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Research Article

Searching for novel antagonists of adenosine A1 receptors among azolo[1,5-a]pyrimidine nitro derivatives

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Abstract

Introduction: Ligands of adenosine A_1Rs are potential candidates for the development of drugs for the treatment of paroxysmal supraventricular tachycardia, angina pectoris, hypertriglyceridemia, type 2 diabetes mellitus, neuropathic pain, and heart failure. At the same time, there is a deficiency of drugs that can regulate the functions of A_1 receptors. A number of A_1-antagonists are at the various stages of clinical trials; other drugs are not very selective or are characterized by an insufficient breadth of their therapeutic action. Therefore, the search for new medicinal compounds for the prevention and treatment of A_1-depended diseases among nitro derivatives of tetrazolo[1,5-*a*]pyrimidine and 1,2,4-triazolo[1,5-*a*]pyrimidine is of scientific interest.

Materials and methods: The search for active compounds was carried out by *in silico* and *in vitro* methods. At the first stage, a computer forecast of A_1-antagonistic activity was carried out using the Microcosm BioS software. At the second stage, the prediction results were verified *in vitro* in a model of isolated mouse atria.

Results and discussion: Based on the results of the prediction by the method of maximum similarity to standards, the most active compounds **III**, **VIII**, and **XVII** were selected. After testing the prediction results by the isolated atria method, the compound **VIII** was characterized by A_1-blocking effect *in vitro* at a concentration of 10 μmol/L.

Conclusion: The most promising compound with A_1-blocking effect *in vitro* was identified; it is a derivative of tetrazolo[1,5-*a*]pyrimidine under the code of **VIII**. It is of interest for us for further in-depth study of its pharmacological properties.

Keywords

adenosine 1 type receptor, isolated tissue, Microcosm Bios, tetrazolo[1,5- a]pyrimidine, 1,2,4-triazolo[1,5-a]pyrimidine.

Introduction

Adenosine receptors (ARs) are targets for the development of new methods of pharmacological correction of various diseases (Manjunath et al. 2009; Jamwal et al. 2019). Adenosine is an endogenous purine-based nucleoside expressed nearly in all body tissues (Saini et al. 2022). It exhibits multiple biological effects and regulates a number of physiological functions, including the functioning of the cardiovascular system (Headrick et al. 2011; Albrecht-Küpper et al. 2012; Guieu et al. 2020). It is known that adenosine regulates myocardial function and the intensity of coronary circulation, and also has a pronounced vasodilatory effect (Reiss et al. 2019). At the same time, the clinical potential of A_1Rs regulation has not been fully realized to date. In modern medicine, only a few drugs with A_1 antagonistic properties are used.

Caffeine causes most of its biological effects via antagonizing all types of ARs. When acting as nonselective AR antagonist (Chen et al. 2017), caffeine, used acutely, is doing the opposite of activation of adenosine receptors, due to removal of the adenosinergic tonus (Ribeiro and Sebastião 2010). Synthetic xanthines, analogues of caffeine – Tonapofylline (BG-9928), Rolofylline (KW-3902 or MK-7418) and Derenofylline (SLV-320) were first announced in 2010–2012 and went through the stages of clinical trials (Sureechatchaiyan et al. 2018) for the treatment of congestive heart failure, acute decompensated heart failure and renal dysfunction (Pang et al. 2011). These compounds are more selective A_1R antagonists (Ensor and Russell 2010; Teerlink et al. 2012).

Single administration of Rolofylline in patients with heart failure and impaired renal function produced a consistently increased diuresis and natriuresis without compromising renal function (Ponikowski et al. 2010). In phase III clinical trials, the A_1R antagonist Rolofylline was not sufficiently effective in worsening renal function in patients with acute heart failure (Voors et al. 2011). Clinical trials of Derenophylline and Tonapofylline were terminated for reasons beyond the effects of the drugs. Taking this into account, the issue of developing and creating new A_1-antagonists remains very relevant.

In this regard, this study is focused on continuing the search for new A_1R antagonists among pyrimidine derivatives as possible drug candidates for subsequent use in medical practice. Analysis of the chemical structure of known A_1-antagonists (Tonapofylline and Rolofylline are derivatives of imidazopyrimidines and Derenofylline is pyrrolo[2,3-d]pyrimidine) suggests a high prospect of searching for potential A_1R antagonists among pyrimidine derivatives. The current investigation is aimed to study the A_1R antagonism potential of earlier synthesized nitro derivatives of tetrazolo[1,5-*a*]pyrimidine (Savateev et al. 2018) and 1,2,4-triazolo[1,5-*a*]pyrimidine (Rusinov et al. 2017).

Materials and methods

Experimental design

At the first stage, a database was formed *in silico* on the structure of the reference ligands of adenosine A_1 receptors studied by the world scientific community using the search engines IUPHAR, Tocris, SelleckChem. Thus, 20 selective A_1 adenosine receptor antagonists were selected. Then, a database was formed on the structure of 25 new chemical compounds, derivatives of azolo[1,5-*a*]pyrimidine. The data on the structure of 25 new compounds were collected and generated using ChemFinder 9.0, a ChemOffice 9.0 software package (URL: http://www.cambridgesoft.com/12).

The processing of the data set and their translation into QL language descriptors were carried out using the utilities of the IT Microcosm software package; the following modules were used: ActUtil, TranQL2, and MakeData (Vassiliev et al. 2014). First, using the ActUtil utility, a data set consisting of * .actv and * .tba files was created. Second, the VMNC.sdf file was processed in the TranQL2 module to obtain * .qll files. At the last stage, the final data set was obtained using the MakeData utility.

The most active substances according to *in silico* forecast were tested for their A_1-antagonistic activity with isolated tissue technique *in vitro*.

Predicted affinity for adenosine A_1 receptors of new compounds using the Microcosm BioS software

In this study, the prediction of affinity for adenosine A_1 receptors was carried out using the Microcosm BioS v.18.1.9 system, which includes the original QSAR database containing verified, structured and processed information on the chemical structure and activity level of the known compounds studied by the world scientific community at various types of biological activity.

The specified QSAR database was formed outside the scope of this study, using information obtained from three well-known international search engines: ChEMBL (URL: https://www.ebi.ac.uk/chembl/), BindingDB (URL: https://www.bindingdb.org/) and PubChem (URL: https://pubchem.ncbi.nlm.nih.gov). The primary dataset was checked for correct chemical structural formulas, so incorrect and duplicate entries were removed from it.

Experimental animals

The experiments were carried out on 30 white outbred mice m=18–30 g, obtained from the Rappolovo Nursery, Leningrad region (Russia). The animals were kept in a vivarium with a natural light regimen on a standard diet of laboratory animals, with access to food and water *ad libitum*. The vivarium maintained standard conditions in accordance with Order No. 51 of August 29, 2014 of the Chief State Sanitary Doctor of the Russian Federation

"On Approval of Sanitary Regulations 2.2.1.3218-14 "Sanitary and Epidemiological Requirements for Managing, Equipping and Maintaining Experimental Biological Clinics (Vivariums)" on a special hygienic wood filler (LLC Production Complex GlavRezerv). Twelve hours before the start of the experiment, the animals were deprived of access to food, while access to water remained free. The experimental procedures on animals were carried out in accordance with the Local Ethics Committee of Volgograd State Medical University, Volgograd, Russia (Minutes No. IRB 00005839 IORG 0004900 (OHRP)). All the experiments were carried out in accordance with "The Guidelines for Conducting Preclinical Studies of Drugs" (Mironov 2012).

Isolated atria technique

After cervical dislocation of the rodents, the heart was removed and both atria were isolated. The isolated samples of the left and right atria were fixed in a 20 ml bath, filled with Krebs-Henseleit nutrient solution with constant oxygenation of 95% O_2-5% CO_2 and a temperature of 37 °C in a 4-channel system for maintaining the vital functions of isolated tissues TISSUEBATH4 (Biopac Systems, Inc., USA). The isolated atria were fixed on an isometric sensor TSD125C with a sensitivity range of 0–50 g at an isometric load of 1 g. The organ was left for adaptation for 45–60 min before the start of the experiment. During the adaptation period and the subsequent experiment, the buffer solution in the bath was replaced every 10–15 min.

A_1-antagonistic activity of compounds under study

The A_1-antagonistic activity of novel nitro derivatives of azolo[1,5-*a*]pyrimidines was investigated by addition of the tested compound (200 µl) 3 min before the introduction of adenosine (200 µl) with an exposure for 30 s before a registered decrease in chronotropism of atria, working in their own rhythm (without stimulation). Between each administration of adenosine, the isolated atrial sample was left to relax for at least 10–15 min to return the atrial chronotropism to the initial level. The reference drug was caffeine at an equimolar concentration of 10 µmol/L. The A_1-antagonistic effect of the test substances and the control sample was assessed by a degree of suppression of adenosine-induced decrease in chronotropism of the isolated atrial tissue in comparison with the effect of adenosine obtained in control measurements (Δ%).

Contractions of isolated atria were recorded using AcqKnowledge 4.0 software (Biopac Systems, Inc., USA). The number of isolated atria contractions was measured over a 30-second interval with subsequent calculation of the heart rate. The amount of atrial chronotropism suppression (Δ%) was calculated by the formula:

$$\Delta\,\% = 100 - \left(\frac{\Delta HR_{control}}{\Delta HR_{treated}} \times 100\right),$$

where $\Delta HR_{control}$ – the difference between the baseline heart rate and the heart rate calculated after adenosine administration; $\Delta HR_{treated}$ – the difference between the baseline heart rate and the heart rate calculated after adenosine administration in mice under the influence of the test compounds.

Statistical analysis

Statistical analysis of the obtained data was carried out in the GraphPad Prism 6.0 software using the Kruskal-Wallis test and post hoc Dunn's test. The data are presented as mean ± standard error of mean (M±SEM). The $p<0.05$ values were considered statistically significant.

Results and discussion

Results of *in silico* prediction of the adenosine A_1 activity levels of new chemical compounds.

On this basis, the QSAR database was calculated using six specially created programs, containing the QL-descriptor representation of chemical structural information, in the form of working files in the format developed earlier when creating the IT Microcosm package (Vassiliev et al. 2014).

The QSAR database obtained in this way includes information on the structure of 625888 known chemical compounds tested by world scientific studies for 11509 different types of biological activity, with details of a type of biotarget, test organism and the measured activity indicator. In total, this database contains information on 6016 biotargets, on 325 species of test organisms, indicating the quantitative values of activity for 4 different indicators.

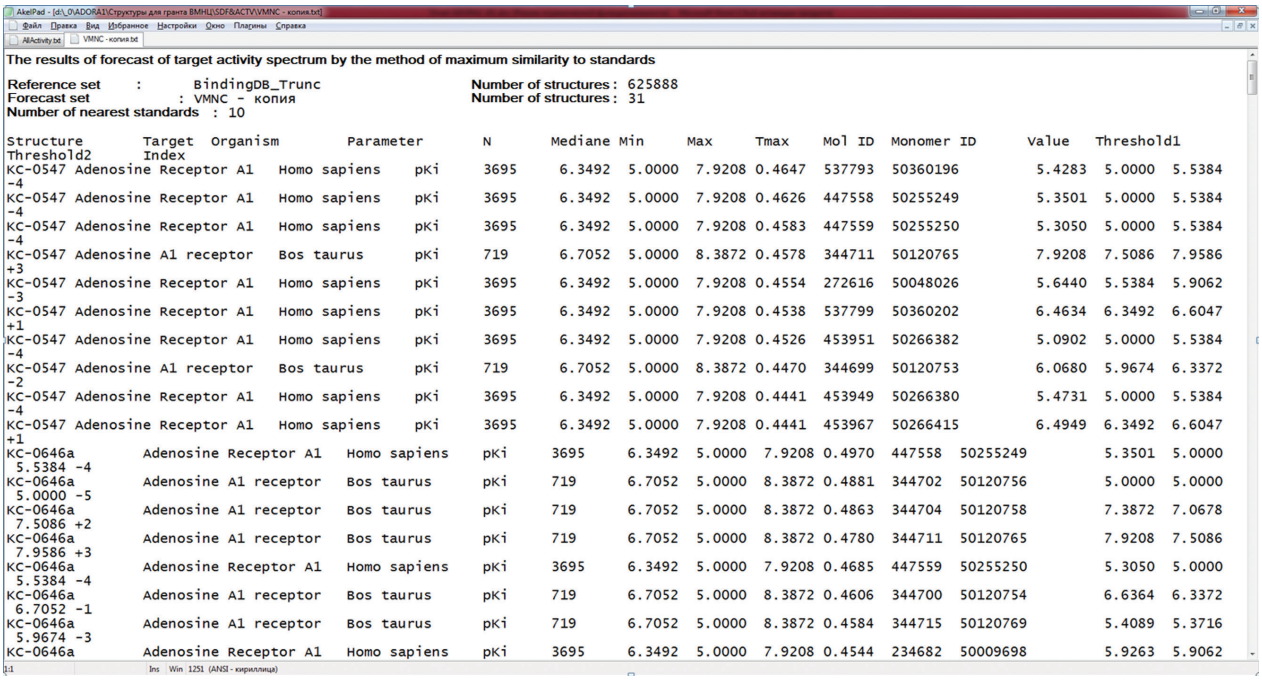
The specified QSAR base is part of the Microcosm BioS system, designed to predict the spectrum of targeted biological activity of new chemical compounds.

The QSAR-base of the Microcosm Bios v18.1.9 system contains information on the structure and level of affinity for the adenosine A_1 receptor of 7455 compounds studied in experimental tests on five different organisms, including data for 5373 compounds for *Homo sapiens*. The calculation of the predicted spectrum of targeted biological activity of new chemical compounds was carried out using the original Microcosm BioS system by the method of maximum similarity to standards. The well-known compounds studied by the world scientific community for A_1-antagonistic activity were used as standards. Information about these compounds was accumulated in the above-described Microcosm BioS QSAR database.

The forecast results were saved as a tab-delimited text file; part of the primary listing is shown in Fig. 1.

The final results of the prediction in Microcosm BioS of new compounds adenosine A_1 receptor affinity are shown in Table 1.

In total, according to the prediction data by the method of maximum structural similarity to the standards,



The results of forecast of target activity spectrum by the method of maximum similarity to standards

Reference set : BindingDB_Trunc Number of structures: 625888
Forecast set : VMNC - копия Number of structures: 31
Number of nearest standards : 10

Structure	Target	Organism	Parameter	N	Mediane	Min	Max	Tmax	Mol ID	Monomer ID	Value	Threshold1	Threshold2	Index
KC-0547	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4647	537793	50360196	5.4283	5.0000	5.5384	-4
KC-0547	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4626	447558	50255249	5.3501	5.0000	5.5384	-4
KC-0547	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4583	447559	50255250	5.3050	5.0000	5.5384	-4
KC-0547	Adenosine A1 receptor	Bos taurus	pKi	719	6.7052	5.0000	8.3872	0.4578	344711	50120765	7.9208	7.5086	7.9586	+3
KC-0547	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4554	272616	50048026	5.6440	5.5384	5.9062	-3
KC-0547	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4538	537799	50360202	6.4634	6.3492	6.6047	+1
KC-0547	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4526	453951	50266382	5.0902	5.0000	5.5384	-4
KC-0547	Adenosine A1 receptor	Bos taurus	pKi	719	6.7052	5.0000	8.3872	0.4470	344699	50120753	6.0680	5.9674	6.3372	-2
KC-0547	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4441	453949	50266380	5.4731	5.0000	5.5384	-4
KC-0547	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4441	453967	50266415	6.4949	6.3492	6.6047	+1
KC-0646a	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4970	447558	50255249	5.3501	5.0000	5.5384	-4
KC-0646a	Adenosine A1 receptor	Bos taurus	pKi	719	6.7052	5.0000	8.3872	0.4881	344702	50120756	5.0000	5.0000	5.0000	-5
KC-0646a	Adenosine A1 receptor	Bos taurus	pKi	719	6.7052	5.0000	8.3872	0.4863	344704	50120758	7.3872	7.0678	7.5086	+2
KC-0646a	Adenosine A1 receptor	Bos taurus	pKi	719	6.7052	5.0000	8.3872	0.4780	344711	50120765	7.9208	7.5086	7.9586	+3
KC-0646a	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4685	447559	50255250	5.3050	5.0000	5.5384	-4
KC-0646a	Adenosine A1 receptor	Bos taurus	pKi	719	6.7052	5.0000	8.3872	0.4606	344700	50120754	6.6364	6.3372	6.7052	-1
KC-0646a	Adenosine A1 receptor	Bos taurus	pKi	719	6.7052	5.0000	8.3872	0.4584	344715	50120769	5.4089	5.3716	5.9674	-3
KC-0646a	Adenosine Receptor A1	Homo sapiens	pKi	3695	6.3492	5.0000	7.9208	0.4544	234682	50009698	5.9263	5.9062		

Figure 1. The beginning of listing the results of the spectrum prediction of A_1-antagonistic activity levels in the Microcosm BioS v.18.1.9 system.

Table 1. Prediction of adenosine A_1 receptor affinity by the method of maximum similarity to standards

Number	Code	Ind	$Ind_{20\%}$	Ind_{Med}
1	**III**	0.5	0.6	2
2	**VIII**	1.2	1.3	2
3	**XVII**	0.4	0.5	1
4	**XI**	0.1	0.3	1
5	**X**	0.4	0.4	1
6	**IX**	0.4	0.4	1
7	**XII**	0.6	0.6	1
8	**1D**	-0.9	-1.1	-2
9	**II**	-1.8	-2.0	-2
10	**XIV**	-1.9	-2.1	-2
11	**XIII**	-1.1	-1.3	-2
12	**VI**	-1.4	-1.6	-2
13	**IV**	-2.5	-2.5	-3
14	**VII**	-1.6	-1.9	-3
15	**1G**	-1.9	-2.0	-3
16	**I**	-2.0	-2.4	-4
17	**V**	-2.9	-3.1	-4
18	**1A**	-2.8	-3.0	-4
19	**1E**	-3.0	-3.3	-4
20	**XVI**	-2.5	-2.9	-4
21	**XV**	-3.7	-3.9	-4
22	**1B**	-3.9	-4.4	-5
23	**1C**	-3.2	-3.9	-5
24	**1H**	-4.1	-4.3	-5
25	**1F**	-4.5	-4.9	-5

Note: Ind – average value of activity level indices; $Ind_{20\%}$ – 20% truncated mean of activity level indices; Ind_{Med} – median activity indices.

7 compounds (highlighted in color) are promising for studying their adenosine A_1 receptor affinity, having three non-negative averaged estimates in total. The most interesting for experimental testing are 3 compounds (highlighted in green), in which all three calculated scores are at least 2 points, which corresponds to a sufficiently high activity.

Results of testing new compounds on isolated tissue model

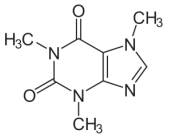
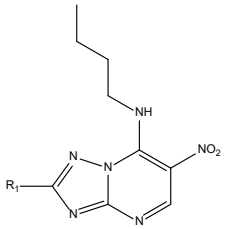
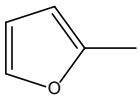
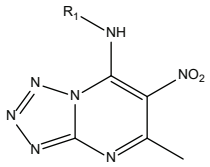
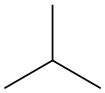
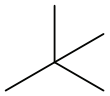
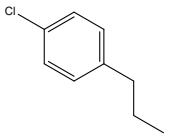
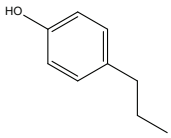
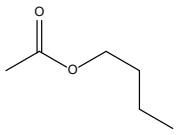
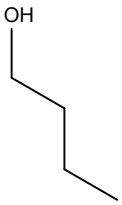
The results of the study of A_1-antagonistic activity of 6 nitro derivatives of tetrazolo[1,5-*a*]pyrimidine and 1 derivative of 1,2,4-triazolo[1,5-*a*]pyrimidine are shown in Table 2.

Only one of the seven tested compounds was characterized by an A_1-blocking effect *in vitro* at a concentration of 10 μmol/L: **VIII**. It is confirmed by more than 45% suppression relative to the control measurements, and, compared to the reference drug caffeine, A_1-blocking effect of compounds was inferior by 1.3 times. Compounds **XII** and **IX** did not show any A_1-antagonistic activity. Derivative of 1,2,4-triazolo[1,5-*a*]pyrimidine **III** was inferior to caffeine in terms of its antagonistic activity against A_1-adenosine receptors by 1.5 times.

Conclusion

In the course of the study, *in silico* prediction of adenosine A_1 receptor affinity of 25 new compounds was made using the method of maximum structural similarity to the reference standards. As a result of the prediction, 7 promising compounds with the expected moderate or high A_1-antagonistic activity were identified, which were recommended for experimental studies. Of these, three

Table 2. A_1-inhibitory activity of compounds under study (at a concentration of 10 μmol/L)

Compound	R_1	Inhibition of adenosine negative chronotropic effect, Δ% (M±SEM)
	Comparison drug	
Caffeine		60.5±3.7
	 derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidine	
III		40.1±3.0
	 derivatives of tetrazolo[1,5-*a*]pyrimidine	
VIII		45.9±10.7
IX		0.0±0.0*
X		10.5±3.0*
XI		38.3±5.6
XII		0.0±0.0*
XVII		28.1±3.0

Note: * – differences are significant compared to caffeine ($p<0.05$, Kruskal-Wallis test, post hoc Dunn`s test).

compounds were recommended to be tested for their A_1-antagonistic activity as a priority.

Seven new nitro derivatives of azolo[1,5-*a*]pyrimidines were tested for A_1-antagonistic activity *in vitro*. The results of *in silico* prediction of activity of the compounds under study were confirmed for compound **VIII**. In terms of isolated atria technique, the inhibition of adenosine negative chronotropic effect was about 45%, under the influence of this substance. So, compound **VIII** is of interest for us for further in-depth study of its pharmacological properties.

Conflict of interests

The authors declare no conflict of interests.

Acknowledgements

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