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ANTIBACTERIAL AND ANTIMONOAMINOXIDASE PROPERTIES OF NEW SPYROOXOINDOLINES

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Antibacterial and antimonoamineoxidase properties of new substituted spiro[chromene-4,3'-indolines] and spiro[indoline-3,4'-pyrano[3,2-h]quinolines] were studied. The antibacterial properties were studied in relation to four strains of gram-positive and gram-negative bacteria, and antimonoamine oxidase – in 50% rat brain homogenate. The correlation between the antibacterial and antimonoamineoxidase activities of the synthesized compounds and the biological properties of compounds with a lipophilicity coefficient (logP) and molecular refraction (MR) were studied.

Spiro[chromene-4,3'-indolines] – spiro[indolin-3,4'-pyrano[3,2-h]quinolines] – antibacterial properties – antimonoamineoxidase properties – molecular descriptors

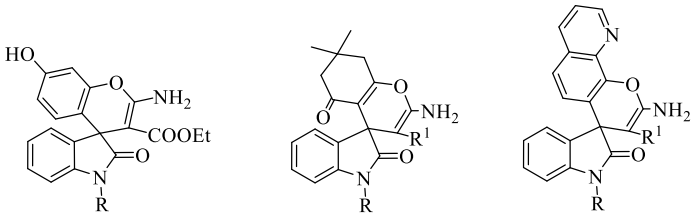
Հետազոտվել են տեղակալված նոր սպիրո[քրոմեն-4,3′-ինդոլինների] և սպիրո[ինդոլին-3,4′ պիրոնո[3,2-h]քինոլինների] հակաբակտերիալ և հակամոնոամինոօքսիդազային հատկությունները: Հակաբակտերիալ հատկությունները հետազոտվել են գրամբացասական և գրամդրական չորս շտամների նկատմամբ, իսկ հակամոնոամինոօքսիդազայինները՝ առնետների ուղեղի 50 տոկոսանոց հոմոգենատի նկատմամբ: Ուսումնասիրվել է սինթեզված միացությունների հակաբակտերիալ և հակամոնոամինոօքսիդազային հատկությունների և միացությունների կենսաբանական հատկությունների հարաբերակցությունը լիպոֆիլության գործակցի (logP) և մոլեկուլային ռեֆրակցիայի միջև:

Սպիրո[քրոմեն-4,3′-ինդոլիններ] – սպիրո[ինդոլին-3,4′-պիրոնո[3,2-h]քինոլիններ] – հակաբակտերիալ հատկություններ – հակամոնոամինոօքսիդազային հատկություններ – մոլեկուլյար դեսկրիպտորներ

Исследованы антибактериальные и антимоноаминооксидазные свойства новых замещеннных спиро**[**хромен-4,3'-индолинов] и спиро[индолин-3,4'-пирано[3,2-h]хинолинов]. Антибактериальные свойства изучены в отношении четырех штаммов грамположительных и грамотрицательных бактерий, а антимоноаминооксидазные ⁻ в 50 %-ном гомогенате мозга крыс. Изучена корреляция между антибактериальной и антимоноаминооксидазной активностью синтезированных соединений и биологическими свойствами соединений с коэффициентом липофильности (logP) и молекулярной рефракцией.

Спиро[хромен-4,3'-индолины]⁻ спиро[индолин-3,4'-пирано[3,2-h]хинолины]⁻ антибактериальные свойства ⁻ антимоноаминооксидазные свойства ⁻ молекулярные дескрипторы

The logic of research to find new potential drugs involves the study of various types of biological activity of new synthesized compounds in order to identify the most promising scaffolds and their subsequent optimization. In this regard, in this study, we studied the antibacterial and antimonoamineoxidase properties of new spiroheterooxindolines 1a-e, 2a-f, 3a-e [4,5], the relationship of the activity of the compounds with the calculated physicochemical descriptors, and an attempt was made to trace a possible parallelism between the antibacterial and antimonoamine oxidase activities of the compounds.



1a-e 2a-f 3a-e

1a-e: R = CH_3 (a), C_2H_5 (b), **C_3H_7** (c), $CH_2CH = CH_2$ (d); CH_2Ph (e);
2a-f: R, R^1 = CH_3, CN (a), C_2H_5, CN (b), C_3H_7, CN (c), C_4H_9, CN (d), CH_2Ph, CN (e), CH_2COOEt, COOEt (f);
3a-e: R, R^1 = C_2H_5, CN (a), C_3H_7, CN (b), C_4H_9, CN (c), $CH_2C_6H_5$, CN (d), $CH_2CH = CH_2$, COOEt (e).

The relevance of the search for new antibacterial drugs is due to various factors, such as an increase in the risks of infections associated with globalization and mass migration, the emergence of resistance of microorganisms to antibacterial drugs used in clinical practice, side effects of the latter and others. At the same time, the search for new active drugs – monoamine oxidase inhibitors is also very promising, taking into account both the observed growth dynamics of various depressive states and the need for new active and safe antidepressants [1].

It is also noteworthy that in recent years there has been evidence that individual monoamine oxidase (MAO) and polyaminoxidase (PAO) inhibitors also inhibit the enzyme lysine-specific demethylase 1 (LSD1) *in vitro*, since this enzyme has a certain homology with the family aminoxidases [6]. Since tumor growth in the xenograft model of colorectal cancer and neuroblastoma is inhibited by LSD1 inhibitors, it can be assumed that inhibitors of aminooxidases and, in particular, MAO, can have an antitumor effect [7].

In this sense, a comparison of the antibacterial and anti-MAO activities of the compounds may be important for the detection of antitumor properties, since often the antibacterial activity of chemical compounds is used for the primary indication of antitumor properties.

The obtained biological test data are also compared with the most commonly used integral molecular descriptors: lipophilicity (logP) and molecular polarizability (MR), shown in the table.

Materials and methods. The antibacterial activity of the compounds was studied by the methods of "diffusion in agar" according to the described method [3]. 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*) differing in sensitivity to antibacterial drugs, control – antibacterial drug furazolidone. The source of monoamine oxidase (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; in the obtained 50% homogenate, the MAO activity was determined by the described method [2]. Each compound was tested in 3-4 experiments, from which the average data were derived, the control drug – indopane.

Molecular descriptors lipophilicity (logP) and molecular polarizability (MR) were obtained using the computer program ACD / ChemSketch (version ACD / Labs 6.00).

Results and Discussion. The results of biological studies of spiro[chromeno-4,3'-indolines] 1a-e, 2a-f and spiro[indolin-3,4'-pyrano[3,2-h]quinolines] 3a-e are shown in the tab. 1.

Table 1. Antibacterial and antimonoaminooxidative activity and calculated physicochemical descriptors of compounds 1a-e, 2a-f, 3a-e and control antibacterial drug furazolidone.

Compounds	Antibacterial activity (*mm*). [a] / Strains [b]				Inhibition MAO activity in % of control*		logP	MR (±0.4) sm^3
	A	**B**	**C**	**D**				
1a	–	–	–	–	49	< 0,05	3.82±0.63	96.62
1b	–	–	–	–	42	< 0,05	4.35±0.63	101.25
1c	–	–	–	–	73	< 0,05	4.88±0.63	105.88
1d	–	–	–	–	60	–	4.28±0.75	105.65
1e	–	–	–	–	37 **	< 0,05	5.63±0.65	121.33
2a	17	15	18	16	77	< 0,05	5.35±0.75	93.79
2b	0	0	15	15	17**	–	5.88±0.75	98.42
2c	0	0	0	0	–	< 0,05	6.42±0.75	103.05
2d	0	0	13	12	73	< 0,05	6.95±0.75	107.68
2e	0	0	0	0	75	< 0,05	7.15±0.75	118.50
2f	–	–	–	–	68	< 0,05	6.45±0.75	120.71
3a	10	10	0	0	55	< 0,05	4.23±0.75	103.90
3b	13	10	15	12	70	< 0,05	4.76±0.75	108.53
3c	15	10	12	10	–		5.29±0.75	113.16
3d	10	10	0	0	–		5.51±0.75	123.98
3e	–	–	–	–	60	< 0,05	4.93±0.65	119.47
Furazolidone	25	24	24	24	–	–	-0.04±0.41	50.61***
Indopane	–	–	–	–	86	–	1.73±0.22	56.20***

a. The diameter of the zone of no microbial growth (mm).

b. Strains: **A**. *S. aureus 209p*, B. *S. aureus 1*, C. *S. flexneri 6858*, D. *E. coli 0-55*.

* The concentration of compounds is 1 μmol / ml sample, the substrate is serotonin (5-HT).

** Reliability was not calculated due to the low activity of the compounds.

*** Furazolidone, MR 50.61±0.5 sm^3. Indopane, MR 56.20±0.3 sm^3.

Studies of the antibacterial activity of the studied spiroheterooxindolines with fragments of dimedone and quinoline showed that some of them have antimicrobial properties. In the series of dimedone derivatives, a moderate antibacterial effect with respect to all four strains used was found in compound 2a with a methyl group at the isatin nitrogen atom: a further increase in the size of the substituent in this position leads to a significant decrease in activity, especially with respect to gram-positive staphylococci, until the activity disappears (compounds 2b-e). In this series, a decrease in antibacterial activity correlates with an increase in lipophilicity coefficient (logP) and an increase in molecular polarizability (MR). Among the quinoline derivatives, only compounds 3b, 3c showed some antibacterial effect on all four bacterial strains, while derivatives 3a, 3d were only weak in relation to gram-positive staphylococci; however, no relationship was observed between antibacterial activity and the values of integral molecular descriptors in this series.

When studying the antimonoamineoxidase activity of spiroheterooxindolines, it was found that all the studied compounds (with the exception of derivatives 1b, 1e and 2b, which showed relatively weak activity) have a sufficiently pronounced antimonoamineoxidase effect (inhibition of the enzyme activity in the range of 49-77%), that does not depend on the lipophilicity coefficient (logP) and molecular polarizability (MR) values. It can be noted that, in a series of studied groups of compounds, the highest antibacterial and antimonoamineoxidase activity was shown by the dimedone 2a derivative. You can also notice that compounds 2a, 2d, 3b, exhibiting a slightly more pronounced antibacterial effect against gram-negative cocci (with the exception of compound 2e, which is completely devoid of antibacterial properties), also have a pronounced antimonoamineoxidase activity (inhibition of enzyme activity of more than 70 %). The last observation, however, requires additional research on a larger number of derivatives.

Thus, compounds exhibiting antibacterial and antimonoamineoxidase properties were found in the spiroheterooxindoline series, and only in the series of dimedone derivatives was a certain correlation between the size of the substituent at the nitrogen atom in the isatin fragment and the increase in lipophilicity coefficient (logP) and molecular polarizability (MR). At the same time, the studied substances were significantly inferior in activity to the control preparations furazolidone (d = 24–25 mm) and indopane (86 ± 6 %).

REFERENCES

1. *Geldenhuys W.J, Darvesh A.S., Funk M.O., Van der Schyf C. J., Carroll R.T.* Identification of novel monoamine oxidase B inhibitors by structure-based virtual screening. Bioorg. Med. Chem. Lett., *20,* 17, pp. 5295-5298, 2010.
2. *Harutyunyan A.A., Sukasyan R.S., Grigoryan A.S.* MAO – Inhibiting properties of some new substituted pyrimidines and condenced azaheterocycles. Biolog. Journ. Armenia, *68,* 1, c. 60-61, 2016.
3. *Pershin G.N.* Methods of experimental chemotherapy. M., Medicine, p. 507-533, 1971.
4. *Pogosyan S. A., Avakimyan Dzh. A., Stepanyan H. M.* Synthesis of new heterocyclic systems-substituted spiro[chromene-4,3′-indoles] and spiro[indole-3,4′-quinolines]. Russ. J. Org. Chem., *52,* 9, p. 1308-1311, 2016.
5. *Poghosyan S. A., Paronikyan P. V., Stepanyan G. M., Grigoryan A. G.* Synthesis and study of biological activity of derivatives of spiro[chromene-4,3'-indolines] and spiro[indoline-3,4'- quinolines]. Chem. J. Armenia, *69,* 4. pp. 518-524, 2016.
6. *Schulte J.H, Lim S., Schramm A., Friedrichs N., Koster J., Versteeq R., Ora I., Klein-Hitpass L., Kuhfittig-Kulle S., Metzger E., Schüle R., Eggert A., Buettner R., Kirfel J.* Lysine-specific demethylase 1 is strongly expressed in poorly differentiated neuroblastoma: implycations for therapy. Cancer Res., *69,* 5, p. 2065-2071, 2009.
7. *Singh M.M., Manton C.A., Bhat K.P., Tsai W.W., Aldape K., Barton M.C., Chandra J.* Inhibition of LSD1 sensitizes glioblastoma cells to histone deacetylase inhibitors. Neuro-Oncology *13,* 8, p.894-903, 2011. doi:10.1093/neuonc/nor049

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