THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMIDRAZONE DERIVATIVES OBTAINED IN REACTION WITH *CIS*-1,2,3,6-TETRAHYDROPHTHALIC ANHYDRIDE

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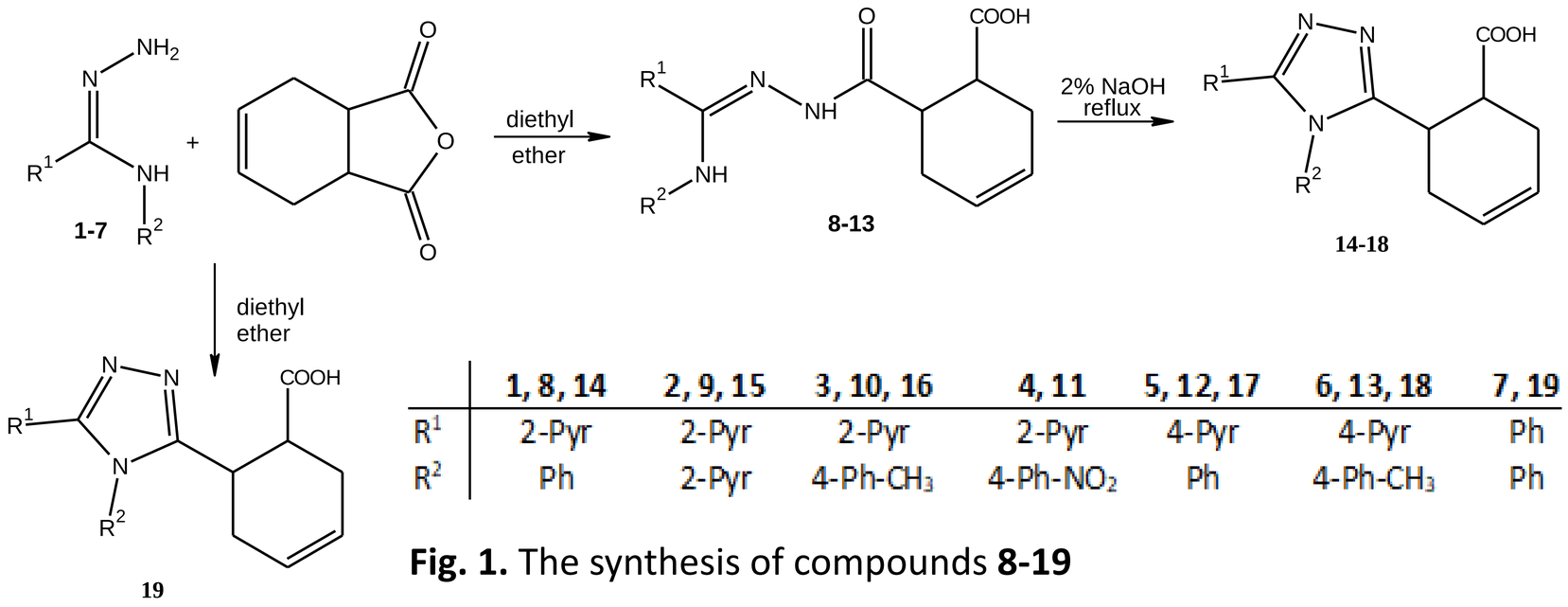
Introduction

Amidrazone derivatives are known for the broad biological activity: antimicrobial, anti-inflammatory, antiparasitic, antitumor and others [1]. Searching for new drugs twelve new derivatives were obtained in reaction of N^3-substituted amidrazones with *cis*-1,2,3,6-tetrahydrophthalic anhydride (**Fig. 1**). The structures of obtained linear compounds **8-13** and 1,2,4-triazole derivatives **14-19** were confirmed by ^{1}H NMR, ^{13}C NMR and MS.



	1, 8, 14	2, 9, 15	3, 10, 16	4, 11	5, 12, 17	6, 13, 18	7, 19
R^1	2-Pyr	2-Pyr	2-Pyr	2-Pyr	4-Pyr	4-Pyr	Ph
R^2	Ph	2-Pyr	4-Ph-CH_3	4-Ph-NO_2	Ph	4-Ph-CH_3	Ph

Fig. 1. The synthesis of compounds **8-19**

Toxicity and anti-inflammatory activity of compounds **14-17** and **19** (at concentrations of 10, 50 and 100 µg/mL) were studied in human peripheral blood mononuclear cells (PBMC). The influence of compounds on cytokine production (TNF-α, IL-6 and IL-10) was examined in PBMC cultures stimulated by lipopolysaccharide (LPS) ant their antiproliferative actrvity in PBMC cultures stimulated by phytohaemagglutinin (PHA).

Results

Triazole derivatives **14-17** and **19** showed low toxicity towards PBMC cultures at concentration range 10-100 µg/mL (**Fig. 2-3**). Only compound **19** showed significant antiproliferative activity in PBMC cultures stimulated by phytohaemagglutinin at the highest dose (results not shown).

The compounds **14-17** and **19** showed a beneficial effect on cytokine synthesis: inhibition of pro-inflammatory TNF-α and increase of anti-inflammatory IL-10. (**Fig. 4-5**). Two linear compounds showed moderate antibacterial activity: derivative **10** inhibited growth of *Mycobacterium smegmatis* and derivative **12** of *Staphylococcus aureus* with minimum inhibitory concentrations MICs = 64 µg/mL.

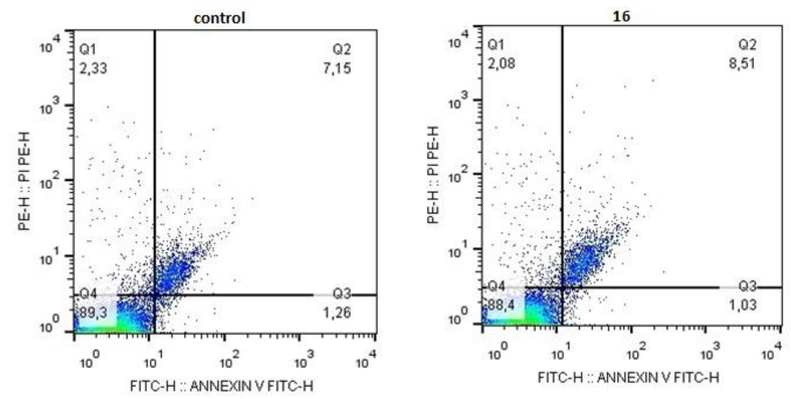


Fig. 2. Control PBMC culture

Fig. 3. Toxicity of **16** (100µg/mL)

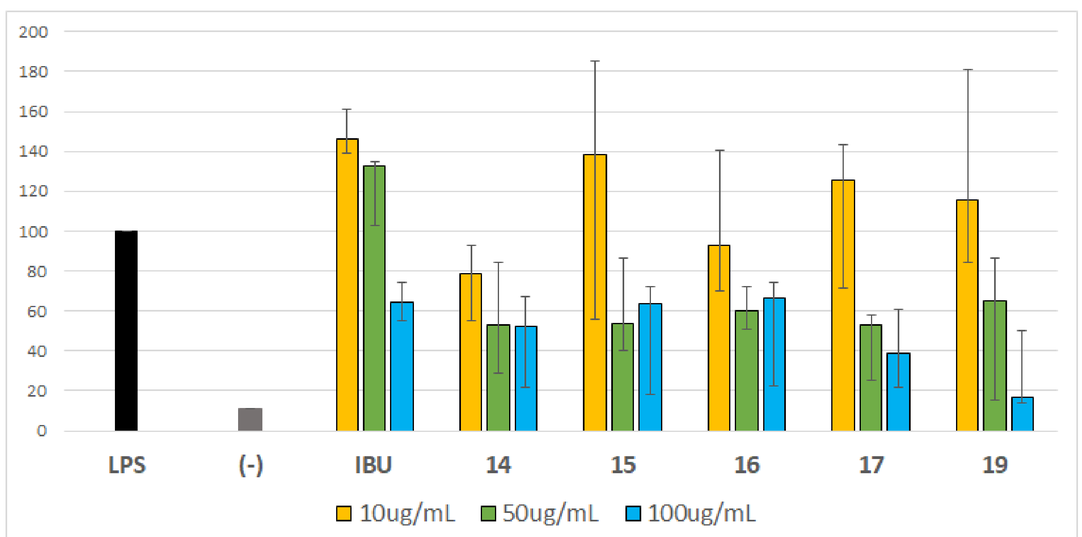


Fig. 4. The influence of compounds on TNF-α production

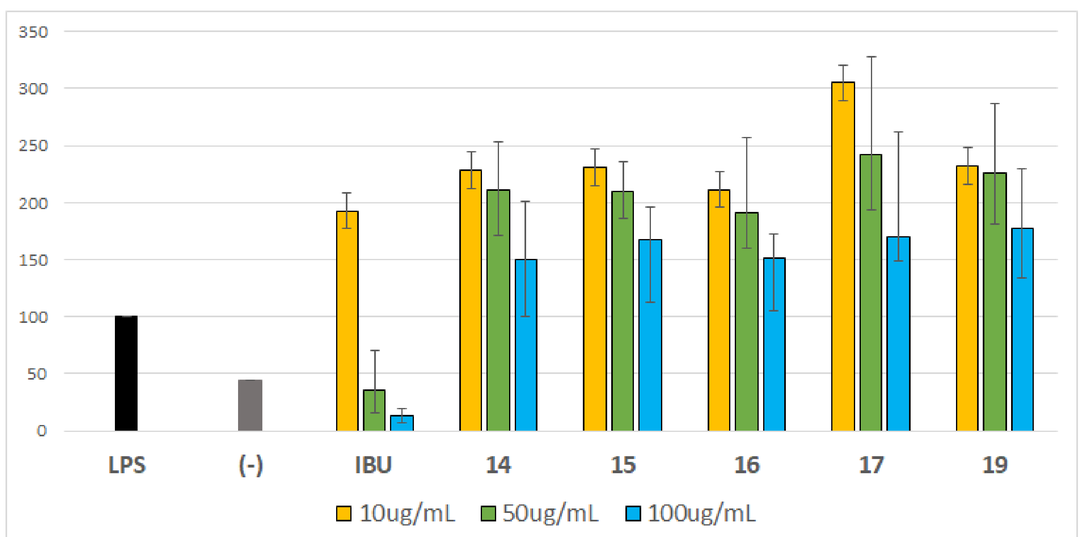


Fig. 5. The influence of compounds on IL-10 production

Conclusion

Five obtained 1,2,4-triazole derivatives **14-17** and **19** showed a strong anti-inflammatory activity. The strongest effect was observed for compound **19** (possesing two phenyl substituents), which also showed antiproliferative properties and deserves further research. Cyclic compounds **14-17** and **19** showed no antimicrobial activity, however two linear derivatives **10** and **12** moderately inhibited growth *M. smegmatis* and *S. aureus.*

References

1. Paprocka, R.; Wiese-Szadkowska, M.; Kosmalski et. all. A Review of the Biological Activity of Amidrazone Derivatives. Pharmaceuticals 2022, 15, 1219. https://doi.org/10.3390/ph15101219.

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