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Synthesis of Triazolyl-Substituted 3-Aminopiperidines by Huisgen-1,3-Dipolar Cycloaddition – New Scaffolds for Combinatorial Chemistry

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Dedicated to the memory of Professor Herbert Schumann

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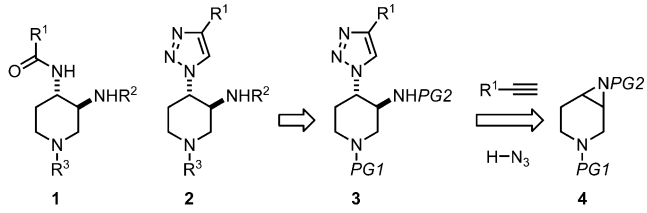
Orthogonally *N*-protected (Boc and Cbz) 4-(1,2,3-triazol-4-yl)-substituted 3-aminopiperidines are new scaffolds for combinatorial chemistry. They were prepared from a piperidine building block by a sequence of nucleophilic aziridine ring opening with NaN_3 and subsequent copper-catalyzed Huisgen 1,3-dipolar cycloaddition with ten different alkynes. Constitution and relative configuration of the major as well as minor products were established by single-crystal X-ray structure analysis of bromophenylsulfonyl derivatives.

Introduction

The piperidine moiety is a leading structural motif in alkaloids[1] and one of the privileged structures in medicinal chemistry.[2] Progress on the preparation of piperidine derivatives has continuously been reviewed.[3] In the course of our efforts on the preparation of new piperidine building blocks[4] we envisioned 4-triazolyl-substituted aminopiperidines **2** as topological and electronic mimics[5] of compounds **1** with an acylamino-function at the 4-position (Scheme 1). Compounds with scaffold **1** have proved to be inhibitors of factor Xa[6] and antagonists of CC chemokine receptor 2.[7] From a retrosynthetic point of view racemic scaffolds **2** simply derive from aziridine **4** by ring-opening with hyrazoic acid[8] followed by regioselective copper-catalyzed Huisgen 1,3-dipolar cycloaddition[9] with different alkynes. Orthogonal protective groups *PG1* and *PG2* in intermediate products **3** should allow for subsequent and independent introduction of residues R^2 and R^3 in members of the final product library **2**. Preparation of racemic building block **4** with *PG1* = Cbz and *PG2* = Boc on a multigram scale in five steps starting from pyridine was recently reported.[10]



Scheme 1. Synthetic plan for 3-amino-4-triazoylpiperidines **2** as mimics of 3,4-diaminopiperidine derivatives **1**.

Results and Discussion

Ring-opening of racemic aziridine with NaN_3 was performed on a 30 g scale under protic conditions (NH_4Cl, MeOH, H_2O) and gave azidopiperidine **5** in 93% yield (Scheme 2). With two carbamate-protective groups, broad signals were observed in NMR spectra at 23 °C. At 70 °C and in [D_8]toluene two partly doubled signal sets could be observed, which integrate to a ratio of 5:1. Therefore, we assume the formation of two racemic regioisomers **5a** and **5b**, which did not separate upon chromatography. Constitutions and relative *trans*-configurations of isomers **5a** and **5b** were unequivocally established by X-ray single crystal structure of derived triazoles at a later stage.

Copper-catalyzed Huisgen 1,3-dipolar cycloadditions were performed at 23 °C in a reductive milieu (sodium ascorbate). Aqueous 2-methoxyethanol (2-ME) was the solvent. Catalyst as well as reductant were added to the reaction mixture at the beginning and for another time after about 12 h in order to achieve full conversion. Small excess (1.2 equiv.) of alkynes was applied, except for propyne, where we used 1 atm (balloon technique). Ten different aliphatic (Table 1, entries 1–4), aromatic (entries 5 and 6) and heteraromatic (entries 7–10) alkynes were submitted to this procedure, three of them with a hydroxy function (entries

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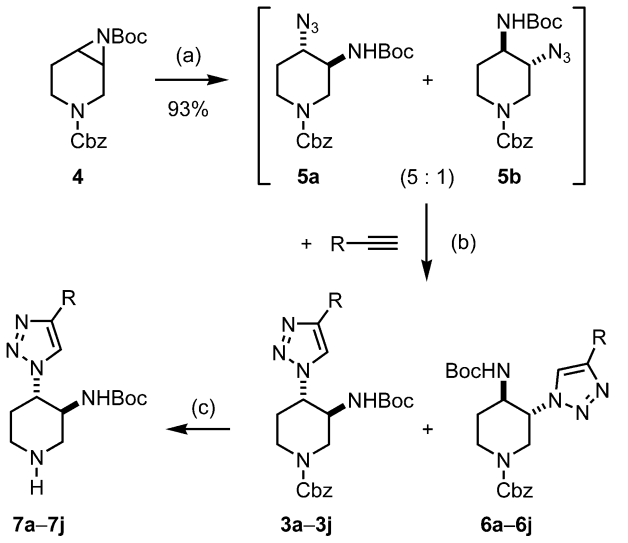


Scheme 2. Synthesis of 3-(Boc-amino)-4-triazolylpiperidines **7**. Reagents and conditions: (a) 2 equiv. NaN_3, 1 equiv. NH_4Cl, MeOH, H_2O, 65 °C, 16 h; (b) + 1.2 equiv. R–C≡CH, 2 × 0.1 equiv. Na ascorbate, 2 × 0.01 equiv. $CuSO_4$, 2-methoxyethanol (2-ME), H_2O, 23 °C, 20 h; (c) procedure 1 for **3a**–**3i**: cat. Pd/C, 3 bar H_2, *i*PrOH, 70 °C, 8 h; procedure 2 for **3j**: 4 equiv. KOH, *i*PrOH, H_2O, 80 °C, 16 h.

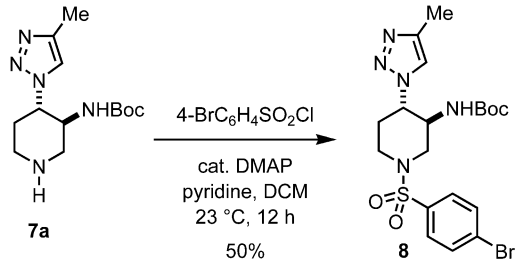
3–5). Triazoles were obtained as mixtures of regioisomers **3** and **6**, except for R = 3-pyridyl and methylimidazolyl (entries 8 and 9), where no regioisomers **6h** and **6i** could be observed. The latter could either be due to kinetic effects during formation of regioisomers **6** or they could have been lost during workup and purification. In all other cases major isomers **3** and regioisomers **6** could be separated by column chromatography with major products **3** always being the more polar isomers. Ratios of isolated materials **3** and **6** (4:1 to 8:1) were in the same order of magnitude as the ratio of starting materials **5a** and **5b** (5:1), except for R = 1-hydroxycyclohexyl with ratio 11:1 (entry 4). With a range of 46–74% the yields of isolated major isomers **3** were good, except for the thienyl derivative (entry 10, 28% yield of **3j**). Due to hindered rotation along the two carbamate C–N bonds (*E*/*Z* isomers), two broad and partly doubled signal sets were observed in the NMR spectra of all compounds. Moreover, two alkynes are chiral and were applied in racemic form, thus, products **3c**, **6c** and **7c** as well as **3e**, **6e** and **7e** were obtained as mixtures of two diastereoisomers, which again led to partly doubling of NMR signal sets.

The hydrogenolytic Cbz-deprotection of the major triazoles **3** proceeded within a couple of hours with satisfying yields (56–88%) when performed at elevated temperature (70 °C) and elevated H_2 pressure (3 bar) (Table 1). Two exceptions were first the 3-pyridyl derivative **3h** (entry 8) which gave only 26% yield of compound **7h**. Secondly, thienyl derivative **3j** gave no conversion, not even at higher temperatures and pressures. This behaviour might be attributed to poisoning of the Pd-catalyst by the sulfur from the substrate. This might actually be also the reason for low yield of **3j** in the copper-catalyzed cycloaddition. Nevertheless, we were – after some experimentation – able to cleave the Cbz group from this substrate **3j** by saponification with a mixture of aqueous KOH and *i*PrOH. Compound **7j** was isolated in 66% yield after workup.

Table 1. Residues R and yields of isolated products.

Entry	R	Product **3**	Regioisomer **6**	Ratio **3** / **6**	Product **7**
1	Me—	**3a**, 57%	**6a**, 10%	5.7 : 1	**7a**, 88%
2		**3b**, 46%	**6b**, 12%	3.8 : 1	**7b**, 84%
3		**3c**, 65%	**6c**, 8%	8.1 : 1	**7c**, 81%
4		**3d**, 65%	**6d**, 6%	11 : 1	**7d**, 79%
5		**3e**, 58%	**6e**, 10%	5.8 : 1	**7e**, 82%
6		**3f**, 46%	**6f**, 12%	3.8 : 1	**7f**, 85%
7		**3g**, 67%	**6g**, 9%	7.4 : 1	**7g**, 56%
8		**3h**, 67%	**6h**, 0%	–	**7h**, 26%
9		**3i**, 74%	**6i**, 0%	–	**7i**, 83%
10		**3j**, 28%	**6j**, 9%	3.1 : 1	**7j**, 66%

We planned to obtain a X-ray single crystal structure in order to prove the constitution and relative configuration of our major products, but we failed to obtain single crystals of compounds **3a**–**3j** and **7a**–**7j**. Therefore, we have prepared *p*-bromobenzenesulfonamide **8** from methyl derivative **7a** by conversion with the respective sulfonyl chloride (Scheme 3). Compound **8** with bromine and sulfur as heavy atoms showed good crystallinity and suitable single crystals were obtained and investigated.[11] The ORTEP plot (Figure 1) shows the triazole moiety clearly in the 4-position of the piperidine ring. Moreover, residues in the 3- and 4-position are in relative *trans*-configuration as expected for the S_N2-type aziridine ring opening of the starting material **4**.



Scheme 3. Derivatization of racemic piperidine **7a** by sulfonamide formation.

Furthermore, the methyl group is in the 4-position of the 1-triazolyl ring, which is the expected and the only regiochemistry of copper-catalyzed Huisgen 1,3-dipolar cycloadditions.[9] The piperidine ring is in almost perfect chair conformation with three substituents in equatorial positions.

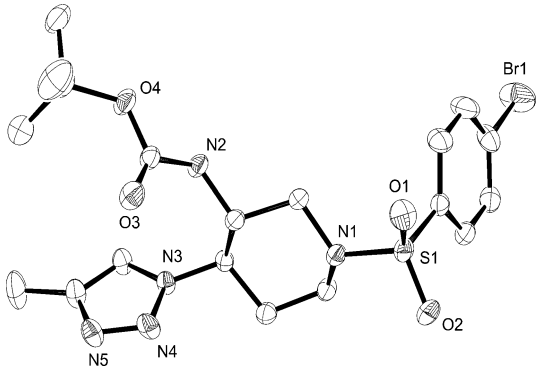
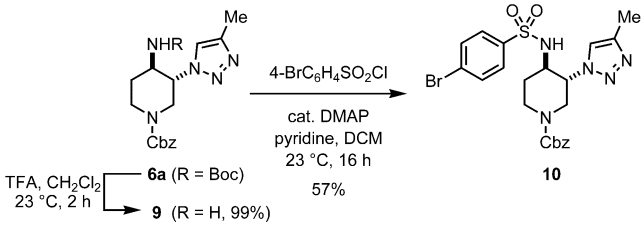


Figure 1. ORTEP representation of the structure of compound **8** in the solid state. The unit cell contains solvent ($CDCl_3$), which is omitted.

In order to prove furthermore the constitution of minor products **6**, the Boc protecting group of compound **6a** was cleaved with TFA and the resulting primary amine **9** converted into the sulfonamide **10** (Scheme 4). Again, a material with good crystallinity was obtained and submitted to X-ray diffraction. It crystallized with two equivalents of MeOH in the unit cell. Figure 2 shows the ORTEP representation of compound **10**. As expected, the triazole moiety is now in the 3-position. Sulfonamide and triazole residues are in relative *trans*-configuration at the piperidine ring. The methyl group is located at the 4-position of the triazole ring.



Scheme 4. Derivatization of regioisomeric piperidine **6a** by sulfonamide formation.

In summary, we have reported on the multigram-scale synthesis of new orthogonally Boc- and Cbz-protected 3-aminopiperidines **3** with a triazole ring in the 4-positions, which are interesting and new scaffolds for combinatorial chemistry. The triazole rings were installed by a copper-catalyzed Huisgen 1,3-dipolar cycloaddition reaction of a respective 4-azidopiperidine **5** with ten different alkynes. This organic azide was prepared by ring opening reaction of an *N*-Boc-aziridine **4** with NaN_3, which proceeded with limited regioselectivity. A inseparable mixture (ratio 5:1) of 4- and 3-azidopiperidines **5a** and **5b** was obtained. When submitted to the 1,3-dipolar cycloaddition, this mixture resulted in regioisomeric triazoles **3** and **6**, which were now separable by chromatography. The Cbz group of major isomers **3** was deprotected by either catalytic hydrogenation or saponification with KOH, H_2O, *i*PrOH. The constitution and relative configuration of major as well as minor regioisomers **7** and **6** was established by X-ray single-crystal structure analysis of sulfonamide derivatives **8** and **10**.

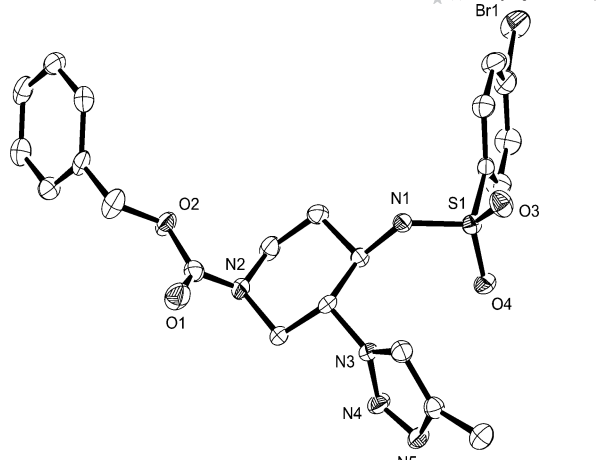


Figure 2. ORTEP representation of the structure of compound **10** in the solid state. The unit cell contains solvent (MeOH), which is omitted.

Experimental Section

General Methods: Preparative column chromatography was carried out using Merck SiO_2 (0.035–0.070 mm, type 60 A) with hexane, ethyl acetate (EA), or MeOH as eluents. TLC was performed on Merck SiO_2 F_{254} plates on aluminium sheets. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 500. Multiplicities of carbon signals were determined with DEPT experiments. Spectra of all Boc- and Cbz-protected compounds showed broad, partly doubled signal sets due to hindered rotation along the carbamate C–N bond (*E*,*Z* isomers). MS and HRMS spectra were obtained with a Finnigan MAT 95 (EI) and a Waters Q-TOF Premier (ESI, positive mode) spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond-ATR unit. Elemental analyses were measured with a Euro EA-CHNS from HEKAtech. Aziridine **4** was prepared as reported previously.[10] All other starting materials were commercially available.

***trans*-4-Azido-1-(benzyloxycarbonyl)-3-(*tert*-butyloxycarbonylamino)-piperidine (5a) and *trans*-3-Azido-1-(benzyloxycarbonyl)-4-(*tert*-butyloxycarbonylamino)piperidine (5b):** Aziridine **4** (26.4 g, 79.5 mmol), NaN_3 (10.3 g, 159 mmol) and NH_4Cl (4.25 g, 79.5 mmol) were suspended in MeOH (70 mL) and H_2O (40 mL) and the resulting mixture was stirred for 16 h at 65 °C. After cooling to ambient temperature, H_2O (50 mL) and EA (100 mL) were added and the two layers were separated. The aqueous layer was extracted with EA (2 × 100 mL). The combined organic phases were dried with $MgSO_4$. After filtration, the solvent was evaporated. A mixture of the azidocarbamates **5a** and **5b** (27.65 g, 73.65 mmol, 93%, R_f = 0.42, hexanes/EA, 2:1) remained as a yellowish resin, which was used without further purification. NMR specta showed broad signals at 23 °C. At 70 °C two signal sets were observed, due to the two regioisomers (ratio **5a/5b** = 5:1 by ^{1}H NMR). ^{1}H NMR ([D$_8$]toluene, 500 MHz, 343 K): δ = 1.39 (s, 9 H, isomer A), 1.39 (s, 9 H, isomer B), 2.64–2.72 (m, 1 H), 2.73–2.86

(m, 1 H, both isomers), 2.99–3.11 (m, 1 H, both isomers), 3.16–3.23 (m, 1 H, isomer A), 3.23–3.31 (m, 1 H, isomer B), 3.45–3.56 (m, 1 H, both isomers), 3.61–3.70 (m, 1 H, isomer B), 3.80 (dd, J = 3.8, J = 13.4 Hz, 1 H; isomer A), 3.85–3.93 (m, 1 H, isomer B), 3.94–4.02 (m, 1 H, isomer A), 4.18–4.28 (m, 1 H, both isomers), 4.96–5.04 (m, 2 H, both isomers), 6.96–6.99 (m, 3 H, both isomers), 7.06–7.09 (m, 2 H, both isomers) ppm. $^{13}C\{^1H\}$ NMR ([D_8]toluene, 125 MHz, 343 K): δ = 28.58 (3 CH_3; isomer A), 28.86 (3 CH_3; isomer B), 41.67 (CH_2; isomer B), 41.77 (CH_2; isomer A), 46.61 (CH_2; both isomers), 50.24 (CH; both isomers), 60.74 (CH; isomer A), 60.87 (CH; isomer B), 61.49 (CH_2; isomer B), 61.65 (CH_2; isomer A), 67.64 (CH_2), 79.77 (C; both isomers), 128.37 (2 CH; both isomers), 128.74 (CH; both isomers), 128.77 (2 CH; both isomers), 137.60 (C; both isomers), 155.17 (C; both isomers), 155.34 (C; isomer A), 155.49 (C; isomer B) ppm. IR (ATR): $\tilde{\nu}$ = 3006 (w), 2971 (w), 2935 (w), 2863 (w), 2361 (w), 2342 (w), 1737 (m), 1709 (m), 1673 (s), 1529 (m), 1476 (m), 1444 (m), 1366 (m), 1304 (m), 1280 (m), 1241 (s), 1158 (s), 1098 (m), 1078 (m), 1019 (m), 964 (m), 765 (m), 753 (m), 700 (m), 645 (m), 613 (m) cm^{-1}. HRMS (ESI): calcd. 398.1804 (for $C_{18}H_{25}N_5NaO_4$); found 398.1808 [M + Na^+]. $C_{18}H_{25}N_5O_4$ (375.42).

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-(4-methyl-1,2,3-triazol-1-yl)piperidine (3a):** Sodium ascorbate (670 mg, 3.22 mmol) and $CuSO_4$ (0.33 mmol, 66 mL of a 5 × 10^{-3} mol/L aqueous solution) were added to a degassed solution of azidocarbamate **5a/5b** (12.1 g, 32.2 mmol) in 2-ME (150 mL) and H_2O (25 mL). Subsequently, the cooled reaction flask (ca. –20 °C) was evacuated and then filled with 1 atm of propyne (balloon technique) and the mixture was warmed up to 23 °C and further stirred for 12 h. More sodium ascorbate (670 mg, 3.22 mmol) and $CuSO_4$ (0.33 mmol, 66 mL of a 5 × 10^{-3} mol/L aqueous solution) were then added and the mixture was further stirred under an atmosphere of propyne (balloon technique) for 8 h at 23 °C. DCM (100 mL) was added to the mixture and the two layers were stirred until dissolution of the solid was observed (ca. 1 h). After addition of brine (100 mL), the layers were separated and the aqueous layer was extracted with DCM (2 × 100 mL). The combined organic layers were dried with $MgSO_4$. After filtration, the solvents were evaporated and the residue submitted to chromatography (SiO_2, EA). In the first fraction (R_f = 0.51, EA) regioisomer **6a** was obtained (1.27 g, 3.06 mmol, 10%) as a colorless solid, m.p. 143 °C. Major isomer **3a** (7.56 g, 18.5 mmol, 57%) was eluted as the second fraction (R_f = 0.33, EA) and also as a colorless solid, m.p. 183 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (s, 9 H), 2.09 (d, J = 12.1 Hz, 1 H), 2.31 (s, 3 H), 2.84–3.06 (m, 1 H), 3.01–3.29 (m, 1 H), 3.93–4.03 (m, 1 H), 4.16–4.41 (m, 1 H), 4.40 (d, J = 11.4 Hz, 1 H), 4.41–4.72 (m, 3 H), 4.98–5.25 (m, 2 H), 7.27–7.40 (m, 6 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 10.61 (CH_3), 27.98 (3 CH_3), 31.36 (CH_2), 43.06 (CH_2), 47.92 (CH_2), 51.28 (CH), 60.40 (CH), 67.53 (CH_2), 79.68 (C), 120.34 (CH), 127.89 (2 CH), 128.11 (CH), 128.44 (2 CH), 136.01 (C), 142.87 (C), 154.75 (C), 154.98 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3224 (w), 3134 (w), 3097 (w), 3036 (w), 3040 (w), 2977 (w), 2934 (w), 1709 (s), 1564 (m), 1547 (m), 1423 (m), 1312 (m), 1242 (m), 1169 (m), 963 (m), 730 (m) cm^{-1}. MS (ESI): m/z (%) = 438 (6) [M + Na^+], 382 (100), 338 (65). $C_{21}H_{29}N_5O_4$ (415.49): C 60.71, H 7.04, N 16.86; found C 60.48, H 7.63, N 17.00.

***trans*-1-(Benzyloxycarbonyl)-4-[(*tert*-butyloxycarbonyl)amino]-3-(4-methyl-1,2,3-triazol-1-yl)piperidine (6a):** ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.31 (s, 9 H), 1.98–2.12 (m, 1 H), 2.12–2.23 (m, 1 H), 2.32 (s, 3 H), 2.89–3.12 (m, 2 H), 3.78–3.87 (m, 1 H), 4.20–4.37 (m, 1 H), 4.40 (d, J = 13.0 Hz, 1 H), 4.60–4.70 (m, 1 H), 4.74 (d, J = 7.7 Hz, 1 H), 5.07–5.25 (m, 2 H), 7.29–7.43 (m, 6 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 10.72 (CH_3), 28.03 (3 CH_3), 31.46 (CH_2), 43.63 (CH_2), 47.40 (CH_2), 51.59 (CH), 61.20 (CH), 67.50 (CH_2), 79.81 (C), 119.81 (CH), 127.60 (2 CH), 128.08 (CH), 128.46 (2 CH), 136.22 (C), 142.18 (C), 154.90 (C), 155.00 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3239 (w), 3128 (w), 3056 (w), 2972 (w), 2930 (w), 2324 (w), 2170 (w), 2066 (w), 2035 (w), 1980 (w), 1707 (s), 1554 (m), 1434 (m), 1310 (m), 1242 (s), 1779 (m), 1682 (s), 1164 (m), 1135 (m), 1012 (m), 749 (m), 694 (m) cm^{-1}. HRMS (ESI): calcd. 438.2117 (for $C_{21}H_{29}N_5NaO_4$); found 438.2108 [M + Na^+]. $C_{21}H_{29}N_5O_4$ (415.49): C 60.71, H 7.04, N 16.86; found C 60.41, H 7.29, N 17.07.

General Procedure A ([3+2] Cycloaddition): Azidocarbamate **5a/5b** (1 equiv.) and the respective alkyne (1.2 equiv.) were dissolved in a mixture of 2-ME (4.5 L/mol) and H_2O (1 L/mol). Sodium ascorbate (0.1 equiv.) and $CuSO_4$ (0.01 equiv. as an aqueous solution, c = 5 × 10^{-3} mol/L) were added whilst stirring and the resulting mixture was degassed (freeze, pump, thaw). After stirring for 12 h at 23 °C, an another amount of sodium ascorbate (0.1 equiv.) and $CuSO_4$ (0.01 equiv.) were added and the mixture was stirred for further 8 h at 23 °C. Then DCM (4 l/mol) was added to the mixture and the two layers were stirred until dissolution of the solid was observed (ca. 1 h). After addition of brine (4 L/mol), the layers were separated and the aqueous layer was extracted with DCM (2 × 4 L/mol). The combined organic layers were dried with $MgSO_4$. After filtration, the solvents were evaporated and the colored residue submitted to chromatography on SiO_2.

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-(4-cyclohexyl-1,2,3-triazol-1-yl)piperidine (3b):** Following the general procedure with azidocarbamate **5a/5b** (6.60 g, 16.0 mmol) and ethynylcyclohexane (2.09 g, 19.2 mmol) yielded the triazole **3b** (4.02 g, 6.28 mmol, 46%, R_f = 0.28, hexane/EA, 1:1), m.p. 165 °C, together with its regioisomer **6b** (0.68 g, 1.68 mmol, 12%, R_f = 0.41, hexane/EA, 1:1), m.p. 184 °C, both as colorless solids. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.26 (s, 9 H), 1.28–1.35 (m, 4 H), 1.61–1.68 (m, 1 H), 1.69–1.75 (m, 2 H), 1.92–2.03 (m, 3 H), 2.09–2.16 (m, 1 H), 2.61–2.71 (m, 1 H), 2.84–3.11 (m, 2 H), 3.73–3.82 (m, 1 H), 4.12–4.39 (m, 2 H), 4.52–4.71 (m, 2 H), 5.00–5.21 (m, 2 H), 7.23–7.34 (m, 6 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 26.01 (CH_2), 26.10 (2 CH_2), 28.15 (3 CH_3), 31.38 (CH_2), 32.88 (CH_2), 33.01 (CH_2), 35.28 (CH), 42.64 (CH_2), 47.48 (CH_2), 51.64 (CH), 60.40 (CH), 67.65 (CH_2), 80.16 (C), 117.80 (CH), 128.07 (2 CH), 128.22 (CH), 128.57 (2 CH), 136.27 (C), 153.75 (C), 154.89 (C), 155.02 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3216 (w), 3123 (w), 3036 (w), 2928 (m), 2853 (w), 2361 (w), 1709 (s), 1548 (m), 1475 (m), 1445 (m), 1422 (m), 1364 (m), 1309 (m), 1268 (m), 1242 (s), 1156 (s), 1132 (m), 1069 (m), 1057 (m), 1041 (m), 1019 (m), 997 (m), 963 (m), 872 (m), 773 (m), 732 (m), 693 (m) cm^{-1}. HRMS (ESI): calcd. 484.2924 (for $C_{26}H_{38}N_5O_4$); found 484.2920 [M + H^+]. $C_{26}H_{37}N_5O_4$ (483.60).

***trans*-1-(Benzyloxycarbonyl)-4-[(*tert*-butyloxycarbonyl)amino]-3-(4-cyclohexyl-1,2,3-triazol-1-yl)piperidine (6b):** ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.24 (s, 9 H), 1.28–1.35 (m, 4 H), 1.35–1.40 (m, 1 H), 1.60–1.68 (m, 2 H), 1.68–1.78 (m, 2 H), 1.90–1.99 (m, 2 H), 1.99–2.06 (m, 1 H), 2.61–2.70 (m, 1 H), 2.82–2.94 (m, 1 H), 3.05–3.18 (m, 1 H), 3.87–3.97 (m, 1 H), 4.15–4.33 (m, 1 H), 4.39–4.58 (m, 3 H), 4.97–5.14 (m, 2 H), 7.12–7.33 (m, 6 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 25.98 (CH_2), 26.05 (2 CH_2), 28.12 (3 CH_3), 31.51 (CH_2), 32.84 (CH_2), 32.93 (CH_2), 35.22 (CH), 43.16 (CH_2), 48.16 (CH_2), 52.48 (CH), 60.43 (CH), 67.64 (CH_2), 79.85 (C), 118.41 (CH), 128.02 (2 CH), 128.19 (CH), 128.52 (2 CH), 136.13 (C), 153.36 (C), 154.81 (C), 154.92 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2927 (w), 2031 (w), 2032 (w), 2013 (w), 1981 (w), 1703 (vs), 1434 (m), 1310 (m), 1226 (m), 1164 (m), 1130 (m), 1011 (m), 753 (m),

699 (m) cm^{-1}. HRMS (ESI): calcd. 506.2743 (for $C_{26}H_{37}N_5NaO_4$); found 506.2744 [M + Na^+]. $C_{26}H_{37}N_5O_4$ (483.60): C 64.57, H 7.71, N 14.48; found C 64.06, H 7.94, N 14.23.

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-[4-(1-hydroxyethyl)-1,2,3-triazol-1-yl]piperidine (3c):** Following the general procedure A with azidocarbamate **5a/5b** (9.4 g, 25 mmol) and 1-butyne-3-ol (2.13 g, 30.4 mmol) yielded the triazole **3c** (7.23 g, 16.2 mmol, 65%, R_f = 0.24, EA), m.p. 153 °C, together with its regioisomer **6c** (0.91 g, 2.0 mmol, 8%, R_f = 0.42, EA), m.p. 68 °C (dec.), both as colorless solids. Both compounds are obtained as mixtures of two diastereoisomers. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.32 (s, 9 H), 1.55 (d, J = 6.5 Hz, 3/2 H), 1.56 (d, J = 6.5 Hz, 3/2 H), 2.05–2.15 (m, 1 H), 2.15–2.30 (m, 1 H), 2.48–2.68 (m, 1 H), 2.92–3.14 (m, 2 H), 3.77–3.87 (m, 1 H), 4.22–4.44 (m, 2 H), 4.65–4.85 (m, 2 H), 5.00–5.08 (m, 1 H), 5.09–5.25 (m, 2 H), 7.30–7.41 (m, 5 H), 7.55 (s, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 23.04 (CH_3), 28.11 (3 CH_3), 31.36 (CH_2), 42.56 (CH_2), 47.24 (CH_2), 51.65 (CH), 56.68 (CH), 61.35 (CH), 67.55 (CH_2), 79.99 (C), 119.03 (CH), 127.91 (2 CH), 128.13 (CH), 128.49 (2 CH), 136.20 (C), 152.27 (C), 154.93 (C), 155.03 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3352 (w), 2980 (w), 2930 (w), 2323 (w), 1681 (s), 1522 (m), 1428 (m), 1314 (m), 1231 (m), 1156 (m), 1072 (m), 727 (m), 694 (m) cm^{-1}. MS (ESI): *m*/*z* (%) = 468 (100) [M + Na^+], 452 (24), 412 (10), 396 (5). $C_{22}H_{31}N_5O_5$ (445.51): C 59.31, H 7.01, N 15.72; found C 59.10, N 7.32, N 15.54.

***trans*-1-(Benzyloxycarbonyl)-4-[(*tert*-butyloxycarbonyl)amino]-3-[4-(1-hydroxyethyl)-1,2,3-triazol-1-yl]piperidine (6c):** ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (s, 9 H), 1.55 (d, J = 6.5 Hz, 3/2 H), 1.56 (d, J = 6.5 Hz, 3/2 H), 1.68–1.80 (m, 1 H), 2.09 (d, J = 10.8 Hz, 1 H), 2.45–2.66 (br. s, 1 H), 2.87–3.07 (br. s, 1 H), 3.14–3.31 (m, 1 H), 3.95–4.05 (m, 1 H), 4.19–4.43 (br. s, 1 H), 4.43–4.62 (m, 2 H), 4.62–4.79 (br. s, 1 H), 4.99–5.07 (m, 1 H), 5.07–5.21 (m, 2 H), 7.29–7.39 (m, 5 H), 7.55 (s, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 23.05 (CH_3), 28.07 (3 CH_3), 31.44 (CH_2), 43.12 (CH_2), 47.81 (CH_2), 52.36 (CH), 58.72 (CH), 62.74 (CH), 67.63 (CH_2), 79.90 (C), 119.66 (CH), 127.92 (2 CH), 128.17 (CH), 128.49 (2 CH), 135.00 (C), 152.21 (C), 154.81 (C), 155.08 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3326 (w), 2978 (w), 2326 (w), 2170 (w), 1682 (s) 1231 (m), 1169 (m), 697 (m) cm^{-1}. HRMS (ESI): calcd. 468.2217 (for $C_{22}H_{31}N_5NaO_5$); found 468.2230 [M + Na^+]. $C_{22}H_{31}N_5O_5{\cdot}H_2O$: C 57.01, H 7.18, N 15.11; found 57.48, H 7.10, N 15.20 (monohydrate). $C_{22}H_{31}N_5O_5$ (445.51).

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-[4-(1-hydroxycyclohexyl)-1,2,3-triazol-1-yl]piperidine (3d):** Following the general procedure A with azidocarbamate **5a/5b** (7.50 g, 20.0 mmol) and 1-ethynyl-1-cyclohexanol (2.98 g, 24.0 mmol) yielded the triazole **3d** (6.66 g, 13.0 mmol, 65%, R_f = 0.48, EA), m.p. 144 °C, together with its regioisomer **6d** (0.60 g, 1.2 mmol, 6%, R_f = 0.63, EA), m.p. 180 °C, both as colorless solids. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.33 (s, 9 H), 1.49–1.58 (m, 1 H), 1.58–1.66 (m, 1 H), 1.67–1.80 (m, 4 H), 1.81–1.90 (m, 2 H), 1.90–2.00 (m, 2 H), 2.02–2.15 (m, 1 H), 2.15–2.26 (m, 1 H), 2.32–2.65 (br. s, 1 H), 2.92–3.16 (m, 2 H), 3.80–3.90 (m, 1 H), 4.21–4.46 (m, 2 H), 4.63–4.86 (m, 2 H), 5.06–5.27 (m, 2 H), 7.30–7.41 (m, 5 H), 7.58 (s, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 21.89 (2 CH_2), 25.32 (2 CH_2), 28.12 (3 CH_3), 31.39 (CH_2), 38.12 (CH_2), 42.62 (CH_2), 47.39 (CH_2), 51.45 (CH), 61.44 (CH), 67.53 (CH_2), 69.30 (C), 79.91 (C), 118.54 (CH), 127.90 (2 CH), 128.12 (CH), 128.49 (2 CH), 136.19 (C), 154.86 (C), 154.92 (C), 154.96 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3330 (br., m), 2934 (m), 2862 (w), 2324 (w), 2164 (w), 2051 (w), 1982 (w), 1694 (s), 1433 (m), 1239 (s), 1206 (m), 1162 (s) cm^{-1}. HRMS (ESI): calcd. 500.2873 (for $C_{26}H_{38}N_5O_5$); found 500.2875 [M + H^+]. $C_{26}H_{37}N_5O_5$ (499.60).

***trans*-1-(Benzyloxycarbonyl)-4-[(*tert*-butyloxycarbonyl)amino]-3-[4-(1-hydroxycyclohexyl)-1,2,3-triazol-1-yl]piperidine (6d):** ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.31 (s, 9 H), 1.48–1.59 (m, 2 H), 1.59–1.66 (m, 1 H), 1.66–1.81 (m, 4 H), 1.81–1.89 (m, 2 H), 1.90–2.00 (m, 2 H), 2.05–2.13 (m, 1 H), 2.35–2.60 (br. s, 1 H), 2.87–3.07 (m, 1 H), 3.13–3.27 (m, 1 H), 3.94–4.08 (m, 1 H), 4.19–4.43 (m, 1 H), 4.45–4.64 (m, 2 H), 4.65–4.82 (m, 1 H), 5.04–5.22 (m, 2 H), 7.29–7.40 (m, 5 H), 7.58 (s, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 21.86 (2 CH_2), 25.32 (2 CH_2), 28.13 (3 CH_3), 31.42 (1/2 CH_2), 31.53 (1/2 CH_2), 37.95 (1/2 CH_2), 38.08 (1/2 CH_2), 43.11 (CH_2), 47.93 (CH_2), 52.26 (CH), 60.21 (1/2 CH), 60.34 (1/2 CH), 67.64 (CH_2), 69.34 (C), 79.83 (C), 119.01 (CH), 127.98 (2 CH), 128.20 (CH), 128.51 (2 CH), 136.02 (C), 154.81 (C), 155.00 (C), 155.50 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3436 (w), 3240 (w), 3143 (w), 3055 (w), 2980 (w), 2930 (w), 2853 (w), 1700 (m), 1686 (s), 1314 (m), 1233 (m), 1162 (m), 1134 (m) cm^{-1}. HRMS (ESI): calcd. 522.2692 (for $C_{26}H_{37}N_5NaO_5$); found 522.2682 [M + Na^+]. $C_{26}H_{37}N_5O_5$ (499.60).

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-[4-(1-hydroxy-1-phenylmethyl)-1,2,3-triazol-1-yl]piperidine (3e):** Following the general procedure A with azidocarbamate **5a/5b** (6.20 g, 16.5 mmol) and 3-phenyl-1-propyne-3-ol (2.62 g, 19.8 mmol) yielded the triazole **3e** (4.86 g, 9.57 mmol, 58%, R_f = 0.23, EA), m.p. 73 °C, together with its regioisomer **6e** (0.86 g, 1.68 mmol, 10%, R_f = 0.42, EA), m.p. 178 °C, both as colorless solids. Both compounds are obtained as mixtures of two diastereoisomers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.29 (s, 9 H), 2.03–2.17 (m, 2 H), 2.87–3.11 (br. s, 2 H), 3.36–3.53 (m, 1 H), 3.67–3.82 (br. s, 2 H), 4.18–4.40 (m, 2 H), 4.62–5.00 (m, 1 H), 5.05–5.22 (m, 2 H), 5.99 (s, 1 H), 7.20–7.48 (m, 11 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 28.09 (3 CH_3), 31.18 (CH_2), 42.52 (CH_2), 47.11 (CH_2), 51.73 (CH), 60.37 (CH), 67.50 (CH_2), 68.85 (CH), 80.02 (C), 120.50 (CH), 126.41 (2 CH), 127.82 (CH), 127.96 (2 CH), 128.15 (CH), 128.45 (2 CH), 128.50 (2 CH), 136.18 (C), 141.83 (C), 142.92 (C), 151.32 (C), 154.92 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3330 (m, br), 3063 (w), 2977 (w), 2933 (w), 2869 (w), 2363 (w), 2323 (w), 1681 (s), 1434 (m), 1366 (m), 1310 (m), 1236 (s), 1163 (s), 1120 (m), 1046 (m), 1018 (m), 970 (m), 735 (m), 698 (s) cm^{-1}. HRMS (ESI): calcd. 530.2379 (for $C_{27}H_{33}N_5NaO_5$); found 530.2378 [M + Na^+]. $C_{27}H_{33}N_5O_5$ (507.58): C 63.89, H 6.55, N 13.80; found C 64.17, H 7.08, N 14.00.

***trans*-1-(Benzyloxycarbonyl)-4-[(*tert*-butyloxycarbonyl)amino]-3-[4-(1-hydroxy-1-phenylmethyl)-1,2,3-triazol-1-yl]piperidine (6e):** ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.28 (s, 9 H), 1.66–1.82 (m, 2 H), 2.00–2.12 (m, 1 H), 2.83–3.04 (m, 1 H), 3.14–3.30 (m, 1 H), 3.85–4.01 (m, 1 H), 4.18–4.40 (m, 1 H), 4.40–4.78 (m, 3 H), 4.98–5.22 (s, 2 H), 6.02 (br. s, 1 H), 7.28–7.39 (m, 8 H), 7.40–7.49 (m, 3 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 28.07 (3 CH_3), 31.18 (CH_2), 43.03 (CH_2), 47.68 (CH_2), 52.52 (CH), 60.35 (CH), 67.63 (CH_2), 68.88 (CH), 79.88 (C), 121.01 (CH), 126.44 (2 CH), 127.79 (CH), 127.99 (2 CH), 128.19 (CH), 128.43 (2 CH), 128.50 (2 CH), 136.01 (C), 141.92 (C), 151.15 (C), 154.79 (C), 154.92 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3395 (br., m), 2976 (w), 2934 (w), 2170 (w), 2145 (w), 2050 (w), 2027 (w), 1986 (w), 1707 (s), 1667 (s), 1438 (m), 1312 (s), 1225 (m), 1312 (s), 1225 (m), 1158 (s), 1135 (s), 1014 (m), 732 (m), 697 (s) cm^{-1}. MS (ESI): *m*/*z* (%) = 530 (3) [M + Na^+], 474 (100), 450 (35). $C_{27}H_{33}N_5O_5$ (507.58): C 63.89, H 6.55, N 13.80; found C 64.04, H 6.83, N 13.67.

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-(4-phenyl-1,2,3-triazol-1-yl)piperidine (3f):** Following the general procedure with azidocarbamate **5a/5b** (5.70 g, 13.8 mmol) and phenylacetylene (1.86 g, 18.2 mmol) yielded the triazole **3f** (3.00 g,

6.28 mmol, 46%, R_f = 0.25, hexane/EA, 1:1), m.p. 204 °C, together with its regioisomer **6f** (0.80 g, 1.68 mmol, 12%, R_f = 0.35, hexane/EA, 1:1), m.p. 202 °C, both as colorless solids. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.28 (s, 9 H), 2.07–2.21 (m, 1 H), 2.21–2.31 (m, 1 H), 2.98–3.18 (m, 2 H), 3.88–4.02 (m, 1 H), 4.26–4.52 (m, 2 H), 4.73–4.98 (m, 2 H), 5.08–5.28 (m, 2 H), 7.28–7.46 (m, 8 H), 7.78–7.86 (m, 2 H), 7.90 (br. s, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 28.07 (3 CH_3), 31.44 (CH_2), 42.68 (CH_2), 47.36 (CH_2), 51.80 (CH), 61.30 (CH), 67.65 (CH_2), 80.23 (C), 118.56 (CH), 125.66 (2 CH), 128.02 (2 CH), 128.16 (CH), 128.20 (CH), 128.56 (2 CH), 128.81 (2 CH), 130.49 (C), 136.30 (C), 147.75 (C), 154.02 (2 C) ppm. IR (ATR): $\tilde{\nu}$ = 3631 (w), 3356 (w), 3292 (w), 2972 (w), 2940 (w), 2360 (w), 2324 (w), 1708 (m), 1686 (s), 1518 (s), 1367 (m), 1307 (m), 1248 (m), 1231 (m), 1162 (s), 1053 (m), 1022 (m), 865 (m), 763 (s), 693 (s) cm^{-1}. HRMS (ESI): calcd. 500.2274 (for $C_{26}H_{31}N_5NaO_4$); found 500.2287 [M + Na$^+$]. $C_{26}H_{31}N_5O_4$ (477.56).

***trans*-1-(Benzyloxycarbonyl)-4-[(*tert*-butyloxycarbonyl)amino]-3-(4-phenyl-1,2,3-triazol-1-yl)piperidine (6f):** ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.17 (s, 9 H), 1.62–1.77 (m, 1 H), 1.98–2.05 (m, 1 H), 2.80–3.04 (m, 1 H), 3.14–3.36 (m, 1 H), 3.95–4.07 (m, 1 H), 4.11–4.34 (m, 1 H), 4.22–4.67 (m, 2 H), 4.85–4.97 (m, 1 H), 4.97–5.19 (m, 2 H), 7.08–7.42 (m, 8 H), 7.65–7.76 (m, 2 H), 7.81 (s, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 28.04 (3 CH_3), 31.41 (CH_2), 43.17 (CH_2), 48.05 (CH_2), 52.56 (CH), 60.67 (CH), 67.69 (CH_2), 80.03 (C), 119.00 (CH), 125.65 (2 CH), 128.00 (2 CH), 128.09 (CH), 128.22 (CH), 128.54 (2 CH), 128.76 (2 CH), 130.41 (C), 136.10 (C), 147.44 (C), 154.84 (C), 155.05 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3359 (s), 3286 (s), 2978 (s), 2936 (m), 1708 (s), 1689 (s), 1521 (s), 1368 (m), 1308 (m), 1249 (m), 1165 (s), 1024 (m), 765 (s), 695 (s) cm^{-1}. HRMS (ESI): calcd. 500.2274 (for $C_{26}H_{31}N_5NaO_4$); found 500.2260 [M + Na$^+$]. $C_{26}H_{31}N_5O_4$ (477.56).

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-[4-(2-pyridyl)-1,2,3-triazol-1-yl]piperidine (3g):** Following the general procedure A with azidocarbamate **5a/5b** (4.60 g, 12.3 mmol) and 2-ethynylpyridine (1.52 g, 14.7 mmol) yielded the triazole **3g** (4.03 g, 8.27 mmol, 67%, R_f = 0.31, EA), m.p. 165 °C, together with its regioisomer **6g** (0.55 g, 1.13 mmol, 9%, R_f = 0.42, EA), m.p. 193 °C, both as colorless solids. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (s, 9 H), 2.12–2.31 (m, 2 H), 2.93–3.18 (m, 2 H), 3.76–3.92 (m, 1 H), 4.20–4.48 (m, 2 H), 4.65–4.78 (m, 1 H), 4.77–4.96 (m, 1 H), 5.10–5.29 (m, 2 H), 7.21–7.25 (m, 1 H), 7.31–7.41 (m, 5 H), 7.77 (t, J = 7.7 Hz, 1 H), 8.13 (d, J = 7.6 Hz, 1 H), 8.21 (s, 1 H), 8.58 (d, J = 4.4 Hz, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 28.02 (3 CH_3), 31.12 (CH_2), 42.63 (CH_2), 47.20 (CH_2), 52.01 (CH), 61.35 (CH), 67.53 (CH_2), 79.87 (C), 120.03 (CH), 121.25 (CH), 122.71 (CH), 127.89 (2 CH), 128.08 (CH), 128.47 (2 CH), 136.27 (C), 136.68 (CH), 148.21 (C), 149.35 (CH), 150.08 (C), 154.93 (2 C) ppm. IR (ATR): $\tilde{\nu}$ = 3354 (w), 3258 (w), 2984 (w), 2941 (w), 2361 (w), 1711 (m), 1697 (s), 1517 (m), 1421 (m), 1313 (m), 1231 (s), 1182 (m), 1163 (s), 773 (m) cm^{-1}. MS (ESI): m/z (%) = 501 (15) [M + Na$^+$], 444 (100), 401 (25). $C_{25}H_{30}N_6O_4$ (478.54): C 62.75, H 6.32, N 17.56; found C 63.06, H 6.79, N 17.90.

***trans*-1-(Benzyloxycarbonyl)-4-[(*tert*-butyloxycarbonyl)amino]-3-[4-(2-pyridyl)-1,2,3-triazol-1-yl]piperidine (6g):** ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.25 (s, 9 H), 1.64–1.85 (m, 2 H), 2.07–2.20 (m, 1 H), 2.92–3.09 (m, 1 H), 3.29–3.45 (m, 1 H), 4.00–4.11 (m, 1 H), 4.18–4.45 (m, 1 H), 4.47–4.77 (m, 2 H), 5.03–5.23 (m, 2 H), 7.20–7.25 (m, 1 H), 7.28–7.41 (m, 5 H), 7.77 (t, J = 7.7 Hz, 1 H), 8.14 (d, J = 7.8 Hz, 1 H), 8.22 (s, 1 H), 8.57 (d, J = 4.4 Hz, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 27.97 (3 CH_3), 31.27 (CH_2), 43.12 (CH_2), 47.61 (CH_2), 52.75 (CH), 60.79 (CH), 67.59 (CH_2), 79.77 (C), 120.05 (CH), 121.90 (CH), 122.68 (CH), 127.91 (2 CH), 128.12 (CH), 128.46 (2 CH), 136.05 (C), 136.69 (CH), 147.93 (C), 149.27 (CH), 150.03 (C), 154.77 (C), 154.91 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3347 (w), 2980 (w), 2938 (w), 1696 (s), 1682 (s), 1312 (m), 1224 (m), 1158 (m), 1132 (m) cm^{-1}. HRMS (ESI): calcd. 479.2407 (for $C_{25}H_{31}N_6O_4$); found 479.2404 [M + H$^+$]. $C_{25}H_{30}N_6O_4$ (478.54).

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-[4-(3-pyridyl)-1,2,3-triazol-1-yl]piperidine (3h):** Following the general procedure A with azidocarbamate **5a/5b** (6.50 g, 17.3 mmol) and 3-ethynylpyridine (4.25 g, 41.2 mmol) yielded the triazole **3h** (5.64 g, 11.6 mmol, 67%, R_f = 0.18, MeOH) as a colorless solid, m.p. 177 °C. In this case no regioisomer **6h** could be isolated. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.29 (s, 9 H), 2.08–2.24 (m, 1 H), 2.24–2.34 (m, 1 H), 2.95–3.18 (m, 2 H), 3.88–3.98 (m, 1 H), 4.24–4.53 (m, 2 H), 4.63–4.95 (m, 2 H), 5.07–5.29 (m, 2 H), 7.31–7.42 (m, 6 H), 7.96 (s, 1 H), 8.16 (d, J = 7.7 Hz, 1 H), 8.58 (d, J = 4.2 Hz, 1 H), 9.00 (s, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 28.05 (3 CH_3), 31.45 (CH_2), 42.63 (CH_2), 47.30 (CH_2), 51.71 (CH), 61.81 (CH), 67.66 (CH_2), 80.20 (C), 119.17 (CH), 123.72 (CH), 126.59 (C), 128.01 (2 CH), 128.22 (CH), 128.55 (2 CH), 132.89 (CH), 136.17 (C), 144.60 (C), 146.94 (CH), 149.22 (CH), 154.96 (C), 155.08 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3368 (w), 2975 (w), 2932 (w), 2872 (w), 2361 (w), 2324 (w), 2164 (w), 1701 (s), 1684 (s), 1517 (m), 1315 (m), 1224 (s), 1164 (s), 977 (m), 726 (m), 707 (m), 694 (m) cm^{-1}. HRMS (ESI): calcd. 501.2226 (for $C_{25}H_{30}N_6NaO_4$); found 501.2225 [M + Na$^+$]. $C_{25}H_{30}N_6O_4$ (478.55).

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-[4-(1-methylimidazol-5-yl)-1,2,3-triazol-1-yl]piperidine (3i):** Following the general procedure with azidocarbamate **5a/5b** (8.00 g, 21.3 mmol) and 5-ethynyl-1-methyl-1-imidazole (2.71 g, 25.6 mmol) yielded the triazole **3i** (7.55 g, 15.7 mmol, 74%, R_f = 0.21, EA/MeOH, 10:1) as a colorless solid, m.p. 158 °C. The regioisomer **6i** could not be isolated. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.29 (s, 9/2 H), 1.32 (s, 9/2 H), 1.69–1.88 (m, 1 H), 2.07–2.20 (m, 1 H), 2.22–2.32 (m, 1 H), 2.94–3.18 (m, 2 H), 3.90 (s, 3 H), 4.22–4.49 (m, 2 H), 4.76–4.91 (m, 2 H), 4.08–5.29 (m, 2 H), 7.20–7.34 (m, 1 H), 7.27 (s, 1 H), 7.32–7.37 (m, 1 H), 7.37–7.41 (m, 3 H), 7.50 (s, 1 H), 7.77 (s, 1 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 27.98 (3 CH_3), 31.35 (CH_2), 33.24 (CH_3), 42.50 (CH_2), 47.19 (CH_2), 51.45 (CH), 61.60 (CH), 67.49 (CH_2), 79.81 (C), 119.88 (CH), 123.24 (C), 127.85 (2 CH), 128.07 (CH), 128.43 (2 CH), 128.45 (CH), 136.06 (C), 138.09 (C), 139.28 (CH), 154.82 (C), 155.01 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3353 (w), 2977 (w), 2936 (w), 2322 (w), 1719 (s), 1692 (m), 1677 (s), 1525 (s), 1464 (m), 1449 (m), 1442 (m), 1417 (m), 1392 (m), 1369 (m), 1312 (s), 1264 (m), 1251 (m), 1221 (s), 1189 (m), 1160 (s), 1125 (m), 1113 (m), 1081 (m), 1066 (m), 1045 (m), 1021 (m), 996 (m), 971 (m), 910 (m), 867 (m), 796 (m), 779 (m), 765 (m), 733 (s), 698 (m), 658 (m), 638 (m) cm^{-1}. HRMS (ESI): calcd. 482.2516 (for $C_{24}H_{32}N_7O_4$); found 482.2509 [M + H$^+$]. $C_{24}H_{31}N_7O_4$ (481.55).

***trans*-1-(Benzyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-[4-(2-thienyl)-1,2,3-triazol-1-yl]piperidine (3j):** Following the general procedure with azidocarbamate **5a/5b** (4.50 g, 12.0 mmol) and 2-ethynylthiophene (1.54 g, 14.2 mmol) yielded the triazole **3j** (1.65 g, 3.40 mmol, 28%, R_f = 0.21, hexane/EA, 1:1), m.p. 174 °C, together with its regioisomer **6j** (0.52 g, 1.08 mmol, 9%, R_f = 0.28 hexane/EA, 1:1), m.p. 199 °C, both as colorless solids. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.32 (s, 9 H), 2.06–2.22 (m, 1 H), 2.22–2.31 (m, 1 H), 2.94–3.18 (m, 2 H), 3.87 (ddd, J = 4.6, J = 10.0, J = 18.6 Hz, 1 H), 4.22–4.47 (m, 1 H), 4.60–4.74 (m, 1 H), 4.74–4.90 (m, 1 H), 5.09–5.27 (m, 2 H), 7.06–7.09 (m, 1 H), 7.28–7.31 (m, 1 H), 7.31–

7.42 (m, 6 H), 7.76 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 28.09 (3 CH_3), 31.34 (CH_2), 42.64 (CH_2), 47.31 (CH_2), 51.82 (CH), 61.31 (CH), 67.64 (CH_2), 80.26 (C), 118.18 (CH), 124.17 (CH), 125.03 (CH), 127.57 (2 CH), 128.01 (CH), 128.19 (CH), 128.55 (2 CH), 132.79 (C), 136.28 (C), 142.80 (C), 155.00 (2 C) ppm. IR (ATR): $\tilde{\nu}$ = 3266 (w), 2983 (w), 2936 (w), 1702 (s), 1528 (m), 1433 (m), 1313 (m), 1272 (m), 1228 (m), 1164 (m), 1072 (m), 724 (m), 699 (m) cm^{-1}. HRMS (ESI): calcd. 506.1838 (for $C_{24}H_{29}N_5NaO_4S$); found 506.1835 [M + Na^+]. $C_{24}H_{29}N_5O_4S$ (483.59).

***trans*-1-(Benzyloxycarbonyl)-4-[(*tert*-butyloxycarbonyl)amino]-3-[4-(2-thienyl)-1,2,3-triazol-1-yl]piperidine (6j):** ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.28 (s, 9 H), 1.72–1.87 (m, 1 H), 2.07–2.17 (m, 1 H), 2.89–3.10 (m, 1 H), 3.21–3.34 (m, 1 H), 3.99–4.10 (m, 1 H), 4.20–4.46 (m, 1 H), 4.49–4.81 (m, 2 H), 5.04–5.26 (m, 2 H), 7.06 (dd, *J* = 3.7, *J* = 4.9 Hz, 1 H), 7.28–7.30 (m, 1 H), 7.31–7.39 (m, 6 H), 7.77 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 28.01 (3 CH_3), 31.29 (CH_2), 43.09 (CH_2), 47.94 (CH_2), 52.43 (CH), 56.41 (CH), 67.66 (CH_2), 79.80 (C), 118.64 (CH), 124.13 (CH), 124.98 (CH), 127.52 (CH), 127.99 (2 CH), 128.20 (CH), 128.51 (2 CH), 132.64 (C), 136.02 (C), 142.49 (C), 154.77 (C), 155.04 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3266 (w), 3110 (w), 2975 (w), 2929 (w), 1697 (s), 1435 (m), 1313 (m), 1225 (m), 1162 (m), 1132 (m), 700 (m) cm^{-1}. HRMS (ESI): calcd. 506.1838 (for $C_{24}H_{29}N_5NaO_4S$); found 506.1831 [M + Na^+]. $C_{24}H_{29}N_5O_4S$ (483.59): C 59.92, H 6.04, N 14.48, S 6.63; found C 59.92, H 6.28, N 14.35, S 6.37.

General Procedure B (Hydrogenation of Triazoles 3): Triazole **3** (ca. 5 g, ca. 10 mmol) was dissolved in warm (ca. 50 °C) *i*PrOH (150 mL), then Pd/C (ca. 1 g, 20% w/w Pd) was added and the suspension shaken under an atmosphere of hydrogen (3 atm) at 70 °C for 8 h. After cooling to ambient temperature, the catalyst was separated by filtration. The solvents were evaporated and the residue chromatographed on SiO_2 (MeOH, for **7h**: EtOH/Et_3N, 8:1) to yield the piperidines **7** as colorless solids.

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-(4-methyl-1,2,3-triazol-1-yl)piperidine (7a):** Following the general procedure B with triazole **3a** (9.80 g, 23.6 mmol) yielded the piperidine **7a** (5.80 g, 20.7 mmol, 88%, R_f = 0.41, MeOH) as a colorless solid, m.p. 185 °C. ^1H NMR (CD_3OD, 500 MHz): δ = 1.28 (s, 9 H), 2.08–2.15 (m, 2 H), 2.28 (s, 3 H), 2.54 (dd, *J* = 11.4, *J* = 12.5 Hz, 1 H), 2.63–2.73 (m, 1 H), 3.09–3.21 (m, 2 H), 3.30 (dt, *J* = 1.6, *J* = 3.3 Hz, 1 H), 3.85 (dt, *J* = 4.7, *J* = 10.9 Hz, 1 H), 4.38–4.62 (m, 1 H), 7.67 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ = 10.56 (CH_3), 28.60 (3 CH_3), 34.05 (CH_2), 45.66 (CH_2), 51.41 (CH_2), 53.76 (CH), 64.04 (CH), 80.11 (C), 122.46 (CH), 143.65 (C), 157.30 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3357 (m), 3291 (w), 3206 (w), 3146 (w), 2975 (w), 2939 (m), 2862 (w), 2361 (w), 2323 (w), 1984 (w), 1688 (s), 1308 (s), 1251 (s), 1229 (m), 1174 (s), 1162 (m), 1149 (s), 896 (m), 651 (m) cm^{-1}. HRMS (ESI): calcd. 282.1930 (for $C_{13}H_{24}N_5O_2$); found 282.1924 [M + H^+]. $C_{13}H_{23}N_5O_2$ (281.36): C 55.50, H 8.24, N 24.89; found C 55.59, H 8.56, N 24.59.

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-(4-cyclohexyl-1,2,3-triazol-1-yl)piperidine (7b):** Following the general procedure B with triazole **3b** (2.81 g, 5.81 mmol) yielded the piperidine **7b** (1.71 g, 4.89 mmol, 84%, R_f = 0.40, MeOH) as a colorless solid, m.p. 195 °C. ^1H NMR (CD_3OD, 500 MHz): δ = 1.27–1.33 (m, 10 H), 1.36–1.49 (m, 4 H), 1.71–1.78 (m, 1 H), 1.77–1.86 (m, 2 H), 1.97–2.06 (m, 2 H), 2.07–2.16 (m, 2 H), 2.54 (t, *J* = 11.9 Hz, 1 H), 2.62–2.76 (m, 2 H), 3.11–3.20 (m, 2 H), 3.87 (dt, *J* = 4.5, *J* = 10.9 Hz, 1 H), 4.44 (dt, *J* = 4.5, *J* = 10.8 Hz, 1 H), 7.71 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ = 27.12 (CH_2), 27.19 (2 CH_2), 28.64 (3 CH_3), 34.07 (CH_2), 34.16 (CH_2), 34.19 (CH_2), 36.51 (CH), 45.63 (CH_2), 51.45 (CH_2), 53.55 (CH), 64.03 (CH), 80.08 (C), 120.53 (CH), 153.95 (C), 157.27 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3377 (w), 3216 (w), 2977 (w), 2924 (m), 2853 (w), 1689 (s), 1518 (s), 1366 (m), 1308 (m), 1249 (m), 1227 (m), 1165 (s), 1055 (m), 1020 (m), 951 (m), 869 (m) cm^{-1}. HRMS (ESI): calcd. 372.2375 (for $C_{18}H_{31}N_5NaO_2$); found 372.2381 [M + Na^+]. $C_{18}H_{31}N_5O_2$ (349.47).

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-[4-(1-hydroxyethyl)-1,2,3-triazol-1-yl]piperidine (7c):** Following the general procedure B with triazole **3c** (7.20 g, 16.2 mmol) yielded the piperidine **7c** (4.06 g, 14.0 mmol, 81%, R_f = 0.37, MeOH), m.p. 194 °C, as a colorless solid. The compound is obtained as a mixture of two diastereoisomers, which lead to partly doubled signal sets in the NMR spectra. ^1H NMR (CD_3OD, 500 MHz): δ = 1.29 (s, 9 H), 1.50 (d, *J* = 6.5 Hz, 3/2 H), 1.51 (d, *J* = 6.5 Hz, 3/2 H), 2.09–2.16 (m, 2 H), 2.54 (t, *J* = 11.9 Hz, 1 H), 2.62–2.74 (m, 1 H), 3.10–3.22 (m, 2 H), 3.87 (ddd, *J* = 5.3, *J* = 10.7, *J* = 15.9 Hz, 1 H), 4.48 (dd, *J* = 9.6, *J* = 16.7 Hz, 1 H), 4.94 (q, *J* = 6.5 Hz, 1 H), 7.84 (s, 1/2 H), 7.85 (s, 1/2 H) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ = 23.89 (1/2 CH_3), 23.80 (1/2 CH_3), 28.66 (3 CH_3), 34.17 (CH_2), 45.62 (CH_2), 51.39 (CH_2), 53.64 (1/2 CH), 53.73 (1/2 CH), 63.64 (1/2 CH), 63.72 (1/2 CH), 63.92 (1/2 CH), 64.04 (1/2 CH), 80.17 (C), 121.30 (1/2 CH), 121.42 (1/2 CH), 153.29 (1/2 C), 153.45 (1/2 C), 157.28 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3358 (m), 3276 (w), 3148 (w), 2980 (m), 2945 (m), 2866 (w), 2734 (w), 2164 (w), 2051 (w), 1981 (w), 1689 (s), 1524 (s), 1308 (m), 1232 (m), 1165 (m), 1022 (m), 868 (m) cm^{-1}. HRMS (ESI): calcd. 312.2036 (for $C_{14}H_{26}N_5O_3$); found 312.2043 [M + H^+]. $C_{14}H_{25}N_5O_3$ (311.38).

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-[4-(1-hydroxycyclohexyl)-1,2,3-triazol-1-yl]piperidine (7d):** Following the general procedure B with triazole **3d** (1.95 g, 3.80 mmol) yielded the piperidine **7d** (1.10 g, 3.01 mmol, 79%, R_f = 0.34, MeOH) as a colorless solid, m.p. 193 °C. ^1H NMR (CD_3OD, 500 MHz): δ = 1.29 (s, 9 H), 1.35–1.42 (m, 1 H), 1.44–1.55 (m, 2 H), 1.55–1.64 (m, 1 H), 1.69–1.84 (m, 4 H), 1.94–2.05 (m, 2 H), 2.07–2.15 (m, 2 H), 2.54 (t, *J* = 11.9 Hz, 1 H), 2.62–2.72 (m, 1 H), 3.09–3.21 (m, 2 H), 3.87 (dd, *J* = 4.5, *J* = 10.9 Hz, 1 H), 4.43–4.51 (m, 1 H), 7.84 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ = 23.14 (2 CH_2), 26.61 (2 CH_2), 28.68 (3 CH_3), 34.24 (CH_2), 38.91 (1/2 CH_2), 39.01 (1/2 CH_2), 45.63 (CH_2), 51.46 (CH_2), 53.63 (CH), 63.95 (CH), 70.30 (C), 80.20 (C), 121.04 (CH), 156.54 (C), 157.34 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3404 (w), 3365 (w), 3237 (w), 3059 (w), 2932 (m), 2860 (w), 2658 (w), 2367 (w), 2346 (w), 1982 (w), 1710 (s), 1514 (m), 1504 (m), 1305 (m), 1255 (m), 1231 (m), 1163 (s), 1059 (m), 1024 (m), 954 (m), 890 (m), 874 (m) cm^{-1}. HRMS (ESI): calcd. 388.2326 (for $C_{18}H_{31}N_5NaO_3$); found 388.2316 [M + Na^+]. $C_{18}H_{31}N_5O_3$ (365.47).

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-[4-(1-hydroxy-1-phenylmethyl)-1,2,3-triazol-1-yl]piperidine (7e):** Following the general procedure B with triazole **3e** (5.50 g, 10.8 mmol) yielded the piperidine **7e** (3.30 g, 8.84 mmol, 81%, R_f = 0.41, MeOH) as a colorless solid, m.p. 191 °C. ^1H and ^{13}C NMR showed partly doubled signal sets. ^1H NMR (CD_3OD, 500 MHz): δ = 1.25 (s, 9/2 H) 1.26 (s, 9/2 H), 2.06–2.19 (m, 2 H), 2.48–2.57 (m, 1 H), 2.60–2.73 (m, 1 H), 3.06–3.19 (m, 2 H), 3.85 (dt, *J* = 4.3, *J* = 10.7 Hz, 1 H), 4.44–4.53 (m, 1 H), 5.88 (s, 1 H), 7.21–7.29 (m, 1 H), 7.29–7.36 (m, 2 H), 7.38–7.47 (m, 2 H), 7.76 (s, 1/2 H), 7.79 (s, 1/2 H) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ = 28.48 (3/2 CH_3), 28.69 (3/2 CH_3), 33.99 (1/2 CH_2), 34.08 (1/2 CH_2), 45.12 (CH_2), 51.28 (CH_2), 53.49 (1/2 CH), 53.67 (1/2 CH), 63.67 (1/2 CH), 63.89 (1/2 CH), 70.07 (1/2 CH), 70.23 (1/2 CH), 80.22 (C), 122.16 (1/2 CH), 122.60 (1/2 CH), 127.72 (CH), 127.84 (CH), 128.69 (CH), 129.42 (2 CH), 144.23 (1/2 C), 144.28 (1/2 C), 152.19 (1/2 C), 152.41 (1/2 C), 157.28 (C)

ppm. IR (ATR): $\tilde{\nu}$ = 3292 (w), 3136 (w), 2970 (w), 2865 (w), 2839 (w), 2702 (w), 2659 (w), 2358 (w) 2326 (w), 2164 (w), 2111 (w), 1981 (w), 1738 (m), 1687 (s), 1521 (m), 1366 (m), 1230 (m), 1164 (m), 1040 (m), 1021 (m), 718 (m) cm^{-1}. HRMS (ESI): calcd. 374.2192 (for $C_{19}H_{28}N_5O_3$); found 374.2184 [M + H^+]. $C_{19}H_{27}N_5O_3$ (373.46): C 61.11, H 7.29, N 18.75; found 60.92, H 7.73, N 18.48.

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-(4-phenyl-1,2,3-triazol-1-yl)piperidine (7f):** Following the general procedure B with triazole **3f** (2.22 g, 4.65 mmol) yielded the piperidine **7f** (1.36 g, 3.95 mmol, 85%, R_f = 0.35, MeOH) as a colorless solid, m.p. 216 °C. ^{1}H NMR (CD_3OD, 500 MHz): δ = 1.15 (s, 9 H), 2.10–2.18 (m, 2 H), 2.52 (t, J = 12.0 Hz, 1 H), 2.60–2.70 (m, 1 H), 3.07–3.17 (m, 2 H), 3.87 (dt, J = 4.1, J = 10.7 Hz, 1 H), 4.46 (dt, J = 7.4, J = 9.8 Hz, 1 H), 7.23–7.30 (m, 1 H), 7.32–7.39 (m, 2 H), 7.70–7.78 (m, 2 H), 8.22–8.30 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ = 28.52 (3 CH_3), 33.97 (CH_2), 45.66 (CH_2), 51.37 (CH_2), 53.79 (CH), 64.51 (CH), 80.27 (C), 121.28 (CH), 126.65 (2 CH), 129.29 (CH), 129.95 (2 CH), 131.83 (C), 148.44 (C), 157.42 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3364 (w), 2980 (w), 2936 (w), 1685 (s), 1517 (s), 1366 (m), 1247 (m), 1248 (m), 1161 (s), 1050 (m), 1023 (m), 764 (s), 694 (s) cm^{-1}. HRMS (ESI): calcd. 344.2087 (for $C_{18}H_{26}N_5O_2$); found 344.2088 [M + H^+]. $C_{18}H_{25}N_5O_2$ (343.42).

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-[4-(2-pyridyl)-1,2,3-triazol-1-yl]piperidine (7 g):** Following the general procedure B with triazole **3g** (4.03 g, 8.27 mmol) yielded the piperidine **7g** (1.60 g, 4.59 mmol, 56%, R_f = 0.23, MeOH) as a colorless solid, m.p. 218 °C. ^{1}H NMR showed a partly doubled signal set. ^{1}H NMR (CD_3OD, 500 MHz): δ = 1.19 (s, 9 H), 2.18–2.26 (m, 1 H), 2.27 (dd, J = 3.5, J = 12.2 Hz, 1/2 H), 2.32 (dd, J = 3.5, J = 12.2 Hz, 1/2 H), 2.58 (t, J = 11.9 Hz, 1 H), 2.72 (t, J = 11.9 Hz, 1 H), 3.15–3.23 (m, 2 H), 3.92 (dt, J = 10.6, J = 4.2 Hz, 1 H), 4.49–4.58 (m, 1 H), 7.30–7.45 (m, 1 H), 7.90 (t, J = 7.5 Hz, 1 H), 8.06 (s, 1 H), 8.38–8.48 (m, 1 H), 8.50–8.66 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ = 28.52 (3 CH_3), 33.79 (CH_2), 45.66 (CH_2), 51.32 (CH_2), 54.01 (CH), 64.60 (CH), 80.19 (C), 121.40 (CH), 123.63 (CH), 124.39 (CH), 138.80 (CH), 148.20 (C), 150.44 (CH), 151.18 (C), 157.32 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3282 (w, br) 3240 (w), 3139 (w), 3062 (w), 2971 (w), 2932 (w), 2861 (w), 2364 (w) 2325 (w), 2051 (w), 2982 (w), 2694 (s), 1532 (m), 1365 (m), 1301 (s), 1253 (m), 1230 (s), 1166 (s), 1052 (s), 997 (m), 871 (m), 784 (s), 742 (s), 710 (m), 680 (m) cm^{-1}. HRMS (ESI): calcd. 345.2039 (for $C_{17}H_{25}N_6O_2$); found 345.2031 [M + H^+]. $C_{17}H_{24}N_6O_2$ (344.41).

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-[4-(3-pyridyl)-1,2,3-triazol-1-yl]piperidine (7h):** Following the general procedure B with triazole **3h** (2.10 g, 4.31 mmol) yielded the piperidine **7h** (0.38 g, 1.10 mmol, 26%, R_f = 0.28, EtOH/NEt_3, 8:1) as a colorless solid, m.p. 206 °C. ^{1}H NMR (CD_3OD, 500 MHz): δ = 1.21 (s, 9 H), 2.18–2.35 (m, 2 H), 2.65 (t, J = 11.4 Hz, 1 H), 2.70–2.84 (m, 1 H), 3.16–3.29 (m, 2 H), 3.90–4.09 (m, 1 H), 4.44–4.65 (m, 1 H), 7.47–7.56 (m, 1 H), 8.26 (d, J = 7.1 Hz, 1 H), 8.48–8.58 (m, 2 H), 8.97–9.05 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ = 28.54 (3 CH_3), 33.68 (CH_2), 45.59 (CH_2), 51.15 (CH_2), 53.75 (CH), 64.63 (CH), 80.26 (C), 122.31 (CH), 125.61 (CH), 128.82 (C), 134.83 (CH), 144.93 (C), 147.22 (CH), 149.52 (CH), 157.35 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3356 (w), 3238 (w), 2932 (w), 2366 (w), 2345 (w), 1982 (w), 1681 (m), 1522 (m), 1367 (m), 1308 (m), 1253 (m), 1230 (m), 1162 (s), 1051 (m), 1023 (m), 949 (m), 864 (m), 798 (m), 778 (m), 710 (m), 621 (m), 610 (m) cm^{-1}. HRMS (ESI): calcd. 367.1858 (for $C_{17}H_{24}N_6NaO_2$); found 367.1850 [M + Na^+]. $C_{17}H_{24}N_6O_2$ (344.41).

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-[4-(1-methylimidazol-5-yl)-1,2,3-triazol-1-yl]piperidine (7i):** Following the general procedure B with triazole **3i** (7.55 g, 15.8 mmol) yielded the piperidine **7i** (4.48 g, 12.9 mmol, 83%, R_f = 0.11, MeOH) as a colorless solid, m.p. 88 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.15 (s, 9 H), 2.07–2.15 (m, 2 H), 2.48 (t, J = 12.0 Hz, 1 H), 2.56–2.66 (m, 1 H), 2.99–3.15 (m, 2 H), 3.75 (s, 3 H), 3.82 (dt, J = 4.5, J = 10.9 Hz, 1 H), 4.40–4.47 (m, 1 H), 7.13 (s, 1 H), 7.61 (s, 1 H), 8.14 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 28.56 (3 CH_3), 33.60 (CH_2), 33.84 (CH_3), 45.62 (CH_2), 51.32 (CH_2), 53.77 (CH), 64.66 (CH), 80.19 (C), 122.66 (CH), 125.25 (C), 128.48 (CH), 138.31 (C), 140.76 (CH), 157.34 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3354 (w), 3205 (w), 3085 (w), 2980 (w), 2943 (w), 2859 (w), 1684 (s), 1519 (s), 1367 (m), 1309 (m), 1252 (m), 1229 (m), 1161 (m), 1117 (m), 1022 (m), 950 (m), 861 (m), 660 (m), 644 (m), 613 (m) cm^{-1}. HRMS (ESI): calcd. 348.2148 (for $C_{16}H_{26}N_7O_2$); found 348.2141 [M + H^+]. $C_{16}H_{25}N_7O_2$ (347.42).

***trans*-3-[(*tert*-Butyloxycarbonyl)amino]-4-[4-(2-thienyl)-1,2,3-triazol-1-yl]piperidine (7j):** A solution of triazole **3j** (4.20 g, 8.70 mmol) and KOH (1.95 g, 34.8 mmol) in 150 mL *i*PrOH and 15 mL H_2O was stirred at 80 °C for 16 h. Subsequently, the solvent was removed in vacuo. The colorless residue was washed with water until the pH was neutral (ca. 3 × 150 mL). It was then purified by chromatography (R_f = 0.38, MeOH) to yield triazole **7j** (2.10 g, 5.72 mmol, 66%) as a colorless solid, m.p. 198 °C. ^{1}H NMR (CD_3OD, 500 MHz): δ = 1.23 (s, 9 H), 2.16–2.25 (m, 2 H), 2.59 (t, J = 11.8 Hz, 1 H), 2.64–2.81 (m, 1 H), 3.09–3.24 (m, 2 H), 3.91 (dt, J = 4.1, J = 10.7 Hz, 1 H), 4.47–4.58 (m, 1 H), 7.06–7.11 (m, 1 H), 7.36–7.42 (m, 2 H), 8.18 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (CD_3OD, 125 MHz): δ = 28.55 (3 CH_3), 33.73 (CH_2), 45.50 (CH_2), 51.23 (CH_2), 53.72 (CH), 64.42 (CH), 80.32 (C), 120.83 (CH), 125.44 (CH), 126.19 (CH), 128.67 (CH), 133.85 (C), 143.48 (C), 154.37 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3355 (w), 2979 (w), 2935 (w), 1683 (s), 1520 (m), 1366 (m), 1307 (m), 1161 (s), 1048 (m), 846 (m), 792 (m), 777 (m), 697 (m), 665 (w), 646 (m) cm^{-1}. HRMS (ESI): calcd. 372.1470 (for $C_{16}H_{23}N_5NaO_2S$); found 372.1478 [M + Na^+]. $C_{16}H_{23}N_5O_2S$ (349.45).

***trans*-1-(4-Bromophenylsulfonyl)-3-[(*tert*-butyloxycarbonyl)amino]-4-(4-methyl-1,2,3-triazol-1-yl)piperidine (8):** A solution of triazole **7a** (100 mg, 0.36 mmol), *p*-bromobenzenesulfonyl chloride (91 mg, 0.36 mmol) and DMAP (10 mg, 0.1 mmol) in a mixture of CH_2Cl_2 (4 mL) and pyridine (0.2 mL) was stirred at room temperature for 48 h. Subsequently, water (10 mL) was added and the mixture was further stirred at room temperature for 10 min. The layers were then separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated to furnish the sulfonyl amide **8** as a colorless solid (90 mg, 0.18 mmol, 50%), m.p. 332 °C. Single crystals were obtained from $CDCl_3$. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 2.21–2.35 (m, 2 H), 2.31 (s, 3 H), 2.76–2.85 (m, 1 H), 2.85–2.95 (m, 1 H), 3.71–3.82 (m, 2 H), 3.98 (ddd, J = 4.0, J = 8.4, J = 16.8 Hz, 1 H), 4.52–4.61 (m, 1 H), 4.85–4.87 (m, 1 H), 7.35 (s, 1 H), 7.62–7.73 (m, 4 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 9.62 (CH_3), 27.36 (3 CH_3), 30.69 (CH_2), 44.41 (CH_2), 48.71 (CH_2), 50.63 (CH), 60.35 (CH), 79.41 (C), 120.20 (CH), 127.89 (C), 128.60 (2 CH), 132.22 (2 CH), 134.63 (C), 142.58 (C), 155.13 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3151 (w), 3095 (w), 2981 (w), 2946 (w), 2854 (w), 2356 (w), 2164 (w), 1691 (m), 1575 (w), 1557 (w), 1432 (m), 1408 (m), 1389 (m), 1363 (m), 1350 (m), 1309 (m), 1291 (m), 1166 (s), 1091 (m), 1069 (m), 1046 (m), 1033 (m), 1011 (m), 955 (m), 907 (m), 835 (m), 826 (m), 736 (s) cm^{-1}. HRMS (CI): calcd. 500.0967 (for $C_{19}H_{27}BrN_5O_4S$); found 500.0979 [M + H^+]. $C_{19}H_{26}BrN_5O_4S$ (500.41).

***trans*-4-Amino-1-(benzyloxycarbonyl)-3-(4-methyl-1,2,3-triazol-1-yl)piperidine (9):** TFA (3.6 mL) was added to a solution of triazole

6a (0.45 g, 1.08 mmol) in CH_2Cl_2 (18 mL) and the resulting mixture was stirred at 23 °C for 2 h. Subsequently, a saturated aqueous solution of $NaHCO_3$ was added until pH was 7–8 (ca. 6 mL). The layers were then separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to yield the title compound **9** (0.34 g, 1.07 mmol, 99%) as a colorless resin, which needed no further purification. ^{1}H NMR showed a partly doubled signal set. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.24–1.38 (m, 2 H), 1.37–1.50 (m, 1 H), 1.90–1.94 (m, 1/2 H), 1.94–1.98 (m, 1/2 H), 2.28 (s, 3 H), 2.82–3.00 (m, 1 H), 3.10–3.26 (m, 1 H), 3.31–3.56 (m, 1 H), 3.92 (dt, J = 4.5, J = 10.5 Hz, 1 H), 4.09–4.28 (m, 1 H), 4.28–4.45 (m, 1 H), 5.01–5.12 (m, 2 H), 7.21–7.34 (m, 6 H) ppm. ^{13}C{1H} NMR ($CDCl_3$, 125 MHz): δ = 10.76 (CH_3), 33.26 (CH_2), 43.01 (CH_2), 47.48 (CH_2), 52.84 (CH), 64.60 (CH), 67.58 (CH_2), 121.69 (CH), 127.98 (2 CH), 128.20 (CH), 128.54 (2 CH), 136.27 (CH), 143.09 (C), 154.95 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3368 (w), 3306 (w), 2944 (w), 2866 (w), 1693 (vs), 1470 (m), 1429 (s), 1295 (m), 1216 (s), 1187 (m), 1108 (m), 1048 (m), 968 (m), 799 (m), 763 (m), 732 (s), 698 (s) cm^{-1}. HRMS (ESI): calcd. 338.1593 (for $C_{16}H_{21}N_5NaO_2$); found 338.1595 [M + Na$^+$]. $C_{16}H_{21}N_5O_2$ (315.38).

***trans*-1-(Benzyloxycarbonyl)-4-[(4-bromophenyl)sulfonylamino]-3-(4-methyl-1,2,3-triazol-1-yl)piperidine (10):** Triazole **9** (0.28 g, 0.89 mmol), *p*-bromobenzenesulfonyl chloride (230 mg, 0.89 mmol) and DMAP (20 mg, 0.18 mmol) were stirred in a mixture of pyridine (5.6 mL) and CH_2Cl_2 (11 mL) at 23 °C for 16 h. Subsequently, water (5 mL) was added and the mixture was further stirred at 23 °C for 10 min. The layers were then separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, EA, R_f = 0.50) to yield title compound **10** (0.27 g, 0.51 mmol, 57%) as colorless crystals, m.p. 122 °C. Single crystals were obtained from MeOH. ^{1}H NMR showed a partly doubled signal set. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.61 (dd, J = 4.3, J = 12.5 Hz, 1/2 H), 1.66 (dd, J = 4.3, J = 12.5 Hz, 1/2 H), 1.98–2.02 (m, 1/2 H), 2.02–2.05 (m, 1/2 H), 2.14 (s, 3 H), 2.79–2.98 (m, 1 H), 3.15–3.31 (m, 1 H), 3.66–3.81 (m, 1 H), 4.08–4.23 (m, 1 H), 4.28–4.46 (m, 2 H), 4.94–4.15 (m, 2 H), 6.15–6.26 (m, 1 H), 7.09 (s, 1 H), 7.17–7.31 (m, 5 H), 7.34–7.38 (m, 2 H), 7.43–7.47 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 10.74 (CH_3), 32.86 (CH_2), 42.86 (CH_2), 47.63 (CH_2), 55.85 (CH), 59.97 (CH), 67.78 (CH_2), 122.02 (CH), 127.44 (C), 127.97 (2 CH), 128.00 (2 CH), 128.31 (CH), 128.58 (2 CH), 123.23 (2 CH), 135.95 (C), 139.79 (C), 143.11 (C), 154.84 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3087 (w), 3034 (w), 2920 (w), 2886 (w), 2850 (w), 1697 (s), 1474 (m), 1433 (m), 1338 (s), 1306 (m), 1240 (s), 1162 (m), 1138 (s), 1091 (m), 1067 (m), 762 (s), 740 (s), 707 (m), 678 (m), 609 (s) cm^{-1}. HRMS (EI, 70 eV): calcd. 533.0732 (for $C_{22}H_{24}BrN_5O_4S$); found 533.0719 [M$^+$]. $C_{22}H_{24}BrN_5O_4S$ (534.43).

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[11] CCDC-757872 (for **8**) and -757873 (for **10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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