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Molecular modeling of galanthamine derivatives comprising peptide moiety: methods, targets and accuracy of results

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Using parametrical and semi-empirical quantum-chemical methods, three important descriptors of a series of peptides, linked to the molecule of galanthamine, were calculated. Studied compounds are planned as drugs for the prevention and treatment of Alzheimer's disease. The descriptors: polarizability, hydration energy and log P, undoubtedly have a bearing on the ability of the compounds to form strong enzyme-inhibitory complexes. Optimal geometries of the investigated peptides, as well as the intramolecular hydrogen bonds that define their structure were found. The most reliable structures defined on the basis of calculated descriptors are suggested.

Keywords: Alzheimer's disease, Galanthamine, Nicotinic acid, Isonicotinic acid, Cholinesterase inhibitor

INTRODUCTION

The Alzheimer's disease (AD) is a neurodegenerative illness which, due to brain disturbances, affects millions of people worldwide. In 1991, it was suggested that β-amyloid protein plays as a key factor in the development of AD [1,2]. Galanthamine (Gal) (Fig. 1) is one of the most useful in medicinal practice inhibitors of the β-amyloid aggregation and the toxicity of the β-amyloid peptide [3]. It is an inhibitor with moderate acetylcholinesterase (AcChE) and low butyryl-cholinesterase (BuChE) inhibition activity.

Nicotinic acid is a β-secretase inhibitor, it also increases the levels of good cholesterol (HDL cholesterol) and improves the penetration through blood brain barrier (BBB) [4,5].

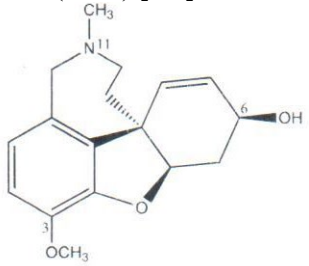

Fig. 1. (-) Galanthamine structure

Galanthamine derivatives containing either in position 6 or in position 11 di-and tripeptides modified with N-(3,4-dichlorophenyl)-D,L-Ala or shortened analogues of β-secretase inhibitor OM 99-2 were synthesized and investigated in our previous study [6-8].

The aim of this study is the modeling of unsynthesized hybrid molecules composed by the galanthamine, a peptide fragment, Boc-group or nicotinic/isonicotinic acid moiety in position P4 or P5. Thus, we can suggest the creation of new molecules possessing more than one important part for the AD treatment.

Peptides are not agreeable subjects for quantum-chemical investigation. The reasons are several. Firstly, the peptides have many single bonds around which rotation happens, which leads to the existence of many local minima in the hyper-surface of the potential energy of the molecule, evoking high probability to miss the global one and not to find the most likely spatial structure. On the other hand, optimization procedures taking into account the influence of the environment, typical for the living organisms, should be performed. This further complicates the task, although the solvent influence (most commonly water) through only one additional term in the Hamiltonian of the system, rather than by explicit methods, could be expressed. Last but not least, peptides usually contain many atoms, making it impossible to use more precise quantum-chemical methods.

Therefore, the use of purely parametric and semi-empirical quantum-chemical methods is imperative in most of the cases.

In order to optimize the synthetic jobs of new peptide inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BCH), we decided to perform some preliminary quantum chemistry studies and calculate a series of molecular descriptors for these peptides.

The main question arising here is which descriptors should be calculated so to receive an appropriate information for the peptides possessing the mentioned above inhibitory activity.

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Inhibitory activity of the compounds primarily depends on the spatial and functional congruence with enzymes and, as a consequence, from the forces of attraction inside the enzyme-inhibitory complexes. Since the intermolecular interactions primarily depend on the polarizability of the molecules, it was the first descriptor chosen to be computed [9].

The new drugs design is a process of optimization of both the interaction between ligand and receptor and the ability of the drug to reach its receptor. This makes lipophilicity an important descriptor that correlates well with the biological activity of different substances [10]. Obviously, the next important descriptor worthy to be computed is log P. The calculation of log P of a compound is much easier, quicker and cheaper than determining it by conventional experimental "shakeflask" [11,12] or chromatographic methods [12-14]. There are different approaches to its theoretical calculation [15]. The most common among them is classified as a "fragment constant" method in which the structure of a molecule is divided into fragments (atoms or groups), and the contribution of each group is summed up (sometimes a factor of structural correction is added) [16]. The routine application of these approaches, however, requires careful verification of their validity through comparisons with other experimental or theoretical data. The many QSARs found are proof of the significance of this descriptor. Though recent attempts have been made to calculate log P by using a series of quantum chemical molecular descriptors [17] the parametric computational methods are without a serious alternative.

Another descriptor we decided to calculate was the "hydration energy" that is related to the stability of the found conformations of the investigated peptides. The implemented in Hyperchem 8.0 hydration energy calculation method was created for peptides and proteins [18]. The calculations are based on the "solvent-accessible surface energy" of the molecules, calculated by the approximate method of Still and co-workers [19,20].

The only data for the inhibitory activity of peptides resembling ours are given in [8]. Four peptides show a marked inhibitory activity against BuChE. The biological activity, as well as the calculated polarizability, hydration energy and log P values of these compounds are shown in Table 1. Ultimately, the above descriptors were firstly calculated for peptides already tested for inhibitory activity. Comparison of the descriptors values of the active peptides with the values of those to be synthesized can provide valuable information as to which of them could be promising enzyme inhibitors.

25 hybrid compounds were investigated in this study. By the proximity of their descriptors and spatial structure with those of the active peptides studied earlier, we will judge whether a compound is promising.

EXPERIMENTAL

All calculations in this work were done using the program package Hyperchem 8.0 Professional edition [21]. This package was chosen because of convenience: it provides an easy creation of the input geometries, amino acid data base and the QSAR module for the calculation of important molecular descriptors. AM1 Hamiltonian is implemented [22] in HyperChem 8.0. We chose a gradient norm limit of 0.01kcal/Å for the geometry optimization.

The polarizability was calculated using the semi-empirical quantum-chemical method AM1. Calculation of log P and hydration energy were carried out using atomic parameters derived by Ghose, Pritchett and Crippen [23,24].

RESULTS AND DISCUSSION

Descriptors given in Table 1 were calculated for the already tested compounds that have shown good inhibition activities towards BuChE. They are our ***lead compounds***, because all other investigated structures (from Table 2 and 3) were compared with them.

It was not possible to present here all the spatial structures found. That is why we will describe here the most important intramolecular interactions in each of them.

The first peptide is **(I)** 6-O-[Boc-Val-Asn-Leu-Ala-Gly]-Galantamine (Table 2.) The spatial structure found for this peptide is characterized by three hydrogen bonds: the first is between the hydrogen from the amino group of Gly and the oxygen from Leu (2.222 Å), the second is between the oxygen from Ala and the hydrogen from the amino group of Val (2.191Å), and the third is between N-H of the α-amino group of Asn and the oxygen from Val (2.318 Å). The mean polarizability of the peptide is 383.855 au, less than that of the lead compounds. It is significantly more hydrophilic (log P = –3.53) than the most active peptides. Only the hydration energy is close to that of the most active peptide (–9.54 kcal/mol).

In the next peptide Val is added between Ala and Gly in the first peptide: **(II)** 6-O-[Boc-Val-Asn-Leu-Ala-Val-Gly]-Galantamine. Here the molecular shape is almost linear until to the Leu.

Table 1. Calculated descriptors of compounds reported earlier [8] possesing good inhibition activities towards BuChE

№	Compounds	Polarizability	Hydration energy	Log P	IC50
		au	kcal/mol		μM
(A)	6-O-[Boc-Asn-Leu-Ala-Gly]-Galanthamine	383.204	–10.19	–2.57	17.87
(B)	6-O-[Boc-Val-Asn-Leu-β-Ala-Val-Gly]-Galanthamine	433.162	–8.71	–2.60	6.70
(C)	11-N-demethyl-11-N-N[Boc-Asp(Asn-Leu-Ala-Val-NH-Bzl]-Galanthamine	513.172	–16.21	–2.29	5.96
(D)	11-N-demethyl-11-N-N-[Boc-Asp(Val-Asn-Leu-β-Ala-Val-NH-Bzl]-Galanthamine	549.590	–19.35	–2.78	9.31

The β-amide group of the Asn is turned to the Val and forms two relatively strong hydrogen bonds that determine the found spatial structure, as it is shown on Figure 2.

Inclusion of Val is a reason for the increase of the mean polarizability (441.683 au) and the lipophilicity (–3.20). The addition of Val changes these two descriptors in the appropriate direction, but the hydration energy is still high (–15.12 kcal/mol).

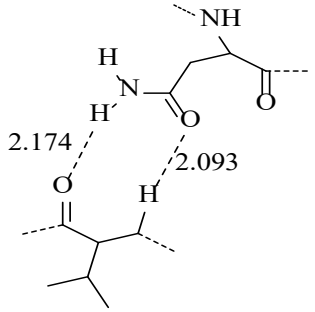

Fig. 2. Hydrogen bonds in 6-O-[Boc-Val-Asn-Leu-Ala-Val-Gly]-Galantamine.

(III) 11-N-Demethyl-11-N-N-[Boc-Asp(Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine. Its spatial structure is more compact than the foregoing. The reason is most probably related to the increased number of groups which can participate in hydrogen bonds: the urethane group of Boc-protection groups, the β-amide group of Asn, and the Val-NHBzl group at the last position. It is also significant that the peptide bond between Boc-Asp and Asn is formed through the β-carboxyl group of the first amino acid. This leads to the initial right turn of a chain followed by another turm to the left. More significant hydrogen bonds: between C=O from urethane protecting group and H-N from amino group of Asn (2.07 Å), C=O from α-peptide group of Asn and H-N from β-Ala (2.24 Å), and C=O from benzyl amide and H-N from β-amid group of Asn (2.15 Å). Mean polarizability is 520.103 au, log P is –2.28 and hydration energy is –13.67 kcal/mol. Here, the calculated descriptors are very close to those of the lead compounds. High polarizability, significantly lower hydrophilicity and approximately the same hydration energy as the previous peptide. The primary structures of the peptides in the next group of compounds are obtained by some changes in the primery structure of the previous peptides. In all of them, the N-terminal amino group of the amino acid Asp is linked to nicotinic or isonicotinic acid through an amide link.

(1) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp (Val-Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine. This peptide has an interesting β-turn structure with hearpin at Val and Asn. There are relatively weak hydrogen bonds between carbonyl oxygen from the ester function between Asn and NorGal, and the H-atom from the Leu. The mean polarizability is 571.270 au, log P is –3.62, and hydration energyis –19.35 kcal/mol. This peptide has appropriate polarizability, hydration energy, but it is too hydrophilic.

(2) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp (Val-Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine. In this peptide Ala in peptide **1** is replaced by -β-Ala. Several intramolecular hydrogen bonds define the spatial structure of this peptide, the most significant of which is between oxygen of Leu and hydrogen from the amino group of the C-

Table 2. Calculated descriptors of new analogues of compounds reported earlier [8]

№	Compounds	Polarizability	Hydration energy	Log P
		Au	kcal/mol	
(I)	6-O-[Boc-Val-Asn-Leu-Ala-Gly]-Galantamine	383.855	–9.54	–3.53
(II)	6-O-[Boc-Val-Asn-Leu-Ala-Val-Gly]-Galantamine	441.683	–15.12	–3.20
(III)	11-N-Demethyl-11-N-N-[Boc-Asp(Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine	520. 103	–13.67	–2.28

terminal Val. Mean polarizability 575.2 au, log P –3.97, hydration energy –20. 49 kcal/mol.

(12) 11-N-Demethyl-11-N-N-[isonicotinoyl-Asp-(Val-Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine. Here isonicotinic acid moiety instead of nicotinic acid was included. Its mean polarizability (570.953 au), log P (–3.74), and the hydration energy (–19.46 kcal/mol) are almost the same as in **(1)** 11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Val-Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine (Table 3) peptide. Here again the lipophilicity is very low, and the hydration energy is slightly larger. Replacing nicotinic acid by isonicotinic acid does not lead to dramatic changes in the chosen descriptors and in the spatial structure.

(13) 11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Val-Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine. Polarizability: 573.581 au; log P: –3.59; hydration energy: –19.73 kcal/mol.

(3) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp(NVal-Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine. In this peptide Val in peptide **2** is replaced by NVal in position P_3. No strong hydrogen bonds. Polarizability is 571.23 au, log P is –3.98 and hydration energy is –20.18 kcal/mol.

(4) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp(NVal-Asn-Leu-β-Ala-NVal-NH-Bzl)]-Galanthamine. In peptide **3** Val in position P_2' was replaced by NVal. The mean polarizability is almost the same (571.785 au), log P is –3.98, slightly reduced comparing to the previous, but the hydration energy (–20.10 kcal/mol) is slightly increased compared to the previous one.

(5) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp(NVal-Asn-Leu-Ala-NVal-NH-Bzl)]-Galanthamine. Here β-Ala in peptide **4** is replaced by Ala. The structure is similar to that of the previous peptides. There is a hearpin at NVal and Asn and two important H-bonds at the same atoms as in previous peptides. Mean polarizability: 579.048 au, log P: –3.12, hydration energy: –18.97 kcal/mol. The polarizability and hydration energy are appropriate but the peptide is too hydrophilic.

(14) 11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(NVal-Asn-Leu-β-Ala-NVal-NH-Bzl)]-Galanthamine. Here nicotinic acid in peptide **4** was replaced by isonicotinic acid. There is one more significant hydrogen bond between the urethane carbonyl oxygen and the Ala N-H and at least two weaker ones. Mean polarizability is higher relative to the previous peptide (571.201 au) as well as log P (–3.75) and the hydration energy is slightly decreased (–19.42 kcal/mol).

(6) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp (Tle-Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine. In this peptide Val in peptide **2** is replaced by Tle in position P_3. The only stronger hydrogen bond (2.25 Å) in this peptide is between the oxygen of the Leu and hydrogen from the C-terminal benzylamide. Polarizability is (578.35 au), log P is (–3.47) and hydration energy is –19.56 kcal/mol.

(7) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp (Tle-Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine. Polarizability here is 575.535 au; log P is –3.11, and the hydration energy is –18.77 kcal/mol.

(15) 11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Tle-Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine. Polarizability of this peptide is 577.463 au; log P is –3.47; and the hydration energy is –19.57 kcal/mol.

(16) 11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Tle-Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine. Its polarizability is 575.913 au, log P is –3.23, and hydration energy is –18.86 kcal/mol.

Several optimized structures were considered for each of the last peptides by variation of the input geometry. The only descriptor for which different values were obtained is the polarizability. The difference between them does not exceed 7 au, which is about 1%. In this case the average values of polarizability are shown in tables 3 and 4.

In the next group of compounds the Val residue in position P_3 was removed.

(8) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp (Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine. As a result of this change, the average polarizability decreased to 520.479 au, the hydration energy to –18.12 kcal/mol and log P increased in hydrophilic direction –4.07. Compared with the previous compounds, this peptide is too hydrophilic.

Replacement of Ala with β-Ala gives the next peptide.

(9) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp (Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine. The spatial structure of the β-Ala analogue is interesting. After initial rotation to the right at Leu, the direction of rotation changes to the left. The structure is fixed by the presence of three relatively strong hydrogen bonds. First is between the oxygen of the amide group of nicotinic acid and the hydrogen from the β-amide group between Asp and Asn; the second is between the oxygen of the peptide bond between Asn and Leu, and the third is between the hydrogen from the Asn β-amide group and the oxygen from the benzylamide group at the end of the peptide. The values of the descriptors do not differ significantly from those of peptide 11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine. This peptide has a mean polarizability 519.703 au, log P –4.43 and

hydration energy –18.31 kcal/mol. The peptide is slightly more hydrophilic than **(8)** 11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine.

(17) 11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine. Mean polarizability is 519.682 au, log P is –4.07, and hydration energy is –18.06 kcal/mol. The peptide is too hydrophilic.

(18) 11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine. Mean polarizability is 518.606 au, log P is –4.43, and hydration energy is –18.63 kcal/mol.

Replacement of Asn with Asp gives the next peptides:

(10) 11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Asp-Leu-Ala-Val-NH-Bzl)]-Galanthamine.

Surprisingly, the optimal geometry we obtained for this peptide significantly differs from that of the previous peptides. Three strong hydrogen bonds are identified for it: between the oxygen of the nicotinic acid and the hydrogen from the amide group between Asp and Asp (2.09 Å), the oxygen from the peptide bond between Asp and Leu (2.15 Å) and the carboxyl hydrogen of Asp and the oxygen from the benzamide group. The mean polarizability is 518.322 au, log P is –3.21, and the hydration energy is –19.38 kcal/mol. The only desired change here concerns log P toward lower hydrophilicity.

The optimized structure of the next peptide **(11)** 11-N-Demethyl-11-N-N-[nicotinoyl-Asp (Asp-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine is similar to the structure of the previous peptide, but hydrogen bonds are stronger. Its average polarizability is 517.134 au, log P is –3.56, and its hydration energy is –20.14 kcal/mol.

The following two peptides are analogues of the previous two in which nicotinic acid is replaced by isonicotinic acid. This change does not lead to noticeable differences in spatial structures compared to the previous peptides, or to noticeable differences in the calculated descriptors. It has only to be said that the substitution of β-amide group by the carboxyl group significantly reduces the value of log P of the corresponding peptide.

(19) 11-N-Demethyl-11-N-N-[Iso-nicotinoyl-Asp(Asp-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine. Mean polarizability: 516.246 au, log P: –3.56, and hydration energy: –20.50 kcal/mol.

The last peptides are too hydrophilic compared to the previous ones.

(20) 11-N-Demethyl-11-N-N-[Iso-nicotinoyl-Asp(Asp-Leu-Ala-Val-NH-Bzl)]-Galanthamine. Mean polarizability: 517.364 au, log P: –3.21, and hydration energy: –19.76 kcal/mol.

Table 3. Calculated descriptors of galanthamine derivatives containing peptide fragment and nicotinic acid.

№	Compounds	Polarizability	Hydration energy	Log P
		au	kcal/mol	
(1)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Val-Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine	571.270	–19.35	–3.62
(2)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Val-Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine	575.2	–20. 49	–3.97
(3)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(NVal-Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine	571.23	–20.18	–3.98
(4)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(NVal-Asn-Leu-β-Ala-NVal-NH-Bzl)]-Galanthamine	571.785	–20.10	–3.98
(5)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(NVal-Asn-Leu-Ala-NVal-NH-Bzl)]-Galanthamine	579.048	–18.97	–3.12
(6)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Tle-Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine	578.35	–19.56	–3. 47
(7)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Tle-Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine	575.535	–18.77	–3.11
(8)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine	520.479	–18.12	–4.07
(9)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine	519.703	–18.31	–4.43
(10)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Asp-Leu-Ala-Val-NH-Bzl)]-Galanthamine	518.322	–19.38	–3.21
(11)	11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Asp-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine	517.134	–20.14	–3.56

Table 4. Calculated descriptors of galanthamine derivatives containing peptide fragment and isonicotinic acid.

№	Compounds	Polarizability	Hydration energy	Log P
		au	kcal/mol	
(12)	11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Val-Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine	570.953	–19.46	–3.74
(13)	11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Val-Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine	573.581	–19.73	–3.59
(14)	11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(NVal-Asn-Leu-β-Ala-NVal-NH-Bzl)]-Galanthamine	571.201	–19.42	–3.75
(15)	11-N-Demethyl-11-N-N-[Iso-nicotinoyl-Asp(Tle-Asn-Leu-b-Ala-Val-NH-Bzl)]-Galanthamine	577.463	–19.57	–3.47
(16)	11-N-Demethyl-11-N-N-[Iso-nicotinoyl-Asp(Tle-Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine	575.913	–18.86	–3.23
(17)	11-N-Demethyl-11-N-N-[Iso-nicotinoyl-Asp(Asn-Leu-Ala-Val-NH-Bzl)]-Galanthamine	519.682	–18.06	–4.07
(18)	11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Asn-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine	518.606	–18.63	–4.43
(19)	11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Asp-Leu-β-Ala-Val-NH-Bzl)]-Galanthamine	516.246	–20.50	–3.56
(20)	11-N-Demethyl-11-N-N-[isonicotinoyl-Asp(Asp-Leu-Ala-Val-NH-Bzl)]-Galanthamine	517.364	–19.76	–3.21

CONCLUSIONS

We have chosen three important descriptors, characterising the primary and spatial structure of investigated compounds. These descriptors were calculated for the so called „lead compounds“, compounds possessing inhibitory activity toward BuChE and the values obtained were used for comparison to the planned for synthesis compounds. High polarizability (between 500 and 515 au), hydration energy of about –16 ÷ –17 kcal/mol and log P lower than –3.53 were calculated as important data.

The closest lipophilicity to the lead compounds possess peptides 5, 7, 10, 16 and 20. The rest of the peptides are too hydrophilic (log P higher than –3.23).

Several peptides have close polarizability (lower than 520 au): 9, 10, 11 and 17, 18, 19 and 20. The remaining peptides are of too polarizable.

All planed peptides have higher hydration energy than the lead compounds (higher than 18 kcal/mol).

Assuming that the slightlly higher polarizability is not necessarily undesirable feature, and comparing by the log P it becomes clear that peptides **10** (11-N-Demethyl-11-N-N-[nicotinoyl-Asp(Asp-Leu-Ala-Val-NH-Bzl)]-Galanthamine) and **20** (11-N-Demethyl-11-N-N-[Iso-nicotinoyl-Asp(Asp-Leu-Ala-Val-NH-Bzl)]-Galanthamine) are the most suitable for synthesis.

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МОЛЕКУЛНО МОДЕЛИРАНЕ НА ПРОИЗВОДНИ НА ГАЛАНТАМИН, СЪДЪРЖАЩИ ПЕПТИДНА ЧАСТ: МЕТОДИ, ЦЕЛИ И ТОЧНОСТ НА РЕЗУЛТАТИТЕ

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(Резюме)

С използване на чисто параметрични и полуемпирични квантово-химични методи са изчислени три важни дескриптора на серия от пептиди, свързани с молекулата на галантамина. Изследваните съединения са планирани като лекарства за превенция и лечение на болестта на Алцхаймер. Дескрипторите поляризуемост, енергия на хидратация и log P несъмнено имат отношение към способността на съединенията да образуват здрави ензим-инхибиращи комплекси. Установени са оптималните геометрии на изследваните пептиди, както и вътремолекулните водородни връзки, които определят структурата им. Предложени са най-достоверните структури, дефинирани на основата на изчислените дескриптори.