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Research Article

Chemoproteomic analysis of the promising candidate molecule of the indole derivative with lab code SV-1010 and other non-steroidal anti-inflammatory drugs

Pavel A. Galenko-Yaroshevsky[1], Ivan Yu. Torshin[2], Andrei N. Gromov[2], Ivan A. Reyer[2], Olga A. Gromova[2], Tereza R. Glechyan[1], Konstantin F. Suzdalev[3], Andrey V. Zadorozhniy[4], Anait V. Zelenskaya[1]

1 Kuban State Medical University, 4 Mitrofan Sedin St., Krasnodar 350063 Russia
2 Federal Research Center "Informatics and Management" of the Russian Academy of Sciences, 42 Vavilov St., Moscow 119333 Russia
3 Southern Federal University, 7 Zorge St., Rostov-on-Don 344090 Russia
4 Rostov State Medical University, 29 Nakhichevansky Lane, Rostov-on-Don 344022 Russia

Corresponding author: Pavel A. Galenko-Yaroshevsky (galenko.yarochevsky@gmail.com)

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Abstract

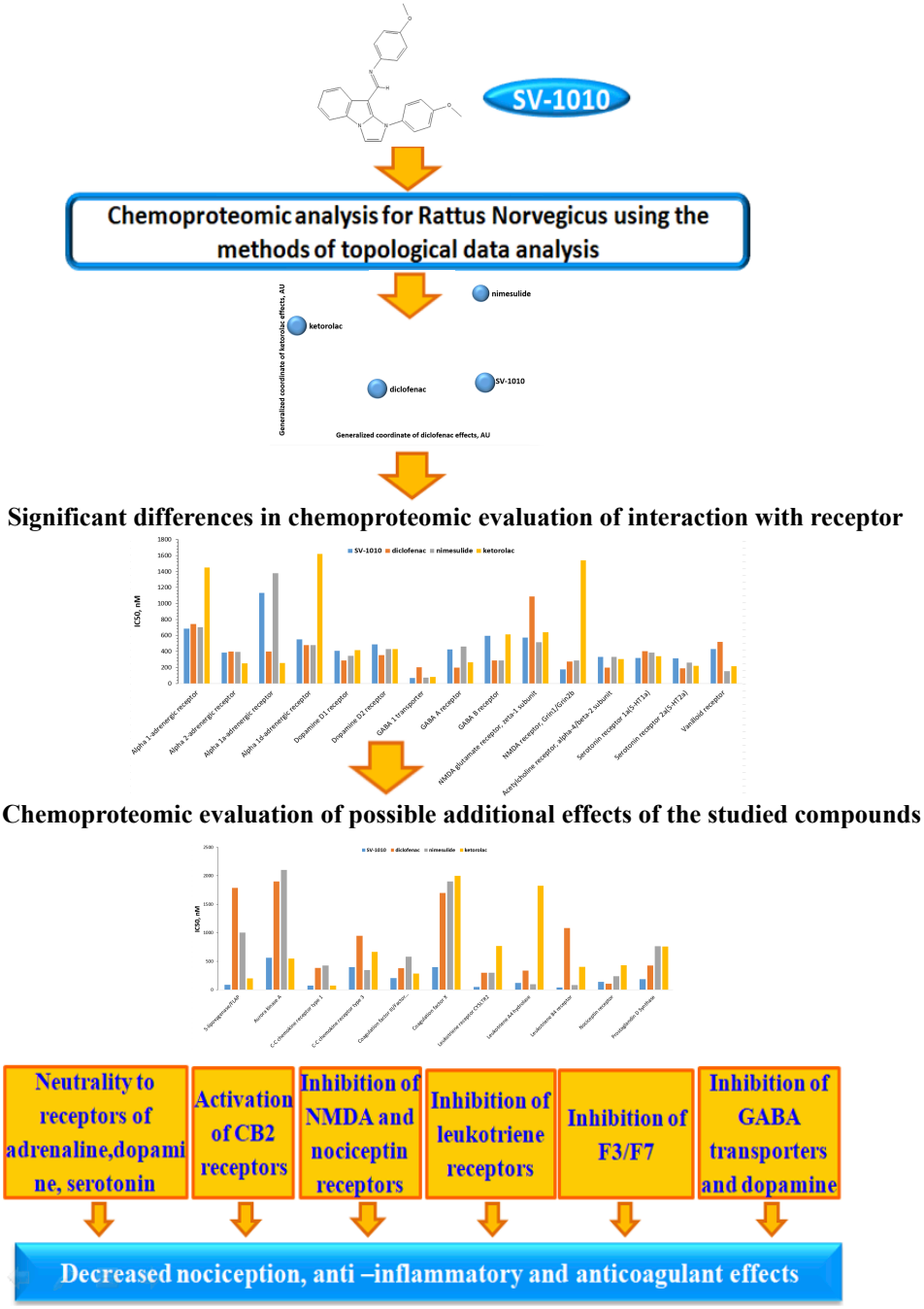
Introduction: For effective and safe pharmacotherapy of pain, it is important to evaluate the mechanisms and spectrum of action of non-steroidal anti-inflammatory drugs (NSAIDs), including their effect on the proteom, central effect, as well as pain relieving and anti-inflammatory effects. **The aim of the study** was to evaluate the complex of differences between the promising candidate-molecule of indole derivative SV-1010 and the well-known NSAIDs.

Material and Methods: Chemoproteomic moduling of pharmacological effects of SV-1010 and NSAID diclofenac, nimesulide and ketorolac on the rat proteom by means of topological analysis of chemographs.

Results: The significant differences in the effects of the studied molecules were found for 820 proteins of the rat proteom. SV-1010, to a lesser degree than the other molecules, can inhibit dopamine D1- and D2-type receptors and, at the same time, stimulate the release of dopamine in the neostriatum (EC50 = 27 nM). SV-1010, to a greater extent than the other molecules, can inhibit the GABA conveyor (EC50 = 65 nM) and the NMDA receptors Grin1/Grin2b (IC50 175 nM). SV-1010 can activate Cannabinoid CB2 receptors, inhibit enzymes of leukotriene biosynthesis, CC receptors of pro-inflammatory chemokines and leukotrienes.

Conclusion: The chemoreactomic and chemoproteomic profiling of SV-1010 indicated its potential central effect through dopaminergic and GABA-neurotransmission and additional anti-inflammatory mechanisms, which can help increase pain-relieving effects.

Graphical abstract



Keywords

diclofenac, ketorolac, machine learning, nimesulide, chemoinformatics, indole derivative SV-1010

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat pain and inflammatory conditions. Reducing the synthesis of pro-inflammatory prostaglandins by inhibiting cyclooxygenase-2 (COX-2), NSAIDs are an important alternative to opioid analgesics, the use of which is significantly limited due to the addiction development. The central mechanisms of the analgesic effect of NSAIDs may, theoretically, be implemented also by means of changes in neurotransmitter systems that are not directly related to the modulation of the prostaglandin metabolism (Torshin et al. 2018; Gromova et al. 2020).

Issues of efficiency and safety of NSAID pharmacotherapy are especially important for patients with chronic diseases. A promising direction for the development of effective and safe analgesics is the search for candidate-molecules with a multi-target pharmacological effect. Such molecules, for instance, can not only inhibit the COX-enzymes, but also other targeted proteins.

To search for and analyze molecules with the required multi-target effect *in silico*, methods for predicting the properties of molecules are necessary based on their chemical structure. The pharmacological/biological properties of molecules can be evaluated by applying a conglomerate of methods of chemoinformational analysis of molecules developed at the scientific school of member of the Russian Academy of Sciences Yu.I. Zhuravlev as "Chemoreactomic Analysis". The use of such methods makes it possible to evaluate the "spectra" of the pharmacological effects of drugs, by determining the differences in the molecular-pharmacological mechanisms of the effects of NSAIDs and other drugs (Torshin 2023).

The aim of the study was to evaluate the complex of differences between the promising candidate-molecule of Indole derivative SV-1010 and the well-known NSAIDs.

Materials and Methods

The studied compounds

The indole derivative with lab code SV-1010 was synthesized at the laboratory of the Department of Chemistry of Natural and High Molecular Compounds of the Faculty of Chemistry, Southern Federal University, Rostov-on-Don, Russia, by the earlier described method (Suzdalev et al. 2016). Diclofenac (Ozon LLC, Russia), nimesulide (Izvarino Pharma, Russia), and ketorolac (Sintez OJSC, Russia).

Experiment design

A flowchart of research design is presented in Figure 1.

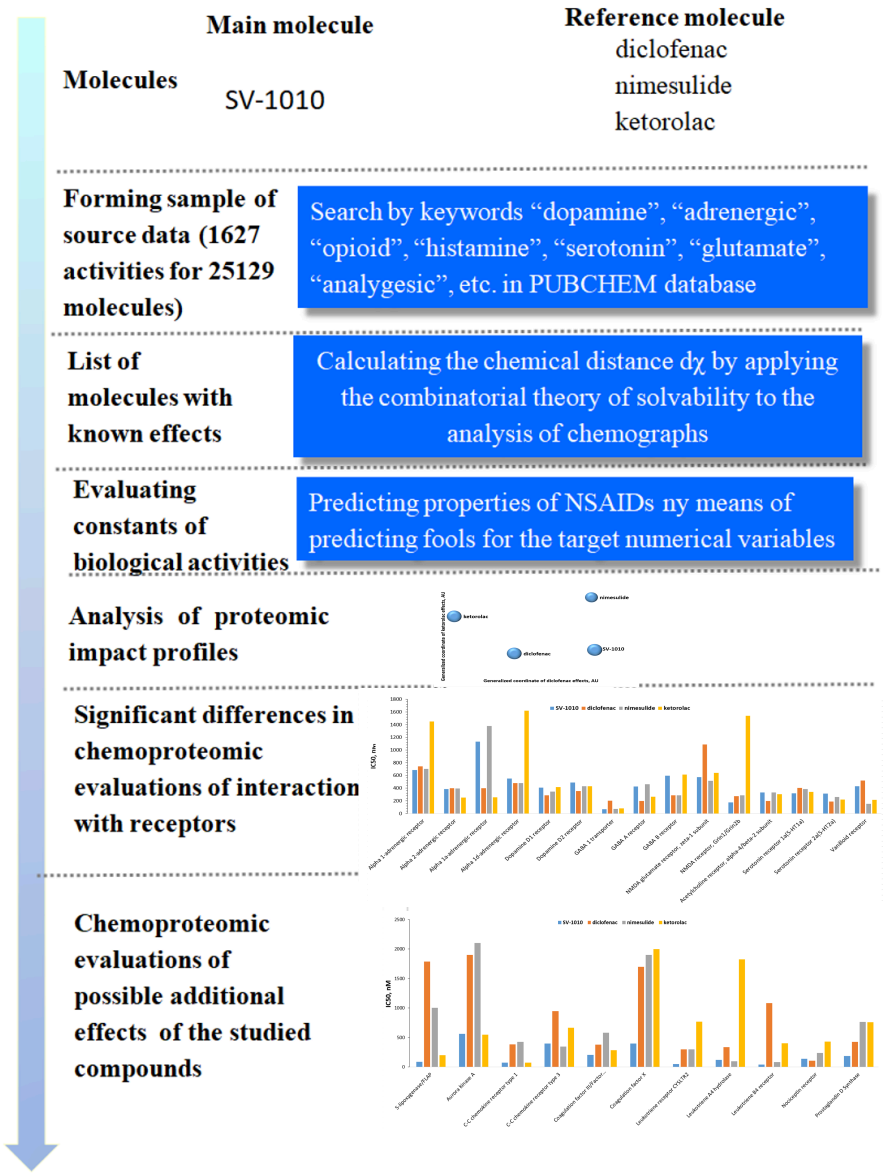


Figure 1. Flowchart of research design.

The source data (selected from the PUBCHEM database using the keywords describing the central effect ("dopamine", "adrenergic", "opioid", "histamine", "serotonin", "glutamate", "analygesic", etc., 35 terms in total) were sampled.

A list of molecules with known effects which are the closest to each of the studied molecules was made through calculating the chemical distance dχ by applying the combinatorial theory of solvability to the analysis of chemographs.

Constants of biological activities were evaluated and the properties of NSAIDs were predicted by applying predicting fools for the target numerical variables.

The proteomic impact profiles were analyzed.

The significance of the differences in chemoproteomic evaluations of interactions with receptors was determined.

Experimental research models

Within the post-genome paradigm, the molecule of any drug "mimics" certain metabolites and, joining various proteins of the proteome, produces the effects characteristic of this drug. An analysis of the pharmacological "capacities" of SV-1010, diclofenac, nimesulide, ketorolac was carried out on the basis of a chemoinformational approach, i.e. comparing the chemical structure of the studied molecules with the structures of millions of other molecules, the molecular and pharmacological properties of which are known. The analysis procedure is based on the latest machine learning technologies developed within the theory of topological and metrical analysis of feature vectors (Torshin 2023). A chemoinformational analysis makes it possible to find molecules similar to the studied ones (Fig. 2) and, accordingly, to evaluate the physiological, pharmacological and other properties of the studied molecule using the available information about the properties of the molecules that are closest to the molecules studied in structure.

The chemoreactomic analysis of the NSAID mechanisms of action was carried out in 3 stages. At the first stage, a sample of the source data was formed. For this purpose, by using the keywords describing the central effect ("dopamine", "adrenergic", "opioid", "histamine", "serotonin", "glutamate", "analgesic", etc., 35 terms in total), the relevant biological activities of the molecules were extracted from the PUBCHEM database. In total, 1627 activities were found for 25129 molecules.

At the second stage of the analysis, a list of the molecules with known effects that are closest to each of the studied molecules (Fig. 2) was made. This was carried out by calculating the "metric chemical distance" dχ between the molecules. The procedures for calculating the metrics dχ are based on applying the combinatorial theory of solvability to the analysis of chemographs (χ-graphs) – mathematical objects used to describe the structures of the molecules (Torshin 2023).

At the third stage, for each molecule, all the available information was extracted from the databases about the experimental measurement of various biological properties of this molecule, and biological activities were evaluated by calculating the corresponding constants (binding constants, inhibition constants, etc.). Adjustment of metric weights of dχ and prediction of the central effects of the studied NSAIDs were carried out by modern methods for predicting the target numerical variables.

A quantitative evaluation of the effects of the studied substances was carried out by calculating an inhibition constant (Ki, IC50) and an activation constant (EC50) of the corresponding receptors, a dissociation constant of NSAID receptor complexes (Kd), as well as an evaluation of a degree of receptor activation/inhibition (as percentage of the effects of the corresponding endogenous ligands), according to the previously described method (Gromova et al. 2020). To obtain the assessments of the values of the constants presented in the tables below, the results of 5 to 216 independent chemoproteomic experiments (an average of 14 experiments per a receptor type) were analyzed.

Results

The results of chemoproteomic profiling of four molecules with the NSAID properties (SV-1010, diclofenac, nimesulide, ketorolac) on the rat (*Rattus Norvegicus*) proteome made it possible to evaluate the effects of NSAIDs on adrenergic, serotonin, dopamine, angiotensin, opioid, cannabinoid and bradykinin receptors; neuronal receptors of GABA, glutamate, acetylcholine, histamine, and vanilloids.

Within the chemoproteomic profiling of the studied molecules, an analysis of interactions (primarily, inhibition) of over 1200 proteins of the rat proteome was carried out. This sample of proteins was formed on the basis of reliable information about the binding of each of these proteins with various ligands. Significant differences in the effects of the studied molecules were

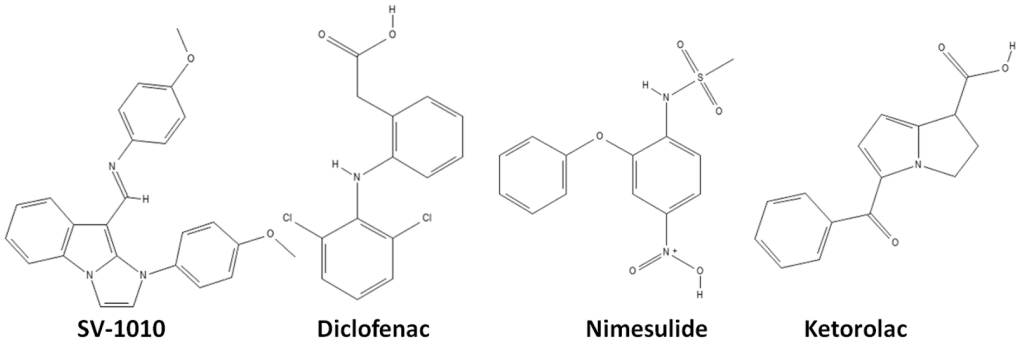


Figure 2. Chemical formulas of the studied molecules.

found for 820 proteins. The percentages of proteins of the rat proteome with similar effect were significantly different between the pairs of molecules (Table 1).

Table 1. Percentage of proteins of the rat proteome (sample of 820 proteins) with similar effect of each pair of molecules

Similarity	SV-1010	Diclofenac	Nimesulide	Ketorolac
SV-1010	100 %	52 %	40 %	22 %
Diclofenac	52 %	100 %	28 %	50 %
Nimesulide	40 %	28 %	100 %	35 %
Ketorolac	22 %	50 %	35 %	100 %

On the metric graph (Fig. 3), each compound is shown with one point, which, in turn, corresponds to the 820-dimensional vector reflecting the interactions of the compound with a sample of proteome proteins. The points corresponding to diclofenac and ketorolac were located along the horizontal and vertical axes of the two fundamental components, respectively. Therefore, the horizontal and vertical axes were conditionally defined as a "generalized coordinate of diclofenac effects" and a "generalized coordinate of ketorolac effects". Figure 3 shows that the interaction of SV-1010 with a sample of proteome proteins is significantly different from the interactions of all the other NSAID molecules.

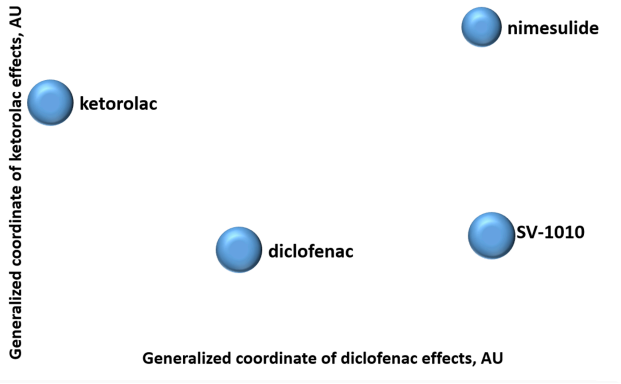


Figure 3. Metric graph of the similarity of the profiles of the proteomic effects of SV-1010, diclofenac, nimesulide and ketorolac. ***Note:*** The graph was made by projecting 820-dimensional vectors for each compound to the plane. While projecting, the coordinate axes correspond to two fundamental vector components. The larger the distance between the points, the more differences in the proteomic profiles of the corresponding compounds. The distances between the proteomic profiles were estimated by the Kolmogorov metric.

A chemoproteomic analysis of the central effects of the studied substances through evaluating their impact on various types of neuroreceptors made it possible to identify differences in the interactions between the studied molecules and receptors of adrenaline, dopamine, serotonin, GABA, glutamate, etc. (Fig. 4).

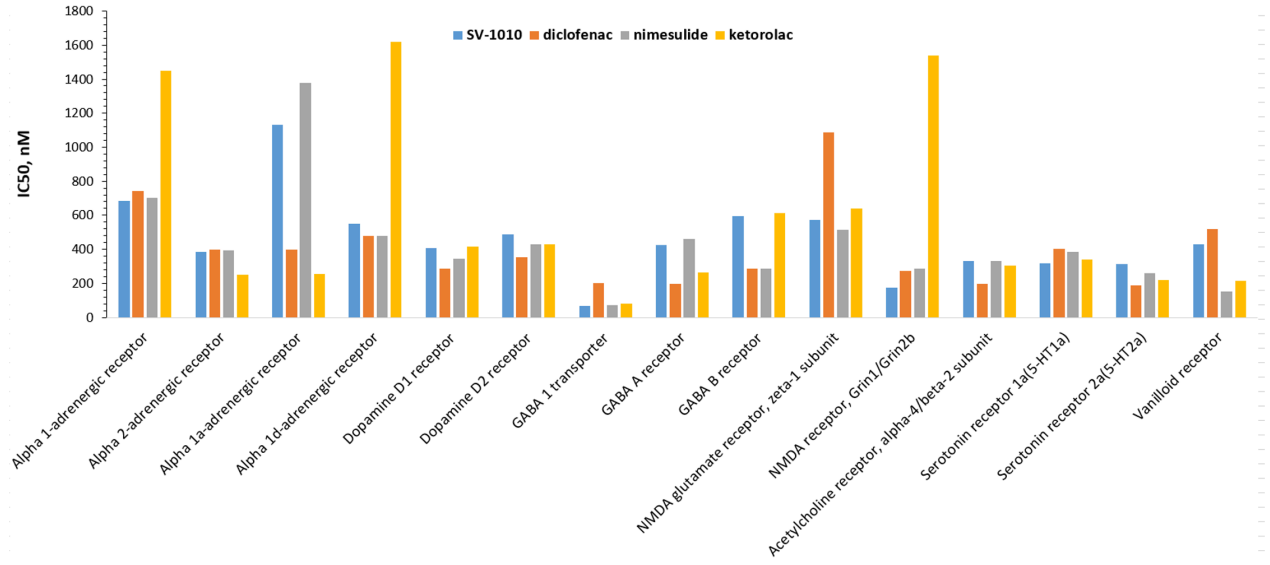


Figure 4. Chemoproteomic evaluations of the central effects of the studied compounds through assessing the impact on various types of neuroreceptors.

Even if SV-1010 affects adrenergic signals, this affect is comparable to the effects of other NSAIDs on the receptors of the same subtype (Fig. 4). Towards alpha 1-adrenergic receptors, the SV-1010 effects were much weaker (IC50 1129 nM) than, for example, the effects of diclofenac (IC50 397 nM). Non-interference in adrenergic signals is important, in particular, to reduce cardiotoxicity of NSAIDs.

SV-1010 to a lesser extent than the other molecules can inhibit dopamine D1- and D2-type receptors. At the same time, this compound can stimulate the release of dopamine in neostriatum (EC50 27 nM). Dopamine systems of the brain are also involved in the central regulation of chronic pain: a low level of dopamine activity is the cause of a pain increase (Li et al. 2019).

SV-1010 can affect GABA A and B receptors to a lesser extent than diclofenac and nimesulide (Fig. 4) and, to a greater extent than the other molecules, can inhibit GABA transporter protein GAT1 (IC50 65 nM, whereas other molecules – 72-200 nM). Inhibition of GAT1 transporter leads to prolongation of inhibitory postsynaptic currents,

which can reduce nociception. Compared to the other molecules, SV-1010 can, to a greater extent, inhibit NMDA zeta-1 (IC50 570 nM) and Grin1/Grin2b (IC50 175 nM) receptors. NMDA receptors in the synapses of primary afferent excitatory neurons support chronic pain caused by chemotherapy or nerve injury. The selective allosteric inhibitor of NMDA Grin1/Grin2b receptors not only exerts its own analgesic properties, but also enhances analgesia of morphine in the pain model in mice (Harris et al. 2023).

SV-1010 had a weak, but differentiated effect on various types of serotonin receptors. In the case of 5-HT1a receptors, the inhibitory effects were comparable to those of the other molecules, and as for 5-HT2a receptors, SV-1010 exerted the smallest inhibitory effect (IC50 315 nM, whereas for the other molecules – IC50 188-259 nM).

Vanilloid receptors (TRPV1) get activated under the influence of various non-specific stimuli that can cause pain (heat, acidosis, a change in transmembrane potential) and trigger a rapid pain reaction. A chemoproteomic analysis showed that all the studied molecules can inhibit vanilloid receptors (first of all, nimesulide and ketorolak, IC50 200 and 250 nM, respectively).

Chemoproteomic evaluations of possible additional (anti-inflammatory, anticoagulant) effects of the studied substances can activate CB2 cannabinoid receptors, inhibit enzymes of leukotrienes biosynthesis, proinflammatory CC chemokine receptors and leukotrienes, and, possibly, may exert a weak anticoagulant effect (Fig. 5).

Interestingly, the chemoproteomic analysis of additional pharmacological effects resulted in a complex of differences in effect of the studied substances on the metabolism of leukotrienes – potent chemoattractants participating in inflammation, immune response and nociception. In particular, leukotrienes play an important role in exacerbation of bronchial asthma. Cysteinyl leukotrienes LTC4, LTD4, and LTE4 are inflammatory lipid mediators that are secreted with leukocytes and act through the three main G-protein-coupled receptors (CysLT1R, CysLT2R, and CysLT3R). LTD4 is the most potent bronchoconstrictor with high affinity for CysLT1R (Al-Azzam and Elsalem 2020; Qahtani 2023).

Leukotriene receptor antagonists reduce the exacerbation of bronchial asthma. The use of CysLT1R antagonists, such as montelucast, has a beneficial effect on asthma patients, especially in cases of those resistant to corticosteroids (Qahtani 2023). A review of 37 studies (n=6128) of patients with mild and moderate asthma confirmed that in adolescents and adults with persistent asthma, the use of leukotriene receptor antagonists – montelucast, zafirlucast, and pranlucast (including together with inhaled corticosteroids) – is useful for reducing the number of episodes of asthma exacerbation and improving the lung function (Chauhan et al. 2017).

The 5-lipoxygenase/FLAP enzyme is necessary for biosynthesis of leukotrienes by means of ALOX5 enzyme (5-lipoxygenase), attaching ALOX5 to the cell membrane. Inhibiting lipoxygenase/FLAP blocks leukotriene biosynthesis (Dixon et al. 1990). Among the studied substances, SV-1010 had the lowest value of the inhibition constant (IC50 87 nM, the others – 200-1789 nM), which can be important for inhibiting the biosynthesis of pro-inflammatory leukotriens. The leukotriene *A4* hydrolase (epoxyde hydrolase) enzyme, which catalyzes the final stage of the biosynthesis of the pro-inflammatory mediator, leukotriene B4 (Tholander et al. 2008), can be inhibited by the SV-1010 (119 nM) molecule and nimesulide molecule (95 nM).

The studied molecules are also different in terms of their effects on leukotriene receptors. The CYSLTR2 receptor of pro-inflammatory cysteinyl leukotrienes, involved in allergic inflammation, acts through the G-protein by activating the phosphatidylinositol-calcium signal transduction system. The ranking order of affinity for leukotrienes is "LTC4 ~ LTD4 >> LTE4". This receptor can be inhibited by the SV-1010 molecule (IC50 50 nM) more effectively than by those of the reference drugs (IC50 299-770 nM). Among the studied molecules, SV-1010 can most effectively suppress leukotrien receptor B4 (IC50 39 nM, the other molecules – 50-1100 nM).

The anti-inflammatory effect of SV-1010 can also be exerted through CC receptors of pro-inflammatory

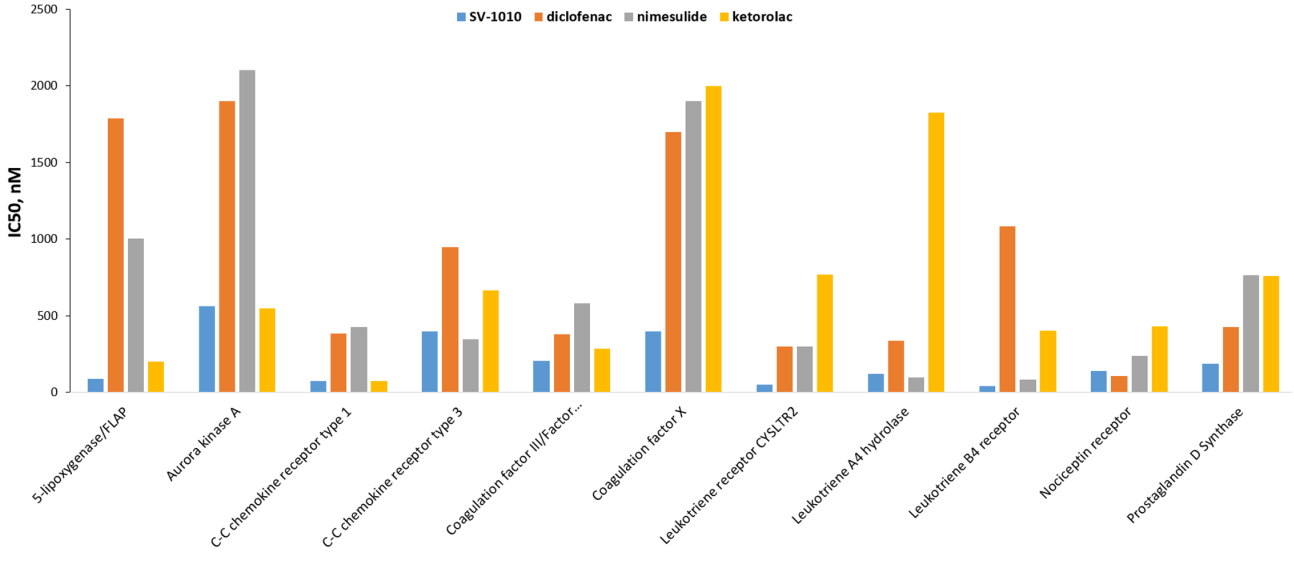


Figure 5. Chemoproteomic evaluations of possible additional (anti-inflammatory, anticoagulant) effects of the studied compounds.

chemokines. Pro-inflammatory CC chemokine receptor type-1, acting through MIP-1-alpha, RANTES and MCP-3 proteins and increasing the level of intracellular calcium ions, can be inhibited by SV-1010 (72 nM). CC chemokine receptor type-3 can be suppressed by SV-1010 (205 nM). SV-1010 also inhibits prostaglandin D-synthase (IC50 187 nM, the other molecules – 420-782 nM), which catalyzes the transformation of PGH2 to PGD2 (prostaglandin, involved in regulating body temperature and pain reactions). PGD2 is produced by mast cells and leukocytes and plays a role in the development of atherosclerosis (Kanaoka et al. 2000).

The cannabinoid 2 receptor is involved in the modulation of inflammatory reactions and nociceptive signal transduction. Activation of CB2 receptors through SV-1010 (IC50 41 nM) can play a therapeutic role in the treatment of neurodegenerative diseases (Feng and Song 2003).

The G-protein receptor of the endogenous neuropeptide nociceptin, which changes the activity of pain neurons, plays a role in the modulation of nociception and the perception of pain (Serhan et al. 2001). In particular, arrestin proteins adjust the signal transduction through G-proteins and mediate the activation of alternative signal pathways, which lead to the activation of MAP-kinases. This receptor can be inhibited by SV-1010 (141 nM) and diclofenac (108 nM).

Weak anticoagulant effects of SV-1010 can be observed through the impact on blood coagulation factors. A complex of blood coagulation factors III/VII is the initiator of the so-called "external" blood coagulation cascade. With factor III involved, factor VII turns into factor VIIa, by means of factors Xa, XIIa, IXa or thrombin in the presence of calcium ions. The inhibition constant of this complex by the SV-1010 molecule was 250 nM. Factor Xa is vitamin K-dependent glycoprotein, which turns prothrombin into thrombin in the presence of factor Va, calcium and phospholipids in the process of blood coagulation. The inhibition constant by the SV-1010 molecule was IC50 = 399 nM.

Aurora kinase A, a mitotic serine/threonine kinase, which facilitates the regulation of the cell cycle, is required for the initial activation of the CDK1 cyclin-dependent kinase in centrosomes. The regulatory component of p53/TP53 pathway is crucial for the oncogenic cell transformation. Inhibitors of Aurora kinaze A are promising antitumor drugs (Walter et al. 2000). The value of the inhibition constant by the SV-1010 molecule was high (IC50 500 nM).

Chemoreactomic modeling of experimental effects of NSAIDs in rats

The above described modeling of the activity of the target proteins of the rat proteome corresponds to a decrease in the intensity of nociceptive signals, whereas a weak intervention of NSAIDs in adrenergic and other neurotransmitter systems corresponds to a decrease in central side effects. The chemoreactomic modeling of the results of the experimental studies of the tested molecules in rats and mice (Table 2) showed that in the tail withdrawal test in rats the activities of all four substances were comparable (ED50 0.25-0.37 mg/kg).

In chemoreactomic modeling of nociceptive experiments on different pain models in mice, more differentiated results were obtained. For instance, in a model of inhibiting pain caused by acetic acid, the most effective was SV-1010 (33.7%), the least – ketorolac (14%), with the corresponding values of the ED50 constants of 22-24 mg/kg for SV-1010, diclofenac, and nimesulide and 33 mg/kg for ketorolac). In the phenylquinon on model, SV-1010 and nimesulide had the lowest values of ED50 (7-7.3 mg/kg).

Table 2. Results of chemoreactomic modeling of analgetic effects in rats and mice for different pain models

Experiment	Const..	Units	SV-1010	Diclofenac	Nimesulide	Ketorolac
Analgesic effect in the tail withdrawal test in rats	mg/kg	ED50	0.362	0.259	0.362	0.367
Analgesic activity in ICR mice was evaluated as a change in the pain threshold at a dose of 25 μmoL/kg, orally introduced as a single dose, with activity measured after 30 minutes by means of the tail withdrawal test (when compared to control)	%	-	22.76	29.92	25.62	26.17
Analgesic activity in Swiss mice was evaluated as inhibiting writhes (abdominal contractions, cramps) caused by acetic acid, at a dose of 50 mg/kg, administered orally one hour before the use of acetic acid (when compared to control)	%	-	33.72	30.42	30.42	14.35
Analgesic activity towards inhibiting writhes caused by phenylquinon subcutaneously administered to mice	mg/kg	ED50	13.73	10.65	16.14	12.64
Analgesic activity in mice towards inhibiting writhes caused by acetic acid	mg/kg	ED50	23.95	21.96	24.18	32.53
Analgesic activity towards inhibiting writhes caused by phenylquinon subcutaneously introduced to mice	mg/kg	ED50	7.323	15.72	7.022	14.99
Analgesic activity in the tail-pinch test in mice	mg/kg	ED50	5.032	7.87	5.057	7.733

***Note*:** Const.. – Constants, Units – unit of measurement.

Discussion

The chemoproteomic modeling of the pharmacological effects of the promising SV-1010 molecule in comparison with the well-known NSAIDs (diclofenac, nimesulide, ketorolak) on the rat proteome showed that significant differences in the effects of the studied molecules were found for 820 proteome proteins. The interaction of SV-1010 with a sample of proteome proteins was significantly different from such of the reference drugs. In particular, SV-1010, to a lesser extent than the other studied NSAID molecules, can inhibit dopamine D1 and D2 receptors and, at the same time, can stimulate the release of dopamine in neostriatum (EC50 = 27 nM). To a greater extent than the other molecules, SV-1010 can inhibit GABA transporter (EC50 = 65 nM) and NMDA receptors Grin1/Grin2b (IC50 175 nM), which can reduce nociception. Besides, SV-1010 can activate cannabinoid CB2 receptors, inhibit leukotriene biosynthesis enzymes, receptors of pro-inflammatory CC chemokines and leukotrienes.

The chemoreactomic modeling of the results of experimental studies of the tested molecules in rats and mice showed that in the tail withdrawal test in rats, the activities of all the four tested substances were comparable (ED50 0.25-0.37 mg/kg). In the chemoreactomic modeling of nociceptive experiments on different pain models in mice, the results obtained were more differentiated.

Conclusion

Thus, chemoproteomic and chemoreactomic profilings of candidate molecule SV-1010 indicated additional molecular-pharmacological properties, which were less expressed in the reference molecules. These properties (including a potential central effect through dopaminergic, GABA-ergic and glutamate neurotransmission) can help enhance the analgesic effects of the compound in question in certain groups of patients. Further studies may involve a pharmacoinformation profiling of this molecule for a more detailed study.

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Conflict of interests

Authors declare no conflict of interests.

Data availability

All of the data that support the findings of this study are available in the main text.

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Author Contributions

- **Pavel A. Galenko-Yaroshevsky,** corresponding member of the Russian Academy of Sciences, Holder of Advanced Doctorate (Doctor of Science) in Medical Sciences, Professor, Head of the Department of Pharmacology, Kuban State Medical University, Krasnodar, Russia; e-mail: Galenko.Yarochevsky@gmail.com; **ORCID ID** https://orcid.org/0000-0003-3190-1437. The author's contribution: concept development – shaping the idea and research direction; developing and designing methodology, and formulating the key aims and tasks.

- **Ivan Yu. Torshin**, Candidate of Physical and Mathematical Sciences (PhD), Candidate of Chemical Sciences (PhD), lead research fellow, Federal Research Center "Informatics and Management" of the Russian Academy of Sciences, Moscow, Russia; e-mail: tiy135@yahoo.com; **ORCID ID** https://orcid.org/0000-0002-2659-7998. The author's contribution: conducting research, developing and designing methodology, and writing the text of the article.

- **Andrey N. Gromov**, research engineer, Federal Research Center "Informatics and Management" of the Russian Academy of Sciences, Moscow, Russia; e-mail: gromlogin@gmail.com; **ORCID ID** https://orcid.org/0000-0001-7507-191X. The author's contribution: conducting research, developing and designing methodology, and writing the text of the article.

- **Ivan A. Reyer,** Candidate of Technical Sciences (PhD), research fellow, Federal Research Center "Informatics and Management" of the Russian Academy of Sciences, Moscow, Russia; e-mail: reyer@forecsys.ru; **ORCID ID** https://orcid.org/0000-0002-7928-053X. The author's contribution: conducting research, developing and designing methodology, and writing the text of the article.

- **Olga A. Gromova,** Holder of an Advanced Doctorate (Doctor of Science) in Medical Sciences, Professor, lead research fellow, Federal Research Center "Informatics and Management" of the Russian Academy of Sciences, Moscow, Russia; e-mail: unesco.gromova@gmail.com; **ORCID ID** https://orcid.org/0000-0002-7663-710X. The author's contribution: conducting research, developing and designing methodology, and writing the text of the article.

- **Tereza R. Glechyan**, Teaching fellow, Department of Pharmacology, Kuban State Medical University, Krasnodar, Russia; e-mail: t_g91@mail.ru; **ORCID ID** https://orcid.org/0009-0002-4983-2433. The author's contribution: analyzing and interpreting the data obtained and participating in research design.

- **Konstantin F. Suzdalev**, Candidate of Chemical Sciences (PhD), Associate Professor of the Department of Chemistry of Natural and High Molecular Compounds, Southern Federal University, Rostov-on-Don, Russia; e-mail: konsuz@gmail.com; **ORCID ID** https://orcid.org/0000-0003-4879-0577. The author's contribution: analyzing and interpreting the research results and participating in research design.

- **Andrey V. Zadorozhniy**, Candidate of Medical Sciences (PhD), Associate Professor, Head of the Department of Dentistry No. 4, Rostov State Medical University, Rostov-on-Don, Russia; e-mail: stomvr1@gmail.com; **ORCID ID** https://orcid.org/0000-0001-9552-8542. The author's contribution: editing and preparing the article text, participating in research design, and correcting the final draft of the article.

- **Anait V. Zelenskaya,** Candidate of Medical Sciences (PhD), Associate Professor, Department of Pharmacology, Kuban State Medical University, Krasnodar, Russia; e-mail: anait_06@mail.ru; **ORCID ID** https://orcid.org/0000-0001-9512-2526. The author's contribution: analyzing and interpreting the research results, preparing and editing the text of the article, and participating in research design.