27 (s, 1 H, $H_{ox.}$), 8.18 (d, 1 H, *J* = 2.2 Hz, $H_{ar.}$), 7.94 (d, 1 H, *J* = 1.9 Hz, $H_{ar.}$), 7.90 (s, 1 H, $H_{ox.}$), 7.87 (dd, 1 H, *J* = 1.9, 8.8 Hz, $H_{ar.}$), 7.64-7.57 (m, 2 H, $H_{ar.}$), 7.38-7.33 (m, 3 H, $H_{ar.}$), 7.22-7.07 (m, 6 H, $H_{ar.}$), 5.01 (s, 2 H, CH_2), 2.14 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 157.1, 154.9, 154.2, 150.3, 146.8, 137.6, 137.6, 135.8, 134.0, 132.9, 130.6, 128.9, 128.8, 128.5, 128.2, 126.6, 125.6, 125.4, 124.4, 124.4, 121.5, 117.7, 115.6, 114.4, 77.6, 16.4.

Inhibition data for a**-chymotrypsin:**

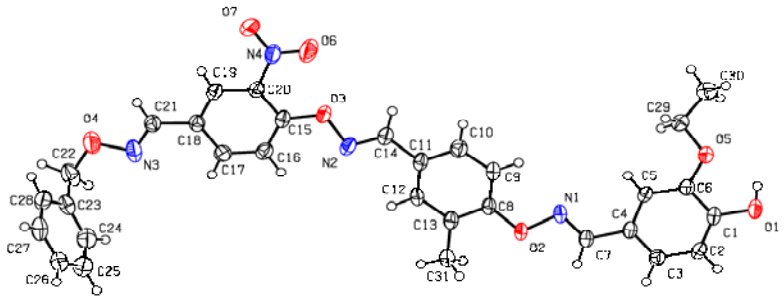
Assay conditions: 5 μg.mL^{-1} α-Chymotrypsin (from Bovine Pancreas, Sigma C-7762), 500 μM *N*-succinyl-Ala-Ala-Pro-Phe p-nitroanilide (Sigma S-7388), 5 mM aq. Bis Tris, pH 7.2, 26 °C. 40 μL assays were run in half-area clear polystyrene 96-well plates (Costar). Release of 4-nitroaniline was followed spectroscopically at 405 nm using a microtiter-plate reader. Inhibition of proteolytic activity was studied in the presence of 10 μM inhibitor for screening the oxime oligomer library. IC_{50} values of most active compounds (compounds with more than 90% inhibition) were measured under the same conditions in the presence of different concentration of inhibitor.

Basic crystallographic data for oligomer 19:



Identification code	**19**
Crystal shape	plate
Crystal colour	colourless
Crystal size	0.40 x 0.40 x 0.10 mm
Empirical formula	C28 H23 N3 O4
Formula weight	465.49
Crystal system	Monoclinic
Space group	P 2_1/c
Unit cell dimensions	a = 10.1436(11) A alpha = 90 deg. b = 8.0346(6) A beta = 96.601(10) deg. c = 29.122(4) A gamma = 90 deg.
Volume	2357.7(4) A^3
Cell refinement parameters Reflections Angle range	 16444 2.02 < theta < 29.63
Z	4
Density (calculated)	1.311 g/cm^3
Radiation used	MoK\a
Wavelength	0.71073 A
Linear absorption coefficient	0.089 mm^-1
Temperature	153(2) K

Basic crystallographic data for oligomer 41:



Identification code	**41**
Crystal shape	plate
Crystal colour	yellow
Crystal size	0.35 x 0.35 x 0.10 mm
Empirical formula	C31 H28 N4 O7
Formula weight	568.57
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 10.2388(8) A alpha = 85.466(10) deg. b = 11.3897(10) A beta = 73.957(9) deg. c = 12.7626(10) A gamma = 76.834(10) deg.
Volume	1392.6(2) A^3
Cell refinement parameters Reflections Angle range	 6472 2.12 < theta < 25.940
Z	2
Density (calculated)	1.356 g/cm^3
Radiation used	MoK\a
Wavelength	0.71073 A
Linear absorption coefficient	0.098 mm^-1
Temperature	153(2) K