The assessment of sulfonylecalix[4]arene derivatives as inhibitors of protein tyrosine phosphatases

**Aim.** To compare sulfonylecalix[4]arene derivatives containing ionizable or non-ionizable substituents at the upper rim of the macrocycle as inhibitors of protein tyrosine phosphatase 1B (PTP1B) and other PTPs.

**Results and discussion.** The properties of sulfonylecalix[4]arene with four phosphonic acid groups introduced at the upper rim were compared with those of the macrocycles containing four non-ionizable tert-butyl or trifluoroacetamide functions. The sulfonylecalix[4]arene tetrakis-methylphosphonic acid was found to inhibit PTP1B with IC\textsubscript{50} value in the low-micromolar range without selectivity over other PTPs, such as TC-PTP, MEG1, MEG2, SHP2, and PTPβ. At the same time, modification of sulfonylecalix[4]arene with trifluoroacetamide substituents led to inhibition of PTP1B with IC\textsubscript{50} of 1.4 μM and 4- to 28 fold selectivity over the other PTPs. In order to understand the ability of inhibiting PTP1B by sulfonylecalix[4]arene with introduced trifluoroacetamide groups the molecular docking and molecular dynamic simulations were performed. The inhibition mechanism was discussed.

**Experimental part.** The activities of the test compounds in vitro were examined spectrophotometrically measuring the rate of hydrolysis of p-nitrophenyl phosphate as a substrate of PTPs. The molecular docking was performed by AutoDock Vina.

**Conclusions.** This study can start an approach to develop new inhibitors of PTPs by variations in the non-ionogenic substituents on the upper rim of sulfonylecalix[4]arene scaffold.

**Key words:** sulfonylecalix[4]arene; protein tyrosine phosphatase; inhibition; molecular docking; molecular dynamics
The addition or removal of a phosphoryl group in proteins is known to control their stability, and modulate the enzyme activity. Approximately 30% of cellular proteins can be in a phosphorylated form [1]. Tyrosine phosphorylation is essential for many cellular processes, such as growth, differentiation, survival, cell communications, cell migration, and the immune response [2]. Aberrant tyrosine phosphorylation proved to be associated with human diseases, including cancers, diabetes, rheumatoid arthritis, and hypertension [3, 4]. During the last decade, the extensive data concern the activity of PTP1B leading to inhibition of insulin signaling, and the activity of SHP-2 as an oncogene and promoter of the growth factor signaling [2, 5]. In those instances where the PTPs activity is inappropriately high, the inhibitors of these enzymes can be regarded as possible therapeutic agents. Although such agents are permanently studied, PTP-targeted drugs have not yet been available. It is all because the highly charged and highly conserved nature of the PTP active site. For this reason, potent inhibitors of PTPs tend to have a negatively charged group, which may limit their cell permeability and bioavailability.

Such synthetic macrocycles as calixarenes have diverse applications in chemistry and biology [6-8] due to their unique conformational features and the possibility for modifications both at lower and upper rims [9, 10]. It has been shown that calix[4]arenes can be useful as a platform for designing bioactive compounds with the possibility of targeting enzymes and other proteins [11]. For instance, calix[4]arene derivatives with covalently bound phosphonic acid groups exhibit inhibitory effects towards PTP1B and some other PTPs [12]. We also observed that phosphonate monoesters on the thiocalix[4]arene framework were more effective and selective PTP1B inhibitor [13]. An unsubstituted sulfonylcalixarene containing four bridging SO₂ groups turned out to be promising bioactive compound with the inhibitory activity towards protein tyrosine phosphatase ME2G and selectivity over some other PTPs [14]. These data provided a basis for further investigation of sulphonylcalix[4]arene derivatives in searching for substances with desired biological properties. Our next efforts for designing the macrocyclic inhibitors of PTPs directed towards sulfonylcalixarenes contained: i) non-cleavable phosphonic acid groups, which mimicked the phosphorylated tyrosine fragment and ii) non-ionizable functions, such as tert-butyl or trifluoroacetamide groups, which could improve the cell permeability. The aim of this work was to compare the structural diverse sulfonylcalix[4]arene derivatives containing ionizable or non-ionizable substituents at the upper rim of the macrocycle as inhibitors of PTP1B and other PTPs.

Inhibitory activities of sulfonylcalix[4]arene derivatives 1-3 (Fig. 1) were assessed in vitro against PTP1B, T-cell protein tyrosine phosphatase (TC-PTP), Src homology-2 domain containing protein tyrosine phosphatase 2 (SHP2), megakaryocyte protein-tyrosine phosphatases MEG1 and MEG2, and PTPβ. In the experiments, p-nitrophenyl phosphate was used as a substrate. The values of IC₅₀ were calculated from dose-dependent curves as concentrations of the test compound, which decreased the enzyme activity to 50%.

As seen from Tab. 1, sulfonylcalix[4]arene tetraethyl phosphonic acid 1 demonstrated approximately the same inhibition effects on the activities of all PTPs in the low micromolar range of IC₅₀ values, and there was no selectivity for one over the other. Replacement of the phosphonic acid groups with tert-butyl substituents resulted in a dramatic decrease in the inhibitory effect of the less charged compound. The sulfonylcalix[4]arene 2 functionalized by the non-ionizable tert-butyl group was a weak inhibitor of PTP1B, MEG2, SHP2, and PTPβ and did not affect the activity of TC-PTP, MEG1. At the same time, the modification of sulfonylcalix[4]arene with trifluoroacetamide substituents (compound 3) provided the inhibition of PTP1B with IC₅₀ value of 1.4 μM and 4- to 28 fold selectivity over the other PTPs. In this case, the selective inhibition of PTP1B can be attributed to the non-phosphonate upper rim substituents of sulfonylcalix[4]arene 3.

According to the Lineweaver-Burk plots, the effect of inhibitors 3 on the activity of PTP1B was in agreement with a competitive type of inhibition (Fig. 2). The apparent Kᵢ value was of 1.5 μM. The inhibition mechanism suggests that sulfonylcalix[4]arene derivative 3 bound by the enzyme at the substrate binding site.

The molecular modeling by AutoDock Vina was performed to get insights into the binding mechanism of compound 3 with PTP1B. Two groups of X-ray structures of PTP1B having the open or closed WPD-loop were used for the calculations. It is known that the calix[4]arene backbone exists in four different conformations, they are cone, partial cone, 1,2-alternate, 1,2-diagonal, and half-cone. This is why it is important to use different conformations of the calix[4]arene scaffold during the docking procedure. The best fit was provided by the cone conformer, which is known to be the most stable conformation of calix[4]arenes. The docking poses were filtered by using the pose-docking module in AutoDock Vina.

**Fig. 1. Chemical structures of sulfonylcalix[4]arene derivatives 1-3**
Sulfonylcalix[4]arene derivatives 1-3 as inhibitors of protein tyrosine phosphatases*

| Inhibitor | PTP-1B  | TC-PTP | MEG2 | MEG1 | SHP2 | PTP-β  |
|----------|---------|--------|------|------|------|--------|
| 1        | 0.17 ± 0.04 | 0.4 ± 0.01 | 0.23 ± 0.04 | 0.2 ± 0.04 | 0.35 ± 0.01 | 0.3 ± 0.04 |
| 2        | 8.13 ± 1.1 | n/i** | 18 ± 4.1 | n/i | 14 ± 5.9 | 11 ± 1.4 |
| 3        | 1.4 ± 0.26 | 9.6 ± 0.26 | 5.73 ± 0.5 | 40 ± 2 | 11 ± 4 | 38 ± 4 |

Notes: * – IC_{50} values are the means of 2-3 assays ± standard deviations; ** – No inhibition was observed at 10 µM

Fig. 2. The Lineweaver-Burk plot for inhibition of PTP1B by trifluoroacetamide derivative of sulfonylcalix[4]arene. The concentration of inhibitor 3 was 1.5 µM

Table 2

| Conformation of the ligand | ∆G (kcal/mol) |
|---------------------------|---------------|
|                           | 1NL9 | 1PH0 | 1Q6M | 2CM8 |
| Cone                      | -8.6 | -8.5 | -8.1 | -6.3 |
| Partial cone              | -7.2 | -7.5 | -7.7 | -7.4 |
| 1,2-Alternate             | -7.4 | -7.4 | -7.4 | -5.7 |
| 1,3-Alternate             | -7.2 | -6.7 | -6.9 | -6.1 |

and 1,3-alternate, depending on the number and nature of substituents at the lower or upper rim [15]. The molecular docking of these four conformers of compound 3 to the active site of PTP1B (PDB codes 1NL9, 1PH0, 1Q6M, 2CM8) showed that there were no sufficient differences in the docking energy calculated for the conformations with the open and closed WPD-loop (Tab. 2).

The docking results obtained for sulfonylcalix[4]arene-tetrakis-trifluoroacetamide 3 were further optimized by 1 ns molecular dynamics simulations to assess the complex stability. After the molecular docking operations, the most favorable PTP1B structure was chosen to be with the open WPD loop (PDB code 1NL9). The 1 ns MD simulation was carried out for PTP1B alone, as well as in complexes with compound 3 represented by four conformations. The root mean square deviation (RMSD) was calculated for backbone atoms of the crystal structure in order to monitor its structural changes. As shown in Fig. 3, the final RMSD values for all simulation trajectories were less than 1.5 Å, indicating that the enzyme structures had reached the equilibrium states with little alterations during the entire simulations. It should be noted that the cone conformation of compound 3 had a little higher alterations during the complexation with PTP1B suggesting its lower preferability in comparison with three others. The analysis of the ligand positioning after 1 ns molecular dynamics simulation was followed by rescoring with Autodock Vina to find out the final free energies of binding, which were -8.25, -7.7, -9.34, and -6.91 kcal/mol for cone, partial cone, 1,2-alternate, 1,3-alternate conformers, respectively. This results suggested that the 1,2-alternate conformation was the most preferable.

The root mean square fluctuations (RMSF) being a significant parameter to study the motion of the key residues interacted with the ligand were calculated for all amino acid residues of the PTP1B. The key amino acids residues that are important for the substrate and inhibitors binding to PTP1B belong to P-loop (His214-Arg221), WPD loop (Thr177-Pro185), the substrate recognition loop (Lys36, Val49, and Lys120), and the secondary binding site (Tyr20-Phe52, and Arg254) [16-18]. As compared to free protein, most of the residues of the enzyme-inhibitor complex had lower RMSF values less than 1.4 Å (Fig. 4). These data point that binding of compound 3 reduced the flexibility of the active site residues, thus leading to the stable complex.

The analysis of the complex of compound 3 with PTP1B (Fig. 5) showed that one of phenyl rings of the inhibitor was involved in the π-π interaction with Phe182 of the WPD-loop. There were hydrogen bonds between SO_2 groups of the sulfonylcalixarene skeleton and amino acid residues Lys116, Gly183, Arg221, Gln266, and Gln262. One OH group on the bottom rim of the macrocyclic scaffold formed hydrogen bonds with Gln266 and Thr263. An additional set of hydrogen bonds was provided by trifluoroacetamide functions and residues of Arg24 and Arg221.

Table 1

| Sulfonylcalix[4]arene derivatives 1-3 as inhibitors of protein tyrosine phosphatases* |
|-----------------------------------------------|
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Notes: * – IC_{50} values are the means of 2-3 assays ± standard deviations; ** – No inhibition was observed at 10 µM
upper-rim substituents were directed to the region of the active site of PTP1B preventing the access of the substrate to Cys215.

**Experimental section**

Commercially available protein tyrosine phosphatases PTP1B, TC-PTP, MEG1, MEG2, SHP2, and PTPβ were purchased from Sigma-Aldrich. Previously developed protocols were used for the synthesis of sulfonylcalix[4]arene tetrakis-methylphosphonic acid 1 [19], tetrakis-tert-butylsulfonylcalix[4]arene 2 [20, 21], sulfonylcalix[4]arene-tetrakis-trifluoroacetamide 3 [22].

**The in vitro study of PTPs inhibition**

The assay solution contained 50 mM Bis-Tris (pH 7.2), 1 vol % of dimethyl sulfoxide, 100 mM NaCl, 2 mM DTT, 3 mM EDTA. Concentrations of p-nitrophenyl phos-
phate were of 2 mM for PTP1B, TC-PTP, 5 mM for MEG1, MEG2, 7 mM for SHP2, and 1 mM for PTPβ corresponding to Kᵦ values of the enzymes. The final volume of the assay solution was 0.5 ml. The mixture was thermostated at 25 °C (MEG1, MEG2), 37 °C (PTP1B) and 30 °C (TC-PTP, SHP2, PTPβ) for 5 min, and the reaction was initiated by addition of the enzyme (4-8 nM in the reaction mixture). The p-nitrophenol released was determined by reading the absorbance at 410 nm (ε = 18,000 M⁻¹ cm⁻¹).

**Computer modeling**

The molecular docking studies were performed by AutoDock Vina [23] program using X-ray crystals of four centroids of PTP1B clusters (PDB codes: 1NL9, 1PHO, 1Q6M, 2CM8) [24]. The structures of four ligand conformers were prepared by program Avogadro and optimized in MMFF94s force field [25]. The conformers were docked to the active site region of PTP1B. The ligands presented and water molecules were removed from PDB-files before calculations.

Molecular dynamic simulations (MD) of the complexes was performed with NAMD 2.10 [26] using the CHARMM27 and the CHARMM36 force field. The topology parameters for all conformers of compound 3 were built using SwissParam server [27]. The preliminary preparation of the parameter files for PTP1B was performed by means of VMD 1.9.2 [28]. MD was performed in an NPT ensemble using the Langevin thermostat and pressure control. Energy minimization was performed for 10 ps before the simulation, and the subsequent molecular dynamics for 100 ps was conducted at the temperature of 310 K and 1 atm pressure. One step of MD was 1 fs with preservation of trajectories for further analysis after every 50 fs.

**Conclusions**

Sulfonylcalix[4]arene can be used as a novel scaffold for designing PTPs inhibitors. The sulfonylcalix[4]arene-tetrakis-trifluoroacetamide was found to inhibit PTP1B with IC₅₀ value in the micromolar range and selectivity over other PTPs, such as TC-PTP, MEG1, MEG2, SHP2, and PTPβ. This approach provides a way to new PTP1B inhibitors functionalized by non-ionizable groups on the upper rim of the macrocycle.

**Conflicts of Interests:** authors have no conflict of interests to declare.

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