Հայաստանի Գիտությունների Ազգային Ակադեմիա
Национальная Академия Наук Армении
National Academy of Sciences of Armenia

Հայաստանի Կենսաբանական Հանդես
Биологический Журнал Армении
Biological Journal of Armenia

• Փորձարարական և տեսական հոդվածներ • Экспериментальные и теоретические статьи • • Experimental and theoretical articles •

Biolog. Journal of Armenia, 1 (75), 2023

DOI:10.54503/0366-5119-2023.75.1-40

ANTIMONOAMINE OXIDASE ACTIVITY OF BIS-TRIAZOLE DERIVATIVES LINKED BY PHENYLENE AND OCTAMETHYLENE LINKERS

A.S. GRIGORYAN, S.V. DILANYAN, A.A. HARUTYUNYAN

Scientific and Technological Center of Organic and Pharmaceutical Chemistry of the National Academy of Sciences of the Republic of Armenia
harutyunyan.artur@yahoo.com

The antimonoamine oxidase activity of bis-triazole derivatives bound by a phenyl and octamethylene linkers was studied. The acetic acid residue and its derivatives act as substituents in the target bis-triazoles, imparting polar properties to the compounds. *In vitro* experiments have shown that most of the synthesized compounds exhibit antimonoamineoxidase activity.

An attempt was made to compare the antimonoamineoxidase properties of the compounds with the known integral molecular descriptors: lipophilicity, molar refraction, polarizability and molar volume, obtained using the ACD/ChemSketch program (version ACD/Labs 6.00), as well as with data on inhibition of tumor DNA methylation.

Substituted bis-1,2,4-triazoles – 1,4-phenylene linker – octamethylene linker – antiMAO activity – integral molecular descriptors – DNA methylation inhibitors – structure-activity relationship

Ուսումնասիրվել են բիս-տրիազոլի ածանցյալների հակամոնոամին օքսիդազային ակտիվությունները, որոնք կապված են ֆենիլ և օկտամեթիլեն կապիչներով: Քացախաթթվի մնացորդը և դրա ածանցյալները թիրախային բիս-տրիազոլներում գործում են որպես փոխարինիչներ՝ միացություններին հաղորդելով բևեռային հատկություն: Հետազոտությունների *In vitro* փորձերը ցույց են տվել, որ սինթեզված միացությունների մեծ մասը ցուցաբերում են հակամոնոամինօքսիդազային ակտիվություն: Ուսումնասիրությունների նպատակն է եղել համեմատել միացությունների հակամոնոամինօքսիդազային հատկությունները հայտնի ինտեգրալ մոլեկուլային նկարագրիչների հետ՝ լիպոֆիլություն, մոլային բեկում, բևեռացում և մոլային ծավալ, որոնք ստացվել են ACD/ChemSketch ծրագրի միջոցով (տարբերակ ACD/Labs 6.00), ինչպես նաև տվյալներ ուռուցքի ԴՆԹ-ի մեթիլացման արգելակման վերաբերյալ:

Փոխարինված բիս-1,2,4-տրիազոլներ – 1,4-ֆենիլենային կապող – օկտամեթիլեն կապող – հակաMAO ակտիվություն – ինտեգրալ մոլեկուլային նկարագրիչներ – ԴՆԹ-ի մեթիլացման ինհիբիտորներ – կառուցվածք-ակտիվություն հարաբերություններ

Изучена антимоноаминоксидазная активность производных бис-триазолов, связанных фениленовым и октаметиленовым линкерами. В качестве заместителей в целевых бистриазолах выступает остаток уксусной кислоты и ее производные, придающие соединениям полярные свойства. В опытах *in vitro* показано, что большинство синтезированных соединений проявляют антимоноаминоксидазную активность.

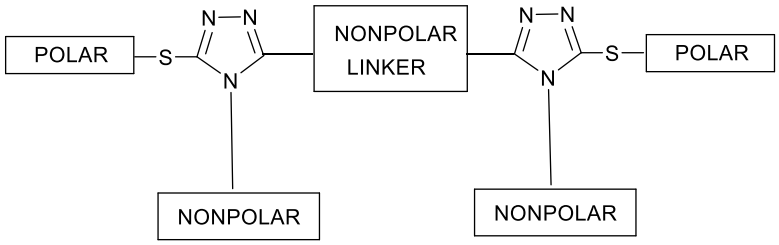
Предпринята попытка сравнить антимоноаминоксидазные свойства соединений с известными интегральными молекулярными дескрипторами: липофильностью, молярной рефракцией, поляризуемостью и молярным объемом, полученными с помощью программы

ACD/ChemSketch (версия ACD/Labs 6.00), а также с данными по ингибированию метилирования опухолевой ДНК.

Замещенные бис-1,2,4-триазолы – 1,4-фениленовый линкер – октаметиленовый линкер – антиМАО активность – интегральные молекулярные дескрипторы – ингибиторы метилирования ДНК – связь структура-активность

The functionalization of ring systems of heterocycles by a set of substituents with different stereoelectronic properties is considered as a well-developed strategy for the discovery of new drugs. In addition, in recent years, the number of studies on the discovery of potential drugs based on heterocyclic compounds with new structural features, in particular, bis -heterocycles.

Given the rather wide range of biological properties exhibited by substituted 1,2,4-triazoles [4], we studied the antimonoamine oxidase activity of two series of substituted bis-1,2,4-triazoles [2], the generalized construction of which is shown in Scheme 1.



Scheme 1. Generalized structure of the synthesized bis-triazoles with the arrangement of polar

A feature of the studied compounds is the dimeric structure of the molecules, in which two fragments of 1,2,4-triazole are linked by a hydrophobic linker in the form of a benzene ring or an octamethylene chain. In addition, in position 4 of the rings of 1,2,4-triazoles there are hydrophobic phenyl and allyl groups, and in position 5 there is a residue of thioacetic acid and its derivatives exhibiting hydrophilic properties.

In the case of bis-triazoles linked via an aromatic phenyl linker, an extended π-conjugation chain is formed, covering both triazole rings and the phenyl group. This feature of the structure gives the molecule a certain rigidity in terms of the spatial arrangement of linearly connected triazole rings, since rotation is possible only around the axis passing between the C1–C4 atoms of the benzene ring (structure A, fig. 1).

A different picture emerges in the case of bis-triazoles linked via a flexible and sufficiently extended octamethylene linker, where, due to the absence of a π-conjugation chain, different mutual spatial orientations of heterocycles are admissible (structure B, fig. 1).

In this regard, we note that we have previously shown that, in this series, bis-triazoles A with a rigid phenyl linker, in contrast to analogs B with an octamethylene linker, significantly more strongly inhibit the level of tumor DNA methylation [1]. It is also appropriate to raise the question of a possible relationship between the level of monoamine oxidase inhibition and tumor DNA methylation, which can be used for preliminary indication of the antitumor properties of compounds, since DNA methylation inhibitors are considered as potential anticancer compounds.

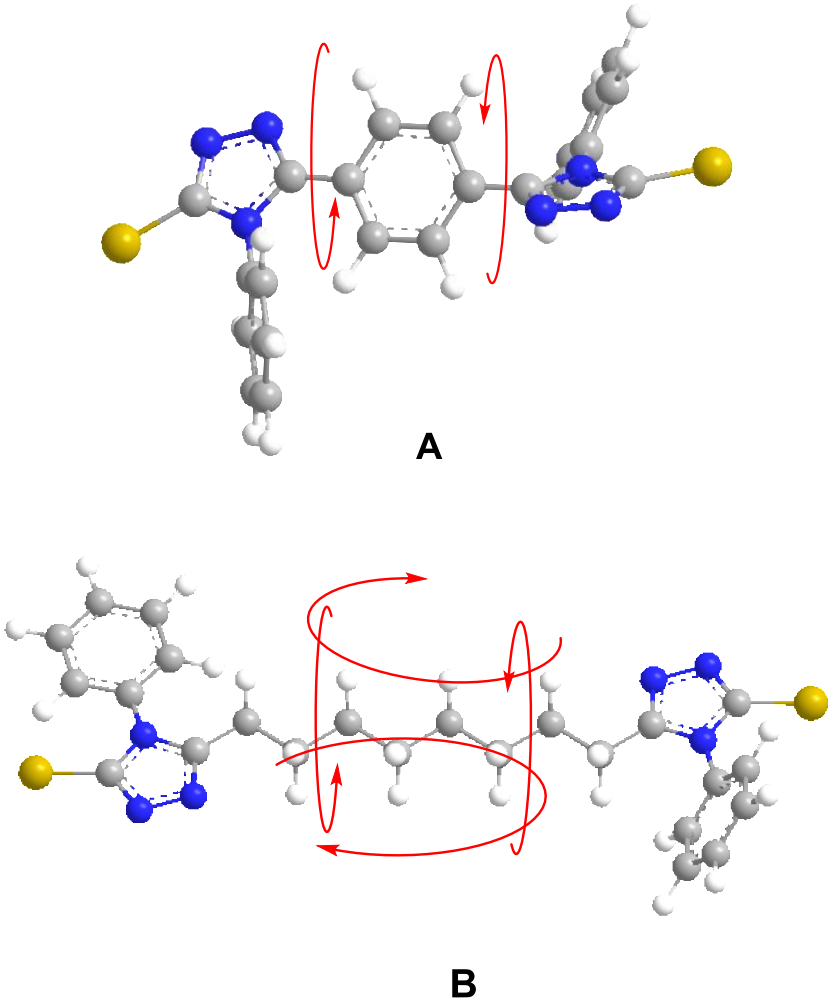
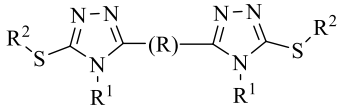


Fig. 1. Spatial image of bis-triazoles on a 3D-model

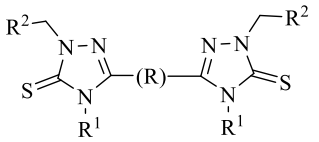
In order to establish structural requirements for the maximum manifestation of antimonoamine oxidase properties, the values of several physicochemical descriptors, such as lipophilicity of compounds (logP), molar refraction (MR) as a measure of the volume occupied by a group of atoms, polarizability (Pol) of molecules, that is, the ability to acquire a dipole moment in an electric field and a molar volume (MV), which characterizes the packing density of molecules.

Thus, we present the results of studying the antimonoamineoxidase activity of bis-1,2,4-triazoles **1-21** (Scheme 2) and discuss the effect of steric and electronic factors of substituents in the ring of 1,2,4-triazole and the linker on the biological activity of the compounds. Note that the antimonoamine oxidase properties of the most active bis-triazoles **9,17,18,21** were already briefly discussed in the previous communication without a detailed comparison of the biological activity and the values of physicochemical descriptors [3].

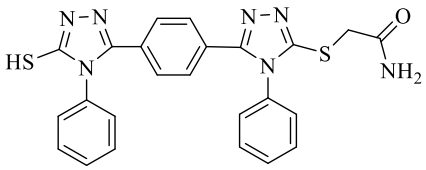
Scheme 2. Structure of synthesized bis-triazoles



1-15



16-20



21

1-15: R, R^1, R^2 = 1,4-(C_6H_4), Ph, H (**1**); 1,4-(C_6H_4), All, H (**2**); $(CH_2)_8$, Ph, H (**3**); $(CH_2)_8$, All, H (**4**); 1,4-(C_6H_4), Ph, CH_2CONH_2 (**5**); 1,4-(C_6H_4), Ph, CH_2COOH (**6**); 1,4-(C_6H_4), All, CH_2CONH_2 (**7**); 1,4-(C_6H_4), All, CH_2COOH (**8**); 1,4-(C_6H_4), All, CH_2COOEt (**9**); $(CH_2)_8$, Ph, CH_2CONH_2 (**10**); $(CH_2)_8$, Ph, CH_2COOH (**11**); $(CH_2)_8$, Ph, CH_2COOEt (**12**); $(CH_2)_8$, Ph, CH_2(2-ClC_6H_4) (**13**); $(CH_2)_8$, All, CH_2CONH_2 (**14**); $(CH_2)_8$, All, CH_2COOH (**15**).
16-20: R, R^1, R^2 = 1,4-(C_6H_4), Ph, CH_2CN (**16**); 1,4-(C_6H_4), Ph, $N(CH_2)_5$ (**17**); 1,4-(C_6H_4), All, CH_2CN (**18**); $(CH_2)_8$, Ph, $N(CH_2)_5$ (**19**); $(CH_2)_8$, All, CH_2CN (**20**).

Materials and methods. The source of monoamine oxidase (MAO) was a 50% rat brain homogenate, which was obtained by homogenizing the brain in a glass homogenizer with an equal (by weight) volume of a 2.5% Arcopal solution. Activity (MAO) was determined in the resulting homogenate. Oxygen saturation was carried out for 5 min at 37°C and then the samples were incubated in an oxygen atmosphere for 45 min at 37°C. The reaction was stopped by adding 0.2 ml of 50% trichloroacetic acid. The protein precipitate was separated by centrifugation at 3000 rpm. In the protein-free supernatant, the ammonia content was determined by isomeric distillation for 24 h, followed by neslerization and photometry on a FEK-56-2 photometer-nephelometer. MAO activity is expressed as % of control; indopan was used as a control drug.

Each compound was tested in 3-4 experiments, the obtained results were processed statistically according to Student – Fisher.

Results and Discussion. According to the data obtained, most of the substituted bis-triazoles connected via a phenyl linker exhibit moderate anti-MAO-ase activity, practically independent of the nature of the substituents in the N^4 and N^2 positions of the triazole ring or at the S atom (tab. 1). The starting mercapto derivatives **1–4**, regardless of the substituents at the N^4 atom, exhibit antimonoamineoxidase properties similar to their alkylated products.

A slightly different picture emerges when regularities are established between the structure and activity for triazoles **10-15**, in which both rings are linked by an octamethylene linker. Compounds **10–13**, in which the phenyl group is located at the N^4 position, exhibit rather weak antiMAO activity (enzyme inhibition 27–37 %), while the

replacement of this group with an allyl group in compounds **14,15** leads to a significant increase in inhibitory properties (enzyme inhibition 60,65 %). Note that some compounds in the series of bis-substituted triazoles (compounds **2,7,8,11,15,18,21**) inhibit the level of DNA methylation in the range of 31.3-67.2 %, and compound **6** – at the level of 82.8 % (control – natural antibiotic doxorubicin 67.2 %).

No correlation was noted between antimonoamineoxidase activity and the level of DNA methylation inhibition.

Molecular descriptors such as lipophilicity (LogP), molar refraction (MR), polarizability (Pol) and molar volume (MV) obtained using the ACD/ChemSketch program (ACD/Labs version 6.00)

Table 1. Antimonoaminooxidase activity compounds **1-21** and calculated physicochemical descriptors

Соединение	MAO, %*	p	LogP	MR*	Pol*	MV*
1	58±1.6	< 0,05	8.07±0.83	125.97	49.93	301.7
2	78±3.0	< 0,05	5.35±0.81	103.04	40.85	260.6
3	70±2.6	< 0,05	7.92±0.79	137.74	54.60	362.3
4	58±1.6	< 0,05	5.19±0.77	114.81	45.51	321.3
5	60±1.8	< 0,05	5.70±0.82	150.91	59.82	365.4
6	53±1,4	< 0,05	7.59±0.80	148.78	58.98	366.4
7	72±2.6	< 0,05	2.97±0.80	127.98	50.73	324.5
8	66±1,8	< 0,05	4.87±0.78	125.86	49.89	325.5
9	78±2,4	< 0,05	6.86±0.79	145.0	57.48	406.4
10	32	-	5.54±0.78	162.68	64.49	426.0
11	32	-	7.44±0.76	160.55	63.64	427.0
12	37	-	9.42±0.77	179.69	71.23	507.8
13	27	-	12.91±0.72	207.34	82.19	559.8
14	60±2.0	< 0.05	2.82±0.76	139.75	55.40	385.1
15	65±1,6	< 0,05	4.71±0.73	137.63	54.56	386.1
16	62±2,2	< 0,05	1.34±0.86	150.04	59.48	371.5
17	70±2,8	< 0,05	4.89±0.90	185.90	73.69	470.7
18	70±1,8	< 0,05	-0.50±0.88	127.11	50.39	330.5
19	56±1,8	< 0,05	5.60±0.90	198.97	78.87	541.8
20	60±1,6	< 0,05	0.21±0.87	140.19	55.57	401.7
21	78±1,8	< 0,05	6.88±0.83	138.44	54.88	333.6

MAO: inhibition of monoaminooxidase (MAO), concentration 1 мкмоль/мл.
MR* (Molar Refractivity): N±0.5sm^3; Pol*(Polaribility): N±0,5 10^{-24} sm^3;
MV* (Molar Volume): N±7.0 sm^3, **F** – furazolidone, **I** – indopane.

If in a number of studied compounds there is no correlation between the lipophilicity of the compounds (LogP) and the level of MAO inhibition, then a certain correlation is observed with respect to other descriptors used. With the exception of triazoles **17** and **19**, for almost all compounds inhibiting monoamine oxidase, the value of the volume of molecules (MR) is in the range of 103.04-150.91±0.5sm^3, while for low-active compounds **10**-**13**, the volume of molecules is in the range of 160.55-207.34±0.5sm^3. The value of polarizability (Pol) for active molecules is within 40.85-59.82±0.5 10^{-24} sm^3, and for inactive compounds **10**-**13** - 63.64-82.19±0.5 10^{-24} sm^3.

Finally, the molar volume of more active compounds is in the range of 260.6-406.4±7.0 sm^3, and for low-active compounds **10-13** - in the range of 426.0-559.8±7.0 sm^3. Thus, bis-triazoles **10-13**, in which two triazole fragments are linked by an octamethylene linker, have increased calculated values of molar refraction descriptors, polarizability, and molar volume, along with weak antiMAO activity. The exceptions are two bis-derivatives with an N^4-phenyl group and a piperidine residue **17** and **19**, which, regardless of the nature of the linker and the values of the above descriptors, exhibit certain anti-MAO properties, inhibiting the activity of the enzyme by 70 and 56%, respectively.

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Received on 27.09.2022