Supporting Information

Novel Heterobivalent Tacrine Derivatives As Cholinesterase Inhibitors With Notable Selectivity Towards Butyrylcholinesterase

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Content. Detailed experimental and analytical data including spectral assignments for compounds **1-8**, **11a-h**, **12a-f**, **13a-h**, **14a-f**, **15a-h**, **16a-f** and **AS-1397**, as well as kinetic data for inhibition of acetylcholinesterase from *Electrophorus electricus* by compound **15h**.

General methods and materials. Melting points were determined on a Boëtius melting point apparatus, and are not corrected. Several compounds were prepared using the Büchi Glas Uster autoclave 'TinyClave'. Thin-layer chromatography was performed on Merck aluminium sheets, silica gel 60 F_{254}. Preparative column chromatography was performed on Merck silica gel 60, 70-230 mesh. ^{13}C NMR spectra (125 MHz) and ^{1}H NMR spectra (500 MHz) were recorded on a Bruker Avance DRX 500 spectrometer ^{13}C NMR signals were assigned on the basis of ^{13}C/^{1}H correlation experiments (HSQC, HMBC).

9-Chloro-1,2,3,4-tetrahydroacridine (8). 1,2,3,4-Tetrahydro-9[10*H*]-acridinone (**7**) (1.99 g, 10.0 mmol) was added to phosphorus oxychloride (10.0 ml, 107.0 mmol), and the reaction mixture was heated at 130°C for 3 hours. After cooling to room temperature, ice was added to the green solution to quench excess phosphorus oxychloride, and the volume was extended to 220 ml with water. When adjusting pH 10 using a solution of sodium hydroxide (13 g, 325 mmol) in water (30 ml), a yellowish solid precipitated. The reaction mixture was extracted with ethyl acetate (2 × 250 ml), dried (sodium sulfate) and the combined organic layers were evaporated in vacuo. Flash column chromatography using ethyl acetate and silica gel yielded the final product **8** (1.69 g, 78 %) as yellow crystals.
Mp. 64-67 °C, lit. 65-67 °C (E. T. Michalson, S. D'Andrea, S., J. P. Freeman, J. Szmuszkovicz *Heterocycles* **1990**, *30*, 415–425); **^{1}H NMR** ($CDCl_3$) δ 1.88-1.97 (m, 4 H), 3.00 (t, 2 H, *J* = 6.3 Hz), 3.10 (t, 2 H, *J* = 6.2 Hz), 7.51 (ddd, 1 H, *J* = 1.3 6.9 8.3 Hz), 7.64 (ddd, 1 H, *J* = 1.5 6.9 8.4 Hz), 7.95 (dd, 1 H, *J* = 8.5 Hz), 8.14 (dd, 1 H, *J* = 1.3 8.5 Hz); **^{13}C NMR** ($CDCl_3$) δ 22.62, 22.66, 27.49, 34.20, 123.67, 125.38, 126.45, 128.65, 128.85, 129.22, 141.40, 146.70, 159.50. Anal. ($C_{13}H_{12}ClN$) C, H, N.

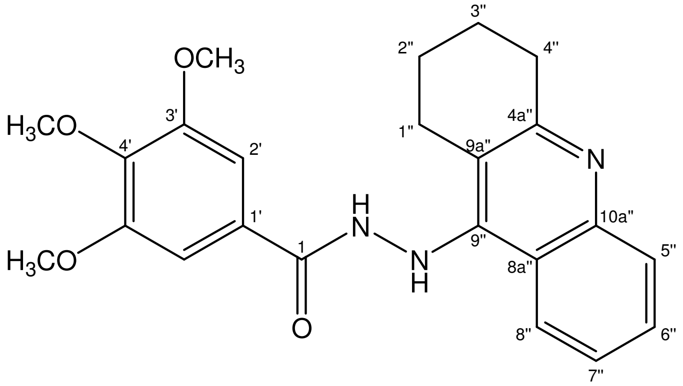
9-Hydrazino-1,2,3,4-tetrahydroacridine (17). In a sealed tube, 9-chloro-1,2,3,4-tetrahydroacridine (**8**) (2.18 g, 10.0 mmol) and a solution of hydrazine hydrate (100%, 1.0 ml, 20.6 mmol) in ethanol (5 ml) were heated at 140 °C for 5 hours. After cooling to room temperature, the reaction mixture was neutralized with concentrated hydrochloric acid and the precipitate was collected by suction filtration. Washing with diethyl ether and drying over phosphorus(V) oxide yielded the hydrochloride as a very hygroscopic powder (J. Patočka, J. Bajgar, J. Fusek *Coll. Czech. Chem. Commun.* **1977**, *42*, 2975–2981). Adding 1M sodium hydroxide solution (10 ml) to an aqueous solution of the hydrochloride liberated the base that was extracted with dichloromethane (3 × 20 ml), dried (sodium sulfate) and recrystallized from ethyl acetate / *n*-hexane to give **17** (1.26 g, 59 %) was orange needles.
Mp. 95-98 °C; **^{1}H NMR** ($CDCl_3$) δ 1.85-1.93 (m, 4 H), 2.75 (t, 2 H, *J* = 6.0 Hz), 3.04 (t, 2 H, *J* = 6.0 Hz), 3.98 (s, 2 H), 5.75 (bs, 1 H), 7.35 (ddd, 1 H, *J* = 1.6 7.0 8.4 Hz), 7.54 (ddd, 1 H, *J* = 1.6 6.9 8.4 Hz), 7.88 (app. d, 1 H, *J* = 8.5 Hz), 8.39 (dd, 1 H, *J* = 1.0 8.5 Hz); **^{13}C NMR** ($CDCl_3$) δ 22.70, 22.91, 24.63, 33.99, 115.59, 119.63, 123.21, 123.85, 128.38, 128.61, 147.39, 150.10, 158.45.

Methyl 3,4,5-trimethoxybenzoate (3). 3,4,5-Trimethoxybenzoic acid (**1**) (2.12 g, 10.0 mmol) was dissolved in anhydrous dichloromethane (20 ml) with catalytic amounts of N,N-dimethylformamide. Upon stirring, oxalyl chloride (1.0 ml, 11.6 mmol) was added. Once the gas evolution has ceased, remaining hydrogen chloride, excess oxalyl chloride and the solvent were removed by evaporation in vacuo. In a separate flask, sodium (0.23 g, 10.0 mmol) was added to anhydrous methanol (20 ml) and the solution was added to the acyl chloride obtained in the first reaction. Stirring at room temperature for 5 hours yielded a suspension that was evaporated in vacuo. Extracting the solid residue with dichloromethane (3 × 50 ml) after addition of a saturated solution of sodium hydrogen carbonate (50 ml), drying with anhydrous sodium sulfate and evaporation in vacuo yielded the final product which was purified by flash column chromatography using ethyl acetate to obtain **3** (1.88 g, 83 %) as white crystals .
Mp. 73-76 °C, lit. 81-82 °C (R. Saijo, G. Nonaka, I. Nishioka *Chem. Pharm. Bull. Jpn.* **1989**, *37*, 2063–2070); **^{1}H NMR** ($CDCl_3$) δ 3.88 (s, 12 H), 7.27 (s, 2 H); **^{13}C NMR** ($CDCl_3$) δ 52.19, 56.21, 60.88, 106.78, 125.12, 142.16, 152.91, 166.68. Anal. ($C_{11}H_{14}O_5$) C, H, N.
Methyl 3-(3,4,5-trimethoxyphenyl)propanoate (4). 3-(3,4,5-Trimethoxyphenyl)propanoic acid (**2**) (2.40 g, 10.0 mmol) was reacted as described above (2.10 g, 83%, white crystals).
Mp. 45 °C; **^{1}H NMR** (DMSO-d_6) δ 2.62 (t, 2 H, J = 7.7 Hz), 2.77 (t, 2 H, J = 7.7 Hz), 3.61 (s, 3 H), 3.59 (s, 3 H), 3.73 (s, 6 H), 6.51 (s, 2 H); **^{13}C NMR** (DMSO-d_6) δ 30.77, 35.14, 51.41, 55.94, 60.06, 105.68, 136.00, 136.32, 152.88, 172.85. Anal. ($C_{13}H_{18}O_5$) C, H: calcd, 7.13, found 7.65, N.

3,4,5-Trimethoxybenzohydrazide (5). Methyl 3,4,5-trimethoxybenzoate (**3**) (1,13 g, 5.0 mmol) was added to a mixture of hydrazine hydrate (100%, 2.5 ml, 51.4 mmol) and absolute ethanol (20 ml), and the solution was refluxed for about 24 hours. The course of the reaction was followed by TLC (toluene : acetone : methanol, 7 : 2 : 1) and once no more ester could be detected, it was evaporated in vacuo. The crude product was recrystallized from ethanol to afford **5** (0.85 g, 75 %) as white needles.
Mp 155-158 °C, lit. 162 °C (F. Clemence, C. Joliveau-Maushart, J. Meier, J. Cerede, F. Delevallee, J. Benzoni, R. Deraedt *Eur. J. Med. Chem.* **1985**, *20*, 257–266); **^{1}H NMR** (DMSO-d_6) δ 3.69 (s, 3 H), 3.80 (s, 6 H), 4.44 (s, 2 H), 7.15 (s, 2 H), 9.67 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 56.11, 60.17, 104.65, 128.57, 139.95, 152.73, 165.48. Anal. ($C_{10}H_{14}N_2O_4$ • 0.5 H_2O) C, H, N.

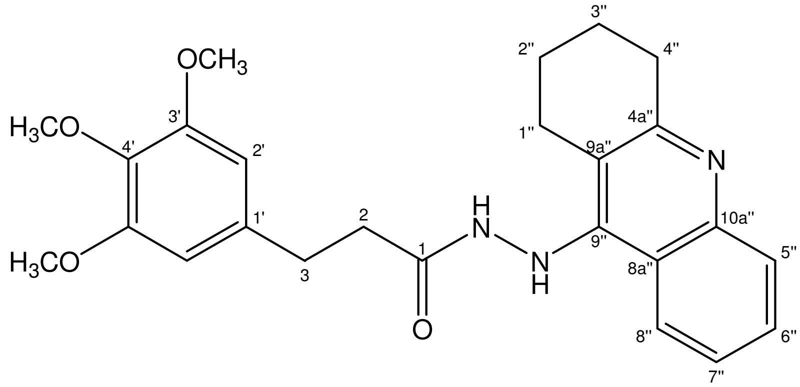
3-(3,4,5-Trimethoxyphenyl)propanohydrazide (6). Methyl 3-(3,4,5-trimethoxyphenyl)-propanoate (**4**) (1.27 g, 5.0 mmol) was reacted as described above (0.99 g, 78%, white needles).
Mp. 122-125 °C, lit. 127-128 °C (J. V. Prata, D. T. Clemente, S. Prabhakar, A. M. Lobo, I. Mourato, P. S. Branco *J. Chem. Soc. Perkin Trans. 1* **2002**, 513–528); **^{1}H NMR** (DMSO-d_6) δ 2.31 (t, 2 H, J = 7.9 Hz), 2.74 (t, 2 H, J = 7.9 Hz), 3.60 (s, 3 H), 3.73 (s, 6 H), 4.15 (s, 2 H), 6.48 (s, 2 H), 8.93 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 31.48, 35.26, 55.93, 60.06, 105.60, 135.88, 137.04, 152.83, 170.93. Anal. ($C_{12}H_{18}N_2O_4$) C, H, N.

N'-1,2,3,4-Tetrahydroacridin-9-yl-3,4,5-trimethoxybenzohydrazide (15a). 9-Chloro-1,2,3,4-tetrahydroacridine (**8**) (0.44 g, 2.0 mmol) and 3,4,5-trimethoxybenzohydrazide **5** (0.45 g, 2.0 mmol), dissolved in absolute ethanol (20 ml) were heated at 140 °C for 24 hours in a sealed tube. Cooling to room temperature yielded the hydrochloride as a yellow precipitate that was collected by suction filtration and dissolved in ethanol (5 ml) and water (20 ml). After addition of a 1M sodium hydroxide solution (2 ml), the base **15a** precipitated as orange needles that were filtered off. (0.64 g, 79 %).



Mp. 241-244°C. Anal. ($C_{23}H_{25}N_3O_4 \cdot 0.5\ H_2O$) C, H, N.

N’-1,2,3,4-Tetrahydroacridin-9-yl-3-(3,4,5-trimethoxyphenyl)propanohydrazide (16a). 3-(3,4,5-Trimethoxyphenyl)propanohydrazide (**6**) (0.51 g, 2.0 mmol) was reacted as described above. The hydrochloride was recrystallized from nitromethane and the final base was recovered by extraction using ethyl acetate (0.57 g, 65 %, yellow powder).



Mp. 196°C; **^{1}H NMR** (DMSO-d_6) δ 1.69-1.82 (m, 4 H, 2´´-H, 3´´-H), 2.42 (t, 2 H, J = 7.6 Hz, 2-H), 2.69-2.73 (m, 4 H, 1´´-H, 3-H), 2.90 (t, 2 H, J = 6.0 Hz, 4´´-H), 3.60 (s, 3 H, C4´-OCH3), 3.66 (s, 6 H, C3´-OCH3), 6.43 (s, 2 H, 2´-H), 7.30 (app. t, 1 H, J = 7.3 Hz, 7´´-H), 7.51 (ddd, 1 H, J = 1.3, 6.8, 8.3 Hz, 6´´-H), 7.71 (app. d, 2 H, J = 6.6 Hz, 8´´-H, CON<u>H</u>NH), 8.30 (app. d, 1 H, J = 8.5 Hz, 5´´-H), 10.04 (s, 1 H, CONHN<u>H</u>); **^{13}C NMR** (DMSO-d_6) δ 22.44 (C2´´), 22.68 (C3´´), 24.93 (C1´´), 31.01 (C3), 33.73 (C4´´), 34.73 (C2), 55.85 (C3´-OCH3), 60.02 (C4´-OCH3), 105.58 (C2´), 115.78 (C9a´´), 119.13 (C8a´´), 123.03 (C5´´), 123.54 (C7´´), 127.97 (C6´´), 128.40 (C8´´), 135.90 (C1´), 136.76 (C4´), 146.74 (C10a´´), 148.61 (C9´´), 152.81 (C3´), 158.24 (C4a´´), 171.33 (C1). Anal. ($C_{25}H_{29}N_3O_4$) C, H: calcd, 6.71, found 7.15, N.

Ethyl 5-aminopentanoate hydrochloride (10e). General procedure for ω-amino-carboxylic esters 10e-h. Thionyl chloride (2.2 ml, 30.0 mmol) was added dropwise to anhydrous ethanol (50 ml) while cooling. Subsequently, 5-aminopentanoic acid (**9e**) (2.34 g, 20.0 mmol) was added and the reaction mixture was stirred for 12 hours. The solvent was evaporated in vacuo and the crude product was recrystallized from ethyl acetate to give the hydrochloride **10e** that was directly used in the next step. The esters **10e**-**h** were obtained in yields higher than 90 %.

Ethyl 9-aminononanoate hydrochloride (10i). Ethyl hydrogen sebacate (5.54 g, 24.0 mmol) was dissolved in toluene (30 ml), and diphenyl phosphoryl azide (5.6 ml, 26.0 mmol) and triethyl amine (3.6 ml, 26.0 mmol) were added. The solution was heated to 80°C for 2 hours to allow isocyanate formation. Subsequently, anhydrous *tert*-butanol (20 ml) was added and the reaction mixture was refluxed for 12 hours. After cooling to room temperature the solvent was evaporated in vacuo, and the remaining residue was taken up in diethyl ether (100 ml). Filtering through silica gel, washing with diethyl ether (100 ml) and evaporation in vacuo yielded the Boc-protected ethyl 9-amino-nonanoate as a colorless oil. For deprotection, this oil was dissolved in ethyl acetate (20 ml) and 4M hydrochloric acid in ethyl acetate (20 ml) was added. **10i** (4.40 g, 77 %) was recovered by suction filtration as a white precipitate. **Mp.** 129-132 °C, lit. 125 °C (C. Temple, R. D. Elliott, J. A. Montgomery *J. Med. Chem.* **1988**, *31*, 697–700);**^{1}H NMR** (DMSO-d_6) δ 1.16 (t, 3 H, J = 7.1 Hz), 1.25 (bs, 8 H), 1.45-1.59 (m, 4 H), 2.25 (t, 2 H, J = 7.4 Hz), 2.71 (app. t, 2 H, J = 7.7 Hz), 4.03 (q, 2 H, J = 7.2 Hz), 8.03 (s, 3 H); **^{13}C NMR** (DMSO-d_6) δ 14.26, 24.54, 25.90, 27.01, 28.44, 28.46, 28.57, 33.63, 38.80, 59.74, 172.98.

Ethyl ((3,4,5-trimethoxybenzoyl)amino)acetate (11b). General procedure for amides 11b-i. 3,4,5-Trimethoxybenzoic acid (**1**) (2.12 g, 10.0 mmol) was dissolved in anhydrous dichloromethane (20 ml) with catalytic amounts of N,N-dimethylformamide. Oxalyl chloride (1.0 ml, 11.6 mmol) was added while stirring, and once the gas evolution had ceased it was evaporated to dryness. The residue was again dissolved in dichloromethane (10 ml), and ethyl aminoacetate hydrochloride (**10b**) (1.40 g, 10.0 mmol) was suspended in the solution. Dropwise addition of N-ethyl-N,N-diisopropylamine (3.5 ml, 20.0 mmol) yielded a clear solution which sometimes contained some precipitated N-ethyl-N,N-diisopropylamine hydrochloride. Washing with water and a saturated solution of sodium hydrogen carbonate, drying with anhydrous sodium sulfate and evaporation in vacuo yielded a crude product which was further purified by recrystallization from ethyl acetate / *n*-hexane to give **11b** (1.83 g, 62 %) as white crystals.
Mp. 104-107 °C, lit. 109 °C (R. M. Acheson, D. A. Booth, R. Brettle, A. M. Harris *J. Chem. Soc*. **1960**, 3457-3461);**^{1}H NMR** (DMSO-d_6) δ 1.20 (t, 3 H, J = 6.9 Hz), 3.71 (s, 3 H), 3.82 (s, 6 H), 3.98 (d, 2 H, J = 6.0 Hz), 4.12 (q, 2 H, J = 7.0 Hz), 7.20 (s, 2 H), 8.86 (t, 1 H, J = 5.8 Hz); **^{13}C NMR** (DMSO-d_6) δ 14.23, 41.51, 56.14, 60.21, 60.54, 105.05, 128.93, 140.37, 152.75, 166.13, 170.04. Anal. ($C_{14}H_{19}NO_6$) C, H, N.

Ethyl 3-((3,4,5-trimethoxybenzoyl)amino)propanoate (11c). Ethyl 3-aminopropanoate hydrochloride (**10c**) (1.54 g, 10.0 mmol) was reacted as described above (2.76 g, 89 %, white crystals).
Mp. 65-68°C; **^{1}H NMR** (DMSO-d_6) δ 1.17 (t, 3 H, J = 7.1 Hz), 2.56 (t, 2 H, J = 6.9 Hz), 3.47 (app. q, 2 H, J = 7.0 Hz), 3.69 (s, 3 H), 3.81 (s, 6 H), 4.06 (q, 2 H, J = 7.1 Hz), 7.15 (s, 2 H), 8.48 (t, 1 H); **^{13}C NMR** (DMSO-d_6) δ 14.20, 34.00, 35.74, 56.15, 60.05, 60.19, 104.96, 129.66, 140.14, 152.68, 165.85, 171.44. Anal. ($C_{15}H_{21}NO_6$) C, H, N.

Ethyl 4-((3,4,5-trimethoxybenzoyl)amino)butanoate (11d). Ethyl 4-aminobutanoate hydrochloride (**10d**) (1.68 g, 10.0 mmol) was reacted as described above (2.47 g, 76 %, white crystals).
Mp. 73-76 °C, lit. 74-75 °C (O. S. Fominova, S. Y. Skachilova, A. I. Ermakov, M. G. Pleshakov *Zh. Org. Khim.* **1977**, *13*, 1922–1926); **^{1}H NMR** ($CDCl_3$) δ 1.22 (t, 3 H, J = 7.1 Hz), 1.94 (app. quint, 2 H, J = 6.7 Hz), 2.43 (t, 2 H, J = 6.8 Hz), 3.47 (app. q, 2 H, J = 6.3 Hz), 3.85 (s, 3 H), 3.88 (s, 6 H), 4.10 (q, 2 H, J = 7.2 Hz,), 6.76 (bs, 1 H), 7.02 (s, 2 H); **^{13}C NMR** ($CDCl_3$) δ 14.14, 24.08, 32.26, 40.08, 56.22, 60.69, 60.86, 104.25, 129.82, 140.73, 153.11, 167.01, 174.23. Anal. ($C_{16}H_{23}NO_6$) C, H: calcd, 7.13, found 7.58, N.

Ethyl 5-((3,4,5-trimethoxybenzoyl)amino)pentanoate (11e). Ethyl 5-aminopentanoate hydrochloride (**10e**) (1.82 g, 10.0 mmol) was reacted as described above (3.02 g, 89 %, white crystals).

Mp. 97-100 °C; **^{1}H NMR** (DMSO-*d$_6$*) δ 1.16 (t, 3 H, *J* = 7.1 Hz), 1.48-1.60 (m, 4 H), 2.32 (t, 2 H, *J* = 7.1 Hz), 3.24 (app. q, 2 H, *J* = 5.8 Hz), 3.69 (s, 3 H), 3.81 (s, 6 H), 4.04 (q, 2 H, *J* = 7.0 Hz), 7.16 (s, 2 H), 8.37 (t, 1 H, *J* = 5.7 Hz); **^{13}C NMR** (DMSO-*d$_6$*) δ 14.24, 22.15, 28.78, 33.33, 38.98, 56.14, 59.79, 60.18, 104.92, 129.96, 140.01, 152.67, 165.59, 172.92. Anal. $C_{17}H_{25}NO_6$) C, H, N.

Ethyl 6-((3,4,5-trimethoxybenzoyl)amino)hexanoate (11f). Ethyl 6-aminohexanoate hydrochloride (**10f**) (1.96 g, 10.0 mmol) was reacted as described above (2.20 g, 62 %, white lints).
Mp. 76-79 °C, lit. 83-84.5 °C (P. Novak, J. Jary *Coll. Czech. Chem. Commun.* **1973**, *38*, 2621–2626); **^{1}H NMR** (DMSO-*d$_6$*) δ 1.15 (t, 3 H, *J* = 7.1 Hz), 1.30 (app. quint, 2 H, *J* = 7.3 Hz), 1.51 (app. quint, 2 H, *J* = 7.6 Hz), 1.55 (app. quint, 2 H, *J* = 7.9 Hz), 2.28 (t, 2 H, *J* = 7.6 Hz), 3.23 (app. q, 2 H, *J* = 6.6 Hz), 3.69 (s, 3 H), 3.81 (s, 6 H), 4.03 (q, 2 H, *J* = 7.2 Hz), 7.15 (s, 2 H), 8.34 (t, 1 H, *J* = 5.7 Hz); **^{13}C NMR** (DMSO-*d$_6$*) δ 14.24, 24.37, 26.07, 29.00, 33.59, 39.21, 56.14, 59.75, 60.18, 104.92, 130.02, 139.99, 152.66, 165.56, 172.95. Anal. ($C_{18}H_{27}NO_6$) C, H: calcd, 7.70, found 8.12, N.

Ethyl 7-((3,4,5-trimethoxybenzoyl)amino)heptanoate (11g). Ethyl 7-aminoheptanoate hydrochloride (**10g**) (2.10 g, 10.0 mmol) was reacted as described above (2.91 g, 79 %, white lints).
Mp. 83-86 °C; **^{1}H NMR** (DMSO-*d$_6$*) δ 1.16 (t, 3 H, *J* = 7.1 Hz), 1.29 (app. quint, 4 H, *J* = 7.3 Hz), 1.46-1.56 (m, 4 H), 2.26 (t, 2 H, *J* = 7.4 Hz), 3.23 (app. q, 2 H, *J* = 6.6 Hz), 3.68 (s, 3 H), 3.81 (s, 6 H), 4.03 (q, 2 H, *J* = 7.1 Hz), 7.15 (s, 2 H), 8.33 (t, 1 H, *J* = 5.5 Hz); **^{13}C NMR** (DMSO-*d$_6$*) δ 14.25, 24.52, 26.28, 28.32, 29.15, 33.60, 39.37, 56.14, 59.74, 60.18, 104.91, 130.04, 139.98, 152.66, 165.56, 172.98. Anal. ($C_{19}H_{29}NO_6$) C, H, N.

Ethyl 8-((3,4,5-trimethoxybenzoyl)amino)octanoate (11h). Ethyl 8-aminooctanoate hydrochloride (**10h**) (2.24 g, 10.0 mmol) was reacted as described above (3.05 g, 80 %, white lints).
Mp. 82-85 °C; **^{1}H NMR** (DMSO-*d$_6$*) δ 1.16 (t, 3 H, *J* = 7.1 Hz), 1.28 (bs, 6 H), 1.46-1.55 (m, 4 H), 2.25 (t, 2 H, *J* = 7.4 Hz), 3.23 (app. q, 2 H, *J* = 6.6 Hz), 3.69 (s, 3 H), 3.81 (s, 6 H), 4.03 (q, 2 H, *J* = 7.1 Hz), 7.15 (s, 2 H), 8.33 (t, 1 H, *J* = 5.5 Hz); **^{13}C NMR** (DMSO-*d$_6$*) δ 14.25, 24.54, 26.48, 28.52, 28.54, 29.27, 33.63, 39.37, 56.14, 59.73, 60.18, 104.91, 130.04, 139.98, 152.66, 165.54, 172.99. Anal. ($C_{20}H_{31}NO_6$) C, H: calcd, 8.19, found 8.69, N.

Ethyl 9-((3,4,5-trimethoxybenzoyl)amino)nonanoate (11i). Ethyl 9-aminononanoate hydrochloride (**10i**) (2.38 g, 10.0 mmol) was reacted as described above (3.24 g, 82 %, white crystals).
Mp. 80-83 °C; **^{1}H NMR** (DMSO-*d$_6$*) δ 1.15 (t, 3 H, *J* = 7.3 Hz), 1.22-1.32 (m, 8H), 1.46-1.55 (m, 4 H), 2.25 (t, 2 H, *J* = 7.4 Hz), 3.23 (app. q, 2 H, *J* = 6.6 Hz), 3.69 (s, 3 H), 3.81 (s, 6 H), 4.03 (q, 2 H, *J* = 7.1 Hz), 7.15 (s, 2 H), 8.33 (t, 1 H, *J* = 5.7 Hz); **^{13}C NMR** (DMSO-*d$_6$*) δ 14.24, 24.57, 26.56, 28.51, 28.73, 28.74, 29.29, 33.64, 39.40, 56.13, 59.72, 60.17, 104.90, 130.04, 139.97, 152.65, 165.52, 172.99. Anal. ($C_{21}H_{33}NO_6$) C, H, N.

Ethyl ((3-(3,4,5-trimethoxyphenyl)propanoyl)amino)acetate (12b). General procedure for amides 12b-f. 3-(3,4,5-Trimethoxyphenyl)propanoic acid **2** (2.40 g, 10.0 mmol) was reacted with ethyl aminoacetate hydrochloride (**10b**) (1.40 g, 10.0 mmol) by the same procedure described for the preparation of **11b**. The crude product was purified by recrystallization from ethyl acetate / *n*-hexane to afford **12b** (2.29 g, 70 %) as white crystals.
Mp. 66-69 °C; **^{1}H NMR** ($CDCl_3$) δ 1.26 (t, 3 H, *J* = 7.1 Hz), 2.52 (t, 2 H, *J* = 7.7 Hz), 2.90 (t, 2 H, *J* = 7.7 Hz), 3.79 (s, 3 H), 3.82 (s, 6 H), 4.00 (d, 2 H, *J* = 5.1 Hz), 4.19 (q, 2 H, *J* = 7.1 Hz), 5.92 (bs, 1 H), 6.40 (s, 2 H); **^{13}C NMR** ($CDCl_3$) δ 14.10, 31.86, 38.20, 41.37, 56.05, 60.80, 61.56, 105.21, 136.38, 136.47, 153.21, 169.94, 172.05. Anal. ($C_{16}H_{23}NO_6$) C, H, N.

Ethyl 3-((3-(3,4,5-trimethoxyphenyl)propanoyl)amino)propanoate (12c). Ethyl 3-amino-propanoate hydrochloride (**10c**) (1.54 g, 10.0 mmol) was reacted as described above (3.22 g, 95 %, yellow oil).
^{1}H NMR (DMSO-d_6) δ 1.17 (t, 3 H, *J* = 7.1 Hz), 2.34 (t, 2 H, *J* = 7.7 Hz,), 2.40 (t, 2 H, *J* = 7.0 Hz), 2.72 (t, 2 H, *J* = 7.9 Hz), 3.25 (app. q, 2 H, *J* = 6.5 Hz), 3.60 (s, 3 H), 3.73 (s, 6 H), 4.04 (q, 2 H, *J* = 7.1 Hz), 6.48 (s, 2 H), 7.88 (t, 1 H, *J* = 5.5 Hz); **^{13}C NMR** (DMSO-d_6) δ 14.18, 31.52, 34.04, 34.80, 37.08, 55.88, 60.00, 60.05, 105.59, 135.85, 137.11, 152.81, 171.39, 171.61.

Ethyl 4-((3-(3,4,5-trimethoxyphenyl)propanoyl)amino)butanoate (12d). Ethyl 4-amino-butanoate hydrochloride (**10d**) (1.68 g, 10.0 mmol) was reacted as described above (3.21 g, 91 %, white crystals).
Mp. 41-44 °C; **^{1}H NMR** (DMSO-d_6) δ 1.17 (t, 3 H, *J* = 7.3 Hz), 1.61 (app. quint, 2 H, *J* = 7.3 Hz), 2.23 (t, 2 H, *J* = 7.6 Hz), 2.34 (t, 2 H, *J* = 7.7 Hz), 2.73 (t, 2 H, *J* = 7.7 Hz), 3.04 (app. q, 2 H, *J* = 6.5 Hz), 3.60 (s, 3 H), 3.73 (s, 6 H), 4.03 (q, 2 H, *J* = 7.2 Hz), 6.48 (s, 2 H), 7.79 (t, 1 H, *J* = 5.5 Hz); **^{13}C NMR** (DMSO-d_6) δ 14.21, 24.74, 31.05, 31.57, 37.19, 37.88, 55.89, 59.85, 60.05, 105.60, 135.86, 137.16, 152.81, 171.45, 172.71. Anal. ($C_{18}H_{27}NO_6$) C, H, N.

Ethyl 5-((3-(3,4,5-trimethoxyphenyl)propanoyl)amino)pentanoate (12e). Ethyl 5-amino-pentanoate hydrochloride (**10e**) (1.82 g, 10.0 mmol) was reacted as described above (3.53 g, 96 %, yellow oil).
^{1}H NMR (DMSO-d_6) δ 1.16 (t, 3 H, *J* = 7.1 Hz), 1.36 (app. quint, 2 H, *J* = 7.3 Hz), 1.47 (app. quint, 2 H, *J* = 7.5 Hz), 2.25 (t, 2 H, *J* = 7.4 Hz), 2.34 (t, 2 H, *J* = 7.9 Hz), 2.73 (t, 2 H, *J* = 7.7 Hz), 3.02 (app. q, 2 H, *J* = 6.5 Hz), 3.60 (s, 3 H), 3.73 (s, 6 H), 4.03 (q, 2 H, *J* = 7.0 Hz), 6.48 (s, 2 H), 7.76 (t, 1 H, *J* = 5.5 Hz); **^{13}C NMR** (DMSO-d_6) δ 14.99, 22.75, 29.45, 32.36, 34.00, 37.96, 38.86, 56.63, 60.52, 60.79, 106.34, 136.59, 137.93, 153.55, 172.05, 173.61.

Ethyl 6-((3-(3,4,5-trimethoxyphenyl)propanoyl)amino)hexanoate (12f). Ethyl 6-amino-hexanoate hydrochloride (**10f**) (1.96 g, 10.0 mmol) was reacted as described above (3.37 g, 88 %, white crystals).
Mp. 61-64 °C; **^{1}H NMR** ($CDCl_3$) δ 1.22 (t, 3 H, *J* = 7.3 Hz), 1.28 (app. quint, 2 H, *J* = 7.7 Hz), 1.44 (app. quint, 2 H, *J* = 7.3 Hz), 1.58 (app. quint, 2 H, *J* = 7.6 Hz), 2.26 (t, 2 H, *J* = 7.4 Hz), 2.43 (t, 2 H, *J* = 7.6 Hz), 2.88 (t, 2 H, *J* = 7.6 Hz), 3.20 (app. q, 2 H, *J* = 6.6 Hz), 3.79 (s, 3 H), 3.81 (s, 6 H), 4.09 (q, 2 H, *J* = 7.2 Hz), 5.53 (bs, 1 H), 6.40 (s, 2 H); **^{13}C NMR** ($CDCl_3$) δ 14.21, 24.34, 26.23, 29.14, 32.20, 34.02, 38.66, 39.29, 56.06, 60.26, 60.81, 105.26, 136.35, 136.67, 153.18, 172.09, 173.60. Anal. ($C_{20}H_{31}NO_6$) C, H, N.

N-(2-Hydrazino-2-oxoethyl)-3,4,5-trimethoxybenzamide (13b). General procedure for hydrazides 13b-i and 14b-f. Ethyl ((3,4,5-trimethoxybenzoyl)amino)acetate (**11b**) (1,49 g, 5.0 mmol) was added to a mixture of hydrazine hydrate (100%, 2.5 ml, 51.4 mmol) and absolute ethanol (20 ml), and the solution was refluxed for about 24 hours. The course of the reaction was followed by TLC (toluene : acetone : methanol, 7 : 2 : 1) and once no more ester could be detected the solvent and excess hydrazine were removed by evaporation. The crude product was recrystallized from ethanol to obtain **13b** (1.02 g, 72 %) as a white powder.
Mp. 161-164 °C, lit. 167-168 °C (H. Roehnert *Arch. Pharm.* **1962**, *295*, 697–706); **^{1}H NMR** (DMSO-d_6) δ 3.70 (s, 3 H), 3.82 (d, 2 H, *J* = 5.7 Hz), 3.82 (s, 6 H), 4.20 (s, 2 H), 7.21 (s, 2 H), 8.65 (t, 1 H, *J* = 5.8 Hz), 9.08 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 41.58, 56.15, 60.21, 105.17, 129.41, 140.19, 152.65, 166.04, 168.48. Anal. ($C_{12}H_{17}N_3O_5$) C: calcd 50.88, found 50.37, H, N.

N-(3-Hydrazino-3-oxopropyl)-3,4,5-trimethoxybenzamide (13c). Ethyl 3-((3,4,5-trimethoxybenzoyl)amino)propanoate (**11c**) (1.56 g, 5.0 mmol) was reacted as described above (1.00 g, 67 %, white crystals).
Mp. 168-171 °C; **^{1}H NMR** (DMSO-d_6) δ 2.13 (t, 2 H, J = 7.3 Hz), 3.44 (app. q, 2 H, J = 5.7 Hz), 3.68 (s, 3 H), 3.81 (s, 6 H), 3.88 (4.16 (s, 2 H), 7.16 (s, 2 H), 8.45 (t, 1 H, J = 5.7 Hz), 9.01 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 33.81, 36.26, 56.14, 60.20, 104.95, 129.80, 140.06, 152.67, 165.72, 169.89. Anal. ($C_{13}H_{19}N_3O_5$) C, H, N.

N-(4-Hydrazino-4-oxobutyl)-3,4,5-trimethoxybenzamide (13d). Ethyl 4-((3,4,5-trimethoxybenzoyl)amino)butanoate (**11d**) (1.63 g, 5.0 mmol) was reacted as described above (1.06 g, 68 %, white crystals).
Mp. 104-107 °C; **^{1}H NMR** (DMSO-d_6) δ 1.74 (app. quint, 2 H, J = 7.3 Hz), 2.07 (t, 2 H, J = 7.4 Hz), 3.23 (app. q, 2 H, J = 6.5 Hz), 3.69 (s, 3 H,), 3.81 (s, 6 H), 4.20 (s, 2 H), 7.16 (s, 2 H), 8.40 (t, 1 H, J = 5.5 Hz), 8.94 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 25.49, 31.23, 39.20, 56.15, 60.19, 104.93, 129.93, 140.02, 152.67, 165.66, 171.45. Anal. ($C_{14}H_{21}N_3O_5$) C, H, N: calcd 13.50, found 12.68.

N-(5-Hydrazino-5-oxopentyl)-3,4,5-trimethoxybenzamide (13e). Ethyl 5-((3,4,5-trimethoxybenzoyl)amino)pentanoate (**11e**) (1.70 g, 5.0 mmol) was reacted as described above (1.16 g, 71 %, white crystals).
Mp. 151-154 °C; **^{1}H NMR** (DMSO-d_6) δ 1.43-1.57 (m, 4 H), 2.04 (t, 2 H, J = 7.1 Hz), 3.23 (app. q, 2 H, J = 6.4 Hz), 3.69 (s, 3 H), 3.81 (s, 6 H), 4.12 (s, 2 H), 7.16 (s, 2 H), 8.36 (t, 1 H, J = 5.7 Hz), 8.90 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 22.99, 29.05, 33.30, 39.19, 56.15, 60.19, 104.92, 129.98, 140.00, 152.67, 165.56, 171.60. Anal. ($C_{15}H_{23}N_3O_5 \cdot 0.5\ H_2O$) C, H, N.

N-(6-Hydrazino-6-oxohexyl)-3,4,5-trimethoxybenzamide (13f). Ethyl 6-((3,4,5-trimethoxybenzoyl)amino)hexanoate (**11f**) (1.77 g, 5.0 mmol) was reacted as described above (1.36 g, 80 %, white crystals).
Mp. 102-105 °C; **^{1}H NMR** (DMSO-d_6) δ 1.26 (app. quint, 2 H, J = 7.6 Hz), 1.51 (app. sext, 4 H, J = 7.1 Hz), 2.01 (t, 2 H, J = 7.4 Hz), 3.22 (app. q, 2 H, J = 6.6 Hz), 3.69 (s, 3 H), 3.81 (s, 6 H), 4.11 (s, 2 H), 7.16 (s, 2 H), 8.43 (t, 1 H, J = 5.7 Hz), 8.88 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 25.15, 26.35, 29.13, 33.52, 39.34, 56.15, 60.18, 104.92, 130.02, 139.98, 152.66, 165.55, 171.67. Anal. ($C_{16}H_{25}N_3O_5$) C, H, N.

N-(7-Hydrazino-7-oxoheptyl)-3,4,5-trimethoxybenzamide (13g). Ethyl 7-((3,4,5-trimethoxybenzoyl)amino)heptanoate (**11g**) (1.84 g, 5.0 mmol) was reacted as described above (1.16 g, 66 %, white crystals).
Mp. 130-133 °C; **^{1}H NMR** (DMSO-d_6) δ 1.21-1.33 (m, 4 H), 1.49 (app. sext, 4 H, J = 6.8 Hz), 1.99 (t, 2 H, J = 7.4 Hz), 3.22 (app. q, 2 H, J = 6.6 Hz), 3.69 (s, 3 H), 3.81 (s, 6 H), 4.12 (s, 2 H), 7.15 (s, 2 H), 8.43 (t, 1 H, J = 5.5 Hz), 8.87 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 25.30, 26.39, 28.55, 29.24, 33.52, 39.37, 56.15, 60.18, 104.91, 130.04, 139.97, 152.66, 165.55, 171.71. Anal. ($C_{17}H_{27}N_3O_5$) C, H: calcd 7.70, found 8.28, N: calcd 11.89, found 11.20.

N-(8-Hydrazino-8-oxooctyl)-3,4,5-trimethoxybenzamide (13h). Ethyl 8-((3,4,5-trimethoxybenzoyl)amino)octanoate (**11h**) (1.91 g, 5.0 mmol) was reacted as described above (1.19 g, 65 %, white crystals).
Mp. 132-135 °C; **^{1}H NMR** (DMSO-d_6) δ 1.18-1.32 (m, 6 H), 1.43-1.54 (m, 4 H), 1.99 (t, 2 H, J = 7.4 Hz), 3.23 (app. q, 2 H, J = 6.6 Hz), 3.69 (s, 3 H), 3.81 (s, 6 H), 4.11 (s, 2 H), 7.15 (s, 2 H), 8.34 (t, 1 H, J = 5.7 Hz), 8.86 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 25.30, 26.54, 28.64, 28.73, 29.32, 33.54, 39.40, 56.14, 60.18, 104.91, 130.04, 139.97, 152.66, 165.54, 171.72. Anal. ($C_{18}H_{29}N_3O_5$) C, H: calcd 7.95, found 8.63, N.

N-(9-Hydrazino-9-oxononyl)-3,4,5-trimethoxybenzamide (13i). Ethyl 9-((3,4,5-trimethoxybenzoyl)amino)nonanoate (**11i**) (1.98 g, 5.0 mmol) was reacted as described above (1.46 g, 77 %, white crystals).
Mp. 133-136 °C; **^{1}H NMR** (DMSO-d_6) δ 1.17-1.33 (m, 8H), 1.42-1.54 (m, 4 H), 1.98 (t, 2 H, J = 7.4 Hz), 3.22 (app. q, 2 H, J = 6.6 Hz), 3.68 (s, 3 H), 3.81 (s, 6 H), 4.12 (bs, 2 H), 7.15 (s, 2 H), 8.36 (t, 1 H, J = 5.5 Hz), 8.88 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 25.38, 26.67, 28.80, 28.87, 28.88, 29.38, 33.58, 39.46, 56.15, 60.22, 104.86, 130.06, 139.93, 152.69, 165.56, 171.76. Anal. ($C_{19}H_{31}N_3O_5$) C, H, N: calcd 11.02, found 10.39.

N-(2-Hydrazino-2-oxoethyl)-3-(3,4,5-trimethoxyphenyl)propanamide (14b). Ethyl ((3,4,5-trimethoxyphenyl)propanoyl)amino)acetate (**12b**) (1.63 g, 5.0 mmol) was reacted as described above (1.16 g, 75 %, white lints).
Mp. 167-170 °C; **^{1}H NMR** (DMSO-d_6) δ 2.42 (t, 2 H, J = 7.9 Hz), 2.74 (t, 2 H, J = 7.9 Hz), 3.61 (s, 3 H), 3.64 (d, 2 H, J = 5.7 Hz), 3.74 (s, 6 H), 4.17 (s, 2 H), 6.50 (s, 2 H), 8.03 (t, 1 H, J = 5.8 Hz), 8.97 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 31.40, 36.98, 40.88, 55.91, 60.07, 105.59, 135.84, 137.21, 152.84, 168.43, 171.88. Anal. ($C_{14}H_{21}N_3O_5$) C, H, N.

N-(3-Hydrazino-3-oxopropyl)-3-(3,4,5-trimethoxyphenyl)propanamide (14c). Ethyl ((3-(3,4,5-trimethoxyphenyl)propanoyl)amino)propanoate (**12c**) (1.70 g, 5.0 mmol) was reacted as described above (1.32 g, 81 %, white crystals).
Mp. 147-150 °C; **^{1}H NMR** (DMSO-d_6) δ 2.16 (t, 2 H, J = 7.3 Hz,), 2.33 (t, 2 H, J = 7.9 Hz), 2.72 (t, 2 H, J = 6.7 Hz), 3.23 (app. q, 2 H, J = 6.3 Hz), 3.60 (s, 3 H), 3.73 (s, 6 H), 4.12 (bs, 2 H), 6.48 (s, 2 H), 7.83 (t, 1 H, J = 5.5 Hz), 8.96 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 31.55, 33.81, 35.41, 37.18, 55.91, 60.07, 105.58, 135.85, 137.19, 152.83, 169.84, 171.50. Anal. ($C_{15}H_{23}N_3O_5$) C, H, N.

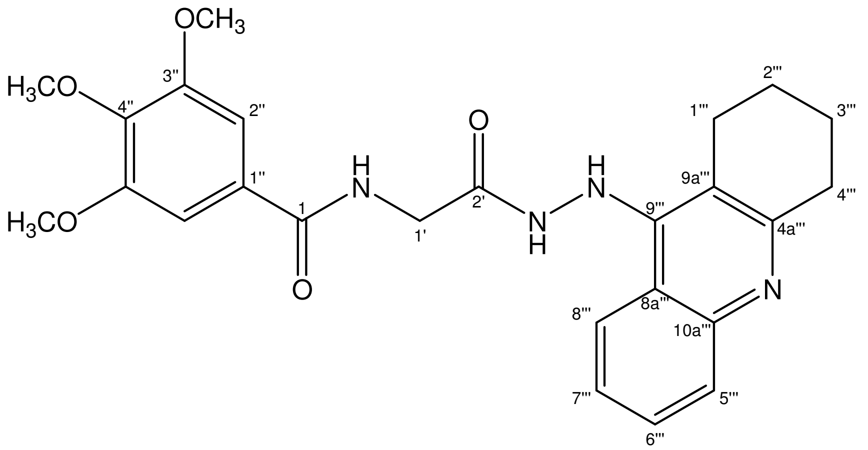
N-(4-Hydrazino-4-oxobutyl)-3-(3,4,5-trimethoxyphenyl)propanamide (14d). Ethyl ((4-(3,4,5-trimethoxyphenyl)propanoyl)amino)butanoate (**12d**) (1.77 g, 5.0 mmol) was reacted as described above (0.87 g, 51 %, white crystals).
Mp. 137-140 °C; **^{1}H NMR** (DMSO-d_6) δ 1.58 (app. quint, 2 H, J = 7.3 Hz), 1.98 (t, 2 H, J = 7.6 Hz), 2.34 (app. dd, 2 H, J = 7.9 8.8 Hz), 2.73 (t, 2 H, J = 7.9 Hz), 3.01 (app. q, 2 H, J = 6.6 Hz), 3.60 (s, 3 H), 3.73 (s, 6 H), 4.13 (s, 2 H), 6.48 (s, 2 H), 7.79 (t, 1 H, J = 5.5 Hz), 8.88 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 25.61, 31.12, 31.62, 37.26, 38.31, 55.90, 60.07, 105.59, 135.85, 137.21, 152.82, 171.36, 171.41. Anal. ($C_{16}H_{25}N_3O_5$) C, H, N.

N-(5-Hydrazino-5-oxopentyl)-3-(3,4,5-trimethoxyphenyl)propanamide (14e). Ethyl ((5-(3,4,5-trimethoxyphenyl)propanoyl)amino)pentanoate (**12e**) (1.84 g, 5.0 mmol) was reacted as described above (1.09 g, 62 %, white crystals).
Mp. 123-126 °C; **^{1}H NMR** (DMSO-d_6) δ 1.33 (app. quint, 2 H, J = 7.3 Hz), 1.45 (app. quint, 2 H, J = 7.5 Hz), 1.98 (t, 2 H, J = 7.3 Hz), 2.33 (t, 2 H, J = 7.7 Hz), 2.73 (t, 2 H, J = 7.9 Hz), 3.01 (app. q, 2 H, J = 6.5 Hz), 3.60 (s, 3 H), 3.73 (s, 6 H), 4.11 (s, 2 H), 6.48 (s, 2 H), 7.75 (t, 1 H, J = 5.5 Hz), 8.87 (s, 1 H); **^{13}C NMR** (DMSO-d_6) δ 22.82, 28.96, 31.63, 33.19, 37.25, 38.33, 55.90, 60.07, 105.95, 135.84, 137.23, 152.81, 171.28, 171.54. Anal. ($C_{17}H_{27}N_3O_5$) C, H, N.

N-(6-Hydrazino-6-oxohexyl)-3-(3,4,5-trimethoxyphenyl)propanamide (14f). Ethyl ((6-(3,4,5-trimethoxyphenyl)propanoyl)amino)hexanoate (**12f**) (1.91 g, 5.0 mmol) was reacted as described above (1.48 g, 81 %, white crystals).
Mp. 99-102 °C; **^{1}H NMR** (DMSO-d_6) δ 1.18 (app. quint, 2 H, J = 7.8 Hz), 1.34 (app. quint, 2 H, J = 7.3 Hz), 1.45 (app. quint, 2 H, J = 7.6 Hz), 1.97 (t, 2 H, J = 7.4 Hz), 2.33 (t, 2 H, J =

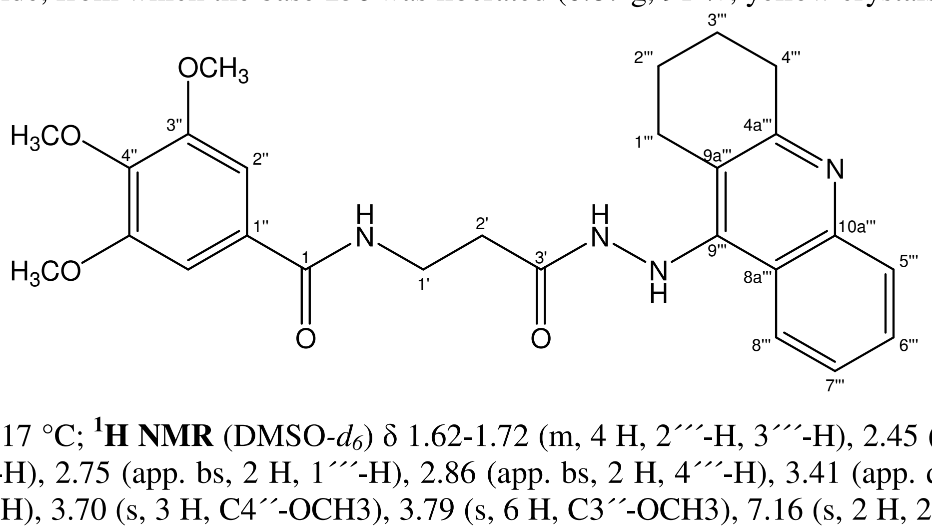
7.7 Hz), 2.73 (t, 2 H, J = 7.7 Hz), 3.00 (app. q, 2 H, J = 6.6 Hz), 3.60 (s, 3 H), 3.73 (s, 6 H), 4.11 (s, 2 H), 6.48 (s, 2 H), 7.73 (t, 1 H, J = 5.5 Hz), 8.86 (s, 1 H); ^{13}**C NMR** (DMSO-d_6) δ 25.07, 26.22, 29.08, 31.63, 33.48, 37.24, 38.45, 55.90, 60.07, 105.60, 135.83, 137.22, 152.80, 171.26, 171.65. Anal. ($C_{18}H_{29}N_3O_5$) C, H, N.

3,4,5-Trimethoxy-N-(2-oxo-2-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)ethyl)-benzamide (15b). General procedure for the final compounds 15b-f and 16b-f. 9-Chloro-1,2,3,4-tetrahydroacridine (**8**) (0.44 g, 2.0 mmol) and N-(2-hydrazino-2-oxoethyl)-3,4,5-trimethoxybenzamide **13b** (0.57 g, 2.0 mmol), dissolved in absolute ethanol (20 ml) were heated at 140 °C for 24 hours in a sealed tube. Cooling to –20 °C yielded the hydrochloride as a yellow precipitate that was collected by suction filtration and dissolved in ethanol (5 ml) and water (20 ml). Adding of 1M sodium hydroxide solution (2 ml) liberated the base as an yellow precipitate. Compound **15b** was filtered off. (0.73 g, 79 %).



Mp. 196°C. Anal. ($C_{25}H_{28}N_4O_5$ • 2 H_2O) C, H, N.

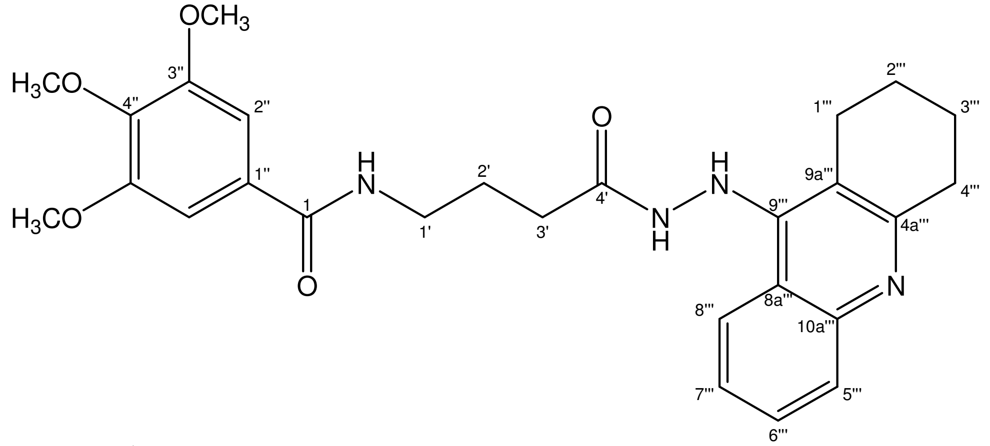
3,4,5-Trimethoxy-N-(3-oxo-3-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)propyl)-benzamide (15c). N-(3-Hydrazino-3-oxopropyl)-3,4,5-trimethoxybenzamide (**13c**) (0.59 g, 2.0 mmol) was reacted as described above. Cooling to room temperature yielded the hydrochloride, from which the base **15c** was liberated (0.87 g, 91 %, yellow crystals).



Mp. 214-217 °C; ^{1}**H NMR** (DMSO-d_6) δ 1.62-1.72 (m, 4 H, 2´´´-H, 3´´´-H), 2.45 (t, 2 H, J = 7.0 Hz, 2´-H), 2.75 (app. bs, 2 H, 1´´´-H), 2.86 (app. bs, 2 H, 4´´´-H), 3.41 (app. q, 2 H, J = 6.4 Hz, 1´-H), 3.70 (s, 3 H, C4´´-OCH3), 3.79 (s, 6 H, C3´´-OCH3), 7.16 (s, 2 H, 2´´-H), 7.23 (ddd, 1 H, J = 1.0, 7.6, 7.7 Hz, 7´´´-H), 7.47 (ddd, 1 H, J = 1.0, 7.4, 7.6 Hz, 6´´´-H), 7.69 (app. d, 1 H, J = 8.2 Hz, 8´´´-H), 7.75 (s, 1 H, CONHNH), 8.31 (app. s, 1 H, 5´´´-H), 8.49 (t, 1 H, J = 5.5 Hz, NHCH$_2$), 10.16 (s, 1 H, CONHNH); ^{13}**C NMR** (DMSO-d_6) δ 22.36 (C2´´´), 22.70 (C3´´´), 25.02 (C1´´´), 33.22 (C2´), 33.68 (C4´´´), 36.02 (C1´), 56.14 (C3´´-OCH3), 60.20 (C4´´-OCH3), 104.98 (C2´´), 115.66 (C9a´´´), 119.04 (C8a´´´), 123.00 (C5´´´), 123.51

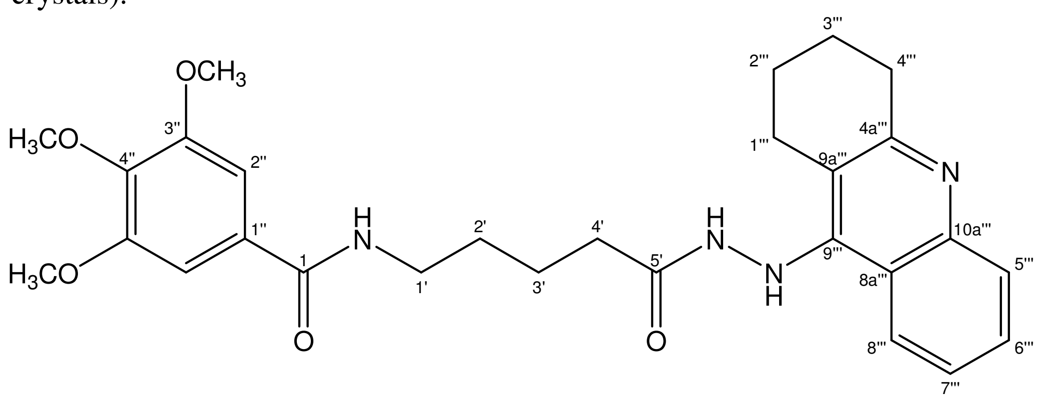
(C7´´´), 127.98 (C6´´´), 128.29 (C8´´´), 129.69 (1´´), 140.12 (C4´´), 146.66 (C10a´´´), 148.59 (C9´´´), 152.69 (C3´´), 158.21 (C4a´´´), 165.77 (C1), 170.48 (C3´). Anal. ($C_{26}H_{30}N_4O_5$ • 1 H_2O) C, H, N.

3,4,5-Trimethoxy-N-(4-oxo-4-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)butyl)-benzamide (15d). N-(4-Hydrazino-4-oxobutyl)-3,4,5-trimethoxybenzamide (**13d**) (0.62 g, 2.0 mmol) was reacted as described above. The hydrochloride was recrystallized from nitromethane, and the base **15d** was liberated (0.60 g, 61 %, yellow crystals).



Mp. 142-145 °C; **^{1}H NMR** (DMSO-*d*$_6$) δ 1.71 (app. quint, 2 H, *J* = 7.3 Hz, 2´-H), 1.75-1.85 (m, 4 H, 2´´´-H, 3´´´-H), 2.17 (t, 2 H, *J* = 7.4 Hz, 3´-H), 2.81 (app. bs, 2 H, 1´´´-H), 2.90 (app. bs, 2 H, 4´´´-H), 3.22 (app. q, 2 H, *J* = 6.5 Hz, 1´-H), 3.69 (s, 3 H, C4´´-OCH3), 3.79 (s, 6 H, C3´´-OCH3), 7.15 (s, 2 H, 2´´-H), 7.31 (ddd, 1 H, *J* = 1.0, 7.6, 7.7 Hz, 7´´´-H), 7.51 (ddd, 1 H, *J* = 1.3, 7.0, 8.3 Hz, 6´´´-H), 7.67 (s, 1 H, CONHNH), 7.70 (app. d, 1 H, *J* = 8.5 Hz, 8´´´-H), 8.31 (app. d, 1 H, *J* = 7.3 Hz, 5´´´-H), 8.38 (app. bs, 1 H, NHCH$_2$), 10.09 (s, 1 H, CONHNH); **^{13}C NMR** (DMSO-*d*$_6$) δ 22.49 (C2´´´), 22.70 (C3´´´), 24.89 (C1´´´), 25.19 (C2´), 30.81 (C3´), 33.73 (C4´´´), 39.14 (C1´), 56.13 (C3´´-OCH3), 60.19 (C4´´-OCH3), 104.92 (C2´´), 115.59 (C9a´´´), 119.10 (C8a´´´), 123.09 (C5´´´), 123.54 (C7´´´), 127.99 (C6´´´), 128.43 (C8´´´), 129.86 (C1´´), 140.04 (C4´´), 146.75 (C10a´´´), 148.71 (C9´´´), 152.67 (C3´´), 158.18 (C4a´´´), 165.64 (C1), 171.86 (C4´). Anal. ($C_{27}H_{32}N_4O_5$ • 1 H_2O) C, H, N.

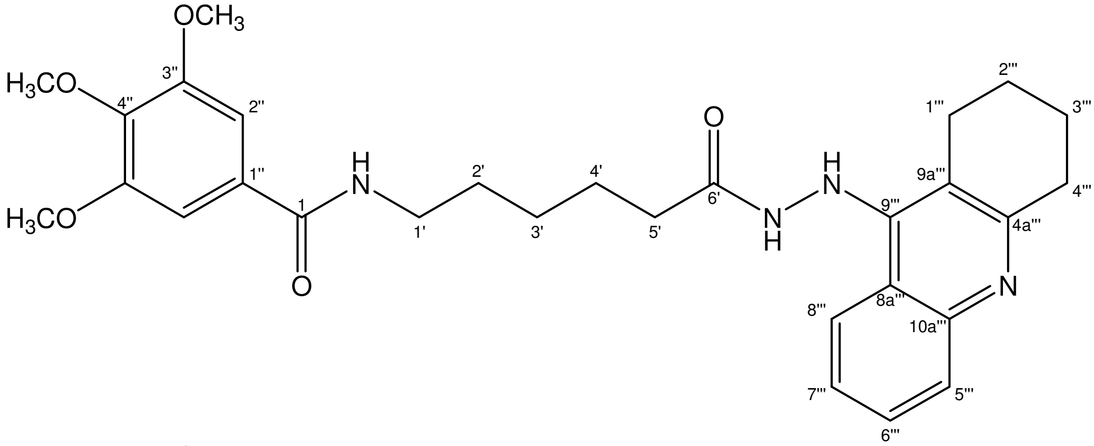
3,4,5-Trimethoxy-N-(5-oxo-5-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)pentyl)-benzamide (15e). N-(5-Hydrazino-5-oxopentyl)-3,4,5-trimethoxybenzamide (**13e**) (0.65 g, 2.0 mmol) was reacted as described above. Cooling to -20°C yields the hydrochloride as an oily layer that is separated by decantation. The base **15e** was then liberated (0.35 g, 34 %, yellow crystals).



Mp. 191-194 °C; **^{1}H NMR** (DMSO-*d*$_6$) δ 1.42-1.55 (m, 4 H, 2´-H, 3´-H), 1.72-1.83 (m, 4 H, 2´´´-H,3´´´-H), 2.13 (t, 2 H, *J* = 6.9 Hz, 4´-H), 2.81 (app. bs, 2 H, 1´´´-H), 2.89 (app. bs, 2 H, 4´´´-H), 3.21 (app. q, 2 H, *J* = 6.1 Hz, 1´-H), 3.69 (s, 3 H, C4´´-OCH3), 3.80 (s, 6 H, C3´´-

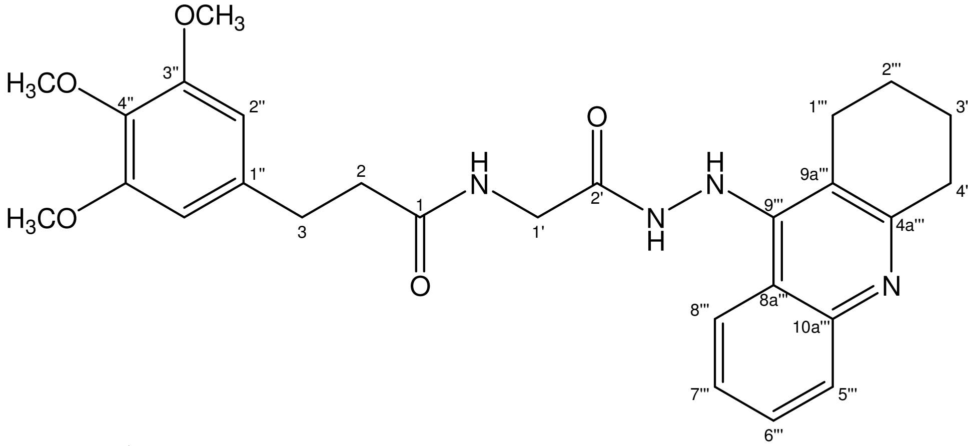
OCH3), 7.15 (s, 2 H, 2´´-H), 7.29 (ddd, 1 H, *J* = 1.0, 7.7, 7.7 Hz, 7´´´-H), 7.48 (ddd, 1 H, *J* = 1.3, 7.6, 7.6 Hz, 6´´´-H), 7.67 (s, 1 H, CONHNH), 7.70 (app. d, 1 H, *J* = 8.5 Hz, 8´´´-H), 8.31 (app. d, 1 H, *J* = 9.8 Hz, 5´´´-H), 8.33 (t, 1 H, *J* = 5.8 Hz, NHCH$_2$), 10.04 (s, 1 H, CONHNH); ^{13}**C NMR** (DMSO-d_6) δ 22.51 (C2´´´), 22.63 (C3´´´), 22.71 (C3´), 24.91 (C1´´´), 29.00 (C2´), 32.85 (C4´), 33.77 (C4´´´), 39.06 (C1´), 56.16 (C3´´-OCH3),60.21 (C4´´-OCH3), 104.92 (C2´´), 115.58 (C9a´´´), 119.10 (C8a´´´), 123.14 (C5´´´), 123.49 (C7´´´), 127.95 (C6´´´), 128.40 (C8´´´, 129.96 (C1´´), 140.03 (C4´´), 146.78 (C10a´´´), 148.79 (C9´´´), 152.68 (C3´´), 158.17 (C4a´´´), 165.54 (C1), 171.98 (C5´). Anal. ($C_{28}H_{34}N_4O_5$) C, H, N.

3,4,5-Trimethoxy-N-(6-oxo-6-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)hexyl)-benzamide (15f). N-(6-Hydrazino-6-oxohexyl)-3,4,5-trimethoxybenzamide (**13f**) (0.68 g, 2.0 mmol) was reacted as described above. The hydrochloride was recrystallized from nitromethane, and the base **15f** was liberated (0.52 g, 50 %, yellow crystals).



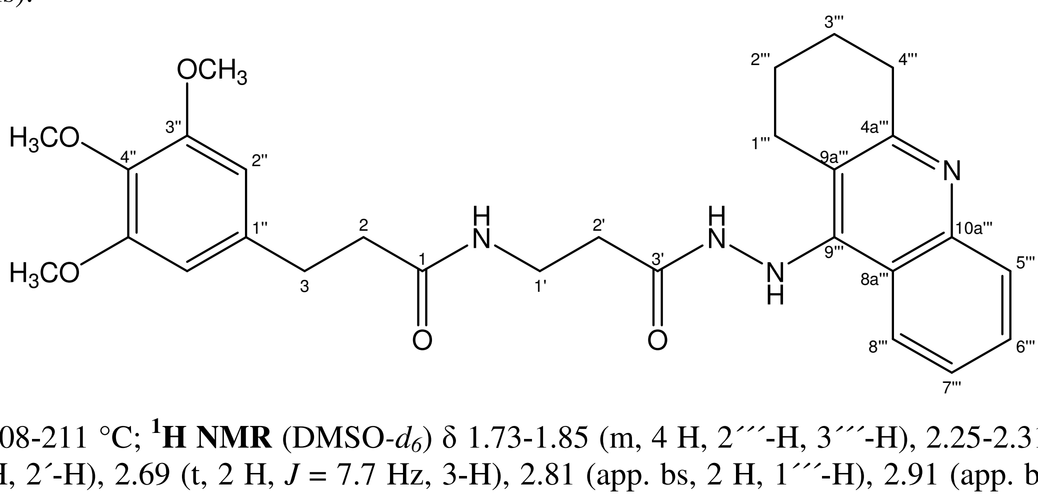
Mp. 172-175 °C; ^{1}**H NMR** (DMSO-d_6) δ 1.23 (app. quint, 2 H, *J* = 7.6 Hz, 3´-H), 1.48 (app. sext, 4 H, *J* = 7.5 Hz, 2´-H, 4´-H), 1.74-1.84 (m, 4 H, 2´´´-H, 3´´´-H), 2.10 (t, *J* = 7.3 Hz, 5´-H), 2.81 (app. bs, 2 H, 1´´´-H), 2.90 (t, *J* = 5.8 Hz, 4´´´-H), 3.18 (app. q, 2 H, *J* = 6.6 Hz, 1´-H), 3.69 (s, 3 H, C4´´-OCH3), 3.80 (s, 6 H, C3´´-OCH3), 7.15 (s, 2 H, 2´´-H), 7.31 (ddd, 1 H, *J* = 1.3, 7.1, 8.4 Hz, 7´´´-H), 7.51 (ddd, 1 H, *J* = 1.3 6.6 8.3 Hz, 6´´´-H), 7.66 (s, 1 H, CONHNH), 7.70 (app. d, 1 H, *J* = 8.2 Hz, 8´´´-H), 8.31 (app. d, 1 H, *J* = 5.7 Hz, 5´´´-H), 8.32 (t, 1 H, *J* = 5.5 Hz, NHCH$_2$), 10.03 (s, 1 H, CONHNH); ^{13}**C NMR** (DMSO-d_6) δ 22.50 (C2´´´), 22.69 (C3´´´), 24.83 (C1´´´,4´), 26.28 (C3´), 29.09 (C2´), 33.08 (C5´), 33.72 (C4´´´), 39.30 (C1´), 56.14 (C3´´-OCH3), 60.18 (C4´´-OCH3), 104.91 (C2´´), 115.51 (C9a´´´), 119.06 (C8a´´´), 123.20 (C5´´´), 123.46 (C7´´´), 127.98 (C6´´´), 128.36 (C8´´´), 130.00 (C1´´), 139.99 (C4´´), 146.75 (C10a´´´), 148.81 (C9´´´), 152.66 (C3´´), 158.08 (C4a´´´), 165.54 (C1), 171.99 (C6´). Anal. ($C_{29}H_{36}N_4O_5$) C, H, N.

3-(3,4,5-Trimethoxyphenyl)-N-(2-oxo-2-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)-ethyl)propanamide (16b). N-(2-hydrazino-2-oxoethyl)-3-(3,4,5-trimethoxyphenyl)propan-amide (**14b**) (0.62 g, 2.0 mmol) was reacted as described above. The hydrochloride was recrystallized from nitromethane, and the base **16b** was liberated (0.31 g, 31 %, yellow crystals).



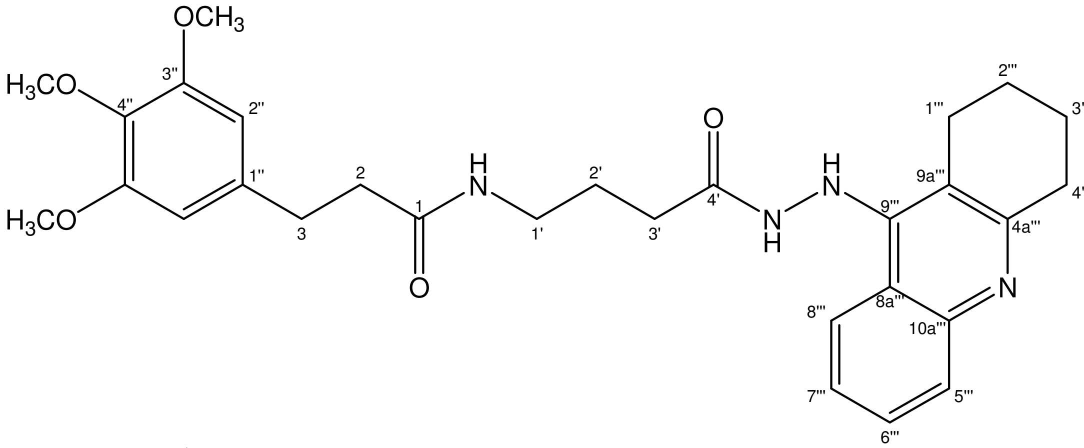
Mp. 225-228 °C; **^{1}H NMR** (DMSO-d_6) δ 1.71-1.87 (m, 4 H, 2´´´-H, 3´´´-H), 2.40 (t, J = 7.6 Hz, 2-H), 2.73 (t, J = 7.6 Hz, 3-H), 2.83 (app. bs, 2 H, 1´´´-H), 2.91 (app. bs, 2 H, 4´´´-H), 3.59 (s, 3 H, C4´´-OCH3), 3.70 (s, 6 H, C3´´-OCH3), 3.73 (d, J = 5.7 Hz, 1´-H), 6.47 (s, 2 H, 2´´-H), 7.32 (app. t, 1 H, J = 7.3 Hz, 7´´´-H), 7.52 (app. t, 1 H, J = 7.3 Hz, 6´´´-H), 7.71 (app. d, 1 H, J = 11.1 Hz, 8´´´-H), 7.73 (s, 1 H, CONHNH), 8.04 (bs, 1 H, NHCH$_2$), 8.30 (app. d, 1 H, J = 7.9 Hz, 5´´´-H), 10.13 (s, 1 H, CONHNH); **^{13}C NMR** (DMSO-d_6) δ 22.51 (C2´´´), 22.75 (C3´´´), 24.90 (C1´´´), 31.42 (C3), 33.77 (C4´´´), 36.96 (C2), 40.20 (C1´), 55.87 (C3´´-OCH3), 60.04 (C4´´-OCH3), 105.57 (C2´´), 116.05 (C9a´´´), 119.24 (C8a´´´), 123.05 (C5´´´), 123.69 (C7´´´), 127.98 (C6´´´), 128.37 (C8´´´), 135.82 (C1´´), 137.16 (C4´´), 146.72 (C10a´´´), 148.55 (C9´´´), 152.82 (C3´´), 158.24 (C4a´´), 169.02 (C1), 171.91 (C2´); Anal. ($C_{27}H_{32}N_4O_5$ • 0.5 H_2O) C, H, N.

3-(3,4,5-Trimethoxyphenyl)-N-(3-oxo-3-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)-propyl)propanamide (16c). N-(3-hydrazino-3-oxopropyl)-3-(3,4,5-trimethoxyphenyl)-propanamide (**14c**) (0.65 g, 2.0 mmol) was reacted as described above. The hydrochloride was recrystallized from nitromethane, and the base **16c** was liberated (0.74 g, 73 %, yellow crystals).



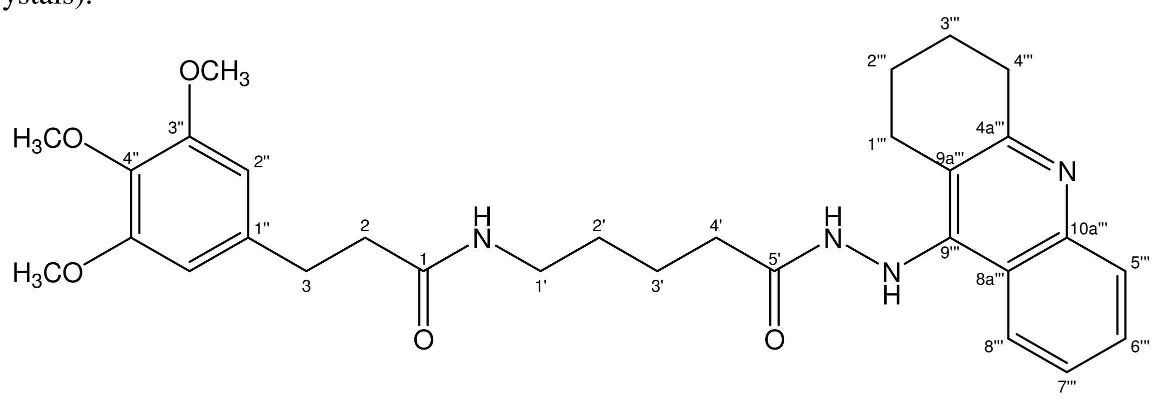
Mp. 208-211 °C; **^{1}H NMR** (DMSO-d_6) δ 1.73-1.85 (m, 4 H, 2´´´-H, 3´´´-H), 2.25-2.31 (m, 4 H, 2-H, 2´-H), 2.69 (t, 2 H, J = 7.7 Hz, 3-H), 2.81 (app. bs, 2 H, 1´´´-H), 2.91 (app. bs, 2 H, 4´´´-H), 3.18 (q, 2 H, J = 6.4 Hz, 1´-H), 3.60 (s, 3 H, C4´´-OCH3), 3.73 (s, 6 H, C3´´-OCH3), 6.46 (s, 2 H, 2´´-H), 7.32 (app. t, 1 H, J = 7.4 Hz, 7´´´-H), 7.50 (app. t, 1 H, J = 7.4 Hz, 6´´´-H), 7.67 (s, 1 H, CONHNH), 7.72 (app. d, 1 H, J = 8.2 Hz, 8´´´-H), 7.83 (t, 1 H, J = 5.5 Hz, NHCH$_2$), 8.29 (app. d, 1 H, J = 8.6 Hz, 5´´´-H), 10.09 (s, 1 H, CONHNH); **^{13}C NMR** (DMSO-d_6) δ 22.49 (C2´´´), 22.74 (C3´´´), 24.94 (C1´´´), 31.53 (C3), 33.26 (C2), 33.77 (C4´´´), 35.02 (C2´), 37.15 (C1´), 55.90 (C3´´-OCH3), 60.07 (C4´´-OCH3), 105.57 (C2´´), 115.70 (C9a´´´), 119.11 (C8a´´´), 123.00 (C5´´´), 123.58 (C7´´´), 127.96 (C6´´´), 128.43 (C8´´´, 135.85 (C1´´), 137.15 (C4´´), 146.77 (C10a´´´), 148.62 (C9´´´), 152.81 (C3´´), 158.21 (C4a´´´), 170.39 (C1), 171.54 (C3´). Anal. ($C_{28}H_{34}N_4O_5$ • 1.5 H_2O) C, H, N.

3-(3,4,5-Trimethoxyphenyl)-N-(4-oxo-4-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)-butyl)propanamide (16d). N-(4-hydrazino-4-oxobutyl)-3-(3,4,5-trimethoxyphenyl)propanamide (**14d**) (0.68 g, 2.0 mmol) was reacted as described above. The hydrochloride was recrystallized from nitromethane, and the base **16d** was liberated (0.62 g, 60 %, yellow crystals).



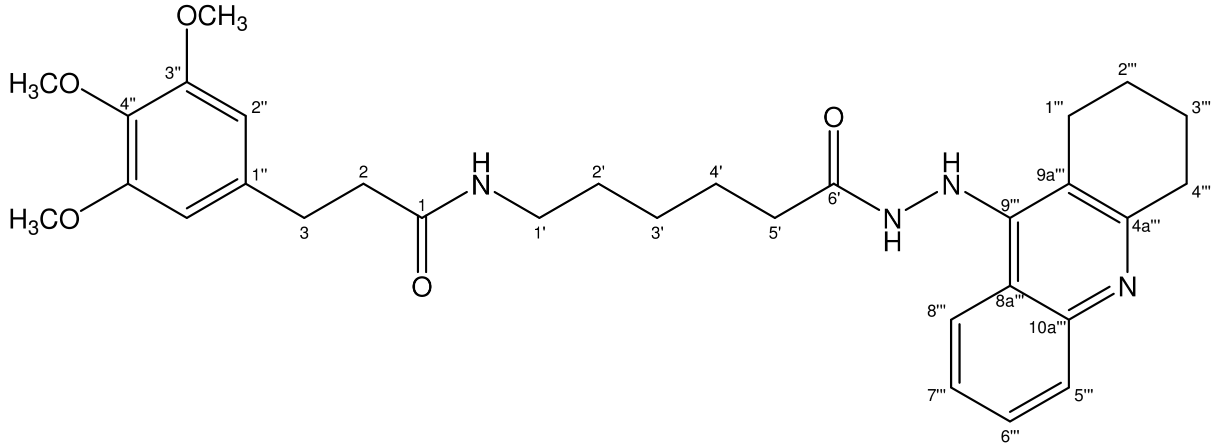
Mp. 138-141 °C; **^{1}H NMR** (DMSO-*d₆*) δ 1.56 (app. quint, 2 H, *J* = 7.3 Hz, 2´-H), 1.75-1.85 (m, 4 H, 2´´´-H, 3´´´-H), 2.08 (t, 2 H, *J* = 7.6 Hz, 3´-H), 2.33 (app. dd, 2 H, *J* = 8.2, 9.1 Hz, 2-H), 2.73 (t, 2 H, *J* = 7.9 Hz, 3-H), 2.81 (app. bs, 2 H, 1´´´-H), 2.90 (app. bs, 2 H, 4´´´-H), 3.00 (app. q, 2 H, *J* = 7.9 Hz, 1´-H), 3.59 (s, 3 H, C4´´-OCH3), 3.71 (s, 6 H, C3´´-OCH3), 6.47 (s, 2 H, 2´´-H), 7.31 (ddd, 1 H, *J* = 1.0, 7.7, 7.7 Hz, 7´´´-H), 7.51 (ddd, 1 H, *J* = 1.3, 6.9, 8.3 Hz, 6´´´-H), 7.66 (s, 1 H, CONHNH), 7.71 (app. d, 1 H, *J* = 8.6 Hz, 8´´´-H), 7.77 (t, 1 H, *J* = 5.5 Hz, NHCH₂), 8.30 (app. d, 1 H, *J* = 8.2 Hz, 5´´´-H), 10.04 (s, 1 H, CONHNH); **^{13}C NMR** (DMSO-*d₆*) δ 22.50 (C2´´´), 22.70 (C3´´´), 24.87 (C1´´´), 25.28 (C2´), 30.73 (C3´), 31.61 (C3), 33.76 (C4´´´), 37.23 (C2), 38.29 (C1´), 55.89 (C3´´-OCH3), 60.06 (C4´´-OCH3), 105.58 (C2´´), 115.61 (C9a´´´), 119.11 (C8a´´´), 123.10 (C5´´´), 123.53 (C7´´´), 127.97 (C6´´´), 128.43 (C8´´´), 135.85 (C1´´), 137.18 (C4´´), 146.79 (C10a´´´), 148.72 (C9´´´), 152.81 (C3´´), 158.18 (C4a´´´), 171.42 (C1), 171.74 (C4´). Anal. ($C_{29}H_{36}N_4O_5$ • 0.5 H_2O) C, H, N.

3-(3,4,5-Trimethoxyphenyl)-N-(5-oxo-5-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)-pentyl)propanamide (16e). N-(5-hydrazino-5-oxobutyl)-3-(3,4,5-trimethoxyphenyl)propanamide (**14e**) (0.71 g, 2.0 mmol) was reacted as described above. The hydrochloride was recrystallized from nitromethane, and the base **16e** was liberated (0.61 g, 53 %, yellow crystals).



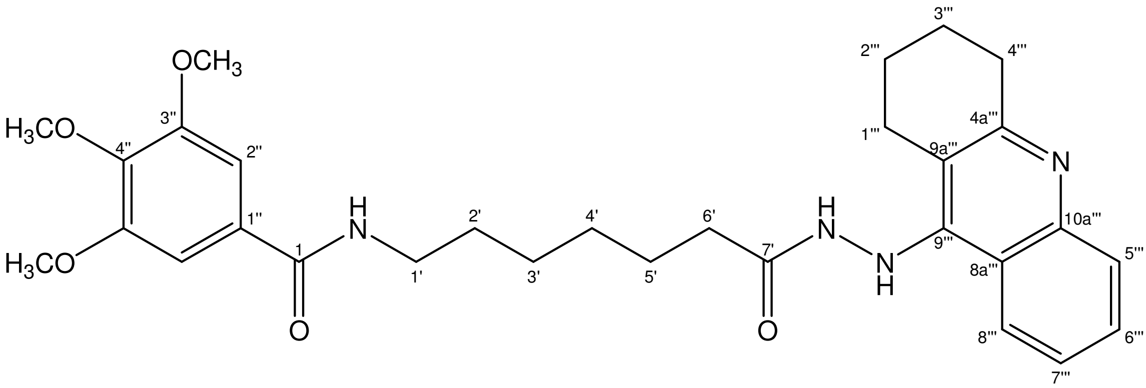
Mp. 85-88 °C; **^{1}H NMR** (DMSO-*d₆*) δ 1.29 (app. quint, 2 H, *J* = 7.1 Hz, 2´-H), 1.42 (app. quint, 2 H, *J* = 7.6 Hz, 3´-H), 1.75-1.84 (m, 4 H, 2´´´-H, 3´´´-H), 2.08 (t, 2 H, *J* = 7.3 Hz, 4´-H), 2.32 (t, 2 H, *J* = 7.9 Hz, 2-H), 2.72 (t, 2 H, *J* = 7.9 Hz, 3-H), 2.81 (app. bs, 2 H, 1´´´-H), 2.90 (app. bs, 2 H, 4´´´-H), 2.98 (app. q, 2 H, *J* = 6.4 Hz, 1´-H), 3.60 (s, 3 H, C4´´-OCH3), 3.72 (s, 6 H, C3´´-OCH3), 6.47 (s, 2 H, 2´´-H), 7.31 (ddd, 1 H, *J* = 1.0, 6.9, 8.4 Hz, 7´´´-H), 7.50 (ddd, 1 H, *J* = 1.3, 7.0, 8.2 Hz, 6´´´-H), 7.65 (s, 1 H, CONHNH), 7.70 (app. d, 1 H, *J* = 8.5 Hz, 8´´´-H), 7.73 (t, 1 H, *J* = 5.9 Hz, NHCH2), 8.31 (app. d, 1 H, *J* = 8.6 Hz, 5´´´-H), 10.03 (s, 1 H, CONHNH); **^{13}C NMR** (DMSO-*d6*) δ 22.40 (C2´´´), 22.52 (C3´´´), 22.71 (C3´), 24.86 (C1´´´), 28.84 (C2´), 31.65 (C3), 32.67 (C4´), 33.77 (C4´´´), 37.25 (C2), 38.18 (C1´), 55.90 (C3´´-OCH3), 60.06 (C4´´-OCH3), 105.59 (C2´´), 115.59 (C9a´´´), 119.11 (C8a´´´), 123.15 (C5´´´), 123.48 (C7´´´), 127.94 (C6´´´), 128.41 (C8´´´), 135.84 (C1´´), 137.21 (C4´´), 146.80 (C10a´´´), 148.76 (C9´´´), 152.81 (C3´´), 158.16 (C4a´´´), 171.28 (C1), 171.92 (C5´). Anal. ($C_{30}H_{38}N_4O_5 \cdot 2\ H_2O$) C, H, N.

3-(3,4,5-Trimethoxyphenyl)-N-(6-oxo-6-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)-hexyl)propanamide (16f). N-(6-hydrazino-6-oxohexyl)-3-(3,4,5-trimethoxyphenyl)propanamide (**14f**) (0.73 g, 2.0 mmol) was reacted as described above. The hydrochloride is recrystallized from nitromethane, and the base **16f** was liberated (0.65 g, 59 %, yellow crystals).



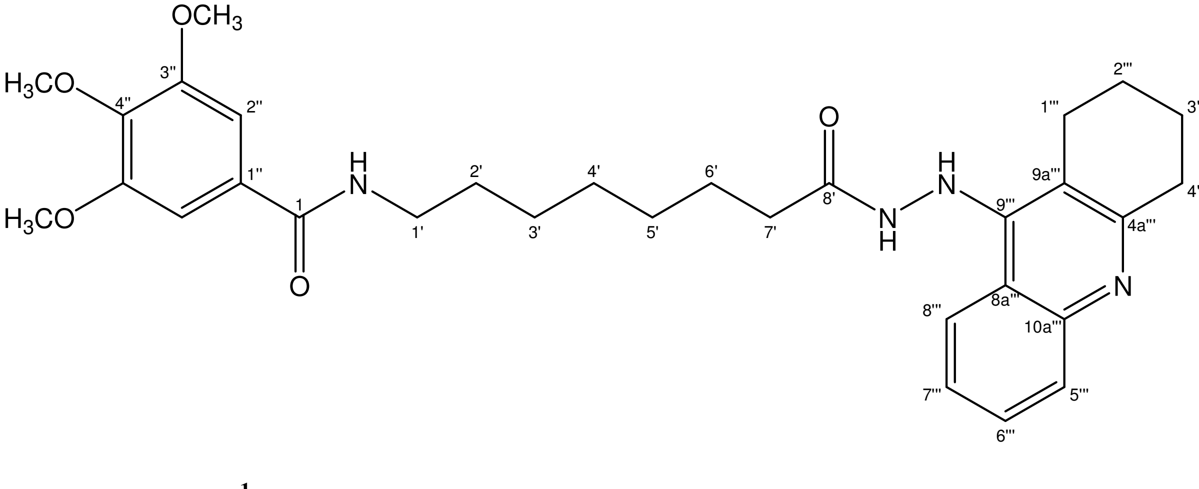
Mp. 107-110 °C; **^{1}H NMR** (DMSO-*d6*) δ 1.14 (app. sext, 2 H, *J* = 7.3 Hz, 3´-H), 1.30 (app. quint, 2 H, *J* = 7.3 Hz, 2´), 1.43 (app. quint, 2 H, *J* = 7.5 Hz, 4´-H), 1.74-1.84 (m, 4 H, 2´´´-H, 3´´´-H), 2.06 (t, 2 H, *J* = 7.4 Hz, 5´-H), 2.32 (t, 2 H, *J* = 7.7 Hz, 2-H), 2.73 (t, 2 H, *J* = 7.7 Hz, 3-H), 2.81 (app. bs, 2 H, 1´´´-H), 2.90 (t, 2 H, *J* = 5.8 Hz, 4´´´-H), 2.95 (app. q, 2 H, *J* = 6.6 Hz, 1´-H), 3.60 (s, 3 H, C4´´-OCH3), 3.72 (s, 6 H, C3´´-OCH3), 6.48 (s, 2 H, 2´´-H), 7.31 (ddd, 1 H, *J* = 1.0, 6.9, 8.4 Hz, 7´´´-H), 7.51 (ddd, 1 H, *J* = 1.3, 6.9, 8.3 Hz, 6´´´-H), 7.65 (s, 1 H, CONHNH), 7.70 (app. d, 1 H, *J* = 5.7 Hz, 8´´´-H), 7.71 (bs, 1 H, NHCH2), 8.31 (app. d, 1 H, *J* = 8.2 Hz, 5´´´-H), 10.02 (s, 1 H, CONHNH); **^{13}C NMR** (DMSO-*d6*) δ 22.53 (C2´´´), 22.72 (C3´´´), 24.76 (C4´), 24.86 (C1´´´), 26.14 (C3´), 29.06 (C2´), 31.63 (C3), 33.04 (C5´), 33.78 (C4´´´), 37.24 (C2), 38.46 (C1´), 55.91 (C3´´-OCH3), 60.08 (C4´´-OCH3), 105.62 (C2´´), 115.58 (C9a´´´), 119.10 (C8a´´´), 123.20 (C5´´´), 123.48 (C7´´´), 127.97 (C6´´´), 128.42 (C8´´´), 135.85 (C1´´), 137.23 (C4´´), 146.81 (C10a´´´), 148.81 (C9´´´), 152.82 (C3´´), 158.16 (C4a´´´), 171.26 (C1), 172.00 (C6´). Anal. ($C_{31}H_{40}N_4O_5 \cdot 0.5\ H_2O$) C, H, N.

3,4,5-Trimethoxy-N-(7-oxo-7-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)heptyl)-benzamide (15g). General procedure for the final compounds 15g-i. 9-Chloro-1,2,3,4-tetrahydroacridine (**8**) (0.44 g, 2.0 mmol) and N-(7-hydrazino-7-oxoheptyl)-3,4,5-trimethoxy-benzamide (**13g**) (0.71 g, 2.0 mmol), dissolved in absolute ethanol (20 ml) were reacted at 140 °C for 24 hours by means of a sealed tube. Cooling to room temperature and evaporation yielded a crude product that was taken up in ethanol (5 ml) and diluted with water (20 ml). Addition of 1M sodium hydroxide solution (2.5 ml) liberated the base as an oily layer. After decantation, the oily residue was suspended in ethyl acetate (25 ml) and shortly refluxed until the final product precipitated. Compound **15g** (0.67 g, 63 %) was obtained as a yellow powder.



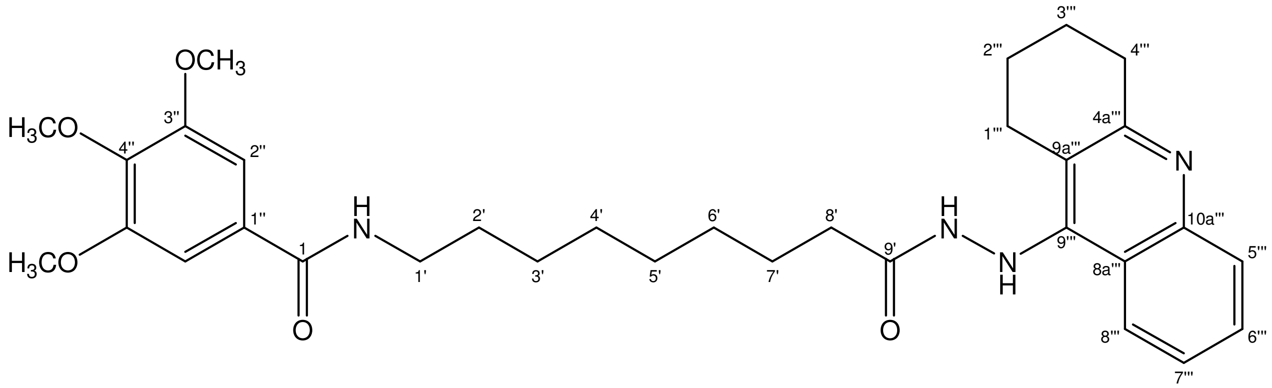
Mp. 190-193 °C; **^{1}H NMR** (DMSO-*d$_6$*) δ 1.16-1.29 (m, 4 H, 3´-H, 4´-H), 1.45 (app. sext, 4 H, *J* = 6.7 Hz, 2´-H, 5´-H), 1.73-1.85 (m, 4 H, 2´´´-H, 3´´´-H), 2.09 (t, *J* = 7.3 Hz, 6´-H), 2.81 (app. bs, 2 H, 1´´´-H), 2.90 (t, *J* = 6.0 Hz, 4´´´-H), 3.20 (app. q, 2 H, *J* = 6.6 Hz, 1´-H), 3.69 (s, 3 H, C4´´-OCH3), 3.81 (s, 6 H, C3´´-OCH3), 7.15 (s, 2 H, 2´´-H), 7.31 (ddd, 1 H, *J* = 1.3, 6.8, 8.3 Hz, 7´´´-H), 7.51 (ddd, 1 H, *J* = 1.3, 6.8, 8.3 Hz, 6´´´-H), 7.69 (s, 1 H, CONHNH), 7.70 (app. d, 1 H, *J* = 7.6 Hz, 8´´´-H), 8.32 (app. d, 1 H, *J* = 5.7 Hz, 5´´´-H), 8.33 (t, 1 H, *J* = 5.7 Hz, NHCH$_2$), 10.04 (s, 1 H, CONHNH); **^{13}C NMR** (DMSO-*d$_6$*) δ 22.47 (C2´´´), 22.67 (C3´´´), 24.81 (C1´´´), 25.01 (C5´), 26.39 (C3´), 28.49 (C4´), 29.23 (C2´), 33.09 (C6´), 33.60 (C1´´´), 39.36 (C1´), 56.14 (C3´´-OCH3), 60.18 (C4´´-OCH3), 104.91 (C2´´), 115.44 (C9a´´´), 118.99 (C8a´´´), 123.25 (C5´´´), 123.49 (C7´´´), 128.08 (C6´´´), 128.16 (C8´´´), 130.04 (C1´´), 139.98 (C4´´), 146.56 (C10a´´´), 148.94 (C9´´´), 152.66 (C3´´), 158.03 (C4a´´´), 165.56 (C1), 172.03 (C7´). Anal. ($C_{30}H_{38}N_4O_5$ • 0.5 H_2O) C, H, N.

3,4,5-Trimethoxy-N-(8-oxo-8-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)octyl)-benzamide (15h). N-(8-Hydrazino-8-oxooctyl)-3,4,5-trimethoxybenzamide (**13h**) (0.73 g, 2.0 mmol) was reacted as described above (0.83 g, 76 %, yellow powder).



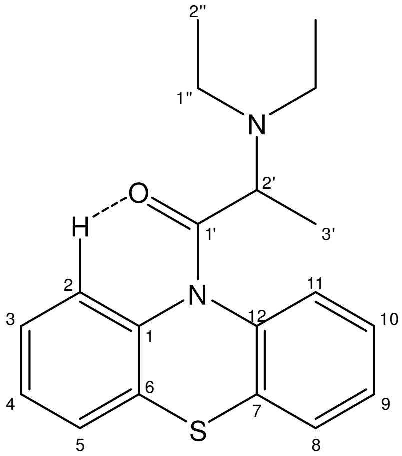
Mp. 184-187 °C; **^{1}H NMR** (DMSO-*d$_6$*) δ 1.12-1.27 (m, 6 H, 3´-H, 4´-H, 5´-H), 1.45 (app. sext, 4 H, *J* = 7.8 Hz, 2´-H, 6´-H), 1.74-1.84 (m, 4 H, 2´´´-H, 3´´´-H), 2.08 (t, *J* = 7.3 Hz, 7´-H), 2.81 (app. bs, 2 H, 1´´´-H), 2.90 (t, *J* = 6.0 Hz, 4´´´-H), 3.21 (app. q, 2 H, *J* = 6.7 Hz, 1´-H), 3.69 (s, 3 H, C4´´-OCH3), 3.81 (s, 6 H, C3´´-OCH3), 7.16 (s, 2 H, 2´´-H), 7.30 (ddd, 1 H, *J* = 1.3, 6.8, 8.4 Hz, 7´´´-H), 7.50 (ddd, 1 H, *J* = 1.0, 6.8, 8.4 Hz, 6´´´-H), 7.68 (s, 1 H, CONHNH), 7.69 (app. d, 1 H, *J* = 7.9 Hz, 8´´´-H), 8.31 (app. d, 1 H, *J* = 9.2 Hz, 5´´´-H), 8.33 (t, 1 H, *J* = 5.7 Hz, NHCH$_2$), 10.03 (s, 1 H, CONHNH); **^{13}C NMR** (DMSO-*d$_6$*) δ 22.49 (C2´´´), 22.68 (C3´´´), 24.81 (C1´´´), 25.00 (C6´), 26.52 (C3´), 28.64 (C4´,5´), 29.30 (C2´), 33.09 (C7´), 33.65 (C4´´´), 39.37 (C1´), 56.14 (C3´´OCH), 60.18 (C4´´OCH), 104.91 (C2´´), 115.47 (C9a´´´), 119.03 (C8a´´´), 123.24 (C5´´´), 123.45 (C7´´´), 128.01 (C6´´´), 128.23 (C8´´´), 130.03 (C1´´), 139.98 (C4´´), 146.64 (C10a´´´), 148.89 (C9´´´), 152.66 (C3´´), 157.98 (C4a´´´), 165.53 (C1), 172.04 (C8´). Anal. ($C_{31}H_{40}N_4O_5$) C, H, N.

3,4,5-Trimethoxy-N-(9-oxo-9-(2-(1,2,3,4-tetrahydroacridin-9-yl)hydrazino)nonyl)-benzamide (15i). N-(9-Hydrazino-9-oxononyl)-3,4,5-trimethoxybenzamide (**13i**) (0.76 g, 2.0 mmol) was reacted as described above (0.61 g, 54 %, yellow powder).



Mp. 162-165 °C; **^{1}H NMR** (DMSO-d_6) δ 1.09-1.33 (m, 8 H, 3´-H, 4´-H, 5´-H, 6´-H), 1.38-1.56 (m, 4 H, 2´-H, 7´-H), 1.73-1.88 (m, 4 H, 2´´´-H, 3´´´-H), 2.07 (t, 2 H, J = 7.1 Hz, 8´-H), 2.82 (bs, 2 H, 1´´´-H), 2.90 (bs, 2 H, 4´´´-H), 3.22 (app. q, 2 H, J = 6.2 Hz, 1´-H), 3.69 (s, 3 H, C4´´-OCH3), 3.81 (s, 6 H, C3´´-OCH3), 7.16 (s, 2 H, 2´´-H), 7.30 (app. t, 1 H, J = 7.3 Hz, 7´´´-H), 7.51 (app. t, 1 H, J = 7.4 Hz, 6´´´-H), 7.64 (s, 1 H, CONHNH), 7.70 (app. d, 1 H, J = 8.2 Hz, 8´´´-H), 8.31 (app. d, 1 H, J = 8.5 Hz, 5´´´-H), 8.34 (t, 1 H, J = 4.7 Hz, NHCH$_2$), 10.02 (s, 1 H, CONHNH); **^{13}C NMR** (DMSO-d_6) δ 22.54 (C2´´´), 22.71 (C3´´´), 24.84 (C1´´´), 25.02 (C7´), 26.61 (C3´), 28.65 (C4´), 28.82 (C–5´,6´), 29.34 (C2´), 33.06 (C8´), 33.78 (C4´´´), 39.42 (C1´), 56.15 (C3´´-OCH3), 60.18 (C4´´-OCH3), 104.91 (C2´´), 115.60 (C9a´´´), 119.12 (C8a´´´), 123.21 (C5´´´), 123.44 (C7´´´), 127.93 (C6´´´), 128.41 (C8´´´), 130.04 (C1´´), 139.98 (C4´´), 146.82 (C10a´´´), 148.83 (C9´´´), 152.66 (C3´´), 158.13 (C4a´´´), 165.54 (C1), 172.06 (C9´). Anal. ($C_{32}H_{42}N_4O_5$ • 0.5 H_2O) C: calcd 67.23, found 67.83, H, N.

10-[2-(Diethylamino)-1-oxopropyl]-10*H*-phenothiazine (AS-1397). A suspension of phenothiazine (20.0 g, 0.10 mol) in toluene (200 ml) was protected from moisture and heated until all phenothiazine was dissolved. While vigorously stirring, 2-bromopropanoyl bromide (16 ml, 0.15 mol) was added and the reaction mixture was slightly refluxed for three hours. Cooling to room temperature resulted in a precipitate, that was stirred over night and subsequently recovered by suction filtration. Cooling the filtrate to -20 °C produced a second fraction that was combined with the former precipitate to obtain 10-(2-bromopropanoyl)-10*H*-phenothiazine. Subsequently a mixture of 10-(2-bromopropanoyl)-10*H*-phenothiazine (21.7 g, 65.0 mmol), N,N-diethylamine (17.4 ml, 0.17 mol) and toluene (100 ml) was refluxed for 5 hours. The precipitated N,N-diethylamine hydrobromide was filtered off and the solution was extracted two times with 1 N hydrochloric acid (100 ml). The pH of the aqueous layer was adjusted to 10 using a concentrated solution of potassium hydroxide to precipitate 10-(2-N,N-diethylaminopropanoyl)-10H-phenothiazine (19.0 g, 60%, white powder).



Mp. 100.5 °C, lit. 100.5 °C (R. Dahlbom, T. Ekstrand *Acta. Chem. Scand.* **1951**, *5*, 102–114); **^{1}H NMR** (DMSO-d_6) δ 0.66 (t, 6 H, *J* = 6.6 Hz, 2´´-H), 1.10 (d, 3 H, *J* = 6.7 Hz, 3´-H), 2.30 (q, 4 H, *J* = 6.5 Hz, 1´´-H), 4.06 (q, 1 H, *J* = 6.4 Hz, 2´-H), 7.28 (bs, 2 H, 4-H, 9-H), 7.36 (dd, 2 H, *J* = 7.3, 7.3 Hz, 5-H, 8-H), 7.52 (bs, 2 H, 3-H, 10-H), 7.59 (d, 1 H, *J* = 6.7 Hz, 11-H), 7.66 (d, 1 H, *J* = 6.3 Hz, 2-H); **^{13}C NMR** (DMSO-d_6) δ 11.56 (C15), 13.93 (C17), 43.38 (C16), 54.37 (C14), 126.66, 126.76, 126.88, 127.55, 127.81, 128.15, 132.17, 133.30, 138.59, 139.03, 168.16 (C13).

Cholinesterase inhibition assays (M. Pietsch, M. Gütschow *J. Med. Chem.* **2005**, *48*, 8270–8288)**.** Cholinesterase inhibition was assayed spectrophotometrically at 25 °C according to the method of Ellman et al. (G. L. Ellman, K. D. Courtney, V. Andres, R. M. Feather-Stone *Biochem. Pharmacol.* **1961**, *7*, 88–95). Assay buffer was 100 mM sodium phosphate, 100 mM NaCl, pH 7.3. Stock solutions of acetylcholinesterase (*Electrophorus electricus:* ~100 U/ml, *Torpedo californica:* ~3 U/ml, *Homo sapiens:* ~3 U/ml) and butyrylcholinesterase *Homo sapiens:* ~10 U/ml) in assay buffer were kept at 0 °C. Appropriate dilutions were prepared immediately before starting the measurement. Acetyl- or butyrylthiocholine (10 mM) and 5,5'-dithio-bis-(2-nitrobenzoic acid) (DTNB) (7 mM) were dissolved in assay buffer and kept at 0 °C. Stock solutions of the inhibitors were prepared in a 1:1 mixture of acetonitrile and 0.1 M HCl. IC_{50} values were calculated from the linear steady-state turnover of the substrate using Equation 1,

$$IC_{50} = \frac{[I]}{\frac{v_0}{v} - 1} \qquad \text{(Eq. 1)}$$

were [I] is the inhibitor concentration, v_0 and v are the rates in the absence and presence of the inhibitor, respectively. For compounds **15a-i**, **16a-f** and AS-1397 IC_{50} values were determined in duplicate on a minimum of at least four different inhibitor concentrations. Inhibition of acetylcholinesterase from *Electrophorus electricus* with compound **15h** was additionally investigated at four different substrate concentrations. Into a cuvette containing 825 µl assay buffer, 50 µl of the DTNB solution, 55 µl acetonitrile, 10 µl of an inhibitor solution, and 10 µl of a cholinesterase solution (~3 U/ml) were added and thoroughly mixed. After incubation for 15 min at 25 °C, the reaction was initiated by adding 50 µl of the acetyl- or butyrylthiocholine solution.

Inhibition of acetylcholinesterase from *Electrophorus electricus* by compound 15h: secondary plots

Slopes and intercepts from the Lineweaver-Burk plot were plotted against the corresponding inhibitor concentrations to allow the determination of K_{ic} and α. Values K_{ic} = 3.23 nM and α = 0.97 were calculated using the linear regression and the values obtained for [I] = 0.