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1,2,3,4-dithiadiazole derivatives as a novel class of calcium signaling modulators

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ABSTRACT

Aberrant calcium signaling is associated with a diverse range of pathologies, including cardiovascular and neurodegenerative diseases, diabetes, cancer, etc… So, therapeutic strategies based on the correction of pathological calcium signaling are becoming extremely in demand. Thus, the development of novel calcium signaling modulators remains highly actual. Previously we found that 1,2,3,4-dithiadiazole derivative 3-(4-nitrophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole-2-oxide can strongly reduce calcium uptake through store-operated calcium (SOC) channels. Here we tested several structurally related compounds and found that most of them can effectively affect SOC channels and attenuate calcium content in the endoplasmic reticulum, thus, establishing 1,2,3,4-dithiadiazoles as a novel class of SOC channel inhibitors. Comparing different 1,2,3,4-dithiadiazole derivatives we showed that previously published 3-(4-nitrophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole-2-oxide and newly tested 3-(3,5-difluorophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole 2-oxide demonstrated the highest efficacy of SOC entry reduction, supposing the important role of electron-withdrawing substituents to realize the inhibitory activity of 1,2,3,4-dithiadiazoles.

1. Introduction

Calcium homeostasis in cells is very important and difficult machinery, including calcium-binding proteins, different ATP-ases and exchangers, calcium storing in the endoplasmic reticulum (ER) and mitochondria, and a large number of calcium-permeable channels [1–3]. Improper regulation of any part of this machinery may result in aberrant intracellular signaling and the development of pathologies. Alterations in calcium signaling were found in a number of diseases with different etiology [4–8]. Pharmacological correction of altered calcium homeostasis is a promising strategy in the therapy of different pathologies and has already implied in clinical practice [9,10]. Thus, screening for the new modulators of calcium signaling is a highly actual task. Store-operated calcium (SOC) channels are a very important and ubiquitously expressed component of calcium homeostasis machinery. It was initially described solely in non-excitable cells [11], but next was found in neurons [12] and cardiomyocytes [13]. Last decades, many pathologies, including such widely spread as cardiovascular [14,15] and neurodegenerative disorders [16–19] were demonstrated to be associated with violations of SOC channels functioning.

Previously we found that 1,2,3,4-dithiadiazole derivative 3-(4-nitrophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole-2-oxide can strongly reduce calcium uptake through the SOC channels [20]. Here we studied several structurally related compounds to estimate their effects on calcium uptake through SOC channels and determine the key substituents required for SOC entry (SOCE) inhibition.

2. Materials and methods

2.1. Cells

HEK293 (Human Embryonic Kidney 293) cell line for research was provided by the shared research facility “Vertebrate Cell Culture Collection” of the Institute of Cytology, Russian Academy of Sciences

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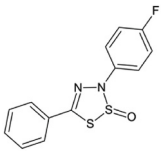
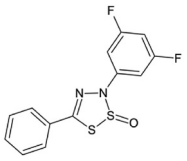
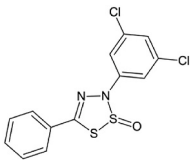
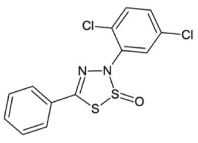
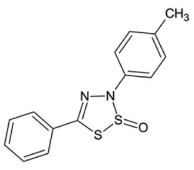
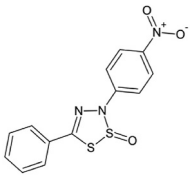
(St. Petersburg, Russia). HEK cells were maintained in Dulbecco's modified Eagle's medium (DMEM) (Biolot, Russia) supplemented with 10 % heat-inactivated fetal bovine serum (Hyclone, USA), 50 units/mL penicillin, and 50 μg/mL streptomycin (Paneco, Russia) under standard cell culture conditions 37 °C, 5 % CO_2.

2.2. Tested compounds

Derivatives of 1,2,3,4-dithiadiazole were obtained from the St. Petersburg State University of Chemistry and Pharmacy (St. Petersburg, Russia). The protocols of synthesis totally corresponded to previously published [21–23]. DMSO was used as a solvent for all 1,2,3,4-dithiadiazoles. Chemical structures and full names of the tested compounds are summarized in Table 1.

Table 1
Tested derivatives of 1,2,3,4-dithiadiazole

N°	Name	Structure	Inhibition index (%)
1	3-(4-fluorophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole 2-oxide		27.0 ± 8.8
2	3-(3,5-difluorophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole 2-oxide		52.7 ± 4.5
3	3-(3,5-dichlorophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole 2-oxide		20.3 ± 8.5
4	3-(2,5-dichlorophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole 2-oxide		42.5 ± 4.7
5	3-(4-methylphenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole 2-oxide		0.2 ± 10.0
6	3-(4-nitrophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole 2-oxide		53.3 ± 4.4

2.3. Fluorescent calcium imaging

Cytosolic calcium dynamics were measured as previously described [20]. Two fluorescent calcium dyes – Fluo-4AM (Thermo Fisher Scientific, USA) and ratiometric Fura-2AM (Thermo Fisher Scientific, USA) were used.

Briefly, for Fluo-4AM measurements the HEK cells in 96-well plates were loaded for 1 h with 4 μM Fluo-4AM dye in the growth media at room temperature and then washed by Hank's Balanced Salt Solution (HBSS): 130 NaCl, 2.5 KCl, 2 $CaCl_2$, 1.2 $MgCl_2$, 10 HEPES and 10 glucose (in mM), pH was adjusted to 7.35 with NaOH. Then cells were pretreated for 30 min with 10 μM tested compounds or 0.1 % DMSO in HBSS. The 96-well plates were read on the Varioskan LUX (Thermo Scientific, USA) illuminated at 495 nm; a fluorescence emission was recorded at 510 nm. After a baseline read, 1 μM of thapsigargin (Sigma, USA) was added to each well. Presented fluorescence signals were normalized on the fluorescence signal before the addition of thapsigargin.

Fura-2AM measurements were performed by loading the HEK cells with 2 μM Fura-2AM for 40 min in HBSS at room temperature, then washed by HBSS for 20 min. Then cells were pretreated for 30 min with 10 μM tested compounds or 0.1 % DMSO in HBSS. Cells were illuminated alternately with 340- and 380-nm excitation light for 100 ms every 2s using a Lambda 10-B filter changer (Sutter Instruments, Novato, CA, USA). The emission signal was detected at 510 nm with a Zyla 4.2 sCMOS camera. The dynamic changes in cytosolic calcium concentration were expressed as the ratio of emission fluorescence intensities at 340 and 380 nm excitation wavelengths (the 340/380 ratio).

To evaluate the ER calcium content, 5 μM ionomycin (Ion) (Sigma, USA) in HBSS (without calcium) was used. HBSS (without calcium): 130 NaCl, 2.5 KCl, 0.2 EGTA, 1.2 MgCl2, 10 HEPES, and 10 Glucose (in mM), pH was adjusted to 7.35 using NaOH. The results of fluorescence studies were proceeded using FiJi/ImageJ software.

2.4. Electrophysiological studies

The patch-clamp technique in the whole-cell configuration was used for ion currents registration. The protocol was taken from previously published studies [20]. Briefly, the ionic currents were measured with an Axopatch 200B amplifier (Axon Instruments) operated under WinWCP_V5.7.6 software. The holding potential was 0 mV. Every 5 s the ramp potential was changed from −100 mV to 100 mV at the rate of 1 V/s. SOC currents were evoked by the application of 1 μM thapsigargin to the external solution and normalized to the membrane capacity (20–40 pF). Traces before the thapsigargin application were used as a template for subtraction.

2.5. Statistics

Statistical analysis was performed using Origin 8.1 (Origin Lab) and Python libraries Scipy and Numpy. To compare the fluorescence intensities the one-way ANOVA ($p < 0.05$) with post-hoc Bonferroni correction was used. The Shapiro-Wilk and Leven tests were used to confirm the normality of the distribution and equal variances respectively. When samples had unequal variances the Welch's *t*-test was used.

3. Results

3.1. 1,2,3,4-Dithiadiazole derivatives reduce thapsigargin-induced calcium response in HEK293 cells

Recently we have reported about the ability of 1,2,3,4-dithiadiazole derivative 3-(4-nitrophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole-2-oxide (compound 6) to affect SOC channels and modulate ER calcium content [20]. Then we suggested that other 1,2,3,4-dithiadiazole derivatives may also inhibit SOCE and aimed to study how the chemical substituents influence on their activity against SOC channels. We tested five

structural analogs of compound 6 named compounds 1–5 (Table 1) for their possibility to affect calcium response in HEK293 cells induced by the application of thapsigargin which blocks the SERCA pump and induces depletion of intracellular calcium stores followed by the activation of SOC channels.

The results of fluorescent calcium measurements showed that pretreatment of HEK293 cells with tested compounds in the concentration of 10 μM for 30 min demonstrated a significant reduction of thapsigargin-induced fluorescent signal for all cases except compound 5 (Fig. 1). We also used DMSO, where all the compounds were dissolved, as a negative control to exclude the possible influence of the solvent and previously studied compound 6 (Table 1) as a positive control. Indexes of inhibition were determined for each compound at 480 s as previously described [20] (Table 1). It should be noted that the inhibition index for compound 6 did not differ significantly from the previously published value, confirming the stability of the compound and validating the correct comparison of the newly tested derivatives with the published one (Fig. 1) [20]. Among the tested derivatives, compounds 2 and 4 demonstrated a high level of inhibition, compounds 1 and 3 had moderate inhibition efficacy and compound 5 did not have an inhibitory effect on thapsigargin-induced calcium response in the concentration of 10 μM (Fig. 1).

To further compare the efficacy of studied compounds we performed experiments demonstrating the dependence of the inhibition index on the concentration of the compound. The results showed that all tested 1,2,3,4-dithiadiazole derivatives can affect intracellular calcium concentration (Fig. 2). At the same time, only compound 2 had IC_{50} equal to 7.4 μM (Fig. 2G) which was similar to IC_{50} equal to 6.2 μM for previously studied compound 6 [20], whereas compound 5 was not able to affect intracellular calcium concentration at the same rate and revealed its activity only in much greater concentrations (Fig. 2J).

3.2. 1,2,3,4-Dithiadiazole derivatives affect ER calcium content

As long as we previously demonstrated that compound 6 can also attenuate ER calcium content [20], we also checked the ability of compounds 1–5 to affect calcium release from ER induced by calcium ionophore ionomycin. The results showed that ionomycin-mediated calcium release was significantly lower in HEK293 cells pretreated with compounds 1–4 for 30 min than in control cells (Fig. 3A–D,F). These data indicated that compounds 1–4 can decrease ER calcium content, whereas compound 5 didn't show significant influence on calcium stores in ER (Fig. 3E and F).

3.3. 1,2,3,4-Dithiadiazole derivatives inhibit activated SOC channels

Next, we performed "acute" experiments using the patch-clamp technique in the whole-cell mode to check whether studied compounds can affect activated SOC channels. We evoked SOCE by application of 1 μM thapsigargin to an extracellular solution and then added 10 μM of tested compounds after currents reached the maximum. The data obtained indicated that compounds 1–4 immediately reduced SOC current (Fig. 4 A–H). At the same time, compound 5 was unable to reduce activated SOC current in the concentration of 10 μM (Fig. 4I and J). Thus, we proved that compounds 1–4 in the concentration of 10 μM can affect activated SOC channels.

4. Discussion

1,2,3,4-dithiadiazoles are a novel and poorly studied class of synthetic molecules, having a good perspective to be used in basic and clinical science. The chemical structure of 1,2,3,4-dithiadiazoles represents two benzene rings linked by heteroatoms-contained ring. Previously we reported the ability of 1,2,3,4-dithiadiazole derivative 3-(4-nitrophenyl)-5-phenyl-3H-1,2,3,4-dithiadiazole-2-oxide (compound 6) to reduce both SOCE and ER calcium content [20]. Here we tested five structural analogs of compound 6 and found that their activity against SOC channels depends on the substituents of the second benzene ring. One can observe a tendency for anti-SOCE activity to be increased with the introduction of electron-withdrawing substituents. Thus, NO_2-containing compound 6 shows a high level of activity (Fig. 1) [20], while the introduction of a weak electron donor – a methyl group – leads to its abolishment for compound 5 (Fig. 1; Fig. 2E,J). The introduction of one or two halogen substituents also leads to the manifestation of activity in the cases of compounds 1–4. But it should be also noted that there is no clear connection with electronic effects (for example, expressed through Hammett constants). On the one hand, one can note the strong (−)-inductive effect of two F atoms, the introduction of which clearly promotes the high activity of compound 2 similar to NO_2-containing compound 6 (Fig. 1; Fig. 2B,G). At the same time, the replacement of two

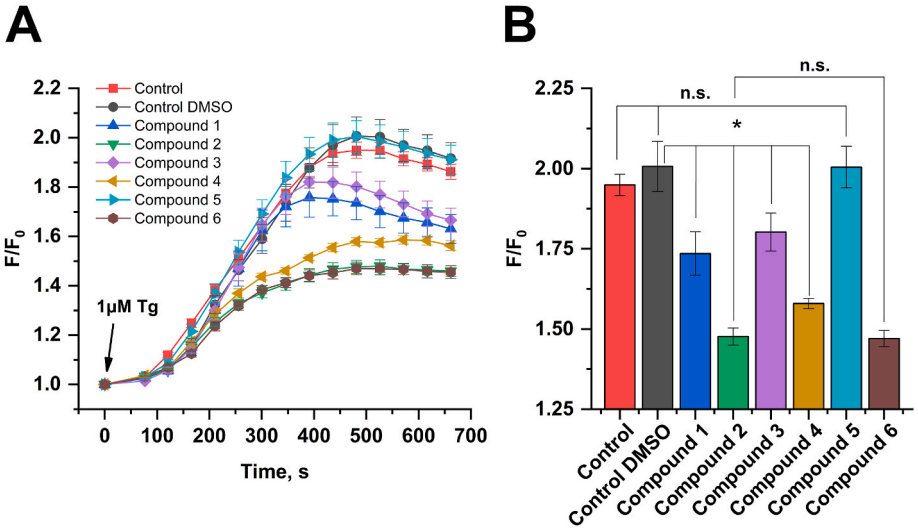


Fig. 1. Primary screening of different 1,2,3,4-dithiadiazole derivatives on their ability to modulate thapsigargin-induced calcium response
(A) Normalized fluorescence of Fluo-4 in HEK293 cells pretreated for 30 min with 10 μM of the tested compounds during the thapsigargin-induced calcium response. Compound 6 was used as a positive control. The curves are plotted as the mean ± SEM. (B) Average fluorescence amplitudes at the steady-state level of the thapsigargin-induced calcium response (480 s). The amplitudes are plotted as the mean ± SEM. Asterisks denote statistically significant differences in amplitudes ($p < 0.05$), n.s. denotes the absence of statistically significant differences ($p > 0.05$).

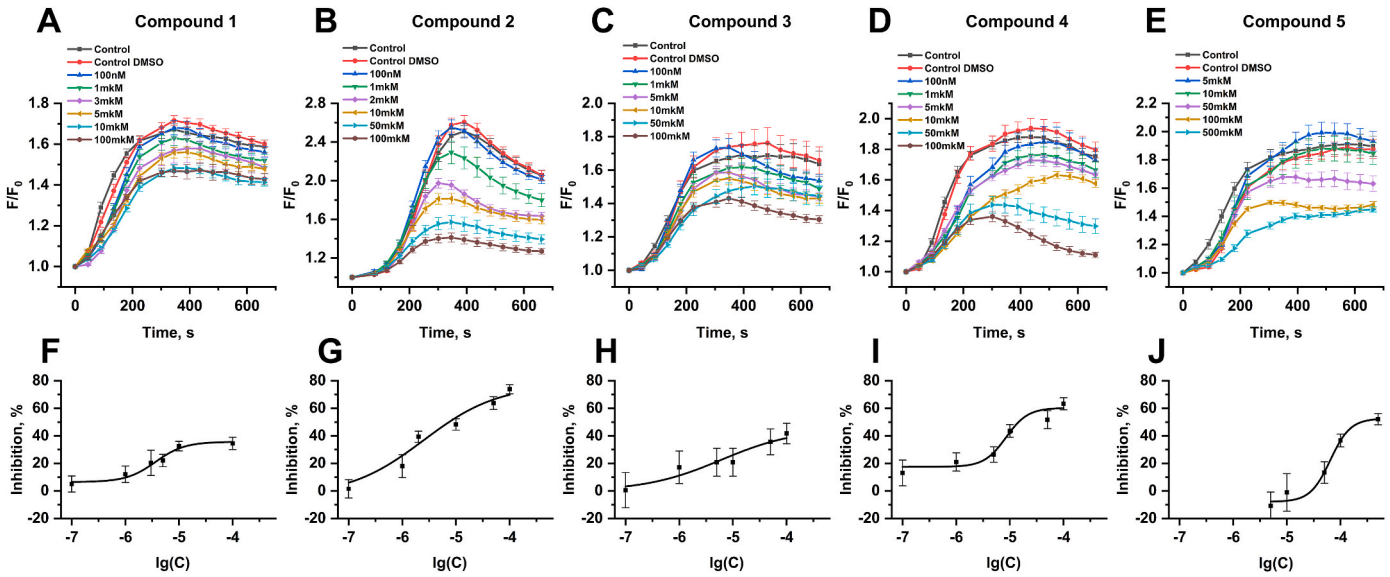


Fig. 2. Dose-dependence of inhibitory effect of 1,2,3,4-dithiadiazole derivatives
(A-E) Normalized fluorescence of Fluo-4 in HEK293 cells pretreated for 30 min with different concentrations of the tested compounds during the thapsigargin-induced calcium response. The curves are plotted as the mean ± SEM. (F–J) Dose-dependence curves for compounds 1–5 respectively. Each value represents the mean ± SEM.

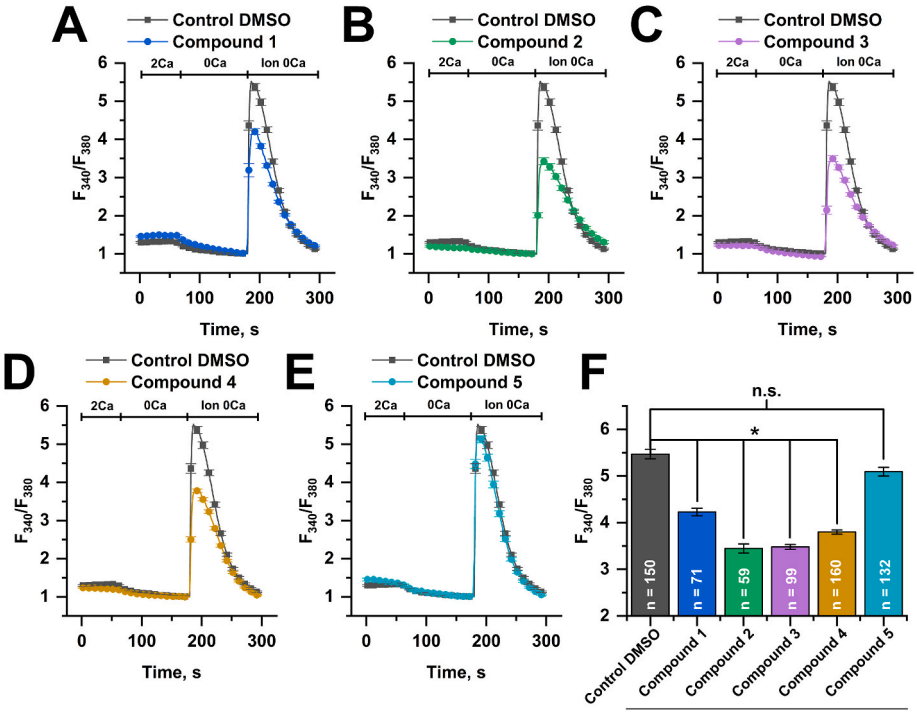


Fig. 3. The effects of 1,2,3,4-dithiadiazole derivatives on calcium content in the ER
(A-E) Ionomycin-induced calcium release in HEK293 cells pretreated for 30 min with either 10 μM of compounds 1–5 (color lines) respectively or DMSO (black line). Above the curves, the solutions that were used are indicated. The curves are plotted as the mean ± SEM. The panel (F) displays the number of cells. (F) Average fluorescence amplitudes at the steady-state level of the ionomycin-induced response (190 s) in HEK293 cells pretreated for 30 min with DMSO or 10 μM of compounds 1–5. The amplitudes are plotted as the mean ± SEM. Asterisks denote statistically significant differences in amplitudes ($p < 0.05$), n.s. denotes the absence of statistically significant differences ($p > 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

F with weaker sigma acceptors, two Cl atoms (compound 3) (Fig. 1; Fig. 2C,H), or the deletion of one F atom (compound 1) (Fig. 1; Fig. 2A,F) significantly decreases the efficacy. On the other hand, the difference in the activity of 3,5-dichloro- (compound 3) (Fig. 1; Fig. 2C,H) and 2, 5-dichloro (compound 4) (Fig. 1; Fig. 2D,I) derivatives indicates the key role of some other factors influencing the biological activity, for example, donor-acceptor interactions of substituents with the active center of the protein target. In this context, one can notice the similarity in the localization and electronic properties of both the oxygen atoms of the NO_2-group and two F atoms in positions 3 and 5 of compounds 6 and

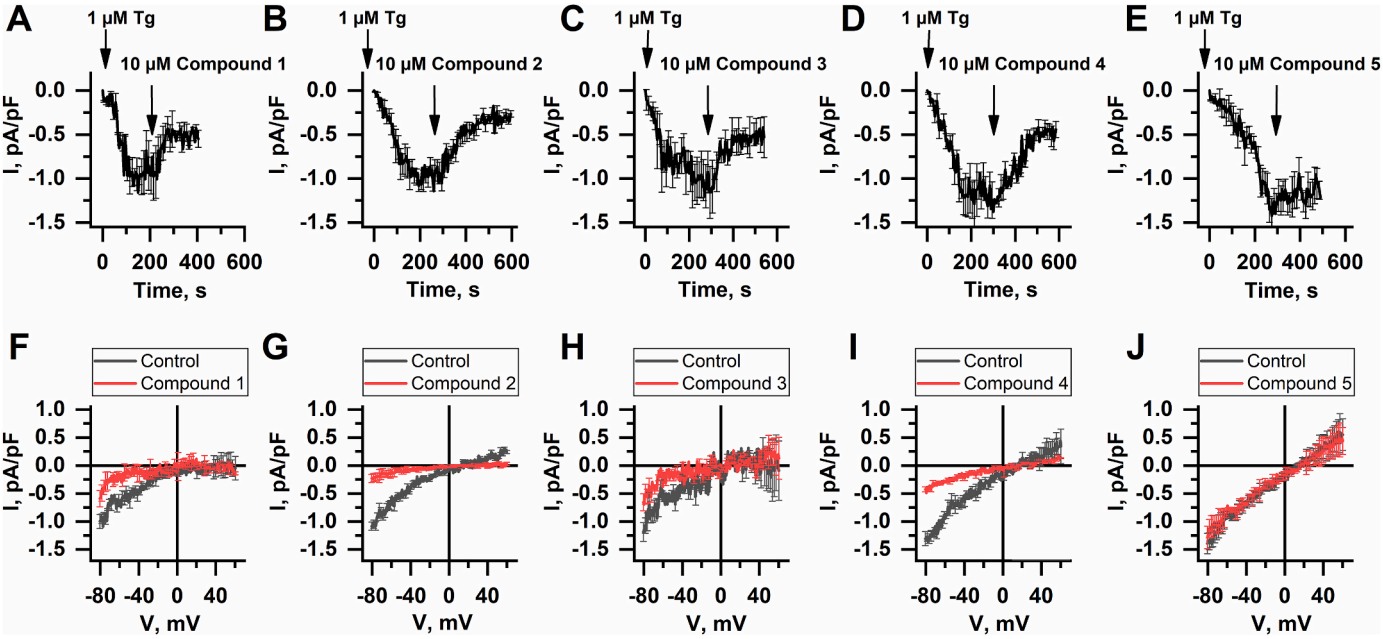


Fig. 4. 1,2,3,4-dithiadiazole derivatives inhibits activated SOC channels
(A–E) Normalized SOC current in HEK293 cells evoked by application of 1 μM thapsigargin and plotted as a function of time at the potential of −80 mV. Each trace shows mean ± SEM. (F–J) Average I–V curves of normalized currents evoked by passive depletion of calcium stores with 1 μM thapsigargin in HEK293 when the currents reached a maximum before adding tested compounds (black line) and at steady-state level after adding 10 μM of tested compound (red line). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2 respectively (Table 1). Thus, to establish the factors determining the activity of the tested compounds, further docking studies with their potential targets responsible for calcium signaling are necessary.

One more interesting observation is that the ability of 1,2,3,4-dithiadiazoles to affect SOC channels is connected with the ability to reduce ER calcium content. Acute experiments that we performed persuasively demonstrated that compounds 1–4 can affect activated SOC channels (Fig. 4), suggesting that the effect on ER calcium content should be separate from the SOCE inhibition activity. Nevertheless, all compounds affecting SOC channels could also reduce ER calcium content, whereas compound 5 did not affect both SOCE and ionomycin-induced calcium release from ER in the concentration of 10 μM (Figs. 3 and 4). It is obvious, that long-term attenuation of the activity of SOC channels may result in the reduction of ER calcium content since calcium uptake through SOC channels is required for intracellular calcium stores refilling. But the significant effect of compounds 1–4 on ionomycin-induced calcium release even after 30 min of preincubation with the cells allows us to suggest that 1,2,3,4-dithiadiazols may affect ER calcium content independently from SOC channels' inhibitory activity since other known SOC channel blockers (BTP2 and CM4620) do not affect ER calcium content after 30 min preincubation (Supplementary Fig. S1). One of the possible explanations is the modulation of physical properties of the membranes by 1,2,3,4-dithiadiazoles which may affect the leakage of calcium ions from ER to cytosol and also may influence the activity of calcium-permeable channels in both ER and plasma membranes. In support of this hypothesis, it was reported that some other members of the 1,2,3,4-dithiadiazoles family affect lipid packing and curvature stress of lipid bilayers [24]. At the same time, the modulation of ER calcium content by tested compounds may be connected with their direct targeting of proteins responsible for calcium release, such as receptors of inositol trisphosphate. In future, we plan to perform molecular docking experiments to find the candidates for 1,2,3,4-dithiadiazoles molecular targets.

In general, in this paper, we established 1,2,3,4-dithiadiazoles as novel class of SOC channel inhibitors and negative modulators of ER calcium content. We studied five compounds and found at least 4 novel SOCE modulators with different indexes of inhibition. Also, we demonstrated the important role of the electron-withdrawing substituents for the efficacy of the SOCE reduction by 1,2,3,4-dithiadiazoles. The future studies will be devoted to finding the direct molecular target of 1,2,3,4-dithiadiazoles and enhancing of their SOC channel inhibitory activity, for example, by introducing the second NO_2 group in different positions.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrc.2023.149333.

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