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Synthesis of a new bis(1,2,4-triazole) derivative with antimicrobial activity

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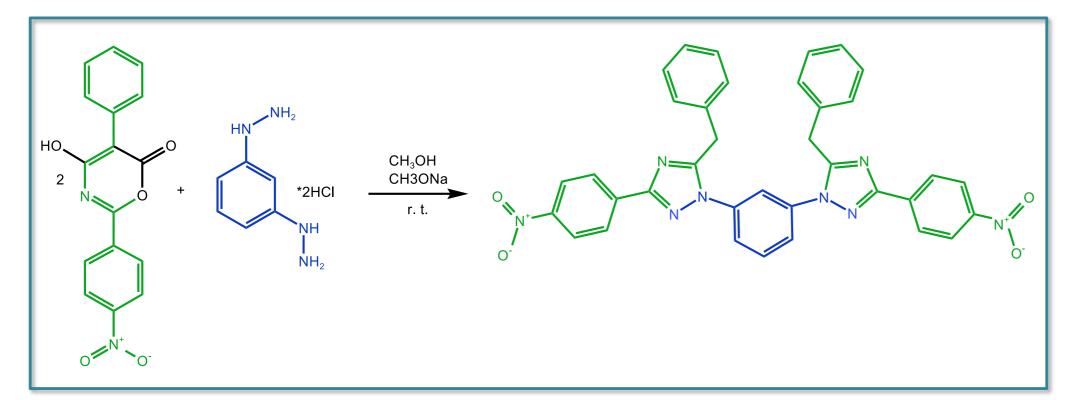
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INTRODUCTION & AIM

The study of compounds related to bis(1H-1,2,4-triazole) derivatives plays an important role in the chemistry of heterocyclic compounds, and these derivatives are also of great significance in modern pharmaceuticals. These structures are active drugs with antifungal and antimicrobial effects (fluconazole, itraconazole) [1]. The literature also notes a wide range of their biological activity: antitumour [2], analgesic [3], and antineurodegenerative. It is known that they can inhibit tumour DNA methylation in sarcoma 180. It is worth noting that some bis(1H-1,2,4-triazole) compounds can be used in the treatment of Alzheimer's disease, and the search for new, more effective pharmacophores for the creation of drugs for the treatment of neurodegenerative diseases is ongoing. Thus, the study of bis(1H-1,2,4-triazole) derivatives is a relevant task in the chemistry of heterocyclic compounds and modern pharmacology.

METHOD

To obtain 1,1'-(benzene-1,3-diyl)bis [5-benzyl-3-(4-nitrophenyl)-1H-1,2,4-triazole], we investigated the reaction of 4-hydroxy-2-(4-nitrophenyl)-5-phenyl-6H-1,3-oxazine-6-one and m-phenylenedihydrazine dihydrochloride (Scheme 1).



Scheme 1. Reaction of 4-hydroxy-2-(4-nitrophenyl)-5-phenyl-6H-1,3-oxazine-6-one and mphenylenedihydrazine dihydrochloride

RESULTS & DISCUSSION

In the ¹H NMR spectrum (Fig. 1) of the obtained compound, resonance signals of protons of the "-CH₂-" group (4.34 (c, 4H)), protons of the phenyl ring (positions 5-8) (7.82 (s, 3H), 7.93 (s, 1H)), aromatic protons of the benzyl radical (7.16-7.27 (m, 10H)), and aromatic protons of the p-nitrophenyl radical (8.29-8.39 (q, 8H)).

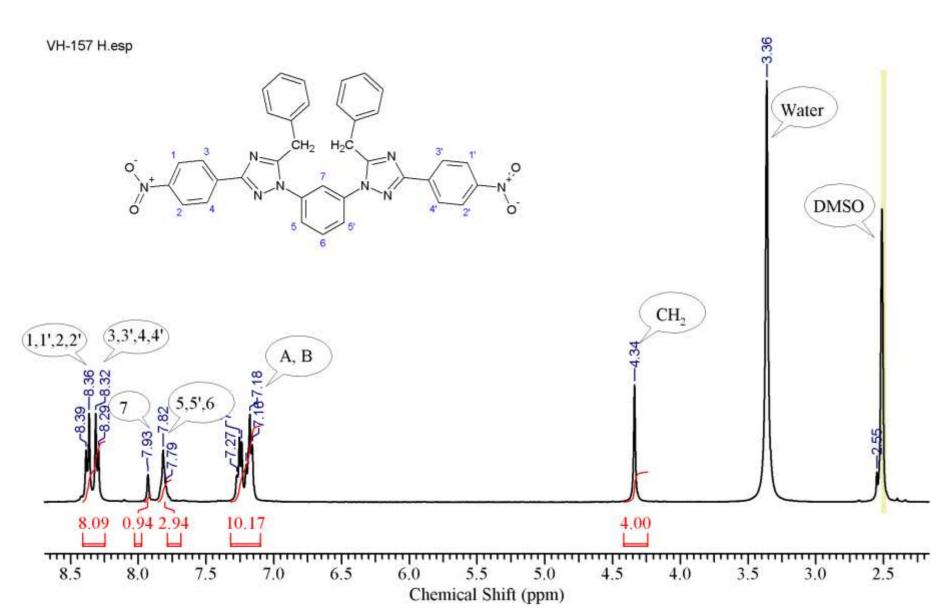


Figure 1. ¹H NMR spectrum of 1,1'-(benzene-1,3-diyl)bis[5-benzyl-3-(4-nitrophenyl)-1H-1,2,4-

In the ¹³C NMR spectrum (Fig. 2) of the obtained compound, the following signals are observed: the node carbon atom of the 4-nitrophenyl radical at 159.40 m.d. – at the nitro group and 157.10 m.d. at the triazole ring; 148.37 and 137.97 m.d. – corresponding to the carbon atoms of the triazole cycle; signals 136.77 – 122.48 m.d. corresponding to the carbon atoms of the benzene rings; and signal 32.48 m.d. - corresponding to the methylene groups.

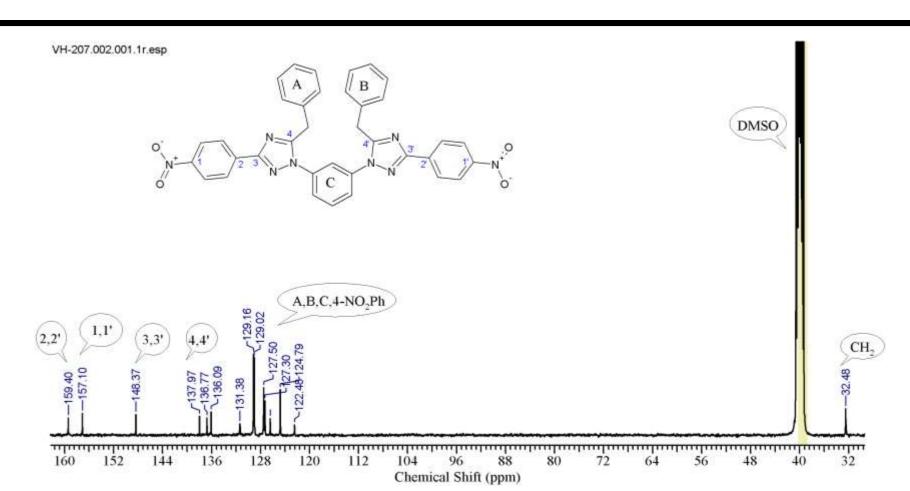


Figure 2. ¹³C NMR spectrum of 1,1'-(benzene-1,3-diyl)bis[5-benzyl-3-(4-nitrophenyl)-1H-1,2,4-triazole]

On the mass spectrum (Fig. 3), we observe an intense signal of a molecular ion of the type [M+Na]⁺ with a value of m/z 657.26._{Mass}

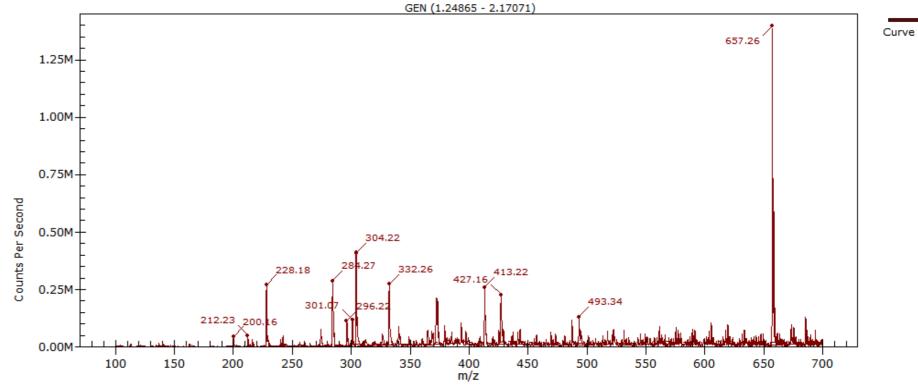


Figure 3. Mass spectrum of 1,1'-(benzene-1,3-diyl)bis[5-benzyl-3-(4-nitrophenyl)-1H-1,2,4-triazole]

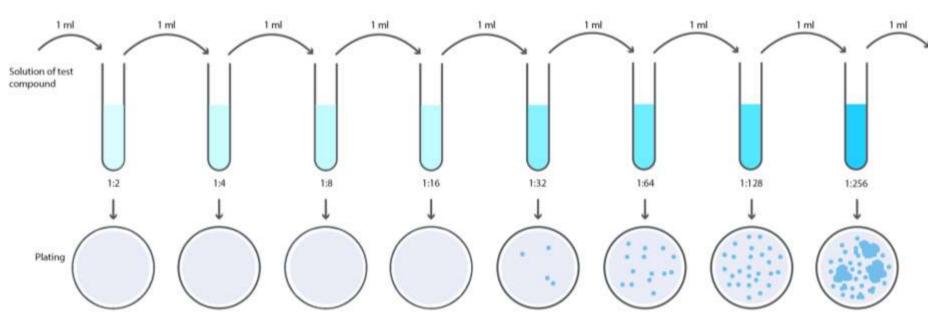


Figure 4. Serial dilution method

- Antibacterial activity was determined by serial dilutions in meat peptone broth (Fig. 4). The minimum inhibitory concentration (MIC) was determined visually by the absence of turbidity compared to the control. To confirm the bacteriostatic effect, cultures were inoculated from tubes without growth onto meat peptone agar, followed by incubation to check for the absence of colony growth.
- Antifungal activity was determined by serial dilutions in Sabouraud liquid medium (Fig. 4). The minimum inhibitory concentration (MIC) was determined by the absence of visible growth (cloudiness) compared to the control. To establish the minimum fungicidal concentration (MFC), tubes without growth were inoculated onto solid Sabouraud medium. The absence of colony growth after incubation indicated a fungicidal effect.

	Staphylococcus aureus		Candida albicans	
	MIC	MBC	MIC	MFC
mcg/ml	62,5	1000	125	1000

Table 1. Results of determining the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) of the synthesised compound against Staphylococcus aureus and Candida albicans

CONCLUSION

- * An effective laboratory method for the synthesis of 1,1'-(benzene-1,3-diyl)bis[5-benzyl-3-(4-nitrophenyl)-1H-1,2,4-triazole] with a yield of 76% has been developed.
- * The structure of the obtained compound was confirmed using physicochemical methods of analysis – ¹H and ¹³C NMR spectroscopy and mass spectrometry.
- * An experimental evaluation of the antibacterial and antifungal activity in vitro against opportunistic pathogens – St. aureus and C. albicans – was carried out.
- * It was found that the compound obtained exhibits pronounced inhibitory activity only against St. aureus.

REFERENCES

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- 3. Cheretaev, I. V.; Chuyan, E. N.; Ravaeva, M. Yu.; et al. Vliyanie 1-gidroksi-1,1-etilidendifosfonovoj kisloty i bis(2-piridil-1,2,4-triazolil-3)propana na bolevuyu chuvstvitel'nost' samok krys. Mezhdunar. Nauchno-Issled. Zh. 2019, *85* (7).