1. Introduction

Nowadays, calcium ion channel blockers play a prominent role in treating hypertension [1]. Within this drug family, the special attention of medical practitioners and research teams is attracted to drugs containing 1,4-dihydropyridine (DHP) core [2, 3]. This is because of their high selectivity towards blood vessels compared to phenylalkylamine and benzothiazepine derivatives [4].

A classic drug that founded the family of DHP-blockers is Nifedipine. Later on, other members, such as Isradipine, Nicardipine, Felodipine, Nimodipine (2nd generation), Amlodipine, Lacidipine and Lercanidipine (3rd generation), were also implemented into medical practice (Fig. 1).

In most DHP blockers, a phenyl radical containing a nitro group or chlorine atom is located in position 4 of the dihydropyridine system; only Isradipine has a fused benzoxadiazole system (Fig. 1). Therefore, one of the promising strategies for the structural modification of DHP derivatives is the introduction of various heterocyclic systems into position 4. The synthesis of DHP derivatives, containing fragments of furan [5], thiophene [6], indole [7], imidazole [8, 9], pyridine [7, 10], pyrazine [11] and others have been reported. Some DHP derivatives containing 1,2,3-triazole fragments...
have also been synthesized [12]; however, in this case, the two heterocycles are connected to each other through a methoxyphenyl fragment [13]. An example of a 1,2,3-triazole-containing DHP derivative is shown in Fig. 2, a.

![DHP-blockers](image1)

**Fig. 1.** The drug family of DHP-blockers

Meanwhile, DHP derivatives have recently attracted attention in addition to their classical role as potential Calcium ion channel blockers. For example, 1,2,3-triazole-derivatives, mentioned above and shown in Fig. 2, b, is considered a promising antidiabetic agent. Compounds containing a thiophene fragment in position 4 affect not only Calcium ion channels but also the transport of chloride ions, which opens up opportunities for treating cystic fibrosis [14].

Some studies have demonstrated that DHP derivatives have an almost classical structure that reveals antimicrobial [15, 16] and antifungal effects. In addition, DHP derivatives, in which 3,5-carbo-ester groups are symmetrically amidated with thiosemicarbazide, showed anticoagulant activity [17]. Finally, symmetrical amidation of 3,5-carbo-ester groups with deacylated melatonin led to the appearance of antioxidant properties against the background of blocking activity concerning Calcium ion channels [18]. Bispyridinium dibromide DHP analogues, shown in Fig. 2, b, were synthesized by quaternization of 4-pyridyl derivative DHP with propargyl bromide and showed antiradical activity [19].

The goal of our study is synthesis and a computer-aided rational design of new, more effective analogs of Nifedipine.

### 2. Planning (methodology) of research

The methodology of our study was as follows: new derivatives combine the DHP fragment and a variable 1,2,3-triazole moiety, which promise to increase biostability, bioavailability, efficacy and binding selectivity to target receptors [2, 12]. First, 45 FDA-approved Nifedipine analogues were docked against the rCav1.1 receptor to estimate the best analogues, which were further used for estimating the binding energy threshold. Second, we generated a virtual library of DHP analogues composed of 796 molecules, all containing 1,2,3-triazole moieties, using evolution/combinatorial principles. Third, to reduce chemical space, the generated library was pre-filtered against the Nifedipine pharmacophore model. Fourth, selected candidates were docked against the rCav1.1 receptor. Finally, eight suggested derivatives were synthesized using the retrosynthetic approaches. The results of our molecular docking calculations can guide and optimize the practical synthesis of new analogues of Nifedipine.

### 3. Materials and Methods

**Chemistry.** Starting materials and reagents were commercially available and used as obtained from Sigma-Aldrich or Fischer Scientific without further purification. NMR spectra were recorded on Bruker AV 400 in DMSO-d6 using TMS as an internal standard. LC/MS spectra were recorded with a Waters UPLC Acquity equipped with a Waters LCT Premier XE Mass Detector for UPLC-HRMS and with Waters Alliance systems. Control of the reactions was carried out using thin-layer chromatography (elucent – ethyl acetate-hexane 1:2) on Fluka silica gel (60 F 254) plates (0.25 mm), and compounds were visualized with UV light (λ=254 nm) or KMnO₄ stain.

**Molecular Docking Setup.** Molecular docking was performed for selected DHP derivatives against the Cryo-EM structure of the rabbit Cav1.1 channel (PDB ID: 6JP5). The co-crystalized ligand and water molecules were removed. All semi-flexible molecular docking calculations were performed using LigandScout software (version 4.4.9) [20] with the built-in AutoDock Vina 1.1 [21]. Docking was performed for rigid receptors and conformationally flexible ligand molecules. For each ligand, three independent runs were performed. The best docking mode corresponds to the highest ligand binding affinity. Molecular graphics and visualization were performed using LigandScout 4.4.9 and VMD 1.9.3 [22].

### 4. Results

**The Structure of Calcium Ion Channel Receptor.** Recently, the high-resolution Cryo-EM structure of the rabbit Cav1.1 channel, also known as the L-type Cav or dihydropyridine receptors (DHPRs), has been resolved [23]. The rCav1.1 is a hetero-multimeric complex containing the pore-forming α1 core subunit and some other auxiliary subunits, such as α2γ-1, β1a, and γ, as shown in Fig. 3.
The DHP derivatives have been widely used for the treatment of hypertension, angina pectoris, and Raynaud’s phenomenon [24]. Therefore, the rCav1.1-Nifedipine complex is a good atomic structural model for in silico screening of novel DHP antagonists.

The CryoEM structure of α1-subunit of the rCav1.1 after removing the co-crystalized water and Nifedipine was used as a target receptor for in silico screening of the DPH library and the molecular docking calculation, as shown in Fig. 3.

Fig. 3. Cryo-EM structure of the rCav1.1-Nifedipine complex. The bound Ca²⁺ ion and Nifedipine are shown as green spheres and as ball-and-sticks. The sugar moieties are omitted for clarity (PDB 6JP5) [23]. The active binding site and the docking cell are shown in red.

Molecular Docking Calculations.

To benchmark our docking procedure and used force-field parameters, we first re-docked Nifedipine against the rCav1.1 receptor using LigandScout software. Fig. 4 compares the experimental X-ray binding mode of Nifedipine in its co-crystallized complex with the rCav1.1 receptor and its best binding mode obtained by molecular docking calculation, as shown in Fig. 3.

Fig. 4. The comparison of the experimental CryoEM structure (green) at the active site of the rCav1.1 (PDB ID: 6JP5) and the best binding mode (red) of Nifedipine estimated by molecular docking calculations.

Molecular Docking Calculations.

To benchmark our docking procedure and used force-field parameters, we first re-docked Nifedipine against the rCav1.1 receptor using LigandScout software. Fig. 4 compares the experimental X-ray binding mode of Nifedipine in its co-crystallized complex with the rCav1.1 receptor and its best binding mode obtained by molecular docking calculation. Our docking results demonstrate a good overlap of the X-ray experimental data and the predicted bound conformation of Nifedipine with the root-mean-square deviation of less than 0.15 nm, as estimated by LigandScout. This agreement allowed us to use this docking procedure further for the large-scale screening of a broad family of DHP analogues.

A series of 45 FDA-approved DHP drugs and existing Calcium ion channel blockers, available in PubChem database (https://pubchem.ncbi.nlm.nih.gov), were docked against the rCav1.1 receptor to identify the hit candidates. The docking was performed against the rCav1.1 receptor using the identical docking procedure. Table 1 summarizes the molecular docking results for the eight hits characterized by their LigandScout binding affinity score, which is higher than the reference ligand Nifedipine.

Table 1 and Fig. 5, a, b, d demonstrate that Elgodipine, Dexniguldipine and Vatanidipine revealed the highest affinity towards the rCav1.1 receptor in terms of AutoDock Vina Binding Affinity and LigandScout Binding Affinity Score. Therefore, the results of Table 1 and Fig. 5, a–h form the basis for further in silico screening of new 1,2,3-triazole-containing DHP analogs.

Nifedipine-Based Pharmacophore Screening.

Next, we carried out in silico screening of our local library composed of 796 Nifedipine analogues containing a 1,2,3-triazole moiety. This library is too big for direct molecular docking. Therefore, the library was pre-filtered by using two different pharmacophore models created based on the cryo-EM structure of the rCav1.1-nifedipine complex (Fig. 6, a, b). First, using the original CryoEM structure of crystal-bound Nifedipine, a 3-point pharmacophore model was built using LigandScout software (Fig. 6, a).

Table 1

<table>
<thead>
<tr>
<th>No.</th>
<th>Ligand Name</th>
<th>AutoDock Vina Binding Affinity (kcal/mol)</th>
<th>LigandScout Binding Affinity Score</th>
<th>M_w (g/mol)</th>
<th>cLogP</th>
<th>PSAa (Å²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Elgodipine</td>
<td>–8.1</td>
<td>–38.5</td>
<td>524.6</td>
<td>5.07</td>
<td>94.2</td>
</tr>
<tr>
<td>2</td>
<td>Dexniguldipine</td>
<td>–9.7</td>
<td>–35.4</td>
<td>609.7</td>
<td>5.84</td>
<td>119.7</td>
</tr>
<tr>
<td>3</td>
<td>Teludipine</td>
<td>–6.7</td>
<td>–34.8</td>
<td>498.6</td>
<td>3.94</td>
<td>94.1</td>
</tr>
<tr>
<td>4</td>
<td>Vatanidipine</td>
<td>–9.0</td>
<td>–34.6</td>
<td>686.8</td>
<td>6.45</td>
<td>122.9</td>
</tr>
<tr>
<td>5</td>
<td>Pranidipine</td>
<td>–7.9</td>
<td>–31.6</td>
<td>448.5</td>
<td>4.26</td>
<td>116.4</td>
</tr>
<tr>
<td>6</td>
<td>Cilnidipine</td>
<td>–8.4</td>
<td>–30.6</td>
<td>492.5</td>
<td>4.28</td>
<td>125.7</td>
</tr>
<tr>
<td>7</td>
<td>Lercanidipine</td>
<td>–8.7</td>
<td>–30.4</td>
<td>611.7</td>
<td>6.52</td>
<td>119.7</td>
</tr>
<tr>
<td>8</td>
<td>Manidipine</td>
<td>–8.6</td>
<td>–25.0</td>
<td>610.7</td>
<td>4.70</td>
<td>122.9</td>
</tr>
<tr>
<td>9</td>
<td>Nifedipine</td>
<td>–7.3</td>
<td>–24.9</td>
<td>346.3</td>
<td>2.18</td>
<td>116.5</td>
</tr>
</tbody>
</table>

Note: a — polar surface area (PSA) is the surface sum over all polar atoms, such as oxygen, nitrogen, sulfur and phosphorus, including also attached hydrogens.
Second, the structure of the rCav1.1-Nifedipine complex was energy-minimized by the empirical MMFF94 force field, following the pharmacophore building. This procedure allowed us to identify additional ligand-receptor interactions, such as H-bonding with Thr935 and Ser1011, resulting in a five-point pharmacophore model, as shown schematically in Fig. 6.

Next, the pharmacophore filtering of our Nifedipine library using 3- and 5-point models allowed gradual narrowing the library chemical space from 796 to up to 124 (using 3-point model) and 26 (using 5-point model) analogs, characterized by a pharmacophore fit score of above Nifedipine reference value of 53.5.

To evaluate the binding affinity of 26 selected candidates, we carried out their molecular docking against the rCav1.1 structure. The docking results for 8 best-binding ligands are summarized in Table 2. The docking poses of the first four best-binding derivatives are shown in Fig. 7, a–d. The best docking pose was selected by two criteria:

![Fig. 5. The best docking poses of eight hit channel blockers at the active site of the rCav1.1 receptor: a – elgodipine; b – dexniguldipine; c – teludipine; d – vatanidipine; e – pranidipine; f – cilnidipine; g – lercanidipine; h – manidipine. The ligand binding pose is colour-coded and overlapped with the experimental binding mode of Nifedipine (green) (PDB ID: 6JP5) versus the molecular docking calculations (colour-coded)](image)

![Fig. 6. Two pharmacophore models of Nifedipine bound to the rCav1.1 receptor (PDB ID: 6JP5) in 3D-representation (left) and a 2D cartoon view (right): a – 3-point model; b – 5-point model)](image)
1) first, the bound conformation of a DHP ring of a studied ligand should match the position of this ring in the co-crystallized rCav1.1-Nifedipine complex, as shown in Fig. 7;

2) second, the best binding pose corresponds to the structure with the most negative LigandScout binding affinity score.

Table 2 shows that among eight 1,2,3-triazole-containing DHP analogues, compounds 5a and 5b revealed the same or higher affinity towards the rCav1.1 receptor than parent Nifedipine in terms of LigandScout Binding Affinity Score. These parameters for 5a and 5b were found to be –25.2 and –24.8, respectively, compared to –24.9 for Nifedipine (Table 1). In terms of AutoDock Vina Binding Affinity, all identified analogues except 5e, are characterized by a higher affinity from –7.5 up to –7.9 kcal/mol, as compared to –7.3 kcal/mol for Nifedipine (Table 1). In addition, most of the selected analogues are characterized by low PSA values below 100 Å². PSA is a commonly used medicinal chemistry criterion for estimating cell permeability, so drug-like molecules with PSA >140 Å² are typically poorly permeable into cell membranes [25, 26]. Finally, our molecular docking results suggest that introducing the 1,2,3-triazole moiety to position 4 of a 1,4-dihydropyridine core offers a promising scaffold for developing novel DHP blockers.

**Table 2** Summary of the molecular docking calculation and physico-chemical parameters for derivatives 5a-h

<table>
<thead>
<tr>
<th>No.</th>
<th>Ligand</th>
<th>AutoDock Vina Binding Affinity (kcal/mol)</th>
<th>LigandScout Binding Affinity Score</th>
<th>M_p (g/mol)</th>
<th>cLogP</th>
<th>PSA (Å²)</th>
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<td>5a</td>
<td>–7.7</td>
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<td>448.9</td>
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<td>95.4</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>–7.7</td>
<td>–24.8</td>
<td>464.4</td>
<td>3.69</td>
<td>95.3</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>–7.3</td>
<td>–23.4</td>
<td>441.4</td>
<td>1.92</td>
<td>141.2</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>–7.9</td>
<td>–22.9</td>
<td>459.4</td>
<td>2.68</td>
<td>147.2</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>–7.1</td>
<td>–22.5</td>
<td>440.1</td>
<td>2.30</td>
<td>95.3</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td>–7.8</td>
<td>–22.4</td>
<td>432.4</td>
<td>2.91</td>
<td>95.3</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
<td>–7.6</td>
<td>–20.8</td>
<td>414.4</td>
<td>2.77</td>
<td>95.4</td>
</tr>
<tr>
<td>8</td>
<td>5h</td>
<td>–7.7</td>
<td>–20.4</td>
<td>420.8</td>
<td>2.64</td>
<td>95.3</td>
</tr>
</tbody>
</table>

**Synthesis of Nifedipine Analogs containing a 1,2,3-Triazole Moiety.**

Based on the docking results, we designed a retrosynthetic plan for the synthesis of new DHP derivatives and synthesized a series of derivatives 5a-h.

The Huesgen dipolar cycloaddition reaction (CuAAC) was used to construct the 1,2,3-triazole scaffold (Fig. 8) [27–29]. Propargyl alcohol was introduced into a click reaction with arylazides (step b), which, in turn, were synthesized by the diazotization reaction of the corresponding arylamines (step a). Next, alcohols 3a–h were subjected to standard oxidation by Pyridinium chlorochromate (PCC) and aldehydes 4a–h were obtained in a yield of 68–79% [30, 31].

The synthesis of the target 1-N-aryl-substituted 1H-1,2,3-triazolyl-1,4-dihydropyridines 5a–h was carried out according to the Hanh reaction by condensation of two equivalents of 1,3-dicarboxyl compound 6, one equivalent of aldehyde 4a–h and ammonium acetate (Fig. 9). The reaction was carried out in ethanol at a temperature of 80–85 °C for 2 hours yielding derivatives 5a–h with yields of 80–96%.

**General method of 2,6-dimethyl-4-(1H-1,2,3-triazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate synthesis (5a–h).**

The mixture of 1H-1,2,3-triazole-4-carbaldehyde 4a–h (1 mmol), methyl/ethyl acetoacetate (2.1 mmol), ammonium acetate (1.5 mmol, 258 mg) was dissolved in ethanol (10 mL). The solution was refluxed for 2 h at 80 °C. After completion of the re-
action, according to TLC data, the reaction mixture was cooled to room temperature. The precipitate was filtered off, washed with ethanol, and crystallized from ethanol. A pure product was obtained with a yield of 80–96 % based on the starting aldehyde.

![Fig. 8. Synthetic way for 1H-1,2,3-triazole-4-carbaldehydes. Reagents and conditions: a – NaN₃, HCl, 0 °C; NaN₃, 2–4 h, rt; b – propargyl alcohol, CuSO₄, sodium ascorbate, THF:H₂O (1:1), rt; c – PCC, CH₂Cl₂, 2 h, rt](image1)

**3.5-Diethyl 4-((1-(5-chloro-2-fluorophenyl)-1H-1,2,3-triazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5a).** White solid, yield 96 % (910 mg). ¹H NMR (400 MHz, DMSO-d₆) δ 8.93 (s, 1H), 8.29 (s, 1H), 6.93–6.76 (m, 2H), 5.16 (s, 1H), 4.43 (dq, J=1.9, 1.0 Hz, 1H), 3.98 (q, J=7.1 Hz, 4H), 2.23 (s, 6H), 1.12 (t, J=7.1 Hz, 6H). MS (ESI+) m/z calculated for C₂₁H₂₂F₂N₅O₄ [M+H]⁺ 440.14, found 440.1.

**3.5-Diethyl 4-((1-(3-chloro-2-fluorophenyl)-1H-1,2,3-triazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5b).** White solid, yield 82 % (395 mg). ¹H NMR (400 MHz, DMSO-d₆) δ 8.94 (s, 1H), 8.45 (d, J=0.5 Hz, 1H), 8.19–8.09 (m, 2H), 7.98–7.88 (m, 2H), 5.14 (s, 1H), 4.11–4.03 (m, 4H), 2.27 (s, 6H), 1.16 (t, J=7.1 Hz, 6H). MS (ESI+) m/z calculated for C₁₉H₁₹F₂N₅O₄ [M+H]⁺ 465.4, found 465.2.

**3.5-Diethyl 2,6-dimethyl-4-((1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (5f).** Yellow solid, yield 94 % (950 mg). ¹H NMR (400 MHz, DMSO-d₆) δ 8.94 (s, 1H), 8.51 (s, 1H), 8.42–8.37 (m, 2H), 8.22–8.18 (m, 2H), 5.15 (s, 1H), 4.06 (p, J=7.2 Hz, 4H), 2.27 (s, 6H), 1.16 (t, J=7.1 Hz, 6H). MS (ESI+) m/z calculated for C₁₉H₁₉F₂N₅O₄ [M+H]⁺ 442.1, found 442.0.

**3.5-Diethyl 4-((1-(2-fluoro-5-nitrophenyl)-1H-1,2,3-triazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5d).** Yellow solid, yield 91 % (245 mg). ¹H NMR (400 MHz, DMSO-d₆) δ 8.27 (s, 1H), 8.16 (s, 1H), 7.79 (d, J=0.6 Hz, 1H), 7.46 (dd, J=10.2, 7.6 Hz, 1H), 5.16 (s, 1H), 4.43 (dq, J=1.9, 1.0 Hz, 1H), 3.98 (q, J=7.1 Hz, 4H), 2.23 (s, 6H), 1.12 (t, J=7.1 Hz, 6H). MS (ESI+) m/z calculated for C₂₁H₂₂N₅O₄ [M+H]⁺ 460.4, found 460.1.

**5. Discussion**

Our computer-aided rational design demonstrated that adding a 1,2,3-triazole ring to existing DHP and Nifedipine scaffolds has a strong potential for developing novel rCav1.1 receptor selective ligands. To follow this strategy, we generated a new chemical library of 796 derivatives combining the DHP fragment and a 1,2,3-triazole moiety using structural modifications of the parent Nifedipine scaffold by evolution/combinatorial principles [26]. The generated library contained new promising virtual molecules; however, it was too large for direct molecular docking calculations. Therefore, we used a multi-step procedure for its gradual reduction. The li-
library size was filtered using two 3D-pharmacophore models of different complexity. The 5-point 3D-pharmacophore screening decreased the chemical space up to 26 hit candidates. The selected ligands were further subjected to molecular docking calculations against the rCav1.1 receptor, which allowed us to reduce the chemical space, ending up with eight hit derivatives 5a-h (Fig. 7, Table 2). The identified hit molecules 5a-h were characterized by the high selectivity and strong binding affinity towards the rCav1.1 receptor. We found that the DHP moiety of Nefidipine and ligands 5a-h interacted mostly with residues T935, Q939, F1008 and M1366 of the rCav1.1 receptor, while the bound conformation of bulky aryl-1,2,3-triazole moieties of ligands 5a-h is stabilized by steric interactions with the receptor residues of F1060 and F1370, respectively.

We used the results of our computer-aided rational design of novel promising antihypertensive agents to set up the retrosynthetic approach for the experimental synthesis of new Nefidipine analogues (Fig. 8, 9). Finally, we performed the retrosynthetic procedure based on the Hanch reaction to obtain new Nefidipine analogues 5a-h bearing a 1,2,3-triazole moiety in position 4.

**Study limitations.** The high-throughput screening of the antihypertensive activity for derivatives 5a-h was not available in our lab. Therefore, direct comparison of the molecular docking and the activity assays is not possible, so the potential therapeutic effect of the selected derivatives is only based on a theoretical predictions.

**The prospects for further research.** The suggested computer-aided screening protocol followed by the retrosynthetic approach for new analogues of Nefidipine, respectively. The selected ligands were further subjected to molecular docking calculations against the rCav1.1 receptor. We found that the DHP moiety of Nefidipine analogues containing a 1,2,3-triazole ring in position 4 was stabilized by steric interactions with the receptor residues of F1060 and F1370, respectively.

**Conflict of interest**

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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**Data availability**

The manuscript has no associated data.

**Use of artificial intelligence**

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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Multicomponent Synthesis of 1,4-Dihydropyridines: A Class of Prominent Calcium Channel Blockers. Current Organic 

anti-diabetic evaluation and molecular docking studies of 4-(1-aryl-1H-1, 2, 3-triazol-4-yl)-1,4-dihydropyridine derivatives as novel 11β-

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