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Bioinspired design for the assembly of Glypromate® neuropeptide conjugates with active pharmaceutical ingredients†

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Neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, are a class of heterogeneous pathologies of the central nervous system (CNS) affecting millions of people worldwide. CNS-related pathologies represent a global health burden in developed and developing countries with no curative treatments currently available. Thus, the development of novel multitarget neuroprotective drugs is a health priority. In this work, a bioinspired methodology in solution-phase for the assembly and regioselective conjugation of Glypromate® neuropeptide with active pharmaceutical ingredients (APIs) is described. The main purpose is to design new hybrid molecules which may offer increased systemic resistance of Glypromate® towards proteases and/or allow the controlled release of both APIs and the neuroprotective peptide within CNS. For the synthesis of such peptide-hybrid compounds (*R*)-1-aminoindane, amantadine, and memantine were selected as APIs for conjugation with Glypromate®. Furthermore, capping strategies are explored to prepare Glypromate® conjugates with more favorable pharmacodynamic profiles by masking polar exposed groups. Overall, this synthetic approach led to the development of a small library of 12 conjugates with improved drug-like properties in comparison with Glypromate®, paving the way for the discovery of novel CNS multitarget drugs. Additionally, by exploring the bis-functionalization of glutamate, the formation of chiral glutarimides is disclosed for the first time employing TBTU as the coupling reagent. This unusual reactivity of TBTU with glutamate offers a new synthetic approach for the preparation of chiral glutarimide alkaloids.

Introduction

Neurodegenerative diseases (NDD) are characterized by the slow and gradual degeneration of Central Nervous System (CNS) neurons, ultimately resulting in neuronal death. Currently, the existing therapeutic approaches only address the symptoms.[1]

Alzheimer's disease (AD) and Parkinson's disease (PD) are the top two common NDD with an estimated 50 million people worldwide living with AD or another type of dementia and 6.2 million with PD.[2] Predictions are worrisome, pointing to 82 and 8.7 million living with dementia and PD by 2030,[2] respectively.

The scarcity of multifactorial therapeutic approaches to manage CNS-related pathologies makes the development of novel drugs an imperative.[3] The rescuing of drugs that were previously thoroughly studied and demonstrated to be clinically safe in humans is considered a privileged methodology for the effective repositioning of known drugs through the development of novel potential bioactive compounds with improved biological and pharmacological profiles.[4] Among these strategies, chemical conjugation of bioactive scaffolds is commonly employed in the development of CNS drugs to achieve synergistic or complementary effects. A paradigmatic example is Ladostigil, which combines the neuroprotective effects of the selective monoamine oxidase (MAO)-B inhibitor rasagiline (Azilect®) with the cholinesterase inhibitory (AChE) activity of rivastigmine.[5] Further studies with the conjugation of two or more anti-Alzheimer's drugs (tacrine, donepezil and rivastigmine) show promising results. For example, tacrine, which is a potent AChE inhibitor (IC_{50} = 167 nM),[6] was the first FDA-approved anti-AD drug in 1993,[7] but was soon withdrawn from the market due to hepatotoxicity issues.[8] This prompted the development of multifunctional anti-AD drugs, such as tacrine conjugates with a 1-azabenzanthrone moiety, which showed higher AChE inhibitory activity than the parent drug (within the nanomolar range) and also anti-Aβ aggregation activity.[7,9]

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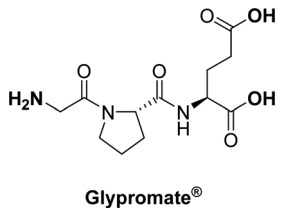
† Electronic supplementary information (ESI) available: NMR spectra (^1H, $^{13}C\{^1H\}$ and DEPT-135) for all the synthesized compounds. See DOI: 10.1039/d0nj04851h



Glypromate®

Fig. 1 Molecular structure of Glypromate®.

Insulin-like growth factor-I (IGF-I), also known as somatomedin C, is a 70-mer peptide hormone that acts as an essential factor for the development and maturation of the CNS and which is also important to neuroplasticity. However, its use as therapeutic agent is restricted due to its poor ability to cross the blood–brain barrier (BBB).[10,11] This protein is cleaved by protease-mediated metabolism into des-*N*-(1-3)-IGF-I and the N-terminal tripeptide glycyl-L-prolyl-L-glutamic acid (also known as GPE or Glypromate®, Fig. 1).

Glypromate® is a promising lead compound candidate for clinical therapies and the metabolite of this tripeptide, cyclo(Pro-Gly), (obtained by the cleavage from C- to N-terminal) is also a small, stable and bioactive molecule in the CNS.[12] Glypromate® stimulates acetylcholine and dopamine release in rat cortex and has neuroprotective properties from hypoxia-ischemia and glutamate induced injuries.[13–15]

The therapeutic potential of this short peptide for CNS-related pathologies led Glypromate® to clinical trials by Neuren Pharmaceuticals to study its effects on brain impairment after major heart surgery.[16] Data suggest that Glypromate® inhibits caspase III dependent apoptosis and despite its excellent safety profile, in December 2008, the company discontinued Glypromate® research after the completion of phase III of clinic trials due to lack of evidence of brain improvement after major heart surgery.[17]

Nonetheless, the neuroprotective properties of Glypromate® are being explored by the development of structurally-related analogues[12,13,18–20] and hybrid molecules containing Glypromate®.[21] Cacciatore and co-workers reported the first successful Glypromate® conjugate with lipoic acid (LA) to generate a LA-Glypromate® hybrid compound.[21] LA-Glypromate® not only demonstrated neuroprotective properties against H_2O_2 and 6-hydroxydopamine (6-OHDA) but also high CNS permeability.[21] These results show that Glypromate® can be successfully covalently conjugated without loss of its intrinsic neuroprotective activity. To the best of our knowledge, despite the success of the repurposing strategy for the rescue of CNS active drugs, only one successful conjugate of Glypromate® has been reported so far in literature.[21]

The scarcity of such hybrid Glypromate® molecules makes imperious the establishment of a reliable methodology for the preparation of valuable multitarget compounds for CNS-related pathologies. In this sense, we sought to contribute for the bioinspired design and the development of an efficient methodology for the assembly of Glypromate® conjugates in solution-phase.

According to literature, the metabolism of Glypromate® occurs from C- to N-terminal, promoted by carboxipeptidases.[22] In this sense, it is reasonable to consider the C-terminal amino acid residue, glutamic acid, as the most adequate site for derivatization and assembly of Glypromate® conjugates with active pharmaceutical ingredients (APIs). This strategy may allow the development of conjugates with improved resistance towards enzymatic degradation and/or the controlled release of APIs and Glypromate®, offering the possibility to tune the balance of hydrophobicity/hydrophilicity to selectively promote the delivery across the BBB. It is known that the functionalization at the C-terminal of this peptide, for example by converting the γ-carboxylic acid into a carboxamide or by reducing it into the corresponding primary alcohol prevented neuronal cell death at 1 mM, the same concentration at which Glypromate® typically display neuroprotective effects.[18,19] Moreover, conversion of both α and γ-carboxylic acid moieties into methyl ester functional groups has proved to improve lipophilicity without compromising the neuroprotective activity of the peptide at 1 mM.[18] Taken together, this data indicates that Glypromate® is quite tolerant to functionalization at the glutamate residue.

The selection of APIs for conjugation with Glypromate® is of utmost importance in order to balance its high hydrophilicity, which is the main cause for the low oral absorption associated with this peptide.[23,24] In this sense, APIs should be hydrophobic enough to tower over the hydrophilicity of Glypromate® and not exceed 180 Da, in order to respect the Lipinski's rule of five concerning the molecular mass of the conjugates.[25] Hence, accordingly to lipophilicity and molecular mass parameters, three APIs used in clinic for neurodegenerative conditions were selected for conjugation with this neuropeptide: (*R*)-1-aminoindane, amantadine, and memantine. Additionally, to further increase the hydrophobicity of the conjugates, exposed polar groups should be masked. To meet this goal, both N-terminal amino group and C-terminal carboxylic acid should be converted into tertiary amine and ester moieties, respectively. Considering that *N*,*N*-dimethylglycine is known to decrease oxidative stress,[26] conversion of N-terminal glycine residue into its *N*,*N*-dimethylated analogue may confer protection against oxidative stress while improving the lipophilicity of the conjugates.

(*R*)-1-Aminoindane (**a**, Fig. 2) is the principal metabolite of Rasagiline (Azilect®), a pharmaceutical used in PD therapy as a MAO-B irreversible inhibitor.[27] This metabolite decreases apoptotic processes and displays a good neuroprotective profile.[27] Amantadine (**b**, Fig. 2) is commercialized as Symmetrel® and employed in PD therapy as a non-competitive antagonist of NMDA receptors, leading to an increase in the amount of endogenous dopamine.[28] Memantine (**c**, Fig. 2) is the API of Namenda® and is used in AD therapy as an antagonist of NMDA receptors.[29]

In this work, the conjugates (**I–VI**) depicted in Fig. 2 were designed in accordance with the goals laid out in this intro in order to explore suitable synthetic routes for the unprecedented development peptide-hybrid molecules of Glypromate® with different APIs by covalent conjugation at the C-terminal site.

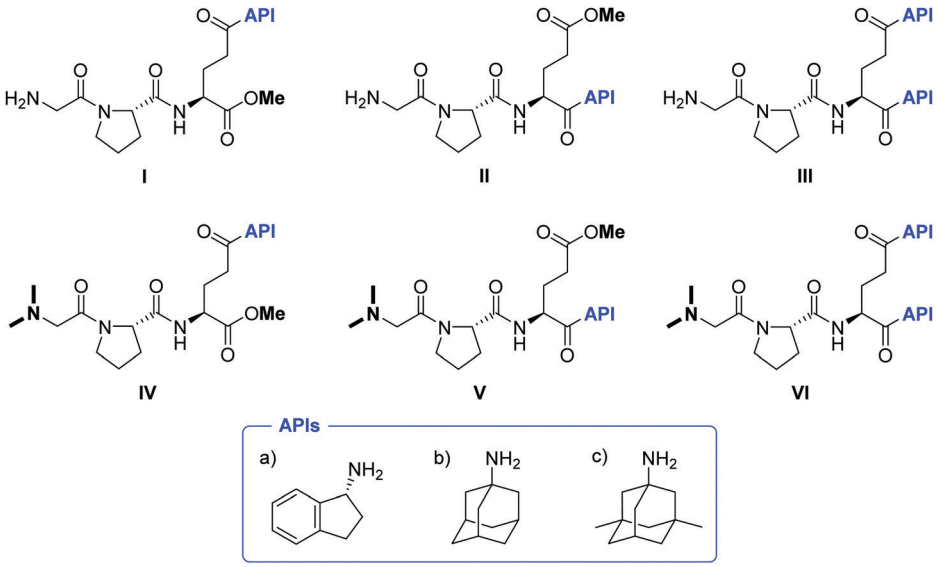
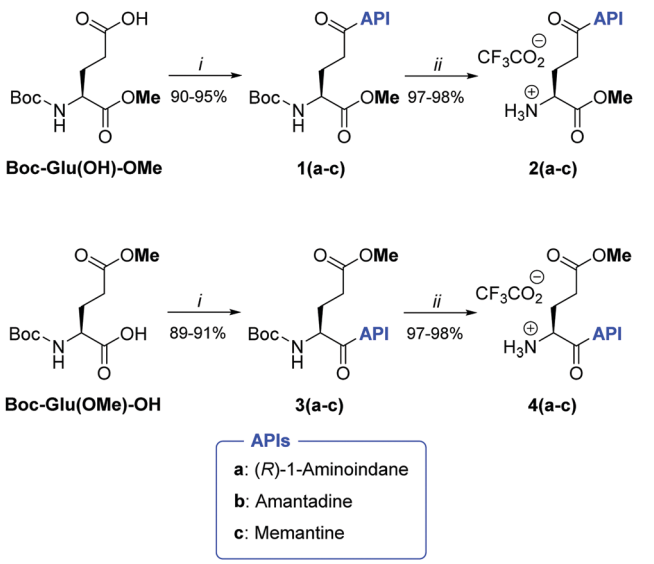


Fig. 2 Glypromate® conjugates **I–VI**.

Results and discussion

The synthesis of conjugates **I**, **II**, **IV** and **V** (Fig. 2) started with the functionalization of the glutamate residue at either the α or the γ carboxylic acid positions, in order to afford monofunctionalized glutamates. For this purpose, the synthesis started with the mono functionalization of commercially available methyl ester glutamate derivatives (Scheme 1).

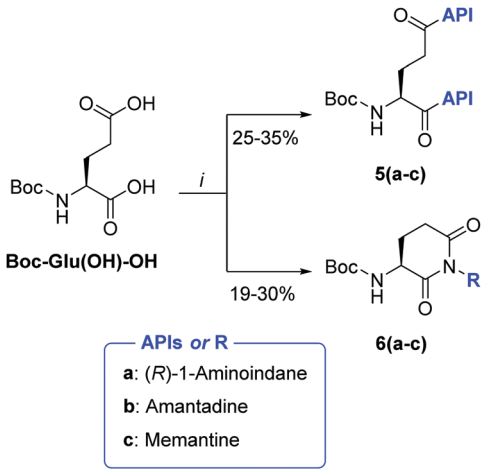
The use of mono methyl ester glutamates (Boc-Glu(OH)-OMe and Boc-Glu(OMe)-OH, Scheme 1) serves two purposes: it allows for the regioselective preparation of monofunctionalized glutamates and at same time the methyl ester moiety acts as a capping strategy for the carboxylic acid. Functionalization of both glutamate derivatives with APIs **a-c** was performed by peptide coupling using standard protocols in solution-phase, namely 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU) and triethylamine as the coupling reagent and tertiary base, respectively.[30] Functionalized glutamates **1(a-c)** and **3(a-c)** were obtained in excellent yields after chromatographic purification (89–95%, Scheme 1). Subsequently, the removal of *tert*-butyloxycarbonyl (Boc) group was performed by acidolysis using trifluoroacetic acid (TFA), delivering glutamates **2(a-c)** and **4(a-c)** as ammonium trifluoroacetates with near quantitative yield (97–98%) without the need of chromatographic purification (Scheme 1).



Scheme 1 Synthesis of functionalized glutamates **2(a-c)** and **4(a-c)**. *Conditions and reagents:* (i) Et_3N, TBTU, API (**a-c**), anhydrous CH_2Cl_2; (ii) TFA, anhydrous CH_2Cl_2.

With monofunctionalized glutamate derivatives in hand, bis-functionalization using Boc-Glu(OH)-OH was explored (Scheme 2).

To accomplish this task, two equivalents of APIs and TBTU were used instead. During the reactions, the formation of two new spots on the TLC were detected, which we initially attributed to the presence of mono and bis-functionalized products. After the addition of an excess of the APIs the reaction mixture remained unchanged, which led us to isolate both compounds in order to identify the products formed. As suspected, the least polar compounds ($R_f \approx 0.9$ in EtOAc) were identified (NMR) as the bis-functionalized glutamates **5(a-c)**, albeit with unexpected low yields (25–35%) in contrast with the yields reported for the mono-functionalized counterparts. Besides glutamates **5(a-c)**, other by-products ($R_f \approx 0.6$ in EtOAc) were isolated. NMR analysis (Fig. S31–S36, ESI†) allowed the unequivocal assignment of these by-products as *N*-substituted (*S*)-3-aminopiperidine-2,6-diones, glutarimides **6(a-c)**. Chiral glutarimides **6(a-c)** were isolated in comparable yields (19–30%) to those reported for bis-functionalized glutamates. To the best of our knowledge, the preparation of chiral glutarimides from glutamate using TBTU is unprecedented. A possible mechanism for the formation of glutarimides **6(a-c)** mediated by TBTU is proposed in Scheme 3.

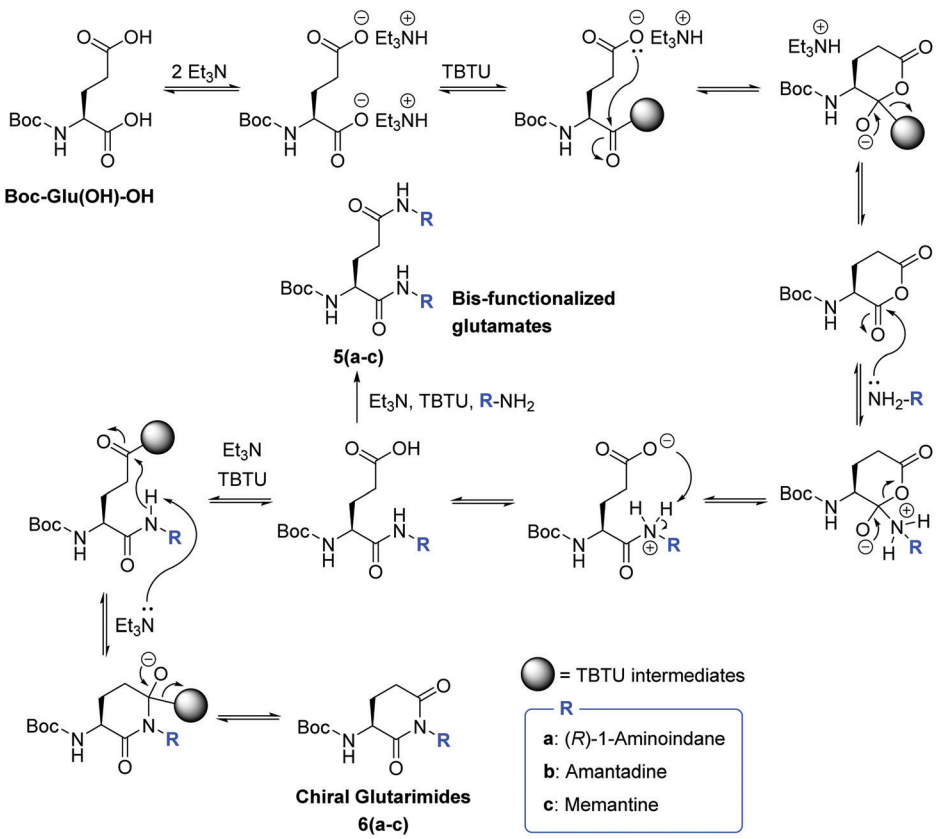


Scheme 2 Synthesis of bis-functionalized glutamates **5(a-c)** and chiral glutarimides **6(a-c)**. *Conditions and reagents:* (i) Et_3N, TBTU, API (**a-c**), anhydrous CH_2Cl_2.

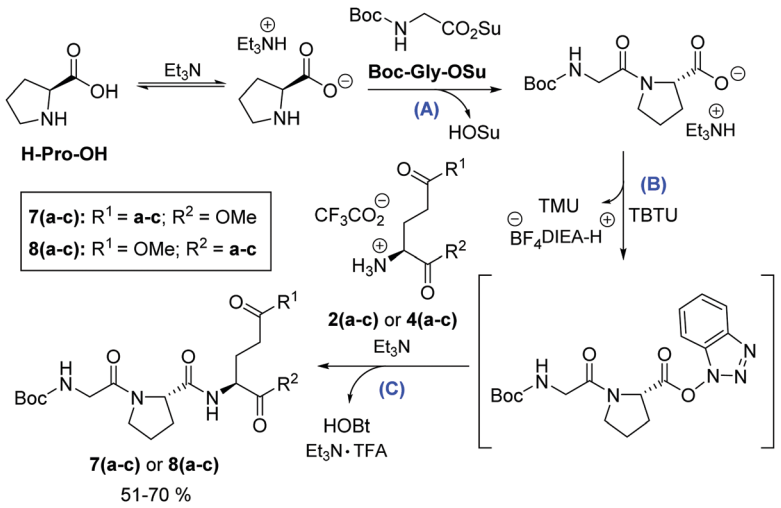
Despite the feasibility of the synthesis of bis-functionalized glutamates **5(a-c)**, along with the formation of chiral glutarimides **6(a-c)**, in this work, these glutamates were not further explored for the assembly of Glypromate® conjugates **III/VI** due to violation of the Lipinski's rule of 5, namely molecular weight over 500 Da (Table S1 of ESI†).

Starting from glutamates **2(a-c)** and **4(a-c)**, the assembly of the corresponding Glypromate® conjugates intermediates, **7(a-c)** and **8(a-c)**, respectively, was performed using a robust and highly efficient one-pot protocol in solution-phase developed in our research group.[31,32] Briefly, the methodology consists in three essential steps (Scheme 4): (A) peptide coupling of proline (*via* a tertiary base like Et_3N) with pre-activated glycine (using *O*-succinimidyl ester derivative, Boc-Gly-OSu); (B) *in situ* activation of the amide-carboxylate intermediate to the corresponding active ester *via* TBTU and (C) coupling of the final amino acid by aminolysis between the functionalized glutamates, **2(a-c)** or **4(a-c)**, and the active esters generated in step B. This one-pot protocol has several advantages such as: (1) no need for isolation of the intermediates; (2) reduction of chemical waste (highly competitive in terms of global E-factor, being superior to solid-phase peptide synthesis (SPPS), classical solution-phase synthesis and mechanochemical approaches such as ball-milling);[32] (4) faster assembly of peptides in comparison with classical iterative approaches; and (5) high overall yield.[32] Additionally, in contrast with SPPS, this methodology allows for the use of bis-functionalized glutamate, which is not attainable by SPPS since one of the carboxylic acids is covalently linked to the resin.[20]

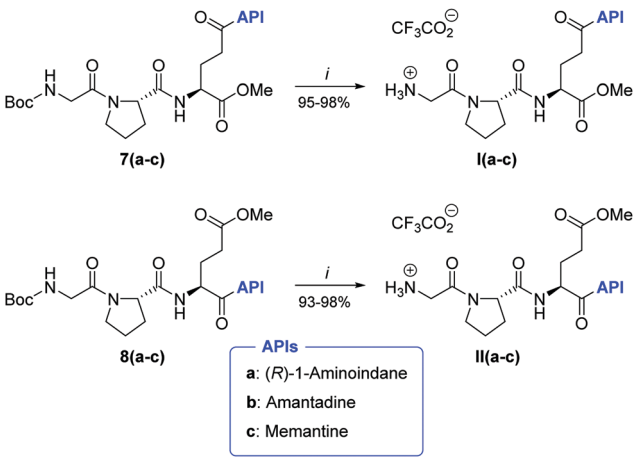
Following this protocol, *N*-Boc conjugates **7(a-c)** and **8(a-c)** were readily prepared in good overall yields (51–70%), as shown in Scheme 4. Conjugates **8(a-c)** were obtained in lower yields (51–69%) in comparison with **7(a-c)**, which is explained by a higher steric hindrance of the glutamates **4(a-c)** in contrast with **2(a-c)**. Note that APIs are covalently linked at α-carboxylate in



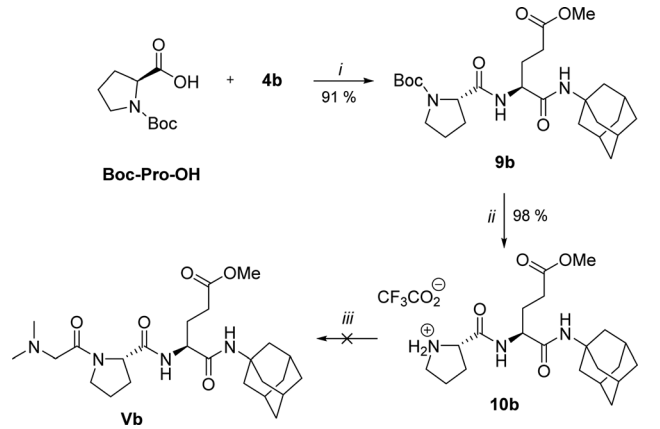
Scheme 3 Mechanism proposed for the synthesis of chiral glutarimides **6(a-c)** mediated by TBTU.



Scheme 4 One-pot assembly of conjugates **7(a-c)** and **8(a-c)**.



Scheme 5 Preparation of conjugates **I(a-c)** and **II(a-c)**. *Conditions and reagents:* (i) TFA, anhydrous CH_2Cl_2.



Scheme 6 Iterative route for the preparation of conjugate **Vb**. *Conditions and reagents:* (i) Et_3N, TBTU, anhydrous CH_2Cl_2; (ii) TFA, anhydrous CH_2Cl_2; (iii) Et_3N, TBTU, *N*,*N*-dimethylglycine, anhydrous CH_2Cl_2.

4(a-c), while in **2(a-c)** they are attached at γ-carboxylate. Steric hindrance in **4(a-c)** is therefore responsible for slowing down the coupling rates, and hence the yields.

The final compounds **I(a-c)** and **II(a-c)** were successfully obtained in practically quantitative yields after cleavage of the N-protecting group by acidolysis using TFA (Scheme 5).

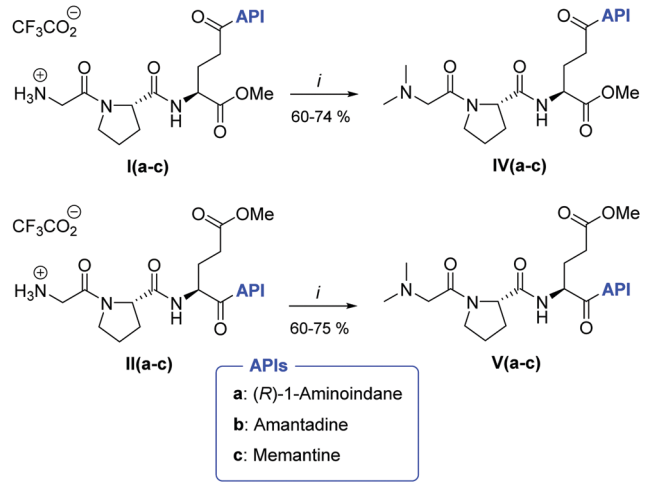
The difference between conjugates **I/II** and **IV/V** lies on the presence of a tertiary amine (*N*,*N*-dimethylglycyl residue) in the latter ones. Since the *N*,*N*-dimethylglycine *O*-succinimidyl ester is not commercially available, the preparation of type **IV** and **V** conjugates following the classical iterative synthesis approach in solution-phase was envisioned. This synthetic route was tested for the preparation of conjugate **Vb** (Scheme 6). For this purpose, Boc-Pro-OH was coupled with glutamate **4b** using the chemistry of TBTU, affording the corresponding dipeptide **9b** in excellent yield (91%). Successful removal of the carbamate was performed by acidolysis using TFA, delivering the ammonium trifluoroacetate **10b** in practically quantitative yield (98%). All the attempts (temperature: 0–40 °C, solvents: CH_2Cl_2, $CHCl_3$, EtOAc; stoichiometry: 1–2 equiv. of each reagent) to synthesize conjugate **Vb** by coupling dipeptide **10b** with *N*,*N*-dimethylglycine were unsuccessful (Scheme 6).

To circumvent this hurdle, reductive amination was attempted by reacting conjugates **I/II** with formaldehyde using $NaBH(OAc)_3$ as the reducing agent (Scheme 7).

After the reductive amination and subsequent removal of the solvent by distillation, the excess of the reductive agent was precipitated upon addition of CH_2Cl_2. Following this workup, conjugates **IV** and **V** were isolated in good yields (60–75%) without the need of chromatographic purifications, except for **IVa**.

Druglike properties and predicted BBB permeability of the Glypromate® conjugates

Evaluation of the physicochemical properties for the novel drug candidates is of great importance to estimate qualitatively oral bioavailability and membrane permeability. Considering the parameters originally proposed by Lipinski and co-workers [molecular weight (MW), partition coefficient (clog *P*), number



Scheme 7 Preparation of conjugates **IV(a-c)** and **V(a-c)** by reductive amination of **I(a-c)** and **II(a-c)**, respectively. *Conditions and reagents:* i. Formaldehyde solution 37 wt% in water, $NaBH(OAc)_3$, 1,2-dichloroethane.

of H-bond acceptors (HBA), number of H-bond donors (HBD)],[33] together with the parameters later suggested by Veber and co-workers [topological polar surface area (^{t}PSA in Å^2), number of rotatable bonds (n_{rotb}), sum of H-bond donors and acceptors][34] the druglike properties were calculated for conjugates **I(a-c)**, **II(a-c)**, **IV(a-c)**, **V(a-c)** and Glypromate®. The results obtained are listed in Table 1.

A close inspection of the clog*P* values obtained for the conjugates with free N-terminal, namely conjugates **I(a-c)** and **II(a-c)**, shows low lipophilicity (clog*P* < 1); the presence of (*R*)-1-aminoindane in compounds **Ia** and **IIa** considerably enhances the lipophilicity, albeit with negative clog*P* values (−0.69 and −1.00, respectively) in contrast with the parent peptide (clog*P* = −4.39).

As expected, *N*,*N*-dimethylation of the glycine residue in compounds type **I** and **II** leads to a substantial increment in lipophilicity (conjugates type **IV** and **V**, respectively). Apart from conjugates with (*R*)-1-aminoindane (**IVa** and **Va**), all the remaining *N*,*N*-dimethylated conjugates display high clog*P* values (clog*P* > 1) within the range of adequate CNS$^+$ drug's clog*P* (<5). ^{t}PSA is a medicinal chemistry metric for evaluation and optimization of a molecule's ability to permeate cells.[36] Molecules with high ^{t}PSA (higher than 140 Å^2) tend to display low ability to permeate cell membranes. For molecules intended to cross the BBB, a ^{t}PSA less than 90 Å^2 is usually required,[35] ideally in the range of 60–70 Å^2.[35,36]

In silico BBB permeation shows that all the conjugates are considered as BBB+ (BB ratio ≥0.1). Except for conjugates **Ia**, **Ic**, **IIa** and **IIc**, all the remaining conjugates display enhanced BBB permeation (BB ratio ranging between 0.535–0.739) comparatively to the parent compound (BB ratio of 0.517). Among the series of compounds, conjugates **IVb** and **Vb** are considered the most promising (high clog*P*: 1.61 and 1.30, low ^{t}PSA: both with 108.05 Å^2, high BB ratio: 0.655 and 0.739, respectively).

Table 1 Calculated druglike properties for conjugates **I(a-c)**, **II(a-c)**, **IV(a-c)**, **V(a-c)** and Glypromate®

Conjugate	MW[a]	clog*P*[a]	HBA[a]	HBD[a]	n_{rotb}[a]	^{t}PSA[a]/Å^2	BB ratio[b]
Ia	430.50	−0.69	9	4	9	130.83	0.443
Ib	448.56	0.39	9	4	9	130.83	0.639
Ic	476.62	0.51	9	4	9	130.83	0.452
IIa	430.50	−1.00	9	4	9	130.83	0.535
IIb	448.56	0.08	9	4	9	130.83	0.719
IIc	476.62	0.20	9	4	9	130.83	0.543
IVa	458.56	0.53	9	2	10	108.05	0.454
IVb	476.62	1.61	9	2	10	108.05	0.655
IVc	504.67	1.73	9	2	10	108.05	0.470
Va	458.56	0.22	9	2	10	108.05	0.552
Vb	476.62	1.30	9	2	10	108.05	0.739
Vc	504.67	1.43	9	2	10	108.05	0.565
Glypromate®	301.30	−4.39	9	5	7	150.03	0.517
CNS$^+$ drugs[35]	<500	<5	<7	<3	<8	<90	

[a] Properties calculated using Cheminformatics software [http://www.molinspiration.com]. [b] *In silico* BBB permeability using Cheminformatics software [http://admet.scbdd.com/calcpre/index/], Category 0: BBB−; Category 1: BBB+; BB ratio ≥0.1: BBB+; BB ratio <0.1: BBB−.

Characterization section

During the characterization of the Glypromate® conjugates it was observed that some of these compounds display a splitting pattern in both ^{1}H and ^{13}C-NMR spectra at room temperature. This phenomenon is attributed to *cis–trans* isomerization (rotamers). It is known that prolyl-containing peptides such as Glypromate® and its derivatives commonly exhibit rotamers in solution.[31,32] The presence of rotamers can be easily proven using variable-temperature NMR (VT-NMR) experiments.[31,32] Using these simple, albeit effective VT-NMR experiments, it is possible to observe the coalescence of the signals as the temperature rises,[31,32] thus excluding epimerization events. Although the methodology employed for the assembly of conjugates is known to preserve the stereochemistry of peptides,[31] and in particular for Glypromate® and its analogues,[32] VT-NMR experiments were performed for conjugate **Ic** as a representative example (Fig. 3).

In Fig. 3, two ^{1}H-NMR spectra (DMSO-d_6, truncated for clarity) of conjugate **Ic** are shown: one recorded at 26 °C (lower) and the other at 100 °C (upper). In the ^{1}H-NMR spectrum recorded at 26 °C is observed the duplication of several signals with 60 : 40 ratio. When the temperature is raised at 100 °C, those signals undergo complete coalescence. This data unambiguously

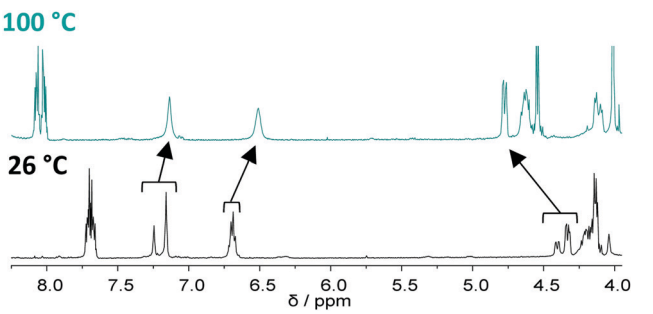


Fig. 3 Sacked ^{1}H-NMR spectra (truncated for clarity) of conjugate **Ic** (400 MHz, DMSO-d_6) at 26 °C and 100 °C.

shows that the origin of the splitting pattern found in the NMR spectra at 26 °C results from *cis–trans* rotamers.

Conclusion

Herein, the feasibility of a bioinspired methodology for the assembly of Glypromate® conjugates was proven with the successful preparation of 12 novel conjugates with (*R*)-1-aminoindane, amantadine and memantine. The key steps are (1) the one-pot synthesis for the assembly of conjugates **7(a-c)**/**8(a-c)** and (2) the reductive amination for the preparation of conjugates **IV/V** from **I/II**, respectively.

Conjugation of Glypromate® with neuroactive APIs and capping of the exposed polar groups proved to be advantageous in regards with lipophilicity (clog*P* up to 1.73) and ^{t}PSA (108.05–130.83 Å^2) parameters, which compare favourably with the parent peptide (clog*P* = −4.39 and ^{t}PSA = 150.03 Å^2). In this sense, conjugates **I/II** and **IV/V** are expected to display better permeation across the BBB than Glypromate®. Globally, among the tested APIs, amantadine and memantine are considered the most suitable for conjugation with Glypromate® in terms of lipophilicity and BBB permeation with emphasis on conjugates **IVb** and **Vb** (clog*P* of 1.61 and 1.30, ^{t}PSA 108.05 A^2, BB ratio: 0.655 and 0.739, respectively). Overall, this methodology constitutes a great advance for the design and assembly of Glypromate® conjugates, paving the way for the discovery of novel multitarget neuroprotective drugs.

Additionally, the formation of chiral glutarimides **6(a-c)** mediated by TBTU during the bis-functionalization of glutamate is unprecedented, offering an alternative route for the preparation of glutarimide alkaloids such as julocrotine and its derivatives.

Experimental section

Chemistry. General data

All chemicals were of reagent grade and were used without further purifications: Boc-Glu(OH)-OMe, Boc-Glu(OMe)-OH, Boc-Gly-OSu, amantadine and triethylamine were obtained from Fluorochem; TBTU was obtained from Bachem; H-Pro-OH, Boc-Pro-OH and Boc-Glu(OH)-OH was obtained from Merk; (*R*)-1-aminoindane was obtained from Alfa Aesar; memantine was obtained from Acros Organics; formaldehyde was obtained from Fisher Scientific; sodium triacetoxyborohydride was obtained from Sigma-Aldrich and trifluoroacetic acid was obtained from VWR. All air sensitive reactions were carried out under argon atmosphere. Analytical TLC was carried out on pre-coated silica gel plates (Merck 60 F_{254}, 0.25 mm) using UV light and an ethanolic solution of phosphomolybdic acid (followed by gentle heating) for visualization. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh).

Apparatus

^{1}H- and ^{13}C-NMR spectra were recorded at Centro de Materiais da Universidade do Porto (CEMUP) with a Bruker Avance III 400 at 400.15 MHz and 100.62 MHz, respectively. The ^{1}H-NMR spectra were calibrated using residual protic signals from deuterated solvents ($CDCl_3$: δ_H = 7.26, δ_C = 77.16; CD_3OD: δ_H = 3.31, δ_C = 49.00; DMSO-d_6: δ_H = 2.50, δ_C = 39.52)[37] and are reported in ppm. The nomenclature used for the assignment of protons and/or carbons for each α-amino acid residue in the peptide chains was made using a single letter system in subscript for the amino acid residue (G: glycine; P: L-proline; E: L-glutamic acid) and indicating the proton (or group of protons) and/or the carbons in the structures by starting the numeration at the carbonyl carbon of each α-amino acid residue. Assignment of protons and/or the carbons relative to the APIs scaffolds are indicated in subscript as follows: (*R*)-1-aminoindane (a); amantadine (b); memantine (c). Optical rotations were measured on a JASCO P-2000 thermostated polarimeter using a sodium lamp and are reported as follows: α_D^θ expressed in (°) (dm^{-1}) (g^{-1}), in which θ is temperature in Celsius and *c* (g per 100 mL, solvent). Melting points were determined using a STUART Scientific, model SMP1, and are not corrected. Solvents were removed in a Büchi rotavapor.

General protocols

(A.1) Glutamate mono-functionalization. To a solution of the appropriate glutamate mono methyl ester (1 equiv.) in anhydrous CH_2Cl_2 (25 mL) in a round-bottom flask was subsequentially added Et_3N (3 equiv.), TBTU (1.1 equiv.) and the appropriate bioactive amine (1.2 equiv.). The resulting solution was stirred for 2 h at RT under an inert atmosphere (Ar). After reaction completion, the solvent was removed using a rotatory evaporator. The residue obtained was dissolved in EtOAc (100 mL), transferred into a separatory funnel and washed with saturated aqueous solution of $NaHCO_3$ (3 × 100 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated. The resulting residue was purified by chromatographic column using an appropriated eluent, specified for each compound.

(A.2) Glutamate bis-functionalization and preparation of glutarimides. To a solution of Boc-Glu(OH)-OH (1 equiv.) in anhydrous CH_2Cl_2 (25 mL) in a round-bottom flask was subsequentially added Et_3N (4 equiv.), TBTU (2.2 equiv.) and the appropriate bioactive amine (2.2 equiv.). The resulting solution was stirred for 2 h at RT under an inert atmosphere (Ar). Work-up and purification follow the same protocol described in A.1.

(B) One-pot assembly of conjugates. To a solution of L-proline (1 equiv.) in anhydrous CH_2Cl_2 (25 mL) in a round-bottom flask was added Boc-Gly-OSu (1.1 equiv.), and the reaction was left stirring for 12 h at RT under inert atmosphere (Ar). Next, to this solution was subsequentially added TBTU (1.1 equiv.) and, after 30 min, the appropriate functionalized glutamate (1.2 equiv.). Work-up and purification follow the same protocol described in A.1.

(C) Removal of *N*-Boc protecting group. To a solution of *N*-Boc protected compound (1 equiv.) in anhydrous CH_2Cl_2 (30 mL) in a round-bottom flask was added TFA (30 equiv.), and the reaction was left stirring for 1 h at RT under inert

atmosphere (Ar). After that, the volatiles were removed using a rotatory evaporator.

(D) Reductive amination. To a solution of the conjugate ammonium salt (0.6139 mmol) in DCE (30 mL) in a round bottom flask was subsequentially added CH_2O (37% m/v, 1.54 mmol) and $NaBH(OAc)_3$ (3.069 mmol). The resulting suspension was stirred for 2 h. The solvent was then removed using a rotatory evaporator and CH_2Cl_2 (25 mL) was added to induce the precipitation of excess reductive agent and inorganic salts followed by filtration. The filtrate was concentrated *in vacuo* providing in most cases the *N*,*N*-dimethylated conjugates pure enough to be analytically characterized.

Synthesis of Boc-Glu(aminoindane)-OMe (1a). General protocol A.1, starting from 0.4909 g of Boc-Glu(OH)-OMe. The resulting residue was purified by chromatographic column using EtOAc. Aspect: brown solid. Yield: 95% (0.6720 g). M.p.: 120–122 °C. $[\alpha]_D^{18} = -655.4 \pm 0.1$ (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 7.30–7.14 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 6.23 (d, J = 6.9 Hz, 1H, CONH); 5.43 (q, J = 7.7 Hz, 1H, H_a-1); 5.34 (d, J = 7.5 Hz, 1H, CONH); 4.27 (br s, 1H, H_E-2); 3.72 (s, 3H, CO_2CH_3); 3.00–2.81 (m, 2H, H_a-3); 2.56 (dtd, J = 12.8, 7.9, 4.0 Hz, 1H), 2.36–2.16 (m, 3H); 2.00–1.73 (m, 2H); 1.40 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [172.9 (Cq), 171.8 (Cq), C_E-1 + C_E-5]; 155.8 (Cq, OCONH); [143.5 (Cq), 143.2 (Cq), C_a-3a + C_a-7a]; [128.0 (CH), 126.8 (CH), 124.9 (CH), 124.2 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; 80.2 (Cq, $\underline{C}(CH_3)_3$); [54.9 (CH), 53.2 (CH), C_a-1 + C_E-2]; 52.5 (CH_3,CO_2CH_3); [34.0 (CH_2), 32.8 (CH_2), 30.3 (CH_2), 28.9 (CH_2), C_a-2 + C_a-3 + C_E-3 + C_E-4]; 28.4 (3 × CH_3, $C(\underline{C}H_3)_3$). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{20}H_{29}N_2O_5]^+$ 377.21, found 377.22.

Synthesis of Boc-Glu(amantadine)-OMe (1b). General protocol A.1, starting from 0.5821 g of Boc-Glu(OH)-OMe. The resulting residue was purified by precipitation using Et_2O. Aspect: white solid. Yield: 90% (0.7911 g). M.p.: 190–191 °C. $[\alpha]_D^{16} = +14.5 \pm 0.1$ (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 5.53 (br s, 1H, CONH); 5.27 (d, J = 6.5 Hz, 1H, CONH); 4.25 (m, 1H, H_E-2); 3.72 (s, 3H, CO_2CH_3); [2.23–1.84 (m, 15H), 1.66 (s, 4H), H_E-3 + H_E-4 + H_b-2 + H_b-3 + H_b-10]; 1.42 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [173.0 (Cq), 171.1 (Cq), C_E-1 + C_E-5]; 155.8 (Cq, OCONH); 80.1 (Cq, $\underline{C}(CH_3)_3$); 53.3 (CH, C_E-2), 52.5 (CH_3, CO_2CH_3); 52.1 (Cq, C_b-1); 41.7 (3 × CH_2, C_b-2), 36.5 (3 × CH_2, C_b-3), 33.8, (CH_2, C_E-4), 29.5 (3 × CH, C_b-4), 28.8 (CH_2, C_E-3); 28.4 (3 × CH_3, $C(\underline{C}H_3)_3$). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{21}H_{35}N_2O_5]^+$ 395.25, found 395.23.

Synthesis of Boc-Glu(memantine)-OMe (1c). General protocol A.1, starting from 0.4013 g of Boc-Glu(OH)-OMe. The resulting residue was purified by chromatographic column using EtOAc. Aspect: yellow oil. Yield: 94% (0.6101 g). $[\alpha]_D^{22}$ = +52.2 ± 0.4 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 5.57 (br s, 1H, CONH); 5.29 (d, J = 7.0 Hz, 1H, CONH); 4.27 (br s, 1H, H_E-2); 3.74 (s, 3H, CO_2CH_3); 2.22–2.11 (m, 4H, H_E-3 + H_E-4); [1.71–1.60 (m, 5H), 1.54–1.31 (m, 17H), $C(CH_3)_3$ + H_c-2 + H_c-3 + H_c-4 + H_c-5 + H_c-6 + H_c-7 + H_c-8 + H_c-9 + H_c-10]; 0.85 (s, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [173.0 (Cq), 171.1 (Cq), C_E-1 + C_E-5]; 155.9 (Cq, OCONH); 80.1 (Cq, $\underline{C}(CH_3)_3$); 53.7 (Cq, C_c-1); 53.3 (CH, C_E-2); 52.5 (CH_3, CO_2CH_3); [50.7, 47.6, 42.8, 40.2 (CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10 + C_E-3 + C_E-4]; 32.5 (2 × Cq, C_c-3 + C_c-7); [30.2, 28.5, 21.2, (CH + 5 × CH_3), C_c-11 + C_c-12 + $C(\underline{C}H_3)_3$ + C_c-5]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{23}H_{39}N_2O_5]^+$ 423.29, found 423.26.

Synthesis of Boc-Glu(OMe)-aminoindane (3a). General protocol A.1, starting from 0.4922 g of Boc-Glu(OMe)-OH. The resulting residue was purified by chromatographic column using EtOAc. Aspect: light brown solid. Yield: 91% (0.6454 g). M.p.: 96–98 °C. $[\alpha]_D^{19} = -24.0 \pm 0.1$ (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 7.26–7.12 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 6.56 (d, J = 6.8 Hz, 1H, CONH); 5.43 (q, J = 7.8 Hz, 1H, H_a-1); 5.35 (d, J = 8.0 Hz, 1H, CONH); 4.15 (s, 1H, H_E-2); 3.66 (s, 3H, CO_2CH_3); 3.02–2.77 (m, 2H, H_a-3); [2.64–2.35 (m, 3H); 2.15 (dtd, J = 12.7, 7.3, 5.5 Hz, 1H), H_a-2 + H_E-3]; 1.99–1.73 (m, 2H, H_E-4); 1.41 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [173.9 (Cq), 171.4 (Cq), C_E-1 + C_E-5]; 155.8 (Cq, CONH); [143.4 (Cq), 142.9 (Cq), C_a-3a + C_a-7a]; [128.1 (CH), 126.9 (CH), 124.9 (CH), 124.1 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; 80.2 (Cq, $\underline{C}(CH_3)_3$); [54.7 (CH), 53.9 (CH), C_a-1 + C_E-2]; 51.9 (CH_3, CO_2CH_3); [34.1 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 28.4 (CH_2), C_a-2 + C_a-3 + C_E-3 + C_E-4]; 27.9 (3 × CH_3, $C(\underline{C}H_3)_3$). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{20}H_{29}N_2O_5]^+$ 377.21, found 377.24.

Synthesis of Boc-Glu(OMe)-amantadine (3b). General protocol A.1, starting from 0.5803 g of Boc-Glu(OMe)-OH. The resulting residue was purified by chromatographic column using EtOAc. Aspect: colourless oil. Yield: 89% (0.7798 g). $[\alpha]_D^{18} = -14.3 \pm 0.2$ (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 5.88 (br s, 1H, CONH); 5.26 (d, J = 7.7 Hz, 1H, CONH); 3.99 (s, 1H, H_E-2); 3.67 (s, 3H, CO_2CH_3); 2.54–2.27 (m, 2H, H_E-4); 2.11–1.80 (m, 11H, H_E-3 + H_b-2 + H_b-3); 1.66 (t, 6H, H_b-4); 1.42 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [173.9 (Cq), 170.4 (Cq), C_E-1 + C_E-5]; 155.8 (Cq, OCONH); 79.9 (Cq, $\underline{C}(CH_3)_3$); 54.1 (CH, C_E-2); 51.9 (CH_3, CO_2CH_3); 52.2 (Cq, C_b-1); [41.6, 36.4, 30.4, (6 × CH_2), C_b-2 + C_b-4]; 29.5 (3 × CH, C_b-3); 28.5 (2 × CH_2, C_E-3 + C_E-4); 28.4 (3 × CH_3, $C(\underline{C}H_3)_3$). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{21}H_{35}N_2O_5]^+$ 395.25, found 395.25.

Synthesis of Boc-Glu(OMe)-memantine (3c). General protocol A.1, starting from 0.4021 g of Boc-Glu(OMe)-OH. The resulting residue was purified by chromatographic column using EtOAc. Aspect: white solid with low melting point. Yield: 89% (0.5788 g). $[\alpha]_D^{22} = -16.5 \pm 0.3$ (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 5.94 (br s, 1H, CONH); 5.26 (d, J = 7.9 Hz, 1H, CONH); 4.00 (br s, 1H, H_E-2); 3.68 (s, 3H, CO_2CH_3); 2.59–2.32 (m, 2H, H_E-4); [1.94–1.75 (m, 4H), 1.70–1.56 (m, 4H), 1.51–1.30 (m, 13H), 1.22–1.08 (m, 3H), H_E-3 + $C(CH_3)_3$ + H_c-2 + H_c-3 + H_c-4 + H_c-5 + H_c-6 + H_c-7 + H_c-8 + H_c-9 + H_c-10]; 0.84 (s, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [173.9 (Cq), 170.5 (Cq), C_E-1 + C_E-5]; 155.8 (Cq, OCONH); 80.0 (Cq, $\underline{C}(CH_3)_3$); 53.8 (Cq, C_c-1); 54.1 (CH, C_E-2); 51.9 (CH_3, CO_2CH_3); [50.7, 47.6, 42.8, (6 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 40.2 (2 × CH_2, C_E-3 + C_E-4); 32.5 (2 × Cq, C_c-3 + C_c-7); [30.2, 28.4, 21.2, (CH + 5 × CH_3), C_c-11 + C_c-12 + $C(\underline{C}H_3)_3$ + C_c-5]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{23}H_{39}N_2O_5]^+$ 423.29, found 423.31.

Synthesis of Boc-Glu(aminoindane)-aminoindane (5a) and glutarimide 6a. General protocol A.2, starting from 0.3460 g of Boc-Glu(OH)-OH. The resulting residue was purified by chromatographic column using EtOAc obtaining 0.2340 g (35% yield) of a beige solid identified as **5a** and 0.1450 g (30% yield) of a beige solid identified as **6a**. Analytical data for **5a**: m.p.: 195–196 °C. $[\alpha]_D^{20}$ = +116.6 ± 0.4 (*c*1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz), rotamers present (70 : 30), δ ppm: 7.33–7.09 (m, 8H, H_a-4 + H_a-5 + H_a-6 + H_a-7 + $H_{a'}$-4′ + $H_{a'}$-5′ + $H_{a'}$-6′ + $H_{a'}$-7′); [6.94 (d, *J* = 6.0 Hz, minor), 6.80 (d, *J* = 8.3 Hz, major), 1H, CONH]; [6.30 (d, *J* = 7.0 Hz, major), 6.25 (d, *J* = 8.3 Hz, minor), 1H, CONH]; [5.87 (d, *J* = 4.8 Hz, minor), 5.76 (d, *J* = 7.3 Hz, major), 1H, CONH]; 5.49–5.34 (m, 2H, H_a-1 + $H_{a'}$-1′); 4.21–4.07 (m, 1H, H_E-2); 2.96 (ddd, *J* = 15.6, 8.6, 3.7 Hz, 2H, H_a-3 + $H_{a'}$-3′); 2.84 (dt, *J* = 16.0, 8.0 Hz, 2H, 2 × H_a-3 + $H_{a'}$-3′); 2.60–2.48 (m, 2H); 2.43–2.28 (m, 2H); 2.21–1.93 (m, 2H); 1.86–1.73 (m, 2H); 1.43–1.39 [1.41 (s), 1.40 (s), 9H, $C(CH_3)_3$]. ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [143.4 (Cq), 143.4 (Cq), 143.3 (Cq), 143.1 (Cq), 142.9 (Cq), C_E-1 + C_E-5 + CONH + C_a-3a + C_a-7a + $C_{a'}$-3a′ + $C_{a'}$-7a′]; [128.1 (CH), 126.8 (CH), 124.9 (CH), 124.2 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7 + $C_{a'}$-4′ + $C_{a'}$-5′ + $C_{a'}$-6′ + $C_{a'}$-7′]; 80.2 (Cq, $\underline{C}(CH_3)_3$); [54.9, 54.7, (3 × CH), C_a-1 + $C_{a'}$-1′+ C_E-2]; [33.9 (CH_2), 32.9 (CH_2), 30.4 (CH_2), 30.3 (CH_2), C_a-2 + C_a-3 + $C_{a'}$-2′ + $C_{a'}$-3′ + C_E-3 + C_E-4]; 28.4 (3 × CH_3, $C(\underline{C}H_3)_3$). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{28}H_{36}N_3O_4]^+$ 478.27, found 478.30. Analytical data for **6a**: m.p.: 200–202 °C. $[\alpha]_D^{20}$ = +58.1 ± 0.2 (*c*1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 7.27–7.10 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 6.61 (d, *J* = 8.0 Hz, 1H, CONH); 5.44 (q, *J* = 7.7 Hz, 1H, H_a-1); 4.51 (dd, *J* = 8.9, 2.9 Hz, 1H, H_E-2); 2.98 (ddd, *J* = 15.8, 8.7 Hz, 1H, H_a-3); 2.86 (dt, *J* = 16.0, 8.1 Hz, 1H, H_a-3); 2.69 (dt, *J* = 17.5, 9.8 Hz, 1H); 2.55 (dtd, *J* = 11.8, 7.9, 4.0 Hz, 1H); 2.40 (ddd, *J* = 17.4, 9.4, 3.4 Hz, 1H); 2.23 (ddd, *J* = 18.7, 13.0, 9.5 Hz, 1H); 2.11 (ddt, *J* = 12.9, 9.7, 3.1 Hz, 1H); 1.83 (ddd, *J* = 16.0, 12.9, 8.4 Hz, 1H); 1.47 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [174.0 (Cq), 170.8 (Cq), 149.9 (Cq), 143.2 (Cq), 142.8 (Cq), C_E-1 + C_E-5 + OCONH + C_a-3a + C_a-7a]; [128.1 (CH), 126.8 (CH), 124.8 (CH), 124.2 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; 83.7 (Cq, $\underline{C}(CH_3)_3$); [60.2, 54.8, (2 × CH), C_a-1 + C_E-2]; [33.6 (CH_2), 31.6 (CH_2), 30.2 (CH_2), 22.3 (CH_2), C_a-2 + C_a-3 + C_E-3 + C_E-4]; 27.9 (3 × CH_3, $C(\underline{C}H_3)_3$). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{19}H_{25}N_2O_4]^+$ 345.18, found 345.19.

Synthesis of Boc-Glu(amantadine)-amantadine (5b) and glutarimide 6b. General protocol A.2, starting from 0.8230 g of Boc-Glu(OH)-OH. The resulting residue was purified by chromatographic column using EtOAc obtaining 0.5651 g (33% yield) of a white solid identified as **5b** and 0.3262 g (27% yield) of a white solid identified as **6b**. Analytical data for **5b**: m.p.: 42–45 °C. $[\alpha]_D^{20}$ = +56.8 ± 0.4 (*c*1, CHC_3). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 6.16 (br s, 1H, CONH); 5.59 (d, *J* = 7.3 Hz, 1H, CONH); 5.50 (br s, 1H, CONH); 4.05–3.87 (m, 1H, H_E-2); 2.31–2.13 (m, 2H, H_E-4); 2.12–2.03 (m, 6H); 2.03–1.96 (m, 12H); 1.95–1.82 (m, 2H, H_E-3); 1.73–1.61 (m, 12H); 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [171.9 (Cq), 170.7 (Cq), C_E-1 + C_E-5]; 52.2 (CH, C_E-2); 52.1 (CH_3, CO_2CH_3); 52.2 (Cq, C_b-1); [41.7, 41.6, 36.5, (CH_2), C_b-2 + C_b-4 + $C_{b'}$-2′ + $C_{b'}$-4′]; 29.6 (6 × CH, C_b-3 + $C_{b'}$-3′); 28.5 (3 × CH_3, $C(\underline{C}H_3)_3$). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{30}H_{48}N_3O_4]^+$ 514.36, found 514.39. Analytical data for **6b**: m.p.: 193–195 °C. $[\alpha]_D^{20}$ = −46.5 ± 0.2 (*c*1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 5.61 (br s, 1H, CONH), 4.36 (dd, *J* = 8.9, 2.6 Hz, 1H, H_E-2), 2.73 (dt, *J* = 17.6, 9.9 Hz, 1H), 2.43 (ddd, *J* = 17.5, 9.4, 3.3 Hz, 1H), 2.20 (ddd, *J* = 19.1, 12.9, 9.4 Hz, 1H), 2.14–1.92 (m, 10H), 1.77–1.61 (m, 6H), 1.52 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [174.1 (Cq), 169.7 (Cq), C_E-1 + C_E-5]; 150.0 (Cq, O$\underline{C}$ONH); 83.7 (Cq, $\underline{C}(CH_3)_3$); [60.8 (CH + CH_3), C_E-2 + CO_2CH_3]; 52.3 (Cq, C_b-1); [41.6, 36.4, 31.7, 22.4 (6 × CH_2), C_b-2 + C_b-4];, [29.5, 28.1 (3 × CH, C_c-3) + (3 × CH_3, $C(\underline{C}H_3)_3$)]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{20}H_{31}N_2O_4]^+$ 363.23, found 363.28.

Synthesis of Boc-Glu(memantine)-memantine (5c) and glutarimide 6c. General protocol A.2, starting from 0.7398 g of Boc-Glu(OH)-OH. The resulting residue was purified by chromatographic column using Hex/EtOAc (1 : 2) obtaining 0.4271 g (25% yield) of a yellow oil identified as **5c** and 0.2949 g (19% yield) of a colourless oil identified as **6c**. Analytical data for **5c**: $[\alpha]_D^{23}$ = −5.6 ± 0.1 (*c*1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 6.20 (d, *J* = 6.0 Hz, 1H, CONH), 5.60 (d, *J* = 7.5 Hz, 2H, 2 × CONH), 3.95 (d, 1H, H_E-2), 2.30–2.09 (m, 4H, H_E-3 + H_E-4), 2.01–1.79 (m, 6H), 1.63 (s, 8H), 1.44 (s, 9H, $C(CH_3)_3$), 1.39–1.33 (m, 4H), 1.30–1.24 (m, 4H), 1.18–1.08 (m 4H), 0.83 (d, *J* = 2.5 Hz, 12H, H_c-11 + H_c-12 + $H_{c'}$-11′ + $H_{c'}$-12′). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [172.1 (Cq), 170.9 (Cq), C_E-1 + C_E-5]; 155.9 (Cq, O$\underline{C}$ONH); 79.8 (Cq, $\underline{C}(CH_3)_3$); 53.8 (CH, C_E-2); 53.7 (CH_3, CO_2CH_3); [50.7, 47.6, 42.8, 40.2, (12 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10 + $C_{c'}$-2′ + $C_{c'}$-4′ + $C_{c'}$-6′ + $C_{c'}$-8′ + $C_{c'}$-9′ + $C_{c'}$-10′]; 32.5 (Cq, C_c-1 + $C_{c'}$-1′), 30.2 (6 × CH, C_c-3 + C_c-5 + C_c-7 + $C_{c'}$-3′ + $C_{c'}$-5′ + $C_{c'}$-7′); 28.5 (3 × CH_3, $C(\underline{C}H_3)_3$). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{34}H_{56}N_3O_4]^+$ 570.43, found 570.50. Analytical data for **6c**: $[\alpha]_D^{23}$ = −17.9 ± 0.2 (*c*1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 5.55 (br s, 1H, CONH), 4.28 (dd, *J* = 8.8, 2.7 Hz, 1H, H_E-2), 2.20–2.00 (m, 4H, H_E-3 + H_E-4), 1.75 (d, *J* = 2.9 Hz, 3H), 1.65–1.53 (m, 4H), 1.46 (s, 9H, $C(CH_3)_3$), 1.37 (d, *J* = 2.0 Hz, 2H), 1.31 (d, *J* = 12.1 Hz, 2H), 1.26–1.16 (m, 2H), 0.78 (d, *J* = 1.9 Hz, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [174.1 (Cq), 169.9 (Cq), C_E-1 + C_E-5]; 150.2 (Cq, O$\underline{C}$ONH); 83.8 (Cq, $\underline{C}(CH_3)_3$); [60.8, (CH + CH_3), C_E-2 + CO_2CH_3]; [50.6, 47.7, 42.7, 40.2, 30.2, 22.3 (6 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 32.5 (Cq, C_c-1), 30.1 (3 × CH, C_c-3 + C_c-5 + C_c-7); 28.43 (2 × CH_3, C_c-11 + C_c-12); 28.1 (3 × CH_3, $C(\underline{C}H_3)_3$). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{22}H_{35}N_2O_4]^+$ 391.26, found 391.23.

Synthesis of H-Glu(aminoindane)-OMe (2a). General protocol C, starting from 0.6441 g of **1a**. Aspect: brown oil. Yield: 97% (0.6479 g). $[\alpha]_D^{17}$ = −35.6 ± 0.2 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz) δ ppm: 7.28–7.14 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 5.37 (t, *J* = 7.5 Hz, 1H, H_a-1); 4.15–4.09 (t, *J* = 6.3 Hz, 1H, H_E-2); 3.85 (s, 3H, CO_2CH_3); 3.01 (m, 1H, H_a-3); 2.85 (m, 1H, H_a-3); [2.58–2.42 (m, 3H), 2.22 (dp, *J* = 14.6, 6.9 Hz, 2H), 1.85 (ddd, *J* = 16.0, 12.8, 8.2 Hz, 1H), H_a-2 + H_E-3 + H_E-4]. ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz) δ ppm: [173.8 (Cq), 170.7 (Cq), C_E-1 + C_E-5]; [144.6 (Cq), 144.2 (Cq), C_a-4 + C_a-9]; [128.9 (CH), 127.7 (CH), 125.7 (CH), 124.9 (CH),

C_a-4 + C_a-5 + C_a-6 + C_a-7]; [55.9 (CH), 53.7 (CH), C_a-1 + C_E-2]; 53.6 (CH_3, CO_2CH_3); [34.3 (CH_2), 32.3 (CH_2), 31.0 (CH_2), 27.2 (CH_2), C_a-2 + C_a-3 + C_E-3 + C_E-4]. ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{15}H_{21}N_2O_3]^+$ 277.15, found 277.14.

Synthesis of H-Glu(amantadine)-OMe (2b). General protocol C, starting from 0.7571 g of **1b**. Aspect: yellow oil. Yield: 98% (0.7681 g). $[\alpha]_D^{22}$ = +25.6 ± 0.1 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz) δ ppm: 4.06 (t, *J* = 6.4 Hz, 1H, H_E-2); 3.84 (s, 3H, CO_2CH_3); 2.39 (dd, *J* = 10.5, 4.3 Hz, 2H, H_E-4); 2.21 (m, 11H, H_E-3 + H_b-2 + H_b-3); 1.71 (s, 6H, H_b-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz) δ ppm: [173.2 (Cq), 170.7 (Cq), C_E-1 + C_E-5]; 53.7 (CH, C_E-2); 53.7 (CH_3, CO_2CH_3); 53.0 (Cq, C_b-1); [42.3, 37.5, 33.2 (6 × CH_2), C_b-2 + C_b-4]; 30.9 (3 × CH, C_b-3 + C_b-5 + C_b-7); 27.3 (2 × CH_2, C_E-3, C_E-4). ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{16}H_{27}N_2O_3]^+$ 295.20, found 295.18.

Synthesis of H-Glu(memantine)-OMe (2c). General protocol C, starting from 0.5590 g of **1c**. Aspect: yellow oil. Yield: 98% (0.5659 g). $[\alpha]_D^{21}$ = −8.2 ± 0.9 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 6.08 (br s, 1H, CONH); 4.14 (d, *J* = 7.1 Hz, 1H, H_E-2); 3.82 (s, 3H, CO_2CH_3); [2.54–2.14 (m, 5H), 1.79 (s, 2H), 1.58 (q, *J* = 12.0 Hz, 5H), 1.38–1.25 (m, 5H), 1.14 (s, 2H), H_E-3 + H_E-4 + H_c-2 + H_c-4 + H_c-5 + H_c-6 + H_c-8 + H_c-9 + H_c-10]; 0.85 (s, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [172.5 (Cq), 169.7 (Cq), C_E-1 + C_E-5]; 54.7 (Cq, C_c-1); 53.7 (CH, C_E-2); 52.9 (CH_3, CO_2CH_3); [50.6, 47.2, 42.6, (6 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 39.7 (2 × CH_2, C_E-3 + C_E-4); 32.5 (2 × Cq, C_c-3 + C_c-7); [30.1, 26.1, (CH + 2 × CH_3), C_c-5 + C_c-11 + C_c-12]. ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{18}H_{31}N_2O_3]^+$ 323.23, found 323.27.

Synthesis of H-Glu(OMe)-aminoindane (4a). General protocol C, starting from 0.6173 g of **3a**. Aspect: brown oil. Yield: 98% (0.6274 g). $[\alpha]_D^{21}$ = +60.9 ± 0.3 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz) δ ppm: 7.37–7.11 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 5.41 (t, *J* = 7.3 Hz, 1H, H_a-1); 3.91 (t, *J* = 6.5 Hz, 1H, H_E-2); 3.70 (s, 3H, CO_2CH_3); 3.04 (ddd, *J* = 15.9, 8.7, 4.3 Hz, 1H, H_a-3); 2.90 (m, 1H, H_a-3); [2.62–2.41 (m, 3H); 2.30–2.07 (m, 2H); 1.97–1.83 (m, 1H), H_a-2 + H_E-3 + H_E-4]. ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz) δ ppm: [174.1 (Cq), 169.3 (Cq), C_E-1 + C_E-5]; [144.6 (Cq), 143.7 (Cq), C_a-3a + C_a-7a]; [129.2 (CH), 127.7 (CH), 125.8 (CH), 125.2 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; [56.1 (CH), 53.8 (CH), C_a-1 + C_E-2]; 52.5 (CH_3, CO_2CH_3); [34.3 (CH_2), 31.1 (CH_2), 30.0 (CH_2), 27.7 (CH_2), C_a-2 + C_a-3 + C_E-3 + C_E-4]. ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{15}H_{21}N_2O_3]^+$ 277.15, found 277.19.

Synthesis of H-Glu(OMe)-amantadine (4b). General protocol C, starting from 0.7283 g of **3b**. Aspect: colourless solid with low melting point. Yield: 98% (0.7390 g). $[\alpha]_D^{22}$ = +5.4 ± 0.1 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz) δ ppm: 3.80 (t, *J* = 6.4 Hz, 1H, H_E-2); 3.70 (s, 3H, CO_2CH_3); 2.48 (td, *J* = 7.3, 1.3 Hz, 2H, H_E-4); 2.16–2.01 (m, 11H, H_E-3 + H_b-2 + H_b-3); 1.73 (s, 6H, H_b-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz) δ ppm: [174.2 (Cq), 168.3 (Cq), C_E-1 + C_E-5]; 53.9 (CH, C_E-2); 53.5 (CH_3, CO_2CH_3); 52.5 (Cq, C_b-1); [42.2, 37.3, 30.8 (6 × CH_2), C_b-2 + C_b-4]; 30.1 (3 × CH, C_b-3); 27.8 (2 × CH_2, C_E-3, C_E-4). ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{16}H_{27}N_2O_3]^+$ 295.20, found 295.16.

Synthesis of H-Glu(OMe)-memantine (4c). General protocol C, starting from 0.5281 g of **3c**. Aspect: brown oil. Yield: 97% (0.5292 g). $[\alpha]_D^{21}$ = +7.7 ± 0.9 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 6.90 (br s, 1H, CONH); 4.12 (d, *J* = 7.1 Hz, 1H, H_E-2); 3.70 (s, 3H, CO_2CH_3); [2.56 (q, *J* = 18.2 Hz, 2H), 2.13 (s, 3H), 1.79 (s, 2H), 1.72–1.48 (m, 4H), 1.40–1.24 (m, 5H), 1.14 (s, 2H), H_E-3 + H_E-4 + H_c-2 + H_c-4 + H_c-5 + H_c-6 + H_c-8 + H_c-9 + H_c-10]; 0.84 (s, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [174.5 (Cq), 167.3 (Cq), C_E-1 + C_E-5]; 54.9 (Cq, C_c-1); 53.4 (CH, C_E-2); 52.6 (CH_3, CO_2CH_3); [50.5, 47.1, 42.6, (6 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 39.7 (2 × CH_2, C_E-3 + C_E-4); 32.5 (2 × Cq, C_c-3 + C_c-7); [30.0, 26.8, (CH + 2 × CH_3), C_c-5 + C_c-11 + C_c-12]. ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{18}H_{31}N_2O_3]^+$ 323.23, found 323.28.

Synthesis of Boc-Gly-Pro-Glu(aminoindane)-OMe (7a). General protocol B, starting from 0.1521 g of L-proline. The resulting residue was purified by chromatographic column using EtOAc. Aspect: light brown solid. Yield: 70% (0.4907 g). M.p.: 43–45 °C. $[\alpha]_D^{15}$ = −22.0 ± 0.3 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (85 : 15), δ ppm: 7.34–7.11 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 5.37 (t, *J* = 7.8 Hz, 1H, H_a-1); 4.53–4.30 (m, 2H, H_E-2 + H_P-2); 3.85 (dd, *J* = 16.9, 3.9 Hz, 1H, H_G-2); 3.73 (s, 3H, CO_2CH_3); 3.58–3.46 (m, 3H, H_G-2 + 2H_P-5); 3.00–2.75 (m, 2H, H_a-3); 2.56–2.28 (m, 4H, H_P-3 + H_a-2); 2.24–1.78 (m, 6H, H_P-4 + H_E-3 + H_E-4); [1.41 (s, major), 1.36 (s, minor), 9H, C(CH_3)$_3$]. ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [174.5 (Cq), 174.4 (Cq), 173.6 (Cq), 170.0 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; 158.0 (Cq, CONH); [144.5 (Cq), 144.2 (Cq), C_a-3a + C_a-7a]; [128.8 (CH), 127.7 (CH), 125.7 (CH), 125.4 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; 80.6 (Cq, $\underline{C}(CH_3)_3$); [61.5, 55.8, 52.8, 52.7, (3 × CH + CH_3), C_a-1 + C_E-2 + C_P-2 + CO_2CH_3]; [47.7 (CH_2), 43.7 (CH_2), C_P-5 + C_G-2]; 38.9 (CH, C_P-2); [34.7 (CH_2), 32.9 (CH_2), C_a-2 + C_a-3]; 31.0 (CH_2, C_P-4); 30.3 (CH_2, C_E-4); [28.7, 28.6, 3 × CH_3, C($\underline{C}H_3$)$_3$]; [28.5 (CH_2), 27.8 (CH_2), C_E-3]; [25.9 (CH_2), 23.4 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{27}H_{39}N_4O_7]^+$ 531.28, found 531.32.

Synthesis of Boc-Gly-Pro-Glu(amantadine)-OMe (7b). General protocol B, starting from 0.1671 g of L-proline. The resulting residue was purified by chromatographic column using EtOAc. Aspect: white solid. Yield: 68% (0.5414 g). M.p.: 61–63 °C. $[\alpha]_D^{16}$ = −9.8 ± 0.3 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz), rotamers present (85 : 15), δ ppm: 7.23 (d, *J* = 7.6 Hz, 1H, CONH); [5.84 (br s, major), 5.73 (br s, minor), 1H, CONH]; [5.48 (br s, minor), 5.40 (br s, major), 1H, CONH]; 4.56–4.41 (m, 2H, H_E-2 + H_P-2); 4.05–3.83 (m, 2H, H_G-2); 3.72 (s, 3H, CO_2CH_3); 3.63–3.34 (m, 2H, H_P-5); 2.24–1.84 (m, 17H, H_E-3 + H_E-4 + H_P-3 + H_P-4 + H_b-2 + H_b-3); 1.66 (s, 6H, H_b-4); 1.44 (s, 9H, C(CH_3)$_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz), rotamers present, δ ppm: [172.5 (Cq), 171.4 (Cq), 171.3 (Cq), 168.4 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; 155.9 (Cq, OCONH); 79.9 (Cq, $\underline{C}(CH_3)_3$); [60.5, 52.5, 51.8, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 52.0 (Cq, C_b-1); [47.3 (CH_2), 46.5 (CH_2), 43.3(CH_2), C_G-2 + C_P-5]; [41.5, 36.5 (6 × CH_2), C_b-2 + C_b-4]; [33.2, 32.3, CH_2, C_P-4]; 29.5 (3 × CH, C_b-3); 28.6 (CH_2, C_E-4); 28.5 (3 × CH_3, C($\underline{C}H_3$)$_3$); 28.3 (CH_2, C_E-3); [24.9 (CH_2), 22.9 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{28}H_{45}N_4O_7]^+$ 549.33, found 549.30.

Synthesis of Boc-Gly-Pro-Glu(memantine)-OMe (7c). General protocol B, starting from 0.1088 g of L-proline. The resulting residue was purified by chromatographic column using EtOAc. Aspect: yellow solid with low m.p. Yield: 49% (0.2671 g). $[\alpha]_D^{18}$ = +50.6 ± 0.9 (*c*1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz), rotamers present (80 : 20), δ ppm: 7.69 (dd, J = 5.7, 3.3 Hz, 1H, CONH); [5.83 (s, major), 5.76 (s, minor), 1H, CONH]; [5.47 (s, minor), 5.37 (s, major), 1H, CONH]; 4.56–4.40 (m, 2H, H_E-2 + H_P-2); 4.07–3.84 (m, 2H, H_G-2); 3.72 (s, 3H, CO_2CH_3); 3.64–3.39 (m, 2H, H_P-5); 2.37–1.84 (m, 9H, H_P-3 + H_P-4 + H_E-3 + H_E-4 + H_c-5); [1.83–1.59 (m, 3H), 1.51–1.07 (m, 18H), H_c-4 + H_c-6 + H_c-9, $C(CH_3)_3$ + H_c-2 + H_c-8 + H_c-10); 1.01–0.76 (m, 6H, H_c-11 + H_c-12)]. ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz), rotamers present, δ ppm: [172.3 (Cq), 171.8 (Cq), 167.4 (Cq), 167.0 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; 155.7 (Cq, OCONH); 79.2 (Cq, $\underline{C}(CH_3)_3$); [59.2, 58.7, 51.9, 51.8 (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 51.4 (CH, C_c-5); 52.2 (Cq, C_c-1); [50.3 (CH_2), 46.9 (CH_2), C_G-2 + C_P-5]; [42.3, 32.3, 29.8 (6 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 32.9 (2 × Cq, C_c-3 + C_c-7); [29.0 (CH_2), 28.4 (CH_2), C_P-4]; 28.2 (2 × CH_3, C_c-11 + C_c-12); [27.2 (CH_2), 24.3 (CH_2), 23.3 (CH_2), 22.4 (CH_2), 25.1 (CH_2), 24.9 (CH_2), C_E-4 + C_E-3 + C_P-3]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{30}H_{49}N_4O_7]^+$ 577.36, found 577.35.

Synthesis of Boc-Gly-Pro-Glu(OMe)-aminoindane (8a). General protocol B, starting from 0.1470 g of L-proline. The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated. The resulting residue was purified by chromatographic column using EtOAc. Aspect: light brown solid. Yield: 69% (0.4675 g). M.p.: 48–50 °C. $[\alpha]_D^{16}$ = −13.1 ± 0.1 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz) δ ppm: 7.28–7.12 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 5.36 (t, J = 7.6 Hz, 1H, H_a-1); 4.43–4.29 (m, 2H, H_E-2 + H_P-2); 3.88 (d, J = 17.1 Hz, 1H, H_G-2); 3.75 (d, J = 17.1 Hz, 1H, H_G-2); 3.67 (s, 3H, CO_2CH_3); 3.63–3.49 (m, 2H, H_P-5); 3.05 (ddd, J = 15.8, 8.7, 3.7 Hz, 1H, H_a-3); 2.87 (m, 1H, H_a-3); 2.56–1.77 (m, 10H, H_a-2 + H_P-3 + H_P-4 + H_E-3 + H_E-4); 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz) δ ppm: [175.2 (Cq), 174.6 (Cq), 173.2 (Cq), 170.6 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; 158.2 (Cq, CONH); [144.5 (Cq), 144.4 (Cq), C_a-3a + C_a-7a]; [128.9 (CH), 127.57 (CH), 125.7 (CH), 125.2 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; 80.7 (Cq, $\underline{C}(CH_3)_3$); [62.0, 55.9, 54.4, 52.2, (3 × CH + CH_3), C_a-1 + C_E-2 + C_P-2 + CO_2CH_3]; [47.8 (CH_2), 43.9 (CH_2), C_P-5 + C_G-2]; 38.9 (CH, C_P-2); [34.0 (CH_2), 31.3 (CH_2), 31.1 (CH_2), 30.5 (CH_2), C_a-2 + C_a-3 + C_P-4 + C_E-4]; 28.7 (3 × CH_3, $C(\underline{C}H_3)_3$); 27.7 (CH_2, C_E-3); 25.9 (CH_2, C_P-3). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{27}H_{39}N_4O_7]^+$ 531.28, found 531.30.

Synthesis of Boc-Gly-Pro-Glu(OMe)-amantadine (8b). General protocol B, starting from 0.1691 g of L-proline. The resulting residue was purified by chromatographic column using EtOAc. Aspect: white solid. Yield: 65% (0.5239 g). M.p.: 56–58 °C. $[\alpha]_D^{16}$ = −29.9 ± 0.1 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ ppm: 7.60 (d, J = 7.6 Hz, 1H, CONH); 6.18 (br s, 1H, CONH); 5.40 (br s, 1H, CONH); 4.45 (dd, J = 7.9 Hz, 1H, H_E-2); 4.28 (td, J = 7.6, 4.4 Hz, 1H, H_P-2); 4.14–3.81 (m, 2H, H_G-2); 3.70–3.55 (m, 4H, CO_2CH_3 + H_P-5); 3.48–3.37 (m, 1H, H_P-5); 2.53–2.34 (m, 2H, H_E-4); 2.18–1.90 (m, 15H, H_E-3 + H_P-3 + H_P-4 + H_b-2 + H_b-3); 1.65 (s, 6H, H_b-4); 1.42 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz) δ ppm: [175.5 (Cq), 170.9 (Cq), 169.6 (Cq), 168.8 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; 155.9 (Cq, CONH); 79.9 (Cq, $\underline{C}(CH_3)_3$); [61.1, 53.3, 52.1, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 52.3 (Cq, C_b-1); [46.5 (CH_2), 43.3 (CH_2), C_G-2 + C_P-5]; [41.5, 36.5, (6 × CH_2), C_b-2 + C_b-4]; 30.3 (CH_2, C_P-4); 29.6 (3 × CH, C_b-3); 28.9 (CH_2, C_E-4); 28.5 (3 × CH_3, $C(\underline{C}H_3)_3$); 26.9 (CH_2, C_E-3); 24.9 (CH_2, C_P-3). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{28}H_{45}N_4O_7]^+$ 549.33, found 549.35.

Synthesis of Boc-Gly-Pro-Glu(OMe)-memantine (8c). General protocol B, starting from 0.1089 g of L-proline. The resulting residue was purified by chromatographic column using EtOAc. Aspect: brown oil. Yield: 51% (0.2782 g). $[\alpha]_D^{24}$ = −10.6 ± 0.9 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz), rotamers present (85 : 15), δ ppm: 7.61 (d, J = 7.4 Hz, 1H, CONH); [6.40 (s, minor), 6.29 (s, major), 1H, CONH]; [5.41 (s, major), 5.30 (s, minor), 1H, CONH]; 4.53–4.19 (m, 2H, H_E-2 + H_P-2); 4.08–3.84 (m, 2H, H_G-2); 3.63 (s, 3H, CO_2CH_3); [2.54–2.32 (m, 1H), 2.81–2.62 (m, 1H), H_P-5]; 2.49–1.62 (m, 9H, H_P-3 + H_P-4 + H_E-3 + H_E-4 + H_c-5); 1.84–1.55 (m, 6H, H_c-4 + H_c-6 + H_c-9); 1.43–1.03 (m, 15H, $C(CH_3)_3$ + H_c-2 + H_c-8 + H_c-10); 0.80 (s, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz), rotamers present, δ ppm: [175.3 (Cq), 171.0 (Cq), 169.7 (Cq), 168.7 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; 155.8 (Cq, OCONH); 79.8 (Cq, $\underline{C}(CH_3)_3$); [60.9, 53.2, 52.0, 51.9 (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 51.9 (CH, C_c-5); 53.8 (Cq, C_c-1); [50.6 (CH_2), 47.3 (CH_2), C_G-2 + C_P-5]; [46.4, 42.7, 39.9 (6 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 32.4 (2 × Cq, C_c-3 + C_c-7); [30.4 (CH_2), 30.2 (CH_2), C_P-4]; 30.2 (2 × CH_3, C_c-11 + C_c-12); [29.2 (CH_2), 28.8 (CH_2), C_E-4]; 28.4 (3 × CH_3, $C(\underline{C}H_3)_3$); [27.2 (CH_2), 26.9 (CH_2), C_E-3]; [25.1 (CH_2), 24.9 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{30}H_{49}N_4O_7]^+$ 577.36, found 577.32.

Synthesis of H-Gly-Pro-Glu(aminoindane)-OMe (Ia). General protocol C, starting from 0.4582 g of **7a**. **Ia** was purified by chromatographic column using CH_2Cl_2/MeOH (9 : 1) as eluent. Aspect: white solid. Yield: 97% (0.4562 g). M.p.: 47–48 °C. $[\alpha]_D^{16}$ = −88.8 ± 0.6 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz) δ ppm: 7.36–7.14 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 5.37 (t, J = 7.6 Hz, 1H, H_a-1); 4.55–4.39 (m, 2H, H_E-2 + H_P-2); 3.74 (s, 3H, CO_2CH_3); 3.64–3.33 (m, 4H, 2H_P-5 + 2H_G-2); 2.99–2.77 (m, 2H, H_a-3); 2.57–1.75 (m, 10H, H_a-2 + H_P-3 + H_P-4 + H_E-3 + H_E-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz) δ ppm: [174.6 (Cq), 174.6 (Cq), 174.2 (Cq), 173.5 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [144.5 (Cq), 144.2 (Cq), C_a-3a + C_a-7a]; [128.9 (CH), 127.6 (CH), 125.7 (CH), 125.2 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; [61.5, 55.8, 52.9, 52.8, (3 × CH + CH_3), C_a-1 + C_E-2 + C_P-2 + CO_2CH_3]; [47.5 (CH_2), 43.3 (CH_2), C_P-5 + C_G-2]; 33.0 (CH_2, C_a-2 + C_a-3); 31.0 (CH_2, C_P-4); 30.5 (CH_2, C_E-4); 28.6 (CH_2, C_E-3); 25.7 (CH_2,C_P-3). ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{22}H_{31}N_4O_5]^+$ 431.23, found 431.17.

Synthesis of H-Gly-Pro-Glu(amantadine)-OMe (Ib). General protocol C, starting from 0.4497 g of **7b**. Aspect: yellow solid. Yield: 98% (0.4519 g). M.p.: 54–57 °C. $[\alpha]_D^{16}$ = +32.2 ± 0.4 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (80 : 20), δ ppm: [4.50 (dd, J = 8.3, 3.4 Hz, major), 4.46 (dd, J = 8.7, 2.9 Hz, minor), 1H, H_E-2]; 4.41–4.33 (m, 1H, H_P-2); 3.89 (d, J = 3.2 Hz, 2H, H_G-2); [3.73 (s, minor), 3.72 (s, major), 3H, CO_2CH_3]; 3.67–3.49 (m, 2H, H_P-5); 2.27–2.21 (m, 2H, H_E-4);

2.19–1.82 (m, 15H, H_E-3 + H_P-3 + H_P-4 + H_b-2 + H_b-3); 1.71 (s, 6H, H_b-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [174.3 (Cq), 173.9 (Cq), 173.5 (Cq), 166.0 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [61.4, 61.2, 53.8, 53.4, 52.8, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 52.8 (Cq, C_b-1); [48.5 (CH_2), 47.7 (CH_2), C_G-2 + C_P-5]; [42.3, 42.3, 41.4, 37.5, (6 × CH_2), C_b-2 + C_b-4]; [34.0 (CH_2), 33.9 (CH_2), C_P-4]; 30.9 (3 × CH, C_b-3); 30.7 (CH_2, C_E-4); [28.8 (CH_2), 27.9 (CH_2), C_E-3]; [25.5 (CH_2), 23.4 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M]^+$ Calcd for $[C_{23}H_{37}N_4O_5]^+$ 449.28, found 449.31.

Synthesis of H-Gly-Pro-Glu(memantine)-OMe (Ic). General protocol C, starting from 0.4011 g of **7c**. Aspect: white solid with low melting point. Yield: 95% (0.3903 g). $[\alpha]_D^{19}$ = −36.1 ± 0.2 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (80 : 20), δ ppm: 4.58–4.30 (m, 2H, H_E-2 + H_P-2); 3.90 (d, *J* = 7.5 Hz, 2H, H_G-2); [3.73 (s, minor), 3.72 (s, major), 3H, CO_2CH_3]; 3.64–3.45 (m, 2H, H_P-5); [2.52–1.73 (m, 11H), 1.64 (q, *J* = 11.9 Hz, 4H), 1.36 (dd, *J* = 29.8, 11.4 Hz, 4H), 1.16 (s, 2H), H_P-3 + H_P-4 + H_E-3 + H_E-4 + H_c-2 + H_c-4 + H_c-5 + H_c-6 + H_c-8 + H_c-9 + H_c-10]; 0.85 (s, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [174.0 (Cq), 173.5 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; 54.5 (Cq, C_c-1); [53.5, 52.9, 52.8, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; [51.7 (CH_2), 48.3 (CH_2), C_G-2 + C_P-5]; [43.8 (CH_2), 40.8 (CH_2), 34.1 (CH_2), 33.9 (CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 33.2 (2 × Cq, C_c-3 + C_c-7); [31.6, 30.7, (CH + 2 × CH_3), C_c-5 + C_c-11 + C_c-12]; 30.7 (CH_2, C_P-4); 28.8 (CH_2, C_E-4); 27.9 (CH_2, C_E-3); 23.5 (CH_2, C_P-3). ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{25}H_{41}N_4O_5]^+$ 477.31, found 477.31.

Synthesis of H-Gly-Pro-Glu(OMe)-aminoindane (IIa). General protocol C, starting from 0.4352 g of **8a**. **IIa** was purified by chromatographic column using CH_2Cl_2/MeOH (9 : 1) as eluent. Aspect: brown solid. Yield: 98% (0.4377 g). M.p.: 52–54 °C. $[\alpha]_D^{17}$ = −11.7 ± 0.8 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present, δ ppm: 7.30–7.08 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 5.38 (t, *J* = 7.5 Hz, 1H, H_a-1); 4.51–4.27 (m, 2H, H_E-2 + H_P-2); 3.67 (s, 3H, CO_2CH_3); 3.64–3.35 (m, 4H, 2H_G-2 + 2H_P-5); 3.13–2.73 (m, 2H, H_a-3); 2.60–1.72 (m, 10H, H_a-2 + H_P-3 + H_P-4 + H_E-3 + H_E-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [175.2, 174.4, 173.2, (4 × Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [144.6 (Cq), 144.3 (Cq), C_a-3a + C_a-7a]; [128.9 (CH), 127.6 (CH), 125.7 (CH), 125.1 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; [61.9, 55.8, 54.3, 52.3, (3 × CH + CH_3), C_a-1 + C_E-2 + C_P-2 + CO_2CH_3]; [47.6 (CH_2), 42.6 (CH_2), C_P-5 + C_G-2]; 31.2 (CH_2, C_P-4); 31.1 (CH_2, C_a-2 + C_a-3); 30.7 (CH_2, C_E-4); 27.9 (CH_2, C_E-3); 25.7 (CH_2, C_P-3). ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{22}H_{31}N_4O_5]^+$ 431.23, found 431.19.

Synthesis of H-Gly-Pro-Glu(OMe)-amantadine (IIb). General protocol C, starting from 0.4230 g of **8b**. Aspect: white solid. Yield: 98% (0.4251 g). M.p.: 67–69 °C. $[\alpha]_D^{16}$ = −31.2 ± 0.2 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (85 : 15), δ ppm: 4.51–4.43 (m, 1H, H_E-2); 4.31–4.23 (m, 1H, H_P-2); 3.89 (s, 2H, H_G-2); [3.68 (s, minor), 3.67 (s, major), 3H, CO_2CH_3]; 3.63–3.49 (m, 2H, H_P-5); 2.52–2.34 (m, 2H, H_E-4); 2.11–1.85 (m, 15H, H_E-3 + H_P-3 + H_P-4 + H_b-2 + H_b-3); 1.72 (s, 6H, H_b-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [175.2 (Cq), 173.9 (Cq), 172.2 (Cq), 166.2 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [61.6, 61.2, 54.6, 54.4, 52.4, 52.3, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 53.1 (Cq, C_b-1); [47.7 (CH_2), 42.3 (CH_2), C_G-2 + C_P-5]; [41.5, 37.4, (6 × CH_2), C_b-2 + C_b-4]; [31.3 (CH_2), 31.2 (CH_2), C_P-4]; 30.9 (3 × CH, C_b-3); 30.8 (CH_2, C_E-4); [28.7 (CH_2), 28.3 (CH_2), C_E-3]; [25.7 (CH_2), 23.4 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M]^+$ Calcd for $[C_{23}H_{37}N_4O_5]^+$ 449.28, found 449.33.

Synthesis of H-Gly-Pro-Glu(OMe)-memantine (IIc). General protocol C, starting from 0.2181 g of **8c**. Aspect: brown solid. Yield: 93% (0.2078 g). M.p.: 130–135 °C. $[\alpha]_D^{19}$ = −26.9 ± 0.2 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (80 : 20), δ ppm: 4.51–4.43 (m, 1H, H_E-2); 4.32–4.24 (m, 2H, H_P-2); 3.87 (d, 2H, H_G-2); [3.68 (s, minor), 3.67 (s, major), 3H, CO_2CH_3]; 3.63–3.44 (m, 2H, H_P-5); [2.51–1.80 (m, 12H), 1.69–1.60 (m, 3H), 1.36 (dd, *J* = 30.6, 12.3 Hz, 4H), 1.16 (s, 2H), H_P-3 + H_P-4 + H_E-3 + H_E-4 + H_c-2 + H_c-4 + H_c-5 + H_c-6 + H_c-8 + H_c-9 + H_c-10]; 0.85 (s, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [175.2 (Cq), 173.9 (Cq), 172.3 (Cq), 166.3 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [61.7, 54.4, 52.3, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 54.7 (Cq, C_c-1); [51.7 (CH_2), 48.2 (CH_2), C_G-2 + C_P-5]; [47.7, 43.7, 41.5, 40.7 (6 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 33.2 (2 × Cq, C_c-3 + C_c-7); [31.5, 30.7, (CH + 2 × CH_3), C_c-5 + C_c-11 + C_c-12]; [31.3 (CH_2), 31.1 (CH_2), C_P-4]; [30.7 (CH_2), 31.1 (CH_2), C_E-4]; [28.7 (CH_2), 28.4 (CH_2), C_E-3]; [25.6 (CH_2), 23.4 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{25}H_{41}N_4O_5]^+$ 477.31, found 477.34.

Synthesis of Boc-Pro-Glu(OMe)-amantadine (9b). To a solution of Boc-Pro-OH (0.1091 g, 0.5069 mmol) in anhydrous CH_2Cl_2 (25 mL) prepared in a round-bottom flask was subsequentially added Et_3N (0.21 mL, 1.5 mmol), TBTU (0.1790 g, 0.5575 mmol) and **4b** (0.2484 g, 0.6083 mmol). The resulting solution was stirred for 2 h at RT under an inert atmosphere (Ar). After the reaction, was followed the same purification method described in the general protocol B, using EtOAc for the chromatographic column. Aspect: yellow oil. Yield: 96% (0.2394 g). $[\alpha]_D^{22}$ = −71.4 ± 0.3 (*c*1, $CHCl_3$). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz), rotamers present (50 : 50) δ ppm: [6.26 (s), 6.04 (s), 1H, CONH); 4.38–4.10 (m, 2H, H_E-2 + H_P-2); 3.66 (s, 3H, CO_2CH_3); 3.55–3.30 (m, 2H, H_P-5); 2.52–2.31 (m, 2H, H_E-4); 2.20–1.79 (m, 15H, H_E-3 + H_P-3 + H_P-4 + H_b-2 + H_b-3); 1.65 (s, 6H, H_b-4); 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz), rotamers present, δ ppm: [174.5 (Cq), 172.4 (Cq), 169.8 (Cq), C_E-1 + C_E-5 + C_P-1]; 80.6 (Cq, $\underline{C}(CH_3)_3$); [60.8, 53.3, 51.9, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 52.3 (Cq, C_b-1); [47.2 (CH_2), 41.6 (CH_2), 36.5 (CH_2), 30.3 (CH_2), 30.3 (CH_2), C_P-5 + C_b-2 + C_b-4 + C_P-4]; 29.5 (3 × CH, C_b-3); 28.5 (3 × CH_3, $C(\underline{C}H_3)_3$); [27.2 (CH_2), 24.7 (CH_2), C_E-3 + C_P-3]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{26}H_{42}N_3O_6]^+$ 492.31, found 492.29.

Synthesis of H-Pro-Glu(OMe)-amantadine (10b). General protocol C, starting from 0.1318 g of **9b**. Aspect: colourless oil. Yield: 97% (0.1311 g). $[\alpha]_D^{23}$ = −9.9 ± 0.2 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (70 : 30), δ ppm: 4.22–4.13 (m, 2H, H_E-2 + H_P-2); [3.54 (s, major), 3.53 (s, minor), 3H, CO_2CH_3]; 3.33–3.20 (m, 2H, H_P-5); 2.40–2.20 (m, 4H, H_E-4 + H_E-3); 1.96–1.86 (m, 13H, H_P-3 + H_P-4 + H_b-2 + H_b-3); 1.58

(s, 6H, H_b-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [174.9 (Cq), 171.8 (Cq), 169.6 (Cq), C_E-1 + C_E-5 + C_P-1]; [60.9, 54.7, 52.3 (2 × CH + CH3), C_P-2 + C_E-2 + CO_2CH_3]; 53.1 (Cq, C_b-1); 48.4 (CH_2, C_P-5); [42.3, 37.4, (6 × CH_2), C_b-2 + C_b-4]; 31.0 (CH_2, C_P-4); 30.9 (3 × CH, C_b-3); [28.7 (CH_2), 24.9 (CH_2), C_E-4, C_E-3, C_P-3]. ESI-MS *m*/*z*: $[M]^+$ calcd for $[C_{21}H_{34}N_3O_4]^+$ 392.25, found 392.30.

Synthesis of (*N*,*N*-dimethyl-Gly)-Pro-Glu(aminoindane)-OMe (IVa). General protocol D, starting from 0.3343 g of **Ia**. Purification: chromatographic column using CH_2Cl_2/MeOH (4 : 1) as eluent. Aspect: yellow solid. Yield: 72% (0.2027 g). M.p.: 39–41 °C. $[\alpha]_D^{22}$ = +68.6 ± 0.1 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (80 : 20), δ ppm: 7.28–7.14 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 5.38 (t, *J* = 7.5 Hz, 1H, H_a-1); 4.51–4.39 (m, 2H, H_E-2 + H_P-2); [3.75 (s, minor), 3.73 (s, major), 3H, CO_2CH_3]; 3.63–3.33 (m, 4H, 2H_G-2 + 2H_P-5); 3.05–2.79 (m, 2H, H_a-3); 2.49–1.89 (m, 16H, $(CH_3)_2$-N + H_a-2 + H_P-3 + H_P-4 + H_E-3 + H_E-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [174.6 (Cq), 174.5 (Cq), 174.4 (Cq), 173.5 (Cq), C_E-1 + C_E-5 + C_P-1+ C_G-1]; [144.5 (Cq), 144.4 (Cq), C_a-3a + C_a-7a]; [128.8 (CH), 127.7 (CH), 125.6 (CH), 125.2 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; [61.5, 55.8, 53.1, 52.8, (3 × CH + CH_3), C_a-1 + C_E-2 + C_P-2 + CO_2CH_3]; [48.3 (CH_2), 48.0 (CH_2), C_G-2]; [45.5 (CH_3), 45.4 (CH_3), 45.3 (CH_3), 45.3 (CH_3), $(CH_3)_2$-N]; [34.4 (CH_2), 34.3 (CH_2), C_P-5]; [33.1 (CH_2), 32.9 (CH_2), C_P-4]; 31.0 (CH_2, C_a-2 + C_a-3); 30.5 (CH_2, C_E-4); [28.7 (CH_2), 27.8 (CH_2), C_E-3]; [25.8 (CH_2), 23.3 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{24}H_{35}N_4O_5]^+$ 459.26, found 459.31.

Synthesis of (*N*,*N*-dimethyl-Gly)-Pro-Glu(amantadine)-OMe, IVb. General protocol D, starting from 0.3323 g of **Ib**. Purification: chromatographic column using CH_2Cl_2/MeOH (4 : 1) as eluent. Aspect: white solid. Yield: 72% (0.2027 g). M.p.: 79–81 °C. $[\alpha]_D^{20}$ = −28.8 ± 0.2 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (80 : 20), δ ppm: 4.52–4.44 (m, 1H, H_E-2); 4.39 (dd, *J* = 9.4, 4.8 Hz, 1H, H_P-2); 4.02–3.93 (m, 2H, H_G-2); [3.74 (s, minor), 3.72 (s, major), 3H, CO_2CH_3]; 3.65–3.50 (m, 2H, H_P-5); 2.81 (s, 6H, $(CH_3)_2$N); 2.28–2.20 (m, 2H, H_E-4); 2.14–1.87 (m, 15H, H_E-3 + H_P-3 + H_P-4 + H_b-2 + H_b-3); 1.71 (s, 6H, H_b-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [174.3 (Cq), 173.9 (Cq), 173.5 (Cq), 165.9 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [61.5, 53.8, 53.3 (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 52.8 (Cq, C_b-1); [59.9 (CH_2), 47.9 (CH_2), C_G-2 + C_P-5]; 45.1 (2 × CH_3, $(CH_3)_2$N); [42.3, 37.5, (6 × CH_2), C_b-2 + C_b-4]; [34.0 (CH_2), 33.1 (CH_2), C_P-4]; 30.9 (3 × CH, C_b-3); 30.7 (CH_2, C_E-4); [28.8 (CH_2), 27.7 (CH_2), C_E-3]; [25.6 (CH_2), 23.4 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{25}H_{41}N_4O_5]^+$ 477.31, found 477.26.

Synthesis of (*N*,*N*-dimethyl-Gly)-Pro-Glu(memantine)-OMe (IVc). General protocol D, starting from 0.2914 g of **Ic**. Purification: chromatographic column using CH_2Cl_2/MeOH (4 : 1) as eluent. Aspect: white solid. Yield: 60% (0.1494 g). M.p.: 73–75 °C. $[\alpha]_D^{19}$ = −57.1 ± 0.2 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz), rotamers present (75 : 25), δ ppm: [8.62 (br s, minor), 7.60 (br s, major), 1H, CONH]; [6.05 (br s, major), 5.90 (br s, minor), 1H, CONH]; 4.45 (d, *J* = 5.8 Hz, 2H, H_E-2 + H_P-2); [3.75–3.63 (m, 4H), 3.60–3.34 (m, 3H), CO_2CH_3 + H_G-2 + H_P-5]; [2.71 (s, minor), 2.48 (s, major), 6H, $(CH_3)_2$N]; [2.25–1.74 (m, 11H), 1.60 (q, *J* = 11.8 Hz, 4H), 1.39–1.07 (m, 6H), H_P-3 + H_P-4 + H_E-3 + H_E-4 + H_c-2 + H_c-4 + H_c-5 + H_c-6 + H_c-8 + H_c-9 + H_c-10]; 0.81 (s, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz), rotamers present, δ ppm: [172.5 (Cq), 172.3 (Cq), 171.9 (Cq), 171.8 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [60.7, 52.7, 52.5, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 53.6 (Cq, C_c-1); [50.7 (CH_2), 47.5 (CH_2), 47.2 (CH_2), C_G-2 + C_P-5]; [42.8, 39.9, 33.7, 33.4, 32.1 (6 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 32.4 (2 × Cq, C_c-3 + C_c-7); [30.2, 30.2, (CH + 2 × CH_3), C_c-5 + C_c-11 + C_c-12]; 28.9 (CH_2, C_P-4); [28.2 (CH_2), 26.8 (CH_2), C_E-4]; 25.0 (CH_2, C_E-3); 22.6 (CH_2, C_P-3). ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{27}H_{45}N_4O_5]^+$ 505.34, found 505.31.

Synthesis of (*N*,*N*-dimethyl-Gly)-Pro-Glu(OMe)-aminoindane, Va. General protocol D, starting from 0.3221 g of **IIa**. Purification: chromatographic column using CH_2Cl_2/MeOH (4 : 1) as eluent. Aspect: yellow oil. Yield: 70% (0.1899 g). $[\alpha]_D^{22}$ = −12.2 ± 0.1 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (80 : 20), δ ppm: 7.29–7.09 (m, 4H, H_a-4 + H_a-5 + H_a-6 + H_a-7); 5.38 (t, *J* = 7.6 Hz, 1H, H_a-1); 4.51–4.30 (m, 2H, H_E-2 + H_P-2); [3.68 (minor), 3.67 (s, major), 3H, CO_2CH_3]; 3.59–3.34 (m, 2H, H_G-2); 3.10–2.79 (m, 3H, H_a-3); [2.71–1.80 (m, 17H), 1.35–1.24 (m, 1H), H_P-5 + H_a-2 + $(CH_3)_2$-N + H_P-3 + H_P-4 + H_E-3 + H_E-4]. ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [175.2, 173.2, (4 × Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [144.5 (Cq), 144.3 (Cq), C_a-3a + C_a-7a]; [128.9 (CH), 127.6 (CH), 125.7 (CH), 125.1 (CH), C_a-4 + C_a-5 + C_a-6 + C_a-7]; [61.8, 55.8, 54.3, 52.3, (3 × CH + CH_3), C_a-1 + C_E-2 + C_P-2 + CO_2CH_3]; [48.3 (CH_2), 48.0 (CH_2), C_G-2]; [45.5 (CH_3), 45.5 (CH_3), 45.4 (CH_3), $(CH_3)_2$-N]; [34.2 (CH_2), 33.9 (CH_2), C_P-5]; [31.3 (CH_2), 31.2 (CH_2), C_P-4]; 31.1 (CH_2, C_a-2 + C_a-3); 30.6 (CH_2, C_E-4); 28.1 (CH_2, C_E-3); [26.0 (CH_2), 25.8 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{24}H_{35}N_4O_5]^+$ 459.26, found 459.31.

Synthesis of (*N*,*N*-dimethyl-Gly)-Pro-Glu(OMe)-amantadine (Vb). General protocol D, starting from 0.3208 g of **IIb**. Purification: chromatographic column using CH_2Cl_2/MeOH (4 : 1) as eluent. Aspect: white solid. Yield: 70% (0.1903 g). M.p.: 67–69 °C. $[\alpha]_D^{20}$ = +23.9 ± 0.2 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR (CD_3OD, 400 MHz), rotamers present (85 : 15), δ ppm: 4.46 (dd, *J* = 8.6, 4.1 Hz, 1H, H_E-2); 4.29 (dd, *J* = 8.9, 5.1 Hz, 1H, H_P-2); 3.99 (d, *J* = 3.8 Hz, 2H, H_G-2); [3.69 (s, minor), 3.67 (s, major), 3H, CO_2CH_3]; 3.63–3.48 (m, 2H, H_P-5); 2.83 (s, 6H, $(CH_3)_2$N); 2.50–2.37 (m, 2H, H_E-4); 2.27–1.86 (m, 15H, H_E-3 + H_P-3 + H_P-4 + H_b-2 + H_b-3); 1.72 (s, 6H, H_b-4). ^{13}C-NMR/DEPT-135 (CD_3OD, 101 MHz), rotamers present, δ ppm: [173.8 (Cq), 172.6 (Cq), 170.8 (Cq), 164.5 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [60.3, 59.9, 53.2, 52.9, 51.0, 50.8, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 51.7 (Cq, C_b-1); [58.8 (CH_2), 58.4 (CH_2), 46.4 (CH_2), C_G-2 + C_P-5]; 43.6 (2 × CH_3, $(CH_3)_2$N); [40.9, 36.0, (6 × CH_2), C_b-2 + C_b-4]; [29.9 (CH_2), 29.7 (CH_2), C_P-4]; 29.3 (CH_2, C_E-4); 29.5 (3 × CH, C_b-3); [27.4 (CH_2), 26.8 (CH_2), C_E-3]; [24.4 (CH_2), 21.9 (CH_2), C_P-3]. ESI-MS *m*/*z*: $[M + H]^+$ calcd for $[C_{25}H_{41}N_4O_5]^+$ 477.31, found 477.27.

Synthesis of (*N*,*N*-dimethyl-Gly)-Pro-Glu(OMe)-memantine (Vc). General protocol D, starting from 0.1078 g of **IIc**. Purification: chromatographic column using CH_2Cl_2/MeOH (4 : 1) as eluent. Aspect: white solid. Yield: 60% (0.0553 g). M.p.: 60–63 °C. $[\alpha]_D^{19}$ = −42.6 ± 0.3 (*c*1, CH_3OH). Analytical data: ^{1}H-NMR

($CDCl_3$, 400 MHz), rotamers present (70 : 30), δ ppm: 7.49 (d, J = 7.8 Hz, 1H, CONH); 6.29 (s, 1H, CONH); 4.57–4.21 (m, 2H, H_E-2 + H_P-2); [3.65 (s, minor), 3.64 (s, major), 3H, CO_2CH_3]; 3.58–3.35 (m, 4H, H_G-2 + H_P-5); 2.56 (s, 6H, $(CH_3)_2N$); [2.14–1.77 (m, 10H), 1.61 (s, 4H), 1.38–1.06 (m, 7H), H_P-3 + H_P-4 + H_E-3 + H_E-4 + H_c-2 + H_c-4 + H_c-5 + H_c-6 + H_c-8 + H_c-9 + H_c-10] 0.81 (s, 6H, H_c-11 + H_c-12). ^{13}C-NMR/DEPT-135 ($CDCl_3$, 101 MHz), rotamers present, δ ppm: [174.5 (Cq), 171.6 (Cq), 170.1 (Cq), 171.8 (Cq), C_E-1 + C_E-5 + C_P-1 + C_G-1]; [60.8, 53.4, 51.9, (2 × CH + CH_3), C_P-2 + C_E-2 + CO_2CH_3]; 53.9 (Cq, C_c-1); [50.7 (CH_2), 47.3 (CH_2), 47.1 (CH_2), C_G-2 + C_P-5]; [42.7, 40.1, 39.9, (6 × CH_2), C_c-2 + C_c-4 + C_c-6 + C_c-8 + C_c-9 + C_c-10]; 32.4 (2 × Cq, C_c-3 + C_c-7); [30.4 (CH_2), 32.1 (CH_2), C_P-4]; [30.2, (CH + 2 × CH_3), C_c-5 + C_c-11 + C_c-12]; 28.9 (CH_2, C_E-4); 27.4 (CH_2, C_E-3); [25.0 (CH_2), 22.5 (CH_2), C_P-3]. ESI-MS m/z: $[M + H]^+$ calcd for $[C_{27}H_{45}N_4O_5]^+$ 505.34, found 505.33.

Author contributions

Conceived and designed the experiments: SCSR, IESD. Performed the experiments: SCSR, ACVDS. Analysed the data: SCSR, IESD, XGM and JERB. Wrote the paper: SCSR and IESD. All authors have given approval to the final version of the manuscript. The authors declare no competing financial interest.

Conflicts of interest

There are no conflicts to declare.

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