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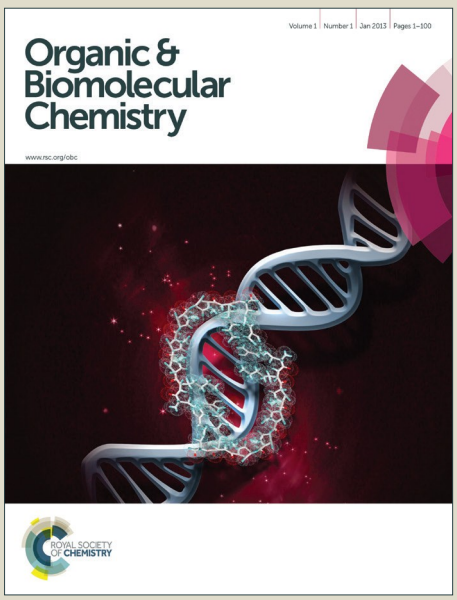

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ARTICLE

Rapid and Scalable Synthesis of Innovative Unnatural α, β or γ-Amino Acids Functionalized with Tertiary Amines on their Side-chain

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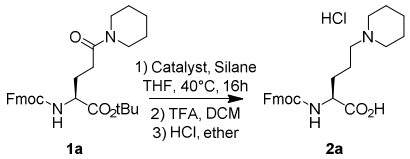
We report a selective ruthenium catalyzed reduction of tertiary amides on the side chain of Fmoc-Gln-OtBu derivatives, leading to innovative unnatural α, β or γ-amino acids functionalized with tertiary amines. Rapid and scalable, this process allowed to build a library of basic unnatural amino acids at the gram-scale and directly usable for liquid- or solid-phase peptide synthesis. The diversity of available tertiary amines allows to modulate the physicochemical properties of the resulting amino acids, such as basicity or hydrophobicity .

Introduction

Whereas peptides are the keystones of most vital processes, only a few peptide-based drugs were marketed in the 20th century. Among other criteria, low bioavailability and metabolic instability led to a global rejection of peptides as drug candidates by the pharmaceutical industry. However, in the last decade, new therapeutic strategies were promoted, and more than 100 peptide-based drugs have already reached the market.[1] In order to circumvent the inherent problems of bioavailability and biostability of peptides, protein-like backbones called peptidomimetics were developed in order to mimic native peptides, but with better pharmacological properties. Unnatural amino acids were then generated from natural amino acids through chemical modifications of this backbone (amine alkylation, backbone extension, cyclization or isosteric replacements).[2] Another great area of interest was the design of "non-natural" side chains, allowing the improvement of interactions between the peptide and its targeted protein. Upon this aspect, a large diversity of side chains were developed, but non-natural amino acids bearing various aromatic side chains were more extensively reported.[2d, 3] In contrast, side chains bearing a basic amino group mimicking ornithine, lysine or arginine derivatives were less well reported. Most of the lysine analogs resulted from a reductive amination between aldehydes and Fmoc-Lys-OH affording monoalkylated or symmetric dialkylated lysine derivatives.[4] Through an alkylation of glycine on solid-phase,

Table 1. Optimization of the reaction conditions



1a 2a

Entry	Catalyst	Mol%	Silane	Equiv.	Yield[b] (%)
1	$Zn(OAc)_2$	3	$(EtO)_3SiH$	8	0
2	$[Ir(COD)Cl]_2$	3	Et_2SiH_2	8	74
3	$[Ir(COD)Cl]_2$	3	TMDS	8	59
4	$Ru_3(CO)_{12}$	3	Et_2SiH_2	8	74
5	$Ru_3(CO)_{12}$	3	$(EtO)_3SiH$	8	60
6	$Ru_3(CO)_{12}$	3	iPr_3SiH	8	0
7	$Ru_3(CO)_{12}$	3	TMDS	8	80
8	$Ru_3(CO)_{12}$	1	TMDS	8	40
9	$Ru_3(CO)_{12}$	5	TMDS	8	80
10	$Ru_3(CO)_{12}$	3	TMDS	2	60
11	$Ru_3(CO)_{12}$	3	TMDS	4	78
12	$Ru_3(CO)_{12}$	3	TMDS	6	81

[a] Reaction conditions: 1) **1a** (0.2 mmol), catalyst, silane, THF (1 mL), 40°C, 16h; 2) TFA/DCM (v : v – 2 mL); 3) HCl 1N in ether (5 mL); [b] Determined by HPLC using caffeine as external standard

Scott et al. reported an interesting synthesis of non-natural racemic amino acids bearing the pyrrolidine ring.[5] Indeed, introduction of azacycles through reductive amination is still challenging.[6] For the first time, we propose in this paper a versatile synthesis of non- natural basic amino acids, bearing a high diversity of cyclic or acyclic tertiary amines on the side chain. Protected by a Fmoc group in the N-terminus, these new non-natural amino acids are directly available for liquid or solid phase peptide synthesis.

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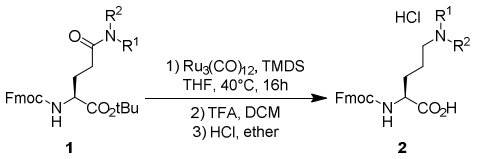
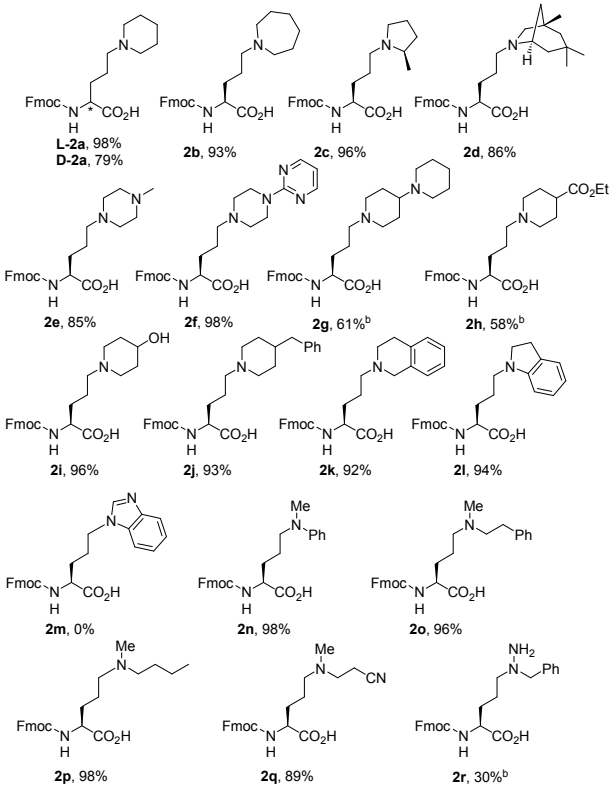
Electronic Supplementary Information (ESI) available: General reaction procedures for Cpds 1, **9** and **10** and compound characterization. Racemization study. See DOI: 10.1039/x0xx00000x

Table 2. Building of a library of α-amino acids functionalized with a large diversity of tertiary amines[a]



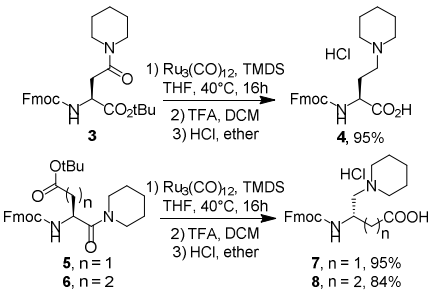
1 2



[a] Reaction conditions: 1) 1 (2 mmol), $Ru_3(CO)_{12}$ (5 mol%), TMDS (16 mmol), THF (10 mL), 40°C, 16h; 2) TFA/DCM (v : v – 20 mL); 3) HCl 1N in ether (30 mL); [b] Yield after column chromatography.

Results and discussion

Metal-catalyzed reductions of carboxamides in combination with silanes were extensively studied in recent years with simple amides such as benzamide derivatives.[7] Our challenge was to look for the selective reduction of the amide function of the glutamate derivative **1** (Table 1), bearing two other reducible groups (ester and carbamate) and one chiral center. Starting from the commercially available Fmoc-L-Glu-OtBu, piperidine was coupled on the side chain to afford amide derivative **1a** in a quantitative yield. We next evaluated three known catalytic systems (Table 1), involving Zn,[7f] Ir,[7k] or Ru,[7r] for reduction of the carboxamide function in a selective manner towards both urethane (Fmoc) and tert-butyl ester functions. As compound **1a** was poorly soluble in toluene, THF was preferred as solvent. Zinc-mediated reduction was not



Scheme 1. Ru-catalyzed synthesis of nor-ornithine analogs and β,γ and γ,δ-diamino acids.

observed (entry 1), whereas $[Ir(COD)Cl]_2$ and $Ru_3(CO)_{12}$ in combination with Et_2SiH_2 or tetramethyldisiloxane (TMDS) produced amine **2a** in high yields at only 40°C (entries 2,3, 4 and 7). As the main goal of this study was to propose a gram-scale synthesis of non-natural basic amino acids, the catalytic system $Ru_3(CO)_{12}$/TMDS was selected as it is cheaper than the system associating an Iridium-based catalyst and Et_2SiH_2. In 2013, Reeves et al. reported that 1% $Ru_3(CO)_{12}$ in the presence of 4 eq. of TMDS at 50°C in toluene was efficient enough to reduce a large set of amides.[7r] In our case, the reduction of the glutamine derivative **1a** required at least 3 mol% of catalyst in THF at 40°C (Table 1, compare entries 7 & 8). Easy to handle, the reaction was carried out under air conditions. The key-step of this procedure appeared to be the purification stage. Indeed, after the completion of the reduction step, the resulting tert-butyl ester was recovered in poor yields (<30%) after normal or reversed phase chromatography, although no side product were observed. Treatment of this tert-butyl ester with trifluoroacetic acid afforded compound **2a** as a TFA salt. Precipitation in ether of this salt led to a medium yield (≈50%). Subsequently, the trifluoroacetate counter-ion was exchanged with HCl 1 M in diethylether, affording a white precipitate **2a** as a hydrochloride salt in 81% yield. As the optimization step was performed in a 100 mg scale, we next extended the scope of the reaction to the gram-scale with a large set of tertiary amines (Table 2). Under these conditions, compounds **2** were globally obtained in good to excellent yields after precipitation in ether. The reaction was compatible with the hindered amine (**2d**) and allowed the introduction of other chiral centers (**2c**, **2d**). Several functional groups were tolerated, such as tertiary amines (**2e**, **2g**), 2-aminopyrimidine (**2f**), ester (**2h**), and alcohol (**2i**). A series of amines bearing an aromatic cycle was also easily synthesized (**2j-o**). Whereas aniline derivatives were well tolerated (**2l**, **2n**), benzimidazole derivative **2m** was not recovered as its precursor amide **1m** was poorly stable. Acyclic amines (**2n-q**) were also easily obtained in high yields. Interestingly, after coupling the Bn-NH-NH-Boc on Fmoc-L-Glu-OtBu, we were able to reduce the hydrazide function to produce the corresponding hydrazine derivative **2r** as a non-natural analog of lysine. In spite of the protonated state of the terminal amine, Fmoc cleavage was observed, explaining the modest yield of 30% for compound **2r**. With yields inferior to 80%, compounds **2g**, **2h**, and **2r** were purified by flash

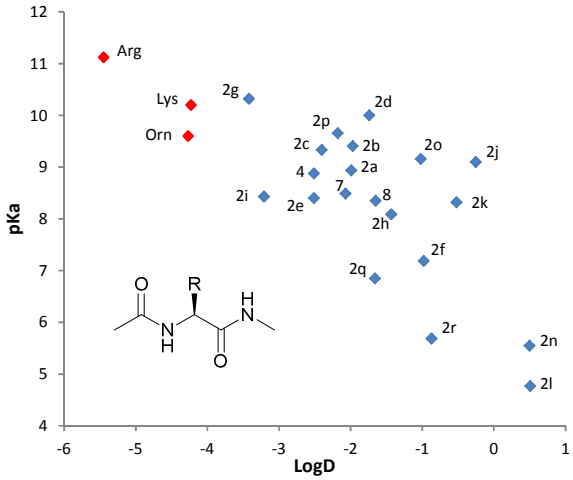
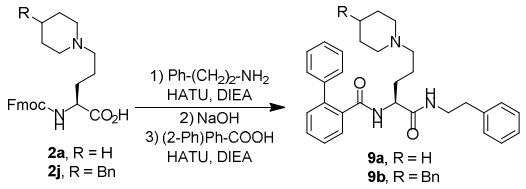


Chart 1. LogD[7.4] and pKa for Ac-Xaa-NHMe[a]

[a] Calculator plugin (Marvin 6.0.2, 2013, http://www.chemaxon.com). LogD was predicted at a pH 7.4 following the method reported by Klopman et al.[8]



Scheme 2. Application of the non-natural amino acid **2a** to the synthesis of **9**, an orally-active antagonist of opioid-induced hyperalgesia

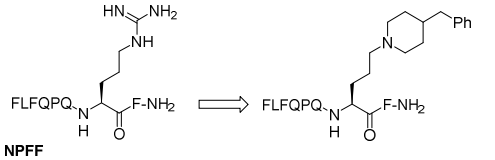


Figure 1. Application of the non-natural amino acid **2j** to the synthesis of an unnatural analog of the endogenous neuropeptide NPFF **10**.

chromatography to remove byproducts. All the other compounds were easily recovered after precipitation with purity higher than 98%. Starting from Fmoc-L-Asp-OtBu, we were able to obtain compound **4**, exhibiting a shorter side-chain than **2a**. Next, we explored the possibility of reducing the carboxamide function on the backbone. Starting from commercially available Fmoc-L-Asp(OtBu)-OH or Fmoc-L-Glu(OtBu)-OH, piperidine was coupled to the C-terminus part to afford compounds **5** and **6**. Ruthenium-based reduction of the resulting carboxamide led to the β,γ-diamino acid **7** and the γ,δ-diamino acid **8** in excellent yields.

The absence of the need for purification by chromatography allowed us to easily produce large quantity of these unnatural amino acids, with 98% minimum purity measured by HPLC and NMR. However, neither of these analytical techniques allows the detection of ruthenium. Using ICP-mass spectrometry, we were able to quantify 2.1% (w/w) of ruthenium after final precipitation. Using resin-bound dimercaptotriazine as a scavenger in a solution of **2a** in a mixture of DCM/MeOH [9:1], we were able to remove up to 90% of the ruthenium, leading to a final 0.2% (w/w) of residual ruthenium. We next evaluated whether this whole synthetic procedure may induce racemization of the Cα of the amino acids formed. To answer this question, both enantiomers **L-2a** and **D-2a** were coupled to H-L-Phe-NH_2 using several standard coupling reagents (BOP, COMU, HATU). By using HPLC, we were able to evaluate the racemization ratio as lower than 1% (Suppl. Data). By repeating this last coupling reaction, we determined that the resulting traces of racemization were occurring during the coupling reaction with H-Phe-NH_2, and not during the reductive process.

This very efficient synthesis allows a rapid and scalable access to a large variety of unnatural N-Fmoc α-, β- or γ-amino acids. These residues can be easily introduced into peptide sequence as mimetic of natural basic amino acids such as ornithine, lysine or arginine. However, these new unnatural amino acids give access to a larger range of basicity and hydrophobicity, depending of the tertiary amine chosen on the side chain. To highlight this concept, we compared the hydrophobicity (LogD) and the basicity (pKa) for the 20 unnatural amino acids synthesized in this paper and compared to ornithine, lysine and arginine (Chart 1). To be as close as possible to a peptide structure, calculation were performed with each amino acid under the form Ac-Xaa-NH-Me. Ornithine, lysine and arginine form a very hydrophilic cluster (LogD < -4) with basicity ranging from 9.6 to 11.2. In contrast, the 20 unnatural amino acids show extended ranges of LogD (from -3.4 to +0.5) and pKa (from 4.7 to 10.3). By introducing these unnatural amino acids into peptide sequences in replacement of basic amino acids such as lysine, ornithine or arginine, we will be able to modulate the physicochemical properties of the resulting peptidomimetics. A first application for these novel non-natural basic amino acids was demonstrated in a liquid-phase synthesis of compounds **9a** and **9b** (Scheme 2), which were recently reported as the first orally active antagonists of NPFF receptors to prevent opioid-induced hyperalgesia in rodents.[9] Starting from compounds **2a** and **2j**, compounds **9a** and **9b** were easily synthesized using standard peptide synthesis. This new strategy appears to be much more efficient and less time-consuming than the previously reported method.[9] More importantly, the availability of the building block **2** allows a fast optimization of the N- and C-terminus in a convergent manner, which is not possible with the reported synthesis.[9] Compounds **9** were initially developed as a peptidomimetic of the corresponding arginine residue.[9] Using standard solid-phase synthesis, we pushed the concept further by replacing the arginine moiety of the neuropeptide FF by the residue **2j** in order to generate a peptidomimetic analog of the peptide NPFF (Fig. 1). Using **2j** immediately after precipitation in ether and using a fmoc-strategy on a Rink-amide resin, we were able to synthesize the peptide **10** with a good purity by HPLC after cleavage. The analysis of the crude peptide by ICP-MS led us to quantify the residual ruthenium as less than 20 ppm. Affinities

of **10** for both NPFF1 and NPFF2 receptors were measured and compared to the endogenous peptide NPFF. Although showing lower affinities than NPFF,[10] compound **10** still shows a significant affinity for NPFF2R, but binds poorly to NPFF1R. These results highlight how these new basic amino acids can be used to generate peptidomimetics with interesting pharmacological profiles.

Conclusion

We have reported an efficient and selective metal-catalyzed amide reduction allowing the rapid production at the gram-scale, of original unnatural basic α-, β- or γ-amino acids, readily available for liquid- or solid-phase peptide synthesis. These new amino acids will constitute important building blocks for the synthesis of future peptidomimetics. The versatility of the process allows the introduction of a very large diversity of basic tertiary amines exhibiting various physicochemical properties, potentially offering a wide spectrum of uses (cell-penetrating peptide, peptidomimetic, etc)

Experimental

General procedure for the reduction of amides into the corresponding amines 2:

TMDS (6.5 mL, 35.7 mmol, 8 equiv.) was added to $Ru_3(CO)_{12}$ (0.144 g, 0.223 mmol, 0.05 equiv.) under air. Mixture was stirred for 5 minutes, then a solution of compound 1 (4.46 mmol, 1 equiv.) in 24 mL of THF was added, and the reaction mixture was stirred for 16 hours under air at 40°C. Volatiles were removed in vacuo. Reaction mixture was diluted with DCM (24 mL), and cooled to 0°C in an ice bath. Trifluoroacetic acid (20 mL) was slowly added at 0°C. After addition, the reaction mixture was stirred at room temperature for 4 hours. Volatiles were removed under reduced pressure, and the resulting mixture was diluted in diethyl ether (10 mL). A solution of HCl (1 M) in diethyl ether (48 mL) was slowly added to the mixture, and the reaction mixture was stirred at room temperature for 5 minutes, affording a white powder after filtration. The powder was next solubilized in DCM with 10% MeOH. To remove residual ruthenium, dimercaptotriazine on silica (SiliaBondDMT from Silicycle, 0.5 mmol/g of resin, 1.8 mmol) was added and the mixture was stirred for 1h at room temperature, and filtered and rinced with DCM. Compounds **2** were recovered after evaporation and lyophilization. Only compounds **2g**, **2h** and **2r** required to be purified by chromatography using a reversed-phase C18 column.

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(piperidin-1-yl)pentanoic acid hydrochloride (L-2a). 98% yield; $[\alpha]_D^{20}$= -10.5 (c = 0.5 in DMF); ^{1}H NMR (DMSO-d6, 400 MHz) : δ = 7.90 (d, *J* = 7.5 Hz, 2H), 7.72 (m, 2H), 7.42 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.33 (dd, *J* = 7.5, 7.5 Hz, 2H), 4.34 – 4.21 (m, 3H), 3.97 (td, *J* = 3.1, 8.6 Hz, 1H), 3.35 (m, 2H), 2.97 (m, 2H), 2.80 (m, 2H), 1.83 – 1.61 (m, 9H), 1.44 – 1.30 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ = 173.9, 156.7, 144.3, 141.2, 128.1, 127.6, 125.7, 120.6, 66.1, 55.8, 53.8, 52.6, 52.3, 47.1, 28.5, 22.8, 21.8, 20.6; HRMS (ESI+) calcd. for $C_{25}H_{30}N_2O_4$ [M + H]+ 423.2278, found 423.2278

(R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(piperidin-1-yl)pentanoic acid hydrochloride (D-2a). 79% yield; $[\alpha]_D^{20}$= +11.5 (c = 0.5 in DMF); ^{1}H NMR (DMSO-d6, 400 MHz) : δ = 7.90 (d, *J* = 7.5 Hz, 2H), 7.72 (m, 2H), 7.42 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.33 (dd, *J* = 7.5, 7.5 Hz, 2H), 4.34 – 4.21 (m, 3H), 3.97 (td, *J* = 3.1, 8.6 Hz, 1H), 3.35 (m, 2H), 2.97 (m, 2H), 2.80 (m, 2H), 1.83 – 1.61 (m, 9H), 1.44 – 1.30 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ = 173.9, 156.7, 144.3, 141.2, 128.1, 127.6, 125.7, 120.6, 66.1, 55.8, 53.8, 52.6, 52.3, 47.1, 28.5, 22.8, 21.8, 20.6; HRMS (ESI+) calcd. for $C_{25}H_{30}N_2O_4$ [M + H]+ 423.2278, found 423.2278

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(azepan-1-yl)pentanoic acid hydrochloride (2b). 93% yield; $[\alpha]_D^{20}$= -9.5 (c = 1.0 in DMF); ^{1}H NMR (DMSO-d6, 400 MHz) : δ = 7.90 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.42 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.34 (dd, *J* = 7.5, 7.5 Hz, 2H), 4.34 – 4.21 (m, 3H), 3.97 (m, 1H), 3.25 – 3.12 (m, 2H), 3.12 – 2.94 (m, 4H), 1.93 – 1.70 (m, 6H), 1.69 – 1.50 (m, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ = 173.3, 156.1, 143.7, 140.6, 127.6, 127.0, 125.2, 120.1, 65.6, 55.6, 53.3, 46.6, 27.9, 26.0, 22.8, 20.4; HRMS (ESI+) calcd. for $C_{26}H_{32}N_2O_4$ $[M + H]^+$ 437.2435, found 437.2438

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-((R)-2-methylpyrrolidin-1-yl)pentanoic acid hydrochloride (2c). 96% yield; $[\alpha]_D^{20}$= -26.2 (c = 0.5 in DMF); ^{1}H NMR (DMSO-d6, 400 MHz) : δ = 7.89 (d, *J* = 7.5 Hz, 2H), 7.73 (m, 2H), 7.42 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.34 (dd, *J* = 7.5, 7.5 Hz, 2H), 4.29 (m, 2H), 4.24 (m, 1H), 3.98 (m, 1H), 3.54 (m, 1H), 3.23 (m, 1H), 2.98 (m, 1H), 2.87 (m, 1H), 2.14 (m, 1H), 1.90 (m, 3H), 1.81 – 1.55 (m, 5H), 1.36 (d, *J* = 6.4 Hz , 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ = 173.4, 156.2, 143.8, 140.6, 127.6, 127.1, 125.2, 120.1, 65.7, 63.4, 53.3, 52.2, 51.3, 46.6, 30.8, 27.9, 21.6, 20.8, 15.1; HRMS (ESI+) calcd. for $C_{25}H_{30}N_2O_4$ $[M + H]^+$ 423.2278, found 423.2271

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-((1S,5R)-1-methyl-6-azabicyclo[3.2.1]octan-6-yl)pentanoic acid hydrochloride (2d). 86% yield; $[\alpha]_D^{20}$= -9.7 (c = 0.5 in DMF); ^{1}H NMR (MeOD-d4, 400 MHz) : δ = 7.80 (d, *J* = 7.5 Hz, 2H), 7.67 (m, 2H), 7.40 (dd, *J* = 7.5 Hz, 2H), 7.32 (dd, *J* = 7.5 Hz, 2H), 4.41 (m, 1H), 4.32 (m, 1H), 4.23 (m, 2H), 3.90 (m, 1H), 3.72 (dd, *J* = 48.4, 12.4 Hz, 1H), 3.20 (m, 2H), 2.88 – 2.73 (m, 1H), 2.08 – 1.52 (m, 10H), 1.22 – 0.96 (m, 9H); ^{13}C NMR (MeOD-d_4, 125 MHz) : δ = 175.2, 158.9, 145.4, 145.2, 142.7, 129.0, 128.4, 126.3, 121.1, 69.0, 68.6, 68.2, 67.0, 64.0, 63.6, 59.0, 54.8, 54.4, 51.6, 48.5, 42.5, 42.4, 42.0, 40.1, 37.1, 33.0, 29.9, 29.7, 29.5, 24.9, 22.9, 22.7, 15.6; HRMS (ESI+) calcd. for $C_{30}H_{38}N_2O_4$ [M + H]+ 491.2904, found 437.2895

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(4-methylpiperazin-1-yl)pentanoic acid hydrochloride (2e). 85% yield; $[\alpha]_D^{20}$= -7.3 (c = 0.5 in DMF); ^{1}H NMR (DMSO-d6, 400 MHz) : δ = 8.52 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.71(d, *J* = 7.5 Hz, 1H), 7.42 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.34 (dd, *J* = 7.5, 7.5 Hz, 2H), 4.34 – 4.19 (m, 3H),

3.96 (m, 1H), 3.75 – 3.59 (m, 4H), 3.54 – 3.30 (m, 4H), 3.24 – 3.05 (m, 2H), 2.81 (s, 3H), 1.95 – 1.60 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ = 173.3, 156.1, 143.7, 140.6, 127.6, 127.1, 125.2, 120.1, 65.6, 53.4, 51.2, 49.5, 47.9, 46.6, 27.8, 20.1; HRMS (ESI+) calcd. for $C_{25}H_{31}N_3O_4$ [M + H]+ 438.2387, found 438.2395

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(4-(pyrimidin-2-yl)piperazin-1-yl)pentanoic acid hydrochloride (2f). 98% yield; $[\alpha]_D^{20}$= -6.3 (c = 1.8 in DMF); ^{1}H NMR (MeOD-d4, 400 MHz) : δ = 8.54 (d, *J* = 5.2 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.40 (dd, *J* = 7.6 Hz, 2H), 7.35 – 7.29 (m, 2H), 6.93 (dd, *J* = 5.2 Hz, 1H), 4.84 (m, 2H), 4.41 (m, 1H), 4.34 (m, 1H), 4.23 (m, 2H), 3.76 – 3.63 (m, 2H), 3.63 – 3.46 (m, 2H), 3.28 – 3.10 (m, 4H), 2.02 – 1.70 (m, 4H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 175.1, 158.9, 158.6, 145.4, 142.7, 128.9, 128.3, 126.3, 121.1, 112.6, 68.2, 57.7, 54.7, 52.5, 42.7, 29.8, 21.9; HRMS (ESI+) calcd. for $C_{28}H_{31}N_5O_4$ [M + H]+ 502.2449, found 502.2458

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-([1,4'-bipiperidin]-1'-yl)pentanoic acid hydrochloride (2g). 61% yield after column chromatography; $[\alpha]_D^{20}$= -6.3 (c = 0.5 in DMF); ^{1}H NMR (DMSO-d6, 400 MHz) : δ = 7.89 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.42 (dd, *J* = 7.5 Hz, 2H), 7.33 (dd, *J* = 7.5 Hz, 2H), 4.33 – 4.18 (m, 3H), 3.95 (m, 1H), 2.99 (m, 5H), 2.53 (m, 4H), 2.20 (m, 2H), 1.89 – 2.05 (m, 2H), 1.78 – 1.43 (m, 12H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ = 173.7, 156.1, 143.7, 140.7, 127.6, 127.0, 125.2, 120.1, 65.6, 56.0, 53.6, 51.2, 49.1, 46.6, 28.5, 25.1, 23.3, 22.1, 22.0; HRMS (ESI+) calcd. for $C_{30}H_{39}N_3O_4$ [M + H]+ 506.3013, found 506.3010

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(4-(ethoxycarbonyl)piperidin-1-yl)pentanoic acid hydrochloride (2h). 58% yield after column chromatography; $[\alpha]_D^{20}$= -7.3 (c = 0.5 in DMF); ^{1}H NMR (MeOD-d4, 400 MHz) : δ = 7.78 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 7.5 Hz, 2H), 7.30 (dd, *J* = 7.5 Hz, 2H), 4.36 (m, 2H), 4.19 (t, *J* = 6.6 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.01 (m, 1H), 3.56 – 3.33 (m, 2H), 3.08 – 2.76 (m, 4H), 2.60 (m, 1H), 2.16 – 2.04 (m, 2H), 2.03 – 1.87 (m, 2H), 1.83 – 1.45 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 178.4, 174.7, 158.1, 145.6, 142.7, 128.9, 128.3, 126.3, 121.1, 67.8, 62.1, 57.8, 56.8, 52.3, 48.6, 31.1, 26.5, 21.5, 14.6; HRMS (ESI+) calcd. for $C_{28}H_{34}N_2O_6$ [M + H]+ 495.2490, found 495.2502

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(4-hydroxypiperidin-1-yl)pentanoic acid hydrochloride (2i). 96% yield; $[\alpha]_D^{20}$= -8.3 (c = 0.5 in DMF); ^{1}H NMR (MeOD-d4, 400 MHz) : δ = 7.79 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 7.5 Hz, 2H), 7.30 (dd, *J* = 7.5 Hz, 2H), 4.37 (m, 2H), 4.20 (t, *J* = 6.6 Hz, 1H), 4.01 (m, 1H), 3.89 (m, 1H), 3.40 – 3.21 (m, 2H), 3.18 – 2.79 (m, 4H), 2.01 (m, 2H), 1.91 – 1.59 (m, 6H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 178.4, 158.1, 145.5, 142.7, 128.9, 128.3, 126.3, 121.1, 67.7, 57.7, 56.9, 48.6, 31.9, 31.2, 21.6; HRMS (ESI+) calcd. for $C_{25}H_{30}N_2O_5$ [M + H]+ 439.2227, found 439.2236

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(4-benzylpiperidin-1-yl)pentanoic acid hydrochloride (2j). 93% yield; $[\alpha]_D^{20}$= -8.3 (c = 0.5 in DMF); ^{1}H NMR (MeOD-d4, 400 MHz) : δ = 7.78 (d, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 7.5 Hz, 2H), 7.34 – 7.24 (m, 4H), 7.22 – 7.13 (m, 3H), 4.40 (dd, *J* = 10.8, 6.5 Hz, 1H), 4.31 (m, 1H), 4.21 (m, 2H), 3.48 (d, *J* = 11.4 Hz, 2H), 3.07 (m, 2H), 2.84 (m, 2H), 2.58 (d, *J* = 6.5 Hz, 2H), 1.96 – 1.72 (m, 7H), 1.50 (m, 2H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 175.0, 158.8, 145.4, 142.7, 140.5, 130.3, 129.6, 128.9, 128.3, 127.5, 126.3, 121.1, 68, 1, 57.7, 54.6, 54.3, 48.4, 43.1, 36.8, 30.6, 29.8, 21.9; HRMS (ESI+) calcd. for $C_{32}H_{36}N_2O_4$ [M + H]+ 513.2748, found 513.2749

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(3,4-dihydroisoquinolin-2(1H)-yl)pentanoic acid hydrochloride (2k). 92% yield; $[\alpha]_D^{20}$= -7.9 (c = 0.8 in DMF); ^{1}H NMR (DMSO-d6, 400 MHz) : δ = 7.90 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.42 (dd, *J* = 7.5 Hz, 2H), 7.34 (dd, *J* = 7.5 Hz, 2H), 7.30 – 7.21 (m, 3H), 7.18 (m, 1H), 4.48 (m, 1H), 4.38 – 4.19 (m, 4H), 4.01 (m, 1H), 3.64 (m, 1H), 3.34 – 3.13 (m, 4H), 3.01 (m, 1H), 1.94 – 1.63 (m, 4H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 173.6, 156.4, 144.0, 141.0, 131.7, 128.8, 127.9, 127.4, 126.9, 125.5, 120.4, 66.0, 54.8, 53.6, 51.9, 48.9, 46.9, 28.2, 25.0, 20.7; HRMS (ESI+) calcd. for $C_{29}H_{30}N_2O_4$ [M + H]+ 471.2278, found 471.2293

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(indolin-1-yl)pentanoic acid hydrochloride (2l). 94% yield; $[\alpha]_D^{20}$= +2.1 (c = 0.6 in MeOH); ^{1}H NMR (MeOD-d4, 400 MHz) : δ = 7.76 (d, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.40 (m, 4H), 7.34 (dd, *J* = 7.5 Hz, 2H), 7.26 (dd, *J* = 7.5 Hz, 2H), 4.32 (m, 2H), 4.18 (m, 2H), 3.91 (m, 2H), 3.56 (m, 2H), 2.17 – 1.67 (m, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ = 173.5, 156.0, 143.6, 140.5, 127.5, 126.9, 125.1, 120.0, 65.5, 53.3, 52.4, 46.5, 28.0, 27.7, 22.1; HRMS (ESI+) calcd. for $C_{28}H_{28}N_2O_4$ [M + H]+ 457.2122, found 457.2136

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(methyl(phenyl)amino)pentanoic acid hydrochloride (2n). 98% yield; $[\alpha]_D^{20}$= -7.2 (c = 1.2 in DMF); ^{1}H NMR (MeOD-d_4, 400 MHz) : δ = 7.72 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.59 (dd, *J* = 7.5 Hz, 2H), 7.31 (dd, *J* = 7.5 Hz, 2H), 7.19 – 7.25 (m, 2H), 7.11 (dd, *J* = 7.5 Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.59 (dd, *J* = 7.5 Hz, 1H), 4.30 (m, 2H), 4.13 (m, 2H), 3.27 (m, 2H), 2.83 (s, 3H), 1.82 (m, 1H), 1.60 (m, 3H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 176.0, 158.7, 150.7, 145.3, 142.7, 130.2, 128.9, 128.3, 126.3, 121.0, 117.9, 114.1, 68.0, 55.3, 53.5, 48.6, 38.9, 30.4, 24.1; HRMS (ESI+) calcd. for $C_{27}H_{28}N_2O_4$ [M + H]+ 445.2122, found 445.2126

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(methyl(phenethyl)amino)pentanoic acid hydrochloride (2o). 96% yield; $[\alpha]_D^{20}$= -8.5 (c = 0.8 in DMF); ^{1}H NMR (MeOD-d_4, 400 MHz) : δ = 7.79 (d, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.39 (dd, *J* = 7.5 Hz, 2H), 7.35 – 7.23 (m, 7H), 4.42 (dd, *J* = 10.1, 6.6 Hz, 1H), 4.33 (m, 1H), 4.22 (m, 2H), 3.38 (m, 2H), 3.22 (m, 2H), 3.06 (m, 2H), 2.91 (s, 3H), 1.96 (m, 1H), 1.90 – 1.70 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ = 173.9, 156.7, 144.2, 141.2, 137.5, 129.2, 129.1, 128.1, 127.6, 127.3,

125.7, 120.6, 66.2, 56.3, 54.8, 53.9, 47.1, 29.8, 28.3, 20.6; HRMS (ESI+) calcd. for $C_{29}H_{32}N_2O_4$ [M + H]+ 473.2435, found 473.2448

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(butyl(methyl)amino)pentanoic acid hydrochloride (2p). 98% yield; $[\alpha]_D^{20}$= -9.9 (c = 1.4 in DMF); ^{1}H NMR (MeOD-d_4, 400 MHz) : δ = 7.79 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.39 (dd, *J* = 7.5 Hz, 2H), 7.31 (dd, *J* = 7.5 Hz, 2H), 4.41 (dd, *J* = 10.3, 6.7 Hz, 1H), 4.33 (m, 1H), 4.22 (m, 2H), 3.22 – 3.00 (m, 4H), 2.82 (s, 3H), 2.12 – 1.59 (m, 6H), 1.38 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 175.1, 158.9, 145.4, 142.7, 129.0, 128.3, 126.3, 121.1, 68.2, 57.5, 56.8, 54.7, 40.8, 29.8, 27.3, 22.0, 21.0, 14.0; HRMS (ESI+) calcd. for $C_{25}H_{32}N_2O_4$ [M + H]+ 425.2435, found 425.2453

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-((2-cyanoethyl)(methyl)amino)pentanoic acid hydrochloride (2q). 89% yield; $[\alpha]_D^{20}$= -7.9 (c = 0.5 in DMF); ^{1}H NMR (MeOD-d_4, 400 MHz) : δ = 7.79 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 7.5 Hz, 2H), 7.30 (dd, *J* = 7.5 Hz, 2H), 4.38 (m, 2H), 4.21 (t, *J* = 6.7 Hz, 1H), 4.07 (m, 1H), 3.07 (t, *J* = 7.0 Hz, 2H), 2.80 (m, 4H), 2.54 (s, 3H), 1.90 – 1.54 (m, 4H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 177.5, 158.5, 145.5, 142.7, 128.9, 128.3, 126.3, 121.1, 119.1, 67.9, 57.5, 56.1, 53.0, 48.6, 41.0, 30.8, 23.1, 15.0; HRMS (ESI+) calcd. for $C_{24}H_{27}N_3O_4$ [M + H]+ 422.2074, found 422.2080

(2S)-5-(1-benzylhydrazin-1-yl)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}pentanoic acid hydrochloride (2r). 30% yield after column chromatography; $[\alpha]_D^{20}$= -7.3 (c = 0.9 in DMF); ^{1}H NMR (MeOD-d_4, 400 MHz) : δ = 7.77 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.48 – 7.32 (m, 7H), 7.28 (dd, *J* = 7.5 Hz, 2H), 4.33 (m, 2H), 4.24 – 4.04 (m, 4H), 3.04 (m, 2H), 1.93 (m, 1H), 1.77 (m, 3H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 175.4, 158.8, 145.2, 142.7, 131.4, 130.2, 128.9, 128.3, 126.3, 121.1, 68.1, 62.4, 57.1, 54.9, 48.5, 29.9, 23.0; MS (ESI+) calcd. for $C_{27}H_{29}N_3O_4$ [M + H]+ 460.2, found 460.2

(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-(piperidin-1-yl)butanoic acid (4). Same procedure than for compounds **2**. 95% yield; $[\alpha]_D^{20}$= -11.3 (c = 0.8 in DMF); ^{1}H NMR (MeOD-d_4, 400 MHz) : δ = 7.79 (d, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 7.5 Hz, 2H), 7.31 (dd, *J* = 7.5 Hz, 2H), 4.46 – 4.32 (m, 2H), 4.27 (m, 1H), 4.22 (t, *J* = 6.8 Hz, 1H), 3.50 (m, 2H), 3.19 (m, 1H), 3.12 (m, 1H), 2.91 (q, *J* = 12.2 Hz, 2H), 2.35 (m, 1H), 2.15 (m, 1H), 1.90 (m, 2H), 1.80 (m, 3H), 1.50 (m, 1H); ^{13}C NMR (MeOD-d_4, 100 MHz) : δ = 174.0, 158.8, 145.4, 142.7, 128.9, 128.3, 126.3, 121.1, 68.2, 55.5, 54.8, 54.5, 53.1, 27.4, 24.4, 22.7; HRMS (ESI+) calcd. for $C_{24}H_{28}N_2O_4$ [M + H]+ 409.2122, found 409.2121

(S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(piperidin-1-yl)butanoic acid hydrochloride (7). Same procedure than for compounds **2**. 95% yield; $[\alpha]_D^{20}$= +2.3 (c = 1.2 in DMF); ^{1}H NMR (DMSO-d_6, 400 MHz) : δ = 7.94 (d, *J* = 7.5 Hz, 2H), 7.74 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.47 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.37 (m, 2H), 4.42 (m, 1H), 4.31 (m, 3H), 3.45 (m, 2H), 3.21 (m, 2H), 2.96 (m, 2H), 2.73 (m, 2H), 2.01 – 1.62 (m, 5H), 1.42 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ = 171.4, 155.5, 143.7, 140.7, 127.6, 127.0, 125.1, 120.1, 65.6, 58.4, 52.9, 51.9, 46.6, 43.6, 37.4, 21.9, 21.1; HRMS (ESI+) calcd. for $C_{24}H_{28}N_2O_4$ [M + H]+ 409.2122, found 409.2123

(S)-4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(piperidin-1-yl)pentanoic acid hydrochloride (8). Same procedure than for compounds **2**. 84% yield; $[\alpha]_D^{20}$= -1.7 (c = 1.1 in DMF); ^{1}H NMR (DMSO-d_6, 400 MHz) : δ = 7.89 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.33 (dd, *J* = 7.5, 7.5 Hz, 2H), 4.45 (dd, *J* = 6.8, 10.4 Hz, 1H), 4.31 (m, 1H), 4.22 (t, *J* = 6.5 Hz, 1H), 3.89 (m, 1H), 3.37 (m, 2H), 3.10 – 2.92 (m, 2H), 2.86 (m, 2H), 2.21 (m, 2H), 1.77 – 1.46 (m, 7H), 1.35 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ =173.8, 155.8, 143.7, 140.7, 127.6, 127.0, 125.2, 120.1, 65.4, 58.7, 52.6, 51.9, 46.7, 45.7, 29.7, 28.1, 21.9, 21.21; HRMS (ESI+) calcd. for $C_{25}H_{30}N_2O_4$ [M + H]+ 423.2278, found 423.2280.

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