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DESIGN OF NEW OPENERS OF ATP-SENSITIVE POTASSIUM CHANNELS OF THE CELL MEMBRANES

Two innovative libraries (413 cyclosulfamides and 709 orthopyridine sulfamides) of potential new openers of ATP-sensitive potassium channels of cell membranes have been created. It is shown experimentally that, at least, ten new original compounds have properties of pharmacological openers of the channels. Seven compounds (Z851154982, Z56762024, Z1269122570, Z31153162, Z45679561, Z756371174, and Z649723638) open channels of both the sarcoplasmic and the mitochondrial membranes. Z734043408 compound is a strong activator of aforementioned channels of the sarcolemmal membrane only. Z31197374 and Z666664306 compounds have showed the affinity only to the K_{ATP} channels of the mitochondrial type. The results of the research can be used by pharmaceutical companies and research institutes.

Keywords: K_{ATP}-channels, new openers, vasodilation effects, mitochondria, and glibenclamide.

Despite a significant progress in the prevention and treatment of cardiovascular disease (CVD), for many years, it remains the leading cause of death (67% or 968 per 100 thousand people (as of 2013)) and disability in the majority of the world countries [1, 2]. In particular, as of March 2015, in Ukraine, in the past 30 years, the incidence of cardiovascular disease among the population increased by 3.5 times, and mortality caused by it grew by 46% [1]. However, in the structure of CVD, the lead has been taken by hypertension and coronary heart disease, as their share reaches 41 and 28%, respectively. Unfortunately, 66% of patients has the latter combined with the former, which leads to extremely negative consequences [1, 2].

One of the new advanced approaches to the prevention and treatment of cardiovascular disease is the design of new drugs based on the activation of ATP-sensitive potassium channels (K_{ATP}). These membrane channels are a powerful endogenous protective mechanism in the case of energy shortage (hypoxia and ischemic tissue [3—5]), which participate in the regulation of vascular tone [6, 7]. It has been established that the K_{ATP}-channels can be opened by pharmacological activators, with their exogenous opening triggering the realization of powerful cardio-protective mechanisms [8—10]. In particular, they possess anti-ischemic, antiarrhythmic, and antioxidant properties; they stimulate membrane stabilization and prevent a reperfusion increase in the resistance of coronary and peripheral vessels [11—14], maintain mitochondrial function in the case of myocardial ischemia-reperfusion and prevent the formation of mitochondrial pores [15, 16], as well as inhibit apoptosis and necrosis in the case of anoxia-reoxygenation of neonatal cardiomyocytes [17, 18]. The pharmacological activators of the

above channels, which reduce myocardial infarction by 40% in experiments with myocardial ischemia-reperfusion have been studied in [19, 20]. Their use for the clinic treatment of coronary heart disease and cardiac angina as antihypertensive drugs has been discussed in [21—24]. However, in the clinic treatment, the known activators of K_{ATP}-channels can lead to complications, including the arrhythmia and inhibition of insulin production [25], which limits their use for the therapeutic purposes. All these factors stimulate the design of new, more specific activators of K_{ATP}-channels. Joint efforts of the Bogomoletz Institute of Physiology of the NAS of Ukraine (Full member of the NAS of Ukraine O. Moibenko) and the Institute for Organic Chemistry of the NAS of Ukraine (prof. L. Yagupolski) have resulted in the creation of new fluorine-containing activators of the above channels [26—29], one of which has been successfully tested in the course of preclinical and toxicological surveys [13, 30]. Currently, the works towards this direction are going on in cooperation with *Ukrorgsintez* LLC (Kyiv). The works are aimed at *in silico* design, the development of advanced Ukrainian-made openers of K_{ATP}-channels, and the creation of competitive innovative library of small molecules against cardiac and cerebral ischemic disease whose action is based on the activation of the above mentioned ionic channels of cell membranes.

MATERIALS AND METHODS

The method statement for the design of new cell membrane K_{ATP} channel activators is described in detail in the patent of Ukraine for utility model [31]. The method foresees the use of a spatial pharmacophoric model identifying the important sites of ligand-receptor interaction and searching the structures of organic compounds in the database, which match this pharmacophoric model, i.e. virtual screening of the database of chemical molecules taking into account the specific features of the selected targets based on *in silico* design. The *Enamine Ltd* (manufacturer) collection [32] consisting of about 1.8 million items was used as primary source of low-molecular compounds. The compounds containing reactive, toxic, metabolically instable and other undesired fragments were excluded.

The property of newly designed compounds to open the K_{ATP}-channels of sarcolemmal membranes was determined using strain-gauge measurements of vasodilating effects and specific inhibitor of the above channels, glibenclamide. The experiments were carried out on isolated rat aortic rings perfused at 37 °C by normal Krebs solution. The animals weighed 0.18—0.2 kg. The isolated vascular rings had a diameter of 2 mm and a width of 1.5 mm. All tests were performed in isometric mode at preset intensity at which they generated maximum power in response to noradrenaline infusion (10 μmol/l).

The chamber was thermostated with an automatic thermostat enabling to maintain temperature of the solution in the chamber at 37 °C, with an accuracy of ±0.5 °C. The working solution was saturated with oxygen using carbogen (a gas mixture of 95% O_2 and 5% CO_2). Before measuring the samples fixed in the experimental chamber were kept for 60 min in normal Krebs solution of the following composition (in mmol/l): NaCl — 120.4; KCl — 5.9; $NaHCO_3$ — 15.5; NaH_2PO_4 — 1.2; $MgCl_2$ — 1.2; $CaCl_2$ — 2.5; and glucose — 11.5. The vasodilation effects of new compounds were studied in doses of 10 and 100 mmol/l at the initial increase in vascular tone by noradrenaline (1 μmol/l). To determine the effects of participation of K_{ATP}-channels in these effects glibenclamide (10 μmol/l), a specific inhibitor was used. It was input into the perfusing solution 5 min before the introduction of new compounds.

The property of newly designed compounds to open the K_{ATP}-channels of inner mitochondrial membrane was studied using suspension of isolated mitochondria of rat heart using glibenclamide as a specific inhibitor of the above channels. The mitochondria were extracted by differential centrifugation [33]. The protein content in the organelle suspension was determined by the Lowry method. The opening of mitochondrial K_{ATP}-channels was studied by spectrophotomet-

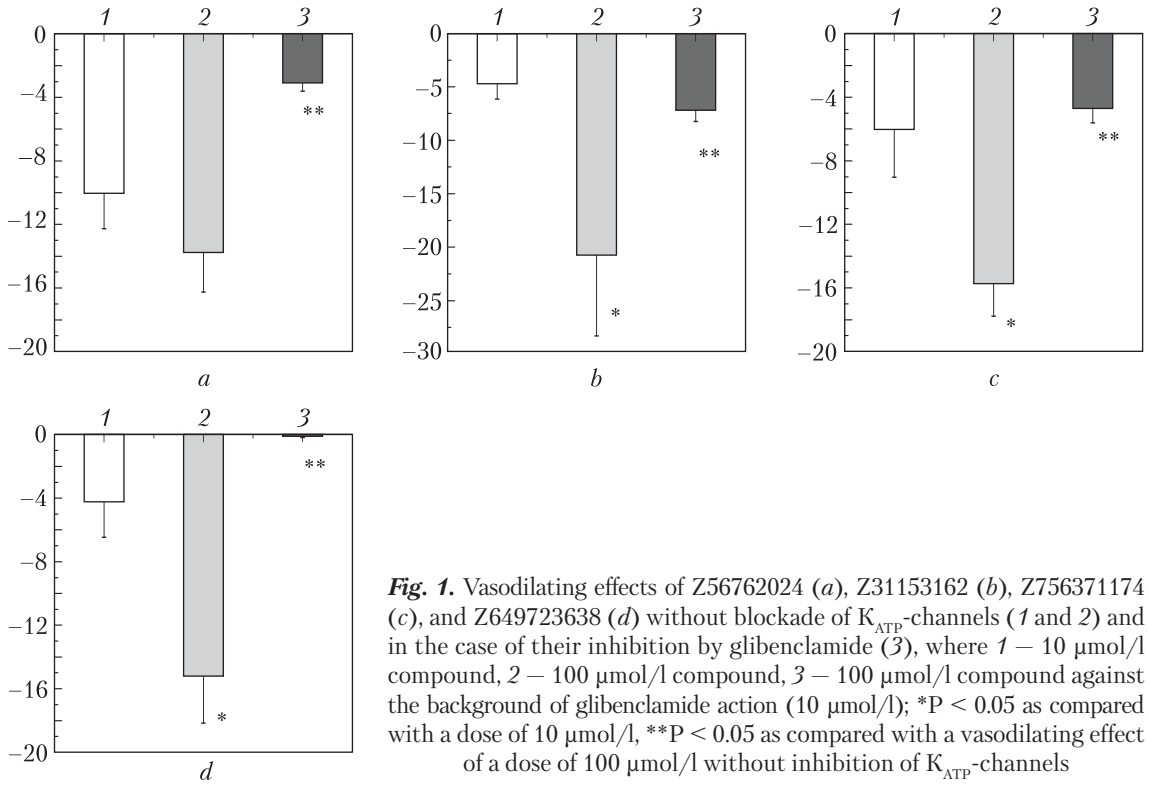

Fig. 1. Vasodilating effects of Z56762024 (*a*), Z31153162 (*b*), Z756371174 (*c*), and Z649723638 (*d*) without blockade of K_{ATP}-channels (*1* and *2*) and in the case of their inhibition by glibenclamide (*3*), where *1* — 10 μmol/l compound, *2* — 100 μmol/l compound, *3* — 100 μmol/l compound against the background of glibenclamide action (10 μmol/l); *P < 0.05 as compared with a dose of 10 μmol/l, **P < 0.05 as compared with a vasodilating effect of a dose of 100 μmol/l without inhibition of K_{ATP}-channels

ric recording of the swelling of mitochondria placed in incubation medium of the following isotonic composition (mmol/l): KCl — 120, tris — HCl — 25, KH_2PO_4 — 3; pH 7.4 (final volume is 3 ml) through measuring the optical density of the mitochondrial suspension at λ = 520 nm, during 15 min. New Ukrainian openers of the above mentioned channels were added to the incubation medium after introduction of mitochondria at a concentration of 100 μmol/l. Glibenclamide (10 μmol/l) was added to the incubation medium 5 min before the introduction of activators.

The reagents for perfusive solutions, noradrenaline and glibenclamide were manufactured by *Sigma-Aldrich* (USA). The new compounds, candidate openers of potassium channels, were manufactured by *Ukrorgsintez* LLC (Kyiv).

The results have been processed by the variation statistics method using *Origin* 7.0 software. The data validity is assessed by the Student t-test. P < 0.05 are deemed statistically valid.

RESULTS OF RESEARCH AND THEIR DISCUSSION

The computer modelling of spatial structure of K_{ATP}-channels and the virtual screening of the chemical molecule database (about 1.8 million compounds [32]) taking into consideration the specific features of selected targets (*in silico* design) have enabled developing two innovative libraries (413 compounds based on cyclosulfamidine core and 709 compounds based on orthopyrimidine sulfamidine core) of new prototypes of anti-ischemic chemical compounds having no world counterparts. This gives reasons to predict a high competitive ability of the innovative product on the global market.

The selective testing of designed compounds *in vitro* has showed that in terms of pharmacological action they can be openers of K_{ATP}-channels of sarcolemmal and mitochondrial cell membranes.

In terms of efficacy of the action on the vascular stripes, the tested compounds could be conventionally divided into *two groups*. Five com-

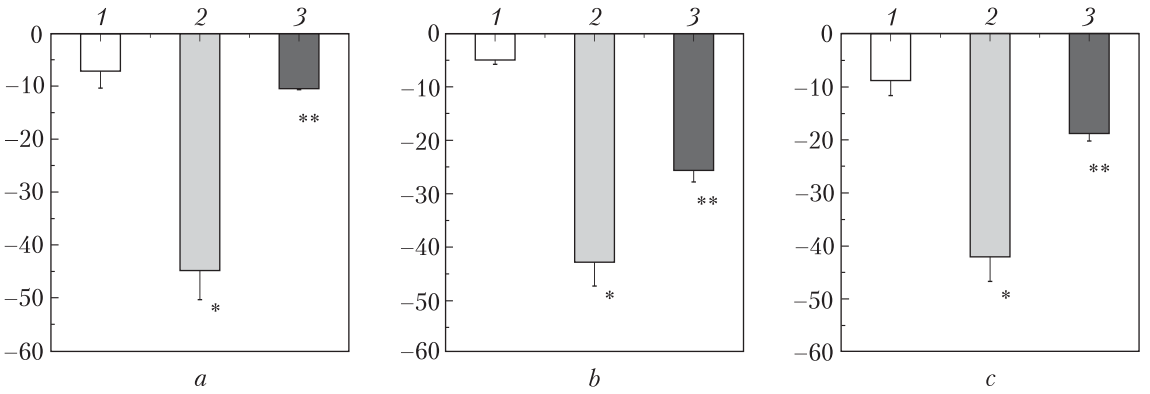

Fig. 2. Vasodilating effects of Z734043408 (*a*), Z1269122570 (*b*), and Z45679561(*c*) without blockade of K_{ATP}-channels (*1* and *2*) and in the case of their inhibition by glibenclamide (*3*), where *1* — 10 μmol/l compound, *2* — 100 μmol/l compound, *3* — 100 μmol/l compound against the background of glibenclamide action (10 μmol/l); *P < 0.05 as compared with a dose of 10 μmol/l, **P < 0.05 as compared with a vasodilating effect of a dose of 100 μmol/l without inhibition of KATP-channels

pounds (Z851154982, Z56762024, Z31153162, Z756371174, and Z649723638) have showed a moderate vasodilation activity — relaxation of rat aorta ring preparations by up to 21% at their concentration in the perfusive chamber 100 μmol/l. Z734043408, Z1269122570, and Z45679561 have showed a quite strong vasodilation activity in similar experiments (about 40% and more).

The experiments have been showed that the vasodilation effects of Z56762024 for doses 10 and 100 μmol/l are 10.04 ± 2.22 (n = 4) and 13.76 ± 2.50% (n = 4), respectively (Fig. 1, *a*). One of the tests for checking whether the compound belongs to the openers of K_{ATP}-channels is inhibition of their vasodilation effects by specific inhibitor of the mentioned channels, glibenclamide [34]. In our experiments, it prevented these effects for 77.54% (n = 3, $P < 0.05$) that can testify to Z56762024 being an opener of the mentioned channels. For similar doses of Z31153162, the vasodilation effects were 4.71 ± 1.45 (n = 4, $P < 0.05$) and 20.74 ± 7.60% (n = 4, $P < 0.05$). Inhibition of K_{ATP}-channels hinders them by 65.38% (n = 3, $P < 0.05$). This means that the mechanism of relaxation of vascular preparations is opening of the above said channels (Fig. 1, *b*).

Similar effects have been reported for Z756371174 (relaxation by 6.06 ± 3.04 (n = 4, $P < 0.05$) and 15.75% ± 1.98% (n = 4, $P < 0.05$), respectively). Under the action of glibenclamide, its vasodilation effect (dose of 100 μmol/l) was 4.75 ± 0.84 (n = 3, $P < 0.05$), i.e. it's action is inhibited by 69.84% (n = 3, $P < 0.05$), (Fig. 1, *c*). Hence, Z756371174 can be deemed an opener of these channels.

Similar results are obtained for Z649723638: the vasodilation dose-dependent effects of relaxation of aorta preparations by 4.25 ± 2.16 (n = 4, $P < 0.05$) and 15.20 ± 2.96% (n = 4, $P < 0.05$) for doses of 10 and 100 μmol/l, respectively, and almost complete inhibition of these effects by the inhibitor of K_{ATP}-channels (Fig. 1, *d*).

The vasodilation effects of Z851154982 for similar doses are 0.55 ± 0.11 (n = 4) and 9.14 ± 2.43% (n = 4), respectively (Table 1).

Glibenclamide inhibits these effects by 86.6% (n = 3, $P < 0.05$), which means that these effects are associated with opening of the mentioned channels. However, a quite insignificant relaxation of vascular stripes shows their low affinity to K_{ATP}-channels of vascular smooth muscle cells. The Z851154982 compound seems to can have other cardio-protective properties, in addition to reduction of muscle tone, which are inherent for pharmacological openers of these channels, in particular, the membrane stabilization effect, inhibition of free

radical processes, activity of phospholipase A_2 and formation of pathogenic (under ischemia conditions) eicosanoids, powewrful influence on nitric. The K_{ATP}-channel openers are known to cause cardio-protective effects at doses that do not change the hemodynamics parameters [11, 13, 19, 35].

Thus, five designed compounds, namely Z851154982, Z56762024, Z31153162, Z756371174, and Z649723638, with moderate vasodilation effects that are inhibited by K_{ATP}-channels inhibitor glibenclamide by 86.6, 77.5, 65.4, 69.8 and 99.9%, respectively, can be deemed pharmacological openers of the mentioned channels (see Table 1).

The study of compounds with strong vasodilating effect has showed that introduction of Z734043408 in perfusive solution at doses 10 and 100 μmol/l caused a relaxation of ring aorta stripes by 7.17 ± 3.27 (n = 4, $P < 0.05$) and 44.91 ± 5.53% (n = 4, $P < 0.05$), respectively (Fig. 2, *a*). In the case of K_{ATP}-channel inhibition, vasodilating effect of compound is 10.57 ± 0.08% (n = 4, $P < 0.05$), i.e. the action of Z734043408 is inhibited by 76.46% (n = 3, $P < 0.05$). Similar results have been reported for Z1269122570 and Z45679561. Z1269122570 in similar doses causes a relaxation of vascular preparations by 5.19 ± 0.69

Table 1

New Compounds Showing Properties of Pharmacological Openers of K_{ATP}-Channels of Sarcolemmal Membranes

No.	Code of compound	Formula	Molecular weight	Vasodilation effect at a dose 100 μmol/l (%)	Inhibition of vasodilation effects, glibenclamide (%)
1	Z851154982	$C_{19}H_{26}N_2O_3$	330.42	9.14	86.60
2	Z56762024	$C_7H_7ClN_2O_2S$	218.66	13.76	77.54
3	Z31153162	$C_{13}H_{13}F_3N_2O_2S$	318.31	20.74	65.38
4	Z756371174	$C_7H_6N_2O_2S$	182.19	15.75	69.84
5	Z649723638	$C_{17}H_{20}F_4N_2O_3$	376.34	15.20	99.90
6	Z734043408	$C_8H_7BrN_2O_2S$	275.12	44.91	76.46
7	Z1269122570	$C_8H_7ClN_2O_2S$	230.67	43.35	39.86
8	Z45679561	$C_{12}H_{10}C_{l2}N_2O_2S$	317.19	42.02	55.38

Table 2

New Compounds Featuring the Properties of Pharmacological Openers of K_{ATP}-Channels of Inner Mitochondrial Membrane

No.	Code of compound	Formula of compound	Molecular weight	Change in matrix volume (%) with respect to native mitochondria	Inhibition of effect by glibenclamide
1	Z31153162	$C_{13}H_{13}F_3N_2O_2S$	318.31	45.00	Full
2	Z45679561	$C_{12}H_{10}Cl_2N_2O_2S$	317.19	58.33	»
3	Z756371174	$C_7H_6N_2O_2S$	182.19	48.39	Partial
4	Z649723638	$C_{17}H_{20}F_4N_2O_3$	376.34	100.00	»
5	Z1269122570	$C_8H_7ClN_2O_2S$	230.67	45.16	Full
6	Z56762024	$C_7H_7ClN_2O_2S$	218.66	42.59	Partial
7	Z31197374	$C_{11}H_{12}N_2O_2S$	236.29	35.19	»
8	Z851154982	$C_{19}H_{26}N_2O_3$	330.42	82.26	Full
9	Z666664306	$C_{11}H_{10}F_2N_2O_3$	256.20	18.33	Partial

($n = 4, P < 0.05$) and 43.35 ± 4.47% ($n = 4, P < 0.05$), respectively (Fig. 2, *b*). In the case of inhibition of K_{ATP}-channels, the vasodilating effect of the compound is 26.07% ± 2.09% ($n = 4$, $P < 0.05$), i.e. glibenclamide inhibits its action by 39.86% ($n = 3$, $P < 0.05$). Z45679561 in similar doses causes a relaxation of aorta preparations by 8.88 ± 2.66 ($n = 4$, $P < 0.05$) and 42.02 ± 4.54 % ($n = 4$, $P < 0.05$), respectively (Fig. 2, *c*). In the case of glibenclamide action, vasodilating effect of this compound decreases by 55.38% ($n = 3$, $P < 0.05$). Hence, the inhibition of vasodilating effects of Z734043408, Z1269122570, and Z45679561 by 76.5, 39.9, and 55.4%, respectively, in the case of inhibition of K_{ATP}-channels means that, at least, one of the mechanisms of action of these new compounds is opening of the above said channels.

Hence, the eight new original compounds (see Table 1), namely, Z851154982, Z56762024, Z31153162, Z756371174, Z649723638, Z734043408, Z1269122570, and Z45679561 have a specific activity with respect to the K_{ATP}-channels of sarcolemmal cell membranes and can be deemed pharmacological openers of these channels. At the same time, the three last compounds have a strong vasodilating effect, i.e. they cause a relaxation of aorta ring stripes by 44.9, 43.4, and 42.0%, respectively, that means their high affinity to SUR subunits of above mentioned membrane channel.

Proceeding from experiments with suspension of isolated mitochondria of rat heart the introduction of Z31153162 into the incubation medium has been established to cause an increase in the matrix volume of mitochondria by 45% as compared with the control (100% is free swelling of native mitochondria). The preliminary introduction of glibenclamide into the incubation medium completely prevents this effect (Table 2). This can be interpreted as the mitochondria swelling due to opening of K_{ATP}-channels of inner mitochondrial membrane, with Z31153162 being an opener of these channels.

Similar results have been obtained for other designed original compounds (see Table 2). In particular, the introduction of Z45679561 into the incubation medium causes a swelling of mitochondria by 58.3% as compared with the control. The preliminary introduction of glibenclamide fully prevents this effect. Z756371174 and Z649723638 increases a matrix volume of mitochondria by 48.4% and twice, respectively, as compared with the control. Glibenclamide partially (~ 70%) prevents this increase. Z56762024, Z31197374, and Z666664306 possess similar properties, as their introduction causes a swelling of mitochondria matrix by 42.6, 35.2, and 18.3% as compared with the control. Also, glibenclamide prevents partially these effects. At the same time, the inhibitor of K_{ATP}-channels completely prevents swelling of mitochondria by 45.2 and 82.3% under the action of Z1269122570 and Z851154982, respectively (see Table 2).

Hence, the nine new original compounds Z666664306, Z851154982, Z56762024, Z31153162, Z756371174, Z649723638, Z1269122570, Z45679561, and Z31197374 demonstrate a specific activity with respect to K_{ATP}-channels of inner mitochondrial membrane. Therefore, the above mentioned original compounds shall be deemed pharmacological openers of these membrane channels.

CONCLUSIONS

The computer modelling of spatial structure of K_{ATP}-channels and the virtual screening of the chemical molecule database taking into consideration the specific features of selected targets (in silico design) have enabled developing two innovative libraries (413 compounds based on cyclosulfamidine core and 709 compounds based on orthopyrimidine sulfamidine core) of candidate openers of the above mentioned ionic channels.

The experiments have showed that the eight original compounds, namely Z851154982, Z56762024, Z31153162, Z756371174, Z649723638, Z734043408, Z1269122570, and Z45679561, have properties of pharmacological openers of K_{ATP}-channels of sarcolemmal cell membrane. The three last compounds are notable for a significant vasodilating action, as they cause a relaxation of aorta ring stripes by 44.9, 43.4, and 42.0%, respectively.

The nine original compounds Z666664306, Z851154982, Z56762024, Z31153162, Z756371174, Z649723638, Z1269122570, Z45679561, and Z31197374 show a specific activity with respect to K_{ATP}-channels of inner mitochondria membrane.

Ten new pharmacological openers of K_{ATP}-channels have been designed. Seven compounds, namely, Z851154982, Z56762024, Z1269122570, Z31153162, Z45679561, Z756371174, and Z649723638, display the properties of openers of both sarcoplasmatic and mitochondrial membranes. At the same time, Z734043408 is a strong opener of the above mentioned channels of the sarcolemmal membrane only. Z31197374 and Z666664306 have affinity to the K_{ATP}-channels of mitochondrial type only.

The research results may be used by the Ukrainian and foreign pharmaceutical corporations for designing innovative drugs and by the R&D institutes for research purposes.

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РОЗРОБЛЕННЯ НОВИХ АКТИВАТОРІВ АТФ-ЧУТЛИВИХ КАЛІЄВИХ КАНАЛІВ КЛІТИННИХ МЕМБРАН

Розроблено дві інноваційні бібліотеки (413 сполук на циклосульфамідиновому ядрі та 709 сполук на ортопіримідинсульфамідиновому ядрі) нових потенційних відкривачів АТФ-чутливих калієвих каналів клітинних мембран. Експериментально показано, що принаймі десять нових оригінальних сполук проявляють властивості фармакологічних активаторів цих каналів. Сім сполук відкривають канали як саркоплазматичної, так і мітохондріальної мембран, а саме Z851154982, Z56762024, Z1269122570, Z31153162, Z45679561, Z756371174 та Z649723638. Водночас сполука Z734043408 є потужним активатором вищезгаданих каналів лише сарколемальної мембрани. Сполуки Z31197374 та Z666664306 проявляють спорідненість лише до $К_{АТФ}$-каналів мітохондріального типу. Результати роботи можуть бути використані фармацевтичними компаніями та науково-дослідними інститутами.

Ключові слова: $К_{АТФ}$-канали, нові активатори, вазодилататорні ефекти, мітохондрії, глібенкламід.

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РАЗРАБОТКА НОВЫХ АКТИВАТОРОВ АТФ-ЧУВСТВИТЕЛЬНЫХ КАЛИЕВЫХ КАНАЛОВ КЛЕТОЧНЫХ МЕМБРАН

Разработаны две инновационные библиотеки (413 соединений на циклосульфамидиновом ядре и 709 соединений на ортопиримидинсульфамидиновом ядре) новых потенциальных активаторов АТФ-чувствительных калиевых каналов клеточных мембран. Экспериментально показано, что по крайней мере десять новых оригинальных соединений проявляют свойства фармакологических активаторов этих каналов. Семь соединений открывают каналы как саркоплазматической, так и митохондриальной мембран. А именно: Z851154982, Z56762024, Z1269122570, Z31153162, Z45679561, Z756371174 и Z649723638. В то же время соединение Z734043408 является мощным активатором вышеупомянутых каналов только сарколемальной мембраны. Соединения Z31197374 и Z666664306 проявляют сродство только к $К_{АТФ}$-каналам митохондриального типа. Результаты работы могут быть использованы фармацевтическими компаниями и научно-исследовательскими институтами.

Ключевые слова: $К_{АТФ}$-каналы, новые активаторы, вазодилататорные эффекты, митохондрии, глибенкламид.

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