NOVEL ANTHRANILIC ACID HYBRIDS – AN ALTERNATIVE WEAPON AGAINST INFLAMMATORY PATHOLOGIES

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Introduction: Anti-inflammatory drugs are used to relieve pain, fever, and inflammation while protecting the cardiovascular system. However, the side effects of currently available medications have limited their usage. Due to the adverse effects, there is a significant need for new drugs.

Keywords: synthesis; hybrid molecules; anthranilic acid; diamides; anti-inflammatory activity; denaturation of albumin

Aim: The current trend of research has shifted towards the synthesis of novel anthranilic acid hybrids as anti-inflammatory agents.

Materials and Methods:

Synthesis of the hybrid molecule 2-amino-N-(3-chlorophenethyl)benzamide 3 and acylation to diamides 4 a–e.

A mixture of 10 mmol isatoic anhydride and 15 mmol 2-(3-chlorophenyl)ethylamine in 30 mL dichloromethane was stirred overnight at rt. The resulting solution was filtered on the neutral Al_2O_3 and concentrated. The obtained benzamide **3** was applied in a reaction with excess of acyl chlorides in 10 mL dichloromethane. Then equimolar amount of $N(C_2H_5)_3$ was added in 10 min. In about 30 min the reaction mixture was washed consequently with diluted HCl (1:4), Na_2CO_3, and H2O, then dried with anhydrous Na_2SO_4, filtered on the short column filled with neutral Al_2O_3, and concentrated.

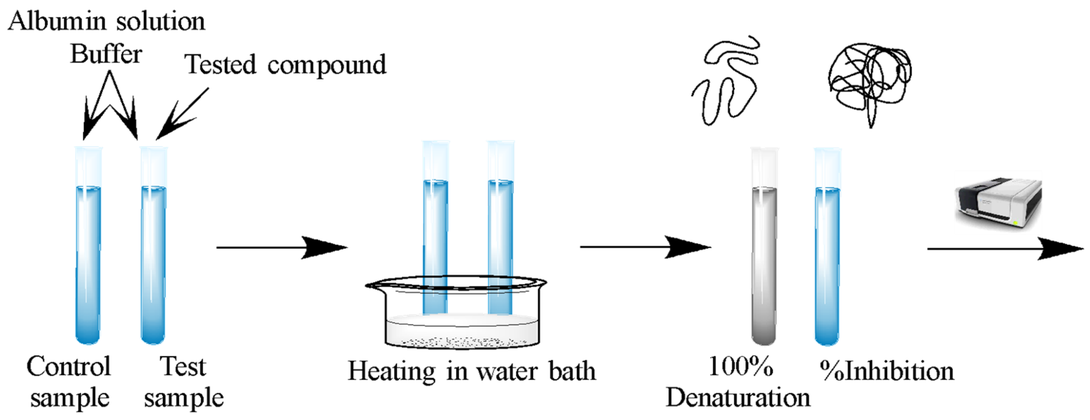
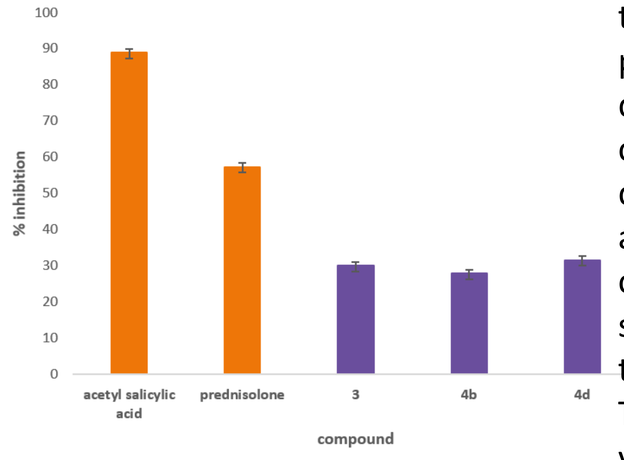


Figure 1. Inhibition of albumin denaturation – methodology and results.



The results showed that all the compounds exhibit a preventive effect on albumin denaturation higher than two common anti-inflammatory drugs – prednisolone and acetylsalicylic acid. The compounds **3**, **4b**, and **4d** scored the best results, 2-3 times higher inhibition effect. The novel molecules exerted a very good anti-inflammatory effect in preventing albumin denaturation.

Results and Discussion: The amides of anthranilic acid are crucial in the treatment of numerous metabolic pathologies in addition to their widespread use as anti-inflammatory drugs.

The phenethylamine class, on the other hand, has received the most interest as a 5-hydroxytryptamine subtype selective agonist.

Considering these facts, a targeted synthesis for novel hybrid diamide molecules as structural analogues of phenylethylamines with incorporated anthranilic acid core was conducted. The chosen synthetic procedure efficiently furnished the desired diamides 4a–e in 78–82% yield (Table 1).

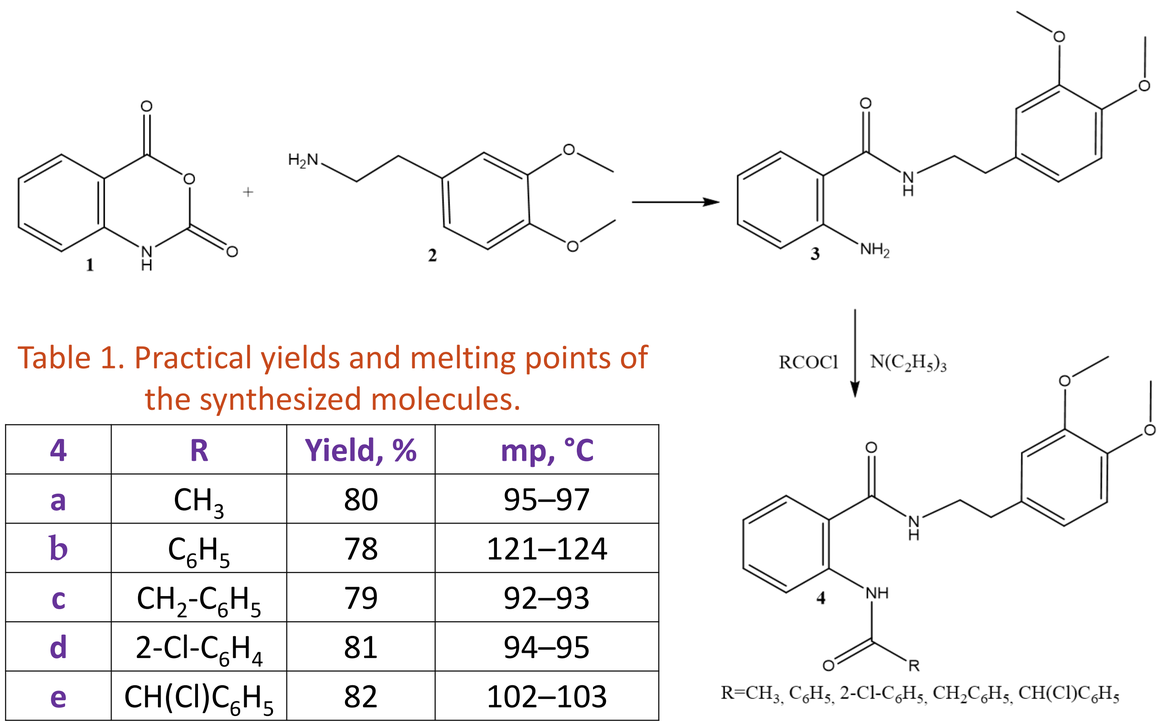


Table 1. Practical yields and melting points of the synthesized molecules.

4	R	Yield, %	mp, °C
a	CH_3	80	95–97
b	C_6H_5	78	121–124
c	CH_2-C_6H_5	79	92–93
d	2-Cl-C_6H_4	81	94–95
e	$CH(Cl)C_6H_5$	82	102–103

Inhibition of albumin denaturation assessment.

- ✓ 0.5 mL of 5% aqueous solution of human albumin.
- ✓ 2.5 mL phosphate-buffered saline (pH 6.3).
- ✓ 0.2 mL DMSO solution of tested compound, at different concentrations (20–500 µg/mL).
- ✓ Heating for 30 min to 80°C.
- ✓ Turbidity was measured spectrophotometrically at 660 nm.
- ✓ The control represents 100% protein denaturation.
- ✓ Commercially available anti-inflammatory drugs prednisolone and acetylsalicylic acid were used for comparison.

Conclusion: In conclusion, novel hybrid diamides of isatoic anhydride with homoveratrylamine were synthesized as novel anti-inflammatory drug candidates with anthranilic acid nucleus.

Based on the experimental data, we can conclude that a collection of novel hybrids was successfully synthesized, and they can be considered as anti-inflammatory drug candidates – alternatives to current therapeutics.

Future preclinical experiments will benefit the novel hybrids as potential drug candidates against inflammatory diseases. To confirm the *in vitro* anti-inflammatory results, tests to evaluate their effect on Interleukin-1 expression and smooth muscles are planned.

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