Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Synthesis, SAR and selectivity of 2-acyl- and 2-cyano-1-hetarylalkyl-guanidines at the four histamine receptor subtypes: a bioisosteric approach

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Contents pages

Experimental section

Chemistry

General conditions

Commercial reagents and chemicals were purchased from Acros Organics (Geel, Belgium), IRIS Biotech GmbH (Marktredwitz, Germany), Alfa Aesar GmbH & Co. KG (Karlsruhe, Germany), Merck KGaA (Darmstadt, Germany), Sigma-Aldrich Chemie GmbH (Munich, Germany), TCI Europe (Zwijndrecht, Belgium) and used without further purification. Deuterated solvents for NMR spectroscopy were from Deutero GmbH (Kastellaun, Germany). All solvents were of analytical grade or distilled prior to use. Millipore water was used throughout for the preparation of buffers and HPLC eluents. If moisture-free conditions were required, reactions were performed in dried glassware under inert atmosphere (argon or nitrogen). Anhydrous DMF was purchased from Sigma-Aldrich Chemie GmbH and stored over 3 Å molecular sieves. Flash chromatography was performed in glass columns on silica gel (Merck silica gel 60, 40 – 63 µM). Automated flash chromatography was performed on a Varian IntelliFlash 310 using pre-packed Varian Superflash columns (Varian, Darmstadt, Germany). Reactions were monitored by TLC on aluminum plates coated with silica gel (Merck silica gel 60 F_{254}, thickness 0.2 mm). The compounds were detected by UV light (254 nm), a 0.3 % solution of ninhydrine in *n*-butanol (amines), a 1.0 % solution of Fast Blue B salt (imidazole containing compounds) in EtOH/H_2O = 30/70 (v/v) or iodine staining. All melting points are uncorrected and were measured on a Büchi 530 (Büchi GmbH, Essen, Germany) apparatus. Lyophilisation was done with a Christ alpha 2-4 LD equipped with a vacuubrand RZ 6 rotary vane vacuum pump. Microwave assisted reactions were performed on an Initiator 2.0 synthesizer (Biotage, Uppsala, Sweden).

Nuclear Magnetic Resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded with Bruker Avance 300 (^{1}H: 300.1 MHz, ^{13}C: 75.5 MHz), Avance 400 (^{1}H: 400.1 MHz, ^{13}C: 100.6 MHz) or Bruker Avance 600 (^{1}H: 600.1 MHz, ^{13}C: 150.9 MHz) NMR spectrometers (Bruker BioSpin GmbH, Rheinstetten, Germany). Chemical shifts are given in δ (ppm) relative to external standards. Abbreviations for the multiplicities of the signals: s (singlet), d (doublet), t (triplet), m (multiplet), brs (broad singlet) and combinations thereof. The multiplicity of carbon atoms (^{13}C-NMR) was determined by DEPT 135 (distortionless enhancement by polarization transfer): "+" primary and tertiary carbon atom (positive DEPT 135 signal), "-" secondary carbon atom (negative DEPT 135 signal), "C_{quat}" quaternary carbon atom. In certain cases 2D-NMR

techniques (COSY, HMQC, HSQC, HMBC, NOESY) were used to assign ^{1}H and ^{13}C chemical shifts. Infrared spectra (IR) were measured on a Bruker Tensor 27 spectrometer equipped with an ATR (attenuated total reflection) unit from Harrick Scientific Products Inc. (Ossinning/NY, US). Mass spectra (MS) were recorded on a Finnigan MAT 95 (EI-MS 70 eV, HR-MS), Finnigan SSQ 710A (CI-MS (NH_3)) and on a Finnigan ThermoQuest TSQ 7000 (ES-MS) spectrometer. The peak-intensity in % relative to the strongest signal is indicated in parenthesis. Elemental analysis (C, H, N, Heraeus Elementar Vario EL III) were performed by the Analytical Department of the University Regensburg and are within ± 0.4 % unless otherwise noted.

Preparative HPLC was performed at room temperature with a system from Knauer (Berlin, Germany) consisting of two K-1800 pumps, a K-2001 detector (UV detection at 220 nm) and a RP-column (VP Nucleodur 100-5 C18 ec, 250 x 21 mm, 5 µm, Macherey Nagel, Düren, Germany) at a flow rate of 18 mL/min. Mixtures of acetonitrile and millipore water were used as mobile phase. Acetonitrile was removed from the eluates under reduced pressure (final pressure: 60 mbar) at 40 °C prior to lyophilization.

Analytical HPLC analysis was performed on a system from Thermo Separation Products (TSP, Egelsbach, Germany) composed of a SN400 controller, a P4000 pump, an AS3000 autosampler, a degasser (Degassex DG-4400, Phenomenex), a Spectra Focus UV-VIS detector and a RP-column thermostated at 30 °C ((a) Eurosphere-100 C18, 250 × 4.0 mm, 5 µm; Knauer, Berlin, Germany; t_0 = 3.32 min; (b) MN Nucleodur 100-5 C18 ec, 250 x 4.0 mm, 5 µm; Macherey Nagel, Düren, Germany; t_0 = 2.68 min; (c) Gemini NX C18, 250 x 4.6 mm, 5 µm; Phenomenex, Aschaffenburg, Germany; t_0 = 3.83 min; (d) Luna C18-2, 150 x 4.6 mm, 4 µm; Phenomenex, Aschaffenburg, Germany; t_0 = 2.88 min) at a flow rate of 0.8 mL/min. UV-detection was done at 220 nm. Mixtures of acetonitrile and 0.05 % aq. TFA were used as mobile phase. Helium degassing was used throughout. Compound purities were calculated as percentage peak area of the analyzed compound by UV detection at 220 nm. Purity of tested compounds was > 95 % as determined by high-performance liquid chromatography.

Preparation of the arylpropylalcohols 8, 10, 14 and 20, and arylpropylamines 27-29

3-(Furan-2-yl)propan-1-ol (7)[1]

To a solution of **6** (10.0 g, 59.4 mmol) in Et_2O (200 mL), $LiAlH_4$ (4.51 g, 118.8 mmol) was added in portions at 0 °C. After addition was complete, the mixture was allowed to warm to ambient temperature and stirred overnight. The mixture was cooled externally with ice and subsequently 4.5 mL H_2O, 4.5 mL NaOH 15 % and 18 mL H_2O were added. Insoluble material was removed by filtration and washed with Et_2O (2 x 50 mL). The combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. Evaporation of the solvent provided a colourless oil that was used without further purification (6.1 g, 81 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.85 – 1.96 (m, 2H, Fur-2-CH_2-C***H***$_2$), 2.73 (t, 2H, ^3J = 7.4 Hz, Fur-2-C***H***$_2$), 3.68 (t, 2H, ^3J = 6.4 Hz, Fur-2-$(CH_2)_2$-C***H***$_2$), 6.01 (m, 1H, Fur-3-***H***), 6.28 (dd, 1H, ^3J = 3.1 Hz, ^3J = 1.9 Hz, Fur-4-***H***), 6.28 (dd, 1H, ^3J = 1.9 Hz, ^4J = 0.8 Hz, Fur-5-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 24.34 (-, Fur-2-CH_2-***C***H_2), 31.03 (-, Fur-2-***C***H_2), 62.09 (-, Fur-2-$(CH_2)_2$-***C***H_2), 105.07 (+, Fur-***C***-3), 110.17 (+, Fur-***C***-4), 140.99 (+, Fur-***C***-5), 155.59 (C_{quat}, Fur-***C***-2). CI-MS (NH_3) *m/z* (%): 127 (100) $[M + H]^+$. $C_7H_{10}O_2$ (126.15).

3-{5-[(Dimethylamino)methyl]furan-2-yl}propan-1-ol (8)[2]

A solution of **7** (5.51 g, 43.7 mmol), dimethylamine · HCl (5.55 g, 68.1 mmol) and paraformaldehyde (2.05 g, 68.1 mmol) in EtOH (100 mL) was refluxed overnight. After removing the solvent under reduced pressure, an aqueous solution of NaOH (1 M, 100 mL) was added and the aqueous layer was extracted with Et_2O (3 x 80 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* yielding a colourless oil (6.8 g, 85 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.82 – 1.94 (m, 2H, Fur-2-CH_2-C***H***$_2$), 2.23 (s, 6H, C***H***$_3$), 2.70 (t, 2H, ^3J = 7.4 Hz, Fur-2-C***H***$_2$), 3.39 (s, 2H, Fur-5-C***H***$_2$), 3.64 (t, 2H, ^3J = 6.4 Hz, Fur-2-$(CH_2)_2$-C***H***$_2$), 5.91 (d, 1H, ^3J = 3.0 Hz, Fur-3-***H***), 6.06 (d, 1H, ^3J = 3.0 Hz, Fur-4-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 24.47 (-, Fur-2-CH_2-***C***H_2), 31.14 (-, Fur-2-***C***H_2), 44.92 (+, 2 ***C***H_3), 55.92 (-, Fur-5-***C***H_2), 61.91 (-, Fur-2-$(CH_2)_2$-***C***H_2), 105.45 (+, Fur-***C***-3), 109.20 (+, Fur-***C***-4), 150.99 (C_{quat}, Fur-***C***-5), 155.59 (C_{quat}, Fur-***C***-2). CI-MS (NH_3) *m/z* (%): 184 (100) $[M + H]^+$. $C_{10}H_{17}NO_2$ (183.25).

3-(1-Trityl-1*H*-imidazol-2-yl)propan-1-ol (10)[3]

9[3] (8.0 g, 23.4 mmol) was dissolved in THF_{abs} (240 mL) under an argon atmosphere and cooled to – 78 °C. *n*-BuLi 1.6 M in hexane (15.6 mL, 25.0 mmol) was added dropwise (internal temperature < – 65 °C) and stirred for 1 h at – 78 °C. Oxirane (ca. 5.9 mL, 5.15 g, 117 mmol) was condensed into THF_{abs} (5 mL) at – 78 °C and added to the mixture. The reaction mixture was allowed to slowly warm to ambient temperature and stirred overnight. After addition of NH_4Cl (1 M, 150 mL), the product was extracted with EtOAc (4 x 70 mL) and the combined organic layers dried over Na_2SO_4. The solvent was removed *in vacuo* and purification by flash chromatography (DCM/MeOH 97.5/2.5 v/v) yielded a white solid (4.5 g, 52 %); mp 154 – 155 °C (ref.[3]: 157.5 – 157.9 °C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.31 – 1.42 (m, 2H, Im-2-CH_2-C***H***$_2$), 2.09 (t, 2H, ^3J = 6.3 Hz, Im-2-C***H***$_2$), 3.50 (t, 2H, ^3J = 5.3 Hz, Im-2-$(CH_2)_2$-C***H***$_2$), 6.68 (d, 1H, ^3J = 1.5 Hz, Im-4-***H***), 6.91 (d, 1H, ^3J = 1.5 Hz, Im-5-***H***), 7.08 – 7.17 (m, 6H, Ph-***H***), 7.29 – 7.38 (m, 9H, Ph-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 29.18, 29.49 (-, Im-2-***C***H_2-***C***H_2), 62.87 (-, Im-2-$(CH_2)_2$-***C***H_2), 75.01 (C_{quat}, ***C***Ph_3), 121.34 (+, Im-***C***-5), 124.73 (+, Im-***C***-4), 127.95 (+, 3 Ph-***C***-4), 128.11 (+, 6 Ph-***C***), 129.89 (+, 6 Ph-***C***), 142.46 (C_{quat}, 3 Ph-***C***-1), 150.45 (C_{quat}, Im-***C***-2). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 369 (44) $[M + H]^+$, 243 (100) $[CPh_3^+]$. Anal. ($C_{25}H_{24}N_2O$) C, H, N. $C_{25}H_{24}N_2O$ (368.47)

4-Iodo-1-trityl-1*H*-pyrazole (12)[4]

To a solution of **11** (5.0 g, 25.8 mmol) and tritylchloride (7.19 g, 25.8 mmol) in DCM (100 mL), NEt_3 (4.3 mL, 3.13 g, 31.0 mmol) was added dropwise at 0 °C. After addition was complete, the mixture was allowed to warm to ambient temperature and stirred for 12 h. The organic layer was washed with H_2O (2 x 30 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the product was crystallized from DCM/hexane and washed with hexane yielding a white solid (7.3 g, 65 %); mp 189 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm] = 6.99 – 7.07 (m, 6H, Ph-***H***), 7.32 – 7.41 (m, 9H, Ph-***H***), 7.44 (d, 1H, ^4J = 0.5 Hz, Pyraz-3-***H***), 7.74 (d, 1H, ^4J = 0.5 Hz, Pyraz-5-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6): δ [ppm] = 57.42 (C_{quat}, Pyraz-***C***-4), 78.53 (C_{quat}, ***C***Ph_3), 127.81 (+, 9 Ph-***C***), 129.49 (+, 6 Ph-***C***), 135.99 (+, Pyraz-***C***-5), 142.36 (C_{quat}, 3 Ph-***C***-1), 144.23 (+, Pyraz-***C***-3). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 437 (1) $[M + H]^+$, 243 (100) $[CPh_3^+]$. Anal. ($C_{22}H_{17}IN_2$) C, H, N. $C_{22}H_{17}IN_2$ (436.29).

3-(1-Trityl-1*H*-pyrazol-4-yl)prop-2-yn-1-ol (13)

To a solution of **12** (10.6 g, 24.3 mmol), $Pd(PPh_3)_2Cl_2$ (0.51 g, 0.7 mmol), CuI (0.23 g, 1.2 mmol) and diisopropylamine (15.5 mL, 11.1 g, 109.4 mmol) in degassed DMF, a solution of propargylalcohol (1.5 g, 26.7 mmol) in THF (10 mL) was added at –15 °C. After addition was complete, the mixture was stirred for 48 h at room temperature. The solvent was removed *in vacuo*, the residue dissolved in 200 mL EtOAc and washed with water (2 x 80 mL). After drying over $MgSO_4$, the solvent was evaporated and the crude product purified by flash chromatography (PE/EtOAc 80/20 v/v) yielding a beige solid (7.2 g, 81 %); mp 194 – 196 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.68 (brs, 1H, O***H***), 4.40 (s, 2H, C$\boldsymbol{H}_2$), 7.09 – 7.17 (m, 6H, Ph-***H***), 7.27 – 7.36 (m, 9H, Ph-***H***), 7.52 (d, 1H, ^4J = 0.5 Hz, Pyraz-***H***), 7.74 (d, 1H, ^4J = 0.5 Hz, Pyraz-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 51.70 (-, ***C***H_2), 77.45 (C_{quat}, ***C***Ph_3), 79.18 (C_{quat}, Pyraz-4-***C***≡C), 88.31 (C_{quat}, Pyraz-4-C≡***C***), 101.26 (C_{quat}, Pyraz-***C***-4), 127.88 (+, 6 Ph-***C***), 127.98 (+, 3 Ph-***C***), 130.12 (+, 6 Ph-***C***), 135.61 (+, Pyraz-***C***-5), 142.22 (+, Pyraz-***C***-3), 142.64 (C_{quat}, 3 Ph-***C***-1). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 729 (12) $[2M + H]^+$, 243 (100) $[CPh_3^+]$. Anal. ($C_{25}H_{20}N_2O \cdot 0.25\ H_2O$) C, H, N. $C_{25}H_{20}N_2O$ (364.44).

3-(1-Trityl-1*H*-pyrazol-4-yl)propan-1-ol (14)

13 (7.1 g, 19.5 mmol) was dissolved in MeOH (200 mL) and hydrogenated over Pd/C (10 %) (0.71 g) at room temperature overnight. After removing the catalyst by filtration over Celite, the solvent was evaporated and the crude product recrystallized from MeCN yielding a beige solid (6.8 g, 95 %); mp 94 – 97 °C (ref.[5]: 129 – 131 °C (Et_2O)). ^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm] = 1.55 – 1.68 (m, 2H, Pyraz-4-CH_2-C$\boldsymbol{H}_2$), 2.42 (t, 2H, ^3J = 7.6 Hz, Pyraz-4-C$\boldsymbol{H}_2$), 3.37 (t, 2H, ^3J = 6.4 Hz, Pyraz-4-$(CH_2)_2$-C$\boldsymbol{H}_2$), 4.39 (brs, 1H, O***H***), 6.98 – 7.42 (m, 16H, Ph-***H*** + Pyraz-***H***), 7.47 (s, 1H, Pyraz-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6): δ [ppm] = 19.84 (-, Pyraz-4-***C***H_2), 33.64 (-, Pyraz-4-CH_2-***C***H_2), 59.83 (-, Pyraz-4-$(CH_2)_2$-***C***H_2), 77.51 (C_{quat}, ***C***Ph_3), 119.74 (C_{quat}, Pyraz-***C***-4), 127.52 (+, 3 Ph-***C***-4), 127.62 (+, 6 Ph-***C***), 129.54 (+, 6 Ph-***C***), 130.17 (+, Pyraz-***C***-5), 138.98 (+, Pyraz-***C***-3), 143.12 (C_{quat}, 3 Ph-***C***-1). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 369 (30) $[M + H]^+$, 243 (100) $[CPh_3^+]$. Anal. ($C_{25}H_{24}N_2O$) C, H, N. $C_{25}H_{24}N_2O$ (368.47).

1-Trityl-1*H*-1,2,4-triazole (16)

To a solution of **15** (6.91 g, 100 mmol) and tritylchloride (27.9 g, 100 mmol) in DCM (100 mL), NEt_3 (13.8 mL, 10.1 g, 100 mmol) was added dropwise. After addition was complete, the mixture was stirred overnight. The organic layer was washed with a saturated solution of NaCl (3 x 30

mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was recrystallized from MeCN yielding a white solid (27.2 g, 87 %); mp 208 °C (ref.[6]: 213 - 214 °C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.09 – 7.19 (m, 6H, Ph-***H***), 7.29 – 7.39 (m, 9H, Ph-***H***), 8.03 (s, 1H, Triaz-***H***), 8.08 (s, 1H, Triaz-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 78.14 (C_{quat}, ***C***Ph_3), 128.09 (+, 6 Ph-***C***), 128.31 (+, 3 Ph-***C***), 130.00 (+, 6 Ph-***C***), 141.92 (C_{quat}, 3 Ph-***C***-1), 145.75 (+, Triaz-***C***-5), 151.91 (+, Triaz-***C***-3). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 623 (22) [2M + H]$^+$, 243 (100) [CPh_3^+]. Anal. ($C_{21}H_{17}N_3$) C, H, N. $C_{21}H_{17}N_3$ (311.38).

1-Trityl-1*H*-1,2,4-triazole-5-carbaldehyde (17)[6]

16 (10.0 g, 32.1 mmol) and TMEDA (4.8 mL, 3.73 g, 32.1 mmol) were dissolved in THF_{abs} (200 mL) under an argon atmosphere and cooled to – 78 °C. *n*-BuLi 1.6 M in hexane (22.1 mL, 35.3 mmol) was added dropwise (internal temperature < – 65 °C) and stirred for 1 h at – 78 °C. Anhydrous DMF (22.6 mL, 21.42 g, 29.3 mmol) was added dropwise to the mixture. After addition was complete, the mixture was stirred for 12 h at – 78 °C. The reaction mixture was allowed to warm to – 30 °C and poured in 200 mL of ice cold H_2O. Extraction with EtOAc (3 x 150 mL), drying over Na_2SO_4 and evaporation of the volatiles gave the crude product. Purification by flash chromatography (PE/EtOAc 70/30 v/v) followed by recrystallization from EtOAc/hexane yielded a white solid (8.8 g, 25.8 mmol); mp 150 – 152 °C (ref.[7]: 156 °C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.05 – 7.17 (m, 6H, Ph-***H***), 7.29 – 7.40 (m, 9H, Ph-***H***), 8.10 (s, 1H, Triaz-3-***H***), 9.15 (s, 1H, CO***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 80.29 (C_{quat}, ***C***Ph_3), 128.12 (+, 6 Ph-***C***), 128.52 (+, 3 Ph-***C***), 129.83 (+, 6 Ph-***C***), 141.65 (C_{quat}, 3 Ph-***C***-1), 150.02 (+, Triaz-C-3), 151.67 (C_{quat}, Triaz-***C***-5), 177.98 (C_{quat}, ***C***=O). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 372 (2) [M + MeOH + H]$^+$, 243 (100) [CPh_3^+]. Anal. ($C_{22}H_{17}N_3O$) C, H, N. $C_{22}H_{17}N_3O$ (339.39).

Ethyl 3-(1-trityl-1*H*-1,2,4-triazol-5-yl)acrylate (18)

To a solution of triethyl phosphonoacetate (6.67 g, 5.90 mL, 29.8 mmol) in THF_{abs} (150 mL) NaH (60 % dispersion in mineral oil) (1.19 g, 29.8 mmol) was added in portions. After stirring for 1 h at ambient temperature, a solution of **17** (8.43 g, 24.8 mmol) in THF_{abs} (75 mL) was added dropwise. When addition was complete, the mixture was stirred overnight at room temperature. The solvent was evaporated and the crude product was taken up in EtOAc (150 mL) and washed with water (3 x 50 mL). The organic layer was dried over Na_2SO_4, evaporated and the crude product purified by flash chromatography (PE/EtOAc 60/40 v/v) giving the *E*- and *Z*-isomer.

Recrystallization from EtOAc/hexane yielded the *E*-isomer and the *Z*-isomer as white solid (*E*: 6.4 g, *Z*: 1.8 g, 67 %); mp (*E*) 184 – 186 °C, mp (*Z*) 145 – 146 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) (*E*)-isomer: δ [ppm] = 1.17 (t, 3H, ^{3}J = 7.1 Hz, C***H***$_3$), 4.06 (q, 2H, ^{3}J = 7.1 Hz, C***H***$_2$), 6.59 (dd, 1H, ^{3}J = 15.4 Hz, ^{5}J = 0.6 Hz, Triaz-5-C***H***), 6.69 (d, 1H, ^{3}J = 15.4 Hz, C***H***CO), 7.06 – 7.17 (m, 6H, Ph-***H***), 7.28 – 7.38 (m, 9H, Ph-***H***), 7.97 (d, 1H, ^{5}J = 0.6 Hz, Triaz-3-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$) (*E*)-isomer: δ [ppm] = 14.12 (+, ***C***H$_3$), 60.65 (-, ***C***H$_2$), 79.02 (C$_{quat}$, ***C***Ph$_3$), 124.59 (+, vinyl-***C***), 128.01 (+, 6 Ph-***C***), 128.23 (+, 3 Ph-***C***), 129.32 (+, vinyl-***C***), 129.97 (+, 6 Ph-***C***), 141.89 (C$_{quat}$, 3 Ph-***C***-1), 149.59 (+, Triaz-***C***-3), 152.39 (C$_{quat}$, Triaz-***C***-5), 165.47 (C$_{quat}$, ***C***=O). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 410 (1) $[M + H]^+$, 243 (100) $[CPh_3^+]$. Anal. *E*-isomer ($C_{26}H_{23}N_3O_2$) C, H, N. $C_{26}H_{23}N_3O_2$ (409.48).

^{1}H-NMR (300 MHz, $CDCl_3$) (*Z*)-isomer: δ [ppm] = 1.24 (t, 3H, ^{3}J = 7.2 Hz, C***H***$_3$), 4.19 (q, 2H, ^{3}J = 7.2 Hz, C***H***$_2$), 5.56 (d, 1H, ^{3}J = 12.0 Hz, Triaz-5-C***H***), 5.68 (d, 1H, ^{3}J = 12.0 Hz, C***H***CO), 7.10 – 7.20 (m, 6H, Ph-***H***), 7.26 – 7.38 (m, 9H, Ph-***H***), 7.96 (s, 1H, Triaz-3-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$) (*Z*)-isomer: δ [ppm] = 14.02 (+, ***C***H$_3$), 60.84 (-, ***C***H$_2$), 78.66 (C$_{quat}$, ***C***Ph$_3$), 125.09 (+, vinyl-***C***), 125.45 (+, vinyl-***C***), 127.85 (+, 6 Ph-***C***), 128.16 (+, 3 Ph-***C***), 130.29 (+, 6 Ph-***C***), 141.72 (C$_{quat}$, 3 Ph-***C***-1), 149.29 (+, Triaz-***C***-3), 151.66 (C$_{quat}$, Triaz-***C***-5), 165.52 (C$_{quat}$, ***C***=O). ES-MS (DCM/MeOH + NH_4OAc) *Z*-isomer *m/z* (%): 410 (100) $[M + H]^+$. Anal. *Z*-isomer ($C_{26}H_{23}N_3O_2$) C, H, N. $C_{26}H_{23}N_3O_2$ (409.48).

Ethyl 3-(1-trityl-1*H*-1,2,4-triazol-5-yl)propanoate (19)[8]

18 (8.0 g, 19.5 mmol) was dissolved in a mixture of EtOH (120 mL) / THF (30 mL) and hydrogenated over Pd/C (10 %) (0.80 g) at room temperature overnight. After removing the catalyst by filtration over Celite, the solvent was evaporated and the crude product recrystallized from hexane/EtOAc yielding a white solid (6.3 g, 79 %); mp 140 – 141 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.19 (t, 3H, ^{3}J = 7.1 Hz, C***H***$_3$), 2.17 – 2.25 (m, 2H, C***H***$_2$), 2.28 – 2.35 (m, 2H, C***H***$_2$), 4.06 (q, 2H, ^{3}J = 7.1 Hz, C***H***$_2$CH$_3$), 7.09 – 7.18 (m, 6H, Ph-***H***), 7.28 – 7.39 (m, 9H, Ph-***H***), 7.87 (s, 1H, Triaz-3-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 14.20 (+, ***C***H$_3$), 24.38 (-, ***C***H$_2$), 31.09 (-, ***C***H$_2$), 60.47 (-, ***C***H$_2$CH$_3$), 77.89 (C$_{quat}$, ***C***Ph$_3$), 127.90 (+, 6 Ph-***C***), 127.93 (+, 3 Ph-***C***), 130.04 (+, 6 Ph-***C***), 141.78 (C$_{quat}$, 3 Ph-***C***-1), 148.63 (+, Triaz-***C***-3), 156.60 (C$_{quat}$, Triaz-***C***-5), 172.18 (C$_{quat}$, ***C***=O). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 412 (100) $[M + H]^+$. Anal. ($C_{26}H_{25}N_3O_2$) C, H, N. $C_{26}H_{25}N_3O_2$ (411.50).

3-(1-Trityl-1*H*-1,2,4-triazol-5-yl)propan-1-ol (20)[8]

To a solution of **19** (6.0 g, 14.6 mmol) in THF_{abs}, $LiAlH_4$ (1.11 g, 29.2 mmol) was added in portions at 0 °C. After addition was complete, the mixture was allowed to warm to room temperature and refluxed for 2 h. Subsequently, under external ice cooling, H_2O (1.1 mL), NaOH 15 % (1.1 mL) and H_2O (4.4 mL) were added, insoluble material filtered off and washed with THF (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated *in vacuo*. Purification by flash chromatography ($CHCl_3$/MeOH 97.5/2.5 v/v) followed by recrystallization from hexane/EtOAc yielded a white solid (4.1 g, 76 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.34 – 1.47 (m, 2H, Triaz-5-CH_2-C***H***$_2$), 2.18 (t, 2H, ^3J = 6.7 Hz, Triaz-5-C***H***$_2$), 3.39 – 3.51 (m, 2H, Triaz-5-$(CH_2)_2$-C***H***$_2$), 3.75 (brs, 1H, O-***H***), 7.06 – 7.17 (m, 6H, Ph-***H***), 7.28 – 7.38 (m, 9H, Ph-***H***), 7.88 (s, 1H, Triaz-3-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 27.27, 29.07 (-, Triaz-5-***C***H_2-***C***H_2), 62.30 (-, Triaz-5-$(CH_2)_2$-***C***H_2), 77.93 (C_{quat}, ***C***Ph_3), 127.91 (+, 6 Ph-***C***), 127.94 (+, 3 Ph-***C***), 129.89 (+, 6 Ph-***C***), 141.92 (C_{quat}, 3 Ph-***C***-1), 148.13 (+, Triaz-***C***-3), 157.82 (C_{quat}, Triaz-***C***-5). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 370 (100) $[M + H]^+$. Anal. ($C_{24}H_{23}N_3O$) C, H, N. $C_{24}H_{23}N_3O$ (369.46).

General procedure for the synthesis of 2-[3-(pyridyl)propyl]isoindoline-1,3-diones (24-26)

To a cold solution (0 °C) of the pertinent 3-pyridylpropan-1-ol (5.0 g, 36.4 mmol) in THF_{abs} (100 mL), phthalimide (5.9 g, 40.1 mmol) and triphenylphosphine (10.52 g, 40.1 mmol) were added. Under external cooling with ice, DIAD (8.11 g, 40.1 mmol) in THF_{abs} (50 mL) was added dropwise. The mixture was allowed to warm and stirred overnight at ambient temperature. After concentration in vacuo, the crude product was subjected to flash chromatography. For analytical purposes a small amount of the purified product was converted into the picrate by addition of a saturated solution of picric acid in EtOH and recrystallized from EtOH/H_2O.

2-[3-(Pyridin-2-yl)propyl]isoindoline-1,3-dione (24)[9]

The title compound was prepared from **21** according to the general procedure and purified by flash chromatography (PE/EtOAc 70/30 v/v) yielding a brownish oil (7.3 g, 75 %); mp (**24** · $C_6H_3N_3O_7$) 139 – 140 °C. ^{1}H-NMR (300 MHz, DMSO-d_6, dipicrate): δ [ppm] = 2.00 – 2.13 (m, 2H, Pyr-2-CH_2-C***H***$_2$), 3.04 (t, 2H, ^3J = 8.0 Hz, Pyr-2-C***H***$_2$), 3.67 (t, 2H, ^3J = 6.5 Hz, Pyr-2-$(CH_2)_2$-C***H***$_2$), 7.81 – 7.92 (m, 5H, Pyr-5-***H*** + Phth-***H***), 7.98 (d, 1H, ^3J = 8.0 Hz, Pyr-3-***H***), 8.44 – 8.52 (m, 1H, Pyr-4-***H***), 8.58 (s, 2H, picrate-***H***), 8.79 (dd, 1H, ^3J = 5.8 Hz, ^4J = 1.7 Hz, Pyr-6-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 27.39 (-, Pyr-2-CH_2-***C***H_2), 30.49 (-, Pyr-2-

CH_2), 36.64 (-, Pyr-2-$(CH_2)_2$-***C***H_2), 122.95 (-, Phth-***C***-4,7), 124.08 (C_{quat}, picrate-***C***-4), 124.47 (+, Pyr-***C***-5), 125.10 (+, picrate-***C***-3,5), 126.56 (+, Pyr-***C***-3), 131.58 (C_{quat}, Phth-***C***-3a,7a), 134.34 (+, Phth-***C***-5,6), 141.75 (C_{quat}, picrate-***C***-2,6), 141.85 (+, Pyr-***C***-6), 145.73 (+, Pyr-***C***-4), 156.28 (C_{quat}, Pyr-***C***-2), 160.69 (C_{quat}, picrate-***C***-1), 167.91 (C_{quat}, ***C***=O). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 267 (100) $[M + H]^+$. Anal. ($C_{16}H_{14}N_2O_2 \cdot C_6H_3N_3O_7$) C, H, N. $C_{16}H_{14}N_2O_2$ (266.29).

2-[3-(Pyridin-3-yl)propyl]isoindoline-1,3-dione (25)[9]

The title compound was prepared from **22** according to the general procedure and purified by flash chromatography (PE/EtOAc 60/40 v/v) yielding a pale yellow solid (5.4 g, 56 %); mp (**25** · $C_6H_3N_3O_7$) 145 – 146 °C. ^{1}H-NMR (300 MHz, DMSO-d_6, dipicrate): δ [ppm] = 1.91 – 2.06 (m, 2H, Pyr-3-CH_2-C***H***$_2$), 2.85 (t, 2H, ^3J = 7.9 Hz, Pyr-3-C***H***$_2$), 3.64 (t, 2H, ^3J = 6.7 Hz, Pyr-3-$(CH_2)_2$-C***H***$_2$), 7.80 – 7.91 (m, 4H, Phth-H), 7.99 (dd, 1H, ^3J = 8.0 Hz, ^3J = 5.7 Hz, Pyr-5- ***H***), 8.52 (ddd, 1H, ^3J = 8.0 Hz, ^4J = 1.9 Hz, ^4J = 1.4 Hz, Pyr-4-***H***), 8.58 (s, 2H, picrate-***H***), 8.77 (dd, 1H, ^3J = 5.7 Hz, ^4J = 1.4 Hz, Pyr-6-***H***), 8.84 (d, 1H, ^4J = 1.9 Hz, Pyr-2-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 28.76 (-, Pyr-3-CH_2-***C***H_2), 28.99 (-, Pyr-3-***C***H_2), 36.72 (- , Pyr-3-$(CH_2)_2$-***C***H_2), 122.92 (-, Phth-***C***-4,7), 124.06 (C_{quat}, picrate-***C***-4), 125.10 (+, picrate-***C***-3,5), 126.54 (+, Pyr-***C***-5), 131.60 (C_{quat}, Phth-***C***-3a,7a), 134.29 (+, Phth-***C***-5,6), 139.99 (+, Pyr-***C***-6), 141.03 (C_{quat}, Pyr-***C***-3), 141.71 (+, Pyr-***C***-2), 141.76 (C_{quat}, picrate-***C***-2,6), 145.60 (+, Pyr-***C***-4), 160.70 (C_{quat}, picrate-***C***-1), 167.94 (C_{quat}, ***C***=O). ES-MS (H_2O/MeCN) *m/z* (%): 267 (100) $[M + H]^+$. Anal. ($C_{16}H_{14}N_2O_2 \cdot C_6H_3N_3O_7$) C, H, N. $C_{16}H_{14}N_2O_2$ (266.29).

2-[3-(Pyridin-4-yl)propyl]isoindoline-1,3-dione (26)[9]

The title compound was prepared from **23** according to the general procedure and purified by flash chromatography (PE/EtOAc 60/40 v/v) yielding a beige solid (7.4 g, 90 %); mp (**26** · $C_6H_3N_3O_7$) 180 – 182 °C. ^{1}H-NMR (300 MHz, DMSO-d_6, picrate): δ [ppm] = 1.95 – 2.07 (m, 2H, Pyr-4-CH_2-C***H***$_2$), 2.95 (t, 2H, ^3J = 7.8 Hz, Pyr-4-C***H***$_2$), 3.64 (t, 2H, ^3J = 6.7 Hz, Pyr-4-$(CH_2)_2$-C***H***$_2$), 7.80 – 7.90 (m, 4H, Phth-***H***), 7.98 (dd, 2H, ^3J = 6.7 Hz, ^4J = 1.5 Hz, Pyr- 3,5-***H***), 8.57 (s, 2H, picrate-***H***), 8.81 (dd, 2H, ^3J = 6.7 Hz, ^4J = 1.5 Hz, Pyr-2,6-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, picrate): δ [ppm] = 27.99 (-, Pyr-4-CH_2-***C***H_2), 32.33 (-, Pyr-4-***C***H_2), 36.77 (-, Pyr-4-$(CH_2)_2$-***C***H_2), 122.90 (-, Phth-***C***-4,7), 124.07 (C_{quat}, picrate-***C***-4), 125.11 (+, picrate-***C***-3,5), 126.79 (+, Pyr-***C***-3,5), 131.59 (C_{quat}, Phth-***C***-3a,7a), 134.26 (+, Phth-***C***-5,6), 141.36 (+, Pyr-***C***-2,6), 141.74 (C_{quat}, picrate-***C***-2,6), 160.70 (C_{quat}, picrate-***C***-1), 162.35 (C_{quat}, Pyr-***C***4), 167.94

(C_{quat}, 2 ***C***=O). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 267 (100) $[M + H]^+$. Anal. ($C_{16}H_{14}N_2O_2 \cdot C_6H_3N_3O_7$) C, H, N. $C_{16}H_{14}N_2O_2$ (266.29).

General procedure for the preparation of the 3-pyridylpropan-1-amines (27-29)

A mixture of the pertinent 2-(3-pyridylpropyl)isoindoline-1,3-dione (1 eq) and hydrazine monohydrate (6 eq) in EtOH was stirred overnight at room temperature. After removal of insoluble material and concentration in vacuo, the crude product was subjected to flash chromatography. For analytical purposes a small amount of the purified product was converted into the dipicrate by addition of a saturated solution of picric acid in EtOH and recrystallized from $EtOH/H_2O$.

3-(Pyridin-2-yl)propan-1-amine (27)[9]

The title compound was prepared from **24** (7.00 g, 26.3 mmol) and hydrazine monohydrate (7.7 mL, 157.8 mmol) in EtOH (200 mL) according to the general procedure and purified by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 80/18/2 v/v/v) yielding a brownish oil (3.6 g, 85 %); mp (**27** · 2 $C_6H_3N_3O_7$) 188 – 190 °C. ^{1}H-NMR (300 MHz, DMSO-d_6, dipicrate): δ [ppm] = 1.91 – 2.04 (m, 2H, Pyr-2-CH_2-C***H***$_2$), 2.79 – 2.93 (m, 2H, Pyr-2-$(CH_2)_2$-C***H***$_2$), 3.03 (t, 2H, ^3J = 7.7 Hz, Pyr-2-C***H***$_2$), 7.72 (brs, 3H, N***H***$_3^+$), 7.82 – 7.93 (m, 2H, Pyr-3,5-***H***), 8.40 – 8.49 (m, 1H, Pyr-4-***H***), 8.59 (s, 2H, picrate-***H***), 8.82 (dd, 1H, ^3J = 5.7 Hz, ^4J = 1.7 Hz, Pyr-6-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 26.21 (-, Pyr-2-CH_2-***C***H_2), 30.28 (-, Pyr-2-***C***H_2), 38.03 (-, Pyr-2-$(CH_2)_2$-***C***H_2), 124.17 (C_{quat}, picrate-***C***-4), 124.37 (+, Pyr-***C***-5), 125.12 (+, picrate-***C***-3,5), 126.14 (+, Pyr-***C***-3), 141.75 (C_{quat}, picrate-***C***-2,6), 142.85 (+, Pyr-***C***-6), 144.97 (+, Pyr-***C***-4), 156.07 (C_{quat}, Pyr-***C***-2), 160.71 (C_{quat}, picrate-***C***-1). ES-MS (MeCN + TFA) *m/z* (%): 137 (100) $[M + H]^+$. Anal. ($C_8H_{12}N_2 \cdot 2\ C_6H_3N_3O_7$) C, H, N. $C_8H_{12}N_2$ (136.19).

3-(Pyridin-3-yl)propan-1-amine (28)[9]

The title compound was prepared from **25** (5.20 g, 19.5 mmol) and hydrazine monohydrate (5.7 mL, 117.0 mmol) in EtOH (150 mL) according to the general procedure and purified by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 80/18/2 v/v/v) yielding a pale yellow oil (2.6 g, 88 %); mp (**28** · 2 $C_6H_3N_3O_7$) 218 °C (dec.). ^{1}H-NMR (300 MHz, DMSO-d_6, dipicrate): δ [ppm] = 1.83 – 1.97 (m, 2H, Pyr-3-CH_2-C***H***$_2$), 2.76 – 2.90 (m, 4H, Pyr-3-C***H***$_2$-CH_2-C***H***$_2$), 7.69 (brs, 3H, N-**H**), 7.99 (dd, 1H, ^3J = 8.1 Hz, ^3J = 6.0 Hz, Pyr-5-***H***), 8.42 (ddd, 1H, ^3J = 8.1 Hz, ^3J = 2.0 Hz, ^4J = 1.4 Hz, Pyr-4-***H***), 8.59 (s, 2H, picrate-***H***), 8.78 – 8.82 (m, 2H, Pyr-6-***H*** + Pyr-2-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 27.70 (-, Pyr-3-CH_2-***C***H_2), 28.39 (-, Pyr-3-***C***H_2),

38.01 (-, Pyr-3-$(CH_2)_2$-***C***H_2), 124.15 (C_{quat}, picrate-***C***-4), 125.12 (+, picrate-***C***-3,5), 126.56 (+, Pyr-***C***-5), 140.16 (C_{quat}, Pyr-***C***-3), 140.69 (+, Pyr-***C***-6), 141.75 (C_{quat}, picrate-***C***-2,6), 142.10 (+, Pyr-***C***-2), 144.98 (+, Pyr-***C***-4), 160.72 (C_{quat}, picrate-***C***-1). ES-MS (H_2O/MeOH + NH_4OAc) *m/z* (%): 137 (100) $[M + H]^+$. Anal. ($C_8H_{12}N_2 \cdot 2\ C_6H_3N_3O_7$) C, H, N. $C_8H_{12}N_2$ (136.19).

3-(Pyridin-4-yl)propan-1-amine (29)[9]

The title compound was prepared from **26** (7.20 g, 27.0 mmol) and hydrazine monohydrate (7.9 mL, 162.0 mmol) in EtOH (250 mL) according to the general procedure and purified by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32% 80/18/2 v/v/v) yielding a colourless oil (2.9 g, 79 %); mp (**29** · 2 $C_6H_3N_3O_7$) 210 – 211 °C (dec.). ^{1}H-NMR (300 MHz, DMSO-d_6, dipicrate): δ [ppm] = 1.86 – 1.99 (m, 2H, Pyr-4-CH_2-C***H***$_2$), 2.77 – 2.90 (m, 2H, Pyr-4-CH_2-CH_2-C***H***$_2$), 2.94 (t, 2H, ^3J = 7.8 Hz, Pyr-4-C***H***$_2$), 7.71 (brs, 3H, N-***H***), 7.92 (dd, 2H, ^3J = 6.7 Hz, ^4J = 1.4 Hz, Pyr-3,5-***H***), 8.59 (s, 2H, picrate-***H***), 8.84 (d, 2H, ^3J = 6.7 Hz, ^4J = 1.4 Hz, Pyr-2,6-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 26.92 (-, Pyr-4-CH_2-***C***H_2), 31.62 (-, Pyr-4-***C***H_2), 38.11 (-, Pyr-4-$(CH_2)_2$-***C***H_2), 124.17 (C_{quat}, picrate-***C***-4), 125.13 (+, picrate-***C***-3,5), 126.62 (+, Pyr-***C***-3,5), 141.74 (C_{quat}, picrate-***C***-2,6), 141.90 (+, Pyr-***C***-2,6), 160.72 (C_{quat}, picrate-***C***-1), 161.17 (C_{quat}, Pyr-***C***-4). ES-MS (H_2O/MeOH + NH_4OAc) *m/z* (%): 137 (100) $[M + H]^+$. Anal. ($C_8H_{12}N_2 \cdot 2\ C_6H_3N_3O_7$) C, H, N. $C_8H_{12}N_2$ (136.19).

Preparation of the di-Cbz-protected arylpropylguanidines 35-38

General procedure

To a solution of the pertinent alcohol (1 eq), the di-Cbz-protected guanidine **33** (1.5 eq) and PPh_3 (1.5 eq) in THF_{abs}, DIAD (1.5 eq) in THF_{abs} was added dropwise at 0 °C. After the addition was complete, the solution was allowed to warm to room temperature and stirred overnight. The solvent was removed *in vacuo* and the crude product purified by flash chromatography.

***N*^{1},*N*^{2}-Bis(benzyloxycarbonyl)-*N*^{1}-(3-{5-[(dimethylamino)methyl]furan-2-yl}propyl)guanidine (35)**

The title compound was prepared from a solution of **8** (2.18 g, 11.9 mmol), **33** (5.84 g, 17.9 mmol), PPh_3 (4.68 g, 17.9 mmol) in THF_{abs} (100 mL) and a solution of DIAD (3.5 mL, 3.61 g, 17.9 mmol) in THF_{abs} (30 mL) according to the general procedure. Purification by flash chromatography (DCM/MeOH/NH_3 (aq.) 32 % 95/3/2 v/v/v) yielded a pale yellow oil. (4.1 g, 70

%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.88 – 2.02 (m, 2H, Fur-2-CH_2-C***H***$_2$), 2.22 (s, 6H, C***H***$_3$), 2.61 (t, 2H, ^{3}J = 7.5 Hz, Fur-2-C***H***$_2$), 3.35 (s, 2H, Fur-5-C***H***$_2$), 4.06 (t, 2H, ^{3}J = 7.5 Hz, Fur-2-$(CH_2)_2$-C***H***$_2$), 5.15 (s, 2H, Ph-C***H***$_2$), 5.23 (s, 2H, Ph-C***H***$_2$), 5.93 (d, 1H, ^{3}J = 3.0 Hz, Fur-3-***H***), 6.00 (d, 1H, ^{3}J = 3.0 Hz, Fur-4-***H***), 9.25 (brs, 1H, N-***H***), 9.44 (brs, 1H, N-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 25.38 (-, ***C***H_2), 26.86 (-, ***C***H_2), 44.47 (-, Fur-2-$(CH_2)_2$-***C***H_2), 44.97 (+, 2 ***C***H_3), 55.96 (-, Fur-5-***C***H_2), 67.06 (-, Ph-***C***H_2), 68.89 (-, Ph-***C***H_2), 105.35 (+, Fur-***C***-3), 109.12 (+, Fur-***C***-4), 127.82 (+, 1 Ph-***C***), 127.95 (+, 2 Ph-***C***), 128.30 (+, 2 Ph-***C***), 128.41 (+, 2 Ph-***C***), 128.80 (+, 3 Ph-***C***), 134.75 (C_{quat}, 1 Ph-***C***-1), 137.06 (C_{quat}, 1 Ph-***C***-1), 150.58 (C_{quat}, Fur-***C***-5), 154.90 (C_{quat}, Fur-***C***-2), 155.96, 160.62, 163.97 (C_{quat}, 2 ***C***=O + ***C***=N). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 493 (100) $[M + H]^+$. $C_{27}H_{32}N_4O_5$ (492.57).

N^1,N^2-Bis(benzyloxycarbonyl)-N^1-[3-(1-trityl-1*H*-imidazol-2-yl)propyl]guanidine (36)

The title compound was prepared from a solution of **10** (3.9 g, 10.6 mmol), **33** (5.20 g, 15.9 mmol), PPh_3 (4.17 g, 15.9 mmol) in THF_{abs} (100 mL) and a solution of DIAD (3.1 mL, 3.22 g, 15.9 mmol) in THF_{abs} (30 mL) according to the general procedure. Purification by flash chromatography (PE/EtOAc 60/40 v/v) yielded a colourless foam-like solid. (5.6 g, 78 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.59 – 1.74 (m, 2H, Im-2-CH_2-C***H***$_2$), 1.93 (t, 2H, ^{3}J = 8.2 Hz, Im-2-C***H***$_2$), 3.75 (t, 2H, ^{3}J = 6.8 Hz, Im-2-$(CH_2)_2$-C***H***$_2$), 5.07 (s, 2H, Ph-C***H***$_2$), 5.08 (s, 2H, Ph-C***H***$_2$), 6.66 (d, 1H, ^{3}J = 1.5 Hz, Im-4-***H***), 6.94 (d, 1H, ^{3}J = 1.5 Hz, Im-5-***H***), 7.03 – 7.09 (m, 6H, Ph-***H***), 7.20 – 7.42 (m, 19H, Ph-***H***), 9.08 (brs, 1H, N-***H***), 9.36 (brs, 1H, N-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 26.95, 27.83 (-, Im-2-***C***H_2-***C***H_2), 44.10 (-, Im-2-$(CH_2)_2$-***C***H_2), 67.10 (+, Ph-***C***H_2), 68.59 (+, Ph-***C***H_2), 74.70 (C_{quat}, ***C***Ph_3), 121.18 (+, Im-***C***-5), 125.49 (+, Im-***C***-4), 127.78 (+, 3 Ph-***C***), 127.83 (+, 1 Ph-***C***), 128.00 (+, 6 Ph-***C***), 128.07 (+, 2 Ph-***C***), 128.10 (+, 2 Ph-***C***), 128.40 (+, 2 Ph-***C***), 128.63 (+, 1 Ph-***C***), 128.73 (+, 2 Ph-***C***), 129.74 (+, 6 Ph-***C***), 134.81 (C_{quat}, Ph-***C***-1), 137.09 (C_{quat}, Ph-***C***-1), 142.53 (C_{quat}, 3 Ph-***C***-1), 149.74 (C_{quat}, Im-***C***-2), 155.80, 160.49, 163.75 (C_{quat}, 2 ***C***=O + ***C***=N). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 678 (100) $[M + H]^+$. $C_{42}H_{39}N_5O_4$ (677.79).

N^1,N^2-Bis(benzyloxycarbonyl)-N^1-[3-(1-trityl-1*H*-pyrazol-4-yl)propyl]guanidine (37)

The title compound was prepared from a solution of **14** (4.4 g, 11.9 mmol), **33** (5.86 g, 17.9 mmol), PPh_3 (4.69 g, 17.9 mmol) in THF_{abs} (100 mL) and a solution of DIAD (3.5 mL, 3.62 g, 17.9 mmol) in THF_{abs} (30 mL) according to the general procedure. Purification by flash chromatography (PE/EtOAc 80/20 v/v) followed by crystallization from DCM/hexane yielded a

white solid. (6.1 g, 76 %); mp 144 – 145 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.73 – 1.89 (m, 2H, Pyraz-4-CH_2-C***H***$_2$), 2.40 (t, 2H, ^{3}J = 7.9 Hz, Pyraz-4-C***H***$_2$), 4.02 (t, 2H, ^{3}J = 7.4 Hz, Pyraz-4-$(CH_2)_2$-C***H***$_2$), 5.13 (s, 2H, Ph-C***H***$_2$), 5.19 (s, 2H, Ph-C***H***$_2$), 7.09 – 7.18 (m, 7H, Ph-***H*** + Pyraz-3-***H***), 7.24 – 7.42 (m, 19H, Ph-***H***), 7.44 (s, 1H, Pyraz-5-***H***), 9.26 (brs, 1H, N-***H***), 9.44 (brs, 1H, N-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 21.66 (-, Pyraz-4-***C***H_2), 29.87 (-, Pyraz-4-CH_2-***C***H_2), 44.65 (-, Pyraz-4-$(CH_2)_2$-***C***H_2), 67.06 (+, Ph-***C***H_2), 68.82 (+, Ph-***C***H_2), 78.37 (C_{quat}, ***C***Ph_3), 119.39 (C_{quat}, Pyraz-***C***-4), 127.64 (+, 3 Ph-***C***), 127.70 (+, 6 Ph-***C***), 127.85 (+, 1 Ph-***C***), 127.96 (+, 2 Ph-***C***), 128.30 (+, 2 Ph-***C***), 128.44 (+, 2 Ph-***C***), 128.82 (+, 2 Ph-***C***), 128.85 (+, 1 Ph-***C***), 130.17 (+, 6 Ph-***C***), 130.36 (+, Pyraz-***C***-5), 134.72 (C_{quat}, 1 Ph-***C***-1), 137.05 (C_{quat}, 1 Ph-***C***-1), 139.10 (+, Pyraz-***C***-3), 143.48 (C_{quat}, 3 Ph-***C***-1), 155.96, 160.67, 163.98 (C_{quat}, 2 ***C***=O + ***C***=N). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 678 (100) $[M + H]^+$. Anal. ($C_{42}H_{39}N_5O_4$) C, H, N. $C_{42}H_{39}N_5O_4$ (677.79).

N^1,N^2-Bis(benzyloxycarbonyl)-N^1-[3-(1-trityl-1*H*-1,2,4-triazol-5-yl)propyl]guanidine (38)

The title compound was prepared from a solution of **20** (3.86 g, 10.4 mmol), **33** (5.14 g, 15.7 mmol), PPh_3 (4.12 g, 15.7 mmol) in THF_{abs} (100 mL) and a solution of DIAD (3.1 mL, 3.17 g, 15.7 mmol) in THF_{abs} (50 mL) according to the general procedure. Purification by flash chromatography (PE/EtOAc 80/20 v/v) followed by recrystallization from EtOAc/hexane yielded a white solid. (6.2 g, 87 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.59 – 1.71 (m, 2H, Triaz-5-CH_2-C***H***$_2$), 2.02 (t, 2H, ^{3}J = 8.1 Hz, Triaz-5-C***H***$_2$), 3.77 (t, 2H, ^{3}J = 6.9 Hz, Triaz-5-$(CH_2)_2$-C***H***$_2$), 5.09 (s, 2H, Ph-C***H***$_2$), 5.10 (s, 2H, Ph-C***H***$_2$), 7.01 – 7.10 (m, 6H, Ph-***H***), 7.19 – 7.42 (m, 19H, Ph-***H***), 7.86 (s, 1H, Triaz-5-***H***), 9.11 (brs, 1H, N-***H***), 9.37 (brs, 1H, N-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 26.37, 26.56 (-,Triaz-5-***C***H_2-***C***H_2), 43.83 (-, Triaz-5-$(CH_2)_2$-***C***H_2), 67.10 (+, Ph-***C***H_2), 68.77 (+, Ph-***C***H_2), 77.66 (C_{quat}, ***C***Ph_3), 127.81 (+, 3 Ph-***C***), 127.83 (+, 6 Ph-***C***), 127.93 (+, 1 Ph-***C***), 128.11 (+, 2 Ph-***C***), 128.20 (+, 2 Ph-***C***), 128.45 (+, 2 Ph-***C***), 128.79 (+, 3 Ph-***C***), 129.75 (+, 6 Ph-***C***), 134.66 (C_{quat}, 1 Ph-***C***-1), 136.97 (C_{quat}, 1 Ph-***C***-1), 141.94 (C_{quat}, 3 Ph-***C***-1), 148.71 (+, Triaz-***C***-3), 155.73, 160.43, 163.76 (C_{quat}, 2 ***C***=O + ***C***=N). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 679 (100) $[M + H]^+$. Anal. ($C_{41}H_{38}N_6O_4$) C, H, N. $C_{41}H_{38}N_6O_4$ (678.78).

Preparation of the di-Cbz-protected arylpropylguanidines 39-43

General procedure

To a solution of the pertinent amine (1 eq) and **34** (0.9 eq) in DCM NEt_3 (1 eq) was added. After stirring overnight at room temperature, the organic layer was washed with saturated $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography.

N^1,N^2-Bis(benzyloxycarbonyl)-N^3-(3-phenylpropyl)guanidine (39)

The title compound was prepared from **30** (0.78 g, 5.8 mmol), **34** (2.39 g, 5.2 mmol) and NEt_3 (0.8 mL, 0.59 g, 5.8 mmol) in DCM (50 mL) according to the general procedure. Purification by flash chromatography (PE/EtOAc 80/20 v/v) yielded a colourless oil (1.8 g, 70 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.86 – 1.99 (m, 1H, Ph-CH_2-C***H***$_2$), 2.68 (t, 2H, ^3J = 7.7 Hz, Ph-C***H***$_2$), 3.42 – 3.52 (m, 2H, Ph-$(CH_2)_2$-C***H***$_2$), 5.14 (s, 2H, Ph-C***H***$_2$-O), 5.19 (s, 2H, Ph-C***H***$_2$-O), 7.14 – 7.45 (m, 15H, Ph-***H***), 8.36 (t, 1H, ^3J = 4.8 Hz, N-***H***), 11.76 (s, 1H, N-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 30.56 (-, Ph-CH_2-***C***H_2), 33.03 (-, Ph-***C***H_2), 40.57 (-, Ph-CH_2-CH_2-***C***H_2), 67.21 (-, Ph-***C***H_2-O), 68.19 (-, Ph-***C***H_2-O), 126.08 (+, 1 Ph-***C***), 127.92 (+, 1 Ph-***C***), 128.16 (+, 2 Ph-***C***), 128.38 (+, 2 Ph-***C***), 128.42 (+, 2 Ph-***C***), 128.48 (+, 2 Ph-***C***), 128.50 (+, 2 Ph-***C***), 128.73 (+, 2 Ph-***C***), 128.81 (+, 1 Ph-***C***), 134.69 (C_{quat}, 1 Ph-***C***), 136.88 (C_{quat}, 1 Ph-***C***), 141.07 (C_{quat}, 1 Ph-***C***), 153.94 (C_{quat}, ***C***=O), 156.05 (C_{quat}, ***C***=N), 163.78 (C_{quat}, ***C***=O). CI-MS (NH_3) *m/z* (%): 446 (99) $[M + H]^+$, 312 (100) $[M – Ph\text{-}CH_2\text{-}OCO + H]^+$. $C_{26}H_{27}N_3O_4$ (445.51).

N^1,N^2-Bis(benzyloxycarbonyl)-N^3-[3-(pyridin-2-yl)propyl]guanidine (40)

The title compound was prepared from **27** (1.71 g, 12.6 mmol), **34** (5.19 g, 11.3 mmol) and NEt_3 (1.7 mL, 1.27 g, 12.6 mmol) in DCM (100 mL) according to the general procedure. Purification by flash chromatography (PE/EtOAc 80/20 v/v) yielded a pale yellow oil (4.3 g, 84 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.99 – 2.11 (m, 2H, Pyr-2-CH_2-C***H***$_2$), 2.85 (t, 2H, ^3J = 7.6 Hz, Pyr-2-C***H***$_2$), 3.45 – 3.54 (m, 2H, Pyr-2-$(CH_2)_2$-C***H***$_2$), 5.12 (s, 2H, PhC***H***$_2$), 5.17 (s, 2H, PhC***H***$_2$), 7.08 (ddd, 1H, ^3J = 7.5 Hz, ^3J = 4.9 Hz, ^4J = 1.2 Hz, Pyr-5-***H***), 7.15 (ddd, 1H, ^3J = 7.8 Hz, ^4J = 1.2 Hz, ^5J = 0.9 Hz, Pyr-3-***H***), 7.56 (ddd, 1H, ^3J = 7.8 Hz, ^3J = 7.5 Hz, ^4J = 1.8 Hz, Pyr-4-***H***), 8.44 (t, 1H, ^3J = 5.0 Hz, N-***H***), 8.51 (ddd, 1H, ^3J = 4.9 Hz, ^4J = 1.8 Hz, ^5J = 0.9 Hz, Pyr-6-***H***), 11.72 (brs, 1H, N-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 28.67 (-, Pyr-2-CH_2-***C***H_2), 35.34 (-, Pyr-2-***C***H_2), 40.63 (-, Pyr-2-$(CH_2)_2$-***C***H_2), 67.17 (-, Ph***C***H_2), 68.16 (-, Ph***C***H_2), 121.26 (+, Pyr-***C***-

5), 122.93 (+, Pyr-***C***-3), 127.93 (+, 1 Ph-***C***), 128.18 (+, 2 Ph-***C***), 128.43 (+, 2 Ph-***C***), 128.52 (+, 2 Ph-***C***), 128.73 (+, 2 Ph-***C***), 128.81 (+, 1 Ph-***C***), 134.70 (C_{quat}, 1 Ph-***C***-1), 136.46 (+, Pyr-***C***-4), 136.86 (C_{quat}, 1 Ph-***C***-1), 149.41 (+, Pyr-***C***-6), 153.82, 156.03, 163.76 (C_{quat}, 2 ***C***=O + ***C***=N), (C_{quat}, ***C***=O), 160.77, (C_{quat}, Pyr-***C***-2). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 447 (100) [M + H]$^+$. $C_{25}H_{26}N_4O_4$ (446.50).

N^1,N^2-Bis(benzyloxycarbonyl)-N^3-[3-(pyridin-3-yl)propyl]guanidine (41)

The title compound was prepared from **28** (1.93 g, 14.2 mmol), **34** (5.86 g, 12.8 mmol) and NEt_3 (2.0 mL, 1.44 g, 14.2 mmol) in DCM (100 mL) according to the general procedure. Purification by flash chromatography (PE/EtOAc 60/40 v/v) yielded a colourless oil (4.4 g, 76 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.86 – 1.99 (m, 2H, Pyr-3-CH_2-C***H***$_2$), 2.67 (t, 2H, ^3J = 7.8 Hz, Pyr-3-C***H***$_2$), 3.43 – 3.54 (m, 2H, Pyr-3-$(CH_2)_2$-C***H***$_2$), 5.13 (s, 2H, PhC***H***$_2$), 5.18 (s, 2H, PhC***H***$_2$), 7.19 (dd, 1H, ^3J = 7.8 Hz, ^3J = 4.8 Hz, ^5J = 0.6 Hz, Pyr-5-***H***), 7.27 – 7.43 (m, 10H, Ph-***H***), 7.51 (ddd, 1H, ^3J = 7.8 Hz, ^4J = 2.1 Hz, ^4J = 1.8 Hz, Pyr-4-***H***), 8.38 (t, 1H, ^3J = 5.1 Hz, N-***H***), 8.42 – 8.49 (m, 2H, Pyr-2,6-***H***), 11.75 (brs, 1H, N-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 30.19, 30.32 (-, Pyr-3-***C***H_2-***C***H_2), 40.38 (-, Pyr-3-$(CH_2)_2$-***C***H_2), 67.23 (-, Ph***C***H_2), 68.26 (-, Ph***C***H_2), 123.40 (+, Pyr-***C***-5), 127.98 (+, 1 Ph-***C***), 128.19 (+, 2 Ph-***C***), 128.45 (+, 2 Ph-***C***), 128.51 (+, 2 Ph-***C***), 128.74 (+, 2 Ph-***C***), 128.86 (+, 1 Ph-***C***), 134.60 (C_{quat}, 1 Ph-***C***-1), 135.78 (+, Pyr-***C***-4), 136.34 (C_{quat}, Pyr-***C***-3), 136.78 (C_{quat}, 1 Ph-***C***-1), 147.72 (+, Pyr-***C***-6), 149.91 (+, Pyr-***C***-2), 153.95, 156.10, 163.73 (C_{quat}, 2 ***C***=O + ***C***=N). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 447 (100) [M + H]$^+$. $C_{25}H_{26}N_4O_4$ (446.50).

N^1,N^2-Bis(benzyloxycarbonyl)-N^3-[4-(pyridin-4-yl)propyl]guanidine (42)

The title compound was prepared from **29** (1.43 g, 10.5 mmol), **34** (4.34 g, 9.5 mmol) and NEt_3 (1.5 mL, 1.06 g, 10.5 mmol) in DCM (100 mL) according to the general procedure. Purification by flash chromatography (PE/EtOAc 40/60 v/v) yielded a colourless oil (3.7 g, 88 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.85 – 2.01 (m, 2H, Pyr-4-CH_2-C***H***$_2$), 2.66 (t, 2H, ^3J = 7.7 Hz, Pyr-4-C***H***$_2$), 3.40 – 3.54 (m, 2H, Pyr-4-$(CH_2)_2$-C***H***$_2$), 5.13 (s, 2H, PhC***H***$_2$), 5.18 (s, 2H, PhC***H***$_2$), 7.12 (dd, 2H, ^3J = 4.4 Hz, ^4J = 1.6 Hz, Pyr-3,5-***H***), 7.28 – 7.43 (m, 10H, Ph-***H***), 8.37 (t, 1H, ^3J = 5.0 Hz, N-***H***), 7.12 (dd, 2H, ^3J = 4.4 Hz, ^4J = 1.6 Hz, Pyr-2,6-***H***), 11.74 (brs, 1H, N-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 29.49, 32.32 (-, Pyr-4-***C***H_2-***C***H_2), 40.35 (-, Pyr-4-$(CH_2)_2$-***C***H_2), 67.25 (-, Ph***C***H_2), 68.29 (-, Ph***C***H_2), 123.81 (+, Pyr-***C***-3,5), 128.01 (+, 1 Ph-***C***), 128.20 (+, 2 Ph-***C***), 128.46 (+, 2 Ph-***C***), 128.51 (+, 2 Ph-***C***), 128.75 (+, 2 Ph-***C***), 128.87 (+, 1 Ph-***C***), 134.58

(C_{quat}, 1 Ph-***C***-1), 136.74 (C_{quat}, 1 Ph-***C***-1), 149.91 (+, Pyr-***C***-2,6), 150.00 (C_{quat}, Pyr-***C***-4), 153.96, 156.10, 163.73 (C_{quat}, 2 ***C***=O + ***C***=N). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 447 (100) [M + H]$^+$. $C_{25}H_{26}N_4O_4$ (446.50).

N^1,N^2-Bis(benzyloxycarbonyl)-N^3-[3-(1*H*-imidazol-1-yl)propyl]guanidine (43)

The title compound was prepared from **31** (2.09 g, 16.7 mmol), **34** (6.90 g, 15.0 mmol) and NEt_3 (2.3 mL, 1.69 g, 16.7 mmol) in DCM (100 mL) according to the general procedure. Purification by flash chromatography (DCM/MeOH 97.5/2.5 v/v) yielded a pale yellow oil (5.4 g, 83 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.00 – 2.14 (m, 2H, Im-1-CH_2-C***H***$_2$), 3.39 – 3.49 (m, 2H, Im-1-$(CH_2)_2$-C***H***$_2$), 4.00 (t, 2H, ^3J = 7.0 Hz, Im-1-C***H***$_2$), 5.13 (s, 2H, Ph-C***H***$_2$), 5.18 (s, 2H, Ph-C***H***$_2$), 6.94 – 6.96 (m, 1H, Im-4-***H***), 7.04 – 7.06 (m, 1H, Im-5-***H***), 7.27 – 7.43 (m, 10H, Ph-***H***), 7.50 – 7.52 (m, 1H, Im-2-***H***), 8.38 (t, 1H, ^3J = 5.6 Hz, N-***H***), 11.72 (brs, 1H, N-***H***). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 30.73 (-, Im-1-CH_2-***C***H_2), 37.93 (-, Im-1-$(CH_2)_2$-***C***H_2), 44.43 (-, Im-1-***C***H_2), 67.29 (-, Ph-***C***H_2), 68.41 (-, Ph-***C***H_2), 118.81 (+, Im-***C***-5), 128.05 (+, 1 Ph-***C***), 128.15 (+, 2 Ph-***C***), 128.49 (+, 2 Ph-***C***), 128.55 (+, 2 Ph-***C***), 128.77 (+, 2 Ph-***C***), 128.92 (+, 1 Ph-***C***), 129.67 (+, Im-***C***-4), 134.50 (C_{quat}, 1 Ph-***C***-1), 136.64 (C_{quat}, 1 Ph-***C***-1), 137.11 (+, Im-***C***-2), 153.94, 156.30, 163.65 (C_{quat}, 2 ***C***=O + ***C***=N). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 436 (100) [M + H]$^+$. $C_{23}H_{25}N_5O_4$ (435.48).

Preparation of the arylpropylguanidines 44-52

General procedure

A mixture of the pertinent di-Cbz-protected guanidine and catalytical amounts of Pd/C (10 %) in MeOH was stirred under an hydrogen atmosphere at room temperature for approximately 3 h (TLC control). After the Cbz-groups were quantitatively cleaved, the catalyst was removed by filtration over Celite and the solvent was evaporated. For analytical purposes a small amount of some compounds (**35**, **39**, **41-43**) was converted into the picrate by addition of a saturated solution of picric acid in EtOH and recrystallization from EtOH/H_2O.

***N*-(3-{5-[(Dimethylamino)methyl]furan-2-yl}propyl)guanidine (44)**

The title compound was prepared from **35** (3.0 g, 6.1 mmol) and Pd/C (10 %) (0.30 g, cat.) in MeOH (150 mL) according to the general procedure yielding a colourless oil (1.3 g, 95 %); mp (**44** · 2 $C_6H_3N_3O_7$) 185 – 187 °C (dec.). ^{1}H-NMR (300 MHz, DMSO-d_6, dipicrate): δ [ppm] =

1.72 – 1.86 (m, 2H, Fur-2-CH_2-C***H***$_2$), 2.65 (t, 2H, ^3J = 7.7 Hz, Fur-2-C***H***$_2$), 2.73 (s, 6H, C***H***$_3$), 3.09 – 3.22 (m, 2H, Fur-2-$(CH_2)_2$-C***H***$_2$), 4.31 (s, 2H, Fur-5-C***H***$_2$), 6.23 (d, 1H, ^3J = 3.2 Hz, Fur-3-***H***), 6.60 (d, 1H, ^3J = 3.2 Hz, Fur-4-***H***), 7.02 (brs, 4H, N-***H***), 7.48 (t, 1H, ^3J = 5.6 Hz, N-***H***), 8.60 (s, 4H, picrate-***H***), 9.73 (brs, 1H, N-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 24.46 (-, ***C***H_2), 26.72 (-, ***C***H_2), 40.01 (-, Fur-2-$(CH_2)_2$-***C***H_2), 41.52 (+, 2 ***C***H_3), 51.80 (-, Fur-5-***C***H_2), 106.77 (+, Fur-***C***-3), 114.94 (+, Fur-***C***-4), 124.14 (C_{quat}, picrate-***C***-4), 125.14 (+, picrate-***C***-3,5), 141.75 (C_{quat}, picrate-***C***-2,6), 142.69 (C_{quat}, Fur-***C***-5), 156.55 (C_{quat}, ***C***=N), 156.81 (C_{quat}, Fur-***C***-2) 160.73 (C_{quat}, picrate-***C***-1). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 225 (100) $[M + H]^+$. Anal. ($C_{11}H_{20}N_4O \cdot 2\ C_6H_3N_3O_7$) C, H, N. $C_{11}H_{20}N_4O$ (224.30).

_N_-[3-(1-Trityl-1_H_-imidazol-2-yl)propyl]guanidine (45)

The title compound was prepared from **36** (5.57 g, 8.2 mmol) and Pd/C (10 %) (0.56 g, cat.) in MeOH (150 mL) according to the general procedure yielding a white solid (3.2 g, 95 %); mp 158 – 162 °C. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.23 – 1.35 (m, 2H, Im-2-CH_2-C***H***$_2$), 2.05 (t, 2H, ^3J = 7.5 Hz, Im-2-C***H***$_2$), 2.85 (t, 2H, ^3J = 7.1 Hz, Im-2-$(CH_2)_2$-C***H***$_2$), 6.80 (d, 1H, ^3J = 1.6 Hz, Im-4-***H***), 6.95 (d, 1H, ^3J = 1.6 Hz, Im-5-***H***), 7.09 – 7.19 (m, 6H, Ph-***H***), 7.32 – 7.44 (m, 9H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 27.72, 28.60 (-, Im-2-***C***H_2-***C***H_2), 41.77 (-, Im-2-$(CH_2)_2$-***C***H_2), 76.50 (C_{quat}, ***C***Ph_3), 122.68 (+, Im-***C***-5), 125.94 (+, Im-***C***-4), 129.33 (+, 3 Ph-***C***), 129.39 (+, 6 Ph-***C***), 131.05 (+, 6 Ph-***C***), 143.67 (C_{quat}, 3 Ph-***C***-1), 150.71 (C_{quat}, Im-***C***-2), 158.74 (C_{quat}, ***C***=N). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 410 (100) $[M + H]^+$. HRMS (EI-MS) calcd. for $C_{26}H_{27}N_5$ $[M^{+\bullet}]$ 409.2267; found 409.2266. $C_{26}H_{27}N_5$ (409.53).

_N_-(3-(1-Trityl-1_H_-pyrazol-4-yl)propyl)guanidine (46)

The title compound was prepared from **37** (5.5 g, 8.1 mmol) and Pd/C (10 %) (0.55 g, cat.) in MeOH (150 mL) according to the general procedure yielding a white solid (3.2 g, 96 %). ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.72 – 1.87 (m, 2H, Pyraz-4-CH_2-C***H***$_2$), 2.53 (t, 2H, ^3J = 7.6 Hz, Pyraz-4-C***H***$_2$), 3.14 (t, 2H, ^3J = 7.0 Hz, Pyraz-4-$(CH_2)_2$-C***H***$_2$), 7.05 – 7.17 (m, 6H, Ph-***H***), 7.24 – 7.38 (m, 10H, Ph-***H*** + Pyraz-3-***H***), 7.49 (s, 1H, Pyraz-5-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 22.08 (-, Pyraz-4-***C***H_2), 31.20 (-, Pyraz-4-CH_2-***C***H_2), 41.85 (-, Pyraz-4-$(CH_2)_2$-***C***H_2), 79.93 (C_{quat}, ***C***Ph_3), 120.83 (C_{quat}, Pyraz-***C***-4), 128.90 (+, 6 Ph-***C***), 128.98 (+, 3 Ph-***C***), 131.22 (+, 6 Ph-***C***), 132.31 (+, Pyraz-***C***-5), 140.31 (+, Pyraz-***C***-3), 144.56 (C_{quat}, 3 Ph-***C***-1), 158.94 (C_{quat}, ***C***=N). EI-MS (70 eV) *m/z* (%): 409 (16) $[M^{+\bullet}]$, 243 (100) $[CPh_3^+]$. HRMS (EI-MS) calcd. for $C_{26}H_{27}N_5$ $[M^{+\bullet}]$ 409.2267; found 409.2265. $C_{26}H_{27}N_5$ (409.53).

_N_-[3-(1-Trityl-1_H_-1,2,4-triazol-5-yl)propyl]guanidine (47)

The title compound was prepared from **38** (4.4 g, 6.5 mmol) and Pd/C (10 %) (0.44 g, cat.) in MeOH (150 mL) according to the general procedure yielding a colourless foam-like solid (2.6 g, 98 %). ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.31 – 1.44 (m, 2H, Triaz-5-CH_2-C***H***$_2$), 2.14 (t, 2H, ^{3}J = 7.5 Hz, Triaz-5-C***H***$_2$), 2.91 (t, 2H, ^{3}J = 7.0 Hz, Triaz-5-$(CH_2)_2$-C***H***$_2$), 7.06 – 7.15 (m, 6H, Ph-***H***), 7.30 – 7.40 (m, 9H, Ph-***H***), 7.92 (s, 1H, Triaz-5-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 27.22, 27.33 (-, Triaz-5-***C***H_2-***C***H_2), 41.53 (-, Triaz-5-$(CH_2)_2$-***C***H_2), 79.53 (C_{quat}, ***C***Ph_3), 129.11 (+, 6 Ph-***C***), 129.15 (+, 3 Ph-***C***), 131.09 (+, 6 Ph-***C***), 143.21 (C_{quat}, 3 Ph-***C***-1), 149.01 (+, Triaz-***C***-3), 158.55, 158.74 (C_{quat}, ***C***=N + Triaz-***C***-5). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 411 (100) $[M + H]^+$. HRMS (EI-MS) calcd. for $C_{25}H_{26}N_6$ $[M^{+\bullet}]$ 410.2219; found 410.2214. $C_{25}H_{26}N_6$ (410.51).

3-Phenylpropylguanidine (48)[10]

The title compound was prepared from **39** (1.72 g, 3.9 mmol) and Pd/C (10 %) (0.17 g, cat.) in MeOH (80 mL) according to the general procedure yielding a colourless foam-like solid (0.65 g, 94 %); mp (**48** · $C_6H_3N_3O_7$) 146 – 148 °C. ^{1}H-NMR (300 MHz, DMSO-d_6, picrate): δ [ppm] = 1.71 – 1.84 (m, 1H, Ph-CH_2-C***H***$_2$), 2.60 (t, 2H, ^{3}J = 7.8 Hz, Ph-C***H***$_2$), 3.06 – 3.16 (m, 2H, Ph-$(CH_2)_2$-C***H***$_2$), 7.00 (brs, 4H, N-***H***), 7.15 – 7.35 (m, 5H, Ph-***H***), 7.45 (t, 1H, ^{3}J = 5.4 Hz, N-***H***), 8.59 (s, 2H, picrate-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, picrate): δ [ppm] = 30.09 (-, Ph-CH_2-***C***H_2), 31.95 (-, Ph-***C***H_2), 40.30 (-, Ph-CH_2-CH_2-***C***H_2), 124.12 (C_{quat}, picrate-***C***-4), 125.13 (+, picrate-***C***-3,5), 125.85 (+, 1 Ph-***C***), 128.14 (+, 2 Ph-***C***), 128.30 (+, 2 Ph-***C***), 141.00 (C_{quat}, Ph-***C***), 141.75 (C_{quat}, picrate-***C***-2,6), 156.57 (C_{quat}, ***C***=N), 160.73 (C_{quat}, picrate-***C***-1). CI-MS (NH_3) *m/z* (%): 178 (100) $[M + H]^+$. Anal. ($C_{10}H_{15}N_3$ · $C_6H_3N_3O_7$) C, H, N. $C_{10}H_{15}N_3$ (177.25).

3-(Pyridin-2-yl)propylguanidine (49)[11]

The title compound was prepared from **40** (4.2 g, 9.4 mmol) and Pd/C (10 %) (0.42 g, cat.) in MeOH (150 mL) according to the general procedure yielding a colourless foam-like solid (1.6 g, 96 %); mp (**49** · 2 $C_6H_3N_3O_7$) 194 – 195 °C. ^{1}H-NMR (300 MHz, DMSO-d_6, dipicrate): δ [ppm] = 1.85 – 1.99 (m, 2H, Pyr-2-CH_2-C***H***$_2$), 2.98 (t, 2H, ^{3}J = 7.8 Hz, Pyr-2-C***H***$_2$), 3.12 – 3.24 (m, 2H, Pyr-2-$(CH_2)_2$-C***H***$_2$), 7.05 (brs, 4H, N-***H***), 7.50 (t, 1H, ^{3}J = 5.6 Hz, N-***H***), 7.81 – 7.92 (m, 2H, Pyr-3,5-***H***), 8.40 – 8.49 (m, 1H, Pyr-4-***H***), 8.59 (s, 2H, picrate-***H***), 8.80 (dd, 1H, ^{3}J = 5.8 Hz, ^{4}J = 1.6 Hz, Pyr-6-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 27.70 (-, Pyr-2-CH_2-***C***H_2),

30.35 (-, Pyr-2-***C***H_2), 39.93 (-, Pyr-2-$(CH_2)_2$-***C***H_2), 124.20 (C_{quat}, picrate-***C***-4), 124.43 (+, Pyr-***C***-5), 125.15 (+, picrate-***C***-3,5), 126.39 (+, Pyr-***C***-3), 141.73 (C_{quat}, picrate-***C***-2,6), 142.29 (+, Pyr-***C***-6), 145.36 (+, Pyr-***C***-4), 156.30 (C_{quat}, Pyr-***C***-2), 156.53 (C_{quat}, ***C***=N), 160.71 (C_{quat}, picrate-***C***-1). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 179 (100) $[M + H]^+$. Anal. ($C_9H_{14}N_4$ · 2 $C_6H_3N_3O_7$) C, H, N. $C_9H_{14}N_4$ (178.23).

3-(Pyridin-3-yl)propylguanidine (50)

The title compound was prepared from **41** (4.31 g, 9.7 mmol) and Pd/C (10 %) (0.43 g, cat.) in MeOH (150 mL) according to the general procedure yielding a colourless foam-like solid (1.7 g, 97 %); mp (**50** · 2 $C_6H_3N_3O_7$) 186 – 187 °C. ^{1}H-NMR (300 MHz, DMSO-d_6, dipicrate): δ [ppm] = 1.76 – 1.94 (m, 2H, Pyr-3-CH_2-C***H***$_2$), 2.80 (t, 2H, ^3J = 7.8 Hz, Pyr-3-C***H***$_2$), 3.08 – 3.22 (m, 2H, Pyr-3-$(CH_2)_2$-C***H***$_2$), 7.03 (brs, 4H, N-***H***), 7.48 (t, 1H, ^3J = 5.5 Hz, N-***H***), 7.99 (dd, 1H, ^3J = 8.0 Hz, ^3J = 5.9 Hz, Pyr-5-***H***), 8.43 (ddd, 1H, ^3J = 8.0 Hz, ^4J = 1.9 Hz, ^4J = 1.5 Hz, Pyr-4-***H***), 8.59 (s, 2H, picrate-***H***), 8.77 – 8.81 (m, 2H, Pyr-2,6-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 28.77 (-, Pyr-3-CH_2-***C***H_2), 29.09 (-, Pyr-3-***C***H_2), 40.03 (-, Pyr-3-$(CH_2)_2$-***C***H_2), 124.16 (C_{quat}, picrate-***C***-4), 125.13 (+, picrate-***C***-3,5), 126.54 (+, Pyr-***C***-5), 140.40 (+, Pyr-***C***-6), 140.62 (C_{quat}, Pyr-***C***-3), 141.74 (C_{quat}, picrate-***C***-2,6), 141.91 (+, Pyr-***C***-2), 145.14 (+, Pyr-***C***-4), 156.53 (C_{quat}, ***C***=N), 160.72 (C_{quat}, picrate-***C***-1). ES-MS (H_2O/MeCN) *m/z* (%): 179 (100) $[M + H]^+$. Anal. ($C_9H_{14}N_4$ · 2 $C_6H_3N_3O_7$) C, H, N. $C_9H_{14}N_4$ (178.23).

3-(Pyridin-4-yl)propylguanidine (51)

The title compound was prepared from **42** (3.65 g, 8.2 mmol) and Pd/C (10 %) (0.37 g, cat.) in MeOH (150 mL) according to the general procedure yielding a colourless foam-like solid (1.4 g, 96 %); mp (**51** · 2 $C_6H_3N_3O_7$) 205 – 207 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.78 – 1.95 (m, 2H, Pyr-4-CH_2-C***H***$_2$), 2.66 (t, 2H, ^3J = 7.8 Hz, Pyr-4-C***H***$_2$), 3.09 – 3.22 (m, 2H, Pyr-4-$(CH_2)_2$-C***H***$_2$), 7.03 (brs, 3H, N-***H***), 7.49 (t, 1H, ^3J = 5.5 Hz, N-***H***), 7.92 (dd, 2H, ^3J = 6.7 Hz, ^4J = 1.4 Hz, Pyr-3,5-***H***), 8.59 (s, 4H, picrate-***H***), 8.82 (d, 2H, ^3J = 6.7 Hz, ^4J = 1.4 Hz, Pyr-2,6-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 28.41 (-, Pyr-4-CH_2-***C***H_2), 32.04 (-, Pyr-4-***C***H_2), 40.14 (-, Pyr-4-$(CH_2)_2$-***C***H_2), 124.15 (C_{quat}, picrate-***C***-4), 125.14 (+, picrate-***C***-3,5), 126.61 (+, Pyr-***C***-3,5), 141.75 (C_{quat}, picrate-***C***-2,6), 141.83 (+, Pyr-***C***-2,6), 156.52 (C_{quat}, ***C***=N), 160.72 (C_{quat}, picrate-***C***-1), 161.58 (Cquart, Pyr-***C***-4). ES-MS (H_2O/MeCN) *m/z* (%): 179 (100) $[M + H]^+$. Anal. ($C_9H_{14}N_4$ · 2 $C_6H_3N_3O_7$) C, H, N. $C_9H_{14}N_4$ (178.23).

***N*-(3-(1*H*-Imidazol-1-yl)propyl)guanidine (52)**[12]

The title compound was prepared from **43** (5.3 g, 12.2 mmol) and Pd/C (10 %) (0.53 g, cat.) in MeOH (150 mL) according to the general procedure yielding a colourless foam-like solid (1.9 g, 95 %); mp (**52** · 2 $C_6H_3N_3O_7$) 190 – 191 °C. ^{1}H-NMR (300 MHz, DMSO-d_6, dipicrate): δ [ppm] = 1.97 – 2.09 (m, 2H, Im-1-CH_2-C***H***$_2$), 3.08 – 3.18 (m, 2H, Im-1-$(CH_2)_2$-C***H***$_2$), 4.21 (t, 2H, ^3J = 7.1 Hz, Im-1-C***H***$_2$), 7.07 (brs, 4H, N-***H***), 7.48 (t, 1H, ^3J = 5.7 Hz, N-***H***), 7.70 – 7.73 (m, 1H, Im-4-***H***), 7.75 – 7.78 (m, 1H, Im-5-***H***), 8.60 (s, 4H, picrate-***H***), 9.08 – 9.11 (m, 1H, Im-2-***H***). ^{13}C-NMR (75 MHz, DMSO-d_6, dipicrate): δ [ppm] = 28.81 (-, Im-1-CH_2-***C***H_2), 37.79 (-, Im-1-$(CH_2)_2$-***C***H_2), 46.02 (-, Im-1-***C***H_2), 120.03, 121.03 (+, Im-***C***-4,5), 124.17 (C_{quat}, picrate-***C***-4), 125.14 (+, picrate-***C***-3,5), 135.35 (+, Im-***C***-2), 141.75 (C_{quat}, picrate-***C***-2,6), 156.55 (C_{quat}, ***C***=N), 160.73 (C_{quat}, picrate-***C***-1). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 168 (100) $[M + H]^+$. Anal. ($C_7H_{13}N_5$ · 2 $C_6H_3N_3O_7$) C, H, N. $C_7H_{13}N_5$ (167.21).

Preparation of the N^G-acylated arylpropylguanidines 57-78

General procedure 1

A solution of the pertinent carboxylic acid (1 eq) and CDI (1.2 eq) in THF_{abs} (15 mL) was stirred for 1 h under argon atmosphere at room temperature. In a separate vessel, NaH (60 % dispersion in mineral oil) (2 eq) was added to a solution of the pertinent guanidine (1 eq) in THF_{abs} (15 mL) under argon atmosphere, stirred for 45 min at 30 – 35 °C and allowed to cool to ambient temperature. Both mixtures were merged and stirred for 5 h under argon atmosphere. EtOAc (50 mL) was added and the organic phase was washed with H_2O (3 x 20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography or preparative HPLC. Compounds purified by preparative HPLC were dried by lyophilization and obtained as trifluoroacetates.

General procedure 2

A solution of the pertinent carboxylic acid (1 eq) and CDI (1.2 eq) in anhydrous DMF (10 mL) was stirred for 1 h under argon atmosphere at room temperature. In a separate vessel, NaH (60 % dispersion in mineral oil) (2 eq) was added to a solution of the pertinent guanidine (1 eq) in anhydrous DMF (10 mL) under argon atmosphere, stirred for 45 min at 30 – 35 min and allowed

to cool to ambient temperature. Both mixtures were merged and stirred for 5 h under argon atmosphere. After evaporation of the solvent, the crude product was subjected to flash chromatography or preparative HPLC. Compounds purified by preparative HPLC were dried by lyophilization and obtained as trifluoroacetic acid salts.

N^1-(3-Phenylbutanoyl)-N^2-(3-phenylpropyl)guanidine (57)

The title compound was prepared from **53** (164 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **48** (177 mg, 1.0 mmol) according to the general procedure 1. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 50/50) yielded a white solid (92 mg, 21 %); mp 118 – 119 °C. ^{1}H-NMR (300 MHz, $(CD_3)_2CO$, trifluoroacetate): δ [ppm] = 1.30 (d, 3H, ^3J = 7.0 Hz, PhC***H***$_3$CH), 1.95 – 2.05 (m, 2H, Ph-CH$_2$-C***H***$_2$), 2.73 (t, 2H, ^3J = 7.8 Hz, Ph-C***H***$_2$), 2.75 (dd, 1H, ^2J = 15.0 Hz, ^3J = 7.7 Hz, PhCH$_3$CH-C***H***$_2$), 2.87 (dd, 1H, ^2J = 15.0 Hz, ^3J = 7.5 Hz, PhCH$_3$CH-C***H***$_2$), 3.27 – 3.39 (m, 1H, PhC***H***), 3.40 (t, 2H, ^3J = 7.1 Hz, Ph-CH$_2$-CH$_2$-C***H***$_2$), 7.14 – 7.36 (m, 10H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 22.28 (+, Ph***C***H$_3$CH), 30.76, 33.66 (-, Ph-***C***H$_2$-***C***H$_2$), 37.67 (+, PhCH$_3$***C***H), 42.06 (-, Ph-CH$_2$-CH$_2$-***C***H$_2$), 46.29 (-, PhCH$_3$CH-***C***H$_2$), 127.31 (+, Ph-***C***-4), 127.77 (+, Ph-***C***-4), 127.93 (+, 2 Ph-***C***), 129.46 (+, 2 Ph-***C***), 129.65 (+, 2 Ph-***C***), 129.72 (+, 2 Ph-***C***), 142.02 (C$_{quat}$, Ph-***C***-1), 146.41 (C$_{quat}$, Ph-***C***-1), 152.27 (C$_{quat}$, ***C***=N), 175.91 (C$_{quat}$, ***C***=O). IR (cm^{-1}) = 3245, 2960, 1706, 1656, 1594, 1197, 1140. HRMS (EI-MS) calcd. for $C_{20}H_{25}N_3O$ [$M^{+\bullet}$] 323.1998; found 323.1995. $C_{20}H_{25}N_3O \cdot$ TFA (437.46).

N^1-(3,3-Diphenylpropanoyl)-N^2-(3-phenylpropyl)guanidine (58)

The title compound was prepared from **55** (226 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **48** (177 mg, 1.0 mmol) according to the general procedure 1. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 55/45) yielded a white solid (141 mg, 28 %); mp 138 – 140 °C. ^{1}H-NMR (300 MHz, $(CD_3)_2CO$, trifluoroacetate): δ [ppm] = 1.92 – 2.03 (m, 2H, Ph-CH$_2$-C***H***$_2$), 2.70 (t, 2H, ^3J = 7.7 Hz, Ph-C***H***$_2$), 3.34 (d, 2H, ^3J = 8.1 Hz, Ph$_2$CH-C***H***$_2$), 3.39 (t, 2H, ^3J = 7.0 Hz, Ph-CH$_2$-CH$_2$-C***H***$_2$), 4.65 (t, 1H, ^3J = 8.1 Hz, Ph$_2$C***H***), 7.12 – 7.42 (m, 15H, Ph-***H***). ^{13}C-NMR (75 MHz, $(CD_3)_2CO$, trifluoroacetate): δ [ppm] = 30.36, 33.40 (-, Ph-***C***H$_2$-***C***H$_2$), 41.60 (-, Ph-CH$_2$-CH$_2$-***C***H$_2$), 43.08 (-, Ph$_2$CH-***C***H$_2$), 47.67 (+, Ph$_2$***C***H), 126.90 (+, 1 Ph-***C***-4), 127.44 (+, 2 Ph-***C***-4), 128.64 (+, 4 Ph-***C***), 129.30 (+, 2 Ph-***C***), 129.32 (+, 2 Ph-***C***), 129.43 (+, 4 Ph-***C***), 142.00 (C$_{quat}$, 1 Ph-***C***-1), 144.35

(C_{quat}, 2 Ph-***C***-1), 155.47 (C_{quat}, ***C***=N), 175.81 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3247, 2971, 1704, 1661, 1598, 1193, 1142. HRMS (EI-MS) calcd. for $C_{25}H_{27}N_3O$ [$M^{+\bullet}$] 385.2154; found 385.2168. $C_{25}H_{27}N_3O$ · TFA (499.52).

N^1-(3-Phenylbutanoyl)-N^2-[3-(pyridin-2-yl)propyl]guanidine (59)

The title compound was prepared from **53** (164 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **49** (178 mg, 1.0 mmol) according to the general procedure 2. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 15/85, 20 min: 35/65) yielded a colourless oil (421 mg, 76 %). ^{1}H-NMR (400 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 1.31 (d, 3H, ^3J = 7.0 Hz, PhC***H***$_3$CH), 2.07 – 2.16 (m, 2H, Pyr-2-CH_2-C***H***$_2$), 2.73 (dd, 1H, ^2J = 15.3 Hz, ^3J = 7.3 Hz, PhCH$_3$CH-C***H***$_2$), 2.79 (dd, 1H, ^2J = 15.3 Hz, ^3J = 7.8 Hz, PhCH$_3$CH-C***H***$_2$), 3.12 (t, 2H, ^3J = 8.0 Hz, Pyr-2-C***H***$_2$), 3.26 – 3.36 (m, 1H, overlap with solvent, PhCH$_3$C***H***), 3.39 (t, 2H, ^3J = 6.8 Hz, Pyr-2-$(CH_2)_2$-C***H***$_2$), 7.14 – 7.30 (m, 5H, Ph-***H***), 7.86 (ddd, 1H, ^3J = 7.7 Hz, ^3J = 5.9 Hz, ^4J = 1.2 Hz, Pyr-5-***H***), 7.94 (ddd, 1H, ^3J = 8.1 Hz, ^4J = 1.2 Hz, ^5J = 0.8 Hz, Pyr-3-***H***), 8.46 (ddd, 1H, ^3J = 8.1 Hz, ^3J = 7.7 Hz, ^4J = 1.6 Hz, Pyr-4-***H***), 8.71 (ddd, 1H, ^3J = 5.9 Hz, ^4J = 1.6 Hz, ^5J = 0.8 Hz, Pyr-6-***H***). ^{13}C-NMR (100 MHz, CD_3OD, trifluoroacetate, HSQC, HMBC): δ [ppm] = 22.28 (+, Ph***C***H$_3$CH), 28.39 (-, Pyr-2-CH_2-***C***H$_2$), 31.84 (-, Pyr-2-***C***H$_2$), 37.59 (+, PhCH$_3$***C***H), 41.62 (-, Pyr-2-$(CH_2)_2$-***C***H$_2$), 46.07 (-, PhCH$_3$CH-***C***H$_2$), 126.09 (+, Pyr-***C***-5), 127.66 (+, Ph-***C***-4), 127.92 (+, 2 Ph-***C***), 128.23 (+, Pyr-***C***-3), 129.63 (+, 2 Ph-***C***), 143.29 (+, Pyr-***C***-6), 146.43 (C_{quat}, Ph-***C***-1), 147.33 (+, Pyr-***C***-4), 155.29 (C_{quat}, ***C***=N), 157.88 (C_{quat}, Pyr-***C***-2), 175.91 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3066, 2964, 1668, 1602, 1178, 1127. HRMS (EI-MS) calcd. for $C_{19}H_{24}N_4O$ [$M^{+\bullet}$] 324.1950; found 324.1951. $C_{19}H_{24}N_4O$ · 2 TFA (552.47).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(pyridin-2-yl)propyl]guanidine (60)

The title compound was prepared from **55** (226 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **49** (178 mg, 1.0 mmol) according to the general procedure 2. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 25/75, 20 min: 45/55) yielded a semisolid compound (264 mg, 43 %). ^{1}H-NMR (300 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 2.02 – 2.16 (m, 2H, Pyr-2-CH_2-C***H***$_2$), 3.08 (t, 2H, ^3J = 7.9 Hz, Pyr-2-C***H***$_2$), 3.26 (d, 2H, ^3J = 8.0 Hz, Ph$_2$CHC***H***$_2$), 3.39 (t, 2H, ^3J = 6.8 Hz, Pyr-2-$(CH_2)_2$-C***H***$_2$), 4.59 (t, 1H, ^3J = 8.0 Hz, Ph$_2$C***H***), 7.14 – 7.33 (m, 10H, Ph-***H***), 7.82 (ddd, 1H, ^3J = 7.7 Hz, ^3J = 5.8 Hz, ^4J = 1.2 Hz, Pyr-5-***H***), 7.90 (ddd, 1H, ^3J = 8.2 Hz, ^4J = 1.2 Hz, ^5J = 0.8 Hz, Pyr-3-***H***), 8.46 (ddd,

1H, ^{3}J = 8.2 Hz, ^{3}J = 7.7 Hz, ^{4}J = 1.7 Hz, Pyr-4-***H***), 8.71 (ddd, 1H, ^{3}J = 5.8 Hz, ^{4}J = 1.6 Hz, ^{5}J = 0.8 Hz, Pyr-6-***H***). ^{13}C-NMR (75 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 28.41 (-, Pyr-2-CH_2-***C***H_2), 32.10 (-, Pyr-2-***C***H_2), 41.71 (-, Pyr-2-$(CH_2)_2$-***C***H_2), 43.81 (-, Ph_2CH-***C***H_2), 48.00 (+, Ph_2***C***H), 125.94 (+, Pyr-***C***-5), 127.82 (+, 2 Ph-***C***-4), 128.03 (+, Pyr-***C***-3), 128.84 (+, 4 Ph-***C***), 129.73 (+, 4 Ph-***C***), 143.77 (-, Pyr-***C***-6), 144.56 (C_{quat}, 2 Ph-***C***-1), 146.81 (+, Pyr-***C***-4), 155.21 (C_{quat}, ***C***=N), 158.15 (C_{quat}, Pyr-***C***-2), 175.42 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3064, 2971, 2901, 1668, 1599, 1179, 1127. HRMS (EI-MS) calcd. for $C_{24}H_{26}N_4O$ [$M^{+\bullet}$] 386.2107; found 386.2105. $C_{24}H_{26}N_4O$ · 2 TFA (614.54).

N^1-(3-Phenylbutanoyl)-N^2-[3-(pyridin-3-yl)propyl]guanidine (61)

The title compound was prepared from **53** (164 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **50** (178 mg, 1.0 mmol) according to the general procedure 2. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 15/85, 20 min: 35/65) yielded a colourless oil (355 mg, 64 %). ^{1}H-NMR (300 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 1.32 (d, 3H, ^{3}J = 7.0 Hz, PhC***H***$_3$CH), 1.95 – 2.09 (m, 2H, Pyr-3-CH_2-C***H***$_2$), 2.73 (dd, 1H, ^{2}J = 15.3 Hz, ^{3}J = 7.4 Hz, $PhCH_3$CH-C***H***$_2$), 2.80 (dd, 1H, ^{2}J = 15.3 Hz, ^{3}J = 7.7 Hz, $PhCH_3$CH-C***H***$_2$), 2.90 (t, 2H, ^{3}J = 8.0 Hz, Pyr-3-C***H***$_2$), 3.24 – 3.33 (m, 1H, overlap with solvent, $PhCH_3$C***H***), 3.35 (t, 2H, ^{3}J = 7.0 Hz, Pyr-3-$(CH_2)_2$-C***H***$_2$), 7.12 – 7.32 (m, 5H, Ph-***H***), 7.86 (dd, 1H, ^{3}J = 8.0 Hz, ^{3}J = 5.8 Hz, Pyr-5-***H***), 8.39 (d, 1H, ^{3}J = 8.0 Hz, Pyr-4-***H***), 8.56 – 8.80 (m, 2H, Pyr-2-***H*** + Pyr-6-***H***). ^{13}C-NMR (75 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 22.36 (+, Ph***C***H_3CH), 29.79 (-, Pyr-3-CH_2-***C***H_2), 30.61 (-, Pyr-3-***C***H_2), 37.68 (+, $PhCH_3$***C***H), 41.83 (-, Pyr-3-$(CH_2)_2$-***C***H_2), 46.10 (-, $PhCH_3$CH-***C***H_2), 127.72 (+, Ph-***C***-4), 127.97 (+, 2 Ph-***C***), 128.31 (+, Pyr-***C***-5), 129.68 (+, 2 Ph-***C***), 141.22 (+, Pyr-***C***-6), 142.88 (+, Pyr-***C***-2), 143.15 (C_{quat}, Pyr-***C***-3), 146.46 (C_{quat}, Ph-***C***-1), 147.62 (+, Pyr-***C***-4), 155.23 (C_{quat}, ***C***=N), 176.05 (C_{quat}, ***C***=O). IR (cm^{-1}) = 2971, 2901, 1668, 1603, 1177, 1130. HRMS (EI-MS) calcd. for $C_{19}H_{24}N_4O$ [$M^{+\bullet}$] 324.1950; found 324.1946. $C_{19}H_{24}N_4O$ · 2 TFA (552.47).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(pyridin-3-yl)propyl]guanidine (62)

The title compound was prepared from **55** (226 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **50** (178 mg, 1.0 mmol) according to the general procedure 2. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 15/85, 20 min: 45/55) yielded a white solid (384 mg, 62 %); mp 48 – 52 °C. ^{1}H-NMR (300 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 1.94 – 2.08 (m, 2H, Pyr-3-CH_2-C***H***$_2$), 2.88 (t, 2H, ^{3}J = 8.0

Hz, Pyr-3-C***H***$_2$), 3.26 (d, 2H, ^3J = 8.0 Hz, Ph$_2$CHC***H***$_2$), 3.33 (t, 2H, overlap with solvent, ^3J = 6.9 Hz, Pyr-3-(CH$_2$)$_2$-C***H***$_2$), 4.59 (t, 1H, ^3J = 8.0 Hz, Ph$_2$C***H***), 7.12 – 7.34 (m, 10H, Ph-***H***), 7.87 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 6.0 Hz, ^5J = 0.7 Hz, Pyr-5-***H***), 8.37 (ddd, 1H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, ^4J = 1.4 Hz, Pyr-4-***H***), 8.64 (dd, 1H, ^3J = 6.0 Hz, ^4J = 1.4 Hz, Pyr-6-***H***), 8.71 (dd, 1H, ^4J = 2.0 Hz, ^5J = 0.7 Hz, Pyr-2-***H***). ^{13}C-NMR (75 MHz, CD$_3$OD, trifluoroacetate): δ [ppm] = 29.74 (-, Pyr-3-CH$_2$-***C***H$_2$), 30.60 (-, Pyr-3-***C***H$_2$), 41.84 (-, Pyr-3-(CH$_2$)$_2$-***C***H$_2$), 43.79 (-, Ph$_2$CH-***C***H$_2$), 48.07 (+, Ph$_2$***C***H), 127.81 (+, Ph-***C***-4), 128.27 (+, Pyr-***C***-5), 128.85 (+, 2 Ph-***C***), 129.72 (+, 2 Ph-***C***), 141.30 (+, Pyr-***C***-6), 142.96 (+, Pyr-***C***-2), 143.07 (C$_{quat}$, Pyr-***C***-3), 144.55 (C$_{quat}$, Ph-***C***-1), 147.51 (+, Pyr-***C***-4), 155.16 (C$_{quat}$, ***C***=N), 175.52 (C$_{quat}$, ***C***=O). IR (cm^{-1}) = 2973, 2901, 1668, 1599, 1180, 1128. HRMS (EI-MS) calcd. for C$_{24}$H$_{26}$N$_4$O [M$^{+\bullet}$] 386.2107; found 386.2110. C$_{24}$H$_{26}$N$_4$O · 2 TFA (614.54).

N^1-(3-Phenylbutanoyl)-N^2-[3-(pyridin-4-yl)propyl]guanidine (63)

The title compound was prepared from **53** (164 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **51** (178 mg, 1.0 mmol) according to the general procedure 2. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 15/85, 20 min: 35/65) yielded a colourless semisolid compound (312 mg, 56 %). ^{1}H-NMR (300 MHz, CD$_3$OD, trifluoroacetate): δ [ppm] = 1.31 (d, 3H, ^3J = 7.0 Hz, PhC***H***$_3$CH), 1.99 – 2.12 (m, 2H, Pyr-4-CH$_2$-C***H***$_2$), 2.73 (dd, 1H, ^2J = 15.2 Hz, ^3J = 7.4 Hz, PhCH$_3$CH-C***H***$_2$), 2.80 (dd, 1H, ^2J = 15.2 Hz, ^3J = 7.7 Hz, PhCH$_3$CH-C***H***$_2$), 3.01 (t, 2H, ^3J = 8.0 Hz, Pyr-4-C***H***$_2$), 3.20 – 3.33 (m, 1H, overlap with solvent, PhCH$_3$C***H***), 3.37 (t, 2H, ^3J = 7.0 Hz, Pyr-4-(CH$_2$)$_2$-C***H***$_2$), 7.13 – 7.31 (m, 5H, Ph-***H***), 7.98 (d, 2H, ^3J = 6.8 Hz, Pyr-3,5-***H***), 8.74 (d, 2H, ^3J = 6.8 Hz, Pyr-2,6-***H***). ^{13}C-NMR (75 MHz, CD$_3$OD, trifluoroacetate): δ [ppm] = 22.34 (+, Ph***C***H$_3$CH), 29.07 (-, Pyr-4-CH$_2$-***C***H$_2$), 33.97 (-, Pyr-4-***C***H$_2$), 37.70 (+, PhCH$_3$***C***H), 41.84 (-, Pyr-4-(CH$_2$)$_2$-***C***H$_2$), 46.11 (-, PhCH$_3$CH-***C***H$_2$), 127.71 (+, Ph-***C***-4), 127.99 (+, 2 Ph-***C***), 128.58 (+, Pyr-***C***-3,5), 129.68 (+, 2 Ph-***C***), 142.53 (+, Pyr-***C***-2,6), 146.46 (C$_{quat}$, Ph-***C***-1), 155.28 (C$_{quat}$, ***C***=N), 164.69 (C$_{quat}$, Pyr-***C***-4), 176.11 (C$_{quat}$, ***C***=O). IR (cm^{-1}) = 2969, 2901, 1666, 1639, 1177, 1128. HRMS (EI-MS) calcd. for C$_{19}$H$_{24}$N$_4$O [M$^{+\bullet}$] 324.1950; found 324.1960. C$_{19}$H$_{24}$N$_4$O · 2 TFA (552.47).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(pyridin-4-yl)propyl]guanidine (64)

The title compound was prepared from **55** (226 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **51** (178 mg, 1.0 mmol) according to the general procedure 2. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 15/85,

20 min: 45/55) yielded a white solid (388 mg, 63 %); mp 93 – 94 °C. ^{1}H-NMR (300 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 1.95 – 2.10 (m, 2H, Pyr-4-CH_2-C***H***$_2$), 2.95 (t, 2H, ^{3}J = 8.0 Hz, Pyr-4-C***H***$_2$), 3.26 (d, 2H, ^{3}J = 8.0 Hz, Ph_2CHCH_2), 3.34 (t, 2H, overlap with solvent, ^{3}J = 7.0 Hz, Pyr-4-$(CH_2)_2$-C***H***$_2$), 4.59 (t, 1H, ^{3}J = 8.0 Hz, Ph_2C***H***), 7.13 – 7.33 (m, 10H, Ph-***H***), 7.88 (d, 1H, ^{3}J = 6.6 Hz, Pyr-3,5-***H***), 8.69 (d, 1H, ^{3}J = 6.6 Hz, Pyr-2,6-***H***). ^{13}C-NMR (75 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 29.09 (-, Pyr-4-CH_2-***C***H_2), 33.82 (-, Pyr-4-***C***H_2), 41.88 (-, Pyr-4-$(CH_2)_2$-***C***H_2), 43.82 (-, Ph_2CH-***C***H_2), 48.08 (+, Ph_2***C***H), 127.82 (+, 2 Ph-***C***-4), 128.19 (+, Pyr-***C***-3,5), 128.85 (+, 4 Ph-***C***), 129.72 (+, 4 Ph-***C***), 143.50 (+, Pyr-***C***-2,6), 145.54 (C_{quat}, 2 Ph-***C***-1), 155.17 (C_{quat}, ***C***=N), 163.19 (C_{quat}, Pyr-***C***-4), 175.52 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3091, 1677, 1596, 1594, 1199, 1133. HRMS (EI-MS) calcd. for $C_{24}H_{26}N_4O$ [$M^{+\bullet}$] 386.2107; found 386.2105. $C_{24}H_{26}N_4O \cdot 2$ TFA (614.54).

***N*^{1}-(3-{5-[(Dimethylamino)methyl]furan-2-yl}propyl)-*N*^{2}-(3-phenylbutanoyl)guanidine (65)**

The title compound was prepared from **53** (164 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **44** (224 mg, 1.0 mmol) according to the general procedure 1. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 30/70) yielded a pale brownish oil (208 mg, 35 %). ^{1}H-NMR (300 MHz, D_2O, trifluoroacetate): δ [ppm] = 1.24 (d, 3H, ^{3}J = 7.0 Hz, PhC***H***$_3$CH), 1.82 – 1.95 (m, 2H, Fur-2-CH_2-C***H***$_2$), 2.63 (t, 2H, ^{3}J = 7.4 Hz, Fur-2-C***H***$_2$), 2.68 – 2.79 (m, 8H, N(C***H***$_3$)$_2$ + $PhCH_3$CH-C***H***$_2$), 3.15 – 3.28 (m, 3H, Fur-2-$(CH_2)_2$-C***H***$_2$ + $PhCH_3$C***H***), 4.14 (d, 1H, ^{2}J = 14.9 Hz, Fur-5-C***H***$_2$), 4.19 (d, 1H, ^{2}J = 14.9 Hz, Fur-5-C***H***$_2$), 6.10 (d, 1H, ^{3}J = 3.2 Hz, Fur-3-***H***), 6.50 (d, 1H, ^{3}J = 3.2 Hz, Fur-4-***H***), 7.17 – 7.37 (m, 5H, Ph-***H***). ^{13}C-NMR (75 MHz, D_2O, trifluoroacetate): δ [ppm] = 21.29 (+, Ph***C***H_3CH), 24.53 (-, Fur-2-***C***H_2), 25.43 (-, Fur-2-CH_2-***C***H_2), 36.61 (+, $PhCH_3$***C***H), 40.66 (-, Fur-2-$(CH_2)_2$-***C***H_2), 41.93 (+, N(***C***H_3)$_2$), 45.07 (-, $PhCH_3$CH-***C***H_2), 53.03 (-, Fur-5-***C***H_2), 107.23 (+, Fur-***C***-3), 115.59 (+, Fur-***C***-4), 126.98 (+ , 2 Ph-***C***), 127.06 (+, Ph-***C***-4), 128.99 (+, 2 Ph-***C***), 142.04 (C_{quat}, Fur-***C***-5), 145.02 (C_{quat}, Ph-***C***-1), 152.76 (C_{quat}, ***C***=N), 157.65 (C_{quat}, Fur-***C***-2), 176.00 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3032, 2964, 1669, 1602, 1594, 1177, 1132. HRMS (EI-MS) calcd. for $C_{21}H_{30}N_4O_2$ [$M^{+\bullet}$] 370.2369; found 370.2370. $C_{21}H_{30}N_4O_2 \cdot 2$ TFA (598.54).

***N*^{1}-(3-{5-[(Dimethylamino)methyl]furan-2-yl}propyl)-*N*^{2}-[3-(thiophen-2-yl)butanoyl]-guanidine (66)**

The title compound was prepared from **54**[13] (170 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **44** (224 mg, 1.0 mmol) according to the

general procedure 1. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 27.5/72.5) yielded a pale brownish oil (72 mg, 12 %). ^{1}H-NMR (300 MHz, D_2O, trifluoroacetate): δ [ppm] = 1.33 (d, 3H, ^{3}J = 7.0 Hz, ThioC***H***$_3$CH), 1.84 – 1.97 (m, 2H, Fur-2-CH$_2$-C***H***$_2$), 2.69 – 2.87 (m, 10H, Fur-2-C***H***$_2$ + + ThioCH$_3$CH-C***H***$_2$ + N(C***H***$_3$)$_2$), 3.36 (t, 2H, ^{3}J = 6.7 Hz, Fur-2-(CH$_2$)$_2$-C***H***$_2$), 3.48 – 3.62 (m, 1H, ThioCH$_3$C***H***), 4.17 (d, 1H, ^{2}J = 14.7 Hz, Fur-5-C***H***$_2$), 4.22 (d, 1H, ^{2}J = 14.7 Hz, Fur-5-C***H***$_2$), 6.13 (d, 1H, ^{3}J = 3.2 Hz, Fur-3-***H***), 6.52 (d, 1H, ^{3}J = 3.2 Hz, Fur-4-***H***), 6.89 (ddd, 1H, ^{3}J = 3.5 Hz, ^{4}J = 1.3 Hz, ^{4}J = 0.7 Hz, Thio-3-***H***), 6.94 (dd, 1H, ^{3}J = 5.0 Hz, ^{3}J = 3.5 Hz, Thio-4-***H***), 7.24 (dd, 1H, ^{3}J = 5.0 Hz, ^{4}J = 1.3 Hz, Thio-5-***H***). ^{13}C-NMR (75 MHz, D_2O, trifluoroacetate): δ [ppm] = 22.28 (+, Thio***C***H$_3$CH), 24.55 (-, Fur-2-***C***H$_2$), 25.44 (-, Fur-2-CH$_2$-***C***H$_2$), 31.96 (+, ThioCH$_3$***C***H), 40.75 (-, Fur-2-(CH$_2$)$_2$-***C***H$_2$), 41.92 (+, N(***C***H$_3$)$_2$), 46.02 (-, ThioCH$_3$CH-***C***H$_2$), 53.03 (-, Fur-5-***C***H$_2$), 107.27 (+, Fur-***C***-3), 115.58 (+, Fur-***C***-4), 123.74, 123.97 (+, Thio-***C***-3,4), 127.25 (+, Thio-***C***-5), 142.04 (C$_{quat}$, Fur-***C***-5), 148.87 (C$_{quat}$, Thio-***C***-2), 152.75 (C$_{quat}$, ***C***=N), 157.64 (C$_{quat}$, Fur-***C***-2), 175.47 (C$_{quat}$, ***C***=O). IR (cm^{-1}) = 2989, 2901, 1663, 1178, 1130. HRMS (EI-MS) calcd. for $C_{19}H_{28}N_4O_2S$ [$M^{+\bullet}$] 376.1933; found 376.1930. $C_{19}H_{28}N_4O_2S$ · 2 TFA (604.56).

N^1-(3-{5-[(Dimethylamino)methyl]furan-2-yl}propyl)-N^2-(3,3-diphenylpropanoyl)guanidine (67)

The title compound was prepared from **55** (226 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **44** (224 mg, 1.0 mmol) according to the general procedure 1. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 35/65) yielded a brownish oil (176 mg, 27 %). ^{1}H-NMR (300 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 1.89 – 2.02 (m, 2H, Fur-2-CH$_2$-C***H***$_2$), 2.73 (t, 2H, ^{3}J = 7.5 Hz, Fur-2-C***H***$_2$), 2.83 (s, 6H, N(C***H***$_3$)$_2$), 3.22 – 3.33 (m, 4H, overlap with solvent, Fur-2-(CH$_2$)$_2$-C***H***$_2$ + Ph$_2$CH-C***H***$_2$), 4.30 (s, 2H, Fur-5-C***H***$_2$), 4.58 (t, 1H, ^{3}J = 8.0 Hz, Ph$_2$C***H***), 6.18 (d, 1H, ^{3}J = 3.2 Hz, Fur-3-***H***), 6.58 (d, 1H, ^{3}J = 3.2 Hz, Fur-4-***H***), 7.13 – 7.34 (m, 10H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 25.97 (-, Fur-2-***C***H$_2$), 27.34 (-, Fur-2-CH$_2$-***C***H$_2$), 41.82 (-, Fur-2-(CH$_2$)$_2$-***C***H$_2$), 42.76 (+, N(***C***H$_3$)$_2$), 43.86 (-, Ph$_2$CH***C***H$_2$), 48.08 (+, Ph$_2$***C***H), 54.09 (-, Fur-5-***C***H$_2$), 108.48 (+, Fur-***C***-3), 116.61 (+, Fur-***C***-4), 127.83 (+ , 2 Ph-***C***-4), 128.84 (+, 4 Ph-***C***), 129.73 (+, 4 Ph-***C***), 143.86 (C$_{quat}$, Fur-***C***-5), 144.53 (C$_{quat}$, 2 Ph-***C***-1), 155.09 (C$_{quat}$, ***C***=N), 158.84 (C$_{quat}$, Fur-***C***-2), 175.54 (C$_{quat}$, ***C***=O). IR (cm^{-1}) = 2989, 2901, 1663, 1599, 1174, 1126. HRMS (EI-MS) calcd. for $C_{26}H_{32}N_4O_2$ [$M^{+\bullet}$] 432.2525; found 432.2531. $C_{26}H_{32}N_4O_2$ · 2 TFA (660.60).

N^1-(3-{5-[(Dimethylamino)methyl]furan-2-yl}propyl)-N^2-[3-phenyl-3-(thiazol-2-yl)-propanoyl]guanidine (68)

The title compound was prepared from **56**[13] (233 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **44** (224 mg, 1.0 mmol) according to the general procedure 1. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 27.5/72.5) yielded a brownish semisolid compound (134 mg, 17 %). ^{1}H-NMR (400 MHz, D_2O, trifluoroacetate): δ [ppm] = 1.82 – 1.93 (m, 2H, Fur-2-CH_2-C***H***$_2$), 2.63 (t, 2H, ^3J = 7.3 Hz, Fur-2-C***H***$_2$), 2.73 (s, 6H, N(C***H***$_3$)$_2$), 3.23 (t, 2H, ^3J = 6.8 Hz, Fur-2-$(CH_2)_2$-C***H***$_2$), 3.34 (dd, 1H, ^2J = 16.6 Hz, ^3J = 8.2 Hz, PhThiazCH-C***H***$_2$), 3.48 (dd, 1H, ^2J = 16.6 Hz, ^3J = 7.2 Hz, PhThiazCH-C***H***$_2$), 4.13 (d, 1H, ^2J = 14.5 Hz, Fur-5-C***H***$_2$), 4.17 (d, 1H, ^2J = 14.5 Hz, Fur-5-C***H***$_2$), 5.05 (dd, 1H, ^3J = 8.2 Hz, ^3J = 7.2 Hz, PhThiazC***H***), 6.08 (d, 1H, ^3J = 3.2 Hz, Fur-3-***H***), 6.47 (d, 1H, ^3J = 3.2 Hz, Fur-4-***H***), 7.29 – 7.40 (m, 5H, Ph-***H***), 7.64 (d, 1H, ^3J = 3.6 Hz, Thiaz-5-***H***), 7.80 (d, 1H, ^3J = 3.6 Hz, Thiaz-4-***H***). ^{13}C-NMR (100 MHz, D_2O, trifluoroacetate, HSQC, HMBC): δ [ppm] = 24.44 (-, Fur-2-***C***H_2), 25.33 (-, Fur-2-CH_2-***C***H_2), 40.75 (-, Fur-2-$(CH_2)_2$-***C***H_2), 41.57 (-, PhThiazCH***C***H_2), 41.84 (+, N(***C***H_3)$_2$), 43.19 (+, PhThiaz***C***H), 52.94 (-, Fur-5-***C***H_2), 107.17 (+, Fur-***C***-3), 115.48 (+, Fur-***C***-4), 122.05 (+, Thiaz-***C***-5), 127.86 (+ , 2 Ph-***C***), 128.65 (+, Ph-***C***-4), 129.52 (+, 2 Ph-***C***), 138.19 (+, Thiaz-***C***-4), 138.62 (C_{quat}, Ph-***C***-1), 141.93 (C_{quat}, Fur-***C***-5), 152.55 (C_{quat}, ***C***=N), 157.54 (C_{quat}, Fur-***C***-2) 173.07 (C_{quat}, ***C***=O), 175.11 (C_{quat}, Thiaz-***C***-2). IR (cm^{-1}) = 2989, 2901, 1669, 1173, 1130. HRMS (EI-MS) calcd. for $C_{23}H_{29}N_5O_2S$ [$M^{+\bullet}$] 439.2042; found 439.2040. $C_{23}H_{29}N_5O_2S \cdot 3$ TFA (781.64).

N^1-[3-(1*H*-Imidazol-1-yl)propyl]-N^2-(3-phenylbutanoyl)guanidine (69)

The title compound was prepared from **53** (164 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **52** (167 mg, 1.0 mmol) according to the general procedure 2. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 15/85, 20 min: 35/65) yielded a colourless oil (275 mg, 51 %). ^{1}H-NMR (600 MHz, D_2O, trifluoroacetate): δ [ppm] = 1.24 (d, 3H, ^3J = 7.0 Hz, PhC***H***$_3$CH), 2.11 – 2.19 (m, 2H, Im-1-CH_2-C***H***$_2$), 2.68 (dd, 1H, ^2J = 15.0 Hz, ^3J = 9.1 Hz, PhCH_3CH-C***H***$_2$), 2.75 (dd, 1H, ^2J = 15.0 Hz, ^3J = 6.4 Hz, PhCH_3CH-C***H***$_2$), 3.18 – 3.25 (m, 1H, PhCH_3C***H***), 3.28 (t, 2H, ^3J = 6.7 Hz, Im-1-$(CH_2)_2$-C***H***$_2$), 4.22 (t, 2H, ^3J = 7.2 Hz, Im-1-C***H***$_2$), 7.20 – 7.34 (m, 5H, Ph-***H***), 7.35 – 7.36 (m, 1H, Im-4-***H***), 7.41 – 7.43 (m, 1H, Im-5-***H***), 8.66 – 8.67 (m, 1H, Im-2-***H***). ^{13}C-NMR (150 MHz, D_2O, trifluoroacetate, HSQC, HMBC): δ [ppm] = 21.23 (+, Ph***C***H_3CH), 27.64 (-, Im-1-CH_2-***C***H_2), 36.43 (+, PhCH_3***C***H), 38.30 (-, Im-1-$(CH_2)_2$-***C***H_2), 44.90 (-, PhCH_3CH-***C***H_2), 46.53 (-, Im-1-

CH_2), 120.01 (+, Im-***C***-4), 121.64 (+, Im-***C***-5), 126.88 (+, 2 Ph-***C***), 126.97 (+, Ph-***C***-4), 128.90 (+, 2 Ph-***C***), 134.54 (+, Im-***C***-2), 144.97 (C_{quat}, Ph-***C***-1), 152.92 (C_{quat}, ***C***=N), 175.91 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3138, 2989, 2901, 1667, 1601, 1174, 1132. HRMS (EI-MS) calcd. for $C_{17}H_{23}N_5O$ [$M^{+\bullet}$] 313.1903; found 313.1899. $C_{17}H_{23}N_5O \cdot 2$ TFA (541.44).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(1*H*-imidazol-1-yl)propyl]guanidine (70)

The title compound was prepared from **55** (226 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **52** (224 mg, 1.0 mmol) according to the general procedure 2. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 20/80, 20 min: 40/60) yielded a white solid (162 mg, 27 %); mp 48 – 52 °C. ^{1}H-NMR (300 MHz, D_2O, trifluoroacetate): δ [ppm] = 2.01 – 2.13 (m, 2H, Im-1-CH_2-C***H***$_2$), 3.19 (d, 2H, ^3J = 8.1 Hz, Ph_2CHCH_2), 3.21 (t, 2H, ^3J = 6.8 Hz, Im-1-$(CH_2)_2$-C***H***$_2$), 4.14 (t, 2H, ^3J = 7.2 Hz, Im-1-C***H***$_2$), 4.45 (t, 1H, ^3J = 8.1 Hz, Ph_2C***H***), 7.12 – 7.29 (m, 11H, Ph-***H*** + Im-4-***H***), 7.32 – 7.35 (m, 1H, Im-5-***H***), 8.58 – 8.61 (m, 1H, Im-2-***H***). ^{13}C-NMR (75 MHz, D_2O, trifluoroacetate): δ [ppm] = 27.60 (-, Im-1-CH_2-***C***H_2), 38.32 (-, Im-1-$(CH_2)_2$-***C***H_2), 42.10 (-, Ph_2CH-***C***H_2), 46.38 (+, Ph_2***C***H), 46.50 (-, Im-1-***C***H_2), 119.98 (+, Im-***C***-4), 121.60 (+, Im-***C***-5), 127.16 (+, 2 Ph-***C***-4), 127.45 (+, 4 Ph-***C***), 129.05 (+, 4 Ph-***C***), 134.51 (+, Im-***C***-2), 142.91 (C_{quat}, 2 Ph-***C***-1), 152.87 (C_{quat}, ***C***=N), 175.09 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3149, 3068, 2969, 1665, 1603, 1178, 1132. HRMS (EI-MS) calcd. for $C_{22}H_{25}N_5O$ [$M^{+\bullet}$] 375.2059; found 375.2055. $C_{22}H_{25}N_5O \cdot 2$ TFA (603.51).

N^1-(3-Phenylbutanoyl)-N^2-[3-(1-trityl-1*H*-pyrazol-4-yl)propyl]guanidine (71)

The title compound was prepared from **53** (164 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **46** (409 mg, 1.0 mmol) according to the general procedure 2. Purification by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 95/3/2 v/v/v) yielded a colourless foam-like solid (410 mg, 74 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.27 (d, 3H, ^3J = 6.9 Hz, PhC***H***$_3$CH), 1.75 – 1.89 (m, 2H, Pyraz-4-CH_2-C***H***$_2$), 2.43 – 2.56 (m, 3H, Pyraz-4-C***H***$_2$ + $PhCH_3$CH-C***H***$_2$), 2.62 (dd, 1H, ^2J = 14.6 Hz, ^3J = 6.2 Hz, $PhCH_3$CH-C***H***$_2$), 3.07 (t, 2H, ^3J = 6.9 Hz, Pyraz-4-$(CH_2)_2$-C***H***$_2$), 3.24 – 3.38 (m, 1H, $PhCH_3$C***H***), 7.08 – 7.37 (m, 21H, Ph-***H*** + Pyraz-3-***H***), 7.48 (s, 1H, Pyraz-5-***H***). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 556 (66) $[M + H]^+$, 466 (100). $C_{36}H_{37}N_5O$ (555.71).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(1-trityl-1*H*-pyrazol-4-yl)propyl]guanidine (72)

The title compound was prepared from **55** (226 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **46** (409 mg, 1.0 mmol) according to the general procedure 2. Purification by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 95/3/2 v/v/v) yielded a colourless oil (430 mg, 70 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.69 – 1.86 (m, 2H, Pyraz-4-CH_2-C***H***$_2$), 2.48 (t, 2H, ^3J = 7.4 Hz, Pyraz-4-C***H***$_2$), 2.97 – 3.08 (m, 4H, Pyraz-4-$(CH_2)_2$-C***H***$_2$ + Ph_2CHCH_2), 4.63 (t, 1H, ^3J = 7.8 Hz, Ph_2C***H***), 7.05 – 7.37 (m, 26H, Ph-***H*** + Pyraz-3-***H***), 7.46 (s, 1H, Pyraz-5-***H***). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 618 (83) [M + H]$^+$, 528 (100). $C_{41}H_{39}N_5O$ (617.78).

N^1-(3-Phenylbutanoyl)-N^2-[3-(1-trityl-1*H*-imidazol-2-yl)propyl]guanidine (73)

The title compound was prepared from **53** (164 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **45** (409 mg, 1.0 mmol) according to the general procedure 1. Purification by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 95/3/2 v/v/v) yielded a pale yellow oil (290 mg, 52 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.28 (d, 3H, ^3J = 6.9 Hz, PhC***H***$_3$CH), 1.36 – 1.52 (m, 2H, Im-2-CH_2-C***H***$_2$), 1.84 (t, 2H, ^3J = 5.7 Hz, Im-2-C***H***$_2$), 2.55 (dd, 1H, ^2J = 14.8 Hz, ^3J = 8.2 Hz, $PhCH_3$CH-C***H***$_2$), 2.69 (dd, 1H, ^2J = 14.8 Hz, ^3J = 6.4 Hz, $PhCH_3$CH-C***H***$_2$), 3.07 (t, 2H, ^3J = 7.4 Hz, Im-2-$(CH_2)_2$-C***H***$_2$), 3.26 – 3.38 (m, 1H, $PhCH_3$C***H***), 6.78 (d, 1H, ^3J = 1.5 Hz, Im-4-***H***), 6.89 (d, 1H, ^3J = 1.5 Hz, Im-5-***H***), 7.05 – 7.39 (m, 20H, Ph-***H***). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 556 (100) [M + H]$^+$. $C_{36}H_{37}N_5O$ (555.71).

N^1-[3-(Thiophen-2-yl)butanoyl]-N^2-[3-(1-trityl-1*H*-Imidazol-2-yl)propyl]guanidine (74)

The title compound was prepared from **54**[13] (170 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **45** (409 mg, 1.0 mmol) according to the general procedure 1. Purification by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 95/3/2 v/v/v) yielded a pale yellow foam-like solid (310 mg, 55 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.34 – 1.54 (m, 5H, ThioC***H***$_3$CH + Im-2-CH_2-C***H***$_2$), 1.85 (t, 2H, ^3J = 7.1 Hz, Im-2-C***H***$_2$), 2.60 (dd, 1H, ^2J = 15.0 Hz, ^3J = 8.4 Hz, ThioCH_3CH-C***H***$_2$), 2.78 (dd, 1H, ^2J = 15.0 Hz, ^3J = 6.6 Hz, ThioCH_3CH-C***H***$_2$), 3.09 (t, 2H, ^3J = 7.4 Hz, Im-2-$(CH_2)_2$-C***H***$_2$), 3.55 – 3.70 (m, 1H, ThioCH_3C***H***), 6.77 – 6.94 (m, 4H, Thio-3,4-***H*** + Im-4,5-***H***), 7.04 – 7.16 (m, 7H, Ph-***H***, Thio-5-***H***), 7.27 – 7.39 (m, 9H, Ph-***H***). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 562 (100) [M + H]$^+$. $C_{34}H_{35}N_5OS$ (561.74).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(1-trityl-1*H*-imidazol-2-yl)propyl]guanidine (75)

The title compound was prepared from **55** (226 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **45** (409 mg, 1.0 mmol) according to the general procedure 1. Purification by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 95/3/2 v/v/v) yielded a pale yellow foam-like solid (380 mg, 62 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.30 – 1.42 (m, 2H, Im-2-CH_2-C***H***$_2$), 1.81 (t, 2H, ^3J = 5.6 Hz, Im-2-C***H***$_2$), 3.03 (t, 2H, ^3J = 7.1 Hz, Im-2-$(CH_2)_2$-C***H***$_2$), 3.12 (d, 2H, ^3J = 7.9 Hz, Ph_2CHCH_2), 4.62 (t, 1H, ^3J = 7.9 Hz, Ph_2CH), 6.77 (d, 1H, ^3J = 1.5 Hz, Im-4-***H***), 6.85 (d, 1H, ^3J = 1.5 Hz, Im-5-***H***), 7.04 – 7.40 (m, 25H, Ph-***H***). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 618 (100) $[M + H]^+$. $C_{41}H_{39}N_5O$ (617.78).

N^1-[3-Phenyl-3-(thiazol-2-yl)propanoyl]-N^2-[3-(1-trityl-1*H*-imidazol-2-yl)propyl]guanidine (76)

The title compound was prepared from **56**[13] (233 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **45** (409 mg, 1.0 mmol) according to the general procedure 1. Purification by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 95/3/2 v/v/v) yielded a brownish oil (300 mg, 48 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.35 – 1.50 (m, 2H, Im-2-CH_2-C***H***$_2$), 1.81 (t, 2H, ^3J = 5.7 Hz, Im-2-C***H***$_2$), 2.96 – 3.10 (m, 3H, Im-2-$(CH_2)_2$-C***H***$_2$ + PhThiazCH-C***H***$_2$), 3.39 (dd, 1H, ^2J = 16.0 Hz, ^3J = 8.2 Hz, PhThiazCH-C***H***$_2$), 5.00 (dd, 1H, ^3J = 8.2 Hz, ^3J = 7.2 Hz, PhThiazC***H***), 6.76 (d, 1H, ^3J = 1.5 Hz, Im-4-***H***), 6.87 (d, 1H, ^3J = 1.5 Hz, Im-5-***H***), 7.14 – 7.41 (m, 21H, Ph-***H*** + Thiaz-5-***H***), 7.66 (d, 1H, ^3J = 3.5 Hz, Thiaz-4-***H***). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 625 (100) $[M + H]^+$. $C_{38}H_{36}N_6OS$ (624.80).

N^1-(3-Phenylbutanoyl)-N^2-[3-(1-trityl-1*H*-1,2,4-triazol-3-yl)propyl]guanidine (77)

The title compound was prepared from **53** (164 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **47** (411 mg, 1.0 mmol) according to the general procedure 2. Purification by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 95/3/2 v/v/v) yielded a colourless foam-like solid (470 mg, 84 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.27 (d, 3H, ^3J = 6.9 Hz, PhC***H***$_3$CH), 1.41 – 1.57 (m, 2H, Triaz-5-CH_2-C***H***$_2$), 1.95 (t, 2H, ^3J = 5.9 Hz, Triaz-5-C***H***$_2$), 2.48 (dd, 1H, ^2J = 14.6 Hz, ^3J = 8.9 Hz, $PhCH_3CH$-C***H***$_2$), 2.62 (dd, 1H, ^2J = 14.6 Hz, ^3J = 8.5 Hz, $PhCH_3CH$-C***H***$_2$), 3.04 (t, 2H, ^3J = 7.5 Hz, Triaz-5-$(CH_2)_2$-C***H***$_2$), 3.24 – 3.39 (m, 1H, $PhCH_3C$***H***), 7.05 – 7.14 (m, 6H, Ph-***H***), 7.23 – 7.38 (m, 14H, Ph-***H***),

7.88 (s, 1H, Triaz-3-***H***). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 557 (100) $[M + H]^+$. $C_{35}H_{36}N_6O$ (556.70).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(1-trityl-1*H*-1,2,4-triazol-3-yl)propyl]guanidine (78)

The title compound was prepared from **55** (226 mg, 1.0 mmol), CDI (195 mg, 1.2 mmol), NaH (60 % dispersion in mineral oil) (80 mg, 2.0 mmol) and **47** (411 mg, 1.0 mmol) according to the general procedure 2. Purification by flash chromatography ($CHCl_3$/MeOH/NH_3 (aq.) 32 % 95/3/2 v/v/v) yielded a colourless foam-like solid (580 mg, 94 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.37 – 1.51 (m, 2H, Triaz-5-CH_2-C***H***$_2$), 2.88 (t, 2H, ^3J = 5.8 Hz, Triaz-5-C***H***$_2$), 2.99 (t, 2H, ^3J = 7.6 Hz, Triaz-5-$(CH_2)_2$-C***H***$_2$), 3.04 (d, 2H, ^3J = 7.8 Hz, Ph_2CHCH_2), 4.63 (t, 1H, ^3J = 7.8 Hz, Ph_2C***H***), 7.00 – 7.40 (m, 25H, Ph-***H***), 7.86 (s, 1H, Triaz-3-***H***). ES-MS (DCM/MeOH + NH_4OAc) *m/z* (%): 619 (100) $[M + H]^+$. $C_{40}H_{38}N_6O$ (618.77).

Preparation of the N^G-acylated arylpropylguanidines 79-86

The pertinent trityl-protected N^G-acylated arylpropylguanidine was stirred for 5 h in a mixture of TFA (5.0 mL) and DCM (20 mL). After removing the solvent *in vacuo*, the crude product was purified by preparative HPLC. All compounds were dried by lyophilization and obtained as trifluoroacetic acid salts.

N^1-[3-(1*H*-Imidazol-2-yl)propyl]-N^2-(3-phenylbutanoyl)guanidine (79)

The title compound was prepared from **73** (280 mg, 0.50 mmol) according to the general procedure. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 27.5/72.5) yielded a colourless semisolid compound (79 mg, 29 %). ^{1}H-NMR (300 MHz, D_2O, trifluoroacetate): δ [ppm] = 1.20 (d, 3H, ^3J = 7.0 Hz, PhC***H***$_3$CH), 1.90 – 2.05 (m, 2H, Im-2-CH_2-C***H***$_2$), 2.64 (dd, 1H, ^2J = 15.0 Hz, ^3J = 8.9 Hz, $PhCH_3CH$-C***H***$_2$), 2.71 (dd, 1H, ^2J = 15.0 Hz, ^3J = 6.4 Hz, $PhCH_3CH$-C***H***$_2$), 2.91 (t, 2H, ^3J = 7.7 Hz, Im-2-C***H***$_2$), 3.10 – 3.22 (m, 1H, $PhCH_3C$***H***), 3.26 (t, 2H, ^3J = 6.7 Hz, Im-2-$(CH_2)_2$-C***H***$_2$), 7.13 (s, 2H, Im-4,5-***H***), 7.14 – 7.33 (m, 5H, Ph-***H***). ^{13}C-NMR (75 MHz, D_2O, trifluoroacetate): δ [ppm] = 21.36 (+, Ph***C***H_3CH), 22.58 (-, Im-2-***C***H_2), 24.95 (-, Im-2-CH_2-***C***H_2), 36.41 (+, $PhCH_3$***C***H), 40.33 (-, Im-2-$(CH_2)_2$-***C***H_2), 44.88 (-, $PhCH_3CH$-***C***H_2), 118.59 (+, Im-***C***-4,5), 126.93 (+, 2 Ph-***C***), 127.01 (+, Ph-***C***-4), 128.95 (+, 2 Ph-***C***), 145.04 (C_{quat}, Ph-***C***-1), 146.18 (C_{quat}, Im-***C***-2), 152.92 (C_{quat}, ***C***=N), 175.95 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3114, 2939, 2719,

1662, 1626, 1179, 1128. HRMS (EI-MS) calcd. for $C_{17}H_{23}N_5O$ [$M^{+\bullet}$] 313.1903; found 313.1906. $C_{17}H_{23}N_5O \cdot 2$ TFA (541.44).

N^1-[3-(1*H*-Imidazol-2-yl)propyl]-N^2-[3-(thiophen-2-yl)butanoyl]guanidine (80)

The title compound was prepared from **74** (280 mg, 0.50 mmol) according to the general procedure. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 27.5/72.5) yielded a beige semisolid compound (99 mg, 36 %). ^{1}H-NMR (300 MHz, D_2O, trifluoroacetate): δ [ppm] = 1.28 (d, 3H, ^3J = 7.0 Hz, ThioC***H***$_3$CH), 1.94 – 2.07 (m, 2H, Im-2-CH$_2$-C***H***$_2$), 2.65 (dd, 1H, ^2J = 15.2 Hz, ^3J = 8.8 Hz, ThioCH$_3$CH-C***H***$_2$), 2.74 (dd, 1H, ^2J = 15.2 Hz, ^3J = 6.3 Hz, ThioCH$_3$CH-C***H***$_2$), 2.94 (t, 2H, ^3J = 7.7 Hz, Im-2-C***H***$_2$), 3.29 (t, 2H, ^3J = 6.8 Hz, Im-2-(CH$_2$)$_2$-C***H***$_2$), 3.44 – 3.58 (m, 1H, ThioCH$_3$C***H***), 6.85 (ddd, 1H, ^3J = 3.5 Hz, ^4J = 1.2 Hz, ^4J = 0.6 Hz, Thio-3-***H***), 6.90 (dd, 1H, ^3J = 5.0 Hz, ^3J = 3.5 Hz, Thio-4-***H***), 7.16 (s, 2H, Im-4,5-***H***), 7.19 (dd, 1H, ^3J = 5.0 Hz, ^4J = 1.2 Hz, Thio-5-***H***). ^{13}C-NMR (75 MHz, D_2O, trifluoroacetate): δ [ppm] = 22.26 (+, ThioCH***C***H$_3$), 22.59 (-, Im-2-***C***H$_2$), 24.96 (-, Im-2-CH$_2$-***C***H$_2$), 31.79 (+, ThioCH$_3$***C***H), 40.36 (-, Im-2-(CH$_2$)$_2$-***C***H$_2$), 45.89 (-, ThioCH$_3$CH-***C***H$_2$), 118.59 (+, Im-***C***-4,5), 123.67, 123.90 (+, Thio-***C***-3,4), 127.17 (+, Thio-***C***-5), 146.19 (C$_{quat}$, Im-***C***-2), 148.88 (C$_{quat}$, Thio-***C***-2), 152.94 (C$_{quat}$, ***C***=N), 175.42 (C$_{quat}$, ***C***=O). IR (cm^{-1}) = 3121, 2989, 2901, 1663, 1625, 1594, 1180, 1128. HRMS (EI-MS) calcd. for $C_{15}H_{21}N_5OS$ [$M^{+\bullet}$] 319.1467; found 319.1472. $C_{15}H_{21}N_5OS \cdot 2$ TFA (547.47).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(1*H*-imidazol-2-yl)propyl]guanidine (81)

The title compound was prepared from **75** (370 mg, 0.60 mmol) according to the general procedure. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 35/65) yielded a colourless semisolid compound (115 mg, 32 %). ^{1}H-NMR (300 MHz, D_2O, trifluoroacetate): δ [ppm] = 1.86 – 2.02 (m, 2H, Im-2-CH$_2$-C***H***$_2$), 2.88 (t, 2H, ^3J = 7.7 Hz, Im-2-C***H***$_2$), 3.17 (d, 2H, ^3J = 8.1 Hz, Ph$_2$CHC***H***$_2$), 3.23 (t, 2H, ^3J = 6.7 Hz, Im-2-(CH$_2$)$_2$-C***H***$_2$), 4.44 (t, 1H, ^3J = 8.1 Hz, Ph$_2$C***H***), 7.06 (s, 2H, Im-4,5-***H***), 7.10 – 7.30 (m, 10H, Ph-***H***). ^{13}C-NMR (75 MHz, D_2O, trifluoroacetate): δ [ppm] = 22.58 (-, Im-2-***C***H$_2$), 24.90 (-, Im-2-CH$_2$-***C***H$_2$), 40.37 (-, Im-2-(CH$_2$)$_2$-***C***H$_2$), 42.09 (-, Ph$_2$CH-***C***H$_2$), 46.33 (+, Ph$_2$***C***H), 118.54 (+, Im-***C***-4,5), 127.17 (+, 2 Ph-***C***-4), 127.48 (+, 4 Ph-***C***), 129.07 (+, 4 Ph-***C***), 142.95 (C$_{quat}$, 2 Ph-***C***-1), 146.14 (C$_{quat}$, Im-***C***-2), 152.85 (C$_{quat}$, ***C***=N), 175.08 (C$_{quat}$, ***C***=O). IR (cm^{-1}) = 3114, 2990, 2902, 1663, 1623, 1180, 1129. HRMS (EI-MS) calcd. for $C_{22}H_{25}N_5O$ [$M^{+\bullet}$] 375.2059; found 375.2059. $C_{22}H_{25}N_5O \cdot 2$ TFA (603.51).

N^1-[3-(1*H*-Imidazol-2-yl)propyl]-N^2-[3-phenyl-3-(thiazol-2-yl)propanoyl]guanidine (82)

The title compound was prepared from **76** (270 mg, 0.43 mmol) according to the general procedure. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 27.5/72.5) yielded a pale yellow semisolid compound (140 mg, 45 %). ^{1}H-NMR (300 MHz, D_2O, trifluoroacetate): δ [ppm] = 1.91 – 2.06 (m, 2H, Im-2-CH_2-C***H***$_2$), 2.92 (t, 2H, ^3J = 7.7 Hz, Im-2-C***H***$_2$), 3.24 – 3.37 (m, 3H, Im-2-$(CH_2)_2$-C***H***$_2$ + PhThiazCH-C***H***$_2$), 3.45 (dd, 1H, ^2J = 16.6 Hz, ^3J = 7.4 Hz, PhThiazCH-C***H***$_2$), 4.90 (dd, 1H, ^3J = 7.7 Hz, ^3J = 7.4 Hz, PhThiazC***H***), 7.11 (s, 2H, Im-4,5-***H***), 7.24 – 7.37 (m, 5H, Ph-***H***), 7.52 (d, 1H, ^3J = 3.5 Hz, Thiaz-5-***H***), 7.70 (d, 1H, ^3J = 3.5 Hz, Thiaz-4-***H***). ^{13}C-NMR (75 MHz, D_2O, trifluoroacetate): δ [ppm] = 22.57 (-, Im-2-***C***H_2), 24.92 (-, Im-2-CH_2-***C***H_2), 40.41 (-, Im-2-$(CH_2)_2$-***C***H_2), 41.67 (-, PhThiazCH-***C***H_2), 43.43 (+, PhThiaz***C***H), 118.54 (+, Im-***C***-4,5), 121.49 (+, Thiaz-***C***-5), 127.83 (+, 2 Ph-***C***), 128.44 (+, Ph-***C***-4), 129.44 (+, 2 Ph-***C***), 139.31 (C_{quat}, Ph-***C***-1), 139.53 (+, Thiaz-***C***-4), 146.16 (C_{quat}, Im-***C***-2), 152.81 (C_{quat}, ***C***=N), 173.41, 174.37 (C_{quat}, Thiaz-***C***-2 + ***C***=O). IR (cm^{-1}) = 3117, 2902, 1663, 1624, 1181, 1129. HRMS (EI-MS) calcd. for $C_{19}H_{22}N_6OS$ [$M^{+\bullet}$] 382.1576; found 382.1577. $C_{19}H_{22}N_6OS \cdot 2$ TFA (724.55).

N^1-(3-Phenylbutanoyl)-N^2-[3-(1*H*-pyrazol-4-yl)propyl]guanidine (83)

The title compound was prepared from **71** (400 mg, 0.72 mmol) according to the general procedure. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 20/80, 20 min: 45/65) yielded a pale yellow semisolid compound (210 mg, 54 %). ^{1}H-NMR (300 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 1.32 (d, 3H, ^3J = 7.0 Hz, PhC***H***$_3$CH), 1.82 – 1.97 (m, 2H, Pyraz-4-CH_2-C***H***$_2$), 2.60 (t, 2H, ^3J = 7.6 Hz, Pyraz-4-C***H***$_2$), 2.60 (dd, 2H, ^2J = 15.1 Hz, ^3J = 7.6 Hz, PhCH_3CH-C***H***$_2$), 2.75 (dd, 1H, ^2J = 15.1 Hz, ^3J = 7.5 Hz, PhCH_3CH-C***H***$_2$), 3.23 – 3.37 (m, 3H, overlap with solvent, PhCH_3C***H*** + Pyraz-4-$(CH_2)_2$-C***H***$_2$), 7.13 – 7.33 (m, 5H, Ph-***H***), 7.62 (s, 2H, Pyraz-3,5-***H***). ^{13}C-NMR (75 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 21.87 (-, Pyraz-4-***C***H_2), 22.30 (+, Ph***C***H_3CH), 30.22 (-, Pyraz-4-CH_2-***C***H_2), 37.69 (+, PhCH_3***C***H), 41.92 (-, Pyraz-4-$(CH_2)_2$-***C***H_2), 46.21 (-, PhCH_3CH-***C***H_2), 121.22 (C_{quat}, Pyraz-***C***-4), 127.75 (+, Ph-***C***-4), 127.95 (+, 2 Ph-***C***), 129.70 (+, 2 Ph-***C***), 133.85 (+, Pyraz-***C***-3,5), 146.43 (C_{quat}, Ph-***C***-1), 155.08 (C_{quat}, ***C***=N), 176.00 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3092, 2968, 1662, 1594, 1176, 1133. HRMS (EI-MS) calcd. for $C_{17}H_{23}N_5O$ [$M^{+\bullet}$] 313.1903; found 313.1898. $C_{17}H_{23}N_5O \cdot 2$ TFA (541.44).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(1*H*-pyrazol-4-yl)propyl]guanidine (84)

The title compound was prepared from **72** (420 mg, 0.68 mmol) according to the general procedure. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 30/70, 20 min: 50/50) yielded a pale yellow semisolid compound (205 mg, 50 %). ^{1}H-NMR (300 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 1.80 – 1.94 (m, 2H, Pyraz-4-CH_2-C***H***$_2$), 2.56 (t, 2H, ^3J = 7.6 Hz, Pyraz-4-C***H***$_2$), 3.24 (t, 2H, ^3J = 7.0 Hz, Pyraz-4-$(CH_2)_2$-C***H***$_2$), 3.25 (d, 2H, ^3J = 8.0 Hz, Ph_2CHCH_2), 4.59 (t, 1H, ^3J = 8.0 Hz, Ph_2CH), 7.11 – 7.34 (m, 10H, Ph-***H***), 7.51 (s, 2H, Pyraz-3,5-***H***). ^{13}C-NMR (75 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 21.87 (-, Pyraz-4-***C***H_2), 30.27 (-, Pyraz-4-CH_2-***C***H_2), 41.94 (-, Pyraz-4-$(CH_2)_2$-***C***H_2), 43.90 (-, Ph_2CH-***C***H_2), 48.06 (-, Ph_2***C***H), 120.76 (C_{quat}, Pyraz-***C***-4), 127.84 (+, 2 Ph-***C***-4), 128.84 (+, 4 Ph-***C***), 129.74 (+, 4 Ph-***C***), 133.82 (+, Pyraz-***C***-3,5), 144.51 (C_{quat}, Ph-***C***-1), 154.98 (C_{quat}, ***C***=N), 175.46 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3026, 2923, 1663, 1599, 1183, 1129. HRMS (EI-MS) calcd. for $C_{22}H_{25}N_5O$ [$M^{+\bullet}$] 375.2059; found 375.2049. $C_{22}H_{25}N_5O \cdot 2$ TFA (603.51).

N^1-(3-Phenylbutanoyl)-N^2-[3-(1*H*-1,2,4-triazol-3-yl)propyl]guanidine (85)

The title compound was prepared from **77** (450 mg, 0.81 mmol) according to the general procedure. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 15/85, 20 min: 40/60) yielded a white solid (220 mg, 50 %); mp 58 – 62 °C. ^{1}H-NMR (400 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 1.32 (d, 3H, ^3J = 7.0 Hz, Ph***H***$_3$CH), 2.01 – 2.11 (m, 2H, Triaz-3-CH_2-C***H***$_2$), 2.69 – 2.80 (m, 2H, $PhCH_3$CH-C***H***$_2$), 2.88 (t, 2H, ^3J = 7.3 Hz, Triaz-3-C***H***$_2$), 3.26 – 3.36 (m, 1H, overlap with solvent, $PhCH_3$C***H***), 3.37 (t, 2H, ^3J = 7.1 Hz, Triaz-3-$(CH_2)_2$-C***H***$_2$), 7.14 – 7.31 (m, 5H, Ph-***H***), 8.39 (s, 1H, Triaz-5-***H***). ^{13}C-NMR (75 MHz, CD_3OD, trifluoroacetate, HSQC): δ [ppm] = 22.29 (+, Ph***C***H_3CH), 24.20 (-, Triaz-3-***C***H_2), 26.94 (-, Triaz-3-CH_2-***C***H_2), 37.60 (+, $PhCH_3$***C***H), 41.69 (-, Triaz-3-$(CH_2)_2$-***C***H_2), 46.25 (-, $PhCH_3$CH-***C***H_2), 127.75 (+, Ph-***C***-4), 127.92 (+, 2 Ph-***C***), 129.72 (+, 2 Ph-***C***), 146.45 (C_{quat}, Ph-***C***-1), 146.91 (+, Triaz-***C***-5), 155.22 (C_{quat}, ***C***=N), 159.51 (C_{quat}, Triaz-***C***-3), 175.80 (C_{quat}, ***C***=O). IR (cm^{-1}) = 3086, 2971, 2931, 1669, 1602, 1178, 1130. HRMS (EI-MS) calcd. for $C_{16}H_{22}N_6O$ [$M^{+\bullet}$] 314.1855; found 314.1853. $C_{16}H_{22}N_6O \cdot 2$ TFA (542.43).

N^1-(3,3-Diphenylpropanoyl)-N^2-[3-(1*H*-1,2,4-triazol-3-yl)propyl]guanidine (86)

The title compound was prepared from **78** (560 mg, 0.93 mmol) according to the general procedure. Purification by preparative HPLC (MeCN/0.1 % TFA (aq.): 0 min: 20/80, 20 min: 50/50) yielded a white solid (228 mg, 41 %); mp 65 – 68 °C. ^{1}H-NMR (300 MHz, CD_3OD,

trifluoroacetate): δ [ppm] = 1.98 – 2.12 (m, 2H, Triaz-3-CH_2-C***H***$_2$), 2.88 (t, 2H, ^3J = 7.3 Hz, Triaz-3-C***H***$_2$), 3.25 (d, 2H, ^3J = 7.9 Hz, Ph_2CHCH_2), 3.36 (t, 2H, ^3J = 7.1 Hz, Triaz-3-$(CH_2)_2$-C***H***$_2$), 4.59 (t, 1H, ^3J = 7.9 Hz, Ph_2CH), 7.11 – 7.32 (m, 10H, Ph-***H***), 8.42 (s, 1H, Triaz-5-***H***). ^{13}C-NMR (75 MHz, CD_3OD, trifluoroacetate): δ [ppm] = 24.19 (-, Triaz-3-***C***H_2), 26.89 (-, Triaz-3-CH_2-***C***H_2), 41.70 (-, Triaz-3-$(CH_2)_2$-***C***H_2), 43.92 (-, Ph_2CH-***C***H_2), 47.96 (+, Ph_2***C***H), 127.83 (+, 2 Ph-***C***-4), 128.82 (+, 4 Ph-***C***), 129.74 (+, 4 Ph-***C***), 144.54 (C_{quat}, 2 Ph-***C***-1), 146.87 (+, Triaz-***C***-5), 155.14 (C_{quat}, ***C***=N), 159.50 (C_{quat}, Triaz-***C***-3), 175.28 (C_{quat}, ***C***=O). IR (cm^{-1}) = 2970, 2901, 1662, 1598, 1183, 1129. HRMS (EI-MS) calcd. for $C_{21}H_{24}N_6O$ [$M^{+\bullet}$] 376.2012; found 376.2004. $C_{21}H_{24}N_6O$ · 2 TFA (604.50).

Preparation of the isoureas 90-91

General procedure[14, 15]

A solution of the pertinent amine (1 eq) and diphenyl cyanocarbonimidate (**87**, 1 eq) in 2-propanol was stirred for 1 h. After evaporation of the solvent, the product was crystallized from Et_2O.

1-Cyano-3-methyl-2-phenylisourea (90)[16]

The title compound was prepared from a 33 % solution of methylamine (**88**) in EtOH (0.73 mL, 5.9 mmol) and **87** (1.0 g, 4.2 mmol) in 2-propanol (50 mL) according to the general procedure yielding a white solid (0.55 g, 75 %); mp 119 °C (ref.[17]: 125 – 126 °C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 3.1 (d, 3 H, ^3J = 4.8 Hz C***H***$_3$), 7.10 (d, 2H, ^3J = 7.8 Hz, Ph-***H***), 7.28 (t, 1H, ^3J = 7.3 Hz, Ph-***H***-4), 7.41 (t, 2H, ^3J = 7.5 Hz, Ph-***H***). CI-MS (NH_3) *m/z* (%): 193 (100) [M + NH_4]$^+$, 176 (80) [M + H]$^+$. $C_9H_9N_3O$ (175.19).

1-Cyano-2-phenyl-3-[2-(phenylthio)ethyl]isourea (91)[17]

The hydrochloride of **89** was converted into the base by passing a basic ion exchanger (Merck, ion exchanger III, mobile phase: MeOH). The title compound was then prepared from **89** (free base, 0.77 g, 5.0 mmol) and **87** (1.0 g, 4.2 mmol) in 2-propanol (50 mL) according to the general procedure yielding a white solid (0.93 g, 74 %); mp 95 – 96 °C (ref.[17]: 110 °C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 3.18 (t, 2H, ^3J = 6.7 Hz, Ph-S-C***H***$_2$), 3.55 – 3.69 (m, 2H, Ph-S-CH_2-C***H***$_2$), 7.10 (m, 3H, Ph-***H***), 7.30 (m, 3H, Ph-***H***), 7.40 (m, 4H, Ph-***H***). CI-MS (NH_3) *m/z* (%): 298 (100) [M + H]$^+$. $C_{16}H_{15}N_3OS$ (297.37).

Preparation of the cyanoguanidines 107-133

General Procedure[18, 19]

The isourea (1 eq) and the pertinent amine (1 eq) in MeCN were heated under microwave irradiation at 150 °C for 15 min. After removal of the solvent in vacuo, the crude product was purified by flash chromatography (DCM/MeOH 98/2 – 80/20 v/v).

2-Cyano-1-methyl-3-[4-(2-methyl-1*H*-imidazol-4-yl)butyl]guanidine (107)

The title compound was prepared from **92** (0.08 g, 0.52 mmol) and **90** (0.092 g, 0.52 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a yellow solid (0.08 g, 66 %); mp 50 °C. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.59 (m, 4H, 2 C***H***$_2$), 2.31 (s, 3H, C***H***$_3$), 2.54 (t, 2H, ^{3}J = 6.9 Hz, C***H***$_2$-Im), 2.77 (s, 3H, C***H***$_3$-N), 3.20 (t, 2H, ^{3}J = 6.8 Hz, C***H***$_2$-N), 6.62 (s, 1H, Im-***H***-5). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 13.36 (+, Im-***C***H_3), 27.09 (-, ***C***H_2), 27.61 (-, ***C***H_2), 28.70 (+, ***C***H_3), 30.02 (-, ***C***H_2), 42.46 (-, ***C***H_2-N), 117.08 (+, Im-***C***-5), 120.29 (C_{quat}, ***C***≡N), 137.44 (C_{quat}, Im-***C***-4), 145.14 (C_{quat}, Im-***C***-2), 161.97 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_{11}H_{18}N_6$ [$M^{+\bullet}$] 234.1597; found 234.1593. IR (cm^{-1}) = 3289 (N-H), 2938, 2861 (C-H), 2164 (C≡N), 1580 (C=N), 1422, 1369, 1177, 1060. Anal. ($C_{11}H_{18}N_6 \cdot 0.95\ H_2O$) C, H, N. $C_{11}H_{18}N_6$ (234.30).

2-Cyano-1-[4-(2-methyl-1*H*-imidazol-4-yl)butyl]-3-[2-(phenylthio)ethyl]guanidine (108)

The title compound was prepared from **92** (0.08 g, 0.52 mmol) and **91** (0.156 g, 0.52 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a yellow solid (0.1 g, 54 %); mp 60 °C. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.58 (m, 4H, 2 C***H***$_2$), 2.30 (s, 3H, C***H***$_3$), 2.52 (t, 2H, ^{3}J = 7.0 Hz, C***H***$_2$-Im), 3.11 (m, 4H, 2 C***H***$_2$-N), 3.39 (t, 2H, ^{3}J = 6.9 Hz, C***H***$_2$-S), 6.60 (s, 1H, Im-***H***-5), 7.17 (t, 1H, ^{3}J = 7.3 Hz, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.38 (m, 2H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 13.44 (+, Im-***C***H_3), 27.19 (-, ***C***H_2), 27.62 (-, ***C***H_2), 29.80 (-, ***C***H_2), 33.56 (-, ***C***H_2-S), 42.26 (-, ***C***H_2-N), 42.57 (-, ***C***H_2-N), 116.98 (+, Im-***C***-5), 119.99 (C_{quat}, ***C***≡N), 127.33 (+, Ph-***C***-4), 130.15 (+, 2 Ph-***C***), 130.45 (+, 2 Ph-***C***), 136.99 (C_{quat}, Ph-***C***-1), 137.62 (C_{quat}, Im-***C***-4), 145.17 (C_{quat}, Im-***C***-2), 161.11 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_{18}H_{24}N_6S$ [$M^{+\bullet}$] 356.1783; found 356.1787. IR (cm^{-1}) = 3253 (N-H), 3150, 2928, 2865 (C-H), 2163 (C≡N), 1572 (C=N), 1423, 1351, 1179, 1025. Anal. ($C_{18}H_{24}N_6S \cdot 0.5\ H_2O$) C, H, N. $C_{18}H_{24}N_6S$ (356.49)

2-Cyano-1-methyl-3-[3-(2-methyl-1*H*-imidazol-4-yl)propyl]guanidine (109)

The title compound was prepared from **93** (0.05 g, 0.36 mmol) and **90** (0.063 g, 0.36 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a yellow solid (0.04 g, 50 %); mp 48 °C. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.84 (m, 2H, C***H***$_2$), 2.34 (s, 3H, C***H***$_3$), 2.56 (t, 2H, ^{3}J = 7.4 Hz, C***H***$_2$-Im), 2.78 (s, 3H, C***H***$_3$-N), 3.22 (t, 2H, ^{3}J = 7.0 Hz, C***H***$_2$-N), 6.69 (s, 1H, Im-***H***-5). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 13.25 (+, Im-***C***H$_3$), 24.67 (-, ***C***H$_2$), 28.72 (+, ***C***H$_3$), 30.21 (-, ***C***H$_2$), 42.17 (-, ***C***H$_2$-N), 116.59 (+, Im-***C***-5), 120.26 (C$_{quat}$, ***C***≡N), 137.17 (C$_{quat}$, Im-***C***-4), 145.31 (C$_{quat}$, Im-***C***-2), 162.00 (C$_{quat}$, ***C***=N). HRMS (ES-MS) calcd. for $C_{10}H_{16}N_6$ $[M+H]^+$ 221.1515; found 221.1509. IR (cm^{-1}) = 3277 (N-H), 2938, 2881 (C-H), 2162 (C≡N), 1572 (C=N), 1421, 1366, 1174, 1051. Anal. ($C_{10}H_{16}N_6$ · 0.5 H_2O · 0.2 CH_3OH) C, H, N. $C_{10}H_{16}N_6$ (220.27).

2-Cyano-1-[3-(2-methyl-1*H*-imidazol-4-yl)propyl]-3-[2-(phenylthio)ethyl]guanidine (110)

The title compound was prepared from **93** (0.05 g, 0.36 mmol) and **91** (0.11 g, 0.36 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a yellow solid (0.05 g, 41 %); mp 52 °C. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.81 (m, 2H, C***H***$_2$), 2.30 (s, 3H, C***H***$_3$), 2.53 (t, 2H, ^{3}J = 7.4 Hz, C***H***$_2$-Im), 3.09 (t, 2H, ^{3}J = 6.8 Hz, C***H***$_2$-N), 3.15 (t, 2H, ^{3}J = 6.8 Hz, C***H***$_2$-N), 3.39 (t, 2H, ^{3}J = 7.0 Hz, C***H***$_2$-S), 6.64 (s, 1H, Im-***H***-5), 7.16 (t, 1H, ^{3}J = 7.3 Hz, Ph-***H***-4), 7.27 (m, 2H, Ph-***H***), 7.38 (m, 2H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 13.46 (+, Im-***C***H$_3$), 24.82 (-, ***C***H$_2$), 30.05 (-, ***C***H$_2$), 33.55 (-, ***C***H$_2$-S), 42.28 (-, ***C***H$_2$-N), 42.29 (-, ***C***H$_2$-N), 116.39 (+, Im-***C***-5), 119.99 (C$_{quat}$, ***C***≡N), 127.33 (+, Ph-***C***-4), 130.16 (+, 2 Ph-***C***), 130.44 (+, 2 Ph-***C***), 136.98 (C$_{quat}$, Ph-***C***-1), 137.54 (C$_{quat}$, Im-***C***-4), 145.37 (C$_{quat}$, Im-***C***-2), 161.16 (C$_{quat}$, ***C***=N). HRMS (EI-MS) calcd. for $C_{17}H_{22}N_6S$ $[M^{+\bullet}]$ 342.1627; found 342.1624. IR (cm^{-1}) = 3254 (N-H), 3122, 2927 (C-H), 2156 (C≡N), 1572 (C=N), 1425, 1355, 1183, 1025. Anal. ($C_{17}H_{22}N_6S$ · 0.4 CH_3OH) C, H, N. $C_{17}H_{22}N_6S$ (342.46)

2-Cyano-1-methyl-3-[4-(5-methyl-1*H*-imidazol-4-yl)butyl]guanidine (111)[20]

The title compound was prepared from **94** (0.08 g, 0.52 mmol) and **90** (0.092 g, 0.52 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.07 g, 57 %); mp 48 °C. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.56 (m, 4H, 2 C***H***$_2$), 2.14 (s, 3H, C***H***$_3$), 2.53 (t, 2H, ^{3}J = 7.0 Hz, C***H***$_2$-Im), 2.77 (s, 3H, C***H***$_3$-N), 3.19 (t, 2H, ^{3}J = 6.8 Hz, C***H***$_2$-N), 7.45 (s, 1H, Im-***H***-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 10.46 (+, Im-***C***H$_3$), 25.79 (-,

CH_2), 28.01 (-, ***C***H_2), 28.33 (+, ***C***H_3), 29.99 (-, ***C***H_2), 42.50 (-, ***C***H_2-N), 120.36 (C_{quat}, ***C***≡N), 127.04 (C_{quat}, Im-***C***-5), 132.18 (C_{quat}, Im-***C***-4), 133.93 (+, Im-***C***-2), 161.94 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_{11}H_{18}N_6$ [$M^{+\bullet}$] 234.1597; found 234.1596. IR (cm^{-1}) = 3233 (N-H), 3149, 2936, 2859 (C-H), 2163 (C≡N), 1586 (C=N), 1452, 1418, 1369, 1175. Anal. ($C_{11}H_{18}N_6 \cdot 0.9\ H_2O$) C, H, N. $C_{11}H_{18}N_6$ (234.30).

2-Cyano-1-[4-(5-methyl-1*H*-imidazol-4-yl)butyl]-3-[2-(phenylthio)ethyl]guanidine (112)

The title compound was prepared from **94** (0.08 g, 0.52 mmol) and **91** (0.156 g, 0.52 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.15 g, 81 %); mp 56 °C. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.55 (m, 4H, 2 C***H***$_2$), 2.14 (s, 3H, C***H***$_3$), 2.53 (t, 2H, ^3J = 7.0 Hz, C***H***$_2$-Im), 3.11 (m, 4H, 2 C***H***$_2$-N), 3.39 (t, 2H, ^3J = 7.0 Hz, C***H***$_2$-S), 7.17 (t, 1H, ^3J = 7.3 Hz, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.39 (m, 2H, Ph-***H***), 7.43 (s, 1H, Im-***H***-2). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 10.38 (+, Im-***C***H_3), 25.82 (-, ***C***H_2), 28.01 (-, ***C***H_2), 29.73 (-, ***C***H_2), 33.57 (-, ***C***H_2-S), 42.25 (-, ***C***H_2-N), 42.59 (-, ***C***H_2-N), 119.99 (C_{quat}, ***C***≡N), 127.34 (+, Ph-***C***-4), 130.15 (+, 2 Ph-***C***), 130.21 (C_{quat}, Im-***C***-5), 130.47 (+, 2 Ph-***C***), 130.85 (C_{quat}, Im-***C***-4), 133.94 (+, Im-***C***-2), 136.99 (C_{quat}, Ph-***C***-1), 161.10 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_{18}H_{24}N_6S$ [$M^{+\bullet}$] 356.1783; found 356.1790. IR (cm^{-1}) = 3249 (N-H), 2922, 2864 (C-H), 2159 (C≡N), 1573 (C=N), 1437, 1350, 1232, 1088. Anal. ($C_{18}H_{24}N_6S \cdot 0.4\ H_2O$) C, H, N. $C_{18}H_{24}N_6S$ (356.49)

2-Cyano-1-[4-(1*H*-1,2,3-triazol-5-yl)butyl]-3-methylguanidine (113)

The title compound was prepared from **95** (0.05 g, 0.36 mmol) and **90** (0.063 g, 0.36 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a colourless oil (0.07 g, 88 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.58 (m, 2H, C***H***$_2$), 1.70 (m, 2H, C***H***$_2$), 2.76 (t, 2H, ^3J = 7.6 Hz, C***H***$_2$-Triazol), 2.78 (s, 3H, C***H***$_3$-N), 3.22 (t, 2H, ^3J = 7.0 Hz, C***H***$_2$-N), 7.58 (s, 1H, Triazol-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 24.97 (-, ***C***H_2), 27.43 (-, ***C***H_2), 28.65 (+, ***C***H_3), 29.91 (-, ***C***H_2), 42.26 (-, ***C***H_2-N), 120.23 (C_{quat}, ***C***≡N), 139.98 (+, Triazol-***C***-5), 141.59 (C_{quat}, Triazol-***C***-4), 161.98 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_9H_{15}N_7$ [$M^{+\bullet}$] 221.1389; found 221.1389. IR (cm^{-1}) = 3290 (N-H), 3136, 2933, 2860 (C-H), 2159 (C≡N), 1574 (C=N), 1367. Anal. ($C_9H_{15}N_7 \cdot 0.3\ H_2O$) C, H, N. $C_9H_{15}N_7$ (221.26).

2-Cyano-1-[4-(1*H*-1,2,3-triazol-5-yl)butyl]-3-[2-(phenylthio)ethyl]guanidine (114)

The title compound was prepared from **95** (0.05 g, 0.36 mmol) and **91** (0.106 g, 0.36 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a colourless oil (0.12 g, 97 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.55 (m, 2H, C***H***$_2$), 1.69 (m, 2H, C***H***$_2$), 2.75 (t, 2H, ^{3}J = 7.5 Hz, C***H***$_2$-Triazol), 3.09 (t, 2H, ^{3}J = 6.6 Hz, C***H***$_2$-N), 3.15 (t, 2H, ^{3}J = 6.9 Hz, C***H***$_2$-N), 3.40 (t, 2H, ^{3}J = 7.0 Hz, C***H***$_2$-S), 7.17 (m, 1H, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.37 (m, 2H, Ph-***H***), 7.58 (s, 1H, Triazol-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 24.99 (-, ***C***H$_2$), 27.46 (-, ***C***H$_2$), 29.72 (-, ***C***H$_2$), 33.53 (-, ***C***H$_2$-S), 42.27 (-, ***C***H$_2$-N), 42.40 (-, ***C***H$_2$-N), 119.95 (C_{quat}, ***C***≡N), 127.32 (+, Ph-***C***-4), 130.15 (+, 2 Ph-***C***), 130.43 (+, 2 Ph-***C***), 137.00 (C_{quat}, Ph-***C***-1), 138.03 (+, Triazol-***C***-5), 140.13 (C_{quat}, Triazol-***C***-4), 161.12 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_{16}H_{21}N_7S$ [$M^{+\bullet}$] 343.1579; found 343.1573. IR (cm^{-1}) = 3272 (N-H), 3137, 2931, 2860 (C-H), 2160 (C≡N), 1571 (C=N), 1438, 1356. Anal. ($C_{16}H_{21}N_7S \cdot 0.2\ CH_3OH$) C, H, N. $C_{16}H_{21}N_7S$ (343.45)

1-[2-(2-Aminopyrimidin-4-ylamino)ethyl]-2-cyano-3-[2-(phenylthio)ethyl]guanidine (115)

The title compound was prepared from N^4-(2-aminoethyl)pyrimidine-2,4-diamine dihydrochloride **97** (0.03 g, 0.14 mmol) and **91** (0.04 g, 0.14 mmol) in MeCN (4.5 mL) according to the general procedure. To deprotonate the amine 0.12 mL DIPEA were added to the mixture. Flash chromatography yielded a colourless oil (0.045 g, 90 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 3.08 (t, 2H, ^{3}J = 6.9 Hz, C***H***$_2$-N), 3.33 (t, 2H, ^{3}J = 7.0 Hz, C***H***$_2$-N), 3.40 (t, 2H, ^{3}J = 6.9 Hz, C***H***$_2$-S), 3.54 (m, 2H, C***H***$_2$-N), 5.99 (d, 1H, ^{3}J = 6.7 Hz, Py-***H***-5), 7.17 (t, 1H, ^{3}J = 7.3 Hz, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.38 (m, 2H, Ph-***H***), 7.57 (d, 1H, ^{3}J = 6.6 Hz, Py-***H***-6). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 33.47 (-, ***C***H$_2$-S), 40.91 (-, ***C***H$_2$-N), 42.41 (-, ***C***H$_2$-N), 43.02 (-, ***C***H$_2$-N), 95.02 (+, Py-***C***-5), 120.02 (C_{quat}, ***C***≡N), 127.38 (+, Ph-***C***-4), 130.18 (+, 2 Ph-***C***), 130.47 (+, 2 Ph-***C***), 136.92 (C_{quat}, Ph-***C***-1), 147.10 (+, Py-***C***-6), 160.16 (C_{quat}, ***C***=N), 161.35 (C_{quat}, Py-***C***), 165.36 (C_{quat}, Py-***C***). HRMS (EI-MS) calcd. for $C_{16}H_{20}N_8S$ [$M^{+\bullet}$] 356.1532; found 356.1539. IR (cm^{-1}) = 3305 (N-H), 3053, 2986 (C-H), 2162 (C≡N), 1654, 1564 (C=N), 1530, 1433, 1362, 1199. $C_{16}H_{20}N_8S$ (356.45)

2-Cyano-1-[5-(2-methyl-1*H*-imidazol-1-yl)pentyl]-3-[2-(phenylthio)ethyl]guanidine (116)

The title compound was prepared from **98** (0.1 g, 0.6 mmol) and **90** (0.1 g, 0.6 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a colourless oil (0.07 g, 47 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.32 (m, 2H, C***H***$_2$), 1.57 (m, 2H, C***H***$_2$), 1.76

(m, 2H, C***H***$_2$), 2.35 (s, 3H, Im-C***H***$_3$), 2.77 (s, 3H, C***H***$_3$-N), 3.18 (t, 2H, ^3J = 7.1 Hz, C***H***$_2$-N), 3.92 (t, 2H, ^3J = 7.2 Hz, C***H***$_2$-Im), 6.79 (d, 1H, ^3J = 1.4 Hz, Im-***H***), 6.99 (d, 1H, ^3J = 1.4 Hz, Im-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 12.59 (+, Im-***C***H$_3$), 24.65 (-, ***C***H$_2$), 28.73 (+, ***C***H$_3$), 30.09 (-, ***C***H$_2$), 31.38 (-, ***C***H$_2$), 42.38 (-, ***C***H$_2$-N), 46.90 (-, ***C***H$_2$-Im), 120.26 (C$_{quat}$, ***C***≡N), 120.84 (+, Im-***C***-5), 126.75 (+, Im-***C***-4), 145.75 (C$_{quat}$, Im-***C***-2), 161.98 (C$_{quat}$, ***C***=N). HRMS (EI-MS) calcd. for $C_{12}H_{20}N_6$ [$M^{+\bullet}$] 248.1749; found 248.1745. IR (cm^{-1}) = 3226 (N-H), 2948, 2857 (C-H), 2168 (C≡N), 1584 (C=N), 1498, 1369, 1280, 1107. Anal. ($C_{12}H_{20}N_6 \cdot 0.2\ H_2O$) C, H, N. $C_{12}H_{20}N_6$ (248.33).

2-Cyano-1-[5-(2-methyl-1*H*-imidazol-1-yl)pentyl]-3-[2-(phenylthio)ethyl]guanidine (117)

The title compound was prepared from **98** (0.1 g, 0.6 mmol) and **91** (0.178 g, 0.6 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a colourless oil (0.1 g, 45 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.31 (m, 2H, C***H***$_2$), 1.55 (m, 2H, C***H***$_2$), 1.74 (m, 2H, C***H***$_2$), 2.33 (s, 3H, Im-C***H***$_3$), 3.10 (m, 4H, 2 C***H***$_2$), 3.39 (t, 2H, ^3J = 6.9 Hz, C***H***$_2$-S), 3.90 (t, 2H, ^3J = 7.2 Hz, C***H***$_2$-Im), 6.79 (d, 1H, ^3J = 1.4 Hz, Im-***H***), 6.97 (d, 1H, ^3J = 1.4 Hz, Im-***H***), 7.18 (t, 1H, ^3J = 7.3 Hz, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.38 (m, 2H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 12.56 (+, Im-***C***H$_3$), 24.72 (-, ***C***H$_2$), 29.90 (-, ***C***H$_2$), 31.38 (-, ***C***H$_2$), 33.57 (-, ***C***H$_2$-S), 42.25 (-, ***C***H$_2$-N), 42.53 (-, ***C***H$_2$-N), 46.96 (-, ***C***H$_2$-Im), 119.98 (C$_{quat}$, ***C***≡N), 120.91 (+, Im-***C***-5), 126.53 (+, Im-***C***-4), 127.35 (+, Ph-***C***-4), 130.21 (+, 2 Ph-***C***), 130.37 (+, 2 Ph-***C***), 137.02 (C$_{quat}$, Ph-***C***-1), 145.72 (C$_{quat}$, Im-***C***-2), 161.10 (C$_{quat}$, ***C***=N). HRMS (EI-MS) calcd. for $C_{19}H_{26}N_6S$ [$M^{+\bullet}$] 370.1940; found 370.1935. IR (cm^{-1}) = 3250 (N-H), 2933, 2858 (C-H), 2160 (C≡N), 1578 (C=N), 1480, 1356, 1179, 1088. Anal. ($C_{19}H_{26}N_6S \cdot 0.7\ H_2O$) C, H, N. $C_{19}H_{26}N_6S$ (370.57).

1-[4-(3-Amino-1*H*-1,2,4-triazol-5-yl)butyl]-2-cyano-3-methylguanidine (118)

The title compound was prepared from **99** (0.12 g, 0.31 mmol) and **90** (0.06 g, 0.34 mmol) in MeCN (4.5 mL) according to the general procedure. To deprotonate the amine 0.29 mL DIPEA were added to the mixture. Flash chromatography and subsequent preparative HPLC (millipore water without TFA was used as mobile phase) yielded a white semisolid (0.06 g, 82 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.56 (m, 2H, C***H***$_2$), 1.68 (m, 2H, C***H***$_2$), 2.66 (t, 2H, ^3J = 7.2 Hz, C***H***$_2$-Triazol), 2.78 (s, 3H, C***H***$_3$-N), 3.20 (t, 2H, ^3J = 7.1 Hz, C***H***$_2$-N). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 26.07 (-, ***C***H$_2$), 27.96 (-, ***C***H$_2$), 28.77 (+, ***C***H$_3$), 29.91 (-, ***C***H$_2$), 42.31 (-, ***C***H$_2$-N), 120.35 (C$_{quat}$, ***C***≡N), 160.00 (C$_{quat}$, Triazol-***C***), 160.92 (C$_{quat}$, Triazol-***C***), 161.96 (C$_{quat}$,

C=N). HRMS (EI-MS) calcd. for $C_9H_{16}N_8$ [$M^{+\bullet}$] 236.1498; found 236.1503. IR (cm^{-1}) = 3168 (N-H), 3094, 2940 (C-H), 2167 (C≡N), 1576 (C=N), 1366, 1201, 1131, 1060. Anal. ($C_9H_{16}N_8 \cdot 0.7\ H_2O$) C, H, N. $C_9H_{16}N_8$ (236.28).

1-[4-(3-Amino-1*H*-1,2,4-triazol-5-yl)butyl]-2-cyano-3-[2-(phenylthio)ethyl]guanidine (119)

The title compound was prepared from **99** (0.1 g, 0.26 mmol) and **91** (0.09 g, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. To deprotonate the amine 0.17 mL DIPEA were added to the mixture. Flash chromatography yielded a white semisolid (0.06 g, 64 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.55 (m, 2H, C***H***$_2$), 1.68 (m, 2H, C***H***$_2$), 2.56 (t, 2H, ^3J = 7.1 Hz, C***H***$_2$-Triazol), 3.11 (m, 4H, 2 C***H***$_2$-N), 3.40 (t, 2H, ^3J = 6.6 Hz, C***H***$_2$-S), 7.18 (t, 1H, ^3J = 7.2 Hz, Ph-***H***-4), 7.29 (m, 2H, Ph-***H***), 7.39 (m, 2H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 25.95 (-, ***C***H$_2$), 27.87 (-, ***C***H$_2$), 29.64 (-, ***C***H$_2$), 33.52 (-, ***C***H$_2$-S), 42.31 (-, ***C***H$_2$-N), 42.39 (-, ***C***H$_2$-N), 120.01 (C_{quat}, ***C***≡N), 127.31 (+, Ph-***C***-4), 130.15 (+, 2 Ph-***C***), 130.43 (+, 2 Ph-***C***), 137.01 (C_{quat}, Ph-***C***-1), 160.73 (C_{quat}, Triazol-***C***), 160.91 (C_{quat}, Triazol-***C***), 161.10 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_{16}H_{22}N_8S$ [$M^{+\bullet}$] 358.1688; found 358.1690. IR (cm^{-1}) = 3246 (N-H), 2928, 2857 (C-H), 2159 (C≡N), 1569 (C=N), 1453, 1346, 1087, 1068. Anal. ($C_{16}H_{22}N_8S \cdot 0.6\ H_2O$) C, H, N. $C_{16}H_{22}N_8S$ (358.46)

1-[3-(3-Amino-1*H*-1,2,4-triazol-5-ylamino)propyl]-2-cyano-3-methylguanidine (120)

The title compound was prepared from **100** (0.063 g, 0.4 mmol) and **90** (0.07 g, 0.4 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.05 g, 53 %); mp 154 °C. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.75 (m, 2H, C***H***$_2$), 2.79 (s, 3H, C***H***$_3$-N), 3.20 (t, 2H, ^3J = 6.5 Hz, C***H***$_2$-N), 3.27 (t, 2H, ^3J = 6.6 Hz, C***H***$_2$-N). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 28.75 (+, ***C***H$_3$), 30.79 (-, ***C***H$_2$), 39.88 (-, ***C***H$_2$), 41.09 (-, ***C***H$_2$), 120.46 (C_{quat}, ***C***≡N), 162.06 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_8H_{15}N_9$ [$M^{+\bullet}$] 237.1450; found 237.1450. IR (cm^{-1}) = 3283 (N-H), 2945, 2864 (C-H), 2155 (C≡N), 1561 (C=N), 1420, 1342. Anal. ($C_8H_{15}N_9 \cdot 1.1\ H_2O$) C, H, N. $C_8H_{15}N_9$ (237.27).

1-[3-(3-Amino-1*H*-1,2,4-triazol-5-ylamino)propyl]-2-cyano-3-[2-(phenylthio)ethyl]guanidine (121)

The title compound was prepared from **100** (0.047 g, 0.3 mmol) and **91** (0.09 g, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.05 g, 46 %); mp 142 °C. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.71 (m, 2H, C***H***$_2$), 3.09 (t,

2H, ^{3}J = 7.4 Hz, C***H***$_2$-N), 3.18 (m, 4H, 2 C***H***$_2$-N), 3.41 (t, 2H, ^{3}J = 7.4 Hz, C***H***$_2$-S), 7.17 (t, 1H, ^{3}J = 7.3 Hz, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.38 (m, 2H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 30.73 (-, ***C***H$_2$), 33.48 (-, ***C***H$_2$-S), 39.85 (-, ***C***H$_2$), 41.02 (-, ***C***H$_2$), 42.39 (-, ***C***H$_2$), 120.42 (C_{quat}, ***C***≡N), 127.30 (+, Ph-***C***-4), 130.17 (+, 2 Ph-***C***), 130.36 (+, 2 Ph-***C***), 137.03 (C_{quat}, Ph-***C***-1), 161.32 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_{15}H_{21}N_9S$ [$M^{+\bullet}$] 359.1641; found 359.1630. IR (cm^{-1}) = 3283 (N-H), 3016, 2946, 2864 (C-H), 2155 (C≡N), 1561 (C=N), 1420, 1342, 1083. Anal. ($C_{15}H_{21}N_9S \cdot 0.2\ CH_3OH \cdot 0.7\ H_2O$) C, H, N. $C_{15}H_{21}N_9S$ (359.45)

1-[4-(3-Amino-1*H*-1,2,4-triazol-5-ylamino)butyl]-2-cyano-3-methylguanidine (122)

The title compound was prepared from **101** (0.068 g, 0.4 mmol) and **90** (0.07 g, 0.4 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.06 g, 60 %); mp 192 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm] = 1.45 (m, 4H, 2 C***H***$_2$), 2.65 (d, 3H, ^{3}J = 4.3 Hz, C***H***$_3$-N), 2.98 (m, 2H, C***H***$_2$-N), 3.07 (m, 2H, C***H***$_2$-N). ^{13}C-NMR (75 MHz, DMSO-d_6): δ [ppm] = 26.50 (-, ***C***H$_2$), 26.58 (-, ***C***H$_2$), 28.16 (+, ***C***H$_3$), 40.77 (-, ***C***H$_2$), 42.33 (-, ***C***H$_2$), 118.22 (C_{quat}, ***C***≡N), 159.87 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_9H_{17}N_9$ [$M^{+\bullet}$] 251.1607; found 251.1613. IR (cm^{-1}) = 3321 (N-H), 2944, 2870 (C-H), 2151 (C≡N), 1566 (C=N), 1531, 1138, 941. Anal. ($C_9H_{17}N_9 \cdot 0.5\ H_2O$) C, H, N. $C_9H_{17}N_9$ (251.29).

1-[4-(3-Amino-1*H*-1,2,4-triazol-5-ylamino)butyl]-2-cyano-3-[2-(phenylthio)ethyl]guanidine (123)

The title compound was prepared from **101** (0.052 g, 0.3 mmol) and **91** (0.09 g, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white solid (0.08 g, 71 %); mp 230 °C dec.. ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.57 (m, 4H, 2 C***H***$_2$), 3.07 (t, 2H, ^{3}J = 7.4 Hz, C***H***$_2$-N), 3.14 (m, 4H, 2 C***H***$_2$-N), 3.39 (t, 2H, ^{3}J = 7.3 Hz, C***H***$_2$-S), 7.16 (m, 1H, Ph-***H***-4), 7.27 (m, 2H, Ph-***H***), 7.37 (m, 2H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 26.33 (-, ***C***H$_2$), 26.54 (-, ***C***H$_2$), 30.94 (-, ***C***H$_2$-S), 40.45 (-, ***C***H$_2$), 40.86 (-, ***C***H$_2$), 42.31 (-, ***C***H$_2$), 117.90 (C_{quat}, ***C***≡N), 125.55 (+, Ph-***C***-4), 127.67 (+, 2 Ph-***C***), 128.97 (+, 2 Ph-***C***), 135.56 (C_{quat}, Ph-***C***-1), 159.00 (C_{quat}, ***C***=N). HRMS (EI-MS) calcd. for $C_{16}H_{23}N_9S$ [$M^{+\bullet}$] 373.1797; found 373.1789. IR (cm^{-1}) = 3153 (N-H), 2939, 2863 (C-H), 2151 (C≡N), 1557 (C=N), 1417, 1354, 1300, 1091. Anal. ($C_{16}H_{23}N_9S \cdot 1.3\ H_2O$) C, H, N. $C_{16}H_{23}N_9S$ (373.48)

1-[3-(3-Amino-1*H*-1,2,4-triazol-5-ylthio)propyl]-2-cyano-3-methylguanidine (124)

The title compound was prepared from **102** (0.12 g, 0.69 mmol) and **90** (0.12 g, 0.69 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography and subsequent preparative HPLC (millipore water without TFA was used as mobile phase) yielded a white semisolid (0.04 g, 23 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.89 (m, 2H, C***H***$_2$), 2.79 (s, 3H, C***H***$_3$-N), 3.05 (t, 2H, ^{3}J = 6.9 Hz, C***H***$_2$-N), 3.32 (t, 2H, ^{3}J = 6.7 Hz, C***H***$_2$-S). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 28.75 (+, ***C***H$_3$), 29.71 (-, ***C***H$_2$), 30.92 (-, ***C***H$_2$), 40.81 (-, ***C***H$_2$), 120.59 (C$_{quat}$, ***C***≡N), 135.88 (C$_{quat}$, Triazol-***C***-5), 146.31 (C$_{quat}$, Triazol-***C***-2), 162.00 (C$_{quat}$, ***C***=N). HRMS (EI-MS) calcd. for $C_8H_{14}N_8S$ [$M^{+\bullet}$] 254.1062; found 254.1059. IR (cm^{-1}) = 3311 (N-H), 2936 (C-H), 2154 (C≡N), 1568 (C=N), 1494, 1368, 1268, 1093. Anal. ($C_8H_{14}N_8S \cdot 0.8\ CH_3OH$) C, H, N. $C_8H_{14}N_8S$ (254.32).

1-[3-(3-Amino-1*H*-1,2,4-triazol-5-ylthio)propyl]-2-cyano-3-[2-(phenylthio)ethyl]guanidine (125)

The title compound was prepared from **102** (0.07 g, 0.4 mmol) and **91** (0.12 g, 0.4 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white semisolid (0.03 g, 20 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.84 (m, 2H, C***H***$_2$), 3.03 (t, 2H, ^{3}J = 6.7 Hz, C***H***$_2$), 3.11 (t, 2H, ^{3}J = 7.3 Hz, C***H***$_2$), 3.25 (t, 2H, ^{3}J = 6.3 Hz, C***H***$_2$), 3.42 (t, 2H, ^{3}J = 7.3 Hz, C***H***$_2$-S-Ph), 7.17 (m, 1H, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.39 (m, 2H, Ph-***H***). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 29.52 (-, ***C***H$_2$), 30.85 (-, ***C***H$_2$-S), 33.46 (-, ***C***H$_2$-S), 40.63 (-, ***C***H$_2$-N), 42.43 (-, ***C***H$_2$-N), 119.62 (C$_{quat}$, ***C***≡N), 127.27 (+, Ph-***C***-4), 130.13 (+, 2 Ph-***C***), 130.34 (+, 2 Ph-***C***), 137.08 (C$_{quat}$, Ph-***C***-1), 139.91 (C$_{quat}$, Triazol-***C***-5), 147.29 (C$_{quat}$, Triazol-***C***-2), 161.20 (C$_{quat}$, ***C***=N). HRMS (EI-MS) calcd. for $C_{15}H_{20}N_8S_2$ [$M^{+\bullet}$] 376.1232; found 376.1242. IR (cm^{-1}) = 3311 (N-H), 3199, 2936 (C-H), 2154 (C≡N), 1568 (C=N), 1368, 1268, 1094. Anal. ($C_{15}H_{20}N_8S_2 \cdot CH_3OH$) C, H, N. $C_{15}H_{20}N_8S_2$ (376.50)

2-Cyano-1-methyl-3-[3-(pyridin-2-ylamino)propyl]guanidine (126)

The title compound was prepared from **103** (0.05 g, 0.33 mmol) and **90** (0.057 g, 0.33 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white semisolid (0.07 g, 91 %); ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.74 (m, 2H, C***H***$_2$), 2.92 (d, 3H, ^{3}J = 4.8 Hz, C***H***$_3$-N), 3.33 (m, 2H, C***H***$_2$), 3.46 (m, 2H, C***H***$_2$), 5.06 (brs, 1H, N***H***), 5.91 (brs, 1H, N***H***), 6.45 (d, 1H, ^{3}J = 8.4 Hz, Py-***H***-3), 6.55 (m, H, Py-***H***-5), 7.05 (brs, 1H, N***H***), 7.39 (m, 1H, Py-***H***-4), 7.97 (m, 1H, Py-***H***-6). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 28.42 (+, ***C***H$_3$),

30.00 (-, ***C***H_2), 38.05 (-, ***C***H_2-N), 38.15 (-, ***C***H_2-N), 109.16 (+, Py-***C***-3), 112.81 (+, Py-***C***-5), 120.39 (C_{quat}, ***C***≡N), 137.91 (+, Py-***C***-4), 146.48 (+, Py-***C***-6), 158.68 (C_{quat}, ***C***=N), 160.61 (C_{quat}, Py-***C***-2). HRMS (EI-MS) calcd. for $C_{11}H_{16}N_6$ [$M^{+\bullet}$] 232.1436; found 232.1437. IR (cm^{-1}) = 3270 (N-H), 2929, 2861 (C-H), 2158 (C≡N), 1568 (C=N), 1511, 1417, 1359, 1152. Anal. ($C_{11}H_{16}N_6$ · 0.3 H_2O) C, H, N. $C_{11}H_{16}N_6$ (232.28)

2-Cyano-1-[2-(phenylthio)ethyl]-3-[3-(pyridin-2-ylamino)propyl]guanidine (127)

The title compound was prepared from **103** (0.05 g, 0.33 mmol) and **91** (0.098 g, 0.33 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white semisolid (0.1 g, 85 %); ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.73 (m, 2H, C***H***$_2$), 3.11 (t, 2H, ^3J = 6.7 Hz, C***H***$_2$-N), 3.24 (m, 2H, C***H***$_2$), 3.45 (m, 4H, 2 C***H***$_2$), 4.95 (brs, 1H, N***H***), 5.99 (brs, 1H, N***H***), 6.42 (d, 1H, ^3J = 8.4 Hz, Py-***H***-3), 6.54 (m, H, Py-***H***-5), 7.04 (brs, 1H, N***H***), 7.19 (m, 1H, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.37 (m, 3H, Ph-***H*** + Py-***H***-4), 8.02 (m, 1H, Py-***H***-6). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 30.01 (-, ***C***H_2), 33.03 (-, ***C***H_2-S), 38.18 (-, ***C***H_2-N), 38.55 (-, ***C***H_2-N), 41.02 (-, ***C***H_2-N), 108.96 (+, Py-***C***-3), 112.98 (+, Py-***C***-5), 118.85 (C_{quat}, ***C***≡N), 126.70 (+, Ph-***C***-4), 129.22 (+, 2 Ph-***C***), 129.77 (+, 2 Ph-***C***), 134.21 (C_{quat}, Ph-***C***-1), 137.76 (+, Py-***C***-4), 147.02 (+, Py-***C***-6), 158.64 (C_{quat}, ***C***=N), 159.69 (C_{quat}, Py-***C***-2). HRMS (EI-MS) calcd. for $C_{18}H_{22}N_6S$ [$M^{+\bullet}$] 354.1627; found 354.1627. IR (cm^{-1}) = 3263 (N-H), 3053, 2949 (C-H), 2159 (C≡N), 1567 (C=N), 1509, 1481, 1300. Anal. ($C_{18}H_{22}N_6S$ · 0.2 CH_3OH) C, H, N. $C_{18}H_{22}N_6S$ (354.47)

2-Cyano-1-methyl-3-[4-(pyridin-2-ylamino)butyl]guanidine (128)

The title compound was prepared from **104** (0.05 g, 0.3 mmol) and **90** (0.053 g, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white semisolid (0.06 g, 81 %); ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.63 (m, 4H, 2 C***H***$_2$), 2.79 (d, 3H, ^3J = 4.7 Hz, C***H***$_3$-N), 3.25 (m, 4H, 2 C***H***$_2$), 5.04 (brs, 1H, N***H***), 5.83 (brs, 1H, N***H***), 6.00 (brs, 1H, N***H***), 6.40 (d, 1H, ^3J = 8.4 Hz, Py-***H***-3), 6.53 (m, H, Py-***H***-5), 7.39 (m, 1H, Py-***H***-4), 7.98 (d, 1H, ^3J = 4.1 Hz, Py-***H***-6). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 26.58 (-, 2 ***C***H_2), 28.49 (+, ***C***H_3), 41.41 (-, ***C***H_2-N), 41.61 (-, ***C***H_2-N), 107.56 (+, Py-***C***-3), 112.69 (+, Py-***C***-5), 119.97 (C_{quat}, ***C***≡N), 137.79 (+, Py-***C***-4), 147.22 (+, Py-***C***-6), 158.58 (C_{quat}, ***C***=N), 160.61 (C_{quat}, Py-***C***-2). HRMS (EI-MS) calcd. for $C_{12}H_{18}N_6$ [$M^{+\bullet}$] 246.1593; found 246.1593. IR (cm^{-1}) = 3288 (N-H), 2987, 2970, 2940 (C-H), 2158 (C≡N), 1569 (C=N), 1513, 1443, 1370, 1027. Anal. ($C_{12}H_{18}N_6$ · 0.4 CH_3OH) C, H, N. $C_{12}H_{18}N_6$ (246.31)

2-Cyano-1-[2-(phenylthio)ethyl]-3-[4-(pyridin-2-ylamino)butyl]guanidine (129)

The title compound was prepared from **104** (0.05 g, 0.3 mmol) and **91** (0.09 g, 0.3 mmol) in MeCN (4.5 mL) according to the general procedure. Flash chromatography yielded a white semisolid (0.08 g, 72 %); ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.65 (m, 4H, 2 C***H***$_2$), 3.09 (t, 2H, ^{3}J = 6.4 Hz, C***H***$_2$-N), 3.14 (m, 2H, C***H***$_2$), 3.32 (m, 2H, C***H***$_2$), 3.44 (m, 2H, C***H***$_2$), 4.96 (brs, 1H, N***H***), 5.69 (brs, 2H, 2 N***H***), 6.42 (d, 1H, ^{3}J = 8.4 Hz, Py-***H***-3), 6.56 (m, H, Py-***H***-5), 7.20 (m, 1H, Ph-***H***-4), 7.29 (m, 2H, Ph-***H***), 7.34 (m, 2H, Ph-***H***), 7.42 (m, 1H, Py-***H***-4), 8.01 (m, 1H, Py-***H***-6). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = 26.26 (-, ***C***H_2), 26.60 (-, ***C***H_2), 33.16 (-, ***C***H_2-S), 41.02 (-, ***C***H_2-N), 41.26 (-, ***C***H_2-N), 41.65 (-, ***C***H_2-N), 107.83 (+, Py-***C***-3), 112.86 (+, Py-***C***-5), 118.41 (C_{quat}, ***C***≡N), 126.73 (+, Ph-***C***-4), 129.25 (+, 2 Ph-***C***), 129.67 (+, 2 Ph-***C***), 134.63 (C_{quat}, Ph-***C***-1), 138.05 (+, Py-***C***-4), 146.85 (+, Py-***C***-6), 158.25 (C_{quat}, ***C***=N), 159.77 (C_{quat}, Py-***C***-2). HRMS (EI-MS) calcd. for $C_{19}H_{24}N_6S$ [$M^{+\bullet}$] 368.1783; found 368.1788. IR (cm^{-1}) = 3270 (N-H), 2987, 2901 (C-H), 2158 (C≡N), 1567 (C=N), 1508, 1437, 1329. Anal. ($C_{19}H_{24}N_6S \cdot 0.35\ CH_3OH$) C, H, N. $C_{19}H_{24}N_6S$ (368.50)

1-[2-(4-Aminopyrimidin-2-ylamino)ethyl]-2-cyano-3-methylguanidine (130)

The title compound was prepared from N^2-(2-aminoethyl)pyrimidine-2,4-diamine dihydrochloride **105** (0.034 g, 0.15 mmol) and **90** (0.027 g, 0.15 mmol) in MeCN (4.5 mL) according to the general procedure. To deprotonate the amine 0.13 mL DIPEA were added to the mixture. Flash chromatography yielded a colourless oil (0.03 g, 85 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 2.78 (s, 3H, C***H***$_3$-N), 3.35 (t, 2H, ^{3}J = 5.6 Hz, C***H***$_2$-N), 3.48 (t, 2H, ^{3}J = 5.6 Hz, C***H***$_2$-N), 5.90 (d, 1H, ^{3}J = 6.2 Hz, Py-***H***-5), 7.69 (d, 1H, ^{3}J = 6.1 Hz, Py-***H***-6). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 28.75 (+, ***C***H_3), 41.37 (-, ***C***H_2-N), 43.55 (-, ***C***H_2-N), 97.20 (+, Py-***C***-5), 120.48 (C_{quat}, ***C***≡N), 153.75 (+, Py-***C***-6), 162.14 (C_{quat}, ***C***=N), 162.25 (C_{quat}, Py-***C***), 166.54 (C_{quat}, Py-***C***). HRMS (EI-MS) calcd. for $C_9H_{14}N_8$ [$M^{+\bullet}$] 234.1341; found 234.1337. IR (cm^{-1}) = 3064 (N-H), 2876 (C-H), 2168 (C≡N), 1655, 1566 (C=N), 1421, 1360, 1231, 1175. $C_9H_{14}N_8$ (234.26).

1-[2-(4-Aminopyrimidin-2-ylamino)ethyl]-2-cyano-3-[2-(phenylthio)ethyl]guanidine (131)

The title compound was prepared from N^2-(2-aminoethyl)pyrimidine-2,4-diamine dihydrochloride **105** (0.039 g, 0.17 mmol) and **91** (0.051 g, 0.17 mmol) in MeCN (4.5 mL) according to the general procedure. To deprotonate the amine 0.14 mL DIPEA were added to the mixture. Flash chromatography yielded a colourless oil (0.05 g, 83 %); ^{1}H-NMR (300 MHz,

CD_3OD): δ [ppm] = 3.10 (t, 2H, ^3J = 6.9 Hz, C***H***$_2$-N), 3.25 (m, 2H, C***H***$_2$-N), 3.43 (m, 4H, 2 C***H***$_2$), 5.91 (d, 1H, ^3J = 6.2 Hz, Py-***H***-5), 7.16 (t, 1H, ^3J = 8.5 Hz, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.37 (m, 2H, Ph-***H***), 7.66 (d, 1H, ^3J = 6.2 Hz, Py-***H***-6). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 33.45 (-, ***C***H$_2$-S), 41.23 (-, ***C***H$_2$-N), 42.54 (-, ***C***H$_2$-N), 43.25 (-, ***C***H$_2$-N), 97.42 (+, Py-***C***-5), 120.31 (C_{quat}, ***C***≡N), 127.33 (+, Ph-***C***-4), 130.20 (+, 2 Ph-***C***), 130.75 (+, 2 Ph-***C***), 137.04 (C_{quat}, Ph-***C***-1), 153.41 (+, Py-***C***-6), 161.40 (C_{quat}, ***C***=N), 162.07 (C_{quat}, Py-***C***), 166.19 (C_{quat}, Py-***C***). HRMS (EI-MS) calcd. for $C_{16}H_{20}N_8S$ [$M^{+\bullet}$] 356.1532; found 356.1524. IR (cm^{-1}) = 3225 (N-H), 3064, 2962, 2876 (C-H), 2168 (C≡N), 1655, 1566 (C=N), 1421, 1360, 1175. $C_{16}H_{20}N_8S$ (356.45)

1-[3-(4-Aminopyrimidin-2-ylamino)propyl]-2-cyano-3-methylguanidine (132)

The title compound was prepared from *N*^{2}-(3-aminopropyl)pyrimidine-2,4-diamine dihydrochloride **106** (0.05 g, 0.2 mmol) and **90** (0.036 g, 0.2 mmol) in MeCN (4.5 mL) according to the general procedure. To deprotonate the amine 0.17 mL DIPEA were added to the mixture. Flash chromatography yielded a colourless oil (0.04 g, 81 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.76 (m, 2H, C***H***$_2$), 2.79 (s, 3H, C***H***$_3$-N), 3.26 (t, 2H, ^3J = 6.5 Hz, C***H***$_2$-N), 3.39 (t, 2H, ^3J = 6.5 Hz, C***H***$_2$-N), 5.90 (d, 1H, ^3J = 6.4 Hz, Py-***H***-5), 7.65 (d, 1H, ^3J = 6.3 Hz, Py-***H***-6). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 28.76 (+, ***C***H$_3$), 30.62 (-, ***C***H$_2$), 38.79 (-, ***C***H$_2$-N), 39.69 (-, ***C***H$_2$-N), 97.06 (+, Py-***C***-5), 120.65 (C_{quat}, ***C***≡N), 151.54 (+, Py-***C***-6), 160.83 (C_{quat}, ***C***=N), 162.05 (C_{quat}, Py-***C***), 166.33 (C_{quat}, Py-***C***). HRMS (EI-MS) calcd. for $C_{10}H_{16}N_8$ [$M^{+\bullet}$] 248.1498; found 248.1493. IR (cm^{-1}) = 3064 (N-H), 2962, 2876 (C-H), 2168 (C≡N), 1655, 1566 (C=N), 1421, 1360, 1334. $C_{10}H_{16}N_8$ (248.29).

1-[3-(4-Aminopyrimidin-2-ylamino)propyl]-2-cyano-3-[2-(phenylthio)ethyl]guanidine (133)

The title compound was prepared from *N*^{2}-(3-aminopropyl)pyrimidine-2,4-diamine dihydrochloride **106** (0.03 g, 0.12 mmol) and **91** (0.037 g, 0.12 mmol) in MeCN (4.5 mL) according to the general procedure. To deprotonate the amine 0.17 mL DIPEA were added to the mixture. Flash chromatography yielded a yellow oil (0.04 g, 90 %); ^{1}H-NMR (300 MHz, CD_3OD): δ [ppm] = 1.71 (m, 2H, C***H***$_2$), 3.11 (t, 2H, ^3J = 7.0 Hz, C***H***$_2$-N), 3.18 (t, 2H, ^3J = 6.3 Hz, C***H***$_2$-N), 3.37 (t, 2H, ^3J = 6.5 Hz, C***H***$_2$-N), 3.42 (t, 2H, ^3J = 6.5 Hz, C***H***$_2$-S), 5.90 (d, 1H, ^3J = 6.3 Hz, Py-***H***-5), 7.17 (t, 1H, ^3J = 7.3 Hz, Ph-***H***-4), 7.28 (m, 2H, Ph-***H***), 7.39 (m, 2H, Ph-***H***), 7.66 (d, 1H, ^3J = 6.3 Hz, Py-***H***-6). ^{13}C-NMR (75 MHz, CD_3OD): δ [ppm] = 30.60 (-, ***C***H$_2$), 33.46 (-, ***C***H$_2$-S), 38.56 (-, ***C***H$_2$-N), 39.58 (-, ***C***H$_2$-N), 42.37 (-, ***C***H$_2$-N), 97.00 (+, Py-***C***-5), 120.66 (C_{quat}, ***C***≡N), 127.29 (+, Ph-***C***-4), 130.17 (+, 2 Ph-***C***), 130.33 (+, 2 Ph-***C***), 137.06 (C_{quat}, Ph-***C***-1), 152.31

(+, Py-***C***-6), 161.23 (C_{quat}, ***C***=N), 162.11 (C_{quat}, Py-***C***), 166.32 (C_{quat}, Py-***C***). HRMS (EI-MS) calcd. for $C_{17}H_{22}N_8S$ [$M^{+\bullet}$] 370.1688; found 370.1692. IR (cm^{-1}) = 3173 (N-H), 3064, 2962, 2876 (C-H), 2168 (C≡N), 1655, 1566 (C=N), 1421, 1360, 1175. $C_{17}H_{22}N_8S$ (370.48)

Pharmacological methods

Materials

Histamine dihydrochloride was purchased from Alfa Aesar GmbH & Co. KG (Karlsruhe, Germany). Thioperamide hydrochloride was synthesized according to a previously described method.[21] Iodophenpropit dihydrobromide was from Tocris Bioscience (Ellisville, USA). The H_4R antagonist JNJ-7777120 was synthesized according to ref[22]. [^{3}H]Mepyramine, [^{3}H]tiotidine, [^{3}H]N^{α}-methylhistamine and [^{3}H]histamine were from PerkinElmer Life Sciences (Boston, MA). [γ^{32}P]GTP and [γ^{33}P]GTP were synthesized according to a previously described method.[23] [^{32}P]P_i (8,500 – 9,100 Ci/mmol orthophosphoric acid) was from PerkinElmer Life Sciences (Boston, MA, USA), [^{33}P]P_i (3000 Ci/mmol orthophosphosphoric acid) was from Hartmann Analytic (Braunschweig, Germany). Guanosine diphosphate (GDP) was from Sigma-Aldrich Chemie GmbH (Munich, Germany), unlabeled GTPγS was from Roche (Mannheim, Germany). [^{35}S]GTPγS was from PerkinElmer Life Sciences (Boston, MA) or Hartmann Analytic GmbH (Braunschweig, Germany). GF/C filters were from Whatman Ltd. (Maidstone, UK). Glycerol-3-phosphate dehydrogenase, triose phosphate isomerase, glyceraldehyde-3-phosphate dehydrogenase and lactate dehydrogenase were from Roche (Mannheim, Germany). 3-Phosphoglycerate kinase, L-α-glycerol phosphate and adenosine triphosphate were from Sigma-Aldrich Chemie GmbH (Munich, Germany).

[^{35}S]GTPγS binding assay[24, 25]

[^{35}S]GTPγS binding assays were performed as previously described for the H_2R,[26, 27] H_3R[28, 29] and H_4R.[30] H_2R assays: Sf9 insect cell membranes expressing the hH_2R-$G\alpha_s$ fusion protein were employed, H_3R assays: Sf9 insect cell membranes coexpressing the hH_3R, mammalian $G\alpha_{i2}$ and $G\beta_1\gamma_2$ were employed, H_4R assays: Sf9 insect cell membranes coexpressing the hH_4R, mammalian $G\alpha_{i2}$ and $G\beta_1\gamma_2$ were employed.

The respective membranes were thawed, sedimented by a 10 min centrifugation at 4 °C and 13,000 *g*. Membranes were resuspended in binding buffer (12.5 mM $MgCl_2$, 1 mM EDTA, and

75 mM Tris/HCl, pH 7.4). Each assay tube contained Sf9 membranes expressing the respective HR subtype (15 – 30 µg protein/tube), 1 µM GDP, 0.05 % (w/v) bovine serum albumin, 0.2 nM [^{35}S]GTPγS and the investigated ligands (dissolved in millipore water or in a mixture (v/v) of 80 % millipore water and 20 % DMSO) at various concentrations in binding buffer (total volume 250 µL). All H_4R assays additionally contained 100 mM NaCl.

For the determination of pK_B values (antagonist mode of the [^{35}S]GTPγS Binding Assay) histamine was added to the reaction mixtures (final concentrations: H_2R: 1 µM; H_3/$_4$R: 100 nM). Incubations were conducted for 90 min at 25 °C and shaking at 250 rpm. Bound [^{35}S]GTPγS was separated from free [^{35}S]GTPγS by filtration through GF/C filters, followed by three washes with 2 ml of binding buffer (4 °C) using a Brandel Harvester. Filter-bound radioactivity was determined after an equilibration phase of at least 12 h by liquid scintillation counting. The experimental conditions chosen ensured that no more than 10 % of the total amount of [^{35}S]GTPγS added was bound to filters. Non-specific binding was determined in the presence of 10 µM unlabeled GTPγS.

Steady-state GTPase activity assay

GTPase activity assays were essentially performed as previously described.[13, 30-32] Due to changeover from [^{32}P] to [^{33}P] for safety and practical reasons, recent experiments were performed with [γ^{33}P]GTP. In this case, due to the lower energy of $^{33}P_i$, quantification was performed by liquid scintillation counting in a LS6500 liquid scintillation counter (Beckman-Coulter, Munich, Germany) using Optiphase Supermix® (Perkin Elmer, Rodgau, Germany). Apart from that, the experimental protocols are identical and the results are the same. Therefore, in the following, the procedure is only described for the use of [γ^{32}P]GTP.

H_1R assays: Sf9 insect cell membranes coexpressing the hH_1R and RGS4 were employed, H_2R assays: Sf9 insect cell membranes expressing the hH_2R-Gsα_S fusion protein were used, H_3R assays: Sf9 insect cell membranes coexpressing the hH_3R, mammalian Gα_{i2}, G$\beta_1\gamma_2$ and RGS4 were employed, H_4R assays: Sf9 insect cell membranes coexpressing the hH_4R-RGS19 fusion protein, mammalian Gα_{i2} and G$\beta_1\gamma_2$ were used. The respective membranes were thawed, sedimented by centrifugation at 4 °C and 13,000 *g* for 10 min Membranes were resuspended in 10 mM Tris/HCl, pH 7.4. Each assay tube contained Sf9 membranes expressing the respective HR subtype (10 – 20 µg protein/tube), $MgCl_2$ ($H_{1,2}$R assays: 1.0 mM, $H_{3,4}$R assays: 5.0 mM), 100 µM EDTA, 100 µM ATP, 100 nM GTP, 100 µM adenylyl imidophosphate, 5 mM creatine

phosphate, 40 µg creatine kinase and 0.2 % (w/v) bovine serum albumin in 50 mM Tris/HCl, pH 7.4 and the investigated ligands at various concentrations. All H_4R assays additionally contained 100 mM NaCl. For the determination of pK_B values (antagonist mode of the GTPase activity assay) histamine was added to the reaction mixtures (final concentrations: H_1R: 200 nM; H_2R: 1 µM; $H_{3,4}R$: 100 nM).

Reaction mixtures (80 µL) were incubated for 2 min at 25 °C. After the addition of 20 µL of [γ^{32}P]GTP (0.1 µCi/tube), reaction mixtures were incubated for 20 min at 25 °C. Reactions were terminated by the addition of 900 µL slurry consisting of 5 % (w/v) activated charcoal and 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 13,000 *g*. 600 µL of the supernatant were removed and $^{32}P_i$ was determined by liquid scintillation counting. 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 due to 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 $^{32}P_i$.

Data analysis and pharmacological parameters

All data are presented as mean of N independent experiments ± SEM. Agonist potencies were given as pEC_{50} values (-log of the molar concentration of the agonist causing 50 % of the maximal response). Maximal responses (intrinsic activities) were expressed as α values. The α value of histamine was set to 1.00, α values of other compounds were referred to this value.

IC_{50} values were converted to pK_B values using the Cheng-Prussoff equation.[33] pK_i values were analyzed by nonlinear regression and best fit to one-site (monophasic) competition isotherms. pEC_{50} and pK_B values from the functional [^{35}S]GTPγS and GTPase assays were analyzed by nonlinear regression and best fit to sigmoidal dose-response curves (GraphPad Prism 5.0 software, San Diego, CA).

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 the isolated spontaneously beating guinea pig right atrium

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.[34] 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. pEC_{50} differences were not corrected since two successive curves for histamine were virtually superimposable ($n > 10$). *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.

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