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Synthesis and study of biological activity of maleimide and triarylmethane derivatives

Abstract

The creation of new antimicrobial drugs does not lose its relevance. The development of pathogen resistance to the drugs used (including MDR - multidrug resistance) is considered a serious problem in the modern world and requires a continuous search for new compounds with antibacterial and antifungal activity, as well as the development of new approaches to the treatment of infectious diseases.

Despite the abundance of work in this field, some promising areas of synthesis of potential biologically active low-molecular compounds remain unexplored. In particular, derivatives of triindolylmethyl (turbomycin A) have high antibacterial activity, but toxicity limits their practical use. Related derivatives of di(indole-3-yl)phenylmethyl (turbomycin B) have been poorly studied and are of interest for the search for compounds with antimicrobial activity.

Maleimide derivatives are also extremely promising in this regard, as substances with a wide variety of biological activity have been found among them: protein kinase inhibitors, antibacterial, antifungal, as well as antitumor and anti-tuberculosis drugs. One of the directions of obtaining selective antimicrobial agents is the creation of hybrid compounds containing at least two biologically active fragments (pharmacophores). The creation of such hybrid molecules opens up new prospects in the modification of known drugs, and due to the influence of some maleimide derivatives on bacterial protein kinases, it can provide significant assistance in the fight against bacterial pathogens with MDR.

Previously, derivatives of 3-(arylamino)maleimide were obtained, which showed weak antifungal activity. The antibacterial activity of 3-(arylthio)maleimides and interaction of 3,4-bis(ariltio)maleimides with proteins is known, but without a detailed study of their properties, methods of synthesis and structure-activity relationship. Triindolylmethyl derivatives were also obtained before, but only symmetric derivatives with N-alkyl substituents were studied.

The main goal of the present work is the synthesis of new derivatives of maleimide and triarylmethane with antibacterial or antifungal activity. **The following objectives have been proposed:**

1. Development of methods for obtaining and synthesis of a series of new derivatives of 3,4-bis(arylthio)maleimide, 3-(arylamino)maleimide, 3-(indole-1-il)maleimide and (3-arylthio)maleimide.

2. Synthesis of new triarylmethane derivatives containing an indole fragment.

3. Synthesis of new hybrid compounds – maleimides conjugated with triarylmethane derivatives.

4. Study of the structure - biological activity relationship of the obtained compounds.

Scientific novelty

A method has been developed for the synthesis of new 3-(arylamino)-4-brommaleimides, 3,4-bis(arylthio)maleimide, 3-(arylamino)-4-(arylthio)maleimides and 3-(arylthio)-4-(indoline-1-yl)-maleimides. New derivatives of triindolylmethane and triindolylmethylium have been obtained, including those containing a maleimide fragment in their structure. New hybrid compounds – maleimides conjugated with triarylmethyl derivatives have been obtained. More than 90 new compounds have been synthesized, of which 40 have been analyzed for the structure -biological activity relationship. The antibacterial and antifungal activity of 3,4-bis(arylthio) was revealed for the first time (MIC 0.5 – 2 mcg/ml on *Staphylococcus* strains). Weak antibacterial activity of 3-hydroxy-4-(arylthio)maleimides and 3-(arylthio)-4-chlormaleimides was revealed (MPC 4 – 16 mcg/ml). New derivatives of (4-(alkylamino)phenyl)bis(1H-indole-3-yl)methylium and (1-alkylindoline-5-yl)bis(1-butyl-1H-indole-3-yl)methylium for the first time showed high antimicrobial activity against gram-positive (MIC 0.13 – 1 mcg/ml on *S. aureus*), gram-negative bacteria (MIC 2-4 mcg/ml on *E. coli*), as well as *A. niger* fungi (MIC 0.25 – 0.5 mcg/ml). The effect of the maleimide substituent on the antibacterial and antifungal properties of triindolylmethylium derivatives and their cytotoxicity against fibroblast cells was studied.

The theoretical and practical significance lies in the development of new preparative methods for the synthesis of 3-(arylamino)maleimides, 3-(ariltio)maleimides and triarylmethane derivatives, the study of ways to modify them and their structure – biological activity relationship. The leading compounds that have shown high antibacterial and antifungal activity are promising for in-depth study *in vivo*.

Theses to be sustained

1. New methods of synthesis and transformation of 3-(arylthio)maleimides and 3-(arylamino)maleimides.

2. Methods of synthesis of arylbis(indole-3-yl)methanes and arylbis(indole-3-yl)methylium salts, as well as triindolylmethanes and triindolylmethylium derivatives which have a maleimide fragment in their structure.

3. Data on the structure – biological activity relationship for new derivatives of triarylmethane and maleimide, including conjugates of maleimide fragment with triarylmethylium derivatives.