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ANTIBACTERIAL AND MAO-INHIBITING PROPERTIES OF NEW STYRYL DERIVATIVES OF PYRIMIDINES, QUINAZOLINES AND BIS-QUINAZOLINES

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The antibacterial properties of new pyrimidines, styrylderivatives of pyrimidines, quinazolines and bis-quinazolines were studied with respect to four strains of gram-positive and gram-negative bacteria. It has been established that styryl derivatives of pyrimidines, quinazolines and bis-quinazolines show some antibacterial and antimonoaminooxidase activity. An attempt was made to compare the biological properties of the compounds with known integral molecular descriptors: lipophilicity, molar refraction, polarizability, molar volume, index of refraction and surface tension obtained using the ACD / ChemSketch software (version ACD / Labs 6.00). In the series of styrylquinazolines, a compound with high antimonoamine oxidase activity has been identified.

Styrylpyrimidines – styrylderivatives of quinazolines and bisquinazolines – antibacterial activity – antimonoaminooxidase activity – molecular descriptors – structure-activity relations

Հետազոտվել են նոր պիրիմիդինների, նրանց ստիրիլածանցյալների և պիրիդո[1,2-a] պիրիմիդինների հակաբակտերիային հատկությունները գրամդրական և գրամբացասական բակտերիաների չորս շտամների նկատմամբ: Հաստատվել է, որ նշված շարքերի միացությունները ցուցաբերում են որոշակի ակտիվություն: Փորձ է արվել համեմատելու միացությունների հակաբակտերիային հատկությունները հայտնի ինտեգրալային մոլեկուլային դեսկրիպտորների՝ լիպոֆիլության, մոլեկուլային ռեֆրակցման և մոլյար ծավալի հետ ստացված ACD / ChemSketch (տարբերակ ACD / Labs 6.00) ծրագրային փաթեթի օգնությամբ:

Ստիրիլպիրիմիդիններ պիրիդո[1,2-a]պիրիմիդիններ ստիրիլածանցյալներ մոլեկուլային դեսկրիպտորներ կառուցվածք ակտիվություն

Изучены антибактериальные и антимоноаминооксидазные свойства стирилпроизводных пиримидинов, хиназолинов и бис-хиназолинов в отношении четырех штаммов грамположительных и грамотрицательных бактерий. Было установлено, что стирилпроизводные пиримидинов, хиназолинов и бис-хиназолинов обладают некоторой антибактериальной и антимоноаминооксидазной активностью. Была предпринята попытка сравнить биологические свойства соединений с известными интегральными молекулярными дескрипторами: липофильностью, молярной рефракцией, поляризуемостью, молярным объемом, индексом рефракции и поверхностным натяжением, полученными с использованием программного продукта ACD / ChemSketch (версия ACD / Labs 6.00). В ряду стирилхиназолинов выявлено соединение с высокой антимоноаминооксидазной активностью.

Стирилпиримидины – стирилпроизводные хиназолинов и бис-хиназолинов – антибактериальная активность – антимоноаминооксидазная активность – молекулярные дескрипторы – зависимость структура – активность

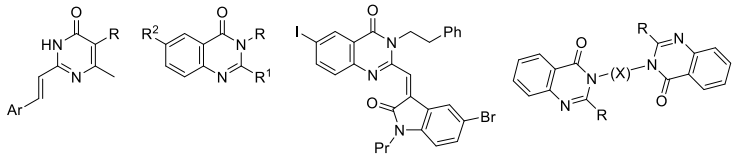
The search for new drugs based on substituted pyrimidines and condensed pyrimidines is associated with the widespread distribution in wildlife and the high and versatile biological activity of many of their derivatives [4]. In recent years, quinazolines have attracted considerable attention, many of whose derivatives exhibit a wide spectrum of biological activity. Taking this into account, and in continuation of ongoing studies on the synthesis and study of the biological properties of substituted pyrimidines and quinazolines [1-3], in this study we present the results of tests of the antibacterial and antimonoamine oxidase properties of new substituted pyrimidines, quinazolines and bis-quinazolines. In addition, a qualitative consideration of the possible relationship between the biological properties of synthesized compounds and several calculated physicochemical descriptors was carried out, and preliminary generalizations on the relationship between the structure and biological activity were proposed. It is known that the search for new low-toxic and active antibacterial drugs continues to be an urgent problem of medical and pharmaceutical chemistry and medicine. It is also very important to introduce new antidepressant drugs into medical practice in light of the constant increase in the growth of mental illness. In addition, it seems promising to study the possible parallelism between the inhibition of growth of a number of strains of gram-positive and gram-negative bacteria and the level of inhibition of monoamine oxidase (MAO). The latter assumption is supported by data on the relationship between MAO-inhibiting and antitumor activities for a number of compounds [5], and microbial models can act as preliminary test systems for the primary detection of antitumor activity. That is, the study of the antimonoamine oxidase activity of the synthesized compounds may also be useful as a preliminary available test system for detecting antitumor activity, since the direct study of the latter activity is much more laborious.

Materials and methods. The antibacterial activity of the compounds was studied by the methods of "diffusion in agar" according to the described method [6]. In the experiments, standard reference strains of microorganisms were used (L.A. Tarasevich State Institute of Medical Biological Preparations, Russia): two strains of gram-positive staphylococcus (*Staphylococcus aureus 209p* and *S. aureus 1*) and gram-negative bacilli (*Shigella flexneri 6858, Esherichia coli 0-55*), control – antibacterial drug furazolidone.

The source of monoamineoxidase (MAO) was 50 % rat brain homogenate, which was obtained by homogenizing the brain in a glass homogenizer with an equal by weight volume of 2.5 % Arcopal solution [3]. Serotonin (5-OT) creatinine sulfate monohydrate was used as a substrate, which was added to the samples after a 30-minute preincubation of the enzyme with the test substance at room temperature.Each compound was tested in 3-4 experiments, from which the average data were derived, the control drug – indopane. Molecular descriptors were obtained using the computer program ACD / ChemSketch (version ACD / Labs 6.00).

Results and Discussion. The chemical structures and results of biological studies of pyrimidines **1a-d**, quinazolines **2a-t** and bis-quinazolines **3a-l** are shown in the tab. 1.

Substituted pyrimidines 1a-d exhibit some antibacterial properties in all four strains; however, these properties depend little both on the substituents at position 5 of the pyrimidine ring and on the number of chlorine atoms in the styryl group. Since the numerical values of the calculated descriptors of the compounds are quite close, it can be assumed that the revealed relatively small antibacterial effect is due to a greater extent to the pyrimidine fragment and the styryl group at position 2 of the ring, rather than to substituents in the side chains of the compounds. Most of the substituted quinazolines 2a-t, regardless of the substituents in the ring and the size of the physicochemical descriptors, do not exhibit antibacterial properties at all.



1a-d **2a-s** **2t** **3a-l**

1a-d: R, Ar = *n*-Amyl, 4-ClC_6H_4 **(a)**, *n*-Amyl, 2,4-$Cl_2C_6H_3$ **(b),** CH_2Ph, 4-ClC_6H_4 **(c)**, CH_2Ph, 2,4-$Cl_2C_6H_4$ **(d).**

2a-t: R,R^1,R^2 = CH_2CH_2Ph, Me, I **(a)**, 4-$NMe_2C_6H_4$, Me, H **(b)**, 4-$SO_2NH_2C_6H_4$, Me, H **(c)**, 2-(3-Me-N^1-PhC_3HN_2), Me, H **(d)**, CH_2CH_2Ph, PhCH=CH, I **(e),** CH_2CH_2Ph, 4-ClC_6H_4CH=CH, I **(f)**,CH_2CH_2Ph, 2,4-$Cl_2C_6H_3CH$=CH, I **(g)**, CH_2CH_2Ph, 4-$NMe_2C_6H_4CH$=CH), I **(h),** CH_2CH_2Ph, 4-$NO_2C_6H_4CH$=CH, I **(i)**, CH_2CH_2Ph, 4-*i*-PrC_6H_4CH=CH, I **(j)**, 4-$NMe_2C_6H_4$, 4-ClC_6H_4CH=CH, H **(k)**, 4-$NMe_2C_6H_4$, 2,4-$Cl_2C_6H_3CH$=CH, H **(l)**,4-$NMe_2C_6H_4$, 4-$NMe_2C_6H_4CH$=CH, H **(m)**, 4-$SO_2NH_2C_6H_4$, 3-$NO_2C_6H_4CH$=CH, H **(n)**, 3-methyl-1-phenyl-1*H*-pyrazol-5-yl-, 4-ClC_6H_4CH=CH, H **(o)**, 3-methyl-1-phenyl-1*H*-pyrazol-5-yl-, 2,4-$Cl_2C_6H_3CH$=CH, H **(p)**, CH_2CH_2Ph,1-methyl-1*H*-indol-3-yl-CH=CH, I **(q),** 4-ClC_6H_4, 5-nitrofuran-2-yl-CH=CH, I **(r),** 2-MeC_6H_4, 5-nitrofuran-2-yl-CH=CH, H **(s)**.

3a-l: R, X = Me, $(CH_2)_4$ **(a)**, 4-ClC_6H_4CH=CH, $(CH_2)_4$ **(b)**, 2,4-$Cl_2C_6H_3CH$=CH, $(CH_2)_4$ **(c)**, PhCH=CH, $CH_2CH_2N(Ac)CH_2CH_2$ **(d)**, 4-$NO_2C_6H_4CH$=CH, $CH_2CH_2N(Ac)CH_2CH_2$ **(e)**, Me, $CH_2CH_2\{N[2,4\text{-}(NO_2)_2C_6H_3]\}CH_2CH_2$ **(f)**, Me, $(CH_2)_6$ **(g)**, PhCH=CH, $(CH_2)_6$ **(h)**, 4-FC_6H_4CH=CH, $(CH_2)_6$ **(i)**, 2,4-$Cl_2C_6H_3CH$=CH, $(CH_2)_6$ **(j)**, thiophen-2-yl-CH=CH, $(CH_2)_6$ **(k)**, pyridin-3-yl-CH=CH, $(CH_2)_6$ **(l)**.

Only in compounds 2n, 2r, and 2s, which contain a fragment of known antibacterial drugs, sulfonamide and nitrofuran, weak antibacterial properties can be noted. In this series, the distinct appearance in some of the compounds (2f, 2g, 2o, 2p, 2q) of pronounced antimonoamine oxidase properties (inhibition of MAO activity within 33-52 %) in the complete absence of antibacterial properties is noteworthy. Moreover, compound 2h is a fairly strong MAO inhibitor, and the derivative with an iodine atom in the 2i ring is a very strong MAO inhibitor, blocking the enzyme activity by 91 %. Note that the latter compound is significantly more active in anti-MAO activity than the known reference drug indopane (inhibition of MAO activity by 86 %). In the indicated series of compounds, the values of the molar refraction descriptor MR are in the range 128.07 ± 0.5sm3-138.5 ± 0.5sm3, the polarizability P is in the range 50.77-54.91 10-24 cm3, and for other descriptors, including the lipophilicity coefficient LogP, the scatter of parameters is higher. Regarding antibacterial activity, the patterns in the values of physicochemical descriptors are less obvious. The antibacterial activity of bis-quinazolines 3a-l is insignificant, does not depend on the presence of a styryl moiety, and weakly changes when passing from a four-membered methylene linker (compounds 3a-c) to a six-membered one (compounds 3g-l). The greatest effect on the antibacterial activity of bis-quinazolines is exerted by the introduction into the molecule of a five-membered N-diethylamine linker and groups containing an NO2 group (compounds 3e, 3f). Thus, the introduction of a 4-nitrostyrile group into compound 3d leads to a significant increase in antibacterial activity against all used strains; The substitution of the central nitrogen atom of the linker with a 2,4-dinitrophenyl group (compound 3f) has a similar effect.

Table 1. Antibacterial and antimonoaminooxidase (antiMAO) activity and calculated physicochemical descriptors

C	Antibacterial activity, mm Strains				MAO, %*	LogP	MR*	P*	MV*	IR*	ST*
	A	B	C	D							
1	2	3	4	5	6	7	8	9	10	11	12
1a	10	13	11	10	-	5.86±0.63	91.59	36.31	279.6	1.568	38.9
1b	13	13	13	13	-	6.47±0.64	96.19	38.13	288.9	1.580	40.2
1c	14	14	11	10	-	5.46±0.64	98.44	39.02	284.1	1.609	43.2
1d	12	12	10	10	-	6.07±0.63	103.04	40.85	293.4	1.619	44.4
2a	0	0	0	0	16	2.83±0.64	93.57	37.09	250.2	1.670	48.6
2b	0	0	0	0	-	1.26±0.62	84.50	33.50	241.7	1.616	42.5
2c	0	0	0	0	-	-0.42±0.62	83.37	33.05	217.5	1.692	61.5
2d	10	10	10	10	-	0.86±0.66	94.41	37.42	250.9	1.676	49.9
2e	0	0	0	0	-	5.56±0.66	123.47	48.94	335.1	1.658	48.4
2f	0	0	0	0	51	6.15±0.66	128.07	50.77	344.3	1.666	49.3
2g	0	0	0	0	51	6.76±0.66	132.67	52.59	353.6	1.673	50.2
2h	0	0	0	0	91	5.67±0.66	136.27	54.02	376.2	1.644	46.1
2i	0	0	0	0	74	5.29±0.66	129.13	51.19	340.3	1.683	55.6
2j	0	0	0	0	-	6.90±0.66	136.93	54.28	381.5	1.636	44.4
2k	10	10	10	10	-	4.59±0.64	119.00	47.17	335.8	1.626	44.9
2l	0	0	10	10	-	5.20±0.64	123.60	49.00	345.0	1.635	45.8
2m	0	0	10	13	-	4.10±0.64	127.21	50.43	367.6	1.608	42.1
2n	10	10	12	0	-	2.05±0.64	118.93	47.14	307.5	1.700	66.3
2o	0	12	0	0	52	4.19±0.68	128.91	51.10	344.9	1.670	50.3
2p	0	0	10	10	33	4.80±0.68	133.51	52.93	354.2	1.677	51.2
2q	0	0	0	0	34	5.88±0.66	138.52	54.91	364.6	1.684	50.4
2r	11	11	11	10	-	4.96±0.67	116.68	46.25	291.8	1.731	63.2
2s	11	10	12	0	-	3.36±0.64	103.85	41.17	280.2	1.663	54.8
2t	10	10	10	10	-	6.50±0.78	151.54	60.07	390.4	1.703	54.2
3a	14	13	13	11	63	0.49±0.73	109.09	43.24	296.3	1.657	50.1
3b	0	0	0	0	51	7.14±0.79	178.09	70.60	484.0	1.657	50.8
3c	14	13	13	11	63	8.36±0.80	187.29	74.25	502.5	1.668	52.0
3d	10	10	10	10	-	4.78±0.82	182.73	72.44	504.7	1.643	50.3
3e	18	18	18	16	-	4.24±0.84	194.05	76.93	514.9	1.677	60.3
3f	17	17	17	17	-	1.66±0.75	149.47	59.25	385.2	1.703	64.2
3g	10	12	12	13	64	1.66±0.75	118.31	46.90	328.4	1.639	48.2
3h	10	14	12	10	62	6.71±0.77	178.11	70.60	497.6	1.634	48.2
3i	0	0	0	0	47	6.81±0.86	177.85	70.50	503.2	1.624	46.2
3j	0	0	0	0	62	9.12±0.80	196.51	77.90	534.5	1.656	50.8
3k	0	0	0	0	-	6.07±0.80	175.29	69.49	462.4	1.682	54.4
3l	10	12	10	11	9	4.23±0.78	175.00	69.37	474.8	1.658	51.8
F	25	24	24	24	-	-0.04±0.41	50.61	20.06	135.5	1.669	73.5
I	-	-	-	-	86	1.73±0.22	56.20	22.28	155.2	1.643	50.3

Strains. A: *S. aureus 209 p*; B: *S. aureus 1*; C: *S. flexneri* 6858; D: *E.coli 0-55*.
MAO: inhibition of monoaminooxidase (MAO), concentration 1 мкмоль/мл.
MR* (Molar Refractivity): N±0.5sm^3; P*(Polarizability) : N±0.5 10^{-24} sm^3;
MV* (Molar Volume):N±7.0 sm^3; IR* (Index of Refraction): N±0,05;ST*
(Surface Tension) : N±0,07 *dyne/sm*
F – furazolidone, **I** – indopane.

A number of bis-quinazolines linked by methylene units of various lengths also differ little in their ability to inhibit MAO. In this series of compounds, the relationships between the values of physicochemical descriptors and the biological activity of compounds are not obvious.

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