ЕКСПЕРИМЕНТАЛЬНА ТА КЛІНІЧНА ФАРМАКОЛОГІЯ

Recommended by Doctor of Medicine, Professor N. I. Filimonova

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The study of the antimicrobial activity of ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrole-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives

Aim. To find compounds with the antimicrobial activity in the series of N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrol-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives.

Materials and methods. The antimicrobial activity was studied by the agar diffusion method.

Results and discussion. The antimicrobial screening data revealed the pronounced biological activity of ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrol-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives against gramnegative (*Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa*) and grampositive (*Staphylococcus aureus*, *Bacillus subtilis*) bacteria and as well as against *Candida albicans* fungi.

Conclusions. The antibacterial activity of ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrol-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives has been studied. The compounds with a significant level of the antimicrobial activity against gramnegative bacteria (*Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa*), grampositive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*), as well as against fungi (*Candida albicans*) have been found. According to the data of the microbiological screening the most active compounds appeared to be ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrol-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) **1** and ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrol-5'-methyl-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) **2**.

Key words: *bis-spiro-2-oxindole; double drugs; bacteria; antibacterial agents*

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Дослідження антимікробної активності похідних етилен-N,N'-*біс*(спіроіндол-3,3'-піроло[3,4-*c*]пірол-2a',5a'-дигідро-2,2',6'(1*H*,1'*H*,5'*H*)-триону)

Мета роботи – виявлення сполук з антимікробною активністю в ряду похідних етилен-N,N'-*біс*(спіроіндол-3,3'-піроло[3,4-*c*]пірол-2a',5a'-дигідро-2,2',6'(1*H*,1'*H*,5'*H*)-триону).

Матеріали та методи. Дослідження антимікробної активності методом дифузії в агар у модифікації колодязів.

Результати та їх обговорення. Дані мікробіологічного скринінгу показали виражену біологічну дію похідних етилен-N,N'-*біс*(спіроіндол-3,3'-піроло[3,4-*c*]пірол-2a',5a'-дигідро-2,2',6'(1*H*,1'*H*,5'*H*)-триону) відносно грамнегативних *Proteus vulgaris, Escherichia coli*, *Pseudomonas aeruginosa* і грампозитивних бактерій *Staphylococcus aureus*, *Bacillus subtilis* та грибів *Candida albicans*.

Висновки. Досліджено антибактеріальну активність похідних етилен-N,N'-*біс*(спіроіндол-3,3'-піроло[3,4-*c*]пірол-2a',5a'-дигідро-2,2',6'(1*H*,1'*H*,5'*H*)-триону). Виявлені сполуки зі значним рівнем біологічної активності відносно грамнегативних бактерій: *Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa*, грампозитивних бактерій: *Staphylococcus aureus*, *Bacillus subtilis* та грибів *Candida albicans*. За даними мікробіологічного скринінгу найбільш активними виявились сполуки: етилен-N,N'-*біс*(спіроіндол-3,3'-піроло[3,4-*c*]пірол-2a',5a'-дигідро-2,2',6'(1*H*,1'*H*,5'*H*)-трион) **1** та етилен-N,N'-*біс*(спіроіндол-3,3'-піроло[3,4-*c*]пірол-5'-метил-2a',5a'-дигідро-2,2',6'(1*H*,1'*H*,5'*H*)-трион) **2**.

Ключові слова: *біс-спіро-2-оксіндол; подвійні ліки; бактерії; антибактеріальні засоби*

Е. И. Сюмка, Т. П. Осолодченко, В. П. Черных, Л. А. Шемчук

Исследование антимикробной активности производных этилен-N,N'-*бис*(спироиндол-3,3'-пирроло[3,4-*c*]пиррол-2a',5a'-дигидро-2,2',6'(1*H*,1'*H*,5'*H*)-триона)

Цель работы – обнаружение соединений с антимикробной активностью в ряду производных этилен-N,N'-*бис*(спироиндол-3,3'-пирроло[3,4-*c*]пиррол-2a',5a'-дигидро-2,2',6'(1*H*,1'*H*,5'*H*)-триона).

Материалы и методы. Исследование антимикробной активности методом диффузии в агар в модификации колодцев.

Результаты и их обсуждение. Данные микробиологического скрининга показали выраженное биологическое действие синтезированных соединений относительно грамотрицательных *Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa*, грамположительных бактерий *Staphylococcus aureus*, *Bacillus subtilis* и грибов *Candida albicans*.

Выводы. Исследована антибактериальная активность производных этилен-N,N'-*бис*(спироиндол-3,3'-пирроло[3,4-*c*]пиррол-2a',5a'-дигидро-2,2',6'(1*H*, 1'*H*,5'*H*)-триона). Обнаружены соединения со значительным уровнем биологической активности относительно грамотрицательных бактерий: *Proteus vulgaris*, *Escherichia coli*, *Pseudomonas eruginosa*, грамположительных бактерий: *Staphylococcus aureus*, *Bacillus subtilis* и грибов *Candida albicans*. По данным микробиологического скрининга наиболее активными оказались соединения: этилен-N,N'-*бис*(спироиндол-3,3'-пирроло[3,4-*c*]пиррол-2a',5a'-дигидро-2,2',6'(1*H*,1'*H*,5'*H*)-трион) **1** и этилен-N,N'-*бис*(спироиндол-3,3'-пирроло[3,4-*c*]пиррол-5'-метил-2a',5a'-дигидро-2,2',6'(1*H*,1'*H*,5'*H*)-трион) **2**.

Ключевые слова: *бис-спиро-2-оксиндол; двойные лекарства; бактерии; антибактериальные средства*

According to the data published by the WHO, infectious diseases are the 4th ranked cause of mortality in the world. More than 17 million people die of an infectious pathology per year [1]. Difficulties of treatment and prevention of these diseases are caused by a variety of biological forms of causative agents, permanent arising of resistant forms of strains and by emergence of new kinds of dangerous pathogens. Therefore, creation of new antimicrobial drugs is topical issue of medicinal chemistry.

Recently, in synthetic chemistry much attention is paid to spirocombined pyrrolooxindoles, which core is the basis of natural alkaloids that exhibit a pronounced antibacterial activity [2]. The spatial arrangement of the pyrrolooxindole core is the probable reason for its strong binding with tridimensional sites of biotargets in a microbial cell [3]. Since most of the known inhibitors of microbial enzymes have a plane or almost plane structure, they can not bind with specific fragments into biotargets above and below of the molecule plane. This is the cause of their low selectivity [4].

On the other hand, such chemical classes as *bis*-spirooxindoles, dispirioxindoles and bis-spiroindoles are of great interest for creation of double drugs. It has been proven that development of biologically active compounds comprising two similar pharmacophors bound by the covalent bond leads to a significant increase of the biological activity [5]. Thus, the bis-spirooxindole core is the basis of such alkaloids as *geleganidine C*, *geleganimine B*, *bipleiophylline* possessing the antibacterial activity (Fig. 1) [6-9].

Thus, the search of new antimicrobial agents among derivatives of *bis*-spiro-2-oxindole-3,3′-pyrrole is the promising way to create new effective drugs.

Earlier it was found [10] that [3+2]-cycloaddition of two-fold excess of azomethine ylides generated *in situ* from isatines and aminoacids to 1,6-bismaleinimidohexane led to formation of hexamethylene-N,N'-*bis*-spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrol-2a',5a'-dihydro-2,2',6'(1*H*,3'*H*,5'*H*)-triones. These compounds showed a significant antibacterial activity. In continuation of the studies devoted to the search of new antibacterial agents we synthesized the series of ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrole-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives [11] (Fig. 2).

N,N'-Di(3-carboxypropenoyl)-1,2-ethylendiamine was used as a dipolarophile for preparing compounds cited above. This reagent is similar to the antibacterial drug Ethambutol ((2S,2'S)-2,2'-(Ethane-1,2-diyldiimino)dibutan-1-ol) by its chemical structure [12]. The aim of the current research was to investigate the antibacterial properties of the substances synthesized against standard types of microorganisms (gram-positive and gram-negative).

Materials and methods

The microbiological studies were performed at the premises of the State Institution "Institute of Microbiology and Immunology named after I. I. Mechnikov of the National Academy of Medical Sciences of Ukraine".

According to the WHO recommendations [13, 14] and recommendations of the Ministry of Health of Ukraine [15, 16] *Staphylococcus aureus* – ATCC 25923, *Escherichia coli* – ATCC 25922, *Pseudomonas aeruginosa* ATCC – 27853, *Bacillus subtilis* ATCC – 6633, *Proteus vulgaris* – ATCC 4636 and *Candida albicans* – ATCC 885/653 were used as test-strains in our study.

In vitro evaluation of the antimicrobial activity of the compounds synthesized was performed using the agar diffusion method.

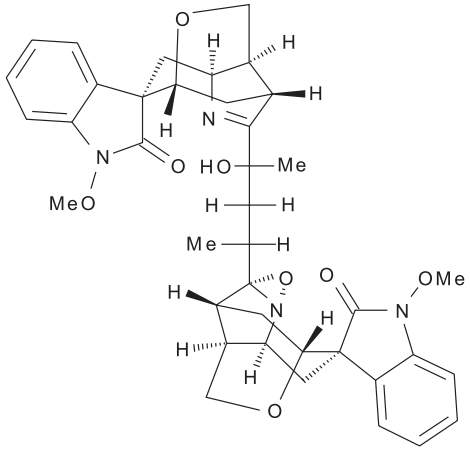
The suspension of microorganisms was prepared on a Densi-La-Meter device (PLIVA-Lachema, Czech Republic; with the wavelength of 540 nm) according to the instruction No. 163-2006 "Standardization of preparation of microbial suspensions" [17-19]. Synchronization of cultures was carried out at the temperature of 4 °C. The microbial load was 10^7 microbial cells per 1 ml of the medium and was determined according to McFarland standard. For experiments the 18-24-hour culture of microorganisms was used. For the research Muller- Hinton agar and Saburo-dextrose agar (for *C. albicans*) were used.

The sample of the compound studied (1 mg) was dissolved in 1 mL of DMSO. 0.3 mL of the solution was taken and introduced into wells on Petri dish with microbial strains. Petri dishes were dried for 30-40 min at room temperature and kept in a thermostat for 18 to 24 h at 37 °C.

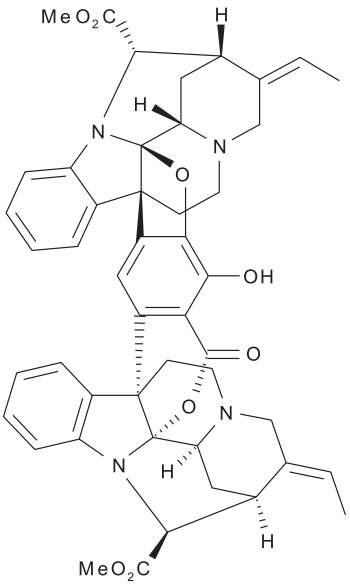
The level of the antimicrobial activity was determined as diameters of inhibition growth zones around the well with the compound studied. The results obtained were compared with the strain growth in the control test.

Results and discussion

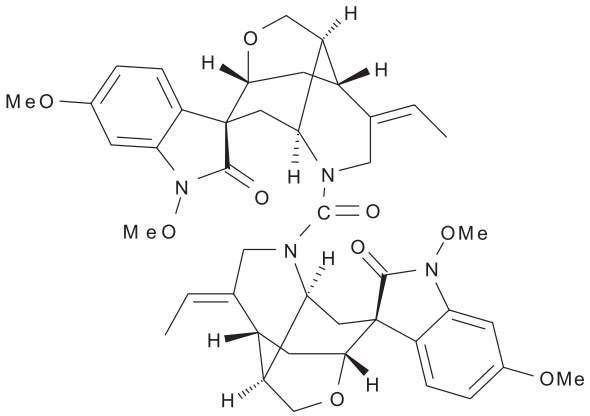
The results of the antimicrobial activity of ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrole-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives **1-10** are given in Table.



geleganimine B
antibacterial and anti-inflammatory activity



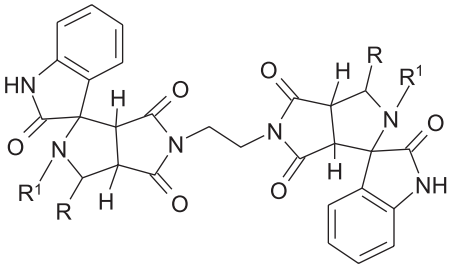
bipleiophylline
cytotoxic and antimicrobial activity



geleganidine C
cytotoxic and antimicrobial activity

Fig. 1. Alkaloids containing the *bis*-spirooxindole core

The hexamethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo [3,4-*c*]pyrrole-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives previously studied showed a high antibacterial activity against *Staphylococcus aureus* and a moderate fungicidal activity against *Candida albicans* [10]. Ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrole-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives **1-10** showed a wider range of the antimicrobial activity. All microorganisms were sensitive to compounds **1-10**. Thus, the growth inhibition zones for all compounds synthesized against *Proteus vulgaris* were on average 1 mm larger compared to the reference drug (Synthomycine). The growth inhibition zones against *Escherichia coli* were on average 2 mm, while against *Pseudomonas aeruginosa* was 5 mm larger for the compounds studied compared to the reference drug. In the case of gram-positive bacteria compounds **1-10** also showed a high activity (the growth inhibition zones against *Staphylococcus aureus*, *Bacillus subtilis* were on average 3 mm larger compared to the reference drug). But the highest level of activity was found in relation to *Candida albicans* fungi. The growth inhibition zones against fungi were on average 7 mm larger compared to the reference drug (Metronidazole). Thus, in general, the compounds synthesized were even more active than the reference drugs Syntomycin and Metronidazole.

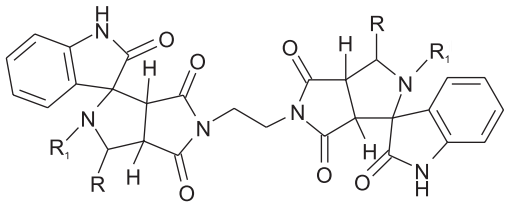


R = H, CH_3, *i*-Pr, *i*-Bu, Ph, Bn, 4-OH-C_6H_4-CH_2-, CH_2OH;
R^1 = H, CH_3; R=R^1 = CH_2-CH_2-CH_2

Fig. 2. The general formula of ethylene-N,N'-bis(spiroindole-3,3'-pyrrolo[3,4-c]pyrrole-2a',5a'-dihydro-2,2',6'(1H,1'H,5'H)-trione) derivatives

Table

The antimicrobial activity of ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrole-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives **1**-**10**



Compound	Diameter of the growth inhibition zones*, mm					
	Grampositive bacteria		Gramnegative bacteria			Fungi
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*P. vulgaris*	*C. albicans*
1 (R = R^1 = H)	16	20	20	22	19	23
2 (R = CH_3; R^1 = H)	16	20	20	21	19	23
3 (R = i-Pr; R^1 = H)	19	21	19	22	18	22
4 (R = i-Bu; R^1 = H)	20	20	18	22	17	23
5 (R = Ph; R^1 = H)	16	21	17	22	16	22
6 (R = i-Pr; R^1 = H)	19	19	20	22	18	23
7 (R = Bn; R^1 = H)	16	20	18	22	17	22
8 (R = 4-OH-C_6H_4- -CH_2-; R^1 = H)	15	20	18	22	17	22
9 (R = H; R^1 = CH_3)	17	20	19	21	18	23
10 (R = R^1 = CH_2-CH_2--CH_2)	15	21	19	22	18	22
Control	growth	growth	growth	growth	growth	growth
Synthomycine	14	17	17	17	17	0
Metronidazole	14	16	14	0	0	14

Note: * – The data presented are the mean values for three experiments relative to each microorganism culture.

CONCLUSIONS

The antibacterial activity of ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrol-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) derivatives has been studied. The compounds with a significant level of the antimicrobial activity against gramnegative bacteria (*Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa*), grampositive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*), as well as against fungi (*Candida albicans*) have been found. According to the data of the microbiological screening the most active compounds appeared to be ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrol-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) **1** and ethylene-N,N'-*bis*(spiroindole-3,3'-pyrrolo[3,4-*c*]pyrrol-5′-methyl-2a',5a'-dihydro-2,2',6'(1*H*,1'*H*,5'*H*)-trione) **2**.

Conflict of Interest: authors have no conflict of interests to declare.

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