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α,α-Cyclopentaneglycine Dipeptides Capped with Biaryls as Tachykinin NK_2 Receptor Antagonists

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The NK_2 receptor belongs to the family of tachykinin neurotransmitters. It has been reported to be involved in several pathological conditions, and selective antagonists are potentially useful drugs for the treatment of asthma, irritable bowel syndrome, cystitis, and depression. Starting from in-house capped dipeptide libraries, we were able to identify a number of molecules with sub-nanomolar binding affinity for the hNK_2 receptor. All were characterized by a rigid core structure with a strong constraint induced by an α,α-cyclopentaneglycine fragment. Herein we report the further elaboration of three initial basic structures. The planar benzothiophene group was substituted with a series of biphenyl and heterobiphenyl moieties that are well tolerated in terms of receptor affinity. The new compounds also maintained good antagonist potency in an in vitro functional assay, and a number of them showed significant in vivo activity after intravenous administration in our guinea pig model.

Introduction

The tachykinins are a family of neuropeptides widely distributed in the mammalian central and peripheral nervous systems. They produce a wide range of biological effects including smooth muscle contraction and relaxation, vasodilatation, activation of the immune system, regulation of pain transmission and neurogenic inflammation. These effects are mediated by the stimulation of three distinct receptor subtypes named NK_1, NK_2, and NK_3.[1] The three natural mammalian tachykinins are able to activate all of the receptors, although substance P displays the highest affinity for NK_1, neurokinin A for NK_2 and neurokinin B for NK_3. Because of the involvement of tachykinin NK_2 receptors in a number of pathological conditions, selective antagonists are considered potential candidates for the treatment of asthma, irritable bowel syndrome, and urinary bladder hyperreflexia.[2] At present, two NK_2 receptor antagonists are undergoing clinical trials: the small molecule saredutant (currently in phase III for major depressive disorders and general anxiety disorders)[3] from Sanofi–Aventis, and the bicyclic hexapeptide nepadutant (phase II) from Menarini.

As part of a project aimed at the identification of a series of small, orally available antagonists for the human tachykinin NK_2 receptor (hNK_2), starting from one of our in-house peptide libraries and after a few rounds of optimization, we identified compounds **1**,[4] **2** and **3**[5] as suitable leads (Figure 1). In fact they showed sub-nanomolar affinity for the hNK_2 receptor, good antagonist potency at the guinea pig NK_2 receptor in a functional test (guinea pig colon smooth muscle contractility assay, GPC) and **1**, when tested for functional activity on guinea pig NK_1 and NK_3 receptors, was totally inactive.[6] However, their activity after intravenous (iv) administration in our animal model was not satisfactory. This encouraged us to explore further modifications of the basic structure to improve the in vivo activity after iv administration, which was considered an essential requirement before starting any oral dosing test. To reach this goal we undertook a number of optimization strategies working on the hypothesis that the lack of in vivo activity may be due to metabolic instability or to excessive local lipophilicity.

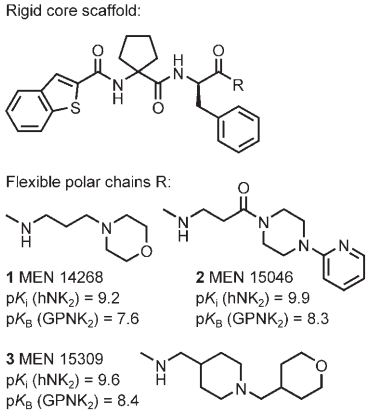

Figure 1. Leads for the synthesis of new NK_2 antagonists.

Herein we report the work aimed at the introduction of modifications on the N-terminal acyl group, in order to modulate the local chemical properties (i.e., improving slightly local polarity or block positions theoretically susceptible to metabolic oxidation). At the same time both aromaticity and the pla-

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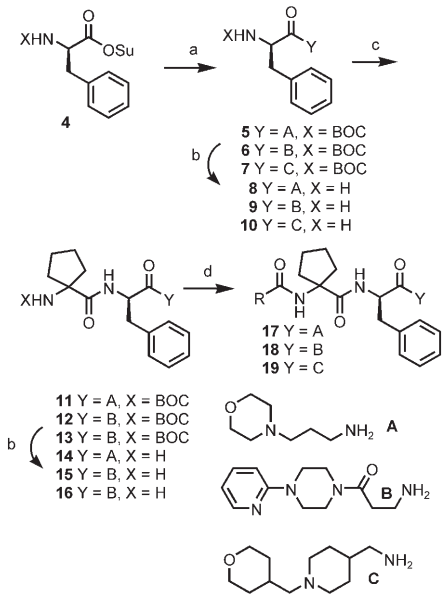
narity of the acyl group had to be conserved, because from previous experience we knew them to be essential for good binding affinity. Biphenyls and heterobiphenyls systems with *para* and *meta* junctions between the two aromatic moieties were considered to assure the required planarity, while *ortho* substituents on both the aromatic rings were avoided.

Once prepared, the compounds were submitted to binding affinity evaluation on the hNK_2 receptor. Those with $pK_i \geq 8.5$ were progressed to the functional test on the GPC assay, and finally, when the antagonist potency pK_B was ≥ 7.5, an in vivo evaluation was performed (iv dosing).

Results and Discussion

Synthesis

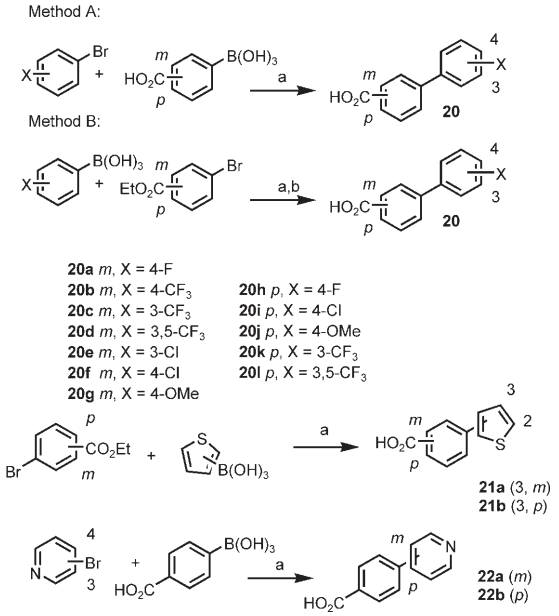
All the compounds were prepared according to the general sequence shown in Scheme 1. The *N*-hydroxysuccinimidyl ester of Boc-protected D-phenylalanine (**4**) was treated with amines **A**, **B**, or **C** to obtain respectively compounds **5**, **6**, and **7**. Boc group deprotection with 4 N HCl in dioxane afforded the corresponding amines **8**, **9**, and **10**.



Scheme 1. a) A, B or C, CH_2Cl_2, RT; b) 4 N HCl in dioxane, RT; c) EDAC, DMF, HOBt, Boc-1-amino-1-cyclopentane carboxylic acid, DIPEA, DMF, RT; d) RCO_2H, EDAC, HOBt, DIPEA, DMF, RT.

Reaction of these amines with Boc-1-amino-1-cyclopentane carboxylic acid in standard coupling conditions, followed by a second treatment with a dioxane solution of HCl, gave amines **14**, **15**, and **16**. Final products **17**, **18**, or **19** were respectively obtained by coupling of **14**, **15**, and **16** with opportune carboxylic acids in standard coupling conditions.

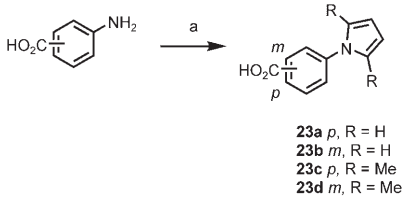
When not commercially available, biphenylcarboxylic acids **20** were prepared (Scheme 2) either by Suzuki coupling of an opportunely substituted aryl bromide with 3- or 4-carboxyphenylboronic acid (Method A) or by coupling of the substituted



Scheme 2. a) K_2CO_3, $Pd(OAc)_2$, PPh_3, 1,4-dioxane; b) NaOH, H_2O/MeOH.

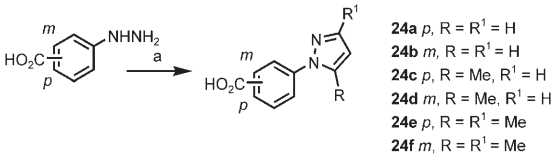
phenylboronic acid with 3- and 4-bromobenzoate ethyl esters, followed by basic hydrolysis (Method B).

Thiophene derivatives **21** were prepared by starting from 2- and 3-thiophene boronic acids by Method B, whereas pyridine derivatives **22** were obtained by Method A, starting from the corresponding bromopyridine. Pyrrole derivatives were obtained by condensation of 3- and 4-aminobenzoic acids with 2,5-dimethoxytetrahydrofuran (compounds **23a** and **23b**) or 2,5-hexanedione (compounds **24a** and **24b**) in acidic media (Scheme 3).



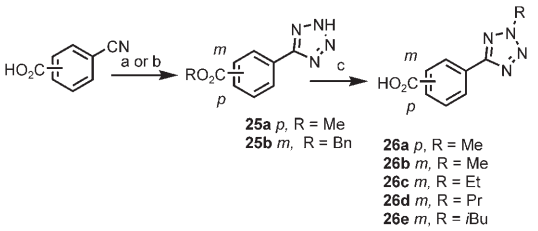
Scheme 3. a) 2,5-dimethoxytetrahydrofuran or 2,5-hexanedione, AcOH, THF.

As general procedure, carboxyphenyl pyrazoles were prepared through condensation of 3- or 4-hydrazinobenzoic acids with an opportune 1,3-dicarbonyl compound (Scheme 4). Finally, tetrazoles were prepared from 3- or 4-cyanobenzoate



Scheme 4. a) 1,1,3,3-tetramethoxypropane or acetylacetaldehyde dimethylacetal or 2,4-pentanedione, AcOH/H_2O (1:1).

methyl or benzyl esters by treatment with trimethylsilylazide followed by alkylation with trimethylsilyldiazomethane in the case of methyl tetrazole, and with an opportune alkyl bromide for the others (Scheme 5). The regioselectivity of tetrazole alkylation was unequivocally established by NOE-diff and NOESY experiments.



Scheme 5. a) $TMSN_3$, Bu_2SiO, toluene, reflux; b) trimethylsilyldiazomethane or RBr and K_2CO_3; c) NaOH THF/H_2O; d) H_2, 5% Pd/C, MeOH.

In vitro pharmacology

The binding affinity (pK_i) at the human tachykinin NK_2 receptor was evaluated for all the compounds, and the results are reported in Tables 1–3. The naked biphenyl derivatives **27**[7] and **74** confirmed that this was a viable path from a steric and overall conformational point of view. Classical substituents aimed to block oxidative metabolism or finely modulate lipophilicity and solubility were tolerated with the exception of the mono- (**34** and **35**) and bis-CF_3 derivatives (**36** and **37**). The combination of *p*-substituted biphenyl with amine C seemed to be particularly attractive, because all the compounds prepared, except the *p*-MeO derivative, had sub-nanomolar pK_i values.

Interestingly, compounds with either *para* or *meta* junctions between the two rings were almost equivalent in terms of affinity for the receptor. Amine B was not used in conjunction with biphenyls because of solubility problems. The introduction of a heterocycle as second ring in the biaryl system also seemed to be generally well tolerated.

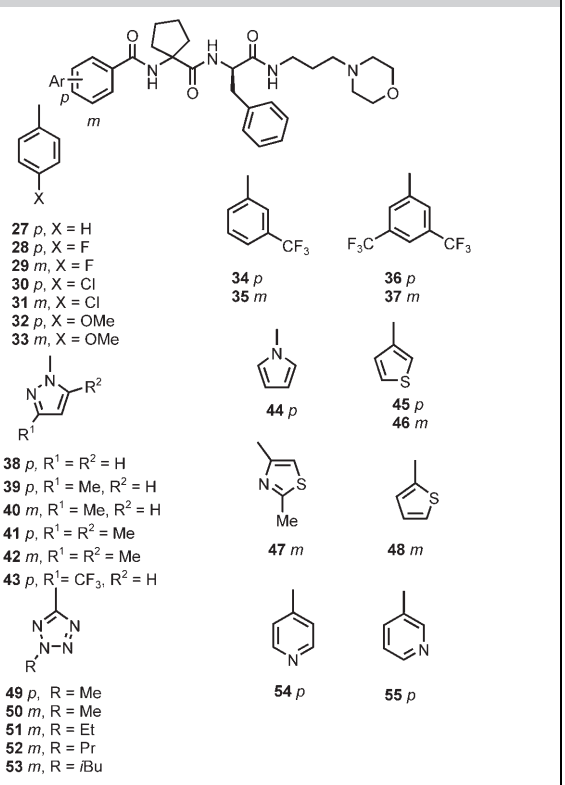
Pyrazoles were preferred in the *para* junction, with the 3-methyl derivatives (**39** and **65**) being the best performers over the dimethyl-substituted or unsubstituted derivatives. Surprisingly, tetrazoles were preferred with a *meta* junction between the two aromatic rings, with the affinity for the receptor growing in parallel with the length of the aliphatic chain.

Pyridines were characterized by a drop in potency (compounds **54** and **55**); nevertheless compound **73** maintained an acceptable value of affinity ($pK_i = 8.1$). The *p*-pyrrole was generally the best performing heterocycle. Amine A gave a product of the same pK_i value as the biphenyl, while amines B and C produced derivatives displaying sub-nanomolar affinity. 3-Thiophene resulted in a compound with the highest binding affinity (**63**, $pK_i = 10.1$; Table 2).

In view of the testing in our animal model, the most active molecules ($pK_i \geq 8.5$) were evaluated for functional antagonist potency in guinea pig isolated proximal colon (GPC-pK_B; see Table 4 below). It was observed that antagonist potency at the guinea pig receptor was at least one log unit lower than the affinity for the human receptor. This was a general trend for this series and seems not to be dependent on the species, but rather by the different experimental conditions used to estimate the affinity (radioligand binding) and the antagonist potency (smooth muscle contractility assay in the GPC).

A similar pattern was observed when a few compounds were tested for functional activity on isolated urinary bladder (HUB). Furthermore, in spite of its high pK_i value, compound **63** had an even greater loss in potency, as did other members of the family bearing amine B as carboxy-terminal capping group. The best potency in the functional test was showed by the pyrrole derivative **70** ($pK_B = 8.7$; Table 4).

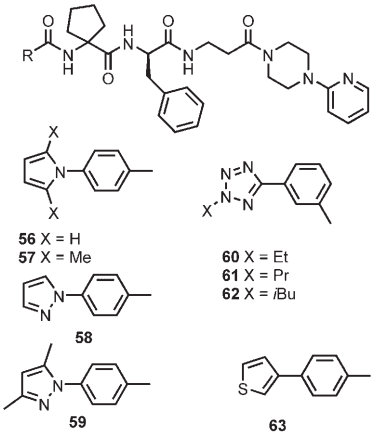
Table 1. Binding affinity of compounds bearing substituted *para*- or *meta*-biphenyls or heterobiphenyls as N-terminal capping groups and amine A toward the hNK_2 receptor.



Compd	pK_i[a]	Compd	pK_i[a]
1	9.2	**41**	7.5
27	8.8	**42**	<7
28	7.9	**43**	7.1
29	7.7	**44**	8.7
30	8.4	**45**	8.8
31	8.5	**46**	7.6
32	8.0	**47**	7.5
33	8.2	**48**	8.3
34	7.5	**49**	<7
35	7.4	**50**	7.7
36	7.1	**51**	7.6
37	7.7	**52**	8.0
38	7.7	**53**	8.1
39	8.0	**54**	<7
40	7.1	**55**	7.4

[a] Each value is the mean of three determinations.

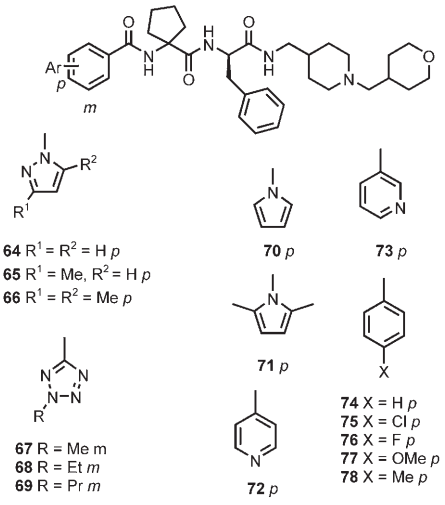
Table 2. Binding affinity of compounds bearing substituted *para*- or *meta*-biphenyls or heterobiphenyls as N-terminal capping groups and amine B toward the hNK_2 receptor.



Compd	pK_i[a]	Compd	pK_i[a]
2	9.9	**60**	8.6
56	9.8	**61**	9.1
57	9.4	**62**	9.0
58	8.6	**63**	10.1
59	9.0		

[a] Each value is the mean of three determinations.

Table 3. Binding affinity of compounds bearing substituted *para*- or *meta*-biphenyls or heterobiphenyls as N-terminal capping groups and amine C toward the hNK_2 receptor.



Compd	pK_i[a]	Compd	pK_i[a]
3	9.6	**71**	8.4
64	8.7	**72**	7.8
65	8.9	**73**	8.1
66	8.3	**74**	9.5
67	8.4	**75**	9.6
68	8.2	**76**	9.4
69	8.2	**77**	8.7
70	9.6	**78**	9.5

[a] Each value is the mean of three determinations.

Table 4. Functional activity in guinea pig isolated proximal colon.

Compd	pK_B[a]	Compd	pK_B[a]
nepadutant	8.5	**62**	8.1
1	7.6	**63**	8.0
2	8.3	**64**	7.5
3	8.4	**65**	7.5
31	6.5	**70**	8.7
44	7.6	**74**	8.0
45	7.1	**75**	7.9
56	8.6	**76**	7.7
57	7.7	**78**	7.6
59	8.0		

[a] $pK_B = -\log K_B$; antagonist potency values for guinea pig NK_2 receptor estimated toward [βAla^8]NKA(4-10)-induced contractions of the guinea pig isolated colon (GPC) in the presence of the NK_1-receptor-selective antagonist SR140333.

In vivo pharmacology

As anticipated, compounds showing a $pK_B \geq 7.5$ were tested in our animal model.[8] The potency in inhibiting colonic contractions induced by the selective tachykinin NK_2 receptor agonist [βAla^8]neurokinin A(4-10) ([βAla^8]NKA(4-10), 3 nmol kg^{-1} iv) in guinea pig was evaluated after iv administration at a cut-off dose of 3 μmol kg^{-1}. The results, obtained after iv administration of the antagonist, are expressed both as maximal inhibitory effect reached (%i_{max}) and as Σ*i*%max (Table 5). The latter value is expressed as the sum of the percent inhibition relative to the sum of the control (basal) colon contractions induced by the selective agonist at nine time-point observations (5, 30, 60, 90, 120, 150, 180, 210, and 240 min) after iv administration of the antagonist (Σ(%*i*)) and further calculated as the sum of the theoretical maximal percent inhibition (Σ(%$i_{max\text{-}th}$)), which is a constant and equal to 900. The mean percent inhibition over the entire experiment is expressed as:

$$\Sigma i\,\%\text{max} = \frac{\Sigma(\%\, i)}{\Sigma(\%\, i_{\text{max-th}})} \times 100$$

Table 5. In vivo evaluation of selected compounds.[a]

Compd	Σ*i*%max[b]	%i_{max} ± SEM[c]	Compd	Σ*i*%max[b]	%i_{max} ± SEM[c]
nepadutant	96	99 ± 1	**64**	26	68 ± 15
44	6	61 ± 7	**70**	70	99 ± 1
56	67	94 ± 3	**74**	60	97 ± 6
57	5	71 ± 6	**75**	0	46 ± 28
59	30	78 ± 10	**76**	88	92 ± 4
63	37	73 ± 12	**78**	69	79 ± 8

[a] Inhibition of colonic contractions induced by [βAla^8]NKA(4-10) in guinea pig after iv administration at 3 μmol kg^{-1}, except for nepadutant, for which the dose was 0.3 μmol kg^{-1}. [b] Σ*i*%max = [Σ(%*i*)/Σ(%$i_{max\text{-}th}$)] × 100 = mean percent inhibition over the entire experiment, that is, the sum of the percent inhibition relative to the basal colon contraction of [βAla^8]NKA(4-10) at nine observation times (5, 30, 60, 90, 120, 150, 180, 210, and 240 min) after administration of the antagonist and further calculated as the percentage of the theoretical maximal response (Σ(%$i_{max\text{-}th}$) = 900 %). [c] Maximal inhibitory effect as percent inhibition of the control response.

This parameter gives a measure of the activity during the entire experimental period therefore allowing the evaluation of both the intensity and the duration of the antagonist effect. The maximal inhibition corresponds to $\Sigma i\%max = 100$, while the absence of effect results in $\Sigma i\%max = 0$.

The initial reference compounds **1**, **2**, and **3** showed very limited in vivo inhibitory activity if any. Indeed for **1** the $\Sigma i\%max$ value was 0.5 at a dose of 1 $\mu mol\,kg^{-1}$ (iv), for **2** $\Sigma i\%max = 53$ at a dose of 10 $\mu mol\,kg^{-1}$ (in this case intraperitoneal (ip) administration was necessary because of the low aqueous solubility), and for **3** a $\Sigma i\%max$ value of 53 was measured at a dose of 3 $\mu mol\,kg^{-1}$ (iv).

The results for the in vivo testing (Table 5) show that our first endpoint was reached: at a dose of 3 $\mu mol\,kg^{-1}$ iv, compounds **56**, **59, 70**, **74**, and **78**, all having reasonable aqueous solubility at pH 7.4, resulted in significant antagonist activity on our animal model over a period of 240 min.

Conformational analysis

The arylacylcyclopentane-D-phenylalanine system is quite rigid, and its 3D shape is crucial for receptor affinity. In order to get more insight into the structural aspects of our molecules, we have compared the solution conformation of a few representative compounds with the recently published X-ray crystal structure of the NK_2 antagonist MEN 15596 (Figure 2, **79**).[9] This structure, which places the two aromatic moieties in two opposite directions, agrees with the pharmacophoric model for the NK_2 antagonists determined with the auxilium of mutagenesis studies.[3]

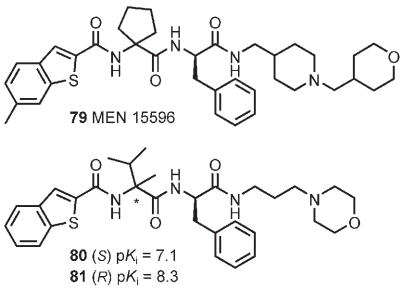


Figure 2. Compound for X-ray crystallographic structural determination (MEN 15596, **79**) and for conformational analysis in solution (compounds **80** and **81**).

The conformational analysis of representative compounds was carried out by the use of NMR spectroscopy and molecular modeling: the compounds were analyzed through NAMFIS, a methodology that classifies the structures obtained by molecular modeling with regard to their relative capability of reproducing NMR data.[10] At first, compounds **80** and **81**, containing the two enantiomeric fragments of α-methylvaline were prepared (Figure 2). These amino acids have, in fact, the capability of inducing a secondary structure similar to the one induced by the α,α-cyclopentyl[11,12] fragment, but are easier to study by NMR spectroscopy because of their asymmetric core. The binding affinity of the two model compounds **80** (*S* isomer) and **81** (*R* isomer) were respectively $pK_i = 7.1$ and $pK_i = 8.3$.

The analysis of experimental data showed that both **80** and **81** are present in solution with more than one conformation. Among these structures one has the three hydrophobic groups, benzothiophene, methylvaline and phenyl, in a reciprocal position analogous to one of the corresponding groups, benzothiophene, cyclopentane and phenyl, in the crystal structure of **79** (Figure 3). In addition to this it has been evaluated that the molar fraction (χ) of this conformation, increases going from compound **80** ($\chi \sim 0.2$) to compound **81** ($\chi \sim 0.8$). This is in qualitative agreement with the observed biological activity: **80** $pK_i = 7.1$, **81** $pK_i = 8.3$. An analogous conformational study carried out for **30** and **46** shows that for both compounds the supposed bioactive conformation is present in solution in a considerable amount (Figure 3 b).

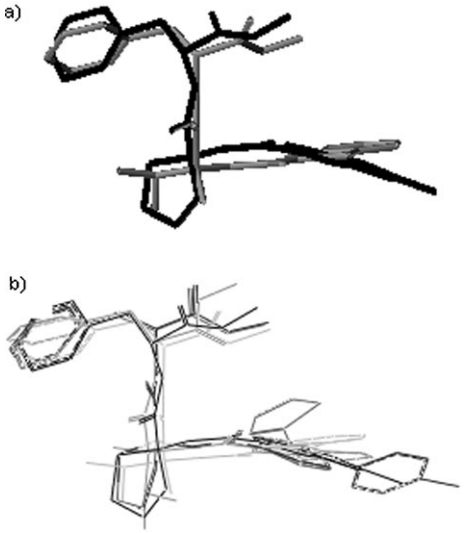


Figure 3. a) Superposition of the crystal structure of **79** (black) with the solution major conformation for **81** (gray). b) Superposition of **79** (black), **30**, **46**, **80**, and **81** (fading gray tonalities respectively); the C-terminal portion, being very flexible, is not reported.

Conclusions

Through elaboration of the leads which emerged from the capped dipeptides libraries prepared in house, we have been able to find very potent NK_2 antagonists in vitro, both on the isolated enzyme and in the functional test, and endowed with significant activity in our animal model after intravenous administration. In addition the NMR conformational analysis of this class of molecules confirmed the hypothesis that the supposed active conformation obtained from the crystal structure of an analogous compound was also the major conformation in solution.

Experimental Section

Chemistry. Commercial chemicals and solvents were of reagent grade and used without further purification. Merck silica gel (Kie-

selgel 60) was used for analytical thin-layer chromatography (TLC, F_{254} plates) and flash chromatography (230–400 mesh).

Purity was evaluated by analytical HPLC on a Waters Alliance system fitted with a UV-PDA 996 diode array detector. The solvents were (A): H_2O + 0.1% TFA and (B): MeCN + 0.1% TFA. System A: Symmetry RP-C_{18} column, 3.5 μM, 4.6×100 mm, λ = 214 nm; 1 min 10%(B), then 10→80%(B) over 10 min, flow = 1.0 mL min^{-1}. System B: Inertsil ODS-3 column, 3.5 μM, 3×50 mm, λ = 214 nm; 20→50%(B) over 8 min, flow = 0.8 mL min^{-1}. System C: Luna RP-C_{18} column, 5 μM, 4.6×100 mm, λ = 214 nm; 1 min 10%(B), then 10→80%(B) over 10 min, flow = 1.0 mL min^{-1}. System D: Vydac column, 3.5 μM, 4.6×100 mm, λ = 214 nm; 10→90%(B) over 20 min, flow = 1.0 mL min^{-1}.

Preparative reversed-phase HPLC was performed on a Waters 600E apparatus with a Jasco 874 UV detector or on a Waters Delta-Prep 3000 apparatus. The mobile phases were the same as for the analytical systems. Gradient elution was employed. The column used was a Symmetry Prep C_{18}, 7 μM, 19×300 mm. Peak detection was at 220 and 254 nm. Chemical yields are not optimized.

NMR experiments were recorded on a Varian 300 MHz spectrometer (equipped with a 5 mm inverse probe) or on a Bruker Avance 400 MHz and are referenced to residual solvent signals: $CDCl_3$ (δ 7.26) or [D_6]DMSO (δ 2.49). Chemical shifts are reported in δ units (ppm) and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q), quintets (quin), multiplets (m), broad signals (br), or very broad signals (v br). Coupling constants (*J*) are reported in hertz (Hz). Mass spectra were recorded with a Water Alliance 2795 HPLC system fitted with a UV-PDS 996 diode array detector.

4′-Fluorobiphenyl-3-carboxylic acid (20a). 4-Fluorobromobenzene (500 mg, 2.86 mmol), $Pd(AcO)_2$ (25 mg, 0.11 mmol), PPh_3 (150 mg, 0.572 mmol) and 3-carboxyphenylboronic acid (712 mg, 4.29 mmol) were sequentially added to a suspension of K_2CO_3 (572 mg, 5.72 mmol) in 1,4-dioxane (10 mL) under N_2. The resulting mixture was stirred at 85 °C for 24 h. After cooling, saturated $NH_4Cl_{(aq)}$ and *n*-hexane were added, and the two phases were separated. 1 N HCl was added to the aqueous layer and that was then extracted three times with *n*-hexane. The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo to give crude **20a** (450 mg, 73% yield) used as such without any further purification.

4′-Trifluoromethylbiphenyl-3-carboxylic acid (20b). 4-Bromotrifluorotoluene (642 mg, 2.86 mmol) was submitted to the same reaction conditions used for the preparation of **20a** to obtain **20b** (472 mg, 62% yield) which was pure enough to be used as such without any further purification.

3′-Trifluoromethylbiphenyl-3-carboxylic acid (20c). 3-Bromotrifluorotoluene (642 mg, 2.86 mmol) was submitted to the same reaction conditions used for the preparation of **20a** to obtain **20c** (484 mg, 63% yield) which was pure enough to be used as such without any further purification.

3′,5′-Bis-trifluoromethylbiphenyl-3-carboxylic acid (20d). 3,5-Bistrifluoromethylbromobenzene (838 mg, 2.86 mmol) was submitted to the same reaction conditions used for the preparation of **20a** to obtain **20d** (620 mg, 65% yield) which was pure enough to be used as such without any further purification.

3′-Chlorobiphenyl-3-carboxylic acid (20e). 3-Bromoethylbenzoate (315 μL, 1.96 mmol), $Pd(OAc)_2$ (10 mg, 0.004 mmol), PPh_3 (105 mg, 0.40 mmol), and 4-chlorophenylboronic acid (460 mg, 2.94 mmol) were sequentially added to a suspension of K_2CO_3 (540 mg, 0.54 mmol) in 1,4-dioxane (10 mL) under N_2 and the resulting mixture was stirred at 80 °C for 16 h. After cooling, saturated $NH_4Cl_{(aq)}$ and *n*-hexane were added, and the two phases were separated. The aqueous layer was back extracted with *n*-hexane (3×20 mL). The combined organic phases were dried over Na_2SO_4 filtered and concentrated in vacuo. The crude product was purified by flash chromatography (5% EtOAc in petroleum ether) to obtain a white solid. This solid was dissolved in 1 N NaOH 1:1 MeOH/water (20 mL) and stirred at room temperature for 16 h. Concentrated HCl was then added dropwise. The desired product precipitated as a white solid which was filtered off, washed with water, and dried in vacuo to give **20e** (251 mg, 55% yield) which was pure enough to be used as such without any further purification.

4′-Methoxybiphenyl-3-carboxylic acid (20g). 4-Methoxyphenylboronic acid (450 mg, 2.94 mmol) was submitted to the same reaction conditions used for the preparation of **20e** to obtain **20g** (194 mg, 43% yield) which was pure enough to be used ad such without any further purification.

4′-Fluorobiphenyl-4-carboxylic acid (20h). 4-Fluorobromobenzene (500 mg, 2.86 mmol) was submitted to the same reaction used for the preparation of **20a** to obtain crude **20h** (465 mg, 75% yield) which was used as such without any further purification.

4′-Chlorobiphenyl-4-carboxylic acid (20i). 4-Chlorophenylboronic acid (460 mg, 2.94 mmol) was submitted to the same reaction conditions used for the preparation of **20e** to obtain **20i** (322 mg, 71% yield) which was pure enough to be used as such without any further purification. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.27 (2H, d), 7.47 (2H, d), 7.62 (2H, d), 7.95 (2H, d), 11.95 ppm (1H, brs); MS *m/z* calcd for $C_{13}H_9ClO_2$: 232.0, found: 230.9 ([*M*−H]$^-$, 100%), 231.9 (33%).

4′-Methoxybiphenyl-4-carboxylic acid (20j). 4-Bromoethylbenzoate (450 mg, 1.96 mmol) was submitted to the same reaction conditions used for the preparation of **20e** to obtain **20j** (192 mg, 43% yield) which was pure enough to be used as such without any further purification.

3′-Trifluoromethylbiphenyl-4-carboxylic acid (20k). 3-Bromotrifluorotoluene (400 μL, 2.86 mmol) was submitted to the same reaction conditions used for the preparation of **20a** to obtain **20k** (441 mg, 58% yield) as a pale brown solid that was pure enough to be used as such without any further purification; MS *m/z* calcd for $C_{14}H_9F_3O_2$: 266.1, found: 264.9 ([*M*−H]$^-$, 100%).

3′,5′-Bis-trifluoromethylbiphenyl-4-carboxylic acid (20l). 3,5-bis-(trifluoromethyl)bromobenzene (490 μL, 2.86 mmol) was submitted to the same reaction conditions used for the preparation of **20a** to obtain **20i** 582 mg, 61% yield) as a very pale yellow solid that was pure enough to be used as such without any further purification; MS *m/z* calcd for $C_{15}H_8F_6O_2$: 334.0, found: 332.9 ([*M*−H]$^-$, 100%).

3-Thiophen-3-ylbenzoic acid (21a). 3-Bromoethylbenzoate (450 mg, 1.96 mmol), was submitted to the same reaction conditions used for the preparation of **20e** and **21a** was obtained as white solid (260 mg, 65% yield).

4-Thiophen-3-ylbenzoic acid (21b). 4-Bromoethylbenzoate (450 mg, 1.96 mmol) was submitted to the same reaction conditions used for the preparation of **20e** and **21b** was obtained as a white solid (260 mg, 65% yield). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.50–7.62 (1H, m), 7.63–7.72 (1H, m) 7.81 (2H, d), 8.00 (2H, d), 8.17 (1H, d), 12.98 ppm (1H, brs).

3-Pyridin-4-ylbenzoic acid (22a). $Pd(AcO)_2$ (23 mg, 0.1 mmol) and PPh_3 (105 mg, 0.4 mmol) were added to a degassed solution of 3-Bromopyridine (193 μL, 2.0 mmol), and 4-carboxyphenylboronic acid (330 mg, 2.0 mmol) in a solution of Na_2CO_3 (0.42 g, 3.96 mmol) in H_2O/CH_3CN (10+10 mL). The resulting mixture was stirred at 90 °C under nitrogen for 24 h. The hot suspension was filtered. The filtrate was concentrated to about half of the original volume and washed with CH_2Cl_2 (2×20 mL). The aqueous layer was then acidified with concentrated HCl and the resulting precipitate was collected by filtration washing with water. **22a** was obtained as a white solid (330 mg, 77% yield) and used as such without any further purification. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.52–7.63 (1H, m), 7.81 (2H, d), 8.05 (2H, d), 8.17 (1H, d), 8.63 (1H, d), 8.93 (1H, s), 13.05 ppm (1H, brs).

4-Pyridin-4-ylbenzoic acid (22b). $Pd(AcO)_2$ (23 mg, 0.1 mmol) and PPh_3 (105 mg, 0.4 mmol) were added to a degassed solution of 4-bromopyridine hydrochloride (388 mg, 2.0 mmol), and 4-carboxyphenylboronic acid (330 mg, 2.0 mmol) in a solution of Na_2CO_3 (0.42 g, 3.96 mmol) in H_2O/CH_3CN (10+10 mL). The resulting mixture was stirred at 90 °C under nitrogen for 24 h. The hot suspension was cooled down and the desired product precipitated out of solution as a sodium salt. The solid was collected by filtration washed with CH_2Cl_2 and water to give **22b** (340 mg, 77% yield) and used as such without any further purification. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.67–7.78 (4H, m), 7.97 (2H, d), 8.62 ppm (2H, d).

4-Pyrrol-1-ylbenzoic acid (23a). A mixture of 4-aminobenzoic acid (1.00 g, 7.30 mmol), 5-dimethoxytetrahydrofuran (1.0 mL, 7.7 mmol) and acetic acid (7 mL) in a 50 mL Erlenmeyer flask was irradiated at 200 W for 1 min (NOTE: the acid must be completely solubilized in acetic acid before the addition of the keto-derivative). A solid was obtained which was collected by filtration and washed with diethyl ether. Trituration with hot acetonitrile followed by filtration and drying in vacuo gave the crude pyrrolyl acid **23a** (800 mg, 59% yield). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=6.32 (1H, s), 7.47 (1H, s), 7.71 (2H, d), 8.99 (2H, d), 12.88 ppm (1H, brs); MS *m/z* calcd for $C_{11}H_9NO_2$: 187.1, found: 185.1 $[M-H]^-$.

3-Pyrrol-1-ylbenzoic acid (23b). Starting with 3-aminobenzoic acid (1.00 g, 5.76 mmol) and following the same procedure as **23a**, acid **23b** was obtained in 64% Yield (700 mg); MS *m/z* calcd for $C_{11}H_9NO_2$: 187.1, found: 185.21 $[M-H]^-$.

4-(2,5-Dimethylpyrrol-1-yl)benzoic acid (23c). A mixture of methyl 4-aminobenzoate (815 mg, 5.00 mmol), hexane-2,5-dione (1.14 g, 10.0 mmol) and *p*-toluenesulfonic acid (catalytic amount) in a 3 mL stoppered vial was irradiated at 400 W for 1 min. Then the mixture was diluted with diethyl ether (30 mL) and the organic layer washed with 1N HCl (3×15 mL), 5% Na_2CO_3 (15 mL) and brine, dried over Na_2SO_4 and concentrated to obtain crude **23c** methyl ester (760 mg, 66%). This solid was suspended in 1:1 MeOH/2N NaOH (30 mL) and heated at 80 °C until the complete disappearance of starting material (TLC control, silica, dichloromethane). The solution was filtered and acidified with concd HCl. A precipitate was formed, which was filtered off and dried in vacuo to obtain crude **23c** (436 mg, 40%).^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.00 (6H, s), 5.83 (2H, s), 7.42 (2H, d), 8.04 (2H, d), 13.08 ppm (1H, brs); MS *m/z* calcd for $C_{13}H_{13}NO_2$: 215.1, found: 213.9 $[M-H]^-$.

3-(2,5-Dimethylpyrrol-1-yl)benzoic acid (23d). Following the same conditions as for **23c**, methyl 3-aminobenzoate (3.00 g, 97%, 19.2 mmol) was converted into **23d** (70%) ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.90 (3H, s), 5.83 (2H, s), 7.48 (1H, d), 7.62 (2H, m), 8.00 (1H, d), 13.20 ppm (1H, brs); MS *m/z* calcd for $C_{13}H_{13}NO_2$: 215.1, found: 213.8 $[M-H]^-$.

4-Pyrazol-1-ylbenzoic acid (24a). A mixture of 4-hydrazino benzoic acid (500 mg, 98%, 3.29 mmol), acetic acid (1.5 mL), water (0.5 mL) and 1,1,3,3-tetramethyoxypropane (0.6 mL, 98%, 3.70 mmol) in a stoppered vial was irradiated at 200 W for 1 min. The mixture was then treated with dichloromethane, filtered and dried in vacuo to obtain the desired product **24a** (250 mg, 40% yield). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=6.61 (1H, s), 7.78 (1H, s), 7.93 (2H, d), 8.00 (2H, d), 8.57 (1H, s), 12.46 ppm (1H, brs); MS *m/z* calcd for $C_{10}H_8N_2O_2$: 188.1, found: 186.8 $[M-H]^-$.

3-Pyrazol-1-ylbenzoic acid (24b). The same procedure used for the preparation of **24a** was followed using 3-hydrazinobenzoic acid as starting material (45% yield); MS *m/z* calcd for $C_{10}H_8N_2O_2$: 188.1, found: 186.9 $[M-H]^-$.

4-(5-Methylpyrazol-1-yl)benzoic acid (24c). A solution of 4-hydrazinobenzoic acid (500 mg, 3.22 mmol), acetyl acetaldehyde (1.06 mL, 3.55 mmol) in AcOH/water 3:1 (16 mL) was heated in a microwave oven at 200 W for 1 min. A solid was formed which was collected by filtration and dried in vacuo (50%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.20 (3H, s), 6.32 (1H, s), 7.80 (2H, d), 8.00 (2H, d), 8.40 ppm (1H, s); MS *m/z* calcd for $C_{11}H_{10}N_2O_2$: 202.0, found: 200.8 $[M-H]^-$.

3-(5-Methylpyrazol-1-yl)benzoic acid (24d). A suspension of 3-hydrazino benzoic acid (1.00 g, 6.58 mmol) in AcOH/water 1:1 (24 mL) was heated until total dissolution of the reagent. Acetyl acetaldehyde dimethyl acetal (1.06 mL, 90%, 7.23 mmol) was then added dropwise. A solid separated, which was collected by filtration washed with water and dried in vacuo to afford crude **24d** (600 mg, 42% yield). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.24 (3H, s), 6.31 (1H, s), 7.55 (1H, m), 7.58 (1H, d), 8.00 (1H, d), 8.27 (1H, s), 8.41 (1H, s), 13.14 ppm (1H, brs); MS *m/z* calcd for $C_{11}H_{10}N_2O_2$: 202.0, found: 200.9 $[M-H]^-$.

4-(3,5-Dimethylpyrazol-1-yl)benzoic acid (24e). A solution of 4-hydrazinobenzoic acid (500 mg, 98%, 3.22 mmol) and 2,4-pentanedione (329 mg, 3.29 mmol) in MeOH (2 mL) in a stoppered vial was irradiated at 200 W for 1 min. A solid was formed on cooling which was collected by filtration, triturated with dichloromethane and dried in vacuo to give crude **24e** (500 mg, 72%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.13 (3H, s), 2.34 (3H, s), 6.10 (1H, s), 7.58 (2H, d), 8.00 (2H, d), 13.08 ppm (1H, brs); MS *m/z* calcd for $C_{12}H_{12}N_2O_2$: 216.1, found: 214.9 $[M-H]^-$.

3-(3,5-Dimethylpyrazol-1-yl)benzoic acid (24f). A suspension of 3-hydrazino benzoic acid (1.00 g, 6.44 mmol) in water/AcOH 1:1 (20 mL) was heated until complete dissolution, then 2,4-pentanedione (0.66 g, 6.59 mmol) was added dropwise. A white solid separated, which was collected by filtration and dried in vacuo to obtain crude **24f** (600 mg, 43%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.14 (3H, s), 2.27 (3H, s), 6.14 (1H, s), 7.65 (1H, dd), 7.79 (1H, d), 7.89 (1H, d), 8.00 (1H, s), 13.21 ppm (1H, brs); MS *m/z* calcd for $C_{12}H_{12}N_2O_2$: 216.1, found: 215 $[M-H]^-$.

3-(2*H*-Tetrazol-5-yl)benzoic acid benzyl ester (25b). A solution of benzyl 3-cyanobenzoate (6.25 g, 263 mmol), trimethylsilyl azide (6.00 g, 2.00 equiv) and Bu_2SnO (2.63 g, 11.5 mmol) in toluene (280 mL) was held at reflux for 10 h. At the end of the reaction (TLC control, silica, dichloromethane), solvent was distilled off in vacuo. The residue was dissolved in MeOH and concentrated again to obtain crude **25b**, which was used as such without further purification; MS *m/z* calcd for $C_{15}H_{12}N_4O_2$: 280.1, found: 279.0 $[M-H]^-$.

4-(2-Methyl-2*H*-tetrazol-5-yl)benzoic acid (26a). A solution of methyl 4-cyano benzoate (1.60 g, 10.0 mmol), trimethylsilyl azide (2.63 mL, 20 mmol) and Bu_2SnO (250 mg, 1.10 mmol) in toluene (110 mL) was held at reflux for 10 h. At the end of the reaction (TLC control, silica, dichloromethane) the solvent was distilled off in vacuo. The residue was dissolved in MeOH, concentrated again and then partitioned between 10% $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic layer was extracted with 10% $NaHCO_3$ (50 mL). The combined aqueous extracts were acidified to pH 2 with 10% $HCl_{(aq)}$ and extracted with EtOAc (2×50 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude methyl 4-(2H-tetrazol-5-yl)benzoate (900 mg, 45% yield). Part of this product (500 mg, 2.45 mmol) was dissolved in THF (7 mL). A 2 N hexane solution of $TMSCHN_2$ (2.2 equiv) was added dropwise, and the resulting mixture was stirred until the end of the reaction (HPLC control). The mixture was diluted with EtOAc and washed with 2 N $NaOH_{(aq)}$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to obtain the crude 4-(2-Methyl-2H-tetrazol-5-yl)benzoic acid methyl ester, which was purified by flash chromatography (silica, $CHCl_3$/MeOH 9:1). A portion of this purified product (167.7 mg, 0.77 mmol) was dissolved in 1:1 MeOH/2 N NaOH and stirred 1 h at room temperature. Upon acidification with conc. HCl a product separated, which was filtered off and dried in vacuo to afford **26a** (140 mg, 90% yield). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ =4.44 (3H, s), 8.08 (2H, d), 8.17 ppm (2H, d); MS *m/z* calcd for $C_9H_8N_4O_2$: 204.1, found: 203.0 $[M-H]^-$.

3-(2-Methyl-2*H*-tetrazol-5-yl)benzoic acid (26b). 25b (500 mg, 2.45 mmol) was dissolved in THF (7 mL). A 2 N hexane solution of $TMSCHN_2$ (2.2 equiv) was added dropwise and stirring was continued till the end of the reaction (HPLC control). The mixture was diluted with EtOAc and washed with 2 N $NaOH_{(aq)}$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to obtain the crude methyl ester as a white solid. Catalytic hydrogenolysis (MeOH, 5% Pd/C) afforded the desired product **26b** (306 mg, 61% yield); MS *m/z* calcd for $C_9H_8N_4O_2$: 204.1, found: 202.8 $[M-H]^-$.

3-(2-Ethyl-2*H*-tetrazol-5-yl)benzoic acid (26c). A mixture of **25b** (1.00 g, 3.57 mmol), iodoethane (0.57 mL, 2.0 equiv) and K_2CO_3 (1.00 g, 10.7 mmol) in DMF (6 mL) was shaken at room temperature in a stoppered tube for 12 h. At the end of the reaction (HPLC control) the mixture was diluted with water (150 mL) and extracted with EtOAc (2×100 mL). The collected organic layers were washed with water (3×50 mL) and brine (100 mL), then dried over Na_2SO_4 and concentrated in vacuo to obtain the crude benzyl 3-(2-ethyl-2H-tetrazol-5-yl)benzoate as a white solid (1.00 g) which was purified by flash chromatography (silica, hexane/EtOAc 8:2). Catalytic hydrogenolysis of the purified benzyl ester (MeOH, 5% Pd/C, H_2) afforded **26c** (436 mg, 56% yield). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.58 (3H, t), 4.80 (2H, q), 7.68 (1H, dd), 8.06 (1H, d), 8.26 (1H, d), 8.61 (1H, s), 13.42 ppm (1H, brs); MS *m/z* calcd for $C_{10}H_{10}N_4O_2$: 218.1, found: 219.0 $[M+H]^+$.

3-(2-Propyl-2*H*-tetrazol-5-yl)benzoic acid (26d). A mixture of **25b** (500 mg, 1.78 mmol), allyl bromide (0.3 mL, 3.56 mmol) and K_2CO_3 (500 mg, 5.34 mmol) in DMF (3 mL) was shaken at room temperature in a stoppered tube for 12 h. At the end of the reaction (HPLC control) the mixture was diluted with water (70 mL) and extracted with EtOAc (2×50 mL). The collected organic layers were washed with water (3×25 mL) and brine (50 mL), then dried over Na_2SO_4 and concentrated in vacuo to obtain the crude 3-(2-allyl-2H-tetrazol-5-yl)benzoate as a colorless oil (500 mg). Catalytic hydrogenation of this oil (MeOH, 5% Pd/C) afforded **26d** (230 mg, 56%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=0.95 (3H, t), 2.00 (2H, m), 4.72 (2H, t), 7.70 (1H, dd), 8.06 (1H, d), 8.25/1H, d), 8.59 ppm (1H, s); MS *m/z* calcd for $C_{11}H_{12}N_4O_2$: 232.1, found: 230.0 $[M-H]^-$.

3-(2-Isobutyl-2*H*-tetrazol-5-yl)benzoic acid (26e). A mixture of **25b** (500 mg, 1.78 mmol) and K_2CO_3 (500 mg, 5.34 mmol) in DMF (3 mL) was shaken at room temperature in a stoppered tube for 12 h. At the end of the reaction (HPLC control) the mixture was diluted with water (70 mL) and extracted with EtOAc (2×50 mL). The collected organic layers were washed with water (3×25 mL) and brine (50 mL), then dried over Na_2SO_4 and concentrated in vacuo to obtain the crude benzyl ester of **26e** as a colorless oil which was then submitted to catalytic hydrogenation (MeOH, 5% Pd/C, H_2) affording **26e** (257 mg, 58%). NMR (300 MHz, [D$_6$]DMSO): δ= 0.95 (6H, d), 2.36 (1H, m), 4.51 (2H, d), 7.7 (1H, dd), 8.10 (1H, d), 8.30 (1H, d), 8.60 ppm (1H, s); MS *m/z* calcd for $C_{12}H_{14}N_4O_2$: 246.1, found: 245.1 $[M-H]^-$.

(*R*)-2-Amino-*N*-(3-morpholin-4-ylpropyl)-3-phenylpropionamide dihydrochloride (8). A solution of Boc-D-phe-OSu (500 mg, 1.38 mmol) in dry THF (5 mL) was stirred at room temperature under nitrogen. Amine A (0.20 mL, 1.33 mmol) was added and stirring was continued for 1.5 h. The solvent was distilled off and the oily residue was dissolved in EtOAc. The organic solution was washed with 1 N $NaHCO_2$, water and brine and then dried over Na_2SO_4. Elimination of the solvent under reduced pressure afforded crude **5** in 88% yield (474 mg). This crude was dissolved in 4N HCl in dioxane (50 mL) and stirred at room temperature until complete Boc deprotection. The solvent was then distilled off under reduced pressure and the residue was triturated with diethyl ether to obtain the crude product (300 mg, 79%), which was used as such without further purification; MS *m/z* calcd for $C_{16}H_{25}N_3O_2$: 291, found: 292.1 $[M+H]^+$.

(*R*)-2-Amino-*N*-[3-oxo-3-(4-pyridin-2-yl-piperazin-1-yl)propyl]-3-phenylpropionamide hydrochloride (9). A solution of amine C hydrochloride salt (2.05 g, 5.95 mmol) and DIPEA (3.0 mL, 18 mmol) in CH_2Cl_2 (30 mL) was cooled in an ice bath. A solution of Boc-D-phe-OSu (2.16 g, 5.95 mmol) in CH_2Cl_2 (30 mL) was added dropwise. At the end of the reaction (HPLC control) the organic layer was washed with 2 N NaOH (2 times), water and dried over Na_2SO_4. Elimination of the solvent under reduced pressure afforded the crude **7** (2.82 g). treatment of this crude with 4N HCl in dioxane (100 mL) for 2 h, followed by elimination of the solvent under reduced pressure, trituration with diethyl ether and filtration, afforded **10** in quantitative yield. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ =MS *m/z* calcd for $C_{21}H_{27}N_5O_2$: 381.2, found: 382.1 $[M+H]^+$.

1-Aminocyclopentanecarboxylic acid [(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethyl]amide dihydrochloride (14). A solution of Boc-1-aminocyclopentane carboxylic acid (2.50 g, 10.9 mmol), HOBt (2.54 g, 16.6 mmol) and EDAC (2.54 g, 13.3 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 1 h, then a solution of **8** (4.50 g, 10.9 mmol) and DIPEA (3.79 mL, 22.1 mmol) in DMF (50 mL) was added dropwise. The resulting mixture was stirred at room temperature overnight. Then it was washed with 1 N HCl (3 times), 5% $NaHCO_3$ (3 times), water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. This crude product was dissolved in 4 N HCl in dioxane (100 mL) and stirred at room temperature for 1 h. The solvent was then distilled off in vacuo and the solid residue was triturated with diethyl ether/MeOH 9:1 to obtain crude **14** (1.12 g, 22%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.61–1.94 (9H, m), 1.94 (1H, m), 2.91–3.24 (8H, m), 3.36 (2H, m), 3.9 (4H, m), 4.52 (1H, m), 7.24 (5H, m),

8.24 (3H, brs), 8.36 (1H, dd), 8.61 ppm (1H, d); MS *m/z* calcd for $C_{22}H_{34}N_4O_3$: 402.3, found: 403.1 $[M+H]^+$.

1-Aminocyclopentanecarboxylic acid ((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethyl)amide hydrochloride (15). A solution of Boc-1-aminocyclopentane carboxylic acid (711 mg, 3.10 mmol), DCC (637.4 mg, 3.10 mmol) and HOBt (419,25 mg, 3.10 mmol) in 1:1 DMF/CH_2Cl_2 (10 mL) was stirred at room temperature for 4 h. Then a solution of amine 9 (1.50 g, 3.30 mmol) and DIPEA (1.57 mL, 9.30 mmol) in 1:1 DMF/CH_2Cl_2 (10 mL) was added and stirring was continued at room temperature until the end of the reaction (HPLC control). Then it was washed with 1 N HCl (3 times), 5% $NaHCO_3$ (3 times), water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. This crude product was dissolved in 4 N HCl in dioxane (100 mL) and stirred at room temperature for 1 h. The solvent was then distilled off in vacuo and the solid residue was triturated with diethyl ether/MeOH 9:1 to obtain crude 15 (922.5 mg). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.74$ (7H, m), 2.16 (1H, m), 2.50 (2H, m), 2.88 (1H, dd), 3.06 (1H, dd), 3.32 (2H, m), 3.64–3.75 (8H, m), 4.54 (1H, m), 6.94 (1H, t), 7.16 (1H, dd), 7.28 (5H, m), 7.96 (1H, brm), 8.04 (1H, d), 8.16 (3H, brs), 8.28 (1H, dd), 8.44 ppm (1H, dd); MS *m/z* calcd for $C_{27}H_{36}N_6O_3$: 492.3, found: 493.2 $[M+H]^+$.

General synthesis of compounds 17, 18 and 19. A solution of the acid (1.2 mmol), HOBt (1.2 mmol) and DCC (2 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 1 h. Then a solution of amine A, B or C (1.0 mmol) and DIPEA (2 mmol) in CH_2Cl_2 (10 mL) was added dropwise. Some drops of DMF were added when necessary to solubilize the starting amine or acid. Stirring was continued at room temperature for 24 h. Then the organic layer was washed with 2N NaOH, brine and dried over Na_2SO_4, filtered and concentrated to obtain the crude products, which were purified by preparative HPLC.

4′-Fluorobiphenyl-4-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}amide trifluoroacetate (28). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = =1.44$–2.10 (9H, m) 2.20 (1H, m), 2.85 (2H, dd), 2.90–3.40 (8H, m), 3.60 (2H, m), 4.00 (2H, m), 4.40 (1H, m), 7.18 (5H, m), 7.33 (2H, m), 7.65 (1H, dd), 7.83 (5H, m), 8.00 (2H, d), 8.75 ppm (1H, brs), 9.00 81H, brs); MS *m/z* calcd for $C_{35}H_{41}FN_4O_4$: 600.3, found: 601.1 $[M+H]^+$; HPLC purity: system A, $>98\%$, $t_R = 10.01$ min.

4′-Fluorobiphenyl-3-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}amide trifluoroacetate (29). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.45$–2.00 (9H, m), 2.30 (3H, m), 2.90 (1H, dd), 3.00–3.50 (9H, m), 3.60 (2H, m), 3.95 (2H, m), 4.40 (1H, m), 7.15 (5H, m), 7.40 (2H, t), 7.60 (1H, t), 7.80 (6H, m), 8.20 (1H, s), 8.80 (1H, s), 9.68 ppm (1H, brs); MS *m/z* calcd for $C_{35}H_{41}FN_4O_4$: 600.3, found 601.1 $[M+H]^+$; HPLC purity: system A, $>98\%$, $t_R = 10.01$ min.

4′-Chlorobiphenyl-4-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}amide (30). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.40$–1.70 (8H, m), 1.75 (1H, m), 1.94 (1H, m), 2.25 (6H, m), 2.84 (1H, dd), 3.10 (2H, m), 3.18 (1H, dd), 3.52 (4H, m), 4.40 (1H, m), 7.18 (5H, m), 7.60 (2H, d), 7.60 (1H, m), 7.80 (5H, m), 8.04 (2H, d), 8.70 ppm (1H, s); MS *m/z* calcd for $C_{35}H_{41}ClN_4O_4$: 616.28, found: 617.2 $[M+H]^+$; HPLC purity: system C, 95%, $t_R = 8.29$ min.

4′-Chlorobiphenyl-3-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}amide (31). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.45$–1.80 (8H, m), 1.80 (1H, m), 1.96 (1H, m), 2.30 (6H, m), 2.85 (1H, dd), 3.15 (2H, m), 3.20 (1H, dd), 3.52 (4H, m), 4.40 (1H, m), 7.20 (5H, m), 7.55 (2H, d), 7.60 (1H, t), 7.62 (2H, t), 7.77 (2H, d), 7.82 (1H, d), 7.99 (1H, d), 8.10 (1H, d), 8.37 (1H, s), 8.87 ppm (1H, s); MS *m/z* calcd for $C_{35}H_{41}ClN_4O_4$: 616.28, found: 617.2 $[M+H]^+$; HPLC purity: system C, 94%, $t_R = 8.29$ min.

4′-Methoxybiphenyl-4-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl} amide trifluoroacetate (32). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.42$–2.00 (9H, m), 2.22 (1H, m), 2.88 (1H, dd), 3.04 (2H, m), 3.25 (6H, m), 3.62 (2H, m), 3.82 (3H,s), 3.98 (2H, m), 4.42 (1H, m), 7.07 (2H, d), 7.18 (5H, m), 7.69 (2H, d), 7.80 (2H, d), 7.84 (1H, d), 8.0 (2H, d), 8.71 (1H, s), 9.5 ppm (1H, brs); MS *m/z* calcd for $C_{36}H_{44}N_4O_5$: 612.3, found: 613.3 $[M+H]^+$; HPLC purity: system D, 98%, $t_R = 7.28$ min.

4′-Methoxybiphenyl-3-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl} amide trifluoroacetate (33). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.50$–2.00 (9H, m), 2.24 (1H, m), 2.87 (1H, dd), 3.00 (2H, m), 3.19–3.56 (6H, m), 3.60 (2H, m), 4.96 (2H, m), 4.41 (1H, m), 7.09 (2H, d), 7.19 (5H, m), 7.54 (1H, dd), 7.69 (2H, d), 7.82 (4H, m), 8.15 (1H, s), 8.78 (1H, s), 9.50 ppm (1H, brs); MS *m/z* calcd for $C_{36}H_{44}N_4O_5$: 812.3, found: 813.3 $[M+H]^+$; HPLC purity: system D, 98%, $t_R = 7.28$ min.

3′-Trifluoromethylbiphenyl-4-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-amide (34). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.40$–1.75 (8H, m), 1.80 (1H, m), 1.95 (1H, m), 2.30 (6H, m), 2.85 (1H, dd), 3.07 (2H, m), 3.20 (1H, dd), 3.54 (4H, m), 4.40 (1H, m), 7.18 (1H, t), 7.20 (5H, m), 7.53 (1H, d), 7.65–7.75 (4H, m), 7.77 (1H, d), 7.80 (2H, m), 8.70 ppm (1H, s); MS *m/z* calcd for $C_{36}H_{41}F_3N_4O_4$: 650.3, found: 651.7 $[M+H]^+$; HPLC purity: system A, 92%, $t_R = 8.03$ min.

3′-Trifluoromethylbiphenyl-3-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}amide (35). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.40$–1.73 (8H. m), 1.74 (1H, m), 1.94 (1H, m), 2.25 (6H, m), 2.85 (1H, dd), 3.10 (3H, m), 3.18 (1H, dd), 3.52 (4H, m), 4.40 (1H, m), 7.18 (1H, t), 7.20 (5H, m), 7.52–7.69 (4H, m), 7.76 (1H, d), 7.80 (1H, d), 7.85 (1H, d), 8.00 (2H, m), 8.75 ppm (1H, s); MS *m/z* calcd for $C_{36}H_{41}F_3N_4O_4$: 650.3, found: 651.8 $[M+H]^+$; HPLC purity: system C, 95%, $t_R = 8.03$ min.

3′,5′-Bis-trifluoromethylbiphenyl-4-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}amide trifluoroacetate (36). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.45$–2.00 (9H, m), 2.25 (1H, m), 2.90 (1H, dd), 3.00–3.30 (7H, m), 3.40 (2H, m), 3.70 (2H, m), 3.95 (2H, m), 4.40 (1H, m), 7.20 (5H, m), 7.60 (2H, d), 7.80 (1H, t), 7.87 (1H, d), 8.00 (2H, d), 8.29 (1H, s), 8.40 (2H, s), 9.70 ppm (1H, brs); MS *m/z* calcd for $C_{37}H_{40}F_6N_4O_4$: 718.3, found: 719.1 $[M+H]^+$; HPLC purity: system A, $>98\%$, $t_R = 10.03$ min.

3′,5′-Bis-trifluoromethylbiphenyl-3-carboxylic acid {1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}amide trifluoroacetate (37). ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.42$–1.70 (8H, m), 1.80 (1H, m),1.91 (1H, m), 2.25 (6H, m), 2.85 (1H, dd), 3.10 (2H, m), 3.20 (1H, dd), 3.35 (4H, m), 4.42 (1H, m), 7.20 (5H, m), 7.57 (1H, dd), 7.70 (1H, t), 7.83 (1H, d), 8.00 (1H, d), 8.10 (1H, d), 8.18 (1H, s), 8.29 (1H, s), 8.40 (2H, s), 8.85 ppm (1H, s); MS *m/z* calcd for $C_{37}H_{40}F_6N_4O_4$: 718.3, found: 719.1 $[M+H]^+$; HPLC purity: system A, 94%, $t_R = 10.03$ min.

***N*-{1-[(*R*)-1-(3-Morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-4-pyrazol-1-ylbenzamide trifluoroacetate (38).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = .1.44$–1.95 (9H, m), 2.20 (1H, m), 2.91 (1H, m), 2.95–3.28 (9H, m), 3.40 (2H, m), 3.93 (2H, m), 4.42 (1H, m), 6.62 (1H, d), 7.18 (5H, m), 7.73 (1H, dd), 7.80 (1H,

s), 7.84 (1H, d), 7.98 (2H, d), 8.07 (2H, d), 8.62 (1H, d), 8.71 (1H, s), 9.66 ppm (1H, brs); MS *m/z* calcd for $C_{32}H_{40}N_6O_4$: 572.3. Found: 573.2 $[M+H]+$; HPLC purity: system A, >97%, t_R=7.03 min.

4-(3-Methylpyrazol-1-yl)-*N*-{1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamol)-2-phenylethylcarbamoyl]cyclopentyl}benzamide trifluoroacetate (39, MEN 15197). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ= 1.45–2.00 (9H, m), 2.25 (1H, m), 2.30 (3H, m), 2.85–3.50 (10H, m), 3.60 (2H, m), 4.00 (2H, m), 4.40 (1H, m), 6.45 (1H, s), 7.20 (5H, m), 7.75 (1H, m), 7.90 (3H, m), 8.05 (2H, d), 8.50 81H, s), 8.75 (1H, s), 9.55 ppm (1H, brs); MS *m/z* calcd for $C_{33}H_{42}N_6O_4$: 586.3 Found 587.3 $[M+H]^+$; HPLC purity: system B, 95.3%, t_R=4.79 min.

3-(3-Methylpyrazol-1-yl)-*N*-{1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}benzamide trifluoroacetate (40). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.45–2.00 (9H, m), 2.25 (1H, m), 2.30 (3H, s), 2.85–3.35 (10H, m), 3.60 (2H, m), 4.00 (2H, m), 4.40 (1H, m), 6.42 (1H, s), 7.20 (5H, m), 7.60 (1H, m), 7.80 (2H, m), 7.90 (1H, d), 7,95 (1H, d), 8.30 (1H, s), 8.45 (1H, s), 8.85 (1H, s), 9.55 ppm (1H, brs); MS *m/z* calcd for $C_{33}H_{42}N_6O_4$: 586.1, found: 587.3 $[M+H]^+$; HPLC purity: system B, 96.2%, t_R= 4.70 min.

4-(3,5-Dimethylpyrazol-1-yl)-*N*-{1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}benzamide trifluoroacetate (41). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.45–1.97 (9H, m), 2.18 (3H, s), 2.20 (1H, m), 2.30 (3H, s), 2.90 (1H, dd), 12.95–3.30 (9H, m), 3.60 (2H, m), 3.95 (2H, m), 4.40 (1H, m), 6.15 (1H, s), 7.20 (5H, m), 7.60 (2H, d), 7.65 (1H, d), 7.75 (1H, dd), 7.90 (1H, d), 8.05 (2H, d), 8.80 (1H, s), 9.57 ppm (1H, brs); MS *m/z* calcd for $C_{34}H_{44}N_6O_4$: 600.3. Found: 601.3 $[M+H]^+$; HPLC purity: system A, >97%, t_R=6.75 min.

3-(3,5-Dimethylpyrazol-1-yl)-*N*-{1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}benzamide trifluoroacetate (42). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.40–1.98 (9H, m), 2.20 (3H, s), 2.30 (1H, m), 2.35 (3H, s), 2.85–3.40 (10H, m), 3.60 (2H, m), 4.00 (2H, m), 4.40 (1H, m), 6.12 (1H, s), 7.20 (5H, m), 7.60 (1H, dd), 7.70 (1H, s), 7.75 (1H, dd), 7.90 (2H, m), 8.10 (1H, s), 8.85 (1H, s), 9.55 ppm (1H, brs); MS *m/z* calcd for $C_{34}H_{44}N_6O_4$: 600.2 Found 601.3 $[M+H]^+$; HPLC purity: system B, 98%, t_R=4.56 min.

***N*-{1-[(*R*)-1-(3-Morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-4-(3-trifluoromethylpyrazol-1-yl)benzamide hydrochloride (43).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.43–2.00 (9H, m), 2.22 (1H, m), 2.91 (1H, dd), 3.00 (2H, m), 3.07 (2H, m), 3.22 (3H, m), 3.35 (2H, m), 3.69 (2H, m), 3.95 (2H, m), 4.43 (1H, m), 7.15 (5H, m), 7.67 (2H, d), 7.74 (1H, dd), 7.74 (1H, dd), 7.87 (1H, d), 7.93 (1H, s), 8.09 (2H d), 8.87 ppm (1H, s); MS *m/z* calcd for $C_{33}H_{39}F_3N_6O_4$: 640.3, found: 641.3 $[M+H]^+$; HPLC purity: system D, 95.5%, t_R=7.37 min.

***N*-{1-[(*R*)-1-(3-Morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-4-pyrrol-1-ylbenzamide trifluoroacetate (44).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.40–2.00 (9H, m), 2.20 (1H, m), 2.93 (1H, dd), 3.00–3.40 (9H, m), 3.75 (2H, m), 3.95 (2H, m), 4.40 (1H, m), 6.35 (2H, s), 7.17 (5H, m), 7.54 (2H, s), 7.73 (2H, d), 7.81 (1H, t), 7.87 (1H, d), 8.00 (2H, d), 8.85 (1H, s), 9.70 ppm (1H, brs); MS *m/z* calcd for $C_{33}H_{41}N_5O_4$: 571.3, found: 572.3 $[M+H]^+$; HPLC purity: system C, 95%, t_R=7.32 min.

***N*-{1-[(*R*)-1-(3-Morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-4-thiophen-3-ylbenzamide (45).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.42 (8H, m), 1.73 (1H, m), 1.90 (1H, m), 2.23 (6H, m), 2.85 (1H, dd), 3.16 (2H, m), 3.19 (1H, dd), 3.58 (4H, m), 4.42 (1H, m), 7.15 (5H, m), 7.54 (1H, dd), 7.65 (2H, m), 7.73 (1H, d), 7.85 (2H, d), 7.96 (2H, d), 8.03 (1H, s), 8.63 ppm (1H, s); MS *m/z* calcd for $C_{33}H_{40}N_4O_4S$: 588.28, found: 589.2 $[M+H]^+$; HPLC purity: system D, 95%, t_R=7.57 min.

***N*-{1-[(*R*)-1-(3-Morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-3-thiophen-3-ylbenzamide (46).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.58 (8H, m), 1.77 (1H, m), 1.96 (1H, m), 2.23 (6H, m), 2.82 (1H, dd), 3.08 (2H, m), 3.19 (1H, dd), 3.50 (4H, m), 4.43 (1H, m), 7.16 (5H, m), 7.58 (2H, dd), 7.63 (1H, d), 7.74 (1H, d), 7.84 (2H, m), 7.92 (1H, dd), 7.96 (1H, d), 8.21 81H, s), 8.74 ppm (1 h, s); MS *m/z* calcd for $C_{33}H_{40}N_4O_4S$: 588.2, found: 589.3 $[M+H]^+$; HPLC purity: system D, 96%, t_R=7.61 min.

3-(2-Methylthiazol-4-yl)-*N*-{1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}benzamide hydrochloride (47). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.48–2.00 (9H, m), 2.26 (1H, m), 2.78 (3H, s), 2.96 (3H, m), 3.06 (2H, m), 3.17 (3H, m), 3.30 (2H, m), 3.91 (2H, m), 4.43 (1H, m), 7.17 (5H, m), 7.56 (1H, dd), 7.78 (1H, m), 7.89 (2H, m), 8.00 (1H, s), 8.09 (1H, d), 8.46 (1H, s), 8.78 ppm (1H, s); MS *m/z* calcd for $C_{33}H_{41}N_5O_4S$: 603.3, found: 604.2 $[M+H]^+$; HPLC purity: system D, 96.1%, t_R=6.87 min.

***N*-{1-[(*R*)-1-(3-Morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-3-thiophen-2-ylbenzamide (48).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.54 (8H, M), 1.73 (1H, m), 1.92 (1H, m), 2.23 (6H, m), 2.85 (H, dd), 3.11 (2H, m), 3.19 (1H. dd), 3.50 (4H, m), 4.46 (1H, m), 7.15 (5H, m), 7.54 (1H, dd), 7.61 (3H, m), 7.88 (3H, m), 8.15 (1H, s), 8.81 ppm (1H, s). $C_{33}H_{40}N_4O_4S$: 588.1, found: 589.2 $[M+H]^+$; HPLC purity: system D, 91%, t_R=7.57 min.

4-(2-Methyl-2*H*-tetrazol-5-yl)-*N*-{1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}benzamide trifluoroacetate (49). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.60 (6H, m), 1.90 (3H, m), 2.20 (1H, m), 2.90 (1H, dd), 2.95–3.25 (9H, m), 3.65 (2H, m), 3.95 (2H, m), 4.40 (1H, m), 4.50 (3H, s), 7.20 (5H, m), 7.75 (1H, dd), 7.90 (1H, d), 8.1 (2H, d), 8.20 (2H, d), 8.85 (1H, s), 9.95 ppm (1H, brs); MS *m/z* calcd for $C_{31}H_{40}N_8O_4$: 588.2, found: 589.2 $[M+H]^+$; HPLC purity: system B, 98.3%, t_R=3.77 min.

3-(2-Methyl-2*H*-tetrazol-5-yl)-*N*-{1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}benzamide trifluoroacetate (50). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.45–2.03 (9H, m), 2.25 (1H, m), 2.90 (1H, dd), 3.00 (2H, m), 3.20 (5H, m), 3.40 (2H, m), 3.65 (2H, m), 3.95 (2H, m), 4.40 (1H, m), 4,45 (3H, s), 2.20 (5H, m), 7.70 (1H, t), 7.75 (1H, dd), 7.95 (1H, d), 8.10 (1H, d), 8.25 (1H, d), 8.60 (1H, s), 9.00 (1H, s), 9.60 ppm (1H, brs); MS *m/z* calcd for $C_{31}H_{40}N_8O_4$: 588.3 Found 589.3 $[M+H]^+$; HPLC purity: system B, 98.53%, t_R=4.20 min.

3-(2-Ethyl-2*H*-tetrazol-5-yl)-*N*-{1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}benzamide trifluoroacetate (51). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.43–2.00 (7H, m), 1.62 (3H, t), 2.01 (1H, m), 2.90 (1H, dd), 3.00 (2H, m), 3.21 (5H, m), 3.38 (2H, m), 3.61 (2H, dd), 3.98 (2H, m), 4.43 (1H, m), 4.36 (2H, q), 7.19 (5H, m), 7.76 (1H, dd), 7.93 (1H, d), 8.09 (1H, d), 8.26 (1H, d), 8.59 (1H, s), 8.98 (1H, s), 9.71 ppm (1H, brs); MS *m/z* calcd for $C_{32}H_{42}N_8O_4$: 602.2, found: 603.1 $[M+H]^+$; HPLC purity: system D, 96%, t_R=6.97 min.

***N*-{1-[(*R*)-1-(3-Morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-3-(2-propyl-2*H*-tetrazol-5-yl)benzamide trifluoroacetate (52).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=0.91 (3H, t), 1.35–1.74 (4H, m), 1.74–2.07 (7H, m), 2.25 (1H, m), 2.88 (1H, dd), 3.00 (2H, m), 3.18 (5H, m), 3.87 (2H, m), 3.60 (2H, m), 3.95 (2H, m), 4.39 (1H, m), 4.75 (2H, t), 7.19 (5H, m), 7.79 (1H, dd), 7.88 (1H, d), 8.05 (1H, d), 8.23 (1H, d), 8.60 (1H, s), 8.93 (1H, s), 9.65 ppm (1H, brs); MS *m/z* calcd for $C_{33}H_{44}N_8O_4$: 616.2, found: 617.1 $[M+H]^+$; HPLC purity: system D, >98%, t_R=7.58 min.

3-(2-Isobutyl-2*H*-tetrazol-5-yl)-*N*-{1-[(*R*)-1-(3-morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}benzamide trifluoroacetate (53). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.98 (6H, d), 1.50–2.00 (9H, m), 2.25 (1H, m), 2.37 (1H, m), 2.90–3.40 (10H, m), 3.62 (2H, m), 3.98 (2H, m), 4.40 (1H, m), 4.65 (2H, d), 7.20 (5H, m), 7.70 (1H, dd), 7.77 (1H, dd), 7.90 (1H, d), 8.07 (1H, d), 8.25 (1H, d), 8.60 (1H, s), 8.95 (1H, s), 9.60 ppm (1H, brs); MS *m/z* calcd for $C_{34}H_{46}N_8O_4$: 630.3, found: 631.3 $[M+H]^+$; HPLC purity: system A, >98%, t_R = 8.03 min.

***N*-{1-[(*R*)-1-(3-Morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-4-pyridin-4-ylbenzamide trifluoroacetate (54).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.48–1–78 (9H, m), 2–00 (1H, m), 2.90 (1H, dd), 3.00–3.30 (8H, m), 3.40 (2H, m), 3.65 (2H, m), 3.95 (2H, m), 4.40 (1H, m), 7.20 (5H, m), 7.80 (2H, dd), 7.87 (3H, m), 8.00 (2H, d), 8.10 (2H, d), 8.75 (2H, d), 8.85 (1H, s), 9.70 ppm (1H, brs); MS *m/z* calcd for $C_{34}H_{41}N_5O_4$: 583.3, found: 584.3 $[M+H]^+$; HPLC purity: system A, >99%, t_R = 5.47 min.

***N*-{1-[(*R*)-1-(3-Morpholin-4-ylpropylcarbamoyl)-2-phenylethylcarbamoyl]cyclopentyl}-4-pyridin-3-ylbenzamide (55).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.46–1.67 (8H, m), 1.79 (1H, m), 1.96 (1H, m), 2,29 (6H, m), 2.83 (1H, dd), 3.08 (2H, m), 3.17 (1H, dd), 3.54 (4H, m), 4.46 (1H, m), 7.17 (5H, m), 7.54 (1H, t), 7.75 (1H, d), 7.87 (2H, d), 8.04 (2H, d), 8.17 (1H, d), 8.62 (1H, s), 8.67 (1H, s), 8.96 ppm (1H, s); MS *m/z* calcd for $C_{34}H_{41}N_5O_4$: 583.3, found: 584.1 $[M+H]^+$; HPLC purity: system D, 96%, t_R = 5.01 min.

***N*-(1-{(*R*)-1-[3-Oxo-3-(4-pyridin-2-ylpiperazin-1-yl)propylcarbamoyl]-2-phenylethylcarbamoyl}cyclopentyl)-4-pyrrol-1-ylbenzamide (56).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.44–1.70 (6H, m),1.83 (1H, m), 1.96 (1H, m), 2.23 (1H, m), 2.50 (1H, m), 2.87 (1H, dd), 3.15 (1H, dd), 3.36 (2H, m), 3.50 (6H, m), 3.57 (2H, m), 4.50 (1H, m), 6.30 (2H, s), 6.66 (1H, d), 6.81 (1H, d), 7.15 (5H, m), 7.50 (1H, s), 7.55 (1H, m), 7.72 (2H, m), 7.72 (2H, d), 8.00 (2H, d), 8.10 (1H, d), 8.60 ppm (1H, s); MS *m/z* calcd for $C_{38}H_{43}N_7O_4$: 661.3, found: 662.2 $[M+H]^+$; HPLC purity: system A, 97.5%, t_R = 7.72 min.

4-(2,5-Dimethylpyrrol-1-yl)-*N*-(1-{1-[3-oxo-3-(4-pyridin-2-ylpiperazin-1-yl)propylcarbamoyl]-2-phamylethylcarbamoyl}cyclopentyl)-benzamide (57). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.66 (m, 6H), 1.84 (1H, m), 1.94 (1H, m), 2.00 (6H, s), 2.20 (1H, m), 2.56 (1H, m), 2.88 (1H, dd), 3.16 (1H, dd), 3.32 (2H, m), 3.50 (4H, m), 3.52 (4H, m), 4.46 (1H, m), 5.84 (2H, s), 6.64 (1H, dd), 6.84 (1H, d), 7.16 (5H, m), 7.40 (2H, d), 7.54 (1H, m), 7.72 (1H, m), 8.00 (2H, d), 8.08 (1H, d), 8.70 ppm (1H, s); MS *m/z* calcd for $C_{40}H_{47}N_7O_4$: 689.2, found: 690.2 $[M+H]^+$; HPLC purity: system D, 95.4%, t_R = 7.69 min.

***N*-(1-{(*R*)-1-[3-Oxo-3-(4-pyridin-2-ylpiperazin-1-yl)propylcarbamoyl]-2-phenylethylcarbamoyl}cyclopentyl)-4-pyrazol-1-ylbenzamide (58).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.44–1.73 (6H, m), 1.83 (1H, m), 1.96 (1H, m), 2.25 (1H, m), 2.50 (1H, m), 2.87 (1H, dd), 3.19 (1H, dd), 3.33 (2H, m), 3.50 (6H, m), 3.58 (2H, m), 4.46 (1H, m), 6.60 (1H, s), 6.64 (1H, dd), 6.83 (1H, d), 7.15 (5H, m), 7.54 (1H, dd), 7.69 (1H, dd), 7.621H, d), 7.75 (1H, s), 7.98 (2H, dd), 8.04 (2H, d), 8.10 (1H, d), 8.64 ppm (2H, m); MS *m/z* calcd for $C_{37}H_{42}N_8O_4$: 662.3, found: 663.2 $[M+H]^+$; HPLC purity: system A, 96.9%, t_R = 6.93 min.

4-(3,5-Dimethylpyrazol-1-yl)-*N*-(1-{(*R*)-1-[3-oxo-3-(4-pyridin-2-ylpiperazin-1-yl)propylcarbamoyl]-2-phenylethylcarbamoyl}cyclopentyl)benzamide (59). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.56 (6H, m), 1.80 (1H. m), 1.92 (1H, m), 2.18 (3H, s), 2.24 (1H, m), 2.36 (3H, s), 2.50(1H, m), 2.84 (1H, dd), 3.14 (1H, dd), 3.50 (8H, m), 4.45 (1H, m), 6.12 (1H, s), 6.64 (1H, dd), 6.80 (1H, d), 7.12 (5H, m), 7.52 (1H, m), 7.60 (d, 2H), 7.68 (1H, dd), 7.72 (1H, dd), 8.0 (2H, d), 8.08 (1H, d), 8.68 ppm (1H, s); MS *m/z* calcd for $C_{39}H_{46}N_8O_4$: 690.8, found: 691.2 $[M+H]^+$; HPLC purity: system D, 91.7%, t_R = 6.66 min.

3-(2-Ethyl-2*H*-tetrazol-5-yl)-*N*-(1-{(*R*)-1-[3-oxo-3-(4-pyridin-2-ylpiperazin-1-yl)propylcarbamoyl]-2-phenylethylcarbamoyl}cyclopentyl)benzamide (60). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.47–1.76 (6H, m), 1.59 (3H, t), 1.80 (1H, m), 1.96 (1H, m), 2.23 (1H, m), 2.50 (1H, m), 2.85 (1H, dd), 3.15 (1H, dd), 3.34 (2H, m), 3.47 (6H, m), 3.59 (2H, m), 4.45 (1H, m), 4.76 (2H, q), 6.66 (1H, dd), 6.81 (1H, d), 7.17 (5H, m), 7.55 (1H, dd), 7.70 (2H, m), 7.76 (1H, dd), 8.08 (2H, m), 8.21 (1H, d), 8.59 (1H, s), 8.87 ppm (1H, s); MS *m/z* calcd for $C_{37}H_{44}N_{10}O_4$: 692.3 Found 693.4 $[M+H]^+$; HPLC purity: system A, 97.9%, t_R = 7.23 min.

3-(2-Butyl-2*H*-tetrazol-5-yl)-*N*-(1-{(*R*)-1-[3-oxo-3-(4-pyridin-2-ylpiperazin-1-yl)propylcarbamoyl]-2-phenylethylcarbamoyl}cyclopentyl)benzamide (61). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.91 (3H, t), 1.31 (2H, m), 1.44–1.80 (6H, m), 1.88 (1H, m), 1.96 (3H, m), 2.24 (1H, m), 2.50 (1H, m), 2.84 (1H, dd), 3.16 (1H, dd), 3.31 (2H, m), 3.47 (6H, m), 3.55 (2H, m), 4.47 (1H, m), 4.73 (2H, t), 6.66 (1H, dd), 6.84 (1H, d), 7.16 (5H, m), 7.50 (1H, dd), 7.69 (2H, m), 7.77 (1H, d), 8.07 (2H, m), 8.24 (1H, d), 8.60 (1H, s), 8.85 ppm (1H, s); MS *m/z* calcd for $C_{39}H_{48}N_{10}O_4$: 720.4, found: 721.3 $[M+H]^+$; HPLC purity: system A, 97.9%, t_R = 8.12 min.

3-(2-Isobutyl-2*H*-tetrazol-5-yl)-*N*-(1-{(*R*)-1-[3-oxo-3-(4-pyridin-2-yl-piperazin-1-yl)propylcarbamoyl]-2-phenylethylcarbamoyl}cyclopentyl)benzamide (62). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.96 (6H, d), 1.25 (4H, m), 2.00 (3H, m), 2.25 (1H, m), 2.42 (3H, m), 2.50 (1H, m), 2.92 (1H, dd), 3.10 (1H, dd), 3.37 (2H, m), 3.50 (8H, m), 4.50 (1H, m), 4.62 (2H, d), 6.75 (1H, dd), 6.96 (1H, d), 7.08 (1H, dd), 7.17 (5H, m), 7.42 (1H, dd), 7.54 (1H, dd), 7.67 (2H, m), 8.00 (1H, d), 8.08 (1H, d), 8.20 (1H, d), 8.50 ppm (2H, m); MS *m/z* calcd for $C_{39}H_{48}N_{10}O_4$: 720.4. Found: 721.3 $[M+H]^+$; HPLC purity: system A, >98%, t_R = 7.98 min.

***N*-(1-{(*R*)-1-[3-Oxo-3-(4-pyridin-2-yl-piperazin-1-yl)propylcarbamoyl]-2-phenylethylcarbamoyl}cyclopentyl)-4-thiophen-3-ylbenzamide (63).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.44–1.75 (8H, m), 1.75 (1H, m), 1.96 (1H, m), 2.25 (1H, m) 2.85 (1H, dd), 3.19 (1H, dd), 3.54 (8H, m), 4.48 (1H, m), 6.69 (1H, dd), 6.83 (1H, d), 7.17 (5H, m), 7.37 (1H, dd), 7.69 (3H, m), 7.77 (1H, d), 7.85 (2H, d), 8.00 (2H, d), 8.04 (1H,s), 8.12 (1H, d), 8.60 ppm (1H, s); MS *m/z* calcd for $C_{38}H_{42}N_6O_4S$: 678.3 Found 679.4 $[M+H]^+$; HPLC purity: system A, 98%, t_R = 7.96 min.

***N*-[1-((*R*)-2-Phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]-4-pyrazol-1-ylbenzamide trifluoroacetate (64).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.13–2.08 (18H, m), 2.31 (1H, m), 2.74 (2H, m), 2.94 (3H, m), 3.04 (1H, m), 3.19 (1H, m), 3.30 (2H, m), 3.50 (2H, m), 3.85 (2H, m), 4.47 (1H, m), 6.64 (1H, s), 7.17 (5H, m), 7,66 (2H, m), 7.85 (1H, d), 8.00 (2H, d), 8.09 (2H, d), 8.64 (1H, s), 8.72 (1H, s), 8.76 (1H, brs), 9.00 ppm (1H, brs); MS *m/z* calcd for $C_{37}H_{48}N_6O_4$: 640.4, found: 641.4 $[M+H]^+$; HPLC purity: system A, 94.5%, t_R = 7.09 min.

4-(3-Methylpyrazol-1-yl)-*N*-[1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]benzamide trifluoroacetate (65). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.13–2.06 (18H, m), 2.25 (3H, s), 2.25 (1H, m), 2.72 (2H, m), 2.89 (3H, m), 3.04 (1H, m), 3.17 (1H, m), 3.30 (2H, m), 3.50 (2H, m), 3.85 (2H, m), 4.42 (1H, m), 6.40 (1H, s), 7.17 (5H, m), 7.62 (2H, m), 7.83 (1H, d), 7.91 (2H, d), 8.02 (2H, d), 8.47 (1H, s), 8.66 (1H, s), 8.72 (1H, brs), 8.94 ppm (1H, brs); MS *m/z* calcd for $C_{38}H_{50}N_6O_4$: 654.4, found: 655.3 $[M+H]^+$; HPLC purity: system A, 93.8%, t_R = 7.34 min.

4-(3,5-Dimethylpyrazol-1-yl)-*N*-[1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]benzamide trifluoroacetate (66). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.13–2.09 (17H, m), 2.22 (3H, s), 2.29 (1H, m), 2.40 (3H, m), 2.89 (2H, m), 2.93 (4H, m), 3.07 (1H, m), 3.20 (1H, m), 3.31 (1H, m), 3.95 (4H, m), 4.44 (1H, m), 6.15 (1H, s), 7.17 (5H, 1H9, 7.66 (2H, m), 7.84 (1H, d), 8.04 (2H, d), 8.75 (1H, brs), 9.0 ppm 81H, brs; MS *m/z* calcd for $C_{39}H_{52}N_6O_4$: 668.4. Found: 669.3 $[M+H]^+$; HPLC purity: system A, >98%, t_R = 7.23 min.

3-(2-Methyl-2*H*-tetrazol-5-yl)-*N*-[1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]benzamide trifluoroacetate (67). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.25 (2H, m), 1.39 (2H, m), 1.48–1.92 (12H, m), 2.00 (1H, m), 2.28 (1H, m), 2.80–3.16 (10H, m), 3.31 (2H, m), 3.86 (2H, m), 4.45 (1H, m), 4.47 (3H, s), 7.16 (5H, m), 7.65 (2H, m), 7.73 (1H, dd), 7.86 (1H, dd), 8.08 (1H, d), 8.24 (1H, d), 8.57 (1H, d), 8.89 (1H, brs), 8.94 ppm (1H, s); MS *m/z* calcd for $C_{36}H_{48}N_8O_4$: 656.3, found: 657.3 $[M+H]^+$; HPLC purity: system A, 91.5%, t_R = 7.07 min.

3-(2-Ethyl-2*H*-tetrazol-5-yl)-*N*-[1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]benzamide trifluoroacetate (68). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.24 (2H, m), 1.43 (2H, m), 1.50–1.91 (11H, m), 1.61 (3H, t), 2.06 (2H, m), 2.30 (1H, m), 3.74–3.26 (10H, m), 3.35 (2H, m), 3.87 (2H, m), 4.48 (1H, m), 4.87 (2H, q), 7.17 (5H, m), 7.69 (2H, m), 7.89 (1H, m), 8.09 (1H, d), 8.26 (1H, d), 8.63 (1H, s), 8.78 (1H, brs), 8.96 ppm (1H, s); MS *m/z* calcd for $C_{37}H_{50}N_8O_4$: 670.4. Found: 671.2 $[M+H]^+$; HPLC purity: system A, <98%, t_R = 7.47 min.

***N*-[1-((*R*)-2-Phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]-3-(2-propyl-2*H*-tetrazol-5-yl)benzamide trifluoroacetate (69).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.91 (3H, t), 1.11–2.07 (21H, m), 2.27 (1H, m), 2.77–3.18 (8H, m), 3.32 (2H, m), 3.84 (2H, m), 4.45 (1H, m), 4.73 (2H, t), 7.14 (5H, m), 7.68 (2H, m), 7.82 (1H, d), 8.09 (1H, d), 8.27 (1H, d), 8.27 (1H, d), 8.61 (1H, s), 8.77 (1H, brs), 8.95 ppm (1H, s); MS *m/z* calcd for $C_{38}H_{52}N_8O_4$: 684.4. Found: 685.4 $[M+H]^+$; HPLC purity: system A, 91.2%, t_R = 7.83 min.

***N*-[1-((*R*)-2-Phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]-4-pyrrol-1-yl-benzamide trifluoroacetate (70).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.21 (2H, m), 1.37 (2H, m), 1.44–2.06 (15H, m), 2.27 (1H, m), 2.67–3.00 (5H, m), 3.08 (1H, m), 3.19 (2H, m), 3.33 (2H, m),3.46 (2H, m), 3.85 (2H, m), 4.44 (1H, m), 6.34 (2H, s), 7.17 (5H, m), 7.54 (2H, s), 7.64 (1H, m), 7.73 (2H, d), 7.81 (1H, m), 8.00 (2H, d), 8.64 (1H, s), 8.71 (1H, brs), 9.00 ppm (1H, brs); MS *m/z* calcd for $C_{38}H_{49}N_5O_4$: 639.4, found: 640.4 $[M+H]^+$; HPLC purity: system A, >98%, t_R = 7.86 min.

4-(2,5-Dimethylpyrrol-1-yl)-*N*-[1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]benzamide trifluoroacetate (71). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.13–1.90 (18H, m), 2.00 (6H, s), 2.18 (2H, m), 2.67–3.20 (8H, m), 3.35 (2H, m), 3.80 (2H, m), 4.45 (1H, m), 7.17 (5H, m), 7.40 (2H, s), 7.73 (2H, d), 7.81 (1H, dd), 8.00 (2H, d), 8.10 (1H, d), 8.70 (1H, brs), 9.00 ppm (1H, brs); MS *m/z* calcd for $C_{40}H_{53}N_5O_4$: 667.4. Found: 668.4 $[M+H]^+$; HPLC purity: system A, 92.6%, t_R = 8.28 min.

***N*-[1-((*R*)-2-Phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]-4-pyridin-4-yl-benzamide trifluoroacetate (72).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.96–1.87 (18H, m), 2.00 (3H, m), 2.29 (1H, m), 2.66 (2H, m), 2.96 (3H, m), 3.18 (3H, m), 3.82 (2H, m), 4.50 (1H, m), 7.18 (5H, m), 7.50 (1H, m), 7.82 (3H, m), 7.96 (2H, d), 8.02 (2H, d), 8.69 (1H, d), 8.77 ppm (1H, s); MS *m/z* calcd for $C_{39}H_{49}N_5O_4$: 651.3, found: 652.5 $[M+H]^+$; HPLC purity: system A, >97%, t_R = 5.58 min.

***N*-[1-((*R*)-2-Phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]-4-pyridin-3-yl-benzamide trifluoroacetate (73).** ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.95–1.95 (18H, m), 2.0 (3H, m), 2.28 (1H, m), 2.67 (2H, m), 2.91 (3H, m), 3.19 (3H, m), 3.78 (2H, m), 4.45 (1H, m), 7.19 (5H, m), 7.50 (2H, m), 7.78 (1H, d), 7.87 (2H, d), 8.05 (2H, d), 8.15 (1H, d), 8.62 (1H, s), 8.70 (1H, s), 9.0 ppm (1H, s); MS *m/z* calcd for $C_{39}H_{49}N_5O_4$: 651.3, found: 652.3 $[M+H]^+$; HPLC purity: system A, 94%, t_R = 5.58 min.

Biphenyl-4-carboxylic acid [1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]amide trifluoroacetate (74). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.09–2.05 (17H, m), 2.21 (1H, m), 2.62–3.30 (10H, m), 3.40 (2H, m), 3.87 (2H, m), 4.45 (1H, m), 7.20 (5H, m), 7.45 (m, 3H), 7.70 (1H, t), 7.77 (2H, d), 7.80 (3H, m), 8.00 (2H, d), 8.75 ppm (2H, brs); MS *m/z* calcd for $C_{40}H_{50}N_4O_4$: 650.4. Found: 651.4[$M+H]^+$; HPLC purity: system A, 94%, t_R = 7.92 min.

4′-Chlorobiphenyl-4-carboxylic acid [1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]amide (75). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.95–1.82 (18H, m), 1.95 (1H, m), 2.00 (2H, d), 2.18 (1H, m), 2.66 (2H, m), 2.84 (2H, m), 2.95 (1H, m), 3.14 (3H, m), 3.73 (2H, m), 4.45 (1H, m), 7.14 (5H, m), 7.43 (1H, dd), 7.54 (2H, d), 7.75 (3H, m), 8.00 (2H, d), 8.68 ppm (1H, s); MS *m/z* calcd for $C_{40}H_{50}N_4O_4$: 684.34. Found: 685.4 $[M+H]^+$; HPLC purity: system A, 95%, t_R = 8.86 min.

4′-Fluorobiphenyl-4-carboxylic acid [1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]amide trifluoroacetate (76). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.20 (2H, m), 1.40 (2H, m), 1.45–1.85 (12H, m), 1.95 (2H, m), 2.25 (1H, m), 2.75 (2H, m), 2.90 (4H, m), 3.05 (1H, m), 3.20 (2H, m), 3.25 (4H, m), 3.45 (2H, m), 3.80 (2H, m), 4.45 (1H, m), 7.20 (5H, m), 7.35 (2H, m), 7.65 (1H, dd), 7.80 (5H, m), 8.00 (2H, d), 8.70 (2H, brs), 9.00 ppm (1H, brs); MS *m/z* calcd for $C_{40}H_{49}FN_4O_4$: 668.4. Found: 669.3 $[M+H]^+$; HPLC purity: system A, >98%, t_R = 8.40 min.

4′-Methoxybiphenyl-4-carboxylic acid [1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]amide (77). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.20 (2H, m), 1.40 (2H, m), 1.45–1.85 (12H, m), 1.95 (2H, m), 2.25 (1H, m), 2.75 (2H, m), 2.90 (4H, m), 3.05 (1H, m), 3.20 (4H, m), 3.45 (2H, m), 3.80 (3H, s), 3.80 (2H, m), 4.45 (1H, s), 7.05 (2H, m), 7.20 (5H, m), 7.75 (6H, m), 7.95 (2H, dd), 8.70 (2H, brs), 9.0 ppm (1H, brs); MS *m/z* calcd for $C_{41}H_{52}N_4O_5$: 680.4. Found: 681.4 $[M+H]^+$; HPLC purity: system A, 98%, t_R = 8.27 min.

4′-Methylbiphenyl-4-carboxylic acid [1-((*R*)-2-phenyl-1-{[1-(tetrahydropyran-4-ylmethyl)piperidin-4-ylmethyl]carbamoyl}ethylcarbamoyl)cyclopentyl]amide trifluoroacetate (78). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.20 (2H, m), 1.40 (2H, m), 1.50–1.85 (12H, m), 1.95 (2H, m), 2.25 (1H, m), 2.40 (3H, s), 2.75 (2H, m), 2.90 (4H, m), 3.05 (1H, m), 3.25 (4H, m), 3.45 (2H, m), 3.80 (2H, m), 4.45 (1H, m), 7.20 (5H, m), 7.30 (2H, m), 7.65 (3H, m), 7.80 (3H, m), 8.00 (2H, dd), 8.85 (2H, brs), 8.95 ppm (1H, brs); MS *m/z* calcd for $C_{41}H_{52}N_4O_4$: 664.4. Found: 665.4 $[M+H]^+$; HPLC purity: system A, >98%, t_R = 8.64 min.

Conformational analysis NMR. Samples were dissolved in DMSO-6d at a concentration of about 5 nM. For assignment of the spin systems, ^{1}H NMR and COESY spectra were recorded on a Varian 300 MHz or on a Bruker Avance 400 MHz. For the structural analysis ROESY and TROESY[13] spectra have been collected at 292 K with mixing times varying from 100 to 300 ms and in the phase-sensitive mode using states-TPPI. No evidence of spin diffusion was observed up to a mixing time of 300 ms. The spectral width was 4789 Hz in both dimensions, with 2000 points in t2 and 256 data points in t1 conformational searches were performed using the Monte Carlo method.

Molecular modeling. The computational study of **30**, **46**, **80**, and **81** was performed with SYBYL 6.91 (Tripos Inc.). Conformational searches were carried out using the Grid Search module including all rotatable single bonds. The resulting conformers were minimized by using the MMFF94 force field with a dielectric constant of 46.7 (DMSO). Duplicate structures were identified, applying a rms threshold of 0.2 Å on heavy atoms, and eliminated. The occurrence and relevance of the final conformers were determined employing NMR data with the help of the NAMFIS program.

Binding experiments. All compounds were tested for their ability to displace [^{125}I]neurokinin A bound to recombinant hNK$_2$ receptor in a cell membrane preparation as reported previously.[8] The radioligand was from Amersham Biosciences (Buckinghamshire, UK). Non specific binding was determined in the presence of unlabeled neurokinin A (1 μM). The affinity of test compounds was expressed in terms of pK_i ($-\log K_i$), derived from the equation:

$$K_i = \frac{IC_{50}}{1 + [\text{radioligand}]\, K_d^{-1}}$$

Organ bath experiments. The experiments were performed on guinea pig (Dunkin Hartley, Charles River, Italy) isolated proximal colon circular smooth muscle preparation (GPC). All experiments were performed in oxygenated (96% O_2 and 4% CO_2) Krebs–Henseleit solution. The preparations were set up according to methods previously described.[8] The activity of test compounds at tachykinin NK$_2$ receptors in GPC was assessed against selective NK$_2$ receptor agonist [βAla^8]NKA(4-10) in the presence of the NK$_1$ receptor selective antagonist SR 140333 (1 μM). The antagonist affinity of all test compounds (15 min incubation period) was expressed as pK_B (negative logarithm of K_B, the antagonist dissociation constant), which was estimated as the mean of the individual values obtained with the equation:

$$pK_B = \log[(\text{dose ratio}) - 1] - \log[\text{antagonist concentration}]$$

In vivo experiments. All the experiments were performed in accordance with the Declaration of Helsinki, with the principles and the guidelines of the European Union regulations and the local ethical committee as described elsewhere.[5] Briefly, male Dunkin Hartley guinea pigs (Charles River, Italy) weighing 350–400 g were anaesthetized with urethane (1.5 g kg^{-1} sc) and a polyethylene catheter was inserted into the left jugular vein for intravenous (iv) administration of drugs. Guinea pigs were mechanically ventilated with a ventilation pump at a rate of 50 strokes min^{-1} and a respiration volume of 10 mL kg^{-1}. The body temperature was kept constant at 36 °C by a thermoregulated lamp. The abdomen was opened, and a latex balloon, which was obtained from a condom head, was connected to a PE90 polyethylene catheter, inserted into the proximal colon at about 2–3 cm from the cecum, and filled with 0.5 mL of saline. The intracolonic balloon was connected to a pressure transducer (Transpac IV, Abbott, Italy) for intraluminal pressure recorded by mean of a MacLab/8S ML 780 data acquisition system (ADInstruments, UK). Five minutes before starting the experiments, the guinea pigs were treated with the ganglionic blocker hexamethonium bromide (13.8 μmol kg^{-1} iv) and followed by continuous infusion of the same solution at a rate of 300 μL h^{-1} to prevent reflex cholinergic responses. The compounds in their vehicle (DMSO) were administered iv (0.3–3 μmol kg^{-1}) in a volume of 100 μL kg^{-1}. The selective NK$_2$ receptor agonist [βAla^8]NKA(4-10) (3 nmol kg^{-1}, iv) was administered two or three times before the antagonist of the vehicle in order to stabilize the colon contractile responses, and the challenge was repeated at 5, 30 and then every 30 min until 4 h after antagonist administration.

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