

# Influence of 1,4-dihydropyridine derivatives on rat paw edema, biosynthesis of glucocorticoid hormone and its binding activity to glucocorticoid receptor

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The influence of the 1,4-dihydropyridine derivatives OSI-7725 and OSI-7727 on acute inflammation, glucocorticoid hormone (GH) synthesis and specific GH binding to glucocorticoid receptor (GR) activity was investigated. Since several 1,4-dihydropyridines (DHPs) possess anti-inflammatory properties, we first studied the effect of racemate OSI-7725 and its (+) enantiomer OSI-7727 in a model of rat paw edema induced by carrageenan. These compounds had a preventative effect in this model of inflammation and decreased edema development at a most effective dose of 0.1 mg/kg by 26.6% and 41.6%, respectively. Both compounds were ineffective when added after carrageenan injection. Subsequent experiments *in vivo* showed that OSI-7725 and OSI-7727 at a dose of 5 mg/kg stimulated GH synthesis in rat adrenal. They induced an increase in total, transcortin-bound and free corticosterone levels in plasma 2 h following intraperitoneal administration. The pretreatment with metyrapone, an inhibitor of steroid synthesis, abolished the stimulatory effects of the compounds tested, indicating a steroidal component in the mechanism of action of DHPs. Further experiments *in vitro* showed that these DHPs inhibited dexamethasone (DEX) binding to GR. More active in this model was OSI-7725. It inhibited specific ligand-receptor binding by 80% at concentrations  $10^{-5}$  and  $10^{-4}$  M. OSI-7727 was active only at a concentration of  $10^{-4}$  M.  $IC_{50}$  values of these compounds were 3.59 and 5.52  $\mu$ M, respectively. The results show a significance of these DHPs in the regulation of vitally important processes and provide an evidence of involvement of fine mechanisms through which the pharmacological effects of DHPs can be released. This could extend the potential of the application of these substances.

**Key words:** 1,4-dihydropyridine, glucocorticoid hormone, glucocorticoid receptor

## INTRODUCTION

4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-diester are a group of compounds exhibiting different physiological properties. Their activity is determined by the dihydropyridine ring, and their pharmacokinetic properties are dependent on the side chains [1]. Nowadays, derivatives of DHP are widely used for the treatment of various coronary and heart system diseases, though the mechanism of action of these drugs is not fully elucidated [2–4]. It is known that they modulate more often voltage-gated L-type calcium channels [5]. Furthermore, these compounds also interact with the diverse receptors and ion channels, such as potassium, sodium channels and of the G-protein coupled receptors [6, 7]. However, there

is not enough data on the interaction between DHP and GR. Nifedipine is known to reduce the binding of [<sup>3</sup>H]-triamcinolone acetonide to GR from brain cytosol fractions of rats by 58% [8]. It has been discovered that spirocyclic dihydropyridine derivatives selectively bind the GR. They completely antagonize the DEX-mediated induction of enzymes involved in gluconeogenesis and glutamine metabolism [9]. Our previous studies have shown that some DHPs display anti-inflammatory, long-term neuromodulatory and neuroprotective actions [10–12]. These effects might be due to their high lipophilicity which allows molecules to penetrate cell membranes and modulate intracellular processes [13]. Though DHPs are widely known as biologically active compounds, their influence on GH-GR interaction and GH synthesis *in vivo* is still not sufficiently explored. It is known that steroids regulate numerous physiological processes most

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of which rely on the ability of the hormone-bound glucocorticoid receptor (GR) to change the expression of target genes. Therefore, the possible effect of DHPs on the dynamics of GH biosynthesis and GH to GR binding activity could be of great clinical importance and open new application possibilities of these compounds. Besides, most of DHPs applied in scientific research and therapy are racemates, but only one enantiomer usually exposes a significant activity. For example, ( $\pm$ )Bay K 8644 is the racemate of two isomers where one enantiomer, (-)Bay K 8644, plays the role of an active agonist, whereas the second, (+)Bay K 8644, is a weak antagonist. The racemate ( $\pm$ )Bay K 8644 acts on the calcium channels as an agonist, because the agonistic isomer is approximately 16-fold more potent than the antagonistic one [14]. The aim of this study was to investigate the influence of the racemate OSI-7725 and its (+) enantiomer OSI-7727 on rat paw edema, GH synthesis and activity of GH binding to GR.

## MATERIALS AND METHODS

**Animals.** Male Wistar rats (Laboratory Animal Centre, Institute of Immunology, Vilnius University, Lithuania) weighing 150–180 g each, were used for experiments throughout the study. Each experimental group consisted of six rats. All procedures were carried out in accordance with the guidelines of the European Union, local laws and police and were approved by the Ethics Committee of Animal Experimentation.

**Reagents.** The following 1,4-dihydropyridine derivatives were synthesized at the Latvian Institute of Organic Synthesis (Riga, Latvia): racemate OSI-7725, (2,6-dimethyl-3-[2'-propoxyethoxycarbonil]-5-[methoxycarbonil]-4-2-(2"-difluoromethoxyphenyl)1,4-dihydropyridine; OSI-7727 is its (+) enantiomer. Other reagents were purchased from Fluka, Sigma, Serva (Germany), Merck (USA) and Amersham (UK).

**Model of rat paw edema.** Experiments were performed as described by Winter [15]. The animals were anaesthetized. Carrageenan (100  $\mu$ l 2% solution in saline) was injected subcutaneously into the right hind paw. Differences in the weight of the injected and uninjected paw were determined as an indicator of inflammation (paw edema). The anti-inflammatory properties of OSI-7725 and OSI-7727 were studied by injecting various doses (0.1, 0.25, 0.5 and 1 mg/kg) of these drugs intraperitoneally 3 h before or after administration of carrageenan. Negative control rats were injected with the same volume of solvent (15% PEG saline solution). Prednisolone (100 mg/kg) served as a positive control.

**Assay of measurement of corticosterone level.** We investigated the influence of OSI-7725 and OSI-7727 on the level of GH by measuring the total, transcortin-bound and free forms of corticosterone. OSI-7725 and OSI-7727 were administered intraperitoneally at a dose 5 mg/kg. Samples of blood were collected 2, 3 and 4 h following the injections of drugs. Metyrapone, an inhibitor of ste-

roid biosynthesis, was used at a single dose 300 mg/kg. Blood plasma protein fractionation was performed by gel chromatography on a Sephadex G-50 column (0.9  $\times$  15 cm). Corticosterone concentration was determined by a competitive protein binding radioassay using rat serum as a source of corticosteroid-binding globulin [16]. Standard curves were constructed from an assay using [ $^3$ H]-corticosterone (Amersham), nonlabelled corticosterone (Serva) and Norit A (Serva) as described elsewhere [17].

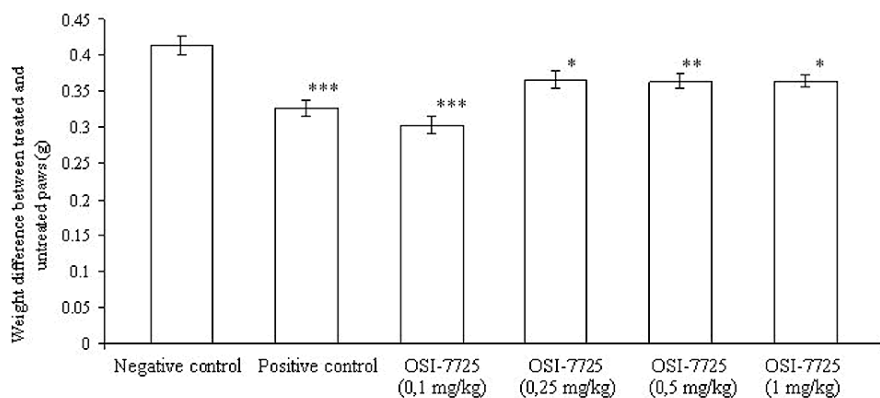
**Preparation of cytosol.** Livers were perfused *in situ* through the portal vein with ice-cold saline (0.9% NaCl) by the technique described earlier [18]. Then liver slices were homogenized in the ice-cold buffer (10 mM Tris-HCl, pH 7.4, 1.5 mM EDTA, 2mM  $\beta$ -mercaptoethanol, and 1 mM PMSF). The homogenate was centrifuged at 105000g at 0–4 °C for 1 h [19]. The upper lipid layer was discarded, and the resulting supernatant was designated as cytosol.

**Steroid binding assay.** For determining the extent and specificity of steroid binding, aliquots of the cytosol were incubated with 10 nM [1,2,4- $^3$ H]-DEX (42.0 Ci/mmol, Amersham) at 4 °C for 2 h in the absence or presence of a 1000-fold molar excess of non-labelled DEX to determine specific steroid binding [20]. For *in vitro* competition experiments, the substances in incubation medium were tested in a concentration range from 10 $^{-3}$  M to 10 $^{-8}$  M. After incubation (at 0–4 °C for 2 h) non-bound radioactivity was removed by the dextran-coated charcoal technique [16] with some modifications. A suspension of 100  $\mu$ l of 5% charcoal/0.5% dextran was added to each Eppendorf tube containing 250  $\mu$ l of reaction mixture. The samples were thoroughly mixed, allowed to stand in an ice-water bath for 5 min, and then centrifuged (12,500g, 1 min). 200  $\mu$ l aliquots in 2 ml of dioxane scintillation liquid were used for radioactivity measurements. All experiments were repeated at least four times.

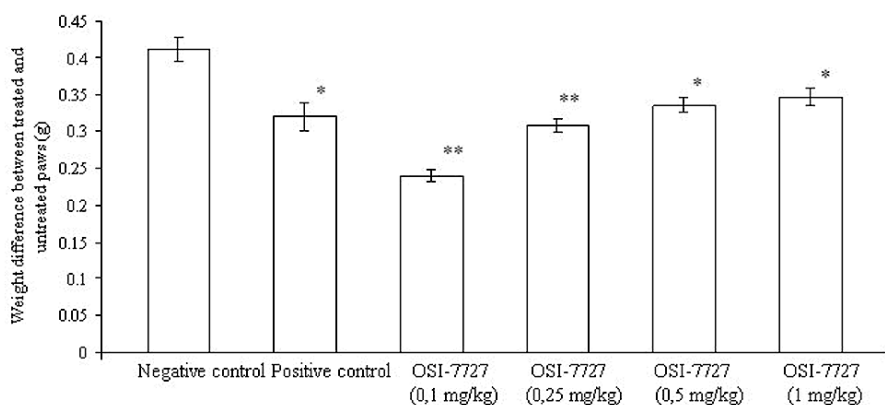
**Statistical analysis.** All results were expressed as the arithmetic mean  $\pm$  SE. Differences between groups were evaluated by analysis of variance (ANOVA) complemented by Student's t-test. All calculations were performed using Microsoft Excel (version 7.0) and Sigma Plot (version 9.0).

## RESULTS

The anti-inflammatory properties of OSI-7725 and OSI-7727 were evaluated using a model of rat paw edema. Figures 1 and 2 show that these compounds reduced paw edema development. We observed the maximum activity when the administered dose of compounds was 0.1 mg/kg. At this dose OSI-7725 and OSI-7727 reduced edema formation in comparison with negative control by 26.6% and 41.6%, respectively. Other doses were less effective. Both compounds suppressed edema only when administered before carrageenan treatment, since administration of test DHPs after carrageenan injection did not reduce the development of paw edema. This shows that the anti-inflammatory action of OSI-7725 and



**Fig. 1.** Influence of OSI-7725 on carrageenan-induced rat paw edema. The influence of the test compound on edema development was evaluated by measuring weight difference between carrageenan-treated and untreated paws. OSI-7725 was administered 3 h before carrageenan injection. Negative control animals received the same volume of solvent of the test compound, and positive control were given prednisolone at a dose 100 mg/kg. There were  $n=12$  animals in each group. Statistically significant differences between the negative control and test groups (or positive control) were  $*p < 0.05$ ,  $**p < 0.01$  and  $***p < 0.001$ , respectively. Data are presented as mean  $\pm$  SE



**Fig. 2.** Influence of OSI-7727 on carrageenan-induced rat paw edema. The influence of the test compound on edema development was evaluated by measuring weight difference between carrageenan-treated and untreated paws. OSI-7727 was administered 3 h before carrageenan injection. Negative control animals received the same volume of solvent of the test compound and positive control were given prednisolone at a dose 100 mg/kg. There were  $n=12$  animals in each group. Statistically significant differences between the negative control and test groups (or positive control) were  $*p < 0.01$  and  $**p < 0.001$ , respectively. Data are presented as mean  $\pm$  SE

OSI-7727 has a preventative effect. The (+) enantiomeric form of DHP OSI-7727 has shown a more effective inhibition of edema development. This supports the suggestion that pharmacological effect is a feature of only one enantiomer form, thus the effect of a racemate is reduced.

Results of this work showed a considerable effect of the test drugs on rat plasma corticosterone level (Table 1). Thus, OSI-7725 and OSI-7727 caused a prolonged (2–4 h) elevation of all forms (total, transcortin-bound, and free) of corticosterone. Following two hours after injections of DHPs the most significant effect has been observed and did not change during all the period of investigation. It is clear that OSI-7725 and OSI-7727 stimulate corticoste-

rone synthesis, since the pretreatment with metyrapone, an inhibitor of steroid biosynthesis, completely blocked the DHP-induced elevation of corticosterone concentration (Table 2). These findings indicate that in the action of DHPs a steroidal mechanism can be involved. The number of the chemical substances that directly affect biosynthesis of GH is not large, and the property of DHPs to induce synthesis of endogenous hormone (corticosterone) offers new opportunities for the application of these compounds. It is known that the biological activity of GH is manifested after binding with GR. Since we determined that the synthesis of these hormones could be stimulated by DHP, we decided to investigate their influence on the GH-GR complex. For this purpose we used the synthetic hormone [ $^3\text{H}$ ]-DEX. The data showed that both compounds inhibited specific ligand-receptor binding. OSI-7725 was active at concentrations  $10^{-5}$  and  $10^{-4}$  M, whereas OSI-7727 only at  $10^{-4}$  M (Table 3). Their apparent  $\text{IC}_{50}$  values were 3.59 and 5.52  $\mu\text{M}$ , respectively. The precise mechanism of DHPs effect on hormone binding activity remains unclear. It is quite possible that they act allosterically or bind to GR.

## DISCUSSION

Some of DHPs are known to exhibit anti-inflammatory properties [21–23]. However, the effect of enantiomeric forms of DHPs on the inflammation process is still unexplored. We evaluated the anti-inflammatory effect of the newly synthesized racemic form of DHP, OSI-7725, and its (+) enantiomer OSI-7727. The present results showed that DHPs suppressed the development of rat paw edema only when they were administered before carrageenan treatment, since administration of these compounds after carrageenan injection did not reduce paw edema. At the same time the steroidal anti-inflammatory drug prednisolone significantly inhibited edema formation when added either before or after injection of carrageenan. According to our present and previous experimental data, the anti-inflammatory action of DHPs on rat paw edema has a preventative effect but does not

Table 1. Influence of OSI-7725 and OSI-7727 on corticosterone concentration in blood

Compound	Dose (mg/kg)	Time after DHP administration (h)	Corticosterone concentration ( $\mu\text{g}\%$ )		
			Total	Transcortin-bound	Free
Control	-		26.19 $\pm$ 2.92	25.38 $\pm$ 3.02	0.76 $\pm$ 0.12
OSI-7725	5	2.0	91.29 $\pm$ 6.67	76.52 $\pm$ 3.43	9.77 $\pm$ 1.53
		3.0	85.78 $\pm$ 2.81*	75.46 $\pm$ 2.79*	9.32 $\pm$ 0.05
		4.0	89.43 $\pm$ 4.0	79.2 $\pm$ 4.02	9.23 $\pm$ 0.03**
Control	-		25.45 $\pm$ 7.35	23.05 $\pm$ 6.94	2.4 $\pm$ 1.22
OSI-7727	5	2.0	99.76 $\pm$ 8.01	83.12 $\pm$ 7.35	8.64 $\pm$ 1.16*
		3.0	90.63 $\pm$ 7.58	83.67 $\pm$ 6.93	6.02 $\pm$ 1.41
		4.0	87.92 $\pm$ 2.61	79.0 $\pm$ 1.9	6.92 $\pm$ 1.03

The influence of compounds on the corticosterone level was evaluated by measuring transcortin-bound and free corticosterone concentrations. Control animals received the same volume of solvent of compound tested. There were six animals in each group. Statistically significant differences between corticosterone concentrations of the control and test groups were \* $p < 0.05$  and \*\* $p < 0.01$ , respectively. Data are presented as mean  $\pm$  SE.

Table 2. Influence of OSI-7725 and OSI-7727 on the corticosterone concentration in blood after the administration of metyrapone

Compound	Dose (mg/kg)	Time after DHP administration (h)	Total corticosterone concentration ( $\mu\text{g}\%$ )
Control			20.81 $\pm$ 4.68
OSI-7725	5	2	89.75 $\pm$ 4.39*
Metyrapone+	300 + 5	2	15.89 $\pm$ 3.55
OSI-7725			
OSI-7727	5	2	96.24 $\pm$ 8.96*
Metyrapone+	300 + 5	2	15.32 $\pm$ 4.02
OSI-7727			

Metyrapone was administered as a single dose. Control animals received the same volume of solvent of the compound tested. There were six animals in each group. Statistically significant differences between corticosterone concentrations of the control and test groups were \* $p < 0.05$ . Data are presented as mean  $\pm$  SE.

Table 3. Influence of OSI-7725 and OSI-7727 on [ $^3\text{H}$ ]-dexamethasone binding activity to GR *in vitro* (% of control)

Compound	[ $^3\text{H}$ ]-dexamethasone binding activity at tested concentration (M)					
	$10^{-8}$	$10^{-7}$	$10^{-6}$	$10^{-5}$	$10^{-4}$	$10^{-3}$
OSI-7725	105.07 $\pm$ 6.1	103.19 $\pm$ 3.2	82.23 $\pm$ 7.4	36.28 $\pm$ 7.9*	10.79 $\pm$ 0.9*	n.a.
OSI-7727	n.a.	119.53 $\pm$ 8.9	100.78 $\pm$ 7.4	85.51 $\pm$ 4.9	24.98 $\pm$ 2.2*	12.8 $\pm$ 1.3*
Negative contr.	113.8 $\pm$ 4.5	103.2 $\pm$ 8.0	91.0 $\pm$ 19.8	101.6 $\pm$ 13.9	77.2 $\pm$ 2.3	n.a.
Positive contr.	64.8 $\pm$ 12.5	23.9 $\pm$ 8.6	1.3 $\pm$ 0.9	0.6 $\pm$ 0.4	n.a.	n.a.

Piracetam was used as a negative control (non-binding compound). Corticosterone was used as a positive control (binding compound). Statistically significant differences between the positive control and test groups were \* $p < 0.01$ ; n.a. – not analyzed. Data are presented as mean  $\pm$  SE.

display a therapeutic one [11]. It shows that these DHPs do not mimic steroid action. The possibility that these compounds have several distinct mechanisms of action *in vivo* is also suggested by the fact that their anti-inflammatory effect seemed to diminish at higher doses. This could happen if at higher doses these DHPs induce mechanisms that oppose anti-inflammatory activity. The fact that the (+) enantiomeric form of DHP OSI-7727 has shown a more effective inhibition of edema development supports the suggestion that the pharmacological effect

is a feature of only one enantiomer form. However, to declare this without evaluating activity of the second enantiomer would be wrong, because enantiomeric forms may exhibit opposite activities [14], and thus the effect of a racemate could be lower.

It is thought that the anti-inflammatory effect of DHPs calcium channel blockers is a result of calcium channel blockage. Moreover, it has been shown that inflammation induced by carrageenan is effectively suppressed by the calcium channel antagonist nifedipine and is

enhanced by the calcium agonist Bay K8644 [21]. However, the fact that cerebrocrast, a DHP derivative which does not act as a calcium channel antagonist but effectively suppresses carrageenan-induced inflammation [11], allowed speculating that the anti-inflammatory action of these substances is associated with other mechanisms (independent on calcium channel blocking). The ability of OSI-7725 and OSI-7727 to stimulate the synthesis of GH might explain the anti-inflammatory mechanism of DHPs. To evaluate the effects of DHPs on corticosterone production and anti-inflammatory action, different doses of these compounds were tested. 0.1 mg/kg of these compounds effectively suppressed edema development, while the dose that stimulated GH production was 5 mg/kg. The lower doses (0.1–1.0 mg/kg) did not change GH concentration. The fact that 0.1 mg/kg of OSI-7725 and OSI-7727 exhibited a preventative but not a therapeutic anti-inflammatory action shows that the anti-inflammatory action of these compounds is not directly connected to GH production. However, the ability of DHPs to stimulate the synthesis of GH at higher doses is remarkable and could provide a new potential in the application of these substances. The biological activity of GH is manifested after binding with GR. After activation, the GH-GR complex translocates to the nucleus where it binds to GRE activating or suppressing gene transcription [24, 25]. GR, acting as a monomer, binds to other transcription factors and inhibits the transcription of target genes [25, 26]. It has been demonstrated that synthetic steroids influence the specific binding of GHs to their receptors and thus modify their interaction with DNA [27]. The capability of DHPs to influence GH-GR interaction, re-presented in this work, shows a possible further influence of these compounds on gene expression. Moreover, it was discovered that the spirocyclic dihydropyridine derivatives act as selective antagonists of GR and completely antagonize the DEX-mediated induction of enzymes involved in gluconeogenesis and glutamine metabolism [9]. Furthermore, the DHPs (nifedipine, nicardipine, etc.) can activate CYP2B1 and CYP3A1 genes in the rat liver, and this ability is mainly dependent on the features of DHP structure: length of the side chain at the 3rd position of the dihydropyridine ring and the position of the nitro group in the nitrophenyl substituent [28]. Although the precise mechanism of this action remains unclear, it is known that nifedipine and nicardipine are DEX-type inducers of hepatic P450 enzymes. Our data show that DHPs can inhibit DEX binding to GR. Therefore it is quite possibly that activation of CYP genes by these DHPs is GR-mediated. According to results of this study, OSI-7725 and OSI-7727 display a preventative anti-inflammatory action, stimulate the synthesis of GH and inhibit GH binding activity. These data provide an evidence of the involvement of fine mechanisms through which the pharmacological effects of DHPs can be released.

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**1,4-DIHDROPIRIDINO DARINIŲ POVEIKIS ŽIURKĖS  
PĖDOS EDEMAI, GLIUKOKORTIKOIDINIŲ  
HORMONŲ SINTEZEI IR JŲ SAŲEIKA SU  
GLIUKOKORTIKOIDŲ RECEPTORIAIS AKTYVUMUI**

**Santrauka**

Buvo tiriamas 1,4-dihidropiridino darinių OSI-7725 ir OSI-7727 poveikis ūminiam uždegimui, gliukokortikoidinių hormonų (GH) sintezei ir specifinės GH sąveikos su gliukokortikoidų receptoriais (GR) aktyvumui. Kadangi kai kurie 1,4-dihidropiridiniai (DHP) pasižymi priešuždegiminėmis savybėmis, pirmiausia ištyrėme racemato OSI-7725 ir jo (+) enantiomero OSI-7727 poveikį karagenanu indukuotai žiurkės pėdos edemai. Tiriamieji junginiai pasižymėjo prevenciniu priešuždegiminiu po-

veikiu. Aktyviausiai edemos vystymąsi (atitinkamai 26,6% ir 41,6%) slopino 0,1 mg/kg šių DHP dozė. Abu junginiai buvo neefektyvūs suleidus juos po karagenano injekcijos. Tolesniais eksperimentais *in vivo* nustatyta, kad 5 mg/kg šių junginių dozė stimuliuoja GH sintezę žiurkių antinksčiuose. Bendras, su transkortinu susijęs ir laisvas kortikosterono kiekis kraujo plazmoje padidėjo po 2 h suleidus tiriamųjų junginių. Panaudojus steroidinių hormonų biosintezės antinksčiuose inhibitorių metiroponą, stimuliuojantis DHP poveikis visiškai išnyko. *In vitro* atlikti eksperimentai rodo, kad tiriamieji DHP inhibuoja deksametazono sąveiką su GR. OSI-7725 aktyvumas pasireiškė esant  $10^{-5}$  ir  $10^{-4}$  M jo koncentracijoms. Specifinę ligando sąsają su receptoriu jis inhibavo 80%. OSI-7727 aktyvus buvo tik esant  $10^{-4}$  M jo koncentracijai. Šių junginių  $IC_{50}$  reikšmės buvo 3,59 ir 5,52  $\mu$ M atitinkamai. Gauti rezultatai rodo tiriamųjų DHP svarbą reguliuojant gyvybiškai svarbius procesus bei subtilius DHP farmakologinio veikimo mechanizmus.