INTRODUCTION
Alzheimer’s disease (AD) is a neurodegenerative disorder, characterized by a decline in cognitive functions and described by Alois Alzheimer in 1906.[1] The disease is considered as the most common form of dementia with aging as main risk factor, which progresses slowly, but once diagnosed, death occurs on average nine years later.[2] The cerebral deposition of amyloid β peptide (Aβ) is an early and critical feature of Alzheimer's disease and its generation depends on proteolytic cleavage of the transmembrane amyloid precursor protein (APP) [3] by two unknown proteases: β-secretase and γ-secretase. During this cleavage two...
different Aβ peptides, with the major species being Aβ40 and Aβ42 are generated.\(^2, 4,5\) Aggregation of the more hydrophobic Aβ42 leads to formation of oligomers, which eventually results in development of plaques.\(^6,7\) It is believed that the oligomers, rather than the plaques, are one of the reasons for causing the disease.\(^8\) Having this in mind the conclusion arises, that the future development of β-secretase, known also as β-site amyloid cleaving enzyme (BACE) inhibitors may prove beneficial for the treatment of Alzheimer's disease.\(^9\) At present the two AD therapies that are applied merely ameliorate the symptoms of the disease,\(^6,10-12\) whereas these standard treatments do not affect the underlying pathogenesis of AD, which raises the enormous medical need for new therapies. The cholinergic hypothesis of Alzheimer’s disease (AD) has spurred the development of numerous structural classes of compounds with different pharmacological profile aimed at increasing central cholinergic neurotransmission.\(^13\) The piperazine moiety has proven to be an important pharmacophore, found in a large number of biologically active molecules. Due to the high number of positive hits encountered in biological screens with this heterocycle and its congeners, the piperazine moiety is widely recognized as a ‘privileged scaffold’ in medicinal chemistry. Moreover, piperazine ring systems are the key structural elements in a vast array of natural products as well as being a large class of biologically active compounds. Examples include indinavir, an HIV-protease inhibitor, glivec, a potent antiproliferative agent, several compounds acting at receptors in the CNS such as arylpiperazines, powerful 5-HT\(_1\) ligands, leመonomycin, ecteinascidin 743, TAN-1251A , and dragmacidins B and C.\(^14\) Keeping in mind, that the β-site amyloid precursor protein cleaving enzyme 1 (BACE1) active site is displayed in an endosomal compartment that is slightly acidic (pH ~ 5), more basic compounds like piperidines\(^15\) or piperazines may accumulate inside the compartment to a larger degree than less basic analogs. Thus guided by structure-based design and using X-ray crystallography in conjunction with molecular modeling, novel potent piperazinone based peptidomimetic inhibitors of BACE1 have been synthesized and extensive SAR models have been generated around both the prime and non-prime side binding pockets.\(^16\) In addition recently a dual inhibitor of AChE and BACE1 with N-benzylpiperidine ethyl as C-terminus have also been discovered and reported. The investigated compound had shown potent inhibitory activities for BACE1, and could reduce endogenous Aβ1–40 production in APP transgenic mice.\(^17\) A new series of chiral β-secretase 1 inhibitors possessing a N-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropyl) arylsulfonamido structure have also been synthesized and their enantiomeric activity dependency had been observed. Some derivatives had been predicted to be able to cross the blood-brain barrier, suggesting that they may reach
and inhibit β-secretase 1, inside the central nervous system. According to the obtained from the researchers biological results and docking studies, had been asserted that the β-secretase 1 inhibitory activity of this type of compounds does not show a significant dependency upon the absolute configuration of the chiral carbon in the central hydroxyethylamino linker.[18]

Drug target identification, which includes many distinct algorithms for finding genes and proteins, is the first step in drug discovery. When 3D structures of the targets are available, the problem of target identification is usually converted to finding the best interaction mode between the potential target candidates and probe small molecules. PharmMapper Server is a freely accessed web-server designed to identify potential target candidates for the given probe small molecules (drugs, natural products, or other newly discovered compounds with binding targets unidentified) using pharmacophore mapping approach. Benefited from the highly efficient and robust mapping method, PharmMapper bears high throughput ability and can identify the potential target candidates from the database within a few hours.[19] The aim of our study was to attempt to identify a potential target candidate for seven newly synthesized by us piperazine derivatives with amide structure and to determine their pharmacophore interactions with the enzyme β-secretase 1 (BACE1).

MATERIALS AND METHODS

Apparatuses And Devices

The used chromatographic system for TLC control and purity elucidation is based on an alluminium sheets Silica gel F254 (Merck, Darmstadt, Germany), using CHCl₃/CH₃CH₂OH/Acetone as a mobile phase with detection at UV 254 nm. The corresponding melting points were determined on an electrothermal apparatus (Büchi, Switzerland) in an open capillary tube and are uncorrected. Yields were calculated for purified products. The FT-IR spectra were recorded on a Nikolet iS 10 FT-IR Spectrometer in KBr. The ¹H-NMR spectra were registered at 250 MHz on spectrometer Bruker-Spectrospin WM250MHz (Faenlanden, Switzerland) as δ (ppm) relative to TMS as internal standard and the coupling constants (J) are expressed in Hertz (Hz). All OH and NH protons were D₂O exchangeable. Elemental analyses were performed by the microanalytical laboratory of Faculty of Pharmacy (Medical University Sofia) on Eurovector EA 3000 analyser. All names were generated by using ACD/Name Version 2.51.[20] The starting materials were of commercially available research-grade chemicals (Merck, Darmstadt, Germany).
General Procedure For The Synthesis of Benzhydrilpyperazines.

Benzhydrilpyperazine (4.0 g, 0.016 mol) is diluted in 50 ml anhydrous benzene and triethylamine (1.6 g, 0.016 mol) is added. Further the corresponding acidic chloride is added drop wise at room temperature, under stirring. After the total addition of the chloride the temperature is risen to boil and the reaction mixture is boiled under reflux and stirring for 6 hours. At the end of the reaction time the benzene is removed under lower pressure and the oily residue is diluted in chloroform, which is washed with water and let to dry on anhydrous sodium sulfate. The obtained crude product is processed eligibly and isolated.

Synthesis of 1-(Diphenylmethyl)-4-(2,2-Dimethylpropionyl)-Piperazine (2a)

It is obtained according to the general synthetic method from 0.016 mol (1.93 g) pyvaloylchloride. The crude product crystallizes from ethanol and is re-crystallized from ethanol. M.p. 100-101°C Yield 3.23 g (60%). IR: 2850 – 2930 (νCH₂, νCH₃), 3015 (νAr – H), 1652 (νCO – Amide I), 708, 744, 752 (δAr – H). \(^1\)H-NMR: 1.24 (s, 9H, CH₃), 2.62-2.69 [m, 4H, piperazine], 3.55-3.65 [m, 4H, piperazine], 5.45 (s, 1H, CH₂N), 7.24-7.27 [m, 2H, benzene], 7.26- 7.32 [m, 4H, benzene]. 7.39-7.44 [m, 4H, benzene]. C₂₂H₂₃N₂O Mr = 336.48 Calc.: %C – 78.53; %H – 8.39; %N – 8.33; found: %C – 78.63; %H – 8.48; %N – 8.14.

Synthesis of 1-(Diphenylmethyl)-4-(4-Chlorobenzoyl)-Piperazine (2b)

It is obtained according to the general synthetic method from 0.016 mol (2.8 g) 4-chlorobenzoyl chloride. The crude product crystallizes from ethanol and is re-crystallized from ethanol. M.p. 98-99°C Yield 4.19 g (67%). IR: 2860 – 2940 (νCH₂, νCH₃), 3030 (νAr – H), 1649 (νCO – Amide I), 715, 723, 770 (δAr – H), 639 (νC – Cl). \(^1\)H-NMR: 1.24 (s, 9H, CH₃), 2.62-2.69 [m, 4H, piperazine], 3.55-3.65 [m, 4H, piperazine], 5.45 (s, 1H, CH₂N), 7.24-7.27 [m, 2H, benzene], 7.26– 7.32 [m, 4H, benzene], 7.39-7.44 [m, 4H, benzene], 7.51,7.53 [d, 2H, C₆H₆-Cl, J=1.5Hz], 7.64,7.67 [d, 2H, C₆H₆-CO, J=8.7Hz]. C₂₄H₂₂ClN₂O Mr = 390.91 Calc.: %C – 73.74; %H – 5.93; %Cl – 9.07; %N – 7.17; found: %C – 73.94; %H – 5.94; %Cl – 9.02 %N – 7.47.

Synthesis of 1-(Diphenylmethyl)-4-(2-Chlorobenzoyl)-Piperazine (2c)

It is obtained according to the general synthetic method from 0.016 mol (2.8 g) 2-chlorobenzoyl chloride. The crude product crystallizes from ethanol. The obtained product is chromatographically pure and is not further purified. M.p. 139-140°C Yield 4.38 g (70%). IR: 2800 – 2900 (νCH₂, νCH₃), 3090 (νAr – H), 1650 (νCO – Amide I), 712, 750, 770 (δAr
– H), 650 (vC – Cl). \(^1\)H-NMR: 1.24 (s, 9H, CH\(_3\)), 2.62-2.69 [m, 4H, piperazine], 3.55-3.65 [m, 4H, piperazine], 5.45 (s, 1H, CH\(_2\)-), 2.74-7.27 [m, 2H, benzene], 7.26- 7.32 [m, 4H, benzene], 7.38-7.42 [m, 1H, C\(_6\)H\(_5\)-CO], 7.39-7.44 [m, 4H, benzene], 7.49-7.52 [m, 1H, C\(_6\)H\(_5\)-CO], 7.53-7.54 [m, 1H, C\(_6\)H\(_5\)-CO], 7.87-7.91 [m, 1H, C\(_6\)H\(_5\)-CO]. C\(_24\)H\(_23\)ClN\(_2\)O Mr = 390.91 Calc.: %C – 73.74; %H – 5.93; %Cl – 9.07; %N – 7.17, found: %C – 73.84; %H – 6.03; %Cl – 9.05; %N – 7.37.

Synthesis of 1-(Diphenylmethyl)-4-(3,4-Dimethylbenzoyl)-Piperazine (2d)

It is obtained according to the general synthetic method from 0.03 mol (4.5 g) 3,4-dimethylbenzoyl chloride. The crude product crystallizes from ethanol and is re-crystallized from ethanol. M.p. 148-150°C Yield 7.61 g (66%). IR: 2820 – 2950 (vCH\(_2\), vCH\(_3\)), 3100 (vAr – H), 1653 (vCO – Amide I), 708, 738, 768 (δAr – H). \(^1\)H-NMR: 1.24 (s, 9H, CH\(_3\)), 2.27 (s, 3H, C\(_6\)H\(_5\)-CH\(_3\)), 2.40 (s, 3H, C\(_6\)H\(_5\)-CH\(_3\)), 2.62-2.69 [m, 4H, piperazine], 3.55-3.65 [m, 4H, piperazine], 5.45 (s, 1H, CH\(_2\N\)-CO], 7.26- 7.32 [m, 4H, benzene], 7.39-7.44 [m, 4H, benzene], 7.51,7.52 [d, 1H, C\(_6\)H\(_5\)-CO, J=1.9Hz]. C\(_{26}\)H\(_{28}\)N\(_2\)O Mr = 384.52 Calc.: %C – 81.21; %H – 7.34; %N – 7.29, found: %C – 81.32; %H – 7.56; %N – 6.96.

Synthesis of 1-(4-benzhydrylpiprazine-1-yl)-2-propylpentane-1-on (2e)

It is obtained according to the general synthetic method from 0.016 mol (2.60 g) 2-propylpentanoyl chloride (valproyl chloride). The crude product is oily liquid with pale yellow color. Yield – 2.96 g (49%). IR: 2855 – 2936 (vCH\(_2\), vCH\(_3\)), 3025 (vAr – H), 1650 (vCO – Amide I), 708, 742, 750 (δAr – H). \(^1\)H-NMR: 0.88-0.91 (m, 6H, 2xCH\(_2\)CH\(_2\)CH\(_3\)), 1.28-1.36 (m, 4H, 2xCH\(_2\)CH\(_2\)CH\(_3\)), 1.48-1.53 (m, 4H, 2xCH\(_2\)CH\(_2\)CH\(_3\)), 2.34-2.62 (m, 1H, CHCO), 2.62-2.69 [m, 4H, piperazine], 3.55-3.65 [m, 4H, piperazine], 5.45 (s, 1H, CH\(_2\)N), 7.24-7.27 [m, 2H, benzene], 7.26- 7.32 [m, 4H, benzene], 7.39-7.44 [m, 4H, benzene]. C\(_{22}\)H\(_{28}\)N\(_2\)O Mr = 336.48 Calc.: %C – 79.32; %H – 9.05; %N – 7.40, found: %C – 79.34; %H – 9.09; %N – 7.35.

Synthesis of 1-(4-Benzhydrylpiprazine-1-Yl)-2-(2,4-Dichlorophenoxy)-Ethanone (2f)

It is obtained according to the general synthetic method from 0.016 mol (3.83 g) 2,4-dichlorophenoxyacetyl chloride. The crude product is waxy and crystallizes after addition of water. The obtained compound is chromatographically pure and is not further purified. M.p. - 83 – 85°C. Yield – 5.30 g (70%). IR: 2800 – 2900 (vCH\(_2\), vCH\(_3\)), 3020 (vAr – H), 1651
(vCO – Amide I), 1288, (vC – O – C), 706, 746, 758 (δAr – H), 644 (vC – Cl). 1H-NMR: 1.24 (s, 9H, CH3), 2.62-2.69 [m, 4H, piperazine], 3.55-3.65 [m, 4H, piperazine], 4.15 (s, 2H, CO-CH2-O), 5.45 (s, 1H, CH2N), 7.14-7.18 [q, 1H, C6H5, J1=5.1Hz, J2=8.2Hz], 7.23-7.28 [m, 2H, benzene], 7.24-7.27 [m, 1H, C6H5], 7.26- 7.32 [m, 4H, benzene], 7.39-7.44 [m, 4H, benzene], 7.64-7.66 [q, 1H, C6H5, J1=5.1Hz, J2=1.8Hz]. C25H24Cl2N2O2 Mr = 455.38 Calc.: %C – 65.94; %H – 5.31; %Cl – 15.57; %N – 6.15, found: %C – 65.92; %H – 5.30; %Cl – 15.55; %N – 6.10.

Synthesis of 7-[2-(4-Benzhydripiperazine-1-Yl)-2-Oxethyl]-1, 3-Dimethyl-3, 7-Dihydropurine-2, 6-Dione (2g).
It is obtained according to the general synthetic method from 0.016 mol (4.07 g) theophylline-7-acyl chloride. The crude product crystallizes from ethanol and is re-crystallized from ethanol. M.p. – 243 - 245°C. Yield – 3.45 g (46%). IR: 2863 – 2928 (vCH2, vCH3), 3100p (vAr – H), 1709, 1661 (vCO – xanthine ring), 1651 (vCO – Amide I), 1549, 1608p (vC=C, vC=N), 696, 709 (δAr – H). 1H-NMR: 1.24 (s, 9H, CH3), 2.62-2.69 [m, 4H, piperazine], 3.55-3.65 [m, 4H, piperazine], 3.30 (s, 3H, N1-CH3), 3.31 (s, 3H, N1-CH3), 4.69 (s, 1H, COCH2N), 5.45 (s, 1H, CH2N), 7.24-7.27 [m, 2H, benzene], 7.26- 7.32 [m, 4H, benzene], 7.39-7.44 [m, 4H, benzene], 7.65 (s, 1H, xanthine). C26H28N6O3 Mr = 472.55 Calc.: %C – 66.09; %H – 5.97; %N – 17.78, found: %C – 66.06; %H – 5.87; %N – 17.65.

The PharmMapper calculates these ligands' fit score of an extracted and stored as a library ligand dataset in mol2 format pharmacophore model’s ligands from PDB. This process generates a nearly 7 000x7 000 score matrix. After this, when a new molecule is submitted, the fit score to each pharmacophore is calculated first, and then every fit score of a specific pharmacophore is compared to the fit score matrix to measure its score level among all the scores of the pharmacophore. This process adds up to the pure fit score with more statistical meaning and confidence comparing with random pharmacophore matching.

RESULTS AND DISCUSSION
Chemistry Results Using the above described synthetic approaches seven piperazine derivatives with amide structure were obtained in our laboratory with good yields. The synthesis was performed according to the presented below Scheme 1:
Scheme 1. General Scheme For Synthesis of The Target Piperazine Derivatives.

The reaction is led in anhydrous benzene. The reactants are used in 1:1 molar ratio, whereas triethylamine is used as an HCl acceptor in 1:1 ratio against the acidic chloride. The reaction is followed by TLC till exhaustion of the acidic chloride and the reaction time was determined to be 6 hours. The yields of the purified isolated product are between 46% - 70%. The obtained compounds are cream-colored crystal substances (2a-d, g). 2e is highly viscose oily liquid, soluble in chloroform, benzene and DMFA. Compound 2g is crystallized from ethanol and re-crystallized from the same solvent; when obtained 2f is a waxy-like compound, which is dissolved in minimum ethanol and crystallized with water addition. It is re-crystallized from water-alcohol mixture. All of the obtained compounds are insoluble in water. Their structure is confirmed with FTIR and $^1$H-NMR spectral data.

Structure Elucidation

In the IR-spectra of the investigated compounds the following characteristic absorption bands, divided to the following area are observed:

1. 2800 – 3100 cm$^{-1}$ – In this area the stretching vibrations for methyl and methylene group are observed for all of the compounds, as well as the vibrations for aromatic system. In the spectral data for all compounds, the corresponding absorption bands for secondary amino groups are missing, since all the structures are tertiary amides and are inactive in this area of the IR-spectra.
2. 1800 – 1300 cm\(^{-1}\) – In this area the stretching vibrations for the carbonyl groups of the xanthine ring are observed, as well as for the C=C and C=N groups; the absorption band for the amide carbonyl group (Amide I) for all compounds is also present. The band for amide II (\(\delta\)NH) is missing, since the derivatives are tertiary amides. Also in this area may be found the absorption bands of bending vibrations for the methyl and methylene groups. Both carbonyl groups of the xanthine fragment of the structures are non-equivalent. The junction of the carbonyl group at 6\(^{th}\) place is stronger, than the one on 2\(^{nd}\) place, due to the presence of a double bond in the heterocycle in an \(\alpha,\beta\)-position.

3. 756 – 747 cm\(^{-1}\) – The absorption in this area is with maximum at about 750 cm\(^{-1}\) and is characteristic for the methylxanthines.\(^{[21]}\) Here are found the deformational vibrations for aromatic system and also for the carbon-chlorine vibration at about 640 cm\(^{-1}\). The obtained \(^1\)H-NMR spectral data confirm the proposed structures.

**Pharmacological Results**

Conventional virtual screening of chemical libraries has been used widely to search for new leads in drug development for a protein target.\(^{[22]}\) As the deposited structures of biomolecules in the Protein Data Bank (PDB) increase substantially in the past decades, searching for the targets of a given drug or small compounds (also known as inverse screening, target fishing, off-target prediction, etc.) has become a useful approach.\(^{[23]}\) When the 3D structures of the targets are available, the problem of target identification is usually converted to finding the best interaction mode between the potential target candidates and probe small molecules. The importance of striving for and maintaining drug-like physicochemical properties during the hit and lead optimization process is also widely discussed and well documented, and many published studies have suggested optimal ranges and/or limits for key molecule descriptors such as size, lipophilicity, H-bonding characteristics, rotatable bond and aromatic ring counts, particularly with regard to the design of orally administered drugs.\(^{[24]}\) Thus Pharmacophore, which is the spatial arrangement of features that is essential for a molecule to interact with a specific target receptor, has been accepted as an alternative method despite of molecular docking for drug target identification, applied as the first step in drug discovery. Backed up by a large pharmacophore database annotated with target information the freely accessible web server Pharmmapper may serve as a valuable tool for identifying targets for a novel synthetic compounds, newly isolated natural products, compounds with defined structure or existing drugs with unknown mechanism of action. Keeping this in mind and using the reverse pharmacophore mapping procedure, accepted in PharmMapper tool, we aligned the
newly synthesized by us 7 piperazine amide derivatives to 2241 human protein targets, from which the top 300 targets were analyzed. By the flexible alignment of these structures the calculated and recorded pharmacophores were obtained and the candidate targets were prioritized, based on the corresponding fit values and z-scores. It was of high interest for us to present the model derived for a possible pharmacophore interaction of each of the synthesized molecules with β-secretase 1, since it was categorized as the probable target for the compounds of interest. The obtained results are presented on Fig. 1, Whereas It Was Observed, That For Compounds 2b And 2c, More Than One Pharmacophore Interactions Are Possible.

Fig. 1. Representation of The Pharmacophore Interactions of The Newly Synthesized Compounds with The Target B-Secretase 1.

One of the major hurdles for target identification is the effectiveness of scoring functions. To evaluate the binding affinity of the small ligand and a protein target, an accurate yet generally applicable scoring function is essential. In the used approach the corresponding scoring functions are defined as fit score and z’ score, whereas the corresponding z’-score is a score generated from the molecule’s fit score and a library score matrix calculated beforehand. It combines the fit score and its corresponding vector in the score matrix together and normalizes it to a vector with a mean of zero and a standard deviation of one. The obtained values of the calculated fit and z’-scores for the pharmacophore matching of the target structures with beta secretase 1 enzyme are presented in Table 1.
Table 1. Corresponding Fit And Z’-Scores For Interaction of The Newly Synthesized Compounds with The B-Secretase 1 Enzyme.

<table>
<thead>
<tr>
<th>ID</th>
<th>Beta-secretase 1</th>
<th>Hydrophobic</th>
<th>Positive</th>
<th>Negative</th>
<th>Donor</th>
<th>Acceptor</th>
<th>Aromatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fit score</td>
<td>z’-score</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>a (39)</td>
<td>2.996</td>
<td>-0.215043</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>b (3)</td>
<td>3.683</td>
<td>2.49531</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>b (4)</td>
<td>3.379</td>
<td>0.966691</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>c (77)</td>
<td>2.986</td>
<td>-0.663522</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>c (148)</td>
<td>2.959</td>
<td>-0.0816365</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>d (14)</td>
<td>3.669</td>
<td>1.81453</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>e (18)</td>
<td>3.485</td>
<td>2.2018</td>
<td>5</td>
<td>0</td>
<td>1</td>
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<td>1</td>
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<td>f (11)</td>
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<td>7</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>g (29)</td>
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<td>0.595302</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

From the obtained results was observed, that the presence of four carbon atoms in the side chain of the substituent is important for the interaction with the target molecule. As it may be seen from Table 1 and the presented on Fig. 1 structures, the most important pharmacophoric property is the hydrophobicity of the molecule, whereas the compound with highest fit score was established to be compound 2f. On the other hand it should be noted, that compared to the fit score z’-score not only applys the pharmacophore matching method but also consider some statistic factor lying behind, say, normal distribution a randomly given molecule’s fit score may follow. Generally, large positive z’-score should indicates high significance of the target to a query compound, as well, large negative z’-score indicates the target may not be significant enough. Thus the obtained z’-score will adds up to the pure fit score with more statistical meaning and confidence comparing.\textsuperscript{[19,27]} From the presented in Table 1 z’-score values is visible, that compound 2b is of high significance to the target with more statistical meaning and confidence, based on its highest result.

**CONCLUSION**

In the presented work seven benzhydrylpiperazine derivatives were synthesized. Their structure was elucidated using TLC methodology and proven with the corresponding IR, $^1$H-NMR spectral analysis. The PharmMapper server was used for prediction of the degree of interaction of the obtained structures with Beta-secretase 1 enzyme, based on the most applied pharmacophoric features. From the performed experiments was established, that the most significant pharmacophoric parameter is the hydrophobicity of the molecule, whereas for compound 2f with highest fit score, the significance of this parameter is greatest. Based on the presented results may be concluded, that structures with 4-7 hydrophobic positions and...
aromatic ring or four carbon atoms in the side chain are of interest in further evaluation of piperazine bearing structures with \( \beta \)-secretase 1 activity.

REFERENCES


15. Predicted pKa values for simple 4- benzylpiperidine and 4-methoxypiperidine are _10–11 (SciFinder 2007).