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Synthesis 3- (8 - Benzodioxocin – 1, 6 - Il) - 4-H-Coumarin

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ABSTRACT

A new modified chemical compound of coumarin with a 1,6-benzodioxocin fragment has been synthesized in a more convenient and efficient way under the conditions of the Kneuvenagel reaction. Several chemical and physical properties have been studied. The results of the prediction of the spectrum of biological activity and the prediction of possible side and toxic effects of the chemical compound 3- (8 - benzodioxocin - 1,6 - yl) - 4-H-coumarin, based on clinical manifestations, are presented.

Keywords: synthesis, coumarin, benzodioxocin fragment, Knevenagel reaction, biological activity.

Recently, there has been an increase in interest in the chemical compound coumarins - natural biologically active substances sensitive to changes in environmental conditions.

Previously, the authors synthesized 3-heteroaryl-4H-coumarins with 1,3-benzodioxole, 1,4-benzodioxane and 1,5-benzodioxepane fragments [1, 2]. When carrying out primary screening for antimycobacterial activity with the obtained compounds in [3, 4], it was noted that unsubstituted 3-heteroaryl-4H-coumarin with a 1,5-benzodioxepane fragment was more active (86%) than with 1,3-benzodioxole and 1,4-benzodioxane fragments.

From the results obtained, it can be seen that it is these compounds that can be modified to achieve antimycobacterial activity up to 90% or more, they are promising in terms of the synthesis of antituberculosis drugs on their basis.

Thus, the presence of an unsubstituted hetaryl fragment in the structure of synthetic coumarin analogs made it possible to search for the preparation of an analog of 3-heteroaryl-4H-coumarin with an expansion of the heterocycle size in ring B, which is sensitive to changes in environmental conditions.

A more convenient and efficient way to obtain this compound is synthesis under the conditions of the Kneuvenagel reaction, which flows under milder conditions and with higher yields [1].

A mixture of 10 mmol of heteroarylacetonitrile **(1)**, 10 mmol of unsubstituted aldehyde **(2)**, 0.12 ml of piperidine and 10 ml of 95% ethanol was refluxed for 6 hours. Then the reaction mixture was hydrolyzed with 5 ml of 2 N HCl hydrochloric acid for 1 h. After cooling, the precipitate was filtered off and washed with 1% aqueous $NaHCO_3$ solution. The residue was crystallized from ethyl acetate (Fig. 1).

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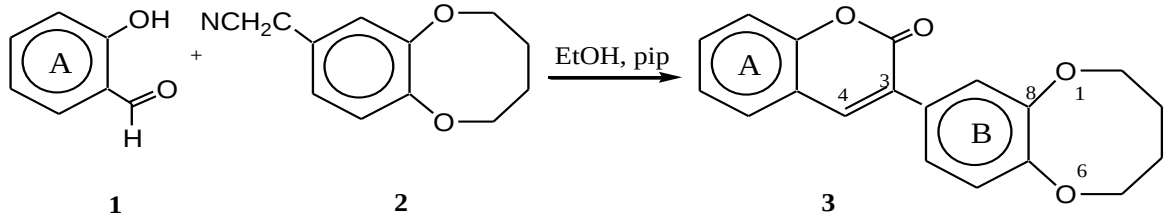
Monitoring the progress of the reaction and determination of the individuality of the synthesized compound **(3)** was carried out by thin layer chromatography (TLC) on Silufol UV-254 plates (eluent benzene: ethanol, 9: 1).

Compound 3- (8 - benzodioxocin - 1,6 - yl) - 4-H-coumarin **(3)** is a colorless crystalline substance, readily soluble in most organic solvents and insoluble in water. Easily detected by blue fluorescence in UV light.



1 **2** **3**

Figure 1. Synthesis of 3- (8 - benzodioxocin - 1,6 - yl) - 4-H-coumarin under the conditions of the Kneuvenagel reaction

Chemical properties

$C_{19}H_{16}O_4$, M.m. 308.10. Elemental analysis: C, 74.01; H, 5.23; O, 20.76.

Physical properties

Boiling point [p = 1 atm]: 738.87 K, melting point [p = 1 atm]: 539.86 K, critical temperature: 963.45 K, critical pressure: 24.006 bar, critical volume: 837.50 cm/mol, heat of formation [T = 298.15 K, p = 1 atm]: -357.85 kJ/mol, Gibbs energy [T = 298.15 K, p = 1 atm]: -44.530 kJ/mol, ideal heat capacity gas for [T = 298.15 K and p = 1 atm]: 313.93 J/(mol.K).

The 1H-NMR spectrum was recorded on a Unity-400 + instrument (Varian, USA, 400 MHz) in $CDC1_3$. The yield was 1.90 g (80%).

The PASS Online computer system (a program for predicting the spectrum of biological activity of substances) [5] made it possible to predict the spectrum of biological activity of a substance based on its structural formula, including pharmacological effects and mechanisms of action. It was shown that the effectiveness of this approach in screening a synthesized new substance **(3)** was over 80% (Fig. 2).

The forecast results include the names of the activity and the estimates of the probabilities (Pa) of "to be active".

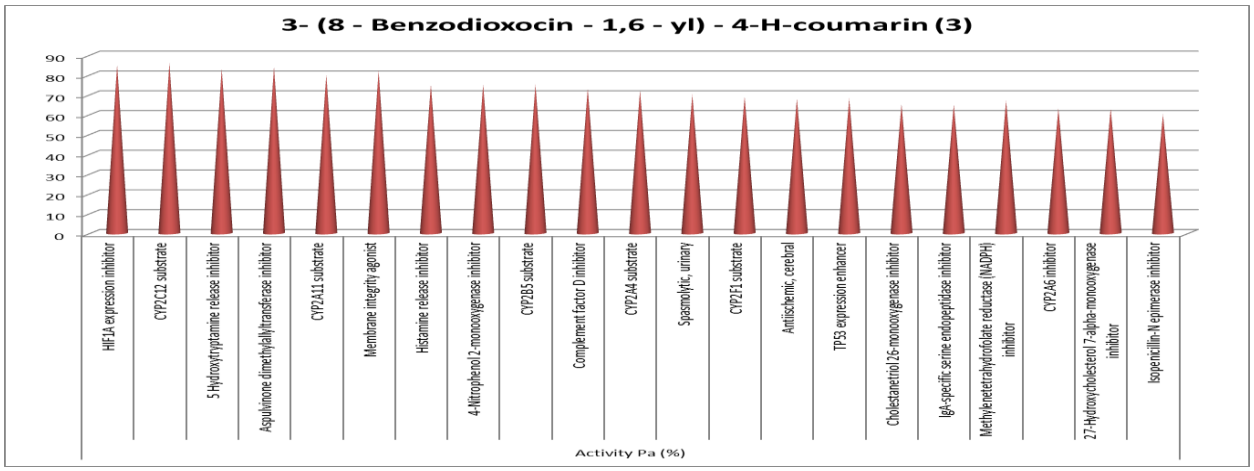


Figure 2. Prediction of the spectrum of biological activity of the chemical compound 3- (8 - benzodioxocin - 1,6 - yl) - 4-H-coumarin (3)

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The prognosis of possible side and toxic effects of compound **(3)** showed over 60%, based on clinical manifestations, which are sometimes observed in several or even one patient (Fig. 3).

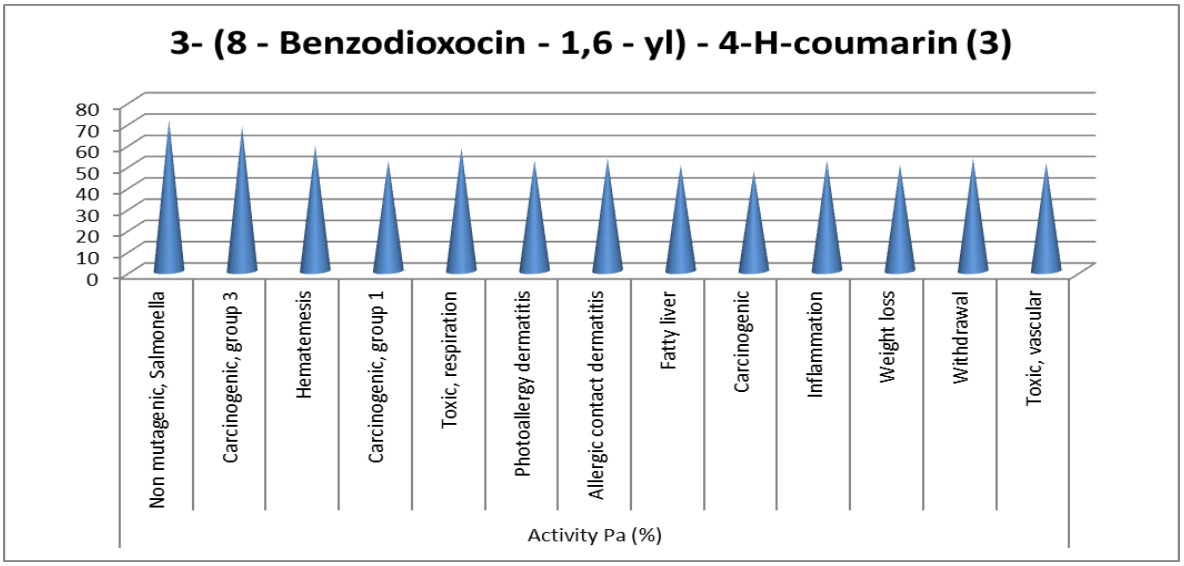

Figure 3. Prediction of possible side and toxic effects of compound 3- (8 - benzodioxocin - 1,6 - yl) - 4-H-coumarin (3)

Conclusions

Thus, the synthesized new compound 3-heteroaryl-4H-coumarin with a 1,6-benzodioxocine fragment, an expanded size of the heterocycle in ring B, which in the future can serve as the basis for an anti-tuberculosis drug, additionally predicts other biologically active activities. By changing the structure of coumarins molecules, it is possible to increase the absolute indicators of their activity in biological tests.

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