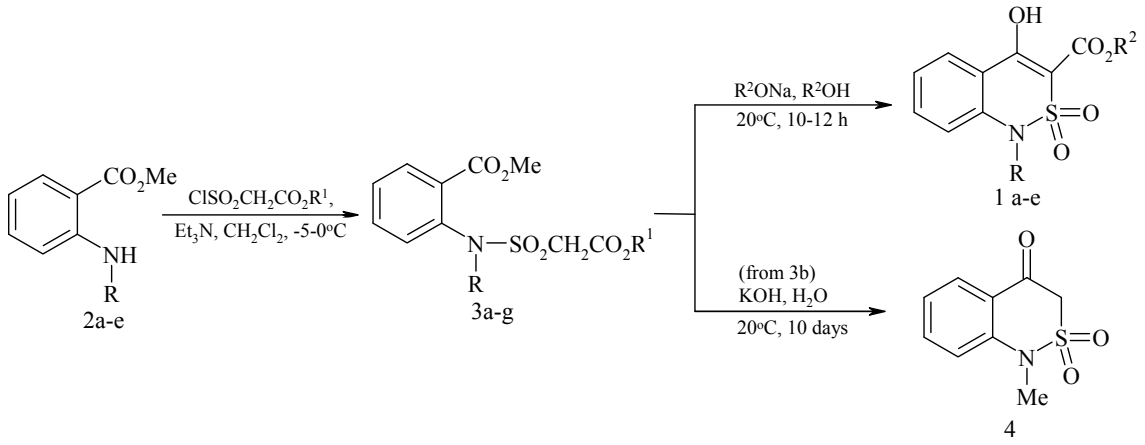
SYNTHESIS, STRUCTURE, AND ANALGESIC ACTIVITY OF 1-R-4-HYDROXY-2,2-DIOXO-1*H*-2λ^6,1-BENZOTHIAZINE-3-CARBOXYLATES

Barakat W., Petrushova L. A., Ukrainets I.V.
The National University of Pharmacy, Kharkiv, Ukraine
dika-l1@yandex.ru

Chemical modification is the simplest and the most widely applied way of improving the pharmacological and pharmaceutical properties of biologically active substances. An interesting extension of the studies in this direction is the replacement of carbonyl in position 2 by a sulfonyl group in the molecules of oxicams to obtain 4-hydroxy-2,1-benzothiazine 2,2-dioxides and to study their analgesic activity. The results of our investigation, devoted to 1-R-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylates **1**, are given in the present communication.

The synthesis of the desired alkyl-2,1-benzothiazine-3- carboxylic acids **1** was achieved by a route analogous to the preparation of the quinoline analogs , with only difference that upon acylation of methyl anthranilates **2** we used alkyl chlorosulfonylacetates instead of alkyl malonyl chlorides.



1–**3 a, 3f**,**g** R = H; **1**–**3 b** R = Me; **1**–**3 c** R = Et, **1**–**3 d** R = All, **1**–**3 e** R = Ph; **3 a** R^1 = Et, **b**,**d**–**f** R^1 = Me, **c**,**g** R^1 = *i*-Pr; **1 a** R^2 = Et, **b**–**e** R^2 = Me

The structures of the synthesized compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy. Screening investigations of the analgesic properties of esters **1a-e** were carried out on the standard model of heat-induced pain (tail-flick test) enabling judgment of the central effect on the nociceptive system.

The highest activity of all the groups of the substances studied was revealed by methyl 1-allyl-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzo-thiazine-3-carboxylate (**1d**), the analgesic effect of which (+71.1%) exceeded that of all the reference compounds used in the experiment.