SYNTHESIS OF INDOLINE-THIAZOLIDINONE HYBRIDS AS POTENTIAL BIOLOGICALLY ACTIVE COMPOUNDS

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Introduction. Thiazole/thiazolidinone derivatives constitute an important class of therapeutic agents in medicinal chemistry with antitrypanosomal, antiviral, anticancer, antioxidant, anti-inflammatory, and antimicrobial activities. Thus, the thiazole ring is present in several drugs, such as meloxicam, penicillin, monobactam, sulfathiazole, thiabendazole, and ritonavir. This makes this heterocyclic fragment an ideal candidate for constructing more potent and safer drug candidates, especially in treating infectious diseases. Therefore, it was envisaged that combining thiazolidinone with other pharmacophores, especially indole fragments, would generate molecular templates with new pharmacological profiles and lower toxicity. Thus, many commercial drugs and biologically active molecules have been identified among indole-based derivatives. Continuing this theme, we designed and synthesized new indoline-thiazolidinone hybrid molecules and screened their biological activities.

Aim. Based on the Knoevenagel condensation reaction, the synthesis of new rhodanine-indoline hybrid molecules for screening antibacterial, antifungal, anti-inflammatory, and anti-allergic activities was accomplished.

Materials and Methods. Organic synthesis, NMR spectroscopy, agar diffusion method, microdilution susceptibility method, ELISA studies, molecular docking.

Results and Discussion. The reaction between rhodanine-3-propionic/ethanesulfonic acids with indole-carbaldehydes in an acetic acid medium providing a series of 5-indolylmethylene rhodanine-3-carboxylic/sulfonic acid derivatives. Based on the esterification reaction with methanol in sulfuric acid, 5-indolylmethylene rhodanine-3-propionic acid was transformed into an appropriate ester to further evaluate the antimicrobial activity. Antimicrobial activity screening identified compounds with significant effects against tested microorganisms with MIC/MBC/MFC values in the range of 25-50 μg/mL. It was determined that the hit compound (3-[5-(1*H*-indol-3-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-propionic acid) with antimicrobial activity decreased IgE levels in sensitized guinea pigs by 33–86% and reduced IgA, IgM, IL-2, and TNF-α, indicating anti-inflammatory and anti-allergic activities. According to the SwissADME web tool, target predictions for mentioned compound potentially have an affinity for lysosomal protective protein, Thromboxane-A synthase, and PPARγ. Furthermore, the molecular docking confirmed that the studied 2-thioxo-4-thiazolidinone derivative showed good bonding with LLP and TXAS, leading to stable protein-ligand complexes.

Conclusion. Considering the above, the tested indoline-thiazolidinone hybrid molecules are justified as a fruitful template for the search for a new class of multitarget therapeutic agents.