Supporting Information

Acylguanidines as Bioisosteres of Guanidines: N^G-Acylated Imidazolylpropylguanidines, a New Class of Histamine H_2 Receptor Agonists

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3-[1-(Triphenylmethyl)-1*H*-imidazol-4-yl]propanol (10). This compound was synthesized starting from urocanic acid according to the method published[1].

3-Phenylbutan-1-ol (12).[2] To a suspension of $LiAlH_4$ (15 mmol) in 50 mL abs. THF was slowly added a solution of 3-phenylbutyric acid (12.2 mmol) in abs. THF and stirred for 2 h. After cooling of the flask (ice bath), water was added cautiously to decompose excess hydride. Then 20 mL of 10% H_2SO_4 was added and a clear solution resulted. The solution was extracted three times with $CHCl_3$, washed with water, dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography. Yield 45 %; colorless oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.23 (m, 5H, Ph), 3.54 (m, 2H, C*H*$_2$OH), 2.88 (m, 1H, CH$_3$C*H*), 1.85 (q, 2H, *J* = 6.9 Hz, *J* = 13.8 Hz, CH$_3$CHC*H*$_2$), 1.27 (d, 3H, *J* = 7.0 Hz, CH$_3$); MS (PI-EIMS), *m/z*: 150 ([M]$^+$), 105 ([PhCHCH$_3$]$^+$), 91 ([C_7H_7]$^+$); $C_{10}H_{14}O$ (150.2).

***N*,*N*'-Bis(benzyloxycarbonyl)guanidine (13)** and ***N*,*N*'-bis(benzyloxycarbonyl)-*N*''-trifluoromethanesulfonylguanidine (21).** These compounds were synthesized according to the method published.[3]

***N*-Trityl-2-(1-trityl-1*H*-imidazol-4-yl)ethanamine (19).**[4] To a solution of histamine dihydrochloride (20 mmol) and Et_3N (80 mmol) in 50 mL $CHCl_3$ was added dropwise a solution of trityl chloride (50 mmol) in 50 mL $CHCl_3$ under external cooling with ice. The mixture was allowed to warm up at ambient temperature and stirred for 20 h. The solvent was evaporated under reduced pressure, and the solid residue was suspended in 100 mL of water. After stirring for 1 h, the product was extracted with $CHCl_3$ (2 x 100 mL), dried over anhydrous Na_2SO_4 and evaporated. Yield 62 %; colorless crystalline solid; mp 202-203 °C; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.42-7.30 (m, 7H, Ph-*H* and Im-2-*H*), 7.31-7.08 (m, 24H, Ph-*H*), 6.50 (s, 1H, Im-5-*H*), 2.73 (t, *J* = 6.2 Hz, 2H, Im-C*H*$_2$), 2.40 (t, *J* = 6.3 Hz, 2H, C*H*$_2$NH$_2$); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc), *m/z*: 596 (MH$^+$); $C_{43}H_{37}N_3$ (595.8).

2-(1-Trityl-1*H*-imidazol-4-yl)ethanamine (20).[4] To a solution of **19** (0.017 mol) in 47.5 mL CH_2Cl_2 at 0 °C, 2.5 mL of TFA was added drop by drop. After stirring for 10 min at the same temperature, the mixture was allowed to warm to rt and was stirred for additional 45 min. After removing the solvent, the residue was neutralised with saturated sodium bicarbonate solution and then extracted with $CHCl_3$ (4 x 50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. After removing the solvent, the residue was chromatographed with $CHCl_3$/MeOH/TEA (94 : 5 : 1) on silica. Yield 68 %; yellowish sticky oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.40 (s, 1H, Im-2-C*H*), 7.35-7.28 (m, 9H, Ph-*H*), 7.18-7.10 (m, 6H, Ph-*H*), 6.60 (s, 1H, Im-5-C*H*), 2.97 (t, *J* = 6.7 Hz, 2H, C*H*$_2$NH$_2$), 2.70 (t, *J* = 6.7 Hz, 2H, Im-4-C*H*$_2$), 1.78 (s br., 2H, CH$_2$N*H*$_2$); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc), *m/z*: 354 (MH$^+$), 243 ([Ph_3C]$^+$); $C_{24}H_{23}N_3$ (353.5).

General procedure for the synthesis of ketones 24a-d

A 250 mL three-necked flask fitted with a magnetic pellet was connected to a sidearm dumper that contained of the pertinent benzonitrile (ArCN) (23 mmol), to a pressure equalizing addition funnel, and to the Schlenk line by a vacuum adapter. The apparatus was purged with N_2 for 30 min, and then 23 mmol of the appropriate heteroarylbromide (ArBr) and 100 mL of Et_2O were added sequentially by syringe to the flask via the addition funnel. Then, 14 mL of 1.6 M solution (23 mmol) of ^{n}BuLi in hexane and 20 mL of Et_2O were transferred to the addition funnel. The flask was cooled to -78 °C, and the ^{n}BuLi solution was added dropwise to the ethereal ArBr solution. After complete addition, the resulting red solution of 2-lithioaren was stirred for 20 min, and then ArCN was added in several portions over 5 min. The reaction mixture was stirred at -78 °C for 1 h, the cold bath was removed, and the mixture was allowed to warm to room temperature with stirring over night. The resulting red-

violet slurry was poured into 100 mL of cold (0 °C) 3 M HCl. After the mixture had been stirred for 20 min, the organic and aqueous fractions were separated, 3 M NaOH was added to the aqueous fraction until the mixture was slightly basic to litmus, and the aqueous fraction was extracted with ether (3 x 100 mL). The combined organic fractions were dried over $MgSO_4$ and filtered, and solvent was removed by rotatory evaporation to leave dark orange oil. The residue was purified by flash column chromatography.

Phenyl(pyridin-2-yl)methanone (24a). Synthesized from 2-bromopyridine and benzonitrile. Yield 77 %; colorless crystalline solid; mp 42 °C (Lit.[5] 42 °C); ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.73 (m, 1H, Pyr-6-*H*), 8.05 (m, 3H, Pyr-*H* & Ph-*H*), 7.90 (m, 1H, Pyr-*H*), 7.59 (m, 1H, Pyr-*H*), 7.48 (m, 3H, Ph-*H*); EI-MS, *m/z* (rel. intensity, %): 183 ($M^{+\cdot}$, 63), 105 ([M – Pyr]$^+$, 100), 78 ([Pyr]$^+$, 18), 77 ([Ph]$^+$, 84); $C_{12}H_9NO$ (183.2).

4-Fluorophenyl(pyridin-2-yl)methanone (24b).[6] Synthesized from 2-bromopyridine and 4-fluorobenzonitrile. Yield 69 %; colorless crystalline solid; mp 68-69 °C; ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.73 (m, 1H, Pyr-6-*H*), 8.21-8.11 (m, 2H, Ar-*H*), 8.06 (m, 1H, Pyr-*H*), 7.93 (m, 1H, Pyr-*H*), 7.50 (ddd, 1H, *J* = 1.4 Hz, *J* = 4.7 Hz, *J* = 7.7 Hz, Pyr-*H*), 7.22-7.12 (m, 2H, Ar-*H*); EI-MS, *m/z* (rel. intensity, %): 201 ($M^{+\cdot}$, 40), 173 ([M – CO]$^+$, 79), 123 ([M – Pyr]$^+$, 100), 95 ([M - Pyr-CO]$^+$, 63); $C_{12}H_8FNO$ (201.2).

Phenyl(thiazol-2-yl)methanone (24c). Synthesized from 2-bromothiazole and benzonitrile. Yield 86 %; colorless crystalline solid; mp 35-37 °C (Lit.[7] 44-46 °C); ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.50-8.45 (m, 2H, Ph-*H*), 8.10 (d, *J* = 3.0 Hz, 1H, Thiaz-4-*H*), 7.72 (d, *J* = 3.0 Hz, 1H, Thiaz-5-*H*), 7.68-7.6 (m, 1H, Ph-*H*), 7.57-7.49 (m, 2H, Ph-*H*); EI-MS, *m/z* (rel. intensity, %): 189 ($M^{+\cdot}$, 41), 161 ([M – CO]$^+$, 54), 105 ([M – Thiaz]$^+$, 100), 77 ([M – Thiaz-CO]$^+$, 77); $C_{10}H_7NOS$ (189.2).

3,4-Difluorophenyl(thiazol-2-yl)methanone (24d). Synthesized from 2-bromothiazole and 3,4-difluorobenzonitrile. Yield 87 %; colorless crystalline solid; mp 59-60 °C; ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.09 (d, *J* = 3.0 Hz, 1H, Thiaz-4-*H*), 7.75 (d, *J* = 3.0 Hz, 1H, Thiaz-5-*H*), 7.30 (m, 3H, Ar-*H*), EI-MS, *m/z* (rel. intensity, %): 225 ($M^{+\cdot}$, 44), 197 ([M – CO]$^+$, 40), 141 ([M – Thiaz]$^+$, 100), 113 ([M – Thiaz-CO]$^+$, 59), 58 (15); $C_{10}H_5F_2NOS$ (225.2).

General procedure for the synthesis of the ethyl propenoates 25a-d, 29

To a stirred suspension of sodium hydride (0.74 g, 18.5 mmol as 60 % dispersion in oil) in 20 mL of dry THF, triethyl phosphonoacetate (3.95 g, 17.4 mmol) under nitrogen atmosphere was added at a rate such that the reaction temperature was maintained at 30-35 °C. The mixture was stirred at room temperature for 1 h and the solution of the pertinent ketone (18 mmol) in 40 mL of THF was added dropwise over 30 min. The mixture was refluxed for 16-24 h and poured into ice water, extracted with diethyl ether, washed with water, dried and concentrated to give a mixture of *E* and *Z* isomeric ethyl esters, as an oil. The residue was separated by flash column chromatography.

(*E/Z*)-Ethyl 3-phenyl-3-(pyridin-2-yl)propenoate (25a).[8] Synthesized from phenyl(pyridin-2-yl)methanone (**24a**). Yield 72 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 252 ($M^{+\cdot}$, 96), 224 ([M – Et]$^+$, 90), 208 ([M – OEt]$^+$, 35), 180 ([M – CO_2Et]$^+$, 100), 167 ([M – CHCOOEt]$^+$, 9); $C_{16}H_{15}NO_2$ (253.3).

(*E/Z*)-Ethyl 3-(4-fluorophenyl)-3-(pyridin-2-yl)propenoate (25b). Synthesized from 4-fluorophenyl(pyridin-2-yl)methanone (**25b**). Yield 75 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 271 (($M^{+\cdot}$, 78), 242 ([M – Et]$^+$, 68), 226 ([M – OEt]$^+$, 47), 198 ([M – CO_2Et]$^+$, 100); $C_{16}H_{14}FNO_2$ (271.3).

(*E/Z*)-Ethyl 3-phenyl-3-(thiazol-2-yl)propenoate (25c). Synthesized from phenyl(thiazol-2-yl)-methanone (**22c**). Yield 79 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 259 ($M^{+\cdot}$, 45), 230 ([M –

Et]$^+$, 70), 214 ([M – OEt]$^+$, 40), 186 ([M – CO_2Et]$^+$, 100), 173 ([M – $CHCO_2Et$]$^+$, 3); $C_{14}H_{13}NO_2S$ (259.3).

(*E/Z*)-Ethyl 3-(3,4-difluorophenyl)-3-(thiazol-2-yl)propenoate (25d). Synthesized from 3,4-difluorophenyl(thiazol-2-yl)methanone (**22d**). Yield 68 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 295 ($M^{+\cdot}$, 27), 266 ([M – Et]$^+$, 26), 250 ([M – OEt]$^+$, 49), 222 ([M – CO_2Et]$^+$, 100); $C_{14}H_{11}F_2NO_2S$ (295.3).

(*E/Z*)-Ethyl 3-(thiophen-2-yl)but-2-enoate (29).[9] Synthesized from 1-(thiophenyl-2-yl)ethanone (**28**). Yield 83 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 196 ($M^{+\cdot}$, 53), 151 ([M – OEt]$^+$, 100), 124 ([M – CO_2Et]$^+$, 57), 111 ([M – $CHCO_2Et$]$^+$, 15); $C_{10}H_{12}O_2S$ (196.3).

General procedure for the synthesis of the ethyl propanoates 26a-d, 30

The ethyl acrylates were dissolved in THF (100 mL) and 10 % Pd/C (cat.) was added, and the mixture was stirred at room temperature for 12 h under a hydrogen atmosphere. The catalyst was filtered off through Celite pad and the filtrate was concentrated to obtain the corresponding ethyl propanoates.

Ethyl 3-phenyl-3-(pyridin-2-yl)propanoate (26a).[10] Synthesized from ethyl 3-phenyl-3-(pyridin-2-yl)propenoate (**25a**). Yield 96 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 255 ($M^{+\cdot}$, 19), 254 (17), 210 ([M – OEt]$^+$, 20), 182 ([M – CO_2Et]$^+$, 100), 167 ([M – CH_2CO_2Et]$^+$, 60); $C_{16}H_{17}NO_2$ (255.3). ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.54 (m, 1H, Pyr-6-*H*), 7.52 (m, 1H, Pyr-4-*H*), 7.35- 7.00 (m, 7H, Pyr-3-*H*, Pyr-5-*H* and 5 Ph-*H*), 6.64 (dd, *J* = 8.8 Hz, *J* = 6.8 Hz, 1H, C*H*CH_2COOEt), 4.03 (ddq, *J* = 8.7 and 6.8 Hz, 2H, COOC$H_2$$CH_3$), 3.44 (dd, *J* = 8.7 Hz, *J* = 16.0 Hz, 1H, CH_2COOEt), 2.98 (dd, *J* = 6.8 Hz, *J* = 16.0 Hz, 1H, CH_2COOEt), 1.12 (t, *J* = 7.1 Hz, 3H, $COOCH_2$CH_3).

Ethyl 3-(4-fluorophenyl)-3-(pyridin-2-yl)propanoate (26b). Synthesized from ethyl 3-(4-fluorophenyl)-3-(pyridin-2-yl)propenoate **(25b).** Yield 93 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 273 ($M^{+\cdot}$, 19), 228 ([M – OEt]$^+$, 18), 200 ([M – CO_2Et]$^+$, 100), 185 ([M – CH_2CO_2Et]$^+$, 55); $C_{16}H_{16}FNO_2$ (273.3). ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.53 (m, 1H, Pyr-6-*H*), 7.54 (m, 1H, Pyr-4-*H*), 7.33-7.25 (m, 2H, 2 Ph-*o*-*H*), 7.16-7.05 (m, 2H, Pyr-*H*), 7.03-6.89 (m, 2H, 2 Ph-*m*-*H*), 4.62 (ddq, *J* = 8.2 and 7.1 Hz, 1H, C*H*CH_2COOEt), 4.02 (q, *J* = 7.1 Hz, 2H, COOC$H_2$$CH_3$), 3.40 (dd, *J* = 8.2 Hz, *J* = 15.9 Hz, 1H, CH_2COOEt), 2.96 (dd, *J* = 7.1 Hz, *J* = 15.9 Hz, 1H, CH_2COOEt), 1.11 (t, *J* = 7.1 Hz, 3H, $COOCH_2$CH_3).

Ethyl 3-phenyl-3-(thiazol-2-yl)propanoate (26c). Synthesized from ethyl 3-phenyl-3-(thiazol-2-yl)propenoate (**25c**). Yield 91 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 261 ($M^{+\cdot}$, 45), 216 ([M – OEt]$^+$, 18), 188 ([M – CO_2Et]$^+$, 100), 173 ([M – CH_2CO_2Et]$^+$, 28); $C_{14}H_{15}NO_2S$ (261.3). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.71 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.50-7.20 (m, 5H, Ph-*H*), 7.18 (d, *J* = 3.3 Hz, 1H, Thiaz-5-*H*), 4.90 (ddq, *J* = 7.9 and 7.1 Hz, 1H, C*H*CH_2COOEt), 4.06 (q, *J* = 7.1 Hz, 2H, COOC$H_2$$CH_3$), 3.45 (dd, *J* = 7.9 Hz, *J* = 16.1 Hz, 1H, CH_2COOEt), 2.96 (dd, *J* = 7.5 Hz, *J* = 16.1 Hz, 1H, CH_2COOEt), 1.14 (t, *J* = 7.1 Hz, 3H, $COOCH_2$CH_3).

Ethyl 3-(3,4-difluorophenyl)-3-(thiazol-2-yl)propanoate (26d). Synthesized from ethyl 3-(3,4-difluorophenyl)-3-(thiazol-2-yl)propenoate (**25d**). Yield 88 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 297 ($M^{+\cdot}$, 34), 252 ([M – OEt]$^+$, 17), 224 ([M – CO_2Et]$^+$, 100), 209 ([M – CH_2CO_2Et]$^+$, 33); $C_{14}H_{13}F_2NO_2S$ (297.3). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.23 (d, *J* = 3.3 Hz, 1H, Thiaz-5-*H*), 7.22-7.04 (m, 3H, Ar-*H*), 4.85 (ddq, *J* = 7.5 and 7.8 Hz, 1H, C*H*CH_2CO), 4.08 (q, *J* = 7.1 Hz, 2H, COOCH_2), 3.41 (dd, *J* = 7.5 Hz, *J* = 16.3 Hz, 1H, CH_2COOEt), 3.01 (dd, *J* = 7.8 Hz, *J* = 16.3 Hz, 1H, CH_2COOEt), 1.17 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).

Ethyl 3-(thiophen-2-yl)butanoate (30).[9] Synthesized from (*E*)-ethyl 3-(thiophen-2-yl)but-2-enoate (**29**). Yield 96 %; colorless oil; EI-MS, *m/z* (rel. intensity, %): 198 ($M^{+\cdot}$, 17), 169 ([M – Et]$^+$, 5),

151 ([M – OEt]$^+$, 23), 124 ([M – CO_2Et]$^+$, 56), 111 ([M – CH_2CO_2Et]$^+$, 100); $C_{10}H_{14}O_2S$ (198.3). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.12 (m, 1H, Thio-5-*H*), 6.90 (m, 1H, Thio-3-*H*), 6.83 (m, 1H, Thio-4-*H*), 4.11 (ddq, *J* = 7.1 Hz, O*CH*$_2$), 3.59 (m, 1H, C*H*CH_2CO), 2.68 (dd, *J* = 6.9 Hz, *J* = 15.4 Hz, 1H, C*H*$_2$CO), 2.54 (dd, *J* = 7.9 Hz, *J* = 15.4 Hz, 1H, C*H*$_2$CO), 1.38 (d, *J* = 6.9 Hz, 3H, C*H*$_3$CHCH$_2$CO), 1.22 (t, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$).

General procedure for the synthesis of propanoic acids (27a-d, 31)

To a solution of the pertinent ethyl ester (5.0 mmol) in 20 mL of dimethoxyethane was added a solution of LiOH (7.5 mmol) in 5 mL of water, and the mixture was stirred at room temperature for 3 h. The pH of the reaction mixture was adjusted with aqueous HCl to 6 (**27a,b**) or 3 (**27c,d,31**), and the solution was extracted twice with 300 mL portions of EtOAc. The combined extracts were dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the desired product.

3-Phenyl-3-(pyridin-2-yl)propanoic acid (27a).[10] Synthesized from ethyl 3-phenyl-3-(pyridin-2-yl)propanoate **(26a).** Yield 96 %; colorless crystalline solid; mp 105 °C; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.98 (br, 1H, COO*H*), 8.53 (m, 1H, Pyr-6-*H*), 7.61 (m, 1H, Pyr-4-*H*), 7.35-7.10 (m, 7H, 2 Pyr-*H* and 5 Ph-*H*), 4.64 (ddq, *J* = 5.2 Hz, *J* = 8.2 Hz, 1H, C*H*CH_2COOH), 3.37 (dd, *J* = 8.2 Hz, *J* = 15.9 Hz, 1H, C*H*$_2$COOH), 3.06 (dd, *J* = 5.2 Hz, *J* = 15.9 Hz, 1H, C*H*$_2$COOH); EI-MS, *m/z* (rel. intensity, %): 227 (M$^{+\cdot}$, 27), 226 (28), 182 ([M – CO_2H]$^+$, 100), 167 ([M – CH_2CO_2H]$^+$, 62); $C_{14}H_{13}NO_2$ (227.3).

3-(4-Fluorophenyl)-3-(pyridin-2-yl)propanoic acid (27b). Synthesized from ethyl 3-(4-fluorophenyl)-3-(pyridin-2-yl)propanoate (**26b**). Yield 97 %; colorless crystalline solid; mp 127 °C; ^{1}H-NMR ($CDCl_3$) δ (ppm): 11.85 (br. 1H, COO*H*), 8.56 (m, 1H, Pyr-6-*H*), 7.66 (m, 1H, Pyr-4-*H*), 7.20 (m, 4H, 2 Pyr-*H* and 2 Ph-*H*), 6.96 (m, 2H, 2 Ph-*H*), 4.63 (ddq, *J* = 5.5 Hz, *J* = 8.2 Hz, 1H, C*H*CH_2COOH), 3.34 (dd, *J* = 8.2 Hz, *J* = 15.9 Hz, 1H, C*H*$_2$COOH), 3.07 (dd, *J* = 5.5, *J* = 15.9 Hz, 1H, C*H*$_2$COOH); EI-MS, *m/z* (rel. intensity, %): 245 (M$^{+\cdot}$, 32), 227 ([M – OH]$^+$, 5), 200 ([M – CO_2H]$^+$, 100), 185 ([M – CH_2CO_2H]$^+$, 51); $C_{14}H_{12}FNO_2$ (245.2).

3-Phenyl-3-(thiazol-2-yl)propanoic acid (27c). Synthesized from ethyl 3-phenyl-3-(thiazol-2-yl)propanoate (**26c**). Yield 82 %; colorless crystalline solid; mp 208 °C ; ^{1}H-NMR ($CDCl_3$ + CD_3OD) δ (ppm): 7.70 (d, *J* = 3.4 Hz, 1H, Thiaz-4-*H*), 7.21-7.43 (m, 6H, Ph-*H* and Thiaz-5-*H*), 4.89 (ddq, *J* = 7.1 and 8.0 Hz, C*H*CH_2CO), 3.45 (dd, *J* = 8.0 Hz, *J* = 16.5 Hz, 1H, C*H*$_2$CO), 3.07 (dd, *J* = 7.1 Hz, *J* = 16.5 Hz, 1H, C*H*$_2$CO); EI-MS, *m/z* (rel. intensity, %): 233 (M$^{+\cdot}$, 51), 215 ([M – OH]$^+$, 7), 188 ([M – CO_2H]$^+$, 100), 173 ([M – CH_2CO_2H]$^+$, 40); $C_{12}H_{11}NO_2S$ (233.3).

3-(3,4-Difluorophenyl)-3-(thiazol-2-yl)propanoic acid (27d). Synthesized from ethyl 3-(3,4-difluorophenyl)-3-(thiazol-2-yl)propanoate (**26d**). Yield 92 %; colorless crystalline solid; mp 90 °C; ^{1}H-NMR ($CDCl_3$) δ (ppm): 10.70 (s br, 1H, COO*H*), 7.72 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.25 (d, *J* = 3.3 Hz, 1H, Thiaz-5-*H*), 7.20-7.02 (m, 3H, Ar-*H*), 4.84 (t, *J* = 7.4 Hz, C*H*CH_2CO), 3.44 (dd, *J* = 7.4 Hz, *J* = 16.7 Hz, 1H, C*H*$_2$CO), 3.05 (dd, *J* = 7.4 Hz, *J* = 16.7 Hz, 1H, C*H*$_2$CO); EI-MS, *m/z* (rel. intensity, %): 269 (M$^{+\cdot}$, 30), 251 ([M – OH]$^+$, 6), 224 ([M – CO_2H]$^+$, 100), 210 ([M – CH_2CO_2H]$^+$, 24); $C_{12}H_9F_2NO_2S$ (269.3).

3-(Thiophen-2-yl)butanoic acid (31).[11] Synthesized from ethyl 3-(thiophen-2-yl)butanoate (**30**). Yield 95 %; oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.13 (m, 1H, Thio-5-*H*), 6.94-6.89 (m, 1H, Thio-4-*H*), 6.86-6.83 (m, 1H, Thio-3-*H*), 3.61 (m, 1H, C*H*CH_2CO), 2.76 (dd, *J* = 6.6 Hz, *J* = 15.7 Hz, 1H, C*H*$_2$CO), 2.62 (dd, *J* = 8.0 Hz, *J* = 15.7 Hz, 1H, C*H*$_2$CO), 1.43 (d, *J* = 6.9 Hz, 3H, C*H*$_3$CHCH$_2$CO), EI-MS, *m/z* (rel. intensity, %): 170 (M$^{+\cdot}$, 44), 154 ([M – OH]$^+$, 6), 125 ([M – CO_2H]$^+$, 8), 111 ([M – CH_2CO_2H]$^+$, 100); $C_8H_{10}O_2S$ (170.2).

1-(Pyridin-2-yl)ethanol (32a). This compound was synthesized according to the method published[12].

1-(Thiazol-2-yl)ethanol (32b). This compound was synthesized according to the method published[13].

General procedure for the preparation of the tosylates 33a,b

To a stirred solution of alcohol **32a** or **32b** (29 mmol) and DMAP (7.1 g, 58 mmol) in CH_2Cl_2 (100 mL) was added MsCl (5.6 mL, 72.5 mmol) at 0 °C. The mixture was stirred for 10 min at the same temperature and for an additional time (see below) at rt. Ice water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residual oil was purified by column chromatography on flash silica gel (elution with a mixture of EtOAc and hexane).

1-(Pyridin-2-yl)ethyl methanesulfonate (33a).[14] Synthesized from 1-(pyridin-2-yl)ethanol (**32a**); stirred for 1 h. Yield 96 %; colorless oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.52 (m, 1H, Pyr-6-*H*), 7.69 (m, 1H, Pyr-4-*H*), 7.40 (m, 1H, Pyr-3-*H*), 7.25 (m, 1H, Pyr-5-*H*), 5.71 (quart, *J* = 6.6 Hz, 1H, PyrC*H*(OMs)), 2.86 (s, 3H, SO_2CH_3), 1.68 (d, *J* = 6.6 Hz, $CHCH_3$); CI-MS (NH_3), *m/z* (rel. intensity, %): 202 (MH^+); $C_8H_{11}NO_3S$ (201.2).

1-(Thiazol-2-yl)ethyl methanesulfonate (33b). Synthesized from 1-(thiazol-2-yl)ethanol (**32b**); stirred for 16 h. Yield 96 %; colorless oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.34 (d, *J* = 3.3 Hz, 1H, Thiaz-5-*H*), 5.36 (q, *J* = 6.8 Hz, 1H, C*H*OMs), 3.66 (s, 3H, SO_2CH_3), 1.96 (d, , *J* = 6.8 Hz, 3H, $CHCH_3$); CI-MS (NH_3), *m/z* (rel. intensity, %): 208 (MH^+); $C_6H_9NO_3S_2$ (207.3).

General procedure for the preparation of the 2-substituted dimethyl malonates 34a,b

To a suspension of sodium hydride (72 mg, 3.0 mmol) in THF (6.0 mL) was added dimethyl malonate (3.22 mmol) at 0 °C. After the hydrogen formation had ceased at room temperature, the mixture was added to a solution of 1-(pyridin-2yl)ethyl methanesulfonate (**33a**) or 1-(thiazol-2yl)ethyl methanesulfonate (**33b**) (1.0 mmol) in DMSO (4.0 mL). The reaction mixture was warmed to 60 °C and stirred until the reaction was completed (12 h). After cooling, EtOAc and water were added. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water, brine and dried over $MgSO_4$. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (eluent: mixture of EtOAc and hexane) to give the products.

Dimethyl 2-[1-(pyridin-2-yl)ethyl]malonate (34a).[15] Synthesized from 1-(pyridin-2-yl)ethyl methanesulfonate (**33a**). Yield 82 %; colorless oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.49 (m, 1H, Pyr-6-*H*), 7.61 (m, 1H, Pyr-4-*H*), 7.23 (m, 1H, Pyr-3-*H*), 7.11 (m, 1H, Pyr-5-*H*), 4.17 (d, *J* = 10.4 Hz, C*H*(CO_2Me)$_2$), 3.77 (s, 3H, COOC*H*$_3$), 3.70 (dq, *J* = 7.0 Hz, *J* = 10.4 Hz, 1H, C*H*CH_3), 3.54 (s, 3H, COOC*H*$_3$), 1.23 (d, *J* = 7.0 Hz, 3H, CH*C*H$_3$); CI-MS (NH_3), *m/z* (rel. intensity, %): 238.0 (MH^+, 100); $C_{12}H_{15}NO_4$ (237.3).

Dimethyl 2-[1-(thiazol-2-yl)ethyl]malonate (34b). Synthesized from 1-(thiazol-2-yl)ethyl methanesulfonate (**33b**). Yield 87 %; colorless oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.59 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.16 (d, , *J* = 3.3 Hz, 1H, Thiaz-5-*H*), 3.98 (d, *J* = 10.3 Hz, C*H*(CO_2Me)$_2$), 3.93 (dq, J = 6.7 Hz, *J* = 10.3 Hz, 1H, C*H*CH_3), 3.68 (s, 3H, COOC*H*$_3$), 3.56 (s, 3H, COOC*H*$_3$), 1.38 (d, *J* = 6.7 Hz, 3H, CH*C*H$_3$); EI-MS, *m/z* (rel. intensity, %): 243 ($M^{+\cdot}$, 9), 212 ([M – 2 x Me]$^+$, 17), 184 ([M – CO_2Me]$^+$, 100), 180 ([M – 2 x OMe]$^+$, 21), 152 ([C_7H_7NOS]$^+$, 97), 124 ([M – 2 x CO_2Me]$^+$, 29), 112 ([M – CH(CO_2Me)$_2$]$^+$, 38); $C_{10}H_{13}NO_4S$ (243.3).

General procedure for the preparation of 3-heteroarylbutanoic acids (35a,b)

A solution of diester **34a** or **34b** (1 mmol) in MeOH (3 mL) was treated with NaOH (2.2 N, 1.8 mL) in water, the resulting mixture was heated to reflux, and the reaction was monitored by TLC. When no starting material remained (12-18 h), the reaction mixture was allowed to come to room temperature. Volatiles were removed *in vacuo* and the crude dicarboxylic acid was taken up in AcOH (6 mL) and heated to reflux. The reaction was monitored by TLC, and when no starting material remained (12-18 h), the solution was concentrated *in vacuo*. The resultant crude acid was dissolved in water (5 mL), extracted with EtOAc (3 x 3 mL), and the combined extracts were dried over $MgSO_4$ and concentrated to give product.

3-(Pyridin-2-yl)butanoic acid (35a). Synthesized from dimethyl 2-[1-(pyridin-2-yl)ethyl]malonate (**34a**); refluxed for 15 h each time. Yield 87 %; yellow oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.45 (m, 1H, Pyr-6-*H*), 7.77 (m, 1H, Pyr-4-*H*), 7.36 (m, 1H, Pyr-3-*H*), 7.25 (m, 1H, Pyr-5-*H*), 3.40 (m, 1H, CH_3CHCH_2), 2.80 (dd, *J* = 7.4 Hz, *J* = 15.6 Hz, 1H, CH_2CO), 2.63 (dd, *J* = 7.1 Hz, *J* = 15.6 Hz, 1H, CH_2CO), 1.32 (d, *J* = 6.9 Hz, 3H, CH_3CHCH_2CO); EI-MS, *m/z* (rel. intensity, %): 165 ($M^{+\cdot}$, 4), 150 ([M – OH]$^+$, 6), 132 ([M – O_2H]$^+$, 12), 120 ([M – CO_2H]$^+$, 100), 106 ([M – CH_2CO_2H]$^+$, 62); $C_9H_{11}NO_2$ (165.2).

3-(Thiazol-2-yl)butanoic acid (35b). Synthesized from dimethyl 2-[1-(thiazol-2-yl)ethyl]malonate (**34b**); refluxed for 15 h each time. Yield 91 %; colorless oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.42 (s, COOH), 7.71 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.22 (d, , *J* = 3.3 Hz, 1H, Thiaz-5-*H*), 3.75 (m, 1H, $CHCH_2CO_2H$), 2.90 (dd, *J* = 6.9 Hz, *J* = 16.0 Hz, 1H, $CHCH_2CO_2H$), 2.65 (dd, *J* = 7.3 Hz, *J* = 16.0 Hz, 1H, $CHCH_2CO_2H$), 1.45 (d, *J* = 7.0 Hz, 3H, CH_3CH); EI-MS, *m/z* (rel. intensity, %): 171 ($M^{+\cdot}$, 21), 156 ([M – Me]$^+$, 7), 126 ([M – CO_2H]$^+$, 100), 112 ([M – CH_2CO_2H]$^+$, 23); $C_7H_9NO_2S$ (171.2).

General procedure for the preparation of cyclohexylalkanoic acids (37a,b)

0.5 g of Rh/Al_2O_3 was added to solution of the corresponding phenylalkanoic acid (9 mmol) in acetic acid (30 mL). The mixture was hydrogenated 40 h with constant stirring at 5-6 bar H_2 pressure, filtered through celite pad, washed with acetic acid, and the solvent was removed *in vacuo*. The remaining crude solid was purified by column chromatography on silica gel (eluent: mixture of EtOAc and petrol ether) to give the product.

2-Cyclohexylpropanoic acid (37a)[16]**.** Synthesized from 2-phenylpropanoic acid. Yield 92 %; colorless crystalline solid; mp 56-58 °C; ^{1}H-NMR ($CDCl_3$) δ (ppm): 11.52 (br s, COOH), 2.28 (m, 1H, -CH_3CH-), 1.67 (m, 6H, cHex-CH_2), 1.23 (m, 3H, cHex-CH_2, cHex-CH), 1.13 (d, 3H, *J* = 7.04 Hz, CH_3), 1.01 (m, 2H, cHex-CH_2); EI-MS: *m/z* (rel. Intens., %): 157 (MH^+,20), 156 (M^+, 15); $C_9H_{16}O_2$ (156.2).

3-Cyclohexylbutanoic acid (37b)[17]**.** Synthesized from 3-phenylbutyric acid. Yield 75 %; colorless oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 11.40 (br s, COOH), 2.43 (dd, 1H, *J* = 14.9 Hz, *J* = 5.0 Hz, CH**H**), 2.11 (dd, 1H, *J* = 14.9 Hz, *J* = 9.2 Hz, C**H**H), 1.65-1.74 (m, 5H, cHex-CH_2, cHex-CH), 1.87 (m, 1H, CH_3CH), 1.03-1.20 (m, 6H, cHex-CH_2), 0.93 (d, 3H, *J* = 6.8 Hz, CH_3); CI-MS: *m/z* (rel. Intens., %): 188 ([M+NH_4]$^+$, 100); $C_{10}H_{18}O_2$ (170.3).

General procedure for the preparation of 3-(4-halophenyl)propenoic acids (39a,b)

A solution of 4-halobenzaldehyde (70 mmol) and anhydrous NaOAc (61 mmol) were heated to reflux in acetic anhydride (127 mmol) for 6 h. After cooling, the mixture were poured into water and crystallized some days at low temperature. The precipitate were collected and recrystallized.

3-(4-Chlorophenyl)propenoic acid (39a)[18]**.** Synthesized from 4-chlorobenzaldehyde. Yield 20 %; colorless solid, mp 248 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 12.50 (br, 1H, COO*H*), 7.50-7.75 (m, 4H, Ar-*H*), 7.60 (d, 1H, *J* = 16.0 Hz, Ar-C*H*), 6.58 (d, *J* = 1H, 16.0 Hz, C*H*COOH); $C_9H_7ClO_2$ (182.6).

3-(4-Bromophenyl)propenoic acid (39b)[19]**.** Synthesized from 4-bromobenzaldehyde. Yield 32 %; colorless solid; mp 253 °C; ^{1}H-NMR (DMSO-d_6), δ (ppm): 12.50 (br, 1H, COO*H*), 7.50-7.70 (m, 4H, Ar-*H*), 7.59 (d, 1H, *J* = 16.3 Hz, Ar-C*H*), 6.57 (d, *J* = 1H, 16.2 Hz, C*H*COOH); $C_9H_7BrO_2$ (227.1).

General procedure for the synthesis of 3,3-bis(4-halophenyl)propanoic acids (40a,b)

The corresponding 3-(4-halophenyl)propenoic acid (**39a,b**) (22 mmol) and $AlCl_3$ (75 mmol) were added to the corresponding halobenzene (0.29 mol) and stirred at room temperature. After 2 h, more $AlCl_3$ (32.5 mmol) was added and the mixture was stirred for another 1 h. Subsequently, the reaction mixture was poured on a mixture of ice water (50 mL) and conc. HCl (30 mL) and excess halobenzene was removed by steam destillation. The aqueous solution was discarded and the remaining residue dissolved in aqueous $NaHCO_3$ solution. After the addition of a small amount of activated charcoal, the mixture was refluxed for 1 h and filtered after cooling. The filtrate was acidified with 10% HCl/aq (50 mL) and after two days the crystalline solid was recrystallized from MeOH.

3,3-Bis(4-chlorophenyl)propanoic acid (40a). Synthesized from 3-(4-chlorophenyl)propenoic acid (**39a**) and chlorobenzene. Yield 47 %; colorless crystals; mp 194 °C (Lit.[20]: 194-195 °C); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.15-7.31 (m, 8H, Ar-*H*), 4.49 (t, 1H, *J* = 8.0 Hz, C*H*CH_2), 3.03 (d, 2H, *J* = 8.0 Hz, CHC*H*$_2$); $C_{15}H_{12}Cl_2O_2$ (295.2).

3,3-Bis(4-bromophenyl)propanoic acid (40b). Synthesized from 3-(4-bromophenyl)propenoic acid (**39b**) and bromobenzene. Yield 55 %; colorless crystals; mp 198 °C (Lit.[21]: mp 201-202 °C); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.25-7.53 (m, 8H, Ar-*H*), 4.49 (t, 1H, *J* = 8.0 Hz, C*H*CH_2), 3.01 (d, 2H, *J* = 8.0 Hz, CHC*H*$_2$); $C_{15}H_{12}Br_2O_2$ (384.1).

General procedure for the preparation of propenoic acids (42a-c)

The ketones **41a**, **41b** or **41c** (8.7 mmol) and potassium *tert*-butoxide (2.25 g, 20 mmol) were taken in a 250 mL flask with *tert*-butanol (100 mL), and triethyl phosphonoacetate (1.95 g, 8.7 mmol) was added. The mixture was refluxed overnight. After cooling, the solvent was removed on a rotatory evaporator. After addition of 100 mL 1 N NaOH and 75 mL MeOH the mixture was refluxed for 24 h, concentrated *in vacuo* to remove MeOH, diluted with water (300 mL) and extracted with $CHCl_3$ (3 x 75 mL). These $CHCl_3$ extractions were discarded. The aqueous layer was acidified with concentrated hydrochloric acid and extracted again with $CHCl_3$. This $CHCl_3$ layer was washed with brine and water, and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the remaining solid was recrystallized from EtOAc/n-hexane.

(*E*/*Z*)-3,3-Bis(4-fluorophenyl)propenoic acid (42a)[22]**.** Synthesized from bis(4-fluorophenyl)-methanone (**41a**). Yield 91 %; colorless crystalline solid; mp 97-98 °C; EI-MS, *m/z* (rel. intensity, %): 260 ($M^{+\cdot}$, 100), 259 (43), 243 ($[M - OH]^+$, 20), 214 ($[M - CO_2H]^+$, 61), 201 ($[M - CHCO_2H]^+$, 30); $C_{15}H_{10}F_2O_2$ (260.2).

(*E*/*Z*)-3-(4-Fluorophenyl)-3-phenylpropenoic acid (42b)[23]**.** Synthesized from (4-fluorophenyl)-phenylmethanone, a mixture of *E* and *Z* (**41b**). Yield 85 %; colorless crystalline solid; mp 97-98 °C; EI-MS, *m/z* (rel. intensity, %): 242 ($M^{+\cdot}$, 100), 225 ($[M - OH]^+$, 16), 196 ($[M - CO_2H]^+$, 53), 183 ($[M - CHCO_2H]^+$, 16); $C_{15}H_{11}FO_2$ (242.2).

(*E*/*Z*)-3-(3,4-Difluorophenyl)-3-phenylpropenoic acid (42c). Synthesized from (3,4-difluoro-phenyl)phenylmethanone (**41c**). Yield 89 %; colorless crystalline solid; mp 134-136 °C; EI-MS, *m/z* (rel. intensity, %): 260 ($M^{+\cdot}$, 100), 243 ($[M - OH]^+$, 21), 214 ($[M - CO_2H]^+$, 70); $C_{15}H_{10}F_2O_2$ (260.2).

General procedure for the preparation of propanoic acids (43a-c)

0.05 g of Pd/C (10 %) was added to solution of the pertinent acrylic acid (**42a-c**, 8 mmol) in methanol (100 mL). The mixture was hydrogenated with constant stirring at 5 bar H_2 pressure overnight, filtered through celite pad, washed with methanol, and the solvent was removed in *vacuo*. The remaining crude solid was recrystallized from chloroform/n-hexane.

3,3-Bis(4-fluorophenyl)propanoic acid (43a). Synthesized from 3,3-bis(4-fluorophenyl)propenoic acid (**42a**). Yield 94 %; colorless crystalline solid; mp 97-98 °C (Lit.[24]: mp 107-108 °C); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.2-7.1 (m, 4H, Ph-*H*), 7.05-6.80 (m, 4H, Ph-*H*), 4.48 (t, *J* = 7.9 Hz, 1H, Ar_2CH), 3.02 (d, *J* = 7.9 Hz, 2H, CH_2COOH); EI-MS, *m/z* (rel. intensity, %): 262 ($M^{+\cdot}$, 22), 203 ([M – $CH_2CO_2H]^+$, 100), 183 (([M – $FCH_2CO_2H]^+$, 11); $C_{15}H_{12}F_2O_2$ (262.3).

3-(4-Fluorophenyl)-3-phenylpropanoic acid (43b). Synthesized from (4-fluorophenyl)phenylpropenoic acid (**42b**). Yield 96 %; colorless crystalline solid; mp 108-110 °C (Lit.[24]: mp 107-108 °C); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.3-7.1 (m, 7H, Ph-*H*), 6.9-7.0 (m, 2H, Ph-*H*), 4.5 (t, *J* = 8.0 Hz, 1H, Ar_2CH), 3.0 (d, *J* = 8.0 Hz, 2H, CH_2COOH); EI-MS, *m/z* (rel. intensity, %): 244 ($M^{+\cdot}$, 19), 185 ([M – $CH_2CO_2H]^+$, 100), 165 ([M – $FCH_2CO_2H]^+$, 25); $C_{15}H_{13}FO_2$ (244.3).

3-(3,4-Difluorophenyl)-3-phenylpropanoic acid (43c). Synthesized from (3,4-difluorophenyl)-phenylpropenoic acid (**42c**). Yield 92 %; colorless crystalline solid; mp 105-106 °C; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.1-7.3 (m, 3H, Ph-*H*), 7.0-6.8 (m, 5H, Ph-*H*), 4.48 (t, *J* = 7.9 Hz, 1H, Ar_2CH), 3.02 (d, *J* = 7.9 Hz, 2H, CH_2COOH); EI-MS, *m/z* (rel. intensity, %): 262 ($M^{+\cdot}$, 20), 216 (([M – $CO_2H]^+$, 11), 203 (([M – $CH_2CO_2H]^+$, 100), 183 (([M – $FCH_2CO_2H]^+$, 34); $C_{15}H_{12}F_2O_2$ (262.3).

3-(1-Trityl-1*H*-imidazol-4-yl)propanoic acid (44). To a solution of **8** (5 mmol) in THF (50 mL) was added 8 mL of a 1 M solution of LiOH/aq, followed by stirring over night. Subsequently, 10 % HCl/aq was added under ice cooling until pH = 4-5, extracted with EtOAc and washed with saturated NaCl/aq. The organic phase was dried over Na_2SO_4 and the solvent was removed in *vacuo*. The crude product was recrystallized from EtOAc/THF. Yield 83 %; colorless solid; mp 185 °C (Lit.[25]: 188-190 °C); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.41 (d, 1H, *J* = 1.4 Hz, Im-2-*H*), 7.36 (m, 9H, Ph), 7.31 (m, 6H, Ph), 6.70 (s, 1H, Im-5-*H*), 2.82 (t, 2H, *J* = 7.4 Hz, Im-4-CH_2), 2.58 (t, 2H, *J* = 7.3 Hz, CH_2CO); $C_{25}H_{22}N_2O_2$ (382.4).

[(5-Methyl-1*H*-imidazol-4-yl)methylsulfanyl]acetic acid (45).[26] A solution of (5-methyl-1*H*-imidazol-4-yl)methanol (4 g, 21.7 mmol) and sulfanylacetic acid (1.51 mL, 21.7 mmol) in 50 mL acetic acid was refluxed for 24 h. After removing the solvent in *vacuo*, the residue was neutralised by sodium carbonate. The precipitate was filtered off and washed with water, dried and recrystallized from MeOH. Yield 82 %; colorless crystalline solid; mp 170 °C; ^{1}H-NMR (DMSO-d_6) δ (ppm): 14.49 (br s, 1H, COO*H*), 8.93 (s, 1H, Im-2-*H*), 3.89 (s, 2H, Im-4-CH_2S), 3.24 (s, 2H, CH_2COOH), 2.25 (s, 3H, CH_3); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 187 (MH^+); $C_7H_{10}N_2O_2S$ (186.2).

2. Experimental details of the trityl-protected intermediates 47a-52a, 55a-59a, 61a-77a

***N*^{1}-(3,3-Diphenylpropanoyl)-*N*^{2}-[2-(1-trityl-1*H*-imidazol-4-yl)ethyl]guanidine (47a).** Synthesized from 3,3-diphenylpropanoic acid and **23**. Yield 62 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.36-7.05 (m, 26H, Ph-*H* and Im-2-*H*), 6.59 (s, 1H, Im-5-*H*), 4.65 (t, *J* = 7.8 Hz, 1H, Ph_2CH), 3.84 (t, *J* = 6.1 Hz, 2H, CH_2NH), 3.05 (d, *J* = 7.7 Hz, 2H, CH_2CO), 2.71 (t, *J* = 6.0 Hz, 2H, Im-4-CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 604 (MH^+), 1207 ([2M + H]$^+$); $C_{40}H_{37}N_5O$ (603.8).

***N*^{1}-(3,3-Diphenylpropanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (48a).** Synthesized from 3,3-diphenylpropanoic acid and **16**. Yield 55 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$)

δ (ppm): 7.45-7.05 (m, 26 H, Ph-*H* and Im-2-*H*), 6.54 (s, 1H, Im-5-*H*), 4.65 (t, *J* = 7.8 Hz, 1H, Ph_2CH), 3.30 (t, *J* = 6.7 Hz, 2H, CH_2NH), 3.06 (d, *J* = 7.7 Hz, 2H, $COCH_2$), 2.53 (m, 2H, Im-4-CH_2), 1.82 (m, 2H, Im-4-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 618 (MH^+), 1235 ($[2M + H]^+$); $C_{41}H_{39}N_5O$ (617.8).

***N*^{1}-(2,2-Diphenylacetyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (49a).** Synthesized from 2,2-diphenylacetic acid and **16**. Yield 55 %; colorless foam-like solid; a few crystals were obtained from hexane and the structure was determined by x-ray analysis. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.39-7.01 (m, 26H, Ph-*H* and Im-2-*H*), 6.54 (s, 1H, Im-5-*H*), 4.98 (s, 1H, Ph_2CH), 3.24 (t, *J* = 6.7 Hz, 2H, CH_2NH), 2.54 (t, *J* = 6.0 Hz, 2H, Im-4-CH_2), 1.81 (m, 2H, Im-4-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 604 (MH^+), 1207 ($[2M + H]^+$); $C_{40}H_{37}N_5O$ (603.8).

***N*^{1}-[3,3-Bis(4-fluorophenyl)propanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (50a).** Synthesized from 3,3-bis(4-fluorophenyl)propanoic acid (**43a**) and **16**. Yield 61 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.40-6.80 (m, 24H, Ar-*H* and Im-2-*H*), 6.58 (s, 1H, Im-5-*H*), 4.68 (t, *J* = 8.0 Hz, 1H, Ar_2CH), 3.50 (m, 2H, CH_2NH), 3.22 (d, *J* = 8.0 Hz, 2H, $COCH_2$), 2.50 (m, 2H, Im-4-CH_2), 1.85 (m, 2H, Im-4-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 654 (MH^+); $C_{41}H_{37}F_2N_5O$ (653.8).

***N*^{1}-[3-(4-Fluorophenyl)-3-phenylpropanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)-propyl]guanidine (51a).** Synthesized from 3-(4-fluorophenyl)-3-phenylpropanoic acid (**43b**) and **16**. Yield 53 %; colorless foam like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.42-6.73 (m, 25H, Ar-*H* and Im-2-*H*), 6.54 (s, 1H, Im-5-*H*), 4.62 (t, *J* = 7.8 Hz, 1H, Ar_2CH), 3.33 (t, *J* = 6.7 Hz, 2H, CH_2NH), 3.00 (d, *J* = 7.8 Hz, 2H, CH_2CO), 2.53 (m, 2H, Im-4-CH_2), 1.82 (m, 2H, Im-4-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 636 (MH^+), 1273 ($[2M + H]^+$); $C_{41}H_{38}FN_5O$ (635.8).

***N*^{1}-[3-(3,4-Difluorophenyl)-3-phenylpropanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]-guanidine (52a).** Synthesized from 3-(3,4-difluorophenyl)-3-phenylpropanoic acid (**43c**) and **16**. Yield 55 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.40-6.76 (m, 24H, Ar-*H* and Im-2-*H*), 6.55 (s, 1H, Im-5-*H*), 4.63 (t, *J* = 7.7 Hz, 1H, Ar_2CH), 3.34 (t, *J* = 6.7 Hz, 2H, CH_2NH), 3.01 (d, *J* = 7.9 Hz, 2H, $COCH_2$), 2.54 (m, 2H, Im-CH_2), 1.84 (m, 2H, Im-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 654 (MH^+); $C_{41}H_{37}F_2N_5O$ (653.8).

***N*^{1}-[3-Phenyl-3-(pyridin-2-yl)propanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (55a).** Synthesized from 3-phenyl-3-(pyridin-2-yl)propanoic acid (**27a**) and **16**. Yield 50 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.52 (m, 1H, Pyr-6-*H*), 7.56-7.49 (m, 1H, Pyr-4-*H*), 7.40-7.00 (m, 23H, Pyr-3-*H*, -5-*H,* Im-2-*H* and 20 Ph-*H*), 6.56 (s, 1H, Im-5-*H*), 4.80 (ddq, *J* = 8.5 and 6.7 Hz, 1H, Ar_2CH), 3.60 (dd, *J* = 8.5 Hz, *J* = 15.7 Hz, 1H, CH_2CO), 3.45 (t, *J* = 6.8 Hz, 2H, $NHCH_2$), 3.16 (dd, *J* = 6.7 Hz, *J* = 15.7 Hz, 1H, CH_2CO), 2.53 (m, 2H, Im-4-CH_2), 1.86 (m, 2H, Im-4-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 619 (MH^+), 1237 ($[2M - H]^+$); $C_{40}H_{38}N_6O$ (618.8).

***N*^{1}-[3-(4-Fluorophenyl)-3-(pyridin-2-yl)propanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]-guanidine (56a).** Synthesized from 3-(4-fluorophenyl)-3-(pyridin-2-yl)propanoic acid (**27b**) and **16**. Yield 49 %; ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.50 (dm, 1H, Pyr-6-*H*), 7.56 (dt, *J* = 1.8 Hz, *J* = 7.7 Hz,1H, Pyr-4-*H*), 7.41-6.85 (m, 22H, Pyr-3-*H,* -5-*H*, Im-2-*H* and 19 Ph-*H*), 6.54 (s, 1H, Im-5-*H*), 4.73 (dd, *J* = 7.2 and 7.8 Hz, 1H, Ar_2CH), 3.30 (m, 3H, one H of CH_2CO and CH_2NH_2), 2.97 (dd, *J* = 7.2 Hz, *J* = 15.6 Hz, 1H, one H of CH_2CO), 2.54 (m, 2H, Im-4-CH_2), 1.84 (m, 2H, Im-4-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 637 (MH^+); $C_{40}H_{37}FN_6O$ (636.8).

***N*^{1}-[3-Phenyl-3-(thiazol-2-yl)propanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (57a).** Synthesized from 3-phenyl-3-(thiazol-2-yl)propanoic acid (**27c**) and **16**. Yield 46 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.67 (d, *J* = 3.4 Hz, 1H, Thiaz-4-*H*), 7.40-6.98 (m,

22H, Ph-*H*, Thia-5-*H,* Im-2-*H*), 6.55 (s, 1H, Im-5-*H*), 4.99 (ddq, *J* = 7.7 Hz, 1H, C*H*CH_2CO), 3.51 (dd, *J* = 7.7 Hz, *J* = 15.9 Hz, 1H, one H of CH_2CO), 3.40 (t, 2H, NHCH_2), 2.98 (dd, *J* = 7.7 Hz, *J* = 15.9 Hz, 1H, one H of CH_2CO), 2.54 (m, 2H, Im-4-CH_2), 1.84 (m, 2H, Im-4-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 625 (MH^+); $C_{38}H_{36}N_6OS$ (624.8).

***N*^{1}-[3-(3,4-Difluorophenyl)-3-(thiazol-2-yl)propanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]-guanidine (58a).** Synthesized from 3-(3,4-difluorophenyl)-3-(thiazol-2-yl)propanoic acid (**27d**) and **16**. Yield 52 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.95 (s br, H, N*H*), 7.64 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.40-6.98 (m, 20H, Ph-*H*, Thiaz-5-*H,* Im-2-*H*), 6.55 (s, 1H, Im-5-*H*), 4.96 (m, 1H, C*H*CH_2CO), 3.32 (m, 3H, CH_2NH and one H of COCH_2), 2.98 (dd, *J* = 7.7 Hz, *J* = 15.9 Hz, 1H, one H of CH_2CO), 2.54 (m, 2H, Im-4-CH_2), 1.84 (m, 2H, Im-4-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 243 ($[Ph_3C]^+$), 661 (MH^+), 1321 ($[2M + H]^+$), 1343 ($[2M + Na]^+$); $C_{38}H_{34}F_2N_6OS$ (660.8).

***N*^{1}-[3-(1-Benzyl-1*H*-imidazol-2-yl)-3-(3,4-difluorophenyl)propanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (59a).** Synthesized from 3-(1-benzyl-1*H*-imidazol-2-yl)-3-(3,4-difluorophenyl)propanoic acid and **16**. Yield 55 %; colorless foam-like solid; ^{1}H-NMR (CD_3OD) δ (ppm): 10.53 (s, 1H), 9.03 (s, 1H), 8.08 (s, 1H), 7.51-6.96 (m, 24H, Im-*H*, Ph-*H*), 5.30 (m, 2H, PhCH_2), 4.80 (m, 1H, C*H*CH_2CO), 3.78 (dd, *J* = 10.6 Hz, *J* = 16.8 Hz, 1H, one H of COCH_2), 3.36 (m, 2H, CH_2NH), 3.23 (dd, *J* = 5.2 Hz, *J* = 16.8 Hz, 1H, one H of COCH_2), 2.83 (t, *J* = 7.3 Hz, 2H, Im-4-CH_2), 2.00 (m, 2H, Im-4-CH_2CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 734 (MH^+); $C_{45}H_{41}F_2N_7O$ (733.9).

***N*^{1}-(3-Phenylbutyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propanoyl]guanidine (61a).** Synthesized from (1-trityl-1*H*-imidazol-4-yl)propanoic acid (**44**) and **17**. Yield 23 %; pale yellow foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.31-7.10 (m, 16H, CPh_3, Im-2-*H*), 6.58 (d, 1H, *J* = 1.0 Hz, Im-5-*H*), 3.05 (t, 2H, *J* = 7.1 Hz, Im-4-C$H_2$$CH_2$), 2.87 (m, 2H, NHC$H_2$), 2.75 (m, 3H, Im-4-$CH_2CH_2$, C*H*$CH_3$), 1.87 (m, 2H, NHC$H_2CH_2$), 1.23 (d, 3H, *J* = 7.0, CH_3); ES-MS (CH_2Cl_2/MeOH + NH_4OAc) *m/z* (%): 556 (MH^+, 100); $C_{36}H_{37}N_5O$ (555.7).

***N*^{1}-(2-Phenylpropanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (62a).** Synthesized from 2-phenylpropanoic acid and **16**. Yield 45 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.44 (d, 3H, J = 7.1 Hz, CH_3), 1.84 (m, 2H, Im-CH_2C$H_2$$CH_2$), 2.55 (t, 2H, J = 6.1 Hz, Im-C$H_2$$CH_2$$CH_2$), 3.30 (t, 2H, J = 6.7 Hz, Im-$CH_2$$CH_2CH_2$), 3.64 (m, 1H, COC*H*$CH_3$), 6.54 (s, 1H, Im-5-H), 7.08-7.34 (m, 21H, CPh_3, Ph, Im-2-H), 8.01 (s, 1H, NH); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* (%): 542 (MH^+, 100); $C_{35}H_{35}N_5O$ (541.7).

***N*^{1}-(3-Phenylbutanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (63a).** Synthesized from 3-phenylbutanoic acid and **16**. Yield 47 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.32 (d, 3H, *J* = 6.9 Hz, CH_3), 1.87 (m, 2H, Im-CH_2C$H_2$$CH_2$), 2.56 (m, 4H, Im-C$H_2$$CH_2$$CH_2$, $COCH_2$), 3.35 (m, 3H, Im-$CH_2$$CH_2CH_2$, $COCH_2$C*H*CH_3), 6.55 (s, 1H, Im-5-H), 7.07-7.37 (m, 21H, CPh_3, Ph, Im-2-H); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 556 (MH^+, 100); $C_{36}H_{37}N_5O$ (555.7).

***N*^{1}-[3-(Thiophen-2-yl)butanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (64a).** Synthesized from 3-(thiophen-2-yl)butanoic acid (**31**) and **16**. Yield 47 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.41-7.29 (m, 10H, Ph-*H)*, 7.52-7.05 (m, 7H, Ph-*H*, Im-2-*H* and Thio-5-*H*), 6.91-6.83 (m, 2H, Thio-*H*) 6.57 (s, 1H, Im-5-*H*), 3.67 (m, 1H, $COCH_2$C*H*), 3.58 (m, 2H, NHCH_2), 2.79 (dd, *J* = 6.6 Hz, *J* = 15.1 Hz, 1H, one H of CH_2CO), 2.61 (dd, *J* = 8.1 Hz, *J* = 15.1 Hz, 1H, one H of CH_2CO), 2.58 (m, 2H, Im-4-*C*H_2), 2.00 (m, 2H, Im-4-CH_2CH_2), 1.36 (d, *J* = 7.0 Hz, 3H, *C*H_3); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 562 (MH^+); $C_{34}H_{35}N_5OS$ (561.7).

***N*^{1}-[3-(Pyridin-2-yl)butanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (65a).** Synthesized from 3-(pyridin-2-yl)butanoic acid (**35a**) and **16**. Yield 52 %; colorless foam-like solid; ^{1}H-NMR

($CDCl_3$) δ (ppm): 8.57 (m, 1H, Pyr-6-*H*), 7.52 (m, 1H, Pyr-4-*H*), 7.63-7.00 (m, 18H, Pyr-3-*H*, -5-*H,* Im-2-*H* and Ph-*H*), 6.55 (s, 1H, Im-*H*-5), 3.62 (m, 1H, C*H*CH_2CO), 3.45 (m, 2H, CH_2NH), 3.00 (dd, *J* = 8.3 Hz, *J* = 16.6 Hz, 1H, one H of CH_2CO), 2.90 (dd, *J* = 6.2 Hz, *J* = 16.6 Hz, 1H, one H of CH_2CO), 2.83 (t, *J* = 7.6 Hz, 2H, Im-4-CH_2), 2.01 (m, 2H, Im-4-CH_2CH_2), 1.41 (d, *J* = 7.0 Hz, 3H, CH_3CH); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 557 (MH^+); $C_{35}H_{36}N_6O$ (556.7).

***N*^{1}-[3-(Thiazol-2-yl)butanoyl]-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (66a).** Synthesized from 3-(thiazol-2-yl)butanoic acid (**35b**) and **16**. Yield 55 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.65 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.41-7.05 (m, 17H, Ph-*H*, Thiaz-5-*H* and Im-2-*H*), 6.58 (s, 1H, Im-5-*H*), 3.85 (m, 1H, C*H*CH_2CO), 3.51 (t, *J* = 6.5 Hz, 2H, NHCH_2), 3.11 (dd, *J* = 7.3 Hz, *J* = 16.0 Hz, 1H, one H of COCH_2), 2.81 (dd, *J* = 6.9 Hz, *J* = 16.0 Hz, 1H, one H of COCH_2), 2.57 (m, 2H, Im-4-CH_2), 1.89 (m, 2H, Im-4-CH_2CH_2), 1.46 (d, *J* = 7.0 Hz, 3H, *C*H_3); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 563 (MH^+); $C_{33}H_{34}N_6OS$ (562.7).

***N*^{1}-Benzoyl-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (67a).** Synthesized from benzoic acid and **16**. Yield 52 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.91 (m, 2H, Im-CH_2C$H_2$$CH_2$), 2.61 (t, 2H, *J* = 5.9 Hz, Im-C$H_2$$CH_2$$CH_2$), 3.45 (t, 2H, *J* = 6.4 Hz, Im-$CH_2$$CH_2CH_2$), 6.56 (s, 1H, Im-5-H), 7.13-7.37 (m, 19H, CPh_3, Ph, Im-2-H), 8.17 (d, 2H, Ph); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* (%): 514 (MH^+, 100), 243 (Ph_3C^+, 50); $C_{33}H_{31}N_5O$ (513.6).

***N*^{1}-Phenylacetyl-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (68a).** Synthesized from 2-phenylacetic acid and **16**. Yield 47 %, colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.83 (m, 2H, Im-CH_2C$H_2$$CH_2$), 2.55 (t, 2H, *J* = 6.1 Hz, Im-C$H_2$$CH_2$$CH_2$), 3.32 (t, 2H, *J* = 6.7 Hz, Im-$CH_2$$CH_2CH_2$), 3.58 (s, 2H, COC$H_2$), 6.54 (s, 1H, Im-5-H), 7.09-7.38 (m, 21H, CPh_3, Ph, Im-2-H), 8.01 (s, 1H, NH); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 528 (MH^+, 100); $C_{34}H_{33}N_5O$ (527.7).

***N*^{1}-(3-Phenylpropanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (69a).** Synthesized from 3-phenylpropanoic acid and **16**. Yield 67 %, colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87 (m, 2H, Im-CH_2C$H_2$$CH_2$), 2.59 (m, 4H, Im-C$H_2$$CH_2$$CH_2$, COC$H_2$$CH_2$), 2.98 (t, 2H, *J* = 8.1 Hz, Im-$CH_2$$CH_2CH_2$), 3.56 (t, 2H, *J* = 6.7 Hz, COCH_2CH_2), 6.56 (s, 1H, Im-5-H), 7.11-7.35 (m, 21H, CPh_3, Ph, Im-2-H), 8.02 (s, 1H, NH); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 542 (MH^+, 100); $C_{35}H_{35}N_5O$ (541.7).

***N*^{1}-(4-Phenylbutanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (70a).** Synthesized from 4-phenylbutanoic acid and **16**. Yield 54 %, colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.87 (m, 2H, Im-CH_2C$H_2$$CH_2$), 1.97 (m, 2H, COC$H_2CH_2$$CH_2$), 2.38 (m, 2H, COC$H_2$$CH_2$$CH_2$), 2.56 (m, 2H, Im-C$H_2$$CH_2$$CH_2$), 2.65 (m, 2H, COC$H_2$$CH_2CH_2$), 3.39 (m, 2H, Im-$CH_2$$CH_2CH_2$), 6.55 (s, 1H, Im-5H), 7.06-7.40 (m, 21H, CPh_3, Ph, Im-2H), 8.01 (s, 1H, NH); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 556 (MH^+, 100); $C_{36}H_{37}N_5O$ (555.7).

***N*^{1}-(5-Phenylpentanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (71a).** Synthesized from 5-phenylpentanoic acid and **16**. Yield 45 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.66 (m, 4H, COCH_2CH_2C$H_2$$CH_2$), 1.87 (m, 2H, Im-$CH_2CH_2$$CH_2$), 2.29 (t, 2H, *J* = 7.2 Hz, COC$H_2$$CH_2$$CH_2$$CH_2$), 2.59 (m, 4H, Im-C$H_2$$CH_2$$CH_2$, COC$H_2$$CH_2$$CH_2CH_2$), 3.34 (t, 2H, *J* = 6.6 Hz, Im-$CH_2$$CH_2CH_2$), 6.54 (s, 1H, Im-5-H), 7.10-7.36 (m, 21H, CPh_3, Ph, Im-2-H); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 570 (MH^+, 100); $C_{37}H_{39}N_5O$ (569.7).

***N*^{1}-(2-Cyclohexylpropanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (72a).** Synthesized from 2-cyclohexylpropanoic acid (**37a**) and **16**. Yield 60 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.06 (d, 3H, *J* = 6.9 Hz, CH_3), 1.22 (m, 7H, cHex-CH_2, cHex-CH), 1.68 (m, 4H, cHex-CH_2), 1.88 (m, 2H, Im-CH_2C$H_2$$CH_2$), 2.08 (m, 1H, CH_3C*H*), 2.56 (t, 2H, *J* = 6.2 Hz, Im-C$H_2$$CH_2$$CH_2$), 3.33 (t, 2H, *J* = 6.8 Hz, Im-$CH_2$$CH_2CH_2$), 6.55 (s, 1H, Im-5-H), 7.12-7.34 (m, 16H,

CPh_3, Im-2-H); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 549 (MH^+, 100), 243 (Ph_3C^+, 30); $C_{35}H_{41}N_5O$ (547.7).

***N*^{1}-(3-Cyclohexylbutanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (73a).** Synthesized from 3-cyclohexylbutanoic acid (**37b**) and **16**. Yield 29 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (d, 3H, *J* = 6.8 Hz, CH_3), 1.00-1.19 (m, 6H, cHex-CH_2), 1.67 (m, 6H, cHex-CH_2), 1.89 (m, 3H, Im-$CH_2CH_2CH_2$, CH_3CH), 2.13 (dd, 1H, ^{2}J = 14.3 Hz, *J* = 9.4 Hz, C*H*H), 2.47 (dd, 1H, ^2J = 14.5 Hz, *J* = 4.7 Hz, CH*H*), 2.57 (t, 2H, ^3J=5.8 Hz, Im-$CH_2CH_2CH_2$), 3.44 (t, 2H, *J* = 6.6 Hz, Im-$CH_2CH_2CH_2$), 6.57 (s, 1H, Im-5-H), 7.11-7.34 (m, 16H, CPh_3, Im-2-H); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 562 (MH^+, 100); $C_{36}H_{43}N_5O$ (561.8).

***N*^{1}-Cyclohexylcarbonyl-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (74a).** Synthesized from cyclohexanecarboxylic acid and **16**. Yield 59 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.34 (m, 6H, cHex-CH_2), 1.74 (m, 2H, Im-$CH_2CH_2CH_2$), 1.89 (m, 4H, cHex-CH_2), 2.46 (t, 1H, *J* = 5.8 Hz, cHex-CH), 2.56 (t, 2H, *J* = 10.4 Hz, Im-$CH_2CH_2CH_2$), 3.45 (t, 2H, *J* = 6.5 Hz, Im-$CH_2CH_2CH_2$), 6.56 (s, 1H, Im-5-H), 7.12-7.35 (m, 16H, CPh_3, Im-2-H), 8.02 (s, 1H, NH); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 520 (MH^+, 100), 243 (Ph_3C^+); $C_{33}H_{37}N_5O$ (519.7).

***N*^{1}-Cyclohexylacetyl-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (75a).** Synthesized from cyclohexylacetic acid and **16**. Yield 66 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.94 (m, 2H, Im-$CH_2CH_2CH_2$), 1.21 (m, 4H, cHex-CH_2), 1.74 (m, 7H, cHex-CH_2, cHex-CH), 2.14 (d, 2H, *J* = 6.1 Hz, $COCH_2$), 2.56 (m, 2H, Im-$CH_2CH_2CH_2$), 3.34 (t, 2H, *J* = 6.7 Hz, Im-$CH_2CH_2CH_2$), 6.55 (s, 1H, Im-5-H), 7.11-7.34 (m, 16H, CPh_3, Im-2-H); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 534 (MH^+, 100); $C_{34}H_{39}N_5O$ (533.7).

***N*^{1}-(3-Cyclohexylpropanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (76a).** Synthesized from 3-cyclohexylpropanoic acid and **16**. Yield 30 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.26 (m, 5H, cHex-CH_2, cHex-CH), 1.55 (m, 7H, cHex-CH_2, $COCH_2CH_2$), 1.88 (m, 2H, Im-$CH_2CH_2CH_2$), 2.35 (t, 2H, *J* = 8.2 Hz, $COCH_2CH_2$), 2.57 (t, 2H, *J* = 6.0 Hz, $ImCH_2CH_2CH_2$), 3.40 (t, 2H, *J* = 6.6 Hz, Im-$CH_2CH_2CH_2$), 3.72 (m, 1H, cHex-CH), 6.57 (s, 1H, Im-5-H), 7.11-7.34 (m, 16H, CPh_3 , Im-2-H), 7.61 (s, 1H, NH); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 548 (MH^+, 100), 243 (Ph_3C^+, 20); $C_{35}H_{41}N_5O$ (547.7).

***N*^{1}-(4-Cyclohexylbutanoyl)-*N*^{2}-[3-(1-trityl-1*H*-imidazol-4-yl)propyl]guanidine (77a).** Synthesized from 4-cyclohexylbutanoic acid and **16**. Yield 57 %; colorless foam-like solid; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (m, 4H, $COCH_2CH_2CH_2$), 1.18 (m, 7H, cHex-CH_2, cHex-CH), 1.62 (m, 4H, cHex-CH_2), 1.86 (m, 2H, Im-$CH_2CH_2CH_2$), 2.23 (m, 2H, $COCH_2CH_2CH_2$), 2.57 (t, 2H, *J* = 6.1 Hz, Im-$CH_2CH_2CH_2$), 3.34 (t, 2H, *J* = 6.7 Hz, Im-$CH_2CH_2CH_2$), 6.56 (s, 1H, Im-5-H), 7.12-7.34 (m, 16H, Im-2-H, CPh_3); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): *m/z* 562 (MH^+, 100); $C_{36}H_{45}N_5O$ (561.7).

3. Experimental details of 61 and of the N^1-acyl-N^2-[1*H*-imidazol-4-yl)alkyl]guanidines 47-52, 55, 57-60, 62, 65-77

N^1-(3,3-Diphenylpropanoyl)-N^2-[2-(1*H*-imidazol-4-yl)ethyl]guanidine (47). Yield 92% (deprotection of compound **47a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.81 (s, 1H, Im-2-*H*), 7.35 (s, 1H, Im-*H*-5), 7.32-7.12 (m, 10H, Ph-*H*), 4.57 (t, *J* = 8.0 Hz, 1H, C*H*CH_2CO), 3.58 (t, *J* = 6.7 Hz, 2H, C*H*$_2$NH), 3.31 (m, 1H, N*H*), 3.25 (d, *J* = 8.0 Hz, 2H, COC*H*$_2$), 3.03 (t, *J* = 6.7 Hz, 2H, Im-4-C*H*$_2$); ^{13}C-NMR (CD_3OD) δ (ppm): 175.5 (quart, *C*O), 162.6 (quart, *C*=NH), 144.4 (quart, Ph-*C*-1), 135.2 (+, Im-*C*-2), 131.4 (quart, Im-*C*-4), 129.6, 128.8, 127.8 (+, Ph-*C*), 118.1 (+, Im-*C*-5), 48.0 (+, *C*HCH$_2$CO), 43.7 (-, CO*C*H$_2$), 41.0 (-, *C*H$_2$NH$_2$), 28.3 (-, Im-4-*C*H$_2$); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 361 (MH^+); HRMS [EI-MS]: *m/z*, calculated for ($C_{21}H_{23}N_5O$) 361.1903, found: 361.1901; $C_{21}H_{23}N_5O$ ·2 TFA (589.5).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(1*H*-imidazol-4-yl)propyl]guanidine (48). Yield 92% (deprotection of compound **48a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 7.40 (s, 1H, Im-2-*H*), 7.10-7.35 (m, 10H, Ph-*H*), 4.65 (t, *J* = 7.7 Hz, 1H, Ph$_2$C*H*), 3.26 (t, *J* = 6.5 Hz, 2H, C*H*$_2$NH), 3.06 (d, *J* = 7.7 Hz, 2H, C*H*$_2$CO), 2.59 (m, 2H, Im-4-C*H*$_2$), 1.82 (m, 2H, Im-4-CH$_2$C*H*$_2$); ^{13}C-NMR (CD_3OD) □ (ppm): 183.5 (quart, *C*O), 161.7 (quart, *C*=NH), 145.0 (quart, Ph-*C*-1), 134.6 (quart, Im-*C*-4), 134.2 (+, Im-*C*-2), 128.4, 128.0, 126.0 (+, Ph-*C*), 47.4 (+, Ph$_2$*C*H), 46.5 (-, CO*C*H$_2$), 40.0 (-, NH*C*H$_2$), 29.1 (-, Im-4-CH$_2$*C*H$_2$), 22.9 (-, Im-4-*C*H$_2$); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 376.2 (MH^+); HRMS [FAB (CH_2Cl_2/MeOH)]: *m/z*, calculated for $[C_{21}H_{23}N_5O + H]^+$ 376.2132, found: 376.2137; $C_{22}H_{25}N_5O$ · 2 TFA (603.5).

N^1-Diphenylacetyl-N^2-[3-(1*H*-imidazol-4-yl)propyl]guanidine (49). Yield 92% (deprotection of compound **49a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.74 (s, 1H, Im-2-*H*), 7.86 (s, 1H, Im-5-*H*), 7.40-7.10 (m, 10H, Ph-*H*), 5.27 (s, 1H, Ph$_2$C*H*), 3.35 (t, *J* = 6.7 Hz, 2H, C*H*$_2$NH), 2.80 (t, *J* = 7.6 Hz, 2H, Im-4-C*H*$_2$), 2.01 (m, 2H, Im-4-CH$_2$C*H*$_2$); ^{13}C-NMR (CD_3OD) δ (ppm): 176.1 (quart, *C*O), 155.4 (quart, *C*=NH), 139.0 (quart, Ph-*C*-1), 134.8 (quart, Im-*C*-4), 134.2 (+, Im-*C*-2), 129.9, 129.7, 128.7 (+, Ph-*C*), 117.1 (+, Im-*C*-5), 59.4 (+, Ph$_2$*C*H), 41.6 (-, *C*H$_2$NH$_2$), 27.8 (-, Im-4-CH$_2$*C*H$_2$) 22.5 (-, Im-4-*C*H$_2$); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 362 (MH^+); HRMS [EI-MS]: *m/z*, calculated for [$C_{21}H_{23}N_5O$] 361.1903, found: 361.1903; $C_{21}H_{23}N_5O$ · 2 TFA (589.5).

N^1-[3,3-Bis(4-fluorophenyl)propanoyl]-N^2-[3-(1*H*-imidazol-4-yl)propyl]guanidine (50). Yield 85% (deprotection of compound **50a**); colorless sticky oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.42 (s, 1H, Im-2-*H*), 7.12-7.22 (m, 4H, Ar-*H*), 6.86-6.97 (m, 4H, Ar-*H*), 6.73 (s, 1H, Im-5-*H*), 4.62 (t, *J* = 7.9 Hz, 1H, Ar$_2$C*H*), 3.28 (t, *J* = 6.7 Hz, 2H, NHC*H*$_2$), 2.98 (d, *J* = 7.9 Hz, 2H, C*H*$_2$CO), 2.58 (m, 2H, Im-4-C*H*$_2$), 1.83 (m, 2H, Im-4-CH$_2$C*H*$_2$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 183.2 (quart, *C*O), 161.2 (quart, d, *J* = 244.2 Hz, 2C, *C*F), 161.9 (quart, *C*=NH), 140.0 (quart, Ar-*C*-1), 134.6 (quart, Im-*C*-4), 134.1 (+, Im-*C*-2), 129.1 (+, d, *J* = 8.0 Hz, 4C, Ar-*C*-2,6), 117.1 (+, Im-*C*-5), 115.2 (+, d, *J* = 21.1 Hz, 4C, Ar-*C*-3,5), 46.8 (-, *C*H$_2$CO), 45.9 (+, Ar$_2$*C*H), 39.9 (-, *C*H$_2$NH), 29.3 (-, Im-4-CH$_2$*C*H$_2$), 22.9 (-, Im-4-*C*H$_2$); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 412 (MH^+); HRMS [EI-MS]: *m/z*, calculated for ($C_{22}H_{23}F_2N_5O$) 411.1871, found: 411.1866; $C_{22}H_{23}F_2N_5O$ · 2 TFA (639.5).

N^1-[3-(4-Fluorophenyl)-3-phenylpropanoyl]-N^2-[3-(1*H*-imidazol-4-yl)propyl]guanidine (51). Yield 91% (deprotection of compound **51a**); colorless sticky oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.41 (s, 1H, Im-2-*H*), 7.10-7.30 (m, 7H, Ar-*H*), 6.87-6.97 (m, 2H, Ar-*H*), 6.72 (s, 1H, Im-5-*H*), 4.64 (t, *J* = 7.9 Hz, 1H, Ar$_2$C*H*), 3.28 (t, *J* = 6.5 Hz, 2H, C*H*$_2$NH), 3.03 (d, *J* = 7.9 Hz, 2H, C*H*$_2$CO), 2.60 (m, 2H, Im-4-C*H*$_2$), 1.83 (m, 2H, Im-4-CH$_2$C*H*$_2$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 183.3 (quart, *C*O), 161.2 (quart, d, *J* = 243.8 Hz, Ar-*C*F), 161.8 (quart, *C*=NH), 144.8 (quart, Ph-*C*-1), 140.6 (quart, d, *J* = 3.3 Hz, Ar-*C*-1), 134.8 (quart, Im-*C*-4), 134.1 (+, Im-*C*-2), 129.2 (+, d, *J* = 8.0 Hz, 2C, Ar-*C*-2,6), 128.4 (+, 2C, Ph-*C*-2,6), 127.8 (+, 2C, Ph-*C*-3,5), 126.1 (+, Ph-*C*-4), 118.0 (+, Im-*C*-5), 115.1 (+, d, *J* = 21.1 Hz, 2C, Ar-*C*-

3,5), 46.6 (-, Ar_2CH), 45.6 (+, $COCH_2$), 39.9 (-, $NHCH_2$), 29.3 (-, Im-4-CH_2CH_2), 22.9 (-, Im-4-CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 394.3 (MH^+); HRMS [EI-MS]: *m/z*, calculated for [$C_{22}H_{24}FN_5O$] 393.1965, found: 393.1964; $C_{22}H_{24}FN_5O \cdot 2$ TFA (621.5).

N^1-[3-(3,4-Difluorophenyl)-3-phenylpropanoyl]-N^2-[3-(1*H*-imidazol-4-yl)propyl]guanidine (52). Yield 91% (deprotection of compound **52a**); colorless sticky oil; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.50 (s, 1H, Im-2-*H*), 7.11-7.27 (m, 3H, Ar-*H*), 6.78-7.06 (m, 5H, Ar-*H*), 6.76 (s, 1H, Im-5-*H*), 4.64 (t, *J* = 7.9 *Hz*, 1H, Ar_2CH), 3.33 (t, *J* = 6.7 Hz, 2H, $NHCH_2$), 3.03 (d, *J* = 7.9 Hz, 2H, CH_2CO), 2.65 (m, 2H, Im-4-CH_2), 1.86 (m, 2H, Im-4-CH_2CH_2); ^{13}C-NMR ($CDCl_3$) δ (ppm): 183.1 (quart, *C*O), 162.9 (quart, d, *J* = 246.8 Hz, 3-*C*F), 161.6 (quart, d, *J* = 245.3 Hz, 4-*C*F), 161.8 (quart, *C*=NH), 144.6 (quart, Ph-*C*-1), 140.0 (quart, d, *J* = 3.3 Hz, Ar-*C*-1), 139.8 (quart, Im-*C*-4), 134.1 (+, Im-*C*-2), 129.9 (+, Ph-*C*-4), 129.3, 129.4 (+, 2C, Ph-*C*-3,5), 123.5 (+, d, *J* = 3.3 Hz, Ar-*C*-6), 118.1 (+, Im-*C*-5), 115.4, 115.1 (+, 2C, Ph-C-2,6), 114.7 (+, d, *J* = 21.3 Hz, Ar-*C*-5), 113.0 (+, d, *J* = 21.1 Hz, Ar-*C*-2), 46.6 (+, Ar_2CHCO), 45.9 (-, $COCH_2$), 39.9 (-, $NHCH_2$), 29.3 (-, Im-4-CH_2CH_2), 22.9 (-, Im-4-CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 412 (MH^+); HRMS [EI-MS]: *m/z*, calculated for [$C_{22}H_{23}F_2N_5O$] 411.1871, found: 411.1866; $C_{22}H_{23}F_2N_5O \cdot 2$ TFA (639.5).

N^1-[3-(1*H*-Imidazol-4-yl)propyl]-N^2-[3-phenyl-3-(pyridin-2-yl)propanoyl]guanidine (55). Yield 85% (deprotection of compound **55a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.80 (m, 1H, Pyr-6-*H*), 8.57 (m, 1H, Pyr-4-*H*), 7.99 (m, 1H, Pyr-5-*H*), 7.58 (d, *J* = 8.3 Hz, 1H, Pyr-3-*H*), 7.46 (m, 1H, Ph-*H*), 7.21-7.39 (m, 6H, Ph-*H and* Im-2-*H*), 4.84 (t overlap with H_2O, 1H, Ar_2CH), 3.61 (dd, *J* = 8.8 Hz *J* = 16.7 Hz, 1H, CH_2CO), 3.40-3.31 (m, 3H, CH_2CO and $NHCH_2$), 2.80 (t, *J* = 7.8 Hz, 2H, Im-4-CH_2), 1.99 (m, 2H, Im-4-CH_2CH_2); ^{13}C-NMR (CD_3OD) δ (ppm): 175.1 (quart, *C*O), 161.7 (quart, Py-*C*-2), 155.1 (quart, *C*=NH), 147.4 (+, Pyr-*C*-6), 142.0 (quart, Ph-*C*-1), 141.8 (+, Im-*C*-2), 134.9 (+, Pyr-*C*-4), 134.5 (quart, Im-*C*-4), 130.1, 129.0, 128.6 (+, Ph-*C*), 125.6 (+, Pyr-*C*-3), 124.4 (+, Pyr-*C*-5), 117.1 (+, Im-*C*-5), 48.1 (+, $COCH_2CH$), 42.2 (-, $COCH_2$), 41.5 (-, $NHCH_2$), 27.8 (-, Im-4-CH_2CH_2), 22.5 (-, Im-4-CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 377 (MH^+) ; HRMS [EI-MS]: *m/z*, calculated for ($C_{21}H_{24}N_6O$) 376.2012, found: 376.2002; $C_{21}H_{24}N_6O \cdot 3$ TFA (718.5);

N^1-[3-(1*H*-Imidazol-4-yl)propyl]-N^2-[3-phenyl-3-(thiazol-2-yl)propanoyl]guanidine (57). Yield 79% (deprotection of compound **57a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.81 (s, 1H, Im-*H*-2), 7.70 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.49 (d, *J* = 3.3 Hz, 1H, Thiaz-5-*H*), 7.35-7.15 (m, 6H, Ph-*H* and Im-5-*H*), 5.04 (t, *J* = 7.7 Hz, 1H, $COCH_2CH$), 3.59 (dd, *J* = 8.2 Hz, *J* = 16.5 Hz, 1H, one of $COCH_2$), 3.38 (m, 3H, CH_2NH and one of $COCH_2$), 2.84 (t, *J* = 7.7 Hz, Im-CH_2), 2.00 (m, 2H, Im-CH_2CH_2); ^{13}C-NMR (CD_3OD) δ (ppm): 174.8 (quart, *C*O), 174.4 (quart, Thiaz-*C*-2), 155.5 (quart, *C*=NH), 142.7 (+, Thiaz-*C*-4), 142.2 (quart, Ph-*C*-1), 134.8 (+, Im-*C*-2), 134.2 (quart, Im-*C*-4), 130.0, 129.8, 129.3, 128.9 (+, Ph-*C*), 121.2 (+, Thiaz-*C*-5), 117.0 (+, Im-*C*-5), 45.2 (+, $CHCH_2CO$), 43.4 (-, CH_2CO), 41.5 (-, CH_2NH), 27.9 (-, $ImCH_2CH_2$), 22.5 (-, Im-CH_2); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 383 (MH^+); HRMS [EI-MS]: *m/z*, calculated for ($C_{19}H_{22}N_6OS$) 382.1576, found 382.1576; $C_{19}H_{22}N_6OS \cdot 2$ TFA (610.5).

N^1-[3-(3,4-Difluorophenyl)-3-(thiazol-2-yl)propanoyl]-N^2-[3-(1*H*-imidazol-4-yl)-propyl]-guanidine (58). Yield 86% (deprotection of compound **58a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.80 (s, 1H, Im-2-*H*), 7.73 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.48 (d, *J* = 3.3 Hz, 1H, Thiaz-5-*H*), 7.35 (s, 1H, Im-5-*H*), 7.35-7.15 (m, 3H, ArC), 5.02 (ddq, *J* = 8.2 and 6.6 Hz, 1H, $CHCH_2CO$), 3.59 (dd, *J* = 8.2 Hz, *J* = 16.5 Hz, 1H, one of CH_2CO), 3.38 (t, *J* = 6.8 Hz, CH_2NH), 3.27 (dd, *J* = 6.6 Hz, *J* = 16.5 Hz, 1H, one of $COCH_2$), 2.84 (t, *J* = 7.7 Hz, Im-4-CH_2), 2.03 (m, Im-4-CH_2CH_2); ^{13}C-NMR (CD_3OD) δ (ppm): 174.5 (quart, Thiaz-*C*-2), 173.1 (quart, *C*O), 155.1 (quart, *C*=NH), 151.3 (quart, dd, *J* = 12.5 Hz, *J* = 247.6 Hz, CF), 150.8 (quart, dd, *J* = 12.6 Hz, *J* = 247.1 Hz, CF), 143.1 (+, Thiaz-*C*-4), 139.6 (quart, Ar-*C*-1), 134.8 (+, Im-*C*-2), 134.2 (quart, Im-*C*-4), 125.7 (+, Ar-*C*-6), 121.3 (+, Thiaz-*C*-5), 118.7 (+, d, *J* = 17.2 Hz, Ar-*C*-5), 118.2 (+, d, *J* = 17.2, Hz, Ar-*C*-2), 117.1 (+, Im-*C*-5), 44.8 (+,

*C*HCH$_2$CO), 43.3 (-, *C*H$_2$CO), 41.5 (-, *C*H$_2$NH), 27.9 (-, Im-4-CH$_2$*C*H$_2$), 22.5 (-, Im-4-*C*H$_2$); ES-MS (CH$_2$Cl$_2$/MeOH + 10 mM NH$_4$OAc): 419 (MH$^+$); HRMS [EI-MS]: *m/z*, calculated for ($C_{19}H_{20}F_2N_6OS$) 418.1387, found 418.1387; $C_{19}H_{20}F_2N_6OS \cdot 2$ TFA (646.5).

***N*^{1}-[3-(1-Benzyl-1*H*-imidazol-2-yl)-3-(3,4-difluorophenyl)propanoyl]-*N*^{2}-[3-(1*H*-imidazol-4-yl)-propyl]guanidine (59).** Yield 87% (deprotection of compound **59a**); colorless sticky oil; ^{1}H-NMR (CD$_3$OD) δ (ppm): 8.79 (s, 1H, Im-2-H), 7.65 (dd, *J* = 1.9 Hz, *J* = 5.8 Hz, Benzyl-Im-4-H and -5-H), 7.35 (s, 1H, Im-5-H), 7.33-7.24 (m, 3H, Ar-H), 7.20-7.00 (m, 4H, Ph-H), 6.90 (m, 1H, Ph-H), 5.51 (s, 2H, PhCH$_2$), 5.13 (t overlap with H$_2$O, 1H, CHCH$_2$CO), 3.62 (AMX, *J* = 9.6 Hz, *J* = 17.6 Hz, CH$_2$CO), 3.45-3.32 (AMX and m overlap, 3H, CH$_2$CO and CH$_2$NH), 2.83 (t, J = 7.8 Hz, 2H, Im-4-CH$_2$), 2.03 (m, 2H, Im-4-CH$_2$CH$_2$); ^{13}C-NMR (CD$_3$OD) δ (ppm): 173.5 (quart, CO), 163.0 (quart, C=NH), 154.9 (quart, C=NH), (quart, Benzyl-Im-C-2), 151.5 (quart, dd, *J* = 12.9 Hz, *J* = 248.9 Hz, CF), 151.3 (quart, dd, *J* = 12.6 Hz, *J* = 248.9 Hz, CF), 148.1 (quart, Benzyl-Im-C-2), 135.1 (quart, Im-C-4), 134.9 (+, Im-C-2), 134.4 (quart, Ar-C-1), 134.3 (quart, Ph-C-1), 130.2, 129.9, 128.6 (+, Ph-C), 125.5 (+, Ar-C-6), 124.8 (+, Benzyl-Im-C-4), 120.6 (+, Benzyl-Im-C-5), 119.2 (+, d, J = 17.7 Hz, Ar-C-5), 118.4 (+, d, J = 18.7 Hz, Ar-C-2), 117.1 (+, Im-C-5), 52.4 (-, PhCH$_2$), 41.6 (-, COCH$_2$), 41.5 (-, NHCH$_2$), 37.6 (+, CHCH$_2$CO), 27.9 (-, Im-4-CH$_2$CH$_2$), 22.4 (-, Im-4-CH$_2$); ES-MS (CH$_2$Cl$_2$/MeOH + 10 mM NH$_4$OAc): 419 (MH$^+$); HRMS (EI-MS): m/z calculated for [$C_{26}H_{27}F_2N_7O$], 491.2245, found 491.2234; $C_{26}H_{27}F_2N_7O \cdot 3$ TFA (833.6).

***N*^{1}-[3-(3,4-Difluorophenyl)-3-(1*H*-imidazol-2-yl)propanoyl]-*N*^{2}-[3-(1*H*-imidazol-4-yl)-propyl]guanidine (60).** Synthesized from **59** by hydrogenation at 7-10 bar over 10% Pd-C catalyst in tetrahydrofuran (addition of 2 equivalents of HCl) overnight. Yield 88%; colorless sticky oil; ^{1}H-NMR (CD$_3$OD) δ (ppm): 8.79 (s, 1H, 1*H*-Im-2-*H*), 7.94 (s, 2H, 2*H*-Im-3-*H* and -4-*H*), 7.47 (s, 1H, 1*H*-Im-5-*H*), 7.41-7.10 (m, 4H, Ar-*H* and N*H*), 5.03 (t overlap with H$_2$O, 1H, C*H*CH$_2$CO), 3.61 (dd, *J* = 8.2 Hz, *J* = 17.2 Hz, C*H*$_2$CO), 3.44 (dd, *J* = 6.9 Hz, *J* = 17.2 Hz, COC*H*$_2$), 3.30 (m, 2H, C*H*$_2$NH), 2.81 (t, *J* = 7.8 Hz, 2H, 1*H*-Im-4-C*H*$_2$), 2.01 (m, 2H, 1*H*-Im-4-CH$_2$C*H*$_2$). ^{13}C-NMR (CDCl$_3$) δ (ppm): 173.4 (quart, *C*O), 155.0 (quart, C=NH), 151.8 (quart, dd, *J* = 12.5 Hz, *J* = 249.0 Hz, CF), 151.4 (quart, dd, *J* = 12.6 Hz, *J* = 248.9 Hz, CF), 148.8 (quart, 2*H*-Im-*C*-2), 135.5 (quart, Ar-*C*-1), 134.9 (+, 1*H*-Im-*C*-2), 134.2 (quart, 1*H*-Im-*C*-4), 125.6 (+, Ar-*C*-6), 120.6 (+, 2*H*-Im-*C*-5), 120.4 (+, 2*H*-Im-*C*-4), 119.4 (+, d, *J* = 17.7 Hz, Ar-C-5), 118.3 (+, d, *J* = 18.1 Hz, Ar-C-2), 117.1 (+, 1*H*-Im-*C*-5), 41.6 (-, *C*H$_2$CO), 40.4 (-, *C*H$_2$NH), 39.1 (+, *C*HCH$_2$CO), 27.8 (-, 1*H*-Im-4-CH$_2$*C*H$_2$), 22.5 (-, 1*H*-Im-4-*C*H$_2$); ES-MS (CH$_2$Cl$_2$/MeOH + 10 mM NH$_4$OAc): 402 (MH$^+$); HRMS: FAB-MS: *m/z* for ([$C_{19}H_{21}F_2N_7O$ + H]$^+$) calcd. 402.1854, found 402.1842; $C_{19}H_{21}F_2N_7O \cdot 3$ TFA (743.5).

***N*^{1}-[3-(1*H*-Imidazol-4-yl)propanoyl]-*N*^{2}-(3-phenylbutyl)guanidine (61).** Yield 84 % (deprotection of compound **61a**); colorless sticky oil; ^{1}H-NMR (CD$_3$OD) δ (ppm): 8.78 (d, 1H, *J* = 1.3 Hz, Im-2-*H*), 7.36 (s, 1H, Im-5-*H*), 7.23 (m, 5H, Ph), 3.17 (t, 2H, *J* = 7.1 Hz, Im-4-C*H*$_2$CH$_2$), 3.06 (t, 2H, *J* = 7.1 Hz, NHC*H*$_2$), 2.90 (t, 2H, *J* = 7.0 Hz, Im-4-CH$_2$C*H*$_2$), 2.82 (dd, 1H, *J* = 7.2 Hz, J=14.5 Hz, NH-CH$_2$CH$_2$C*H*CH$_3$), 1.96 (q, 2H, *J* = 7.3 Hz, NH-CH$_2$C*H*$_2$) 1.28 (d, 3H, *J* = 7.0, C*H*$_3$); ^{13}C-NMR (CD$_3$OD) δ (ppm): 175.68 (quart, *C*O), 155.30 (quart, *C*=NH), 147.30 (quart. Ph-*C*-1), 134.99 (+, Im-*C*-2), 134.17 (quart, Im-*C*-4), 127.90, 128.39, 129.96 (+, arom. *C*H), 117.68 (+, Im-*C*-5), 41.48 (-, Im-4-CH$_2$*C*H$_2$), 39.10 (+, NH-CH$_2$CH$_2$*C*H), 37.19 (-, NH-*C*H$_2$CH$_2$), 36.30 (-, NH-CH$_2$*C*H$_2$), 23.34 (+, *C*H$_3$), 20.13 (-, Im-4-*C*H$_2$); HRMS: HRMS: EI-MS: *m/z* for ($C_{17}H_{23}N_5O$) calcd. 313.1903, found 313.1902; $C_{17}H_{23}N_5O \cdot 2$ TFA (541.4).

***N*^{1}-[3-(1*H*-Imidazol-4-yl)propyl]-*N*^{2}-(2-phenylpropanoyl)guanidine (62).** Yield 33 % (deprotection of compound **62a**); colorless sticky oil; ^{1}H-NMR (CD$_3$OD) δ (ppm): 8.76 (d, 1H, *J* = 1.2 Hz, Im-2-*H*), 7.32 (m, 5H, Ph, Im-5-*H*), 3.90 (q, 1H, *J* = 6.8 Hz, COC*H*CH$_3$), 3.34 (t, 2H, *J* = 7.0 Hz, Im-4-CH$_2$C*H*$_2$), 2.80 (m, 2H, Im-4-CH$_2$CH$_2$CH$_2$); ^{13}C-NMR (CD$_3$OD) δ (ppm): 178.24 (quart, *C*O), 155.53 (quart, *C*=NH), 140.88 (quart. Ph-*C*-1), 134.91 (+, Im-*C*-2), 134.31 (quart, Im-*C*-4), 130.03,

129.73, 128.84 (+, arom. *C*H), 117.13 (+, Im-*C*-5), 48.50 (+, COC*H*), 41.61 (-, Im-4--CH_2CH_2CH), 27.91 (-, Im-4-CH_2CH_2), 22.55 (-, Im-4-CH_2CH_2), 18.65 (+, CH_3); HRMS: EI-MS: *m/z* for ($C_{16}H_{21}N_5O$) calcd. 299.1746, found 299.1745; $C_{16}H_{21}N_5O \cdot 2$ TFA (527.4).

***N*^{1}-[3-(1*H*-Imidazol-4-yl)propyl]-*N*^{2}-[3-(pyridin-2-yl)butanoyl]guanidine (65).** Yield 89% (deprotection of compound **65a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.79 (s, 1H, Im-2-*H*), 8.57 (d, *J* = 8.3 Hz, 1H, Pyr-6-*H*), 8.09 (dt, *J* = 1.7 Hz, *J* = 7.8 Hz, 1H, Pyr-4-*H*), 7.67 (d, *J* = 8.0 Hz, 1H, Pyr-3-*H*), 7.53 (ddd, *J* = 1.0 Hz, *J* = 5.3 Hz, *J* = 6.4 Hz, 1H, Pyr-5-*H*), 7.53 (s, 1H, Im-5-*H*), 3.60 (m, 1H, Ar_2CH), 3.35 (m, 2H, CH_2NH), 3.09 (dd, *J* = 8.3 Hz, *J* = 16.6 Hz, 1H, CH_2CO), 2.92 (dd, *J* = 6.2 Hz, *J* = 16.6 Hz, 1H, CH_2CO), 2.82 (t, *J* = 7.6 Hz, 2H, Im-4-CH_2), 2.01 (m, 2H, Im-4-CH_2CH_2), 1.40 (d, *J* = 7.0 Hz, 3H, CH_3CH); ^{13}C-NMR (CD_3OD) δ (ppm): 175.4 (quart, *C*O), 163.7 (quart, Py-*C*-2), 155.2 (quart, *C*=NH), 146.7 (+, Pyr-*C*-6), 142.5 (+, Pyr-*C*-4), 134.9 (+, Im-*C*-2), 134.3 (+, Im-*C*-4), 125.4 (+, Pyr-*C*-3), 124.8 (+, Pyr-*C*-5), 117.1 (+, Im-*C*-5), 43.4 (-, $COCH_2CH$), 41.5 (-, CH_2NH), 37.4 (+, $COCH_2CH$), 27.9 (-, Im-4-CH_2CH_2), 22.5 (-, Im-4-CH_2), 20.7 (+, CH_3); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 315 (MH^+); HRMS: EI-MS: *m/z* for ($C_{16}H_{22}N_6O$) calcd. 314.1855, found 314.1863; $C_{16}H_{22}N_6O \cdot 3$ TFA (656.5).

***N*^{1}-[3-(1*H*-Imidazol-4-yl)propyl]-*N*^{2}-[3-(thiazol-2-yl)butanoyl]guanidine (66).** Yield 84% (deprotection of compound **66a**) colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.84 (s, 1H, Im-2-*H*), 7.70 (d, *J* = 3.3 Hz, 1H, Thiaz-4-*H*), 7.49 (d, *J* = 3.3 Hz, 1H, Thiaz-5-*H*), 7.28 (s, 1H, Im-*H*-5), 3.90 (m, 1H, $CHCH_2CO$),), 3.38 (m, 2H, CH_2NH), 3.12 (dd, *J* = 8.2 Hz, *J* = 16.5 Hz, 1H, one of $COCH_2$), 2.92 (m, 3H, Im-4-CH_2 and one of $COCH_2$), 2.00 (m, 2H, Im-4-CH_2CH_2), 1.42 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C-NMR (CD_3OD) δ (ppm): 176.4 (quart, *C*O), 175.1 (quart, Thiaz-*C*-2), 155.2 (quart, *C*=NH), 142.7 (+, Thiaz-*C*-4), 134.9 (+, Im-*C*-2), 134.3 (quart, Im-*C*-4), 120.2 (+, Thiaz-*C*-5), 117.1 (+, Im-*C*-5), 44.3 (-, $CHCH_2CO$), 41.6 (-, CH_2NH), 35.1 (+, $CHCH_2CO$), 27.9 (-, Im-4-CH_2CH_2), 22.5 (-, Im-4-CH_2), 21.7 (+, CH_3); ES-MS (CH_2Cl_2/MeOH + 10 mM NH_4OAc): 321.5 (MH^+); HRMS: FAB-MS: *m/z* for ($[C_{14}H_{20}N_6OS + H]^+$) calcd. 321.1498, found 321.1508; $C_{14}H_{20}N_6OS \cdot 2$ TFA (548.5).

***N*^{1}-Benzoyl-*N*^{2}-[3-(1*H*-imidazol-4-yl)propyl]guanidine (67).** Yield 19 % (deprotection of compound **67a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.81 (d, 1H, *J* = 1.3 Hz, Im-2-*H*), 8.00 (m, 2H, Ph), 7.69 (m, 1H, Ph), 7.56 (m, 2H, Ph), 7.38 (s, 1H, Im-5-*H*), 3.485 (t, 2H, *J* = 6.9 Hz, Im-4-$CH_2CH_2CH_2$), 2.88 (t, *J* = 7.6 Hz, 2H, Im-4-$CH_2CH_2CH_2$), 2.09 (m, 2H, Im-4-CH_2CH), ^{13}C-NMR (CD_3OD) δ (ppm): 169.93 (quart, *C*O), 155.91 (quart, *C*=NH), 135.27 (quart. Ph-*C*-1), 134.99 (+, Im-*C*-2), 134.31 (quart, Im-*C*-4), 132.75, 130.18, 129.34 (+, arom. *C*H), 117.17 (+, Im-*C*-5), 41.86 (-, Im-4-$CH_2CH_2CH_2$), 28.05 (-, Im-4-CH_2), 22.58 (-, Im-4-CH_2CH_2); HRMS: EI-MS: *m/z* for [$C_{14}H_{17}N_5O$] calcd. 271.1433, found 271.1433; $C_{14}H_{17}N_5O \cdot 2$ TFA (499.4).

***N*^{1}-[3-(1*H*-Imidazol-4-yl)propyl]-*N*^{2}-(phenylacetyl)guanidine (68).**; Yield 21 % (deprotection of compound **68a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.78 (d, 1H, *J* = 1.2 Hz, Im-2-*H*), 7.35 (s, 1H, Im-5-*H*), 7.31 (m, 5H, Ph), 3.79 (s, 2H, $COCH_2$), 3.37 (t, 2H, *J* = 6.9 Hz, Im-4-$CH_2CH_2CH_2$), 2.82 (t, *J* = 7.6 Hz, 2H, Im-4-CH_2CH_2, $COCH_2$), 2.02 (m, 2H, Im-4-CH_2CH_2), ^{13}C-NMR (CD_3OD) δ (ppm): 175.20 (quart, *C*O), 155.47 (quart, *C*=NH), 134.95 (quart. Ph-*C*-1), 134.41 (+, Im-*C*-2), 134.35 (quart, Im-*C*-4), 130.63, 129.82, 128.62 (+, arom. *C*H), 117.13 (+, Im-*C*-5), 44.40 (-, $COCH_2$), 41.61 (-, Im-4-$CH_2CH_2CH_2$), 27.93 (-, Im-4-CH_2), 22.55 (-, Im-4-CH_2CH_2); HRMS: EI-MS: *m/z* for [$C_{15}H_{19}N_5O$] calcd. 285.1590, found 285.1590; $C_{15}H_{19}N_5O \cdot 2$ TFA (513.4).

***N*^{1}-[3-(1*H*-Imidazol-4-yl)propyl]-*N*^{2}-(3-phenylpropanoyl)guanidine (69).** Yield 45 % (deprotection of compound **69a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.74 (d, 1H, *J* = 1.2 Hz, Im-2-*H*), 7.32 (s, 1H, Im-5-*H*), 7.22 (m, 5H, Ph), 3.35 (t, 2H, *J* = 6.9 Hz, $COCH_2CH_2$), 2.94 (t, 2H, *J* = 7.3 Hz, Im-4-$CH_2CH_2CH_2$), 2.79 (q, 4H, *J* = 8.3 Hz, Im-4-CH_2CH_2, $COCH_2$), 2.01 (m, 2H, Im-4-CH_2CH_2); ^{13}C-NMR (CD_3OD) δ (ppm): 176.63 (quart, *C*O), 155.33 (quart, *C*=NH), 141.36 (quart. Ph-

C-1), 134.86 (+, Im-*C*-2), 134.28 (quart, Im-*C*-4), 127.49, 129.50, 129.61 (+, arom. *C*H), 117.13 (+, Im-*C*-5), 41.53 (-, Im-4-$CH_2CH_2CH_2$), 39.49 (-, $COCH_2$), 31.30 (-, Im-4-CH_2), 27.99 (-, $COCH_2CH_2$), 22.54 (-, Im-4-CH_2CH_2); HRMS: EI-MS: *m/z* for [$C_{16}H_{21}N_5O$] calcd. 291.1746, found 291.1747; $C_{16}H_{21}N_5O \cdot 2$ TFA (527.4).

***N*^{1}-[3-(1*H*-Imidazol-4-yl)propyl]-*N*^{2}-(4-phenylbutanoyl)guanidine (70).** Yield 27 % (deprotection of compound **70a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.80 (d, 1H, *J* = 1.3 Hz, Im-2-*H*), 7.36 (s, 1H, Im-5-*H*), 7.22 (m, 5H, Ph), 3.37 (m, 2H, Im-4-$CH_2CH_2CH_2$), 2.83 (t, 2H, *J* = 7.5 Hz, $COCH_2CH_2CH_2$), 2.67 (t, 2H, *J* = 7.3 Hz, Im-4-CH_2), 2.49 (t, 2H, *J* = 7.3 Hz, $COCH_2$), 1.99 (m, 4H, Im-4-CH_2CH_2, $COCH_2CH_2$); ^{13}C-NMR (CD_3OD) δ (ppm): 177.24 (quart, *C*O), 155.36 (quart, *C*=NH), 142.61 (quart. Ph-*C*-1), 134.93 (+, Im-*C*-2), 134.33 (quart, Im-*C*-4), 130.83, 130.22, 129.73, 129.61, 127.14 (+, arom. *C*H), 117.14 (+, Im-*C*-5), 41.53 (-, Im-4-$CH_2CH_2CH_2$), 37.15 (-, $COCH_2$), 35.94 (-, $COCH_2CH_2CH_2$), 27.99 (-, Im-4-CH_2), 27.21 (-, Im-4-CH_2CH_2), 22.56 (-, $COCH_2CH_2$); HRMS: EI-MS: *m/z* for [$C_{17}H_{23}N_5O$] calcd. 313.1903, found 313.1903; $C_{17}H_{23}N_5O \cdot 2$ TFA (541.4).

***N*^{1}-[3-(1*H*-Imidazol-4-yl)propyl]-*N*^{2}-(5-phenylpentanoyl)guanidine (71).** Yield 24 % (deprotection of compound **71a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.76 (d, 1H, *J* = 1.3 Hz, Im-2-*H*), 7.33 (s, 1H, Im-5-*H*), 7.17 (m, 5H, Ph), 3.36 (t, 2H, *J* = 6.9 Hz, Im-4-$CH_2CH_2CH_2$), 2.82 (t, 2H, *J* = 7.7 Hz, Im-4-$CH_2CH_2CH_2$), 2.61 (t, 2H, *J* = 6.7 Hz, CH_2Ph), 2.48 (t, 2H, *J* = 6.5 Hz, $COCH_2$), 2.01 (m, 2H, Im-4-$CH_2CH_2CH_2$), 1.65 (m, 4H, $COCH_2CH_2CH_2$), ^{13}C-NMR (CD_3OD) δ (ppm): 177.42 (quart, *C*O), 155.39 (quart, *C*=NH), 143.33 (quart. Ph-*C*-1), 134.99 (+, Im-*C*-2), 134.23 (quart, Im-*C*-4), 129.47, 129.39, 126.85 (+, arom. *C*H), 117.14 (+, Im-*C*-5), 41.44 (-, Im-4-$CH_2CH_2CH_2$), 37.56 (-, $COCH_2$), 36.48 (- ,$COCH_2CH_2CH_2CH_2$), 31.81 (-, $COCH_2CH_2CH_2$), 27.99 (-, Im-4-CH_2), 25.02 (-, Im-4-CH_2CH_2), 22.54 (-, $COCH_2CH_2$); HRMS: EI-MS: *m/z* for [$C_{18}H_{25}N_5O$] calcd. 327.2059, found 327.2056; $C_{18}H_{25}N_5O \cdot 2$ TFA (555.5).

***N*^{1}-(2-Cyclohexylpropanoyl)-*N*^{2}-[3-(1*H*-imidazol-4-yl)propyl]guanidine (72).** Yield 47 % (deprotection of compound **72a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.80 (d, 1H, *J* = 1.0 Hz, Im-2-*H*), 7.37 (d, 1H, *J* = 1.4 Hz, Im-5-*H*), 3.39 (t, 2H, *J* = 7.0 Hz, Im-4-$CH_2CH_2CH_2$), 2.84 (t, 2H, *J* = 7.0 Hz, Im-4-$CH_2CH_2CH_2$), 2.37 (m, 1H, $CHCH_3$), 2.04 (m, 2H, Im-4-CH_2CH_2), 1.69 (m, 6H, cHex-CH_2), 1.24 (m, 4H, cHex-CH_2), 1.14 (d, 3H, *J* = 6.5 Hz, CH_3), 1.00 (m, 1H, cHex); ^{13}C-NMR (CD_3OD) δ (ppm): 180.75 (quart, *C*O), 155.42 (quart, *C*=NH), 134.96 (+, Im-*C*-2), 134.33 (quart, Im-*C*-4), 117.13 (+, Im-*C*-5), 42.08 (+, cHex-CH), 41.64 (-, Im-4-$CH_2CH_2CH_2$), 32.30 (-, Im-4-CH_2), 27.36, 27.95 (-, cHex-CH_2), 27.30 (-, Im-4-CH_2CH_2), 22.59 (-, cHex-CH_2), 22.31 (+, $CHCH_3$), 14.12 (+, CH_3); HRMS: EI-MS: *m/z* for [$C_{16}H_{27}N_5O$] calcd. 305.2216, found 305.2212; $C_{16}H_{27}N_5O \cdot 2$ TFA (533.4).

***N*^{1}-(3-Cyclohexylbutanoyl)-*N*^{2}-[3-(1*H*-imidazol-4-yl)propyl]guanidine (73).** Yield 44 % (deprotection of compound **73a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.79 (d, 1H, *J* = 0.7 Hz, Im-2-*H*), 7.36 (s, 1H, Im-5-*H*), 3.37 (dd, 2H, *J* = 6.0 Hz, *J* = 12.9 Hz, Im-4-$CH_2CH_2CH_2$), 2.84 (t, 2H, *J* = 7.7 Hz, Im-4-$CH_2CH_2CH_2$), 2.56 (dd, 1H, *J* = 15.0 Hz, *J* = 5.1 Hz, CH*H*), 2.22 (dd, 1H, J = 15 Hz, J = 9.1 Hz, C*H*H), 2.04 (m, 3H, Im-4-CH_2CH_2, $CHCH_3$), 1.68-1.90 (m, 5H, cHex-CH_2, cHex-CH), 1.04-1.21 (m, 6H, cHex-CH_2), 0.91 (d, 3H, *J* = 6.8 Hz, CH_3); ^{13}C-NMR (CD_3OD) δ (ppm): 177.54 (quart, *C*O), 154.40 (quart, *C*=NH), 134.94 (+, Im-*C*-2), 134.34 (quart, Im-*C*-4), 117.14 (+, Im-*C*-5), 43.94 (+, cHex-CH), 42.71 (-, Im-4-$CH_2CH_2CH_2$), 41.47 (-, $COCH_2$), 36.44 (+, CH_3CH), 31.48 (-, cHex-CH_2), 30.03 (-, Im-4-CH_2), 27.99, 28.85 (-, cHex-CH_2), 27.74 (-, Im-4-CH_2CH_2), 22.57 (-, cHex-CH_2), 16.61 (+, CH_3); HRMS: EI-MS: *m/z* for [$C_{17}H_{29}N_5O$] calcd. 319.2372, found 319.2372; $C_{17}H_{29}N_5O \cdot 2$ TFA (547.4).

***N*^{1}-Cyclohexylcarbonyl-*N*^{2}-[3-(1*H*-imidazol-4-yl)propyl]guanidine (74).** Yield 27 % (deprotection of compound **74a**); colorless sticky oil; ^{1}H-NMR (CD_3OD) δ (ppm): 8.78 (d, 1H, *J* = 0.9 Hz, Im-2-*H*), 7.35 (s, 1H, Im-5-*H*), 3.38 (t, 2H, *J* = 6.9 Hz, Im-4-$CH_2CH_2CH_2$), 2.83 (t, 2H, *J* = 7.7 Hz, Im-4-

C*H*$_2$CH$_2$CH$_2$), 2.42 (m, 1H, cHex-C*H*), 2.03 (m, 2H, Im-4-CH$_2$C*H*$_2$), 1.80 (m, 5H, cHex-CH$_2$), 1.33 (m, 2H, cHex-CH$_2$), ^{13}C-NMR (CD$_3$OD) δ (ppm): 180.46 (quart, *C*O), 155.89 (quart, *C*=NH), 134.94 (+, Im-*C*-2), 134.34 (quart, Im-*C*-4), 117.18 (+, Im-*C*-5), 46.70 (+, cHex-*C*H), 41.58 (-, Im-4-CH$_2$CH$_2$*C*H$_2$), 29.91 (-, Im-4-*C*H$_2$), 27.99 (-, Im-4-CH$_2$*C*H$_2$), 26.68, 26.27, 22.63 (-, cHex-*C*H$_2$), HRMS: EI-MS: *m/z* for [C$_{14}$H$_{23}$N$_5$O] calcd. 277.1903, found 277.1900; C$_{14}$H$_{23}$N$_5$O · 2 TFA (505.4).

***N*^{1}-Cyclohexylacetyl-*N*^{2}-[3-(1*H*-imidazol-4-yl)propyl]guanidine (75).** Yield 18 % (deprotection of compound **75a**); colorless sticky oil;; ^{1}H-NMR (CD$_3$OD) δ (ppm): 8.79 (s, 1H, Im-2-*H*), 7.35 (s, 1H, Im-5-*H*), 3.37 (t, 2H, *J* = 7.7 Hz, Im-4-CH$_2$CH$_2$C*H*$_2$), 2.83 (t, 2H, *J* = 7.6 Hz, Im-4-C*H*$_2$CH$_2$CH$_2$), 2.33 (d, 1H, J = 6.9 Hz, COC*H*$_2$), 2.02 (m, 2H, Im-4-CH$_2$C*H*$_2$), 1.75 (m, 6H, cHex-CH$_2$), 1.12 (m, 5H, cHex-CH$_2$), ^{13}C-NMR (CD$_3$OD) δ (ppm): 177.78 (quart, *C*O), 155.45 (quart, *C*=NH), 134.94 (+, Im-*C*-2), 134.34 (quart, Im-*C*-4), 117.15 (+, Im-*C*-5), 41.54 (-, Im-4-CH$_2$CH$_2$*C*H$_2$), 38.42 (+, cHex-*C*H), 35.47 (-, CO*C*H$_2$), 34.13 (-, cHex-*C*H$_2$), 32.93 (-, COCH$_2$*C*H$_2$), 28.00 (-, Im-4-*C*H$_2$), 27.63 (-, Im-4-CH$_2$*C*H$_2$), 27.35, 22.56; HRMS: EI-MS: *m/z* for [C$_{15}$H$_{25}$N$_5$O] calcd. 291.2059, found 291.2059; C$_{15}$H$_{25}$N$_5$O · 2 TFA (519.4).

***N*^{1}-(3-Cyclohexylpropanoyl)-*N*^{2}-[3-(1*H*-imidazol-4-yl)propyl]guanidine (76).** Yield 56 % (deprotection of compound **76a**); colorless sticky oil; ^{1}H-NMR (CD$_3$OD) δ (ppm): 8.80 (d, 1H, *J* = 1.2 Hz, Im-2-*H*), 7.37 (d, 1H, , *J* = 0.7 Hz, Im-5-*H*), 3.39 (t, 2H, *J* = 7.0 Hz, Im-4-CH$_2$CH$_2$C*H*$_2$), 2.84 (t, 2H, *J* = 7.5 Hz, Im-4-C*H*$_2$CH$_2$CH$_2$), 2.48 (t, 2H, *J* = 7.5 Hz, COC*H*$_2$), 2.04 (m, 2H, Im-4-CH$_2$C*H*$_2$), 1.72 (m, 5H, cHex-CH$_2$, cHex-CH), 1.54 (q, 2H, COCH$_2$C*H*$_2$), 1.24 (m, 4H, cHex-CH$_2$), 0.94 (m, 2H, cHex-CH$_2$); ^{13}C-NMR (CD$_3$OD) δ (ppm): 177.78 (quart, *C*O), 155.45 (quart, *C*=NH), 134.94 (+, Im-*C*-2), 134.34 (quart, Im-*C*-4), 117.15 (+, Im-*C*-5), 41.54 (-, Im-4-CH$_2$CH$_2$*C*H$_2$), 38.42 (+, cHex-CH), 35.47 (-, CO*C*H$_2$), 34.13 (-, cHex-*C*H$_2$), 32.93 (-, COCH$_2$*C*H$_2$), 28.00 (-, Im-4-*C*H$_2$), 27.63 (-, Im-4-CH$_2$*C*H$_2$), 27.35, 22.56 (-, cHex-CH$_2$); HRMS: EI-MS: *m/z* for [C$_{16}$H$_{27}$N$_5$O] calcd. 305.2216, found 305.2213; C$_{16}$H$_{27}$N$_5$O · 2 TFA (533.4).

***N*^{1}-(4-Cyclohexylbutanoyl)-*N*^{2}-[3-(1*H*-imidazol-4-yl)propyl]guanidine (77).** Yield 26 % (deprotection of compound **77a**); colorless sticky oil; ^{1}H-NMR (CD$_3$OD) δ (ppm): 8.79 (d, 1H, *J* = 1.4 Hz, Im-2-*H*), 7.36 (d, 1H, , *J* = 1.0 Hz, Im-5-*H*), 3.38 (t, 2H, *J* = 6.9 Hz, Im-4-CH$_2$CH$_2$C*H*$_2$), 2.84 (t, 2H, *J* = 7.7 Hz, Im-4-C*H*$_2$CH$_2$CH$_2$), 2.45 (t, 2H, J = 7.4 Hz, COC*H*$_2$), 2.03 (m, 2H, Im-4-CH$_2$C*H*$_2$), 1.68 (m, 7H, COCH$_2$C*H*$_2$, cHex-CH$_2$, cHex-CH), 1.22 (m, 6H, cHex-CH$_2$), 0.90 (m, 2H, COCH$_2$CH$_2$C*H*$_2$); ^{13}C-NMR (CD$_3$OD) δ (ppm): 177.54 (quart, *C*O), 155.41 (quart, *C*=NH), 134.93 (+, Im-*C*-2), 134.34 (quart, Im-*C*-4), 117.14 (+, Im-*C*-5), 41.54 (-, Im-4-CH$_2$CH$_2$*C*H$_2$), 38.71 (+, cHex-CH), 38.05 (-, CO*C*H$_2$), 37.81 (-, COCH$_2$CH$_2$*C*H$_2$), 34.41 (-, cHex-*C*H$_2$), 27.99 (-, cHex-*C*H$_2$), 27.78 (-, Im-4-*C*H$_2$), 27.47 (-, Im-4-CH$_2$*C*H$_2$), 22.93 (-, COCH$_2$*C*H$_2$), 22.56 (-, cHex-CH$_2$); HRMS: EI-MS: *m/z* for [C$_{17}$H$_{29}$N$_5$O] calcd. 319.2379, found 319.2377; C$_{17}$H$_{29}$N$_5$O · 2 TFA (547.4).

4. HPLC-Data of the acylguanidines 46-77

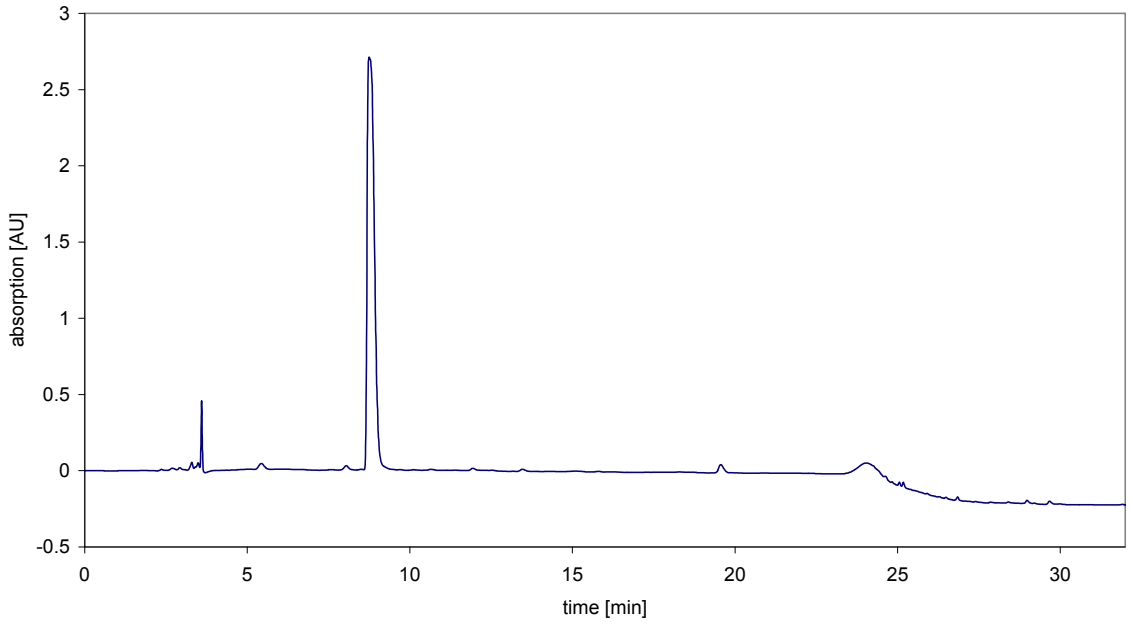
Analytical chromatography was performed on a Thermo Separation Products system equipped with a SN 400 controller, P4000 pump, an AS3000 autosampler and a Spectra Focus UV-VIS detector (Darmstadt, Germany). The columns were either: Column A: Nucleodur (Macherey-Nagel, Düren, Germany) 100-5 C18 ec (250 x 4.0, 5 µm), t_0 (0.8 mL/min) = 2.30 min; Column B: Luna (Phenomenex, Aschaffenburg, Germany) C18 (150 x 4.6, 4 µm), t_0 (0.7 mL/min) = 2.88 min; Column C: Eurospher-100 (Knauer, Berlin, Germany) C-18 (250 x 4.0, 5 µm), t_0 (0.7 mL/min) = 3.32 min; Column D: Purospher (Agilent Technologies, Böblingen, Germany) 100 C18 (250 x 4.0, 5 µm); Column E: Synergi Hydro-RP (Phenomenex, Aschaffenburg, Germany) (250 x 4.6, 4 µm), t_0 (0.8 mL/min) = 3.10 min. The temperature was 30 °C and the UV detection was set to 254 and 210 nm. Aqueous TFA was prepared with Millipore water. $k' = (t_R - t_0)/t_0$.

Table 1. Retention times, capacity factors (k') and purities of compounds **46-77**.

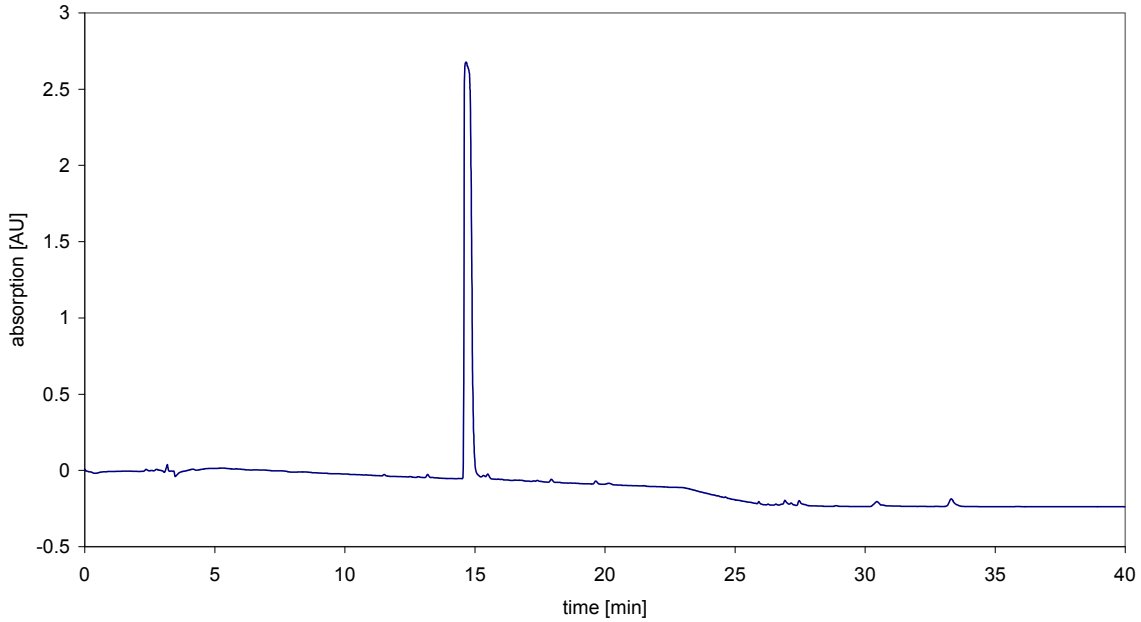
No	t_R [min]	k'	mobile phase	column	purity [%]
46	8.75	2.80	0 min: 0.05% TFA/MeCN 97/3, 20 min: 85/15	A	93
47	14.66	5.37	0 min: 0.05% TFA/MeCN 95/5, 20 min: 50/50	A	97
48	16.51	4.73	0 min: 0.05% TFA/MeCN 80/20, 20 min: 64/36	B	100
49	14.72	4.11	0 min: 0.05% TFA/MeCN 90/10, 20 min: 75/25	B	100
50	19.50	5.77	0 min: 0.05% TFA/MeCN 80/20, 20 min: 64/36	B	95
51	18.18	5.31	0 min: 0.05% TFA/MeCN 80/20, 20 min: 64/36	B	85
52	18.59	5.45	0 min: 0.05% TFA/MeCN 80/20, 20 min: 68/32	B	97
53	4.60 8.36	0.00 0.82	0.1% TFA/MeOH 20/80 0.1% TFA/MeOH 30/70	D	>96
54	4.99 9.42	0.08 1.05	0.1% TFA/MeOH 20/80 0.1% TFA/MeOH 30/70	D	>94
55	14.27	3.95	0 min: 0.05% TFA/MeCN 90/10, 20 min: 80/20	B	86
56	17.51	5.08	0 min: 0.05% TFA/MeCN 90/10, 20 min: 80/20	B	90
57	10.91	2.79	0 min: 0.05% TFA/MeCN 80/20, 20 min: 70/30	B	95
58	12.62	3.38	0 min: 0.05% TFA/MeCN 80/20, 20 min: 62/38	B	100
59	13.78	3.78	0 min: 0.05% TFA/MeCN 80/20, 20 min: 70/30	B	98
60	9.12	2.17	0 min: 0.05% TFA/MeCN 90/10, 20 min: 75/25	B	80
61	12.76	2.85	0 min: 0.05% TFA/MeCN 90/10, 20 min: 40/60	C	100
62	11.77	2.55	0 min: 0.05% TFA/MeCN 90/10, 20 min: 40/60	C	92
63	9.54	1.27	0 min: 0.05% TFA/MeCN 80/20, 20 min: 64/36	B	91

64	13.00	3.19	0 min: 0.05% TFA/MeCN 80/20, 20 min: 70/30	E	95
65	13.00	3.51	0 min: 0.05% TFA/MeCN 98/2, 20 min: 85/15	B	95
66	11.95	3.15	0 min: 0.05% TFA/MeCN 97/3, 20 min: 65/35	B	100
67	16.23	4.63	0 min: 0.05% TFA/MeCN 90/10, 20 min: 90/10	B	97
68	10.37	2.13	0 min: 0.05% TFA/MeCN 90/10, 20 min: 40/60	C	99
69	11.98	2.61	0 min: 0.05% TFA/MeCN 90/10, 20 min: 40/60	C	100
70	13.26	2.99	0 min: 0.05% TFA/MeCN 90/10, 20 min: 40/60	C	84
71	14.69	3.43	0 min: 0.05% TFA/MeCN 90/10, 20 min: 40/60	C	99
72	13.89	3.19	0 min: 0.05% TFA/MeCN 90/10, 20 min: 40/60	C	99
73	17.12	4.94	0 min: 0.05% TFA/MeCN 80/20, 20 min: 64/36	B	100
74	13.14	3.56	0 min: 0.05% TFA/MeCN 90/10, 20 min: 70/30	B	100
75	12.89	2.89	0 min: 0.05% TFA/MeCN 90/10, 20 min: 40/60	C	100
76	14.61	4.07	0 min: 0.05% TFA/MeCN 80/20, 20 min: 64/36	B	100
77	16.39	3.94	0 min: 0.05% TFA/MeCN 90/10, 20 min: 40/60	C	97

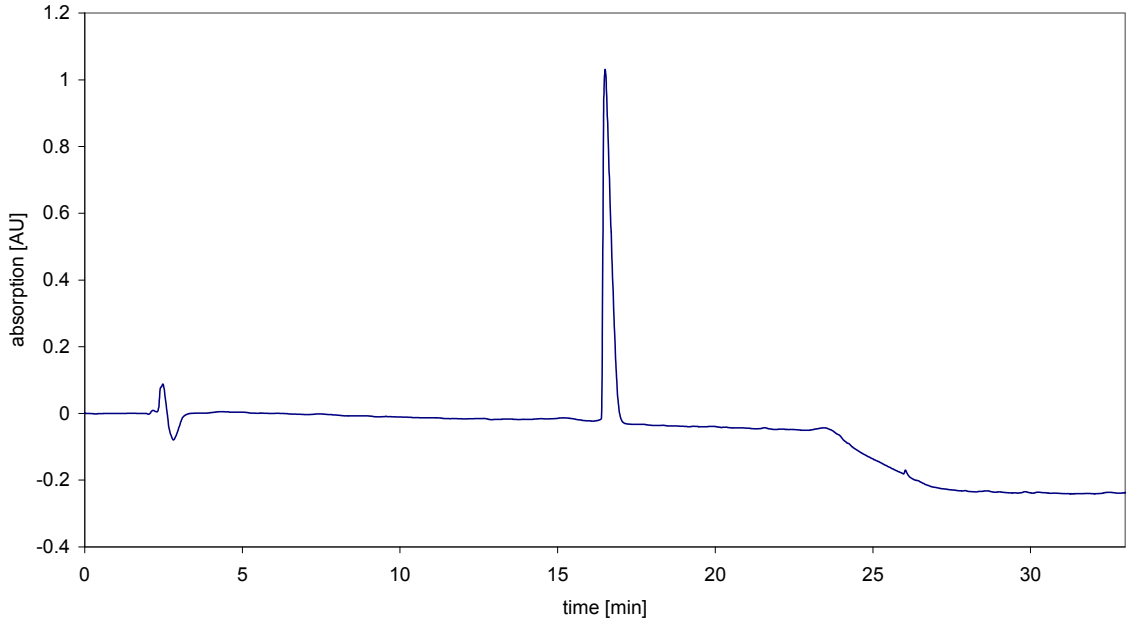
HPLC-tracing of compound **46**



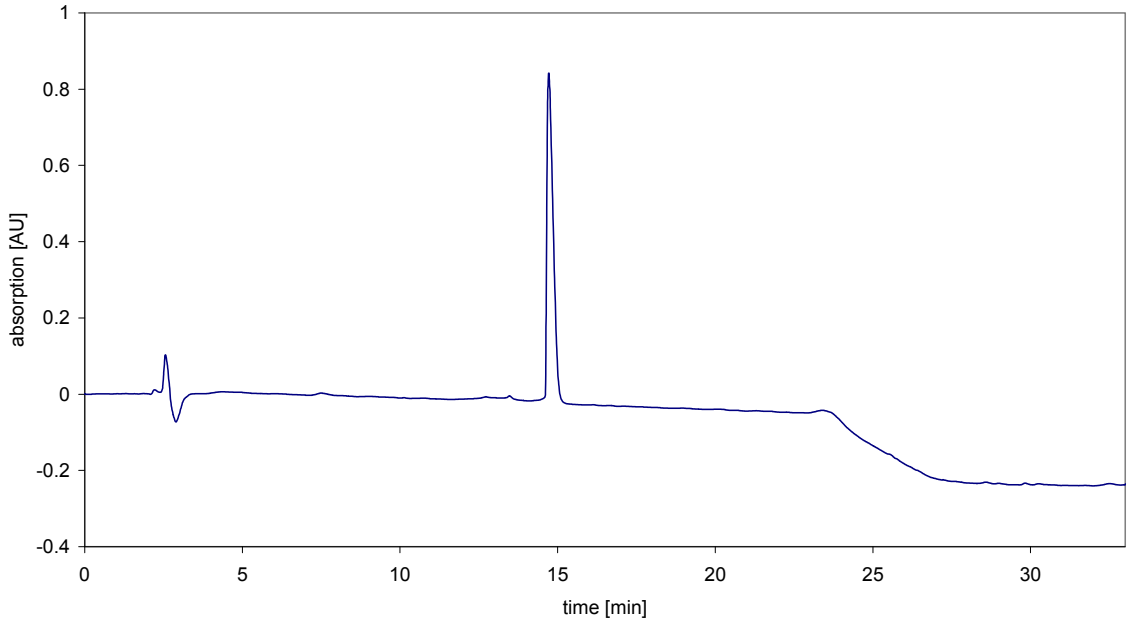
HPLC-tracing of compound **47**



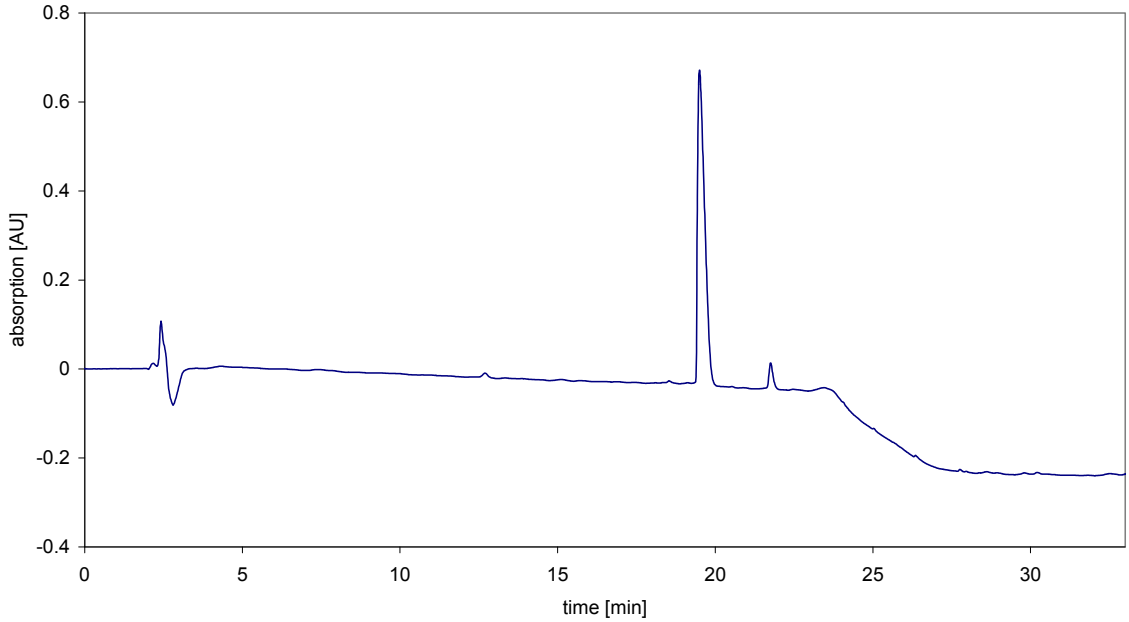
HPLC-tracing of compound **48**



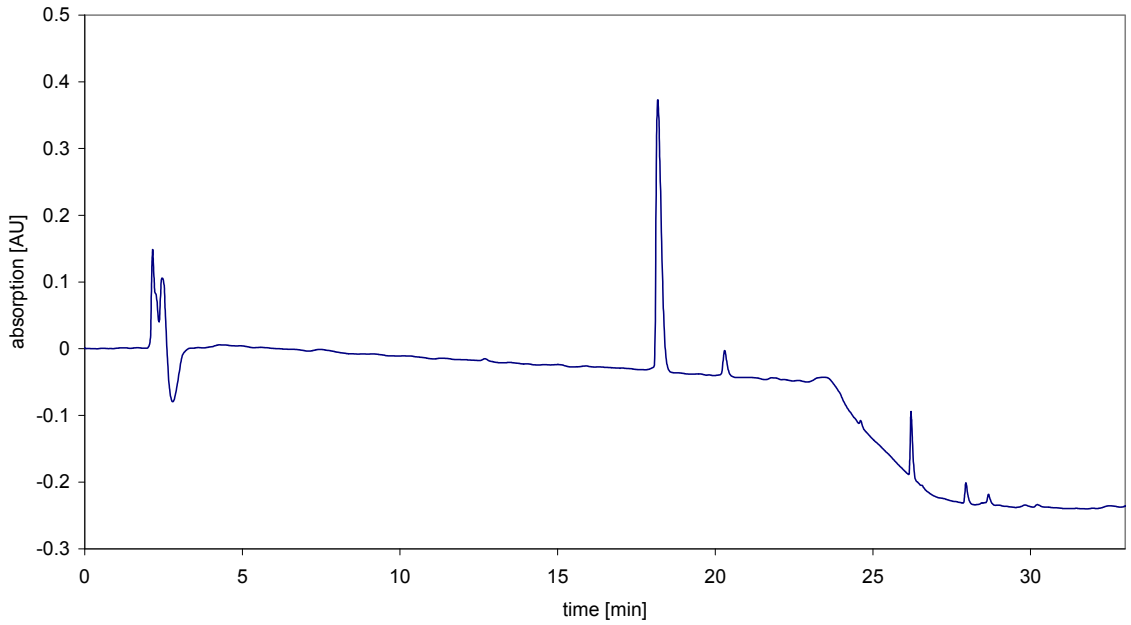
HPLC-tracing of compound **49**



HPLC-tracing of compound **50**



HPLC-tracing of compound **51**



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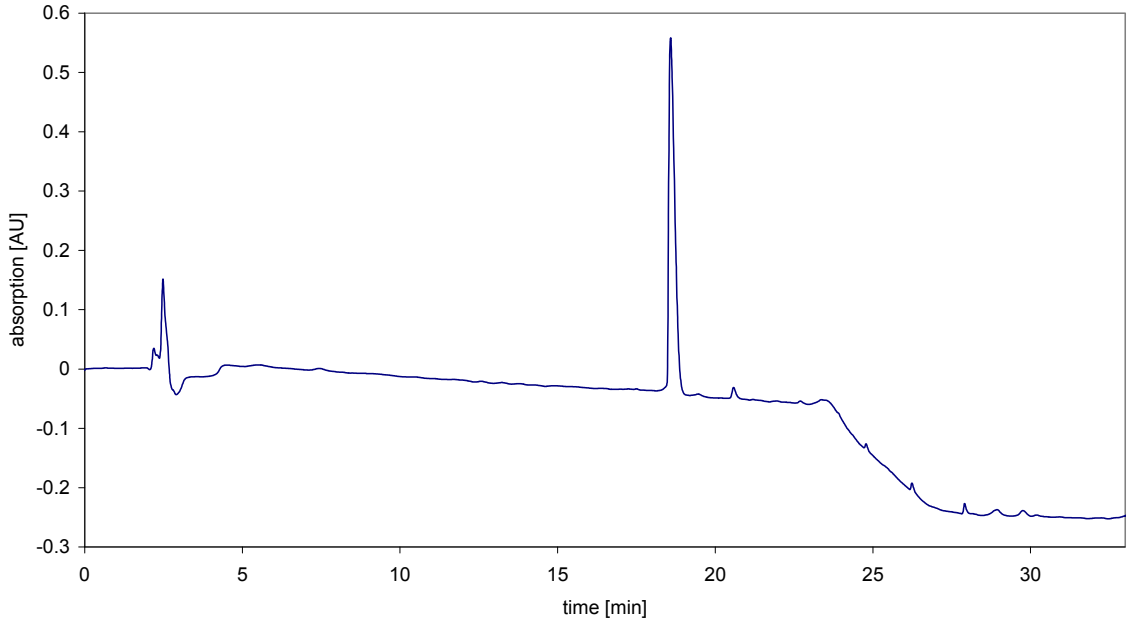

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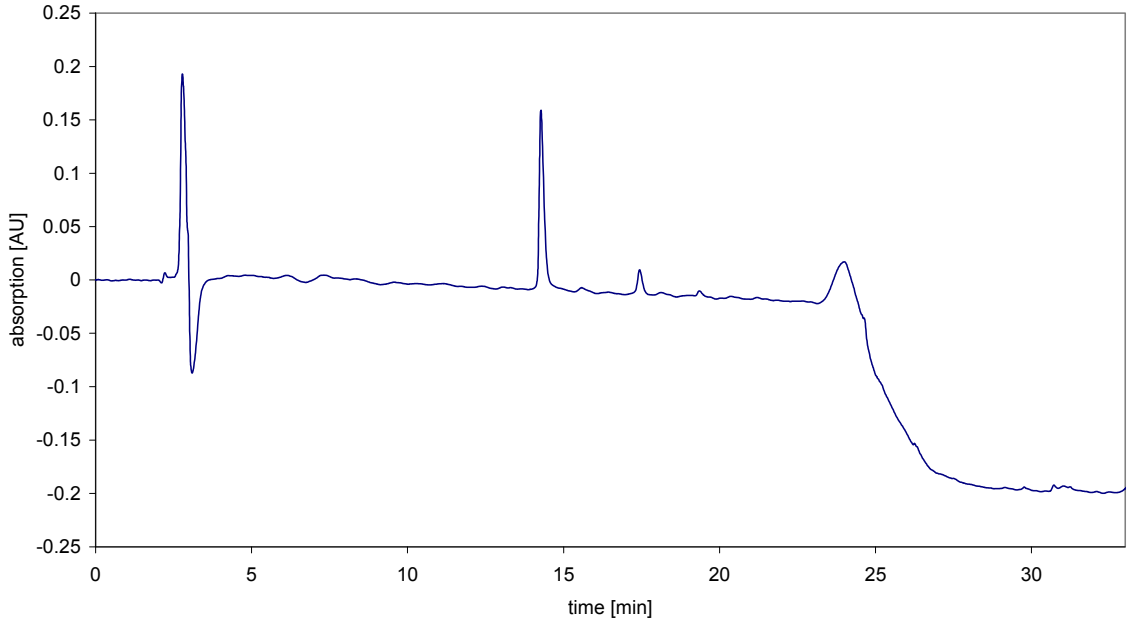
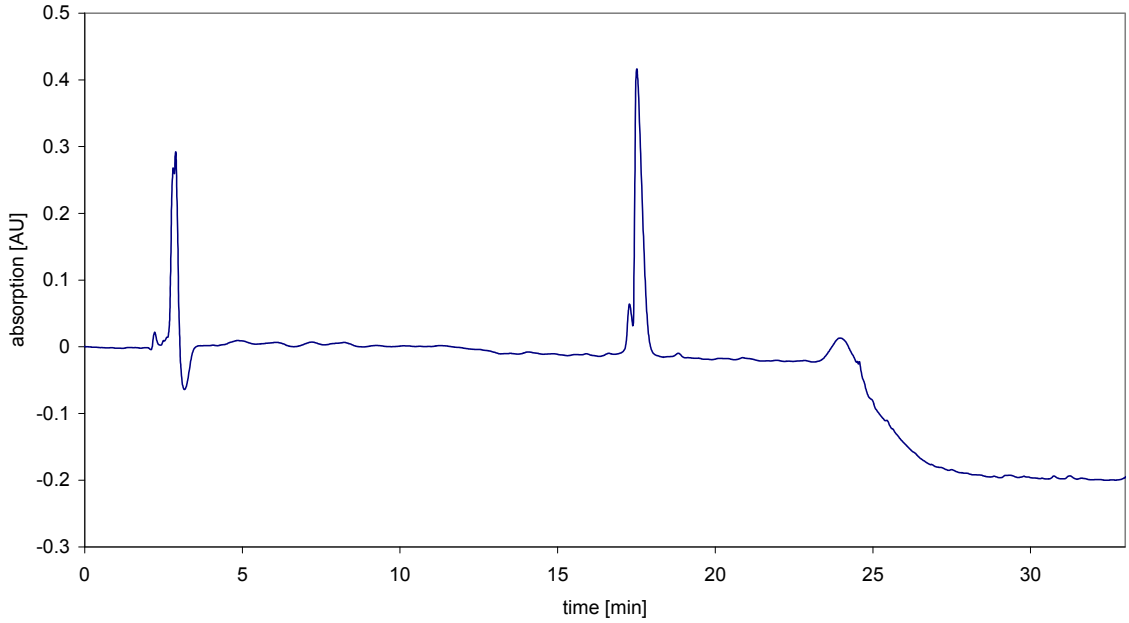
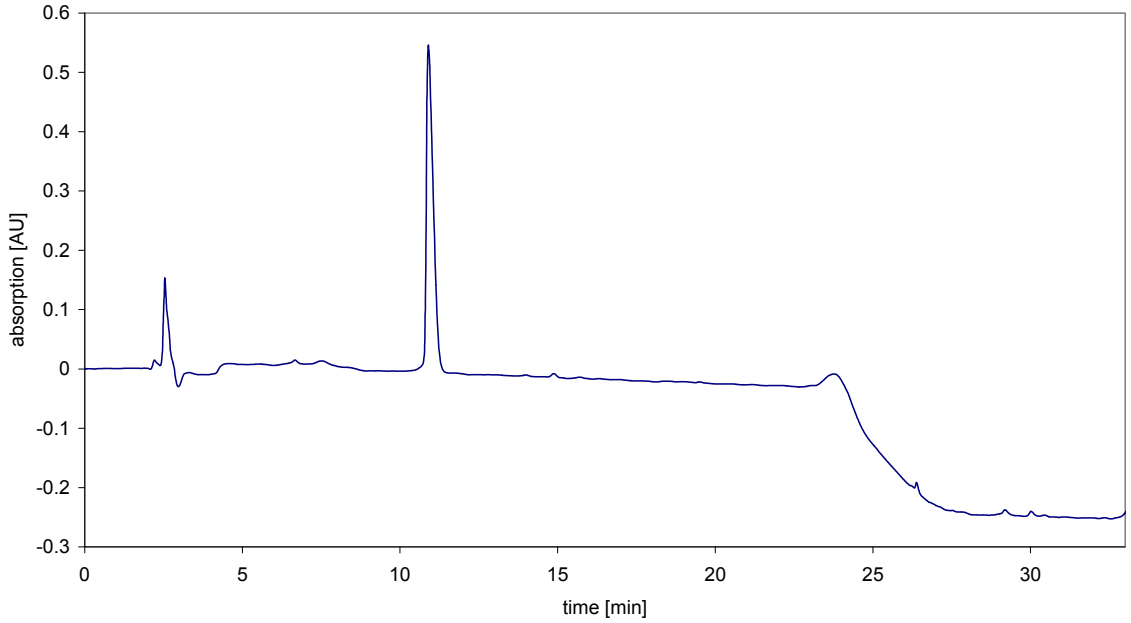


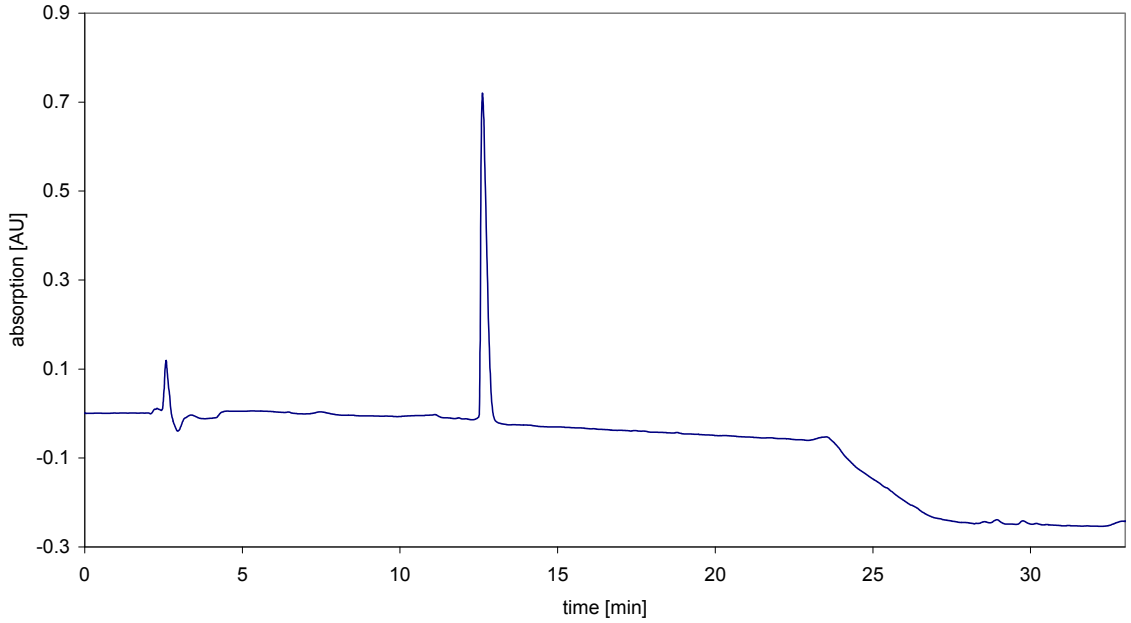
HPLC-tracing of compound **56**



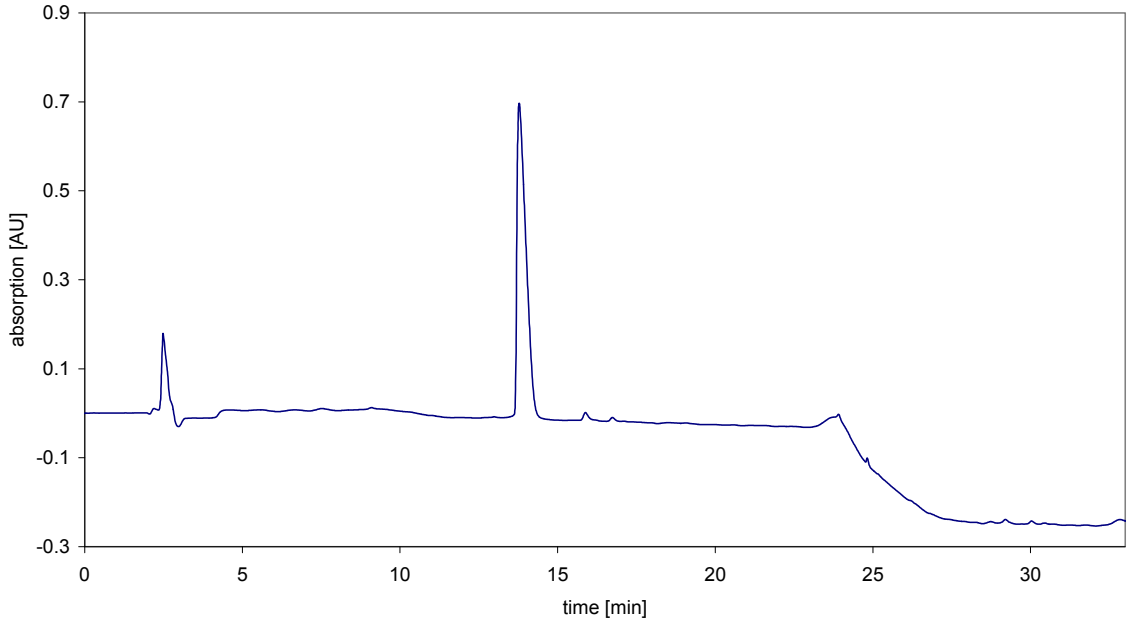
HPLC-tracing of compound **57**



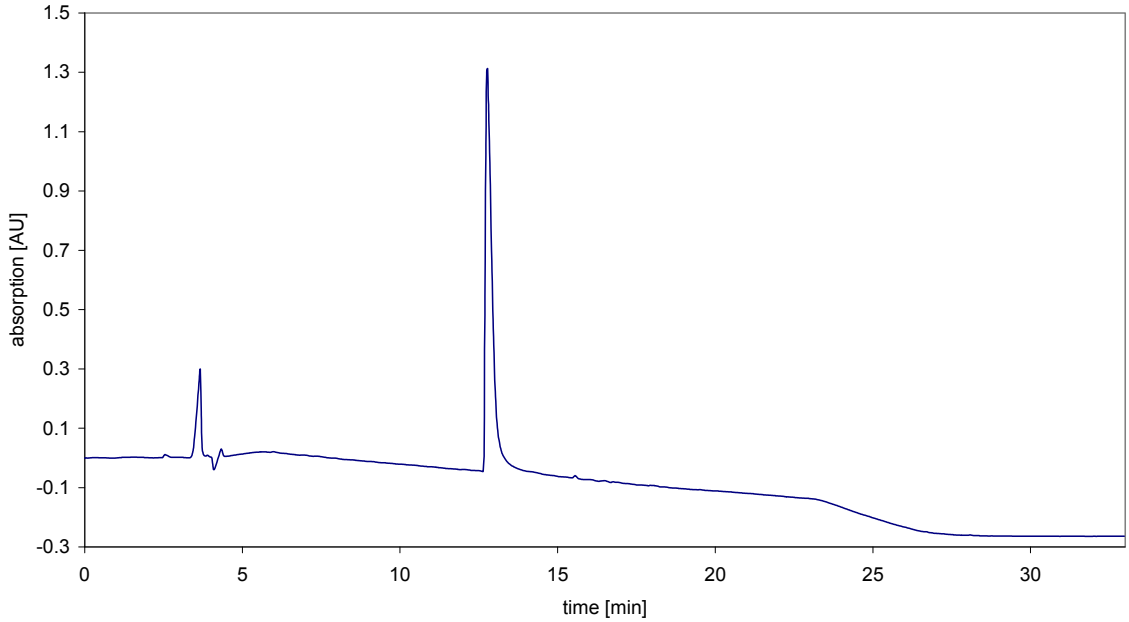
HPLC-tracing of compound **58**



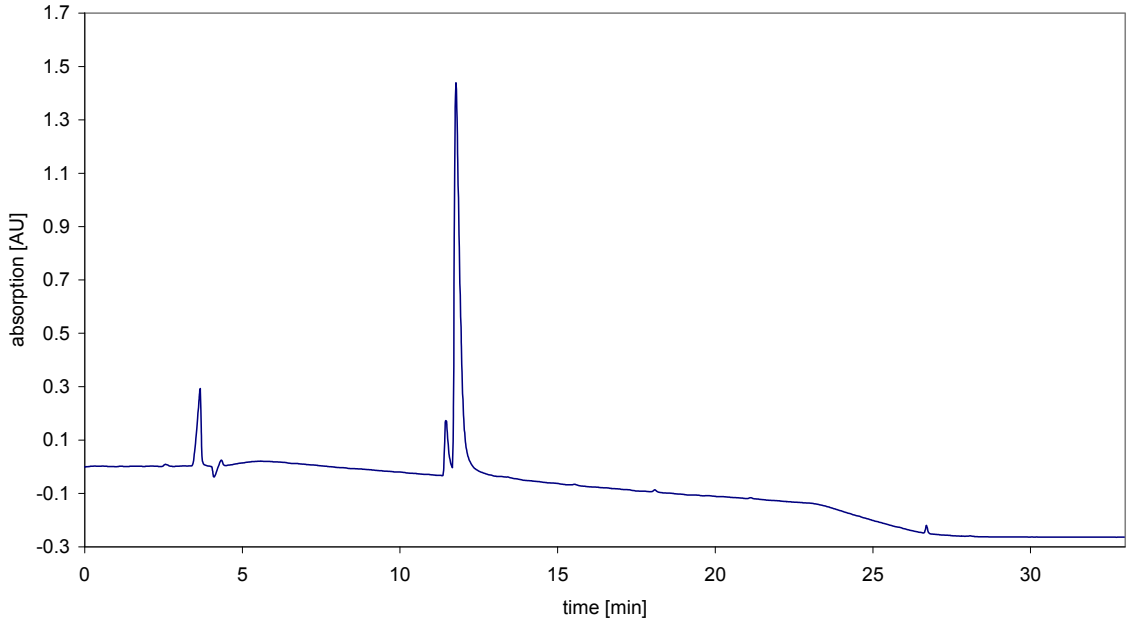
HPLC-tracing of compound **59**



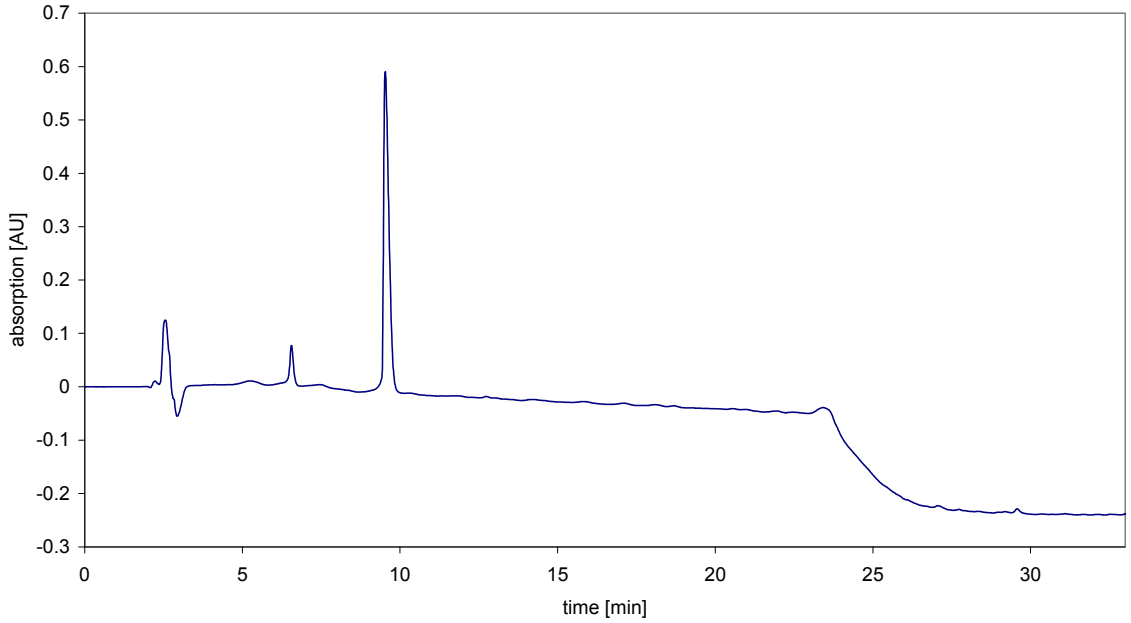
HPLC-tracing of compound **61**



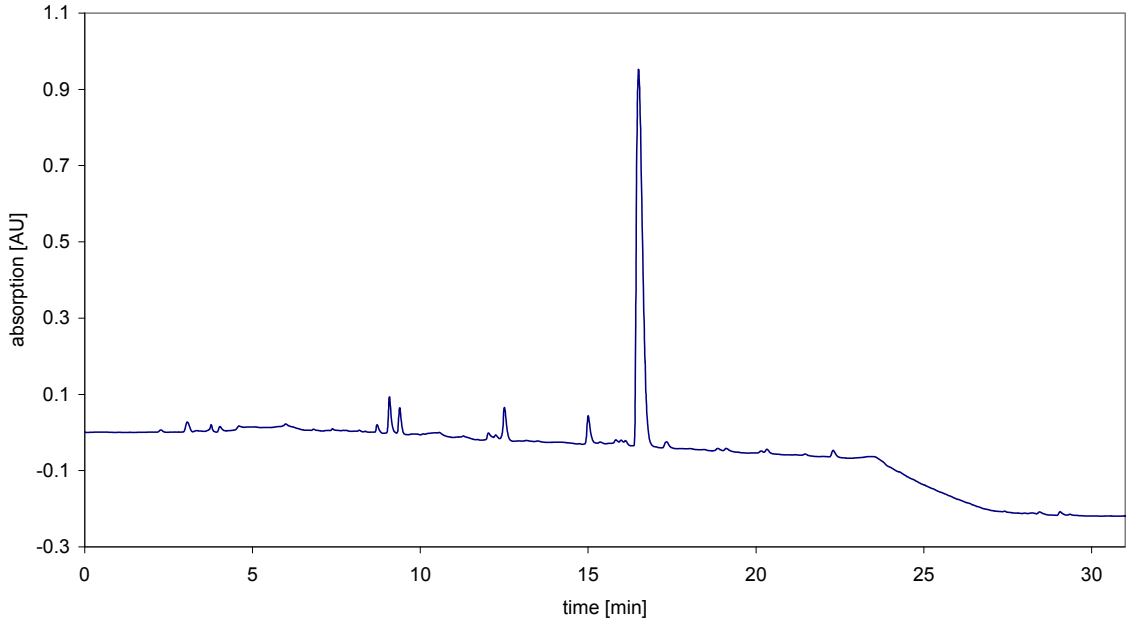
HPLC-tracing of compound **62**



HPLC-tracing of compound **63**



HPLC-tracing of compound **64**



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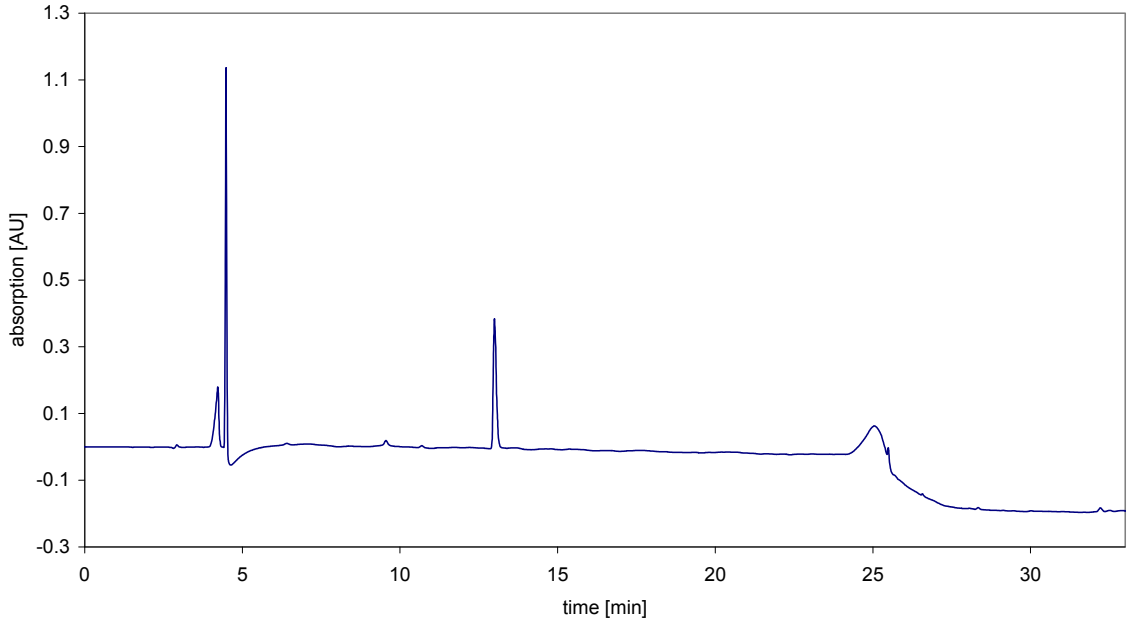
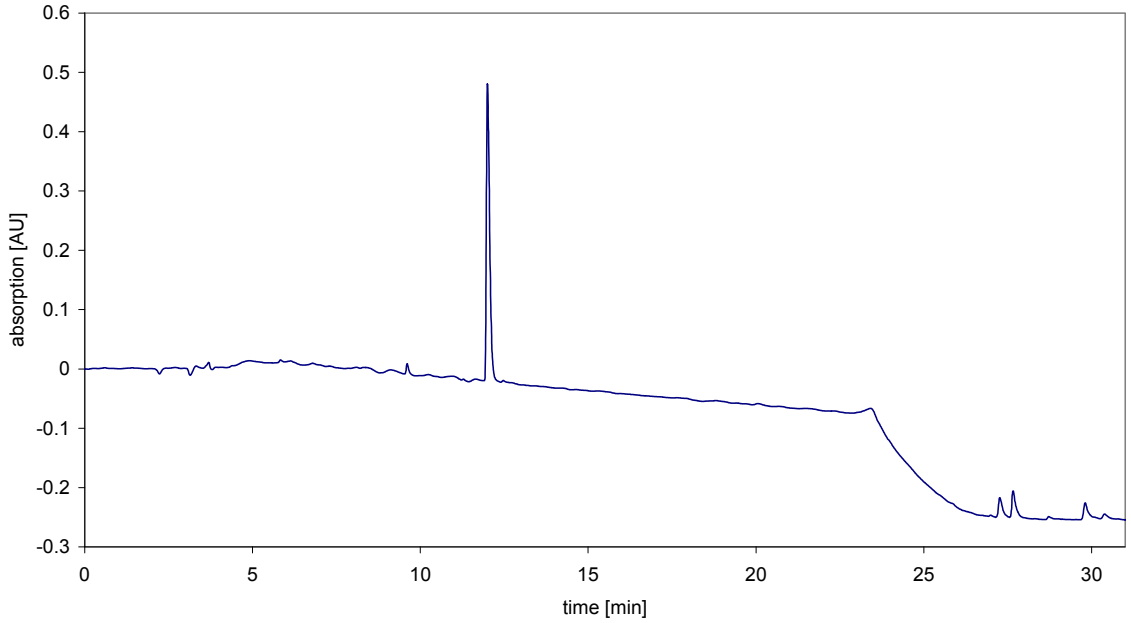
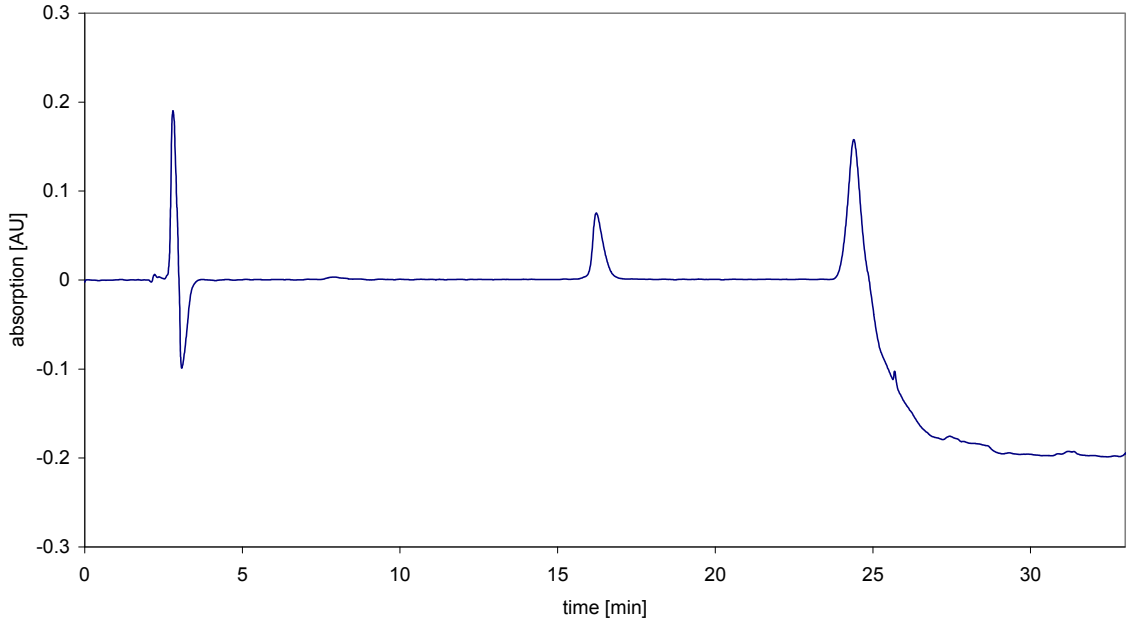


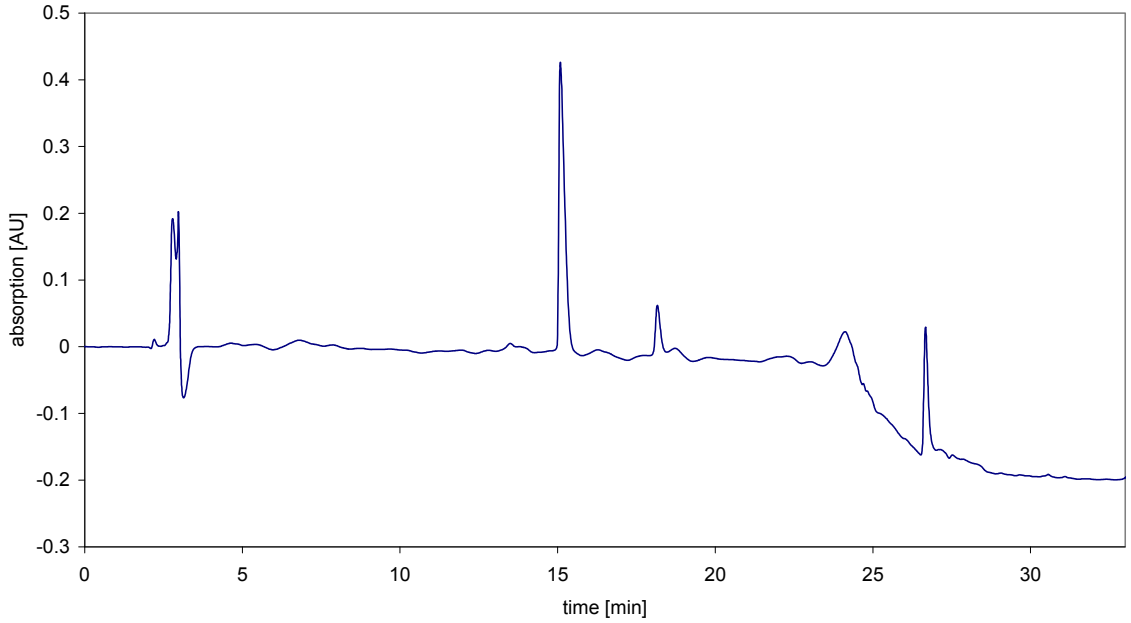
HPLC-tracing of compound **66**



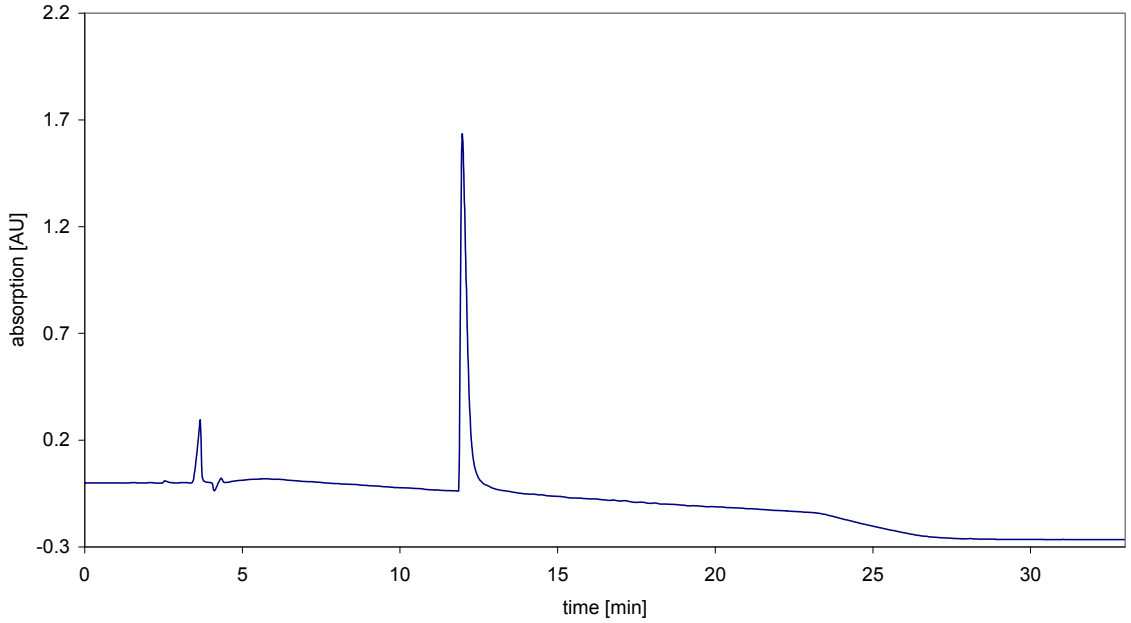
HPLC-tracing of compound **67**



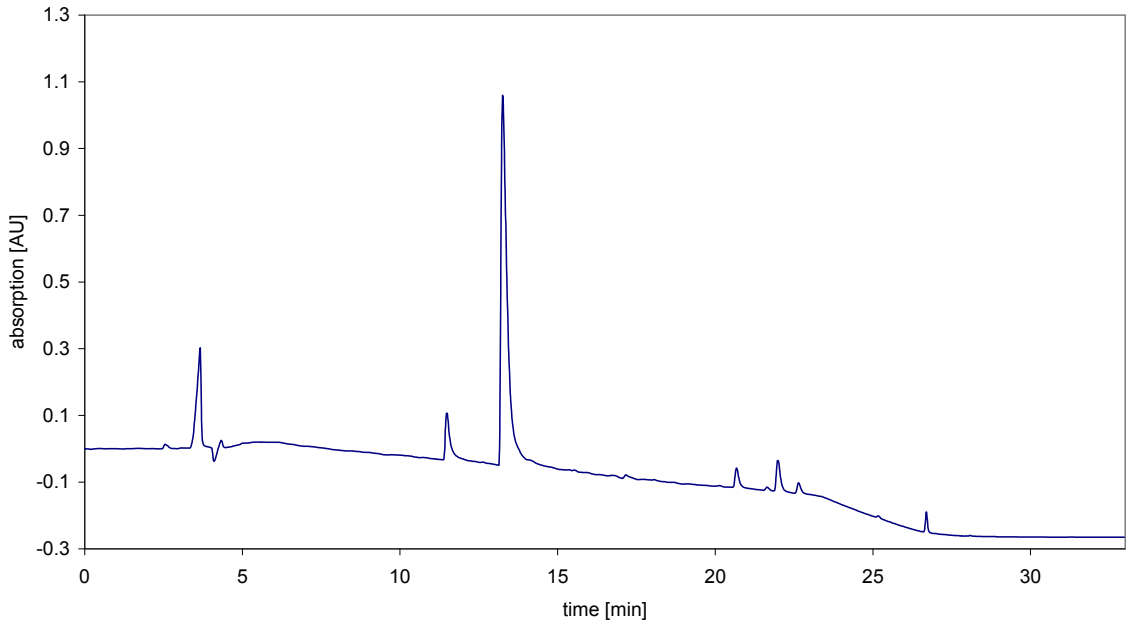
HPLC-tracing of compound **68**



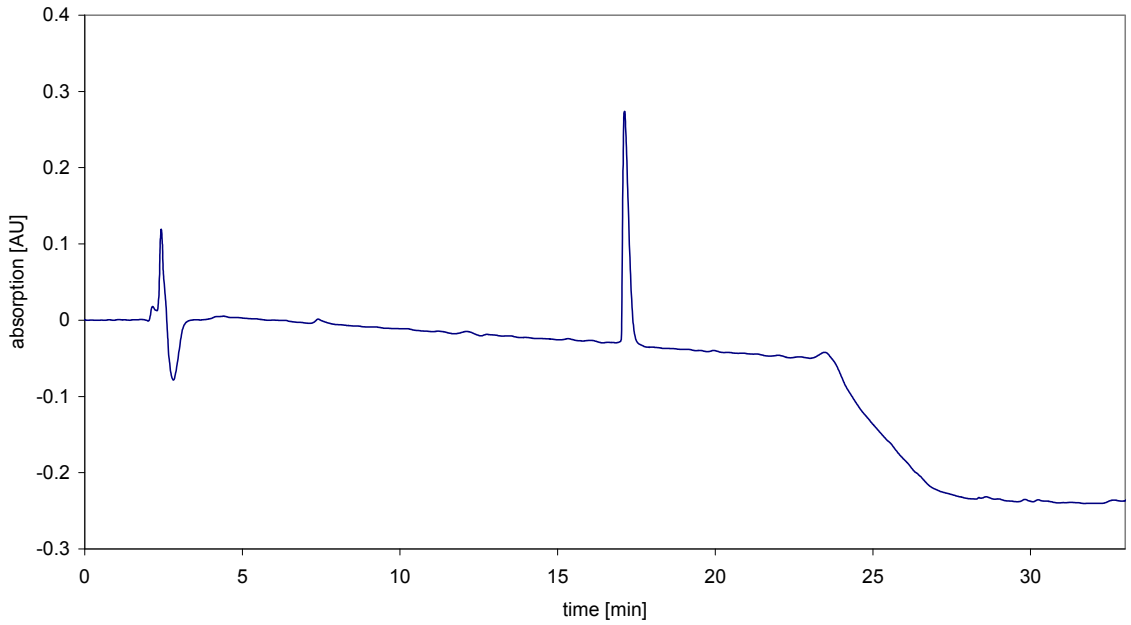
HPLC-tracing of compound **69**



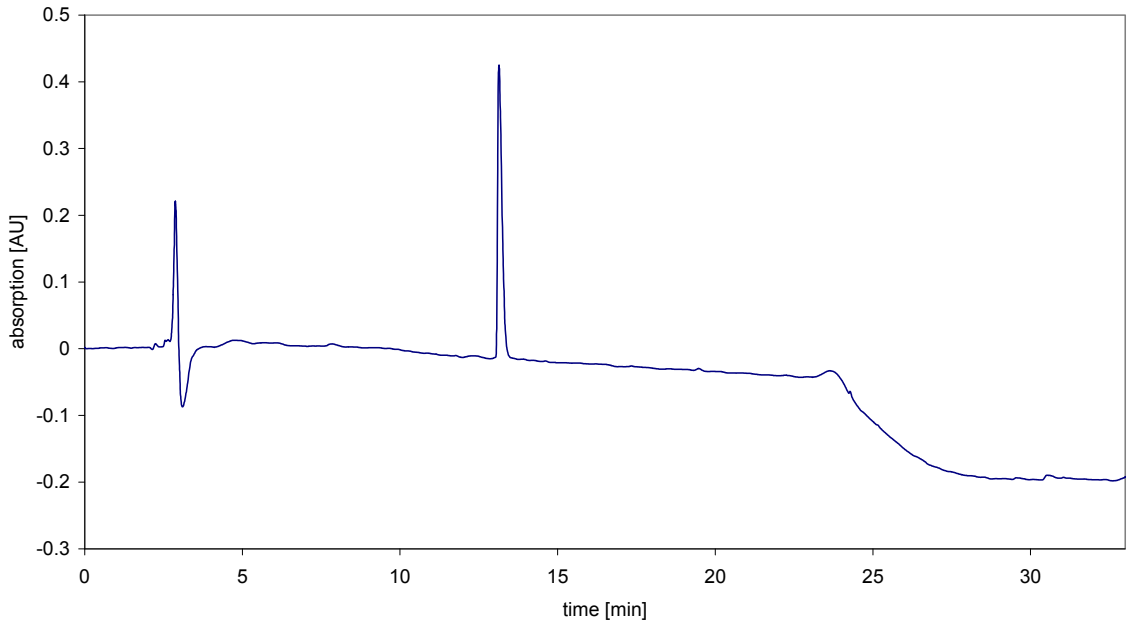
HPLC-tracing of compound **70**



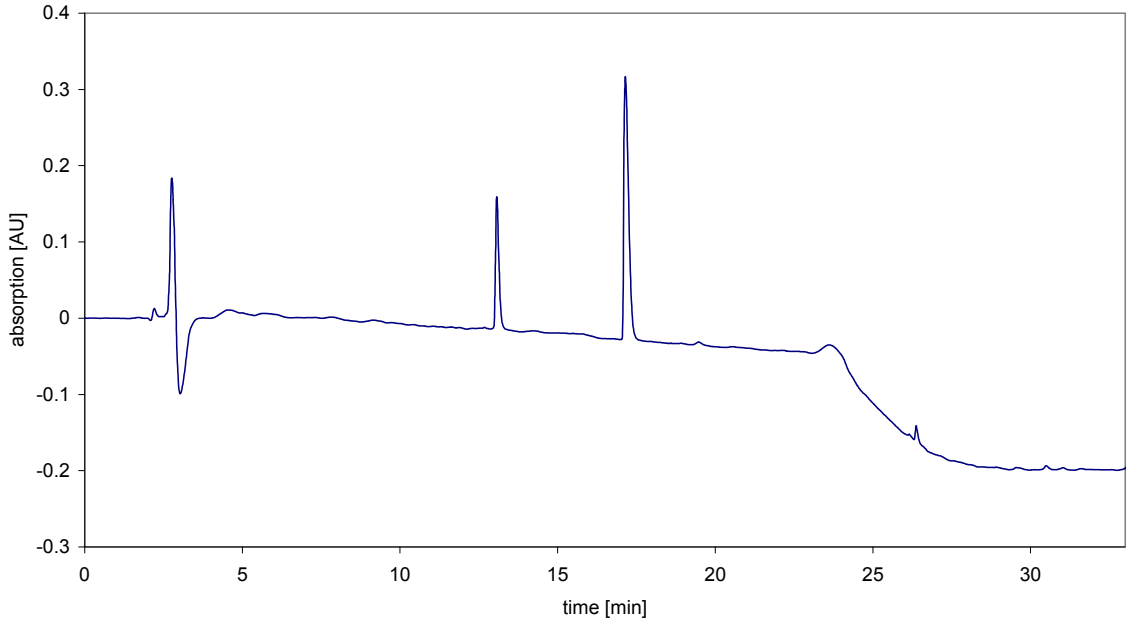
HPLC-tracing of compound **73**



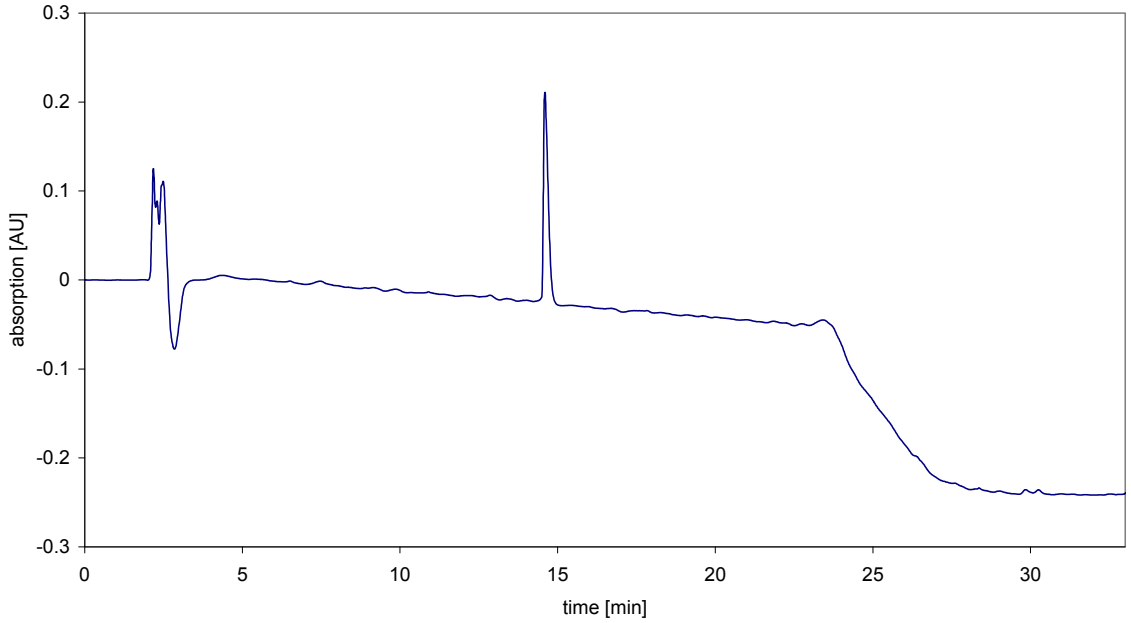
HPLC-tracing of compound **74**



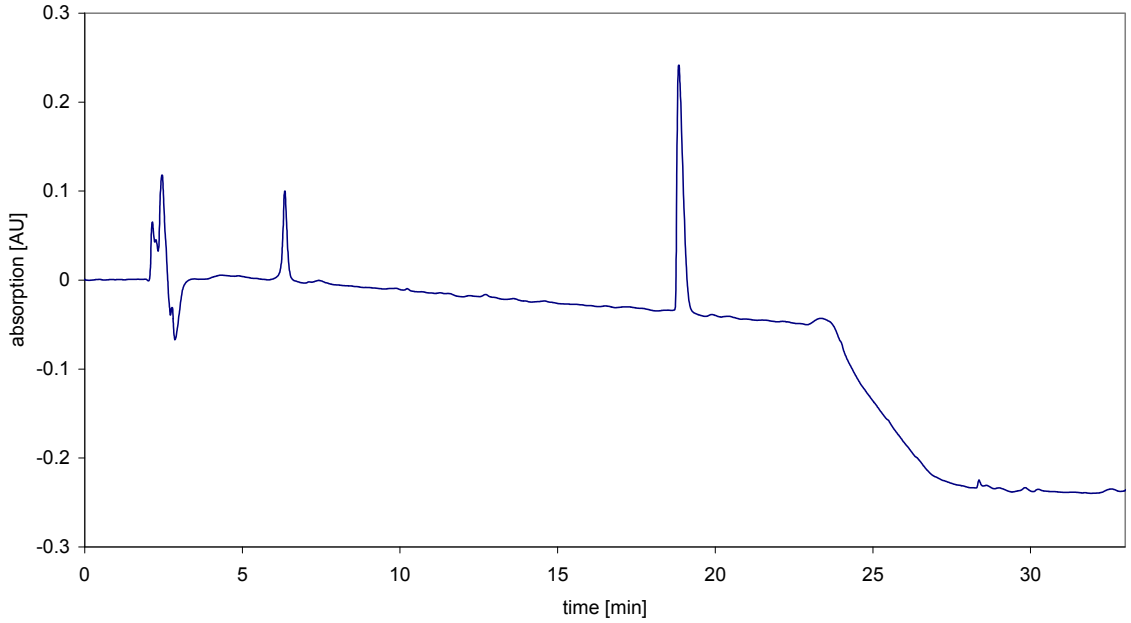
HPLC-tracing of compound **75**



HPLC-tracing of compound **76**



HPLC-tracing of compound **77**



5. Pharmacological methods

Investigations on isolated guinea pig organs

Histamine H_1 receptor assay on the isolated guinea pig ileum. Guinea pigs of either sex (250-500 g) were stunned by a blow on the neck and exsanguinated. The ileum was rapidly removed, rinsed and cut into segments of 1.5-2 cm length. The tissues were mounted isotonically (preload of 5 mN) in a jacketed 20-mL organ bath that was filled with Tyrode's solution of the following composition [mM]: NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.0, NaH_2PO_4 0.4, $NaHCO_3$ 11.9, and glucose 5.0. The solution additionally contained atropine to block cholinergic M receptors at a concentration not affecting H_1 receptors (0.05 μM). The solution was aerated with 95% O_2-5% CO_2 and warmed to a constant temperature of 37 °C. During an equilibration period of 80 min, the tissues were stimulated three times with histamine (1 μM, then 10 μM) followed by washout. Up to four cumulative concentration-response curves were determined on each organ preparation: a first to histamine (0.01-30 μM), and the second to fourth curve to histamine in the presence of increasing concentrations of antagonist (incubation time 10–15 min). pEC_{50} differences were not corrected since four successive curves for histamine were superimposable ($n > 10$).

Histamine H_2 receptor assay on isolated guinea pig right atrium (spontaneously beating). Hearts were rapidly removed from guinea pigs used for studies on the ileum (see above). The right atrium was quickly dissected and set up isometrically in Krebs-Henseleit solution under a diastolic resting force of 5 mN in a jacketed 20 mL-organ bath of 32.5 °C as previously described.[27] The bath fluid (composition [mM]: NaCl 118.1, KCl 4.7, $CaCl_2$ 1.8, $MgSO_4$ 1.64, KH_2PO_4 1.2, $NaHCO_3$ 25.0, glucose 5.0, sodium pyruvate 2.0) was equilibrated with 95% O_2-5% CO_2 and additionally contained (*RS*)-propranolol (0.3 μM) to block β-adrenergic receptors and mepyramine (1 μM) to block H_1-receptors. Experiments were started after 30 min of continuous washing and an additional equilibration period of 15 min. *Antagonists:* Two successive concentration-frequency curves to histamine (0.1-30 μM) were established, the first in the absence and the second in the presence of the compound under study (incubation time 30 min). Two successive curves for histamine displayed a significant desensitization of 0.13 ± 0.02 (N = 16 control organs). This value was used to correct each individual experiment. *Agonists:* Two successive concentration-frequency curves were established, the first to histamine (0.1-30 μM) and the second for the agonist under study in the absence or presence of cimetidine (10 μM, 30 min incubation time). Furthermore, the sensitivity to 30 μM cimetidine was routinely checked at the end of each H_2R agonist concentration-effect curve established in the absence of an H_2 receptor antagonist, and a significant reduction of frequency was always observed after 15–45 min.

Calcium assays with U-373 MG cells

Cells and culture conditions. The human U-373 MG (HTB 17) glioblastoma/astrocytoma cell line was obtained from the American Type Culture Collection (Rockville, MD, USA). Cell banking and quality control were performed according to the "seed stock concept". Cells were grown in Eagle´s minimum essential medium containing L-glutamine, 2.2 g/L $NaHCO_3$, 110 mg/L sodium pyruvate (Sigma, Deisenhofen, Germany), and 10% (v/v) FCS (GIBCO, Eggenstein, Germany). The cells were cultured in a water-saturated atmosphere of 95% air and 5% carbon dioxide at 37 °C in 75-cm² culture flasks (Costar, Tecnomara, Fernwald, Germany) and were serially passaged following trypsinization using trypsin (0.05%, v/v) / EDTA (0.02%, v/v) (Roche Diagnostics, Mannheim, Germany).

Preparation of the cells. Adherently growing U-373 MG cells were trypsinized and transferred from a 75-cm^2 flask to 175-cm^2 flask (Nunclon, 178883, Nunc, Wiesbaden, Germany) 5-6 days before the experiment. At approx. 80% confluence cells were trypsinized, the suspension ($2\text{-}4 \cdot 10^5$ cells per mL), was centrifuged for 10 min at 200 g and room temperature. After resuspension in 10 mL of loading buffer (25 mM HEPES (Sigma, Deisenhofen, Germany), 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 1.5 mM $CaCl_2$, 10 mM glucose), pH 7.4, cell number was determined with a hemocytometer

(Neubauer, improved), and the cells were adjusted to a density of $1.3 \cdot 10^6$ per mL by addition of an appropriate volume of loading buffer.

Loading of the cells with Ca^{2+} indicator Fura-2/AM. To three volumes of the prepared cell suspension, one volume of loading dispersion was added, before the cells were incubated in the dark at room temperature for 30 min. The loading dispersion was freshly made by mixing 10 mL of loading buffer, containing 2 % bovine serum albumin (BSA), with 50 µL of Pluronic-F-127 (Molecular Probes, Eugene, Oregon, USA) (20 % in DMSO), and 40 µL of Fura-2/AM (Molecular Probes, Eugene, Oregon, USA) (1 mM in anhydrous DMSO).

Cells were centrifuged (200 g, 7 min), resuspended in fresh loading buffer and allowed to stand for another 30 min at room temperature in the dark. After two washing/centrifugation cycles (loading buffer, 200 g, 7 min) and adjustment of the cell number to a value of 10^6 /mL, cells were incubated for at least 15 min at 20 °C in the dark.

Fluorimetric determination of intracellular $[Ca^{2+}]$. 1 mL-aliquots of loading buffer were filled into disposable acrylic cuvettes (Sarstedt, No. 67.755, Nuembrecht, Germany), which were thermostatted at 30 °C in an incubator hood (Infors AG, Bottmingen, Switzerland). Immediately after addition of 1 mL of the Fura-2/AM loaded cell suspension and a magnetic stirrer, the cuvette was placed into the thermostatted (25 °C) stirred cell holder of a LS 50 B Luminescence Spectrometer (Perkin Elmer, Ueberlingen, Germany), equipped with a fast filter accessory. Fluorescence signals were registered (instrument settings: excitation 340/380 nm, emission 510 nm, slits 10 nm, resolution 0.1, stirrer low) for 300 s after addition of 10 µL of 6 mM histamine dihydrochloride dissolved in millipore water.

Calculation of Ca^{2+} concentrations. Calcium concentrations were calculated from dual wavelength fluorescence intensities according to the Grynkiewicz equation:

$$\left[Ca^{2+}\right] = K_d \cdot \frac{(R - R_{\min})}{(R_{\max} - R)} \cdot SFB$$

were K_d (224 nM) is the dissociation constant of the Fura-2-Ca^{2+}-complex, R is the experimental fluorescence ratio value (F_{340} / F_{380}), R_{min} and R_{max} are the fluorescence value ratios (F_{340} / F_{380}) under Ca^{2+}-free and Ca^{2+}-saturation conditions, respectively, and SFB is the ratio of fluorescence intensities for Ca^{2+}-free/Ca^{2+}-bound indicator, measured at 380 nm. R_{min}, R_{max} and SFB were determined by calibration experiments, performed in every test series.

To measure R_{max}, 10 µL of an aqueous solution of 2 % digitonin (Sigma, Deisenhofen, Germany), were pipetted into the cuvette, wheras R_{min} was determined after subsequent addition of 50 µL of a 0.6 M EGTA solution (in 1 M Tris/HCl, pH 8.7).

Investigation of histamine H_1 receptor antagonists on U-373 MG cells:[28] To determine the histamine H_1 receptor antagonism on U-373 MG cells, the inhibition of the (submaximal) increase in $[Ca^{2+}]_i$ elicited by 30 µM histamine was measured. Prior to stimulation with histamine the cells were incubated with the putative antagonists for 15 min in the dark with stirring. The inhibition (%) was calculated as follows:

$$\text{Inhibition [\%]} = \left(100 - \frac{[Ca^{2+}]_i\text{-increase (antagonist + 30 µM hist.) [µM]}}{[Ca^{2+}]_i\text{-increase (control) [µM]}}\right) \cdot 100$$

At least seven concentrations of the antagonists were used and at least two independent experiments were carried out on different days. The mean values of the resulting inhibition curves were used to

calculate IC_{50} and pK_B values, respectively.

Calculation of IC_{50} values: IC_{50} values were calculated from at least two antagonist concentrations [B], inhibiting the agonist-stimulated increase in intracellular [Ca^{2+}] between 20 and 80 %. The mean percentual inhibition values P with SEM < 10 %, determined from at least 3 independent experiments, performed on different days, were logit transformed, according to the equation

$$\text{logit (P)} = \log \frac{P}{100 - P}$$

and IC_{50} values (logit P = 0) were determined from the plot logit (P) versus log [B] with the slope n according to

$$\log \frac{P}{100 - P} = n \cdot \log [B] - n \cdot \log IC_{50}$$

by linear regression.

K_B values were calculated according to the Cheng-Prusoff equation with EC_{50} = 5.37 µM for histamine.

Determination of histamine receptor agonism and antagonism in GTPase assays

Generation of recombinant baculoviruses, cell culture and membrane preparation. Recombinant baculoviruses encoding human H_1R or a fusion protein of the human H_2R with $G_{s\alpha S}$ were prepared as described.[29, 30] Receptors were N-terminally tagged with the FLAG epitope and C-terminally tagged with a hexahistidine tag. The cDNA of the human H_3R was kindly provided by Dr. Robin Thurmond (Johnson & Johnson Research and Development, La Jolla, CA), and the cDNA of the human H_4R was from the UMR cDNA Resource Center at the University of Missouri-Rolla (Rolla, MO). Baculoviruses for the human H_3R and a fusion protein of the human H_4R with the RGS-protein GAIP were prepared in analogy to the procedures for the H_1R and the H_2R-$G_{s\alpha S}$ fusion protein[29, 30] using the BaculoGOLD transfection kit (BDPharmingen, San Diego, CA) according to the manufacturer's instructions.

Sf9 cells were cultured in 250- or 500-mL disposable Erlenmeyer flasks at 28 °C under rotation at 150 r.p.m in SF 900 II medium (Invitrogen, Carlsbad, CA) supplemented with 5 % (v/v) fetal calf serum (Biochrom, Berlin, Germany) and 0.1 mg/mL gentamicin (Cambrex Bio Science, Walkersville, MD). Cells were maintained at a density of 0.5 – 6.0 x 10^6 cells/mL. After initial transfection, high-titer virus stocks were generated by two sequential virus amplifications. In the first amplification, cells were seeded at 2.0 x 10^6 cells/mL and infected with a 1:100 dilution of the supernatant from the initial transfection. Cells were cultured for 7 days, resulting in the death of virtually the entire cell population. The supernatant fluid of this infection was harvested and stored under light protection at 4 °C. In a second amplification, cells were seeded at 3.0 x 10^6 cells/mL and infected with a 1:20 dilution of the supernatant fluid from the first amplification. Cells were cultured for 48 h, and the supernatant fluid was harvested. After the 48 h culture period, the majority of cells showed signs of infections (e.g. altered morphology, viral inclusion bodies), but most of the cells were still intact. The supernatant fluid from the second amplification was stored under light protection at 4 °C and used as routine virus stock for membrane preparations.

In infections for membrane preparation, cells were sedimented by centrifugation and suspended in fresh medium at 3.0 x 10^6 cells/mL. Cells were infected with 1:100 dilutions of high-titer baculovirus stocks encoding the various histamine receptors, histamine receptor fusion proteins, G-protein subunits and RGS proteins. Cells were cultured for 48 h before membrane preparation. Sf9 membranes were prepared as described,[31] using 1 mM EDTA, 0.2 mM phenylmethylsulfonyl fluoride, 10 µg/mL benzamidine and 10 µg/mL leupeptin as protease inhibitors. Membranes were suspended in binding

buffer (12.5 mM $MgCl_2$, 1 mM EDTA and 75 mM Tris/HCl, pH 7.4) and stored at -80 °C until use. Protein concentrations were determined using the DC protein assay kit (Bio-Rad, Hercules, CA).

Synthesis of [γ-^{32}P]GTP. [γ-^{32}P]GTP was synthesized by enzymatic phosphorylation of GDP according to a previously described procedure.[32] [^{32}P]P_i (8,500-9,100 Ci/mmol orthophosphoric acid) was from PerkinElmer Life Sciences (Boston, MA, USA). All unlabeled nucleotides, glycerol-3-phosphate dehydrogenase, triose phosphate isomerase, glyceraldehyde-3-phosphate dehydrogenase, and lactate dehydrogenase were from Roche (Mannheim, Germany). 3-Phosphoglycerate kinase and L-glycerol-3-phosphate was from Sigma.

Steady-state GTPase activity assay with Sf9 insect cell membranes expressing histamine H_{1-4} receptors. Membranes were thawed, sedimented and resuspended in 10 mM Tris/HCl, pH 7.4. In the case of the H_1R and H_2R, Sf9 membranes expressing either H_1R isoforms plus RGS4 or H_2R-$G_{s\alpha}$ fusion proteins, respectively, were used.[33, 34] H_3R-regulated GTP hydrolysis was determined with membranes co-expressing human H_3R, mammalian $Gi_{\alpha 2}$, $G_{\beta 1\gamma 2}$ and RGS4. Human H_4R activity was measured with membranes co-expressing an H_4R-RGS19 fusion protein with $Gi_{\alpha 2}$ and $G_{\beta 1\gamma 2}$. Assay tubes contained Sf9 membranes (10-20 µg of protein/tube), $MgCl_2$ (H_1R, H_2R: 1.0 mM; H_3R, H_4R: 5.0 mM), 100 µM EDTA, 100 µM ATP, 100 nM GTP, 100 µM adenylyl imidodiphosphate, 5 mM creatine phosphate, 40 µg creatine kinase and 0.2 % (w/v) bovine serum albumin in 50 mM Tris/HCl, pH 7.4, as well as ligands at various concentrations. In H_4R assays, NaCl (final concentration of 100 mM) was included. Reaction mixtures (80 µL) were incubated for 2 min at 25 °C before the addition of 20 µL [γ-^{32}P]GTP (0.1 µCi/tube). Reactions were conducted for 20 min at 25 °C and terminated by the addition of 900 µL of slurry consisting of 5% (w/v) activated charcoal suspended in 50 mM NaH_2PO_4, pH 2.0. Charcoal absorbs nucleotides but not P_i. Charcoal-quenched reaction mixtures were centrifuged for 7 min at room temperature at 15.000 *g*. Sixhundred µL of the supernatant fluid were removed, and $^{32}P_i$ was determined by liquid scintillation counting. Enzyme activities were corrected for spontaneous degradation of [γ-^{32}P]GTP. Spontaneous [γ-^{32}P]GTP degradation was determined in tubes containing all components described above, plus a high concentration of unlabeled GTP (1 mM) that, by competition with [γ-^{32}P]GTP, prevents [γ-^{32}P]GTP hydrolysis by enzymatic activities present in Sf9 membranes. Spontaneous [γ-^{32}P]GTP degradation was <1 % of the total amount of radioactivity added. The experimental conditions chosen ensured that not more than 10% of the total amount of [γ-^{32}P]GTP added was converted to $^{32}P_i$. All experimental data were analyzed by non-linear regression with the Prism 4 program (GraphPad Software, San Diego, CA).

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