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ORIGINAL PAPER

Synthesis and docking of novel piperidine renin inhibitors

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Abstract A series of 4-triazolyl-substituted piperidine derivatives were synthesized from *N*-Boc protected *trans*-4-ethynyl-3-hydroxypiperidine and tested as novel renin inhibitors. Piperidine derivatives containing a 1-substituted 1,2,3-triazol-5-yl substituent were found to be most active. Molecular docking experiments provide a rank order that is in agreement with experimental data. Furthermore, all compounds explore the S1 and the S3 subpockets through the piperidine substituents.

Keywords Alkyne · Triazole · Renin inhibitor · Molecular docking

Introduction

Renin is a highly selective aspartic protease that catalyzes the hydrolysis of angiotensinogen, a protein secreted from the liver, to the decapeptide angiotensin-I [1]. Angiotensin-I is further processed by the angiotensin-converting enzyme (ACE) to give the octapeptide angiotensin-II, a potent vasoconstrictor and the dominant signal peptide produced by the renin-angiotensin system (RAS). Renin catalyzes the rate-determining step in the formation of angiotensin-II and for several decades has been an established therapeutic target for drug development in relation to hypertension [1].

Renin inhibitors that were discovered early on were often found to exhibit poor oral absorption and low bioavailability because of their peptidic nature, and further development into non-peptide peptidomimetic drugs has been sought [2–4]. At the turn of the century, substituted piperidine derivatives were reported as a new class of renin inhibitors [5–8]. In later years, substituted piperidines have proven to be efficient scaffolds for the development of novel non-peptide aspartic protease inhibitors, particularly toward renin [9–11].

Previously, renin inhibitors based on piperidine derivatives bearing C-4-substituted 1,2,3-triazol-1-yl moieties have been reported [8]. Herein, we report the synthesis of a series of piperidine derivatives with N-substituted 1,2,3-triazol-4-yl or -5-yl substituents in the 4-position, evaluation of their biological activity and selectivity towards renin, and the development of a computational docking protocol to predict their activity.

Results and discussion

Chemistry

We have recently reported the regioselective ring opening of racemic oxirane **1** (Scheme 1) using the lithium acetylide of ethynyltrimethylsilane with addition of trimethylaluminium and activation of the epoxide using boron trifluoride-diethyl ether complex [12]. This reaction cleanly gave the 3-hydroxy-4-(trimethylsilylethynyl)piperidine derivative in 80 % yield. Subsequent removal of the TMS

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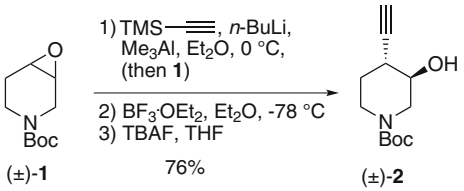


Scheme 1

group can either be carried out using TBAF in THF in 95 % yield (76 % combined yield from **1**) as previously reported [12] or by use of K_2CO_3 in methanol to give piperidine building block **2** in 92 % yield for the deprotection step.

We have now utilized this new piperidine building block for the preparation of a number of novel *trans*-3,4-disubstituted piperidine derivatives (Scheme 2). The terminal alkyne of piperidine (±)-**2** was converted into either 1,4-disubstituted 1,2,3-triazoles (±)-**3** (method A) or 1,5-disubstituted 1,2,3-triazoles (±)-**4** (method B) through copper and ruthenium catalysis, respectively. Either of these 4-triazolyl-substituted piperidines was further derivatized by conversion of the secondary alcohol at the piperidine 3-position into ether derivatives (method C) or ester derivatives (method D).

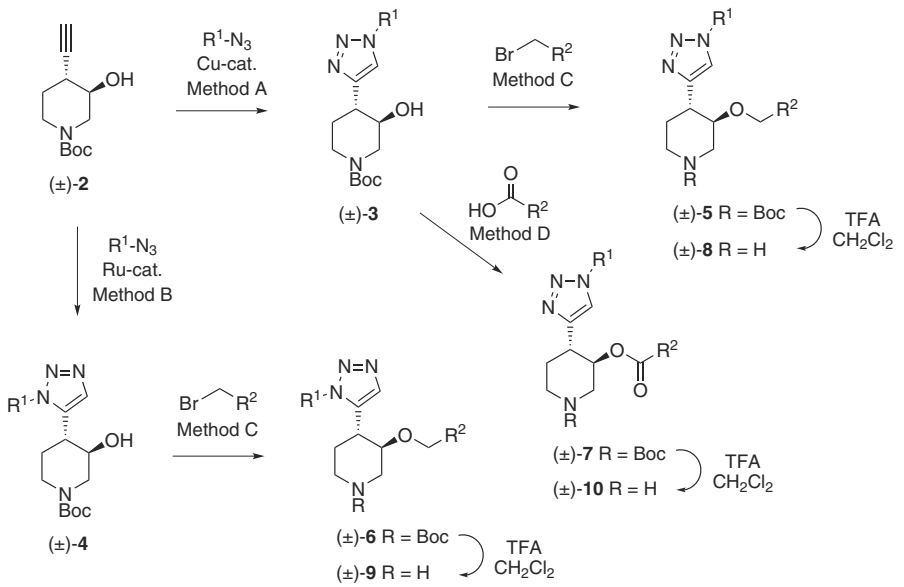
Finally, trifluoroacetic acid-mediated deprotection of the piperidine Boc-protecting group furnished 11 piperidine derivatives (Fig. 1). We were also interested in introducing an acetamide-substituted phenyl ring of the R^1 side chain of **9aa** (see Fig. 1), and toward this end two new azides were prepared (Scheme 3).

It turned out that reduction of the nitro group of **11** and **12** using stannous chloride in concentrated hydrochloric acid as described by Evans and Walker [13] gave a high degree of halogen exchange. Unfortunately, the chlorides were inseparable from the bromides. When the reduction was carried out using iron powder in acetic acid, followed by acetylation using acetyl chloride, only about 5 % of the chlorinated analogs of **13** and **14** were observed. The two bromides could then be converted to the desired azides **15** and **16** by treatment with sodium azide in DMSO [14]. The corresponding chlorides were unreactive under these conditions. *N*-Boc protected *trans*-4-ethynylpiperidin-3-ol (**2**) was alkylated with 2-(bromomethyl)naphthalene using method C to give *N*-Boc protected *trans*-4-ethynyl-3-(naphthalen-2-ylmethoxy)piperidine (**17**) in 80 % yield (see experimental part). This material was allowed to react with azides **15** or **16** under ruthenium catalysis (method B), which followed by Boc deprotection gave compounds **9da** and **9ea** (Fig. 2). In order to also introduce an alkyl group on the acetamide groups, ruthenium catalyzed cycloadditon (method B) was carried out first, followed by concurrent N- and O-alkylation using method C, which after Boc deprotection gave compounds **9fa** and **9ga** (Fig. 2).

Inhibitory activity toward renin

The 15 piperidine derivatives (see Figs. 1 and 2) were tested for their ability to inhibit recombinant human renin using the fluorimetric assay SensoLyte®520 Renin Assay Kit. All compounds were tested as the racemic mixture, initially at a concentration of 75 μM and then at 5 μM for the most active compounds. The use of two different endpoint concentrations is motivated by the need to distinguish the activity of the inhibitors. The endpoint concentration of 75 μM enabled us to separate the activity of the initial ligand series, whereas the use of 5 μM provided more details of the most active compounds. The inhibitory activity expressed as the remaining renin proteolytic

Scheme 2



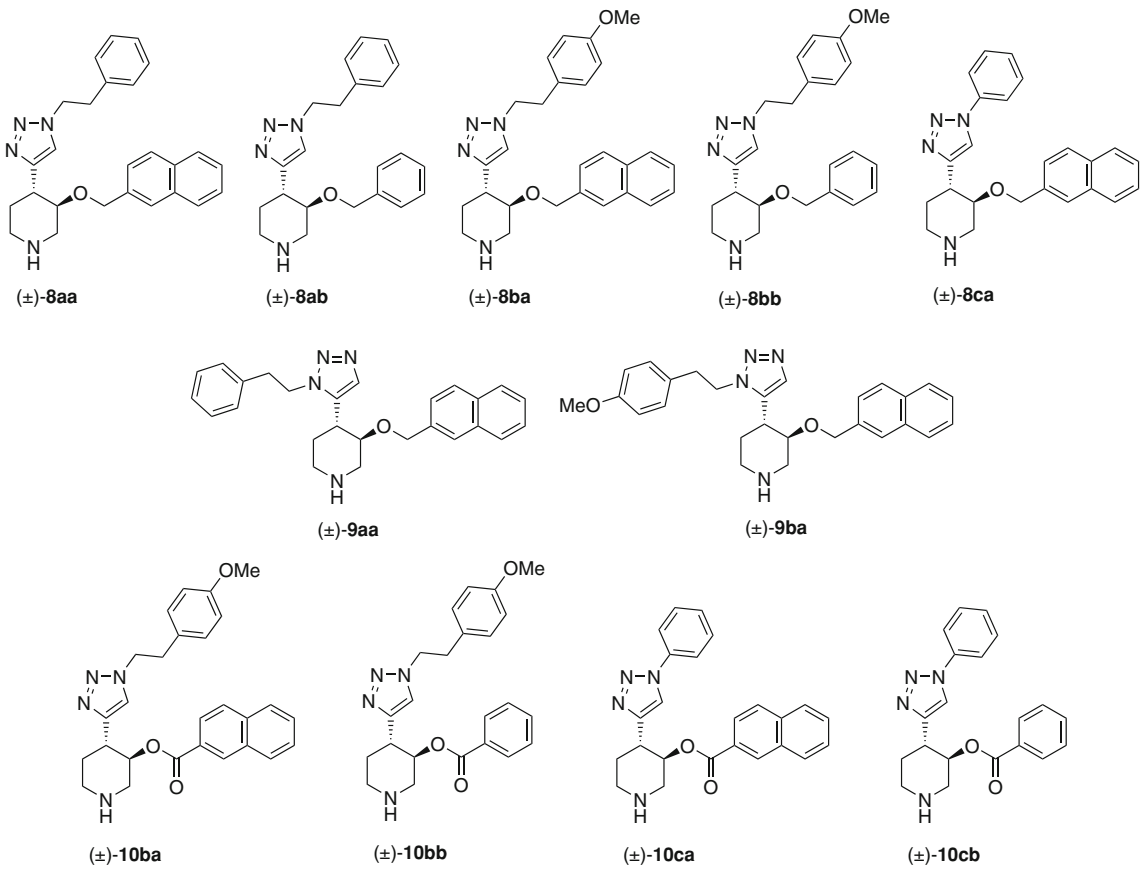
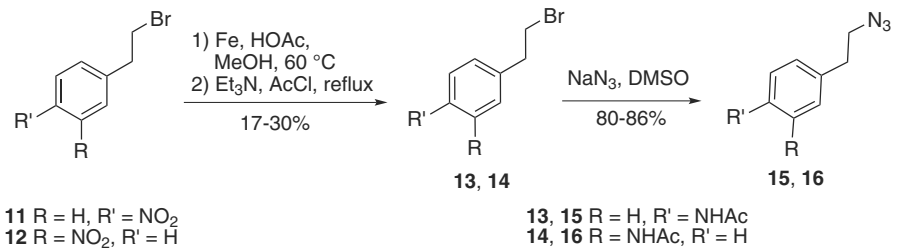


Fig. 1 Structures of the initial piperidine derivatives

Scheme 3



activity at these concentrations is compiled in Table 1. All the 4-triazolyl-substituted piperidine derivatives were found to inhibit renin with varying potency. As has been found for other piperidine-based renin inhibitors, a large substituent at the piperidine C-3 results in higher inhibitory activity, i.e. derivative **8aa** shows higher activity than **8ab**. Conversion of the secondary hydroxyl group of the initial piperidine building block into an ester instead of an ether did not influence the inhibitory activity to any large extent. Inhibitors containing 1,5-disubstituted 1,2,3-triazoles were found to be more active than their isomers containing 1,4-disubstituted 1,2,3-triazoles. **9ga**, which contains a tertiary aryl amide in the R^1 side chain, was found to be the most active compound, with 93 % inhibition of renin at 5 μM. For this compound the IC_{50} was determined to be 631 nM for the racemic mixture, with a narrow 95 % confidence interval of 580–687 nM. The remaining compounds with 1,5-disubstituted triazolyl substituents were all found to inhibit renin to approximately 50 % at 5 μM. All compounds were also tested for activity against a second aspartic protease, beta-secretase 1 (BACE1). All compounds in this study showed more than 50 % remaining BACE1 activity at 300 μM compound concentration (data not shown), indicating that our substituted piperidines have selectivity for renin over other members of this protease family.

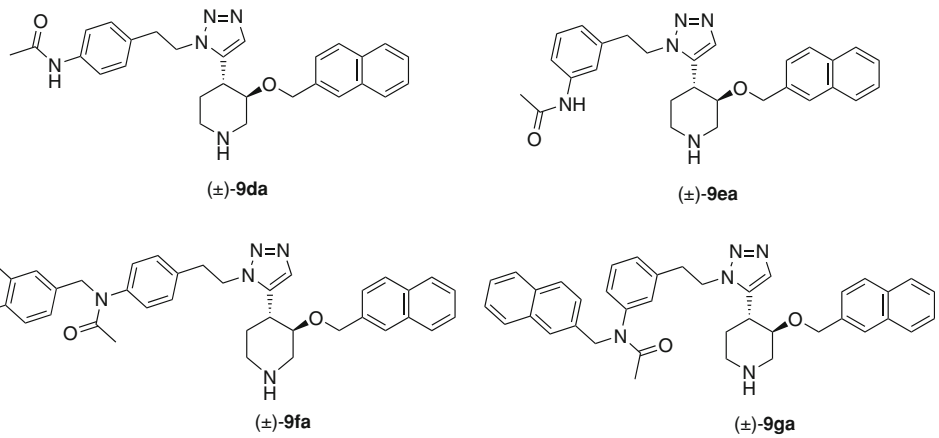


Fig. 2 Piperidine derivatives containing an acetamide group

Table 1 Renin inhibitory activity and scoring of piperidine derivatives

Compound	Remaining renin activity/%		Scoring
	5 μM[a]	75 μM[b]	kJ/mol
8aa	95	32	−31.8
8ab	–	71	−29.7
8ba	84	21	−32.7
8bb	–	77	−29.7
8ca	71	20	−31.4
9aa	37	2	−32.7
9ba	51	–	−31.4
9da	48	–	−28.1
9ea	43	–	−30.1
9fa	35[c]	–	−30.1
9ga	7[d]	–	−36.8
10ba	89	22	−32.7
10bb	–	73	−30.1
10ca	91	30	−31.4
10cb	–	66	−28.5

[a] Average of three parallels (<10 % spread)

[b] Average of two parallels (<8 % spread)

[c] Tested at 4 μM concentration

[d] IC_{50} = 631 nM for the racemic mixture

Molecular docking study

Four piperidine-based renin inhibitors with known binding modes and affinities were selected to develop a docking procedure suitable for the compounds in this study. An important aspect in ligand-binding modeling with aspartic protease targets is the orientation of the characteristic flap that covers the active site cleft of these proteases. This particular region closes upon substrate binding to accommodate the required spatial arrangement during catalysis and opens up to release the products after catalysis. However, when inhibitors bind to aspartic proteases, the orientation of the flap has been found to depend on the nature of the ligand [15]. For a recent and comprehensive review, please see [16]. When the ligand is able to form strong interactions with residues in the flap, especially through hydrogen bonding, the flap will be in a closed form. In contrast, ligands that interact weakly with the flap will lead to a complex with an open form. Ligand-induced effects on active site residues must also be considered. In order to take the uncertainties with respect to ligand-induced effects on the flap and active site residues into account, a selection of experimental crystal structures were included as targets in the docking protocol. The following complexes were used: 3OAG [9], 2FS4 [17], 3OAD [9], and 3O9L [9]. To assess the docking protocol, the four experimental ligands in these complexes were docked into their respective target structures using Glide [18]. RMSD values lower than 0.5 Å were obtained for the top ranked docking solutions, and the docking scores were within 0.85 kJ/mol of the reported experimental IC_{50} values. Based on the reproducibility of the complex crystal structures and agreement of the predicted binding affinities with experimental values, we conclude that the docking protocol is satisfactory for our system. However, when performing cross-docking of the four ligands, variations in the binding mode as well as the scoring are observed, but the rank order of the ligands is still reproduced. The difference between the docking score and experimental data increased slightly to 2.5 kJ/mol.

Comparison of the region underneath the flap in crystal structures of the two aspartic proteases renin (2FS4) and BACE1 (2OHN) reveals that the former has residues with smaller side chains in this region. Consequently, more space is available to accommodate larger ligand moieties in the S1 site of renin compared to BACE1 and is a plausible explanation for the observed selectivity between the two proteases. Attempts to dock our compounds to BACE1 (2OHN) produced solutions with docking scores corresponding to low mM affinity (−21 kJ/mol), consistent with

the kinetic assay results. In the in silico docking with the established docking protocol for renin described above, the closed form of the flap produced fewer docking solutions and with significantly lower affinities compared with the reported inhibition activities in Table 1. However, docking of the substituted piperidines shown in Figs. 1 and 2 into the active site cleft of renin (PDB code: 2FS4) gave binding affinities ranging from approximately −16.8 to −42.0 kJ/mol depending on the substitution pattern of the ligand and its stereochemistry. Our findings support that the (3*R*,4*R*) enantiomer was favored over the (3*S*,4*S*) enantiomer for all compounds, possibly because of a less favorable interaction with the catalytic aspartate dyad of the latter. This is also consistent with the orientation of the piperidine substituents in the crystal structures examined. The docking scores for all compounds are given in Table 1 along with the experimental inhibition results. The energies reported in Table 1 are averages of the top five docking solutions of the (3*R*,4*R*) enantiomers. It is clear that most of the compounds are correctly predicted in terms of scoring value. In the experimental assay all compounds were evaluated as racemic mixtures, and it is to be expected that one of the enantiomers will have a stronger binding affinity than the other because of the tendency of handedness in biological systems. The substituted piperidine with the highest inhibition potency was **9ga**, where we reported an IC_{50} value of 631 nM. In view of the docking observations the (3*R*,4*R*) enantiomer would most likely obtain a significantly better inhibition activity in the lower nM range than the (3*S*,4*S*) enantiomer.

The docking experiments reveal that our compounds explore the S1 and S3 binding pockets of renin. The triazole side chain is placed under the flap in subsite S1, whereas the ether-linked naphthyl explores the S3 pocket. Figure 3 shows the top-ranked docking solution of compound **9ga**.

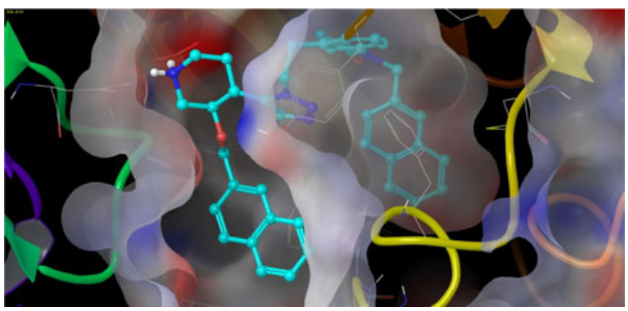


Fig. 3 Top-ranked docking solution of **9ga** to renin (PDB code: 2FS4). The triazole is located in subsite S1, the triazole-linked naphthyl group is tucked under the flap, and the ether linked naphthyl group is located in S3. The piperidine nitrogen forms hydrogen bonds to the aspartate dyad

The positively charged nitrogen atom is in an optimal position relative to the two catalytic aspartates, with hydrogen bond distances of 3.1 Å to OD1 of Asp219 and to OD2 of Asp33. This is in agreement with crystal structures of renin where ligands containing piperidine derivatives are bound. The top-ranked docking pose of **9ga** has one of the naphthyl groups placed in the S3 pocket, and the other, which is attached to the triazole branch, is tucked under the flap (see Fig. 3). Tyr78 at the tip of the flap interacts through stacking interactions with the triazole and the benzyl ring. We did not observe any hydrogen bonds between **9ga** and the flap region, hence indicating only weaker van der Waals interactions. Some of the other docking poses of **9ga** explore the S1 site differently, but maintain the S3 interactions as well as a similar orientation of the piperidine. In this second observed binding mode, the naphthyl previously tucked underneath the flap partially explores the S1′ site. However, the docking score for this orientation is lower in comparison to the top-ranked solution. In addition, stacking interactions are potentially present between the phenyl group and Trp 40, His 40, and Phe 114 in the S1 site, as well as with Phe119 in the S3 subsite for this latter docking pose.

Conclusions

In this study, we utilized a new piperidine building block toward the synthesis of a series of novel 4-triazolyl-substituted piperidine renin inhibitors. Piperidines with N-substituted 1,2,3-triazol-5-yl substituents were generally found to be more active than the isomeric compounds containing a 1,4-disubstituted 1,2,3-triazole moiety. The most active inhibitor was found to inhibit renin with an IC_{50} in the mid nM range as the racemic mixture, and all compounds presented in this study were more potent toward renin compared to BACE1. Through molecular docking of all final compounds, we were able to establish a method to predict inhibitory potency toward renin for these molecules. The insight gained in this study will be applied toward the design and synthesis of new inhibitors based on the presented scaffold.

Experimental

All starting materials, reagents, and solvents were obtained from Sigma-Aldrich and used without purification unless otherwise noted. 2-(Azidoethyl)benzene (R^1 side chain **a**) and 1-(2-azidoethyl)-4-methoxybenzene (R^1 side chain **b**) were prepared following the literature procedures [14]. Alkyne **2** and triazoles **3a**, **3b**, and **4a** were prepared as previously reported by us [12]. Anhydrous solvents were

obtained from an anhydrous solvent delivery system (mBraun SPS-800 system). Flash column chromatography was performed using silica gel from J.T. Baker ("Baker Analyzed," 0.063–0.200 mm) supplied by Chiron AS (Norway). TLC analysis was done using Macherey-Nagel aluminum plates coated with silica gel 60 with fluorescent indicator UV_{254} supplied by Chiron AS (Norway) with visualization using ultraviolet light or a solution of 2 % ninhydrin in ethanol containing 10 drops of conc. sulfuric acid per 100 cm^3 of the solution.

Purification by reversed-phase high performance liquid chromatography (RP-HPLC) was performed using a C_{18} column (Ascentis® C18, 5 μm, 21.2 × 250 mm, Supelco Corp., Bellefonte, PA, USA) with a mixture of water and acetonitrile (both containing 0.1 % TFA) as mobile phase and UV detection at 220 nm. Analytical RP-HPLC was performed using a C_{18} column (Ascentis® C18, 5 μm, 4.6 × 250 mm, Supelco Corp., Bellefonte, PA, USA).

NMR spectra were recorded using a Bruker Spectrospin AC. The chemical shifts are reported in parts per million relative to TMS, and the coupling constants are given in Hz. ^{13}C peaks marked with * were identified from cross peaks in HSQC spectra. Accurate mass determinations were performed using a Thermo Scientific LTQ Orbitrap MS (University of Tromsø).

*Azidobenzene (R^1 side chain **c**)*

A suspension of 0.50 cm^3 aniline (5.49 mmol) in 6 cm^3 acetic acid and conc. sulfuric acid (ratio 2.25:1) was cooled to 0 °C in an ice bath. A mixture of 2.9 cm^3 $NaNO_2$ (2 M in H_2O) was added dropwise to the suspension, and the resulting mixture was stirred at 0 °C for 1 h. To the obtained solution 2.9 cm^3 urea (2 M in H_2O) and 2.4 cm^3 NaN_3 (2.5 M in H_2O) were added and the mixture was stirred for another 3 h at 0 °C. The reaction was quenched with 50 cm^3 ice-cold H_2O and made basic with 40 % aq. NaOH. This aqueous mixture was extracted with hexane (3 × 50 cm^3), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane) to give the title compound as a yellow liquid (0.49 g, 75 %); $R_f = 0.53$ (hexane). Analytical data are in accordance with those reported in the literature [19].

N-[4-(2-Bromoethyl)phenyl]acetamide
(**13**, $C_{10}H_{12}BrNO$)
4-Nitrophenylethyl bromide (0.100 g, 0.43 mmol) was dissolved in a mixture of 1.6 cm^3 acetic acid and 0.75 cm^3 methanol and heated to 65 °C. Fe powder (87 mg) was added slowly to this solution. The reaction mixture was stirred at 65 °C for 20 h, after which the solvent was removed under reduced pressure. The resulting residue was co-evaporated with toluene. CH_2Cl_2 (10 cm^3) was added to the residue, and the resulting solution was washed with 5 cm^3 concentrated NH_3 solution and 5 cm^3 saturated aqueous NaCl solution. The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. The resulting product was dissolved in 0.4 cm^3 dry CH_2Cl_2, 0.13 cm^3 Et_3N (0.95 mmol) and 1.6 cm^3 acetyl chloride (0.95 mmol) were added, and the mixture was stirred under reflux for 2.5 h. The reaction mixture was then quenched with 1 cm^3 0.1 M NaOH, layers were separated, and the aqueous mixture was extracted with 5 cm^3 CH_2Cl_2. The organic phase was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by flash column chromatography (hexane/EtOAc, 2:1) gave **13** as a yellow solid (17 mg, 17 %). M.p.: 86.5–87.3 °C; $R_f = 0.22$ (hexane/EtOAc, 2:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$ (d, $J = 8.3$ Hz, 2H), 7.26 (s, 1H), 7.16 (d, $J = 8.3$ Hz, 2H), 3.54 (t, $J = 7.6$ Hz, 2H), 3.12 (t, $J = 7.6$ Hz, 2H), 2.17 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 168.9$, 137.1, 135.1, 129.5, 120.5, 39.1, 33.4, 24.8 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}BrNO$ 242.0184, found 242.0184 and 244.0161.

N-[3-(2-Bromoethyl)phenyl]acetamide
(**14**, $C_{10}H_{12}BrNO$)
The title compound was prepared from 1.10 g 3-nitrophenylethyl bromide (4.78 mmol) as described for bromide **13**. Purification by flash column chromatography (hexane/EtOAc, 2:1) gave the title compound as a yellow solid (0.347 g, 30 %). M.p.: 136.0–137.3 °C; $R_f = 0.2$ (hexane/EtOAc, 2:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$ (s, 1H), 7.38–7.23 (m, 3H), 6.96 (d, $J = 7.4$ Hz, 1H), 3.56 (t, $J = 7.5$ Hz, 2H), 3.14 (t, $J = 7.5$ Hz, 2H), 2.18 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 168.8$, 140.2, 138.5, 129.5, 124.9, 120.4, 118.7, 39.6, 33.1, 24.9 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}BrNO$ 242.0184, found 242.0187 and 244.0165.

N-[4-(2-Azidoethyl)phenyl]acetamide
(**15**, $C_{10}H_{12}N_4O$) *(R^1 side chain **d**)*
To a solution of 0.153 g bromide **13** (0.63 mmol) in 0.6 cm^3 DMSO was added 2.20 cm^3 of a solution of NaN_3 in DMSO (0.5 M, 1.10 mmol). The resulting mixture was stirred overnight at room temperature before 25 cm^3 H_2O was added. The aqueous mixture was extracted three times with Et_2O (3 × 15 cm^3), and the combined organic layers were washed with H_2O (2 × 25 cm^3) and 25 cm^3 saturated aqueous NaCl solution before it was dried over $MgSO_4$. After filtration the solvent was evaporated under reduced pressure to give the title compound as a yellow solid (0.110 g, 86 %). M.p.: 89.2–90.8 °C; $R_f = 0.20$ (hexane/EtOAc, 2:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$ (d, $J = 8.2$ Hz, 2H), 7.20–7.16 (apparent d, $J = 8.2$ Hz, 3H),

3.68 (t, $J = 7.4$ Hz, 2H), 3.03 (t, $J = 7.4$ Hz, 2H), 2.17 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 168.6$, 136.7, 134.1, 129.4, 120.3, 52.6, 34.9, 24.7 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}N_4O$ 205.1089, found 205.1104, *m/z* $[2\ M + H]^+$ calcd for $C_{20}H_{25}N_8O_2$ 409.2101, found 409.2091.

N-[3-(2-Azidoethyl)phenyl]acetamide (**16**, $C_{10}H_{12}N_4O$) *(R^1 side chain **e**)*

The title compound was prepared from 0.107 g bromide **14** (0.44 mmol) as described for azide **15** and was obtained as a colorless oil (71 mg, 80 %). $R_f = 0.33$ (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.79$ (s, 1H), 7.52 (s, 1H), 7.39 (d, $J = 7.8$ Hz, 1H), 7.22 (t, $J = 7.8$ Hz, 1H), 6.93 (d, $J = 7.5$ Hz, 1H), 3.47 (t, $J = 7.2$ Hz, 2H), 2.84 (t, $J = 7.2$ Hz, 2H), 2.14 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 168.8$, 139.4, 138.6, 129.5, 125.0, 120.5, 118.5, 52.6, 35.6, 24.9 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{10}H_{12}N_4NaO$ 227.0903, found 227.0897.

General procedure for copper-catalyzed cycloadditions: method A

To a solution of alkyne **2** (1.0 mmol) and an azide (1.0 mmol) in a mixture of H_2O and CH_2Cl_2 (1:1, 0.05 mmol/cm^3) were added $CuSO_4{\cdot}5H_2O$ (0.05 mmol) and sodium ascorbate (0.15 mmol). The reaction mixture was stirred at room temperature until TLC showed full conversion of the starting material after which the mixture was filtered, and the precipitate was washed with H_2O. The filtrate was extracted with EtOAc (3×10 cm^3), and the organic layers were combined with the precipitate. These combined layers were washed with 10 cm^3 H_2O and 10 cm^3 saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

(±)-tert-Butyl trans-3-hydroxy-4-(1-phenyl-1H-1,2,3-triazol-4-yl)piperidine-1-carboxylate (**3c**, $C_{18}H_{24}N_4O_3$)

Triazole **3c** was prepared from 0.308 g alkyne **2** (1.37 mmol) and 0.163 g azidobenzene (1.37 mmol) using method A. The reaction mixture was stirred at room temperature for 3 h, after which TLC analysis indicated full conversion of the starting material. The crude product was purified by flash column chromatography (hexane/EtOAc, 1:1) to give the title compound as a colorless solid (0.420 g, 89 %). M.p.: 130.4–132.3 °C; $R_f = 0.19$ (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.84$ (s, 1H), 7.72 (d, $J = 8.0$ Hz, 2H), 7.52 (t, $J = 8.0$ Hz, 2H), 7.48–7.41 (m, 1H), 4.48–4.33 (m, 1H), 4.31–4.07 (m, 1H), 3.83–3.69 (m, 1H), 2.94–2.66 (m, 3H), 2.15–2.05 (m, 1H), 1.85–1.69 (m, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 155.1$, 146*, 137.5, 130.1, 129.2, 120.9, 119.3, 80.3, 70.7, 50.0, 43.6, 41.8, 29.7, 28.8 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{24}N_4NaO_3$ 367.1746, found 367.1740.

General procedure for ruthenium-catalyzed cycloadditions: method B

A solution of alkyne **2** (1.0 mmol) in dry THF (15 cm^3/mmol) was heated in an oil bath to 80 °C. To this mixture $Cp^*RuCl(PPh_3)_2$ (0.01 mmol) and azide (1.1 mmol) were added. The reaction mixture was stirred at 80 °C until TLC analysis showed full conversion of the starting material. The solvent was removed using a rotary evaporator. The crude reaction mixture was purified by flash column chromatography.

(±)-tert-Butyl trans-3-hydroxy-4-[1-(4-methoxyphenethyl)-1H-1,2,3-triazol-5-yl]piperidine-1-carboxylate (**4b**, $C_{21}H_{30}N_4O_4$)

The title compound was prepared from 0.114 g alkyne **2** (0.51 mmol) and 98 mg 1-(2-azidoethyl)-4-methoxybenzene (0.56 mmol) using method B. The reaction mixture was stirred for 20 h at 80 °C, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 1:4) gave **4b** as a colorless solid (0.173 g, 84 %). M.p.: 142.4–144.3 °C; $R_f = 0.3$ (hexane/EtOAc, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$ (s, 1H), 6.94 (d, $J = 8.3$ Hz, 2H), 6.79 (d, $J = 8.3$ Hz, 2H), 4.65–4.46 (m, 2H), 4.31–4.19 (m, 1H), 4.10–3.98 (m, 1H), 3.75 (s, 3H), 3.48–3.37 (m, 1H), 3.21–3.08 (m, 2H), 2.65 (s, 1H), 2.57–2.42 (m, 2H), 2.24–2.13 (m, 1H), 1.53–1.43 (m, 10H), 1.39–1.28 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 159.0$, 154.7, 139.6, 130.5, 130.3, 120.0, 114.4, 80.5, 71.6, 55.7, 51*, 50.1, 44*, 40.5, 36.4, 30.3, 28.7 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{30}N_4NaO_4$ 425.2165, found 425.2159.

(±)-tert-Butyl trans-4-[1-(4-acetamidophenethyl)-1H-1,2,3-triazol-5-yl]-3-(naphthalen-2-ylmethoxy)piperidine-1-carboxylate (**6da**, $C_{33}H_{39}N_5O_4$)

The title compound was prepared from 37 mg alkyne **17** (0.10 mmol) and 23 mg azide **15** (0.11 mmol) using method B. The reaction was stirred at 80 °C for 20 h. Purification by flash column chromatography (hexane/EtOAc, 1:9) gave the title compound as a colorless oil (37 mg, 65 %). $R_f = 0.25$ (hexane/EtAOc, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.80$–7.61 (m, 3H), 7.58–7.52 (m, 1H), 7.51–7.41 (m, 3H), 7.38–7.30 (m, 3H), 6.99–6.90 (m, 1H), 6.84 (d, $J = 7.9$ Hz, 1H), 4.72–4.25 (m, 5H), 4.10–3.84 (m, 1H), 3.21–2.94 (m, 3H), 2.89–2.71 (m, 1H), 2.55–2.39 (m, 1H), 2.31–2.18 (m, 1H), 2.12 (s, 3H), 1.61–1.19 (m, 11H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 168.7$, 154.6, 146*, 137.4, 135.0, 134.8, 133.4, 133.2,

132.4, 132.3, 129.7, 129.4, 128.9, 128.8, 128.2, 128.0, 126.6, 125.7, 120.4, 80.5, 79.0, 72.2, 49.9, 47*, 43*, 38.7, 36.5, 28.7, 24.8 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{40}N_5O_4$ 570.3080, found 570.3078.

(±)-tert-Butyl trans-4-[1-(3-acetamidophenethyl)-1H-1,2,3-triazol-5-yl]-3-(naphthalen-2-ylmethoxy)piperidine-1-carboxylate (**6ea**, $C_{33}H_{39}N_5O_4$)

The title compound was prepared from 0.12 g alkyne **17** (0.33 mmol) and 74 mg azide **16** (0.36 mmol) using method B. The reaction was stirred at 80 °C for 22 h. Purification by flash column chromatography (hexane/EtOAc, 1:6) gave the title compound as a colorless oil (0.142 g, 76 %). $R_f = 0.27$ (hexane/EtAOc, 1:6); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.88$–7.64 (m, 3H), 7.58–7.42 (m, 2H), 7.39–7.32 (m, 2H), 7.30–7.24 (m, 2H), 7.14 (t, $J = 7.8$ Hz, 1H), 7.03–6.88 (m, 1H), 6.80–6.53 (m, 1H), 4.67–4.42 (m, 4H), 4.31 (d, $J = 11.4$ Hz, 1H), 4.07–3.94 (m, 1H), 3.18–2.95 (m, 3H), 2.63–2.34 (m, 2H), 2.32–2.19 (m, 1H), 2.13 (s, 3H), 1.58–1.49 (m, 1H), 1.43 (s, 9H), 1.33–1.19 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 168.8$, 154.6, 135.0, 133.4, 133.3, 132.4, 132.3, 130.6, 129.6, 128.9, 128.6, 128.2, 128.0, 126.8, 126.6, 126.4, 125.7, 124.9, 120.5, 118.6, 80.5, 79.1, 72.1, 49.6, 47*, 43*, 38.6, 37.1, 29*, 28.7, 24.9 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{33}H_{39}N_5NaO_4$ 592.2893, found 592.2900.

(±)-tert-Butyl trans-4-[1-(4-acetamidophenethyl)-1H-1,2,3-triazol-5-yl]-3-hydroxypiperidine-1-carboxylate (**18**, $C_{22}H_{31}N_5O_4$)

The title compound was prepared from 43 mg alkyne **2** (0.19 mmol) and 43 mg azide **15** (0.21 mmol) using method B. The reaction mixture was stirred at 80 °C for 21 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (EtOAc) gave the title compound as a colorless solid (73 mg, 90 %). M.p.: 208.7–209.5 °C; $R_f = 0.24$ (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 8.1$ Hz, 2H), 7.31–7.13 (m, 2H), 6.98 (d, $J = 8.1$ Hz, 2H), 4.57 (t, $J = 7.4$ Hz, 3H), 4.30–4.18 (m, 1H), 4.09–3.90 (m, 1H), 3.53–3.35 (m, 1H), 3.24–3.03 (m, 2H), 2.74–2.42 (m, 3H), 2.23–1.98 (m, 4H), 1.46 (s, 9H), 1.38–1.32 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 170.2$, 156.1, 147*, 135.6, 130.5, 131.1, 129.7, 120.6, 80.6, 71.5, 50*, 49.3, 44*, 40*, 36.5, 29*, 28.6, 24.5 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{32}N_5O_4$ 430.2454, found 430.2459.

(±)-tert-Butyl trans-4-[1-(3-acetamidophenethyl)-1H-1,2,3-triazol-5-yl]-3-hydroxypiperidine-1-carboxylate (**19**, $C_{22}H_{31}N_5O_4$)

The title compound was prepared from 0.12 g alkyne **2** (0.33 mmol) and 74 mg azide **16** (0.36 mmol) using method B. The reaction mixture was stirred at 80 °C for 21 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 1:9) gave the title compound as a colorless oil (0.197 g, 82 %). $R_f = 0.26$ (hexane/EtOAc, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.64$ (s, 1H), 7.52–7.00 (m, 3H), 6.80 (d, $J = 7.4$ Hz, 1H), 4.61 (t, $J = 6.7$ Hz, 2H), 4.36–4.18 (m, 1H), 4.20–3.95 (m, 1H), 3.49–3.34 (m, 1H), 3.30–3.05 (m, 2H), 2.60–2.44 (m, 2H), 2.26–2.20 (m, 1H), 2.15 (s, 3H), 1.55–1.34 (m, 10H), 1.39–1.16 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 169.0$, 154.8, 150*, 138.9, 138*, 137*, 130*, 129.7, 125.2, 118.9, 80.5, 71.4, 50*, 49.5, 43*, 40*, 36.9, 30.5, 28.7, 24.9 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{32}N_5O_4$ 430.2454, found 430.2457.

General procedure for the formation of ether linkages: method C

To a secondary alcohol (0.2 mmol) was added a suspension of NaH (60 wt % in mineral oil, 0.4 mmol) in 5 cm^3 DMF. After stirring for 30 min at room temperature, a mixture of tetrabutylammonium iodide (TBAI, 0.02 mmol) and an alkyl bromide (0.2 mmol) in 1 cm^3 DMF was added, and the reaction mixture was stirred at room temperature until TLC analysis indicated full conversion of the alcohol. The reaction was quenched by addition of 10 cm^3 H_2O, and the aqueous mixture was extracted with 20 cm^3 EtOAc. The organic layer was washed with 10 % aqueous HCl (2×10 cm^3), saturated aqueous $NaHCO_3$ solution (2×10 cm^3), and H_2O (2×10 cm^3) and dried over $MgSO_4$. After removal of the drying agent by filtration, the solvent was removed under vacuum. The crude product was purified by flash column chromatography.

(±)-tert-Butyl trans-3-(naphthalene-2-ylmethoxy)-4-(1-phenethyl-1H-1,2,3-triazol-4-yl)piperidine-1-carboxylate (**5aa**, $C_{31}H_{36}N_4O_3$)

The title compound was prepared from 55 mg alcohol **3a** (0.15 mmol) and 66 mg 2-(bromomethyl)naphthalene (0.30 mmol) using method C. The reaction mixture was stirred for 20 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 1:1) gave **5aa** as a colorless oil (39 mg, 70 %). $R_f = 0.18$ (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.83$–7.74 (m, 3H), 7.60 (s, 1H), 7.48–7.40 (m, 2H), 7.29–7.15 (m, 4H), 7.05–6.97 (m, 2H), 6.93 (s, 1H), 4.78–4.63 (m, 1H), 4.54–4.29 (m, 4H), 4.06–3.97 (m, 1H), 3.63–3.52 (m, 1H), 3.09 (t, $J = 7.1$ Hz, 2H), 2.96–2.75 (m, 3H), 2.09–1.98 (m, 1H), 1.89–1.76 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 155.0$, 148.7, 137.6, 136.2, 133.7, 133.4, 129.1, 129.0, 128.4, 128.3, 128.0, 127.4, 126.9, 126.5, 126.27, 126.25, 122.0, 80.1, 77.6, 72.2, 51.7, 47*, 43*, 40.4,

37.0, 30.5, 28.8 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{31}H_{36}N_4NaO_3$ 535.2685, found 535.2693.

(±)-tert-Butyl trans-3-benzyloxy-4-(1-phenethyl-1H-1,2,3-triazol-4-yl)piperidine-1-carboxylate
(**5ab**, $C_{27}H_{34}N_4O_3$)
The title compound was prepared from 60 mg alcohol **3a** (0.18 mmol) and 43 mm^3 benzyl bromide (0.36 mmol) using method C. The reaction mixture was stirred for 20 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 2:1) gave **5ab** as a colorless oil (53 mg, 64 %). $R_f = 0.33$ (hexane/EtOAc, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.32–7.19$ (m, 6H), 7.14 (d, $J = 6.9$ Hz, 2H), 7.08 (d, $J = 6.7$ Hz, 2H), 7.00 (s, 1H), 4.61–4.42 (m, 4H), 4.31 (d, $J = 11.1$ Hz, 1H), 4.02 (d, $J = 13.2$ Hz, 1H), 3.58–3.49 (m, 1H), 3.15 (t, $J = 7.2$ Hz, 2H), 2.93–2.56 (m, 3H), 2.08–1.97 (m, 1H), 1.89–1.76 (m, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 155.0, 148.5, 138.6, 137.5, 129.1, 129.0, 128.6, 128.1, 128.0, 127.4, 122.0, 80.1, 77.4, 72.0, 51.8, 48*, 43*, 40.2, 37.1, 30.4, 28.8$ ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{27}H_{34}N_4NaO_3$ 485.2529, found 485.2526.

(±)-tert-Butyl trans-4-[1-(4-methoxyphenethyl)-1H-1,2,3-triazol-4-yl]-3-(naphthalene-2-ylmethoxy)piperidine-1-carboxylate (**5ba**, $C_{32}H_{38}N_4O_4$)
The title compound was prepared from 0.229 g alcohol **3b** (0.57 mmol) and 0.252 g 2-(bromomethyl)naphthalene (1.14 mmol) using method C. The reaction mixture was stirred for 21 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 1:1) gave **5ba** as a colorless oil (0.245 g, 79 %). $R_f = 0.17$ (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.83–7.71$ (m, 3H), 7.61 (s, 1H), 7.49–7.21 (m, 2H), 7.27–7.21 (m, 1H), 6.95 (s, 1H), 6.91 (d, $J = 8.5$ Hz, 2H), 6.74 (d, $J = 8.5$ Hz, 2H), 4.77–4.62 (m, 1H), 4.53–4.30 (m, 4H), 4.07–3.97 (m, 1H), 3.71 (s, 3H), 3.64–3.52 (m, 1H), 3.02 (t, $J = 7.2$ Hz, 2H), 2.96–2.74 (m, 3H), 2.09–1.96 (m, 1H), 1.90–1.76 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 158.9, 154.9, 148.5, 136.0, 133.5, 133.3, 130.0, 129.4, 128.3, 128.2, 128.0, 126.9, 126.5, 126.3, 126.2, 122.0, 114.4, 80.1, 77*, 72.2, 55.5, 51.9, 48*, 44*, 40.3, 36.2, 30.5, 28.7$ ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{32}H_{38}N_4NaO_4$ 565.2791, found 565.2772.

(±)-tert-Butyl trans-3-benzyloxy-4-[1-(4-methoxyphenethyl)-1H-1,2,3-triazol-4-yl]piperidine-1-carboxylate
(**5bb**, $C_{28}H_{36}N_4O_4$)
The title compound was prepared from 98 mg alcohol **3b** (0.24 mmol) and 57 mm^3 benzylbromide (0.48 mmol) using method C. The reaction mixture was stirred for 22 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 1:1) gave **5bb** as a colorless oil (0.106 g, 89 %). $R_f = 0.31$ (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30–7.20$ (m, 3H), 7.14 (d, $J = 6.5$ Hz, 2H), 7.01–6.94 (m, 3H), 6.78 (d, $J = 8.5$ Hz, 2H), 4.60–4.41 (m, 3H), 4.31 (d, $J = 11.6$ Hz, 2H), 4.00 (d, $J = 13.4$ Hz, 1H), 3.74 (s, 3H), 3.59–3.46 (m, 1H), 3.09 (t, $J = 7.2$ Hz, 2H), 2.96–2.83 (m, 2H), 2.83–2.72 (m, 1H), 2.11–1.95 (m, 1H), 1.90–1.77 (m, 1H), 1.46 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 159.2, 155.0, 148.6, 138.7, 130.0, 129.6, 128.7, 128.1, 128.0, 122.0, 114.7, 80.2, 77.6, 72.1, 55.6, 52.0, 47*, 43*, 40.3, 36.3, 30.5, 28.8$ ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{37}N_4O_4$ 493.2815, found 493.2813.

(±)-tert-Butyl trans-3-(naphthalen-2-ylmethoxy)-4-(1-phenyl-1H-1,2,3-triazol-4-yl)piperidine-1-carboxylate
(**5ca**, $C_{29}H_{32}N_4O_3$)
The title compound was prepared from 80 mg alcohol **3c** (0.23 mmol) and 0.101 g 2-(bromomethyl)naphthalene (0.46 mmol) using method C. The reaction mixture was stirred for 5 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 2:1) gave **5ca** as a colorless oil (98 mg, 88 %). $R_f = 0.31$ (hexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.76–7.64$ (m, 3H), 7.61 (d, $J = 11.4$ Hz, 2H), 7.52 (d, $J = 7.2$ Hz, 2H), 7.46–7.33 (m, 5H), 7.24 (d, $J = 7.2$ Hz, 1H), 4.80 (d, $J = 11.4$ Hz, 1H), 4.63–4.41 (m, 2H), 4.18–4.06 (m, 1H), 3.70–3.59 (m, 1H), 3.08–2.96 (m, 1H), 2.95–2.73 (m, 2H), 2.19–2.08 (m, 1H), 2.04–1.87 (m, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 155.0, 149.5, 137.6, 136.0, 133.6, 133.4, 130.0, 128.7, 128.5, 128.2, 128.0, 127.1, 126.5, 126.32, 126.28, 120.6, 120.0, 80.2, 77.6, 72.3, 47.7, 43.9, 40.6, 30.5, 28.8$ ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{33}N_4O_3$ 485.2553, found 485.2552.

(±)-tert-Butyl trans-3-(naphthalene-2-ylmethoxy)-4-(1-phenethyl-1H-1,2,3-triazol-5-yl)piperidine-1-carboxylate
(**6aa**, $C_{31}H_{36}N_4O_3$)
The title compound was prepared from 60 mg alcohol **4a** (0.16 mmol) and 71 mg 2-(bromomethyl)naphthalene (0.32 mmol) using method C. The reaction mixture was stirred for 19 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 1:1) gave **6aa** as a colorless solid (45 mg, 55 %). M.p.: 108.8–112.6 °C; $R_f = 0.17$ (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.81–7.69$ (m, 3H), 7.49–7.41 (m, 2H), 7.37 (s, 1H), 7.34 (s, 1H), 7.23–7.14 (m, 3H), 6.98 (d, $J = 8.3$ Hz, 1H), 6.93 (d, $J = 6.9$ Hz, 2H), 4.66–4.37 (m, 4H), 4.31 (d, $J = 8.0$ Hz, 1H), 4.06–3.94 (m, 1H), 3.20–3.07 (m, 3H), 2.53–2.36 (m, 2H), 2.25–2.13 (m, 1H), 1.59–1.49 (m, 1H), 1.42 (s, 9H), 1.31–1.20 (m, 1H) ppm; ^{13}C NMR

(101 MHz, $CDCl_3$): δ = 154.7, 139.6, 138.4, 135.1, 133.6, 133.5, 130.7, 129.3, 129.0, 128.7, 128.3, 128.1, 127.2, 126.9, 126.6, 126.5, 125.8, 80.6, 79.3, 72.4, 49.9, 48*, 44*, 38.9, 37.3, 30.3, 28.8 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{31}H_{36}N_4NaO_3$ 535.2685, found 535.2670.

(±)-tert-Butyl trans-4-[1-(4-methoxyphenethyl)-1H-1,2,3-triazol-5-yl]-3-(naphthalene-2-ylmethoxy)piperidine-1-carboxylate (**6ba**, $C_{32}H_{38}N_4O_4$)

The title compound was prepared from 0.116 g alcohol **4b** (0.29 mmol) and 0.128 g 2-(bromomethyl)naphthalene (0.58 mmol) using method C. The reaction mixture was stirred for 18 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 1:1) gave the title compound as a colorless oil (0.141 g, 89 %). R_f = 0.35 (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.69 (m, 3H), 7.50–7.42 (m, 2H), 7.39–7.33 (m, 2H), 7.01–6.92 (m, 1H), 6.83 (d, J = 8.2 Hz, 2H), 6.73 (d, J = 8.2 Hz, 2H), 4.67–4.52 (m, 2H), 4.52–4.40 (m, 2H), 4.35–4.27 (m, 1H), 4.10–3.96 (m, 1H), 3.73 (s, 3H), 3.18–3.01 (m, 3H), 2.53–2.37 (m, 2H), 2.24–2.14 (m, 1H), 1.62–1.44 (m, 1H), 1.42 (s, 9H), 1.34–1.22 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8, 154.6, 139.6, 135.0, 133.4, 133.3, 130.7, 130.3, 130.1, 128.6, 128.2, 128.0, 126.8, 126.6, 126.4, 125.7, 114.3, 80.6, 79.0, 72.2, 55.6, 50.1, 48*, 44*, 38.7, 36.3, 30.2, 28.7 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{39}N_4O_4$ 543.2971, found 543.2973.

(±)-tert-Butyl trans-4-ethynyl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylate (**17**, $C_{23}H_{27}NO_3$)

The title compound was prepared from 60 mg alcohol **2** (0.30 mmol) and 0.132 g 2-(bromomethyl)naphthalene (0.60 mmol) using method C. Purification of the crude product by flash column chromatography (hexane/EtOAc, 9:1) gave **17** as a colorless solid (88 mg, 80 %). M.p.: 60.9–64.7 °C; R_f = 0.30 (hexane/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.77 (m, 4H), 7.52–7.41 (m, 3H), 4.87 (d, J = 12.0 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 3.81–3.68 (m, 1H), 3.61–3.51 (m, 1H), 3.50–3.40 (m, 2H), 3.39–3.30 (m, 1H), 2.77–2.69 (m, 1H), 2.15 (d, J = 2.1 Hz, 1H), 2.10–2.00 (m, 1H), 1.61–1.50 (m, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.2, 136.2, 133.8, 133.5, 128.5, 128.3, 128.1, 126.8, 126.4, 126.2, 84.9, 80.0, 75.8, 72.0, 71.4, 45*, 41*, 33.3, 28.8, 28.4 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{27}NNaO_3$ 388.1889, found 388.1870.

(±)-tert-Butyl trans-3-(naphthalen-2-ylmethoxy)-4-[1-[4-[N-(naphthalen-2-ylmethyl)acetamido]phenethyl]-1H-1,2,3-triazol-5-yl]piperidine-1-carboxylate
(**6fa**, $C_{44}H_{47}N_5O_4$)

The title compound was prepared from 60 mg alcohol **18** (0.14 mmol) and 62 mg 2-(bromomethyl)naphthalene (0.28 mmol) using method C. Purification by flash column chromatography (hexane/EtOAc, 1:6) gave the title compound as a colorless oil (70 mg, 71 %). R_f = 0.27 (hexane/EtOAc, 1:6); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.63 (m, 6H), 7.53 (s, 1H), 7.50–7.32 (m, 7H), 6.99–6.91 (m, 1H), 6.85 (d, J = 7.6 Hz, 2H), 6.79 (d, J = 7.6 Hz, 2H), 4.97 (s, 2H), 4.74–4.56 (m, 2H), 4.55–4.40 (m, 2H), 4.34 (d, J = 11.6 Hz, 1H), 4.20–4.00 (m, 1H), 3.34–2.98 (m, 3H), 2.70–2.30 (m, 3H), 1.85 (s, 3H), 1.70–1.53 (m, 2H), 1.44 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.7, 154.6, 150*, 141.9, 139.1, 137*, 135.3, 134.8, 133.6, 133.4, 133.1, 131.0, 130.2, 128.7, 128.6, 128.2, 128.1, 128.0, 127.6, 127.03, 126.95, 126.6, 126.5, 126.4, 126.3, 126.2, 125.8, 80.8, 79.0, 72.3, 53.2, 49.2, 48*, 44*, 38.9, 36.1, 30*, 28.7, 23.1 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{44}H_{48}N_5O_4$ 710.3706, found 710.3711.

(±)-tert-Butyl trans-3-(naphthalen-2-ylmethoxy)-4-[1-[3-[N-(naphthalen-2-ylmethyl)acetamido]phenethyl]-1H-1,2,3-triazol-5-yl]piperidine-1-carboxylate
(**6ga**, $C_{44}H_{47}N_5O_4$)

The title compound was prepared from 20 mg alcohol **19** (0.035 mmol) and 23 mg 2-(bromomethyl)naphthalene (0.11 mmol) using method C. Purification by flash column chromatography (hexane/EtOAc, 1:9) gave the title compound as a colorless oil (18 mg, 72 %). R_f = 0.26 (hexane/EtOAc, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.63 (m, 6H), 7.53–7.51 (m, 1H), 7.50–7.39 (m, 4H), 7.38–7.31 (m, 3H), 7.11 (t, J = 7.8 Hz, 1H), 6.97–6.90 (m, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.60 (s, 1H), 5.00 (d, J = 14.6 Hz, 1H), 4.89 (d, J = 14.6 Hz, 1H), 4.66–4.47 (m, 2H), 4.45–4.34 (m, 2H), 4.29 (d, J = 11.6 Hz, 1H), 4.05–3.98 (m, 1H), 3.22–3.08 (m, 2H), 3.07–2.96 (m, 1H), 2.69–2.33 (m, 3H), 1.82 (s, 3H), 1.65–1.52 (m, 1H), 1.49–1.37 (m, 10H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5, 154.5, 147*, 143.5, 139.6, 135.3, 134.8, 133.5, 133.4, 133.0, 130.9, 128.9, 128.7, 128.5, 128.2, 128.1, 128.02, 127.97, 127.72, 127.67, 126.99, 126.96, 126.7, 126.5, 126.4, 126.2, 125.8, 123.0, 122.5, 121.1, 80.7, 79.0, 72.3, 60.7, 49.2, 49*, 45*, 38.8, 36.4, 30*, 28.7, 23.1, 21.4 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{44}H_{48}N_5O_4$ 710.3706, found 710.3681.

General procedure for the formation of ester linkages: method D

To a solution of an alcohol (0.5 mmol) in 5 cm^3 dry CH_2Cl_2 were added a carboxylic acid (0.75 mmol), DMAP (0.9 mmol), and DCC (0.9 mmol). The reaction mixture was stirred at room temperature until TLC analysis indicated full conversion of the alcohol. The reaction mixture

was diluted with 25 cm^3 Et_2O and washed with 25 cm^3 5 % citric acid and 25 cm^3 saturated aqueous NaCl solution before it was dried over $MgSO_4$. After removal of the drying agent by filtration, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

(±)-tert-Butyl trans-3-(2-naphthoyloxy)-4-[1-(4-methoxyphenethyl)-1H-1,2,3-triazol-4-yl]piperidine-1-carboxylate (**7ba**, $C_{32}H_{36}N_4O_5$)

The title compound was prepared from 90 mg alcohol **3b** (0.40 mmol) and 57 mg 2-naphthoic acid (0.33 mmol) using method D. The reaction mixture was stirred for 20 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 1:1) gave **7ba** as a colorless oil (96 mg, 77 %). $R_f = 0.22$ (hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.54$ (s, 1H), 7.99 (d, $J = 8.7$ Hz, 1H), 7.93 (d, $J = 8.2$ Hz, 1H), 7.88–7.81 (m, 2H), 7.62–7.49 (m, 2H), 7.10 (s, 1H), 6.86 (d, $J = 8.2$ Hz, 2H), 6.69 (d, $J = 8.2$ Hz, 2H), 5.25–5.15 (m, 1H), 4.45 (t, $J = 7.2$ Hz, 2H), 4.26–4.14 (m, 1H), 3.98–3.87 (m, 1H), 3.70 (s, 3H), 3.40–3.15 (m, 3H), 3.03 (t, $J = 7.2$ Hz, 2H), 2.27–2.17 (m, 1H), 1.91–1.78 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.1$, 158.9, 155.0, 147.8, 136.0, 132.8, 131.6, 129.9, 129.7, 129.2, 128.7, 128.5, 128.1, 127.4, 127.1, 125.6, 121.2, 114.4, 80.4, 71.9, 55.5, 52.2, 47*, 43*, 38.5, 36.2, 29*, 28.7 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{32}H_{36}N_4NaO_5$ 579.2583, found 579.2580.

(±)-tert-Butyl trans-3-benzoyloxy-4-[1-(4-methoxyphenethyl)-1H-1,2,3-triazol-4-yl]piperidine-1-carboxylate (**7bb**, $C_{28}H_{34}N_4O_5$)

The title compound was prepared from 98 mg alcohol **3b** (0.24 mmol) and 46 mg benzoic acid (0.38 mmol) using method D. The reaction mixture was stirred for 21 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 1:2) gave **7bb** as a colorless oil (95 mg, 75 %). $R_f = 0.35$ (hexane/EtOAc, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$ (d, $J = 7.3$ Hz, 1H), 7.98 (d, $J = 7.4$ Hz, 2H), 7.51–7.37 (m, 2H), 7.09 (s, 1H), 6.89 (d, $J = 8.5$ Hz, 2H), 6.73 (d, $J = 8.5$ Hz, 2H), 5.19–5.06 (m, 1H), 4.47 (t, $J = 7.0$ Hz, 2H), 4.26–4.00 (m, 1H), 3.95–3.84 (m, 1H), 3.75 (s, 3H), 3.38–3.11 (m, 3H), 3.05 (t, $J = 6.9$ Hz, 2H), 2.24–2.13 (m, 1H), 1.87–1.74 (m, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 165.8$, 158.9, 155.0, 147.7, 133.5, 130.0, 129.9, 129.2, 128.74, 128.71, 121.2, 114.5, 80.4, 77.6, 71.7, 55.6, 52.2, 46.6, 38.3, 36.2, 30.0, 28.7 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{35}N_4O_5$ 507.2608, found 507.2600.

(±)-tert-Butyl trans-3-(2-naphthoyloxy)-4-(1-phenyl-1H-1,2,3-triazol-4-yl)piperidine-1-carboxylate (**7ca**, $C_{29}H_{30}N_4O_4$)

The title compound was prepared from 73 mg alcohol **3c** (0.21 mmol) and 55 mg 2-naphthoic acid (0.32 mmol) using method D. The reaction mixture was stirred for 20 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 2:1) gave **7ca** as a colorless solid (75 mg, 72 %). M.p.: 174.9–177.1 °C; $R_f = 0.25$ (hexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.56$ (s, 1H), 8.01 (d, $J = 8.5$ Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 1H), 7.87–7.80 (m, 3H), 7.62 (d, $J = 7.9$ Hz, 2H), 7.59–7.48 (m, 2H), 7.47–7.40 (m, 2H), 7.39–7.33 (m, 1H), 5.41–5.29 (m, 1H), 4.38–4.25 (m, 1H), 4.12–3.99 (m, 1H), 3.55–3.43 (m, 1H), 3.40–3.20 (m, 2H), 2.39–2.28 (m, 1H), 2.07–1.89 (m, 1H), 1.46 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.1$, 155.0, 148.8, 137.3, 136.0, 132.8, 131.6, 130.0, 129.7, 129.0, 128.7, 128.6, 128.1, 127.1, 125.5, 120.8, 119.2, 80.5, 71.8, 49.5, 48*, 42*, 38.7, 30*, 28.7 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{30}N_4NaO_4$ 521.2165, found 521.2167.

(±)-tert-Butyl trans-3-benzoyloxy-4-(1-phenyl-1H-1,2,3-triazol-4-yl)piperidine-1-carboxylate (**7cb**, $C_{25}H_{28}N_4O_4$)

The title compound was prepared from 0.105 g alcohol **3c** (0.30 mmol) and 56 mg benzoic acid (0.46 mmol) using method D. The reaction mixture was stirred for 18 h, after which TLC analysis indicated full conversion of the starting material. Purification by flash column chromatography (hexane/EtOAc, 2:1) gave the **7cb** as a colorless solid (0.130 g, 96 %). M.p.: 155.3–157.4 °C; $R_f = 0.34$ (hexane/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.01$ (d, $J = 7.6$ Hz, 2H), 7.83 (s, 1H), 7.64 (d, $J = 7.8$ Hz, 2H), 7.54 (t, $J = 7.3$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 2H), 7.44–7.36 (m, 3H), 5.34–5.23 (m, 1H), 4.19–4.15 (m, 1H), 4.07–3.96 (m, 1H), 3.49–3.37 (m, 1H), 3.35–3.12 (m, 2H), 2.36–2.23 (m, 1H), 2.03–1.88 (m, 1H), 1.45 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 165.9$, 157.2, 148.8, 137.3, 133.5, 130.1, 130.03, 130.01, 129.0, 128.7, 120.8, 119.1, 80.5, 71.6, 46.7, 42.4, 38.5, 30.0, 28.7 ppm; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{28}N_4NaO_4$ 471.2008, found 471.2004.

General procedure for Boc deprotection: method E

The Boc-protected piperidine derivative was dissolved in a mixture of CH_2Cl_2 and TFA (1:1, 2 cm^3/mmol), and the reaction mixture was stirred at room temperature for 30 min, after which all starting material was consumed. The solvents were removed under reduced pressure, and the residue was co-evaporated with toluene (2 × 25 cm^3), CH_3CN (2 × 25 cm^3), and CH_2Cl_2 (2 × 25 cm^3) to afford

the amine as its TFA salt. The crude product was purified by semi-preparative HPLC using a C18 column. Fractions of equal purity were pooled and concentrated under vacuum before the aqueous solution was lyophilized. All final compounds were found to be of higher than 95 % purity (HPLC).

(±)-trans-3-(Naphthalene-2-ylmethoxy)-4-(1-phenethyl-1H-1,2,3-triazol-4-yl)piperidine (**8aa**, $C_{26}H_{28}N_4O$)
The title compound was prepared from 50 mg Boc-protected piperidine **5aa** (0.1 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **8aa** as a colorless powder (16 mg, 40 %). ^{1}H NMR (400 MHz, MeOH-d_4): $\delta = 7.87–7.79$ (m, 3H), 7.71 (s, 1H), 7.52 (s, 1H), 7.51–7.45 (m, 2H), 7.36–7.30 (m, 1H), 7.21–7.09 (m, 3H), 7.05 (d, $J = 6.9$ Hz, 2H), 4.70 (d, $J = 9.8$ Hz, 1H), 4.65–4.47 (m, 3H), 3.94–3.85 (m, 1H), 3.52–3.42 (m, 1H), 3.35–3.28 (m, 1H), 3.26–3.18 (m, 1H), 3.17–3.04 (m, 4H), 2.33–2.21 (m, 1H), 2.09–1.96 (m, 1H) ppm; ^{13}C NMR (101 MHz, MeOH-d_4): $\delta = 148.4$, 139.5, 137.2, 135.52, 135.45, 130.6, 130.5, 130.1, 129.8, 129.6, 128.9, 128.8, 128.2, 128.1, 127.8, 125.3, 75.5, 74.0, 53.4, 47.3, 44.2, 38.2, 37.7, 27.2 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{29}N_4O$ 413.2341, found 413.2339.

(±)-trans-3-Benzyloxy-4-(1-phenethyl-1H-1,2,3-triazol-4-yl)-piperidine (**8ab**, $C_{22}H_{26}N_4O$)
The title compound was prepared from 52 mg Boc-protected piperidine **5ab** (0.11 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **8ab** as a colorless oil (34 mg, 65 %). ^{1}H NMR (400 MHz, MeOH-d_4): $\delta = 8.03–8.00$ (m, 1H), 7.58 (s, 1H), 7.34–7.27 (m, 3H), 7.25–7.14 (m, 5H), 7.09 (d, $J = 6.6$ Hz, 2H), 4.67–4.56 (m, 2H), 4.53 (d, $J = 11.8$ Hz, 1H), 4.45 (d, $J = 11.8$ Hz, 1H), 3.90–3.83 (m, 1H), 3.49–3.38 (m, 1H), 3.34–3.25 (m, 1H), 3.24–3.15 (m, 3H), 3.15–3.02 (m, 2H), 2.33–2.21 (m, 1H), 2.08–1.96 (m, 1H) ppm; ^{13}C NMR (101 MHz, MeOH-d_4): $\delta = 148.4$, 139.8, 139.6, 130.7, 130.5, 130.4, 130.3, 130.0, 129.9, 128.8, 125.3, 75.5, 73.9, 53.5, 47.2, 44.1, 38.3, 37.5, 27.0 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{27}N_4O$ 363.2185, found 363.2184.

(±)-trans-4-[1-(4-Methoxyphenethyl)-1H-1,2,3-triazol-4-yl]-3-(naphthalen-2-ylmethoxy)piperidine
(**8ba**, $C_{27}H_{30}N_4O_2$)
The title compound was prepared from 0.100 g Boc-protected piperidine **5ba** (0.18 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **8ba** as a colorless solid (62 mg, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.04–9.81$ (m, 1H), 9.46–9.25 (m, 1H), 7.84–7.70 (m, 3H), 7.64 (s, 1H), 7.51–7.42 (m, 2H), 7.33–7.22 (m, 1H), 7.00–6.87 (m, 3H), 6.77 (d, $J = 8.5$ Hz, 2H), 4.66 (d, $J = 11.7$ Hz, 1H), 4.51 (d, $J = 11.7$ Hz, 1H), 4.47–4.27 (m, 2H), 4.02–3.93 (m, 1H), 3.72 (s, 3H), 3.59–3.43 (m, 1H), 3.38–3.23 (m, 1H), 3.18–3.09 (m, 1H), 3.09–2.92 (m, 4H), 2.41–2.25 (m, 1H), 2.11–1.96 (m, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 158.8$, 147.1, 136.4, 133.6, 133.4, 130.6, 130.3, 128.7, 128.6, 128.5, 127.1, 127.0, 126.9, 126.7, 123.5, 114.7, 74.7, 71.9, 55.8, 51.6, 45.7, 42.8, 36.9, 35.8, 26.9 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{31}N_4O_2$ 443.2447, found 443.2438.

(±)-trans-3-Benzyloxy-4-[1-(4-methoxyphenethyl)-1H-1,2,3-triazol-4-yl]piperidine (**8bb**, $C_{23}H_{28}N_4O_2$)
The title compound was prepared from 0.100 mg Boc-protected piperidine **5bb** (0.20 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **8bb** as a colorless solid (50 mg, 50 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.75–9.56$ (m, 1H), 9.39–9.20 (m, 1H), 7.33–7.24 (m, 3H), 7.21–7.13 (m, 2H), 7.07 (s, 1H), 6.99 (d, $J = 8.6$ Hz, 2H), 6.80 (d, $J = 8.6$ Hz, 2H), 4.57–4.43 (m, 3H), 4.36 (d, $J = 11.6$ Hz, 1H), 3.99–3.89 (m, 1H), 3.75 (s, 3H), 3.60–3.49 (m, 1H), 3.43–3.30 (m, 1H), 3.20–2.93 (m, 5H), 2.40–2.29 (m, 1H), 2.14–1.99 (m, 1H) ppm; ^{13}C NMR (101 MHz, MeOH-d_4): $\delta = 159.1$, 146*, 137.5, 130.0, 129.1, 128.8, 128.4, 128.3, 122.2, 114.6, 73.8, 72.4, 55.6, 52.3, 45.8, 42.7, 36.7, 36.1, 26.0 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{29}N_4O_2$ 393.2291, found 393.2283.

(±)-trans-3-(Naphthalen-2-ylmethoxy)-4-(1-phenyl-1H-1,2,3-triazol-4-yl)piperidine (**8ca**, $C_{24}H_{24}N_4O$)
The title compound was prepared from 47 mg Boc-protected piperidine **5ca** (0.097 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **8ca** as a colorless solid (28 mg, 57 %). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.02–8.93$ (m, 1H), 8.85–8.73 (m, 1H), 8.68 (s, 1H), 7.89–7.82 (m, 3H), 7.82–7.74 (m, 2H), 7.70 (s, 1H), 7.60 (t, $J = 7.8$ Hz, 2H), 7.53–7.43 (m, 3H), 7.33–7.26 (m, 1H), 4.78 (d, $J = 12.2$ Hz, 1H), 4.63 (d, $J = 12.2$ Hz, 1H), 4.04–3.93 (m, 1H), 3.65–3.55 (m, 1H), 3.35–3.23 (m, 2H), 3.16–3.01 (m, 2H), 2.26–2.16 (m, 1H), 2.14–2.01 (m, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 148.5$, 137.6, 136.4, 133.6, 133.4, 130.8, 129.5, 128.7, 128.54, 128.47, 127.12, 127.06, 126.9, 126.7, 122.0, 120.8, 74.6, 71.8, 45.7, 42.8, 37.1, 26.7 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{25}N_4O$ 385.2028, found 385.2021.

(±)-trans-3-(Naphthalen-2-ylmethoxy)-4-(1-phenethyl-1H-1,2,3-triazol-5-yl)piperidine (**9aa**, $C_{26}H_{28}N_4O$)
The title compound was prepared from 75 mg Boc-protected piperidine **6aa** (0.15 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **9aa** as a colorless solid (38 mg, 45 %). ^{1}H NMR (400 MHz, MeOH-d_4): $\delta = 7.88–7.82$ (m, 1H), 7.82–7.73 (m, 2H), 7.55–7.44 (m, 4H), 7.28–7.17 (m, 3H), 7.06–6.96 (m, 3H), 4.74–4.55 (m, 3H), 4.43 (d, $J = 11.9$ Hz, 1H), 3.80–3.68

(m, 1H), 3.58–3.47 (m, 1H), 3.37–3.31 (m, 1H), 3.26–3.09 (m, 2H), 2.98–2.89 (m, 1H), 2.89–2.78 (m, 1H), 2.78–2.67 (m, 1H), 1.85–1.71 (m, 1H), 1.57–1.46 (m, 1H) ppm; ^{13}C NMR (101 MHz, MeOH-d_4): δ = 140.8, 140.0, 136.4, 135.5, 135.4, 132.1, 131.0, 130.6, 130.3, 129.8, 129.6, 129.0, 128.8, 128.3, 128.2, 127.5, 77.5, 74.1, 51.6, 48.0, 45.2, 38.4, 38.1, 28.3 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{29}N_4O$ 413.2341, found 413.2334.

(±)-trans-4-[1-(4-Methoxyphenethyl)-1H-1,2,3-triazol-5-yl]-3-(naphthalen-2-ylmethoxy)piperidine
(**9ba**, $C_{27}H_{30}N_4O_2$)
The title compound was prepared from 50 mg Boc-protected piperidine **6ba** (0.092 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **9ba** as a colorless solid (30 mg, 74 %). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.84–7.79 (m, 1H), 7.78–7.69 (m, 2H), 7.50–7.41 (m, 4H), 6.99 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 4.67 (d, J = 11.9 Hz, 1H), 4.63–4.47 (m, 2H), 4.39 (d, J = 11.9 Hz, 1H), 3.77–3.66 (m, 4H), 3.57–3.46 (m, 1H), 3.38–3.28 (m, 1H), 3.15–2.97 (m, 2H), 2.96–2.77 (m, 2H), 2.75–2.64 (m, 1H), 1.86–1.72 (m, 1H), 1.62–1.49 (m, 1H) ppm; ^{13}C NMR (101 MHz, MeOH-d_4): δ = 160.1, 140.0, 135.6, 134.6, 134.5, 131.1, 130.9, 129.4, 128.9, 128.7, 128.1, 127.4, 127.3, 126.6, 115.1, 76.6, 73.2, 55.7, 51.1, 47.2, 44.3, 37.2, 36.7, 27.6 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{31}N_4O_2$ 443.2447, found 443.2435.

(±)-N-[4-[2-[5-[trans-3-(Naphthalen-2-ylmethoxy)piperidin-4-yl]-1H-1,2,3-triazol-1-yl]ethyl]phenyl]acetamide
(**9da**, $C_{28}H_{31}N_5O_2$)
The title compound was prepared from 30 mg **6da** (0.053 mmol) using method E. Purification by semi-preparative HPLC and lyophilization gave the TFA salt of **9da** as a colorless solid. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.85–7.78 (m, 1H), 7.77–7.69 (m, 2H), 7.68–7.59 (m, 2H), 7.49–7.42 (m, 3H), 7.34 (d, J = 7.8 Hz, 2H), 7.06–6.97 (m, 1H), 6.91 (d, J = 7.8 Hz, 2H), 4.70–4.52 (m, 3H), 4.49–4.28 (m, 1H), 3.73–3.61 (m, 1H), 3.61–3.48 (m, 1H), 3.21–3.00 (m, 3H), 3.00–2.76 (m, 2H), 2.72–2.51 (m, 1H), 2.06 (s, 3H), 1.82–1.67 (m, 1H), 1.68–1.52 (m, 1H) ppm; ^{13}C NMR (101 MHz, MeOH-d_4): δ = 171.6, 138.6, 135.6, 134.6, 133.1, 133.0, 130.4, 130.1, 129.4, 128.9, 128.7, 128.0, 127.4, 127.3, 127.0, 126.6, 122.1, 76.8, 73.5, 50.8, 47.3, 44.5, 37.4, 37.0, 27.5, 23.7 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{32}N_5O_2$ 470.2556, found 470.2537.

(±)-N-[3-[2-[5-[trans-3-(Naphthalen-2-ylmethoxy]piperidin-4-yl]-1H-1,2,3-triazol-1-yl]ethyl]phenyl]acetamide
(**9ea**, $C_{28}H_{31}N_5O_2$)
The title compound was prepared from 0.127 g **6ea** (0.22 mmol) using method E. Purification by semi-preparative HPLC and lyophilization gave the TFA salt of **9ea** as a colorless solid (0.100 g, 78 %). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.84–7.78 (m, 1H), 7.78–7.68 (m, 2H), 7.50–7.44 (m, 2H), 7.42 (s, 2H), 7.33 (s, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 7.4 Hz, 1H), 4.75–4.51 (m, 3H), 4.38 (d, J = 12.0 Hz, 1H), 3.76–3.63 (m, 1H), 3.55–3.41 (m, 1H), 3.35–3.24 (m, 1H), 3.22–3.12 (m, 1H), 3.12–3.01 (m, 1H), 2.90 (t, J = 11.4 Hz, 1H), 2.85–2.73 (m, 1H), 2.73–2.62 (m, 1H), 2.09 (s, 3H), 1.84–1.69 (m, 1H), 1.50–1.40 (m, 1H) ppm; ^{13}C NMR (101 MHz, MeOH-d_4): δ = 171.8, 140.1, 140.0, 135.6, 134.6, 134.5, 130.2, 129.4, 128.9, 128.7, 128.0, 127.4, 127.3, 126.6, 126.1, 122.4, 120.2, 76.7, 73.2, 50.8, 47.2, 44.2, 37.7, 37.2, 27.4, 23.8 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{32}N_5O_2$ 470.2556, found 470.2553.

(±)-N-[4-[2-[5-[trans-3-(Naphthalen-2-ylmethoxy]piperidin-4-yl]-1H-1,2,3-triazol-1-yl]ethyl]phenyl]-N-(naphthalen-2-ylmethyl)acetamide (**9fa**, $C_{39}H_{39}N_5O_2$)
The title compound was prepared from 50 mg **6fa** (0.07 mmol) using method E. Purification by semi-preparative HPLC and lyophilization gave the TFA salt of the title compound as a colorless solid (24 mg, 47 %). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.84–7.66 (m, 5H), 7.65 (d, J = 8.6 Hz, 1H), 7.51–7.37 (m, 7H), 7.35–7.23 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 7.6 Hz, 2H), 6.83 (d, J = 7.9 Hz, 2H), 4.95 (s, 3H), 4.67 (d, J = 11.8 Hz, 1H), 4.51 (t, J = 7.4 Hz, 2H), 4.37 (d, J = 11.7 Hz, 1H), 3.86–3.71 (m, 1H), 3.65–3.54 (m, 1H), 3.28–3.20 (m, 1H), 3.16–3.05 (m, 3H), 3.03–2.89 (m, 1H), 1.85–1.73 (m, 5H) ppm; ^{13}C NMR (101 MHz, MeOH-d_4): δ = 173.0, 142.3, 139.7, 139.1, 136.0, 135.6, 134.7, 134.6, 134.5, 134.2, 131.1, 129.4, 129.3, 129.2, 129.0, 128.8, 128.7, 128.3, 128.2, 127.40, 127.37, 127.3, 127.0, 126.8, 76.8, 73.3, 53.8, 50.1, 47.1, 44.2, 37.1, 36.2, 27.9, 22.6 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{40}N_5O_2$ 610.3182, found 610.3177.

(±)-N-[3-[2-[5-[trans-3-(Naphthalen-2-ylmethoxy]piperidin-4-yl]-1H-1,2,3-triazol-1-yl]ethyl]phenyl]-N-(naphthalen-2-ylmethyl)acetamide (**9ga**, $C_{39}H_{39}N_5O_2$)
The title compound was prepared from 17 mg **6ga** (0.024 mmol) using method E. Purification by semi-preparative HPLC and lyophilization gave the TFA salt of the title compound as a colorless solid. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.82–7.77 (m, 2H), 7.77–7.68 (m, 4H), 7.52–7.38 (m, 7H), 7.31 (d, J = 8.4 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 7.01–6.92 (m, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.63 (s, 1H), 5.00–4.84 (m, 4H), 4.62 (d, J = 11.8 Hz, 1H), 4.55–4.42 (m, 2H), 4.35 (d, J = 11.8 Hz, 1H), 3.80–3.68 (m, 1H), 3.60–3.51 (m, 1H), 3.17–3.00 (m, 3H), 3.00–2.87 (m, 2H), 1.86–1.70 (m, 5H) ppm; ^{13}C NMR (126 MHz, MeOH-d_4): δ = 172.9,

143.8, 140.8, 139.6, 136.0, 135.5, 134.7, 134.6, 134.5, 134.2, 131.5, 130.8, 129.8, 129.7, 129.5, 129.3, 128.9, 128.8, 128.7, 128.7, 128.4, 128.1, 127.8, 127.5, 127.5, 127.4, 127.3, 127.0, 126.7, 76.8, 73.3, 53.8, 50.2, 47.1, 44.2, 37.1, 36.5, 27.8, 22.8 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{40}N_5O_2$ 610.3182, found 610.3207.

(±)-trans-4-[1-(4-Methoxyphenethyl)-1H-1,2,3-triazol-4-yl]piperidin-3-yl 2-naphthoate (**10ba**, $C_{27}H_{28}N_4O_3$)
The title compound was prepared from 95 mg Boc-protected piperidine **7ba** (0.18 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **10ba** as a colorless solid (50 mg, 40 %). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.18–8.95$ (m, 2H), 8.67 (s, 1H), 8.14 (d, $J = 8.0$ Hz, 1H), 8.11–7.98 (m, 4H), 7.74–7.61 (m, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 6.60 (d, $J = 8.4$ Hz, 2H), 5.47–5.38 (m, 1H), 4.48 (t, $J = 7.0$ Hz, 2H), 3.63–3.54 (m, 4H), 3.54–3.43 (m, 1H), 3.37–3.24 (m, 2H), 3.24–3.12 (m, 1H), 2.96 (t, $J = 6.9$ Hz, 2H), 2.31–2.19 (m, 1H), 2.19–2.04 (m, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 164.8$, 157.8, 145.4, 135.2, 132.0. 131.1, 129.5, 129.4, 129.3, 128.9, 128.4, 127.8, 127.2, 126.4, 124.9, 122.5, 113.6, 69.1, 54.8, 50.9, 44.2, 41.7, 34.9, 25.7 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{29}N_4O_3$ 457.2240, found 457.2235.

(±)-trans-4-[1-(4-Methoxyphenethyl)-1H-1,2,3-triazol-4-yl]piperidin-3-yl benzoate (**10bb**, $C_{23}H_{26}N_4O_3$)
The title compound was prepared from 95 mg Boc-protected piperidine **7bb** (0.19 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **10bb** as a colorless solid (55 mg, 53 %). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.13–8.91$ (m, 2H), 8.04–7.95 (m, 3H), 7.69 (t, $J = 7.4$ Hz, 1H), 7.55 (t, $J = 7.7$ Hz, 2H), 6.91 (d, $J = 8.5$ Hz, 2H), 6.67 (d, $J = 8.5$ Hz, 2H), 5.39–5.30 (m, 1H), 4.49 (t, $J = 7.0$ Hz, 2H), 3.66 (s, 3H), 3.58–3.50 (m, 1H), 3.45–3.37 (m, 1H), 3.34–3.09 (m, 3H), 2.98 (t, $J = 7.0$ Hz, 2H), 2.26–2.15 (m, 1H), 2.14–2.00 (m, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 165.6$, 158.8, 146.3, 134.7, 130.5, 130.4, 130.3, 130.0, 129.7, 123.4, 114.6, 69.9, 55.9, 51.8, 45.1, 42.6, 35.8, 35.8, 26.6 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{27}N_4O_3$ 407.2083, found 407.2077.

(±)-trans-4-(1-Phenyl-1H-1,2,3-triazol-4-yl)piperidin-3-yl 2-naphthoate (**10ca**, $C_{24}H_{22}N_4O_2$)
The title compound was prepared from 75 mg Boc-protected piperidine **7ca** (0.15 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **10ca** as a colorless solid (35 mg, 46 %). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.65$ (s, 1H), 8.05 (s, 1H), 7.97 (s, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.28–7.22 (m, 3H), 7.06 (d, $J = 8.0$ Hz, 2H), 6.96–6.82 (m, 2H), 6.78 (t, $J = 7.8$ Hz, 2H), 6.68 (t, $J = 7.4$ Hz, 1H), 5.05–4.66 (m, 1H), 2.87–2.79 (m, 2H), 2.65–2.40 (m, 3H), 1.68–1.58 (m, 1H), 1.58–1.50 (m, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 164.8$, 147.5, 137.5, 136.1, 132.9, 132.1, 130.8, 130.3, 129.8, 129.6, 129.3, 128.7, 128.0, 127.3, 125.9, 122.1, 120.8, 69.8, 44.9, 42.2, 35.7, 25.8 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_4O_2$ 399.1821, found 399.1820.

(±)-trans-4-(1-Phenyl-1H-1,2,3-triazol-4-yl)piperidin-3-yl benzoate (**10cb**, $C_{20}H_{20}N_4O_2$)
The title compound was prepared from 50 mg Boc-protected piperidine **7cb** (0.11 mmol) using method E. Purification by semi-preparative RP-HPLC afforded **10cb** as a colorless solid (28 mg, 55 %). ^{1}H NMR (400 MHz, MeOH-d_4): $\delta = 8.50$ (s, 1H), 8.05 (d, $J = 7.2$ Hz, 2H), 7.76 (d, $J = 7.9$ Hz, 2H), 7.63 (t, $J = 7.4$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 2H), 7.52–7.43 (m, 3H), 5.61–5.51 (m, 1H), 3.84–3.75 (m, 1H), 3.67–3.52 (m, 2H), 3.43–3.24 (m, 2H), 2.54–2.41 (m, 1H), 2.41–2.27 (m, 1H) ppm; ^{13}C NMR (101 MHz, MeOH-d_4): $\delta = 167.4$, 148.7, 139.2, 135.8, 131.8, 131.7, 131.2, 131.0, 130.6, 123.3, 122.4, 71.0, 46.9, 44.3, 37.4, 27.6 ppm; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}N_4O_2$ 349.1665 found: 349.1661.

In vitro fluorimetric assays

The SensoLyte®520 Renin Assay Kit Fluorimetric (AnaSpec, CA, USA, supplied by Biosite, Sweden) was used to determine the inhibitory activity of the final compounds at 5 μM and 75 μM following the endpoint protocol for 96-well microtiter plate experiments as described by the manufacturer. Two different endpoint concentrations were used in order to differentiate the activity of the compounds. Briefly, test compounds were dissolved in DMSO and diluted with the assay buffer provided with the kit. The final DMSO level in the assay did not exceed 1 %. Test compounds and renin were added to the wells of a black 96-well microtiter plate (Non-Binding Surface, Corning, NY, USA) and incubated while protected from light for 30 min at 37 °C. Pre-incubated substrate, 30 min at 37 °C, was then added to each well before being gently shaken and further incubated for 15 min at 37 °C. The fluorescence signal was then immediately read at Ex/Em wavelengths 490/520 nm with a SpectraMax M2^e (Molecular Devices Corp., CA, USA) and the results processed using SOFTMAX®PRO software, version 5.2 (Molecular Devices Corp., CA, USA). Controls included in every experiment were the signal from the test compound alone, inhibition control by the provided kit inhibitor, a 100 % activity control, and a vehicle control containing DMSO at the same concentration as in the test compound solution. The mean of the substrate background was subtracted from the RFU of all parallels. The

SensoLyte®520 assay was also used for determining the IC_{50} value for compound **9ga**. The assay protocol was followed as stated in the manual for kinetic reading with the exception that data were collected every 30 s instead of every 60 s as recommended in the instructions. The same instrument and wavelength settings as described for the endpoint assay were applied. The concentration range applied for the IC_{50} determination was 10 nM to 15 μM, with 12 different concentrations in total, each tested in 3 parallels. The DMSO concentration did not exceed 1 %. The inhibitor supplied with the assay kit was used as the 100 % inhibition of renin at a concentration set to 100 μM, and the 100 % activity assay control was used as the 0 % inhibition value in the analysis and set to a concentration of 1 nM. The data were normalized and analyzed with non-linear regression, one site Fit IC_{50} using GraphPad Prism v5.00 (GraphPad Software Inc., CA, USA).

The BACE1 (β-secretase) FRET Assay Kit, Red (PanVera), was used to determine the inhibition effect of the final compounds at 300 μM against β-secretase. The manufacturer's protocol for endpoint assay was followed, with the exception of an increase to four times the recommended volumes of all solutions to achieve appropriate signals. The test compounds were dissolved in DMSO and diluted with 50 mM sodium acetate pH 4.5 buffer. The final DMSO content in the assay did not exceed 10 %. The substrate and test compounds were added to a black 96-well microtiter plate (Non-Binding Surface, Corning, NY, USA) and mixed. BACE1 enzyme was added to start the reactions, and the plate was gently shaken. The microtiter plate was incubated at room temperature for 60 min protected from light before 2.5 M sodium acetate was added to immediately stop the enzymatic reaction. The signals were read on a SpectraMax M2^e (Molecular Devices Corp., CA, USA) at Ex/Em wavelength 545/585 nm. All resulting data were processed using the SOFTMAX®PRO software, version 5.2 (Molecular Devices Corp., CA, USA). The mean substrate background was subtracted from all signals, along with the compounds' own signals. Assay controls included a 100 % activity control with the same amount of DMSO as the test compounds, an inhibitor control with the commercial inhibitor β-secretase inhibitor IV (Calbiochem®, no. 565788, Merck), and a test of the signal from the compounds alone. All endpoint data were normalized using GraphPad Prism, v5.00 (GraphPad Software Inc., CA, USA).

Molecular docking

The coordinates of four piperidine-based inhibitors in complex with renin were obtained from the protein data bank (PDB codes: 3OAG [9], 3OAD [9], 2FS4 [17], and 3O9L [9]). All complexes were prepared using the Protein Preparation Wizard in Maestro [20]. Crystallographic water molecules were removed, and all hydrogen atoms added. Hydrogen-bonding patterns were analyzed and optimized, and Asp219 was protonated on the innermost oxygen, as suggested by Friedman and Caflisch [21]. Finally, the molecular structures were energy minimized prior to docking experiments. The ligand library was built in LigPrep [17], and the generated docking grids were prepared in Glide [17] by centering on the catalytic aspartate dyad.

Molecular docking was carried out using the Glide program [11]. Based on information from experimental crystal structures of renin complexed with piperidine-based inhibitors, three constraints were applied to reduce the number of false poses. The charged nitrogen atom in the piperidine ring was required to be placed within a sphere of 1-Å radius of the corresponding nitrogen position in the 2FS4 structure, and the two hydrogens of the piperidine nitrogen were required to be within hydrogen-bonding distance to the two catalytic aspartates. The grid generation and docking were repeated to obtain a more customized constraint system for our system.

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