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Research Article

Assessment of possible biomarkers of individual representatives of 1,4-dihydropyridines by methods of molecular docking and predictor analysis

Elena Yu. Bibik[1], Ivan A. Nekrasa[2], Vladislav V. Bibik[3], Konstantin A. Frolov[1,4], Sergej G. Krivokolysko[1,4]

1 St. Luke Lugansk State Medical University; 1G 50-letiya Oborony Luganska kvartal, Lugansk 291045 Russia;
2 LLC "IMC Clinic №.1"; 25 Averyanov St., Bldg 1, Dmitrov 141800 Russia;
3 Regional Center for the Development of Giftedness "Intellectual Reserve of the Republic", 36 Komarova kvartal, Lugansk 291045 Russia;
4 Vladimir Dahl Lugansk State Medical University; 20a Molodezhny kvartal, Bldg 7, Lugansk 291034 Russia.

Corresponding author: Elena Yu. Bibik (helen_bibik@mail.ru)

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Abstract

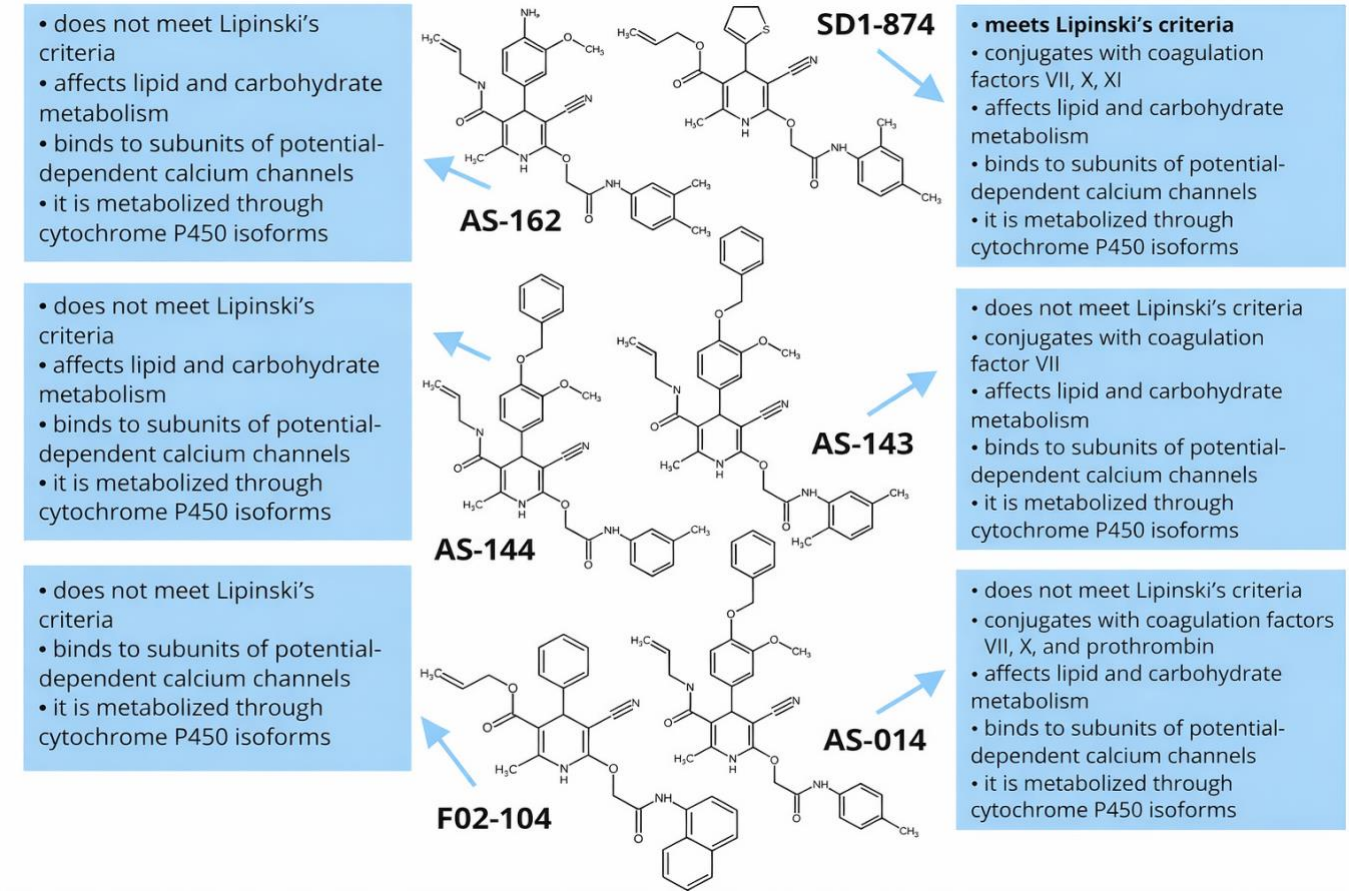
Introduction: Some of the promising classes of chemical compounds for research are 1,4-dihydropyridines, which have potential biological activity and low toxicity. The use of modern technologies for the analysis of substances *in silico* makes it possible to predict their potential biological effects with a high degree of probability, thereby facilitating further preclinical studies.

Materials and Methods: For the purpose of predictive analysis and molecular docking, 6 new compounds of the 1,4-dihydropyridine group were selected with lab codes SD1-874, F02-104, AS-143, AS-014, AS-144, AS-162. The studied compounds were subjected to predictive analysis in silico. Based on its results, the ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) parameters were predicted. PASS Online, Molinspiration Property Calculation Service and OSIRIS Property Explorer services were used for predictor analysis. Molecular docking was carried out using the GalaxyWEB Sagittarius service, followed by evaluation of the results using the RCSB Protein Data Bank and UniProt Consortium databases. Based on the results of the calculation of physical and chemical parameters, the presence of Lipinski's criteria was evaluated in all the samples studied.

Results and Discussion: Of the 6 compounds under consideration, the SD1-874 sample has potential oral activity, according to Lipinski's criteria. Based on the results of predictive analysis *in silico*, all the studied substances, except SD1-874, are potentially capable of blocking calcium channels. SD1-874 probably has an effect on lipid and carbohydrate metabolism. Evaluating the results of molecular docking, three groups of proteins can be distinguished with which the studied samples can potentially conjugate: a group of proteins that regulate the processes of apoptosis, mitosis, and DNA transcription, a group of proteins that affect blood clotting, and a group that affects the metabolism of lipoproteins, lipids, and glucose. The ability to conjugate with calcium channel subunits is also noted; however, the probability of such an interaction by the molecular docking program is estimated as unlikely. All the studied compounds interact with various isoforms of cytochrome P450.

Conclusion. According to the results of predictor analysis and the results of molecular docking, among the 6 compounds of 1,4-dihydropyridines selected for analysis, the compound with lab codes SD1-874 is considered the most promising for further study due to the presence of oral bioactivity.

Graphical Abstract



The results of predictive analysis and molecular docking for selected new compounds of 1,4-dihydropyridines.

Keywords

preclinical studies, in silico analysis, 1,4-dihydropyridines

Introduction

Of particular interest to specialists in the fields of chemistry, biology, pharmacy and medicine are new organic compounds from a number of cyanothioacetamide derivatives. This is due to the fact that cyanothioacetamide is an easily accessible and versatile reagent capable of participating in reactions due to the presence of several nucleophilic and electrophilic centers (Bibik et al. 2021; Bochev et al. 2025).

Pyridine and dihydropyridine are part of vitamins, coenzymes, alkaloids, antibiotics, and other compounds. Pyridine and dihydropyridine scaffolds in a drug are considered important structural components because they affect their pharmacological properties. Thus, the pyridine component can improve biochemical activity, since it helps to increase the rate of chemical reactions. In addition, it stabilizes drugs, increases their permeability through membranes, and facilitates the binding of new compounds to blood proteins (Krivokolysko et al. 2022; Bocheva et al. 2023; Dotsenko et al. 2023).

Cyanothioacetamide readily reacts by condensation and cyclization with a wide range of reagents. This circumstance causes a significant variety of possible products of such reactions – sulfur- and nitrogen-containing heterocyclic compounds, which in many cases are structural fragments of natural molecules; among them – a large number of biologically active compounds have been found (Krivokolysko et al. 2021; Ketova et al. 2024). The functionalization of the

pyridine scaffold due to active groups (for example, cyano- or amino groups) leads to an expansion or change in the spectrum of biological activity.

The search for new compounds with biological activity and their subsequent study is one of the most resource-intensive tasks in pharmacological research (Schlander et al. 2021; Simoens and Huys 2021). *In silico* computer modeling of new compounds makes it possible to predict their positive and negative potential biological effects, as well as, partially, pharmacokinetic and pharmacodynamic properties, which greatly simplifies and accelerates the drug development process (Khedkar and Auti 2014).

Despite the widespread popularity of dihydropyridines as calcium channel blockers and blood pressure lowering agents, a number of preclinical studies indicate that some of the 1,4-dihydropyridines have other properties, such as analgesic, decongestant, cardioprotective, antihypertensive, anti-inflammatory, neuroprotective, antithrombotic effects; many 1,4-dihydropyridine derivatives have antimicrobial and insecticidal effects (Bibik et al. 2023).

1,4-dihydropyridines are a promising group of low-toxic heterocyclic compounds with potentially high biological activity. Computer modeling (*in silico*) helps predict their biological effects, simplifying and speeding up subsequent research (Oleynik et al. 2023).

The purpose of this study was to evaluate possible biomarkers of individual representatives of compounds of the 1,4-dihydropyridine group with lab codes SD1-874, F02-104, AS-144, AS-014, AS-0143, AS-143 using molecular docking and predictor analysis methods.

Materials and Methods

Studied compounds

For the purpose of predictive analysis and molecular docking, 6 new compounds of the 1,4-dihydropyridine group with lab codes SD1-874, F02-104, AS-144, AS-014, AS-0143, AS-143 were selected (Table 1).

Research design

The studied compounds were subjected to predictive analysis *in silico*. Based on its results, the ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) parameters were predicted. For the purpose of predictive analysis, the following services were used: PASS Online (www.way2drug.com/PassOnline/predict.php), Molinspiration Property Calculation Service (www.molinspiration.com/cgi/properties), and OSIRIS Property Explorer (www.organic-chemistry.org/prog/peo). PASS Online and Molinspiration Property Calculation Service were used to calculate the physical and chemical properties of compounds, assess the degree of oral bioavailability, and predict teratogenic, carcinogenic, embryotoxic, and local irritant effects. The OSIRIS Property Explorer contains a database of the properties of 3,300 drugs and 15,000 commercially available compounds (Fluka). It can be used to calculate the solubility measure (logS). In addition, the risks of side effects – mutagenic, oncogenic and reproductive – were assessed. Thanks to the OSIRIS Property Explorer software service, similarities with already known drugs (drug-likeness) have been identified, and a general assessment of potential pharmacological effects for the studied samples has been carried out.

The molecular docking was carried out using the service GalaxyWEB Sagittarius (www.galaxy.seoklab.org) with subsequent evaluation of the results using RCSB Protein Data Bank databases (www.rcsb.org) and the UniProt Consortium (www.uniprot.org).

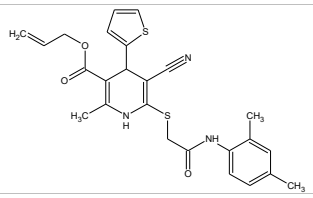
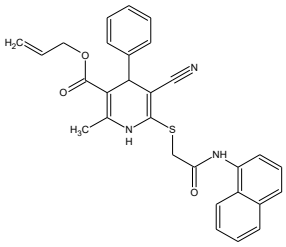
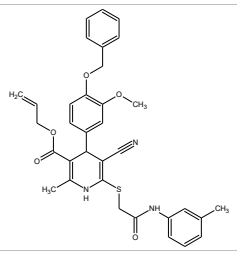
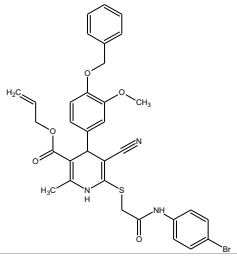
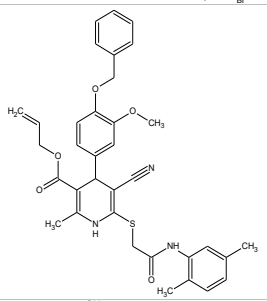
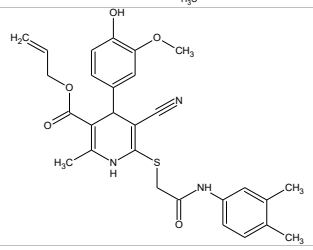
Based on the results of the calculation of physical and chemical parameters, the presence of Lipinski's criteria was assessed in all the studied samples (Lipinski et al. 1997), suggesting the presence of oral bioactivity.

Results and Discussion

According to Lipinski's criteria, the following compound has oral bioactivity: SD1-874. Samples with lab codes AS-014, AS-129, AS-143, AS-144, and F02-104, according to the Lipinski's criteria, do not have potential oral bioactivity due to inconsistencies in two or more points.

Compound SD1-874 is highly likely to have an effect on lipid and carbohydrate metabolism, and is capable of exhibiting the properties of a neurotransmitter reuptake inhibitor, according to the results of predictor analysis (Table 2). The presence of local irritant and oncogenic effects is assumed.

Table 1. Structural formulas of the studied compounds

Allyl 5-cyano-6-({2-[(2,4-dimethylphenyl)amino]-2-oxoethyl}thio)-2-methyl-4-(2-thienyl)-1,4-dihydropyridine-3-carboxylate SD1-874	
allyl 5-cyano-2-methyl-6-{[2-(1-naphthylamino)-2-oxoethyl]thio}-4-phenyl-1,4-dihydropyridine-3-carboxylate F02-104	
allyl 4-[4-(benzyloxy)-3-methoxyphenyl]-5-cyano-2-methyl-6-({2-[(3-methylphenyl)amino]-2-oxoethyl}thio)-1,4-dihydropyridine-3-carboxylate AS-144	
allyl 4-[4-(benzyloxy)-3-methoxyphenyl]-6-({2-[(4-bromophenyl)amino]-2-oxoethyl}thio)-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylate AS-014	
allyl 4-[4-(benzyloxy)-3-methoxyphenyl]-5-cyano-6-({2-[(2,5-dimethylphenyl)amino]-2-oxoethyl}thio)-2-methyl-1,4-dihydropyridine-3-carboxylate AS-143	
allyl 5-cyano-6-({2-[(3,4-dimethylphenyl)amino]-2-oxoethyl}thio)-4-(4-hydroxy-3-methoxyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate AS-162	

According to the results of molecular docking, the studied substance SD1-874 potentially affects the processes of proliferation and apoptosis (Table 3, rows 1, 3, 5, 22), the blood coagulation system (rows 2, 12, 24), the production of the amyloid precursor protein (row 4), the cell's response to oxidative stress (row 6) and the cascade of immune response reactions (rows 7, 25), glucose, lipoprotein and fatty acid homeostasis (row 15), the activity of stromelysin-1 and collagenase-3, which promote the degradation of extracellular matrix proteins (rows 9, 10), by estrogen receptors (row 23), alpha-1-antichymotrypsin, involved in the conversion of angiotensin-1 to angiotensin-2 (row 14), binds to potential-dependent calcium channels (rows 8, 16, 19), and acetylcholinesterase (row 17). According to the results of molecular docking, SD1-874 is metabolized through cytochrome P450 isoforms (rows 11, 13, 20, 21).

Table 2. The results of the predictor analysis of compound SD1-874

№	Pa	Pi	Potential effect

1.	0.333	0.256	Cerebral anti-ischemic
2.	0.276	0.243	Neurotransmitter reuptake inhibitor
3.	0.227	0.225	Expression enhancer of 2 HMG-CoA reductase
4.	0.227	0.218	An insulin inhibitor
5.	0.288	0.209	Anaphylotoxin receptor antagonist
6.	0.161	0.154	Antiviral (Hepatitis B)
7.	0.166	0.133	Inhibition of falcipain-3
8.	0.164	0.125	Decreased secretory function of the stomach
9.	0.148	0.123	Skin irritation
10.	0.177	0.122	Thiol protease inhibitor

Table 3. Results of molecular docking of compound SD1-874

№	Protein name	Pre-test assessment	ΔG_{bind} kcal/mol	Overall assessment
1	Bcl-2-like protein 1	0.660	-20.429	0.864
2	Coagulation factor X	0.448	-25.058	0.698
3	Apoptosis regulator Bcl-2	0.258	-20.670	0.465
4	Beta-secretase 1	0.234	-22.874	0.463
5	Histone deacetylase 7	0.213	-24.255	0.455
6	Kelch-like ECH-associated protein 1	0.241	-20.214	0.443
7	Macrophage metalloelastase	0.186	-21.977	0.405
8	Voltage-dependent L-type calcium channel subunit alpha-1D	0.171	-22.742	0.398
9	Collagenase 3	0.143	-25.531	0.398
10	Stromelysin-1	0.143	-23.747	0.381
11	Cytochrome P450 2B6	0.110	-26.758	0.377
12	Coagulation factor VII	0.182	-19.481	0.377
13	Cytochrome P450 2C19	0.106	-26.934	0.376
14	Alpha-1-antichymotrypsin	0.121	-25.418	0.375
15	Peroxisome proliferator-activated receptor gamma	0.122	-25.246	0.374
16	Voltage-dependent L-type calcium channel subunit alpha-1C	0.138	-23.614	0.374
17	Acetylcholinesterase	0.109	-26.433	0.374
18	Dihydroorotate dehydrogenase (quinone), mitochondrial	0.154	-21.748	0.371
19	Voltage-dependent L-type calcium channel subunit alpha-1C	0.136	-23.447	0.370
20	Cytochrome P450 2A7	0.067	-29.953	0.367
21	Cytochrome P450 2F1	0.082	-28.382	0.366
22	von Hippel-Lindau disease tumor suppressor	0.163	-20.199	0.365
23	Estrogen receptor	0.091	-27.361	0.365
24	Coagulation factor XI	0.108	-25.295	0.361
25	Integrin alpha-L	0.148	-21.320	0.361

Compound F02-104 has effects related to the blockade of potential-dependent calcium channels (Table 4). Local irritant, oncogenic and mutagenic properties may be present.

Table 4. Results of predictor analysis of compound F02-104

№	Pa	Pi	Potential effect
1.	0.834	0.002	Blocker of potential-dependent calcium channels
2.	0.692	0.005	Antihypertensive
3.	0.676	0.002	Calcium channel blocker
4.	0.630	0.008	Cardiotonic
5.	0.584	0.004	Therapy of heart failure
6.	0.551	0.030	Antianginal
7.	0.508	0.101	Cerebral anti-ischemic
8.	0.458	0.015	Anti-ischemic
9.	0.455	0.002	L-type Calcium channel blocker
10.	0.423	0.034	Regulation of calcium transport

According to the results of molecular docking, the investigated substance F02-104 potentially affects the processes of mitosis, proliferation and apoptosis (Table 5, rows 1, 4, 9, 11, 18, 25), homeostasis of glucose, lipoproteins and fatty acids (rows 3, 5, 6, 13), blood clotting (row 7), intercellular signal transmission (row 10), production of amyloid precursor protein (row 22), cascade of cell reactions to stress and immune response (rows 12, 15), regulation of the action

of steroid and thyroid hormones (rows 17, 24), the activity of stromelysin-1 and collagenase-3, contributing to the degradation of extracellular matrix proteins (rows 8, 16), binds to MAP kinase (row 2), estrogen receptors (row 19), and L-type calcium channels. According to the results of molecular docking, F02-104 is metabolized through cytochrome P450 isoforms (rows 14, 20, 23).

Table 5. Results of molecular docking of compound F02-104

№	Protein name	Pre-test assessment	ΔG_{bind} kcal/mol	Overall assessment
1	Bcl-2-like protein 1	0.720	-23.755	0.957
2	Mitogen-activated protein kinase 14	0.577	-26.772	0.845
3	Peroxisome proliferator-activated receptor gamma	0.512	-26.377	0.776
4	Replication protein A 70 kDa DNA-binding subunit	0.431	-17.849	0.610
5	Peroxisome proliferator-activated receptor gamma	0.314	-28.374	0.597
6	Free fatty acid receptor 1	0.273	-29.653	0.569
7	Coagulation factor VII	0.308	-25.885	0.566
8	Stromelysin-1	0.269	-27.965	0.549
9	Induced myeloid leukemia cell differentiation protein Mcl-1	0.307	-24.091	0.548
10	Ephrin type-A receptor 2	0.263	-27.923	0.542
11	E3 ubiquitin-protein ligase Mdm2	0.288	-23.627	0.524
12	Nuclear receptor ROR-gamma	0.237	-28.585	0.523
13	Peroxisome proliferator-activated receptor delta	0.207	-31.002	0.517
14	Cytochrome P450 2B6	0.227	-28.668	0.513
15	Integrin alpha-L	0.255	-25.369	0.509
16	Collagenase 3	0.220	-28.175	0.502
17	Nuclear receptor coactivator 2	0.195	-30.191	0.496
18	Apoptosis regulator Bcl-2	0.263	-23.210	0.495
19	Estrogen receptor	0.212	-28.047	0.492
20	Cytochrome P450 2D6	0.198	-28.853	0.486
21	Dihydroorotate dehydrogenase (quinone), mitochondrial	0.208	-26.945	0.477
22	Beta-secretase 1	0.221	-24.894	0.470
23	Vitamin D 25-hydroxylase	0.172	-28.933	0.461
24	Nuclear receptor coactivator 1	0.182	-27.885	0.461
25	Histone deacetylase 7	0.220	-23.970	0.460

Compound AS-143 has effects similar to the above described compounds associated with the blockade of potential-dependent calcium channels (Table 6). Local irritant properties may be present.

Table 6. Results of predictive analysis of compound AS-143

№	Pa	Pi	Potential effect
1.	0.769	0.002	Blocker of potential-dependent calcium channels
2.	0.667	0.002	Calcium channel blocker
3.	0.611	0.010	Antihypertensive
4.	0.582	0.011	Cardiotonic
5.	0.547	0.031	Antianginal
6.	0.457	0.005	Therapy of heart failure
7.	0.449	0.016	Anti-ischemic
8.	0.441	0.150	Cerebral anti-ischemic
9.	0.402	0.041	Regulation of calcium transport
10.	0.368	0.222	Anti-eczema

According to the results of molecular docking, the studied substance AS-143 potentially affects the processes of mitosis, proliferation and apoptosis (Table 7, rows 1, 4, 6, 8), homeostasis of glucose, lipoproteins and fatty acids (rows 3, 9, 14, 15, 22, 24), blood clotting (row 7), intercellular signal transmission (row 2), production of amyloid precursor protein (row 5), cascade of cell reactions to stress and immune response (rows 10, 11, 19), regulation of the action of steroid and thyroid hormones (rows 12, 13, 15), affects the cell's response to oxidative stress (row 18), binds to potential-dependent calcium channels (row 17), MAO-B (row 20), inhibits ACE (row 23), and acetylcholinesterase (row 25). According to the results of molecular docking, AS-143 is metabolized through cytochrome P450 isoforms (row 16, 21).

Compound AS-014 is highly probable according to the results of predictive analysis (Table 8), which can it be attributed to blockers of potential-dependent calcium channels. As a result, the substance potentially has antihypertensive, antianginal, anti-ischemic, cardio- and

cerebroprotective effects. There is also a potential chance of increased expression of mitochondrial HMG-CoA-synthetase 2, which may play a positive role in dyslipidemia. Oncogenic and locally irritating side effects may occur.

Table 7. Results of molecular docking of compound AS-143

№	Protein name	Pre-test assessment	ΔG_{bind} kcal/mol	Overall assessment
1	Induced myeloid leukemia cell differentiation protein Mcl-1	0.751	-27.298	1.024
2	Ephrin type-A receptor 2	0.431	-31.310	0.744
3	3-hydroxy-3-methylglutaryl-coenzyme A reductase	0.491	-25.106	0.743
4	Bcl-2-like protein 1	0.465	-26.726	0.732
5	Beta-secretase 1	0.455	-25.742	0.712
6	E3 ubiquitin-protein ligase Mdm2	0.410	-28.369	0.694
7	Coagulation factor VII	0.287	-30.243	0.589
8	Apoptosis regulator Bcl-2	0.294	-26.864	0.563
9	Free fatty acid receptor 1	0.249	-30.694	0.556
10	Peptidyl-prolyl cis-trans isomerase FKBP5	0.286	-25.645	0.542
11	Nuclear receptor ROR-gamma	0.224	-31.031	0.534
12	Nuclear receptor coactivator 1	0.200	-31.949	0.520
13	Neuropeptide Y receptor type 1	0.205	-31.005	0.515
14	Peroxisome proliferator-activated receptor gamma	0.181	-32.575	0.507
15	Nuclear receptor coactivator 2	0.201	-28.860	0.490
16	Cytochrome P450 2C9	0.133	-34.110	0.474
17	Voltage-dependent L-type calcium channel subunit alpha-1D	0.160	-30.895	0.469
18	Kelch-like ECH-associated protein 1	0.181	-28.486	0.465
19	Arachidonate 5-lipoxygenase-activating protein	0.148	-31.531	0.463
20	Amine oxidase [flavin-containing] B	0.093	-36.399	0.457
21	Cytochrome P450 2C8	0.136	-31.861	0.455
22	Peroxisome proliferator-activated receptor gamma	0.126	-32.495	0.451
23	Angiotensin-converting enzyme	0.186	-26.056	0.447
24	Peroxisome proliferator-activated receptor alpha	0.107	-33.783	0.445
25	Acetylcholinesterase	0.132	-31.273	0.444

Table 8. Results of predictive analysis of compound AS-014

№	Pa	Pi	Potential effect
1.	0.814	0.002	Calcium channel blocker (potential-dependent)
2.	0.691	0.002	Calcium channel blocker
3.	0.595	0.011	Antihypertensive
4.	0.556	0.013	Cardiotonic
5.	0.514	0.039	Antianginal
6.	0.481	0.033	Expression enhancer of HMG-CoA synthetase-2
7.	0.445	0.006	Therapy of heart failure
8.	0.427	0.019	Anti-ischemic
9.	0.405	0.003	L-type calcium channel blocker
10.	0.394	0.189	Cerebral anti-ischemic

According to the results of molecular docking, the studied substance is potentially capable of binding to a number of proteins that affect the mechanisms of mitosis, apoptosis, and cell proliferation (Table 9, rows 1, 2, 4, 6, 9, 14), transmission of intercellular (row 3) and synaptic (row 22) signals, homeostasis of glucose, lipoproteins and fatty acids (rows 5, 7, 11, 14, 25), the

cell's response to oxidative stress (row 10), production of the amyloid precursor protein (row 8) and blood clotting (rows 12, 24), endocrine (rows 13, 16, 25) and immune (rows 15, 17, 23) regulation; potentially inhibits angiotensin-converting enzyme (ACE) (row 19) and blocks calcium channels (rows 20, 21). According to the results of molecular docking, AS-014 is metabolized through cytochrome P450 isoforms (row 18).

Table 9. Results of molecular docking of compound AS-014.

№	Protein name	Pre-test assessment	ΔG_{bind} kcal/mol	Overall assessment
1	Induced myeloid leukemia cell differentiation protein Mcl-1	0.576	-27.825	0.854
2	Bcl-2-like protein 1	0.485	-27.536	0.760
3	Ephrin type-A receptor 2	0.372	-30.640	0.678
4	E3 ubiquitin-protein ligase Mdm2	0.375	-26.623	0.641
5	Peroxisome proliferator-activated receptor gamma	0.237	-35.169	0.588
6	Apoptosis regulator Bcl-2	0.287	-26.897	0.556
7	Free fatty acid receptor 1	0.258	-28.962	0.548
8	Beta-secretase 1	0.266	-27.617	0.542
9	Nuclear receptor ROR-gamma	0.223	-31.260	0.535
10	Kelch-like ECH-associated protein 1	0.261	-27.199	0.533
11	3-hydroxy-3-methylglutaryl-coenzyme A reductase	0.287	-23.242	0.519
12	Coagulation factor VII	0.227	-27.498	0.502
13	Nuclear receptor coactivator 1	0.201	-29.959	0.501
14	Peroxisome proliferator-activated receptor gamma	0.155	-33.738	0.492
15	Peptidyl-prolyl cis-trans isomerase FKBP5	0.242	-24.350	0.486
16	Neuropeptide Y receptor type 1	0.187	-29.713	0.484
17	Macrophage metalloelastase	0.187	-28.431	0.471
18	Cytochrome P450 2C9	0.134	-33.099	0.465
19	Angiotensin-converting enzyme	0.186	-27.740	0.463
20	Voltage-dependent L-type calcium channel subunit alpha-1D	0.162	-29.607	0.459
21	Voltage-dependent T-type calcium channel subunit alpha-1G	0.162	-29.169	0.454
22	Amine oxidase [flavin-containing] B	0.094	-35.536	0.450
23	Arachidonate 5-lipoxygenase-activating protein	0.125	-31.982	0.445
24	Coagulation factor X	0.154	-28.426	0.439
25	Nuclear receptor coactivator 2	0.204	-23.363	0.438

Compound AS-144 has similar effects to AS-014 associated with blockade of potential-dependent calcium channels (Table 10). There may be local irritating effects.

Table 10. The results of predictive analysis of the AS-144 compound

№	Pa	Pi	Potential effect
1.	0.816	0.002	Calcium channel blocker (potential-dependent)
2.	0.718	0.002	Calcium channel blocker
3.	0.619	0.009	Antihypertensive
4.	0.575	0.012	Cardiotonic
5.	0.546	0.031	Antianginal
6.	0.477	0.005	Therapy of heart failure
7.	0.448	0.016	Anti-ischemic
8.	0.435	0.156	Cerebral anti-ischemic
9.	0.411	0.003	L-type calcium channel blocker
10.	0.397	0.043	Regulation of calcium transport

According to the results of molecular docking, the studied substance AS-144 potentially affects the processes of mitosis, proliferation and apoptosis (Table 11, rows 1, 5, 7, 8), homeostasis of glucose, lipoproteins and fatty acids (rows 2, 9, 16), blood clotting (rows 6, 19, 22), the transmission of intercellular signals (row 4), the production of amyloid precursor protein (row 3), the cascade of cell reactions to stress and immune response (rows 11, 13, 21), the regulation of the action of steroid and thyroid hormones (rows 10, 14, 17), affects the activity of stromelysin-1, contributing to the degradation of extracellular matrix proteins (row 12), binds to

potential-dependent calcium channels (row 15), orexin (row 24) and estrogen (row 25) receptors, inhibits angiotensin-converting enzyme (ACE) (row 23) and acetylcholinesterase (row 20). According to the results of molecular docking, AS-144 is metabolized through cytochrome P450 isoforms (row 18).

Table 11. Results of molecular docking of compound AS-144

№	Protein name	Pre-test assessment	ΔG_{bind} kcal/mol	Overall assessment
1	Induced myeloid leukemia cell differentiation protein Mcl-1	0.586	-28.008	0.866
2	3-hydroxy-3-methylglutaryl-coenzyme A reductase	0.580	-24.110	0.821
3	Beta-secretase 1	0.565	-25.500	0.820
4	Ephrin type-A receptor 2	0.418	-31.770	0.735
5	Bcl-2-like protein 1	0.473	-24.082	0.714
6	Coagulation factor VII	0.400	-25.656	0.656
7	E3 ubiquitin-protein ligase Mdm2	0.350	-26.787	0.618
8	Apoptosis regulator Bcl-2	0.326	-27.080	0.597
9	Free fatty acid receptor 1	0.250	-30.085	0.551
10	Neuropeptide Y receptor type 1	0.224	-32.399	0.548
11	Peptidyl-prolyl cis-trans isomerase FKBP5	0.243	-25.873	0.502
12	Stromelysin-1	0.174	-31.841	0.492
13	Nuclear receptor ROR-gamma	0.191	-29.879	0.490
14	Nuclear receptor coactivator 1	0.178	-30.646	0.484
15	Voltage-dependent L-type calcium channel subunit alpha-1D	0.179	-29.693	0.476
16	Peroxisome proliferator-activated receptor gamma	0.127	-34.543	0.472
17	Nuclear receptor coactivator 2	0.171	-29.856	0.469
18	Cytochrome P450 2C9	0.136	-32.849	0.464
19	Prothrombin	0.195	-26.862	0.464
20	Acetylcholinesterase	0.138	-31.363	0.451
21	Arachidonate 5-lipoxygenase-activating protein	0.149	-29.918	0.448
22	Coagulation factor X	0.162	-28.496	0.447
23	Angiotensin-converting enzyme	0.181	-26.315	0.444
24	Orexin/Hypocretin receptor type 1	0.142	-30.214	0.444
25	Estrogen receptor	0.130	-31.276	0.443

Compound AS-162 has effects similar to those of AS-014 related to the blockade of potential-dependent calcium channels (Table 12). There may be local irritant and oncogenic effects.

Table 12. The results of predictive analysis of the AS-162 compound

№	Pa	Pi	Potential effect
1.	0.695	0.003	Calcium channel blocker (potential-dependent)
2.	0.614	0.010	Antihypertensive
3.	0.608	0.023	Inhibition of insulin
4.	0.589	0.010	Cardiotonic
5.	0.584	0.003	Calcium channel blocker
6.	0.533	0.034	Antianginal
7.	0.458	0.005	Therapy of heart failure
8.	0.418	0.020	Anti-ischemic
9.	0.409	0.038	Regulation of calcium transport
10.	0.385	0.135	Inhibition of CYP2C8

According to the results of molecular docking, the studied substance AS-162 potentially affects the processes of mitosis, proliferation and apoptosis (Table 13, rows 1, 10, 12, 18), homeostasis of glucose, lipoproteins and fatty acids (rows 3, 5, 13, 17, 24), blood coagulability (rows 2, 6, 11), the transmission of intercellular signals (row 9), the production of the amyloid precursor protein (row 4), the cascade of cell reactions to stress and the immune response (rows 8, 19), the regulation of the action of steroid and thyroid hormones (rows 7, 15, 22), affects the cell response on oxidative stress (row 20), the activity of stromelysin-1, which promotes the degradation of extracellular matrix proteins (row 14), binds to MAP kinase (row 16), acetylcholinesterase (row 21), and estrogen (row 23) receptors. According to the results of molecular docking, AS-162 is metabolized through cytochrome P450 isoforms (row 25).

Table 13. Results of molecular docking of compound AS-162

№	Protein name	Pre-test assessment	ΔG_{bind} kcal/mol	Overall assessment
1	Bcl-2-like protein 1	0.525	-23.146	0.757
2	Coagulation factor VII	0.486	-21.860	0.704
3	Free fatty acid receptor 1	0.417	-28.290	0.700
4	Beta-secretase 1	0.436	-24.075	0.677
5	3-hydroxy-3-methylglutaryl-coenzyme A reductase	0.427	-21.556	0.643
6	Prothrombin	0.417	-22.419	0.641
7	Nuclear receptor coactivator 2	0.265	-29.749	0.562
8	Nuclear receptor ROR-gamma	0.284	-27.646	0.560
9	Ephrin type-A receptor 2	0.289	-26.244	0.552
10	E3 ubiquitin-protein ligase Mdm2	0.275	-26.637	0.541
11	Coagulation factor X	0.261	-26.541	0.526
12	Induced myeloid leukemia cell differentiation protein Mcl-1	0.278	-24.783	0.526
13	Peroxisome proliferator-activated receptor gamma	0.311	-20.948	0.520
14	Stromelysin-1	0.225	-28.754	0.512
15	Nuclear receptor coactivator 1	0.220	-27.111	0.491
16	Mitogen-activated protein kinase 14	0.243	-24.754	0.491
17	Peroxisome proliferator-activated receptor gamma	0.195	-28.901	0.484
18	Suppressor of tumorigenicity 14 protein	0.252	-22.743	0.479
19	Interleukin-2	0.219	-23.663	0.456
20	Kelch-like ECH-associated protein 1	0.218	-23.478	0.453
21	Acetylcholinesterase	0.150	-30.191	0.452
22	Neuropeptide Y receptor type 1	0.199	-25.161	0.451
23	Estrogen receptor	0.191	-25.515	0.446
24	Peroxisome proliferator-activated receptor delta	0.153	-29.247	0.446
25	Cytochrome P450 2B6	0.154	-28.676	0.441

Of the 6 compounds under consideration, SD1-874 has potential oral activity, according to Lipinski's criteria.

The results of predictive analysis and molecular docking demonstrate different results in terms of predicted potential effects. It is worth noting here that the predictor analysiscompares the structure of the studied compound with the already known drugs and bioactive molecules, while the molecular docking services predict which proteins and with what strength the studied substance can bind to in the body.

According to the results of predictive analysis, all the studied substances, with the exception of SD1-874, are potentially capable of blocking calcium channels. SD1-874 demonstrates the ability to influence lipid and carbohydrate metabolism, taking into account the results of *in silico* analysis.

When analyzing the data obtained during molecular docking, three of the most pronounced groups of proteins with which the studied samples can conjugate become noticeable: a group of proteins that regulate the processes of apoptosis, mitosis and DNA transcription, a group of proteins that affect blood clotting and a group of proteins that affect the metabolism of lipoproteins, lipids, and glucose. There is also the possibility of conjugation with calcium channel subunits; however, the probability of such an interaction by the molecular docking program is estimated as unlikely. All the studied compounds interact with various isoforms of cytochrome P450.

Most likely, when the studied 1,4-dihydropyridines are conjugated with specific proteins, their inhibition will occur. Given the extremely high binding force (ΔG_{bind} is less than -20 kcal/mol)), such a bond is likely to be stable and irreversible.

To recapitulate the preceding discussion, it can be assumed that the studied samples have anticoagulant properties by acting on several links of the blood coagulation system at once. A similar effect can be expected only in the case of oral bioavailability and passage through the cytochrome P450 system in an unchanged form with oral administration or in the case of parenteral administration of compounds.

If conjugation of the studied samples with coagulation factors does not occur, hypoglycemic/hypolipidemic effects or blocking of potential-dependent calcium channels are most likely.

The presence of the effects associated with the processes of mitosis, apoptosis, and DNA transcription seems unlikely, due to the strict regulation and control of these mechanisms at the intracellular level, as well as a high chance of conjugation of compounds with any targets before entering the cell.

Conclusion

According to the results of predictor analysis and the results of molecular docking, among the 6 compounds of a certain number of 1,4-dihydropyridines selected for analysis, compounds with lab code SD1-874 is considered the most promising for further study. This substance meets all Lipinski's criteria, which makes it possible for oral administration. Most likely, these compounds will have an anticoagulant effect by inhibiting several coagulation factors at once. Probably an interaction with potential-dependent calcium channels. In addition to the effect on the hemostasis system, it is impossible to exclude the presence of a number of additional pleiotropic effects, including hypolipidemic.

Compounds with lab codes SD1-874, F02-104, AS-143, AS-014, AS-144, and AS-162 are likely to be of interest for study as biologically active substances with parenteral administration. The range of their potential effects also includes anticoagulant, hypolipidemic, and hypotensive properties.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

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

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Author Contribution

- **Elena Yu. Bibik,** Doctor Habil. of Medical Sciences, Professor, Head of the Department of Fundamental and Clinical Pharmacology of the St. Luke Lugansk State Medical University, Lugansk, Russia; e-mail: helen_bibik@mail.ru; **ORCID ID:** https://orcid.org/0000-0001-7470-608X. Coordination of research, planning and writing the manuscript.
- **Ivan A. Nekrasa,** Candidate of Medical Sciences, LLC "IMC Clinic №.1"; Dmitrov, Russia; e-mail: ivannekrasa@mail.ru; **ORCID ID:** https://orcid.org/0000-0001-9980-126X. Conducting experiments, the analysis and interpretation of the data and facts obtained.
- **Vladislav V. Bibik,** educator of the Regional Center for the Development of Giftedness "Intellectual Reserve of the Republic"; Lugansk, Russia; e-mail: vvbibik09@gmail.com. The analysis and interpretation of the data and facts obtained.
- **Konstantin A. Frolov**, Candidate of Chemical Sciences, Associate Professor, Leading Chief Researcher at the Scientific Research Laboratory of St. Luke Luhansk State Medical University of the Ministry of Health of the Russian Federation, Associate Professor at the Department of Chemistry and High Technologies Vladimir Dahl Lugansk State Medical University, Lugansk, Russia; e-mail: ka.frolov@inbox.ru; **ORCID ID:** https://orcid.org/0000-0002-8045-7582. The analysis and interpretation of the data and facts obtained.
- **Sergej G. Krivokolysko,** Doctor Habil. of Chemical Sciences, Professor, Chief Researcher at the Scientific Research Laboratory of St. Luke Luhansk State Medical University of the Ministry of Health of the Russian Federation, Head of the Department of Chemistry and Innovative Technologies, Head of the ChemEx Research Laboratory, Vladimir Dahl Lugansk State Medical University, Lugansk, Russia; e-mail: ksg-group-lugansk@mail.ru; **ORCID ID:** https://orcid.org/0000-0001-9879-9217. The analysis and interpretation of the data and facts obtained.