Articles

Utilization of an Intramolecular Hydrogen Bond To Increase the CNS Penetration of an NK_1 Receptor Antagonist

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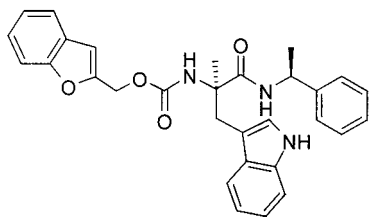
This paper describes the synthesis and physical and biological effects of introducing different substituents at the α-position of the tryptophan containing neurokinin-1 receptor antagonist [(*R*)-2-(1*H*-indol-3-yl)-1-methyl-1-((*S*)-1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (**CI 1021**). The described compounds all exhibit less than 5 nM binding affinities for the human neurokinin-1 receptor and selectivity over the tachykinin NK_2 and NK_3 receptor subtypes. Application of variable temperature nuclear magnetic resonance spectroscopy studies of the amide and urethane protons was utilized to determine the existence of an intramolecular hydrogen bond. This intramolecular hydrogen bond increases the apparent lipophilicity to allow increased central nervous system penetration and pharmacological activity (gerbil foot tap test) in the case of the highest affinity compound [(*S*)-1-dimethylaminomethyl-2-(1*H*-indol-3-yl)-1-((*S*)-1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (**PD 174424**) over those analogues that could not form an intramolecular hydrogen bond.

Introduction

Substance P has been shown to display preferential affinity for the neurokinin-1 (NK_1) tachykinin receptor,[1] and it is widely acknowledged that this, and other tachykinin agonists, play a major role in various biological processes including pain transmission, vasodilation, bronchoconstriction, activation of the immune system, and neurogenic inflammation.[2] Indeed, in recent years the tachykinin area has been a focus of attention for the pharmaceutical industry with many examples of antagonists for each of the tachykinin receptors.[3−6]

We have previously reported on the design of the selective NK_1 receptor antagonist **1** (**CI 1021**, hNK_1 IC_{50} = 1.05 nM).[7] Although this compound has an excellent pharmacological profile with oral bioavailability of 50−60% (dog) and a half-life of greater than 6 h (dog), it



CI 1021

does exhibit poor aqueous solubility (<2 μg/mL) and a modest brain−plasma ratio (brain homogenate to plasma is 0.6 in the rat) for a centrally acting compound. We now report on the further development of compounds from this class which retain nanomolar affinity binding for the NK_1 receptor and selectivity over the neurokinin-2 and -3 receptors (NK_2 and NK_3), as well as possessing increased aqueous solubility and a greater potential to penetrate the CNS. We have previously published on the structure−activity relationship (SAR) studies on the N- and C-terminal substitutions of the tryptophan moiety to give compound **1**.[7] The SAR of the α-methyl group was then examined further. The desmethyl analogue (**12**, **PD 160226**,[8] Table 1) exhibited good receptor binding affinity at the NK_1 receptor (IC_{50} 0.73 nM). To aid our understanding of the SAR of this series of compounds, we sought to vary the nature of the group at the α-position and probe this portion of the molecule to determine its influence on the receptor binding affinity of these compounds. We reasoned that inclusion of appropriate heteroatoms at the α-carbon atom could potentially lead to the formation of an intramolecular hydrogen bond with one of the neighboring N−H's from the urethane and amide groups. This would effectively remove one donor hydrogen and one acceptor atom from the molecule, which would then lead to a higher apparent lipophilicity and, hence, may increase membrane permeability[9] while hopefully retaining increased aqueous solubility due to the presence of the heteroatom. When the X-ray crystal structure of **1** (Figure 1) was examined, it was found that the hydrogen atoms associated with the amide and urethane groups were both pointing in the same general alignment with respect to each other and with the α-methyl group of the tryptophan moiety.[10] With the use of

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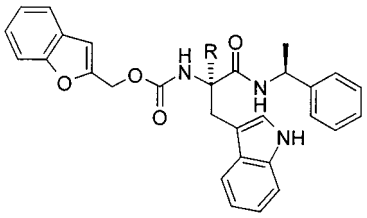
Table 1. Table Showing Some of the in Vitro Data for the Compounds Described



compd	R	IC_{50} (nM)[a]
12	H	0.73 ± 0.19 (3)
1	CH_3	1.05 ± 1.00 (51)
11a	CH_2CH_3	0.96 ± 0.25 (8)
11b	$CH_2CH_2CH_3$[b]	0.85 ± 0.47 (3)
11c	$CH_2CH(CH_3)_2$	3.79 ± 2.18 (2)
11d	CH_2OCH_3	0.70 ± 0.34 (11)
11e	$CH_2N(CH_3)_2$	0.46 ± 0.17 (7)

[a] IC_{50} is the concentration producing half-maximal inhibition of specific binding at the receptor and is an arithmetic mean given with the standard deviation. The number of experiments are indicated in brackets. ([^{125}I]-Bolton Hunter-Substance P to NK_1 receptors in IM9 cells.[7]) [b] Mixture (3:2) of diastereomers at the Trp center.

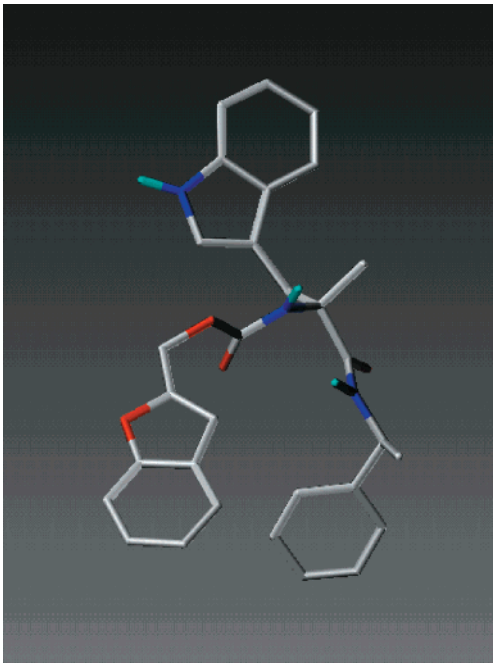


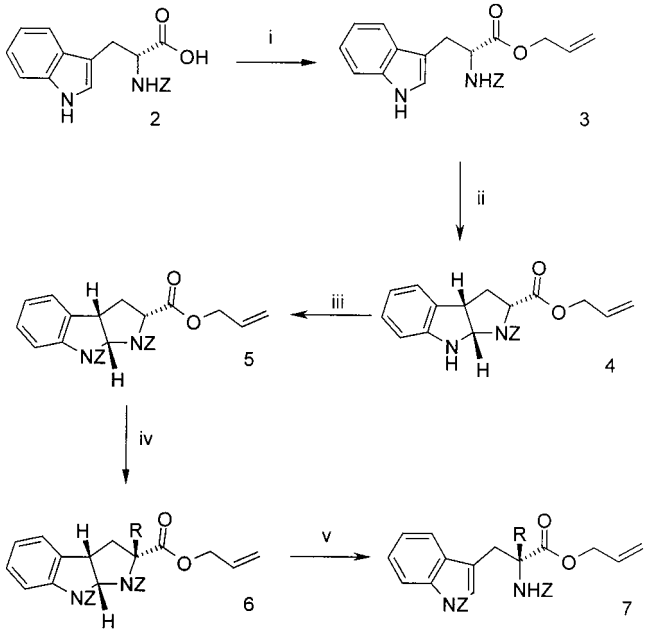
Figure 1. Conformation of **1** obtained from X-ray crystallography.

molecular modeling,[11] a selection of compounds incorporating different α-substituents were proposed with the aim of investigating intramolecular hydrogen bonding and their effects on CNS penetration. The key synthetic step to these compounds is an efficient and predictive enantiomeric synthesis of α-substituted tryptophan derivatives.

Chemistry

The α-methyl group of **1** serves as a conformational constraint for the "backbone" of the molecule as well as decreasing the potential for enzymatic hydrolysis and racemization in vivo.[12] It was hypothesized that the α-substituent could be further adapted to give additional conformational restriction of **1** via the introduction of a bulkier alkyl group (ethyl, propyl, isobutyl) or the development of an internal hydrogen bond by the introduction of heteroatom containing substituents (e.g., methoxymethylene and dimethylaminomethylene). The latter would also have the potential to increase the aqueous solubility via intermolecular hydrogen bonds to water.

Scheme 1[a]

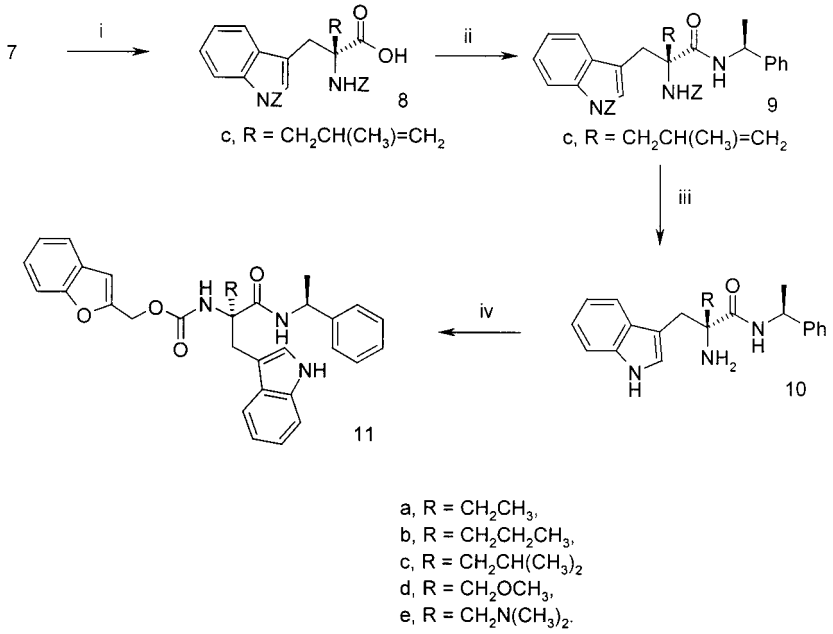


a, R = CH_2CH_3,
b, R = $CH_2CH_2CH_3$,
c, R = $CH_2CH(CH_3)=CH_2$,
d, R = CH_2OCH_3,
e, R = $CH_2N(CH_3)_2$.

[a] Reagents: (i) allyl alcohol, DCC, DMAP, CH_2Cl_2, 89%; (ii) TFA, 52%; (iii) ZCl, Na_2CO_3 (aq), 1,4-dioxane, 92%; (iv) LHMDS, RX, DMPU, THF; (v) TFA, CH_2Cl_2 or H_2SO_4, MeOH, H_2O.

There is literature precedent for the enantioselective synthesis of α-methyltryptophan, and these methods include chemical syntheses with varying degrees of enantiopurity[13−16] and enzymatic resolutions which give excellent enantioselectivity.[17,18] As a consequence of our previous success with the method described by Crich et al.[19] in which the α-alkylation of Trp was achieved with high enantioselectivity, it was decided to pursue this approach in attempting to introduce α-substituents incorporating heteroatoms stereoselectively. The general synthesis of these types of compounds described by Crich has been slightly modified.[20] This modified synthesis has been further modified due to low yields obtained in the hydrolysis of the tryptophan methyl ester when large groups were incorporated into the α-position—presumably as a consequence of unfavorable steric interactions. Therefore, the allyl ester was chosen as an acid protecting group as it is stable to the acidic conditions required for both the ring-cyclization and ring-opening, and it can be easily removed using catalytic palladium in the presence of a nucleophile.[21] The synthesis started with the allyl esterification of (*R*)-*N*-benzyloxycarboxytryptophan, **2**, using *N*,*N*′-dicyclohexylcarbodiimide (DCC) as the condensing agent in excellent yield (Scheme 1). It was found that partial racemization of the α-center occurred when 4-(dimethylamino)pyridine (DMAP) was used as catalyst. The absence of

Scheme 2[a]



[a] Reagents: (i) $Pd(PPh_3)_4$, morpholine, THF; (ii) amine, HBTU, DIPEA, DMF; (iii) $Pd(OH)_2$-C, EtOH; (iv) $BfCH_2OCOCl$, TEA, EtOAc or $BfCH_2OCONP$, DMAP, DMF.

DMAP resulted in longer reaction times but no racemization. The cyclization reaction to give **4** was catalyzed using trifluoroacetic acid (TFA),[19] and the desired tricycle was isolated as a single diastereomer in moderate yield (52%). A second *N*-benzyloxycarboxy (*Z*) protecting group was introduced at the indoline nitrogen using basic conditions in excellent yield. The enantiospecific alkylations at the "α-carbon" proceeded in good yield using lithium bis(trimethylsilyl)amide (LHMDS) as base in conjunction with the cosolvent 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) at low temperature.[20] Iodoethane had to be freshly distilled from sodium in order to facilitate a clean reaction in high yield to give **6a**. Iodomethylmethyl ether was chosen to give the ether, **6d**, and the nitrogen containing compound **6e** was obtained using Eschenmoser's salt as the electrophile. These alkylated tricyclic intermediates were then ring-opened using TFA in dichloromethane. The *N*,*N*-dimethylaminomethyl compound **6e** was found to be quite stable to these conditions, even the omission of solvent and conducting the reaction in neat TFA did not provide any marked improvement. Various acidic conditions were tried, and the use of sulfuric acid in methanol was found to give the optimal yield of ring-opened Trp ester, **7e**. The ester hydrolyses were facile when tetrakis(triphenylphosphine)palladium(0) was used in conjunction with a large excess of morpholine,[21] all giving near quantitative yields of the free acids (Scheme 2). No attempt was made at purification, and the acids were coupled to (*S*)-1-phenylethylamine using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HBTU) and base in *N*,*N*-dimethylformamide (DMF). Compound **9e** gave only a moderate yield in the coupling reaction, and this can probably be attributed to the enhanced steric encumbrance of the large *N*,*N*-dimethylaminomethylene group so close to the reaction center. The hydrogenolysis of the two *Z* protecting groups proceeded in near quantitative yield to give the free amine and indole nitrogens. Initially these free amines were acylated with 4-nitrophenyl activated carbonates[7] though it was subsequently found that the corresponding chloroformates gave cleaner and more rapid reactions in higher yields, as exemplified by compound **11e**, **PD 174424**, which could not be obtained via the activated carbonate.

Results and Discussion

It can be seen from Table 1 that the choice of α-substituent has a minimal effect on the binding affinity of the ligands to the NK_1 receptor. The more sterically demanding isobutyl group (**11c**, **PD 307496**, 3.46 nM), for example, has only 3- to 5-fold lower affinity than the corresponding hydrogen (**12**, 0.73 nM) or methyl substituted derivatives (**1**, 0.55 nM). The compounds with a heteroatom in their α-substituent retain the subnanomolar binding affinities for the NK_1 receptor. Most interestingly, the dimethylaminomethylene group (**11e,** 0.46 nM) exhibited the highest affinity. A comparison of the ethyl (**11a**, **PD 170541**, 0.96 nM) or propyl (**11b**, **PD 207746**, 0.85 nM, 3:2 diastereomeric mixture) substituents with the methoxymethyl (**11d**, **PD 170540**, 0.70 nM) substituent shows that the presence of the heteroatom has no marked effect on the binding of these ligands. However, comparing the sterically similar isobutyl and dimethylaminomethylene substituents, a noticeable difference in binding affinity is observed, **11e** retains (or even increases) affinity for the NK_1 receptor, while its all-carbon analogue, **11c**, is about 8 times less active.

Compounds **1** and **11e** were compared to see if the inclusion of an amine function has any beneficial effect on aqueous solubility. Compound **1** exhibits low aqueous solubility (2 μg/mL), and in a vehicle of PEG 400/ethanol/water (40:15:45) it also exhibits low solubility (0.76 mg/mL). Compound **11e**, however, has the potential to form ammonium salts, and consequently its hydrochloride exhibits superior solubility in both water

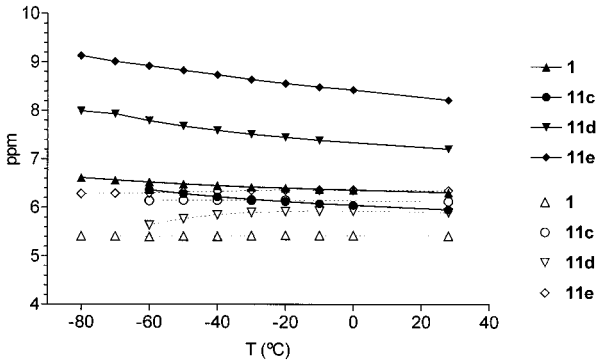


Figure 2. Temperature dependence of the urethane (dashed line) and amide (continuous line) protons in CD_2Cl_2 (8 mg/0.7 mL).

Table 2. Temperature Dependence of the Amide and Urethane Protons in Deutero-dichloromethane

compd	amide H (ppb/K)[a]	urethane H (ppb/K)[a]
1	2.78	−0.09
11c	4.55[b]	0.11[b]
11d	7.22	−2.95[b]
11e	8.43	−0.65

[a] Parts per billion per Kelvin, over the temperature range −80 °C to 28 °C. [b] Parts per billion per Kelvin, over the temperature range −60 °C to 28 °C.

(0.5−0.7 mg/mL) and the PEG 400/ethanol/water vehicle (10 mg/mL).

Recent literature has suggested that the chemical shift of "acidic" protons, when examined by proton nuclear magnetic resonance spectroscopy (NMR), show temperature dependencies if hydrogen bonding occurs in the system.[22] This effect manifests itself as a change in chemical shift of the hydrogen bonding proton, of the hydrogen bond, as the bond is strengthened or weakened by a variation in temperature. A lowering of the temperature is more likely to develop the strength of an inter-/intra-molecular hydrogen bond due to the raising of the energy barriers of rotation.[23] The choice of solvent also has a pivotal role. The use of a hydrogen bonding solvent (e.g., deutero-dimethyl sulfoxide or deutero-methanol) will encourage the formation of a compound−solvent hydrogen bond rather than a compound−compound interaction. Deuterodichloromethane is the solvent of choice for low temperature NMR studies due to its superior physical properties over other solvents (e.g., deutero-chloroform, mp −64.1 °C[24]). A study over a range of temperatures is desired as this allows the calculation of the temperature dependence of the chemical shift in parts per billion per Kelvin (ppb/K). Studies with a tripeptide substrate have indicated that a value in excess of about 5 ppb/K indicates the presence of a geometrically optimal hydrogen bond.[23]

From Figure 2 and the results shown in Table 2, it can be seen that there is a difference in the chemical shifts for the compounds chosen for the low temperature NMR studies. Using **1** as a "benchmark" (compound **12** was insoluble in deuterodichloromethane), it can be seen that the amide proton (∼6.4 ppm) and the urethane proton (∼5.4 ppm) are unaffected by the change in temperature. Likewise, **11c**, the isobutyl analogue, shows little effect with the change in temperature from 28 °C to −60 °C. The urethane protons of **11d** and **11e** are again largely unchanged by the drop in temperature, indicating that none of these hydrogen atoms are involved in hydrogen bonding, either inter- or intramolecularly. However, the amide proton of **11d** (the methoxymethylene compound) shows a large change in chemical shift (0.9 ppm at 28 °C) from that of **1**, and **11e** (the *N*,*N*-dimethylaminomethylene compound) shows an even greater shift (1.9 ppm at 28 °C). Both of these amide protons also exhibit a temperature dependence, as seen in Figure 2, where the chemical shift of the amide proton moves downfield with decreasing temperature (0.78 and 0.91 ppm for **11d** and **11e**, respectively) for the temperature range 28 °C to −80 °C. From Table 2 it can be seen that both of these compounds have large ppb/K values indicating that the amide proton is involved in hydrogen bonding, the large ppb/K values being indicative of the strengthening of the hydrogen bond with decreasing temperature. This hydrogen bond must be to the heteroatom in the α-substituent as the amide hydrogen in the analogous carbon compound **11c** exhibits a very different resonance shift under the same conditions. This suggests that the intramolecular hydrogen bond from the heteroatom to the amide hydrogen, making a six-membered ring, is favored over its five-membered equivalent[25] to the urethane proton, as there is no evidence of temperature dependence for this proton.

An *N*,*N*-dimethylamino group was incorporated onto the α-methyl group of the X-ray crystal structure of **1** and, using the modeling software, an intramolecular hydrogen bond was formed separately to the urethane and amide hydrogens. After minimizing the energy of the system to allow the incorporation of the new moiety, it was found that there was a bias toward the amidic hydrogen bond in both energy (relative $\Delta E = 3.1$ K cal mol^{-1}) and bond lengths (2.1 and 2.4 Å for the urethane and amide hydrogen bonds, respectively). Figure 3 shows the two structures and their respective hydrogen bonds.

Compound **1** has been shown to have a good pharmacokinetic profile; however, for a centrally acting compound its brain penetration is not remarkable, and in fact the compound shows selectivity for the plasma over the brain (brain homogenate-to-plasma ratio is 0.6).[26] This modest ratio is, however, sufficient to exhibit centrally mediated effects when dosed orally. In comparison, **11e** has an increased preference for the brain over plasma (brain homogenate-to-plasma ratio is 6.0, Figure 4). Clearly there is a marked improvement in CNS penetration with these compounds when the *N*,*N*-dimethylamine group is introduced onto the α-carbon of **1**. As we have shown with the NMR studies previously described, we believe that the amide hydrogen is involved in an intramolecular hydrogen bond with the nitrogen atom of the α-substituent. As hypothesized, this hydrogen bond removes one of the hydrogen bond donor moieties and one of the nitrogen acceptor groups. Both of these groups are hydrophilic portions of the molecule, and the hydrogen bond has the effect of making the compound more lipophilic, and thus more able to cross membranes, such as the blood−brain barrier, and hence increase the ratio of brain to plasma.

To further substantiate this hypothesis of the development of an intramolecular hydrogen bonded compound being more brain penetrant, **11e** was compared

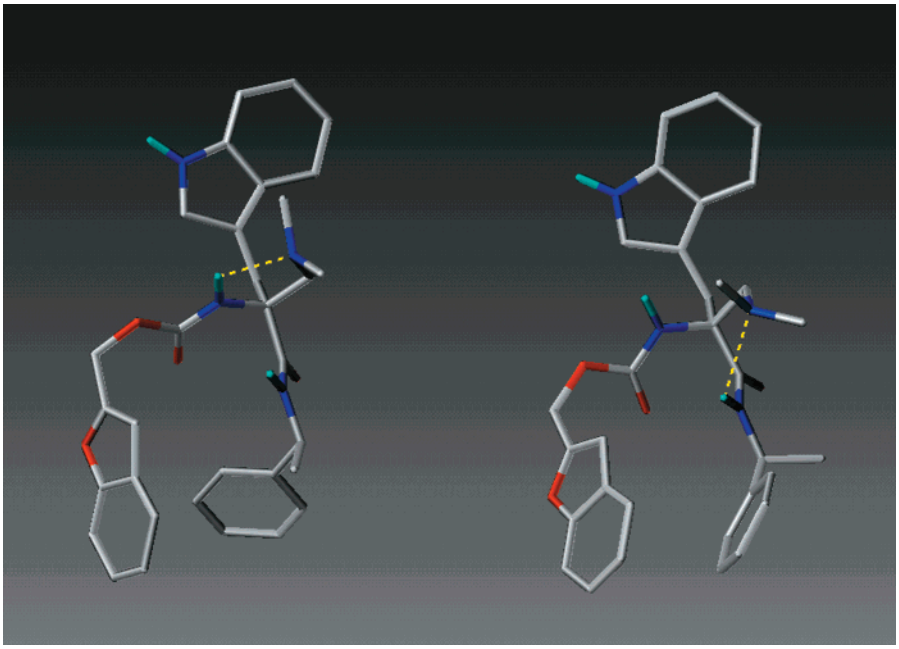


Figure 3. Representation of **11e** with a five-membered hydrogen bonded (yellow line) ring to the urethane (left) and a six-membered hydrogen bonded (yellow line) ring to the amide (right).

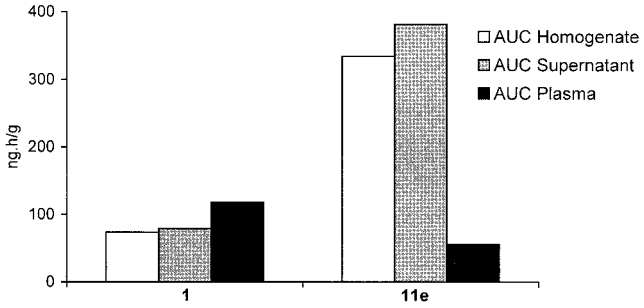


Figure 4. Area under the curve (AUC, 0−1 h) results for compounds **1** and **11e** in rats (n = 2) after a 0.5 mg/kg iv administration.[26]

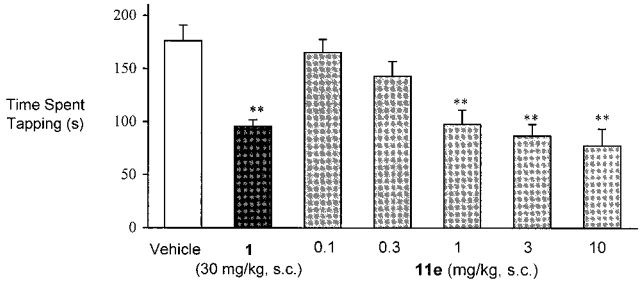


Figure 5. Effect of **11e** on [Sar^9, Met(O$_2$)^{11}]substance P induced foot tapping in the gerbil. Compound **11e** (0.1−10 mg/kg) or vehicle was administered 1 h before and **1** (30 mg/kg) 0.5 h before 30 nmol [Sar^9, Met(O$_2$)^{11}]substance P (icv). The duration of foot tapping was recorded for 5 min immediately following anesthesia. Results are shown as the mean (vertical bars show SEM) of 9−12 animals per group. $^{**}P < 0.01$, significantly different from the vehicle treated control group (one-way ANOVA followed by Dunnett's t-test).

to **1** in the gerbil foot tapping paradigm as a model of CNS activity.[27] Intracerebroventricularly (icv) administered Substance P elicits a centrally mediated hind foot tapping in the gerbil. This effect has been shown to be antagonized by a centrally penetrating compound when administered subcutaneously (sc), but not antagonized by a peripheral selective compound administered via the same route of administration, though the peripheral selective compound can antagonize the effect when administered icv.[27] Compounds **1** and **11e** have very similar in vitro affinities for the gerbil NK$_1$ receptor (IC$_{50}$ = 5.9 and 5.5 nM, respectively) and would be expected to have a similar pharmacological effect.

A duration study showed that **11e** blocked the [Sar^9, Met(O$_2$)^{11}]substance P induced foot tapping response in gerbils at 1 h pretreatment time. Compound **1** was used as a positive control and was administered 0.5 h before [Sar^9, Met(O$_2$)^{11}]substance P. Duration of foot tapping was determined as previously described. [27]

Compound **11e** (0.1−10 mg/kg, sc), administered 1 h before [Sar^9, Met(O$_2$)^{11}]substance P (30 nmol/animal, icv), antagonized the foot tapping response with a minimum effective dose (MED) of 1 mg/kg (Figure 5). This dose produced a magnitude of antagonism similar to that of the 30 mg/kg dose of **1**. We have previously demonstrated that following similar administration, **1** antagonizes the foot tapping response with a MED of 10 mg/kg.[27] Taking into account the MED's and magnitude of antagonism, **11e** appears to be 10−30-fold more potent than **1** in this paradigm.

Conclusions

We have shown that the α-substituent of **1** can be modified without any deleterious effect on the in vitro binding affinity of the compounds for the NK$_1$ receptor and still show selectivity over the other tachykinin receptors (**11e**, hNK$_2$ IC$_{50}$ = 671 nM, hNK$_3$ IC$_{50}$ = IA). We have also shown that when the α-substituent incorporates a heteroatom there is a development of an intramolecular hydrogen bond to the amide hydrogen, resulting in the formation of a six-membered hydrogen bonded ring. The presence of a heteroatom (nitrogen) in **11e** has also been shown to increase the aqueous solubility, via formation of a salt, of this compound in comparison with compound **1**. The presence of an intramolecular hydrogen bond has been substantiated

by the temperature dependence of the amide proton at low temperature in the NMR studies, by the increased brain penetration, and also pharmacologically in the gerbil foot tapping paradigm, where the increase in efficacy is indicative of an increase in the brain penetration.

Experimental Section

General Procedures. Melting points were determined on a Mettler FP80 or a Reichert Thermovar hot-stage apparatus. Proton NMR spectra were recorded on a Varian Unity +400 MHz spectrometer using deuterochloroform as the solvent at 298 K unless otherwise stated; chemical shifts are recorded in ppm downfield from tetramethylsilane. IR spectra are recorded with the compound neat on a sodium chloride disk on a Perkin-Elmer System 2000 Fourier transform spectrophotometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with a Finnigan MAT TSQ70 or Fisons VG trio-2A instrument. Accurate mass spectra were obtained from EPSRC Nation Mass Spectrometry Service Center, Swansea, U.K. Elemental analyses are within ±0.4% of theoretical values and were determined either by Medac Ltd., Uxbridge, UK., or Butterworth, Teddington, U.K. Normal phase silica gel used for chromatography was Merck no. 9385 (230−400 mesh) supplied by E. Merck, A. G. Darmstadt, Germany. Anhydrous solvents were purchased in septum-capped bottles from Fluka Chemicals Ltd., Glossop, U.K.

(*R*)-2-Benzyloxycarbonylamino-3-(1*H*-indol-3-yl)-propionic Acid Allyl Ester (3). A solution of (*R*)-*N*-CBZ-tryptophan (1.00 g, 29.6 mmol), *N*,*N*′-dicyclohexylcarbodiimide (640 mg, 31.1 mmol), *N*,*N*-dimethyl-4-aminopyridine (36 mg, 2.96 mmol), and dichloromethane (10 mL) was stirred for 10 min, and then allyl alcohol (0.22 mL, 32.5 mmol) was added. After 30 min the mixture was filtered and the solvent removed in vacuo. The product was purified by chromatography (33% EtOAc in heptane) to yield a clear oil which solidified on standing. Recrystallization (EtOAc/heptane) gave an amorphous solid (1.00 g, 89%): mp 83−85 °C; δ_H 3.32 (2H, d, IndCH_2, J = 5.2 Hz), 4.56 (2H, bs, CH_2O), 4.74 (1H, dt, α-H, J = 7.8, 7.8 Hz), 5.11 (2H, m, CH_2O), 5.20−5.32 (3H, m, NH, =CH_2), 5.82 (1H, m, CH), 6.96 (1H, d, arom, J = 2.0 Hz), 7.08 (1H, t, arom, J = 7.4 Hz), 7.18 (1H, d, arom, J = 7.2 Hz), 7.34 (6H, m, arom), 7.52 (1H, d, arom, J = 8.0 Hz), 8.04 (1H, bs, NH); ν_{max} 3410, 3361, 3060, 1713, 1512, 1205, 743 cm^{-1}; *m*/*z* 378 (MH$^+$, 18%), 130 (100%); $[\alpha]_D^{20}$ +14.5° (*c* = 0.75, MeOH). Anal. ($C_{22}H_{22}N_2O_4$) C, H, N.

(2*r*,3a*S*,8a*S*)-3,3a,8,8a-Tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1,2-dicarboxylic Acid 2-Allyl Ester 1-Benzyl Ester (4). Compound **3** (17.25 g, 45.6 mmol) was dissolved in trifluoroacetic acid (100 mL) and stirred at room temperature for 3 h. The mixture was concentrated (∼50 mL) in vacuo, and then added dropwise to a well-stirred mixture of $NaHCO_3$ (15%, 1 L) and dichloromethane (500 mL). [19] After the addition, the organics were washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The product was purified by chromatography (20−50% Et_2O in heptane) to yield a clear oil (8.90 g, 52%): δ_H this compound exhibited rotamers, hence the broad signals 2.64 (2H, m, CH_2), 3.83−4.25 (3H, m, CH, CH_2O), 4.58 (0.5H, dd, a−H, J = 1.9, 8.3 Hz), 4.68 (0.5H, m, α-H), 4.75 (0.5H, bs, 0.5 NH), 5.05−5.26 (4.5H, m, CH_2O, =CH_2, 0.5 NH), 5.50 (1H, m, CH=), 5.60 (1H, t, CH, J = 6.4 Hz), 6.58 (1H, m, arom), 6.67 (1H, m, arom), 7.01 (2H, m, arom), 7.28−7.40 (4H, m, arom), 7.41 (1H, m, arom); ν_{max} 3400, 1702, 1416, 747 cm^{-1}; *m*/*z* 378 (MH$^+$, 90%), 130 (100%); $[\alpha]_D^{20}$ −144.9° (*c* = 1.62, MeOH). Anal. ($C_{22}H_{22}N_2O_4$) C, H, N.

(2*R*,3a*S*,8a*R*)-3,3a,8,8a-Tetrahydro-2*H*-pyrrolo[2,3-*b*]-indole-1,2-dicarboxylic Acid 2-Allyl Ester 1-Dibenzyl Ester (5). [20]Benzyl chloroformate (8.01 g, 47.0 mmol, 6.7 mL) was added to a stirred mixture of amine 4 (8.90 g, 23.5 mmol), Na_2CO_3·10H_2O (13.43 g, 47.0 mmol), 1,4-dioxan (100 mL), and water (10 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed in vacuo, the product was extracted into EtOAc, and the organics were washed with water, 10% HCl, and brine and dried ($MgSO_4$). The product was purified by chromatography (25% EtOAc in heptane) to give a clear oil (10.39 g, 86%): δ_H 2.55 (1H, m, CH_2), 2.65 (1H, d, C*H*H, J = 13.2 Hz), 3.85 (1H, dd, OCH*H*, J = 5.2, 13.2 Hz), 4.01 (1H, t, CH, J = 7.0 Hz), 4.12 (1H, m, OC*H*H), 4.69 (1H, t, α-H, J = 8.0 Hz), 4.80−5.24 (6H, m, 2 × CH_2O, =CH_2), 5.50 (1H, m, CH=), 6.51 (1H, d, CH, J = 6.0 Hz), 6.98 (1H, t, arom, J = 7.4 Hz), 7.10 (1H, m, arom), 7.19 (1H, t, arom, J = 7.6 Hz), 7.27−7.38 (10H, m, arom), 7.63 (1H, bs, arom); ν_{max} 3065, 3033, 1716, 1483, 1416, 1266, 1173, 753 cm^{-1}; *m*/*z* 513 (MH$^+$, 100); $[\alpha]_D^{20}$ +2.6° (*c* = 0.11, MeOH).

(2*R*,3a*S*,8a*R*)-2-Propyl-2,3,3a,8a-tetrahydro-pyrrolo-[2,3-*b*]indole-1,2,8-tricarboxylic Acid 2-Allyl Ester 1,8-Dibenzyl Ester (6a). LHMDS (7.81 mL, 7.81 mmol, 1 M in THF) was added to a solution of compound **5** (2.00 g, 3.91 mmol) and DMPU (0.47 mL, 3.91 mmol) in THF (30 mL) at −78 °C under dry N_2. After 2 h at this temperature, iodoethane (1.22 g, 7.81 mmol) was added, and the mixture allowed to warm to room temperature overnight.[19] The solvent was removed in vacuo, and the product was extracted into EtOAc, washed with 10% HCl and brine, and dried ($MgSO_4$). Purification was achieved by chromatography (15−20 EtOAc in heptane) to leave a clear oil (1.66 g, 79%): δ_H 0.81 (3H, t, CH_2CH_3, J = 7.4 Hz), 1.88 (1H, m, CH*H*CH_3), 2.32 (1H, bs, C*H*HCH_3), 2.46 (1H, dd, IndCH*H*, J = 7.4, 13.6 Hz), 2.62 (1H, d, IndC*H*H, J = 13.6 Hz), 3.63 (1H, dd, CH*H*O, J = 5.2, 13.6 Hz), 3.87 (1H, t, CH, J = 6.8 Hz), 4.09 (1H, dd, CH*H*O, J = 5.6, 13.2 Hz), 5.08 (6H, m, 2 × CH_2O, =CH_2), 5.39 (1H, m, =CH), 6.43 (1H, d, CH, J = 6.0 Hz), 6.99 (1H, t, arom, J = 7.4 Hz), 7.07 (1H, d, arom, J = 7.6 Hz), 7.18 (1H, t, arom, J = 7.6 Hz), 7.27−7.37 (10H, m, arom), 7.55 (1H, d, arom, J = 7.2 Hz); ν_{max} 1716, 1482, 1410, 1267, 750 cm^{-1}; HRMS for $C_{32}H_{33}N_2O_6$ requires 541.234, found 541.234 (MH$^+$, 100%); $[\alpha]_D^{20}$ + 13.5° (*c* = 0.80, MeOH).

(2*R*,3a*S*,8a*R*)-2-Allyl-2-but-3-enoyl-2,3,3a,8a-tetrahydro-pyrrolo[2,3-*b*]indole-1,8-dicarboxylic Acid Dibenzyl Ester (6b). Procedure as for the preparation of compound **6a** to give an oil (0.55 g, 26%): δ_H 2.50−2.63 (3H, m, C*H*HC=C, CH_2), 3.10−3.25 (1H, m, CH*H*C=C), 3.66 (1H, dd, CH*H*O, J = 5.5, 13.3 Hz), 3.85 (1H, t, J = 6.3 Hz, C*H*), 4.12 (1H, dd, C*H*HO, J = 7.1, 14.2 Hz), 4.99−5.27 (8H, m, 2 × =CH_2, 2 × CH_2O), 5.36−5.46 (1H, m, =CH), 5.55−5.66 (1H, m, =CH), 6.38 (1H, d, CH, J = 6.3 Hz), 6.99 (1H, t, J = 7.3 Hz, arom), 7.07 (1H, d, arom, J = 7.3 Hz), 7.18 (1H, t, arom, J = 7.7 Hz), 7.28−7.38 (10H, m, arom), 7.55 (1H, bd, arom, J = 6.8 Hz); ν_{max} 1714, 1409, 1273, 750 cm^{-1}; MS (ES$^+$) 576.16 (MH$^+$ + Na, 100%), 553.26 (M$^+$ + H, 99%).

(2*S*,3a*S*,8a*R*)-2-(2-Methyl-allyl)-2,3,3a,8a-tetrahydro-pyrrolo[2,3-*b*]indole-1,2,8-tricarboxylic Acid 2-Allyl Ester 1,8-Dibenzyl Ester (6c). Procedure as for the preparation of compound **6a** to give an oil (0.46 g, 21%): δ_H 1.65 (3H, s, CH_3), 2.50−2.56 (2H, m, C*H*HC=C, C*H*Hind), 2.76 (1H, dd, CH*H*ind, J = 7.8, 13.9 Hz), 3.2−3.3 (1H, m, CH*H*C=C), 3.62−3.68 (1H, m, CH*H*O), 3.85 (1H, t, J = 6.8 Hz, C*H*), 4.13 (1H, dd, C*H*HO, J = 5.3, 12.8 Hz), 4.76−5.23 (8H, m, 2 × =CH_2, 2 × CH_2O), 5.33−5.43 (1H, m, =CH), 6.43 (1H, d, CH, J = 6.3 Hz), 7.00 (1H, t, J = 7.4 Hz, arom), 7.07 (1H, d, arom, J = 7.3 Hz), 7.18 (1H, t, arom, J = 7.7 Hz), 7.23−7.35 (10H, m, arom), 7.57 (1H, d, arom, J = 7.1 Hz); ν_{max} 2950, 1717, 1482, 1410, 1333, 1269, 750 cm^{-1}; MS (ES$^+$) 589 (M$^+$ + Na, 100%), 567 (M$^+$ + H, 99%).

(2*S*,3a*S*,8a*R*)-2-Methoxymethyl-2,3,3a,8a-tetrahydro-pyrrolo[2,3-*b*]indole-1,2,8-tricarboxylic Acid 2-Allyl Ester 1,8-Dibenzyl Ester (6d). Procedure as for the preparation of compound **6a** to give a clear oil (1.66 g, 76%): δ_H 2.52 (1H, dd, CH*H*, J = 1.2, 13.2 Hz), 2.82 (1H, dd, C*H*H, J = 8.0, 13.6 Hz), 3.26 (3H, s, OCH_3), 3.58 (1H, d, CH*H*O, J = 7.6 Hz), 3.78 (1H, dddd, OC*H*H, J = 1.6, 1.6, 5.6, 13.2 Hz), 3.90 (1H, t, CH, J = 7.0 Hz), 4.06 (1H, bs, C*H*HO), 4.17 (1H, dd, OCH*H*, J = 5.6, 13.2 Hz), 4.96−5.16 (6H, m, 2 × CH_2O, =CH_2), 5.38 (1H, m, =CH), 6.44 (1H, d, CH, J = 6.0 Hz), 6.99 (1H, m, arom), 7.08 (1H, d, arom, J = 7.2 Hz), 7.19 (1H, t, arom, J = 7.6 Hz),

7.25−7.34 (10H, m, arom), 7.59 (1H, d, arom, J = 8.0 Hz); ν_{max} 1717, 1483, 1412, 1335, 1274, 751 cm^{-1}; m/z 557 (MH$^+$, 100%); $[\alpha]_D^{20}$ +9.6° (c = 0.75, MeOH). Anal. ($C_{32}H_{32}N_2O_7$) C, H, N.

(2*S*,3a*S*,8a*R*)-2-Dimethylaminomethyl-2,3,3a,8a-tetrahydro-pyrrolo[2,3-*b*]indole-1,2,8-tricarboxylic Acid 2-Allyl Ester 1,8-Dibenzyl Ester (6e). Procedure as for the preparation of compound **6a** to give a clear oil (1.90, 76%): δ_H 2.23 (6H, s, 2 × CH_3), 2.40 (1H, d, IndCH*H*, J = 13.2 Hz), 2.66 (1H, d, CH*H*N, J = 14.4 Hz); 3.00 (1H, dd, IndC*H*H, J = 8.2, 13.4 Hz), 3.29 (1H, bs, C*H*HN), 3.69 (1H, dddd, OCH*H*, J = 1.6, 2.9, 5.8, 13.3 Hz), 3.94 (1H, t, CH, J = 7.0 Hz), 4.11 (1H, bs, CH*H*N), 4.93−5.33 (7H, m, 2 × CH_2O, =CH, =CH_2), 6.40 (1H, d, CH, J = 6.4 Hz), 6.99 (1H, t, arom, J = 7.4 Hz), 7.06 (1H, d, arom, J = 7.6 Hz), 7.18 (1H, t, arom, J = 7.6 Hz), 7.26−7.37 (10H, m, arom), 7.58 (1H, bs, arom); ν_{max} 2947, 1717, 1483, 1412, 1331, 1267, 1043, 1020, 750 cm^{-1}; HRMS for $C_{33}H_{36}N_3O_6$ requires 570.2604, found 570.260$_4$ (MH$^+$, 100%); $[\alpha]_D^{19}$ −0.4° (c = 0.49, MeOH).

3-((*R*)-2-Allyloxycarbonyl-2-benzyloxycarbonylamino-butyl)-indole-1-carboxylic Acid Benzyl Ester (7a). TFA (2 mL) was added to a solution of compound **6a** (1.66 g, 3.07 mmol) in dichloromethane (10 mL), and the resulting solution was stirred at room temperature for 24 h. The solvent was removed, and the residue was diluted with EtOAc, the organics were washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The product was purified by chromatography (15% EtOAc in heptane) to yield a clear gum (1.14 g, 69%): δ_H 0.82 (3H, t, CH_2CH_3, J = 7.4 Hz), 1.99, 2.60 (2H, 2 × m, CH_2CH_3), 3.23 (1H, d, IndCH*H*, J = 10.4 Hz), 3.74 (2H, d, IndC*H*H, J = 10.4 Hz), 4.46 (1H, d, OCH*H*, J = 6.0 Hz), 4.57 (1H, d, C*H*HO, J = 12.8 Hz), 5.09 (2H, dd, CH_2O, J = 12.4, 18.4 Hz), 5.21 (1H, d, =CH*H*, J = 14.4 Hz), 5.30 (1H, d, =C*H*H, J = 10.4 Hz), 5.41 (2H, dd, CH*H*O, J = 12.4, 16.8 Hz), 5.74 (1H, s, NH), 5.80 (1H, m, =CH), 7.11 (1H, t, arom, J = 7.6 Hz), 7.25−7.47 (13H**,** m, arom), 8.17 (1H, bd, arom, J = 5.6 Hz); ν_{max} 3419, 1736, 1500, 14456, 1399, 1250, 1085 cm^{-1}; HRMS for $C_{32}H_{33}N_2O_6$ requires 541.234, found 541.234 (MH$^+$, 100%); $[\alpha]_D^{20}$ +8.1° (c = 0.57, MeOH).

3-((*R*)-2-Allyloxycarbonyl-2-benzyloxycarbonylamino-pent-4-enyl)-indole-1-carboxylic Acid Benzyl Ester (7b). Procedure as for the preparation of compound **7a** to give an oil (0.48 g, 92%): δ_H 2.66−2.72 (1H, m, C*H*HC=), 3.26 (1H, d, C*H*Hind, J = 14.4 Hz), 3.27−3.35 (1H, m, CH*H*C=), 3.77 (1H, d, CH*H*ind, J = 14.4 Hz), 4.43−4.48 (1H, m, OCH*H*), 4.55 (1H, dd, *OCH*H, J = 5.7, 13.1 Hz), 5.03−5.12 (4H, m, OCH_2, =CH_2), 5.20 (1H, d, =CH, J = 10.3 Hz), 5.29 (1H, d, =C*H*H, J = 17.1 Hz), 5.37−45 (2H, m, CH_2Ph), 5.57−5.67 (1H, m, =CH), 5.72 (1H, s, NH), 7.12 (1H, t, arom, J = 7.6 Hz) 7.26−7.48 (13H, m, arom), 8.12 (1H, bd, arom, J = 4.9 Hz); ν_{max} 3416, 1736, 1455, 1249, 1083, 748 cm^{-1}; MS (ES$^+$) 575.29 (M$^+$ + Na, 63%), 553.32 (M$^+$ + H, 100%).

3-((*R*)-2-Allyloxycarbonyl-2-benzyloxycarbonylamino-4-methyl-pent-4-enyl)-indole-1-carboxylic Acid Benzyl Ester (7c). Procedure as for the preparation of compound **7a** to give an oil (0.33 g, 79%): δ_H 1.63 (3H, s, CH_3), 2.70 (1H, d, C*H*HC=C, J = 13.9 Hz), 3.23 (1H, d, C*H*Hind, J = 14.4 Hz), 3.41 (1H, d, CH*H*C=C, J = 13.8 Hz), 3.87 (1H, d, CH*H*ind, J = 14.4 Hz), 4.41−4.53 (2H, m, OCH_2), 4.70 (1H, s, C*H*H=C), 4.80 (1H, s, CH*H*=C), 5.02 (1H, d, C*H*HPh, J = 12.2 Hz), 5.11 (1H, d, CH*H*Ph, J = 12.2 Hz), 5.30 (1H, d, =C*H*H, J = 17.7 Hz), 5.41 (2H, dd, CH_2Ph, J = 12.2, 15.9 Hz), 5.78−5.86 (2H, m, NH, =CH), 7.12 (1H, t, arom, J = 7.4 Hz) 7.25−7.49 (13H, m, arom), 8.13 (1H, bs, arom); ν_{max} 3418, 2946, 1722, 1498, 1455, 1398, 1358, 1249, 1083, 1048, 747 cm^{-1}; MS (ES$^+$) 589 (M$^+$ + Na, 100%), 567 (M$^+$ + H, 43%).

3-((*S*)-2-Allyloxycarbonyl-2-benzyloxycarbonylamino-3-methoxy-propyl)-indole-1-carboxylic Acid Benzyl Ester (7d). Procedure as for the preparation of compound **6a** to give a clear oil (1.19 g, 72%): δ_H 3.32 (3H, s, OCH_3), 3.24 (1H, d, IndCH*H*, J = 14.4 Hz), 3.60 (1H, d, IndC*H*H, J = 14.4 Hz), 3.77 (1H, d, CH*H*O, J = 9.2 Hz), 4.13 (1H, d, C*H*HO, J = 9.2 Hz), 4.49 (1H, dd, OCH*H*, J = 4.8, 12.8 Hz), 4.61 (1H, dd, OC*H*H, J = 5.2, 12.8 Hz), 5.09 (2H, s, CH_2O), 5.11 (1H, d, =CH*H*, J = 10.8 Hz), 5.28 (1H, d, =C*H*H, J = 17.2 Hz), 5.41 (2H, dd, CH_2O, J = 12.0, 14.8 Hz), 5.75 (2H, m, =CH, NH), 7.14 (1H, t, arom, J = 8.0 Hz), 7.28−7.47 (13H, m, arom), 8.15 (1H, bd, arom, J = 6.4 Hz); ν_{max} 3418, 3352, 1736, 1501, 1456, 1399, 1250, 1087, 749 cm^{-1}; m/z 557 (MH$^+$, 100%); $[\alpha]_D^{20}$ +13.0° (c = 0.67, MeOH).

3-((*S*)-Allyloxycarbonyl-benzyloxycarbonylamino-(dimethylamino)-propyl)-indole-1-carboxylic Acid Benzyl Ester (7e). A solution of compound **6** (5.82 g, 10.2 mmol) in methanol (20 mL) was treated with a mixture of cH_2SO_4/H_2O (23/18 mL), and the resultant mixture was stirred at room temperature for 24 h. This solution was added dropwise to a mixture of saturated $NaHCO_3$ and ice, the product was extracted with EtOAc, and the organics were washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The material was purified by chromatography (10−25% EtOAc in heptane) to give a straw colored gum (3.46 g, 59%): δ_H 2.26 (6H, s, 2 × CH_3), 2.83 (1H, d, CH*H*N, J = 13.6 Hz), 3.23 (1H, d, IndCH*H*, J = 14.4 Hz), 3.32 (1H, d, C*H*HN, J = 13.6 Hz), 3.64 (1H, dd, IndC*H*H, J = 14.4 Hz), 4.49 (1H, d, CH*H*O, J = 13.2 Hz), 4.59 (1H, d, C*H*HO, J = 6.0 Hz), 5.08 (2H, dd, CH_2O, J = 12.4, 27.6 Hz), 5.23 (1H, d, =CH*H*, J = 10.4 Hz), 5.34 (1H, d, =C*H*H, J = 14.4 Hz), 5.41 (2H, s, CH_2O), 5.85 (1H, m, =CH), 6.00 (1H, s, NH), 7.14 (2H, m, arom), 7.25−7.48 (12 H, m, arom), 8.15 (1H, bd, arom, J = 6.4 Hz); ν_{max} 3418, 1736, 1456, 1248, 1084, 1037, 748 cm^{-1}; m/z 570 (MH$^+$, 100%); $[\alpha]_D^{19}$ −12.6° (c = 0.27, MeOH).

3-((*R*)-2-Benzyloxycarbonylamino-2-carboxy-butyl)-indole-1-carboxylic Acid Benzyl Ester (8a). Tetrakis(triphenylphosphine)palladium (0) (50 mg, 43 μmol) was added to a solution of compound **7a** (1.14 g, 2.11 mmol) in THF (10 mL). After 5 min, morpholine (1.84 g, 21.1 mmol) was added, and the mixture stirred at room temperature for 30 min. EtOAc was added, and the organics were washed with 10% HCl and brine and dried ($MgSO_4$). After removal of the solvent in vacuo, a clear glass was obtained (1.01 g, 95%): δ_H 0.86 (3H, t, CH_2CH_3, J = 7.6 Hz), 1.99 (1H, m, CH*H*CH_3), 2.51 (1H, m, C*H*HCH_3), 3.30 (1H, d, IndCH*H*, J = 14.9 Hz), 3.71 (1H, d, IndC*H*H, J = 14.4 Hz), 5.07 (2H, dd, CH_2O, J = 12.4, 19.2 Hz), 5.40 (2H, s, CH_2O), 5.60 (1H, s, NH), 7.10 (1H, t, arom, J = 7.4 Hz), 7.24−7.52 (13H, m, arom), 8.10 (1H, bs, arom); ν_{max} 3409, 1732, 1455, 1400, 1250, 1086, 745 cm^{-1}; HRMS for $C_{29}H_{29}N_2O_6$ requires 501.2026, found 501.2026 (MH$^+$).

3-((*R*)-2-Benzyloxycarbonylamino-2-carboxy-pent-4-enyl)-indole-1-carboxylic Acid Benzyl Ester (8b). Procedure as for the preparation of compound **8a** to give a solid (0.44 g, 98%): δ_H 2.67−2.73 (1H, m, C*H*HCH=), 3.20−3.26 (1H, m, CH*H*CH=), 3.32 (1H, d, CH*H*Ind, J = 14.7 Hz), 3.73 (1H, d, CH*H*ind, J = 14.4 Hz), 5.03−5.12 (4H, m, 2 × OCH_2, 2 × =CH_2), 5.39 (2H, s, OCH_2Ph), 5.61−5.68 (2H, s, NH, CH=), 7.10 (1H, t, arom, J = 7.6 Hz), 7.23−7.65 (13H, m, arom), 8.11 (1H, br s, arom); ν_{max} 3405, 1731, 1455, 1399, 1249, 1084, 747 cm^{-1}; MS (ES$^-$) 511 (M$^-$ − H, 100%).

3-((*R*)-2-Benzyloxycarbonylamino-2-carboxy-4-methyl-pent-4-enyl)-indole-1-carboxylic Acid Benzyl Ester (8c). Procedure as for the preparation of compound **8a** to give a solid (0.28 g, quantitative): δ_H 1.65 (3H, s, CH_3), 2.71 (1H, d, C*H*HCH=, J = 13.7 Hz), 3.27 (1H, d, C*H*Hind, J = 14.9 Hz), 3.35 (1H, d, CH*H*C=, J = 13.9 Hz), 3.84 (1H, d, CH*H*ind, J = 14.9 Hz), 4.74 (1H, s, C=C*H*H), 4.80 (1H, s, C=CH*H*), 5.02 (1H, d, OC*H*HPh, J = 12.2 Hz), 5.11 (1H, d, OCH*H*Ph, J = 12.5 Hz), 5.39 (2H, s, OCH_2Ph), 5.79 (1H, s, NH), 7.09 (1H, t, arom, J = 7.3 Hz), 7.23−7.65 (13H, m, arom), 8.11 (1H, br s, arom); ν_{max} 3408, 3033, 2948, 1731, 1500, 1455, 1399, 1358, 1248, 1083, 747 cm^{-1}; MS (ES$^-$) 526 (M$^-$, 33%), 525 (M$^-$ − H, 100%).

3-((*S*)-2-Benzyloxycarbonylamino-2-carboxy-3-methoxy-propyl)-indole-1-carboxylic Acid Benzyl Ester (8d). Procedure as for the preparation of **8a** to give a clear glass (1.11 g, 100%): δ_H 3.33 (1H, d, IndCH*H*, J = 14.7 Hz), 3.37 (3H, s, OCH_3), 3.60 (1H, d, IndC*H*H, J = 14.4 Hz), 3.84 (1H, d, CH*H*O, J = 9.3 Hz), 3.99 (1H, d, C*H*HO, J = 8.8 Hz), 5.09 (2H, s, CH_2O), 5.40 (2H, s, CH_2O), 5.71 (1H, s, NH), 7.14 (1H, t, arom, J = 7.6 Hz), 7.27−7.52 (13H, m, arom), 8.18 (1H, dd, arom, J = 6.8 Hz); ν_{max} 3411, 1732, 1456, 1399, 1250, 1086, 748 cm^{-1}.

3-((*S*)-Benzyloxycarbonylamino-carboxy-(dimethylamino)-propyl)-indole-1-carboxylic Acid Benzyl Ester (8e). Procedure as for the preparation of compound **8a** to give a straw colored foam (690 mg, quant.): δ_H 2.55 (6H, bs, N(CH_3)$_2$), 2.60 (2H, bs, CH_2N), 3.20, 3.46 (2H, dd, CH_2Ind, J = 14.0 Hz), 4.90 (2H, d, CH_2O, J = 12.0, 58.4 Hz), 5.36 (2H, dd, CH_2O, J = 12.4, 26.0 Hz), 6.45 (1H, s, NH), 7.08 (1H, bs, arom), 7.18−7.70 (13H, m, arom), 8.10 (1H, bs, arom); ν_{max} 3373, 1731, 1633, 1485, 1456, 1401, 1358, 1249, 1085, 748 cm^{-1}; HRMS for $C_{30}H_{32}N_3O_6$ requires 530.229, found 530.229 (MH$^+$).

3-[(*R*)-2-Benzyloxycarbonylamino-2-((*S*)-1-phenyl-ethylcarbamoyl)-butyl]-indole-1-carboxylic Acid Benzyl Ester (9a). A mixture of compound **8a** (1.01 g, 2.02 mmol), HBTU (766 mg, 2.02 mmol), and DIPEA (0.70 mL, 2.02 mmol) in DMF (10 mL) was stirred at room temperature for 10 min. Then (*S*)-methylbenzylamine (244 mg, 2.02 mmol) and DIPEA (0.70 mL, 2.02 mmol) were added, and the resulting solution was stirred for 8 h. The solvent was removed, and the product was extracted into EtOAc, washed with 10% HCl, 10% K_2CO_3, and brine, and dried ($MgSO_4$). Purification by chromatography gave a clear glass which was recrystallized (EtOAc/heptane) to yield white crystals (980 mg, 80%): δ_H 0.77 (3H, t, CH_2CH_3, J = 7.4 Hz), 1.26 (3H, d, $CHCH_3$, J = 6.8 Hz), 1.74 (1H, m, $CHHCH_3$), 2.40 (1H, m, $CHHCH_3$), 3.31 (1H, d, IndCHH, J = 14.9 Hz), 3.54 (1H, d, IndCHH, J = 14.9 Hz), 4.99 (1H, dq, $CHCH_3$, J = 7.0, 8.5 Hz), 5.04 (2H, dd, $PhCH_2O$, J = 13.0, 27.2 Hz), 5.42 (2H, s, CH_2O), 5.83 (1H, bs, NH), 6.01 (1H, d, NH, J = 7.6 Hz), 7.17−7.55 (19H, m, arom), 8.15 (1H, d, arom, J = 6.4 Hz); ν_{max} 3346, 1728, 1644, 1485, 1455, 1399, 1249, 1079, 747 cm^{-1}; m/z 604.4 (MH$^+$, 100%); $[\alpha]_D^{20}$ −38.1° (c = 0.48, MeOH). Anal. ($C_{37}H_{37}N_3O_5$) C, H, N.

3-[(*R*)-2-Benzyloxycarbonylamino-2-((*S*)-1-phenyl-ethylcarbamoyl)-pent-4-enyl]-indole-1-carboxylic Acid Benzyl Ester (9b). Procedure as for the preparation of compound **9a** to give a white solid (295 mg, 61%): δ_H 1.30 (3H, d, $CHCH_3$, J = 6.8 Hz), 2.65−2.89 (2H, m, CH_2CH═), 3.37−3.50 (2H, m, CH_2Ind), 4.97−5.10 (5H, m, ═CH_2, CH_2O, $CHCH_3$), 5.38−5.45 (2H, m, OCH_2), 5.59−5.68 (2H, m, NHZ, CH═), 6.25 (1H, d, NHCO, J = 7.1 Hz), 6.29 (1H, m, NH), 7.13−7.55 (19H, m, arom), 8.16 (1H, bs, arom); ν_{max} 3335, 1727, 1643, 1484, 1455, 1398, 1249, 1083, 747 cm^{-1}; MS (ES$^-$) 615 (M$^-$, 50%), 614 (M$^-$ − H, 100%); 2:1 mixture of diastereomers.

3-[(*R*)-2-Benzyloxycarbonylamino-4-methyl-2-((*S*)-1-phenyl-ethylcarbamoyl)-pent-4-enyl]-indole-1-carboxylic Acid Benzyl Ester (9c). Procedure as for the preparation of compound **9a** to give a white solid (0.24 g 74%): δ_H 1.27 (3H, d, $CHCH_3$, J = 6.8 Hz), 1.59 (3H, s, ═CCH_3), 2.61 (1H, d, $CHHC$═, J = 14.2 Hz), 2.95−3.01 (1H, m, $CHHC$═), 3.32−3.60 (2H, m, CH_2Ind), 4.56−4.77 (2H, 2 × s, ═CH_2), 4.90−5.12 (3H, m, OCH_2, $CHCH_3$), 5.42 (2H, s, OCH_2), 5.82 (1H, s, NHZ), 6.21 (1H, d, NHCO, J = 7.1 Hz), 7.08−7.56 (19H, m, arom), 8.16 (1H, bs, arom); ν_{max} 3355, 1727, 1640, 1484, 1455, 1398, 1358, 1249, 1078, 746 cm^{-1}; MS (ES$^-$) 629 (M$^-$, 42%), 628 (M$^-$ − H,100%).

3-[(*S*)-2-Benzyloxycarbonylamino-3-methoxy-2-((*S*)-1-phenyl-ethylcarbamoyl)-propyl]-indole-1-carboxylic Acid Benzyl Ester (9d). Procedure as for the preparation of compound **8a** to give a clear glass (1.04 g, 78%): δ_H 1.37 (3H, d, $CHCH_3$, J = 6.8 Hz), 3.35 (3H, s, OCH_3), 3.39 (1H, d, IndCHH, J = 15.2 Hz), 3.47 (1H, d, $CHHO$, J = 9.2 Hz), 3.66 (1H, d, IndCHH, J = 14.4 Hz), 4.16 (1H, d, $CHHO$, J = 8.0 Hz), 4.98 (1H, m, $CHCH_3$), 5.03 (2H, bs, CH_2O), 5.40 (2H, bs, CH_2O), 6.02 (1H, bs, NH), 7.14−7.53 (20 H, m, arom, NH), 8.14 (1H, bs, arom); ν_{max} 3350, 1732, 1653, 1488, 1455, 1398, 1249, 1084, 748 cm^{-1}; m/z 620 (MH$^+$, 100%); $[\alpha]_D^{20}$ −21.7° (c = 0.53, MeOH). Anal. ($C_{37}H_{37}N_3O_6$) C, H, N.

3-[(*S*)-Benzyloxycarbonylamino-(dimethylamino)-((*S*)-1-phenyl-ethylcarbamoyl)-propyl]-indole-1-carboxylic Acid Benzyl Ester (9e). Procedure as for the preparation of compound **8a** to afford white crystals (EtOAc/heptane) (150 mg, 34%): mp 102−107 °C; δ_H 1.38 (3H, d, $CHCH_3$, J = 6.8 Hz), 2.14 (6H, s, 2 × CH_3), 2.43 (1H, d, $CHHN$, J = 14.4 Hz), 3.35 (1H, d, $CHHN$, J = 14.4 Hz), 3.38 (1H, d, IndCHH, J = 15.2 Hz), 3.63 (1H, d, IndCHH, J = 15.2 Hz), 4.98 (1H, dq, $CHCH_3$, J = 7.2, 7.2 Hz), 5.02 (2H, dd, CH_2O, J = 12.4, 28.8 Hz), 5.40 (2H, s, CH_2O), 6.40 (1H, s, NH), 7.15−7.55 (19H, m, arom, NH), 8.16 (H, s, arom), 8.28 (1H, s, arom); ν_{max} 3373, 1732, 1666, 1486, 1250, 1077, 747 cm^{-1}; m/z 633 (MH$^+$, 100%), 486 (37%); $[\alpha]_D^{20}$ −34.6° (c = 0.36, MeOH). Anal. ($C_{38}H_{40}N_4O_5$) C, H, N.

(*R*)-2-Amino-2-(1*H*-indol-3-ylmethyl)-*N*-((*S*)-1-phenyl-ethyl)-butyramide (10a). A mixture of compound **9a** (980 mg, 1.63 mmol), 10% palladium hydroxide on carbon, and methanol (20 mL) was hydrogenated at 50 psi at 30 °C. After 90 min, the mixture was filtered through Kieselguhr, and upon removal of the solvent in vacuo a clear glass was obtained (503 mg, 92%): δ_H 0.97 (3H, t, CH_2CH_3, J = 7.4 Hz), 1.42 (3H, d, $CHCH_3$, J = 6.8 Hz), 1.55 (3H, m, $CHHCH_3$, NH_2), 2.10 (1H, m, $CHHCH_3$), 2.78 (1H, d, IndCHH, J = 14.0 Hz), 3.46 (1H, d, IndCHH, J = 14.0 Hz), 5.06 (1H, dq, $CHCH_3$, J = 7.2, 7.2 Hz), 6.71 (1H, bs, NH), 7.07−7.35 (8H, m, arom), 7.60 (1H, d, arom, J = 19.6 Hz), 7.80 (1H, d, arom, J = 7.6 Hz), 7.86 (2H, bs, NH); ν_{max} 3294, 1644, 1512, 1456, 743 cm^{-1}; HRMS for $C_{21}H_{26}N_3O_1$ requires 336.2076, found 336.2076 (MH$^+$).

(*R*)-2-Amino-2-(1*H*-indol-3-ylmethyl)-pent-4-enoic Acid ((*S*)-1-phenyl-ethyl)-amide (10b). Procedure as for the preparation of compound **10a** to give a white solid (100 mg 65%): δ_H 0.93 (3H, d, CH_3, J = 7.2 Hz), 1.13−1.54 (5H, m, 3 × CH, NH_2), 1.42 (3H, d, CH_3, J = 6.8 Hz), 2.76 (1H, d, CHHInd, J = 14.2 Hz), 3.48 (1H, d, CHHInd, J = 14.2 Hz), 5.01−5.09 (1H, m, $CHCH_3$), 6.69 (1H, d, NH, J2.0 Hz), 7.04−7.37 (8H, m, arom, NH), 7.59 (1H, d, arom, J = 8.1 Hz), 7.80−7.82 (1H, m, arom), 8.02 (1H, s, NH); ν_{max} 3296, 1644, 1510, 1455, 742 cm^{-1}; MS (ES$^+$) 699 (2M + H$^+$, 100%), 372 (M$^+$ + Na), 350 (MH$^+$); 2:1 mixture of diastereomers only peaks for major diastereomer shown.

(*R*)-2-Amino-2-(1*H*-indol-3-ylmethyl)-4-methyl-pent-4-anoic Acid ((*S*)-1-phenyl-ethyl)-amide (10c). Procedure as for the preparation of compound **10a** to give a white solid (130 mg 98%): δ_H 0.77 (3H, d, CH_3, J = 6.6 Hz), 0.97 (3H, d, CH_3, J = 6.6 Hz), 1.24 (3H, d, CH_3, J = 6.8 Hz), 1.38−1.49 (1H, m, $CHHCH(CH_3)_2$), 1.60−1.69 (1H, m, $CH(CH_3)_2$), 2.02−2.12 (1H, m, $CHHCH(CH_3)_2$), 2.71(1H, d, CHHInd, J = 13.9 Hz), 3.47 (1H, d, CHHHInd, J = 13.6 Hz), 5.00−5.06 (1H, m, NHCH), 6.67 (1H, d, arom, J = 2.2 Hz), 7.02−7.38 (8H, m, arom), 7.60 (1H, d, arom, J = 7.8 Hz), 7.79−7.82 (1H, m, arom) 8.16 (1H, s, NH); ν_{max} 3293, 2954, 2927, 2869, 1646, 1508, 1455, 1341, 1212, 1159, 1124, 1104, 1010, 878, 807, 746 cm^{-1}; MS (ES$^+$) 727 (2M$^+$ + H, 100%), 364 (M$^+$ + H, 53%).

(*S*)-2-Amino-3-(1*H*-indol-3-yl)-2-methoxymethyl-*N*-((*S*)-1-phenyl-ethyl)-propionamide (10d). Procedure as for the preparation of compound **10a** to give a pink colored foam (630 mg, quant.): δ_H (DMSO-d_6) 1.36 (3H, d, $CHCH_3$, J = 6.8 Hz), 3.26 (3H, s, OCH_3), 3.37 (2H, s, IndCH_2), 3.66 (1H, d, CHHO, J = 10.0 Hz), 4.17 (1H, d, CHHHO, J = 10.0 Hz), 4.90 (1H, dq, $CHCH_3$, J = 6.8, 6.8 Hz), 7.00−7.38 (8H, m, arom), 7.70 (1H, d, arom, J = 7.6 Hz), 8.17 (3H, bs, NH, NH_2), 8.94 (1H, d, arom, J = 7.6 Hz), 11.17 (1H, d, NH, J = 1.2 Hz); ν_{max} 3419, 3213, 3057, 1667, 1494, 1458, 1106, 746 cm^{-1}; HRMS for $C_{21}H_{26}N_3O_2$ requires 352.2025, found 352.2025 (MH$^+$); $[\alpha]_D^{19}$ −9.2° (c = 0.66, MeOH). Anal. ($C_{21}H_{25}N_3O_2$·0.4 H_2O) C, H, N.

(*S*)-2-Amino-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-*N*-((*S*)-1-phenyl-ethyl)-propionamide (10e). Procedure as for the preparation of compound **10a** to give a clear glass (342 mg, quant.): δ_H 1.42 (3H, d, $CHCH_3$, J = 7.2 Hz), 2.32 (6H, s, N(CH_3)$_2$), 2.46 (1H, d, CHHN, J = 12.4 Hz), 2.83 (1H, d, CHHInd, J = 14.0 Hz), 3.13 (1H, d, CHHN, J = 12.4 Hz), 3.20 (1H, d, CHHInd, J = 14.0 Hz), 5.00 (1H, dq, $CHCH_3$, J = 7.2, 7.2 Hz), 6.74 (1H, s, arom), 7.03−7.25 (6H, m, arom), 7.33 (1H, d, arom, J = 8.0 Hz), 7.61 (1H, d, arom, J = 8.0 Hz), 8.14 (1H, d, CONH, J = 8.0 Hz), 8.42 (1H, s, NH); HRMS for $C_{22}H_{29}N_4O$ requires 365.2341, found 365.2341 (MH$^+$); $[\alpha]_D^{19}$ +4.5° (c = 0.56, MeOH).

[(*R*)-1-(1*H*-Indol-3-ylmethyl)-1-((*S*)-1-phenyl-ethylcarbamoyl)-propyl]-carbamic Acid Benzofuran-2-yl Methyl Ester (11a). Compound **10a** (503 mg, 1.50 mmol), (2-benzofuranyl)methyl 4-nitrophenyl carbonate[7] (470 mg, 1.50 mmol), and DMAP (200 mg) in DMF (10 mL) were stirred at room

temperature for 7 days. The solvent was removed in vacuo and the product extracted into EtOAc. The organics were washed with 10% HCl, 10% K_2CO_3, and brine and dried ($MgSO_4$). Purification by chromatography (25−30% EtOAc in heptane) gave a white foam (167 mg, 22%): mp 69−72 °C; δ_H 0.80 (3H, t, CH_2CH_3, J = 7.6 Hz), 1.22 (3H, d, CHCH_3, J = 7.6 Hz), 1.87, 2.40 (2H, 2 × m, CH_2CH$_3$), 3.45 (2H, dd, IndCH_2, J = 15.2, 32.4 Hz), 4.96 (1H, dq, CHCH$_3$, J = 6.8, 6.8 Hz), 5.19 (2H, s, CH_2O), 5.83 (1H, s, NH), 6.01 (1H, d, NH, J = 7.2 Hz), 6.74 (1H, s, arom), 6.84 (1H, d, arom, J = 7.0 Hz), 7.06 (1H, t, arom, J = 6.6 Hz), 7.14−7.32 (9H, m, arom), 7.46 (1H, d, arom, J = 8.0 Hz), 7.58 (2H, m, arom), 7.86 (1H, s, NH); ν_{max} 3357, 2972, 1720, 1649, 1489, 1454, 1073, 742 cm^{-1}; HRMS for $C_{31}H_{32}N_3O_4$ requires 510.2393, found 510.239$_3$ (MH$^+$); $[\alpha]_D^{20}$ −32.2° (c = 0.35, MeOH). Anal. ($C_{31}H_{31}N_3O_4$·0.2H_2O) C, H, N.

[(*R*)-1-(1*H*-Indol-3-ylmethyl)-1-((*S*)-1-phenyl-ethylcarbamoyl)-but-3-enyl]-carbamic Acid Benzofuran-2-ylmethyl Ester (11b). A solution of 2-benzofuranylmethanol (40 mg, 258 μmol) in EtOAc (1 mL) at 0 °C under dry N_2 was treated with triphosgene (33 mg, 110 μmol) followed by DIPEA (59 μL, 341 μmol). After 30 min, the reaction mixture was filtered, and the filtrate was treated with compound **10b** (90 mg, 258 μmol) and allowed to warm to room temperature and stirred for 30 min. The mixture was diluted with EtOAc and washed with 10% K_2CO_3 and brine and dried ($MgSO_4$). The crude material was purified by chromatography (0−30% EtOAc in heptane) to give a white foam (20 mg, 16%): δ_H 0.84 (3H, d, CHCH_3, J = 7.3 Hz), 1.04−1.14 (1H, m, CH), 1.22 (3H, d, CH_3, J = 7.2 Hz), 1.20−1.37 (1H, m, CH), 1.72−1.81 (1H, m, CH), 2.20−2.37 (1H, m, CH), 3.40 (1H, d, CHH, J = 14.9 Hz), 3.51 (1H, d, CHH, J = 15.1 Hz), 4.94 (1H, dq, CHCH$_3$, J = 7.1, 7.1 Hz), 5.15−5.22 (2H, m, CH_2O), 5.85 (1H, s, NH), 6.04 (1H, s, NH, J = 7.6 Hz), 6.72 (1H, s, arom), 6.83 (1H, d, arom, J = 2.4 Hz), 7.03−7.07 (1H, m, arom), 7.10−7.32 (9H, m, arom), 7.45−7.56 (3H, m, arom), 7.86 (1H, bs, NH); ν_{max} 3354, 2961, 1716, 1650, 1489, 1454, 133, 1067, 741 cm^{-1}; HRMS for $C_{32}H_{34}N_3O_4$ requires 524.2551, found 524.2549 (MH$^+$); 3:2 mixture of diastereomers, only peaks for major diastereomers shown; $[\alpha]_D^{25}$ −7.2° (c = 0.29, $CHCl_3$). Anal. ($C_{32}H_{33}N_3O_4$) C, H, N.

[(*R*)-1-(1*H*-Indol-3-ylmethyl)-3-methyl-1-((S)-1-phenyl-ethylcarbamoyl)-butyl]-carbamic Acid Benzofuran-2-ylmethyl Ester (11c). Procedure as for the preparation of compound **11b** to give a white foam: δ_H 0.69 (3H, d, CHCH_3, J = 6.4 Hz), 0.86 (3H, d, CH_3, J = 6.4 Hz), 1.15 (3H, d, CH_3, J = 7.2 Hz), 1.61 (1H, m, CHH), 2.48 (1H, m, CHH), 3.29 (1H, d, CHH, J = 15.2 Hz), 3.61 (1H, d, CHH, J = 15.2 Hz), 4.88 (1H, dq, CHCH$_3$, J = 7.2, 7.2 Hz), 5.19 (2H, dd, CH_2O, J = 13.2, 16.8 Hz), 5.86 (1H, d, NH, J = 7.2 Hz), 6.22 (1H, s, NH), 6.72 (1H, s, arom), 6.88 (1H, d, arom, J = 2.0 Hz), 7.04−7.32 (10H, m, arom), 7.46 (1H, d, arom, J = 8.0 Hz), 7.55 (2H, m, arom, J = 6.8 Hz), 7.83 (1H, bs, NH); ν_{max} 3354, 1714, 1645, 1488, 741 cm^{-1}; m/z 537.85 (M$^+$, 100%); $[\alpha]_D^{25}$ −23.1° (c = 0.64, $CHCl_3$). Anal. ($C_{33}H_{35}N_3O_4$) C, H, N.

[(*S*)-2-(1*H*-Indol-3-yl)-1-methoxymethyl-1-((*S*)-1-phenyl-ethylcarbamoyl)-ethyl]-carbamic Acid Benzofuran-2-ylmethyl Ester (11d). Procedure as for the preparation of compound **11b** to give a white foam (436 mg, 46%): mp 63−66 °C; δ_H 1.40 (3H, d, CHCH_3, J = 6.8 Hz), 3.37 (3H, s, OCH_3), 3.46 (1H, d, IndCHH, J 1.2 Hz), 3.58 (1H, d, IndCHH, J 1.2 Hz), 3.50 (1H, d, CHHO, J = 9.2 Hz), 4.08 (1H, d, CHHO, J = 9.2 Hz), 5.00 (1H, dq, CHCH$_3$, J = 6.8, 6.8 Hz), 5.18 (2H, dd, CH_2O, J = 13.2, 18.4 Hz), 6.74 (1H, s, arom), 6.74 (1H, d, arom, J = 7.2 H), 6.76 (1H, d, arom, J = 2.4 Hz), 7.03 (1H, dt, arom, J = 0.4, 7.2 Hz), 7.14 (1H, t, arom, J = 7.2 Hz), 7.22−7.33 (8H, m, arom), 7.47 (1H, d, arom, J = 8.4 Hz), 7.56 (2H, d, arom, J = 6.8 Hz), 7.75 (1H, s, NH); ν_{max} 3337, 1713, 1661, 1494, 1455, 1246, 1065, 743 cm^{-1}; HRMS for $C_{31}H_{32}N_3O_5$ requires 526.2342, found 526.234$_2$ (MH$^+$); $[\alpha]_D^{20}$ −33.4° (c = 0.47, MeOH). Anal. ($C_{31}H_{31}N_3O_5$·0.2 H_2O) C, H, N.

[(*S*)-1-Dimethylaminomethyl-2-(1*H*-indol-3-yl)-1-((*S*)-1-phenyl-ethylcarbamoyl)-ethyl]-carbamic Acid Benzofuran-2-ylmethyl Ester (11e). Procedure as for the preparation of compound **11b** to give a white foam (28 mg, 20%): mp 55−60 °C; δ_H 1.40 (3H, d, CHCH_3, J = 8.4 Hz), 2.16 (6H, s, 2 × CH_3), 2.50 (1H, d, CHHN, J = 13.7 Hz), 3.29 (1H, d, CHHN, J = 13.7 Hz), 3.54 (2H, dd, IndCH_2, J = 14.7, 26.9 Hz), 5.00 (1H, q, CHCH$_3$, J = 6.8 Hz), 5.21 (2H, s, CH_2O), 6.47 (1H, bs, NH), 6.76 (1H, s, arom, J = 7.2 Hz), 6.79 (1H, d, arom, J = 2.4 Hz), 7.04 (1H, t, arom, J = 7.4 Hz), 7.12 (1H, t, arom, J = 7.0 Hz), 7.23−7.25 (8H, m, arom), 7.49 (1H, d, arom, J = 8.4 Hz), 7.56 (2H, bd, arom, J = 7.6 Hz), 7.64 (1H, bs, NH), 8.17 (1H, bs, NH); ν_{max} 3360, 1716, 1652, 1488, 1455, 741 cm^{-1}; m/z 539 (MH$^+$, 100%), 391 (46%). Anal. ($C_{32}H_{34}N_4O_4$) C, H, N.

Further characterized as the HCl salt: mp 192−197 °C (IPA); $[\alpha]_D^{23}$ −89.9° (c = 0.50, MeOH).

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