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Synthesis, biological evaluation and docking studies of octane-carboxamide based renin inhibitors with extended segments toward S3′ site of renin

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ABSTRACT

Eighteen octane-carboxamide based renin inhibitors with extended segments for mimicking P3′ unit of angiotensinogen have been synthesized. The biological evaluation identified novel renin inhibitors with more potent activity than aliskiren. Molecular docking studies showed that the extended amide-tails matched the P3′ position of angiotensinogen and exerted interactions with the S3′ site of renin. An unexpected π–π stacking interaction was observed during docking study for compound 9r, which could be a reasonable explanation for the outstanding potency of this compound. Further study is in progress to reveal a feasibility for developing novel renin inhibitors based on the possible non-classical interactions between the ligands and the new subsite of renin.

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1. Introduction

Renin, which initiates the generation of the potent vasoconstrictor angiotensin II (Ang II) by cleavaging of the Leu[10]-Val[11] peptide bond of angiotensinogen, is the first and rate-limiting step of renin-angiotensinogen system (RAS). It has been recognized as a promising drug target for hypertension control for decades.[1,2] In contrast to angiotensin-converting enzyme (ACE), renin exhibits a remarkably high specificity since angiotensinogen is its only known physiological substrate.[1] That is to say, renin inhibition will not cause undesirable side effects resulting from interference on side metabolic pathways. Given the high specificity and upstream position of renin in the RAS cascade, inhibition of renin is thought to achieve more complete renin-angiotensin system blockade.[3]

Early renin inhibitors were designed based on peptidic or peptidomimetic scaffold which suffered from low stability and poor oral bioavailability in human.[4] None of the first-generation peptidic renin inhibitors successfully went through clinical testing due to short duration of action and weak blood-pressure-lowering activity. By means of molecular modeling and X-ray crystal structure determination, new generation of non-peptidic renin inhibitors were identified, and significant improvement in pharmacokinetic and pharmacodynamic profiles has been achieved.[1] Aliskiren was identified as a transition-state mimetic non-peptide renin inhibitor (Fig. 1), and was approved by FDA as the first antihypertensive drug from the renin inhibitor category.[5] Aliskiren shows dose-dependent oral activity, long durations of antihypertensive action and end organ protective effects in experimental and clinical studies.[6–8] Systematic investigations on structural modifications of classical dipeptide transition state mimics (TSMs) renin inhibitors have been carried out in the past decade.[9–12] On the other hand, a number of renin inhibitors with new chemotypes have also been identified recently,[13] and a few compounds have entered clinical trials.

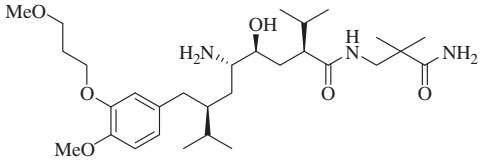

Figure 1. Structure of aliskiren.

There are eight amino acids located left and right of the Leu[10]-Val[11] cleavage site of angiotensinogen, which binds to subsites of human renin. The corresponding positions of the octapeptide sequence are positions P5 to P3′.[14] Intense studies have been performed in the area between P4 and P2′ to identify non-peptide renin inhibitors, indicating that the P3, P1, P1′ and P2′ positions are critical for binding.[9,10] On the other hand, there are few studies concerning the impact of the P3′ position binding to renin.[15] Herein, we describe synthesis and biological evaluation of a series of novel aliskiren analogues which possess extended segments to mimick P3′ position binding to renin. The terminal amide of aliskiren plays as an anchor that tack the amide tail of aliskiren in S2′

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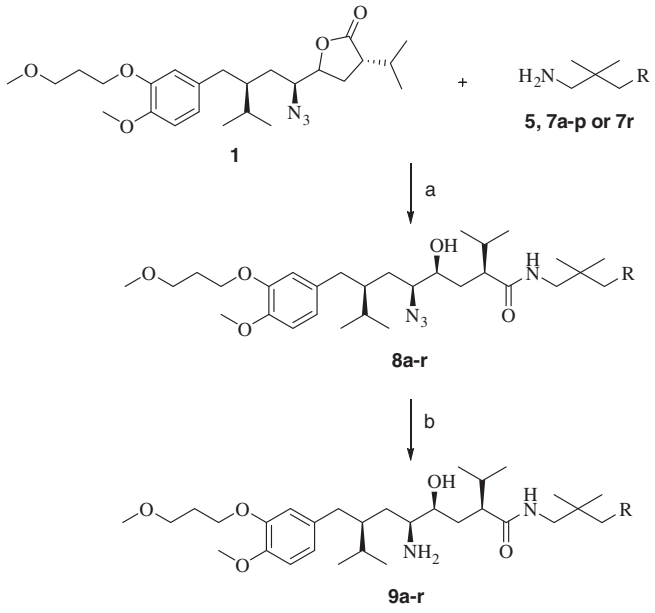


Scheme 1. Reagents and conditions: (a) 2-hydroxypyridine, TEA, 65 °C, 5–8 h; (b) H_2, Pd/C, *tert*-butyl methyl ether, ethanolamine, 25 °C, 0.5–1 h.

position, forming hydrogen bond with Arg74.[5] We designed inhibitors containing amide bioisosteres at the position of terminal amide, which act as alternative anchors fixing the tail at the S2′ position, and may lead the extended moieties to S3′ site. Moreover, molecular docking studies have been performed to confirm the binding mode of the test compounds.

2. Results and discussion

2.1. Chemistry

The synthesis of compounds **9a–r** is outlined in Scheme 1. Ring-opening of lactone **1**, which was readily prepared following the literature procedures,[16] with amines **5** or **7a–r** in the presence of 2-hydroxypyridine afforded octanamides **8a–r**. Hydrogenative reduction of **8a–r** in the presence of Pd/C provided the target compounds **9a–r**.

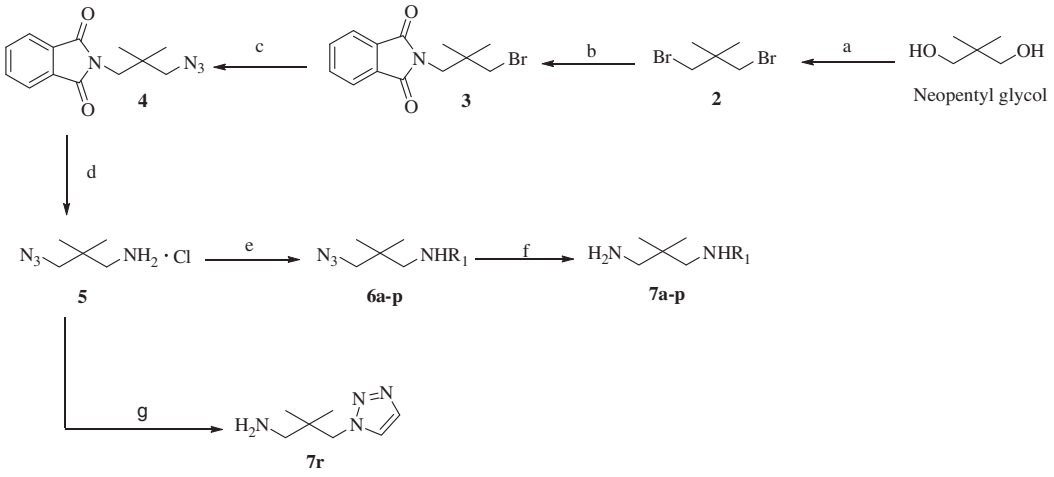
Amines **7a–r** were prepared from neopentyl glycol according to the synthetic route depicted in Scheme 2. 1,3-Dibromo-2,2-dimethylpropane (**2**) was obtained by reaction of neopentyl glycol with triphenylphosphine and bromine in acetonitrile.[17] Alkylation of **2** with potassium phthalimide yielded 2-(3-bromo-2,2-dimethylpropyl) isoindoline-1,3-dione (**3**). Azidation of **3** with NaN_3 in DMF gave azide **4**. Dephthaloylation of **4** in the present of 85% hydrazine hydrate afforded amine **5**. Derivatization of **5** by acid anhydride, acyl halide, sulfonyl halide or sulfamide gave the corresponding azide compounds **6a–p**. Hydrogenative reduction of **6a–p** furnished amine compounds **7a–p**. 'Click' chemical reaction of **5** with acetylene in the presence of $CuSO_4$[18] provided triazole **7r**.

2.2. Renin inhibitory activity and SAR analysis

Eighteen aliskiren analogues (**9a–r**) and aliskiren were tested in renin fluorimetric assay[19] with 'SensoLyte™ 390 Renin Assay Kit' at six different concentrations from 500 to 0.16 nM. The assay result (Tables 1) showed that most of the test compounds exhibited potent inhibitory activity against renin, with IC_{50} values ranging between 0.2 and 5 nM. Incorporation of sulfonamide group (for **9n**: IC_{50} = 0.91 nM), dimethylurea group (for **9o**: IC_{50} = 0.36 nM), aminosulfamide group (for **9p**: IC_{50} = 0.79 nM), and triazole group (for **9r**: IC_{50} = 0.2 nM) into the carboxamide moiety of aliskiren resulted in significant increases in potency. It seems that the introduction of hydrophilicity into this moiety is beneficial for renin inhibitory activity. Compounds with short hydrophobic chains (e.g., **9a**, **9b** and **9f**) had relatively weak inhibitory activity, while compounds with large hydrophobic groups (e.g., **9d**, **9e**, **9g**, **9h**, **9j** and **9l**) showed relatively high potency in comparison with aliskiren. Within this series of compounds, triazole **9r** was the most potent one that was 10-fold more potent than aliskiren (IC_{50} = 2.21 nM).

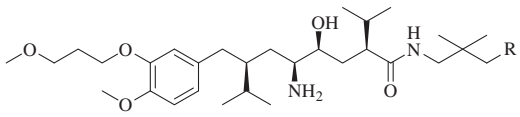
2.3. Docking study

Aliskiren was docked with renin to confirm the effectiveness of the docking method[20] that we used in this study. The docking runs were performed applying the genetic algorithm of GOLD Renin structure used as receptor in docking was obtained from the protein data bank (PDB code: 2v0z). The docking conformation was compared with that of aliskiren from crystallographic determination, resulting in an RMSD value of 0.7597 Å. This result demonstrated that GOLD program could successfully make prediction of



Scheme 2. Synthesis of the amino compounds **7a–r**. Reagents and conditions: (a) PPh_3, Br_2, CH_3CN, 80 °C, 10 h, 65%; (b) potassium phthalimide, DMF, 10 h, 90 °C, 63%; (c) NaN_3, DMF, 8 h, 100 °C, 93%; (d) (i) 85% hydrazine hydrate, ethanol, 80 °C, 4 h; (ii) hydrogen chloride, 93%; (e) acid anhydride/acyl halide/sulfonyl halide, TEA, CH_2Cl_2, 8–12 h, 47–83%, or sulfonamide, dioxane, 105 °C, 15 h, 85%; (f) H_2, 10% Pd/C, 15–20 min, 80–97%; (g) acetylene, $CuSO_4{\cdot}5H_2O$, TEA, CH_2Cl_2, 8–12 h, 84.4%.

Table 1
Renin inhibitory activity of aliskiren and compounds **9a–r**



9a-r

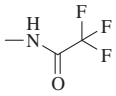
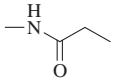
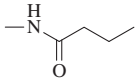
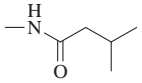
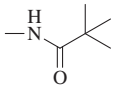
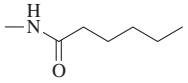
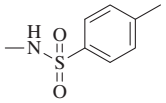
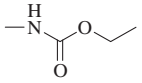
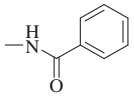
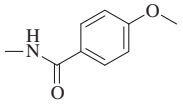
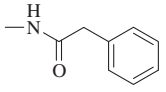
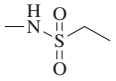
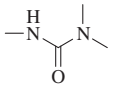
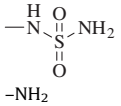
ID	R	IC_{50}[a]
9a		2.17
9b		4.85
9c		1.08
9d		1.12
9e		1.48
9f		4.13
9g		0.83
9h		1.15
9i		0.81
9j		1.02
9k		3.84
9l		1.64
9m		4.23
9n		0.91
9o		0.36
9p		0.79
9q	$-NH_2$	2.88
9r		0.2

Table 1 (*continued*)

ID	R	IC_{50}[a]
Aliskiren[b]		2.21

[a] The IC_{50} values were measured via renin fluorimetric assay.
[b] Aliskiren was used as a positive control.

the mode of aliskiren binding to human renin. The overlay of docking conformation and crystallographic conformation of alikiren is depicted in Figure 2.

There has been no direct unequivocal definition of S3′ site, just prediction based on the crystallographic determination of recombinant human renin.[21] The residues Glu134, Val198, Glu200, Leu222, Asp300, Pro302, Pro307, Thr308 were thought to form the S3′ pocket (the numbering according to 2v0z) before. Since

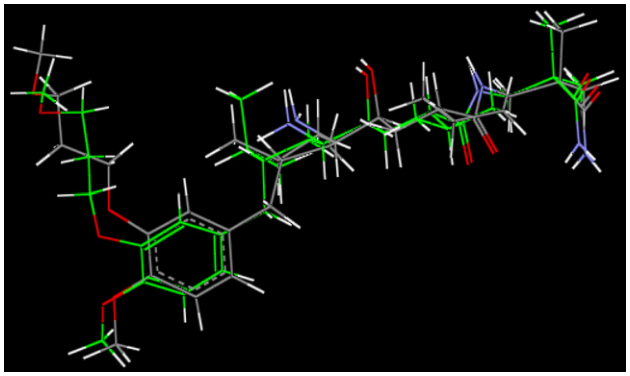


Figure 2. Overlay of binding conformations of aliskiren from docking (colored by atom: carbons: black; oxygens: red; nitrogens: blue; hydrogens: gray) and crystallographic determination (showed in pure color of green) (RMSD 0.7597 Å).

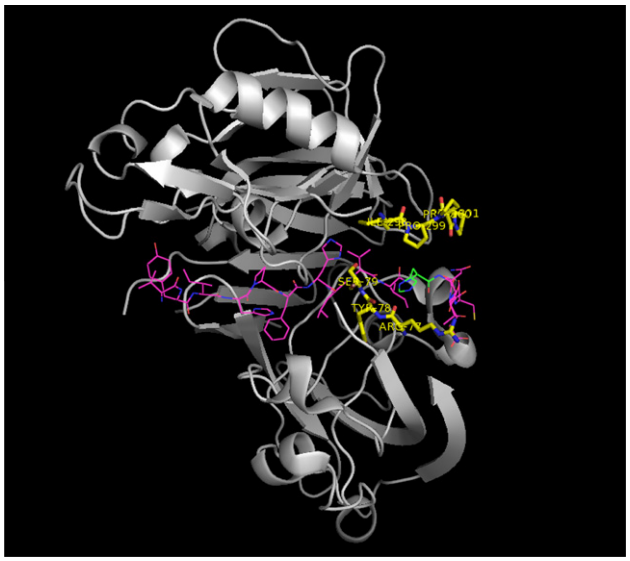


Figure 3. Redefinition of the S3′ pocket directly based on crystal structure of human angiotensinogen (colored by atom: carbons: purple; oxygens: red; nitrogens: blue; hydrogens: gray) (His13 in the P3′ position: carbons in green) complexed with human renin (**PDB** code: 2x0b). The residues (colored by atom: carbons: yellow; oxygens: red; nitrogens: blue) Leu73, Arg74, Tyr75, Ser76, Ile291, Pro292, Pro293, Pro294 were defined as S3′ pocket (the numbering according to 2v0z).

crystal structure of human angiotensinogen complexed with renin (PDB code: 2x0b) was available recently,[22] we tried to redefine the S3′ pocket directly based on the structure of receptor–ligand complex (see Fig. 3).

Compound **9d** was docked into the binding site of renin to seek the binding mode of the extended amide-tail derivatives with renin. The result showed that **9d** was nicely bound to the five aliskiren-binding site pockets on renin ($S3^{sp}$, S3, S1, S1′, S2′), and its binding conformation was stabilized by seven hydrogen bonds with Try 14 (bond length: Try 14 N–H···O = 3.067 Å; bond angle: Try 14 N–H···O = 134.9°), Asp 32 (with 5-NH_2, bond length: Asp 32 = O···H–N 1.855 Å, bond angle: Asp 32 = O···H–N 165.9°; with 4-OH, bond length: Asp 32 = O···H–O 2.040 Å, bond angle: Asp 32 = O···H–O 174.2°), Asp 215 (bond length: Asp 215 = O···H–N 1.802 Å; bond angle: Asp 215 = O···H–N 146.3°), Gly 34 (bond length: Gly34 N–H···O = 1.95 Å; bond angle: Gly34 N–H···O = 172.0°), Ser 76 (bond length: Ser 76 N–H···O = 2.425 Å; bond angle: Ser 76 N–H···O = 148.8°) and Arg 74 (bond length: Arg 74 = O···H–N 1.653 Å; bond angle: Arg 74 = O···H–N 165.6°) (see Fig. 4 for detailed locations of hydrogen bonds). The docked binding conformation showed that the retro-amide bioisostere

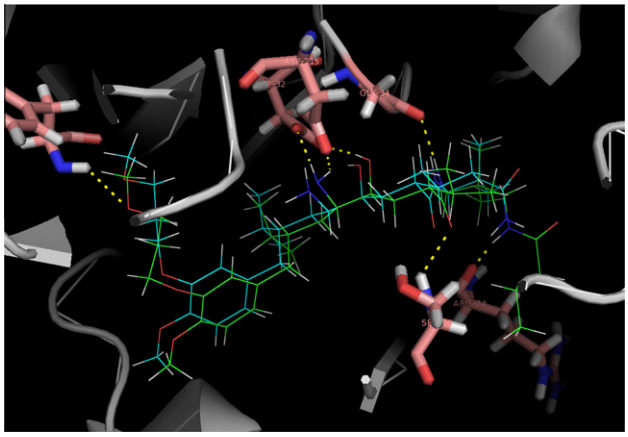


Figure 4. Overlay of conformation of aliskiren from crystal structure (**PDB** code: 2v0z) (colored by atom: carbons: sky blue; oxygens: red; nitrogens: blue; hydrogens: gray) and compound **9d** (colored by atom: carbons: green; oxygens: red; nitrogens: blue; hydrogens: gray) docked with human renin (**PDB** code: 2v0z). The binding conformation of **9d** and seven hydrogen bonds (showed as yellow dotted lines) with corresponding amino acid residues (colored by atom: carbons: pink; oxygens: red; nitrogens: blue; hydrogens: gray).

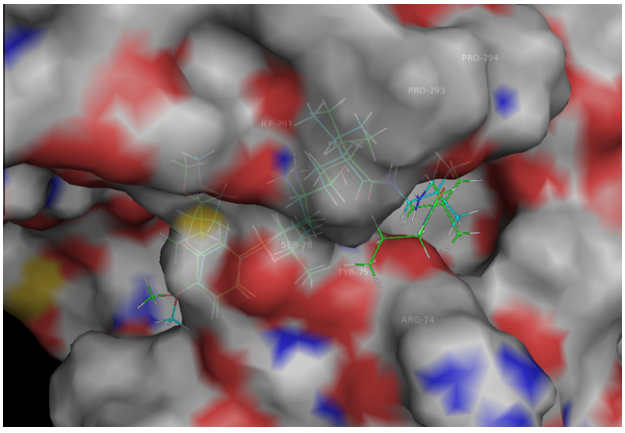


Figure 5. The extended segment of **9d** (colored by atom: carbons: green; oxygens: red; nitrogens: blue; hydrogens: gray) binding with S3′ site pocket (residues Leu73, Arg74, Tyr75, Ser76, Ile291, Pro292, Pro293 and Pro294).

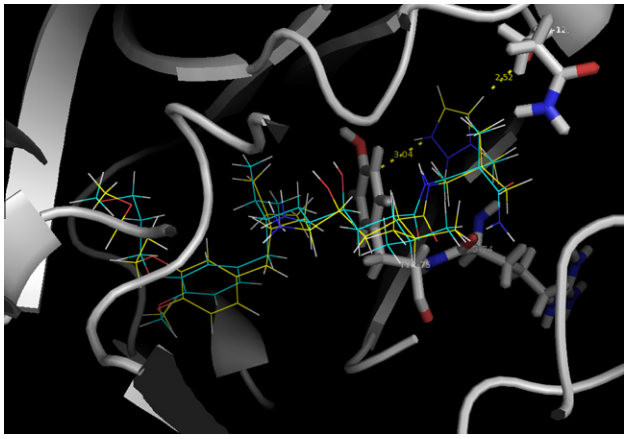


Figure 6. Overlay of conformation of aliskiren from crystal structure (**PDB** code: 2v0z) (colored by atom: carbons: sky blue; oxygens: red; nitrogens: blue; hydrogens: gray) and compound **9r** (colored by atom: carbons: yellow; oxygens: red; nitrogens: blue; hydrogens: gray) docked with human renin (**PDB** code: 2v0z). The unusual binding mode of **9r**: probable hydrogen bond with Gln 128 and π–π stacking interaction with Tyr 75 (showed as yellow dotted lines).

entirely anchors the tail at the S2′ position, and the extended amide-tail moiety of **9d** stretched directly to our new defined S3′ site pocket (see Figs. 4 and 5). Other compounds were also docked with renin, and most of them were found to have the same binding mode with **9d**, except for compound **9r**. The binding result of **9r** showed no hydrogen-bonding interaction with Arg 74. The terminal 1,2,3-triazole group stretched in an opposite direction from S3′ site pocket. The 5-H of 1,2,3-triazole ring formed a C–H···O = hydrogen bond with Gln 128 (bond length: Gln 128 = O···H–C 2.517 Å; bond angle: Gln 128 = O···H–C 173.3°). A probable π–π stacking interaction (center distance: 4.67; closest atom distance: 4.5; lambda angle: 30°; theta angle: 60°) was also found between the aromatic 1,2,3-triazole ring and benzene ring of Tyr 75 (see Fig. 6). This unique binding mode of **9r** could be a reasonable explanation for the particularly high potency of this compound.

3. Conclusions

A series of renin inhibitors with extended amide-tail based on aliskiren have been synthesized and biologically evaluated. Most of the synthesized aliskiren analogues showed higher potency than aliskrien. SAR analysis showed that introduction of hydrophilicity into the amide-tail moiety of aliskiren resulted in significant increases in potency. Compound **9r** was the most potent one among this series of compounds, and was 10-fold more potent than aliskiren. We redefined the S3′ site based on the recently published crystal structure data, and molecular docking was performed to disclose the binding mode of these renin inhibitors. Analysis of the binding conformation of **9d** with renin revealed that the extended segments at the amide-tail did stretch to the S3′ site pocket of renin, and mimicked the P3′ site of angiotensinogen binding to renin. An unexpected π–π stacking interaction was also observed in docking study on **9r** with renin. It could be one of the contributors for the outstanding potency of this compound. Further study is in progress to reveal a feasibility for developing novel renin inhibitors based on the possible non-classical interactions between the ligands and the new subsite of renin.

4. Experimental

SensoLyte™ 390 Renin Assay Kit(Fluorimetric) was purchased from AnaSpec, Inc. Other reagents were purchased from commercial suppliers and were dried and purified when necessary.

Fluorescence intensity was measured with EnVision 2104 Multilabel Reader (PerkinElmer). ^{1}H and ^{13}C NMR spectra were recorded using both Bruker AVANCE-300 (300 MHz) and Bruker AVANCE-500 (500 MHz). Low-resolution mass spectra (MS) and High-resolution mass spectra (HRMS) were obtained using Waters MicroMass Q-Tof (ESI). Optical rotation data were recorded on Jasco p-1020 Polarimeter. Melting Points were checked with Tianfen RY-1 Melting Point Apparatus.

4.1. Chemistry

4.1.1. 1,3-Dibromo-2,2-dimethylpropane (2)

To a solution of triphenylphosphine (26.2 g, 0.1 mol) in acetonitrile (50 mL) was added dropwise a solution of liquid bromine (5.13 ml, 0.1 mol) in acetonitrile (30 mL) at 0 °C, then neopentyl glycol (5.2 g, 0.05 mol) was added. The reaction mixture was heated to 80 °C, and refluxed for 10 h. The solvent was removed under vacuum, light yellow oil **2** (7.5 g, 65%) was obtained by vacuum distillation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 6H), 3.41 (s, 2H), 3.47 (s, 2H).

4.1.2. 2-(3-Bromo-2,2-dimethylpropyl)isoindoline-1,3-dione (3)

A solution of **2** (1.0 g, 4.4 mmol), potassium phthalimide (0.4 g, 2.2 mmol) in DMF (10 mL) was stirred at 90 °C for 10 h. The mixture was poured into H_2O (30 mL) and the suspension was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc, 20:1) gave **3** (0.41 g, 63%) as a white solid: mp 75–76.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 6H), 3.38 (s, 2H), 3.70 (s, 2H), 7.72–7.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 37.6, 44.5, 46.2, 123.3, 131.9, 134.1, 168.7; MS (ESI) *m*/*z* 318.0 $[M+Na]^+$.

4.1.3. 2-(3-Azido-2,2-dimethylpropyl)isoindoline-1,3-dione (4)

A mixture of **3** (0.48 g, 1.6 mmol) and NaN_3 (0.13 g, 1.9 mmol) in DMF (2 mL) was stirred at 100 °C for 8 h. The reaction mixture was poured into H_2O (10 mL) and the suspension was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc, 20:1) gave **4** (0.39 g, 93%) as a white solid: mp 61–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 6H), 3.24 (s, 2H), 3.59 (s, 2H), 7.72–7.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 38.0, 45.7, 60.8, 123.3, 131.9, 134.1, 168.9; MS (ESI) *m*/*z* 281.1 $[M+Na]^+$.

4.1.4. 3-Azido-2,2-dimethylpropan-1-amine (5)

To a solution of **4** (2.6 g, 10 mmol) in ethanol (40 mL) was added 85% hydrazine hydrate (3.12 mL, 50 mmol), and the resulting mixture was stirred at 80 °C for 4 h. The mixture was cooled to room temperature, and the insoluble solids were filtered. The filtrate was poured into H_2O (40 mL), extracted with ethyl ether (2 × 40 mL). The combined organic layer was dried (Na_2SO_4), and then treated with hydrogen chloride. The solution was concentrated under reduced pressure to afford **5** (1.83 g, 93%) as a light yellow solid: mp 86–89 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (s, 6H), 2.66 (s, 2H), 3.48 (s, 2H), 8.25 (br, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.5, 34.5, 45.8, 58.3; MS (ESI) *m*/*z* 129.1 $[M+H]^+$.

4.2. General procedure for the preparation of 6a–o

To a solution of 0.6–1.5 mmol of **5**, triethylamine (2.4 equiv) in CH_2Cl_2 (5 mL) was added slowly acid anhydride (1–1.2 equiv), acyl halide (1–1.2 equiv), or sulfonyl halide (1–1.2 equiv) at 0 °C. The reaction mixture was stirred at 25 °C for 8–12 h. The reaction was quenched with water (15 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated. The title compound was obtained from the residue by means of flash chromatography.

4.2.1. *N*-(3-Azido-2,2-dimethylpropyl)acetamide (6a)

Starting with **5** (164 mg, 1 mmol) and acetic anhydride (110 μL, 1.2 mmol), **6a** (110 mg, 65%) was obtained as a colorless oil after purification by flash chromatography (hexane:EtOAc, 8:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 6H), 2.04 (s, 3H), 3.15–3.19 (m, 4H), 6.04 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 23.3, 23.9, 36.3, 47.4, 60.8, 170.3; MS(ESI) *m*/*z* 193.2 $[M+Na]^+$.

4.2.2. *N*-(3-Azido-2,2-dimethylpropyl)-2,2,2-trifluoroacetamide (6b)

Starting with **5** (100 mg, 0.6 mmol) and trifluoroacetic anhydride (100 μL, 0.72 mmol), **6b** (66 mg, 49%) was obtained as a colorless oil after purification by flash chromatography (hexane:EtOAc, 20:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 6H), 3.35–3.28(m, 4H), 6.69(br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 36.0, 48.0, 61.0, 114.0, 134.1; MS(ESI) *m*/*z* 247.1 $[M+Na]^+$.

4.2.3. *N*-(3-Azido-2,2-dimethylpropyl)propionamide (6c)

Starting with **5** (164 mg, 1 mmol) and propionic andydride (156 μL, 1.2 mmol), **6c** (151 mg, 82%) was obtained as a colorless oil after purification by flash chromatography (hexane:EtOAc, 8:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 6H), 1.17 (t, J = 7.7 Hz, 3H), 2.23 (q, J = 15.2, 7.6 Hz, 2H), 3.16 (s, 1H), 3.18 (s, 3H), 5.71 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0, 23.2, 29.9, 36.4, 47.3, 60.9, 174.0; MS(ESI) *m*/*z* 185.1 $[M+H]^+$.

4.2.4. *N*-(3-Azido-2,2-dimethylpropyl)butyramide (6d)

Starting with **5** (164 mg, 1 mmol) and propionic andydride (154 μL, 1.2 mmol), **6d** (120 mg, 65%) was obtained as a colorless oil after purification by flash chromatography (hexane:EtOAc, 8:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89–0.99 (m, 9H), 1.70 (m, 2H), 2.19 (t, J = 7.3 Hz, 2H), 3.13–3.24 (m, 4H), 5.69 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 19.2, 23.3, 36.4, 38.9, 47.2, 60.9, 173.1; MS(ESI) *m*/*z* 199.1 $[M+H]^+$.

4.2.5. *N*-(3-Azido-2,2-dimethylpropyl)-3-methylbutanamide (6e)

Starting with **5** (164 mg, 1 mmol) and isoveryl chloride (146 μL, 1.2 mmol), **6e** (145 mg, 68.3%) was obtained as a white solid after purification by flash chromatography (hexane:EtOAc, 5:1): mp 43–44 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95–0.98 (m, 12H), 2.05–2.17 (m, 2H), 3.16–3.18 (m, 4H), 5.69 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 23.3, 26.1, 36.4, 46.3, 47.2, 60.9, 172.6; MS(ESI) *m*/*z* 235.1 $[M+Na]^+$.

4.2.6. *N*-(3-Azido-2,2-dimethylpropyl)pivalamide (6f)

Starting with **5** (164 mg, 1 mmol) and pivalyl chloride (147 μL, 1.2 mmol), **6f** (170 mg, 80.1%) was obtained as a colorless oil after purification by flash chromatography (hexane:EtOAc, 5:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.20 (s, 9H), 2.56 (s, 2H), 2.70 (br, 1H), 3.13–3.18 (m, 2H), 5.99 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 27.6, 35.0, 38.7, 48.4, 51.1, 61.2, 178.8; MS(ESI) *m*/*z* 235.1 $[M+Na]^+$.

4.2.7. *N*-(3-Azido-2,2-dimethylpropyl)hexanamide (6g)

Starting with **5** (164 mg, 1 mmol) and *n*-caproic anhydride (277 μL, 1.2 mmol), **6g** (180 mg, 79.5%) was obtained as a colorless oil after purification by flash chromatography (hexane:EtOAc, 5:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88–0.94 (m, 9H), 1.32–1.34 (m, 4H), 1.64 (br, 2H), 2.19 (t, J = 7.4 Hz, 2H), 3.15–3.18 (m, 4H), 5.69 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.4, 23.3, 25.5, 31.5, 36.9, 47.2, 60.1, 173.3; MS(ESI) *m*/*z* 249.2 $[M+Na]^+$.

4.2.8. *N*-(3-Azido-2,2-dimethylpropyl)-4-methylbenzene sulfonamide (6h)

Starting with **5** (200 mg, 1.2 mmol) and *p*-toluenesulfonyl chloride (232 mg, 1.2 mmol), **6h** (280 mg, 83.3%) was obtained as a white solid after purification by flash chromatography (hexane:EtOAc, 5:1): mp 79–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 6H), 2.43 (s, 3H), 2.56 (s, 2H), 2.70 (br, 1H), 3.13–3.18 (m, 2H), 7.26–7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 23.6, 34.2, 51.8, 53.1, 59.8, 127.0, 129.7, 137.2, 142.9; MS(ESI) *m*/*z* 257.0 $[M+H]^+$.

4.2.9. Ethyl (3-azido-2,2-dimethylpropyl)carbamate (6i)

Starting with **5** (200 mg, 1.2 mmol) and ethyl chlorocarbonate (116 μL, 1.2 mmol), **6i** (180 mg, 75%) was obtained as a colorless oil after purification by flash chromatography (hexane:EtOAc, 5:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 6H), 2.43 (s, 3H), 2.56 (s, 2H), 2.70 (br, 1H), 3.13–3.18 (m, 2H), 7.26–7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 23.6, 34.2, 51.8, 53.1, 59.8, 127.0, 129.7, 137.2, 142.9; MS(ESI) *m*/*z* 257.0 $[M+H]^+$.

4.2.10. *N*-(3-Azido-2,2-dimethylpropyl)benzamide (6j)

Starting with **5** (164 mg, 1 mmol) and benzoyl chloride (130 μL, 1.1 mmol), **6j** (160 mg, 69%) was obtained as a white solid after purification by flash chromatography (hexane:EtOAc, 5:1): mp 52–54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 6H), 3.27 (s, 2H), 3.38 (d, *J* = 6.3 Hz, 2H), 6.47 (br, 1H), 7.42–7.78 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 36.5, 48.0, 61.2, 126.8, 128.6, 131.5, 134.6, 167.6; MS(ESI) *m*/*z* 255.1 $[M+Na]^+$.

4.2.11. *N*-(3-Azido-2,2-dimethylpropyl)-4-methoxybenzamide (6k)

Starting with **5** (164 mg, 1 mmol) and 4-methoxybenzoyl chloride (140 μL, 1 mmol), **6k** (165 mg, 63%) was obtained as a white solid after purification by flash chromatography (hexane:EtOAc, 5:1): mp 88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 6H), 3.25 (s, 2H), 3.35 (d, *J* = 6.4 Hz, 2H), 3.84 (s, 3H), 6.39 (br, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 36.6, 47.9, 55.3, 61.2, 113.8, 126.9, 128.6, 162.2, 167.1; MS(ESI) *m*/*z* 263.2 $[M+H]^+$.

4.2.12. *N*-(3-Azido-2,2-dimethylpropyl)-2-phenylacetamide (6l)

Starting with **5** (164 mg, 1 mmol) and phenylacetyl chloride (160 μL, 1.2 mmol), **6l** (161 mg, 65%) was obtained as a colorless oil after purification by flash chromatography (hexane:EtOAc, 5:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 6H), 3.03 (s, 2H), 3.10 (d, *J* = 6.2 Hz, 2H), 3.60 (s, 2H), 5.68 (br, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 36.1, 44.0, 47.6, 61.0, 127.5, 129.0, 129.4, 134.9, 171.1; MS(ESI) *m*/*z* 269.1 $[M+Na]^+$.

4.2.13. *N*-(3-Azido-2,2-dimethylpropyl)methanesulfonamide (6m)

Starting with **5** (250 mg, 1.5 mmol) and methylsulfonyl chloride (201 mg, 1.75 mmol), **6m** (206 mg, 67%) was obtained as a light yellow solid after purification by flash chromatography (hexane:EtOAc, 5:1): mp 45–46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 6H), 2.97 (s, 3H), 2.98 (d, *J* = 6.2 Hz, 2H), 3.20 (s, 2H), 4.74 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 35.8, 40.0, 45.7, 50.8; MS(ESI) *m*/*z* 205.1 $[M-H]^-$.

4.2.14. *N*-(3-Azido-2,2-dimethylpropyl)ethanesulfonamide (6n)

Starting with **5** (200 mg, 1.2 mmol) and ethanesulfonyl chloride (115 μL, 1.2 mmol), **6n** (104 mg, 47.3%) was obtained as a white solid after purification by flash chromatography (hexane:EtOAc, 5:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 6H), 1.37 (t, *J* = 7.4 Hz, 3H), 2.95 (d, *J* = 6.9 Hz, 2H), 3.05 (q, *J* = 7.4 Hz, 2H), 3.24 (s, 2H), 4.86 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.20, 23.1, 35.9, 46.6, 50.7, 59.7; MS(ESI) *m*/*z* 243.1 $[M+Na]^+$.

4.2.15. 3-(3-Azido-2,2-dimethylpropyl)-1,1-dimethylurea (6o)

Starting with **5** (164 mg, 1 mmol) and *N*,*N*-dimethylcarbamoyl chloride (90 μL, 1 mmol), **6o** (95 mg, 47.7%) was obtained as a colorless oil after purification by flash chromatography (hexane:EtOAc, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 6H), 2.92 (s, 6H), 3.15 (d, *J* = 6.2 Hz, 2H), 3.19 (s, 2H), 4.67 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 36.2, 49.0, 61.1, 158.5; MS(ESI) *m*/*z* 222.1 $[M+Na]^+$.

4.2.16. *N*-(3-Azido-2,2-dimethylpropyl)aminosulfamide (6p)

Compound **5** (200 mg, 1.2 mmol) was dissolved in ethyl ether (5 mL) and was neutralized by 0.5 N NaOH. The solution was concentrated carefully under reduced pressure. The residue was dissolved in dioxane (10 mL), and then sulfonamide (900 mg, 5.2 mmol) was added. The resulting mixture was heated to 105 °C, and refluxed for 15 h. The mixture was poured into H_2O (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc, 4:1) gave **6p** (210 g, 85%) as a light yellow solid: mp 69–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 6H), 2.97 (d, *J* = 7.1 Hz, 2H), 3.23 (s, 2H), 4.76 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 35.7, 51.1, 59.9; MS(ESI) *m*/*z* 206.1 $[M-H]^-$.

4.3. General procedure for the preparation of 7a–p

A solution of **6a**–**p** (0.15–0.75 mmol) in methanol (5–10 mL) was hydrogenated in the presence of 20 mg of 10% Pd/C (moist) at 25 °C over 15–20 min. The reaction mixture was filtered and the solids were washed with methanol. The filtrate was concentrated under reduced pressure to give the amine products.

4.3.1. *N*-(3-Amino-2,2-dimethylpropyl)acetamide (7a)

Starting with **6a** (60 mg, 0.35 mmol), **7a** (45 mg, 90%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 6H), 1.52 (br, 1H), 1.98 (s, 3H), 2.54 (s, 2H), 3.15 (d, *J* = 5.8 Hz, 2H), 6.92 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 23.5, 34.8, 48.6, 51.4, 170.1; MS(ESI) *m*/*z* 145.1 $[M+H]^+$.

4.3.2. *N*-(3-Amino-2,2-dimethylpropyl)-2,2,2-trifluoroacetamide (7b)

Starting with **6b** (32 mg, 0.14 mmol), **7b** (27 mg, 94%) was obtained as a white solid: mp 86–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 6H), 1.67 (br, 2H), 2.73 (s, 2H), 3.28 (s, 2H), 9.73 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 33.6, 51.0, 52.5, 118.1, 156.9; MS(ESI) *m*/*z* 199.0 $[M+H]^+$.

4.3.3. *N*-(3-Amino-2,2-dimethylpropyl)propionamide (7c)

Starting with **6c** (100 mg, 0.54 mmol), **7c** (80 mg, 94%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 6H), 1.52 (br, 1H), 1.98 (s, 3H), 2.54 (s, 2H), 3.15 (d, *J* = 5.8 Hz, 2H), 6.92 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 23.5, 34.8, 48.6, 51.4, 170.1; MS(ESI) *m*/*z* 159.1 $[M+H]^+$.

4.3.4. *N*-(3-Amino-2,2-dimethylpropyl)butyramide (7d)

Starting with **6d** (80 mg, 0.40 mmol), **7d** (60 mg, 87%) was obtained as a white solid: mp 105–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 6H), 0.95 (t, *J* = 7.3 Hz, 3H), 1.65 (m, 2H), 1.67 (br, 2H), 2.16 (t, *J* = 7.3 Hz, 2H), 2.53 (s, 2H), 3.15 (d, *J* = 5.9 Hz, 2H), 6.83 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 19.3, 23.5, 38.9, 48.3, 51.4, 173.1; MS(ESI) *m*/*z* 173.1 $[M+H]^+$.

4.3.5. *N*-(3-Amino-2,2-dimethylpropyl)-3-methylbutanamide (7e)

Starting with **6e** (80 mg, 0.40 mmol),**7e** (65 mg, 95%) was obtained as a colorless oi: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 6H), 0.96 (d, J = 6.2 Hz, 6H), 1.90 (br, 2H), 2.03–2.14 (m, 3H), 2.54 (s, 2H), 3.16 (d, J = 5.8 Hz, 2H), 6.80 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 23.6, 26.1, 35.0, 46.4, 48.2, 51.3, 172.6; MS(ESI) m/z 187.1 $[M+H]^+$.

4.3.6. *N*-(3-Amino-2,2-dimethylpropyl)pivalamide (7f)

Starting with **6f** (96 mg, 0.45 mmol), **7f** (78 mg, 92%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 6H), 1.21 (s, 9H), 3.15–3.18 (m, 4H), 5.95 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 27.6, 36.4, 38.8, 47.4, 61.2, 178.5; MS(ESI) m/z 187.2 $[M+H]^+$.

4.3.7. *N*-(3-Amino-2,2-dimethylpropyl)hexanamide (7g)

Starting with **6g** (170 mg, 0.75 mmol), **7g** (145 mg, 97%) was obtained as a white solid: mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.30–1.34 (m, 4H), 1.65 (br, 2H), 2.18 (t, J = 7.4 Hz, 2H), 2.53 (s, 2H), 3.15 (d, J = 5.9 Hz, 2H), 6.85 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.4, 23.5, 25.6, 31.5, 35.0, 37.0, 48.3, 51.4, 173.3; MS(ESI) m/z 201.2 $[M+H]^+$.

4.3.8. *N*-(3-Amino-2,2-dimethylpropyl)-4-methylbenzene-sulfon-amide (7h)

Starting with **6h** (100 mg, 0.35 mmol), **7h** (66 mg, 80.5%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 6H), 2.42 (s, 3H), 2.58 (s, 2H), 2.79 (s, 2H), 4.98 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 27.6, 36.4, 38.8, 47.4, 61.2, 178.5; MS(ESI) m/z 235.1 $[M+Na]^+$.

4.3.9. Ethyl (3-amino-2,2-dimethylpropyl)carbamate (7i)

Starting with **6i** (90 mg, 0.45 mmol), **7i** (76 mg, 97%) was obtained as a gray solid: mp 90–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 6H), 1.24 (t, J = 7.0 Hz, 3H), 1.95 (br, 2H), 2.52 (s, 2H), 3.06 (d, J = 6.1 Hz, 2H), 4.07–4.12 (m, 2H), 5.54 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 23.2, 35.5, 38.8, 49.2, 50.6, 60.7, 157.1; MS(ESI) m/z 175.0 $[M+H]^+$.

4.3.10. *N*-(3-Amino-2,2-dimethylpropyl)benzamide (7j)

Starting with **6j** (60 mg, 0.26 mmol), **7j** (50 mg, 94%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 6H), 1.81 (br, 2H), 2.68 (s, 2H), 3.37 (d, J = 5.3 Hz, 2H), 7.38–7.82 (m, 5H), 8.42 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 34.6, 50.1, 52.1, 126.9, 128.4, 131.1, 134.8, 167.3; MS(ESI) m/z 207.2 $[M+H]^+$.

4.3.11. *N*-(3-Amino-2,2-dimethylpropyl)-4-methoxybenzamide (7k)

Starting with **6k** (105 mg, 0.40 mmol), **7k** (83 mg, 87.7%) was obtained as a white solid: mp 74–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 6H), 1.80 (br, 2H), 2.68 (s, 2H), 3.36 (d, J = 5.3 Hz, 2H), 3.83 (s, 3H), 6.90 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 8.25 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 34.7, 50.0, 52.1, 55.3, 113.6, 127.2, 128.7, 161.9, 166.9; MS(ESI) m/z 237.2 $[M+H]^+$.

4.3.12. *N*-(3-Amino-2,2-dimethylpropyl)-2-phenylacetamide (7l)

Starting with **6l** (120 mg, 0.49 mmol), **7l** (100 mg, 93%) was obtained as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 6H), 1.80 (br, 2H), 2.68 (s, 2H), 3.36 (d, J = 5.3 Hz, 2H), 3.83 (s, 3H), 6.90 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 8.25 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 34.7, 50.0, 52.1, 55.3, 113.6, 127.2, 128.7, 161.9, 166.9; MS(ESI) m/z 237.2 $[M+H]^+$.

4.3.13. *N*-(3-Amino-2,2-dimethylpropyl)methanesulfonamide (7m)

Starting with **6m** (100 mg, 0.49 mmol), **7m** (70 mg, 80%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 6H), 2.64 (s, 2H), 2.93 (s, 3H), 3.01 (s, 2H), 3.01–3.40 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 34.4, 39.7, 51.6, 52.9; MS(ESI) m/z 181.1 $[M+H]^+$.

4.3.14. *N*-(3-Amino-2,2-dimethylpropyl)ethanesulfonamide (7n)

Starting with **6n** (60 mg, 0.27 mmol), **7n** (50 mg, 94%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 6H), 1.36 (t, J = 7.4 Hz, 3H), 2.61 (s, 2H), 2.98–3.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 23.6, 34.4, 46.2, 52.0, 53.3; MS(ESI) m/z 195.1 $[M+H]^+$.

4.3.15. 3-(3-Amino-2,2-dimethylpropyl)-1,1-dimethylurea (7o)

Starting with **6o** (100 mg, 0.50 mmol), **7o** (83 mg, 95%) was obtained as a gray solid: mp 115–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 6H), 2.17 (br, 2H), 2.56 (s, 2H), 2.89 (s, 6H), 3.13 (d, J = 5.3 Hz, 2H), 5.98 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 34.9, 36.2, 50.1, 51.3, 158.9; MS(ESI) m/z 174.2 $[M+H]^+$.

4.3.16. *N*-(3-Amino-2,2-dimethylpropyl)aminosulfamide (7p)

Starting with **6p** (60 mg, 0.29 mmol), **7p** (51 mg, 97%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 6H), 2.65 (s, 2H), 3.02 (s, 2H), 7.57 (s, 1H), 3.00–4.00 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 34.2, 51.8, 53.4; MS(ESI) m/z 180.0 $[M-H]^-$.

4.3.17. 2,2-Dimethyl-3-(1*H*-1,2,3-triazol-1-yl)propan-1-amine (7r)

To a mixture of **5** (164 mg, 1 mmol), 1 N aqueous $CuSO_4{\cdot}5H_2O$ (100 μL, 0.1 mmol) and Et_3N (167 μL, 1.2 mmol) in CH_2Cl_2 (10 mL) was introduced a stream of acetylene gas for 2 h. The mixture was poured into H_2O (20 mL) and extracted with ethyl ether (2 × 20 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford **7r** (0.13 g, 84.4%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 6H), 1.49 (br, 2H), 2.44 (s, 2H), 4.29 (s, 2H), 7.57 (s, 1H), 7.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 36.7, 49.4, 56.9, 124.8, 133.2; MS(ESI) m/z 155.1 $[M+H]^+$.

4.4. General procedure for the preparation of 8a–r

A mixture of 0.11 mmol of **1**, **5**/**7a**–**p**/**7r** (2–5 equiv), triethylamine (10 equiv) and 2-hydroxypyridine (0.2 equiv) was stirred at 65 °C over 5–8 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure. To the residue was added 1 M aqueous sodium hydrogen carbonate, and extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated to afford the crude product.

4.4.1. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(3-amino-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy) benzyl)-8-methylnonanamide (8q)

Starting with **1** (50 mg, 0.11 mmol) and **5** (41 mg, 0.25 mmol), **8q** (41 mg, 63.1%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −14.2 (*c* 0.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87–0.96 (m, 18H), 1.35–1.45 (m, 1H), 1.50–2.00 (m, 6H), 2.07–2.12 (m, 3H), 2.48–2.54 (m, 3H), 2.92 (br, 1H), 3.15 (s, 2H), 3.08–3.28 (m, 2H), 3.36 (s, 3H), 3.41 (br, 1H), 3.58 (t, J = 6.3 Hz, 2H), 3.84 (s, 3H), 4.10 (t, J = 6.6 Hz, 2H), 5.85 (br, 1H), 6.69–6.81 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.8, 20.3, 21.2, 23.4, 29.6, 29.8, 30.2, 32.1, 34.2, 37.5, 42.5, 47.2, 51.1, 56.1, 58.6, 60.9, 66.1, 66.8, 69.4,

71.9, 111. 9, 114.2, 121.2, 133.7, 147.8, 148.5, 175.5; MS(ESI) *m*/*z* 612.3 $[M+Na]^+$; HRMS for $C_{30}H_{52}N_7O_5$+H calcd 590.4030, found 590.4035.

4.4.2. (2*S*,4*S*,5*S*,7*S*)-*N*-(3-Acetamido-2,2-dimethylpropyl)-5-azido-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxy propoxy)benzyl)-8-methylnonanamide (8a)

Starting with **1** (50 mg, 0.11 mmol) and **7a** (39.5 mg, 0.25 mmol), **8a** (33 mg, 49.6%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −21.6 (*c* 0.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86–0.96 (m, 18H), 1.32 (m, 1H), 1.61–1.80 (m, 5H), 1.91 (m, 1H), 2.03 (s, 3H), 2.09 (t, *J* = 6.5 Hz, 2H), 2.12 (br, 1H), 2.50 (m, 2H), 2.92 (m, 3H), 3.12 (m, 2H), 3.36 (s, 3H), 3.42 (br, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 3H), 6.46 (br, 1H), 6.67–6.80 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.9, 20.3, 21.2, 23.3, 23.6, 23.9, 29.6, 30.0, 31.9, 34.3, 36.1, 37.5, 42.5, 45.8, 46.1, 51.2, 56.1, 58.6, 66.2, 66.4, 69.4, 72.0, 112. 0, 114.4, 121.3, 133.9, 147.9, 148.5, 171.1, 176.4; MS(ESI) *m*/*z* 606.4 $[M+H]^+$; HRMS for $C_{32}H_{55}N_5O_6$+H calcd 606.4231, found 606.4235.

4.4.3. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(2,2-dimethyl-3-(2,2,2-trifluor oacetamido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8b)

Starting with **1** (50 mg, 0.11 mmol) and **7b** (49.5 mg, 0.25 mmol), **8b** (45 mg, 62.0%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −5.4 (*c* 0.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88–0.96 (m, 18H), 1.35–1.40 (m, 1H), 1.50–1.91 (m, 6H), 2.07–2.14 (m, 3H), 2.27 (br, 1H), 2.40–2.47 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.56–2.62 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.83–3.00 (m, 3H), 3.12–3.19 (dd, *J* = 14.4, 6.9 Hz, 2H), 3.30 (br, 1H), 3.36 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.84 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 3H), 6.16 (br, 1H), 6.69–6.81 (m, 3H), 8.54 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 19.6, 20.2, 21.1, 23.5, 23.6, 29.6, 30.1, 30.4, 32.4, 34.1, 36.7, 37.6, 42.5, 45.4, 46.7, 50.7, 56.1, 58.6, 66.2, 66.7, 69.4, 72.0, 111. 9, 114.3, 121.3, 133.7, 147.9, 148.5, 157.6, 158.1, 177.3; MS(ESI) *m*/*z* 660.4 $[M+H]^+$; HRMS for $C_{32}H_{52}N_5O_6F_3$+H calcd 660.3948, found 660.3959.

4.4.4. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(2,2-dimethyl-3-propionamidopropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8c)

Starting with **1** (50 mg, 0.11 mmol) and **7c** (46.5 mg, 0.25 mmol), **8c** (40 mg, 57.4%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −6.6 (*c* 0.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.97 (m, 18H), 1.82 (t, *J* = 7.6 Hz, 3H), 1.30–1.40 (m, 1H), 1.59–1.92 (m, 7H), 2.05–2.22 (m, 3H), 2.22–2.35 (m, 2H), 2.50 (d, *J* = 7.1 Hz, 1H), 2.83–2.99 (m, 3H), 3.11–3.23 (m, 2H), 3.36 (s, 3H), 3.36–3.50 (br, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.84 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 3H), 6.38 (br, 1H), 6.69–6.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0, 17.4, 20.0, 20.3, 21.3, 23.5, 23.9, 29.5, 29.6, 29.9, 31.8, 34.4, 36.1, 37.5, 42.5, 45.6, 46.0, 51.2, 56.1, 58.6, 66.1, 66.4, 69.4, 72.0, 111. 9, 114.3, 121.2, 133.9, 147.8, 148.5, 175.1, 176.4; MS(ESI) *m*/*z* 642.4 $[M+Na]^+$; HRMS for $C_{33}H_{56}N_5O_6$+-Na calcd 642.4207, found 642.4214.

4.4.5. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(3-butyramido-2,2-dimethyl-propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxy-propoxy)benzyl)-8-methylnonanamide (8d)

Starting with **1** (50 mg, 0.11 mmol) and **7d** (43 mg, 0.25 mmol), **8d** (39 mg, 56%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −29.8 (*c* 0.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.98 (m, 21H), 1.26–1.34 (m, 1H), 1.59–2.00 (m, 9H), 2.00–2.23 (m, 5H), 2.50 (d, *J* = 7.1 Hz, 2H), 2.84–2.90 (m, 3H), 3.10–3.23 (m, 2H), 3.36 (s, 3H), 3.36–3.55 (br, 1H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.4 Hz, 3H), 6.30 (br, 1H), 6.68–6.99 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 17.3, 19.2, 20.0, 20.3, 21.3, 23.5, 23.9, 29.5, 29.8, 31.8, 34.4, 36.0, 37.5, 42.4, 45.5, 46.0, 51.2, 56.1, 58.6, 66.1, 66.3, 69.4, 72.0, 111. 9, 114.2, 121.2, 133.8, 147.8, 148.4, 174.2, 176.4; MS(ESI) *m*/*z* 656.4 $[M+Na]^+$; HRMS for $C_{34}H_{60}N_5O_6$+H calcd 634.4544, found 634.4550.

4.4.6. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(2,2-dimethyl-3-(3-methyl butan-amido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8e)

Starting with **1** (50 mg, 0.11 mmol) and **7e** (46.5 mg, 0.25 mmol), **8e** (65 mg, 91.5%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −37.4 (*c* 0.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.97 (m, 24H), 1.30–1.40 (m, 1H), 1.58–2.00 (m, 7H), 2.05–2.20 (m, 6H), 2.50 (d, *J* = 7.1 Hz, 2H), 2.84–2.91 (m, 3H), 3.11–3.24 (m, 2H), 3.36 (s, 3H), 3.42 (br, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.84 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 3H), 6.32 (br, 1H), 6.69–6.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 20.0, 20.2, 20.5, 21.3, 22.4, 23.6, 23.8, 24.0, 26.1, 29.6, 29.8, 31.8, 34.4, 36.0, 37.5, 42.4, 45.5, 46.1, 51.2, 56.1, 58.6, 66.1, 66.3, 69.4, 72.0, 111. 9, 114.3, 121.2, 133.8, 147.8, 148.4, 173.7, 176.3; MS(ESI) *m*/*z* 670.5 $[M+Na]^+$; HRMS for $C_{35}H_{61}N_5O_6$+Na calcd 670.4520, found 670.4526.

4.4.7. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(2,2-dimethyl-3-pivalami do-propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxy-propoxy)benzyl)-8-methylnonanamide (8f)

Starting with **1** (50 mg, 0.11 mmol) and **7f** (46.6 mg, 0.25 mmol), **8f** (42 mg, 58.8%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −33.4 (*c* 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.97 (m, 18H), 1.23 (s, 9H), 1.26–1.35 (m, 1H), 1.55–2.00 (m, 6H), 2.00–2.25 (m, 3H), 2.50 (d, *J* = 6.6 Hz, 2H), 2.77–2.95 (m, 4H), 3.13–3.22 (m, 2H), 3.36 (s, 3H), 3.41 (br, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.47 (br, 1H), 6.68–6.80 (m, 4H), 6.84 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 20.0, 20.2, 21.3, 23.5, 23.9, 27.6, 29.5, 29.6, 29.8, 31.8, 34.4, 37.5, 38.9, 42.4, 45.3, 45.9, 51.2, 56.1, 58.6, 66.1, 66.3, 69.4, 72.1, 111. 9, 114.3, 121.2, 133.8, 147.8, 148.4, 176.3, 179.9; MS(ESI) *m*/*z* 670.5 $[M+Na]^+$; HRMS for $C_{35}H_{61}N_5O_6$+Na calcd 670.4520, found 670.4528.

4.4.8. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(3-hexanamido-2,2-dimethyl propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxy propoxy)benzyl)-8-methylnonanamide (8g)

Starting with **1** (50 mg, 0.11 mmol) and **7g** (50 mg, 0.25 mmol), **8g** (60 mg, 82.4%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −28.3 (*c* 0.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.96 (m, 21H), 1.26–1.41 (m, 5H), 1.58–1.81 (m, 8H), 1.81–2.00 (m, 1H), 2.00–2.25 (m, 5H), 2.49 (d, *J* = 7.1 Hz, 2H), 2.84–2.94 (m, 3H), 3.12–3.22 (m, 2H), 3.36 (s, 3H), 3.43 (br, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.84 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.39 (br, 1H), 6.69–6.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 17.3, 20.0, 20.2, 21.3, 22.3, 23.5, 23.9, 25.5, 29.5, 29.6, 29.8, 31.4, 31.8, 34.3, 36.0, 36.9, 37.5, 42.4, 45.6, 46.0, 51.2, 56.1, 58.6, 66.1, 66.4, 69.4, 72.0, 111. 9, 114.3, 121.2, 133.8, 147.8, 148.4, 174.4, 176.4; MS(ESI) *m*/*z* 662.5 $[M+H]^+$; HRMS for $C_{36}H_{63}N_5O_6$+H calcd 662.4857, found 662.4838.

4.4.9. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(2,2-dimethyl-3-(4-methylphenyl sulfonamido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8h)

Starting with **1** (50 mg, 0.11 mmol) and **7h** (64 mg, 0.25 mmol), **8h** (36 mg, 45.6%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −3.0 (*c* 0.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76–0.93 (m, 18H),1.30–1.40 (m, 1H), 1.49–1.85 (m, 6H), 2.02–2.13 (m, 3H), 2.40 (s, 3H), 2.42–2.66 (m, 4H), 2.82–2.98 (m, 2H), 3.23–3.35 (m, 2H), 3.35 (s, 3H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.84 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.12 (br, 2H), 6.69–6.81 (m, 3H), 7.26–7.73 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 19.7, 20.2, 21.0, 21.4, 23.6, 23.8, 29.6, 29.8, 30.2, 32.1, 34.2, 35.7, 37.5, 42.5, 46.4, 50.1, 50.7, 56.1, 58.6,

66.1, 66.5, 69.4, 71.9, 111. 9, 114.3, 121.3, 126.9, 129.6, 133.7, 137.3,143.0, 147.8, 148.4, 176.6; MS(ESI) *m*/*z* 740.4 [M+Na]$^+$; HRMS for $C_{37}H_{59}N_5O_7S$+ Na calcd 740.4033, found 740.4052.

4.4.10. Ethyl (3-((2*S*,4*S*,5*S*,7*S*)-5-Azido-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methyl nonanamido)-2,2-dimethylpropyl)carbamate (8i)

Starting with **1** (50 mg, 0.11 mmol) and **7i** (43.5 mg, 0.25 mmol), **8i** (40 mg, 57%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −27.5 (*c* 0.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.96 (m, 18H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.30–1.39 (m, 1H), 1.50–2.00 (m, 6H), 2.07–2.12 (m, 3H), 2.50(d, *J* = 7.0 Hz, 2H), 2.88–3.22 (m, 5H), 3.36 (s, 3H), 3.43 (br, 1H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.84 (s, 3H), 4.10 (m, 4H), 5.47 (br, 1H), 6.59 (br, 1H),6.71–6.80 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 17.4, 19.9, 20.3, 21.2, 23.3, 23.7, 29.6, 30.0, 31.9, 34.3, 36.1, 37.5, 42.5, 45.6, 47.7, 51.2, 56.1, 58.6, 66.1, 66.5, 69.4, 72.1, 111. 9, 114.2, 121.2, 133.8, 147.8, 148.4, 157.8, 176.1; MS(ESI) *m*/*z* 658.4 [M+Na]$^+$; HRMS for $C_{33}H_{57}N_5O_7$+-Na calcd 658.4156, found 658.4172.

4.4.11. *N*-(3-((2*S*,4*S*,5*S*,7*S*)-5-Azido-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methyl nonanamido)-2,2-dimethylpropyl)benzamide (8j)

Starting with **1** (50 mg, 0.11 mmol) and **7j** (51.5 mg, 0.25 mmol), **8j** (41 mg, 55.8%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −28.3 (*c* 0.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82–0.96 (m, 18H), 1.35–1.45 (m, 1H), 1.57–2.01 (m, 6H), 2.01–2.13 (m, 2H), 2.20 (m, 1H), 2.48 (m, 3H), 2.85–3.25 (m, 4H), 3.36 (s, 3H), 3.30–3.47 (m, 2H), 3.59 (t, *J* = 6.2 Hz, 2H), 3.84 (s, 3H), 4.09 (t, *J* = 6.5 Hz, 2H), 6.67–6.78 (m, 4H),7.43–7.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 19.9, 20.3, 21.3, 23.7, 24.0, 29.6, 29.7, 30.1, 32.0, 34.3, 36.6, 37.5, 42.5, 46.1, 51.1, 56.1, 58.6, 66.1, 66.4, 69.4, 72.1, 111. 9, 114.3, 121.2, 127.0, 128.6, 131.6, 133.8, 134.1, 147.8, 148.4, 168.1, 176.6; MS(ESI) *m*/*z* 690.4 [M+Na]$^+$; HRMS for $C_{37}H_{57}N_5O_6$+Na calcd 690.4207, found 690.4211.

4.4.12. *N*-(3-((2*S*,4*S*,5*S*,7*S*)-5-Azido-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methyl nonanamido)-2,2-dimethylpropyl)-4-methoxybenzamide (8k)

Starting with **1** (50 mg, 0.11 mmol) and **7k** (59 mg, 0.25 mmol), **8k** (45 mg, 58.6%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −29.9 (*c* 0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82–0.98 (m, 18H), 1.35–1.45 (m, 1H), 1.57–2.00 (m, 6H), 2.00–2.15 (m, 2H), 2.19 (m, 1H), 2.48 (d, *J* = 7.1 Hz, 2H), 2.38–2.52 (br, 1H), 2.85–3.25 (m, 4H), 3.36 (s, 3H), 3.40 (m, 2H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 4.09 (t, *J* = 6.4 Hz, 2H), 6.67–6.78 (m, 4H), 7.27 (br, 1H), 6.95–7.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 19.9, 20.3, 21.3, 23.7, 24.0, 29.6, 30.0, 31.9, 34.4, 36.5, 37.5, 42.5, 45.9, 46.1, 51.2, 55.4, 56.1, 58.6, 66.1, 66.4, 69.4, 72.1, 111.9, 113.8, 114.3, 121.2, 126.3, 128.9, 133.8, 147.8, 148.4, 162.3, 167.6, 176.5; MS(ESI) *m*/*z* 698.5 [M+H]$^+$; HRMS for $C_{38}H_{59}N_5O_7$+H calcd 698.4493, found 698.4506.

4.4.13. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(2,2-dimethyl-3-(2-phenyl acetamido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8l)

Starting with **1** (50 mg, 0.11 mmol) and **7l** (55 mg, 0.25 mmol), **8l** (42 mg, 56%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −30.5 (*c* 0.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77–0.96 (m, 18H), 1.30–1.40 (m, 1H), 1.55–2.00 (m, 7H), 2.00–2.22 (m, 3H), 2.50–2.51 (d, *J* = 7.1 Hz, 2H), 2.77–3.17 (m, 5H), 3.35 (s, 3H), 3.45 (br, 1H), 3.57 (m, 4H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.16 (br, 1H), 6.69–6.83 (m, 4H), 7.28–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 20.0, 20.2, 21.3, 23.4, 23.8, 29.5, 29.6, 29.8, 31.7, 34.2, 36.2, 37.5, 42.5, 43.9, 45.4, 46.2, 51.2, 56.1, 58.6, 66.1, 66.3, 69.4, 71.9, 111.9, 114.3, 121.2, 127.1, 127.5, 129.1, 129.2, 133.9, 134.8, 147.8, 148.4, 172.3, 176.2; MS(ESI) *m*/*z* 682.5 [M+H]$^+$; HRMS for $C_{38}H_{59}N_5O_6$+H calcd 682.4544, found 682.4532.

4.4.14. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(2,2-dimethyl-3-(methyl sulfonamido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8m)

Starting with **1** (50 mg, 0.11 mmol) and **7m** (45 mg, 0.25 mmol), **8m** (35 mg, 49.6%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −20.1 (*c* 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72–0.95 (m, 18H), 1.30–1.40 (m, 1H), 1.50–1.95 (m, 6H), 2.05–2.18 (m, 3H), 2.44–2.70 (m, 3H), 2.74–3.20 (m, 5H), 2.90 (s, 3H), 3.35 (s, 3H), 3.37 (br, 1H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.6 Hz, 2H), 5.95 (br, 1H), 6.18 (br, 1H), 6.69–6.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 19.7, 20.3, 21.1, 23.5, 23.7, 29.6, 29.9, 30.2, 32.1, 34.1, 35.8, 37.6, 39.8, 42.5, 46.4, 50.0, 50.7, 56.1, 58.6, 66.2, 66.6, 69.4, 72.0, 112.0, 114.4, 121.3, 133.8, 147.9, 148.5, 176.8; MS(ESI) *m*/*z* 642.4 [M+H]$^+$; HRMS for $C_{31}H_{55}N_5O_7S$+H calcd 642.3900, found 642.3909.

4.4.15. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(3-(ethylsulfonamido)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8n)

Starting with **1** (50 mg, 0.11 mmol) and **7n** (49 mg, 0.25 mmol), **8n** (35 mg, 48.5%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −16.9 (*c* 0.34, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89–0.96 (m, 18H), 1.30–1.40 (m, 1H), 1.35 (t, *J* = 7.4 Hz, 3H), 1.50–1.95 (m, 6H), 2.04–2.18 (m, 3H), 2.44–2.60 (m, 2H), 2.60–2.68 (m, 1H), 2.72–2.83 (m, 2H), 2.91 (br, 1H), 2.97–3.09 (m, 1H), 3.13–3.25 (m, 1H), 3.37 (s, 3H), 3.41 (br, 1H), 3.59 (t, *J* = 6.2 Hz, 2H), 3.85 (s, 3H), 4.11 (t, *J* = 6.5 Hz, 2H), 5.87 (br, 1H), 6.18 (br, 1H), 6.71–6.84 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.2, 17.6, 19.8, 20.3, 21.1, 23.5, 23.6, 29.6, 29.9, 30.2, 32.1, 34.1, 35.9, 37.6, 42.5, 46.3, 46.7, 50.0, 50.7, 56.1, 58.6, 66.2, 66.6, 69.4, 72.0, 112.0, 114.3, 121.3, 133.8, 147.9, 148.5, 176.7; MS(ESI) *m*/*z* 678.4 [M+Na]$^+$; HRMS for $C_{32}H_{57}N_5O_7S$+Na calcd 678.3876, found 678.3888.

4.4.16. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(3-(3,3-dimethylureido)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8o)

Starting with **1** (50 mg, 0.11 mmol) and **7o** (43.3 mg, 0.25 mmol), **8o** (54 mg, 77%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −49.1 (*c* 0.41, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.96 (m, 18H), 1.26–1.35 (m, 1H), 1.55–2.00 (m, 6H), 2.05–2.22 (m, 3H), 2.51 (m, 2H), 2.79–3.30 (m, 5H), 2.93 (s, 6H), 3.36 (s, 3H), 3.45 (br, 1H), 3.57 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 5.07 (br, 1H), 6.68–6.80 (m, 3H), 7.15 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 20.1, 20.2, 21.3, 23.4, 24.0, 29.4, 29.6, 31.7, 34.6, 35.8, 36.3, 37.5, 42.5, 45.2, 47.5, 51.2, 56.1, 58.6, 66.1, 66.5, 69.4, 72.1, 111.9, 114.3, 121.2, 133.9, 147.8, 159.0, 176.1; MS(ESI) *m*/*z* 635.5 [M+H]$^+$; HRMS for $C_{33}H_{58}N_6O_6$+H calcd 635.4496, found 635.4508.

4.4.17. (2*S*,4*S*,5*S*,7*S*)-5-Azido-N-(2,2-dimethyl-3-(sulfamoy lamino)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8p)

Starting with **1** (50 mg, 0.11 mmol) and **7p** (45.3 mg, 0.25 mmol), **8p** (45 mg, 63.6%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −12.5 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.96 (m, 18H), 1.30–1.40 (m, 1H), 1.50–2.00 (m, 6H), 2.03–2.18 (m, 4H), 2.38–2.65 (m, 2H), 2.70–3.23 (m, 5H), 3.37 (s, 3H), 3.44 (br, 1H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.85 (s, 3H), 4.11 (t, *J* = 6.5 Hz, 2H), 4.83 (br, 2H), 5.82 (br, 1H), 6.17 (br, 1H), 6.72–6.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 19.5, 20.3, 21.2, 23.8, 23.9, 29.5, 30.0, 30.1, 32.2, 34.1, 35.5, 37.5, 42.6, 46.5, 50.3, 50.9, 56.1, 58.6, 66.1, 66.6, 69.4, 71.8, 111.8, 114.2, 121.3, 133.8, 147.7, 148.3,

176.9; MS(ESI) *m*/*z* 665.4 $[M+Na]^+$; HRMS for $C_{30}H_{54}N_6O_7S$+Na calcd 665.3668, found 665.3668.

4.4.18. (2*S*,4*S*,5*S*,7*S*)-5-Azido-*N*-(2,2-dimethyl-3-(1H-1,2,3-triazol-1-yl)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (8r)

Starting with **1** (50 mg, 0.11 mmol) and **7r** (38.5 mg, 0.25 mmol), **8r** (43 mg, 64%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −19.2 (*c* 0.27, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86–0.97 (m, 18H), 1.30–1.40 (m, 1H), 1.50–2.00 (m, 6H), 2.04–2.22 (m, 3H), 2.50 (m, 2H), 2.93–3.18 (m, 4H), 3.35 (s, 3H), 3.44 (br, 1H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 4.20 (s, 2H), 6.40 (br, 1H), 6.68–6.80 (m, 3H), 7.67 (s, 1H), 7.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.9, 20.2, 21.2, 23.9, 24.0, 29.6, 29.7, 30.1, 32.0, 34.1, 37.1, 37.5, 42.5, 46.2, 51.1, 56.1, 57.5, 58.6, 66.2, 66.6, 69.4, 71.9, 111.9, 114.3, 121.2, 125.1, 133.6, 133.8, 147.8, 148.5, 176.1; MS(ESI) *m*/*z* 638.4 $[M+Na]^+$; HRMS for $C_{33}H_{53}N_7O_5$+Na calcd 638.4006, found 638.4014.

4.5. General procedure for the preparation of 9a–r

A solution of **8a**–**r** (0.02–0.05 mmol) and ethanolamine (1 equiv) in methyl *tert*-butyl ether (5 mL) was hydrogenated in the presence of 5 mg of 10% Pd/C (moist) at 25 °C over 0.5–1 h. The reaction mixture was filtered and the solids were washed with CH_2Cl_2. The filtrate was washed with 2 N NaOH aqueous solution, dried and concentrated under reduced pressure.

4.5.1. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(3-amino-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-8-methylnonanamide (9q)

Starting with **8q** (37 mg, 0.06 mmol), **9q** (30 mg, 89%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −8.8 (*c* 0.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84–1.00 (m, 18H), 1.15–1.48 (m, 3H), 1.60–2.00 (m, 11H), 2.34 (br, 1H), 2.46–2.51 (d, *J* = 6.8 Hz, 2H), 2.52 (s, 2H), 3.04–3.27 (m, 3H), 3.36 (s, 3H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.3 Hz, 2H), 6.68–6.82 (m, 3H), 6.85 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 20.1, 20.4, 21.3, 23.6, 23.7, 27.0, 29.6, 30.5, 34.8, 35.2, 35.3, 37.8, 42.6, 47.5, 51.0, 51.4, 54.6, 56.0, 58.7, 66.2, 69.4, 72.1, 111. 8, 114.3, 121.2, 134.2, 147.7, 148.3, 175.7; MS(ESI) *m*/*z* 538.4 $[M+H]^+$; HRMS for $C_{30}H_{55}N_3O_5$+H calcd 538.4220, found 538.4226.

4.5.2. (2*S*,4*S*,5*S*,7*S*)-*N*-(3-Acetamido-2,2-dimethylpropyl)-5-amino-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxy-propoxy)benzyl)-8-methylnonanamide (9a)

Starting with **8a** (25 mg, 0.04 mmol), **9a** (21 mg, 87.9%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −15.7 (*c* 0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85–0.97 (m, 18H), 1.25–1.43 (m, 3H), 1.66–2.22 (m, 10H), 2.02 (s, 3H), 2.48 (m, 1H), 2.31 (br, 1H), 2.89–3.11 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.3 Hz, 2H), 6.48 (br, 1H), 6.68–6.79 (m, 3H), 6.94 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 20.0, 20.3, 21.2, 23.5, 23.6, 23.7, 29.6, 29.7, 30.5, 34.8, 35.4, 36.3, 37.8, 42.6, 45.6, 46.3, 51.3, 54.6, 56.1, 58.7, 66.2, 69.4, 72.0, 111. 9, 114.4, 121.2, 134.1, 147.8, 148.4, 170.7, 176.9; MS(ESI) *m*/*z* 580.4 $[M+H]^+$; HRMS for $C_{32}H_{58}N_3O_6$+H calcd 580.4326, found 580.4332.

4.5.3. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2,2-dimethyl-3-(2,2,2-trifluoro acetamido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9b)

Starting with **8b** (17.5 mg, 0.03 mmol), **9b** (14 mg, 83.3%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −4.8 (*c* 0.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85–0.96 (m, 18H), 1.26–1.39 (m, 3H), 1.65–2.00 (m, 5H), 2.07–2.24 (m, 6H), 2.43–2.53(m, 2H), 2.98–3.21 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.6 Hz, 2H), 6.36 (br, 1H), 6.67–6.79 (m, 3H), 8.71 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 17.8, 19.8, 20.3, 21.2, 23.5, 23.6, 29.6, 30.0, 30.4, 30.7, 34.8, 35.6, 36.6, 37.9, 42.6, 45.3, 46.6, 51.1, 54.6, 56.0, 58.6, 66.3, 69.4, 71.9, 111. 9, 114.4, 121.2, 134.0, 147.8, 148.4, 177.7; MS(ESI) *m*/*z* 634.4 $[M+H]^+$; HRMS for $C_{32}H_{54}N_3O_6F_3$+H calcd 634.4043, found 634.4048.

4.5.4. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2,2-dimethyl-3-propion-amidopropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9c)

Starting with **8c** (14.8 mg, 0.024 mmol), **9c** (13 mg, 91.5%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −7.2 (*c* 0.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84–0.96 (m, 18H), 1.18–1.21 (m, 3H), 1.15–1.45 (m, 3H), 1.60–1.95 (m, 5H), 1.95–2.29 (m, 8H), 2.46–2.48 (m, 2H), 2.90–3.17 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.49 (br, 1H), 6.68–6.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 17.4, 19.9, 20.3, 21.2, 23.6, 23.8, 27.0, 29.6, 30.0, 30.4, 34.8, 35.4, 36.3, 37.8, 42.5, 45.4, 46.2, 51.3, 54.6, 56.0, 58.7, 66.2, 69.4, 72.0, 111. 8, 114.4, 121.2, 134.1, 147.7, 148.3, 174.5, 176.8; MS(ESI) *m*/*z* 594.4 $[M+H]^+$; HRMS for $C_{33}H_{59}N_3O_6$+H calcd 594.4482, found 594.4487.

4.5.5. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(3-butyramido-2,2-dimethyl-propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxy-propoxy)benzyl)-8-methylnonanamide (9d)

Starting with **8d** (20 mg, 0.031 mmol), **9d** (16 mg, 83%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −7.8 (*c* 0.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84–0.98 (m, 21H), 1.18–1.45 (m, 3H), 1.62–1.95 (m, 6H), 1.95–2.27 (m, 8H), 2.23 (br, 1H), 2.47 (d, *J* = 7.0 Hz, 2H), 2.90–3.14 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.48 (br, 1H), 6.68–6.82 (m, 3H), 6.85 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 17.6, 19.9, 20.0, 20.3, 21.2, 23.6, 23.8, 2, 29.6, 29.7, 30.4, 34.8, 35.3, 36.2, 37.8, 39.0, 42.5, 45.4, 46.2, 51.3, 54.7, 56.1, 58.6, 66.2, 69.4, 72.0, 111. 9, 114.4, 121.2, 134.1, 147.8, 148.4, 173.7, 176.8; MS(ESI) *m*/*z* 608.5 $[M+H]^+$; HRMS for $C_{34}H_{61}N_3O_6$+H calcd 608.4629, found 608.4643.

4.5.6. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2,2-dimethyl-3-(3-methyl-butanamido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9e)

Starting with **8e** (28 mg, 0.043 mmol), **9e** (24 mg, 89.2%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −5.3 (*c* 0.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84–0.97 (m, 24H), 1.19–1.44 (m, 3H), 1.66–2.00 (m, 6H), 2.00–2.21 (m, 7H), 2.31 (br, 1H), 2.47 (d, *J* = 6.6 Hz, 2H), 2.91–3.20 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.52 (br, 1H), 6.68–6.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 20.1, 20.3, 21.2, 22.5, 23.6, 23.8, 29.6, 29.7, 30.4, 34.8, 35.4, 36.2, 37.8, 42.5, 45.4, 46.1, 46.4, 51.3, 54.6, 56.0, 58.6, 66.2, 69.4, 72.1, 111. 8, 114.4, 121.2, 134.2, 147.8, 148.3, 173.1, 176.7; MS(ESI) *m*/*z* 622.5 $[M+H]^+$; HRMS for $C_{35}H_{63}N_3O_6$+H calcd 622.4795, found 622.4806.

4.5.7. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2,2-dimethyl-3-pivalamidopropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9f)

Starting with **8f** (32 mg, 0.045 mmol), **9f** (26 mg, 84.4%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −7.9 (*c* 0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84–0.96 (m, 18H), 1.24 (s, 9H), 1.15–1.45 (m, 3H), 1.61–2.00 (m, 6H), 2.00–2.22 (m, 4H), 2.31 (br, 1H), 2.47 (d, *J* = 6.7 Hz, 2H), 2.88–3.19 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.84 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.55 (br, 1H), 6.68–6.79 (m, 3H), 6.97 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 20.1, 20.3, 21.2, 23.6, 23.8, 27.7, 29.6, 30.3, 34.7, 35.4, 36.3, 37.8, 38.9, 42.5, 45.2, 45.9, 51.3, 54.6, 56.0, 58.7, 66.2, 69.4, 72.1, 111. 8, 114.3, 121.2, 134.1, 147.7, 148.3, 159.8, 176.6, 179.3;

MS(ESI) *m*/*z* 622.5 $[M+H]^+$; HRMS for $C_{31}H_{63}N_3O_6$+H calcd 622.4795, found 622.4790.

4.5.8. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(3-hexanamido-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9g)

Starting with **8g** (32 mg, 0.049 mmol), **9g** (26 mg, 84.7%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −6.9 (*c* 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.96 (m, 21H), 1.26–1.50 (m, 7H), 1.66–2.00 (m, 6H), 2.00–2.27 (m, 8H), 2.31 (br, 1H), 2.47 (d, *J* = 6.5 Hz, 2H), 2.92–3.17 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.52 (br, 1H), 6.68–6.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 17.4, 20.1, 20.3, 21.2, 22.4, 23.6, 23.8, 25.6, 29.6, 29.7, 30.4, 34.8, 35.4, 36.3, 37.0, 37.8, 42.5, 45.4, 46.2, 51.3, 54.6, 56.0, 58.7, 66.2, 69.4, 72.1, 111. 8, 114.4, 121.2, 134.2, 147.8, 148.3, 173.8, 176.7; MS(ESI) *m*/*z* 636.4 $[M+H]^+$; HRMS for $C_{36}H_{65}N_3O_6$+H calcd 636..4952, found 636.4958.

4.5.9. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2,2-dimethyl-3-(4-methylphenylsulfonamido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9h)

Starting with **8h** (28.8 mg, 0.044 mmol), **9h** (26 mg, 93.8%) was obtained as a colorless oil: $[\alpha]_D^{23}$ 5.1 (*c* 0.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73–0.94 (m, 18H), 1.15–1.45 (m, 3H), 1.61–1.90 (m, 5H), 2.00–2.21 (m, 5H), 2.26 (br, 1H), 2.40 (s, 3H), 2.40–2.57 (m, 3H), 2.60–2.57 (m, 3H), 2.61–2.67 (m, 1H), 2.77–2.88 (m, 1H), 2.99 (br, 1H), 3.22–3.31 (m, 1H), 3.36 (s, 3H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.84 (s, 3H), 4.09 (t, *J* = 6.5 Hz, 2H), 6.23 (br, 1H), 6.71–6.79 (m, 3H), 7.24–7.75 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 20.0, 20.2, 21.1, 21.4, 23.6, 23.8, 29.6, 29.9, 30.3, 34.8, 35.3, 35.6, 37.8, 42.6, 46.6, 50.0, 51.0, 51.3, 54.7, 56.0, 58.6, 66.2, 69.4, 71.8, 111. 9, 114.4, 121.2, 127.0, 129.5, 134.1, 142.7, 147.8, 176.9; MS(ESI) *m*/*z* 692.4 $[M+H]^+$; HRMS for $C_{37}H_{61}N_3O_7S$+H calcd 692.4308, found 692.4311.

4.5.10. Ethyl(3-((2*S*,4*S*,5*S*,7*S*)-5-amino-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamido)-2,2-dimethylpropyl)carbamate (9i)

Starting with **8i** (31 mg, 0.049 mmol), **9i** (26 mg, 87.5%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −9.3 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.96 (m, 18H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.15–1.45 (m, 3H), 1.61–1.95 (m, 5H), 1.95–2.22 (m, 5H), 2.30 (br, 1H), 2.48 (m, 2H), 2.86–3.19 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.83 (s, 3H), 4.10 (m, 4H), 5.84 (br, 1H), 6.40 (br, 1H), 6.68–6.79 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 17.4, 20.0, 20.3, 21.2, 23.4, 23.5, 29.6, 29.7, 30.4, 34.8, 35.4, 36.3, 37.8, 42.6, 46.1, 47.5, 51.3, 54.6, 56.0, 58.7, 60.7, 66.2, 69.4, 72.1, 111. 8, 114.4, 121.2, 134.2, 147.8, 148.3, 157.6, 176.4; MS(ESI) *m*/*z* 610.4 $[M+H]^+$; HRMS for $C_{33}H_{59}N_3O_7$+H calcd 610.4431, found 610.4441.

4.5.11. *N*-(3-((2*S*,4*S*,5*S*,7*S*)-5-Amino-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamido)-2,2-dimethylpropyl)benzamide (9j)

Starting with **8j** (48 mg, 0.073 mmol), **9j** (43 mg, 91.3%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −11.8 (*c* 0.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72–1.00 (m, 18H), 1.15–1.45 (m, 3H), 1.61–2.00 (m, 6H), 2.00–2.35 (m, 5H), 2.46 (m, 2H), 2.96–3.36 (m, 5H), 3.36 (s, 3H), 3.57 (t, *J* = 6.1 Hz, 2H), 3.82 (s, 3H), 4.09 (t, *J* = 6.6 Hz, 2H), 6.51 (br, 1H), 6.66–6.77 (m, 3H), 7.45–7.96 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 20.0, 20.3, 21.3, 23.8, 27.0, 29.6, 29.7, 30.4, 34.8, 35.5, 36.7, 37.8, 42.6, 45.6, 46.4, 51.3, 54.6, 56.0, 58.6, 66.2, 69.4, 72.1, 111.8, 114.3, 121.2, 127.1, 128.5, 131.2, 134.1, 134.5, 147.7, 148.3, 167.5, 177.0; MS(ESI) *m*/*z* 642.4 $[M+H]^+$; HRMS for $C_{37}H_{59}N_3O_6$+H calcd 642.4482, found 642.4485.

4.5.12. *N*-(3-((2*S*,4*S*,5*S*,7*S*)-5-Azido-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamido)-2,2-dimethylpropyl)-4-methoxybenzamide (9k)

Starting with **8k** (28 mg, 0.04 mmol), **9k** (24 mg, 89%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −13.3 (*c* 0.49, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.97 (m, 18H), 1.15–1.45 (m, 3H), 1.60–2.00 (m, 6H), 2.00–2.18 (m, 3H), 2.18–2.51 (m, 5H), 3.03–3.35 (m, 5H), 3.35 (s, 3H), 3.57 (t, *J* = 6.1 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 4.09 (t, *J* = 6.6 Hz, 2H), 6.50 (br, 1H), 6.66–6.77 (m, 3H), 6.93–7.96 (m, 4H), 7.75 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 20.0, 20.3, 21.3, 23.8, 29.6, 29.7, 30.4, 34.8, 35.5, 36.6, 37.8, 42.6, 45.6, 46.4, 51.3, 54.6, 55.3, 56.0, 58.6, 66.2, 69.4, 72.1, 111.8, 113.7, 114.4, 121.2, 126.8, 128.9, 134.1, 147.8, 148.3, 162.0, 167.1, 176.9; MS(ESI) *m*/*z* 672.4 $[M+H]^+$; HRMS for $C_{38}H_{61}N_3O_7$+H calcd 672.4588, found 672.4593.

4.5.13. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2,2-dimethyl-3-(2-phenylacetamido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9l)

Starting with **8l** (35 mg, 0.051 mmol), **9l** (31 mg, 92%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −9.3 (*c* 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78–0.96 (m, 18H), 1.15–1.45 (m, 3H), 1.60–2.20 (m, 10H), 2.34 (br, 1H), 2.48 (d, *J* = 6.8 Hz, 2H), 2.83–3.13 (m, 5H), 3.36 (s, 3H), 3.57 (m, 4H), 3.83 (s, 3H), 4.10 (t, *J* = 6.6 Hz, 2H), 6.57 (br, 1H), 6.65–6.79 (m, 4H), 7.27–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 20.1, 20.3, 21.2, 23.5, 23.7, 27.0, 29.6, 30.4, 34.7, 35.3, 36.4, 37.8, 42.5, 44.0, 45.8, 45.9, 51.2, 54.6, 56.0, 58.6, 66.2, 69.4, 72.1, 111.8, 114.4, 121.2, 127.1, 128.8, 129.2, 134.2, 135.3, 147.8, 148.3, 171.7, 176.5; MS(ESI) *m*/*z* 656.5 $[M+H]^+$; HRMS for $C_{38}H_{61}N_3O_6$+H calcd 656.4639, found 656.4643.

4.5.14. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2,2-dimethyl-3-(methylsulfonamido)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9m)

Starting with **8m** (34 mg, 0.053 mmol), **9m** (31 mg, 95%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −6.0 (*c* 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86–0.96 (m, 18H), 1.15–1.45 (m, 3H), 1.60–2.00 (m, 6H), 2.00–2.20 (m, 4H), 2.28 (br, 1H), 2.39–2.56 (m, 2H), 2.86–3.21 (m, 5H), 2.89 (s, 3H), 3.36 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.6 Hz, 2H), 6.23 (br, 2H), 6.68–6.80 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 20.0, 20.3, 21.1, 23.6, 23.7, 27.0, 29.6, 30.0, 30.5, 34.8, 35.4, 35.8, 37.9, 39.8, 42.6, 46.6, 50.0, 51.0, 54.7, 56.1, 58.6, 66.3, 69.4, 71.9, 111.9, 114.4, 121.2, 134.1, 147.8, 148.4, 177.1; MS(ESI) *m*/*z* 616.4 $[M+H]^+$; HRMS for $C_{31}H_{57}N_3O_7S$+H calcd 616.3995, found 616.4003.

4.5.15. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(3-(ethylsulfonamido)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9n)

Starting with **8n** (35 mg, 0.053 mmol), **9n** (29 mg, 86.3%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −5.9(*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85–0.96 (m, 18H), 1.15–1.45 (m, 3H), 1.35 (t, *J* = 7.4 Hz, 3H), 1.55–2.00 (m, 6H), 2.00–2.17 (m, 4H), 2.25 (br, 1H), 2.50 (m, 2H), 2.70 (m, 2H), 2.90–3.23 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.29 (br, 2H), 6.68–6.79 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.2, 17.5, 20.0, 20.3, 21.2, 23.6, 23.7, 27.0, 29.6, 29.9, 30.5, 34.8, 35.5, 35.8, 37.9, 42.7, 46.6, 49.9, 51.0, 54.7, 56.1, 58.6, 66.3, 69.4, 72.0, 111.9, 114.4, 121.2, 134.1, 147.8, 148.4, 177.0; ESI-MS *m*/*z* 630.4 $[M+H]^+$; HRMS for $C_{32}H_{59}N_3O_7S$+H calcd 630.4152, found 630.4157.

4.5.16. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(3-(3,3-dimethylureido)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9o)

Starting with **8o** (28 mg, 0.044 mmol), **9o** (24 mg, 89.6%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −14.7 (*c* 0.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.83–0.96 (m, 18H), 1.15–1.45 (m, 3H), 1.60–2.00 (m, 6H), 2.00–2.20 (m, 4H), 2.44 (br, 1H), 2.47 (d, *J* = 6.8 Hz, 2H), 2.93 (s, 6H), 2.90–3.20 (m, 5H), 3.36 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 5.59 (br, 2H), 6.68–6.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 20.1, 20.3, 21.3, 23.6, 23.8, 27.0, 29.6, 30.3, 34.7, 35.4, 35.8, 36.0, 36.3, 37.8, 42.5, 45.8, 46.9, 51.4, 54.5, 56.1, 58.6, 66.2, 69.4, 72.2, 111.9, 114.4, 121.2, 134.2, 147.7, 148.3, 159.0, 176.5; MS(ESI) *m*/*z* 609.5 $[M+H]^+$; HRMS for $C_{33}H_{60}N_4O_6$+H calcd 609.4591, found 609.4603.

4.5.17. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2,2-dimethyl-3-(sulfamoylamino)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (9p)

Starting with **8p** (34 mg, 0.053 mmol), **9p** (29 mg, 89%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −5.8 (*c* 0.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85–0.95 (m, 18H), 1.15–1.45 (m, 3H), 1.55–2.00 (m, 5H), 2.00–2.15 (m, 3H), 2.30 (br, 1H), 2.38–2.59 (m, 2H), 2.80 (br, 2H), 2.95–3.25 (m, 6H), 3.36 (s, 3H), 3.36 (br, 1H), 3.57 (t, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 6.26 (br, 1H), 6.68–6.80 (m, 3H), 7.69 (s, 1H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 19.8, 20.3, 21.1, 23.7, 23.9, 29.6, 30.0, 30.6, 34.3, 35.2, 35.4, 37.8, 42.8, 46.6, 50.4, 51.1, 54.5, 56.1, 58.6, 66.3, 69.4, 72.2, 111.9, 114.6, 121.3, 134.2, 147.8, 148.3, 176.8; MS(ESI) *m*/*z* 617.4 $[M+H]^+$; HRMS for $C_{30}H_{56}N_4O_7S$+H calcd 617.3948, found 617.3956.

4.5.18. (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2,2-dimethyl-3-(1*H*-1,2,3-triazol-1-yl)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (29r)

Starting with **8r** (28 mg, 0.045 mmol), **9r** (25 mg, 93.3%) was obtained as a colorless oil: $[\alpha]_D^{23}$ −6.6 (*c* 0.31, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82–0.98 (m, 18H), 1.15–1.45 (m, 3H), 1.55–2.15 (m, 7H), 2.00–2.15 (m, 2H), 2.24 (br, 1H), 2.32 (br, 1H), 2.48 (m, 2H), 3.01–3.21 (m, 3H), 3.36 (s, 3H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.83 (s, 3H), 4.09 (t, *J* = 6.5 Hz, 2H), 4.21 (s, 2H), 6.38 (br, 1H), 6.66–6.79 (m, 3H), 7.69 (s, 1H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 20.0, 20.3, 21.3, 23.7, 23.9, 29.6, 29.7, 30.5, 34.8, 35.5, 37.0, 37.8, 42.6, 46.2, 51.2, 54.6, 56.1, 57.3, 58.7, 66.3, 69.4, 72.1, 111.9, 114.5, 121.2, 125.1, 133.5, 134.2, 147.8, 148.4, 176.2; MS(ESI) *m*/*z* 590.4 $[M+H]^+$; HRMS for $C_{32}H_{55}N_5O_5$+H calcd 590.4281, found 590.4293.

4.6. In vitro renin fluorimetric assay

The Sensolyte 390 Renin assay kit was used to determine the activity and IC_{50} values of 19 compounds against renin enzyme. Each of the test compounds in DMSO was diluted at 6 different concentrations of 500, 100, 20, 4, 0.8 and 0.16 nM in assay buffer (pH 7.4). The renin substrate was diluted 1:100 in assay buffer before test. To set up enzymatic reaction, the test compounds and renin solution were added into the microplate wells. Each well of a 384-well plate contained 28 μL of renin solution and 5 μL of test compound. The vehicle control contained diluted renin and diluted vehicle DMSO. The plate was incubated at 37 °C for 30 min, and at the same time, the renin substrate solution was incubated at 37 °C. To each well was added 17 μL of renin substrate solution. All the reagents were mixed completely by shaking the plate gently for no more than 30 s. Fluorescence intensity was immediately measured at Ex/Em = 330 nm/390 nm and the data were recorded continuously (each minute) for 15 min.

4.7. Molecular docking

The protein structure of renin used in the docking studies was obtained from the protein data bank with the code 2v0z. All hydrogen atoms were added, and an active site of a sphere was set around the internal ligand. Then the internal inhibitor and water molecules were removed. All the eighteen novel ligands and aliskiren were drawn and all hydrogen atoms were added. Incorrect atom type was modified, and the structures were energy minimized using 'Steepest Descent', 'Conjugated Gradient' and 'Powell algorithms' method subsequently with a convergence gradient value of 0.001 kcal/(mol Å), 1000 max iterations, saved as mol2 format using SYBYL 6.9 package.

Molecular docking was performed using software of GOLD that applied genetic algorithm. The number of generic algorithm runs was set to 20. Define the active site using a sphere (point: 32.129, 14.886, 87.994; radius: 13 Å). Other parameters were the default.

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